

Supporting Information

Increasing the Efficiency of Ligands for the FK506-Binding Protein 51 by Conformational Control

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Compound	Scaffold	R ₁	R ₂	K _i (μM) (LE)
2h	2			>100
3h	3			>100
4h	4			>100
2g*	2			>100
4g*	4			19.7±0.5 (0.18)
4j	4			>100

Table S1 FK506 binding domain of FKBP51 binding affinities for mono- and bicyclic α -keto amide ligands, determined by a fluorescence polarization assay.^[4] Ligand efficiency (LE) is defined as the ratio of Gibbs free energy (ΔG) to the number of non-hydrogen atoms of the compound: $LE = (\Delta G)/N$, where $\Delta G = -RT \ln K_i$ with RT equal to 0.6 and N is the number of non-hydrogen atoms.^[1]
 * Diastereomeric mixture.

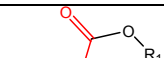
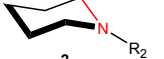
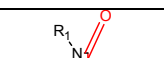
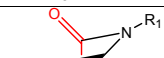
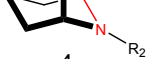
Compound	PDB number	Scaffold	C ¹ -Tyr ¹¹³ -O dipolar distance (Å)	O ¹ -Ile ⁸⁷ -N bond distance (Å)	angle O ¹ -C ¹ -Tyr ¹¹³ -O	dihedral angle O ¹ -C ¹ -C ² -N ⁷	dihedral angle Val ⁸⁶ -C ¹ -Ile ⁸⁷ -N ⁷ -O ¹ -C ¹
FK506 ^[5]	3O5R		3.2	2.9	101°	179°	144°
2j (comp 3f-1 ^[2])	4DRN		3.5	2.9	114°	193°	197°
2k (comp 3f-2 ^[2])	4DRP		3.5	2.8	111°	191°	164°
2i (comp 2a ^[2])	4DRK		3.2	2.9	107°	185°	175°
2l (comp 20 ^[3])	4DRQ	2	3.1	3.0	99°	185°	158°
2d	4JFM		3.2	2.9	89°	189°	163°
5a	4JFI		3.4	2.8	86°	153°	97°
3d (conformation1)	4JFJ		3.1	2.9	95°	160°	126°
3d (conformation2)	4JFJ	3	3.2	2.8	94°	158°	122°
4c (conformation1)	4JFL		3.0	2.8	102°	173°	144°
4c (conformation2)	4JFL		3.0	2.9	102°	172°	147°
4d (conformation1)	4JFK		3.0	2.8	102°	175°	158°
4d (conformation2)	4JFK	4	3.0	2.8	102°	175°	152°

Table S2 Quantification of the C¹=O interactions with FKBP51 for the known cocrystallized FKBP51 ligands and for bicycles of this work.

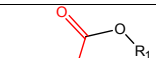
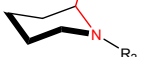
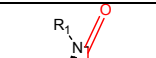

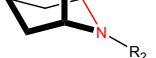
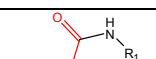
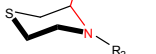
Compound	Scaffold	N ⁷ -Tyr ¹¹³ -O distance (Å)	O ^a -Tyr ¹¹³ -O distance (Å)	pyramidalization ^(a)	dihedral angle Tyr ¹¹³ -N ⁷	dihedral angle Tyr ¹¹³ -S=O ^a	angle Tyr ¹¹³ -C ⁴ -O ⁴ -N ⁷	angle Tyr ¹¹³ -C ⁴ -O ⁴ -S=O ^a
FK506 ^[5]		3.6	2.6	176°	-5°	7°	160°	119°
2j (comp 3f-1 ^[2])		3.9	2.7	180°	-24°	6°	143°	118°
2k (comp 3f-2 ^[2])		3.7	2.6	182°	-28°	13°	154°	126°
2i (comp 2a ^[2])		3.6	2.6	181°	-1°	21°	155°	119°
2l (comp 20 ^[3])	2	3.8	3.4	146°	5°	8°	144°	104°
2d		4.6	4.2	192°	-1°	7°	125°	94°
5a		3.5	2.6	182°	-8°	15°	157°	120°
3d (conformation1)		3.3	3.6	139°	8°	11°	141°	99°
3d (conformation2)	3	3.2	3.6	140°	7°	11°	141°	99°
4c (conformation1)		3.1	2.8	136°	9°	6°	160°	108°
4c (conformation2)		3.0	2.7	132°	16°	5°	161°	108°
4d (conformation1)		3.3	3.2	136°	5°	6°	148°	100°
4d (conformation2)	4	3.3	3.2	139°	3°	6°	148°	100°
1J4H (in FKBP12) ^[7]		4.0	3.5	159°	13°	9°	151°	108°
1J4I (in FKBP12) ^[7]		3.9	3.5	179°	21°	22°	147°	109°

Table S3 Quantification of the N⁷ and S=O^a interactions with Tyr¹¹³ of FKBP51 for the known cocrystallized FKBP51 ligands and for bicycles of this work. ^(a) The pyramidal is quantified by the angle of S-N⁷ vs the C²-N⁷-C⁶ plane.

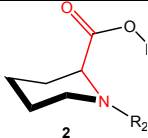
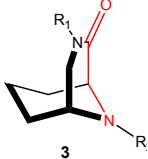
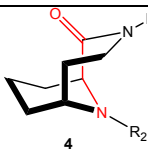
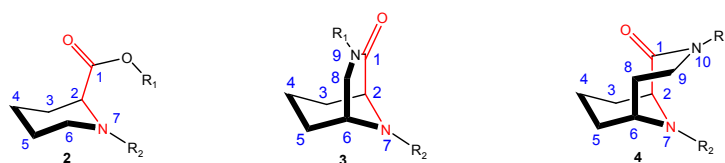
Compound	Scaffold	S=O ^b - Tyr ⁵⁷ - Ar-C ³ distance (Å)	S=O ^b - Phe ⁶⁷ - Ar-C ³ distance (Å)	S=O ^b - Phe ¹³⁰ - Ar-C ³ distance (Å)	S=O ^a - Phe ⁶⁷ - Ar-C ³ distance (Å)	S=O ^a - Tyr ¹¹³ -Ar- C ³ distance (Å)	S=O ^a - Phe ¹³⁰ - Ar-C ⁴ distance (Å)	Ar-C- Asp ⁶⁸ -O distance(Å)	Ar-C- Tyr ¹¹³ -O distance (Å)
FK506 ^[5]									
2j (comp 3f-1 ^[2])	 2								
2k (comp 3f-2 ^[2])									
2i (comp 2a ^[2])									
2l (comp 20 ^[3])									
2d		3.6	3.4	3.4	3.8	3.6	3.5	3.0(C ¹⁰)	3.0(C ¹⁴)
5a		3.5	3.3	3.5	3.8	3.8	3.6	3.4(C ¹⁰)	3.4(C ¹⁵)
3d (conformation1)	 3							3.42(C ²³)	3.6(C ¹⁹)
3d (conformation2)									
4c (conformation1)	 4	3.3	3.6	3.5	3.7	3.5	3.4	3.0(C ¹⁷)	3.6(C ¹²)
4c (conformation2)		3.3	3.6	3.5	3.7	3.5	3.4	3.3(C ¹²)	3.1(C ¹⁷)
4d (conformation1)		3.4	3.5	3.5	3.7	3.3	3.5	2.7(C ¹³)	2.9(C ¹⁸)
4d (conformation2)		3.5	3.6	3.4	3.8	3.2	3.6	2.7(C ¹⁸)	3.2(C ¹³)
4d (conformation1)		3.4	3.5	3.4	3.8	3.3	3.4	2.9(C ¹³)	3.0(C ¹⁸)
4d (conformation2)		3.4	3.5	3.4	3.8	3.3	3.4	2.7(C ¹⁸)	3.4(C ¹³)

Table S4 Quantification of the aromatic hydrogen bonds for the known cocrystallized FKBP51 ligands and for bicycles of this work.



