Supporting Information

Benzodiazepinone Derivatives as CRTH2 Antagonists

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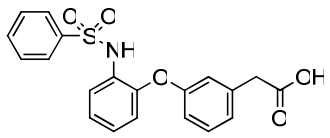
Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Dry organic solvents (DriSolv) were purchased from EMD Chemicals and packaged under nitrogen in Sure Seal bottles. Reactions were monitered using thin-layer chromatography on 250 µm plates or using Agilent 1100 series LCMS with UV detection at 254 nm and a low resonance electrospray mode (ESI). Purification of title compounds was accomplished by flash column chromatography using silica gel 60 (particle size 0.04-0.063 mm, 230-400 mesh) or medium pressure liquid chromatography on a CombiFlash Companion (Teledyne Isco) with RediSep normal phase silica gel. ^{1}H NMR spectra were recorded on a Bruker spectrometer (400 or 500 MHz) at ambient temperature. Chemical shifts are reported in ppm relative to $CDCl_3$ or DMSO and coupling constants (J) are reported in hertz (Hz). Purity of final compounds was ≥95% based on analytical HPLC and NMR analysis.

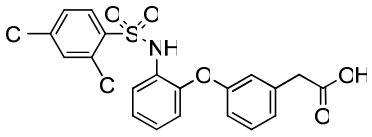
Synthetic procedures of compounds **1** and **3** were reported in patent US 7321001. Their NMR and MS data is listed below.

3-(2-Benzenesulfonylamino-phenoxy)phenylacetic acid (1)



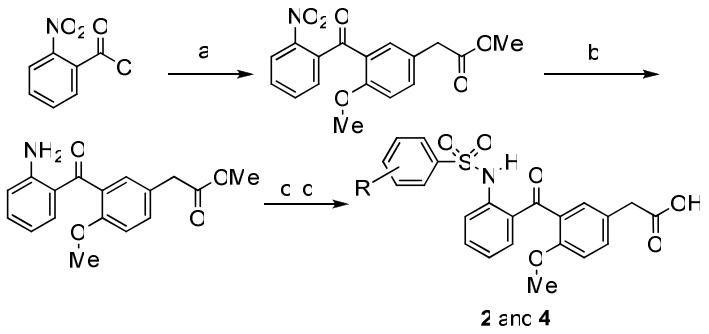
^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.38 (br s, 1H), 9.98 (br s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 7.37 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.07 – 6.99 (m, 3H), 6.67 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 6.57 (s, 1H), 6.55 (s, 2H), 6.48 (m, 1H), 3.52 (s, 2H). MS (ESI) [M-H]$^-$: 382.

3-[2-(2,4-Dichlorobenzenesulfonyl)amino-phenoxy]phenylacetic acid (3)



^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.4 (br s, 1H), 10.19 (br s, 1H), 7.77 (d, J = 12 Hz, 1H), 7.54 (s, 1H), 7.44 (dd, J_1 = 7 Hz, J_2 = 3 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 7.19 (m, 2H), 7.11 (m, 1H), 6.98 (d, J = 8 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 6.75 (s, 1H), 6.44 (m, 1H), 3.52 (s, 2H). MS (ESI) [M-H]$^-$: 450.

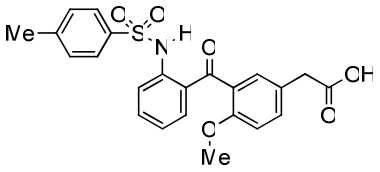
Synthesis of compounds **2** and **4**:



Methyl 2-(4-methoxy-3-(2-nitrobenzoyl)phenyl)acetate Step a: To a solution of 2-nitrobenzoyl chloride (0.66 mL, 5 mmol) and 4-methoxyphenylacetic acid (0.79 mL, 5 mmol) in 1,2-dichloroethane (3 mL) at 0 °C, was added aluminum chloride (0.8 g, 6 mmol). The mixture was then warmed to 25 °C and stirred for 2 h. The mixture was acidified with concentrated HCl to pH2 and extracted with EtOAc twice. The combined organic layers were washed with sodium bicarbonate solution, dried and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). Yield 1.3 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, 1H), 7.93 (s, 1H), 7.72 (t, 1H), 7.59 (t, 1H), 7.48 (m, 1H), 7.41 (d, 1H), 6.86 (d, 1H), 3.73 (s, 3H), 3.65 (s, 2H), 3.49 (s, 3H). MS (ESI) $[M+H]^+$: 330.

