Towards the evaluation in an animal disease model: Fluorinated 17β-HSD1 inhibitors showing strong activity towards both the human and the rat enzyme

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1. **Chart S1: Overview on synthesized compounds 1-38**

![Chemical structures](image)

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2. **Supplementary table S1: HPLC purity control of final compounds**

The purity of the compounds was evaluated by LC/MS. The Surveyor®-LC-system consisted of a pump, an auto sampler, and a PDA detector. Mass spectrometry was performed on a TSQ® Quantum (ThermoFisher, Dreieich, Germany). The triple quadrupole mass spectrometer was equipped with an electrospray interface (ESI). The system was operated by the standard software Xcalibur®. A RP C18 NUCLEODUR® 100-5 (3 mm) column (Macherey-Nagel GmbH, Düren, Germany) was used as stationary phase. All solvents were HPLC grade. In a gradient run the percentage of acetonitrile (containing 0.1 % trifluoroacetic acid) was increased from an initial concentration of 0% at 0 min to 100 % at 15 min and kept at 100 % for 5 min. The injection volume was 15 µL and flow rate was set to 800 µL/min. MS analysis was carried out at a needle voltage of 3000 V and a capillary temperature of 350 °C. Mass spectra were acquired in positive mode from 100 to 1000 m/z and UV spectra were recorded at the wave length of 254 nm.

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**Supplementary table S1: HPLC Purity Control of Final Compounds**

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3. **Supplementary table S2. Calculated pK\(\text{a}\) values for the OH group at Ring A computed using the GALAS algorithm of ACD/Percepta (ACDLabs).**

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4. **Supplementary table S3. Biological data of 17β-HSD1 inhibitors of other compound classes**

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ᵃ Human placenta, cytosolic fraction, substrate [³H]-E1, 500 nM, cofactor NADH, 500 µM; ᵇ Mean value of three determinations, standard deviation less than 15%; ᶜ Mouse recombinant enzyme, expressed in HEK 293, substrate [³H]-E1, 10 nM, cofactor NADH, 500 µM; ᵈ Inhibition @ 1µM (inhibitor concentration).
Figure S1. Overlay of 1FDT (green) and 3HB5 (grey) showing NADP (yellow carbon), estradiol (green carbon) and E2B (white carbon). A transparent surface around Lys195 of 1FDT is shown to indicate the overlap of this side chain with E2B as mentioned in the main text. Additionally, the constrained four-feature pharmacophore model (white dashed circles) is shown (Ia: essential hydrogen-bond acceptor, Ib: projected donor for Ia, Ila: essential hydrogen-bond donor, Ilb: projected acceptor for Ia).
Figure S2. Application of the pharmacophore-guided docking protocol to E2B (A) and compound 33 (B) as control experiment. A) Grey: original coordinates of 3HB5 after structure preparation via LigX protocol of MOE (default parameters), white: docking result for co-crystalized inhibitor E2B. The RMSD value between both binding poses is 0.3758 Å. B) Grey: coordinates of the modelled h17β-HSD1:33 complex based on the docking of compound 30, white: similar docking result obtained through direct application of pharmacophore-guided docking protocol. The RMSD value between both binding poses is 2.4312 Å.
Figure S3. Sequence alignment of human (1FDS_A) mouse (NP_034605) and rat (NP_036983) 17β-HSD1.

Figure S4. Phi-Psi plots of h17β-HSD1 (PDB-ID 3HB5) and homology models of m17β-HSD1 as well as r17β-HSD1. Outliers are shown as red crosses.
9. **Supplementary Figure S5**

**Figure S5.** Overlay of residues that are different for mouse and rat isoforms and in proximity to the ligand binding site Met193/Tyr194/His194, Leu197/Val198/Glu198, Leu220/Leu220/Gln220 and Arg281/Arg281/Gln281 of h17β-HSD1 (3HB5, green), and homology models m17β-HSD1 (white) and r17β-HSD1. The space occupied by inhibitor 33 is shown as a blue surface. Residues inside a 4.5Å perimeter around the inhibitor are shown as a blue wire. Only residues Met193/Tyr194/His194 are inside this perimeter.

10. **Synthesis, ^1^H NMR and ^13^C NMR spectra of target compounds**

4-Bromo-N-(4-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)-2-trifluoromethoxybenzenesulfonamide (4).

The title compound was prepared by reaction of (5-(4-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (1) (100 mg, 0.34 mmol) and 4-bromo-2-trifluoromethoxybenzenesulfonyl chloride (172 mg, 0.51 mmol) according to Method C. The product was purified by CC (DCM); yield: 36% (72 mg). ^1^H NMR (500 MHz, CD$_3$OD) δ 9.30 (br. s, 1H), 8.42 (br. s, 1H), 7.82 (d, $J = 8.9$ Hz, 1H), 7.54 – 7.51 (m, 2H), 7.50 – 7.48 (m, 2H), 7.48 – 7.46 (m, 1H), 7.27 – 7.21 (m, 2H), 7.18 – 7.15 (m, 1H), 7.11 (dd, $J = 2.2$, 1.7
Hz, 1H), 7.10 – 7.06 (m, 2H), 6.94 (ddd, J = 8.1, 2.5, 1.0 Hz, 1H); 13C NMR (125 MHz, CD3OD) δ 188.11, 156.45, 152.18, 148.75, 145.99, 141.99, 139.02, 137.05, 136.42, 136.31, 132.55, 130.56, 129.97, 129.71, 129.66, 128.99, 127.38, 124.28, 123.88, 123.41, 123.40, 121.26, 121.22, 121.16, 119.86, 119.07, 115.88; MS (ESI): 600.16 (M+H)+ ; HPLC purity ≥ 95% (Rt = 13.37 min).

3-Cyano-N-(4-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (5).

The title compound was prepared by reaction of (5-(4-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (1) (100 mg, 0.34 mmol) and 3-cyano benzencesulfonyl chloride (103 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 48% (74 mg). 1H NMR (500 MHz, CD3OD) δ 9.15 (br. s, 1H), 8.43 (br. s, 1H), 8.06 (t, J = 1.5 Hz, 1H), 7.95 (ddd, J = 8.0, 1.8, 1.1 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.61 – 7.57 (m, 1H), 7.57 – 7.56 (m, 1H), 7.55 (ddd, J = 3.1, 0.9 Hz, 2H), 7.33 (t, J = 5.2 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.12 (dd, J = 4.5, 2.2 Hz, 2H), 7.11 – 7.09 (m, 1H), 6.95 (ddd, J = 8.1, 2.5, 1.1 Hz, 1H); 13C NMR (125 MHz, CD3OD) δ 189.73, 158.91, 153.81, 143.04, 142.67, 140.50, 139.47, 137.92, 137.39, 132.36, 131.73, 131.57, 131.25, 130.75, 128.36, 125.33, 122.45, 121.25, 120.64, 119.54, 118.20, 116.48, 114.68, 112.05; MS (ESI): 461.24 (M+H)+ ; HPLC purity ≥ 97% (Rt = 11.53 min).

N-(3-(5-(3-Hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (6).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and benzencesulfonyl chloride (90 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 14% (20 mg). 1H NMR (500 MHz, acetone-d6) δ 9.21 (br. s, 1H), 8.78 (br. s, 1H), 7.90 – 7.85 (m, 2H), 7.70 (d, J = 4.0 Hz, 1H), 7.62 (tt, J = 2.6, 1.8 Hz, 2H), 7.56 (tt, J = 8.3, 1.3 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.41 – 7.39 (m, 1H), 7.38 – 7.34 (m, 2H), 7.34 – 7.33 (m, 1H), 7.28 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.14 (ddd, J = 7.9, 2.6, 1.2 Hz, 1H); 13C NMR (125 MHz, acetone-d6) δ 187.71, 158.44, 152.34, 150.65, 143.51, 140.74, 140.21, 139.79, 136.78, 135.09, 133.88, 131.11, 130.60, 130.05, 128.01, 125.61, 124.59, 123.01, 121.90, 121.09, 120.30, 118.76, 116.29; MS (ESI): 436.13 (M+H)+ ; HPLC purity ≥ 95% (Rt = 11.84 min).