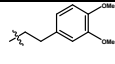

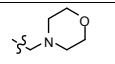

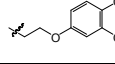

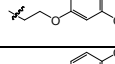

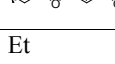




Compound	Scaffold	R ₁	R ₂	K _i (μM) (LE)
FK506	2	-	-	0.01±0.003 (0.24) ^[4]
Rapamycin	2	-	-	0.0006±0.0002 (0.2) ^[4]
2i	2			0.01±0.003 (0.26) ^[4]
2k	2			0.04±0.007 (0.21) ^[3]
2d	2			0.002±0.0001 (0.35)
3d	3			0.07±0.0004 (0.19)
4d	4			0.001±0.0003 (0.22)
2e	2	Et		0.2±0.004 (0.38)
3e	3	H		0.1±0.0005 (0.42)
4e	4	H		0.06±0.002 (0.41)

Table S5 FKBP12 binding affinities of monocyclic or conformationally constrained FKBP ligands. Affinities were measured by a fluorescence polarization assay using purified human FKBP12.^[4] Ligand efficiency (LE) is defined as the ratio of Gibbs free energy (ΔG) to the number of non-hydrogen atoms of the compound: $LE = (\Delta G)/N$, where $\Delta G = -RT \ln K_i$ with RT equal to 0.6 and N is the number of non-hydrogen atoms.^[1]

Table S6. Data collection and refinement statistics

Dataset	5a	3d	4d	4c	2d
PBD code	4JFI	4JFJ	4JFK	4JFL	4JFM
Data collection					
Beamline	SLS X10SA	ESRF ID14-4	SLS X06DA	SLS X06DA	SLS X10SA
Wavelength	1.0	0.93927	1.0	1.0	0.97157
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions					
a, b, c (Å)	42.05, 54.19, 55.96	42.34, 54.41, 56.56	42.27, 54.45, 56.41	42.05, 55.96, 57.86	42.16, 54.50, 56.42
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å) *	27.98 – 1.05 (1.11 – 1.05)	33.89 – 1.08 (1.14 – 1.08)	39.17 – 1.15 (1.21 – 1.15)	42.16 – 1.2 (1.26 – 1.2)	42.16 – 1.02 (1.08 – 1.02)
R_{merge} *	0.061 (0.402)	0.051 (0.415)	0.027 (0.099)	0.070 (0.283)	0.066 (0.457)
I / σ *	16.2 (3.0)	12.9 (3.0)	28.3 (9.6)	12.8 (3.4)	21.2 (4.6)
Completeness (%) *	95.3 (72.9)	98.7 (99.6)	98.7 (92.6)	98.1 (90.5)	85.3 (49.7)
Redundancy *	5.5 (3.8)	3.5 (3.4)	4.7 (3.5)	5.1 (3.3)	11.7 (8.2)
Refinement					
Resolution (Å)	20 – 1.05	20 – 1.08	20 – 1.15	20 – 1.2	20 – 1.02
No. reflections	54565	53082	44001	38222	53412
$R_{\text{work}} / R_{\text{free}}$	0.1372 / 0.1580	0.1443 / 0.1689	0.1291 / 0.1509	0.1413 / 0.1740	0.1479 / 0.1705
No. atoms	1273	1364	1404	1376	1233
Protein	1014	1053	1067	1056	1029
Ligand/ion	38	72	74	72	35
Water	221	239	263	248	169
B -factors (Å ²)	15.03	12.18	13.08	15.18	10.31
Protein	10.97	9.84	9.81	11.36	12.35
Ligand/ion	19.59	16.90	15.10	24.25	21.05
Water	32.90	21.07	25.82	28.82	26.10
R.m.s. deviations					
Bond lengths (Å)	0.025	0.010	0.013	0.013	0.026
Bond angles (°)	2.190	1.559	1.684	1.642	2.075

*Values in parentheses are for highest-resolution shell.

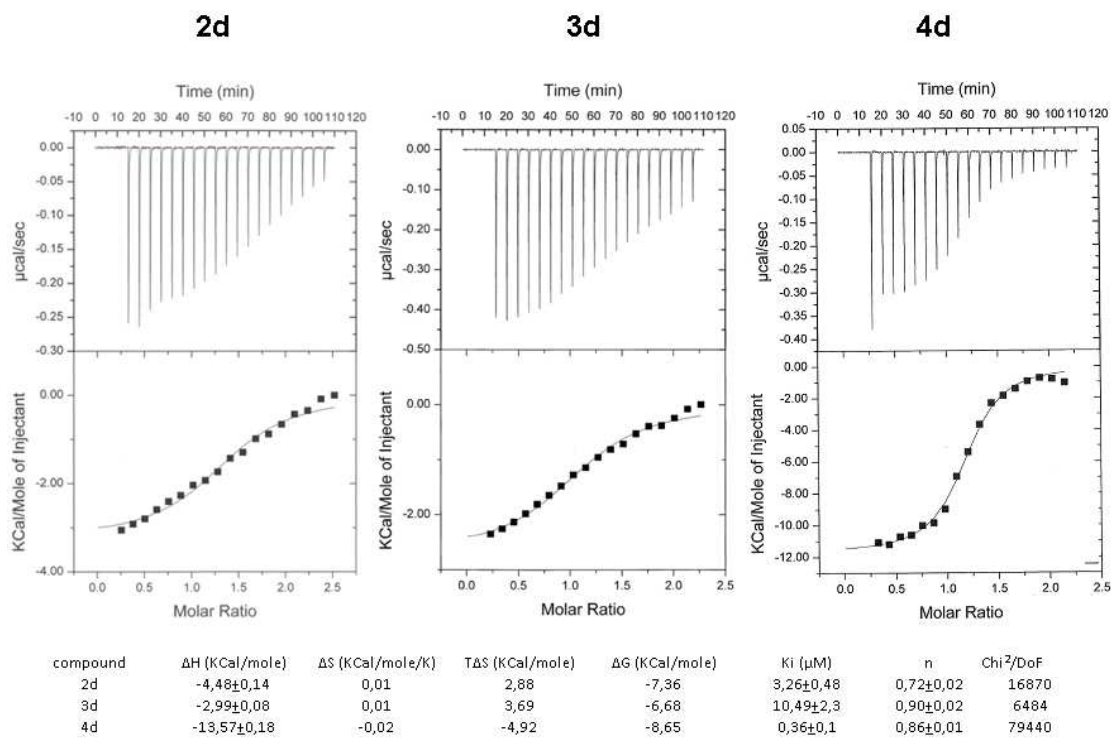
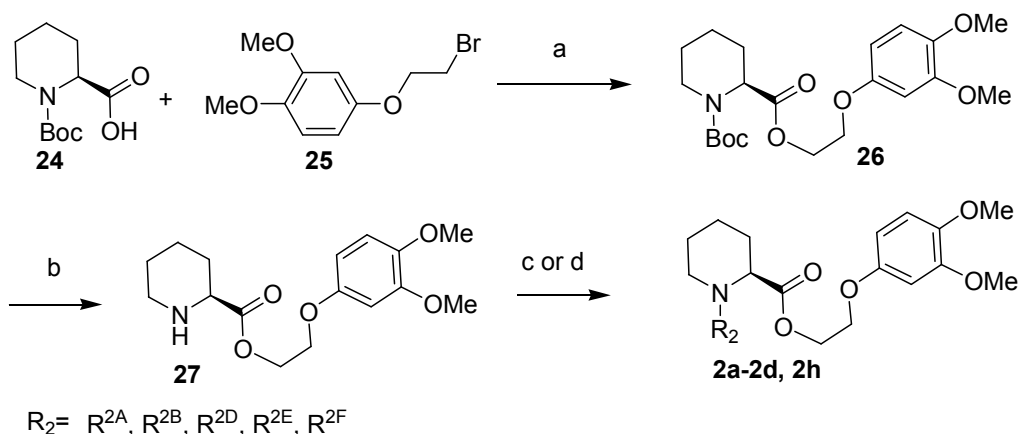
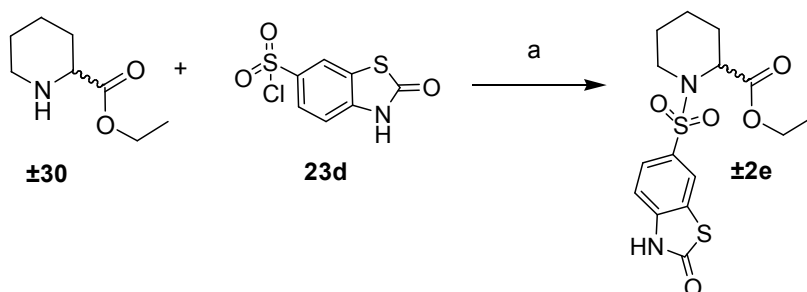


