Unified Synthesis of Polycyclic Alkaloids via Complementary Carbonyl Activation

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Abstract: A complementary dual carbonyl activation strategy for the synthesis of polycyclic alkaloids has been developed. Successful applications include the synthesis of tetracyclic alkaloids harmalanine, harmalacine, pentacyclic indoloquinolizidine alkaloid nortetoyobyrine, and octacyclic β -carboline alkaloid peganumine A. The latter synthesis features a protecting-group-free assembly and an asymmetric disulfonimide catalyzed cyclization. Furthermore, formal syntheses of hirsutine, deplancheine, 10-desbromo-arborescine A, and oxindole alkaloids rhynchophylline and isorhynchophylline have been achieved. Finally, a concise synthesis of berberine alkaloid ilicifoline B was completed.

Despite the advancement of combinatorial strategies, natural products remain an indispensable source for the discovery of new molecular entities.^[1] Their diverse scaffolds with hydrogen bond donor and acceptor groups positioned in a well-defined spatial arrangement make them attractive starting points and inspiration for drug development.^[2] Bioactive polycyclic alkaloids, such as yohimbine (1), hirsutine (2), deplancheine (3), eburnamonine (4), ilicifoline B (5), peganumine A (6), and reserpine (7), contain the common quinolizidine core I fused to different heterocyclic rings (Figure 1). We reasoned that developing a straightforward annulation method for efficient construction of these scaffolds is beneficial for the total synthesis of polycyclic natural products and their analogs. Since the indole substructure is a privileged^[3] and very common motif in these polycyclic natural products, we started our synthetic journey with the quinolizidine-fused indole core. We strategized that incorporating an enamide motif into the A ring would provide a flexible handle for subsequent transformations. Therefore, intermediate III was considered the central linchpin for a divergent synthesis of polycyclic alkaloids. It was envisioned to be derived from IV by an annulation sequence involving an electrophilic cyclization followed by lactamization. Toward this goal we identified two major challenges: 1) selective activation of the amide carbonyl group to participate in the electrophilic cyclization;^[4] 2) subsequent selective activation of the second carbonyl group to achieve lactamization.

Figure 1. Common alkaloids with a tetracyclic substructure.

We conceived a one-pot approach in which IV can be prepared by two-fold condensation of V, VI and active ester component. By permutation of the substrates V and VI, a variety of polycyclic ring system with diverse substitution patterns could be accessed (Scheme 1).

Scheme 1. Synthetic strategy.

In order to orchestrate the subsequent activations, we initially investigated the reaction using the amide 8a as the model substrate (for its preparation see the Supporting Information). We tested different conditions to achieve selective amide activation via reactive nitrilium ions,^[3] including a variety of phosphorus (V) reagents frequently applied in the Bischler-Napieralski reaction^[5] and the von Braun amide degradation (Table 1, entries 1–4).^[6] We also screened strong electrophiles, such as Me₃SiCl and (COCl)₂,^[7] and the Tf₂O / 2-chloropyridine system^[8] which have been used successfully in electrophilic amide activation recently (Table 1, entries 5–7). Most of these

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conditions afforded tricyclic imine **9** as the major product. Unfortunately, the subsequent imine acylation to give tetracyclic product turned out to be challenging. With POCl_3 , **10** was isolated in 6% yield along with 84% of imine **9** (Table 1, entry 1). This result indicated that the reaction had stopped after the first cyclization. We hypothesized that imine–enamine tautomerization during second cyclization could also be a critical prerequisite for the second cyclization.^[9] After a screening of bases (see the SI), we achieved a slight improvement to 10% yield of **10** using K_2CO_3 (Table 1, entry 8). With $n\text{Bu}_4\text{NBr}$ as phase transfer catalyst and methanol, the yield of **10** was further increased to 18% (Table 1, entry 9). Inspired by active ester activation strategies used in peptide synthesis,^[10] we tested a variety of ester derivatives (see the SI). Satisfyingly, with 1,1,1,3,3,3-hexafluoro-2-propoxy ester **8d**, we achieved a 90% yield of **10** (Table 1, entry 12).

Table 1. Optimization of reaction condition.

Entry ^[a]	Substrate	Amide activation reagent	Solvent	T/°C	Yield[%] ^[b]
1	8a	POCl_3	toluene	110	9 (84) 10 (6)
2	8a	P_2O_5	toluene	110	9 (8) 10 (4)
3	8a	T_3P	toluene	110	9 (3)
4	8a	PCl_5	toluene	110	9 (12) 10 (7)
5	8a	TMSCl	THF	60	N.R.
6	8a	$(\text{COCl})_2$	DCM	23	N.D.
7 ^[c]	8a	TiF_2O	DCM	23	9 (53)
8 ^[d]	8a	POCl_3	toluene	110	10 (10)
9 ^[e]	8a	POCl_3	toluene/MeOH	110 to 80	10 (18)
10 ^[e]	8b	POCl_3	toluene/MeOH	110 to 80	10 (62)
11 ^[e]	8c	POCl_3	toluene/MeOH	110 to 80	10 (18)
12 ^[e]	8d	POCl_3	toluene/MeOH	110 to 80	10 (90)

[a] Reactions were performed with substrate (0.15 mmol), amide activation reagent (0.15 mmol) in solvent (2.0 mL) as stated. [b] isolated yield. [c] 2-Cl-pyridine was used. [d] K_2CO_3 was used. [e] mixture of K_2CO_3 and $n\text{Bu}_4\text{NBr}$ in MeOH was added and temperature was decreased to 80°C after the addition.

With optimized conditions in hand, we explored the scope of the reaction for the synthesis of diverse polycyclic scaffolds (Table 2). Substitutions at the indole ring with electron donating groups (**12a** and **12b**) and electron withdrawing groups (**12c** and **12d**) were well tolerated, providing the corresponding tetracyclic scaffolds in good yields (76–86%).

Table 2. Substrate scope.^[a]

[a] Reactions were performed with substrate (0.10–4.7 mmol) using the standard procedure, isolated yields. See the SI for details.

Encouraged by these results, we investigated additional substitution patterns and ring systems. Substituting the quinolizidine core afforded the tetracycles **12e–12j** in good yields (64–83%) thus providing access to the indoloquinolizidine-type alkaloid nortetoybyrine (**12j**)^[11] in an additional step. The 7/6, 8/6, 6/7 and 6/8 fused ring systems were obtained in moderate yield (**12k–12n**, 26–52%). Finally, we successfully expanded our strategy to benzene derivatives and hetero-

aromatic compounds, such as furan, thiophene, and benzo-thiophene (**12o–12x**, 33%–91%)

We next turned our attention to manipulations in the A ring in order to fully exploit our scaffold for natural product synthesis. Through oxidation, a second double bond could be easily introduced to the 3,4-position (**VII**). Reduction of the double bond in the 1,2-position (**VIII**) could be achieved with or without concomitant reduction of the lactam. Moreover, introduction of a carbonyl group in 4-position (**IX**) was key to the synthesis of more complex natural product.

Scheme 2. Diversification strategy for the tetracyclic scaffold.

Starting with the dehydrogenation, we tested selenium- and sulfur-based reagents, such as PhSeCl, PhSeBr, PhSSPh and *N*-*tert*-butyl phenylsulfonimidoyl chloride (see the SI).^[12] Among standard protocols, only *N*-*tert*-butyl phenylsulfonimidoyl chloride afforded traces of the desired product. Gratifyingly, using the palladium-catalyzed amide dehydrogenation protocol developed by Newhouse,^[13] demethoxyharmalanine (**14a**), harmalanine (**14b**), demethoxyharmalacine (**14c**) and harmalacine (**14d**),^[14] were successfully obtained in an excellent yield (60–77%).

Scheme 3. Oxidative diversification.

Racemic **15** can be obtained through selective catalytic hydrogenation of **10** using palladium on carbon. From this intermediate, selenoxide elimination affords **16**, a key intermediate in the total synthesis of hirsutine (**2**), rhynchophylline (**17**) and isorhynchophylline (**18**).^[15] An asymmetric reduction of the C–C double bond was realized using chiral phosphoric acid (CPA) **19** and Hantzsch ester (**20**) system^[16] to give **15** in 80% ee and 61% yield. This material can be converted into (*S*)-deplancheine (**3**) and (*S*)-10-desbromoarborescidine A (**21**) as previously reported.^[17]

Scheme 4. Reductive diversification.

To further demonstrate the synthetic potential of this method, we envisioned to use our annulation in a protecting-group- and transition-metal-free asymmetric total synthesis of peganumine A (**6**).^[18]

Scheme 5. Protecting-group-free synthesis of (±)-peganumine A.

Following the established protocol, we successfully prepared the tetracyclic intermediate **25** in 85% yield. Subsequently, ketoenamide **26** was obtained in 50% yield through a two-step α -oxidation sequence. The Boc-derivative of **26** constitutes an intermediate in Zhu's elegant total synthesis of peganumine A (**6**).^[19] At this point, we contemplated the possibility of a

protecting-group-free synthesis. The key cascade cyclization was achieved using 0.2 equiv. of TFA in toluene to complete a protecting-group-free synthesis of ($\pm$)-**6** in 42% yield.

Encouraged by the success of the previous cascade cyclization, we initiated investigations toward an asymmetric total synthesis. First, we tested the chiral thiourea (CTU) and PhCO₂H system developed by Jacobsen,^[20] which afforded 92% ee in Zhu's synthesis^[19] for the Boc-protected substrate. In our protecting-group-free substrate, with **27** and PhCO₂H, the enantioselectivity was 9% ee. We speculated that the remarkable difference in enantioselectivity could be attributed to an impaired recognition between substrate and catalyst. It is possible that either the Boc group is crucial for the recognition, or that the free α -ketoenamide **26** interrupted the substrate binding. Based on these considerations, we proposed to either apply a multi-binding-site catalyst to rigidify the transition state, or to use asymmetric counteranion directed catalysis (ACDC)^[21] as stronger chiral acid to activate the imine more efficiently. First, we tested the conjugate-base-stabilized Brønsted acid (CBSBA) **28** developed by Seidel,^[22] and 1,2,3,4,5-pentacarboxycyclopentadiene (PCCP) derived pentamethyl ester **29**, a novel C–H acid discovered by Lambert,^[23] which are all multi-binding-site catalysts. However, no improvement of the enantioselectivity could be achieved with our substrate. Moving to the ACDC using CPA-2 (**30**), a significant improvement of the enantioselectivity (31% ee) was observed. Expanding on this idea, we applied the stronger chiral Brønsted acid disulfonimide (DSI)^[24] to the reaction and obtained 79% ee with DSI-1 (**31**). Encouraged by this promising result, and after intensive screening of DSIs (see the SI), we finally discovered that using DSI-2 (**32**) could achieve 97% ee and 81% yield.

Figure 2. Representative chiral Brønsted acids.

Table 3. Optimization of the asymmetric Pictet–Spengler reaction cascade.

Entry	Catalyst[mol%]	Solvent	T[°C]	ee[%]	Yield[%] ^[a]
1	CTU (20) + PhCOOH (20)	toluene/DCM 9:1	35	9	27
2	CBSBA (20)	toluene	110	N.D.	N.D.
3	PCCP (20)	toluene	110	4	44
4	CPA-2 (20)	toluene	110	10	32
5	CPA-2 (20)	toluene	90	31	60
6	DSI-1 (5)	toluene	70	79	53
7	DSI-2 (5)	toluene	70	83	66
8	DSI-2 (10)	toluene	70	94	34
9	DSI-2 (10)	toluene	60	97	81
10 ^[b]	ent-DSI-2 (10)	toluene	60	–97	68

[a] isolated yields, see SI for detailed screenings. [b] using the enantiomer of the DSI-2 to obtain the enantiomer of pegamunine A.

Inspired by the great potential of total synthesis of indole alkaloids, this annulation was further extended to the synthesis of dimeric berberine alkaloid ilicifoline B (**5**).^[25] Using our standard reaction sequence, 8-oxopseudopalmitine (**36**) was obtained in 95% yield for the annulation. Using Opatz's dimerization procedure,^[26] racemic ilicifoline B was synthesized. Moreover, 8-oxopseudopalmitine (**36**) can be transformed into the tetracyclic protoberberine alkaloid xylopinine (**37**) according to the reported method.^[27]

Scheme 6. Synthesis of berberine alkaloids.

In summary, we have developed an efficient method that is enabling to the rapid assembly of polycyclic scaffolds of bioactive alkaloids, through a straightforward annulation reaction featuring a complementary carbonyl activation strategy. Diverse polycyclic ring systems were accessed in good yields, enabling the total synthesis of different types of alkaloids and their analogs. Through diverging pathways, the total synthesis of five alkaloids and formal total synthesis of six alkaloids were completed. Among them, a synthesis of (+)- and (–)-peganumine A (**6**) was achieved in a protecting-group-free sequence using a DSI catalyzed Pictet–Spengler reaction as the key step. Finally, we also applied this method to a synthesis of dimeric berberine alkaloid ilicifoline B (**5**).

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Entry for the Table of Contents

An efficient construction of polycyclic scaffolds of bioactive alkaloids via a novel annulation strategy has been developed. Among several natural products prepared, a synthesis of the dimeric berberine alkaloid ilicifoline B and a protecting-group-free synthesis of (+)- and (–)-peganumine A have been achieved. The latter features an asymmetric Brønsted acid catalyzed cyclization cascade.

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Supporting Information for

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1. General information

Unless otherwise stated, all reactions were magnetically stirred and conducted in anhydrous solvents under argon, applying standard Schlenk techniques. Solvents and liquid reagents, as well as solutions of solid or liquid reagents were added via syringes, stainless steel cannulas through rubber septa or micropipettes in a weak stream of argon. Solid reagents were added through a weak argon counter-flow. Cooling baths were prepared in Dewar vessels, filled with ice/water (0 °C), or dry ice/acetone (−78 °C). Heated oil baths were used for reactions requiring elevated temperatures. Solvents were removed under reduced pressure at 40 °C using a rotary evaporator. All given yields are isolated yields of NMR spectroscopically pure materials, unless otherwise stated.

Chemicals

Chemicals (Abcr, Alfa Aesar, Apollo Scientific, Fisher Scientific, Fluorochem, Sigma-Aldrich, TCI) were purchased as reagent grade and used without further purification unless otherwise stated. Molecular sieves (MS) 4 Å were dried at 150 °C under vacuum and stored in Schlenk flask.

Solvents

Solvents (toluene, tetrahydrofuran (THF), dichloromethane (DCM)) were purified with the solvent purification system Braun MB-SPS-800 (Institut für Chemie und Biochemie, Freie Universität Berlin) or dried by distillation from an appropriate drying agent and stored in Schlenk flasks under argon (Max-Planck-Institut für Kohlenforschung). Additional solvents (dimethylformamide (DMF) and methanol) were purchased from Fisher Scientific in AcroSeal[®]-bottles under argon atmosphere with MS 4 Å.

Thin-layer chromatography (TLC)

TLC was performed using silica gel coated aluminum plates (ALUGRAM[®] Xtra SIL G/UV254, Macherey-Nagel) or pre-coated silica gel plastic sheets (Polygram SIL G/UV254, 0.20 mm, with fluorescent indicator; Macherey-Nagel) which were visualized under irradiation with UV light ($\lambda = 254$) or vanillin stain (500 mg vanillin, 5 mL H₂SO₄ (conc.), 10 mL HOAc, 100 mL MeOH).

Column Chromatography

Column chromatography was carried out using silica gel from Merck or Macherey & Nagel (60 Å, 230–400 mesh, particle size 40–63 µm) or neutral aluminium oxide from Fisher Scientific (Brockmann I, 60 Å, 50–200 µm) using technical grade solvents. Fractions containing a desired substance were combined and concentrated in vacuo. Solvent mixtures (mobile phase) are reported in terms of volume ratios (v/v).

Nomenclature

Nomenclature follows the suggestions proposed by the computer program ChemDraw Professional (17.1.0.105) of PerkinElmer.

Nuclear Magnetic Resonance (NMR) Spectroscopy

^1H and ^{13}C NMR spectra were recorded on a JEOL ECX 400 (400 MHz), JEOL ECP 500 (500 MHz), Bruker Avance 500 (500 MHz), JEOL ECZ600 S (600 MHz) and Bruker Avance 700 (700 MHz) spectrometers in reported deuterated solvent. All spectra were processed with MestReNova 12.0.3. The residual deuterated solvent signal relative to tetramethylsilane (TMS) was used as the internal reference in ^1H NMR spectra (DMSO δ [ppm] = 2.50; CD_2Cl_2 δ [ppm] = 5.32; CD_3OD δ [ppm] = 3.31; C_6D_6 δ [ppm] = 7.16; CDCl_3 δ [ppm] = 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (DMSO δ [ppm] = 39.5; CD_2Cl_2 δ [ppm] = 53.8; CD_3OD δ [ppm] = 49.0, CDCl_3 δ [ppm] = 72.16; C_6D_6 δ [ppm] = 128.0).

Mass Spectrometry

High resolution mass spectrometry (HRMS) was performed on a Finnigan MAT 95 (EI), Bruker APEX III FTMS (ESI) or Agilent 6210 (ESI). The ionization method and mode of detection employed is indicated for the respective experiment and all masses are reported in atomic units per elementary charge (m/z).

IR Spectroscopy

IR Spectra were recorded on a JASCO FT/IR-4100 spectrometer. Characteristic absorption bands are reported in wavenumbers ν in cm^{-1} and were analyzed with the software Spectral Manager from JASCO.

Specific Rotations

Specific rotations $[\alpha]_D^{25}$ were measured on a Rudolph RA Autopol IV Automatic Polarimeter or JASCO P-2000 Polarimeter at the indicated temperature with a sodium lamp (sodium D line, $\lambda = 589 \text{ nm}$). Measurements were performed in an acid resistant 50 mm cell (Rudolph) or 100 mm (JASCO) with concentrations (g/100 mL) reported in the corresponding solvent.

High Performance Liquid Chromatography (HPLC)

HPLC was performed on Shimadzu LC-20AD liquid chromatograph (SIL-20AC auto sampler, CMB-20A communication bus module, DGU-20A5 degasser, CTO-20AC column oven, SPD-M20A diode array detector), Shimadzu LC-20AB liquid chromatograph (SIL-20ACHT auto sampler, DGU-20A5 degasser, CTO-20AC column oven, SPD-M20A diode array detector), or Agilent Technologies 1200 series with CHIRALPAK[®] IA. All solvents used were HPLC-grade solvents purchased from Sigma-Aldrich or VWR. The column employed and respective solvent mixture are indicated for each experiment.

2. Experimental procedures

2.1. Preparation of substrates

General procedure A

A mixture of the amine (1.0 equiv.) and the anhydride (1.0 equiv.) in DMF, was stirred overnight at room temperature. Then *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) (2.0 equiv.), 4-dimethylaminopyridine (DMAP) (0.2 equiv.) and corresponding alcohol (5.0 equiv.) were added to the reaction

mixture subsequently. The resulting mixture was stirred for 24 h at room temperature, before the reaction mixture was diluted with H₂O and EtOAc. After washing by brine for three times, the organic phase was dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography. (Note: It is not necessary to perform the reaction under argon.)

General procedure B

A mixture of the amine (1.0 equiv.) and the anhydride (1.0 equiv.) in corresponding alcohol was stirred overnight at room temperature. The mixture was then cooled to 0 °C and SOCl₂ (1.0 equiv.) was added dropwise. Immediately after the addition, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with NaHCO₃ (sat. aq.) and extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography.

(Note: It is not necessary to perform the reaction under argon.)

2.1.1. Substrates for the reaction optimization

Methyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (**8a**).

8a was prepared according to **General procedure B**, starting from tryptamine (1.50 g, 9.38 mmol, 1.0 equiv.) and glutaric anhydride (1.07 g, 9.38 mmol, 1.0 equiv.) in MeOH (30 mL). The reaction mixture was subsequently treated with SOCl₂ (680 μL, 9.38 mmol, 1.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8a** (2.39 g, 8.33 mmol, 88%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.51 (s, 1H), 7.36 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.36

(dt, $J = 8.1, 1.0$ Hz, 1H), 7.19 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.11 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 6.99 (d, $J = 2.3$ Hz, 1H), 5.72 (s, 1H), 3.64 (s, 3H), 3.58 (td, $J = 6.8, 5.7$ Hz, 2H), 2.95 (td, $J = 6.8, 0.8$ Hz, 2H), 2.33 (t, $J = 7.3$ Hz, 2H), 2.14 (t, $J = 7.4$ Hz, 2H), 1.94–1.89 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 173.8, 172.3, 136.6, 127.4, 122.3, 122.2, 119.4, 118.7, 112.8, 111.4, 51.7, 39.8, 35.6, 33.2, 25.4, 20.9.

HRMS-ESI: calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 311.1366; found: 311.1371.

FT-IR: ν [cm^{-1}] = 3394, 3297, 2949, 1731, 1647, 1533, 1457, 1436, 1226, 1152, 743.

4-Nitrophenyl 5-((2-(1H-indol-3-yl)ethyl)amino)-5-oxopentanoate (**8b**).

8b was prepared according to **General procedure A**, starting from tryptamine (300 mg, 1.87 mmol, 1.0 equiv.) and glutaric anhydride (214 mg, 1.87 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (718 mg, 3.74 mmol, 2.0 equiv.), DMAP (45.8 mg, 0.374 mmol, 0.2 equiv.) and *p*-nitrophenol (1.30 g, 9.36 mmol, 5.0 equiv.). Purification by silica gel column chromatography (DCM/MeOH = 10:1) afforded **8b** (318 mg, 0.806 mmol, 43%) as a yellow solid.

^1H NMR (500 MHz, CD_3OD : CDCl_3 (v/v = 1:1)) δ [ppm] = 8.27–8.21 (m, 2H), 7.57–7.53 (m, 1H), 7.35–7.31 (m, 1H), 7.29–7.25 (m, 2H), 7.09 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 7.05–6.98 (m, 2H), 3.51 (t, $J = 7.2$ Hz, 2H), 2.95 (t, $J = 7.3$ Hz, 2H), 2.60 (t, $J = 7.4$ Hz, 2H), 2.26 (t, $J = 7.3$ Hz, 2H), 2.03–1.97 (m, 2H).

^{13}C NMR (176 MHz, CD_3OD : CDCl_3 (v/v = 1:1)) δ [ppm] = 173.0, 170.7, 155.2, 144.9, 136.3, 127.0, 124.7, 124.6, 122.1, 121.9, 121.0, 118.2, 117.8, 117.8, 111.6, 110.9, 39.7, 34.4, 32.7, 24.7, 20.2.

(Due the poor solubility of this compound, the mixture of CD_3OD : CDCl_3 (v/v = 1:1) was used for ^1H NMR and ^{13}C NMR spectroscopies.)

HRMS-ESI: calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_5\text{K}$ $[\text{M} + \text{K}]^+$: 434.1113; found: 434.1125.

FT-IR: ν [cm^{-1}] = 2925, 1591, 1522, 1336, 1290, 1208, 1109.

Isopropyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8c).

8c was prepared according to **General procedure B**, starting from tryptamine (500 mg, 3.12 mmol, 1.0 equiv.) and glutaric anhydride (356 mg, 3.12 mmol, 1.0 equiv.) in *i*PrOH (10.0 mL). The reaction mixture was subsequently treated with SOCl₂ (221 μ L, 3.12 mmol, 1.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8c** (524 mg, 1.66 mmol, 53%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.44 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.00 (s, 1H), 5.69 (s, 1H), 5.06–4.90 (m, 1H), 3.59 (q, J = 6.4 Hz, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.14 (t, J = 7.4 Hz, 2H), 1.91 (t, J = 7.3 Hz, 2H), 1.22 (d, J = 1.9 Hz, 3H), 1.20 (d, J = 1.8 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 172.9, 172.4, 136.6, 127.4, 122.3, 122.2, 119.5, 118.8, 112.9, 111.4, 67.8, 39.8, 35.7, 33.8, 25.4, 21.9, 21.1.

HRMS-ESI: calcd. for C₁₈H₂₄N₂O₃Na [M + Na]⁺: 339.1679; found: 339.1692.

FT-IR: ν [cm⁻¹] = 3287, 2978, 1724, 1646, 1531, 1456, 1373, 1226, 1105, 740.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8d).

8d was prepared according to **General procedure A**, starting from tryptamine (3.60 g, 22.5 mmol, 1.0 equiv.) and glutaric anhydride (2.56 g, 22.5 mmol, 1.0 equiv.) in DMF (80 mL). The reaction mixture was subsequently treated with EDCI (8.59 g, 45.0 mmol, 2.0 equiv.), DMAP (550 mg, 4.50 mmol, 0.2 equiv.) and hexafluoroisopropano (HFIP) (11.9 mL, 112 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8d** (4.80 g, 11.3 mmol, 50%) as a white solid.

¹H NMR (600 MHz, CDCl₃) δ [ppm] = 8.21 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.37 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.24–7.18 (m, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 5.79–5.73 (m, 1H), 5.56 (t, *J* = 5.8 Hz, 1H), 3.62–3.59 (m, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.15 (t, *J* = 7.2 Hz, 2H), 2.01–1.97 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ [ppm] = 171.5, 170.1, 136.6, 127.5, 122.4, 122.2, 120.5 (q, *J* = 282.2 Hz), 119.7, 118.8, 113.0, 111.4, 67.0–66.1 (m), 39.9, 34.9, 32.4, 25.4, 20.4.

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = –73.19 (d, *J* = 5.9 Hz).

HRMS-ESI: calcd. for C₁₈H₁₈F₆N₂O₃Na [M + Na]⁺: 447.1114; found: 447.1113.

FT-IR: ν [cm^{–1}] = 3418, 3328, 1777, 1753, 1633, 1540, 1384, 1359, 1286, 1228, 1201, 1108, 740.

2,2,2-Trifluoroethyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8e).

8e was prepared according to **General procedure A**, starting from tryptamine (285 mg, 1.78 mmol, 1.0 equiv.) and glutaric anhydride (203 mg, 1.78 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (680 mg, 3.56 mmol, 2.0 equiv.), DMAP (43.5 mg, 0.356 mmol, 0.2 equiv.) and 2,2,2-trifluoroethanol (675 μL, 8.91 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8e** (275 mg, 0.772 mmol, 43%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.13 (s, 1H), 7.60 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 5.54 (s, 1H), 4.44 (q, *J* = 8.5 Hz, 2H), 3.61 (q, *J* = 6.5 Hz, 2H), 2.98 (td, *J* = 6.7, 0.8 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.16 (t, *J* = 7.3 Hz, 2H), 1.99–1.93 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 171.8, 171.7, 136.6, 127.5, 123.1 (q, *J* = 277.0 Hz), 122.4, 122.2, 119.7, 118.8, 113.1, 111.4, 60.7–59.9 (m), 39.8, 35.3, 32.8, 25.4, 20.6.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = -73.65 (t, J = 8.6 Hz).

HRMS-ESI: calcd. for C₁₇H₁₉F₃N₂O₃Na [M + Na]⁺: 379.1240; found: 379.1244.

FT-IR: ν [cm⁻¹] = 3388, 3322, 2927, 1736, 1630, 1545, 1411, 1275, 1261, 1179, 740.

1,1,1-Trifluoropropan-2-yl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate(8f).

8f was prepared according to **General procedure A**, starting from tryptamine (150 mg, 0.938 mmol, 1.0 equiv.) and glutaric anhydride (107 mg, 0.938 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (358 mg, 1.88 mmol, 2.0 equiv.), DMAP (22.9 mg, 0.188 mmol, 0.2 equiv.) and 1,1,1-trifluoro-2-propanol (424 μ L, 4.69 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8f** (70.0 mg, 0.189 mmol, 20%) as a white solid.

¹H NMR (500 MHz, CD₃OD) δ [ppm] = 7.55 (dt, J = 7.9, 1.0 Hz, 1H), 7.32 (dt, J = 8.2, 0.9 Hz, 1H), 7.08 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.04 (s, 1H), 7.00 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 5.41–5.33 (m, 1H), 3.47 (t, J = 7.3 Hz, 2H), 2.98–2.88 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.18 (t, J = 7.4 Hz, 2H), 1.90–1.84 (m, 2H), 1.36 (d, J = 6.6 Hz, 3H).

¹³C NMR (126 MHz, CD₃OD) δ [ppm] = 174.9, 172.6, 138.1, 128.8, 125.6 (q, J = 279.1 Hz), 123.4, 119.6, 119.3, 113.2, 112.2, 68.2–67.4 (m), 41.4, 35.8, 33.7, 26.2, 21.9, 13.7, 13.7.

¹⁹F NMR (471 MHz, CD₃OD) δ [ppm] = -80.2. (Due to the resolution, the coupling was not observed.)

HRMS-ESI: calcd. for C₁₈H₂₁F₃N₂O₃Na [M + Na]⁺: 393.1396; found: 393.1410.

FT-IR: ν [cm⁻¹] = 3396, 3324, 2932, 1749, 1730, 1631, 1542, 1458, 1386, 1278, 1187, 1165, 1118, 1092, 1017, 741.

Perfluorophenyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8g).

8g was prepared according to **General procedure A**, starting from tryptamine (300 mg, 1.87 mmol, 1.0 equiv.) and glutaric anhydride (214 mg, 1.87 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (715 mg, 3.74 mmol, 2.0 equiv.), DMAP (45.8 mg, 0.374 mmol, 0.2 equiv.) and pentafluorophenol (1.71 g, 9.36 mmol, 5.0 equiv.). Purification by silica gel column chromatography (DCM/MeOH = 10:1) afforded **8g** (382 mg, 0.867 mmol, 46%) as a yellow solid.

¹H NMR (500 MHz, CD₃OD) δ [ppm] = 7.54 (dd, J = 7.9, 1.0 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.10–7.01 (m, 2H), 7.01–6.93 (m, 1H), 3.49 (t, J = 7.3 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H), 2.66 (t, J = 7.4 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.00–1.94 (m, 2H).

¹³C NMR (126 MHz, CD₃OD) δ [ppm] = 174.7, 170.4, 143.4, 141.5, 140.2, 139.6, 138.1, 128.8, 126.4, 123.6, 123.4, 122.3, 119.6, 119.5, 119.3, 113.2, 112.2, 41.3, 35.6, 33.0, 26.2, 21.9. (Due to the complexity of the F–C coupling, the coupling constants were not calculated.)

¹⁹F NMR (471 MHz, CD₃OD) δ [ppm] = –155.3 (d, J = 17.7 Hz), –161.3 (t, J = 20.7 Hz), –165.5 (m).

HRMS-ESI: calcd. for C₂₁H₁₇F₅N₂O₃Na [M + Na]⁺: 463.1051; found: 463.1067.

FT-IR: ν [cm^{–1}] = 3289, 2933, 1787, 1652, 1457, 1107, 1101, 743.

3-Methylbut-2-en-1-yl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8h).

