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Supplementary Materials for

Identification and optimization of molecular glue compounds that inhibit a non-covalent E2 enzyme-ubiquitin complex

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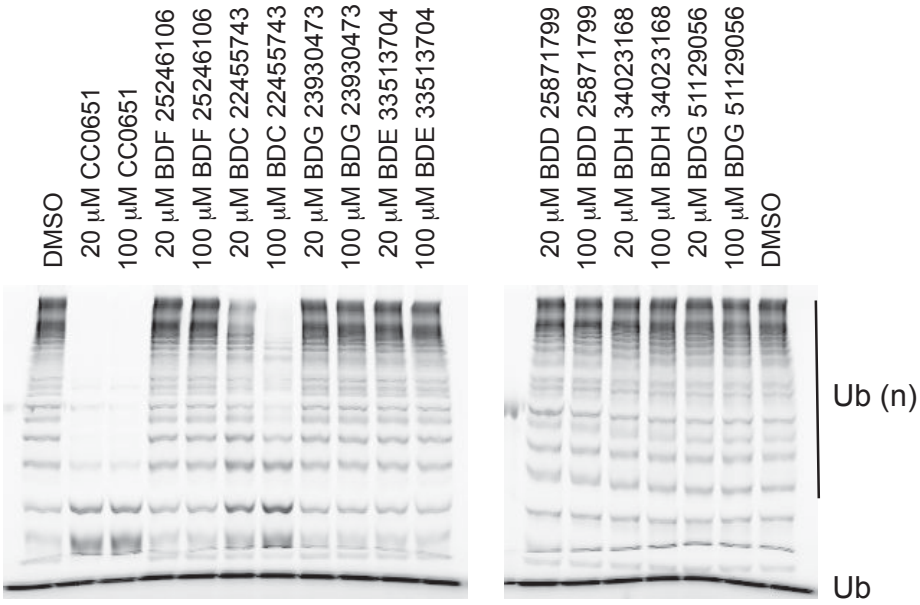
The PDF file includes:

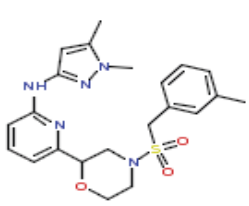
Other Supplementary Material for this manuscript includes the following:

Supplementary Figure S1. Validation of top 7 initial screen hits in a CDC34A-mediated in vitro ubiquitination reaction. (A) Activity in a gel-based assay for poly-Ub chain formation. The experiment was performed only once for hit triage purposes. (B) Chemical structures of top 7 hits identified in the TR-FRET screen for stabilizers of the non-covalent interaction between CDC34A and ubiquitin.

A



B



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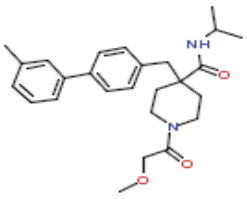

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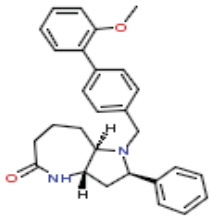

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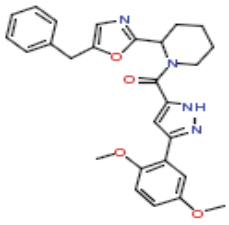

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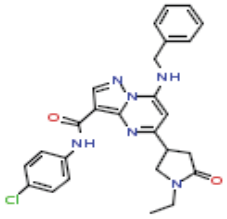

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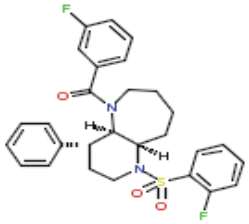

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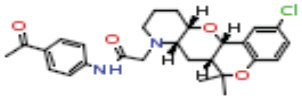
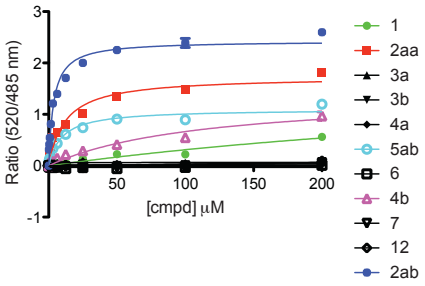
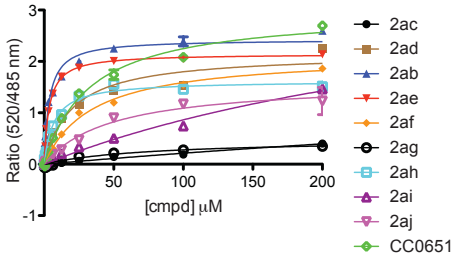
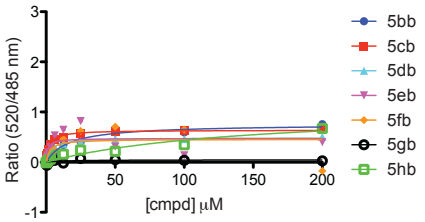


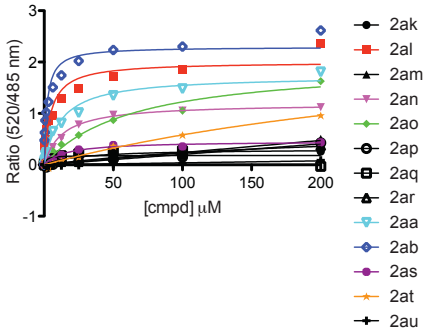
BDG 51129056

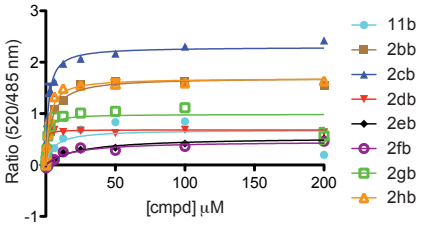
Supplementary Figure S2. Binding curves for inhibitor-induced stabilization of CDC34A to ubiquitin using a TR-FRET assay. Plotted values correspond to the mean, n=3.

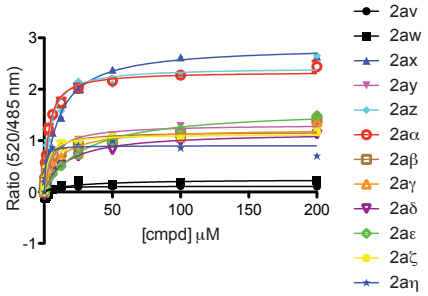




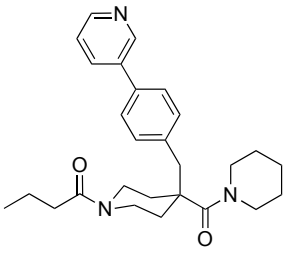








Supplementary Figure S3. Inactive analogs of hit **1** in the custom CDC34A chemical library.



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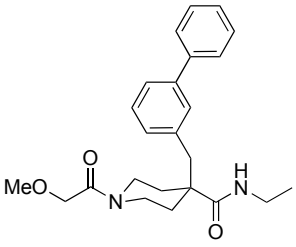
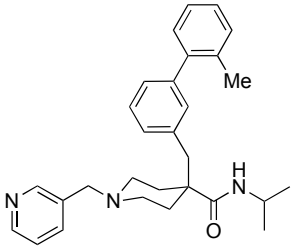
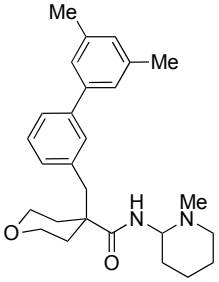


BDC22464246



BDC22465961



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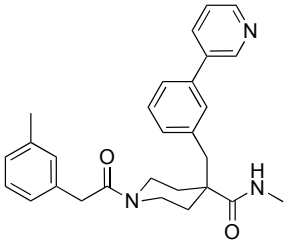
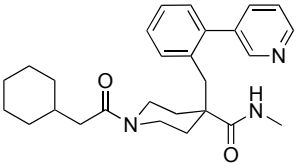


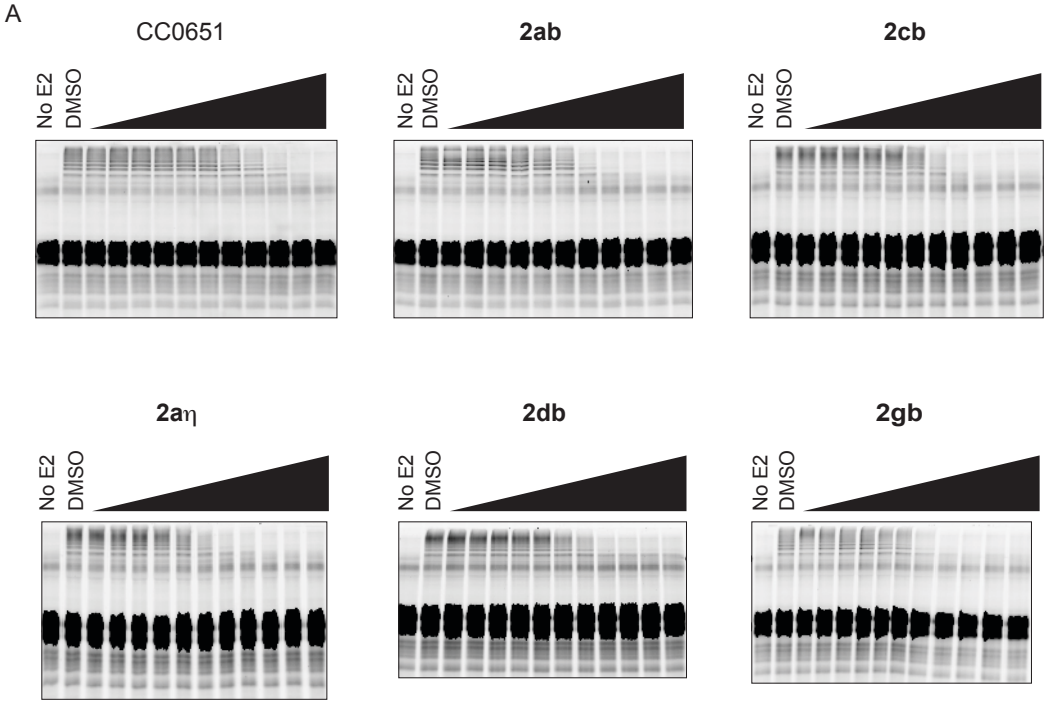
BDC22460670



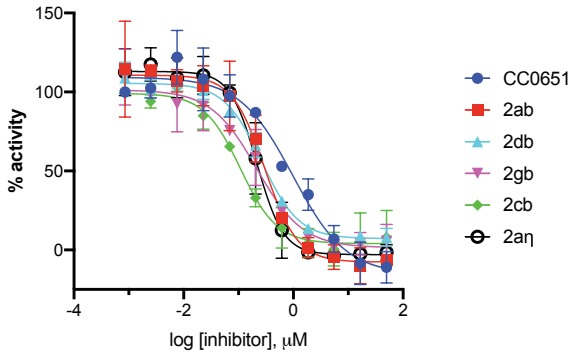
BDC22440387

Supplementary Figure S4. Inhibition of SCF^{SKP2}-mediated p27 polyubiquitination by isonipecotamide analogs. (A) Fluorescein-labeled p27 reaction products obtained in the presence of increasing concentrations of the indicated inhibitors as resolved by SDS-PAGE. Concentrations of inhibitors tested ranged from 0.00084 μM to 50 μM in 3-fold increments. Experiment was performed twice and representative gels from one experiment are shown. (B) Quantification of p27 polyubiquitination. Percent inhibition of p27 polyubiquitination for each inhibitor concentration represents the mean from two experiments. (C) Calculated IC_{50} values from panel B. IC_{50} values represent the mean +/- variance, n=2.