3-Cyano-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (8).
The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 3-cyanobenzenesulfonyl chloride (103 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 50% (78 mg). \(^1\)H NMR (500 MHz, acetone-d\(_6\)) \(\delta\) 9.39 (br. s, 1H), 8.76 (br. s, 1H), 8.24 – 8.19 (m, 1H), 8.14 (ddd, \(J = 8.0, 1.9, 1.1\) Hz, 1H), 8.07 – 8.02 (m, 1H), 7.84 – 7.78 (m, 1H), 7.71 (d, \(J = 4.0\) Hz, 1H), 7.62 (t, \(J = 1.8\) Hz, 1H), 7.57 (ddd, \(J = 7.8, 1.8, 1.0\) Hz, 1H), 7.53 (d, \(J = 4.0\) Hz, 1H), 7.41 (td, \(J = 7.9, 3.0\) Hz, 2H), 7.37 (dt, \(J = 7.6, 1.3\) Hz, 1H), 7.33 (dd, \(J = 2.2, 1.6\) Hz, 1H), 7.30 (ddd, \(J = 8.1, 2.1, 0.9\) Hz, 1H), 7.14 (ddd, \(J = 7.9, 2.5, 1.2\) Hz, 1H); \(^{13}\)C NMR (125 MHz, acetone-d\(_6\)) \(\delta\) 187.69(C=O), 158.44(C-OH), 152.03(C), 143.64(C), 141.97(C), 140.18(C), 139.03(C), 137.33(CH), 136.76(CH), 135.31(C), 132.18(CH), 131.56(CH), 131.49(CH), 131.33(CH), 130.61(CH), 125.78(CH), 123.72(CH), 122.42(CH), 121.10(CH), 120.32(CH), 119.44(CH), 117.87(C), 116.29(CH), 114.34(C); MS (ESI): 461.17 (M+H\(^+\))\(^{+}\); HPLC purity \(\geq\) 98% (R\(_t\) = 11.96 min).

Thiophene-2-sulfonic acid (3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)amide (9).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and thiophene-2-sulfonyl chloride (93 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 34% (50 mg). \(^1\)H NMR (500 MHz, acetone-d\(_6\)) \(\delta\) 9.06 (br. s, 1H), 8.59 (br. s, 1H), 7.82 (dd, \(J = 5.0, 1.3\) Hz, 1H), 7.74 – 7.67 (m, 2H), 7.65 – 7.60 (m, 1H), 7.55 (d, \(J = 7.7\) Hz, 1H), 7.52 (d, \(J = 4.0\) Hz, 1H), 7.44 – 7.32 (m, 5H), 7.17 – 7.09 (m, 2H); \(^{13}\)C NMR (125 MHz, acetone-d\(_6\)) \(\delta\) 187.78, 158.45, 152.34, 143.55, 141.13, 140.19, 139.55, 136.84, 135.13, 133.84, 133.62, 131.17, 130.62, 128.42, 125.68, 123.36, 122.17, 121.12, 120.35, 118.97, 116.32; MS (ESI): 442.02 (M+H\(^+\))\(^{+}\); HPLC purity \(\geq\) 98% (R\(_t\) = 11.96 min).

3-Methoxy-N-(3-(5-(3-methoxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (10a).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-methoxyphenyl)methanone (2a) (770 mg, 2.49 mmol) and 3-methoxybenzenesulfonyl chloride (772 mg, 3.73 mmol) according to Method C. The product was purified by CC (hexane/ethyl acetate 3:2); yield: 92% (1100 mg). \(^1\)H NMR (500 MHz, DMSO-d\(_6\)) \(\delta\) 10.49 (br. s, 1H), 7.73 (d, \(J = 4.0\) Hz, 1H), 7.54 (d, \(J = 4.0\) Hz, 1H), 7.48 (ddd, \(J = 9.2, 8.0, 6.1\) Hz,
4H), 7.44 – 7.40 (m, 1H), 7.36 (dt, \( J = 14.8, 4.8 \text{ Hz}, 2H \)), 7.33 (dd, \( J = 2.5, 1.5 \text{ Hz}, 1H \)), 7.31 – 7.29 (m, 1H), 7.26 (ddd, \( J = 8.2, 2.7, 1.0 \text{ Hz}, 1H \)), 7.18 (ddd, \( J = 8.3, 2.6, 0.9 \text{ Hz}, 1H \)), 7.15 (ddd, \( J = 8.1, 2.1, 0.9 \text{ Hz}, 1H \)), 3.84 (s, 3H), 3.77 (s, 3H); \(^{13}\text{C NMR} \text{ (125 MHz, DMSO-}d_6\text{)} \delta\)

186.71, 159.37, 159.23, 151.22, 141.61, 140.50, 138.72, 138.59, 136.79, 133.30, 130.57, 130.35, 129.87, 125.36, 121.71, 121.12, 120.59, 118.86, 118.76, 118.55, 117.02, 113.46, 111.66, 55.56, 55.36; \( \text{MS (ESI)}: 479.06 \text{(M+H)}^+\).

3-Hydroxy-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (10).

The title compound was prepared by reaction of 3-methoxy-N-(3-(5-(3-methoxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (10a) (100 mg, 0.21 mmol) and boron tribromide (7.5 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 97:3); yield: 74% (70 mg). \(^1\text{H NMR} \text{ (500 MHz, CD}_3\text{OD)} \delta \) 7.67 (d, \( J = 4.0 \text{ Hz}, 1H \)), 7.48 (t, \( J = 1.8 \text{ Hz}, 1H \)), 7.45 (ddd, \( J = 7.7, 1.7, 1.0 \text{ Hz}, 1H \)), 7.43 (d, \( J = 4.0 \text{ Hz}, 1H \)), 7.38 (ddd, \( J = 14.4, 6.6 \text{ Hz}, 1H \)), 7.34 – 7.29 (m, 3H), 7.29 – 7.24 (m, 2H); 7.23 – 7.19 (m, 1H), 7.14 (ddd, \( J = 8.1, 2.1, 0.9 \text{ Hz}, 1H \)), 7.07 (dd, \( J = 8.0, 2.5, 1.1 \text{ Hz}, 1H \)); \(^{13}\text{C NMR} \text{ (125 MHz, CD}_3\text{OD)} \delta 189.76(\text{C=O}), 159.28(\text{C-OH}), 158.93(\text{C-OH}), 153.82(\text{C}), 143.47(\text{C}), 141.91(\text{C}), 140.43(\text{C}), 140.13(\text{C}), 137.75(\text{CH}), 135.46(\text{CH}), 131.21(\text{CH}), 131.13(\text{CH}), 130.77(\text{CH}), 125.74(\text{CH}), 123.36(\text{CH}), 122.58(\text{CH}), 121.31(\text{CH}), 121.08(\text{CH}), 120.71(\text{CH}), 119.41(\text{CH}), 119.03(\text{CH}), 116.51(\text{CH}), 114.87(\text{CH}); \( \text{MS (ESI): 452.18 (M+H)}^+)\); HPLC purity ≥ 95% (\( R_t = 10.98 \text{ min} \)).

