Supporting Data

Discovery of Tetralones as Potent and Selective Inhibitors of Acyl-CoA: Diacylglycerol *O*-Acyltransferase 1

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Experimental Section

Fluorescence-based human DGAT1 assay (CPM assay). Recombinant human and rat DGAT1 and DGAT2 were expressed in Sf9 insect cells using a baculovirus expression system. Microsomal membranes were prepared from infected cells at GlaxoSmithKline and were used as a source of enzyme for the *in vitro* inhibition studies. The fluorescence-based assay indirectly measures triglycerol (TG) from diacylglycerol (DAG) using a fluorescent 7-diethylamino-3-(4-maleimidophenyl)-4-methylcoumarin (CPM) dye as a measure of DGAT1 enzyme inhibitory activity. Briefly, 1 μg/mL human DGAT1 microsomes were equilibrated with test compounds for 15 minutes. Substrate solution containing 50 μM C10-DAG and 3 μM C10-CoA was added and further incubated for 60 minutes at 22ºC in the dark. The reaction was stopped by the addition of a solution containing a potent DGAT1 inhibitor and 50 μM CPM and incubated for an additional 30 minutes at 22ºC in the dark followed by detection of fluorescent signal by Envision 2104 multiplate reader (Excitation 405 nm, Emission 480 nm).

Radiometric human DGAT1 and DGAT2 assays and rat DGAT1 assay (LE assay). Lipid extraction (LE) assay is a radiometric assay which directly measures radiolabeled TG formation as a measure of DGAT1 activity using tritium [^{3}H] labelled decanoyl-CoA (C10-CoA) as one of the substrate. Test compounds along with 25 μM C10-DAG and 0.05 μg/mL hDGAT1 in HEPES buffer (50 mM HEPES, pH 7.5, 2 mM $MgCl_2$, 1 mM CHAPS) were incubated for 30 minutes at room temperature. DGAT1 substrate, 0.5 μM C10-CoA and 5.5 nCi/well of [^{3}H]-C10-CoA were then added and incubated for 60 minutes at room temperature. The newly formed [^{3}H] labelled TG was extracted into organic phase and counted using Microbeta multiplate reader, Perkin Elmer (Downers Grove, IL, USA). Human DGAT2 assay was performed similarly by using 2 μg/ml human DGAT2 microsomes with 25 μM C10-DAG and 0.1 μM C10-

CoA in the reaction mixture. Rat DGAT1 assay was developed using 0.5 μg/mL rat DGAT1 enzyme while keeping all conditions identical to the human DGAT1 assay.

Cell-based DGAT1 assay in C2C12 mouse myoblast cells. Cell based assay measures the TG formation by endogenous DGAT1 using labelled [^{14}C] oleic acid as a substrate and tracer during the TG neo-synthesis in C2C12 mouse myoblast cells. C2C12 cells were incubated with test compounds followed by 20 min incubation with [^{14}C] Sodium Oleate with 0.001% fatty acid free BSA (Bovine Serum Albumin). Lipids were extracted, resolved on TLC (thin layer chromatography) plates and quantified by phosphorimager (Bio-Rad, Quarry Bay, Hong Kong).

Solubility. Kinetic solubility of the compounds in pION buffer was determined using pION μSOL Explorer in a high-throughput, 96 well format method at pH 7.4 with incubation time of 18 hours.

Vibrational Circular Dichroism (VCD). *Ab initio* VCD analysis is an extension of electronic CD (ECD) into the mid-IR range. It involves differential absorption of circularly polarized IR (Infrared) radiation. VCD spectra can be accurately calculated using quantum mechanics (QM) methods. *Ab initio* VCD experiment can determine absolute configuration using VCD measurement, provide an estimate of a molecule's solution phase conformational state, and confirm structure using IR spectrum. ECD and VCD spectra of the two enantiomers were measured and compared with theoretical predictions. CompareVOA (BioTools, Inc) is used for estimation of Confidence Limit and BioTools Chiral IR VCD spectrometer is used for measuring spectra. The combination of computational and spectroscopic work allowed absolute stereochemistry to be determined. Stereochemistry of ***S*-12a** and ***R*-12a** was determined from their ethyl ester precursors (compounds ***S*-11a** and ***R*-11a**). Stereochemistry of ***S*-12g** and ***R*-12g** was determined from their ethyl ester precursors (compounds ***S*-11g** and ***R*-11g**).

Pharmacokinetics. All animal studies were performed in compliance with the Guide for the Care and Use of Laboratory Animals as published by the US National Institutes of Health and were approved by the Institutional Animal Care and Use Committee of GlaxoSmithKline. Mouse, rat and dog pharmacokinetic studies were conducted in male animals using single administration. Mouse (C57BL/6J, male, n=3, ~4-6 weeks old) were obtained from Bioneeds Ltd., Bangalore, India. Rats (Sprague-Dawley, male, n=3, ~6-8 weeks old) were obtained from National Institute of Nutrition (NIN), Hyderabad, India. Dog (Beagle, male, n=3, ~11-29 months old) were obtained from Marshall Bioresources, Beijing, China. Plasma pharmacokinetic parameters were reported as mean and range for n=3 animals for all studies except for mouse as in the mouse PK study composite study design was followed. Solution formulations for intravenous administration contained 20% hydroxyl β- cyclodextrin in saline (mouse PK study) or 20% (v/v) dimethyl acetamide, 40% tetraethylene glycol in water (rat PK study) or 60% PEG400 in water (dog PK studies). Formulation containing 0.5% methyl cellulose (MC) and Tween 80 (98:2) was used for oral pharmacokinetic studies for all the species.

Table 1S. Pharmacokinetics (%F in rats) and *in vivo* efficacy (% Inhibition of TG and plasma level in mice) of tetralones **26a-d**.

Compound #	%F in rat[a]	% TG Inh. @ 0.3 mg/kg PO[b]	Plasma level of drug (ng/mL) @ 0.3 mg/kg PO[b]	% TG Inh. @ 1 mg/kg PO[b]	Plasma level of drug (ng/mL) @ 1 mg/kg PO[b]
26a	23				
26b	51	15.8	42.1	56.5	167.7
26c	35				
26d	48	76	36	97.6	106

[a]Dose is 1 mg/kg IV [20% (v/v) dimethyl acetamide, 40% tetraethylene glycol in water) and 2 mg/kg PO (0.5% MC and Tween 80 (98:2)], n=3 Sprague-Dawley male rats. [b]Overnight fasted Swiss Albino mice (male, 4-6 weeks old, n=6 per group) were challenged with an oral bolus of corn oil (5 mL/kg) 30 min post compound administration. TG inhibition was measured at 2.5 h post corn oil challenge, and compound level in terminal plasma sample was measured at 3 h post compound dosing.

Mouse model of hypertriglyceridemia. All animal studies were performed in compliance with the Guide for the Care and Use of Laboratory Animals as published by the US National Institutes of Health and were approved by the Institutional Animal Care and Use Committee of GlaxoSmithKline. Overnight fasted Swiss Albino mice (male, 4-6 weeks old, n=6 per group, Bioneeds Ltd., Bangalore, India) were challenged with an oral bolus of corn oil (5 mL/kg) 30 minutes post compound administration. TG inhibition was measured at 3 hour post compound dosing (i.e. 2.5 hour post corn oil challenge), and compound level in terminal plasma sample was measured at 3 hour post compound dosing by a colorimetric glycerophosphate oxidase method (Transasia Bio-medicals Ltd., India, in technical collaboration with ERBA Mannheim GmbH, Germany) read on a Spectramax Plus 384 (Molecular Devices, Sunnyvale, CA, USA). Statistical analysis was performed using ANOVA-Bonferroni Test.

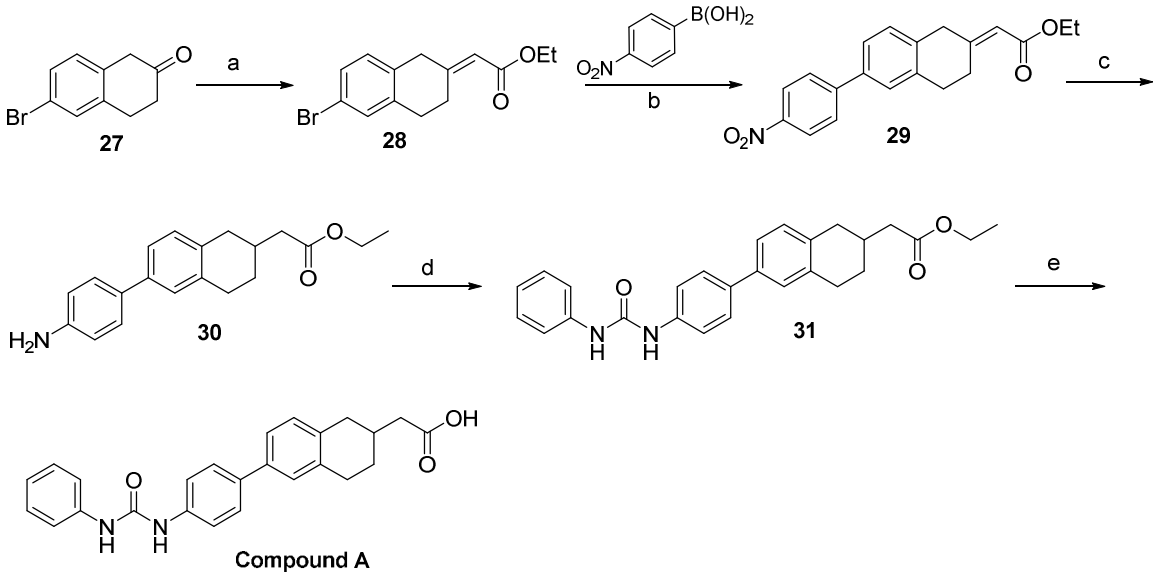
Oral bioavailability (F) was determined from the ratio of dose-normalized AUC from the oral dosing of 10 mg/kg over the dose-normalized AUC from the intravenous dosing of 1 mg/kg.

***In Silico* Mutagenicity Prediction**. DEREK (Deductive Estimation of Risk from Existing Knowledge) is a software program which provides structural alert for mutagenicity based on the knowledge database. eHOMO (Energy of the Highest Occupied Molecular Orbital) prediction is a QM descriptor correlated with the reactivity of a molecule towards oxidation, which could correlate to compounds requiring metabolic activation to become genotoxic. Compounds **21a-g** and **24a-d** were evaluated for mutagenicity *by in silico* DEREK and eHOMO prediction models.

Ames Test. The bacterial mutation assay (Ames Test) is a short-term reverse mutation assay that uses standard plate incorporation test with *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and *Escherichia coli* WP2*uvrA* (pKM101) in the presence and absence of the metabolic activating S9-mix.

Chemistry. Reactions were carried out at ambient / room temperature (25 °C) unless otherwise mentioned. Overnight reaction means longer than 15 hrs. NMR spectra were recorded on a Varian 300 MHz (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz) or 400 MHz (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) spectrometer with tetramethyl silane as internal standard or referenced to the residual solvent signal. Two-dimensional NMRs (H-H-COSY, NOESY, HSQC, and HMBC) were used for the assignment of the intermediates and final compounds. High resolution mass spectra were measured on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Syaept G2 HDMS, Waters, Milford, MA). Samples were infused at 3μL/min, and spectra were obtained in positive or negative ionization mode with a resolution of 15000 (fwhm) using leucine enkephalin as lock mass. Precoated aluminum sheets (Merck TLC-cards, 254 nm) were used for TLC. Purities of the compounds were verified to be >95% by HPLC analysis. HPLC conditions to assess purity were as follows: Shimadzu HPLC equipped with a LC-20AT pump, a DGU-20A5 degasser, and a SPD-20A UV detector; Inertsil ODS-3 (4 μm, 4.6 mm × 100 mm) or Symmetry C18 column (5 μm, 4.6 mm × 150 mm); gradient elution of H_2O/CH_3CN or H_2O/MeOH from 95/5 to 5/95 in 15 min; flow rate, 1 mL/min; wavelength, UV 254 nm. Preparative HPLC purifications were performed on a Phenomenex Gemini 110A column (C18, 10 μm, 21.2 mm × 250 mm). Column chromatography was performed on silica gel 60 Å, 0.035−0.070 mm (Acros Organics). All reagents and solvents were obtained from commercial sources and were used as received. Moisture sensitive reactions were performed under an argon atmosphere using oven dried glassware. Chiral separations were carried out on chiral column CHIRAL PAK ODH (4.6x250 mm) 5m using 15-30% ethanol or isopropanol in hexane at the flow rate of: 0.8-1.0 mL/min in presence or absence of diethylamine (0.1%) as per the requirement. Absolute stereochemical determination was assigned by VCD (Vibrational Circular Dichroism) using CompareVOA (BioTools, Inc) for estimation of Confidence Limit and BioTools Chiral IR VCD spectrometer for measuring spectra.

Synthesis of 2-(6-(4-(3-Phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (Compound A)



Reagents and conditions: a) $Ph_3P{=}CHCO_2Et$, NaH, DMF; b) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O; c) Pd/C, MeOH, H_2; d) PhNCO, Et_3N, THF; e) LiOH, THF-H_2O.

Ethyl 2-(6-bromo-3,4-dihydronapthalen-2(1*H*)-ylidene)acetate (28): $Ph_3P{=}CHCO_2Et$ (5 g, 22.22 mmol) was added to an ice cold solution of 6-Bromo-2-tetralone **27** (5.0 g, 22.22 mmol) and NaH (0.69 g, 28.88 mmol) in DMF (40 mL). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (2X100 mL). The organic layer was dried over sodium sulfate, filtered and removed under reduced pressure to obtain the crude product which was purified by flash chromatography using 2% ethyl acetate in hexanes to afford title compound **28** (4.0 g, 61%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 2H), 6.96 (d, J = 7.8 Hz, 1H), 6.33 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.22 (s, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.21 (t, J = 7.8 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{14}H_{16}BrO_2^+$ $[M + H]^+$ = 294, found 295.

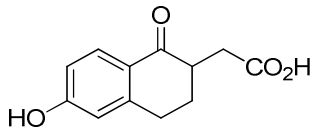
Ethyl 2-(6-(4-nitrophenyl)-3,4-dihydronapthalen-2(1*H*)-ylidene)acetate (29): Compound **28** (4.0 g, 13.55 mmol) was reacted with 4-nitrophenyl boronic acid (2.25 g, 13.55 mmol) as per the procedure described for the synthesis of compound **9a** to obtain the desired product **29** (4.0 g, 87%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 9.3 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.40 (m, 2H), 7.12 (d, J = 7.8 Hz, 1H), 6.41 (s, 1H), 4.19 (q, J = 7.8 Hz, 2H), 3.25 (s, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.41 (t, J = 7.8 Hz, 2H), 1.28 (t, J = 6.9 Hz, 3H).

Ethyl 2-(6-(4-aminoophenyl)-1,2,3,4-tetrahydronapthalen-2-yl)acetate (30): Excess 10% Pd/C (1.0 g) was added to compound **29** (4.0 g, 11.86 mmol) in 30 mL of ethanol. The mixture was stirred under H_2 atmosphere at room temperature for 18 h. The reaction mixture was filtered over celite bed, filtrate was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulfate, filtered and removed in vacuum. The crude product was washed with diethyl ether and pentane to afford title compound **30** (3.2 g, 87%) as solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 7.40 (d, J = 8.4 Hz, 2H), 7.26 (m, 2H), 7.05 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 8.8 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 2.86-2.78 (m, 3H), 2.50-2.35 (m, 3H), 2.12 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H), 1.20 (t, J = 6.8 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{20}H_{24}NO_2^+$ $[M + H]^+$ = 310, found 310.

Ethyl 2-(6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (31): Phenyl isocyanate (0.084 g, 0.71 mmol) was added to compound **30** (0.2 g, 0.64 mmol) and triethylamine (0.098 g, 0.96 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and product purified by flash chromatography using 1% methanol in chloroform to afford title compound **31** (0.14 g, 50%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (bs, 1H), 8.65 (bs, 1H), 7.60-7.40 (m, 6H), 7.3-7.21 (m, 4H), 7.10 (d, J = 8.4 Hz, 1H), 6.95 (m, 1H), 4.12 (q, J = 6.9 Hz, 2H), 2.9 (m, 3H), 2.45 (m, 3H), 2.15 (m, 1H), 1.90 (m, 1H), 1.45 (m, 1H), 1.2 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{27}H_{29}N_2O_3^+$ $[M + H]^+$ = 429, found 429.

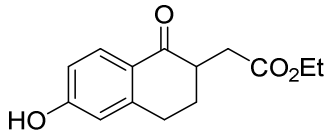
2-(6-(4-(3-Phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (Compound A): Lithium hydroxide (0.068 g, 1.62 mmol) was added to compound **31** (0.14 g, 0.327 mmol) in 10 mL of THF-water (3:1). Reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuum, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 ^{o}C, and solids were collected by filtration and dried under vacuum to afford title compound (**Compound A**) (0.1 g, 76%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.13 (bs, 1H), 7.56-7.42 (m, 6H), 7.40-7.24 (m, 4H), 7.10 (d, J = 8.4 Hz, 1H), 7.0-6.94 (m, 1H), 2.90-2.71 (m, 3H), 2.45 (m, 1H), 2.29 (d, J = 6.9 Hz, 2H), 2.10 (m, 1H), 1.91 (m, 1H), 1.42 (m, 1H). LRMS (ESI^{+}) *m/z* calcd $C_{25}H_{25}N_2O_3^{+}$ $[M + H]^{+}$ = 401, found 401.

Synthesis of 2-(1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (Compound B)



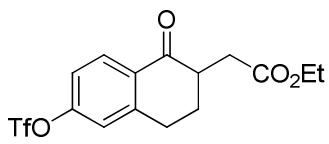
6e

2-(6-Hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (6e): Compound **4** was converted to compound **6e** using the procedure described for the synthesis of **6a** to obtain the desired compound in 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 10.3 (bs, 1H), 7.73 (d, J = 8.4 Hz, 1H), 6.7 (m, 1H), 6.6 (m, 1H), 3.3-2.93 (m, 2H), 2.84-2.77 (m, 1H), 2.68 (m, 1H), 2.35 (m, 1H), 2.1 (m, 1H), 1.85 (m, 1H). LRMS (ESI^{+}) *m/z* calcd $C_{12}H_{13}O_4^{+}$ $[M + H]^{+}$ = 221, found 221.



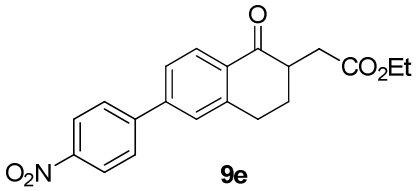
7e

Ethyl 2-(6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (7e): **7e** was prepared by similar procedures described for **7a** and using **6e** as starting material to obtain **7e** as a solid with 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 6.26 (bs, 1H), 4.2 (q, J = 6.8 Hz, 2H), 3.1-2.85 (m, 4H), 2.4 (m, 1H), 2.2 (m, 1H), 1.95 (m, 1H), 0.8 (t, J = 6.8 Hz, 3H). LRMS (ESI^{+}) *m/z* calcd $C_{14}H_{17}O_4^{+}$ $[M + H]^{+}$ = 249, found 249.



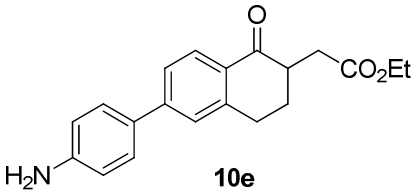
8e

Ethyl 2-(1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (8e): **8e** was prepared by similar procedures described for **8a** and using **7e** as starting material to obtain **8e** as a solid with 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.8 Hz, 1H), 7.24-7.12 (m, 2H), 4.2 (q, *J* = 6.8 Hz, 2H), 3.2 (m, 1H), 3.1-2.9 (m, 3H), 2.5 (m, 1H), 2.3 (m, 1H), 2.0 (m, 1H), 1.2 (t, *J* = 6.8 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{15}H_{16}F_3O_6S^+$ $[M + H]^+$ = 381, found 381.