A



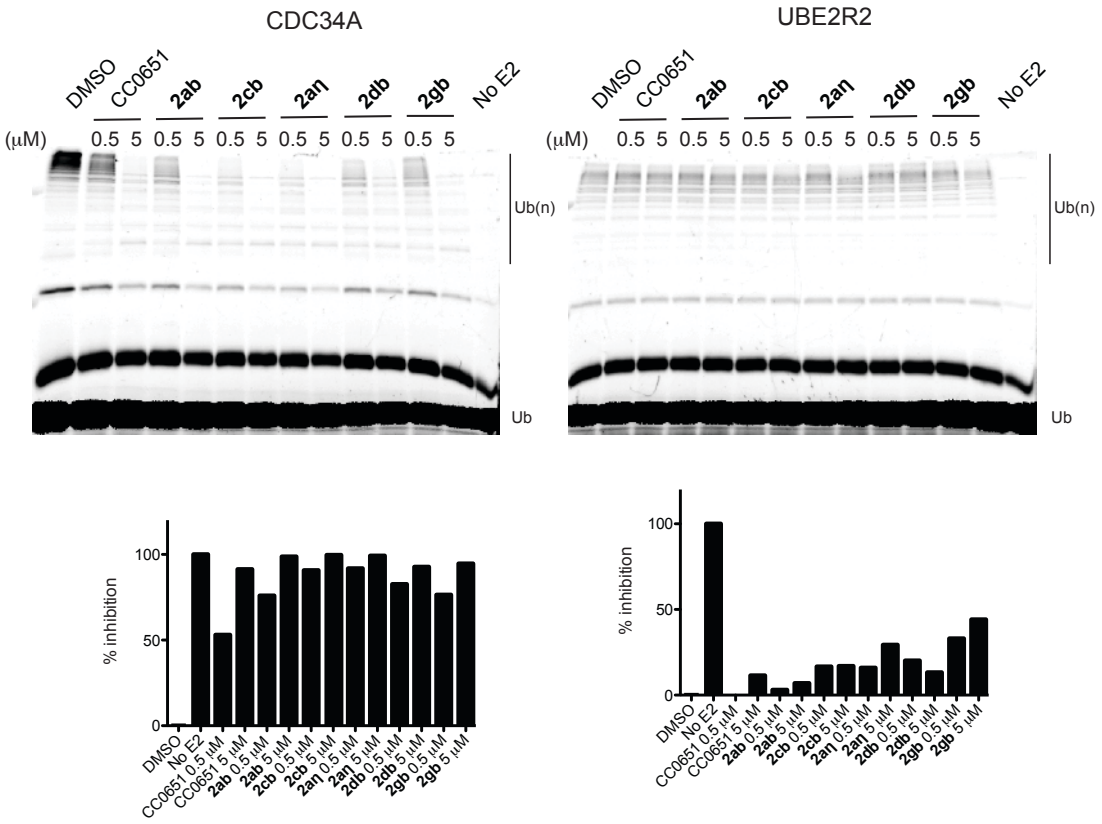
B



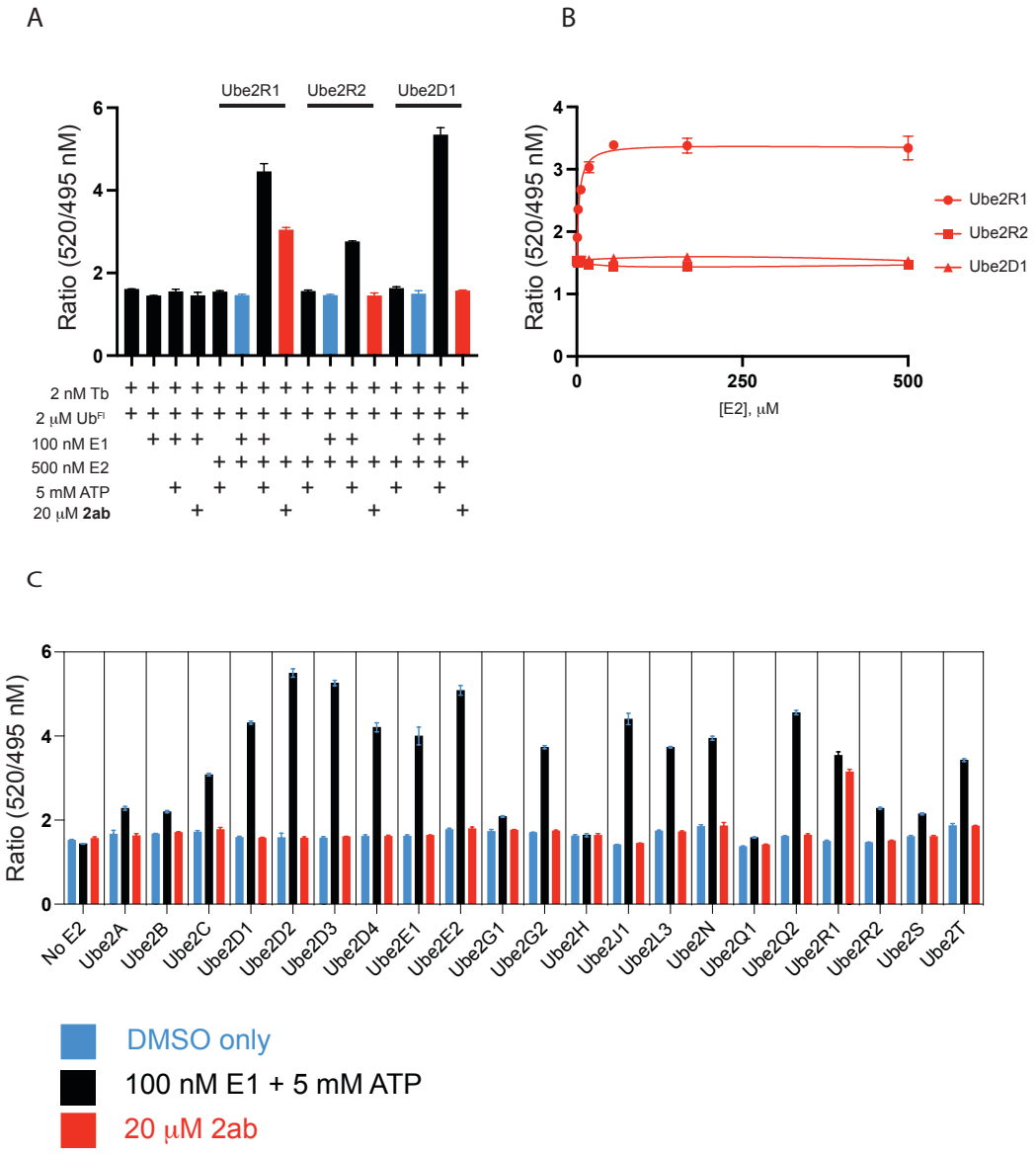
C

compound	p27-$Ub_{(n)}$ IC_{50}
CC0651	1.02 ± 0.19 μM
2ab	0.294 ± 0.054 μM
2cb	0.106 ± 0.026 μM
2aη	0.245 ± 0.139 μM
2db	0.263 ± 0.035 μM
2gb	0.194 ± 0.096 μM

Supplementary Figure S5. Isonipecotamide analogs do not inhibit UBE2R2-mediated ubiquitin chain formation. Representative results are shown for one of two separate experiments. Quantification shown at bottom.

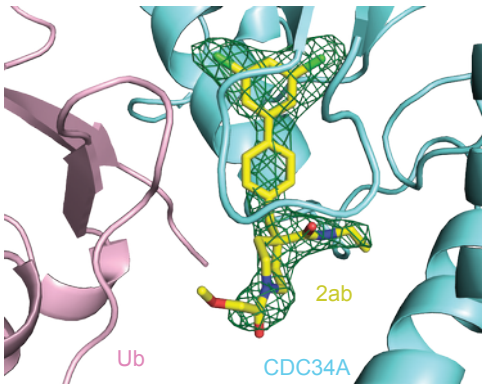


Supplementary Figure S6. Specificity of E2 enzyme inhibition by isonipecotamide **2ab**. (A) Validation of TR-FRET assay for charging of E2 enzymes with Ub. (B) E2 concentration dependence of TR-FRET signal stimulated by isonipecotamide **2ab**. (C) Assessment of E2-Ub complex formation for a panel of 21 human E2 enzymes in the presence or absence of 20 μM isonipecotamide **2ab**. TR-FRET signal of charged E2s served as a positive control for each assay. Experiments shown were performed twice in triplicate. Representative results for one experiment are shown. Values shown are the mean +/- SEM from one experiment (n=3).



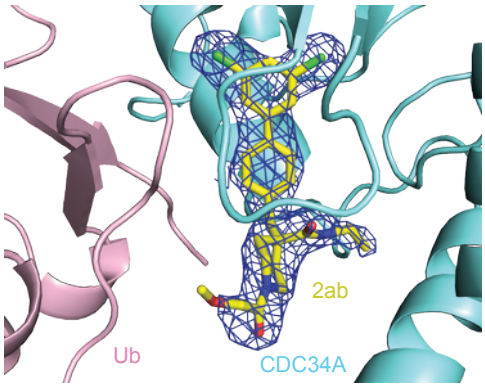
Supplementary Figure S7. Modeling of **2ab** inhibitor coordinates from unbiased electron density maps.

A



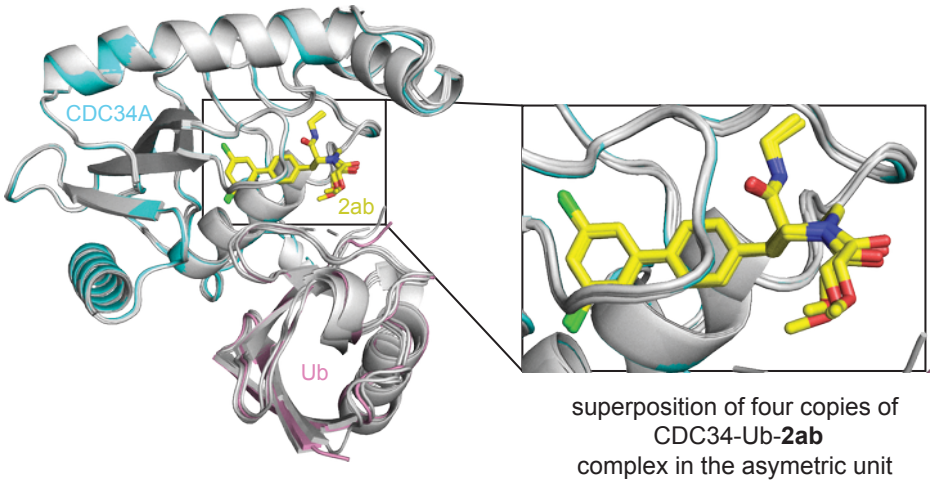
|Fo-Fc| electron density in green
contoured at 2.5 σ
prior to refinement with compound

B



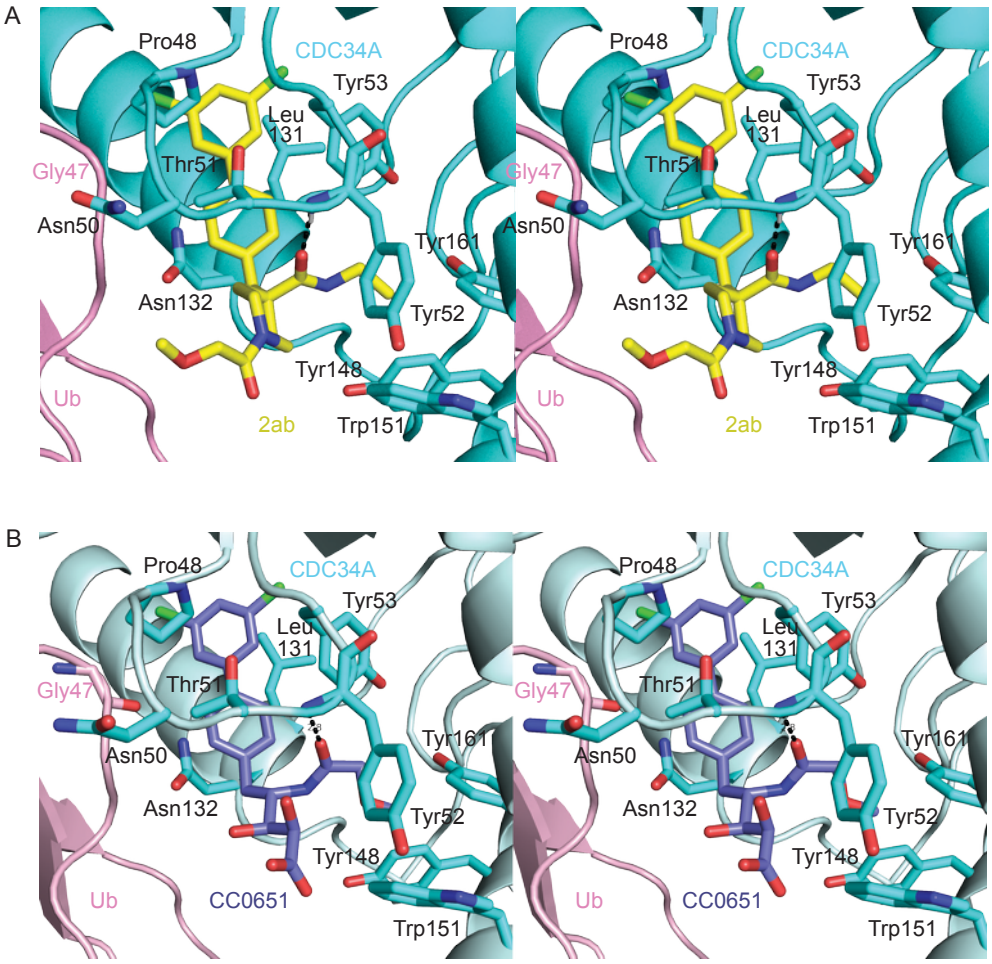
|2Fo-Fc| electron density in blue
contoured at 1.0 σ
from final refinement

C



superposition of four copies of
CDC34-Ub-**2ab**
complex in the asymetric unit

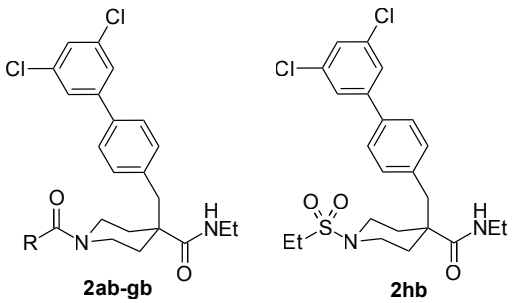
Supplementary Figure S8. Detailed stereo view of **2ab** in the CDC34A-Ub binding pocket.



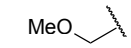
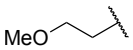
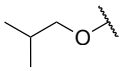
Supplementary Table S1. Molecular formula strings and primary screen TR-FRET data for all compounds in custom CDC34A chemical library. Provided as separate file in Microsoft Excel format.

Supplementary Table S2. Molecular formula strings and TR-FRET assay data for all new compounds reported in this study. Provided as separate file in Microsoft Excel format.

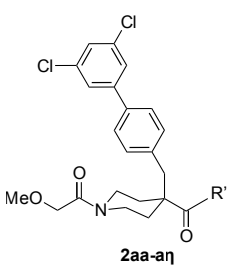
Supplementary Table S3. SAR for western acylpiperidine isonipecotamide analogs in the **2** series. EC_{50} values represent the mean +/- SD, n=3. IC_{50} values represent the mean +/- variance, n=2.



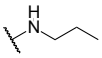
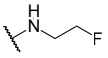
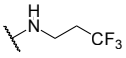
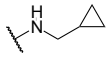
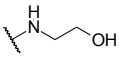
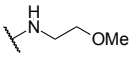
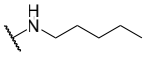
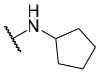
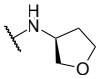
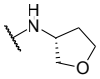
2ab-gb **2hb**

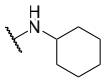
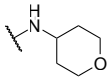
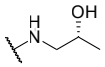
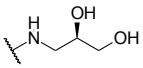
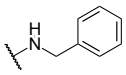
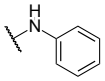
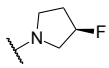
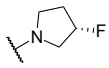
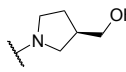
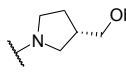
	R	TR-FRET EC_{50} (μM)	Ub IC_{50} (μM)
2ab (UM0130896)		**3.6 ± 0.3**	0.09
2bb (UM0131269)		4.1 ± 0.4	–
2cb (UM0131536)		1.9 ± 0.1	0.06
2db (UM0131271)		0.44 ± 0.06	0.20
2eb (UM0131175)		23 ± 4	–
2fb (UM0131176)		17 ± 5	–
2gb (UM0131272)		1.7 ± 0.1	0.11
2hb (UM0131270)	N/A	2.5 ± 0.2	0.14

Supplementary Table S4. SAR for eastern carboxamide isonipecotamide analogs in the **2** series. EC_{50} values represent the mean +/- SD, n=3. IC_{50} values represent the mean +/- variance, n=2.

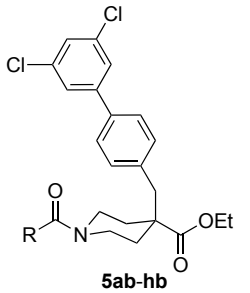


2aa-aη

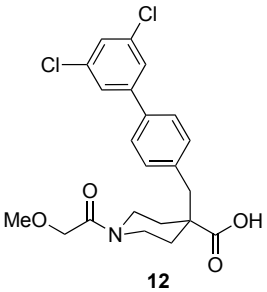
	R'	TR-FRET EC_{50} (μM)	Ub IC_{50} (μM)
2aa (UM0130744)		12 ± 2	
2ab (UM0130896)		3.6 ± 0.3	0.09
2ac (UM0130899)		> 100	
2ad (UM0130895)		20 ± 3	
2ae (UM0131194)		3.5 ± 0.1	0.02
2af (UM0131537)		35 ± 3	
2ag (UM0131538)		76 ± 32	
2ah (UM0131192)		7.3 ± 0.7	
2ai (UM0130898)		> 100	
2aj (UM0130897)		48 ± 11	
2ak (UM0131541)		26 ± 8	
2al (UM0131069)		4.7 ± 0.8	
2am (UM0130955)		> 100	
2an (UM0130901)		13 ± 2	
2ao (UM0131203)		63 ± 9	
2ap (UM0131204)		> 100	

	R'	TR-FRET EC_{50} (μM)	Ub IC_{50} (μM)
2aq (UM0130931)		6.1 ± 2.4	
2ar (UM0130930)		> 100	
2as (UM0131542)		15 ± 3	
2at (UM0130900)		> 100	
2au (UM0130929)		> 100	
2av (UM0131184)		3.5 ± 1.9	
2aw (UM0131183)		21 ± 17	
2ax (UM0131539)		10 ± 1	
2ay (UM0131185)		6.2 ± 0.5	
2az (UM0131540)		4.0 ± 0.4	
2aα (UM0131193)		3.2 ± 0.3	0.12
2aβ (UM0131329)		3.6 ± 0.6	
2aγ (UM0131328)		9.7 ± 1.4	
2aδ (UM0131211)		16 ± 2	
2aε (UM0131212)		28 ± 3	
2aζ (UM0131247)		2.7 ± 0.3	0.15
2aη (UM0131605)		0.76 ± 0.10	0.03

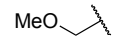
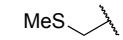
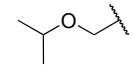
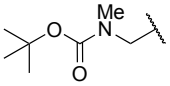
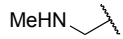
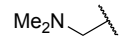
Supplementary Table S5. SAR for isonipecotate analogs in the **5** series. EC_{50} values represent the mean +/- SD, n=3.



