Electronic Supplementary Material (ESI) for MedChemComm.

Supporting Information

Discovery of Cyclopropyl Chromane-Derived Pyridopyrazine-1,6-Dione γ-Secretase Modulators with Robust Central Efficacy

Martin Pettersson,*[,a] Douglas S. Johnson,[a] Danica A. Rankic,*[,d] Gregory W. Kauffman,[a] Christopher W. am Ende,[d] Todd W. Butler,[d] Brian Boscoe,[d] Edelweiss Evrard,[a] Christopher J. Helal,[d] John M. Humphrey,[d] Antonia F. Stepan,[a] Cory M. Stiff,[d] Eddie Yang,[d] Longfei Xie,[d] Kelly R. Bales,[b] Eva Hajos-Korcsok,[b] Stephen Jenkinson,[g] Betty Pettersen,[f] Leslie R. Pustilnik,[e] David S. Ramirez,[g] Stefanus J. Steyn,[c] Kathleen M. Wood,[b] and Patrick R. Verhoest.[a]

[a]*Neuroscience and Pain Medicinal Chemistry,* [b]*Neuroscience and Pain Research Unit,* [c]*Pharmacokinetics, Dynamics and Metabolism; Pfizer Worldwide Research and Development, Cambridge, Massachusetts 02139.*

[d]*Neuroscience and Pain Medicinal Chemistry,* [e]*Primary Pharmacology Group,* [f]*Drug Safety R&D; Pfizer Worldwide Research and Development, Groton, Connecticut 06340.*

[g]*Global Safety Pharmacology; Pfizer Worldwide Research and Development, La Jolla, California 92121.*

Cell-Based Aβ Production Assay

The ability of compounds to modulate production of Aβ42 was determined using human WT-APP over-expressing CHO cells (CHO-APP). Cells were plated at 22,000 cells/100 µL well in 96-well tissue culture treated, clear plates (Falcon) in DMEM/F12-based medium and incubated for 24 hours at 37 ^{o}C. Compounds for testing were diluted in 100% DMSO to achieve an eleven point, half-log, dose response for IC_{50} determinations. Compounds were added in fresh medium to achieve 1% final DMSO. Appropriate vehicle or inhibitor controls were added into control wells individually to obtain minimum or maximum inhibition values, respectively, for the assay signal window before the plates were incubated for ~24 hours at 37 ^{o}C. This procedure produces conditioned media in each well which is tested for Aβ42 levels in an ELISA assay. Coating of ELISA assay plates was initiated by addition of 50 µL/well of an Aβ42 cleavage site-specific antibody 10G3 (Rinat, Pfizer Inc., San Francisco, CA) at 3 µg/mL in 0.1 M $NaHCO_3$ (pH 9.0) into black 384-well Maxisorp® plates (Nunc) and incubated overnight at 4 ^{o}C. The capture antibody was then aspirated from the ELISA assay plates and plates were washed 3 x 100 µL with Wash Buffer (Dulbecco's PBS, 0.05% Tween 20). 90 µL/well of Blocking Buffer (Dulbecco's PBS, 1.0% BSA (Sigma A7030)) was then added to plates. Ambient temperature incubation was allowed to proceed for a minimum of two hours. Blocking buffer was then removed and 20 µL/well Assay Buffer (Dulbecco's PBS, 1.0% BSA (Sigma A7030), 0.05% Tween 20) was then added. At this point, 35 µL (in duplicate) of experimental conditioned media (described above) were transferred into wells of the blocked ELISA plates containing the capture antibody, followed by overnight incubation at 4 ^{o}C. After overnight incubation of the ELISA

assay plates at 4 °C, unbound Aβ peptides were removed via (3 x 100 µL) washes with Wash Buffer. Europium (Eu)-labeled (custom-labeled, PerkinElmer) Aβ(1-16) 6E10 monoclonal antibody (Covance #SIG-39320) was added, (50 µL /well Eu-6e10 @ 1:10,000, 20 µM EDTA) in Assay Buffer. Incubation at ambient temperature for a minimum of 2 hours was followed by (3 x 100 µL) washes with Wash Buffer, before 30 µL/well of Delfia Enhancement Solution (PerkinElmer) was added. Following a 30- to 60-minute ambient temperature incubation, the plates were read on an EnVision plate reader (PerkinElmer) using standard DELFIA TRF settings. Data analysis including inhibitory IC_{50} determination was performed using nonlinear regression fit analysis (in-house software) and the appropriate plate mean values for the maximum and minimum inhibition controls. Cell toxicity was also measured in the corresponding remaining cells after removal of the conditioned media for the Aβ42 assay, by a colorimetric cell proliferation assay (CellTiter 96® AQ_{ueous} One Solution Cell Proliferation Assay, Promega) according to the manufacturer's instructions.

All animal experiments were carried out in strict accordance with federal, state, local and institutional guidelines governing the use of laboratory animals in research and were reviewed and approved by Pfizer Institutional Animal Care and Use Committee.

Langendorff Isolated Heart Model[1,2]

Male Wistar Han rats (250-550 g; Charles River Laboratories, Wilmington, MA) were anesthetized to a surgical plane of anesthesia using isoflurane. After rapid extraction, the hearts were cannulated via the aorta onto the Langendorff-perfusion system and were constantly perfused in a retrograde manner with warmed (37 °C) modified Tyrode's solution (in mM: 118 NaCl, 4.5 KCl, 1.8 $CaCl_2$, 1.2 KH_2PO_4, 1.2 $MgSO_4$, 11 Glucose, 25 $NaHCO_3$, 2 Na pyruvate; pH = 7.4; equilibrated with 95% O_2 / 5% CO_2; 37 °C). The hearts were allowed to beat at an intrinsic rate driven by the sinoatrial node. A liquid-filled latex balloon connected to a pressure transducer was used to record pressure from the left

[1] Langendorff, O. Geschichtliche betrachtungen zur methode des überlebenden warmblüterherzens. *Muench. Med. Wochenschr*. **1903**, *50*, 508-509.

[2] Skrzypiec-Spring, M.; Grotthus, B.; Szelag, A.; Shulz, R. Isolated heart perfusion according to Langendorff - Still viable in the new millennium. *J. Pharmacol. Toxicol. Method*s **2007**, *55*, 113-126.

ventricle of the heart, which allowed for the measurement of heart rate, left ventricular pressure, and contractility. Coronary artery perfusion pressure was recorded via a pressure transducer positioned in the perfusion apparatus close to the aortic cannula. Each heart was allowed to stabilize while being perfused with modified Tyrode's solution for approximately 60 minutes, after which time a 10 minute baseline was recorded before increasing concentrations of test article or vehicle (0.1% (v/v) DMSO in modified Tyrode's solution) were each perfused for approximately 5 minutes. One minute of data for each parameter were averaged at the end of each treatment period. Test groups were compared to a time-matched vehicle control group. EC_{50} or IC_{50} values were generated using GraphPad Prism software. Statistical significance was determined by performing an unpaired 2-tailed Student's T-test comparing parameters from compound-treated hearts to time-matched vehicle control hearts.

All studies were approved by the local Institutional Animal Care and Use Committee (IACUC) and conformed to the Guide for the Care and Use of Laboratory Animals (Eighth Edition).

Methods for Dose-Escalation Study in Rats

Single escalating dose studies were completed in Sprague-Dawley rats. Rats (3/sex/dose) received escalating doses of compounds **30**, **32**, **44** and **45** by oral gavage. These compounds were suspended in 0.5% methylcellulose with 0.1% Polysorbate 80 and administered at a dosage volume of 10 mL/kg of body weight. Monitored endpoints included clinical signs, monitored continuously for the first several hours and/or intermittently throughout the dosing day, body weight for dosage calculation, and plasma compound levels at 1, 4, 8 and 24 hrs post-dose. All procedures performed on these animals were in accordance with regulations and established guidelines and were reviewed and approved by the Institutional Animal Care and Use Committee or through an ethical review process.

Rat Dose-Escalation Study Results: Summary of Exposure Values (C_{max}) and Clinical Signs in Sprague-Dawley Rats for Compounds 30, 32, 44, and 45

Compound	Dose (mg/kg)	Total Mean C_{max} (ng/mL)	Free Mean C_{max} (ng/mL)	Total Mean C_{max} (μM)	Free Mean C_{max} (nM)	Findings
30	30	2910	102	5.84	205	Lethality in 1/6 rats at 4 hrs post-dose[a]. Clinical signs in this animal consisted of decreased activity and ataxia starting at about 1 hr post-dose, and rough haircoat, hunched posture and coolness to the touch starting at about 3.5 hrs post-dose. Decreased activity was observed in 3 other rats starting at about 1 hr post-dose and resolving by the end of the day.
	100	NC[b]	NC	NC	NC	Lethality in 6/6 rats within 40 minutes after dosing. Decreased activity and ataxia were observed immediately prior to death in 2/6 rats.
32	30	3280	115	6.4	223	None
	100	9110	319	17.7	620	Lethality in 1/6 rats at about 5 hrs post-dose. Clinical signs in this rat included decreased activity, ataxia and coolness to the touch starting at about 2 hrs post dose and recumbency at about 3 hrs post-dose.
44	30	6430	116	12.9	232	None
	100	27900	592	56.0	1190	None
	300	45000	810	90.2	1620	None
45	30	9590	105	18.6	204	None
	100	26400	290	51.3	563	None
	300	31300	344	60.9	670	Transient decreases in activity in 2/6 rats and hunched posture in 1/6 rats starting at about 2 hrs post-dose and resolving by next day.

[a]C_{max} value in this rat was 6000 ng/mL total. [b]NC = not collected. Plasma drug levels at 0.5 hr post-dose in 2 of these rats were 5290-7050 ng/mL total.

Experimental procedure for determining the effect of compound 44 on Aβ42 in rat

Male Sprague-Dawley rats weighing 254-326 g were orally administered vehicle or GSM **44** at 10 or 40 mg/kg. Brains were collected at 1, 4, 8, 11, 16 and 20 hours post-dose with 4 rats per group. Brains were homogenized in 0.4% DEA/50 mM sodium chloride, incubated overnight at 4 °C, then centrifuged at 135,000xg for 1 hour. Brain supernatant was collected, run over solid-phase extraction to remove nonspecific signal and then concentrated for Aβ42, Aβ40 and Aβ total DELFIA analysis.

Brain Aβ efficacy data following 10 and 40 mg/kg of compound 44.

Time post-dose (hour)	% Change of Aβ42 vs vehicle and sem				% Change of Aβ40 vs vehicle and sem				% Change of Aβ Total vs vehicle and sem			
	10 mg/kg	sem	40 mg/kg	sem	10 mg/kg	sem	40 mg/kg	sem	10 mg/kg	sem	40 mg/kg	sem
1	-14	5	-40	4	-12	4	-34	2	3	6	-17	2
4	-40	8	-62	2	-35	7	-65	2	-16	8	-24	2
8	-13	5	-63	3	-6	3	-66	3	5	4	-19	6
11	-9	5	-56	2	-11	2	-60	2	-8	3	-24	4
16			-23	2			-16	2			-1	5
20			-7	7			-9	2			-3	2

Aβ = Amyloid-β isoform ending in carboxy-terminal amino acid 42; sem = standard error of the mean.

Compound 44 exposure data from the Aβ-lowering efficacy study in rat

Analyte	Dose (mg/Kg)	C_{max} (ng/mL)	T_{max} (Hours)	AUC (ng*Hours/mL)	C_{max} (nM)	AUC (nM.hr)	C_{max}, unbound (nM)	AUC, unbound (nM.hr)
Plasma	10	740	4	4250	1484	8526	27	153
	40	4610	4	38800	9248	77834	166	1401
Cerebellum	10	976	4	5060	1958	10150	11	55
	40	6140	4	49400	12317	99097	67	535
CSF	10	5.74	4	31.5	12	63	12	63
	40	41.5	4	314	83	630	83	630

Computational Chemistry Detail

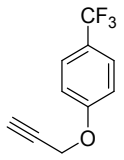
The computational work-flow involved a Monte Carlo Multiple Minimum (MCMM) protocol in MacroModel (Schrödinger Inc.), using default parameters with the following modifications: OPLS2.1 force field, water solvation, extended torsion sampling, energy window of 5.0 kcal/mol and redundant conformer elimination at an RMSD of 0.75 Å. All conformations were then optimized in Jaguar using default parameters for Restricted DFT (6-31G**, B3LYP functional, Accurate SCF convergence, no solvation). Post-QM optimization structures were further analyzed using the Redundant Conformer Elimination tool in Maestro, and single-point QM energies, using the PBF water solvation model, were computed for all remaining, unique conformers. Conformer probabilities were computed from the relative, aqueous QM energies using the Boltzmann Population script in Maestro.

Chemistry Experimental Section

General Information. All solvents and reagents were obtained from commercial sources and were used as received. All reactions were monitored by TLC (TLC plates F254, Merck) or UPLC-MS analysis (Waters Acquity, ESCI +/-, APCI +/-). Gas chromatography – mass spectrometry (GC-MS) was performed with an Agilent 5890 GC Oven and an Agilent 5973 Mass Selective Detector. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using deuterated solvent on a Varian 400 MHz instrument. All ^{1}H NMR shifts are reported in δ units (ppm) relative to the signals for chloroform (7.27 ppm) and methanol (3.31 ppm). All ^{13}C shifts are reported in δ units (ppm) relative to the signals for chloroform (77.0 ppm) and methanol (49.1 ppm) with ^{1}H-decoupled observation. All coupling constants (*J* values) are reported in hertz (Hz). NMR abbreviations are as follows: br, broadened; s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets. High-resolution mass spectra (HRMS) were acquired on an Agilent model 6220 MS (TOF). Optical rotations were determined with a Jasco P-2000 polarimeter. Column chromatography was carried out on silica gel 60 (32-60 mesh, 60 Å) or on pre-packed Biotage™ or ISCO columns. HPLC purity analysis of the final test compounds was carried out using one of five methods. Method A: UPLC/UV/MS using a Waters Acquity CSH C18 column, 2.1 × 50 mm, with 1.7 µm particles; UV purity detected at 215 nm; Mass spectrometer ESI positive/negative switching, acquiring from *m/z* 150 to 1000; Mobile phase A = 0.1% formic acid in water (*v*/*v*); Mobile phase B = 0.1% formic acid in acetonitrile (*v*/*v*); Gradient beginning at 95% A, 5% B, increasing to 100% B over 1.2 min, and remaining at 100% B until 1.5 min; Flow rate: 1.0 mL/min. Method B: Column: Waters Atlantis dC18 4.6

× 50, 5 µm; Mobile phase A: 0.05% TFA in water (v/v); Mobile phase B: 0.05% TFA in acetonitrile (v/v); Gradient: 95.0% H_2O/5.0% acetonitrile, linear to 5% H_2O/95% acetonitrile in 4.0 min, HOLD at 5% H_2O/95% acetonitrile to 5.0 min. Flow rate: 2 mL/min. Purity detected at 215 nm. Mass spectrometer ESI positive acquiring from m/z 160 to 2000 Da. Method C: UPLC/UV. Chembiotek Research International, Kolkata, India. Column: Agilent Zorbax SB C18, 50 × 4.6 mm, 1.8 µm; UV purity detected at 220 nm; Mobile phase A = 0.05% TFA in water; Mobile phase B = acetonitrile. Method D: UPLC/UV. Chembiotek Research International, Kolkata, India. Column: Waters Atlantis dC18, 50 × 4.6 mm, 1.8 µm; UV purity detected at 220 nm; Mobile phase A = 0.05% TFA in water; Mobile phase B = acetonitrile. Method E: UPLC/UV/MS using Chiral Technologies CHIRALPAK® AS-H column, 4.6 × 100 mm, 5 µm; Mass spectrometer ESI positive, acquiring from *m/z* 160 to 650; Mobile phase A = CO_2; Mobile phase B = methanol; 80:20 A/B hold for 10 min; Column temperature: 40 ºC; Back pressure: 120 Bar; Flow rate: 1.5 mL/min. All final compounds were determined to have a purity of >95% by one of the aforementioned methods unless stated otherwise.

Synthesis of 7-(4-methyl-1H-imidazol-1-yl)-2-{[6-(trifluoromethyl)-2H-chromen-4-yl]methyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (20).

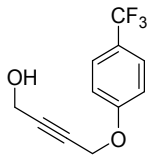


13

*1-(Prop-2-yn-1-yloxy)-4-(trifluoromethyl)benzene (**13**).*

Potassium carbonate (22.2 g, 161 mmol) was added to a solution of 4-trifluoromethylphenol (**12**) (8.68 g, 53.5 mmol) and 3-bromopropyne (15.9 g, 107 mmol) in DMF (10 mL), and the

reaction was stirred at room temperature for 16 h. The mixture was poured into 100 mL water, and the mixture was extracted with diethyl ether (3 × 40 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford the title compound as a yellow oil (10.71 g, 53.5 mmol, 100%). GCMS *m/z* 199 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 9.0 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 4.75 (d, *J* = 2.3 Hz, 2H), 2.56 (t, 1H).

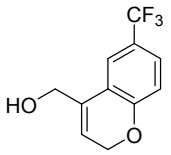


14

*4-[4-(Trifluoromethyl)phenoxy]but-2-yn-1-ol (**14**)*.

To a solution of compound 1-(prop-2-yn-1-yloxy)-4-(trifluoromethyl)benzene (**13**) (3.4 g, 17.0 mmol) in THF (50 mL) was added *n*-BuLi (2.5 M in hexanes, 8.15 mL, 20.4 mmol) at –78 °C. The reaction was stirred at –78 °C for 30 min, whereupon paraformaldehyde (2.3 g) was added. The cooling bath was removed, and the mixture was allowed to slowly warm to room temperature and was stirred for 2 h. The reaction mixture was quenched with ice (100 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (gradient: 0% to 30% EtOAc in heptane) to afford the title compound as a yellow solid (2.19 g, 9.52 mmol, 56%). GCMS *m/z* 230 (M^+); ^{1}H NMR (400

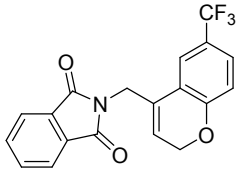
MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2 H), 4.79 (t, *J* = 1.8 Hz, 2H), 4.32 (t, *J* = 1.8 Hz, 2H).



15

*[6-(Trifluoromethyl)-2*H*-chromen-4-yl]methanol (**15**).*[3]

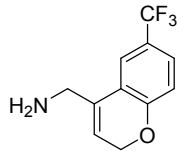
Indium(III) iodide (209 mg, 0.422 mmol) was added to 4-[4-(trifluoromethyl)phenoxy]but-2-yn-1-ol (**14**) (485 mg, 2.11 mmol) in THF (12 mL). The reaction mixture was refluxed for 18 h. After cooling to room temperature, it was treated with saturated aqueous $NaHCO_3$ solution (30 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (gradient: 0% to 50% EtOAc in heptane) to afford the title compound **15** as a yellow solid (352 mg, 1.53 mmol, 73%). GCMS *m/z* 230 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.47 (m, 1H), 7.39 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 5.92 (dt, *J* = 3.3, 1.9 Hz, 1H), 4.80 – 5.00 (m, 2H), 4.40 – 4.59 (m, 2H).



*2-{[6-(Trifluoromethyl)-2*H*-chromen-4-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione*.

[3] Prepared according to the procedure described by Qiu, W.-W.; Surendra, K.; Yin, L.; Corey, E.J. Selective formation of six-membered oxa- and carbocycles by the In(III)-activated ring closure of acetylenic substrates. *Org. Lett.* **2011**, *13*, 5893-5895.

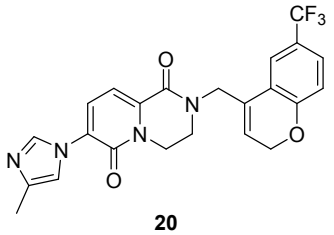
Diisopropyl azodicarboxylate (0.35 mL, 1.7 mmol) was slowly added to a mixture of [6-(trifluoromethyl)-2*H*-chromen-4-yl]methanol **(15)** (352 mg, 1.53 mmol), phthalimide (248 mg, 1.69 mmol) and triphenylphosphine (448 mg, 1.71 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 h and then concentrated under vacuum. The resulting residue was purified by silica gel chromatography (gradient: 0% to 20% EtOAc in heptane) to afford the title compound as a white solid (316 mg, 0.88 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.98 (m, 2H), 7.71 – 7.81 (m, 2H) 7.63 – 7.67 (m, 1H), 7.40 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.77 (t, *J* = 3.7 Hz, 1H), 4.80 – 4.92 (m, 2H), 4.65 (m, 2H).



16

*1-[6-(Trifluoromethyl)-2*H*-chromen-4-yl]methanamine (**16**).*

Hydrazine hydrate (50%, 0.3 mL, 4.4 mmol) was added to a solution of 2-{[6-(trifluoromethyl)-2*H*-chromen-4-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (316 mg, 0.88 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred at room temperature for 18 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 0% to 10% [2M ammonia in MeOH] in CH_2Cl_2) to afford the title compound as a yellow oil (114 mg, 0.50 mmol, 57%). LCMS *m/z* 230.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.48 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.78 – 5.96 (m, 1H), 4.89 (dt, *J* = 3.5, 1.8 Hz, 2H), 3.69 (m, 2H), 1.46 (br s, 2H).



