Optimization of Small Molecules that Sensitize HIV-1 Infected Cells to Antibody Dependent Cellular Cytotoxicity

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Supporting Information

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Summary of Crystallographic Data

Table S1. Data collection and refinement statistics

	LM/HT $gp120_{CRF01\_AE}$ $core_e$ - (S)-MCG-IV-226
Data collection	
Wavelength, Å	1.033
Space group	$P2_12_12_1$
Cell parameters	
a, b, c,	66.4, 66.9, 85.4
α, β, γ, °	90, 90, 90
Complexes/a.u.	1
Resolution, (Å)	50-2.4 (2.53-2.4)
# of reflections	
Total	35,416
Unique	12,065
R_{merge}[a], %	16.4 (74.9)
R_{pim}[b], %	10.2 (46.9)
$CC_{1/2}$[c]	0.98 (0.63)
I/σ	3.4 (0.8)
Completeness, %	79.1 (82.3)
Redundancy	2.9 (2.8)
Refinement Statistics	
Resolution, Å	50.0 – 2.4
R[d] %	21.6
R_{free}[e], %	27.5
# of atoms	
Protein	2,667
Water	80
Ligand/Ion	179
Overall B value $(Å)^2$	
Protein	30
Water	28
Ligand/Ion	40
RMSD[f]	
Bond lengths, Å	0.006
Bond angles, °	1.0
Ramachandran[g]	
favored, %	96.4
allowed, %	3.6
outliers, %	0.0
PDB ID	6OOO

Values in parentheses are for highest-resolution shell

[a] $R_{merge} = \sum|I - \langle I \rangle| / \sum I$, where I is the observed intensity and $\langle I \rangle$ is the average intensity obtained from multiple observations of symmetry-related reflections after rejections

[b] R_{pim} = as defined in (Weiss, 2001)

[c] $CC_{1/2}$ = as defined by Karplus and Diederichs (Karplus and Diederichs, 2012)

[d] $R = \sum||F_o| - |F_c|| / \sum|F_o|$, where F_o and F_c are the observed and calculated structure factors, respectively

[e] R_{free} = as defined by Brünger (Brunger, 1997)

[f] RMSD = Root mean square deviation

[g] Calculated with MolProbity

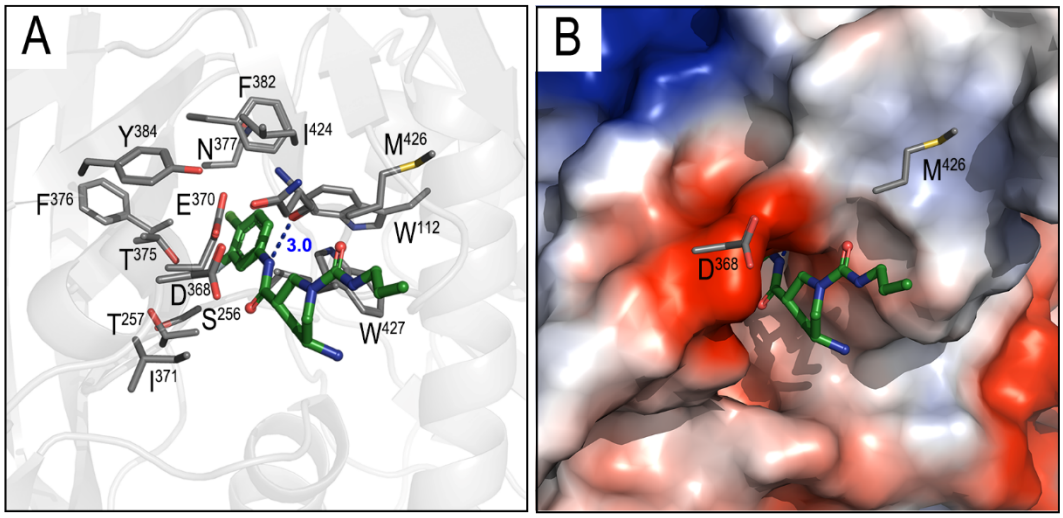


Figure S1. Crystal structure of **21a** in complex with LM/HT $gp120_{CRF01\_AE}$ $core_{e.}$

(A) Details of **21a** interaction with gp120 core. **21a** is shown as ribbon-ball-stick and side chains of gp120 residues (as determined by PISA software) contributing to **21a** binding are shown as sticks. The H-bond is shown as blue dashes.

(B) Blow-up view into **21a** binding pocket. The electrostatic potential is displayed over the molecular surface of gp120 colored red for negative, blue for positive and white for apolar. **21a** is shown in a ribbon and stick and Asp^{368}, Gly^{472} and Met^{426} are shown as sticks.

Computational Modeling

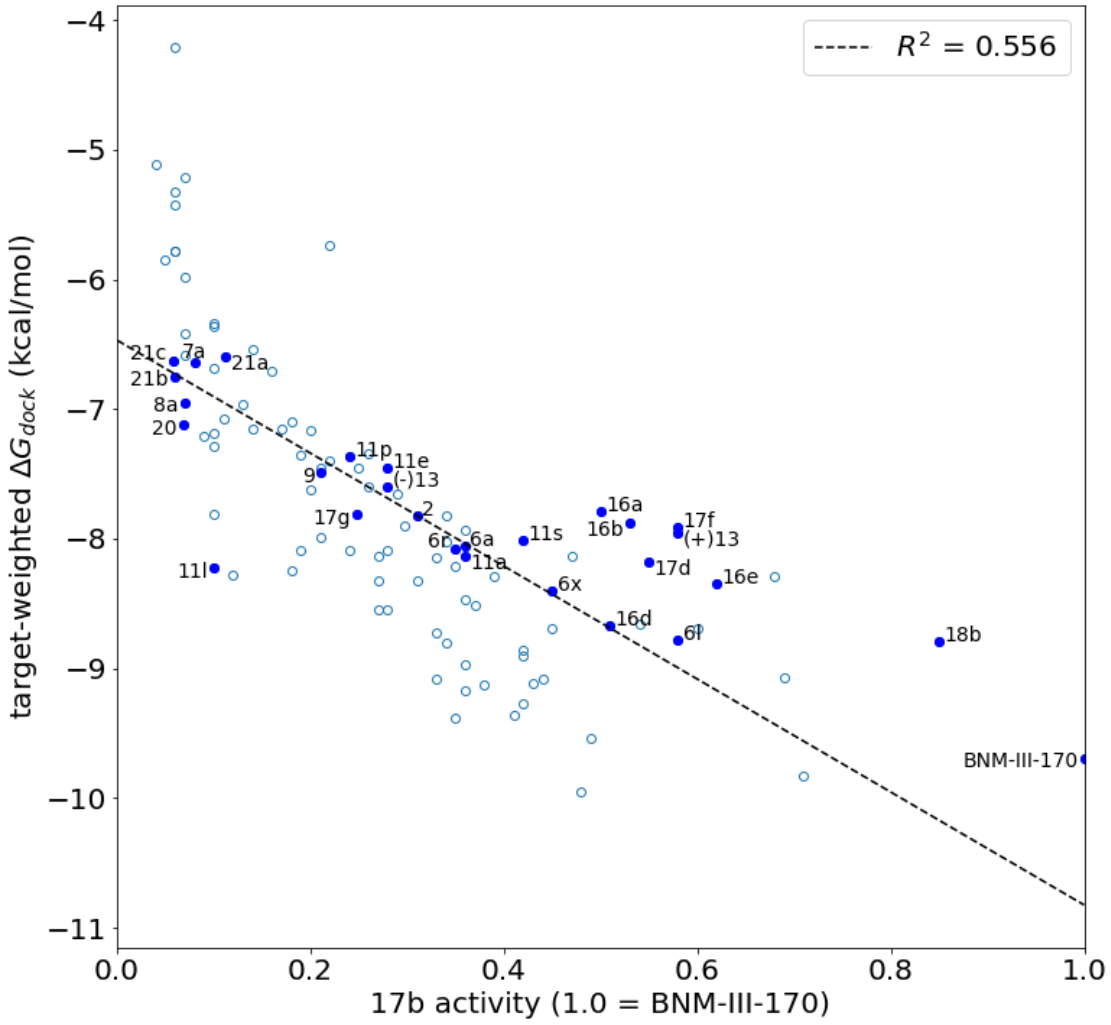


Figure S2. Correlation between 17b binding activity and target-weighted docking scores for all compounds. Solid symbols highlight compounds explicitly presented in the main text, and each is labeled with its unique code. Each target-weighted ΔG is a linear combination of scores across seven crystallographic targets, with weights computed such that $(R^2 - 1)^2$ is minimal for a linear fit over all compounds. Schrodinger Suite[4] and AutoDock[5] were used docking simulations.

A relationship between 17b CBE and predicted binding affinities ⊿G of best-aligned conformations with crystallographic ligands is presented in Figure S2. Generally, the better a compound is predicted to bind computationally, the more active it is in the 17b assay (R^2 = 0.556 overall). The compounds that contribute the most to the lower correlation include those with amides and ester linkages, the 4-position regioisomer, and the pyrrolidine, morpholine and piperazine analogs. In particular, docking predictions for compounds **7**–**11** (Table 1) have favorable binding affinities despite the fact that they have low 17b activities. However, compounds **16**–**18**, specifically with carbamate, urea, and guanidine moieties, are predicted to have good binding affinities and high 17b activity. Compound **18b** is the furthest right point in Figure S2 and appears to be the most active in the 17b assay, and it has a very favorable score. In line with experimental observations,

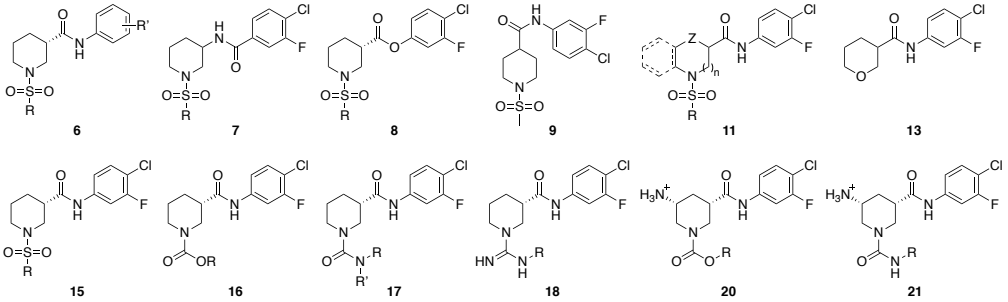
our calculations predicted that 3-amino substitutions (compounds **20**–**21**) do not directly H-bond with Asp368 and have very low predicted binding affinities.

Docking scores were computed for all compounds across seven crystallographic targets. Five of these targets are derived from co-crystals with a selection of compounds in this publication and are pending publication (Ding and Grenier *et al*.[6]), one is unpublished with BNM-III-170 bound (Pazgier, private communication), and one exists in the PDB (5F4P). Protein preparation was carried using Maestro. Bound crystallographic ligands and waters were removed. Missing loops and residues are constructed with Prime module of the Schrodinger Suite, with capped terminal residues. A restrained minimization step was performed using the OPLS_2005 force fields. *De novo* docking calculations are performed with Autodock software. The structure preparation, run, and analysis of docking simulations are carried out using AutoDock Tools (ADT). The rigid and flexible roots of each ligand were defined in a manner that amide bonds were made nonrotatable. Polar hydrogens and Gasteiger charges were added and subsequently nonpolar hydrogens were merged onto their respective heavy atoms for docking energy evaluations. A grid was placed on the active site region to encompass all amino acid residues surrounding the ligand to be docked in the Phe43 cavity with a box size at 40x40x44 $Å^3$. Autogrid4 was used to make grid maps with a grid spacing of 0.375 Å. Autodock4 was used to dock the 100 conformers for each ligand using the Lamarckian Genetic Algorithm (LGA) to search for the best conformers. The population size was set to 150 and the energy evaluation was set to 2500000 with default docking parameters were used.

Each target was assigned a weight factor w_j such that $\Sigma w_j = 1$ and the quantity $(R^2\text{-}1)^2$ is minimized, where R^2 refers to a linear fit of weighted score $\Sigma w_j s_{ij}$ vs. normalized 17b activity, where s_{ij} is the docking score of compound i on target j. The optimal R^2 was 0.556, while the R^2 for a straight average was 0.49, and the R^2 on the single best target was 0.516.

Summary of Cell-Based ELISA Results

Table S2. Cell-Based ELISA Results



Compound Name	#	R	R'	Z	n	Fused Ring	17b binding [a]
(S)-MCG-II-153	**2**	Me	4-Cl	-	-	-	0.20/0.31
(R)-MCG-II-156	**3**	Me	4-Cl	-	-	-	0.08
(S)-MCG-III-027-A02	**6a**	Me	4-Br	-	-	-	0.36
(S)-MCG-III-027-A03	**6b**	Me	4-F	-	-	-	0.12
(S)-MCG-III-027-A04	**6c**	Me	4-CF_3	-	-	-	0.17
(S)-MCG-III-027-B01	**6d**	Me	3-Cl	-	-	-	0.10
(S)-MCG-III-027-B02	**6e**	Me	3-Br	-	-	-	0.10
(S)-MCG-III-027-B03	**6f**	Me	3-F	-	-	-	0.13
(S)-MCG-III-027-B04	**6g**	Me	3-CF_3	-	-	-	0.07
(S)-MCG-III-027-B05	**6h**	Me	3-OMe	-	-	-	0.06
(S)-MCG-III-027-C01	**6i**	Me	2-Cl	-	-	-	0.06
(S)-MCG-III-027-C02	**6j**	Me	2-OMe	-	-	-	0.14
(S)-MCG-III-027-D04	**6k**	Me	2,4-diF	-	-	-	0.07
(S)-MCG-III-027-D05	**6l**	Me	4-Cl-3-F	-	-	-	0.46/0.58
(S)-MCG-III-085-A02	**6m**	Me	3-Cl-4-F	-	-	-	0.22
(S)-MCG-III-085-A03	**6n**	Me	3,4-diCl	-	-	-	0.19
(S)-MCG-III-085-A04	**6o**	Me	3,4-diF	-	-	-	0.10
(S)-MCG-III-085-A05	**6p**	Me	3-Br-4-Cl	-	-	-	0.16
(S)-MCG-III-085-A06	**6q**	Me	4-Br-3-Cl	-	-	-	0.14
(S)-MCG-III-085-C01	**6r**	Et	4-Cl-3-F	-	-	-	0.35
(S)-MCG-III-085-C02	**6s**	Et	3-Cl-4-F	-	-	-	0.20
(S)-MCG-III-085-C03	**6t**	Et	3,4-diCl	-	-	-	0.25
(S)-MCG-III-085-C04	**6u**	Et	3,4-diF	-	-	-	0.26
(S)-MCG-III-085-C05	**6v**	Et	3-Br-4-Cl	-	-	-	0.26
(S)-MCG-III-085-C06	**6w**	Et	4-Br-3-Cl	-	-	-	0.34
(S)-MCG-III-085-D01	**6x**	Ph	4-Cl-3-F	-	-	-	0.45
(S)-MCG-III-085-D02	**6y**	Ph	3-Cl-4-F	-	-	-	0.18
(S)-MCG-III-085-D03	**6z**	Ph	3,4-diCl	-	-	-	0.20
(S)-MCG-III-085-D04	**6aa**	Ph	3,4-diF	-	-	-	0.28
(S)-MCG-III-085-D05	**6ab**	Ph	3-Br-4-Cl	-	-	-	0.10
(S)-MCG-III-085-D06	**6ac**	Ph	4-Br-3-Cl	-	-	-	0.19
(S)-MCG-III-116-A01	**15a**	3-pyridine	4-Cl-3-F	-	-	-	0.41

(S)-MCG-III-116-A02	**15b**	N-Me Imidazole	4-Cl-3-F	-	-	-	0.24
(S)-MCG-III-116-A03	**15c**	Cyclohexyl	4-Cl-3-F	-	-	-	0.36
(S)-MCG-III-116-A05	**15d**	4-OMe-Ph	4-Cl-3-F	-	-	-	0.29
(S)-MCG-III-116-A06	**15e**	4-CN-Ph	4-Cl-3-F	-	-	-	0.31
(S)-MCG-III-117	**15f**	4-(NHC(O)Me)-Ph	4-Cl-3-F	-	-	-	0.21
(S)-MCG-III-132	**15g**	CF_3	4-Cl-3-F	-	-	-	0.27
(S)-MCG-III-128	**15h**	4-Br-Ph	4-Cl-3-F	-	-	-	0.21
(±)-MCG-III-157-C01	**7a**	Me	-	-	-	No	0.08
(±)-MCG-III-157-C02	**7b**	Et	-	-	-	No	0.07
(±)-MCG-III-157-C04	**7c**	N-Me Imidazole	-	-	-	No	0.04
(S)-MCG-III-213-A01	**8a**	Me	-	-	-	No	0.07
(S)-MCG-III-213-A02	**8b**	Et	-	-	-	No	0.07
(S)-MCG-III-213-A03	**8c**	Ph	-	-	-	No	0.05
(S)-MCG-III-213-A04	**8d**	N-Me Imidazole	-	-	-	No	0.10
MCG-III-101	**9**	-	-	-	-	No	0.21
(±)-MCG-III-196	**10a**	-	-	O	1	No	0.34
(±)-MCG-III-210	**10b**	-	-	NBoc	1	No	0.22
(±)-MCG-III-216-A01	**10c**	-	-	NH	1	No	0.21
(±)-MCG-III-209	**10d**	-	-	-	-	Yes	0.42
(±)-MCG-III-157-A01	**11a**	Me	-	CH_2	0	No	0.36
(±)-MCG-III-157-A02	**11b**	Et	-	CH_2	0	No	0.27
(±)-MCG-III-157-A03	**11c**	Ph	-	CH_2	0	No	0.33
(±)-MCG-III-157-A04	**11d**	N-Me Imidazole	-	CH_2	0	No	0.34
(±)-MCG-III-211-A01	**11e**	Me	-	O	1	No	0.28
(±)-MCG-III-211-A02	**11f**	Et	-	O	1	No	0.33
(±)-MCG-III-211-A03	**11g**	Ph	-	O	1	No	0.28
(±)-MCG-III-211-A04	**11h**	N-Me Imidazole	-	O	1	No	0.35
(±)-MCG-III-212-A01	**11i**	Me	-	NBoc	1	No	0.06
(±)-MCG-III-212-A03	**11j**	Ph	-	NBoc	1	No	0.06
(±)-MCG-III-212-A04	**11k**	N-Me Imidazole	-	NBoc	1	No	0.06
(±)-MCG-III-216-A02	**11l**	Me	-	NH	1	No	0.10
(±)-MCG-III-212-A02	**11m**	Et	-	NH	1	No	0.36
(±)-MCG-III-216-A03	**11n**	Ph	-	NH	1	No	0.11
(±)-MCG-III-216-A04	**11o**	N-Me Imidazole	-	NH	1	No	0.10
(±)-MCG-III-214-A01	**11p**	Me	-	CH_2	1	Yes	0.24
(±)-MCG-III-214-A03	**11q**	Ph	-	CH_2	1	Yes	0.09
(±)-MCG-III-214-A04	**11r**	N-Me Imidazole	-	CH_2	1	Yes	0.18
(±)-MCG-III-157-B01	**11s**	Me	-	CH_2	1	No	0.42
(±)-MCG-III-157-B02	**11t**	Et	-	CH_2	1	No	0.68
(±)-MCG-III-157-B03	**11u**	Ph	-	CH_2	1	No	0.43
(±)-MCG-III-157-B04	**11v**	N-Me Imidazole	-	CH_2	1	No	0.69
(±)-MCG-III-207	**13**	-	-	-	-	-	0.48
(+)-MCG-III-207	**(+)-13**	-	-	-	-	-	0.58
(-)-MCG-III-207	**(-)-13**	-	-	-	-	-	0.28

(S)-MCG-III-115	**14**	-	-	-	-	-	0.39
(S)-MCG-III-188-A01	**16a**	Me	-	-	-	-	0.50
(S)-MCG-III-188-A02	**16b**	Et	-	-	-	-	0.53
(S)-MCG-III-188-A03	**16c**	Ph	-	-	-	-	0.47
(S)-MCG-IV-058	**16d**	*n*-Pr	-	-	-	-	0.51
(S)-MCG-IV-061	**16e**	*i*-Bu	-	-	-	-	0.62
(S)-MCG-IV-267	**16f**	$(CH_2)_2NH_3^+$	-	-	-	-	0.30
(S)-MCG-IV-031-A02	**17a**	Et	H	-	-	-	0.37
(S)-MCG-IV-031-A03	**17b**	Me	Me	-	-	-	0.71
(S)-MCG-IV-031-A04	**17c**	Et	Me	-	-	-	0.54
(S)-MCG-IV-031-A05	**17d**	*n*-Pr	H	-	-	-	0.55
(S)-MCG-IV-031-A06	**17e**	*i*-Bu	H	-	-	-	0.42
(S)-MCG-IV-210	**17f**	$(CH_2)_2NH_3^+$	-	-	-	-	0.58
(S)-MCG-IV-211	**17g**	$(CH_2)_3NH_3^+$					0.25
(S)-MCG-IV-053-A01	**18a**	Me	-	-	-	-	0.42
(S)-MCG-IV-053-A05	**18b**	*n*-Pr	-	-	-	-	0.85
(S)-MCG-IV-053-A06	**18c**	*i*-Bu	-	-	-	-	0.60
(3R,5S)-MCG-IV-272	**20**	$(CH_2)_2NH_3^+$	-	-	-	-	0.07
(3R,5S)-MCG-IV-226	**21a**	*n*-Pr	-	-	-	-	0.11
(3R,5S)-MCG-IV-273	**21b**	$(CH_2)_2NH_3^+$	-	-	-	-	0.06
(3R,5S)-MCG-IV-274	**21c**	$(CH_2)_3NH_3^+$	-	-	-	-	0.06
(S)-MCG-IV-024-A02	**S30a**	Me	-	-	-	-	0.38
(S)-MCG-IV-024-B02	**S30b**	Et	-	-	-	-	0.36
(S)-MCG-IV-050-A01	**S32a**	Me	-	-	-	-	0.44
(S)-MCG-IV-050-A02	**S32b**	Et	-	-	-	-	0.49
(S)-MCG-IV-063-A01	**S33a**	Me	H	-	-	-	0.33
(S)-MCG-IV-063-A02	**S33b**	Et	H	-	-	-	0.35
(S)-MCG-IV-063-A03	**S33c**	Me	Me	-	-	-	0.48
(S)-MCG-IV-063-A05	**S33e**	*n*Pr	H	-	-	-	0.45
(S)-MCG-IV-063-A06	**S33f**	*i*Bu	H	-	-	-	0.36

[a]The fold over BNM-III-170 (5 μM) of Cell-Based ELISA with MCG Analogs (50 μM) - 17b readout, 2G12 and DMSO normalized (17b binding in presence of BNM-III-170 =1 and in the absence of CD4mc is <0.05). Values reported represent the average of experiments performed in quadruplicate.

Experimental Methods

Cell-based ELISA

Detection of trimeric HIV-1_{JRFL}EnvΔCT at the surface of HOS cells was performed by cell-based ELISA, as previously described.[7] Briefly, HOS cells were seeded in T-75 flasks ($3x10^6$ cells per flask) and transfected the next day with 22.5 μg of Env-expressing plasmids using the standard polyethylenimine (PEI, Polyscience Inc, PA, USA) transfection method. Twenty-four hours after transfection, cells were plated in 384-wells plates ($2x10^4$ cells per well). One day later, cells were incubated in blocking buffer (washing buffer [25 mM Tris, ph 7.5, 1.8 mM CaCl2, 1.0 mM MgCl2, pH 7.5 and 140 mM NaCl] supplemented with 10 mg/ml non-fat dry milk and 5 mM Tris pH 8.0) for 30 minutes and then co-incubated for 1 h at room temperature with either the anti-CoRBS 17b Ab or the bNAb 2G12 (1μg/ml) and with the compounds (50μM), sCD4 (10μg/ml) or the

compounds' vehicle (DMSO) diluted in blocking buffer. A horseradish peroxidase-conjugated antibody specific for the Fc region of human IgG (Pierce) was then incubated with the samples for 45 minutes at room temperature. For all conditions, cells were washed 5 times with blocking buffer and 5 times with washing buffer. HRP enzyme activity was determined after the addition of 20 µl per well of a 1:1 mix of Western Lightning oxidizing and luminol reagents (Perkin Elmer Life Sciences). Light emission was measured with an LB 941 TriStar luminometer (Berthold Technologies). 17b binding results presented in Table 1 and Table S2 were normalized to those obtained in the presence of the small CD4-mimetic BNM-III-170 (17b binding in presence of BNM-III-170 =1 and in the absence of CD4mc is <0.05).

Flow cytometry analysis of cell-surface staining

Cell surface staining was performed as previously described.[8] Primary CD4 T cells were isolated from 3 different healthy donors and infected with HIV-1_{CH58TF}. Binding of HIV-1-infected cells by sera (1:1,000 dilution) or antibodies (5µg/ml) in the presence or absence of 50µM compounds was performed 48 hours after infection. Cells were then incubated at 37 °C for 1hour followed by adding anti-human Alexa Fluor-647 (Invitrogen) secondary Abs for 20 minute. Primary CD4 T cells infected with HIV-1_{CH58TF} were then stained intracellularly for HIV-1 p24, using the Cytofix/Cytoperm Fixation/ Permeabilization Kit (BD Biosciences, Mississauga, ON, Canada) and the fluorescent anti-p24 mAb (PE-conjugated anti-p24, clone KC57; Beckman Coulter/Immunotech). The percentage of infected or transfected cells (p24+ cells or GFP+, respectively) was determined by gating the living cell population on the basis of the AquaVivid viability dye staining. Samples were analyzed on an LSRII cytometer (BD Biosciences), and data analysis was performed using FlowJo vX.0.7 (Tree Star, Ashland, OR, USA).

ADCC FACS-based assay

Measurement of ADCC using the FACS-based assay was performed at 48h post-infection as previously described.[8,9,10] Briefly, HIV-1_{CH58TF} infected primary CD4+ T cells were stained with viability (AquaVivid; Thermo Fisher Scientific) and cellular (cell proliferation dye eFluor670; eBioscience) markers and used as target cells. Autologous PBMC effectors cells, stained with another cellular marker (cell proliferation dye eFluor450; eBioscience), were added at an effector: target ratio of 10:1 in 96-well V-bottom plates (Corning, Corning, NY). Briefly, infected primary CD4+ T cells were incubated with HIV+ sera (1:1000), in the presence of 50 µM of compounds or with equivalent volume of vehicle (DMSO). The plates were subsequently centrifuged for 1 min at 300 g, and incubated at 37°C, 5% CO2 for 4 to 6 h before being fixed in a 2% PBS-formaldehyde solution. Samples were analyzed on an LSRII cytometer (BD Biosciences). Data analysis was performed using FlowJo vX.0.7 (Tree Star). The percentage of ADCC was calculated with the following formula: (% of p24+ cells in Targets plus Effectors) − (% of p24+ cells in Targets plus Effectors plus sera) / (% of p24+ cells in Targets) by gating on infected lived target cells.

Statistical analyses

Statistics were analyzed using GraphPad Prism version 6.01 (GraphPad, San Diego, CA, USA). Every data set was tested for statistical normality and this information was used to apply the appropriate (parametric or nonparametric) statistical test. P values <0.05 were considered significant; significance values are indicated as * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.

Isothermal titration calorimetry

Isothermal titration calorimetry (ITC) was carried out using a VP- ITC microcalorimeter from MicroCal/Malvern Instruments (Northampton, MA, USA). In all titration experiments, the gp120 and the different inhibitors were equilibrated with PBS, pH 7.4, with 2 % DMSO. The titrations were performed at 25 °C by injecting 10 µL aliquots of inhibitor solution into the calori- metric cell

(volume ~ 1.4 mL) containing gp120 at a concentration of 2 μM. The inhibitor concentration was 30 – 60 μM. The heat evolved upon each injection of inhibitor was obtained from the integral of the calorimetric signal. The heat associated with binding to gp120 in the cell was obtained by subtracting the heat of dilution from the heat of reaction. The individual heats were plotted against the molar ratio, and the enthalpy change (ΔH) and association constant (Ka = 1/Kd) were obtained by nonlinear regression of the data. The change in Gibbs energy (ΔG) was calculated from the affinity according to the relation ΔG = −RT ln Ka, where Ka is the association constant (Ka = 1/Kd), R is the gas constant (1.987 cal/(K·mol)), and T is the ab- solute temperature in kelvin. -TΔS was calculated from the relation ΔG = ΔH − TΔS.