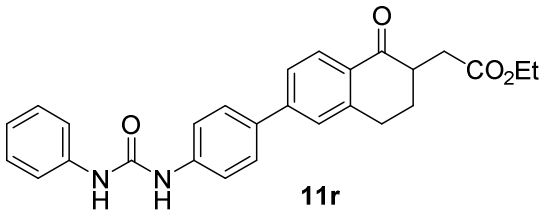
9e

Ethyl 2-(6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (9e): **9e** was prepared using similar procedures described for **9a** and using **8e** as a starting material**.** Compound **9e** was obtained as a pale yellow solid with a yield of 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.4 (d, *J* = 7.6 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.5 (s, 1H), 4.2 (q, *J* = 6.8 Hz, 2H), 3.3-3.0 (m, 4H), 2.5 (m, 1H), 2.3 (m, 1H), 2.05 (m, 1H), 1.3 (t, *J* = 6.8 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{20}H_{20}NO_5^+$ $[M + H]^+$ = 354, found 354.



10e

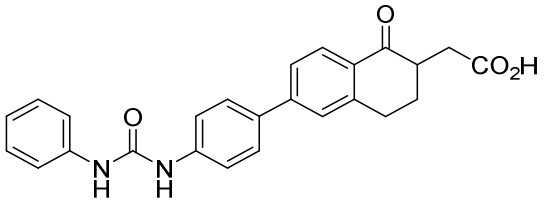
Ethyl 2-(6-(4-aminophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (10e): 10% Pd/C (0.2 g) was added to a solution of compound **9e** in 30 mL of ethanol, and the mixture was stirred at room temperature for 3 h under the positive H_2 atm. The reaction mixture was filtered over celite bed, filtrate was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was washed with diethyl ether and pentane to afford title compound (0.8 g, 80%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 1H), 7.46-7.39 (m, 4H), 6.75 (m, 2H), 4.19 (m, 2H), 3.8 (bs, 2H), 3.14-3.04 (m, 4H), 2.42 (m, 1H), 2.26 (m ,1H), 2.0 (m, 1H), 1.29 (m, 3H). LRMS (ESI^+) *m/z* calcd $C_{20}H_{22}NO_3^+$ $[M + H]^+$ = 324, found 324.



11r

Ethyl 2-(1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11r): 3-Phenyl isocyanate was reacted with compound **10e** using the procedure described for the synthesis of **11a** to

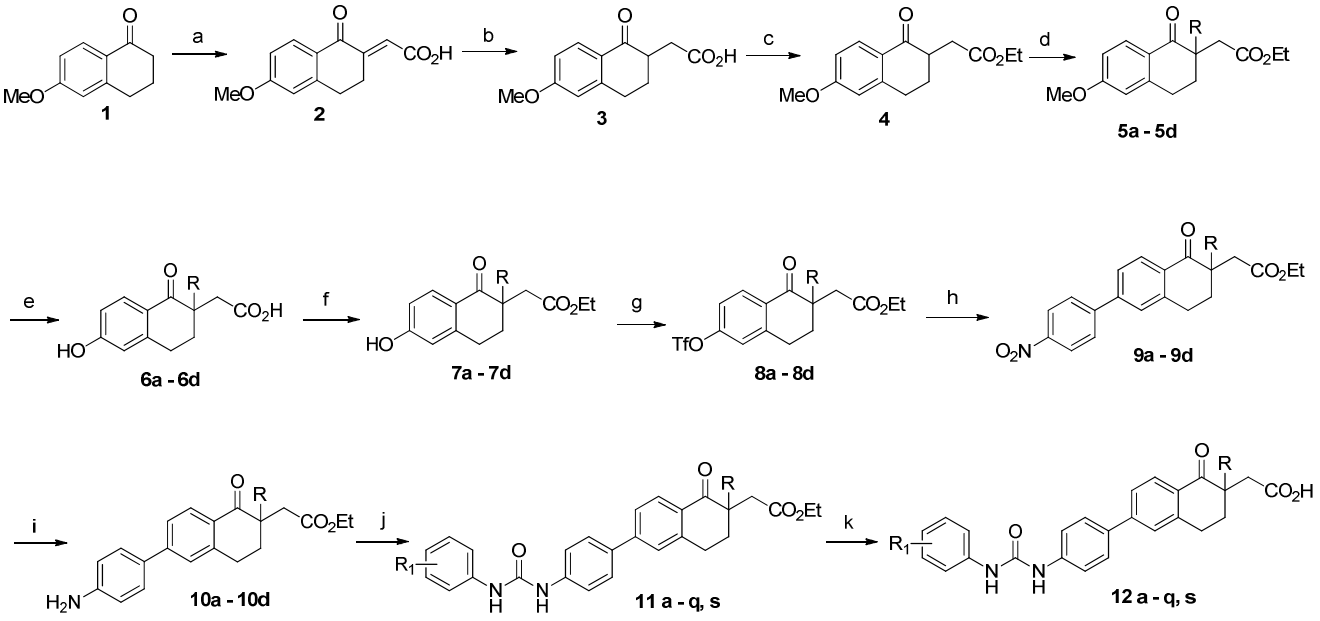
obtain the desired compound **11r** as a white solid with a yield of 65%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.85 (bs, 1H), 8.71 (bs, 1H), 7.90 (d, J = 3.3 Hz, 1H), 7.79-7.42 (m, 8H), 7.29 (t, J = 6 Hz, 2H), 6.98 (t, J = 5.4 Hz, 1H), 4.09 (q, J = 5.8 Hz, 2H), 3.2-2.6 (m, 5H), 2.2-1.9 (m, 2H), 1.2 (t, J = 5.4 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{27}N_2O_4^+$ $[M + H]^+$ = 443.2, found 443.2.



Compound B

2-(1-Oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (Compound B): Compound **11r** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound (**Compound B**) as a white solid with a yield of 58%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 7.9 (d, J = 8.1 Hz, 1H), 7.7-7.45 (m, 8H), 7.25 (t, J = 7.5 Hz, 2H), 6.95 (t, J = 7.8 Hz, 1H), 3.2-2.85 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{27}N_2O_4^+$ $[M + H]^+$ = 415.1, found 415. HRMS calcd for $C_{25}H_{23}N_2O_4$ $[M+H]^+$ = 415.1658, found 415.1653.

Synthesis of Compounds 12a-12q, 12s

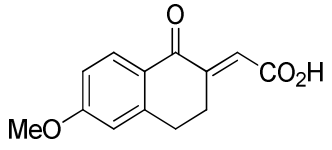


5a-10a: R = Et
5b-10b: R = Me
5c-10c: R = CH_2CF_3
5d-10d: R = n-Pr

11a, 12a: R = Et, R_1 = 3-CF_3
11b, 12b: R = Et, R_1 = 3-Me
11c, 12c: R = Et, R_1 = 3-Cl
11d, 12d: R = Et, R_1 = 3-OMe
11e, 12e: R = Et, R_1 = 3-F
11f, 12f: R = Et, R_1 = 4-CF_3
11g, 12g: R = Et, R_1 = 4-Cl
11h, 12h: R = Et, R_1 = 4-Me
11i, 12i: R = Et, R_1 = 2-CF_3

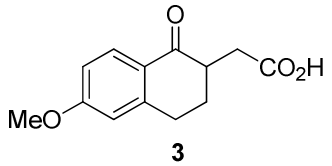
11j, 12j: R = Me, R_1 = 3-CF_3
11k, 12k: R = Me, R_1 = 3-Me
11l, 12l: R = Me, R_1 = 3-Cl
11m, 12m: R = Me, R_1 = 3-OMe
11n, 12n: R = Me, R_1 = 3-F
11o, 12o: R = Me, R_1 = H
11p, 12p: R = Et, R_1 = H
11q, 12q: R = n-Pr, R_1 = H
11s, 12s: R = CH_2CF_3, R_1 = H

Reagents and conditions: a) Glyoxalic acid, H_2SO_4, diglyme; b) Zn, AcOH; c) $MeSO_3H$, EtOH; d) Alkyl halide, NaH, DMF; e) Aq. HBr; f) CH_3SO_3H, EtOH; g) Tf_2O, CH_2Cl_2, Et_3N; h) 4-Nitrophenyl boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O; i) Fe-NH_4Cl, EtOH-H_2O; j) R_1PhNCO, Et_3N, THF; k) LiOH, THF-H_2O.



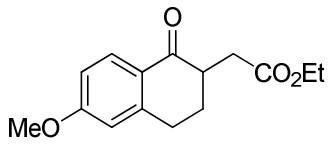
2

2-(6-Methoxy-1-oxo-3,4-dihydronaphthalen-2(1H)-ylidene)acetic acid (2): Glyoxalic acid (30 mL, 303 mmol) and water (14 mL) were added to a stirred solution of 6-methoxy tetralone (25 g, 141 mmol) in diglyme (50 mL) followed by sulfuric acid (6.5 mL, 35 mmol). The reaction mixture was heated at 85 °C overnight. The reaction mixture was cooled to 0 ^oC, and resulting solids were filtered off and washed with water (3x25 mL), dried under reduced pressure to afford title compound **2** (28 g, 85%) as an off-white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 12.9 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.0 (m, 2H), 6.6 (s, 1H), 3.8 (s, 3H), 3.3 (m, 2H), 3.0 (m, 2H). LRMS (ESI^+) *m/z* calcd $C_{13}H_{13}O_4^+$ $[M + H]^+$ = 233, found 233.



3

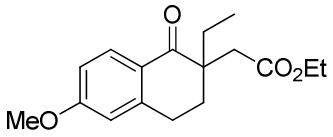
2-(6-Methoxy-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl)acetic acid (3): Zinc (19.6 g, 300 mmol) was added to compound **2** (28 g, 120 mmol) in acetic acid –water mixture (300 mL), and the reaction mixture was stirred at 80 ^oC for 2 h. Reaction mixture was then cooled and filtered over celite bed. It was then concentrated *in vacuo.* Water (50 mL) was added to the resultant residue. The resulting solids were collected by filtration and dried under vacuum to afford title compound **3** (27 g, 95%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 7.8 (d, J = 8.4 Hz, 1H), 6.9 (m, 2H), 3.8 (s, 3H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.7 (m, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 1.9 (m, 1H). LRMS (ESI^+) *m/z* calcd $C_{13}H_{15}O_4^+$ $[M + H]^+$ = 235.1, found 235.1.



4

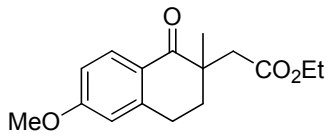
Ethyl 2-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (4): Methane sulfonic acid (20 mL) was added to compound **3** (20 g, 47 mmol) in ethanol (150 mL), and the mixture was stirred at room temperature for 5 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate, and the organic layer was washed with brine solution. The organic layer was dried over sodium sulfate, filtered and evaporated under vacuum to afford title compound **4** (10 g, 71%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.8 Hz, 1H), 6.82 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.67

(s, 1H), 4.2 (m, 2H), 3.8 (s, 3H), 3.12-2.89 (m, 4H), 2.4 (m, 1H), 2.26 (m, 1H), 1.98 (m, 1H), 1.28 (t, J = 7.6 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{15}H_{19}O_4^+$ $[M + H]^+$ = 263.1, found 263.1.



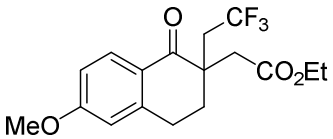
5a

Ethyl 2-(2-ethyl-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (5a): To an ice-cold solution of compound **4** (7 g, 26.8 mmol) in DMF (80 mL) was added NaH (1.93 g, 80.4 mmol) portion wise, and the reaction mixture was stirred for 10 min. Ethyl iodide (20.91 g, 134.03 mmol) was then added, and the mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with ice water and extracted with ethyl acetate. Aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum to obtain title compound **5a** (7g, 90%) as a white solid. LRMS (ESI$^+$) *m/z* calcd $C_{17}H_{23}O_4^+$ $[M + H]^+$ = 291, found 291.



5b

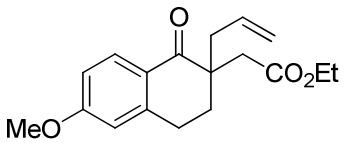
Ethyl 2-(6-methoxy-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (5b): 5b was prepared similar way as described for **5a** except methyl iodide was used instead of ethyl iodide to obtain the desired compound **5b** (10 g, 88%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, J = 8.4 Hz, 1H), 6.84 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 6.62 (d, J_1 = 1.6 Hz, 1H), 4.1 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.0-2.7 (m, 2H), 2.5 – 2.1 (m, 2H), 1.8 – 1.5 (m, 2H), 1.23 (s, 3H), 1.2 (t, J =7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{16}H_{21}O_4^+$ $[M + H]^+$ = 277, found 277.



5c

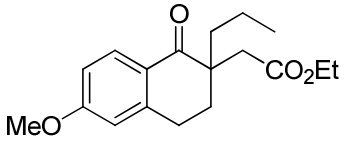
Ethyl 2-(6-methoxy-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (5c): To a solution of compound **4** (3 g, 11.4 mmol) in DMF (10 mL) was added an ice cold solution of NaH (1.14 g, 28.5 mmol) in DMF (20 mL) over a period of 30 min, and the reaction mixture was stirred for 10 min. 2,2,2-Trifluoroethyl iodide (5.9 g, 28.22 mmol) was then added, and the mixture was stirred for 2 h at room temperature. The reaction was then brought to 0 ^{o}C. Excess NaH was quenched with ice water and extracted with ethyl acetate (2X50 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum to obtain the title compound **5c** (1.5 g, 38%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 9.3 Hz, 1H), 6.85 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 4.1 (q, J

= 6.9 Hz, 2H), 3.86 (s, 3H), 3.05-2.9 (m, 4H), 2.6-2.4 (m, 4H), 1.23 (t, *J* = 6.9 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{17}H_{20}F_3O_4^+$ $[M + H]^+$ = 345, found 345.



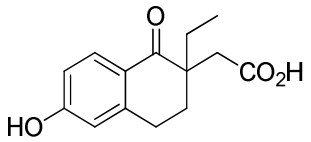
5d'

Ethyl 2-(2-allyl-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (5d') was prepared similar way as **5a** except allyl bromide was used instead of ethyl bromide to obtain the desired product **5d'** with a 65% yield . ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 12.4, 1H), 6.84 (d, J = 12, 1H), 6.66 (d, *J* = 2.1, 1H), 5.8 (m, 1H), 5.3-5.1 (m, 2H), 4.1 (q, *J* = 9.6, 2H), 3.85 (s, 3H), 3.1-2.82 (m, 3H), 2.5-2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 1.3 (t, *J* = 9.2, 3H). LRMS (ESI^+) *m/z* calcd $C_{18}H_{23}O_4^+$ $[M + H]^+$ = 303, found 304.



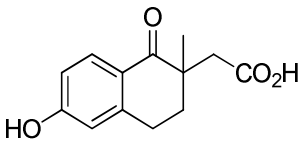
5d

Ethyl 2-(2-propyl-6-methoxy-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl) acetate (5d): 10% Pd/C (2 g) was added to compound **5d'** (5.5 g, 18.2 mmol) in ethanol (50 mL) and the resulting mixture was stirred under hydrogen atmosphere at room temperature for 10 h. Reaction mixture was filtered through a pad of celite, the filtrate was concentrated under reduced pressure and purified by flash chromatography using 4% ethyl acetate in hexanes to afford **5d** (2.3 g, 41%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.8, 1H), 6.82 (d, *J* = 8.8, 1H), 6.65 (d, *J* = *2.4*, 1H), 4.1 (q, *J* = 7.2, 2H), 3.84 (s, 3H), 2.92-2.82 (m, 2H), 2.52-2.38 (m, 2H), 1.83 (m, 1H), 1.51 (m, 1H), 1.4-1.25 (m, 4H), 1.2 (t, *J* = 7.6 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{18}H_{25}O_4^+$ $[M + H]^+$ = 305.17, found 306.



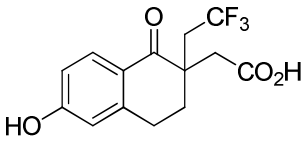
6a

2-(2-Ethyl-6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (6a): Aqueous HBr (120 mL) was added to compound **5a** (7.8 g, 26.9 mmol), and the reaction mixture was refluxed for 3 h. The reaction mixture was then brought to room temperature and extracted with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and removed under reduced pressure to give crude product which was purified by flash chromatography using 30% ethyl acetate in pet ether to afford title compound **6a** (3.5 g, 53%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 10.3 (s, 1H), 7.8 (d, *J* = 8.4 Hz, 1H), 6.7 (d, *J* = 7.4 Hz, 1H), 6.6 (s, 1H), 3.0 (m, 1H), 2.7 (m, 2H), 2.4 (m, 2H), 1.9 (m, 1H), 1.7-1.5 (m, 2H), 0.9 (t, *J* = 7.6 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{14}H_{17}O_4^+$ $[M + H]^+$ = 249.1, found 249.1.



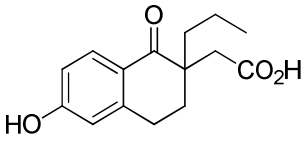
6b

2-(6-Hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (6b) was prepared in the same fashion as **6a** except **5b** was used to obtain the title compound **6b** with a yield of 80%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (bs, 1H), 10.29 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 6.7 (m, 1H), 6.62 (m, 1H), 3.0-2.71 (m, 3H), 2.49-2.33 (m, 2H), 1.8 (m, 1H), 1.1 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{13}H_{15}O_4^+$ $[M + H]^+$ = 235, found 235.



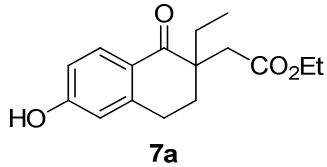
6c

2-(6-Hydroxy-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (6c): Aqueous HBr (15 mL) was added to compound **5c** (1.5 g, 4.36 mmol), and the reaction mixture was refluxed overnight. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The combined organic layers were washed with water, brine and then dried over sodium sulfate, filtered and concentrated *in vacuo* to afford crude compound (1.2 g) as a solid, which was carried forward to the next step without further purification.



6d

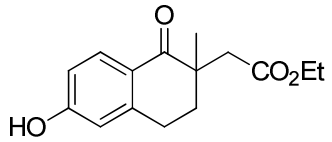
2-(2-Propyl-6-hydroxy-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl) acetic acid (6d) was prepared similarly to the procedure described for **6a** except **5d** was used instead of **5a** to obtain **6d** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2-11.8 (bs, 1H), 10.3 (s, 1H), 7.73 (d, J = 8.1, 1H), 6.7 (d, J = 9.3, 1H), 6.6 (d, J = 2.1, 1H), 2.93 (m, 1H), 2.77-2.67 (m, 2H), 2.4-2.3 (m, 2H), 1.92 (m, 1H), 1.54 (m, 1H), 1.4-1.1 (m, 3H) 0.81 (t, J = 7.2, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{15}H_{19}O_4^+$ $[M + H]^+$ = 263.1, found 262.



7a

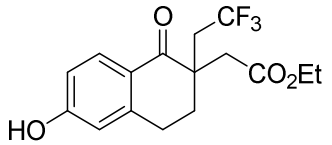
Ethyl 2-(2-ethyl-6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (7a): Methane sulfonic acid (6 mL) was added to a solution of compound **6a** (3.5 g, 14.17 mmol) in ethanol (50 mL), and the reaction mixture was stirred at room temperature for 16 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and washed with brine solution. The organic

layer was dried over sodium sulfate, filtered and removed under reduced pressure to give crude product which was purified by flash chromatography using 20% ethyl acetate in pet ether to afford title compound (3.2 g, 82%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.2 (s, 1H), 8.0 (d, J = 8.4 Hz, 1H), 6.7 (d, J = 7.4 Hz, 1H), 6.6 (s, 1H), 4.0 (m, 2H), 3.2-2.7 (m, 3H), 2.5-2.3 (m, 2H), 2.2-1.9 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.8 (t, J = 7.6 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{16}H_{21}O_4^+$ $[M + H]^+$ = 277.1, found 277.1.



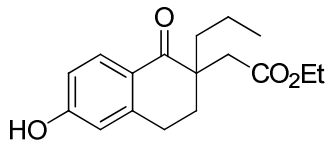
7b

Ethyl 2-(6-hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (7b): Compound **6b** was converted to compound **7b** using the procedure described for the synthesis of **7a** to obtain the desired product as a white solid with a yield of 77%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J = 9.0 Hz, 1H), 6.72 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 6.63 (s, 1H), 4.1 (q, J = 6.9 Hz, 2H), 3.06-2.8 (m, 3H), 2.5-2.33 (m, 2H), 1.9 (m, 1H), 1.3-1.18 (m, 6H).