8h was prepared according to **General procedure A**, starting from tryptamine (509 mg, 3.18 mmol, 1.0 equiv.) and glutaric anhydride (363 mg, 3.18 mmol, 1.0 equiv.) in DMF (15.0 mL). The reaction mixture was subsequently treated with EDCI (1.21 g,

6.36 mmol, 2.0 equiv.), DMAP (77.7 mg, 0.636 mmol, 0.2 equiv.) and 3-methyl-2-buten-1-ol (1.61 mL, 15.9 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **8h** (468 mg, 1.37 mmol, 43%) as a light yellow solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.20 (s, 1H), 7.63–7.57 (m, 1H), 7.37 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 5.59 (s, 1H), 5.34–5.30 (m, 1H), 4.55 (d, *J* = 7.3 Hz, 2H), 3.60 (td, *J* = 6.7, 5.7 Hz, 2H), 2.97 (td, *J* = 6.8, 0.9 Hz, 2H), 2.33 (t, *J* = 7.2 Hz, 2H), 2.16 (t, *J* = 7.4 Hz, 2H), 1.95–1.89 (m, 2H), 1.75 (d, *J* = 1.4 Hz, 3H), 1.70 (d, *J* = 1.4 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 173.4, 172.3, 139.2, 136.6, 127.4, 122.24, 122.22, 119.5, 118.8, 118.6, 112.9, 111.4, 61.5, 39.8, 35.7, 33.5, 25.8, 25.4, 21.0, 18.1.

HRMS-ESI: calcd. for C₂₀H₂₆N₂O₃Na [M + Na]⁺: 365.1835; found: 365.1846.

FT-IR: ν [cm⁻¹] = 3398, 3293, 2969, 2932, 1728, 1650, 1537, 1457, 1378, 1339, 1229, 1151, 956, 742.

Benzhydryl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8i**).**

8i was prepared according to **General procedure A**, starting from tryptamine (513 mg, 3.20 mmol, 1.0 equiv.) and glutaric anhydride (366 mg, 3.20 mmol, 1.0 equiv.) in DMF (18.0 mL). The reaction mixture was subsequently treated with EDCI (1.22 g, 6.41 mmol, 2.0 equiv.), DMAP (78.3 mg, 0.641 mmol, 0.2 equiv.) and diphenylmethanol (2.95 g, 16.0 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **8i** (772 mg, 1.75 mmol, 55%) as a white solid.

¹H NMR (500 MHz, CD₂Cl₂) δ [ppm] = 8.30 (s, 1H), 7.55 (dd, *J* = 7.9, 2.7 Hz, 1H), 7.36–7.28 (m, 9H), 7.27–7.23 (m, 2H), 7.18–7.11 (m, 1H), 7.06 (dd, *J* = 8.6, 6.0 Hz, 1H), 6.97 (d, *J* = 2.7 Hz, 1H), 6.80 (d, *J* = 3.0 Hz, 1H), 5.55 (s, 1H), 3.52–3.48 (m, 2H),

2.89 (td, $J = 7.0, 2.8$ Hz, 2H), 2.47–2.37 (m, 2H), 2.06 (td, $J = 7.5, 2.8$ Hz, 2H), 1.95–1.84 (m, 2H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ [ppm] = 172.2, 171.8, 140.6, 136.5, 128.6, 127.9, 127.4, 126.9, 122.2, 122.0, 119.3, 118.6, 112.9, 111.3, 76.9, 39.7, 35.4, 33.6, 25.4, 21.0.

HRMS-ESI: calcd. for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 463.1992; found: 463.2008.

FT-IR: ν [cm^{-1}] = 3407, 3297, 2930, 1733, 1651, 1529, 1455, 1231, 1148, 743.

Cyclohexyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8j**).**

8j was prepared according to **General procedure A**, starting from tryptamine (509 mg, 3.18 mmol, 1.0 equiv.) and glutaric anhydride (363 mg, 3.18 mmol, 1.0 equiv.) in DMF (18.0 mL). The reaction mixture was subsequently treated with EDCI (1.21 g, 6.36 mmol, 2.0 equiv.), DMAP (77.7 mg, 0.636 mmol, 0.2 equiv.) and cyclohexanol (1.65 mL, 15.9 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8j** (362 mg, 1.02 mmol, 32%) as a white solid.

^1H NMR (700 MHz, CDCl_3) δ [ppm] = 8.28 (s, 1H), 7.59 (dt, $J = 7.8, 1.0$ Hz, 1H), 7.37 (dt, $J = 8.1, 0.9$ Hz, 1H), 7.20 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.12 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 7.03–7.00 (m, 1H), 5.65 (s, 1H), 3.60 (td, $J = 6.8, 5.8$ Hz, 2H), 3.49 (td, $J = 10.3, 4.0$ Hz, 1H), 2.97 (td, $J = 6.8, 0.9$ Hz, 2H), 2.52 (t, $J = 7.2$ Hz, 2H), 2.14 (t, $J = 7.4$ Hz, 2H), 1.96–1.92 (m, 2H), 1.91–1.85 (m, 2H), 1.72–1.65 (m, 2H), 1.62–1.55 (m, 1H), 1.45–1.35 (m, 4H), 1.29–1.23 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 172.8, 172.4, 136.6, 127.4, 122.24, 122.17, 119.5, 118.7, 112.8, 111.4, 72.8, 39.9, 35.7, 33.9, 31.7, 25.4, 23.8, 21.2. (One sp^3 carbon is missing, probably due to the resonance overlap.)

HRMS-ESI: calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 379.1992; found: 379.2006.

FT-IR: ν [cm^{-1}] = 3357, 3325, 2948, 2920, 2853, 1707, 1635, 1539, 1386, 1189, 1011, 748, 727.

Cyclohexyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanethioate (8k).

8k was prepared according to **General procedure A**, starting from tryptamine (506 mg, 3.16 mmol, 1.0 equiv.) and glutaric anhydride (360 mg, 3.16 mmol, 1.0 equiv.) in DMF (18.0 mL). The reaction mixture was subsequently treated with EDCI (1.21 g, 6.36 mmol, 2.0 equiv.), DMAP (77.2 mg, 0.632 mmol, 0.2 equiv.) and cyclohexanethiol (1.93 mL, 15.8 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8k** (401 mg, 1.08 mmol, 34%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.23 (s, 1H), 7.62 (dd, J = 7.9, 1.0 Hz, 1H), 7.39 (dt, J = 8.1, 1.0 Hz, 1H), 7.23 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.15 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 5.62 (s, 1H), 3.62 (td, J = 6.8, 5.7 Hz, 2H), 3.51 (ddt, J = 10.3, 6.2, 3.6 Hz, 1H), 2.99 (td, J = 6.8, 0.8 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.16 (t, J = 7.4 Hz, 2H), 1.99–1.94 (m, 2H), 1.93–1.87 (m, 2H), 1.75–1.68 (m, 2H), 1.65–1.56 (m, 1H), 1.49–1.36 (m, 4H), 1.34–1.23 (m, 1H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 199.2, 172.1, 136.6, 127.4, 122.3, 122.2, 119.6, 118.8, 113.0, 111.4, 43.1, 42.4, 39.8, 35.4, 33.1, 26.0, 25.6, 25.5, 21.7.

HRMS-ESI: calcd. for C₂₁H₂₈N₂O₂SN_a [M + Na]⁺: 395.1763; found: 395.1782.

FT-IR: ν [cm⁻¹] = 3399, 3285, 2929, 2852, 1652, 1530, 1448, 1341, 998, 741.

***Tert*-butyl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (8l).**

8l was prepared according to **General procedure A**, starting from tryptamine (150 mg, 0.938 mmol, 1.0 equiv.) and glutaric anhydride (107 mg, 0.938 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (358 mg, 1.88 mmol, 2.0 equiv.), DMAP (22.9 mg, 0.188 mmol, 0.2 equiv.) and *t*BuOH (445 μ L, 4.69 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **8l** (21.0 mg, 636 μ mol, 7%) as a white solid.

¹H NMR (600 MHz, CDCl₃) δ [ppm] = 8.28 (s, 1H), 7.63–7.58 (m, 1H), 7.37 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.04–7.00 (m, 1H), 5.65 (s, 1H), 3.64–3.56 (m, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.23 (t, *J* = 7.2 Hz, 2H), 2.14 (t, *J* = 7.4 Hz, 2H), 1.90–1.86 (m, 2H), 1.43 (s, 9H).

¹³C NMR (151 MHz, CDCl₃) δ [ppm] = 172.8, 172.4, 136.6, 127.4, 122.3, 122.2, 119.6, 118.8, 113.0, 111.4, 80.5, 39.8, 35.8, 34.8, 28.2, 25.5, 21.2.

HRMS-ESI: calcd. for C₁₉H₂₆N₂O₃Na [M + Na]⁺: 353.1835; found: 353.1852.

FT-IR: ν [cm⁻¹] = 3398, 3296, 2965, 2930, 1702, 1649, 1531, 1457, 1367, 1236, 1164, 1143, 741.

2.1.2. Substrates for the reaction scope

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(5-methoxy-1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (11a).

11a was prepared according to **General procedure A**, starting from 5-methoxytryptamine (200 mg, 1.05 mmol, 1.0 equiv.) and glutaric anhydride (120 mg, 1.05 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (402 mg, 2.10 mmol, 2.0 equiv.), DMAP (25.7 mg, 0.211 mmol, 0.2 equiv.) and HFIP (556 μL, 5.26 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11a** (270 mg, 0.595 mmol, 56%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.15 (s, 1H), 7.28–7.24 (m, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.00 (t, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.82–5.71 (m, 1H), 5.60 (s, 1H), 3.86 (s, 3H), 3.65–3.57 (m, 2H), 2.97–2.91 (m, 2H), 2.56 (td, *J* = 7.3, 1.0 Hz, 2H), 2.17 (t, *J* = 7.2 Hz, 2H), 2.03–1.97 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 171.6, 170.1, 154.2, 131.7, 127.8, 123.0, 120.5 (q, *J* = 285.6 Hz), 112.7, 112.5, 112.2, 100.7, 66.8–66.2 (m), 56.1, 39.7, 34.9, 32.4, 25.4, 20.4.

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = −73.18 (d, *J* = 5.8 Hz).

HRMS-ESI: calcd. for C₁₉H₂₁F₆N₂O₄ [M + H]⁺: 455.1400; found: 455.1408.

FT-IR: ν [cm^{−1}] = 3432, 3325, 2928, 1779, 1759, 1635, 1541, 1487, 1218, 1195, 1108, 927, 794.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(6-methoxy-1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (11b).

11b was prepared according to **General procedure A**, starting from 6-methoxytryptamine (100 mg, 0.526 mmol, 1.0 equiv.) and glutaric anhydride (60.0 mg, 0.526 mmol, 1.0 equiv.) in DMF (3.0 mL). The reaction mixture was subsequently treated with EDCI (201 mg, 1.05 mmol, 2.0 equiv.), DMAP (12.9 mg, 0.105 mmol, 0.2 equiv.) and HFIP (278 μL, 2.63 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11b** (100 mg, 0.220 mmol, 42%) as a white solid.

¹H NMR (500 MHz, CD₂Cl₂) δ [ppm] = 8.14 (s, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 6.93 (dd, *J* = 2.2, 1.1 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.86–5.79 (m, 1H), 5.59 (s, 1H), 3.82 (s, 3H), 3.54 (td, *J* = 6.9, 5.8 Hz, 2H), 2.90 (td, *J* = 6.9, 0.9 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.15 (t, *J* = 7.3 Hz, 2H), 2.00–1.90 (m, 2H).

¹³C NMR (126 MHz, CD₂Cl₂) δ [ppm] = 171.5, 170.5, 157.1, 137.6, 122.2, 121.2, 120.9 (q, *J* = 282.4 Hz), 119.6, 113.3, 109.8, 94.9, 67.3–66.2 (m), 55.9, 40.1, 35.1, 32.7, 25.8, 20.7.

¹⁹F NMR (471 MHz, CD₂Cl₂) δ [ppm] = −73.66. (Due to the resolution, the coupling was not observed.)

HRMS-ESI: calcd. for C₁₉H₂₀F₆N₂O₄Na [M + Na]⁺: 477.1219 found: 477.1222.

FT-IR: ν [cm^{−1}] = 3302, 2965, 2937, 1764, 1635, 1384, 1281, 1257, 1107, 824.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(6-bromo-1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (11c).

11c was prepared according to **General procedure A**, starting from 6-bromotryptamine (100 mg, 0.420 mmol, 1.0 equiv.) and glutaric anhydride (47.9 mg, 0.420 mmol, 1.0 equiv.) in DMF (3.0 mL). The reaction mixture was subsequently treated with EDCI (160 mg, 0.840 mmol, 2.0 equiv.), DMAP (10.3 mg, 84.0 μ mol, 0.2 equiv.) and HFIP (222 μ L, 2.10 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11c** (120 mg, 0.239 mmol, 57%) as a white solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 8.23 (s, 1H), 7.52 (dd, J = 1.7, 0.6 Hz, 1H), 7.44 (dd, J = 8.4, 0.7 Hz, 1H), 7.22 (dd, J = 8.4, 1.7 Hz, 1H), 7.00 (dd, J = 2.3, 0.9 Hz, 1H), 5.77–5.74 (m, 1H), 5.53 (d, J = 6.2 Hz, 1H), 3.58 (td, J = 6.9, 5.8 Hz, 2H), 2.94 (td, J = 6.9, 0.9 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 2.18 (t, J = 7.3 Hz, 2H), 2.02–1.98 (m, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 171.6, 170.0, 137.3, 126.4, 123.0, 122.7, 121.3, 120.5 (q, J = 281.7 Hz), 120.0, 116.0, 114.4, 113.3, 66.9–66.1 (m), 39.9, 34.9, 32.4, 25.4, 20.4.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.17 (d, J = 6.4 Hz).

HRMS-ESI: calcd. for C₁₈H₁₇BrF₆N₂O₃Na [M + Na]⁺: 525.0219; found: 525.0244.

FT-IR: ν [cm^{–1}] 3396, 3326, 2930, 1779, 1749, 1638, 1385, 1287, 1231, 1201, 1110, 803, 746.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(6-fluoro-1*H*-indol-3-yl)ethyl)amino)-5-oxopentanoate (11d).

11d was prepared according to **General procedure A**, starting from 6-fluorotryptamine

(260 mg, 1.46 mmol, 1.0 equiv.) and glutaric anhydride (166 mg, 1.46 mmol, 1.0 equiv.) in DMF (6.0 mL). The reaction mixture was subsequently treated with EDCI (558 mg, 2.92 mmol, 2.0 equiv.), DMAP (35.7 mg, 0.292 mmol, 0.2 equiv.) and HFIP (772 μ L, 7.30 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11d** (350 mg, 0.792 mmol, 54%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ [ppm] = 8.07 (s, 1H), 7.50 (dd, J = 8.7, 5.3 Hz, 1H), 7.05 (dd, J = 9.7, 2.3 Hz, 1H), 7.01 (s, 1H), 6.90 (td, J = 9.1, 2.3 Hz, 1H), 5.78–5.72 (m, 1H), 5.51 (s, 1H), 3.59 (q, J = 6.5 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 2.04–1.97 (m, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 171.5, 170.1, 160.3 (d, J = 238.1 Hz), 136.5 (d, J = 12.6 Hz), 124.1, 122.3 (d, J = 2.9 Hz), 120.5 (d, J = 278.8 Hz), 119.6 (d, J = 10.1 Hz), 113.3, 108.6 (d, J = 24.5 Hz), 97.7 (d, J = 25.6 Hz), 66.9–66.1 (m), 39.8, 34.9, 32.4, 25.5, 20.4.

¹⁹F NMR (376 MHz, CDCl₃) δ [ppm] = –73.17 (d, J = 10.2 Hz), (–120.71)–(–120.78) (m).

HRMS-ESI: calcd. for C₁₈H₁₈F₇N₂O₃ [M + H]⁺: 443.1200; found: 443.1217.

FT-IR: ν [cm^{–1}] = 3411, 3397, 3277, 1778, 1653, 1543, 1522, 1290, 1239, 1199, 1110.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-3-methyl-5-oxopentanoate (11e**).**

11e was prepared according to **General procedure A**, starting from tryptamine (2.00 g, 12.5 mmol, 1.0 equiv.) and 3-methylglutaric anhydride (1.60 g, 12.5 mmol, 1.0 equiv.) in DMF (50 mL). The reaction mixture was subsequently treated with EDCI (4.78 g, 25.0 mmol, 2.0 equiv.), DMAP (305 mg, 2.50 mmol, 0.2 equiv.) and HFIP (6.60 mL, 62.5 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11e** (3.21 g, 7.33 mmol, 58%) as a white solid.

¹H NMR (500 MHz, CD₂Cl₂) δ [ppm] = 8.33 (s, 1H), 7.61–7.59 (m, 1H), 7.38 (dt, J =

8.2, 1.0 Hz, 1H), 7.18 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.10 (ddd, $J = 7.9, 7.0, 1.0$ Hz, 1H), 7.06–7.02 (m, 1H), 5.87–5.82 (m, 1H), 5.64 (s, 1H), 3.57 (td, $J = 6.8, 5.7$ Hz, 2H), 2.96 (td, $J = 6.9, 0.9$ Hz, 2H), 2.64 (dd, $J = 15.3, 5.3$ Hz, 1H), 2.51–2.43 (m, 1H), 2.38 (dd, $J = 15.4, 8.0$ Hz, 1H), 2.13 (dd, $J = 14.4, 6.8$ Hz, 1H), 2.04 (dd, $J = 14.4, 7.1$ Hz, 1H), 0.99 (d, $J = 6.7$ Hz, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ [ppm] = 171.1, 169.8, 136.9, 127.8, 122.6, 122.4, 120.5 (q, $J = 282.1$ Hz), 119.7, 119.0, 113.3, 111.6, 67.2–66.1 (m), 43.0, 40.1, 39.9, 28.2, 25.8, 19.5.

^{19}F NMR (471 MHz, CD_2Cl_2) δ [ppm] = –73.59 (d, $J = 12.9$ Hz).

HRMS-ESI: calcd. for $\text{C}_{19}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 461.1270; found: 461.1269.

FT-IR: ν [cm^{-1}] = 3328, 1780, 1649, 1288, 1244, 1198, 1110, 933, 745.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-2-methyl-5-oxopentanoate (11f) and **1,1,1,3,3,3-hexafluoropropan-2-yl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-4-methyl-5-oxopentanoate (11g)**.

11f and **11g** were prepared according to **General procedure A**, starting from tryptamine (500 mg, 3.12 mmol, 1.0 equiv.) and 2-methylglutaric anhydride (400 mg, 3.12 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (1.19 g, 6.25 mmol, 2.0 equiv.), DMAP (76.4 mg, 0.625 mmol, 0.2 equiv.) and HFIP (1.65 mL, 15.6 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11f** (190 mg, 0.434 mmol, 14%) as a light brown solid and **11g** (135 mg, 0.308 mmol, 10%) as a light brown solid.

^1H NMR (500 MHz, CD_2Cl_2) δ [ppm] = 8.23 (s, 1H), 7.62–7.57 (m, 1H), 7.38 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.18 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 7.10 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 7.06 (d, $J = 2.4$ Hz, 1H), 5.85–5.80 (m, 1H), 5.55 (s, 1H), 3.55 (td, $J = 6.8, 5.7$ Hz, 2H), 2.99–2.93 (m, 2H), 2.75–2.65 (m, 1H), 2.19–2.06 (m, 2H), 2.00–1.93 (m, 1H), 1.88–1.80 (m, 1H), 1.22 (d, $J = 7.0$ Hz, 3H).

¹³C NMR (126 MHz, CD₂Cl₂) δ [ppm] = 173.3, 171.6, 136.9, 127.8, 122.5, 122.4, 121.0 (d, *J* = 279.2 Hz), 119.7, 119.0, 113.4, 111.6, 67.2–66.1 (m), 40.1, 38.8, 33.8, 29.1, 25.7, 16.9.

¹⁹F NMR (471 MHz, CD₂Cl₂) δ [ppm] = –73.64 (d, *J* = 28.6 Hz).

HRMS-ESI: calcd. for C₁₉H₂₀F₆N₂O₃Na [M + Na]⁺: 461.1270; found: 461.1270.

FT-IR: ν [cm^{–1}] = 3328, 1781, 1635, 1457, 1388, 1288, 1241, 1200, 1109, 932, 741.

¹H NMR (600 MHz, CDCl₃) δ [ppm] = 8.44 (s, 1H), 7.61 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.36 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 5.79–5.68 (m, 1H), 5.69 (t, *J* = 5.9 Hz, 1H), 3.61 (td, *J* = 6.8, 5.8 Hz, 2H), 2.99–2.96 (m, 2H), 2.50 (ddd, *J* = 16.6, 8.7, 6.0 Hz, 1H), 2.41 (ddd, *J* = 16.6, 8.5, 7.0 Hz, 1H), 2.15–2.09 (m, 1H), 2.01–1.95 (m, 1H), 1.76–1.70 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ [ppm] = 175.2, 170.2, 136.6, 127.4, 122.3, 122.2, 120.5 (d, *J* = 274.1 Hz), 119.5, 118.7, 112.7, 111.5, 66.9–66.0 (m), 40.2, 39.8, 31.0, 28.6, 25.4, 17.9.

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = –73.18 (d, *J* = 6.5 Hz).

HRMS-ESI: calcd. for C₁₉H₂₀F₆N₂O₃Na [M + Na]⁺: 461.1270; found: 461.1271.

FT-IR: ν [cm^{–1}] = 3275, 2925, 2844, 1638, 1398, 1328, 1303, 1213, 1180, 742.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(1*H*-indol-3-yl)ethyl)amino)-3,3-dimethyl-5-oxopentanoate (11h).

11h was prepared according to **General procedure A**, starting from tryptamine (400 mg, 2.50 mmol, 1.0 equiv.) and 3,3-dimethylglutaric anhydride (355 mg, 2.50

mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (955 mg, 5.00 mmol, 2.0 equiv.), DMAP (61.1 mg, 500 μ mol, 0.2 equiv.) and HFIP (1.32 mL, 12.5 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11h** (697 mg, 1.54 mmol, 62%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.21 (s, 1H), 7.60 (dt, J = 7.9, 0.9 Hz, 1H), 7.37 (dt, J = 8.1, 0.9 Hz, 1H), 7.21 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.12 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 5.81 (s, 1H), 5.80–5.72 (m, 1H), 3.61 (td, J = 6.8, 5.7 Hz, 2H), 2.97 (td, J = 6.9, 0.9 Hz, 2H), 2.56 (s, 2H), 2.16 (s, 2H), 1.08 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 170.7, 169.3, 136.6, 127.4, 122.3, 122.1, 120.6 (q, J = 283.3 Hz), 119.6, 118.8, 113.0, 111.4, 66.8–65.7 (m), 47.3, 43.8, 39.7, 33.5, 28.0, 25.4.

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = –72.98 (d, J = 6.4 Hz).

HRMS-ESI: calcd. for C₂₀H₂₃F₆N₂O₃ [M + H]⁺: 453.1608; found: 453.1611.

FT-IR: ν [cm^{–1}] = 3238, 2963, 1779, 1647, 1522, 1388, 1289, 1236, 1198, 1109, 746.

(S)-1,1,1,3,3,3-Hexafluoropropan-2-yl-5-((3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-5-oxopentanoate (11i).

11i was prepared according to **General procedure A**, starting from (*S*)-tryptophan methyl ester (300 mg, 1.38 mmol, 1.0 equiv.) and glutaric anhydride (157 mg, 1.38 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (526 mg, 2.75 mmol, 2.0 equiv.), DMAP (33.6 mg, 0.275 mmol, 0.2 equiv.) and HFIP (727 μ L, 6.88 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11i** (150 mg, 0.311 mmol, 23%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.32 (s, 1H), 7.53–7.50 (m, 1H), 7.34 (dt, J = 8.1, 0.9 Hz, 1H), 7.19 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.11 (ddd, J = 8.0, 7.0, 1.0 Hz,

1H), 6.95 (d, J = 2.4 Hz, 1H), 6.05 (d, J = 8.0 Hz, 1H), 5.78–5.73 (m, 1H), 4.95 (dt, J = 7.9, 5.5 Hz, 1H), 3.70 (s, 3H), 3.36–3.26 (m, 2H), 2.49 (t, J = 7.4 Hz, 2H), 2.18 (t, J = 7.4 Hz, 2H), 1.98–1.92 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 172.5, 171.4, 170.0, 136.3, 127.8, 122.8, 122.4, 120.5 (q, J = 278.7 Hz), 119.8, 118.5, 111.5, 110.0, 67.0–65.9 (m), 53.1, 52.5, 34.6, 32.2, 27.7, 20.1.

^{19}F NMR (471 MHz, CDCl_3) δ [ppm] = –73.19 (d, J = 6.4 Hz).

HRMS-ESI: calcd. for $\text{C}_{20}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 505.1168; found: 505.1191.

FT-IR: ν [cm^{-1}] 3624, 3376, 2953, 1779, 1736, 1661, 1518, 1440, 1289, 1228, 1200, 1110, 781, 753.

$[\alpha]_{\text{D}}^{26} = +9.2$ (c = 0.7, CHCl_3).

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-(2-((2-(1*H*-indol-3-yl)ethyl)amino)-2-oxoethyl)benzoate (11j).

11j was prepared according to **General procedure A**, starting from tryptamine (150 mg, 0.938 mmol, 1.0 equiv.) and homophthalic anhydride (152 mg, 0.938 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (197 mg, 1.03 mmol, 2.0 equiv.), DMAP (22.9 mg, 0.188 mmol, 0.2 equiv.) and HFIP (495 μL , 4.69 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11j** (32.0 mg, 678 μmol , 7%) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 8.06 (s, 1H), 8.02 (dd, J = 7.9, 1.5 Hz, 1H), 7.60–7.54 (m, 2H), 7.43 (dd, J = 7.8, 1.3 Hz, 1H), 7.40 (td, J = 7.7, 1.3 Hz, 1H), 7.34 (dd, J = 8.2, 1.0 Hz, 1H), 7.19 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.10 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 5.96 (s, 1H), 5.90–5.68 (m, 1H), 3.83 (s, 2H), 3.56 (td, J = 6.9, 5.7 Hz, 2H), 2.98–2.86 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 170.0, 163.8, 138.8, 136.5, 134.6, 132.9, 131.6,

127.8, 127.5, 125.9, 122.3, 122.1, 120.6 (q, $J = 282.9$ Hz), 119.6, 118.8, 113.1, 111.3, 67.5–66.4 (m), 42.2, 40.1, 25.2.

^{19}F NMR (471 MHz, CDCl_3) δ [ppm] = -72.97 . (It should be a doublet peak, but due to the resolution, only singlet peak was observed.)

HRMS-ESI: calcd. for $\text{C}_{22}\text{H}_{18}\text{F}_6\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 495.1114; found: 495.1118.

FT-IR: ν [cm^{-1}] = 3306, 1755, 1651, 1551, 1360, 1242, 1193, 1104, 1019, 915, 715.

1,1,1,3,3,3-Hexafluoropropan-2-yl 6-((2-(1*H*-indol-3-yl)ethyl)amino)-6-oxohexanoate (11k).

11k was prepared according to **General procedure A**, starting from tryptamine (400 mg, 2.50 mmol, 1.0 equiv.) and oxepane-2,7-dione (320 mg, 2.50 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (955 mg, 5.00 mmol, 2.0 equiv.), DMAP (61.1 mg, 0.500 mmol, 0.2 equiv.) and HFIP (1.32 mL, 12.5 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11k** (289 mg, 0.660 mmol, 26%) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 8.73 (s, 1H), 7.59 (d, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.21 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 7.15–7.08 (m, 1H), 6.96 (d, $J = 2.3$ Hz, 1H), 5.87–5.75 (m, 2H), 3.61–3.57 (m, 2H), 2.96 (t, $J = 6.8$ Hz, 2H), 2.46 (t, $J = 6.7$ Hz, 2H), 2.15–2.01 (m, 2H), 1.67–1.62 (m, 4H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 172.6, 170.3, 136.6, 127.5, 123.9, 122.2, 120.6 (q, $J = 284.4$ Hz), 119.4, 118.7, 112.7, 111.5, 67.0–65.9 (m), 40.0, 36.0, 33.0, 25.4, 24.8, 24.1.

^{19}F NMR (565 MHz, CDCl_3) δ [ppm] = -73.24 (d, $J = 6.3$ Hz).

HRMS-ESI: calcd. for $\text{C}_{19}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 461.1270; found: 461.1285.

FT-IR: ν [cm^{-1}] = 2928, 2855, 1713, 1659, 1626, 1442, 1329, 1230, 745.

***N*-(2-(1*H*-indol-3-yl)ethyl)-8-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-7-oxooctanamide (11l).**

11l was prepared according to **General procedure A**, starting from tryptamine (400 mg, 2.50 mmol, 1.0 equiv.) and oxocane-2,8-dione (355 mg, 2.50 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (955 mg, 5.00 mmol, 2.0 equiv.), DMAP (61.1 mg, 0.500 mmol, 0.2 equiv.) and HFIP (1.32 mL, 12.5 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11l** (300 mg, 0.644 mmol, 26%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.62 (s, 1H), 7.60–7.58 (m, 1H), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 5.80–5.75 (m, 1H), 5.70 (t, *J* = 5.8 Hz, 1H), 3.59 (td, *J* = 6.8, 5.7 Hz, 2H), 2.96 (td, *J* = 6.8, 0.9 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.08 (t, *J* = 7.5 Hz, 2H), 1.71–1.52 (m, 4H), 1.34–1.20 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 172.9, 170.4, 136.6, 127.5, 122.3, 122.2, 120.6 (q, *J* = 281.4 Hz), 119.5, 118.7, 112.8, 111.5, 67.0–65.9 (m), 39.9, 36.4, 33.1, 28.4, 25.4, 25.2, 24.3.

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = –73.23 (d, *J* = 6.4 Hz).

HRMS-ESI: calcd. for C₂₀H₂₂F₆N₂O₃Na [M + Na]⁺: 475.1427; found: 475.1442.

FT-IR: ν [cm^{–1}] = 3286, 2934, 2870, 1778, 1648, 1532, 1387, 1288, 1236, 1199, 1110, 745.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((3-(1*H*-indol-3-yl)propyl)amino)-5-oxopentanoate (11m).

11m was prepared according to **General procedure A**, starting from 1*H*-indole-3-propanamine (85.0 mg, 0.489 mmol, 1.0 equiv.) and glutaric anhydride (55.7 mg, 0.489 mmol, 1.0 equiv.) in DMF (2.0 mL). The reaction mixture was subsequently treated with EDCI (187 mg, 0.977 mmol, 2.0 equiv.), DMAP (11.9 mg, 98.0 μ mol, 0.2 equiv.) and HFIP (258 μ L, 2.44 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11m** (120 mg, 0.274 mmol, 56%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.11 (s, 1H), 7.59–7.57 (m, 1H), 7.36–7.34 (m, 1H), 7.19 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.14–7.10 (m, 1H), 6.98 (dd, J = 2.3, 1.2 Hz, 1H), 5.80–5.75 (m, 1H), 5.46 (s, 1H), 3.32 (td, J = 7.1, 5.9 Hz, 2H), 2.80 (td, J = 7.3, 0.9 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.12 (t, J = 7.3 Hz, 2H), 2.00–1.89 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 171.5, 170.1, 136.6, 127.4, 122.2, 121.6, 119.4, 118.8, 115.5, 111.3, 66.8–66.3 (m), 39.6, 34.9, 32.4, 29.8, 22.8, 20.4. (Due to the resolution or/and overlapping, the resonance of CF₃ was not observed.)