Protein Purification and X-ray Crystallography

CRF01_AE core e expression and purification

Plasmids encoding the layers mutant gp120 extended core ($core_e$) protein, LM/HT $gp120_{CRF01\_AE}$ $core_e$, were transfected into GnT1$^-$ cells using Xtremegene (SigmaAldrich) transfection reagent as per manufacturer's instruction. Following seven days of culture growth at 37°C and 8% CO2, cell supernatant was filtered and passed over a 17b affinity column to isolate expressed gp120. gp120 was eluted with 0.1 M glycine pH 3.0 into tubes containing 1 M Tris-HCl pH 8.5 to immediately raise the pH. The protein was then deglycosylated with 10 units/μg of Endo H_f (NE Biolabs) overnight at 37°C. Endo H_f was removed by passage over an amylose resin column followed by gel filtration chromatography on a Superdex 200 16/60 column (GE Healthcare, Piscataway, NJ) equilibrated with 5 mM Tris-HCl pH 7.2 and 150 mM sodium chloride. The protein was concentrated to approximately 5 mg/ml for use in crystallization trials.

Crystallization of gp120 LM-HT cores complex with CD4mc

Deglycosylated LM/HT $gp120_{CRF01\_AE}$ $core_e$ (5 mg/ml) was crystalized by the hanging drop method in 5-10% PEG 1500, 6% PEG 400 and 0.1 M HEPES pH7.5. Crystals were allowed to grow fully prior to soaking with CD4 mimetic. All mimetics were solubilized with DMSO at a concentration of 10 mM and diluted with crystallization buffer to 100 nM prior to use in crystal soaks. Briefly, 0.4 μl of 100 nM mimetic was added to the 0.4 μl hanging drop containing the gp120 crystals prior to incubation for 4 hours. Crystals were then flash frozen in liquid nitrogen following a brief soak in crystallization buffer containing 15% MPD for cryoprotection and 50 nM of the CD4 mimetic.

Small Molecule Synthesis

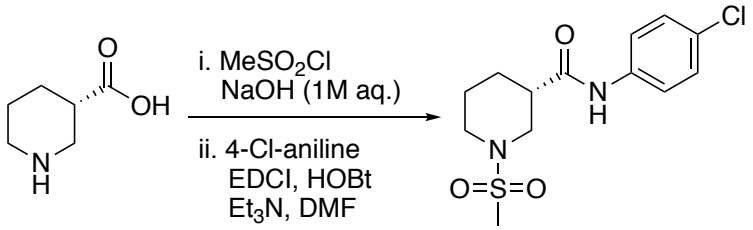
General Information

All reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen, unless otherwise stated. All solvents were reagent or high-performance liquid chromatography (HPLC) grade. Anhydrous CH_2Cl_2, toluene, ether and THF were obtained from the Pure Solve™ PS-400 system under an argon atmosphere. All reagents were purchased from commercially available sources and used as received. Reactions were magnetically stirred under a nitrogen atmosphere, unless otherwise noted and reactions were monitored by either thin layer chromatography (TLC) with 250 μm SiliaPlate™ pre-coated TLC plates or analytical ultra-performance liquid chromatography (UPLC). Yields refer to chromatographically or spectroscopically pure compounds. Optical rotations were measured on a JASCO P-2000 polarimeter. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance III 500-MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to chloroform (δ 7.26), dimethyl sulfoxide (δ 2.50), acetone (δ 2.05), methanol (δ 3.31), or acetonitrile (δ 1.94) for ^{1}H NMR, and chloroform (δ 77.0), dimethyl sulfoxide (δ 39.4), acetone (δ 29.8) or

methanol (δ 49.0) for ^{13}C NMR. Accurate mass measurements (AMM) were recorded at the University of Pennsylvania Mass Spectroscopy Service Center on either a Waters LCT Premier XE LC/MS or a Waters GC-TOF Premier system. Preparative scale UPLC was performed with a Waters AutoPurification system equipped with: a Sunfire C18 OBD column (10 μm packing material, 30 x 150 mm column dimensions); a 2767 sample manager; a 2545 binary gradient module; a system fluidics organizer; a 2489 UV-Vis dual wavelength (210 and 254 nm) detector; and MassLynx software with the FractionLynx application manager. Solvent systems were comprised of H_2O and acetonitrile containing 0.1% trifluoroacetic acid. Evaporation was performed using a Genevac EZ-2 Plus Evaporating System. SFC analyses were performed with a JASCO system equipped with a PU-280-CO_2 plus CO_2 Delivery System, a CO-2060 plus Intelligent Column Thermostat/Selector, an HC-2068-01 Heater Controller, a BP-2080 plus Automatic Back Pressure Regulator, an MD-2018 plus Photodiode Array Detector (200-648 nm), and PU 2080 plus Intelligent HPLC Pumps. The purity of new compounds was judged by NMR and LCMS (>95%).

Experimental Procedures

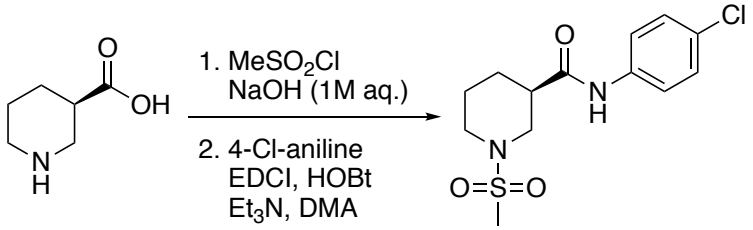
Synthesis of (*S*)-MCG-II-153 (**2**)



i. To a precooled (0 °C) solution of (S)-3-piperidinecarboxylic acid (100. mg, 0.774 mmol) in 1 M aq. NaOH (3.8 mL) under N2 atmosphere was added dropwise methanesulfonyl chloride (0.07 mL, 0.9 mmol). The resulting mixture was stirred at 0 °C for 2 h, then allowed to warm to room temperature and stirred for 2 h. The aqueous solution was washed with ether then acidified with 1 N aq. HCl to pH 3 and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x) then iPrOH:CHCl3 (30:70, 3x). The combined organic layers were dried over MgSO4, and concentrated in vacuo to afford the desired product, which was carried forward without additional purification (30 mg, crude 14% yield).

ii. To a precooled (0 °C) solution of (*S*)-mesylated piperidine intermediate (16 mg, 0.077 mmol), 4-chloroaniline (9.8 mg, 0.077 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (22 mg, 0.12 mmol) and 1-hydroxybenzotriazole hydrate (10. mg, 0.077 mmol) in DMF (0.8 mL) under N_2 atmosphere was added triethylamine (0.01 mL, 0.08 mmol). The resulting solution was allowed to warm to room temperature and stirred for 18 h, then concentrated *in vacuo*. The resulting residue was taken up in EtOAc and H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (SiO_2, 50:50 hexanes: EtOAc) afforded the product as a white solid (15 mg, 70% yield, 89.5% *ee*). **$[\alpha]_D^{22}$** +6.75 (c. 0.14, CH_3OH); **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.56 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 3.83 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.70 (d, *J* = 12.0 Hz, 1H), 2.91 (t, *J* = 11.3 Hz, 1H), 2.86 (s, 2H), 2.81 – 2.71 (m, 1H), 2.71 – 2.59 (m, 1H), 2.10 – 1.98 (m, 1H), 1.97 – 1.83 (m, 1H), 1.68 (t, *J* = 10.3 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.07, 136.47, 129.12, 121.21, 100.12, 48.03, 46.40, 43.51, 34.87, 27.38, 24.01; **IR** (ATR) ν_{max} 3296, 1651, 1525, 1322, 1156, 826, 506 cm^{-1}; **AMM** (ESI) *m/z* 339.0552 [calc for $C_{13}H_{17}ClN_2O_3SNa$ $(M+Na)^+$ 339.0546].

Synthesis of (*R*)-MCG-II-156 (**3**)

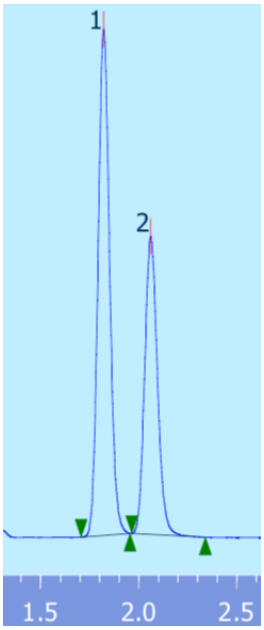


i. To a precooled (0 °C) solution of (*R*)-3-piperidinecarboxylic acid (100. mg, 0.774 mmol) in 1 M aq. NaOH (3 mL) under N_2 atmosphere was added dropwise methanesulfonyl chloride (0.07 mL, 0.9 mmol). The resulting mixture was allowed to

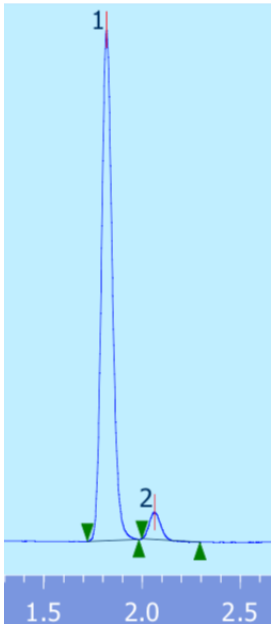
warm to room temperature and stirred for 3 h. The aqueous solution was then acidified with 1 N aq. HCl to pH 3 and diluted with iPrOH:$CHCl_3$ (30:70). The layers were separated, and the aqueous phase was extracted with iPrOH:$CHCl_3$ (30:70, 3x). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo* to afford the desired product, which was carried forward without additional purification (62 mg, 30% crude yield).

ii. To a precooled (0 °C) solution of (*R*)-mesylated piperidine intermediate (40. mg, 0.19 mmol), 4-chloroaniline (25 mg, 0.19 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (56 mg, 0.29 mmol) and 1-hydroxybenzotriazole hydrate (26 mg, 0.19 mmol) in dimethylacetamide (1.9 mL) under N_2 atmosphere was added triethylamine (0.03 mL, 0.2 mmol). The resulting solution was allowed to warm to room temperature and stirred for 16 h, then quenched with H_2O and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (SiO_2, 50:50 hexanes: EtOAc) afforded the product as a white solid (29 mg, 48% yield, 65.9% *ee*). **[α]$_D^{23}$** -7.25 (c. 0.13, CH_3OH); **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.70 (d, *J* = 11.5 Hz, 1H), 2.91 (t, *J* = 11.3 Hz, 1H), 2.86 (s, 2H), 2.80 – 2.71 (m, 1H), 2.71 – 2.61 (m, 1H), 2.09 – 1.98 (m, 1H), 1.95 – 1.84 (m, 1H), 1.73 – 1.58 (m, 1H); **^{13}C NMR** (126 MHz, DMSO) δ 171.33, 137.93, 128.57, 126.78, 120.72, 47.72, 45.42, 42.77, 39.52, 34.36, 26.56, 23.83; **IR** (ATR) ν_{max} 3297, 1656, 1524, 1321, 1141, 984, 826, 499 cm^{-1}; **AMM** (ESI) *m/z* 339.0563 [calc for $C_{13}H_{17}ClN_2O_3SNa$ $(M+Na)^+$ 339.0546].

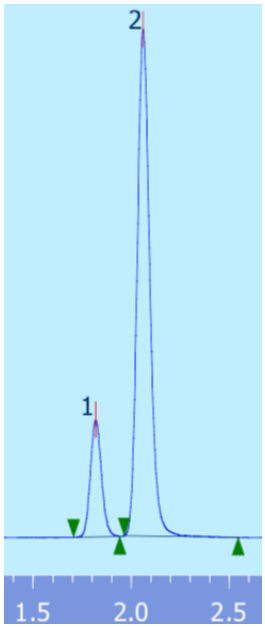
Enantiomeric excess determined by SFC (see figure below):



(+)-(*S*)-**2** + (-)-(R)-**3**



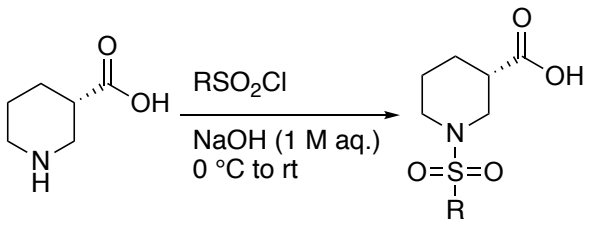
(+)-(*S*)-**2** er = 95:5



(-)-(*R*)-**3** *er* = 83:17

Method: column: ChiralPak AS-H; eluent: 15% MeOH in supercritical CO_2; flow rate: 4 mL/min; pressure: 12 MPa. Retention times: (+)-(*S*)-**2**: 1.8 min, (-)-(*R*)-**3**: 2.1 min.

General Synthesis of Analogs **6**



4 **5**

To a precooled (0 °C) solution of (*S*)-3-piperidinecarboxylic acid (1 eq) in 1 M aq. NaOH (0.2-0.5 M) under N_2 atmosphere was added dropwise R-sulfonyl chloride (1.2 eq). The resulting mixture was allowed to warm to room temperature and stirred for 14-23 h, then diluted with ether. The aqueous layer was washed with ether (1x) then acidified to pH 1 with 1 M aq. HCl. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (21-96% yield).

5a, R = Me (21% yield)

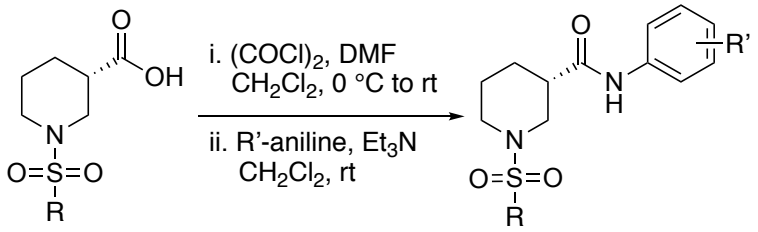
$[\alpha]_D^{22}$ +20.24 (c. 0.13, CH_3OH); **^{1}H NMR** (500 MHz, Methanol-*d*$_4$) δ 3.40 (dd, *J* = 13.0, 3.9 Hz, 1H), 3.31 (s, 5H), 3.28 – 3.15 (m, 2H), 3.10 – 3.00 (m, 1H), 2.87 – 2.76 (m, 1H), 2.17 – 2.07 (m, 1H), 2.00 – 1.87 (m, 1H), 1.87 – 1.72 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.03, 77.16, 47.29, 46.11, 40.92, 35.39, 26.55, 24.23; **IR** (ATR) ν_{max} 3245, 2960, 2942, 2860, 1732, 1694, 1317, 1153, 1140, 780, 519 cm^{-1}; **AMM** (ESI) *m/z* 208.0650 [calc for $C_7H_{14}NO_4S$ $(M+H)^+$ 208.0644].

5b, R = Et (34% yield)

$[\alpha]_D^{22}$ +21.69 (c. 0.24, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.86 (dd, *J* = 12.4, 3.8 Hz, 1H), 3.66 – 3.58 (m, 1H), 3.06 (dd, *J* = 12.5, 9.7 Hz, 1H), 2.98 (q, *J* = 7.4 Hz, 2H), 2.89 (ddd, *J* = 12.4, 10.3, 3.2 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.15 – 2.05 (m, 1H), 1.89 – 1.78 (m, 1H), 1.72 – 1.58 (m, 2H), 1.35 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.53, 77.16, 47.24, 46.12, 44.67, 41.18, 26.66, 24.56, 8.00; **IR** (ATR) ν_{max} 2945, 2863, 1708, 1452, 1130, 967, 750, 573, 509 cm^{-1}; **AMM** (ESI) *m/z* 222.0810 [calc for $C_8H_{16}NO_4S$ $(M+H)^+$ 222.0800].

5c, R = Ph (96% yield)

$[\alpha]_D^{22}$ -11.7 (c. 0.13, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.81 – 7.74 (m, 2H), 7.65 – 7.58 (m, 1H), 7.58 – 7.50 (m, 2H), 3.81 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.64 – 3.52 (m, 1H), 2.73 – 2.62 (m, 1H), 2.57 (t, *J* = 10.8 Hz, 1H), 2.41 (td, *J* = 11.3, 3.0 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.86 – 1.75 (m, 1H), 1.73 – 1.58 (m, 1H), 1.49 – 1.33 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.51, 136.00, 132.98, 129.19, 127.59, 77.16, 47.38, 46.28, 40.76, 26.17, 23.86; **IR** (ATR) ν_{max} 2950, 1733, 1197, 1167, 737, 571 cm^{-1};
AMM (ESI) *m/z* 270.0805 [calc for $C_{12}H_{16}NO_4S$ $(M+H)^+$ 270.0800].



5 **6**

i. To a precooled (0 °C) solution of common intermediate **5** (1.0 eq) in CH_2Cl_2 (0.2 M) under N_2 atmosphere was added dropwise oxalyl chloride (1.05 eq) then DMF (0.04 eq). The resulting mixture was stirred at 0 °C for 25-35 min. then concentrated *in vacuo* and used directly.
ii. To a precooled (0 °C) solution of acid chloride intermediate (1 eq) in CH_2Cl_2 (0.05 M) was added triethylamine (1 eq) then a solution of acid chloride (1.1 eq.) in CH_2Cl_2 (0.05 M). The resulting mixture were allowed to warm to room temperature and stirred for 16 h then quenched with DMSO (0.5 mL), filtered through celite and purified by mass-directed isolation using ultra-performance liquid chromatography.

(*S*)-MCG-III-027-A02 (**6a**)
R = Me, R' = 4-Br (20% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.71 (t, *J* = 2.0 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.11 – 7.04 (m, 1H), 3.75 (dd, *J* = 12.1, 3.7 Hz, 1H), 3.58 (d, *J* = 11.1 Hz, 1H), 3.16 (dd, *J* = 12.1, 9.1 Hz, 1H), 3.00 – 2.89 (m, 2H), 2.84 (s, 3H), 2.71 – 2.61 (m, 1H), 2.01 – 1.95 (m, 1H), 1.92 – 1.81 (m, 2H); **AMM** (ESI) *m/z* 383.0070 [calc for $C_{13}H_{17}BrN_2O_3SNa$ $(M+Na)^+$ 383.0041].

(*S*)-MCG-III-027-A03 (**6b**)
R = Me, R' = 4-F (29% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.55 – 7.44 (m, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 3.86 – 3.67 (m, 1H), 3.57 (d, *J* = 11.8 Hz, 1H), 3.17 (dd, *J* = 12.0, 9.0 Hz, 1H), 2.97 – 2.89 (m, 1H), 2.83 (s, 3H), 2.71 – 2.60 (m, 1H), 2.00 – 1.95 (m, 1H), 1.77 – 1.57 (m, 2H); **AMM** (ESI) *m/z* 323.0839 [calc for $C_{13}H_{17}FN_2O_3SNa$ $(M+Na)^+$ 323.0842].

(*S*)-MCG-III-027-A04 (**6c**)
R = Me, R' = 4-CF_3 (15% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 3.74 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.21 (dd, *J* = 12.1, 8.8 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.85 (s, 3H), 2.76 – 2.67 (m, 1H), 2.06 – 1.97 (m, 1H), 1.94 – 1.84 (m, 2H); **AMM** (ESI) *m/z* 373.0825 [calc for $C_{14}H_{17}F_3N_2O_3SNa$ (M+Na)+ 373.0810].

(*S*)-MCG-III-027-B01 (**6d**)
R = Me, R' = 3-Cl (26% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.71 (t, *J* = 2.0 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.11 – 7.05 (m, 1H), 3.75 (dd, *J* = 12.0, 3.7 Hz, 1H), 3.63 – 3.53 (m, 1H), 3.16 (dd, *J* = 12.1, 9.1 Hz, 1H), 2.99 – 2.89 (m, 2H), 2.84 (s, 3H), 2.71 – 2.63 (m, 1H), 2.01 – 1.95 (m, 1H), 1.93 – 1.81 (m, 2H); **AMM** (ESI) *m/z* 339.0552 [calc for $C_{13}H_{17}ClN_2O_3SNa$ $(M+Na)^+$ 339.0546].

(*S*)-MCG-III-027-B02 (**6e**)
R = Me, R' = 3-Br (24% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.86 (t, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 3.74 (dd, *J* = 12.1, 3.7 Hz, 1H), 3.57 (d, *J* = 11.6 Hz, 1H), 3.17 (dd, *J* = 12.1, 8.9 Hz, 1H), 3.00 – 2.90 (m, 2H), 2.84 (s, 3H), 2.71 – 2.61 (m, 1H), 2.01 – 1.95 (m, 1H), 1.93 – 1.81 (m, 3H); **AMM** (ESI) *m/z* 383.0041 [calc for $C_{13}H_{17}BrN_2O_3SNa$ $(M+Na)^+$ 383.0041].

(*S*)-MCG-III-027-B03 (**6f**)
R = Me, R' = 3-F (32% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 7.53 (dt, *J* = 10.9, 2.3 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.80 (td, *J* = 8.2, 2.5 Hz, 1H), 3.76 (dd, *J* = 12.1, 3.8 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.15 (dd, *J* = 12.0, 9.2 Hz, 1H), 2.99 – 2.88 (m, 2H), 2.84 (s, 3H), 2.74 – 2.63 (m, 1H), 2.06 – 1.97 (m, 1H), 1.95 – 1.83 (m, 2H); **AMM** (ESI) *m/z* 323.0850 [calc for $C_{13}H_{17}FN_2O_3SNa$ $(M+Na)^+$ 323.0842].

(*S*)-MCG-III-027-B04 (**6g**)
R = Me, R' = 3-CF_3 (30% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.95 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 3.75 (d, *J* = 12.6 Hz, 1H), 3.57 (d, *J* = 11.9 Hz, 1H), 3.20 (dd, *J* = 12.1, 8.8

Hz, 1H), 2.97 (m, 1H), 2.84 (s, 3H), 2.70 (m, 1H), 2.00 (m, 1H), 1.95 – 1.82 (m, 2H); **AMM** (ESI) *m/z* 373.0835 [calc for $C_{14}H_{17}F_3N_2O_3SNa$ $(M+Na)^+$ 373.0810].

(*S*)-MCG-III-027-B05 (**6h**)
R = Me, R' = 3-OMe (42% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.32 (s, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.05 – 6.97 (m, 1H), 6.66 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.91 – 3.72 (m, 4H), 3.65 – 3.56 (m, 1H), 3.10 (dd, *J* = 12.1, 9.4 Hz, 1H), 2.90 – 2.83 (m, 2H), 2.82 (s, 3H), 2.69 – 2.58 (m, 1H), 2.06 – 1.96 (m, 2H), 1.77 – 1.65 (m, 1H); **AMM** (ESI) *m/z* 335.1048 [calc for $C_{14}H_{20}N_2O_4SNa$ $(M+Na)^+$ 335.1041].

(*S*)-MCG-III-027-C01 (**6i**)
R = Me, R' = 2-Cl (29% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.88 (s, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 3.93 – 3.82 (m, 1H), 3.68 (d, *J* = 11.8 Hz, 1H), 3.08 (dd, *J* = 12.0, 9.6 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.83 (s, 3H), 2.74 – 2.64 (m, 1H), 2.15 – 2.05 (m, 1H), 1.93 (d, *J* = 12.0 Hz, 2H); **AMM** (ESI) *m/z* 339.0571 [calc for $C_{13}H_{17}ClN_2O_3SNa$ $(M+Na)^+$ 339.0546].

(*S*)-MCG-III-027-C02 (**6j**)
R = Me, R' = 2-OMe (13% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.11 (s, 1H), 7.09 – 7.03 (m, 1H), 6.98 – 6.92 (m, 1H), 6.91 – 6.85 (m, 1H), 3.90 (s, 3H), 3.82 (d, *J* = 11.6 Hz, 1H), 3.64 (d, *J* = 12.0 Hz, 1H), 3.14 – 3.04 (m, 1H), 2.90 – 2.82 (m, 1H), 2.81 (s, 3H), 2.71 – 2.62 (m, 1H), 2.04 – 1.98 (m, 1H), 1.95 – 1.86 (m, 1H), 1.86 – 1.79 (m, 1H), 1.77 – 1.67 (m, 1H); **AMM** (ESI) *m/z* 335.1039 [calc for $C_{14}H_{20}N_2O_4SNa$ $(M+Na)^+$ 335.1041].

(*S*)-MCG-III-027-D04 (**6k**)
R = Me, R' = 2,4-diF (14% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.22 – 8.12 (m, 1H), 7.60 (s, 1H), 6.92 – 6.83 (m, 2H), 3.81 (d, *J* = 12.1 Hz, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 3.16 – 3.06 (m, 1H), 2.88 (t, *J* = 10.8 Hz, 1H), 2.82 (s, 3H), 2.73 – 2.61 (m, 1H), 2.09 – 1.99 (m, 1H), 1.96 – 1.87 (m, 1H), 1.86 – 1.79 (m, 1H), 1.79 – 1.69 (m, 1H); **AMM** (ESI) *m/z* 341.0762 [calc for $C_{13}H_{16}F_2N_2O_3SNa$ $(M+Na)^+$ 341.0747].

(*S*)-MCG-III-027-D05 (**6l**)
R = Me, R' = 4-Cl-3-F (11% yield)
$[\alpha]_D^{23}$ +4.31 (c. 0.083, CH_3OH); **^{1}H NMR** (500 MHz, Acetonitrile-d_3) δ 8.70 (s, 1H), 7.72 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.24 (ddd, *J* = 8.8, 2.4, 1.1 Hz, 1H), 3.79 (ddt, *J* = 11.8, 3.6, 1.6 Hz, 1H), 3.61 (d, *J* = 11.7 Hz, 1H), 2.87 (dd, *J* = 11.8, 10.7 Hz, 1H), 2.78 (s, 3H), 2.72 (td, *J* = 11.5, 2.9 Hz, 1H), 2.58 (tt, *J* = 10.7, 3.9 Hz, 1H), 2.00 (d, *J* = 7.6 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.66 – 1.55 (m, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 174.03, 160.08, 158.13, 140.39, 140.31, 131.53, 117.34, 117.31, 116.09, 115.94, 109.33, 109.12, 47.09, 45.02, 40.40, 34.89, 28.45, 25.53; **IR** (ATR) ν_{max} 2990, 1665, 1529, 1422, 1322, 1201, 1166, 815, 491 cm^{-1}; **AMM** (ESI) *m/z* 357.0457 [calc for $C_{13}H_{16}ClFN_2O_3SNa$ $(M+Na)^+$ 357.0452].

(*S*)-MCG-III-085-A02 (**6m**)
R = Me, R' = 3-Cl-4-F (16% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.58 (s, 1H), 7.85 – 7.79 (m, 1H), 7.45 – 7.38 (m, 1H), 7.18 (td, *J* = 9.1, 1.0 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.62 (d, *J* = 11.8 Hz, 1H), 2.87 (t, *J* = 11.2 Hz, 1H), 2.79 (s, 3H), 2.72 (td, *J* = 11.6, 3.1 Hz, 1H), 2.57 (tt, *J* = 10.8, 4.0 Hz, 2H), 2.04 – 1.98 (m, 1H), 1.89 – 1.80 (m, 1H), 1.67 – 1.56 (m, 2H); **AMM** (ESI) *m/z* 357.0447 [calc for $C_{13}H_{16}ClFN_2O_3SNa$ $(M+Na)^+$ 357.0452].

(*S*)-MCG-III-085-A03 (**6n**)
R = Me, R' = 3,4-diCl (15% yield)
^{1}H NMR (500 MHz, Acetonitrile-*d*3) δ 8.67 (s, 1H), 7.89 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.47 – 7.39 (m, 2H), 3.83 – 3.74 (m, 1H), 3.66 – 3.57 (m, 1H), 2.87 (dd, *J* = 11.8, 10.6 Hz, 1H), 2.79 (s, 3H), 2.72 (td, *J* = 11.6, 2.9

Hz, 1H), 2.59 (tt, *J* = 10.8, 3.9 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.90 – 1.82 (m, 1H), 1.67 – 1.56 (m, 2H); **AMM** (ESI) *m/z* 373.0159 [calc for $C_{13}H_{16}Cl_2N_2O_3SNa$ $(M+Na)^+$ 373.0156].

