Supporting Information

Expedient Access to Saturated Nitrogen Heterocycles by Photoredox Cyclization of Imino-Tethered Dihydropyridines

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General Information

Unless otherwise noted, all reactions were performed in oven-dried glassware and carried out under an atmosphere of argon or nitrogen with magnetic stirring. All column chromatography was performed using a CombiFlash Rf+ Automated Flash Chromatography System with a 200 mL/min max flow rate, 200 psi, and 200–400 nm UV variable wavelength detector, and Silica RediSep Rf gold columns (Normal Phase) or C18 Silica RediSep Rf gold columns (Reversed Phase). Thin layer chromatography was performed on SiliCycle[®] 250 µm 60 Å plates. Visualization was accomplished with 254 nm UV light, KMnO₄ stain, or I₂.

NMR spectra were recorded on Bruker Ascend 400 MHz spectrometer at ambient temperature. Chemical shifts (δ) are reported in parts per million (ppm) from CDCl₃ (¹H: 7.26 ppm, ¹³C: 77.16 ppm), CD₂Cl₂ (¹H: 5.32 ppm, ¹³C: 54.0 ppm), or CD₃CN (¹H: 1.94 ppm, ¹³C: 1.32 ppm) with multiplicity (*s* = singlet, br. *s* = broad singlet, *d* = doublet, *t* = triplet, *q* = quartet, and *m* = multiplet) and coupling constants (in Hz).

Low-resolution mass spectra were recorded on a Waters Acquity BEH uPLC-MS with C18 column (50 mm \times 2.1 mm, 1.7) at 40 °C. The solvents employed were: A = 0.1% *v/v* solution of ammonium hydroxide in water; B = 0.1% *v/v* solution of ammonium hydroxide in acetonitrile. The gradient employed was as follows:

Time Flow Rate (minutes) (mL/min) % A % B 0 0.8 95 5 0.1 0.8 95 5 1.5 0.8 5 95 2.0 0.8 5 95 2.1 0.8 95 5 3 0.8 95 5.

Unless otherwise stated, all starting materials were obtained from commercial sources including Sigma-Aldrich, TCI, Matrix, Alfa-Aesar, and Oakwood Scientific. Anhydrous Cu(OAc)₂ and CsOAd were obtained from Sigma-Aldrich and stored in an argon-filled glovebox.

Photoredox Reactor Set-Up

All photoredox reactions were irradiated by a blue Kessil PR160 440 nm lamp (max intensity), with cooling to *ca*. 27 °C with an internal fan, and magnetic stirring using a Corning PC-410D stir plate.



Experimental Procedures

Photoredox Cyclization Procedures

General Procedure A



To an oven-dried scintillation vial, 3 Å molecular sieves (*ca.* 400 mg) were added to a solution of amino-DHP reagent **1** (1.0 equiv.), aldehyde **2** (0.95 equiv.) in anhydrous CH_2Cl_2 (0.1 M). The resultant mixture was then stirred for 12 h at room temperature. Next, the solution was filtered through a Celite plug and concentrated under reduced pressure yielding the corresponding imine **3**. Next, to a Schlenk pressure tube were added: the above-prepared imine **3**, iridium photocatalyst [Ir(dF(CF₃)ppy)₂(bpy)]PF₆ (**PC2**, 3 mol%), lithium dibutylphosphate [(BuO)₂PO₂]Li (30 mol%), and CH₂Cl₂/TFE 4:1 ν/ν (0.075 M). The resultant solution was then purged of oxygen with two freeze-pump-thaw cycles. Afterwards, the tube was irradiated with blue LED light for 12-16 h, while the mixture was stirred at 500 rpm and cooled with an internal fan to *ca.* 27 °C. Upon completion, the reaction mixture was filtered through a Celite plug, the filtrate was concentrated under reduced pressure, and the crude residue was purified by reverse-phase flash chromatography (C18, eluent: water/MeCN with 0.1% TFA as modifier). The pure fractions were combined and concentrated under reduced pressure. Final lyophilization afforded pure, dry product **4** as the corresponding TFA salt.

General Procedure B

Same as General Procedure A except that 0.1% NH₄OH was used as modifier for the reverse-phase chromatographic purification.



Imine **3** was prepared as described in General Procedure A. To a Schlenk pressure tube were added: the above-prepared imine **3**, iridium photocatalyst Ir(dFppy)₃ (**PC4**, 3 mol%), potassium acetate (2.0 equiv.), and MeCN/TFE 4:1 v/v (0.075 M). The resultant solution was then purged of oxygen with two freeze-pump-thaw

cycles. Afterwards, the tube was irradiated with blue LED light for 12-16 h, while the mixture was stirred at 500 rpm and cooled with an internal fan to *ca*. 27 °C. Upon completion, the reaction mixture was filtered through a Celite plug, the filtrate was concentrated under reduced pressure, and the crude residue was purified by reverse-phase flash chromatography (C18, eluent: water/MeCN with 0.1% TFA or NH₄OH as modifier). The pure fractions were combined and concentrated under reduced pressure. Final lyophilization afforded pure, dry product **4**.

Formal Bond Dissociation Free Energy Calculations

"BDFE" (kcal/mol) = 2.3RTpK_a + $23.06E^{*ox}$ + 54.9

Entry	Photooxidant	$E^{*^{\mathrm{ox}}}$ (V vs SCE)	Base	pK _a (DMSO)	"BDFE"
1	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6(PC1)$	+1.21	[CH ₃ CO ₂]NBu ₄	12	99
2	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (PC2)	+0.97	[CH ₃ CO ₂]NBu ₄	12	94
3	Ir(ppy) ₃ (PC3)	+0.31	[CH ₃ CO ₂]NBu ₄	12	78
4	Ir(dFppy) ₃ (PC4)	+0.36	[CH ₃ CO ₂]NBu ₄	12	80
5	4CzIPN (PC5)	+1.35	[CH ₃ CO ₂]NBu ₄	12	102
6	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	+0.97	[CF ₃ CO ₂]NBu ₄	7	87
7	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (PC2)	+0.97	[(BuO) ₂ PO ₂]NBu ₄	5	84

Full Optimizations Table



2	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[CH ₃ CO ₂]NBu ₄	none	MeCN	33
3	CO ₂ Et	[Ir(dF(Me)ppy) ₂ (dtbbpy)]PF ₆ (PC3)	[CH ₃ CO ₂]NBu ₄	none	MeCN	27
4	CO ₂ Et	[Ir(dFppy) ₂ (dtbbpy)]PF ₆ (PC4)	[CH ₃ CO ₂]NBu ₄	none	MeCN	30
5	CO ₂ Et	Ir(ppy) ₃ (PC5)	[CH ₃ CO ₂]NBu ₄	none	MeCN	18
6	CO ₂ Et	Ir(dFppy) ₃ (PC6)	[CH ₃ CO ₂]NBu ₄	none	MeCN	20
7	CO ₂ Et	4CzIPN (PC7)	[CH ₃ CO ₂]NBu ₄	none	MeCN	16
8	CO ₂ Et	[Ru(bpy) ₃]PF ₆ (PC8)	[CH ₃ CO ₂]NBu ₄	none	MeCN	9
9	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	2,6-Lutidine	none	MeCN	0
10	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[PhCO ₂]NBu ₄	none	MeCN	31
11	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (PC2)	[CF ₃ CO ₂]NBu ₄	none	MeCN	36
12	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	none	MeCN	41
13	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(PhO) ₂ PO ₂]NBu ₄	none	MeCN	25
14	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	Bi(OTf) ₃	MeCN	39
15	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	Sc(OTf) ₃	MeCN	35
16	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	Cu(OTf) ₂	MeCN	26
17	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	Zn(OTf) ₂	MeCN	29
18	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	Me ₃ SiOTf	MeCN	10
19	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (PC2)	2,6-Lutidine	Me ₃ SiOTf	MeCN	40
20	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	$Mg(NTf_2)_2$	MeCN	45
21	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (PC2)	[(BuO) ₂ PO ₂]NBu ₄	$Ca(NTf_2)_2$	MeCN	47
22	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]NBu ₄	LiNTf ₂	MeCN	49
23	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (PC2)	[(BuO) ₂ PO ₂] ₂ Mg	none	MeCN	48
24	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂] ₂ Ca	none	MeCN	50
25	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	MeCN	51
26	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	CH_2Cl_2	58
27	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	DMF	36
28	CO ₂ Et	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	[(BuO) ₂ PO ₂]Li	none	MeCN/TFE 4:1	45
29	CO ₂ Et	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	CH ₂ Cl ₂ /TFE 4:1	67
30	CO ₂ <i>i</i> -Pr	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	CH ₂ Cl ₂ /TFE 4:1	80
31	CO ₂ t-Bu	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	CH ₂ Cl ₂ /TFE 4:1	77
32	CN	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	CH ₂ Cl ₂ /TFE 4:1	n.d. ^b
33	CO ₂ <i>i</i> -Pr	none	[(BuO) ₂ PO ₂]Li	none	CH ₂ Cl ₂ /TFE 4:1	0
34	CO ₂ <i>i</i> -Pr	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6(PC2)$	[(BuO) ₂ PO ₂]Li	none	CH ₂ Cl ₂ /TFE 4:1	0^c
35	CO ₂ <i>i</i> -Pr	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆ (PC2)	none	none	CH ₂ Cl ₂ /TFE 4:1	< 5

^{*a*} % yield of isolated product. ^{*b*} No desired product was observed. The reaction led to numerous side products. ^{*c*} Reaction performed in the absence of blue light irradiation.

Complete List of N-Heterocyclic Products



Scheme S1. List of N-heterocyclic products.

Starting Material Synthesis Procedures

General Procedure A: Morpholine-Forming Amino-DHP Reagents (Step 1)



To a solution composed of amino-alcohol **0** (1.0 equiv.), tetrabutylammonium iodide (0.1 equiv.), and potassium carbonate (2.0 equiv.) in anhydrous MeCN (0.5 M) was added benzyl bromide (2.05 equiv.) dropwise at room temperature. The reaction mixture was stirred at room temperature for 18 h, and then concentrated under reduced pressure. The crude residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding dibenzyl-protected amino-alcohol **1**.

General Procedure B: Morpholine-Forming Amino-DHP Reagents (Step 2)



Sodium hydride (60% in mineral oils, pre-washed with pentane, 2.0 equiv.) was placed in an oven-dried two-necked flask, evacuated and placed under a nitrogen atmosphere. Anhydrous THF (0.3 M) was then added, and the solution was cooled down to 0 °C. Next, dibenzyl-protected amino-alcohol 1 in anhydrous THF was added dropwise, and the resultant solution was warmed up to room temperature and stirred for 3 h. The reaction mixture was cooled down to 0 °C, and DMAP (0.02 equiv.), tetrabutylammonium iodide (0.1 equiv.), and 2-bromo-1,1-dimethoxyethane (3.0 equiv.) were added. The mixture was stirred at 0 °C for 1 h followed by refluxing for 12-18 h. The reaction mixture was quenched with aqueous NH₄Cl at 0 °C, and ethyl acetate was added. The aqueous layer was extracted with ethyl acetate, and the organic layers were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 ν/ν). Pure fractions were combined and concentrated under reduced pressure, yielding acetal product **2**.



To a cooled (0 °C) solution of dibenzyl-protected acetal **2** (1.0 equiv.) in THF (0.3 M) was added aqueous 6 N HCl (10 equiv.). The reaction mixture was warmed up to room temperature and stirred for 7 h. Upon completion, the reaction was quenched with saturated aqueous NaHCO₃ at 0 °C, and methylene chloride was added. The aqueous layer was extracted with methylene chloride, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure, yielding dibenzyl-protected aldehyde product **3**. The crude product was used in the next step as such, without further purification.

General Procedure D: Morpholine-Forming Amino-DHP Reagents (Step 4): Ethyl-ester and Nitrile Hantzsch esters



A mixture of aldehyde **3** (1.0 equiv.), ethyl acetoacetate or 3-oxobutanenitrile (1.0 equiv.), ethyl 3aminocrotonate or 3-aminocrotononitrile (1.0 equiv.), and trifluoroacetic acid (1.1 equiv.) in diglyme (0.3 M) was heated to 95 °C and stirred overnight. Upon completion, the reaction was cooled down to room temperature, quenched with aqueous NaHCO₃, and ethyl acetate was added. Next, the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was then purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding dibenzyl-protected DHP product **4**.

General Procedure E: Morpholine-Forming Amino-DHP Reagents (Step 4): iso-Propyl and tert-Butyl Hantzsch esters



A mixture of aldehyde **3** (1.0 equiv.), *iso*-propyl acetoacetate (2.1 equiv.), and aqueous ammonium hydroxide (6.1 equiv.) in ethanol (0.3 M) was heated to 80 °C and stirred for 20 h. Upon completion, the reaction was cooled down to room temperature, quenched with aqueous NaHCO₃, and ethyl acetate was added. Next, the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over

anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was then purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding dibenzyl-protected DHP product **4**.

General Procedure F: Morpholine-Forming Amino-DHP Reagents (Step 5)



A suspension composed of dibenzyl-protected amino-DHP 4 (1.0 equiv.) and Pd/C (0.1 equiv.) in absolute ethanol (0.1 M) was evacuated and backfilled with hydrogen gas. The reaction mixture was then pressurized at 3 bar, and stirred at room temperature for 4-6 h. Upon completion, the mixture was filtered through a Celite plug, and the filtrate was concentrated under reduced pressure. Next, the crude product was purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 3:2 v/v with 0.1% NH₄OH as modifier). Pure fractions were combined and evaporated under reduced pressure. Lyophilization yielded pure, dry amino-DHP reagent 5.

General Procedure G: Thiomorpholine- and Piperazine-Forming Amino-DHP Reagents (Step 1)



To a two-necked round-bottomed flask with a Dean-Stark apparatus attached were added: primary amine **6** (1.0 equiv.), Et₃N (3.5 equiv.), phthalic anhydride (1.0 equiv.), and anhydrous toluene (0.1 M). The reaction mixture was then refluxed for 2 days. Upon completion, the solution was cooled down to room temperature, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding phthalimide-protected amine **7**.

General Procedure H: Morpholine-Forming Amino-DHP Reagents: Pyrrolidino Amines



To a cooled (0 °C) solution of Boc-protected pyrrolidino amine **8** (1.0 equiv.) in anhydrous CH_2Cl_2 (0.25 M) was added trifluoroacetic acid (50 equiv.) dropwise over 10 min. After an additional 15 min of stirring at 0 °C, the reaction mixture was warmed up to room temperature and stirred for 6 h. The mixture was then concentrated under reduced pressure and then lyophilized, yielding the trifluoroacetate salt of free pyrrolidine **9**.

General Procedure I: Thiomorpholine-Forming Amino-DHP Reagents (Step 2)



To a solution composed of phthalimide-protected thiol 7 (1.0 equiv.), tetrabutylammonium iodide (0.1 equiv.), and potassium carbonate (2.05 equiv.) in anhydrous MeCN (0.5 M) was added 2-bromo-1,1-dimethoxyethane (2.05 equiv.). The reaction mixture was heated to reflux for 18-20 h, and then concentrated under reduced pressure. The crude residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding phthalimide-protected thioether acetal **10**.

General Procedure J: Piperazine-Forming Amino-DHP Reagents (Step 2)



To a suspension of phthalimide-protected primary amine 7 (1.0 equiv.) and sodium triacetoxyborohydride (2.1 equiv.) in 1,2-dichloroethane (0.3 M) was added 2,2-dimethoxyacetaldehyde (60% w/w aqueous solution, 1.05 equiv.). The resultant suspension was stirred vigorously at room temperature for 12-16 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃, and extracted with methylene

chloride. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v first to remove the bis-alkylation byproduct, followed by CH₂Cl₂/MeOH 95:5 v/v to elute the desired mono-alkylation product). Pure fractions were combined and concentrated under reduced pressure, yielding phthalimide protected amino-acetal **11**.

General Procedure K: Piperazine-Forming Amino-DHP Reagents (Step 3): p-Tosyl Piperazines



A solution of phthalimide protected amino-acetal **11** (1.0 equiv.) and Et_3N (1.3 equiv.) in anhydrous CH_2Cl_2 (0.3 M) was cooled down to 0 °C. Next, *p*-toluenesulfonyl chloride (1.3 equiv.) was added in one portion, and the resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then brought to room temperature and stirred for 14 h. The crude mixture was loaded directly onto silica gel and purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding *p*-tosyl protected amino-acetal **12**.

General Procedure L: Piperazine-Forming Amino-DHP Reagents (Step 3): Cbz Piperazines



A solution of phthalimide protected amino-acetal **11** (1.0 equiv.) and Et_3N (2.1 equiv.) in anhydrous CH_2Cl_2 (0.6 M) was cooled down to -78 °C. Next, benzyl chloroformate (1.5 equiv.) was added dropwise over 10 min. The resultant mixture was stirred at -78 °C for 15 min, and then warmed up to room temperature. After stirring for a further 14 h, the solution was concentrated under reduced pressure, and the crude residue was loaded directly onto silica gel and purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding Cbz protected amino-acetal **13**.

General Procedure M: Thiomorpholine- and Piperazine-Forming Amino-DHP Reagents (Step 4)



To a cooled (0 °C) solution of phthalimide-protected acetal **10**, **12**, or **13** (1.0 equiv.) in THF (0.3 M) was added aqueous 6 N HCl (10 equiv.). The reaction mixture was warmed up to room temperature and stirred for 7 h. Upon completion, the reaction was quenched with saturated aqueous NaHCO₃ at 0 °C, and methylene chloride was added. The aqueous layer was extracted with methylene chloride, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure, yielding phthalimide-protected aldehyde product **14**, **15**, or **16**. The crude product was used in the next step as such, without further purification.

General Procedure N: Thiomorpholine- and Piperazine-Forming Amino-DHP Reagents (Step 5)



A mixture of phthalimide-protected aldehyde 14, 15, or 16 (1.0 equiv.), tetrabutylammonium hydrogensulfate (0.12 equiv.), *iso*-propyl acetoacetate (1.05 equiv.), *iso*-propyl 3-aminocrotonate (1.05 equiv.) in diglyme (0.3 M) was heated to 85 °C and stirred for 20 h. Upon completion, the reaction was cooled down to room temperature, quenched with aqueous NaHCO₃, and ethyl acetate was added. Next, the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was then purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Pure fractions were combined and concentrated under reduced pressure, yielding phthalimide-protected DHP product 17, 18, or 19.

General Procedure O: Thiomorpholine- and Piperazine-Forming Amino-DHP Reagents (Step 6)



To a solution of phthalimide-protected DHP **17**, **18**, or **19** (1.0 equiv.) in absolute methanol (0.3 M) was added hydrazine (50% *w/w* aqueous solution, 10 equiv.). The reaction mixture was heated to 50 °C and stirred for 9-12 h. The mixture was then filtered through a Celite plug, and the filtrate was concentrated under reduced pressure. Next, the crude product was purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 3:2 v/v with 0.1% NH₄OH as modifier). Pure fractions were combined and evaporated under reduced pressure. Lyophilization yielded pure, dry amino-DHP reagent **20**, **21**, or **22**.

General Procedure P: Metal Phosphate Salts



An oven-dried scintillation vial was charged with either dibutyl phosphate **23** or diphenyl phosphate **24** (1.0 equiv.) and absolute ethanol (0.5 M) under a nitrogen atmosphere. Next, either LiOEt (1.0 M solution in ethanol, 1.0 equiv.), $Ca(OMe)_2$ (1.0 equiv.), or $Mg(Ot-Bu)_2$ (1.0 equiv.) was added in one portion. The reaction mixture was then heated to 50 °C and stirred for 6 h. After cooling down to room temperature, the solution was concentrated under reduced pressure, yielding the various metal phosphate salts as off-white solids.

Characterization of Starting Materials

Complete List of Synthesized Amino-DHP Reagents



Scheme S2. List of synthesized amino-DHP reagents.

Morpholine-Forming Amino-DHP Reagents

N,N-Dibenzyl-2-(2,2-dimethoxyethoxy)ethan-1-amine



Synthesized according to General Procedure B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 95% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.71 (*t*, *J* 6.2 Hz, 2H), 3.38 (*s*, 6H), 3.44 (*d*, *J* 5.1 Hz, 2H), 3.58-3.62 (*m*, 2H), 3.65 (*s*, 4H), 4.47 (*t*, *J* 5.2 Hz, 1H), 7.20-7.26 (*m*,

2H), 7.28-7.34 (*m*, 4H), 7.36-7.40 (*m*, 4H).

