Supporting Information

Structure-Activity Study of Dihydrocinnamic Acids and Discovery of the Potent FFA1 (GPR40) Agonist TUG-469

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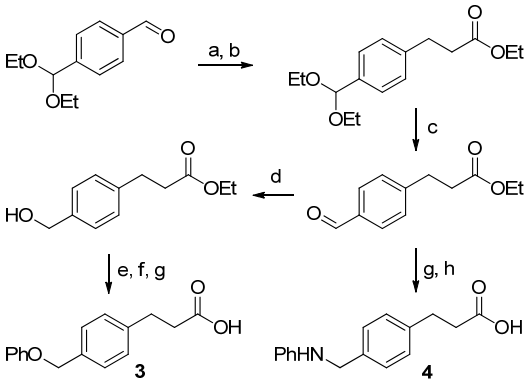
Contents

Synthesis of compounds with inverted linkers

Compounds **3** and **4**, corresponding to **1** and **2** with inverted central linkers, were synthesized as outlined in Scheme S1. Reacting the benzaldehyde in a Wittig reaction followed by nickel boride catalyzed reduction and acetal hydrolysis furnish the central aldehyde intermediate, which is transformed to compound **3** by reduction, mesylation, substitution by phenoxide and hydrolysis, and to **4** by ester hydrolysis and reductive amination with aniline. Experimental procedures are given below.

Scheme S1. [a]



[a] Reagents and conditions: (a) Ethyl 3-bromopropanoate, PPh_3, $NaHCO_3$ (aq), 2 h; (b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, EtOH, 2 h; c) 0.5M HCl, 10 min; (d) $NaBH_4$, EtOH, 2 h; (e) Et_3N, MsCl, THF, 0°C, 1 h; (f) K_2CO_3, phenol, acetone, 1 d; (g) LiOH, THF, H_2O; (h) aniline, $NaBH(OAc)_3$, CH_2Cl_2, 1 h.

Synthetic procedures and compound characterization

General

All commercial available starting materials and solvents were used without further purification, unless otherwise stated. THF was freshly distilled from sodium/benzophenone. DMF and DIPEA were dried over 4Å sieves. Purification by flash chromatography was carried out using silica gel 60 (0.040-0.063 mm, Merck). ^{1}H and ^{13}C NMR spectra were calibrated relative to TMS internal standard or residual solvent peak. Purity was determined by HPLC and/or NMR. HPLC analysis was performed using a Dionex 120 C18 column (5µ, 4.6×150 mm); flow: 1 mL/min; 10% acetonitrile in water (0-1 min), 10-100% acetonitrile in water (1-10 min), 100% acetonitrile (11-15 min), with both solvents containing 0.05 % TFA as modifier; UV detection at 254 nm. High-resolution mass spectra (HRMS) were obtained on a Thermo Finnigan TSQ 700 using electrospray ionization (ESI), Bruker micrOTOF-Q II (ESI) or an IonSpec 4.7 T Ultima FTMS using DHB matrix (MALDI). Electron ionization mass spectra were obtained on a Thermo Finnigan SSQ 710 (EI).

Arabic compound numbers in the Supporting Information are identical to compound numbers in the paper. Intermediates not mentioned in the paper are referred to consecutively with capital letters.

General procedure I for ether synthesis

The phenol (1 equiv) in acetone (~10 mL/g phenol) was added the benzyl halide (1 equiv) and K_2CO_3 (2 equiv) and stirred at room temperature until consumption of the starting materials as indicated by TLC. The reaction was added H_2O and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum.

General procedure II for ester hydrolysis

The ester (1 equiv) dissolved in 1,4-dioxane or THF (~5 mL/mmol ester) was added $LiOH{\cdot}H_2O$ (2-3 equiv) in H_2O (~2 mL/mmol ester). The reaction was stirred at room temperature until complete consumption of the starting material as indicated by TLC, typically after 1-12 hours. The reaction was added water, acidified with 3% HCl until pH <1 and extracted with EtOAc (3x). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum.

General procedure III for reductive amination

Arylamine (1 equiv) in CH_2Cl_2 (10 mL/mmol arylamine) in a dry flask under inert atmosphere was added the benzaldehyde (1 equiv) and $NaBH(OAc)_3$ (2 equiv). The reaction was stirred at room temperature until consumption of the starting material as indicated by TLC. The reaction mixture was added water and extracted with EtOAc (3x). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography and/or recrystallized.

General procedure IV for Suzuki coupling[1]

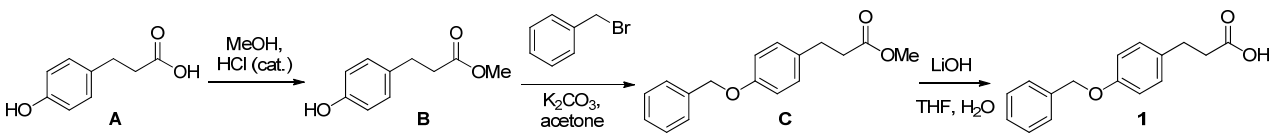
The aryl halide (1 equiv), arylboronic acid (1.5 equiv), $Pd(OAc)_2$ (0.02 equiv) and K_2CO_3 (1 equiv) in PEG-400 (4 mL/mmol) was stirred under open air at 45 ^oC until consumption of the starting material as indicated by TLC. The reaction was cooled to room temperature, added water and extracted with EtOAc (3x). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum before purification by flash chromatography.

General procedure V for aldehyde reduction

A solution of the aldehyde in anhydrous EtOH was added $NaBH_4$ (0.5 equiv) and stirred at room temperature until consumption of the starting material as indicated by TLC. The solvent was evaporated and the residual reaction mixture was dissolved in EtOAc. The solution was washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum to give the product, which was used directly in the next step without further purification.

General procedure VI for bromination

A solution of the alcohol (1 equiv) in THF under argon was added PBr_3 (2 equiv) and stirred at room temperature until consumption of starting material as indicated by TLC. The reaction mixture was added EtOAc, washed with saturated $NaHCO_3$ (3x), dried over $MgSO_4$ and concentrated before purification by flash chromatography.

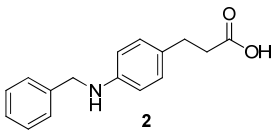


3-(4-(Benzyloxy)phenyl)propanoic acid (1). Acetyl chloride (20 mL, 0.28 mol) was added drop-wise to MeOH (150 mL) at 0 ^oC under inert atmosphere and 3-(4-hydroxyphenyl)propanoic acid (**A**, 15.1 g, 0.09 mol) was added subsequently in small portions. The mixture was refluxed for 1½ h,

cooled to room temperature and concentrated under vacuum. The residual oil was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated under vacuum to give 15.9 g (97%) of **B** as a clear oil which was used directly in the next step: R_f = 0.72 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.03 (d, *J* = 8.1 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.71-5.58 (m, 1H), 3.67 (s, 3H), 2.87 (t, *J* = 7.7 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.9, 154.2, 132.3, 129.3, 115.3, 51.7, 36.0, 30.0; EI-MS *m*/*z* 180 (M^+).

Methyl 3-(4-(benzyloxy)phenyl)propanoate (**C**) was prepared from benzyl bromide (66 µL, 0.56 mmol) and methyl 3-(4-hydroxyphenyl)propanoate (**B**, 100 mg, 0.56 mmol) according to the general procedure I to give 127 mg (85%) of a clear oil: R_f = 0.30 (EtOAc:petroleum ether, 1:5); ^{1}H NMR (DMSO-d_6) δ 7.46-7.37 (m, 5H), 7.13 (dt, *J* = 9.0 Hz, 1.8 Hz, 2H), 6.91 (dt, *J* = 8.7 Hz, 1.8 Hz, 2H), 5.06 (s, 2H), 3.57 (s, 3H), 2.77 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H) 2.59 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 172.3, 156.2, 136.7, 132.1, 128.7, 127.9, 127.2, 127.1, 114.1, 68.6, 50.7, 34.7, 28.9; EI-MS *m*/*z* 270 (M^+).

The title compound **1** was prepared from methyl 3-(4-(benzyloxy)phenyl)propanoate (**C**, 100 mg, 0.37 mmol) according to the general procedure II to give 61 mg (64%) of a white and crystalline product (purity >99% by HPLC): R_f = 0.16 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:1); ^{1}H NMR (DMSO-d_6) δ 7.48-7.30 (m, 5H), 7.18-7.12 (m, 2H), 6.98-6.95 (m, 2H), 5.09 (s, 2H), 2.75 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H), 2.49 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 173.8, 156.6, 137.2, 133.0, 129.2, 128.4, 127.7, 127.6, 114.6, 69.1, 35.5, 29.5; EI-MS *m*/*z* 256 (M^+).



