Supporting Information

Discovery of a Novel Series of CRTH2 (DP2) Receptor Antagonists Devoid of Carboxylic Acids.

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General:

The HPLC data provided were obtained as follows:

Column Waters XbridgeTM C8 50 mm x 4.6 mm at a flow of 2 mL/min; 8 min gradient from 0.1 % TFA in H2O to 0.07 % TFA in CH3CN.

The MS data provided were obtained using a LC/MS Waters ZMD (ESI)

The NMR data were obtained on a Bruker DPX-300MHz.

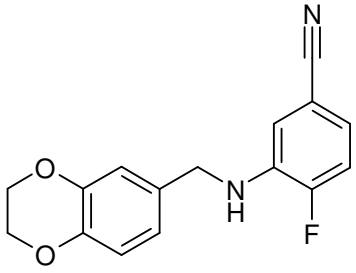
Preparative HPLC purifications were performed with a mass directed autopurification Fractionlynx from Waters equipped with a Sunfire Prep C18 OBD column 19x100 mm 5 μm, unless otherwise reported. All HPLC purifications were performed with a gradient of ACN/H_2O or ACN/H_2O/HCOOH (0.1%).

The microwave chemistry was performed on a single mode microwave reactor Emrys™ Optimiser from Personal Chemistry

cLogD values were calculated using ACD/PhysChem Suite, version 12.01, .

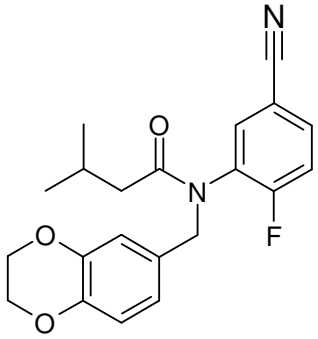
Typical procedures for the synthesis of the products 20-67:

3-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amino]-4-fluorobenzonitrile



A suspension of 1,4-benzodioxan-6-carboxaldehyde (1.03 g; 6.27 mmol) and 3-amino-4-fluorobenzonitrile (997 mg; 7.32 mmol) in toluene (100 ml) was treated with *p*-toluenesulphonic acid monohydrate (10 mg; 0.06 mmol). A Dean-Stark trap was added and the suspension heated at reflux during 20 h, after which the reaction solution was cooled and concentrated to give a yellow solid. This was dissolved in MeOH (100 ml) and DCM (300 ml). The solution was cooled to -10 °C then treated with three portions of $NaBH_4$ (441 mg; 11.7 mmol each, 20 minutes apart). After stirring at room temperature for 3 h, the solution was concentrated then dissolved in DCM and washed with aqueous HCl (1 N). The layers were separated and the organic layer dried on $MgSO_4$ and concentrated to give the Title compound (1.88 g, 90%) as an orange oil, which was used without further purification. ^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.27-7.16 (m, 1H), 7.02-6.93 (m, 2H), 6.90-6.68 (m, 4H), 4.25 (d, *J*= 6.3 Hz, 2H), 4.20 (s, 4H). HPLC (Condition A): Rt 4.04 min (HPLC purity 89.2%).

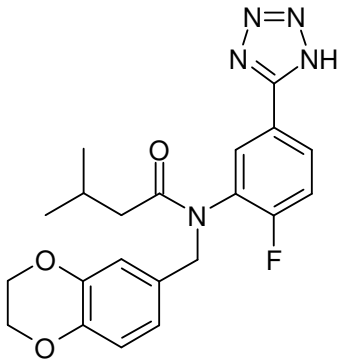
N-(5-cyano-2-fluorophenyl)-*N*-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-3-methylbutanamide



A solution of 3-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amino]-4-fluorobenzonitrile (392 mg; 1.38 mmol) and *N*-methyl morpholine (NMM; 0.60 ml) in DMF (5 ml) was treated with isovaleryl chloride (0.60 ml; 4.9 mmol). The reaction solution was heated at 50°C for 2 h then

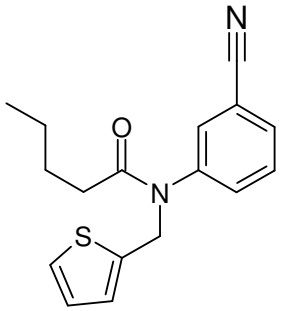
cooled and the solvent removed under vacuum. The residue was dissolved in DCM and washed with an aqueous solution (1 N) of HCl then with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried with $MgSO_4$ then concentrated to give a residue, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc, to give the Title compound (338 mg, 67%) as a yellow solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.01-7.73 (m, 2H), 7.56 (t, *J*= 9.1 Hz, 1H), 6.83-6.51 (m, 3H), 4.98-4.56 (m, 2H), 4.18 (s, 4H), 2.17-1.75 (m, 2H), 1.03-0.66 (m, 7H). MS (ESI^+): 369.2. HPLC (Condition A): Rt 4.32 min (HPLC purity 93.1%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[2-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-3-methylbutanamide (41)



A solution of *N*-(5-cyano-2-fluorophenyl)-*N*-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-3-methylbutanamide (338 mg; 0.92 mmol) and trimethylsilyl azide (0.30 ml; 2.29 mmol) in toluene (20 ml) was treated with dibutyltin oxide (12 mg; 0.05 mmol). The solution was heated at reflux for 8 h then cooled and the solvent removed under vacuum. The residue was dissolved in DCM then washed with an aqueous solution (1 N) of HCl. The organic layer was dried on $MgSO_4$, concentratedunder vacuum and the residue purified by Preparative HPLC to give the Title compound (244 mg, 65%) as a white solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.11-7.94 (m, 1H), 7.92-7.84 (m, 1H), 7.59 (t, *J*= 9.2 Hz, 1H), 6.82-6.56 (m, 3H), 4.82 (d, 1H), 4.66 (d, 1H), 4.17 (s, 4H), 2.16-1.83 (m, 3H), 0.87-0.69 (m, 6H). MS (ESI^-): 410.2. HPLC (Condition A): Rt 3.75 min (HPLC purity 98.9%).

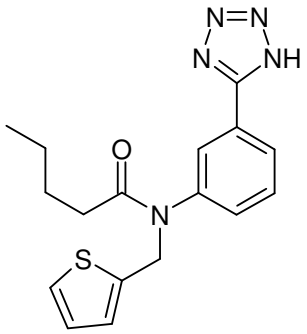
***N*-(3-cyanophenyl)-*N*-(2-thienylmethyl)pentanamide**



A solution of 3-[(2-thienylmethyl)amino]benzonitrile (527.00 mg; 2.46 mmol) and NMM (0.50 ml) in DMF (2 ml) was treated with valeryl chloride (0.50 ml; 4.2 mmol). The reaction solution was heated at 50°C for 16 h then cooled and the solvent removed under vacuum. The residue was dissolved in DCM and washed with an aqueous solution (1 N) of HCl then with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried with $MgSO_4$ then concentrated to give a residue, which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc, to give the Title compound (520 mg, 71%) as a yellow oil.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.80 (d, *J*= 7.7 Hz, 1H), 7.74 (t, *J*= 1.8 Hz, 1H), 7.59 (t, *J*= 7.9 Hz, 1H), 7.50-7.44 (m, 1H), 7.42 (dd, *J*= 5.1, 1.3 Hz, 1H), 6.89 (dd, *J*= 5.1, *J*= 3.4 Hz, 1H), 6.84-6.79 (m, 1H), 5.02 (s, 2H), 2.14-1.95 (m, 2H), 1.45 (quintet, *J*= 7.4 Hz, 2H), 1.18 (sextet, *J*= 7.4 Hz, 2H), 0.76 (t, 3H). MS (ESI^+): 299.0. HPLC (Condition A): Rt 3.93 min (HPLC purity 99.4%).

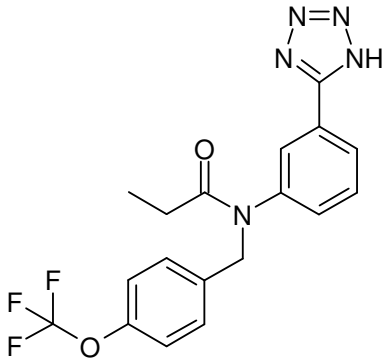
***N*-[3-(1*H*-tetrazol-5-yl)phenyl]-*N*-(2-thienylmethyl)pentanamide**



A suspension of *N*-(3-cyanophenyl)-*N*-(2-thienylmethyl)pentanamide (520 mg; 1.74 mmol), copper (I) oxide (7 mg; 0.05 mmol) in DMF (3 ml) and MeOH (0.3 ml) was placed in a sealed vial and treated with trimethylsily azide (0.50 ml; 3.82 mmol). After stirring for 10 minutes at RT, the mixture was heated at 80 °C for 16. The solution was concentrated uder vacuum, then diluted with EtOAc and washed with an aqueous solution (1 N) of HCl. After extraction with

an aqueous solution (0.1 N) of NaOH (3 times), the combined aqueous phases were acidified with aqueous HCl (1 N) until pH 2 and extracted with EtOAc. The organic phase was dried on $MgSO_4$ and concentrated to give the Title compound (385 mg, 65%) as a white solid.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.00 (d, *J*= 7.8 Hz, 1H), 7.83 (s, 1H), 7.64 (t, *J*= 7.8 Hz, 1H), 7.42 (dd, *J*= 5.1, *J*= 1.3 Hz, 1H), 7.39-7.32 (m, 1H), 6.89 (dd, *J*= 5.1, *J*= 1.3 Hz, 1H), 6.85-6.80 (m, 1H), 5.04 (s, 2H), 2.20-1.94 (m, 2H), 1.47 (q, *J*= 7.4 Hz, 2H), 1.17 (sextet, *J*= 7.3 Hz, 2H), 0.75 (t, *J*= 7.3 Hz, 3H). MS (ESI⁻): 340.1. HPLC (Condition A): Rt 3.61 min (HPLC purity 99.8%).

_N_-[3-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(trifluoromethoxy)benzyl]propanamide



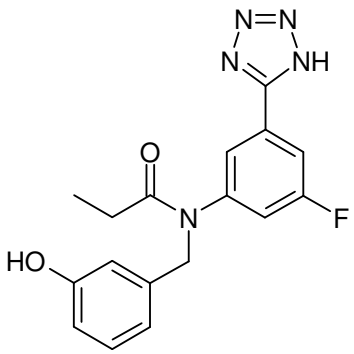
Step 1: N-(3-cyanophenyl)-N-[4-(trifluoromethoxy)benzyl]propanamide
A cooled (0 °C) solution of *N*-(3-cyanophenyl)propanamide (200 mg; 1.15 mmol) in DMF (5 ml) was treated with NaH (60% dispersion in mineral oil; 60 mg; 1.15 mmol), followed after 10 min by treatment of 4-(trifluoromethoxy)benzyl bromide (230 µl; 1.44 mmol). The reaction was stirred at 0 °C for 2 h, then iPrOH was added to quench the reaction. The solution was diluted with EtOAc and washed four times with brine. The organic phase was dried on $MgSO_4$ and concentrated under vacuum, to give a residue which was purified by flash column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc, to give the Title compound (348 mg, 87%) as a colourless oil.
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.61 (m, 1H), 7.55 (m, 1H), 7.36-7.33 (m, 2H), 7.09 (d, *J*= 8.8, 2H), 7.05 (d, *J*= 8.8, 2H), 4.70 (s, 2H), 1.88 (m, 2H), 0.73 (t, *J*= 7.3 Hz, 3H). MS (ESI⁻): 348.9. HPLC (Condition A): Rt 4.01 min (HPLC purity 99.7%).

