Probing Chemical Space with Alkaloid-Inspired Libraries

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Supplementary Information

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**Supplementary Table 1.** Comprehensive list of references associated with bioactivity in the *Stemona*, cylindricine/lepadiformine/fasicularin, *Amaryllidaceae* and Lupin families of alkaloids.

| Alkaloid Family | Reviews / original biological activity articles |
|-----------------|--------------------------------------------------|
| **Stemona alkaloids** | • Reviews<sup>1,3</sup>  
• Antitussive<sup>4,8</sup>  
• Insecticidal, antifeedant, larvicidal<sup>9,15</sup>  
• neuromuscular<sup>16</sup>  
• anthelmintic<sup>17</sup>  
• AChE inhibition<sup>14,18-20</sup>  
• Reversal of MDR-cancers<sup>21,22</sup> |
| **cylindricine/lepadiformine/fasicularin** | • Review<sup>23</sup>  
• cytotoxicity<sup>24-27</sup>  
• cardiovascular actions<sup>28,29</sup> |
| **Amaryllidaceae alkaloids** | • Review<sup>30</sup>  
• serotonin reuptake inhibition<sup>31</sup>  
• 5-hydroxytryptamine reuptake inhibition<sup>32</sup>  
• PDE4 inhibition<sup>32,33</sup>  
• AChE inhibition<sup>34</sup>  
• antileukemic<sup>35</sup>  
• cytotoxicity<sup>36</sup> |
| **Lupin alkaloids** | • Reviews: cytisine<sup>37,38</sup> sparteine<sup>38</sup>  
• anti-arrythmic<sup>39</sup>  
• nicotinic ester agonism<sup>40</sup>/antagonism<sup>38,41</sup>  
• acetylcholine agonist: (cytisine – many different studies. For examples of early work on bioactivity with *in vivo* studies see<sup>42-44</sup>; for later work with radiolabelled cytisine see<sup>45-46</sup>) |
Supplementary Table 2. Average bioavailability properties and fraction sp³ hybridized carbon atoms of scaffolds, library members and reference set compounds.

|          | Drugs | NPs | Commercial | Alk NP | Scaffolds | Sparteine library | Stenine library | Mesembrine library | Cylindricine library | All libraries |
|----------|-------|-----|------------|--------|-----------|-------------------|-----------------|-------------------|---------------------|---------------|
| m/w      | 361   | 629 | 414        | 319    | 243       | 354               | 364             | 311               | 387                 | 355           |
| XlogP    | 2.7   | 1.5 | 2.4        | 2.0    | 2.3       | 3.7               | 3.5             | 2.7               | 6.1                 | 4.0           |
| HBD      | 1.5   | 4.9 | 1.5        | 1.3    | 0.7       | 1.2               | 0.6             | 0.4               | 1.0                 | 0.8           |
| HBA      | 5.4   | 10.8| 6.8        | 4.4    | 2.5       | 4.8               | 4.5             | 4.3               | 3.8                 | 4.3           |
| % Pass Lipinski (4/4) | 85    | 42  | 95         | 90     | 100       | 83                | 100             | 100               | 13                  | 72            |
| % Pass Lipinski (3/4) | 98    | 53  | 100        | 100    | 100       | 100               | 100             | 100               | 100                 | 100           |
| RotB     | 6.3   | 9.7 | 5.7        | 2.8    | 1.7       | 5.2               | 3.0             | 2.0               | 6.3                 | 4.1           |
| tPSA     | 69    | 183 | 98         | 54     | 33        | 48                | 47              | 38                | 35                  | 42            |
| % Pass Veber | 88    | 33  | 95         | 95     | 100       | 100               | 100             | 100               | 100                 | 100           |
| Fsp3 C atoms | 0.41  | 0.64| 0.23       | 0.65   | 0.77      | 0.73              | 0.75            | 0.57              | 0.58                | 0.66          |
Supplementary Figure 1. Alkaloid natural product reference set for PCA analysis (20 structures).
Supplementary Figure 2. Representative scaffolds used in PCA analysis (14 structures).
Supplementary Figure 3. Representative library compounds used in PCA analysis (29 structures) (continued on next page).
Supplementary Figure 3 (continued). Representative library compounds used in PCA analysis (29 structures).

Supplementary Table 3. Composition of reference set of drugs, commercial library compounds and natural products used in PCA.

| Compounds                  | Drugs (40 compounds)                  | Commercial screening libraries (20 compounds; pubchem compound CIDs) | Natural products (60 compounds) |
|----------------------------|---------------------------------------|---------------------------------------------------------------------|--------------------------------|
|                            | Lipitor                               | ChemBridge: 5771429                                                | cephamycin C                    |
|                            | Lexapro                               | 5309975                                                             | sperguain                       |
|                            | Topamax                               | 5309246                                                             | forsokolin                      |
|                            | Coreg                                 | 5309020                                                             | daptomycin                      |
|                            | Valtrex                               | 5771496                                                             | echinocandin B                  |
|                            | Zetia                                 | 24740046                                                            | calicheamicin g1                |
|                            | Abilify                               | 24740046                                                            | lipstatin                       |
|                            | Cymbalta                              | Zephix                                                                    | bleomycin                       |
|                            | Seroquel                               | Avandia                                                             | brefeldin A                     |
|                            | Toprol                                 | Celebrex                                                             | cytochalasin B                  |
|                            | Zoloft                                 | Tricor                                                               | epothilone B                    |
|                            | Levaquin                               | Concerta                                                             | apoptolidin                     |
|                            | Valtrex                               | Concerta                                                             | lactacystin                     |
|                            | Adderall                              | Zyprexa                                                              | duocarmycin A                   |
|                            | Actos                                 | Zyrtec                                                              | zaragozic acid A                |
|                            | Lamictal                              | Imitrex                                                              | misoridine                      |
|                            | Cymbalta                              |                                                                     | SQ26180                         |
|                            | Valtral                               |                                                                     | thienamycin                     |
|                            | Valtrex                               |                                                                     | validamycin                     |
|                            | Tricor                                 |                                                                     | avermectin B1a                  |
|                            | Benazepril                            |                                                                     | cyclosporin A                   |
|                            | Concerta                              |                                                                     | geldanamycin                     |
|                            | Celebrex                              |                                                                     | actinin                         |
|                            | Tricor                                 |                                                                     | discodermolide                  |
|                            | Risperdal                             |                                                                     | monensin                        |
|                            | Benazepril                            |                                                                     | cayuculin A                     |
|                            | Concerta                              |                                                                     | amphotericin B                  |
|                            | Rapamycin                              |                                                                     | adriamycin                      |
|                            | Rapamycin                              |                                                                     | ginkgolide B                    |
|                            | Rapamycin                              |                                                                     | coformycin                      |
|                            | Rapamycin                              |                                                                     | arglabin                        |
|                            | Rapamycin                              |                                                                     | bestatin                        |
|                            | Rapamycin                              |                                                                     | midecamycin A1                  |
|                            | Rapamycin                              |                                                                     | taxol                           |
|                            | Rapamycin                              |                                                                     | pseudomonic acid A              |
|                            | Rapamycin                              |                                                                     | trapoxin B                      |
|                            | Rapamycin                              |                                                                     | vircristine                      |
|                            | Rapamycin                              |                                                                     | colchicines                     |
|                            | Rapamycin                              |                                                                     | trichostatin                    |
|                            | Rapamycin                              |                                                                     | fumagillin                      |
|                            | Rapamycin                              |                                                                     | staurosporine                   |
|                            | Rapamycin                              |                                                                     | erthyromycin A                  |
|                            | Rapamycin                              |                                                                     | streptomycin                    |
|                            | Rapamycin                              |                                                                     | quinine                         |
|                            | Rapamycin                              |                                                                     | rifamycin B                     |
|                            | Rapamycin                              |                                                                     | mycobactin S                    |
II. Supplementary Methods

A. Experimental procedures and characterization data for *Stemona* alkaloid-inspired scaffolds.

**Supplementary Figure 4.** Synthesis of *Stemona* alkaloid-inspired scaffolds

General procedure A: Oxidation of vinylic alcohols

**Butylvinylketone, S1c**

\[
\begin{align*}
\text{nBu} & \quad \text{O} \quad \text{C} \\
\text{s} & \quad \text{Bu} \\
\end{align*}
\]

Concentrated H$_2$SO$_4$ (48.8 mL, 880 mmol) was added dropwise over 10 min to a solution of sodium dichromate (65.6 g, 220 mL) in water (150 mL) at 0 °C. The resulting bright orange solution was stirred at 0 °C for a further 15 min, then added portionwise to a pre-cooled solution of 3-hydroxyhept-1-ene$^4$ (45.7 g, 400 mmol) in Et$_2$O (150 mL) at 0 °C. The biphasic mixture was stirred vigorously at 0 °C for 2 – 4 h. The organic layer was removed, and the aqueous extracted with Et$_2$O (2 x 100 mL). The combined organics were washed with saturated aq NaHCO$_3$ (100 mL), water (100 mL) and brine (100 mL), dried (Na$_2$SO$_4$) and concentrated to afford a brown oil. The residue was purified by chromatography (silica gel, 9:1 hexanes : ethyl acetate) to afford the title compound (34.8 g, 78%) as a yellow oil. The data closely matches that previously reported.$^4$
5-Phenylpent-1-en3-one, S1d

Following general procedure A, reaction of 3-hydroxyl-5-phenylpent-1-ene\(^{50}\) (83.8 g, 517 mmol) provided the title compound (57.7 g, 70%) as a yellow oil. \(\delta \)\(^{1}H\) (400 MHz, CDCl\(_3\)) 7.42-7.17 (5H, m), 6.40 (1H, dd, J 17.7, 10.5), 6.26 (1H, dd, J 17.7, 1.1), 5.87 (1H, dd, J 10.5, 1.1), 3.10-2.88 (4H, m); \(\delta \)\(^{13}C\) (100 MHz, CDCl\(_3\)) 199.8 (C), 141.1 (C), 136.5 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH\(_2\)), 126.2 (CH), 41.2 (CH\(_2\)), 29.8 (CH\(_2\)). The data closely matches that previously reported.\(^{51}\)

(Z)-tert-Butyl(hepta-1,3-dien-3-yloxy)dimethylsilane, S2c

In an analogous method to Carreño et al.,\(^{52}\) KHMDS (235 mL, 0.91 M in THF, 214 mmol) was added dropwise over 30 min to a solution of butylvinylketone S1c (20.0 g, 178 mmol) and TBSOTf (49.1 mL, 214 mmol) in dry THF (800 mL) at -78 °C under argon. After the addition was complete, the reaction mixture was stirred at -78 °C for 30 min then at room temperature for 1h, then quenched with sat. aq. NaHCO\(_3\) (150 mL) and extracted with Et\(_2\)O (3 x 300 mL). The combined organics were washed with brine (200 mL), dried (Na\(_2\)SO\(_4\)) and concentrated to afford a yellow oil. The residue was purified by chromatography (silica gel, 100% hexanes) to afford the title compound (24.7 g, 61%) as a colourless oil. \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2958, 1362, 1254; \(\delta \)\(^{1}H\) (500 MHz, CDCl\(_3\)) 6.16 (1H, dd, J 17.2, 10.8), 5.31-5.25 (1H, m), 4.95 (1H, ddd, J 10.8, 1.6, 0.6), 4.79 (1H, t, J 7.3), 2.10-2.05 (2H, m), 1.41-1.33 (2H, m), 1.00 (9H, s), 0.91 (3H, t, J 7.4), 0.11 (6H, s); \(\delta \)\(^{13}C\) (125 MHz, CDCl\(_3\)) 148.3 (C), 135.7 (CH), 116.0 (CH), 111.8 (CH\(_2\)), 28.2 (CH\(_3\)), 26.0 (CH\(_3\)), 22.8 (CH\(_3\)), 18.5 (C), 13.9 (CH\(_3\)), -3.7 (CH\(_3\)).

(Z)-tert-Butyldimethyl(5-phenylpenta-1,3-dien-3-yloxy)silane, S2d

KHMDS (250 mL, 0.91 M in THF, 225 mmol) was added dropwise over 30 min to a solution of enone S1d (40.0 g, 250 mmol) and TBSOTf (68.8 mL, 300 mmol) in dry THF (1000 mL) at -78 °C under argon. After the addition was complete, the reaction mixture was stirred at -78 °C for 1.5 h, then quenched with sat. aq. NaHCO\(_3\) (300 mL), warmed to room temperature and extracted with Et\(_2\)O (3 x 500 mL). The combined organics were washed with brine (300 mL), dried (Na\(_2\)SO\(_4\)) and concentrated to afford a yellow oil. The residue was purified by chromatography (silica gel, 100% hexanes) to afford the title compound (47.1 g, 76% w.r.t KHMDS) as a colourless oil. \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2931, 1359, 1255; \(\delta \)\(^{1}H\) (500 MHz, CDCl\(_3\)) 7.35-7.21 (5H, m), 6.24 (1H, dd, J 17.1, 10.8), 5.41 (1H, dd, J 17.1, 1.0), 5.08-5.01 (2H,
m), 3.52 (2H, d, J 7.3), 1.07 (9H, s), 0.20 (6H, s); δC (125 MHz, CDCl₃) 148.9 (C), 141.2 (C), 135.5 (CH), 128.42 (CH), 128.39 (CH), 125.9 (CH), 114.1 (CH), 112.8 (CH₂), 32.3 (CH₂), 26.0 (CH₃), 18.5 (C), −3.5 (CH₃).

General procedure B: Diels-Alder/Schmidt reaction

\[(8aS,9R,12aR)-9\text{-Methyl} \text{octahydrobenzo}[b]\text{pyrrolo}[1,2-\alpha]\text{azepine-5,10(1H,6H)}\text{-dione, 3b} \]

Titanium tetrachloride (1 M in dichloromethane, 100 mmol) was added dropwise to a solution of azide 53 (7.15 g, 40 mmol) and \((Z)\text{-}\text{tert-butyldimethyl(penta-1,3-dien-3-yloxy)silane} 52 (19.8 g, 100 \text{ mmol)}\) in anhydrous dichloromethane (500 mL) at 0 °C under argon. The resulting red/brown solution was stirred at 0 °C for 2 h, then allowed to warm slowly to room temperature overnight. The reaction mixture was quenched with water (100 mL) and stirred at room temperature for 1 h. The organic layer was removed, and the aqueous extracted with dichloromethane (3 x 100 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a brown oil. The residue was purified by chromatography (silica gel, 95:5 ethyl acetate: methanol) to afford the title compound (5.0 g, 53%) as a cream solid foam. A portion of this was recrystallised from hexanes and ethyl acetate to afford colourless needles. Mp 133-135 °C; νmax (film)/cm⁻¹ 2943, 1708, 1611; δH (500 MHz, CDCl₃) 3.87-3.81 (1H, m), 3.29 (1H, ddd, J 11.7, 11.7, 7.1), 2.78-2.74 (1H, m), 2.61 (1H, dd, J 12.3, 6.4), 2.51 (1H, ddt, J 15.0, 6.4, 1.4), 2.37-2.22 (4H, m), 1.97-1.88 (1H, m), 1.88-1.65 (6H, m), 1.39-1.27 (1H, m), 1.08-1.02 (1H, m), 0.88 (3H, d, J 6.7); δC (125 MHz, CDCl₃) 210.3 (C), 173.8 (C), 66.0 (C), 52.1 (CH), 49.2 (CH₃), 47.2 (CH), 40.1 (CH₂), 38.32 (CH₂), 38.25 (CH₂), 28.1 (CH₂), 27.1 (CH₂), 22.8 (CH₂), 20.6 (CH₂), 12.4 (CH₃); m/z (ESI⁺) found [M+H]⁺ 236.1674. C₁₄H₂₂NO₂⁺ requires 236.1645.

\[(8aS,9R,12aR)-9\text{-Propyl} \text{octahydrobenzo}[b]\text{pyrrolo}[1,2-\alpha]\text{azepine-5,10(1H,6H)}\text{-dione, 3c} \]

Following general procedure B, reaction with azide (7.0 g, 39.1 mmol) and diene S2c (22.1 g, 97.7 mmol) provided the title compound (4.5 g, 44%) as a colourless solid. A portion this was recrystallised from hexanes and ethyl acetate to afford colourless needles. Mp 86.5 – 88.0 °C; νmax (film)/cm⁻¹ 2954, 1707, 1613; δH (500 MHz, CDCl₃) 3.98 (1H, dd, J 11.9, 8.4), 3.43 (1H, ddd, J 11.9, 11.9, 7.0), 2.76 (1H, dd, J 12.2, 6.2), 2.70-2.61 (2H, m), 2.48-2.37 (4H, m), 2.07-1.99 (1H, m), 1.96-1.72 (7H, m), 1.50-1.40 (1H, m), 1.28-1.11 (4H, m), 0.90 (3H, t, J 7.2); δC (125 MHz, CDCl₃) 210.0 (C), 173.7 (C), 65.9 (C), 52.5 (CH), 50.3 (CH), 49.2 (CH₂), 40.3 (CH₂), 38.8 (CH₂), 38.3 (CH₃), 29.1 (CH₂), 28.4
(CH₃), 27.4 (CH₂), 22.9 (CH₂), 20.6 (CH₂), 20.5 (CH₂), 14.1 (CH₃); m/z (ESI+) found [M+H]+ 264.1994. C₁₆H₂₆NO₂⁺ requires 264.1958.

(8aS,9R,12aR)-9-Benzylotahydrobenzo[b]pyrrolo[1,2-a]azepine-5,10(1H,6H)-dione, 3d

Following general procedure B, reaction with azide (12.3 g, 68.6 mmol) and diene S2d (47.1 g, 172 mmol) provided the title compound (11.9 g, 56%) as a colourless solid. A portion this was recrystallised from hexanes and ethyl acetate to afford colourless needles. Mp 117-119 °C; ν_max (film)/cm⁻¹ 2945, 1709, 1611; δ_H (500 MHz, CDCl₃) 7.29-7.26 (2H, m), 7.22-7.18 (1H, m), 7.14-7.11 (2H, m), 3.95-3.90 (1H, m), 3.37-3.31 (1H, m), 3.15 (1H, dd, J 14.3, 6.1), 3.06-3.02 (1H, m), 2.72-2.68 (1H, m), 2.63 (1H, dd, J 15.0, 6.6), 2.53-2.38 (5H, m), 2.06-2.01 (1H, m), 1.92-1.74 (6H, m), 1.44-1.35 (1H, m), 1.31-1.22 (1H, m); δ_C (125 MHz, CDCl₃) 209.2 (C), 173.6 (C), 139.6 (C), 128.7 (CH), 128.6 (CH), 126.3 (CH), 65.8 (C), 54.6 (CH), 49.3 (CH), 49.2 (CH₂), 40.2 (CH₂), 38.6 (CH₂), 38.3 (CH₂), 32.1 (CH₂), 29.1 (CH₂), 27.3 (CH₂), 22.7 (CH₂), 20.5 (CH₂); m/z (ESI+) found [M+H]+ 312.1982. C₂₀H₂₆NO₂⁺ requires 312.1958.

General procedure D: L-Selectride reduction of ketones

(8aS,10S,12aR)-10-Hydroxydecahydrobenzo[b]pyrrolo[1,2-a]azepin-5(1H)-one, S3a

L-Selectride (1M in tetrahydrofuran, 33.9 mL) was added dropwise to a solution of ketone 3a⁵⁴ (3.0 g, 13.6 mmol) in anhydrous tetrahydrofuran (180 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 4 h, then allowed to warm slowly to room temperature overnight. The mixture was then cooled to 0 °C, quenched carefully with 30% aq. H₂O₂ (15 mL) and 2M NaOH (20 mL), then extracted with dichloromethane (3 x 100 mL). The combined organics were washed with brine (100 mL), dried (Na₂SO₄) and concentrated. The crude product was purified by automated column chromatography (40 g silica column, 0% MeOH in CH₂Cl₂ for 3 min, then 0 to 10% over 10 min, the 10% for 5 min) to afford the title compound (2.73 g, 90%) as a pale yellow oil. A portion was recrystallised from hexanes and ethyl acetate to afford colourless plates. Mp 112.5-114.5 °C; ν_max (film)/cm⁻¹ 3380, 2926, 1592; δ_H (500 MHz, CDCl₃) 4.09-4.06 (1H, m), 3.80-3.75 (1H, m), 3.54-3.47 (1H, m), 2.67-2.58 (2H, m), 2.55-2.45 (1H, m), 2.40-2.36 (1H, m), 2.30 (1H, td, J 13.1, 5.3), 1.97 (1H, dt, J 9.0, 5.0), 1.94-1.69 (9H, m), 1.49-1.37 (2H, m); δ_C (125 MHz, CDCl₃) 174.5 (C), 66.4 (C), 65.2 (CH),
49.0 (CH₂), 43.9 (CH), 39.0 (CH₂), 38.6 (CH₂), 38.4 (CH₂), 34.7 (CH₂), 31.4 (CH), 24.3 (CH₂), 23.7 (CH₂), 20.3 (CH₂); m/z (ESI+) found [M+H⁺] 224.1660. C₁₃H₂₂NO₂⁺ requires 224.1645.

\((8aS,10S,12aR)-5\text{-Oxododecahydrobenzo}[b]pyrrolo[1,2-\alpha]azepin-10-yl 4-bromobenzoate, S₆\)

Triethylamine (75 µL, 0.54 mmol) was added to a solution of alcohol S₃ₐ (100 mg, 0.45 mmol), 4-bromobenzoyl chloride (150 mg, 0.67 mmol) and DMAP (66 mg, 0.54 mmol) in anhydrous CH₂Cl₂ (5 mL) at room temperature under argon. The reaction mixture was stirred for 7.5 h, then water (5 mL) was added. The organic layer was removed and the aqueous extracted with CH₂Cl₂ (2 x 5 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a yellow oil. The crude product was purified by automated column chromatography (4 g silica column, 0 to 100% EtOAc in hexanes over 15 min) followed by recrystallisation from EtOAc to afford the title compound (130 mg, 71%) as cream plates. Mp 104-107 °C; ν_max (film)/cm⁻¹ 2928, 1711, 1612; δ_H (500 MHz, CDCl₃) 7.90 (2H, d, J 8.3), 7.62 (2H, d, J 8.3), 5.25 (1H, br s), 3.84-3.78 (1H, m), 3.56-3.47 (1H, m), 2.74-2.66 (1H, m), 2.52-2.35 (3H, m), 2.32-2.23 (1H, m), 2.13 (1H, td, J 15.5, 4.4), 2.06-1.94 (3H, m), 1.92-1.70 (6H, m), 1.54-1.44 (2H, m); δ_C (125 MHz, CDCl₃) 174.2 (C), 165.2 (C), 131.9 (CH), 131.0 (CH), 129.5 (C), 128.2 (C), 68.8 (CH), 66.0 (C), 49.2 (CH₂), 43.5 (CH), 39.0 (CH₂), 38.6 (CH₂), 35.7 (CH₂), 34.4 (CH₃), 28.5 (CH₂), 24.7 (CH₂), 23.7 (CH₂), 20.3 (CH₂); m/z (ESI+) found [M+H⁺] 406.1023. C₂₀H₂₅BrNO₃⁺ requires 406.1012.

\((8aS,9R,10S,12aR)-10\text{-Hydroxy-9-methyldecahydrobenzo}[b]pyrrolo[1,2-\alpha]azepin-5(1H)-one, S₃b\)

Following general procedure D, reaction with ketone 3b (2.65 g, 11.3 mmol) and L-Selectride (1.0 M in tetrahydrofuran, 28.2 mL) provided the title compound (2.54 g, 95%) as a pale yellow crystalline solid. Mp 189-191 °C; ν_max (film)/cm⁻¹ 3389, 2932, 1591; δ_H (500 MHz, CDCl₃) 3.85-3.34 (1H, m), 2.62 (1H, ddt, J 14.9, 6.9, 1.4), 2.50-2.42 (2H, m), 2.26-2.16 (2H, m), 1.98-1.66 (6H, m), 1.47 (1H, dt, J 12.7, 3.1), 1.38-1.24 (2H, m), 1.06 (3H, t, J 7.2); δ_C (125 MHz, CDCl₃) 173.9 (C), 68.3 (CH), 67.0 (C), 49.0 (CH), 48.1 (CH₂), 37.9 (CH₂), 37.8 (CH₃), 36.9 (CH), 30.5 (CH₂), 27.2 (CH₂), 22.9 (CH₂), 22.7 (CH₂), 19.3 (CH₂), 15.2 (CH₃); m/z (ESI+) found [M+H⁺] 238.1817. C₁₄H₂₄NO₃⁺ requires 238.1802.
Following general procedure D, reaction with ketone 3c (1.16 g, 4.4 mmol) and L-Selectride (1.0 M in tetrahydrofuran, 10.9 mL) provided the title compound (1.11 g, 95%) as a pale yellow crystalline solid. Mp 134-135 °C; ν\textsubscript{max} (film)/cm\textsuperscript{-1} 3391, 2953, 1593; δ\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 3.85-3.78 (2H, m), 3.43-3.36 (1H, m), 2.58 (1H, dd, J 15.0, 6.9), 2.48-2.40 (2H, m), 2.28-2.18 (3H, m), 1.89-1.60 (8H, m), 1.53-1.22 (7H, m), 0.90 (3H, t, J 7.3); δ\textsubscript{C} (125 MHz, CDCl\textsubscript{3}) 174.9 (C), 68.0 (C), 67.8 (CH), 49.1 (CH\textsubscript{2}), 48.0 (CH), 43.0 (CH), 39.0 (CH\textsubscript{2}), 38.8 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 31.7 (CH\textsubscript{2}), 28.3 (CH\textsubscript{2}), 24.4 (CH\textsubscript{2}), 23.8 (CH\textsubscript{2}), 20.2 (CH\textsubscript{2}), 20.1 (CH\textsubscript{2}), 14.3 (CH\textsubscript{3}); m/z (ESI+) found [M+H]\textsuperscript{+} 266.2134. C\textsubscript{16}H\textsubscript{28}NO\textsubscript{2}\textsuperscript{+} requires 266.2115.

Following general procedure D, reaction with ketone 3d (2.50 g, 8.0 mmol) and L-Selectride (1.0 M in tetrahydrofuran, 20.1 mL) provided the title compound (2.29 g, 91%) as a colourless solid foam. A portion of this was recrystallised from ethyl acetate and tetrahydrofuran to afford colourless plates. Mp 169-171 °C; ν\textsubscript{max} (film)/cm\textsuperscript{-1} 3388, 2926, 1593; δ\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 7.29-7.26 (2H, m), 7.21-7.17 (3H, m), 3.84-3.74 (2H, m), 3.41-3.34 (1H, m), 2.92 (1H, dd, J 13.4, 8.7), 2.67-2.57 (2H, m), 2.50-2.20 (4H, m), 2.07-1.97 (2H, m), 1.86-1.57 (6H, m), 1.53-1.47 (1H, m), 1.37-1.22 (2H, m); δ\textsubscript{C} (125 MHz, CDCl\textsubscript{3}) 174.9 (C), 140.6 (C), 128.9 (CH), 128.5 (CH), 126.1 (CH), 68.0 (C), 66.5 (CH), 49.1 (CH\textsubscript{2}), 48.5 (CH), 45.7 (CH), 38.9 (CH\textsubscript{2}), 38.8 (CH\textsubscript{2}), 36.5 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 28.7 (CH\textsubscript{2}), 24.3 (CH\textsubscript{2}), 23.7 (CH\textsubscript{2}), 20.2 (CH\textsubscript{2}); m/z (ESI+) found [M+H]\textsuperscript{+} 314.2127. C\textsubscript{20}H\textsubscript{28}NO\textsubscript{2}\textsuperscript{+} requires 314.2115.
4-Nitrophenyl (8a\textsubscript{S},10S,12aR)-5-oxododecahydrobenzo[b]pyrrolo[1,2-α]azepin-10-yl carbonate, S4a

4-Nitrophenylchloroformate (2.88 g, 14.3 mmol) was added in one portion to a solution of alcohol S3a (2.13 g, 9.54 mmol) and pyridine (1.54 mL, 19.1 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (50 mL) at 0 °C under argon. The resulting suspension was stirred at room temperature for 1.5 h, then diluted with CH\textsubscript{2}Cl\textsubscript{2} (200 mL) and washed quickly with 1M HCl (50 mL) and brine (50 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated to afford a colourless solid foam. The crude product was purified by automated column chromatography (40 g silica column, 0 to 100% EtOAc in hexanes over 5 min, then 100% EtOAc for 10 min) to afford the title compound (2.81 g, 76%) as a white amorphous solid. Mp 159-160 °C; \( \nu_{\text{max}} \) (film)/cm\textsuperscript{-1} 2946, 1760, 1614; \( \delta_{\text{H}} \) (500 MHz, CDCl\textsubscript{3}) 8.45-8.18 (2H, m), 7.49-7.32 (2H, m), 5.03-4.86 (1H, m), 3.86-3.78 (1H, m), 3.56-3.49 (1H, m), 2.70 (1H, dd, J 15.0, 6.7), 2.48 (1H, t, J 13.3), 2.44-2.31 (2H, m), 2.27 (1H, td, J 14.1, 3.5), 2.14-2.06 (2H, m), 2.06-1.91 (3H, m), 1.89-1.72 (5H, m), 1.54-1.44 (2H, m); \( \delta_{\text{C}} \) (125 MHz, CDCl\textsubscript{3}) 174.3 (C), 155.5 (C), 151.8 (C), 145.4 (C), 125.3 (CH), 121.9 (CH), 74.0 (CH), 65.8 (C), 49.1 (CH\textsubscript{2}), 43.3 (CH), 39.0 (CH\textsubscript{2}), 38.4 (CH\textsubscript{2}), 35.5 (CH\textsubscript{2}), 34.0 (CH\textsubscript{2}), 28.3 (CH\textsubscript{2}), 24.5 (CH\textsubscript{2}), 23.6 (CH\textsubscript{2}), 20.3 (CH\textsubscript{2}); \( m/z \) (ESI+) found [M+H]\textsuperscript{+} 389.1727. C\textsubscript{20}H\textsubscript{25}N\textsubscript{2}O\textsubscript{6} requires 389.1702.