7c

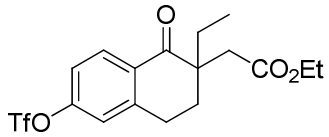
Ethyl 2-(6-hydroxy-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (7c): Methane sulfonic acid (2 mL) was added to compound **6c** (1.2 g, 3.97 mmol) in ethanol (15 mL), and the reaction mixture was stirred at room temperature for 12 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and washed with brine water. The organic layer was dried over sodium sulfate, filtered, and solvent was concentrated *in vacuo.* The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to give title compound (0.9 g, 62%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 9.2 Hz, 1H), 6.75 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 4.1 (q, J = 6.8 Hz, 2H), 3.0-2.8 (m, 4H), 2.62-2.5 (m, 2H), 2.4 (m, 1H), 2.3 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{16}H_{18}F_3O_4^+$ $[M + H]^+$ = 331, found 329.



7d

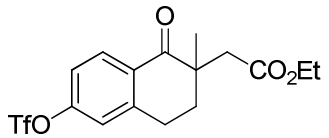
Ethyl 2-(2-propyl-6-hydroxy-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl) acetate (5): It was prepared similar to the procedure described for **7a** using **6d** as starting material to obtain **7d** as a white solid with a yield of 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 8, 1H), 6.72 (d, J = 8, 1H), 6.6 (d, J = 2.4, 1H),

4.1 (q, J = 7.2, 2H), 3.1-2.76 (m, 3H), 2.5-2.37 (m, 2H), 2 (m, 2H), 1.7-1.5 (m, 2H), 1.38 (m, 1H), 1.2 (t, J = 7.2, 3H), 0.87 (t, J = 7.2, 3H). LRMS (ESI^+) *m/z* calcd $C_{17}H_{23}O_4^+$ $[M + H]^+$ = 291, found 291.



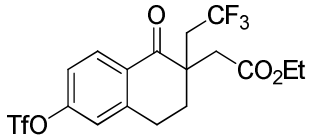
8a

Ethyl 2-(2-ethyl-1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (8a): Triflic anhydride (3.28 g, 11.6 mmol) was added to an ice-cold solution of compound **7a** (3.2 g, 11.6 mmol) and pyridine (1.01 g, 12.7 mmol) in dichloromethane (40 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane and extracted with brine. The organic layer was dried over sodium sulfate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 5% ethyl acetate in pet ether to obtain title compound **8a** (3 g, 63%) as viscous liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.2 (d, J = 8.4 Hz, 1H), 7.3-7.2 (m, 2H), 4.2 (m, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 1.0 (t, J = 7.6 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{17}H_{20}F_3O_6S^+$ $[M + H]^+$ = 409, found 408.1.



8b

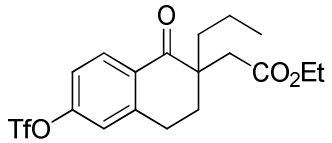
Ethyl 2-(2-methyl-1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (8b): 8b was prepared similar to the procedure described for **8a** using **7b** as starting material to obtain **8b** as viscous liquid with a yield of 53%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 8.4 Hz, 1H), 7.2 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 7.16 (s, 1H), 4.1 (q, J = 7.8 Hz, 2H), 3.2 -2.9 (m, 3H), 2.52-2.4 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{16}H_{18}F_3O_6S^+$ $[M + H]^+$ = 395, found 395.



8c

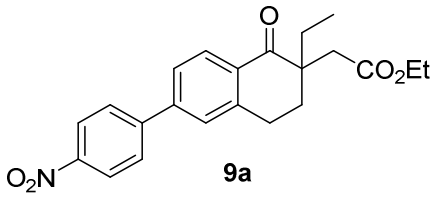
Ethyl 2-(1-oxo-2-(2,2,2-trifluoroethyl)-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (8c): Triflic anhydride (1.33 g, 4.71 mmol) was added to an ice-cold solution of compound **7c** (1.3 g, 3.93 mmol) and pyridine (0.34 g, 4.72 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 2 h. It was then diluted with dichloromethane (100 mL) and washed with saturated brine. The organic layer was dried over sodium sulfate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 5% ethyl acetate in hexanes to give title compound (1.1 g, 61%) as syrup. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 9.0 Hz, 1H), 7.28-7.18 (m,

2H), 4.12 (q, J = 7.2 Hz, 2H), 3.09 (t, J = 6.3 Hz, 2H), 2.95-2.8 (m, 2H), 2.66-2.45 (m, 3H), 2.34 (m, 1H), 1.24 (t, J = 6.9 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{17}H_{17}F_6O_6S^+$ $[M + H]^+$ = 463, found 463.



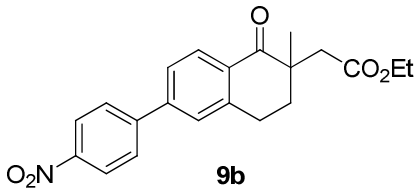
8d

Ethyl 2-(2-propyl-1-oxo-6-(trifluoromethylsulfonyloxy)-1, 2, 3, 4-tetrahydronaphthalen-2-yl) acetate (8d): **8d** was prepared similar to the procedure described for **8a** except **7d** was used as starting material to obtain **8d** as syrup (47% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 8.4, 1H), 7.20 (d, J = 8.4, 1H), 7.15 (s, 1H), 4.08 (t, J = 6.9, 2H), 3.2-2.87 (m, 3H), 2.55-2.44 (m, 2H), 2.06 (m, 1H), 1.7-1.3 (m, 4H), 1.21 (t, J = 6.9, 3H), 0.9 (t, J = 6.9, 3H). LRMS (ESI^+) *m/z* calcd $C_{18}H_{22}F_3O_6S^+$ $[M + H]^+$ = 423, found 423.



9a

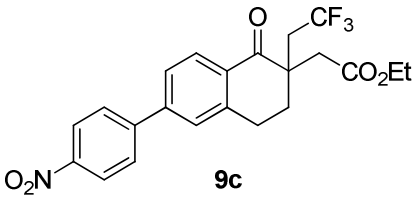
Ethyl 2-(2-ethyl-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (9a): $Pd(PPh_3)_4$ (0.02 g, 0.017 mmol) was added to a solution of compound **8a** (0.6 g, 1.47 mmol) in 14 mL of 1,4 dioxane-H_2O (2:1) mixture under argon atmosphere, followed by cesium carbonate (1.44 g, 4.41 mmol) and 4-nitrophenyl boronic acid (0.246 g, 1.47 mmol). The reaction mixture was degassed for 5 min and refluxed for 4 h. Solvent was then removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulfate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 15% ethyl acetate in pet ether to afford title compound (0.5 g, 89%) as pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.4 (d, J = 9.0 Hz, 2H), 8.2 (d, J = 8.4 Hz, 1H), 7.8 (d, J = 8.4 Hz, 2H), 7.6 (d, J = 7.6 Hz, 1H), 7.5 (s, 1H), 4.1 (m, 2H), 3.2-2.9 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.9 (t, J = 7.6 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{22}H_{24}NO_5^+$ $[M + H]^+$ = 382.1, found 382.2.



9b

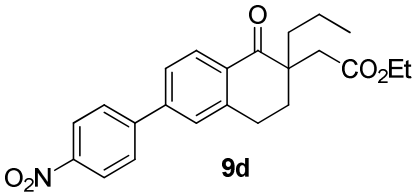
Ethyl 2-(2-methyl-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (9b): **9b** was prepared similar to the procedure described for **9a** except **8b** was used as starting material. Compound **9b** was obtained as a pale yellow solid with a yield of 69%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 7.8 Hz, 1H), 7.76 (m, 2H), 7.58 (m, 1H), 7.46 (s, 1H), 4.1 (m, 2H), 3.2-2.95 (m, 3H), 2.5

(m, 2H), 2.0 (m, 1H), 1.3 (s, 3H), 1.25 (m, 3H). LRMS (ESI^+) *m/z* calcd $C_{21}H_{22}NO_5^+$ $[M + H]^+$ = 368.1, found 368.1.



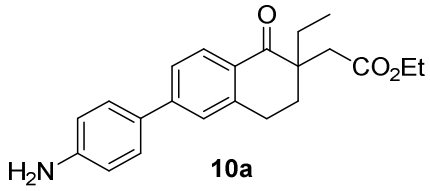
9c

Ethyl 2-(6-(4-nitrophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (9c): $Pd(PPh_3)_4$ (0.022 g, 0.02 mmol) was added to a solution of compound **8c** (0.9 g, 1.94 mmol) in 13 mL of 1,4 dioxane-H_2O (3:1) mixture under argon atmosphere, followed by cesium carbonate (1.9 g, 5.8 mmol) and 4-nitro phenyl boronic acid (0.35 g, 2.09 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 4 h, and solvent was then removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulfate, filtered and removed under reduced pressure. The product was purified by flash chromatography to afford title compound (0.4 g, 47%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.6 (m, 1H), 7.5 (s, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.13 (t, *J* = 6.0 Hz, 2H), 2.95-2.85 (m, 2H), 2.7-2.58 (m, 2H), 2.5 (m, 1H), 2.4 (m, 1H), 1.25 (t, *J* = 6.8 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{22}H_{21}F_3NO_5^+$ $[M + H]^+$ = 436.1, found 436.



9d

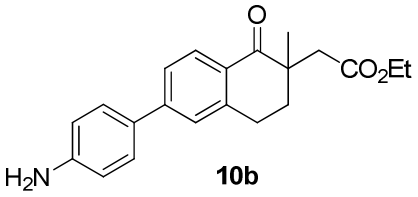
Ethyl 2-(2-propyl-6-(4-nitrophenyl)-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl) acetate (9d): **9d** was prepared similarly to the procedure described for **9a** except **8d** was used as starting material. Compound **9d** was obtained as an off white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 9.6, 2H), 8.18 (d, *J* = 8.4, 1H), 7.76 (d, *J* = 9.2, 2H), 7.55 (d, *J* = 8, 1H), 7.47 (s,1H), 4.1 (q, *J* = 7.2, 2H), 3.2 (m, 1H), 3.0 (m, 2H), 2.5 (m, 2H), 2.1 (m, 1H), 1.7 (m, 1H), 1.6 (m, 1H), 1.42 (m, 1H), 1.3 (m, 1H), 1.24 (t, *J* = 7.2, 3H), 0.9 (t, *J* = 7.2, 3H). LRMS (ESI^+) *m/z* calcd $C_{23}H_{26}NO_5^+$ $[M + H]^+$ = 396, found 396.



10a

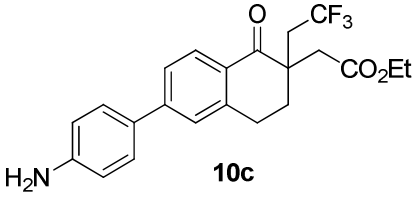
Ethyl 2-(6-(4-aminophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (10a): Iron powder (0.24 g, 4.3 mmol) was added to a solution of compound **9a** (0.55 g, 1.44 mmol) in 30 mL of ethanol-water mixture (2:1) followed by NH_4Cl (0.039 g, 0.72 mmol). The reaction mixture was stirred and refluxed for 4 h. The solvent was removed under reduced pressure, and residue was partitioned between

ethyl acetate and water. The separated organic layer was dried over sodium sulphate and filtered. The filtrate was concentrated under reduced pressure, and the residue was triturated with n-pentane to afford title compound **10a** (0.3 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, *J* = 8.4 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 2H), 7.6-7.3 (m, 4H), 4.1 (m, 2H), 3.8 (bs, 2H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.6-2.4 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.3 (t, *J* = 7.6 Hz, 3H), 0.9 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{22}H_{26}NO_3^+$ $[M + H]^+$ = 352.2, found 352.2.



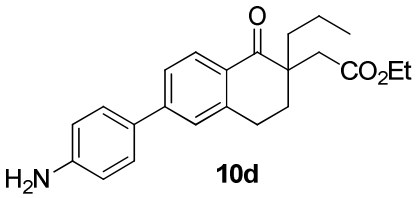
10b

Ethyl 2-(6-(4-aminophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (10b): Compound **9b** was converted to compound **10b** using the procedure described for the synthesis of **10a** to obtain the desired compound as an off white solid with a yield of 66 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.49-7.46 (m, 3H), 7.37 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.11 (m, 2H), 3.8 (bs, 2H), 3.11-2.9 (m, 3H), 2.5-2.39 (m, 2H), 1.96 (m, 1H), 1.29 (s, 3H), 1.2 (m, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{21}H_{24}NO_3^+$ $[M + H]^+$ = 338.1, found 338.2.



10c

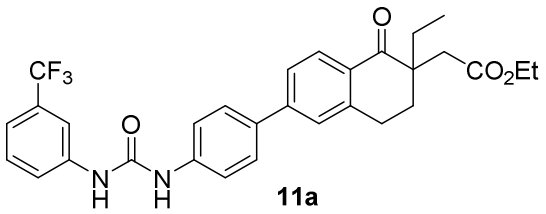
Ethyl 2-(6-(4-aminophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (10c): Iron powder (0.12 g, 2.3 mmol) was added to **9c** (0.4 g, 0.9 mmol) in 15 mL of ethanol-water mixture (2:1) followed by NH_4Cl (0.024 g, 0.45 mmol), and the reaction mixture was refluxed for 4 h. The solvent was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulfate, filtered and removed *in vacuo* to give title compound (0.2 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.6-7.45 (m, 4H), 6.65 (d, *J* = 9.0 Hz, 2H), 5.44 (bs, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.1-2.8 (m, 4H), 2.75-2.6 (m, 2H), 2.38 (m, 1H), 2.15 (m, 1H), 1.14 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{22}H_{23}F_3NO_3^+$ $[M + H]^+$ = 406, found 406.



10d

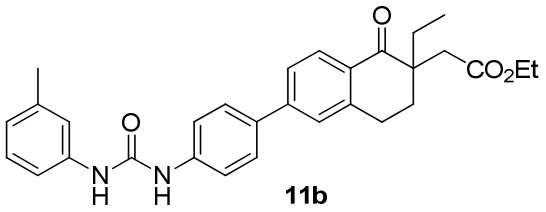
Ethyl 2-(6-(4-aminophenyl)-2-propyl-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl) acetate (10d): Compound **9d** was converted to compound **10d** using the procedure described for the synthesis of **10a** to obtain the desired compound as an off white solid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (d, *J* =

8.4, 2H), 7.6-7.4 (m, 4H), 6.8-6.7 (d, J = 8.4, 1H), 4.1 (m, 2H), 3.8 (bs, 2H), 3.2-2.9 (m, 3H), 2.6-2.4 (m, 2H), 2.1 (m, 1H), 1.7 (m, 2H), 1.3 (m, 2H), 1.2 (m, 3H), 0.9 (m,3H). LRMS (ESI^+) *m/z* calcd $C_{23}H_{28}NO_3^+$ $[M + H]^+$ = 366.2, found 366.



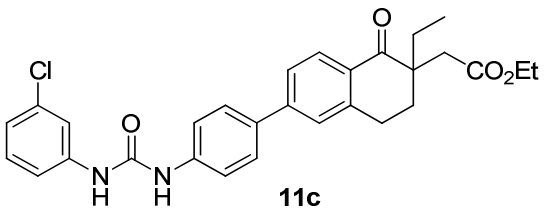
11a

Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11a): 3-(Trifluoromethyl) phenyl isocyanate (0.084 mL, 0.56 mmol) was added to a solution of compound **10a** (0.2 g, 0.56 mmol) and triethylamine (0.234 mL, 1.70 mmol) in THF (4 mL). The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 25-30% ethyl acetate in pet ether to afford title compound (0.25 g, 81%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, 8.4 Hz, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.5-7.3 (m, 9H), 7.1 (s, 1H), 4.1 (q, J = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.4-1.2 (m, 5H), 0.9 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{30}H_{30}F_3N_2O_4^+$ $[M + H]^+$ = 539.2, found 539.2.



11b

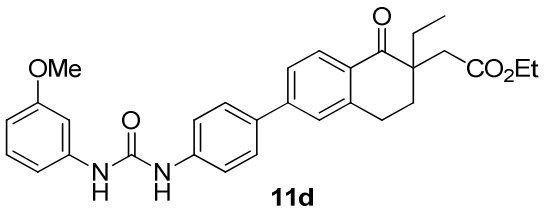
Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(m-tolyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11b): 3-Methyl phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11b** as a white solid with a yield of 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 7.5 Hz, 1H), 7.48-7.40 (m, 2H), 7.38-7.28 (m, 5H), 7.22-7.12 (m, 4H), 6.88 (d, J = 6.6 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.15-2.72 (m, 3H), 2.55-2.4 (m, 2H), 2.27 (s, 3H), 2.05 (m, 1H), 1.8-1.58 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 0.9 (t , J = 7.5 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{30}H_{33}N_2O_4^+$ $[M + H]^+$ = 485.2, found 485.1.



11c

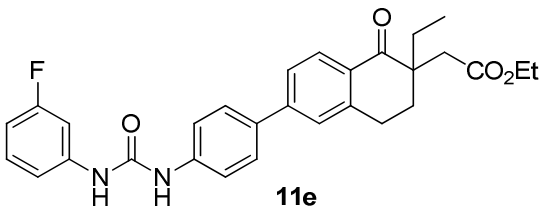
Ethyl 2-(6-(4-(3-(3-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11c): 3-Chloro phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11c** as a white solid (69% yield). ^{1}H NMR

(400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.54-7.46 (m, 3H), 7.44-7.34 (m, 4H), 7.28-7.20 (m, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.94-6.8 (m, 2H), 4.10 (q, *J* = 6.8 Hz, 2H), 3.12 (m, 1H), 3.0 (d, *J* = 16.4 Hz, 1H), 2.95 (m, 1H), 2.50 (d, *J* = 15.6 Hz, 1H), 2.48 (m, 1H), 2.08 (m, 1H), 1.82-1.64 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{29}H_{30}ClN_2O_4^+$ $[M + H]^+$ = 505.2, found 505.2.



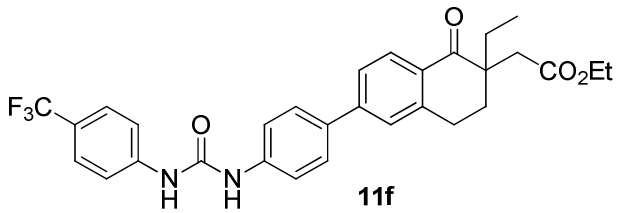
11d

Ethyl 2-(2-ethyl-6-(4-(3-(3-methoxyphenyl)ureido)phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11d) 3-Methoxy phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11d** as a white solid with a yield of 72%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.48-7.34 (m, 5H), 7.32-7.14 (m, 4H), 7.09 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.64 (m, 1H), 4.11 (q, *J* = 6.8 Hz, 2H), 3.76 (s, 3H), 3.08 (m, 1H), 3.01 (d, *J* = 15.6 Hz, 1H), 2.88 (m, 1H), 2.49 (d, *J* = 16.0 Hz, 1H), 2.46 (m, 1H), 2.05 (m, 1H), 1.80-1.62 (m, 2H), 1.21 (t, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{30}H_{33}N_2O_5^+$ $[M + H]^+$ = 501.2, found 501.



11e

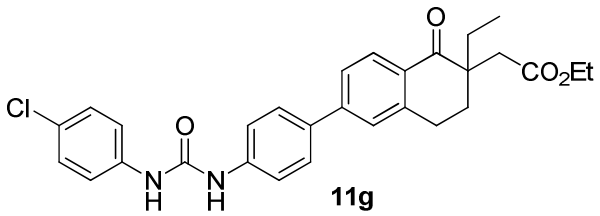
Ethyl 2-(2-ethyl-6-(4-(3-(3-fluorophenyl)ureido)phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11e): 3-Fluoro phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11e** as a white solid with a yield of 62%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.52-7.28 (m, 7H), 7.22-7.05 (m, 4H), 6.76 (m, 1H), 4.11 (q, *J* = 6.9 Hz, 2H), 3.22-2.85 (m, 3H), 2.52-2.46 (m, 2H), 1.92 (m, 1H), 1.82-1.45 (m, 2H), 1.21 (t, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{29}H_{30}FN_2O_4^+$ $[M + H]^+$ = 489.2, found 489.3.



