

Supporting Information

3,5-Disubstituted-indole-7-carboxamides as IKK β inhibitors: Optimization of Oral Activity via the C3 Substituent

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Example Number	Mean IKK β FRET pIC ₅₀	IKK β FRET n (number assay points included in mean)	IKK β FRET SEM
1	5.8	4	0.18
2	7.6	15	0.13
3	7.8	2	0.06
4	8.0	4	0.23
5	8.1	1	--
6	7.5	3	0.59
7	8.2	2	0.14
8	7.7	3	0.09
9	8.1	9	0.12
10	8.0	2	0.21
11	8.1	2	0.07
12	6.9	1	--
13	7.2	3	0.08
14	7.1	6	0.05
15	7.4	3	0.09
16	6.3	2	0.03
17	6.7	2	0.03
18	7.7	2	0.09
19	6.3	1	--
20	7.1	4	0.10
21	7.0	2	0.01
22	7.4	2	0.02
23	7.1	3	0.07
24	8	8	0.06
25	6.8	2	0.05
26	7.9	3	0.03
27	8.1	3	0.14
(R)-28	8.1	3	0.11

Table S1. Mean, N numbers, and Standard Error of the Mean (SEM) for IKK β FRET assay data for all compounds.

Example Number	Mean Monocyte IC50_UM	Monocyte Assay n (number assay points included in mean)	Monocyte Assay SEM
2	0.19	2	0.05
4	0.05	2	0.02
6	0.20	2	0.05
9	0.14	2	0.02
10	0.50	2	0.27
24	0.08	3	0.04
26	0.43	2	0.27
27	0.11	1	--
(R)-28	0.13	1	--

Table S2. Mean, N numbers, and Standard Error of the Mean (SEM) for monocyte potency.

Example Number	ChemAxon calculated pKa_most basic center
3	8.99
4	8.58
5	8.46
6	6.3
7	8.93
8	10.13
9	8.45
10	7.2
11	5.53

Table S3. Calculated pKa data for compounds in Table 2. pKa was calculated using the ChemAxon pKa calculator.

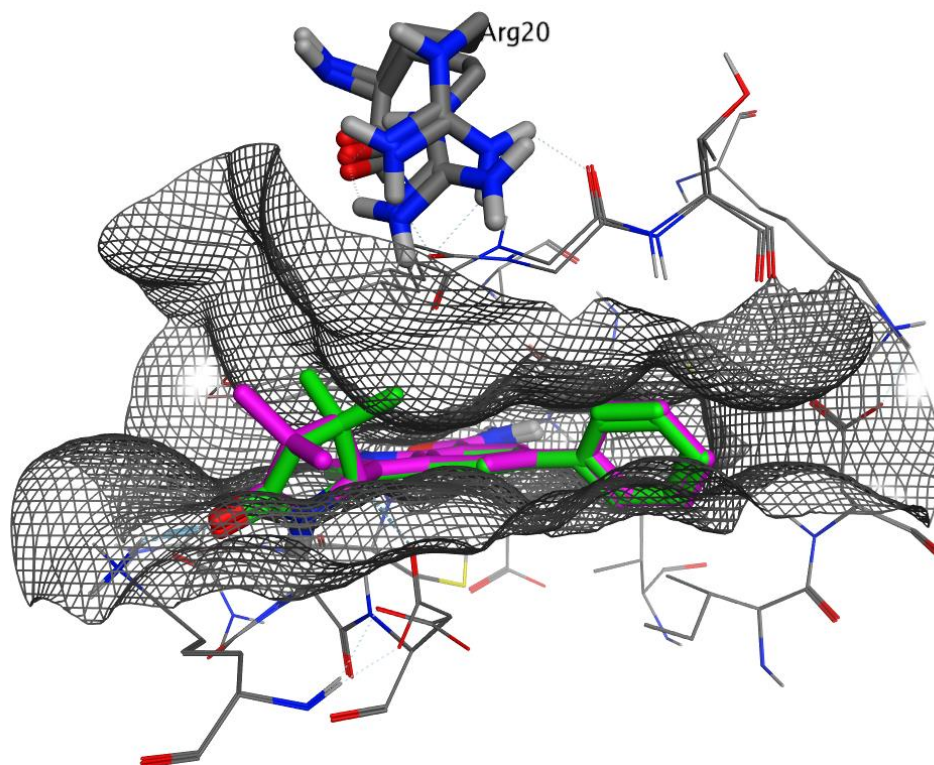


Figure S1. Docking overlay of compounds **17** (green) and **18** (magenta). Compound **17** shows a slight perturbation to Arg20 driven by the lipophilic *gem*-dimethyl in contact with the polar Arg20. This polarity mismatch results in lower potency for **17**.

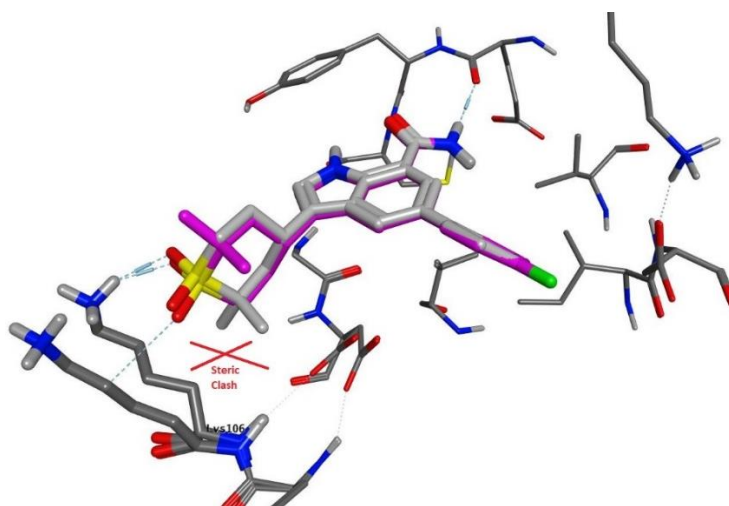


Figure S2. The compound **(S)-28** enantiomer causes a steric clash between the dimethyl and Lys106 resulting in a loss of the hydrogen bond between Lys106 and the sulfone. **(R)-28** is shown in magenta, **(S)-28** is shown in gray.

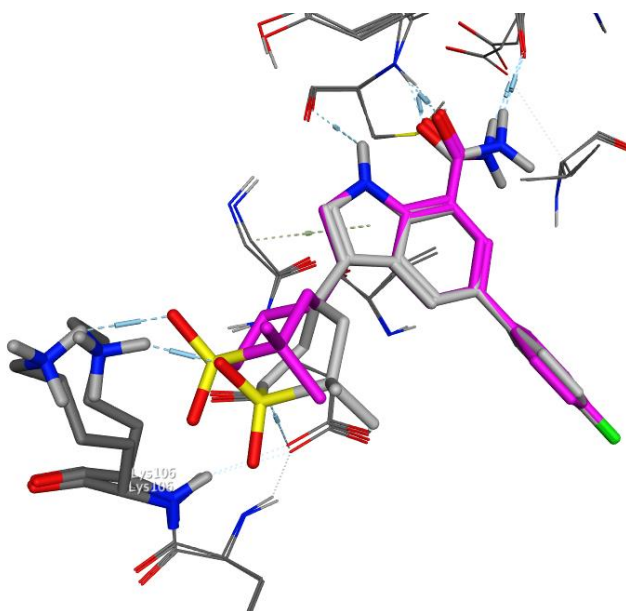


Figure S3. To maintain the H-bond with Lys106, the **(S)-28** cyclic sulfonamide must rotate and adopt a boat conformation. **(R)-28** is shown in magenta, **(S)-28** is shown in gray.

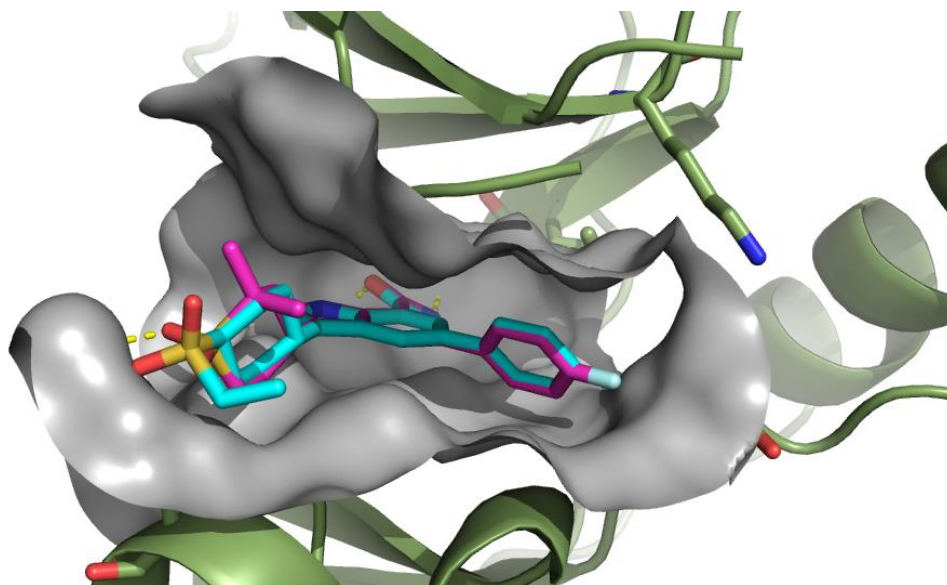


Figure S4. The compound **(R)-28** (magenta) dimethyl tucks up under the glycine rich loop and aligns with the protein conformation of compound **2** (teal).

IKK2 Assay

Recombinant human IKK2 (residues 1-737) was expressed in baculovirus as a C-terminal GST-tagged fusion protein, and its activity was assessed using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Briefly, IKK2 (5 nM final) diluted in assay buffer (50 mM HEPES, 10 mM MgCl₂, 1 mM CHAPS pH 7.4 with 1 mM DTT and 0.01% w/v BSA) was added to wells containing various concentrations of compound or DMSO vehicle (3% final). The reaction was initiated by the addition of GST-IκBα substrate (25 nM final)/ATP (1 μM final), in a total volume of 30 μl. The reaction was incubated for 30 minutes at room temperature, then terminated by the addition of 15 μl of 50 mM EDTA. Detection reagent (15 μl) in buffer (100 mM HEPES pH 7.4, 150 mM NaCl and 0.1% w/v BSA) containing anti-phosphoserine-IκBα-32/36 monoclonal antibody 12C2 (Cell Signalling Technology, Beverly Massachusetts, USA) labelled with W-1024 europium chelate (Wallac OY, Turku, Finland), and an APC-labelled anti-GST antibody (Prozyme, San Leandro, California, USA) was added and the reaction was further incubated for 60 minutes at room temperature. The degree of phosphorylation of GST-IκBα was measured using a Packard Discovery plate reader (Perkin-Elmer Life Sciences, Pangbourne, UK) as a ratio of specific 665 nm energy transfer signal to reference europium 620 nm signal.

Monocyte Assay

Effect of IKK-β inhibition on human monocyte stimulated cytokine production was assessed as follows: Monocytes were isolated from heparinized whole blood by Ficoll gradient, followed by purification of CD14⁺ cells using MACS magnetic cell separation beads. Isolated monocytes were then adhered to 96-well culture plates at 1 x 10⁶ cells/mL in RPMI 1640 10% FBS (JRH Biosciences, Lenexa KS) for 2h. Test compounds are added to the wells 30 minutes prior to stimulation with a final vehicle concentration of 0.1% DMSO. Monocytes were activated by the addition of 200 ng/mL endotoxin (LPS; *E. coli* serotype 026:B6)(Sigma, St. Louis, MO.) and incubated for 24 hrs at 37 C. Cell-free supernates were analyzed by Alphascreen™ (Perkin Elmer, Waltham, MA.) for TNF-α using R&D Systems matched pair Abs. Viability of the cells was determined by 10% trypan blue exclusion.

Inhaled LPS-induced Lung Neutrophilia in the Rat

Rats were dosed orally 30 min prior to LPS administration. Rats were placed into a modified Rubbermaid box that contained an inflow and outflow. A nebulizer containing 100 ug/ml LPS (lipopolysaccharide, serotype 026:B6 from Sigma Chemical Co.) was connected to the inflow

port and LPS was driven into the box at a rate of 4.5 ml/min for 20 min. After LPS challenge, the rats were returned to their cages. 4 hours later, rats were euthanized with Fatal Plus (1 ml/rat, i.p.). Terminal bleeds were taken via the carotid artery for DMPK compound analysis. A 14 gauge metal cannula was placed into the trachea and the lungs were lavaged 5 times with 5 ml Dulbecco's PBS (without calcium and magnesium).

The bronchoalveolar lavage (BAL) fluid was centrifuged for 10 min at 3000 rpm. The supernatant was discarded and the cell pellet re-suspended in 5 ml PBS. Slides were made on a cytospin (Shandon) at 300 rpm for 5 min for differential cell counts, then stained with Diff-Quick solution. Total cell counts were performed using a hemocytometer and Tuerkes solution for staining.

Total number of mononuclear cells, neutrophils and eosinophils were determined by multiplying the differential percentage and the total cell type. Each compound was reported as percent inhibition of neutrophilia.

LPS-induced TNF α Production in Rat Blood

Male Lewis rats (Charles River) were fasted for 18 hr prior to compound administration, then dose orally with vehicle or compound 30 min prior to euthanasia. Rats were euthanized with CO₂ and exsanguinated via cardiac puncture with heparinized syringes. The blood was plated, treated with PBS or LPS (serotype 026:B6, Sigma L3755, 20 ug/ml) and incubated for 2 hr at 37°C. The plates were centrifuged and the plasma was removed for analysis of TNF α using an ELISA kit (R&D Systems Rat TNF α #SRTA00).

Inhaled LPS-induced Lung Neutrophilia in the Dog

Adult male Beagle dogs (9-14 kg, Marshall Research) were fasted 18 hr prior to the study. Compound or vehicle was administered orally (2 ml/kg) via a gastric feeding tube 30 min prior to LPS instillation. Animals were then anesthetized with propofol (6 mg/kg iv), placed in dorsal recumbency and maintained at an infusion rate of 0.2 – 0.4 mg/kg/min i.v. Supplemental oxygen (100%) was provided intranasally and ECG, blood pressure, body temperature and SpO₂ were monitored continuously throughout the procedure. Blood samples were collected by venipuncture into heparinized vacutainers at appropriate timepoints.

After stabilization, bronchoscopy was performed. The video-coupled bronchoscope (Pentax EPK-1000 with an EG-2470K scope and Olympus wash pipes) was inserted into the cranial

bronchi and 2 ml sterile saline was administered using a catheter delivery system followed by 2 ml air to clear the catheter. 2 ml LPS (4 ng/kg, serotype O:113, US Pharmacopeia, Rockville, MD) was administered into the contralateral bronchi. The dog was permitted to wake and was placed in a holding cage until BAL.

Six hours after LPS instillation, the dog was again anesthetized as described above. the bronchoscope was wedged into the dependent bronchi that received saline earlier. A sterile catheter was passed through the biopsy port and 2x20 ml sterile saline was introduced via the catheter and then withdrawn. The same procedure was then done in the contralateral bronchi which had received LPS. The dog was allowed to awaken immediately after the procedure was completed.

The same dogs were used throughout the study allowing a washout time of 4 weeks between LPS administration. For each use, the bronchus that received LPS was alternated so that the same bronchus would not be exposed to LPS again for 8 weeks to avoid tolerance.

BAL fluid was processed as described above for rats.

General Synthetic Chemistry and Characterization Details

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. All final compounds for testing were purified to 95% purity or greater unless noted otherwise. Purity was assessed by LC/MS and/or ^1H NMR. All temperatures are expressed in $^{\circ}\text{C}$ (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted. ^1H NMR spectra were recorded on a Bruker DPX400, a Bruker DPX250, a Bruker AC400, or a Varian Inova 400. Chemical shifts are expressed in parts per million (ppm, δ units). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Low-resolution mass spectra (MS) were recorded on a JOEL JMS-AX505HA, JOEL SX-102, or a SCIEX-APIiii spectrometer; LC-MS were recorded on Waters ZQ or PE Sciex Single Quadrupole LC/MS API-150 spectrometers. Preparative HPLC refers to methods where the material was purified by high performance liquid chromatography on a HPLC ABZ+ 5 μm column (10 cm x 21.2 mm i.d.) with 0.1% formic acid in water and 0.05% formic acid in acetonitrile utilizing gradient elution at a flow rate of 8 ml/min and UV detection at 254nm. Unless otherwise stated, silica flash column chromatography and Combiflash refers to the purification of material using RedisepTM pre-packed silica flash columns on an ISCO sq16x machine with the stated solvent systems. HPLC was obtained with a Luna C18 4.6x150mm 3 micron column using a mobile phase of water (0.1% TFA) and acetonitrile and a run time of 20

mins. A mobile phase gradient of 2% to 95% acetonitrile over 18 mins then holding for 2 mins was used..

High Resolution MS

High Resolution mass spectrometry was measured on the Xevo G2-S ToF MS operating in electrospray ionization, positive (ESI+). The system was calibrated using sodium formate. The sample was introduced by LC, 1 μ l of 10 μ M in 30% DMSO in acetonitrile to the MS. Data was collected and processed with MassLynx v4.1 SCN884 software.

High Resolution mass spectrometry was measured on the Orbitrap Thermo Exactive Plus MS operating in electrospray ionization, positive (ESI+). The system was calibrated using LTQ VELOS POS ION CAL solution. The sample was introduced by LC, 1.0 μ l of 10 μ M in 30% DMSO in acetonitrile to the MS. Data was collected and evaluated using Xcalibur software.

VCD

Experimental:

5-bromo-3-[(4*S*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-1*H*-indole-7-carboxamide and its enantiomer 5-bromo-3-[(4*R*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-1*H*-indole-7-carboxamide were dissolved in DMSO- d_6 (5.1mg/85 μ l) and placed in a 100 μ m pathlength cell with BaF₂ windows. IR and VCD spectra were recorded on a ChiralIR2X™ VCD spectrometer (BioTools, Inc.) equipped with dual *PEM* accessory, with 4 cm^{-1} resolution, 10-hour collection, and instrument optimized at 1400 cm^{-1} . The IR spectra of DMSO- d_6 was also measured using the same cell. The baselines of the IR spectra were corrected by subtracting the IR of the solvent from those of the samples, and the baseline corrected VCD spectrum of each sample was obtained by subtracting the VCD of the enantiomer from that of each sample and then divide by two.

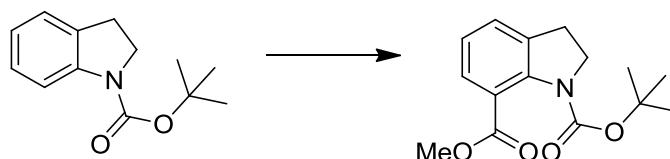
VCD calculations:

A conformational search on 5-bromo-3-[(4*S*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-1*H*-indole-7-carboxamide was carried out using MOE at LowMode using PCModel with MMFF94 forcefield and DMSO molecules included to better simulate experimental conditions. The geometry optimization, frequency, and IR and VCD intensity calculations of five unique conformers resulted from the conformational search were carried out at the DFT level (B3LYP/6-311G(d,p)) with Gaussian 03 (Gaussian Inc., Wallingford, CT) on a Linux Cluster.

The Gaussian output files were converted to VCD and IR spectra using Lorentzian bands with 6-cm⁻¹ half-width and the calculated frequencies were scaled by 0.98. The final population ratios used to generate VCD and IR spectra: 0.27*C1 + 0.57*C3 + 0.08*C10 + 0.00*C13 + 0.08*C14. Conformers resulted from Gaussian calculations were selected to generate the Boltzmann summed IR and VCD spectra. Comparing the observed VCD and IR spectra with the calculated spectra, the absolute configuration of the enantiomers was assigned as (*R*)-, and or (*S*)-.

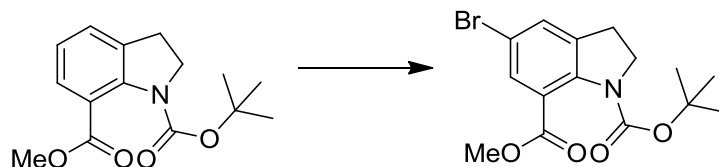
Compound Preparation Procedures

1-(1,1-Dimethylethyl) 7-methyl-2,3-dihydro-1H-indole-1,7-dicarboxylate



1,1-dimethylethyl 2,3-dihydro-1H-indole-1-carboxylate (5 g, 22.8 mmol) and *N,N,N,N*-tetramethyl-1,2-ethanediamine (4.6 mL, 30.5 mmol) was dissolved in dry diethyl ether (300 mL) and cooled to -78 °C in an acetone/dry ice bath. *Sec*-butyl lithium (1.4 M solution in cyclohexane, 17.6 mL, 24.6 mmol) was added dropwise over 10 minutes and the reaction left stirring for 90 minutes at this temperature. Methyl chloroformate (8.8 mL, 10.8 g, 100 mmol) was added to the mixture and the reaction was allowed to warm to room temperature over 1 hour. Water was added carefully to the mixture and the organic layer separated and washed 3 times with more water. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 4.91 g (78%) of the title compound as a gummy yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.44 (s, 9 H) 3.06 (t, *J*=8.2 Hz, 2 H) 3.69 (s, 3 H) 4.02 (t, *J*=8.3 Hz, 2 H) 7.06 (t, *J*=7.5 Hz, 1 H) 7.35 (d, *J*=7.5 Hz, 1 H) 7.39 (dd, *J*=7.4, 1.1 Hz, 1 H) MS *m/z* 278 (M+1)⁺ 3.18 min.

1-(1,1-Dimethylethyl)7-methyl-5-bromo-2,3-dihydro-1H-indole-1,7-dicarboxylate



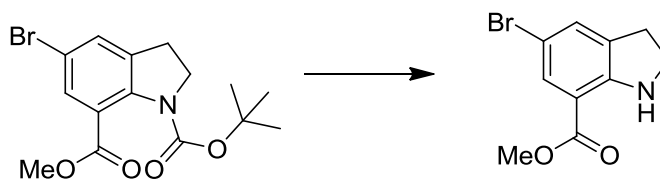
1-(1,1-dimethylethyl) 7-methyl 2,3-dihydro-1H-indole-1,7-dicarboxylate (3.1 g, 11.2 mmol) and *N*-bromosuccinimide (2.0 g, 11.2 mmol) were dissolved in dry dichloromethane (100 mL) and stirred under a nitrogen atmosphere at room temperature for 16 hours. The reaction was

partitioned with sodium hydroxide solution (2 M), separated and washed with more sodium hydroxide solution. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give 3.55 g (89%) of the title compound as a gummy red solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.41 (s, 9 H) 3.09 (t, *J*=8.3 Hz, 2 H) 3.70 (s, 3 H) 4.02 (t, *J*=8.3 Hz, 2 H) 7.46 (s, 1 H) 7.60 (s, 1 H); MS *m/z* 356/358 (1:1 ratio) (*M*+1)⁺ 3.52 min.

Alternatively, the title compound could be made according to the following procedure:

To a solution of 1-*tert*-butyl 7-methyl indoline-1,7-dicarboxylate (18 g, 64.9 mmol) in 200 mL of DCM was added NBS (18 g, 71.5 mmol). The mixture was stirred overnight at room temperature. The reaction solution was concentrated and the residue was washed with H₂O, extracted with DCM. The combined organic layer was concentrated and the residue was purified by chromatography column on silica gel to get the product as a brown solid (21 g, 91 %).

Methyl 5-bromo-2,3-dihydro-1H-indole-7-carboxylate



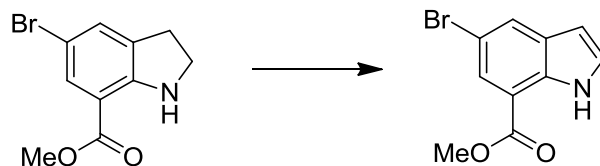
1-(1,1-dimethylethyl) 7-methyl 5-bromo-2,3-dihydro-1H-indole-1,7-dicarboxylate (9 g, 25 mmol) was dissolved in trifluoroacetic acid (6 mL) and stirred at room temperature for 16 hours. Dichloromethane and sodium hydroxide solution (2 M) were added and the organic layer washed twice with sodium hydroxide solution until the aqueous layer pH > 7. The organic layer was then concentrated *in vacuo* to give 6.5 g (100%) of the title compound as a brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.99 (t, *J*=8.5 Hz, 2 H) 3.61 (t, *J*=8.4 Hz, 2 H) 3.78 (s, 3 H) 6.72 (s, 1 H) 7.28 (d, *J*=1 Hz, 1 H) 7.46 (d, *J*=2 Hz, 1 H); MS *m/z* 256/258 (1:1 ratio) (*M*+1)⁺ 3.32 min.

Alternatively, the title compound can be made according to the following procedure:

A solution of 5-Bromo-2,3-dihydro-indole-1,7-dicarboxylic acid 1-*tert*-butyl ester 7-methyl ester (17.2 g, 48.3 mol) in 100 mL of TFA was stirred at room temperature for 18 hours. After checked by TLC, 2 N NaOH solution was added to bring the solution to pH=8~9, then extracted with DCM. The combined organic layer was dried over MgSO₄, evaporated to give the product (11.5 g, 93%).