4-Nitrophenyl (8a\textsubscript{S},9R,10S,12aR)-9-Methyl-5-oxododecahydrobenzo[b]pyrrolo[1,2-α]azepin-10-yl carbonate, S4b

Following general procedure E, reaction of alcohol S3b (2.90 g, 12.2 mmol) provided the title compound (2.71 g, 55%) as a cream solid foam. \( \nu_{\text{max}} \) (film)/cm\textsuperscript{-1} 2956, 1759, 1612; \( \delta_{\text{H}} \) (500 MHz, CDCl\textsubscript{3}) 8.29-8.26 (2H, m), 7.40-7.37 (2H, m), 4.90 (1H, br s), 3.88-3.83 (1H, m), 3.48-3.41 (1H, m), 2.66 (1H, dd, J 15.1, 7.0), 2.48-2.40 (2H, m), 2.24-2.12 (2H, m), 2.08-2.02 (1H, m), 1.99-1.68 (7H, m), 1.55 (1H, ddd, J 12.0, 3.7, 3.7), 1.47-1.42 (1H, m), 1.40-1.32 (1H, m), 1.07 (3H, d, J 7.1); \( \delta_{\text{C}} \) (125 MHz, CDCl\textsubscript{3}) 174.6 (C), 155.6 (C), 152.3 (C), 145.4 (C), 125.3 (CH), 121.9 (CH), 77.9 (CH), 67.2 (C), 49.5 (CH), 49.1 (CH\textsubscript{2}), 39.0 (CH\textsubscript{2}), 38.8 (CH\textsubscript{2}), 37.2 (CH), 28.5 (CH\textsubscript{2}), 27.7 (CH\textsubscript{2}), 24.0 (CH\textsubscript{2}), 23.5 (CH\textsubscript{2}), 20.2 (CH\textsubscript{2}), 15.9 (CH\textsubscript{3}); \( m/z \) (ESI+) found [M+H]\textsuperscript{+} 403.1884. C\textsubscript{21}H\textsubscript{27}N\textsubscript{2}O\textsubscript{6} requires 403.1864.

4-Nitrophenyl (8a\textsubscript{S},9R,10S,12aR)-5-oxo-9-propyldodecahydrobenzo[b]pyrrolo[1,2-α]azepin-10-yl carbonate, S4c
Following general procedure E, reaction of alcohol S3c (1.11 g, 4.2 mmol) provided the title compound (1.20 g, 67%) as a colourless solid foam. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2947, 1761, 1614; $\delta_H$ (500 MHz, CDCl$_3$) 8.35-8.28 (2H, m), 7.45-7.38 (2H, m), 5.01 (1H, br s), 4.14 (1H, d, J 7.1), 3.91 (1H, dd, J 12.6, 7.2), 3.49 (1H, dd, J 7.8, 2.7), 2.76 (1H, dd, J 15.1, 6.9), 2.49 (2H, dd 16.2, 10.8), 2.22 (1H, dd, J 13.6, 4.7), 2.13-1.80 (10H, m), 1.80-1.67 (3H, m), 1.54-1.32 (6H, m), 1.28 (1H, t, J 7.1), 0.99-0.91 (3H, m); $\delta_C$ (125 MHz, CDCl$_3$) 174.8 (C), 155.6 (C), 152.2 (C), 125.3 (CH), 121.9 (CH), 76.7 (CH), 67.4 (C), 49.3 (CH$_2$), 47.3 (CH), 42.2 (CH), 39.0 (CH$_2$), 38.6 (CH$_2$), 31.5 (CH$_2$), 28.6 (CH$_2$), 27.7 (CH$_2$), 24.4 (CH$_3$), 23.5 (CH$_3$), 20.2 (CH$_3$), 19.9 (CH$_3$), 14.2 (CH$_3$); m/z (ESI+) found [M+H]$^+$ 431.2202. C$_{23}$H$_{31}$N$_2$O$_6^+$ requires 431.2177.

(8aS,9R,10S,12aR)-9-Benzyl-5-oxodecahydrobenzo[b]pyrrolo[1,2-a]azepin-10-yl 4-nitrophenyl carbonate, S4d

Following general procedure E, reaction of alcohol S3d (2.19 g, 7.0 mmol) provided the title compound (2.49 g, 74%) as a colourless amorphous solid. Mp 211-213 °C; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2958, 1760, 1611; $\delta_H$ (500 MHz, CDCl$_3$) 8.35-8.32 (2H, m), 7.47-7.43 (2H, m), 7.34-7.31 (2H, m), 7.27-7.22 (1H, m), 7.17-7.13 (2H, m), 4.84 (1H, br s), 3.89-3.84 (1H, m), 3.45-3.39 (1H, m), 2.87 (1H, dd, J 13.6, 8.1), 2.73-2.66 (2H, m), 2.51-2.43 (2H, m), 2.34-2.29 (1H, m), 2.23 (1H, ddd, J 13.6, 13.6, 4.6), 2.13-2.02 (3H, m), 1.92-1.59 (6H, m), 1.48 (1H, dd, J 13.6, 5.1), 1.40-1.31 (1H, m); $\delta_C$ (125 MHz, CDCl$_3$) 174.4 (C), 155.6 (C), 152.2 (C), 145.4 (C), 139.1 (C), 128.8 (CH), 128.7 (CH), 126.7 (CH), 125.4 (CH), 121.9 (CH), 76.0 (CH), 67.0 (C), 49.1 (CH$_2$), 47.6 (CH), 44.9 (CH), 39.0 (CH$_2$), 38.8 (CH$_2$), 36.0 (CH$_2$), 28.3 (CH$_3$), 28.0 (CH$_3$), 24.4 (CH$_3$), 23.4 (CH$_3$), 20.2 (CH$_3$); m/z (ESI+) found [M+H]$^+$ 479.2169. C$_{27}$H$_{31}$N$_2$O$_6^+$ requires 479.2177.

General procedure F: Reductive amination with ammonium acetate
(8aS,9R,10S,12aR)-10-Amino-9-methyldecahydrobenzo[b]pyrrolo[1,2-a]azepin-5(1H)-one, 4b and (8aS,9R,10R,12aR)-10-amino-9-methyldecahydrobenzo[b]pyrrolo[1,2-a]azepin-5(1H)-one, S5b

Ammonium acetate (20.0 g, 260 mmol) was added to a solution of ketone 3b (6.11 g, 26.0 mmol) in anhydrous methanol (100 mL) under argon. Sodium cyanoborohydride (12.3 g, 195 mmol) was then added, and the resulting yellow solution stirred at room temperature for 7 h. After this time, an additional aliquot of ammonium acetate (20.0 g, 260 mmol) and sodium cyanoborohydride (12.3 g, 195 mmol) was added and the mixture stirred overnight at room temperature, then concentrated under reduced pressure to remove the methanol. The residue was diluted with 2M NaOH until basic, then extracted with dichloromethane (10 x 50 mL). The combined organics were dried (Na$_2$SO$_4$) and concentrated to afford a yellow oil (6.7 g). The crude ~2:1 diastereomeric mixture of products was purified by automated column chromatography (2 g batches of crude material on a 130 g C18 column, 10 to 30 % acetonitrile in basic water over 5 min, then 30-50% over 15 min, then 100% acetonitrile for 5 min) to afford the (9R,10S) isomer 4b (3.66 g, 60%) and the (9R,10R) isomer S5b (1.76 g, 29%) as colourless amorphous solids.

(8aS,9R,10S,12aR) isomer 4b: Mp 106-108 °C; $\nu_{max}$ (film)/cm$^{-1}$ 3374, 2930, 1603; $\delta$H (500 MHz, CDCl$_3$) 3.82-3.77 (1H, m), 3.45-3.39 (1H, m), 3.06 (1H, t, J 3.7), 2.60 (1H, ddt, J 15.0, 7.0, 1.4), 2.51-2.42 (2H, m), 2.35 (1H, ddd, J 13.5, 13.5, 2.5), 2.22 (1H, td, J 13.5, 4.5), 2.02-1.97 (1H, m), 1.95-1.90 (1H, m), 1.89-1.64 (5H, m), 1.60-1.55 (1H, m), 1.46-1.42 (1H, m), 1.33-1.24 (2H, m), 1.01 (3H, d, J 7.3); $\delta$C (125 MHz, CDCl$_3$) 171.8 (C), 68.4 (C), 50.1 (CH), 49.04 (CH$_2$), 48.96 (CH), 48.96 (CH), 38.9 (CH$_2$), 37.2 (CH), 31.8 (CH$_2$), 28.9 (CH$_2$), 24.0 (CH$_2$), 23.7 (CH$_2$), 20.2 (CH$_2$), 16.7 (CH$_3$); m/z (ESI$^+$) found [M+H]$^+$ 237.1984. C$_{14}$H$_{25}$N$_2$O requires 237.1961.

(8aS,9R,10R,12aR) isomer S5b: Mp 97-99 °C; $\nu_{max}$ (film)/cm$^{-1}$ 3374, 2930, 1603; $\delta$H (500 MHz, MeOD) 3.84-3.78 (1H, m), 3.41-3.31 (1H, m), 2.81 (1H, ddd, J 11.5, 11.5, 5.4), 2.70-2.66 (1H, m), 2.61-2.53 (2H, m), 2.24 (1H, ddd, J 13.5, 13.5, 5.0), 2.01-1.71 (8H, m), 1.61-1.56 (2H, m), 1.52-1.36 (2H, m), 1.04 (3H, d, J 6.8); $\delta$C (125 MHz, MeOD) 176.8 (C), 69.5 (C), 51.8 (CH$_2$), 50.5 (CH), 50.4 (CH$_2$), 41.2 (CH$_2$), 40.3 (CH$_2$), 39.0 (CH), 32.7 (CH$_3$), 28.7 (CH$_2$), 26.7 (CH$_2$), 24.4 (CH$_2$), 21.2 (CH$_3$), 17.5 (CH$_3$); m/z (ESI$^+$) found [M+H]$^+$ 237.1978. C$_{14}$H$_{25}$N$_2$O requires 237.1961.

(8aS,9R,10S,12aR)-10-Amino-9-propyldecahydrobenzo[b]pyrrolo[1,2-a]azepin-5(1H)-one, 4c and (8aS,9R,10R,12aR)-10-amino-9-propyldecahydrobenzo[b]pyrrolo[1,2-a]azepin-5(1H)-one, S5c
Following general procedure F, reaction of ketone 3c (5.50 g, 13.7 mmol) provided the (9R,10S) isomer 4c (3.66 g, 66%) and the (9R,10R) isomer S5c (880 mg, 16%) as pale yellow oils. **(8aS,9R,10S,12aR) isomer 4c:** \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3405, 2927, 1603; \(\delta_{\text{n}}\) (500 MHz, CDCl\(_3\)) 3.83-3.78 (1H, m), 3.46-3.39 (1H, m), 3.14 (1H, br s), 2.64-2.57 (1H, m), 2.52-2.33 (3H, m), 2.26 (1H, ddd, J 13.4, 13.4, 4.4), 1.90-1.48 (9H, m), 1.40-1.22 (6H, m), 0.92 (3H, t, J 7.1); \(\delta_{\text{C}}\) (125 MHz, CDCl\(_3\)) 174.8 (C), 68.3 (C), 49.1 (CH\(_3\)), 48.3 (CH), 47.5 (CH), 42.3 (CH), 39.1 (CH\(_2\)), 38.9 (CH\(_2\)), 32.5 (CH\(_2\)), 31.9 (CH\(_3\)), 28.9 (CH\(_2\)), 24.5 (CH\(_2\)), 23.8 (CH\(_3\)), 20.19 (CH\(_2\)), 20.15 (CH\(_3\)), 14.3 (CH\(_3\)); \(m/z\) (ESI\(^{+}\)) found [M+H]\(^{+}\) 265.2309. 

C\(_{16}H\(_{29}\)N\(_2\)O\(^{+}\)) requires 265.2274. **(8aS,9R,10R,12aR) isomer S5c:** \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3375, 2935, 1604; \(\delta_{\text{n}}\) (500 MHz, CDCl\(_3\)) 3.82-3.77 (1H, m), 3.35-3.28 (1H, m), 2.69 (1H, br s), 2.59-2.48 (2H, m), 2.37 (1H, ddd, J 13.9, 13.9), 2.04 (1H, ddd, J 13.5, 13.5, 4.9), 1.85-1.25 (14H, m), 1.15-1.05 (2H, m), 0.85 (3H, t, J 7.0); \(\delta_{\text{C}}\) (125 MHz, CDCl\(_3\)) 174.3 (C), 67.4 (C), 49.1 (CH\(_3\)), 48.4 (CH), 45.9 (CH), 45.8 (CH), 39.5 (CH\(_2\)), 38.7 (CH\(_2\)), 33.7 (CH\(_3\)), 31.0 (CH\(_2\)), 28.1 (CH\(_2\)), 25.6 (CH\(_2\)), 23.4 (CH\(_2\)), 20.3 (CH\(_2\)), 19.4 (CH\(_2\)), 14.2 (CH\(_3\)); \(m/z\) (ESI\(^{+}\)) found [M+H]\(^{+}\) 265.2301. C\(_{16}H\(_{29}\)N\(_2\)O\(^{+}\)) requires 265.2274.

Following general procedure F, reaction of ketone 3d (9.40 g, 30.2 mmol) provided the (9R,10S) isomer 4d (6.85 g, 73%) and the (9R,10R) S5d isomer (1.05 g, 11%) as pale yellow oils. The (9R,10R) isomer solidified to a yellow solid upon standing. **(8aS,9R,10S,12aR) isomer 4d:** \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3376, 2926, 1604; \(\delta_{\text{n}}\) (500 MHz, CDCl\(_3\)) 7.32-7.27 (2H, m), 7.23-7.17 (3H, m), 3.84-3.78 (1H, m), 3.39 (1H, ddd, J 12.3, 9.7, 7.7), 3.06 (1H, dd, J 3.6, 3.6), 2.79 (1H, dd, J 13.5, 8.2), 2.71-2.60 (2H, m), 2.53-2.43 (3H, m), 2.28 (1H, ddd, J 13.5, 13.5, 3.8), 2.14-2.10 (1H, m), 2.07-2.02 (1H, m), 1.87-1.55 (6H, m), 1.50-1.45 (1H, m), 1.38-1.33 (1H, m), 1.32-1.22 (1H, m); \(\delta_{\text{C}}\) (125 MHz, CDCl\(_3\)) 174.4 (C), 140.3 (C), 128.7 (CH), 128.5 (CH), 126.2 (CH), 68.2 (C), 49.1 (CH\(_3\)), 48.5 (CH), 46.8 (CH), 45.1 (CH), 39.0 (CH\(_3\)), 38.9 (CH\(_2\)), 37.0 (CH\(_3\)), 32.0 (CH\(_2\)), 29.3 (CH\(_3\)), 24.4 (CH\(_2\)), 23.7 (CH\(_2\)), 20.1 (CH\(_2\)); \(m/z\) (ESI\(^{+}\)) found [M+H]\(^{+}\) 313.2282. C\(_{20}H\(_{31}\)N\(_2\)O\(^{+}\)) requires 313.2274. **(8aS,9R,10R,12aR) isomer S5d:** Mp 72-74 °C; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3365, 2939, 1598; \(\delta_{\text{n}}\) (500 MHz, CDCl\(_3\)) 7.30 (2H, t, J 7.3), 7.21 (1H, t, J 7.3), 7.16 (2H, t, J 7.3), 3.84-3.76 (1H, m), 3.28-3.23 (1H, m), 3.12 (1H, ddd, J 13.8, 4.9), 2.94 (1H, ddd, J 11.2, 11.2, 5.4), 2.62-2.55 (2H, m), 2.43-2.36 (2H, m), 2.12 (1H, dddd, J 13.4, 13.4, 5.0, 1.3), 2.04-1.91 (3H, m), 1.84-1.76 (1H, m), 1.73-1.35 (6H, m), 1.29-1.17 (2H, m); \(\delta_{\text{C}}\) (125 MHz, CDCl\(_3\)) 174.1 (C), 139.9 (C), 128.60
B. Experimental procedures and characterization data for cylindricine-inspired scaffolds.

Supplementary Figure 5. Synthesis of cylindricine-inspired scaffolds

General procedure G: Synthesis of cyclobutanones 6a-h

Spiro[3.5]nonan-1-on, 6a

In an analogous method to Guérot et al., THF (110 mL) was added to solid potassium bis(trimethylsilyl)amide (7.5 g, 38 mmol) in an oven-dried flask. The solution was cooled to -45 °C and aged for 15 min. Cyclopropyldiphenylsulfonium tetrafluoroborate (13.0 g, 41 mmol) was then added and the solution stirred at -45 °C for 30 min. A solution of cyclohexanone (2.8 mL, 27 mmol) in THF (25 mL) was then added and the solution was allowed to warm to room temperature over 4 h and stirred overnight. The reaction was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with water, dried (MgSO₄) and
concentrated. The resulting oil was dissolved in anhydrous benzene (100 mL) and to the solution was added lithium tetrafluoroborate (0.10 g, 1.0 mmol). The solution was heated at reflux for 3 h, then cooled to room temperature and concentrated to an oil. The crude product was purified by automated column chromatography (40 g silica column, 0 to 10% EtOAc in hexanes over 30 min) to afford the title compound (2.2 g, 59%) as a colorless oil as a single diastereomer. The 1H and 13C NMR data closely matched that previously reported.

(4S,7S)-7-methylspiro[3.5]nonan-1-one, 6b

Following general procedure G, reaction with 4-methylcyclohexanone (1.8 mL, 15 mmol) provided the title compound (1.3 g, 62%) as a colorless viscous oil as a single diastereomer. 1H NMR (400 MHz, CDCl₃) δ 2.92 – 2.85 (m, 2H), 2.00 – 1.89 (m, 2H), 1.70 (t, J = 8.5, 8.5 Hz, 2H), 1.59 – 1.48 (m, 2H), 1.46 – 1.36 (m, 2H), 1.35 – 1.24 (m, 3H), 0.88 (d, J = 5.9 Hz, 3H). 13C NMR (100 MHz, CDCl₃) δ 216.3, 65.1, 41.3, 33.5, 32.1, 25.2; m/z (ESI+) found [M+H]+ 153.1354. C₁₀H₁₇O⁺ requires 153.1274.

(4S,7S)-7-propylspiro[3.5]nonan-1-one, 6c

Following general procedure G, reaction with 4-propylcyclohexanone (2.0 mL, 13 mmol) provided the title compound (1.6 g, 74%) as a colorless oil as a single diastereomer. 1H NMR (400 MHz, CDCl₃) δ 2.83 – 2.74 (m, 2H), 1.90 – 1.79 (m, 2H), 1.67 – 1.56 (m, 2H), 1.54 – 1.44 (m, 2H), 1.35 – 1.25 (m, 2H), 1.24 – 1.12 (m, 4H), 1.12 – 1.00 (m, 3H), 0.75 (t, J = 7.1, 7.1 Hz, 3H). 13C NMR (101 MHz, CDCl₃) δ 215.8, 65.0, 40.8, 38.5, 36.2, 32.9, 29.6, 24.7, 20.0, 14.4; m/z (ESI+) found [M+H]+ 181.1581. C₁₂H₂₁O⁺ requires 181.1587.

(4S,7S)-7-phenylspiro[3.5]nonan-1-one, 6d
Following general procedure G, reaction with 4-phenylcyclohexanone (3.0 g, 17 mmol) provided the title compound (2.4 g, 70%, 20:1 dr) as a colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32 – 7.20 (m, 4H), 7.20 – 7.13 (m, 1H), 3.01 – 2.89 (m, 2H), 2.45 (tt, \(J = 12.0, 12.0, 3.6, 3.6\) Hz, 1H), 2.17 – 2.04 (m, 2H), 1.99 – 1.83 (m, 2H), 1.82 – 1.71 (m, 4H), 1.58 (td, \(J = 13.3, 13.3, 3.8\) Hz, 2H). \(^1^3\)C NMR (126 MHz, DMSO) \(\delta\) 214.9, 146.7, 128.3, 126.5, 125.9, 63.2, 42.4, 40.5, 32.7, 30.7, 24.1; \(m/z\) (ESI+) found [M+H]\(^+\) 215.1430. C\(_{15}\)H\(_{19}\)O\(^+\) requires 215.1430.

\((4S,7S)-7-(p\text{-}tolyl)\text{spiro}[3.5]\text{nonan-1-one, 6e}\)

Following general procedure G, reaction with 4-tolylcyclohexanone (1.9 g, 10 mmol) provided the title compound (1.6 g, 72%, 7:1 dr) as a colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.15 – 7.05 (m, 3H), 2.95 (t, \(J = 8.4, 8.4\) Hz, 1H), 2.40 (tt, \(J = 12.0, 12.0, 3.6, 3.6\) Hz, 1H), 2.29 (s, 2H), 2.10 (d, \(J = 13.8\) Hz, 2H), 1.94 – 1.80 (m, 2H), 1.80 – 1.71 (m, 3H), 1.61 – 1.52 (m, 2H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 143.9, 135.4, 129.0, 126.8, 64.1, 43.2, 40.8, 33.7, 31.1, 24.7, 20.9; \(m/z\) (ESI+) found [M+H]\(^+\) 229.1577. C\(_{16}\)H\(_{21}\)O\(^+\) requires 229.1587.

\((4S,7S)-7-(o\text{-}tolyl)\text{spiro}[3.5]\text{nonan-1-one, 6f}\)

Following general procedure G, reaction with 4-o-tolylcyclohexanone (1.9 g, 10 mmol) provided the title compound (1.6 g, 72%) as a colorless solid as a single diastereomer. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.27 (dd, \(J = 7.7, 0.8\) Hz, 1H), 7.16 (td, \(J = 7.5, 1.8\) Hz, 1H), 7.12 – 7.03 (m, 2H), 2.96 (t, \(J = 8.4\) Hz, 2H), 2.65 (tt, \(J = 12.1, 3.3\) Hz, 1H), 2.31 (s, 3H), 2.17 – 2.08 (m, 2H), 1.88 (ddd, \(J = 25.5, 13.3, 3.4\) Hz, 2H), 1.72 – 1.58 (m, 2H), 1.48 (dd, \(J = 13.8, 13.8\) Hz, 2H), 0.96 – 0.84 (m, 3H), 0.83 – 0.71 (m, 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.6, 135.1, 129.2, 126.8, 64.1, 43.2, 40.8, 33.7, 31.1, 24.7, 20.9; \(m/z\) (ESI+) found [M+H]\(^+\) 247.1624. C\(_{17}\)H\(_{22}\)O\(^+\) requires 247.1629.

Following general procedure G, reaction with 4-o-tolylcyclohexanone (4.0 g, 20.0 mmol) provided the title compound (3.1 g, 72%) as a colorless solid as a single diastereomer. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.27 (dd, \(J = 7.7, 0.8\) Hz, 1H), 7.16 (td, \(J = 7.5, 1.8\) Hz, 1H), 7.12 – 7.03 (m, 2H), 2.96 (t, \(J = 8.4\) Hz, 2H), 2.65 (tt, \(J = 12.1, 3.3\) Hz, 1H), 2.31 (s, 3H), 2.17 – 2.08 (m, 2H), 1.88 (ddd, \(J = 25.5, 13.3, 3.4\) Hz, 2H), 1.72 – 1.58 (m, 2H), 1.48 (dd, \(J = 13.8, 13.8\) Hz, 2H), 0.96 – 0.84 (m, 3H), 0.83 – 0.71 (m, 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.6, 135.1, 129.2, 126.8, 64.1, 43.2, 40.8, 33.7, 31.1, 24.7, 20.9; \(m/z\) (ESI+) found [M+H]\(^+\) 247.1624. C\(_{17}\)H\(_{22}\)O\(^+\) requires 247.1629.
Hz, 2H), 1.78 (t, \( J = 8.4 \) Hz, 2H), 1.69 (dd, \( J = 13.8, 3.3 \) Hz, 2H), 1.65 – 1.56 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 215.3, 144.7, 134.9, 130.1, 126.2, 125.8, 125.7, 64.2, 40.9, 39.1, 33.9, 30.2, 24.8, 19.4; \( m/z \) (ESI+) found [M+H]^+ 229.1557. C\(_{16}\)H\(_{21}\)O requires 229.1587.

\( ^{45,7S} \)-7-(4-methoxyphenyl)spiro[3.5]nonan-1-one, 6g

\[ \text{O} \]
\[ \text{OMe} \]

Following general procedure G, reaction with 4-methoxyphenylcyclohexanone\(^{58}\) (1.0 g, 4.9 mmol) provided the title compound (0.89 g, 78%) as a colorless solid as a single diastereomer. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.14 (d, \( J = 8.7 \) Hz, 2H), 6.82 (d, \( J = 8.7 \) Hz, 2H), 3.77 (s, 3H), 2.95 (t, \( J = 8.4, 8.4 \) Hz, 2H), 2.39 (tt, \( J = 11.9, 11.9, 3.6, 3.6 \) Hz, 1H), 2.09 (d, \( J = 13.7 \) Hz, 2H), 1.97 – 1.69 (m, 6H), 1.68 – 1.48 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 215.6, 158.0, 139.3, 127.9, 113.9, 64.3, 55.4, 42.9, 41.0, 33.9, 31.4, 24.9; \( m/z \) (ESI+) found [M+H]^+ 245.1551. C\(_{16}\)H\(_{21}\)O\(_2\) requires 245.1536.

\( ^{45,7S} \)-7-(4-chlorophenyl)spiro[3.5]nonan-1-one, 6h

\[ \text{Cl} \]

Following general procedure G, reaction with 4-chlorophenylcyclohexanone\(^{60}\) (1.6 g, 7.7 mmol) provided the title compound (1.2 g, 67%) as a colorless solid. \(^1\)H NMR (500 MHz, DMSO) \( \delta \) 7.40 – 7.27 (m, 2H), 7.27 – 7.13 (m, 2H), 3.08 – 2.86 (m, 2H), 2.50 – 2.44 (m, 1H), 2.06 (d, \( J = 13.8 \) Hz, 2H), 1.76 – 1.70 (m, 3H), 1.70 – 1.64 (m, 3H), 1.59 – 1.50 (m, 2H). \(^{13}\)C NMR (126 MHz, DMSO) \( \delta \) 214.9, 145.6, 130.4, 128.4, 128.2, 63.1, 41.7, 40.5, 32.6, 30.5, 24.0; \( m/z \) (ESI+) found [M+H]^+ 249.1048. C\(_{15}\)H\(_{18}\)ClO\(_2\) requires 249.1041.
General procedure H: Azido Schmidt reaction with cyclobutanones 6

1-(2-Hydroxyethyl)-1-azaspiro[4.5]decan-2-one, 8aa

Boron trifluoride etherate (2.3 mL, 27 mmol) was added to a solution of cyclobutanone 6a (0.75 g, 5.4 mmol) in dichloromethane (40 mL) at -78° C under argon. The mixture was stirred at -78° C for 30 min then a solution of azidoalcohol 7a (1.4 g, 16 mmol) in dichloromethane (10 mL) was added. The solution was stirred at -78° C for 3 h then allowed to warm to room temperature and stirred for an additional 12 h. The reaction was then concentrated on a rotary evaporator and the resulting oil was dissolved in 15% aqueous potassium hydroxide solution and stirred for 30 min, then extracted with dichloromethane (x 3). The combined organics were washed with water, dried (MgSO₄) and concentrated. The crude product was purified by automated column chromatography (40 g silica column, 0 to 100% EtOAc in hexanes over 30 min) to afford the title compound (0.74 g, 70%) as a colorless viscous oil. 

$^1$H NMR (400 MHz, CDCl₃) δ 4.17 (J = 5.3 Hz, 1H), 3.65 (q, J = 5.1 Hz, 2H), 3.34 – 3.20 (m, 2H), 2.33 (t, J = 8.1 Hz, 2H), 1.89 (t, J = 8.1 Hz, 2H), 1.72 – 1.57 (m, 3H), 1.44 (dd, J = 8.9, 3.0 Hz, 4H), 1.33 (ddt, J = 16.3, 8.1, 4.3 Hz, 2H), 1.03 (qt, J = 12.9, 3.7 Hz, 1H). 

$^{13}$C NMR (101 MHz, CDCl₃) δ 177.3, 64.6, 63.8, 43.0, 35.1, 29.2, 29.1, 25.0, 22.9.

(5R,8S)-1-(2-Hydroxyethyl)-8-propyl-1-azaspiro[4.5]decan-2-one, 8ca

Following general procedure H, reaction with cyclobutanone 6c (1.2 g, 6.7 mmol) and azidoalcohol 7a (1.7 g, 20 mmol) provided the title compound (1.1 g, 68%) as a colorless oil. 