(*S*)-MCG-III-085-A04 (**6o**)
R = Me, R' = 3,4-diF (15% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.60 (s, 1H), 7.77 – 7.66 (m, 1H), 7.25 – 7.14 (m, 2H), 3.83 – 3.75 (m, 1H), 3.66 – 3.58 (m, 1H), 2.87 (dd, *J* = 11.8, 10.6 Hz, 1H), 2.78 (s, 3H), 2.72 (td, *J* = 11.6, 2.9 Hz, 1H), 2.57 (tt, *J* = 10.8, 3.9 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.90 – 1.82 (m, 1H), 1.67 – 1.55 (m, 2H); **AMM** (ESI) *m/z* 341.0736 [calc for $C_{13}H_{16}F_2N_2O_3SNa$ $(M+Na)^+$ 341.0747].

(*S*)-MCG-III-085-A05 (**6p**)
R = Me, R' = 3-Br-4-Cl (9% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.65 (s, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 3.83 – 3.76 (m, 1H), 3.61 (d, *J* = 11.9 Hz, 1H), 2.87 (dd, *J* = 11.8, 10.6 Hz, 1H), 2.79 (s, 3H), 2.72 (td, *J* = 11.6, 2.9 Hz, 1H), 2.58 (tt, *J* = 10.7, 3.8 Hz, 1H), 2.03 – 1.98 (m, 1H), 1.90 – 1.82 (m, 1H), 1.67 – 1.55 (m, 2H); **AMM** (ESI) *m/z* 416.9674 [calc for $C_{13}H_{16}BrClN_2O_3SNa$ $(M+Na)^+$ 416.9651].

(*S*)-MCG-III-085-A06 (**6q**)
R = Me, R' = 4-Br-3-Cl (24% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.66 (s, 1H), 7.90 (d, *J* = 2.5 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.79 (ddt, *J* = 11.7, 3.7, 1.7 Hz, 1H), 3.65 – 3.57 (m, 1H), 2.87 (dd, *J* = 11.8, 10.6 Hz, 1H), 2.79 (s, 3H), 2.77 – 2.68 (m, 1H), 2.58 (tt, *J* = 10.8, 3.9 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.90 – 1.81 (m, 1H), 1.67 – 1.53 (m, 2H); **AMM** (ESI) *m/z* 416.9650 [calc for $C_{13}H_{16}BrClN_2O_3SNa$ $(M+Na)^+$ 416.9651].

(*S*)-MCG-III-085-C01 (**6r**)
R = Et, R' = 4-Cl-3-F (18% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.69 (s, 1H), 7.72 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.28 – 7.20 (m, 1H), 3.86 – 3.74 (m, 1H), 3.64 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.06 – 2.93 (m, 3H), 2.83 (td, *J* = 11.8, 2.9 Hz, 1H), 2.61 – 2.49 (m, 2H), 2.04 – 1.97 (m, 1H), 1.86 – 1.77 (m, 1H), 1.71 – 1.50 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** (ESI) *m/z* 371.0599 [calc for $C_{14}H_{18}ClFN_2O_3SNa$ $(M+Na)^+$ 371.0608].

(*S*)-MCG-III-085-C02 (**6s**)
R = Et, R' = 3-Cl-4-F (21% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.57 (s, 1H), 7.81 (dd, *J* = 6.8, 2.6 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.17 (t, *J* = 9.0 Hz, 1H), 3.81 (ddt, *J* = 12.2, 3.7, 1.7 Hz, 1H), 3.68 – 3.58 (m, 1H), 3.04 – 2.92 (m, 3H), 2.83 (td, *J* = 11.7, 2.8 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.03 – 1.96 (m, 1H), 1.87 – 1.76 (m, 1H), 1.70 – 1.50 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** (ESI) *m/z* 371.0618 [calc for $C_{14}H_{18}ClFN_2O_3SNa$ $(M+Na)^+$ 371.0608].

(*S*)-MCG-III-085-C03 (**6t**)
R = Et, R' = 3,4-diCl (20% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.65 (s, 1H), 7.89 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.47 – 7.38 (m, 2H), 3.81 (ddt, *J* = 12.2, 3.7, 1.7 Hz, 1H), 3.68 – 3.59 (m, 1H), 3.05 – 2.92 (m, 3H), 2.83 (td, *J* = 11.7, 2.9 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.04 – 1.97 (m, 1H), 1.89 – 1.78 (m, 1H), 1.70 – 1.50 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** (ESI) *m/z* 387.0302 [calc for $C_{14}H_{18}Cl_2N_2O_3SNa$ $(M+Na)^+$ 387.0313].

(*S*)-MCG-III-085-C04 (**6u**)
R = Et, R' = 3,4-diF (23% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.58 (s, 1H), 7.75 – 7.66 (m, 1H), 7.24 – 7.13 (m, 2H), 3.85 – 3.76 (m, 1H), 3.68 – 3.58 (m, 1H), 3.04 – 2.93 (m, 3H), 2.83 (td, *J* = 11.7, 2.8 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.04 – 1.96 (m, 1H), 1.87 – 1.78 (m, 1H), 1.70 – 1.51 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** (ESI) *m/z* 355.0882 [calc for $C_{14}H_{18}F_2N_2O_3SNa$ $(M+Na)^+$ 355.0904].

(*S*)-MCG-III-085-C05 (**6v**)
R = Et, R' = 3-Br-4-Cl (11% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.66 (s, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 3.85 – 3.75 (m, 1H), 3.63 (d, *J* = 12.4 Hz, 1H), 3.05 – 2.93 (m, 3H), 2.83 (td, *J* =

11.7, 2.8 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.04 – 1.97 (m, 1H), 1.88 – 1.78 (m, 2H), 1.70 – 1.50 (m, 3H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** (ESI) *m/z* 430.9807 [calc for $C_{14}H_{18}BrClN_2O_3SNa$ $(M+Na)^+$ 430.9808].

(*S*)-MCG-III-085-C06 (**6w**)
R = Et, R' = 4-Br-3-Cl (24% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.67 (s, 1H), 7.90 (d, *J* = 2.5 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.35 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.67 – 3.58 (m, 1H), 3.04 – 2.93 (m, 3H), 2.83 (td, *J* = 11.7, 2.8 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.04 – 1.97 (m, 1H), 1.86 – 1.78 (m, 1H), 1.71 – 1.49 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** (ESI) *m/z* 430.9834 [calc for $C_{14}H_{18}BrClN_2O_3SNa$ $(M+Na)^+$ 430.9808].

(*S*)-MCG-III-085-D01 (**6x**)
R = Ph, R' = 4-Cl-3-F (16% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.61 (s, 1H), 7.77 – 7.71 (m, 2H), 7.71 – 7.63 (m, 2H), 7.63 – 7.56 (m, 2H), 7.35 (t, *J* = 8.6 Hz, 1H), 7.23 – 7.15 (m, 1H), 3.85 – 3.76 (m, 1H), 3.62 (d, *J* = 11.7 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.38 (t, *J* = 11.1 Hz, 2H), 2.26 (td, *J* = 11.7, 2.9 Hz, 1H), 1.88 (dd, *J* = 13.3, 3.6 Hz, 1H), 1.81 – 1.73 (m, 1H), 1.65 – 1.50 (m, 1H), 1.46 – 1.32 (m, 1H); **AMM** (ESI) *m/z* 419.0588 [calc for $C_{18}H_{18}ClFN_2O_3SNa$ $(M+Na)^+$ 419.0608].

(*S*)-MCG-III-085-D02 (**6y**)
R = Ph, R' = 3-Cl-4-F (21% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.49 (s, 1H), 7.80 – 7.70 (m, 3H), 7.70 – 7.62 (m, 1H), 7.62 – 7.55 (m, 2H), 7.41 – 7.32 (m, 1H), 7.15 (t, *J* = 9.1 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.67 – 3.58 (m, 1H), 2.54 (tt, *J* = 11.1, 3.8 Hz, 1H), 2.38 (t, *J* = 11.1 Hz, 1H), 2.25 (td, *J* = 11.7, 2.9 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.82 – 1.72 (m, 1H), 1.63 – 1.50 (m, 1H), 1.45 – 1.34 (m, 1H); **AMM** (ESI) *m/z* 419.0610 [calc for $C_{18}H_{18}ClFN_2O_3SNa$ $(M+Na)^+$ 419.0608].

(*S*)-MCG-III-085-D03 (**6z**)
R = Ph, R' = 3,4-diCl (16% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.53 (s, 1H), 7.80 – 7.72 (m, 2H), 7.68 (q, *J* = 6.9 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.10 (m, 2H), 3.83 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.64 (d, *J* = 11.5 Hz, 1H), 2.65 – 2.51 (m, 1H), 2.40 (t, *J* = 11.1 Hz, 1H), 2.28 (td, *J* = 11.7, 3.0 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.84 – 1.75 (m, 1H), 1.66 – 1.52 (m, 1H), 1.42 (qd, *J* = 12.5, 3.9 Hz, 1H); **AMM** (ESI) *m/z* 435.0310 [calc for $C_{18}H_{18}Cl_2N_2O_3SNa$ $(M+Na)^+$ 435.0313].

(*S*)-MCG-III-085-D04 (**6aa**)
R = Ph, R' = 3,4-diF (19% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.53 (s, 1H), 7.81 – 7.72 (m, 2H), 7.68 (q, *J* = 6.9 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.12 (m, 2H), 3.83 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.64 (d, *J* = 11.5 Hz, 1H), 2.63 – 2.50 (m, 1H), 2.40 (t, *J* = 11.1 Hz, 1H), 2.28 (td, *J* = 11.7, 3.0 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.84 – 1.74 (m, 1H), 1.59 (qt, *J* = 12.3, 4.1 Hz, 1H), 1.42 (qd, *J* = 12.5, 3.9 Hz, 1H); **AMM** (ESI) *m/z* 403.0910 [calc for $C_{18}H_{18}F_2N_2O_3SNa$ $(M+Na)^+$ 403.0904].

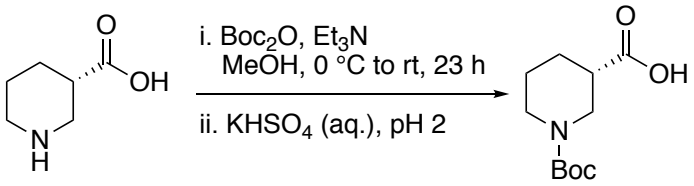
(*S*)-MCG-III-085-D05 (**6ab**)
R = Ph, R' = 3-Br-4-Cl (7% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.64 (s, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.73 – 7.67 (m, 1H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.51 – 7.40 (m, 2H), 3.83 (dd, *J* = 11.6, 3.9 Hz, 1H), 3.64 (d, *J* = 12.0 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.40 (t, *J* = 11.1 Hz, 1H), 2.28 (td, *J* = 11.8, 3.0 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.83 – 1.76 (m, 1H), 1.59 (tdd, *J* = 12.7, 8.3, 4.1 Hz, 1H), 1.41 (qd, *J* = 12.6, 3.9 Hz, 1H); **AMM** (ESI) *m/z* 478.9834 [calc for $C_{18}H_{18}BrClN_2O_3SNa$ $(M+Na)^+$ 478.9808].

(*S*)-MCG-III-085-D06 (**6ac**)
R = Ph, R' = 4-Br-3-Cl (10% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.60 (s, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.34 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.64 (d, *J* = 11.5 Hz, 1H), 2.58 (tt, *J* = 11.0, 3.8 Hz, 1H), 2.40 (t, *J* = 11.1 Hz, 1H), 2.28 (td, *J* = 11.8,

3.0 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.83 – 1.75 (m, 1H), 1.66 – 1.53 (m, 1H), 1.47 – 1.34 (m, 1H); **AMM** (ESI) *m/z* 478.9834 [calc for $C_{18}H_{18}BrClN_2O_3SNa$ $(M+Na)^+$ 478.9808].

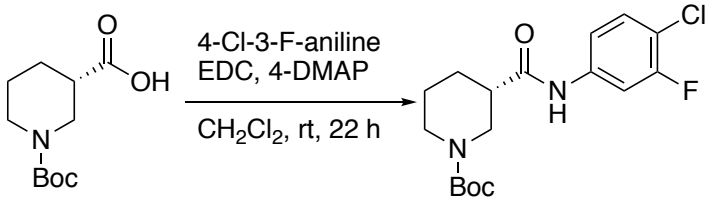
*Analogs **6ad**-**6ak** prepared from intermediate **14**

Synthesis of Common Intermediate **14** (MCG-III-115)



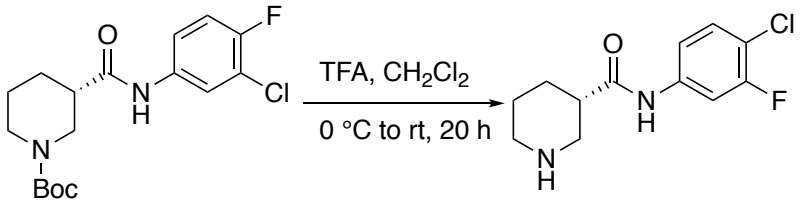
S2

To a precooled (0 °C) solution of (*S*)-3-piperidinecarboxylic acid (1.00 g, 7.74 mmol) in MeOH (38 mL) under N_2 atmosphere was added triethylamine (2.2 mL, 15 mmol) then dropwise Boc anhydride (2.1 mL, 9.3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 23 h, then concentrated *in vacuo*. The crude residue was taken up in H_2O, cooled to 0 °C and acidified with aq. $KHSO_4$ to pH 2. The aqueous solution was diluted with EtOAc and the biphasic solution was stirred for 10 min. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with 1 M aq. HCl then brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the product as a white solid (1.63 g, 92% yield). **$[\alpha]_D^{23}$** -17.8 (c. 0.64, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.11 (s, 1H), 3.88 (d, *J* = 13.4 Hz, 1H), 3.05 (s, 1H), 2.93 – 2.81 (m, 1H), 2.56 – 2.42 (m, 1H), 2.13 – 1.99 (m, 1H), 1.72 (dt, *J* = 13.1, 3.9 Hz, 1H), 1.63 – 1.68 (m, 1H), 1.46 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.09, 154.87, 80.08, 45.68, 43.87, 41.24, 28.51, 27.30, 24.24; **IR** (ATR) ν_{max} 3150, 1731, 1657, 1474, 1144, 849 cm^{-1}; **AMM** (ESI) *m/z* 230.1413 [calc for $C_{11}H_{20}NO_4$ $(M+H)^+$ 230.1392].



S2 **S3**

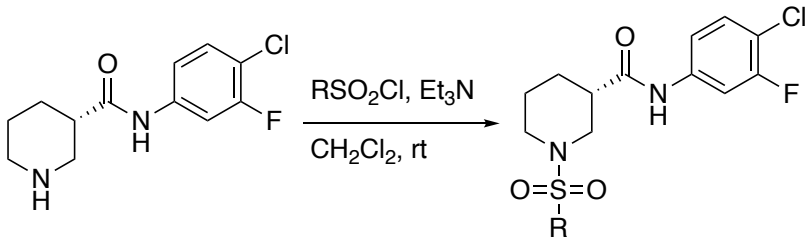
To a flask charged with intermediate **S2** (2.00 , 8.72 mmol), 4-chloro-3-fluoroaniline (1.52 g, 8.72 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.84 g, 9.60 mmol) and 4-dimethylaminopyridine (1.17 g, 9.60 mmol) at room temperature under N_2 atmosphere was added CH_2Cl_2 (43 mL). The resulting mixture was stirred at room temperature for 22 h, then quenched with H_2O. The biphasic solution was stirred for 30 min, then the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed sequentially with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) afforded the product as a white solid (2.50 g, 80% yield). **$[\alpha]_D^{23}$** +51.0 (c. 0.42, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 7.70 (dd, *J* = 11.3, 2.3 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 3.85 – 3.67 (m, 1H), 3.58 (d, *J* = 41.0 Hz, 2H), 3.43 – 3.21 (m, 1H), 2.58 – 2.44 (m, 1H), 2.21 – 2.03 (m, 1H), 1.93 – 1.80 (m, 1H), 1.69 – 1.54 (m, 1H), 1.46 (s, 10H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.67, 159.06, 157.10, 155.48, 138.54, 130.43, 115.85, 115.82, 115.54, 108.55, 108.35, 80.71, 77.16, 45.50, 44.92, 43.73, 28.57, 27.73, 24.10; **IR** (ATR) ν_{max} 3095, 2943, 1656, 1605, 1493, 1147, 857 cm^{-1}; **AMM** (ESI) *m/z* 357.1396 (ESI) *m/z* [calc for $C_{17}H_{23}ClFN_2O_3$ $(M+H)^+$ 357.1381].



S3 **14**

To a precooled (0 °C) solution of intermediate **S3** (1.07 g, 3.00 mmol) in CH_2Cl_2 under N_2 atmosphere was added dropwise trifluoroacetic acid (1.2 mL, 15 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 20 h, then concentrated *in vacuo*. The crude residue was taken up in H_2O and the resulting mixture was cooled to 0 °C then slowly neutralized with powdered $NaHCO_3$. The aqueous layer was diluted with CH_2Cl_2, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (722 mg, 94% yield). **$[\alpha]_D^{23}$** +2.6 (c. 0.72, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 10.87 (s, 1H), 7.67 (dd, *J* = 11.2, 2.4 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.17 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.28 (d, *J* = 12.2 Hz, 1H), 3.11 (d, *J* = 11.3 Hz, 1H), 2.96 (d, *J* = 12.1 Hz, 1H), 2.83 – 2.73 (m, 1H), 2.63 – 2.56 (m, 1H), 2.10 – 2.01 (m, 1H), 1.83 – 1.71 (m, 2H), 1.66 – 1.54 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.00, 159.07, 157.11, 138.67, 138.59, 130.35, 115.92, 115.89, 115.08, 114.94, 108.52, 108.31, 47.79, 46.47, 41.78, 27.52, 22.60; **IR** (ATR) ν_{max} 3275, 2425, 1670, 1604, 1490, 1201, 857, 719 cm^{-1}; **AMM** (ESI) *m/z* 257.0842 [calc for $C_{12}H_{15}ClFN_2O$ $(M+H)^+$ 256.0857].

General Synthesis of Analogs **15a-15h**



14 **15a-15h**

To separate solutions of common intermediate **14** (20. mg, 0.078 mmol) and triethylamine (30 µL, 0.2 mmol) in CH_2Cl_2 (0.5 mL) at ambient temperature was added R-sulfonyl chloride (0.12 mmol). The resulting mixtures were stirred for 18-72 h, then diluted with wet dimethyl sulfoxide (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (7-91% yield).

(*S*)-MCG-III-116-A01 (**15a**)
R = 3-pyridine, R' = 4-Cl-3-F (91% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.98 (s, 1H), 8.90 – 8.79 (m, 1H), 8.61 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.37 (t, *J* = 8.7 Hz, 1H), 7.25 – 7.15 (m, 1H), 3.89 (d, *J* = 10.7 Hz, 1H), 3.70 (d, *J* = 11.5 Hz, 1H), 2.67 – 2.48 (m, 2H), 2.42 (td, *J* = 11.8, 2.9 Hz, 1H), 1.86 – 1.72 (m, 1H), 1.68 – 1.52 (m, 1H), 1.52 – 1.34 (m, 1H); **AMM** (ESI) *m/z* 398.0728 [calc for $C_{17}H_{18}ClFN_3O_3S$ $(M+H)^+$ 398.0741].

(*S*)-MCG-III-116-A02 (**15b**)
R = N-Me imidazole, R' = 4-Cl-3-F (68% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.64 (s, 1H), 7.70 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.62 (d, *J* = 1.4 Hz, 1H), 7.54 (d, *J* = 1.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.22 (ddd, *J* = 8.8, 2.4, 1.2 Hz, 1H), 3.80 (ddd, *J* = 11.7, 3.7, 1.9 Hz, 1H), 3.71 (s, 3H), 3.63 (d, *J* = 12.1 Hz, 1H), 2.65 (t, *J* = 11.1 Hz, 1H), 2.58 (ddt, *J* = 10.8, 7.2, 3.5 Hz, 1H), 2.52 (td, *J* = 11.9, 3.0 Hz, 1H), 1.93 – 1.89 (m, 1H), 1.85 – 1.74 (m, 1H), 1.65 – 1.52 (m, 1H), 1.52 – 1.39 (m, 1H); **AMM** (ESI) *m/z* 401.0858 [calc for $C_{16}H_{19}ClFN_4O_3S$ $(M+H)^+$ 401.0850].

(*S*)-MCG-III-116-A03 (**15c**)
R = cyclohexyl, R' = 4-Cl-3-F (19% yield)

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.71 (s, 1H), 7.72 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.28 – 7.20 (m, 1H), 3.86 – 3.76 (m, 1H), 3.63 (dt, *J* = 12.6, 3.9 Hz, 1H), 3.09 (dd, *J* = 12.6, 10.3 Hz, 1H), 3.02 (tt, *J* = 12.0, 3.5 Hz, 1H), 2.98 – 2.89 (m, 1H), 2.52 (tt, *J* = 10.6, 3.9 Hz, 1H), 2.09 – 1.97 (m, 3H), 1.87 – 1.74 (m, 3H), 1.73 – 1.61 (m, 2H), 1.60 – 1.48 (m, 1H), 1.42 (qd, *J* = 12.4, 3.5 Hz, 2H), 1.29 (qt, *J* = 12.7, 3.3 Hz, 2H), 1.18 (qt, *J* = 12.7, 3.2 Hz, 1H); **AMM** (ESI) *m/z* 403.1252 [calc for $C_{18}H_{25}ClFN_2O_3S$ $(M+H)^+$ 403.1258].

(*S*)-MCG-III-116-A05 (**15d**)
R = 4-OMe-Ph, R' = 4-Cl-3-F (38% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.69 (s, 1H), 7.75 – 7.65 (m, 3H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.13 – 7.04 (m, 2H), 3.87 (s, 3H), 3.84 – 3.76 (m, 1H), 3.61 (d, *J* = 11.7 Hz, 1H), 2.58 (tt, *J* = 11.0, 3.8 Hz, 1H), 2.37 (t, *J* = 11.1 Hz, 1H), 2.25 (td, *J* = 11.7, 2.9 Hz, 2H), 1.90 (dd, *J* = 13.2, 3.7 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.59 (qt, *J* = 12.4, 4.0 Hz, 1H), 1.40 (qd, *J* = 12.5, 3.9 Hz, 1H); **AMM** (ESI) *m/z* 427.0902 [calc for $C_{19}H_{21}ClFN_2O_4S$ $(M+H)^+$ 427.0895].

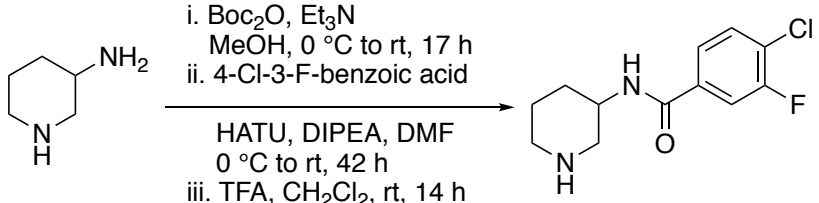
(*S*)-MCG-III-116-A06 (**15e**)
R = 4-CN-Ph, R' = 4-Cl-3-F (7% yield)
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (q, *J* = 5.4, 3.0 Hz, 3H), 7.84 (d, *J* = 18.1 Hz, 1H), 7.65 (d, *J* = 10.8 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.9 Hz, 1H), 3.67 (d, *J* = 12.3 Hz, 1H), 3.52 (d, *J* = 11.5 Hz, 1H), 2.96 – 2.84 (m, 1H), 2.78 – 2.56 (m, 2H), 2.01 – 1.82 (m, 2H), 1.82 – 1.69 (m, 2H); **AMM** (ESI) *m/z* 422.0743 [calc for $C_{19}H_{18}ClFN_3O_3S$ $(M+H)^+$ 422.0741].

(*S*)-MCG-III-117 (**15f**)
R = 4-(NHC(O)Me)-Ph, R' = 4-Cl-3-F (42% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.66 (s, 1H), 8.60 (s, 1H), 7.80 – 7.74 (m, 2H), 7.73 – 7.64 (m, 2H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.25 – 7.17 (m, 1H), 3.83 – 3.76 (m, 1H), 3.60 (d, *J* = 11.5 Hz, 1H), 2.63 – 2.51 (m, 1H), 2.40 (t, *J* = 11.1 Hz, 1H), 2.29 (td, *J* = 11.6, 2.9 Hz, 1H), 2.10 (s, 3H), 1.92 – 1.84 (m, 1H), 1.83 – 1.75 (m, 1H), 1.65 – 1.52 (m, 1H), 1.48 – 1.36 (m, 1H); **AMM** (ESI) *m/z* 454.1022 [calc for $C_{20}H_{22}ClFN_3O_4S$ $(M+H)^+$ 454.1004].

(*S*)-MCG-III-132 (**15g**)
R = CF_3, R' = 4-Cl-3-F (13% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.67 (s, 1H), 7.69 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.38 (t, *J* = 8.6 Hz, 1H), 7.29 – 7.19 (m, 1H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.83 (d, *J* = 13.1 Hz, 1H), 3.38 – 3.22 (m, 1H), 3.21 – 3.07 (m, 1H), 2.61 (tt, *J* = 11.1, 3.9 Hz, 1H), 2.40 – 2.22 (m, 2H), 2.08 (d, *J* = 12.6 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.79 – 1.54 (m, 3H); **AMM** 411.0157 (ESI) *m/z* [calc for $C_{13}H_{13}ClF_4N_2O_3SNa$ $(M+Na)^+$ 411.0169].

(*S*)-MCG-III-128 (**15h**)
R = 4-Br-Ph, R' = 4-Cl-3-F (49% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.64 (s, 1H), 7.81 – 7.75 (m, 2H), 7.72 – 7.62 (m, 3H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.23 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.86 – 3.77 (m, 1H), 3.63 (d, *J* = 11.8 Hz, 1H), 2.58 (tt, *J* = 11.1, 3.8 Hz, 1H), 2.53 – 2.42 (m, 1H), 2.34 (td, *J* = 11.8, 2.9 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.81 (dt, *J* = 13.6, 3.5 Hz, 1H), 1.66 – 1.52 (m, 1H), 1.50 – 1.37 (m, 1H); **AMM** 496.9738 (ESI) *m/z* [calc for $C_{18}H_{17}BrClFN_2O_3SNa$ $(M+Na)^+$ 496.9714].