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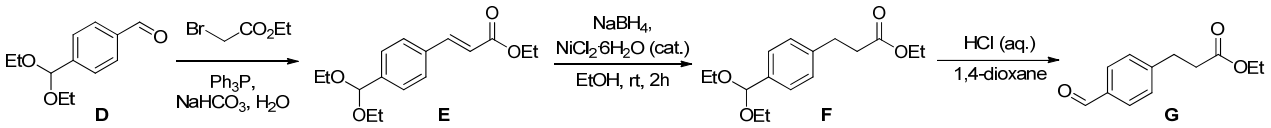
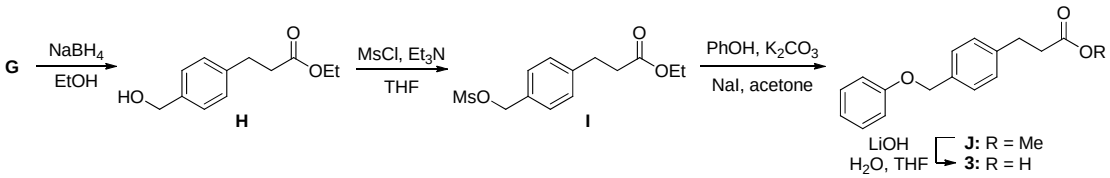
3-(4-(Benzylamino)phenyl)propanoic acid (2). The title compound was prepared from 3-(4-aminophenyl)propanoic acid (100 mg, 0.61 mmol) and benzaldehyde (0.060 mL, 0.61 mmol) according to the general procedure III to give 82 mg (53%) of a white solid after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:8) (>95% pure by NMR): R_f = 0.23 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 2H), 7.42–7.23 (m, 5H), 7.09–6.93 (m, 2H), 6.65–6.50 (m, 2H), 4.29 (s, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 179.2, 146.6, 139.5, 129.2, 129.1, 128.6, 127.5, 127.2, 113.1, 48.5, 36.0, 29.8; ESI-MS *m*/*z* 256.1 ($M+H^+$).



Ethyl 3-(4-formylphenyl)propanoate (G). 4-(Diethoxymethyl)benzaldehyde (**D**, 1.94 g, 9.3 mmol) and ethyl 2-bromoacetate (2.44 g, 14.6 mmol) in saturated aqueous $NaHCO_3$ (20 mL) was added PPh_3 (3.44 g, 13.1 mmol) and stirred for 2 hours. The reaction mixture was added chloroform washed with water and brine, dried over $MgSO_4$, concentrated before purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:10→1:1) to give 2.20 g (85%) of **E** as a clear oil: R_f = 0.61 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.54-7.47 (m, 4H), 6.44 (d, *J* = 16.0 Hz, 1H), 5.51 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.66-3.50 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 167.0, 144.2, 141.3, 134.4, 127.9, 127.2, 118.4, 101.0, 61.1, 60.5.

Ethyl 3-(4-(diethoxymethyl)phenyl)acrylate (**E**, 281 mg, 1.01 mmol) in ethanol and under argon atmosphere was added $NiCl_2·6H_2O$ (27 mg, 0.11 mmol) and $NaBH_4$ (42 mg, 1.11 mmol). The reaction was stirred overnight. The reaction mixture was quenched with water and extracted with EtOAc (x3), washed with brine, dried over $MgSO_4$, concentrated and dried under vacuum to give 257 mg (91%) of **F** as a clear oil: R_f = 0.61 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.47 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.65-3.48 (m, 4H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.8, 140.6, 137.1, 128.1, 126.8, 101.5, 61.0, 60.4, 35.9, 30.7, 15.2, 14.2.

Ethyl 3-(4-(diethoxymethyl)phenyl)propanoate (**F**, 250 mg, 0.96 mmol) in 1,4-dioxane (4 mL) was added 0.5 M HCl (2 mL) and stirred for ten minutes. The reaction mixture was added water and extracted with EtOAc (x3), washed with brine, dried over $MgSO_4$, and concentrated before purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:3) to provide 138 mg (80%) of **G** as a clear oil: R_f = 0.38 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.66 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 191.9, 172.3, 147.9, 134.8, 130.0, 129.0, 60.6, 35.2, 31.0, 14.1.

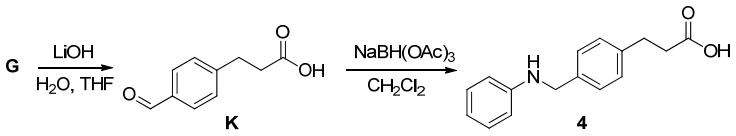


3-(4-(Phenoxymethyl)phenyl)propanoic acid (3). Ethyl 3-(4-(hydroxymethyl)phenyl)propanoate (**H**) was prepared from ethyl 3-(4-formylphenyl)propanoate (**G**, 178 mg, 0.86 mmol) according to the general procedure V to give 163 mg (91%) of a clear oil: R_f = 0.32 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.64 (s, 2H), 4.12 (q, *J* = 6.8 Hz, 2H), 2.94 (d, *J* = 7.8 Hz, 2H), 2.61 (d, *J* = 7.8 Hz, 2H), 1.76 (s, 1H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 140.1, 138.9, 128.5, 127.2, 65.1, 60.4, 35.9, 30.6, 14.2.

Ethyl 3-(4-(hydroxymethyl)phenyl)propanoate (**H**, 174 mg, 0.83 mmol) in THF (8 mL) was added Et_3N (0.18 mL, 1.30 mmol) and methanesulfonyl chloride (0.21 mL, 0.87 mmol) at 0ºC. The reaction was stirred for one hour. The reaction mixture was added water and extracted with EtOAc (x3), washed with brine, dried over $MgSO_4$, concentrated and dried under vacuum to give 234 mg (98%) of **I** as a clear oil: R_f = 0.45 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 5.21 (s, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.97 (t, *J* = 7.6 Hz, 2H), 2.90 (s, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.6, 142.1, 131.3, 129.2, 128.9, 71.4, 60.5, 38.3, 35.6, 30.6, 14.2.

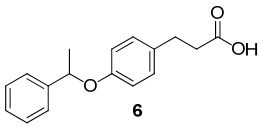
Ethyl 3-(4-(phenoxymethyl)phenyl)propanoate (**J**) was prepared from ethyl 3-(4-(methylsulfonyl-oxymethyl)phenyl)propanoate (**I**, 124 mg, 0.43 mmol and phenol (41 mg, 0.43 mmol) according to the general procedure I with addition of NaI (65 mg, 0.43 mmol) to give 117 mg (95%) of a yellow oil: R_f = 0.73 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.41–7.17 (m, 7H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.02–6.85 (m, 3H), 5.02 (s, 2H), 4.44 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 158.8, 140.4, 135.0, 129.5, 128.6, 127.8, 120.9, 114.9, 69.8, 60.5, 35.9, 30.7, 14.2, 5.7.

The title compound was prepared from ethyl 3-(4-(phenoxymethyl)phenyl)propanoate (**J**, 103 mg, 0.36 mmol) according to the general procedure II. The product was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:1) to produce 64 mg (69%) of **3** as a white solid (purity >95% by NMR): R_f = 0.27 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (acetone-d_6) δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.19–7.05 (m, 4H), 6.93–6.74 (m, 3H), 4.94 (s, 2H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 174.0, 159.9, 141.7, 136.2, 130.3, 129.8, 129.6, 129.3, 128.6, 121.5, 115.7, 70.2, 35.9, 31.3; ESI-MS *m*/*z* 279.1 ($M+Na^+$).



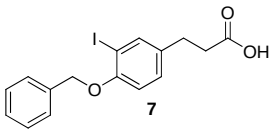
3-(4-(Phenylaminomethyl)phenyl)propanoic acid (4). 3-(4-Formylphenyl)propanoic acid (**K**) was prepared from ethyl 3-(4-(diethoxymethyl)phenyl)propanoate (**G**, 118 mg, 0.61 mmol) according to the general procedure II to give 101 mg (100%) of a white solid: R_f = 0.15 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (DMSO-d_6) δ 12.19 (s, 1H), 9.97 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.60 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 192.7, 173.6, 148.4, 134.5, 129.6, 129.1, 34.6, 30.5.

The title compound was prepared from 3-(4-formylphenyl)propanoic acid (**K**, 51 mg, 0.31 mmol) and aniline (24 mg, 0.31 mmol) according to the general procedure III. The product was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:1) to produce 36 mg (49%) of **4** as a white solid (purity 97% by HPLC): R_f = 0.48 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.29 (d, *J* = 7.6 Hz, 2H), 7.24-6.85 (m, 4H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 4.29 (s, 2H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.67 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.9, 148.1, 139.1, 137.5, 129.2, 128.5, 127.8, 117.6, 112.9, 48.0, 35.5, 30.2; ESI-MS *m*/*z* 278.1 ($M+Na^+$).



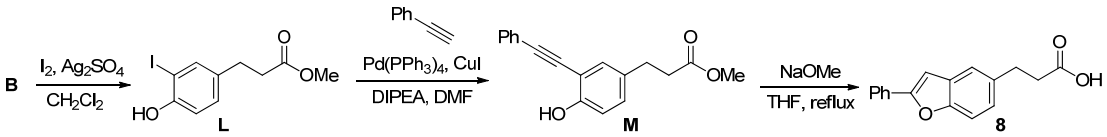
3-(4-(1-Phenylethoxy)phenyl)propanoic acid (6). Methyl 3-(4-(1-phenylethoxy)phenyl)-propanoate was prepared from (1-bromoethyl)benzene (262 mg, 1.42 mmol) and methyl 3-(4-hydroxyphenyl)propanoate (265 mg, 1.47 mmol) according to the general procedure I to give 42 mg (10%): R_f = 0.25 (EtOAc:petroleum ether, 1:7); ^{1}H NMR ($CDCl_3$) δ 7.37-7.31 (m, 3H), 7.26-7.23 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 5.26 (q, *J* = 6.5 Hz, 1H), 3.64 (s, 3H), 2.83 (t, *J* = 7.8 Hz, 2H), 2.55 (t, *J* = 7.8 Hz, 2H), 1.61 (d, *J* = 6.8 Hz, 3H).