$^1$H NMR (400 MHz, CDCl₃) δ 4.31 (t, J = 5.0, 5.0 Hz, 1H), 3.58 (q, J = 5.2, 5.2, 5.1 Hz, 2H), 3.21 (t, J = 5.5, 5.5 Hz, 2H), 2.25 (t, J = 8.1, 8.1 Hz, 2H), 1.84 (t, J = 8.1, 8.1 Hz, 2H), 1.68 – 1.35 (m, 7H), 1.31 – 1.04 (m, 6H), 0.79 (t, J = 7.0, 7.0 Hz, 3H). 

$^{13}$C NMR (100 MHz, CDCl₃) δ 176.8, 64.6, 62.9, 42.8, 32.4, 30.6, 29.5, 29.2, 29.0, 26.2, 20.8, 14.2; m/z (ESI+) found [M+H]$^+$ 240.1966. C₁₄H₂₆NO₂$^+$ requires 240.1955.
(5S,8S)-1-(2-Hydroxyethyl)-8-phenyl-1-azaspiro[4.5]decan-2-one, 8da

Following general procedure H, reaction with cyclobutanone 6d (1.5 g, 7.0 mmol) and azidoalcohol 7a (1.7 g, 21 mmol) provided the title compound (1.7 g, 87%) as a colorless oil. \(^1\)H NMR (500 MHz, DMSO) δ 7.43 – 7.31 (m, 4H), 7.20 (td, \(J = 7.3, 0.4\) Hz, 1H), 4.69 (br s, 1H), 3.28 (t, \(J = 6.9\) Hz, 2H), 2.99 – 2.90 (m, 3H), 2.25 – 2.11 (m, 4H), 1.95 – 1.85 (m, 4H), 1.63 (td, \(J = 13.0, 3.6\) Hz, 2H), 1.37 – 1.29 (m, 2H). \(^13\)C NMR (126 MHz, DMSO) δ 174.1, 143.4, 128.4, 128.2, 125.6, 62.6, 59.1, 41.9, 34.9, 30.7, 29.6, 28.7, 26.3; \(m/z\) (ESI+) found [M+H]\(^+\) 274.1806. C\(_{17}\)H\(_{24}\)NO\(_2\)\(^+\) requires 274.1798.

(5S,8S)-1-(2-Hydroxyethyl)-8-[p-tolyl]-1-azaspiro[4.5]decan-2-one, 8ea

Following general procedure H, reaction with cyclobutanone 6e (800 mg, 3.5 mmol) and azidoalcohol 7a (900 mg, 10.5 mmol) provided the title compound (860 mg, 85%) as a colorless oil. \(^1\)H NMR (500 MHz, DMSO) δ 7.28 (d, \(J = 8.0\) Hz, 2H), 7.15 (d, \(J = 7.9\) Hz, 2H), 4.68 (br s, 1H), 3.28 (d, \(J = 7.1\) Hz, 2H), 2.91 (t, \(J = 7.2\) Hz, 3H), 2.28 (s, 3H), 2.21 (t, \(J = 7.9\) Hz, 2H), 2.18 – 2.09 (m, 2H), 1.98 – 1.77 (m, 3H), 1.67 – 1.54 (m, 2H), 1.31 (d, \(J = 13.2\) Hz, 2H). \(^13\)C NMR (126 MHz, DMSO) δ 174.0, 140.1, 134.4, 129.0, 127.1, 62.7, 59.1, 41.8, 34.4, 30.5, 29.5, 28.7, 26.2, 20.5; \(m/z\) (ESI+) found [M+H]\(^+\) 288.1968. C\(_{18}\)H\(_{26}\)NO\(_2\)\(^+\) requires 288.1955.
(5S,8S)-1-(2-Hydroxyethyl)-8-(4-methoxyphenyl)-1-azaspiro[4.5]decan-2-one, 8ga and (5S,8S)-2-(2-Hydroxyethyl)-8-(4-methoxyphenyl)-2-azaspiro[4.5]decan-1-one, 9ga

Following general procedure H, reaction with cyclobutanone 6g (1.0 g, 4.1 mmol) and azidoalcohol 7a (1.1 g, 12.3 mmol) provided the title compounds 8ga (930 mg, 75%) and 9ga (120 mg, 10%) as colorless oils.

8ga: $^1$H NMR (500 MHz, DMSO) $\delta$ 7.30 (d, $J = 8.4$ Hz, 2H), 6.93 – 6.88 (m, 2H), 4.69 (t, $J = 5.7$ Hz, 1H), 3.74 (s, 3H), 3.30-3.26 (m, 2H), 2.97 – 2.85 (m, 3H), 2.21 (t, $J = 7.9$ Hz, 2H), 2.16 – 2.05 (m, 2H), 1.97 – 1.81 (m, 4H), 1.62 (td, $J = 12.9$, 3.5 Hz, 2H), 1.30 (d, $J = 13.2$ Hz, 2H). $^{13}$C NMR (100 MHz, DMSO) $\delta$ 174.0, 157.0, 134.9, 128.1, 113.6, 62.6, 59.0, 54.9, 41.8, 34.0, 30.4, 29.5, 28.7, 26.3; m/z (ESI+) found [M+H]$^+$ 304.1885. C$_{18}$H$_{26}$NO$_3$ requires 304.1913.

9ga: $^1$H NMR (500 MHz, DMSO) $\delta$ 7.30 (d, $J = 8.3$ Hz, 2H), 6.92 – 6.86 (m, 2H), 4.69 (s, 1H), 3.78 – 3.66 (m, 3H), 3.31 – 3.25 (m, 3H), 2.99 – 2.85 (m, 3H), 2.21 (t, $J = 7.9$ Hz, 2H), 2.12 (dd, $J = 14.1$, 2.6 Hz, 2H), 1.97 – 1.81 (m, 3H), 1.62 (td, $J = 12.9$, 3.5 Hz, 2H), 1.30 (d, $J = 13.2$ Hz, 2H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 174.0, 157.1, 134.9, 128.2, 113.7, 62.7, 59.1, 54.9, 41.8, 34.0, 30.5, 29.5, 28.7, 26.4; m/z (ESI+) found [M+H]$^+$ 304.1910. C$_{18}$H$_{26}$NO$_3$ requires 304.1913.

(5S,8S)-8-(4-Chlorophenyl)-1-(2-hydroxyethyl)-1-azaspiro[4.5]decan-2-one, 8ha and (5S,8S)-8-(4-Chlorophenyl)-2-(2-hydroxyethyl)-2-azaspiro[4.5]decan-1-one, 9ha

Following general procedure H, reaction with cyclobutanone 6h (500 mg, 2.0 mmol) and azidoalcohol 7a (500 mg, 6.0 mmol) provided the title compounds 8ha (450 mg, 72%) and 9ha (40 mg, 7%) as colorless oils.
8ha: \( ^1H \) NMR (500 MHz, DMSO) δ 7.49 – 7.31 (m, 4H), 4.67 (t, \( J = 5.8 \) Hz, 1H), 3.31 – 3.24 (m, 2H), 3.00 – 2.85 (m, 3H), 2.22 (t, \( J = 7.9 \) Hz, 2H), 2.13 (d, \( J = 11.6 \) Hz, 2H), 1.98 – 1.82 (m, 4H), 1.68 – 1.51 (m, 2H), 1.32 (d, \( J = 13.3 \) Hz, 2H). \(^{13}C\) NMR (126 MHz, DMSO) δ 174.1, 142.3, 130.2, 129.3, 128.2, 62.6, 59.1, 41.9, 34.4, 30.5, 29.5, 28.7, 26.1; m/z (ESI+) found [M+H]+ 308.1402. C\(_{17}\)H\(_{23}\)ClNO\(_2\)+ requires 308.1409.

9ha: \( ^1H \) NMR (500 MHz, DMSO) δ 7.38 – 7.31 (m, 2H), 7.29 – 7.21 (m, 2H), 4.70 (t, \( J = 5.2 \) Hz, 1H), 3.47 (dd, \( J = 10.8, 5.6 \) Hz, 2H), 3.35 (d, \( J = 4.7 \) Hz, 2H), 3.21 (t, \( J = 5.9 \) Hz, 2H), 2.54 (dd, \( J = 7.9, 3.6 \) Hz, 1H), 2.16 (qd, \( J = 12.7, 3.5 \) Hz, 2H), 1.84 (d, \( J = 13.8 \) Hz, 2H), 1.76 (t, \( J = 6.8 \) Hz, 2H), 1.64 – 1.51 (m, 2H), 1.41 (td, \( J = 13.2, 3.8 \) Hz, 2H); \(^{13}C\) NMR (126 MHz, DMSO) δ 177.6, 146.1, 130.2, 128.6, 128.2, 58.6, 44.6, 43.9, 41.7, 41.1, 34.6, 33.7, 28.9; m/z (ESI+) found [M+H]+ 308.1420. C\(_{17}\)H\(_{23}\)ClNO\(_2\)+ requires 308.1417.

1-(3-hydroxypropyl)-1-azaspiro[4.5]decan-2-one, 8ab

Following general procedure H, reaction with cyclobutanone 6a (500 mg, 2.0 mmol) and azidoalcohol 7b (1.8 g, 17.4 mmol) provided the title compound (430 mg, 35%) as a colorless oil. \(^1H\) NMR (500 MHz, DMSO) δ 4.70 (t, \( J = 5.7 \) Hz, 1H), 3.43 – 3.33 (m, 3H), 3.10 (t, \( J = 7.2 \) Hz, 2H), 2.18 (t, \( J = 8.0 \) Hz, 2H), 1.81 (t, \( J = 8.0 \) Hz, 2H), 1.68 – 1.60 (m, 2H), 1.56 (dd, \( J = 11.7, 5.2 \) Hz, 2H), 1.51 (dd, \( J = 13.0, 3.9 \) Hz, 2H), 1.42 – 1.26 (m, 4H), 1.15 – 1.01 (m, 1H). \(^{13}C\) NMR (126 MHz, DMSO) δ 174.0, 63.0, 59.5, 41.4, 40.7, 34.5, 28.7, 28.4, 24.5, 22.6; m/z (ESI+) found [M+H]+ 212.1650. C\(_{12}\)H\(_{22}\)NO\(_2\)+ requires 212.1642.

(5S,8S)-1-(3-Hydroxypropyl)-8-methyl-1-azaspiro[4.5]decan-2-one, 8bb and (5S,8S)-2-(3-hydroxypropyl)-8-methyl-2-azaspiro[4.5]decan-1-one, 9bb

Following general procedure H, reaction with cyclobutanone 6b (750 mg, 4.9 mmol) and azidoalcohol 7b (1.5 g, 15 mmol) provided the title compounds 8bb (440 mg, 40%) and 9bb (500 mg, 45%) as colorless oils.
8bb: $^1$H NMR (400 MHz, CDCl$_3$) δ 3.61 – 3.42 (m, 2H), 3.38 – 3.25 (m, 2H), 2.33 (t, $J = 7.9$ Hz, 2H), 1.87 (dd, $J = 9.9$, 6.1 Hz, 3H), 1.78 (td, $J = 13.2$, 3.9 Hz, 2H), 1.69 – 1.53 (m, 5H), 1.51 – 1.39 (m, 2H), 1.19 (d, $J = 12.9$ Hz, 2H), 0.95 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.5, 65.1, 58.2, 35.2, 33.2, 29.21, 29.20, 29.1, 28.3, 25.6, 17.0; m/z (ESI+) found [M+H]$^+$ 226.1778. C$_{13}$H$_{24}$NO$_2$$^+$ requires 226.1798.

9bb: $^1$H NMR (400 MHz, CDCl$_3$) δ 3.71 (s, 1H), 3.43 (t, $J = 5.5$ Hz, 2H), 3.40 – 3.29 (m, 2H), 3.21 (t, $J = 6.9$ Hz, 2H), 1.92 – 1.74 (m, 4H), 1.67 – 1.58 (m, 2H), 1.58 – 1.40 (m, 6H), 1.32 – 1.14 (m, 2H), 0.91 (d, $J = 6.0$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.3, 58.0, 44.3, 38.5, 33.3, 32.0, 30.0, 29.4, 29.3, 20.3; m/z (ESI+) found [M+H]$^+$ 226.1776. C$_{13}$H$_{24}$NO$_2$$^+$ requires 226.1798.

(5S,8S)-1-(3-hydroxypropyl)-8-phenyl-1-azaspiro[4.5]decan-2-one, 8db and (5S,8S)-2-(3-hydroxypropyl)-8-phenyl-2-azaspiro[4.5]decan-1-one, 9db

Following general procedure H, reaction with cyclobutanone 6d (1.5 g, 7.0 mmol) and azidoalcohol 7b (2.1 g, 21 mmol) provided the title compounds 8db (840 mg, 42%) and 9db (800 mg, 40%) as colorless oils.

8db: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.28 (d, $J = 4.4$ Hz, 4H), 7.19 – 7.12 (m, 1H), 4.25 (s, 1H), 3.42 (t, $J = 5.7$ Hz, 2H), 3.23 – 3.11 (m, 2H), 3.03 – 2.90 (m, 1H), 2.36 (dd, $J = 8.4$, 7.4 Hz, 2H), 2.19 (dtd, $J = 12.0$, 4.1, 3.5, 1.7 Hz, 2H), 1.95 (t, $J = 7.9$ Hz, 2H), 1.93 – 1.81 (m, 2H), 1.74 (td, $J = 12.9$, 3.7 Hz, 2H), 1.55 – 1.39 (m, 2H), 1.32 (dt, $J = 13.4$, 3.1 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.4, 143.0, 128.5, 127.2, 125.9, 64.6, 58.1, 35.4, 35.3, 33.0, 31.0, 30.3, 29.2, 26.8.

9db: $^1$H NMR (500 MHz, DMSO) δ 7.31 – 7.26 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.13 (m, 1H), 4.45 (br s, 1H), 3.43 – 3.36 (m, 2H), 3.27 (t, $J = 6.8$ Hz, 2H), 3.20 (t, $J = 7.1$ Hz, 2H), 2.58 – 2.51 (m, 1H), 2.25 – 2.12 (m, 2H), 1.82 (d, $J = 13.8$ Hz, 2H), 1.77 (t, $J = 6.8$ Hz, 2H), 1.63 – 1.53 (m, 3H), 1.42 (td, $J = 13.3$, 3.8 Hz, 2H). $^{13}$C NMR (126 MHz, DMSO) δ 177.5, 147.1, 128.3, 126.7, 125.8, 58.4, 43.1, 42.4, 41.3, 39.0, 34.6, 33.9, 30.1, 29.0; m/z (ESI+) found [M+H]$^+$ 288.1936. C$_{18}$H$_{26}$NO$_2$$^+$ requires 288.1955.
(SS,SR)-1-((S)-2-Hydroxy-2-phenylethyl)-8-methyl-1-azaspiro[4.5]decan-2-one, 8bc

Following general procedure H, reaction with cyclobutanone 6b (500 mg, 3.3 mmol) and azidoalcohol 7c (1.6 g, 9.9 mmol) provided the title compound (520 mg, 55%) as a colorless oil. 

$^1$H NMR (500 MHz, DMSO) $\delta$ 7.37 – 7.30 (m, 4H), 7.26 – 7.20 (m, 1H), 5.49 (d, $J = 4.5$ Hz, 1H), 4.88 (dt, $J = 7.3, 4.9$ Hz, 1H), 3.26 – 3.10 (m, 2H), 2.22 (t, $J = 8.1$ Hz, 2H), 1.89 – 1.66 (m, 4H), 1.64 – 1.51 (m, 2H), 1.51 – 1.42 (m, 1H), 1.33 – 1.23 (m, 1H), 1.18 (dd, $J = 13.0, 2.4$ Hz, 1H), 0.93 (d, $J = 7.2$ Hz, 3H), 0.80 (dd, $J = 12.4, 2.5$ Hz, 1H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 175.1, 143.9, 127.9, 127.0, 126.0, 70.7, 63.4, 48.4, 28.8, 28.6, 28.4, 27.9, 27.9, 25.2, 16.9; m/z (ESI+) found [M+H]$^+$ 288.1973. C$_{18}$H$_{26}$NO$_2$ requires 288.1958.

(5S,SR)-1-((S)-3-Hydroxy-3-phenylpropyl)-8-phenyl-1-azaspiro[4.5]decan-2-one, 8dd and (5S,SR)-2-((S)-3-hydroxy-3-phenylpropyl)-8-phenyl-2-azaspiro[4.5]decan-1-one, 9dd

Following general procedure H, reaction with cyclobutanone 6d (500 mg, 2.3 mmol) and azidoalcohol 7d (1.2 g, 6.6 mmol) provided the title compounds 8dd (340 mg, 40%) and 9dd (340 mg, 40%) as colorless oils.

8dd: 

$^1$H NMR (500 MHz, DMSO) $\delta$ 7.32 (d, $J = 4.4$ Hz, 4H), 7.29 – 7.22 (m, 4H), 7.22 – 7.17 (m, 2H), 5.26 (d, $J = 4.3$ Hz, 1H), 4.52 – 4.38 (m, 1H), 3.10 – 2.95 (m, 2H), 2.94 – 2.85 (m, 1H), 2.26 – 2.17 (m, 2H), 2.08 (d, $J = 11.3$ Hz, 2H), 1.97 – 1.82 (m, 4H), 1.76 – 1.59 (m, 4H), 1.38 – 1.28 (m, 2H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 173.8, 145.4, 143.7 (u), 128.3, 128.0, 127.2, 126.7, 125.6, 125.6, 70.3, 62.8, 39.2, 36.7, 35.6, 31.3, 30.9, 30.3, 28.8, 26.6, 26.6; m/z (ESI+) found [M+H]$^+$ 364.2286. C$_{24}$H$_{30}$NO$_2$ requires 364.2285.

9dd: 

$^1$H NMR (500 MHz, DMSO) $\delta$ 7.29 (m, 10H), 5.32 (s, 1H), 4.55 (s, 1H), 3.40, 3.26 (s, 4H), 2.51 (s, 1H), 2.21 (d, $J = 11.0$ Hz, 2H), 1.77 (m, 6H), 1.58 (d, $J = 7.9$ Hz, 2H), 1.41 (d, $J = 10.8$ Hz, 2H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 177.5, 147.1, 145.9, 128.2, 128.0, 126.7, 126.7, 125.7, 125.7, 70.3, 43.1, 42.5, 41.3, 39.2, 36.8, 34.6, 33.9, 29.0; m/z (ESI+) found [M+H]$^+$ 364.2286. C$_{24}$H$_{30}$NO$_2$ requires 364.2271.
Following general procedure H, reaction with cyclobutanone 6f (500 g, 2.2 mmol) and azidoalcohol 7b (1.2 g, 6.6 mmol) provided the title compounds 8fd (310 mg, 38%) and 9fd (330 mg, 40%) as colorless oils.

8fd: $^1$H NMR (500 MHz, DMSO) $\delta$ 7.35 – 7.27 (m, 4H), 7.26 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 7.11 – 7.07 (m, 1H), 5.36 (d, $J = 4.2$ Hz, 1H), 4.64 – 4.48 (m, 1H), 3.44 – 3.36 (m, 1H), 3.34 – 3.26 (m, 1H), 3.03 – 2.88 (m, 1H), 2.28 (s, 3H), 2.26 – 2.20 (m, 2H), 1.96 – 1.70 (m, 10H), 1.62 – 1.45 (m, 2H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 173.9, 145.6, 144.2, 135.2, 130.3, 128.0, 126.7, 126.0, 125.8, 125.6, 70.4, 61.7, 40.4, 39.3, 38.0, 34.4, 33.9, 33.7, 32.7, 28.9, 27.3, 27.2, 19.2; m/z (ESI+) found [M+H]$^+$ 378.2438. C$_{25}$H$_{32}$NO$_2$ + requires 378.2428.

9fd: $^1$H NMR (500 MHz, DMSO) $\delta$ 7.39 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 7.26 – 7.19 (m, 2H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.11 (d, $J = 7.0$ Hz, 1H), 7.04 (td, $J = 7.4$, 1.2 Hz, 1H), 5.33 (d, $J = 4.4$ Hz, 1H), 4.63 – 4.46 (m, 1H), 3.39 (t, $J = 7.4$ Hz, 2H), 3.25 (t, $J = 6.8$ Hz, 2H), 2.75 – 2.63 (m, 1H), 2.29 (s, 3H), 2.27 – 2.14 (m, 2H), 1.89 – 1.82 (m, 2H), 1.82 – 1.75 (m, 2H), 1.75 – 1.68 (m, 2H), 1.54 – 1.38 (m, 4H); $^{13}$C NMR (126 MHz, DMSO) $\delta$ 177.5, 145.9, 145.3, 134.6, 130.0, 128.0, 126.7, 126.0, 125.7, 125.4, 70.3, 43.1, 41.1, 39.1, 38.7, 36.8, 35.0, 34.6, 34.5, 28.4, 19.0; m/z (ESI+) found [M+H]$^+$ 378.2449. C$_{25}$H$_{32}$NO$_2$ + requires 378.2428.

**General procedure I: Lactam reduction**

2-((5R*,8S*)-8-propyl-1-azaspiro[4.5]decan-1-yl)ethanol, 10ca

Lithium aluminum hydride (1M solution in diethyl ether, 2.5 mL, 2.5 mmol) was added to a solution of lactam 8ca (0.14 g, 0.56 mmol) in anhydrous THF (2.0 mL) under argon. The reaction was heated
at reflux for 8 h, then cooled to 0° C and quenched by slow addition of sodium sulfate decahydrate (excess). The reaction was allowed to warm to rt and filtered through Celite® to remove the salts. The filtrate was concentrated, dissolved in ethyl acetate (50 mL), and washed with brine (3x50 mL). The combined organics were dried (Na$_2$SO$_4$) and concentrated to afford the title compound (0.10 g, 78%) as a colorless solid, which was used without further purification.\textsuperscript{1}H NMR (400 MHz, CDCl$_3$) $\delta$ 3.69 – 3.60 (m, 4H), 3.56 (t, $J = 5.4$ Hz, 2H), 2.86 – 2.76 (m, 1H), 2.65 (t, $J = 5.4$ Hz, 1H), 1.73 (dd, $J = 4.1$, 2.5 Hz, 3H), 1.70 – 1.58 (m, 5H), 1.58 – 1.47 (m, 4H), 1.27 (ddd, $J = 7.0$, 4.4, 2.7 Hz, 3H), 1.09 (s, 1H), 0.96 – 0.82 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 62.4, 62.3, 58.8, 50.0, 49.7, 34.1, 33.0, 31.9, 29.9, 27.6, 27.0, 21.0, 14.3; $m/z$ (ESI+) found [M+H]$^+$ 226.2220. C$_{14}$H$_{28}$NO$^+$ requires 226.2165.

2-\((5R,8S)\)-Phenyl-1-azaspiro[4.5]decan-1-yl)ethanol, 10da

Following general procedure I, reaction with lactam 8da (2.2 g, 8.1 mmol) provided the title compound (1.4 g, 65%) as an oil.\textsuperscript{1}H NMR (500 MHz, DMSO) $\delta$ 7.39 – 7.26 (m, 4H), 7.71 (d, $J = 1.6$, 7.5 Hz, 1H), 4.28 (s, 1H), 3.39 – 3.35 (m, 2H), 2.88 – 2.87 (m, 1H), 2.74 (t, $J = 7.0$ Hz, 2H), 2.35 (tt, $J = 6.8$ Hz, 2H), 2.66 – 1.99 (m, 2H), 1.82 – 1.65 (m, 4H), 1.67 – 1.57 (m, 2H), 1.48 – 1.41 (m, 2H), 1.18 – 1.12 (m, 2H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 144.7, 128.2, 127.0, 125.4, 62.9, 60.7, 50.6, 50.5, 37.7, 35.2, 29.4, 28.0, 20.8; $m/z$ (ESI+) found [M+H]$^+$ 260.1989. C$_{17}$H$_{26}$NO$^+$ requires 260.1976.

\((S,S,S)\)-1-\((3\text{-Hydroxypropyl})\)-8-phenyl-1-azaspiro[4.5]decan-2-one , 10db

Following general procedure I, reaction with lactam 8db (1.0 g, 3.5 mmol) provided the title compound (620 mg, 65%) as an oil.\textsuperscript{1}H NMR (400 MHz, CDCl$_3$) $\delta$ 7.27 (dt, $J = 12.9$, 7.5 Hz, 4H), 7.16 – 7.08 (m, 1H), 3.83 – 3.67 (m, 2H), 2.88 – 2.82 (m, 2H), 2.79 (d, $J = 5.4$ Hz, 1H), 2.61 – 2.48 (m, 2H), 2.02 (dd, $J = 12.2$, 6.5, 2.9 Hz, 2H), 1.79 – 1.65 (m, 10H), 1.22 (ddd, $J = 17.7$, 7.8, 4.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 145.1, 128.3, 127.3, 125.6, 65.2, 64.0, 50.0, 49.3, 38.8, 35.5, 29.8, 28.5, 20.8.
General procedure J: Cyclobutanone reduction

Spiro[3.5]nonan-1-ol, S9a

\[
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbf{OH}}};
\end{tikzpicture}}
\]

Sodium borohydride (2.5 g, 66 mmol) was added to a solution of cyclobutanone 6a (3.6 g, 26 mmol) in THF (120 mL), followed by dropwise addition of methanol (12 ml). The solution was stirred at room temperature for 8 h. The reaction was quenched by the slow addition of acetone at 0° C. Water was then added and the solution extracted dichloromethane (x3). The combined organics were washed with brine, dried (\(\text{Na}_2\text{SO}_4\)) and concentrated. The crude product was purified by automated column chromatography (40 g silica column, 0 to 30% EtOAc in hexanes over 30 min) to afford the title compound (3.5 g, 95%) as a colorless oil. The NMR data closely matched that previously reported.$^{61}$

(1R,4R,7S)-7-Propylspiro[3.5]nonan-1-ol, S9c

\[
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbf{OH}}};
\end{tikzpicture}}
\]

Following general procedure J, reaction with ketone 6c (1.8 g, 10 mmol) provided the title compound (1.7 g, 94%) as a colorless oil.$^1$H NMR (400 MHz, CDCl$_3$) \(\delta\) 3.88 (t, \(J = 7.4\) Hz, 1H), 2.24 – 2.09 (m, 1H), 2.01 – 1.92 (m, 1H), 1.70 (dddd, \(J = 11.7, 10.4, 9.0, 7.2\) Hz, 1H), 1.62 – 1.46 (m, 3H), 1.45 – 1.38 (m, 1H), 1.32 – 1.09 (m, 9H), 1.09 – 0.95 (m, 1H), 0.82 (t, \(J = 7.2\) Hz, 3H).$^{13}$C NMR (101 MHz, CDCl$_3$) \(\delta\) 74.9, 45.2, 38.5, 37.9, 36.1, 30.3, 30.1, 29.3, 27.3, 26.6, 20.2, 14.4 (dn).

(1R,4S,7S)-7-Phenylspiro[3.5]nonan-1-ol, S9d

\[
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbf{OH}}};
\end{tikzpicture}}
\]

Following general procedure J, reaction with ketone 6d (5.4 g, 25 mmol) provided the title compound (5.3 g, 97%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) \(\delta\) 7.37 – 7.19 (m, 5H), 4.10 (t, \(J = 7.3\) Hz, 1H), 2.53 (qd, \(J = 9.7, 8.5, 3.2\) Hz, 1H), 2.40 – 2.24 (m, 2H), 1.88 – 1.77 (m, 5H), 1.75 – 1.63 (m,
1H), 1.62 – 1.50 (m, 2H), 1.49 – 1.30 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 147.5, 128.3, 126.9, 125.9, 75.0, 44.6, 43.7, 39.1, 31.9, 31.9, 30.7, 27.5, 26.9.

C. Experimental procedures and characterization data for sparteine-inspired scaffolds.

Supplementary Figure 6. Synthesis of sparteine-inspired scaffolds

Bicyclo[2.2.1]heptane-2,5-dione, S11

In a 1L round bottom flask, 2, 5-norbornadiene (100 g, 1.08 mol) and 97% formic acid (600 mL) was added under an argon atmosphere. The reaction was refluxed at $120 \, ^\circ C$ for 24h then the formic acid was distilled off and the diformate S10 was obtained by vacuum distillation (120-130 ºC at 10 mmHg) as a clear liquid. The crude diformate (198.7 g, 1.07 mol) was placed in a 3L round bottom flask and dissolved in THF (1.5 l). The solution was cooled to 0 ºC and a solution of NaOH (424 g) in water (600 mL) was added via a dropping funnel over 30 min. The reaction mixture was stirred at room temperature for 10 h then extracted with ethyl acetate. The aqueous layer was saturated with sodium chloride then extracted again with ethyl acetate. The combined organics were dried (MgSO$_4$) and concentrated to obtain the crude diol (100 g) as a colorless solid. The diol was vacuum dried for 4h and transferred to a three-neck 4L round bottom flask fitted with a mechanical stirrer. Anhydrous dimethylsulfoxide (225 mL) was added and the mixture was stirred till the solution became
completely clear. The solution was diluted with dichloromethane (800 mL) and phosphorous pentoxide (450 g, 1.58 mol) was added. The reaction mixture was stirred vigorously for 1 h at rt then cooled to 0 °C and triethylamine (661 mL, 4.75 mol) was added dropwise over 1 h. After the addition was complete, the reaction was stirred at 0 °C for 1 h, then quenched with 10% aqueous HCl (800 mL) and extracted with dichloromethane (4 x 600 mL). The combined organics were dried (MgSO₄) and concentrated. The crude product was purified by chromatography (silica gel, 70:30 hexanes: ethyl acetate) to obtain the title compound (80 g, 60%) as a colorless oil. δ\(^{(1)}\)H (400 MHz, CDCl₃) 2.98 – 2.77 (m, 2H), 2.36 – 2.14 (m, 2H), 2.11 – 1.80 (m, 4H); δ\(^{(13)}\)C (100 MHz, CDCl₃) 212.3, 48.5, 38.8, 36.2. The spectral data was consistent with that previously reported.