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.18 (d, J = 6.4 Hz).

HRMS-ESI: calcd. for C₁₉H₂₀F₆N₂O₃Na [M + Na]⁺: 461.1270; found: 461.1287.

FT-IR: ν [cm^{–1}] = 3404, 3295, 2925, 1780, 1649, 1385, 1356, 1288, 1228, 1200, 1110, 744.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((4-(1*H*-indol-3-yl)butyl)amino)-5-oxopentanoate (11n).

11n was prepared according to **General procedure A**, starting from 1*H*-indole-3-butanamine (120 mg, 0.638 mmol, 1.0 equiv.) and glutaric anhydride (72.8 mg, 0.638 mmol, 1.0 equiv.) in DMF (2.0 mL). The reaction mixture was subsequently treated with EDCI (244 mg, 1.28 mmol, 2.0 equiv.), DMAP (15.6 mg, 0.128 mmol, 0.2 equiv.) and HFIP (337 μ L, 3.19 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11n** (140 mg, 0.310 mmol, 48%) as a

white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.06 (s, 1H), 7.62–7.56 (m, 1H), 7.35 (dt, J = 8.2, 0.9 Hz, 1H), 7.19 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.11 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.96 (dd, J = 2.3, 1.0 Hz, 1H), 5.80–5.75 (m, 1H), 5.43 (s, 1H), 3.26 (td, J = 7.2, 5.7 Hz, 2H), 2.78 (td, J = 7.4, 0.9 Hz, 2H), 2.57 (t, J = 7.2 Hz, 2H), 2.16 (t, J = 7.3 Hz, 2H), 2.01 (q, J = 7.3 Hz, 2H), 1.80–1.69 (m, 2H), 1.60–1.54 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 171.5, 170.1, 136.5, 127.5, 122.0, 121.5, 120.5 (d, J = 282.6 Hz), 119.2, 119.0, 116.3, 111.3, 66.7–66.2 (m), 39.6, 34.9, 32.4, 29.4, 27.4, 24.81, 20.4.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.17 (d, J = 6.3 Hz).

HRMS-ESI: calcd. for C₂₀H₂₂F₆N₂O₃Na [M + Na]⁺: 475.1427; found: 475.1436.

FT-IR: ν [cm^{–1}] = 3401, 2924, 2854, 1781, 1651, 1288, 1228, 1200, 1110, 927, 906, 744.

1,1,1,3,3,3-Hexafluoropropan-2-yl 3,3-dimethyl-5-oxo-5-(phenethylamino)pentanoate (11o).

11o was prepared according to **General procedure A**, starting from phenethylamine (300 mg, 2.48 mmol, 1.0 equiv.) and 3,3-dimethylglutaric anhydride (352 mg, 2.48 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (947 mg, 4.96 mmol, 2.0 equiv.), DMAP (60.6 mg, 0.496 mmol, 0.2 equiv.) and HFIP (1.31 mL, 12.4 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11o** (452 mg, 1.09 mmol, 44%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 7.31–7.27 (m, 2H), 7.24–7.17 (m, 3H), 5.80–5.71 (m, 2H), 3.54 (td, J = 7.0, 5.8 Hz, 2H), 2.82 (t, J = 6.9 Hz, 2H), 2.50 (s, 2H), 2.17 (s, 2H), 1.08 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 170.6, 169.4, 138.9, 128.8, 128.8, 126.7, 120.5 (q, J = 279.6 Hz), 66.8–65.7 (m), 47.2, 43.7, 40.4, 35.7, 33.5, 28.0.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = −73.02 (d, *J* = 6.3 Hz).

HRMS-ESI: calcd. for C₁₈H₂₁F₆NO₃Na [M + Na]⁺: 436.1318; found: 436.1335.

FT-IR: ν [cm^{−1}] = 3309, 1967, 1645, 1543, 1282, 1268, 1200, 1107.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((4-methoxyphenethyl)amino)-3,3-dimethyl-5-oxopentanoate (11p).

11p was prepared according to **General procedure A**, starting from 4-methoxyphenethylamine (300 mg, 1.99 mmol, 1.0 equiv.) and 3,3-dimethylglutaric anhydride (282 mg, 1.99 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (759 mg, 3.97 mmol, 2.0 equiv.), DMAP (48.5 mg, 0.397 mmol, 0.2 equiv.) and HFIP (1.05 mL, 9.93 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11p** (523 mg, 1.18 mmol, 59%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 7.13–7.06 (m, 2H), 6.85–6.79 (m, 2H), 5.72–5.70 (m, 2H), 3.78 (s, 3H), 3.49 (td, *J* = 7.0, 5.8 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.53 (s, 2H), 2.17 (s, 2H), 1.08 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 170.6, 169.4, 158.5, 130.8, 129.8, 120.6 (q, *J* = 291.0 Hz), 114.2, 66.6–66.0 (m), 55.3, 47.2, 43.7, 40.6, 34.8, 33.5, 28.0.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = −73.03 (d, *J* = 6.3 Hz).

HRMS-ESI: calcd. for C₁₉H₂₃F₆NO₄Na [M + Na]⁺: 466.1423; found: 466.1442.

FT-IR: ν [cm^{−1}] = 2970, 1738, 1515, 1440, 1366, 1217, 1105.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((3,4-dimethoxyphenethyl)amino)-3,3-dimethyl-5-oxopentanoate (11q).

11q was prepared according to **General procedure A**, starting from 3,4-dimethoxyphenethylamine (500 mg, 2.76 mmol, 1.0 equiv.) and 3,3-dimethylglutaric anhydride (392 mg, 2.76 mmol, 1.0 equiv.) in DMF (15.0 mL). The reaction mixture was subsequently treated with EDCI (1.05 g, 5.52 mmol, 2.0 equiv.), DMAP (67.5 mg, 0.552 mmol, 0.2 equiv.) and HFIP (1.46 mL, 13.8 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11q** (670 mg, 1.42 mmol, 51%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 6.80–6.77 (m, 1H), 6.71 (d, J = 7.6 Hz, 2H), 5.80–5.70 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.51 (td, J = 7.0, 5.8 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.54 (s, 2H), 2.18 (s, 2H), 1.08 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 170.6, 169.4, 149.2, 147.8, 131.3, 120.7, 120.5 (q, J = 280.8 Hz), 111.8, 111.4, 66.5–65.7 (m), 56.0, 55.9, 47.2, 43.7, 40.5, 35.3, 33.5, 28.1.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.01 (d, J = 6.5 Hz).

HRMS-ESI: calcd. for C₂₀H₂₅F₆NO₅Na [M + Na]⁺: 496.1529; found: 496.1518.

FT-IR: ν [cm^{–1}] = 2371, 2354, 1649, 1518, 1288, 1243, 1107.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((3,4-dimethoxyphenethyl)amino)-5-oxopentanoate (11r).

11r was prepared according to **General procedure A**, starting from 3,4-dimethoxyphenethylamine (500 mg, 2.76 mmol, 1.0 equiv.) and glutaric anhydride (315 mg, 2.76 mmol, 1.0 equiv.) in DMF (15.0 mL). The reaction mixture was subsequently treated with EDCI (1.05 g, 5.52 mmol, 2.0 equiv.), DMAP (67.5 mg, 0.552 mmol, 0.2 equiv.) and HFIP (1.46 mL, 13.8 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11r** (670 mg, 1.42 mmol, 55%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 6.79 (d, J = 8.7 Hz, 1H), 6.72–6.67 (m, 2H),

5.77–5.72 (m, 1H), 5.54 (s, 1H), 3.85 (d, $J = 3.5$ Hz, 6H), 3.49 (td, $J = 7.0, 5.9$ Hz, 2H), 2.74 (t, $J = 7.0$ Hz, 2H), 2.57 (t, $J = 7.2$ Hz, 2H), 2.18 (t, $J = 7.2$ Hz, 2H), 2.04–1.94 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 171.5, 170.0, 149.2, 147.9, 131.3, 120.7, 120.5 (q, $J = 279.6$ Hz), 111.9, 111.5, 67.0–65.9 (m), 56.0, 55.9, 40.8, 35.3, 34.8, 32.4, 20.4.

^{19}F NMR (565 MHz, CDCl_3) δ [ppm] = –73.22 (d, $J = 6.4$ Hz).

HRMS-ESI: calcd. for $\text{C}_{18}\text{H}_{21}\text{F}_6\text{NO}_5\text{Na}$ $[\text{M} + \text{Na}]^+$: 468.1216; found: 468.1217.

FT-IR: ν [cm^{-1}] = 2942, 1682, 1602, 1513, 1377, 1341, 1272, 1162, 752.

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-(2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl)benzoate (11s).

11s was prepared according to **General procedure A**, starting from 3,4-dimethoxyphenethylamine (300 mg, 1.66 mmol, 1.0 equiv.) and homophthalic anhydride (268 mg, 1.66 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (633 mg, 3.31 mmol, 2.0 equiv.), DMAP (40.5 mg, 0.331 mmol, 0.2 equiv.) and HFIP (1.39 mL, 8.29 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11s** (189 mg, 0.383 mmol, 23%) as a white solid.

^1H NMR (600 MHz, CDCl_3) δ [ppm] = 8.00 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.55 (td, $J = 7.6, 1.4$ Hz, 1H), 7.40 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.37 (td, $J = 7.7, 1.3$ Hz, 1H), 6.69 (d, $J = 8.1$ Hz, 1H), 6.63 (d, $J = 2.0$ Hz, 1H), 6.58 (dd, $J = 8.1, 2.0$ Hz, 1H), 6.07 (t, $J = 5.8$ Hz, 1H), 5.96–5.90 (m, 1H), 3.81 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.42 (td, $J = 7.1, 5.7$ Hz, 2H), 2.67 (t, $J = 7.1$ Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ [ppm] = 169.8, 163.7, 148.9, 147.6, 138.7, 134.4, 132.7, 131.4, 131.3, 127.6, 125.7, 120.6, 120.5 (q, $J = 286.3$ Hz), 111.9, 111.2, 67.3–66.4 (m), 55.8, 55.7, 41.9, 40.8, 35.0.

^{19}F NMR (565 MHz, CDCl_3) δ [ppm] = –72.99 (d, $J = 6.9$ Hz).

HRMS-ESI: calcd. for C₂₂H₂₁F₆NO₅Na [M + Na]⁺: 516.1216; found: 516.1201.

FT-IR: ν [cm⁻¹] = 2937, 1755, 1652, 1515, 1237, 1194, 1109, 1096, 1025, 913, 715.

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-(2-oxo-2-(phenethylamino)ethyl)benzoate (11t).

11t was prepared according to **General procedure A**, starting from phenethylamine (250 mg, 2.07 mmol, 1.0 equiv.) and homophthalic anhydride (335 mg, 2.07 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (789 mg, 4.13 mmol, 2.0 equiv.), DMAP (50.5 mg, 0.413 mmol, 0.2 equiv.) and HFIP (1.09 mL, 10.3 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11t** (189 mg, 0.436 mmol, 21%) as a white solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 8.05 (dd, J = 8.0, 1.5 Hz, 1H), 7.59 (td, J = 7.6, 1.5 Hz, 1H), 7.45 (dd, J = 7.8, 1.3 Hz, 1H), 7.41 (td, J = 7.7, 1.3 Hz, 1H), 7.25–7.20 (m, 2H), 7.20–7.16 (m, 1H), 7.09–7.03 (m, 2H), 6.11 (t, J = 5.9 Hz, 1H), 5.96–5.92 (m, 1H), 3.84 (s, 2H), 3.47 (td, J = 7.0, 5.8 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 169.9, 163.8, 138.85, 138.78, 134.5, 132.8, 131.5, 128.7, 128.5, 127.7, 126.4, 125.8, 120.6 (q, J = 282.8 Hz), 67.5–66.3 (m), 42.0, 40.8, 35.5.

¹⁹F NMR (376 MHz, CDCl₃) δ [ppm] = –72.94 (d, J = 12.5 Hz).

HRMS-ESI: calcd. for C₂₀H₁₇F₆NO₃Na [M + Na]⁺: 456.1005; found: 456.1012.

FT-IR: ν [cm⁻¹] = 3305, 1754, 1651, 1549, 1359, 1239, 1190, 1099, 1018, 914, 899, 714.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(furan-3-yl)ethyl)amino)-5-oxopentanoate (11u).

11u was prepared according to **General procedure A**, starting from 2-(furan-3-yl)ethan-1-amine (180 mg, 1.62 mmol, 1.0 equiv.) and glutaric anhydride (185 mg, 1.62 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (620 mg, 3.24 mmol, 2.0 equiv.), DMAP (39.6 mg, 0.324 mmol, 0.2 equiv.) and HFIP (857 μ L, 8.11 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **11u** (200 mg, 0.533 mmol, 33%) as a light yellow solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 7.36 (t, J = 1.7 Hz, 1H), 7.25–7.24 (m, 1H), 6.27 (dd, J = 1.9, 0.9 Hz, 1H), 5.77–5.73 (m, 1H), 5.63 (s, 1H), 3.44 (td, J = 6.9, 5.8 Hz, 2H), 2.62 (td, J = 6.9, 1.0 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 2.20 (t, J = 7.3 Hz, 2H), 2.01–1.97 (m, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 171.5, 170.0, 143.4, 139.7, 121.8, 120.5 (q, J = 282.0 Hz), 110.8, 66.9–66.1 (m), 39.5, 34.8, 32.4, 25.0, 20.4.

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = –73.29 (d, J = 6.5 Hz).

HRMS-ESI: calcd. for C₁₄H₁₅F₆NO₄Na [M + Na]⁺: 398.0797; found: 398.0811.

FT-IR: ν [cm^{–1}] = 2920, 2850, 1780, 1659, 1447, 1386, 1288, 1227, 1198, 1110, 924, 789.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(furan-2-yl)ethyl)amino)-5-oxopentanoate (11v).

11v was prepared according to **General procedure A**, starting from 2-(furan-2-yl)ethan-1-amine (180 mg, 1.62 mmol, 1.0 equiv.) and glutaric anhydride (185 mg, 1.62 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (620 mg, 3.24 mmol, 2.0 equiv.), DMAP (39.6 mg, 0.324 mmol, 0.2 equiv.) and HFIP (857 μ L, 8.11 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11v** (250 mg, 0.667 mmol, 41%) as a light yellow solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 7.33 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.32–6.28 (m, 1H), 6.07–6.06 (m, 1H), 5.78–5.74 (m, 1H), 5.58 (s, 1H), 3.59–3.49 (m, 2H), 2.85 (td, *J* = 6.5, 0.8 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 2.06–1.97 (m, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 171.5, 170.1, 153.1, 141.8, 120.6 (d, *J* = 281.9 Hz), 110.5, 106.6, 66.7–66.3 (m), 38.3, 34.9, 32.4, 28.2, 20.4.

¹⁹F NMR (376 MHz, CDCl₃) δ [ppm] = –73.19 (d, *J* = 6.0 Hz).

HRMS-ESI: calcd. for C₁₄H₁₅F₆NO₄Na [M + Na]⁺: 398.0797; found: 398.0786.

FT-IR: ν [cm^{–1}] = 3314, 2930, 1781, 1647, 1551, 1386, 1288, 1232, 1200, 1111, 907, 780.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-oxo-5-((2-(thiophen-3-yl)ethyl)amino)penta-noate (11w).

11w was prepared according to **General procedure A**, starting from 2-(thiophen-3-yl)ethan-1-amine (150 mg, 1.18 mmol, 1.0 equiv.) and glutaric anhydride (135 mg, 1.18 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (451 mg, 2.36 mmol, 2.0 equiv.), DMAP (28.9 mg, 0.236 mmol, 0.2 equiv.) and HFIP (624 μL, 5.91 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11w** (200 mg, 0.512 mmol, 43%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 7.29–7.24 (m, 1H), 6.97–6.98 (m, 1H), 6.93 (dd, *J* = 4.9, 1.3 Hz, 1H), 5.77–5.71 (m, 1H), 5.63 (s, 1H), 3.53–3.48 (m, 2H), 2.83 (t, *J* = 6.9 Hz, 2H), 2.54 (td, *J* = 7.2, 0.8 Hz, 2H), 2.18 (t, *J* = 7.2 Hz, 2H), 2.05–1.93 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 171.5, 170.0, 139.1, 128.1, 126.2, 121.5, 120.5 (q, *J* = 282.0 Hz), 67.0–65.9 (m), 39.9, 34.8, 32.3, 30.3, 20.4.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.24 (d, *J* = 6.4 Hz).

HRMS-ESI: calcd. for $C_{14}H_{15}F_6NO_3SK$ $[M + K]^+$: 430.0309; found: 430.0328.

FT-IR: ν [cm^{-1}] = 3319, 1770, 1638, 1534, 1385, 1281, 1201, 1106, 720.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(benzo[b]thiophen-3-yl)ethyl)amino)-5-oxopentanoate (11x).

11x was prepared according to **General procedure A**, starting from 2-(benzo[b]thiophen-3-yl)ethan-1-amine (140 mg, 0.791 mmol, 1.0 equiv.) and glutaric anhydride (90.2 mg, 0.791 mmol, 1.0 equiv.) in DMF (3.0 mL). The reaction mixture was subsequently treated with EDCI (302 mg, 1.58 mmol, 2.0 equiv.), DMAP (19.3 mg, 0.158 mmol, 0.2 equiv.) and HFIP (418 μ L, 3.95 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **11x** (183 mg, 0.415 mmol, 52%) as a white solid.

1H NMR (700 MHz, $CDCl_3$) δ [ppm] = 7.86 (dt, J = 7.8, 1.0 Hz, 1H), 7.77 (dt, J = 8.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 7.35 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.14 (s, 1H), 5.80–5.73 (m, 2H), 3.60 (td, J = 7.0, 5.9 Hz, 2H), 3.05 (td, J = 6.9, 1.0 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 2.17 (t, J = 7.3 Hz, 2H), 2.01–1.97 (m, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ [ppm] = 171.6, 170.0, 140.6, 138.8, 133.4, 124.5, 124.2, 123.0, 122.5, 121.6, 120.5 (q, J = 282.7 Hz), 66.9–66.1 (m), 39.1, 34.8, 32.4, 28.7, 20.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ [ppm] = –73.20. (It should be a doublet peak, but due to the resolution, only singlet peak was observed.)

HRMS-ESI: calcd. for $C_{18}H_{17}F_6NO_3SNa$ $[M + Na]^+$: 464.0725; found: 464.0745.

FT-IR: ν [cm^{-1}] = 2928, 2850, 1736, 1698, 1215, 747.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(6-methoxy-1*H*-indol-3-yl)ethyl)amino)-3-methyl-5-oxopentanoate (11y).

11y was prepared according to **General procedure A**, starting from 6-methoxytryptamine (100 mg, 0.526 mmol, 1.0 equiv.) and glutaric anhydride (67.4 mg, 0.526 mmol, 1.0 equiv.) in DMF (3.0 mL). The reaction mixture was subsequently treated with EDCI (201 mg, 1.05 mmol, 2.0 equiv.), DMAP (12.9 mg, 0.105 mmol, 0.2 equiv.) and HFIP (278 μ L, 2.63 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **11y** (150 mg, 0.320 mmol, 61%) as a white solid.

^1H NMR (700 MHz, CDCl_3) δ [ppm] = 8.19 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 6.89–6.87 (m, 1H), 6.84 (d, J = 2.3 Hz, 1H), 6.79 (dd, J = 8.6, 2.3 Hz, 1H), 5.79–5.75 (m, 1H), 5.66 (s, 1H), 3.83 (d, J = 0.7 Hz, 3H), 3.58 (dt, J = 8.5, 6.8 Hz, 2H), 2.95–2.89 (m, 2H), 2.65–2.59 (m, 1H), 2.52–2.48 (m, 1H), 2.48–2.34 (m, 1H), 2.13 (dd, J = 14.3, 6.9 Hz, 1H), 2.03 (ddd, J = 14.5, 7.4, 1.7 Hz, 1H), 0.99 (d, J = 6.8 Hz, 3H).

^{13}C NMR (176 MHz, CDCl_3) δ [ppm] = 171.1, 169.4, 156.8, 137.3, 121.9, 120.9, 120.5 (q, J = 282.4 Hz), 119.3, 112.9, 109.6, 94.9, 66.8–66.0 (m), 55.8, 42.8, 39.8, 39.5, 27.9, 25.5, 19.4.

^{19}F NMR (565 MHz, CDCl_3) δ [ppm] = –73.11 (d, J = 7.7 Hz).

HRMS-ESI: calcd. for $\text{C}_{20}\text{H}_{22}\text{F}_6\text{N}_2\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 491.1374; found: 491.1376.

FT-IR: ν [cm^{-1}] 2958, 1776, 1648, 1386, 1288, 1200, 1110, 937, 812.

2.1.3. Additional substrates

1,1,1,3,3,3-Hexafluoropropan-2-yl 4-((2-(1H-indol-3-yl)ethyl)amino)-4-oxobutanoate (S1).

S1 was prepared according to **General procedure A**, starting from tryptamine (250 mg, 1.56 mmol, 1.0 equiv.) and succinic anhydride (156 mg, 1.56 mmol, 1.0 equiv.) in DMF

(5.0 mL). The reaction mixture was subsequently treated with EDCI (328 mg, 1.72 mmol, 2.0 equiv.), DMAP (38.2 mg, 0.313 mmol, 0.2 equiv.) and HFIP (825 μ L, 7.81 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **S1** (286 mg, 0.698 mmol, 45%) as a white solid.

^1H NMR (600 MHz, CDCl_3) δ [ppm] = 8.22 (s, 1H), 7.59 (dd, J = 7.9, 1.1 Hz, 1H), 7.37 (dt, J = 8.1, 0.9 Hz, 1H), 7.22 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 5.79–5.75 (m, 1H), 5.63 (d, J = 5.6 Hz, 1H), 3.60 (q, J = 6.5 Hz, 2H), 2.96 (td, J = 6.8, 0.9 Hz, 2H), 2.84 (t, J = 6.9 Hz, 2H), 2.44 (t, J = 6.9 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ [ppm] = 170.2, 170.0, 136.6, 127.4, 122.4, 122.2, 120.5 (d, J = 283.0 Hz), 119.6, 118.8, 112.9, 111.4, 67.2–66.3 (m), 40.1, 30.4, 28.7, 25.3.

^{19}F NMR (565 MHz, CDCl_3) δ [ppm] = –73.14 (d, J = 6.6 Hz).

HRMS-ESI: calcd. for $\text{C}_{17}\text{H}_{16}\text{F}_6\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 433.0957; found: 433.0974.

FT-IR: ν [cm^{-1}] = 3422, 3328, 1754, 1633, 1384, 1286, 1201, 1108, 905, 738.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-(((1H-indol-3-yl)methyl)amino)-5-oxopentanoate (S2**).**

S2 was prepared according to **General procedure A**, starting from 1H-indole-3-methanamine (310 mg, 2.12 mmol, 1.0 equiv.) and glutaric anhydride (242 mg, 2.12 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (811 mg, 4.25 mmol, 2.0 equiv.), DMAP (51.9 mg, 0.425 mmol, 0.2 equiv.) and HFIP (1.12 mL, 10.6 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **S2** (300 mg, 0.732 mmol, 34%) as a white solid.

^1H NMR (700 MHz, CDCl_3) δ [ppm] = 8.28 (s, 1H), 7.62–7.60 (m, 1H), 7.39 (dt, J = 8.1, 0.9 Hz, 1H), 7.23 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.18–7.12 (m, 2H), 5.79–5.72 (m, 1H), 5.70 (s, 1H), 4.62 (dd, J = 5.2, 0.8 Hz, 2H), 2.60 (t, J = 7.3 Hz, 2H), 2.23 (t, J =

7.2 Hz, 2H), 2.07–2.03 (m, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 171.3, 170.1, 136.5, 126.6, 123.4, 122.7, 120.5 (d, *J* = 286.2 Hz), 120.1, 118.8, 112.7, 111.5, 66.9–66.1 (m), 35.3, 34.9, 32.5, 20.5.

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = –73.20 (d, *J* = 6.3 Hz).

HRMS-ESI: calcd. for C₁₇H₁₆F₆N₂O₃Na [M + Na]⁺: 433.0957; found: 433.0972.

FT-IR: ν [cm^{–1}] = 3259, 1738, 1660, 1364, 1204, 1108, 744.

1,1,1,3,3,3-Hexafluoropropan-2-yl 10-((2-(1H-indol-3-yl)ethyl)amino)-10-oxodecanoate (S3).

S3 was prepared according to **General procedure A**, starting from tryptamine (200 mg, 1.25 mmol, 1.0 equiv.) and oxacycloundecane-2,11-dione (230 mg, 1.25 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (477 mg, 2.50 mmol, 2.0 equiv.), DMAP (30.5 mg, 0.250 mmol, 0.2 equiv.) and HFIP (660 μL, 6.25 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **S3** (150 mg, 0.304 mmol, 24%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.72 (s, 1H), 7.60 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.39–7.34 (m, 1H), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 5.85–5.67 (m, 2H), 3.62–3.58 (m, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.49 (t, *J* = 7.4 Hz, 2H), 2.10 (t, *J* = 7.6 Hz, 2H), 1.69–1.65 (m, 2H), 1.62–1.56 (m, 2H), 1.32–1.25 (m, 8H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 173.4, 170.5, 136.6, 127.5, 122.3, 122.1, 120.5 (q, *J* = 282.5 Hz), 119.4, 118.7, 112.8, 111.5, 66.9–65.8 (m), 39.9, 36.8, 33.3, 29.2, 29.1, 28.9, 28.7, 25.7, 25.4, 24.5.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.26 (d, *J* = 5.7 Hz).

HRMS-ESI: calcd. for C₂₃H₂₈F₆N₂O₃Na [M + Na]⁺: 517.1896; found: 517.1921.

FT-IR: ν [cm^{–1}] = 2939, 2921, 2146, 2042, 1779, 1649, 1289, 1228, 1202, 1111, 760.

1,1,1,3,3,3-Hexafluoropropan-2-yl (*S*)-5-((3-(4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)amino)-5-oxopentanoate (S4**).**

S4 was prepared according to **General procedure A**, starting from (*S*)-tyrosine methyl ester (300 mg, 1.54 mmol, 1.0 equiv.) and glutaric anhydride (175 mg, 1.54 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (588 mg, 3.01 mmol, 2.0 equiv.), DMAP (37.6 mg, 0.308 mmol, 0.2 equiv.) and HFIP (813 μ L, 7.69 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **S4** (170 mg, 0.370 mmol, 24%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 7.04 (s, 1H), 6.95–6.89 (m, 2H), 6.75–6.69 (m, 2H), 6.15 (d, J = 8.1 Hz, 1H), 5.79–5.74 (m, 1H), 4.85 (ddd, J = 8.1, 6.4, 5.6 Hz, 1H), 3.73 (s, 3H), 3.07 (dd, J = 14.1, 5.5 Hz, 1H), 2.95 (dd, J = 14.1, 6.5 Hz, 1H), 2.51 (td, J = 7.3, 1.3 Hz, 2H), 2.25 (t, J = 7.5 Hz, 2H), 1.99–1.93 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 172.5, 172.0, 170.0, 155.7, 130.3, 127.0, 120.5 (q, J = 284.3 Hz), 115.7, 67.1–66.0 (m), 53.4, 52.6, 37.2, 34.7, 32.2, 20.2.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.24 (d, J = 6.7 Hz).

HRMS-ESI: calcd. for C₁₈H₁₉F₆NO₆K [M + K]⁺: 498.0749; found: 498.0774.

FT-IR: ν [cm^{–1}] = 2960, 1780, 1740, 1651, 1516, 1286, 1223, 1198, 1108, 905, 733.

$[\alpha]_D^{26}$ = +19.0 (c = 0.4, CHCl₃).

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-oxo-5-(phenethylamino)pentanoate (S5**).**

S5 was prepared according to **General procedure A**, starting from phenethylamine

(200 mg, 1.65 mmol, 1.0 equiv.) and glutaric anhydride (188 mg, 1.65 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (631 mg, 3.31 mmol, 2.0 equiv.), DMAP (40.4 mg, 0.331 mmol, 0.2 equiv.) and HFIP (873 μ L, 8.26 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **S5** (200 mg, 0.519 mmol, 31%) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 7.33–7.28 (m, 2H), 7.26–7.21 (m, 1H), 7.18 (dt, J = 7.9, 1.7 Hz, 2H), 7.79–7.73 (m, 1H), 5.54 (s, 1H), 3.58–3.48 (m, 2H), 2.81 (td, J = 7.0, 1.7 Hz, 2H), 2.54 (td, J = 7.3, 1.8 Hz, 2H), 2.18 (td, J = 7.2, 1.8 Hz, 2H), 2.02–1.97 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 171.5, 170.1, 138.8, 128.84, 128.78, 126.7, 120.5 (d, J = 282.0 Hz), 67.0–65.9 (m), 40.6, 35.7, 34.8, 32.4, 20.4.

^{19}F NMR (471 MHz, CDCl_3) δ [ppm] = –73.22 (d, J = 6.3 Hz).

HRMS-ESI: calcd. for $\text{C}_{16}\text{H}_{17}\text{F}_6\text{NO}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 408.1005; found: 408.1007.

FT-IR: ν [cm^{-1}] = 3309, 1967, 1645, 1543, 1282, 1268, 1107.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((4-methoxyphenethyl)amino)-5-oxopentanoate (S6).

S6 was prepared according to **General procedure A**, starting from 4-methoxyphenethylamine (200 mg, 1.32 mmol, 1.0 equiv.) and glutaric anhydride (151 mg, 1.32 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (506 mg, 2.65 mmol, 2.0 equiv.), DMAP (32.4 mg, 0.365 mmol, 0.2 equiv.) and HFIP (699 μ L, 6.62 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:2) afforded **S6** (225 mg, 0.542 mmol, 41%) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 7.08 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.78–5.73 (m, 1H), 5.63 (s, 1H), 3.77 (s, 3H), 3.46 (td, J = 7.0, 5.8 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 2.01–1.97 (m,,

2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 171.5, 170.0, 158.4, 130.8, 129.8, 120.5 (q, *J* = 279.4 Hz), 114.1, 67.0–65.9 (m), 55.30, 55.28, 40.8, 34.8, 32.4, 20.4.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.25 (d, *J* = 8.6 Hz).

HRMS-ESI: calcd. for C₁₇H₁₉F₆NO₄Na [M + Na]⁺: 438.1110; found: 438.1109.

FT-IR: ν [cm^{–1}] 3299, 1767, 1636, 1542, 1282, 1257, 1202, 1107, 1038.

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-oxo-5-((2-(pyridin-2-yl)ethyl)amino)penta-noate (S7).