20

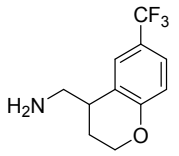
*7-(4-Methyl-1*H*-imidazol-1-yl)-2-{[6-(trifluoromethyl)-2*H*-chromen-4-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**20**).*

Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane (DABAL-Me_3) (77 mg, 0.3 mmol) was added to a solution of 1-[6-(trifluoromethyl)-2*H*-chromen-4-yl]methanamine (**16**) (48 mg, 0.2 mmol) in THF (10 mL) at room temperature. The mixture was stirred at 45 °C for 45 min and then at 65 °C for 15 min. 7-(4-Methyl-1*H*-imidazol-1-yl)-3,4-dihydropyrido[2,1-*c*][1,4]oxazine-1,6-dione (lactone **7**)[4] (77 mg, 0.3 mmol) was then added, and the mixture was heated at reflux for 5 h. After the reaction mixture had been cooled to 0 °C, 1 N NaOH (20 mL) was carefully added, with vigorous stirring, to quench the reaction. Water (30 mL) was then added, resulting in a cloudy, light yellow slurry. The aqueous mixture was extracted with MTBE (20 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow residue was dissolved in CH_2Cl_2 (10 mL) at 0 °C and methanesulfonic anhydride (37 mg, 0.21 mmol) was added drop-wise. The reaction mixture was stirred at 0 °C for 30 min, whereupon 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 195 mg, 1.4 mmol) was added, and the mixture was stirred at room temperature for 18 h. TLC analysis revealed that the ring closure was not complete, and the reaction mixture was therefore treated with additional TBD (195 mg, 1.4 mmol), whereupon it was stirred at room temperature for 18 h.

[4] Prepared according to the procedure described by Pettersson, M.; Johnson, D. S.; Humphrey, J. M.; Butler, T. W.; am Ende, C. W.; Fish, B. A.; Green, M. E.; Kauffman, G. W.; Mullins, P. B.; O'Donnell, C. J.; Stepan, A. F.; Stiff, C. M.; Subramanyam, C.; Tran, T. P.; Vetelino, B. C.; Yang, E.; Xie, L.; Bales, K. R.; Pustilnik, L. R.; Steyn, S. J.; Wood, K. M.; Verhoest, P. R. Design of pyridopyrazine-1,6-dione γ-secretase modulators that align potency, MDR efflux ratio, and metabolic stability. *ACS Med. Chem. Lett.* **2015**, *6*, 596–601.

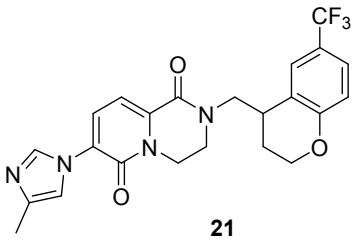
The reaction was poured into saturated aqueous $NaHCO_3$ solution (30 mL), and the subsequent mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel chromatography (gradient: 0% to 6% [2 M ammonia in MeOH] in CH_2Cl_2) to afford the title compound **20** as a yellow oil (27 mg, 56 μmol, 28%). LCMS *m/z* 457.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.42 (s, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.18 – 7.27 (m, 1H), 7.03 (s, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.82 (t, *J* = 3.5 Hz, 1H), 4.82 (d, *J* = 3.5 Hz, 2H), 4.55 (s, 2H), 4.10 – 4.24 (m, 2H), 3.44 – 3.59 (m, 2H), 2.12 – 2.23 (m, 3H).

Synthesis of 7-(4-methyl-1H-imidazol-1-yl)-2-{[6-(trifluoromethyl)-3,4-dihydro-2H-chromen-4-yl]methyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (21).



17

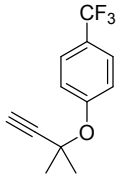
*1-[6-(Trifluoromethyl)-3,4-dihydro-2*H*-chromen-4-yl]methanamine (**17**)*. To a Parr reactor charged with methanol and wetted $Pd(OH)_2$ on carbon (20 wt%, 42.3 mg, 0.06 mmol Pd) was added a solution of 1-[6-(trifluoromethyl)-2*H*-chromen-4-yl]methanamine (**16**) (69 mg, 0.3 mmol) in MeOH (20 mL). The Parr reactor was sealed, purged with nitrogen gas (3×) and hydrogen gas (3×), and then charged with hydrogen gas (40 psi). After 4 h, the Parr reactor was depressurized and purged with nitrogen gas (3×). The reaction mixture was filtered through Celite®, and the solids were washed with methanol. The combined filtrate and washings were concentrated under reduced pressure to afford the title compound as a yellow oil, which was used directly in the subsequent step without further purification (61 mg, 0.26 mmol, 88%). LCMS *m/z* 232.1 $[M+H]^+$.



21

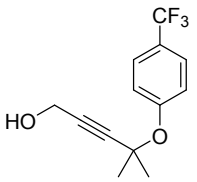
*7-(4-Methyl-1*H*-imidazol-1-yl)-2-{[6-(trifluoromethyl)-3,4-dihydro-2*H*-chromen-4-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**21**)*. DABAL-Me_3 (97 mg, 0.37 mmol) was added to a solution of 1-[6-(trifluoromethyl)-3,4-dihydro-2*H*-chromen-4-yl]methanamine (61 mg, 0.26 mmol) in THF (10 mL) at room temperature. The mixture was stirred at 45 °C for 45 min and then at 65 °C for 15 min. Lactone **7** (97 mg, 0.4 mmol) was added, and the mixture was heated at reflux for 5 h. After the reaction mixture had been cooled to 0 °C, 1 N NaOH (20 mL) was carefully added, with vigorous stirring, to quench the reaction. Water (30 mL) was then added to give a cloudy, light yellow slurry. The mixture was extracted with MTBE (20 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow residue, which was dissolved in THF (20 mL). Triphenylphosphine (94.5 mg, 0.36 mmol) and DIAD (76.4 mg, 0.36 mmol) were added sequentially at room temperature. The reaction was stirred for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (gradient: 0% to 6% [2 M NH_3 in MeOH] in CH_2Cl_2) to afford the title compound as a yellow oil (63.7 mg, 0.15 mmol 57%). LCMS *m/z* 459.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 1.2 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.39 (s, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.17 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.44 – 4.52 (m, 1H), 4.28 – 4.39 (m, 3H), 4.23 (dd, *J* = 13.7, 10.1 Hz, 1H), 3.66 – 3.81 (m, 2H), 3.46 (dd, *J* = 13.7, 5.5 Hz, 1H), 3.22 – 3.35 (m, 1H), 2.31 (s, 3H), 2.04 – 2.20 (m, 1H), 1.91 (dq, *J* = 14.3, 3.2 Hz, 1H).

Synthesis of 2-{[2,2-dimethyl-6-(trifluoromethyl)-2H-chromen-4-yl]methyl}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (28)



1-[(2-Methylbut-3-yn-2-yl)oxy]-4-(trifluoromethyl)benzene.

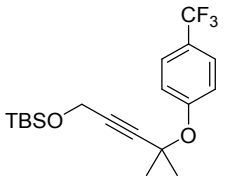
The title compound was synthesized from 4-(trifluoromethyl)phenol (80.5 g, 497 mmol) using the method described for synthesis of 1-chloro-4-[(2-methylbut-3-yn-2-yl)oxy]benzene (see below). The product was isolated as a colorless oil (88.6 g, 388 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (br d, J = 8.6 Hz, 2H), 7.30 (br d, J = 8.8 Hz, 2H), 2.63 (s, 1H), 1.70 (s, 6H).



4-Methyl-4-[4-(trifluoromethyl)phenoxy]pent-2-yn-1-ol.

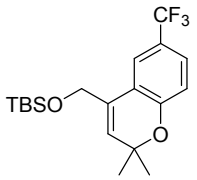
To a solution of 1-[(2-methylbut-3-yn-2-yl)oxy]-4-(trifluoromethyl)benzene (7.40 g, 32.4 mmol) in THF (125 mL) cooled to −78 °C was added *n*-BuLi (2.5 M solution in hexanes, 15.7 mL, 39.2 mmol) drop-wise over 20 min. The reaction mixture was stirred for 15 min at −78 °C, whereupon paraformaldehyde (1.46 g, 48.6 mmol) was added portion-wise, and the reaction mixture was allowed to warm to room temperature over 16 h. It was then quenched by addition of saturated aqueous NH_4Cl solution, and the resulting mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was

purified by silica gel chromatography (gradient: 0% to 50% EtOAc in heptane) to afford the product as a light yellow oil (5.44 g, 21.1 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 4.32 (s, 2H), 1.69 (s, 6H).



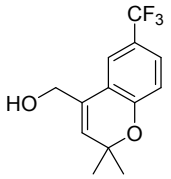
tert-Butyl(dimethyl)({4-methyl-4-[4-(trifluoromethyl)phenoxy]pent-2-yn-1-yl}oxy)silane.

Imidazole (2.34 g, 34.0 mmol) was added to a solution of 4-methyl-4-[4-(trifluoromethyl)phenoxy]pent-2-yn-1-ol (5.86 g, 22.7 mmol) in CH_2Cl_2 (90 mL) at 0 °C. TBSCl (5.13 g, 34.0 mmol) was then added slowly, in a portion-wise manner, and the reaction mixture was allowed to stir at room temperature for 4 h. An aqueous 1 M HCl solution was added, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 0% to 10% EtOAc in heptane) to afford the title compound as a pale yellow oil, which was used directly in the following step (9.66 g, ≤ 22.7 mmol, assumed quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H, assumed; partially obscured by solvent peak), 4.35 (s, 2H), 1.68 (s, 6H), 0.90 (s, 9H), 0.09 (s, 6H).



tert-*Butyl{[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methoxy}dimethylsilane.*

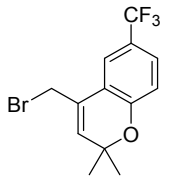
(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (191 mg, 0.247 mmol) was added to a solution of *tert*-butyl(dimethyl)({4-methyl-4-[4-(trifluoromethyl)phenoxy]pent-2-yn-1-yl}oxy)silane from the previous step (9.66 g, ≤22.7 mmol) in CH_2Cl_2 (100 mL), and the reaction mixture was stirred at room temperature for 18 h. The reaction was incomplete as determined by GCMS, and additional gold catalyst (96 mg, 0.13 mmol) was added and stirring was continued for 24 h. Again, incomplete conversion was observed by GCMS and additional gold catalyst (96 mg, 0.13 mmol) was added, and stirring was continued for a further 24 h, which allowed for completion of the reaction. Water (250 mL) was added, and the mixture was stirred for 15 min. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and filtered through a pad of silica gel on top of a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure to afford the product as a yellow oil (8.24 g, 22.1 mmol, 97% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 7.38 (br d, J = 8.5 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.70 – 5.73 (m, 1H), 4.49 (d, J = 1.5 Hz, 2H), 1.45 (s, 6H), 0.93 (s, 9H), 0.12 (s, 6H).



*[2,2-Dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methanol.*

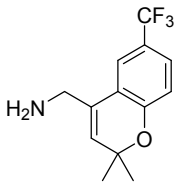
Tetrabutylammonium fluoride (1 M solution in THF, 16.2 mL, 16.2 mmol) was added drop-wise to a solution of *tert*-butyl{[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methoxy}dimethylsilane (4.02 g, 10.8 mmol) in CH_2Cl_2 (43 mL) at 0 °C, and the reaction mixture was stirred for 4 h. Water was added, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered through a 1 inch plug

of silica gel, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 0% to 50% EtOAc in heptane) to provide the title compound as an off-white solid (2.26 g, 8.75 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (br s, 1H), 7.40 (br d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.77 (br s, 1H), 4.52 (br s, 2H), 1.46 (s, 6H).



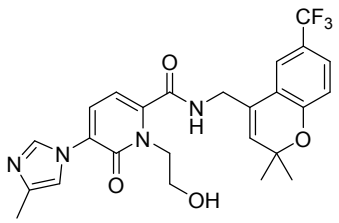
*4-(Bromomethyl)-2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromene.*

Carbon tetrabromide (5.26 g, 15.0 mmol) was added to a 0 °C solution of [2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methanol (2.52 g, 9.76 mmol) in CH_2Cl_2 (50 mL). A solution of triphenylphosphine (4.06 g, 15.2 mmol) in CH_2Cl_2 (5 mL) was then added drop-wise over 15 min. The reaction mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature. The reaction mixture was then adsorbed onto diatomaceous earth and purified via silica gel chromatography (gradient: 0% to 50% EtOAc in heptane) to afford the title compound as a colorless oil (2.08 g, 6.48 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br d, *J* = 1.7 Hz, 1H), 7.43 (br dd, *J* = 8.6, 1.9 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.87 (s, 1H), 4.25 (s, 2H), 1.46 (s, 6H).



*1-[2,2-Dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methanamine.*

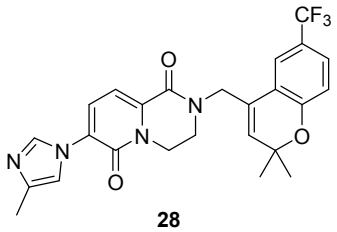
Concentrated aqueous NH_4OH solution (42 mL) was added to a solution of 4-(bromomethyl)-2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromene (2.08 g, 6.48 mmol) in dioxane (42 mL) and the reaction mixture was heated at 50 °C for 16 h. Water was added, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 0% to 10% MeOH in CH_2Cl_2) to afford the title compound as a colorless oil (1.16 g, 4.51 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.41 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.70 – 5.72 (m, 1H), 3.70 (d, *J* = 1.4 Hz, 2H), 1.45 (s, 6H), 1.31 (br s, 2H).



N-*{[2,2-Dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide.*

DABAL-Me_3 (2.09 g, 7.91 mmol) was added to a solution of 1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methanamine (1.36 g, 5.27 mmol) in THF (50 mL), and the mixture was stirred for 5 min at room temperature. Lactone **7** (1.42 g, 5.79 mmol) was added and the reaction mixture was heated at 70 °C for 2 h before being cooled and stirred at room temperature for 16 h. The reaction was then *carefully* poured into 1 M aqueous NaOH solution and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the title compound as a foamy yellow solid, which was used directly in the subsequent reaction without further purification (2.43 g, 4.84 mmol, 92%). LCMS *m/z* 503.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (br t, *J* = 5.0 Hz, 1H), 7.83 (br s, 1H), 7.53 (br s, 1H), 7.43 (br d, *J* = 8.6 Hz,

1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.93 (br s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.41 (d, *J* = 7.6 Hz, 1H), 5.83 (s, 1H), 4.45 (d, *J* = 5.1 Hz, 2H), 4.19 – 4.26 (m, 2H), 3.98 – 4.05 (m, 2H), 1.86 (s, 3H), 1.47 (s, 6H).



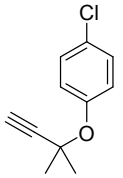
28

*2-{[2,2-Dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**28**)*

Triethylamine (1.19 mL, 8.54 mmol) was added to a suspension of *N*-{[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide from the previous step (2.43 g, 4.84 mmol) in THF (40 mL). The mixture was cooled to −20 °C and a solution of methanesulfonyl chloride (0.58 mL, 7.25 mmol) in THF (10 mL) was added drop-wise over 15 min. The reaction mixture was stirred for 10 min at −20 °C and then allowed to warm to room temperature. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) (1.98 g, 13.5 mmol) was added, and stirring was continued for 3.5 h whereupon the reaction was quenched with water. The aqueous mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 0% to 10% MeOH in CH_2Cl_2) which did not afford complete separation. The fractions were recombined and dissolved in THF (40 mL). TBD (1.98 g, 13.5 mmol) was added, and the reaction was stirred for 16 h. After dilution with water, the mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced

pressure. The residue was triturated with EtOAc and heptane and filtered to afford a yellow solid, which was purified by silica gel chromatography (gradient: 0% to 10% MeOH in CH_2Cl_2). The purified material was triturated with EtOAc and heptane to afford the title compound as an off-white powder (668 mg, 1.38 mmol). The filtrate from the trituration was concentrated and recrystallized from EtOAc and heptane, subjected to silica gel chromatography (gradient: 0% to 10% MeOH in CH_2Cl_2) and subsequently triturated with EtOAc and heptane, providing the title compound as a yellow solid (527 mg, 1.09 mmol). These lots were analytically identical and were combined into a single lot of the title compound (1.20 g, 2.48 mmol, 51%). Purity = 100% by UV, 94% by ELSD (Method A); m.p. 196.5 – 197 °C; LCMS *m/z* 485.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.52 (br d, *J* = 2 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.41 (br dd, *J* = 8.5, 2 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.12 – 7.14 (m, 1H), 6.91 (br d, *J* = 8.6 Hz, 1H), 5.74 (br s, 1H), 4.62 (d, *J* = 1.0 Hz, 2H), 4.25 – 4.29 (m, 2H), 3.52 – 3.57 (m, 2H), 2.31 (d, *J* = 1.0 Hz, 3H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 155.8, 155.6, 138.9, 136.4, 133.8, 132.4, 130.6, 127.25, 127.3 (q, $^3J_{CF}$ = 3.7 Hz), 126.0, 124.1 (q, $^1J_{CF}$ = 271 Hz), 123.3 (q, $^2J_{CF}$ = 33 Hz), 120.8 (q, $^3J_{CF}$ = 3.7 Hz), 119.5, 117.2, 114.4, 109.0, 76.8, 47.2, 42.5, 39.7, 27.8, 13.6.; HRMS *m/z*, calcd $[M+H]^+$ 485.1795, observed 485.1794.

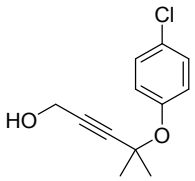
Synthesis of 2-[(6-chloro-2,2-dimethyl-2H-chromen-4-yl)methyl]-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (29).



[5] Prepared according to the procedure developed by Godfrey, J. D.; Mueller, R. H.; Sedergran, T. C. Improved synthesis of aryl 1,1-dimethylpropargyl ethers. Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405-6408.

1-Chloro-4-[(2-methylbut-3-yn-2-yl)oxy]benzene.[5]

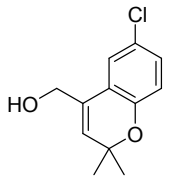
To a stirred solution of 2-methylbut-3-yn-2-ol (28.7 mL, 293 mmol) in acetonitrile (300 mL) was added DBU (60 mL, 401 mmol). The mixture was cooled to between –5 °C and –10 °C using an ice-salt bath. TFAA (41.4 mL, 293 mmol) was added drop-wise over 20 min while maintaining the internal temperature at or below 0 °C. The reaction was stirred at 0 °C for 30 min. To a second round-bottom flask charged with 4-chlorophenol (25.0 g, 195 mmol) in acetonitrile (300 mL) and cooled in an ice-salt bath was added DBU (56.8 mL, 380 mmol) and $CuCl_2$ (250 mg, 1.86 mmol), affording a light brown solution. While keeping this solution at –5 °C, the previously prepared solution was added drop-wise via cannula and the reaction was stirred at 0 °C for 1 h; the cold bath was then removed and the reaction was stirred at ambient temperature for 12 h. The reaction mixture was quenched with ice water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by silica gel chromatography (gradient: 2% to 5% EtOAc in hexane) to provide the title compound as an oil (20.0 g, 103 mmol, 53%). GCMS *m/z* 194 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 – 7.15 (m, 4H), 3.69 (s, 1H), 1.57 (s, 6H).



4-(4-Chlorophenoxy)-4-methylpent-2-yn-1-ol.

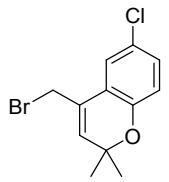
To a solution of 1-chloro-4-[(2-methylbut-3-yn-2-yl)oxy]benzene (20.0 g, 103 mmol) in THF (200 mL) was added *n*-BuLi (2.5 M in hexanes, 61.9 mL, 155 mmol) drop-wise at –78 °C and the reaction was stirred at –78 °C for 30 min. Paraformaldehyde (6.5 g, 72 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for an

additional 2 h. The reaction mixture was quenched with ice water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude oil was purified by silica gel chromatography (5% EtOAc in hexanes) to afford the title compound as an oil (17 g, 76 mmol, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 5.21 (t, J = 6 Hz, 1H), 4.10 (d, J = 5.9 Hz, 2H), 1.56 (s, 6H).