2-(2-(Dibenzylamino)ethoxy)acetaldehyde



Synthesized according to General Procedure C. Used in the next step as such, without further purification. Colorless oil. 97% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.76 (*t*, *J* 5.9 Hz, 2H), 3.63 (*t*, *J* 5.9, 2H), 3.68 (*s*, 4H), 4.0 (*s*, 2H), 7.25 (*s*, 2H), 7.30-7.34 (*m*, 2H), 7.34-7.34 (*m*, 4H), 7.36-7.40 (*m*, 4H), 9.68 (*s*, 1H).

Diethyl 4-((2-(dibenzylamino)ethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure D. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 75% yield. **¹H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.26 (*t*, *J* 7.1 Hz, 6H), 2.20 (*s*, 6H), 2.59 (*t*, *J* 5.9 Hz, 2H), 3.27 (*d*, *J* 5.0 Hz, 2H), 3.52 (*t*, *J* 5.8 Hz, 2H), 3.60 (*s*, 4H), 4.09-4.20 (*m*, 5H), 7.19-7.25 (*m*, 2H), 7.30 (*m*, 4H), 7.33-7.37 (*m*, 4H).

Diethyl 4-((2-aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-CO₂Et)



Synthesized according to General Procedure F. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 3:2 ν/ν with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 86% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.27 (*t*, *J* 7.1 Hz, 6H), 2.26 (*s*, 6H), 2.75 (*t*, *J* 5.0 Hz, 2H), 3.27 (*d*, *J* 5.8 Hz, 2H), 3.41 (*t*, *J* 5.0 Hz, 2H), 4.05-4.23 (*m*, 5H). ¹³C-NMR (101

MHz, CDCl₃), δ , ppm: 14.4, 19.2, 34.2, 41.7, 59.7, 72.3, 74.2, 100.3, 145.6, 168.0. **MS**: *m/z* calcd. for C₁₆H₂₇N₂O₅ [M+H]⁺ 327.2, found 327.4.

4-((2-Aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (1a-CN)



Synthesized according to General Procedures D and F. Purified by reversephase flash chromatography (C18, eluent: water/MeCN 4:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 94% yield (over two steps). ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 2.05 (*s*, 6H), 2.80 (*t*, *J* 5.1 Hz, 2H), 3.37-3.44 (*m*, 1 H), 3.47-3.57 (*m*, 4H). ¹³**C-NMR** (101 MHz,

methanol- d_4), δ , ppm: 18.2, 38.2, 42.2, 73.7, 75.1, 81.6, 120.6, 150.4. **MS**: m/z calcd. for C₁₂H₁₇N₄O [M+H]⁺ 233.1, found 233.2.

Diisopropyl 4-((2-aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-CO₂i-Pr)



Synthesized according to General Procedures D and F. Purified by reversephase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 87% yield (over two steps). ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.27 (*d*, *J* 6.2 Hz, 12H), 2.26 (*s*, 6H), 2.75 (*t*, *J* 5.1 Hz, 2H), 3.29 (*d*, *J* 5.8 Hz, 2H), 3.42 (*t*, *J* 5.1 Hz,

2H), 4.18 (*t*, *J* 5.8 Hz, 1H), 5.06 (*sept.*, *J* 6.2 Hz, 2H). ¹³C-NMR (101 MHz, CDCl₃), δ, ppm: 19.4, 22.0, 22.1, 34.3, 42.0, 66.9, 73.0, 74.2, 101.0, 144.9, 167.4. MS: *m/z* calcd. for C₁₈H₃₁N₂O₅ [M+H]⁺ 355.2, found 355.4.

Di-tert-butyl 4-((2-aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-CO₂t-Bu)



Synthesized according to General Procedures D and F. Purified by reversephase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 89% yield (over two steps). ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.51 (*s*, 18H), 2.25 (*s*, 6H), 2.79 (*t*, *J* 5.1 Hz, 2H), 3.28 (*d*, *J* 5.9 Hz, 2H), 3.46 (*t*, *J* 5.1 Hz, 2H), 4.14 (*t*, *J* 5.9 Hz, 1H). ¹³C-NMR (101 MHz, CDCl₃), δ , ppm: 19.5, 28.2, 28.4, 41.9, 72.9, 74.2, 79.6, 102.1, 144.1, 167.3. MS: *m/z* calcd. for C₂₀H₃₅N₂O₅ [M+H]⁺ 383.3, found 383.6.

1-((Dibenzylamino)methyl)cyclobutan-1-ol

2H), 3.66 (*s*, 4H), 4.04 (*s*, 1H), 7.27-7.38 (*m*, 10H).

N,N-Dibenzyl-1-(1-(2,2-dimethoxyethoxy)cyclobutyl)methanamine



Synthesized according to General Procedure B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 75% yield. An inseparable mixture of product and starting material was obtained (*approx.* 1:1), separated in later steps. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.11 (*dt*, J 11.1,

8.8 Hz, 1H), 1.58-1.64 (*m*, 1H), 2.06-2.18 (*m*, 4H), 2.62 (*s*, 2H), 3.37 (*s*, 6H), 3.41 (*d*, *J* 5.3 Hz, 2H), 3.67 (*d*, *J* 1.9 Hz, 6H), 4.44 (*t*, *J* 5.2 Hz, 1H), 7.33-7.44 (*m*, 10H).

Diisopropyl 4-((1-((dibenzylamino)methyl)cyclobutoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate



Synthesized according to General Procedures C and E. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 30% yield (over two steps). ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 0.96-1.06 (*m*, 1H), 1.25 (*t*, *J* 6.5 Hz, 12H), 1.40-1.55 (*m*, 1H), 1.80-1.97 (*m*, 4H), 2.12 (*s*, 6H), 2.50 (*s*, 2H), 3.25 (*d*, *J* 4.4 Hz, 2H), 3.60 (*s*, 4H), 4.05 (*t*, *J* 4.2 Hz, 1H),

5.07 (sept., J 6.2 Hz, 2H), 5.23 (s, 1H), 7.19-7.25 (m, 2H), 7.28-7.33 (m, 4H), 7.35-7.39 (m, 4H).

Diisopropyl 4-((1-(aminomethyl)cyclobutoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1b)



Synthesized according to General Procedure F. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 65% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.28 (d, J 6.2 Hz, 12H), 1.48-1.56 (m, 1H), 1.64-1.75 (m, 1H), 1.75-1.86 (m, 2H), 1.97-2.09 (m, 2H), 2.25 (s, 6H), 2.70 (s,

2H), 3.11 (*d*, *J* 5.8 Hz, 2H), 4.05 (*t*, *J* 5.8 Hz, 1H), 5.03 (*sept.*, *J* 6.2 Hz, 2H). ¹³C-NMR (101 MHz, methanol*d*₄), δ , ppm: 13.2, 18.8, 22.5, 30.3, 36.3, 46.5, 68.5, 80.0, 100.9, 148.3, 169.9. MS: *m*/*z* calcd. for C₂₁H₃₅N₂O₅ [M+H]⁺ 395.3, found 395.4.

(S)-N,N-Dibenzyl-1-(2,2-dimethoxyethoxy)propan-2-amine



Synthesized according to General Procedures A and B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 64% yield (over two steps). ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.08 (*d*, *J* 6.7 Hz, 3H), 2.99-3.09 (*m*, 1H), 3.39 (*s*, 6H), 3.41-3.47 (*m*, 3H), 3.56-3.62 (*m*, 2H), 3.63-3.69

(*m*, 1H), 3.70-3.76 (*m*, 2H), 4.49 (*t*, *J* 5.3 Hz, 1H), 7.18-7.24 (*m*, 2H), 7.27-7.32 (*m*, 4H), 7.39 (*d*, *J* 7.5 Hz, 4H).

(S)-2-(2-(Dibenzylamino)propoxy)acetaldehyde



Synthesized according to General Procedure C. Used in the next step as such, without further purification. Colorless oil. 94% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.12 (*d*, *J* 6.7 Hz, 3H), 3.05-3.13 (*m*, 1H), 3.48 (*dd*, *J* 9.7, 6.2 Hz, 1H), 3.60 (*d*, *J* 13.9 Hz, 2H), 3.69 (*dd*, *J* 9.7, 6.4 Hz, 1H), 3.72-3.78 (*m*, 2H), 3.99 (*s*, 2H), 7.20-7.24 (*m*,

2H), 7.30 (*t*, *J* 7.5 Hz, 4H), 7.38-7.41 (*m*, 4H), 9.72 (*s*, 1H).

Diisopropyl (S)-4-((2-(dibenzylamino)propoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure E. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 43% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 0.99-1.04 (*m*, 3H), 1.25 (*d*, *J* 6.2 Hz, 12H), 2.17-2.23 (*m*, 6H), 2.84-2.93 (*m*, 1H), 3.22-3.32 (*m*, 2H), 3.39-3.48 (*m*, 2H), 3.53-3.60 (*m*, 2H), 3.68 (*d*, *J* 13.9 Hz, 2H), 4.06-4.11 (*m*, 1H), 5.05

(*sept.*, *J* 6.2 Hz, 2H), 5.29-5.37 (*m*, 1H), 7.17-7.23 (*m*, 2H), 7.25-7.27 (*m*, 2H), 7.28-7.30 (*m*, 2H), 7.33-7.38 (*m*, 4H).

Diisopropyl (S)-4-((2-aminopropoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1c)



Synthesized according to General Procedure F. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 97% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.24 (*s*, 3H), 1.28 (*d*, *J* 6.2 Hz, 12H), 2.29 (*s*, 6H), 3.25-3.40 (*m*, 4H), 3.52 (*br. d*, *J* 6.4 Hz, 1H), 4.08 (*t*, *J* 5.1 Hz, 1H), 5.06 (*d*, *J*

6.2 Hz, 2H), 5.81-6.15 (*br. s*, 2H), 6.45 (*s*, 1H). ¹³**C-NMR** (101 MHz, CDCl₃), δ , ppm: 16.6, 19.4, 22.1, 34.6, 47.7, 67.1, 73.8, 74.9, 100.3, 145.8, 167.8. **MS**: *m/z* calcd. for C₁₉H₃₃N₂O₅ [M+H]⁺ 369.2, found 369.4.

(3R,4R)-4-(Dibenzylamino)tetrahydrofuran-3-ol



Synthesized according to General Procedure A (3 equiv. of K_2CO_3 were used). Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 85% yield.

¹**H-NMR** (400 MHz, CDCl₃), *δ*, ppm: 3.31 (*br. t, J* 9.8 Hz, 1H), 3.63-3.78 (*m*, 5H), 3.8 (*br. s*, 1H), 3.86-3.93 (*m*, 1H), 3.93-4.00 (*m*, 2H), 4.20 (*br. s*, 1H), 7.27-7.38 (*m*, 10H).

(3R,4R)-N,N-Dibenzyl-4-(2,2-dimethoxyethoxy)tetrahydrofuran-3-amine



Diisopropyl 4-((((3R,4R)-4-(dibenzylamino)tetrahydrofuran-3-yl)oxy)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedures C and E (the aldehyde was not isolated due to instability). Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 37% yield (over two steps). ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.24-1.29 (*m*, 12H), 2.19-2.26 (*m*, 6H), 3.20-3.29 (*m*, 1H), 3.30-3.36 (*m*, 1H), 3.51-3.57 (*m*, 1H), 3.68-3.77 (*m*, 3H), 3.78-3.81 (*m*, 4H),

3.88-4.00 (*m*, 1H), 4.10 (*t*, *J* 3.5 Hz, 1H), 5.09 (*sept.*, *J* 6.2 Hz, 2H), 5.32-5.39 (*m*, 1H), 7.18-7.25 (*m*, 2H), 7.27-7.32 (*m*, 4H), 7.32-7.37 (*m*, 4H).

Diisopropyl 4-((((3R,4R)-4-aminotetrahydrofuran-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1f)



Synthesized according to General Procedure F. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 3:2 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 95% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.26-1.31 (*m*, 12H), 2.28 (*d*, *J* 3.3 Hz, 6H), 3.25-3.35 (*m*, 1H), 3.35-3.48 (*m*, 3H), 3.71-3.75 (*m*, 1H), 3.75-3.80 (*m*, 1H), 3.85-3.92 (*m*, 2H), 4.15

(*t*, *J* 5.0 Hz, 1H), 5.02-5.13 (*m*, 2H), 5.57 (*s*, 1H). ¹³C-NMR (101 MHz, CDCl₃), δ, ppm: 19.4, 19.6, 22.1, 34.7, 54.0, 67.1, 71.4, 72.5, 72.9, 79.2, 100.6, 100.7, 145.2, 145.4, 167.3, 167.4. MS: *m/z* calcd. for C₂₀H₃₃N₂O₆ [M+H]⁺ 397.2, found 397.3.

(R)-1-(Dibenzylamino)propan-2-ol

 $Bn \bigvee_{\substack{n \\ Bn}} OH$ Synthesized according to General Procedure A. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 92% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.08 (d, J 6.1 Hz, 3H), 2.43 (d, J 6.6 Hz, 2H), 3.28 (s, 1H), 3.42 (d, J 13.5 Hz, 2H), 3.83-3.92 (m, 3H), 7.25-7.45 (m, 10H).

(R)-N,N-Dibenzyl-2-(2,2-dimethoxyethoxy)propan-1-amine



Synthesized according to General Procedure B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 ν/ν). Colorless oil. 67% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.12 (*d*, *J* 6.1 Hz, 3H), 2.44 (*dd*, *J* 13.2, 6.2 Hz, 1H), 2.61 (*dd*, *J* 13.2, 5.8 Hz, 1H), 3.37 (*s*, 6H), 3.43-3.64 (*m*, 5H),

 $3.65-3.74\ (m,\,2\mathrm{H}),\,4.45\ (t,\,J\,5.2\ \mathrm{Hz},\,1\mathrm{H}),\,7.20-7.26\ (m,\,2\mathrm{H}),\,7.28-7.34\ (m,\,4\mathrm{H}),\,7.34-7.39\ (m,\,4\mathrm{H}).$

(R)-2-((1-(Dibenzylamino)propan-2-yl)oxy)acetaldehyde



Synthesized according to General Procedure C. Used in the next step as such, without further purification. Colorless oil. 99% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.16 (*d*, *J* 6.2 Hz, 3H), 2.43-2.54 (*m*, 1H), 2.71 (*dd*, *J* 13.4, 6.2 Hz, 1H), 3.58-3.62 (*m*, 1H), 3.65 (*s*, 4H), 4.08 (*d*, *J* 3.2 Hz, 2H), 7.28-7.41 (*m*, 10H), 9.69 (*s*, 1H).

Diisopropyl (R)-4-(((1-(dibenzylamino)propan-2-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate



Synthesized according to General Procedure E. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 71% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 0.95 (*d*, *J* 6.1 Hz, 3H), 1.14-1.18 (*m*, 12H), 2.10 (*s*, 6H), 2.25-2.39 (*m*, 2H), 3.24 (*d*, *J* 4.8 Hz, 2H), 3.37-3.42 (*m*, 1H), 3.42-3.54 (*m*, 4H), 3.97 (*t*, *J* 4.7 Hz, 1H), 4.91-5.02 (*m*, 2H), 5.10 5.22 (*a*, 4H), 5.24 5.29 (*a*, 4H)

2H), 5.19-5.23 (m, 1H), 7.11-7.16 (m, 2H), 7.19-7.22 (m, 4H), 7.24-7.29 (m, 4H).

Diisopropyl (R)-4-(((1-aminopropan-2-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1d)



∎OH

NBn₂

Synthesized according to General Procedure F. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 66% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.04 (*d*, *J* 6.1 Hz, 3H), 1.29 (*br. d*, *J* 6.1 Hz, 12H), 2.28 (*s*, 6H), 2.50-2.58 (*m*, 1H), 2.66 (*dd*, *J* 13.2, 3.2 Hz, 1H), 3.19 (*dd*, *J* 9.1,

5.8 Hz, 1H), 3.26-3.36 (*m*, 1H), 3.43 (*dd*, *J* 9.1, 5.2 Hz, 1H), 4.15 (*t*, *J* 5.4 Hz, 1H), 5.09 (*dt*, *J* 12.2, 6.0 Hz, 2H), 5.64 (*br. s*, 1H). ¹³**C-NMR** (101 MHz, CDCl₃), *δ*, ppm: 16.9, 19.4, 19.5, 22.0, 22.1, 35.0, 47.6, 66.9, 71.6, 77.2, 100.9, 101.3, 144.6, 145.0, 167.4, 167.6. **MS**: *m/z* calcd. for C₁₉H₃₃N₂O₅ [M+H]⁺ 369.2, found 369.3.

(3S,4R)-4-(Dibenzylamino)tetrahydrofuran-3-ol

Synthesized according to General Procedure A. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 94% yield. ¹H-NMR (400 MHz, CDCl₃), δ ,

ppm: 1.25-1.38 (*m*, 1H), 3.40 (*br. t, J* 7.6 Hz, 1H), 3.63-3.80 (*m*, 5H), 3.82-3.88 (*m*, 1H), 3.99-4.09 (*m*, 2H), 4.54 (*br. s*, 1H), 7.28-7.43 (*m*, 10H).

(3R, 4S)-N,N-Dibenzyl-4-(2, 2-dimethoxyethoxy)tetrahydrofuran-3-amine



Synthesized according to General Procedure B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 86% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 3.36-3.44 (*m*, 6H), 3.45-3.52 (*m*, 3H), 3.68-3.73 (*m*, 5H), 3.90-3.97 (*m*, 2H), 4.08 (*dd*, *J* 9.9, 6.1 Hz, 1H), 4.23-4.28 (*m*, 1H), 4.47 (*t*, *J* 5.2 Hz, 1H), 7.28-7.44 (*m*, 10H).

2-(((3S,4R)-4-(Dibenzylamino)tetrahydrofuran-3-yl)oxy)acetaldehyde



Synthesized according to General Procedure C. Used in the next step as such, without further purification. Colorless oil. 99% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 3.45-3.50 (*m*, 1H), 3.60-3.73 (*m*, 5H), 3.87-4.08 (*m*, 5H), 4.19-4.24 (*m*, 1H), 7.25-7.38 (*m*, 10H), 9.60 (*s*, 1H).

Diisopropyl 4-((((3S,4R)-4-(dibenzylamino)tetrahydrofuran-3-yl)oxy)methyl)-2,6dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure E. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 *v/v*). Colorless oil. 53% yield. ¹**H-NMR** (400 MHz, CDCl₃), *δ*, ppm: 1.26-1.36 (*m*, 12H), 2.12-2.35 (*m*, 6H), 3.15-3.27 (*m*, 1H), 3.30 (*br. dd*, *J* 9.2, 4.7 Hz, 2H), 3.56-3.77 (*m*, 2H), 3.80-3.97 (*m*, 2H), 4.02-4.09 (*m*, 1H), 4.11-4.22 (*m*, 2H), 5.10 (*dq*, *J* 15.9, 6.2 Hz, 2H), 5.30 (*s*, 1H), 7.26-7.41 (*m*, 10H).

Diisopropyl 4-((((3S,4R)-4-aminotetrahydrofuran-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1g)



Synthesized according to General Procedure F. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 96% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.25-1.30 (*m*, 12H), 2.26 (*s*, 6H), 3.27-3.31 (*m*, 2H), 3.31-3.35 (*m*, 1H), 3.51 (*dd*, *J* 8.9, 2.1 Hz, 1H), 3.62 (*dd*, *J* 9.9, 2.0 Hz, 1H), 3.7 (*br. d*, *J* 4.9 Hz, 1H), 3.83-3.91 (*m*, 1H), 3.96-4.05 (*m*, 1H), 4.17 (*t*, *J* 5.6

Hz, 1H), 5.06 (*dq*, *J* 12.2, 6.2 Hz, 2H), 5.57 (*s*, 1H). ¹³C-NMR (101 MHz, CDCl₃), δ , ppm: 19.5, 19.6, 22.1, 34.2, 57.0, 67.0, 66.9, 69.1, 71.9, 72.1, 74.1, 86.6, 100.76, 100.7, 144.9, 145.0, 167.3, 167.4. MS: *m/z* calcd. for C₂₀H₃₃N₂O₆ [M+H]⁺ 397.2, found 397.3.