\((15,4S,6S)\)-6-(4-azidobutyl)spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-5-one, 12

Methanesulfonyl chloride (4.83 mL, 62.4 mmol) was added dropwise to a solution of \((15,4S,6S)\)-6-(4-hydroxybutyl)spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-5-one (S12)\(^{(63)}\) (10 g, 41.6 mmol) in dichloromethane (200 mL) at 0 °C under argon. Triethylamine (8.68 mL, 62.4 mmol) was then added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The combined organics were dried (Na₂SO₄) and concentrated to afford the crude mesylate product. The product was dried over high vacuum for 30 min and the residue was dissolved in DMF (100 mL). Sodium azide (9.42 g, 14.5 mmol) was added to the solution and the mixture was heated at 50 °C for 7 h, then diluted with water and extracted with ethyl acetate. The combined organics were dried (Na₂SO₄) and concentrated. The crude product was purified by chromatography (90:10 hexanes/ethyl acetate) to afford the title compound (10.1 g, 92%) as a colorless liquid. δ\(^{(1)}\)H (400 MHz, CDCl₃) 4.15 – 3.57 (m, 2H), 3.27 (t, \(J = 6.8\) Hz, 2H), 2.56 (dd, \(J = 38.1, 3.6\) Hz, 2H), 2.23 – 1.97 (m, 3H), 1.92 – 1.26 (m, 8H); δ\(^{(13)}\)C (100 MHz, CDCl₃) 217.7, 115.0, 65.4, 63.5, 52.7, 51.2, 49.2, 45.9, 39.1, 36.5, 28.8, 26.7, 25.7. The spectral data was consistent with that previously reported.\(^{(63)}\)

\((7S,10S,10aS)\)-octahydro-7,10-methanopyrido[1,2-a]azepine-6,9-dione, 13

TiCl₄ (20.7 mL, 188.5 mmol) was added dropwise by syringe to a solution of azide 12 (10.0 g, 37.7 mmol) in dichloromethane (350 mL) at 0 °C under argon. The resulting yellow precipitate was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with water and extracted with dichloromethane. The combined organics were dried (Na₂SO₄) and concentrated to afford an oil. The crude product was purified by chromatography (silica gel, 100% EtOAc) to afford
the title compound (4.5 g, 62%) as a colorless solid. $\delta_H$ (400 MHz, CDCl$_3$) 4.53 (ddt, $J = 13.4, 4.1, 2.0$ Hz, 1H), 3.30 (ddd, $J = 11.8, 4.2, 2.6$ Hz, 1H), 3.05 (dt, $J = 5.4, 1.9$ Hz, 1H), 2.47 (dt, $J = 5.7, 3.4$ Hz, 1H), 2.41–2.24 (m, 3H), 2.18–2.02 (m, 2H), 1.85–1.51 (m, 3H), 1.40–1.10 (m, 3H); $\delta_C$ (100 MHz, CDCl$_3$) 214.7, 171.7, 59.2, 50.5, 43.7, 41.8, 41.0, 30.6, 30.6, 25.0, 24.2. The spectral data was consistent with that previously reported.

(7S,10S,10aS)-hexahydro-1H-spiro[7,10-methanopyrido[1,2-a]azepine-9,2'-[1,3]dioxolan]-6(2H)-one, 14

Chlorotrimethylsilane (13.1 mL, 103 mmol) was added dropwise to a solution of lactam 13 (5.0 g, 25.9 mmol) in dry ethylene glycol (80 mL) at room temperature under argon. The reaction mixture was stirred for 6 h at room temperature then water (50 mL) was added and the mixture extracted with diethyl ether (3 x 50 mL). The combined organics were dried (Na$_2$SO$_4$) and concentrated. The crude product was purified by chromatography (silica gel, 70:30 ethyl acetate/hexanes) to afford the title compound (4.29 g, 70%) as a colorless solid. Mp 90–91 °C; $\nu_{max}$ (film)/cm$^{-1}$ 2940, 1638; $\delta_H$ (400 MHz, CDCl$_3$) 4.52 (1H, ddt, $J_{13.3, 4.2, 2.0}$), 4.04–3.69 (4H, m), 3.19 (1H, dt, $J_{12.3, 2.9}$), 2.69 (1H, ddd, $J 7.3, 4.5, 1.6$), 2.36 (1H, td, $J 13.0, 3.2$), 2.27–1.98 (5H, m), 1.87–1.73 (2H, m), 1.70–1.58 (1H, m), 1.58–1.46 (1H, m), 1.42–1.16 (2H, m); $\delta_C$ (100 MHz, CDCl$_3$) 174.3, 117.1, 65.2, 63.3, 61.2, 46.0, 42.2, 42.0, 41.2, 32.5, 29.8, 25.3, 25.0; m/z (ESI+) found [M+H]$^+$ 238.143. C$_{13}$H$_{20}$NO$_3$ requires 238.1438.

(7S,9S,10S,10aS)-9-hydroxyoctahydro-7,10-methanopyrido[1,2-a]azepin-6(2H)-one, S13

Sodium borohydride (196 mg, 5.18 mmol) was added to a solution of lactam 13 (500 mg, 2.58 mmol) in methanol (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, then quenched with 10% aqueous NaOH and extracted with ethyl acetate. The combined organics were dried (MgSO$_4$) and concentrated. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound (444 mg, 88%) as a colorless solid as a single diastereomer. Mp 110–111 °C; $\nu_{max}$ (film)/cm$^{-1}$ 1623, 2931, 3355 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 4.60–4.38 (m, 2H), 3.32 (d, $J = 12.4$ Hz, 1H), 3.12 (s, 1H), 2.67–2.51 (m, 1H), 2.48–2.19 (m, 4H), 1.80 (dd, $J = 12.8, 1.6$ Hz, 1H), 1.75–1.53 (m, 5H), 1.43–1.10 (m, 2H); $\delta_C$ (100 MHz, CDCl$_3$) 175.1, 75.3, 62.7, 43.1, 42.2, 42.1, 38.3, 31.8, 30.6, 25.5, 25.2; m/z (ESI+) found [M+H]$^+$ 196.1330. C$_{13}$H$_{18}$NO$_3$ requires 196.1332.
To a solution of alcohol S13 (50 mg, 0.25 mmol) in dichloromethane (3 mL) was added triethylamine (0.071 mL, 0.51 mmol) and N,N-dimethylaminopyridine (2 mg). p-Bromobenzoyl chloride (84 mg, 0.38 mmol) was then added and the reaction mixture stirred at room temperature for 8 h. The solvent was evaporated and the crude reaction mixture was purified by chromatography (silica gel, 60:40 ethyl acetate/hexanes) to obtain the title compound (89 mg, 92%) as a colorless solid. Mp 130-132 °C; ν\text{max} (film)/cm\textsuperscript{-1} 1647, 1716, 2938; δ\text{H} (400 MHz, CDCl\textsubscript{3}) 7.93 – 7.76 (m, 2H), 7.67 – 7.50 (m, 2H), 5.50 – 5.37 (m, 1H), 4.66 – 4.52 (m, 1H), 3.36 (ddd, J = 12.3, 7.5, 4.7 Hz, 1H), 2.83 – 2.70 (m, 2H), 2.56 (m, 1H), 2.41 (td, J = 13.0, 3.1 Hz, 1H), 2.00 – 1.80 (m, 4H), 1.81 – 1.53 (m, 3H), 1.45 – 1.13 (m, 2H); δ\text{C} (100 MHz, CDCl\textsubscript{3}) 174.2, 165.9, 132.0, 131.2, 128.9, 128.5, 77.1, 62.2, 42.2, 41.6, 41.5, 35.2, 31.8, 30.5, 25.6, 25.3; m/z (ESI+) found [M+H]\textsuperscript{+} 378.0695. C\textsubscript{18}H\textsubscript{21}BrNO\textsubscript{3}\textsuperscript{+} requires 378.0699.

General procedure K: Grignard addition to lactam; reduction of aminal

(6R,7S,10S,10aS)-6-methyloctahydro-7,10-methanopyrido[1,2-\alpha]azepin-9(6H)-one, 15a

MeMgCl (2.8 mL, 8.4 mmol, 3M in THF) was added dropwise to a stirring solution of lactam 13 (500 mg, 2.1 mmol) in dry THF (20 mL). The mixture was heated at 60 °C for 3 h, then cooled to 0 °C and NaBH\textsubscript{3}CN (792 mg, 12.6 mmol) added followed by glacial acetic acid (1.0 mL). The reaction mixture was stirred for 1 h at room temperature then quenched with 10% aqueous NaOH (10 mL) and extracted with ethyl acetate (3 x 50mL). The combined organics were dried (MgSO\textsubscript{4}) and concentrated. The residue was dissolved in conc. HCl (2 mL) and acetone (20 mL) and refluxed for 2 h. The reaction mixture was cooled to 0 °C and basified to pH >10 by addition of 10 % aqueous NaOH and extracted with ethyl acetate. The combined organics were dried (MgSO\textsubscript{4}) and concentrated. The crude product was purified by chromatography (silica gel, 1:4:0.5 ethyl acetate/hexanes/\text{NH}_4\text{OH}) to afford the title compound (354 mg, 87%) as a colorless oil as a single diastereomer. ν\text{max} (film)/cm\textsuperscript{-1}; δ\text{H} (400 MHz, CDCl\textsubscript{3}) 3.05 (m, 1H), 2.43 (m, 1H), 2.33 – 2.22 (m, 2H), 2.14 (m,1H), 2.06 – 1.91 (m, 3H), 1.86 – 1.77 (m, 1H), 1.75 – 1.61 (m, 3H), 1.61 – 1.10 (m, 5H), 1.06 (d, J = 6.3 Hz, 3H); δ\text{C} (100 MHz, CDCl\textsubscript{3}) 218.6, 67.5, 61.1, 52.2, 51.2, 40.5, 39.8, 37.3, 30.3, 25.9, 24.6, 19.0; m/z (ESI+) found [M+H]\textsuperscript{+} 194.1530. C\textsubscript{12}H\textsubscript{18}NO\textsubscript{3}\textsuperscript{+} requires 194.1539.
Following general procedure K, reaction of lactam 13 (500 mg, 2.1 mmol) and n-butylmagnesium chloride (2M in THF, 4.2 ml, 8.4 mmol) provided the title compound (400 mg, 88%) as a colorless oil. ν_{max} (film)/cm⁻¹ 2933, 1741; δ_{H} (400 MHz, CDCl₃) 3.08 (d, J = 11.2 Hz, 1H), 2.42 (s, 1H), 2.27 – 2.03 (m, 3H), 2.01 – 1.84 (m, 3H), 1.71 (dd, J = 11.0, 3.6 Hz, 1H), 1.67 – 1.55 (m, 3H), 1.55 – 1.02 (m, 10H), 0.83 (dd, J = 10.0, 4.0 Hz, 3H); δ_{C} (100 MHz, CDCl₃) 218.1, 67.5, 66.4, 52.1, 51.1, 39.8, 36.8, 36.6, 31.3, 30.4, 29.6, 25.8, 24.5, 23.1, 14.1; m/z (ESI+) found [M+H]^+ 236.2004. C_{15}H_{26}NO_{+} requires 236.2009.

Following general procedure K, reaction of lactam 13 (500 mg, 2.1 mmol) and benzylmagnesium chloride (2M in THF, 4.2 ml, 8.4 mmol) provided the title compound (429 mg, 87%) as a colorless liquid. ν_{max} (film)/cm⁻¹ 1740, 2935 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.30 (dd, J = 10.1, 4.5 Hz, 2H), 7.21 (dd, J = 8.4, 6.3 Hz, 1H), 7.17 – 7.08 (m, 2H), 3.34 (d, J = 11.2 Hz, 1H), 3.20 (dd, J = 13.6, 4.1 Hz, 1H), 2.58 (ddd, J = 9.9, 4.1, 1.4 Hz, 1H), 2.41-2.36 (m, 2H), 2.27 – 2.14 (m, 2H), 2.07 – 1.78 (m, 4H), 1.78 – 1.38 (m, 6H), 1.35 – 1.14 (m, 1H); δ_{C} (100 MHz, CDCl₃) 217.7, 139.8, 129.4, 128.5, 126.1, 67.7, 67.5, 52.1, 51.3, 39.5, 37.6, 36.6, 35.2, 30.4, 25.9, 24.5; m/z (ESI+) found [M+H]^+ 270.1855. C_{18}H_{24}NO_{+} requires 270.1852.

4-Nitrophenyl carbonate, 39

4-nitropheryl chloroformate (1.86 g, 9.2 mmol) was added to a solution of alcohol S13 (1.5 g, 7.68 mmol) and pyridine (0.92 ml, 11.5 mmol) in anhydrous THF (40 ml) at room temperature under argon. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the crude residue was purified by chromatography (silica gel, 7:3 EtOAc/hexane) to afford the
title compound (2.62 g, 95%) as a colorless solid. $\nu$ \text{max} (film)/cm$^{-1}$ 1740, 2935 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 8.32 – 8.24 (m, 2H), 7.42 – 7.30 (m, 2H), 5.26 (dt, $J = 10.9$, 5.6 Hz, 1H), 4.67 – 4.49 (m, 1H), 3.47 – 3.34 (m, 1H), 2.81 – 2.70 (m, 2H), 2.57 (ddd, $J = 14.4$, 10.6, 7.8 Hz, 1H), 2.44 (td, $J = 13.1$, 3.1 Hz, 1H), 2.10 – 1.62 (m, 7H), 1.51 – 1.20 (m, 2H); $\delta_C$ (100 MHz, CDCl$_3$) 173.8, 155.5, 152.3, 145.6, 125.5, 122.0, 81.2, 62.2, 42.3, 41.6, 41.4, 35.1, 31.6, 30.3, 25.6, 25.2. $m/z$ (ESI+) found [M+H]$^+$ 361.1392. C$_{18}$H$_{21}$N$_2$O$_6$ requires 361.1394.

(75,95,10S,10aS)-decahydro-7,10-methanopyrido[1,2-\alpha]azepin-9-ol, 41

Lithium aluminum hydride (784 mg, 20.71 mmol) was added to a solution of lactam 13 (2.0 g, 10.3 mmol) in methanol (quantity) at 0 °C. The reaction mixture was refluxed for 4 h, then cooled, quenched with 10% aqueous NaOH and extracted with ethyl acetate. The combined organics were dried (Na$_2$SO$_4$) and concentrated to afford the crude amino alcohol, which was purified by flash column chromatography (silica gel, 1:5:0.5 EtOAc/hexane/aq.NH$_3$) to obtain the title product (1.5g, 80%) as a colorless oil. $\nu$ \text{max} (film)/cm$^{-1}$ 3394, 2932; $\delta_H$ (400 MHz, CDCl$_3$) 4.20 (s, 1H), 4.15 – 4.05 (m, 1H), 2.64 – 2.46 (m, 2H), 2.09 – 1.94 (m, 2H), 1.94 – 1.78 (m, 3H), 1.78 – 1.63 (m, 2H), 1.49 (t, $J = 15.2$ Hz, 1H), 1.45 – 1.12 (m, 6H), 1.02 – 0.85 (m, 1H); $\delta_C$ (100 MHz, CDCl$_3$) 74.5, 68.0, 62.6, 55.5, 42.3, 41.8, 38.8, 34.7, 30.6, 25.4, 24.3.

General procedure L: Reduction of ketones 15a-c

(6R,7S,9S,10aS)-6-methyldecahydro-7,10-methanopyrido[1,2-\alpha]azepin-9-ol, 16a

Sodium borohydride (978 mg, 25.85 mmol) was added to a solution of amine 15a (2.0 g, 10.3 mmol) in methanol (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, then quenched with 10% aqueous NaOH and extracted with ethyl acetate. The combined organics were dried (Na$_2$SO$_4$) and concentrated to afford the crude amino-alcohols. Purification by chromatography (silica gel, 1:4:0.5 EtOAc/hexane/aq.NH$_3$) provided the title compound (1.59 g, 79%) as a colorless oil. $\nu$ \text{max} (film)/cm$^{-1}$ 3392, 2932; $\delta_H$ (400 MHz, CDCl$_3$) 4.28 (m, 2H), 3.14 (m, 1H), 2.19 (qd, $J = 6.3$, 1.5 Hz, 1H), 2.13 – 1.93 (m, 3H), 1.92 – 1.85 (m, 1H), 1.84 – 1.75 (m, 1H), 1.73 – 1.30 (m, 9H), 1.03 (d, $J = 6.3$ Hz, 3H); $\delta_C$ (100 MHz, CDCl$_3$) 74.4, 68.6, 63.3, 51.9, 43.2, 42.5, 39.9, 37.8, 31.7, 26.2, 25.1, 18.6.

S37
(6R,7S,9S,10S,10aS)-6-butyldecahydro-7,10-methanopyrido[1,2-a]azepin-9-ol, 16b

Following general procedure L, reaction of ketone 15b (2.0 g, 8.42 mmol) provided the title compound (1.6 g, 80%) as a colorless oil. ν_{max} (film)/cm^{-1} 3393, 2944; δ_{H} (400 MHz, CDCl_{3}) 4.64 – 3.97 (m, 2H), 3.23 (d, J = 11.3 Hz, 1H), 2.22 – 1.79 (m, 6H), 1.79 – 0.97 (m, 15H), 0.88 (t, J = 7.1 Hz, 3H); δ_{C} (100 MHz, CDCl_{3}) 74.4, 69.1, 68.7, 52.0, 43.3, 39.7, 38.7, 38.1, 32.0, 31.2, 29.9, 26.3, 25.1, 23.2, 14.2.

(6R,7S,9S,10S,10aS)-6-benzyldecahydro-7,10-methanopyrido[1,2-a]azepin-9-ol, 16c

Following general procedure L, reaction of ketone 15c (1.8 g, 6.68 mmol) provided the title compound (1.57 g, 87%) as a colorless oil. ν_{max} (film)/cm^{-1} 3394, 2930; δ_{H} (400 MHz, CDCl_{3}) 7.34 – 7.25 (m, 2H), 7.25 – 7.18 (m, 1H), 7.18 – 7.12 (m, 2H), 4.60 – 4.19 (m, 2H), 3.47 (m, 1H), 3.21 (dd, J = 13.2, 3.5 Hz, 1H), 2.57 – 2.32 (m, 2H), 2.28 – 1.90 (m, 4H), 1.89 – 1.61 (m, 5H), 1.61 – 1.38 (m, 4H), 1.37 – 1.11 (m, 1H); δ_{C} (100 MHz, CDCl_{3}) 140.3, 129.4, 128.4, 125.9, 74.2, 70.0, 69.2, 52.2, 43.3, 39.4, 37.7, 37.3, 37.2, 31.9, 26.2, 25.0.
D. Experimental procedures and characterization data for mesembrine-inspired scaffolds.

Supplementary Figure 7. Synthesis of *Stemona* alkaloid-inspired scaffolds

![Synthesis of *Stemona* alkaloid-inspired scaffolds](image)

4-Hydroxy-6-((4-methoxybenzyl)oxy)-3-methylenehexan-2-one, S15

DABCO (4.63 g, 38.3 mmol) was added to a solution of 3-(4-methoxybenzyl)oxy)-propan-1-al in 2-octanol (40 ml) at room temperature, followed by methyl vinyl ketone (12.7 ml, 153 mmol). The reaction mixture was stirred at room temperature for 16 h, then the reaction mixture was directly loaded onto a silica gel column and eluted with 60:40 hexanes:ethyl acetate to afford the title compound (21.5 g, 64%) as a viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3463, 2862, 1736, 1671, 1612, 1512, 1243; $\delta$H (400 MHz, CDCl$_3$) 7.29 – 7.21 (m, 2H), 6.92 – 6.83 (m, 2H), 6.14 (s, 2H), 4.70 (dt, $J$ = 7.8, 3.9 Hz, 1H), 4.51 – 4.38 (m, 2H), 3.81 (s, 3H), 3.75 – 3.57 (m, 3H), 2.34 (s, 3H), 2.03 – 1.92 (m, 1H), 1.84 – 1.71 (m, 1H); $\delta$C (100 MHz, CDCl$_3$) 200.0, 159.5, 150.3, 130.0, 129.5, 125.9, 114.0, 73.2, 70.1, 68.8, 55.4, 36.0, 26.5; m/z (ESI+) found [M+H]$^+$ 265.1458. C$_{15}$H$_{21}$O$_4$+: requires 265.1440.
General procedure M: Synthesis of enones via Rh(I) catalyzed 1,4-addition

**(E)-3-Benzyl-6-((4-methoxybenzyl)oxy)hex-3-en-2-one, S16a**

This enone was synthesized using a modified procedure previously reported by Gendrineau and co-workers. Phenyl boronic acid (0.97 g, 8 mmol) was added to a solution of hydroxyketone S15 (1.05 g, 4.0 mmol) in methanol (5 ml) in a sealed tube. [Rh(cod)OH]₂ (18.2 mg, 0.04 mmol) was then added and the mixture heated at 100 ºC for 2 h. The reaction mixture was then cooled transferred to a round bottom flask and the solvent evaporated under reduced to pressure to obtain the crude product. The crude product was purified by chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford the title compound (1.10 g, 86%, E:Z >95:5) as a colorless viscous oil. ν<sub>max</sub> (film)/cm<sup>-1</sup> 2928, 2833, 1660, 1611, 1510, 1243; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.28 – 7.18 (m, 4H), 7.16 – 7.10 (m, 3H), 6.91 – 6.86 (m, 2H), 6.82 (t, J = 7.0 Hz, 1H), 4.44 (s, 2H), 3.81 (s, 3H), 3.68 (s, 2H), 3.54 (t, J = 6.4 Hz, 2H), 2.61 (q, J = 6.5 Hz, 2H), 2.32 (s, 3H); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 199.2, 159.4, 142.2, 141.8, 139.9, 130.3, 129.5, 128.5, 128.4, 126.0, 114.0, 72.8, 68.3, 55.4, 31.3, 30.2, 26.0; m/z (ESI+) found [M+H]<sup>+</sup> 325.1795. C<sub>21</sub>H<sub>25</sub>O<sub>3</sub>: requires 325.1804.

**(E)-6-((4-methoxybenzyl)oxy)-3-(4-methylbenzyl)hex-3-en-2-one, S16b**

Following general procedure M, reaction of hydroxyketone S15 (6.0 g, 22.7 mmol) with 4-methylphenyl boronic acid (6.22 g, 45.5 mmol) provided the title compound (6.5 g, 85%, E:Z >95:05) as a colorless viscous oil. ν<sub>max</sub> (film)/cm<sup>-1</sup> 2925, 2830, 1657, 1610, 1513, 1240; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.27 – 7.23 (m, 2H), 7.02 (s, 4H), 6.91 – 6.86 (m, 2H), 6.79 (t, J = 7.0 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.64 (s, 2H), 3.55 (t, J = 6.4 Hz, 2H), 2.61 (q, J = 6.5 Hz, 2H), 2.29 (d, J = 10.5 Hz, 6H); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 199.2, 159.3, 142.2, 141.3, 136.6, 135.3, 130.2, 129.3, 129.0, 128.2, 113.8, 72.7, 68.2, 55.3, 30.6, 30.0, 25.9, 21.1; m/z (ESI+) found [M+H]<sup>+</sup> 339.1982. C<sub>22</sub>H<sub>27</sub>O<sub>3</sub>: requires 339.1960.
(E)-3-(4-chlorobenzyl)-6-((4-methoxybenzyl)oxy)hex-3-en-2-one, S16c

Following general procedure M, reaction of hydroxyketone S15 (1.0 g, 3.78 mmol) with 4-chlorophenyl boronic acid (1.2 g, 7.57 mmol) provided the title compound (0.97 g, 67%, E:Z = >95:05) as a colorless viscous oil. ν\text{max} (film)/cm\textsuperscript{-1} 2858, 2857, 1655, 1612, 1511, 1490, 1245; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.29 – 7.20 (m, 2H), 7.19 – 7.13 (m, 2H), 7.09 – 7.03 (m, 2H), 6.91 – 6.86 (m, 2H), 6.81 (t, J = 7.0 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.62 (s, 2H), 3.55 (t, J = 6.3 Hz, 2H), 2.58 (q, J = 6.5 Hz, 2H), 2.31 (s, 3H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 199.0, 159.4, 142.2, 141.8, 138.4, 131.7, 130.2, 129.8, 129.5, 128.5, 114.0, 72.9, 68.2, 55.4, 30.7, 30.2, 25.9; m/z (ESI+) found [M+H]\textsuperscript{+} 359.1430. C\textsubscript{21}H\textsubscript{24}ClO\textsubscript{3}: requires 359.1414.

(E)-3-(4-methoxybenzyl)-6-((4-methoxybenzyl)oxy)hex-3-en-2-one, S16d

Following general procedure M, reaction of 4-hydroxyketone S15 (2.0 g, 7.57 mmol) with 4-methoxyphenyl boronic acid (2.3 g, 15.2 mmol) provided the title compound (1.7 g, 63%, E:Z >95:05) as a colorless viscous oil. ν\text{max} (film)/cm\textsuperscript{-1} 2933, 2836, 1665, 1611, 1509, 1245; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.28 – 7.22 (m, 2H), 7.08 – 7.03 (m, 2H), 6.89 (dt, J = 9.5, 2.9 Hz, 2H), 6.82 – 6.72 (m, 3H), 4.45 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.61 (s, 2H), 3.55 (t, J = 6.4 Hz, 2H), 2.61 (q, J = 6.6 Hz, 2H), 2.30 (s, 3H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 199.2, 159.4, 157.9, 142.5, 141.3, 131.9, 130.3, 129.4, 129.3, 113.9, 113.9, 72.8, 68.3, 55.4, 55.3, 30.4, 30.1, 26.0; m/z (ESI+) found [M+H]\textsuperscript{+} 355.1935. C\textsubscript{22}H\textsubscript{27}O\textsubscript{4}: requires 355.1909.

General procedure N: Synthesis of hydroxy enones S17

(E)-3-benzyl-6-hydroxyhex-3-en-2-one, S17a

DDQ (19.81 g, 87.29 mmol) was added to a solution of enone S16a (23.6 g, 72.74 mmol) in dichloromethane (720 ml) and water (37 ml) at room temperature. The initial green reaction mixture was stirred at room temperature for 16 h. A color change to red-orange was observed within 30 min.
The reaction mixture was then carefully quenched with saturated aqueous NaHCO$_3$ and filtered through a celite plug with dichloromethane washings (250 ml). The combined organics were washed with water (2 x 150 ml), dried (MgSO$_4$) and concentrated. The crude product was purified by chromatography (silica gel, 80:20 hexane:ethyl acetate) to afford the title compound (12.3 g, 83%) as a viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3416, 2924, 1716, 1660, 1494, 1453; $\delta_h$ (400 MHz, CDCl$_3$) 7.27 – 7.20 (m, 2H), 7.15 (dd, $J = 7.6, 6.1$ Hz, 3H), 6.85 (t, $J = 7.1$ Hz, 1H), 3.82 – 3.64 (m, 4H), 2.59 (q, $J = 6.4$ Hz, 2H), 2.34 (s, 3H); $\delta_c$ (100 MHz, CDCl$_3$) 199.2, 142.7, 141.1, 139.8, 128.5, 128.3, 126.0, 61.4, 32.8, 31.3, 25.9; $m/z$ (ESI+) found [M+H]$^+$ 205.1230. C$_{13}$H$_{17}$O$_2$: requires 205.1229.

(E)-6-hydroxy-3-(4-methylbenzyl)hex-3-en-2-one, S17b

Following general procedure N, reaction of enone S16b (5.9 g, 17.54 mmol) provided the title compound (3.5 g, 91%) as a viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3425, 2924, 1718, 1662, 1513; $\delta_h$ (400 MHz, CDCl$_3$) 7.10 – 6.97 (m, 4H), 6.83 (t, $J = 7.1$ Hz, 1H), 3.76 (q, $J = 6.1$ Hz, 2H), 3.66 (s, 2H), 2.58 (q, $J = 6.5$ Hz, 2H), 2.36 – 2.23 (m, 6H); $\delta_c$ (100 MHz, CDCl$_3$) 199.3, 142.8, 141.0, 136.7, 135.5, 129.2, 128.2, 61.4, 32.7, 30.8, 25.9, 21.1; $m/z$ (ESI+) found [M+H]$^+$ 219.1370. C$_{14}$H$_{19}$O$_2$: requires 219.1385.