Step 2: N-[3-(1H-tetrazol-5-yl)phenyl]-N-[4-(trifluoromethoxy)benzyl]propanamide
A suspension of *N*-(3-cyanophenyl)-*N*-[4-(trifluoromethoxy)benzyl]propanamide (348 mg; 1.00 mmol), copper (I) oxide (7 mg; 0.05 mmol) in DMF (2.7 ml) and MeOH (0.3 ml) was placed in a sealed vial and treated with trimethylsily azide (170 µl; 1.30 mmol). After stirring

for 10 minutes at RT, the mixture was heated at 80 °C for 16. The solution was concentrated uder vacuum, then diluted with EtOAc and washed with an aqueous solution (1 N) of HCl. After extraction with an aqueous solution (0.1 N) of NaOH (3 times), the combined aqueous phases were acidified with aqueous HCl (1 N) until pH 2 and extracted with EtOAc. The organic phase was dried on $MgSO_4$ and concentrated to give the Title compound (254 mg, 65%) as a white solid.

^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.91 (d, *J*= 7.7 Hz, 1H), 7.82 (t, *J*= 1.8 Hz, 1H), 7.56 (t, *J*= 7.9 Hz, 1H), 7.47 (ddd, *J*= 7.9, *J*= 1.8, *J*= 1.0 Hz, 1H), 7.28 (d, *J*= 8.8, 2H), 7.23 (d, *J*= 8.8, 2H), 4.89 (s, 2H), 2.09 (m, 2H), 0.92 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 390.1. HPLC (Condition A): Rt 3.21 min (HPLC purity 99.8%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(3-hydroxybenzyl)propanamide (55)



Step 1: N-(3-cyano-5-fluorophenyl)-N-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]propanamide

A solution of *N*-(3-cyano-5-fluorophenyl)-*N*-(3-iodobenzyl)propanamide (Intermediate 30 ; 304 mg; 0.74 mmol), bis(pinacolato)diboron (415 mg; 1.63 mmol) in DMSO (4 mL) was treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (50 mg; 0.07 mmol) and potassium acetate (273 mg; 2.78 mmol) and heated in a microwave reactor at 120 °C for 30 min. The resulting mixture was cooled to RT, diluted with EtOAc and washed with brine. The collected organics were dried and concentrated under reduced pressure to give a residue which was by column chromatography (silica), eluting with cyclohexane containing increasing amounts of EtOAc, to give the title compound as a clear oil (143 mg, 47%).

^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 7.88-7.82 (m, 1H), 7.70 (t, *J* = 1.4 Hz, 1H), 7.64 (dt, *J* = 9.9, 2.2 Hz, 1H), 7.59-7.54 (m, 1H), 7.50 (s, 1H), 7.37-7.33 (m, 2H), 4.98 (s, 2H), 2.30-2.16 (m, 2H), 1.31 (s, 12H), 1.00 (t, *J* = 7.3 Hz, 3H). HPLC (Condition A): Rt 4.80 min (HPLC purity 75.2%).

Step 2: N-(3-cyano-5-fluorophenyl)-N-(3-hydroxybenzyl)propanamide

A solution of *N*-(3-cyano-5-fluorophenyl)-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]propanamide (143 mg; 0.35 mmol) and MeOH (20 ml) was treated with a 33% aqueous solution of H_2O_2 (10.00 ml). The mixture was stirred for 1 h then carefully poured into a $Na_2S_2O_3$ (sat) solution. The solution was extracted with EtOAc (3 times), dried and concentrated under reduced pressure to give a clear oil, which was used without further purification.

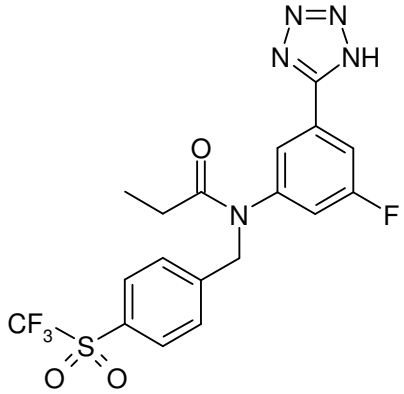
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 7.33 (d, *J* = 7.2 Hz, 1H), 7.22-7.11 (m, 2H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.84-6.76 (m, 2H), 6.60 (d, *J* = 7.4 Hz, 1H), 4.83 (s, 2H), 2.22-2.08 (m, 2H), 1.13 (t, *J* = 7.4 Hz, 3H). HPLC (Condition A): Rt 3.26 min (HPLC purity 90.6%).

Step 3: N-[3-fluoro-5-(1H-tetrazol-5-yl)phenyl]-N-(3-hydroxybenzyl)propanamide

Following the general method (using copper (I) oxide), starting from *N*-(3-cyano-5-fluorophenyl)-*N*-(3-hydroxybenzyl)propanamide, the title compound was obtained as a white solid after purification by preparative HPLC.

^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 9.38 (s, 1H), 7.83-7.64 (m, 2H), 7.33 (d, *J* = 9.7 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.68-6.58 (m, 3H), 4.87 (m, 2H), 2.33-2.14 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H). MS (ESI$^+$): 342.1. HPLC (Condition A): Rt 2.83 min (HPLC purity 95.2%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-{4-[(trifluoromethyl)sulfonyl]benzyl}propanamide (54)



Step 1: N-(3-cyano-5-fluorophenyl)-N-{4-[(trifluoromethyl)sulfonyl]benzyl}propanamide

A cooled solution (-15 °C) of *N*-(3-cyano-5-fluorophenyl)-*N*-{4-[(trifluoromethyl)thio]benzyl}propanamide (100 mg; 0.26 mmol) in DCM (10 ml) was treated with 3-chloroperbenzoic acid (130 mg; 0.53 mmol). The reaction suspension was allowed to warm to RT and stirred for 16 h, then treated with a further portion of 3-chloroperbenzoic

acid (230 mg; 1.33 mmol) and with DCM (10 ml). After 72 h the reaction mixture was poured into an aqueous (1 N) solution of NaOH and the phases separated. The organic layer was dried and concentrated under reduced pressure to give the title compound as a clear oil in 71% yield.

^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 8.08 (d, *J* = 8.3 Hz, 2H), 7.91-7.85 (m, 1H), 7.83 (s, 1H), 7.78 (dt, *J* = 9.8, 2.2 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 5.11 (s, 2H), 2.33 (q, *J* = 7.3 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). HPLC (Condition A): Rt 4.70 min (HPLC purity 94.4%).

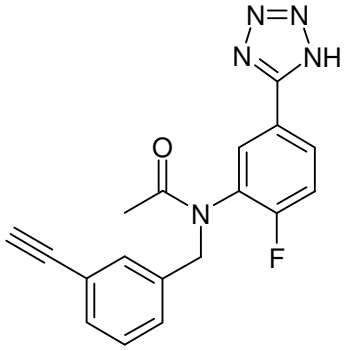
Step 2: N-[3-fluoro-5-(1H-tetrazol-5-yl)phenyl]-N-{4-[(trifluoromethyl)sulfonyl]benzyl}propanamide

Following the general method (using copper (I) oxide), starting from *N*-(3-cyano-5-fluorophenyl)-*N*-{4-[(trifluoromethyl)sulfonyl]benzyl}propanamide, the title compound was obtained as a white solid in 68% yield.

^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 8.09 (d, *J* = 8.4 Hz, 2H), 7.86-7.78 (m, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.61 (dt, *J* = 9.8, 2.0 Hz, 1H), 5.14 (s, 2H), 2.28 (q, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). MS (ESI$^-$): 456.2. HPLC (Condition A): Rt 4.21 min (HPLC purity 94.8%).

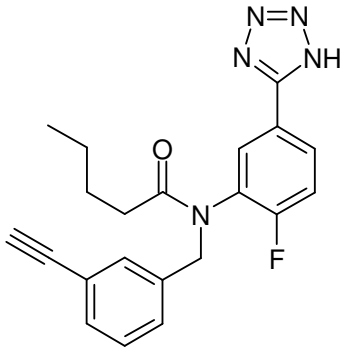
Characterization of final products

_N_-(3-ethynylbenzyl)-_N_-[2-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]acetamide (12)



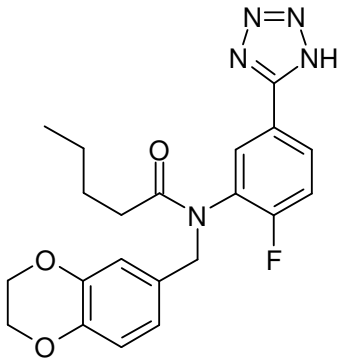
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.12-7.87 (m, 2H), 7.57 (t, *J*= 9.2 Hz, 1H), 7.39-7.20 (m, 4H), 5.07-4.74 (m, 2H), 4.11 (s, 1H), 1.87 (s, 3H). MS (ESΙ): 334.2. HPLC (Condition A): Rt 3.28 min (HPLC purity 99.6%).

_N_-(3-ethynylbenzyl)-_N_-[2-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]pentanamide (14)



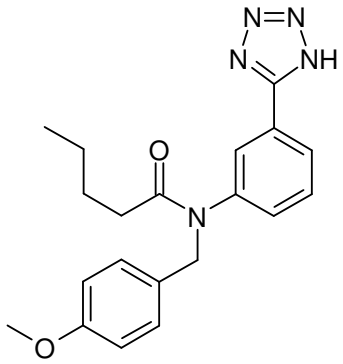
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.10-7.91 (m, 2H), 7.57 (t, 1H), 7.39-7.17 (m, 4H), 4.85 (s, 2H), 4.12 (s, 1H), 2.20-1.94 (m, 2H), 1.47 (quintet, *J*= 7.6 Hz, 2H), 1.17 (sextet, *J*= 7.4 Hz, 2H), 0.75 (t, *J*= 7.3 Hz, 3H). MS (ESΙ): 376.3. HPLC (Condition A): Rt 4.13 min (HPLC purity 95.2%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[2-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]pentanamide (15)



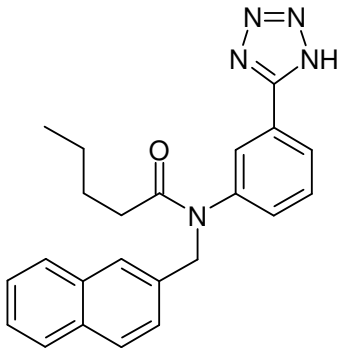
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.10-8.00 (m, 1H), 7.98-7.86 (m, 1H), 7.59 (t, *J*= 9.2 Hz, 1H), 6.82-6.56 (m, 3H), 4.81 (d, *J*= 14.6 Hz, 1H), 4.67 (d, *J*= 14.6 Hz, 1H), 4.17 (s, 4H), 2.17-1.92 (m, 2H), 1.55-1.40 (m, 2H), 1.26-1.08 (m, 2H), 0.75 (t, *J*= 7.3 Hz, 3H). MS (ESI⁻): 410.2. HPLC (Condition A): Rt 3.79 min (HPLC purity 99.9%).

_N_-(4-methoxybenzyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]pentanamide (16)



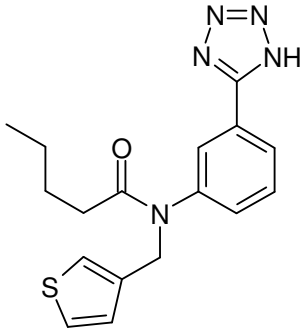
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.96 (d, *J*= 7.8 Hz, 1H), 7.82 (s, 1H), 7.59 (t, *J*= 7.9 Hz, 1H), 7.31 (d, *J*= 8.0 Hz, 1H), 7.10 (d, *J*= 8.6 Hz, 2H), 6.83 (d, *J*= 8.6 Hz, 2H), 4.85 (s, 2H), 3.10 (3, 3H), 2.22-2.01 (m, 2H), 1.48 (quintet, *J*= 7.5 Hz, 2H), 1.28-1.08 (m, 2H), 0.76 (t, 3H). MS (ESI⁻): 364.1. HPLC (Condition A): Rt 3.72 min (HPLC purity 99.2%).