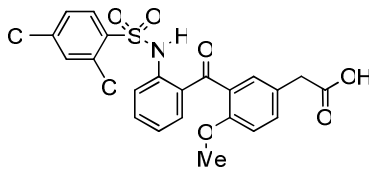
Methyl 2-(3-(2-aminobenzoyl)-4-methoxyphenyl)acetate Step b: Iron (0.4 g, 7.11 mmol) was added to a mixture of methyl 2-(4-methoxy-3-(2-nitrobenzoyl)phenyl)acetate (0.78 g, 2.37 mmol) in acetic acid (15 mL) and water (6 mL). The mixture was stirred at 65 °C for 20 h, cooled, neutralized with sodium bicarbonate solution and extracted with EtOAc twice. The combined organic layers were dried and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). Yield 0.64 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.17 (s, 1H), 6.95 (d, 1H), 6.70 (d, 1H), 6.54 (t, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.60 (s, 2H). MS (ESI) $[M+H]^+$: 300.

2-(4-Methoxy-3-(2-(4-methylphenylsulfonamido)benzoyl)phenyl)acetic acid (2)



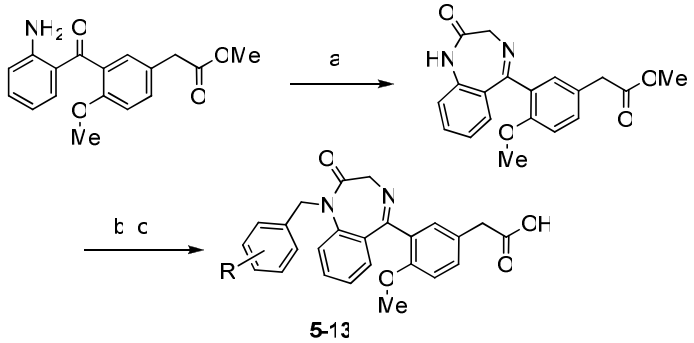
Step c and d: 4-Methylphenyl sulfonyl chloride (0.21 g, 1.1 mmol) was added to a mixture of methyl 2-(3-(2-aminobenzoyl)-4-methoxyphenyl)acetate (0.3 g, 1 mmol) and 2,6-lutidine (150 mg, 1.4 mmol) in THF (5 mL) at r.t.. The mixture was then heated and stirred at 60 °C for 12 h. After cooling to r.t., water (3 mL) and 10 N NaOH (1 mL) were added. The mixture was stirred at r.t. for 2 hours, acidified to pH2 with HCl, and extracted with EtOAc. The organic layer was washed with brine three times, dried with $MgSO_4$, and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). Yield: 0.26 g (59%). ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.34 (br s, 1H), 10.98 (br s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.57-7.30 (m, 7H), 7.12 (m, 2H), 3.58 (s, 3H), 3.57 (s, 2H). MS (ESI) $[M+H]^+$: 440.

2-(3-(2-(2,4-Dichlorophenylsulfonamido)benzoyl)-4-methoxyphenyl)acetic acid (4)



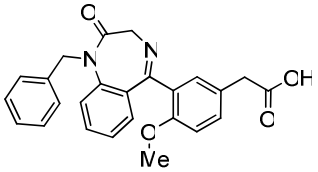
Compound **4** was synthesized as compound **2** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.34 (br s, 1H), 11.51 (br s, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.91 (s, 1H), 7.69 (d, J = 6.8 Hz, 1H), 7.52 (m, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 3.59 (s, 3H), 3.58 (s, 2H). MS (ESI) $[M+H]^+$: 494.

Synthesis of compounds **5-13**:



Methyl 2-(4-methoxy-3-(2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)phenyl)acetate Step a: Methyl 2-(3-(2-aminobenzoyl)-4-methoxyphenyl)acetate (385 mg, 1.3 mmol) and glycine methyl ester HCl salt (246 mg, 1.95 mmol) in dry pyridine (6 mL) was stirred at 130 °C for 36 h. The glycine salt (100 mg) was added four times during the heating. After the cooling, the mixture was treated with water and extracted with EtOAc twice. The combined organic layers were dried and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). Yield 180 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.38 (m, 2H), 7.22 (d, 1H), 7.10 (m, 2H), 6.84 (d, 1H), 4.32 (s, 2H), 3.69 (s, 3H), 3.57 (s, 2H), 3.52 (s, 3H). MS (ESI) $[M+H]^+$: 339.