The title compound was prepared from ethyl 3-(4-(1-phenylethoxy)phenyl)propanoate (42 mg, 0.15 mmol) according to the general procedure II to give a white and crystalline product (purity >99% by HPLC): R_f = 0.37 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.37-7.30 (m, 3H), 7.25-7.22 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.26 (q, *J* = 6.4 Hz, 1H), 2.83 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.61 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.6, 156.6, 143.3, 132.2, 129.1, 128.6, 127.4, 125.5, 116.0, 76.0, 35.7, 29.7, 24.4; ESI-HRMS calcd for $C_{17}H_{18}O_3Na$ ($M+Na^+$) 293.1149, found 293.1139.



3-(4-(Benzyloxy)-3-iodophenyl)propanoic acid (7). Methyl 3-(4-(benzyloxy)-3-iodophenyl)-propanoate was prepared from methyl 3-(4-hydroxy-3-iodophenyl)propanoate (**L** (below), 70 mg, 0.23 mmol) and benzyl bromide (0.03 mL, 0.25 mmol) according to the general procedure I to give 73 mg (80%) of a clear oil after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:5): R_f = 0.20 (EtOAc:petroleum ether, 1:6); ^{1}H NMR ($CDCl_3$) δ 7.64-7.63 (m, 1H), 7.49-7.47 (m, 2H), 7.41-7.28 (m, 3H), 7.12 (dd, *J* = 8.7 Hz, 1.8 Hz, 2H), 6.76-6.75 (m, 2H), 5.11 (s, 2H), 3.66 (s, 3H), 2.85 (t, *J* = 7.2 Hz, 2H) 2.58 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.1, 155.8, 139.2, 136.6, 135.1, 129.2, 128.5, 127.8, 127.0, 112.7, 86.8, 70.9, 51.6, 35.7, 29.5; MALDI-MS *m*/*z* 419 ($M+Na^+$).

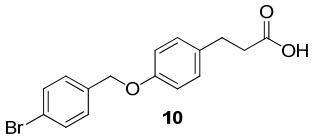
The title compound was prepared from methyl 3-(4-(benzyloxy)-3-iodophenyl)propanoate (65 mg, 0.16 mmol) according to the general procedure II to give 53 mg (85%) of the pure title compound as a white solid (purity >99% HPLC): R_f = 0.36 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.65-7.64 (m, 1H), 7.50-7.47 (m, 2H), 7.41-7.28 (m, 3H), 7.11 (dd, *J* = 8.7 Hz, 1.8 Hz, 2H), 6.79-6.75 (m, 2H), 5.12 (s, 2H), 2.86 (t, *J* = 7.2 Hz, 2H) 2.64 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.4, 155.9, 139.2, 136.5, 134.7, 129.2, 128.5, 127.9, 127.0, 112.7, 86.9, 71.0, 35.5, 29.2; MALDI-MS *m*/*z* 405 ($M+Na^+$).



3-(2-Phenylbenzofuran-5-yl)propanoic acid (8). Methyl 3-(4-hydroxyphenyl)propanoate (**B**, 1009 mg, 5.60 mmol), I_2 (1417 mg, 5.60 mmol) and Ag_2SO_4 (1733 mg, 5.60 mmol) was dissolved in CH_2Cl_2 (100 mL) and stirred over night. The solution was filtered, washed with $Na_2S_2O_4$ saturated water, brine, dried over $MgSO_4$, concentrated and purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 0:1→1:0) to give 1161 mg (68%) of a white solid **L**: R_f = 0.54 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.49 (d, *J* = 2.1 Hz, 1H), 7.07 (dd, *J* = 2.3, 8.3 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 5.31 (s, 1H), 3.67 (s, 3H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.2, 153.3, 137.8, 134.6, 130.1, 115.0, 85.5, 51.7, 35.7, 29.2; EI-MS *m*/*z* 306 (M^+).

A dry Schlenk flask was charged with $Pd(PPh_3)_4$ (21 mg, 0.02 mmol), CuI (11 mg, 0.06 mmol), methyl 3-(4-hydroxy-3-iodophenyl)propanoate (**L**, 103 mg, 0.34 mmol) and evacuated and backfilled with argon before addition of ethynylbenzene (151 mg, 1.47 mmol), DMF (5 mL) and DIPEA (0.15 mL, 0.84 mmol). The reaction was heated to 65 °C and stirred over night. The reaction was cooled to room temperature, neutralized with saturated aqueous ammonium chloride, added water and extracted with EtOAc (x3). The organic phases were combined, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified by dry column chromatography (SiO_2, EtOAc:petroleum ether, 1:90→90:1) to give 63 mg (66%) of **M** as a brown oil: R_f = 0.55 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.55-7.51 (m, 2H), 7.37-7.35 (m, 3H), 7.25 (s, 1H), 7.11-7.08 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.76 (s, 1H), 3.67 (s, 3H), 2.88 (t, *J* = 7.7 Hz, 3H), 2.60 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.2, 153.3, 137.8, 134.6, 130.1, 115.0, 85.5, 51.7, 35.7, 29.5; EI-MS *m*/*z* 280 (M^+).

A dry flask was added NaH (60% in mineral oil, 18 mg, 0.45 mmol), evacuated and backfilled with argon before addition of dry THF. The mixture was cooled to 0 °C and dry MeOH (5 mL) was slowly added to the mixture. The mixture was allowed to reach room temperature, methyl 3-(4-hydroxy-3-(phenylethynyl)phenyl)propanoate (**M**) in dry THF (2 mL) was added, and the mixture was refluxed over night. The reaction mixture was added water and extracted with EtOAc (x3). The organic phases were combined, washed with brine, dried over $MgSO_4$, concentrated and purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:20→1:0) to give 28 mg (61%) of **8** as a white solid (purity 95% by HPLC): R_f = 0.04 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (DMSO-d_6) δ, 7.90 (d, *J* = 7.5 Hz, 2H) 7.53-7.47 (m, 3H), 7.37 (s, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.18 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 2.92 (t, *J* = 7.7 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 173.9, 155.0, 153.0, 136.0, 129.8, 129.1, 128.9, 128.8, 125.2, 124.6, 120.4, 110.8, 102.0, 36.0, 30.4; ESI-HRMS calcd for $C_{17}H_{14}O_3Na$ ($M+Na^+$) 289.0836, found 289.0843.

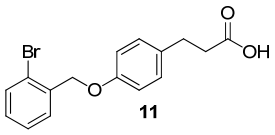


10

3-(4-(4-Bromobenzyloxy)phenyl)propanoic acid (10). Methyl 3-(4-(4-bromobenzyloxy)phenyl)-propanoate was prepared from 4-bromobenzyl bromide (148 mg, 0.59 mmol) and methyl 3-(4-hydroxyphenyl)propanoate (108 mg, 0.60 mmol) according to the general procedure I to give 181 mg (88%) of a clear oil: R_f = 0.30 (EtOAc:petroleum ether, 1:5); ^{1}H NMR (DMSO-d_6) δ 7.58 (dt, *J* = 8.4 Hz, 2.4 Hz, 2H), 7.39 (dt, *J* = 8.4 Hz, 2.4 Hz, 2H), 7.13 (dt, *J* = 8.7 Hz, 3 Hz, 2H), 6.90 (dt, *J*

= 8.7 Hz, 2.4 Hz, 2H), 5.05 (s, 2H), 3.57 (s, 3H), 2.76 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H), 2.55 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 172.2, 156.0, 136.2, 132.3, 130.8, 129.2, 128.7, 120.3, 114.2, 67.8, 50.7, 34.6, 28.9; EI-MS *m*/*z* 348 (M^+).

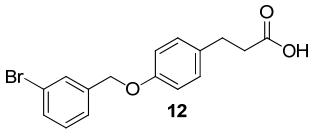
The title compound was prepared from methyl 3-(4-(4-bromobenzyloxy)phenyl)propanoate (100 mg, 0.29 mmol) according to the general procedure II to give 74 mg (75%) of a white and crystalline product (purity >95% by NMR): R_f = 0.14 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:1); ^{1}H NMR (DMSO-d_6) δ 7.64-7.56 (m, 2H), 7.45-7.38 (m, 2H), 7.19-7.12 (m, 2H), 6.96-6.88 (m, 2H), 5.07 (s, 2H), 2.76 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H), 2.50 (dt, *J* = 7.2 Hz, 1.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 173.8, 156.4, 136.8, 133.2, 131.3, 129.7, 129.2, 120.8, 114.6, 68.3, 35.5, 29.5; ESI-HRMS calcd for $C_{16}H_{15}BrO_3Na$ ($M+Na^+$) 357.0097, found 357.0086.