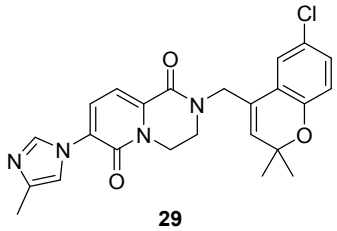
*(6-Chloro-2,2-dimethyl-2*H*-chromen-4-yl)methanol.*

To a stirred solution of 4-(4-chlorophenoxy)-4-methylpent-2-yn-1-ol (17 g, 76 mmol) in CH_2Cl_2 (150 mL) was added (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate (293 mg, 0.379 mmol) under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 2 h, whereupon TLC analysis indicated that all of the starting material was consumed. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% EtOAc in hexanes) to afford the title compound as a light yellow liquid (12 g, 54 mmol, 70%). GCMS *m/z* 224 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (d, J = 2.1 Hz, 1H), 7.14 (dd, J = 8.5, 2.2 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 5.78 (s, 1H), 5.1 (t, J = 5.4 Hz, 1H), 4.25 (d, J = 5.3 Hz, 2H), 1.36 (s, 6H).



*4-(Bromomethyl)-6-chloro-2,2-dimethyl-2*H-*chromene*.

To a 0 °C, stirred solution of (6-chloro-2,2-dimethyl-2*H*-chromen-4-yl)methanol (1.00 g, 4.46 mmol) in CH_2Cl_2 (10 mL) was added carbon tetrabromide (1.63 g, 4.91 mmol), followed by a solution of triphenylphosphine (1.29 g, 4.91 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 16 h, whereupon it was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 0% to 5% EtOAc in hexane) to afford the title compound as a brown liquid (800 mg, 2.79 mmol, 63%). GCMS *m/z* 288 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 2.4 Hz, 1H), 7.11 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.82 (s, 1H), 4.19 (s, 2H), 1.41 (s, 6H).



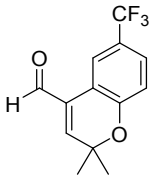
29

*2-[(6-Chloro-2,2-dimethyl-2*H-*chromen-4-yl)methyl]-7-(4-methyl-1*H-*imidazol-1-yl)-3,4-dihydro-2*H-*pyrido[1,2-*a*]pyrazine-1,6-dione (**29**)*.

A solution of 4-(bromomethyl)-6-chloro-2,2-dimethyl-2*H*-chromene (800 mg, 2.78 mmol) in methanolic ammonia (10 mL) was heated in a sealed tube at 80 °C for 5 h. The mixture was allowed to cool to room temperature and was concentrated under reduced pressure. The resulting residue was triturated with pentane and then dissolved in CH_2Cl_2. The corresponding solution was basified using saturated aqueous $NaHCO_3$ solution and then extracted with 5% MeOH in CH_2Cl_2 (3 × 20 mL). The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a brown liquid,

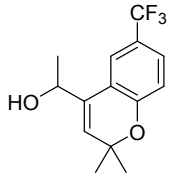
which was dissolved in THF (5.0 mL). To this solution was added DABAL-Me_3 (621 mg, 2.42 mmol) at room temperature and the reaction was heated to 40 °C for 45 min. Lactone **7** (297 mg, 1.21 mmol) was added and the reaction was heated to 65 °C for 5 h. The reaction was allowed to cool to room temperature and aqueous 1 N NaOH solution (2 mL) was added. The resulting slurry was diluted with water and extracted with 5% MeOH in CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was triturated with 10% EtOAc in hexane to afford an off-white solid which was dissolved in CH_2Cl_2 (5 mL). To this solution was added triethylamine (245 μL, 1.76 mmol) followed by methanesulfonyl chloride (109 μL, 1.41 mmol) at −10 °C. The reaction was stirred at room temperature for 2 h, whereupon it was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a brown solid which was dissolved in THF (5 mL). To this solution was added TBD (447 mg, 3.2 mmol) at room temperature. The reaction mixture was stirred for 16 h, whereupon it was concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (2% MeOH in CH_2Cl_2) to afford the title compound as a yellow solid (140 mg, 0.31 mmol, 11%). LCMS *m/z* 451 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.40 (s, 1H), 7.32 (s, 1H), 7.17 (m, 2H), 6.82 (d, J = 8.6 Hz), 4.49 (s, 2H), 4.25 (m, 2H), 3.62 (m, 2H), 2.14 (s, 3 H), 1.38 (s, 6H).

Synthesis of 2-{(1*S*)-1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (30) and 2-{(1*R*)-1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (31).



*2,2-dimethyl-6-(trifluoromethyl)-2*H-*chromene-4-carbaldehyde.*

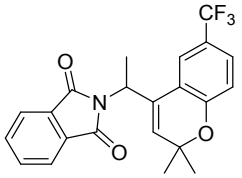
To a solution of [2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]methanol (*vide supra*) (2.0 g, 7.7 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Dess-Martin periodinane (3.4 g, 7.7 mmol). The reaction was allowed to warm slowly to room temperature over 18 h. The mixture was diluted with diethyl ether and filtered through a pad of Celite® and silica gel. The filtrate was washed with aqueous 1 M NaOH solution and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound (1.8 g, 7.0 mmol, 90%) as an off-white solid which was used without further purification. GCMS *m/z* 256 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.54 (d, *J* = 1.6 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.53 (s, 1H), 1.56 (s, 6H).



*1-[2,2-dimethyl-6-(trifluoromethyl)-2*H-*chromen-4-yl]ethanol*.

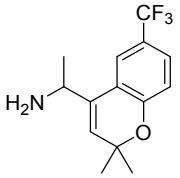
To a stirred solution of 2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromene-4-carbaldehyde (1.3 g, 5.1 mmol) in THF (15 mL) was added CH_3MgBr (3.0 M solution in diethyl ether, 2.5 mL, 7.6 mmol) drop-wise at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (1.5 mL), diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and solvent evaporated under reduced pressure to afford the title compound (1.1 g, 4.0 mmol, 79%) as a brown liquid, which was used without further purification. GCMS *m/z* 272 (M^+);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (br d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 6.87 (br d, *J* = 8.4 Hz, 1H), 5.78 (s, 1H), 1.46 (d, 3H), 1.44 (s, 3H), 1.42 (s, 3H).



*2-{1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione.*

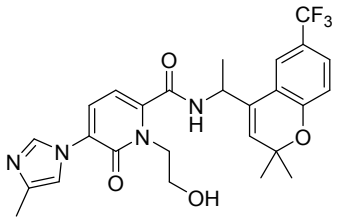
To a solution of 1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethanol (1.1 g, 4.0 mmol), phthalimide (714 mg, 4.85 mmol) and triphenylphosphine (1.27 g, 4.85 mmol) in THF (11 mL) was added diisopropyl azadicarboxylate (962 μL, 4.85 mmol) drop-wise at room temperature. The reaction was allowed to stir for 16 h, whereupon the mixture was diluted with EtOAc. The solution was washed with water and with brine, and the organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to afford the title compound (1.4 g, 3.5 mmol, 86%) as a brown solid. GCMS *m/z* 401 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.67 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.50 (s, 1H), 7.29 (br d, *J* = 8.4 Hz, 1H), 6.82 (br d, *J* = 8.4 Hz, 1H), 6.01 (s, 1H), 4.83 (q, *J* = 7 Hz, 1H), 1.72 (d, *J* = 7 Hz, 3H), 1.44 (s, 3H), 1.42 (s, 3H).



*1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethanamine*.

To a stirred solution of 2-{1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (1.4 g, 3.5 mmol) in ethanol (15 mL) was added hydrazine hydrate

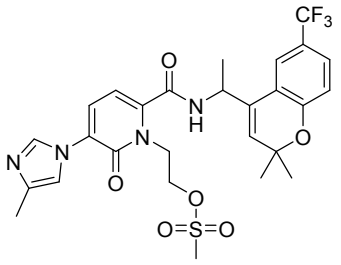
(847 μL, 17.5 mmol) at room temperature. The reaction was stirred at room temperature for 6 h and then evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 and filtered. The filtrate was washed with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford the title compound as a yellow oil, which was used without further purification (0.90 g, 3.3 mmol 94%). GCMS *m/z* 271 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.6 Hz, 1H), 7.37 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.77 (s, 1H), 4.10 (q, *J* = 6.5 Hz, 1H), 1.51 (s, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.33 (d, *J* = 6.6 Hz, 3H).



N-*{1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide.*

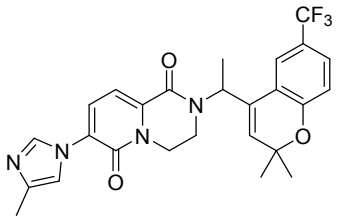
To a solution of 1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethanamine (0.90 g, 3.3 mmol) in THF (10 mL) at room temperature was added bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3) (1.7 g, 6.6 mmol). The mixture was heated to 40 °C for 45 min, at which point lactone **7** (813 mg, 3.32 mmol) was added and the temperature was increased to 65 °C for 5 h. The mixture was cooled to room temperature and *carefully* treated with aqueous 1 N NaOH solution (1 mL). The resultant slurry was diluted with water and extracted with 5% MeOH in CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was triturated with hexanes to afford the title compound as an off-white solid (1.2 g, 2.3 mmol, 70%). LCMS *m/z* 517 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, *J* = 8.6 Hz, 1H), 7.57 (s, 1H), 7.82 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 8.6 Hz,

1H), 6.87 (s, 1H), 6.34 (d, *J* = 7.8 Hz, 1H) 5.84 (s, 1H), 5.31 (p, *J* = 7.0 Hz, 1H), 4.56 (br s, 1H), 4.09 − 4.27 (m, 2H), 3.97 − 4.05 (m, 2H), 1.72 (s, 3H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.49 (s, 3H), 1.44 (s, 3H).



*2-[6-({1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}carbamoyl)-3-(4-methyl-1*H*-imidazol-1-yl)-2-oxopyridin-1(2*H*)-yl]ethyl methanesulfonate.*

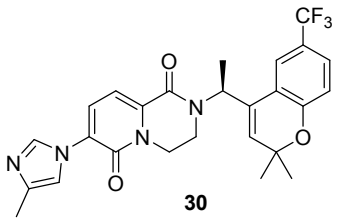
To a solution of *N*-{1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide (1.2 g, 2.3 mmol) in CH_2Cl_2 (12 mL) at −10 °C was added triethylamine (648 µL, 4.65 mmol) followed by drop-wise addition of methanesulfonyl chloride (270 µL, 3.49 mmol). The reaction was warmed to room temperature and allowed to stir for 2 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the title compound as an off-white solid, which was used without further purification (1.3 g, 2.2 mmol, 94%). LCMS *m/z* 595 $[M+H]^+$.



*2-{1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione*.

To a stirred solution of 2-[6-({1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}carbamoyl)-3-(4-methyl-1*H*-imidazol-1-yl)-2-oxopyridin-1(2*H*)-yl]ethyl methanesulfonate (1.3 g, 2.2 mmol) in DMF (10 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (1.19 g, 8.52 mmol). The mixture was stirred at room temperature for 16 h. After completion of the reaction, the mixture was concentrated under reduced pressure, and the residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel chromatography (eluent: 3% MeOH in CH_2Cl_2) to afford the title compound as a white solid (600 mg, 1.2 mmol, 49%). LCMS *m/z* 499 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.36 − 7.41 (m, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.10 (s, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.90 − 5.99 (m, 1H), 5.83 (d, *J* = 1.2 Hz, 1H), 4.07 − 4.17 (m, 1H), 3.96 − 4.06 (m, 1H), 3.42 (ddd, *J* = 13.6, 7.1, 3.9 Hz, 1H), 2.28 (s, 3H), 3.06 − 3.16 (m, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.59 (s, 3H), 1.40 (s, 3H).

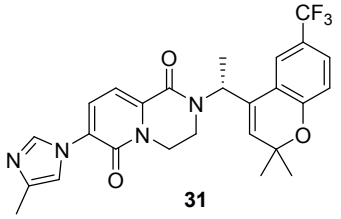
Samples of the two enantiomers were obtained via chiral HPLC (Column: Chiral Technologies CHIRALPAK® IC, 5 μm; Mobile phase: 0.1% diethylamine in methanol).



30

*2-{(1*S*)-1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**30**).* Retention time: 8.9 min (Column: Chiral Technologies CHIRALPAK® IC, 4.6 x 250 mm, 5 μm; Mobile phase: 0.1% diethylamine in methanol; Flow rate: 1.0 mL/minute). mp: 182.5 – 183 °C; LCMS *m/z* 499.2 $[M+1]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (d, *J* = 1.3 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H),

7.50 (br d, J = 1.8 Hz, 1H), 7.40 (br dd, J = 8.5, 2.2 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.27 – 7.29 (m, 1H), 6.92 (br d, J = 8.4 Hz, 1H), 6.08 (d, J = 1.5 Hz, 1H), 5.88 (qd, J = 6.9, 1.4 Hz, 1H), 4.06 – 4.12 (m, 2H), 3.63 (ddd, J = 13.8, 5.8, 4.7 Hz, 1H), 3.11 – 3.19 (m, 1H), 2.22 (d, J = 1.1 Hz, 3H), 1.58 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.3, 157.6, 157.4, 138.9, 138.1, 136.3, 133.8, 131.4, 130.6, 130.4, 127.8 (q, $^3J_{CF}$ = 3.7 Hz), 125.9 (q, $^1J_{CF}$ = 270.0 Hz), 124.2 (q, $^2J_{CF}$ = 32.3 Hz), 121.9 (q, $^3J_{CF}$ = 3.7 Hz), 121.8, 118.7, 116.6, 110.1, 78.5, 48.6, 41.7, 39.2, 28.8, 27.2, 15.1, 13.3; $[\alpha]_D^{22}$ –45.3 (*c* 0.65, MeOH); HRMS *m/z*, calcd $[M+H]^+$ for $C_{26}H_{25}F_3N_4O_3$ 499.1957, observed 499.1857.

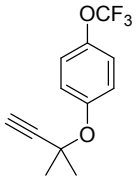


31

*2-{(1*R*)-1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**31**).*

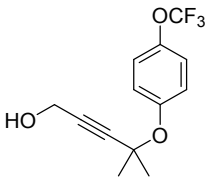
Retention time: 11.2 min (Column: Chiral Technologies CHIRALPAK® IC, 4.6 x 250 mm, 5 µm; Mobile phase: 0.1% diethylamine in methanol; Flow rate: 1.0 mL/minute); LCMS *m/z* 499.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (br s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.43 − 7.50 (m, 2H), 7.37 (br s, 1H), 7.11 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.10 (br s, 1H), 5.74 (br q, J = 7 Hz, 1H), 3.96 − 4.11 (m, 2H), 3.54 − 3.62 (m, 1H), 3.02 − 3.11 (m, 1H), 2.13 (s, 3H), 1.52 (s, 3H), 1.38 − 1.44 (m, 6H).

Synthesis of 2-{(1S)-1-[2,2-dimethyl-6-(trifluoromethoxy)-2H-chromen-4-yl]ethyl}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (32).



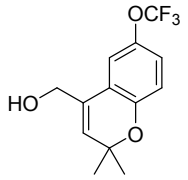
1-[(2-Methylbut-3-yn-2-yl)oxy]-4-(trifluoromethoxy)benzene.

4-(Trifluoromethoxy)phenol (8.02 g, 45.1 mmol) was converted to the title compound according to the method described for synthesis of 1-chloro-4-[(2-methylbut-3-yn-2-yl)oxy]benzene (see above). The product was isolated as a colorless liquid (7.5 g, 30.7 mmol, 68%). GCMS *m/z* 244 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (br d, half of AB quartet, *J* = 9.3 Hz, 2H), 7.13 (br d, half of AB quartet, *J* = 9.0 Hz, 2H), 2.59 (s, 1H), 1.65 (s, 6H).



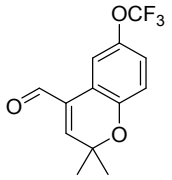
4-Methyl-4-[4-(trifluoromethoxy)phenoxy]pent-2-yn-1-ol.

To a solution of 1-[(2-methylbut-3-yn-2-yl)oxy]-4-(trifluoromethoxy)benzene (7.15 g, 29.3 mmol) in THF (70 mL) at −78 °C was added *n*-BuLi (2.24 M solution in hexanes, 19.6 mL, 43.9 mmol) drop-wise. The reaction mixture was stirred at −78 °C for 30 min and paraformaldehyde (1.92 g, 63.9 mmol) was added. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 2 h, whereupon it was quenched with ice and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 3% to 7% EtOAc in hexanes), which afforded the title compound as an off-white solid (6.0 g, 22 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (AB quartet, J_{AB} = 9.2 Hz, $\Delta\nu_{AB}$ = 22.4 Hz, 4H), 4.32 (d, *J* = 6.2 Hz, 2H), 1.64 (s, 6H).



*[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]methanol.*

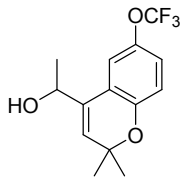
4-Methyl-4-[4-(trifluoromethoxy)phenoxy]pent-2-yn-1-ol (4.9 g, 17 mmol) was converted to the title compound using the method described for synthesis of (6-chloro-2,2-dimethyl-2*H*-chromen-4-yl)methanol (see above). The title compound was isolated as an off-white solid (3.5 g, 13 mmol, 71%). GCMS *m/z* 274 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (br d, *J* = 2 Hz, 1H), 7.00 (br d, *J* = 9 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.76 (br s, 1H), 4.48 (dd, *J* = 5.8, 1.1 Hz, 2H), 1.55 (t, *J* = 5.9 Hz, 1H), 1.45 (s, 6H).



*2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromene-4-carbaldehyde.*

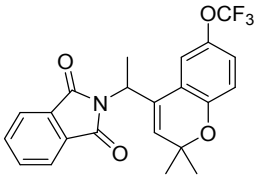
To a solution of [2,2-dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]methanol (2.2 g, 8.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added Dess-Martin periodinane (6.80 g, 16.0 mmol). The reaction mixture was stirred for 3 h at room temperature, whereupon it was diluted with ice water (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). This mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (eluent: 30% EtOAc in hexanes), which provided the title compound as a yellow liquid (1.5 g, 5.5 mmol, 69%). GCMS *m/z* 272 (M^+);

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.14 − 8.17 (m, 1H), 7.08 (br d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.51 (s, 1H), 1.55 (s, 6H).



*1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethanol.*

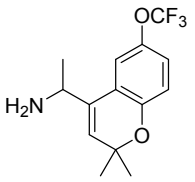
To a solution of 2,2-dimethyl-6-(trifluoromethoxy)-2*H*-chromene-4-carbaldehyde (1.5 g, 5.5 mmol) in THF (100 mL) at 0 °C was added MeMgBr (3 M solution in diethyl ether, 2.75 mL, 8.25 mmol). The reaction mixture was stirred for 2 h at room temperature, quenched with ice water (50 mL) and saturated aqueous NH_4Cl solution (50 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel (30% EtOAc in hexanes), which provided the product as a yellow liquid (1.1 g, 3.8 mmol, 69%). GCMS *m/z* 288 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (br d, *J* = 2.6 Hz, 1H), 6.99 (br d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.79 (br s, 1H), 4.79 (br q, *J* = 6.4 Hz, 1H), 1.46 (d, *J* = 6.5 Hz, 3H), 1.44 (s, 3H), 1.42 (s, 3H).



*2-{1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione.*

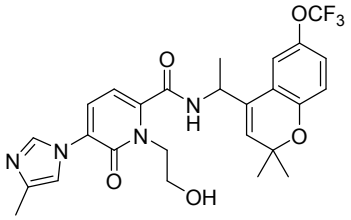
To a solution of 1-[2,2-dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethanol (1.5 g, 5.2 mmol) in THF (100 mL) at 0 °C was added triphenylphosphine (1.5 g, 5.7 mmol) and

phthalimide (0.84 g, 5.7 mmol), followed by diisopropyl azodicarboxylate (1.13 mL, 5.74 mmol). The reaction mixture was stirred for 12 h at room temperature. Ice water (30 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 5% to 10% EtOAc in hexanes) to afford the title compound as a yellow liquid (1.2 g, 2.9 mmol, 56%). GCMS *m/z* 417 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.09 − 7.12 (m, 1H), 6.91 (br d, *J* = 9.0 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.02 (br s, 1H), 5.39 (br q, *J* = 7.0 Hz, 1H), 1.72 (d, *J* = 7.0 Hz, 3H), 1.52 (s, 3H), 1.43 (s, 3H).



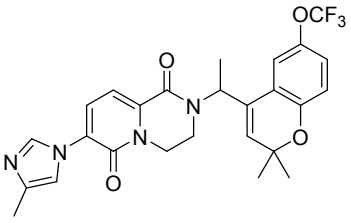
*1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethanamine.*

To a solution of 2-{1-[2,2-dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (1.5 g, 3.6 mmol) in ethanol (100 mL) at 0 °C was added hydrazine monohydrate (0.90 g, 18 mmol). The reaction mixture was stirred for 12 h at room temperature, whereupon it was filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound as a light yellow liquid (0.90 g, 3.1 mmol, 86%). LCMS *m/z* 288.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (br d, *J* = 2.2 Hz, 1H), 7.09 (br d, *J* = 9 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 5.86 (br s, 1H), 3.91 (br q, *J* = 6.4 Hz, 1H), 1.72 (br s, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H).