5ab-**hb**



12

	R	TR-FRET EC_{50} (μM)
5ab (UM0131530)		9.5 ± 1.2
5bb (UM0131441)		16 ± 3
5cb (UM0131442)		2.4 ± 0.3
5db (UM0131438)		3.7 ± 0.6
5eb (UM0131439)		6.3 ± 0.9
5fb (UM0131440)		9.6 ± 1.5
5gb (UM0131443)		> 100
5hb (UM0131330)		> 100
12 (UM0130893)	N/A	> 100

Supplementary Table S6. X-ray structure data collection and refinement statistics.

	CDC34A$^{7-184}$ - Ub - **2ab**
Data collection	
X-ray source	APS-24-IDC
Space group	P1
Unit cell	
a, b, c, Å	55.8, 72.0, 76.5
α, β, γ, °	70.1, 79.1, 80.4
Resolution range, Å*	67.3-2.47 (2.54-2.47)
Unique reflections	34543
Completeness, %*	88.1 (89.0)
Mean I/σ *	8.1 (1.1)
Rmerge, %*	0.049 (0.839)
*CC1/2**	0.998 (0.515)
Wilson B-factor	56.6
Redundancy *	2.1 (2.1)
Refinement statistics	
Resolution Range, Å*	67.3-2.47
R_{factor}, %*	22.9 (39.5)
Free R_{factor}, %*	27.0 (42.2)
Free R reflections, %	5.12
Free R reflections, no.*	1767 (158)
Residues built	
CDC34A	7-100, 110-184
Ubiquitin	1-74
Compound	4
Water molecules	30
Mean B-factor, Å^2	
CDC34A/Ub	81.6
Compound	64.9
Water	65.4
R.M.S deviations	
Bond lengths (Å)	0.013
Bond angles (°)	2.03
Ramachandran Plot	
Favoured (%)	97.5
Allowed	2.4
Disallowed	0.1
PDB code:	7M2K

* values in parentheses are for highest resolution shell

Supplementary Materials and Methods

Detailed Chemical Methods and Characterizations

Abbreviations

The following abbreviations and formulas have been used: ca. = circa (approximately), d = days, DIEA = *N*,*N*-diisopropylethylamine (Hünig's base), DTT = dithiothreitol, h = hours, HATU = [dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylidene]-dimethylazanium;hexafluorophosphate, HOAc = acetic acid, $MgSO_4$ = magnesium sulfate, TEA = triethylamine (NEt_3), TFA = trifluoroacetic acid, $NaHCO_3$ = sodium hydrogencarbonate, and Na_2SO_4 = sodium sulphate.

Chemicals

Starting materials and reagents were obtained from Aldrich except the following. From Alpha-Aesar: *N*-Boc-sarcosine, (methylthio)acetic acid. From Apollo Scientific: methoxyacetyl chloride. From Ark Pharm: 3-oxetanamine, (S)-tetrahydrofuran-3-amine hydrochloride, (*R*)-3-aminotetrahydrofuran hydrochloride. From ChemBridge: isopropoxyacetic acid. From Enamine: [(3R)-pyrrolidin-3-yl]methanol, [(3*S*)-pyrrolidin-3-yl]methanol. From Fluka: (*R*)-3-amino-1,2-propanediol. From Lancaster: (*R*)-(+)-tetrahydro-2-furoic acid, (*S*)-(-)-tetrahydro-2-furoic acid, dimethylaminoacetyl chloride hydrochloride. From Matrix Scientific: 4-aminotetrahydropyran. From Strem Chemicals: dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium(II) dichloromethane adduct (i.e. $PdCl_2$(dppf)-DCM).

Solvents were obtained from Fischer Scientific (Waltham, MA), including *N*,*N*-dimethyl formamide (DMF), dimethylsulfoxide (DMSO), acetonitrile (MeCN), dichloromethane (DCM), ethyl acetate (EtOAc), and toluene (MePh). Anhydrous DMF was obtained using a Pure Solv™ (Innovative Technology Inc., Newburyport, MA) solvent purification system. Anhydrous MeCN, DCM, and DMSO were prepared by repeatedly (1-3x) treating the solvents with activated molecular sieves (4 Å, ca. 20% by volume) under nitrogen for >2 d total exposure time.

General procedures for chemical synthesis

Unless stated otherwise, reactions were conducted at room temperature. Ice baths were used for reactions at 0 °C and stirring hotplates (IKA Inc., Wilmingtin, NC) in conjuction with oil baths or metal molds for heated reactions. The statement “concentrated in vacuo” implies that a rotary evaporator (rotavap) was used with a bath temperature of 30-50 °C and a vacuum of up to 1-10 Torr to distill solutions for the recovery of solids. Products obtained as oils, due to residual solvent, were dried using a vaccum line or lyophilizer system equipped with a high vaccum pump operating at ca. 200 mTorr for several hours to obtain solids.

Normal-phase Medium-Pressure Liquid Chromatography (MPLC) was performed on CombiFlash Rf instruments (Teledyne Isco Inc., Lincoln, NE) using the corresponding disposable silica-charged columns (RediSep™). Samples were loaded either as silica adsorbates

or as organic solvent solutions (e.g. DCM). Preparatory HPLC purifications were performed on an Agilent 1200 instrument equipped with reverse-phase columns (Kinetex^{TM}, 5 µm C18 100A AXIA, 21.2 x 100 mm, Phenomenex Inc., Torrance, CA) and a UV diode array detector (monitoring at 220.2 and 254.2 nm). Prior to the injection (injection volume: 0.05-1.8 mL), crude products were dissolved in DMSO, DMF, or MeCN, optionally treated with a few drops of acid (TFA or HOAc), water, and filtered. Mobile phase flow rates were 20 mL/min of strong solvent mixture "B" [MeOH/ H_2O/ TFA (95: 5: 0.1)] in weak solvent mixture "A" [H_2O/ MeOH/ TFA (95: 5: 0.1)] using gradients (0-7 min, X% "B" in "A"; then 7-19 min, X to 100% "B"; then 19-25 min 100% "B") which vary as follows. Method 1: X = 50% "B". Method 2: X = 30% "B". Method 3: X = 70% "B". Method 4: X = 50% "B", HCO_2H (0.05) as acid instead of TFA (0.1).

High-Resolution Mass Spectrometry (HRMS) data were recorded on an Agilent LC/MSD TOF (model 61969A) system. Compound HRMS data is given for the lightest isotope; however, the expected distinct isotope patterns arising from dichloro substitution were observed. Analytical HPLC-MS (LCMS) traces were recorded on an Agilent system (HPLC model 1260, Quadrupole MS model 6120) equipped with an Atmospheric-Pressure Chemical Ionization (APCI) chamber (nebulizer pressure: 5.8 psi, dry gas flow rate: 3.0 L/min, drying temperature: 180 ºC, capillary voltage: 5.5 kV) and a reversed-phase column (Agilent Poroshell 120, EC-C18, 2.7 µm, 2.1 x 30 mm) using strong solvent mixture "B" [MeOH/ H_2O/ AcOH (95: 5: 0.1)] in weak solvent mixture "A" [H_2O/ MeOH/ AcOH (95: 5: 0.1)] as mobile phase, a flow rate of 1.50 mL/ min, and a linear gradient (0.0 – 0.5 min, 0 to 100% "B" in "A"; then 0.5 – 2.0 min, 100% "B"). Analytical HPLC-ELS traces were recorded on a Agilent system (1200 series HPLC, 1260 infinity ELSD) equipped with a reverse-phase column (Zorbax, SB-Phenyl 3.5 µm, 4.6 x 30 mm) using strong solvent mixture "B" [MeOH/ H_2O/ TFA (95: 5: 0.05)] in weak solvent mixture "A" [H_2O/ MeOH/ TFA (95: 5: 0.05)] as mobile phase, a flow rate of 1.0 mL/ min, and a linear gradient (0.0 – 1.5 min, 0 to 100% "B" in "A"; then 1.5 – 4.0 min, 100% "B"). A Varian 400-MR spectrometer was used to record ^{1}H and ^{13}C-NMR spectra. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS).

Chemical synthesis and characterization of intermediates and analogs

(9) 1-*tert*-Butyl 4-ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidine-1,4-dicarboxylate

A suspension of 1-*tert*-butyl 4-ethyl 4-(4-bromobenzyl)piperidine-1,4-dicarboxylate (isonipecotate **8**, 1.00 g, 2.35 mmol, 1 equiv), 3,5-dichlorophenylboronic acid (895 mg, 4.69 mmol, 2 equiv), and $NaHCO_3$ (493 mg, 5.86 mmol, 2.5 equiv) in a dioxane (12 ml)/ water (4 ml) mix was degassed using nitrogen bubbling and treated with $PdCl_2$(dppf)-DCM complex (192 mg, FW 816.65, 235 µmol, 0.1 equiv). After heating at 90 °C for 0.5 h, the reaction was cooled, quenched with water, and repeatedly (3x) extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by normal-phase MPLC (40 g silica gel cartridge) using a gradient of EtOAc in hexanes. The collected fraction was concentrated in vacuo to afford isonipecotate **9** (1.094 g, MW 492.43, 2.222 mmol, 95 % yield) as a colorless oil. In other batches the product was obtained as an oily foam or as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3 H), 1.41-1.50 (m, 11 H), 2.11 (d, J = 12.9 Hz, 2 H), 2.76-2.89 (m, 4 H), 3.95 (br s, 2 H), 4.13 (q,

J = 7.3 Hz, 2 H), 7.13 (d, J = 7.8 Hz, 2 H), 7.32 (t, J = 1.8 Hz, 1 H), 7.39-7.46 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 28.4, 33.3, 41.4 (very broad, 2 C), 46.2, 47.2, 60.6, 79.5, 125.5, 126.7, 127.0, 130.6, 135.2, 136.9, 137.0, 143.8, 154.8, 174.7. HRMS (ESI-TOF) *m/z:* $[M+H–Boc]^+$ Calcd for $C_{21}H_{24}Cl_2NO_2$ 392.1179; found 392.1153.

(10) 1-(tert-Butoxycarbonyl)-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carboxylic acid

A solution of isonipecotate **9** (1.0 g, 2.0 mmol, 1 equiv) in a dioxane (100 ml)/ water (100 ml) mix was treated with lithium hydroxide (monohydrate form, 1.7 g, FW 41.96, 41 mmol, 20 equiv). After stirring at 80°C for 12 – 24 h, the reaction was quenched with HCl(aq) (3 M), diluted with water, and repeatedly (3x) extracted with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4, and filtered. The fitrate was concentrated in vacuo to afford isonipecotic acid **10** (ca. 0.9 g, ca. 2.0 mmol, MW 464.38). LCMS: Tr 1.63 min, m/z $462^–$, 364^+ $[M+H–Boc]^+$. The product was used in subsequent steps without further purification.

In another batch, isonipecotate **9** (365 mg, 741 µmol, 1 equiv) in the dioxane/water mix (6 mL, 1:1) was treated instead with sodium hydroxide (410 mg, 10.3 mmol, 14 equiv) and heated at 110 °C for 5 days. After workup isonipecotic acid **10** (340 mg, 732 µmol, 99% yield) was obtained as a colorless foam.

Analytically pure material was obtained by purifying an aliquot of isonipecotic acid **10** (ca. 0.7 g) by normal-phase MPLC (40 g silica gel cartridge) using MeOH (30%) in EtOAc as eluent. The collected fraction was concentrated in vacuo and an aliquot (ca. 10 mg) of the purified matierial was re-purified by preparatory HPLC (Method 3). The collected fraction was concentrated in vacuo and dried under high vaccum to afford isonipecotic acid **10** (3.8 mg, 8.2 µmol) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.46-1.54 (m, 2 H), 2.06-2.14 (m, 2 H), 2.87-2.96 (m, 4 H), 3.96 (br. s, 2 H), 7.19 (d, J = 8.3 Hz, 2 H), 7.30 (t, J = 1.8 Hz, 1 H), 7.38-7.44 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M–H]^–$ Calcd for $C_{24}H_{26}Cl_2N_2O_4$ 462.1244; found 462.1264.

(11b) Typical procedures S1b and 11b: 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethylpiperidine-4-carboxamide

Procedure S1b: A DMF (4 mL) solution of isonipecotic acid **10** (250 mg, 538 µmol, 1 equiv), HATU (246 mg, 646 µmol, 1.2 equiv), and ethylamine (269 µL, 2.0 M in THF, 538 µmol, 1 equiv) was treated with DIEA (188 µL, 1.08 mmol, 2 equiv). After stirring at 0 °C for 0.3 h the solution was quenched with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined organic layers were repeatedly (8x) washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue was purified by normal-phase MPLC (40 g silica gel cartridge) using a gradient of EtOAc in DCM. The collected fraction was concentrated in vacuo to afford isonipecotamide **S1b** (SMILES string: O=C(NCC)C1(CCN(C(OC(C)(C)C)=O)CC1)CC2=CC=C(C3=CC(Cl)=CC(Cl)=C3)C=C2 , 217 mg, MW 491.45, 442 µmol, 82 % yield over 2 steps) as a colorless oil. In other batches the product was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.0 Hz, 3 H), 1.46 (s, 9 H), 1.49-1.63 (m, 2 H), 1.90-2.07 (m, 2 H), 2.85 (br. s., 2 H), 3.03 (br. t, J = 11.5 Hz, 2

H), 3.23 (quin, *J* = 6.7 Hz, 2 H), 3.80-3.92 (m, 2 H), 5.21 (t, *J* = 5.3 Hz, 1 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.31-7.33 (m, 1 H), 7.39-7.46 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ calcd for $C_{26}H_{33}Cl_2N_2O_3$: 491.1863; found: 491.1869.

Procedure 11b: A DCM (2 mL) solution of isonipecotamide **S1b** (165 mg, 336 µmol, 1 equiv) was treated with TFA (129 µL, 1.68 mmol, 5 equiv). After stirring for 12 – 24 h the mixture was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo to afford isonipecotamide **11b** (TFA salt form, 125 mg, FW 505.36, 247 µmol, 74 % yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 1.13 (t, *J* = 7.4 Hz, 3 H), 1.63-1.86 (m, 2 H), 2.33 (br. d, *J* = 14.1 Hz, 2 H), 2.83-3.02 (m, 4 H), 3.18-3.33 (m, 4 H), 3.33-3.39 (m, 1 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 7.40-7.42 (m, 1 H), 7.52-7.61 (m, 4 H), 7.88 (br. t, *J* = 5.3 Hz, 1 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ calcd for $C_{26}H_{31}Cl_2N_2O_4$: 391.1338; found: 391.1363.

In other batches the preparative chromatography step was omitted, quantitative conversion after 0.5 h was ascertained by LCMS (Tr: 1.21 min, m/z 391^+ $[M+H]^+$), and the crude oily solid was used directly in subsequent steps without further purification.