(S)-2-(2-(2,2-Dimethoxyethoxy)-2-phenylethyl) isoindoline-1,3-dione



Synthesized according to General Procedures G and B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 44% yield (over two steps). ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 3.13-3.21 (*m*, 6H), 3.21-3.27 (*m*, 1H), 3.41-3.48 (*m*, 1H), 3.77 (*dd*, *J* 13.9, 4.8 Hz, 1H), 4.07

(*dd*, *J* 13.9, 9.1 Hz, 1H), 4.35 (*t*, *J* 5.3 Hz, 1H), 4.79 (*dd*, *J* 9.1, 4.7 Hz, 1H), 7.29-7.34 (*m*, 1H), 7.34-7.40 (*m*, 2H), 7.41-7.46 (*m*, 2H), 7.72 (*dd*, *J* 5.5, 3.1 Hz, 2H), 7.82-7.90 (*m*, 2H).

(S)-2-(2-(1,3-Dioxoisoindolin-2-yl)-1-phenylethoxy)acetaldehyde



Synthesized according to General Procedure M. Used in the next step as such, without further purification. Colorless oil. 97% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 3.70-3.84 (*m*, 2H), 3.89-3.97 (*m*, 1H), 4.06-4.15 (*m*, 1H), 4.74 (*dd*, *J* 9.2, 4.3 Hz, 1H), 7.26-7.39 (*m*, 5H), 7.63-7.70 (*m*, 2H), 7.77-7.83 (*m*, 2H), 9.47 (*s*, 1H).





Synthesized according to General Procedure N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 *v/v*). Colorless oil. 59% yield. ¹H-NMR (400 MHz, CDCl₃), *δ*, ppm: 1.03-1.20 (*m*, 12H), 2.06 (*s*, 3H), 2.33 (*s*, 3H), 3.09 (*dd*, *J* 9.1, 2.9 Hz, 1H), 3.22 (*dd*, *J* 9.1, 3.6 Hz, 1H), 3.62 (*dd*, *J* 13.8, 4.3 Hz, 1H), 3.87 (*t*, *J* 3.1 Hz, 1H), 3.95 (*dd*, *J* 13.8, 9.5

Hz, 1H), 4.66 (*dd*, *J* 9.5, 4.3 Hz, 1H), 4.83-5.00 (*m*, 2H), 5.47 (*s*, 1H), 7.28-7.34 (*m*, 5H), 7.74 (*dd*, *J* 5.4, 3.0 Hz, 2H), 7.85 (*dd*, *J* 5.4, 3.1 Hz, 2H).

Diisopropyl (S)-4-((2-amino-1-phenylethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1e)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 73% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.16-1.29 (m, 12H), 2.25 (d, J 4.8 Hz, 6H), 2.65 (d, J 6.2 Hz, 2H), 3.02-3.12 (m, 1H), 3.17 (dd, J 8.4, 5.8 Hz, 1H), 4.11 (t, J

5.6 Hz, 1H), 4.16 (*t*, *J* 6.2 Hz, 1H), 5.0 (*dsept.*, *J* 9.8, 6.2 Hz, 2H), 7.19-7.34 (*m*, 5H). ¹³C-NMR (101 MHz, methanol-*d*₄), δ, ppm: 18.7, 18.9, 22.46, 22.54, 36.1, 49.9, 68.3, 68.4, 73.3, 84.5, 100.7, 101.1, 127.8, 128.9, 129.6, 142.0, 148.2, 148.5, 169.76, 169.84. MS: *m/z* calcd. for C₂₄H₃₅N₂O₅ [M+H]⁺ 431.3, found 431.4.

tert-Butyl (3R,4S)-3-(1,3-dioxoisoindolin-2-yl)-4-hydroxypyrrolidine-1-carboxylate



Synthesized according to General Procedure G. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 78% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.48 (*s*, 9H), 2.29 (*br. s*, 1H), 3.29 (*dd*, *J* 11.1, 7.3 Hz, 1H), 3.70 (*dd*, *J* 10.6, 9.4 Hz, 1H), 3.94 (*br. s*, 2H), 4.62 (*br. d*, *J* 8.3 Hz, 1H), 4.97-5.06 (*m*, 1H), 7.73-7.78 (*m*, 2H), 7.84-

7.89 (m, 2H).

2-((3R,4S)-4-Hydroxypyrrolidin-3-yl)isoindoline-1,3-dione, TFA Salt



2-((3R,4S)-4-(2,2-Dimethoxyethoxy)-1-tosylpyrrolidin-3-yl)isoindoline-1,3-dione



Synthesized according to General Procedures K and B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 *v/v*). Colorless oil. 28% yield (over two steps). ¹**H-NMR** (400 MHz, CDCl₃), *δ*, ppm: 2.46 (*s*, 3H), 3.26 (*s*, 3H), 3.30 (*s*, 3H), 3.35 (*dd*, *J* 10.3, 4.9 Hz, 1H), 3.39-3.46 (*m*, 3H), 3.64-3.73 (*m*, 2H), 4.33 (*t*, *J* 5.1 Hz, 1H), 4.58-4.71 (*m*, 2H), 7.36 (*d*, *J* 8.0 Hz, 2H), 7.71-7.77 (*m*, 4H), 7.80-7.86 (*m*, 2H).

2-(((3S,4R)-4-(1,3-Dioxoisoindolin-2-yl)-1-tosylpyrrolidin-3-yl)oxy)acetaldehyde



Synthesized according to General Procedure M. Used in the next step as such, without further purification. Colorless oil. 93% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.47 (*s*, 3H), 3.40-3.48 (*m*, 2H), 3.69-3.76 (*m*, 2H), 4.04 (*s*, 2H), 4.60 (*q*, *J* 6.2 Hz, 1H), 4.75 (*td*, *J* 8.7, 5.9 Hz, 1H), 7.37 (*d*, *J* 8.0 Hz, 2H), 7.72-7.78 (*m*, 4H), 7.81-7.87 (*m*, 2H), 9.54 (*s*, 1H).

Diisopropyl 4-((((3S,4R)-4-(1,3-dioxoisoindolin-2-yl)-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 66% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.09-1.26 (*m*, 12H), 2.05-2.30 (*m*, 6H), 2.44-2.48 (*m*, 3H), 3.18 (*dd*, *J* 9.4, 4.4 Hz, 1H), 3.26 (*td*, *J* 10.2, 4.5 Hz, 2H), 3.37 (*t*, *J* 9.1 Hz, 1H), 3.55-3.68 (*m*, 2H), 3.96 (*t*, *J* 4.4 Hz, 1H), 4.46-4.51 (*m*, 1H), 4.52-4.62 (*m*, 1H), 4.86 (*quint.*, *J* 6.3 Hz, 1H), 5.02 (*quint.*, *J* 6.2 Hz, 1H), 5.43 (*s*, 1H), 7.34 (*d*, *J* 8.1 Hz, 2H), 7.69-7.76 (*m*, 4H), 7.81 (*br. dd*, *J* 5.4, 3.1 Hz, 2H).

Diisopropyl 4-((((3S,4R)-4-amino-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1h)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 76% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.25 (t, J 5.3 Hz, 12H), 2.23 (s, 6H), 2.43 (s, 3H), 2.99 (dd, J 10, 3.9 Hz, 1H), 3.10 (dd, J 10.5, 3.2 Hz, 1H), 3.15-3.27 (m, 3H), 3.39 (dd, J 10.0, 5.8 Hz, 1H), 3.49 (dd, J 10.5, 5.5 Hz, 1H), 3.54-3.59 (m, 1H), 4.07 (t, J 5.3 Hz, 1H), 4.98-5.08 (m, 2H), 5.53 (s, 1H), 7.32 (d, J 8.1 Hz, 2H), 7.70 (d, J

8.2 Hz, 2H). ¹³C-NMR (101 MHz, CDCl₃), *δ*, ppm: 19.4, 19.6, 21.5, 22.1, 34.3, 51.2, 53.5, 55.6, 67.00, 67.02, 72.4, 84.3, 100.4, 100.5, 127.5, 129.6, 133.9, 143.4, 145.1, 145.2, 167.2, 167.3. **MS**: *m/z* calcd, for C₂₇H₄₀N₃O₇S [M+H]⁺ 550.3, found 550.5.

tert-Butyl (3S,4S)-3-(1,3-dioxoisoindolin-2-yl)-4-hydroxypyrrolidine-1-carboxylate



Synthesized according to General Procedure G. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 95% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.49 (d, J 8.6 Hz, 9H), 3.18-3.25 (m, 1H), 3.68-3.85 (m, 3H), 4.60-4.69 (m, 1H), 4.75-4.85 (m, 1H), 7.80-7.85 (m, 2H), 7.85-7.90 (m, 2H).

2-((3S,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)isoindoline-1,3-dione



Synthesized according to General Procedures H and K. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 64% yield (over two steps). ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.47 (*s*, 3H), 3.27 (*dd*, *J* 10.3, 5.9 Hz, 1H), 3.44-3.51 (*m*, 1H), 3.74 (*dd*, *J* 10.3, 7.0 Hz, 1H), 3.85 (*t*, *J* 9.4 Hz, 1H), 4.44-4.54 (*m*, 1H), 4.86 (*q*, *J* 6.6 Hz, 1H), 7.37 (*d*, *J* 8.1 Hz, 2H), 7.73-7.78 (*m*, 4H), 7.80-7.85 (*m*, 2H).

2-((3S,4S)-4-(2,2-Dimethoxyethoxy)-1-tosylpyrrolidin-3-yl)isoindoline-1,3-dione



Synthesized according to General Procedure B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 38% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.46 (*s*, 3H), 3.26 (*s*, 3H), 3.30 (*s*, 3H), 3.35 (*dd*, *J* 10.4, 4.9 Hz, 1H), 3.38-3.46 (*m*,

3H), 3.64-3.73 (*m*, 2H), 4.33 (*t*, *J* 5.1 Hz, 1H), 4.58-4.72 (*m*, 2H), 7.36 (*d*, *J* 8.1 Hz, 2H), 7.71-7.77 (*m*, 4H), 7.79-7.86 (*m*, 2H).

Diisopropyl 4-((((3S,4S)-4-(1,3-dioxoisoindolin-2-yl)-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedures M and N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 68% yield (over two steps). ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.15 (*dd*, *J* 15.1, 6.2 Hz, 6H), 1.25 (*dd*, *J* 6.2, 2.5 Hz, 6H), 2.10 (*s*, 3H), 2.23 (*s*, 3H), 2.45 (*s*, 3H), 3.18 (*dd*, *J* 9.5, 4.5 Hz, 1H), 3.26 (*td*, *J* 10.3, 4.5 Hz, 2H), 3.37 (*t*, *J* 9.1 Hz, 1H), 3.56-3.66 (*m*, 2H), 3.96 (*t*, *J* 4.3 Hz, 1H), 4.46-4.52 (*m*, 1H), 4.53-4.61 (*m*, 1H), 4.86 (*dt*, *J* 12.4, 6.2 Hz, 1H), 5.02 (*dt*, *J* 12.5, 6.2 Hz, 1H), 5.43 (*s*, 1H), 7.34 (*d*, *J* 8.0 Hz, 2H), 7.69-7.76 (*m*, 4H), 7.81 (*br. dd*, *J* 5.50, 3.06

Hz, 2H).

Diisopropyl 4-((((3S,4S)-4-amino-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1i)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 62% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.10-1.14 (*m*, 12H), 2.11 (*s*, 6H), 2.30 (*s*, 3H), 2.87 (*dd*, *J* 10.0, 4.0 Hz, 1H), 2.97 (*dd*, *J* 10.5, 3.4 Hz, 1H), 3.03-3.14 (*m*, 3H), 3.23-3.32 (*m*, 1H), 3.36 (*dd*, *J* 10.5, 5.5 Hz, 1H), 3.39-3.51 (*m*, 1H), 3.95 (*t*, *J* 5.4 Hz, 1H), 4.90 (*dtt*, *J* 9.4, 6.2, 3.1 Hz, 2H), 5.41 (*s*, 1H), 7.19 (*d*, *J* 8.0 Hz, 2H), 7.57 (*d*, *J* 8.2 Hz, 2H). ¹³C-NMR (101 MHz, CDCl₃), δ , ppm: 18.8, 19.0, 21.3, 21.9,

33.8, 51.0, 53.2, 55.4, 66.5, 72.3, 83.9, 99.4, 99.5, 127.3, 129.4, 133.5, 143.2, 145.8, 145.9, 167.2, 167.3. **MS**: *m/z* calcd. for C₂₇H₄₀N₃O₇S [M+H]⁺ 550.3, found 550.5.

N,N-Dibenzyl-3-(2,2-dimethoxyethoxy)propan-1-amine



Synthesized according to General Procedure B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 v/v). Colorless oil. 70% yield. **¹H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.81 (*quint.*, J 6.8 Hz, 2H), 2.50 (*t*, J

7.0 Hz, 2H), 3.36 (*s*, 6H), 3.39 (*d*, *J* 5.3 Hz, 2H), 3.49 (*t*, *J* 6.7 Hz, 2H), 3.55 (*s*, 4H), 4.40 (*t*, *J* 5.2 Hz, 1H), 7.21-7.26 (*m*, 2H), 7.28-7.37 (*m*, 8H).

2-(3-(Dibenzylamino)propoxy)acetaldehyde

Synthesized according to General Procedure C. Used in the next step as such, without further purification. Colorless oil. 99% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.79-1.86 (*m*, 2H), 2.54 (*t*, *J* 6.7 Hz, 2H), 3.51-3.56 (*m*, 6H), 3.89 (*s*, 2H), 7.25 (*br. d*, *J* 7.1 Hz, 2H), 7.31-7.36 (*m*, 8H), 9.57 (*s*, 1H).

Diisopropyl 4-((3-(dibenzylamino)propoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure E. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 4:1 *v/v*). Colorless oil. 61% yield. ¹**H-NMR** (400 MHz, CDCl₃), *δ*, ppm: 1.25 (*d*, *J* 6.2 Hz, 12H), 1.67-1.77 (*m*, 2H), 2.17 (*s*, 6H), 2.42-2.49 (*m*, 2H), 3.21 (*d*, *J* 4.9 Hz, 2H), 3.38 (*t*, *J* 6.4 Hz, 2H), 3.55 (*s*, 4H), 4.05 (*t*, *J* 4.8 Hz, 1H), 5.04 (*quint.*, *J* 6.3 Hz, 2H), 5.14 (*s*, 4.14), 5.04 (*quint.*, *J* 6.3 Hz, 2H), 5.14 (*s*, 4.14), 5.04 (*quint.*, *J* 6.14), 5.14 (*s*, 4.14), 5.14 (*s*, 5.14), 5.14 (*s*,

1H), 7.20-7.25 (*m*, 2H), 7.31 (*t*, *J* 7.5 Hz, 4H), 7.35-7.39 (*m*, 4H).

Diisopropyl 4-((3-aminopropoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1q)



Synthesized according to General Procedure F. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 ν/ν with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 92% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.29 (*d*, *J* 6.2 Hz, 12H), 1.67 (*quint.*, *J* 6.2 Hz, 2H), 2.30 (*s*, 6H), 2.78 (*t*, *J* 6.5 Hz, 2H), 3.30 (*d*, *J* 5.0 Hz, 2H), 3.50 (*t*, *J* 5.9 Hz,

2H), 4.15 (*t*, *J* 5.0 Hz, 1H), 5.09 (*quint.*, *J* 6.2 Hz, 2H), 5.77 (*s*, 1H). ¹³C-NMR (101 MHz, CDCl₃), δ , ppm: 19.5, 22.0, 22.1, 32.7, 34.5, 40.0, 66.9, 69.7, 74.4, 100.6, 145.4, 167.4. MS: *m/z* calcd. for C₁₉H₃₃N₂O₅ [M+H]⁺ 369.2, found 369.6.

Thiomorpholine-Forming Amino-DHP Reagents 2-(2-Mercaptoethyl)isoindoline-1,3-dione



Synthesized according to General Procedure G. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 95% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.44 (*t*, *J* 8.6 Hz, 1H), 1.54 (*br. s*, 1H), 2.81-2.89 (*m*, 2H), 3.90 (*t*, *J* 7.2 Hz, 2H), 7.72-7.77 (*m*,

2H), 7.85-7.90 (*m*, 2H).

2-(2-((2,2-Dimethoxyethyl)thio)ethyl)isoindoline-1,3-dione



Synthesized according to General Procedure I. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). White solid. 66% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.78 (*d*, *J* 5.4 Hz, 2H), 2.91 (*t*, *J* 7.0 Hz, 2H), 3.39 (*s*, 6H), 3.92 (*t*, *J* 6.9 Hz, 2H), 4.52 (*t*, *J* 5.4 Hz, 1H), 7.70-7.76

2-((2-(1,3-Dioxoisoindolin-2-yl)ethyl)thio)acetaldehyde



Synthesized according to General Procedure M. Used in the next step as such, without further purification. Colorless oil. 98% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.55 (*s*, 1H), 2.80 (*t*, *J* 6.5 Hz, 2H), 3.32 (*d*, *J* 3.4 Hz, 2H), 3.91 (*t*, *J* 6.5 Hz, 2H), 7.72-7.78 (*m*, 2H), 7.84-7.90 (*m*, 2H), 9.51 (*s*, 1H).

Diisopropyl dicarboxylate

4-(((2-(1,3-dioxoisoindolin-2-yl)ethyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-



Synthesized according to General Procedure N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 52% yield. ¹H-NMR (400 MHz, CDCl₃), δ, ppm: 1.25-1.33 (*m*, 12H), 2.30 (*s*, 6H), 2.58 (*d*, *J* 6.0 Hz, 2H), 2.83 (*t*, *J* 6.9 Hz, 2H), 3.89 (*t*, *J* 6.9 Hz, 2H), 4.19 (*t*, *J* 5.9 Hz, 1H), 5.08 (*sept.*, *J* 6.2 Hz, 2H), 5.62 (*s*, 1H), 7.68-7.75 (*m*, 100)

2H), 7.81-7.86 (m, 2H).

Diisopropyl 4-(((2-aminoethyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1j)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 45% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.29 (*dd*, *J* 6.1, 4.3 Hz, 12H), 2.30 (*s*, 6H), 2.48 (*d*, *J* 6.1 Hz, 2H), 2.61 (*t*, *J* 6.2 Hz, 2H), 2.81-2.89 (*m*, 2H), 4.16 (*t*, *J* 6.0 Hz, 1H),

5.08 (*sept.*, *J* 6.2 Hz, 2H), 5.75 (*s*, 1H). ¹³**C-NMR** (101 MHz, CDCl₃), δ , ppm: 19.5, 22.05, 22.06, 33.3, 36.5, 38.0, 40.7, 67.1, 102.6, 144.7, 167.3. **MS**: *m/z* calcd. for C₁₈H₃₁N₂O₄S [M+H]⁺ 371.2, found 371.2.

2-(2-((2,2-dimethoxyethyl)thio)propyl)isoindoline-1,3-dione



Synthesized according to General Procedures G and B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 52% yield (over two steps). ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.32 (*d*, *J* 7.0 Hz, 3H), 2.81 (*qd*, *J* 13.3, 5.6 Hz, 2H), 3.25-3.33 (*m*, 1H), 3.36 (*d*, *J* 5.3 Hz, 6H), 3.70-3.78 (*m*, 1H), 3.85 (*dd*, *J* 13.9, 7.0 Hz, 1H), 4.49 (*t*, *J* 5.6 Hz, 1H),

^{7.71-7.76 (}m, 2H), 7.83-7.89 (m, 2H).

2-((1-(1,3-Dioxoisoindolin-2-yl)propan-2-yl)thio)acetaldehyde



Synthesized according to General Procedure M. Used in the next step as such, without further purification. Colorless oil. 95% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.35 (*d*, *J* 6.9 Hz, 3H), 3.19 (*sext.*, *J* 7.0 Hz, 1H), 3.31-3.42 (*m*, 2H), 3.81 (*qd*, *J* 14.2, 7.1 Hz, 2H), 7.74-7.79 (*m*, 2H), 7.87-7.91 (*m*, 2H), 9.56 (*t*, *J* 3.2 Hz, 1H).