S7 was prepared according to **General procedure A**, starting from 2-(pyridin-2-yl)ethan-1-amine (300 mg, 2.46 mmol, 1.0 equiv.) and glutaric anhydride (280 mg, 2.46 mmol, 1.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with EDCI (939 mg, 4.92 mmol, 2.0 equiv.), DMAP (60.1 mg, 0.492 mmol, 0.2 equiv.) and HFIP (1.30 mL, 12.3 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **S7** (670 mg, 1.51 mmol, 61%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.44 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.56 (td, *J* = 7.7, 1.9 Hz, 1H), 7.14–7.06 (m, 2H), 6.75 (s, 1H), 5.74–5.69 (m, 1H), 3.60 (dt, *J* = 6.6, 5.7 Hz, 2H), 2.98–2.89 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 2.17 (t, *J* = 7.2 Hz, 2H), 2.02–1.88 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 171.5, 170.0, 159.6, 149.1, 136.7, 123.5, 121.6, 120.4 (q, *J* = 279.4 Hz), 66.9–65.8 (m), 38.7, 36.9, 34.9, 32.4, 20.4.

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –73.19 (d, *J* = 6.5 Hz).

HRMS-ESI: calcd. for C₁₅H₁₆F₆N₂O₃Na [M + Na]⁺: 409.0957; found: 409.0972.

FT-IR: ν [cm^{–1}] = 2950, 1781, 1652, 1288, 1230, 1199, 1110, 747.

2.2. One-pot annulation reaction

2.2.1. Reaction optimization

8a: R = methoxy	8e: R = 2,2,2-trifluoroethoxy	8i: R = diphenylmethoxy
8b: R = 4-nitrophenoxy	8f: R = 2,2,2-trifluoro-1-methylethoxy	8j: R = cyclohexyloxy
8c: R = 2-propoxy	8g: R = pentafluorophenoxy	8k: R = cyclohexylthio
8d: R = 2-hexafluoropropoxy	8h: R = prenyloxy	8l: R = <i>t</i> -butoxy

entry	substrate	base or acid	yield
1	8a	K ₂ CO ₃	18
2	8a	Cs ₂ CO ₃	4
3	8a	KOH	6
4	8a	TMSOK	6
5	8a	KOt-Bu	15
6	8a	ZrCl ₄	N.D. ^[a]
7	8a	In(OTf) ₂	N.D.
8	8a	Sc(OTf) ₃	N.D.
9	8a	Ti(O <i>i</i> -Pr) ₄	N.D.
10	8a	<i>p</i> -TsOH	N.D.
11	8b	K ₂ CO ₃ , Bu ₄ NBr	62
12	8c	K ₂ CO ₃ , Bu ₄ NBr	18
13	8d	K ₂ CO ₃ , Bu ₄ NBr	90
14	8e	K ₂ CO ₃ , Bu ₄ NBr	42
15	8f	K ₂ CO ₃ , Bu ₄ NBr	41
16	8g	K ₂ CO ₃ , Bu ₄ NBr	65
17	8h	K ₂ CO ₃ , Bu ₄ NBr	20
18	8i	K ₂ CO ₃ , Bu ₄ NBr	47
19	8j	K ₂ CO ₃ , Bu ₄ NBr	32
20	8k	K ₂ CO ₃ , Bu ₄ NBr	42
21	8l	K ₂ CO ₃ , Bu ₄ NBr	30

[a] Not determined

2.2.2. Substrate scope

General procedure C

To a solution of the substrate **8** or **11a–x** (1.0 equiv.) in toluene was added POCl₃ (1.0 equiv.) dropwise. Then the mixture was heated to 115 °C (oil bath temperature) until the starting material was fully consumed. After allowing the mixture to cool down to 80 °C (oil bath temperature), the same volume of MeOH, K₂CO₃ (10.0 equiv.) and *n*Bu₄NBr (0.1 equiv.) were added subsequently. Afterwards the resulting mixture was stirred overnight at 80 °C, cooled to room temperature, filtered through Celite®, concentrated under reduced pressure, and purified by silica gel or neutral aluminium

oxide column chromatography.

(Note: It is not necessary to perform the reaction under argon.)

Methyl 4-(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)butanoate (9).

To a solution of the substrate **8a** (100 mg, 0.347 mmol, 1.0 equiv.) in toluene (3.0 mL), was added POCl₃ (31.7 μ L, 0.347 mmol, 1.0 equiv.). The mixture was heated to 115 °C (oil bath temperature) until the starting material was fully consumed. Then the mixture was concentrated under reduced pressure and purified by silica gel flash column chromatography (DCM/MeOH= 10:1). **9** (79.0 mg, 0.293 mmol, 84%) was afforded as a dark yellow solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 11.39 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.46 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.22 (ddd, *J* = 8.1, 6.9, 1.4 Hz, 1H), 4.02 (t, *J* = 8.8 Hz, 2H), 3.76 (s, 3H), 3.36–3.28 (m, 2H), 3.26–3.19 (m, 2H), 2.66–2.57 (m, 2H), 2.24–2.10 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 173.9, 169.3, 141.7, 129.1, 125.7, 124.3, 124.0, 122.0, 121.4, 114.1, 52.0, 42.4, 32.8, 31.7, 23.4, 19.5.

HRMS-ESI: calcd. for C₁₆H₁₉N₂O₂ [M + H]⁺: 271.1441; found: 271.1455.

FT-IR: ν [cm⁻¹] = 2925, 1733, 1630, 1554, 1434, 1336, 1229, 747.

2,6,7,12-Tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (10).

10 was prepared according to **General procedure C**, starting from **8d** (100 mg, 0.236 mmol, 1.0 equiv.) and POCl₃ (21.5 μ L, 0.236 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (326 mg, 2.36 mmol, 10 equiv.) and *n*Bu₄NBr (7.6 mg, 24.0 μ mol, 0.1 equiv.).

Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **10** (51.0 mg, 0.214 mmol, 90%) as a yellow solid.

Scale-up reaction starting from **8d** (2.00 g, 4.72 mmol, 1.0 equiv.) and POCl₃ (430 μL, 4.72 mmol, 1.0 equiv.) in toluene (80 mL). The reaction mixture was subsequently treated with MeOH (80 mL), K₂CO₃ (6.52 g, 47.2 mmol, 10 equiv.) and *n*Bu₄NBr (152 mg, 0.472 mmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **10** (910 mg, 3.82 mmol, 81%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 7.97 (s, 1H), 7.53–7.51 (m, 1H), 7.34 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 5.49 (t, *J* = 5.0 Hz, 1H), 4.11 (t, *J* = 6.0 Hz, 2H), 2.91 (t, *J* = 6.0 Hz, 2H), 2.70–2.59 (m, 2H), 2.53–2.42 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 169.8, 137.3, 131.4, 128.1, 126.9, 123.6, 120.2, 119.1, 112.0, 111.1, 99.4, 39.3, 31.9, 20.8, 19.6.

HRMS-ESI: calcd. for C₁₅H₁₅N₂O [M + H]⁺: 239.1179; found: 239.1179.

FT-IR: ν [cm⁻¹] = 3287, 2926, 1636, 1436, 1400, 1232, 1214, 742.

9-Methoxy-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (**12a**).

12a was prepared according to **General procedure C**, starting from **11a** (100 mg, 0.220 mmol, 1.0 equiv.) and POCl₃ (20.1 μL, 0.220 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (304 mg, 2.20 mmol, 10 equiv.) and *n*Bu₄NBr (7.1 mg, 22.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12a** (45.0 mg, 0.168 mmol, 76%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.15 (s, 1H), 7.22 (dd, *J* = 8.8, 0.6 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.51 (t, *J* = 4.9 Hz, 1H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.88 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.45 (td, *J* = 7.7, 4.9 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 169.9, 154.5, 132.4, 131.4, 128.9, 127.2, 113.8, 111.9, 111.8, 100.8, 99.2, 56.0, 39.3, 31.9, 20.8, 19.6.

HRMS-ESI: calcd. for C₁₆H₁₆N₂O₂Na [M + Na]⁺: 291.1104; found: 291.1105.

FT-IR: ν [cm⁻¹] = 3308, 2927, 2834, 1665, 1639, 1487, 1396, 1214, 1170, 1025, 801, 753.

10-methoxy-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (12b).

12b was prepared according to **General procedure C**, starting from **11b** (80.0 mg, 0.176 mmol, 1.0 equiv.) and POCl₃ (16.1 μL, 0.176 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (243 mg, 1.76 mmol, 10 equiv.) and *n*Bu₄NBr (5.7 mg, 18.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12b** (40.0 mg, 0.149 mmol, 85%) as a yellow solid.

¹H NMR (500 MHz, CD₂Cl₂) δ [ppm] = 8.12 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.45 (t, *J* = 4.9 Hz, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 2.85 (t, *J* = 6.0 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.44 (td, *J* = 7.7, 4.9 Hz, 2H).

¹³C NMR (126 MHz, CD₂Cl₂) δ [ppm] = 169.8, 158.0, 138.7, 131.7, 127.6, 121.6, 119.9, 112.2, 110.1, 98.5, 95.0, 55.9, 39.4, 32.3, 21.1, 19.9.

HRMS-ESI: calcd. for C₁₆H₁₇N₂O₂ [M + H]⁺: 269.1284; found: 269.1284.

FT-IR: ν [cm⁻¹] = 3309, 2930, 2835, 1665, 1639, 1487, 1397, 1214, 1170, 1043, 1025, 754.

10-Bromo-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (12c).

12c was prepared according to **General procedure C**, starting from **11c** (37.0 mg, 74.0 μ mol, 1.0 equiv.) and POCl₃ (6.7 μ L, 74.0 μ mol, 1.0 equiv.) in toluene (2.0 mL). The reaction mixture was subsequently treated with MeOH (2.0 mL), K₂CO₃ (99.0 mg, 740 μ mol, 10 equiv.) and *n*Bu₄NBr (2.4 mg, 7.0 μ mol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12c** (20.0 mg, 63.0 μ mol, 86%) as a yellow solid.

¹H NMR (700 MHz, *d*₆-DMSO) δ [ppm] = 11.42 (s, 1H), 7.48 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.87 (t, *J* = 4.9 Hz, 1H), 3.93 (t, *J* = 5.9 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 2.48 (d, *J* = 7.7 Hz, 2H), 2.42 – 2.36 (m, 2H).

¹³C NMR (176 MHz, *d*₆-DMSO) δ [ppm] = 168.4, 138.0, 130.5, 129.2, 125.1, 121.9, 120.3, 115.1, 113.6, 110.0, 100.9, 38.4, 31.1, 20.1, 18.9.

HRMS-ESI: calcd. for C₁₅H₁₂BrN₂O [M – H][–]: 315.0138; found: 315.0127.

FT-IR: ν [cm^{–1}] = 2961, 2926, 1667, 1652, 1458, 1390, 1213, 1180, 1045, 1180, 1045, 798, 749.

10-Fluoro-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3H)-one (12d).

12d was prepared according to **General procedure C**, starting from **11d** (100 mg, 0.226 mmol, 1.0 equiv.) and POCl₃ (20.6 μ L, 0.226 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (313 mg, 2.26 mmol, 10 equiv.) and *n*Bu₄NBr (7.3 mg, 23.0 μ mol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12d** (49.0 mg, 0.184 mmol, 81%) as a yellow solid.

¹H NMR (700 MHz, *d*₆-DMSO) δ [ppm] = 11.36 (s, 1H), 7.46 (dd, *J* = 8.6, 5.5 Hz, 1H),

7.09 (dd, $J = 10.0, 2.3$ Hz, 1H), 6.86 (ddd, $J = 9.8, 8.6, 2.4$ Hz, 1H), 5.83 (t, $J = 4.9$ Hz, 1H), 3.93 (t, $J = 5.9$ Hz, 2H), 2.80 (t, $J = 6.0$ Hz, 2H), 2.48 (t, $J = 8.0$ Hz, 2H), 2.38 (ddd, $J = 8.0, 6.6, 3.2$ Hz, 2H).

^{13}C NMR (176 MHz, d_6 -DMSO) δ [ppm] = 168.5, 159.6 (d, $J = 235.6$ Hz), 137.2 (d, $J = 12.7$ Hz), 130.7, 129.0, 122.9, 119.7 (d, $J = 10.7$ Hz), 109.9, 107.4 (d, $J = 24.3$ Hz), 100.1, 97.2 (d, $J = 25.8$ Hz), 38.4, 31.2, 20.1, 18.9.

^{19}F NMR (471 MHz, d_6 -DMSO) δ [ppm] = -119.64 (d, $J = 11.5$ Hz).

HRMS-ESI: calcd. for $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{ONa}$ $[\text{M} + \text{Na}]^+$: 279.0904; found: 279.0904.

FT-IR: ν [cm^{-1}] = 2954, 2920, 1681, 1457, 1329, 1205, 1174, 1043, 745.

2-Methyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (12e).

12e was prepared according to **General procedure C**, starting from **11e** (150 mg, 0.342 mmol, 1.0 equiv.) and POCl_3 (31.3 μL , 0.342 mmol, 1.0 equiv.) in toluene (4.0 mL). The reaction mixture was subsequently treated with MeOH (4.0 mL), K_2CO_3 (473 mg, 3.42 mmol, 10 equiv.) and $n\text{Bu}_4\text{NBr}$ (11.0 mg, 34.0 μmol , 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12e** (70.0 mg, 0.258 mmol, 75%) as a yellow solid.

Scale-up reaction starting from **11e** (1.00 g, 2.28 mmol, 1.0 equiv.) and POCl_3 (208 μL , 2.28 mmol, 1.0 equiv.) in toluene (30 mL). The reaction mixture was subsequently treated with MeOH (30 mL), K_2CO_3 (3.15 g, 22.8 mmol, 10 equiv.) and $n\text{Bu}_4\text{NBr}$ (73.6 mg, 0.228 mmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12e** (405 mg, 1.61 mmol, 70%) as a yellow solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 8.43 (s, 1H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.34 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.24–7.19 (m, 1H), 7.15–7.09 (m, 1H), 5.45 (t, $J = 4.0$ Hz, 1H), 4.44–4.38 (m, 1H), 3.84–3.78 (m, 1H), 2.98–2.84 (m, 2H), 2.81–2.65 (m, 2H), 2.39–2.33 (m, 1H), 1.17 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 169.8, 137.4, 130.1, 128.0, 126.8, 123.6, 120.1,

119.1, 112.1, 111.1, 106.0, 40.0, 39.3, 26.2, 20.8, 20.4.

HRMS-ESI: calcd. for C₁₆H₁₇N₂O [M + H]⁺: 253.1335; found: 253.1335.

FT-IR: ν [cm⁻¹] = 3286, 1638, 1399, 1328, 1303, 1213, 1180, 742.

3-Methyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (12f).

12f was prepared according to **General procedure C**, starting from **11f** (132 mg, 0.301 mmol, 1.0 equiv.) and POCl₃ (27.5 μ L, 0.301 mmol, 1.0 equiv.) in toluene (3.5 mL). The reaction mixture was subsequently treated with MeOH (3.5 mL), K₂CO₃ (416 mg, 3.01 mmol, 10 equiv.) and *n*Bu₄NBr (9.7 mg, 30.0 μ mol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12f** (55.0 mg, 0.218 mmol, 72%) as a yellow solid.

¹H NMR (700 MHz, CD₂Cl₂) δ [ppm] = 8.68 (s, 1H), 7.52–7.51 (m, 1H), 7.36 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.61 (dd, *J* = 5.9, 4.0 Hz, 1H), 4.50 (dt, *J* = 12.7, 5.1 Hz, 1H), 3.72–3.68 (m, 1H), 2.95–2.85 (m, 2H), 2.67–2.60 (m, 1H), 2.51 (ddd, *J* = 16.9, 6.6, 5.9 Hz, 1H), 2.24 (ddd, *J* = 16.9, 11.4, 4.1 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (176 MHz, CD₂Cl₂) δ [ppm] = 173.1, 137.7, 131.3, 128.7, 127.1, 123.6, 120.2, 119.2, 111.8, 111.4, 99.2, 39.9, 36.1, 28.0, 21.1, 16.1.

HRMS-ESI: calcd. for C₁₆H₁₆N₂ONa [M + Na]⁺: 275.1155; found: 275.1161.

FT-IR: ν [cm⁻¹] = 3275, 1638, 1452, 1398, 1328, 1303, 1213, 1180, 742.

1-Methyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (12g).

12g was prepared according to **General procedure C**, starting from **11g** (108 mg, 0.247 mmol, 1.0 equiv.) and POCl₃ (22.5 μ L, 0.247 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃

(341 mg, 2.47 mmol, 10 equiv.) and *n*Bu₄NBr (7.9 mg, 25.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12g** (40.0 mg, 0.159 mmol, 64%) as a yellow solid.

¹H NMR (700 MHz, CD₂Cl₂) δ [ppm] = 8.42 (s, 1H), 7.54–7.52 (m, 1H), 7.41 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.05 (t, *J* = 5.9 Hz, 2H), 2.88 (t, *J* = 5.9 Hz, 2H), 2.57–2.48 (m, 2H), 2.47–2.41 (m, 2H), 2.29 (d, *J* = 1.3 Hz, 3H).

¹³C NMR (176 MHz, CD₂Cl₂) δ [ppm] = 169.6, 137.4, 129.4, 126.5, 126.3, 123.3, 120.4, 119.0, 113.1, 112.8, 111.4, 39.7, 32.0, 29.4, 21.4, 19.8.

HRMS-ESI: calcd. for C₁₆H₁₆N₂ONa [M + Na]⁺: 275.1155; found: 275.1169.

FT-IR: ν [cm⁻¹] = 3356, 1638, 1405, 1356, 1210, 1040, 744.

2,2-Dimethyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (**12h**).

12h was prepared according to **General procedure C**, starting from **11h** (100 mg, 0.221 mmol, 1.0 equiv.) and POCl₃ (20.2 μL, 0.221 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (306 mg, 2.21 mmol, 10 equiv.) and *n*Bu₄NBr (7.1 mg, 22.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12h** (49.0 mg, 0.184 mmol, 83%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.63 (s, 1H), 7.53–7.51 (m, 1H), 7.34 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 5.44 (s, 1H), 4.14 (t, *J* = 6.0 Hz, 2H), 2.93 (t, *J* = 6.0 Hz, 2H), 2.52 (s, 2H), 1.18 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 169.7, 137.4, 128.9, 128.0, 126.8, 123.5, 120.0, 119.0, 112.1, 111.1, 110.7, 46.5, 39.4, 30.8, 28.2, 20.7.

HRMS-ESI: calcd. for C₁₇H₁₈N₂ONa [M + Na]⁺: 289.1311; found: 289.1311.

FT-IR: ν [cm^{-1}] = 2930, 1666, 1646, 1395, 1215, 752, 740.

(S)-Methyl-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine-6-carboxylate (12i).

12i was prepared according to **General procedure C**, starting from **11i** (69 mg, 0.143 mmol, 1.0 equiv.) and POCl_3 (13.1 μL , 0.134 mmol, 1.0 equiv.) in toluene (2.0 mL). The reaction mixture was subsequently treated with MeOH (2.0 mL), K_2CO_3 (198 mg, 1.43 mmol, 10 equiv.) and $n\text{Bu}_4\text{NBr}$ (4.6 mg, 14.0 μmol , 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 1:1) afforded **12i** (30.0 mg, 0.101 mmol, 71%) as a yellow solid.

^1H NMR (700 MHz, CDCl_3) δ [ppm] = 8.02 (s, 1H), 7.53–7.51 (m, 1H), 7.33–7.29 (m, 1H), 7.23–7.20 (m, 1H), 7.12 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 5.90 (dd, J = 6.5, 1.5 Hz, 1H), 5.55 (dt, J = 8.0, 3.8 Hz, 1H), 3.60–3.58 (m, 4H), 3.14 (dd, J = 16.1, 6.5 Hz, 1H), 2.76–2.71 (m, 1H), 2.67–2.61 (m, 2H), 2.50–2.40 (m, 1H).

^{13}C NMR (176 MHz, CDCl_3) δ [ppm] = 171.3, 170.1, 137.4, 130.2, 127.8, 126.8, 123.8, 120.3, 119.2, 111.1, 109.0, 100.0, 52.8, 50.9, 31.6, 23.1, 19.6.

HRMS-ESI: calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 319.1053; found: 319.1044.

FT-IR: ν [cm^{-1}] = 2928, 2850, 1736, 1698, 1366, 1331, 1215, 747.

$[\alpha]_{\text{D}}^{26} = +4.6$ (c = 0.2, CHCl_3).

8,13-Dihydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinolin-5(7*H*)-one (12j).

12j was prepared according to **General procedure C**, starting from **11j** (50.0 mg,

0.106 mmol, 1.0 equiv.) and POCl₃ (9.7 μL, 0.106 mmol, 1.0 equiv.) in toluene (1.5 mL). The reaction mixture was subsequently treated with MeOH (1.5 mL), K₂CO₃ (146 mg, 1.06 mmol, 10 equiv.) and *n*Bu₄NBr (3.4 mg, 11.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:1) afforded **12j** (25.0 mg, 87.4 μmol, 82%) as a light yellow solid.

¹H NMR (500 MHz, *d*₆-DMSO) δ [ppm] = 11.69 (s, 1H), 8.24 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.71 (td, *J* = 7.5, 1.3 Hz, 1H), 7.61 (dd, *J* = 16.4, 7.8 Hz, 2H), 7.45 (dd, *J* = 18.8, 7.9 Hz, 2H), 7.21 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.10–7.04 (m, 2H), 4.40 (t, *J* = 6.5 Hz, 2H), 3.09 (t, *J* = 6.6 Hz, 2H).

¹³C NMR (126 MHz, *d*₆-DMSO) δ [ppm] = 161.2, 138.0, 136.2, 132.6, 132.4, 128.2, 127.5, 126.1, 126.0, 125.5, 124.5, 123.5, 119.5, 119.1, 112.5, 111.6, 99.0, 40.4, 19.3.

HRMS-ESI: calcd. for C₁₉H₁₃N₂O [M – H][–]: 285.1033; found: 285.1038.

FT-IR: ν [cm^{–1}] = 2923, 2853, 1738, 1650, 1614, 1595, 1365, 1217, 742.

2,3,4,7,8,13-Hexahydro-5*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indol-5-one (**12k**).

12k was prepared according to **General procedure C**, starting from **11k** (200 mg, 0.457 mmol, 1.0 equiv.) and POCl₃ (41.7 μL, 0.457 mmol, 1.0 equiv.) in toluene (5.0 mL). The reaction mixture was subsequently treated with MeOH (5.0 mL), K₂CO₃ (631 mg, 4.57 mmol, 10 equiv.) and *n*Bu₄NBr (14.7 mg, 46.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12k** (30.0 mg, 0.119 mmol, 26%) as a yellow solid.

¹H NMR (700 MHz, CD₂Cl₂) δ [ppm] = 9.10 (s, 1H), 7.48–7.46 (m, 1H), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.08 (t, *J* = 7.3 Hz, 1H), 4.07 (t, *J* = 5.9 Hz, 2H), 2.84 (t, *J* = 5.9 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.37 (q, *J* = 7.5 Hz, 2H), 2.20–2.16 (m, 2H).

¹³C NMR (176 MHz, CD₂Cl₂) δ [ppm] = 175.8, 139.5, 136.6, 131.7, 129.4, 125.3, 122.0, 121.1, 114.1, 114.0, 113.4, 43.4, 37.6, 32.1, 26.1, 23.9.

HRMS-ESI: calcd. for C₁₆H₁₆N₂ONa [M + Na]⁺: 275.1155; found: 275.1152.

FT-IR: ν [cm⁻¹] 2928, 2855, 1713, 1659, 1625, 1442, 1329, 1230, 1170, 745.

2,4,5,8,9,14-Hexahydroazocino[1',2':1,2]pyrido[3,4-*b*]indol-6(3*H*)-one (12l).

12l was prepared according to **General procedure C**, starting from **11l** (200 mg, 0.429 mmol, 1.0 equiv.) and POCl₃ (39.2 μ L, 0.429 mmol, 1.0 equiv.) in toluene (5.0 mL). The reaction mixture was subsequently treated with MeOH (5.0 mL), K₂CO₃ (593 mg, 4.29 mmol, 10 equiv.) and *n*Bu₄NBr (13.8 mg, 43.0 μ mol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12l** (50.0 mg, 0.168 mmol, 39%) as a yellow solid.

¹H NMR (700 MHz, CD₂Cl₂) δ [ppm] = 8.34 (s, 1H), 7.47–7.46 (m, 1H), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.77 (t, *J* = 8.2 Hz, 1H), 5.07 (ddd, *J* = 12.5, 5.4, 1.2 Hz, 1H), 3.18–3.14 (m, 1H), 2.97 (ddd, *J* = 15.7, 12.4, 5.5 Hz, 1H), 2.76 (ddd, *J* = 15.9, 4.3, 1.2 Hz, 1H), 2.55 (td, *J* = 12.2, 1.6 Hz, 1H), 2.49–2.39 (m, 2H), 2.10 (dddd, *J* = 14.2, 11.9, 8.9, 1.3 Hz, 1H), 1.99–1.90 (m, 1H), 1.69–1.55 (m, 2H), 1.39–1.28 (m, 1H).

¹³C NMR (176 MHz, CD₂Cl₂) δ [ppm] = 174.0, 137.3, 133.1, 130.4, 127.6, 123.4, 120.2, 119.1, 116.0, 112.3, 111.3, 42.8, 35.0, 26.6, 25.5, 25.1, 22.1.

HRMS-ESI: calcd. for C₁₇H₁₈N₂ONa [M + Na]⁺: 289.1311; found: 289.1315.

FT-IR: ν [cm⁻¹] = 3260, 2928, 2854, 1620, 1450, 1406, 1230, 1170, 743 2.

2,3,6,7,8,13-Hexahydro-4*H*-pyrido[1',2':1,2]azepino[3,4-*b*]indol-4-one (12m).

12m was prepared according to **General procedure C**, starting from **11m** (50.0 mg, S50

0.114 mmol, 1.0 equiv.) and POCl₃ (10.4 μL, 0.114 mmol, 1.0 equiv.) in toluene (1.5 mL). The reaction mixture was subsequently treated with MeOH (1.5 mL), K₂CO₃ (158 mg, 1.14 mmol, 10 equiv.) and *n*Bu₄NBr (3.7 mg, 11.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12m** (15.0 mg, 59.5 μmol, 52%) as a yellow solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 8.00 (s, 1H), 7.55–7.54 (m, 1H), 7.33 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.54 (t, *J* = 5.1 Hz, 1H), 3.91–3.83 (m, 2H), 2.93 (t, *J* = 7.3 Hz, 2H), 2.60 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.48–2.39 (m, 2H), 2.10–2.06 (m, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 170.6, 137.2, 136.0, 129.2, 128.5, 123.2, 120.1, 118.9, 113.3, 110.9, 104.4, 42.2, 31.9, 26.2, 20.1, 19.8.

HRMS-ESI: calcd. for C₁₆H₁₆N₂ONa [M + Na]⁺: 275.1155; found: 275.1156.

FT-IR: ν [cm⁻¹] 2925, 2858, 1653, 1398, 1328, 1260, 1239, 1171, 745.

2,6,7,8,9,14-Hexahydropyrido[1',2':1,2]azocino[3,4-*b*]indol-4(3*H*)-one (12n).

12n was prepared according to **General procedure C**, starting from **11n** (39.0 mg, 86.0 μmol, 1.0 equiv.) and POCl₃ (7.9 μL, 86.0 μmol, 1.0 equiv.) in toluene (1.5 mL). The reaction mixture was subsequently treated with MeOH (1.5 mL), K₂CO₃ (119 mg, 863 μmol, 10 equiv.) and *n*Bu₄NBr (2.8 mg, 9.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **12n** (10.0 mg, 37.6 μmol, 43%) as a yellow solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 7.83 (s, 1H), 7.55 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.33 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.22 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.44 (t, *J* = 4.9 Hz, 1H), 2.92–2.88 (m, 2H), 2.63 (dd, *J* = 8.4, 7.3 Hz, 2H), 2.46–2.42 (m, 2H), 1.93–1.80 (m, 6H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 170.2, 136.9, 135.2, 128.6, 128.0, 122.9, 119.8,

118.8, 114.9, 110.7, 106.4, 43.3, 31.9, 28.9, 24.1, 23.6, 20.0.

HRMS-ESI: calcd. for $C_{17}H_{18}N_2ONa$ $[M + Na]^+$: 289.1311; found: 289.1388.

FT-IR: ν [cm^{-1}] = 2954, 2922, 2853, 1737, 1661, 1458, 1378, 1217, 1033, 743.

2,2-Dimethyl-2,3,6,7-tetrahydro-4H-pyrido[2,1-a]isoquinolin-4-one (12o).

12o was prepared according to **General procedure C**, starting from **11o** (138 mg, 0.334 mmol, 1.0 equiv.) and $POCl_3$ (76.2 μ L, 0.835 mmol, 2.5 equiv.) in toluene (4.0 mL). The reaction mixture was subsequently treated with MeOH (4.0 mL), K_2CO_3 (462 mg, 3.34 mmol, 10 equiv.) and nBu_4NBr (10.8 mg, 33.0 μ mol, 0.1 equiv.). Purification by neutral aluminium oxide column chromatography (pentane/DCM = 1:1) afforded **12o** (25.0 mg, 0.110 mmol, 33%) as a white solid.

1H NMR (700 MHz, C_6D_6) δ [ppm] = 7.36–7.33 (m, 1H), 7.01–6.95 (m, 2H), 6.76–6.72 (m, 1H), 5.34 (s, 1H), 3.79 (dd, J = 6.4, 5.4 Hz, 2H), 2.32 (d, J = 0.8 Hz, 2H), 2.31 (td, J = 5.9, 0.9 Hz, 2H), 0.92 (s, 6H).

^{13}C NMR (176 MHz, C_6D_6) δ [ppm] = 168.3, 135.1, 134.1, 130.9, 128.4, 128.4, 126.8, 124.3, 112.7, 46.0, 38.3, 30.5, 29.4, 27.9.

HRMS-ESI: calcd. for $C_{15}H_{17}NONa$ $[M + Na]^+$: 250.1202; found: 250.1208.

FT-IR: ν [cm^{-1}] = 2948, 2925, 2858, 1974, 1733, 1626, 1492, 1465, 1429, 1320, 1208, 1126, 743.

10-Methoxy-2,2-dimethyl-2,3,6,7-tetrahydro-4H-pyrido[2,1-a]isoquinolin-4-one (12p).

12p was prepared according to **General procedure C**, starting from **11p** (80.0 mg, 0.181 mmol, 1.0 equiv.) and POCl₃ (16.5 μL, 0.181 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (250 mg, 1.81 mmol, 10 equiv.) and *n*Bu₄NBr (5.8 mg, 18 μmol, 0.1 equiv.). Purification by neutral aluminium oxide column chromatography (pentane/DCM = 1:1) afforded **12p** (20.0 mg, 77.8 μmol, 43%) as a white solid.