(2ab) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethyl-1-(2-methoxyacetyl) piperidine-4-carboxamide

A dry DMSO (0.8 ml) solution of HATU (40.6 mg, 107 µmol, 1.2 equiv) and methoxyacetic acid (8.9 µl, 116 µmol, 1.3 equiv) under nitrogen was treated with DIEA (47 µl, 269 µmol, 3 equiv). After 5 min the resulting yellow solution was added to isonipecotamide **11b** (TFA salt form, 45 mg, FW 505.36, 89 µmol, 1 equiv). After 1 h additional activated acylating agent was prepared (0.6 equiv) and added to effect reaction completion. The reaction was quenched with AcOH (0.05 mL, 873 µmol, 10 equiv) and the crude was purified by preparatory HPLC (Method 4). The collected fraction, eluting at 9.5 – 10.5 min, was concentrated in vacuo and lyophilized to afford isonipecotamide **2ab** (30 mg, MW 463.40, 64 µmol, 72 % yield) as a white powdery solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.2 Hz, 3 H), 1.43-1.71 (m, 2 H), 1.95 (d, *J* = 13.7 Hz, 1 H), 2.20 (d, *J* = 14.9 Hz, 1 H), 2.72-3.02 (m, 3 H), 3.09-3.32 (m, 3 H), 3.43 (br. s., 3 H), 3.73 (d, *J* = 14.5 Hz, 1 H), 4.04-4.19 (m, 2 H), 4.30 (d, *J* = 12.5 Hz, 1 H), 5.22 (t, *J* = 5.1 Hz, 1 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.33 (d, *J* = 0.8 Hz, 1 H), 7.42 (d, *J* = 0.8 Hz, 2 H), 7.45 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 33.2, 34.6, 34.7, 39.2, 42.6, 46.1, 46.8, 59.2, 72.0, 125.6, 126.9, 127.3, 130.9, 135.5, 136.9, 137.3, 143.7, 167.6, 173.3. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{29}Cl_2N_2O_3$ 463.1550; found 463.1560.

(2aa) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-isopropyl-1-(2-methoxyacetyl) piperidine-4-carboxamide

Procedure **S1b** was employed using isopropylamine (11 mg, 187 µmol, 1 equiv) as the amine component, modified amounts of isonipecotic acid **10** (87 mg, 187 µmol, 1 equiv), HATU (78 mg, 206 µmol, 1.1 equiv), DIEA (98 µL, 562 µmol, 3 equiv), and MeCN (1 mL) as solvent. The workup was omitted and EtOAc in hexanes was used for the MPLC mobile phase to ultimately afford isonipecotamide **S1a** (SMILES string: O=C(NC(C)C)C1(CCN(C(OC(C)(C)C)=O)CC1)CC2=CC=C(C3=CC(Cl)=CC(Cl)=C3)C=C2 ,

28 mg, MW 505.48, 56 µmol, 30% yield) as a colorless solid. LCMS: Tr 1.60 min, m/z 405^+ $[M+H–Boc]^+$, $503^–[M–H]^–$, $563^–[M+OAc]^–$

Procedure **11b** was employed using isonipecotamide **S1a** (26.5 mg, 52 µmol, 1 equiv) as substrate along with modified quantities of TFA (0.5 ml, 6.5 mmol, 124 equiv) and DCM (1 mL). HPLC purification was omitted to ultimately afford, for direct use in the next step, isonipecotamide **11a** (TFA salt form, LCMS: Tr 1.23 min, m/z 405+ $[M+H]^+$, $463^–[M+OAc]^–$, FW 519.38, 52 µmol assumed).

An MeCN (2 mL) solution of isonipecotamide **11a** (TFA salt form, 52 µmol assumed, 1 equiv), methoxyacetic acid (4.7 mg, 52 µmol, 1 equiv), and HATU (22 mg, 57 µmol, 1.1 equiv) was treated with an MeCN (0.4 mL) solution of DIEA (27 µL, 0.16 mmol, 3 equiv) dropwise over 1 min. After stirring for 0.3 h the reaction was concentrated in vacuo and the residue was purified by preparatory HPLC using a gradient of MeCN (containing 5% H_2O, 0.1% TFA) in water (containing 5% MeCN, 0.1% TFA). The collected fraction was concentrated in vacuo and lyophilized to afford isonipecotamide **2aa** (24 mg, MW 477.42, 50 µmol, 96% yield over 2 steps) as a colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.7 Hz, 3 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 1.45-1.70 (m, 2 H), 1.94 (br d, *J* = 14.1 Hz, 1 H), 2.19 (br d, *J* = 13.7 Hz, 1 H), 2.80 (d, *J* = 13.3 Hz, 1 H), 2.85-2.99 (m, 2 H), 3.15-3.27 (m, 1 H), 3.42 (s, 3 H), 3.73 (br d, *J* = 14.1 Hz, 1 H), 4.02-4.17 (m, 3 H), 4.30 (br d, *J* = 13.7 Hz, 1 H), 5.01 (d, *J* = 7.4 Hz, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.33 (t, *J* = 1.8 Hz, 1 H), 7.40-7.43 (m, 2 H), 7.44 (d, *J* = 8.2 Hz, 2 H). LCMS: Tr 1.44 min, m/z 477^+ $[M+H]^+$, $475^–$ $[M–H]^–$, $535^–$ $[M+OAc]^–$.

(12) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxylic acid

A DCM (7.5 mL) solution of isonipecotic acid **10** (700 mg, 1.51 mmol, 1 equiv) was treated with TFA (0.6 mL, 7.5 mmol, 5 equiv). After stirring for 12 – 24 h the reaction mixture was concentrated in vacuo to afford isonipecotic acid **S2** (TFA salt form, SMILES string: OC(C1(CCNCC1)CC2=CC=C(C3=CC(Cl)=CC(Cl)=C3)C=C2)=O.O=C(O)C(F)(F)F , LCMS: Tr 1.23 min, m/z 364+ $[M+H]^+$, $362^–[M–H]^–$, 1.51 mmol assumed). The totality of the product was used directly in the next step without further purification.

A DCM (7.3 mL) solution of isonipecotic acid **S2** (1.51 mmol assumed) and TEA (612 µL, 4.39 mmol, 3 equiv) at 0 °C was treated with methoxyacetyl chloride (175 mg, 1.61 mmol, 1.1 equiv). The reaction warmed to room temperature, stirred for 2 h, and quenched with aqueous citric acid solution. The mixture was repeatedly (3x) extracted with EtOAc and the combined extracts were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the residue was purified by normal-phase MPLC (40 g silica gel cartridge) using a gradient of EtOAc in hexanes. The collected fraction was concentrated in vacuo to afford isonipecotic acid **12** (570 mg, 1.3 mmol, 87% yield over 2 steps) as a white solid. The anhydride side product was identified in other MPLC fractions (LCMS: Tr 1.83 min, m/z 450^+ $[M+H–RCO_2H+MeOH]^+$, $434^–$ $[M–RCO_2H+H2O–H]^–$). The bulk of the product was used in subsequent steps, while an aliquot was purified by preparatory HPLC (Method 2) to obtain analytically pure material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.63 (m, 2 H), 2.19 (d, *J* = 13.3 Hz, 2 H), 2.79 (t, *J* = 13.9 Hz, 1 H), 2.85-3.03 (m, 2 H), 3.18 (t, *J* = 12.1 Hz, 1 H), 3.41 (s, 3 H), 3.80 (d, *J* = 14.5 Hz, 1 H), 4.02-

4.20 (m, 2 H), 4.47 (d, J = 14.1 Hz, 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 7.31-7.35 (m, 1 H), 7.42 (d, J = 1.6 Hz, 2 H), 7.44 (d, J = 8.2 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{22}H_{24}Cl_2NO_4$ 436.1077; found: 436.1117.

(2bb) Typical Procedure 2bb involving acid chloride: 1-Butyryl-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethylpiperidine-4-carboxamide

A DCM (0.5 mL) solution of isonipecotamide **12b** (TFA salt form, 25 mg, 49 µmol, 1 equiv) and TEA (21 µL, 148 µmol, 3 equiv) at 0 °C was treated with butyryl chloride (5.3 mg, 49 µmol, 1 equiv). After stirring for 0.5 h the reaction was quenched with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined extracts were repeatedly washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo to afford isonipecotamide **2bb** (17 mg, MW 461.42, 37 µmol, 76 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3 H), 1.05 (t, J = 7.2 Hz, 3 H), 1.38-1.72 (m, 4 H), 2.23 (d, J = 12.5 Hz, 1 H), 2.28-2.39 (m, 2 H), 2.73-3.03 (m, 3 H), 3.15-3.33 (m, 3 H), 3.72 (d, J = 13.7 Hz, 1 H), 4.33 (d, J = 13.7 Hz, 1 H), 5.21 (t, J = 5.7 Hz, 1 H), 7.16 (d, J = 7.8 Hz, 2 H), 7.34 (t, J = 1.8 Hz, 1 H), 7.40-7.49 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{31}Cl_2N_2O_2$ 461.1757; found: 461.1771.

(2cb) Typical Procedure 2cb involving carboxylic acid: 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethyl-1-(3-methoxypropanoyl)piperidine-4-carboxamide

A DMF (0.8 mL) solution of isonipecotamide **12b** (TFA salt form, 40 mg, 79 µmol, 1 equiv), HATU (45 mg, 119 µmol, 1.5 equiv), and 3-methoxypropanoic acid (8.3 mg, 79 µmol, 1 equiv) at 0 °C was treated with DIEA (42 µL, 237 µmol, 3 equiv). After stirring for 0.3 h the reaction was quenched with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined extracts were repeatedly (8x) washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo to afford isonipecotamide **2cb** (28 mg, MW 477.42, 59 µmol, 75 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.24 Hz, 2 H), 1.47-1.65 (m, 2 H), 1.93 (d, J = 14.5 Hz, 1 H), 2.20 (d, J = 13.3 Hz, 1 H), 2.59-2.66 (m, 2 H), 2.76-2.99 (m, 3 H), 3.20-3.31 (m, 3 H), 3.36 (s, 3 H), 3.70 (td, J = 6.5, 1.57 Hz, 2 H), 3.73-3.81 (m, 1 H), 4.28-4.38 (m, 1 H), 5.22 (t, J = 5.3 Hz, 1 H), 7.16 (d, J = 8.2 Hz, 2 H), 7.34 (t, J = 1.76 Hz, 1 H), 7.42-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{31}Cl_2N_2O_3$: 477.1706; found: 477.1708.

(2db) Isobutyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(ethylcarbamoyl)piperidine-1-carboxylate

Procedure **2bb** was employed using isobutyl chlorofomate (6.5 µl, 49 µmol, 1 equiv) as acylating agent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2db** (23 mg, MW 491.45, 46 µmol, 94 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 0.95 (s, 3 H), 1.04 (t, J = 7.2 Hz, 3 H), 1.48-1.59 (br m, 2 H), 1.87-2.13 (m, 3 H), 2.86, (br. s., 2 H), 3.08 (t, J = 11.7 Hz, 3 H), 3.19-3.31 (m, 2 H), 3.86 (d, J = 6.3 Hz, 2 H), 3.88-4.00 (m, 2 H), 5.17 (t, J = 5.5 Hz, 1 H), 7.17 (d, J = 8.2 Hz, 2 H), 7.34 (t, J =

1.8 Hz, 1 H), 7.39-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{33}Cl_2N_2O_3$: 491.1863; found: 491.1861.

(2eb) (R)-4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethyl-1-(tetrahydrofuran-2-carbonyl)piperidine-4-carboxamide

Procedure **2cb** was employed using (*R*)-(+)-tetrahydro-2-furoic acid (7 mg, 59 µmol, 1 equiv) as the acyl component along with modified quantities of isonipecotamide **12b** (TFA salt form, 30 mg, 59 µmol, 1 equiv), HATU (27 mg, 71 µmol, 1.2 equiv), DIEA (21 µL, 119 µmol, 2 equiv), and DMF (0.6 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2eb** (21 mg, MW 489.43, 44 µmol, 74 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.2 Hz, 3 H), 1.55-1.80 (m, 2 H), 2.22-2.48 (m, 2 H), 2.84-3.10 (m, 10 H), 3.21-3.34 (m, 4 H), 3.39-3.53 (m, 3 H), 6.44 (t, *J* = 3.9 Hz, 1 H), 7.19 (d, *J* = 8.2 Hz, 1 H), 7.33 (t, *J* = 1.8 Hz, 1 H), 7.40-7.49 (m, 3 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{31}Cl_2N_2O_3$: 489.1706, found: 489.2197.

(2fb) (S)-4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethyl-1-(tetrahydrofuran-2-carbonyl)piperidine-4-carboxamide

Procedure **2cb** was employed using (*S*)-(-)-tetrahydro-2-furoic acid (7 mg, 59 µmol, 1 equiv) as the acyl component along with modified quantities of isonipecotamide **12b** (TFA salt form, 30 mg, 59 µmol, 1 equiv), HATU (27 mg, 71 µmol, 1.2 equiv), DIEA (21 µL, 119 µmol, 2 equiv), and DMF (0.6 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2fb** (21 mg, MW 489.43, 42 µmol, 71 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.24 Hz, 3 H), 1.58-1.86 (m, 1 H), 2.37 (t, *J* = 10.8 Hz, 2 H), 2.84-3.11 (m, 10 H), 3.17-3.34 (m, 4 H), 3.38-3.54 (m, 2 H), 6.33-6.51 (m, 1 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 7.33 (t, *J* = 1.6 Hz, 1 H), 7.40-7.50 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{31}Cl_2N_2O_3$: 489.1706, found: 489.2231.

(2gb) 1-Benzoyl-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethylpiperidine-4-carboxamide

Procedure **2bb** was employed using benzoyl chloride (7 mg, 49 µmol, 1 equiv) as acylating agent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2gb** (21 mg, MW 495.44, 41 µmol, 84 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.2 Hz, 3 H), 1.40-1.54 (m, 1 H), 1.65-1.83 (m, 1 H), 2.06 (d, *J* = 11.4 Hz, 2 H), 2.87 (d, *J* = 11.0 Hz, 2 H), 3.05-3.32 (m, 4 H), 3.54-3.73 (m, 1 H), 4.32-4.48 (m, 1 H), 5.21 (t, *J* = 5.3 Hz, 1 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.33 (t, *J* = 1.8 Hz, 1 H), 7.36-7.48 (m, 9 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{29}H_{31}Cl_2N_2O_2$: 495.1601; found: 495.1612.

(2hb) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethyl-1-(ethylsulfonyl)piperidine-4-carboxamide

Procedure **2bb** was employed using ethanesulfonyl chloride (6.4 mg, 49 µmol, 1 equiv) as "acylating" agent, increased DCM (1 mL) volume, and 1 h at room temperature as the reaction conditions. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide

2hb (18 mg, MW 483.45, 38 µmol, 77 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93-1.11 (m, 3 H), 1.30-1.43 (m, 3 H), 1.53-1.80 (m, 3 H), 2.12 (d, *J* = 13.3 Hz, 2 H), 2.87-3.03, (m, 4 H), 3.16-3.34 (m, 2 H), 3.67 (d, *J* = 12.5 Hz, 2 H), 5.18 (t, *J* = 4.5 Hz, 1 H), 7.10-7.20 (m, 2 H), 7.30-7.36 (m, 1 H), 7.39 -7.55 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{23}H_{29}Cl_2N_2O_3S$: 483.1270; found: 483.1275.