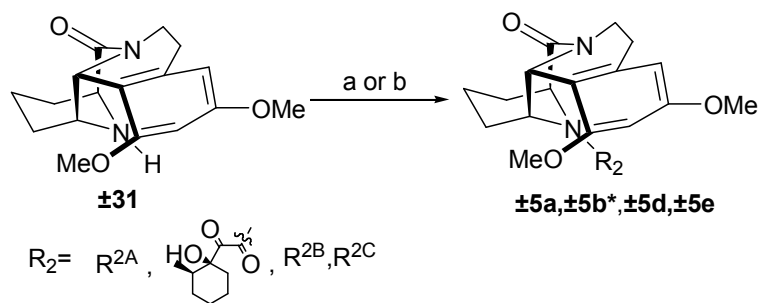
Table S7 Thermodynamic parameters for binding of compounds **2d**, **3d** and **4d** to the FK506 binding domain of FKBP51.



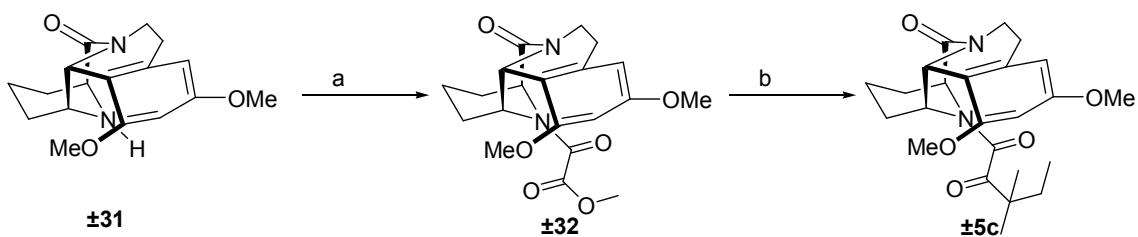
Scheme S1 Synthesis of monocyclic ligands **2a-2d**, **2h**: a) K_2CO_3 , acetone, reflux, overnight, 100%. b) 20% TFA in DCM, RT, 2h, 100%. c) **23a** ($R^{2A}\text{-OH}$) or **23e** ($R^{2B}\text{-OH}$), TEA, HATU, DCM, RT, overnight, 42% for **2a**, 84% for **2h**. d) **23b-23d** ($R^{2D-E}\text{-Cl}$), DIPEA, DCM, RT, overnight, 20%-48% for **2b-2d**.



Scheme S2 Synthesis of monocyclic ligands **2e**: a) DIPEA, DCM, RT, overnight, 91%.



Scheme S3 Synthesis of polycyclic ligands **5a**, **5b***, **5d** and **5e**: a) **23a** or **23g***, HATU, DIPEA, rt, 16h, b) **23b** or **23f**, DIPEA, CH_2Cl_2 , RT, 1.5h. *Mixture of Diastereomers.



Scheme S4 Synthesis of polycyclic ligands $\pm 5c$: a) Monomethyl oxalyl chloride, TEA, DCM, 0°C, 70%. b) 1,1-Dimethylpropylmagnesium chloride, THF, -78°C, 96%

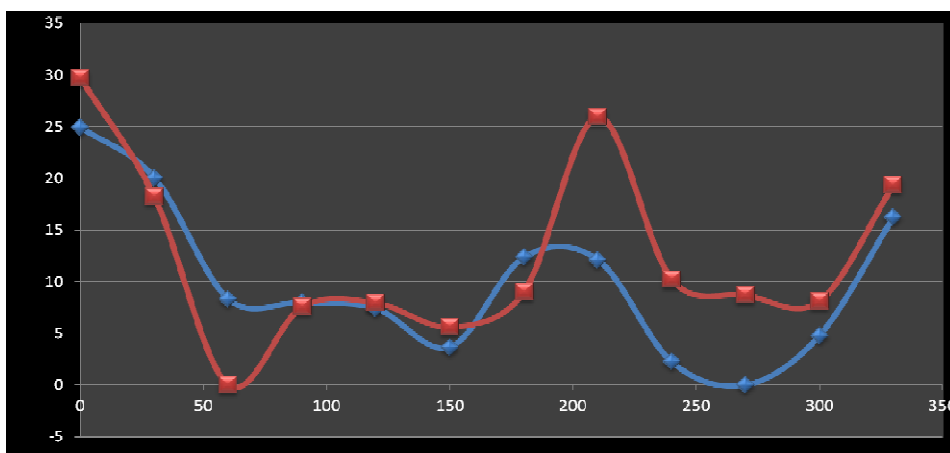


Figure S1 Dihedral angle plots for **3f** (red) and **4f** (blue) around the $C^1-N^7-S^{10/11}-C^{11/12}$ bond. Energies are depicted in kJ/mol.

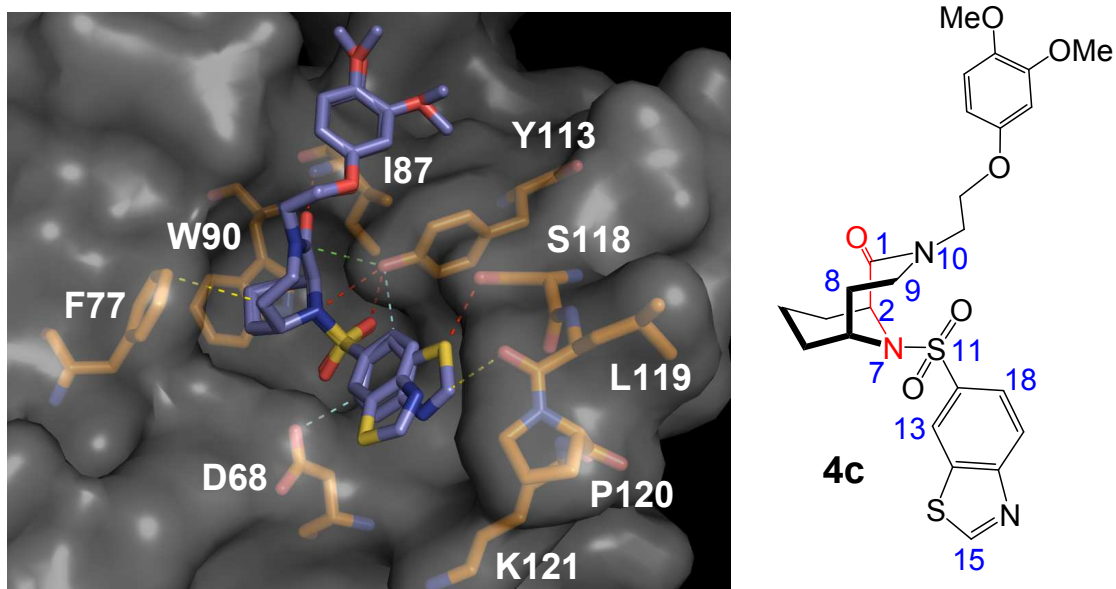


Figure S2 Cocystal structure of **4c** in complex with the FK506-binding domain of FKBP51