11f

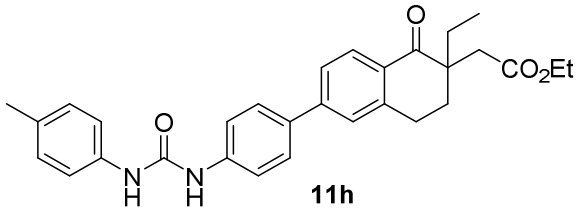
Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(4-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11f): 4-Trifluoromethyl phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11f** as a white solid with a yield of 58%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.0 (d, *J* = 8.4 Hz, 1H), 7.7 (bs, 1H), 7.52-

7.42 (m, 5H), 7.38-7.32 (m, 2H), 7.28-7.20 (m, 4H), 4.1 (q, J = 7.2 Hz, 2H), 3.14-2.8 (m, 3H), 2.55-2.4 (m, 2H), 2.05 (m, 1H), 1.8-1.64 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{30}H_{30}F_3N_2O_4^+$ $[M + H]^+$ = 539.2, found 539.2.



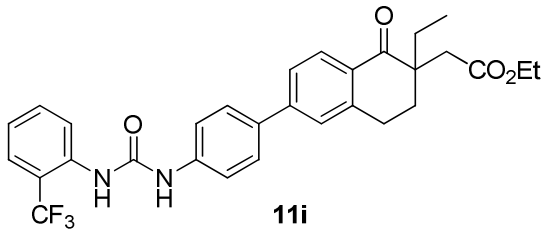
11g

Ethyl 2-(6-(4-(3-(4-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11g): 4-Chloro phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11g** as a white solid with 60 % yield. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 7.8 Hz, 1H), 7.48-7.32 (m, 6H), 7.32-7.26 (m, 2H), 7.24-7.16 (m, 4H), 4.09 (q, J = 7.2 Hz, 2H), 3.10 (m, 1H), 3.02 (d, J = 15.9 Hz, 1H), 2.88 (m, 1H), 2.48 (d, J = 16.2 Hz, 1H), 2.42 (m, 1H), 2.05 (m, 1H), 1.8-1.62 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.8 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{29}H_{30}ClN_2O_4^+$ $[M + H]^+$ = 505.1, found 505.



11h

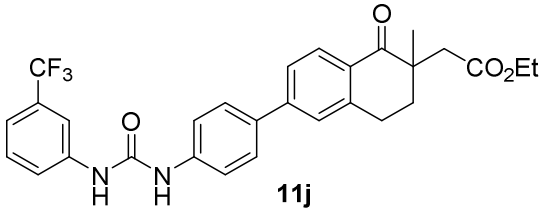
Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(p-tolyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11h): 4-Methyl phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11h** as a white solid with a yield of 65%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 1H), 7.54-7.48 (m, 2H), 7.46-7.32 (m, 4H), 7.23 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.93 (m, 1H), 6.78 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.10 (m, 1H), 2.96 (d, J = 16.2 Hz, 1H), 2.9 (m, 1H), 2.49 (d, J = 15.9 Hz, 1H), 2.46 (m, 1H), 2.07 (m, 1H), 1.82-1.62 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 6.9 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{30}H_{33}N_2O_4^+$ $[M + H]^+$ = 485.2, found 485.2.



11i

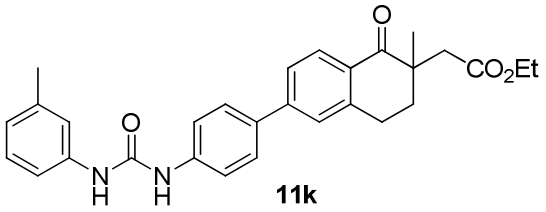
Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(2-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11i): 2-Trifluoromethyl phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11i** as a white solid with a yield of 54%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.12-8.02 (m, 2H), 7.64-7.52 (m, 4H),

7.50-7.34 (m, 4H), 7.24-7.16 (m, 2H), 7.04 (m, 1H), 4.10 (q, J = 6.9 Hz, 2H), 3.20-2.85 (m, 3H), 2.55-2.40 (m, 2H), 2.08 (m, 1H), 1.82-1.6 (m, 2H), 1.22 (t, J = 7.8 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{30}H_{30}F_3N_2O_4^+$ $[M + H]^+$ = 539.2, found 539.



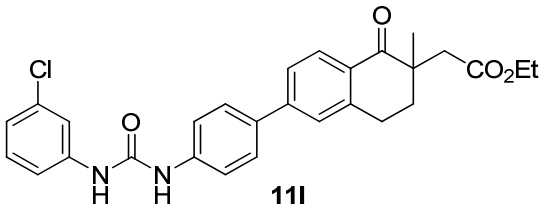
11j

Ethyl 2-(2-methyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydro naphthalen-2-yl)acetate (11j): 3-Trifluoromethyl phenyl isocyanate was reacted with compound **10b** using the procedure described for the synthesis of **11a** to obtain the desired compound **11j** as a white solid with a yield of 55%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 7.8 Hz, 1H), 7.7 (s, 1H), 7.62 (m, 1H), 7.5-7.42 (m, 2H), 7.4-7.3 (m, 6H), 7.1 (m, 1H), 4.1 (q, J = 7.2 Hz, 2H), 3.2-2.9 (m, 3H), 2.56-2.44 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{29}H_{28}F_3N_2O_4^+$ $[M + H]^+$ = 525.1, found 525.



11k

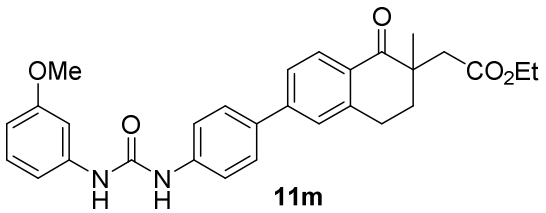
Ethyl 2-(2-methyl-1-oxo-6-(4-(3-(m-tolyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11k): 3-Methyl phenyl isocyanate was reacted with compound **10b** using the procedure described for the synthesis of **11a** to obtain the desired compound **11k** as a white solid with a yield of 62%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.0 Hz, 1H), 7.58-7.34 (m, 6H), 7.24-7.10 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.80 (s, 1H), 6.64 (s, 1H), 4.10 (q, J = 6.8 Hz, 2H), 3.18-3.04 (m, 1H), 3.02-2.90 (m, 2H), 2.50 (d, J = 15.6 Hz, 1H), 2.44 (m, 1H), 2.35 (s, 3H), 1.97 (m, 1H), 1.29 (s, 3H), 1,21 (t, J = 6.8 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{29}H_{31}N_2O_4^+$ $[M + H]^+$ = 471.2, found 471.



11l

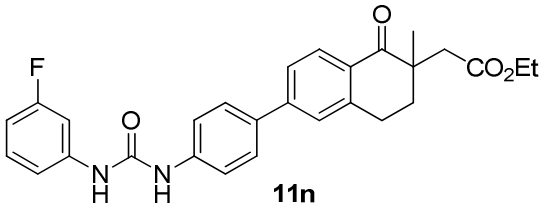
Ethyl 2-(6-(4-(3-(3-chlorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11l): 3-Chloro phenyl isocyanate was reacted with compound **10b** using the procedure described for the synthesis of **11a** to obtain the desired compound **11l** as a white solid with a yield of 66%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 7.8 Hz, 1H), 7.48-7.4 (m, 3H), 7.38-7.26 (m, 5H), 7.24-7.14 (m,

3H), 7.02 (m, 1H), 4.1 (q, J = 7.2 Hz, 2H), 3.18-2.90 (m, 3H), 2.55-2.40 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{28}H_{28}ClN_2O_4^+$ $[M + H]^+$ = 491.1, found 491.



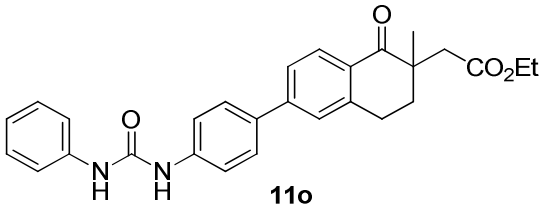
11m

Ethyl 2-(6-(4-(3-(3-methoxyphenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11m): 3-Methoxy phenyl isocyanate was reacted with compound **10b** using the procedure described for the synthesis of **11a** to obtain the desired compound **11m** as a white solid with a yield of 58%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H), 7.48-7.34 (m, 5H), 7.32-7.14 (m, 4H), 7.09 (m, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.64 (m, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.68 (s, 3H), 3.20-2.90 (m, 3H), 2.54-2.38 (m, 2H), 1.95 (m, 1H), 1.30 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{29}H_{31}N_2O_5^+$ $[M + H]^+$ = 487.2, found 487.



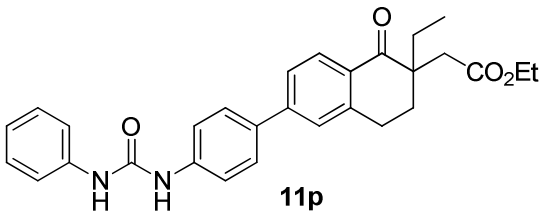
11n

Ethyl 2-(6-(4-(3-(3-fluorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11n): 3-Fluoro phenyl isocyanate was reacted with compound **10b** using the procedure described for the synthesis of **11a** to obtain the desired compound **11n** as a white solid with a yield of 59%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, J = 8.1 Hz, 1H), 7.48-7.28 (m, 7H), 7.24-7.02 (m, 4H), 6.76 (m, 1H), 4.11 (q, J = 6.9 Hz, 2H), 3.2-2.85 (m, 3H), 2.55-2.38 (m, 2H), 1.95 (m, 1H), 1.28 (s, 3H), 1.21 (t, J = 6.9 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{28}H_{28}FN_2O_4^+$ $[M + H]^+$ = 475.1, found 475.



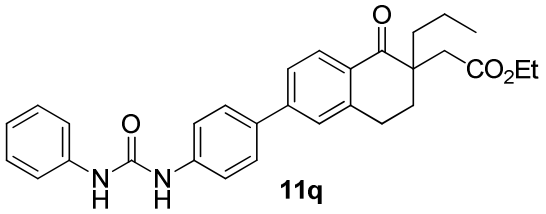
11o

Ethyl 2-(2-methyl-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11o): Phenyl isocyanate was reacted with compound **10b** using the procedure described for the synthesis of **11a** to obtain the desired compound **11o** as a white solid with a yield of 66%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.46-7.28 (m, 8H), 7.12 (m, 1H), 6.97 (s, 1H), 6.92 (s, 1H), 4.10 (q, J = 6.9 Hz, 2H), 3.18-3.06 (m, 1H), 3.04-2.88 (m, 2H), 2.52-2.42 (m, 2H), 1.95 (dt, J = 13.2, 4.8 Hz, 1H), 1.29 (s, 3H), 1.21 (t, J = 6.9 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{28}H_{29}N_2O_4^+$ $[M + H]^+$ = 457.2, found 457.2.



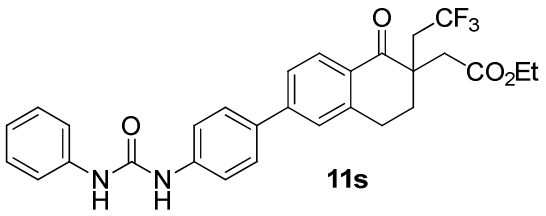
11p

Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11p): Phenyl isocyanate was reacted with compound **10a** using the procedure described for the synthesis of **11a** to obtain the desired compound **11p** as a white solid with a yield of 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 1H), 7.54-7.40 (m, 5H), 7.38-7.28 (m, 6H), 7.16-7.04 (m, 2H), 4.08 (q, *J* = 6.4 Hz, 2H), 3.16-2.80 (m, 3H), 2.52-2.4 (m, 2H), 2.05 (m, 1H), 1.8-1.62 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{29}H_{31}N_2O_4^+$ $[M + H]^+$ = 471.2, found 471.2.



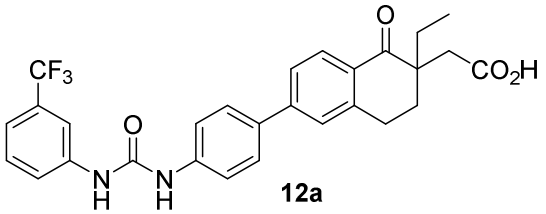
11q

Ethyl 2-(1-oxo-6-(4-(3-phenylureido)phenyl)-2-propyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (11q): 3-Phenyl isocyanate was reacted with compound **10d** using the procedure described for the synthesis of **11a** to obtain the desired compound **11q** as a white solid with a yield of 75%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.71 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.7 (d, *J* = 8.4 Hz, 2H), 7.65-7.55 (m, 4H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.3 (t, *J* = 6.9 Hz, 2H), 7.0 (t, *J* = 7.8 Hz, 1H), 4.1 (q, *J* = 7.8 Hz, 2H), 3.1-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 - 2.3 (m, 2H), 2.0 (m, 1H), 1.6 (m, 1H), 1.5-1.3 (m, 2H), 1.2 (m, 1H), 1.15 (t, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{30}H_{33}N_2O_4^+$ $[M + H]^+$ = 485.2, found 485.



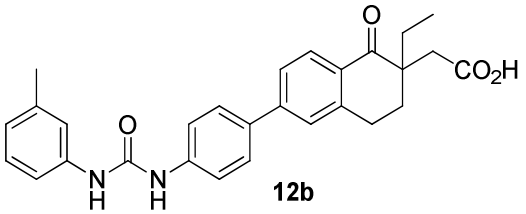
11s

Ethyl 2-(1-oxo-6-(4-(3-phenylureido)phenyl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (11s): Phenyl isocyanate (0.035 g, 0.3 mmol) was added to a solution of compound **10c** (0.12 g, 0.3 mmol) and triethylamine (0.06 g, 0.6 mmol) in THF (5 mL) and stirred at room temperature overnight. The solvent was removed under reduced pressure and product purified by flash chromatography using 20% ethyl acetate in hexanes to afford **11s** (0.08 g, 66%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, 8.4 Hz, 1H), 7.6-7.45 (m, 5H), 7.42-7.35 (m, 5H), 7.19 (m, 1H), 6.6 (s, 1H), 6.5 (s, 1H), 4.1 (q, *J* = 7.2 Hz, 2H), 3.1 (m, 2H), 2.9 (m, 2H), 2.63 (m, 2H), 2.5-2.3 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{29}H_{28}F_3N_2O_4^+$ $[M + H]^+$ = 525.2, found 526.



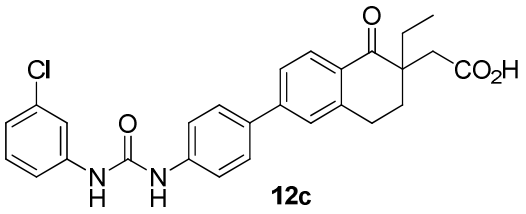
12a

2-(2-Ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12a): Lithium hydroxide (0.054 g, 1.38 mmol) was added to a solution of compound **11a** (0.25 g, 0.46 mmol) in 3 mL of ethanol-water (2:1) mixture. The mixture was stirred at room temperature for 12 h. After the solvent was removed *in vacuo*, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified to pH 2 with 2N aqueous HCl. The resulting solid was collected by filtration, triturated with n-pentane and diethyl ether and dried under vacuum to afford title compound **12a** (0.15 g, 63%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 8.1 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7 -7.5 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (t, J = 7.8 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{26}F_3N_2O_4^+$ $[M + H]^+$ = 511.2, found 511. HRMS calcd = 511.1845, found 511.1844.



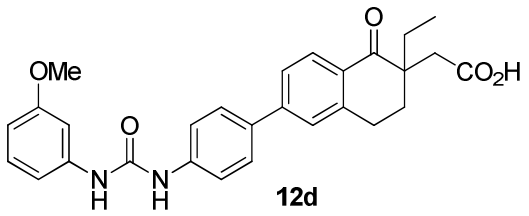
12b

2-(2-Ethyl-1-oxo-6-(4-(3-(m-tolyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12b): Compound **11b** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12b** as a white solid with a yield of 60%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.0 (bs, 1H), 8.8 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7-7.5 (m, 6H), 7.31 (s, 1H), 7.28-7.1 (m, 2H), 6.8 (d, J = 7.5 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 2.0 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t, J = 6.9 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{29}N_2O_4^+$ $[M + H]^+$ = 457.2, found 457.



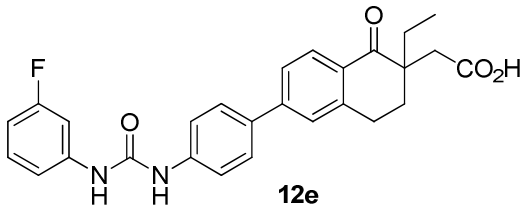
12c

2-(6-(4-(3-(3-Chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12c): Compound **11c** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12c** as a white solid with a yield of 62%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.0 (bs, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.73-7.56 (m, 6H), 7.3 (m, 3H), 7.02 (m, 1H), 3.2-2.7 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.75-1.45 (m, 2H), 0.9 (t, J = 7.5 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{26}ClN_2O_4^+$ $[M + H]^+$ = 477.1, found 477.



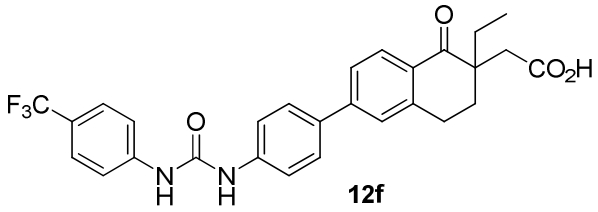
12d

2-(2-Ethyl-6-(4-(3-(3-methoxyphenyl)ureido)phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12d): Compound **11d** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12d** as a white solid with a yield of 55%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.6-9.0 (bs, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.66-7.48 (m, 6H), 7.26 (s, 1H), 7.16 (t, J = 8.4 Hz, 1H), 7.0 (d, J = 8.4 Hz, 1H), 6.56 (m, 1H), 3.8 (s, 3H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.4 Hz, 1H), 2.4 (m, 1H), 2.3 (d, J = 16.2 Hz, 1H), 2.0 (m, 1H), 1.78-1.5 (m, 2H), 0.85 (t, J = 6.9 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{29}N_2O_5^+$ $[M + H]^+$ = 473.1, found 473.



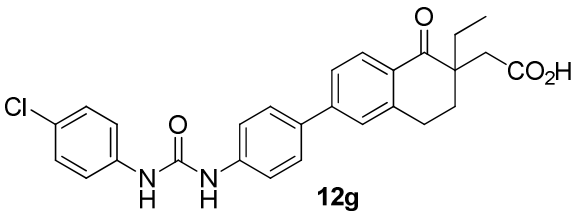
12e

2-(2-Ethyl-6-(4-(3-(3-fluorophenyl)ureido)phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12e): Compound **11e** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12e** as a white solid with a yield of 72%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7-7.4 (m, 7H), 7.3 (m, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.8 (t, J = 6.8 Hz, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 1.9 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t, J = 7.6 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{26}FN_2O_4^+$ $[M + H]^+$ = 461.1, found 461. HRMS calcd for $C_{27}H_{26}FN_2O_4$ $[M+H]^+$ = 461.1877, found 461.1874.



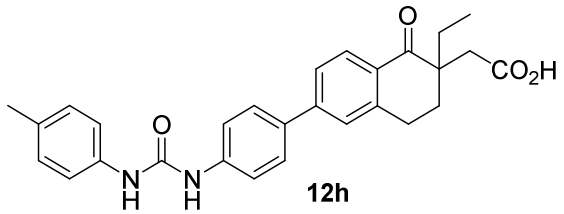
12f

2-(2-Ethyl-1-oxo-6-(4-(3-(4-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12f): Compound **11f** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12f** as a white solid with a yield of 63%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.8-7.5 (m, 10H), 3.2-2.9 (m, 2H), 2.85-2.7 (d, J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1,8-1.45 (m, 2H), 0.95 (m, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{26}F_3N_2O_4^+$ $[M + H]^+$ = 511.1, found 511. HRMS calcd for $C_{28}H_{26}F_3N_2O_4$ $[M+H]^+$ = 511.1845, found 511.1844.