(2ab) Typical Procedure TS4 involving amidation: 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-ethyl-1-(2-methoxyacetyl)piperidine-4-carboxamide

A DMF (0.3 mL) solution of isonipecotic acid **12** (20 mg, 46 µmol, 1 equiv), HATU (21 mg, 55 µmol, 1.2 equiv), and ethylamine (23 µL, 2.0 M solution in THF, 46 µmol, 1 equiv) at 0 °C was treated with DIEA (16 µl, 92 µmol, 2 equiv). After stirring for 0.3 h the reaction was quenched with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined extracts were repeatedly (8x) washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo and the resulting oil was dried under high vacuum to afford isonipecotamide **2ab** (12 mg, MW 463.40, 25 µmol, 54 % yield) as a white flaky solid. Characterization gave identical analytical data to the batch obtained by the acylation in DMSO method.

(2ac) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using ammonium hydroxide solution (3.1 µL, 28% w/v in water, 14.8 M, 46 µmol, 1 equiv) as the amine component, a modified amount of DIEA (9.6 µL, 55 µmol, 1.2 equiv), and MeCN (0.3 mL) as solvent. Purification by preparatory HPLC (Method 2) ultimately afforded isonipecotamide **2ac** (18 mg, MW 435.34, 42 µmol, 91 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46-1.73 (m, 2 H), 1.99 (d, *J* = 14.1 Hz, 1 H), 2.15 (d, *J* = 12.9 Hz, 1 H), 2.89 (d, *J* = 3.5 Hz, 2 H), 2.92-3.02 (m, 1 H), 3.25 (t, *J* = 11.7 Hz, 1 H), 3.42 (s, 3 H), 3.75 (d, *J* = 13.7 Hz, 1 H), 4.10 (q, *J* = 13.0 Hz, 2 H), 4.35 (d, *J* = 13.3 Hz, 1 H), 5.45 (br. s., 1 H), 5.70 (br. s., 1 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 7.34 (s, 1 H), 7.42-7.50 (m, 4 H). MS *m/z:* 435.2 $[M+H]^+$.

(2ad) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-methylpiperidine-4-carboxamide

Procedure TS4 was employed using methylamine (23 µL, 2.0 M in THF, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ad** (11 mg, MW 449.37, 25 µmol, 55 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49-1.71 (m, 2 H), 1.89-2.01 (m, 1 H), 2.15-2.25 (m, 1 H), 2.76 (d, *J* = 4.7 Hz, 3 H), 2.78-3.03 (m, 3 H), 3.14-3.29 (m, 1 H), 3.43 (s, 3 H), 3.68-3.88 (m, 1 H), 4.01-4.17 (m, 2 H), 4.25-4.35 (m, 1 H), 5.24 (d, *J* = 4.7 Hz, 1 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 7.34 (s, 1 H), 7.42-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{23}H_{27}Cl_2N_2O_3$: 449.1393; found: 449.1452.

(2ae) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-propylpiperidine-4-carboxamide

Procedure TS4 was employed using propylamine (4 mg, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ae** (26 mg, MW 477.42, 54 µmol, 79 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.4 Hz, 3 H), 1.36-1.50 (m, 2 H), 1.50-1.71 (m, 2 H), 1.97 (d, *J* = 12.9 Hz, 1 H), 2.23 (d, *J* = 11.7 Hz, 1 H), 2.71-3.03 (m, 3 H), 3.06-3.34 (m, 3 H), 3.40-3.58 (br s, 3 H), 3.65-3.80 (m, 1 H), 4.03-4.20 (br m, 2 H), 4.20-4.45 (br m, 1 H), 5.32 (t, *J* = 4.9 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 7.34 (t, *J* = 1.6 Hz, 1 H), 7.40-7.50 (m, 4 H). Broad peaks in the 3.4 – 4.5 range were attributed to the presence of rotamers. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{31}Cl_2N_2O_3$: 477.1706; found: 477.1704.

(2af) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-(2-fluoroethyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using 2-fluoroethylamine (7 mg, HCl salt form, FW 99.54, 69 µmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2af** (21 mg, MW 481.39, 44 µmol, 64 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.72 (m, 2 H), 2.04 (d, *J* = 13.7 Hz, 1 H), 2.22 (d, *J* = 12.5 Hz, 1 H), 2.79-3.01 (m, 3 H), 3.23 (t, *J* = 11.9 Hz, 1 H), 3.44 (s, 3 H), 3.51 (q, *J* = 4.7 Hz, 1 H), 3.58 (q, *J* = 5.1 Hz, 1 H), 3.77 (d, *J* = 13.7 Hz, 1 H), 4.06-4.20 (m, 2 H), 4.29-4.36 (m, 1 H), 4.39 (t, *J* = 4.5 Hz, 1 H), 4.50 (t, *J* = 4.5 Hz, 1 H), 5.67 (t, *J* = 5.5 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 7.32-7.36 (m, 1 H), 7.43 (d, *J* = 2.0 Hz, 2 H, 7.46 (d, *J* = 8.2 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{28}Cl_2FN_2O_3$: 481.1456; found: 481.1467.

(2ag) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-(3,3,3-trifluoropropyl)piperidine-4-carboxamide

Procedure TS4 was employed using 3,3,3-trifluoropropan-1-amine (10.3 mg, HCl salt form, FW 149.54, 69 µmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ag** (11.4 mg, MW 531.39, 21 µmol, 31 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.72 (m, 2 H), 1.98 (d, *J* = 14.5 Hz, 1 H), 2.17 (d, *J* = 11.7 Hz, 1 H), 2.28 (td, *J* = 10.6, 5.9 Hz, 2 H), 2.80-3.01 (m, 3 H), 3.20 (t, *J* = 12.3 Hz, 1 H), 3.38-3.57 (m, 5 H), 3.75 (d, *J* = 14.1 Hz, 1 H), 4.02-4.18 (m, 2 H), 4.30 (d, *J* = 13.7 Hz, 1 H), 5.55 (t, *J* = 5.7 Hz, 1 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 7.35 (s, 1 H), 7.41-7.49 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{28}Cl_2F_3N_2O_3$: 531.1424; found: 531.1415.

(2ah) N-(Cyclopropylmethyl)-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using cyclopropanemethylamine (5 mg, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ah** (30.3 mg, MW 489.43, 62 µmol, 90 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (d, *J* = 4.3 Hz, 2 H), 0.43-0.56 (m, 2 H), 0.77-0.93 (m, 1 H), 1.41-1.74 (m, 2 H), 1.98 (d, *J* = 12.9 Hz, 1 H), 2.27 (d, *J* = 11.4 Hz, 1 H), 2.57-3.15 (m, 5 H), 3.18-3.41 (m, 1 H), 3.46-3.83 (br m, 3 H), 4.04-4.48 (br m, 4 H), 5.34-5.41 (m, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.31-7.36 (m, 1 H), 7.40-7.48 (m, 4 H). Broad peaks in the 3.5 – 4.5 range were attributed to the presence of rotamers. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{31}Cl_2N_2O_3$: 489.1706; found: 489.1712.

(2ai) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-(2-hydroxyethyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using ethanolamine (2.8 µL, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ai** (13.5 mg, MW 479.40, 28 µmol, 61 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.73 (m, 2 H), 2.02 (d, *J* = 14.1 Hz, 1 H), 2.21 (d, *J* = 13.7 Hz, 1 H), 2.76-3.05 (m, 3 H), 3.23 (t, *J* = 11.5 Hz, 1 H), 3.30-3.51 (m, 5 H), 3.60-3.80 (m, 3 H), 3.99-4.17 (m, 2 H), 4.26 (d, *J* = 13.7 Hz, 1 H), 6.06 (t, *J* = 5.3 Hz, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.33 (s, 1 H), 7.40-7.54 (m, 4 H). MS *m/z:* 479.2 $[M+H]^+$.

(2aj) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-(2-methoxyethyl)piperidine-4-carboxamide

Procedure TS4 was employed using 2-methoxyethylamine (4 µL, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aj** (20.6 mg, MW 493.42, 42 µmol, 91 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15-1.74 (m, 2 H), 2.01 (d, *J* = 13.7 Hz, 1 H), 2.19 (d, *J* = 13.3 Hz, 1 H), 2.70-3.00 (m, 3 H), 3.14-3.29 (m, 4 H), 3.33-3.51 (m, 7 H), 3.74 (d, *J* = 13.7 Hz, 1 H), 3.96-4.20 (m, 2 H), 4.32 (d, *J* = 13.7 Hz, 1 H), 5.70-5.87 (m, 1 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.33 (t, *J* = 1.6 Hz, 1 H), 7.39-7.52 (m, 4 H). MS *m/z:* 493.2.

(2ak) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-pentylpiperidine-4-carboxamide

Procedure TS4 was employed using *N*-amylamine (9 mg, HCl salt form, FW 123.62, 69 µmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ak** (18 mg, MW 505.48, 35 µmol, 51 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3 H), 1.13-1.25 (m, 2 H), 1.25-1.34 (m, 2 H), 1.35-1.45 (m, 2 H), 1.47-1.70 (m, 2 H), 1.95 (d, *J* = 12.9 Hz, 1 H), 2.20 (d, *J* = 13.7 Hz, 1 H), 2.76-3.02 (m, 3 H), 3.09-3.31 (m, 3 H), 3.44 (s, 3 H), 3.64-3.79 (m, 1 H), 4.01-4.18 (m, 2 H), 4.30 (d, *J* = 14.5 Hz, 1 H), 5.22 (t, *J* = 5.5 Hz, 1 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.34

(s, 1 H), 7.40-7.49 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{27}H_{35}Cl_2N_2O_3$: 505.2019; found: 505.2045.

(2al) N-Cyclopropyl-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using cyclopropylamine (5 µL, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2al** (22 mg, FW 475.41, 46 µmol, 66 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30-0.44 (m, 2 H), 0.73-0.81 (m, 2 H), 1.46-1.72 (m, 2 H), 1.89-1.99 (m, 1 H), 2.18-2.25 (m, 1 H), 2.66 (dd, *J* = 7.0, 3.9 Hz, 1 H), 2.78-2.99 (m, 3 H), 3.24 (t, *J* = 11.4 Hz, 1 H), 3.42 (s, 3 H), 3.74 (d, *J* = 14.5 Hz, 1 H), 4.05-4.21 (m, 2 H), 4.29 (d, *J* = 13.7 Hz, 1 H), 5.41 (d, *J* = 2.4 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 7.33-7.37 (m, 1 H), 7.44 (d, *J* = 1.6 Hz, 2 H), 7.47 (d, *J* = 8.2 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{29}Cl_2N_2O_3$ $[M+H]^+$: 475.1550; found: 475.1561.

(2am) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-(oxetan-3-yl)piperidine-4-carboxamide

Procedure TS4 was employed using 3-oxetanamine (2.5 mg, 34 µmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (15 mg, 34 µmol, 1 equiv), HATU (16 mg, 41 µmol, 1.2 equiv), DIEA (12 µL, 69 µmol, 2 equiv), and DMF (0.2 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2am** (5.4 mg, MW 491.41, 11 µmol, 32 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38-1.79 (m, 2 H), 1.94-2.39 (m, 2 H), 2.74-3.02 (m, 3 H), 3.07-3.28 (m, 1 H), 3.42 (s, 3 H), 3.50-3.84 (m, 1 H), 4.00-4.35 (m, 5 H), 4.77-4.92 (m, 2 H), 4.95-5.10 (m, 1 H), 5.74 (d, *J* = 7.0 Hz, 1 H), 6.99-7.23 (m, 2 H), 7.35 (s, 1 H), 7.39-7.58 (m, 4 H). Additional small peaks of ca. 50% relative intensity were observed and attributed to the presence of rotamers: 3.41 (s, 3 H), 3.85-4.00 (m, 1 H), 4.35-4.60 (m, 3 H). MS *m/z:* 491.2 $[M+H]^+$.

(2an) N-Cyclopentyl-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using cyclopentylamine (4 mg, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2an** (11 mg, MW 503.46, 21 µmol, 46 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02-1.30 (m, 2 H), 1.41-1.71 (m, 4 H), 1.86-2.04 (m, 5 H), 2.19 (d, *J* = 12.9 Hz, 1 H), 2.73-3.00 (m, 3 H), 3.21 (t, *J* = 11.2 Hz, 1 H), 3.43 (s, 3 H), 3.73 (d, *J* = 13.7 Hz, 1 H), 4.00-4.25 (m, 3 H), 4.29 (d, *J* = 14.1 Hz, 1 H), 5.11 (d, *J* = 7.0 Hz, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.34 (t, *J* = 1.8 Hz, 1 H), 7.41-7.49 (m, 4 H). MS *m/z:* 503.2 $[M+H]^+$.

(2ao) (S)-4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

Procedure TS4 was employed using (*S*)-tetrahydrofuran-3-amine (9 mg, HCl salt form, FW 123.58, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ao** (29 mg, MW 505.43, 57 µmol, 83 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.74 (m, 3 H), 1.94-2.06 (m, 1 H), 2.15-2.36 (m, 2 H), 2.70-3.03 (m, 3 H), 3.37-3.54 (m, 4 H), 3.69-3.87 (m, 5 H), 3.96-4.19 (m, 2 H), 4.25-4.36 (m, 1 H), 4.47-4.58 (m, 1 H), 5.41 (d, *J* = 7.0 Hz, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.33-7.37 (m, 1 H), 7.43 (d, *J* = 2.0 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{31}Cl_2N_2O_4$: 505.1655; found: 505.1665.

(2ap) (R)-4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

Procedure TS4 was employed using (*R*)-3-aminotetrahydrofuran (9 mg, HCl salt form, FW 123.58, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ap** (31 mg, MW 505.43, 60 µmol, 88 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.76 (m, 3 H), 1.91-2.05 (m, 1 H), 2.15-2.38 (m, 2 H), 2.74-3.02 (m, 3 H), 3.35-3.56 (m, 4 H), 3.66-3.83 (m, 5 H), 4.02-4.21 (m, 2 H), 4.23-4.37 (m, 1 H), 4.43-4.60 (m, 1 H), 5.39 (d, *J* = 7.0 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 7.35 (t, *J* = 1.8 Hz, 1 H), 7.43 (d, *J* = 2.0 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{31}Cl_2N_2O_4$: 505.1655; found: 505.1662.

(2aq) N-Cyclohexyl-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using cyclohexylamine (5 mg, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aq** (16 mg, MW 517.49, 31 µmol, 67 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86-1.18 (m, 3 H), 1.34 (q, *J* = 11.9 Hz, 2 H), 1.47-1.69 (m, 5 H), 1.79 (t, *J* = 11.4 Hz, 2 H), 1.95 (d, *J* = 14.1 Hz, 1 H), 2.18 (d, *J* = 13.7 Hz, 1 H), 2.68-3.01 (m, 3 H), 3.20 (t, *J* = 11.5 Hz, 1 H), 3.41 (s, 3 H), 3.64-3.86 (m, 2 H), 4.01-4.18 (m, 2 H), 4.29 (d, *J* = 13.3 Hz, 1 H), 5.17 (d, *J* = 7.8 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 7.33 (s, 1 H), 7.38-7.48 (m, 4 H). MS *m/z:* 517.2 $[M+H]^+$.