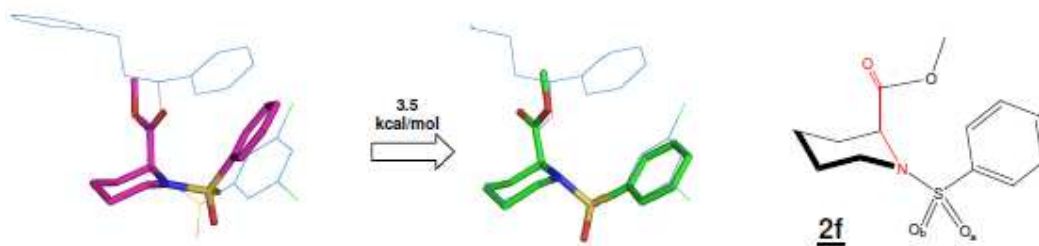


Figure S3 Overlay of the monocyclic core scaffold **2f** in its lowest-energy conformation (pink) and in a conformation (green) that corresponds to compound **2j** bound to FKBP51 (blue lines, 4DRQ). This reorganization requires 3.5 kcal/mol of conformational energy.

Synthetic procedures

Methyl 6-(cyanomethyl) picolinate (9)

Step 1: To 100 mL anhydrous THF under argon at -78°C was added butyl lithium (6.02 g, 94mmol) followed by addition of acetonitrile (4.06g, 99mmol) and stirred for 30min. Then 6-bromopicolinic acid **8** (2.5g, 12.38mmol) in 100 mL anhydrous THF cooled on ice was added dropwise. After 2 h at -78°C and 30 min at room temperature, the reaction mixture was concentrated *in vacuo*, dissolved in DCM (100 mL) and extracted with saturated NaHCO_3 solution (3 x 100 mL). The aqueous layers were acidified with 10% HCl, and extracted with DCM (6 x 100 mL). The collected organic layers were dried over MgSO_4 and concentrated *in vacuo*. This crude product was used for next reaction without further purification.

TLC [20% MeOH, 0.2% TFA in CHCl_3]: $R_f = 0.04$

Yield: 1.76g, 10.9mmol (87.7%)

^1H NMR (300 MHz, CDCl_3): $\delta = 8.1$ (d, 1H, $J = 7.8$ Hz), 8.05 (t, 1H, $J = 7.8, 7.8$ Hz), 7.75 (d, 1H, $J = 7.8$ Hz), 4.08 (s, 2H)

^{13}C NMR (75 MHz, CDCl_3): $\delta = 163.7, 150.1, 146.7, 140.3, 126.9, 123.7, 116.1, 26.5$

HRMS: 163.0504 $[\text{M} + \text{H}]^+$, 185.0321 $[\text{M} + \text{Na}]^+$, calculated 163.0508 $[\text{M} + \text{H}]^+$.

Step 2: 13.35 mL 2M TMSCHN_2 in Et_2O (3.05g, 26.7mmol) was added dropwise to 6-(cyanomethyl) picolinic acid from step 1 (1.31g, 8.1mmol) in 27 mL anhydrous MeOH at 0°C . After stirring at room temperature for 5h, the reaction was quenched with saturated NaHCO_3 solution (100 mL), extracted with DCM (6 x 100 mL). The organic layers were dried over MgSO_4 and concentrated *in vacuo*. The pure product was obtained by flash chromatography with hexane: EtOAc 1:1.

TLC [Hexane: EtOAc 1:1]: $R_f = 0.54$

Yield: 750mg, 4.3mmol (52.7%)

^1H NMR (300 MHz, CDCl_3): $\delta = 8.01$ -8.06 (m, 1H), 7.87 (t, 1H, $J = 7.8, 7.8$ Hz), 7.64 (d, 1H), 4.02 (s, 2H), 3.94 (s, 3H)

^{13}C NMR (300 MHz, CDCl_3): $\delta = 165.0, 151.1, 148.1, 138.6, 125.5, 124.4, 116.6, 53.0, 26.6$

HRMS: 177.0649 $[\text{M} + \text{H}]^+$, 199.0472 $[\text{M} + \text{Na}]^+$, calculated 177.0664 $[\text{M} + \text{H}]^+$.

Ethyl 6-cyanopicolinate (7)

CuCN (31.1g, 348mmol) was added to a solution of ethyl 6-bromopicolinate **6** (16g, 69.5mmol) in 608 mL pyridine. The mixture was heated under reflux for 16 h, filtered through celite and concentrated *in vacuo*. Saturated NaHCO_3 solution (100 mL) was added and extracted with DCM (6 x 100 mL). The organic layers were dried over MgSO_4 and concentrated *in vacuo*. The mixture was purified with flash chromatography in hexane: EtOAc 1:1.

TLC [Hexane: EtOAc 1:1]: $R_f = 0.65$

Yield: 7.3g, 41.4mmol (60%)

^1H NMR (600 MHz, CDCl_3): $\delta = 8.32$ (dd, 1H, $J = 1.2, 8.0$ Hz), 8.04 (t, 1H, $J = 7.9, 7.9$ Hz), 7.88 (dd, 1H, $J = 1.1, 7.8$ Hz), 4.52 (q, 2H, $J = 7.1, 7.1, 7.1$ Hz), 1.40 (t, 3H, $J = 7.1, 7.1$ Hz)

^{13}C NMR (300 MHz, CDCl_3): $\delta = 163.8, 150.1, 138.7, 134.2, 131.4, 128.1, 116.6, 62.9, 14.4$

HRMS: 177.0669 $[\text{M} + \text{H}]^+$, calculated 177.0664 $[\text{M} + \text{H}]^+$.

Ethyl 6-((tert-butoxycarbonylamino)methyl)picolinate (10)

To a solution of ethyl 6-cyanopicolinate **7** (7.87g, 44.7mmol) in 350 mL MeOH was added Boc_2O (19.5g, 89mmol), catalytic amounts of Raney nickel and degased with argon. The reaction was stirred under 1 atm H_2 at room temperature for 24 h, filtered through celite and concentrated *in vacuo*. The mixture was purified with flash chromatography in EtOAc: DCM 1:5.

TLC [EtOAc: DCM 1:5]: $R_f = 0.34$

Yield: 8.74g, 31.2mmol (68%)

^1H NMR (300 MHz, CDCl_3): $\delta = 7.98$ (d, 1H, $J = 7.7$ Hz), 7.79 (t, 1H, $J = 7.8, 7.8$ Hz), 7.48 (d, 1H, $J = 7.8$ Hz), 5.51 (s, 1H), 4.48-4.58 (m, 2H), 4.40-4.48 (m, 2H), 1.44 (s, 9H), 1.34-1.42 (m, 3H)

^{13}C NMR (75 MHz, CDCl_3): $\delta = 165.0, 158.6, 156.0, 147.7, 137.6, 125.1, 123.7, 79.7, 61.9, 45.9, 28.4, 14.3$

HRMS: 281.1505 $[\text{M} + \text{H}]^+$, calculated 281.1501 $[\text{M} + \text{H}]^+$.

Methyl 6-(2-(tert-butoxycarbonylamino) ethyl) picolinate (11)

To a solution of methyl 6-(cyanomethyl) picolinate **9** (0.75g, 4.3mmol) in 54 mL MeOH was added Boc₂O (1.858g, 8.5mmol), catalytic amounts of Raney nickel and degased with argon. The reaction was stirred under 1 atm H₂ at room temperature for 24 h, filtered through celite and concentrated *in vacuo*. The mixture was purified with flash chromatography in EtOAc: DCM 1:2.