2-(3-(1-Benzyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-4-methoxyphenyl)acetic acid (5)

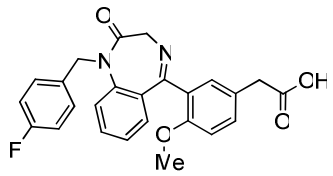


Step b: t-BuOK (9.1 mg, 0.081 mmol) was added to a mixture of methyl 2-(4-methoxy-3-(2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)phenyl)acetate (25 mg, 0.074 mmol) and benzyl bromide (12.7 mg, 0.074 mmol) in DMF (0.5 mL) at ambient temperature. The mixture was stirred at ambient temperature for 16 h. The mixture was treated with water and extracted with EtOAc twice. The combined organic layers were dried and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). Yield 22 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.24 (m, 5H), 7.15 (m, 1H), 7.09 (m, 1H), 6.86 (d, 1H), 5.52 (d, 1H), 5.01 (d, 1H), 4.96 (d, 1H), 3.93 (d, 1H), 3.73 (s, 3H), 3.62 (s, 2H), 3.34 (s, 3H). MS (ESI) $[M+H]^+$: 429.

Step c: The product obtained (22 mg) above was dissolved in THF/MeOH/water (2:2:1; 2mL) and treated with LiOH (8.4 mg, 0.2 mmol). The mixture was stirred at ambient temperature for 3 h, acidified to pH3, and extracted with EtOAc twice. The combined organic layers were dried and

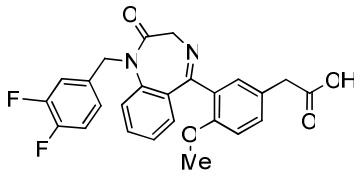
concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). Yield 19 mg (90%). ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3(br s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.51 (m, 1H), 7.35-7.10 (m, 8H), 7.01 (m, 2H), 5.39 (d, J = 15.8 Hz, 1H), 5.07 (d, J = 15.9 Hz, 1H), 4.63 (d, J = 10.3 Hz, 1H), 3.84 (d, J = 10.5 Hz, 1H), 3.55 (s, 2H), 3.30 (s, 3H). MS (ESI) $[M+H]^+$: 415. Calcd. for $C_{25}H_{22}N_2O_4$ $[M+H]^+$: 415.1658; Found: 415.1652.

2-(3-(1-(4-Fluorobenzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-4-methoxyphenyl)acetic acid (6)



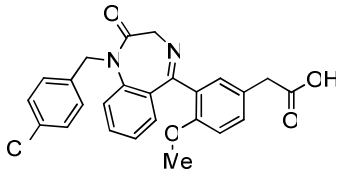
Compound **6** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.52 (m, 1H), 7.34 (m, 1H), 7.20 (m, 3H), 7.10 (m, 3H), 7.00 (m, 2H), 5.39 (d, J = 15.8 Hz, 1H), 5.04 (d, J = 15.9 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 3.82 (d, J = 10.5 Hz, 1H), 3.55 (s, 2H), 3.27 (s, 3H). MS (ESI) $[M+H]^+$: 433. Calcd. for $C_{25}H_{21}FN_2O_4$ $[M+H]^+$: 433.1564; Found: 433.1564.

2-(3-(1-(3,4-Difluorobenzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-4-methoxyphenyl)acetic acid (7)



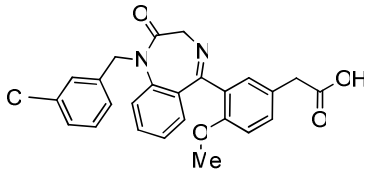
Compound **7** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.53 (m, 1H), 7.34 (m, 3H), 7.16 (m, 3H), 7.00 (m, 2H), 5.36 (d, J = 15.8 Hz, 1H), 5.06 (d, J = 15.9 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 3.84 (d, J = 10.5 Hz, 1H), 3.57 (s, 2H), 3.33 (s, 3H). MS (ESI) $[M+H]^+$: 451. Calcd. for $C_{25}H_{20}F_2N_2O_4$ $[M+H]^+$: 451.1469; Found: 451.1475.