Diisopropyl 4-(((1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 61% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.23-1.31 (*m*, 15H), 2.27 (*d*, *J* 6.2 Hz, 6H), 2.66 (*d*, *J* 5.5 Hz, 2H), 3.12-3.20 (*m*, 1H), 3.64-3.71 (*m*, 1H), 3.75 (*d*, *J* 6.7 Hz, 1H), 4.19 (*t*, *J* 5.6 Hz, 1H), 4.99-5.11 (*m*, 2H), 5.55 (*s*,

1H), 7.72 (*dd*, *J* 5.4, 3.1 Hz, 2H), 7.83-7.87 (*m*, 2H).

Diisopropyl 4-(((1-aminopropan-2-yl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (11)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 66% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.19-1.24 (*m*, 3H), 1.25-1.31 (*m*, 12H), 2.29 (*d*, *J* 1.2 Hz, 6H), 2.49-2.55 (*m*, 2H), 2.62-2.69 (*m*, 1H), 2.73-2.84 (*m*, 2H), 4.16 (*t*, *J*

5.8 Hz, 1H), 5.02-5.13 (*m*, 2H), 5.79 (*s*, 1H). ¹³C-NMR (101 MHz, CDCl₃), δ, ppm: 18.9, 19.5, 19.6, 22.06, 22.07, 33.8, 36.3, 43.7, 47.0, 67.1, 102.5, 144.7, 167.3. MS: *m*/*z* calcd. for C₁₉H₃₃N₂O₄S [M+H]⁺ 385.2, found 385.2.

2-(1-Mercaptopropan-2-yl)isoindoline-1,3-dione



Synthesized according to General Procedure G. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 ν/ν , followed by CH₂Cl₂/MeOH 95:5). White solid. 89% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.32-1.41 (*m*, 1H), 1.56 (*d*, *J* 7.0 Hz, 3H), 2.94 (*ddd*, *J* 13.7, 7.7, 5.9 Hz, 1H), 3.21 (*dt*, *J* 13.8, 9.7 Hz, 1H), 4.39 (*dquint.*, *J* 9.7, 6.7 Hz, 1H), 7.71-7.76 (*m*, 2H), 7.82-7.88 (*m*, 2H).

2-(1-((2,2-Dimethoxyethyl)thio)propan-2-yl)isoindoline-1,3-dione



Synthesized according to General Procedure B. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 1:1 v/v). Colorless oil. 69% yield.

¹**H-NMR** (400 MHz, CDCl₃), *δ*, ppm: 1.57 (*d*, *J* 7.0 Hz, 3H), 2.63-2.78 (*m*, 2H), 3.03 (*dd*, *J* 13.8, 5.4 Hz, 1H), 3.25 (*dd*, *J* 13.8, 10.2 Hz, 1H), 3.37 (*d*, *J* 3.2 Hz, 6H), 4.46-4.58 (*m*, 2H), 7.70-7.76 (*m*, 2H), 7.82-7.88 (*m*, 2H).

2-((2-(1,3-Dioxoisoindolin-2-yl)propyl)thio)acetaldehyde



Synthesized according to General Procedure M. Used in the next step as such, without further purification. Colorless oil. 96% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.55 (*d*, *J* 7.0 Hz, 3H), 2.76 (*dd*, *J* 14.1, 5.0 Hz, 1H), 3.12-3.24 (*m*, 2H), 3.26-3.37 (*m*, 1H), 4.43-4.54 (*m*, 1H), 7.70-7.77 (*m*, 2H),

7.81-7.88 (*m*, 2H), 9.46 (*dd*, *J* 4.3, 2.6 Hz, 1H).

Diisopropyl 4-(((2-(1,3-dioxoisoindolin-2-yl)propyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate



Synthesized according to General Procedure N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 *v/v*). Colorless oil. 73% yield. ¹H-NMR (400 MHz, CDCl₃), *δ*, ppm: 1.34 (*br. d, J* 6.2 Hz, 12H), 1.54-1.58 (*m*, 3H), 2.28 (*d, J* 3.3 Hz, 6H), 2.33-2.43 (*m*, 1H), 2.58-2.66 (*m*, 1H), 2.94-3.02 (*m*, 1H), 3.07-3.17 (*m*, 1H), 4.18 (*dd, J* 7.0, 5.0 Hz, 1H),

4.47-4.55 (m, 1H), 5.09 (sept., J 6.2 Hz, 2H), 5.60 (s, 1H), 7.69-7.73 (m, 2H), 7.82 (dd, J 5.4, 3.1 Hz, 2H).

Diisopropyl 4-(((2-aminopropyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1k)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:2 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 42% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.12 (*d*, *J* 6.4 Hz, 3H), 1.24-1.32 (*m*, 12H), 2.30 (*s*, 6H), 2.41-2.48 (*m*, 1H), 2.51-2.58 (*m*, 1H), 2.61-2.68 (*m*, 1H), 2.95-3.07 (*m*,

1H), 4.17 (*t*, *J* 6.0 Hz, 1H), 5.08 (*sept.*, *J* 6.2 Hz, 2H), 5.72 (*s*, 1H). ¹³C-NMR (101 MHz, CDCl₃), δ , ppm: 19.5, 22.1, 23.0, 33.4, 38.7, 43.1, 45.9, 67.0, 67.0, 102.5, 102.6, 144.5, 144.8, 167.2, 167.3. MS: *m/z* calcd. for C₁₉H₃₃N₂O₄S [M+H]⁺ 385.2, found 385.3.

Piperazine-Forming Amino-DHP Reagents 2-(2-((2,2-Dimethoxyethyl)amino)ethyl)isoindoline-1,3-dione



Synthesized according to General Procedure J. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 57% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.80 (*d*, *J* 5.5 Hz, 2H), 2.96 (*t*, *J* 6.5 Hz, 2H), 3.39 (*s*, 6H), 3.83 (*t*, *J*

6.4 Hz, 2H), 4.39-4.48 (m, 1H), 7.71-7.77 (m, 2H), 7.83-7.91 (m, 2H).

N-(2,2-Dimethoxyethyl)-N-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-methylbenzenesulfonamide



Synthesized according to General Procedure K. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 92% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 2.33 (*s*, 3H), 3.41-3.46 (*m*, 8H), 3.54 (*t*, *J* 6.1 Hz, 2H), 3.91 (*t*, *J* 6.0 Hz, 2H), 4.57 (*t*, *J* 5.2 Hz, 1H), 7.17 (*d*, *J* 8.1 Hz, 2H), 7.64 (*d*, *J* 8.2 Hz, 2H), 7.70-7.75 (*m*, 2H), 7.80-7.85 (*m*, 2H).

N-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-4-methyl-N-(2-oxoethyl)benzenesulfonamide



Synthesized according to General Procedure M. Used in the next step as such, without further purification. White solid. 99% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 2.31-2.35 (*m*, 3H), 3.47-3.51 (*m*, 2H), 3.78-3.85 (*m*, 2H), 4.04-4.10 (*m*, 2H), 7.16-7.21 (*m*, 2H), 7.59-7.63 (*m*, 2H), 7.71-7.77 (*m*,

2H), 7.82-7.87 (*m*, 2H), 9.65 (*s*, 1H).

Diisopropyl 4-(((N-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). White oil. 58% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.31 (*d*, *J* 6.2 Hz, 12H), 2.12-2.19 (*m*, 3H), 2.29 (*s*, 6H), 3.34 (*d*, *J* 6.9 Hz, 2H), 3.86 (*br. dd*, *J* 13.7, 4.9 Hz, 4H), 4.26 (*t*, *J* 6.9 Hz, 1H), 5.07 (*dt*, *J* 12.5, 6.2 Hz, 2H), 5.82 (*s*, 1H), 6.94 (*d*, *J* 8.1 Hz, 2H), 7.48 (*d*, *J* 8.2 Hz, 2H), 7.64-7.69 (*m*, 2H), 7.72-7.76 (*m*, 2H).

Diisopropyl 4-(((N-(2-aminoethyl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1n)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:2 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 30% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.29 (t, J 5.6 Hz, 12H), 2.28 (s, 6H), 2.40 (s, 3H), 2.86 (t, J 6.5 Hz, 2H), 2.97 (d, J 6.7 Hz, 2H), 3.30 (t, J 6.5 Hz, 2H), 4.22 (t, J 6.7 Hz, 1H), 5.00-5.12 (m, 2H), 5.90 (s, 1H), 7.25 (d, J 8.1 Hz, 2H), 7.61 (d, J 8.1 Hz, 2H). ¹³C-NMR (101 MHz, CDCl₃), δ , ppm: 19.7, 21.5, 22.10, 22.14, 32.4, 39.3, 50.4, 51.4, 67.3, 100.9, 127.2, 129.5, 137.4,

142.8, 145.6, 166.9. **MS**: m/z calcd. for C₂₅H₃₈N₃O₆S [M+H]⁺ 508.2, found 508.5.

Benzyl (2,2-dimethoxyethyl)(2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate



Synthesized according to General Procedure L. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 1:1 v/v), followed by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:1 v/v with 0.1% TFA as modifier), then lyophilized. White fluffy oil. 61% yield. Mixture of hydrolyzed product and the desired acetal (*approx.* 1:4). The product is rotameric. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 3.32-3.44 (*m*, 8H), 3.64-3.73 (*m*, 2H), 3.84-3.95 (*m*, 2H), 4.36-4.58 (*m*, 1H), 4.94-5.05 (*m*, 2H), 7.24-7.37 (*m*, 5H), 7.70-

7.84 (*m*, 4H).

Diisopropyl 4-((((benzyloxy)carbonyl)(2-(1,3-dioxoisoindolin-2-yl)ethyl)amino)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedures M and N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). White solid. 58% yield (over two steps). The product is rotameric. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.19-1.27 (*m*, 12H), 2.10-2.35 (*m*, 6H), 3.20 (*br. d*, *J* 6.5 Hz, 2H), 3.60-3.69 (*m*, 2H), 3.79-3.94 (*m*, 2H), 4.10-4.19 (*m*, 1H), 4.84 (*d*, *J* 18.5 Hz, 2H), 4.93-5.05 (*m*, 2H), 5.46-5.79 (*m*, 1H), 7.17-7.26 (*m*, 3H), 7.27-7.31 (*m*, 2H), 7.64-7.80 (*m*, 4H).

Diisopropyl 4-(((2-aminoethyl)((benzyloxy)carbonyl)amino)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1m)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:2 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 40% yield. ¹**H-NMR** (400 MHz, CDCl₃), δ , ppm: 1.25 (*br. d, J* 5.9 Hz, 12H), 2.10-2.32 (*m*, 6H), 2.83 (*dt, J* 19.5, 6.1 Hz, 2H), 3.12-3.27 (*m*, 2H), 3.34-3.44 (*m*, 2H), 4.12-4.21 (*m*, 1H), 4.97-5.10 (*m*, 4H), 5.64-6.22 (*m*, 1H), 7.28-7.37 (*m*, 5H). **MS**: *m/z* calcd. for C₂₆H₃₈N₃O₆ [M+H]⁺ 488.3, found 488.7.

tert-Butyl (S)-(2-(1,3-dioxoisoindolin-2-yl)propyl)carbamate



Synthesized according to General Procedure G. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 92% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.26-1.44 (*m*, 9H), 1.47 (*br. d*, *J* 7.0 Hz, 3H), 3.37 (*dt*, *J* 14.2, 4.9 Hz, 1H), 3.65-3.85 (*m*, 1H), 4.47-4.58 (*m*, 1H), 4.84 (*br. s*, 1H), 7.69-7.75 (*m*, 2H), 7.81-7.86 (*m*, 2H).

(S)-2-(1-Aminopropan-2-yl)isoindoline-1,3-dione, TFA Salt



Synthesized according to General Procedure H. Used in the next step as such, without further purification. Colorless oil. 96% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.53 (d, J 7.0 Hz, 3H), 3.26 (dd, J 13.3, 4.0 Hz, 1H), 3.69 (dd, J 13.2, 10.4 Hz, 1H), 4.63 (ddd, J 10.6, 6.9, 3.9 Hz, 1H), 7.81-7.86 (m,

2H), 7.87-7.93 (*m*, 2H).

(S)-2-(1-((2,2-Dimethoxyethyl)amino) propan-2-yl) isoindoline-1,3-dione



Synthesized according to General Procedure J. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 56% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.47 (*d*, *J* 7.0 Hz, 3H), 2.66-2.72 (*m*, 1H), 2.75-2.82 (*m*, 1H), 2.91 (*dd*, *J* 12.5, 5.5 Hz, 1H), 3.25-3.30 (*m*, 1H), 3.32 (*d*, *J* 1.0 Hz, 6H), 4.36 (*t*, *J*

5.4 Hz, 1H), 4.41-4.51 (*m*, 1H), 7.68-7.74 (*m*, 2H), 7.79-7.86 (*m*, 2H).

(S)-N-(2,2-Dimethoxyethyl)-N-(2-(1,3-dioxoisoindolin-2-yl)propyl)-4-methylbenzenesulfonamide



Synthesized according to General Procedure K. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 *ν/ν*). Colorless oil. 94% yield. ¹**H-NMR** (400 MHz, CDCl₃), *δ*, ppm: 1.46 (*d*, *J* 7.2 Hz, 3H), 2.33 (*s*, 3H), 3.23-3.31 (*m*, 2H), 3.35 (*s*, 3H), 3.39-3.45 (*m*, 4H), 4.00 (*dd*, *J* 14.7, 9.7 Hz, 1H), 4.49 (*t*, *J* 5.1 Hz, 1H), 4.66-4.76 (*m*, 1H), 7.17 (*d*, *J* 8.2 Hz, 2H), 7.61 (*d*, *J* 8.2 Hz, 2H), 7.67-7.72 (*m*, 2H), 7.76-7.83 (*m*, 2H).

(S)-N-(2-(1,3-Dioxoisoindolin-2-yl)propyl)-4-methyl-N-(2oxoethyl)benzenesulfonamide



Synthesized according to General Procedure M. Used in the next step as such, without further purification. White solid. 73% yield. ¹H-NMR (400 MHz,

CDCl₃), *δ*, ppm: 1.50 (*d*, *J* 7.1 Hz, 3H), 2.38 (*s*, 3H), 3.06 (*dd*, *J* 14.6, 3.9 Hz, 1H), 3.94 (*s*, 2H), 4.03-4.11 (*m*, 1H), 4.52 (*ddt*, *J* 10.7, 7.1, 3.4 Hz, 1H), 7.23 (*d*, *J* 8.1 Hz, 2H), 7.62 (*d*, *J* 8.2 Hz, 2H), 7.71-7.77 (*m*, 2H), 7.83 (*dd*, *J* 5.4, 3.1 Hz, 2H), 9.54 (*s*, 1H).

Diisopropyl (S)-4-(((N-(2-(1,3-dioxoisoindolin-2-yl)propyl)-4-methylphenyl)sulfonamido)methyl)-2,6dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedures M and N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). White solid. 54% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.28-1.40 (*m*, 12H), 1.52 (*d*, *J* 7.1 Hz, 3H), 2.12-2.19 (*m*,

6H), 2.34 (*s*, 3H), 3.20 (*dd*, *J* 14.2, 3.7 Hz, 1H), 3.39 (*dd*, *J* 13.8, 9.8 Hz, 1H), 3.77 (*dd*, *J* 15.3, 2.7 Hz, 1H), 4.20-4.30 (*m*, 2H), 4.74-4.85 (*m*, 1H), 4.98-5.08 (*m*, 1H), 5.09-5.20 (*m*, 1H), 5.79 (*s*, 1H), 6.89 (*d*, *J* 8.1 Hz, 2H), 7.42 (*d*, *J* 8.2 Hz, 2H), 7.63-7.67 (*m*, 2H), 7.67-7.71 (*m*, 2H).

Diisopropyl (S)-4-(((N-(2-aminopropyl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate (10)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:2 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 77% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.01 (*d*, *J* 6.4 Hz, 3H), 1.29 (*td*, *J* 6.4, 4.7 Hz, 12H), 2.24 (*s*, 3H), 2.31 (*s*, 3H), 2.39 (*s*, 3H), 2.91-2.99 (*m*, 1H), 3.00-3.08 (*m*, 1H), 3.09-3.20 (*m*, 2H), 3.22-3.32 (*m*, 1H), 4.24 (*t*, *J* 6.8 Hz, 1H), 4.97-5.15 (*m*, 2H), 5.93 (*s*, 1H), 7.25 (*d*, *J* 8.1 Hz, 2H), 7.62 (*d*, *J* 8.2 Hz, 2H). ¹³C-NMR (101 MHz, CDCl₃), δ , ppm: 19.7, 19.8, 21.3, 21.4, 22.09,

22.14, 32.2, 44.2, 50.5, 57.1, 67.28, 67.34, 100.8, 101.0, 127.2, 129.5, 137.6, 142.7, 145.7, 145.8, 166.8, 166.9. **MS**: *m/z* calcd. for C₂₆H₄₀N₃O₆S [M+H]⁺ 522.3, found 522.4.

tert-Butyl (1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)carbamate



Synthesized according to General Procedure G. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 78% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.21 (*d*, *J* 6.72 Hz, 3H), 1.26 (*s*, 9H), 3.63-3.75 (*m*, 2H), 3.96-4.19 (*m*, 1H), 4.66 (*br. d*, *J* 7.5 Hz, 1H), 7.68-7.76 (*m*, 2H), 7.86 (*dd*, *J* 5.3, 3.1 Hz, 2H).

2-(2-Aminopropyl)isoindoline-1,3-dione, TFA Salt



Synthesized according to General Procedure H. Used in the next step as such, without further purification. Colorless oil. 99% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.35 (d, J 6.72 Hz, 3H), 3.59-3.71 (m, 1H), 3.85-3.93 (m, 2H), 7.83-7.88 (m, 2H), 7.89-7.95 (m, 2H).

2-(2-((2,2-Dimethoxyethyl)amino)propyl)isoindoline-1,3-dione



Synthesized according to General Procedure J. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v, followed by CH₂Cl₂/MeOH 95:5). White solid. 63% yield. ¹H-NMR (400 MHz, methanol-*d*₄), δ , ppm: 1.10 (*d*, *J* 6.5 Hz, 3H), 2.75 (*qd*, *J* 12.5, 5.4 Hz, 2H),

3.04-3.12 (*m*, 1H), 3.33 (*d*, *J* 4.8 Hz, 6H), 3.58-3.65 (*m*, 1H), 3.66-3.74 (*m*, 1H), 4.40 (*t*, *J* 5.4 Hz, 1H), 7.79-7.84 (*m*, 2H), 7.84-7.90 (*m*, 2H).

N-(2,2-Dimethoxyethyl)-N-(1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)-4-methylbenzenesulfonamide



Synthesized according to General Procedure K. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). Colorless oil. 92% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.11 (*d*, *J* 7.0 Hz, 3H), 2.30 (*s*, 3H), 3.26-3.33 (*m*, 1H), 3.39-3.46 (*m*, 4H), 3.49-3.57 (*m*, 4H), 3.93 (*dd*, *J* 14.1, 8.9

Hz, 1H), 4.30 (*ddd*, *J* 8.8, 7.0, 5.1 Hz, 1H), 4.66 (*t*, *J* 4.9 Hz, 1H), 7.14 (*d*, *J* 8.1 Hz, 2H), 7.63 (*d*, *J* 8.3 Hz, 2H), 7.68-7.73 (*m*, 2H), 7.79-7.85 (*m*, 2H).

N-(1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)-4-methyl-N-(2-oxoethyl)benzenesulfonamide



Synthesized according to General Procedure M. Used in the next step as such, without further purification. White solid. 87% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.04 (*d*, *J* 6.9 Hz, 3H), 2.25 (*s*, 3H), 3.47 (*dd*, *J* 14.5, 4.0 Hz, 1H), 3.67 (*dd*, *J* 14.5, 10.9 Hz, 1H), 3.77-3.84 (*m*, 1H), 3.95 (*d*, *J* 18.6

Hz, 1H), 4.27-4.38 (*m*, 1H), 7.06 (*d*, *J* 8.0 Hz, 2H), 7.58 (*d*, *J* 8.3 Hz, 2H), 7.70-7.76 (*m*, 2H), 7.76-7.83 (*m*, 2H), 9.65 (*d*, *J* 1.7 Hz, 1H).