(2ar) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-(tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide

Procedure TS4 was employed using 4-aminotetrahydropyran (5 mg, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ar** (16 mg, MW 519.46, 31 µmol, 69 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.46 (m, 2 H), 1.50-1.68 (m, 2 H), 1.77 (t, *J* = 11.7 Hz, 2 H), 1.98 (d, *J* = 13.7 Hz, 1 H), 2.18 (d, *J* = 12.9 Hz, 1 H), 2.79-3.02 (m, 3 H), 3.22 (t, *J* = 11.7 Hz, 1 H), 3.36-3.51 (m, 5 H), 3.74 (d, *J* = 13.7 Hz, 1 H), 3.91 (d, *J* = 11.0 Hz, 2 H), 3.95-4.05 (m, 1 H), 4.05-

4.18 (m, 2 H), 4.28 (d, J = 13.3 Hz, 1 H), 5.20 (d, J = 7.8 Hz, 1 H), 7.17 (d, J = 7.8 Hz, 2 H), 7.34 (s, 1 H), 7.39-7.47 (m, 4 H). MS *m/z:* 519.2 $[M+H]^+$.

(2as) N-(tert-Butyl)-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using *tert*-butylamine (8 mg, HCl salt form, 69 mmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2as** (22 mg, MW 491.45, 45 µmol, 65 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9 H), 1.45-1.54 (m, 1 H), 1.54-1.64 (m, 1 H), 1.87-1.96 (m, 1 H), 2.15 (dd, J = 13.3, 1.6 Hz, 1 H), 2.74-3.00 (m, 3 H), 3.15-3.28 (m, 1 H), 3.43 (s, 3 H), 3.65-3.77 (m, 1 H), 4.11 (d, J = 14.1 Hz, 2 H), 4.26-4.36 (m, 1 H), 5.01 (s, 1 H), 7.21 (d, J = 8.2 Hz, 2 H), 7.34 (t, J = 2.0 Hz, 1 H), 7.40-7.50 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{33}Cl_2N_2O_3$: 491.1863; found: 491.1896.

(2at) (R)-4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-(2-hydroxypropyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using (*R*)-(–)-1-amino-2-propanol (6 µL, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2at** (13 mg, MW 493.42, 27 µmol, 59 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6.3 Hz, 3 H), 1.46-1.70 (m, 2 H), 2.02 (d, J = 12.9 Hz, 1 H), 2.21 (d, J = 12.5 Hz, 1 H), 2.74-3.13 (m, 3 H), 3.22 (t, J = 12.3 Hz, 1 H), 3.39 (s, 3 H), 3.69 (d, J = 13.7 Hz, 1 H), 3.87 (m, 1 H), 4.09 (dd, J = 24.0, 12.0 Hz, 2 H), 4.26 (d, J = 12.9 Hz, 1 H), 5.76 (br. s., 2 H), 6.14 (m, 1 H), 7.16 (d, J = 7.8 Hz, 2 H), 7.33 (s, 1 H), 7.39-7.49 (m, 4 H). Additional small peaks of 12 - 45% relative intensity were observed and attributed to the presence of rotamers: δ 1.33 (d, J = 6.3 Hz, 3 H), 3.47 (d, J = 4.7 Hz, 1 H), 7.11 (d, J = 7.8 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{31}Cl_2N_2O_4$: 493.1655; found: 493.1708.

(2au) (R)-4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N-(2,3-dihydroxypropyl)-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using (*R*)-3-amino-1,2-propanediol (4.2 mg, 46 µmol, 1 equiv) as the amine component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2au** (14 mg, MW 509.42, 27 µmol, 58 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.74 (m, 2 H), 2.01 (d, J = 14.1 Hz, 1 H), 2.21 (d, J = 13.3 Hz, 1 H), 2.75-3.04 (m, 3 H), 3.14-3.44 (m, 6 H), 3.45-3.62 (m, 2 H), 3.64-3.85 (m, 2 H), 3.96-4.17 (m, 2 H), 4.28 (d, J = 14.5 Hz, 1 H), 6.06 (br. s., 1 H), 7.16 (d, J = 7.8 Hz, 2 H), 7.34 (s, 1 H), 7.40-7.54 (m, 4 H). MS *m/z:* 509.2 $[M+H]^+$.

(2av) N-Benzyl-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl) piperidine-4-carboxamide

Procedure TS4 was employed using benzylamine (7.5 µL, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2av** (29 mg, MW 525.47, 54 µmol, 79 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.71 (m, 2 H), 1.99 (d, *J* = 12.9 Hz, 1 H), 2.17-2.24 (m, 1 H), 2.78-3.04 (m, 3 H), 3.25 (td, *J* = 12.5, 2.7 Hz, 1 H), 3.42 (s, 3 H), 3.75 (d, *J* = 13.7 Hz, 1 H), 4.02-4.19 (m, 2 H), 4.24-4.44 (m, 3 H), 5.47 (t, *J* = 5.1 Hz, 1 H), 7.11 (d, *J* = 8.2 Hz, 2 H), 7.12-7.18 (m, 2 H), 7.28-7.33 (m, 3 H), 7.35-7.37 (m, 2 H), 7.38 (s, 1 H), 7.41 (d, *J* = 2.0 Hz, 2 H). HRMS HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{29}H_{31}Cl_2N_2O_3$: 525.1706; found: 525.1714.

(2aw) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N-phenylpiperidine-4-carboxamide

Procedure TS4 was employed using aniline (6.3 µL, 69 µmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aw** (15 mg, MW 511.44, 30 µmol, 43 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56-1.79 (m, 2 H), 2.32 (d, *J* = 14.1 Hz, 1 H), 2.82-3.07 (m, 4 H), 3.33 (t, *J* = 11.9 Hz, 1 H), 3.44 (s, 3 H), 3.81 (d, *J* = 14.5 Hz, 1 H), 4.05-4.22 (m, 2 H), 4.40 (d, *J* = 13.7 Hz, 1 H), 6.80 (s, 1 H), 7.10-7.24 (m, 3 H), 7.28-7.36 (m, 4 H), 7.38-7.46 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{28}H_{29}Cl_2N_2O_3$: 511.1550; found: 511.1554.

(2ax) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)-N,N-dimethylpiperidine-4-carboxamide

Procedure TS4 was employed using dimethylamine (35 µL, 2.0 M solution in THF, 69 µmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ax** (16 mg, MW 463.40, 35 µmol, 50 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.49 (m, 1 H), 1.53-1.67 (m, 1 H), 2.38 (d, *J* = 13.7 Hz, 2 H), 2.80-2.96 (m, 2 H), 3.00-3.10 (m, 7 H), 3.23-3.36 (m, 1 H), 3.42 (s, 3 H), 3.69 (d, *J* = 14.1 Hz, 1 H), 4.09 (q, *J* = 14.0 Hz, 2 H), 4.34 (d, *J* = 12.5 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 2 H), 7.33 (s, 1 H), 7.40-7.51 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{29}Cl_2N_2O_3$: 463.1550; found: 463.1557.

(2ay) 4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-N,N-diethyl-1-(2-methoxyacetyl)piperidine-4-carboxamide

Procedure TS4 was employed using diethylamine (7.2 µL, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2ay** (15 mg, MW 491.45, 31 µmol, 45 % yield) as a white flaky solid. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 1.19 (br. s., 4 H), 1.42 (td, *J* = 12.7, 3.9 Hz, 1 H), 1.58 (td, *J* = 12.8, 2.9 Hz, 1 H), 2.32 (t, *J* = 12.5 Hz, 2 H), 2.52 (br. s., 6 H), 2.80-3.12 (m, 3 H), 3.27-3.47 (m, 4 H), 3.69 (d, *J* = 13.3 Hz, 1 H), 4.01-4.19 (m, 2 H), 4.33-4.46 (m, 1 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 7.31-7.35 (m, 1 H), 7.40-7.47 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{33}Cl_2N_2O_3$: 491.1863; found: 491.1879.

(2az) 1-(4-(Azetidine-1-carbonyl)-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using azetidine (6.5 mg, HCl salt form, FW 93.56, 69 mmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. After purification by preparatory HPLC (Method 1), the residue was repurified by normal-phase MPLC (4 g silica gel cartridge) using a gradient of EtOAc in hexanes. The collected fraction was concentrated in vacuo to afford isonipecotamide **2az** (14 mg, MW 475.41, 29 µmol, 42 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, CD_3OD) δ 1.42-1.60 (m, 2 H), 1.98-2.10 (m, 2 H), 2.10-2.29 (m, 2 H), 2.80-2.99 (m, 3 H), 3.04-3.16 (m, 1 H), 3.39 (s, 3 H), 3.59-3.80 (m, 3 H), 3.92-4.05 (m, 2 H), 4.06-4.21 (m, 2 H), 4.21-4.32 (m, 1 H), 7.24-7.32 (m, 2 H), 7.37-7.44 (m, 1 H), 7.54-7.67 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{29}Cl_2N_2O_3$: 475.1550; found: 475.1558.

(2aα) 1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(pyrrolidine-1-carbonyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using pyrrolidine (5 mg, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aα** (31 mg, MW 489.43, 63 µmol, 91 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.62 (m, 2 H), 1.66-1.86 (m, 4 H), 2.30-2.57 (m, 2 H), 2.73-2.98 (m, 3 H), 3.02-3.36 (m, 3 H), 3.39-3.79 (m, 6 H), 4.09 (d, *J* = 1.6 Hz, 2 H), 4.26-4.48 (m, 1 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 7.32 (t, *J* = 1.8 Hz, 1 H), 7.38-7.48 (m, 4 H). MS *m/z:* 489.2 $[M+H]^+$.

(2aβ) (R)-1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(3-fluoropyrrolidine-1-carbonyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using (*R*)-3-fluoropyrrolidine (6.2 mg, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aβ** (>5 mg, MW 507.42, >10 µmol, >14% yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 1 H), 1.39-1.60 (m, 2 H), 2.13-2.28 (m, 2 H), 2.29-2.57 (m, 3 H), 2.69-3.04 (m, 3 H), 3.14-3.34 (m, 2 H), 3.42 (s, 3 H), 3.71 (d, *J* = 14.5 Hz, 1 H), 4.00-4.19 (m, 2 H), 4.35 (t, *J* = 14.7 Hz, 1 H), 5.11 (br. s., 1 H), 5.24 (br. s., 1 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.33 (s, 1 H), 7.41-7.50 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{30}Cl_2FN_2O_3$ 507.1612; found: 507.1619.

(2aγ) (S)-1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(3-fluoropyrrolidine-1-carbonyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using (*S*)-3-fluoropyrrolidine (6.2 mg, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2γ** (12 mg, MW 507.42, 24 µmol, 34 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37-1.66 (m, 2 H), 1.67-1.97 (m, 2 H), 2.20 (t, *J* = 13.3 Hz, 1 H), 2.29-2.57 (m, 2 H), 2.70-3.07 (m, 3 H), 3.12-3.34 (m, 2 H), 3.42 (s, 3 H), 3.52-3.88 (m, 2 H), 3.97-4.20 (m, 2 H), 4.35 (t, *J* = 15.1 Hz, 1 H), 5.10 (br. s., 1 H), 5.24 (br. s., 1 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 7.33 (s, 1 H), 7.41-7.47 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{30}Cl_2FN_2O_3$: 507.1612; found: 507.1628.

(2aδ) (R)-1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(3-(hydroxymethyl)pyrrolidine-1-carbonyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using [(3*R*)-pyrrolidin-3-yl]methanol (7 mg, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aδ** (26 mg, MW 519.46, 49 µmol, 72 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35-1.69 (m, 3 H), 1.83-2.02 (m, 1 H), 2.23-2.53 (m, 3 H), 2.76-3.01 (m, 3 H), 3.18-3.49 (m, 8 H), 3.55-3.85 (m, 4 H), 4.10 (q, *J* = 13.7 Hz, 2 H), 4.21-4.44 (m, 1 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.32-7.35 (m, 1 H), 7.40-7.52 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{27}H_{33}Cl_2N_2O_4$: 519.1812; found: 519.1811.

(2aε) (S)-1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(3-(hydroxymethyl)pyrrolidine-1-carbonyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using [(3*S*)-pyrrolidin-3-yl]methanol (7 mg, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aε** (15 mg, MW 519.46, 29 µmol, 43 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.70 (m, 3 H), 1.83-2.01 (m, 1 H), 2.22-2.56 (m, 4 H), 2.74-3.06 (m, 3 H), 3.19-3.34 (m, 1 H), 3.41 (s, 3 H), 3.52-3.94 (m, 6 H), 4.11 (q, *J* = 13.0 Hz, 2 H), 4.26-4.43 (m, 1 H), 7.15 (d, *J* = 7.4 Hz, 2 H), 7.34 (s, 1 H), 7.40-7.51 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{27}H_{33}Cl_2N_2O_4$: 519.1812; found: 519.1809.

(2aζ) 1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(morpholine-4-carbonyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using morpholine (6 µL, 69 µmol, 1 equiv) as the amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv),

HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (14 µL, 83 µmol, 1.2 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotamide **2aζ** (22 mg, MW 505.43, 43 µmol, 62 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35-1.53 (m, 1 H), 1.54-1.71 (m, 1 H), 2.28 (d, *J* = 13.3 Hz, 2 H), 2.82-3.13 (m, 3 H), 3.28-3.46 (m, 4 H), 3.64-3.79 (m, 9 H), 4.02-4.18 (m, 2 H), 4.33 (d, *J* = 14.1 Hz, 1 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 7.34 (t, *J* = 2.0 Hz, 1 H), 7.40-7.51 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{31}Cl_2N_2O_4$: 505.1655; found: 505.1654.

(2aη) 1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(piperidine-1-carbonyl)piperidin-1-yl)-2-methoxyethanone

Procedure TS4 was employed using piperidine (7 µL, 69 µmol, 1 equiv) as amine component along with modified quantities of isonipecotic acid **8** (30 mg, 69 µmol, 1 equiv), HATU (31 mg, 83 µmol, 1.2 equiv), DIEA (36 µL, 206 µmol, 3 equiv), and DMF (0.7 mL) precursor/ reagents/ solvent. After purification by preparatory HPLC (Method 1), the residue was repurified by normal-phase MPLC (4 g silica gel cartridge) using a gradient of MeOH in DCM. The collected fraction was concentrated in vacuo and dried under high vaccum to afford isonipecotamide **2aη** (15 mg, MW 503.46, 30 µmol, 44 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33-1.46 (m, 1 H), 1.50-1.67 (m, 5 H), 1.68-1.76 (m, 2 H), 2.22-2.34 (m, 2 H), 2.83-2.95 (m, 2 H), 3.03-3.13 (d, *J* = 16.0 Hz, 1 H), 3.28-3.44 (m, 4 H), 3.60-3.76 (m, 5 H), 3.93-4.18 (m, 2 H), 4.34 (d, *J* = 12.9 Hz, 1 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 7.32 (t, *J* = 2.0 Hz, 1 H), 7.40-7.47 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{27}H_{33}Cl_2N_2O_3$: 503.1863; found: 503.1891.