N-*{1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide.*

1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethanamine (287 mg, 1.0 mmol) was converted to the title compound, which was obtained as a light yellow solid (300 mg, 0.56 mmol, 56%), according to the method described for synthesis of *N*-{1-[2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromen-4-yl]ethyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide (*vide supra*). LCMS *m/z* 533.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, *J* = 8.1 Hz, 1H), 8.13 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.32 (s, 1H), 7.24 − 7.27 (m, 1H), 7.16 (br d, *J* = 9 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 5.91 (s, 1H), 4.96 − 5.05 (m, 1H), 4.91 (dd, *J* = 5.3, 5.1 Hz, 1H), 4.19 − 4.27 (m, 2H), 3.53 − 3.68 (m, 2H), 2.14 (s, 3H), 1.34 − 1.41 (m, 9H).

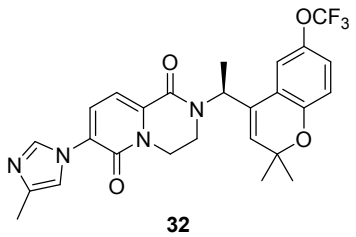


*2-{1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione.*

To a solution of *N*-{1-[2,2-dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide (350 mg, 0.657 mmol) in CH_2Cl_2 (20 mL) at –10 °C was added NEt_3 (0.18 mL, 1.32 mmol)

followed by methanesulfonyl chloride (0.061 mL, 0.789 mmol). The cold bath was removed and the reaction was stirred at ambient temperature for 3 h. The reaction mixture was quenched with ice water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and with brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford a yellow liquid, which was dissolved in THF (20 mL). To this solution was added TBD (310 mg, 2.23 mmol) and the reaction mixture was stirred for 12 h at room temperature. The reaction was quenched with aqueous 1 M NaOH solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (eluent: 10% MeOH in CH_2Cl_2), followed by preparative HPLC (column: Dr. Maisch HPLC GmbH Reprosil-Gold C18, 5 μm; Mobile phase A: 20 mM aqueous ammonium acetate; Mobile phase B: acetonitrile; Gradient: 10% to 100% B) to provide the racemic title compound as an off-white solid (95 mg, 0.18 mmol, 27%). LCMS *m/z* 515.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.12 (br s, 1H), 7.04 − 7.07 (m, 1H), 6.97 − 7.02 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 5.87 (br q, *J* = 7 Hz, 1H), 5.83 (s, 1H), 4.24 (ddd, *J* = 14.5, 7.0, 4.0 Hz, 1H), 3.82 (ddd, *J* = 14.5, 8.0, 4.0 Hz, 1H), 3.38 − 3.47 (m, 1H), 3.18 (ddd, *J* = 13.5, 7.0, 4 Hz, 1H), 2.28 (s, 3H), 1.59 (s, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.38 (s, 3H).

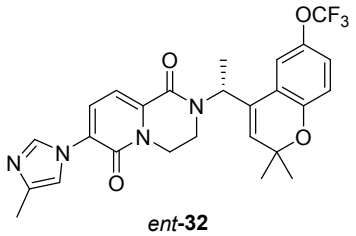
Samples of the two enantiomers were obtained via chiral HPLC (Column: Chiral Technologies CHIRALPAK® IC, 4.6 x 250 mm, 5 μm; Mobile phase: 0.1% diethylamine in MeOH (v/v); Flow rate: 1.0 mL/minute).



32

*2-{(1*S*)-1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**32**).*

m.p. 174 – 174.5 °C; LCMS *m/z* 515.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.12 (br s, 1H), 7.04 – 7.07 (m, 1H), 7.00 (br d, *J* = 9 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 5.87 (br q, *J* = 7 Hz, 1H), 5.82 – 5.84 (m, 1H), 4.24 (ddd, *J* = 14.2, 7.0, 3.9 Hz, 1H), 3.82 (ddd, *J*=14.2, 8.4, 4.0 Hz, 1H), 3.43 (ddd, *J*=13.4, 8.4, 3.9 Hz, 1H), 3.18 (ddd, *J* = 13.4, 7.0, 3.9 Hz, 1H), 2.28 (s, 3H), 1.59 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 155.5, 151.5, 142.8, 138.8, 136.3, 133.9, 131.9, 130.5, 129.9, 127.3, 122.8, 120.6, 120.4 (q, $^1J_{CF}$ = 256.0), 118.0, 116.6, 114.5, 108.9, 76.3, 47.0, 40.1, 37.8, 28.6, 26.1, 14.8, 13.6; $[\alpha]_D^{22}$ –47.9 (c 0.86, MeOH); HRMS *m/z*, calcd $[M+H]^+$ 515.1901, observed 515.1893; Retention time: 7.35 minutes (Column: Chiral Technologies CHIRALPAK® IC, 4.6 x 250 mm, 5 µm; Mobile phase: 0.1% diethylamine in methanol; Flow rate: 1.0 mL/minute).

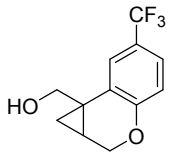


ent-**32**

*2-{(1*R*)-1-[2,2-Dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]ethyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (ent-**32**).*

LCMS *m/z* 515.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.12 (br s, 1H), 7.05 − 7.07 (m, 1H), 7.00 (br d, *J* = 9 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 5.87 (br q, *J* = 7 Hz, 1H), 5.82 − 5.84 (m, 1H), 4.24 (ddd, *J* = 14.2, 7.0, 3.9 Hz, 1H), 3.82 (ddd, *J* = 14.2, 8.4, 3.9 Hz, 1H), 3.43 (ddd, *J* = 13.4, 8.2, 4.1 Hz, 1H), 3.18 (ddd, *J* = 13.5, 7, 4 Hz, 1H), 2.28 (s, 3H), 1.6 (s, 3H, assumed; obscured by water peak), 1.47 (d, *J* = 6.7 Hz, 3H), 1.39 (s, 3H). Retention time: 10.24 min, using HPLC conditions identical to those described above for compound **32**.

Synthesis of 7-(4-methyl-1H-imidazol-1-yl)-2-{[(1aS,7bS)-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (33) and 7-(4-methyl-1H-imidazol-1-yl)-2-{[(1aR,7bR)-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methyl}-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (40)

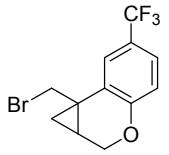


34

*[6-(Trifluoromethyl)-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methanol (**34**)*

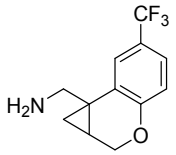
To a solution of 1-[6-(trifluoromethyl)-2*H*-chromen-4-yl]methanamine (**16**) (2.3 g, 10 mmol) in CH_2Cl_2 (40 mL) was added diiodomethane (2.47 mL, 30 mmol) at 0 ºC followed by slow addition of diethylzinc (1 M solution in hexanes, 15 mL, 15 mmol). The cold bath was removed and the reaction was stirred at ambient temperature for 3 h. Aqueous $NaHSO_4$ solution (50 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL) and CH_2Cl_2 (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (gradient: 0% to

50% EtOAc in heptane) to afford the title compound as a yellow solid (2.1 g, 8.8 mmol, 88%). GCMS *m/z* 244 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 2.0 Hz, 1H), 7.31 − 7.40 (m, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 4.37 (dd, *J* = 10.7, 1.0 Hz, 1H), 4.10 (d, 1H), 3.91 − 4.03 (m, 1H), 3.82 (d, *J* = 11.7 Hz, 1H), 1.75 (ddt, *J* = 8.5, 5.7, 1.5 Hz, 1H), 1.23 (t, *J* = 5.3 Hz, 1H), 1.10 (dd, *J* = 8.6, 5.1 Hz, 1H).



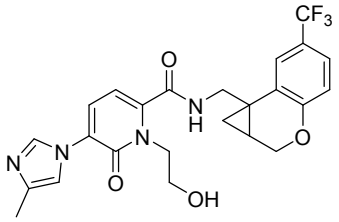
*7b-(Bromomethyl)-6-(trifluoromethyl)-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene.*

To a solution of [6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanol (2.1 g, 8.8 mmol) and carbon tetrabromide (3.48 g, 10.5 mmol) in dry CH_2Cl_2 (40 mL) was added triphenylphosphine (2.8 g, 10.5 mmol) at room temperature. The reaction was stirred at room temperature for 18 h, whereupon only 50% conversion was observed by TLC analysis. Additional carbon tetrabromide (1.8 g, 5.3 mmol) and triphenylphosphine (1.4 g, 5.2 mmol) were added to the reaction mixture, and the reaction was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (gradient: 0% to 10% EtOAc in heptane) to afford the title compound as a viscous, colorless oil (1.9 g, 6.2 mmol, 70%). GCMS *m/z* 306, 308 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.0 Hz, 1H), 7.35 – 7.45 (m, 1 H), 6.93 (d, *J* = 8.6 Hz, 1H), 4.34 (d, *J* = 10.5 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 3.89 – 4.01 (m, 1H), 3.43 (d, *J* = 10.9 Hz, 1H) 1.85 (ddt, *J* = 8.7, 6.2, 1.6 Hz, 1H), 1.56 (t, *J* = 5.7 Hz, 1H), 1.21 – 1.36 (m, 1H).



*1-[6-(Trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanamine (**35**)*

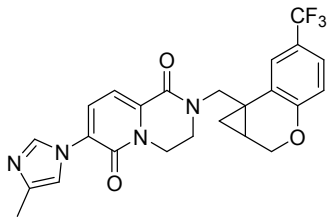
7b-(Bromomethyl)-6-(trifluoromethyl)-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene (1.9 g, 6.2 mmol) was dissolved in 7 M ammonia in MeOH (11.5 mL, 80.5 mmol). The mixture was heated at 50 ºC for 18 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 0% to 8% [2M ammonia in MeOH] in CH_2Cl_2) to afford the title compound as a yellow solid (1.4 g, 5.8 mmol, 93%). LCMS *m/z* 244.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.80 (d, *J* = 1.6 Hz, 1H), 7.45 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 4.40 (d, *J* = 10.9 Hz, 1H), 4.05 – 4.18 (m, 2H), 3.36 (s, 2H), 2.86 (d, *J* = 14.4 Hz, 1H), 2.02 (ddt, *J* = 8.5, 6.2, 1.9 Hz 1H), 1.34 (dd, *J* = 8.8, 5.3 Hz, 1H), 1.21 – 1.29 (m, 1H).



*1-(2-Hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-*N*-{[6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-1,6-dihydropyridine-2-carboxamide.*

DABAL-Me_3 (2.25 g, 8.78 mmol) was added to a solution of 1-[6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanamine (1.38 g, 5.67 mmol) in THF (100 mL) at room temperature. The reaction mixture was stirred at 45 ºC for 45 min and then at 65 ºC for 15 min. Lactone **7** (2.08 g, 8.49 mmol) was added to the reaction, and the mixture was heated at reflux for 5 h. After the reaction mixture had cooled to 0 ºC, an aqueous 1 N NaOH

solution (50 mL) was *carefully* added with vigorous stirring to quench the reaction. Water (50 mL) was added and the slurry was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was recrystallized from EtOH (20 mL) to afford the title compound as a white solid (1.21 g, 2.48 mmol, 44%). LCMS *m/z* 489.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.18 (d, *J* = 1.2 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.24 (s, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 7.4 Hz, 1H), 4.55 (d, *J* = 14.4 Hz, 1H), 4.38 (d, *J* = 10.5 Hz, 1H), 4.22 – 4.35 (m, 2H), 4.04 (d, *J* = 9.4 Hz, 1H), 3.79 (dt, *J* = 11.2, 5.5 Hz, 1H), 3.69 (dt, *J* = 11.3, 5.7 Hz, 1H), 3.20 (d, *J* = 14.4 Hz, 1H), 2.24 (s, 3H), 1.98 (dd, *J* = 8.4, 6.1 Hz, 1H), 1.15 – 1.29 (m, 2H).

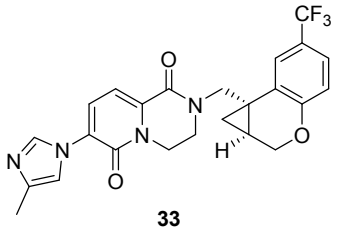


*7-(4-Methyl-1*H*-imidazol-1-yl)-2-{[6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione.*

To a solution of 1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-*N*-{[6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-1,6-dihydropyridine-2-carboxamide (1.21 g, 2.48 mmol) and triphenylphosphine (0.86 g, 3.23 mmol) in THF (80 mL) was added diethyl azodicarboxylate (0.68 mL, 3.23 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 0% to 8% [2M ammonia in MeOH] in CH_2Cl_2) to afford the title compound as a white solid (970 mg, 2.05 mmol, 83%). LCMS *m/z*

472.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.27 (m, 1H), 7.68 – 7.74 (m, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.29 (s, 1H), 7.11 (s, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.18 (d, *J* = 14.8 Hz, 1H), 4.32 – 4.48 (m, 2H), 4.02 – 4.16 (m, 2H), 3.53 – 3.69 (m, 2H), 3.01 (d, *J* = 14.8 Hz, 1H), 2.28 (s, 3H), 1.87 (dd, *J* = 8.6, 5.9 Hz, 1H), 1.25 (t, *J* = 5.5 Hz, 1H), 1.16 (dd, *J* = 8.6, 5.5 Hz, 1H). The racemic material was separated into compound **33** and its enantiomer using the following conditions: Column: Chiral Technologies CHIRALPAK® AD-H, 4.6 × 250 mm, 5 µm; column temp: 40 ºC; Mobile phase A: CO_2, Mobile phase B: 0.1% ammonium hydroxide in EtOH; Isocratic: 60:40 A/B hold for 5 min; Backpressure: 120 Bar; Flow rate: 1.5 mL/min).

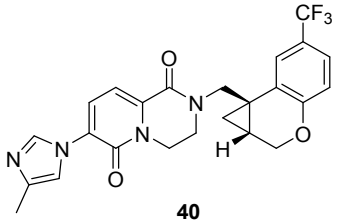
*7-(4-Methyl-1*H*-imidazol-1-yl)-2-{[(1a*S*,7b*S*)-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**33**)*



33

LCMS *m/z* 472.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.27 (m, 1H), 7.68 – 7.74 (m, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.29 (s, 1H), 7.11 (s, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.18 (d, *J* = 14.8 Hz, 1H), 4.32 – 4.48 (m, 2H), 4.02 – 4.16 (m, 2H), 3.53 – 3.69 (m, 2H), 3.01 (d, *J* = 14.8 Hz, 1H), 2.28 (s, 3H), 1.87 (dd, *J* = 8.6, 5.9 Hz, 1H), 1.25 (t, *J* = 5.5 Hz, 1H), 1.16 (dd, *J* = 8.6, 5.5 Hz, 1H); Retention time: 3.08 minutes (Column: Chiral Technologies CHIRALPAK® AD-H, 4.6 × 250 mm, 5 µm; column temp: 40 ºC; Mobile phase A: CO_2, Mobile phase B: 0.1% ammonium hydroxide in EtOH; Isocratic: 60:40 A/B hold for 5 min; Backpressure: 120 Bar; Flow rate: 1.5 mL/min).

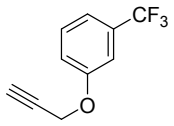
*7-(4-Methyl-1*H*-imidazol-1-yl)-2-{[(1a*R*,7b*R*)-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**40**)*



40

LCMS *m/z* 472.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.27 (m, 1H), 7.68 – 7.74 (m, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.29 (s, 1H), 7.11 (s, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.18 (d, *J* = 14.8 Hz, 1H), 4.32 – 4.48 (m, 2H), 4.02 – 4.16 (m, 2H), 3.53 – 3.69 (m, 2H), 3.01 (d, *J* = 14.8 Hz, 1H), 2.28 (s, 3H), 1.87 (dd, *J* = 8.6, 5.9 Hz, 1H), 1.25 (t, *J* = 5.5 Hz, 1H), 1.16 (dd, *J* = 8.6, 5.5 Hz, 1H); Retention time: 3.13 minutes, using HPLC conditions identical to those described above for compound **33**.

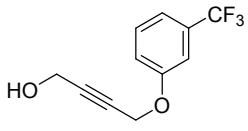
Synthesis of 7-(4-methyl-1*H*-imidazol-1-yl)-2-{[(1a*S*,7b*S*)-5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (41)



1-(Prop-2-yn-1-yloxy)-3-(trifluoromethyl)benzene.

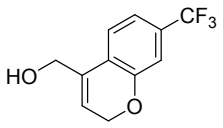
To a stirred solution of 3-(trifluoromethyl)phenol (25 g, 154 mmol) in acetone (350 mL) was added potassium carbonate (27.7 g, 201 mmol) and propargyl bromide (20.2 g, 170 mmol). The reaction mixture was refluxed for 16 h, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (300 mL) and extracted with

EtOAc (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 0% to 15% EtOAc in hexanes) to afford the title compound as a colorless liquid (22 g, 110 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.73 (d, *J* = 2.3 Hz, 2H), 2.5 (t, *J* = 2.3 Hz, 1H).



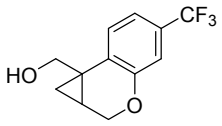
4-[3-(Trifluoromethyl)phenoxy]but-2-yn-1-ol.

To a stirred solution of 1-(prop-2-yn-1-yloxy)-3-(trifluoromethyl)benzene (22.0 g, 110 mmol) in THF (220 mL) at –78 °C was added *n*-BuLi (2.3 M in hexanes, 45.2 mL, 104 mmol), and the reaction mixture was stirred at –78 °C for 30 min. Paraformaldehyde (6.93g, 77 mmol) was added, and the mixture was warmed to room temperature and was stirred for 3 h. The reaction was quenched with water (300 mL) and extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 0% to 30% EtOAc in hexanes) to afford the title compound as a brown liquid (23 g, 99 mmol, 90%). GCMS *m/z* 230 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.18 (s, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 4.76 (s, 2H), 4.30 (d, *J* = 5.9 Hz, 2H), 1.68 (t, *J* = 6.2 Hz, 1H).



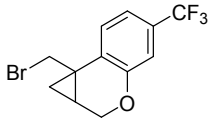
*[7-(Trifluoromethyl)-2*H*-chromen-4-yl]methanol.*

To a solution of 4-[3-(trifluoromethyl)phenoxy]but-2-yn-1-ol (2.0 g, 8.7 mmol) in CH_2Cl_2 (20 mL) was added (acetonitrile)[(2-biphenyl)di-*tert*-butyl phosphine]gold(l) hexafluoroantimonate (336 mg, 0.44 mmol). The mixture was stirred at room temperature for 2 h and then diluted with CH_2Cl_2. The mixture was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: 20% EtOAc in hexanes) to afford the title compound as a light yellow oil (650 mg, 2.8 mmol, 32%). GCMS *m/z* 230 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 5.95 (br s, 1H), 4.87 (br s, 2H), 4.50 (br s, 2H).



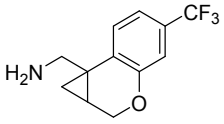
[5-(Trifluoromethyl)-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methanol.

Diiodomethane (0.88 mL, 10.9 mmol) was added to a solution of [7-(trifluoromethyl)-2*H*-chromen-4-yl]methanol (500 mg, 2.2 mmol) in CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C, and a solution of diethylzinc (1 M in hexanes, 5.4 mL, 5.4 mmol) was added and the reaction was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 and then quenched with an aqueous 1 N $NaHSO_4$ solution. The mixture was separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: 30% EtOAc in hexanes) to afford the title compound as a yellow oil (270 mg, 1.12 mmol, 51%). GCMS *m/z* 244 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.08 (d, *J* = 1.5 Hz, 1H), 4.36 (d, *J* = 10.3 Hz, 1H), 4.10 (d, *J* = 12.2 Hz, 1H), 3.95 – 3.89 (m, 1H), 3.79 (d, *J* = 11.7 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.30 – 1.25 (m, 1H), 1.09 (dd, *J* = 5.1, 8.6 Hz, 1H).



*7b-(Bromomethyl)-5-(trifluoromethyl)-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene*.

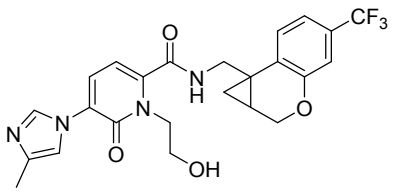
Carbon tetrabromide (733 mg, 2.21 mmol) and triphenylphosphine (580 mg, 2.21 mmol) were added to a solution of [5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanol (270 mg, 1.1 mmol) in CH_2Cl_2 (5 mL), and the reaction mixture was stirred at room temperature for 16 h. The reaction was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 0% to 5% EtOAc in hexanes) to afford the title compound as a colorless oil (250 mg, 0.80 mmol, 73%). GCMS *m/z* 306 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.10 (s, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.14 (d, *J* = 11.2 Hz, 1H), 3.91 (d, *J* = 10.8 Hz, 1H), 3.42 (d, *J* = 11.2 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.60 (t, *J* = 5.6 Hz, 1H), 1.30 (dd, *J* = 5.1, 8.6 Hz, 1H).



*1-[5-(Trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanamine*.