_N_-(2-naphthylmethyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]pentanamide (17)



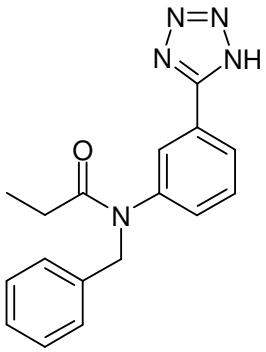
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.98-7.77 (m, 5H), 7.66 (s, 1H), 7.57 (t, *J*= 7.9 Hz, 1H), 7.50-7.36 (m, 4H), 5.10 (s, 2H), 2.17 (br s, 2H), 1.52 (quintet, *J*= 7.6 Hz, 2H), 1.20 (m, 2H), 0.76 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 384.2. HPLC (Condition A): Rt 4.18 min (HPLC purity 96.7%).

_N_-[3-(1_H_-tetrazol-5-yl)phenyl]-_N_-(3-thienylmethyl)pentanamide (19)



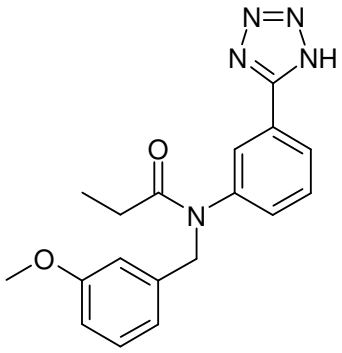
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.98 (d, *J*= 7.7 Hz, 1H), 7.84 (s, 1H), 7.62 (t, *J*= 7.9 Hz, 1H), 7.47 (dd, *J*= 4.9, 3.0 Hz, 1H), 7.41-7.34 (m, 1H), 7.23 (s, 1H), 6.97 (dd, *J*= 4.9, *J*= 1.2 Hz, 1H), 4.89 (s, 2H), 2.21-1.98 (m, 2H), 1.48 (quintet, *J*= 7.4 Hz, 2H), 1.17 (hex, *J*= 7.3 Hz, 2H), 0.75 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 340.2. HPLC (Condition A): Rt 3.67 min (HPLC purity 97.7%).

_N_-benzyl-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (20)



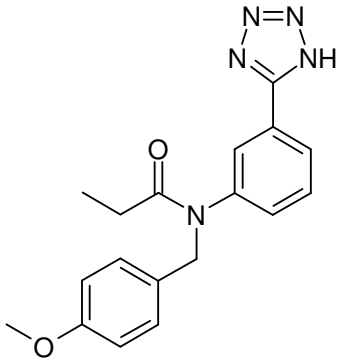
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm]. 1H NMR (DMSO-d6) δ 7.95 (d, *J*= 7.7 Hz, 1H), 7.86 (s, 1H), 7.60 (t, *J*= 7.9 Hz, 1H), 7.43-7.36 (m, 1H), 7.33-7.16 (m, 5H), 4.93 (s, 2H), 2.25-2.06 (m, 2H), 0.98 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 306.2. HPLC (Condition A): Rt 3.10 min (HPLC purity 99.9%).

_N_-(3-methoxybenzyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (21)



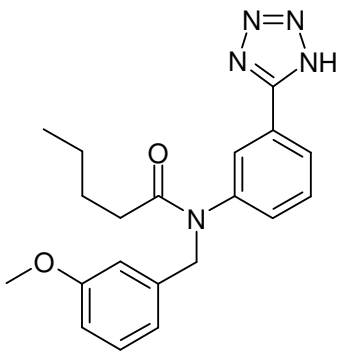
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.95 (d, *J*= 7.9 Hz, 1H), 7.88 (s, 1H), 7.60 (t, *J*= 7.9 Hz, 1H), 7.41 (t, *J*= 7.9 Hz, 1H), 7.20 (t, *J*= 7.9 Hz, 1H), 6.80-6.75 (m, 3H), 4.91 (s, 2H), 3.68 (s, 3H), 2.16 (m, 2H), 0.98 (t, *J*= 7.3 Hz, 3H). MS (ESI⁻): 336.2. HPLC (Condition A): Rt 3.18 min (HPLC purity 98.1%).

_N_-(4-methoxybenzyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (22)



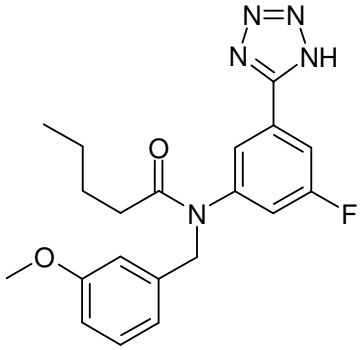
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.95 (d, *J*= 7.9 Hz, 1H), 7.83 (s, 1H), 7.59 (t, *J*= 7.9 Hz, 1H), 7.33 (d, *J*= 7.9 Hz, 1H), 7.10 (d, *J*= 8.6 Hz, 2H), 6.83 (d, *J*= 8.6 Hz, 2H), 4.85 (s, 2H), 3.69 (s, 3H), 2.10 (m, 2H), 0.96 (t, *J*= 7.4 Hz, 3H). MS (ESI⁻): 336.1. HPLC (Condition A): Rt 3.11 min (HPLC purity 95.9%).

_N_-(3-methoxybenzyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]pentanamide (23)



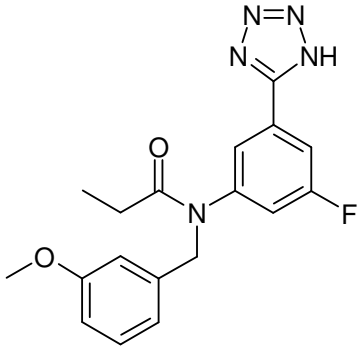
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.96 (d, *J*= 7.8 Hz, 1H), 7.86 (s, 1H), 7.61 (t, *J*= 7.9 Hz, 1H), 7.44-7.33 (m, 1H), 7.20 (t, *J*= 7.8 Hz, 1H), 6.84-6.70 (m, 3H), 4.90 (s, 2H), 3.69 (s, 3H), 2.24-2.04 (br s, 2H), 1.49 (quintet, *J*= 7.5 Hz, 2H), 1.19 (hex, *J*= 7.5 Hz, 2H), 0.76 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 364.1. HPLC (Condition A): Rt 3.34 min (HPLC purity 96.6%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(3-methoxybenzyl)pentanamide (24)



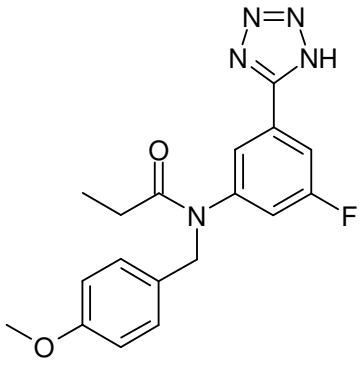
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.83-7.70 (m, 2H), 7.44 (dt, *J*= 9.8, *J*= 2.1 Hz, 1H), 7.21 (t, *J*= 7.8 Hz, 1H), 6.83-6.73 (m, 3H), 4.92 (s, 2H), 3.69 (s, 3H), 2.31-2.15 (m, 2H), 1.50 (quintet, *J*= 7.4 Hz, 2H), 1.21 (sextet, *J*= 7.4 Hz, 2H), 0.78 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 382.3. HPLC (Condition A): Rt 3.98 min (HPLC purity 98.7%). m.p. = 118-120 °C.

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(3-methoxybenzyl)propanamide (25)



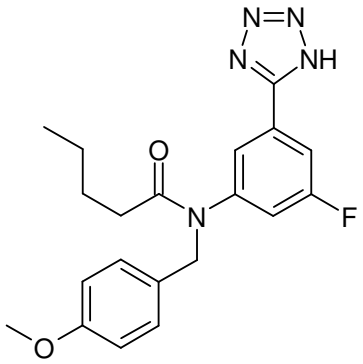
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.82-7.71 (m, 2H), 7.45 (dt, *J*= 9.8, *J*= 2.1 Hz, 1H), 7.21 (t, *J*= 7.8 Hz, 1H), 6.85-6.72 (m, 3H), 4.92 (s, 2H), 3.69 (s, 3H), 2.33-2.14 (m, 2H), 0.99 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 354.3. HPLC (Condition A): Rt 3.42 min (HPLC purity 97.9%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(4-methoxybenzyl)propanamide (26)



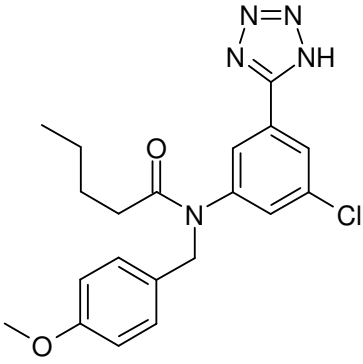
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.77 (d, *J*= 8.9 Hz, 1H), 7.69 (s, 1H), 7.39 (d t, *J*= 9.7, *J*= 2.0 Hz, 1H), 7.12 (d, *J*= 8.6 Hz, 2H), 6.83 (d, *J*= 8.6 Hz, 2H), 4.88 (s, 2H), 3.69 (s, 3H), 2.30-2.10 (m, 2H), 0.98 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 354.3. HPLC (Condition A): Rt 3.39 min (HPLC purity 97.9%). m.p. = 158-160 °C.

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(4-methoxybenzyl)pentanamide (27)



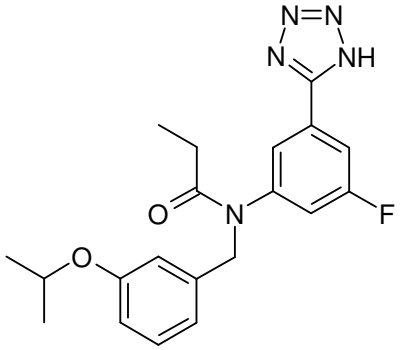
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.77 (d, *J*= 8.9 Hz, 1H), 7.67 (s, 1H), 7.42-7.34 (m, 1H), 7.11 (d, *J*= 8.6 Hz, 2H), 6.83 (d, *J*= 8.6 Hz, 2H), 4.87 (s, 2H), 3.69 (s, 3H), 2.27-2.11 (m, 2H), 1.49 (quintet, *J*= 7.5 Hz, 2H), 1.20 (sextet, *J*= 7.2 Hz, 2H), 0.77 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 382.4. HPLC (Condition A): Rt 3.97 min (HPLC purity 94.6%). m.p. = 122-125 °C.

_N_-[3-chloro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(4-methoxybenzyl)pentanamide (28)



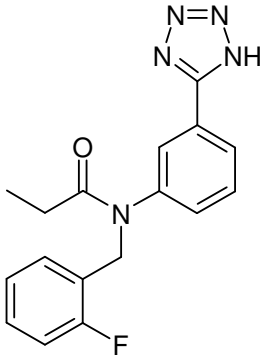
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.98 (m, 1H), 7.76 (m; 1H), 7.54 (t, *J*= 1.9; 1H), 7.10 (d, *J*= 8.6; 2H), 6.83 (d, *J*= 8.6; 2H), 4.86 (s, 2H), 2.16 (m, 2H), 1.48 (quintet, *J*= 7.3 Hz, 2H), 1.18 (sextet, *J*= 7.3 Hz, 2H), 0.76 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 398.2. HPLC (Condition A): Rt 4.31 min (HPLC purity 93.6%).