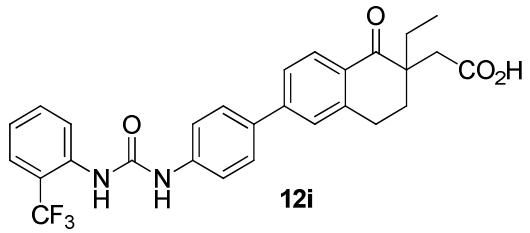
12g

2-(6-(4-(3-(4-Chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12g): Compound **11g** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12g** as a white solid with a yield of 65%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 8.95 (2s, 2H), 7.9 (d, J = 7.8 Hz, 1H) , 7.7 (d, J = 8.4 Hz, 2H), 7.6 (m, 4H), 7.5 (d, J = 8.4 Hz, 2H), 7.3 (d, J = 8.4 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.5 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, J = 7.5 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{26}ClN_2O_4^+$ $[M + H]^+$ = 477.1, found 477. HRMS calcd for $C_{27}H_{26}ClN_2O_4$ $[M+H]^+$ = 477.1581, found 477.1579.



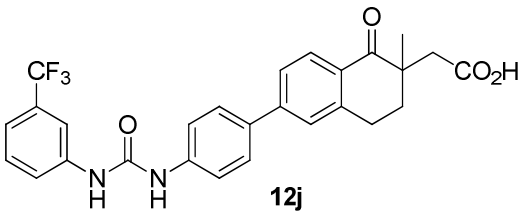
12h

2-(2-Ethyl-1-oxo-6-(4-(3-(p-tolyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12h): Compound **11h** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12h** as a white solid with a yield of 69%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.0-8.6 (bs, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.62-7.54 (m, 5H), 7.36 (d, J = 8.4 Hz, 2H), 7.1 (d, J = 8.4 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.4 Hz, 1H), 2.4 (m, 2H), 2.25 (s, 3H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{29}N_2O_4^+$ $[M + H]^+$ = 457.2, found 457.2. HRMS calcd for $C_{28}H_{29}N_2O_4$ $[M+H]^+$ = 457.2127, found 457.2124.



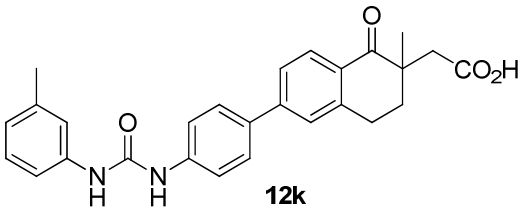
12i

2-(2-Ethyl-1-oxo-6-(4-(3-(2-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12i): Compound **11i** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12i** as a white solid with a yield of 55%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.7 (bs, 1H), 8.35 (bs, 1H), 7.9 (d, J = 8.4 Hz, 2H), 7.7-7.5 (m, 8H), 7.3 (t, J = 6.3 Hz, 1H), 3.3-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (m , 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{26}F_3N_2O_4^+$ $[M + H]^+$ = 511.1, found 511. HRMS calcd for $C_{28}H_{26}F_3N_2O_4$ $[M+H]^+$ = 511.1845, found 511.1844.



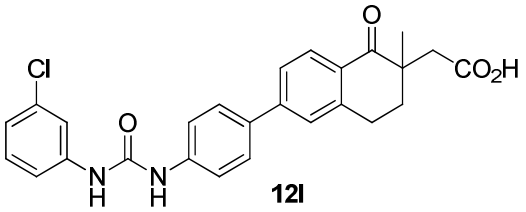
12j

2-(2-Methyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12j): Compound **11j** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12j** as a white solid with a yield of 54%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.16 (bs, 1H), 9.04 (bs, 1H), 8.04 (m, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.7 (d, J = 8Hz, 2H), 7.66-7.56 (m, 5H), 7.52 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 3.2-2.9 (m, 2H), 2.6 (d, J = 15.6 Hz, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{24}F_3N_2O_4^+$ [M + H]$^+$ = 497.1, found 497. HRMS calcd for $C_{27}H_{24}F_3N_2O_4$ [M+H]$^+$ = 497.1688, found 497.1685.



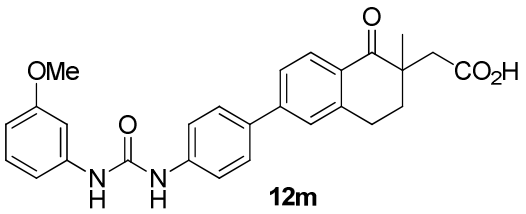
12k

2-(2-Methyl-1-oxo-6-(4-(3-(m-tolyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12k); Compound **11k** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12k** as a white solid with a yield of 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (bs, 1H), 8.9 (bs, 1H), 7.9 (d, J = 7.5 Hz, 1H), 7.7-7.5 (m, 6H), 7.32 (s, 1H), 7.25 (m, 1H), 7.23 (t, J = 7.8 Hz, 1H), 6.8 (d, J = 7.8 Hz, 1H), 3.3-2.9 (m, 2H), 2.85 (d, J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 1.9 (m, 1H), 1.2 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{25}N_2O_4^-$ [M - H]$^-$ = 441.1, found 441. HRMS calcd for $C_{27}H_{27}N_2O_4$ [M+H]$^+$ = 443.1971, found 443.1967.



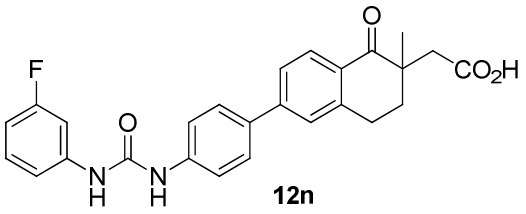
12l

2-(6-(4-(3-(3-Chlorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12l): Compound **11l** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12l** as a white solid with a yield of 58%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, J = 8 Hz, 1H), 7.76 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.5 (s, 1H), 7.48-7.36 (m, 5H), 7.25 (t, J = 12 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 3.2-2.8 (m, 2H), 2.7-2.5 (m, 2H), 2.2 (d, J = 15 Hz, 1H), 1.75 (d, J = 12 Hz, 1H), 1.2 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{26}H_{24}ClN_2O_4^+$ [M + H]$^+$ = 463.1, found 463.



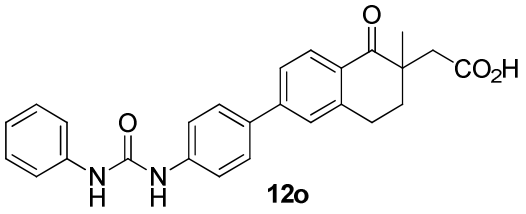
12m

2-(6-(4-(3-(3-Methoxyphenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12m): Compound **11m** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12m** as a white solid with a yield of 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.15 (bs, 1H), 9.05 (bs, 1H), 7.8 (d, J = 8 Hz, 2H), 7.75-7.55 (m, 5H), 7.2 (m, 2H), 6.95 (d, J = 6 Hz, 1H), 6.55 (m, 1H), 3.75 (s, 3H), 3.3-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{27}N_2O_5^+$ $[M + H]^+$ = 459.1, found 459. HRMS calcd for $C_{27}H_{27}N_2O_5$ $[M+H]^+$ = 459.1920, found 459.1917.



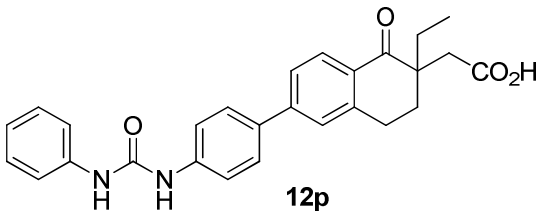
12n

2-(6-(4-(3-(3-Fluorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12n): Compound **11n** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12n** as a white solid with a yield of 59%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 7.8 (d, J = 8 Hz, 2H), 7.7 (d, J = 8.8 Hz, 2H), 7.65-7.55 (m, 3H), 7.5 (d, J = 12.4 Hz, 1H), 7.3 (q, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 6.8 (m, 1H), 3.2-2.85 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{26}H_{24}FN_2O_4^+$ $[M + H]^+$ = 447.1, found 447.



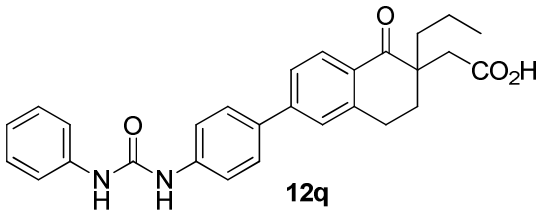
12o

2-(2-Methyl-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12o): Compound **11o** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12o** as a white solid with a yield of 52%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.85 (bs, 1H), 8.75 (bs, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.74-7.54 (m, 6H), 7.46 (d, J = 7.8 Hz, 2H), 7.3 (t, J = 7.5 Hz, 2H), 6.98 (t, J = 7.8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16 Hz, 1H), 2.4 (d, J = 16.2 Hz, 2H), 1.9 (m, 1H), 1.2 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{26}H_{25}N_2O_4^+$ $[M + H]^+$ = 429.1, found 429. HRMS calcd for $C_{26}H_{25}N_2O_4$ $[M+H]^+$ = 429.1814, found 429.1811.



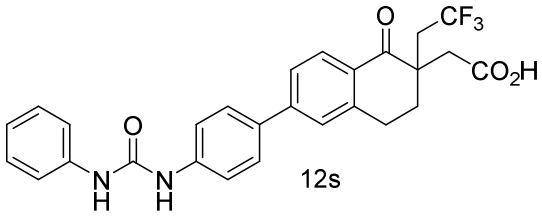
12p

2-(2-Ethyl-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12p): Compound **11p** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12p** as a white solid with a yield of 62%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.2-8.8 (m, 2H), 7.8 (d, J = 8.4 Hz, 1H), 7.7-7.55 (m, 6H), 7.45 (d, J = 8.4 Hz, 2H), 7.3 (t, J = 7.5 Hz, 2H), 6.95 (t, J = 7.5 Hz, 1H), 3.2-2.6 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, J = 7.8 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{27}N_2O_4^+$ $[M + H]^+$ = 443.1, found 443. HRMS calcd for $C_{27}H_{27}N_2O_4$ $[M+H]^+$ = 443.1971, found 443.1967.



12q

2-(1-Oxo-6-(4-(3-phenylureido)phenyl)-2-propyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12q): Compound **11q** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12q** as a white solid with a yield of 65%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 9.1-8.9 (s, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.68-7.56 (m, 6H), 7.48-7.46 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 6.97 (t, J = 7.6 Hz, 1H), 3.08-2.92 (m, 2H), 2.80 (d, J = 16.4 Hz, 1H), 2.40 (m, 1H), 1.96 (m, 1H), 1.61 (m, 1H), 1.45-1.15 (m, 4H), 0.84 (m, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{29}N_2O_4^+$ $[M + H]^+$ = 457.2, found 457. HRMS calcd for $C_{28}H_{29}N_2O_4$ $[M+H]^+$ = 457.2127, found 457.2124.

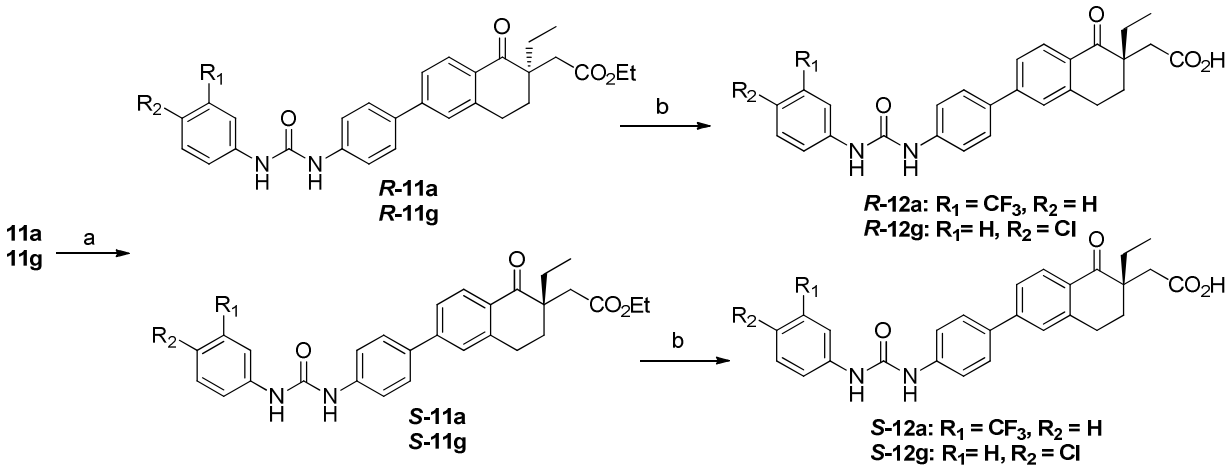


12s

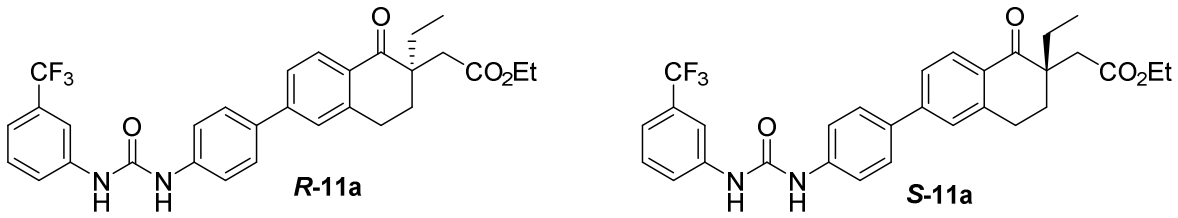
2-(1-oxo-6-(4-(3-phenylureido)phenyl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12s): Compound **11s** was hydrolysed using the procedure described for synthesis of compound **12a** to obtain the desired compound **12s** as a white solid with a yield of 66%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.15 (bs, 1H), 8.95 (bs, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.7 -7.62 (m, 4H), 7.57 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 3.2-2.9 (m, 3H), 2.83-2.67 (m, 2H), 2.6-2.45 (m, 2H), 2.15 (m, 1H). LRMS (ESI$^+$) m/z calcd $C_{27}H_{22}F_3N_2O_4^-$[M -H]$^-$ = 495.1, found 495.

Chiral Separation of Ureidotetralones

Racemic Compound **11a** and **11g** was separated into R & S isomers ***R*-** and ***S*-11a** and ***R*-** and ***S*-11g** respectively using chiral separation. The absolute stereo chemical determination was assigned using Vibrational Circular Dichroism. These separated esters ***R*-** and ***S*-11a** and ***R*-** and ***S*-11g** were hydrolysed further using the procedure described for synthesis of compound **12** to yield ***R*-** and ***S*-12a** and ***R*-** and ***S*-12g** respectively as shown below.

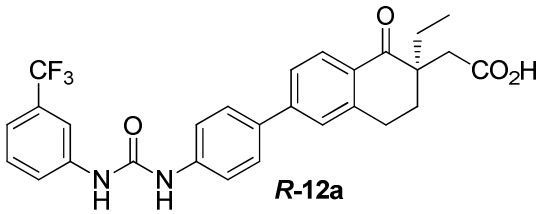


Reagents and conditions: a) Chiral Separation; b) LiOH, THF-H_2O.



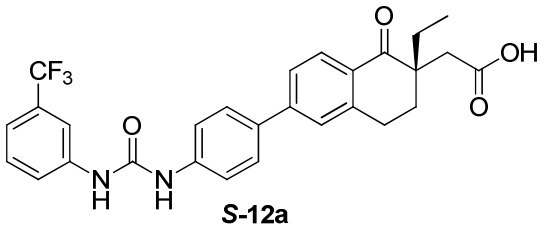
(*S*)-Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (*S*-11a): Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (**11a**) (0.5 g) was racemic mixture with 1:1 enantiomeric ratio and was separated on chiral column to obtain single enantiomer of ***S*-11a** (0.17 g, 15.67 min RT, Optical rotation +22 (c1 $CHCl_3$)) and ***R*-11a** (0.168 g, 20.16 min RT, Optical rotation -22 (c1 $CHCl_3$)) using conditions as described here: [Column: CHIRAL PAK ODH (4.6x250 mm) 5µ; Mobile phase: A: Hexane, B: Ethanol; A: B (Iso) 85:15; Flow rate: 0.8 mL/min]. Absolute configurations were confirmed by VCD studies. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, 8.4 Hz, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.5-7.3 (m, 9H), 7.1 (s, 1H), 4.1 (q, *J* = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.4-1.2 (m, 3H), 0.9 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{30}H_{30}F_3N_2O_4^+$ $[M + H]^+$ = 539.2, found 539.2 ORD +22 (c1 $CHCl_3$).

Compound ***R*-11a** ORD -22 (c1 $CHCl_3$).



***R*-12a**

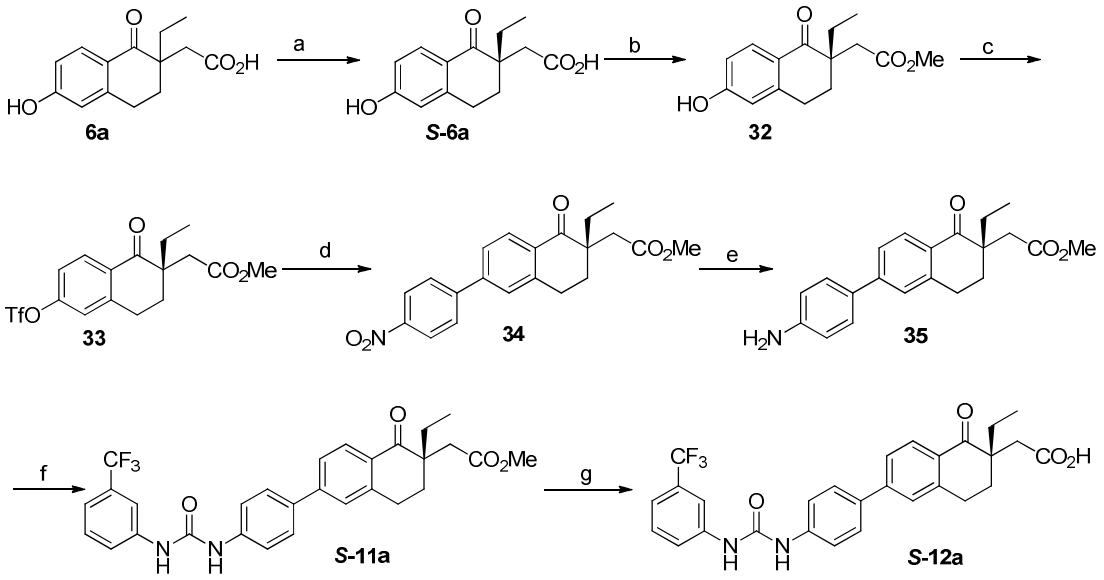
(*R*)-2-(2-ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (*R*-12a): Compound ***R*-11a** was hydrolysed using the procedure described for the synthesis of **12a** to yield title compound ***R*-12a** (0.08g, 72%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.22 (bs, 1H), 9.09 (bs, 1H), 8.05 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.6-7.4 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (t, J = 5.7 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{26}F_3N_2O_4^+$ $[M + H]^+$ = 511.1, found 511. HRMS calcd for $C_{28}H_{26}F_3N_2O_4$ $[M+H]^+$ = 511.1845, found 511.1845.



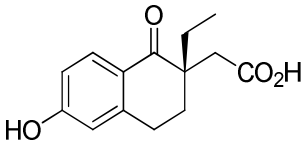
***S*-12a**

(*S*)-2-(2-Ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (*S*-12a): Lithium hydroxide (0.028 g, 0.67 mmol) was added to a solution of ***S*-11a** (0.12 g, 0.22 mmol) in 4 mL of ethanol-water (3:1) mixture, and the reaction mixture was stirred at room temperature for 16 h. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 ^{o}C, and solids were collected by filtration, triturated with n-pentane and dried under vacuum to afford title compound ***S*-12a** (0.08 g, 72%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.22 (bs, 1H), 9.09 (bs, 1H), 8.05 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.6-7.4 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (t, J = 5.7 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{26}F_3N_2O_4^+$ $[M + H]^+$ = 511.1, found 511. HRMS calcd for $C_{28}H_{26}F_3N_2O_4$ $[M+H]^+$ = 511.1845, found 511.1844.