11

3-(4-(2-Bromobenzyloxy)phenyl)propanoic acid (11). Methyl 3-(4-(2-bromobenzyloxy)phenyl)-propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (94 mg, 0.52 mmol) and 2-bromobenzyl bromide (125 mg, 0.50 mmol) according to the general procedure I to give 113 mg (65%) of a yellow oil after purification by flash chromatography (SiO_2, EtOAc:cyclohexane, 1:30→1:15): R_f = 0.66 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.59-7.52 (m, 2H), 7.32 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.20-7.11 (m, 3H), 6.90 (dt, *J* = 8.7 Hz, 2.1 Hz, 2H), 5.10 (s, 2H), 3.66 (s, 3H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.0, 136.4, 133.1, 132.6, 129.3, 129.1, 128.8, 127.5, 122.2, 114.9, 51.6, 35.9, 30.1; EI-MS *m*/*z* 348 (M^+).

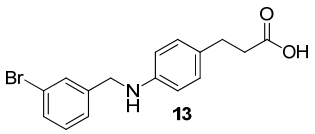
The title compound was prepared from methyl 3-(4-(2-bromobenzyloxy)phenyl)propanoate (86 mg, 0.25 mmol) according to the general procedure II to give 77 mg (93 %) of a white crystalline product (purity >99% HPLC): R_f = 0.34 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.56 (t, *J* = 8.7 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.20-7.12 (m, 3H), 6.94-6.90 (m, 2H), 5.11 (s, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.65 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.8, 157.0, 136.4, 132.8, 132.6, 129.3, 129.2, 128.9, 127.5, 122.2, 115.0, 69.5, 35.8, 29.7; ESI-HRMS calcd for $C_{16}H_{15}BrO_3Na$ ($M+Na^+$) 357.0097, found 357.0115.



12

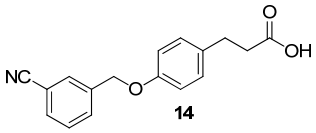
3-(4-(3-Bromobenzyloxy)phenyl)propanoic acid (12). Methyl 3-(4-(3-bromobenzyloxy)phenyl)-propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (90 mg, 0.50 mmol) and 3-bromobenzyl bromide (125 mg, 0.50 mmol) according to the general procedure I to give 170 mg (65%) of a yellow oil after purification by flash chromatography (SiO_2, EtOAc:cyclohexane, 1:10): R_f = 0.44 (EtOAc:cyclohexane, 1:3); ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 1H), 7.45-7.43 (m, 1H), 7.35-7.33 (m, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.11 (dt, *J* = 8.4 Hz, 2.7 Hz, 2H), 6.88 (dt, *J* = 8.7 Hz, 2.4 Hz, 2H), 5.00 (s, 2H), 3.66 (s, 2H), 2.89 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.0, 139.5, 133.2, 131.0, 130.3, 130.1, 129.3, 125.8, 122.7, 114.8, 69.1, 51.6, 35.9, 30.1; EI-MS *m*/*z* 348 (M^+).

The title compound was prepared from methyl 3-(4-(3-bromobenzyloxy)phenyl)propanoate (140 mg, 0.40 mmol) according to the general procedure II to give 132 mg (98 %) of a white crystalline product (purity >99% by HPLC): R_t = 12.35 (HPLC); ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 1H), 7.46-7.42 (m, 1H), 7.35-7.32 (m, 1H), 7.24 (t, *J* = 7.65 Hz, 1H), 7.14-7.11 (m, 2H), 6.90-6.86 (m, 2H), 5.00 (s, 2H), 2.90 (t, *J* = 7.65 Hz, 2H), 2.65 (t, *J* = 7.50 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.5, 157.1, 139.4, 132.8, 131.0, 130.3, 130.1, 129.3, 125.8, 122.7, 114.9, 69.1, 35.7, 29.7; ESI-HRMS calcd for $C_{16}H_{15}BrO_3Na$ ($M+Na^+$) 357.0097, found 357.0097.



13

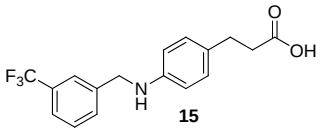
3-(4-(3-Bromobenzylamino)phenyl)propanoic acid (13). The title compound was prepared from 3-(4-aminophenyl)propanoic acid (1002 mg, 6.06 mmol) and 3-bromobenzaldehyde (0.70 mL, 6.0 mmol) according to the general procedure III to give 1418 mg (71%) of a yellow crystalline product after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:1) and recrystallized (EtOAc:petroleum ether, 1:1) (purity 99% by HPLC): R_f = 0.14 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.51 (s, 1H), 7.39 (d, *J* = 6.7 Hz, 1 H), 7.37-7.16 (m, 3H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.55 (d, *J* = 10.8 Hz, 2H), 4.28 (s, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.61 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 179.3, 146.4, 142.2, 130.5, 130.5, 130.4, 129.7, 129.3, 126.1, 122.9, 113.3, 48.1, 36.2, 29.9; ESI-HRMS calcd for $C_{16}H_{17}BrNO_2$ ($M+H^+$) 334.0438, found 334.0440.



14

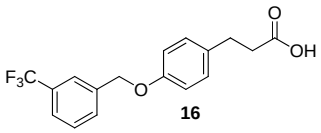
3-(4-(3-Cyanobenzyloxy)phenyl)propanoic acid (14). Methyl 3-(4-(3-cyanobenzyloxy)phenyl)-propanoate was prepared from 3-(bromomethyl)benzonitrile (572 mg, 2.78 mmol) and methyl 3-(4-hydroxyphenyl)propanoate (501 mg, 2.78 mmol) according to the general procedure I to give 630 mg (77%) of a yellow oil: R_f = 0.40 (EtOAc:cyclohexane, 1:5); ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.67-7.58 (m, 2H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.06 (s, 2H), 3.66 (s, 3H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.3, 136.7, 138.9, 133.5, 131.5, 131.4, 130.6, 129.4, 129.3, 118.6, 114.8, 112.7, 68.7, 51.2, 35.8, 30.0.

The title compound was prepared from methyl 3-(4-(3-cyanobenzyloxy)phenyl)propanoate (151 mg, 0.51 mmol) according to the general procedure II to give 134 mg (93%) of a pale yellow solid (purity >99% by HPLC): R_f = 0.27 (EtOAc:cyclohexane, 1:1); ^{1}H NMR (DMSO-d_6) δ 12.10 (s, 1H), 7.93 (s, 1H), 7.85-7.78 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 5.16 (s, 2H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 174.4, 156.8, 139.6, 133.9, 132.9, 132.1, 131.5, 130.3, 129.8, 119.2, 115.2, 112.0, 68.5, 36.1, 30.0; ESI-HRMS calcd for $C_{17}H_{15}NO_3Na$ ($M+Na^+$) 304.0944, found 304.0948.



15

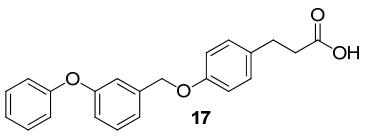
3-(4-(3-(Trifluoromethyl)benzylamino)phenyl)propanoic acid (15). The title compound was prepared from 3-(4-aminophenyl)propanoic acid (142 mg, 0.86 mmol) and 3-trifluoro-methylbenzaldehyde (150 mg, 0.86 mmol) according to general procedure III. The product was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:2→1:1) to produce 110 mg (39%) of a yellow syrup (purity >99% by HPLC): R_f = 0.46 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 1H), 7.61–7.48 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.56 (d, *J* = 8.5 Hz, 2H), 4.77 (s, 1H), 4.37 (s, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.7, 146.3, 140.7, 131.0 (q, *J* = 32.3 Hz), 130.7, 130.7 (q, *J* = 1.0 Hz), 130.1, 129.7, 129.2, 124.1 (q, *J* = 271.0 Hz), 124.1 (t, *J* = 3.0 Hz), 113.18, 48.1, 35.9, 29.8; ESI-HRMS calcd for $C_{17}H_{16}F_3NO_2Na$ ($M+Na^+$) 346.1026, found 346.1030.



16

3-(4-((3-(Trifluoromethyl)benzyl)oxy)phenyl)propanoic acid (16). Methyl 3-(4-(3-(trifluoromethyl)benzyloxy)phenyl)propanoate was prepared from 3-trifluoromethylbenzyl bromide (250 µL, 1.64 mmol) and methyl 3-(4-hydroxyphenyl)propanoate (271 mg, 1.47 mmol) according to the general procedure I to give 432 mg (86%) of a white solid after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:4): R_f = 0.44 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.65–7.54 (m, 2H), 7.54–7.46 (m, *J* = 7.7 Hz, 1H), 7.17–7.09 (m, *J* = 8.5 Hz, 2H), 6.94–6.87 (m, 2H), 5.08 (s, 2H), 3.66 (s, 3H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.0, 138.2, 133.4, 131.1, 131.0 (q, *J* = 32.3 Hz), 129.4, 129.1, 124.7 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 273.7 Hz), 124.1 (q, *J* = 4.0 Hz), 114.9, 69.3, 51.6, 35.9, 30.1; ESI-MS *m*/*z* 361.1 ($M+Na^+$).

The title compound was prepared from methyl 3-(4-(3-(trifluoromethyl)benzyloxy)phenyl)-propanoate (406 mg, 1.19 mmol) according to the general procedure II to give 369 mg (95%) of the pure title compound as a white solid (purity >99% by HPLC): R_t = 12.26 min (HPLC); ^{1}H NMR (DMSO-d_6) δ 12.09 (s, 1H), 7.80 (s, 1H), 7.73 (dd, *J* = 24.1 Hz, 7.7 Hz, 2H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.97 – 6.91 (m, 2H), 5.18 (s, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.48 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 173.7, 156.3, 138.8, 133.3, 131.5, 129.5, 129.2, 129.1 (q, *J* = 31.3 Hz), 124.4 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 273.7 Hz), 123.8 (q, *J* = 4.0 Hz), 114.6, 68.2, 35.4, 29.4; ESI-MS calcd for $C_{17}H_{15}F_3O_3Na$ ($M+Na^+$) 347.0866, found 347.0877.