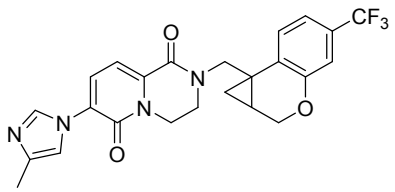
A solution of 7b-(bromomethyl)-5-(trifluoromethyl)-1,1a,2,7b-tetrahydrocyclopropa-[*c*]chromene (250 mg, 0.81 mmol) in 7 N ammonia in MeOH (5 mL, 35 mmol) was stirred at 90 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 5% MeOH in CH_2Cl_2, and the mixture was filtered and concentrated under reduced pressure. The crude residue was triturated with pentane to afford the title compound as an off-white solid (180 mg, 0.74 mmol, 90%). LCMS *m/z* 244 $[M+H]^+$; ^{1}H NMR (400

MHz, DMSO-d_6) δ 7.91 – 7.79 (m, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 14.2 Hz, 1H), 3.96 (d, *J* = 10.3 Hz, 1H), 2.78 (d, *J* = 13.7 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.35 (dd, *J* = 5.1, 8.6 Hz, 1H), 1.13 (t, *J* = 5.4 Hz, 1H).



*1-(2-Hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo*-N-*{[5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-1,6-dihydropyridine-2-carboxamide*.

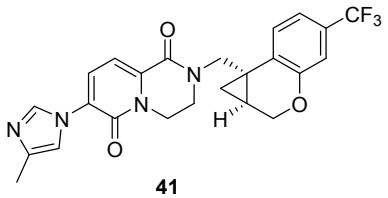
DABAL-Me_3 (632 mg, 2.47 mmol) was added to a solution of 1-[5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanamine (300 mg, 1.24 mmol) in THF (5 mL). The reaction mixture was heated to 40 °C for 45 min and then lactone **7** (302 mg, 1.24 mmol) was added. The reaction was heated to 65 °C for 5 h, whereupon the mixture was cooled to room temperature and quenched with aqueous 1 N NaOH (2 mL). The resulting slurry was diluted with water and extracted with 5% MeOH in CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was triturated with 10% EtOAc in hexanes to afford the title compound as an off-white solid (350 mg, 0.72 mmol, 58%). LCMS *m/z* 489.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 – 9.05 (m, 1H), 8.10 (s, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.32 – 7.24 (m, 2H), 7.10 (s, 1H), 6.30 (d, *J* = 7.3 Hz, 1H), 4.90 (t, *J* = 5.6 Hz, 1H), 4.34 (d, *J* = 10.8 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.94 (d, *J* = 10.8 Hz, 1H), 3.60 – 3.50 (m, 2H), 3.22 – 3.17 (m, 1H), 2.13 (s, 3H), 1.98 (t, *J* = 7.3 Hz, 1H), 1.28 – 1.23 (m, 1H), 1.11 – 1.05 (m, 1H).



*7-(4-Methyl-1*H*-imidazol-1-yl)-2-{[5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione* (*rac-**41***).

Methanesulfonyl chloride (0.83 mL, 1.08 mmol) was added to a solution of 1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-*N*-{[5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-1,6-dihydropyridine-2-carboxamide (350 mg, 0.72 mmol) and triethylamine (0.2 mL, 1.4 mmol) in CH_2Cl_2 (5 mL) at –10 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in a mixture of THF (2.5 mL) and DMF (2.5 mL) and TBD (337 mg, 2.42 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, whereupon the reaction was concentrated under reduced pressure. The crude residue was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified using silica gel chromatography (eluent: 4% MeOH in CH_2Cl_2) to afford the title compound as an off-white solid (130 mg, 0.28 mmol, 39%). LCMS *m/z* 470 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.12 – 7.08 (m, 2H), 5.23 (d, *J* = 14.7 Hz, 1H), 4.39 (d, *J* = 10.8 Hz, 1H), 4.29 – 4.21 (m, 1H), 4.20 – 4.11 (m, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 3.63 (t, *J* = 7.1 Hz, 2H), 2.95 (d, *J* = 14.7 Hz, 1H), 2.27 (s, 3H), 1.89 – 1.84 (m, 1H), 1.29 (t, *J* = 5.4 Hz, 1H), 1.15 (dd, *J* = 5.4, 8.8 Hz, 1H).

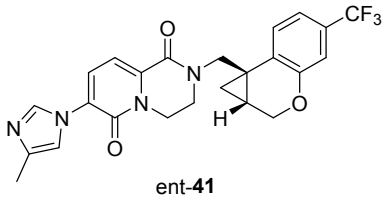
The racemate (100 mg) was separated into its enantiomers using chiral HPLC (Column: CHIRALPAK AD-H, 21 × 250 mm, 5 µm; mobile phase: MeOH/diethylamine: 100/0.1 (v/v); flow rate: 20 mL/min. U.V.: 345 nm. Runtime: 35 min.



41

*7-(4-methyl-1*H*-imidazol-1-yl)-2-{[(1a*S*,7b*S*)-5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**41**)*

LCMS *m/z* 470 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.12 – 7.08 (m, 2H), 5.23 (d, *J* = 14.7 Hz, 1H), 4.39 (d, *J* = 10.8 Hz, 1H), 4.29 – 4.21 (m, 1H), 4.20 – 4.11 (m, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 3.63 (t, *J* = 7.1 Hz, 2H), 2.95 (d, *J* = 14.7 Hz, 1H), 2.27 (s, 3H), 1.89 – 1.84 (m, 1H), 1.29 (t, *J* = 5.4 Hz, 1H), 1.15 (dd, *J* = 5.4, 8.8 Hz, 1H). Retention time: 8.84 min (Column: CHIRALPAK® AD-H, 21 × 250 mm, 5 µm; mobile phase: MeOH/diethylamine: 100/0.1 (v/v); flow rate: 20 mL/min. U.V.: 345 nm. Runtime: 35 min.)

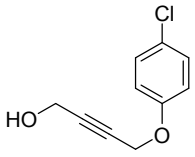


ent-**41**

*7-(4-Methyl-1*H*-imidazol-1-yl)-2-{[(1a*R*,7b*R*)-5-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (ent-**41**)*

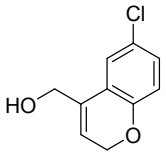
LCMS *m/z* 470 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.12 – 7.08 (m, 2H), 5.23 (d, *J* = 14.7 Hz, 1H), 4.39 (d, *J* = 10.8 Hz, 1H), 4.29 – 4.21 (m, 1H), 4.20 – 4.11 (m, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 3.63 (t, *J* = 7.1 Hz, 2H), 2.95 (d, *J* = 14.7 Hz, 1H), 2.27 (s, 3H), 1.89 – 1.84 (m, 1H), 1.29 (t, *J* = 5.4 Hz, 1H), 1.15 (dd, *J* = 5.4, 8.8 Hz, 1H); Retention time = 11.02 min (Column: CHIRALPAK® AD-H, 21 × 250 mm, 5 μm; mobile phase: MeOH/diethylamine: 100/0.1 (v/v); flow rate: 20 mL/min. U.V.: 345 nm. Runtime: 35 min)

Synthesis of 2-{[(1a*S*,7b*S*)-6-chloro-1a,2-dihydrocyclopropa[c]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-a]pyrazine-1,6-dione (42).



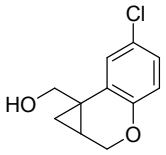
4-(4-Chlorophenoxy)but-2-yn-1-ol.

To a solution of 4-chlorophenol (10 g, 93 mmol) and but-2-yne-1,4-diol (9.55 g, 111 mmol) in THF (100 mL) was added triphenylphosphine (29.1 g, 111 mmol) at room temperature and the reaction mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (22.0 mL, 111 mmol) was added drop-wise, and the reaction was allowed warm to room temperature and stirred for 14 h. The reaction mixture was diluted with EtOAc and water. The layers were separated and the organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue obtained was purified by silica gel chromatography (gradient: 10% to 15% EtOAc in hexanes) to afford the title compound (7.4 g, 38 mmol, 40%) as a white solid. GCMS *m/z* 196 (M^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.88 (m, 2H), 4.70 (m, 2H), 4.30 (d, *J* = 5.9 Hz, 2H).



*(6-Chloro-2*H*-chromen-4-yl)methanol.*

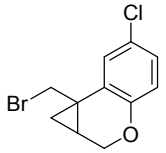
To a solution of 4-(4-chlorophenoxy)but-2-yn-1-ol (7.4 g, 37.8 mmol) in CH_2Cl_2 (158 mL) was added (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (0.146 g, 0.189 mmol) at room temperature. The reaction was stirred for 2 h, whereupon it was diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 25% to 30% EtOAc in hexanes) to afford the title compound (4.5 g, 23 mmol, 61%) as an off-white solid. GCMS *m/z* 196 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 2.4 Hz, 1H), 7.07 (dd, *J* = 2.4, 8.6 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.88 (t, *J* = 3.5 Hz, 1H), 4.80 (m, 2H), 4.45 (dd, *J* = 1.3, 5.8 Hz, 2H).



*(6-Chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methanol.*

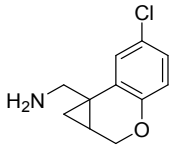
To a solution of (6-chloro-2*H*-chromen-4-yl)methanol (1.0 g, 5.1 mmol) in CH_2Cl_2 (50 mL) was added diiodomethane (2.46 mL, 30.6 mmol) at 0 °C followed by the slow addition of diethylzinc (1 M in hexanes, 15.3 mL, 15.3 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 3 h. The reaction was filtered and the solids were washed with CH_2Cl_2. The combined filtrate and washings were then quenched with aqueous 1 M $NaHSO_4$ solution and extracted with CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure and purified by silica gel chromatography (gradient: 30% to 50% EtOAc in hexanes) to afford the title compound as a solid (0.58 g, 2.8 mmol,

54%). GCMS *m/z* 210 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.5 Hz, 1H), 7.03 (dd, *J* = 2.5, 8.6 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 4.29 (d, *J* = 10.6 Hz, 1H), 4.03 (dd, *J* = 4.4, 11.7 Hz, 1H), 3.88 (d, *J* = 10.6 Hz, 1H), 3.75 (dd, *J* = 6.5, 11.7 Hz, 1H), 1.68 (m, 1H), 1.21 (t, *J* = 5.3 Hz, 1H), 1.04 (dd, *J* = 5.0, 8.4 Hz, 1H).



7b-(Bromomethyl)-6-chloro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene.

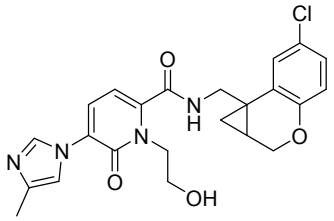
To a solution of (6-chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methanol (0.58 mg, 2.8 mmol) and carbon tetrabromide (1.83 g, 5.52 mmol) in dry CH_2Cl_2 (34 mL) was added triphenylphosphine (1.44 g, 5.52 mmol), and the reaction was stirred at room temperature for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water, and the combined organic fractions were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by silica gel chromatography (eluent: 10% EtOAc in hexanes) to afford the title compound as a viscous, colorless oil (500 mg, 1.8 mmol, 66%). GCMS *m/z* 274 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 4.25 (d, *J* = 10.7 Hz, 1H), 4.05 (d, *J* = 11.2 Hz, 1H), 3.86 (d, *J* = 10.6 Hz, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 1.77 (m, 1H), 1.53 (m, 1H), 1.25 (m, 1H).



(6-Chloro-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl)methanamine.

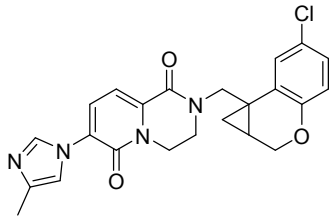
A mixture of 7b-(bromomethyl)-6-chloro-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene (460 mg, 1.68 mmol) and 7 N ammonia in MeOH (7 mL, 49 mmol) was heated at 70 °C in a sealed tube for 3 h. The reaction was cooled to room temperature and the mixture was

concentrated under reduced pressure. The resulting residue was triturated with 20% diethyl ether in pentane to afford the title compound as a yellow solid (300 mg, 1.43 mmol, 85%). LCMS *m/z* 210 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, *J* = 2.4 Hz, 1H), 7.56 (br s, 2H), 7.15 (dd, *J* = 2.4, 8.6 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.30 (d, *J* = 10.6 Hz, 1H), 3.96 (d, *J* = 14.1 Hz, 1H), 3.89 (d, *J* = 10.3 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 1.98 (m, 1H), 1.29 (dd, *J* = 4.8, 8.6 Hz, 1H), 1.05 (m, 1H).



N-*[(6-Chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methyl]-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide.*

To a solution of (6-chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methanamine (450 mg, 2.15 mmol) in THF (36 mL) at room temperature was added DABAL-Me_3 (1.1 g, 4.3 mmol). The reaction mixture was heated to 50 °C for 45 min, whereupon lactone **7** (792 mg, 3.23 mmol) was added. The reaction was stirred at 65 °C for 5 h, and was then cooled to room temperature and carefully quenched with aqueous 1 N NaOH solution (1 mL). The resulting slurry was diluted with water and extracted with 5% MeOH in CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with hexanes to afford the title compound as a yellow solid (700 mg, 1.54 mmol, 71%). LCMS *m/z* 455 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (br s, 1H), 8.10 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.30 (s, 1H), 7.10 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.28 (d, *J* = 7.5 Hz, 1H), 4.85 (t, *J* = 5.2 Hz, 1H), 4.20 (m, 4H), 3.86 (d, *J* = 10.6 Hz, 1H), 3.54 (m, 2H), 3.17 (m, 1H), 2.14 (s, 3H), 1.92 (m, 1H), 1.20 (m, 1H), 1.01 (m, 1H).

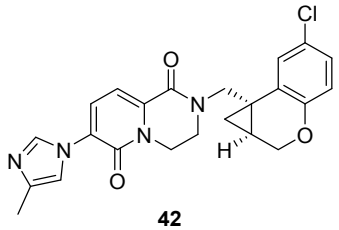


*2-[(6-Chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methyl]-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (rac-**42**)*.

To a solution of *N*-[(6-chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methyl]-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide (700 mg, 1.54 mmol) in CH_2Cl_2 (56 mL) was added triethylamine (0.43 mL, 3.08 mmol,) at room temperature. The mixture was cooled in an ice/salt bath, and methanesulfonyl chloride (0.18 mL, 2.31 mmol) was added drop-wise over 5 min. The cooling bath was removed and the reaction stirred at room temperature for 2 h. The mixture was partitioned between CH_2Cl_2 and water, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in a mixture of THF (15 mL) and DMF (2 mL), and TBD (644 mg, 4.62 mmol) was added at room temperature. The reaction mixture was stirred for 14 h and then quenched with water with vigorous stirring. The resulting mixture was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 2% MeOH in CH_2Cl_2) to afford the title compound as a white solid (380 mg, 0.87 mmol, 56%). LCMS *m/z* 437 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.37 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.06 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.03 (d, *J* = 14.4 Hz, 1H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.25 (m, 1H), 4.04 (m, 1H), 3.98 (d, *J* = 10.7 Hz, 1H), 3.77 (m, 1H), 3.55 (m, 1H), 2.96 (d, *J* = 14.5 Hz, 1H), 2.14 (s, 3H), 2.08 (m, 1H), 1.12 (m, 1H), 0.98 (m, 1H).

The racemate was separated into its enantiomers (compounds **42** and ent-**42**) via chiral HPLC separation (Column: Chiral Technologies CHIRALPAK® IA, 5 μm; Mobile phase: 0.1% diethylamine in MeOH; flow rate: 1.0 mL/min).

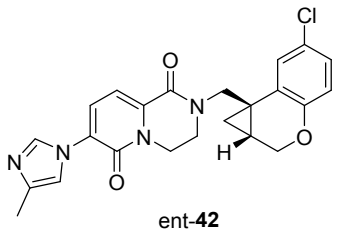
*2-{[(1a*S*,7b*S*)-6-Chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**42**).*



42

LCMS *m/z* 437 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.37 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.06 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.03 (d, *J* = 14.4 Hz, 1H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.25 (m, 1H), 4.04 (m, 1H), 3.98 (d, *J* = 10.7 Hz, 1H), 3.77 (m, 1H), 3.55 (m, 1H), 2.96 (d, *J* = 14.5 Hz, 1H), 2.14 (s, 3H), 2.08 (m, 1H), 1.12 (m, 1H), 0.98 (m, 1H); Retention time = 8.85 min (Column: Chiral Technologies CHIRALPAK® IA, 5 μm; Mobile phase: 0.1% diethylamine in MeOH; flow rate: 1.0 mL/min).

*2-{[(1a*R*,7b*R*)-6-Chloro-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (ent-**42**).*

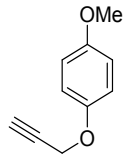


ent-**42**

LCMS *m/z* 437 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.37 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.06 (dd, *J* = 2.5, 8.5 Hz,

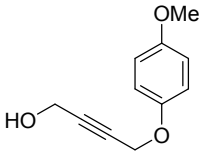
1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.03 (d, *J* = 14.4 Hz, 1H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.25 (m, 1H), 4.04 (m, 1H), 3.98 (d, *J* = 10.7 Hz, 1H), 3.77 (m, 1H), 3.55 (m, 1H), 2.96 (d, *J* = 14.5 Hz, 1H), 2.14 (s, 3H), 2.08 (m, 1H), 1.12 (m, 1H), 0.98 (m, 1H); Retention time = 11.79 min (Column: Chiral Technologies CHIRALPAK® IA, 5 μm; Mobile phase: 0.1% diethylamine in MeOH; flow rate: 1.0 mL/min).

Synthesis of 2-{[(1aS,7bS)-6-methoxy-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methyl}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (43).



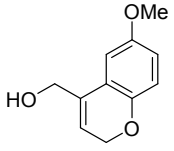
1-Methoxy-4-(prop-2-yn-1-yloxy)benzene.

To a slurry of 4-methoxyphenol (6.51 g, 52.4 mmol) and potassium carbonate (21.7 g, 157 mmol) in DMF (40 mL) was added propargyl bromide (15.6 g, 105 mmol). The reaction mixture was stirred at room temperature for 2 h, whereupon it was poured into aqueous 0.5 N NaOH solution (150 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with aqueous 1 N NaOH solution (50 mL), aqueous 3 N LiCl solution (20 mL), and brine (25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the title compound as a yellow oil, which was used without further purification (8.18 g, 50.4 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.97 (m, 2 H), 6.83 – 6.89 (m, 2H), 4.65 (d, *J* = 2.3 Hz, 2H), 3.78 (s, 3H), 2.51 (t, *J* = 2.3 Hz, 1H).



4-(4-Methoxyphenoxy)but-2-yn-1-ol.

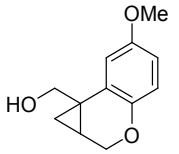
To a stirred solution of 1-methoxy-4-(prop-2-yn-1-yloxy)benzene (8.18 g, 50.4 mmol) in THF (150 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes, 24.2 mL, 60.5 mmol). The reaction mixture was stirred at –78 °C for 30 min. Paraformaldehyde (2.27 g, 75.7 mmol) was added and the mixture was warmed to room temperature and stirred for 1.5 h. After consumption of starting material was observed by TLC, the reaction mixture was quenched with water (250 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (120 – 140 °C, 0.4 torr) to afford the title compound as an orange oil (6.98 g, 36.3 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.96 (m, 2H), 6.82 – 6.89 (m, 2H) 4.69 (t, J = 1.8 Hz, 2H), 4.32 (t, J = 1.8 Hz, 2H), 3.78 (s, 3H), 1.60 (br s, 1H).



*(6-Methoxy-2*H*-chromen-4-yl)methanol.*

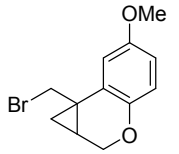
To a solution of 4-(4-methoxyphenoxy)but-2-yn-1-ol (6.98 g, 36.3 mmol) in dry CH_2Cl_2 (75 mL) was added indium(III) iodide (5.0 g, 10.2 mmol). The reaction mixture was stirred at room temperature for 18 h and was then poured into saturated aqueous $NaHCO_3$ solution (100 mL). The mixture was diluted with EtOAc (200 mL) and filtered through a pad of Celite®. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and

evaporated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 5% to 40% EtOAc in hexanes) to afford the title compound (6.18 g, 31.9 mmol, 88%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 – 6.82 (m, 2H), 6.68 – 6.75 (m, 1H), 5.91 (t, *J* = 3.7 Hz, 1H), 4.72 – 4.78 (m, 2H), 4.49 (d, *J* = 1.2 Hz, 2H), 3.78 (s, 3H).