Alternative enantioselective synthesis of *S*-12a:



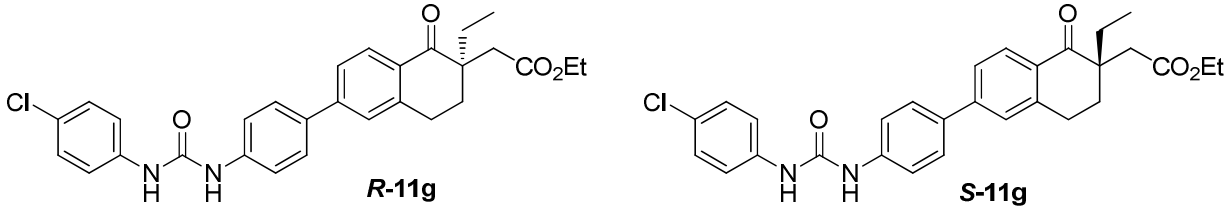
Reagents and conditions: a) Cinchonidine, IPA-H_2O; b) H_2SO_4, MeOH; c) Tf_2O, CH_2Cl_2, Et_3N; d) 4-Nitrophenyl boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O; e) Fe-NH_4Cl, EtOH-H_2O; f) 3-CF_3PhNCO, Et_3N, THF; g) LiOH, THF-H_2O.



***S*-6a**

(*S*)-2-(2-ethyl-6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (*S*-6a): Cinchonidine (11.85 g, 40.3 mmol) was added to a solution of racemic mixture of **6a** (10 g, 40.3 mmol), in isopropyl alcohol (64 mL) and water (16 mL), and the mixture was heated to 80 ^oC 4 h. The resulting solution was stirred at room temperature for 16 h, and the residue was filtered and washed with a mixture of isopropyl alcohol (10 mL) and water (10 mL). The residue was dissolved in 6N HCl (40 mL) and extracted with ethyl acetate (2x50 mL). The organic layers were washed with water, brine solution, dried and concentrated to afford the title compound (1.3 g, 26%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 10.2 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 6.70 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.60 (d, J = 1.2 Hz, 1H), 3.0-2.88 (m, 1H), 2.77 (m, 1H), 2.7 (d, J = 16.8 Hz, 1H), 2.38 (m, 1H), 2.31 (d, J = 16.4 Hz, 1H), 1-95-1.85 (m, 1H), 1.62 (m, 1H), 1.48 (m, 1H), 0.8 (t, J = 7.2 Hz, 3H).

Examples **32**, **33**, **34**, **35**, ***S*-11a** and ***S*-12a** were synthesized from chiral ***S*-6a** using the similar procedures as described for the synthesis of **12a.**

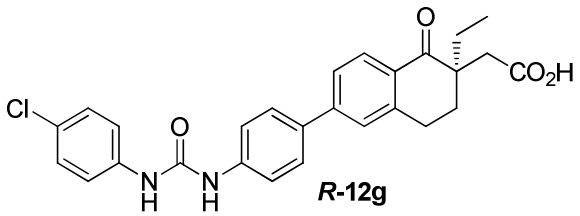


***R*-11g** ***S*-11g**

Compound ***R*-11g** & ***S*-11g** were obtained by chiral separation of racemic compound **11g**.

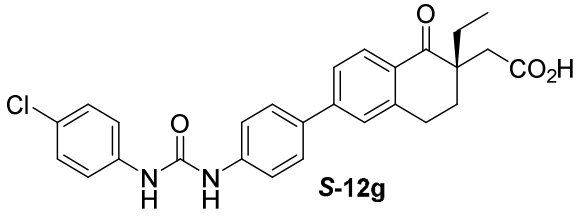
Ethyl (*R*)-2-(6-(4-(3-(4-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (*R*-11g): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.45-7.36 (m, 3H), 7.34-7.28 (m, 6H), 7.24-7.18 (m, 3H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.15-3.05 (m, 1H), 3.02 (d, *J* = 16.0 Hz, 1H), 2.88 (m, 1H), 2.48 (d, *J* = 16.4 Hz, 1H), 2.44 (m, 1H), 2.05 (dt, *J* = 10.4, 4.4 Hz, 1H), 1.82-1.62 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{29}H_{30}ClN_2O_4^+$ $[M + H]^+$ = 505.1, found 505.

Ethyl (*S*)-2-(6-(4-(3-(4-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (*S*-11g): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.44-7.36 (m, 3H), 7.36-7.28 (m, 6H), 7.24-7.18 (m, 3H), 4.09 (q, *J* = 6.8 Hz, 2H), 3.15-3.05 (m, 1H), 3.02 (d, *J* = 16.4 Hz, 1H), 2.88 (m, 1H), 2.48 (d, *J* = 16.4 Hz, 1H), 2.44 (m, 1H), 2.05 (dt, *J* = 10.4, 4.4 Hz, 1H), 1.80-1.62 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{29}H_{30}ClN_2O_4^+$ $[M + H]^+$ = 505.1, found 505.



***R*-12g**

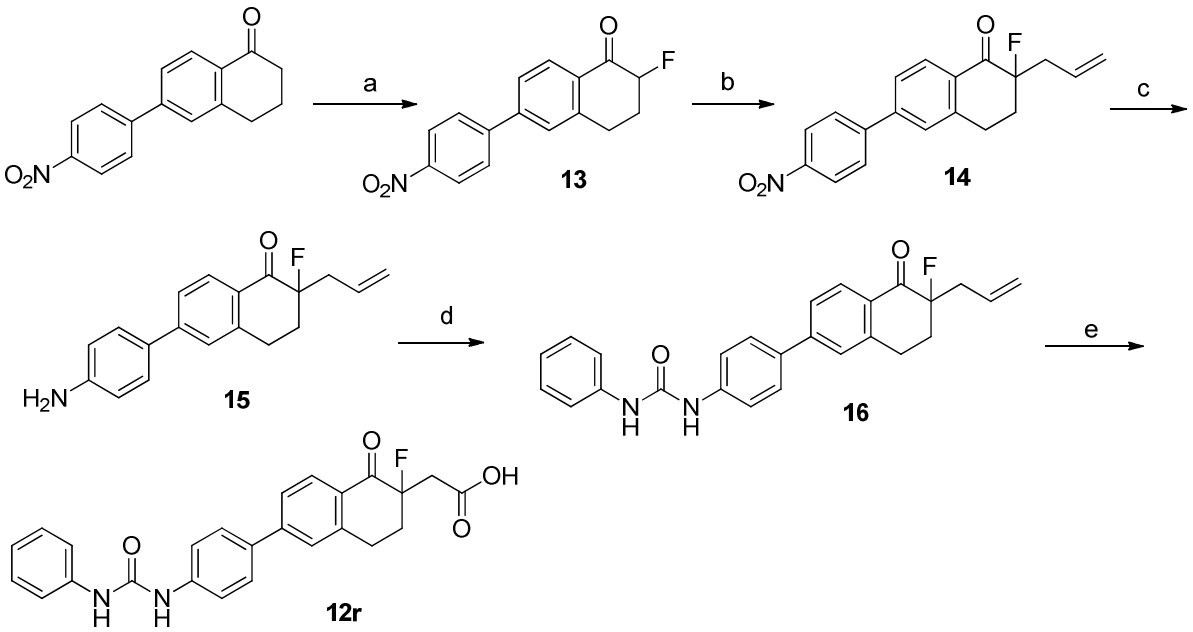
(*R*)-2-(6-(4-(3-(4-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (*R*-12g): Compound ***R*-11g** was hydrolysed using the procedure described for the synthesis of **12a** to yield title compound ***R*-12g** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.1 (bs, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.7-7.54 (m, 6H), 7.5 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 3.2-2.9 (m, 2H), 2.79 (d, *J* = 16.8 Hz, 1H), 2.45 (m, 1H), 2.41 (d, *J* = 16.4 Hz, 1H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{26}ClN_2O_4^+$ $[M + H]^+$ = 477.1, found 477. HRMS calcd for $C_{27}H_{26}ClN_2O_4$ $[M+H]^+$ = 477.1581, found 477.1580.



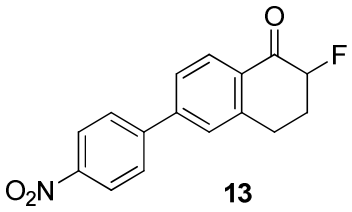
***S*-12g**

(*S*)-2-(6-(4-(3-(4-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (*S*-12g): Compound ***S*-11g** was hydrolysed using the procedure described for the synthesis of **12a** to yield title compound ***S*-12g** as a white solid.^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.1 (bs, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.7-7.54 (m, 6H), 7.5 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 3.2-2.9 (m, 2H), 2.79 (d, *J* = 16.8 Hz, 1H), 2.45 (m, 1H), 2.41 (d, *J* =16.4 Hz, 1H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{27}H_{26}ClN_2O_4^+$ $[M + H]^+$ = 477.1, found 477. HRMS calcd for $C_{27}H_{26}ClN_2O_4$ $[M+H]^+$ = 477.1581, found 477.1581.

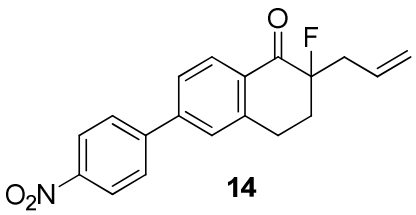
Synthesis of 2-(2-fluoro-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12r)



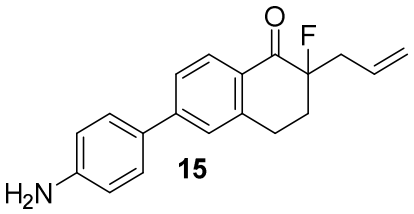
Reagents and conditions: a) Selectfluor, MeOH; b) Allyl bromide, TBAI, KOH; c) Fe/NH_4Cl, EtOH, H_2O; d) PhNCO, Et_3N, THF; e) $KMnO_4$, $NaIO_4$, acetone-H_2O.



2-Fluoro-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (13): Selectfluor (1.27 g, 3.58 mmol) was added to 6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one which was obtained from 6-methoxy-1-tetralone (**1**) by using similar procedures described for **6a** (demethylation), **8a** (triflation) and **9a** (Suzuki coupling) (0.8 g, 2.99 mmol) in 20 mL of methanol. The reaction mixture was refluxed for 4 h, and the solvent was then removed under vacuum to obtain the residue. The residue was dissolved in dichloromethane. Insoluble materials were filtered, and filtrate was washed with water followed by brine solution. The organic layer was dried over sodium sulfate, filtered and concentrated to afford title compound (0.6 g, 70%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (m, 2H), 8.20 (d, *J* = Hz, 1H), 7.75 (m, 2H), 7.65 (m, 1H), 7.52 (s, 1H), 5.30-5.10 (m, 1H), 3.30 (m, 2H), 2.65 (m, 1H), 2.40 (m, 1H). LRMS (ESI^+) *m/z* calcd $C_{16}H_{13}FNO3^+$ $[M + H]^+$ = 286, found 286.

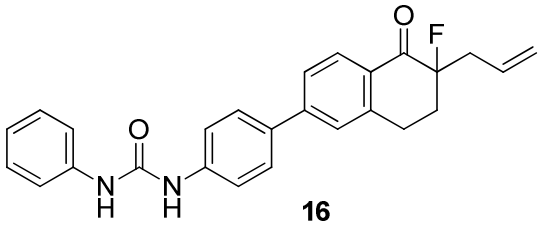


2-Allyl-2-fluoro-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (14): Allyl bromide (1.89 g, 15.7 mmol) was added to a solution of **13** (3.0 g, 10.5 mmol), KOH (1.17 g, 21.0 mmol) and TBAI (0.77 g, 2.00 mmol) in Toluene (120 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with water and ethyl acetate. The separated organic layer was washed with water, brine solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography using 10% ethyl acetate in hexanes to afford title compound (2.5 g, 73%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38-8.32 (m, 2H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.80-7.75 (m, 2H), 7.61 (m, 1H), 7.50 (s, 1H), 5.86 (m, 1H), 5.23 (d, *J* =8.4 Hz, 2H), 3.25-3.09 (m, 2H), 2.77-2.25 (m, 4H). LRMS (ESI^{+}) *m/z* calcd $C_{19}H_{17}FNO_3^{+}$ $[M + H]^{+}$ = 326.1, found 326.



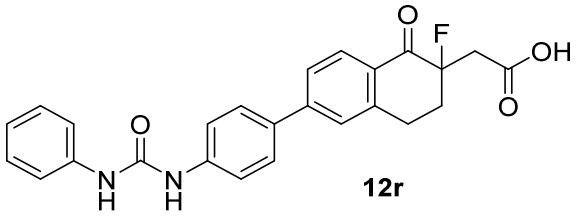
15

2-Allyl-6-(4-aminophenyl)-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (15): Iron powder (0.214 g, 3.86 mmol) and NH_4Cl (0.040g, 0.74 mmol) was added to a solution of **14** (0.51g, 1.53 mmol) in 25 mL of ethanol-water (2:1) mixture. The reaction mixture was refluxed for 2 h, and solvent was removed under reduced pressure. The crude product was purified by flash chromatography using 2% methanol in chloroform to afford title compound (0.3 g, 66%) as a solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.5 Hz, 1H), 7.53 (dd, J_1 = 1.2 Hz, J_2 = 8.1 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.39 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.98-5.84 (m, 1H), 5.29-5.20 (m, 2H), 3.84 (bs, 2H), 3.16-2.97 (m, 2H), 2.80-2.54 (m, 2H), 2.46-2.33 (m, 2H). LRMS (ESI^{+}) *m/z* calcd $C_{19}H_{19}FNO^{+}$ $[M + H]^{+}$ = 296.1, found 296.



16

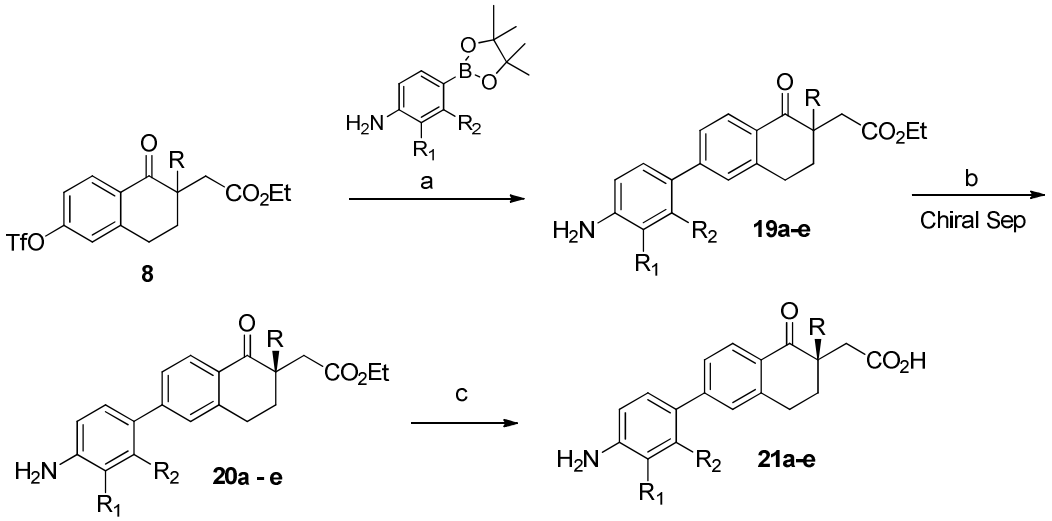
1-(4-(6-Allyl-6-fluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)phenyl)-phenyl)urea (16): Phenyl isocyanate was reacted with compound **15** using the procedure described for the synthesis of **11a** to obtain the desired compound **16** as a white solid with a yield of 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.5 Hz, 1H), 7.62 - 7.45 (m, 6H), 7.42 - 7.32 (m, 5H), 7.30 - 7.15 (m, 2H), 5.94 - 5.76 (m, 1H), 5.29 - 5.15 (m, 2H), 3.25 – 3.0 (m, 2H), 2.80 - 2.55 (m, 2H), 2.48 - 2.32 (m, 2H). LRMS (ESI^{+}) *m/z* calcd $C_{26}H_{24}FN_2O_2^{+}$ $[M + H]^{+}$ = 415.1, found 415.



12r

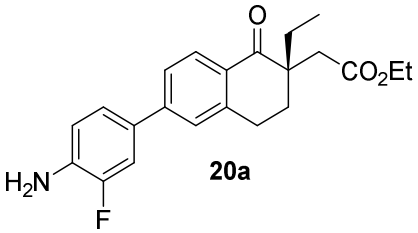
2-(2-Fluoro-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (12r): $KMnO_4$ (0.196 g, 1.24 mmol) was added to a solution of **16** (0.25 g, 0.6 mmol) and $NaIO_4$ (1.28 g, 6 mmol) in 35 mL of acetone-water (2:1) mixture. The reaction mixture was stirred at room temperature overnight. After the solvent was removed *in vacuo*, the residue was dissolved in water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and removed under reduced pressure to obtain the crude product which was purified by the preparative HPLC to afford title compound (0.075 g, 26%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.60 (bs, 1H), 8.88 (bs, 1H), 8.73 (bs, 1H), 7.95 (d, J = 8.4Hz, 1H), 7.71 (t, J = 8.8 Hz, 4H), 7.59 (d, J =8.4 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.17 (m, 2H), 3.16-3.04 (m, 2H), 2.93 (m, 1H), 2.89 (m, 1H). LRMS (ESI$^+$) m/z calcd $C_{25}H_{22}FN_2O_4^+$ $[M + H]^+$ = 433.1, found 433. HRMS calcd for $C_{25}H_{22}FN_2O_4$ $[M+H]^+$ = 433.1564, found 433.1561.

Syntheses of Compounds 21a-e:



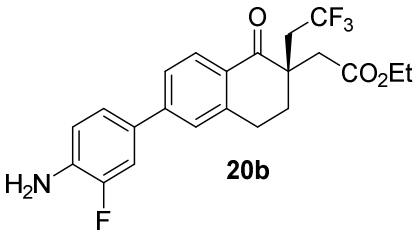
19a, **20a**, **21a**: R = Et, R_1 = F, R_2 = H
19b, **20b**, **21b**: R = CH_2CF_3, R_1 = F, R_2 = H
19c, **20c**, **21c**: R = Me, R_1 = H, R_2 = Cl
19d, **20d**, **21d**: R = Et, R_1 = H, R_2 = Cl
19e, **20e**, **21e**: R = CH_2CF_3, R_1 = H, R_2 = Cl

Reagents and conditions: a) Substituted 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O; b) Chiral Separation; c) LiOH, THF-H_2O.



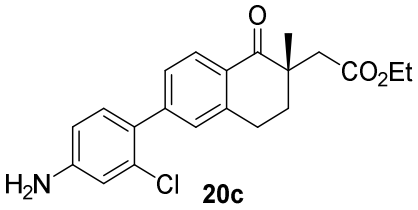
20a

Ethyl (*S*)-2-(6-(4-amino-3-fluorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (20a): Compound **8a** (3.5 g, 8.57 mmol) was reacted with 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.03 g, 8.57 mmol) as per the procedure described for the synthesis of **9a** to afford title compound **19a** (1.8 g, 56%) as solid. Compound **19a** was purified and racemate was separated using chiral prep to obtain **20a** as the desired *S* isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 - 8.14 (m, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.20 - 7.37 (m, 4H), 6.84 (t, *J* = 8.56 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.86 (bs, 2H), 3.03 - 3.22 (m, 1H), 2.87 - 2.99 (m, 2H), 2.39 - 2.56 (m, 1H), 2.39 - 2.51 (m, 1H), 2.08 (dt, *J* = 13.6, 4.2 Hz, 1H), 1.61 - 1.83 (m, 2H), 1.22 (t, *J* = 7.09 Hz, 3H), 0.92 (t, *J* = 7.34 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{22}H_{25}FNO_3^+$ $[M + H]^+$ = 370.1, found 370.



20b

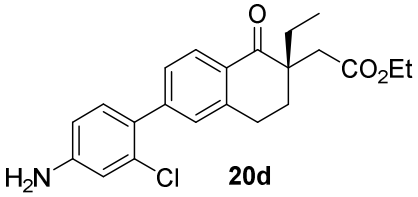
Ethyl (*S*)-2-(6-(4-amino-3-fluorophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (20b): Compound **8c** was reacted with 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as per the procedure described for the synthesis of **9a** to obtain desired compound **19b** (1.8 g, 56%) as solid. Compound **19b** was purified and racemate was separated using chiral prep to obtain **20b** as the desired S isomer as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.38 (s, 1H), 7.22 - 7.33 (m, 2H), 6.85 (t, *J* = 8.4 Hz, 1H), 4.14 (q, *J* = 7.6 Hz, 2H), 3.85 - 3.92 (m, 2H), 3.05 - 3.13 (m, 2H), 2.85 - 2.95 (m, 2H), 2.56 - 2.69 (m, 2H), 2.41 - 2.50 (m, 1H), 2.31 - 2.39 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{22}H_{22}F_4NO_3^+$ $[M + H]^+$ = 424.1, found 424.