***N*-[3-fluoro-5-(1*H*-tetrazol-5-yl)phenyl]-*N*-(3-isopropoxybenzyl)propanamide (29)**



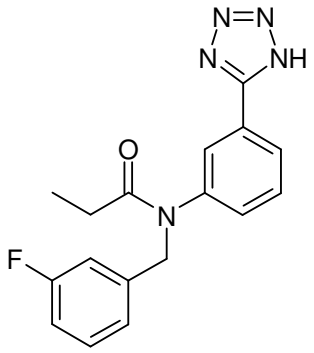
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 7.82-7.69 (m, 2H), 7.44 (d t, *J* = 9.8, 2.1 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.81-6.69 (m, 3H), 4.91 (s, 2H), 4.51 (sep, *J* = 6.0 Hz, 1H), 2.32-2.14 (m, 2H), 1.17 (d, *J* = 6.0 Hz, 6H), 0.99 (t, *J* = 7.4 Hz, 3H). MS (ESI$^+$): 384.2. HPLC (Condition A): Rt 3.92 min (HPLC purity 95.5%).

***N*-(2-fluorobenzyl)-*N*-[3-(1*H*-tetrazol-5-yl)phenyl]propanamide (30)**



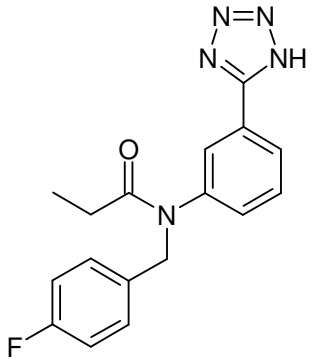
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.98 (d, *J*= 7.9 Hz, 1H), 7.90-7.85 (m, 1H), 7.60 (t, *J*= 7.9 Hz, 1H), 7.48-7.41 (m, 1H), 7.40-7.22 (m, 2H), 7.19-7.04 (m, 2H), 4.98 (s, 2H), 2.26-2.02 (m, 2H), 0.97 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 324.2. HPLC (Condition A): Rt 3.12 min (HPLC purity 99.7%).

***N*-(3-fluorobenzyl)-*N*-[3-(1*H*-tetrazol-5-yl)phenyl]propanamide (31)**



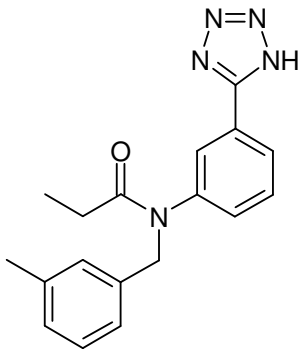
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.97 (d, *J*= 7.9 Hz, 1H), 7.91-7.86 (m, 1H), 7.62 (t, *J*= 7.9 Hz, 1H), 7.48-7.40 (m, 1H), 7.39-7.28 (m, 1H), 7.12-6.99 (m, 3H), 4.94 (s, 2H), 2.27-2.04 (m, 2H), 0.98 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 324.2. HPLC (Condition A): Rt 3.21 min (HPLC purity 99.0%).

_N_-(4-fluorobenzyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (32)



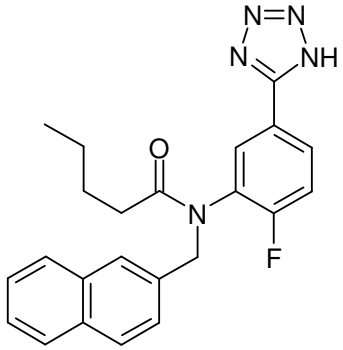
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.96 (d, *J*= 7.9 Hz, 1H), 7.84 (s, 1H), 7.60 (t, *J*= 7.9 Hz, 1H), 7.42-7.33 (m, 1H), 7.29-7.19 (m, 2H), 7.16-7.05 (m, 2H), 4.91 (s, 2H), 2.22-2.05 (m, 2H), 0.97 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 324.2. HPLC (Condition A): Rt 3.22 min (HPLC purity 97.5%).

_N_-(3-methylbenzyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (33)



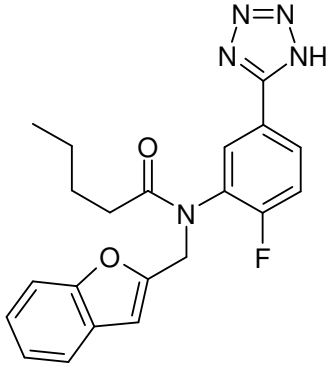
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 7.95 (d, *J* = 7.6 Hz, 1H), 7.87 (s, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.06-6.93 (m, 3H), 4.89 (s, 2H), 2.24 (s, 3H), 2.21-2.06 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). MS (ESI$^+$): 322.1. HPLC (Condition A): Rt 3.37 min (HPLC purity 98.2%).

***N*-[2-fluoro-5-(1*H*-tetrazol-5-yl)phenyl]-*N*-(2-naphthylmethyl)pentanamide (34)**



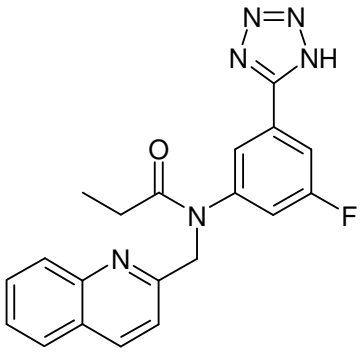
^{1}H NMR (300MHz, DMSO-d$_6$) δ [ppm] 8.07-7.97 (m, 2H), 7.92-7.75 (m, 3H), 7.67 (s, 1H), 7.60-7.36 (m, 4H), 5.05 (s, 2H), 2.24-1.99 (m, 2H), 1.58-1.45 (m, 2H), 1.28-1.13 (m, 2H), 0.77 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 402.0. HPLC (Condition A): Rt 4.53 min (HPLC purity 99.1%).

***N*-(1-benzofuran-2-ylmethyl)-*N*-[2-fluoro-5-(1*H*-tetrazol-5-yl)phenyl]pentanamide (35)**



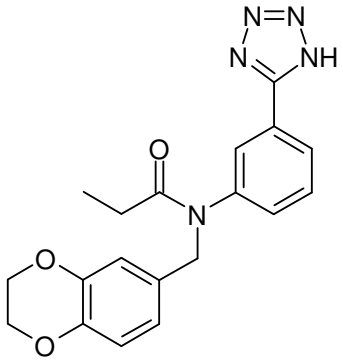
^{1}H NMR (300MHz, DMSO-d$_6$) δ [ppm] 8.15-7.92 (m, 2H), 7.66-7.45 (m, 3H), 7.32-7.13 (m, 2H), 6.70 (s, 1H), 5.20-4.95 (m, 2H), 2.22-1.94 (m, 2H), 1.67-1.42 (m, 2H), 1.41-1.09 (m, 2H), 0.98-0.68 (m, 3H). MS (ESI$^-$): 392.2. HPLC (Condition A): Rt 4.15 min (HPLC purity 98.5%).

***N*-[3-fluoro-5-(1*H*-tetrazol-5-yl)phenyl]-*N*-(quinolin-2-ylmethyl)propanamide (36)**



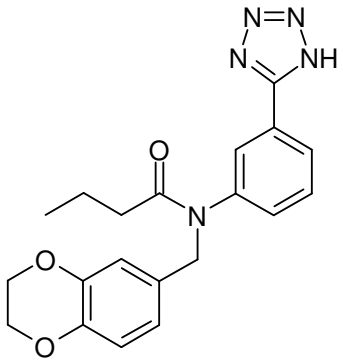
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 8.39 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), 8.02-7.96 (m, 2H), 7.83-7.73 (m, 2H), 7.69 (d, *J* = 9.6 Hz, 1H), 7.65-7.57 (m, 2H), 5.26 (s, 2H), 2.42-2.24 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H). MS (ESI$^+$): 377.4. HPLC (Condition A): Rt 2.38 min (HPLC purity 99.8%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (37)



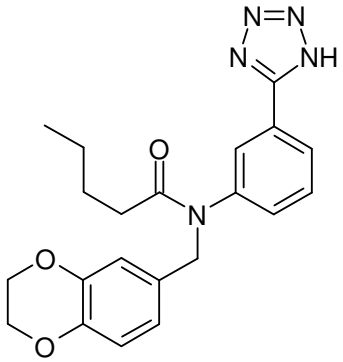
^{1}H NMR (300MHz, DMSO-d$_6$) δ [ppm] 7.96 (d, *J*= 7.6 Hz, 1H), 7.84 (s, 1H), 7.61 (t, *J*= 7.9 Hz, 1H), 7.41-7.34 (m, 1H), 6.74 (d, *J*= 8.2 Hz, 1H), 6.69 (d, *J*= 1.9 Hz, 1H), 6.62 (dd, *J*= 8.2, *J*= 1.9 Hz, 1H), 4.80 (s, 2H), 4.18 (s, 4H), 2.20-2.03 (m, 2H), 0.96 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 364.2. HPLC (Condition A): Rt 2.55 min (HPLC purity 96.9%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]butanamide (38)



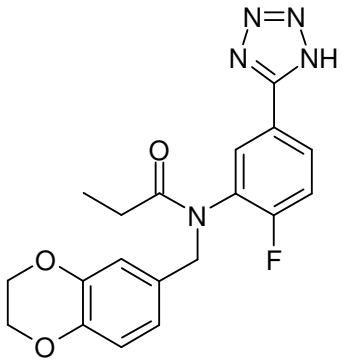
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.97 (d, *J*= 7.8 Hz, 1H), 7.83 (s, 1H), 7.61 (t, *J*= 7.8 Hz, 1H), 7.39-7.31 (m, 1H), 6.74 (d, *J*= 8.2 Hz, 1H), 6.68 (d, *J*= 1.9 Hz, 1H), 6.62 (dd, *J*= 8.2, *J*= 1.9 Hz, 1H), 4.80 (s, 2H), 4.18 (s, 4H), 2.17-2.00 (m, 2H), 1.51 (sextet, *J*= 7.3 Hz, 2H), 0.78 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 378.2. HPLC (Condition A): Rt 3.29 min (HPLC purity 99.5%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]pentanamide (39)



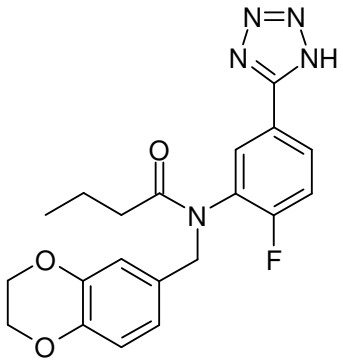
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.96 (d, *J*= 7.7 Hz, 1H), 7.80 (s, 1H), 7.61 (t, *J*= 7.9 Hz, 1H), 7.34 (d, *J*= 8.4 Hz, 1H), 6.73 (d, 1H), 6.69-6.58 (m, 2H), 4.78 (s, 2H), 4.16 (s, 4H), 2.09 (br s, 2H), 1.46 (quintet, *J*= 7.5 Hz, 2H), 1.16 (q, *J*= 7.1 Hz, 2H), 0.74 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 392.2. HPLC (Condition A): Rt 3.60 min (HPLC purity 100.0%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[2-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]propanamide (40)



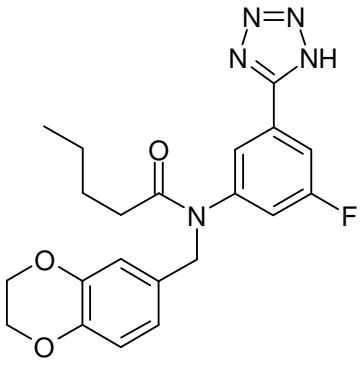
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.12-7.86 (m, 2H), 7.59 (t, *J*= 9.3 Hz, 1H), 6.84-6.55 (m, 3H), 4.80 (d, *J*= 14.4 Hz, 1H), 4.68 (d, *J*= 14.4 Hz, 1H), 4.17 (s, 4H), 2.23-1.89 (m, 2H), 0.96 (t, *J*= 7.3 Hz, 3H). MS (ESI⁻): 382.2. HPLC (Condition A): Rt 3.21 min (HPLC purity 100.0%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[2-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]butanamide (42)



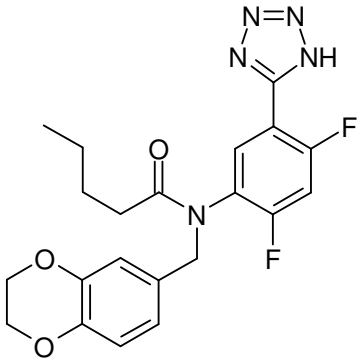
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.11-8.00 (m, 1H), 7.96-7.87 (m, 1H), 7.59 (t, *J*= 9.2 Hz, 1H), 6.80-6.57 (m, 3H), 4.81 (d, *J*= 14.6 Hz, 1H), 4.67 (d, *J*= 14.6 Hz, 1H), 4.17 (s, 4H), 2.17-1.90 (m, 2H), 1.59-1.43 (m, 2H), 0.78 (t, *J*= 7.4 Hz, 3H). MS (ESI⁻): 396.1. HPLC (Condition A): Rt 3.50 min (HPLC purity 99.3%).