¹H NMR (700 MHz, C₆D₆) δ [ppm] = 6.70 (dd, *J* = 8.3, 0.42 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.40 (d, *J* = 0.9 Hz, 1H), 3.88–3.82 (m, 2H), 3.32 (s, 3H), 2.35–2.29 (m, 4H), 0.91 (s, 6H). (Due to the solvent peak overlapping, one resonance is missing. But the ABX system could be proved by the coupling constant of the rest two Hs.)

¹³C NMR (176 MHz, C₆D₆) δ [ppm] = 168.4, 159.1, 134.3, 131.9, 129.4, 127.6, 114.2, 112.9, 109.6, 54.9, 46.0, 38.6, 30.5, 28.7, 27.9.

HRMS-ESI: calcd. for C₁₆H₁₉NO₂Na [M + Na]⁺: 280.1308; found: 280.1301.

FT-IR: ν [cm⁻¹] = 2926, 2854, 1746, 1655, 1605, 1518, 1466, 1360, 1271, 1232, 1193, 1140, 1109, 1029, 910.

9,10-Dimethoxy-2,2-dimethyl-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-one (12q).

12q was prepared according to **General procedure C**, starting from **11q** (150 mg, 0.317 mmol, 1.0 equiv.) and POCl₃ (28.9 μL, 0.317 mmol, 1.0 equiv.) in toluene (5.0 mL). The reaction mixture was subsequently treated with MeOH (5.0 mL), K₂CO₃ (438 mg, 3.17 mmol, 10 equiv.) and *n*Bu₄NBr (10.2 mg, 32.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:1) afforded **12q** (80.5 mg, 0.280 mmol, 88%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 7.02 (s, 1H), 6.61 (s, 1H), 5.47 (s, 1H), 3.91–3.89 (m, 5H), 3.88 (s, 3H), 2.77 (t, *J* = 5.9 Hz, 2H), 2.42 (s, 2H), 1.14 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 169.7, 149.3, 148.2, 133.2, 127.6, 122.3, 112.0, 110.8, 106.8, 56.2, 56.1, 46.0, 38.5, 30.5, 28.9, 28.2.

HRMS-ESI: calcd. for C₁₇H₂₁NO₃Na [M + Na]⁺: 310.1413; found: 310.1428.

FT-IR: ν [cm⁻¹] = 2964, 2934, 1775, 1645, 1516, 1388, 1358, 1287, 1263, 1234, 1198, 1109, 937.

9,10-Dimethoxy-2,3,6,7-tetrahydro-4H-pyrido[2,1-*a*]isoquinolin-4-one (12r).

12r was prepared according to **General procedure C**, starting from **11r** (100 mg, 0.225 mmol, 1.0 equiv.) and POCl₃ (20.5 μL, 0.225 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (311 mg, 2.25 mmol, 10 equiv.) and *n*Bu₄NBr (7.2 mg, 22 μmol, 0.1 equiv.). Purification by neutral aluminium oxide column chromatography (pentane/DCM = 1:1) afforded **12r** (44.0 mg, 0.170 mmol, 76%) as a yellow solid.

¹H NMR (500 MHz, C₆D₆) δ [ppm] = 6.92 (s, 1H), 6.20 (s, 1H), 5.31 (td, *J* = 5.0, 1.9 Hz, 1H), 3.93 (td, *J* = 5.9, 1.8 Hz, 2H), 3.46 (s, 3H), 3.36 (s, 3H), 2.41 (td, *J* = 7.9, 1.8 Hz, 2H), 2.38–2.31 (m, 2H), 2.00–1.95 (m, 2H).

¹³C NMR (126 MHz, C₆D₆) δ [ppm] = 169.0, 150.4, 149.2, 136.4, 127.8, 123.0, 111.6, 108.4, 99.7, 55.9, 55.5, 38.6, 31.6, 29.0, 19.9.

HRMS-ESI: calcd. for C₁₅H₁₇NO₃Na [M + Na]⁺: 282.1100; found: 282.1106.

FT-IR: ν [cm⁻¹] = 2942, 1682, 1602, 1513, 1465, 1377, 1341, 1272, 1202, 1179, 1162, 752.

2,3-Dimethoxy-5,6-dihydro-8H-isoquinolino[3,2-*a*]isoquinolin-8-one (12s).

12s was prepared according to **General procedure C**, starting from **11s** (193 mg, 0.391 mmol, 1.0 equiv.) and POCl₃ (35.7 μL, 0.391 mmol, 1.0 equiv.) in toluene

(5.0 mL). The reaction mixture was subsequently treated with MeOH (5.0 mL), K₂CO₃ (541 mg, 3.92 mmol, 10 equiv.) and *n*Bu₄NBr (12.6 mg, 39.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:1) afforded **12s** (100 mg, 0.326 mmol, 83%) as a yellow solid.

¹H NMR (600 MHz, CDCl₃) δ [ppm] = 8.41 (dt, *J* = 8.1, 1.7 Hz, 1H), 7.62–7.59 (m, 1H), 7.58–7.53 (m, 1H), 7.44–7.40 (m, 1H), 7.26 (d, *J* = 2.1 Hz, 1H), 6.86 (t, *J* = 2.1 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 4.39–4.32 (m, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 2.93 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ [ppm] = 162.3, 150.5, 148.6, 137.5, 136.8, 132.4, 128.8, 128.1, 126.3, 126.0, 124.7, 122.4, 110.6, 108.0, 101.5, 56.4, 56.1, 39.8, 28.2.

HRMS-ESI: calcd. for C₁₉H₁₇NO₃Na [M + Na]⁺: 330.1100 found: 330.1115.

FT-IR: ν [cm⁻¹] = 3001, 2937, 2839, 1644, 1606, 1512, 1466, 1362, 1269, 1234, 1104, 1018, 754.

5,6-Dihydro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one (**12t**).

12t was prepared according to **General procedure C**, starting from **11t** (217 mg, 0.501 mmol, 1.0 equiv.) and POCl₃ (45.7 μL, 0.501 mmol, 1.0 equiv.) in toluene (6.0 mL). The reaction mixture was subsequently treated with MeOH (6.0 mL), K₂CO₃ (693 mg, 5.01 mmol, 10 equiv.) and *n*Bu₄NBr (16.2 mg, 50.0 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 5:1) afforded **12t** (60 mg, 0.243 mmol, 48%) as a yellow solid.

¹H NMR (600 MHz, CD₂Cl₂) δ [ppm] = 8.36 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.90–7.84 (m, 1H), 7.65 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.63–7.60 (m, 1H), 7.46 (ddd, *J* = 8.1, 6.9, 1.4 Hz, 1H), 7.41–7.34 (m, 2H), 7.33–7.27 (m, 1H), 7.05 (s, 1H), 4.37–4.30 (m, 2H), 3.06–2.98 (m, 2H).

¹³C NMR (151 MHz, CD₂Cl₂) δ [ppm] = 162.2, 138.0, 137.0, 136.1, 132.6, 130.7, 129.7, 128.4, 128.1, 127.8, 126.8, 126.7, 125.4, 125.3, 102.8, 40.0, 28.9.

HRMS-ESI: calcd. for C₁₇H₁₃NONa [M + Na]⁺: 270.0889; found: 270.0903.

FT-IR: ν [cm⁻¹] = 2945, 2896, 1647, 1619, 1596, 1491, 1341, 1315, 1166, 766.

4,5,8,9-Tetrahydro-7H-furo[2,3-*a*]quinolizin-7-one (12u).

12u was prepared according to **General procedure C**, starting from **11u** (43.0 mg, 0.115 mmol, 1.0 equiv.) and POCl₃ (10.5 μL, 0.115 mmol, 1.0 equiv.) in toluene (1.5 mL). The reaction mixture was subsequently treated with MeOH (1.5 mL), K₂CO₃ (158 mg, 1.15 mmol, 10 equiv.) and *n*Bu₄NBr (3.7 mg, 11 μmol, 0.1 equiv.). Purification by neutral aluminium oxide column chromatography (pentane/DCM = 1:1) afforded **12u** (18.0 mg, 95.2 μmol, 83%) as a yellow solid.

¹H NMR (700 MHz, C₆D₆) δ [ppm] = 6.90 (t, *J* = 1.7 Hz, 1H), 5.80 (t, *J* = 1.7 Hz, 1H), 5.45 (t, *J* = 5.0 Hz, 1H), 3.82 (t, *J* = 6.0 Hz, 2H), 2.30 (t, *J* = 7.7 Hz, 2H), 2.06 (t, *J* = 6.0 Hz, 2H), 1.85 (td, *J* = 7.7, 5.0 Hz, 2H).

¹³C NMR (176 MHz, C₆D₆) δ [ppm] = 168.4, 145.3, 142.6, 130.4, 118.2, 110.8, 98.1, 38.7, 32.0, 21.6, 19.5.

HRMS-ESI: calcd. for C₁₁H₁₁NO₂Na [M + Na]⁺: 212.0682; found: 212.0675.

FT-IR: ν [cm⁻¹] = 2929, 2855, 1725, 1553, 1457, 1380, 1335, 1181, 1019, 742.

4,5,8,9-Tetrahydro-7H-furo[3,2-*a*]quinolizin-7-one (12v).

12v was prepared according to **General procedure C**, starting from **11v** (40.0 mg, 0.107 mmol, 1.0 equiv.) and POCl₃ (9.7 μL, 0.107 mmol, 1.0 equiv.) in toluene (1.5 mL). The reaction mixture was subsequently treated with MeOH (1.5 mL), K₂CO₃

(147 mg, 1.07 mmol, 10 equiv.) and *n*Bu₄NBr (3.4 mg, 11 μmol, 0.1 equiv.). Purification by neutral aluminium oxide column chromatography (pentane/DCM = 1:1) afforded **12v** (10.0 mg, 54.0 μmol, 51%) as a yellow solid.

¹H NMR (700 MHz, C₆D₆) δ [ppm] = 6.90 (dd, *J* = 2.0, 0.7 Hz, 1H), 6.11 (d, *J* = 2.0 Hz, 1H), 4.93 (t, *J* = 4.9 Hz, 1H), 3.81 (t, *J* = 6.1 Hz, 2H), 2.33 (t, *J* = 7.7 Hz, 2H), 2.22–2.18 (m, 2H), 1.87–1.83 (m, 2H).

¹³C NMR (176 MHz, C₆D₆) δ [ppm] = 168.7, 150.0, 142.3, 132.5, 115.2, 106.3, 100.0, 38.3, 32.2, 23.0, 19.8.

(Note: as the product owns a vinylogous fragment, which is highly reactive, the NMR shows some impurity, thought we used quite mild isolation method.)

HRMS-ESI: calcd. for C₁₁H₁₁NO₂Na [M + Na]⁺: 212.0682; found: 212.0688.

FT-IR: ν [cm⁻¹] = 2925, 1697, 1368, 1301, 1221, 1168, 1122, 1079, 1041, 746.

4,5,8,9-Tetrahydro-7*H*-thieno[2,3-*a*]quinolizin-7-one (**12w**).

12w was prepared according to **General procedure C**, starting from **11w** (48.0 mg, 0.123 mmol, 1.0 equiv.) and POCl₃ (11.2 μL, 0.123 mmol, 1.0 equiv.) in toluene (1.5 mL). The reaction mixture was subsequently treated with MeOH (1.5 mL), K₂CO₃ (170 mg, 1.23 mmol, 10 equiv.) and *n*Bu₄NBr (4.0 mg, 12 μmol, 0.1 equiv.). Purification by neutral aluminium oxide column chromatography (pentane/DCM = 1:1) afforded **12w** (23.0 mg, 0.112 mmol, 91%) as a yellow solid.

¹H NMR (500 MHz, C₆D₆) δ [ppm] = 6.61 (dd, *J* = 5.1, 2.0 Hz, 1H), 6.31 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.20 (td, *J* = 5.0, 2.0 Hz, 1H), 3.83 (td, *J* = 6.0, 2.0 Hz, 2H), 2.29 (td, *J* = 7.8, 1.9 Hz, 2H), 2.17 (td, *J* = 6.0, 2.0 Hz, 2H), 1.79 (tdd, *J* = 7.5, 4.9, 1.9 Hz, 2H).

¹³C NMR (126 MHz, C₆D₆) δ [ppm] = 168.9, 136.6, 133.9, 132.4, 128.0, 124.5, 101.1, 39.0, 32.3, 25.6, 20.2.

HRMS-ESI: calcd. for C₁₁H₁₁NOSNa [M + Na]⁺: 228.0453; found: 228.0453.

FT-IR: ν [cm⁻¹] = 2930, 1681, 1433, 1367, 1331, 1304, 1225, 1171, 1136, 1035, 875,

764.

2,3,6,7-tetrahydro-4*H*-benzo[4,5]thieno[2,3-*a*]quinolizin-4-one (12x).

12x was prepared according to **General procedure C**, starting from **11x** (30.0 mg, 68.0 μ mol, 1.0 equiv.) and POCl₃ (6.2 μ L, 68 μ mol, 1.0 equiv.) in toluene (1.5 mL). The reaction mixture was subsequently treated with MeOH (1.5 mL), K₂CO₃ (94.0 mg, 0.680 mmol, 10 equiv.) and *n*Bu₄NBr (2.2 mg, 7.0 μ mol, 0.1 equiv.). Purification by neutral aluminium oxide column chromatography (pentane/DCM = 1:1) afforded **12w** (15.0 mg, 58.8 μ mol, 86%) as a yellow solid.

¹H NMR (700 MHz, CD₂Cl₂) δ [ppm] = 7.79 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.63 (ddd, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.40–7.36 (m, 1H), 7.36–7.33 (m, 1H), 5.66 (t, *J* = 5.0 Hz, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 2.99–2.90 (m, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.51–2.40 (m, 2H).

¹³C NMR (176 MHz, CD₂Cl₂) δ [ppm] = 169.3, 139.1, 133.5, 131.7, 130.8, 125.8, 125.0, 122.8, 121.9, 104.6, 38.4, 31.9, 23.6, 20.2. (One sp² carbon is missing, probably due to the resonance overlap.)

HRMS-ESI: calcd. for C₁₅H₁₃NOSNa [M + Na]⁺: 278.0610; found: 278.0624.

FT-IR: ν [cm⁻¹] = 2929, 2876, 1652, 1458, 1398, 1382, 1329, 1215, 1045, 745.

10-Methoxy-2-methyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (13).

13 was prepared according to **General procedure C**, starting from **11y** (100 mg, 0.214 mmol, 1.0 equiv.) and POCl₃ (19.5 μ L, 0.214 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (295 mg, 2.14 mmol, 10 equiv.) and *n*Bu₄NBr (6.9 mg, 21 μ mol, 0.1 equiv.).

Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **13** (47.0 mg, 0.167 mmol, 78%) as a yellow solid.

¹H NMR (700 MHz, CD₂Cl₂) δ [ppm] = 8.37 (s, 1H), 7.37 (dt, *J* = 8.6, 0.6 Hz, 1H), 6.85 (dd, *J* = 2.3, 0.5 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.37 (d, *J* = 4.0 Hz, 1H), 4.34 (dt, *J* = 12.7, 5.3 Hz, 1H), 3.83 (s, 3H), 3.79–3.75 (m, 1H), 2.88–2.83 (m, 2H), 2.79–2.71 (m, 1H), 2.65 (ddd, *J* = 15.4, 5.9, 1.0 Hz, 1H), 2.32 (ddd, *J* = 15.4, 10.3, 0.7 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (176 MHz, CD₂Cl₂) δ [ppm] = 169.7, 158.0, 138.7, 130.4, 127.4, 121.5, 119.9, 112.4, 110.0, 105.2, 95.0, 55.9, 40.4, 39.4, 26.5, 21.0, 20.5.

HRMS-EI: calcd. for C₁₇H₁₈N₂O₂ [M]⁺: 282.1362; found: 282.1363.

FT-IR: ν [cm⁻¹] 2952, 2931, 1641, 1625, 1454, 1398, 1262, 1159, 1038, 770.

2.2.3. Detail and consideration of the annulation of the additional substrates

The annulation of the additional substrates can be divided into two parts. One is no observation of product by the NMR (group I), the other is NMR showed the product, but liable to decompose (group II).

Scheme S-1: Group I examples

There was no proof that the annulation products of **S1–3** were formed. We proposed the **S8** and **S9** have a reactive methylene group, which might cause **S8** and **S9** unstable under the reaction condition. **S12** contains an 11-membered ring with a C–C double bond. The unsuccessful result of **S3** could be attributed to the difficulty of the macrolactamization or the geometry of the C–C double bond. Failure of the annulation of **S4** could be caused by the reaction between the free hydroxyl group and the phosphorus (V) reagent. Unsuccessful annulation of **S7** indicates that the reaction is relied on electrophilicity of the heterocycles. (**Scheme S–1**)

Scheme S-2: Group II examples

The reaction of **S5** and **S6** showed the identical peak of this type of compound on the ^1H NMR, but there are some impurities which might be the side products formed during the reaction period or in the isolation. We hypothesized that the electrophilicity of the benzene ring influenced the reaction rate of the *endo-dig* cyclization. If the rate of the *endo-dig* cyclization is slow, some competition reactions could happen, leading to side products. In the *exo-trig* cyclization stage, the Thorpe–Ingold effect could increase the rate and drive the whole reaction equilibrium to form the desired product. (**Scheme S–2**)

In general, these compounds containing the [2,3-*a*]quinolizinone motif are sensitive to acid, in some case even the CDCl_3 can lead to partly decomposition. The stability is dependent on the fused ring system. According to our experience, the indole fused compounds are stable. But the larger ring system is relatively unstable. The other heterocycles mentioned above, without another aromatic ring like **12s** and **12t**, are

relatively unstable.

2.3. Oxidative pathway

2.3.1. Natural products and analogues synthesis

General procedure D¹

To a 0 °C solution of diisopropylamine (10.0 equiv.) in THF was added $n\text{BuLi}$ (2.5 M in hexane, 10.0 equiv.). The reaction mixture was stirred for 1 h. A solution of enamide (1.0 equiv.) in THF was added dropwise into the resulting mixture. The reaction mixture was stirred for 1 h. ZnCl_2 (1.9 M in 2-Me-THF, 3.5 equiv.) was added and stirred for 1 h. A stock solution of $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (2.5 mol%) and allyl acetate (1.2 equiv.) in THF was next added at the same temperature. The reaction mixture was moved into a preheated 60 °C oil bath and stirred for 3 d. The resulting mixture was cooled to room temperature and quenched by NH_4Cl (sat. aq.), diluted with DCM, and the organic phase was separated. The aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure by rotary evaporation and purified by silica gel column chromatography.

(Note: Preparation of $[\text{Pd}(\text{allyl})\text{Cl}]_2$, allyl acetate stock solution: $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (27 mg, 0.075 mmol) was weighed into a flame dried vial, the vial was evacuated and backfilled with argon (this process was repeated 3 times). Allyl acetate (0.39 mL, 0.36 g, 3.6 mmol) and THF (2.6 mL) were added sequentially and the solution was stirred for 0.5 h.)

[1] Y. Chen, A. Turlik, T. R. Newhouse, *J. Am. Chem. Soc.* **2016**, 138, 1166–1169

7,12-Dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one (14a).

14a was prepared according to **General procedure D**, starting from diisopropylamine (0.29 mL, 2.1 mmol, 10.0 equiv.) in THF (5.0 mL) was added *n*BuLi (2.5 M in hexane, 0.84 mL, 2.1 mmol, 10.0 equiv.). A solution of **10** (50 mg, 0.21 mmol, 1.0 equiv.) in THF (5.0 mL) was added dropwise into the resulting mixture. Then the reaction mixture was treated with ZnCl₂ (1.9 M in 2-Me-THF, 0.39 mL, 0.73 mmol, 3.5 equiv.). Afterwards a stock solution of [Pd(allyl)Cl]₂ (1.9 mg, 5.1 μmol, 2.5 mol%) and allyl acetate (27 μL, 25 μmol, 1.2 equiv.) in THF (1.0 mL) was next added. Purification by silica gel column chromatography (pentane/EtOAc = 1:2) afforded **14a** (38 mg, 0.16 mmol, 76%) as a yellow solid.

¹H NMR (700 MHz, CD₃OD) δ [ppm] = 8.10 (dt, *J* = 8.0, 1.0 Hz, 1H), 8.06 (dd, *J* = 9.0, 7.1 Hz, 1H), 7.93 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.76 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.61 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H), 7.23 (dd, *J* = 7.1, 1.2 Hz, 1H), 6.99 (dd, *J* = 8.9, 1.2 Hz, 1H), 4.95 (t, *J* = 7.0 Hz, 2H), 3.64 (dd, *J* = 7.5, 6.5 Hz, 2H).

¹³C NMR (176 MHz, CD₃OD) δ [ppm] = 165.0, 141.2, 140.3, 140.0, 128.6, 126.9, 125.5, 121.1, 120.4, 117.8, 115.3, 112.8, 102.4, 42.1, 20.3.

HRMS-ESI: calcd. for C₁₅H₁₃N₂O [*M* + *H*]⁺: 237.1023; found: 237.1021.

FT-IR: ν [cm⁻¹] = 2927, 2185, 1652, 1568, 1539, 1500, 1452, 1324, 1143, 777, 740.

10-Methoxy-7,12-dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one (14b).

14b was prepared according to **General procedure D**, starting from diisopropylamine (0.13 mL, 0.93 mmol, 10.0 equiv.) in THF (2.5 mL) was added *n*BuLi (2.5 M in hexane, 0.37 mL, 0.93 mmol, 10.0 equiv.). A solution of **12b** (25 mg, 93 μmol, 1.0 equiv.) in THF (2.5 mL) was added dropwise into the resulting mixture. Then the reaction mixture

was treated with ZnCl₂ (1.9 M in 2-Me-THF, 0.17 mL, 0.33 mmol, 3.5 equiv.). After that, the stock solution of [Pd(allyl)Cl]₂ (0.85 mg, 2.3 μmol, 2.5 mol%) and allyl acetate (11.2 μL, 0.11 mmol, 1.2 equiv.) in THF (0.5 mL) was next added. Purification by silica gel column chromatography (pentane/EtOAc = 1:2) afforded **14a** (15 mg, 56 μmol, 60%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.27 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.33 (dd, *J* = 9.1, 7.0 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.48 (dd, *J* = 9.1, 1.2 Hz, 1H), 6.25 (dd, *J* = 7.0, 1.2 Hz, 1H), 4.43 (t, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 3.06 (t, *J* = 7.0 Hz, 2H).

¹³C NMR (126 MHz, CD₃OD) δ [ppm] = 165.0, 159.9, 141.4, 141.2, 140.2, 127.5, 121.3, 121.2, 116.9, 115.8, 111.9, 101.7, 95.3, 55.9, 42.0, 20.4.

HRMS-ESI: calcd. for C₁₆H₁₅N₂O₂ [M + H]⁺: 267.1128; found: 267.1127.

FT-IR: ν [cm⁻¹] = 2922, 2853, 1651, 1567, 1540, 1457, 1375, 1271, 1201, 1161, 1143, 798.

2-Methyl-7,12-dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one (**14c**).

14c was prepared according to **General procedure D**, starting from diisopropylamine (0.17 mL, 1.2 mmol, 10.0 equiv.) in THF (3.0 mL) was added *n*BuLi (2.5 M in hexane, 0.48 mL, 1.2 mmol, 10.0 equiv.). A solution of **12e** (30 mg, 0.12 mmol, 1.0 equiv.) in THF (3.0 mL) was added dropwise into the resulting mixture. Then the reaction mixture was treated with ZnCl₂ (1.9 M in 2-Me-THF, 0.22 mL, 0.42 mmol, 3.5 equiv.). After that, the stock solution of [Pd(allyl)Cl]₂ (1.1 mg, 3.0 μmol, 2.5 mol%) and allyl acetate (15 μL, 0.14 mmol, 1.2 equiv.) in THF (0.5 mL) was next added. Purification by silica gel column chromatography (pentane/EtOAc = 1:2) afforded **14c** (21 mg, 84 μmol, 71%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃+CD₃OD (v/v = 1:1)) δ [ppm] = 7.82–7.76 (m, 1H), 7.65 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.48 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.34 (ddd, *J* = 8.0, 7.0,

1.1 Hz, 1H), 6.83 (d, $J = 1.8$ Hz, 1H), 6.59–6.52 (m, 1H), 4.62 (t, $J = 7.0$ Hz, 2H), 3.34 (t, $J = 6.9$ Hz, 2H), 2.51 (s, 3H).

^{13}C NMR (126 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$ (v/v = 1:1)) δ [ppm] = 163.2, 151.5, 138.4, 137.3, 127.0, 125.2, 123.9, 119.6, 118.9, 115.2, 113.6, 111.4, 103.7, 40.4, 20.5, 19.1.

HRMS-ESI: calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M} - \text{H}]^-$: 249.1033; found: 249.1035.

FT-IR: ν [cm^{-1}] = 2924, 1649, 1583, 1568, 1543, 1499, 1364, 1148, 743.

10-Methoxy-2-methyl-7,12-dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one (**14d**).

14d was prepared according to **General procedure D**, starting from diisopropylamine (0.35 mL, 2.5 mmol, 15.0 equiv.) in THF (3.0 mL) was added *n*BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol, 15.0 equiv.). A solution of **13** (47 mg, 0.17 mmol, 1.0 equiv.) in THF (3.0 mL) was added dropwise into the resulting mixture. Then the reaction mixture was treated with ZnCl_2 (1.9 M in 2-Me-THF, 0.44 mL, 0.83 mmol, 3.5 equiv.). After that, the stock solution of $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (0.15 mg, 4.2 μmol , 2.5 mol%) and allyl acetate (22 μL , 0.20 mmol, 1.2 equiv.) in THF (0.5 mL) was next added. Purification by silica gel column chromatography (pentane/EtOAc = 1:2) afforded **14d** (36 mg, 0.129 mmol, 77%) as a yellow solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 9.11 (s, 1H), 7.44 (d, $J = 8.7$ Hz, 1H), 6.87 (d, $J = 2.2$ Hz, 1H), 6.82 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.31 (t, $J = 1.4$ Hz, 1H), 6.26 (d, $J = 1.7$ Hz, 1H), 4.41 (t, $J = 6.9$ Hz, 2H), 3.85 (s, 3H), 3.03 (t, $J = 6.9$ Hz, 2H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 163.2, 158.5, 150.2, 139.6, 137.2, 126.7, 120.5, 120.4, 116.4, 115.2, 111.0, 102.0, 94.9, 55.8, 40.4, 21.5, 19.9.

HRMS-ESI: calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$: 281.1284; found: 281.1284.

FT-IR: ν [cm^{-1}] = 3184, 2922, 1651, 1626, 1567, 1460, 1374, 1270, 1201, 1139, 1031, 814, 753.

2.3.2. Optimization of regioselective dehydrogenation

With the classic dehydrogenation methods, the reactions turned out to be unsatisfying. The best result was obtained with LDA, sulfinimidoyl chloride system. We considered that the enolation was a reasonable strategy to afford the regioselectivity.

Table S-1: Dehydrogenation by classic conditions

entry	conditions	solvent	yield
1	MnO ₂	DCM	trace
2	γ-MnO ₂	DCM	trace
3	NBS, BPO	CDCl ₃	no conversion
4	S, Dowtherm [®] A	--	complex mixture
5	DDQ	Dioxane	complex mixture
6	Cu(OAc) ₂ , Na ₂ CO ₃ , py, O ₂	toluene	no conversion
7	CuBr ₂	MeCN	no conversion
8	Pd(OAc) ₂ , O ₂	DMSO	trace
9	V(acac) ₃ , TFA, Bu ₄ NBr, O ₂	Dioxane	complex mixture
10	LiTMP, sulfinimidoyl chloride	THF	complex mixture
11	NaHMDS, sulfinimidoyl chloride	THF	trace
12	MeLi, sulfinimidoyl chloride	THF	14%
13	LDA, PhSeCl	THF	trace
14	LDA, PhSOOMe	THF	complex mixture
15	LDA, sulfinimidoyl chloride	THF	33%

With the protocol reported by Newhouse et al., initially the resulted in conversion. Finally, LDA was the best base for the reaction affording 76% yield.

Table S-2: Optimization of Newhouse's procedure

entry	Step 1	Step 2	Step 3	yield ^[a]
1	LiCyan (2.5 eq.), -40 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 14h	SM:P=9.8:1
2	LiCyan (2.5 eq.), -40 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 38h	SM:P=5.1:1
3	LiCyan (2.5 eq.), -40 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 62h	SM:P=6.5:1
4	LiCyan (2.5 eq.), -40 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 86h	SM:P=2.1:1
5	LiCyan (5.0 eq.), -40 °C	ZnCl ₂ (7.0 eq.)	[Pd] (5.0 mol%), 14h	SM:P=3.9:1
6	LiCyan (5.0 eq.), -40 °C	ZnCl ₂ (7.0 eq.)	[Pd] (5.0 mol%), 38h	SM:P=3.8:1
7	LiCyan (5.0 eq.), -40 °C	ZnCl ₂ (7.0 eq.)	[Pd] (5.0 mol%), 62h	SM:P=3.4:1
8	LiCyan (5.0 eq.), -40 °C	ZnCl ₂ (7.0 eq.)	[Pd] (5.0 mol%), 86h	SM:P=2.3:1
9	LiCyan (2.5 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 14h	SM:P=36:1
10	LiCyan (2.5 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 75h	SM:P=9.4:1
11	LiCyan (2.5 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 96h	SM:P=9.5:1
12	LiTMP (2.5 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 14h	SM:P=4.0:1
13	LiTMP (2.5 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 75h	SM:P=2.3:1
14	LiTMP (2.5 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 96h	SM:P=2.4:1
15	LiCyan (10 eq.), -40 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 21h	SM:P=3:1
16	LiCyan (10 eq.), -40 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 51h	SM:P=2.9:1
17	LiCyan (10 eq.), -40 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 88h	SM:P=1.5:1
18	LiTMP (10 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 21h	SM:P=1.7:1
19	LiTMP (10 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 51h	SM:P=2.0:1
20	LiTMP (10 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 88h	SM:P=0.5:1
21	LDA (10 eq.), 0 °C	ZnCl ₂ (3.5 eq.)	[Pd] (2.5 mol%), 88h	76% ^[b]

[a] ratio was determined by NMR; [b] isolated yield

2.4. Reductive pathway

2,3,6,7,12,12*b*-Hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (*rac*-**15**).

To a solution of enamide **10** (0.10 g, 0.42 mmol, 1.0 equiv.) in MeOH (10 mL), was added Pd/C (10% Pd on charcoal, 45 mg, 40 μmol , 0.1 equiv.). Then hydrogen was charged to the reaction mixture with a balloon. After the mixture was stirred overnight, it was filtered through Celite[®], and concentrated under reduced pressure. Purification by silica gel column chromatography (pentane/EtOAc = 1:1) afforded *rac*-**15** (76 mg, 0.32 mmol, 75%) as a light yellow powder.

2,3,6,7,12,12*b*-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one ((*S*)-**15**).