Methyl 5-bromo-1H-indole-7-carboxylate



Methyl 5-bromo-2,3-dihydro-1H-indole-7-carboxylate (6.5 g, 25 mmol) was dissolved in tetrahydrofuran (100 mL). Activated manganese dioxide (5 μm particle size, 22 g, 250 mmol) was added and the mixture stirred at room temperature for 16 hours. A further 22 g of activated manganese dioxide was added and the reaction stirred for 96 hours. The reaction was then filtered through celite and concentrated *in vacuo* to give 5.1 g (80%) of the title compound as a beige solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 3.94 (s, 3 H) 6.58 (d, $J=3$ Hz, 1 H) 7.48 (d, $J=3$ Hz, 1 H) 7.8 (d, $J=2$ Hz, 1 H) 8.07 (d, $J=1.8$ Hz, 1 H) 11.39 (bs, 1 H); MS m/z 252/254 (1:1 ratio) (M-1) 3.41 min.

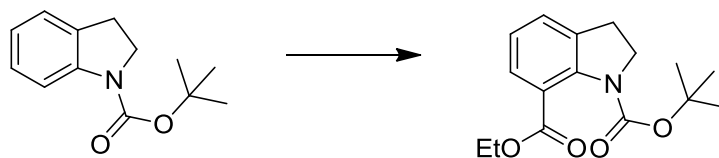
Alternatively, the title compound can be prepared as follows:

To a solution of 5-Bromo-2,3-dihydro-1H-indole-7-carboxylic acid methyl ester (11.5 g, 45.1 mmol) in 100mL THF was added MnO_2 (39.2 g, 451 mmol). Then the mixture was stirred overnight at room temperature. The reaction was filtered and the filtrate was concentrated (10 g, 88%).

Alternatively, the title compound can also be prepared as follows:

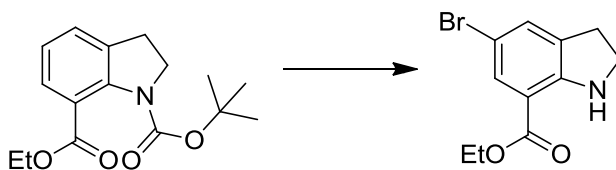
MeI (7.81 mL, 125 mmol) was added to a mixture of 5-bromo-1H-indole-7-carboxylic acid (10 g, 41.7 mmol) and Na_2CO_3 (17.66 g, 167 mmol) in DMF (50 mL). The reaction mixture was stirred at room temperature for 2 h and filtered through a pad of silica gel (500 g), eluting with Et_2O (600 mL). The eluent was washed with water (1 x 100 mL) and concentrated under reduced pressure, giving 9.65 g (91%) of the title compound. LC/MS: m/z 253.8 (M), 2.15 min.

1-(1,1-Dimethylethyl) 7-ethyl 2,3-dihydro-1H-indole-1,7-dicarboxylate



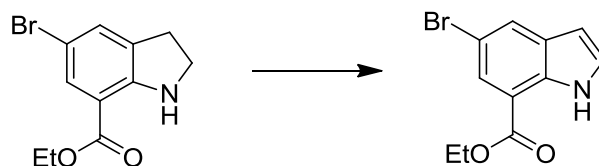
A 1.3 M solution of *sec*-butyl lithium in cyclohexanes (1642 mL, 2.13 mol) was added dropwise to a solution of 1,1-dimethylethyl 2,3-dihydro-1*H*-indole-1-carboxylate (300 g, 1.37 mol) and *N,N,N',N'*-tetramethyl-1,2-ethanediamine (248 mL, 1.64 mol) in dry diethyl ether (2.5 L) at -78 °C. The reaction mixture was stirred for 2 hours at this temperature and ethyl chloroformate (143.9 mL, 1.50 mol) was added dropwise to the mixture at -78 °C. After the addition, the reaction was allowed to warm to room temperature overnight. Water (1 L) was added carefully to the mixture and the organic layer was separated and dried (Na₂SO₄). The solution was concentrated and the residue was purified by silica-gel column chromatography (PE: EA = 10:1), giving 150 g (38%) of the title compound.

Ethyl 5-bromo-2,3-dihydro-1*H*-indole-7-carboxylate



NBS (51.3 g, 0.29 mol) was added in several portions to a solution of 1-(1,1-dimethylethyl) 7-ethyl 2,3-dihydro-1*H*-indole-1,7-dicarboxylate (140.3g, 0.48 mol) in CH₂Cl₂ (1200 mL) and the reaction mixture was stirred at room temperature overnight. The reaction solution was washed with 2 M NaOH (500 mL) and water (500 mL), and was then dried (Na₂SO₄). The solution was concentrated in vacuo to 500 mL and TFA (130 mL, 1.69 mol) was added. The mixture was stirred at room temperature overnight. A solution of 2 M NaOH was added to bring the reaction mixture to pH > 8. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 300 mL). The combined organic layers were dried (Na₂SO₄) and the solvent was evaporated, giving 129.1 g (99%) of the title compound.

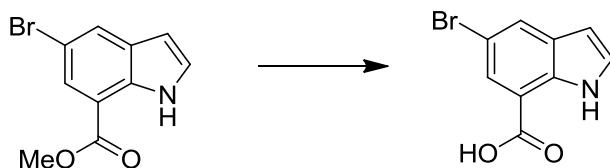
Ethyl 5-bromo-1*H*-indole-7-carboxylate



DDQ (119.3 g, 525.7mmol) was added in several portions to a solution of ethyl 5-bromo-2,3-dihydro-1*H*-indole-7-carboxylate (129.1 g, 0.48 mmol) in CHCl₃ (1500 mL) and the mixture was stirred for 2 h. The reaction was filtered and the solid was washed with CHCl₃ (3 x 500 mL). The filtrate was washed with 5% NaOH (3 x 500 mL), H₂O (500 mL) and brine (500 mL) then dried over Na₂SO₄. The solution was evaporated and the residue was recrystallized with EtOH,

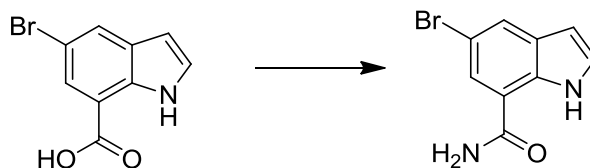
giving 88 g (69%) of the title compound. LC/MS: m/z 267.0 (M+H), 1.25 min, 100% ; ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 1.40 (t, $J=7.15$ Hz, 3 H) 4.40 (q, $J=7.19$ Hz, 2 H) 6.49 (t, $J=2.64$ Hz, 1 H) 7.27 (t, $J=2.64$ Hz, 1 H) 7.78 - 8.06 (m, 2 H) 9.82 (br. s., 1 H).

5-Bromo-1H-indole-7-carboxylic acid



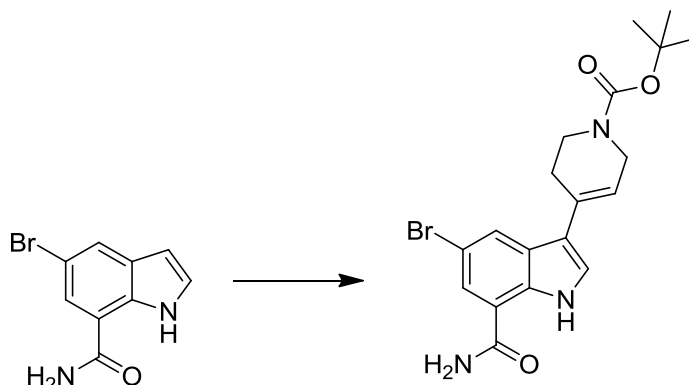
Methyl 5-bromo-1H-indole-7-carboxylate (5 g, 19.7 mmol) was dissolved in methanol (200 mL) and a solution of lithium hydroxide (0.99 g, 41 mmol) in water (10 mL) was added. The mixture was heated at reflux for 50 hours. The methanol was removed *in vacuo* and the residue diluted with aqueous hydrochloric acid (2 M). The resulting precipitate was filtered off and dried in a heated vacuum pistol to give 4.7 g (99%) of the title compound as a beige solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 6.54 (dd, $J=2.0, 3.2$ Hz, 1 H) 7.42 (t, $J=2.8$ Hz, 1 H) 7.77 (d, $J=2$ Hz, 1 H) 8.03 (d, $J=1.8$ Hz, 1 H) 11.27 (s, 1 H) 13.1-13.7 (bs, 1 H); LC/MS m/z 238/240 (1:1 ratio) (M-1) 3.41 min.

5-Bromo-1H-indole-7-carboxamide



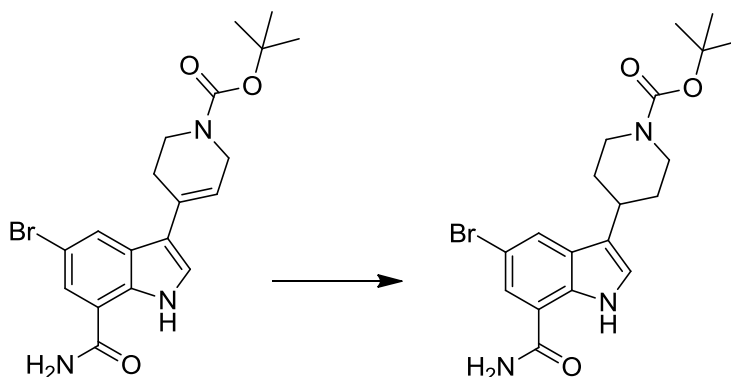
To a solution of 5-bromo-1H-indole-7-carboxylic acid (10.0 g, 42 mmol) in CH_2Cl_2 (100 mL) at room temperature, EDC (9.66 g, 50.4 mmol), HOBt (6.81 g, 50.4 mmol) and NH_3 (2.0 M in MeOH, 84 mL, 168 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue partitioned between ethyl acetate (100 mL) and water (100 mL). The water layer was extracted with ethyl acetate (2 x 100 mL) and the combined organic phase was dried over MgSO_4 and concentrated to give 10 g (98%) of the title compound as a crude product. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.27 (s, 1H) 8.16 (br s, 1H) 7.93 (s, 1H) 7.85 (s, 1H) 7.53 (br s, 1H) 7.39 (s, 1H) 6.48 (s, 1H) LC/MS: m/z 240.0 (M+H) 1.95 min.

1,1-dimethylethyl-4-[7-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate



To a solution of 5-bromo-1*H*-indole-7-carboxamide (10 g, 41.84 mmol) in methanol (5mL), 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (684 mg, 3.42 mmol) and sodium methoxide (0.5 M in THF, 13.7 mL, 6.84 mmol) were added. The reaction mixture was stirred at reflux temperature for 16 hours. All solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure, and purified by flash column chromatography (ethyl acetate/hexane, 1/1) to yield the desired product (7.4 g, 43 %). LC/MS: m/z 420.0 ($M+H$), 2.35 min; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.43 (s, 9 H) 3.07 (s, 2 H) 3.55 (t, $J=5.65$ Hz, 2 H) 4.03 (br. s., 2 H) 6.00 - 6.19 (m, 1 H) 7.42 (s, 1 H) 7.48 - 7.63 (m, 1 H) 7.87 (s, 1 H) 8.13 (s, 1 H) 8.16 - 8.40 (m, 1 H) 11.20 - 11.52 (m, 1 H)

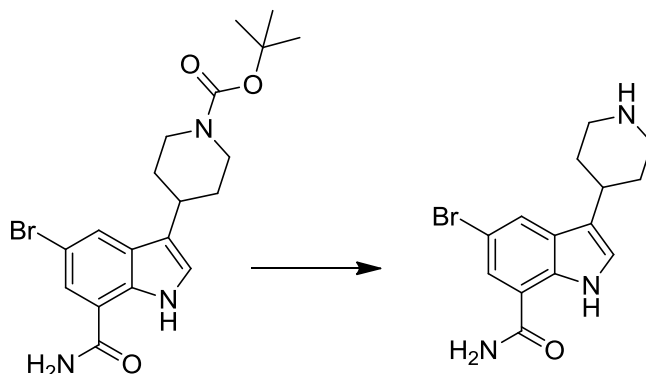
1,1-dimethylethyl-4-[7-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]-1-piperidine carboxylate



To a solution of 1,1-dimethylethyl 4-[7-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate (7.41g, 17.64 mmol) in ethanol (600 mL), platinum oxide (200 mg, 5%) was added. The reaction mixture was hydrogenated under an atmosphere of H_2 balloon for

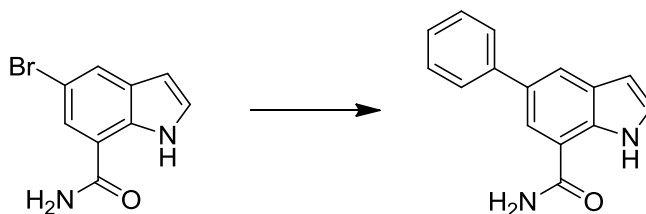
16 hours. The resulting mixture was filtered through celite and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (Ethyl acetate/Hexane, 1:4 to 2:1 v/v) to give the desired product (3.6g, 48%). LC/MS: m/z 422.0 (M+H), 2.25 min, 87%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.32 - 1.63 (m, 12 H) 1.91 (d, $J=12.05$ Hz, 2 H) 2.74 - 3.06 (m, 3 H) 4.05 (d, $J=11.54$ Hz, 2 H) 7.15 (s, 1 H) 7.46 (br. s., 1 H) 7.83 (s, 1 H) 7.94 (s, 1 H) 8.14 (br. s., 1 H) 11.03 (br. s., 1 H)

5-bromo-3-(4-piperidiny)-1H-indole-7-carboxamide



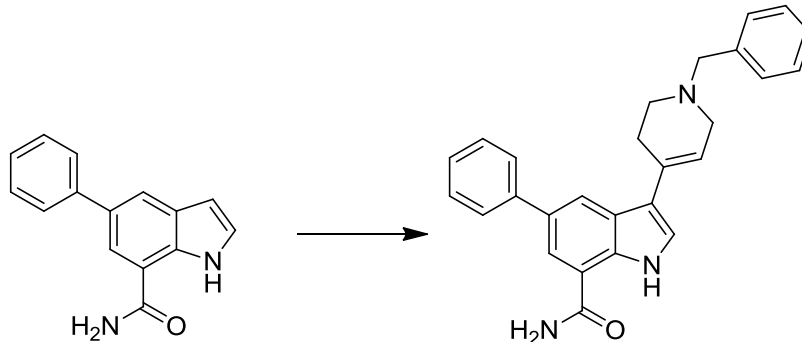
To a solution of 1,1-dimethylethyl 4-[7-(aminocarbonyl)-5-bromo-1H-indol-3-yl]-1-piperidinecarboxylate (1.56 g, 3.7 mmol) in methanol (10 mL), HCl in dioxane (4M, 35.5 mL) was added. The reaction mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the resulting residue was partitioned between ethyl acetate (50 mL) and 5% of aqueous NaOH (50 mL). The aqueous layer was washed with ethyl acetate (2x50 mL) and the combined organic phases were dried and concentrated under reduced pressure to give desired product (685 mg, 58%), which was used in the next step without further purification. LC/MS: m/z 321.05 (M+) 0.48 min, 100%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.39 - 1.60 (m, 2 H) 1.74 - 1.93 (m, 2 H) 2.56 - 2.71 (m, 2 H) 2.84 (tt, $J=11.78$, 3.51 Hz, 1 H) 3.00 (d, $J=12.13$ Hz, 2 H) 7.11 (s, 1 H) 7.46 (br. s., 1 H) 7.82 (d, $J=1.77$ Hz, 1 H) 7.91 (d, $J=1.77$ Hz, 1 H) 8.06 - 8.23 (m, 1 H) 10.98 (br. s., 1 H).

Synthesis of 5-phenyl-1H-indole-7-carboxamide (1)



To a 5 L three necked flask was charged 5-bromo-1*H*-indole-7-carboxamide (60 g, 0.251 mole, 1 eq). This was followed by the addition of phenyl boronic acid (91.88 g, 0.753 mole, 3 eq) and potassium phosphate tribasic (106 g, 0.502 mole, 2 eq). Nitrogen purged 1,4-dioxane (1.2 L, 20 vol wrt **12**) was then charged to the flask followed by water (1.2 L, 20 vol wrt **12**). 2'-(dimethylamino)-2-biphenyl-palladium(II) chloride dinorbornylphosphine complex (7.03 g, 0.0126 mole, 0.05 eq) was then added and the reaction mixture was heated to reflux for 3 hrs. The reaction mixture was cooled to room temperature and then was filtered through celite. The filtrate was then partitioned between ethyl acetate and brine. The layers were separated and the organic was concentrated in vacuo. The residue was then dissolved in acetonitrile/water (550 mL/50 mL, 10 vol wrt **12**) with heating. The solution was then treated with water (1.5 L, 30 vol wrt **12**) with stirring. The solid was formed collected by filtration and was washed with 3:1 water/acetonitrile followed by hot water it was then dried in vacuo at 40 °C to yield the desired product (57.69 g). LCMS *m/z* 237 (M+H), 98%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.52 - 6.57 (m, 1 H) 7.27 - 7.42 (m, 3 H) 7.47 (t, *J*=7.68 Hz, 2 H) 7.78 (d, *J*=7.30 Hz, 2 H) 8.02 (s, 2 H) 8.23 (br. s., 1 H) 11.11 (br. s., 1 H).

5-Phenyl-3-[1-(phenylmethyl)-1,2,3,6-tetrahydro-4-pyridinyl]-1*H*-indole-7-carboxamide



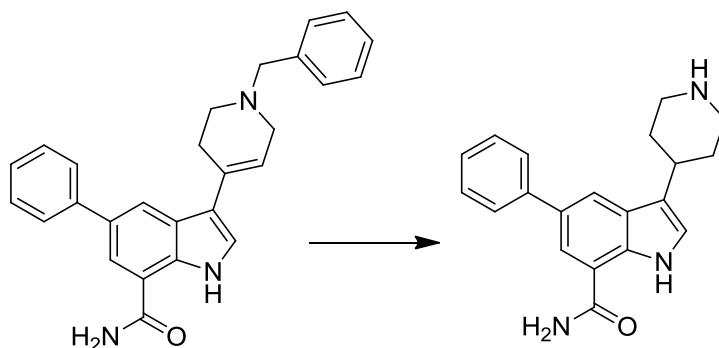
To the solution of 5-phenyl-1*H*-indole-7-carboxamide (3.11 g, 12 mmol) in methanol (100 mL) was added benzyl piperidone (7.4 g, 36 mmol), followed by 156 mL of NaOMe (0.5 M in MeOH). The reaction mixture was then heated at 80°C overnight. The solution was cooled to ambient temperature and the solvent removed under reduced pressure, and the resulting residue redissolved in a bilayer of ethyl acetate and 5% sodium hydroxide solution. The organic phase was washed with brine, dried over potassium carbonate, and the solvent removed under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂ : MeOH : NH₄OH = 96:3:1) to provide the desired product (2.66 g, 51%). LCMS *m/z* 407.22 (M+), 100%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.53 (br. s., 2 H) 2.63 - 2.72 (m, 2 H) 3.12 (br. s., 2 H)

3.59 (s, 2 H) 6.22 (br. s., 1 H) 7.21 - 7.40 (m, 8 H) 7.46 (t, $J=7.65$ Hz, 3 H) 7.78 (d, $J=7.53$ Hz, 2 H) 8.02 (s, 1 H) 8.19 (s, 1 H) 8.27 (br. s., 1 H) 11.17 (br. s., 1 H).

Alternative synthesis:

To a 5 L three necked flask was charged 85% wt Phosphoric acid (423 mL, 6.16 moles, 25 eq), benzyl piperidone (142 mL, 0.733 mole, 3 eq) and glacial acetic acid (400 mL). The resulting mixture was heated to 90°C. A solution of 5-phenyl-1*H*-indole-7-carboxamide (57.69 g, 0.244 mole, 1 eq) in glacial acetic acid (755 mL) was then added portion wise. The reaction was then maintained at 90°C overnight. The reaction mixture was cooled to room temperature. It was then divided into two equal portions and each was added slowly to separate stirring mixtures of ice/0.88 ammonia (1 L/1 L). A dry ice/acetone bath was also used to control the exotherm. Ethyl acetate (600 mL) was then added to the mixture with stirring. It was then filtered and the solid was washed well with ethyl acetate. The filtrate was then separated and the aqueous layer was re-extracted with ethyl acetate. The organics were then dried over magnesium sulfate and filtered before the two batches were combined and evaporated under reduced pressure. The residue was then dissolved in 3% (3.5M ammonia in methanol) in DCM (300 mL). The solid precipitate was then collected by filtration and was then dried in vacuo to yield the desired product. (42.25 g).

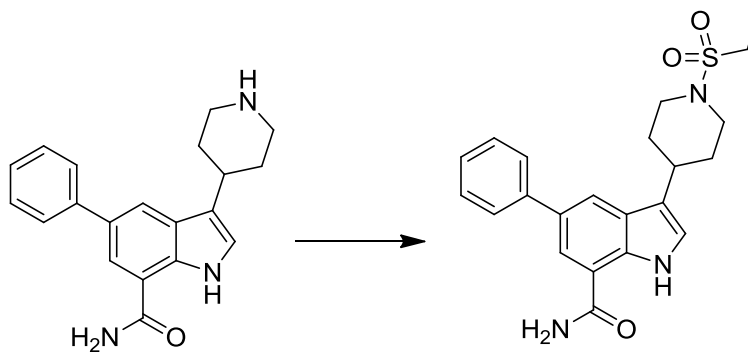
5-Phenyl-3-(4-piperidiny)-1*H*-indole-7-carboxamide



To the solution of 5-Phenyl-3-[1-(phenylmethyl)-1,2,3,6-tetrahydro-4-pyridinyl]-1*H*-indole-7-carboxamide (2.66 g, 6.5 mmol) in ethanol (150 mL) and acetic acid (3 mL) was added Pd(OH)₂ (20% by weight on carbon) (0.8 g,) at ambient temperature. The solution was stirred under 1 atm of hydrogen for 2 days. The reaction mixture was then filtered through Celite, neutralized with 5% sodium hydroxide solution, and extracted with ethyl acetate. The solvent was removed under reduced pressure to yield the desired product (1.45 g, 70%). LCMS m/z 319.17 (M⁺), 100%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.48 - 1.68 (m, 2 H) 1.91 (d, $J=12.05$ Hz, 2 H) 2.69

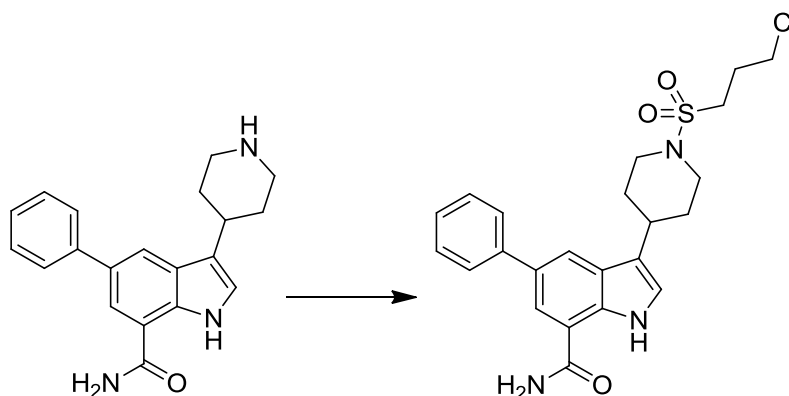
(t, $J=11.29$ Hz, 2 H) 2.89 - 3.11 (m, 3 H) 3.16 (s, 1 H) 7.09 (s, 1 H) 7.28 - 7.42 (m, 2 H) 7.47 (t, $J=7.65$ Hz, 2 H) 7.78 (d, $J=7.53$ Hz, 2 H) 7.99 (d, $J=4.77$ Hz, 2 H) 8.22 (br. s., 1 H) 10.84 (br. s., 1 H).

Synthesis of 3-[1-(ethanesulfonyl)-4-piperidiny]-5-phenyl-1*H*-indole-7-carboxamide (2)



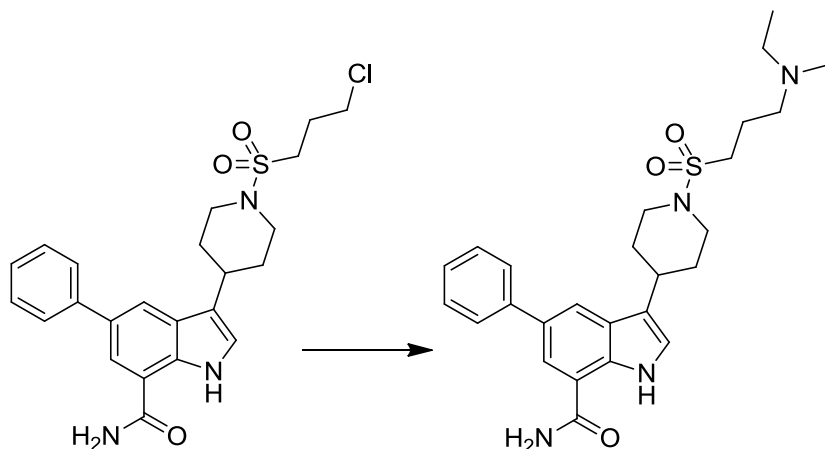
5-(phenyl)-3-(4-piperidiny)-1*H*-indole-7-carboxamide (16 mg, 0.04 mmol), ethanesulfonyl chloride (0.004 mL, 0.08 mmol) and triethylamine (0.016 mL, 0.12 mmol) were added. The reaction mixture was stirred at 0°C for 30 min. after which time the mixture was partitioned between CH₂Cl₂ and water. The aqueous phase was extracted with CH₂Cl₂ and the combined organic phase dried over MgSO₄ and concentrated under reduced pressure. The resulting residue was purified by reverse phase HPLC (CH₃CN/Water, 0.1 % TFA) to give the title compound (12.8 mg, 62%). LC/MS: m/z 412.0 (M+H), 2.18 min, 100%. HRMS : Molecular Formula C₂₂H₂₅N₃O₃S, Mass Found 412.1687 (M+H), Mass Required 412.1689 (M+H); HPLC 94%; ¹H NMR (400MHz, DMSO-*d*₆) δ = 10.92 (d, $J=1.3$ Hz, 1H), 8.23 (br. s., 1H), 8.02 (d, $J=5.5$ Hz, 2H), 7.80 (d, $J=7.5$ Hz, 2H), 7.48 (t, $J=7.7$ Hz, 2H), 7.43 - 7.30 (m, 2H), 7.16 (d, $J=2.3$ Hz, 1H), 4.10 (q, $J=5.2$ Hz, 3H), 3.73 (d, $J=12.0$ Hz, 2H), 3.14 - 2.96 (m, 5H), 2.09 (d, $J=11.5$ Hz, 2H), 1.75 - 1.59 (m, 2H).