_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]pentanamide (43)



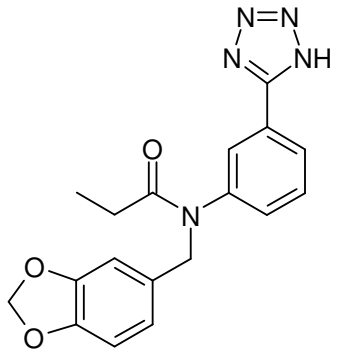
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.78 (d, *J*= 9.8 Hz, 1H), 7.67 (s, 1H), 7.38 (dt, *J*= 9.8, *J*= 2.0 Hz, 1H), 6.75 (d, *J*= 8.2 Hz, 1H), 6.70 (d, *J*= 2.0 Hz, 1H), 6.63 (dd, *J*= 8.2, 2.0 Hz, 1H), 4.81 (s, 2H), 4.18 (s, 4H), 2.26-2.11 (m, 2H), 1.49 (quintet, *J*= 7.8 Hz, 2H), 1.19 (hex, *J*= 7.4 Hz, 2H), 0.77 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 410.2. HPLC (Condition A): Rt 3.87 min (HPLC purity 93.6%).

_N_-[2,4-difluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)pentanamide (44)



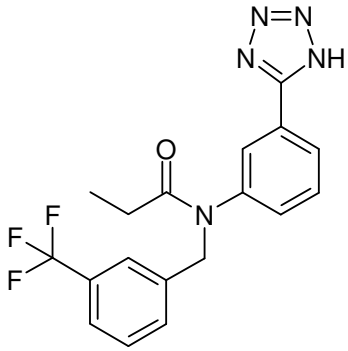
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.92 (t, *J*= 8.0 Hz, 1H), 7.72 (t, *J*= 10.2 Hz, 1H), 6.83-6.57 (m, 3H), 4.76 (d, *J*= 14.6 Hz, 1H), 4.66 (d, *J*= 14.6 Hz, 1H), 4.18 (s, 4H), 2.18-1.89 (m, 2H), 1.47 (quintet, *J*= 7.4 Hz, 2H), 1.18 (sextet, *J*= 7.5 Hz, 2H), 0.77 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 428.1. HPLC (Condition A): Rt 3.88 min (HPLC purity 99.6%).

_N_-(1,3-benzodioxol-5-ylmethyl)-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (45)



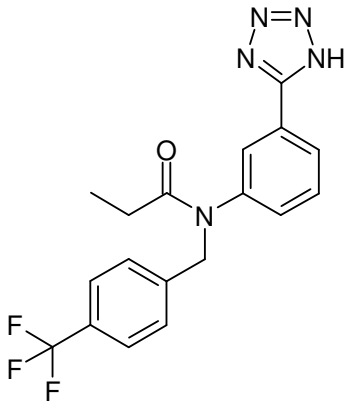
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.97 (d, *J*= 7.7 Hz, 1H), 7.84 (s, 1H), 7.61 (t, *J*= 7.9 Hz, 1H), 7.42-7.34 (m, 1H), 6.82-6.75 (m, 2H), 6.62 (dd, *J*= 8.0, *J*= 1.4 Hz, 1H), 5.97 (s, 2H), 4.83 (s, 2H), 2.21-2.04 (m, 2H), 0.97 (t, 3H). MS (ESI$^-$): 350.2. HPLC (Condition A): Rt 3.09 min (HPLC purity 100.0%).

_N_-[3-(1_H_-tetrazol-5-yl)phenyl]-_N_-[3-(trifluoromethyl)benzyl]propanamide (46)



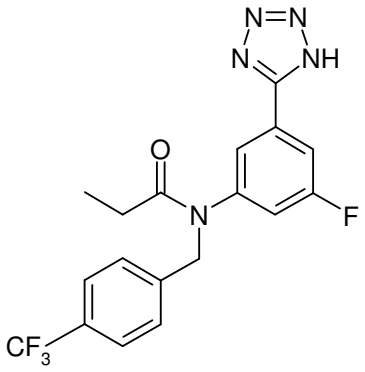
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.97 (d, *J*= 7.8 Hz, 1H), 7.87 (m, 1H), 7.64-7.53 (m, 5H), 7.42 (ddd, *J*= 7.8 Hz, *J*= 2.0 Hz, *J*= 1.0 Hz, 1H), 5.02 (s, 2H), 2.16 (m, 2H), 0.98 (t, *J*= 7.4 Hz, 3H). MS (ESI$^-$): 374.1. HPLC (Condition A): Rt 4.31 min (HPLC purity 99.7%).

_N_-[3-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(trifluoromethyl)benzyl]propanamide (47)



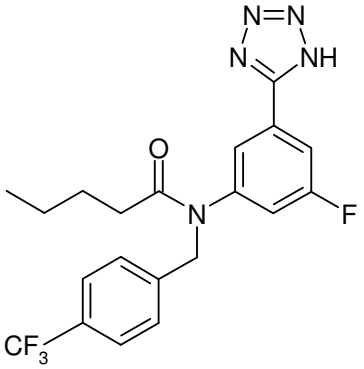
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] δ 7.97 (d, *J*= 7.8 Hz, 1H), 7.91 (t, *J*= 1.6 Hz, 1H), 7.68-7.59 (m, 3H), 7.47-7.43 (m, 3H), 5.02 (s, 2H), 2.17 (m, 2H), 0.98 (t, *J*= 7.4 Hz, 3H). MS (ESI⁻): 374.3. HPLC (Condition A): Rt 3.76 min (HPLC purity 99.6%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(trifluoromethyl)benzyl]propanamide (48)



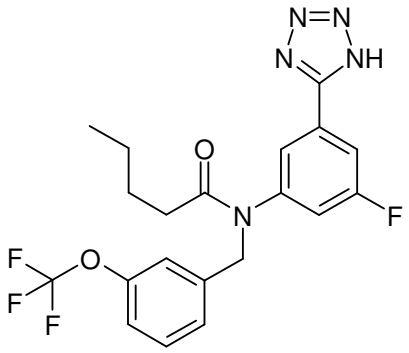
^{1}H NMR (300 MHz, DMSO-d6) δ 7.86 – 7.72 (m, 2H), 7.67 (d, *J* = 8.1, 2H), 7.59 – 7.50 (m, 1H), 7.47 (d, *J* = 8.0, 2H), 5.04 (s, 2H), 3.45 (brs, *J* = 9.9, 0H), 2.36 – 2.13 (m, 2H), 0.99 (t, *J* = 7.4, 3H). MS (ESI⁻): 392.0. HPLC (Condition A): Rt 4.21 min (HPLC purity 98.5%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(trifluoromethyl)benzyl]pentanamide (49)



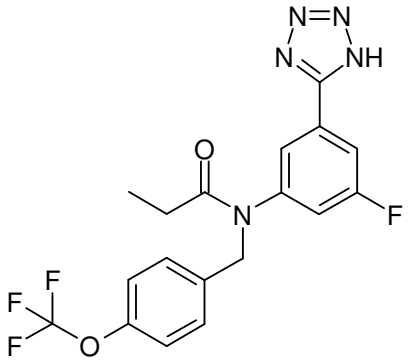
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 7.82-7.74 (m, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.54-7.43 (m, 3H), 5.04 (s, 2H), 2.30-2.17 (m, 2H), 1.50 (quin, *J* = 7.4 Hz, 2H), 1.20 (sex, *J* = 7.4 Hz, 2H), 0.78 (t, *J* = 7.3 Hz, 3H). MS (ESI⁻): 420.4. HPLC (Condition A): Rt 4.53 min (HPLC purity 96.2%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[3-(trifluoromethoxy)benzyl]pentanamide (50)



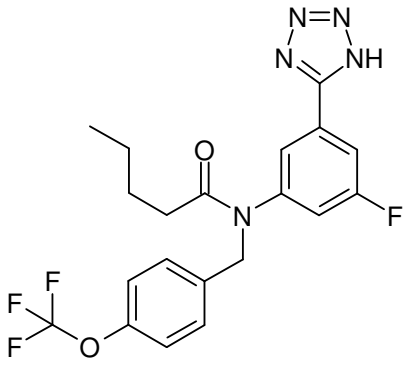
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.78 (d, *J*= 9.2 Hz, 1H), 7.70 (s, 1H), 7.47-7.41 (m, 2H), 7.29-7.18 (m, 3H), 4.99 (s, 2H), 2.22 (m, 2H), 1.50 (quintet, *J*= 7.5 Hz, 2H), 1.20 (sextet, *J*= 7.5 Hz, 2H), 0.77 (t, *J*= 7.5 Hz, 3H). MS (ESI$^-$): 436.2. HPLC (Condition A): Rt 4.57 min (HPLC purity 97.5%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(trifluoromethoxy)benzyl]propanamide (51)



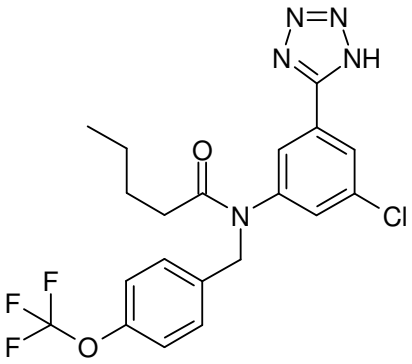
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.83-7.75 (m, 1H), 7.73 (s, 1H), 7.49 (dt, *J*= 9.8, *J*= 2.1 Hz, 1H), 7.36 (d, *J*= 8.5 Hz, 2H), 7.29 (d, *J*= 8.5 Hz, 2H), 4.97 (s, 2H), 2.29-2.15 (m, 2H), 0.98 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 408.1. HPLC (Condition A): Rt 4.12 min (HPLC purity 98.0%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(trifluoromethoxy)benzyl]pentanamide (52)



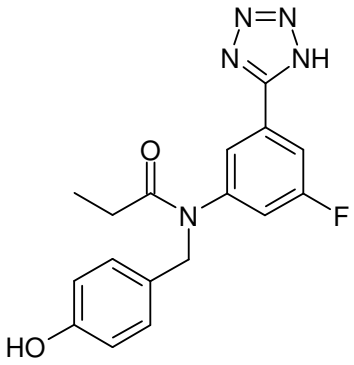
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 7.79 (d, *J*= 8.9 Hz, 1H), 7.71 (s, 1H), 7.47 (dt, *J*= 9.7, *J*= 2.1 Hz, 1H), 7.35 (d, *J*= 8.5 Hz, 2H), 7.29 (d, *J*= 8.5 Hz, 2H), 4.97 (s, 2H), 2.27-2.15 (m, 2H), 1.50 (quin, *J*= 7.5 Hz, 2H), 1.20 (septet, *J*= 7.5 Hz, 2H), 0.77 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 436.2. HPLC (Condition A): Rt 4.61 min (HPLC purity 99.0%).