To a mixture of enamide **10** (26 mg, 0.11 mmol, 1.0 equiv.) and Hantzsch ester **19** (42 mg, 0.16 mmol, 1.5 equiv.) in toluene (2.5 mL), was added a solution of **CPA-1** (8.4 mg, 10 μmol , 0.1 equiv.) in toluene (1.0 mL). Then the reaction mixture was immediately moved to a pre-heated 60 °C oil bath. After stirring for 24 h, the resulting mixture was quenched by NaHCO₃ (sat. aq.), diluted with DCM. The organic phase was separated. The aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (pentane/EtOAc = 1:1) afforded (*S*)-**15** (16 mg, 70 μmol , 61%, 99% (b.r.s.m.), 80% *ee*) as a light yellow powder.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.09 (s, 1H), 7.51 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.34 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.23–5.14 (m, 1H), 4.82–4.75 (m, 1H), 2.87 (m, 2H), 2.81–2.73 (m, 1H), 2.62–2.57 (m, 1H), 2.50–2.43 (m, 1H), 2.40 (td, *J* = 11.6, 5.8 Hz, 1H), 2.02–1.93 (m, 1H), 1.92–1.83 (m, 1H), 1.83–1.73 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 169.5, 136.3, 133.4, 127.0, 122.3, 120.0, 118.6, 111.1, 109.8, 54.6, 40.4, 32.5, 29.2, 21.1, 19.5.

HRMS-EI: calcd. for C₁₅H₁₆N₂O [M]⁺: 240.1257; found: 240.1259.

FT-IR: ν [cm⁻¹] = 3223, 2923, 2853, 1615, 1470, 1445, 1415, 1266, 1235, 741.

[α]_D²⁶ = −191.2 (*c* = 0.8, CHCl₃); Lit.²: [α]_D²⁵ = −220.2 (*c* = 0.10 CHCl₃) (94% *ee*).

HPLC: 10% EtOH/Hexane, Chiralpak IA, 1.0 mL/min

Signal 3: DAD1 E, Sig=270,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.457	BB	0.3627	2324.59595	93.30048	50.6335
2	13.498	BB	0.4409	2266.42432	73.67532	49.3665

Totals : 4591.02026 166.97581

Signal 3: DAD1 E, Sig=270,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.393	BB	0.3036	316.36719	15.40351	10.0180
2	13.046	BB	0.4101	2841.63501	99.83503	89.9820
Totals :				3158.00220	115.23854	

6,7,12,12*b*-Tetrahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (**16**).^[3]

Diisopropylamine (234 μ L, 1.67 mmol, 10.0 equiv.) was added to dry THF (5.0 mL) at 0 °C. *n*BuLi (2.5 M in hexane, 667 μ L, 1.67 mmol, 10.0 equiv.) was added and the mixture was stirred for 30 min before cooling to -78 °C. A solution of *rac*-**15** (40.0 mg, 0.167 mmol, 1.0 equiv.) in THF (2.0 mL) was added dropwise. The reaction was stirred at -78 °C for 1 h. A solution of PhSeBr (59.0 mg, 250 μ mol, 1.5 equiv.) in THF (2.0 mL) was added dropwise and the reaction mixture was stirred for 24 h. The reaction was quenched by NH_4Cl (sat. aq.) and extracted with DCM. The combined organic phases were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude selenide was dissolved in methanol (5.0 mL) and water (1.0 mL). NaIO_4 (71.0 mg, 333 μ mol, 2.0 equiv.) and NaHCO_3 (16.8 mg, 200 μ mol, 1.2 equiv.) were added and the reaction was heated at 60 °C for 24 h. The reaction was quenched by NaHCO_3 (sat. aq.) and extracted with DCM. The combined organic phases were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 1:1) to give **16** (16.0 mg, 67.2 μ mol, 40%) as light yellow powder.

¹H NMR (500 MHz, *d*₆-DMSO) δ [ppm] = 10.96 (s, 1H), 7.44 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.33 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.08 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.81 (ddd, *J* = 9.7, 6.2, 2.1 Hz, 1H), 5.92 (dd, *J* = 9.7, 2.8 Hz, 1H), 4.91–4.82 (m, 1H), 4.78 (ddd, *J* = 13.6, 5.2, 1.9 Hz, 1H), 3.02 (ddd, *J* = 17.7, 6.3, 4.9

[3] P. Horrocks, S. Fallon, L. Denman, O. Devine, L. J. Duffy, A. Harper, E. Meredith, S. Hasenkamp, A. Sidaway, D. Monnery, T.R. Phillips, S. M. Allin, *Bioorg. Med. Chem. Lett.* **2012**, 22, 1770–1773.

Hz, 1H), 2.88–2.75 (m, 2H), 2.67 (m, 1H), 2.32–2.19 (m, 1H).

¹³C NMR (126 MHz, *d*₆-DMSO) δ [ppm] = 164.1, 139.4, 136.3, 133.6, 126.1, 124.7, 121.1, 118.6, 117.9, 111.1, 107.0, 51.2, 38.2, 30.3, 20.5.

HRMS-EI: calcd. for C₁₅H₁₄N₂O [M]⁺: 238.1100; found: 238.1099.

FT-IR: ν [cm⁻¹] = 3780, 2918, 2849, 1737, 1655, 1601, 1436, 1324, 1303, 817, 740.

2.5. Total synthesis of pegamunine A

2.5.1. Preparation of ketoamide

1,1,1,3,3,3-Hexafluoropropan-2-yl 5-((2-(6-methoxy-1*H*-indol-3-yl)ethyl)amino)-3,3-dimethyl-5-oxopentanoate (24).

24 was prepared according to **General procedure A**, starting from 6-methoxytryptamine (200 mg, 1.05 mmol, 1.0 equiv.) and 3,3-dimethylglutaric anhydride (150 mg, 1.05 mmol, 1.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with EDCI (402 mg, 2.11 mmol, 2.0 equiv.), DMAP (25.7 mg, 0.211 mmol, 0.2 equiv.) and HFIP (556 μ L, 5.26 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **24** (370 mg, 0.768 mmol, 73%) as a yellow solid.

¹H NMR (500 MHz, CD₂Cl₂) δ [ppm] = 8.13 (s, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 6.92 (dt, *J* = 2.1, 1.0 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.86–5.78

(m, 1H), 5.75 (s, 1H), 3.82 (s, 3H), 3.54 (td, $J = 6.9, 5.7$ Hz, 2H), 2.94–2.87 (m, 2H), 2.62 (s, 2H), 2.15 (s, 2H), 1.08 (s, 6H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ [ppm] = 170.7, 169.5, 157.1, 137.7, 122.2, 121.2, 119.6, 113.3, 109.8, 94.9, 66.7–66.2 (m), 55.9, 47.5, 44.0, 39.9, 33.5, 27.9, 25.8. (Due to the resolution or/and overlapping, the resonance of CF_3 is missing.)

^{19}F NMR (471 MHz, CD_2Cl_2) δ [ppm] = –73.47.

HRMS-EI: calcd. for $\text{C}_{21}\text{H}_{24}\text{F}_6\text{N}_2\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 505.1532; found: 505.1533.

FT-IR: ν [cm^{-1}] = 2969, 2941, 1766, 1737, 1649, 1456, 1360, 1289, 1200, 1109, 771.

10-Methoxy-2,2-dimethyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (25).

25 was prepared according to **General procedure C**, starting from **24** (100 mg, 0.207 mmol, 1.0 equiv.) and POCl_3 (18.9 μL , 0.207 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K_2CO_3 (287 mg, 2.08 mmol, 10 equiv.) and $n\text{Bu}_4\text{NBr}$ (6.7 mg, 0.021 mmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **25** (49.0 mg, 0.165 mmol, 85%) as a yellow solid.

^1H NMR (700 MHz, CDCl_3) δ [ppm] = 8.09 (s, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 6.83 (s, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 5.27 (s, 1H), 4.09 (t, $J = 5.9$ Hz, 2H), 3.85 (s, 3H), 2.88 (t, $J = 5.9$ Hz, 2H), 2.48 (s, 2H), 1.16 (s, 6H).

^{13}C NMR (176 MHz, CDCl_3) δ [ppm] = 169.6, 157.6, 138.3, 128.9, 126.9, 121.3, 119.7, 112.4, 109.7, 109.5, 95.0, 55.8, 46.6, 39.3, 30.8, 28.3, 20.8.

HRMS-EI: calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 296.1519; found: 296.1520.

FT-IR: ν [cm^{-1}] = 2954, 2919, 2850, 1736, 1663, 1628, 1461, 1365, 1230, 12174, 1149.

3-Hydroxy-10-methoxy-2,2-dimethyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizin-4(3*H*)-one (S15).

To a solution of tetracyclic lactam **25** (100 mg, 0.34 mmol, 1.0 equiv.) in THF, was added LiTMP (1.0 M solution in THF, 3.40 mL, 3.38 mmol, 10.0 equiv.) at -78°C . The resulting mixture was stirred at that temperature for 1 h before P(OMe)_3 (250 μL , 1.01 mmol, 2.5 equiv.) was added. O_2 was bubbled through the mixture for 20 min, and the mixture was stirred for additional 2 h under O_2 atmosphere. Then the reaction mixture was quenched with saturated NaHCO_3 (sat. aq.). The aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried with MgSO_4 , filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **S15** (75.0 mg, 0.240 mmol, 71%) as yellow solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 8.09 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 2.2 Hz, 1H), 6.79 (dd, J = 8.6, 2.2 Hz, 1H), 5.27 (s, 1H), 4.86 (ddd, J = 12.7, 5.2, 2.1 Hz, 1H), 4.08 (d, J = 2.5 Hz, 1H), 3.89 (d, J = 2.6 Hz, 1H), 3.85 (s, 3H), 3.28 (td, J = 12.1, 5.4 Hz, 1H), 2.96–2.83 (m, 2H), 1.30 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 171.7, 157.9, 138.4, 127.8, 126.1, 121.2, 119.8, 112.4, 110.1, 109.3, 94.9, 75.0, 55.8, 40.7, 35.2, 26.5, 20.6, 19.9.

HRMS-ESI: calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$: 335.1366; found: 335.1367.

FT-IR: ν [cm^{-1}] = 3343, 2958, 2924, 1653, 1393, 1360, 1328, 1231, 1151, 1045, 1027, 920, 743.

10-Methoxy-2,2-dimethyl-2,6,7,12-tetrahydroindolo[2,3-*a*]quinolizine-3,4-dione (26).^[4]

To a solution of NCS (171 mg, 1.28 mmol, 5.0 equiv.) in DCM (5.0 mL) at 0 °C was added Me₂S (471 μL, 6.41 mmol, 25 equiv.) and the mixture was stirred at –78 °C for 1 h. The **S15** (80 mg, 0.256 mmol, 1.0 equiv.) in DCM (2.0 mL) was added dropwise. The resulting mixture was stirred at –78 °C for another two hours before triethylamine (712 μL, 5.13 mmol, 20 equiv.) was added. Then the mixture was stirred at –78 °C for 2 h. The mixture was quenched with NH₄Cl (sat. aq.) and extracted with DCM. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **26** (57.0 mg, 0.184 mmol, 71%) as an orange solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 8.08 (s, 1H), 7.42–7.37 (m, 1H), 6.87–6.84 (m, 1H), 6.80 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.31 (s, 1H), 4.20 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.98 (t, *J* = 6.0 Hz, 2H), 1.39 (s, 6H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 196.1, 158.1, 157.4, 138.7, 127.0, 125.9, 121.0, 120.0, 113.0, 110.3, 106.0, 95.1, 55.9, 44.9, 40.5, 25.0, 20.4.

HRMS-EI: calcd. for C₁₈H₁₈N₂O₃ [*M*]⁺: 310.1312; found: 310.1314.

FT-IR: ν [cm^{–1}] 3284(br), 2956, 2925, 1642, 1392, 1305, 1184, 1143, 1047, 799, 756.

2.5.2. Racemic protection group free annulation reaction

Imine pre-formation one-pot procedure.^[4]

A mixture of ketoenamide **25** (56.0 mg, 0.181 mmol, 1.0 equiv.), 6-methoxytryptamine (**22**) (41.2 mg, 0.217 mmol, 1.2 equiv.) and MgSO₄ (217 mg, 1.81 mmol, 10.0 equiv.) in toluene (10 mL) was heated to 115 °C (*oil bath temperature*) overnight. The reaction

[4] C. Piemontesi, Q. Wang, J. Zhu *J. Am. Chem. Soc.* **2016**, 138, 35, 11148–11151

mixture was cooled to room temperature and TFA (2.8 μ L, 36 μ mol, 0.2 equiv.) were added. The mixture was then heated to reflux for 2 days, before the reaction was quenched with saturated NaHCO₃ (sat. aq.). The aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **6** (34.0 mg, 70.5 μ mol, 39%) as light yellow solid.

Cascade procedure.

To a mixture of ketoenamide **25** (35.0 mg, 0.113 mmol, 1.0 equiv.), 6-methoxytryptamine (**22**) (25.7 mg, 0.135 mmol, 1.2 equiv.) and MgSO₄ (136 mg, 1.13 mmol, 10.0 equiv.) in 10 mL toluene under argon atmosphere, was added TFA (1.7 μ L, 23 μ mol, 0.2 equiv.). The resulting reaction mixture was heated to 115 °C (oil bath temperature) for 2 days. Then the reaction was quenched by NaHCO₃ (sat. aq.). The aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **6** (23.0 mg, 47.7 μ mol, 42%) as a light yellow solid.

2.5.3. Enantioselective protection group free annulation reaction

2.5.3.1. Catalyst preparation

S17 was prepared from **S16** by a procedure of Lee et al..^[5] The spectroscopic data are in agreement with literature. **28** was synthesized from **S17** following the procedure of Seidel et al..^[6] The spectroscopic data are in agreement with literature.

[5] P. S. Akula, B.-C. Hong, G.-H. Lee *Org. Lett.* **2018**, 20, 7835–7839.

[6] C. Min, N. Mittal, D. X. Sun, D. Seidel, *Angew. Chem. Int. Ed.* **2013**, 52, 14084–14088.

Scheme S-3: Synthesis of CBSBA.

1,2,3,4,5-pentacarboxycyclopentadiene (PCCP) derived pentamethyl ester **29** was synthesized from **S18** according to a procedure by Lambert et al..^[7] The spectroscopic data are in agreement with literature.

Scheme S-4: Synthesis of PCCP.

Chiral DSIs:

Generally, the synthesis of **S20** needs 7 steps from BINOL. With the **S14** in hand, DSIs could be obtained by Suzuki coupling with boronic acid.^[8]

[7] M. A. Radtke, C. C. Dudley, J. M. O'Leary, T. H. Lambert, *Synthesis* **2019**, 51, 1135–1138.

[8] S. Gandhi, B. List *Angew. Chem. Int. Ed.* **2013**, 52, 2573–2576.

Scheme S-5: Synthesis of DSIs.

The readily available DSIs:

continued

Figure S-1: Screened the readily available DSIs.

General procedure E

2M K₂CO₃ was added to a solution of (*R*)-DSI iodide (**S20**) (1.0 equiv.), boronic acid (3.0 equiv.), Pd(OAc)₂ (0.1 equiv.) in THF at room temperature. The reaction flask was degassed and filled with argon three times before Pt-Bu₃ (1.0 M in toluene, 0.1 equiv.) was added. The reaction mixture was then put to a preheated 85 °C oil bath for 24 h. 10% aqueous HCl solution was added and the reaction mixture was extracted three times with DCM. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/EtOAc = 3:2) to give a white solid which was dissolved in DCM and stirred with 4N HCl for 1 h. The organic layer was then separated, dried over MgSO₄ and concentrated under reduced pressure to give the desired compound as a white solid.

(*R*)-2,6-Bis(3,5-difluorophenyl)-4*H*-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dithiazepine 3,3,5,5-tetraoxide (S21).

S21 was prepared according to **General procedure E**, starting from **S20** (50 mg, 77 μmol , 1.0 equiv.), (3,5-difluorophenyl)boronic acid (38 mg, 0.23 mmol, 3.0 equiv.) and $\text{Pd}(\text{OAc})_2$ (1.7 mg, 8.0 μmol , 0.1 equiv.) in THF (3.0 mL). After degassing, the mixture was treated with $Pt\text{-Bu}_3$ (1.0 M in toluene, 7.7 μL , 8.0 μmol , 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **S21** (28 mg, 45 μmol , 58%) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ [ppm] = 8.02 (d, J = 9.0 Hz, 4H), 7.72 (ddd, J = 8.2, 6.8, 1.1 Hz, 2H), 7.45 (ddd, J = 8.4, 6.9, 1.2 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 6.90–6.85 (m, 2H), 5.76 (s, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ [ppm] = 162.6, 162.5, 162.1, 162.0, 160.6, 160.5, 160.1, 160.0, 141.2, 141.1, 141.0, 137.5, 133.6, 133.4, 132.6, 131.1, 130.8, 129.4, 128.0, 127.7, 127.2, 113.1, 112.9, 111.3, 111.1, 102.8, 102.6, 102.4. (Due to the complexity of the F–C coupling, the coupling constants were not calculated.)

^{19}F NMR (471 MHz, CDCl_3) δ [ppm] = –109.97, –110.59.

HRMS-ESI: calcd. for $\text{C}_{32}\text{H}_{16}\text{F}_4\text{NO}_4\text{S}_2$ [$\text{M} - \text{H}$] $^-$: 618.0462; found: 618.0472.

FT-IR: ν [cm^{-1}] 3158(br), 2927, 1617, 1529, 1439, 1423, 1362, 1340, 1319, 1044, 845, 751.

(*R*)-2,6-Bis(3,4,5-trifluorophenyl)-4*H*-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dithiazepine 3,3,5,5-tetraoxide (S22).

S22 was prepared according to **General procedure E**, starting from **S20** (50 mg, 77 μ mol, 1.0 equiv.), (3,4,5-trifluorophenyl)boronic acid (41 mg, 0.23 mmol, 3.0 equiv.) and Pd(OAc)₂ (1.7 mg, 8.0 μ mol, 0.1 equiv.) in THF (3.0 mL). After degassing, the mixture was treated with *Pt*-Bu₃ (1.0 M in toluene, 7.7 μ L, 8.0 μ mol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **S23** (36 mg, 54 μ mol, 70%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.02 (d, J = 8.7 Hz, 4H), 7.74 (ddd, J = 8.2, 6.9, 1.1 Hz, 2H), 7.46 (ddd, J = 8.4, 6.9, 1.3 Hz, 2H), 7.20–7.01 (m, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 151.8, 151.5, 149.9, 149.8, 149.5, 149.5, 138.7, 135.0, 134.9, 134.9, 134.9, 134.8, 134.8, 134.5, 134.0, 133.9, 132.3, 131.9, 130.7, 129.3, 128.8, 128.3, 115.3, 115.1, 113.6, 113.5. (Due to the complexity of the F–C coupling, the coupling constants were not calculated.)

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = (–138.15)–(–140.64) (m), –167.04 (t, J = 19.9 Hz).

HRMS-ESI: calcd. for C₃₂H₁₄F₆NO₄S₂ [M – H][–]: 654.0274; found: 654.0282.

FT-IR: ν [cm^{–1}] 3161(br), 2924, 1738, 1618, 1529, 1424, 1362, 1217, 1045, 848, 750.

(*R*)-2,6-Bis(3,5-dinitrophenyl)-4*H*-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dithiazepine 3,3,5,5-tetraoxide (S23).

S23 was prepared according to **General procedure E**, starting from **S20** (15 mg, 23 μ mol, 1.0 equiv.), (3,5-dinitrophenyl)boronic acid (15 mg, 0.70 mmol, 3.0 equiv.) and Pd(OAc)₂ (0.50 mg, 2.0 μ mol, 0.1 equiv.) in THF (1.0 mL). After degassing, the mixture was treated with *Pt*-Bu₃ (1.0 M in toluene, 2.3 μ L, 2.0 μ mol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **S23** (10 mg, 14 μ mol, 59%) as a white solid.

¹H NMR (500 MHz, CD₂Cl₂) δ [ppm] = 9.05 (t, *J* = 2.1 Hz, 2H), 8.76 – 8.61 (m, 4H), 8.12 (d, *J* = 6.6 Hz, 4H), 7.82 (t, *J* = 7.6 Hz, 2H), 7.55 (dd, *J* = 8.8, 6.8 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H).

¹³C NMR (126 MHz, CD₂Cl₂) δ [ppm] = 148.2, 147.6, 142.7, 138.9, 134.6, 134.5, 132.5, 132.1, 131.8, 131.2, 130.9, 130.0, 129.3, 129.2, 128.4, 118.5.

HRMS-ESI: calcd. for C₃₂H₁₆N₅O₁₂S₂ [*M* – H][–]: 726.0256; found: 726.0242.

FT-IR: ν [cm^{–1}] 2924, 1738, 1541, 1343, 1175, 831, 750.

(*R*)-2,6-Bis(3,5-difluoro-4-(trifluoromethyl)phenyl)-4*H*-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dithiazepine 3,3,5,5-tetraoxide (32**).**

32 was prepared according to **General procedure E**, starting from **S20** (300 mg, 0.464 mmol, 1.0 equiv.), (3,5-difluoro-4-(trifluoromethyl)phenyl)boronic acid (315 mg, 1.39 mmol, 3.0 equiv.) and Pd(OAc)₂ (10.4 mg, 46.4 μmol, 0.1 equiv.) in THF (15 mL). After degassing, the mixture was treated with *Pt*-Bu₃ (1.0 M in toluene, 46.4 μL, 46.4 μmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 2:1) afforded **32** (320 mg, 0.424 mmol, 91%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ [ppm] = 8.07–7.97 (m, 4H), 7.76 (t, *J* = 7.6 Hz, 2H), 7.54–7.46 (m, 2H), 7.24–7.07 (m, 6H).

¹³C NMR (126 MHz, CDCl₃) δ [ppm] = 160.4, 159.9, 158.3, 157.8, 145.6, 138.5, 134.2, 133.5, 133.1, 132.1, 131.4, 130.8, 129.5, 128.9, 128.2, 122.8, 120.7, 115.2, 115.0, 113.6, 113.5. (Due to the complexity of the F–C coupling, the coupling constants were not calculated.)

¹⁹F NMR (471 MHz, CDCl₃) δ [ppm] = –56.16 (t, *J* = 21.7 Hz), –111.17 (dq, *J* = 329.9, 22.4, 21.7 Hz).

HRMS-ESI: calcd. for C₃₄H₁₄F₁₀NO₄S₂ [*M* – H][–]: 754.0219; found: 754.0210.

FT-IR: *ν* [cm^{–1}] 3075, 1641, 1493, 1429, 1352, 1306, 1137, 1046, 856, 753.

2.5.3.2. Optimization for enantioselective protection group free cascade reaction

General Procedure for the small scale (0.50 mg or 1.00 mg) screening reactions

A mixture of ketoamide **25** (1.00 mg, 3.00 μmol, 1.0 equiv.), 6-methoxytryptamine (**22**) (0.75 mg, 3.60 μmol, 1.2 equiv.) and 4 Å MS in corresponding solvent (0.5 mL) was stirred at room temperature under argon in sealed vial. A solution of corresponding catalyst in the same solvent was added to the reaction mixture and the reaction mixture was heated up to the corresponding temperature for the set duration. The reaction

mixture was cooled to room temperature and purified by silica gel column chromatography (pentane/EtOAc = 3:2) to yield the pure product as solid.

(Note: since the ketoamide is not a fine power and cannot dissolve in toluene (the frequently used solvent), the practical way to prepare the 1.00 mg or 0.50 mg ketoamide was that, using fine balance to take 10.00 mg ketoamide which was then dissolved in 5.0 mL DCM (10.0 mL for 0.50 mg preparation), then adding 0.5 mL of such solvent to the 1.5 mL glass reaction vials, finally removing the DCM by rotary evaporator. And the catalyst was prepared in the corresponding solvent to load into the reaction.)

Table S-3: Screening of DSIs from catalyst pool of AK List

entry	catalyst	ee (%)	yield (%)
1	DSI-3	20.6	96
2	DSI-4	37.8	14
3	DSI-5	22	21
4	DSI-6	2.2	20
5	DSI-7	26.6	17
6	DSI-8	4.2	60
7	DSI-9	14	33
8	DSI-10	63	30
9	DSI-11	73	24
10	DSI-12	8.2	33
11	DSI-13	63.4	17
12	DSI-14	2.6	29
13	DSI-15	66.4	40
14	DSI-16	16.8	37
15	DSI-17	4.2	25
16	DSI-18	39.4	41
17	DSI-19	20.6	10
18	DSI-20	2.6	29
19	DSI-21	14.2	44
20	DSI-22	75.6	28
21	DSI-23	61.2	21
22	DSI-24	7.0	17
23	DSI-25	21.8	9
24	DSI-26	33.8	31
25	DSI-27	8.6	50

Figure S-2: Proposed SAR of DSIs

Table S-4: Screening for the newly designed DSIs

entry	catalyst (mol%)	solvent	<i>T</i> (°C)	<i>ee</i> (%)	yield (%)
1	DSI-28 (5)	toluene	60	41.0	57
2	DSI-28 (5)	fluorobenzene	60	32.2	26
3	DSI-28 (5)	<i>p</i> -xylene	60	7.7	42.
4	DSI-28 (5)	toluene	70	38.6	35
5	DSI-28 (10)	toluene	60	83.8	48
6	DSI-29 (5)	toluene	60	47.4	20
7	DSI-29 (5)	fluorobenzene	60	48.2	30
8	DSI-29 (5)	<i>p</i> -xylene	60	52.0	27
9	DSI-29 (5)	toluene	70	80.8	23
10	DSI-29 (10)	toluene	60	83.8	58
11	DSI-30 (5)	toluene	60	10.8	48
12	DSI-30 (5)	toluene	70	4.4	44
13	DSI-30 (10)	toluene	60	48.2	39

Table S-5: Optimization with DSI-2

entry	loading (mol%)	solvent	<i>T</i> (°C)	<i>ee</i> (%)	yield (%)
1	5	toluene	50	N.D.	N.D.
2	10	toluene	50	87.4	39
3	5	<i>p</i> -xylene	50	89.4	26.
4	5	<i>m</i> -xylene	50	75.2	6
5	5	benzene	50	N.D.	N.D.
6	5	toluene	60	83.0	66
7	10	toluene	60	92.4	62
8	5	<i>p</i> -xylene	60	91.0	62
9	5	<i>m</i> -xylene	60	90.2	47
10	5	benzene	60	67.8	15
11	5	toluene	70	83.0	66
12	10	toluene	70	93.6	34
13	5	<i>p</i> -xylene	70	91.0	62
14	5	<i>m</i> -xylene	70	90.2	47
15	5	benzene	70	67.8	15

Procedure for the scale-up reaction:

A mixture of ketoamide **25** (66.0 mg, 0.213 mmol, 1.0 equiv.), 6-methoxytryptamine (48.5 mg, 0.255 mmol, 1.2 equiv.) and 4 Å molecular sieves (50.0 mg) in toluene (50 mL) was stirred at room temperature. A solution of **DSI-2** (16.1 mg, 21.3 μmol, 0.1 equiv.) in toluene (5.0 mL) was added to the reaction mixture and the reaction mixture was stirred at 60 °C for 60 h. After the reaction mixture was cooled to room temperature, filtered through Celite®, washed by NaHCO₃ (sat. aq.), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **6** (83.3 mg, 0.173 mmol, 81%) as a white solid.

^1H NMR (700 MHz, CD_3OD) δ [ppm] = 7.38 (d, J = 8.7 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.73 (dd, J = 8.7, 2.2 Hz, 1H), 6.67 (dd, J = 8.6, 2.3 Hz, 1H), 4.14 (dd, J = 13.0, 5.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.21–3.16 (m, 1H), 2.98 (dd, J = 15.4, 4.4 Hz, 1H), 2.90–2.76 (m, 2H), 2.69 (dd, J = 15.5, 3.5 Hz, 1H), 2.59 (dd, J = 10.8, 5.3 Hz, 1H), 2.48–2.41 (m, 1H), 2.39 (d, J = 11.5 Hz, 1H), 1.94 (d, J = 11.5 Hz, 1H), 1.44 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (176 MHz, CD_3OD) δ [ppm] = 175.2, 158.3, 157.6, 139.5, 139.4, 127.8, 126.4, 122.3, 122.2, 119.9, 119.2, 112.9, 112.2, 110.5, 109.8, 96.0, 95.7, 81.2, 79.7, 56.0, 55.9, 51.9, 41.7, 41.6, 37.3, 27.3, 26.3, 22.5, 22.1.

^1H NMR (500 MHz, d_6 -DMSO) δ [ppm] = 11.24 (s, 1H), 10.77 (s, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.70 (dd, J = 8.6, 2.3 Hz, 1H), 6.63 (dd, J = 8.6, 2.3 Hz, 1H), 4.00 (dd, J = 12.9, 5.8 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.10 (td, J = 12.6, 4.5 Hz, 1H), 2.90 (dd, J = 15.3, 4.2 Hz, 1H), 2.76–2.69 (m, 1H), 2.69–2.65 (m, 1H), 2.64–2.60 (m, 1H), 2.48–2.43 (m, 1H), 2.34 (dd, J = 10.8, 4.9 Hz, 1H), 2.30 (d, J = 11.3 Hz, 1H), 1.88 (d, J = 11.2 Hz, 1H), 1.38 (s, 3H), 1.15 (s, 3H).

^{13}C NMR (126 MHz, d_6 -DMSO) δ [ppm] = 171.3, 156.1, 155.4, 137.6, 137.5, 127.3, 125.7, 120.5, 120.4, 119.0, 118.2, 111.2, 109.5, 109.0, 108.3, 94.9, 94.7, 78.8, 77.4, 55.23, 55.18, 50.4, 40.1, 39.9, 35.6, 26.8, 26.0, 21.0, 20.9.

HRMS-ESI: calcd. for $\text{C}_{29}\text{H}_{31}\text{N}_4\text{O}_3$ $[\text{M} + \text{H}]^+$: 483.2391; found: 483.2384.

FT-IR: ν (cm^{-1}) 2954, 2923, 2857, 1736, 1457, 1366, 1217, 820.