3-{1-[(3-chloropropyl)sulfonyl]-4-piperidiny}-5-phenyl-1*H*-indole-7-carboxamide



To a solution of 5-phenyl-3-(4-piperidiny)-1*H*-indole-7-carboxamide (404 mg, 1.26 mmol) in CH₂Cl₂ at 0°C, triethylamine (0.7 mL, 5.04 mmol) and 3-chloropropanesulfonyl chloride (0.23 mL, 1.89 mmol) were added. The reaction mixture was stirred at 0°C for 30 min. The reaction mixture was partitioned between CH₂Cl₂ (100 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x100 mL). The combined organic phase was washed with brine (50 mL), dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure and purified via filtration through an SPE Cartridge (Aminopropyl NH₂, 500 mg/6 mL) to give the title compound (370 mg, 64%). LCMS *m/z* 460.0 (M+H).

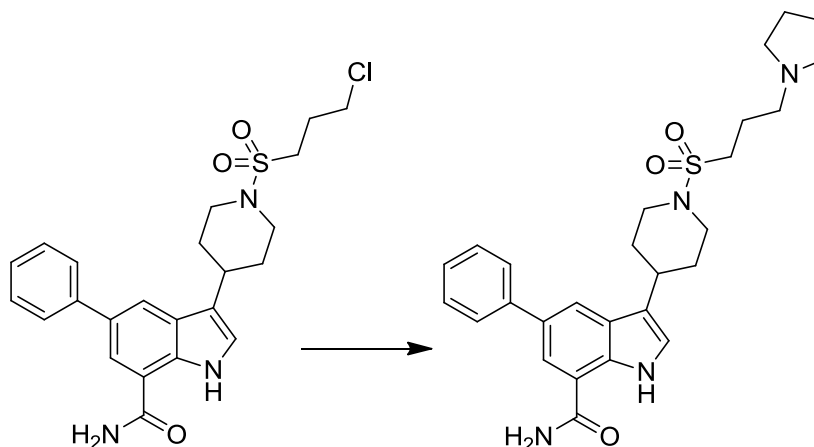
Synthesis of 3-(1-[[3-(diethylamino)propyl]sulfonyl]-4-piperidiny)-5-phenyl-1*H*-indole-7-carboxamide (3)



3-(1-[(3-chloropropyl)sulfonyl]-4-piperidiny)-5-phenyl-1*H*-indole-7-carboxamide (15 mg, 0.033 mmol) and diethylamine (13 eq) were allowed to react in the presence of K₂CO₃ (23 mg, 0.166 mmol) and sodium iodide (70 mg). The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by reverse phase HPLC eluting with 10% B to 80%

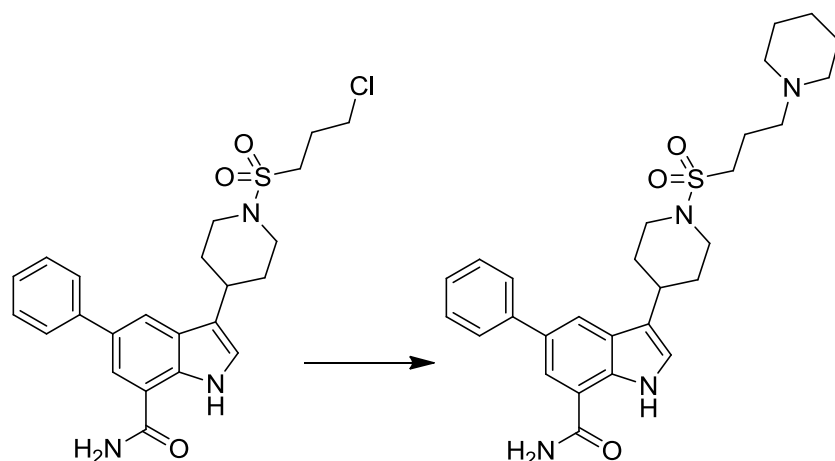
B, where A = H₂O (0.1% trifluoroacetic acid) and B = CH₃CN (0.1% trifluoroacetic acid) to give the title compound (6.7 mg, 41%). LC/MS: m/z 496.2 (M⁺) 0.72 min, 100%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.34 (t, *J*=7.33 Hz, 6 H) 1.74 - 1.91 (m, 2 H) 2.13 - 2.29 (m, 4 H) 3.01 - 3.14 (m, 3 H) 3.19 (s, 2 H) 3.23 - 3.28 (m, 4 H) 3.33 - 3.39 (m, 2 H) 3.82 - 3.97 (m, 2 H) 7.21 (s, 1 H) 7.27 - 7.36 (m, 1 H) 7.44 (s, 2 H) 7.71 (dd, *J*=8.21, 1.14 Hz, 2 H) 7.95 (d, *J*=1.52 Hz, 1 H) 8.00 (d, *J*=1.52 Hz, 1 H)

Synthesis of 5-phenyl-3-(1-[[3-(1-pyrrolidinyl)propyl]sulfonyl]-4-piperidinyl)-1*H*-indole-7-carboxamide (4)



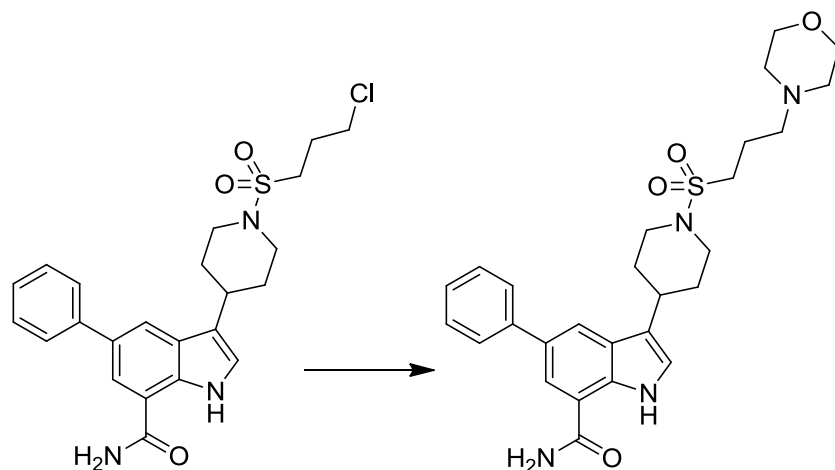
3-{1-[[3-(chloromethyl)sulfonyl]-4-piperidinyl]-5-phenyl-1*H*-indole-7-carboxamide (60 mg, 0.13 mmol) and pyrrolidine (46.2 mg, 0.65 mmol) were allowed to react in the presence of K₂CO₃ (77 mg, 0.56 mmol) and NaI (Cat. 2.13 mg) in CH₃CN at 80 °C overnight. The resulting residue was purified by reverse phase HPLC eluting with 10% B to 80% B, where A = H₂O (0.1% trifluoroacetic acid) and B = CH₃CN (0.1% trifluoroacetic acid) to give the title compound (27 mg, 42%). LC/MS m/z 495.2 (M+H), 2.03 min, 94.7%; HRMS : Molecular Formula C₂₇H₃₄N₄O₃S, Mass Found 495.2428 (M+H), Mass Required 495.2430 (M+H); HPLC 97%; ¹H NMR (400MHz, DMSO-*d*₆) δ = 10.95 (d, *J*=1.8 Hz, 1H), 9.55 (br. s., 1H), 8.24 (br. s., 1H), 8.02 (s, 2H), 7.84 - 7.75 (m, 2H), 7.54 - 7.30 (m, 4H), 7.17 (d, *J*=2.3 Hz, 1H), 3.74 (d, *J*=12.1 Hz, 2H), 3.60 (d, *J*=5.3 Hz, 2H), 3.29 - 3.19 (m, 4H), 3.10 - 2.98 (m, 5H), 2.17 - 2.09 (m, 3H), 2.08 - 1.97 (m, 3H), 1.87 (dd, *J*=4.9, 7.5 Hz, 2H), 1.76 - 1.63 (m, 2H)

Synthesis of 5-phenyl-3-(1-[[3-(1-piperidinyl)propyl]sulfonyl]-4-piperidinyl)-1*H*-indole-7-carboxamide (5)



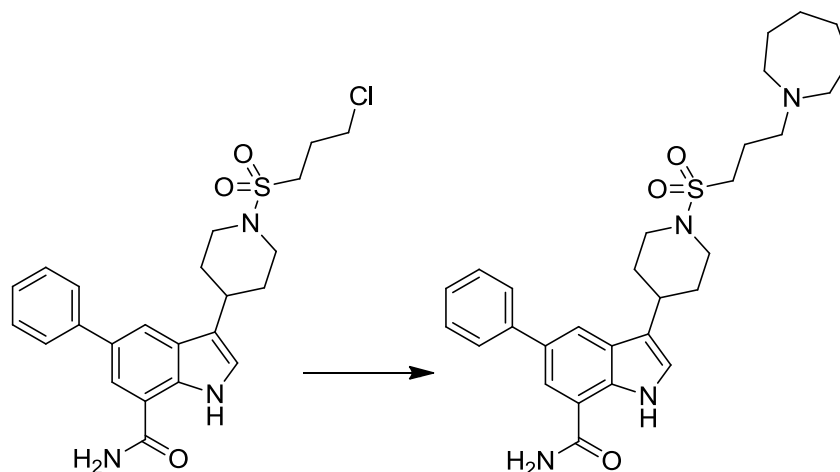
3-{1-[(3-chloropropyl)sulfonyl]-4-piperidinyl}-5-phenyl-1*H*-indole-7-carboxamide (62 mg, 0.13 mmol) and piperidine (55.25 mg, 0.65 mmol) were allowed to react in the presence of K_2CO_3 (72 mg, 0.56 mmol) and NaI (Cat. 2.0 mg) in CH_3CN at reflux for 2 days. The reaction mixture was cooled and worked up with 5% $NaHCO_3$ and EtOAc. The organics were concentrated and the resulting residue purified by reverse phase HPLC eluting with 10% B to 80% B, where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) to give the title compound (31.5 mg, 46%). LC/MS m/z 509.2 ($M+H$); 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.33 - 1.48 (m, 1 H) 1.54 - 1.77 (m, 5 H) 1.83 (d, $J=14.40$ Hz, 2 H) 2.03 - 2.20 (m, 4 H) 2.84 - 2.98 (m, 2 H) 3.00 - 3.12 (m, 3 H) 3.14 - 3.26 (m, 6 H) 3.74 (d, $J=12.13$ Hz, 2 H) 7.17 (d, $J=2.27$ Hz, 1 H) 7.28 - 7.37 (m, 1 H) 7.41 (br. s., 1 H) 7.49 (t, $J=7.71$ Hz, 2 H) 7.74 - 7.85 (m, 2 H) 8.02 (s, 2 H) 8.24 (br. s., 1 H) 10.95 (d, $J=2.02$ Hz, 1 H).

Synthesis of 3-(1-{[3-(4-morpholinyl)propyl]sulfonyl}-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide (6)



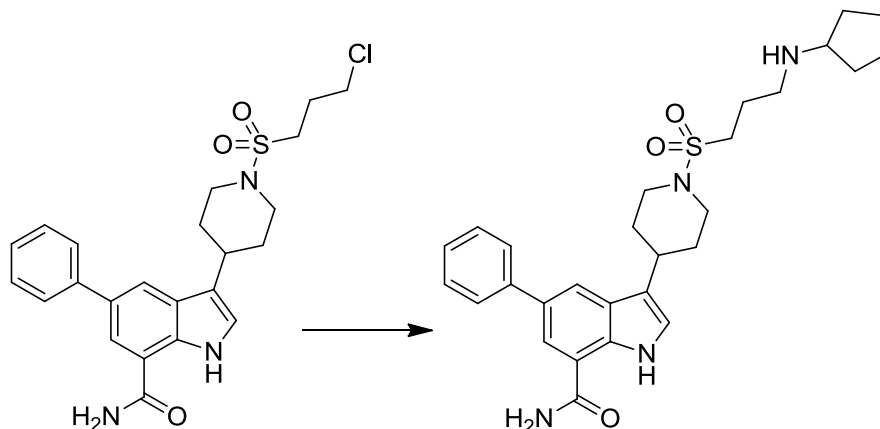
3-{1-[(3-chloropropyl)sulfonyl]-4-piperidinyl}-5-phenyl-1*H*-indole-7-carboxamide (60 mg, 0.13 mmol) and morpholine (56.63 mg, 0.65 mmol) were allowed to react in the presence of K₂CO₃ (77 mg, 0.56 mmol) and NaI (Cat. 2.13 mg) in CH₃CN at reflux overnight. The reaction mixture was cooled and worked up with EtOAc and water and concentrated. The resulting residue was purified by reverse phase HPLC eluting with 10% B to 80% B, where A = H₂O (0.1% trifluoroacetic acid) and B = CH₃CN (0.1% trifluoroacetic acid) to give the title compound (20 mg, 30%). LC/MS *m/z* 510.0 (M⁺), 2.2 min, 100%; HRMS : Molecular Formula C₂₇H₃₄N₄O₄S, Mass Found 511.2373 (M+H), Mass Required 511.2379 (M+H); HPLC 92%; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.95 (d, 1H, *J*=2.0 Hz), 9.5-9.7 (m, 1H), 8.23 (br s, 1H), 8.02 (s, 2H), 7.79 (dd, 2H, *J*=1.1, 8.5 Hz), 7.5-7.5 (m, 2H), 7.4-7.4 (m, 1H), 7.3-7.4 (m, 1H), 7.17 (d, 1H, *J*=2.3 Hz), 4.0-4.1 (m, 2H), 3.75 (br d, 2H, *J*=11.9 Hz), 3.65 (br t, 2H, *J*=12.1 Hz), 3.4-3.5 (m, 4H), 3.2-3.3 (m, 4H), 3.0-3.2 (m, 4H), 2.1-2.2 (m, 2H), 1.6-1.8 (m, 2H).

Synthesis of 3-(1-{[3-(4-azapanyl)propyl]sulfonyl}-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide (7)



This compound was prepared in a fashion analogous to compound 6. Thus 3-{1-[(3-chloropropyl)sulfonyl]-4-piperidinyl}-5-phenyl-1*H*-indole-7-carboxamide (20 mg, 0.043 mmol) and azapane (28 μ L, 0.215 mmol) were allowed to react in the presence of K₂CO₃ (23.7 mg) and sodium iodide (70 mg) to give the title compound (10.8 mg, 48%). LC/MS *m/z* 523.4 (M+H) 1.75 min, 99%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.54 - 1.71 (m, 1 H) 1.72 - 2.21 (m, 8 H) 2.22 - 2.40 (m, 2 H) 2.80 (t, *J*=12.25 Hz, 1 H) 2.88 - 3.12 (m, 6 H) 3.13 - 3.24 (m, 2 H) 3.45 (d, *J*=10.86 Hz, 1 H) 3.54 - 3.70 (m, 1 H) 3.78 (d, *J*=11.62 Hz, 1 H) 3.87 (d, *J*=11.12 Hz, 2 H) 7.20 (s, 1 H) 7.27 - 7.36 (m, 1 H) 7.44 (s, 2 H) 7.71 (d, *J*=8.08 Hz, 2 H) 7.95 (s, 1 H) 8.00 (s, 1 H).

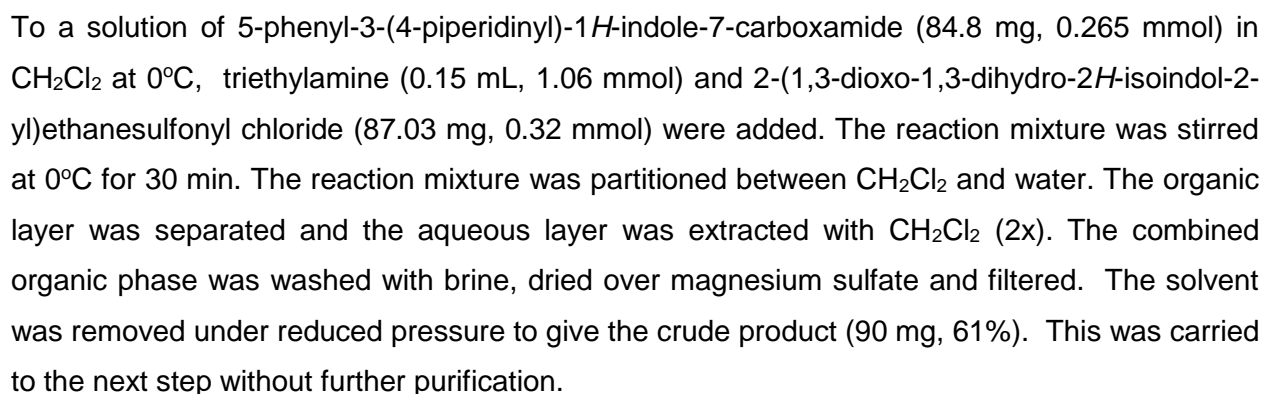
Synthesis of 3-(1-[[3-(4-aminocyclopentyl)propyl]sulfonyl]-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide (8)



This compound was prepared in a fashion analogous to compound 6. Thus 3-{1-[(3-chloropropyl)sulfonyl]-4-piperidinyl}-5-phenyl-1*H*-indole-7-carboxamide (20 mg, 0.043 mmol) and cyclopentylamine (54 μ l) were allowed to react in the presence of K_2CO_3 (60 mg) and sodium iodide (2 mg) in DMF (2mL) to give the title compound (17.9 mg, 32%). LC/MS m/z 509.4 (M+H) 1.80 min; 1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.54 - 1.94 (m, 11 H) 2.03 - 2.31 (m, 7 H) 3.01 - 3.17 (m, 3 H) 3.23 (t, $J=7.45$ Hz, 4 H) 3.58 (quin, $J=6.95$ Hz, 1 H) 3.90 (d, $J=12.13$ Hz, 2 H) 7.20 - 7.26 (m, 1 H) 7.30 - 7.38 (m, 1 H) 7.46 (t, $J=7.71$ Hz, 2 H) 7.73 (d, $J=7.33$ Hz, 2 H) 7.94 - 7.99 (m, 1 H) 8.02 (s, 1 H).

Synthesis of 3-{1-[(2-aminoethyl)sulfonyl]-4-piperidinyl}-5-phenyl-1*H*-indole-7-carboxamide (9)

3-(1-[[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]sulfonyl]-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide



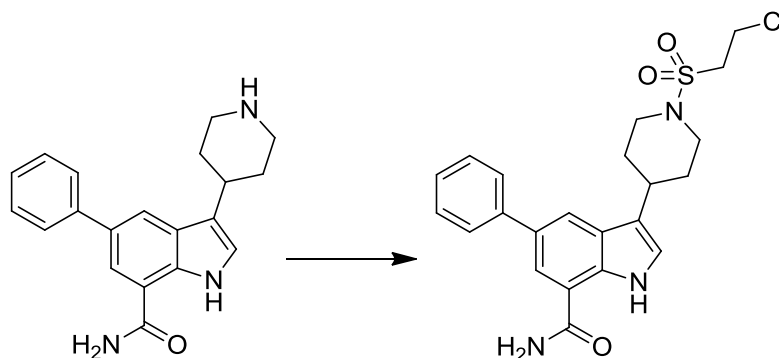
The reaction scheme shows the conversion of a benzimidazole derivative to a benzimidazole derivative with a piperidine ring. The starting material on the left is 2-((2-aminocarbonyl-5-phenyl-1H-benzimidazol-1-yl)methyl)-1H-benzimidazole-5-carboxamide. It features a benzimidazole core with a phenyl group at position 5 and an amide group at position 2. The imidazole ring is substituted at position 2 with a (2-aminocarbonyl-5-phenyl-1H-benzimidazol-1-yl)methyl group. The reaction arrow points to the product on the right, which is 2-((2-aminocarbonyl-5-phenyl-1H-benzimidazol-1-yl)piperidin-1-yl)-1H-benzimidazole-5-carboxamide. The product is identical to the starting material, except that the methyl group on the piperidine ring has been replaced by a (2-aminocarbonyl-5-phenyl-1H-benzimidazol-1-yl) group.

25

and B = CH₃CN (0.1% trifluoroacetic acid) to give the title compound (26.9 mg, 50%). LC/MS *m/z* 426.17 (M⁺), 2.06 min, 96.5%; HRMS : Molecular Formula C₂₂H₂₆N₄O₃S, Mass Found 427.1802 (M+H), Mass Required 427.1804 (M+H); HPLC 98%; ¹H NMR (DMSO-d₆, 400 MHz) δ 10.96 (br s, 1H), 8.24 (br s, 1H), 8.02 (s, 2H), 7.80 (br d, 2H, *J*=7.8 Hz), 7.49 (br t, 2H, *J*=7.7 Hz), 7.42 (br d, 1H, *J*=3.0 Hz), 7.3-7.4 (m, 1H), 7.17 (s, 1H), 3.75 (br d, 2H, *J*=11.6 Hz), 3.40 (br t, 2H, *J*=6.9 Hz), 3.2-3.3 (m, 2H), 3.0-3.1 (m, 4H), 2.14 (br d, 2H, *J*=11.9 Hz), 1.6-1.8 (m, 2H), 1.2-1.4 (m, 1H), 0.8-0.9 (m, 1H).

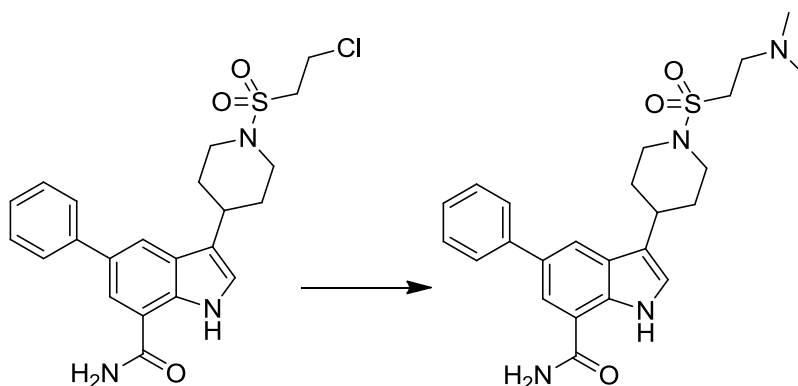
Synthesis of 3-(1-[[2-(dimethylamino)ethyl]sulfonyl]-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide (10)

3-{1-[(2-chloroethyl)sulfonyl]-4-piperidinyl}-5-phenyl-1*H*-indole-7-carboxamide



To a solution of 5-phenyl-3-(4-piperidinyl)-1*H*-indole-7-carboxamide (65 mg, 0.2 mmol) in CH₂Cl₂ (5 mL) at 0°C, triethylamine (0.11 mL, 0.8 mmol) and 2-chloroethanesulfonyl chloride (0.042 mL, 0.4 mmol) were added. After stirring at 0°C for 30 min. the reaction mixture was partitioned between CH₂Cl₂ and water. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic phase was dried over magnesium sulfate and the solvent removed under reduced pressure. The resulting residue was purified by filtration through an SPE Cartridge (Aminopropyl NH₂, 500mg/6mL) to give the desired product (26 mg, 32%). LC/MS *m/z* 445.0 (M+H).