3-Methoxy-N-(3-(5-(3-methoxybenzoyl)thiophene-2-yl)phenyl)benzamide (11a).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-methoxyphenyl)methanone (2a) (770 mg, 2.49 mmol) and 3-methoxybenzoyl chloride (425 mg, 3.73 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.75:0.25); yield: 61% (672 mg). \(^1\text{H NMR} \text{ (500 MHz, CDCl}_3\text{)} \delta 8.04 (t, \( J = 1.8 \text{ Hz}, 1H \)), 7.95 (br. s, 1H), 7.65 – 7.61 (m, 2H), 7.47 – 7.43 (m, 3H), 7.42 – 7.39 (m, 3H), 7.37 (dd, \( J = 4.4, 2.1 \text{ Hz}, 3H \)), 7.12 (ddd, \( J = 8.1, 2.7, 1.1 \text{ Hz}, 1H \)), 7.08 (ddd, \( J = 7.6, 2.6, 1.5 \text{ Hz}, 1H \)), 3.86 (s, 3H), 3.85 (s, 3H); \(^{13}\text{C NMR} \text{ (125 MHz, CDCl}_3\text{)} \delta 187.73, 165.65, 160.08, 159.65, 152.58, 142.40, 139.34, 138.76, 136.15, 135.87, 134.25, 129.90, 129.86, 129.42, 124.30, 122.49, 121.65, 120.62, 118.67, 118.59, 118.27, 117.80, 113.69, 112.53, 55.51, 55.48; \( \text{MS (ESI): 444.21 (M+H)}^+)\).
The title compound was prepared by reaction of 3-methoxy-N-(3-(5-(3-methoxybenzoyl)thiophene-2-yl)-phenyl)benzamide (11a) (74 mg, 0.17 mmol) and boron tribromide (1.00 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 99:1); yield: 69% (48 mg). \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 8.21 (t, \(J = 1.8\) Hz, 1H), 7.74 (ddd, \(J = 8.1, 2.0, 0.9\) Hz, 1H), 7.72 (d, \(J = 4.0\) Hz, 1H), 7.56 (ddd, \(J = 4.0, 2.0, 1.2\) Hz, 2H), 7.46 (t, \(J = 7.9\) Hz, 1H), 7.42 (ddd, \(J = 7.6, 1.6, 1.0\) Hz, 1H), 7.40 – 7.36 (m, 2H), 7.36 – 7.32 (m, 2H), 7.27 (dd, \(J = 2.2, 1.7\) Hz, 1H), 7.08 (ddd, \(J = 8.0, 2.5, 1.2\) Hz, 1H), 7.02 (ddd, \(J = 8.1, 2.5, 1.0\) Hz, 1H); \(^13\)C NMR (125 MHz, CD\(_3\)OD) \(\delta\) 189.80, 159.00, 158.93, 154.44, 143.31, 140.95, 140.51, 137.81, 137.54, 135.15, 130.77, 130.73, 125.70, 123.23, 122.75, 121.30, 120.68, 119.99, 119.67, 119.49, 119.45, 116.52, 115.59; MS (ESI): 416.15 (M+H\(^+\))^+; HPLC purity \(\geq\) 95% (Rt = 10.93 min).

3-Hydroxy-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)-N-methyl-benzamide (12).

The title compound was prepared by reaction of 3-methoxy-N-(3-(5-(3-methoxybenzoyl)-thiophene-2-yl)phenyl)-N-methylbenzamide (12a) (290 mg, 0.63 mmol) and boron tribromide (3.80 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 98:2); yield: 56% (151 mg). \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 7.55 (d, \(J = 4.0\) Hz, 1H), 7.46 (dd, \(J = 7.8, 0.9\) Hz, 1H), 7.41 (s, 1H), 7.30 (d, \(J = 4.0\) Hz, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.24 (m, 1H), 7.21 – 7.18 (m, 1H), 7.13 (dd, \(J = 2.2, 1.7\) Hz, 1H), 7.12 – 7.08 (m, 1H), 6.98 – 6.92 (m, 2H), 6.70 – 6.68 (m, 1H), 6.67 (d, \(J = 7.6\) Hz, 1H), 6.62 – 6.59 (m, 1H), 3.40 (s, 3H); \(^13\)C NMR (125 MHz, CD\(_3\)OD) \(\delta\) 189.67, 173.12, 158.40, 158.13, 153.13, 146.69, 143.69, 140.40, 138.40, 137.65, 135.59, 131.22, 130.78, 130.26, 128.45, 126.07, 126.00, 125.65, 121.31, 120.74, 120.52, 118.03, 116.52, 116.20, 32.86; MS (ESI): 430.19 (M+H\(^+\))^+; HPLC purity \(\geq\) 95% (Rt = 10.96 min).

4-Cyano-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (13).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxy-phenyl)methanone (2) (100 mg, 0.34 mmol) and 4-cyanobenzenesulfonyl chloride (103 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 51% (80 mg). \(^1\)H NMR (500 MHz, acetone-d\(_6\)) \(\delta\) 9.65 (br. s, 1H), 8.91 (br. s, 1H), 8.07 – 8.02 (m, 2H), 8.02 – 7.97 (m, 2H), 7.71 (d, \(J = 4.0\) Hz, 1H), 7.64 (t, \(J = 1.8\) Hz, 1H), 7.57 (ddd, \(J = 7.8, 1.7, 1.0\) Hz, 1H), 7.53 (d, \(J = 4.0\) Hz, 1H), 7.41 (td, \(J = 7.7, 1.4\) Hz, 2H), 7.37 (dt, \(J = 7.6, 1.3\) Hz, 1H), 7.35 – 7.32 (m, 1H), 7.28
N-(3-(5-(3-Hydroxybenzoyl)thiophene-2-yl)phenyl)-2-nitrobenzenesulfonamide (14).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 2-nitrobenzenesulfonyl chloride (113 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 23% (37 mg). $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 9.54 (br. s, 1H), 8.48 (br. s, 1H), 8.08 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.98 (dd, $J = 7.9$, 1.2 Hz, 1H), 7.90 (td, $J = 7.7$, 1.4 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.73 (t, $J = 1.8$ Hz, 1H), 7.71 (d, $J = 4.0$ Hz, 1H), 7.62 – 7.57 (m, 1H), 7.55 (d, $J = 4.0$ Hz, 1H), 7.46 – 7.39 (m, 2H), 7.39 – 7.32 (m, 3H), 7.14 (dd, $J = 7.9$, 2.5, 1.2 Hz, 1H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 187.70(C=O), 158.43(C-OH), 152.05(C), 144.60(C), 143.65(C), 140.18(C), 139.06(C), 136.77(CH), 135.30(C), 134.12(CH), 131.31(CH), 130.61(CH), 128.81(CH), 125.77(CH), 123.67(CH), 122.34(CH), 121.10(CH), 120.32(CH), 119.32(CH), 118.03(C), 117.32(C), 116.28(CH); MS (ESI): 461.15 (M+H)$^+$; HPLC purity $\geq$ 99% (R$_t$ = 11.99 min).