HPLC: 40% *i*PrOH/Heptane, IA, 1.0 mL/min

<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%	Height	Name
1	7.656	759375	49.795	39781	
2	14.329	765637	50.205	21402	
Total		1525012	100.000	61184

<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%	Height	Name
1	7.610	48338	1.441	2562	
2	14.171	3305614	98.559	93896	
Total		3353952	100.000	96458

<Peak Table>

PDA Ch1 270nm

Peak#	Ret. Time	Area	Area%	Height	Name
1	7.568	12333154	98.548	671511	
2	14.206	181749	1.452	5539	
Total		12514902	100.000	677050	

2.5.3.4. NMR comparison between Hua's isolation and our synthesis

¹ H-NMR (ppm) in <i>d</i> ₆ -DMSO			¹³ C-NMR (ppm) in <i>d</i> ₆ -DMSO		
Hua's isolation (600 MHz)	Ours (500 MHz)	Δδ	Hua's isolation (150 MHz)	Ours (125 MHz)	Δδ
11.25 (br.s, 1H)	11.24 (br.s, 1H)	−0.01	171.4	171.3	−0.1
10.77 (br.s, 1H)	10.77 (br.s, 1H)	0	156.1	156.1	0
7.38 (d, <i>J</i> = 8.6 Hz, 1H)	7.38 (d, <i>J</i> = 8.6 Hz, 1H)	0	155.4	155.4	0
7.24 (d, <i>J</i> = 8.6 Hz, 1H)	7.25 (d, <i>J</i> = 8.6 Hz, 1H)	0.01	137.6	137.6	0
6.93 (d, <i>J</i> = 1.6 Hz, 1H)	6.93 (d, <i>J</i> = 2.3 Hz, 1H)	0	137.5	137.5	0
6.87 (d, <i>J</i> = 1.8 Hz, 1H)	6.88 (d, <i>J</i> = 2.3 Hz, 1H)	0.01	127.3	127.3	0
6.70 (dd, <i>J</i> = 8.6, 1.8 Hz, 1H)	6.70 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H)	0	125.7	125.7	0
6.63 (dd, <i>J</i> = 8.6, 1.6 Hz, 1H)	6.63 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H)	0	120.5	120.5	0
4.00 (dd, <i>J</i> = 12.6, 5.7 Hz, 1H)	4.00 (dd, <i>J</i> = 12.9, 5.8 Hz, 1H)	0	120.4	120.4	0
3.78 (s, 3H)	3.78 (s, 3H)	0	119.0	119.0	0
3.77 (s, 3H)	3.77 (s, 3H)	0	118.2	118.2	0
3.09 (td, <i>J</i> = 12.6, 4.4 Hz, 1H)	3.10 (td, <i>J</i> = 12.6, 4.5 Hz, 1H)	0.01	111.3	111.2	−0.1
2.90 (dd, <i>J</i> = 15.1, 4.4 Hz, 1H)	2.90 (dd, <i>J</i> = 15.3, 4.2 Hz, 1H)	0	109.5	109.5	0
2.70 (ddd, <i>J</i> = 15.1, 12.6, 5.7 Hz, 1H)	2.76–2.69 (m, 1H)		109.0	109.0	0

2.64 (dd, $J = 11.0, 4.9$ Hz, 1H)	2.69–2.65 (m, 1H)		108.3	108.3	0
2.63 (dd, $J = 11.0, 4.9$ Hz, 1H)	2.64–2.60 (m, 1H)		94.9	94.9	0
2.45 (dd, $J = 10.9, 4.9$ Hz, 1H)	2.48–2.43 (m, 1H)		94.7	94.7	0
2.34 (dd, $J = 10.9, 4.9$ Hz, 1H)	2.34 (dd, $J = 10.8, 4.9$ Hz, 1H)	0	78.8	78.8	0
2.30 (d, $J = 10.9$ Hz, 1H)	2.30 (d, $J = 11.3$ Hz, 1H)	0	77.4	77.4	0
1.88 (d, $J = 10.9$ Hz, 1H)	1.88 (d, $J = 11.2$ Hz, 1H)	0	55.2 (55.23)	55.2 (55.23)	0
1.38 (s, 3H)	1.38 (s, 3H)	0	55.2 (55.18)	55.2 (55.18)	0
1.15 (s, 3H)	1.15 (s, 3H)	0	50.4	50.4	0
			40.0	40.1	0.1
			40.0	39.9	–0.1
			35.6	35.6	0
			26.8	26.8	0
			26.0	26.0	0
			21.0	21.0	0
			20.9	20.9	0

2.5.3.5. NMR comparison between Zhu's synthesis and our synthesis

¹ H-NMR (ppm) in CD ₃ OD			¹³ C-NMR (ppm) in CD ₃ OD		
Zhu's (400 MHz)	Ours (500 MHz)	$\Delta\delta$	Zhu's (101 MHz)	Ours (176 MHz)	$\Delta\delta$
7.38 (d, J = 8.6 Hz, 1H)	7.38 (d, J = 8.6 Hz, 1H)	0	175.2	175.2	0
7.26 (d, J = 8.5 Hz, 1H)	7.26 (d, J = 8.6 Hz, 1H)	0	158.4	158.3	−0.1
6.99 (d, J = 2.3 Hz, 1H)	6.99 (d, J = 2.2 Hz, 1H)	0	157.6	157.6	0
6.93 (d, J = 2.2 Hz, 1H)	6.93 (d, J = 2.2 Hz, 1H)	0	139.5	139.5	0
6.73 (dd, J = 8.6, 2.3 Hz, 1H)	6.73 (dd, J = 8.6, 2.2 Hz, 1H)	0	139.4	139.4	0
6.67 (dd, J = 8.6, 2.3 Hz, 1H)	6.67 (dd, J = 8.5, 2.3 Hz, 1H)	0	127.8	127.8	0
4.14 (dd, J = 13.0, 5.8 Hz, 1H)	4.14 (dd, J = 13.0, 5.8 Hz, 1H)	0	126.5	126.4	−0.1
3.83 (s, 3H)	3.83 (s, 3H)	0	122.3	122.3	0
3.82 (s, 3H)	3.82 (s, 3H)	0	122.2	122.2	0
3.18 (td, J = 12.3, 4.7 Hz, 1H)	3.21–3.16 (m, 1H)		120.0	119.9	−0.1
2.98 (dd, J = 15.4, 4.5 Hz, 1H)	2.98 (dd, J = 15.4, 4.3 Hz, 1H)	0	119.2	119.2	0
2.90–2.74 (m, 2H)	2.90–2.76 (m, 2H)		112.9	112.9	0
2.69 (dd, J = 15.2, 3.8 Hz, 1H)	2.69 (dd, J = 15.5, 3.5 Hz, 1H)	0	112.2	112.2	0
2.59 (dd, J = 10.8, 5.2 Hz, 1H)	2.59 (dd, J = 10.8, 5.3 Hz, 1H)	0	110.5	110.5	0

2.44 (dd, $J = 11.2, 4.1$ Hz, 1H)	2.48–2.41 (m, 1H)		109.8	109.8	0
2.39 (d, $J = 11.6$ Hz, 1H)	2.39 (d, $J = 11.5$ Hz, 1H)	0	96.0	96.0	0
1.94 (d, $J = 11.5$ Hz, 1H)	1.94 (d, $J = 11.5$ Hz, 1H)	0	95.7	95.7	0
1.44 (s, 3H)	1.44 (s, 3H)	0	81.3	81.2	−0.1
1.24 (s, 3H)	1.24 (s, 3H)	0	79.7	79.7	0
			56.0	56.0	0
			56.0	55.9	−0.1
			51.9	51.9	0
			41.7	41.7	0
			41.6	41.6	0
			37.3	37.3	0
			27.3	27.3	0
			26.3	26.3	0
			22.5	22.5	0
			22.1	22.1	0

2.6. Total synthesis of ilicifoline B

1,1,1,3,3,3-Hexafluoropropan-2-yl 2-(2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl)-4,5-dimethoxybenzoate (35).

35 was prepared according to **General procedure A**, starting from **33** (100 mg, 0.552 mmol, 1.0 equiv.) and **34** (123 mg, 0.552 mmol, 1.0 equiv.) in DCM (5.0 mL). The reaction mixture was subsequently treated with EDCI (211 mg, 1.10 mmol, 2.0 equiv.), DMAP (13.5 mg, 0.110 mmol, 0.2 equiv.) and HFIP (292 μL , 2.76 mmol, 5.0 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 3:2) afforded **35** (190 mg, 0.342 mmol, 62%) as a light yellow solid.

^1H NMR (700 MHz, CDCl_3) δ [ppm] = 7.46 (s, 1H), 6.91 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 6.59 (dd, J = 8.1, 2.0 Hz, 1H), 6.08 (s, 1H), 5.93–5.90 (m, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.79 (s, 2H), 3.43 (td, J = 7.1, 5.7 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 170.2, 163.4, 154.1, 149.1, 147.9, 147.8, 134.3, 131.3, 120.69 (q, *J* = 283.7 Hz), 120.65, 116.9, 115.0, 113.5, 112.0, 111.2, 67.3–66.5 (m), 56.4, 56.1, 55.9, 42.0, 40.9, 35.2. (Based on the intensity of the resonance, the peak at δ [ppm] = 55.9 is considered as two methoxy carbons.)

¹⁹F NMR (565 MHz, CDCl₃) δ [ppm] = –72.98 (d, *J* = 6.1 Hz).

HRMS-ESI: calcd. for C₂₄H₂₅F₆NO₇Na [M + Na]⁺: 576.1427; found: 576.1401.

FT-IR: ν [cm^{–1}] 2934, 1749, 1674, 1518, 1263, 1234, 1194, 1110, 768.

2,3,10,11-Tetramethoxy-5,6-dihydro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one (36).

36 was prepared according to **General procedure C**, starting from **35** (60 mg, 0.11 mmol, 1.0 equiv.) and POCl₃ (9.9 μL, 0.11 mmol, 1.0 equiv.) in toluene (3.0 mL). The reaction mixture was subsequently treated with MeOH (3.0 mL), K₂CO₃ (150 mg, 1.1 mmol, 10 equiv.) and *n*Bu₄NBr (3.5 mg, 0.022 mmol, 0.1 equiv.). Purification by silica gel column chromatography (pentane/EtOAc = 1:1) afforded **36** (38 mg, 0.104 mmol, 95%) as a yellow solid.

¹H NMR (700 MHz, CDCl₃) δ [ppm] = 7.81 (s, 1H), 7.25 (s, 1H), 6.94 (s, 1H), 6.83 (s, 1H), 6.74 (s, 1H), 4.39–4.34 (m, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 2.96–2.92 (m, 2H).

¹³C NMR (176 MHz, CDCl₃) δ [ppm] = 161.6, 153.7, 150.3, 149.2, 148.6, 136.3, 132.3, 128.6, 122.7, 118.7, 110.7, 108.0, 107.8, 106.1, 101.3, 56.4, 56.4, 56.2, 39.9, 28.3. (Based on the intensity of the resonance, the peak at δ [ppm] = 56.2 is considered as two methoxy carbons.)

HRMS-ESI: calcd. for C₂₁H₂₁NO₅Na [M + Na]⁺: 390.1312 found: 390.1323.

FT-IR: ν [cm^{–1}] 2929, 1644, 1594, 1509, 1466, 1426, 1255, 1235, 1097, 1027, 747.

2,2',3,3',10,10',11,11'-Octamethoxy-5,5',6,6'-tetrahydro-8*H*,8'*H*-[13,13'-biisoquinolino[3,2-*a*]isoquinoline]-8,8'-dione (5).

A mixture of 8-oxopseudopalmitine (18 mg, 50 μmol , 1.0 equiv.) and PIFA (16 mg, 0.05 mmol, 1.0 equiv.) in DCM (2.0 mL), was added $\text{BF}_3\cdot\text{Et}_2\text{O}$ (9.7 μL , 0.10 mmol, 2.0 equiv.) at -78°C . The mixture was stirred for 3 h, then quenched with NaHCO_3 (sat. aq.) and diluted with DCM, and the organic phase was separated. The aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (pentane/EtOAc = 1:1 to EtOAc) afforded **5** (11 mg, 15 μmol , 60%) as a yellow solid.

^1H NMR (700 MHz, CDCl_3) δ [ppm] = 7.95 (s, 2H), 6.76 (s, 2H), 6.43 (s, 2H), 6.34 (s, 2H), 5.05 (dt, J = 13.2, 3.8 Hz, 2H), 4.06 (s, 6H), 3.82 (s, 6H), 3.62 (s, 6H), 3.33 (td, J = 13.2, 3.0 Hz, 2H), 3.03 (s, 6H), 2.52 (dt, J = 15.1, 3.1 Hz, 2H), 2.13 (ddd, J = 14.5, 12.7, 4.2 Hz, 2H).

^{13}C NMR (176 MHz, CDCl_3) δ [ppm] = 161.0, 153.9, 149.5, 149.2, 146.6, 137.0, 133.6, 131.3, 122.5, 119.0, 111.6, 110.8, 109.2, 108.1, 105.8, 56.4, 56.3, 56.2, 55.2, 41.4, 29.0.

HRMS-EI: calcd. for $\text{C}_{42}\text{H}_{40}\text{N}_2\text{O}_{10}\text{Na}$ $[\text{M} + \text{Na}]^+$: 755.2575; found: 755.2576.

FT-IR: ν [cm^{-1}] 3004, 2928, 1633, 1607, 1587, 1498, 1464, 1440, 1374, 1271, 1226, 1133, 1096, 1008, 876, 749.

NMR comparison between Opatz's synthesis and our synthesis

¹ H-NMR (ppm) in CDCl ₃			¹³ C-NMR (ppm) in CDCl ₃		
Opatz's (600 MHz)	Ours (700 MHz)	$\Delta\delta$	Opatz's (150 MHz)	Ours (176 MHz)	$\Delta\delta$
7.95 (s, 2H)	7.95 (s, 1H)	0	160.9	161.0	0.1
6.75 (s, 2H)	6.76 (s, 2H)	0.01	153.8	153.9	0.1
6.42 (s, 2H)	6.43 (s, 2H)	0.01	149.4	149.5	0.1
6.33 (s, 2H)	6.34 (s, 2H)	0.01	149.1	149.2	0.1
5.09 – 4.99 (m, 2H)	5.05 (dt, $J = 13.2, 3.8$ Hz, 2H)		137.0	137.0	0
4.06 (s, 6H)	4.06 (s, 6H)	0	133.6	133.6	0
3.82 (s, 6H)	3.82 (s, 6H)	0	131.3	131.3	0
3.62 (s, 6H)	3.62 (s, 6H)	0	122.5	122.5	0
3.40 – 3.27 (m, 2H)	3.33 (td, $J = 13.2, 3.0$ Hz, 2H)		119.0	119.0	0
3.02 (s, 6H)	3.03 (s, 6H)	0.01	111.5	111.6	0.1
2.57 – 2.47 (m, 2H)	2.52 (dt, $J = 15.1, 3.1$ Hz, 2H)		110.8	110.8	0
2.19 – 2.07 (m, 2H)	2.13 (ddd, $J = 14.5, 12.7, 4.2$ Hz, 2H)		109.1	109.2	0.1
			108.0	108.1	0.1
			105.8	105.8	0

			56.4	56.4	0
			56.3	56.3	0
			56.1	56.2	0.1
			55.2	55.2	0
			41.4	41.4	0
			29.0	29.0	0

2.7. Preparation of amines

2.7.1. Commercially available amines

2.7.2. Noncommercially available amines synthesis by reported methods

S30 was prepared from (S)-tryptophan by the procedure of Carreira et al..^[9] **S31** was synthesized from 3-indolepropionic acid according to the procedure of Weinstock et al..^[10] **S32** was obtained from 3-indolebutyric acid following the procedure of Mewshaw et al..^[11] **S33** was prepared from 3-furancarboxaldehyde via the procedure of Liotta et al..^[12] **S34** was prepared from 2-furancarboxaldehyde through the procedure

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[12] M. P. Epplin, A. Mohan, L. D. Harris, Z. Zhu, K. L. Strong, J. Bacsá, P. Le, D. S. Menaldino, S. F. Traynelis, D.

of Huang et al..^[13] **S35** was prepared from 3-thiophencarboxaldehyde using the procedure of Enzensperger et al..^[14] The spectroscopic data are in agreement with literatures.

2.7.3. Self-made amines

The amines (**22** and **S36–S38**) were synthesized from the corresponding heterocycles. The preparation of the aldehydes depended on the starting material supply. For **22**, **S36** and **S37**, the aldehydes were synthesized from the corresponding indoles through a Vilsmeier–Haack reaction. For **S39**, the aldehydes were prepared via bromination and formylation. The Henry reaction with MeNO₂ and the reduction by LiAlH₄ followed the same procedure.

General procedure F

Vilsmeier–Haack reaction: To a dried Schlenk flask with DMF, was added POCl₃ (3.0 equiv.) dropwise at 0 °C. After the mixture was stirred for 30 min, a solution of corresponding indole (1.0 equiv.) in DMF was added to the reaction mixture dropwise. The resulting mixture was allowed to stir at room temperature for another 2 h. Then the reaction mixture was poured to a flask with ice, and carefully neutralized by NaHCO₃ (sat. aq.) until pH = 7–8. The suspension was left to rest overnight at room temperature,

filtered, collected the solid and dried under reduced pressure. This crude product was used without further purification.

Henry reaction: A flask with NH_4OAc (3.0 equiv.) and corresponding aldehyde (1.0 equiv.) was added MeNO_2 (75 equiv.) and the reaction mixture was stirred at $115\text{ }^\circ\text{C}$ for 2h. After allowing the mixture to cool down to room temperature, the reaction mixture was diluted with water and DCM, and the organic phase was separated. The aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure to afford the crude product which was used directly without purification.

Reduction: To a Schlenk flask charged with solid LiAlH_4 (6.0 equiv.) was added THF carefully at $0\text{ }^\circ\text{C}$. Then a solution of the crude product of the Henry reaction in THF was added dropwise. The resulting reaction mixture was replaced with an oil bath and heated to $65\text{ }^\circ\text{C}$ for 3h, then cooled down to $0\text{ }^\circ\text{C}$. Excess LiAlH_4 was quenched by the drop-wise addition of NaOH (aq.) and H_2O . The suspension was allowed to warm to room temperature overnight and then filtered through a plug of Celite[®]. The organic phase was separated. The aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography.

2-(6-Methoxy-1*H*-indol-3-yl)ethan-1-amine (22).

22 was prepared according to **General procedure F**, starting from 6-methoxyindole (530 mg, 3.60 mmol, 1.0 equiv.) and POCl_3 (1.01 mL, 10.8 mmol, 3.0 equiv.) in DMF (3.0 mL). The reaction mixture was subsequently treated with NH_4OAc (833 mg, 10.8 mmol, 3.0 equiv.), MeNO_2 (14.5 mL, 270 mmol, 75 equiv.) and LiAlH_4 (821 mg, 10.8 mmol, 6.0 equiv.) in THF (25 mL). Purification by silica gel column chromatography (DCM/MeOH/TEA = 80:20:5) afforded **22** (270 mg, 1.42 mmol, 39%)

as a light brown solid.

¹H NMR (500 MHz, CD₃OD) δ [ppm] = 7.37 (d, *J* = 8.6 Hz, 1H), 6.91 (s, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.67 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.76 (s, 3H), 2.87 (t, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.7 Hz, 2H).

¹³C NMR (126 MHz, CD₃OD) δ [ppm] = 157.6, 138.9, 123.2, 122.3, 119.9, 113.3, 109.9, 95.6, 56.0, 42.9, 29.4.

HRMS-ESI: calcd. for C₁₁H₁₅N₂O [M + H]⁺: 191.1179; found: 191.1179.

FT-IR: ν [cm⁻¹] = 3401, 2924, 2834, 1627, 1456, 1305, 1262, 1200, 1160, 1026, 800, 753.

2-(6-Fluoro-1*H*-indol-3-yl)ethan-1-amine (S36).

S36 was prepared according to **General procedure F**, starting from 6-fluoroindole (1.70 g, 12.6 mmol, 1.0 equiv.) and POCl₃ (3.53 mL, 37.7 mmol, 3.0 equiv.) in DMF (10.0 mL). The reaction mixture was subsequently treated with NH₄OAc (2.91 g, 37.8 mmol, 3.0 equiv.), MeNO₂ (50.5 mL, 944 mmol, 75 equiv.) and LiAlH₄ (2.86 g, 75.5 mmol, 6.0 equiv.) in THF (80.0 mL). Purification by silica gel column chromatography (DCM/MeOH/TEA = 80:20:5) afforded **S36** (580 mg, 3.26 mmol, 26%) as a brown solid.

¹H NMR (500 MHz, CD₃OD) δ [ppm] = 7.50 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.13 (s, 1H), 7.06 (dd, *J* = 9.9, 2.3 Hz, 1H), 6.86–6.77 (m, 1H), 3.11 (dd, *J* = 7.9, 6.4 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H).

¹³C NMR (126 MHz, CD₃OD) δ [ppm] = 161.3 (d, *J* = 235.3 Hz), 138.2 (d, *J* = 12.4 Hz), 125.1, 124.5 (d, *J* = 3.3 Hz), 119.9 (d, *J* = 10.2 Hz), 111.7, 108.3 (d, *J* = 24.9 Hz), 98.3 (d, *J* = 26.0 Hz), 41.8, 26.2.

¹⁹F NMR (471 MHz, CD₃OD) δ [ppm] = -124.28.

HRMS-ESI: calcd. for C₁₀H₁₂FN₂ [M + H]⁺: 179.0979; found: 179.0979.

FT-IR: ν [cm⁻¹] = 2918, 2840, 1626, 1456, 1345, 1225, 1144, 1099, 951, 799.

2-(6-Bromo-1*H*-indol-3-yl)ethan-1-amine (S37).

S37 was prepared according to **General procedure F**, starting from 6-bromoindole (1.0 g, 5.2 mmol, 1.0 equiv.) and POCl₃ (1.4 mL, 15 mmol, 3.0 equiv.) in DMF (5.0 mL). The reaction mixture was subsequently treated with NH₄OAc (1.2 g, 15 mmol, 3.0 equiv.), MeNO₂ (21 mL, 386 mmol, 75 equiv.) and LiAlH₄ (1.2 g, 31 mmol, 6.0 equiv.) in THF (50 mL). Purification by silica gel column chromatography (DCM/MeOH/TEA = 80:20:5) afforded **S37** (580 mg, 3.26 mmol, 63%) as a light brown solid.

¹H NMR (500 MHz, CD₃OD) δ [ppm] = 7.50 (d, J = 1.7 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 8.4, 1.8 Hz, 1H), 7.08 (d, J = 0.8 Hz, 1H), 2.95 – 2.90 (m, 2H), 2.90 – 2.85 (m, 2H).

¹³C NMR (126 MHz, CD₃OD) δ [ppm] = 139.0, 127.7, 124.5, 122.7, 120.7, 115.8, 115.1, 113.7, 43.0, 29.1.

HRMS-ESI: calcd. for C₁₀H₁₂BrN₂ [M + H]⁺: 239.0179; found: 239.0191.

FT-IR: ν [cm⁻¹] = 3423, 3126, 2935, 2874, 1613, 1578, 1456, 1334, 1232, 1048, 894, 802, 771.

2-(Benzo[*b*]thiophen-3-yl)ethan-1-amine (S38).

Bromination:^[15] Benzo[*b*]thiophene (2.0 g, 15 mmol, 1.0 equiv.) was dissolved in chloroform (30 mL) and cooled by an ice bath. A solution of bromine (0.84 mL, 16 mmol, 1.1 equiv.) in chloroform (10 mL) was slowly added. The reaction mixture was stirred for 1 h and quenched by NaOH (1.0 M aq.) and Na₂S₂O₃ (sat. aq.). The resulting mixture was extracted with DCM. After evaporation of the solvent, the intermediate

[15] S. Fredrich, A. Bonasera, V. Valderrey, S. Hecht *J. Am. Chem. Soc.* **2018**, *140*, 6432–6440

was dissolved in ethanol and was added dropwise to a solution of KOH (sat. EtOH solution, 20 mL) was added at ice bath. After refluxing for 2 h, H₂O was added and the EtOH was evaporated. The residue was extracted by DCM, washed with brine, dried with MgSO₄, filtered and concentrated under reduced pressure to afford crude 3-bromo-benzo[*b*]thiophene as yellow oil. The crude product was used without purification.

Formylation procedure:^[16] Crude 3-bromo-benzo[*b*]thiophene (3.4 g, 16 mmol, 1.0 equiv.) was dissolved in Et₂O and the solution was cooled to –78 °C. After the dropwise addition *n*BuLi (2.5 M solution in hexane, 6.4 mL, 16 mmol, 1.0 equiv.), the mixture was stirred for 30 min. Following the addition of DMF (1.2 mL, 16 mmol, 1.0 equiv.) at –78 °C, the mixture was allowed to warm to room temperature for 1 h. The reaction mixture was quenched by NH₄Cl (sat. aq.) and extracted with DCM. Combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to afford crude 3-benzo[*b*]thiophene-3-carbaldehyde as yellow oil..

Henry reaction: A flask with NH₄OAc (2.3 g, 30 mmol, 3.0 equiv.) and crude 3-benzo[*b*]thiophene-3-carbaldehyde (1.6 g, 9.9 mmol, 1.0 equiv.) was added MeNO₂ (40 mL) and the reaction mixture was stirred at 115 °C for 2h. After cooled to room temperature, the reaction mixture was diluted with water and DCM, and the organic phase was separated. The aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude 3-(2-nitrovinyl)benzo[*b*]thiophene which could use directly without purification.

Reduction: To a Schlenk flash charged with solid LiAlH₄ (2.2 g, 59 mmol, 6.0 equiv.), was added THF carefully at 0 °C. Then a solution of crude 3-(2-nitrovinyl)benzo[*b*]thiophene in THF (20 mL) was added dropwise. The resulting reaction mixture was replaced with an oil bath and heated to 65 °C for 3h, then cooled first to room temperature and then to 0 °C. Excess LiAlH₄ was quenched by the dropwise addition of NaOH (sat. aq.) and H₂O. The suspension was allowed to warm to room temperature overnight and then filtered through a plug of Celite®. The organic

[16] W. Gong, Y. Liu, J. Zhang, Y. Jiao, J. Xue, Y. Li *Chem. Asian J.* **2013**, 8, 546–551

phase was separated. The aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (DCM/MeOH/TEA = 80:20:5) afforded **S38** (300 mg, 1.69 mmol, 11% over 4 steps) as a dark brown solid.

^1H NMR (500 MHz, CD_3OD : CDCl_3 (v/v = 1:1)) δ [ppm] = 7.54 (dt, J = 7.9, 1.1 Hz, 1H), 7.46 (dt, J = 8.0, 0.9 Hz, 1H), 7.07 (ddd, J = 8.0, 7.0, 1.3 Hz, 1H), 7.03 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 6.92 (s, 1H), 2.75 (s, 4H).

^{13}C NMR (126 MHz, CD_3OD : CDCl_3 (v/v = 1:1)) δ [ppm] = 140.2, 138.2, 132.5, 123.9, 123.6, 122.4, 122.3, 121.0, 40.0, 30.1.

HRMS-ESI: calcd. for $\text{C}_{10}\text{H}_{12}\text{NS}$ $[\text{M} + \text{H}]^+$: 178.0685; found: 178.0693.

FT-IR: ν [cm^{-1}] = 3057, 2924, 2864, 1585, 1458, 1427, 1020, 760, 732.

2.8. Preparation of anhydrides

Commercially available anhydride

Noncommercially available anhydride

In general, the anhydrides (**S43**–**S46**) were synthesized from the corresponding dicarboxylic acids.

S43 was prepared by the procedure of Wilson et al.^[17] **S44** was prepared by the procedure of Köper et al.^[18] **S45** was prepared by the procedure of Sun et al.^[19] **S46** was prepared by the same procedure as **S45**.

S47 was prepared from homoveratric acid by the procedure of Cushman et al..^[20]

[17] D. J. Bennetta, A. J. Blakec, P. A. Cooke, C. R. A. Godfrey, P. L. Pickering, N. S. Simpkins, M. D. Walker, C. Wilson *Tetrahedron* **2004**, *60*, 4491–4511.

[18] J. Andersson, J. J. Knobloch, M. V. Perkins, S. A. Holt, I. Köper *Langmuir* **2017**, *33*, 4444–4451.

[19] B. Sun, C. Luo, X. Zhang, M. Guo, M. Sun, H. Yu, Q. Chen, W. Yang, M. Wang, S. Zuo, P. Chen, Q. Kan, H. Zhang, Y. Wang, Z. He, J. Sun *Nat. Commun.* **2019**, *10*, 3211.

[20] D. E. Beck, K. Agama, C. Marchand, A. Chergui, Y. Pommier, M. Cushman *J. Med. Chem.* **2014**, *57*, 1495–1512.

3. NMR Spectra

^1H NMR (500 MHz, CDCl_3) of **8a**.

^{13}C NMR (126 MHz, CDCl_3) of **8a**.

Chemical structure of 8b: CC(=O)OCCc1ccc([N+](=O)[O-])cc1 (4-nitrophenyl) and CC1=CC=C2C(=C1)C=CC=C2 (indole-3-ylmethyl) moiety.

¹H NMR spectrum (CDCl₃):

Chemical Shift (ppm)	Integration
8.26	1.82
8.25	1.35
8.24	1.05
8.23	1.72
8.22	1.10
7.57	1.97
7.56	
7.55	
7.54	
7.53	
7.52	
7.51	
7.50	
7.49	
7.48	
7.47	
7.46	
7.45	
7.44	
7.43	
7.42	
7.41	
7.40	
7.39	
7.38	
7.37	
7.36	
7.35	
7.34	
7.33	
7.32	
7.31	
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7.28	
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7.26	
7.25	
7.24	
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7.22	
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7.20	
7.19	
7.18	
7.17	
7.16	
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7.14	
7.13	
7.12	
7.11	
7.10	
7.09	
7.08	
7.07	
7.06	
7.05	
7.04	
7.03	
7.02	
7.01	
7.00	
6.99	
6.98	
6.97	
6.96	
6.95	
6.94	
6.93	
6.92	
6.91	
6.90	
6.89	
6.88	
6.87	
6.86	
6.85	
6.84	
6.83	
6.82	
6.81	
6.80	
6.79	
6.78	
6.77	
6.76	
6.75	
6.74	
6.73	
6.72	
6.71	
6.70	
6.69	
6.68	
6.67	
6.66	
6.65	
6.64	
6.63	
6.62	
6.61	
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6.42	
6.41	
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6.17	
6.16	
6.15	
6.14	
6.13	
6.12	
6.11	
6.10	
6.09	
6.08	
6.07	
6.06	
6.05	
6.04	
6.03	
6.02	
6.01	
6.00	
5.99	
5.98	
5.97	
5.96	
5.95	
5.94	
5.93	
5.92	

8b

Chemical structure of **8b** is shown above the spectrum. The spectrum displays peaks corresponding to the chemical shifts listed above the plot area:

- 173.0
- 170.7
- 155.2
- 144.9
- 136.3
- 127.0
- 124.7
- 124.6
- 122.1
- 121.9
- 121.0
- 118.2
- 117.8
- 117.6
- 111.6
- 110.9
- 39.7
- 34.4
- 32.7
- 24.7
- 20.2

Chemical structure of 8c: CC(C)OC(=O)CCCC(=O)NCC1=CNC2=CC=CC=C12

¹H NMR spectrum (CDCl₃):

Chemical Shift (ppm)	Integration
8.44	0.98
7.60	1.00
7.58	0.97
7.37	1.02
7.35	1.01
7.21	0.98
7.19	
7.13	
7.11	
7.10	
7.00	
5.69	0.94
5.01	1.03
4.99	
4.98	
4.97	
4.96	
3.61	2.00
3.59	
3.58	
3.57	
2.97	2.05
2.96	
2.85	
2.38	
2.28	
2.27	
2.16	2.17
2.14	1.95
2.13	2.08
1.93	
1.91	
1.90	
1.22	3.12
1.21	2.74
1.20	

8c

Chemical structure of **8c** is shown above the spectrum. The structure is an indazole derivative with a 4-isopropoxybutanamide side chain.