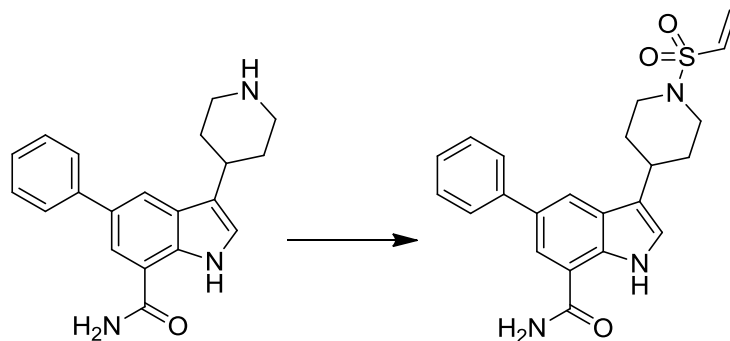
3-(1-[[2-(dimethylamino)ethyl]sulfonyl]-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide (10)



To a solution of 3-(1-[(2-chloroethyl)sulfonyl]-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide (26 mg, 0.063 mmol) in CH₃CN (5 mL), dimethylamine (0.16 mL, 0.315 mmol), K₂CO₃ (35 mg, 0.252 mmol) and NaI (cat. 0.5 mg) were added. The reaction mixture was stirred at 80°C for 16 hours. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The resulting residue was purified by reverse phase HPLC (CH₃CN/water, 0.1 % TFA) to give title compound (14 mg, 48%). LC/MS *m/z* 455.2 (M+H); HRMS : Molecular Formula C₂₄H₃₀N₄O₃S, Mass Found 455.2112 (M+H), Mass Required 455.2117 (M+H); ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.83 (dd, *J*=12.76, 3.41 Hz, 2 H) 2.13 - 2.24 (m, 2 H) 2.33 (s, 1 H) 3.00 (s, 6 H) 3.05 - 3.18 (m, 3 H) 3.53 - 3.69 (m, 4 H) 3.91 (d, *J*=12.13 Hz, 2 H) 7.08 - 7.26 (m, 3 H) 7.29 - 7.37 (m, 1 H) 7.45 (t, *J*=7.71 Hz, 2 H) 7.69 - 7.76 (m, 2 H) 7.97 (d, *J*=1.52 Hz, 1 H) 8.01 (d, *J*=1.26 Hz, 1 H)

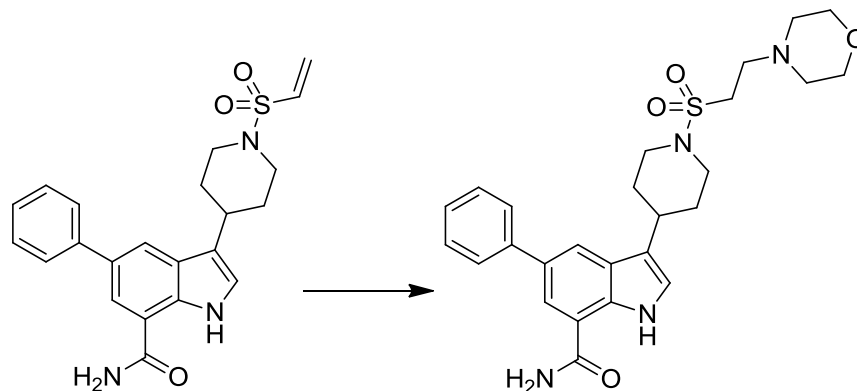
Synthesis of 3-(1-[[2-(morpholino)ethyl]sulfonyl]-4-piperidinyl)-5-phenyl-1*H*-indole-7-carboxamide (11)

3-[1-(ethenylsulfonyl)-4-piperidinyl]-5-phenyl-1*H*-indole-7-carboxamide



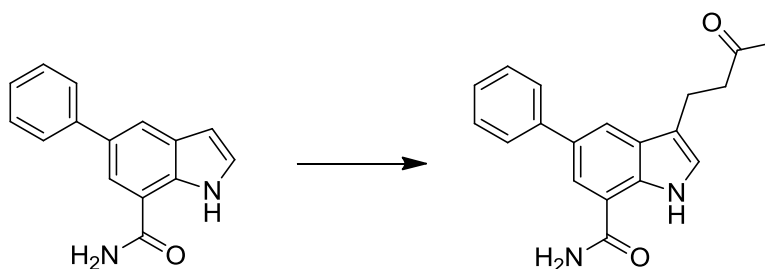
To a solution of 5-phenyl-3-(4-piperidiny)-1*H*-indole-7-carboxamide (260 mg, 0.8 mmol) in CH₂Cl₂ at 0°C, triethylamine (0.44 mL, 3.2 mmol) and 2-chloroethylsulfonyl chloride (0.168 mL, 1.6 mmol) were added. The reaction mixture was stirred at 0°C for 30 min. The reaction mixture was partitioned between CH₂Cl₂ (100 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x100 mL). The combined organic phase was washed with brine (50 mL), dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure and purified via filtration through an SPE Cartridge (Aminopropyl NH₂, 500 mg/6 mL) to give the title compound (245 mg, 75%). LCMS *m/z* 410 (M+H).

3-(1-([2-(morpholino)ethyl]sulfonyl)-4-piperidiny)-5-phenyl-1*H*-indole-7-carboxamide (11)



To a solution of 3-[1-(ethenylsulfonyl)-4-piperidiny]-5-phenyl-1*H*-indole-7-carboxamide (26 mg, 0.063 mmol) in CH₃CN (1.0 mL), was added morpholine (5eq). The reaction solution was heated to 80°C over night. After which time the reaction mixture was purified by reverse phase HPLC (water/ CH₃CN, 0.1 % TFA 3-70%) to give the title compound (5 mg, 16%). LC/MS: *m/z* 497.6 (M+H), 1.64 min ; ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.87 (qd, *J*=12.59, 4.03 Hz, 2 H) 2.24 (d, *J*=11.33 Hz, 2 H) 3.15 (td, *J*=12.21, 2.27 Hz, 3 H) 3.56 - 3.63 (m, 2 H) 3.64 - 3.72 (m, 2 H) 3.88 - 4.02 (m, 3 H) 7.24 (s, 1 H) 7.30 - 7.38 (m, 1 H) 7.43 - 7.53 (m, 2 H) 7.73 (dd, *J*=8.06, 1.26 Hz, 2 H) 7.97 (d, *J*=1.51 Hz, 1 H) 8.03 (d, *J*=1.51 Hz, 1 H)

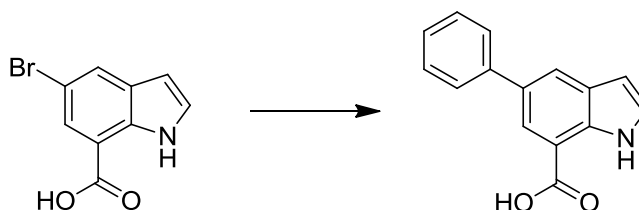
Synthesis of (3-oxobutyl)-5-phenyl-1*H*-indole-7-carboxamide (12)



To a solution of 5-phenyl-1H-indole-7-carboxamide (0.118g, 0.5 mmol) and methyl vinylketone (0.035g, 0.5 mmol) in acetonitrile (2 mL) was added bismuth triflate (0.0098g, 0.015 mmol). After 2 hrs at ambient temperature the reaction mixture was diluted with acetonitrile (5 mL), filtered and concentrated. The resulting residue was purified via silica gel chromatography using DCM and ethyl acetate to give the title compound (0.080g, 52%). LC/MS: m/z 306.00 (M⁺), 3.01 min, 100%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.07 - 2.22 (m, 3 H) 2.79 - 2.90 (m, 2 H) 2.91 - 3.07 (m, 2 H) 7.13 (s, 1 H) 7.27 - 7.42 (m, 2 H) 7.47 (t, $J=7.28$ Hz, 2 H) 7.81 (d, $J=7.78$ Hz, 2 H) 8.00 (d, $J=5.27$ Hz, 2 H) 8.22 (br. s., 1 H) 10.86 (br. s., 1 H).

Synthesis of 3-(2-(methylsulfonyl)ethyl)-5-phenyl-1H-indole-7-carboxamide (13)

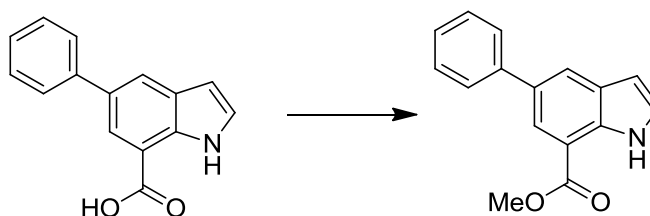
5-phenyl-1H-indole-7-carboxylic acid



To a solution of 5-bromo-1H-indole-7-carboxylic acid (10 g, 41.8 mmol) in dioxane (150 mL) and water (50 mL) was added phenylboronic acid (19.5 g, 159.9 mmol), cesium carbonate (26.0 g, 79.8 mmol), 1,3-Bis(2,4,6-trimethylphenyl) imidazolium chloride (2.8g, 8.2mmol), and palladium acetate (0.9g, 4.01mmol). The reaction mixture was stirred at ambient temperature for 15 min, and then was refluxed at 80 C for 15 hr. The organic solvent was removed under reduced pressure and the water layer was adjusted to pH=1-2 with 6M hydrochloric acid before ethyl acetate (350 mL) was added into it. The organic layer was washed with water (100 mL x 3), dried and concentrated at 45 C to a thick oil (approximately 40 mL solvent left), cooled to -20 C, and filtered. The solid was washed with cold ethyl acetate (10 mL x 3), and collected. The filtrate was concentrated to a thick oil at 45 C, then was cooled to -20 C and an off-white solid was obtained. The suspension was filtered and washed with cold ethyl acetate (5 mL x 3). The

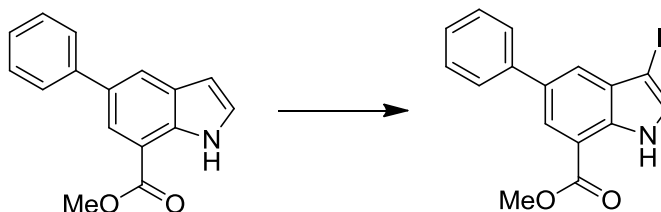
filtrate was discarded after 3 iterations of the above procedure. LCMS m/z 237.0 (M^+), 3.45 min, 100%.

Methyl 5-phenyl-1H-indole-7-carboxylate



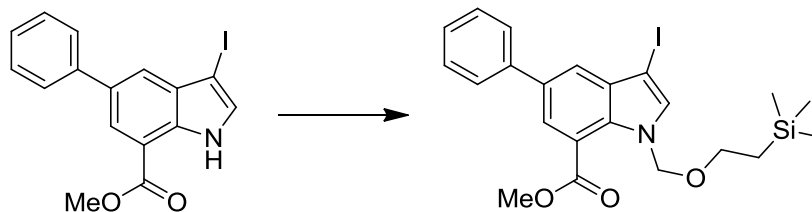
Carbonyl di-imidazole (CDI) (684 mg, 4.2 mmol) was added to the mixture of 5-phenyl-1H-indole-7-carboxylic acid (1.00 g, 4.2 mmol) in DCM (20 mL) at ambient temperature. After 30 minutes, MeOH (0.51 mL, 12.6 mmol) was added. The final mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure. Water and ethyl acetate were added. The layers were separated and the aqueous layer was extracted with ethyl acetate once. The combined organics were dried, filtered and concentrated to give 1.20 g of the crude title compound. This was used directly in the next step without further purification.

Methyl 3-iodo-5-phenyl-1H-indole-7-carboxylate



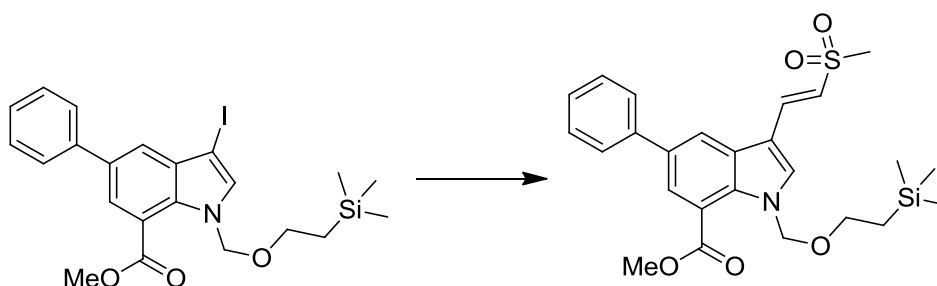
The mixture of methyl 5-phenyl-1H-indole-7-carboxylate (1.02 g, 4.06 mmol), N-iodosuccinimide (NIS) (1.00 g, 4.4 mmol) and DCM (50 mL) was stirred at ambient temperature overnight. Ethyl acetate and aq. Na_2SO_3 were added. The layers were separated and the organic layer was washed with 2N NaOH and brine. The organics were dried, filtered and concentrated to give 1.1 g of the crude title compound as a solid which was used directly in the next step without further purification.

Methyl 3-iodo-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-7-carboxylate



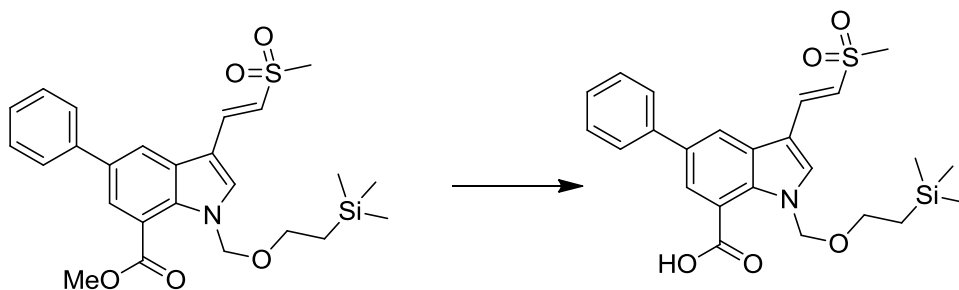
NaH (106 mg, 4.4 mmol) was added to the solution of methyl 3-iodo-5-phenyl-1H-indole-7-carboxylate (1.11 g, 2.9 mmol) in DMF (20 mL). The mixture was stirred for 10 minutes at ambient temperature before SEMCl (0.62 mL, 3.5 mmol) was added. The mixture was stirred for 1 hour. Water and ethyl acetate were added. The layers were separated and the aqueous layer was extracted with ethyl acetate once. The combined organics were washed with brine, dried, filtered and concentrated. The residue was purified via silica gel chromatography to give 1.28 g of the title compound.

(E)-methyl 3-(2-(methylsulfonyl)vinyl)-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-7-carboxylate



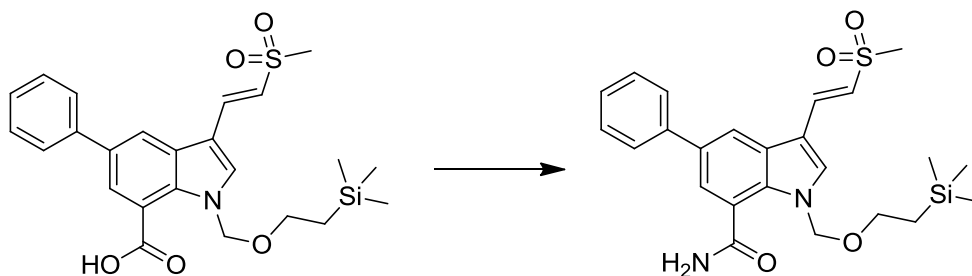
To a microwave vial was added methyl 3-iodo-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-7-carboxylate (319 mg, 0.63 mmol), (methylsulfonyl)ethene (80 mg, 0.75 mmol), Pd(OAc)₂ (14 mg, 0.063 mmol), PPh₃ (33 mg, 0.12 mmol), Et₃N (0.35 mL, 2.5 mmol) and DMF (6 mL). The mixture was heated to 120 C for 20 minutes via microwave. The reaction mixture was purified via reverse phase HPLC using TFA as modifier to give 71 mg of the title compound. LC/MS: m/z (M+h) 486.1, 2.65, 100%.

(E)-3-(2-(methylsulfonyl)vinyl)-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-7-carboxylic acid



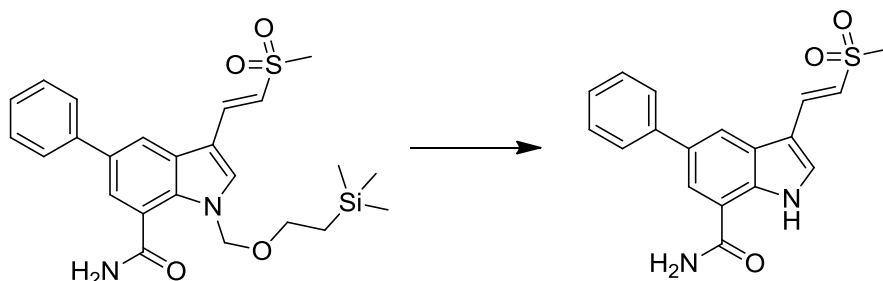
To a microwave vial was added (E)-methyl 3-(2-(methylsulfonyl) vinyl)-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-7-carboxylate (71 mg, 0.14 mmol), LiOH (17 mg, 0.73 mmol), water (0.5 mL) and MeOH (1 mL). The mixture was heated to 80 C for 30 minutes via microwave. The solvent was removed and the pH of the residue was adjusted to 5-6. Water and ethyl acetate were added. The layers were separated and the aqueous layer was extracted once with ethyl acetate. The combined organics were dried with MgSO₄, filtered and concentrated to provide 0.068 g of crude title compound which would be used in the next step without further purification. LC/MS: m/z (M+H) 472.0, 2.26, 85%.

(E)-3-(2-(methylsulfonyl)vinyl)-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-7-carboxamide



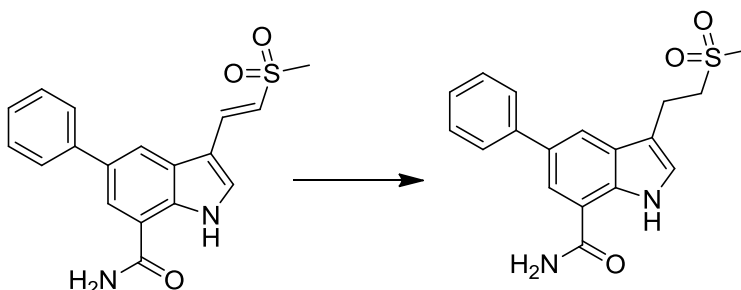
To the solution of (E)-3-(2-(methylsulfonyl) vinyl)-5-phenyl-1-((2-(trimethylsilyl)ethoxy) methyl)-1H-indole-7-carboxylic acid (85 mg, 0.18 mmol) in DCM (5 mL) was added HOBt (29 mg, 0.22 mmol), EDC (42 mg, 0.22 mmol) and 2N NH₃ (in MeOH, 0.36 mL, 0.72 mmol). The mixture was stirred at ambient temperature overnight. The solvent was removed and the residue was partitioned in ethyl acetate and water. The layers were separated and the aqueous layer was extracted once with ethyl acetate. The combined organics were dried with MgSO₄, filtered and concentrated to 0.120 g of the crude title compound which was used in the next step without further purification. LC/MS: m/z 458.2, 2.51, 17%, m/z 413.0, 2.11, 31% (Note : The title compound from the crude isolate appeared to fragment under the LC/MS conditions providing a number of masses greater than the starting material and indicative of the desired product.)

(E)-3-(2-(methylsulfonyl)vinyl)-5-phenyl-1H-indole-7-carboxamide



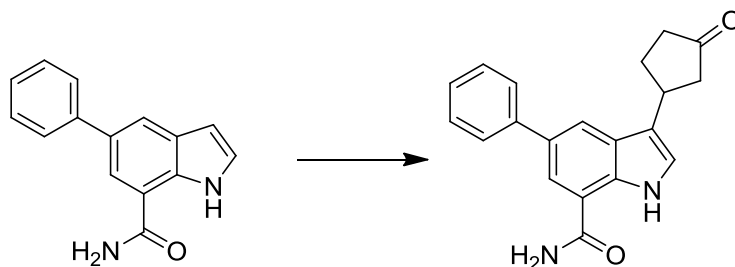
The mixture of (E)-3-(2-(methylsulfonyl) vinyl)-5-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-7-carboxamide (85 mg, 0.18 mmol) and 1M TBAF (in THF) (0.9 mL, 0.9 mmol) in THF (5 mL) was stirred at 72 C overnight. The solvent was removed and the residue was purified via reverse phase HPLC using TFA as modifier to give 7 mg of the title compound. LC/MS: m/z 355.9 (M+H), 2.08, 87%.

3-(2-(methylsulfonyl)ethyl)-5-phenyl-1H-indole-7-carboxamide



PtO₂ (1 mg, 0.04 mmol) was added to the solution of (E)-3-(2-(methylsulfonyl) vinyl)-5-phenyl-1H-indole-7-carboxamide (5 mg, 0.014 mmol) in MeOH (2 mL) at room temp. The final mixture was purged with H₂ and stirred under H₂ balloon overnight. The solvent was removed and the residue was purified using reverse phase HPLC using TFA as modifier to give 2 mg of the title compound. LC/MS: m/z 326.0 (M-NH₂), 1.66 min, 100% ; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.01 (s, 3 H) 3.15 - 3.24 (m, 2 H) 3.47 - 3.56 (m, 2 H) 7.28 (d, *J*=2.26 Hz, 1 H) 7.30 - 7.37 (m, 1 H) 7.40 (br. s., 1 H) 7.48 (t, *J*=7.78 Hz, 2 H) 7.73 - 7.88 (m, 2 H) 7.96 - 8.10 (m, 2 H) 8.23 (br. s., 1 H) 10.98 (s, 1 H)

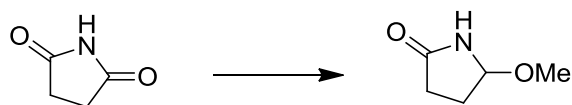
Synthesis of 3-(3-oxocyclopentyl)-5-phenyl-1H-indole-7-carboxamide (14)



To a solution of 5-phenyl-1H-indole-7-carboxamide (1.0 g, 4.2 mmol) and cyclopentenone (4.24 mmol, 348 mg) in dry acetonitrile (20 mL) was added bismuth triflate (3 mol%, 0.127 mmol, 83 mg). The resultant mixture was stirred at room temperature for 18hr. The mixture was pre-absorbed onto silica and purified on a 20 g silica Bondelut cartridge, eluting with dichloromethane, then, cyclohexane: ethyl acetate 2:1 to give the title compound as a white powder (600 mg, 45%). LC/MS m/z 318.0, 3.03 min; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.93 - 2.13 (m, 1 H) 2.25 - 2.49 (m, 4 H) 2.70 (dd, $J=17.82, 7.28$ Hz, 1 H) 3.64 - 3.83 (m, 1 H) 7.16 - 7.25 (m, 1 H) 7.28 - 7.43 (m, 2 H) 7.48 (t, $J=7.65$ Hz, 2 H) 7.77 - 7.87 (m, 2 H) 8.00 - 8.12 (m, 2 H) 8.23 (br. s., 1 H) 10.94 (s, 1 H)

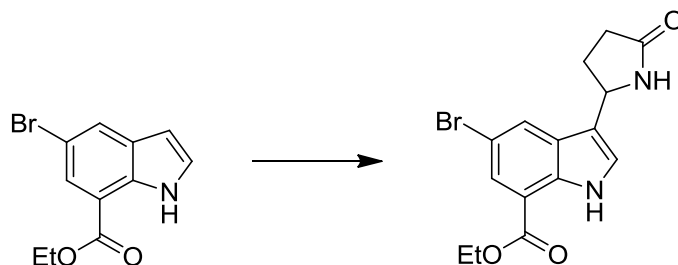
Synthesis of 3-(5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (15)

s5-methoxypyrrolidin-2-one



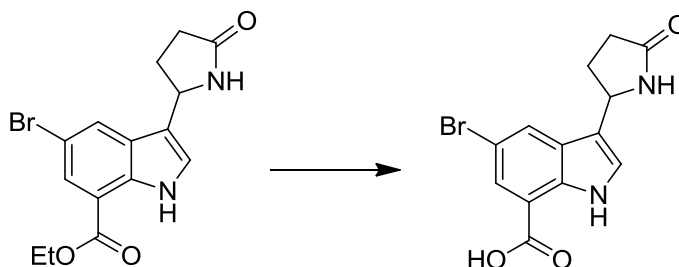
Succinimide (2g) was diluted in 200 mL of methanol, and the solution was cooled to 0°C. Sodium borohydride (2.9 g) was added, note gas evolution. Approximately every 20 minutes during the course of the reaction, 2-3 drops of 4N HCl in dioxane was added at 0°C. The mixture was stirred at 0°C for a total of 5h. Enough 4N HCl in dioxane was added to achieve pH=4 (pH paper), and a white precipitate had formed. The mixture was stirred at 0°C for another 1h, then neutralized with 6N aqueous NaOH. The mixture was concentrated, water was added, and the mixture was extracted with dichloromethane. The combined organics were dried over sodium sulfate, filtered, and concentrated to afford a clear, colorless oil which was used in the next step (340 mg).

Ethyl 5-bromo-3-(5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate



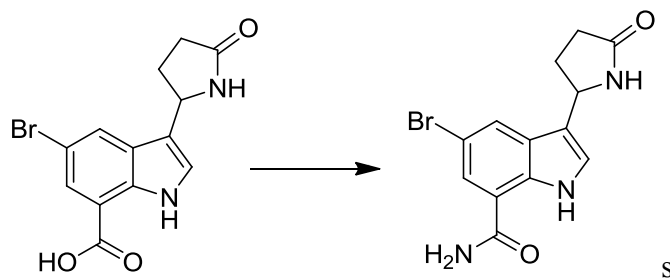
NbCl_5 (414 mg, 2.57 mmol) was diluted in 15 mL of dichloromethane at 0 C. 5-methoxypyrrolidin-2-one was added as a solution in 5 mL of dichloromethane at 0 C. The mixture was stirred at 0 C for 30 minutes, then ethyl 5-bromo-1H-indole-7-carboxylate indole (690 mg) was added as a solution in 5 mL of dichloromethane. The mixture was slowly allowed to warm (ice bath melted over 2h), then the reaction progress was checked by LC/MS. Minor starting material remained, but looked ok. Quenched by the addition of saturated aqueous sodium bicarbonate, extract with dichloromethane. The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was triturated from methanol to afford the desired as an off white solid. This was used in the next step without further purification.