TLC [EtOAc: DCM 1:2]: R_f = 0.54

Yield: 860mg, 3.1mmol (76%)

¹H NMR (300 MHz, CDCl₃) δ = 7.90 (dd, 1H, J = 1.0, 7.8 Hz), 7.69 (t, 1H, J = 7.8, 7.8 Hz), 7.31 (d, 1H, J = 7.7 Hz), 3.92 (s, 3H), 3.48 (d, 2H, J = 5.9 Hz), 3.01 (t, 2H, J = 6.6, 6.6 Hz), 1.34 (s, 9H)

¹³C NMR (300 MHz, CDCl₃) δ = 165.7, 159.9, 155.9, 147.5, 137.3, 126.7, 122.9, 79.0, 52.7, 39.9, 37.8, 28.3

HRMS : m/z: found 281.1457 [M + H]⁺, 303.1287 [M + Na]⁺, calculated 281.1501 [M + H]⁺.

Ethyl 6-((tert-butoxycarbonylamino)methyl)piperidine-2-carboxylate (**12**)

To a solution of ethyl 6-((tert-butoxycarbonylamino)methyl)picolinate **10** (8.74g, 31.2mmol) in 150 mL AcOH was added catalytic amounts of PtO₂ and degassed with argon in a hydrogenation reactor (Roth). The reaction was stirred at room temperature under H₂ (40bar) for 3 days. **10** was not fully converted. The reaction mixture was filtered through celite, concentrated *in vacuo* and purified with flash chromatography in EtOAc. The retrieval of **10** was used with the same procedure until 100% converted.

TLC [EtOAc]: R_f = 0.38

Yield: 4.35g, 15.2mmol (49%)

¹H NMR (600 MHz, CDCl₃) δ = 5.07 (s, 1H), 4.14-4.2 (m, 2H), 3.33 (dd, 1H, J = 2.8, 11.5 Hz), 3.23-3.35 (m, 1H), 2.90-3.05 (m, 1H), 2.66-2.70 (m, 1H), 1.97-2.05 (m, 3H), 1.86-1.92 (m, 1H), 1.59-1.65 (m, 1H), 1.4-1.48 (m, 10H), 1.32-1.4 (m, 1H), 1.03-1.12 (m, 1H).

¹³C NMR (300 MHz, CDCl₃) δ = 175.0, 156.3, 79.3, (60.9, 61.0), (58.7, 58.8), 55.7, 46.0, (29.1, 29.1), (29.0, 29.0), (28.4, 28.4), 23.9, (14.1, 14.2)

MS (ESI) m/z: found 287.2 [M + H]⁺, calculated 287.20 [M + H]⁺.

Methyl 6-(2-(tert-butoxycarbonylamino) ethyl) piperidine-2-carboxylate (**13**)

To a solution of methyl 6-(2-(tert-butoxycarbonylamino) ethyl) picolinate **11** (644mg, 2.3mmol) in 33 mL AcOH was added catalytic amounts of PtO₂ and degassed with argon in a hydrogenation reactor (Roth). The reaction was stirred at room temperature under H₂ (50bar) for 2 days, filtered through celite, concentrated *in vacuo* and purified with flash chromatography in EtOAc.

TLC [EtOAc]: R_f = 0.31

Yield: 646mg, 2.3mmol (98 %)

¹H NMR (300 MHz, CDCl₃) δ = 4.81-4.95 (m, 1H), 3.66 (s, 3H), 3.25-3.42 (m, 1H), 3.05-3.25 (m, 2H), 2.85-3.00 (m, 1H), 2.48-2.60 (m, 1H), 1.95-2.05 (m, 1H), 1.85-1.95 (m, 1H), 1.45-1.65 (m, 3H), 1.38 (s, 9H), 1.15-1.38 (m, 2H), 0.95-1.1 (m, 1H)

¹³C NMR (300 MHz, CDCl₃) δ = 173.5, 156.0, 79.0, 59.1, 54.1, 51.9, 37.5, 37.0, 31.7, 29.2, 28.3, 24.3

HRMS : m/z: found 287.1876 [M + H]⁺, calculated 287.1971 [M + H]⁺.

1-Benzyl 2-ethyl 6-((tert-butoxycarbonylamino)methyl)piperidine-1,2-dicarboxylate (**14**)

To a solution of ethyl 6-((tert-butoxycarbonylamino)methyl)piperidine-2-carboxylate **12** (4.35g, 15.2mmol) in 50 mL DCM at 0°C was added benzyl chloroformate (3.89g, 22.8mmol) dropwise followed by addition of N,N-diisopropylethylamine (7.85g, 60.8mmol). After stirring at room temperature for 5 h, a saturated NH₄Cl solution (20 mL) was added and extracted with DCM (4 x 20 mL). The organic layers were dried over MgSO₄, concentrated *in vacuo* and purified with flash chromatography in hexane: EtOAc 3:1

TLC [Hexane :EtOAc 3:1]: R_f = 0.26

Yield: 6.14g, 14.6mmol (96%)

¹H NMR (300 MHz, CDCl₃) δ = 7.25-7.4 (m, 5H), 5.2-5.4 (m, 1H), 5.0-5.1 (m, 1H), 4.7-5.0 (m, 1H), 4.36-4.52 (m, 1H), 4.06-4.3 (m, 1H), 3.3-3.5 (m, 1H), 2.9-3.14 (m, 1H), 2.18-2.35 (m, 1H), 1.5-1.8 (m, 6H), 1.3-1.5 (m, 10H), 1.1-1.3 (m, 3H)

¹³C NMR (300 MHz, CDCl₃) δ = 173.4, 157.1, 156.4, 136.8, 128.7, 128.2, 128.0, 79.1, 67.8, 61.8, 53.4, 50.5, 42.6, 28.7, 26.3, 16.5, 14.3

MS (ESI) m/z: found 421.22 [M + H]⁺, calculated 421.23 [M + H]⁺

HRMS : m/z: found 421.2333 [M + H]⁺, calculated 421.2339 [M + H]⁺.

1-Benzyl 2-methyl 6-(2-(tert-butoxycarbonylamino) ethyl) piperidine-1, 2-dicarboxylate (15)

To a solution of methyl 6-(2-(tert-butoxycarbonylamino)ethyl)piperidine-2-carboxylate **13** (646mg, 2.3mmol) in 7 mL DCM at 0°C was added benzyl chloroformate (578mg, 3.4mmol) dropwise followed by addition of N,N-diisopropylethylamine (1167mg, 9mmol). After stirring at room temperature for 6 h, a saturated NH₄Cl solution (20 mL) was added and extracted with DCM (4 x 20 mL). The organic layers were dried over MgSO₄, concentrated *in vacuo* and purified with flash chromatography in hexane: EtOAc 2:1

TLC [Hexane :EtOAc 2:1]: R_f = 0.46

Yield: 812mg, 1.9mmol (86%)

¹H NMR (300 MHz, CDCl₃) δ = 7.28-7.42 (m, 5H), 5.02-5.26 (m, 2H), 4.78-5.01 (m, 0.5H), 4.66-4.70 (m, 0.5H), 4.20-4.44 (m, 1H), 3.55-3.73 (m, 3H), 2.85-3.45 (m, 2H), 2.19-2.34 (m, 1H), 1.45-1.75 (m, 7H), 1.42 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) δ = 172.9, 156.5, 156.1, 136.4, 128.5, 128.5, 128.1, 127.5, 126.9, 78.9, 67.6, 52.5, 52.1, 48.4, 37.5, 33.3, 28.7, 28.4, 25.8, 15.9

HRMS : m/z: found 421.2437 [M + H]⁺, calculated 421.2339 [M + H]⁺.

Benzyl 2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (16)

Step 1: 1-Benzyl 2-ethyl 6-((tert-butoxycarbonylamino)methyl)piperidine-1,2-dicarboxylate **14** (6.11g, 15mmol) in 50% TFA in DCM was stirred at room temperature for 1 h and then concentrated *in vacuo*. DCM was added and evaporated for 3 times to remove the TFA. It was used for the next step without further purification.