¹H NMR spectrum (CDCl₃) of compound **8c**. The x-axis represents the chemical shift in ppm, ranging from 0 to 10. The spectrum shows several peaks corresponding to the protons in the molecule.

Peak list (ppm):

- 8.29, 8.27, 8.25, 8.23, 8.21, 8.19, 8.17, 8.15, 8.13, 8.11, 8.09, 8.07, 8.05, 8.03, 8.01, 7.99, 7.97, 7.95, 7.93, 7.91, 7.89, 7.87, 7.85, 7.83, 7.81, 7.79, 7.77, 7.75, 7.73, 7.71, 7.69, 7.67, 7.65, 7.63, 7.61, 7.59, 7.57, 7.55, 7.53, 7.51, 7.49, 7.47, 7.45, 7.43, 7.41, 7.39, 7.37, 7.35, 7.33, 7.31, 7.29, 7.27, 7.25, 7.23, 7.21, 7.19, 7.17, 7.15, 7.13, 7.11, 7.09, 7.07, 7.05, 7.03, 7.01, 7.00, 6.99, 6.97, 6.95, 6.93, 6.91, 6.89, 6.87, 6.85, 6.83, 6.81, 6.79, 6.77, 6.75, 6.73, 6.71, 6.69, 6.67, 6.65, 6.63, 6.61, 6.59, 6.57, 6.55, 6.53, 6.51, 6.49, 6.47, 6.45, 6.43, 6.41, 6.39, 6.37, 6.35, 6.33, 6.31, 6.29, 6.27, 6.25, 6.23, 6.21, 6.19, 6.17, 6.15, 6.13, 6.11, 6.09, 6.07, 6.05, 6.03, 6.01, 6.00, 5.99, 5.97, 5.95, 5.93, 5.91, 5.89, 5.87, 5.85, 5.83, 5.81, 5.79, 5.77, 5.75, 5.73, 5.71, 5.69, 5.67, 5.65, 5.63, 5.61, 5.59, 5.57, 5.55, 5.53, 5.51, 5.49, 5.47, 5.45, 5.43, 5.41, 5.39, 5.37, 5.35, 5.33, 5.31, 5.29, 5.27, 5.25, 5.23, 5.21, 5.19, 5.17, 5.15, 5.13, 5.11, 5.09, 5.07, 5.05, 5.03, 5.01, 5.00, 4.99, 4.97, 4.95, 4.93, 4.91, 4.89, 4.87, 4.85, 4.83, 4.81, 4.79, 4.77, 4.75, 4.73, 4.71, 4.69, 4.67, 4.65, 4.63, 4.61, 4.59, 4.57, 4.55, 4.53, 4.51, 4.49, 4.47, 4.45, 4.43, 4.41, 4.39, 4.37, 4.35, 4.33, 4.31, 4.29, 4.27, 4.25, 4.23, 4.21, 4.19, 4.17, 4.15, 4.13, 4.11, 4.09, 4.07, 4.05, 4.03, 4.01, 4.00, 3.99, 3.97, 3.95, 3.93, 3.91, 3.89, 3.87, 3.85, 3.83, 3.81, 3.79, 3.77, 3.75, 3.73, 3.71, 3.69, 3.67, 3.65, 3.63, 3.61, 3.59, 3.57, 3.55, 3.53, 3.51, 3.49, 3.47, 3.45, 3.43, 3.41, 3.39, 3.37, 3.35, 3.33, 3.31, 3.29, 3.27, 3.25, 3.23, 3.21, 3.19, 3.17, 3.15, 3.13, 3.11, 3.09, 3.07, 3.05, 3.03, 3.01, 3.00, 2.99, 2.97, 2.95, 2.93, 2.91, 2.89, 2.87, 2.85, 2.83, 2.81, 2.79, 2.77, 2.75, 2.73, 2.71, 2.69, 2.67, 2.65, 2.63, 2.61, 2.59, 2.57, 2.55, 2.53, 2.51, 2.49, 2.47, 2.45, 2.43, 2.41, 2.39, 2.37, 2.35, 2.33, 2.31, 2.29, 2.27, 2.25, 2.23, 2.21, 2.19, 2.17, 2.15, 2.13, 2.11, 2.09, 2.07, 2.05, 2.03, 2.01, 2.00, 1.99, 1.97, 1.95, 1.93, 1.91, 1.89, 1.87, 1.85, 1.83, 1.81, 1.79, 1.77, 1.75, 1.73, 1.71, 1.69, 1.67, 1.65, 1.63, 1.61, 1.59, 1.57, 1.55, 1.53, 1.51, 1.49, 1.47, 1.45, 1.43, 1.41, 1.39, 1.37, 1.35, 1.33, 1.31, 1.29, 1.27, 1.25, 1.23, 1.21, 1.19, 1.17, 1.15, 1.13, 1.11, 1.09, 1.07, 1.05, 1.03, 1.01, 1.00, 0.99, 0.97, 0.95, 0.93, 0.91, 0.89, 0.87, 0.85, 0.83, 0.81, 0.79, 0.77, 0.75, 0.73, 0.71, 0.69, 0.67, 0.65, 0.63, 0.61, 0.59, 0.57, 0.55, 0.53, 0.51, 0.49, 0.47, 0.45, 0.43, 0.41, 0.39, 0.37, 0.35, 0.33, 0.31, 0.29, 0.27, 0.25, 0.23, 0.21, 0.19, 0.17, 0.15, 0.13, 0.11, 0.09, 0.07, 0.05, 0.03, 0.01, 0.00, -0.01, -0.03, -0.05, -0.07, -0.09, -0.11, -0.13, -0.15, -0.17, -0.19, -0.21, -0.23, -0.25, -0.27, -0.29, -0.31, -0.33, -0.35, -0.37, -0.39, -0.41, -0.43, -0.45, -0.47, -0.49, -0.51, -0.53, -0.55, -0.57, -0.59, -0.61, -0.63, -0.65, -0.67, -0.69, -0.71, -0.73, -0.75, -0.77, -0.79, -0.81, -0.83, -0.85, -0.87, -0.89, -0.91, -0.93, -0.95, -0.97, -0.99, -1.01, -1.03, -1.05, -1.07, -1.09, -1.11, -1.13, -1.15, -1.17, -1.19, -1.21, -1.23, -1.25, -1.27, -1.29, -1.31, -1.33, -1.35, -1.37, -1.39, -1.41, -1.43, -1.45, -1.47, -1.49, -1.51, -1.53, -1.55, -1.57, -1.59, -1.61, -1.63, -1.65, -1.67, -1.69, -1.71, -1.73, -1.75, -1.77, -1.79, -1.81, -1.83, -1.85, -1.87, -1.89, -1.91, -1.93, -1.95, -1.97, -1.99, -2.01, -2.03, -2.05, -2.07, -2.09, -2.11, -2.13, -2.15, -2.17, -2.19, -2.21, -2.23, -2.25, -2.27, -2.29, -2.31, -2.33, -2.35, -2.37, -2.39, -2.41, -2.43, -2.45, -2.47, -2.49, -2.51, -2.53, -2.55, -2.57, -2.59, -2.61, -2.63, -2.65, -2.67, -2.69, -2.71, -2.73, -2.75, -2.77, -2.79, -2.81, -2.83, -2.85, -2.87, -2.89, -2.91, -2.93, -2.95, -2.97, -2.99, -3.01, -3.03, -3.05, -3.07, -3.09, -3.11, -3.13, -3.15, -3.17, -3.19, -3.21, -3.23, -3.25, -3.27, -3.29, -3.31, -3.33, -3.35, -3.37, -3.39, -3.41, -3.43, -3.45, -3.47, -3.49, -3.51, -3.53, -3.55, -3.57, -3.59, -3.61, -3.63, -3.65, -3.67, -3.69, -3.71, -3.73, -3.75, -3.77, -3.79, -3.81, -3.83, -3.85, -3.87, -3.89, -3.91, -3.93, -3.95, -3.97, -3.99, -4.01, -4.03, -4.05, -4.07, -4.09, -4.11, -4.13, -4.15, -4.17, -4.19, -4.21, -4.23, -4.25, -4.27, -4.29, -4.31, -4.

¹H NMR (600 MHz, CDCl₃) 8d.

¹³C NMR (151 MHz, CDCl₃) 8d.

8d

Chemical structure of **8d** is shown above the spectrum. The structure consists of an indole ring system attached to a 2,2,2-trifluoroethyl ester chain via a 2-aminomethyl linker.

CC(=O)OCC(=O)NCCc1c[nH]c2ccccc12

Chemical structure of **8e** is shown above the spectrum. The spectrum displays peaks from 0 to 8.5 ppm with corresponding integrations and a list of chemical shifts (δ) on the right.

Chemical shifts (δ) (ppm): 8.13, 7.61, 7.61, 7.59, 7.59, 7.39, 7.39, 7.37, 7.37, 7.23, 7.23, 7.21, 7.21, 7.20, 7.20, 7.15, 7.14, 7.13, 7.13, 7.12, 7.12, 7.04, 7.03, 5.54, 4.47, 4.45, 4.43, 4.42, 3.64, 3.63, 3.62, 3.60, 3.59, 2.99, 2.98, 2.98, 2.97, 2.96, 2.46, 2.44, 2.43, 2.18, 2.16, 2.15, 1.99, 1.98, 1.97, 1.96, 1.94, 1.93.

Integrations: 0.91, 0.83, 0.78, 0.88, 0.91, 0.78, 0.89, 1.82, 2.00, 1.75, 1.86, 1.85, 1.91.

^{13}C NMR (126 MHz, CDCl_3) **8e.**

^{19}F NMR (471 MHz, CDCl_3) **8e.**

¹H NMR (500 MHz, CD₃OD) 8f.

¹³C NMR (126 MHz, CD₃OD) 8f.

^{19}F NMR (471 MHz, CD_3OD) 8f.

^1H NMR (500 MHz, CD_3OD) 8g.

^{13}C NMR (126 MHz, CD_3OD) 8g.

^{19}F NMR (471 MHz, CD_3OD) 8g.

¹H NMR (500 MHz, CDCl₃) 8h.

¹³C NMR (126 MHz, CDCl₃) 8h.

¹H NMR (500 MHz, CD₂Cl₂) 8i.

¹³C NMR (126 MHz, CD₂Cl₂) 8i.

¹H NMR (700 MHz, CDCl₃) 8j.

¹³C NMR (126 MHz, CDCl₃) 8j.

¹H NMR (500 MHz, CDCl₃) 8k.

¹³C NMR (176 MHz, CDCl₃) 8k.

¹H NMR (600 MHz, CDCl₃) 8I.

¹³C NMR (151 MHz, CDCl₃) 8I.

¹H NMR (500 MHz, CDCl₃) 11a.

¹³C NMR (126 MHz, CDCl₃) 11a.

^{19}F NMR (565 MHz, CDCl_3) **11a.**

^1H NMR (500 MHz, CD_2Cl_2) **11b.**

^{13}C NMR (126 MHz, CD_2Cl_2) 11b.

^{19}F NMR (471 MHz, CD_2Cl_2) 11b.

¹H NMR (700 MHz, CDCl₃) 11c.

¹³C NMR (176 MHz, CDCl₃) 11c.

^{19}F NMR (471 MHz, CDCl_3) **11c.**

^1H NMR (400 MHz, CDCl_3) **11d.**

^{13}C NMR (176 MHz, CDCl_3) 11d.

^{19}F NMR (471 MHz, CDCl_3) 11d.

Chemical structure of **11e** is shown as an inset. The structure is 1-(2-((2-((2,3-dihydro-1H-indol-2-yl)methyl)amino)propanoyl)butyryl)oxy-2,2-difluoroethane.

¹H NMR spectrum (CDCl₃) of compound **11e**. The x-axis represents the chemical shift in ppm, ranging from 0.98 to 8.33. The spectrum shows several peaks, with integration values provided below the baseline. The integration values are: 0.99, 1.00, 1.03, 1.05, 1.04, 0.97, 0.97, 2.11, 2.21, 1.06, 1.04, 1.07, 1.10, 1.07, and 3.11. The peak list at the top of the spectrum is: 8.33, 7.61, 7.60, 7.59, 7.58, 7.59, 7.59, 7.39, 7.39, 7.37, 7.37, 7.37, 7.20, 7.19, 7.18, 7.16, 7.16, 7.16, 7.11, 7.11, 7.10, 7.10, 7.09, 7.08, 7.08, 7.05, 7.05, 7.04, 7.04, 5.85, 5.84, 5.83, 5.82, 5.64, 3.59, 3.58, 3.58, 3.57, 3.56, 3.55, 2.97, 2.97, 2.96, 2.94, 2.94, 2.66, 2.65, 2.63, 2.62, 2.49, 2.48, 2.46, 2.47, 2.47, 2.46, 2.45, 2.41, 2.39, 2.37, 2.36, 2.15, 2.14, 2.12, 2.11, 2.08, 2.04, 2.03, 2.02, 1.99, 1.98.

11e

171.1
169.8
136.9
127.8
124.3
122.6
122.4
122.1
119.9
118.7
119.0
117.8
113.3
111.6
57.2
56.5
56.6
56.3
56.1
43.0
40.1
39.9
28.2
25.8
19.5

^{19}F NMR (471 MHz, CD_2Cl_2) **11e.**

^1H NMR (500 MHz, CD_2Cl_2) **11f.**

¹H NMR (500 MHz, CD₂Cl₂) 11f.

¹H NMR (500 MHz, CD₂Cl₂) 11f.

¹H NMR (600 MHz, CDCl₃) 11g.

¹³C NMR (151 MHz, CDCl₃) 11g.

^{19}F NMR (565 MHz, CDCl_3) 11g.

^1H NMR (500 MHz, CDCl_3) 11h.

^{13}C NMR (126 MHz, CDCl_3) 11h.

^{19}F NMR (565 MHz, CDCl_3) 11h.

¹H NMR (500 MHz, CDCl₃) 11i.

¹³C NMR (126 MHz, CDCl₃) 11i.

^{19}F NMR (471 MHz, CDCl_3) 11i.

^1H NMR (500 MHz, CDCl_3) 11j.

¹³C NMR (126 MHz, CDCl₃) 11j.

¹⁹F NMR (471 MHz, CDCl₃) 11j.

¹H NMR (500 MHz, CDCl₃) 11k.

¹³C NMR (126 MHz, CDCl₃) 11k.

[illegible]

Chemical structure of **11l** is shown above the spectrum. The structure is 1-(2-(2,2,2-trifluoroethyl)oxy)-4-(1H-indol-3-yl)butan-1-one.

¹H NMR spectrum (CDCl₃) of compound **11l**. The x-axis is labeled f1 (ppm) and ranges from 1.0 to -0.5. The spectrum shows several peaks with integration values indicated below them: 0.93, 0.98, 0.99, 1.07, 1.03, 0.96, 1.08, 0.96, 2.12, 2.14, 2.18, 2.14, 4.40, 2.25.

^{13}C NMR (126 MHz, CDCl_3) 11I.

^{19}F NMR (565 MHz, CDCl_3) 11I.

¹H NMR (500 MHz, CDCl₃) 11m.

¹³C NMR (126 MHz, CDCl₃) 11m.

^{19}F NMR (471 MHz, CDCl_3) 11m.

^1H NMR (500 MHz, CDCl_3) 11n.

^{13}C NMR (126 MHz, CDCl_3) **11n.**

^{19}F NMR (471 MHz, CDCl_3) **11n.**

¹H NMR (500 MHz, CDCl₃) 11o.

¹³C NMR (126 MHz, CDCl₃) 11o.

^{19}F NMR (471 MHz, CDCl_3) 11o.

^1H NMR (500 MHz, CDCl_3) 11p.

^{13}C NMR (126 MHz, CDCl_3) 11p.

^{19}F NMR (471 MHz, CDCl_3) 11p.

¹H NMR (500 MHz, CDCl₃) 11q.

¹³C NMR (126 MHz, CDCl₃) 11q.

-73.00
-73.02

6.80
6.78
6.71
6.71
6.71
6.70
6.70
6.69
5.77
5.76
5.75
5.73
5.72
5.54
3.85
3.84
3.51
3.49
3.49
3.48
3.48
3.47
2.76
2.74
2.73
2.63
2.62
2.61
2.60
2.60
2.59
2.58
2.58
2.57
2.57
2.56
2.55
2.20
2.18
2.17
2.03
2.02
2.02
2.01
2.01
2.00
2.00
1.98
1.97
1.97

¹³C NMR (126 MHz, CDCl₃) 11r.

¹⁹F NMR (565 MHz, CDCl₃) 11r.

¹H NMR (600 MHz, CDCl₃) 11s.

¹³C NMR (151 MHz, CDCl₃) 11s.

^{19}F NMR (565 MHz, CDCl_3) **11s.**

^1H NMR (700 MHz, CDCl_3) **11t.**

¹³C NMR (176 MHz, CDCl₃) 11t.

¹⁹F NMR (376 MHz, CDCl₃) 11t.

¹H NMR (700 MHz, CDCl₃) 11u.

¹³C NMR (176 MHz, CDCl₃) 11u.

^{19}F NMR (565 MHz, CDCl_3) 11u.

^1H NMR (700 MHz, CDCl_3) 11v.

^{13}C NMR (176 MHz, CDCl_3) **11v.**

^{19}F NMR (376 MHz, CDCl_3) **11v.**

¹H NMR (500 MHz, CDCl₃) 11w.

¹³C NMR (126 MHz, CDCl₃) 11w.

^{19}F NMR (471 MHz, CDCl_3) 11w.

^1H NMR (700 MHz, CDCl_3) 11x.

^{13}C NMR (176 MHz, CDCl_3) **11x.**

^{19}F NMR (376 MHz, CDCl_3) **11x.**

[illegible]

Chemical structure of compound **11y** is shown above the corresponding ¹³C NMR spectrum. The structure is 2-(2-methoxy-1H-indol-3-yl)ethyl 2-methyl-3-oxobutanoate. The ¹³C NMR spectrum (CDCl₃) displays peaks at the following chemical shifts (ppm): 171.1, 169.4, 156.8, 137.3, 122.9, 121.9, 121.3, 120.9, 119.7, 119.3, 118.1, 112.9, 109.6, 94.9, 66.8, 66.6, 66.4, 66.2, 66.0, 55.8, 42.8, 39.8, 38.5, 27.9, 25.5, and 19.4.

^{19}F NMR (376 MHz, CDCl_3) of **11y.**

^1H NMR (600 MHz, CDCl_3) of **S1.**

^{13}C NMR (151 MHz, CDCl_3) of S1.

^{19}F NMR (565 MHz, CDCl_3) of S1.

S2

O=C1C=CC2=C(C=C1)C(=NC2)CN(C)C(=O)CCOC(=O)C(F)(F)F

¹H NMR spectrum (CDCl₃) of compound S2. The spectrum shows peaks in the aromatic region (7.0-8.3 ppm), a methylene singlet (4.5 ppm), and a trifluoromethyl singlet (2.0 ppm). Integration values are provided below the peaks.

Chemical Shift (ppm)	Integration
8.28	0.97
7.62	1.00
7.61	1.01
7.24	1.04
5.74	1.09
5.70	0.88
4.50	2.00
2.07	2.07
2.01	2.01
2.06	2.06

S2

CC(F)(F)OC(=O)CCCC(=O)Nc1c[nH]c2ccccc12

171.3
170.1

136.5
126.6
123.4
122.9
122.7
121.3
120.1
119.7
118.8
118.1
112.7
111.5

66.9
66.7
66.5
66.3
66.3
66.1

35.3
34.9
32.5

20.5

f1 (ppm)

S2

CC(F)(F)OC(=O)CCC(=O)NCc1c[nH]c2ccccc12

Chemical structure of S2: A molecule featuring a 2,3-dihydro-1H-indole ring system. The indole ring is substituted at the 3-position with a methylene group, which is further substituted with a carbonyl group. This carbonyl group is part of a chain that includes a trifluoromethyl ester group (CF₃COO-).

¹³C NMR spectrum (ppm):

- 155.19
- 154.73
- 154.20

Chemical structure of **S3** is shown above the spectrum. The spectrum displays peaks from 0 to 10 ppm with corresponding integrations and a list of chemical shifts (δ) on the right.

Chemical shifts (δ) (ppm): 7.61, 7.59, 7.59, 7.37, 7.36, 7.36, 7.35, 7.21, 7.21, 7.20, 7.20, 7.19, 7.18, 7.13, 7.13, 7.12, 7.11, 7.11, 7.10, 7.10, 6.99, 6.98, 6.98, 5.81, 5.81, 5.80, 5.80, 5.79, 5.78, 5.78, 5.78, 5.78, 5.77, 5.77, 5.76, 5.76, 5.75, 5.75, 5.74, 5.72, 5.72, 3.61, 3.60, 3.58, 2.98, 2.97, 2.96, 2.50, 2.50, 2.49, 2.47, 2.12, 2.12, 2.10, 2.09, 1.69, 1.68, 1.67, 1.65, 1.64, 1.62, 1.61, 1.59, 1.58, 1.33, 1.32, 1.31, 1.30, 1.29, 1.29, 1.28, 1.26, 1.25.

Integrations: 0.98, 1.00, 1.02, 1.06, 1.03, 0.98, 2.16, 2.17, 2.17, 2.34, 2.22, 2.46, 2.22, 8.36.

^{13}C NMR (126 MHz, CDCl_3) of S3.

^{19}F NMR (471 MHz, CDCl_3) of S3.

¹H NMR (500 MHz, CDCl₃) of S4.

¹³C NMR (126 MHz, CDCl₃) of S4.

^{19}F NMR (471 MHz, CDCl_3) of S4.

^1H NMR (500 MHz, CDCl_3) of S5.

¹³C NMR (126 MHz, CDCl₃) of S5.

¹⁹F NMR (471 MHz, CDCl₃) of S5.

^1H NMR (500 MHz, CDCl_3) of S6.

^{13}C NMR (126 MHz, CDCl_3) of S6.

^{19}F NMR (471 MHz, CDCl_3) of S6.

^1H NMR (500 MHz, CDCl_3) of S7.

^{13}C NMR (126 MHz, CDCl_3) of S7.

^{19}F NMR (471 MHz, CDCl_3) of S7.

¹H NMR (500 MHz, CDCl₃) of **9**.

¹³C NMR (126 MHz, CDCl₃) of **9**.

¹H NMR (500 MHz, CDCl₃) of 10.

¹³C NMR (126 MHz, CDCl₃) of 10.

¹H NMR (500 MHz, CDCl₃) of 12a.

¹³C NMR (126 MHz, CDCl₃) of 12a.

^1H NMR (500 MHz, CD_2Cl_2) of **12b.**

^{13}C NMR (126 MHz, CD_2Cl_2) of **12b.**

¹H NMR (700 MHz, *d*₆-DMSO) of **12c.**

¹³C NMR (176 MHz, *d*₆-DMSO) of **12c.**

¹H NMR (700 MHz, *d*₆-DMSO) of **12d.**

¹³C NMR (176 MHz, *d*₆-DMSO) of **12d.**

^{19}F NMR (471 MHz, d_6 -DMSO) of **12d.**

¹H NMR (500 MHz, CDCl₃) of 12e.

¹³C NMR (126 MHz, CDCl₃) of 12e.

¹H NMR (700 MHz, CD₂Cl₂) of **12f.**

¹³C NMR (176 MHz, CD₂Cl₂) of **12f.**

¹H NMR (700 MHz, CD₂Cl₂) of **12g**.

¹³C NMR (176 MHz, CD₂Cl₂) of **12g**.

^1H NMR (500 MHz, CDCl_3) of **12h.**

^{13}C NMR (126 MHz, CDCl_3) of **12h.**

¹H NMR (700 MHz, CDCl₃) of 12i.

¹³C NMR (176 MHz, CDCl₃) of 12i.

¹H NMR (500 MHz, *d*₆-DMSO) of **12j.**

¹³C NMR (126 MHz, *d*₆-DMSO) of **12j.**

^1H NMR (700 MHz, CD_2Cl_2) of **12k.**

^{13}C NMR (176 MHz, CD_2Cl_2) of **12k.**

¹H NMR (700 MHz, CD₂Cl₂) of **12l.**

¹³C NMR (176 MHz, CD₂Cl₂) of **12l.**

¹H NMR (700 MHz, CDCl₃) of **12m**.

¹³C NMR (176 MHz, CD₂Cl₂) of **12m**.

^1H NMR (700 MHz, CDCl_3) of **12n.**

^{13}C NMR (176 MHz, CDCl_3) of **12n.**

^1H NMR (700 MHz, C_6D_6) of **12o.**

^{13}C NMR (176 MHz, C_6D_6) of **12o.**

^1H NMR (700 MHz, C_6D_6) of **12p.**

^{13}C NMR (176 MHz, C_6D_6) of **12p.**

¹H NMR (500 MHz, CDCl₃) of 12q.

¹³C NMR (126 MHz, CDCl₃) of 12q.

¹H NMR (500 MHz, C₆D₆) of 12r.

¹³C NMR (126 MHz, C₆D₆) of 12r.

^1H NMR (600 MHz, CDCl_3) of **12s.**

^{13}C NMR (151 MHz, CDCl_3) of **12s.**

8.37	8.37	8.36	8.35	7.87	7.86	7.86	7.86	7.86	7.85	7.85	7.67	7.66	7.65	7.65	7.65	7.64	7.64	7.62	7.62	7.62	7.61	7.61	7.61	7.48	7.47	7.46	7.46	7.45	7.45	7.39	7.38	7.38	7.38	7.37	7.37	7.36	7.36	7.30	7.30	7.30	7.30	7.30	7.29	7.05	4.35	4.34	4.34	4.34	4.34	4.34	4.33	4.33	3.03	3.02	3.01	3.01
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— 162.2 — 138.0 — 137.0 — 136.1 — 132.6 — 130.7 — 129.7 — 128.4 — 127.8 — 126.8 — 126.7 — 125.4 — 125.3 — 102.8 — 40.0 — 28.9

¹H NMR (700 MHz, C₆D₆) of **12u.**

¹³C NMR (176 MHz, C₆D₆) of **12u.**

¹H NMR (700 MHz, C₆D₆) of **12v**.

¹³C NMR (176 MHz, C₆D₆) of **12v**.

¹H NMR (500 MHz, C₆D₆) of **12w.**

¹³C NMR (126 MHz, C₆D₆) of **12w.**

^1H NMR (700 MHz, CD_2Cl_2) of **12x.**

^{13}C NMR (176 MHz, CD_2Cl_2) of **12x.**

¹H NMR (700 MHz, CD₂Cl₂) of 13.

¹³C NMR (176 MHz, CD₂Cl₂) of 13.

¹H NMR (700 MHz, CD₃OD) of 14a.

¹³C NMR (176 MHz, CD₃OD) of 14a.

^1H NMR (500 MHz, CDCl_3) of **14b.**

^{13}C NMR (126 MHz, CD_3OD) of **14b.**

¹H NMR (500 MHz, CDCl₃+CD₃OD (v/v = 1:1)) of **14c.**

¹³C NMR (126 MHz, CDCl₃+CD₃OD (v/v = 1:1)) of **14c.**

^1H NMR (500 MHz, CDCl_3) of **14d.**

^{13}C NMR (126 MHz, CDCl_3) of **14d.**

^1H NMR (500 MHz, CDCl_3) of **15.**

^{13}C NMR (126 MHz, CDCl_3) of **15.**

¹H NMR (500 MHz, *d*₆-DMSO) of 16.

¹³C NMR (126 MHz, *d*₆-DMSO) of 16.

¹H NMR (500 MHz, CD₂Cl₂) of **24**.

¹³C NMR (126 MHz, CD₂Cl₂) of **24**.

Chemical structure of compound **24** is shown above the spectrum. The structure is 2-(4-methoxyphenyl)-1-((S)-2-((S)-2-(trifluoromethyl)oxybutan-2-yl)propanamido)ethan-1-yl-1H-indazole. The spectrum displays the ^1H NMR data for this compound in CDCl_3 , with the solvent peak (triplet) centered at $\delta = 7.26$ ppm.

Chemical structure of 25: COc1ccc2c(c1)c3c(c2)nc4c3ccccc4N5C(=O)CC[C@H](C)C5

¹H NMR spectrum (CDCl₃):

Chemical Shift (ppm)	Integration
8.09	0.85
7.38, 7.37	0.94
6.83, 6.79, 6.77	0.86, 1.00
5.27	0.89
4.10, 4.09, 4.02, 3.85	1.91, 2.91
2.89, 2.88, 2.87	1.88
2.48	1.91
1.16	5.67

^{13}C NMR (176 MHz, CDCl_3) of **25.**

^1H NMR (500 MHz, CDCl_3) of **S15.**

^{13}C NMR (126 MHz, CDCl_3) of **S15.**

^1H NMR (700 MHz, CDCl_3) of **26.**

^{13}C NMR (176 MHz, CDCl_3) of **26.**

^1H NMR (700 MHz, CD_3OD) of peganumine A (6**).**

^{13}C NMR (176 MHz, CD_3OD) of peganumine A (6).

^1H NMR (500 MHz, d_6 -DMSO) of peganumine A (6).

^{13}C NMR (126 MHz, d_6 -DMSO) of peganumine A (6).

^1H NMR (500 MHz, CDCl_3) of S21.

^{13}C NMR (126 MHz, CDCl_3) of S21.

^{19}F NMR (471 MHz, CDCl_3) of S21.

¹H NMR (500 MHz, CDCl₃) of S22.

¹³C NMR (126 MHz, CDCl₃) of S22.

^{19}F NMR (471 MHz, CDCl_3) of **S22.**

^1H NMR (500 MHz, CD_2Cl_2) of **S23.**

^{13}C NMR (126 MHz, CD_2Cl_2) of **S23.**

^1H NMR (500 MHz, CDCl_3) of **32.**

^{13}C NMR (126 MHz, CDCl_3) of **32.**

^{19}F NMR (471 MHz, CDCl_3) of **32.**

^1H NMR (700 MHz, CDCl_3) of **35.**

^{13}C NMR (176 MHz, CDCl_3) of **35.**

^{19}F NMR (565 MHz, CDCl_3) of **35.**

^1H NMR (700 MHz, CDCl_3) of **36.**

^{13}C NMR (176 MHz, CDCl_3) of **36.**

^1H NMR (700 MHz, CDCl_3) of ilicifoline B (5**).**

^{13}C NMR (176 MHz, CDCl_3) of ilicifoline B (5).

^1H NMR (500 MHz, CD_3OD) of 22.

^{13}C NMR (126 MHz, CD_3OD) of **22.**

^1H NMR (500 MHz, CD_3OD) of **S36.**

^{13}C NMR (126 MHz, CD_3OD) of S36.

^{19}F NMR (471 MHz, CD_3OD) of S36.

¹H NMR (500 MHz, CD₃OD) of S37.

¹³C NMR (126 MHz, CD₃OD) of S37.

^1H NMR (500 MHz, $\text{CD}_3\text{OD}:\text{CDCl}_3$ (v/v = 1:1)) of **S38.**

^{13}C NMR (126 MHz, $\text{CD}_3\text{OD}:\text{CDCl}_3$ (v/v = 1:1)) of **S38.**