Diisopropyl 4-(((N-(1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)-4-methylphenyl)sulfonamido)methyl)-2,6dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Synthesized according to General Procedure N. Purified by silica gel flash chromatography (eluent: *n*-heptane/EtOAc 3:2 v/v). White solid. 45% yield. The product is rotameric. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.10 (*br. d, J* 6.7 Hz, 3H), 1.35 (*ddd, J* 12.0, 6.3, 3.1 Hz, 12H), 2.26 (*s*, 3H), 2.37 (*s*, 6H), 3.11 (*br. d, J* 6.6 Hz, 2H), 3.63-3.70 (*m*, 1H),

3.76 (*t*, *J* 2.9 Hz, 1H), 4.20-4.27 (*m*, 1H), 4.44 (*t*, *J* 6.9 Hz, 1H), 5.12 (*dq*, *J* 13.1, 6.4 Hz, 2H), 5.85 (*s*, 1H), 7.11 (*d*, *J* 8.1 Hz, 2H), 7.65-7.71 (*m*, 4H), 7.76-7.81 (*m*, 2H).

Diisopropyl 4-(((N-(1-aminopropan-2-yl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate (1p)



Synthesized according to General Procedure O. Purified by reverse-phase flash chromatography (C18, eluent: water/MeCN 1:2 v/v with 0.1% NH₄OH as modifier), then lyophilized. White fluffy solid. 70% yield. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 0.71 (d, J 6.7 Hz, 3H), 1.28-1.37 (m, 12H), 2.34 (d, J 8.0 Hz, 6H), 2.39 (s, 3H), 2.60 (dd, J 13.5, 5.0 Hz, 1H),

2.68 (*dd*, *J* 14.6, 5.8 Hz, 1H), 2.88 (*dd*, *J* 13.5, 8.8 Hz, 1H), 3.05 (*dd*, *J* 14.6, 7.6 Hz, 1H), 3.57-3.68 (*m*, 1H), 4.28 (*dd*, *J* 7.3, 5.9 Hz, 1H), 5.04-5.19 (*m*, 2H), 6.03 (*s*, 1H), 7.24 (*d*, *J* 8.1 Hz, 2H), 7.64 (*d*, *J* 8.2 Hz, 2H). ¹³C-NMR (101 MHz, CDCl₃), δ, ppm: 14.7, 19.5, 20.1, 21.5, 22.13, 22.15, 22.20, 22.24, 34.8, 46.4, 46.6, 58.1, 67.4,

67.5, 101.1, 101.9, 127.3, 129.5, 137.9, 142.8, 145.2, 145.5, 167.1, 167.5. **MS**: m/z calcd. for C₂₆H₄₀N₃O₆S [M+H]⁺ 522.3, found 522.4.

Complete List of Commercially-Available Aldehydes



Scheme S3. List of commercially-available aldehydes.

Product Characterization

3-(4-Methoxyphenyl)morpholine, TFA salt (4aa)



Synthesized according to General Procedure A, using 100 mg (0.23 mmol) of amino-DHP reagent **1a**. White fluffy solid. 80% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 3.35-3.44 (*m*, 2H), 3.81 (*s*, 3H), 3.82-3.98 (*m*, 2H), 4.00-4.15 (*m*, 2H), 4.41 (*dd*, *J* 10.8, 3.61 Hz, 1H), 7.02 (*d*, *J* 8.8 Hz, 2H), 7.43 (*d*, *J* 8.9 Hz, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 45.3, 56.0, 59.8, 64.5, 70.0,

115.9, 125.9, 130.4, 162.6. ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -77.02 (*s*, 3F). **MS**: *m/z* calcd. for C₁₁H₁₆NO₂ [M+H]⁺ 194.1, found 194.3.

3-(4-Bromophenyl)morpholine, TFA salt (4ad)



Synthesized according to General Procedure A, using 112 mg (0.23 mmol) of amino-DHP reagent **1a**. White fluffy solid. 72% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 3.38-3.47 (*m*, 2H), 3.81-3.97 (*m*, 2H), 4.07-4.16 (*m*, 2H), 4.50 (*dd*, *J* 10.8, 3.6 Hz, 1H), 7.43 (*d*, *J* 8.4 Hz, 2H), 7.62-7.71 (*m*, 2H). ¹³C-NMR
(101 MHz, methanol- d_4), δ , ppm: 45.3, 59.5, 64.5, 69.7, 125.4, 130.9, 133.3, 133.9. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -77.04 (*s*, 3F). **MS**: *m/z* calcd. for C₁₀H₁₃BrNO [M+H]⁺ 242.0, found 242.1.

3-(4-Fluorophenyl)morpholine, TFA salt (4ac)



Synthesized according to General Procedure A, using 100 mg (0.23 mmol) of amino-DHP reagent **1a**. White fluffy solid. 60% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 3.37-3.46 (*m*, 2H), 3.83-4.01 (*m*, 2H), 4.04-4.15 (*m*, 2H), 4.50 (*dd*, J 10.8, 3.6 Hz, 1H), 7.18-7.27 (*m*, 2H), 7.56 (*m*, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 45.3, 59.4, 64.5, 69.8, 117.4, 117.6, 130.3, 131.35, 131.44, 163.9, 166.3. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -112.96 (*s*, 3F),

-77.02 (*s*, 1F). **MS**: *m/z* calcd. for C₁₀H₁₃FNO [M+H]⁺ 182.1, found 182.3.

3-(p-Tolyl)morpholine, TFA salt (4ab)



Synthesized according to General Procedure A, using 100 mg (0.23 mmol) of amino-DHP reagent **1a**. White fluffy solid. 58% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 2.37 (*s*, 3H), 3.35-3.49 (*m*, 2H), 3.82-3.96 (*m*, 2H), 4.02-4.16 (*m*, 2H), 4.43 (*dd*, *J* 10.8, 3.6 Hz, 1H), 7.30 (*d*, *J* 8.1 Hz, 2H), 7.37 (*d*, *J* 8.2 Hz, 2H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 21.3, 45.4, 60.0, 64.6, 70.1, 128.8, 131.1, 131.2, 141.7.

¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -76.93 (*s*, 3F). **MS**: *m/z* calcd. for C₁₁H₁₆NO [M+H]⁺ 178.1, found 178.3.

3-(Thieno[2,3-b]pyridin-2-yl)morpholine, TFA salt (4av)



Synthesized according to General Procedure A, using 117 mg (0.25 mmol) of amino-DHP reagent **1a**. White fluffy solid. 68% yield. ¹H-NMR (400 MHz, methanol-*d*₄), δ, ppm: 3.41-3.52 (*m*, 2H), 3.94 (*ddd*, *J* 13.1, 9.6, 3.7 Hz, 1H), 4.03-4.17 (*m*, 2H), 4.31 (*dd*, *J* 12.7, 3.6 Hz, 1H), 4.95-5.02 (*m*, 1H), 7.51 (*dd*, *J* 8.1, 4.7 Hz, 1H), 7.63 (*s*, 1H), 8.31 (*dd*, *J* 8.1, 1.4 Hz, 1H), 8.61 (*br*. *d*, *J* 4.0 Hz, 1H). ¹³C-NMR (101 MHz, methanol-*d*₄), δ, ppm: 44.8, 55.3, 64.8, 69.7, 122.1, 125.1, 134.1,

134.3, 136.3, 149.1, 162.4. ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -77.25 (*s*, 3F). **MS**: *m/z* calcd. for C₁₁H₁₃N₂OS [M+H]⁺ 221.1, found 221.3.

3-(4-(Trifluoromethoxy)phenyl)morpholine, TFA salt (4ag)



Synthesized according to General Procedure A, using 106 mg (0.20 mmol) of amino-DHP reagent **1a**. White fluffy solid. 69% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.39-3.46 (*m*, 2H), 3.84-4.00 (*m*, 2H), 4.08-4.16 (*m*, 2H), 4.56 (*dd*, *J* 10.7, 3.6 Hz, 1H), 7.41 (*d*, *J* 8.3 Hz, 2H), 7.63 (*d*, *J* 8.8 Hz,

2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 45.3, 59.3, 64.6, 69.8, 118.1, 125.8 (q, J^{CF} 256 Hz), 123.1, 131.1, 133.2, 151.7. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -77.13 (s, 3F), -59.54 (s, 3F). MS: m/z calcd. for C₁₁H₁₃F₃NO₂ [M+H]⁺ 248.1, found 248.41.

3-(4-(Trimethylsilyl)phenyl)morpholine, TFA salt (4ae)



Synthesized according to General Procedure C, using 108 mg (0.21 mmol) of amino-DHP reagent **1a**. White fluffy solid. 82% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 0.27 (s, 9H), 3.37-3.48 (m, 2H), 3.83-3.97 (m, 2H), 4.05-4.16 (m, 2H), 4.47 (dd, J 10.9, 3.6 Hz, 1H), 7.47 (d, J 8.0 Hz, 2H), 7.64 (d, J 8.0 Hz, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: -1.2, 45.4, 60.2, 64.6, 70.0, 128.1, 134.5, 135.5, 144.3. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -76.90 (s,

3F). **MS**: *m/z* calcd. for C₁₃H₂₂NOSi [M+H]⁺ 236.1, found 236.2.

3-(4-(Trifluoromethyl)phenyl)morpholine, TFA salt (4af)



Synthesized according to General Procedure A, using 106 mg (0.21 mmol) of amino-DHP reagent **1a**. White fluffy solid. 67% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 3.45 (dd, J 6.9, 2.3 Hz, 2H), 3.87-3.99 (m, 2H), 4.09-4.20 (m, 2H), 4.63 (dd, J 10.6, 3.6 Hz, 1H), 7.72 (m, J 8.3 Hz, 2H), 7.78-7.84 (m, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 45.4, 59.6, 64.6, 69.7, 125.4 (q, J^{CF} 271 Hz), 127.5 (q, J^{CF} 3.7 Hz), 129.8, 133.2 (q, J^{CF} 32.3 Hz), 138.3. ¹⁹F-NMR (376

MHz, methanol- d_4), δ , ppm: -77.10 (s, 3F), -64.49 (s, 3F). **MS**: m/z calcd. for C₁₁H₁₃F₃NO [M+H]⁺ 232.1, found 232.3.

3-(Benzo[b]thiophen-2-yl)morpholine, TFA salt (4au)



Synthesized according to General Procedure A, using 84 mg (0.17 mmol) of amino-DHP reagent **1a**. White fluffy solid. 69% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 3.38-3.52 (*m*, 2H), 3.85-4.00 (*m*, 1H), 4.00-4.16 (*m*, 2H), 4.29 (*dd*, *J* 12.6, 3.6 Hz, 1H), 4.90-4.95 (*m*, 1H), 7.39-7.47 (*m*, 2H), 7.60 (*s*, 1H), 7.85-7.96 (*m*, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 44.9, 55.3, 64.7, 69.9, 123.6, 125.5, 126.4, 126.98, 127.04, 135.6, 140.5, 141.3. ¹⁹F-NMR (376

MHz, methanol- d_4), δ , ppm: -77.06 (s, 3F). **MS**: m/z calcd. for C₁₂H₁₄NOS [M+H]⁺ 220.1, found 220.2.

3-(2,3-Dihydrobenzofuran-5-yl)morpholine, TFA salt (4ak)



Synthesized according to General Procedure A, using 116 mg (0.24 mmol) of amino-DHP reagent **1a**. White fluffy solid. 69% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.23 (t, J 8.7 Hz, 2H), 3.34-3.43 (m, 2H), 3.81-3.96 (m, 2H),

4.01-4.13 (*m*, 2H), 4.38 (*dd*, *J* 10.9, 3.7 Hz, 1H), 4.58 (*t*, *J* 8.7 Hz, 2H), 6.80 (*d*, *J* 8.3 Hz, 1H), 7.18-7.24 (*m*, 1H), 7.34 (*s*, 1H). ¹³C-NMR (101 MHz, methanol-*d*₄), δ , ppm: 30.4, 45.3, 60.1, 64.5, 70.1, 72.9, 110.9, 125.8, 129.3, 130.3, 163.1. ¹⁹F-NMR (376 MHz, methanol-*d*₄), δ , ppm: -76.97 (*s*, 3F). MS: *m*/*z* calcd. for C₁₂H₁₆NO₂ [M+H]⁺ 206.1, found 206.2.

3-(2,5-Dimethylphenyl)morpholine, TFA salt (4ah)



Synthesized according to General Procedure A, using 96 mg (0.20 mmol) of amino-DHP reagent **1a**. White fluffy solid. 82% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 2.33-2.36 (*m*, 3H), 2.40 (*s*, 3H), 3.38-3.45 (*m*, 1H), 3.45-3.56 (*m*, 1H), 3.78-3.95 (*m*, 2H), 4.02 (*dd*, *J* 13.0, 3.6 Hz, 1H), 4.13 (*dd*, *J* 12.9, 3.6 Hz, 1H), 4.66 (*dd*, *J* 10.9, 3.6 Hz, 1H), 7.18 (*q*, *J* 7.8 Hz, 2H), 7.29 (*s*, 1H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 18.9, 21.2, 45.7, 57.0, 64.6, 70.0, 127.5, 131.6, 132.1, 132.6, 135.0, 138.1. ¹⁹**F-NMR** (376

MHz, methanol- d_4), δ , ppm: -76.93 (*s*, 3F). **MS**: *m/z* calcd. for C₁₂H₁₈NO [M+H]⁺ 192.1, found 192.2.

3-(5-Bromopyridin-3-yl)morpholine, TFA salt (4ar)



Synthesized according to General Procedure A, using 106 mg (0.20 mmol) of amino-DHP reagent **1a**. White fluffy solid. 61% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.39-3.50 (*m*, 2H), 3.86-3.95 (*m*, 1H), 4.00 (*dd*, *J* 12.8, 10.5 Hz, 1H), 4.09-4.19 (*m*, 2H), 4.63 (*dd*, *J* 10.3, 3.6 Hz, 1H), 8.24 (*t*, *J* 1.8 Hz, 1H), 8.64-8.73 (*m*, 1H), 8.73-8.83 (*m*, 1H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 45.2, 57.1, 64.6, 69.1,

122.5, 132.3, 140.2, 148.7, 153.2. ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -77.45 (*s*, 3F). **MS**: *m/z* calcd. for C₉H₁₂BrN₂O [M+H]⁺ 243.0, found 243.1.

3-(1-Methyl-1H-indol-3-yl)morpholine, TFA salt (4at)



Synthesized according to General Procedure A, using 108 mg (0.22 mmol) of amino-DHP reagent **1a**. White fluffy solid. 79% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.33-3.40 (*m*, 1H), 3.40-3.51 (*m*, 1H), 3.83 (*s*, 3H), 3.87-3.96 (*m*, 1H), 4.03-4.20 (*m*, 3H), 4.82 (*dd*, *J* 10.2, 3.8 Hz, 1H), 7.12-7.23 (*m*, 1H), 7.23-7.31 (*m*, 1H), 7.40-7.45 (*m*, 1H), 7.46 (*s*, 1H), 7.74 (*d*, *J* 8.0 Hz, 1H). ¹³**C-NMR** (101 MHz,

methanol- d_4), δ , ppm: 33.3, 44.8, 52.6, 64.7, 69.9, 107.1, 111.1, 119.5, 121.4, 123.9, 127.7, 129.9, 138.5. ¹⁹**F**-**NMR** (376 MHz, methanol- d_4), δ , ppm: -77.03 (*s*, 3F). **MS**: *m/z* calcd. for C₁₃H₁₇N₂O [M+H]⁺ 217.1, found 217.2.

3-(Thiophen-2-yl)morpholine, TFA salt (4ao)



Synthesized according to General Procedure A, using 97 mg (0.22 mmol) of amino-DHP reagent **1a**. White fluffy solid. 54% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.36-

3.42 (*m*, 2H), 3.83-3.92 (*m*, 1H), 3.93-4.01 (*m*, 1H), 4.05-4.12 (*m*, 1H), 4.15-4.22 (*m*, 1H), 4.83 (*dd*, *J* 10.0, 3.7 Hz, 1H), 7.14 (*dd*, *J* 5.0, 3.7 Hz, 1H), 7.34 (*d*, *J* 3.4 Hz, 1H), 7.56-7.63 (*m*, 1H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 44.7, 54.7, 64.6, 70.1, 128.8, 129.2, 130.1, 135.0. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -76.99 (*s*, 3F). **MS**: *m/z* calcd. for C₈H₁₁NOS [M+H]⁺ 170.1, found 170.1.

3-(1-Methyl-1H-pyrazol-5-yl)morpholine, TFA salt (4ap)



Synthesized according to General Procedure A, using 96 mg (0.22 mmol) of amino-DHP reagent **1a**. White fluffy solid. 58% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.35-3.53 (*m*, 2H), 3.83-3.94 (*m*, 2H), 3.95-3.98 (*m*, 3H), 4.06-4.16 (*m*, 2H), 4.83 (*dd*, J 10.0, 3.7 Hz, 1H), 6.60 (*d*, J 2.0 Hz, 1H), 7.52 (*d*, J 1.7 Hz, 1H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 37.2, 44.7, 50.8, 64.6, 68.9, 107.3, 136.1, 140.0. ¹⁹**F-NMR** (376

MHz, methanol- d_4), δ , ppm: -77.13 (s, 3F). **MS**: m/z calcd. for C₈H₁₄N₃O [M+H]⁺ 168.1, found 168.4.

3-(Furan-2-yl)morpholine, TFA salt (4an)



Synthesized according to General Procedure A, using 89 mg (0.21 mmol) of amino-DHP reagent **1a**. White fluffy solid. 67% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.40 (*br. d, J* 3.4 Hz, 2H), 3.77-3.89 (*m*, 1H), 3.96-4.03 (*m*, 1H), 4.03-4.10 (*m*, 1H), 4.14-4.21 (*m*, 1H), 4.65 (*dd, J* 10.0, 3.7 Hz, 1H), 6.52 (*dd, J* 3.2, 1.8 Hz, 1H), 6.65 (*d, J* 3.3 Hz, 1H), 7.62-7.67 (*m*, 1H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 44.4, 52.8, 64.7,

67.9, 112.1, 112.2, 145.8, 147.4. ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -76.98 (*s*, 3F). **MS**: *m/z* calcd. for C₈H₁₂NO₂ [M+H]⁺ 154.1, found 154.1.

tert-Butyl 6-(morpholin-3-yl)-indole-1-carboxylate, Free base (4as)



Synthesized according to General Procedure B, using 106 mg (0.18 mmol) of amino-DHP reagent **1a**. White fluffy solid. 73% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 1.68 (*s*, 9H), 2.92-3.01 (*m*, 1H), 3.01-3.12 (*m*, 1H), 3.50 (*t*, *J* 10.8 Hz, 1H), 3.64 (*td*, *J* 11.4, 2.7 Hz, 1H), 3.86 (*dd*, *J* 11.4, 2.9 Hz, 2H), 3.97 (*dd*, *J* 10.3, 3.1 Hz, 1H), 6.58 (*d*, *J* 3.7 Hz, 1H), 7.23-7.28 (*m*, 1H), 7.51-7.55 (*m*, 1H), 7.57-7.61 (*m*, 1H), 8.22 (*s*, 1H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 28.5, 47.4, 62.0, 68.0, 74.3, 85.1, 108.3, 115.0, 122.1, 123.3, 127.4, 131.8, 136.9, 137.5, 151.1. **MS**: *m/z* calcd. for

 $C_{17}H_{23}N_2O_3 [M+H]^+$ 303.2, found 303.58.

3-(Benzo[d][1,3]dioxol-5-yl)morpholine, TFA salt (4am)



Synthesized according to General Procedure A, using 88 mg (0.18 mmol) of amino-DHP reagent **1a**. White fluffy solid. 75% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.34-3.44 (*m*, 2H), 3.80-3.93 (*m*, 2H), 4.03-4.16 (*m*, 2H),

4.39 (*dd*, *J* 10.8, 3.6 Hz, 1H), 6.01 (*s*, 2H), 6.88-6.94 (*m*, 1H), 6.94-7.01 (*m*, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 45.4, 60.0, 64.5, 70.0, 103.3, 109.0, 110.1, 123.2, 127.5, 150.1, 150.7. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -76.96 (*s*, 3F). **MS**: *m/z* calcd. for C₁₁H₁₃NO₃ [M+H]⁺ 208.1, found 208.3.