Synthesis of Analogs 7
Synthesis of Common Intermediate (**S1**)



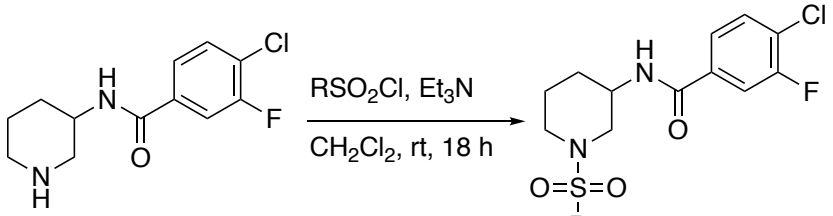
S4

i. To a precooled (0 °C) solution of 3-aminopiperidine (300. mg, 3.00 mmol) in MeOH (15 mL) under N_2 atmosphere was added triethylamine (0.83 mL, 6.0 mmol) then Boc anhydride (0.68 mL, 3.0 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 17 h, then concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 and quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the product as a white solid (573 mg), which was carried forward without additional purification.

ii. To a precooled (0 °C) solution of intermediate (350. mg, 1.75 mmol), 4-chloro-3-fluorobenzoic acid (366 mg, 2.10 mmol) and HATU (731 mg, 1.92 mmol) in DMF (5.8 mL) under N_2 atmosphere was added diisopropylethylamine (0.9 mL, 5 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 42 h, then concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 and the organic layer was washed with sat. aq. $NaHCO_3$. The aqueous phase was then extracted with CH_2Cl_2 (1x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the product as a white solid (528 mg), which was carried forward without additional purification.

iii. To a solution of intermediate (526 mg, 1.47 mmol) in CH_2Cl_2 (7.4 mL) at room temperature under N_2 atmosphere was added trifluoroacetic acid (0.34 mL, 4.4 mmol). The resulting mixture was stirred at room temperature for 14 h, followed by addition of trifluoroacetic acid (0.1 mL, 1.3 mmol). The resulting mixture was stirred for an additional 24 h, then concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 and diluted with H_2O. The layers were separated, and the organic layer was extracted with H_2O (3x). The combined aqueous layers were basified with powdered $NaHCO_3$ to pH 8 then diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (122 mg, 64% yield over 3 steps). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.28, 159.24, 159.10, 157.25, 157.10, 131.23, 131.12, 124.03, 123.23, 123.20, 115.90, 115.72, 49.29, 47.55, 42.96, 28.90, 23.28; **IR** (ATR) ν_{max} 3209, 1674, 1440, 1190, 1133, 801, 724 cm^{-1}; **AMM** 257.0861 (ESI) *m/z* [calc for $C_{12}H_{15}ClFN_2O$ $(M+H)^+$ 257.0857].

General Synthesis of Analogs **7**



S4 **7**

To separate solutions of common intermediate **S4** (24 mg, 0.093 mmol) and triethylamine (40 µL, 0.3 mmol) in dichloromethane (0.6 mL) at 0 °C was added R-sulfonyl chloride (0.14 mmol). The resulting mixtures were stirred for 18 h, then diluted with wet DMSO (1 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (45-57% yield).

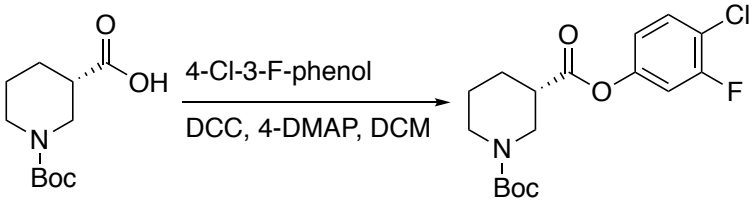
(±)-MCG-III-157-C01 (**7a**)
R = Me (45% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 7.67 (dd, *J* = 10.0, 1.9 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.02 (s, 1H), 4.10 – 3.97 (m, 1H), 3.66 (dd, *J* = 11.7, 3.8 Hz, 1H), 3.50 – 3.34 (m, 1H), 2.98 – 2.86 (m, 1H), 2.78 (s, 3H), 1.92 – 1.82 (m, 1H), 1.75 – 1.63 (m, 1H), 1.63 – 1.53 (m, 1H); **AMM** 357.0455 (ESI) *m/z* [calc for $C_{13}H_{16}ClFN_2O_3SNa$ $(M+Na)^+$ 357.0452].

(±)-MCG-III-157-C02 (**7b**)
R = Et (43% yield)

^{1}H NMR (500 MHz, Acetonitrile-*d*3) δ 7.67 (dd, *J* = 10.1, 1.9 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.01 (s, 1H), 4.07 – 3.92 (m, 1H), 3.70 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.53 – 3.40 (m, 1H), 3.07 – 2.94 (m, 3H), 2.90 (dd, *J* = 11.9, 8.5 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.72 – 1.53 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** 371.0603 (ESI) *m/z* [calc for C14H18ClFN2O3SNa (M+Na)+ 371.0608].

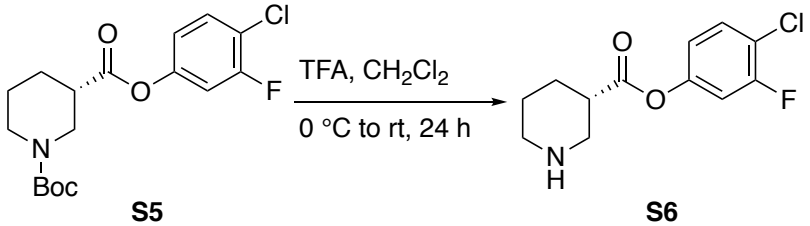
(±)-MCG-III-157-C04 (**7c**)
R = N-Me Imidazole (55% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 7.70 (dd, *J* = 10.1, 1.9 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.60 – 7.53 (m, 2H), 7.40 (s, 1H), 4.07 (tt, *J* = 7.9, 4.1 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 12.2, 3.7 Hz, 1H), 3.40 – 3.30 (m, 1H), 2.96 – 2.85 (m, 2H), 1.88 – 1.80 (m, 1H), 1.80 – 1.71 (m, 1H), 1.67 – 1.47 (m, 2H); **AMM** 423.0685 (ESI) *m/z* [calc for $C_{16}H_{18}ClFN_4O_3SNa$ $(M+Na)^+$ 423.0670].

Synthesis of Analogs 8
Synthesis of Common Intermediate **S6**



S2 **S5**

To a solution of intermediate 2.38 (877 mg, 3.83 mmol), 4-chloro-3-fluorophenol (510 mg, 3.48 mmol), and 4-dimethylaminopyridine (128 mg, 1.04 mmol) in CH_2Cl_2 (24 mL) at room temperature under N_2 atmosphere was added dropwise a solution of N,N'-dicyclohexylcarbodiimide (DCC, 1.2 g, 5.7 mmol) in CH_2Cl_2 (14 mL). The resulting mixture was stirred for 14 h, then filtered and rinsed with minimal CH_2Cl_2. The filtrate was concentrated *in vacuo*. Flash column chromatography (SiO_2, 90:10 hexanes:ethyl acetate, dry loaded on celite) afforded the desired product as a white solid (1.08 g, 87% yield). **$[\alpha]_D^{22}$** -22.1 (c. 0.22, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.38 (t, *J* = 8.5 Hz, 1H), 6.97 (dd, *J* = 9.4, 2.6 Hz, 1H), 6.89 – 6.82 (m, 1H), 4.12 (s, 1H), 3.81 (s, 1H), 3.29 (dd, *J* = 13.3, 9.3 Hz, 1H), 3.10 – 2.92 (m, 1H), 2.71 (s, 1H), 2.12 (d, *J* = 12.4 Hz, 1H), 1.87 – 1.73 (m, 2H), 1.60 – 1.49 (m, 1H), 1.46 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.45, 159.07, 157.08, 154.75, 149.84, 149.77, 130.75, 118.49, 118.31, 118.28, 111.12, 110.93, 80.10, 45.64, 41.34, 34.11, 28.55, 27.18, 24.04; **IR** (ATR) ν_{max} 2948, 1759, 1673, 1426, 1175, 1144, 1127, 997 cm^{-1}; **AMM** 358.1240 (ESI) *m/z* [calc for $C_{17}H_{22}ClFNO_4$ $(M+H)^+$ 358.1221].

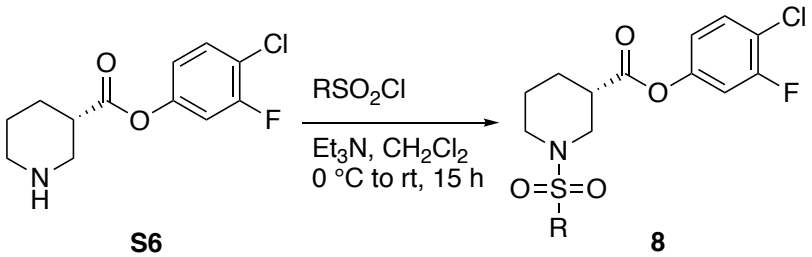


S5 **S6**

To a precooled (0 °C) solution of intermediate **2.54** (1.04 g, 2.91 mmol) in CH_2Cl_2 (15 mL) under N_2 atmosphere was added dropwise trifluoroacetic acid (0.66 mL, 8.7 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 24 h, then concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 and diluted with H_2O. The layers were separated, and the organic layer was extracted with H_2O (3x). The combined aqueous layers were basified with powdered $NaHCO_3$ to pH 8 then diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the product as a colorless oil (418 mg, 84% yield). **^{1}H NMR** (500 MHz, Acetonitrile-d_3) δ 8.71 (s, 1H), 7.97 (s, 1H), 7.53 (t, *J* = 8.6 Hz, 1H), 7.15 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.05 – 6.95 (m, 1H), 3.55 (dd, *J* = 12.5, 3.3 Hz, 1H), 3.36 – 3.23 (m, 2H), 3.23 – 3.12 (m, 2H), 3.08 – 2.94 (m, 1H), 2.26 – 2.14 (m, 1H), 1.92 – 1.81 (m, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 171.25, 160.08, 158.10, 151.17, 151.09, 131.88, 119.76, 119.73, 119.32, 119.18, 112.12, 111.93, 49.00, 45.26, 45.02, 44.92, 39.60, 34.68, 26.01, 25.92, 22.29; **IR** (ATR)

ν_{max} 1753, 1661, 1492, 1427, 1196, 1173, 1149, 1068, 1048, 835, 795, 722 cm^{-1}; **AMM** 258.0695 (ESI) *m/z* [calc for $C_{12}H_{14}ClFNO_2$ $(M+H)^+$ 258.0697].

General Synthesis of Analogs **8**



S6 **8**

To separate precooled (0 °C) solutions of common intermediate **S6** (20. mg, 0.078 mmol) in dichloromethane (0.5 mL) was added triethylamine (30 µL, 0.2 mmol) and R-sulfonyl chloride (0.12 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 15 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (9-45% yield).

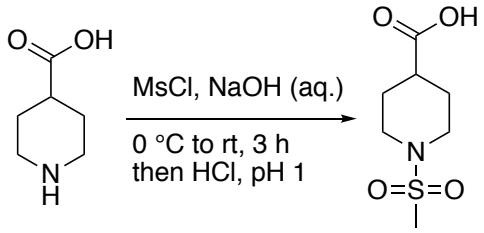
(*S*)-MCG-III-213-A01 (**8a**)
R = Me (9% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 7.52 (t, *J* = 8.6 Hz, 1H), 7.11 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.02 – 6.95 (m, 1H), 3.72 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.41 (dt, *J* = 10.7, 4.7 Hz, 1H), 3.25 (dd, *J* = 11.9, 8.7 Hz, 1H), 3.00 – 2.96 (m, 1H), 2.96 – 2.88 (m, 1H), 2.80 (s, 3H), 2.11 – 2.02 (m, 1H), 1.91 – 1.83 (m, 1H), 1.83 – 1.72 (m, 1H), 1.72 – 1.62 (m, 1H); **AMM** 336.0464 (ESI) *m/z* [calc for $C_{13}H_{16}ClFNO_4S$ $(M+H)^+$ 336.0473].

(*S*)-MCG-III-213-A02 (**8b**)
R = Et (10% yield)
^{1}H NMR (500 MHz, Acetonitrile-*d*3) δ 7.51 (t, *J* = 8.6 Hz, 1H), 7.11 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.01 – 6.96 (m, 1H), 3.76 (dd, *J* = 12.4, 3.9 Hz, 1H), 3.49 – 3.41 (m, 1H), 3.33 (dd, *J* = 12.4, 8.6 Hz, 1H), 3.10 – 3.03 (m, 1H), 3.00 (q, *J* = 7.4 Hz, 2H), 2.89 (tt, *J* = 8.3, 3.9 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.89 – 1.75 (m, 2H), 1.70 – 1.58 (m, 1H), 1.28 (t, *J* = 7.4 Hz, 3H); **AMM** 350.0648 (ESI) *m/z* [calc for C14H18ClFNO4S (M+H)+ 350.0629].

(*S*)-MCG-III-213-A03 (**8c**)
R = Ph (9% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 7.82 – 7.76 (m, 2H), 7.72 – 7.66 (m, 1H), 7.65 – 7.58 (m, 2H), 7.52 (t, *J* = 8.6 Hz, 1H), 7.10 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.01 – 6.95 (m, 1H), 3.60 (d, *J* = 11.2 Hz, 1H), 3.35 – 3.26 (m, 1H), 3.01 – 2.94 (m, 1H), 2.91 (tt, *J* = 8.7, 3.9 Hz, 1H), 2.74 – 2.65 (m, 1H), 1.89 – 1.77 (m, 1H), 1.70 – 1.57 (m, 2H); **AMM** 398.0639 (ESI) *m/z* [calc for $C_{18}H_{18}ClFNO_4S$ $(M+H)^+$ 398.0629].

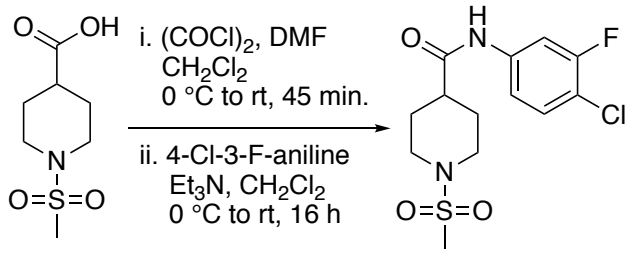
(*S*)-MCG-III-213-A04 (**8d**)
R = N-Me Imidazole (45% yield)
^{1}H NMR (500 MHz, Acetonitrile-*d*3) δ 7.63 (d, *J* = 1.4 Hz, 1H), 7.56 (d, *J* = 1.4 Hz, 1H), 7.51 (t, *J* = 8.6 Hz, 1H), 7.11 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.01 – 6.95 (m, 1H), 3.75 – 3.72 (m, 1H), 3.71 (s, 3H), 3.40 (dd, *J* = 12.3, 5.1 Hz, 1H), 3.10 (dd, *J* = 12.1, 9.1 Hz, 1H), 2.92 (tt, *J* = 9.0, 4.0 Hz, 1H), 2.81 (ddd, *J* = 12.9, 9.6, 3.4 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.87 – 1.78 (m, 1H), 1.70 – 1.56 (m, 2H); **AMM** 402.0697 (ESI) *m/z* [calc for C16H18ClFN3O4S (M+H)+ 402.0691].

Synthesis of Analog 9



S7

To a precooled (0 °C) solution of 4-piperidine carboxylic acid (1.0 g, 7.7 mmol) in 1M aq. NaOH (15 mL) was added methanesulfonyl chloride (0.72 mL, 9.3 mmol). The resulting mixture was stirred at 0 °C to room temperature for 3 h, then quenched slowly with 6 M aq. HCl and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (264 mg, 16% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.73 – 3.62 (m, 2H), 2.94 – 2.83 (m, 2H), 2.79 (s, 3H), 2.11 – 2.01 (m, 2H), 1.94 – 1.77 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.40, 45.14, 39.85, 35.23, 27.51; **IR** (ATR) ν_{max} 2936, 1697, 1320, 1141, 920, 776, 518 cm^{-1}; **AMM** (ESI) *m/z* 208.0641 [calc for $C_7H_{14}NO_4S$ $(M+H)^+$ 208.0644].



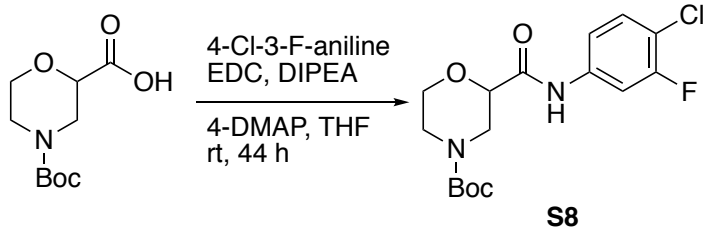
S7 **9**

i. To a precooled (0 °C) solution of intermediate **S7** (100. mg, 0.41 mmol) in CH_2Cl_2 (2 mL) under N_2 atmosphere was added dropwise oxalyl chloride (0.04 mL, 0.4 mmol) then DMF (1 drop). The resulting mixture was allowed to warm to room temperature and stirred for 45 min. then concentrated *in vacuo* and carried forward without additional purification.

ii. To a precooled (0 °C) solution of 4-chloro-3-fluoroaniline (60. mg, 0.41 mmol) and triethylamine (0.1 mL, 0.8 mmol) in CH_2Cl_2 (1 mL) was added a precooled (0 °C) solution of acid chloride intermediate (93 mg, 0.41 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was allowed to warm to room temperature and stirred for 16 h, then quenched with H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 50:50 ethyl acetate: hexanes) afforded the product as a white solid (91 mg, 66% yield). **^{1}H NMR** (500 MHz, Acetonitrile-d_3) δ 8.52 (s, 1H), 7.73 (dd, *J* = 11.9, 2.7 Hz, 1H), 7.37 (dd, *J* = 10.1, 7.3 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 3.75 – 3.63 (m, 2H), 2.84 – 2.68 (m, 5H), 2.50 – 2.36 (m, 1H), 1.83 – 1.68 (m, 2H); **AMM** (ESI) *m/z* 335.0640 [calc for $C_{13}H_{17}ClFN_2O_3S$ $(M+H)^+$ 335.0632].

Syntheses of Common Intermediates 10

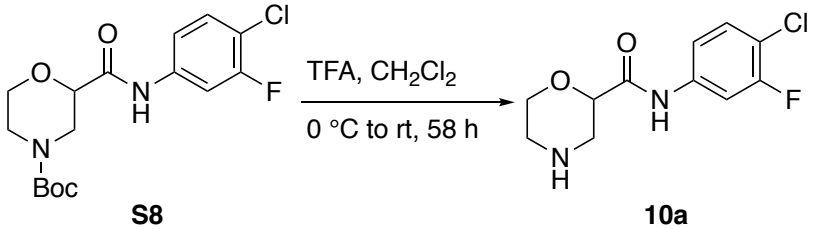
Synthesis of Common Intermediate **10a** (MCG-III-196)



S8

To a precooled (0 °C) solution of 4-Boc-morpholine-2-carboxylic acid (400. mg, 1.73 mmol), 4-chloro-3-fluoroaniline (378 mg, 2.60 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI, 269 mg, 1.73 mmol) and 4-dimethylaminopyridine (42 mg, 0.35 mmol) in tetrahydrofuran (17 mL) under N_2

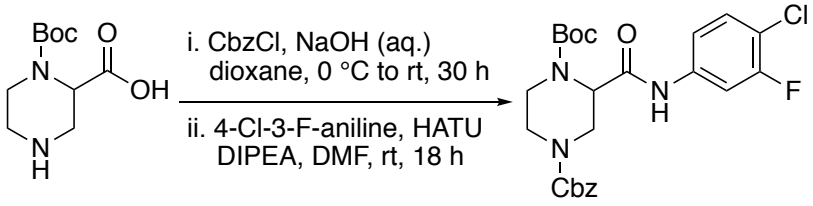
atmosphere was added diisopropylethylamine (0.75 mL, 4.3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 44 h then quenched with sat. aq. $NaHCO_3$ and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 70:30 hexanes:ethyl acetate) afforded the product as a white solid (330 mg, 53% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.34 (s, 1H), 7.66 (dd, *J* = 10.9, 2.4 Hz, 1H), 7.32 (t, *J* = 8.3 Hz, 1H), 7.21 – 7.13 (m, 1H), 4.41 (s, 1H), 4.11 – 3.92 (m, 3H), 3.64 (td, *J* = 11.8, 2.8 Hz, 1H), 3.02 – 2.74 (m, 2H), 1.48 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.04, 159.18, 157.21, 154.61, 137.10, 137.02, 130.70, 116.40, 116.26, 115.88, 115.85, 108.64, 108.44, 80.88, 75.12, 66.88, 46.17, 28.50; **IR** (ATR) ν_{max} 3398, 2925, 1691, 1527, 1416, 1127, 868, 809, 605 cm^{-1}; **AMM** 359.1197 (ESI) *m/z* [calc for $C_{16}H_{21}ClFN_2O_4$ $(M+H)^+$ 359.1174].



S8 **10a**

To a precooled (0 °C) solution of intermediate **2.72** (300. mg, 0.836 mmol) in CH_2Cl_2 (8.4 mL) under N_2 atmosphere was added dropwise trifluoroacetic acid (0.2 mL, 3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 22 h, then cooled to 0 °C before addition of trifluoroacetic acid (0.2 mL, 3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 36 h, then concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 and the solution was quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (233 mg, 98% yield). **^{1}H NMR** (500 MHz, Acetonitrile-d_3) δ 8.92 (s, 1H), 7.70 (dd, *J* = 11.6, 2.4 Hz, 1H), 7.41 (t, *J* = 8.5 Hz, 1H), 7.37 – 7.31 (m, 1H), 4.53 (dd, *J* = 10.7, 2.8 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.99 (ddd, *J* = 13.1, 11.4, 2.6 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.31 (d, *J* = 13.1 Hz, 1H), 3.20 – 3.09 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.16, 157.19, 137.30, 137.23, 130.65, 116.19, 116.05, 115.86, 115.83, 108.59, 108.39, 100.12, 34.26; **IR** (ATR) ν_{max} 3380, 2500, 1708, 1663, 1522, 1426, 1196, 1171, 1130, 1066, 836, 792, 725, 473 cm^{-1}; **AMM** 259.0669 (ESI) *m/z* [calc for $C_{11}H_{13}ClFN_2O_2$ $(M+H)^+$ 259.0650].

Synthesis of Common Intermediate **10b** (MCG-III-210)

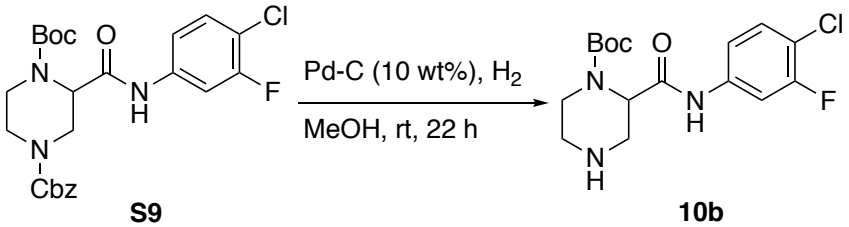


S9

i. To a precooled (0 °C) solution of 1-Boc-piperazine-2-carboxylic acid (500. mg, 2.17 mmol) in 1,4-dioxane (11 mL) under N_2 atmosphere was added 1 M aq. NaOH until pH 11 achieved. To the resulting mixture was then added dropwise benzyl chloroformate (0.31 mL, 2.17 mmol) followed by additional 1 M aq. NaOH to maintain pH 11. The resulting mixture was allowed to warm to room temperature and stirred for 3 h, then cooled to 0 °C before addition of benzyl chloroformate (0.31 mL, 2.17 mmol) and 1 M aq. NaOH to maintain pH 11. The resulting mixture was allowed to warm to room temperature and stirred for 28 h, then cooled to 0 °C and acidified slowly with 1 M aq. HCl to pH 2. The aqueous layer was diluted with EtOAc and the layers were separated then the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the product, which was carried forward.

ii. To a solution of intermediate (586 mg, 1.61 mmol), 4-chloro-3-fluoroaniline (281 mg, 1.93 mmol), and HATU (673 mg, 1.77 mmol) in DMF (8.0 mL) at room temperature under N_2

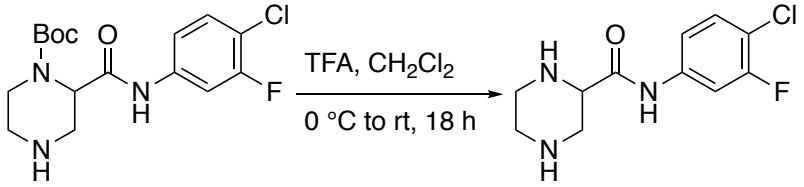
atmosphere was added diisopropylethylamine (0.84 mL, 4.8 mmol). The resulting mixture was stirred at room temperature for 18 h then concentrated *in vacuo*. The resulting residue was taken up in EtOAc and quenched with H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, 50:50 hexanes:EtOAc) afforded the product as a white solid (216 mg, 20% yield over 2 steps). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 7.61 (d, *J* = 10.5 Hz, 1H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.11 – 7.04 (m, 1H), 4.59 (d, *J* = 4.2 Hz, 1H), 3.91 (s, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.05 – 2.92 (m, 2H), 2.88 (dd, *J* = 13.4, 4.3 Hz, 1H), 2.78 (td, *J* = 12.4, 3.5 Hz, 1H), 1.52 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.33, 147.70, 143.90, 139.16, 129.72, 127.25, 125.47, 119.69, 117.66, 114.46, 52.08, 43.73, 38.55, 29.84; **IR** (ATR) ν_{max} 3285, 2925, 2850, 1653, 1525, 1321, 1154, 983, 948, 826, 790, 506 cm^{-1}; **AMM** 492.1708 (ESI) *m/z* [calc for $C_{24}H_{28}ClFN_3O_5$ $(M+H)^+$ 492.1702].



S9 **10b**

To a solution of palladium on carbon (10 wt. %, 17 mg, 0.16 mmol) in MeOH (3 mL) at room temperature under N_2 atmosphere was added a solution of intermediate **2.79** (389 mg, 0.791 mmol) in MeOH (5 mL). The resulting mixture was then backfilled with H_2 (3x) then stirred at room temperature under H_2 atmosphere for 22 h. The resulting mixture was filtered through a bed of celite and rinsed with MeOH. The filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2, 95:5 CH_2Cl_2:MeOH) afforded the product as a white solid (152 mg, 53% yield). **^{1}H NMR** (500 MHz, Acetonitrile-*d*3) δ 9.47 (s, 1H), 7.74 (dd, *J* = 11.6, 2.4 Hz, 1H), 7.45 (t, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 4.01 (s, 1H), 3.51 – 3.43 (m, 1H), 3.37 (dd, *J* = 12.9, 7.5 Hz, 1H), 3.24 – 3.09 (m, 3H), 2.54 (s, 1H), 1.95 (s, 9H); **IR** (ATR) ν_{max} 2456, 1660, 1607, 1533, 1429, 1182, 1137, 867, 797, 724, 596 cm^{-1}; **AMM** 358.1334 (ESI) *m/z* [calc for $C_{16}H_{22}ClFN_3O_3$ $(M+H)^+$ 358.1334].

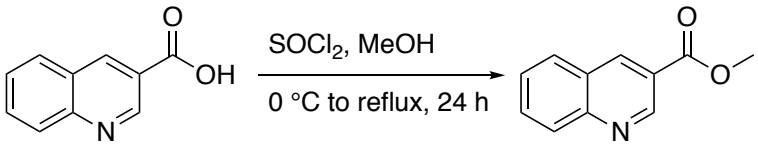
Synthesis of Compound **10c** (MCG-III-216-A01)



10b **10c**

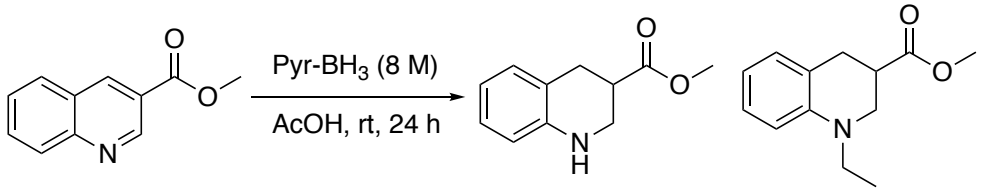
To a precooled (0 °C) solution of **10b** (10. mg, 0.028 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (10 µL, 0.1 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 18 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (13.2 mg, 85% yield).
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.73 (s, 1H), 7.67 (dd, *J* = 11.3, 2.6 Hz, 1H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.35 – 7.24 (m, 1H), 4.34 (s, 1H), 3.67 (s, 1H), 3.47 (dd, *J* = 13.4, 9.1 Hz, 1H), 3.43 – 3.22 (m, 4H), 2.10 – 2.03 (m, 1H); **AMM** 258.0818 (ESI) *m/z* [calc for $C_{11}H_{14}ClFN_3O$ $(M+H)^+$ 258.0809].