(1) N-Isopropyl-1-(2-methoxyacetyl)-4-((3'-methyl-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carboxamide

The synthetic route involving Typical Procedures S1b and 11b was modified to ultimately afford isonipecotamide **1** (16 mg, MW 422.56, 37 µmol, 10% yield from **9**) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.7 Hz, 3 H, *i*-Pr), 1.05 (d, *J* = 6.7 Hz, 3 H, *i*-Pr), 1.49-1.67 (m, 2 H), 1.96 (d, *J* = 14.1 Hz, 1 H), 2.20 (t, *J* = 13.3 Hz, 1 H), 2.42 (s, 3H), 2.79 (d, *J* = 13.3 Hz, 1 H), 2.85-2.99 (m, 2 H), 3.21 (t, *J* = 11.9 Hz, 1 H), 3.42 (s, 3 H), 3.73 (br. d, *J* = 14.1 Hz, 1 H), 4.02-4.17 (m, 3 H), 4.30 (br. d, *J* = 13.3 Hz, 1 H), 4.98 (d, *J* = 7.4 Hz, 1 H), 7.11-7.20 (m, 3 H), 7.29-7.39 (m, 3 H), 7.49 (d, *J* = 8.2 Hz, 2 H). MS m/z: 421^- $[M–H]^-$, 481^- $[M+OAc]^-$.

(S4) tert-Butyl 4-amino-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidine-1-carboxylate

An MePh (5 mL) solution of isonipecotic acid **10** (340 mg, 732 µmol, 1 equiv) and DIEA (141 µl, 805 µmol, 1.1 equiv) was treated with diphenyl phosporyl azide (174 µl, 807 µmol, 1.1 equiv). After stirring the solution at 100°C for 2 h, an aliquot was analyzed by LCMS to reveal 4-isocyanatopiperidine **S3** as the major component (SMILES string: ClC1=CC(Cl)=CC(C(C=C2)=CC=C2CC3(CCN(C(OC(C)(C)C)=O)CC3)N=C=O)=C1 , LCMS: Tr 1.81 min, m/z 361^+, 363.1^+ $[M+H–Boc]^+$) along with an azide adduct side product (LCMS: Tr 1.66 min, m/z 404^+, 406^+ $[M+H–Boc]^+$, 579^- $[M+H–N_3+2(OAc)]^-$). The mixture was concentrated in vacuo, diluted with a THF (3 mL) / H_2O (3 mL) mix, and treated with potassium hydroxide (82 mg, 1.5 mmol, 2 equiv). After stirring for 2 h, the reaction mixture was repeatedly

(3x) extracted with DCM and the combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by normal-phase MPLC using a gradient of EtOAc in hexanes to afford piperidin-4-amine **S4** (SMILES string: NC1(CCN(C(OC(C)(C)C)=O)CC1)CC2=CC=C(C3=CC(Cl)=CC(Cl)=C3)C=C2 , 42 mg, MW 435.39, 96 µmol, 13% yield over 2 steps) as a clear oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 13.3 Hz, 2 H), 1.46 (s, 9 H), 1.54-1.70 (m, 2 H), 1.82 (br. s., 2 H), 2.73 (s, 2 H), 3.23 (t, *J* = 11.2 Hz, 2 H), 3.76 (br. s., 2 H), 7.26 (m, *J* = 8.2 Hz, 2 H), 7.32 (t, *J* = 1.8 Hz, 1 H), 7.44 (d, *J* = 2.0 Hz, 2 H), 7.46-7.51 (m, 2 H).

(3a) Typical Procedures S6a and 3a involving acylation reactions: N-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidin-4-yl)acetamide

Procedure **S6a**: A DCM (1.0 mL) solution of piperidin-4-amine **S4** (20 mg, 46 µmol, 1 equiv) and DIEA (12 mL, 69 µmol, 1.5 equiv) was treated with a DCM solution (55 µL, 1.0 M, 55 µmol, 1.2 equiv) of acetyl chloride. After stirring for ca. 2 h an aliquot was analyzed by LCMS to reveal piperidine-4-amine **S5a** as the major component (SMILES string: ClC1=CC(Cl)=CC(C(C=C2)=CC=C2CC3(CCN(C(OC(C)(C)C)=O)CC3)NC(C)=O)=C1 , LCMS: Tr 1.56 min, m/z 377^+ $[M+H–Boc]^+$, $535^–$$[M+OAc]^–$). The reaction mixture was directly treated with TFA (0.5 mL), stirred for 12-24 h, and concentrated in vacuo to afford piperidine-4-amine **S6a** (TFA salt form, SMILES string: ClC1=CC(Cl)=CC(C(C=C2)=CC=C2CC3(CCNCC3)NC(C)=O)=C1.O=C(O)C(F)(F)F , FW 491.33, 46 µmol assumed). The totality of the product was used directly in the next step without further purification.

To obtain an analytical sample of piperidin-4-amine **S5a**, a modified version of the piperidin-4-amine **S4** (20 mg, 46 mmol, 1 equiv) acylation reaction was conduced using AcOH (2.6 µL, 46 µmol, 1 equiv), HATU (21 mg, 55 µmol, 1.2 equiv), DIEA (16 µL, 92 µmol, 2 equiv) as reagents and DMF (0.3 mL) as solvent. The reaction was diluted with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined extracts were repeatedly (8x) washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo and dried under high vaccum to afford piperidin-4-amine **S5a** (2 mg, MW 477.42, 4 µmol, 9 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.50 (m, 11 H), 1.55-1.68 (m, 2 H), 2.01 (s, 3 H), 2.87-3.00 (m, 2 H), 3.85-3.95 (br. s, 2 H), 4.82 (s, 1 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.32-7.36 (m, 1 H), 7.43-7.49 (m, 4 H). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{30}Cl_2N_2NaO_3$; 499.1526, found 499.1516.

Procedure **3a**: An MeCN (1 mL) solution of piperidin-4-amine **S6a** (TFA salt form, 46 µmol assumed), methoxyacetic acid (5.2 mg, 58 µmol, 1.3 equiv), and DIEA (24 µl, 0.14 mmol, 3 equiv) was treated with HATU (22 mg, 58 µmol, 1.3 equiv). After stirring for 0.5 h, the reaction was quenched with water (0.1 mL), TFA (a few drops), and purified by preparative HPLC. The collected fraction was concentrated in vacuo and dried by lyophilization to afford piperidin-4-amine **3a** (17 mg, MW 449.37, 37 µmol, 81% yield over 2 steps) as a colorless fluffy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.69 (m, 2 H), 1.97 (d, *J* = 14.1 Hz, 1 H), 2.03 (s, 3 H), 2.49 (d, *J* = 13.3 Hz, 1 H), 2.89 (t, *J* = 12.1 Hz, 1 H), 2.97 (d, *J* = 13.3 Hz, 1 H), 3.17-3.33 (m, 2 H), 3.43 (s, 3 H), 3.72 (d, *J* = 13.7 Hz, 1 H), 4.08 (d, *J* = 13.3 Hz, 1 H), 4.15 (d, *J* = 13.3 Hz, 1 H), 4.35

(d, *J* = 14.1 Hz, 1 H), 4.86 (s, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.33 (t, *J* = 2.0 Hz, 1 H), 7.44 (d, *J* = 1.6 Hz, 2 H), 7.47 (d, *J* = 8.2 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{29}H_{37}Cl_2N_2O_5$ 449.1393; found 449.1448.

(3b) N-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidin-4-yl)propionamide

Procedure **S6a** was employed using propionyl chloride (55 µl, 55 µmol, 1.2 equiv) as acylating agent. *N*-Boc deprotection of intermediate piperidine-4-amine **S5b** (SMILES string: ClC1=CC(Cl)=CC(C(C=C2)=CC=C2CC3(CCN(C(OC(C)(C)C)=O)CC3)NC(CC)=O)=C1 , LCMS: Tr 1.60 min, m/z 391^+ $[M+H–Boc]^+$, 549^- $[M+OAc]^–$) gave, after concentration in vacuo, piperidine-4-amine **S6b** (TFA salt form, SMILES string: ClC1=CC(Cl)=CC(C(C=C2)=CC=C2CC3(CCNCC3)NC(CC)=O)=C1.O=C(O)C(F)(F)F , FW 505.36, 46 µmol assumed). The totality of the product was used directly in the next step without further purification.

Procedure **3a** was employed using piperidine-4-amine **S6b** (46 µmol assumed) as precursor to afford piperidine-4-amine **3b** (15.5 mg, MW 463.40, 33 µmol, 73% yield over 2 steps) as a colorless fluffy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.43 Hz, 3 H), 1.58-1.67 (m, 2 H), 1.97 (d, *J* = 13.7 Hz, 1 H), 2.21 (q, *J* = 7.7 Hz, 2 H), 2.49 (d, *J* = 13.7 Hz, 1 H), 2.86 (t, *J* = 11.7 Hz, 1 H), 2.97 (d, *J* = 13.7 Hz, 1 H), 3.19 (t, *J* = 11.7 Hz, 1 H), 3.29 (d, *J* = 13.3 Hz, 1 H), 3.43 (s, 3 H), 3.72 (d, *J* = 13.7 Hz, 1 H), 4.08 (d, *J* = 13.7 Hz, 1 H), 4.14 (d, *J* = 13.3 Hz, 1 H), 4.36 (d, *J* = 13.7 Hz, 1 H), 4.80 (s, 1 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.33 (t, *J* = 2.0 Hz, 1 H), 7.39-7.50 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{29}Cl_2N_2O_3$ 463.1550; found 463.1557.

(S9) 2-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidin-4-yl)-5-methyl-1,3,4-oxadiazole

An MeCN (2 mL) solution of isonipecotic acid **10** (75 mg, 162 µmol, 1 equiv), acethydrazide (18 mg, 242 µmol, 1.5 equiv), and DIEA (138 µL, 0.808 mmol, 5 equiv) was treated with HATU (92 mg, 242 µmol, 1.5 equiv). After stirring for 2 h, the reaction was concentrated in vacuo. The residue was partitioned between EtOAc and water, the organic layer was collected, and the aqueous phase was repeatedly (3x) extracted with EtOAc. The combined organic phases were washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to afford isonipecotamide **S7** (SMILES string: O=C(NNC(C)=O)C1(CCN(C(OC(C)(C)C)=O)CC1)CC2=CC=C(C3=CC(Cl)=CC(Cl)=C3)C=C2 , LCMS: Tr 1.75 min, m/z 420^+ $[M+H–Boc]^+$, 518 $[M–H]^–$) as a yellow oil. The totality of the product was used directly in the next step without further purification.

An MeCN (2 mL) solution of isonipecotamide **S7** (162 µmol assumed, 1 equiv), triphenylphosphine (85 mg, 324 µmol, 2 equiv), and DIEA (85 ml, 486 µmol, 3 equiv) was treated with hexachloroethane (77 mg, 324 µmol, 2 equiv). After stirring for 12 – 24 h the reaction was concentrated in vacuo. The residue partitoned between water and EtOAc, the organic layer was collected, and the aqueous layer was repeatedly (2x) extracted with EtOAc. The combined organic phases were washed with water, brine, dried over Na_2SO_4, and filtered.

The filtrate was concentrated in vacuo and the crude was purified by normal-phase MPLC using a gradient of EtOAc in hexane. The collected fraction was concentrated in vacuo to afford piperidin-4-yl-1,3,4-oxadiazole **S8** (SMILES string: ClC1=CC(Cl)=CC(C(C=C2)=CC=C2CC3(CCN(C(OC(C)(C)C)=O)CC3)C4=NN=C(C)O4)=C1, 61.2 mg, MW 502.43, 121 µmol, 75% yield over 2 steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.68-1.81 (m, 2 H), 2.29 (d, *J* = 12.0 Hz, 2 H), 2.50 (s, 3 H), 2.65-2.95 (br m, 2 H), 3.00 (s, 2 H), 3.87-4.11 (br m, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 7.31-7.33 (m, 1 H), 7.36-7.43 (m, 4 H). LCMS: Tr 1.57 min, m/z 402$^+$ [M+H–Boc]$^+$, 560$^-$[M+OAc]$^-$.

A DCM (2 mL) solution of piperidin-4-yl-1,3,4-oxadiazole **S8** (60 mg, 119 µmol, 1 equiv) was treated with TFA (0.5 ml, 6.5 mmol, 54 equiv). After 2 h the reaction was concentrated in vacuo to afford piperidin-4-yl-1,3,4-oxadiazole **S9** (TFA salt form, SMILES string: ClC1=CC(Cl)=CC(C(C=C2)=CC=C2CC3(CCNCC3)C4=NN=C(C)O4)=C1.O=C(O)C(F)(F)F , LCMS: Tr 1.25 min, m/z 402$^+$ [M+H]$^+$, FW 516.34, 119 µmol assumed). The product was used directly in subsequent steps without further purification.

(4a) Typical Procedure 4a involving acylation: 1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)-2-methoxyethanone

An MeCN (2 mL) solution of piperidin-4-yl-1,3,4-oxadiazole **S9** (TFA salt form, 31.0 mg, 60 µmol, 1 equiv), methoxyacetic acid (8.0 mg, 90 µmol, 1.5 equiv), and DIEA (52 µL, 300 µmol, 5 equiv) was treated with HATU (34.2 mg, 90 µmol). After stirring for 1 h the reaction was concentrated in vacuo and the crude was purified by reverse-phase preparatory HPLC. The collected fraction was concentrated in vacuo to afford piperidin-4-yl-1,3,4-oxadiazole **4a** (20 mg, MW 474.38, 41 µmol, 69% yield over 2 steps) as a white fluffy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (td, *J* = 13.0, 4.5 Hz, 2 H), 2.30-2.43 (m, 2 H), 2.53 (s, 3 H), 2.64 (t, *J* = 12.1 Hz, 1 H), 2.97 (d, *J* = 13.3 Hz, 1 H), 3.02 (d, *J* = 12.5 Hz, 1 H), 3.18 (t, *J* = 12.1 Hz, 1 H), 3.40 (s, 3 H), 3.83 (d, *J* = 13.7 Hz, 1 H), 4.06 (d, *J* = 13.3 Hz, 1 H), 4.14 (d, *J* = 13.7 Hz, 1 H), 4.50 (d, *J* = 14.1 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 7.32 (t, *J* = 2.0 Hz, 1 H), 7.35-7.44 (m, 4 H). LCMS: Tr 1.39 min, m/z 474$^+$ [M+H]$^+$.

(4b) 1-(4-((3',5'-Dichloro-[1,1'-biphenyl]-4-yl)methyl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)-2-phenoxyethanone

Procedure **4a** was employed using 2-phenoxyacetic acid (14 mg, 90 µmol, 1.5 equiv) as acylating agent and a 2 h reaction time to ultimately afford piperidin-4-yl-1,3,4-oxadiazole **4b** (19 mg, MW 536.45, 36 µmol, 60 % yield over 2 steps) as a white fluffy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70-1.81 (m, 2 H), 2.29-2.41 (m, 2 H), 2.52 (s, 3 H), 2.66 (t, *J* = 11.7 Hz, 1 H), 2.93 (d, *J* = 13.7 Hz, 1 H), 2.98 (d, *J* = 12.9 Hz, 1 H), 3.23 (t, *J* = 12.5 Hz, 1 H), 3.99 (d, *J* = 13.7 Hz, 1 H), 4.50 (d, *J* = 14.5 Hz, 1 H), 4.66 (d, *J* = 12.9 Hz, 1 H), 4.70 (d, *J* = 13.3 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 2 H), 6.90-6.96 (m, 2 H), 6.96-7.02 (m, 1 H), 7.27-7.32 (m, 2 H), 7.32 (t, *J* = 2.0 Hz, 1 H), 7.35-7.44 (m, 4 H). LCMS: Tr 1.48 min, m/z 536$^+$ [M+H]$^+$, 594$^-$ [M+OAc]$^-$.