(E)-6-hydroxy-3-(4-chlorobenzyl)hex-3-en-2-one, S17c

Following general procedure N, reaction of enone S16c (6.95 g, 19.4 mmol) provided the title compound (4.0 g, 86%) as a viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3432, 2938, 1719, 1664, 1490; $\delta_h$ (400 MHz, CDCl$_3$) 7.23 – 7.14 (m, 2H), 7.07 (d, $J = 8.3$ Hz, 2H), 6.85 (t, $J = 7.1$ Hz, 1H), 3.77 (q, $J = 5.7$ Hz, 2H), 3.65 (s, 2H), 2.56 (q, $J = 6.5$ Hz, 2H), 2.33 (s, 3H), 1.79 (s, 1H); $\delta_c$ (100 MHz, CDCl$_3$) 199.1, 142.3, 141.6, 138.3, 131.7, 129.7, 128.5, 61.3, 32.7, 30.7, 25.9; $m/z$ (ESI+) found [M+H]$^+$ 239.0825. C$_{13}$H$_{16}$ClO$_2$: requires 239.0839.
(E)-6-hydroxy-3-(4-methoxybenzyl)hex-3-en-2-one, S17d

Following general procedure N, reaction of enone S16d (5.0 g, 14.3 mmol) provided the title compound (2.87 g, 86%) as a viscous oil. $\nu_{\text{max}}$ (film)/ cm$^{-1}$: 3421, 2935, 2836, 1660, 1509; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.09 – 7.03 (m, 2H), 6.85 – 6.74 (m, 3H), 3.79 – 3.74 (m, 5H), 3.63 (s, 2H), 2.59 (q, $J$ = 6.5 Hz, 2H), 2.32 (s, 3H); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 199.3, 157.9, 143.0, 140.8, 131.8, 129.3, 113.9, 61.5, 55.3, 32.8, 30.4, 26.0; m/z (ESI+) found [M+H]$^+$ 235.1330. C$_{14}$H$_{19}$O$_3$+: requires 235.1334.

General procedure O: Synthesis of azido enones

(E)-6-azido-3-benzylhex-3-en-2-one, S18a

In a flame dried round bottom flask flushed with argon, Zn(N$_3$)$_2$.Pyr (36.0 g, 118 mmol) and triphenyl phosphine (30.7 g, 118 mmol) were weighed. A solution of alcohol S17a (12.0 g, 58.8 mmol) in anhydrous toluene (150 ml) was added. The flask was cooled to -78 ºC, then diisopropyl azodicarboxylate (22.6 ml, 118 mmol) was added to dropwise and the reaction mixture warmed to room temperature and stirred for 16 h. On completion the reaction mixture was filtered through a celite plug and the toluene removed under reduced pressure. The crude reaction mixture was diluted with ethyl acetate (150 ml) and washed with water (2 x 100 ml) and brine (100 ml), dried (MgSO$_4$) and concentrated. The crude product was purified by chromatography (silica gel, 90:10 hexane:ethyl acetate) to afford the title compound (8.35 g, 62%) as pale yellow viscous oil. $\nu_{\text{max}}$ (film)/ cm$^{-1}$: 3028, 2925, 2100, 1709, 1664, 1494; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.29 – 7.22 (m, 2H), 7.19 – 7.10 (m, 3H), 6.74 (t, $J$ = 7.1 Hz, 1H), 3.71 (s, 2H), 3.39 (q, $J$ = 6.7 Hz, 2H), 2.59 (q, $J$ = 6.8 Hz, 2H), 2.35 (s, 3H); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 198.8, 143.0, 139.6, 139.4, 128.5, 128.2, 126.1, 50.1, 31.2, 29.0, 25.9; m/z (ESI+) found [2M+H]$^+$ 459.2500. C$_{26}$H$_{31}$N$_6$O$_2$+: requires 459.2508.

(E)-6-azido-3-(4-methylbenzyl)hex-3-en-2-one, S18b

(E)-6-azido-3-(4-methylbenzyl)hex-3-en-2-one, S18b
Following general procedure O, reaction of alcohol S17b (3.4 g, 15.6 mmol) provided the title compound (2.65 g, 70%) as a viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2928, 2092, 1695, 1671, 1513; $\delta_{\text{n}}$ (400 MHz, CDCl$_3$) 7.04 (q, $J = 8.1$ Hz, 4H), 6.71 (t, $J = 7.1$ Hz, 1H), 3.67 (s, 2H), 3.39 (t, $J = 6.8$ Hz, 2H), 2.59 (q, $J = 6.8$ Hz, 2H), 2.39 – 2.24 (m, 6H); $\delta_{\text{c}}$ ($^{13}$C NMR (100 MHz, CDCl$_3$) δ 198.9, 143.3, 139.4, 136.4, 135.7, 129.3, 128.2, 50.3, 30.9, 29.2, 26.0, 21.1; $m/z$ (ESI+) found [2M+H]$^+$ 487.2831. C$_{28}$H$_{35}$N$_6$O$_2$$^+$: requires 487.2821.

(E)-6-azido-3-(4-chlorobenzyl)hex-3-en-2-one, S18c

Following general procedure O, reaction of alcohol S17c (4.0 g, 16.75 mmol) provided the title compound (2.69 g, 61%) as a viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2929, 2102, 1701, 1665, 1490; $\delta_{\text{n}}$ (400 MHz, CDCl$_3$) 7.24 – 7.19 (m, 2H), 7.09 – 7.03 (m, 2H), 6.74 (t, $J = 7.1$ Hz, 1H), 3.66 (s, 2H), 3.42 (t, $J = 6.7$ Hz, 2H), 2.58 (q, $J = 6.8$ Hz, 2H), 2.34 (s, 3H); $\delta_{\text{c}}$ (100 MHz, CDCl$_3$) 198.7, 142.8, 140.1, 138.0, 132.0, 129.7, 128.7, 50.2, 30.7, 29.2, 25.9; $m/z$ (ESI+) found [M+H]$^+$ 264.0910. C$_{13}$H$_{15}$ClN$_3$O$^+$: requires 264.0904.

(E)-6-azido-3-(4-methoxybenzyl)hex-3-en-2-one, S18d

Following general procedure O, reaction of alcohol S17d (2.87 g, 12.24 mmol) provided the title compound (1.95 g, 65%) as a viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2932, 2836, 2100, 1709, 1664, 1609, 1509; $\delta_{\text{n}}$ (400 MHz, CDCl$_3$) 7.07 – 7.02 (m, 2H), 6.82 – 6.76 (m, 2H), 6.70 (t, $J = 7.1$ Hz, 1H), 3.76 (s, 3H), 3.64 (s, 2H), 3.39 (t, $J = 6.8$ Hz, 2H), 2.59 (q, $J = 6.8$ Hz, 2H), 2.33 (s, 3H); $\delta_{\text{c}}$ (100 MHz, CDCl$_3$) 199.0, 158.0, 143.5, 139.3, 131.5, 129.3, 114.0, 55.4, 50.3, 30.5, 29.1, 26.0; $m/z$ (ESI+) found [M+H]$^+$ 260.1385. C$_{14}$H$_{18}$N$_3$O$^+$: requires 260.1399.
General procedure P: Diels Alder/ Schmidt reaction with silyloxy dienes derived from α-benzyl enones

(3aS,4R,7aR)-1-acetyl-4-benzyl-octahydro-5H-indol-5-one, 18a

Triethylamine (1.83 ml, 13.1 mmol) was added to a solution of enone S18a (1.50 g, 6.55 mmol) in anhydrous diethyl ether (15 ml) at 0 °C under argon. TBSOTf (2.26 ml, 9.82 mmol) was then added dropwise to afford a white turbid solution. The reaction mixture was stirred for 30 min at 0 °C, then quenched with saturated aqueous NaHCO₃ (50 ml). The mixture was extracted with diethyl ether (50 ml), dried (MgSO₄) and concentrated to afford the corresponding silyloxydiene 17a (2.31 g) which was used without any purification.

The crude silyloxydiene was transferred to a flame-dried argon-flushed flask and dissolved in anhydrous dichloromethane (15 ml). Methyl vinyl ketone (0.37 ml, 4.51 mmol) was added and the reaction mixture cooled to -78 °C. Boron trifluoride diethyl etherate (0.86 ml, 6.76 mmol) was then added and the reaction mixture stirred at -78 °C for 4 h then warmed to room temperature. A further aliquot of boron trifluoride diethyl etherate (1.14 ml, 9.02 mmol) was then added and the reaction mixture stirred at room temperature for an additional 16 h. The reaction mixture was diluted with dichloromethane (100 ml) and quenched with saturated aqueous NaHCO₃ (100 ml). The organic layer was washed with saturated aqueous NH₄Cl (50 ml), water (50 ml) and brine (100 ml), dried (MgSO₄) and concentrated. The crude product was purified by automated column chromatography (4 g silica column, 0 to 100% EtOAc in hexanes, then 90:10 dichloromethane:methanol) to afford the title compound (672 mg, 55%, endo:exo = 4:1) as yellow viscous oil. ν max (film)/cm⁻¹ 2935, 1710, 1635, 1420; δ H (400 MHz, CDCl₃, major diastereomer) 7.31 – 7.14 (m, 5H), 3.63 – 3.51 (m, 2H), 3.43 (td, J = 10.7, 6.1 Hz, 1H), 3.29 – 3.13 (m, 2H), 2.67 (m, 2H), 2.55 – 2.38 (m, 2H), 2.02 (s, 3H), 1.96 – 1.74 (m, 2H), 1.59 – 1.36 (m, 2H); δ C (100 MHz, CDCl₃, major diastereomer) 209.7, 171.0, 140.3, 129.2, 128.5, 126.3, 62.3, 55.4, 50.6, 49.4, 39.5, 33.6, 29.3, 29.1, 23.2; m/z (ESI+) found [M+H]^+ 272.1545. C_{17}H_{22}NO_{2}^+: requires 272.1651.
(3aS,4R,7aR)-1-acetyl-4-(4-methylbenzyl)octahydro-5H-indol-5-one, 18b

Following general procedure P, reaction of enone **S18b** (4.20 g, 17.3 mmol) provided the title compound (1.68 g, 53%, *endo:*exo = 4:1) as a yellow viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2937, 1711, 1630, 1414; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$, major diastereomer) 7.12–7.02 (m, 4H), 3.58–3.45 (m, 1H), 3.40–3.27 (m, 1H), 3.20 (dt, $J = 14.3, 5.0$ Hz, 1H), 3.12–2.96 (m, 1H), 2.73–2.52 (m, 2H), 2.51–2.19 (m, 6H), 2.14–1.92 (m, 5H), 1.91–1.64 (m, 2H); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$, major diastereomer) 211.5, 169.3, 136.2, 129.3, 128.9, 128.5, 54.9, 50.5, 46.5, 42.5, 37.7, 32.2, 27.0, 25.8, 22.3, 21.0; $m/z$ (ESI+) found [M+H]$^+$ 286.1825. C$_{18}$H$_{24}$NO$_2$+: requires 286.1807.

(3aS,4R,7aR)-1-acetyl-4-(4-chlorobenzyl)octahydro-5H-indol-5-one, 18c

Following general procedure P, reaction of enone **S18c** (5.60 g, 21.2 mmol) provided the title compound (2.72 g, 64%, *endo:*exo = 3:1) as a yellow viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2947, 1711, 1631,1492, 1414; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$, major diastereomer) 7.24 (d, $J = 7.7$ Hz, 2H), 7.11 (d, $J = 7.7$ Hz, 2H), 3.53–3.50 (m, 1H), 3.35 (m, 2H), 3.25–3.16 (m, 2H), 3.09 (dd, $J = 13.4, 6.0$ Hz, 1H), 3.01 (dt, $J = 8.6, 6.0$ Hz, 1H), 2.74–2.53 (m, 2H), 2.51–2.20 (m, 2H), 2.12–1.96 (m, 3H), 1.96–1.57 (m, 2H); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$, major diastereomer) 211.1, 169.4, 137.9, 130.5, 130.2, 128.8, 54.9, 50.5, 46.5, 43.0, 37.8, 32.3, 27.2, 25.9, 22.4; $m/z$ (ESI+) found [M+H]$^+$ 306.1277. C$_{17}$H$_{24}$ClNO$_2$: requires 306.1216.
(3aS,4R,7aR)-1-acetyl-4-(4-methoxybenzyl)octahydro-5H-indol-5-one, 18d

Following general procedure P, reaction of enone S18d (3.20 g, 12.3 mmol) provided the title compound (1.50 g, 60%, endo:exo = 4:1) as a yellow viscous oil. ν max (film)/cm⁻¹ 2944, 1710, 1629, 1511, 1244; δ H (400 MHz, CDCl₃, major diastereomer) 7.08 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 3.76 (s, 3H), 3.60 – 3.44 (m, 2H), 3.41 – 3.25 (m, 1H), 3.17 (dt, J = 14.4, 4.8 Hz, 1H), 3.10 – 2.93 (m, 1H), 2.73 – 2.51 (m, 2H), 2.51 – 2.17 (m, 4H), 2.15 – 1.92 (m, 3H), 1.90 – 1.53 (m, 2H); δ C (100 MHz, CDCl₃, major diastereomer) 211.6, 169.3, 158.2, 130.1, 129.7, 114.1, 114.0, 55.3, 54.9, 50.7, 46.5, 42.7, 37.8, 31.8, 27.2, 25.9; m/z (ESI+) found [M+H]⁺ 302.1768. C₁₈H₂₄NO₃⁺: requires 302.1756.

General procedure Q. Synthesis of silyloxydiene

(E)-((3-benzyl-6-((4-methoxybenzyl)oxy)hexa-1,3-dien-2-yl)oxy)(tert-butyl)dimethylsilane, 22a

Triethylamine (0.43 ml, 3.08 mmol) was added to a solution of enone S16a (500 mg, 1.54 mmol) in anhydrous diethyl ether (5 ml) at 0 °C under argon. TBSOTf (0.53 ml, 2.31 mmol) was then added dropwise. The reaction mixture was stirred for 20 min at 0 °C then diluted with ether, washed with saturated aqueous NaHCO₃, dried (MgSO₄) and concentrated. The crude product was purified by chromatography (basic alumina, 96:4 hexanes:ethyl acetate) to afford the title compound (603 mg, 89%) as a colorless viscous oil. ν max (film)/cm⁻¹ 2930, 2856, 1600, 1512, 1246; δ H (400 MHz, CDCl₃) 7.28 – 7.19 (m, 4H), 7.19 – 7.11 (m, 3H), 6.89 – 6.83 (m, 2H), 6.29 (t, J = 7.3 Hz, 1H), 4.42 (s, 2H), 4.39 – 4.22 (m, 2H), 3.80 (s, 3H), 3.61 (s, 2H), 3.50 (t, J = 6.8 Hz, 2H), 2.47 (q, J = 7.0 Hz, 2H), 0.96 (s, 9H), 0.17 – 0.09 (ms, 6H); δ C (100 MHz, CDCl₃) 159.2, 156.4, 140.1, 135.4, 130.7, 129.4, 128.4, 128.0, 127.1, 125.9, 113.9, 93.1, 72.8, 69.6, 55.4, 33.5, 29.4, 26.1, 18.5, -4.5; m/z (ESI+) found [M+H]⁺ 439.2650. C₁₇H₃₉O₄Si⁺: requires 439.2668.
(E)-tert-butyl(((6-((4-methoxybenzyl)oxy)-3-(4-methylbenzyl)hexa-1,3-dien-2-yl)oxy)dimethylsilane, 22b

Following general procedure Q, reaction of enone S16b (0.79 g, 2.02 mmol) provided the title compound (800 mg, 86%) as a colorless viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2929, 2856, 1612, 1512, 1246; $\delta_H$ (400 MHz, CDCl$_3$) 7.15 – 7.08 (m, 2H), 6.95 – 6.88 (m, 4H), 6.74 (dd, $J = 6.7$, 2.1 Hz, 2H), 6.15 (t, $J = 7.3$ Hz, 1H), 4.29 (s, 2H), 4.25 – 4.08 (m, 2H), 3.67 (s, 3H), 3.44 (s, 2H), 3.37 (t, $J = 6.8$ Hz, 2H), 2.34 (q, $J = 7.0$ Hz, 2H), 2.16 (s, 3H), 0.83 (s, 9H), 0.02 – 0.03 (s, 6H); $\delta_C$ (100 MHz, CDCl$_3$) 159.2, 156.4, 137.0, 135.5, 135.3, 130.7, 129.4, 129.1, 127.8, 127.0, 113.9, 93.0, 72.8, 69.6, 55.4, 33.0, 29.3, 26.1, 21.1, 18.5, -4.5; $m/z$ (ESI+) found [M+H]$^+$ 453.2842. C$_{28}$H$_{41}$SiO$_3$: requires 453.2825.

(E)-tert-butyl(((3-(4-chlorobenzyl)-6-((4-methoxybenzyl)oxy)hexa-1,3-dien-2-yl)oxy)dimethylsilane, 22c

Following general procedure Q, reaction of enone S16c (321 mg, 0.89 mmol) provided the title compound (380 mg, 90%) as a colorless viscous oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2930, 2856, 1612, 1595, 1512, 1247; $\delta_H$ (400 MHz, CDCl$_3$) 7.29 – 7.22 (m, 2H), 7.21 – 7.15 (m, 2H), 7.13 – 7.06 (m, 2H), 6.87 (dd, $J = 6.6$, 2.0 Hz, 2H), 6.29 (t, $J = 7.3$ Hz, 1H), 4.42 (s, 2H), 4.32 – 4.21 (m, 2H), 3.81 (s, 3H), 3.56 (s, 2H), 3.54 – 3.44 (m, 2H), 2.45 (q, $J = 6.9$ Hz, 2H), 0.96 (s, 9H), 0.18 (s, 6H); $\delta_C$ (100 MHz, CDCl$_3$) 159.3, 156.2, 138.6, 135.1, 129.5, 129.4, 128.5, 127.6, 113.9, 93.0, 72.9, 69.5, 65.8, 55.4, 32.8, 29.4, 26.0, 17.2, 14.3, -4.5; HRMS calcd. for C$_{27}$H$_{38}$ClO$_3$Si$: 473.2279$ Found: $473.2277.$

(E)-tert-butyl(((3-(4-methoxybenzyl)-6-((4-methoxybenzyl)oxy)hexa-1,3-dien-2-yl)oxy)dimethylsilane, 22d

(E)-tert-butyl(((3-(4-methoxybenzyl)-6-((4-methoxybenzyl)oxy)hexa-1,3-dien-2-yl)oxy)dimethylsilane, 22d
Following general procedure Q, reaction of enone S16d (356 mg, 1.0 mmol) provided the title compound (450 mg, 96%) as a colorless viscous oil. ν\text{max} (film)/cm\textsuperscript{-1} 2931, 2856, 1611, 1510, 1243; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.28 – 7.22 (t, 2H, 2H), 7.11 – 7.05 (d, 2H, 2H), 6.90 – 6.84 (m, 2H), 6.79 – 6.75 (m, 2H), 6.30 – 6.23 (t, 2H, 2H), 3.83 – 3.74 (d, 2H, 2H), 2.52 – 2.43 (q, 2H, 2H), 1.01 – 0.93 (s, 6H), 0.15 – 0.11 (m, 6H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 159.2, 157.8, 156.4, 135.8, 132.1, 130.7, 129.4, 128.9, 126.9, 113.9, 113.8, 93.0, 72.8, 66.0, 55.4, 55.4, 32.6, 29.3, 26.1, 18.4, -5.6; m/z (ESI+) found [M+H]\textsuperscript{+} 469.2754. C\textsubscript{28}H\textsubscript{41}SiO\textsubscript{4}: requires 469.2774.

General procedure R: Diels Alder reaction of cyclobutenone with silyloxydienes

(1R,5S,6S)-4-benzyl-3-((tert-butyldimethylsilyl)oxy)-5-(2-((4-methoxybenzyl)oxy)ethyl)bicyclo[4.2.0]oct-3-en-7-one, 23a

Diisopropylamine (0.53 ml, 2.97 mol) was added dropwise to a solution of 3-bromocyclobutan-1-one\textsuperscript{66} (400 mg, 2.70 mmol) in anhydrous acetonitrile (1 ml) at 0 °C under argon. The solution was stirred at 0 °C for 1 h when \textsuperscript{1}H NMR analysis of an aliquot showed complete consumption of bromobutanone and formation of cyclobut-2-en-1-one. To this flask was added a solution of silyloxydiene 22a (400 mg, 0.92 mmol) in acetonitrile (1 ml) followed by ZnCl\textsubscript{2} (1.35 ml, 1.0 M solution in Et\textsubscript{2}O). The reaction mixture was then heated at 45 °C for 24 h, then another equivalent of cyclobut-2-en-1-one (0.92 mmol) (prepared separately as described above) was added. The reaction mixture was heated at 45 °C for an additional 24 h, then cooled to room temperature and diluted with diethyl ether. The organic layer was washed with saturated aqueous NaHCO\textsubscript{3} (50 ml) and water (2 x 50 ml), dried (MgSO\textsubscript{4}) and concentrated. The crude product was purified by chromatography (basic alumina, 95:5 hexane:ethyl acetate) to afford the title compound (350 mg, 75%) as a colorless viscous oil. ν\text{max} (film)/cm\textsuperscript{-1} 2925, 2860, 1710, 1651, 1613, 1507, 1246; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.25 – 7.20 (m, 2H), 7.19 – 7.08 (m, 3H), 6.96 – 6.82 (m, 2H), 4.31 – 4.22 (m, 2H), 3.92 – 3.84 (d, 2H, 2H), 2.83 – 2.77 (s, 3H), 3.53 – 3.39 (m, 3H), 3.23 – 3.08 (m, 2H), 2.82 – 2.71 (m, 1H), 2.66 – 2.51 (m, 3H), 2.34 – 2.23 (m, 1H), 1.91 – 1.83 (m, 2H), 0.90 – 0.87 (s, 3H), 0.14 (s, 3H), 0.09 (s, 3H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 212.2, 159.2, 145.5, 141.2, 130.7, 129.4, 128.4, 128.3, 125.6, 116.8, 113.8, 72.1, 67.9, 60.6, 55.4, 51.8, 33.7, 33.5, 32.7, 29.1, 25.9, 23.4, 18.2, -3.4, -3.3. m/z (ESI+) found [M+H]\textsuperscript{+} 507.2925. C\textsubscript{28}H\textsubscript{41}O\textsubscript{4}Si\textsuperscript{+}: requires 507.2931.
(1R,5S,6S)-3-((tert-butyldimethylsilyl)oxy)-5-(2-((4-methoxybenzyl)oxy)ethyl)-4-(4-methylbenzyl)bicyclo[4.2.0]oct-3-en-7-one, 23b

Following general procedure R, reaction of silyloxydiene 22b (300 mg, 0.66 mmol) provided the title compound (252 mg, 72%) as a colorless viscous oil. \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 2930, 2857, 1713, 1650, 1612, 1511, 1246; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 7.18 – 7.13 (m, 2H), 7.05 – 6.96 (q, \( J = 8.0 \) Hz, 4H), 6.87 – 6.81 (m, 2H), 4.35 – 4.19 (m, 2H), 3.83 – 3.75 (s, 4H), 3.51 – 3.38 (m, 3H), 3.17 – 3.05 (dd, \( J = 17.9, 8.8, 3.9 \) Hz, 2H), 2.81 – 2.68 (m, 1H), 2.66 – 2.49 (m, 3H), 2.34 – 2.26 (s, 4H), 1.94 – 1.80 (q, \( J = 7.5, 6.9 \) Hz, 2H), 0.88 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 212.3, 159.2, 145.3, 138.0, 135.0, 130.8, 129.4, 129.0, 128.3, 117.1, 113.8, 72.1, 68.0, 60.7, 55.4, 51.8, 33.7, 33.5, 32.3, 29.1, 25.9, 23.4, 21.2, 18.2, -3.3, -3.4; \( m/z \) (ESI+) found [M+H]+ 521.3093. \( \text{C}_{32}\text{H}_{45}\text{O}_{4}\text{Si}^+ \): requires 521.3087.

(1R,5S,6S)-3-((tert-butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-5-(2-((4-chlorobenzyl)oxy)ethyl)bicyclo[4.2.0]oct-3-en-7-one, 23c

Following general procedure R, reaction of silyloxydiene 22c (205mg, 1.39 mmol) provided the title compound (265 mg, 68%) as a colorless viscous oil. \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 2930, 2856, 1773, 1650, 1612, 1512, 1246; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 7.23 – 7.12 (m, 4H), 7.02 (d, \( J = 8.4 \) Hz, 2H), 6.89 – 6.82 (m, 2H), 4.38 – 4.23 (m, 2H), 3.80 (s, 4H), 3.53 – 3.39 (m, 3H), 3.21 – 3.06 (m, 2H), 2.82 – 2.70 (m, 1H), 2.66 – 2.48 (m, 3H), 2.27 (dd, \( J = 15.5, 3.3 \) Hz, 1H), 1.92 – 1.73 (m, 2H), 0.87 (s, 9H), 0.21 – 0.06 (m, 6H); \( \delta_{\text{C}} \) (125 MHz, CDCl\(_3\)) 212.3, 159.2, 145.8, 139.7, 131.3, 130.6, 129.7, 129.4, 128.4, 116.3, 113.8, 72.3, 67.8, 60.6, 55.4, 51.8, 33.6, 33.5, 32.0, 29.1, 25.8, 23.3, 18.2, -3.3, -3.2; \( m/z \) (ESI+) found [M+H]+ 541.2556. \( \text{C}_{32}\text{H}_{43}\text{ClO}_{5}\text{Si}^+ \): requires 541.2541.
(1R,5S,6S)-3-((tert-butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)bicyclo[4.2.0]oct-3-en-7-one, 23d

Following general procedure R, reaction of silyloxydiene 22d (164mg, 1.11 mmol) provided the title compound (164mg, 55%) as a colorless viscous oil. ν\text{max} (film)/\text{cm}^{-1} 2931, 2856, 1773, 1650, 1611, 1508; δ\text{H} (400 MHz, CDCl\textsubscript{3}) 7.19 – 7.14 (m, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.87 – 6.82 (m, 2H), 6.80 – 6.74 (m, 2H), 4.36 – 4.21 (m, 2H), 3.78 (d, J = 14.1 Hz, 7H), 3.57 – 3.37 (m, 4H), 3.18 – 3.04 (m, 2H), 2.74 (dt, J = 15.3, 5.8 Hz, 1H), 2.66 – 2.47 (m, 3H), 2.26 (dd, J = 15.5, 3.6 Hz, 1H), 1.86 (q, J = 6.5 Hz, 2H), 0.89 (s, 9H), 0.18 – 0.04 (m, 6H); δ\text{C} (125 MHz, CDCl\textsubscript{3}) 212.4, 159.2, 157.7, 145.2, 133.1, 130.7, 129.4, 129.3, 117.2, 113.8, 113.7, 72.2, 68.0, 60.6, 55.4, 55.3, 51.8, 33.7, 33.5, 31.8, 29.1, 25.9, 23.4, 18.2, -3.3, -3.4; m/z (ESI+) found [M+H]\textsuperscript{+} 537.3040. C\textsubscript{32}H\textsubscript{46}O\textsubscript{5}Si\textsuperscript{+}: requires 537.3036.

General procedure S: synthesis of tetrahydroisochromenones

(4aS,5S)-5-benzyl-1-methyl-3,4,4a,5-tetrahydro-6H-isochromen-6-one, 24a

Trifluoromethane sulfonic acid (17.7μl, 0.2 mmol) was added to a solution of silyl enol ether 23a (51.0 mg, 0.2 mmol) in dichloromethane (1 ml) at room temperature. The reaction mixture was stirred at room temperature for 2 h then loaded directly onto a silica gel column and eluted with 80:20 hexanes:ethyl acetate to afford the title compound (34.0 mg, 67%) as an colorless oil. ν\text{max} (film)/\text{cm}^{-1} 2926, 1658, 1612, 1495, 1278; δ\text{H} (400 MHz, CDCl\textsubscript{3}) 7.25 – 7.21 (m, 6H), 5.79 (d, J = 9.8 Hz, 1H), 4.27 (dd, J = 10.9, 3.9, 2.3 Hz, 1H), 3.98 – 3.65 (m, 1H), 3.32 – 3.06 (m, 2H), 2.53 (dt, J = 12.3, 6.8 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.19 (ddt, J = 13.6, 4.7, 2.0 Hz, 1H), 1.97 (d, J = 1.5 Hz, 3H), 1.67 (tdd, J = 12.9, 11.2, 3.9 Hz, 1H); δ\text{C} (100 MHz, CDCl\textsubscript{3}) 199.0, 157.7, 143.9, 140.4, 129.5, 128.4, 126.0, 121.6, 108.3, 66.4, 52.4, 34.9, 31.6, 29.2, 17.0; m/z (ESI+) found [M+H]\textsuperscript{+} 255.1365. C\textsubscript{17}H\textsubscript{19}O\textsubscript{2}: requires 255.1385.
(4aS,5S)-1-methyl-5-(4-methylbenzyl)-3,4,4a,5-tetrahydro-6H-isochromen-6-one, 24b

Following general procedure S, reaction of silyl enol ether 23b (53.6 mg, 0.2 mmol) provided the title compound (35.0 mg, 65%) as a colorless viscous oil. \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2927, 1656, 1610, 1510, 1243; \( \delta_{\text{H}} \) (500 MHz, CDCl\(_3\)) 7.24 (d, \( J = 9.8 \) Hz, 1H), 7.13 – 7.08 (m, 2H), 7.07 – 7.01 (m, 2H), 5.79 (d, \( J = 9.8 \) Hz, 1H), 4.27 (ddd, \( J = 10.9, 3.9, 2.3 \) Hz, 1H), 3.87 – 3.73 (m, 1H), 3.22 (dd, \( J = 14.6, 3.8 \) Hz, 1H), 3.06 (dd, \( J = 14.6, 5.4 \) Hz, 1H), 2.58 – 2.48 (m, 1H), 2.38 (ddd, \( J = 13.7, 5.3, 3.9 \) Hz, 1H), 2.29 (s, 3H), 2.20 (ddt, \( J = 13.5, 4.6, 1.9 \) Hz, 1H), 1.97 (d, \( J = 1.5 \) Hz, 3H), 1.73 – 1.61 (m, 1H); \( \delta_{\text{C}} \) (125 MHz, CDCl\(_3\)) 199.0, 157.5, 143.7, 137.0, 135.3, 129.3, 128.92, 121.5, 108.2, 66.3, 52.21, 34.6, 30.9, 29.1, 21.0, 16.9; \( m/z \) (ESI+) found [M+H]\(^+\) 269.1551. C\(_{18}\)H\(_{21}\)O\(_2\): requires 269.1542.