Step 2: The crude product from step 1 in 300 mL pyridine was heated under reflux for 2 h. The mixture was concentrated *in vacuo* and purified with flash chromatography in EtOAc.

TLC [EtOAc]: R_f = 0.23

Yield: 3.14g, 11.4mmol (76%)

¹H NMR (600 MHz, CDCl₃) δ = 7.28-7.42 (m, 5H), 5.05-5.2 (m, 2H), 4.63-4.77 (m, 1H), 4.43-4.57 (m, 1H), 3.63-3.77 (m, 1H), 3.15-3.24 (m, 1H), 1.89-1.99 (m, 1H), 1.66-1.89 (m, 5H)

¹³C NMR (150 MHz, CDCl₃) δ = 171.4, 154.2, 136.3, 128.8, 128.4, 128.2, 67.8, (54.2, 53.5), (45.9, 45.6), (45.0, 44.1), (30.6, 30.2), (27.8, 27.4), 18.1

HRMS : m/z: found 275.1390 [M + H]⁺, calculated 275.1396 [M + H]⁺.

Benzyl 2-oxo-3, 10-diazabicyclo [4.3.1] decane-10-carboxylate (17)

Step 1: 1-Benzyl 2-methyl 6-(2-(tert-butoxycarbonylamino)ethyl)piperidine-1,2-dicarboxylate **15** (3.6g, 8.6mmol) in 360 mL 50% TFA in DCM was stirring at room temperature for 1 hour and then concentrated *in vacuo*. DCM was added and evaporated for three times to remove the TFA. It was used for the next step without further purification.

TLC [10 %MeOH in CHCl₃]: R_f = 0.31

Step 2: the crude product from step 1 was dissolved in 150 mL pyridine and heated under reflux for overnight. The reaction mixture was concentrated *in vacuo* followed by purification with flash chromatography in EtOAc.

TLC [EtOAc]: R_f = 0.26

Yield: 840mg, 2.9mmol (33 %)

¹H NMR (300 MHz, CDCl₃): δ = 7.28-7.38 (m, 5H), 6.52-6.74 (m, 1H), 5.12-5.24 (m, 2H), 4.96-5.18 (m, 1H), 4.6-4.74 (m, 1H), 3.14-3.22 (m, 1H), 2.88-2.96 (m, 1H), 2.24-2.36 (m, 1H), 2.12-2.24 (m, 1H), 1.88-1.96 (m, 1H), 1.56-1.76 (m, 4H), 1.48-1.56 (m, 1H)

¹³C NMR (150 MHz, CDCl₃): δ = 175.2, (156.0, 155.9), (136.4, 136.3), (128.6, 128.5), 128.2, 128.1, 127.0, 127.8, 67.6, (55.5, 55.3), (46.9, 46.4), (39.3, 39.3), (33.0, 32.9), (29.2, 28.9), (28.1, 27.9), (15.3, 15.3)

MS (ESI) m/z: found 289.15 [M + H]⁺, calculated 289.12 [M + H]⁺.

HRMS : m/z: found 289.1546 [M + H]⁺, calculated 289.1552 [M + H]⁺.

4-(2-Bromoethoxy)-1, 2-dimethoxybenzene (18a)

18a was prepared as described.^[2]

Benzyl 3-(2-(3,4-dimethoxyphenoxy)ethyl)-2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (19a)

To a solution of benzyl 2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate **16** (100mg, 0.4mmol) in 2 mL dry THF under argon at 0°C was added NaH (26mg, 0.9mmol). After stirring for 15 min, **18a** (238mg, 0.9mmol) was added and stirred at room temperature for 5 days. The reaction mixture was concentrated *in vacuo*, acidified with 10% HCl solution (5 mL) and extracted with DCM (4 x 10 mL). The organic phases were dried over MgSO₄, concentrated *in vacuo* and purified with flash chromatography in hexane :EtOAc 2:1

TLC [Hexane :EtOAc 1:2]: R_f = 0.31

Yield: 104mg, 0.2mmol (63%)

¹H NMR (300 MHz, CDCl₃) δ = 7.3-7.42 (m, 5H), 6.74-6.8 (m, 1H), 4.45-4.50 (m, 1H), 4.34-4.42 (m, 1H), 5.07-5.2 (m, 2H), 4.42-4.82 (m, 2H), 4.05-4.25 (m, 2H), 3.9-4.05 (m, 1H), 3.77-3.9 (m, 7H), 3.38-3.62 (m, 2H), 1.92-2.04 (m, 1H), 1.78-1.92 (m, 1H), 1.6-1.78 (m, 4H)

¹³C NMR (75 MHz, CDCl₃) δ = 168.6, 154.2, 153.2, 150.1, 144.0, 136.3, 128.8, 128.4, 128.2, 112.2, 104.2, 100.7, 67.7, 67.0, 56.7, 56.1, 54.5, 53.1, 46.8, 45.4, 30.4, 28.2, 18.5

HRMS : m/z: found 455.2176 [M + H]⁺, calculated 455.2182 [M + H]⁺.

Benzyl 3-ethyl-2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (19b)

To a solution of benzyl 2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate **16** (500mg, 1.8mmol) in 15 mL dry THF under argon at 0°C was added NaH (109mg, 2.7mmol). After stirring for 15 min, ethyl iodide (421mg, 2.7mmol) was added and stirred at room temperature. The reaction was checked with TLC until **16** was fully converted. The mixture was purified with flash chromatography in 4% MeOH in CHCl₃

TLC [5% MeOH in CHCl₃]: R_f = 0.56

Yield: 538mg, 1.8mmol (95%)

¹H NMR (300 MHz, CDCl₃) δ = 7.25-7.45 (m, 5H), 5.03-5.23 (m, 2H), 4.65-4.77 (m, 1H), 4.45-4.65 (m, 1H), 3.55-3.78 (m, 2H), 3.05-3.33 (m, 2H), 1.95-2.07 (m, 1H), 1.55-1.90 (m, 5H), 1.13-1.23 (t, 3H, J = 7.2, 7.2 Hz)

HRMS : m/z: found 303.1703 [M + H]⁺, calculated 303.1709 [M + H]⁺.

Benzyl 3-(2-(3, 4-dimethoxyphenoxy) ethyl)-2-oxo-3, 10-diazabicyclo [4.3.1] decane-10-carboxylate (20a)

To a solution of benzyl 2-oxo-3, 10-diazabicyclo [4.3.1] decane-10-carboxylate **17** (70mg, 0.2mmol) in 2 mL dry THF under argon at 0°C was added NaH (9mg, 0.4mmol) and stirred for 15 min followed by addition of 4-(2-bromoethoxy)-1,2-dimethoxybenzene **18a** (158mg, 0.6mmol). The reaction was stirred at room temperature for 3 days and concentrated *in vacuo*. A 10% HCl solution (5 mL) was added and extracted with DCM (4 x 10 mL). The organic phases were dried over MgSO₄, concentrated *in vacuo* and purified with flash chromatography in hexane: EtOAc 1:3.

TLC [Hexane: EtOAc 1:3]: R_f = 0.49

Yield: 73mg, 0.2mmol (64%)

¹H NMR (600 MHz, CDCl₃): δ = 7.24-7.36 (m, 5H), 6.56 (t, 1H), 6.49 (m, 1H), 6.46-6.48 (m, 1H), 5.12-5.2 (m, 1H), 5.0-5.1 (m, 2H), 4.55-4.65 (m, 1H), 4.0-4.15 (m, 2H), 3.85-3.95 (m, 1H), 3.81-3.84 (m, 6H), 3.55-3.65 (m, 1H), 3.49-3.54 (m, 1H), 3.21-3.27 (m, 1H), 2.3-2.4 (m, 1H), 2.15-2.25 (m, 1H), 1.94-2.01 (m, 1H), 1.4-1.7 (m, 5H)

¹³C NMR (150 MHz, CDCl₃): δ = 172.2, 156.0, 153.1, 149.9, 143.6, 136.3, 128.6, 128.5, 128.1, 127.9, 127.8, 111.9, 103.8, 100.4, 67.5, 67.2, 56.4, 56.2, 55.9, 51.2, 47.8, 45.9, 32.2, 28.8, 28.8, 15.3

HRMS(EI) : m/z: found 468.2261 [M]⁺, calculated 468.2260 [M]⁺.