_N_-[3-chloro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(trifluoromethoxy)benzyl]pentanamide (53)



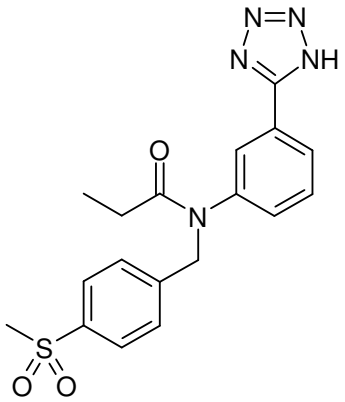
^{1}H NMR (300MHz, DMSO-d_6) δ [ppm] 8.00 (s, 1H), 7.81 (s, 1H), 7.63 (t, *J*= 1.9 Hz, 1H), 7.39-7.26 (m, 4H), 4.96 (s, 2H), 2.29-2.11 (s, 2H), 1.49 (quintet, *J*= 7.3 Hz, 2H), 1.20 (sextet, *J*= 7.3 Hz, 2H), 0.77 (t, *J*= 7.3 Hz, 3H). MS (ESI$^-$): 452.1. HPLC (Condition A): Rt 4.79 min (HPLC purity 96.7%). m.p. = 177-180 °C.

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-(4-hydroxybenzyl)propanamide (56)



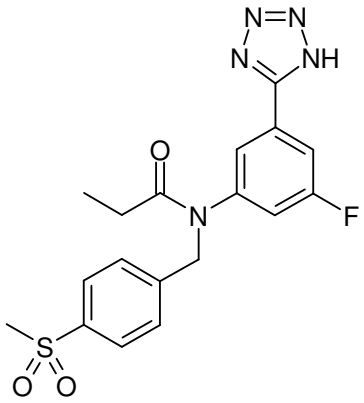
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 9.34 (s, 1H), 7.82-7.74 (m, 1H), 7.68 (s, 1H), 7.38 (dt, *J* = 9.8, 2.1 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 4.84 (s, 2H), 2.29-2.12 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). MS (ESI$^+$): 342.1. HPLC (Condition A): Rt 2.69 min (HPLC purity 97.8%).

_N_-[4-(methylsulfonyl)benzyl]-_N_-[3-(1_H_-tetrazol-5-yl)phenyl]propanamide (57)



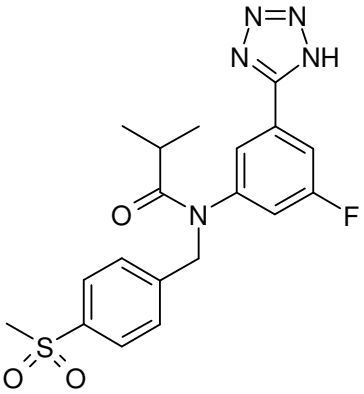
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 7.96 (d, *J* = 7.8 Hz, 1H), 7.92 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.51-7.46 (m, 3H), 5.03 (s, 2H), 3.17 (s, 3H), 2.17 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). MS (ESI$^+$): 386.3. HPLC (Condition A): Rt 2.53 min (HPLC purity 99.6%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(methylsulfonyl)benzyl]propanamide (58)



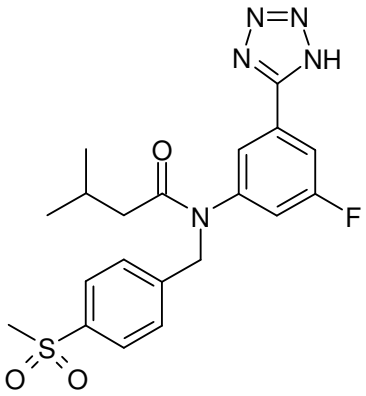
^{1}H NMR (300MHz, DMSO-d6) δ [ppm] 7.90 (d, *J* = 8.4 Hz, 2H), 7.86-7.80 (m, 2H), 7.64-7.53 (m, 3H), 5.10 (s, 2H), 3.22 (s, 3H), 2.37-2.23 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). MS (ESI$^+$): 404.3. HPLC (Condition A): Rt 2.77 min (HPLC purity 99.0%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-2-methyl-_N_-[4-(methylsulfonyl)benzyl]propanamide (59)



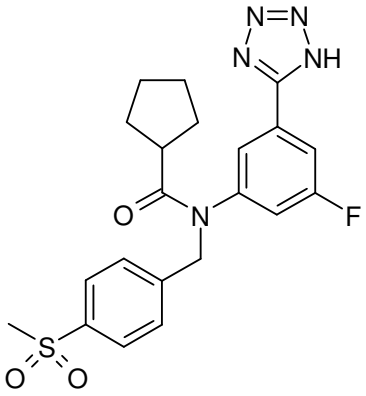
^{1}H NMR (300 MHz, DMSO-d6) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.73 (s, 1H), 7.56 – 7.45 (m, 3H), 5.02 (s, 2H), 3.18 (s, 3H), 2.71 – 2.53 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 6H). MS (ESI$^-$): 416.0. HPLC (Condition A): Rt 2.69 min (HPLC purity 91.5%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-3-methyl-_N_-[4-(methylsulfonyl)benzyl]butanamide (60)



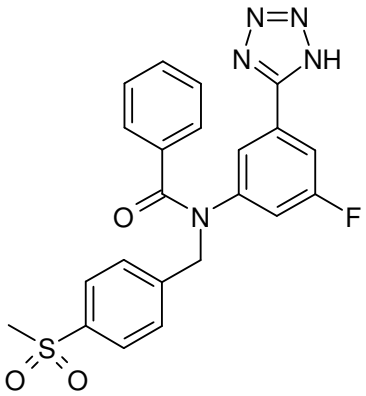
^{1}H NMR (300 MHz, DMSO-d6) δ 8.14 – 7.65 (m, 4H), 7.62 – 7.37 (m, 3H), 5.06 (brs, 2H), 3.18 (s, 3H), 2.22 – 1.92 (m, 3H), 0.93 – 0.72 (m, 6H). MS (ESI⁻): 430.0. HPLC (Condition A): Rt 3.37 min (HPLC purity 96.7%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(methylsulfonyl)benzyl]cyclopentanecarboxamide (61)



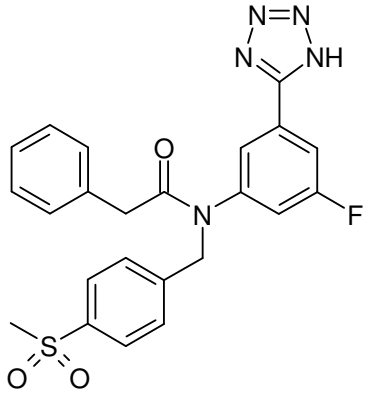
^{1}H NMR (300 MHz, DMSO-d6) δ 7.95 – 7.65 (m, 4H), 7.64 – 7.42 (m, 3H), 5.04 (brs, 2H), 3.20 (s, 3H), 2.78 (brs, 1H), 1.87 – 1.24 (m, 8H). MS (ESI⁻): 442.0. HPLC (Condition A): Rt 3.44 min (HPLC purity 86.9%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(methylsulfonyl)benzyl]benzamide (62)



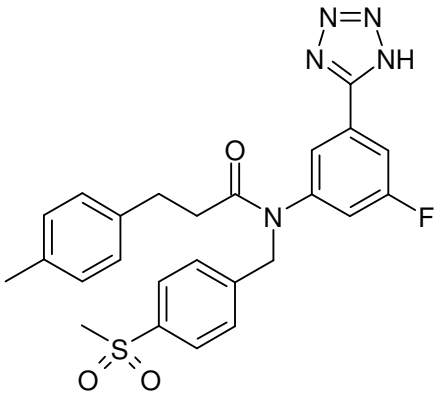
^{1}H NMR (300 MHz, DMSO-d6) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 7.31 – 7.11 (m, 4H), 5.20 (s, 2H), 3.09 (s, 3H). MS (ESI$^-$): 450.0. HPLC (Condition A): Rt 3.22 min (HPLC purity 89.1%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(methylsulfonyl)benzyl]-2-phenylacetamide (63)



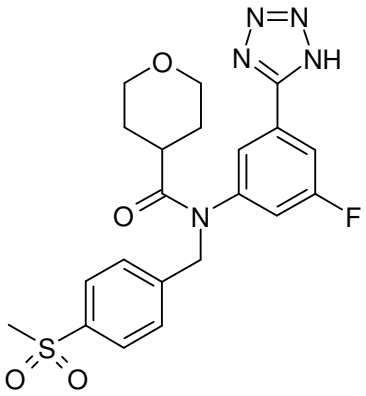
MS (ESI$^-$): 464.0. HPLC (Condition A): Rt 3.43 min (HPLC purity 95.3%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-3-(4-methylphenyl)-_N_-[4-(methylsulfonyl)benzyl]propanamide (64)



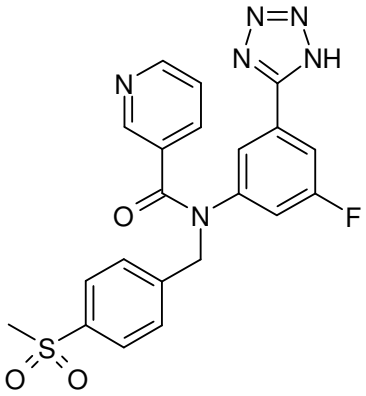
^{1}H NMR (300 MHz, DMSO-d6) δ 7.83 (d, *J* = 7.0 Hz, 3H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.31 – 7.16 (m, 1H), 7.07 – 6.88 (m, 5H), 5.02 (brs, 2H), 3.33 (brs, 2H), 3.19 (s, 3H), 2.87 – 2.73 (m, 2H), 2.23 (s, 3H). MS (ESI$^-$): 492.0. HPLC (Condition A): Rt 3.83 min (HPLC purity 93.0%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(methylsulfonyl)benzyl]tetrahydro-2_H_-pyran-4-carboxamide (65)



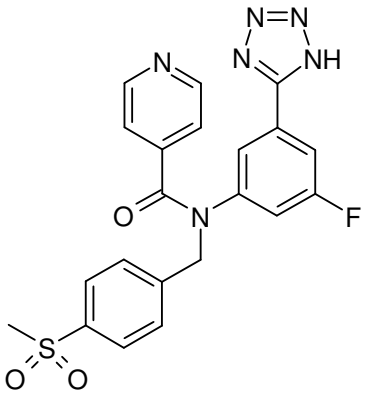
^{1}H NMR (300 MHz, DMSO-d6) δ 7.98 – 7.79 (m, 3H), 7.76 (brs, 1H), 7.57 (d, *J* = 10.1 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 5.03 (s, 2H), 3.78 (d, *J* = 11.0 Hz, 2H), 3.41 (s, 1H), 3.18 (s, 3H), 3.16 – 3.00 (m, 2H), 1.81 – 1.41 (m, 4H). MS (ESI⁻): 457.9. HPLC (Condition A): Rt 2.65 min (HPLC purity 99.3%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(methylsulfonyl)benzyl]nicotinamide (66)



^{1}H NMR (300 MHz, DMSO-d6) δ 8.56 (brd, *J* = 33.7 Hz, 2H), 7.96 – 7.79 (m, 3H), 7.78 – 7.54 (m, 4H), 7.43 (d, *J* = 10.0 Hz, 1H), 7.37 – 7.27 (m, 1H), 5.31 (s, 2H), 3.19 (s, 3H). MS (ESI⁻): 450.9, HPLC (Condition A): Rt 2.08 min (HPLC purity 96.6%).