(4aS,5S)-1-methyl-5-(4-chlorobenzyl)-3,4,4a,5-tetrahydro-6H-isochromen-6-one, 24c

Following general procedure S, reaction of silyl enol ether 23c (57.6 mg, 0.2 mmol) provided the title compound (32.0 mg, 55%) as a colorless viscous oil. \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2927, 1661, 1608, 1491, 1279; \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 7.30 – 7.23 (m, 1H), 7.22 – 7.13 (m, 4H), 5.78 (d, \( J = 9.8 \) Hz, 1H), 4.28 (ddd, \( J = 11.0, 3.9, 2.3 \) Hz, 1H), 3.90 – 3.69 (m, 1H), 3.28 – 3.17 (m, 1H), 3.10 – 3.00 (m, 1H), 2.50 (dt, \( J = 12.2, 6.6 \) Hz, 1H), 2.43 – 2.32 (m, 1H), 2.16 (ddt, \( J = 13.4, 4.6, 1.9 \) Hz, 1H), 1.98 (d, \( J = 1.5 \) Hz, 3H), 1.69 (tdd, \( J = 12.9, 11.2, 3.9 \) Hz, 1H); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 198.8, 158.0, 144.0, 138.8, 131.8, 130.9, 128.5, 121.5, 108.1, 66.3, 52.3, 34.7, 30.9, 29.2, 17.0; HRMS calcd. for C\(_{17}\)H\(_{18}\)ClO\(_2\): 289.0995 Found: 289.1005. \( m/z \) (ESI+) found [M+H]\(^+\) 289.1005. C\(_{17}\)H\(_{18}\)ClO\(_2\): requires 289.0995.
Following general procedure S, reaction of silyl enol ether 23d (43.0 mg, 0.15 mmol) provided the title compound (23.5 mg, 55%) as a colorless viscous oil. ν\textsubscript{max} (film)/cm\textsuperscript{-1} 2926, 1659, 1610, 1510, 1247; δ\textsubscript{n} (400 MHz, CDCl\textsubscript{3}) 7.28 – 7.21 (m, 1H), 7.13 (d, \(J = 8.7\) Hz, 2H), 6.82 – 6.75 (m, 2H), 5.78 (d, \(J = 9.8\) Hz, 1H), 4.27 (ddd, \(J = 10.9, 3.9, 2.3\) Hz, 1H), 3.88 – 3.70 (m, 4H), 3.24 (dd, \(J = 14.6, 3.7\) Hz, 1H), 3.00 (dd, \(J = 14.6, 5.4\) Hz, 1H), 2.60 – 2.47 (m, 1H), 2.36 (ddd, \(J = 13.6, 5.4, 3.7\) Hz, 1H), 2.20 (ddd, \(J = 11.5, 5.3, 2.6\) Hz, 1H), 2.03 – 1.93 (m, 3H), 1.68 (tdd, \(J = 13.0, 11.3, 3.9\) Hz, 1H); δ\textsubscript{c} (100 MHz, CDCl\textsubscript{3}) 199.2, 157.9, 157.7, 143.9, 132.1, 130.5, 121.7, 113.7, 108.3, 66.4, 55.3, 52.4, 34.5, 30.5, 29.2, 17.0; m/z (ESI+) found [M+H]\textsuperscript{+} 285.1475. C\textsubscript{18}H\textsubscript{21}O\textsubscript{3}+: requires 285.1491.
III. Supplementary Methods: Experimental procedures for library synthesis, tabulated results and characterization data for representative library compounds.

A. *Stemona* alkaloid-inspired libraries.

General procedures for library preparation and tabulated results.

Quinolines 25:

Fe$^{0}$ powder (90 mg, 1.6 mmol) was added to a solution of the appropriate nitrobenzaldehyde (0.41 mmol) in ethanol (2 mL) in a microwave vial, followed by 0.1 M HCl (210 μL). The vial was sealed, then heated in an oil bath at 85 °C until complete by TLC (~2 h). The mixture was cooled to rt, then a solution of ketone scaffold 3a (70 mg, 0.32 mmol) in EtOH (1 mL) added, followed by powdered KOH (22 mg, 0.38 mmol). The mixture was heated at 85 °C until complete by TLC (~3 h), then cooled to rt, passed through a celite plug and eluted with dichloromethane, and concentrated under reduced pressure. The residues were subjected to mass-directed preparative HPLC purification to afford pure quinolines 25.

| Compound | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------------|------------|-----------------------|-----------|------------|
| 25(1)c   | 307.1805        | 307.1816   | 21.3                  | 21.7      | 94.6       |
| 25(2)    | 341.1415        | 341.1433   | 21                    | 26.8      | 98.9       |
| 25(3)    | 341.1415        | 341.1430   | 14.8                  | 13.6      | 100        |
| 25(4)    | 337.1911        | 337.1928   | 28.9                  | 26.9      | 100        |
| 25(5)    | 351.1703        | 351.1725   | 15.2                  | 13.6      | 90         |
| 25(6)    | 357.1962        | 357.1997   | 30.2                  | 26.5      | 100        |
Amines 26 (from scaffold 3a)

![Chemical Structure](image)

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the ketone scaffold 3a (80 mg, 0.36 mmol) in anhydrous THF (2 mL) was added. The appropriate amine (0.54 mmol) was added, followed by acetic acid (21 μL, 0.36 mmol). The reactions were shaken at 500 rpm at rt for 1 h, then sodium triacetoxyborohydride (150 mg, 0.72 mmol) added. The reactions were shaken for a further 13 h, then quenched by addition of 2M NaOH (0.5 mL) and shaken for an additional 10 min. Dichloromethane (2 mL) was added to each tube and the reactions passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines 26.

| Compound | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------------|------------|-----------------------|-----------|------------|
| 26{1}    | 313.2275        | 313.2288   | 21.8                  | 19.4      | 95.0       |
| 26{2}    | 381.2148        | 381.2162   | 27.3                  | 19.9      | 98.2       |
| 26{3}    | 327.2431        | 327.2442   | 30.5                  | 26.0      | 100.0      |
| 26{4}    | 343.2380        | 343.2400   | 36.3                  | 29.5      | 100.0      |
| 26{5}    | 331.2180        | 331.2196   | 36.8                  | 31.0      | 100.0      |
| 26{6}    | 347.1885        | 347.1923   | 14.4                  | 11.6      | 100.0      |
| 26{7}    | 439.1241        | 439.1272   | 38.8                  | 24.6      | 100.0      |
| 26{8}    | 327.2431        | 327.2431   | 33.5                  | 28.5      | 100.0      |
| 26{9}    | 347.1885        | 347.1910   | 19.8                  | 15.9      | 97.2       |
| 26{10}   | 331.2180        | 331.2192   | 33.3                  | 28.0      | 90.8       |
| 26{11}   | 343.2380        | 343.2400   | 33.7                  | 27.4      | 100.0      |
| 26{12}   | 391.1380        | 391.1413   | 31.6                  | 22.5      | 100.0      |
| 26{13}   | 347.1885        | 347.1912   | 31.0                  | 24.9      | 100.0      |
| 26{14}   | 343.2380        | 343.2402   | 18.5                  | 15.0      | 100.0      |
| 26{15}   | 331.2180        | 331.2206   | 38.3                  | 32.2      | 100.0      |
| 26{16}   | 327.2431        | 327.2442   | 29.1                  | 24.8      | 100.0      |
| 26{17}   | 381.1495        | 381.1513   | 25.1                  | 18.3      | 96.9       |
| 26{18}   | 373.2486        | 373.2499   | 42.4                  | 31.6      | 100.0      |
| 26{19}   | 349.2086        | 349.2113   | 39.0                  | 31.1      | 100.0      |
| 26{20}   | 415.1759        | 415.1785   | 39.0                  | 26.2      | 100.0      |
Carbamates 27:

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the carbonate scaffold S4a-d (80 mg) in anhydrous dichloromethane (1.5 mL) was added, followed by the appropriate amine. The reactions were shaken at 500 rpm at rt for 48 h, then water (2 mL) added. The reactions were passed through Isolute® hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates 27.

| Compound | Calculated Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|----------------|------------|-----------------------|-----------|------------|
| 27a(1)   | 357.2173       | 357.2189   | 35.9                  | 48.0      | 100.0      |
| 27a(2)   | 391.1783       | 391.1788   | 52.0                  | 63.5      | 100.0      |
| 27a(3)   | 425.2047       | 425.2080   | 54.0                  | 60.6      | 98.1       |
| 27a(4)   | 391.1783       | 391.1790   | 55.0                  | 67.1      | 98.7       |
| 27a(5)   | 371.2329       | 371.2357   | 48.1                  | 61.9      | 100.0      |
| 27a(6)   | 391.1783       | 391.1834   | 49.2                  | 60.0      | 100.0      |
| 27a(7)   | 387.2279       | 387.2265   | 40.1                  | 49.4      | 100.0      |
| 27a(8)   | 425.2047       | 425.2043   | 49.6                  | 55.7      | 100.0      |
| 27a(9)   | 425.1393       | 425.1452   | 48.8                  | 54.8      | 100.0      |
| 27a(10)  | 417.2384       | 417.2370   | 45.0                  | 51.5      | 100.0      |
| 27a(11)  | 347.1966       | 347.1975   | 45.0                  | 61.9      | 100.0      |
| 27a(12)  | 361.2122       | 361.2134   | 28.9                  | 38.2      | 98.4       |
| 27a(13)  | 363.1737       | 363.1761   | 33.7                  | 44.3      | 100.0      |
General procedure for the preparation of amides 28

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold {4b-d} (60 mg) in anhydrous dichloromethane (1.5 mL) was added, followed by the appropriate acid (1.2 equiv), EDC (1.2 equiv) and DMAP (1.2 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then water (2 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were
evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amides 28.

| Compound | Calculated Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------------|------------|-----------------------|-----------|------------|
| 28b(1)  | 341.2224        | 341.2244   | 60.3                  | 70.9      | 93.6       |
| 28b(2)  | 375.1834        | 375.1847   | 13.7                  | 14.6      | 97.4       |
| 28b(3)  | 371.2329        | 371.2342   | 122.3                 | 132.1     | 100.0      |
| 28b(5)  | 409.2098        | 409.2084   | 52.8                  | 51.7      | 100.0      |
| 28b(7)  | 375.1834        | 375.1864   | 5.6                   | 6.0       | 75.4       |
| 28b(8)  | 384.2646        | 384.2683   | 50.6                  | 52.8      | 95.3       |
| 28b(9)  | 355.2380        | 355.2399   | 46.7                  | 52.7      | 98.0       |
| 28b(10)| 409.2098        | 409.2082   | 50.7                  | 49.7      | 98.9       |
| 28b(11)| 409.1444        | N/A        | 0.0                   | 0.0       | N/A        |
| 28b(12)| 443.1708        | 443.1706   | 59.1                  | 53.5      | 98.6       |
| 28b(13)| 321.2537        | 321.2545   | 47.7                  | 59.6      | 100.0      |
| 28b(14)| 363.3006        | 363.3026   | 41.6                  | 45.9      | 100.0      |
| 28b(15)| 319.2380        | 319.2414   | 36.9                  | 46.4      | 100.0      |
| 28b(16)| 319.2380        | 319.2412   | 22.3                  | 28.0      | 100.0      |
| 28b(17)| 347.2693        | 347.2701   | 33.1                  | 38.2      | 100.0      |
| 28b(18)| 335.2329        | 335.2358   | 25.2                  | 30.2      | 97.7       |
| 28b(19)| 367.2380        | 367.2369   | 41.4                  | 45.2      | 100.0      |
| 28b(20)| 303.2067        | 303.2083   | 17.1                  | 22.6      | 100.0      |
| 28b(21)| 365.2224        | 365.2231   | 25.4                  | 27.9      | 100.0      |
| 28b(22)| 361.1944        | 361.1955   | 46.4                  | 51.5      | 100.0      |
| 28b(23)| 342.2176        | 342.2206   | 67.2                  | 78.8      | 80.4       |
| 28b(24)| 431.2693        | 431.2725   | 25.3                  | 23.5      | 100.0      |
| 28c(1) | 369.2537        | 369.2551   | 4.6                   | 5.4       | 89.9       |
| 28c(2) | 403.2147        | 403.2168   | 29.3                  | 31.7      | 100.0      |
| 28c(3) | 399.2642        | 399.2638   | 23.0                  | 25.1      | 100.0      |
| 28c(4) | 383.2693        | 383.2684   | 18.3                  | 20.8      | 100.0      |
| 28c(5) | 437.2411        | 437.2430   | 13.5                  | 13.5      | 96.7       |
| 28c(6) | 412.2959        | 412.2959   | 9.9                   | 10.5      | 100.0      |
| 28c(7) | 403.2147        | 403.2162   | 31.8                  | 34.4      | 100.0      |
| 28c(8) | 412.2959        | 412.2958   | 28.1                  | 29.7      | 98.5       |
| 28c(9) | 383.2693        | 383.2683   | 15.1                  | 17.2      | 100.0      |
| 28c(10)| 437.2411        | 437.2407   | 32.2                  | 32.1      | 100.0      |
| 28c(11)| 437.1757        | 437.1804   | 23.5                  | 23.4      | 100.0      |
| 28c(12)| 471.2021        | 471.2030   | 37.5                  | 34.7      | 94.5       |
| 28c(13)| 349.2850        | 349.2879   | 35.9                  | 44.8      | 98.0       |
| 28c(14)| 391.3319        | 391.3318   | 40.1                  | 44.7      | 96.8       |
| 28c(15)| 347.2693        | 347.2717   | 31.1                  | 39.1      | 94.3       |
| 28c(16)| 347.2693        | 347.2722   | 10.9                  | 13.7      | 100.0      |
| 28c(17)| 375.3006        | 375.3038   | 23.5                  | 27.3      | 100.0      |
| 28c(18)| 363.2642        | 363.2666   | 30.8                  | 37.0      | 100.0      |
| 28c(19)| 395.2693        | 395.2696   | 37.7                  | 41.6      | 100.0      |
| 28c(20)| 331.2380        | 331.2421   | 9.6                   | 12.6      | 96.2       |
| 28c(21)| 393.2537        | 393.2510   | 7.8                   | 8.6       | 95.9       |
| 28c(22)| 389.2257        | 389.2268   | 13.7                  | 15.3      | 71.2       |
| 28c(23)| 370.2489        | 370.2507   | 20.9                  | 24.6      | 100.0      |
| 28c(24)| 459.3006        | 459.3026   | 55.6                  | 52.7      | 100.0      |
| 28d(1) | 417.2537        | 417.2537   | 36.2                  | 41.4      | 98.8       |
| 28d(2) | 451.2147        | 451.2148   | 32.5                  | 34.4      | 98.3       |
| 28d(3) | 447.2642        | 447.2645   | 39.1                  | 41.7      | 97.6       |
| 28d(4) | 431.2693        | 431.2708   | 48.9                  | 54.1      | 100.0      |
| 28d(5) | 485.2411        | 485.2403   | 44.7                  | 44.0      | 95.4       |
| 28d(6) | 460.2959        | 460.2948   | 73.5                  | 76.2      | 96.6       |
| 28d(7) | 451.2147        | 451.2142   | 45.8                  | 48.4      | 99.0       |
| 28d(8) | 460.2959        | 460.2949   | 63.5                  | 65.8      | 95.3       |
General procedure for the preparation of sulfonamides 29

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold 4b-d (70 mg) in anhydrous dichloromethane (2 mL) was added, followed by the appropriate sulfonyl chloride (1.5 equiv) and Et$_3$N (1.5 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then water (2 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure sulfonamides 29.

| Compound | Calculated Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------------|------------|-----------------------|-----------|------------|
| 29b(1)   | 377.1894        | 377.1899   | 48.5                  | 43.0      | 100.0      |
| 29b(2)   | 422.1744        | 422.1725   | 69.6                  | 55.1      | 100.0      |
| 29b(3)   | 391.2050        | 391.2053   | 77.2                  | 65.9      | 100.0      |
Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold 4b-d (60 mg) in anhydrous toluene (2 mL) was added, followed by the appropriate isocyanate (1.5 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure ureas 30.
| 30b(17) | 424.1553 | 424.1563 | 16.4 | 12.9 | 86.1 |
| 30b(18) | 370.2489 | 370.2498 | 16.3 | 14.7 | 92.9 |
| 30b(19) | 360.2282 | 360.2297 | 75.9 | 70.4 | 79.2 |
| 30b(20) | 394.2701 | 394.2721 | 103.0 | 87.3 | 98.7 |
| 30b(21) | 308.2333 | 308.2346 | 27.8 | 30.2 | 97.0 |
| 30b(22) | 336.2646 | 336.2660 | 45.5 | 45.2 | 97.5 |
| 30c(1)  | 384.2646 | 384.2647 | 24.8 | 24.9 | 92.5 |
| 30c(2)  | 398.2802 | 398.2794 | 25.6 | 24.8 | 100.0 |
| 30c(3)  | 418.2256 | 418.2276 | 16.0 | 14.7 | 100.0 |
| 30c(4)  | 414.2751 | 414.2776 | 29.7 | 27.6 | 100.0 |
| 30c(5)  | 452.2520 | 452.2524 | 10.1 | 8.6 | 76.2 |
| 30c(6)  | 414.2751 | 414.2784 | 7.1  | 6.6  | 83.8 |
| 30c(7)  | 452.2520 | 452.2522 | 31.2 | 26.6 | 95.3 |
| 30c(8)  | 409.2598 | 409.2625 | 20.3 | 19.1 | 88.9 |
| 30c(9)  | 398.2802 | 398.2783 | 22.1 | 21.4 | 67.0 |
| 30c(10) | 418.2256 | 418.2296 | 29.1 | 26.8 | 100.0 |
| 30c(11) | 414.2751 | 414.2773 | 29.8 | 27.7 | 86.5 |
| 30c(12) | 452.2520 | 452.2521 | 32.7 | 27.9 | 100.0 |
| 30c(13) | 409.2598 | 409.2621 | 21.6 | 20.3 | 93.6 |
| 30c(14) | 402.2552 | 402.2558 | 30.9 | 29.6 | 72.3 |
| 30c(15) | 426.3115 | 426.3122 | 14.0 | 12.7 | 99.0 |
| 30c(16) | 428.2544 | 428.2579 | 7.1  | 6.4  | 0.9  |
| 30c(17) | 452.1866 | 452.1900 | 22.0 | 18.8 | 96.8 |
| 30c(18) | 398.2802 | 398.2800 | 23.0 | 22.3 | 14.0 |
| 30c(19) | 388.2595 | 388.2631 | 26.8 | 26.6 | 100.0 |
| 30c(20) | 422.3014 | 422.3027 | 18.0 | 16.4 | 94.0 |
| 30c(21) | 336.2646 | 336.2686 | 14.7 | 16.9 | 87.2 |
| 30c(22) | 364.2959 | 364.2971 | 32.8 | 34.7 | 100.0 |
| 30d(1)  | 432.2646 | 432.2662 | 23.7 | 26.2 | 98.5 |
| 30d(2)  | 446.2802 | 446.2825 | 57.8 | 61.8 | 87.2 |
| 30d(3)  | 466.2256 | 466.2288 | 23.0 | 23.5 | 96.8 |
| 30d(4)  | 462.2751 | 462.2765 | 60.5 | 62.5 | 79.1 |
| 30d(5)  | 500.2520 | 500.2492 | 28.6 | 27.3 | 94.3 |
| 30d(6)  | 462.2751 | 462.2749 | 50.4 | 52.0 | 95.3 |
| 30d(7)  | 500.2520 | 500.2531 | 47.0 | 44.8 | 96.7 |
| 30d(8)  | 457.2598 | 457.2616 | 34.4 | 35.9 | 100.0 |
| 30d(9)  | 446.2802 | 446.2808 | 19.4 | 20.7 | 95.3 |
| 30d(10) | 466.2256 | 466.2277 | 27.6 | 28.3 | 100.0 |
| 30d(11) | 462.2751 | 462.2757 | 38.0 | 39.2 | 100.0 |
| 30d(12) | 500.2520 | 500.2528 | 54.6 | 52.1 | 98.1 |
| 30d(13) | 457.2598 | 457.2627 | 59.8 | 62.4 | 86.5 |
| 30d(14) | 450.2552 | 450.2566 | 46.9 | 49.7 | 98.4 |
| 30d(15) | 474.3115 | 474.3122 | 40.2 | 40.4 | 100.0 |
| 30d(16) | 476.2544 | 476.2544 | 40.8 | 40.9 | 90.5 |
| 30d(17) | 500.1866 | - | 0.0 | 0.0 | - |
| 30d(18) | 446.2802 | 446.2841 | 37.8 | 40.4 | 73.9 |
| 30d(19) | 436.2955 | 436.2961 | 51.2 | 56.0 | 100.0 |
| 30d(20) | 470.3014 | 470.3048 | 62.1 | 63.0 | 97.3 |
| 30d(21) | 384.2646 | 384.2675 | 54.0 | 67.1 | 100.0 |
| 30d(22) | 412.2959 | 412.2988 | 51.4 | 59.5 | 98.7 |
Amines 26 and S7b-d from scaffolds 4b-d and S5b-d:

The appropriate aldehyde (1.2 equiv) was added to a solution of amine scaffold 4b-d or S5b-d (200 mg) in anhydrous dichloromethane (6 mL) at rt under argon. Acetic acid (1 equiv) was then added, and the mixture stirred at rt for 1 h. Sodium triacetoxyborohydride (2 equiv) was added, and the mixture stirred at rt for 18 h, then quenched with 2M NaOH (3 mL) and extracted with dichloromethane (3 x 5 mL). The combined organics were dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by Combiflash® automated column chromatography (12 g silica column, 0% MeOH in CH$_2$Cl$_2$ for 3 min, then 0 to 5% over 10 min) to afford pure amines 26 or S7b-d.

| Compound | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|----------------|------------|-----------------------|-----------|------------|
| 26b(1)   | 327.2431       | 327.2487   | 430                   | 80.0      | 95.4       |
| 26b(2)   | 333.1995       | 333.2039   | 360                   | 66.0      | 100.0      |
| 26b(3)   | 333.2901       | 333.2922   | 325                   | 59.0      | 93.2       |
| 26c(1)   | 355.2744       | 355.2302   | 198                   | 73.0      | 98.9       |
| 26c(2)   | 361.2308       | 361.2319   | 213                   | 78.0      | 91.6       |
| 26c(3)   | 361.3214       | 361.3221   | 213                   | 78.0      | 92.1       |
| 26d(1)   | 403.2744       | 403.2726   | 145                   | 56.0      | 98.3       |
| 26d(2)   | 409.2308       | 409.2328   | 230                   | 88.0      | 0.0        |
| 26d(3)   | 409.3214       | 409.3226   | 170                   | 65.0      | 94.7       |
| S7b(1)   | 327.2431       | 327.2454   | 88.8                  | 32.0      | 79.7       |
| S7b(2)   | 333.1995       | 333.2016   | 47.9                  | 17.0      | 81.0       |
| S7b(3)   | 333.2901       | 333.2908   | 77.5                  | 27.4      | 85.2       |
| S7c(1)   | 355.2744       | 355.2742   | 130                   | 48.0      | 96.4       |
| S7c(2)   | 361.2308       | 361.2318   | 143                   | 52.0      | 97.7       |
| S7c(3)   | 361.3214       | 361.3214   | 170                   | 62.0      | 91.8       |
| S7d(1)   | 403.2744       | 403.2743   | 147                   | 57.0      | 95.2       |
| S7d(2)   | 409.2308       | 409.2300   | 152                   | 58.0      | 94.8       |
| S7d(3)   | 409.3214       | 409.3233   | 90                    | 34.0      | 96.6       |
General procedure for the preparation of amines 32

\[ \text{R}^2 \text{H} \stackrel{\text{Na(OAc)}_3 \text{BH}}{\text{N}} \text{R}^1 \text{H} \] 

\( R^1 = \text{Me} \)
\( c = \text{nPr} \)
\( d = \text{Br} \)

A solution of amine 26b-d (150 mg) in dichloromethane (3 mL) was placed in a 2 dram screw cap vial. Formaldehyde (37% aq solution, 3 equiv) was added, followed by acetic acid (1 equiv) and sodium triacetoxyborohydride (3 equiv). The reaction mixture was stirred at rt for 18 h, then quenched with 2M NaOH and passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines 32.

| Compound | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------------|------------|-----------------------|-----------|------------|
| 32b(1)   | 341.2588        | 341.2610   | 97.4                  | 136.3     | 93.9       |
| 32b(2)   | 347.2152        | 347.2141   | 41.5                  | 57.1      | 100.0      |
| 32b(3)   | 347.3057        | 347.3072   | 74.9                  | 103.0     | 94.0       |
| 32c(1)   | 369.2901        | 369.2906   | 76.2                  | 98.5      | 92.9       |
| 32c(2)   | 375.2465        | 375.2458   | 79.9                  | 101.7     | 93.7       |
| 32c(3)   | 375.3370        | 375.3416   | 80.6                  | 102.5     | 90.5       |
| 32d(1)   | 417.2901        | 417.2896   | 97.5                  | 73.2      | 95.6       |
| 32d(2)   | 423.2465        | 423.2450   | 86.8                  | 46.7      | 93.2       |
| 32d(3)   | 423.3370        | 423.3343   | 181.8                 | 97.8      | 90.1       |

Ammones 31b-d and S8b-d:

Amine scaffold 4b-d or S5b-d (150 mg) was dissolved in formic acid (900 μL) and formaldehyde (37% aq solution, 1.4 mL). The reaction mixture was heated at 95 °C for 18 h, then cooled to rt and concentrated under reduced pressure. The residue was made basic with 2M NaOH (2 mL) then extracted with dichloromethane (5 x 3 mL). The combined organics were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was subjected to mass-directed preparative HPLC purification to afford pure amines 31 or S8b-d.
| Compound | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|----------------|------------|----------------------|-----------|------------|
| 31b      | 265.2275       | 265.2284   | 32                   | 28.8      | 100.0      |
| 31c      | 293.2588       | 293.2600   | 55.1                 | 33.1      | 100.0      |
| 31d      | 341.2588       | 341.2588   | 49.2                 | 30.1      | 98.3       |
| S8b      | 265.2275       | 265.2301   | 65.3                 | 39.2      | 97.7       |
| S8c      | 293.2588       | 293.2592   | 187.6                | 112.6     | 95.5       |
| S8d      | 341.2588       | 341.2607   | 60.4                 | 37.0      | 100.0      |

Characterization data for representative library compounds

Quinoline 25[3]

δH (500 MHz, CDCl₃) 8.26 (1H, s), 7.92-7.87 (1H, m), 7.58-7.53 (2H, m), 4.04-3.99 (1H, m), 3.58-3.43 (3H, m), 3.10-3.03 (2H, m), 2.75-2.69 (1H, m), 2.62-2.53 (1H, m), 2.13-1.96 (3H, m), 1.92-1.80 (4H, m), 1.72-1.59 (2H, m); δC (125 MHz, CDCl₃) 173.5, 157.2, 147.7, 133.0, 130.6, 128.9, 128.8, 127.6, 126.1, 125.0, 63.8, 49.3, 43.3, 41.00, 40.97, 38.3, 34.3, 33.3, 23.1, 20.3; m/z (ESI+) found [M+H]+ 341.1430. C₂₀H₂₂ClN₂O requires 341.1415.