3-(Isoquinolin-5-yl)morpholine, TFA salt (4aj)



Synthesized according to General Procedure A, using 86 mg (0.17 mmol) of amino-DHP reagent **1a**. White fluffy solid. 77% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.07 (*br. d, J* 12.4 Hz, 1H), 3.22 (*td, J* 12.0, 3.4 Hz, 1H), 3.43-3.51 (*m*, 1H), 3.70 (*br. d, J* 2.6 Hz, 1H), 3.98 (*br. d, J* 2.9 Hz, 2H), 4.67-4.74 (*m*, 1H), 7.72 (*t, J* 7.8 Hz, 1H), 8.01 (*d, J* 7.2 Hz, 1H), 8.06 (*d, J* 8.2 Hz, 1H), 8.16 (*d, J* 6.2 Hz, 1H), 8.50 (*d, J* 6.1 Hz, 1H), 9.25 (*s,* 1H). ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -77.07 (*s,* 3F). **MS**: *m/z* calcd. for 215 1 found 215 38

 $C_{13}H_{15}N_2O [M+H]^+ 215.1$, found 215.38.

3-(1-Benzyl-imidazol-5-yl)morpholine, TFA salt (4aq)



Synthesized according to General Procedure A, using 89 mg (0.17 mmol) of amino-DHP reagent **1a**. White fluffy solid. 85% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.37-3.52 (*m*, 2H), 3.69 (*dd*, *J* 12.7, 3.6 Hz, 1H), 3.80-3.96 (*m*, 2H), 3.98-4.08 (*m*, 1H), 4.78 (*dd*, *J* 9.0, 3.6 Hz, 1H), 5.48-5.60 (*m*, 1H), 5.60-5.69 (*m*, 1H), 7.34-7.39 (*m*, 2H), 7.43-7.51 (*m*, 3H), 7.98 (*s*, 1H), 8.90 (*s*, 1H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 44.2, 48.9, 52.0, 64.7, 68.6, 123.9, 128.5, 129.4, 130.7, 130.9, 134.6, 138.8. ¹⁹**F-NMR**

(376 MHz, methanol- d_4), δ , ppm: -77.06 (s, 3F). **MS**: m/z calcd. for C₁₄H₁₈N₃O [M+H]⁺ 244.1, found 244.2.

2-(Naphthalen-2-yl)morpholine, TFA salt (4ai)



Synthesized according to General Procedure A, using 91 mg (0.18 mmol) of amino-DHP reagent **1a**. White fluffy solid. 81% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 3.46-3.54 (*m*, 1H), 3.61-3.71 (*m*, 1H), 3.93-4.04 (*m*, 2H), 4.22 (*ddd*, *J* 12.7, 8.8, 3.5 Hz, 2H), 5.43 (*dd*, *J* 10.6, 3.4 Hz, 1H), 7.57-7.64 (*m*, 2H), 7.66-7.73 (*m*, 2H), 8.00 (*t*, *J* 8.6 Hz, 2H), 8.25 (*d*, *J* 8.6 Hz, 1H). ¹³**C-NMR** (101 MHz, methanol-*d*₄), *δ*, ppm:

45.8, 56.0, 64.8, 70.6, 123.3, 125.4, 126.5, 127.9, 128.8, 130.0, 130.5, 131.7, 132.0, 135.7. ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -76.98 (*s*, 3F). **MS**: *m/z* calcd. for C₁₄H₁₆NO [M+H]⁺ 214.1, found 214.3.

tert-Butyl 4-(morpholin-3-yl)indoline-1-carboxylate, Free base (4al)



Synthesized according to General Procedure B, using 99 mg (0.17 mmol) of amino-DHP reagent **1a**. White fluffy solid. 70% yield. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.56 (*s*, 9H), 2.92-2.99 (*m*, 1H), 2.99-3.08 (*m*, 1H), 3.09-3.24 (*m*, 2H), 3.36-3.44 (*m*, 1H), 3.58-3.67 (*m*, 1H), 3.74-3.80 (*m*, 1H), 3.81-3.87

(*m*, 1H), 3.88-3.93 (*m*, 1H), 3.94-4.03 (*m*, 2H), 7.07 (*d*, *J* 7.7 Hz, 1H), 7.17 (*t*, *J* 8.0 Hz, 1H), 7.36-7.80 (*m*, 1H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 26.7, 28.8, 47.4, 58.5, 68.1, 72.8, 82.0, 115.1, 121.2, 129.1, 131.2, 137.4, 144.1, 154.3. MS: *m/z* calcd. for C₁₇H₂₅N₂O₃ [M+H]⁺ 305.2, found 305.3.

3-(6-Phenyl-2,3-dihydroimidazo[2,1-b]thiazol-5-yl)morpholine, Free base (4aw)



Synthesized according to General Procedure B, using 113 mg (0.20 mmol) of amino-DHP reagent **1a**. White fluffy solid. 79% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 2.85-2.96 (*m*, 2H), 3.56-3.70 (*m*, 2H), 3.76-3.83 (*m*, 2H), 3.85-3.90 (*m*, 2H), 4.18 (*dd*, *J* 10.6, 3.3 Hz, 1H), 4.38 (*dt*, *J* 11.3, 7.3 Hz, 1H), 4.63 (*dt*, *J* 11.3, 7.2 Hz, 1H), 7.28-7.34 (*m*, 1H), 7.39 (*t*, *J* 7.5 Hz, 2H), 7.43-7.51 (*m*, 2H). **MS**: *m/z* calcd. for C₁₅H₁₈N₃OS [M+H]⁺ 288.1, found 288.1.

3-(3-Phenylisoxazol-5-yl)morpholine, Free base (4ax)



Synthesized according to General Procedure B, using 125 mg (0.25 mmol) of amino-DHP reagent **1a**. White fluffy solid. 70% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 3.38-3.48 (*m*, 2H), 3.86-3.97 (*m*, 1H), 4.03-4.14 (*m*, 2H), 4.33 (*dd*, *J* 12.7, 3.7 Hz, 1H), 4.94 (*br. d*, *J* 3.7 Hz, 1H), 7.13 (*s*, 1H), 7.47-7.54 (*m*, 3H), 7.83-7.90 (*m*, 2H). ¹³**C-NMR** (101 MHz, methanol-*d*₄), *δ*, ppm: 44.3,

51.4, 64.9, 67.7, 104.1, 128.0, 129.5, 130.4, 131.9, 164.5, 165.8. **MS**: *m/z* calcd. for C₁₃H₁₅N₂O₂ [M+H]⁺ 231.1, found 231.1.

3-(Pyrazolo[1,5-a]pyridin-7-yl)morpholine, Free base (4ay)



Synthesized according to General Procedure B, using 82 mg (0.17 mmol) of amino-DHP reagent **1a**. White fluffy solid. 55% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 2.97-3.04 (*m*, 1H), 3.05-3.14 (*m*, 1H), 3.60-3.74 (*m*, 2H), 3.89 (*s*, 1H), 4.28 (*dd*, *J* 11.0, 3.1 Hz, 1H), 4.76 (*dd*, *J* 8.7, 3.0 Hz, 1H), 6.63 (*d*, *J* 2.2 Hz, 1H), 6.97 (*d*, *J* 7.0 Hz, 1H), 7.21 (*dd*, *J* 8.9, 7.0 Hz, 1H), 7.61 (*d*, *J* 8.8 Hz, 1H), 7.98 (*d*, *J* 2.2 Hz, 1H). **MS**:

m/z calcd. for C₁₁H₁₄N₃O [M+H]⁺ 204.1, found 204.2.

7-(4-Methoxyphenyl)-5-oxa-8-azaspiro[3.5]nonane, TFA salt (4ba)



Synthesized according to General Procedure A, using 90 mg (0.18 mmol) of amino-DHP reagent **1b**. White fluffy solid. 61% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 1.72-1.85 (*m*, 1H), 1.88-1.99 (*m*, 1H), 2.07-2.14 (*m*, 1H), 2.18 (*br. s*, 2H), 2.45 (*ddt*, *J* 12.1, 8.3, 4.0 Hz, 1H), 3.20 (*d*, *J* 12.1 Hz, 1H), 3.57 (*d*, *J* 12.8 Hz, 1H), 3.81 (*s*, 3H), 3.88-4.03 (*m*, 2H), 4.35 (*dd*, *J* 10.4, 3.9

Hz, 1H), 7.02 (*d*, *J* 8.8 Hz, 2H), 7.41 (*d*, *J* 8.8 Hz, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 13.1, 30.8, 32.6, 56.0, 58.7, 64.3, 75.2, 115.9, 125.4, 130.7, 162.6. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -76.93 (*s*, 3F). **MS**: *m/z* calcd. for C₁₄H₂₀NO₂ [M+H]⁺ 234.1, found 234.2.

7-(6-Phenyl-2,3-dihydroimidazo[2,1-b]thiazol-5-yl)-5-oxa-8-azaspiro[3.5]nonane, Free base (4bw)



Synthesized according to General Procedure B, using 127 mg (0.21 mmol) of amino-DHP reagent **1b**. White fluffy solid. 68% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 1.59-1.74 (*m*, 1H), 1.76-1.92 (*m*, 2H), 1.97-2.11 (*m*, 2H), 2.32-2.49 (*m*, 1 H), 2.70 (*dd*, *J* 11.6, 1.7 Hz, 1H), 3.07 (*br*. *d*, *J* 11.6 Hz, 1H), 3.60 (*br*. *dd*, *J* 11.3, 3.5 Hz, 1H), 3.66-3.74 (*m*, 1H), 3.90 (*br*. *t*, *J* 7.2 Hz, 2H), 4.14 (*dd*, *J* 10.8, 3.4 Hz, 1H), 4.34 (*dt*, *J* 11.3, 7.2 Hz, 1H), 4.64 (*dt*, *J* 11.3, 7.2 Hz, 1H), 7.28-7.35 (*m*, 1H), 7.41 (*br*. *t*, *J*

7.6 Hz, 2H), 7.45-7.55 (*m*, 2 H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 13.8, 31.4, 32.9, 36.2, 39.7, 52.6, 53.9, 65.9, 76.8, 127.0, 128.6, 129.2, 129.6, 135.7, 145.2, 151.7. **MS**: *m/z* calcd. for C₁₈H₂₂N₃OS [M+H]⁺ 328.1, found 328.2.

(S)-3-(4-Methoxyphenyl)-5-methylmorpholine, TFA salt (4ca)



Synthesized according to General Procedure A, using 72 mg (0.15 mmol) of amino-DHP reagent 1c. White fluffy solid. 68% yield, 8:1 dr. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.29 (d, J 6.5 Hz, 3H), 3.48-3.56 (m, 1H), 3.60 (dt, J 6.8, 3.5 Hz, 1H), 3.82 (s, 3H), 3.83-3.89 (m, 1H), 4.07 (dd, J 12.5, 3.2 Hz, 2H), 4.44 (dd, J 11.3, 3.4 Hz, 1H), 7.03 (d, J 8.7 Hz, 2H), 7.43 (d, J 8.80 Hz, 2H). ¹³C-

NMR (101 MHz, methanol- d_4), δ , ppm: 14.2, 54.0, 56.0, 60.7, 69.5, 70.2, 115.9, 125.5, 130.5, 162.6. ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -76.94 (*s*, 3F). **MS**: *m/z* calcd. for C₁₂H₁₈NO₂ [M+H]⁺ 208.1, found 208.2.

(2S)-2-Methyl-5-(6-phenyl-2,3-dihydroimidazo[2,1-b]thiazol-5-yl)morpholine, Free base (4dw)



Synthesized according to General Procedure B, using 115 mg (0.20 mmol) of amino-DHP reagent 1d. White fluffy solid. 69% yield, 14:1 dr. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.24 (d, J 6.2 Hz, 3H), 3.06 (dd, J 12.4, 11.2 Hz, 1H), 3.36 (dd, J 12.7, 1.9 Hz, 1H), 3.85-3.97 (m, 1H), 4.02-4.12 (m, 3H), 4.14-4.23 (m, 1H), 4.44-4.51 (m, 1H), 4.64 (dd, J 11.2, 3.7 Hz, 1H), 4.78 (dt, J 10.6, 6.7 Hz, 1H), 7.47-7.56 (m, 5H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 18.5, 36.7, 50.2, 51.0, 51.7, 67.8, 71.2, 120.4, 129.2, 130.1, 130.3, 132.2, 146.7, 154.9. **MS**: m/z calcd. for

 $C_{16}H_{20}N_3OS [M+H]^+ 302.1$, found 302.2.

(2S)-5-(4-Methoxyphenyl)-2-phenylmorpholine, Free base (4ea)



Synthesized according to General Procedure B, using 100 mg (0.18 mmol) of amino-DHP reagent **1e**. White fluffy solid. 77% yield, >14:1 dr. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 2.87 (*dd*, *J* 12.5, 10.6 Hz, 1H), 3.13 (*dd*, *J* 12.5, 2.5 Hz, 1H), 3.59-3.66 (*m*, 1H), 3.78 (*s*, 3H), 3.90 (*dd*, *J* 10.5, 3.2 Hz, 1H), 3.98 (*dd*, *J* 11.1, 3.3 Hz, 1H), 4.57 (*dd*, *J* 10.6, 2.4 Hz, 1H), 6.86-6.98 (*m*, 2H), 7.26-7.31 (*m*, 1H), 7.32-7.37 (*m*, 4H), 7.38-7.43 (*m*, 2H). ¹³C-NMR (101 MHz,

methanol- d_4), δ , ppm: 54.4, 55.8, 60.3, 74.6, 79.6, 115.1, 127.4, 129.0, 129.45, 129.51, 133.0, 141.7, 161.0. **MS**: *m/z* calcd. for C₁₇H₂₀NO₂ [M+H]⁺ 270.1, found 270.4.

tert-Butyl (S)-2,2-dimethyl-4-((3R,6S)-6-phenylmorpholin-3-yl)oxazolidine-3-carboxylate, Free base (4eß)



Synthesized according to General Procedure B, using 112 mg (0.17 mmol) of amino-DHP reagent **1e**. White fluffy solid. 58% yield, >14:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 1.46-1.50 (*m*, 3H), 1.52 (*s*, 9H), 1.59 (*s*, 3H) 2.74 (*br. t, J* 11.7 Hz, 1H), 3.06 (*br. dd, J* 12.5, 2.1 Hz, 1H), 3.21-3.28 (*m*, 1H), 3.51-

3.59 (*m*, 1H), 3.77-4.03 (*m*, 4 H), 4.15 (*br. s*, 1H), 4.42 (*dd*, *J* 10.6, 2.3 Hz, 1H), 7.30-7.37 (*m*, 5H). ¹³C-NMR (101 MHz, methanol-*d*₄), δ, ppm: 22.7, 24.1, 26.4, 27.4, 28.8, 54.1, 54.5, 56.7, 57.2, 58.3, 60.0, 60.2, 64.5, 64.7, 65.8, 70.2, 71.7, 72.0, 80.1, 81.9, 82.1, 95.2, 95.4, 127.3, 129.0, 129.5, 141.6, 154.0, 154.6. MS: *m/z* calcd. for C₂₀H₃₁N₂O₄ [M+H]⁺ 363.2, found 363.4.

rac-(3R,4S,7S)-3-(4-Methoxyphenyl)hexahydro-2H-furo[3,4-b][1,4]oxazine, TFA salt (4fa)



Synthesized according to General Procedure A, using 97 mg (0.19 mmol) of amino-DHP reagent **1f**. White fluffy solid. 55% yield, 9:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.82 (*s*, 3H), 3.83-3.92 (*m*, 2H), 4.00-4.18 (*m*, 5H), 4.39-4.55 (*m*, 2H), 7.03 (*d*, *J* 8.7 Hz, 2H), 7.47 (*d*, *J* 8.8 Hz, 2H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 55.9, 57.56, 57.59, 68.1, 69.7, 73.1, 75.5, 115.4, 129.9, 132.2, 161.4. ¹⁹**F-NMR** (376 MHz, methanol- d_4), δ , ppm: -76.93 (*s*, 3F).

MS: m/z calcd. for C₁₃H₁₈NO₃ [M+H]⁺ 236.1, found 236.3.

rac-tert-Butyl 3-((3R,4S,7S)-hexahydro-2H-furo[3,4-b][1,4]oxazin-3-yl)-1H-indole-1-carboxylate, Free base (4fe)



Synthesized according to General Procedure B, using 173 mg (0.28 mmol) of amino-DHP reagent **1f**. White fluffy solid. 50% yield, 8:1 dr. ¹**H-NMR** (400 MHz, methanol-*d*₄), δ, ppm: 1.68 (*s*, 9H), 3.53 (*td*, *J* 5.0, 1.8 Hz, 1H), 3.71-3.86 (*m*, 4H) 3.91 (*dd*, *J* 9.4, 4.8 Hz, 1H), 4.10 (*dd*, *J* 8.9, 6.7 Hz, 1H), 4.21 (*dd*, *J* 8.6, 4.2 Hz, 1H), 4.36-4.42 (*m*, 1H), 4.57 (*s*, 2H), 7.23-7.28 (*m*, 1H), 7.30-7.35 (*m*,

1H), 7.67-7.72 (*m*, 2H), 8.13 (*d*, *J* 8.2 Hz, 1H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 28.6, 50.8, 56.6, 67.8, 68.2, 73.9, 75.6, 85.2, 116.4, 120.6, 122.0, 123.9, 124.2, 125.8, 130.4, 137.1, 151.1. MS: *m/z* calcd. for C₁₉H₂₅N₂O₄ [M+H]⁺ 345.2, found 345.3.

rac-(3R,4S,7R)-3-(4-Methoxyphenyl)hexahydro-2H-furo[3,4-b][1,4]oxazine, Free base (4ga)



Synthesized according to General Procedure B, using 89 mg (0.17 mmol) of amino-DHP reagent **1g**. White fluffy solid. 66% yield, >14:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.16 (*ddd*, *J* 10.7, 9.2, 7.3 Hz, 1H), 3.50-3.65 (*m*, 3H), 3.68-3.75 (*m*, 1H), 3.78 (*s*, 3H), 3.90 (*dd*, *J* 11.5, 3.6 Hz, 1H), 3.93-4.01 (*m*, 3H), 6.90 (*d*, *J* 8.8 Hz, 2H), 7.35 (*d*, *J* 8.7 Hz, 2H). ¹³**C-NMR** (101 MHz,

methanol- d_4), δ , ppm: 55.8, 61.4, 62.4, 68.0, 69.3, 74.9, 81.4, 115.1, 129.8, 132.5, 161.1. **MS**: *m/z* calcd. for C₁₃H₁₈NO₃ [M+H]⁺ 236.1, found 236.5.

rac-(3R,4S,7R)-3-(4-Methoxyphenyl)-6-tosyloctahydropyrrolo[3,4-b][1,4]oxazine, Free base (4ha)



Synthesized according to General Procedure B, using 100 mg (0.15 mmol) of amino-DHP reagent **1h**. White fluffy solid. 69% yield, 10:1 dr. ¹H-NMR (400 MHz, methanol-*d*₄), δ, ppm: 2.47 (*s*, 3H), 3.17-3.29 (*m*, 2H), 3.42-3.52 (*m*, 1H), 3.73-3.88 (*m*, 6H), 3.96-4.05 (*m*, 1H), 4.15 (*dd*, *J* 13.0, 3.9 Hz, 1H), 4.49 (*dd*, *J* 11.4, 3.8 Hz, 1H), 7.00 (*d*, *J* 8.8 Hz, 2H), 7.38 (*d*, *J* 8.7

Hz, 2H), 7.48 (*d*, *J* 8.1 Hz, 2H), 7.78 (*d*, *J* 8.2 Hz, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 21.7, 46.7, 49.4, 56.0, 58.3, 61.0, 70.5, 76.5, 116.0, 124.7, 128.8, 130.6, 131.4, 135.1, 146.1, 162.7. MS: *m/z* calcd. for C₂₀H₂₅N₂O₄S [M+H]⁺ 389.2, found 389.3.

rac-(3R,4S,7R)-3-(1-Methyl-1H-pyrazol-5-yl)-6-tosyloctahydropyrrolo[3,4-b][1,4]oxazine, Free base (4hp)



Synthesized according to General Procedure B, using 101 mg (0.16 mmol) of amino-DHP reagent **1h**. White fluffy solid. 57% yield, 7:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 2.48 (*s*, 3H), 2.80 (*ddd*, *J* 10.7, 9.5, 7.3 Hz, 1H), 2.96-3.02 (*m*, 1H), 3.04-3.11 (*m*, 1H), 3.32-3.39 (*m*, 1H), 3.45-3.54 (*m*, 1H),

3.59-3.71 (*m*, 2H), 3.87 (*s*, 3H), 3.93 (*dd*, *J* 11.5, 3.4 Hz, 1H), 4.14 (*dd*, *J* 10.7, 3.5 Hz, 1H), 6.28 (*d*, *J* 1.8 Hz, 1H), 7.39 (*d*, *J* 1.7 Hz, 1H), 7.48 (*d*, *J* 8.1 Hz, 2H), 7.78 (*d*, *J* 8.2 Hz, 2H). ¹³C-NMR (101 MHz, methanol-*d*₄), δ, ppm: 21.8, 37.0, 39.8, 50.1, 52.6, 60.6, 72.0, 79.6, 105.7, 128.8, 131.3, 135.3, 139.3, 142.0, 145.6. MS: *m/z* calcd. for C₁₇H₂₃N₄O₃S [M+H]⁺ 363.1, found 363.2.

rac-(3R,4S,7S)-3-(1-Methyl-1H-indol-2-yl)-6-tosyloctahydropyrrolo[3,4-b][1,4]oxazine, Free base (4iz)



Synthesized according to General Procedure B, using 158 mg (0.23 mmol) of amino-DHP reagent **1i**. White fluffy solid. 60% yield, 6:1 dr. ¹H-NMR (400 MHz, methanol-*d*₄), δ, ppm: 2.53 (*s*, 3H), 2.86 (*td*, *J* 10.0, 7.4 Hz, 1H), 3.02-3.09 (*m*, 1H), 3.12 (*t*, *J* 9.7 Hz, 1H), 3.38-3.47 (*m*, 1H), 3.62 (*t*, *J* 11.0 Hz, 1H), 3.66-3.76 (*m*, 2H), 3.82 (*s*, 3H), 4.08 (*dd*, *J* 11.4, 3.4 Hz,

1H), 4.21 (*s*, 1H), 4.26 (*dd*, *J* 10.6, 3.2 Hz, 1H), 6.50 (*s*, 1H), 7.04-7.12 (*m*, 1H), 7.20 (*t*, *J* 7.3 Hz, 1H), 7.45 (*d*, *J* 8.2 Hz, 1H), 7.55 (*d*, *J* 8.0 Hz, 3H), 7.85 (*d*, *J* 8.2 Hz, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 22.0, 30.7, 49.7, 50.3, 53.5, 60.8, 72.7, 79.6, 100.8, 110.7, 120.7, 121.6, 122.7, 128.8, 128.9, 131.4, 135.4, 139.0, 139.5, 145.5. MS: *m/z* calcd. for C₂₂H₂₅N₃O₃S [M+H]⁺ 412.2, found 412.4.