5-bromo-3-(5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid



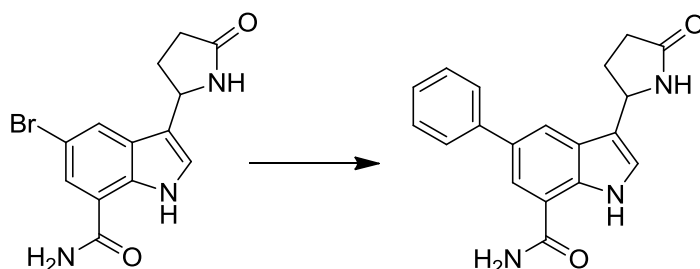
Ethyl 5-bromo-3-(5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate (0.519 g, 1.478 mmol) was diluted in 10 mL methanol, 3.5 mL of 6N NaOH, and 5 mL of water. The mixture was heated to 85C for 1h. The mixture was cooled to ambient temperature, concentrated, and treated with 6N HCl until pH=1 (pH paper). A light, yellow precipitate was obtained and dried at 45C (0.46 g, 96%). LC/MS m/z 322.4/324.9, 0.74 min

5-bromo-3-(5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide



5-bromo-3-(5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid (460 mg), EDCI·HCl (790 mg), HOBt hydrate (232 mg) were diluted in 2 mL of DMF and 12 mL of 0.5M ammonia in dioxane in a microwave vial. The reaction was heated to 100°C for 20 minutes at normal absorption in the microwave. After cooling, ethyl acetate and water were added to the reaction mixture. The aqueous layer was extracted 3x with 50 mL of ethyl acetate, and the combined organics were washed with water (2x50 mL) and dried over sodium sulfate. Concentration followed by trituration from dichloromethane gave the desired product as a cream colored solid (0.361 g, 79%). LC/MS m/z 321.7/323.8, 0.64 min.

3-(5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (15)

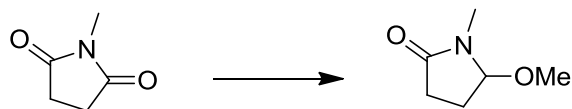


5-bromo-3-(5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide (0.045 g, 0.140 mmol), phenyl boronic acid (0.0204 g, 0.168 mmol), PdCl₂(dppf)-CH₂Cl₂ (0.017 g, 0.021 mmol), and K₂CO₃ (0.083 g, 0.601 mmol) were combined and dioxane (2 mL) and water (1 mL). The suspension was degassed by bubbling argon through mixture for 5 minutes. The reaction was heated via microwave at 100°C for 5 min then cooled and filtered through a thiol SPE cartridge to remove palladium. The solution was concentrated and diluted re-dilute to a total of ~ 3 mL in dmsO, and filtered through a syringe filter. The product was purified via reverse phase HPLC under basic conditions (0.010 g, 22%). LC/MS m/z 342.0 (M+Na⁺), 0.74 min, 100%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.97 - 2.14 (m, 1 H) 2.23 - 2.35 (m, 2 H) 5.05 (t, *J*=6.78 Hz, 1 H) 7.28 (d, *J*=2.01 Hz, 1 H) 7.31 - 7.38 (m, 1 H) 7.43 (br. s., 1 H) 7.49 (t, *J*=7.78 Hz, 2 H) 7.79 (dd, *J*=8.16,

1.13 Hz, 2 H) 8.02 (dd, $J=13.43$, 1.38 Hz, 2 H) 8.11 (s, 1 H) 8.25 (br. s., 1 H) 11.02 (s, 1 H) (98% by ^1H NMR with 2% MeOH).

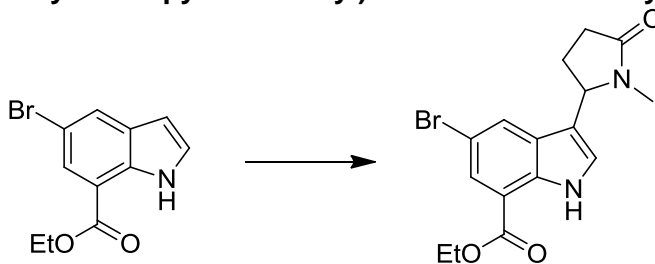
Synthesis of 5-bromo-3-(1-methyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide (16)

5-methoxy-1-methylpyrrolidin-2-one



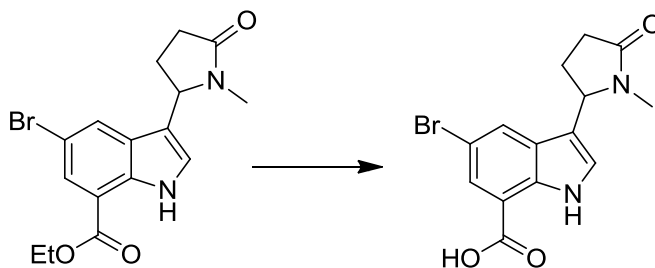
N-methyl succinimide (2g, 17.68 mmol) was diluted in 200 mL of methanol and cooled to 0C. Sodium borohydride (2.5 g, 66.1 mmol) was added in a single portion; noted gas evolution. The reaction was stirred at 0C for 7 h; 1-2 drops of 4N HCl in dioxane were added approximately every 20 minutes (pH remained at ~7-8 by pH paper). When reaction was complete (TLC, 30% ethyl acetate in hexanes; potassium permanganate stain), enough 4N HCl in dioxane was added at 0C to bring the pH to 4. A white precipitate was evident. The mixture was stirred at 0C for another 1h, then neutralized with 1N NaOH and the methanol removed. Extracted with dichloromethane, dried the combined organics over sodium sulfate, and concentrated to afford a clear colorless oil (2g, 88%). This was used without further purification.

Ethyl 5-bromo-3-(1-methyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate



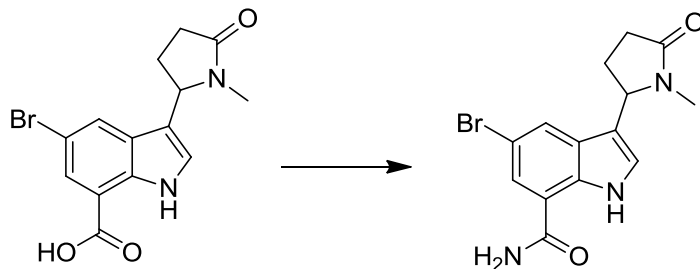
NbCl_5 (1.2 g, 4.44 mmol) was diluted in 40 mL of dichloromethane, and cooled to 0C. 5-methoxy-1-methylpyrrolidin-2-one (1.0 g, 7.74 mmol) was added as a dichloromethane solution (10 mL), and the mixture was stirred at 0C for 30 minutes. Ethyl 5-bromo-2,3-dihydro-1H-indole-7-carboxylate (2 g, 7.46 mmol) was diluted in 20 mL of dichloromethane and added to the mixture. The reaction was stirred for 3h with gradual warming of the ice bath. The mixture was quenched with saturated sodium bicarbonate and extracted with dichloromethane. The combined organics were dried over sodium sulfate, filtered, concentrated, and triturated from methanol to give an off white solid (1.72 g, 63.1%). LC/MS m/z 365.1/367.0 (M+H), 0.96 min.

5-bromo-3-(1-methyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid



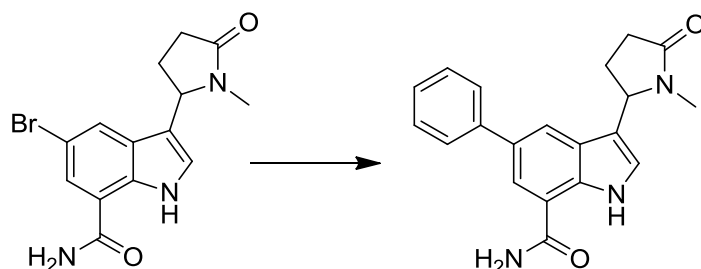
Ethyl 5-bromo-3-(1-methyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate (1.72 g, 4.71 mmol) was diluted in 30 mL methanol and 15 mL water. 6N NaOH (aq, 11 mL) was added, and the reaction was heated at 85°C for about 45 minutes (starting material dissolved). The mixture was cooled to ambient temperature, concentrated, added 10 mL of 6N aq HCl to a pH=1. The product oiled out as a gummy light yellow solid. Added a small amount of methanol, concentrated, and triturated from water. The desired product was obtained as a powder upon scraping. This was dried in a vacuum oven at 45°C (1.41 g, 89%). LC/MS *m/z* 337.1/339.2 (M+H), 0.75 min.

5-bromo-3-(1-methyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide



5-bromo-3-(1-methyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid (0.705 g, 2.091 mmol), EDCI•HCl (1.16 g, 6.05 mmol), HOBT hydrate (0.341 g, 2.27 mmol) were diluted in 2 mL of DMF and 12 mL of 0.5M ammonia in dioxane in a microwave vial. The reaction was heated to 100°C for 20 minutes at normal absorption in the microwave. After cooling, ethyl acetate and water were added to the reaction mixture. The organics were dried over sodium sulfate and concentrated. (Note: the reaction was run 2x on this scale to give 1.09 g, 77%). LC/MS *m/z* 336.1/338, 0.67 min.

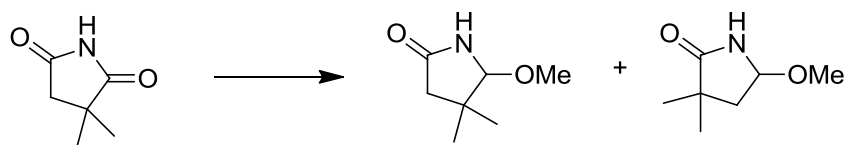
5-bromo-3-(1-methyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide (16)



5-bromo-3-(5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide (0.045 g, 0.140 mmol), phenyl boronic acid (0.0204 g, 0.168 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (0.017 g, 0.021 mmol), and K_2CO_3 (0.083 g, 0.601 mmol) were combined and dioxane (2 mL) and water (1 mL). The suspension was degassed by bubbling argon through mixture for 5 minutes. The reaction was heated via microwave at 100°C for 5 min then cooled and filtered through a thiol SPE cartridge to remove palladium. The solution was concentrated and diluted re-dilute to a total of ~ 3mL in dmsol, and filtered through a syringe filter. The product was purified via reverse phase HPLC under basic conditions (0.010 g, 22%). LC/MS m/z 334.1 (M+H), 0.74 min, 100%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.02 - 2.16 (m, 1 H) 2.28 - 2.47 (m, 3 H) 2.53 (s, 4 H) 4.97 (t, $J=7.03$ Hz, 1 H) 5.76 (s, 1 H) 7.24 - 7.39 (m, 2 H) 7.41 - 7.55 (m, 3 H) 7.68 - 7.79 (m, 2 H) 7.86 (s, 1 H) 8.03 (d, $J=1.26$ Hz, 1 H) 8.26 (br. s., 1 H) 11.14 (s, 1 H).

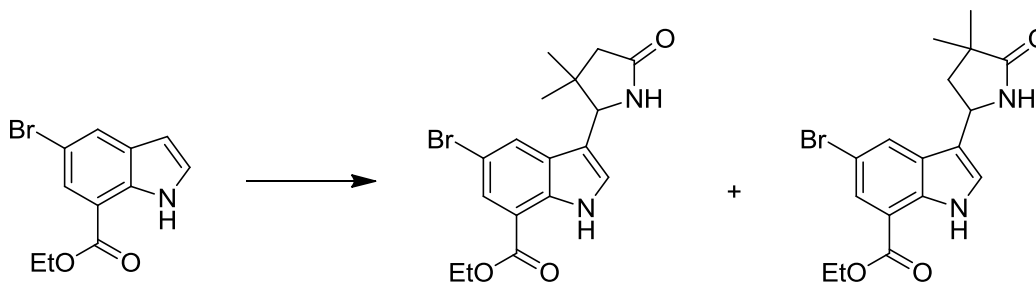
Synthesis of 3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (17) and 3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (18)

5-methoxy-3,3-dimethylpyrrolidin-2-one and 5-methoxy-4,4-dimethylpyrrolidin-2-one



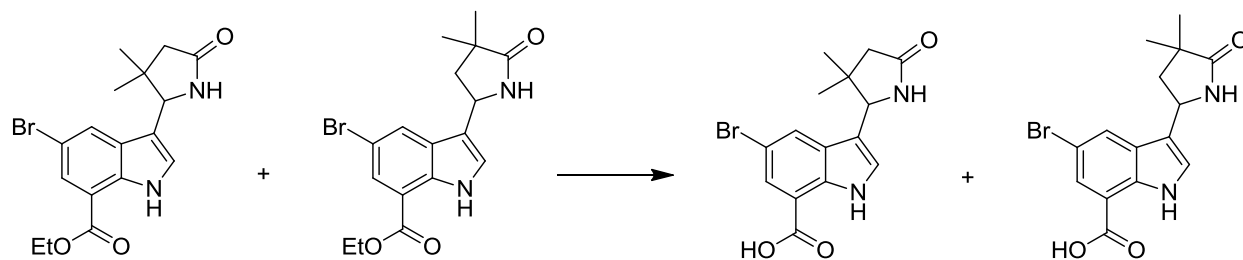
To a flask, 3,3-dimethyl-2,5-pyrrolidinedione (2 g, 15.73 mmol) in methanol (200 mL), NaBH_4 (2.261 g, 59.8 mmol) was added at 0 °C. Approximately every 20 mins during the course of the reaction, 4-5 drops of 4N HCl in dioxane was added at 0 °C for a total of 5 hours. Then enough 4 N HCl in dioxane was added to achieve pH=4 and a white precipitate formed. The mixture was stirred at 0 °C for another 1 hour, then neutralized with 6N aqueous NaOH. The mixture was concentrated, water was added, and the mixture was extracted with CH_2Cl_2 . The combined organics were dried over sodium sulfate, filtered, and concentrated to afford a clear colorless oil which was carried to the next step without further purification.

Ethyl 5-bromo-3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate and ethyl 5-bromo-3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate



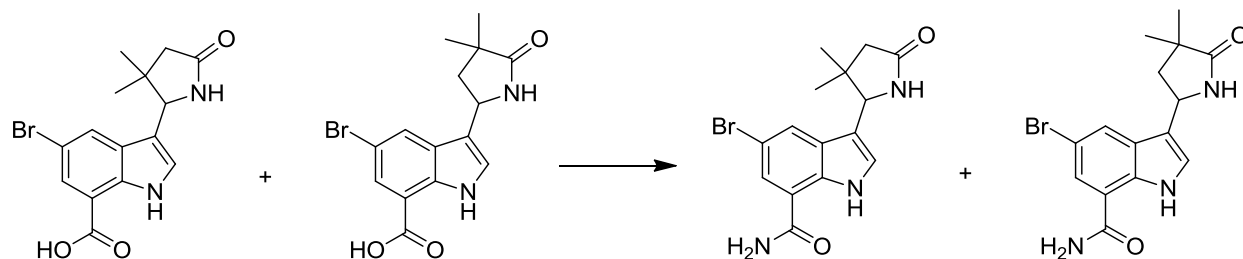
NbCl₅ (1.008 g, 3.73 mmol) was diluted in 5 mL of DCM at 0 °C. A mixture of 5-methoxy-3,3-dimethylpyrrolidin-2-one and 5-methoxy-4,4-dimethylpyrrolidin-2-one was added as a solution in 5 mL of DCM at 0 °C. The mixture was stirred at 0 °C for 30 mins, then ethyl 5-bromo-1H-indole-7-carboxylate (1 g, 3.73 mmol) was added as a solution in 5 mL of DCM. The mixture was slowly allowed to warm over 2 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined layers were washed with saturated NaCl (1 x 20 mL) dried (Mg₂SO₄), and concentrated to give 1.3 g of a mixture of products. This was carried to the next step without further purification. LC/MS: m/z 379.0/380.9 (M+H) 1.08 min; 378.9/380.9 (M+H) 1.18 min

5-bromo-3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid and 5-bromo-3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid



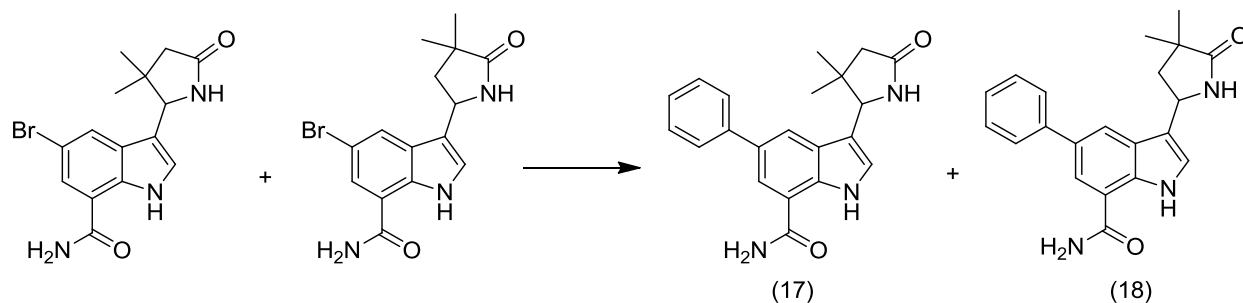
A mixture of ethyl 5-bromo-3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate and ethyl 5-bromo-3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylate was diluted in methanol (20 ml)/ water (5 ml), NaOH (4 ml, 24.00 mmol) was added and the mixture was heated to 85 °C for 1 h. The mixture was cooled to ambient temperature, concentrated and treated with 6N HCl until pH = 1. A white precipitate of the mixture of 5-bromo-3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid and 5-bromo-3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid was obtained. This was carried to the next step without further purification LC/MS: m/z 350.8/352.9 (M+H), 0.82 min; 350.8/352.9, 0.83 min

5-bromo-3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide and 5-bromo-3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide



The mixture of 5-bromo-3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid and 5-bromo-3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxylic acid, EDC (1484 mg, 7.74 mmol), HOBT (435 mg, 2.84 mmol) were diluted in 2 mL of DMF and 12 mL of 0.5 M ammonia in dioxane in a microwave vial. The reaction was heated at 100°C for 20 minutes. The reaction was cooled and water was added and the reaction mixture was extracted with EtOAc. The ethyl acetate layer was dried over magnesium sulfate and concentrated to give a white solid (0.602 g). This was carried to the next step without further purification.

3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (17) and 3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (18)

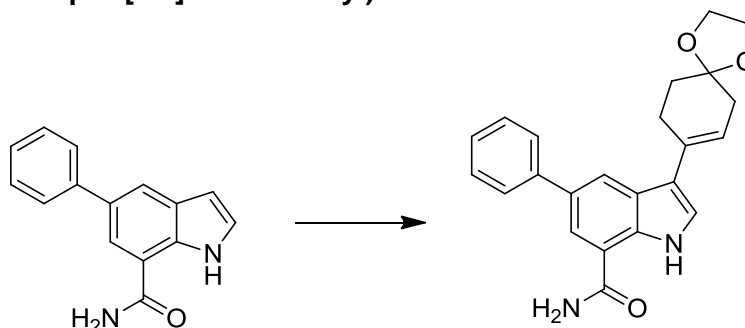


A mixture of 5-bromo-3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide and 5-bromo-3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-1H-indole-7-carboxamide, K_2CO_3 (71.0 mg, 0.514 mmol) and phenyl boronic acid (0.031 g, 0.257 mmol) in dioxane (3 mL) and water (1 mL) and the suspension degassed with nitrogen for 5 mins. $PdCl_2(dppf)$ (12.54 mg, 0.017 mmol) was added, the vial was sealed, and the reaction was heated at 120 °C for 20 mins. LC/MS indicated a complete reaction. EtOAc (3 mL) and water (1 mL) were added, the layers were separated, and the aqueous layer was extracted with EtOAc (4 x 2 mL). the combined organic layers were washed with saturated NaCl (1 x 2 mL), dried (Na_2SO_4), and concentrated under a stream of nitrogen at 50 °C. The crude product was dissolved in DMSO (2 mL), filtered through a 0.2 μm acrodisc, and purified via reverse phase HPLC, eluting at 20 mL/min with a linear

gradient running from 20% CH₃CN/H₂O (0.1% TFA) to 50% CH₃CN/H₂O (0.1% TFA) over 20 min to obtain each isomer as a pure isomer. 3-(3,3-dimethyl-5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (**17**) (19.1 mg, 32 %) LC/MS: m/z 347.8 (M+H), 0.84 min, 97%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 0.82 (s, 3 H) 1.36 (s, 3 H) 2.03 (s, 1 H) 2.29 - 2.50 (m, 2 H) 4.89 - 5.02 (m, 1 H) 7.22 - 7.37 (m, 2 H) 7.45 (t, *J*=7.78 Hz, 2 H) 7.70 (dd, *J*=8.41, 1.13 Hz, 2 H) 7.99 (dd, *J*=13.05, 1.51 Hz, 2 H) and 3-(4,4-dimethyl-5-oxopyrrolidin-2-yl)-5-phenyl-1H-indole-7-carboxamide (**18**) (5.5 mg, 9.2%) LC/MS: m/z 347.8 (M+H), RT 0.85 min, 98%; ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.25 (s, 3 H) 1.29 (s, 3 H) 2.15 - 2.26 (m, 1 H) 2.43 - 2.53 (m, 1 H) 5.05 - 5.23 (m, 1 H) 7.27 - 7.34 (m, 1 H) 7.37 (s, 1 H) 7.41 - 7.49 (m, 2 H) 7.70 (dd, *J*=8.28, 1.25 Hz, 2 H) 7.99 (dd, *J*=16.19, 1.63 Hz, 2 H).

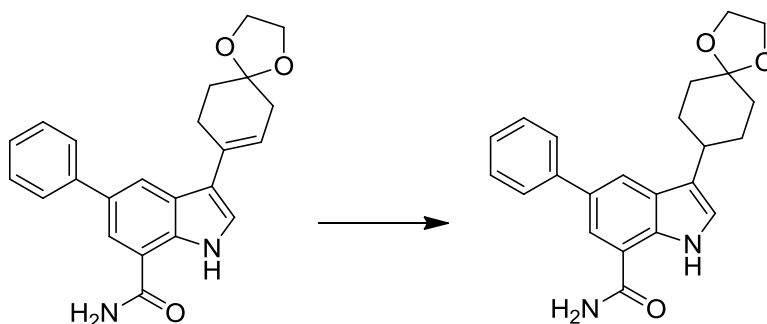
Synthesis of 3-(4-oxocyclohexyl)-5-phenyl-1H-indole-7-carboxamide (**19**)

5-phenyl-3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-indole-7-carboxamide



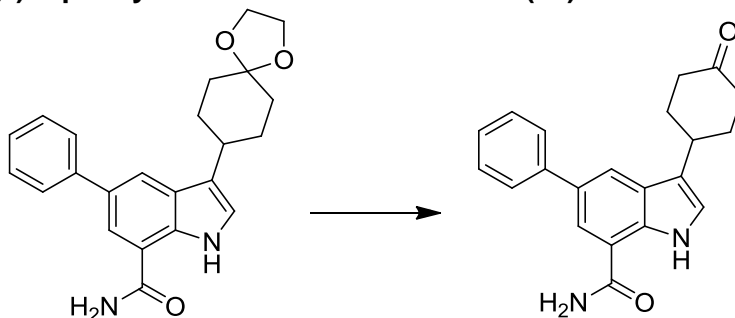
A mixture of 5-phenyl-1H-indole-7-carboxamide (1.06g, 4.5 mmol), 1,4-cyclohexanedione mono ethylene glycol ketal (0.937g, 6mmol) in sodium methoxide (25% w/v, 10 mL) was heated at reflux for 24 hrs. The mixture was evaporated to dryness and taken into ethyl acetate and washed with water (3x100 mL), brine, and dried over magnesium sulfate and concentrated to 1.3g of a gum. This was purified via silica gel chromatography using cyclohexane:ethyl acetate as eluent to give the title compound as a pale yellow solid (1.02g, 61%). LC/MS: m/z 375 (M+H), 3.36 min

5-phenyl-3-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-indole-7-carboxamide



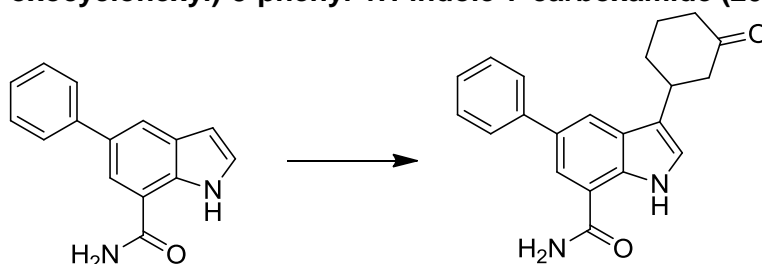
To 10% palladium hydroxide on carbon (0.5 g) under an atmosphere of nitrogen was added a solution of 5-phenyl-3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-indole-7-carboxamide (0.898g, 2.4 mmol) in ethanol (24 mL). The resulting mixture was kept under an atmosphere of hydrogen for 18 hrs. The mixture was filtered through Celite and the filtrate concentrated to give a solid. This was triturated with dichloromethane to afford the title compound as a pale yellow solid (0.860g, 95%). LC/MS: m/z 377 (M+H), 3.39 min

3-(4-oxocyclohexyl)-5-phenyl-1H-indole-7-carboxamide (19)



To a solution of 5-phenyl-3-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-indole-7-carboxamide (0.791g, 2.1 mmol) in acetonitrile was added water (6mL) and bismuth triflate (0.800g) and the solution stirred at 20 C for 16 hrs. The resulting mixture was evaporated to dryness and the resulting gum taken into ethyl acetate (200 mL). The organic phase was washed with water (3x80 mL), dried over magnesium sulfate and concentrated. The resulting solid was triturated with anhydrous ether (50 mL) with stirring and the solid filtered and washed with ether to give the title compound as a pale pink solid (0.650g, 93%). LC/MS: m/z 332.15 (M+), 0.96 min, 98.5%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.07 (t, *J*=7.03 Hz, 1 H) 1.75 - 2.01 (m, 2 H) 2.29 (d, *J*=9.79 Hz, 5 H) 2.59 - 2.78 (m, 2 H) 7.09 - 7.22 (m, 1 H) 7.25 - 7.38 (m, 2 H) 7.42 - 7.55 (m, 2 H) 7.71 - 7.84 (m, 2 H) 7.71 - 7.86 (m, 2 H) 7.92 - 7.92 (m, 1 H) 8.09 (d, *J*=1.00 Hz, 1 H) 8.05 - 8.11 (m, 1 H) 8.16 - 8.36 (m, 1 H) 8.23 (br. s., 1 H) 10.83 (s, 1 H) 10.73 - 10.95 (m, 1 H).