Synthesis of Common Intermediate **10d** (MCG-III-209)



S10

To a precooled (0 °C) solution of quinoline-3-carboxylic acid (1.50 g, 8.66 mmol) in MeOH (43 mL) under N_2 atmosphere was added dropwise thionyl chloride (1.3 mL, 17 mmol). The resulting mixture was heated to reflux and stirred for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 and quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as an off-white solid (1.58 g, 97% yield).[11] **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.43 (s, 1H), 8.82 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.94 – 7.86 (m, 1H), 7.81 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 3.99 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.78, 149.83, 149.57, 139.07, 132.08, 129.33, 129.20, 127.64, 126.95, 123.12, 77.16, 52.59; **IR** (ATR) ν_{max} 3509, 2994, 1714, 1618, 1572, 1497, 1434, 1367, 1290, 1241, 1192, 1100, 791, 769 cm^{-1}; **AMM** 188.0704 (ESI) *m/z* [calc for $C_{11}H_{10}NO_2$ $(M+H)^+$ 188.0712].

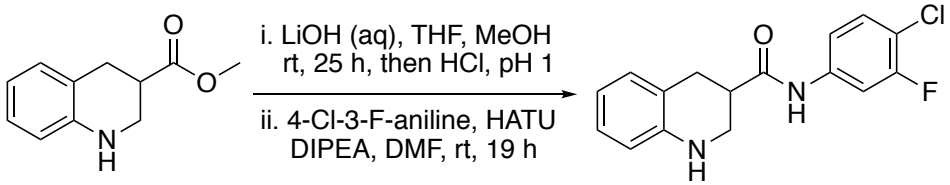


S10 **S11** **S12**

To a precooled (0 °C) solution of intermediate **S10** (1.50 g, 8.01 mmol) in glacial acetic acid (40 mL) under N_2 atmosphere was added 8 M borane pyridine complex (2.0 mL, 16 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 24 h, then concentrated *in vacuo*. The resulting residue was taken up in EtOAc and the solution was cooled to 0 °C and neutralized with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brined, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 80:20 hexanes:EtOAc) afforded the product **S11** (874 mg, 57% yield) and side product **S12** (464 mg, 26% yield).

S11: **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 6.99 (t, *J* = 7.3 Hz, 2H), 6.65 (td, *J* = 7.4, 1.2 Hz, 1H), 6.51 (dd, *J* = 8.4, 1.5 Hz, 1H), 3.74 (s, 3H), 3.55 (ddd, *J* = 11.6, 3.4, 1.3 Hz, 1H), 3.37 (dd, *J* = 11.4, 9.4 Hz, 1H), 3.06 – 2.99 (m, 2H), 2.98 – 2.87 (m, 1H); **AMM** 192.1023 (ESI) *m/z* [calc for $C_{11}H_{14}NO_2$ $(M+H)^+$ 192.1025]. The experimental data agreed with literature precedent.[1]

S12: **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.12 – 7.04 (m, 1H), 7.00 (d, *J* = 7.1 Hz, 1H), 6.67 – 6.56 (m, 2H), 3.74 (s, 3H), 3.53 – 3.42 (m, 2H), 3.42 – 3.35 (m, 1H), 3.34 – 3.24 (m, 1H), 3.04 – 2.89 (m, 3H), 1.15 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.92, 144.09, 129.30, 127.31, 120.43, 115.99, 110.76, 51.76, 49.61, 45.30, 38.29, 30.63, 10.79; **AMM** 220.1351 (ESI) *m/z* [calc for $C_{13}H_{18}NO_2$ $(M+H)^+$ 220.1338].



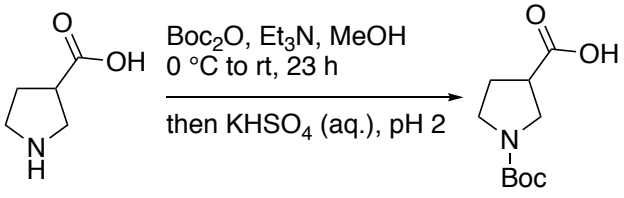
S11 **10d**

i. To a flask charged with intermediate **S11** (786 mg, 4.11 mmol) at room temperature under N_2 atmosphere was added 1 M aq. LiOH (8 mL), THF (24 mL) and MeOH (8 mL). The resulting mixture was stirred at room temperature for 25 h, then concentrated *in vacuo* to remove volatiles. The remaining mixture was quenched with 1 M aq. NaOH and the aqueous phase was washed with Et_2O then cooled to 0 °C and acidified with 1 M aq. HCl to pH 2 and diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the product, which was carried forward without additional purification.

ii. To a solution of intermediate (129 mg, 0.727 mmol), 4-chloro-3-fluoroaniline (128 mg, 0.872 mmol), and HATU (304 mg, 0.800 mmol) in DMF (3.6 mL) at room temperature under N_2

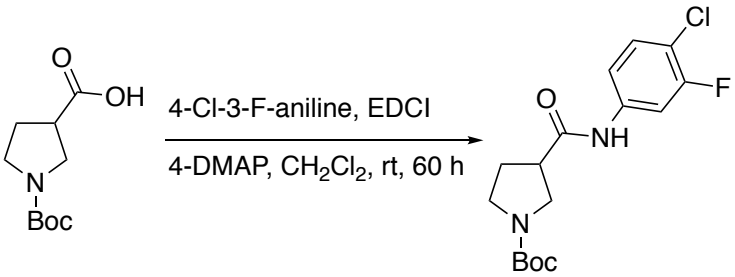
atmosphere was added diisopropylethylamine (0.38 mL, 2.18 mmol). The resulting mixture was stirred at room temperature for 19 h, then concentrated *in vacuo*. The resulting residue was taken up in EtOAc and quenched with H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, 80:20 hexanes:EtOAc) afforded the product as a white solid (195 mg, 17% yield over 2 steps).
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.01 (s, 1H), 7.69 (dd, *J* = 11.7, 2.4 Hz, 1H), 7.40 (t, *J* = 8.5 Hz, 1H), 7.30 – 7.19 (m, 3H), 7.17 – 7.10 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 3.65 – 3.52 (m, 2H), 3.21 – 3.05 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.78, 159.06, 157.10, 143.11, 138.18, 138.10, 130.46, 129.98, 127.50, 119.74, 118.99, 116.08, 115.16, 108.84, 108.63, 77.16, 43.51, 40.19, 38.75, 30.11; **IR** (ATR) ν_{max} 3400, 2928, 1667, 1604, 1531, 1493, 1423, 1385, 840, 747, 556 cm^{-1}; **AMM** 305.0869 (ESI) *m/z* [calc for $C_{16}H_{15}ClFN_2O$ $(M+H)^+$ 305.0857].

Synthesis of Common Intermediate **S1**



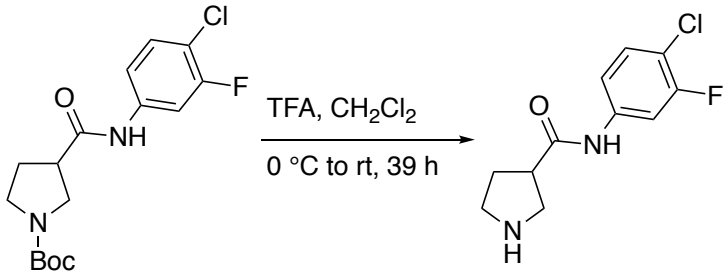
S13

To a precooled (0 °C) solution of pyrrolidine-3-carboxylic acid (300. mg, 2.61 mmol) in MeOH (13 mL) under N_2 atmosphere was added triethylamine (0.7 mL, 3 mmol) then Boc anhydride (0.7 mL, 3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 23 h then concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2 and the solution acidified with sat. aq. $KHSO_4$ to pH 2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (556 mg, 99% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.87 (dt, *J* = 13.4, 4.1 Hz, 1H), 3.21 – 2.94 (m, 1H), 2.85 (t, *J* = 12.5 Hz, 1H), 2.53 – 2.39 (m, 1H), 2.12 – 2.00 (m, 1H), 1.77 – 1.67 (m, 1H), 1.67 – 1.55 (m, 1H), 1.45 (d, *J* = 2.0 Hz, 9H); **^{13}C NMR** (126 MHz, DMSO) δ 174.32, 153.75, 78.65, 40.54, 39.52, 28.13, 28.03, 26.59, 23.80; **IR** (ATR) ν_{max} 2975, 1732, 1660, 1435, 1271, 1144, 849, 767, 640 cm^{-1}; **AMM** (ESI) *m/z* 216.1224 [calc for $C_{10}H_{18}NO_4$ $(M+H)^+$ 216.1236].



S13 **S14**

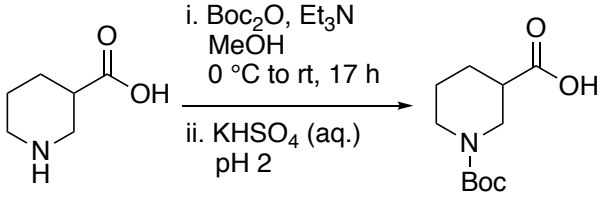
To a precooled (0 °C) solution of 4-chloro-3-fluoroaniline (262 mg, 1.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (316 mg, 1.65 mmol) and 4-dimethylaminopyridine (202 mg, 1.65 mmol) in CH_2Cl_2 (7.5 mL) under N_2 atmosphere was added a solution of intermediate **S13** (323 mg, 1.50 mmol) in CH_2Cl_2 (7.5 mL). The resulting mixture was allowed to warm to room temperature and stirred for 60 h, then quenched with H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, 60:40 hexanes:EtOAc) afforded the product as a white solid (417 mg, 81% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.22 (d, *J* = 8.9 Hz, 1H), 7.58 (dd, *J* = 11.2, 2.4 Hz, 1H), 7.24 – 7.06 (m, 2H), 3.65 – 3.45 (m, 3H), 3.38 – 3.19 (m, 1H), 3.15 – 2.96 (m, 1H), 2.26 – 2.00 (m, 2H), 1.41 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.52, 158.74, 156.78, 154.64, 138.28, 138.20, 130.29, 116.12, 116.09, 115.53, 115.39, 108.68, 108.47, 79.97, 77.16, 48.79, 48.64, 45.76, 45.47, 45.11, 44.31, 29.53, 29.04, 28.43; **AMM** (ESI) *m/z* 343.1228 [calc for $C_{16}H_{21}ClFN_2O_3$ $(M+H)^+$ 343.1225].



S14 **S15**

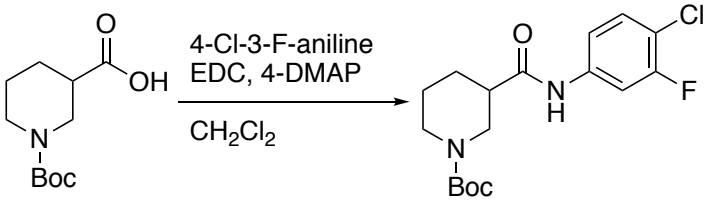
To a precooled (0 °C) solution of intermediate **S14** (139 mg, 0.405 mmol) in CH_2Cl_2 (2 mL) under N_2 atmosphere was added dropwise trifluoroacetic acid (0.2 mL, 2 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 39 h then concentrated *in vacuo*. The resulting residue was taken up in H_2O and the aqueous solution was neutralized with powdered $NaHCO_3$ then diluted with $CHCl_3$. The layers were separated, and the aqueous phase was extracted with $CHCl_3$ (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (35 mg, 36% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 7.61 (dd, *J* = 11.2, 2.5 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.10 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.28 (dd, *J* = 10.3, 2.3 Hz, 1H), 3.19 (ddd, *J* = 10.0, 8.5, 4.2 Hz, 1H), 2.99 – 2.82 (m, 3H), 2.39 (s, 1H), 2.25 – 2.11 (m, 1H), 2.09 – 1.95 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.59, 130.49, 115.76, 108.50, 108.29, 53.57, 50.81, 45.73, 45.66, 29.86, 29.74; **IR** (ATR) ν_{max} 3243, 3187, 3111, 2926, 1674, 1604, 1538, 1492, 1422, 1213, 1061, 863, 814 cm^{-1}; **AMM** (ESI) *m/z* 243.0692 [calc for $C_{11}H_{13}ClFN_2O$ $(M+H)^+$ 243.0700].

Synthesis of Common Intermediate **S18**



S16

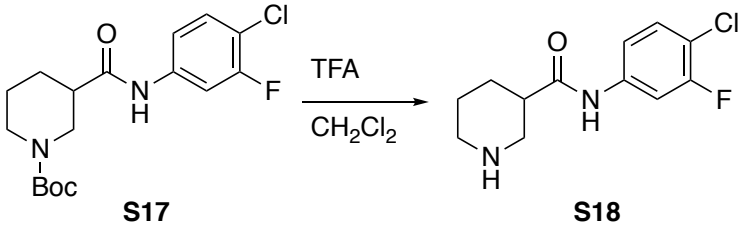
To a precooled (0 °C) solution of piperidine-3-carboxylic acid (300. mg, 2.32 mmol) in MeOH (12 mL) under N_2 atmosphere was added triethylamine (0.65 mL, 4.6 mmol) then dropwise Boc anhydride (0.64 mL, 2.8 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 17 h, then concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 and acidified with aq. $KHSO_4$ to pH 2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with 1 M aq. HCl then brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the product as a white solid (357 mg, 67% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.10 (s, 1H), 3.88 (dt, *J* = 13.4, 4.1 Hz, 1H), 3.23 – 2.93 (m, 1H), 2.93 – 2.80 (m, 1H), 2.56 – 2.42 (m, 1H), 2.14 – 2.01 (m, 1H), 1.80 – 1.56 (m, 2H), 1.46 (d, *J* = 6.8 Hz, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.93, 154.65, 79.98, 48.08, 45.48, 45.20, 43.21, 42.39, 31.11, 28.58; **IR** (ATR) ν_{max} 3177, 2972, 1741, 1665, 1424, 1165, 1131, 868, 831, 765, 648, 581 cm^{-1}; **AMM** 230.1406 (ESI) *m/z* [calc for $C_{11}H_{20}NO_4$ $(M+H)^+$ 230.1392].



S16 **S17**

To a precooled (0 °C) solution of intermediate **S16** (357 mg, 1.56 mmol), hexafluorophosphate azabenzotriazole tetramethyl uranium (HATU, 652 mg, 1.71 mmol), and 4-chloro-3-fluoroaniline (327 mg, 1.87 mmol) in dimethylformamide (5.2 mL) under N_2 atmosphere was added diisopropylethylamine (0.81

mL, 4.7 mmol). The resulting mixture was stirred at room temperature for 45 h, then concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2. The organic layer was washed sequentially with sat. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 60:40 hexanes:EtOAc) afforded the product as a white solid (247 mg, 44% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.81 – 7.58 (m, 1H), 7.37 – 7.05 (m, 2H), 4.00 – 3.79 (m, 1H), 3.68 (s, 1H), 3.45 (s, 1H), 3.19 (s, 1H), 2.62 – 2.42 (m, 1H), 2.16 – 1.98 (m, 1H), 1.98 – 1.82 (m, 1H), 1.74 – 1.58 (m, 1H), 1.47 (s, 10H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.79, 158.98, 157.02, 155.41, 138.61, 130.38, 115.84, 115.81, 115.44, 115.30, 108.50, 108.29, 80.64, 45.60, 44.85, 43.78, 28.52, 24.15; **IR** (ATR) ν_{max} 3150, 1731, 1657, 1474, 1144, 849 cm^{-1}; **AMM** (ESI) *m/z* 357.1393 [calc for $C_{17}H_{23}ClFN_2O_3$ $(M+H)^+$ 357.1381].

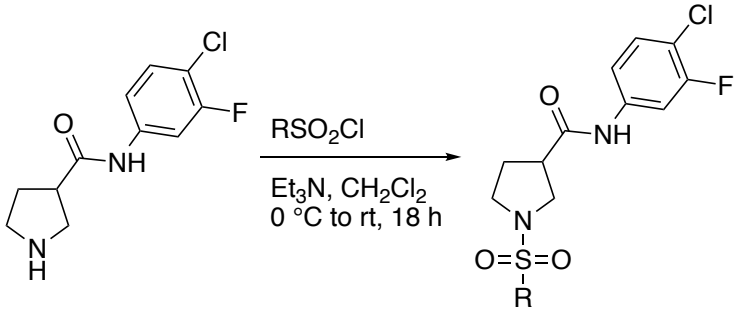


S17 **S18**

To a solution of intermediate **2.102** (247 mg, 0.692 mmol) in CH_2Cl_2 (3.5 mL) at room temperature under N_2 atmosphere was added trifluoroacetic acid (0.16 mL, 2.1 mmol). The resulting mixture was stirred for 38 h, then concentrated *in vacuo*. The crude residue was taken up in CH_2Cl_2 and diluted with water. The layers were separated, and the organic phase was washed with water (3x). The combined aqueous layers were basified to pH 8 with powdered $NaHCO_3$. The aqueous phase was then extracted with CH_2Cl_2 (3x), then the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to afford the product as a white solid (66 mg, 37% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 11.01 (s, 1H), 7.69 (dd, *J* = 11.3, 2.3 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.17 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.26 (dd, *J* = 12.1, 3.2 Hz, 1H), 3.16 – 3.02 (m, 1H), 2.93 (dd, *J* = 12.0, 3.1 Hz, 1H), 2.75 (td, *J* = 10.9, 3.2 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.35 – 2.17 (m, 1H), 2.11 – 1.99 (m, 1H), 1.85 – 1.66 (m, 2H), 1.65 – 1.51 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.27, 159.08, 157.12, 138.66, 138.58, 130.35, 115.89, 115.86, 115.03, 114.88, 108.50, 108.30, 47.92, 46.67, 41.79, 29.82, 27.62, 22.61; **IR** (ATR) ν_{max} 3075, 2920, 2850, 1673, 1604, 1545, 1490, 1420, 1337, 1202, 857, 805, 717 cm^{-1}; **AMM** (ESI) *m/z* 257.0877 [calc for $C_{12}H_{15}ClFN_2O$ $(M+H)^+$ 257.0857].

Synthesis of Analogs 11

General Synthesis of Analogs **11a**-**11d**



S15 **11a**-**11d**

To separate precooled (0 °C) solutions of common intermediate **S15** (18 mg, 0.074 mmol) and triethylamine (30 µL, 0.2 mmol) in dichloromethane (0.5 mL) was added R-sulfonyl chloride (0.11 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 18 h, then diluted with wet DMSO (1 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (22-29 % yield).

(±)-MCG-III-157-A01 (**11a**)

R = Me (29% yield)

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.71 (s, 1H), 7.71 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.39 (t, *J* = 8.6 Hz, 1H), 7.26 (ddd, *J* = 8.8, 2.5, 1.2 Hz, 1H), 3.55 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.49 (dd, *J* = 10.4, 6.2 Hz, 1H), 3.44 –

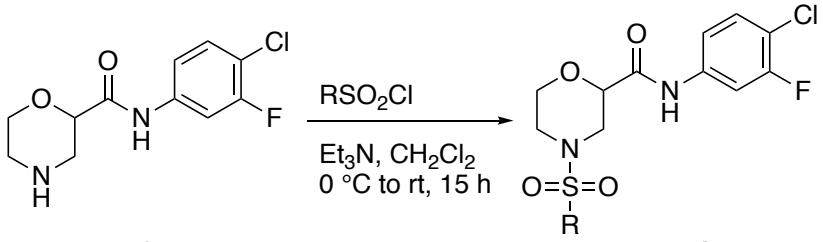
3.30 (m, 2H), 3.17 (p, *J* = 7.2 Hz, 1H), 2.84 (s, 3H), 2.31 – 2.12 (m, 2H); **AMM** 343.0306 (ESI) *m/z* [calc for $C_{12}H_{14}ClFN_2O_3SNa$ $(M+Na)^+$] 343.0295].

(±)-MCG-III-157-A02 (**11b**)
R = Et (23% yield)
^{1}H NMR (500 MHz, Acetonitrile-*d*3) δ 8.68 (s, 1H), 7.71 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.39 (t, *J* = 8.6 Hz, 1H), 7.31 – 7.21 (m, 1H), 3.59 (dd, *J* = 10.1, 7.8 Hz, 1H), 3.51 (dd, *J* = 10.1, 6.4 Hz, 1H), 3.48 – 3.34 (m, 2H), 3.16 (p, *J* = 7.3 Hz, 1H), 3.05 (qd, *J* = 7.3, 2.4 Hz, 2H), 2.30 – 2.11 (m, 2H), 1.30 (t, *J* = 7.4 Hz, 3H); **AMM** 357.0447 (ESI) *m/z* [calc for C13H16ClFN2O3SNa (M+Na)+] 357.0452].

(±)-MCG-III-157-A03 (**11c**)
R = Ph (26% yield)
^{1}H NMR (500 MHz, Acetonitrile-*d*3) δ 8.58 (s, 1H), 7.88 – 7.80 (m, 2H), 7.71 – 7.64 (m, 1H), 7.64 – 7.56 (m, 3H), 7.36 (t, *J* = 8.6 Hz, 1H), 7.21 – 7.13 (m, 1H), 3.54 (dd, *J* = 10.3, 8.0 Hz, 1H), 3.39 – 3.24 (m, 3H), 2.97 (p, *J* = 7.5 Hz, 1H), 2.10 – 2.00 (m, 1H); **AMM** 405.0446 (ESI) *m/z* [calc for $C_{17}H_{16}ClFN_2O_3SNa$ $(M+Na)^+$] 405.0452].

(±)-MCG-III-157-A04 (**11d**)
R = N-Me Imidazole (22% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.56 (s, 1H), 7.69 (s, 1H), 7.66 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.59 (d, *J* = 1.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.21 (dd, *J* = 8.7, 2.1 Hz, 1H), 3.72 (s, 3H), 3.63 (dd, *J* = 10.4, 7.9 Hz, 1H), 3.50 – 3.40 (m, 2H), 3.40 – 3.32 (m, 1H), 3.00 (p, *J* = 7.6 Hz, 1H), 2.14 – 1.96 (m, 2H); **AMM** 409.0521 (ESI) *m/z* [calc for $C_{15}H_{16}ClFN_4O_3SNa$ $(M+Na)^+$ 409.0513].

General Synthesis of Analogs **11e**-**11h**



10a **11e**-**11h**

To separate precooled (0 °C) solutions of common intermediate **10a** (20. mg, 0.077 mmol) in dichloromethane (0.5 mL) was added triethylamine (30 µL, 0.2 mmol) and R-sulfonyl chloride (0.12 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 15 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (41-91% yield).

(±)-MCG-III-211-A01 (**11e**)
R = Me (41% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.84 (s, 1H), 7.72 (dd, *J* = 11.6, 2.3 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.39 – 7.33 (m, 1H), 4.19 (dd, *J* = 10.0, 3.1 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.84 – 3.78 (m, 1H), 3.74 (td, *J* = 11.3, 2.8 Hz, 1H), 3.48 (dq, *J* = 12.1, 2.2 Hz, 1H), 2.98 – 2.85 (m, 2H), 2.82 (s, 3H); **AMM** 337.0448 (ESI) *m/z* [calc for $C_{12}H_{15}ClFN_2O_4S$ $(M+H)^+$ 337.0425].

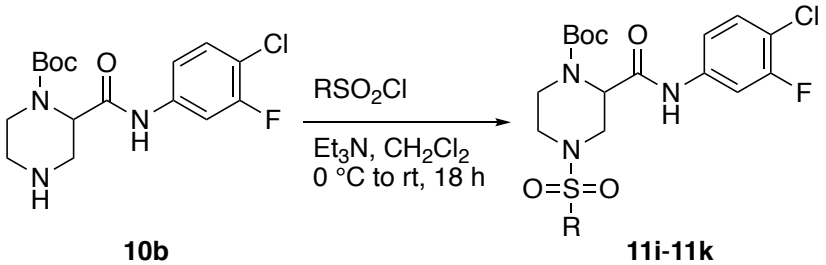
(±)-MCG-III-211-A02 (**11f**)
R = Et (51% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.83 (s, 1H), 7.72 (dd, *J* = 11.7, 2.4 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.39 – 7.33 (m, 1H), 4.16 (dd, *J* = 10.0, 3.1 Hz, 1H), 4.07 (ddd, *J* = 11.6, 3.3, 2.1 Hz, 1H), 3.83 (ddd, *J* = 12.3, 3.1, 1.8 Hz, 1H), 3.71 (ddd, *J* = 11.7, 10.9, 2.8 Hz, 1H), 3.51 (dq, *J* = 12.4, 2.2 Hz, 1H), 3.09 – 2.93 (m, 4H), 1.29 (t, *J* = 7.4 Hz, 3H); **AMM** 351.0597 (ESI) *m/z* [calc for $C_{13}H_{17}ClFN_2O_4S$ $(M+H)^+$ 351.0582].

(±)-MCG-III-211-A03 (**11g**)
R = Ph (55% yield)

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.73 (s, 1H), 7.82 – 7.76 (m, 2H), 7.73 – 7.65 (m, 2H), 7.65 – 7.59 (m, 2H), 7.39 (t, *J* = 8.5 Hz, 1H), 7.34 – 7.28 (m, 1H), 4.19 (dd, *J* = 10.1, 3.0 Hz, 1H), 4.03 (ddd, *J* = 11.7, 3.4, 2.1 Hz, 1H), 3.81 (ddd, *J* = 11.8, 3.1, 1.8 Hz, 1H), 3.74 (td, *J* = 11.3, 2.8 Hz, 1H), 3.50 (dq, *J* = 12.0, 2.2 Hz, 1H), 2.53 – 2.40 (m, 3H); **AMM** 399.0594 (ESI) *m/z* [calc for $C_{17}H_{17}ClFN_2O_4S$ $(M+H)^+$ 399.0582].

(±)-MCG-III-211-A04 (**11h**)
R = N-Me Imidazole (91% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.77 (s, 1H), 7.76 (d, *J* = 1.4 Hz, 1H), 7.69 (dd, *J* = 11.6, 2.4 Hz, 1H), 7.63 (d, *J* = 1.4 Hz, 1H), 7.39 (t, *J* = 8.5 Hz, 1H), 7.35 – 7.29 (m, 1H), 4.19 (dd, *J* = 10.3, 3.1 Hz, 1H), 4.05 (ddd, *J* = 11.7, 3.5, 2.0 Hz, 1H), 3.81 (ddd, *J* = 12.1, 3.1, 1.8 Hz, 1H), 3.72 (s, 5H), 3.52 (dt, *J* = 12.4, 2.2 Hz, 1H), 2.75 (ddd, *J* = 12.3, 11.1, 3.4 Hz, 1H), 2.69 – 2.59 (m, 1H); **AMM** 403.0655 (ESI) *m/z* [calc for $C_{15}H_{17}ClFN_4O_4S$ $(M+H)^+$ 403.0643].

General Synthesis of Analogs **11i-11k**



10b **11i-11k**

To separate precooled (0 °C) solutions of common intermediate **10b** (20. mg, 0.056 mmol) in dichloromethane (0.5 mL) was added triethylamine (20 µL, 0.1 mmol) and R-sulfonyl chloride (0.084 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 15 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (40-78% yield).

(±)-MCG-III-212-A01 (**11i**)
R = Me (40% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.81 (s, 1H), 7.69 (dd, *J* = 11.7, 2.4 Hz, 1H), 7.40 (t, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 4.83 (s, 1H), 4.13 (d, *J* = 12.6 Hz, 1H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.55 (d, *J* = 11.8 Hz, 1H), 3.30 (s, 1H), 3.03 (dd, *J* = 12.6, 4.3 Hz, 1H), 2.83 (dd, *J* = 14.9, 3.1 Hz, 1H), 2.79 (s, 3H), 1.45 (s, 9H); **AMM** 436.1121 (ESI) *m/z* [calc for $C_{17}H_{24}ClFN_3O_5S$ $(M+H)^+$ 436.1109].

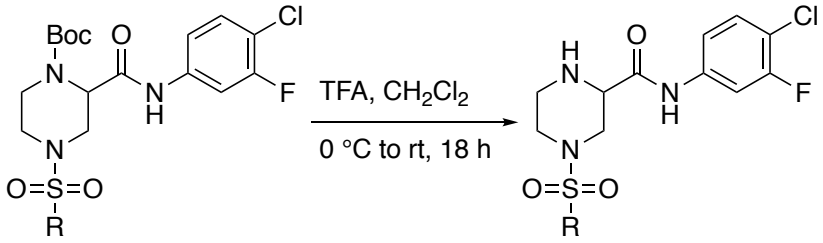
(±)-MCG-III-212-A03 (**11j**)
R = Ph (65% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.82 (s, 1H), 7.77 – 7.73 (m, 2H), 7.72 – 7.65 (m, 2H), 7.59 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.41 (t, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 4.76 (s, 1H), 4.17 (d, *J* = 12.4 Hz, 1H), 3.96 (d, *J* = 13.9 Hz, 1H), 3.60 (d, *J* = 11.8 Hz, 1H), 2.60 (dd, *J* = 12.4, 4.4 Hz, 1H), 2.39 (d, *J* = 11.7 Hz, 2H), 1.39 (s, 9H); **AMM** 498.1280 (ESI) *m/z* [calc for $C_{22}H_{26}ClFN_3O_5S$ $(M+H)^+$ 498.1266].