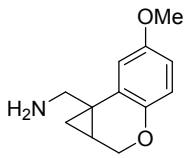
*(6-Methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methanol.*

To a solution of (6-methoxy-2*H*-chromen-4-yl)methanol (0.80 g, 4.1 mmol) in CH_2Cl_2 (25 mL) was added diiodomethane (1.03 mL, 12.5 mmol) at 0 °C followed by slow addition of diethylzinc (1 M solution in hexanes, 6.24 mL, 6.24 mmol). The reaction mixture was allowed to slowly warm to room temperature and stirred for 18 h. The reaction was quenched with saturated $NaHSO_4$ solution and extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 10% to 30% EtOAc in hexanes) to afford the title compound (329 mg, 1.56 mmol, 38%) as a light yellow solid. GCMS *m/z* 206 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 2.7 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.65 (dd, *J* = 8.8, 2.9 Hz, 1H), 4.27 (dd, *J* = 10.5, 1.2 Hz, 1H), 4.08 (d, *J* = 11.7 Hz, 1H), 3.84 – 3.90 (m, 1H), 3.80 (s, 3H), 3.74 (d, *J* = 11.7 Hz, 1 H), 1.68 (ddt, *J* = 8.4, 5.6, 1.6 Hz, 1H), 1.23 – 1.28 (m, 1H), 1.03 (dd, *J* = 8.6, 4.7 Hz, 1H).



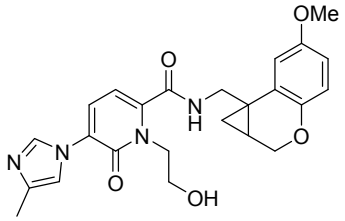
*7b-(Bromomethyl)-6-methoxy-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene.*

To a solution of (6-methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methanol (329 mg, 1.60 mmol) and carbon tetrabromide (661 mg, 1.90 mmol) in dry CH_2Cl_2 (5 mL) was added triphenylphosphine (529 mg, 1.99 mmol) at room temperature. The reaction mixture was stirred for 20 min and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (gradient: 0% to 10% EtOAc in hexanes) to afford the title compound (361 mg, 1.34 mmol, 84%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 3.1 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1 H), 6.65 – 6.70 (m, 1 H), 4.24 (d, *J* = 10.9 Hz, 1H), 4.07 (d, *J* = 10.9 Hz, 1H), 3.85 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3 H), 3.47 (d, *J* = 10.9 Hz, 1H), 1.73 – 1.80 (m, 1H), 1.56 – 1.60 (m, 1H), 1.20 – 1.26 (m, 1 H).



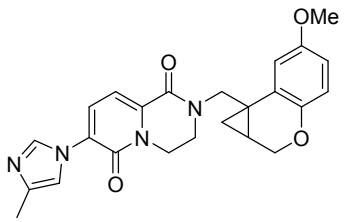
*(6-Methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methanamine.*

A mixture of 7b-(bromomethyl)-6-methoxy-1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene (330 mg, 1.23 mmol) and concentrated ammonium hydroxide (5 mL) in dioxane (5 mL) was heated to 100 °C in a sealed tube for 30 min. The reaction was allowed to cool to room temperature and was subsequently diluted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the title compound (212 mg, 1.03 mmol, 84%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 3.1 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 6.64 (dd, *J* = 8.8, 2.9 Hz, 1H), 4.25 (d, *J* = 10.5 Hz, 1H), 3.90 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.79 (s, 3H), 3.58 (d, *J* = 13.7 Hz, 1H), 2.53 (d, *J* = 13.7 Hz, 1H), 1.55 – 1.64 (m, 1H), 1.18 (t, *J* = 5.3 Hz, 1H), 0.96 (dd, *J* = 8.4, 4.9 Hz, 1H).



1-(2-Hydroxyethyl)-N-*[(6-methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methyl]-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide.*

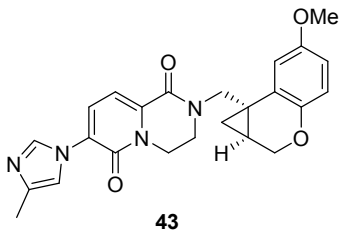
To a solution of (6-methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methanamine (212 mg, 1.03 mmol) in THF (10 mL) at room temperature was added DABAL-Me_3 (341 mg, 1.29 mmol). The mixture was heated to 40 °C for 20 min, whereupon lactone **7** (380 mg, 1.55 mmol) was added. The reaction was heated to reflux for 4 h and then stirred at 50 °C for an additional 18 h. The mixture was cooled to room temperature and *carefully* treated with aqueous 1 N NaOH solution (20 mL), and then EtOAc (50 mL). The quenched reaction mixture was stirred at room temperature for 20 min, whereupon the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and then concentrated under reduced pressure to afford the title compound (320 mg, 0.70 mmol, 68%) as a yellow solid. LCMS *m/z* 451 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.16 (d, *J* = 1.2 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 1.2 Hz, 1H), 7.08 (d, *J* = 3.2 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 4.50 (d, *J* = 14.4 Hz, 1H), 4.27 (q, *J* = 5.5 Hz, 2H), 4.22 (d, *J* = 10.2 Hz, 1H), 3.89 (dd, *J* = 10.7, 1.8 Hz, 1H), 3.76 – 3.82 (m, 1H), 3.75 (s, 3H), 3.66 – 3.73 (m, 1H), 3.09 (d, *J* = 14.4 Hz, 1H), 2.22 (d, *J* = 1.2 Hz, 3H), 1.83 (dd, *J* = 8.2, 5.9 Hz, 1H), 1.09 – 1.19 (m, 2H).



*2-[(6-Methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methyl]-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione*.

To a stirred solution of 1-(2-hydroxyethyl)-*N*-[(6-methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl)methyl]-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide (320 mg, 0.71 mmol) in THF (20 mL) was added triethylamine (0.13 mL, 0.92 mmol) at room temperature, and the mixture was cooled in an ice/salt bath. Methanesulfonyl chloride (68 µL, 0.85 mmol) was added drop-wise over 5 min. The cooling bath was removed and the reaction was stirred at room temperature for 2 h. The reaction was cooled in an ice bath and TBD (300 mg, 2.15 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was partitioned between water (50 mL) and EtOAc (50 mL), and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel chromatography (gradient: 0% to 10% MeOH in EtOAc) to afford the title compound as a light yellow solid (158 mg, 0.36 mmol, 51%). LCMS *m/z* 433 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.26 (d, *J* = 1.4 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.29 (m, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 2.9 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.59 (dd, *J* = 8.8, 2.9 Hz, 1H), 5.27 (d, *J* = 14.5 Hz, 1H), 4.21 – 4.30 (m, 2H), 4.08 – 4.18 (m, 1H), 4.00 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.76 (dd, *J* = 6.2, 4.2 Hz, 1H), 3.69 (s, 3H), 3.60 – 3.68 (m, 1H), 2.88 (d, *J* = 14.8 Hz, 1H), 2.20 – 2.25 (m, 3H), 1.96 (dd, *J* = 8.5, 5.8 Hz, 1H), 1.05 – 1.14 (m, 2H).

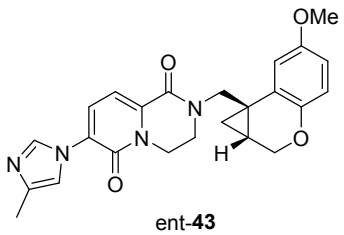
The racemate was separated into its enantiomers (compounds **43** and ent-**43**) via chiral HPLC (column: Chiral Technologies CHIRALPAK® AS-H, 4.6 × 100 mm, 5 µm; Mobile phase: 4:1 carbon dioxide / MeOH; Flow rate: 1.5 mL/minute).



43

*2-{[(1a*S*,7b*S*)-6-Methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (**43**)*

Compound **43** has a retention time of t_R = 8.27 min using the following chiral HPLC method: column: Chiral Technologies CHIRALPAK® AS-H, 4.6 × 100 mm, 5 μm; Mobile phase: 4:1 carbon dioxide / MeOH; Flow rate: 1.5 mL/minute.

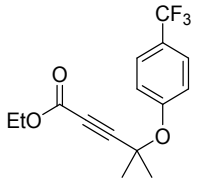


ent-**43**

*2-{[(1a*R*,7b*R*)-6-Methoxy-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione (ent-**43**)*

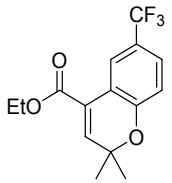
Compound ent-**43** has a retention time of t_R = 6.80 min using the following chiral HPLC method: column: Chiral Technologies CHIRALPAK® AS-H, 4.6 × 100 mm, 5 μm; Mobile phase: 4:1 carbon dioxide / MeOH; Flow rate: 1.5 mL/minute

Synthesis of 1-[2,2-dimethyl-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methanamine.



ethyl 4-methyl-4-[4-(trifluoromethyl)phenoxy]pent-2-ynoate.

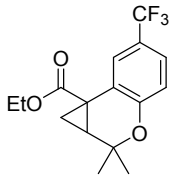
n-BuLi (2.5 M solution in hexanes, 16.0 mL, 40.0 mmol) was added drop-wise to a −78 °C solution of 1-[(2-methylbut-3-yn-2-yl)oxy]-4-(trifluoromethyl)benzene (*vide supra*) (8.2 g, 36 mmol) in THF (100 mL), while the reaction temperature was maintained below −60 °C. The reaction mixture was stirred for 15 min at −78 °C, whereupon ethyl chloroformate (5.30 mL, 53.7 mmol) was added drop-wise, at a rate that maintained the reaction temperature below −70 °C. After 15 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred at that temperature for 30 min. Saturated aqueous NH_4Cl solution (50 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, at which point it was diluted with *tert*-butyl methyl ether (500 mL). The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient: 0% to 5% EtOAc in heptane) to afford the title compound as an oil (10 g, 33 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.59 (m, 2H), 7.24 – 7.29 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.72 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H).



*ethyl 2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromene-4-carboxylate.*

(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (250 mg, 0.32 mmol) was added to a solution of ethyl 4-methyl-4-[4-(trifluoromethyl)phenoxy]pent-2-

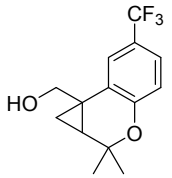
ynoate (10 g, 33 mmol) in 1,2-dichloroethane (100 mL), and the reaction mixture was heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature and then filtered through a pad of silica gel. The silica gel pad was rinsed with dichloromethane (3 × 200 mL). The filtrate was concentrated under reduced pressure to provide the product as an oil (9.6 g, 32 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br d, *J* = 2 Hz, 1H), 7.41 – 7.45 (m, 1H), 6.90 (br d, *J* = 8.5 Hz, 1H), 6.71 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.50 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H).



ethyl 2,2-dimethyl-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[c]chromene-7b(1H)-carboxylate.

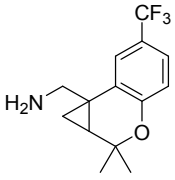
Potassium *tert*-butoxide (1 M solution in THF, 35 mL, 35 mmol) was added to a suspension of trimethylsulfoxonium iodide (7.6 g, 34 mmol) in THF (75 mL), and the mixture was stirred for 30 min. A solution of ethyl 2,2-dimethyl-6-(trifluoromethyl)-2*H*-chromene-4-carboxylate (7.00 g, 23.3 mmol) in THF (25 mL) was added, and the reaction mixture was stirred for 30 min, whereupon it was partitioned between saturated aqueous NH_4Cl solution (100 mL) and *tert*-butyl methyl ether (500 mL). The organic layer was washed with water (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the product as a thick oil, which was used without additional purification (7.3 g, 23 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.18 (m, 1H), 7.35 (ddq, *J* = 8.5, 2.3, 0.7 Hz, 1H), 6.83 – 6.86 (m, 1H), 4.31 (dq, half of ABX_3 pattern, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, half of ABX_3 pattern, *J* = 10.8, 7.1 Hz, 1H), 2.07 (dd, half of ABX pattern, *J* = 9.0, 6.6 Hz, 1H), 1.99 (dd,

half of ABX pattern, *J* = 9.0, 4.4 Hz, 1H), 1.53 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.29 (dd, *J* = 6.6, 4.4 Hz, 1H), 1.28 (s, 3H).



*[2,2-dimethyl-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanol.*

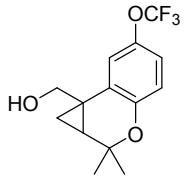
Diisobutylaluminum hydride (1.5 M solution in toluene, 50 mL, 75 mmol) was added drop-wise over 30 min to a −78 °C solution of ethyl 2,2-dimethyl-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromene-7b(1*H*)-carboxylate (7.3 g, 23 mmol) in THF (100 mL). After 15 min at −78 °C, the reaction mixture was warmed to room temperature, stirred for 30 min, and cooled in an ice bath. Half-saturated aqueous citric acid solution (50 mL) was added, the ice bath was removed, and the mixture was stirred at room temperature for 16 h, whereupon it was extracted with diethyl ether (500 mL). The organic layer was washed with water (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 5% to 30% EtOAc in heptane), providing the product as a thick oil (5.7 g, 21 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br d, *J* = 2.2 Hz, 1H), 7.35 (ddq, *J* = 8.4, 2.2, 0.7 Hz, 1H), 6.84 – 6.87 (m, 1H), 4.12 (d, *J* = 11.7 Hz, 1H), 3.73 (d, *J* = 11.7 Hz, 1H), 1.58 (dd, *J* = 8.6, 5.7 Hz, 1H), 1.52 (s, 3H), 1.22 (s, 3H), 1.12 (br dd, *J* = 5.6, 5.1 Hz, 1H), 1.05 (dd, *J* = 8.5, 5.0 Hz, 1H).



*1-[2,2-dimethyl-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanamine.*

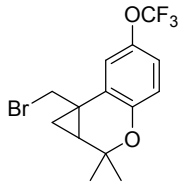
p-Toluenesulfonic anhydride (7.19 g, 22.0 mmol) was added in portions over 10 min to a solution of [2,2-dimethyl-6-(trifluoromethyl)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanol (5.00 g, 18.4 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. Triethylamine (4.0 mL, 29 mmol) was added drop-wise, and stirring was continued at 0 °C for 30 min, whereupon the reaction mixture was allowed to warm to room temperature and stir for 1 hour. *tert*-Butyl methyl ether (500 mL) was added, and the mixture was washed with water (100 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure providing the intermediate tosylate as a thick oil, which was used without further purification (7.80 g, 18.3 mmol, 99%). This material was dissolved in methanol (50 mL), added to a solution of ammonia in methanol (7 M, 300 mL, 2.1 mol) and stirred at room temperature for 24 h. Volatiles were removed under reduced pressure, and the residue was partitioned between *tert*-butyl methyl ether (500 mL) and aqueous 1 M NaOH solution (100 mL) with vigorous stirring for 15 min. The aqueous layer was extracted with *tert*-butyl methyl ether (500 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 0% to 5% MeOH in CH_2Cl_2), providing the product as a thick oil (3.43 g, 12.6 mmol, 69%). LCMS *m/z* 271.9 $[M+1]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.69 (m, 1H), 7.31 –7.36 (m, 1H), 6.86 (br d, *J* = 8.3 Hz, 1H), 3.62 (d, *J* = 13.8 Hz, 1H), 2.51 (d, *J* = 13.8 Hz, 1H), 1.51 (s, 3H), 1.49 (dd, *J* = 8.4, 5.7 Hz, 1H), 1.24 (s, 3H), 1.06 (dd, *J* = 5.5, 5.0 Hz, 1H), 0.97 (dd, *J* = 8.5, 5.0 Hz, 1H).

Synthesis of 2-{[(1a*S*,7b*S*)-2,2-dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa-[c]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (45).



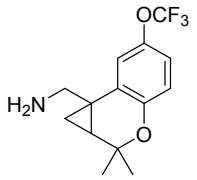
*[2,2-Dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanol.*

Diiodomethane (4.4 mL, 55 mmol) was added to a 0 °C solution of [2,2-dimethyl-6-(trifluoromethoxy)-2*H*-chromen-4-yl]methanol (*vide supra*) (2.5 g, 9.1 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at 0 °C for 10 min, whereupon diethylzinc (1 M in solution in hexanes, 27.3 mL, 27.3 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was diluted with CH_2Cl_2 and aqueous $NaHSO_4$ solution and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 15% to 20% EtOAc in hexanes), which provided the product as an off-white solid (1.9 g, 6.6 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (br d, *J* = 2.6 Hz, 1H), 6.94 (br d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 4.04 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.70 (dd, *J* = 11.9, 6.6 Hz, 1H), 1.50 – 1.56 (m, 2H), 1.50 (s, 3H), 1.19 (s, 3H), 1.15 (dd, *J* = 5.4, 5.3 Hz, 1H), 1.02 (dd, *J* = 8.6, 4.9 Hz, 1H).



*7b-(Bromomethyl)-2,2-dimethyl-6-(trifluoromethoxy)-1,1a,2,7b-tetrahydrocyclopropa[*c*]-chromene.*

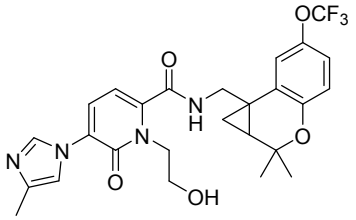
To a solution of [2,2-dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanol (1.9 g, 6.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added carbon tetrabromide (2.6 g, 7.8 mmol), followed by drop-wise addition of a solution of triphenylphosphine (2.0 g, 7.6 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. At this point, the reaction was diluted with CH_2Cl_2 and water was added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution followed by brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (gradient: 0% to 5% EtOAc in hexanes) to afford the title compound as a brown liquid (1.4 g, 4.0 mmol, 61%). GCMS *m/z* 350, 352 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.30 (m, 1H, assumed; obscured by solvent peak), 6.97 (br d, *J* = 9 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 4.18 (d, *J* = 11.0 Hz, 1H), 3.22 (d, *J* = 11.2 Hz, 1H), 1.61 (dd, *J* = 8.7, 6.2 Hz, 1H), 1.48 (s, 3H), 1.46 –1.51 (m, 1H), 1.24 (s, 3H), 1.20 – 1.26 (m, 1H).



*1-[2,2-Dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanamine.*

A solution of 7b-(bromomethyl)-2,2-dimethyl-6-(trifluoromethoxy)-1,1a,2,7b-tetrahydro-cyclopropa[*c*]chromene (1.4 g, 4.0 mmol) in 7 N methanolic ammonia (25 mL, 175 mmol) was heated in a sealed tube at 80 °C for 5 h. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was washed with pentane and dissolved in CH_2Cl_2. After basification with aqueous saturated $NaHCO_3$ solution, the mixture was extracted with a solution of 5% MeOH in CH_2Cl_2. The combined

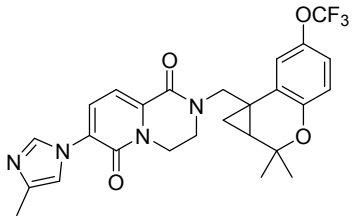
organic layers were washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the product as a brown liquid (600 mg, 2.09 mmol, 52%). LCMS *m/z* 287.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, *J* = 2.7 Hz, 1H), 7.00 (br d, *J* = 9 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 3.20 (d, *J* = 13.4 Hz, 1H), 2.60 (d, *J* = 13.2 Hz, 1H), 1.61 (dd, *J* = 8.4, 5.5 Hz, 1H), 1.41 (s, 3H), 1.11 (s, 3H), 1.00 (dd, *J* = 8.3, 4.4 Hz, 1H), 0.81 (dd, *J* = 5.4, 4.6 Hz, 1H).



N-*{[2,2-Dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methyl}-1-(2-hydroxyethyl)-5-(4-methyl-1H-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide.*

1-[2,2-Dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methanamine (600 mg, 2.09 mmol) was dissolved in THF (6.0 mL), and DABAL-Me_3 (1.0 g, 3.9 mmol) was added. The reaction mixture was warmed to 40 °C for 45 min, whereupon lactone **7** (512 mg, 2.09 mmol) was introduced, and the reaction mixture was heated to 65 °C for 5 h. The reaction was allowed to cool to room temperature. Aqueous 1 N NaOH solution (3 mL) was added, and the resulting slurry was diluted with water and extracted with a solution of 5% MeOH in CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with pentane to afford the product as an off-white solid (800 mg, 1.50 mmol, 72%). LCMS *m/z* 533.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.11 (br t, *J* = 6.0 Hz, 1H), 8.10 (d, *J* = 1.1 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.51 (m, 1H), 7.28 – 7.31 (m, 1H), 7.05 (br d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.18 (d, *J* = 7.6 Hz, 1H), 4.88 (dd, *J* = 5.6,

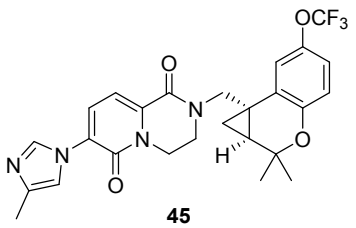
5.4 Hz, 1H), 4.16 – 4.28 (m, 2H), 4.13 (dd, *J* = 14, 6.5 Hz, 1H), 3.53 – 3.60 (m, 2H), 3.21 (dd, *J* = 14, 5 Hz, 1H), 2.13 (s, 3H), 1.88 (dd, *J* = 8.3, 5.6 Hz, 1H), 1.43 (s, 3H), 1.17 (dd, *J* = 8.4, 4.9 Hz, 1H), 1.14 (s, 3H), 0.95 (dd, *J* = 5.5, 5.0 Hz, 1H).