N-(3-(5-(3-Hydroxybenzoyl)thiophene-2-yl)phenyl)-3-nitrobenzenesulfonamide (15).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 3-nitrobenzenesulfonyl chloride (113 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99:1); yield: 40% (65 mg). $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 9.65 (br. s, 1H), 8.28 (br. s, 1H), 8.65 – 8.61 (m, 1H), 8.48 (ddd, $J = 8.2$, 2.2, 1.0 Hz, 1H), 8.24 (ddd, $J = 7.9$, 1.7, 1.0 Hz, 1H), 7.89 (t, $J = 8.1$ Hz, 1H), 7.70 (d, $J = 4.0$ Hz, 1H), 7.64 (t, $J = 1.9$ Hz, 1H), 7.57 (ddd, $J = 7.8$, 1.7, 0.9 Hz, 1H), 7.52 (d, $J = 4.0$ Hz, 1H), 7.41 (td, $J = 7.9$, 2.9 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.34 – 7.29 (m, 2H), 7.13 (ddd, $J = 7.9$, 2.5, 1.2 Hz, 1H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 187.69, 158.43, 151.99, 149.33, 143.66, 142.26, 140.16, 138.95, 136.77, 135.34, 133.73, 132.02, 131.37, 130.61, 128.45, 125.79, 123.85, 122.87, 122.58, 121.10, 120.33, 119.56, 116.29; MS (ESI): 481.15 (M+H)$^+$; HPLC purity $\geq$ 97% (R$_t$ = 12.15 min).
The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 4-nitrobenzenesulfonyl chloride (113 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 46% (74 mg). $^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 9.17 (br. s, 1H), 8.20 (br. s, 1H), 8.44 – 8.37 (m, 2H), 8.16 – 8.10 (m, 2H), 7.70 (d, $J$ = 4.0 Hz, 1H), 7.66 (t, $J$ = 1.9 Hz, 1H), 7.57 (d, $J$ = 7.8 Hz, 1H), 7.53 (d, $J$ = 4.0 Hz, 1H), 7.41 (td, $J$ = 7.9, 1.7 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.34 – 7.28 (m, 2H), 7.14 (ddd, $J$ = 7.9, 2.5, 1.1 Hz, 1H); $^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 187.70(C=O), 158.43(C-OH), 152.03, 151.37, 146.07, 143.66, 140.17, 138.99, 136.77(CH), 135.34, 131.35(CH), 130.61(CH), 129.55(2CH), 125.79(CH), 125.35(2CH), 123.74(CH), 122.38(CH), 121.09(CH), 120.33(CH), 119.37(CH), 116.28(CH); MS (ESI): 481.18 (M+H)$^+$; HPLC purity $\geq$ 97% (R$_t$ = 12.20 min).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 2,3-dinitrobenzenesulfonyl chloride (135 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 23% (40 mg). $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 8.06 (t, $J$ = 1.5 Hz, 1H), 7.95 (ddd, $J$ = 8.0, 1.8, 1.1 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.61 – 7.57 (m, 1H), 7.57 – 7.56 (m, 1H), 7.55 (ddd, $J$ = 3.1, 0.9 Hz, 2H), 7.33 (t, $J$ = 5.2 Hz, 1H), 7.25 (t, $J$ = 7.8 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.12 (ddd, $J$ = 4.5, 2.2 Hz, 2H), 7.11 – 7.09 (m, 1H), 6.95 (ddd, $J$ = 8.1, 2.5, 1.1 Hz, 1H); $^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 187.72(C=O), 158.46(C-OH), 151.85(C), 151.56(C), 149.41(C), 143.79(C), 140.16(C), 137.88(C), 137.73(C), 136.78(CH), 135.50(C), 133.81(CH), 131.46(CH), 130.63(CH), 127.91(CH), 125.96(CH), 124.55(CH), 123.37(CH), 121.52(CH), 121.11(CH), 120.42(CH), 120.37(CH), 116.30(CH); MS (ESI): 526.21 (M+H)$^+$; HPLC purity $\geq$ 97% (R$_t$ = 12.35 min).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 2-fluorobenzenesulfonyl chloride (99 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 57% (88 mg). $^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 9.49 (br. s, 1H), 8.77 (br. s, 1H), 7.96 (td, $J$ = 7.6, 1.8 Hz, 1H), 7.73 – 7.66 (m, 3H), 7.51 (qd,
$J = 1.9, 1.1 \text{ Hz}, 2\text{H}), 7.43 – 7.38 \text{ (m, 2H)}, 7.38 – 7.33 \text{ (m, 4H)}, 7.33 – 7.30 \text{ (m, 1H)}, 7.14 \text{ (ddd, } J = 7.9, 2.5, 1.2 \text{ Hz, 1H}); ^{13}\text{C NMR (125 MHz, acetone-d$_6$) } \delta 187.70(\text{C}=\text{O}), 159.71 \text{ (d, } J = 254.7 \text{ Hz, C}), 158.45(\text{C-OH}), 152.24(\text{C}), 143.56(\text{C}), 140.20(\text{C}), 139.23(\text{C}), 136.83 \text{ (d, } J = 8.8 \text{ Hz, CH}), 136.78(\text{CH}), 135.14(\text{C}), 131.77(\text{CH}), 131.07(\text{CH}), 128.21 \text{ (d, } J = 13.5 \text{ Hz, C}), 125.71 \text{ (d, } J = 3.8 \text{ Hz, CH}), 125.69(\text{C}), 125.65(\text{CH}), 123.11(\text{CH}), 121.48(\text{CH}), 121.08(\text{CH}), 120.31(\text{CH}), 118.33(\text{CH}), 118.01(d, } J = 21.1 \text{ Hz, CH}), 116.30(\text{CH}); \text{ MS (ESI): 454.23 (M+H)$^+$); HPLC purity } \geq 96\% (R_s = 11.85 \text{ min}).

3-Fluoro-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl-phenyl)benzenesulfonamide (19).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 3-fluorobenzenesulfonyl chloride (99 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 53% (82 mg). ^{1}H NMR (500 MHz, acetone-$d_6$) $\delta 9.30$ (br. s, 1H), 8.76 (br. s, 1H), 7.74 – 7.67 (m, 2H), 7.65 – 7.50 (m, 5H), 7.45 – 7.36 (m, 4H), 7.34 – 7.25 (m, 2H), 7.14 (d, $J = 5.4$ Hz, 1H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta 187.69, 158.44, 152.16, 143.59, 140.19, 139.37, 136.78, 135.21, 132.41, 132.35, 131.23, 130.60, 125.70, 124.18 (d, $J = 3.1$ Hz), 123.43, 122.20, 121.09, 120.90, 120.32, 119.13, 116.29, 115.10, 114.90; MS (ESI): 454.15 (M+H)$^+\); HPLC purity $\geq 96\% (R_s = 12.23 \text{ min}).

4-Fluoro-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (20).

The title compound was prepared by reaction of (5-(3-amin-phenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 4-fluorobenzenesulfonyl chloride (99 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 44% (67 mg). ^{1}H NMR (500 MHz, acetone-$d_6$) $\delta 8.06$ (t, $J = 1.5$ Hz, 1H), 7.95 (ddd, $J = 8.0, 1.8, 1.1$ Hz, 1H), 7.86 – 7.81 (m, 1H), 7.61 – 7.57 (m, 1H), 7.57 – 7.56 (m, 1H), 7.55 (dd, $J = 3.1$, 0.9 Hz, 2H), 7.33 (t, $J = 5.2$ Hz, 1H), 7.25 (t, $J = 7.8$ Hz, 1H), 7.22 – 7.17 (m, 1H), 7.12 (dd, $J = 4.5$, 2.2 Hz, 2H), 7.11 – 7.09 (m, 1H), 6.95 (ddd, $J = 8.1, 2.5, 1.1$ Hz, 1H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta 187.70, 166.01$ (d, $J = 252.5$ Hz), 158.43, 152.24, 143.56, 140.20, 139.60, 136.98 (d, $J = 3.0$ Hz), 136.78, 135.17, 131.18, 131.10, 131.03, 130.60, 125.67, 123.24, 122.08, 121.09, 120.30, 118.99, 117.15 (d, $J = 23.0$ Hz), 116.28; MS (ESI): 454.15 (M+H)$^+\); HPLC purity $\geq 96\% (R_s = 12.07 \text{ min}).

4-Bromo-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (21).
The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 4-bromobenzenesulfonyl chloride (130 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 49% (85 mg). $^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 7.81 – 7.78 (m, 2H), 7.77 – 7.74 (m, 2H), 7.71 (d, $J = 4.0$ Hz, 1H), 7.63 (t, $J = 1.8$ Hz, 1H), 7.54 (ddd, $J = 7.8$, 1.8, 1.0 Hz, 1H), 7.52 (d, $J = 4.0$ Hz, 1H), 7.38 (tt, $J = 4.5$, 2.8 Hz, 3H), 7.35 – 7.33 (m, 1H), 7.27 (ddd, $J = 8.1$, 2.1, 0.9 Hz, 1H), 7.14 (ddd, $J = 7.9$, 2.5, 1.2 Hz, 1H); $^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 187.70(C=O), 158.42(C-OH), 152.02(C), 143.68(C), 139.44(C), 136.77(CH), 135.21(C), 133.30(CH), 131.22(CH), 130.61(CH), 129.92(CH), 128.15(C), 125.70(CH), 123.34(CH), 122.10(CH), 121.10(CH), 120.31(CH), 119.04(CH), 116.28(CH); MS (ESI): 515.02 (M+H$^+$)$^+$; HPLC purity ≥ 97% (R$_t = 12.88$ min).