Quinoline 25[1]

δH (500 MHz, CDCl₃) 7.98 (1H, d, J 8.5), 7.86 (1H, s), 7.74 (1H, d, J 8.1), 7.68-7.64 (1H, m), 7.50-7.46 (1H, m), 4.04-3.99 (1H, m), 3.54-3.43 (3H, m), 3.08 (1H, dd, J 17.8, 2.0), 2.99 (1H, d, J 16.5), 2.75-2.69 (1H, m), 2.61-2.55 (1H, m), 2.12-1.60 (9H, m); δC (125 MHz, CDCl₃) 173.6, 156.2, 147.1, 136.2, 129.3, 128.3, 127.6, 127.0, 126.9, 126.1, 63.9, 49.3, 43.4, 41.1, 40.6, 38.3, 34.2, 33.3, 23.1, 20.3; m/z (ESI+) found [M+H]+ 307.1816. C₂₀H₂₃N₂O₂ requires 307.1805.
Amine 26[3]

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) & \ 7.28-7.25 (1H, m), 7.19-7.16 (3H, m), 3.75-3.67 (3H, m), 3.52-3.45 (1H, m), 2.95-2.91 (1H, m), 2.62-2.45 (3H, m), 2.40-2.35 (1H, m), 2.36 (3H, s), 2.23 (1H, ddd, J 13.3, 13.3, 4.9), 1.92-1.63 (10H, m), 1.53-1.44 (1H, m), 1.36 (1H, ddd, J 13.3, 4.2, 2.5); \\
\delta_C (125 \text{ MHz, CDCl}_3) & \ 173.8, 138.6, 136.4, 130.3, 128.6, 127.1, 126.0, 66.6, 51.8, 50.2, 48.7, 43.0, 39.7, 37.2, 35.2, 32.4, 28.4, 25.8, 22.3, 20.4, 19.0; m/z (ESI+) found [M+H]^+ 327.2442. C_{21}H_{30}N_2O^+ requires 327.2431.
\end{align*}
\]

Amine 26[24]

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) & \ 8.54 (1H, d, J 1.7), 8.48 (1H, dd, J 4.8, 1.7), 7.64-7.62 (1H, m), 7.24 (1H, ddd, J 7.8, 4.8, 0.7), 3.78-3.66 (3H, m), 3.49-3.43 (1H, m), 2.90-2.85 (1H, m), 2.58-2.44 (3H, m), 2.36-2.31 (1H, m), 2.19 (1H, ddd, J 13.4, 13.4, 4.7), 1.86-1.58 (10H, m), 1.52-1.42 (1H, m), 1.34 (1H, ddd, J 13.4, 4.2, 2.2); \\
\delta_C (125 \text{ MHz, CDCl}_3) & \ 173.7, 149.6, 148.5, 136.0, 135.7, 123.4, 66.4, 51.2, 49.3, 48.7, 43.0, 39.7, 37.1, 34.8, 32.2, 28.5, 25.6, 22.2, 20.4; m/z (ESI+) found [M+H]^+ 314.2231. C_{19}H_{28}N_2O^+ requires 314.2227.
\end{align*}
\]

Carbamate 27a[3]

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) & \ \text{At ambient temperature, a 4:1 mixture of rotamers was observed. Major rotamer: 7.52-7.40 (4H, m), 5.52 (1H, s), 4.90 (1H, br s), 4.41 (1H, d, J 6.2), 4.38 (1H, d, J 6.2), 3.74-3.68 (1H, m), 3.47-3.40 (1H, m), 2.59-2.53 (1H, m), 2.44-2.23 (3H, m), 2.14-2.08 (1H, m), 1.97-1.92 (1H, m), 1.89-1.53 (9H, m), 1.45-1.33 (2H, m). Minor rotamer (characteristic signals): 5.52 (1H, s), 4.44 (1H, d, J 6.2), 4.35 (1H, d, J 6.2); \\
\delta_C (125 \text{ MHz, CDCl}_3) & \ \text{Major rotamer: 174.1, 155.9, 139.8, 130.75, 130.77 (q, J 32.0), 129.0, 124.1 (d, J 3.5), 124.0 (d, J 3.5), 123.9 (q, J 270), 68.4, 66.0, 48.9, 44.3, 43.4, 38.8, 38.4, 35.6, 34.0, 28.5, 24.6, 23.5, 20.1; m/z (ESI+) found [M+H]^+ 425.2080. C_{22}H_{28}F_3N_3O_3 requires 425.2047.}
\end{align*}
\]
Carbamate 27b\[^1\]

\[\text{\textit{Ph}} \quad \text{\textit{H}} \quad \text{\textit{O}} \quad \text{\textit{Me}}\]

\(\delta_H (500 \text{ MHz, } \text{CDCl}_3)\) At ambient temperature, a 7:3 mixture of rotamers was observed. Major rotamer: 7.33-7.19 (5H, m), 5.50 (1H, br s), 4.85 (1H, br s), 4.45-4.23 (2H, m), 3.83-3.71 (1H, m), 3.43-3.29 (1H, m), 2.62-2.53 (1H, m), 2.46-2.32 (2H, m), 2.11-2.00 (2H, m), 1.95-1.12 (11H, m), 0.96 (3H, d, \(J = 6.9\)). Minor rotamer (characteristic signals): 5.39 (1H, br s), 4.79 (1H, br s), 0.87 (3H, d, \(J = 5.7\)); \(\delta_C (125 \text{ MHz, } \text{CDCl}_3)\) Major rotamer: 174.6, 156.4, 138.6, 128.7, 127.7, 127.5, 71.7, 67.6, 49.8, 49.1, 45.1, 38.9, 38.8, 37.1, 29.0, 27.8, 24.2, 23.6, 20.2, 15.9; \(m/z\) (ESI+) found [M+H]\(^+\) 371.2336. \(\text{C}_{22}\text{H}_{31}\text{N}_{2}\text{O}_{3}^+\) requires 371.2329.

Carbamate 27c\[^4\]

\[\text{Cl} \quad \text{\textit{N}} \quad \text{\textit{O}} \quad \text{\textit{Me}} \quad \text{\textit{nPr}}\]

\(\delta_H (500 \text{ MHz, } \text{CDCl}_3)\) At ambient temperature, a 7:3 mixture of rotamers was observed. Major rotamer: 7.28-7.09 (4H, m), 5.36 (1H, br s), 4.95 (1H, br s), 4.40-4.25 (2H, m), 3.85-3.74 (1H, m), 3.44-3.30 (1H, m), 2.63-2.58 (1H, m), 2.48-2.37 (2H, m), 2.14-1.50 (11H, m), 1.45-1.11 (6H, m), 0.91-0.80 (3H, m). Minor rotamer (characteristic signals): 5.63 (1H, br s), 4.88 (1H, br s); \(\delta_C (125 \text{ MHz, } \text{CDCl}_3)\) Major rotamer: 174.5, 156.3, 140.8, 134.5, 129.9, 127.58, 127.55, 125.6, 70.7, 67.5, 49.1, 47.7, 44.4, 42.2, 38.9, 38.8, 31.7, 29.0, 27.9, 24.6, 23.7, 20.2, 19.9, 14.2; \(m/z\) (ESI+) found [M+H]\(^+\) 433.2284. \(\text{C}_{24}\text{H}_{34}\text{ClN}_{2}\text{O}_{3}^+\) requires 433.2252.

Carbamate 27d\[^{19}\]

\[\text{\textit{N}} \quad \text{\textit{O}} \quad \text{\textit{Me}} \quad \text{\textit{Bn}}\]

\(\delta_H (500 \text{ MHz, } \text{CDCl}_3)\) 7.30-7.26 (2H, m), 7.22-7.18 (1H, m), 7.11-7.08 (2H, m), 4.85 (1H, br s), 3.86-3.79 (1H, m), 3.42-3.27 (5H, m), 2.78 (1H, dd, \(J = 13.6, 7.6\)), 2.68-2.57 (2H, m), 2.47-2.38 (2H, m), 2.24-2.06 (4H, m), 1.97-1.91 (1H, m), 1.88-1.48 (6H, m), 1.42-1.30 (2H, m), 1.25-1.14 (6H, m); \(\delta_C (125 \text{ MHz, } \text{CDCl}_3)\) 174.3, 155.4, 139.7, 128.8, 128.6, 126.3, 70.2, 67.5, 49.1, 47.4, 45.0, 42.0, 41.4, 39.0, 38.9,
36.3, 28.8, 28.0, 24.6, 23.6, 20.2, 14.4, 13.7; m/z (ESI+) found [M+H]^+ 413.2779. C_{25}H_{37}N_{2}O_{3}^+ requires 413.2799.

Amide 28b{3}

δ_{n} (500 MHz, CDCl_{3}) 7.69-7.66 (2H, m), 6.93-6.89 (2H, m), 6.25 (1H, d, J 8.5), 4.30-4.25 (1H, m), 3.82 (3H, s), 3.83-3.78 (1H, m), 3.46-3.39 (1H, m), 2.71-2.65 (1H, m), 2.44 (1H, dd, J 18.0, 18.0), 2.31-2.25 (2H, m), 2.21-2.15 (1H, m), 2.06-1.49 (9H, m), 1.45-1.35 (2H, m), 1.00 (3H, d, J 7.1); δ_{c} (125 MHz, CDCl_{3}) 174.0, 166.7, 162.2, 128.5, 127.1, 113.9, 67.7, 55.5, 50.7, 49.2, 46.8, 39.1, 38.9, 36.7, 29.0, 28.9, 24.4, 23.8, 20.1, 16.5; m/z (ESI+) found [M+H]^+ 371.2342. C_{22}H_{31}N_{2}O_{3}^+ requires 371.2329.

Amide 28c{8}

δ_{n} (500 MHz, CDCl_{3}) 7.26 (1H, t, J 8.2), 7.17 (1H, dd, J 2.4, 1.7), 6.86 (1H, br d, J 8.2), 6.82 (1H, dd, J 8.2, 2.4), 6.31 (1H, d, J 8.5), 4.35-4.30 (1H, m), 3.85-3.79 (1H, m), 3.47-3.41 (1H, m), 2.97 (6H, s), 2.72-2.65 (1H, m), 2.61-2.57 (1H, m), 2.45-2.37 (1H, m), 2.18-1.86 (7H, m), 1.82-1.58 (4H, m), 1.48-1.24 (6H, m), 0.86 (3H, t, J 7.1); δ_{c} (125 MHz, CDCl_{3}) 173.9, 167.8, 150.8, 135.8, 129.3, 115.1, 113.2, 111.3, 67.7, 49.3, 48.6, 45.6, 41.6, 41.0, 40.4, 39.1, 39.0, 32.4, 29.14, 29.08, 24.8, 23.9, 20.09, 20.05, 14.2; m/z (ESI+) found [M+H]^+ 412.2958. C_{26}H_{38}N_{2}O_{3}^+ requires 412.2959.

Amide 28c{13}

δ_{n} (500 MHz, CDCl_{3}) 6.03 (1H, d, J 8.9), 4.04-3.98 (1H, m), 3.68-3.62 (1H, m), 3.30-3.23 (1H, m), 2.50-2.29 (3H, m), 2.04 (2H, td, J 7.9, 1.9), 1.94 (1H, ddd, J 13.7, 13.7, 4.5), 1.85-1.70 (4H, m), 1.66-1.38 (8H, m), 1.29-1.02 (8H, m), 0.77 (3H, t, J 7.4), 0.72 (3H, t, J 7.5); δ_{c} (125 MHz, CDCl_{3}) 174.0, 172.6,
67.6, 49.0, 48.3, 44.6, 41.6, 38.77, 38.76, 36.6, 32.2, 29.2, 28.2, 27.9, 24.8, 23.7, 22.3, 20.0, 19.9, 14.1, 13.8; \( m/z \) (ESI+) found [M+H]^+ 349.2879. \( \text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_2^+ \) requires 349.2850.

**Amide 28d[11]**

\[
\begin{align*}
\delta_\text{H} (500 \text{ MHz, CDCl}_3) & \ 7.88 (1\text{H, br s}), 7.59-7.55 (2\text{H, m}), 7.73-7.26 (2\text{H, m}), 7.23-7.19 (1\text{H, m}), 7.12-7.09 (2\text{H, m}), 6.39 (1\text{H, d, J 8.5}), 4.40-4.35 (1\text{H, m}), 3.81 (1\text{H, dd, J 10.5, 10.5}), 3.40-3.33 (1\text{H, m}), 2.84 (1\text{H, dd, J 13.9, 6.6}), 2.72-2.66 (1\text{H, m}), 2.63-2.54 (2\text{H, m}), 2.46-2.38 (2\text{H, m}), 2.34-2.29 (1\text{H, m}), 2.10-1.89 (3\text{H, m}), 1.80-1.61 (4\text{H, m}), 1.56-1.47 (3\text{H, m}), 1.38-1.28 (1\text{H, m}); \\
\delta_\text{C} (125 \text{ MHz, CDCl}_3) & \ 173.7, 164.9, 139.0, 136.2, 134.6, 133.4, 130.8, 129.3, 128.7, 128.6, 126.5, 125.7, 67.4, 49.3, 47.6, 46.4, 44.3, 39.1, 38.9, 36.4, 29.2, 29.1, 24.7, 23.6, 19.9; \ m/z \ (\text{ESI+}) \ \text{found [M+H]}^+ 485.1770. \ \text{C}_{27}\text{H}_{31}\text{Cl}_2\text{N}_2\text{O}_2^+ \ \text{requires} \ 485.1757.
\end{align*}
\]

**Sulfonamide 29b[2]**

\[
\begin{align*}
\text{Mp} & \ 227-229^\circ \text{C}; \ \nu_{\text{max}} (\text{film})/\text{cm}^{-1} \ 2942, 1591, 1539; \\
\delta_\text{H} (500 \text{ MHz, CDCl}_3) & \ 8.12-8.08 (1\text{H, m}), 7.91-7.86 (1\text{H, m}), 7.78-7.73 (2\text{H, m}), 5.55 (1\text{H, d, J 7.0}), 3.85-3.79 (1\text{H, m}), 3.50-3.41 (2\text{H, m}), 2.71 (1\text{H, dd, J 15.3, 6.7}), 2.49-2.40 (2\text{H, m}), 2.21-2.01 (3\text{H, m}), 1.98-1.90 (1\text{H, m}), 1.86-1.32 (9\text{H, m}), 0.84 (3\text{H, d, J 7.1}); \\
\delta_\text{C} (125 \text{ MHz, CDCl}_3) & \ 174.2 (C), 147.9 (C), 133.9 (C), 133.7 (CH), 132.9 (CH), 130.8 (CH), 125.6 (CH), 67.2 (C), 53.2 (CH), 50.3 (CH), 49.2 (CH\text{$_2$}), 39.1 (CH\text{$_2$}), 39.0 (CH\text{$_2$}), 36.8 (CH), 30.0 (CH\text{$_2$}), 28.6 (CH\text{$_2$}), 23.9 (CH\text{$_3$}), 23.6 (CH\text{$_2$}), 20.0 (CH\text{$_2$}), 16.3 (CH\text{$_3$}); \ m/z \ (\text{ESI+}) \ \text{found [M+H]}^+ 422.1765. \ \text{C}_{20}\text{H}_{28}\text{N}_3\text{O}_5^+ \ \text{requires} \ 422.1744.
\end{align*}
\]

**Sulfonamide 29c[8]**

\[
\begin{align*}
\end{align*}
\]
Mp 207-208 °C; δ_{H} (500 MHz, CDCl$_3$) 7.87-7.83 (2H, m), 7.52-7.49 (2H, m), 5.29 (1H, d, J 7.1), 3.81-3.76 (1H, m), 3.27-3.23 (1H, m), 2.59 (1H, dd, J 15.2, 6.7), 2.41-2.31 (2H, m), 2.07-2.00 (1H, m), 1.92-1.87 (1H, m), 1.84-1.79 (1H, m), 1.76-1.56 (7H, m), 1.53-1.48 (1H, m), 1.38-0.94 (6H, m), 0.78 (3H, t, J 7.1); δ_{C} (125 MHz, CDCl$_3$) 172.5 (C), 137.4 (C), 136.5 (C), 127.5 (CH), 126.8 (CH), 65.2 (C), 48.7 (CH), 47.2 (CH$_2$), 46.3 (CH), 40.2 (CH), 37.1 (CH$_2$), 36.8 (CH$_2$), 30.3 (CH$_2$), 27.3 (CH$_2$), 26.5 (CH$_2$), 22.4 (CH$_3$), 21.6 (CH$_3$), 18.1 (CH$_3$), 18.0 (CH$_2$), 12.1 (CH$_3$); m/z (ESI+) found [M+H]$^+$ 439.1808. C$_{22}$H$_{32}$ClN$_2$O$_3$S$^+$ requires 439.1817.

Sulfonamide 29d{[19]}

\[
\begin{align*}
\delta_{H} (500 MHz, CDCl$_3$) & 7.26-7.21 (2H, m), 7.20-7.16 (1H, m), 6.98-6.95 (4H, m), 4.92 (1H, d, J 7.9), 3.77-3.72 (1H, m), 3.43-3.38 (1H, m), 3.36-3.29 (1H, m), 2.67 (6H, s), 2.67-2.62 (1H, m), 2.58-2.52 (1H, m), 2.44-2.35 (3H, m), 2.29 (3H, s), 2.23-2.18 (1H, m), 2.14-2.09 (1H, m), 2.01 (1H, ddd, J 13.5, 13.5, 5.1), 1.89-1.55 (6H, m), 1.46-1.33 (3H, m), 1.26-1.18 (1H, m); \\
\delta_{C} (125 MHz, CDCl$_3$) & 174.0, 142.5, 139.1, 139.0, 134.1, 132.1, 128.6, 128.5, 126.3, 67.2, 51.1, 49.1, 46.9, 44.2, 38.90, 38.85, 35.9, 29.3, 28.6, 24.3, 23.4, 23.2, 21.0, 19.9; m/z (ESI+) found [M+H]$^+$ 495.2667. C$_{29}$H$_{38}$N$_2$O$_3$S$^+$ requires 495.2676.
\end{align*}
\]

Sulfonamide 29d{[22]}

\[
\begin{align*}
\delta_{H} (500 MHz, CDCl$_3$) & 7.49 (1H, d, J 1.2), 7.46 (1H, d, J 1.2), 7.26-7.22 (2H, m), 7.18-7.14 (1H, m), 7.11-7.08 (2H, m), 5.57 (1H, d, J 7.5), 3.74-3.70 (1H, m), 3.70 (3H, s), 3.52-3.47 (1H, m), 3.30-3.23 (1H, m), 2.78 (1H, dd, J 14.4, 10.2), 2.68 (1H, dd, J 14.4, 5.1), 2.57-2.52 (1H, m), 2.42-2.35 (2H, m), 2.23-2.18 (1H, m), 2.14-2.06 (2H, m), 1.85-1.51 (6H, m), 1.42-1.35 (1H, m), 1.32-1.27 (2H, m), 1.21-1.10 (1H, m); \\
\delta_{C} (125 MHz, CDCl$_3$) & 174.3, 140.2, 139.6, 139.1, 128.7, 128.5, 126.1, 124.4, 67.3, 51.6, 49.0, 46.3, 44.1, 38.8, 38.6, 35.9, 34.0, 29.2, 27.9, 24.5, 23.4, 19.9; m/z (ESI+) found [M+H]$^+$ 457.2260. C$_{24}$H$_{33}$N$_2$O$_3$S$^+$ requires 457.2268.
\end{align*}
\]
Urea 30d[21]

\[
\delta_{\text{H}} \text{(500 MHz, CDCl}_3\text{)} 7.28-7.25 (2\text{H, m}), 7.20-7.17 (1\text{H, m}), 7.14-7.12 (2\text{H, m}), 5.43 (1\text{H, d, } J 8.5), 5.34 (1\text{H, t, } J 5.0), 4.03-4.01 (1\text{H, m}), 3.79-3.75 (1\text{H, m}), 3.37-3.31 (1\text{H, m}), 3.20 (2\text{H, qd, } J 7.2, 5.0), 2.85 (1\text{H, dd, } J 14.0, 6.1), 2.62-2.51 (3\text{H, m}), 2.37 (1\text{H, dd, } J 13.8, 13.8), 2.27-2.22 (1\text{H, m}), 2.15-2.09 (1\text{H, m}), 2.02 (1\text{H, ddd, } J 13.4, 13.4, 4.1), 1.94-1.86 (1\text{H, m}), 1.80-1.63 (5\text{H, m}), 1.53-1.47 (1\text{H, m}), 1.40-1.37 (2\text{H, m}), 1.27-1.19 (1\text{H, m}), 1.09 (3\text{H, t, } J 7.2); \delta_{\text{C}} \text{(125 MHz, CDCl}_3\text{)} 174.2, 158.5, 139.9, 128.7, 128.5, 126.1, 68.0, 49.2, 47.1, 46.2, 44.6, 38.9, 38.8, 36.3, 35.0, 30.2, 28.3, 24.9, 23.6, 20.0, 15.6; m/z (ESI+) found [M+H]+ 384.2675. C_{23}H_{34}N_{3}O_{2}+ requires 384.2646.

Amine 26d[1]

\[
\nu_{\text{max}} \text{(film)/cm}^{-1} 2931, 2868, 1608; \delta_{\text{H}} \text{(500 MHz, CDCl}_3\text{)} 7.40-7.36 (4\text{H, m}), 7.32-7.27 (3\text{H, m}), 7.23-7.19 (1\text{H, m}), 7.12-7.10 (2\text{H, m}), 3.86-3.79 (2\text{H, m}), 3.50 (1\text{H, d, } J 13.1), 3.40 (1\text{H, ddd, } J 12.3, 9.7, 7.7), 2.74 (1\text{H, dd, } J 13.5, 8.2), 2.69-2.62 (3\text{H, m}), 2.56-2.34 (3\text{H, m}), 2.26-2.20 (2\text{H, m}), 2.01-1.96 (1\text{H, m}), 1.92-1.82 (2\text{H, m}), 1.75-1.52 (4\text{H, m}), 1.49-1.45 (1\text{H, m}), 1.36-1.24 (2\text{H, m}); \delta_{\text{C}} \text{(125 MHz, CDCl}_3\text{)} 174.7 (C), 141.0 (C), 140.3 (C), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 126.2 (CH), 68.3 (C), 54.0 (CH), 53.1 (CH)\text{, } 49.1 (CH)\text{, } 48.5 (CH), 45.8 (CH), 39.1 (CH)\text{, } 39.0 (CH)\text{, } 36.7 (CH)\text{, } 29.2 (CH)\text{, } 27.0 (CH)\text{, } 24.7 (CH)\text{, } 23.5 (CH)\text{, } 20.2 (CH); m/z (ESI+) found [M+H]+ 403.2726. C_{29}H_{35}N_{2}O_{2}+ requires 403.2744.

Amine 32b[2]

\[
\delta_{\text{H}} \text{(500 MHz, CDCl}_3\text{)} 7.18 (1\text{H, dd, } J 5.1, 1.2), 6.91 (1\text{H, dd, } J 5.1, 3.4), 6.86 (1\text{H, dd, } J 3.4, 1.2), 3.84-3.78 (2\text{H, m}), 3.74 (1\text{H, d, } J 14.3), 3.45-3.38 (1\text{H, m}), 2.64-2.59 (2\text{H, m}), 2.52-2.38 (2\text{H, m}), 2.23 (3\text{H, s}), 2.19-2.14 (2\text{H, m}), 2.08-1.96 (3\text{H, m}), 1.92-1.85 (1\text{H, m}), 1.76-1.64 (4\text{H, m}), 1.50-1.31 (3\text{H, m}), 1.19 (3\text{H, d, } J 7.3); \delta_{\text{C}} \text{(125 MHz, CDCl}_3\text{)} 174.7, 144.6, 126.2, 124.9, 124.4, 67.9, 59.8, 57.3, 51.4, 49.0, 41.0,
39.8, 39.7, 38.9, 27.9, 27.2, 25.3, 23.6, 20.3, 18.3; m/z (ESI+) found [M+H]^+ 347.2141. C_{20}H_{31}N_{2}OS^+ requires 347.2152.

Amine 31b

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) & \quad 3.80-3.74 (1\text{H, m}), 3.44-3.38 (1\text{H, m}), 2.59-2.54 (1\text{H, m}), 2.48-2.40 (2\text{H, m}), 2.24 (6\text{H, s}), 2.24-2.14 (2\text{H, m}), 2.04-1.94 (4\text{H, m}), 1.85-1.79 (1\text{H, m}), 1.74-1.58 (4\text{H, m}), 1.50-1.44 (1\text{H, m}), 1.38-1.30 (2\text{H, m}), 1.12 (3\text{H, d, } J 7.4); \\
\delta_C (125 \text{ MHz, CDCl}_3) & \quad 174.6, 67.9, 62.6, 50.9, 48.9, 45.7, 40.2, 39.6, 38.5, 27.4, 26.9, 25.7, 23.3, 20.4, 18.6; m/z (ESI+) found [M+H]^+ 265.2284. C_{16}H_{29}N_{2}O^+ requires 265.2274.
\end{align*}
\]
B. Cylindricine-inspired libraries

General procedures for library preparation and tabulated results.

Amines 33

A solution of spiro[3.5]nonan-1-one 6 (90 mg) in DCE (1.5 mL) was added to an oven dried 5 mL microwave reaction vessel. To the solution was added acetic acid (2 equiv.), sodium triacetoxyborohydride (2.25 equiv.), and the appropriate amine (2.25 mmol). The reaction was conducted utilizing a Biotage® Initiator microwave synthesizer equipped with Robot Eight® platform. Reactions were irradiated at 150° for 15 min. Upon completion, the reaction was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines 33.

| Compound | Cal. Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------|------------|-----------------------|-----------|------------|
| 33a[1]   | 244.206   | 244.2074   | 37.9                  | 43        | 94.3       |
| 33a[2]   | 298.1124  | 298.1131   | 32                    | 30        | 93.9       |
| 33a[3]   | 260.2009  | 260.202    | 20                    | 21        | 93         |
| 33a[4]   | 264.1514  | 264.1527   | 41.5                  | 44        | 94.9       |
| 33a[6]   | 248.1809  | 248.1818   | 18.2                  | 20        | 93         |
| 33a(8) | 290.2115 | 290.2115 | 47.1 | 45 | 96.2 |
| 33a(9) | 298.1777 | 298.1796 | 31.5 | 29 | 91.9 |
| 33a(10) | 234.1853 | 234.1857 | 32.4 | 38 | 99.5 |
| 33a(11) | 244.206 | 244.2063 | 21.8 | 25 | 97.5 |
| 33a(12) | 298.1777 | 298.1789 | 25.1 | 23 | 88.3 |
| 33a(13) | 244.206 | 244.2072 | 29.6 | 34 | 86.9 |
| 33a(14) | 248.1809 | 248.181 | 45.7 | 51 | 41.2 |
| 33a(16) | 231.1856 | 231.1859 | 18.9 | 23 | 78.1 |
| 33a(19) | 264.1514 | 264.152 | 8.1 | 8 | 88.9 |
| 33a(20) | 260.2009 | 260.2012 | 34.8 | 37 | 89.3 |
| 33a(21) | 298.1777 | 298.1797 | 62.3 | 58 | 94.8 |
| 33a(26) | 236.1468 | 236.1475 | 21.9 | 26 | 75.9 |
| 33a(28) | 244.206 | 244.2074 | 10.9 | 12 | 88.2 |
| 33a(29) | 332.1388 | 332.14 | 22.4 | 19 | 93.8 |
| 33b(2) | 312.128 | 312.1284 | 51.8 | 42 | 81.7 |
| 33b(3) | 274.2165 | 274.2168 | 43.2 | 40 | 82.8 |
| 33b(4) | 278.167 | 278.1673 | 37.2 | 34 | 82.3 |
| 33b(5) | 278.167 | 278.1679 | 47.3 | 43 | 94.2 |
| 33b(8) | 304.2271 | 304.2279 | 57.3 | 48 | 88.4 |
| 33b(9) | 312.1933 | 312.1941 | 37.4 | 30 | 87.3 |
| 33b(10) | 248.2009 | 248.2006 | 4.5 | 5 | 55.9 |
| 33b(11) | 258.2216 | 258.2222 | 33 | 33 | 95 |
| 33b(12) | 312.1933 | 312.1942 | 76.7 | 62 | 94.8 |
| 33b(13) | 258.2216 | 258.2224 | 55.8 | 55 | 93.7 |
| 33b(14) | 262.1965 | 262.1974 | 48.9 | 47 | 87.8 |
| 33b(16) | 245.2012 | 245.2023 | 70.5 | 73 | 90.3 |
| 33b(23) | 234.1852 | 234.1842 | 0.8 | 1 | 56.7 |
| 33b(24) | 244.206 | 244.2066 | 20.9 | 22 | 89.5 |
| 33b(25) | 274.2165 | 274.2177 | 73.1 | 68 | 94.7 |
| 33d(1) | 320.2373 | 320.2393 | 22.3 | 35 | 77.5 |
| 33d(3) | 336.2322 | 336.2347 | 32.2 | 48 | 90 |
| 33d(4) | 340.1827 | 340.1813 | 44.9 | 66 | 72.7 |
| 33d(5) | 340.1827 | 340.1835 | 50.3 | 74 | 53 |
| 33d(6) | 324.2122 | 324.2149 | 26.2 | 40 | 93.8 |
| 33d(7) | 408.1701 | 408.1729 | 61.3 | 75 | 94.6 |
| 33d(8) | 366.2428 | 366.2454 | 49.3 | 67 | 98.4 |
| 33d(9) | 374.209 | 366.2454 | 93.1 | 124 | 55.1 |
| 33d(10) | 310.2166 | 310.208 | 49.9 | 80 | 96.5 |
| 33d(12) | 374.209 | 374.2096 | 53.6 | 72 | 36.6 |
| 33d(13) | 320.2373 | 320.2396 | 28.6 | 45 | 81.8 |
| 33d(16) | 307.2169 | 307.2085 | 11.7 | 19 | 61.9 |
| 33d(19) | 340.1827 | 340.1841 | 15.6 | 23 | 87.4 |
| 33d(20) | 336.2322 | 336.2346 | 25.8 | 38 | 87.8 |
| 33d(22) | 384.1322 | 384.1329 | 28.4 | 37 | 79.8 |
| 33d(23) | 296.2009 | 296.2029 | 19.5 | 33 | 89.8 |
| 33d(26) | 312.1781 | 312.1801 | 20.4 | 33 | 95.4 |
| 33d(28) | 320.2373 | 320.2397 | 32 | 50 | 91.4 |
| 33d(31) | 374.1437 | 374.1448 | 31.3 | 42 | 94.6 |
Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold S9 (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by the appropriate isocyanate (2 equiv) and Et$_3$N (2.5 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates 34.