*2-{[2,2-Dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[c]chromen-7b(1H)-yl]methyl}-7-(4-methyl-1H-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (rac-**45**).*

To a solution of *N*-{[2,2-dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-1-(2-hydroxyethyl)-5-(4-methyl-1*H*-imidazol-1-yl)-6-oxo-1,6-dihydropyridine-2-carboxamide (800 mg, 1.50 mmol) in CH_2Cl_2 (10 mL) at −10 °C was added triethylamine (524 μL, 3.76 mmol), followed by drop-wise addition of methanesulfonyl chloride (175 μL, 2.26 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide a brown solid, which was dissolved in THF (10 mL). To this solution was added TBD (1.0 g, 7.2 mmol). The reaction mixture was allowed to stir at room temperature for 16 h, whereupon it was concentrated under reduced pressure, diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Preparative HPLC yielded racemic material rac-**45** as a white solid (220 mg, 0.43 mmol, 29% over two steps). LCMS *m/z* 515.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* = 1.0 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.54 (m, 1H), 7.38 (br s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.99 –

7.04 (m, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 4.96 (d, *J* = 14.4 Hz, 1H), 4.06 – 4.23 (m, 2H), 3.65 – 3.81 (m, 2H), 3.00 (d, *J* = 14.9 Hz, 1H), 2.14 (s, 3H), 2.07 (dd, *J* = 8, 6 Hz, 1H), 1.44 (s, 3H), 1.20 (s, 3H), 1.07 (dd, *J* = 8.6, 4.8 Hz, 1H), 0.93 (dd, *J* = 5, 5 Hz, 1H).



45

*2-{[(1a*S*,7b*S*)-2,2-Dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa-[*c*]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2H-pyrido[1,2-*a*]pyrazine-1,6-dione (**45**)*

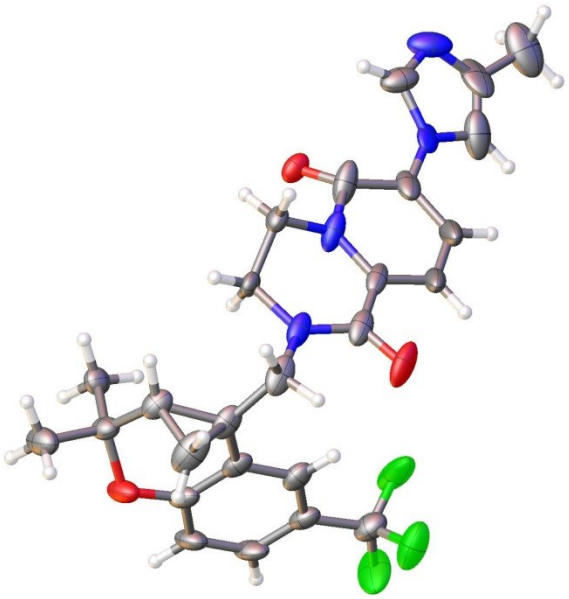
Samples of compound **45** and its enantiomer (ent-**45**) were obtained by separation of 2-{[2,2-dimethyl-6-(trifluoromethoxy)-1a,2-dihydrocyclopropa[*c*]chromen-7b(1*H*)-yl]methyl}-7-(4-methyl-1*H*-imidazol-1-yl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrazine-1,6-dione using chiral HPLC (Column: Chiral Technologies CHIRALPAK® IC, 5 µm; Mobile phase: 0.1% diethylamine in MeOH). Compound **45** was the first-eluting enantiomer (t_R = 8.93 min, see below), obtained as an off-white solid (50 mg, 97 µmol, 23%). Its enantiomer, ent-**45**, was the second-eluting enantiomer (t_R = 11.10 min), also isolated as an off-white solid (50 mg, 97 µmol, 23%).

Characterization data for compound **45**: m.p. 166 – 166.5 °C; LCMS *m/z* 515.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.78 (d, *J*=7.8 Hz, 1H), 7.49 (br s, 1H), 7.25 – 7.35 (m, 2H), 6.95 (br d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 5.11 (d, *J* = 14.8 Hz, 1H), 4.22 – 4.24 (m, 2H), 3.79 – 3.82 (m, 2H), 3.01 (d, *J* = 14.8 Hz, 1H), 2.23 (s, 3H), 1.99 – 2.04 (m, 1H), 1.50 (s, 3H), 1.28 (s, 3H), 1.08 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.9, 157.4, 151.4, 144.4, 138.9, 138.1, 136.3, 131.3, 130.4, 129.2, 122.1 (q, $^1J_{CF}$ = 255 Hz),

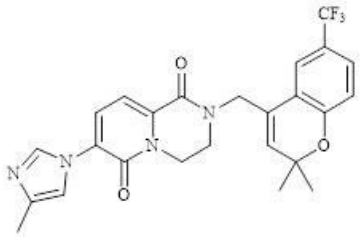
121.0, 120.4, 120.3, 116.6, 110.2, 73.3, 50.9, 45.0, 41.2, 35.7, 28.5, 26.3, 21.5, 16.0, 13.3; $[\alpha]_D^{22}$ –12.1 (c 1.17, MeOH); HRMS *m/z*, calcd $[M+H]^+$ 515.1901, observed 515.1898; Retention time: 8.93 minutes (Column: Chiral Technologies CHIRALPAK® IC, 4.6 x 250 mm, 5 µm; Mobile phase: 0.1% diethylamine in methanol; Flow rate: 1.0 mL/minute).

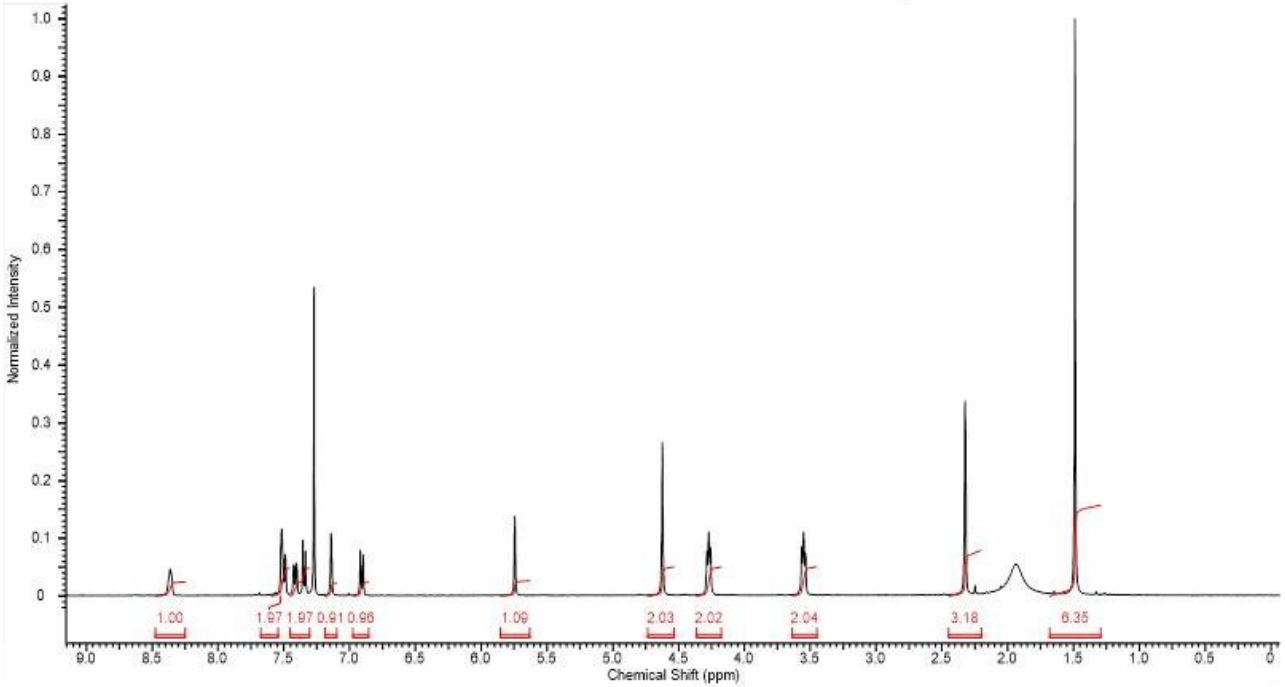
Characterization data for compound ent-**45**: LCMS *m/z* 515.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.78 (d, *J*=7.8 Hz, 1H), 7.49 (br s, 1H), 7.25 – 7.35 (m, 2H), 6.95 (br d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 5.11 (d, *J* = 14.8 Hz, 1H), 4.22 – 4.24 (m, 2H), 3.79 – 3.82 (m, 2H), 3.01 (d, *J* = 14.8 Hz, 1H), 2.23 (s, 3H), 1.99 – 2.04 (m, 1H), 1.50 (s, 3H), 1.28 (s, 3H), 1.08 (d, *J* = 7.4 Hz, 2H); Retention time: 11.10 minutes (Column: Chiral Technologies CHIRALPAK® IC, 4.6 x 250 mm, 5 µm; Mobile phase: 0.1% diethylamine in methanol; Flow rate: 1.0 mL/minute).

Single-crystal X-ray determination of 44

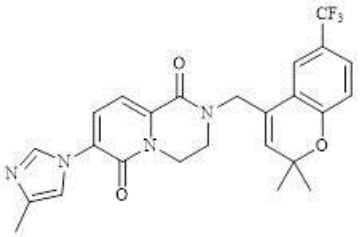


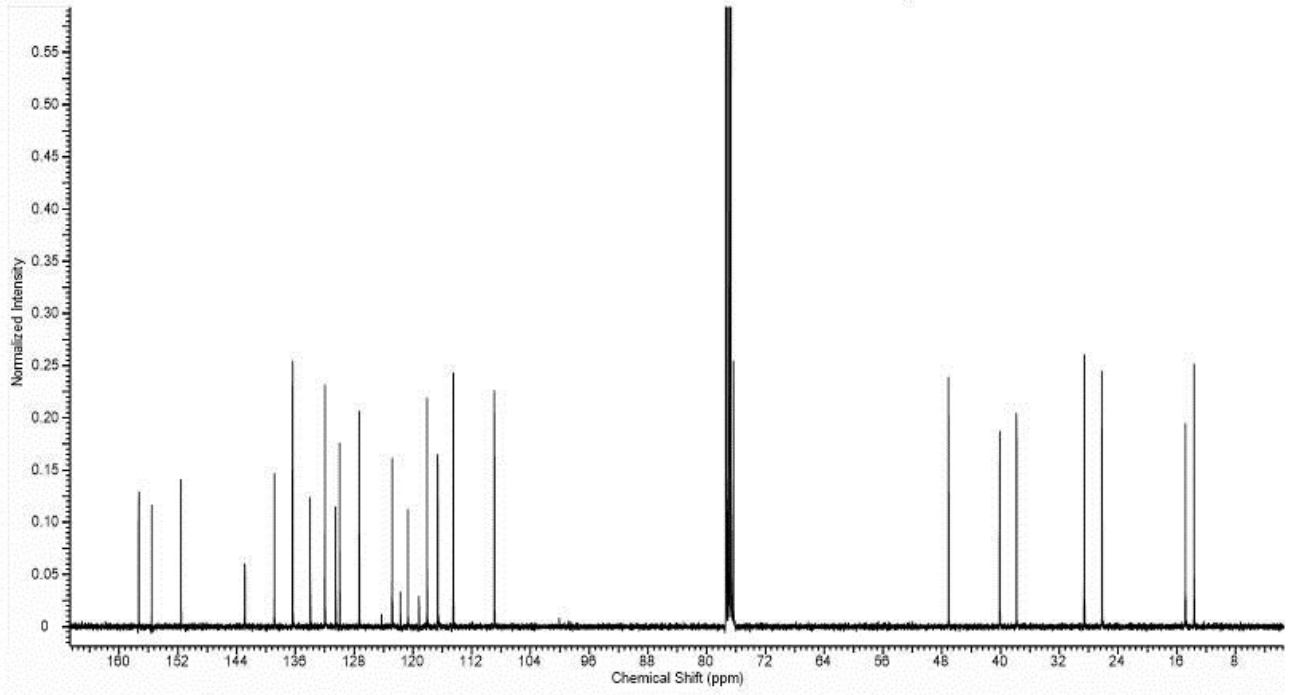
Compound 20


CF3
O
N
N
N
N
O
O

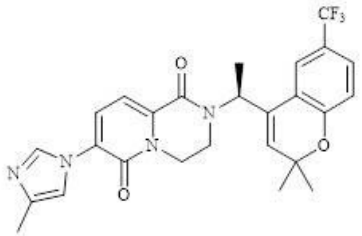

Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.97
1.97
0.91
0.96
1.09
2.03
2.02
2.04
3.18
6.35
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

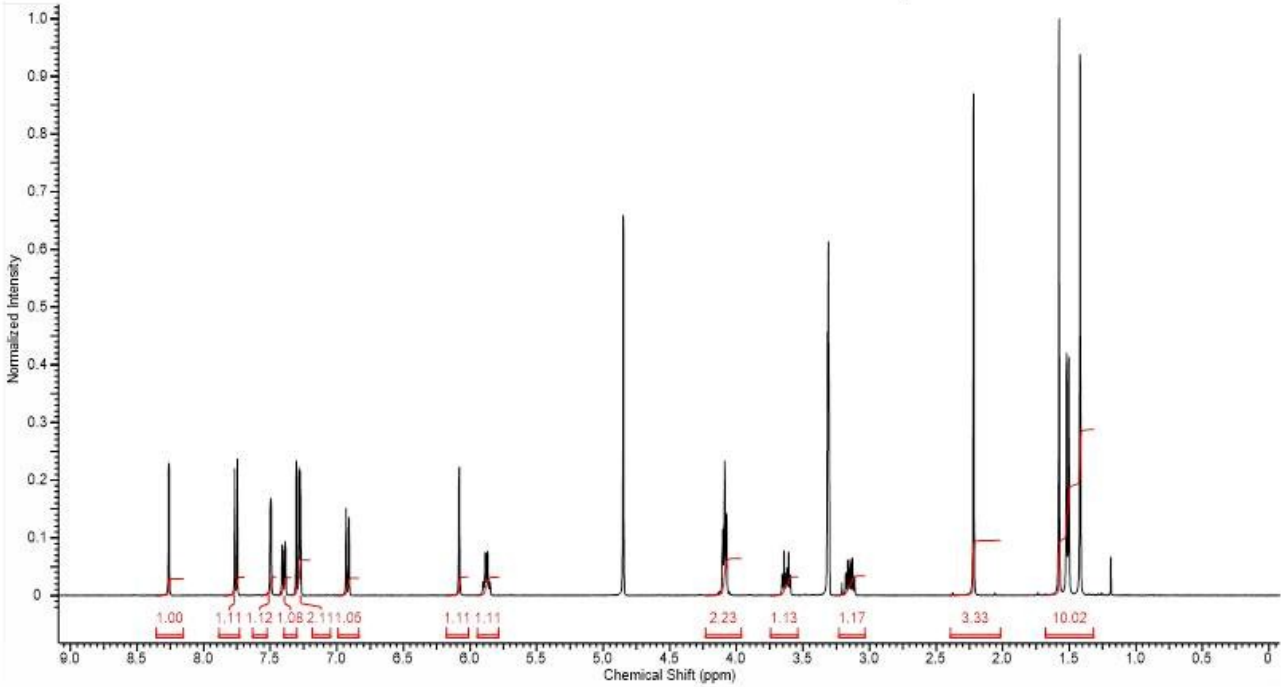
Compound 20


CF3
O
N
N
N
N
O
O

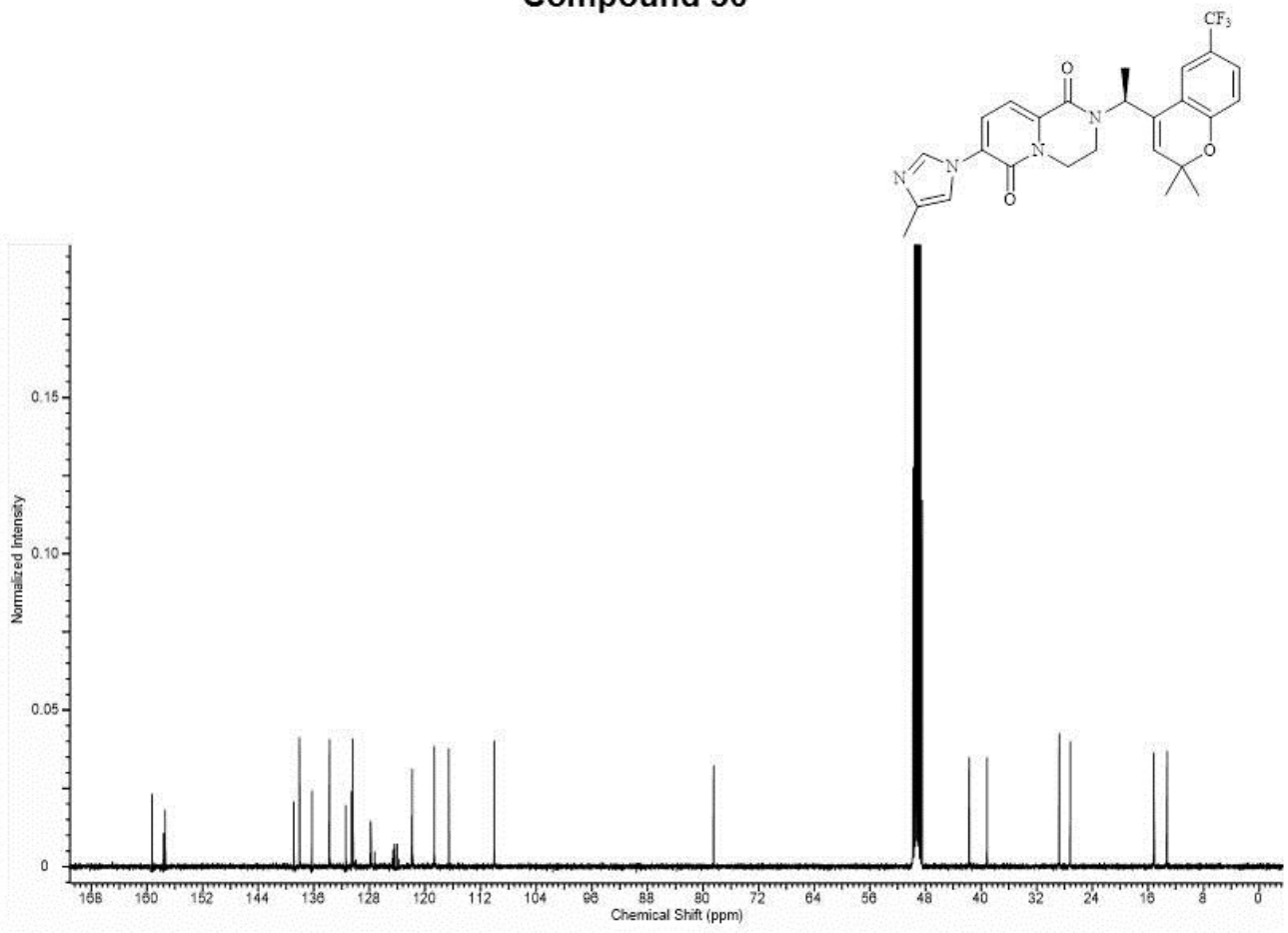

Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

Compound 30

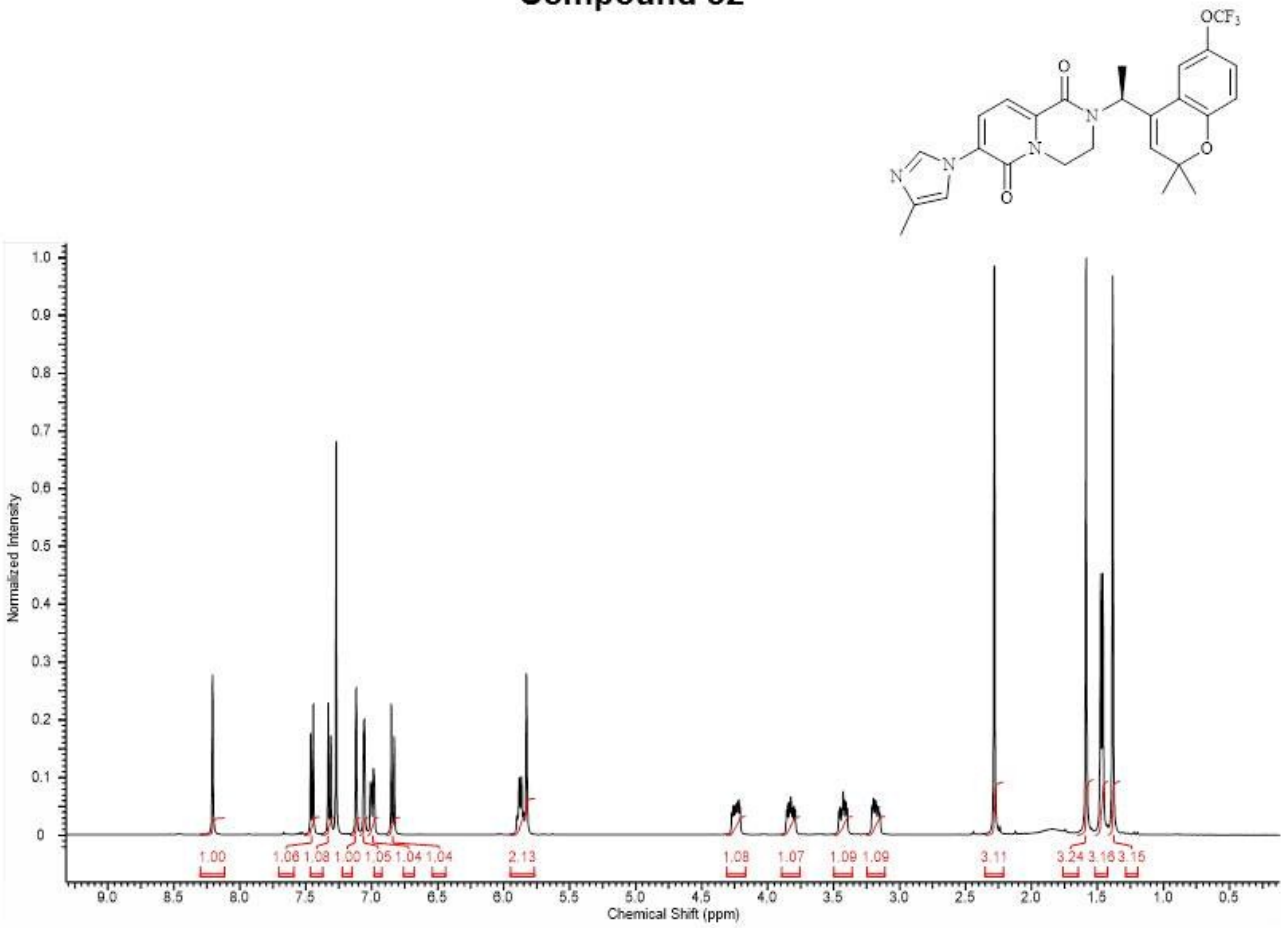

CF3
O
N
N
N
N
O
O


Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.11
1.12
1.08
2.11
1.05
1.11
1.11
2.23
1.13
1.17
3.33
10.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