4-Bromo-2,5-difluoro-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (22).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 4-bromo-2,5-difluoro-benzenesulfonyl chloride (148 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 44% (82 mg). $^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 7.83 – 7.78 (m, 2H), 7.71 (d, $J = 4.0$ Hz, 1H), 7.69 (t, $J = 1.9$ Hz, 1H), 7.57 (ddd, $J = 7.7$, 1.8, 1.0 Hz, 1H), 7.54 (d, $J = 4.0$ Hz, 1H), 7.44 – 7.39 (m, 2H), 7.38 – 7.33 (m, 3H), 7.14 (ddd, $J = 7.9$, 2.5, 1.3 Hz, 1H); $^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 187.70, 158.44, 152.02, 150.65, 143.68, 140.18, 138.56, 136.77, 135.32, 131.35, 130.61, 125.79, 124.58, 123.72, 123.64, 123.42, 121.94, 121.10, 120.32, 118.97, 118.71, 118.48, 116.29; MS (ESI): 551.97 (M+H$^+$)$^+$; HPLC purity ≥ 97% (R$_t = 13.12$ min).

3,5-Dichloro-4-hydroxy-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (23).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (150 mg, 0.51 mmol) and 3,5-dichloro-4-hydroxybenzenesulfonfyl chloride (199 mg, 0.76 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.25:0.75); yield: 45% (120 mg). $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.69 (d, $J = 3.6$ Hz, 2H), 7.63 (d, $J = 4.0$ Hz, 1H), 7.46 (t, $J = 1.8$ Hz, 1H), 7.46 –
7.42 (m, 1H), 7.39 (d, J = 4.0 Hz, 1H), 7.35 (t, J = 5.3 Hz, 1H), 7.34 – 7.31 (m, 1H), 7.31 – 7.28 (m, 1H), 7.24 (dd, J = 2.2, 1.7 Hz, 1H), 7.13 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 7.06 (ddd, J = 8.0, 2.5, 1.1 Hz, 1H); 13C NMR (125 MHz, CD3OD) δ 189.74, 158.88, 154.96, 153.56, 143.55, 140.38, 139.66, 137.76, 135.63, 132.39, 131.34, 130.77, 128.75, 125.84, 123.80, 123.77, 122.72, 121.39, 120.74, 119.63, 116.54; MS (ESI): 520.13 (M+H)+; HPLC purity ≥ 96% (Rt = 11.44 min).

3-Methoxy-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (24).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxy-phenyl)methanone (2) (100 mg, 0.34 mmol) and 3-methoxybenzenesulfonyl chloride (105 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 38% (60 mg). 1H NMR (500 MHz, acetone-d6) δ 9.19 (br. s, 1H), 8.80 (br. s, 1H), 7.68 (d, J = 4.0 Hz, 1H), 7.64 (t, J = 1.8 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.45 – 7.41 (m, 2H), 7.40 – 7.38 (m, 1H), 7.38 – 7.33 (m, 4H), 7.29 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.16 – 7.14 (m, 1H), 7.14 – 7.11 (m, 1H), 3.79 (s, 3H); 13C NMR (125 MHz, acetone-d6) δ 187.78, 160.88, 158.43, 152.37, 143.50, 141.84, 140.19, 139.79, 136.85, 135.08, 131.21, 131.14, 130.63, 125.64, 123.07, 121.97, 121.15, 120.36, 120.07, 119.75, 118.81, 116.33, 113.03, 56.07; MS (ESI): 466.17 (M+H)+; HPLC purity ≥ 99% (Rt = 12.05 min).

N-(3-(3-(5-(3-Hydroxybenzoyl)thiophene-2-yl)phenyl)sulfamoyl)phenyl)acetamide (25).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (80 mg, 0.27 mmol) and 3-acetylaminobenzenesulfonyl chloride (95 mg, 0.41 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99: 1); yield: 70% (93 mg). 1H NMR (500 MHz, acetone-d6) δ 9.46 (br., 1H,NH), 9.10 (br. s, 1H), 8.75 (br. s, 1H), 7.78 (s, 4H), 7.70 (d, J = 4.0 Hz, 1H), 7.62 (t, J = 1.8 Hz, 1H), 7.50 (t, J = 5.8 Hz, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.34 – 7.32 (m, 1H), 7.27 (dd, J = 8.1, 1.2 Hz, 1H), 7.13 (ddd, J = 7.9, 2.5, 1.2 Hz, 1H), 2.08 (s, 3H); 13C NMR (125 MHz, acetone-d6) δ 189.92, 187.72, 158.44, 152.44, 144.54, 143.47, 140.21, 139.99, 136.80, 135.03, 134.32, 131.07, 130.60, 129.23, 128.56, 125.60, 122.83, 121.79, 121.08, 120.31, 119.48, 118.63, 116.30, 114.20, 22.10; MS (ESI): 493.41 (M+H)+; HPLC purity ≥ 97% (Rt = 10.70 min).

N-(3-(5-(3-Hydroxybenzoyl)thiophene-2-yl)phenyl)-2-methylbenzenesulfonamide (26).
The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxy-phenyl)methanone (2) (100 mg, 0.34 mmol) and 2-methylbenzenesulfonyl chloride (97 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 51% (80 mg). 1H NMR (500 MHz, CDCl3) δ 9.30 (br. s, 1H), 8.79 (br. s, 1H), 8.07 – 8.01 (m, 1H), 7.67 (d, J = 4.0 Hz, 1H), 7.58 (t, J = 1.8 Hz, 1H), 7.48 (s, 1H), 7.46 (d, J = 4.0 Hz, 1H), 7.43 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 7.37 (t, J = 7.7 Hz, 3H), 7.32 (ddd, J = 11.8, 2.5, 1.5 Hz, 3H), 7.22 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 7.11 (ddd, J = 7.9, 2.5, 1.2 Hz, 1H), 2.66 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 186.81, 157.54, 151.50, 142.58, 139.31, 138.99, 138.78, 137.30, 135.88, 134.16, 133.17, 132.71, 130.22, 129.95, 129.70, 126.26, 124.68, 121.52, 120.18, 119.79, 119.40, 116.57, 115.38, 19.42; MS (ESI): 450.08 (M+H)+; HPLC purity ≥ 99% (Rt = 12.32 min).

**N-(3-(5-(3-Hydroxybenzoyl)thiophene-2-yl)phenyl)-3-methylbenzenesulfonamide (27).**

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (100 mg, 0.34 mmol) and 3-methylbenzenesulfonyl chloride (97 mg, 0.51 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 64% (100 mg). 1H NMR (500 MHz, acetone-d6) δ 9.15 (br. s, 1H), 8.75 (br. s, 1H), 7.70 (dd, J = 4.5, 2.3 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.62 (t, J = 1.8 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.45 – 7.42 (m, 2H), 7.42 – 7.35 (m, 3H), 7.34 – 7.32 (m, 1H), 7.27 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.14 (ddd, J = 7.9, 2.5, 1.2 Hz, 1H), 2.37 (s, 3H); 13C NMR (125 MHz, acetone-d6) δ 187.69, 158.43, 152.39, 143.50, 140.70, 140.23, 139.87, 136.77, 135.06, 134.55, 131.08, 130.60, 129.90, 128.33, 125.59, 125.18, 122.88, 121.76, 121.09, 120.30, 118.60, 116.29, 21.24; MS (ESI): 450.11 (M+H)+; HPLC purity ≥ 98% (Rt = 13.06 min).