2-(3-(1-(4-Chlorobenzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-4-methoxyphenyl)acetic acid (8)



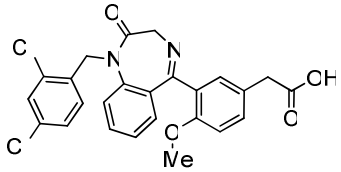
Compound **8** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.52 (m, 1H), 7.35-7.10 (m, 7H), 7.01 (m, 2H), 5.38 (d, J = 15.8 Hz, 1H), 5.06 (d, J = 15.9 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 3.83 (d, J = 10.5 Hz, 1H), 3.56 (s, 2H), 3.26 (s, 3H). MS (ESI) $[M+H]^+$: 449. Calcd. for $C_{25}H_{21}ClN_2O_4$ $[M+H]^+$: 449.1268; Found: 449.1267.

2-(3-(1-(3-Chlorobenzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-4-methoxyphenyl)acetic acid (9)



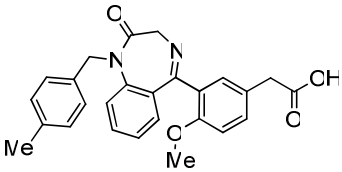
Compound **9** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.53 (m, 1H), 7.37-7.13 (m, 7H), 7.01 (m, 2H), 5.38 (d, J = 15.8 Hz, 1H), 5.08 (d, J = 15.9 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 3.88 (d, J = 10.5 Hz, 1H), 3.56 (s, 2H), 3.26 (s, 3H). MS (ESI) $[M+H]^+$: 449. Calcd. for $C_{25}H_{21}ClN_2O_4$ $[M+H]^+$: 449.1268; Found: 449.1269.

2-(3-(1-(2,4-Dichlorobenzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-4-methoxyphenyl)acetic acid (10)



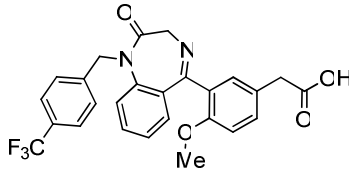
Compound **10** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.62-7.53 (m, 2H), 7.38-7.27 (m, 4H), 7.15 (m, 1H), 7.02 (m, 2H), 5.40 (d, J = 15.8 Hz, 1H), 5.09 (d, J = 15.9 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 3.91 (d, J = 10.5 Hz, 1H), 3.57 (s, 2H), 3.28 (s, 3H). MS (ESI) $[M+H]^+$: 483. Calcd. for $C_{25}H_{20}Cl_2N_2O_4$ $[M+H]^+$: 483.0878; Found: 483.0878.

2-(3-(1-(4-Methylbenzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-4-methoxyphenyl)acetic acid (11)



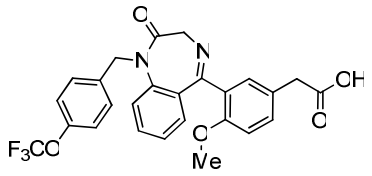
Compound **11** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.52 (m, 1H), 7.37 (m, 1H), 7.14-7.00 (m, 8H), 5.36 (d, J = 15.8 Hz, 1H), 5.01 (d, J = 15.9 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 3.86 (d, J = 10.5 Hz, 1H), 3.53 (s, 2H), 3.35 (s, 3H), 2.24 (s, 3H). MS (ESI) $[M+H]^+$: 429. Calcd. for $C_{26}H_{25}N_2O_4$ $[M+H]^+$: 429.1814; Found: 429.1816.

2-(4-Methoxy-3-(2-oxo-1-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)phenyl)acetic acid (12)