Benzyl 3-(3,4-dimethoxyphenethyl)-2-oxo-3,10-diazabicyclo[4.3.1]decane-10-carboxylate (20b)

To a solution of benzyl 2-oxo-3, 10-diazabicyclo [4.3.1] decane-10-carboxylate **17** (100mg, 0.3mmol) in 2 mL dry THF under argon at 0°C was added NaH (25mg, 0.9mmol) and stirred for 15 min followed by addition of commercially available 3,4-dimethoxyphenethyl bromide **18b** (213mg, 0.9mmol). The mixture was stirred at room temperature for 2 days and concentrated *in vacuo*. A 10% HCl solution (5 mL) was added and extracted with DCM (4 x 10 mL). The organic phases were

dried over MgSO₄, concentrated *in vacuo* and purified with flash chromatography in hexane: EtOAc 1:2.

TLC [Hexane: EtOAc 1:2]: R_f = 0.44

Yield: 39mg, 0.1mmol (25%)

¹H NMR (600 MHz, CDCl₃): δ = 7.27-7.39 (m, 5H), 6.72-6.78 (m, 3H), 5.13-5.17 (m, 2H), 5.09-5.13 (m, 0.5H), 4.99-5.05 (m, 0.5H), 4.45-4.65 (m, 1H), 3.8-3.9 (m, 6H), 3.45-3.77 (m, 4H), 3.27-3.37 (m, 1H), 2.85-2.95 (m, 1H), 2.70-2.85 (m, 2H), 2.30-2.45 (m, 1H), 2.00-2.20 (m, 1H), 1.50-1.80 (m, 3H), 0.86-0.94 (m, 1H)

¹³C NMR (150 MHz, CDCl₃): δ = (171.8, 171.9), (155.7, 155.9), 148.9, (147.6, 147.5), 136.4, (131.6, 131.2), (128.6, 128.5), (128.2, 128.1), (128.0, 127.8), (120.7, 120.7), (112.1, 111.9), (111.2, 111.1), (67.5, 67.5), 56.2, (55.9, 55.9), 53.7, 53.2, (46.6, 46.3), (46.2, 45.7), (33.8, 33.7), (33.3, 31.9), (28.8, 28.7), (15.3, 15.2)

HRMS : m/z: found 468.2484 [M]⁺, calculated 453.2389 [M]⁺.

3-(2-(3,4-Dimethoxyphenoxy)ethyl)-3,9-diazabicyclo[3.3.1]nonan-2-one (21a)

To a solution of benzyl 3-(3,4-dimethoxyphenethyl)-2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate **19a** (104mg, 0.2mmol) in 1 mL anhydrous MeOH was added catalytic amounts of Palladium on carbon and degassed with H₂. The reaction was stirred at room temperature under 1 atm H₂ for 2 h, filtered through celite, concentrated *in vacuo* and used for the next step without further purification.

TLC [MeOH: CHCl₃ 1:9]: R_f = 0.4

Yield: 73mg, 0.2mmol (100%)

¹H NMR (600 MHz, CDCl₃) δ = 6.80 (d, 1H, J = 8.8 Hz), 6.51 (s, 1H), 6.39-6.44 (m, 1H), 4.15-4.25 (m, 2H), 3.9-4 (m, 1H), 3.8-3.89 (m, 7H), 3.54-3.64 (m, 2H), 3.45-3.51 (m, 1H), 3.35-3.43 (m, 1H), 2.39 (s, 1H), 1.55-2 (m, 6H)

¹³C NMR (300 MHz, CDCl₃) δ = 171.4, 153.1, 149.9, 143.7, 111.9, 104.0, 100.5, 66.8, 56.5, 55.9, 54.4, 54.3, 46.6, 45.9, 31.8, 28.9, 18.2

HRMS : m/z: found 321.1808[M + H]⁺, calculated 321.1814[M + H]⁺.

3-Ethyl-3,9-diazabicyclo[3.3.1]nonan-2-one (21b)

To a solution of benzyl 3-ethyl-2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate **19b** (100mg, 0.3mmol) in 1 mL anhydrous MeOH was added catalytic amounts of Palladium on carbon and degassed with H₂. After stirring under 1 atm H₂ at room temperature for 2 h, the reaction mixture was filtered through celite and concentrated *in vacuo*. A 20% HCl solution (5 mL) was added and extracted with DCM (4 x 10 mL). The aqueous layer was basified with saturated NaHCO₃ solution and extracted with DCM (4 x 10 mL). The organic layer was concentrated and used for the next step without further purification.

TLC [5% MeOH in CHCl₃]: R_f = 0.37

Yield: 45mg, 0.3mmol (81%)

¹H NMR (300 MHz, CDCl₃) δ = 3.6-3.73 (m, 2H), 3.53-3.57 (m, 1H), 3.35-3.43 (m, 1H), 3.22-3.35 (m, 1H), 3.13-3.21 (m, 1H), 1.55-2.03 (m, 6H), 1.15-1.23 (t, 3H, J = 7.2, 7.2 Hz)

¹³C NMR (75 MHz, CDCl₃) δ = 171.0, 54.6, 51.5, 46.1, 41.3, 32.2, 29.3, 18.5, 12.3

HRMS : m/z: found 169.1333 [M + H]⁺, calculated 169.1314 [M + H]⁺.

3-(2-(3, 4-Dimethoxyphenoxy) ethyl)-3, 10-diazabicyclo [4.3.1] decan-2-one (22a)

To a solution of benzyl 3-(2-(3, 4-dimethoxyphenoxy) ethyl)-2-oxo-3, 10-diazabicyclo [4.3.1] decan-10-carboxylate **20a** (60mg, 0.1mmol) in 1 mL anhydrous MeOH was added catalytic amounts of Palladium on carbon and degassed with H₂. The reaction was stirred under 1 atm H₂ at room temperature for 1 h, filtered through celite, concentrated *in vacuo* and used for the next step without further purification.

TLC [10% MeOH in CHCl₃]: R_f = 0.17

Yield: 41mg, 0.1mmol (97%)

¹H NMR (600 MHz, CDCl₃): δ = 6.76 (d, 1H), 6.50 (d, 1H), 6.40 (m, 1H), 4.08-4.15 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75-3.82 (m, 3H), 3.33-3.35 (m, 1H), 3.2-3.26 (m, 1H), 2.23-2.24 (m, 1H), 1.98-2.12 (m, 2H), 1.5-1.75 (m, 6H)

¹³C NMR (150 MHz, CDCl₃): δ = 172.2, 153.3, 149.9, 143.6, 111.9, 103.9, 100.5, 67.3, 58.0, 56.4, 55.9, 51.1, 48.0, 45.9, 33.8, 30.3, 29.7, 29.9.

MS (ESI) m/z: found 335.13 [M + H]⁺, calculated 335.19 [M + H]⁺.

3-(3,4-Dimethoxyphenethyl)-3,10-diazabicyclo[4.3.1]decan-2-one (22b)

To a solution of benzyl 3-(3,4-dimethoxyphenethyl)-2-oxo-3,10-diazabicyclo[4.3.1]decan-10-carboxylate **20b** (10mg, 0.02mmol) in 1 mL anhydrous MeOH was added catalytic amounts of Palladium on carbon and degassed with H₂. The reaction was stirred under 1 atm H₂ at room temperature for 1 h, filtered through celite, concentrated *in vacuo* and used for the next step without further purification.