3-(4-Methoxyphenyl)thiomorpholine, TFA salt (4ja)



Synthesized according to General Procedure A, using 115 mg (0.24 mmol) of amino-DHP reagent **1j**. White fluffy solid. 73% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 2.76-2.87 (*m*, 2H), 3.11-3.20 (*m*, 1H), 3.32-3.40 (*m*, 1H), 3.42-3.52 (*m*, 1H), 3.70-3.76 (*m*, 1H), 3.83 (*br. s*, 3H), 4.44 (*dd*, *J* 11.7, 2.3 Hz, 1H), 4.89 (*s*, 5H), 7.0 (*d*, *J* 8.8 Hz, 2H), 7.42 (*d*, *J* 8.8 Hz, 2H). ¹³**C-NMR** (101 MHz, methanol-*d*₄), *δ*, ppm: 24.7, 31.6, 48.6, 56.0, 62.8, 115.9, 129.81, 129.84, 162.4. ¹⁹**F-NMR** (376 MHz,

methanol- d_4), δ , ppm: -76.92 (s, 3F). **MS**: m/z calcd. for C₁₁H₁₆NOS [M+H]⁺ 210.1, found 210.3.

3-(1-Benzyl-1H-imidazol-5-yl)thiomorpholine, Free base (4jq)



Synthesized according to General Procedure B, using 99 mg (0.18 mmol) of amino-DHP reagent **1j**. White fluffy solid. 79% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), δ, ppm: 2.21 (*br. d, J* 13.3 Hz, 1H), 2.32 (*br. dd, J* 13.5, 1.8 Hz, 1H), 2.66-2.78 (*m*, 2H), 2.87-2.96 (*m*, 1H), 3.27 (*dt, J* 12.8, 2.8 Hz, 1H), 3.85 (*dd, J* 10.5, 2.2 Hz, 1H), 5.32 (*s*, 2H), 7.00 (*s*, 1H), 7.18 (*d, J* 7.2 Hz, 2H), 7.31-7.40 (*m*, 3H), 7.73 (*s*, 1H). ¹³**C-NMR** (101 MHz,

methanol- d_4), δ , ppm: 27.6, 33.0, 49.5, 49.9, 53.9, 126.9, 128.3, 129.4, 130.3, 135.6, 138.4, 139.5. **MS**: m/z calcd. for C₁₄H₁₈N₃S [M+H]⁺: 260.1, found 260.1.

3-(Pyrazolo[1,5-a]pyridin-7-yl)thiomorpholine, Free base (4jy)



Synthesized according to General Procedure B, using 80 mg (0.16 mmol) of amino-DHP reagent **1j**. White fluffy solid. 61% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 2.50 (*br. d, J* 13.6 Hz, 1H), 2.87-3.00 (*m*, 3H), 3.20 (*td, J* 12.3, 2.5 Hz, 1H), 3.47 (*dt, J* 12.8, 3.0 Hz, 1H), 4.76 (*dd, J* 8.6, 4.1 Hz, 1H), 6.63 (*d, J* 2.2 Hz, 1H), 6.92 (*d, J* 7.0 Hz, 1H), 7.21 (*dd, J* 8.8, 7.1 Hz, 1H), 7.60 (*d, J* 8.9 Hz, 1H), 7.98 (*d, J* 2.3 Hz, 1H). ¹³C-NMR (101 MHz, methanol-*d*₄), *δ*, ppm: 25.2, 28.2, 48.4, 59.1, 99.6, 113.3, 121.0, 124.7, 135.2, 142.4, 143.1. MS: *m/z* calcd. for C₁₁H₁₄N₃S [M+H]⁺ 220.1, found 220.0. *rac-3-(4-Methoxyphenyl)-5-methylthiomorpholine*, *Free base (4ka)*



Synthesized according to General Procedure B, using 87 mg (0.17 mmol) of amino-DHP reagent **1k**. White fluffy solid. 63% yield, >14:1 dr. ¹H-NMR (400 MHz, methanol-*d*₄), *δ*, ppm: 1.16 (*d*, *J* 6.4 Hz, 3H), 2.36-2.43 (*m*, 2H), 2.45-2.53 (*m*, 1H), 2.73 (*dd*, *J* 13.3, 11.0 Hz, 1H), 3.04-3.14 (*m*, 1H), 3.77 (*s*, 3H), 3.91 (*dd*, *J* 10.9, 2.1 Hz, 1H), 6.89 (*d*, *J* 8.7 Hz, 2H), 7.30 (*d*, *J* 8.6 Hz,

2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 21.2, 32.4, 32.7, 54.3, 54.6, 63.1, 113.5, 127.5, 135.8, 159.2. MS: m/z calcd. for C₁₂H₁₈NOS [M+H]⁺ 224.1, found 224.1.

rac-(3S,5R)-3-Methyl-5-(1-methyl-1H-pyrazol-5-yl)thiomorpholine, Free base (4kp)



Synthesized according to General Procedure B, using 86 mg (0.18 mmol) of amino-DHP reagent **1k**. White fluffy solid. 65% yield, >14:1 dr. ¹H-NMR (400 MHz, methanol- d_4), δ , ppm: 1.42 (d, J 6.6 Hz, 3H), 2.80-2.87 (m, 1H), 2.90-3.00 (m, 2H), 3.21 (dd, J 14.6, 11.6 Hz, 1H), 3.72-3.83 (m, 1H), 3.96 (s, 3H), 4.82 (dd, J 11.6, 2.6 Hz, 1H), 6.56 (d, J 2.0 Hz, 1H), 7.52 (d, J 1.8 Hz, 1H). ¹³C-NMR (101 MHz, methanol- d_4),

 δ , ppm: 19.6, 30.4, 31.1, 37.2, 55.2, 57.7, 106.4, 139.5, 140.0. **MS**: *m*/*z* calcd. for C₉H₁₆N₃S [M+H]⁺ 198.1, found 198.1.

rac-5-(4-Methoxyphenyl)-2-methylthiomorpholine, Free base (4la)



Synthesized according to General Procedure B, using 93 mg (0.19 mmol) of amino-DHP reagent **11**. White fluffy solid. 70% yield, 11:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 1.13 (d, J 6.7 Hz, 3H), 2.47 (dd, J 13.4, 2.1 Hz, 1H), 2.71 (dd, J 12.4, 10.9 Hz, 1H), 2.85-2.92 (m, 1H), 2.93-3.02 (m, 1H), 3.31-3.36 (m, 1H), 3.72-3.76 (m, 1H), 3.77 (s, 3H), 6.85-6.91 (m, 2H), 7.28 (d, d, d and d and

J 8.7 Hz, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 18.8, 35.8, 36.0, 55.8, 57.9, 62.8, 115.1, 128.9, 136.9, 160.8. MS: m/z calcd. for C₁₂H₁₈NOS [M+H]⁺ 224.1, found 224.1.

rac-tert-butyl 4-((3R,6S)-6-Methylthiomorpholin-3-yl)indoline-1-carboxylate, Free base (4ll)



Synthesized according to General Procedure B, using 104 mg (0.17 mmol) of amino-DHP reagent **11**. White fluffy solid. 73% yield, 13:1 dr. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 1.13 (*d*, *J* 6.7 Hz, 3H), 1.56 (*s*, 9H), 2.48 (*dd*, *J* 13.5, 2.0 Hz, 1H), 2.7 (*dd*, *J* 12.5, 10.9 Hz, 1H), 2.88 (*dd*, *J* 13.5, 10.9 Hz, 1H), 2.94-3.04 (*m*, 1H), 3.06-3.20 (*m*, 2H), 3.33 (*br. d*, *J* 2.7 Hz, 1H), 3.83

(*dd*, *J* 10.8, 2.1 Hz, 1H), 3.91-4.03 (*m*, 2H), 7.01 (*d*, *J* 7.7 Hz, 1H), 7.16 (*t*, *J* 7.9 Hz, 1H), 7.66 (*br. s*, 1H). ¹³C-

NMR (101 MHz, methanol-*d*₄), δ, ppm: 18.8, 26.8 (*br. s*), 28.8, 34.7, 35.9, 57.8, 60.1, 82.1 (*br. s*), 114.9 (*br. s*), 120.3, 129.2, 130.5 (*br. s*), 140.7 (*br. s*), 144.1 (*br. s*), 154.2 (*br. s*). **MS**: *m/z* calcd. for C₁₈H₂₇N₂O₂S [M+H]⁺ 335.2, found 335.3.

(2S,5R)-5-(6-(4-Methoxyphenyl)pyridin-2-yl)-2-methylthiomorpholine, Free base (4ly)



Synthesized according to General Procedure B, using 145 mg (0.25 mmol) of amino-DHP reagent **11**. White fluffy solid. 75% yield, >14:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 1.23 (d, J 6.4 Hz, 3H), 2.40-2.56 (m, 2H), 2.68-2.81 (m, 2H), 3.06-3.21 (m, 1H), 3.84 (s, 3H), 4.14

(*dd*, *J* 10.3, 3.2 Hz, 1H), 6.99-7.04 (*m*, 2H), 7.28 (*d*, *J* 7.6 Hz, 1H), 7.68 (*d*, *J* 7.8 Hz, 1H), 7.74-7.82 (*m*, 1H), 7.97-8.03 (*m*, 2H). ¹³**C-NMR** (101 MHz, methanol-*d*₄), δ, ppm: 22.8, 32.8, 34.0, 55.2, 55.9, 64.6, 115.2, 119.9, 129.5, 133.1, 139.2, 158.0, 162.1, 162.3. **MS**: *m/z* calcd. for C₁₇H₂₁N₂OS [M+H]⁺ 301.1, found 301.2.

Benzyl 3-(4-methoxyphenyl)piperazine-1-carboxylate, Free base (4ma)



Synthesized according to General Procedure B, using 108 mg (0.18 mmol) of amino-DHP reagent **1m**. White fluffy solid. 80% yield. ¹H-NMR (400 MHz, methanol-*d*₄), *δ*, ppm: 2.88 (*br. s*, 2H), 2.92-3.08 (*m*, 2H), 3.61 (*br. d*, *J* 9.1 Hz, 1H), 3.76 (*s*, 3H), 4.07 (*br. d*, *J* 10.0 Hz, 2H), 5.14 (*s*, 2H), 6.89 (*br. d*, *J* 8.6 Hz, 2H), 7.25-7.39 (*m*, 7H). ¹³C-NMR (101 MHz, methanol-*d*₄), *δ*, ppm: 44.9 (*br. d*, *J* 22 Hz), 46.8, 51.9 (*br. d*, *J* 19.8 Hz), 55.8, 60.7, 68.5, 115.1, 129.1, 129.25, 129.31,

129.7, 134.1, 138.2, 157.0, 161.0. **MS**: m/z calcd. for C₁₉H₂₃N₂O₃ [M+H]⁺ 327.2, found 327.2.

Benzyl 3-(5-bromopyridin-3-yl)piperazine-1-carboxylate, Free base (4mr)



Synthesized according to General Procedure B, using 112 mg (0.17 mmol) of amino-DHP reagent **1m**. White fluffy solid. 73% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 2.76-3.08 (*m*, 4H), 3.78 (*br. dd*, *J* 10.5, 2.5 Hz, 1H), 4.08 (*br. t*, *J* 12.5 Hz, 2H), 5.14 (*s*, 2H), 7.25-7.42 (*m*, 5H), 8.09 (*br. s*, 1H), 8.51-8.61 (*m*, 2H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 45.1 (*br. s*), 46.4 (*br. s*), 51.2 (*br. s*), 58.1, 68.7, 122.1, 129.1, 129.4, 129.7, 138.1, 139.5, 140.5, 148.1, 151.0, 156.9. **MS**: *m/z* calcd.

for C₁₇H₁₈BrN₃O₂ [M+H]⁺ 376.1, found 376.3.

Benzyl 3-cyclopropylpiperazine-1-carboxylate, Free base (4ma)



Synthesized according to General Procedure B, using 76 mg (0.14 mmol) of amino-DHP reagent **1m**. White fluffy solid. 61% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 0.43 (*br. s*, 1H), 0.54 (*br. dd*, *J* 9.4, 4.5 Hz, 1H), 0.65-0.80 (*m*, 2H), 0.90-1.01 (*m*, 1H), 2.51 (*td*, *J* 10.2, 3.6 Hz, 1H), 3.06 (*td*, *J* 12.0, 3.4 Hz, 1H), 3.20-3.29 (*m*, 1H), 3.31-3.44 (*m*, 2H), 4.10-

4.32 (*m*, 2H), 5.10-5.20 (*m*, 2H), 7.30-7.40 (*m*, 5H). ¹³C-NMR (101 MHz, methanol-*d*₄), δ, ppm: 4.1, 11.7, 41.7 (*br. s*), 44.2 (*br. s*), 46.9 (*br. s*), 61.3, 69.1, 129.4, 129.5, 129.8, 137.8, 156.4. MS: *m/z* calcd. for C₁₅H₂₁N₂O₂ [M+H]⁺ 261.2, found 261.2.

Benzyl 3-(3-phenylisoxazol-5-yl)piperazine-1-carboxylate, Free base (4mx)



Synthesized according to General Procedure B, using 98 mg (0.15 mmol) of amino-DHP reagent **1m**. White fluffy solid. 83% yield. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 3.31-3.36 (*m*, 1H), 3.40-3.51 (*m*, 1H), 3.51-3.62 (*m*, 1H), 3.82 (*q*, *J* 6.5 Hz, 2H), 4.17 (*br. d*, *J* 14.4 Hz, 1H), 4.44 (*br. d*, *J* 13.8 Hz, 1H), 4.87 (*dd*, *J* 9.4, 3.7 Hz, 1H), 5.11-5.26 (*m*, 2H), 7.11 (*s*, 1H), 7.27-7.42 (*m*, 5H), 7.46-7.54 (*m*, 3H), 7.78-7.89 (*m*, 2H). ¹³**C-NMR** (101 MHz, methanol- d_4), δ , ppm: 41.8 (*br. s*), 44.0, 45.1 (*br. s*),

51.2 (*br. s*), 69.3, 104.0, 128.1, 129.4, 129.5, 129.6, 129.8, 130.4, 131.9, 137.7, 156.3, 164.5, 166.3. **MS**: m/z calcd. for C₂₁H₂₂N₃O₃ [M+H]⁺ 364.2, found 364.3.

3-(4-Methoxyphenyl)-1-tosylpiperazine, Free base (4na)



Synthesized according to General Procedure B, using 73 mg (0.12 mmol) of amino-DHP reagent **1n**. White fluffy solid. 76% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), δ, ppm: 2.17 (*t*, *J* 10.9 Hz, 1H), 2.37 (*td*, *J* 11.5, 3.1 Hz, 1H), 2.44 (*s*, 3H), 2.94 (*td*, *J* 12.0, 3.1 Hz, 1H), 3.02-3.14 (*m*, 1H), 3.58-3.70 (*m*, 2H), 3.73-3.80 (*m*, 4H), 6.88 (*d*, *J* 8.7 Hz, 2H), 7.23 (*d*, *J* 8.7 Hz, 2H), 7.42 (*d*, *J* 8.1 Hz, 2H), 7.63 (*d*, *J* 8.2 Hz, 2H). ¹³**C-NMR** (101 MHz, methanol-*d*₄), δ, ppm: 21.6, 46.4, 47.1, 54.0, 55.8, 60.4,

115.2, 129.1, 129.3, 131.1, 133.8, 134.1, 145.6, 161.1. **MS**: m/z calcd. for $C_{18}H_{23}N_2O_3S$ [M+H]⁺ 347.1, found 347.2.

(5S)-3-(4-Methoxyphenyl)-5-methyl-1-tosylpiperazine, Free base (40a)



Synthesized according to General Procedure B, using 95 mg (0.15 mmol) of amino-DHP reagent **10**. White fluffy solid. 86% yield, 10:1 dr. ¹**H-NMR** (400 MHz, methanol-*d*₄), δ, ppm: 1.11 (*d*, *J* 6.2 Hz, 3H), 1.94 (*t*, *J* 10.8 Hz, 1H), 2.04-2.12 (*m*, 1H), 2.48 (*s*, 3H), 3.01 (*ddd*, *J* 9.8, 6.5, 2.9 Hz, 1H), 3.65 (*br. t*, *J* 11.4 Hz, 2H), 3.78-3.90 (*m*, 4H), 6.93 (*m*, *J* 8.6 Hz, 2H), 7.32 (*d*, *J* 8.6 Hz, 2H), 7.48 (*m*, *J* 8.0 Hz,

2H), 7.67 (*d*, *J* 8.1 Hz, 2H). ¹³C-NMR (101 MHz, methanol-*d*₄), δ, ppm: 19.4, 21.9, 52.0, 53.2, 53.7, 56.0, 60.5, 115.2, 129.1, 129.5, 131.2, 134.1, 134.3, 145.5, 160.8. **MS**: *m*/*z* calcd. for C₁₉H₂₅N₂O₃S [M+H]⁺ 361.2, found 361.4.