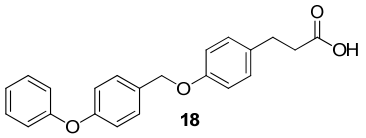


17

3-(4-(3-Phenoxybenzyloxy)phenyl)propanoic acid (17). Methyl 3-(4-(3-phenoxybenzyloxy)-phenyl)propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (90 mg, 0.50 mmol) and 3-phenoxybenzyl chloride (108 mg, 0.50 mmol) according to the general procedure I with addition of NaI (75 mg, 0.50 mmol) to give 170 mg (95%) of a pure yellow oil: R_f = 0.30 (EtOAc:cyclohexane, 1:5); ^{1}H NMR ($CDCl_3$) δ 7.36-7.30 (m, 3H), 7.16-7.08 (m, 5H), 7.02-6.99 (m, 2H), 6.96-6.92 (m, 1H), 6.87 (dt, *J* = 8.7 Hz, 2.1 Hz, 2H), 5.00 (s, 2H), 3.66 (s, 3H), 2.89 (t, *J* = 8.4 Hz, 2H), 2.59 (t, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.5, 157.1, 157.0, 139.2, 133.0,

129.9, 129.8, 129.2, 123.4, 122.0, 119.0, 118.1, 117.7, 114.9, 69.6, 51.6, 35.9, 30.1; EI-MS *m*/*z* 362 (M^+).

The title compound was prepared from methyl 3-(4-(3-phenoxybenzyloxy)phenyl)propanoate (154 mg, 0.43 mmol) according to the general procedure II to give 143 mg (96 %) of a white crystalline product (purity 98% by HPLC): R_f = 0.48 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.36-7.30 (m, 3H), 7.16-7.08 (m, 5H), 7.02-6.99 (m, 2H), 6.96-6.93 (m, 1H), 6.89-6.86 (m, 2H), 5.00 (s, 2H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.4, 157.5, 157.2, 157.0, 139.1, 132.6, 129.9, 129.8, 129.8, 129.3, 123.4, 122.0, 119.0, 118.1, 117.7, 114.9, 69.6, 35.7, 29.8; ESI-HRMS calcd for $C_{22}H_{20}O_4Na$ ($M+Na^+$) 371.1254, found 371.1251.



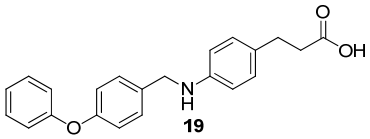
18

3-(4-(4-Phenoxybenzyloxy)phenyl)propanoic acid (18). (4-Phenoxyphenyl)methanol was prepared from 4-phenoxybenzaldehyde (266 mg, 1.31 mmol) according to the general procedure V to give 220 mg (84%) of a white solid: R_f = 0.41 (EtOAc:petroleum ether, 1:3); ^{1}H NMR ($CDCl_3$) δ 7.36-7.30 (m, 4H), 7.10 (t, *J* = 8.4 Hz, 1H), 7.05-6.95 (m, 4H), 4.67 (s, 2H), 1.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 157.2, 156.8, 135.7, 129.7, 128.7, 123.3, 118.9, 118.8, 64.9.

1-(Bromomethyl)-4-phenoxybenzene was prepared from (4-phenoxyphenyl)methanol (95.3 mg, 0.48 mmol) according to the general procedure VI to give 61 mg (48%) of a clear oil after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:5): R_f = 0.68 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.39-7.31 (m, 4H), 7.16-7.09 (m, 1H), 7.05-6.99 (m, 2H), 6.98-6.92 (m, 2H) 4.50 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 157.6, 156.6, 132.4, 130.6, 129.8, 123.7, 119.3, 118.7, 33.3.

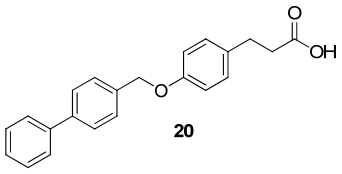
Methyl 3-(4-(4-phenoxybenzyloxy)phenyl)propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (42 mg, 0.23 mmol) and 4-phenoxybenzyl bromide (61 mg, 0.23 mmol) according to the general procedure I. The product was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:3) to produce 60 mg (65%) of a white solid: R_f = 0.29 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.40-7.30 (m, 4H), 7.14-7.08 (m, 3H), 7.04-6.99 (m, 4H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.99 (s, 2H), 3.67 (s, 3H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.9, 157.3, 157.1, 157.0, 132.9, 131.8, 129.8, 129.3, 129.2, 123.4, 119.0, 118.8, 114.9, 69.6, 51.6, 36.0, 30.1.

The title compound was prepared from methyl 3-(4-(4-phenoxybenzyloxy)phenyl)propanoate (54 mg, 0.15 mmol) according to the general procedure II to give 51 mg (97%) of a white solid (purity 98% by HPLC): R_f = 0.27 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (acetone-d_6) δ 7.49 (d, *J* = 8.8 Hz, 2H), 7.42-7.36 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.17-7.12 (m, 1H), 7.05-7.00 (m, 4H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.07 (s, 2H), 2.85 (t, *J* = 7.6, 2H), 2.58 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 173.9, 158.3, 158.1, 157.9, 134.2, 133.5, 130.8, 130.3, 13 0.2, 124.3, 119.7, 119.4, 115.6, 70.0, 36.2, 30.7; ESI-MS *m*/*z* 371.1 (M+Na^+).



19

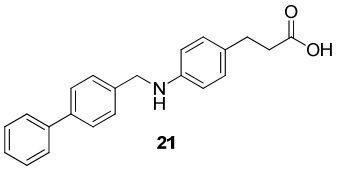
3-(4-(4-Phenoxybenzylamino)phenyl)propanoic acid (19). The title compound was prepared from 3-(4-aminophenyl)propanoic acid (151 mg, 0.91 mmol) and 4-phenoxybenzaldehyde (180 mg, 0.91 mmol) according to general procedure III to give 293 mg (93%) of a pale yellow solid (97% pure by HPLC): R_f = 0.12 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (DMSO-d_6) δ 12.02 (s, 1H), 7.43-7.30 (m, 4H), 7.20-7.05 (m, 1H), 6.99-6.93 (m, 4H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.50 (d, *J* = 8.4 Hz, 2H), 6.04 (s, 1H), 4.20 (s, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 179.2, 155.92, 154.2, 145.9, 134.6, 129.0, 127.8, 127.6, 126.9, 122.2, 117.6, 117.3, 111.3, 45.1, 34.8, 28.6; ESI-MS *m*/*z* 370.2 (M+Na^+).



20

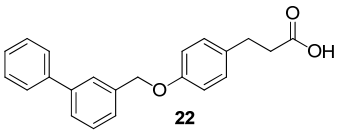
3-(4-(Biphenyl-4-ylmethoxy)phenyl)propanoic acid (20). Methyl 3-(4-(biphenyl-4-ylmethoxy)phenyl)propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (104 mg, 0.57 mmol) and 4-phenylbenzyl chloride (119 mg, 0.57 mmol) according to the general procedure I with addition of NaI (86 mg, 0.57 mmol). The product was recrystallized from acetone to give 119 mg (60%) of a white solid: R_f = 0.69 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$): δ 7.60 (dd, *J* = 8.4 Hz, 8.4 Hz, 4H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.08 (s, 2H), 3.66 (s, 3H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 173.4, 157.3, 140.9, 140.8, 136.1, 132.9, 129.3, 128.8, 127.9, 127.3, 127.1, 127.0, 114.9, 69.8, 51.6, 36.0, 30.1.

The title compound was prepared from methyl 3-(4-(biphenyl-4-ylmethoxy)phenyl)propanoate (233 mg, 1.15 mmol) according to the general procedure II to give 90 mg (80%) of a white solid (purity >99% by HPLC): R_f = 0.24 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (DMSO-d_6) δ 7.75-7.60 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.12 (s, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 173.9, 156.7, 139.8, 139.6, 136.5, 133.1, 129.2, 128.9, 128.2, 127.5, 126.7, 126.7, 114.6, 68.8, 35.6, 29.5; ESI-MS calcd for $C_{22}H_{20}O_3Na$ ($M+Na^+$) 355.1305, found 355.1302.



21

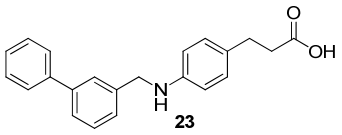
3-(3-(4-(Biphenyl-4-ylmethylamino)phenyl)propanoic acid (21). The title compound was prepared from 3-(4-aminophenyl)propanoic acid (140 mg, 0.85 mmol) and 4-phenylbenzaldehyde (154 mg, 0.85 mmol) according to general procedure III to give 267 mg (95%) of a white solid (98% pure by HPLC): R_f = 0.14 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (DMSO-d_6) δ 11.97 (s, 1H), 7.66-7.57 (m, 4H), 7.47-7.41 (m, 4H), 7.34 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 2H), 6.12 (s, 1H), 4.27 (s, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 174.1, 146.9, 140.1, 139.8, 138.5, 128.9, 128.6, 127.9, 127.7, 127.2, 126.6, 126.5, 112.3, 46.3, 35.9, 29.6; ESI-MS *m*/*z* 354.2 ($M+Na^+$).