20c

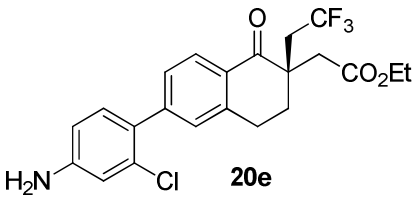
Ethyl (*S*)-2-(6-(4-amino-2-chlorophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (20c): Compound **8b** was reacted with 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as per the procedure described for the synthesis of **9a** to afford title compound **19c** as an off white solid. Compound **19c** was purified and racemate was separated using chiral prep to obtain **20c** as the desired S

isomer. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (d, J = 8 Hz, 1H), 7.36 (dd, J = 7.83, 1.6 Hz, 1H), 7.32 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 2 Hz, 1H), 6.61 (dd, J = 8.4, 2.0 Hz, 1H), 5.61 (s, 2H), 4.01 (q, J = 6.8 Hz, 2H), 2.99 - 3.10 (m, 1H), 2.88 - 2.98 (m, 1H), 2.84 (d, J = 16 Hz, 1H), 2.50 - 2.54 (m, 1H), 2.27 - 2.40 (m, 1H), 1.90 (dt, J = 12, 4.4 Hz, 1H), 1.18 (s, 3H), 1.09 (t, J = 6.8 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{21}H_{23}ClNO_3^+$ $[M + H]^+$ = 372, found 372.



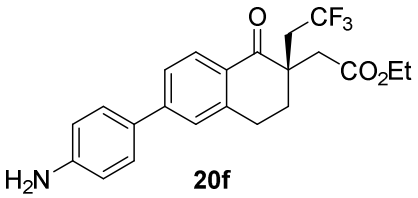
20d

Ethyl (*S*)-2-(6-(4-amino-2-chlorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (20d): Compound **8a** (3.5 g, 8.57 mmol) was reacted with 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as per the procedure described for the synthesis of **9a** to afford title compound **19d** as an off white solid. Compound **19d** was purified and racemate was separated using chiral prep to obtain **20d** as the desired S isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 - 8.14 (m, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.26 (s, 2H), 7.11 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.63 (dd, J = 8.4, 1.96 Hz, 1H), 4.03 - 4.18 (m, 2H), 3.81 (s, 2H), 3.01 - 3.23 (m, 1H), 2.83 - 2.98 (m, 2H), 2.37 - 2.58 (m, 2H), 2.08 (dt, J =13.6, 4.0 Hz, 1H), 1.62 - 1.88 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.6 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{22}H_{25}ClNO_3^+$ $[M + H]^+$ = 386.1, found 386.



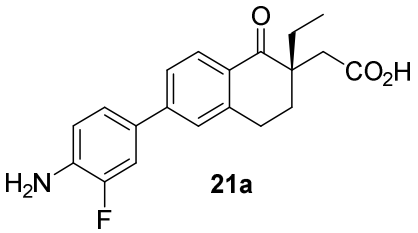
20e

Ethyl (*S*)-2-(6-(4-amino-2-chlorophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (20e): Compound **8c** was reacted with 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as per the procedure described for the synthesis of **9a** to afford title compound **19e** as a white solid. Compound **19e** was purified and racemate was separated using chiral prep to obtain **20e** as the desired *S* isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 2 Hz, 1H), 6.64 (dd, J = 8.4, 2.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.72 - 3.92 (m, 2H), 3.03 - 3.16 (m, 2H), 2.85 - 2.95 (m, 2H), 2.54 - 2.69 (m, 2H), 2.30 - 2.50 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) m/z calcd $C_{22}H_{22}ClF_3NO_3^+$ $[M + H]^+$ = 440, found 439.



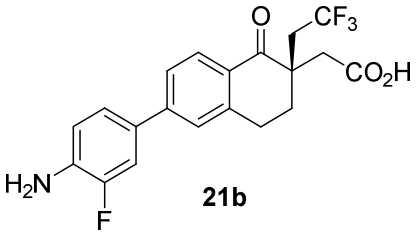
20f

Ethyl (*S*)-2-(6-(4-aminophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (20f): Compound **10c** was separated using chiral prep to obtain **20f** as the desired *S* isomer. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.86 (d, J = 8.1 Hz, 1H), 7.52 - 7.53 (m, 1H), 7.50 - 7.63 (m, 1H), 7.49 - 7.63 (m, 1H), 7.49 - 7.60 (m, 1H), 7.39 - 7.64 (m, 1H), 7.48 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 5.45 (s, 2H), 4.03 (q, J = 7.2 Hz, 2H), 3.01 - 3.14 (m, 2H), 2.79 - 2.98 (m, 2H), 2.58 - 2.72 (m, 2H), 2.28 - 2.44 (m, 1H), 2.08 - 2.22 (m, 1H), 1.17 - 1.18 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{22}H_{23}F_3NO_3^+$ $[M + H]^+$ = 406. found 406.



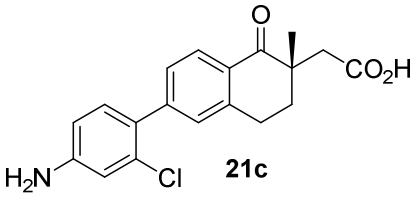
21a

(*S*)-2-(6-(4-amino-3-fluorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (21a): Compound **20a** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **21a** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 7.86 (d, J = 8.31 Hz, 1H), 7.51 - 7.60 (m, 2H), 7.41 - 7.48 (m, 1H), 7.34 (dd, J = 8.4, 2.0 Hz, 1H), 6.85 (t, J = 8.8 Hz, 1H), 5.46 (s, 2 H), 2.99 - 3.13 (m, 1H), 2.85 - 2.97 (m, 1H), 2.77 (d, J = 16.2 Hz, 1H), 2.31 - 2.47 (m, 2H), 1.91 - 2.03 (m, 1H), 1.67 (dq, J = 14.2, 7.2 Hz, 1H), 1.52 (dq, J = 14.2, 7.2 Hz, 1H), 0.83 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{20}H_{21}FNO_3^+$ $[M + H]^+$ = 342, found 342.



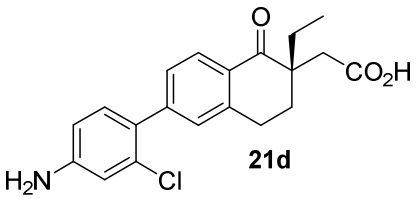
21b

(*S*)-2-(6-(4-amino-3-fluorophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (21b): Compound **20b** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **21b** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.40 (bs, 1H) 7.87 (d, J = 8.1 Hz, 1H), 7.54 - 7.62 (m, 2H), 7.47 (dd, J = 12.9, 1.8 Hz, 1H), 7.36 (dd, J = 8.1, 1.8 Hz, 1H), 6.85 (t, J = 9 Hz, 1H) 5.50 (bs, 2H), 2.88 - 3.17 (m, 3H), 2.64 - 2.85 (m, 2H), 2.55 (d, J = 16.5 Hz, 1H), 2.36 - 2.45 (m, 1H), 2.08 - 2.22 (m, 1H). LRMS (ESI$^+$) *m/z* calcd $C_{20}H_{18}F_4NO_3^+$ $[M + H]^+$ = 396, found 396.



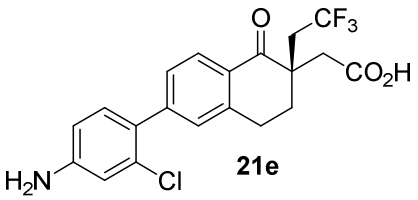
21c

(*S*)-2-(6-(4-amino-2-chlorophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (21c): Compound **20c** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **21c** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.31 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 1.6 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1 H), 5.60 (br s, 2H), 3.02 - 3.17 (m, 1H), 2.88 - 2.99 (m, 1H), 2.82 (d, J = 16 Hz, 1H), 2.44 (dd, J = 12.8, 4.4 Hz, 1H), 2.37 (d, J = 16 Hz, 1H), 1.81 - 1.94 (m, 1H), 1.16 (s, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{19}H_{19}ClNO_3^+$ $[M + H]^+$ = 344, found 344.



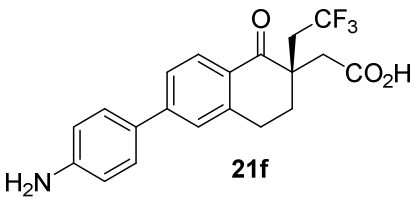
21d

(*S*)-2-(6-(4-amino-2-chlorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (21d): Compound **20d** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **21d** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.84 (d, J = 8.1 Hz, 1H), 7.13 - 7.36 (m, 3H), 7.09 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 8.4, 2.1 Hz, 1H), 5.58 (bs, 2H), 2.83 - 3.01 (m, 2H), 2.64 (d, J = 15.6 Hz, 1H), 2.51 - 2.57 (m, 1H), 2.16 (d, J = 15.6 Hz, 1H), 1.83 - 1.97 (m, 1H), 1.67 (dq, J = 14.2, 7.2 Hz, 1H), 1.51 (dq, J = 14.2, 7.2 Hz, 1H), 0.82 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{20}H_{21}ClNO_3^+$ $[M + H]^+$ = 358, found 358.



21e

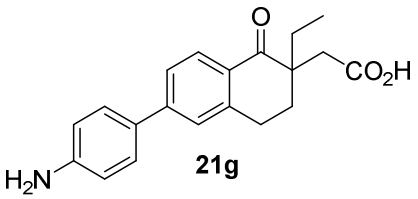
(*S*)-2-(6-(4-amino-2-chlorophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (21e): Compound **20e** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **21e** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.3 (bs, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 2 Hz, 1H), 6.60 (dd, J = 8.4, 2.0 Hz, 1H), 5.62 (br s, 2H), 2.94 - 3.13 (m, 3H), 2.70 - 2.84 (m, 2H), 2.52 (m, 1H), 2.40 - 2.47 (m, 1H), 2.09 - 2.19 (m, 1H). LRMS (ESI$^+$) *m/z* calcd $C_{20}H_{18}ClF_3NO_3^+$ $[M + H]^+$ = 412, found 412.



21f

(*S*)-2-(6-(4-aminophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (21f Compound **20f** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **21f** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.42 (bs, 1H), 7.86 (d, J = 8.1

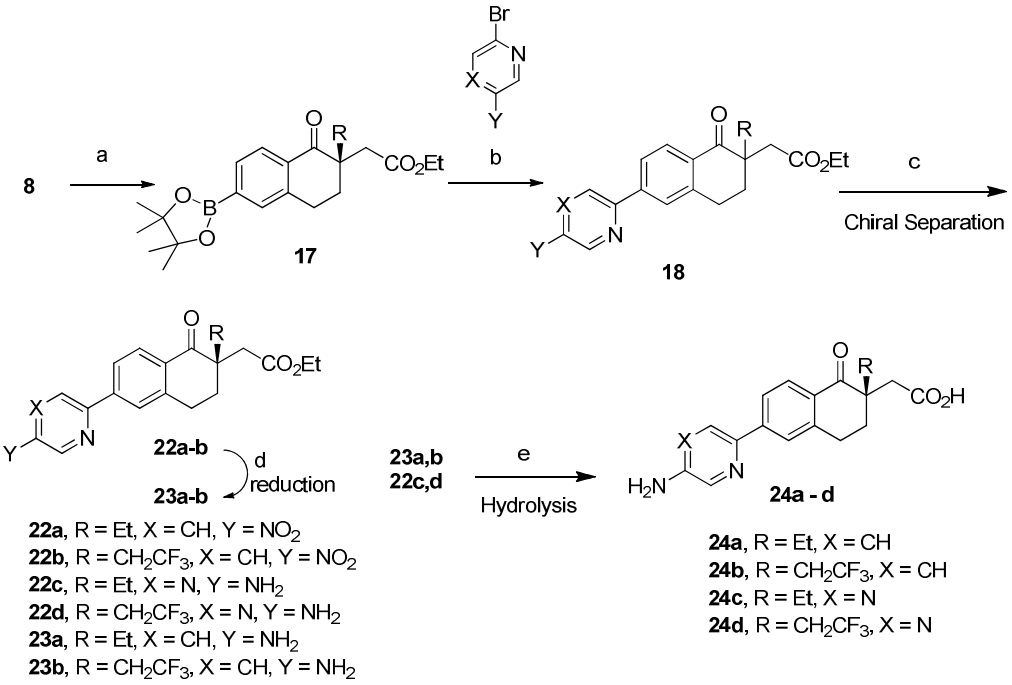
Hz, 1H) 7.55 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 5.44 (bs, 2H), 2.90 - 3.16 (m, 3H), 2.66 - 2.84 (m, 2H), 2.56 (s, 1H), 2.33 - 2.45 (m, 1H), 2.06 - 2.21 (m, 1H). LRMS (ESI^+) *m/z* calcd $C_{20}H_{19}F_3NO_3^+$ $[M + H]^+$ = 378, found 378.



21g

2-(6-(4-Aminophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (21g): Compound **10a** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **21g** as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.10 (bs, 1H), 7.85 (d, *J* = 8.31 Hz, 1H), 7.42-7.54 (m, 4H), 6.65 (d, *J* = 8.31 Hz, 2H), 5.40 (bs, 2H), 2.98-3.11 (m, 1H), 2.85-2.96 (m, 1H), 2.75 (d, *J* = 16.14 Hz, 1H), 2.31-2.47 (m, 3H), 1.96 (d, *J* = 13.21 Hz, 1H), 1.45-1.57 (m, 1H), 0.83 (t, *J* = 7.34 Hz, 3H).

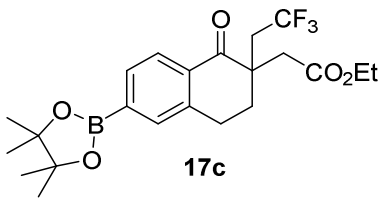
Synthesis of Compounds 24a-d:



22a, R = Et, X = CH, Y = NO_2
22b, R = CH_2CF_3, X = CH, Y = NO_2
22c, R = Et, X = N, Y = NH_2
22d, R = CH_2CF_3, X = N, Y = NH_2
23a, R = Et, X = CH, Y = NH_2
23b, R = CH_2CF_3, X = CH, Y = NH_2

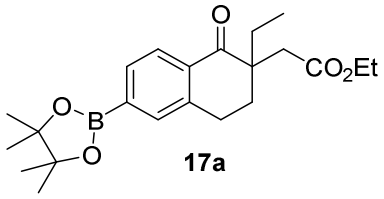
24a, R = Et, X = CH
24b, R = CH_2CF_3, X = CH
24c, R = Et, X = N
24d, R = CH_2CF_3, X = N

Reagents and conditions: a) $PdCl_2$(dppf)-CH_2Cl_2, 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane), KOAc, Dioxane-H_2O; b) Heteroaryl bromide, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O; c) Chiral Separation; d) Fe-NH_4Cl, EtOH-H_2O; e) LiOH, THF-H_2O.



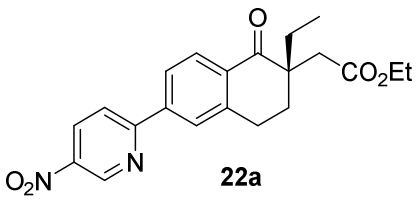
17c

Ethyl 2-(1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (17c): $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.58 g, 0.71 mmol) was added to compound **8c** (6.6 g, 14.27 mmol) in 50 mL of 1,4 dioxane in argon atmosphere, followed by potassium acetate (4.19 g, 42.85 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.62 g, 14.27 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 5 hr, cooled to room température and filtered over celite bed. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound **17c** (5.6 g, 89%) as viscous liquid. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.6-7.7 (m, 1H), 7.70 (s, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.2-2.6 (m, 6H), 2.42-2.0 (m, 2H), 1.23 (m, 12H), 1.05 (t, *J* = 7.2 Hz, 3H).



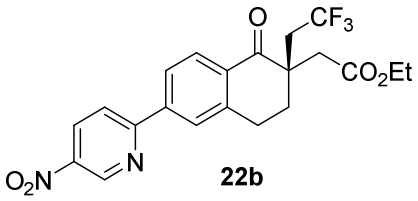
17a

Ethyl 2-(2-ethyl-1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (18a): Compound **8a** was converted to compound **17a** using the procedure described for the synthesis of **17c** with a yield of 58%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.52 (d, *J* = 2.1 Hz, 1H), 8.57 (dd, *J* = 8.7, 2.7 Hz, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.91 - 8.05 (m, 3H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.11 - 3.27 (m, 1H), 2.94 - 3.08 (m, 2H), 2.44 - 2.58 (m, 2H), 2.05 - 2.20 (m, 1H), 1.62 - 1.86 (m, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{22}H_{32}BO_5^+$ $[M + H]^+$ = 387, found 387.



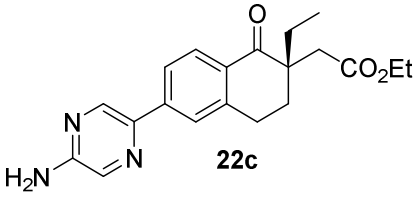
22a

Ethyl (*S*)-2-(2-ethyl-6-(5-nitropyridin-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (22a): Compound **17a** (2.9 g, 7.51 mmol) was reacted with 2-bromo-5-nitro pyridine (1.676 g, 8.26 mmol) as per the procedure described for the synthesis of **9a** to yield the desired compound **18a** (2 g, 63.6%) as solid. Racemate **18a** was separated using chiral prep to obtain **22a** as the desired *S* isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, *J* = 2.4 Hz, 1H), 8.57 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.95 - 8.02 (m, 3H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.13 - 3.23 (m, 1H), 2.95 - 3.05 (m, 2H), 2.48 - 2.56 (m, 2H), 2.11 (dt, *J* = 13.6, 4.4 Hz, 1H), 1.67 - 1.82 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{21}H_{23}N_2O_5^+$ $[M + H]^+$ = 383.1, found 383.



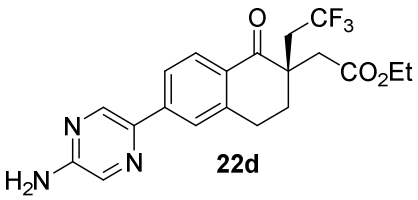
22b

Ethyl (*S*)-2-(6-(5-nitropyridin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (22b): Compound **17c** was reacted with 2-bromo-5-nitro pyridine as per the procedure described for the synthesis of **9a** to yield the desired compound **18b**. Racemate **18b** was separated using chiral prep to obtain **22b** as the desired *S* isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (d, *J* = 2.4 Hz, 1H), 8.58 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.95 - 8.05 (m, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.13 - 3.21 (m, 2H), 2.86 - 2.96 (m, 2H), 2.60 - 2.70 (m, 2H), 2.44 - 2.53 (m, 1H), 2.33 - 2.42 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{21}H_{20}F_3N_2O_5^+$ $[M + H]^+$ = 437, found 437.



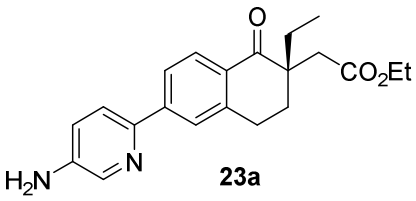
22c

Ethyl (*S*)-2-(6-(5-aminopyrazin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (22c): Compound **17a** was reacted with 5-bromopyrazine-2-amine as per the procedure described for the synthesis of **9a** to yield the desired compound **18c**. Racemate **18c** was separated using chiral prep to obtain **22c** as the desired *S* isomer. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (d, *J* = 1.5 Hz, 1H), 7.99 (d, *J* = 1.5 Hz, 1H), 7.86 - 7.93 (m, 3H), 6.76 (s, 2H), 4.00 (q, *J* = 6.9 Hz, 2H), 2.91 - 3.14 (m, 2H), 2.80 (d, *J* = 16.2 Hz, 1H), 2.30 - 2.46 (m, 2H), 1.94 - 2.04 (m, 1H), 1.49 - 1.75 (m, 2H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{20}H_{24}N_3O_3^+$ $[M + H]^+$ = 354.1, found 354.