(±)-MCG-III-212-A04 (**11k**)
R = N-Me Imidazole (42% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.69 (s, 1H), 7.69 (dd, *J* = 11.7, 2.4 Hz, 1H), 7.54 (s, 2H), 7.41 (t, *J* = 8.6 Hz, 1H), 7.36 – 7.28 (m, 1H), 4.76 (s, 1H), 4.15 (d, *J* = 12.7 Hz, 1H), 3.96 (d, *J* = 13.6 Hz, 1H), 3.67 (s, 3H), 3.61 – 3.53 (m, 1H), 2.85 (d, *J* = 12.7 Hz, 1H), 2.58 (td, *J* = 11.9, 3.6 Hz, 1H), 1.41 (s, 9H); **AMM** 502.1324 (ESI) *m/z* [calc for $C_{20}H_{26}ClFN_5O_5S$ $(M+H)^+$ 502.1327].

Synthesis of Analog **11m**
To a precooled (0 °C) solution of common intermediate **10b** (20. mg, 0.056 mmol) in dichloromethane (0.5 mL) was added triethylamine (20 µL, 0.1 mmol) and ethanesulfonyl chloride (7.9 µL, 0.084 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 15 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance

liquid chromatography (15 mg, 78% yield). **Note: Boc deprotection* **^{1}H NMR** (500 MHz, Acetonitrile-d_3) δ 8.82 (s, 1H), 7.72 (dd, *J* = 11.6, 2.4 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.36 (ddd, *J* = 8.8, 2.4, 0.9 Hz, 1H), 4.16 (dd, *J* = 10.0, 3.1 Hz, 1H), 4.07 (ddd, *J* = 11.7, 3.3, 2.1 Hz, 1H), 3.83 (ddd, *J* = 12.3, 3.2, 1.8 Hz, 1H), 3.72 (td, *J* = 11.3, 2.8 Hz, 1H), 3.51 (dq, *J* = 12.5, 2.2 Hz, 1H), 3.07 – 2.94 (m, 4H), 1.29 (t, *J* = 7.4 Hz, 3H); **AMM** 350.0765 (ESI) *m/z* [calc for $C_{13}H_{18}ClFN_3O_3S$ $(M+H)^+$ 350.0741].

General Synthesis of Analogs **11l** and **11n-11o**



11i-11k **11l**, **11n** and **11o**

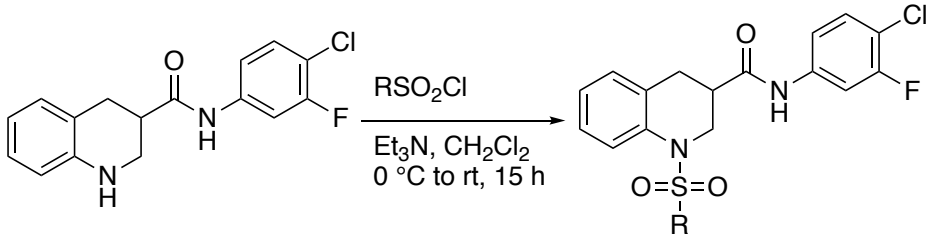
To separate precooled (0 °C) solutions of **11i-11k** (10. mg) in dichloromethane (0.5 mL) was added trifluoroacetic acid (10 µL, 0.1 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 18 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (60-92% yield).

(±)-MCG-III-216-A02 (**11l**)
R = Me (60% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.50 (s, 1H), 7.62 (dd, *J* = 11.3, 2.5 Hz, 1H), 7.43 (t, *J* = 8.5 Hz, 1H), 7.33 – 7.24 (m, 1H), 4.26 (dd, *J* = 10.4, 3.9 Hz, 1H), 4.19 – 4.11 (m, 1H), 3.81 – 3.71 (m, 1H), 3.63 – 3.53 (m, 1H), 3.40 – 3.22 (m, 3H), 2.91 (s, 3H); **AMM** 336.0599 (ESI) *m/z* [calc for $C_{12}H_{16}ClFN_3O_3S$ $(M+H)^+$ 336.0585].

(±)-MCG-III-216-A03 (**11n**)
R = Ph (83% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.54 (d, *J* = 7.5 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.76 – 7.69 (m, 1H), 7.67 – 7.56 (m, 3H), 7.42 (t, *J* = 8.5 Hz, 1H), 7.29 – 7.23 (m, 1H), 4.28 – 4.22 (m, 1H), 4.13 – 4.05 (m, 1H), 3.68 (d, *J* = 13.1 Hz, 1H), 3.51 (dt, *J* = 13.2, 3.3 Hz, 1H), 3.33 – 3.22 (m, 1H), 2.91 – 2.75 (m, 2H); **AMM** 398.0737 (ESI) *m/z* [calc for $C_{17}H_{18}ClFN_3O_3S$ $(M+H)^+$ 398.0741].

(±)-MCG-III-216-A04 (**11o**)
R = N-Me Imidazole (92% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.38 (s, 1H), 7.64 (dd, *J* = 14.0, 1.3 Hz, 2H), 7.60 (dd, *J* = 11.3, 2.4 Hz, 1H), 7.43 (t, *J* = 8.5 Hz, 1H), 7.29 – 7.24 (m, 1H), 4.27 (dd, *J* = 10.6, 3.8 Hz, 1H), 4.25 – 4.20 (m, 1H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.72 (s, 3H), 3.53 (dt, *J* = 13.1, 3.1 Hz, 1H), 3.27 (td, *J* = 12.9, 12.3, 3.8 Hz, 1H), 3.16 – 3.03 (m, 2H); **AMM** 402.0795 (ESI) *m/z* [calc for $C_{15}H_{18}ClFN_5O_3S$ $(M+H)^+$ 402.0803].

General Synthesis of **11p-11r**



10d **11p-11r**

To separate precooled (0 °C) solutions of common intermediate **10d** (20. mg, 0.066 mmol) in dichloromethane (0.5 mL) was added triethylamine (30 µL, 0.2 mmol) and R-sulfonyl chloride (0.098 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 15 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (4-52% yield).

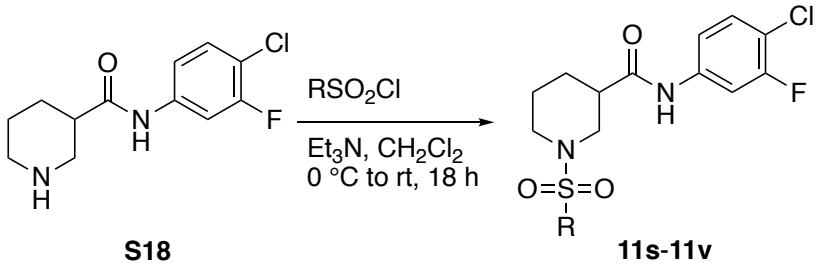
(±)-MCG-III-214-A01 (**11p**)
R = Me (28% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.81 (s, 1H), 7.76 – 7.69 (m, 1H), 7.62 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.40 (t, *J* = 8.6 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.26 – 7.18 (m, 2H), 7.12 (td, *J* = 7.4, 1.2 Hz, 1H), 4.19 (dd, *J* = 13.4, 4.3 Hz, 1H), 3.65 (dd, *J* = 13.3, 9.5 Hz, 1H), 3.10 (d, *J* = 7.8 Hz, 2H), 3.06 – 3.00 (m, 1H), 3.00 (s, 3H); **AMM** 383.0619 (ESI) *m/z* [calc for $C_{17}H_{17}ClFN_2O_3S$ $(M+H)^+$ 383.0632].

(±)-MCG-III-214-A02 (**11q**)
R = Et (4% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.80 (s, 1H), 7.74 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.38 (t, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.68 – 6.57 (m, 2H), 3.54 – 3.46 (m, 2H), 3.31 (dd, *J* = 11.6, 9.3 Hz, 2H), 3.02 – 2.91 (m, 3H), 2.86 – 2.77 (m, 3H).

(±)-MCG-III-214-A03 (**11q**)
R = Ph (43% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.62 (s, 1H), 7.72 – 7.58 (m, 5H), 7.53 – 7.44 (m, 2H), 7.36 (t, *J* = 8.6 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.12 – 7.05 (m, 2H), 4.28 (ddd, *J* = 13.4, 4.8, 1.6 Hz, 1H), 3.69 (ddd, *J* = 11.6, 8.2, 1.9 Hz, 1H), 2.79 – 2.65 (m, 2H), 2.64 – 2.52 (m, 1H); **AMM** 445.0809 (ESI) *m/z* [calc for $C_{22}H_{19}ClFN_2O_3S$ $(M+H)^+$ 445.0789].

(±)-MCG-III-214-A04 (**11r**)
R = N-Me Imidazole (52% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.85 (s, 1H), 7.77 – 7.65 (m, 2H), 7.53 (dd, *J* = 12.3, 1.5 Hz, 2H), 7.39 (t, *J* = 8.5 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.21 – 7.10 (m, 2H), 7.10 – 7.02 (m, 1H), 4.36 (dd, *J* = 13.3, 4.3 Hz, 1H), 3.68 – 3.58 (m, 4H), 3.06 – 2.94 (m, 1H), 2.94 – 2.86 (m, 2H); **AMM** 449.0869 (ESI) *m/z* [calc for $C_{20}H_{19}ClFN_4O_3S$ $(M+H)^+$ 449.0850].

General Synthesis of **11s**-**11v**



S18 **11s**-**11v**

To separate precooled (0 °C) solutions of common intermediate **S18** (20. mg, 0.078 mmol) and triethylamine (30 µL, 0.2 mmol) in dichloromethane (0.5 mL) was added R-sulfonyl chloride (0.12 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 18 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (43-57% yield).

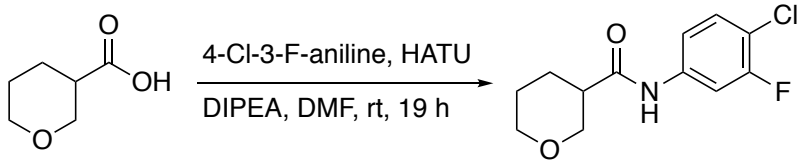
(±)-MCG-III-157-B01 (**11s**)
R = Me (45% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.65 (s, 1H), 7.71 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.28 – 7.19 (m, 1H), 3.84 – 3.74 (m, 1H), 3.65 – 3.56 (m, 1H), 2.88 (dd, *J* = 11.8, 10.6 Hz, 1H), 2.79 (s, 3H), 2.77 – 2.68 (m, 1H), 2.63 – 2.53 (m, 1H), 2.05 – 1.97 (m, 1H), 1.90 – 1.80 (m, 1H), 1.68 – 1.51 (m, 2H); **AMM** 357.0471 (ESI) *m/z* [calc for $C_{13}H_{16}ClFN_2O_3SNa$ $(M+Na)^+$ 357.0452].

(±)-MCG-III-157-B02 (**11t**)
R = Et (43% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.65 (s, 1H), 7.71 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.27 – 7.19 (m, 1H), 3.86 – 3.75 (m, 1H), 3.68 – 3.57 (m, 1H), 3.04 – 2.91 (m, 3H), 2.84 (td, *J* = 11.7, 2.9 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.05 – 1.96 (m, 1H), 1.87 – 1.77 (m, 1H), 1.71 – 1.50 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H); **AMM** 349.0814 (ESI) *m/z* [calc for $C_{14}H_{19}ClFN_2O_3S$ $(M+H)^+$ 349.0789].

(±)-MCG-III-157-B03 (**11u**)
R = Ph (45% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.59 (s, 1H), 7.80 – 7.73 (m, 2H), 7.72 – 7.65 (m, 2H), 7.65 – 7.58 (m, 2H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.26 – 7.17 (m, 1H), 3.87 – 3.78 (m, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.42 (t, *J* = 11.1 Hz, 1H), 2.30 (td, *J* = 11.7, 2.9 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.84 – 1.74 (m, 1H), 1.67 – 1.52 (m, 1H), 1.42 (qd, *J* = 12.6, 3.9 Hz, 1H); **AMM** 419.0621 (ESI) *m/z* [calc for $C_{18}H_{18}ClFN_2O_3SNa$ $(M+Na)^+$ 419.0608].

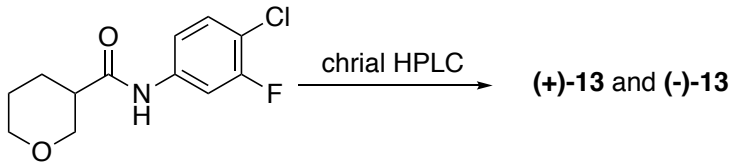
(±)-MCG-III-157-B04 (**11v**)
R = N-Me Imidazole (57% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.61 (s, 1H), 7.73 (s, 1H), 7.69 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.26 – 7.18 (m, 1H), 3.85 – 3.77 (m, 1H), 3.73 (s, 3H), 3.64 (d, *J* = 12.0 Hz, 1H), 2.67 (t, *J* = 11.2 Hz, 1H), 2.62 – 2.47 (m, 2H), 1.85 – 1.76 (m, 1H), 1.59 (qt, *J* = 12.5, 4.0 Hz, 1H), 1.53 – 1.41 (m, 1H); **AMM** 423.0678 (ESI) *m/z* [calc for $C_{16}H_{18}ClFN_4O_3SNa$ $(M+Na)^+$ 423.0670].

Synthesis of Analog 13 (MCG-III-207)



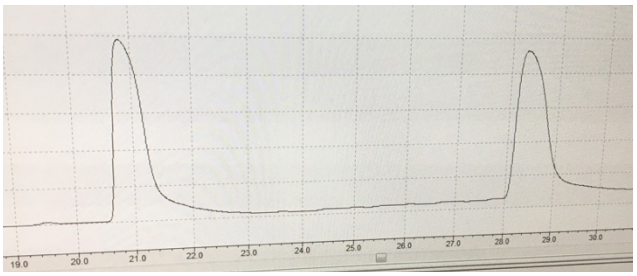
13

To a precooled (0 °C) solution of 4-chloro-3-fluoroaniline (336 mg, 2.31 mmol) and HATU (584 mg, 1.54 mmol) in DMF (8 mL) under N_2 atmosphere was added tetrahydro-2H-pyran-3-carboxylic acid (200. mg, 1.54 mmol) then diisopropylethylamine (0.80 mL, 4.61 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 19 h, then concentrated *in vacuo*. The resulting residue was taken up in EtOAc and quenched with H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 80:30 hexanes:EtOAc) afforded the product as a white solid (345 mg, 87% yield).
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.56 (s, 1H), 7.72 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.27 – 7.19 (m, 1H), 4.00 – 3.91 (m, 1H), 3.82 (dt, *J* = 11.1, 3.6 Hz, 1H), 3.49 (dd, *J* = 11.3, 9.8 Hz, 1H), 3.40 (td, *J* = 11.1, 3.0 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.03 – 1.96 (m, 1H), 1.84 – 1.71 (m, 1H), 1.71 – 1.53 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.36, 159.14, 157.17, 137.94, 137.87, 130.56, 116.01, 115.98, 108.83, 108.62, 68.98, 68.67, 43.60, 38.79, 26.45, 23.77; **AMM** 258.0711 (ESI) *m/z* [calc for $C_{12}H_{14}ClFNO_2$ $(M+H)^+$ 258.0697].



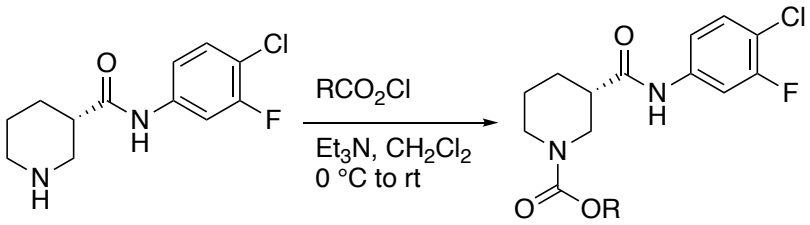
(±)-13

Chiral HPLC purification was performed using a Shimadzu HPLC (5 to 30% reagent alcohol in hexanes, 30 min.) with a chiral normal phase column (ChiralPak AD-H, 5 μM pore size, column dimensions 21 mm x 250 mm).



(-)-**2.109** (MCG-III-207-P1)
Retention time = 21 min.
$[\alpha]_D^{22}$ -36.12 (c. 0.083, CH_3OH)
(+)-**2.109** (MCG-III-207-P2)
Retention time = 28 min.
$[\alpha]_D^{22}$ +27.80 (c. 0.11, CH_3OH)

Synthesis of Analogs 16
General Synthesis of Analogs **16a**-**16e**



14 **16a**-**16e**

To separate precooled (0 °C) solutions of common intermediate **14** (20. mg, 0.078 mmol) in dichloromethane (0.5 mL) was added triethylamine (30 µL, 0.2 mmol) and R-chloroformate (0.12 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 20-60 h, then diluted with wet DMSO (0.5 mL), filtered through celite and purified via mass-directed isolation using ultra-performance liquid chromatography (23-61% yield).

(*S*)-MCG-III-188-A01 (**16a**)
R = Me (23% yield)
$[\alpha]_D^{22}$ +45.6 (c. 0.045, CH_3OH); **^{1}H NMR** (500 MHz, Acetonitrile-d_3) δ 8.61 (s, 1H), 7.71 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 7.28 – 7.20 (m, 1H), 4.11 (d, *J* = 13.2 Hz, 1H), 4.00 – 3.85 (m, 1H), 3.63 (s, 3H), 3.02 (t, *J* = 12.0 Hz, 1H), 2.86 (s, 1H), 2.49 – 2.38 (m, 1H), 1.99 (d, *J* = 12.5 Hz, 1H), 1.78 – 1.62 (m, 2H), 1.53 – 1.37 (m, 1H); **^{13}C NMR** (126 MHz, MeOD) δ 174.42, 160.08, 158.13, 140.41, 140.33, 131.52, 117.33, 117.30, 116.05, 115.91, 109.32, 109.11, 53.38, 47.34, 45.28, 44.95, 40.40, 28.92, 25.41; **IR** (ATR) ν_{max} 3260, 1714, 1695, 1660, 1597, 1532, 1469, 1235, 1207, 1165 cm^{-1}; **AMM** 315.0932 (ESI) *m/z* [calc for $C_{14}H_{17}ClFN_2O_3$ $(M+H)^+$ 315.0912].

(*S*)-MCG-III-188-A02 (**16b**)
R = Et (37% yield)
$[\alpha]_D^{22}$ +36.24 (c. 0.057, CH_3OH); **^{1}H NMR** (500 MHz, Acetonitrile-d_3) δ 8.59 (s, 1H), 7.68 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.24 – 7.16 (m, 1H), 4.11 – 3.98 (m, 3H), 3.89 (d, *J* = 13.3 Hz, 1H), 2.99 (t, *J* = 12.0 Hz, 1H), 2.83 (s, 1H), 2.44 – 2.33 (m, 1H), 1.99 – 1.92 (m, 1H), 1.74 – 1.59 (m, 2H), 1.48 – 1.33 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, MeOD) δ 174.44, 160.09, 158.14, 157.20, 140.43, 140.35, 131.53, 117.31, 117.29, 116.03, 115.89, 109.30, 109.10, 62.82, 47.25, 44.94, 40.40, 28.95, 25.41, 14.93; **IR** (ATR) ν_{max} 3313, 1669, 1536, 1496, 1437, 1198, 1136, 852 cm^{-1}; **AMM** 329.1082 (ESI) *m/z* [calc for $C_{15}H_{19}ClFN_2O_3$ $(M+H)^+$ 329.1068].

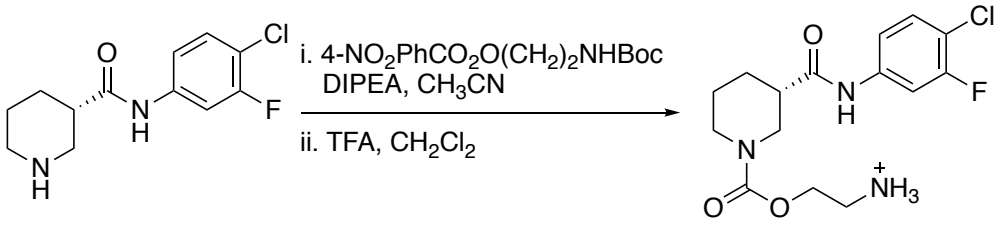
(*S*)-MCG-III-188-A03 (**16c**)
R = Ph (61% yield)

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.58 (s, 1H), 7.68 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.25 – 7.14 (m, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 4.29 – 4.02 (m, 2H), 3.92 (s, 1H), 3.35 – 3.18 (m, 1H), 3.18 – 2.90 (m, 2H), 2.61 – 2.42 (m, 2H), 2.06 – 1.96 (m, 1H), 1.84 – 1.66 (m, 2H), 1.55 (s, 1H); **AMM** 377.1087 (ESI) *m/z* [calc for $C_{19}H_{19}ClFN_2O_3$ $(M+H)^+$ 377.1068].

(*S*)-MCG-IV-058 (**16d**)
R = *n*-Pr (36% yield)
^{1}H NMR (500 MHz, Acetonitrile-*d*3) δ 8.63 (s, 1H), 7.68 (dd, *J* = 11.9, 2.5 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.25 – 7.17 (m, 1H), 4.07 (d, *J* = 13.3 Hz, 1H), 4.01 – 3.84 (m, 3H), 3.00 (s, 1H), 2.84 (s, 1H), 2.46 – 2.34 (m, 3H), 1.77 – 1.62 (m, 2H), 1.62 – 1.50 (m, 2H), 1.50 – 1.33 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); **AMM** (ESI) *m/z* 406.1303 [calc for $C_{18}H_{23}ClFN_3O_3$ $(M+Na)^+$ (ACN) 406.1210].

(*S*)-MCG-IV-061 (**16e**)
R = *i*-Bu (46% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.57 (s, 1H), 7.68 (dd, *J* = 11.9, 2.5 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.23 – 7.16 (m, 1H), 4.12 – 4.03 (m, 1H), 3.94 – 3.85 (m, 1H), 3.78 (d, *J* = 6.6 Hz, 2H), 3.01 (s, 1H), 2.86 (s, 1H), 2.45 – 2.32 (m, 1H), 1.98 – 1.92 (m, 1H), 1.88 – 1.80 (m, 1H), 1.77 – 1.59 (m, 2H), 1.49 – 1.33 (m, 1H), 0.87 (d, *J* = 6.8 Hz, 6H); **AMM** 379.1212 (ESI) *m/z* [calc for $C_{17}H_{22}ClFN_2O_3Na$ $(M+Na)^+$ 379.1201].

Synthesis of Analog **16f**

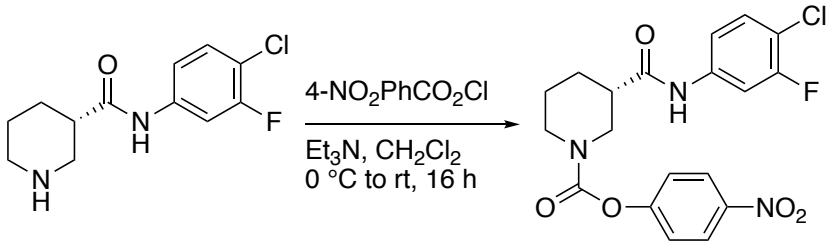


14 **16f**

i. To a solution of intermediate **14** (30. mg, 0.12 mmol) and *tert*-butyl (2-(((4-nitrophenoxy)-carbonyl)oxy)ethyl)carbamate (76 mg, 0.23 mmol) in acetonitrile (1.2 mL) at room temperature was added diisopropylethylamine (60 µL, 0.4 mmol). The resulting mixture was heated to 80 °C in a sealed microwave reaction vessel for 66 h, then concentrated *in vacuo*. The crude residue was taken up in EtOAc and diluted with H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the product, which was carried forward without purification.

ii. To a precooled (0 °C) solution of intermediate (32 mg, 0.071 mmol) in dichloromethane (0.7 mL) under N_2 atmosphere was added dropwise trifluoroacetic acid (0.1 mL, 1 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 18 h, then concentrated *in vacuo.* The crude residue was diluted with wet DMSO (0.5 mL) and purified via mass-directed isolation using ultra-performance liquid chromatography to afford the product as a white solid (26 mg, 77% yield). **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.69 (dd, *J* = 11.6, 2.3 Hz, 1H), 7.38 (t, *J* = 8.3 Hz, 1H), 7.29 – 7.23 (m, 1H), 4.42 (s, 1H), 4.23 (s, 1H), 4.16 – 3.99 (m, 1H), 3.24 (s, 1H), 3.14 – 2.97 (m, 1H), 2.61 – 2.48 (m, 1H), 2.17 – 1.98 (m,2H), 1.88 – 1.73 (m, 2H), 1.54 (d, *J* = 12.4 Hz, 1H); **AMM** 344.1190 (ESI) *m/z* [calc for $C_{15}H_{20}ClFN_3O_3$ $(M)^+$ 344.1177].

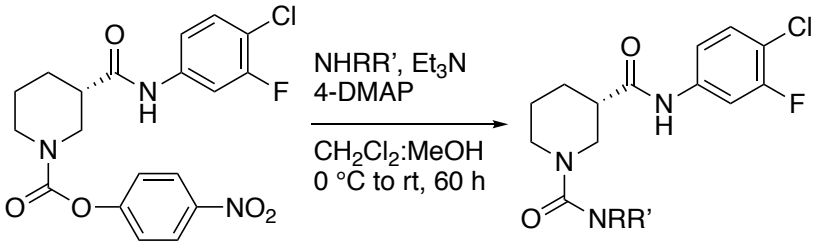
Synthesis of Analogs 17



14 **S19**

To a precooled (0 °C) solution of intermediate **14** (300. mg, 1.17 mmol) and *para*-nitrophenylchloroformate (236 mg, 1.17 mmol) in CH_2Cl_2 (6 mL) under N_2 atmosphere was added dropwise triethylamine (0.33 mL, 2.3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 16 h, then quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 50:50 hexanes:EtOAc) to afford the product as a white solid (125 mg, 48% yield). **$[\alpha]_D^{23}$** +72.7 (c. 0.63, CH_3OH); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.35 (t, *J* = 4.7 Hz, 1H), 8.34 – 8.20 (m, 2H), 7.77 (t, *J* = 9.5 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.46 – 7.37 (m, 2H), 7.33 (d, *J* = 8.9 Hz, 1H), 4.26 – 4.00 (m, 2H), 3.25 – 3.01 (m, 2H), 2.73 – 2.56 (m, 1H), 2.12 – 1.94 (m, 1H), 1.91 – 1.79 (m, 1H), 1.79 – 1.63 (m, 1H), 1.63 – 1.43 (m, 1H); **IR** (ATR) ν_{max} 3075, 1715, 1656, 1606, 1519, 1423, 1344, 1212, 857, 748 cm^{-1}; **AMM** (ESI) *m/z* 422.0936 [calc for $C_{19}H_{18}ClFN_3O_5$ $(M+H)^+$ 422.0919].

General Synthesis of Analogs **17a**-**17e**



S19 **17a**-**17e**

To separated precooled (0 °C) vials charged with NHRR' (0.17 mmol) was added a solution of common intermediate **2.115** (36 mg, 0.085 mmol), triethylamine (20 µL, 0.2 mmol), and 4-dimethylaminopyridine (2 mg, 0.002 mmol) in dichloromethane (0.5 mL) and methanol (0.3 mL). The resulting mixtures were allowed to warm to room temperature and stirred for 60 h, then diluted with wet DMSO (0.5 mL), filtered through celite, and purified via mass-directed isolation using ultra-performance liquid chromatography (13-98%).