22

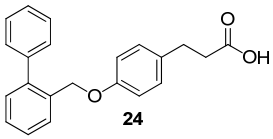
3-(4-(Biphenyl-3-ylmethoxy)phenyl)propanoic acid (22). Methyl 3-(4-(biphenyl-3-ylmethoxy)-phenyl)propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (86 mg, 0.35 mmol) and 3-phenylbenzyl bromide (63 mg, 0.35 mmol) according to the general procedure I to give 85 mg (71%) of a white solid after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:25→1:5): R_f = 0.28 (EtOAc:petroleum ether, 1:5); ^{1}H NMR ($CDCl_3$) δ 7.69-7.60 (s, 1H), 7.61-7.52 (m, 3H), 7.47-7.41 (m, 4H), 7.39-7.34 (m, 1H), 7.14-7.10 (m, 2H), 6.95-6.91 (m, 2H), 5.09 (s, 2H), 3.65 (s, 3H), 2.92-2.87 (t, *J* = 7.2 Hz, 2H) 2.62-2.59 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.3, 141.6, 140.9, 137.6, 132.9, 129.3, 129.0, 128.8, 127.4, 127.2, 126.8, 126.3, 126.3, 114.9, 70.1, 51.6, 35.9, 30.1; EI-MS *m*/*z* 346 (M^+).

The title compound was prepared from methyl 3-(4-(biphenyl-3-ylmethoxy)phenyl)propanoate (109 mg, 0.32 mmol) according to the general procedure II to give 57 mg (54%) of the pure title compound as a white solid (purity 94% HPLC): R_f = 0.44 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 10.25-9.00 (br s, 1H), 7.65-7.51 (m, 4H), 7.47-7.32 (m, 5H), 7.14-7.11 (m, 2H), 6.94-6.91 (m, 2H), 5.09 (s, 2H), 2.91 (t, *J* = 7.2 Hz, 2H) 2.64 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.7, 157.4, 141.6, 140.9, 137.6, 132.6, 129.3, 129.0, 128.8, 127.4, 127.2, 126.8, 126.4, 126.3, 114.9, 70.1, 35.8, 29.8; MALDI-HRMS calcd for $C_{22}H_{20}O_3Na$ (M+Na$^+$) 355.1305, found 355.1307.



23

3-(4-(Biphenyl-3ylmethylamino)phenyl)propanoic acid (23). The title compound was prepared from 3-(4-(3-bromobenzylamino)phenyl)propanoic acid (102 mg, 0.30 mmol) and phenylboronic acid (55 mg, 0.45 mmol) according to the general procedure IV to give 12 mg (12%) of a yellow solid after purification by flash chromatography (SiO_2, acetone:petroleum ether, 1:5→1:3) (purity 95% by HPLC): R_f = 0.17 (acetone:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J* = 7.1 Hz, 2H), 7.54-7.31 (m, 5H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 4.36 (s, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.61 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 179.1, 146.8, 140.2, 135.8, 129.4, 129.3, 129.0, 128.2, 127.6, 127.4, 126.6, 126.5, 126.3, 113.3, 48.8, 36.1, 30.0; ESI-HRMS calcd for $C_{22}H_{21}NO_2Na$ (M+Na$^+$) 354.1465, found 354.1474.

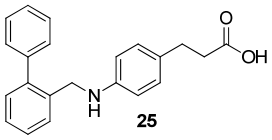


24

3-(4-(Biphenyl-2-ylmethoxy)phenyl)propanoic acid (24). Methyl 3-(4-((2-iodobenzyl)oxy)-phenyl)propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (72 mg, 0.40 mmol) and 2-iodobenzyl bromide (119 mg, 0.40 mmol) according to the general procedure I, with the exception of heating to reflux instead of leaving at room temperature, to give 156 mg (99%) of a pale yellow oil: R_f = 0.47 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, *J* = 7.9 Hz, 1.1 Hz, 1H), 7.50 (dd, *J* = 7.7 Hz, 1.6 Hz, 1H), 7.36 (td, *J* = 7.5 Hz, 1.1 Hz, 1H), 7.19–7.08 (m, 2H), 7.02 (td, *J* = 7.6 Hz, 1.7 Hz, 1H), 6.95–6.86 (m, 2H), 5.01 (s, 2H), 3.67 (s, 3H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.0, 139.3, 133.2, 129.5, 129.3, 128.6, 128.4, 115.0, 97.1, 74.0, 51.6, 36.0, 30.1.

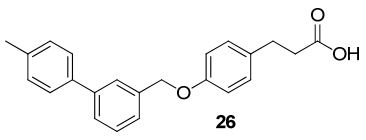
Methyl 3-(4-(biphenyl-2-ylmethoxy)phenyl)propanoat was prepared from methyl 3-(4-(2-iodobenzyloxy)phenyl)propanoate (140 mg, 0.35 mmol), phenylboronic acid (64 mg, 0.53 mmol) according to the general procedure IV to give 31 mg (25%) of a pale yellow oil after purification by flash chromatography (SiO_2, EtOAc:petroleum ether: 1:12): R_f = 0.63 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.65–7.57 (m, 1H), 7.49–7.26 (m, 8H), 7.10–7.03 (m, 2H), 6.82–6.75 (m, 2H), 4.91 (s, 2H), 3.65 (s, 3H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.2, 141.8, 140.5, 134.2, 132.8, 130.1, 129.3, 129.2, 128.3, 128.1, 127.7, 127.3, 114.9, 68.1, 51.6, 36.0, 30.1.

The title compound was prepared from methyl 3-(4-(biphenyl-2-ylmethoxy)phenyl)propanoate (31 mg, 0.09 mmol) according to standard procedure II to give 30 mg (100%) of a pale yellow solid (purity >99% by HPLC): R_f = 0.26 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (MeOH-d_4) δ 7.56 (m, 1H), 7.46–7.18 (m, 8H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 4.86 (s, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.52 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (MeOH-d_4) δ 176.8, 158.4, 143.5, 142.0, 135.6, 134.5, 131.0, 130.6, 130.2, 129.3, 129.1, 128.6, 128.34, 115.8, 69.3, 37.0, 31.2; ESI-MS *m*/*z* 355.1 (M+Na^+).



25

3-(4-(Biphenyl-2-ylmethylamino)phenyl)propanoic acid (25). The title compound was prepared from 3-(4-aminophenyl)propanoic acid (101 mg, 0.61 mmol) and 2-biphenylcarboxaldehyde (0.10 mL, 0.62 mmol) according to the general procedure III to give 8 mg (5%) of a yellow solid after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:6) (purity 90% by HPLC): R_f = 0.24 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.48-7.52 (m, 9H), 6.96 (d, *J* = 7.2 Hz, 2 H), 6.45 (d, *J* = 7.2 Hz, 2H), 4.21 (s, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.60 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 178.6, 146.7, 141.9, 141.1, 136.7, 130.4, 129.2, 129.1, 128.8, 128.6, 128.5, 127.9, 127.4, 127.4, 113.2, 46.6, 36.1, 29.9: ESI-HRMS calcd for $C_{22}H_{21}NO_2Na$ (M+Na^+) 354.1465, found 354.1458.



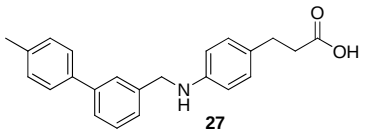
26

3-(4-(4'-Methylbiphenyl-3-ylmethoxy)phenyl)propanoic acid (26). (4'-Methylbiphenyl-3-yl)-methanol was prepared from 3-(4-methylphenyl)benzaldehyde (262 mg, 1.33 mmol) according to the general procedure V to give 238 mg (90%) of a white solid (purity 95% by HPLC): R_f = 0.44 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.51-7.47 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.75 (d, *J* = 6.0 Hz, 2H), 2.39 (s, 3H), 1.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 141.5, 141.3, 138.1, 137.2, 129.5, 129.0, 127.0, 126.3, 125.6, 125.6, 65.4, 21.1.

3-Bromomethyl-4'-methylbiphenyl was prepared from (4'-methylbiphenyl-3-yl)methanol (100 mg, 0.51 mmol) according to the general procedure VI to give 42 mg (31%) of a clear oil after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:5): R_f = 0.64 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.51-7.46 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.34-7.32 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.55 (s, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.8, 138.2, 137.6, 137.4, 129.5, 129.2, 127.7, 127.6, 127.1, 127.0, 33.6, 21.1.

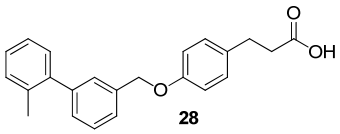
Methyl 3-(4-(4'-methylbiphenyl-3-ylmethoxy)phenyl)propanoate was prepared from methyl 3-(4-hydroxyphenyl)propanoate (29 mg, 0.16 mmol) and 3-(bromomethyl)-4'-methylbiphenyl (42 mg, 0.16 mmol) according to the general procedure I. The product was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:3) to produce 32 mg (55%) of a white solid: R_f = 0.28 (EtOAc:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 1H), 7.55-7.52 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.40-7.36 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.09 (s, 2H), 3.66 (s, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 8.4, 2H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.3, 141.5, 138.0, 137.6, 137.2, 132.9, 129.5, 129.3, 129.0, 127.0, 126.6, 126.1, 126.1, 114.9, 70.2, 51.6, 36.0, 30.1, 21.1.