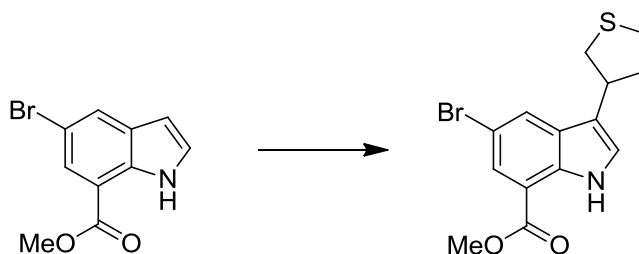
Synthesis of 3-(3-oxocyclohexyl)-5-phenyl-1H-indole-7-carboxamide (20)



A mixture of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.67g, 1.8 mmol) and NaI (0.27g, 1.8 mmol) in acetonitrile (10 mL) was heated via microwave at 100 °C for 10 minutes. To the resulting suspension was added 5-phenyl-1H-indole-7-carboxamide (1.4g, 5.9 mmol) and cyclohexenone (5.9 mmol) and the suspension heated at 140 °C for 10 minutes via microwave. The suspension was filtered and the filtrate adsorbed onto silica gel and purified via silica gel chromatography eluting with DCM and ethyl acetate. The resulting residue was then purified via reverse phase mass directed auto preparative HPLC to give a white powder (200 mg, 10%). LC/MS: m/z 332.15 (M^+), 1.0 min, 100%; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.68 - 2.05 (m, 3 H) 2.08 - 2.22 (m, 1 H) 2.24 - 2.36 (m, 1 H) 2.38 - 2.48 (m, 1 H) 2.53 - 2.63 (m, 1 H) 2.66 - 2.81 (m, 1 H) 7.16 (d, $J=2.26$ Hz, 1 H) 7.27 - 7.42 (m, 2 H) 7.48 (t, $J=7.65$ Hz, 2 H) 7.72 - 7.86 (m, 2 H) 7.96 - 8.08 (m, 2 H) 8.23 (br. s., 1 H) 10.93 (s, 1 H).

Synthesis of 3-(1,1-dioxidotetrahydrothiophen-3-yl)-5-phenyl-1H-indole-7-carboxamide (21)

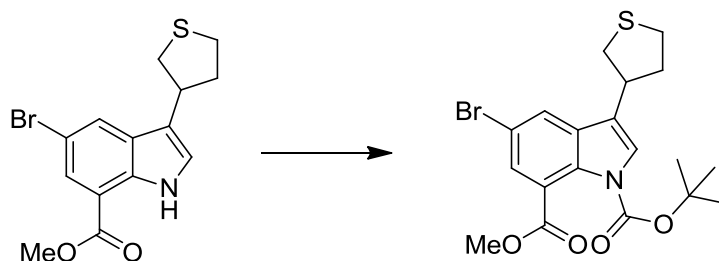
Methyl 5-bromo-3-(tetrahydro-3-thienyl)-1H-indole-7-carboxylate



To the stirred mixture of dihydro-3(2H)-thiophenone (0.167 mL, 1.97 mmol) in DCM (25 mL) under N_2 was added TMS-OTf (0.71 mL, 3.9 mmol) slowly over about 5 minutes at 0 °C (ice-bath). A solution of ethyl 5-bromo-1H-indole-7-carboxylate (0.50 g, 1.97 mmol) in DCM (5 mL) was added dropwise over 60 min, then triethylsilane (1.26 mL, 9.8 mmol) was added in one portion, and the reaction was allowed to warm slowly to room temperature. Then saturated NaHCO_3 and DCM were added, the layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were dried (MgSO_4) and concentrated. The

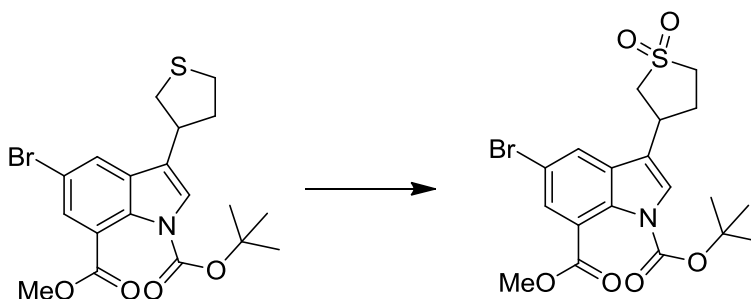
residue was purified using Companion, giving 312 mg (46%) of the title compound. LC/MS: m/z 341.8 (M+H), 2.45 min.

1-(1,1-dimethylethyl) 7-methyl 5-bromo-3-(tetrahydro-3-thienyl)-1*H*-indole-1,7-dicarboxylate



Boc₂O (398 mg, 1.8 mmol) and DMAP (56 mg, 0.46 mmol) were added to a solution of methyl 5-bromo-3-(tetrahydro-3-thienyl)-1*H*-indole-7-carboxylate (312 mg, 0.91 mmol) in CH₃CN (6.5 mL) and DCM (3.5 mL) at RT. The reaction was stirred at room temperature overnight and filtered through a silica gel pad, eluting with DCM. The filtrate was concentrated to give 430 mg crude product. LC/MS: m/z 441.8 (M+H), 2.81 min.

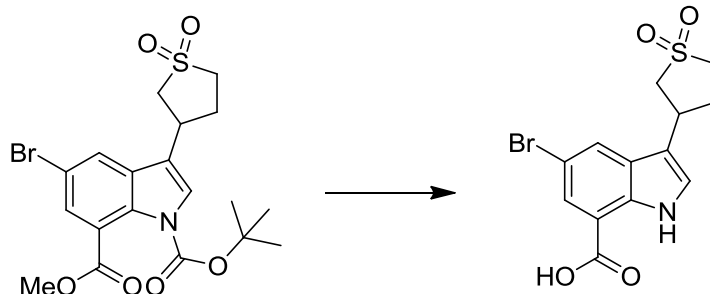
1-(1,1-dimethylethyl) 7-methyl 5-bromo-3-(1,1-dioxidotetrahydro-3-thienyl)-1*H*-indole-1,7-dicarboxylate



Urea•H₂O₂ (2.83 g, 30.1 mmol) was added in a single portion to a solution of TFAA (3.41 mL, 24.5 mmol) in CH₃CN (30 mL). The reaction was stirred at room temperature for 30 min and then cooled to 0 °C (bath temp). To this cold solution was added dropwise a suspension of 1-(1,1-dimethylethyl) 7-methyl 5-bromo-3-(tetrahydro-3-thienyl)-1*H*-indole-1,7-dicarboxylate (3.618 g, 8.18 mmol) in CH₃CN (30 mL) at 0 °C (bath temp). The reaction was stirred at room temperature for 40 min. EtOAc and water were added, the layers were separated, and the aqueous layer was extracted with DCM three times. The combined organic layers were filtered through a pad of silica gel and concentrated. The residue was re-dissolved in ethyl acetate and

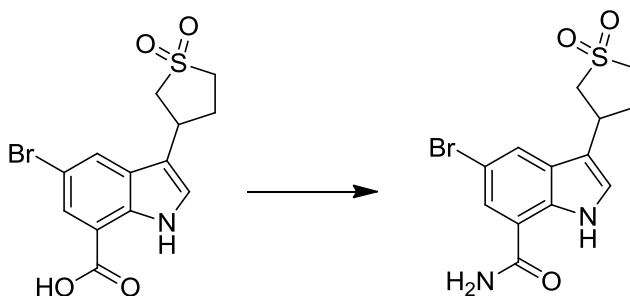
washed with aq. NaHCO₃, filter and concentrated to give a 4.18 g of product. LC/MS: m/z 473.8 (M+H), 2.19 min.

5-bromo-3-(1,1-dioxidotetrahydro-3-thienyl)-1*H*-indole-7-carboxylic acid



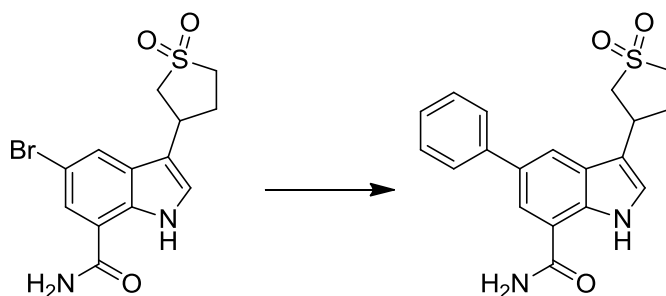
To a microwave vial was added 1-(1,1-dimethylethyl) 7-methyl 5-bromo-3-(1,1-dioxidotetrahydro-3-thienyl)-1*H*-indole-1,7-dicarboxylate (432 mg, 0.91 mmol), LiOH (109 mg, 4.5 mmol), MeOH (6 mL) and H₂O (3 mL). The mixture was heated to 80 °C for 30 min in the microwave. The reaction mixture was then purified via reverse phase HPLC (TFA buffer) to give 99 mg of the title compound. LC/MS: m/z 357.8 (M+H), 1.40 min.

5-bromo-3-(1,1-dioxidotetrahydro-3-thienyl)-1*H*-indole-7-carboxamide



To a solution of 5-bromo-3-(1,1-dioxidotetrahydro-3-thienyl)-1*H*-indole-7-carboxylic acid (36 mg, 0.1 mmol) in DCM (5 mL) was added HOBt (16 mg, 0.12 mmol), and EDC•HCl (23 mg, 0.12 mmol) and 2 M NH₃ in methanol (0.2 mL, 0.4 mmol). The mixture was kept overnight at RT. The mixture was concentrated, and EtOAc and aq. NaHCO₃ were added. The aqueous layer was extracted with ethyl acetate once. The combined organic layers were dried (MgSO₄) and concentrated to give 36 mg of the title compound. LC/MS: m/z 356.7 (M+H), 1.37 min.

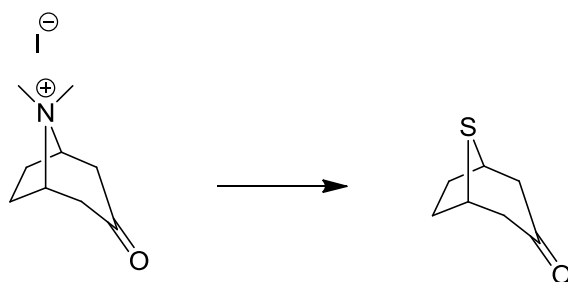
3-(1,1-dioxidotetrahydrothiophen-3-yl)-5-phenyl-1*H*-indole-7-carboxamide (21)



5-Bromo-3-(1,1-dioxidotetrahydro-3-thienyl)-1*H*-indole-7-carboxamide (36 mg, 0.1 mmol), and dioxane water (3:1, 2 mL) were dissolved together. Phenyl boronic acid (18mg, 0.15 mmol), potassium carbonate (421 mg, 0.3 mmol) were added and a stream of Ar was passed through the solution for 5 min and then Pd(PPh₃)₄ was added (12 mg, 0.01 mmol). Argon was passed through the solution for 5 min and then the mixture was heated on the microwave at 150 °C for 20 min. The reaction mixture was concentrated and purified by reverse phase HPLC to afford the title compound (11 mg, 31%). LC/MS: *m/z* 354.7 (M+H), 1.71 min, 100%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17 - 2.38 (m, 1 H) 2.57 - 2.73 (m, 1 H) 3.12 - 3.29 (m, 2 H) 3.31 - 3.44 (m, 1 H) 3.71 (dd, *J*=13.05, 7.53 Hz, 1 H) 3.88 - 4.11 (m, 1 H) 7.22 - 7.38 (m, 2 H) 7.42 (br. s., 1 H) 7.48 (t, *J*=7.65 Hz, 2 H) 7.76 - 7.91 (m, 2 H) 8.04 (d, *J*=1.25 Hz, 1 H) 8.13 (d, *J*=1.00 Hz, 1 H) 8.25 (br. s., 1 H) 11.07 (s, 1 H).

Synthesis of 3-[(3-*endo*)-8,8-Dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-5-phenyl-1*H*-indole-7-carboxamide (22) and 3-[(3-*exo*)-8,8-Dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-5-phenyl-1*H*-indole-7-carboxamide (23)

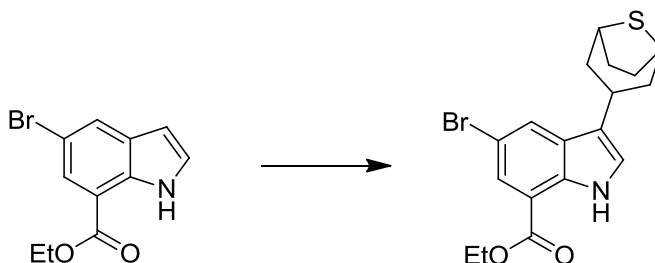
8-Thiabicyclo[3.2.1]octan-3-one



A mixture of 8,8-dimethyl-3-oxo-8-azoniabicyclo[3.2.1]octane iodide (20.0 g, 71.1 mmol) and Na₂S·9H₂O (18.8 g, 78.3 mmol) in H₂O (225 mL) was stirred at 85 °C under N₂ for 2 h. The reaction was allowed to cool, and the mixture was extracted with Et₂O (100 mL × 3). The combined organic layers were washed with 0.1 M HCl and then washed with brine to neutrality. The organic layer was dried and evaporated, and the resulting yellow solid was decolourized by

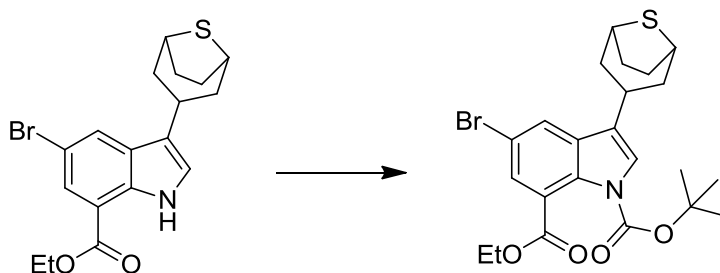
passing in Et₂O through a short column of basic alumina. The eluent was concentrated with a rotary evaporator, giving 4.6 g (45.5%) of the title compound. ¹H NMR (400 MHz, CDCl₃): δ 1.96-2.19 (m, 4 H), 2.62-2.80 (m, 4 H), 3.79-3.84 (m, 2 H).

Ethyl 5-bromo-3-(8-thiabicyclo[3.2.1]oct-3-yl)-1*H*-indole-7-carboxylate



To a solution of 8-thiabicyclo[3.2.1]octan-3-one (1.33 g, 9.32 mmol, 1 eq) in dry dichloromethane (50 mL) was added a spatula tip full of activated 4A molecular sieves (beads). The ketone solution was cooled to 0 °C, and trimethylsilyl triflate (1.7 mL, 9.41 mmol, 1 eq) was added dropwise followed by a solution of ethyl 5-bromo-1*H*-indole-7-carboxylate (2.5 g, 9.32 mmol, 1 eq) in dichloromethane (25 mL). The mixture was stirred at 23 °C overnight, then was cooled to 23 °C and triethylsilane (2.3 mL, 14.4 mmol, 1.5 eq) was added in a single portion. The reaction was stirred at 23 °C for 1.5h, then quenched by the addition of saturated aqueous sodium bicarbonate. The mixture was extracted with dichloromethane, and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by Isco Combiflash, 120 gram column, eluting with 0-30% ethyl acetate in hexanes. The ethyl 5-bromo-3-(8-thiabicyclo[3.2.1]oct-3-yl)-1*H*-indole-7-carboxylate was obtained as a mixture of isomers (2.38 g, 65%). This was carried to the next step.

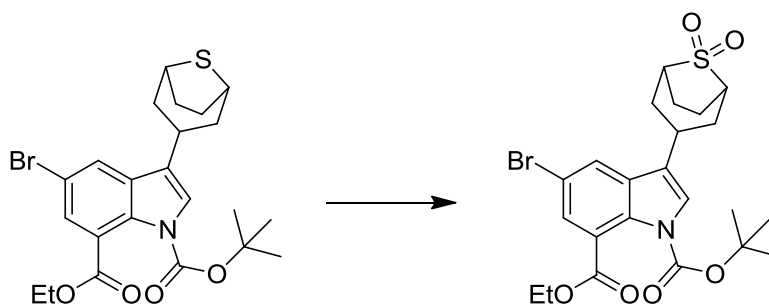
1-(1,1-dimethylethyl) 7-ethyl 5-bromo-3-(8-thiabicyclo[3.2.1]oct-3-yl)-1*H*-indole-1,7-dicarboxylate



To a solution of ethyl 5-bromo-3-(8-thiabicyclo[3.2.1]oct-3-yl)-1*H*-indole-7-carboxylate (2.38 g, 6.0 mmol, mixture of isomers) in acetonitrile (30 mL) and tetrahydrofuran (4 mL) was added di-tert-butyl dicarbonate (2.23 g, 10.2 mmol, 1.7 eq) and 4-dimethylaminopyridine (245 mg, 2

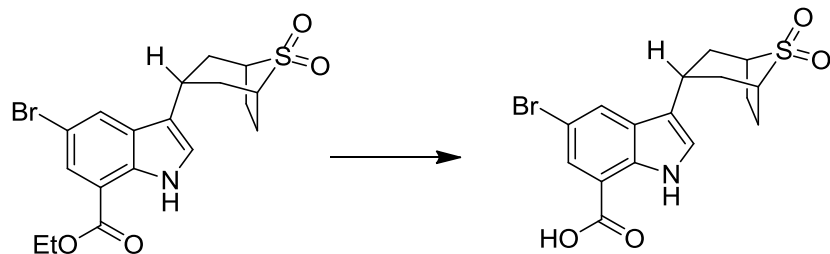
mmol, 0.33 eq). The reaction mixture was stirred at 23 °C overnight, after which time a clear yellow solution was obtained. The mixture was filtered through a thin pad of silica gel, eluting with dichloromethane followed by 50% ethyl acetate in hexanes. After removal of the solvent *in vacuo*, the mixture of isomers of 1-(1,1-dimethylethyl) 7-ethyl 5-bromo-3-(8-thiabicyclo[3.2.1]oct-3-yl)-1*H*-indole-1,7-dicarboxylate was obtained as a yellow residue (3.06 g, 103%). LC/MS: *m/z* 394.0 (M-100), 1.57 min.

1-(1,1-Dimethylethyl) 7-ethyl 5-bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-1,7-dicarboxylate and 1-(1,1-dimethylethyl) 7-ethyl 5-bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-1,7-dicarboxylate



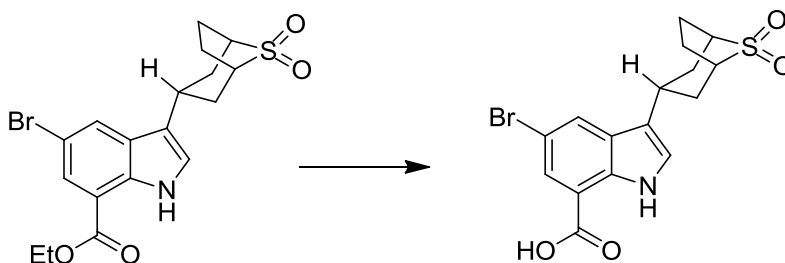
Triflic anhydride (1.62 mL, 2.71 g, 9.59 mmol) was added to acetonitrile (35 mL) at 23 °C. Urea hydrogen peroxide (1.34 g, 14.24 mmol) was subsequently added, and the mixture was stirred at 23 °C for 30 minutes behind a blast shield. (Flask was open to the atmosphere). The peroxide solution was cooled to 0 °C. 1-(1,1-dimethylethyl) 7-ethyl 5-bromo-3-(8-thiabicyclo[3.2.1]oct-3-yl)-1*H*-indole-1,7-dicarboxylate (1.89 g, 3.82 mmol) was dissolved in acetonitrile (50 mL) and cooled to 0 °C. The ice cold peroxide solution prepared above was added dropwise to the indole solution, and the mixture was warmed to 23 °C. After stirring at 23 °C for 45 minutes, water was added and the mixture was extracted with ethyl acetate. The combined organics were dried (Na₂SO₄), concentrated, and purified by Isco Combiflash (120 gram column, 0-40% EtOAc/hexanes gradient), giving 805 mg of 1-(1,1-dimethylethyl) 7-ethyl 5-bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-1,7-dicarboxylate (*endo* isomer) and 338 mg of 1-(1,1-dimethylethyl) 7-ethyl 5-bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-1,7-dicarboxylate (*exo* isomer). Determination of *endo/exo* geometry was based upon small molecule crystallography of the major isomer, which was shown to be *endo*. LC/MS: *m/z* 425.9 (M-100), 1.27 min.

5-bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid



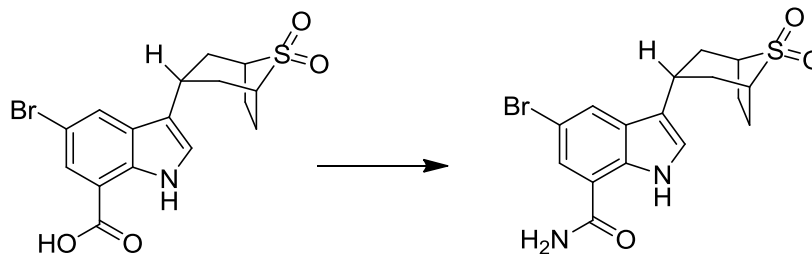
5-bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid (major isomer) (805 mg, 1.53 mmol) was diluted in methanol (10 mL) and water (5 mL). Then 6N NaOH (aq, 3.5 mL, 21 mmol) was added and the whole was heated at 85 °C for 45 minutes. The reaction was cooled to 23 °C, concentrated, and acidified with 6N aq HCl to pH=1 by pH paper. The resultant light yellow solid was isolated by vacuum filtration and washed with water. The solid 5-bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid, was dried in the vacuum oven for 2h with ~45°C heating to afford 480 mg (79%) of the crude title compound. LC/MS: *m/z* 399.9 (M+H), 0.85 min.

5-bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid



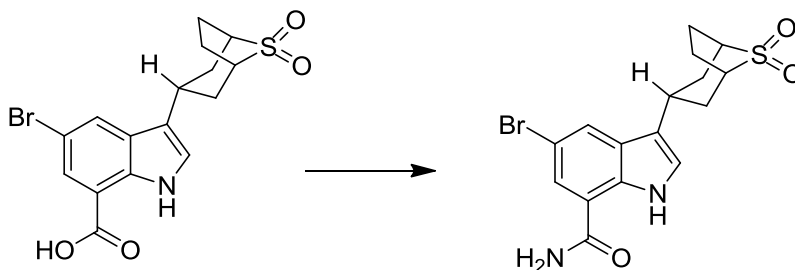
5-bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid ethyl ester (minor isomer) (338 mg, 0.642 mmol) was diluted in methanol (4 mL) and water (2 mL). Then 6N NaOH (aq, 1.75 mL, 10.5 mmol) was added, and the whole was heated at 85 °C. Hydrolysis was much slower than the other isomer. An additional portion of 6N NaOH (5 mL, 30 mmol) was added and the heat was continued at 90 °C for 6 h. The reaction was cooled to 23 °C and concentrated. A solution of 6N aq HCl was added to adjust the pH to a pH=1 by pH paper. The resultant light yellow solid was isolated by vacuum filtration, washing with water. The solid 5-bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid was dried in the vacuum oven for 2 h with ~45 °C heating to afford 153 mg (60%) of the crude title compound. LC/MS: *m/z* 399.9 (M+H), 0.86 min.

5-Bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxamide



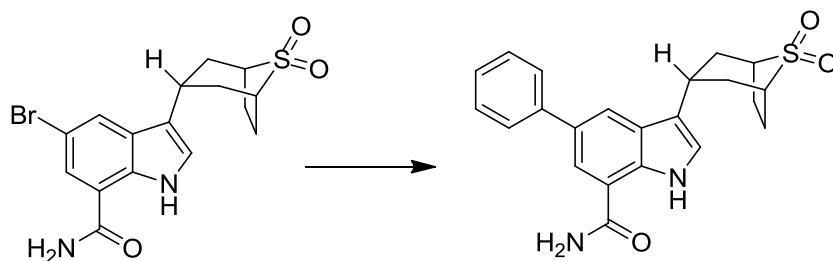
5-bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid (major isomer) (480 mg, 1.21 mmol) (major isomer), HOBt hydrate (185 mg, 1.21 mmol), and EDCI hydrochloride (530 mg, 2.76 mmol) were combined and diluted with 0.5M ammonia in dioxane (10 mL, 5 mmol) and DMF (3 mL). The mixture was heated in a microwave oven under regular absorption at 100 °C for 20 min. The reaction was diluted in ethyl acetate and washed with water. The organic layers were dried (Na₂SO₄), filtered, and concentrated. The residue was triturated from dichloromethane to afford 0.328g (69%) of the title compound. LC/MS: *m/z* 399.0 (M+H), 0.85 min.