(*S*)-MCG-IV-031-A02 (**17a**)
R = Et, R' = H (13% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.90 (s, 1H), 7.71 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 1H), 3.82 (d, *J* = 14.5 Hz, 1H), 3.64 (d, *J* = 13.9 Hz, 1H), 3.17 – 3.07 (m, 5H), 2.90 – 2.82 (m, 2H), 2.44 – 2.33 (m, 1H), 1.80 – 1.67 (m, 1H), 1.64 – 1.53 (m, 1H), 1.47 – 1.34 (m, 1H), 1.31 – 1.19 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 1H), 1.02 (t, *J* = 7.2 Hz, 2H), 0.89 – 0.79 (m, 2H); **AMM** (ESI) *m/z* 328.1248 [calc for $C_{15}H_{20}ClFN_3O_2$ $(M+H)^+$ 328.1228].

(*S*)-MCG-IV-031-A03 (**17b**)
R = Me, R' = Me (32% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.19 (s, 1H), 7.75 (d, *J* = 12.1 Hz, 1H), 7.42 – 7.32 (m, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 3.60 (d, *J* = 13.6 Hz, 1H), 3.47 (d, *J* = 13.1 Hz, 1H), 3.17 (t, *J* = 11.4 Hz, 1H), 2.94 (t, *J* = 11.9 Hz, 1H), 2.79 (d, *J* = 3.4 Hz, 6H), 2.57 – 2.48 (m, 1H), 1.87 – 1.73 (m, 1H), 1.69 – 1.58 (m, 1H), 1.58 – 1.45 (m, 1H), 1.36 – 1.16 (m, 1H); **AMM** (ESI) *m/z* 328.1239 [calc for $C_{15}H_{20}ClFN_3O_2$ $(M+H)^+$ 328.1228].

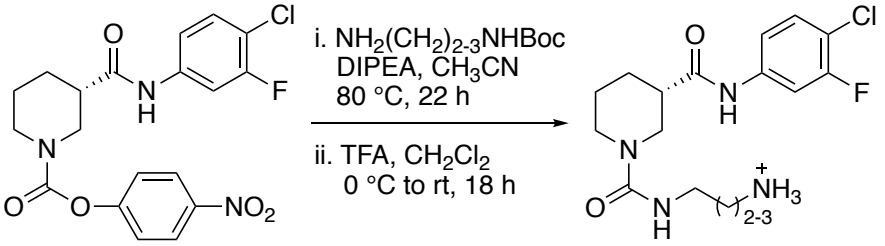
(*S*)-MCG-IV-031-A04 (**17c**)
R = Et, R' = Me (62% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.13 (s, 1H), 7.70 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.33 (t, *J* = 8.5 Hz, 1H), 7.27 – 7.20 (m, 1H), 3.54 (dd, *J* = 13.6, 3.8 Hz, 1H), 3.48 – 3.34 (m, 1H), 3.15 (q, *J* = 7.0 Hz, 2H), 2.99 – 2.87 (m, 1H), 2.75 (s, 3H), 2.56 – 2.46 (m, 1H), 1.82 – 1.72 (m, 1H), 1.72 – 1.55 (m, 2H), 1.55 – 1.43 (m, 1H), 1.07 (t, *J* = 7.1 Hz, 3H); **AMM** (ESI) *m/z* 342.1380 [calc for $C_{16}H_{22}ClFN_3O_2$ $(M+H)^+$ 342.1385].

(*S*)-MCG-IV-031-A05 (**17d**)
R = *n*-Pr, R' = H (98% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.95 (s, 1H), 7.74 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.37 (t, *J* = 8.5 Hz, 1H), 7.31 – 7.21 (m, 1H), 3.93 – 3.84 (m, 1H), 3.70 (d, *J* = 13.4 Hz, 1H), 3.25 – 3.12 (m, 1H), 3.09 (t, *J* = 7.1 Hz, 2H), 2.92 (ddd, *J* = 13.7, 10.7, 3.2 Hz, 1H), 2.51 – 2.38 (m, 1H), 1.85 – 1.71 (m, 1H), 1.71 – 1.57 (m, 1H),

1.56 – 1.39 (m, 3H), 0.94 – 0.79 (m, 3H); **AMM** (ESI) *m/z* 342.1392 [calc for $C_{16}H_{22}ClFN_3O_2$ $(M+H)^+$ 342.1385].

(*S*)-MCG-IV-031-A06 (**17e**)
R = *i*-Bu, R' = H (67% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.97 (d, *J* = 18.4 Hz, 1H), 7.74 (dd, *J* = 12.0, 2.8 Hz, 1H), 7.37 (t, *J* = 8.7 Hz, 1H), 7.26 (d, *J* = 9.2 Hz, 1H), 3.94 – 3.84 (m, 1H), 3.70 (d, *J* = 13.7 Hz, 1H), 3.18 (dd, *J* = 13.5, 9.7 Hz, 1H), 3.04 – 2.86 (m, 3H), 2.45 (dt, *J* = 13.7, 6.2 Hz, 1H), 1.86 – 1.56 (m, 3H), 1.46 (t, *J* = 12.4 Hz, 1H), 1.36 – 1.08 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 6H); **AMM** (ESI) *m/z* 356.1551 [calc for $C_{17}H_{24}ClFN_3O_2$ $(M+H)^+$ 356.1541].

General Synthesis of **17f-17g**



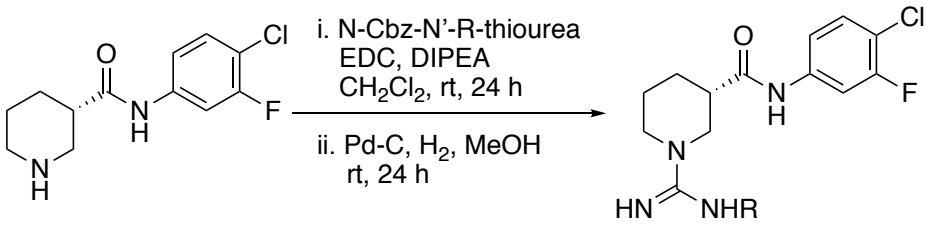
S19 **17f-17g**

i. To separate microwave reactor vials charged with common intermediate **S19** (50. mg, 0.12 mmol) and $NH_2(CH_2)_{2\text{-}3}NHBoc$ (0.36 mmol) was added acetonitrile (1 mL) then diisopropylethylamine (40 µL, 0.2 mmol). The vials were sealed and heated to 80 °C for 22 h, then allowed to cool to room temperature and diluted with $CHCl_3$ and H_2O. The layers were separated, and the aqueous phases were extracted with $CHCl_3$ (3x). The combined organic layers were washed with sat. aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4 and concentrated *in vacuo* to afford the products, which were carried forward without additional purification.
ii. To separate precooled (0 °C) solutions of intermediate (0.12 mmol) in CH_2Cl_2 (1.2 mL) under N_2 atmosphere was added dropwise trifluoroacetic acid (0.1 mL, 1 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 18 h, then concentrated *in vacuo*. The crude residues were diluted with wet DMSO (0.5 mL) and purified via mass-directed isolation using ultra-performance liquid chromatography to afford the products as white solids (7-15% yield).

MCG-IV-210 (**17f**)
R = $(CH_2)_2NH_3^+$, R' = H (15% yield)
^{1}H NMR (500 MHz, Methanol-d_4) δ 7.71 (dd, *J* = 11.5, 2.4 Hz, 1H), 7.40 (t, *J* = 8.4 Hz, 1H), 7.31 – 7.25 (m, 1H), 4.10 – 4.02 (m, 1H), 3.86 (d, *J* = 13.4 Hz, 1H), 3.44 (t, *J* = 5.8 Hz, 2H), 3.17 (dd, *J* = 13.4, 9.9 Hz, 1H), 3.10 – 2.97 (m, 3H), 2.59 – 2.49 (m, 1H), 2.11 – 2.01 (m, 1H), 1.89 – 1.76 (m, 2H), 1.62 – 1.49 (m, 1H); **AMM** 343.1328 (ESI) *m/z* [calc for $C_{15}H_{21}ClFN_4O_2$ $(M)^+$ 343.1337].

MCG-IV-211 (**17g**)
R = $(CH_2)_3NH_3^+$, R' = H (7% yield)
AMM 357.1518 (ESI) *m/z* [calc for $C_{16}H_{23}ClFN_4O_2$ $(M)^+$ 357.1494].

Synthesis of Analogs 18
General Synthesis of Analogs **18a**-**18c**



14 **18a-18c**

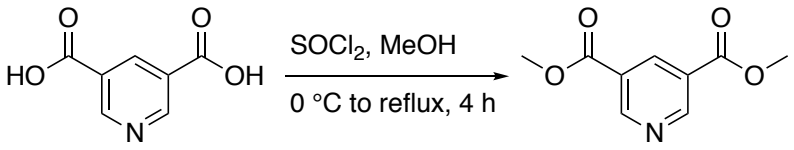
To separate vials charged with N-Cbz-N'-R-thiourea (0.12 mmol) was added a solution of common intermediate **14** (30. mg, 0.12 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI, 34 mg, 0.18 mmol) and diisopropylethylamine (40 µL, 0.3 mmol) in CH_2Cl_2 (0.5 mL). The resulting mixtures were stirred at room temperature for 24 h, then diluted with wet DMSO (0.5 mL), filtered through celite, and purified via mass-directed isolation via ultra-performance liquid chromatography (24-70% yield).

MCG-IV-053-A01 (**18a**)
R = Me, R' = H (70% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 10.02 (s, 1H), 7.84 – 7.74 (m, 1H), 7.43 – 7.32 (m, 1H), 7.06 (s, 1H), 6.55 (s, 1H), 3.92 (d, *J* = 14.0 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 3.26 (dd, *J* = 13.9, 10.0 Hz, 1H), 3.11 (ddd, *J* = 13.8, 11.0, 3.4 Hz, 1H), 2.83 (d, *J* = 4.7 Hz, 3H), 2.81 – 2.71 (m, 1H), 2.04 – 1.97 (m, 1H), 1.91 – 1.80 (m, 1H), 1.80 – 1.71 (m, 1H), 1.63 – 1.48 (m, 1H); **AMM** 313.1245 (ESI) *m/z* [calc for $C_{14}H_{19}ClFN_4O$ $(M+H)^+$ 313.1231].

MCG-IV-053-A05 (**18b**)
R = *n*-Pr, R' = H (24% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.92 (s, 1H), 7.79 (d, *J* = 11.2 Hz, 1H), 7.37 (d, *J* = 5.9 Hz, 1H), 6.90 (s, 1H), 6.55 (s, 2H), 3.88 (d, *J* = 13.9 Hz, 1H), 3.57 (d, *J* = 12.6 Hz, 1H), 3.32 (dd, *J* = 13.8, 9.5 Hz, 1H), 3.21 – 3.09 (m, 1H), 2.83 – 2.71 (m, 1H), 1.90 – 1.80 (m, 2H), 1.80 – 1.68 (m, 2H), 1.66 – 1.48 (m, 3H), 0.99 – 0.87 (m, 3H); **AMM** 341.1557 (ESI) *m/z* [calc for $C_{16}H_{23}ClFN_4O$ $(M+H)^+$ 341.1544].

MCG-IV-053-A06 (**18c**)
R = *i*-Bu, R' = H (32% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.95 (s, 1H), 7.84 – 7.72 (m, 1H), 7.42 – 7.33 (m, 1H), 6.96 (s, 1H), 6.60 (s, 1H), 3.87 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.64 – 3.52 (m, 1H), 3.35 (dd, *J* = 13.9, 9.3 Hz, 1H), 3.17 (ddd, *J* = 13.5, 10.4, 3.4 Hz, 1H), 3.01 (dd, *J* = 7.2, 5.7 Hz, 2H), 2.79 (tt, *J* = 9.1, 4.1 Hz, 2H), 2.05 – 1.97 (m, 1H), 1.92 – 1.83 (m, 2H), 1.80 – 1.70 (m, 1H), 1.62 – 1.51 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 6H); **AMM** 355.1712 (ESI) *m/z* [calc for $C_{17}H_{25}ClFN_4O$ $(M+H)^+$ 355.1701].

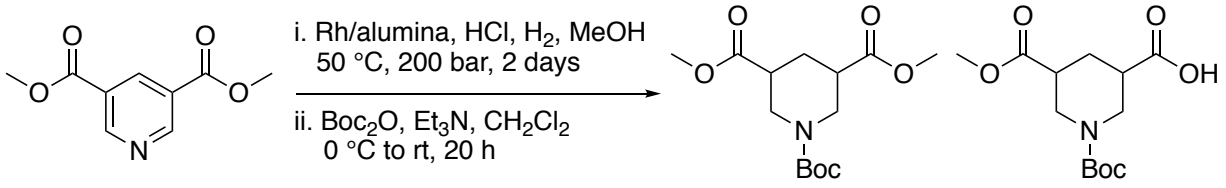
Synthesis of Analogs 20 and 21



S20

To a precooled (0 °C) solution of pyridine-3,5-dicarboxylic acid (10.0 g, 59.8 mmol) in MeOH (100 mL) under N_2 atmosphere was slowly added thionyl chloride (13 mL, 180 mmol). The resulting mixture was allowed to warm to room temperature then heated to reflux and stirred for 4 h. The mixture was then allowed to cool to room temperature and concentrated *in vacuo*. The resulting white solid was taken up in H_2O and the aqueous solution was cooled (0 °C) then neutralized with 10 M aq. NaOH (white ppt formed). The heterogenous mixture was diluted with EtOAc and the bisphasic solution was stirred for 5 min. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (10.4 g, 89% yield). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.35 (d, *J* = 2.1 Hz, 2H), 8.85 (t, *J* = 2.1 Hz, 1H), 3.98 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.05, 154.37, 138.19, 126.15, 52.85; **IR** (ATR) ν_{max} 3074, 2966,

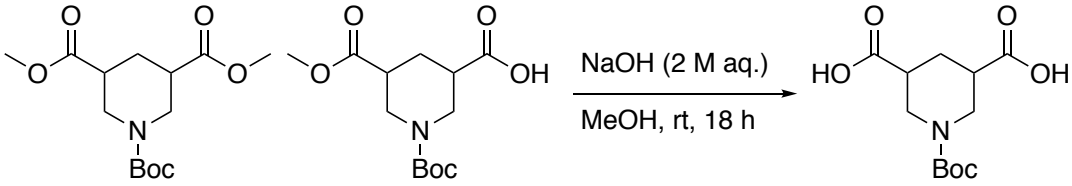
1713, 1445, 1312, 1256, 1108, 979, 745 cm^{-1}; **AMM** (ESI) *m/z* 196.0600 [calc for $C_9H_{10}NO_4$ $(M+H)^+$ 196.0610].



S20 **S21**

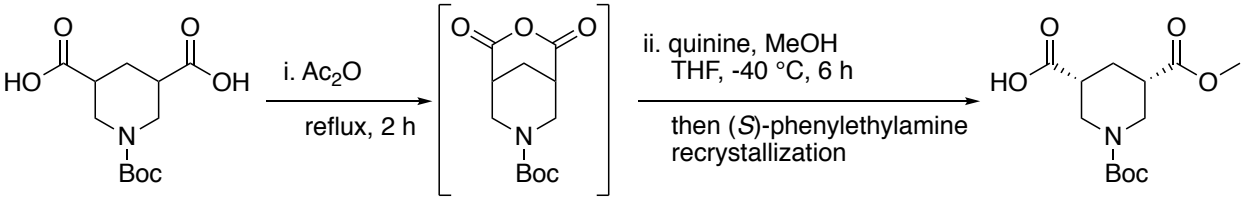
i. To a solution of intermediate **S20** (11.4 g, 58.3 mmol) in MeOH (58 mL) and 6 M aq. HCl (15 mL) was added rhodium on alumina (5%, 1.1 g). The resulting mixture was hydrogenated at 50 °C while stirring under 200 bar pressure in a Parr reactor for 2 days. The reactor was then allowed to cool to room temperature and depressurized to ambient atmosphere. The crude heterogeneous resulting mixture was filtered through a bed of celite and rinsed with MeOH. The filtrate was concentrated *in vacuo*, and the resulting product was carried forward without additional purification.

ii. To a precooled (0 °C) solution of crude intermediate (11.7 g, 58.3 mmol assumed) in CH_2Cl_2 (60 mL) under N_2 atmosphere was added triethylamine (33 mL, 230 mmol) then Boc anhydride (20 mL, 87 mmol). The resulting mixture was then allowed to warm to room temperature and stirred for 16 h, then quenched with H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 75:25 hexanes:EtOAc, dry loaded on celite) afforded the product mixture as a clear colorless oil (3.08 g, 21% yield over 2 steps). The experimental data agreed with literature precedent.[12]



S21 **S22**

To a solution of intermediate **S21** (3.00 g, 9.96 mmol) in MeOH (20 mL) at room temperature under N_2 atmosphere was added 2 M aq. NaOH (10 mL, 20 mmol). The resulting mixture was stirred at room temperature for 18 h then concentrated *in vacuo*. The resulting residue was taken up in sat. aq. $NaHCO_3$ and the aqueous layer was washed with ether (1x) then cooled to 0 °C and acidified with 6 M aq. HCl to pH 2. The solid precipitate was collected by vacuum filtrated and dried to afford the product as a white solid (1.21 g, 45% yield). The experimental data agreed with literature precedent.[2]

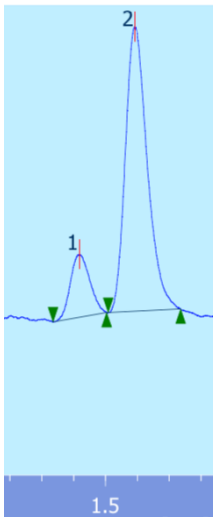


S22 **S23** **(+)-S24**

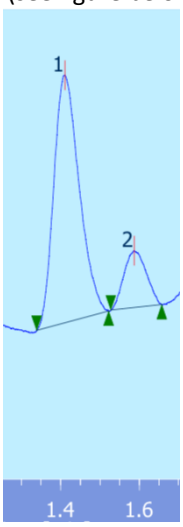
i. To a flask charged with intermediate **S22** (800. mg, 2.93 mmol) and equipped with a reflux condenser at room temperature under N_2 atmosphere was added acetic anhydride (7 mL). The resulting mixture was heated to reflux for 2 h, then allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was taken up in toluene and concentrated *in vacuo* (3x) then the resulting solid was used directly.

ii. To a precooled (-40 °C) solution of intermediate **S23** (1.04 g, 2.91 mmol assumed) and quinine (1.42 g, 4.37 mmol) in THF (16 mL) was slowly added dropwise a solution of MeOH (1.6 mL, 41 mmol) in THF (2 mL). The resulting mixture was stirred at -40 °C for 6 h then allowed to warm to 0 °C and quenched with 1 M aq. HCl and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with 1 M aq. HCl then brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude product (780 mg, 66% *ee*). The resulting solid was suspended in EtOH (3 mL) and warmed to 80 °C followed by addition of (*S*)-phenylethylamine (3 mg, 3 mmol). The resulting mixture was allowed to cool to room temperature and stood still for 19 h. The precipitated solid was collected by vacuum filtration, rinsed with hexanes and dried. The obtained solid was taken up in H_2O and treated with sat. aq. $KHSO_4$ and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (509 mg, 43% yield over 2 steps, 96% ee). The experimental data agreed with literature precedent. The absolute stereochemistry was determined by comparison of literature.[13] **$[\alpha]_D^{23}$** +3.25 (c. 0.09, CH_3OH); **^{1}H NMR** (500 MHz, Methanol-d_4) δ 4.30 (d, *J* = 13.0 Hz, 2H), 3.70 (d, *J* = 2.6 Hz, 3H), 2.73 (s, 2H), 2.59 – 2.34 (m, 3H), 1.75 – 1.56 (m, 1H), 1.47 (d, *J* = 2.6 Hz, 9H).

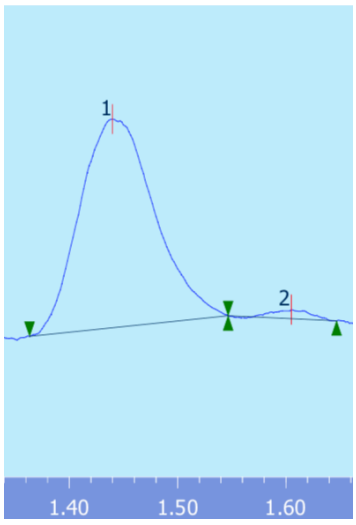
Enantiomeric excess determined by SFC (see figure below):



(-)-**S24*** *er* = 16:84



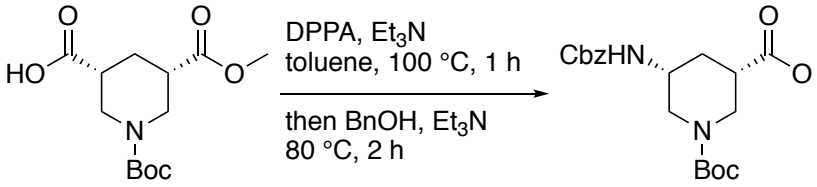
(+)-**S24** er = 83:17
Pre-recrystallization



(+)-**S24** *er* = 98:2
Post-recrystallization

Method: column: ChiralPak AD-H; eluent: 10% MeOH in supercritical CO_2; flow rate: 4 mL/min; pressure: 12 MPa. Retention times: (+)-**2.151**: 1.4 min, (-)-**2.151**: 1.6 min.

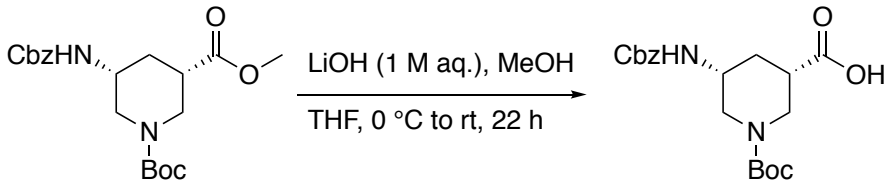
*Compound (-)-**S25** was prepared using the same synthesis employing quinidine instead of quinine.



S24 **S25**

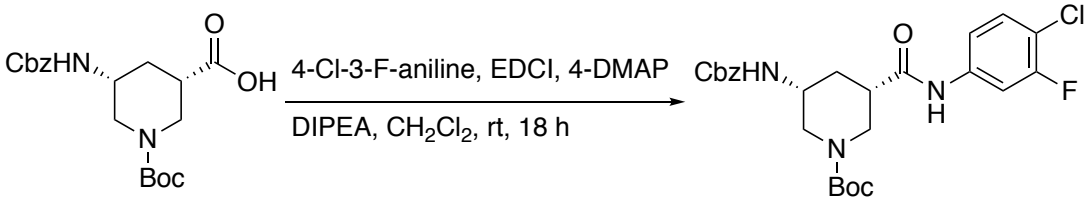
To a solution of intermediate **S24** (550 mg, 1.91 mmol) in toluene (9.6 mL) at room temperature under N_2 atmosphere was added triethylamine (0.32 mL, 2.3 mmol) then diphenyl phosphoryl azide (0.50 mL, 2.3 mmol). The resulting mixture was heated to 100 °C and stirred for 1 h, then allowed to cool to room temperature. To the mixture was then added triethylamine (0.32 mL, 2.3 mmol) and benzyl alcohol (0.5 mL, 4.8 mmol). The resulting mixture was heated to 80 °C and stirred for 2 h, then allowed to cool to room

temperature and quenched with H_2O. The layers were separated, and the aqueous phase was extracted with toluene (3x). The combined organic layers were washed with sat. aq. citric acid, sat. aq. $NaHCO_3$, then brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, 60:40 hexanes:EtOAc) afforded the product as a white solid (727 mg, 28% yield). The experimental data agreed with literature precedent.[12] **$[\alpha]_D^{23}$** -3.15 (c. 0.10, CH_3OH);



S25 **S26**

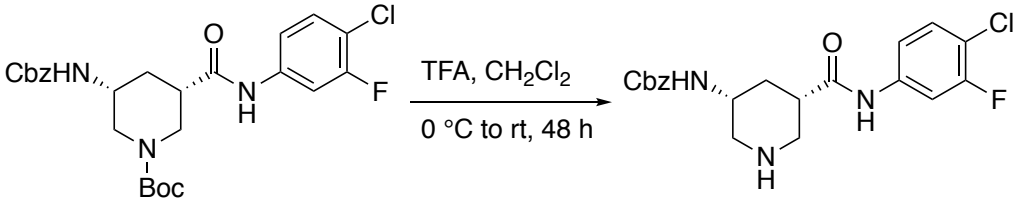
To a precooled (0 °C) solution of intermediate 2.152 (727 mg, 1.85 mmol) in MeOH (6 mL) under N_2 atmosphere was added THF (3 mL) then 1 M aq. LiOH (3 mL). The resulting mixture was allowed to warm to room temperature and stirred vigorously for 22 h, then concentrated *in vacuo*. The resulting residue was taken up in sat. aq. citric acid (white ppt formed) then diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (663 mg, 95% yield). The experimental data agreed with literature precedent.[13] **$[\alpha]_D^{23}$** +5.91 (c. 0.05, CH_3OH); **AMM** 379.1867 (ESI) *m/z* [calc for $C_{19}H_{27}N_2O_6$ $(M+H)^+$ 379.1869].



S26 **S27**

To a precooled (0 °C) solution of intermediate **2.153** (663 mg, 1.75 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (272 mg, 1.75 mmol), and 4-chloro-3-fluoroaniline (383 mg, 2.63 mmol) in CH_2Cl_2 under N_2 atmosphere was added 4-dimethylaminopyridine (43 mg, 0.35 mmol) then diisopropylethylamine (0.8 mL, 4 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 18 h, then quenched with H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed sequentially with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 50:50 hexanes:EtOAc) afforded the product as a white solid (541 mg, 61% yield).

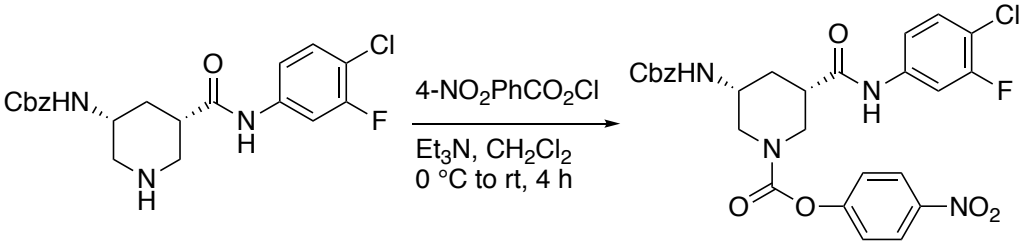
^{1}H NMR (500 MHz, Methanol-d_4) δ 7.64 (dd, J = 11.5, 2.4 Hz, 1H), 7.38 – 7.15 (m, 8H), 5.03 (s, 2H), 4.18 – 3.98 (m, 2H), 3.59 – 3.45 (m, 1H), 3.05 – 2.73 (m, 1H), 2.70 – 2.48 (m, 2H), 2.14 (d, J = 12.8 Hz, 1H), 1.72 – 1.53 (m, 1H), 1.41 (s, 9H); **^{13}C NMR** (126 MHz, MeOD) δ 173.32, 160.02, 158.07, 158.00, 156.19, 140.26, 140.18, 138.16, 131.48, 130.44, 129.42, 128.97, 128.79, 127.02, 122.55, 117.27, 117.25, 116.10, 115.96, 109.31, 109.10, 81.67, 67.49, 49.00, 46.63, 44.14, 34.62, 28.58; **IR** (ATR) ν_{max} 3315, 2935, 1662, 1531, 1421, 1147, 696 cm^{-1}



S27 **S28**

To a precooled (0 °C) solution of intermediate **S27** (1.14 g, 2.25 mmol) in CH_2Cl_2 (23 mL) under N_2 atmosphere was added dropwise trifluoroacetic acid (1.04 mL, 13.5 mmol). The resulting mixture was

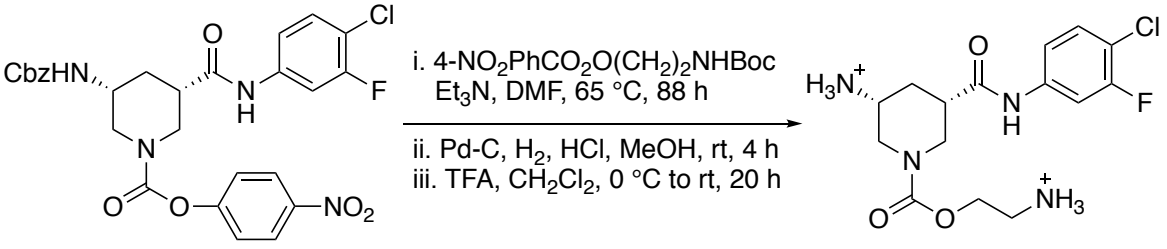
allowed to warm to room temperature and stirred for 18 h, then cooled to 0 °C before addition of trifluoroacetic acid (1.0 mL, 13 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 48 h, then concentrated *in vacuo*. The resulting residue was suspended in H_2O and the resulting aqueous solution was cooled to 0 °C and neutralized with powdered $NaHCO_3$ then diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a white solid (739 mg, 81% yield). **$[\alpha]_D^{23}$** -31.3 (c. 0.13, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 7.64 (d, *J* = 10.9 Hz, 1H), 7.43 – 7.22 (m, 6H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.08 (s, 1H), 5.00 (s, 1H), 3.88 – 3.60 (m, 2H), 3.29 – 3.10 (m, 2H), 3.01 (s, 1H), 2.68 (s, 1H), 2.58 (s, 1H), 1.89 (s, 1H), 1.42 – 1.17 (m, 2H), 0.86 (s, 1H); **IR** (ATR) ν_{max} 3286, 1679,1654, 1545, 1491, 1284, 1062, 693, 618 cm^{-1}; **AMM** 406.1307 (ESI) *m/z* [calc for $C_{20}H_{22}ClFN_3O_3$ $(M+H)^+$ 406.1334].