The title compound was prepared from methyl 3-(4-(4'-methylbiphenyl-3-ylmethoxy)-phenyl)propanoate (32 mg, 0.09 mmol) according to the general procedure II to give 30 mg (98%) of a white solid (purity 97% by HPLC): R_f = 0.20 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (acetone-d_6) δ 7.74 (s, 1H), 7.61-7.53 (m, 3H), 7.48-7.43 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.17 (s, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (acetone-d_6) δ 173.8, 158.3, 142.0, 139.3, 138.8, 138.0, 134.3, 130.3, 130.2, 129.9, 127.7, 127.1, 126.9, 126.8, 115.7, 70.4, 36.2, 30.7, 21.1; MALDI-HRMS calcd for $C_{23}H_{22}O_3Na$ ($M+Na^+$) 369.1462, found 369.1465.



27

3-(4-(4'-Methylbiphenyl-3-ylmethylamino)phenyl)propanoic acid (27). The title compound was prepared from 3-(4-aminophenyl)propanoic acid (151 mg, 0.91 mmol) and 3-(4-methylphenyl)-benzaldehyde (126 mg, 0.64 mmol) according to general procedure III. The product was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:2→1:0) to produce 139 mg (63%) of a pale yellow solid (98% pure by HPLC): R_f = 0.33 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.50-7.47 (m, 3H), 7.42-7.37 (m, 1H), 7.33-7.30 (m, 1H), 7.25-7.23 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 4.36 (s, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.5, 146.7, 141.5, 139.9, 138.1, 137.1, 129.5, 129.2, 129.1, 129.0, 128.9, 127.0, 126.2, 125.9, 113.1, 48.7, 35.9, 29.8, 21.1; ESI-HRMS calcd for $C_{23}H_{23}NO_2Na$ ($M+Na^+$) 368.1622, found 368.1631.

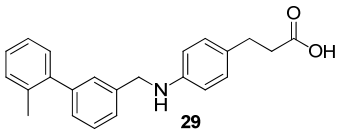


28

3-(4-(2'-Methylbiphenyl-3-ylmethoxy)phenyl)propanoic acid (28). Methyl 3-(4-(2'-methyl-biphenyl-3-ylmethoxy)phenyl)propanoate was prepared from methyl 3-(4-(3-bromobenzyloxy)-phenyl)propanoate (173 mg, 0.50 mmol) and 2-methylphenylboronic acid (102 mg, 0.75 mmol) according to the general procedure IV to give 90 mg (50%) of a white solid: R_f = 0.25 (EtOAc:petroleum ether, 1:5); ^{1}H NMR ($CDCl_3$) δ 7.42-7.38 (m, 3H), 7.29-7.22 (m, 5H), 7.12-7.10 (m, 2H), 6.92-6.89 (m, 2H), 5.08 (s, 2H), 3.66 (s, 3H), 2.89 (t, *J* = 8.1 Hz, 3H), 2.60 (t, *J* = 8.1 Hz, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.3, 142.2, 141.6, 136.9, 135.3, 132.9, 130.3, 129.8, 129.2, 128.7, 128.3, 128.3, 127.3, 125.8, 125.8, 114.9, 70.0, 51.5, 36.0, 30.1, 20.4; EI-MS *m*/*z* 360 (M^+).

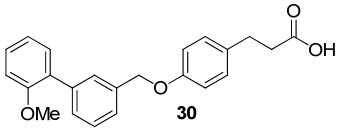
The title compound was prepared from methyl 3-(4-(2'-methylbiphenyl-3-ylmethoxy)phenyl)-propanoate (88 mg, 0.25 mmol) according to the general procedure II to give 76 mg (90%) of the pure title compound as a white solid (purity >99% by HPLC): R_f = 0.04 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:4); ^{1}H NMR ($CDCl_3$) δ 7.40-7.38 (m, 3H), 7.26-7.22 (m, 5H), 7.13-7.11 (m, 2H), 6.93-6.90 (m, 2H), 5.08 (s, 2H), 2.90 (t, *J* = 8.1 Hz, 3H), 2.64 (t, *J* = 8.1 Hz, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.8, 157.3, 142.2, 141.6, 136.9, 135.3, 132.5, 130.3, 129.8, 129.2,

128.8, 128.3, 128.3, 127.2, 125.8, 125.8, 115.0, 70.0, 35.8, 29.7, 20.4; MALDI-HRMS calcd for $C_{23}H_{22}O_3Na$ (M+Na^+) 369.1462, found 369.1476.



29

3-(4(2'-Methylbiphenyl-3-ylmethylamino)phenyl)propanoic acid (29). The title compound was prepared from 3-(4-(3-bromobenzylamino)phenyl)propanoic acid (101 mg, 0.30 mmol) and *o*-tolyl-boronic acid (65 mg, 0.48 mmol) according to the general procedure IV to give 39 mg (37%) of a white solid after purification by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:1) (purity 98% by HPLC): R_f = 0.23 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.37-7.21 (m, 8H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 8.4 Hz, 2H), 4.35 (s, 2H), 2.82 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 8.1 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.1, 146.7, 142.4, 141.8, 139.4, 135.5, 130.5, 129.9, 129.4, 129.2, 128.5, 128.5, 128.2, 127.4, 126.1, 125.9, 113.3, 48.7, 36.2, 30.0, 20.6; ESI-HRMS calcd for $C_{23}H_{23}NO_2Na$ (M+Na^+) 368.1622, found 368.1612.

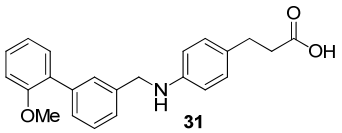


30

3-(4-(2'-Methoxybiphenyl-3-ylmethoxy)phenyl)propanoic acid (30). Methyl 3-(4-(2'-methoxybiphenyl-3-ylmethoxy)phenyl)propanoate was prepared from methyl 3-(4-(3-bromobenzyloxy)phenyl)propanoate (174 mg, 0.50 mmol) and 2-methoxyphenylboronic acid (114 mg, 0.75 mmol) according to the general procedure IV to give 144 mg (77%) of a pale yellow solid: R_f = 0.43 (EtOAc:petroleum ether, 1:4); ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.39-7.30 (m, 5H), 7.12-7.10 (m, 2H), 7.02-6.90 (m, 4H), 5.08 (s, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 2.92-2.86 (t, *J* = 8.1 Hz, 3H), 2.62-2.57 (t, *J* = 8.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.4, 156.4, 138.8, 136.7, 132.8, 130.9, 130.3, 129.2, 129.1, 128.7, 128.7, 128.2, 126.0, 120.8, 114.9, 111.2, 70.1, 55.5, 51.5, 36.0, 30.1; MALDI-MS *m*/*z* 399 (M+Na^+).

The title compound was prepared from methyl 3-(4-(2'-methoxybiphenyl-3-ylmethoxy)-phenyl)propanoate according to the general procedure II to give 53 mg of the pure title compound as a white solid (purity >99% by HPLC): R_f = 0.02 ([EtOAc with 1.25% AcOH]:petroleum ether, 1:4); ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.47-7.30 (m, 5H), 7.13-7.11 (m, 2H), 7.02-6.91 (m, 4H), 5.08 (s, 2H), 3.78 (s, 3H), 2.93-2.87 (t, *J* = 8.1 Hz, 3H), 2.67-2.61 (t, *J* = 8.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.7, 157.5, 156.4, 138.8, 136.7, 132.4, 130.9, 130.4, 129.2, 129.2, 128.7, 128.7, 128.2,

126.0, 120.8, 115.0, 111.2, 70.1, 55.5, 35.8, 29.8; MALDI-HRMS calcd for $C_{23}H_{22}O_4Na$ ($M+Na^+$) 385.1411, found 385.1419.



31

3-(4-(2'-Methoxybiphenyl-3-ylmethylamino)phenyl)propanoic acid (31). The title compound was prepared from 3-(4-(3-bromobenzylamino)phenyl)propanoic acid (101 mg, 0.30 mmol) and 2-methoxyphenylboronic acid (68 mg, 0.45 mmol) according to the general procedure IV to give 28 mg (25%) of a yellow solid after purification by flash chromatography (SiO_2, acetone:petroleum ether, 1:4→1:1) (purity 97% by HPLC): R_f = 0.15 (acetone:petroleum ether, 1:2); ^{1}H NMR ($CDCl_3$) δ 7.52-7.23 (m, 5H), 7.03-6.95 (m, 3H), 6.59 (d, *J* = 8.4 Hz, 2 H), 6.28 (br s, 2H), 4.33 (s, 2H), 3.76 (s, 3H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.60 (t, 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 179.1, 156.6, 146.9, 139.2, 139.0, 131.0, 130.6, 129.3, 129.2, 129.0, 128.9, 128.7, 128.5, 126.4, 121.0, 113.3, 111.4, 55.7, 48.8, 36.3, 30.0; ESI-HRMS calcd for $C_{23}H_{24}NO_3$ ($M+H^+$) 362.1751, found 362.1759.