5-bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxamide



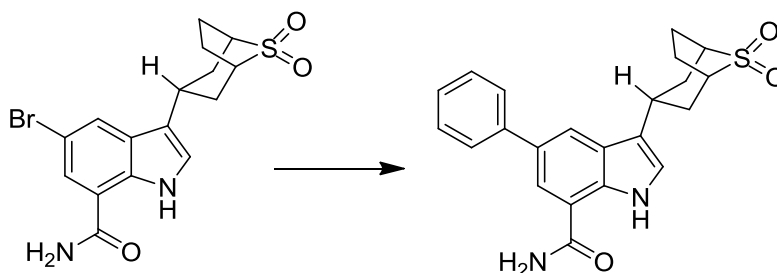
5-Bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxylic acid (minor isomer) (153 mg, 0.38 mmol), HOBt hydrate (59 mg, 0.38 mmol), and EDCI hydrochloride (530 mg, 2.76 mmol) were diluted in 0.5M ammonia in dioxane (3 mL, 1.5 mmol) and DMF (1 mL). The reaction mixture was heated in a microwave oven under regular absorption at 100 °C for 20 min, diluted in ethyl acetate and washed with water. The organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude product was triturated from dichloromethane/hexanes mixture to afford 124 mg (81%) of the title compound. LC/MS: *m/z* 399.0 (M+H), 0.77min.

3-[(3-*endo*)-8,8-Dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-5-phenyl-1*H*-indole-7-carboxamide (22)



5-Bromo-3-[(3-*endo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxamide (45 mg, 0.11 mmol), phenylboronic acid (17 mg, 0.14 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (17 mg, 0.02 mmol), and potassium carbonate (83 mg, 0.6 mmol) were diluted in dioxane (3 mL) and water (1.5 mL) in a 2-5 mL Biotage microwave reaction tube. The mixture was degassed by bubbling argon through for 5 minutes, then the reaction was heated in the microwave at 100 °C for 5 minutes under normal absorption. The crude reaction mixture was filtered through a thiol SPE cartridge (polymer labs) to remove palladium, then was concentrated. The residue was diluted in ~3 mL of DMSO, filtered through a syringe filter, and purified by ammonium hydroxide Gilson HPLC. The product fractions were combined and concentrated in a Genevac EZ2 evaporator, to afford 23.6 mg (53%) of the title compound. LC/MS: *m/z* 395.0 (M+H), 0.92 min, 100%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.19 - 1.35 (m, 1 H) 2.10 - 2.37 (m, 6 H) 2.54 - 2.57 (m, 1 H) 3.12 - 3.26 (m, 2 H) 3.40 - 3.65 (m, 1 H) 7.21 (d, *J*=2.26 Hz, 1 H) 7.29 - 7.37 (m, 1 H) 7.41 (br. s., 1 H) 7.49 (t, *J*=7.78 Hz, 2 H) 7.73 - 7.89 (m, 2 H) 8.03 (d, *J*=1.25 Hz, 1 H) 8.16 - 8.35 (m, 2 H) 10.91 (s, 1 H)

3-[(3-*exo*)-8,8-Dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-5-phenyl-1*H*-indole-7-carboxamide (23)

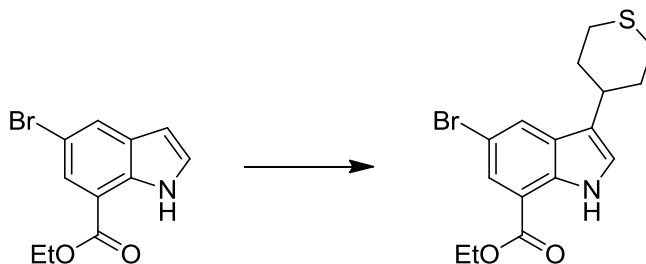


This compound was prepared in a manner analogous to the preparation of 3-[(3-*endo*)-8,8-Dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-5-phenyl-1*H*-indole-7-carboxamide. Thus 5-bromo-3-[(3-*exo*)-8,8-dioxido-8-thiabicyclo[3.2.1]oct-3-yl]-1*H*-indole-7-carboxamide (0.040g, 0.101 mmol), phenyl boronic acid (0.0123g, 0.101 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (17 mg, 0.02 mmol), and

potassium carbonate (83 mg, 0.6 mmol) were reacted to give 0.0133 g (34%) of the title compound. LC/MS: m/z 395.0 (M+H), 0.88 min, 100%.

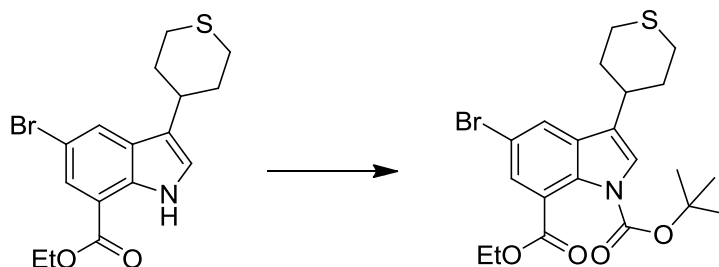
Synthesis of 3-(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-bromo-1*H*-indole-7-carboxamide (24)

Ethyl 5-bromo-3-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-7-carboxylate



TMSOTf (3.38 mL, 18.7 mmol) was added dropwise to a solution of tetrahydro-4*H*-thiopyran-4-one (2.17 g, 18.7 mmol) in DCM (100 mL) at 0 °C (bath temp) under nitrogen. A solution of ethyl 5-bromo-1*H*-indole-7-carboxylate (5 g, 18.7 mmol) in DCM (30 mL) was then added and the reaction was stirred for 30 min. Triethylsilane (4.47 mL, 28.1 mmol) was added and the reaction was allowed to warm to room temperature overnight. The reaction mixture was washed with saturated aqueous Na₂CO₃ (1 x 100 mL), and the organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was washed with MeOH, giving 4.92 g (72%) of the title compound. LC/MS: m/z 367.9 (M+H), 2.79 min.

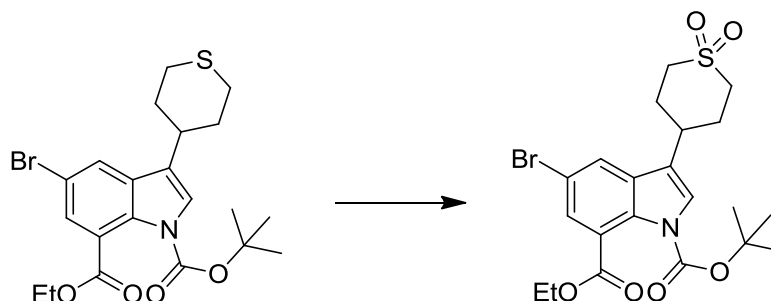
1-(1,1-Dimethylethyl) 7-ethyl 5-bromo-3-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-1,7-dicarboxylate



(Boc)₂O (1.77 g, 8.1 mmol) and DMAP (0.33 g, 2.7 mmol) were added to a solution of ethyl 5-bromo-3-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-7-carboxylate (1.99 g, 5.4 mmol) in THF (4 mL) and CH₃CN (40 mL). The reaction was stirred at room temperature for 20 h. Additional (Boc)₂O (0.6 g, 2.8 mmol) was added and the reaction was stirred for 1 h. The reaction was

concentrated under reduced pressure. The crude product was purified by a plug of silica with DCM, giving 2.36 g (93%) of the title compound. LC/MS: m/z 468.3 (M+H), 3.01 min ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.83 - 1.96 (m, 2 H) 2.01 - 2.13 (m, 2 H) 2.60 - 2.72 (m, 2 H) 2.81 - 2.97 (m, 2 H) 3.12 - 3.23 (m, 2 H) 3.63 (t, $J=7.53$ Hz, 1 H) 7.25 - 7.37 (m, 1 H) 7.39 - 7.56 (m, 4 H) 7.79 (dd, $J=8.16, 1.13$ Hz, 2 H) 7.96 (d, $J=1.00$ Hz, 1 H) 8.03 (d, $J=1.25$ Hz, 1 H) 8.25 (br. s., 1 H) 10.94 (s, 1 H).

1-(1,1-Dimethylethyl) 7-ethyl 5-bromo-3-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-1H-indole-1,7-dicarboxylate



The title compound was prepared in 3 batches. The first batch was prepared as follows:

Urea hydroperoxide (0.37 g, 3.95 mmol) was added in one portion to a mixture of TFAA (0.445 mL, 3.2 mmol) in CH_3CN (30 mL). The reaction was stirred for 30 min and was cooled to 0 °C (bath temp). 1-(1,1-Dimethylethyl) 7-ethyl 5-bromo-3-(tetrahydro-2H-thiopyran-4-yl)-1H-indole-1,7-dicarboxylate (0.5 g, 1.07 mmol) was taken up in CH_3CN (20 mL), cooled to 0 °C (bath temp) and transferred slowly via cannula to the urea hydroperoxide/TFAA mixture. The ice bath was removed, the reaction was allowed to warm to room temperature, and EtOAc (100 mL) and water (40 mL) were added. The organic layer was washed with water (2 x 20 mL) and saturated aqueous NaCl (1 x 20 mL) and was dried (Na_2SO_4). The solution was concentrated under reduced pressure, the residue was dissolved in DCM (5 mL) and filtered through a plug of silica, eluting with EtOAc. The eluent was concentrated under reduced pressure, giving 0.664 g (>95%) of the title compound. LC/MS: m/z 500.4 (M), 2.31 min.

The second batch was prepared as follows:

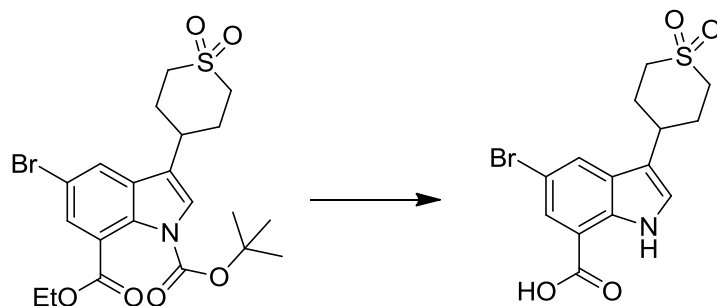
Urea hydroperoxide (0.74 g, 7.9 mmol) was added in one portion to a mixture of TFAA (0.89 mL, 6.4 mmol) in CH_3CN (60 mL). The reaction was stirred for 30 min and was cooled to 0 °C (bath temp). 1-(1,1-Dimethylethyl) 7-ethyl 5-bromo-3-(tetrahydro-2H-thiopyran-4-yl)-1H-indole-1,7-dicarboxylate (1 g, 2.14 mmol) was taken up in CH_3CN (40 mL), cooled to 0 °C (bath temp)

and transferred slowly via cannula to the urea hydroperoxide/TFAA mixture. The ice bath was removed and EtOAc (100 mL) and water (40 mL) were added. The organic layer was washed with water (2 x 40 mL) and saturated aqueous NaCl (1 x 40 mL) then dried (Na₂SO₄). The solution was partly concentrated under reduced pressure and filtered through a plug of silica, eluting with EtOAc. The eluent was concentrated under reduced pressure, giving 1.2 g (>95%) of the title compound.

The third batch was prepared as follows:

Urea hydroperoxide (1.48 g, 15.7 mmol) was added in one portion to a mixture of TFAA (1.78 mL, 12.8 mmol) in CH₃CN (120 mL). The reaction was stirred for 30 min and was cooled to 0 °C (bath temp). 1-(1,1-Dimethylethyl) 7-ethyl 5-bromo-3-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-1,7-dicarboxylate (2 g, 4.27 mmol) was taken up in CH₃CN (80 mL), cooled to 0 °C (bath temp) and transferred slowly via cannula to the urea hydroperoxide/TFAA mixture. The ice bath was removed and EtOAc (200 mL) and water (80 mL) were added. The organic layer was washed with water (2 x 80 mL) and saturated aqueous NaCl (1 x 80 mL) then dried (Na₂SO₄). The solution was concentrated under reduced pressure, giving 2.76 g (>95%) of the title compound. The three batches were combined.

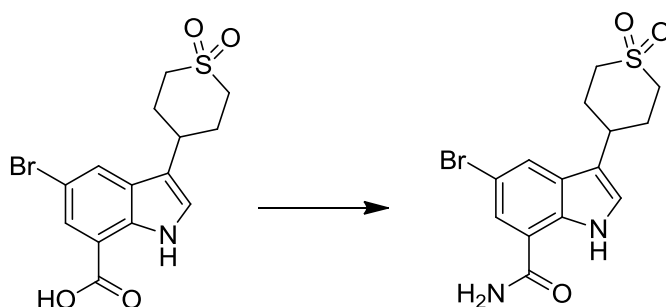
5-Bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-7-carboxylic acid



A solution of 6 M NaOH (12 mL, 72.0 mmol) was added to a suspension of 1-(1,1-dimethylethyl) 7-methyl 5-bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-1,7-dicarboxylate (0.93 g, 1.912 mmol) and 1-(1,1-dimethylethyl) 7-ethyl 5-bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-1,7-dicarboxylate (3.08 g, 6.16 mmol) in MeOH (50 mL) and water (25 mL) in a 250 mL round bottomed flask fitted with a reflux condenser. The reaction was heated at 85 °C (bath temp) for 1.5 h. The MeOH was removed by rotovap, and a solution of 6 M HCl was added until the mixture had attained a pH of ~1 by pH paper. The yellow solid was filtered

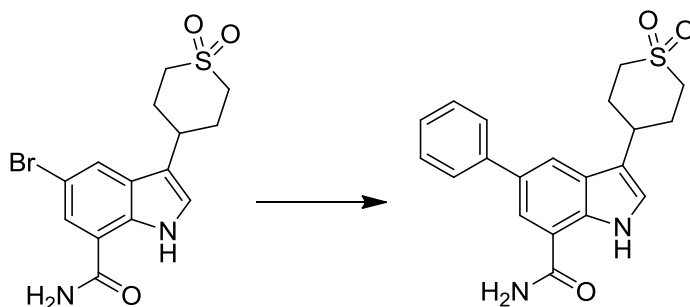
off, and the filtrate was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure, and the residue was combined with the precipitate from the filtration and dried under house vacuum at 45 °C overnight. Recovered 2.98 g (86%) of the title compound. LC/MS: m/z 371.7 (M), 1.62 min.

5-Bromo-3-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-1H-indole-7-carboxamide



A solution of 0.5 M NH₃ in dioxane (12 mL, 6 mmol) was added to a mixture of 5-bromo-3-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-1H-indole-7-carboxylic acid (1.1 g, 2.96 mmol), HOBt (0.455 g, 2.96 mmol), and EDC•HCl (1.54 g, 8.02 mmol) in DMF (4 mL) in a Biotage microwave vial. The vial was sealed, and the reaction was heated at 100 °C for 20 min on regular absorbance in a Biotage Initiator microwave. EtOAc (75 mL) and H₂O (75 mL) were added, the layers were separated, and the aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give a light yellow solid. The solid was washed with DCM (1 x 25 mL) to and aspirated dry to give 2.05 g (96%) of the title compound. LC/MS: m/z 372.8 (M+H), 1.54 min.

3-(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)-5-phenyl-1H-indole-7-carboxamide (24)



To 5-bromo-3-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-1H-indole-7-carboxamide (80 mg, 0.216 mmol) in dioxane and water (4 mL/1 mL) was added phenylboronic acid (36 mg), Pd(PPh₃)₄ (25 mg) and K₂CO₃ (104 mg). The reaction mixture was heated to 150 °C for 20 minutes by microwave irradiation. The organic phase was separated, concentrated, and purified by HPLC

to afford the title compound (23 mg). LC/MS: m/z 368.9 (M+H), 1.73 min, 100%; HPLC: 12.72 min, 100%; HRMS : Molecular Formula $C_{20}H_{20}N_2O_3S$, Mass Found 369.1262 (M+H), Mass Required 369.1267 (M+H); HPLC 98%; 1H NMR (400MHz, DMSO- d_6) δ = 10.95 (br. s., 1H), 8.23 (br. s., 1H), 8.04 (d, $J=13.6$ Hz, 2H), 7.81 - 7.80 (m, 1H), 7.79 (d, $J=7.3$ Hz, 2H), 7.58 - 7.28 (m, 4H), 7.21 (d, $J=2.3$ Hz, 1H), 3.49 - 3.37 (m, 3H), 3.13 (d, $J=12.0$ Hz, 2H), 2.35 (d, $J=13.1$ Hz, 2H), 2.21 - 1.98 (m, 2H)

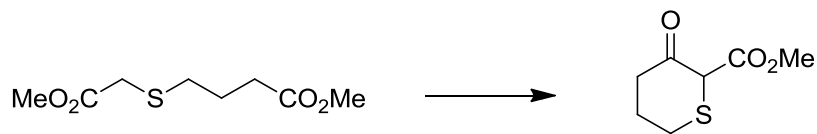
Synthesis of 3-(1,1-Dioxidotetrahydro-2*H*-thiopyran-3-yl)-5-phenyl-1*H*-indole-7-carboxamide (25)

Methyl 4-[[2-(methyloxy)-2-oxoethyl]thio]butanoate



Sodium (3.5 g, 0.15 mol) was added to methanol (150 mL) carefully. After cooling to room temperature, methyl 2-mercaptoacetate (15.6 g, 0.13 mol) was added. The mixture was stirred for 30 mins at room temperature and a little of NaI and methyl 4-chlorobutanoate (20.0 g, 0.15 mol) were added. The reaction mixture was refluxed over night. After cooling to room temperature, the solvent was removed under reduced pressure, then the residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with H_2O (30 mL), brine (30 mL), and dried with Na_2SO_4 . After removing the solvent, 28.3 g of the crude product was obtained (Yield: 94%).

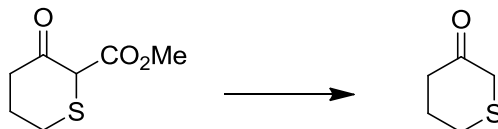
Methyl 3-oxotetrahydro-2*H*-thiopyran-2-carboxylate



To a suspension of sodium (3.5 g, 0.15 mol) in dry toluene (300 mL) was added an excess of methanol (30 mL). After sodium was disappeared, the excess methanol was removed as the methanol-toluene azeotrope. When the distillation temperature had reached 105 °C, Methyl 4-[[2-(methyloxy)-2-oxoethyl]thio]butanoate (28.3 g, 0.14 mol) in toluene (90 mL) was added over a period of ten mins. The methanol-toluene azeotrope was removed by distillation, after the distillation temperature rose to 106 °C, the reaction mixture was cooled to room temperature. The reaction mixture was poured into a mixture of ice (100 g) and 12N HCl (20 mL). The organic layer was removed and the aqueous layer was extracted with three 60 mL portions of

ether and the combined organic layers were dried over Na₂SO₄. After removing the solvent, 23.4 g of crude product was obtained (Yield: 96%).

Dihydro-2*H*-thiopyran-3(4*H*)-one

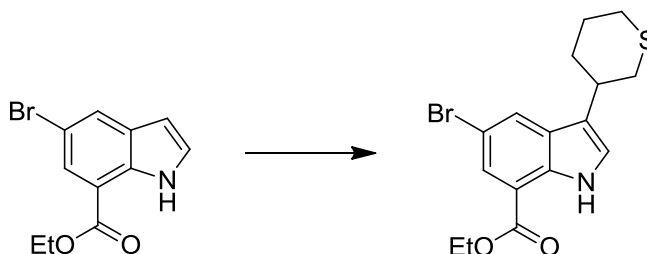


The mixture of S-2 (23.4 g, 0.13 mol) and 2N H₂SO₄ (100 mL) was refluxed over night and then allowed to cool to room temperature. The mixture was extracted with three 30 mL portions of CH₂Cl₂. After the solvent was removed, the residue was fractionated in vacuo, giving 5.7 g of the title compound (obtained at 59 -60 °C/1 mmHg) (Yield: 36.6%).

¹H NMR (400 MHz, CHCl₃): δ 2.42-2.44 (m, 4 H), 2.77-2.79 (m, 2 H), 3.20 (s, 2 H);

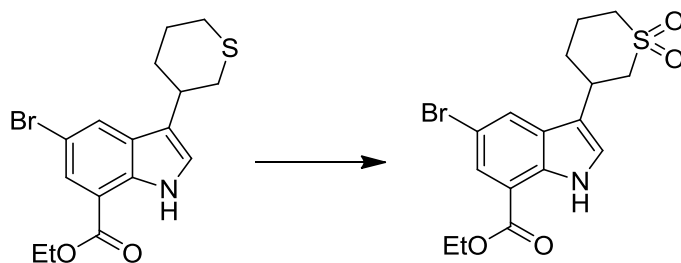
¹³C NMR (100 MHz, CHCl₃): δ 28.4, 33.4, 38.5, 41.7, 203.8.

Ethyl 5-bromo-3-(tetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxylate



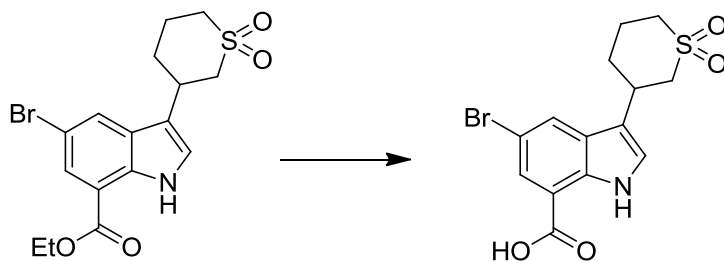
Dihydro-2*H*-thiopyran-3(4*H*)-one (0.217g, 1.86mmol) was dissolved in dichloromethane (23mL) in an oven dried flask containing 3 Å molecular sieves and stirred under argon at 0 °C. TMS-OTf (0.414g, 1.86mmol, 0.33 mL) was added slowly to the mixture over 10 min. Ethyl 5-bromo-1*H*-indole-7-carboxylate (0.5g, 1.86mmol) was dissolved in DCM (7mL) and added to the reaction via syringe pump over 2 hours, after which it was stirred for 3 hours between 0 and 10 °C. The reaction was cooled to 0 °C and triethylsilane (0.325g, 0.44mL, 2.8mmol) was added all at once and the reaction was stirred at room temperature for 18 hours. The reaction was then quenched with a saturated sodium bicarbonate solution and extracted with DCM. The combined organics were washed with water. The combined aqueous layers were back-extracted with DCM. The combined organics were washed with brine, dried with MgSO₄, and concentrated. The crude compound was purified on a Combiflash silica column with 5-25% EA/Hexane to give 0.279g (40%) of the title compound. LC/MS: m/z 369 (M+H), RT= 2.74 min.

Ethyl 5-bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxylate



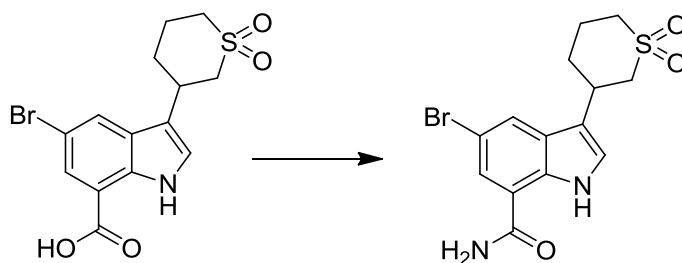
Ethyl 5-bromo-3-(tetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxylate (0.375g, 1.02mmol) was dissolved in 1,2-Dimethoxyethane (DME) (25mL). A solution of 0.0004M EDTA (7mL) was added followed by the portion-wise addition of a suspension of oxone (1.88g, 3.05mmol) and sodium bicarbonate (0.855g, 10.18mmol) in 7 mL water. The reaction was stirred for 3 hours at room temperature. The reaction was diluted with water and extracted with dichloromethane. The combined organics were washed with water 2X. The combined aqueous layers were backwashed with dichloromethane. The combined organics were washed with water, brine, dried with MgSO₄ and concentrated. The crude compound was purified by Combiflash silica column chromatography using 0-10% ethylacetate/ dichloromethane on silica to give 0.290g (71%) of the title compound. LC/MS: m/z 401 (M+H), 1.05 min.

5-Bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxylic acid



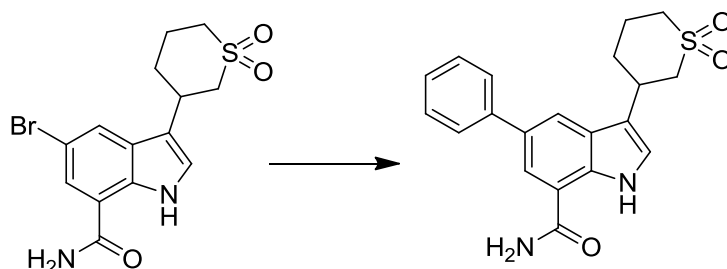
Ethyl 5-bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxylate (0.380g, 0.949mmol), was stirred in a methanol (5mL) / water (3mL) solution. 6M NaOH (1.5mL, 0.900mol, 10eq) was added and the reaction was heated to 85 °C for 1.5 hours. The methanol was concentrated and the aqueous solution was acidified with 6M HCl. The resulting white solid was filtered and dried under vacuum to give 0.325g (92%) of the title compound. LC/MS m/z =373 (M+H), = 0.81 min.