1-Methyl-6-((6S)-6-methyl-4-tosylpiperazin-2-yl)-1H-indole, TFA salt (40s)



Synthesized according to General Procedure A, using 91 mg (0.14 mmol) of amino-DHP reagent **10**. White fluffy solid. 64% yield, 12:1 dr. ¹**H-NMR** (400 MHz, methanol-*d*₄), δ, ppm: 1.38 (*d*, *J* 6.6 Hz, 3H), 2.46 (*s*, 3H), 2.54 (*dd*, *J* 12.8, 11.6 Hz, 1H), 2.92 (*t*, *J* 12.4 Hz, 1H), 3.64-3.73 (*m*, 1H), 3.82 (*s*, 3H), 4.07 (*br. d*, *J* 13.1 Hz, 2H), 4.63 (*dd*, *J* 11.4, 3.1 Hz, 1H), 6.47 (*d*, *J* 2.8 Hz, 1H), 7.09 (*dd*, *J* 8.3, 1.3 Hz, 2H), 4.63 (*dd*, *J* 11.4, 3.1 Hz, 1H), 6.47 (*d*, *J* 2.8 Hz, 1H), 7.09 (*dd*, *J* 8.3, 1.3 Hz, 2H), 4.63 (*dd*, *J* 11.4, 3.1 Hz, 1H), 6.47 (*d*, *J* 2.8 Hz, 1H), 7.09 (*dd*, *J* 8.3, 1.3 Hz, 2H), 4.63 (*dd*, *J* 11.4, 3.1 Hz, 1H), 6.47 (*d*, *J* 2.8 Hz, 1H), 7.09 (*dd*, *J* 8.3, 1.3 Hz, 2H), 4.63 (*dd*, *J* 11.4, 3.1 Hz, 1H), 6.47 (*d*, *J* 2.8 Hz, 1H), 7.09 (*dd*, *J* 8.3, 1.3 Hz, 2H), 4.63 (*dd*, *J* 11.4, 3.1 Hz, 1H), 6.47 (*d*, *J* 2.8 Hz, 1H), 7.09 (*dd*, *J* 8.3, 1.3 Hz, 2H), 4.63 (*dd*, *J* 11.4, 3.1 Hz, 1H), 6.47 (*d*, *J* 2.8 Hz, 1H), 7.09 (*dd*, *J* 8.3, 1.3 Hz, 2H), 4.63 (*dd*, *J* 8.3, 1.3 Hz, 3H), 4.64 (*dd*, *J* 8.3, 1.3 Hz, 3H), 4.65 (*dd*, *J* 8.3, 1.3 Hz), 4.65 (*dd*, *J* 8.3 Hz),

1H), 7.27 (*d*, *J* 3.2 Hz, 1H), 7.47 (*m*, *J* 8.1 Hz, 2H), 7.51-7.56 (*m*, 1H), 7.63 (*d*, *J* 8.2 Hz, 1H), 7.73 (*d*, *J* 8.2 Hz, 2H). ¹³C-NMR (101 MHz, methanol- d_4), δ , ppm: 15.9, 21.7, 33.1, 49.8, 50.1, 54.2, 62.1, 102.1, 110.1, 119.2, 122.8, 126.8, 129.1, 131.5, 131.5, 132.4, 134.0, 138.2, 146.3. ¹⁹F-NMR (376 MHz, methanol- d_4), δ , ppm: -76.88 (s, 3F). MS: *m/z* calcd. for C₂₁H₂₆N₃O₂S [M+H]⁺ 384.2, found 384.3.

(5S)-3-Cyclopropyl-5-methyl-1-tosylpiperazine, Free base (40a)



Synthesized according to General Procedure B, using 76 mg (0.13 mmol) of amino-DHP reagent **10**. White fluffy solid. 55% yield, 13:1 dr. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 0.21-0.34 (*m*, 2H), 0.46-0.54 (*m*, 2H), 0.61 (*dt*, *J* 12.2, 4.4 Hz, 1H), 1.04 (*d*, *J* 6.4 Hz, 3H), 1.83 (*t*, *J* 10.9 Hz, 1H), 1.87-1.95 (*m*, 1H), 1.97-2.07 (*m*, 1H), 2.44 (*s*, 3H), 2.79 (*dq*, *J* 10.0, 6.5, 3.0 Hz, 1H), 3.57 (*dt*, *J* 11.1, 2.2 Hz, 1H), 3.68 (*dd*, *J* 10.9, 2.2 Hz, 1H),

7.43 (*m*, *J* 8.1 Hz, 2H), 7.65 (*d*, *J* 8.2 Hz, 2H). ¹³**C-NMR** (101 MHz, methanol-*d*₄), δ , ppm: 2.8, 3.7, 14.8, 19.0, 21.6, 51.6, 51.8, 53.3, 62.0, 129.1, 131.0, 134.1, 145.6. **MS**: *m*/*z* calcd. for C₁₅H₂₃N₂O₂S [M+H]⁺ 295.1, found 295.1.

rac-5-(4-Methoxyphenyl)-2-methyl-1-tosylpiperazine, Free base (4pa)



Synthesized according to General Procedure B, using 96 mg (0.15 mmol) of amino-DHP reagent **1p**. White fluffy solid. 66% yield, 7:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 1.24 (d, J 7.2 Hz, 3H), 2.46 (s, 3H), 3.28 (s, 1H), 3.33-3.40 (m, 1H), 3.61 (dd, J 14.6, 11.9 Hz, 1H), 3.82 (s, 3H), 4.02 (dd, J 14.6, 3.6 Hz, 1H), 4.20 (dd, J 11.9, 3.7 Hz, 1H), 4.50 (quint., J 6.0 Hz, 1H), 6.99-7.07 (m, 2H), 7.37-7.51 (m, 4H), 7.79 (d, J 8.3 Hz, 2H). ¹³C-NMR (101 MHz,

methanol- d_4), δ , ppm: 14.6, 21.7, 43.2, 47.2, 48.9, 56.0, 59.7, 116.0, 126.0, 128.5, 130.5, 131.5, 138.4, 146.0, 162.8. **MS**: m/z calcd. for C₁₉H₂₅N₂O₃S [M+H]⁺ 361.2, found 361.2.

rac-5-(5-Methyl-4-tosylpiperazin-2-yl)isoquinoline, Free base (4pj)



Synthesized according to General Procedure B, using 102 mg (0.15 mmol) of amino-DHP reagent **1p**. White fluffy solid. 59% yield, >14:1 dr. ¹**H-NMR** (400 MHz, methanol- d_4), δ , ppm: 1.27 (*d*, *J* 6.9 Hz, 3H), 2.45 (*s*, 3H), 2.98-3.13 (*m*, 2H), 3.23 (*dd*, *J* 12.4, 3.9 Hz, 1H), 3.80 (*dd*, *J* 13.3, 2.9 Hz, 1H), 4.24-4.34 (*m*, 1H), 4.44 (*dd*, *J* 10.8, 2.9 Hz, 1H), 7.43 (*d*, *J* 8.1 Hz, 2H), 7.68-7.78 (*m*, 3H), 7.90 (*d*, *J* 6.1 Hz, 1H), 8.06 (*dd*, *J* 13.8, 7.70 Hz, 2H), 8.48 (*d*, *J* 6.1 Hz, 1H), 9.26 (*s*, 1H). ¹³**C-NMR** (101 MHz, methanol-*d*₄), δ, ppm: 15.1, 21.6, 47.3, 49.7, 52.0, 56.9, 117.7, 128.5, 128.9, 129.5, 130.2, 130.5, 131.2, 135.1, 136.9, 139.4, 143.4, 145.4, 154.35. **MS**: *m/z* calcd. for C₂₁H₂₄N₃O₂S [M+H]⁺ 382.2, found 382.2.

3-(Benzo[b]thiophen-2-yl)-1,4-oxazepane, Free base (4qu)



Synthesized according to General Procedure B, using 120 mg (0.23 mmol) of amino-DHP reagent **1q**. White fluffy solid. 59% yield. ¹**H-NMR** (400 MHz, methanol-*d*₄), *δ*, ppm: 1.99-2.08 (*m*, 2H), 3.08 (*ddd*, *J* 13.6, 8.4, 5.0 Hz, 1H), 3.26 (*dt*, *J* 13.9, 5.0 Hz, 1H), 3.79-3.89 (*m*, 2H), 3.92-3.99 (*m*, 1H), 4.11 (*dd*, *J* 12.8, 3.8 Hz, 1H), 4.5 (*dd*, *J* 8.7, 3.7 Hz, 1H), 7.27-7.38 (*m*, 3H), 7.72-7.78 (*m*, 1H), 7.80-7.85 (*m*, 1H). ¹³**C-NMR** (101

MHz, methanol- d_4), δ , ppm: 32.7, 46.4, 62.0, 71.1, 77.1, 123.2, 123.4, 124.7, 125.6, 140.9, 141.1, 144.3. **MS**: m/z calcd. for C₁₃H₁₆NOS [M+H]⁺ 234.1, found 234.1.

NMR and Mass Spectra

Starting Materials

Morpholine-Forming Amino-DHP Reagents N,N-Dibenzyl-2-(2,2-dimethoxyethoxy)ethan-1-amine



2-(2-(Dibenzylamino)ethoxy)acetaldehyde



Diethyl 4-((2-(dibenzylamino)ethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Diethyl 4-((2-aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-CO₂Et)









4-((2-Aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (1a-CN)





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Diisopropyl 4-((2-aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-CO₂i-Pr)







Di-tert-butyl 4-((2-aminoethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-CO₂t-Bu)











N,N-Dibenzyl-1-(1-(2,2-dimethoxyethoxy)cyclobutyl)methanamine

(1:1 ratio with 1-((dibenzylamino)methyl)cyclobutan-1-ol)



Diisopropyl dicarboxylate



Diisopropyl 4-((1-(aminomethyl)cyclobutoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1b)









(S)-N,N-Dibenzyl-1-(2,2-dimethoxyethoxy)propan-2-amine





Diisopropyl (S)-4-((2-(dibenzylamino)propoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Diisopropyl (S)-4-((2-aminopropoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1c)







(3R,4R)-4-(Dibenzylamino)tetrahydrofuran-3-ol



(3R,4R)-N,N-Dibenzyl-4-(2,2-dimethoxyethoxy)tetrahydrofuran-3-amine



Diisopropyl 4-((((3R,4R)-4-(dibenzylamino)tetrahydrofuran-3-yl)oxy)methyl)-2,6-dimethyl-1,4-





Diisopropyl 4-((((3R,4R)-4-aminotetrahydrofuran-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1f)




(R)-1-(Dibenzylamino)propan-2-ol



(R)-N,N-Dibenzyl-2-(2,2-dimethoxyethoxy)propan-1-amine



(R)-2-((1-(Dibenzylamino)propan-2-yl)oxy)acetaldehyde



















(3R, 4S)-N,N-Dibenzyl-4-(2, 2-dimethoxyethoxy)tetrahydrofuran-3-amine



2-(((3S,4R)-4-(Dibenzylamino)tetrahydrofuran-3-yl)oxy)acetaldehyde



Diisopropyl 4-((((3S,4R)-4-(dibenzylamino)tetrahydrofuran-3-yl)oxy)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-((((3S,4R)-4-aminotetrahydrofuran-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1g)







----- m/z

294.2

0-

(S)-2-(2-(2,2-Dimethoxyethoxy)-2-phenylethyl) isoindoline-1,3-dione



(S)-2-(2-(1,3-Dioxoisoindolin-2-yl)-1-phenylethoxy)acetaldehyde



Diisopropyl (*S*)-4-((2-(1,3-dioxoisoindolin-2-yl)-1-phenylethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Diisopropyl (S)-4-((2-amino-1-phenylethoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1e)









tert-Butyl (3R,4S)-3-(1,3-dioxoisoindolin-2-yl)-4-hydroxypyrrolidine-1-carboxylate



2-((3R,4S)-4-Hydroxypyrrolidin-3-yl)isoindoline-1,3-dione, TFA Salt



 $\label{eq:2-(3R,4S)-4-(2,2-Dimethoxy)-1-tosylpyrrolidin-3-yl) is oindoline-1, 3-dione$



2-(((3S,4R)-4-(1,3-Dioxoisoindolin-2-yl)-1-tosylpyrrolidin-3-yl)oxy) a cetal dehyde



Diisopropyl 4-((((3S,4R)-4-(1,3-dioxoisoindolin-2-yl)-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-((((3S,4R)-4-amino-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1h)





tert-Butyl (3S,4S)-3-(1,3-dioxoisoindolin-2-yl)-4-hydroxypyrrolidine-1-carboxylate



2-((3S,4S)-4-Hydroxy-1-tosylpyrrolidin-3-yl)isoindoline-1,3-dione



2-((3S,4S)-4-(2,2-Dimethoxyethoxy)-1-tosylpyrrolidin-3-yl)isoindoline-1,3-dione



Diisopropyl 4-((((3S,4S)-4-(1,3-dioxoisoindolin-2-yl)-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-((((3S,4S)-4-amino-1-tosylpyrrolidin-3-yl)oxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1i)













Diisopropyl 4-((3-(dibenzylamino)propoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-((3-aminopropoxy)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1q)









Thiomorpholine-Forming Amino-DHP Reagents

2-(2-Mercaptoethyl) isoindoline-1,3-dione



2-(2-((2,2-Dimethoxyethyl)thio)ethyl)isoindoline-1,3-dione



 $\label{eq:2-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)thio)} a cetal dehyde$



Diisopropyl 4-(((2-(1,3-dioxoisoindolin-2-yl)ethyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-

dicarboxylate



Diisopropyl 4-(((2-aminoethyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1j)









2-(2-((2,2-Dimethoxyethyl)thio)propyl)isoindoline-1,3-dione





Diisopropyl 4-(((1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-(((1-aminopropan-2-yl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1k)









 $\label{eq:2-1-1} 2-(1-((2,2-Dimethoxyethyl)thio) propan-2-yl) is oindoline-1, 3-dione$



2-((2-(1,3-Dioxoisoindolin-2-yl)propyl)thio)acetaldehyde



Diisopropyl 4-(((2-(1,3-dioxoisoindolin-2-yl)propyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-





Diisopropyl 4-(((2-aminopropyl)thio)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (11)







Piperazine-Forming Amino-DHP Reagents

2-(2-((2,2-Dimethoxyethyl)amino)ethyl)isoindoline-1,3-dione


N-(2,2-Dimethoxyethyl)-N-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-methylbenzenesulfonamide



N-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-4-methyl-N-(2-oxoethyl) benzenesulfonamide



Diisopropyl 4-(((N-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-(((N-(2-aminoethyl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1n)





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Benzyl (2,2-dimethoxyethyl)(2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate



Diisopropyl 4-((((benzyloxy)carbonyl)(2-(1,3-dioxoisoindolin-2-yl)ethyl)amino)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-(((2-aminoethyl)((benzyloxy)carbonyl)amino)methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (1m)







tert-Butyl (S)-(2-(1,3-dioxoisoindolin-2-yl)propyl)carbamate





(S)-2-(1-((2,2-Dimethoxyethyl)amino)propan-2-yl)isoindoline-1,3-dione



(S) - N - (2, 2 - Dimethoxyethyl) - N - (2 - (1, 3 - dioxoisoindolin - 2 - yl) propyl) - 4 - methyl benzenesulfon a mide



(S)-N-(2-(1,3-Dioxoisoindolin-2-yl)propyl)-4-methyl-N-(2-oxoethyl)benzenesulfonamide



Diisopropyl (S)-4-(((N-(2-(1,3-dioxoisoindolin-2-yl)propyl)-4-methylphenyl)sulfonamido)methyl)-2,6dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Diisopropyl (S)-4-(((N-(2-aminopropyl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate (10)







tert-Butyl (1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)carbamate





2-(2-((2,2-Dimethoxyethyl)amino)propyl)isoindoline-1,3-dione



N-(2,2-Dimethoxyethyl)-N-(1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)-4-methylbenzenesulfonamide



N-(1-(1,3-Dioxoisoindolin-2-yl) propan-2-yl)-4-methyl-N-(2-oxoethyl) benzenesulfonamide



Diisopropyl 4-(((N-(1-(1,3-dioxoisoindolin-2-yl)propan-2-yl)-4-methylphenyl)sulfonamido)methyl)-2,6dimethyl-1,4-dihydropyridine-3,5-dicarboxylate



Diisopropyl 4-(((N-(1-aminopropan-2-yl)-4-methylphenyl)sulfonamido)methyl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate (1p)









N-Heterocyclic Products

3-(4-Methoxyphenyl)morpholine, TFA salt (4aa)









3-(4-Bromophenyl)morpholine, TFA salt (4ad)









3-(4-Fluorophenyl)morpholine, TFA salt (4ac)

































3-(4-(Trifluoromethoxy)phenyl)morpholine, TFA salt (4ag)





Aromatic Region (zoomed):


















3-(4-(Trifluoromethyl)phenyl)morpholine, TFA salt (4af)





Aromatic Region (Zoomed):







3-(Benzo[b]thiophen-2-yl)morpholine, TFA salt (4au)

















3-(2,5-Dimethylphenyl)morpholine, TFA salt (4ah)

























3-(Thiophen-2-yl)morpholine, Free base (4ao)

















3-(Furan-2-yl)morpholine, Free base (4an)

























3-(Isoquinolin-5-yl)morpholine, TFA Salt (4aj)









3-(1-Benzyl-imidazol-5-yl)morpholine, TFA Salt (4aq)

















tert-Butyl 4-(morpholin-3-yl)indoline-1-carboxylate, Free base (4al)




Zoomed Carbon:













3-(3-Phenylisoxazol-5-yl)morpholine, Free base (4ax)





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3-(Pyrazolo[1,5-a]pyridin-7-yl)morpholine, Free base (4ay)







7-(4-Methoxyphenyl)-5-oxa-8-azaspiro[3.5]nonane, TFA Salt (4ba)







(S)-3-(4-Methoxyphenyl)-5-methylmorpholine, TFA Salt (4ca)







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(3R,4S,7S)-3-(4-Methoxyphenyl)hexahydro-2H-furo[3,4-b][1,4]oxazine, Free base (4fa)









(3R,4S,7R)-3-(4-Methoxyphenyl)hexahydro-2H-furo[3,4-b][1,4]oxazine, Free base (4ga)









(3R,4S,7R)-3-(4-Methoxyphenyl)-6-tosyloctahydropyrrolo[3,4-b][1,4]oxazine, Free base (4ha)









(2S)-5-(4-Methoxyphenyl)-2-phenylmorpholine, Free base (4ea)







3-(4-Methoxyphenyl)thiomorpholine, Free base (4ja)













Zoomed "methanol" region:







3-(Pyrazolo[1,5-a]pyridin-7-yl)thiomorpholine, Free base (4jy)





3-(4-Methoxyphenyl)-5-methylthiomorpholine, Free base (4ka)









(3S,5R)-3-Methyl-5-(1-methyl-1H-pyrazol-5-yl)thiomorpholine, Free base (4kp)









5-(4-Methoxyphenyl)-2-methylthiomorpholine, Free base (4la)







Benzyl 3-(4-methoxyphenyl)piperazine-1-carboxylate, Free base (4ma)






3-(4-Methoxyphenyl)-1-tosylpiperazine, Free base (4na)









(5S)-3-(4-Methoxyphenyl)-5-methyl-1-tosylpiperazine, Free base (40a)









1-Methyl-6-((6S)-6-methyl-4-tosylpiperazin-2-yl)-1H-indole, TFA salt (40s)































7-(6-Phenyl-2,3-dihydroimidazo[2,1-b]thiazol-5-yl)-5-oxa-8-azaspiro[3.5]nonane, Free base (4bw)









tert-Butyl (S)-2,2-dimethyl-4-((3R,6S)-6-phenylmorpholin-3-yl)oxazolidine-3-carboxylate, Free base (4eß)





tert-Butyl 3-((3R,4S,7S)-hexahydro-2H-furo[3,4-b][1,4]oxazin-3-yl)-1H-indole-1-carboxylate, Free base (4fɛ)







(3R,4S,7R)-3-(1-Methyl-1H-pyrazol-5-yl)-6-tosyloctahydropyrrolo[3,4-b][1,4]oxazine, Free base (4hp)







(3R,4S,7S)-3-(1-Methyl-1H-indol-2-yl)-6-tosyloctahydropyrrolo[3,4-b][1,4]oxazine, Free base (4iz)











(2S,5R)-5-(6-(4-Methoxyphenyl)pyridin-2-yl)-2-methylthiomorpholine, Free base (4ly)







Benzyl 3-(5-bromopyridin-3-yl)piperazine-1-carboxylate, Free base (4mr)





