Biological assays

Materials. Tissue culture media and reagents were purchased from Invitrogen (Karlsruhe, Germany). Sensor microplates and compound source plates were obtained from Corning (Corning, NY). Restriction endonucleases and modifying enzymes were from New England Biolabs, and all other laboratory reagents were from Sigma-Aldrich (Taufkirchen; Germany), unless differently specified.

DNA constructs and generation of stable Flp-In T-REx 293 cells. The coding sequence of human GPR41 and human GPR43 receptor were subcloned from pcDNA3.1(+) into the inducible expression vector, pcDNA5/FRT/TO (Invitrogen) via 5′ HindIII and 3′ XhoI. Correctness of the constructs was verified by restriction endonuclease digestion. The *Flp* recombinase-mediated homologous recombination system (Flp-In™ T-REx™, Invitrogen) was used to generate cell lines stably expressing hGPR41 or hGPR43 in a doxycycline-dependent manner. The Flp-In T-Rex 293 cells (HEK293 cell line with a single integrated Flp Recombination Target (FRT) site) were maintained in high-glucose DMEM (Dulbecco's modified Eagle's medium) supplemented with 10% (v/v) heat-inactivated fetal calf serum, 1% sodium pyruvate, 100 U/ml penicillin, 100 µg/ml streptomycin, 100 µg/ml Zeocin™ (InvivoGen) and 15 µg/ml blasticidin (InvivoGen) at 37 °C in a 5% CO_2 atmosphere. To generate Flp-In T-REx 293 cells able to inducibly express a receptor of interest, the cells were transfected with a mixture containing the desired receptor cDNA in pcDNA5/FRT/TO vector and the pOG44 vector (Invitrogen's expression vector for *Flp* recombinase) (1:9) using calcium phosphate DNA precipitation method. Cells were positively selected with 100 µg/ml Hygromycin B (InvivoGen), colonies were pooled as isogenic populations. To induce expression of receptors cloned into the Flp-In locus, cells were treated with 1 µg/ml doxycycline hyclate (Sigma) for 16 hours.

Cell Culture and Transfection. 1321N1 cells stably transfected with the human GPR40 were kindly provided by Euroscreen (Gosselies, Belgium). hGPR40-1321N1 cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% (v/v) heat-inactivated fetal calf

serum, 1% sodium pyruvate, 100 U/ml penicillin, 100 µg/ml streptomycin, and 400 µg/ml G418. 1321N1, HEK293 cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% (v/v) heat-inactivated fetal calf serum, 1% sodium pyruvate, 100 U/ml penicillin, and 100 µg/ml streptomycin. All cells were kept at 37°C in a 5% CO_2 atmosphere.

Calcium Mobilization Assays. Calcium measurements were performed using a NOVOstar® microplate reader with a built-in pipetor (BMG LabTech, Offenburg, Germany). Cells were seeded in 96-well tissue-culture plates at a density of 30,000 cells per well. On the next day, cells were washed twice in Krebs-HEPES buffer (KHB: 118.6 mM NaCl, 4.7 mM KCl, 1.2 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 11.7 mM *D*-glucose, 10 mM HEPES (free acid), 1.3 mM $CaCl_2$ and 1.2 mM $MgSO_4$, pH 7.4) and loaded with 1.5 µM Oregon Green 488 BAPTA-1/AM (Molecular Probes, Eugene, OR) and 0.03% Pluronic F-127 (Invitrogen, Karlsruhe, Germany) for 1 h (37°C, 5% CO_2). After addition of KHB, microplates were directly transferred to Novostar and kept at 37°C under exclusion of light for 15 min until the measurement was started. For testing of agonists, 20 µl of a ten-fold concentrated test compound solution was injected sequentially into separate wells and fluorescence was measured at 520 nm (bandwidth 25 nm) for 50 intervals of 0.4 seconds each. The excitation wavelength was 485 nm (bandwidth 25 nm).

Dynamic mass redistribution (DMR) optical biosensor assays (Epic™ System). DMR is a novel label-free technology translating receptor activity into optical signatures which represent holistic responses of living cells in a signaling pathway-unbiased manner. The Corning® Epic™ System consisting of a temperature-control unit, an optical detection unit, and an on-board liquid handling unit with robotics was used for this study.[2-3] The system is based on 384-well Epic™ sensor microplates containing a resonant waveguide grating (RWG) biosensor at the bottom of each well. This biosensor measures changes in local index of refraction upon ligand-induced dynamic mass redistribution within a thin layer of cells. Twenty-four hours before the assay, hGPR40-1321N1 cells, hGPR41 Flp-In T-REx 293 or hGPR43 Flp-In T-REx 293 cells (15,000 cells/well) were seeded in fibronectin-coated sensor microplates. For hGPR40-1321N1 cells a starvation step (i.e., plating in serum-free medium) was necessary for sufficient signal detection. On the next day, cells were washed with HBSS buffer (Hanks Balanced Salt Solution with 20 mM HEPES) containing the same percentage of dimethyl sulphoxide as the later added compounds. This is important since some solvents can induce bulk refractive index differences. After at least 1 hour incubation within

the detection system, the sensor plate was scanned and a baseline response was recorded. Then, compound solutions were transferred into the sensor plate using the on-board liquid handling system, and cell responses were recorded for another period of time. All studies were carried out at controlled temperature (28 °C).

Data analysis.

Calcium data were normalized as percentage of the maximum response of standard agonist activity for each assay. The pooled data from at least three experiments carried out in triplicates were analyzed by using nonlinear regression with a sigmoidal dose-response equation (Prism® 4.02, GraphPad Software, San Diego, CA).

Quantification of DMR signals for concentration effect curves was performed by calculation of the area under the curve (AUC) between 0 and 3600 s. EC_{50} value determination by nonlinear regression was performed using Prism 4.02 (Graph Pad, San Diego, CA, USA).

PPAR-LBD Transactivation. A mouse embryo fibroblast cell line was used for PPARγ transfections. Cells were propagated in Dulbeccos Modified Eagle's Media supplemented with 10% fetal calf serum and antibiotics. For transfections, cells were transfected in solution by Metafectene lipofection, essentially according to the manufacturer's (Biontex) instructions and seeded in 100 µL Dulbeccos Modified Eagle's Media supplemented with 10% fetal calf serum and antibiotics in 96-well dishes at 24000 cells/cm2. The transfection plasmid mix included the Gal4-responsive luciferase reporter, the expression vector for the fusion between the Gal4 DNA-binding domain and the ligand binding domain of human PPARγ, and a CMV-Renillas normalization vector. 6 hours after transfection and seeding of cells, the media was supplemented with 100 µL DMEM including the test compounds (1, 10 and 100 µM (final concentration) and 0.2% DMSO). Approx. 18 hours later, cells were harvested and lysates analyzed for Photinus and Renilla luciferase activity by luminometry. All data points were performed in at least triplicate and each sample measured in duplicate. Luminometer raw data was analyzed in Microsoft Excel spreadsheets and presented as column graphs depicting average values of app. 8 replica ± standard deviations.

Insulin secretion. INS-1E cells (a kind gift of C.B. Wollheim, University of Geneva, Switzerland) were cultured in RPMI1640 supplemented with 10% fetal calf serum, 1 mmol/l Hepes, 1 mmol/l Na^+-pyruvate and 10 µmol/l β-mercaptoethanol, seeded at a density of 10 x 10^5 cells/ml in 24-well

plates for 2 days and incubated as described previously.[4] In brief, cells were incubated for 1 h at 37°C in a solution containing (in mmol/l): 140 NaCl, 5.6 KCl, 1.2 $MgCl_2$, 2.6 $CaCl_2$, 10 Hepes, 0.5 g/l bovine serum albumin (fatty acid free, Sigma, Deisenhofen, Germany) and the test substances as indicated. Insulin released into the supernatant and insulin content after acid ethanol extraction were determined by radioimmunoassay (Linco, USA).

References

(1) Han, W.; Liu, C.; Jin, Z. L. In situ generation of palladium nanoparticles: A simple and highly active protocol for oxygen-promoted ligand-free suzuki coupling reaction of aryl chlorides. *Org. Lett.* **2007**, *9*, 4005-4007.

(2) Fang, Y.; Ferrie, A. M.; Fontaine, N. H.; Mauro, J.; Balakrishnan, J. Resonant waveguide grating biosensor for living cell sensing. *Biophys. J.* **2006**, *91*, 1925-1940.

(3) Fang, Y.; Ferrie, A. M.; Fontaine, N. H.; Yuen, P. K. Characteristics of dynamic mass redistribution of epidermal growth factor receptor signaling in living cells measured with label-free optical biosensors. *Analytical Chemistry* **2005**, *77*, 5720-5725.

(4) Ullrich, S.; Berchtold, S.; Ranta, F.; Seebohm, G.; Henke, G.; Lupescu, A.; Mack, A. F.; Chao, C. M.; Su, J. P.; Nitschke, R.; Alexander, D.; Friedrich, B.; Wulff, P.; Kuhl, D.; Lang, F. Serum- and glucocorticoid-inducible kinase 1 (SGK1) mediates glucocorticoid-induced inhibition of insulin secretion. *Diabetes* **2005**, *54*, 1090-1099.