5-Bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxamide



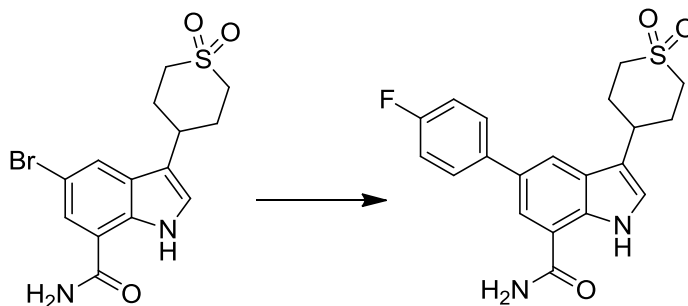
5-bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxylic acid (0.185g, 0.497mmol) was suspended in DMF (2mL) with EDC (0.286g, 1.49mmol, 3eq) and HOBt (0.076, 0.497mmol) in a 10 mL microwave reaction vessel. 0.5M ammonia in 1,4-dioxane (1.9mL, 0.9945mmol, 2 eq) was added and heated on the microwave at 100 °C for 20 minutes. Reaction was diluted with water and extracted with ethyl acetate. The combined organics were washed with 1N NaOH, water, and brine then dried with magnesium sulfate, to give 0.161g (87%) of the title compound. LC/MS: *m/z* 372 (M+H), 0.74 min.

3-(1,1-Dioxidotetrahydro-2*H*-thiopyran-3-yl)-5-phenyl-1*H*-indole-7-carboxamide (25)



5-Bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl)-1*H*-indole-7-carboxamide (0.050 g, 0.134 mmol) and (4-fluorophenyl)boronic acid (0.021 g, 0.174 mmol) was dissolved in a 6:1 solution of 1,4 dioxane (3mL)/water (0.5 mL) in a 20 mL microwave reaction vessel. Potassium carbonate (0.093 , 0.670 mmol) was added and the solution was degassed with Nitrogen. PdCl₂(dppf)₂ (0.017 g, 0.023 mmol) was added and the reaction was heated in a microwave at 100 °C for 20 min. The solution was passed through a StratoSphere SPE PL-Thiol MP SPE column to remove palladium and purified on Gilson preparative HPLC using Acetonitrile/Water with 0.1% TFA. The desired fractions were concentrated, giving 0.016g (30%) of the title compound. LC/MS: *m/z* 369 (M+H), 0.83 min, 93%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.97 - 2.18 (m, 5 H) 3.05 - 3.16 (m, 1 H) 3.18 - 3.31 (m, 2 H) 3.48 - 3.60 (m, 7 H) 7.25 (d, *J*=2.51 Hz, 1 H) 7.30 - 7.43 (m, 2 H) 7.48 (t, *J*=7.78 Hz, 2 H) 7.78 - 7.90 (m, 2 H) 8.02 (d, *J*=1.26 Hz, 1 H) 8.09 (s, 1 H) 8.24 (br. s., 1 H) 11.02 (s, 1 H).

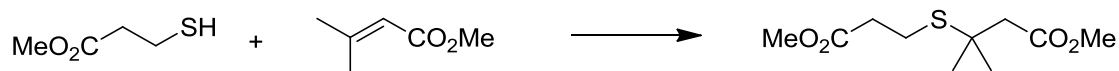
Synthesis of 3-(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-(4-fluorophenyl)-1*H*-indole-7-carboxamide (26)



This compound was prepared in a manner analogous to the preparation of 3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-phenyl-1*H*-indole-7-carboxamide. Thus 5-bromo-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-7-carboxamide (50 mg, 0.216 mmol) in dioxane and water (4 mL/1 mL) was added 4-fluorophenylboronic acid (28 mg), Pd(PPh₃)₄ (25 mg) and K₂CO₃ (104 mg) to yield 17 mg (33%) of the title compound LC/MS: *m/z* 387.0 (M+H), 1.77 min, 100%; HPLC: 13.0 min, 100%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.73-11.09 (m, 1H), 8.17-8.36 (m, 1H), 7.95-8.09 (m, 2H), 7.60-7.87 (m, 2H), 7.38-7.47 (m, 1H), 7.24-7.38 (m, 2H), 3.24-3.55 (m, 3H), 3.01-3.22 (m, 2H), 2.26-2.41 (m, 2H), 2.00-2.23 (m, 2H).

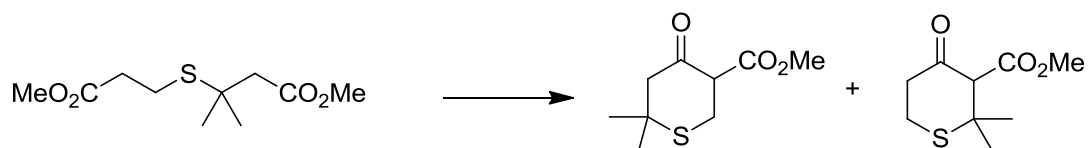
Synthesis of 3-(2,2-Dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-phenyl-1*H*-indole-7-carboxamide (27)

3-(2-Methoxycarbonyl-ethylsulfanyl)-3-methyl-butyrlic acid methyl ester



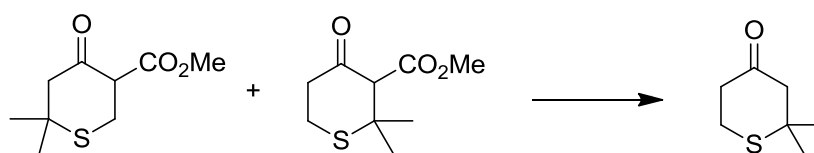
To a well-stirred mixture of methyl 3-methylbut-2-enoate (50.0 g, 438 mmol), 40% Triton B in MeOH (5 mL) and piperidine (4 mL) were added dropwise at 0 °C, then methyl 3-mercaptopropanoate (50 g, 396 mmol) was added. After stirring for 24 h at 60 °C, Et₂O (500 mL) was added, and the organic phase washed thoroughly with 10% H₂SO₄ (150 mL), sat. NaHCO₃ (150 mL), and brine (200 mL) successively, dried over Na₂SO₄ and evaporated under vacuum to give the the title compound as a colorless oil (90.1 g, 97%). ¹H NMR (400 MHz, CDCl₃): δ 2.55-2.59 (m, 4 H), 2.79-2.83 (m, 2 H), 3.67 (s, 3 H), 3.70 (s, 3 H).

6,6-Dimethyl-4-oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester, and 2,2-Dimethyl-4-oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester



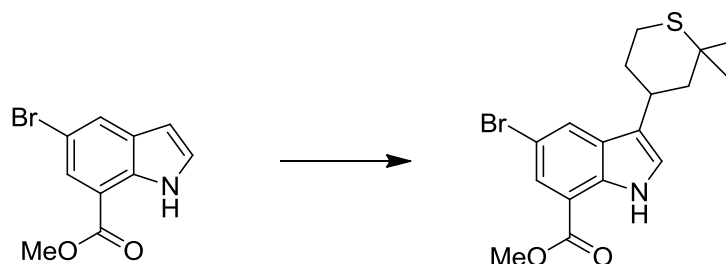
To a freshly prepared LDA solution (89 mL of $i\text{Pr}_2\text{NH}$, 175 mL of 2.5 M BuLi in hexane) in THF (600 mL) was added dropwise a solution of 3-(2-Methoxycarbonyl-ethylsulfanyl) -3-methylbutyric acid methyl ester (50.0 g, 0.21 mol) in THF (1200 mL) at -78°C . After the reaction mixture was stirred overnight at the room temperature, 10% aq. H_2SO_4 solution. (2.0 L) was added, and the mixture was extracted with Et_2O (3×600 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under vacuum to give the title compound as yellow oil (42 g). This was used directly in the next step.

2,2-Dimethyl-tetrahydro-thiopyran-4-one



The mixture of 6,6-Dimethyl-4-oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester and 2,2-Dimethyl-4-oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester (42 g) in 10% aq. H_2SO_4 solution (1000 mL) was heated at reflux for 70 h. Then the mixture was extracted with Et_2O (3×300 mL), the combined organic layer was washed with sat. NaHCO_3 (120 mL) and brine (120 mL), dried over Na_2SO_4 and evaporated under vacuum to give the the title compound as a white solid (5.3 g, 17.7 %, two steps). ^1H NMR (400 MHz, CDCl_3): δ 1.36 (s, 6 H), 2.55 (s, 2 H), 2.59-2.62 (m, 2 H), 2.97-3.00 (m, 2 H).

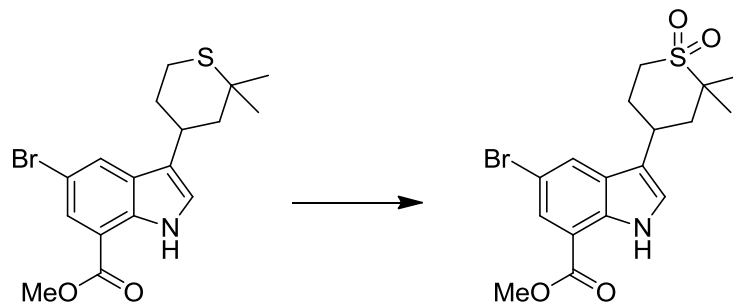
5-Bromo-3-(2,2-dimethyl-tetrahydro-thiopyran-4-yl)-1H-indole-7-carboxylic acid methyl ester



To a solution of 2,2-Dimethyl-tetrahydro-thiopyran-4-one (7.9 g, 55.1 mmol) in DCM (100 mL) was added TMSOTf (10mL, 55.1 mmol) and 5-Bromo-1H-indole-7-carboxylic acid methyl ester

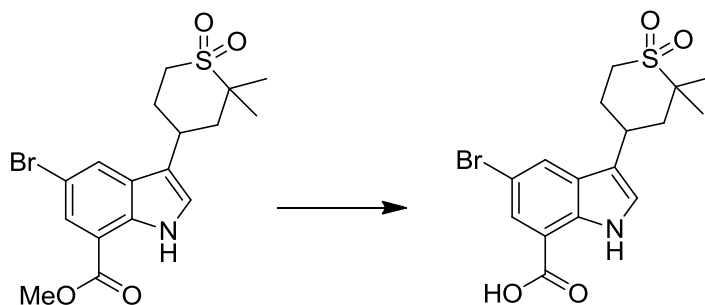
(7.0 g, 27.6 mmol) at 0 °C. After 2 hours, Et₃SiH (15 mL, 110 mmol) was added at 0 °C, then the mixture was stirred for 18 hours. The reaction mixture was quenched with sat. Sodium bicarbonate solution, extracted with DCM (3 × 100 mL). The combined organic layer was dried over MgSO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (PE:EA=50:1 to 30:1) to give the the title compound as a light yellow solid (5.5 g, 52 %). ¹H –NMR δ 1.25 (s, 3H), 1.47 (s, 3H), 1.66 (q, 1H), 1.78 (t, 1H), 1.92 (dd, 1H), 2.25(dd, 1H), 2.56(d, 1H), 2.54~2.59(m, 2H), 3.91(s, 3H), 7.01(d,1H), 7.84(s, 1H), 7.89(s, 1H), 9.57(s, 1H).

5-Bromo-3-(2,2-dimethyl-1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-1H-indole-7-carboxylic acid methyl ester



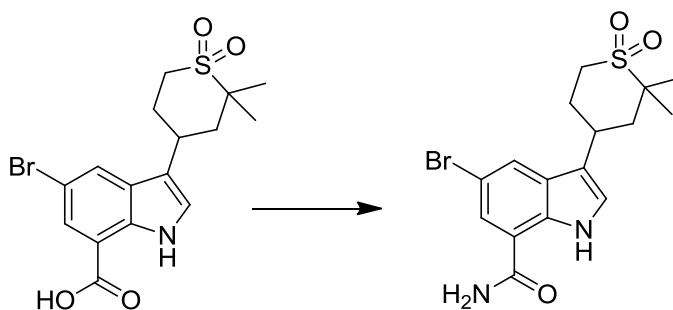
To a solution of 5-bromo-3-(2,2-dimethyl-tetrahydro-thiopyran-4-yl)-1H-indole-7-carboxylic acid methyl ester (5.5 g, 14.4 mmol) in 100 mL DCM was added m-CPBA (7.4 g, 43.3 mmol). The mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated sodium sulfite solution, extracted with DCM (3 × 50 mL). The combined organic layer was dried over MgSO₄ and concentrated under vacuum, the residue was purified by column chromatography on silica gel (PE:EA=30:1→10:1) to give the the title compound as a light yellow solid (5.5 g, 89 %). ¹H NMR δ 1.39(s, 3H), 1.64 (s, 3H), 2.02 (d, 1H), 2.33~2.49 (m, 3H), 3.02 (d, 1H).3.2710~3.41 (m, 2H), 3.96(s, 3H), 7.14(s, 1H), 7.86(s, 1H), 17.96 (s, 1H), 9.72(s, 1H).

(racemic)-5-Bromo-3-(2,2-dimethyl-1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-1H-indole-7-carboxylic acid



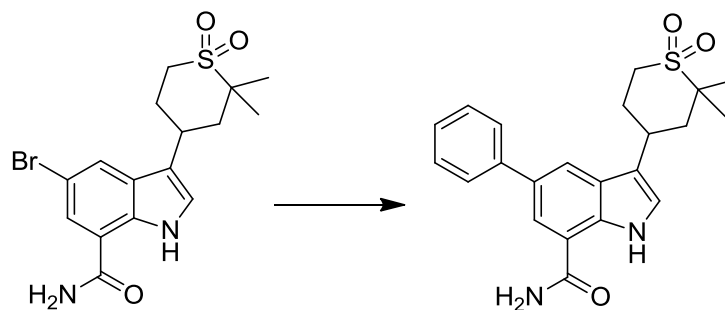
To a solution of 5-bromo-3-(2,2-dimethyl-1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-1H-indole-7-carboxylic acid methyl ester (5.5 g, 13.3 mmol) in 100 mL MeOH was added 3 N LiOH (22 mL, 66.6 mmol). Then the mixture was heated at reflux for 2 hours. The reaction was concentrated and the residue was dissolved in 1N HCl, extracted with DCM (3x50 mL). The combined organic layer was dried over MgSO₄, concentrated under vacuum to give the title compound as a light yellow solid (4.8 g, 94 %).

(racemic)-5-Bromo-3-(2,2-dimethyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-1H-indole-7-carboxamide



(racemic)-5-bromo-3-(1,1-dioxido-2,2-dimethylthian-4-yl)-1H-indole-7-carboxylic acid (490 mg, 1.224 mmol), was placed in a microwave flask and dissolved with DMF (2 mL) and 1,4-Dioxane (8 mL). HOBt (1-hydroxybenzotriazole) (165 mg, 1.224 mmol) and EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) (657 mg, 3.43 mmol) was added. 0.5N NH₃ in dioxane (7.34 mL, 3.67 mmol) was added. The reaction mixture was heated under microwave at 10 °C for 20 minutes. The reaction was diluted with saturated aqueous solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (2X). The organic layers were combined and washed with water, dried (MgSO₄) and the solvent was removed under vacuum. The residue was dissolved in the minimum amount of EtOAc (around 2 mL, sonicating and heating when necessary), precipitated by adding hexane, and then filtering off the solid. This operation was repeated on the filtrate to increase the recovery affording a total of 332 mg of the title compound as a pale yellow powder. LC/MS: m/z 400.9 (M+H), 0.79 min.

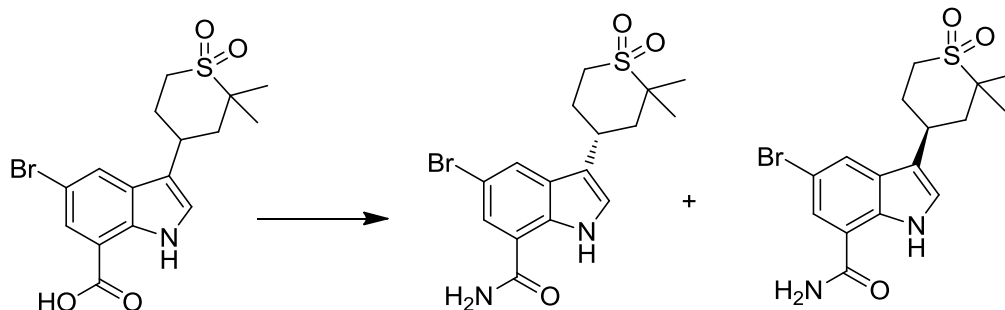
3-(2,2-Dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-phenyl-1*H*-indole-7-carboxamide (27)



5-Bromo-3-(2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-1*H*-indole-7-carboxamide (104 mg, 0.26 mmol) was placed in a microwave vial and dissolved with 1,4-dioxane (6 mL) and water (3 mL). 3-Phenylboronic acid (64 mg, 0.52 mmol) and K_2CO_3 (108 mg, 0.78 mmol) were added. Argon was bubbled in the mixture for 10 min with stirring. $PdCl_2(dppf)$ (10 mg, 0.02 mmol) was added, and argon was bubbled another 10 min. The vial is sealed and heated in a microwave for 5 min at 100 °C on high absorption. The reaction was evaporated to remove most of the dioxane. The residue was partitioned between ethyl acetate and water. The layers were separated, the organic layer was dried ($MgSO_4$), and the solvent was removed under vacuum. The residue was dissolved in DMSO (3 mL), and was purified on a reverse phase HPLC. The desired fractions were concentrated, giving 20 mg (18%) of the title compound. LC/MS: m/z 396.9 ($M+H$), 0.90 min, 98%; HRMS : Molecular Formula $C_{22}H_{24}N_2O_3S$, Mass Found 397.1576 ($M+H$), Mass Required 397.1580 ($M+H$); HPLC 94%; 1H NMR (400 MHz, $CHLOROFORM-d$) δ 10.03-10.27 (m, 1H), 7.86-7.99 (m, 1H), 7.60-7.69 (m, 3H), 7.46-7.57 (m, 2H), 7.37-7.44 (m, 1H), 7.16-7.22 (m, 1H), 3.34-3.54 (m, 2H), 3.02-3.14 (m, 1H), 2.36-2.56 (m, 3H), 2.07-2.20 (m, 1H), 1.67 (s, 3H), 1.44 (s, 3H).

Synthesis of 3-[(4*R*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-5-(4-fluorophenyl)-1*H*-indole-7-carboxamide ((*R*)-28)

5-bromo-3-[(4*S*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-1*H*-indole-7-carboxamide and 5-bromo-3-[(4*R*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-1*H*-indole-7-carboxamide



To a solution of 5-Bromo-3-(2,2-dimethyl-1,1-dioxo-hexahydro-2H-thiopyran-4-yl)-1H-indole-7-carboxylic acid (4.8 g, 12 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (2.4 g, 24 mmol), TBTU (7.7 g, 24 mmol), NH_3 / MeOH (10 mL). The mixture was stirred for 2 hours at room temperature. The reaction solution was washed with water. The organic phase was dried over MgSO_4 , concentrated under vacuum and purified by column chromatography on silica gel (PE:EA=10:1→5:1) to give the racemic product as a yellow solid (3.1 g, 64 %), which was resolved by chiral SFC HPLC to get 5-bromo-3-[(4S)-2,2-dimethyl-1,1-dioxido-tetrahydro-2H-thiopyran-4-yl]-1H-indole-7-carboxamide (1.19 g) and 5-bromo-3-[(4R)-2,2-dimethyl-1,1-dioxido-tetrahydro-2H-thiopyran-4-yl]-1H-indole-7-carboxamide (1.36 g). The absolute configurations of these enantiomers were determined using ab initio VCD analysis. ^1H -NMR δ 1.21 (s, 3H), 1.53 (s, 3H), 1.91-1.99 (m, 2H), 2.09-2.20 (m, 2H), 2.96 (d, 1H), 3.32 (s, 3H), 3.37 (t, 1H), 3.55 (t, 1H), 7.17 (s, 1H), 7.45 (s, 1H), 7.81 (s, 1H), 8.11 (s, 1H), 11.03 (s, 1H).

Optical Rotation Data:

Optical rotations were recorded on a Rudolph AUTOPOL V Automatic Polarimeter at 589 nm using a 0.5 dm thermostat micro-cell held at 25°C and a 2 sec integration. Each enantiomer was dissolved in methanol to a final concentration of 1.02 g/mL

Observed Rotations:

5-bromo-3-[(4R)-2,2-dimethyl-1,1-dioxido-tetrahydro-2H-thiopyran-4-yl]-1H-indole-7-carboxamide: $\alpha = + 0.087^\circ$

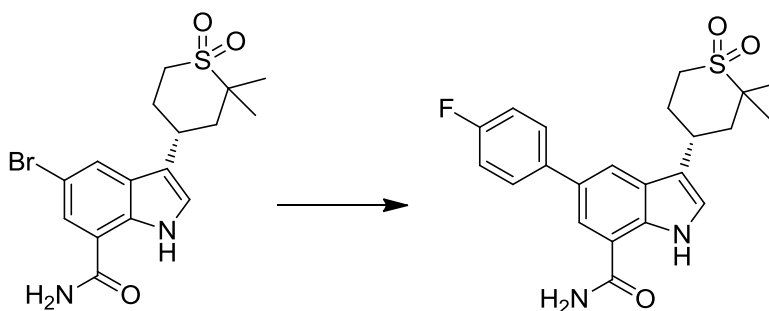
5-bromo-3-[(4S)-2,2-dimethyl-1,1-dioxido-tetrahydro-2H-thiopyran-4-yl]-1H-indole-7-carboxamide: $\alpha = - 0.065^\circ$

Specific Rotations:

5-bromo-3-[(4R)-2,2-dimethyl-1,1-dioxido-tetrahydro-2H-thiopyran-4-yl]-1H-indole-7-carboxamide: $[\alpha]_D = + 17.0^\circ$

5-bromo-3-[(4S)-2,2-dimethyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl]-1H-indole-7-carboxamide: $[\alpha]_D = -12.4^\circ$

Synthesis of 3-[(4R)-2,2-dimethyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl]-5-(4-fluorophenyl)-1H-indole-7-carboxamide ((R)-28)



5-bromo-3-[(4R)-2,2-dimethyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl]-1H-indole-7-carboxamide (200 mg, 0.5 mmol), (4-fluorophenyl)boronic acid (140 mg, 1.000 mmol), potassium carbonate (207 mg, 1.500 mmol), 1,4-dioxane (5 ml), and water (2.500 ml) were combined in a 20 mL microwave flask and degassed with argon for 5 min and then $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ adduct (32.7 mg, 0.040 mmol), was added. Argon was again bubbled through the mixture and then the vial was sealed and microwaved at 100°C on the high setting for 5 min. Reaction was poured through a 500 mg PL-thiol SPE column which had been washed with MeOH. After the reaction was passed through the column, the column was washed with MeOH and the combined eluates concentrated at reduced pressure on a Genevac EZ2 evaporator to afford a brown oil. This was combined with samples prepared in an analogous fashion and purified via reverse phase HPLC using an XBridge 30x150 mm 5u column and a mobile phase of acetonitrile:water+0.1% NH_4OH running at 40 mL/min and a gradient of 35%-60%B at 10 min. From this, 330.1 mg, (53%) of 3-[(4R)-2,2-dimethyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl]-5-(4-fluorophenyl)-1H-indole-7-carboxamide was obtained. LC/MS: m/z 414.14 ($\text{M}+\text{H}$), 0.91 min, 100%; HRMS : Molecular Formula $\text{C}_{22}\text{H}_{23}\text{FN}_2\text{O}_3\text{S}$, Mass Found 415.1481 ($\text{M}+\text{H}$), Mass Required 415.1486 ($\text{M}+\text{H}$); HPLC 99%; ^1H NMR (400 MHz, DMSO-d_6) δ 10.73-11.09 (m, 1H), 8.17-8.36 (m, 1H), 7.95-8.09 (m, 2H), 7.60-7.87 (m, 2H), 7.38-7.47 (m, 1H), 7.24-7.38 (m, 2H), 3.24-3.55 (m, 3H), 3.01-3.22 (m, 2H), 2.26-2.41 (m, 2H), 2.00-2.23 (m, 2H).

Alternative procedure:

(*racemic*)-5-Bromo-3-(1,1-dioxido-2,2-dimethylthian-4-yl)-1H-indole-7-carboxamide (500 mg, 1.252 mmol) was placed in a microwave vial and dissolved with 1,4-dioxane (12 mL) and water (6.00 mL). (4-fluorophenyl)boronic acid (350 mg, 2.504 mmol) and K₂CO₃ (519 mg, 3.76 mmol) were added. Argon was bubbled in the mixture for 10 min with stirring. PdCl₂(dppf) (48.3 mg, 0.100 mmol) was added, and argon was bubbled another 10 mins. The vial was sealed and heated via microwave irradiation for 5 min at 100 °C. The crude material was run through a thiol-SPE cartridge eluting with 2 mL of methanol and the residue evaporated. The residue was sonicated in 10 mL of water. Water was then removed (centrifugation) and the new residue was sonicated in DCM (2 mL), removed by centrifugation, and then methanol (5 mL) removed as well by centrifugation to afford 300 mg of a pale brown powder. This process was repeated a second time and then these samples are combined to afford 550 mg of (*racemic*) 3-(2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-(4-fluorophenyl)-1*H*-indole-7-carboxamide of suitable purity for enantiomer separation.

Enantiomer Separation and Chiral Analytical HPLC

The combined sample of (*racemic*) 3-(2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-(4-fluorophenyl)-1*H*-indole-7-carboxamide was then purified using the OJ 10um 10 x 250 mm column, 50% MeOH, 140 bar, 40 °C. Run time was ~8 minutes. Multiple runs afforded 233 mg of 3-[(4*R*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-5-(4-fluorophenyl)-1*H*-indole-7-carboxamide. Chiral purity was assessed via analytical chiral HPLC using the OJ 10um 10 x 250 mm column, 50% MeOH, 140 bar, 40 °C and a run time of 12 minutes. 3-[(4*R*)-2,2-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl]-5-(4-fluorophenyl)-1*H*-indole-7-carboxamide eluted at 8.24 mins with a chiral purity of >98%. The enantiomer elutes at 6.00 min.