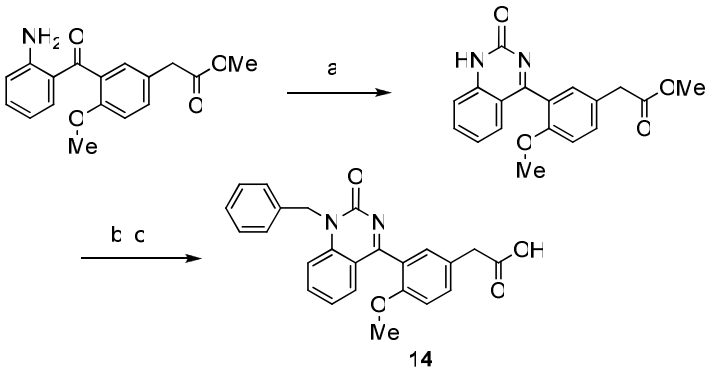
Compound **12** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.65 (m, 3H), 7.58 (m, 1H), 7.41 (m, 3H), 7.32 (m, 1H), 7.19 (m, 1H), 7.06 (m, 2H), 5.48 (d, J = 16.2 Hz, 1H), 5.19 (d, J = 15.9 Hz, 1H), 4.64 (d, J = 10.3 Hz, 1H), 3.96 (d, J = 10.5 Hz, 1H), 3.57 (s, 2H), 3.25 (s, 3H). MS (ESI) $[M+H]^+$: 483. Calcd. for $C_{26}H_{21}F_3N_2O_4$ $[M+H]^+$: 483.1532; Found: 483.1537.

2-(4-Methoxy-3-(2-oxo-1-(4-(trifluoromethoxy)benzyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)phenyl)acetic acid (13)



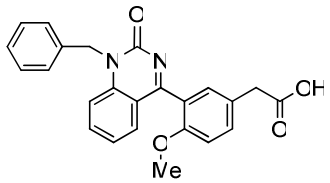
Compound **13** was synthesized as compound **5** above. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.3 (br s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.58 (m, 1H), 7.41 (m, 1H), 7.31-7.25 (m, 5H), 7.17 (m, 1H), 7.03 (m, 2H), 5.43 (d, J = 15.8 Hz, 1H), 5.12 (d, J = 15.9 Hz, 1H), 4.63 (d, J = 10.3 Hz, 1H), 3.93 (d, J = 10.5 Hz, 1H), 3.57 (s, 2H), 3.25 (s, 3H). MS (ESI) $[M+H]^+$: 499. Calcd. for $C_{26}H_{21}F_3N_2O_5$ $[M+H]^+$: 499.1481; Found: 499.1487.

Synthesis of compound **14**:



Methyl 2-(4-methoxy-3-(2-oxo-1,2-dihydroquinazolin-4-yl)phenyl)acetate Step a: KOCN (20 mg, 0.24 mmol) in water (0.1 mL) was added to a mixture of methyl 2-(3-(2-aminobenzoyl)-4-methoxyphenyl)acetate (60 mg, 0.2 mmol) in HOAc (0.5 mL). The mixture was stirred at room temperature overnight, neutralized with sodium bicarbonate solution and extracted with EtOAc twice. The combined organic layers were dried and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). Yield 40 mg (62%). MS (ESI) $[M+H]^+$: 325.

2-(3-(1-Benzyl-2-oxo-1,2-dihydroquinazolin-4-yl)-4-methoxyphenyl)acetic acid (14)



Step b: Lithium hexamethyldisilazane (0.16 mL, 0.16 mmol, 1 M in THF) was added to methyl 2-(4-methoxy-3-(2-oxo-1,2-dihydroquinazolin-4-yl)phenyl)acetate (40 mg, 0.12 mmol) in DMF (0.2 mL) and THF (1.5 mL) at ambient temperature. Then NaI (27 mg, 0.18 mmol) and benzyl bromide (0.019 mL, 0.16 mmol) were added. The mixture was stirred at ambient temperature for 16 h. The mixture was treated with water and extracted with EtOAc twice. The combined organic layers were dried and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). (see also *J. Org. Chem.*, **1995**, 60, 1590) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.40 (m, 8H), 7.18 (t, 1H), 7.06 (d, 1H), 5.62 (dd, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.70 (s, 2H). MS (ESI) $[M+H]^+$: 415.

Step c: The product obtained above was dissolved in THF/MeOH/water (2:2:1, 2mL) and treated with 10 N NaOH (0.1 mL). The mixture was stirred at ambient temperature for 3 h, acidified to pH3, and extracted with EtOAc twice. The combined organic layers were dried and concentrated. The crude product was purified by silica flash column (eluted with EtOAc/Hexanes). The yield was 10 mg (21%) over two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.40 (m, 8H), 7.18 (t, 1H), 7.07 (d, 1H), 5.62 (dd, 2H), 3.78 (s, 3H), 3.70 (s, 2H). MS (ESI) $[M+H]^+$: 401. Calcd. for $C_{24}H_{20}N_2O_4$ $[M+H]^+$: 401.1501; Found: 401.1502.