TLC [10% MeOH in CHCl₃]: R_f = 0.51

Yield: 5mg, 0.02mmol (71%)

MS (ESI) m/z: found 319.42 [M + H]⁺, calculated 319.20 [M + H]⁺.

2-Oxo-2-(3, 4, 5-trimethoxyphenyl) acetic acid (23a)

1-(3,4,5-Trimethoxyphenyl)ethanone (2.93g, 13.9mmol) and selenium dioxide (2.32g, 20.9mmol) in 60 mL pyridine were heated to 100°C for 14 h. The mixture was filtered through celite, concentrated *in vacuo* and purified with flash chromatography in hexane: EtOAc: AcOH 1:15:1.

TLC (Hexane: EtOAc: AcOH 1:15:1): R_f = 0.14

Yield: 2.19g, 9.1mmol (65%)

¹H NMR (600 MHz, CDCl₃) δ = 3.91 (s, 6H), 3.95 (s, 3H), 7.50 (s, 2H)

¹³C NMR (150 MHz, CDCl₃) δ = 56.3, 61.0, 108.0, 127.6, 144.2, 153.1, 165.7, 186.9

HRMS (EI): m/z: found 240.0624 [M]⁺, calculated 240.0634 [M]⁺.

3,3-Dimethyl-2-oxopentanoic acid (23e)

To a suspension of NaOH (175mg, 4.4mmol) and KMnO₄ (543mg, 3.4mmol) in 5 mL water at 0°C was added 3,3-dimethyl-2-pentanone (200mg, 1.8mmol). After stirring for 1 h at 0°C and 3 days at room temperature, the reaction was acidified with concentrated HCl and extracted with DCM (4 x 10 mL). The organic phases were dried over MgSO₄, concentrated *in vacuo* and purified with flash chromatography in hexane: EtOAc 5:1.

TLC [Hexane: EtOAc 5:1]: R_f = 0.45

Yield: 97mg, 0.7mmol (39%)

¹H NMR (300 MHz, CDCl₃) δ = 1.61 (q, 2H, J = 7.5, 7.5, 7.5 Hz), 1.21(s, 6H), 0.91 (t, 3H, J = 7.5, 7.5 Hz),

¹³C NMR (150 MHz, CDCl₃) δ = 9.2, 24.4, 33.1, 42.5, 185.3.

1-Tert-butyl 2-(2-(3,4-dimethoxyphenoxy)ethyl) piperidine-1,2-dicarboxylate (26)

26 was prepared as described.^[2]

2-(3,4-Dimethoxyphenoxy)ethyl piperidine-2-carboxylate (27)

1-tert-Butyl 2-(2-(3,4-dimethoxyphenoxy)ethyl) piperidine-1,2-dicarboxylate **26** (456mg, 1.1mmol) in 10 mL 20% TFA in DCM was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and used for next step without further purification .

TLC [Hexane: EtOAc: TEA 7.5:2.3:0.4]: R_f = 0.19

Yield: 344mg, 1.1mmol (100%)

¹H NMR (600 MHz, CDCl₃) δ = 6.76 (d, 1H, J = 9 Hz), 6.50 (d, 1H, J = 3 Hz), 6.35 (dd, 1H, J = 3.9 Hz), 4.45-4.54 (m, 2H), 4.11 (t, 2H, J = 4.2 Hz), 3.92 (dd, 1H, J = 3.6, 11.4 Hz), 3.83 (s, 3H), 3.82 (s, 3H), 3.55 (d, 1H, J = 12.6 Hz), 2.99-3.04 (m, 1H), 2.24-2.28 (m, 1H), 1.82-1.97 (m, 4H), 1.54-1.61 (m, 1H),

¹³C NMR (150 MHz, CDCl₃) δ = 168.5, 152.7, 149.9, 144.0, 111.7, 103.9, 101.0, 65.9, 64.7, 56.8, 56.4, 55.8, 44.1, 25.6, 21.7, 21.5

HRMS (EI): m/z: found 309.1580 [M]⁺, calculated 309.1576 [M]⁺.

3,9-Diazabicyclo[3.3.1]nonan-2-one (28)

To a solution of benzyl 2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate **16** (84mg, 0.3mmol) in 1 mL anhydrous MeOH was added catalytic amounts of Palladium on carbon and degassed with H₂. After stirring under 1 atm H₂ at room temperature for 2 h, the reaction mixture was filtered through celite, concentrated *in vacuo* and used for the next step without further purification.

TLC [20% MeOH in CHCl₃]: R_f = 0.17

Yield: 35mg, 0.25mmol (82%).

3,10-Diazabicyclo[4.3.1]decan-2-one (29)

To a solution of benzyl 2-oxo-3, 10-diazabicyclo [4.3.1] decane-10-carboxylate **17** (33mg, 0.1mmol) in 1 mL anhydrous MeOH was added catalytic amounts of Palladium on carbon and degassed with H₂. After stirring under 1 atm H₂ at room temperature for 3 h, the reaction mixture was filtered through celite, concentrated *in vacuo* and used for the next step without further purification.

TLC [20% MeOH in CHCl₃]: R_f = 0.26

Yield: 17mg, 0.1mmol (100%).

(S)-2-(3,4-Dimethoxyphenoxy)ethyl 1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carboxylate (2h).

2h was prepared as described.^[3]

2-(3,4-Dimethoxyphenoxy)ethyl 1-(2-((1R,2S)-2-ethyl-1-hydroxycyclohexyl)-2-oxoacetyl)piperidine-2-carboxylate (2g).

2g was prepared as described.^[2]

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one, 5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (31).

The polycycle core **31** was synthesized as previously described.^[6]

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (5a)

The polycycle compound **5a** was synthesized as previously described.^[6]

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-methyl ester-2-oxoacetyl]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (32).

To a solution of **31** (100mg, 0.33 mmol) in 2 mL anhydrous DCM at 0°C was added TEA (50mg, 0.49 mmol) and stirred for 15 mins followed by addition of monomethyl oxalyl chloride (56mg, 0.46 mmol). After stirring 1.5h at 0°C, the reaction was quenched with saturated NaHCO₃ solution (5 mL), extracted with DCM (4 x 10 mL). The organic layers were dried over MgSO₄ and concentrated *in vacuo*. The mixture was purified with flash chromatography in hexane: EtOAc 1:1.

TLC [Hexane: EtOAc 1:1]: R_f = 0.2

Yield: 90mg, 0.23mmol (70%) purity >98%

¹H NMR (300 MHz, CDCl₃) δ = 6.18-6.36 (m, 2H), 5.43-5.46 (m, 0.3H), 5.01-5.04 (m, 0.7H), 4.86-4.92 (m, 1H), 4.81-4.85 (m, 0.7H), 4.62-4.69 (m, 1H), 4.3-4.34 (m, 0.3H), 3.74-3.87 (m, 7H), 2.86-2.96 (m, 1H), 2.66-2.76 (m, 1H), 2.48-2.54 (m, 1H), 2.11-2.22 (m, 1H), 2.03-2.1 (m, 1H), 1.85-1.93 (m, 1H), 1.75-1.85 (m, 2H), 1.5-1.6 (m, 3H)

¹³C NMR (75 MHz, CDCl₃) δ = (168.8, 168.5), (162.4, 159.9), (159.9, 159.8), (157.7, 157.4), (139.7, 138.4), (116.7, 116.1), (105.5, 105.4), (97.6, 97.4), (59.7, 59.0), (55.7, 55.6), (55.6, 55.5), (53.1, 53.0), (52.7, 52.5), 51.5, (48.0, 47.1), (41.1, 41.1), (31.5, 30.8), (30.3, 30.2), (28.4, 27.1), (18.3, 18.2)

HRMS (EI) : m/z: found 389.1718 [M]⁺, calculated 389.1713 [M]⁺.

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