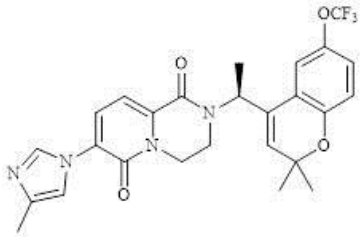
Compound 30

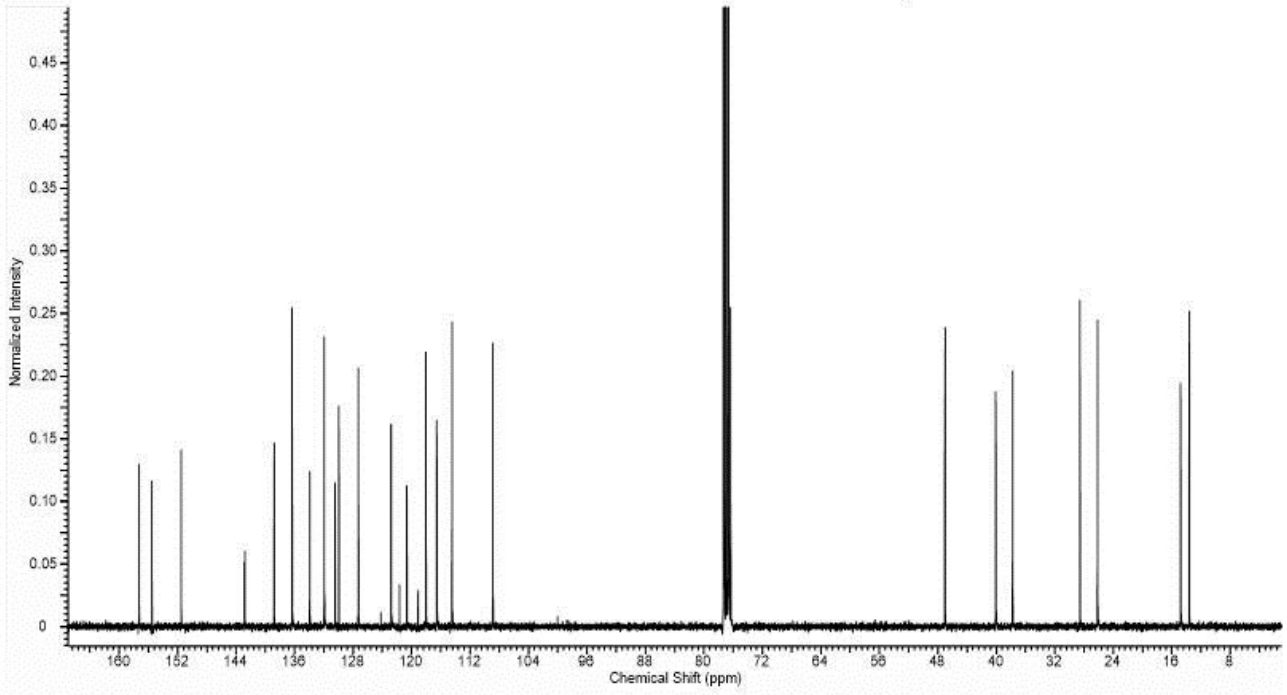

CF3
O
N
N
N
N
O
O
0.15
0.10
0.05
0
Normalized Intensity
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

Compound 32

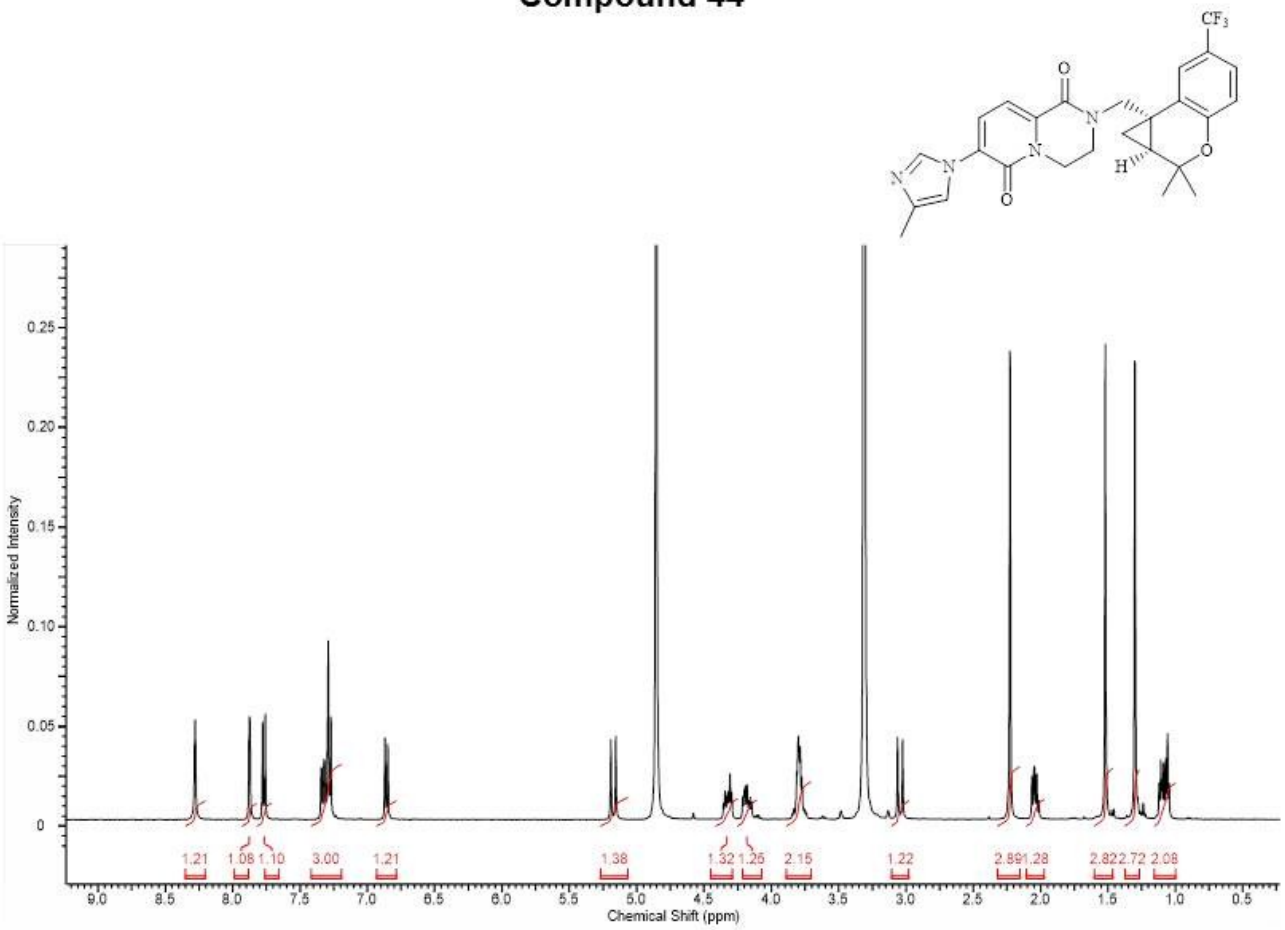

OCF3
O
N
N
N
N
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.06
1.08
1.00
1.05
1.04
1.04
2.13
1.08
1.07
1.09
1.09
3.11
3.24
3.16
3.15
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

Compound 32

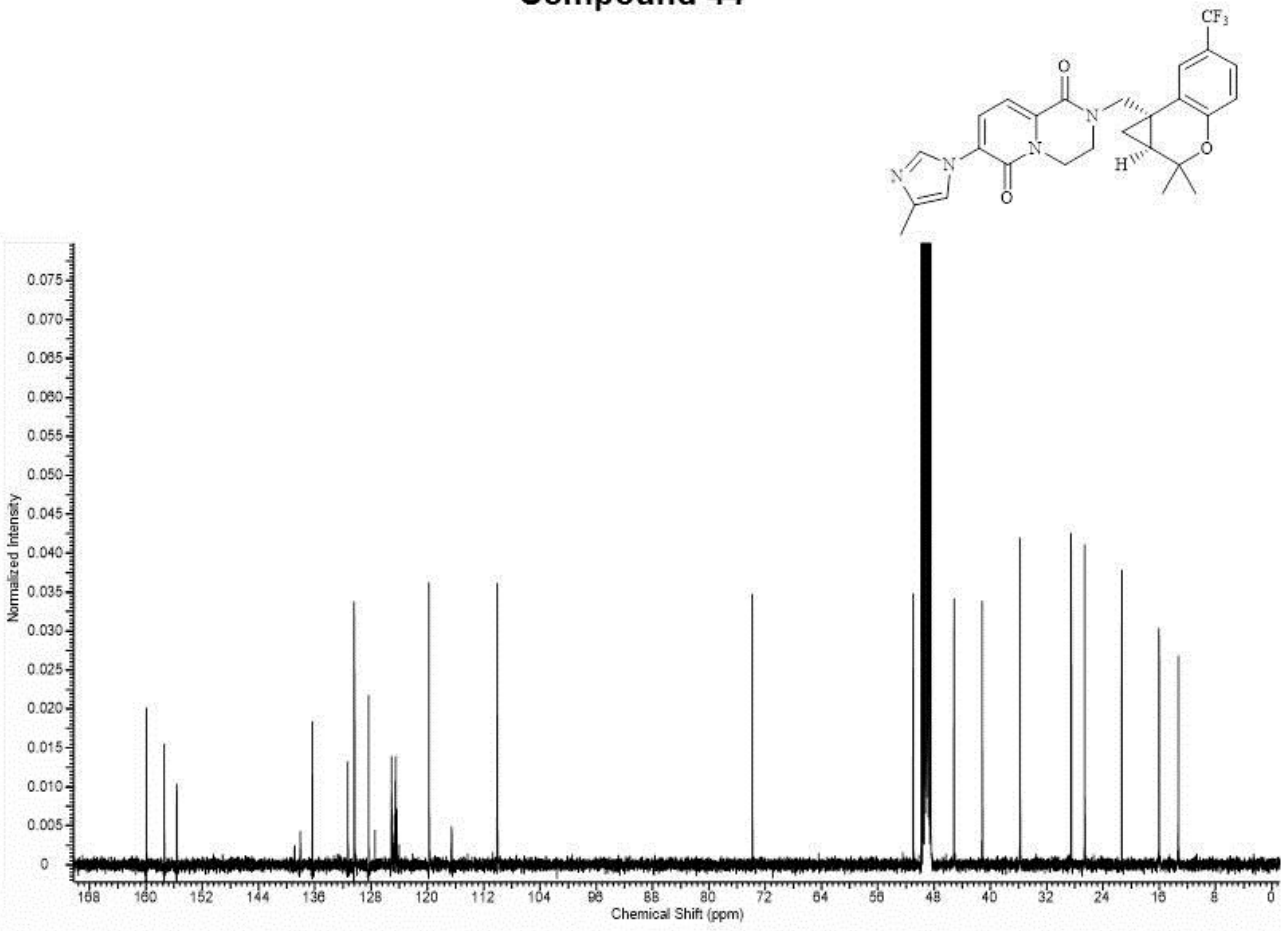

OCF3
O
N
N
N
N
O
O


Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

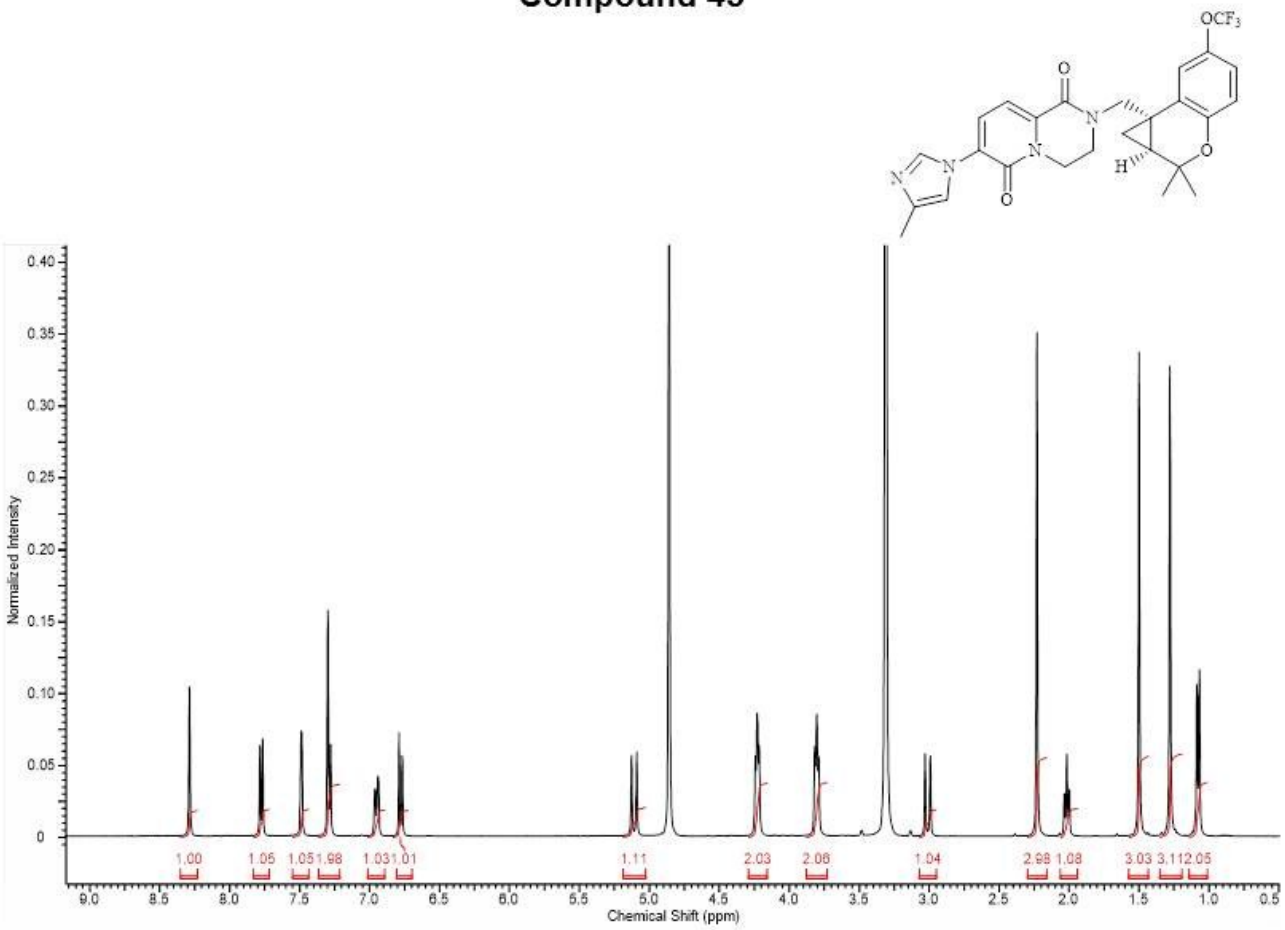
Compound 44


Normalized Intensity
0.25
0.20
0.15
0.10
0.05
0
1.21
1.08
1.10
3.00
1.21
1.38
1.32
1.25
2.15
1.22
2.89
1.28
2.82
2.72
2.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

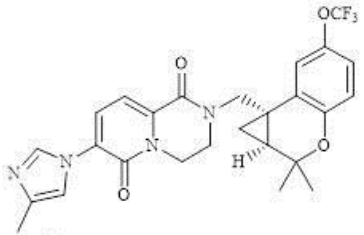
Compound 44

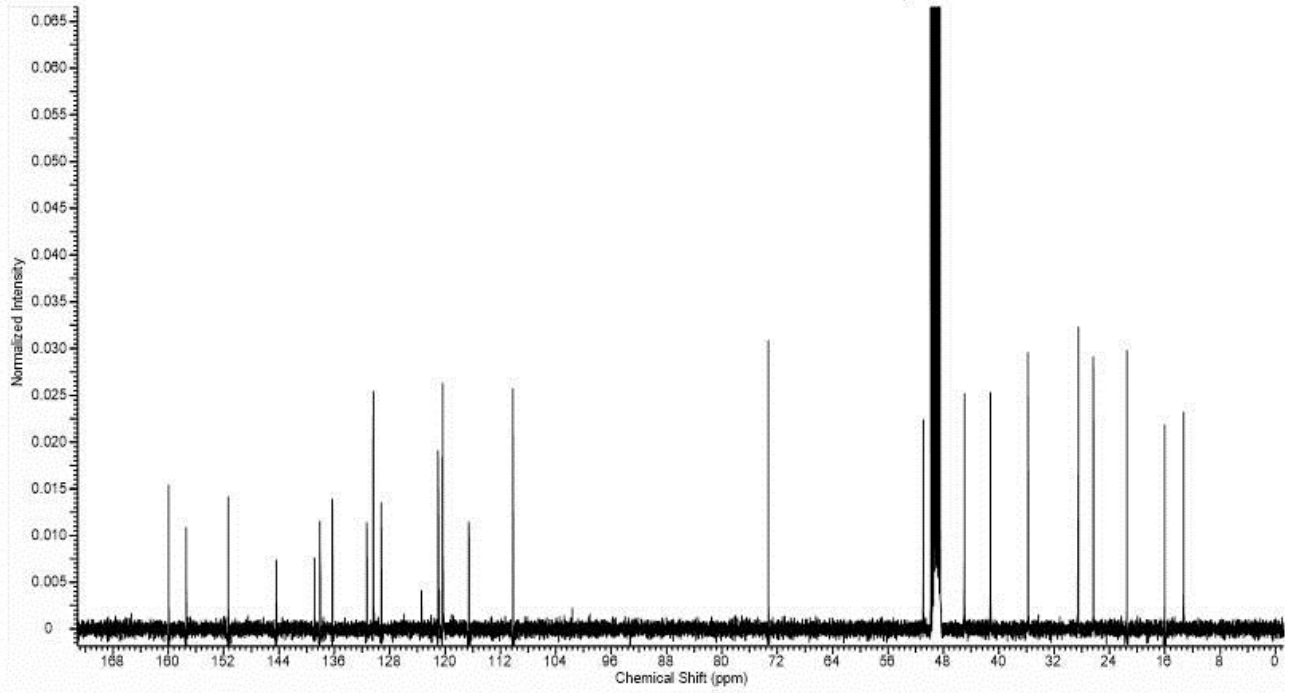

CF3
O
N
N
N
O
H
O
Normalized Intensity
0.075
0.070
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

Compound 45


OCF3
O
N
N
N
N
O
O
H
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.00
1.05
1.05
1.98
1.03
1.01
1.11
2.03
2.06
1.04
2.98
1.08
3.03
3.11
2.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

Compound 45


OCF3
O
N
N
N
O
H
O


Normalized Intensity
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)