**2-Fluoro-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)-4-methoxybenzenesulfonamide (28).**

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-hydroxyphenyl)methanone (2) (200 mg, 0.68 mmol) and 2-fluoro-4-methoxybenzenesulfonyl chloride (228 mg, 1.02 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 99:1); yield: 58% (190 mg). 1H NMR (500 MHz, CD3OD) δ 7.61 (d, J = 4.0 Hz, 1H), 7.58 (ddd, J = 8.7, 2.2, 1.2 Hz, 1H), 7.52 (dd, J = 10.6, 2.2 Hz, 1H), 7.45 (t, J = 1.8 Hz, 1H), 7.41 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.38 (d, J = 4.0 Hz, 1H), 7.34 (t, J =
7.8 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.24 (dd, J = 2.2, 1.7 Hz, 1H), 7.14 (ddd, J = 8.2, 4.8, 3.8 Hz, 2H), 7.06 (ddd, J = 8.1, 2.5, 1.1 Hz, 1H), 3.86 (s, 3H); 13C NMR (125 MHz, CD3OD) δ 189.71, 158.89, 153.6, 153.50 (d, J = 95.3 Hz), 152.47 (d, J = 144.8 Hz), 143.50, 140.37, 139.92, 137.76, 135.51, 132.56 (d, J = 5.6 Hz), 131.25, 130.78, 125.92 (d, J = 3.7 Hz), 125.80, 123.50, 122.55, 121.37, 120.74, 119.39, 116.53, 116.03, 115.86, 114.31 (d, J = 1.6 Hz), 57.00; MS (ESI): 484.26 (M+H)+; HPLC purity ≥ 96% (Rt = 11.75 min).

2-Fluoro-4-hydroxy-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)benzenesulfonamide (29).

The title compound was prepared by reaction of 2-fluoro-N-(3-(5-(3-hydroxybenzoyl)thiophene-2-yl)phenyl)-4-methoxybenzenesulfonamide (22) (155 mg, 0.32 mmol) and boron tribromide (0.96 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 98.5:1.5); yield: 46% (70 mg). 1H NMR (500 MHz, CD3OD) δ 7.60 (d, J = 4.0 Hz, 1H), 7.51 (dd, J = 10.5, 2.2 Hz, 1H), 7.47 (ddd, J = 4.9, 3.1, 1.4 Hz, 2H), 7.39 (dd, J = 7.8, 1.7, 0.9 Hz, 1H), 7.36 (d, J = 4.0 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.23 (m, 1H), 7.13 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 7.06 (ddd, J = 8.0, 2.5, 1.1 Hz, 1H), 6.97 (t, J = 8.4 Hz, 1H); 13C NMR (125 MHz, CD3OD) δ 158.86, 153.72, 152.13 (d, J = 240.4 Hz), 151.11 (d, J = 7.2 Hz), 143.45, 140.37, 139.99, 137.82, 135.48, 131.32 (d, J = 5.4 Hz), 125.87, 125.84, 125.78, 123.48, 122.55, 121.42, 120.76, 119.43, 118.88, 118.85, 116.64, 116.55, 116.47; MS (ESI): 470.43 (M+H)+; HPLC purity ≥ 95% (Rt = 10.57 min).

(5-(3-Aminophenyl)thiophene-2-yl)(3-ethoxy-2,6-difluorophenyl)methanone (30a).

The title compound was prepared by reaction of (5-bromothiophene-2-yl)(3-ethoxy-2,6-difluorophenyl)methanone (II) (450 mg, 1.30 mmol) and 3-aminophenylboronic acid (213 mg, 1.55 mmol), cesium carbonate (1689 mg, 5.18 mmol) and tetrakis(triphenylphosphine) palladium (20 mg, 16 µmol) according to method B. The product was used directly in the subsequent reaction without any characterization; yield: 88% (410 mg).

(5-(3-Aminophenyl)thiophene-2-yl)(2,6-difluoro-3-hydroxyphenyl)methanone (30).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-ethoxy-2,6-difluorophenyl)methanone (30a) (440 mg, 1.22 mmol) and boron tribromide (3.7 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 50% (200 mg). 1H NMR (500 MHz, acetone-d6) δ 9.02 (br. s, 1H), 7.45 (dd,
$J = 7.1, 2.9$ Hz, 1H), 7.33 (d, $J = 4.1$ Hz, 1H), 7.10 (dd, $J = 41.1, 6.5$ Hz, 2H), 7.00 – 6.85 (m, 3H), 6.62 (ddd, $J = 8.0$, 2.1, 0.8 Hz, 1H), 4.75 (br., 2H, NH$_2$); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 179.48, 155.98, 152.23 (dd, $J = 241.6, 6.1$ Hz), 149.34, 148.66 (dd, $J = 249.5, 7.7$ Hz), 143.90 (dd, $J = 10.7, 3.2$ Hz), 137.34, 133.47, 129.97, 125.13, 124.46, 121.00, 116.62 (dd, $J = 9.3, 3.0$ Hz), 115.73, 114.65, 111.62, 111.13 (dd, $J = 22.7, 4.1$ Hz); MS (ESI): 332.12 (M+H)$^+$; HPLC purity $\geq 99\%$ (R$_t = 8.48$ min).

4-Bromo-N-(3-(5-(3-ethoxy-2,6-difluorobenzoyl)thiophene-2-yl)phenyl)-2 trifluoromethoxybenzenesulfonamide (31a).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(3-ethoxy-2,6-difluorophenyl)methanone (30a) (210 mg, 0.58 mmol) and 4-bromo-2-trifluoromethoxybenzenesulfonyl chloride (198 mg, 0.58 mmol) according to Method C. The product was sufficiently pure for use in the subsequent reaction; yield: 65% (250 mg). The product was used in the next step without any characterization.

4-Bromo-N-(3-(5-(2,6-difluoro-3-hydroxybenzoyl)thiophene-2-yl)-phenyl)-2 trifluoromethoxybenzenesulfonamide (31).

The title compound was prepared by reaction of 4-bromo-N-(3-(5-(3-ethoxy-2,6-difluorobenzoyl-thiophene-2-yl)phenyl)-2-trifluoromethoxybenzene-sulfonamide (31a) (250 mg, 0.38 mmol) and boron tribromide (2.3 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 75% (180 mg). $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 9.35 (br. s, 1H), 8.58 (br. s, 1H), 8.03 (d, $J = 8.5$ Hz, 1H), 7.76 (dd, $J = 8.5, 1.8$ Hz, 1H), 7.74-7.72 (m, 1H), 7.68 – 7.65 (m, 1H), 7.62 (dt, $J = 4.1, 0.9$ Hz, 1H), 7.54 (ddd, $J = 7.7, 1.8, 1.0$ Hz, 1H), 7.52 (d, $J = 4.1$ Hz, 1H), 7.42 – 7.37 (m, 1H), 7.32 (ddd, $J = 8.1, 2.2, 1.0$ Hz, 1H), 7.23-7.21 (m, 1H), 7.03 (ddd, $J = 9.1, 8.6, 1.9$ Hz, 1H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 180.68, 154.32, 152.55 (dd, $J = 240.6, 5.8$ Hz), 148.43 (dd, $J = 245.8, 7.7$ Hz), 146.95 (d, $J = 1.8$ Hz), 143.55, 142.66 (ddd, $J = 13.0, 3.2$ Hz), 138.85, 138.17, 134.88, 133.83, 131.81, 131.47, 131.34, 129.12, 126.34, 124.92 (d, $J = 1.9$ Hz), 123.59, 122.15, 120.39 (dd, $J = 9.1, 3.8$ Hz), 120.08, 118.80, 118.01 (dd, $J = 24.0, 19.7$ Hz), 112.44 (dd, $J = 22.8, 3.9$ Hz); MS (ESI): 635.43 (M+H)$^+$; HPLC purity $\geq 99\%$ (R$_t = 13.11$ min).