S28 **S29**

To a precooled (0 °C) solution of intermediate **S28** (99 mg, 0.39 mmol) and 4-nitrophenyl chloroformate (79 mg, 0.39 mmol) in CH_2Cl_2 under N_2 atmosphere was added dropwise triethylamine (0.1 mL, 0.8 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 4 h, then quenched with sat. aq. $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography 10:90 hexanes:EtOAc) afforded the desired product as a white solid (93 mg, 57% yield). **^{13}C NMR** (126 MHz, DMSO) δ 170.93, 168.77, 157.87, 156.06, 155.93, 155.48, 151.73, 144.48, 139.86, 139.41, 136.93, 131.49, 130.45, 130.37, 128.62, 128.33, 127.81, 126.11, 125.05, 122.75, 116.16, 115.73, 112.97, 112.44, 107.53, 107.32, 107.08, 106.87, 67.38, 65.49, 51.37, 48.51, 45.77, 42.35, 42.06, 38.10, 29.80, 28.35, 23.98, 23.24, 22.38, 13.83, 10.74; **IR** (ATR) ν_{max} 3296, 1729, 1677, 1533, 1423, 1344, 1215, 866, 742 cm^{-1}; **AMM** 593.1230 (ESI) *m/z* [calc for $C_{27}H_{24}ClFN_4O_7Na$ $(M)^+$ 593.1215].

Synthesis of Analog **20**



S29 **20**

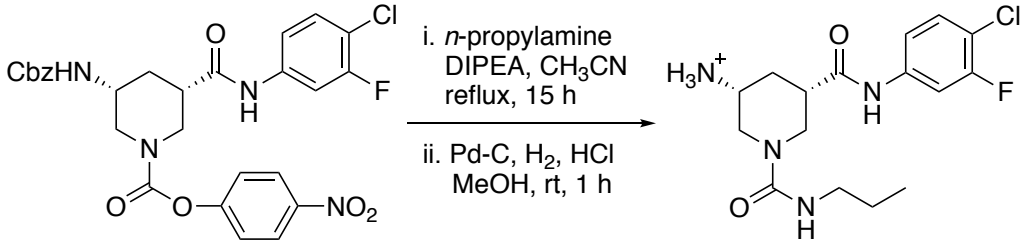
i. To a solution of common intermediate **S29** (30. mg, 0.074 mmol) and 4-NO_2PhCO_2-$O(CH_2)_2NHBoc$ (24 mg, 0.074 mmol) in dimethylformamide (0.7 mL) at room temperature was added triethylamime (30 µL, 0.2 mmol). The microwave reaction vessel was sealed, and the resulting mixture was heated to 65 °C and stirred for 88 h, then allowed to cool to room temperature and diluted with EtOAc and H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the product, which was carried forward without additional purification.

ii. To a solution of intermediate (32 mg, 0.074 mmol) and palladium on carbon (10 wt%, 8 mg, 0.07 mmol) in methanol (2 mL) at room temperature under N_2 atmosphere was added concentrated HCl (few drops). The reaction flask was backfilled with H_2 (3x) and the resulting mixture was stirred under H_2 atmosphere (balloon) for 4 h, then backfilled with N_2, and filtered

through celite and rinsed with MeOH. The filtrate was concentrated *in vacuo* and the crude product was carried forward without additional purification.

iii. To a precooled (0 °C) solution of intermediate (25 mg, 0.054 mmol) in CH_2Cl_2 (0.8 mL) under N_2 atmosphere was added trifluoroacetic acid (30 µL, 0.4 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 20 h, then concentrated *in vacuo*. The crude residue was taken up in wet DMSO (1 mL), filtered through celite, and purified via mass-directed isolation using ultra-performance liquid chromatography to afford the product as a white solid (13 mg, 51% yield over 3 steps). **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.72 (d, *J* = 11.6 Hz, 1H), 7.42 (t, *J* = 8.5 Hz, 1H), 7.22 – 7.34 (m, 1H), 4.24 – 4.44 (m, 2H), 4.02 – 4.22 (m, 1H) 3.37 – 3.57 (m, 3H), 2.89 – 2.77 (m, 1H), 2.24 – 2.40 (m, 1H), 1.88 – 2.04 (m, 1H); **AMM** (ESI) *m/z* 359.1268 [calc for $C_{15}H_{21}ClFN_4O_3$ $(M+H)^+$ 359.1286].

Synthesis of Analog **21a** (MCG-IV-226)

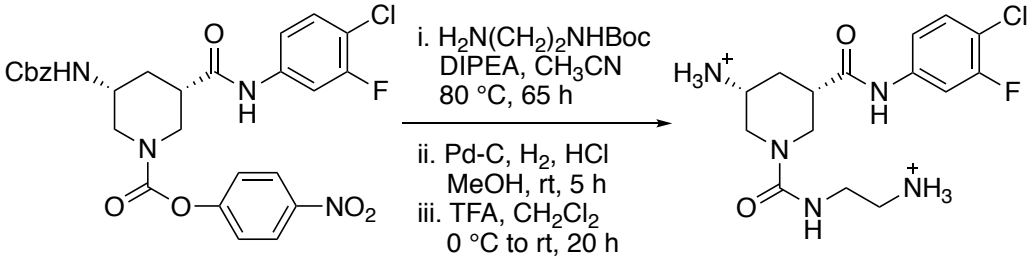


S29 **21a**

i. To a solution of common intermediate **S29** (43 mg, 0.076 mmol) in acetonitrile (1 mL) at room temperature was added triethylamine (30 µL, 0.2 mmol) and n-propylamine (20 µL, 0.2 mmol). The reaction mixture was heated to reflux and stirred for 15 h, then concentrated *in vacuo*. The crude residue was taken up in chloroform and diluted with water. The layers were separated, and the aqueous phase was extracted with chloroform (3x). The combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated *in vacuo* to afford the product, which was carried forward.

ii. To a solution of intermediate (25 mg, 0.051 mmol) and palladium on carbon (10 wt%, 5 mg, 0.05 mmol) in methanol (1 mL) at room temperature under N_2 atmosphere was added concentrated HCl (few drops). The reaction flask was backfilled with H_2 (3x) and the resulting mixture was stirred under H_2 atmosphere (balloon) for 1 h, then backfilled with N_2, and filtered through celite and rinsed with MeOH. The filtrate was concentrated *in vacuo* and the crude residue was diluted with wet DMSO (0.5 mL) and purified via mass-directed isolation using ultra-performance liquid chromatography to afford the product as a white solid (4.7 mg, 28% yield). **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.72 (dd, *J* = 11.6, 2.4 Hz, 1H), 7.41 (t, *J* = 8.5 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 4.17 – 4.05 (m, 1H), 3.93 (dd, *J* = 13.8, 4.0 Hz, 1H), 3.21 – 3.01 (m, 2H), 2.80 – 2.69 (m, 1H), 2.30 (d, *J* = 14.0 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.57 – 1.39 (m, 2H), 1.00 – 0.80 (m, 3H); **AMM** 357.1517 (ESI) *m/z* [calc for $C_{16}H_{23}ClFN_4O_2$ $(M+H)^+$ 357.1494].

Synthesis of Analog **21b** (MCG-IV-273)



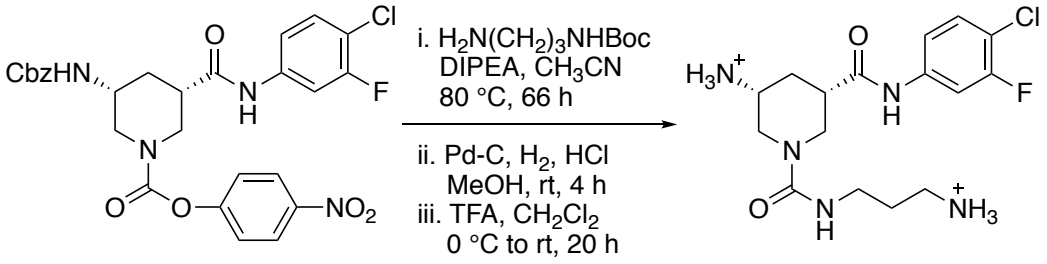
S29 **21b**

i. To a solution of intermediate **2.156** (40 mg, 0.070 mmol) and $H_2N(CH_2)_2NHBoc$ (22 mg, 0.14 mmol) in acetonitrile (1 mL) at room temperature was added diisopropylethylamine (20 µL, 0.1 mmol). The reaction mixture was heated to 80 °C and stirred for 65 h, then concentrated *in vacuo*. The crude residue was taken up in EtOAc and diluted with water. The layers were

separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over $NaSO_4$ and concentrated *in vacuo* to afford the product, which was carried forward.

ii. To a solution of intermediate (35 mg, 0.060 mmol) and palladium on carbon (10 wt%, 6.4 mg, 0.060 mmol) in methanol (1.2 mL) at room temperature under N_2 atmosphere was added concentrated HCl (few drops). The reaction flask was backfilled with H_2 (3x) and the resulting mixture was stirred under H_2 atmosphere (balloon) for 5 h, then backfilled with N_2, and filtered through celite and rinsed with MeOH. The filtrate was concentrated *in vacuo* and the crude product was carried forward without additional purification.

iii. To a precooled (0 °C) solution of intermediate (28 mg, 0.060 mmol) in CH_2Cl_2 (1.2 mL) under N_2 atmosphere was added trifluoroacetic acid (50 µL, 0.6 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 20 h, then concentrated *in vacuo*. The crude residue was taken up in wet DMSO (0.8 mL), filtered through celite, and purified via mass-directed isolation using ultra-performance liquid chromatography to afford the product as a white solid (12 mg, 29% yield over 3 steps). **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.76 – 7.68 (m, 1H), 7.41 (t, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 4.19 – 4.07 (m, 1H), 3.98 – 3.89 (m, 1H), 3.48 – 3.37 (m, 1H), 3.24 – 3.13 (m, 1H), 3.03 (t, *J* = 5.8 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.33 (d, *J* = 13.7 Hz, 1H), 1.99 – 1.87 (m, 1H)



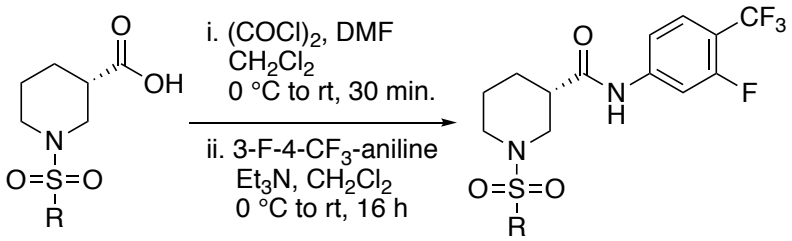
S29 **21c**

i. To a solution of intermediate **2.156** (40 mg, 0.070 mmol) and $H_2N(CH_2)_3NHBoc$ (24 mg, 0.14 mmol) in acetonitrile (1 mL) at room temperature was added diisopropylethylamine (20 µL, 0.1 mmol). The reaction mixture was heated to 80 °C and stirred for 66 h, then concentrated *in vacuo*. The crude residue was taken up in EtOAc and diluted with water. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over $NaSO_4$ and concentrated *in vacuo* to afford the product, which was carried forward.

ii. To a solution of intermediate (23 mg, 0.037 mmol) and palladium on carbon (10 wt%, 4.0 mg, 0.037 mmol) in methanol (0.8 mL) at room temperature under N_2 atmosphere was added concentrated HCl (few drops). The reaction flask was backfilled with H_2 (3x) and the resulting mixture was stirred under H_2 atmosphere (balloon) for 4 h, then backfilled with N_2, and filtered through celite and rinsed with MeOH. The filtrate was concentrated *in vacuo* and the crude product was carried forward without additional purification.

To a precooled (0 °C) solution of intermediate (18 mg, 0.037 mmol) in CH_2Cl_2 (0.8 mL) under N_2 atmosphere was added trifluoroacetic acid (30 µL, 0.4 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 20 h, then concentrated *in vacuo*. The crude residue was taken up in wet DMSO (1 mL), filtered through celite, and purified via mass-directed isolation using ultra-performance liquid chromatography to afford the product as a white solid (13 mg, 32% yield over 3 steps). **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.75 – 7.68 (m, 1H), 7.41 (t, *J* = 8.6 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 4.08 (d, *J* = 14.0 Hz, 1H), 3.90 (d, *J* = 14.3 Hz, 1H), 3.39 (dd, *J* = 14.0, 8.4 Hz, 1H), 3.26 (dd, *J* = 14.9, 7.6 Hz, 1H), 2.94 (s, 1H), 2.78 (d, *J* = 9.9 Hz, 1H), 2.33 (d, *J* = 14.2 Hz, 1H), 1.94 (d, *J* = 8.6 Hz, 1H), 1.86 – 1.72 (m, 2H); **AMM** (ESI) *m/z* 372.1593 [calc for $C_{16}H_{24}ClFN_5O_2$ (MH) 372.1603].

General Synthesis of Analogs S30



5 **S30a**-**S30b**

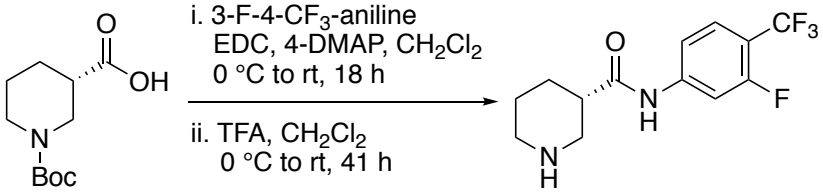
i. To separate precooled (0 °C) solutions of **5** (1.0 eq) in dichloromethane (0.2 M) was added oxalyl chloride (1.1 eq) and dimethylformamide (1-2 drops). The resulting reaction mixtures were allowed to warm to room temperature and stirred for 30 min. then concentrated *in vacuo* and used directly.

ii. To separate precooled (0 °C) solutions of 3-fluoro-4-trifluoromethylaniline (1.0 eq) in dichloromethane (0.05 M) was added triethylamine (1.2 eq) then dropwise a solution of intermediate acid chloride (1.2 eq) in dichloromethane (0.05 M). The resulting mixtures were allowed to warm to room temperature and stirred for 16 h, then diluted with wet DMSO (0.5 mL), filtered through celite, and purified via mass-directed isolation using ultra-performance liquid chromatography to afford the products as white solids (69-73% yield).

MCG-IV-024-A02 (**S30a**)
R = Me (69% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.91 (s, 1H), 7.81 – 7.74 (m, 1H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.62 (d, *J* = 11.7 Hz, 1H), 2.89 (dd, *J* = 11.8, 10.6 Hz, 1H), 2.79 (s, 3H), 2.74 (td, *J* = 11.6, 2.8 Hz, 1H), 2.68 – 2.57 (m, 1H), 2.08 – 1.98 (m, 1H), 1.90 – 1.81 (m, 1H), 1.68 – 1.56 (m, 2H);

MCG-IV-024-B02 (**S30b**)
R = Et (73% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.93 – 8.77 (m, 1H), 7.77 (dd, *J* = 13.5, 1.9 Hz, 1H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 3.87 – 3.78 (m, 1H), 3.67 – 3.59 (m, 1H), 3.05 – 2.93 (m, 3H), 2.84 (td, *J* = 11.8, 2.9 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.07 – 1.98 (m, 1H), 1.87 – 1.78 (m, 1H), 1.71 – 1.51 (m, 2H), 1.27 (t, *J* = 7.4 Hz, 3H);

Syntheses of Common Intermediate **S31**



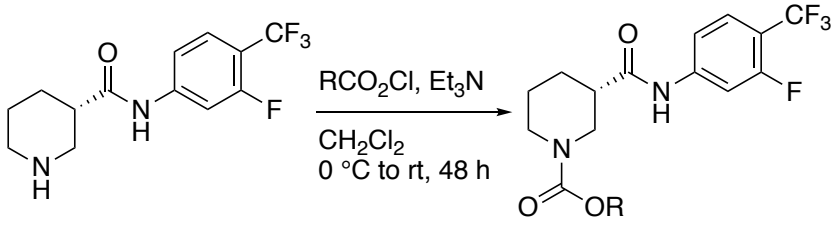
S2 **S31**

i. To a solution of intermediate **S2** (591 mg, 2.58 mmol), 3-fluoro-4-trifluoromethylaniline (462 mg, 2.58 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI, 544 mg, 2.84 mmol) in CH_2Cl_2 (13 mL) at room temperature under N_2 atmosphere was added 4-dimethylaminopyridine (346 mg, 2.84 mmol). The resulting mixture was stirred for 18 h, then quenched with water. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed sequentially with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 80:20 hexanes:ethyl acetate) afforded the product as a white solid (1.00 g).

ii. To a precooled (0 °C) solution of intermediate (1.00 g, 2.56 mmol) in CH_2Cl_2 (12 mL) under N_2 atmosphere was added dropwise trifluoroacetic acid (0.59 mL, 7.7 mmol). The resulting mixture was

allowed to warm to room temperature and stirred for 41 h, then concentrated *in vacuo*. The crude residue was taken up in water, cooled to 0 °C, then slowly neutralized with powdered $NaHCO_3$. The aqueous phase was diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a white solid (678 mg, 68% yield). **$[\alpha]_D^{23}$** -5.0 (c. 0.31, CH_3OH); **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 11.21 (s, 1H), 7.71 (d, *J* = 12.9 Hz, 1H), 7.53 – 7.38 (m, 1H), 7.26 (s, 1H), 3.37 (d, *J* = 37.4 Hz, 1H), 3.28 – 3.18 (m, 1H), 3.14 – 3.01 (m, 1H), 3.01 – 2.92 (m, 1H), 2.78 (t, *J* = 11.2 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.08 – 1.95 (m, 1H), 1.86 – 1.67 (m, 2H), 1.67 – 1.51 (m, 1H), 1.44 (d, *J* = 3.8 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.52, 161.20, 159.18, 143.56, 143.47, 127.38, 123.87, 121.72, 114.51, 114.48, 107.93, 107.73, 77.16, 47.58, 46.32, 46.28, 41.72, 28.42, 28.40, 27.41, 22.45; **IR** (ATR) ν_{max} 3280, 2927, 1679, 1610, 1416, 1319, 1118, 1049, 863, 637 cm^{-1}; **AMM (**ESI) *m/z* 291.1139 [calc for $C_{13}H_{15}N_2F_4O$ $(M+H)^+$ 291.1121].

General Synthesis of Analogs **S32**



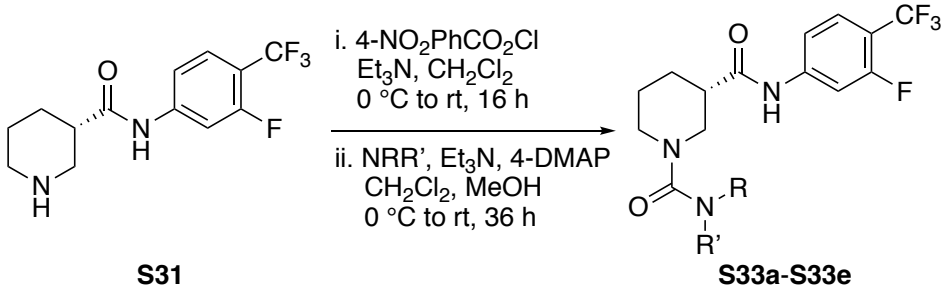
S31 **S32a**-**S32b**

To separated precooled (0 °C) solutions of **S31** (20. mg, 0.069 mmol) in CH_2Cl_2 (1 mL) was added triethylamine (30 µL, 0.2 mmol) then alkylchloroformate (0.10 mmol). The resulting mixtures were allowed to warm to room temperature and stirred for 48 h, then diluted with wet DMSO (0.5 mL), filtered through celite, and purified via mass-directed isolation via ultra-performance liquid chromatography (33-36% yield).

MCG-IV-050-A01 (**S32a**)
R = Me (36% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.87 (s, 1H), 7.78 (dt, *J* = 13.3, 1.5 Hz, 1H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.42 – 7.32 (m, 1H), 4.12 (s, 1H), 3.92 (s, 1H), 3.63 (s, 3H), 3.03 (t, *J* = 11.9 Hz, 1H), 2.87 (s, 1H), 2.54 – 2.42 (m, 1H), 2.06 – 1.97 (m, 1H), 1.78 – 1.62 (m, 2H), 1.54 – 1.39 (m, 1H); **AMM** 371.0986 (ESI) *m/z* [calc for $C_{15}H_{16}F_4N_2O_3Na$ $(M+Na)^+$ 371.0995].

MCG-IV-050-A02 (**S32b**)
R = Et (33% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.90 (s, 1H), 7.83 – 7.73 (m, 1H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.42 – 7.34 (m, 1H), 4.18 – 4.00 (m, 3H), 3.93 (d, *J* = 13.5 Hz, 1H), 3.15 – 2.96 (m, 1H), 2.88 (s, 1H), 2.54 – 2.41 (m, 1H), 2.05 – 1.97 (m, 1H), 1.80 – 1.64 (m, 2H), 1.54 – 1.39 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); **AMM** 385.1149 (ESI) *m/z* [calc for $C_{16}H_{18}F_4N_2O_3Na$ $(M+Na)^+$ 385.1151].

General Synthesis of Analogs **S33**



S31 **S33a**-**S33e**

i. To a precooled (0 °C) solution of common intermediate **S31** (150 mg, 0.571 mmol) and *p*-nitrophenylchloroformate (156 mg, 0.775 mmol) in CH_2Cl_2 (4 mL) under N_2 atmosphere was added dropwise triethylamine (22 µL, 1.6 mmol). The reaction mixture was allowed to warm to room

temperature and stirred for 16 h, then quenched with $NaHCO_3$ (sat. aq.). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, 70:30 hexanes:ethyl acetate) afforded the product, which was carried forward.

ii. To separated precooled (0 °C) vials charged with amine (0.13 mmol) was added a solution of intermediate (30. mg, 0.066 mmol), triethylamine (20 µL, 0.1 mmol) and 4-dimethylaminopyridine (2 mg, 0.002 mmol) in CH_2Cl_2 (0.5 mL) and MeOH (0.5 mL). The resulting mixtures were allowed to warm to room temperature and stirred for 36 h, then diluted with wet DMSO (0.5 mL), filtered through celite, and purified via mass-directed isolation using ultra-performance liquid chromatography (16-19% yield).

MCG-IV-063-A01 (**S33a**)
R = Me, R' = H (19% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.28 (s, 1H), 7.81 (d, *J* = 12.7 Hz, 1H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 3.91 (d, *J* = 14.0 Hz, 1H), 3.73 – 3.63 (m, 1H), 3.14 (dd, *J* = 13.6, 9.5 Hz, 1H), 2.90 (ddd, *J* = 13.7, 10.7, 3.2 Hz, 2H), 2.67 (s, 3H), 1.86 – 1.72 (m, 2H), 1.69 – 1.59 (m, 1H), 1.51 – 1.38 (m, 1H); **AMM** 348.1348 (ESI) *m/z* [calc for $C_{15}H_{18}F_4N_3O_2$ $(M+H)^+$ 348.1335].

MCG-IV-063-A02 (**S33b**)
R = Et, R' = H (19% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.31 (s, 1H), 7.81 (d, *J* = 13.8 Hz, 1H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 3.89 (d, *J* = 13.5 Hz, 1H), 3.71 – 3.62 (m, 1H), 3.24 – 3.10 (m, 3H), 2.97 – 2.86 (m, 1H), 1.89 – 1.72 (m, 2H), 1.69 – 1.57 (m, 1H), 1.51 – 1.39 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H); **AMM** 362.1483 (ESI) *m/z* [calc for $C_{16}H_{20}F_4N_3O_2$ $(M+H)^+$ 362.1492].

MCG-IV-063-A03 (**S33c**)
R = Me, R' = Me (16% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.51 (s, 1H), 7.81 (dd, *J* = 13.5, 1.9 Hz, 1H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 3.61 (dd, *J* = 13.4, 3.8 Hz, 1H), 3.52 – 3.41 (m, 1H), 3.18 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.79 (s, 6H), 2.61 – 2.52 (m, 1H), 1.81 (dtd, *J* = 13.6, 10.1, 3.9 Hz, 1H), 1.69 – 1.58 (m, 1H), 1.57 – 1.45 (m, 1H); **AMM** 362.1494 (ESI) *m/z* [calc for $C_{16}H_{20}F_4N_3O_2$ $(M+H)^+$ 362.1492].

MCG-IV-063-A05 (**S33d**)
R = *n*-Pr, R' = H (17% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.19 (d, *J* = 14.1 Hz, 1H), 7.78 (dd, *J* = 13.4, 1.9 Hz, 1H), 7.56 (t, *J* = 8.4 Hz, 1H), 7.42 – 7.32 (m, 1H), 3.88 (dd, *J* = 13.4, 4.1 Hz, 1H), 3.66 (d, *J* = 13.3 Hz, 2H), 3.21 – 3.11 (m, 2H), 3.07 (t, *J* = 7.1 Hz, 3H), 2.91 (ddd, *J* = 13.3, 10.4, 3.1 Hz, 1H), 2.51 – 2.39 (m, 1H), 1.77 (dtd, *J* = 13.7, 10.5, 3.9 Hz, 1H), 1.68 – 1.55 (m, 1H), 1.51 – 1.36 (m, 3H), 0.84 (t, *J* = 7.4 Hz, 3H); **AMM** 376.1641 (ESI) *m/z* [calc for $C_{17}H_{22}F_4N_3O_2$ $(M+H)^+$ 376.1648].

MCG-IV-063-A06 (**S33e**)
R = *i*-Bu, R' = H (18% yield)
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.29 (s, 1H), 7.81 (d, *J* = 13.5 Hz, 1H), 7.59 (t, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 9.2 Hz, 1H), 5.37 (s, 1H), 3.85 (d, *J* = 13.8 Hz, 1H), 3.71 – 3.55 (m, 1H), 3.26 (dd, *J* = 13.7, 8.9 Hz, 1H), 3.03 – 2.85 (m, 2H), 2.52 – 2.42 (m, 2H), 1.88 – 1.76 (m, 1H), 1.76 – 1.66 (m, 1H), 1.61 (t, *J* = 8.9 Hz, 1H), 1.54 – 1.37 (m, 1H), 0.92 – 0.74 (m, 3H); AMM 412.1631 (ESI) *m/z* [calc for $C_{18}H_{23}F_4N_3O_2Na$ $(M+Na)^+$ 412.1624].

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