_N_-[3-fluoro-5-(1_H_-tetrazol-5-yl)phenyl]-_N_-[4-(methylsulfonyl)benzyl]isonicotinamide (67)



^{1}H NMR (300 MHz, DMSO-d6) δ 8.54 (brs, 2H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.72 (brs, 1H), 7.69 – 7.56 (m, 3H), 7.50 – 7.33 (m, 3H), 5.29 (s, 2H), 3.19 (s, 3H). MS (ESI^{-}): 450.9. HPLC (Condition A): Rt 1.95 min (HPLC purity 97.3%).

Protocols for the in vitro and in vivo assays

Preparation of hCRTH$_2$-CHO expressing cell membranes

Adherent CHO cells expressing hCRTH2 (Euroscreen, Belgium) were cultured in 225 cm^2 cell culture flasks (Corning, USA) in 30ml of medium. After two rinses of phosphate buffered saline (PBS), cells were harvested in 10ml of PBS containing 1mM EDTA, centrifuged at 500 x g for 5 min at 4°C and frozen at –80°C. The pellet was re-suspended in 50 mM Tris-HCl, pH 7.4, 2mM EDTA, 250mM Sucrose, containing protease inhibitor cocktail tablets, (Complete EDTA-free, Roche, Germany) and incubated 30 min at 4°C. Cells were disrupted by nitrogen cavitation (Parr Instruments, USA) at 4°C (800 p.s.i. for 30 min), and centrifuged at 500 x g for 10min at 4°C. Pellet containing nuclei and cellular debris was discarded and supernatant was centrifuged 60 min at 4°C at 45000 x g. Membrane pellet was re-suspended in storage buffer (10mM HEPES/KOH pH 7.4, 1mM EDTA, 250mM sucrose, protease inhibitor cocktail tablets) using Dounce homogenization and frozen in liquid nitrogen, and stored at –80°C.

Radioligand binding assay

The compounds inhibit the binding of PGD_2 to its receptor CRTH2. The inhibitory activity can be investigated by a radioligand binding Scintillation Proximity Assay (SPA) (Sawyer et al., Br. J. Pharmocol 2002, 137, 1163-72). The SPA radioligand binding assay was performed at room temperature in binding buffer (10mM HEPES/KOH pH 7.4, 10mM MnCl2, with protease inhibitor cocktail tablets), containing 1.5nM [^{3}H]PGD2 (Perkin Elmer), 10-50µg/ml of hCRTH$_2$-CHO cell membrane protein and 2mg/ml of Wheat-germ agglutinin Scintillation Proximity Assay beads (RPNQ0001, GE-Healthcare) in a final volume of 100µl in 96 well plates (Corning, USA). Non-specific binding was determined in the presence of 10µM PGD_2 (Cayman, USA). Competing Compounds of Formula (I) were diluted in dimethylsulphoxide so that the total volume of dimethylsulfoxide was kept constant at 1% dimethylsulphoxide. Serial dilutions of 100µM to 100 pM were prepared and 10 µl each of the compounds of Formula (I) stock solutions were added to the binding assay reagents and incubated for 90 min with agitation at room temperature. Binding activity was determined by using a 1450 Micro-beta scintillation counter (Wallac, UK).

[^{35}S]GTPγS binding assay. The [^{35}S]GTPγS binding assay was performed at 30°C with gentle agitation in 96-well scintillating white polystyrene plates (Perkin Elmer, USA), in a final volume of 200µl, containing 2% of dimethylsulphoxide.

Briefly, 10µg of membrane expressing human CRTH2 were incubated in 20mM HEPES/KOH pH 7.4, 10mM $MgCl_2$, 10µg/ml Saponin, 3µM GDP, 150mM NaCl for 10 minutes, with various concentration of PGD_2. Non-specific binding was determined in the presence of 10µM of GTPγS. Antagonist activity of compounds was measured in presence of 80nM of PGD_2. 0.15nM of [^{35}S]GTPγS (reference) were subsequently added to each sample and after incubation of 30min, reactions were stopped by centrifugation at 700 x g, for 10 min. Supernatant was removed and [^{35}S]GTPγS binding was determined using a 1450 Micro-beta scintillation counter. Data were analysed using "Prism" (GraphPad Software, Inc. San Diego, USA).

PGD2-induced Eosinophil Cell Shape assay in Human Whole Blood

The test compounds were diluted in dimethylsulphoxide so that the total volume of dimethylsulfoxide was kept constant at 2% dimethylsulphoxide. Serial dilutions of 200 µM to 0.09 µM were prepared. Samples of 90 µl of human blood from healthy volunteers (Centre de Transfusion Sanguine de Genève) were pre-incubated in polypropylene Falcon tubes (BD 352063) for 20 minutes in a water bath at 37 °C with 10 µl of diluted compounds. For CRTH2 activation, 100 µl PGD_2 (Cayman 12010) at 20 nM was added (10 nM final) to each tube and cells were maintained at 37 °C. Cells treated with PBS were used as a negative control. After 10 minutes, cell activation was stopped with 120 µl Formaldehyde 10% (4% final, Fluka 41650) and cells were rested for 10 minutes at room temperature. Fixed cells were transferred into polypropylene tubes and then treated for 1 hour in a water bath at 37 °C with 2ml of Triton – Surfact-Amps X-100 (Pierce 28314) at 0.166% (0.13% Triton final). After several washes with PBS cells were analyzed by flow cytometry on a FACSCalibur.

Oxidative metabolism. Rat and human liver microsomes were used to screen the metabolic instability resulting from phase I oxidation. Microsomes (final concentration 0.5 mg/mL), 50 mM phosphate buffer pH 7.4, NADPH (final concentration 1.5 mM) and compound (final concentration 1 µM,) were added to the assay plate. The microsome suspension was added to initiate the reaction and the plate was incubated at 37°C.. The reaction was stopped by the addition of cold acetonitrile at the appropriate time points (time 0, 5, 15 and 45 minutes). The

samples were centrifuged at 4000 rpm for 30 minutes at 4 °C to precipitate the proteins. Samples were analyzed by LC-MS/MS. The *in vitro* intrinsic clearance was calculated from the rate of compound disappearance.

Cytochrome P450 inhibition. Seven human recombinant cytochrome P450 isoenzymes were tested (CYP 1A2, CYP 2C9, CYP 2C19, CYP2C8, CYP2B6, CYP 2D6 and CYP 3A4). The aim of this method is to determine the concentration of a compound required to obtain 50% inhibition of the recombinant human cytochrome P450. The assay is based on the Promega P450-Glo™ Screening System, which includes, a luminogenic substrate, an NADPH regeneration system and a Luciferin Detection Reagent.
Upon CYP450 activity, the substrate e.g. Luciferin-ME EGE for 2B6 assay is converted to luciferin EGE, which is converted to D-luciferin by the Luciferin Detection Reagent. The D-luciferin reacts in turn with the Luciferin Detection Reagent to produce light.
The CYP membranes are prepared from baculovirus-infected insect cells and contain human CYP450 and P450 reductase. In order not to be depleted in NADPH cofactor during the course of the reaction, the assay includes a NADPH Regeneration System.
Test compounds are pre-incubated for 15 min at room temperature with the CYP450 enzyme (and appropriate cofactors), in the absence of substrate. Then the enzymatic reaction is initiated by the addition of the substrate, followed by 30 min of incubation at 37°C.
As controls, BLANK and NEUTRAL values are tested on each plate. In the NEUTRAL control, DMSO is added in place of the test compound: it defines the maximum achievable substrate conversion, reflected by the strongest luminescence signal. In the BLANK control, a membrane fraction devoid of cytochrome P450 activity (control membranes prepared from wild type baculovirus-infected cells), substitutes the membranes from CYP450 expressing cells: consequently, no substrate conversion is observed. The amount of control membranes in BLANK controls is calculated to match the amount of membranes proteins brought by the CYP450 positive membranes in the rest of the assay plate. The measured signal in BLANK wells describes the background value. The percentage of inhibition is determined for each inhibitor concentration and the corresponding IC_{50} value is calculated by non-linear curve fitting. The IC_{50} value is determined in triplicate, using 10 different concentrations of test compound. As additional control, the IC_{50} value of one well-characterized CYP inhibitor (called reference control) is determined.

Caco-2 permeability. Caco-2 cells were obtained from Advancell (Barcelona, Spain). The cells were seeded onto 24-well polycarbonate filter membrane (Transwell inserts, surface area: 0.33 cm^2) and grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 1% L-glutamine. Permeability studies were performed with the monolayers cultured for 21 days. Prior to all experiments, the cell monolayer integrity was evaluated by trans epithelial electrical resistance (TEER), values greater than 1000 ohm·per well were used. The permeability studies were initiated by adding an appropriate volume of Hank's balanced salt solution buffer containing 1 µM test compound to either the apical (for apical to basolateral transport; A to B) or basolateral (for basolateral to apical transport; B to A) side of the monolayer. The monolayers were then placed in an incubator at 37 °C. At the end of the incubation time (2 hours) samples were taken from both the apical and basolateral compartments. The concentrations of test compound were analyzed by LC/MS-MS. Permeability coefficient (Papp, 10^{-6} cm/s) was calculated according to the following equation: $Papp = dA/(dt \cdot S \cdot C_0)$, where dA/dt is the flux of the test compound across the monolayer (nmol/s); S is the surface area of the cell monolayer (cm^2); and C_0 is the initial concentration (µM) in the donor compartment.