N-(3-(5-(3-Ethoxy-2,6-difluorobenzoyl)thiophene-2-yl)phenyl)-2 trifluoromethoxybenzenesulfonamide (32a).
The title compound was prepared by reaction of (5-(3-aminophenyl)-thiophene-2-yl)(3-ethoxy-2,6-difluorophenyl)methanone (30a) (210 mg, 0.58 mmol) and 2-trifluoromethoxybenzenesulfonyl chloride (152 mg, 0.58 mmol) according to Method C. The product was sufficiently pure for use in the subsequent reaction; yield: 66% (225 mg). The product was used in the next step without any characterization.

\[ N-(3-(5-(2,6-Difluoro-3-hydroxybenzoyl)thiophene-2-yl)phenyl)-2-trifluoromethoxybenzenesulfonamide (32). \]

The title compound was prepared by reaction of \( N-(3-(5-(3-ethoxy-2,6-difluorobenzoyl)thiophene-2-yl)phenyl)-2-trifluoromethoxybenzenesulfonamide (32a) \) (225 mg, 0.39 mmol) and boron tribromide (2.3 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 44% (142 mg). \( ^1\text{H NMR (500 MHz, acetone-d}_6\text{)} \delta 9.50 (\text{br. s, 1H}), 9.04 (\text{br. s, 1H}), 8.14 – 8.09 (\text{m, 1H}), 7.77 (\text{ddd, } J = 8.4, 7.5, 1.7 \text{ Hz, 1H}), 7.68 – 7.65 (\text{m, 1H}), 7.62 (\text{dt, } J = 4.0, 0.8 \text{ Hz, 1H}), 7.57 – 7.51 (\text{m, 3H}), 7.51 – 7.50 (\text{m, 1H}), 7.38 (\text{tt, } J = 4.6, 2.3 \text{ Hz, 1H}), 7.34 – 7.30 (\text{m, 1H}), 7.25 – 7.17 (\text{m, 1H}), 7.03 (\text{ddd, } J = 10.5, 6.9, 1.9 \text{ Hz, 1H}); ^{13}\text{C NMR (125 MHz, acetone-d}_6\text{)} \delta 180.69, 154.44, 152.55 (\text{dd, } J = 240.6, 5.8 \text{ Hz}), 148.43 (\text{dd, } J = 245.9, 7.8 \text{ Hz}), 146.82 (\text{d, } J = 1.7 \text{ Hz}), 143.48, 142.66 (\text{dd, } J = 12.9, 3.2 \text{ Hz}), 139.17, 138.18, 136.37, 134.77, 132.58, 132.25, 131.25, 128.02, 126.26, 123.28, 124.49 – 120.18 (\text{m}), 121.95, 121.53 (\text{d, } J = 1.8 \text{ Hz}), 120.39 (\text{dd, } J = 9.1, 3.8 \text{ Hz}), 118.50, 118.02 (\text{dd, } J = 23.9, 19.7 \text{ Hz}), 112.45 (\text{dd, } J = 22.8, 3.9 \text{ Hz}); \text{MS (ESI): 556.17 (M+H)}^+; \text{HPLC purity } \geq 99\% (R_t = 12.38 \text{ min}). \]

\[ N-(3-(5-(3-Ethoxy-2,6-difluorobenzoyl)thiophene-2-yl)phenyl)-2-trifluoromethylbenzenesulfonamide (33a). \]

The title compound was prepared by reaction of (5-(3-aminophenyl)-thiophene-2-yl)(3-ethoxy-2,6-difluorophenyl)methanone (30a) (210 mg, 0.58 mmol) and 2-trifluoromethylbenzenesulfonyl chloride (143 mg, 0.58 mmol) according to Method C. The product was sufficiently pure for use in the subsequent reaction; yield: 68% (225 mg). The product was used in the next step without any characterization.

\[ N-(3-(5-(2,6-Difluoro-3-hydroxybenzoyl)thiophene-2-yl)phenyl)-2-trifluoromethylbenzenesulfonamide (33). \]
The title compound was prepared by reaction of N-(3-(5-(3-ethoxy-2,6-difluorobenzoyl)thiophene-2-yl)phenyl)-2-trifluoromethylbenzenesulfonamide (33a) (230 mg, 0.41 mmol) and boron tribromide (2.4 mmol) according to Method A. The product was purified by CC (dichloromethane/methanol 99.5:0.5); yield: 48% (165 mg). \( ^1 \)H NMR (500 MHz, acetone-d\(_6\)) \( \delta \) 9.39 (br. s, 1H), 9.00 (br. s, 1H), 8.30 – 8.25 (m, 1H), 8.03 – 7.98 (m, 1H), 7.87 – 7.82 (m, 2H), 7.68 – 7.65 (m, 1H), 7.62 (dt, \( J = 4.1, 0.9 \) Hz, 1H), 7.55 – 7.51 (m, 2H), 7.42 – 7.37 (m, 1H), 7.32 (dd, \( J = 8.1, 2.2, 1.0 \) Hz, 1H), 7.23-7.21 (m, 1H), 7.06 – 7.00 (m, 1H); \( ^{13} \)C NMR (125 MHz, acetone-d\(_6\)) \( \delta \) 180.69, 152.54 (dd, \( J = 240.6, 5.8 \) Hz), 148.42 (dd, \( J = 245.8, 7.8 \) Hz), 143.51, 142.66 (dd, \( J = 12.9, 3.2 \) Hz), 139.14, 139.11, 138.17, 134.83, 134.47, 133.86, 132.78, 131.32, 129.56 (q, \( J = 6.4 \) Hz), 128.41, 128.15, 126.32, 125.06, 123.37, 122.88, 122.14, 120.39 (dd, \( J = 9.1, 3.8 \) Hz), 118.73, 118.02 (dd, \( J = 24.0, 19.6 \) Hz); MS (ESI): 540.32 (M+H\(^+\))\(^+\); HPLC purity \( \geq \) 99% (R\(_t\) = 12.18 min).

Pyridine-3-sulfonic acid (3-(5-(2,6-difluoro-3-hydroxy-benzoyl)-thiophene-2-yl)-phenyl)-amide (34).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(2,6-difluoro-3-hydroxyphenyl)methanone (30) (100 mg, 0.30 mmol) and pyridine-3-sulfonyl chloride hydrochloride (96 mg, 0.45 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 95:5); yield: 35% (50 mg). \( ^1 \)H NMR (500 MHz, acetone-d\(_6\)) \( \delta \) 8.28 (dd, \( J = 2.4, 0.8 \) Hz, 1H), 8.10 (dd, \( J = 4.7, 1.6 \) Hz, 1H), 7.52-7.49 (m, 1H), 6.96-6.94 (m, 1H), 6.94-6.91 (m, 1H), 6.88 (d, \( J = 4.1 \) Hz, 1H), 6.83 (d, \( J = 7.6 \) Hz, 1H), 6.82-6.80 (m, 1H), 6.71 (t, \( J = 7.9 \) Hz, 1H), 6.55-6.47 (m, 2H), 6.41 (td, \( J = 9.0, 1.6 \) Hz, 1H); \( ^{13} \)C NMR (125 MHz, acetone-d\(_6\)) \( \delta \) 180.8, 154.6, 154.4, 148.7, 143.6, 139.3, 138.3, 137.0, 135.9, 135.0, 131.5, 126.5, 125.1, 123.8, 122.8, 120.4, 119.4, 112.6, 112.4; MS (ESI): 473.28 (M+H\(^+\))\(^+\); HPLC purity \( \geq \) 95% (R\(_t\) = 10.75 min).

1-Methyl-1H-imidazole-4-sulfonic acid (3-(5-(2,6-difluoro-3-hydroxy-benzoyl)-thiophene-2-yl)-phenyl)-amide (35).