(13) Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carboxylate

A DCM (3.4 mL) solution of isonipecotate **9** (333 mg, MW 492.43, 676 µmol, 1 equiv) was treated with TFA (261 µL, 3.39 mmol, 5 equiv). After stirring for 12 – 24 h the reaction mixture was concentrated in vacuo to afford isonipecotate **13** (TFA salt form, LCMS: Tr 1.28 min, m/z 392^+ $[M+H]^+$, FW 506.34, 676 µmol assumed). The product was used directly in subsequent steps without further purification.

(5ab) Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-methoxyacetyl)piperidine-4-carboxylate

A DCM (1 mL) solution of isonipecotate **13** (TFA salt form, 79 mg, FW 506.34, 156 µmol, 1 equiv) and TEA (91 µL, 651 µmol, 4.2 equiv) at 0 °C was treated with methoxyacetyl chloride (28 µL, 307 µmol, 2 equiv). The reaction was allowed to warm to room temperature, stirred for 2 h, and quenched saturated $NaHCO_3$(aq). The mixture was repeatedly extracted with DCM and the combined organic extracts were dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and a small portion of the crude was purified by preparatory HPLC (Method 2). The collected fraction was concentrated in vacuo to afford isonipecotate **5ab** (6 mg, MW 464.38, 12 µmol, 8% yield over 2 steps) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.26 (m, 3 H), 1.40-1.63 (m, 2 H), 2.20 (d, *J* = 13.3 Hz, 2 H), 2.71 (t, *J* = 12.1 Hz, 1 H), 2.80-2.97 (m, 2 H), 3.11 (t, *J* = 12.1 Hz, 1 H), 3.42 (s, 3 H), 3.77 (d, *J* = 13.7 Hz, 1 H), 4.02-4.23 (m, 4 H), 4.45 (d, *J* = 14.1 Hz, 1 H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 1.8 Hz, 1 H), 7.41-7.51 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{28}Cl_2NO_4$: 464.1390; found: 464.1400.

(5bb) Typical Procedure 5bb involving carboxylic acid: Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-(methylthio)acetyl)piperidine-4-carboxylate

A DMF (0.6 mL) solution of isonipecotate **13** (TFA salt form, 30 mg, FW 506.34, 59 µmol, 1 equiv), HATU (34 mg, 89 µmol, 1.5 equiv), and (methylthio)acetic acid (6.3 mg, 59 µmol, 1 equiv) at 0 °C was treated with DIEA (31 µL, 178 µmol, 3 equiv). After 0.3 h the reaction was quenched with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined extracts were repeatedly (8x) washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo and dried under high vaccum to afford isonipecotate **5bb** (12 mg, MW 480.45, 25 µmol, 42 % yield over 2 steps) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (td, *J* = 7.1, 1.76 Hz, 3 H), 1.43-1.67 (m, 2 H), 2.07-2.32 (m, 5 H), 2.72 (t, *J* = 12.9 Hz, 1 H), 2.82-2.98 (m, 2 H), 3.19 (t, *J* = 12.7 Hz, 1 H), 3.27-3.40 (m, 2 H), 3.77 (d, *J* = 13.3 Hz, 1 H), 4.05-4.24 (m, 2 H), 4.47 (d, *J* = 12.9 Hz, 1 H), 7.14 (d, *J* = 6.7 Hz, 2 H), 7.34 (d, *J* = 2.0 Hz, 1 H), 7.40-7.51 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{28}Cl_2NO_3$ 480.1161; found 480.1196.

(5cb) Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-isopropoxyacetyl)piperidine-4-carboxylate

Procedure **5bb** was employed using isopropoxyacetic acid (7 mg, 59 µmol, 1 equiv) as the acyl component. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotate **5cb** (13 mg, 26 µmol, MW 492.4, 44 % yield over 2 steps) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-1.19 (m, 6 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.42-1.58 (m, 2 H), 2.12-2.26 (m, 2

H), 2.70 (t, *J* = 12.3 Hz, 1 H), 2.82-2.93 (m, 2 H), 3.11 (t, *J* = 12.3 Hz, 1 H), 3.23 (br. s., 1 H), 3.65 (dt, *J* = 12.2, 6.21 Hz, 1 H), 3.89 (d, *J* = 13.7 Hz, 1 H), 4.05-4.25 (m, 4 H), 4.43 (d, *J* = 13.7 Hz, 1 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 7.33 (t, *J* = 1.8 Hz, 1 H), 7.42-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{32}Cl_2NO_4$ 492.1703; found 492.1755.

(5db) Ethyl 1-(2-((tert-butoxycarbonyl)(methyl)amino)acetyl)-4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidine-4-carboxylate

Procedure **5bb** was employed using *N*-Boc-sarcosine (23 mg, 119 µmol, 1 equiv) as the acyl component along with modified quantities of isonipecotate **13** (TFA salt form, 60 mg, 119 µmol, 1 equiv), HATU (68 mg, 178 µmol, 1.5 equiv), DIEA (62 µL, 356 µmol, 3 equiv), and DMF (1.2 mL) precursor/ reagents/ solvent. Purification by preparatory HPLC (Method 2) ultimately afforded isonipecotate **5db** (45 mg, MW 563.51, 80 µmol, 68 % yield over 2 steps) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 6.9 Hz, 3 H), 1.48 (s, 9 H), 2.20 (d, *J* = 9.0 Hz, 2 H), 2.70 (t, *J* = 12.5 Hz, 1 H), 2.80-2.97 (m, 5 H), 3.11 (t, *J* = 12.7 Hz, 1 H), 3.62-4.10 (m, 5 H), 4.12-4.28 (m, 3 H), 4.45 (d, *J* = 13.3 Hz, 1 H), 7.13 (d, *J* = 7.8 Hz, 2 H), 7.33 (s, 1 H), 7.41-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{29}H_{37}Cl_2N_2O_5$ 563.2074; found 563.2128, $[M+H–Boc]^+$ Calcd for $C_{24}H_{29}Cl_2N_2O_4$ 463.1550; found: 463.1591

(5eb) Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-(methylamino)acetyl)piperidine-4-carboxylate

A DCM (0.4 mL) solution of isonipecotate **5db** (42 mg, MW 563.51, 75 µmol, 1 equiv) was treated with TFA (29 µl, 373 µmol, 5 equiv). After stirring for 12 – 24 h the reaction mixture was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo and dried under high vacuum to afford isonipecotate **5eb** (24 mg, MW 463.40, 51 µmol, 68 % yield) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 3 H), 1.42-1.63 (m, 2 H), 2.01 (br. s., 2 H), 2.20 (d, *J* = 13.3 Hz, 2 H), 2.72 (t, *J* = 12.1 Hz, 1 H), 2.77-2.96 (m, 5 H), 3.14 (t, *J* = 12.7 Hz, 1 H), 3.49 (d, *J* = 13.3 Hz, 1 H), 3.78-4.09 (m, 2 H), 4.17 (q, *J* = 7.0 Hz, 2 H), 4.40 (d, *J* = 11.0 Hz, 1 H), 7.11 (d, *J* = 7.8 Hz, 2 H), 7.32 (s, 1 H), 7.39-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{24}H_{29}Cl_2N_2O_3$ 463.1550; found 463.1577.

(5fb) Typical Procedure 5fb involving acid chloride: Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(2-(dimethylamino)acetyl)piperidine-4-carboxylate

A DCM (0.6 mL) solution of isonipecotate **13** (TFA salt form, 30 mg, FW 506.34, 59 µmol, 1 equiv) and TEA (25 µL, 180 µmol, 3 equiv) at 0 °C was treated with dimethylaminoacetyl chloride hydrochloride (9.3 mg, FW 158.03, 59 µmol, 1 equiv). After stirring for 0.5 h the reaction quenched with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined extracts were repeatedly washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated under reduced pressure and dried under high vacuum to afford isonipecotate **5fb** (13 mg, MW 477.42, 26 µmol, 45 % yield over 2 steps) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 1.43-1.60 (m, 2 H), 2.11-2.27 (m, 2 H), 2.63-2.76 (m, 1 H), 2.80-2.96 (m, 3 H), 3.05 (s, 6 H), 3.14 (t, *J* = 12.3 Hz, 1 H), 3.48 (d, *J*

= 14.5 Hz, 1 H), 3.94 (d, *J* = 15.7 Hz, 1 H), 4.09-4.27 (m, 3 H), 4.42 (d, *J* = 13.7 Hz, 1 H), 7.12 (d, *J* = 8.2 Hz, 2 H), 7.33 (t, *J* = 1.8 Hz, 1 H), 7.40-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{32}Cl_2N_2O_3$ 477.1706; found 477.1757.

(5gb) 4-Ethyl 1-methyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)piperidine-1,4-dicarboxylate

Procedure **5fb** was employed using methyl chloroformate (5.6 mg, 59 µmol, 1 equiv) as acylating agent. Purification by normal-phase MPLC (4 g silica gel cartridge) using a gradient of EtOAc in hexanes ultimately afforded isonipecotate **5gb** (8.3 mg, MW 450.35, 18 µmol, 31% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3 H) , 1.47 (br t, *J* = 10.4 Hz, 2 H), 2.14 (br d, *J* = 12.9 Hz, 2 H), 2.87 (m, 4 H), 3.69 (s, 3 H), 4.02 (br. s., 2 H), 4.15 (q, *J* = 7.3 Hz, 2 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 7.33 (t, *J* = 1.8 Hz, 1 H), 7.43-7.49 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{23}H_{26}Cl_2NO_4$ 450.1233; found 450.1244.

(5hb) Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-(isoxazole-5-carbonyl)piperidine-4-carboxylate

Procedure **5fb** was employed using isoxazole-5-carbonyl chloride (8 mg, 59 µmol, 1 equiv) as acylating agent. Additional acid chloride (1 equiv) and TEA (1 equiv) were added to effect reaction completion. Purification by preparatory HPLC (Method 1) ultimately afforded isonipecotate **5hb** (>5 mg, MW 487.38, >10 µmol, >17% yield over 2 steps) as a white flaky solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.60 (m, 2 H), 2.19-2.41 (m, 2 H), 2.81-3.02 (m, 3 H), 3.24 (t, *J* = 12.1 Hz, 1 H), 4.08 (d, *J* = 14.5 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 4.55 (d, *J* = 14.1 Hz, 1 H), 6.76 (br. s., 1 H), 7.14 (d, *J* = 7.8 Hz, 2 H), 7.33 (s, 1 H) 7.39-7.56 (m, 4 H), 8.32 (d, *J* = 1.2 Hz, 1 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{25}Cl_2N_2O_4$ 487.1186; found 487.1200.

(6) 1-(4-(3',5'-Dichloro-[1,1'-biphenyl]-4-yl)-4-hydroxypiperidin-1-yl)-2-methoxyethanone

A DMF (2.6 mL) solution of 4-(4-bromophenyl)piperidin-4-ol (**14**, 100 mg, 390 µmol, 1 equiv), HATU (371 mg, 976 µmol, 2.5 equiv), and methoxyacetic acid (70.3 mg, 781 µmol, 2 equiv) at 0 °C was treated with DIEA (170 µL, 976 µmol, 2.5 equiv). After 20 min the ice bath was removed and stirring was continued for 12 – 24 h. The reaction was quenched with water (3 mL) and repeatedly (3x) extracted with EtOAc. The combined organic layers were repeatedly (8x) washed with water, brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified on by reverse-phase preparatory HPLC (Method 3). The collected fraction was concentrated in vacuo to afford piperidin-4-ol **S10** (SMILES string: OC1(CCN(C(COC)=O)CC1)C2=CC=C(Br)C=C2 , 116 mg, FW 328.20, 353 µmol, 91 % yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70-2.00 (m, 4 H), 3.09 (td, *J* = 12.8, 2.2 Hz, 1 H), 3.37 (s, 3 H), 3.46-3.60 (m, 1 H), 3.70 (d, *J* = 13.3 Hz, 1 H), 3.78 (br. s., 1 H), 3.96-4.17 (m, 2 H), 4.42 (d, *J* = 12.9 Hz, 1 H), 7.32 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.2 Hz, 2 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$Calcd for $C_{23}H_{27}Cl_2N_2O_3$: 328.0543; found: 328.0557.

A suspension of piperidin-4-ol **S10** (110 mg, 335 µmol, 1 equiv), 3,5-dichlorophenylboronic acid (128 mg, 670 µmol, 2 equiv) and $NaHCO_3$ (70 mg, 838 µmol, 2.5 equiv) in a dioxane (2.5 mL)/

water (0.8 mL) mix was degassed using nitrogen bubbling and treated with $PdCl_2$(dppf)-DCM complex (27 mg, FW 816.65, 34 µmol, 0.1 equiv). After heating at 90°C for 0.5 h, the reaction was cooled, quenched with water, and repeatedly (3x) extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo and the crude was purified by normal-phase MPLC (40 g silica gel cartridge) using a gradient of EtOAc in hexane. The collected fraction was concentrated in vacuo to afford piperidin-4-ol **6** (102 mg, MW 394.29, 259 µmol, 77 % yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 1.81 (d, *J* = 13.3 Hz, 2 H), 1.96-2.15 (m, 2 H), 3.19 (t, *J* = 12.7 Hz, 1 H), 3.45 (s, 3 H), 3.58 (t, *J* = 12.1 Hz, 1 H), 3.80 (d, *J* = 13.7 Hz, 1 H), 4.13-4.33 (m, 2 H), 4.47 (d, *J* = 12.5 Hz, 1 H), 7.42 (d, *J* = 0.8 Hz, 1 H), 7.60 (d, *J* = 0.8 Hz, 2 H), 7.63 (s, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{20}H_{22}Cl_2NO_3$: 394.0971; found: 394.0977.

(7) Ethyl 4-((3',5'-dichloro-[1,1'-biphenyl]-4-yl)methyl)-1-pentylpiperidine-4-carboxylate

A MeOH (0.5 mL) solution of isonipecotate **13** (TFA salt form, 30 mg, 59 µmol, 1 equiv) and pentanal (24 µL, 230 µmol, 3.9 equiv) was treated with a sodium cyanoborohydride (4.8 mg, 76 µmol, 1.3 equiv) solution in methanol. After stirring for 1 h the reaction was quenched with NaOH(aq) (2.0 mL, 0.1 N) and concentrated in vacuo until the MeOH content was minimized. The resulting aqueous mix was repeatedly (3x) extracted with EtOAc (30 mL) and the combined organic layers were washed with water, brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and, to mitigate boron complexation, a DCM (1 mL) solution of the residue was treated with an HCl solution in MeOH (0.25 mL, 3 M, 0.75 mmol, 13 equiv). After 2 h the reaction mixture was concentrated in vacuo and the crude was purified by preparatory HPLC (Method 1). The collected fraction was concentrated in vacuo to afford isonipecotate **7** (8.4 mg, MW 462.45, 18 µmol, 31% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.9 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.30-1.40 (m, 3 H), 1.60-1.81 (m, 2 H), 2.02-2.22 (m, 2 H), 2.32 (d, *J* = 13.7 Hz, 2 H), 2.66 (d, *J* = 12.5 Hz, 2 H), 2.76-3.01 (m, 6 H), 3.61 (d, *J* = 11.7 Hz, 2 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 7.33 (t, *J* = 2.0 Hz, 1 H), 7.39-7.48 (m, 4 H). HRMS (ESI-TOF) *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{34}Cl_2NO_2$ 462.1961; found 462.1991.