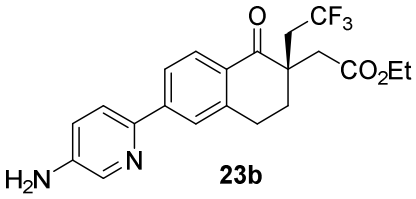
22d

Ethyl (*S*)-2-(6-(5-aminopyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (22d): Compound **17c** was reacted with 5-bromopyrazine-2-amine as per the procedure described for the synthesis of **9a** to yield the desired compound **18d**. Racemate **18d** was separated using chiral prep to obtain **22d** as the desired *S* isomer. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (d, *J* = 1.2 Hz, 1H), 8.0 (d, *J* = 1.2 Hz, 1H), 7.86 - 7.96 (m, 3H), 6.80 (s, 2H), 4.03 (q, *J* = 6.9 Hz, 2H), 2.92 - 3.19 (m, 3H), 2.82 - 2.92 (m, 1H), 2.61 - 2.78 (m, 2H), 2.32 - 2.45 (m, 1H), 2.10 - 2.27 (m, 1H), 1.15 (t, *J* = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{20}H_{21}F_3N_3O_3^+$ $[M + H]^+$ = 408.1, found 408.



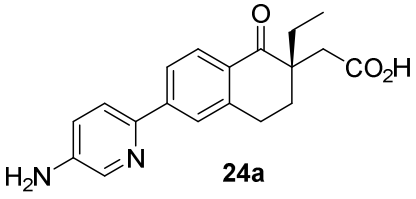
23a

Ethyl (*S*)-2-(6-(5-aminopyridin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (23a): Compound **22a** was converted as per the procedure described for the synthesis of **10a** to desired compound **23a** as a white solid with a yield of 66%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, J = 2.8 Hz, 1H), 7.84 - 7.92 (m, 3H), 7.74 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.4, 2.4 Hz, 1H), 5.66 (s, 2H), 4.00 (q, J = 6.8 Hz, 2H), 3.08 (m, 1H), 2.89 - 2.97 (m, 1H), 2.80 (d, J = 16 Hz, 1H), 2.46 (d, J = 16 Hz, 1H), 2.36 (td, J = 12.4, 5.2 Hz, 1H), 2.00 (dt, J = 13.2, 4.4 Hz, 1H), 1.50 - 1.73 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{21}H_{25}N_2O_3^+$ $[M + H]^+$ = 353, found 353.



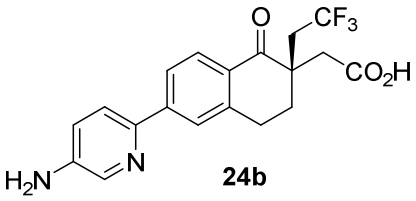
23b

Ethyl (*S*)-2-(6-(5-aminopyridin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (23b): Compound **22b** was converted as per the procedure described for the synthesis of **10a** to desired compound **23b** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, J = 2.8 Hz, 1H), 7.87 - 7.96 (m, 3H), 7.76 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.4, 2.4 Hz, 1H), 5.70 (s, 2H), 4.03 (q, J = 6.8 Hz, 2H), 2.92 - 3.17 (m, 3H), 2.86 (d, J = 16 Hz, 1H), 2.69 - 2.75 (m, 1H), 2.62 - 2.68 (m, 1H), 2.33 - 2.42 (m, 1H), 2.12 - 2.23 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{21}H_{22}F_3N_2O_3^+$ $[M + H]^+$ = 407.1, found 407.



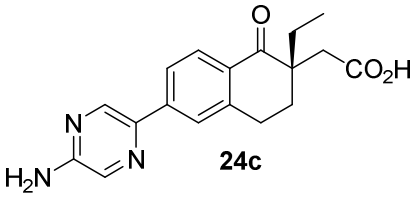
24a

(*S*)-2-(6-(5-Aminopyridin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (24a): Compound **23a** was hydrolysed as per the procedure described for the synthesis of **12a** to obtain the desired compound **24a** as a white solid with a yield of 24%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 8.05 (d, J = 2 Hz, 1H), 7.86 - 7.92 (m, 2H), 7.73 (d, J = 8.4 Hz, 1H), 6.96 - 7.04 (m, 1H), 5.66 (s, 2H), 3.02 - 3.13 (m, 1H), 2.88 - 2.97 (m, 1H), 2.77 (d, J = 16 Hz, 1H), 2.33 - 2.46 (m, 2H), 1.98 (d, J = 11.2 Hz, 1H) 1.67 (m, 1H), 1.52 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{19}H_{21}N_2O_3^+$ $[M + H]^+$ = 325.1, found 325.



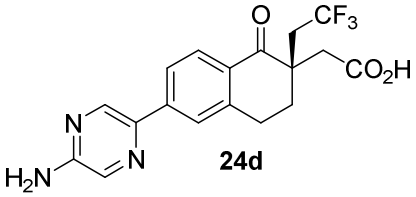
24b

(*S*)-2-(6-(5-Aminopyridin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (24b): Compound **23b** was hydrolysed using similar procedure as described for the synthesis of **12a** to obtain the desired compound **24b** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.37 (bs, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.85 - 7.97 (m, 3H), 7.75 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.4, 2.7 Hz, 1H), 5.69 (s, 2H), 2.92 - 3.16 (m, 3H), 2.65 - 2.86 (m, 2H), 2.58 (s, 1H), 2.42 (d, J = 6.3 Hz, 1H), 2.11 - 2.21 (m, 1H). LRMS (ESI$^+$) *m/z* calcd $C_{19}H_{18}F_3N_2O_3^+$ $[M + H]^+$ = 379, found 379.



24c

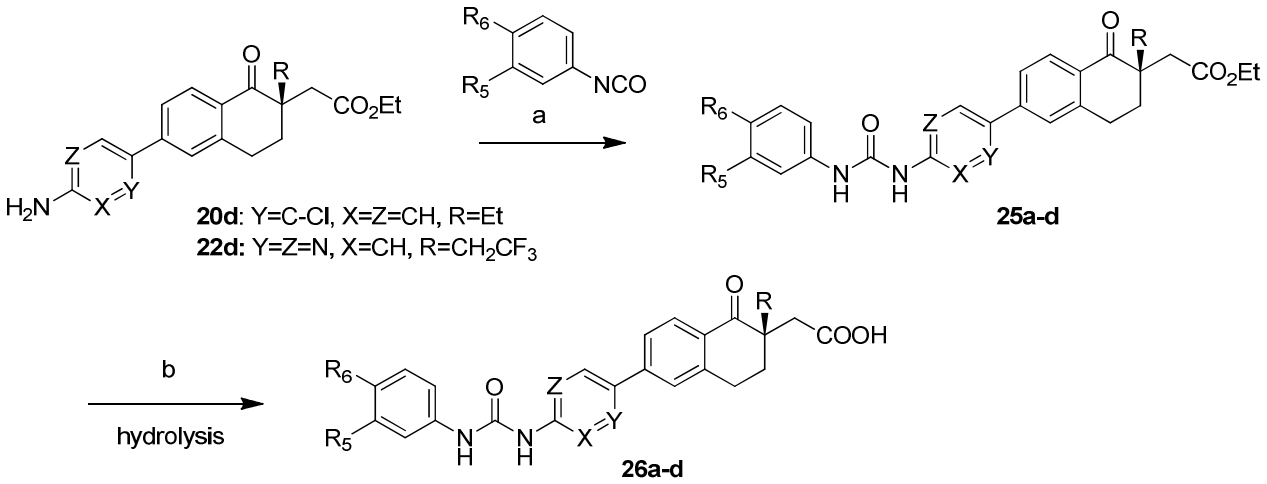
(*S*)-2-(6-(5-Aminopyrazin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (24c): Compound **22c** was hydrolysed using similar procedure as described for the synthesis of **12a** to obtain the desired compound **24c** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (bs, 1H), 8.61 (s, 1H), 7.99 (d, J = 0.96 Hz, 1H), 7.86 - 7.91 (m, 3H), 6.76 (s, 2H), 3.03 - 3.13 (m, 1H), 2.90 - 2.98 (m, 1H), 2.78 (d, J = 16 Hz, 1H), 2.34 - 2.47 (m, 2H), 1.94 - 2.02 (m, 1H), 1.68 (dq, J = 14.4, 7.30 Hz, 1H), 1.52 (dq, J = 14.4, 7.2 Hz, 1H), 0.83 (t, J = 7.6 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{18}H_{20}N_3O_3^+$ $[M + H]^+$ = 326.1, found 326.



24d

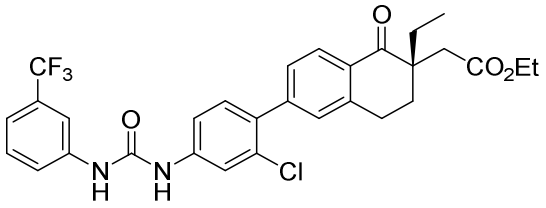
(*S*)-2-(6-(5-Aminopyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (24d): Compound **22d** was hydrolysed using similar procedure as described for the synthesis of **12a** to obtain the desired compound **24d** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (bs, 1H), 8.62 (s, 1H), 7.99 (s, 1H), 7.88 - 7.95 (m, 3H), 2.95 - 3.17 (m, 3H), 2.68 - 2.85 (m, 2H), 2.56 (bs, 1H), 2.40 - 2.46 (m, 1H), 2.09 - 2.20 (m, 1H). LRMS (ESI$^+$) *m/z* calcd $C_{18}H_{17}F_3N_3O_3^+$ $[M + H]^+$ = 380, found 380.

Syntheses of chiral ureido tetralones (26a-d)



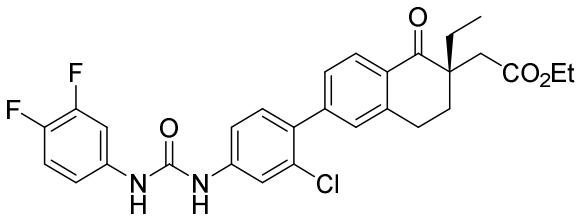
Compound #	R	X	Y	Z	R_5	R_6
25a, 26a	CH_3	CH	C-Cl	CH	CF_3	H
25b, 26b	CH_3	CH	C-Cl	CH	F	F
25c, 26c	CF_3	CH	N	N	CF_3	H
25d, 26d	CF_3	CH	N	N	F	F

Reagents and conditions: a) Substituted phenyl isocyanate, Et_3N, THF; b) LiOH, THF-H_2O.



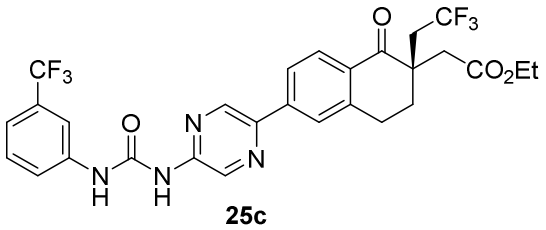
25a

Ethyl (*S*)-2-(6-(2-chloro-4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (25a): Compound **20d** was reacted with 3-trifluoromethyl phenyl isocyanate using similar procedure as described for the preparation of **11a** to obtain the desired compound **25a** as white solid with a yield of 60%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.9 (d, J = 15 Hz, 2H), 8.02 (bs, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.49-7.31 (m, 5H), 4.02 (q, J = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.49-2.2 (m, 2H), 2.02-1.98 (m, 1H), 1.8-1.5 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.8 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{30}H_{29}ClF_3N_2O_4^+$ [M + H]$^+$ = 573.1, found 572.9.



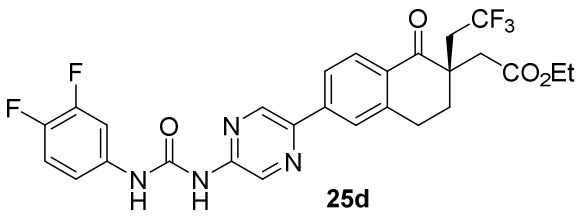
25b

Ethyl (*S*)-2-(6-(2-chloro-4-(3-(3,4-difluorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (25b): Compound **20d** was reacted with 3,4 difluoro phenyl isocyanate using similar procedure as described for the preparation of **11a** to obtain the desired compound **25b** as an off white solid with a yield of 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 8.03 (s, 1H), 7.44-7.37 (m, 3H), 7.35-7.31 (m, 4H), 7.18 (m, 1H), 7.08-6.97 (m, 2H), 4.02 (q, *J* = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 3.14 (m, 1H), 3.04 (d, *J* = 16 Hz, 1H), 2.90 (m, 1H), 2.5 (d, *J* = 16 Hz, 1H), 2.45 (m, 1H), 2.05 (m, 1H), 1.79-1.6 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{29}H_{28}ClF_2N_2O_4^+$ $[M + H]^+$ = 541.1, found 493.



25c

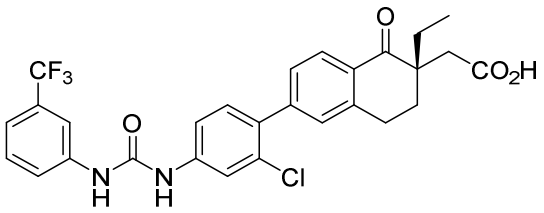
Ethyl (*S*)-2-(1-oxo-2-(2,2,2-trifluoroethyl)-6-(5-(3-(3-(trifluoromethyl)phenyl)ureido)pyrazin-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (25c): Compound **22d** was reacted with 3-trifluoromethyl phenyl isocyanate using similar procedure as described for synthesis of **11a** to obtain the desired compound **25c** as a white solid with a yield of 47%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.91 (s, 1H), 9.88 (s, 1H), 9.18 (s, 1H), 9.05 (s, 1H), 8.1-8.04 (m, 3H), 8.01-7.96 (m, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 4.03 (q, *J* = 6.9 Hz, 2H), 3.34-3.2 (m, 2H), 3.01-2.87 (m, 2H), 2.75-2.65 (m, 2H), 2.49-2.19 (m, 2H), 1.14 (t, *J* = 6.9 Hz, 3H). LRMS (ESI$^+$) *m/z* calcd $C_{28}H_{25}F_6N_4O_4^+$ $[M + H]^+$ = 595.2, found 595.28.



25d

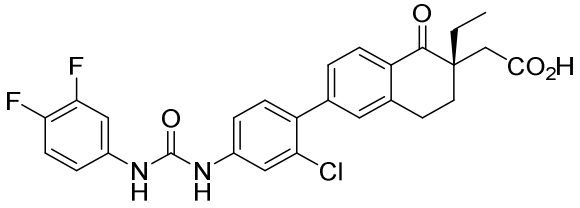
Ethyl (*S*)-2-(6-(5-(3-(3,4-difluorophenyl)ureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (25d): Compound **22d** was reacted with 3,4 difluoro phenyl isocyanate using similar procedure as described for the preparation of **11a** to obtain desired compound **25d** (1 g, 32%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 1H), 9.75 (s, 1H), 9.16 (d, *J* = 1.5 Hz, 1H), 9.03 (d, *J* = 1.5 Hz, 1H), 8.10-7.95 (m, 3H), 7.78-7.68 (m, 1H), 7.48-7.35 (m, 1H), 7.26-7.18 (m, 1H), 4.03 (q, *J* = 7.2

Hz, 2H), 3.26-3.10 (m, 2H), 3.08-2.85 (m, 2H), 2.80-2.64 (m, 2H), 2.48-2.36 (m, 1H), 2.28-2.15 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{27}H_{24}F_5N_4O_4^+$ $[M + H]^+$ = 563.1, found 563.



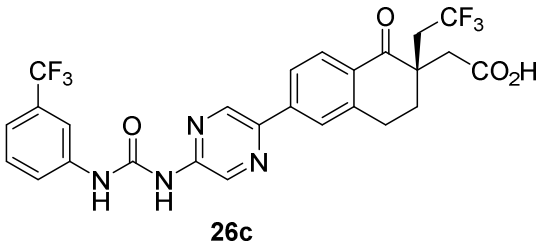
26a

(*S*)-2-(6-(2-chloro-4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (26a): Compound **25a** was hydrolysed using similar procedure as described for the preparation of compound **12a** to obtain title compound **26a** as a white solid with a yield of 55%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.23 (s, 1H), 9.18 (s, 1H), 8.02 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.63-7.58 (m, 1H), 7.56-7.51 (m, 1H), 7.46-7.32 (m, 5H), 3.14-3.04 (m, 1H), 2.97-2.89 (m, 1H), 2.84-2.77 (m, 1H), 2.48-2.36 (m, 2H), 2.02-1.96 (m, 1H), 1.74-1.62 (m, 1H), 1.58-1.50 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{28}H_{25}ClF_3N_2O_4^+$ $[M + H]^+$ = 545.1, found 545.



26b

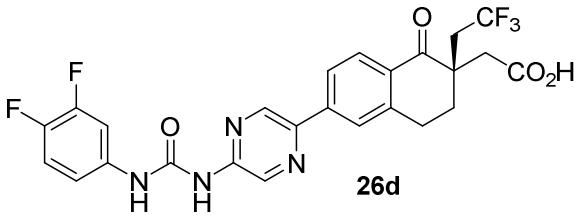
(*S*)-2-(6-(2-chloro-4-(3-(3,4-difluorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (26b): Compound **25b** was hydrolysed using similar procedure as described for the preparation of compound **12a** to obtain title compound **26b** as a yellow solid with a yield of 65%. 1H NMR (300MHz, DMSO-d_6): δ 12.04 (bs, 1H), 9.08 (s, 1H), 9.02 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 1.5 Hz, 1H), 7.68-7.60 (m, 1H), 7.41-7.28 (m, 5H), 7.15 (m, 1H), 3.12-2.98 (m, 1H), 2.96-2.84 (m, 1H), 2.77 (d, J = 15.9 Hz, 1H), 2.46 (m, 1H), 2.36 (d, J = 16.5 Hz, 1H), 1.95 (m, 1H), 1.66 (m, 1H), 1.51 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H). LRMS (ESI^+) *m/z* calcd $C_{27}H_{24}ClF_2N_2O_4^+$ $[M + H]^+$ = 513.1, found 513.1 . HRMS calcd for $C_{27}H_{24}ClF_2N_2O_4$ $[M+H]^+$ = 513.1393, found 513.1357.



26c

(*S*)-2-(1-oxo-2-(2,2,2-trifluoroethyl)-6-(5-(3-(3-(trifluoromethyl)phenyl)ureido)pyrazin-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (26c): Compound **25c** was hydrolysed using similar procedure as described for the preparation of compound **12a** to obtain title compound **26c** as a solid with a yield of 60%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.42 (bs, 1H), 10.08 (s, 1H), 10.02 (s, 1H), 9.18 (s, 1H), 9.03 (s, 1H), 8.14-7.95 (m, 4H), 7.69 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 3.20-2.92 (m, 3H), 2.85-2.65 (m, 2H), 2.60-2.40 (m, 2H), 2.18 (m, 1H). LRMS (ESI$^+$) *m/z* calcd $C_{26}H_{21}F_6N_4O_4^+$ $[M + H]^+$ = 567.1, found 567.



26d

(*S*)-2-(6-(5-(3-(3,4-Difluorophenyl)ureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (26d): Compound **25d** (0.35 g, 0.62 mmol) was hydrolysed using similar procedure as described for the preparation of compound **12a** to afford title compound **26d** (0.255 g, 76%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.42 (bs, 1H), 9.83 (s, 1H), 9.77 (s, 1H), 9.16 (d, J = 1.2 Hz, 1H), 9.02 (d, J = 1.5 Hz, 1H), 8.1-7.94 (m, 3H), 7.78-7.68 (m, 1H), 7.46-7.35 (m, 1H), 7.24 (m, 1H), 3.41-3.35 (m, 1H), 3.20-2.95 (m, 2H), 2.88-2.80 (m, 2H), 2.65-2.55 (m, 1H), 2.50-2.42 (m, 1H), 2.24-2.14 (m, 1H). LRMS (ESI$^+$) *m/z* calcd $C_{25}H_{20}F_5N_4O_4^+$ $[M + H]^+$ = 535.1, found 535. HRMS calcd for $C_{25}H_{20}F_5N_4O_4$ $[M+H]^+$ = 535.1405, found 535.1410.