***In vivo* Pharmacokinetic Evaluation in Mouse.**

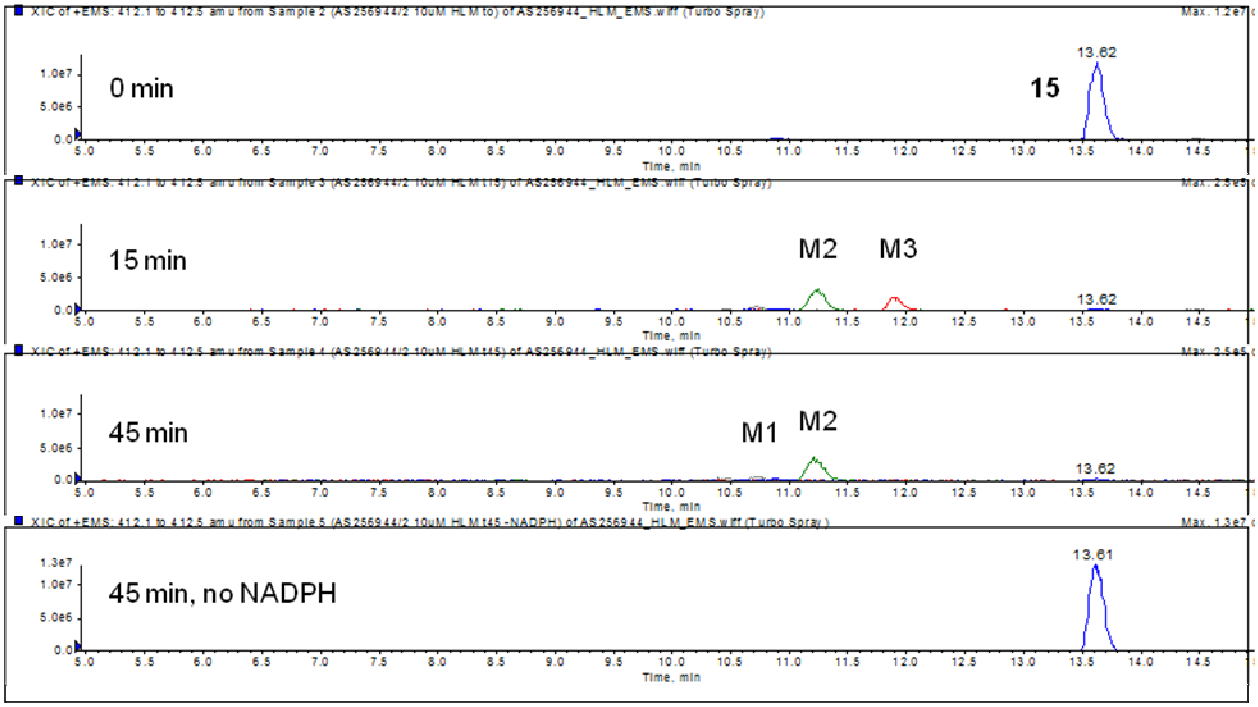
In order to study the pharmacokinetic (PK) profile of test compounds *in vivo*, C57BL/6 female mice were dosed intravenously or after oral gavage. Test compounds were dosed in solution at 1 mg/kg for i.v. route (10% ethanol, 10% N, N-dimethylacetamide, 30% propylene glycol, 50% water, v/v) and in suspension at 5 mg/kg (0.5% carboxymethylcellulose suspension, containing 0.25% Tween 20 in water) for oral gavage. The volume of administration was 2 mL/kg for i.v. dosing and 10 mL/kg for oral gavage. Blood samples (100 µL/time point) were collected at 0.083 (5 min), 0.25, 0.5, 1, 4, 7 and 24 hours post-dose for i.v. dosing, and at 0.5, 1, 4, 7 and 24 h for oral dosing, into heparin-Li+ containing tubes. Blood samples were collected from intracardiac puncture at sacrifice at each time point. Plasma samples were stored frozen (-20 °C to -70 °C) until analysis. For bioanalysis, samples were processed by protein precipitation (acetonitrile, formic acid 0.1%, addition of 3 volumes) after addition of one internal standard and analysed using a sensitive and selective LC/MS/MS method. An aliquot of the resulting supernatant was subject to LC/MS/MS analysis using a reverse phase column (Waters Xterra, C8, (3.5 µm particle size, 2.1 x 50 mm) and a short gradient (1 min) from (Solvent A) 85% water, 15% acetonitrile and 0.1% formic acid to (Solvent B) 90% acetonitrile, 10% water and 0.1% formic acid followed by isocratic

conditions of Solvent B for 3.5 min at 0.4 mL/min. Column effluent was monitored using a Sciex API 4000 triple quadrupole mass spectrometer with a Turbo V electrospray ion source. Unknown concentrations of test compounds were determined using a calibration curve ranging from 1 to 3000 ng/mL.

Metabolite identification experiment on compound **15**

Conditions: Substrate: 10 µM; Human Liver Microsomes: 1 mg/ml; NADPH: 1.5 mg/ml.

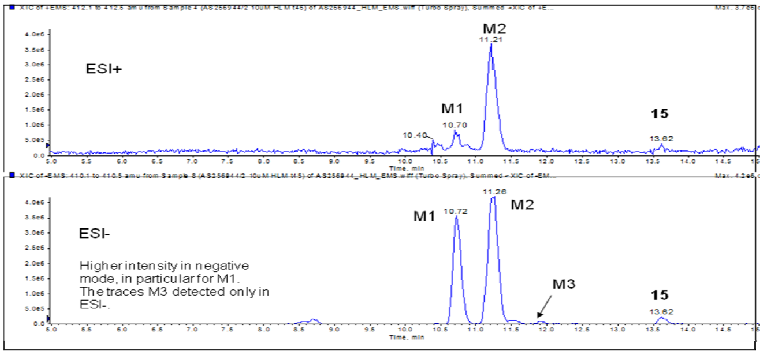
Chromatograms at different timepoints: 10 µM, HLM 1 mg/ml. Extracted ion chromatogram (XIC) for **15** (+412, blue), M3 (+428, red), M2 (+444, green) and M1 (+386, gray). From top to bottom: 0, 15 , 45 and 45 min without NADPH.



Metabolite profile at 45 min. 10 µM, HLM 1 mg/ml, 45 min with NADPH.

Top: sum of XIC for **15** (+412), M3 (+428), M2 (+444) and M1 (+386).

Bottom: sum of XIC for **15** (-410), M3 (-426), M2 (-442) and M1 (-384).



MS2 spectra of M1, M2, M3 and parent compound 15. Precursor +386 for M1, +444 for M2, +428 for M3 and +412 for **15**.

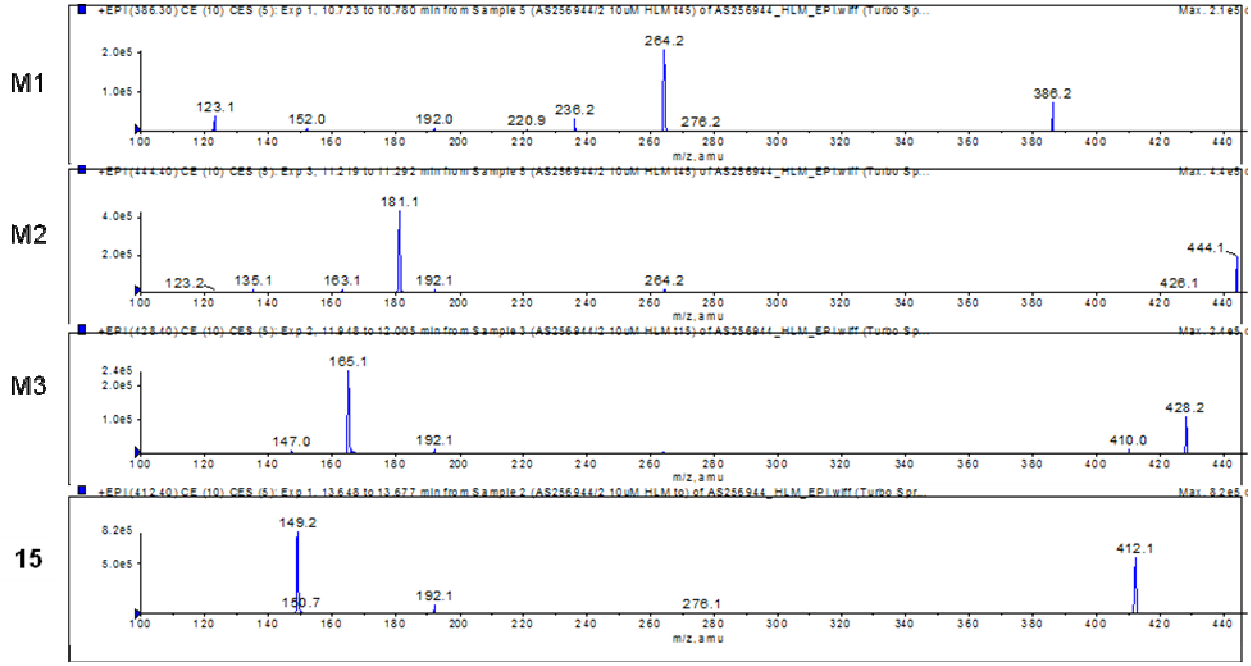
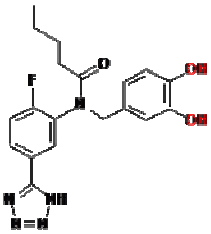
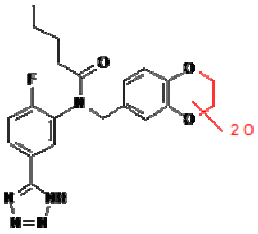


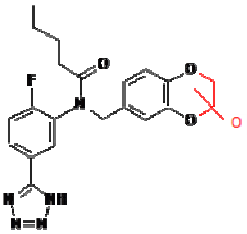
Table of metabolites for compound 15:



M1: 385 Da, RT 10.72 min
Major metabolite at 45 min



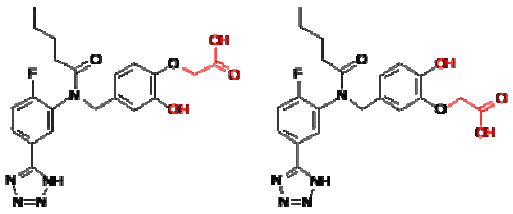
M2: 443 Da, RT 11.24 min
Major metabolite at 45 min



M3: 427 Da, RT 11.88 min
Detected mainly at 15 min.

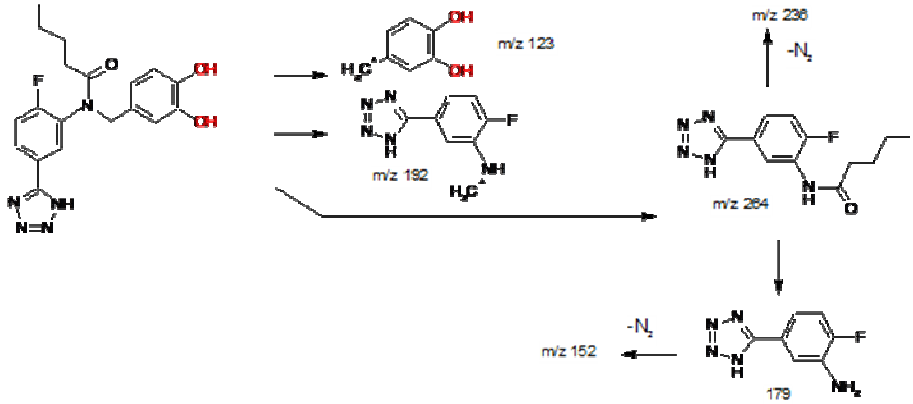
Only traces of M3 are detected after 45 min, suggesting that M3 is an intermediate which is further metabolized into M1 and M2.

Possible structures for M2:

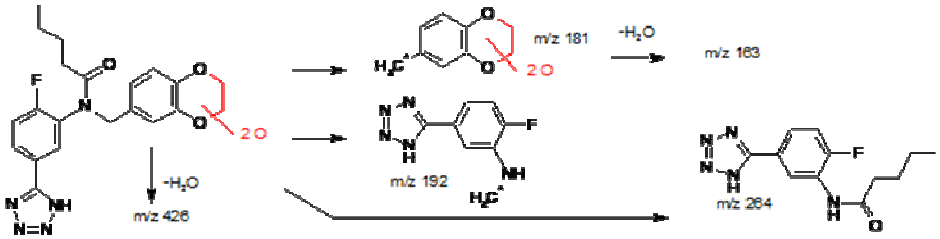


MS fragmentation patterns:

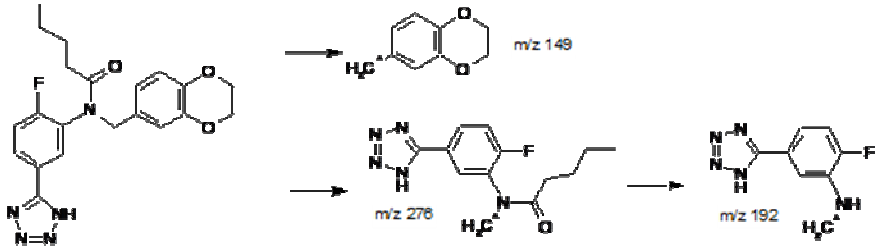
M1, 385 Da



M2, 443 Da



15, 411 Da



M3, 427 Da