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(2,6-difluoro-3-hydroxyphenyl)methanone (30) (100 mg, 0.30 mmol) and 1-methyl-1H-imidazole-4-sulfonyl chloride (81 mg, 0.45 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 95:5); yield: 72% (103 mg). \( ^1 \)H NMR (500 MHz, acetone-d\(_6\)) \( \delta \) 9.17 (s, 1H), 9.01 (s, 1H), 7.75-7.72 (m, 2H), 7.64-7.61 (m, 2H), 7.54 (d, \( J = 4.1 \)
Hz, 1H), 7.50-7.43 (m, 2H), 7.21 (td, J = 9.4, 5.5 Hz, 1H), 7.04 (td, J = 8.8, 1.9Hz, 1H), 3.76 (s, 3H); 13C NMR (125 MHz, acetone-d₆) δ 180.7, 155.1, 153.6, 151.6, 149.5, 147.5, 143.3, 142.7, 140.7, 140.1, 138.3, 134.5, 130.9, 126.2, 122.5, 121.9, 120.4, 118.4, 112.6, 112.4, 34.2; MS (ESI): 476.21 (M+H)+ +; HPLC purity ≥ 98% (R_t = 12.54 min).

**Cyclopropanesulfonic acid (3-(5-(2,6-difluoro-3-hydroxy-benzoyl)-thiophene-2-yl)-phenyl)-amide (36).**

The title compound was prepared by reaction of (5-(3-aminophenyl)thiophene-2-yl)(2,6-difluoro-3-hydroxyphenyl)methanone (30) (100 mg, 0.30 mmol) and cyclopropanesulfonyl chloride (1M in DCM) (63 mg, 0.45 mmol) according to Method C. The product was purified by CC (dichloromethane/methanol 95:5); yield: 56% (73 mg). 1H NMR (500 MHz, acetone-d₆) δ 9.01 (s, 1H), 8.77 (s, 1H), 7.80-7.78 (m, 1H), 7.65 (dt, J = 4.1, 0.9 Hz, 1H), 7.61-7.58 (m, 2H), 7.54-7.44 (m, 2H), 7.21 (td, J = 9.5, 5.4 Hz, 1H), 7.04 (td, J = 9.0, 1.9 Hz, 1H), 2.73-2.67 (m, 1H), 1.07-0.96 (m, 4H); 13C NMR (125 MHz, acetone-d₆) δ 188.7, 154.8, 143.5, 140.6, 138.3 134.9, 131.3, 126.3, 123.1, 122.6, 120.4, 119.2, 112.6, 112.4, 32.4, 5.8; MS (ESI): 436.25 (M+H)+ +; HPLC purity ≥ 97% (R_t = 11.33 min).

**Cyclopropanesulfonic acid (3-bromo-5-methyl-phenyl)-amide (37b).**

The title compound was prepared by reaction of 3-bromo-5-methylaniline (1000 mg, 5.38 mmol, 1 equiv) and cyclopropanesulfonyl chloride (1013 mg, 8.07 mmol, 1.5 equiv) according to Method C. The product was purified by CC (hexane/ethyl acetate 8:2); yield: 77% (1200 mg). 1H NMR (500 MHz, acetone-d₆) δ 8.62 (br. s, 1H), 7.35 (s, 1H), 7.15 (s, 1H), 7.13 (s, 1H), 2.65-2.61 (m, 1H), 2.30 (s, 3H), 1.00-0.95 (m, 4H).

**Cyclopropanesulfonic acid (3-(5-(2,6-difluoro-3-hydroxy-benzoyl)-thiophene-2-yl)-5-methyl-phenyl)-amide (37).**

cyclopropanesulfonic acid (3-methyl-5-(4,4,5,5-tetramethyl-(1,3,2)-dioxaborolan-2-yl)-phenyl)-amide (37a) (150 mg, 0.45mmol, 1.20equiv), (5-bromo-2-thienyl)(2,4-difluoro-3-hydroxyphenyl)-methanone IV (118 mg, 0.37mmol, 1.00equiv), ceasium carbonate (263 mg, 1.11mmol, 3.00equiv) and Pd(PPh₃)₄ (0.002mmol, 0.005equiv) were suspended in a degased mixture of 5mL DME and 5mL water. The mixture was heated to reflux for 3 days under N₂ atmosphere. The mixture was cooled down to room temperature, quenched with water (50
mL), filtered over celite, extracted three times with ethyl acetate (3x50 mL), washed one time with water (50 mL), one time with brine (50 mL), dried over sodium sulphate, filtered and evaporated under reduced pressure. The product was purified by MPLC (0% ethyl acetate to 100% ethyl acetate) followed by preparative TLC (hexane/ethyl acetate 5:5); yield: 18% (30 mg). $^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 8.98 (s, 1H), 8.68 (s, 1H), 7.61 (d, $J = 4.0$ Hz, 1H), 7.57 (s, 1H), 7.55 (d, $J = 4.0$ Hz, 1H), 7.41 (s, 1H), 7.26 (s, 1H), 7.21-7.15 (m, 1H), 7.01 (td, $J = 8.8, 1.8$ Hz, 1H), 2.70-2.65 (m, 1H), 2.38 (s, 3H), 1.02-0.96 (m, 4H); $^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 180.6, 155.0, 143.2, 141.3, 140.4, 138.1, 134.6, 126.1, 123.7, 123.1, 120.3, 116.4, 112.3, 29.7, 21.4, 5.7; MS (ESI): 449.76 (M+H)$^+$; HPLC purity $\geq 95\%$ ($R_t = 11.59$ min).

Cyclopropanesulfonic acid (3-(5-(2,6-difluoro-3-hydroxy-benzoyl)-thiophene-2-yl)-5-methyl-phenyl)-methyl-amide (38).

Cyclopropanesulfonic acid (3-bromo-5-methyl-phenyl)-methyl-amide (38b) (300 mg, 0.86mmol, 1.00equiv), (5-bromo-2-thienyl)(2,4-difluoro-3-hydroxyphenyl)-methanone IV (273 mg, 0.86mmol, 1.00equiv), cesium carbonate (1113 mg, 3.42mmol, 4.00equiv) and Pd(PPh$_3$)$_4$ (0.004mmol, 0.005equiv) were suspended in a degased mixture of 5mL DME and 5mL water. The mixture was heated to reflux for 3 days under N$_2$ atmosphere. The mixture was cooled down to room temperature, quenched with water (50 mL), filtered over celite, extracted three times with ethyl acetate (3x50 mL), washed one time with water (50 mL), one time with brine (50 mL), dried over sodium sulphate, filtered and evaporated under reduced pressure. The product was purified by CC (hexane/ethylacetate 8:2 to 5:5) followed by preparative TLC (dichloromethane/methanol 99:1); yield: 6% (25 mg). $^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 9.04 (s, 1H), 7.71 (s, 1H), 7.65-7.63 (m, 2H), 7.58 (s, 1H), 7.30 (s, 1H), 7.23-7.18 (m, 1H), 7.04 (dt, $J = 9.0, 1.9$ Hz, 1H), 3.41 (s, 3H), 2.68-2.65 (m, 1H), 2.43 (s, 3H), 1.01-0.90 (m, 4H); $^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 180.7, 154.7, 144.2, 140.9, 138.1, 134.4, 129.3, 126.4, 122.5, 112.4, 38.7, 21.2, 4.9; MS (ESI): 463.87 (M+H)$^+$; HPLC purity $\geq 95\%$ ($R_t = 13.75$ min).
11. Representative $^1$HNMR, $^{13}$CNMR and DEPT spectra

- **Compound 1**

![Compound 1 NMR Spectrum](image1)

- **Compound 2**

![Compound 2 NMR Spectrum](image2)
Compound 7

Molecular Weight = 435.52
Molecular Formula = C23H17N04S2

Molecular Weight = 598.42
Molecular Formula = C24H15S2F3N05S2
**Compound 11**
Compound 14 (DEPT)
➢ Compound 17 (DEPT)
- Compound 21 (DEPT)
Compound 28
Compound 31
➢ **Compound 32**

![NMR spectrum](image)

**Molecular Weight:** 555.50

**Molecular Formula:** C24H14F5NO5S2

![NMR spectrum](image)
12. Representative HPLC/MS Chromatograms

Compound 7
Compound 32