| Compound | Cal. Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------|------------|-----------------------|-----------|------------|
| 34a(1)   | 292.1110  | 292.1093   | 65                    | 74        | 92.8       |
| 34a(2)   | 336.0604  | 336.0582   | 57.4                  | 57        | 93.9       |
| 34a(3)   | 276.1405  | 276.1372   | 62.8                  | 76        | 100        |
| 34a(5)   | 290.1751  | 290.1757   | 41.2                  | 47        | 100        |
| 34a(6)   | 274.1802  | 274.1814   | 71.9                  | 87        | 99         |
| 34a(8)   | 326.1373  | 326.1333   | 90.6                  | 93        | 100        |
| 34a(9)   | 274.1802  | 274.1811   | 68.4                  | 83        | 98.8       |
| 34a(10)  | 292.1110  | 292.1064   | 75                    | 86        | 100        |
| 34a(11)  | 258.1499  | 258.1472   | 57                    | 74        | 100        |
| 34a(14)  | 328.2282  | 328.2237   | 107                   | 109       | 68.6       |
| 34a(15)  | 276.1405  | 276.1357   | 76.8                  | 93        | 100        |
| 34a(16)  | 302.1398  | 304.1562   | 90                    | 100       | 95.8       |
| 34a(18)  | 326.1373  | 326.1316   | 72.3                  | 74        | 98.7       |
| 34a(23)  | 316.2271  | 316.2306   | 19.4                  | 20        | 85         |
| 34a(37)  | 288.1958  | 288.1984   | 78.4                  | 91        | 100        |
| 34c(3)   | 318.1875  | 318.1852   | 47.2                  | 49        | 100        |
| 34c(5)   | 330.2074  | 330.2013   | 42.2                  | 43        | 100        |
|    |    |    |    |    |    |
|----|----|----|----|----|----|
| **34c(6)** | 314.2125 | 314.2066 | 32.3 | 34 | 100 |
| **34c(7)** | 318.1875 | 318.1829 | 8.7  | 9  | 100 |
| **34c(9)** | 314.2125 | 314.2058 | 35.3 | 37 | 100 |
| **34c(10)** | 334.1579 | 334.1513 | 44   | 44 | 100 |
| **34c(13)** | 328.2282 | 328.2257 | 18.7 | 19 | 100 |
| **34c(16)** | 344.1867 | 344.1818 | 25.7 | 25 | 100 |
| **34c(18)** | 368.1843 | 368.1804 | 68.4 | 62 | 100 |
| **34c(25)** | 360.2180 | 360.2131 | 10.5 | 10 | 100 |
| **34c(26)** | 320.1689 | 320.1690 | 23.9 | 25 | 100 |
| **34c(30)** | 342.2438 | 342.1933 | 9    | 9  | 100 |
| **34d(1)** | 306.1266 | 306.1212 | 57.1 | 62 | 95.1 |
| **34d(2)** | 412.0917 | 431.1362 | 119  | 96 | 95.5 |
| **34d(3)** | 352.1718 | 352.1686 | 82   | 78 | 100 |
| **34d(4)** | 359.1765 | 359.1739 | 69.3 | 64 | 100 |
| **34d(5)** | 368.1423 | 368.1425 | 31.3 | 28 | 91.5 |
| **34d(7)** | 352.1718 | 352.1712 | 35.3 | 33 | 100 |
| **34d(8)** | 402.1686 | 402.1642 | 90.2 | 75 | 100 |
| **34d(9)** | 350.2115 | 350.2129 | 70.7 | 67 | 100 |
| **34d(10)** | 368.1423 | 368.1389 | 83.5 | 76 | 100 |
| **34d(12)** | 402.1686 | 402.1624 | 83.3 | 69 | 100 |
| **34d(15)** | 384.1725 | 384.1755 | 99.1 | 86 | 100 |
| **34d(16)** | 380.1857 | 380.1871 | 62   | 113| 96.4 |
| **34d(17)** | 359.1765 | 378.2201 | 89.4 | 83 | 100 |
| **34d(18)** | 402.1686 | 402.1681 | 91.4 | 76 | 100 |
| **34d(19)** | 316.2271 | 316.2291 | 29.9 | 32 | 100 |
| **34d(20)** | 406.2741 | 406.2773 | 111.3| 91 | 84.3 |
| **34d(21)** | 374.2326 | 374.2346 | 60.8 | 54 | 98  |
| **34d(22)** | 352.1718 | 352.1731 | 77.3 | 73 | 100 |
| **34d(23)** | 392.2584 | 392.2593 | 19.1 | 16 | 93.8 |
| **34d(25)** | 394.2024 | 394.1989 | 42.6 | 36 | 99  |
| **34d(26)** | 338.1761 | 338.1732 | 69.3 | 68 | 100 |
| **34d(27)** | 348.1969 | 348.1926 | 51.4 | 49 | 100 |
| **34d(28)** | 402.1033 | 402.0957 | 57.6 | 48 | 95.3 |
| **34d(29)** | 370.1624 | 370.1594 | 76.7 | 69 | 100 |
| **34d(30)** | 376.2282 | 376.2230 | 44.7 | 40 | 100 |
| **34d(35)** | 402.1033 | 402.0996 | 88   | 73 | 100 |
Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold S9 (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by sodium hydride (60% in oil, 2 equiv.) and the reactions shaken at 500 rpm for 1 h at room temperature. The appropriate isothiocyanate (2.5 equiv) was then added and the reactions shaken at 500 rpm at room temperature for 18 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure thiocarbamates.

| Compound | Cal. Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|-----------|------------|-----------------------|-----------|------------|
| S19b[1]  | 316.1740  | 316.1748   | 18.8                  | 20        | 100        |
| S19b[2]  | 442.0706  | 442.0708   | 72.9                  | 55        | 92.9       |
| S19b[3]  | 348.1802  | 348.1783   | 78.4                  | 75        | 100        |
| S19b[4]  | 364.1507  | 364.1507   | 33                    | 35        | 99.1       |
| S19b[6]  | 350.1363  | 350.1416   | 53.3                  | 51        | 98.1       |
| S19b[9]  | 442.0706  | 442.0711   | 92.4                  | 70        | 98.2       |
| S19b[11] | 396.0991  | 396.0827   | 110.9                 | 93        | 98.5       |
| S19b[14] | 361.2308  | 361.2310   | 86.8                  | 80        | 94.4       |
| S19b[16] | 378.1663  | 378.1662   | 34.3                  | 30        | 96.8       |
| S19b[17] | 360.2002  | 360.2003   | 60.8                  | 56        | 99.4       |
| S19b[19] | 384.1614  | 384.1615   | 67                    | 58        | 100        |
| S19b[20] | 384.1614  | 384.1617   | 67.6                  | 59        | 100        |
| S19b[23] | 346.1846  | 346.1850   | 74.6                  | 72        | 99.4       |
Carbamates 35 & 36

A.)

\[
\begin{array}{c}
\text{HO} \quad \text{N} \\
\text{R'} \\
\text{R''} \\
\end{array}
\quad \xrightarrow{\text{R}_2\text{NCO}}
\quad
\begin{array}{c}
\text{H}^+ \quad \text{N} \\
\text{R'} \\
\text{R''} \\
\end{array}
\]

\[8\text{aa} \quad R'=\text{H}, n=1, X=\text{O} \]
\[8\text{da} \quad R'=\text{Ph}, n=1, X=\text{O} \]
\[8\text{ea} \quad R'=4-\text{MePh}, n=1, X=\text{O} \]
\[8\text{fa} \quad R'=2-\text{MePh}, n=1, X=\text{O} \]
\[8\text{ha} \quad R'=4-\text{ClPh}, n=1, X=\text{O} \]
\[8\text{ab} \quad R'=\text{H}, n=2, X=\text{O} \]
\[10\text{ca} \quad R'=\text{Pr}, n=1, X=\text{H}_2 \]
\[10\text{da} \quad R'=\text{Ph}, n=1, X=\text{H}_2 \]

Isocyanates:

\[2 \quad R^2=4-\text{Bromophenyl} \]
\[3 \quad R^2=4-\text{Fluorophenyl} \]
\[5 \quad R^2=2-\text{Methoxyphenyl} \]
\[6 \quad R^2=4-\text{Methylphenyl} \]
\[9 \quad R^2=2-\text{Methylphenyl} \]
\[10 \quad R^2=3-\text{Chlorophenyl} \]
\[11 \quad R^2=\text{Phenyl} \]
\[12 \quad R^2=2-(\text{CF}_3)\text{phenyl} \]
\[14 \quad R^2=\text{tButyl} \]
\[15 \quad R^2=4-\text{Chlorobenzyl} \]
\[16 \quad R^2=3,4-\text{Methylenedioxy phenyl} \]
\[18 \quad R^2=3-(\text{CF}_3)\text{phenyl} \]

\[18 \quad R^2=3-\text{Butyl} \]
\[20 \quad R^2=4-\text{Pentylphenyl} \]
\[21 \quad R^2=\text{Ethyl 4-isocyanatobutyrate} \]
\[22 \quad R^2=3-\text{Fluorophenyl} \]
\[23 \quad R^2=4-\text{Ethylphenethyl} \]
\[25 \quad R^2=2,6-\text{dimethoxyphenyl} \]
\[27 \quad R^2=\text{Benzyl} \]
\[31 \quad R^2=3-\text{Cyanophenyl} \]
\[32 \quad R^2=3,4-\text{Dimethylphenyl} \]
\[33 \quad R^2=\text{Ethyl} \]
\[34 \quad R^2=4-\text{Methoxyphenyl} \]
\[35 \quad R^2=3,5-\text{dichlorophenyl} \]

S19b(24) 350.1350 350.1349 84.3 80 97.8
S19b(26) 350.1350 350.1348 73.9 70 97.4
S19b(27) 396.0991 396.0817 87.4 74 95.7
S19b(28) 320.1653 320.1690 23.9 25 100
S19b(1) 350.1583 350.1521 61.1 58 100
S19b(4) 398.1350 398.1356 76.4 64 96.6
S19b(6) 384.1194 384.1162 101.8 88 100
S19b(8) 384.1194 384.1139 97.5 85 100
S19b(9) 476.0550 476.0533 114.5 80 100
S19b(10) 476.0550 476.0496 77.8 54 91
S19b(11) 428.0688 428.0660 113.5 88 100
S19b(12) 378.1896 378.1870 61.1 54 100
S19b(13) 378.1896 378.1869 68.3 60 100
S19b(14) 393.2005 393.1968 92.5 78 98.8
S19b(15) 394.1845 394.1822 74.4 73 100
S19b(17) 394.1845 394.1785 78 66 100
S19b(18) 370.2209 370.2187 69 72 100
S19b(19) 418.1457 418.1417 70.7 56 100
S19b(20) 418.1457 418.1411 91.9 73 89.3
S19b(23) 380.1689 380.1637 71.5 63 100
S19b(24) 398.1350 398.1300 89.3 75 97.1
S19b(25) 428.0688 428.0662 55.4 43 98.7
S19d(3) 382.1646 382.1640 106.5 93 100
S19d(4) 398.1350 398.1338 114.2 96 100
S19d(5) 382.1646 382.1639 94.1 95 85
S19d(14) 350.1583 350.1530 77.2 73 100
Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold 8, 9, 10 or 11 (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by the appropriate isocyanate (2.5 equiv) and Et₃N (2.5 equiv). The reactions were shaken at 500 rpm at rt for 12 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates 35 or 36.

Results for carbamates 35:

| R²   | n | X | R²-N=C=O | Cal. Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|------|---|---|----------|----------|-----------|-----------------------|-----------|------------|
| H    | 1 | O | (3)      | 335.1766 | 335.1775  | 62.8                  | 62        | 78.4       |
| H    | 1 | O | (27)     | 331.2016 | 331.2020  | 54.2                  | 55        | 96.3       |
| Ph   | 1 | O | (2)      | 471.1278 | 471.1280  | 10.6                  | 7         | 99.0       |
| Ph   | 1 | O | (3)      | 411.2079 | 411.2079  | 40.8                  | 33        | 100        |
| Ph   | 1 | O | (11)     | 393.2173 | 393.2184  | 48.1                  | 41        | 100        |
| Ph   | 1 | O | (12)     | 461.2047 | 461.2048  | 72.4                  | 52        | 100        |
| Ph   | 1 | O | (15)     | 441.1940 | 441.1954  | 62.6                  | 47        | 100        |
| Ph   | 1 | O | (20)     | 463.2955 | 463.2962  | 72.6                  | 52        | 98.5       |
| Ph   | 1 | O | (27)     | 407.2329 | 407.2334  | 36                    | 29        | 100        |
| Ph   | 1 | O | (31)     | 418.2125 | 418.2122  | 44.3                  | 35        | 100        |
| 4-Me-Ph | 1 | O | (2)      | 485.1435 | 485.1433  | 40.8                  | 28        | 100        |
| 4-Me-Ph | 1 | O | (3)      | 425.2235 | 425.2271  | 44.3                  | 35        | 100        |
| 4-Me-Ph | 1 | O | (31)     | 432.2282 | 432.2281  | 36                    | 28        | 100        |
| 2-Me-Ph | 1 | O | (2)      | 485.1435 | 485.1438  | 48.1                  | 33        | 100        |
| 2-Me-Ph | 1 | O | (3)      | 425.2235 | 425.2245  | 42.9                  | 34        | 100        |
| 2-Me-Ph | 1 | O | (31)     | 432.2282 | 432.2301  | 46.9                  | 36        | 100        |
| 4-Cl-Ph | 1 | O | (2)      | 427.1783 | 427.1767  | 92.6                  | 72        | 100        |
| 4-Cl-Ph | 1 | O | (3)      | 445.1689 | 445.1688  | 19.2                  | 14        | 100        |
| 4-Cl-Ph | 1 | O | (11)     | 475.2203 | 475.2203  | 12.6                  | 9         | 100        |
| 4-Cl-Ph | 1 | O | (27)     | 308.1412 | 308.1400  | 32.9                  | 36        | 100        |
| 4-Cl-Ph | 1 | O | (31)     | 452.1736 | 452.1724  | 13.4                  | 10        | 100        |
| 4-Cl-Ph | 1 | O | (33)     | 379.1783 | 379.1771  | 31.8                  | 28        | 100        |
| H    | 2 | O | (3)      | 349.1922 | 349.1911  | 51                    | 49        | 88.3       |
| H    | 2 | O | (27)     | 345.2173 | 345.2166  | 32.5                  | 31        | 100        |
| nPr  | 1 | H₂ | (2)     | 423.1641 | 423.1665  | 54.8                  | 43        | 94.4       |
| nPr  | 1 | H₂ | (3)      | 363.2442 | 363.2459  | 49.2                  | 45        | 100        |
| nPr  | 1 | H₂ | (5)      | 375.2642 | 375.2664  | 17.1                  | 15        | 100        |
| nPr  | 1 | H₂ | (9)      | 359.2693 | 359.2737  | 44.4                  | 41        | 100        |
| nPr  | 1 | H₂ | (10)     | 379.2147 | 379.2171  | 63.8                  | 56        | 100        |
| nPr  | 1 | H₂ | (11)     | 345.2536 | 345.2582  | 50.2                  | 48        | 100        |
| nPr  | 1 | H₂ | (27)     | 359.2693 | 359.2723  | 48.7                  | 45        | 97.5       |
| nPr  | 1 | H₂ | (36)     | 375.2642 | 375.2639  | 35.7                  | 32        | 100        |
| Ph   | 1 | H₂ | (2)      | 457.1485 | 457.1491  | 32.7                  | 24        | 100        |
| Ph   | 1 | H₂ | (3)      | 397.2286 | 397.2327  | 32.7                  | 27        | 100        |
| Ph   | 1 | H₂ | (5)      | 409.2485 | 409.2548  | 29.1                  | 24        | 100        |
| Ph   | 1 | H₂ | (9)      | 393.2536 | 393.2570  | 23.6                  | 20        | 100        |
| Ph   | 1 | H₂ | (10)     | 413.1990 | 413.2032  | 28.4                  | 23        | 100        |
| Ph   | 1 | H₂ | (11)     | 379.2380 | 379.2429  | 22.5                  | 20        | 100        |
| Ph   | 1 | H₂ | (22)     | 397.2286 | 397.2330  | 19.4                  | 16        | 100        |
| Ph   | 1 | H₂ | (25)     | 439.2591 | 439.2663  | 19.5                  | 15        | 100        |
| Ph   | 1 | H₂ | (35)     | 447.1600 | 447.1634  | 22.7                  | 17        | 98.9       |
| Ph   | 1 | H₂ | (36)     | 409.2485 | 409.2499  | 39.9                  | 32        | 100        |
Results for carbamates 36:

| R<sup>1</sup> | n | X | R<sup>1</sup>-N=C=O | Cal. Mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|---|---|---|----------------|----------|------------|----------------------|----------|-----------|
| H  | 2 | O | (2) H<sub>2</sub>O | 409.1122 | 409.0811 | 64.6 | 53 | 97.2 |
| H  | 2 | O | (3) | 349.1922 | 349.1912 | 73.2 | 70 | 16.1 |
| H  | 2 | O | (19) | 311.2329 | 311.2306 | 35.8 | 38 | 74.5 |
| H  | 2 | O | (31) | 356.1969 | 356.1710 | 68.2 | 64 | 99.4 |
| Me | 2 | O | (5) | 375.2279 | 375.2251 | 62.9 | 56 | 99.4 |
| Me | 2 | O | (15) | 393.1940 | 393.1906 | 76.8 | 65 | 100 |
| Me | 2 | O | (18) | 413.2047 | 413.2022 | 53.1 | 43 | 100 |
| Me | 2 | O | (21) | 383.2541 | 383.2523 | 67.6 | 59 | 70.3 |
| Me | 2 | O | (22) | 363.2079 | 363.2050 | 74.3 | 68 | 97 |
| Me | 2 | O | (23) | 401.2799 | 401.2781 | 61.3 | 51 | 96.3 |
| Ph | 2 | O | (8) | 475.2203 | 475.2180 | 68.1 | 48 | 100 |
| Ph | 2 | O | (19) | 387.2642 | 387.2617 | 24.3 | 21 | 100 |
| Ph | 2 | O | (21) | 445.2697 | 445.2678 | 57.5 | 43 | 100 |
| Ph | 2 | O | (23) | 463.2955 | 463.2936 | 23.2 | 17 | 100 |
| Ph | 2 | H<sub>2</sub> | (3) | 411.2443 | 411.2440 | 115.4 | 94 | 100 |
| Ph | 2 | H<sub>2</sub> | (19) | 373.2850 | 373.2849 | 101.7 | 91 | 99.1 |

Thiocarbamates 37

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold 8, or 10 (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by sodium hydride (60% in oil, 2 equiv.) and the reactions shaken at 500 rpm for 1 h at room temperature. The appropriate isothiocyanate (2 equiv) was then added and the reactions were shaken at 500 rpm at room temperature for 12 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates 37.
### Characterization data for representative library compounds

**Carbamate 34a[6]**

![Structure of Carbamate 34a](image)

$^1$H NMR (500 MHz, DMSO) δ 9.48 (s, 1H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.06 (d, $J = 8.2$ Hz, 2H), 4.67 (t, $J = 7.9$ Hz, 1H), 2.28 – 2.14 (m, 4H), 2.06 – 1.84 (m, 1H), 1.71 – 1.60 (m, 2H), 1.60 – 1.51 (m, 2H), 1.51 – 1.42 (m, 3H), 1.40 (d, $J = 12.8$ Hz, 1H), 1.37 – 1.29 (m, 2H), 1.26 – 1.08 (m, 2H); $^{13}$C NMR (126 MHz, DMSO) δ 153.2, 136.7, 131.1, 129.1, 118.1, 74.5, 45.4, 40.4, 37.4, 29.7, 25.7, 24.7, 23.8, 22.5, 21.7, 20.3; m/z (ESI+) found [M+H]$^+$ 274.1814. C$_{17}$H$_{24}$NO$_2$ requires 274.1798.

**Carbamate 34d[17]**

![Structure of Carbamate 34d](image)

$^1$H NMR (500 MHz, DMSO) δ 10.14 (s, 1H), 7.96 (s, 1H), 7.78 (d, $J = 8.2$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.50 – 7.45 (m, 1H), 7.16 – 6.98 (m, 5H), 5.01 (t, $J = 7.7$ Hz, 1H), 2.48 – 2.38 (m, 1H), 2.35 – 2.20 (m,
$^1$H NMR (500 MHz, DMSO) $\delta$ 7.30 – 7.25 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.12 (m, 2H), 4.03 (q, $J$ = 7.1 Hz, 2H), 3.90 (t, $J$ = 6.5 Hz, 2H), 3.27 (t, $J$ = 6.8 Hz, 2H), 3.22 (t, $J$ = 7.0 Hz, 2H), 2.98 (dd, $J$ = 12.8, 6.6 Hz, 2H), 2.54-2.51 (m, 1H), 2.27 (t, $J$ = 7.4 Hz, 2H), 2.18 (qd, $J$ = 12.6, 3.4 Hz, 2H), 1.83 (d, $J$ = 13.7 Hz, 2H), 1.77 (dd, $J$ = 12.4, 5.6 Hz, 2H), 1.72 (dd, $J$ = 13.6, 6.8 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.60 – 1.53 (m, 2H), 1.41 (td, $J$ = 13.2, 3.8 Hz, 2H), 1.16 (dd, $J$ = 9.5, 4.8 Hz, 3H); $^{13}$C NMR (126 MHz, DMSO) $\delta$ 177.5, 172.6, 156.2, 147.2, 147.2, 128.3, 126.7, 125.8, 61.5, 59.8, 42.9, 42.4, 41.3, 38.7, 34.5, 33.9, 30.8, 29.0, 26.7, 24.8, 14.1; $m/z$ (ESI+) found [M+H]$^+$ 445.2678. C$_{25}$H$_{37}$N$_2$O$_5$ requires 445.2694.

Carbamate 36db

$^1$H NMR (500 MHz, DMSO) $\delta$ 9.05 (s, 1H), 7.74 – 7.69 (m, 1H), 7.65 (t, $J$ = 7.7 Hz, 1H), 7.53 (d, $J$ = 7.9 Hz, 1H), 7.44 (t, $J$ = 7.6 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.25 – 7.20 (m, 2H), 7.19 – 7.12 (m, 1H), 4.02 (t, $J$ = 6.5 Hz, 2H), 3.31 – 3.20 (m, 4H), 2.54-2.51 (m, 1H), 2.29 – 2.13 (m, 2H), 1.90 – 1.81 (m, 2H), 1.81 – 1.73 (m, 4H), 1.64 – 1.52 (m, 2H), 1.48 – 1.34 (m, 2H); $^{13}$C NMR (126 MHz, DMSO) $\delta$ 177.6, 154.8, 147.2, 135.6, 133.1, 130.0, 128.3, 126.8, 126.6, 126.3 (q, $J$ = 5 Hz), 125.8, 125.1 (q, $J$ = 29 Hz), 123.6 (q, $J$ = 272 Hz), 62.3, 42.9, 42.4, 41.3, 38.5, 34.6, 33.9, 29.0, 26.4; $m/z$ (ESI+) found [M+H]$^+$ 475.2180. C$_{26}$H$_{30}$F$_3$N$_2$O$_5$ requires 475.2200.

Carbamate 36bb
$^1$H NMR (500 MHz, DMSO) δ 9.51 (s, 1H), 7.12 (s, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H), 5.95 (s, 2H), 4.00 (t, $J = 6.5$ Hz, 2H), 3.30 – 3.18 (m, 4H), 1.83 – 1.73 (m, 4H), 1.73 – 1.66 (m, 2H), 1.56 – 1.48 (m, 3H), 1.48 – 1.39 (m, 2H), 1.25 – 1.14 (m, 2H), 0.90 (d, $J = 5.7$ Hz, 3H); $^{13}$C NMR (126 MHz, DMSO) δ 177.8, 153.6, 147.2, 142.3, 133.6, 110.9, 108.1, 100.9, 100.5, 61.9, 43.0, 42.4, 38.7, 32.6, 31.1, 29.5, 29.0, 26.5, 20.3; $m/z$ (ESI+) found [M+H]$^+$ 389.2039. $C_{21}H_{29}N_2O_5$ requires 389.2068.

Carbamate 36db[12]

$^1$H NMR (500 MHz, DMSO) δ 9.07 (s, 1H), 7.75 – 7.70 (m, 1H), 7.67 (t, $J = 7.7$ Hz, 1H), 7.53 (d, $J = 7.9$ Hz, 1H), 7.44 (t, $J = 7.7$ Hz, 1H), 7.27 (ddd, $J = 15.1, 8.0, 4.1$ Hz, 4H), 7.20 – 7.14 (m, 1H), 4.02 (t, $J = 6.5$ Hz, 2H), 3.28 (dd, $J = 12.0, 6.7$ Hz, 4H), 2.53-2.48 (m, 1H), 1.96 (t, $J = 6.9$ Hz, 2H), 1.80 (p, $J = 6.7$ Hz, 2H), 1.73 (d, $J = 10.9$ Hz, 2H), 1.69 – 1.57 (m, 2H), 1.52 (dt, $J = 27.3, 8.8$ Hz, 4H); $^{13}$C NMR (126 MHz, DMSO) δ 177.9, 154.8, 147.0, 135.6, 133.1, 130.0, 128.3, 126.7, 126.6, 126.3 (q, $J = 5$ Hz), 125.9, 125.1 (q, $J = 29$ Hz), 123.6 (q, $J = 272$ Hz), 62.4, 44.0, 43.2, 42.9, 38.8, 32.3, 29.6, 28.6, 26.5; $m/z$ (ESI+) found [M+H]$^+$ 475.2180. $C_{26}H_{30}F_3N_2O_3$ requires 475.2203.

Carbamate 36bb[15]

$^1$H NMR (500 MHz, DMSO) δ 7.71 (t, $J = 6.1$ Hz, 1H), 7.44 – 7.33 (m, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 4.16 (d, $J = 6.2$ Hz, 2H), 3.91 (t, $J = 6.5$ Hz, 2H), 3.23 (d, $J = 7.3$ Hz, 2H), 3.20 (d, $J = 7.3$ Hz, 2H), 1.85 – 1.62 (m, 6H), 1.59 – 1.49 (m, 3H), 1.49 – 1.37 (m, 2H), 1.27 – 1.09 (m, 2H), 0.90 (d, $J = 5.8$ Hz, 3H); $^{13}$C
NMR (126 MHz, DMSO) δ 177.7, 156.5, 138.9, 131.3, 128.9, 128.2, 61.8, 43.1, 42.9, 42.4, 38.7, 32.6, 31.2, 29.5, 29.0, 26.6, 20.4; m/z (ESI+) found [M+H]+ 393.1866. C_{21}H_{30}ClN_{2}O_{3} requires 393.1936.

Carbamate 36bb[5]

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (500 MHz, DMSO) } & \delta 8.31 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.94 – 6.86 (m, 1H), 4.01 (t, J = 6.5 Hz, 2H), 3.80 (s, 3H), 3.30 – 3.18 (m, 4H), 1.82 – 1.74 (m, 4H), 1.74 – 1.66 (m, 2H), 1.58 – 1.48 (m, 3H), 1.48 – 1.40 (m, 2H), 1.27 – 1.12 (m, 2H), 0.90 (d, J = 5.8 Hz, 3H); \\
\text{\textsuperscript{13}C NMR (126 MHz, DMSO) } & \delta 177.7, 153.7, 150.0, 127.0, 124.2, 121.5, 120.3, 111.2, 62.2, 55.6, 42.9, 42.4, 38.7, 32.6, 31.2, 29.5, 29.0, 26.4, 20.3; m/z (ESI+) found [M+H]+ 375.2251. C_{21}H_{31}N_{2}O_{4} requires 375.2275.
\end{align*}
\]

Carbamate 36bb[22]

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (500 MHz, DMSO) } & \delta 9.88 (s, 1H), 7.38 (d, J = 11.8 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.26 – 7.18 (m, 1H), 6.87 – 6.71 (m, 1H), 4.04 (t, J = 6.5, 6.5 Hz, 2H), 3.25 (td, J = 6.9, 6.9, 2.9 Hz, 4H), 1.87 – 1.74 (m, 4H), 1.73 – 1.64 (m, 2H), 1.59 – 1.48 (m, 3H), 1.48 – 1.36 (m, 2H), 1.29 – 1.15 (m, 2H), 0.89 (d, J = 5.8 Hz, 3H); \\
\text{\textsuperscript{13}C NMR (126 MHz, DMSO) } & \delta 177.7, 162.3 (d, J = 239 Hz), 153.3, 141.1 (d, J = 11 Hz), 130.0 (d, J = 10 Hz), 113.9, 108.7 (d, J = 21 Hz), 104.8 (d, J = 26 Hz), 62.2, 42.9, 42.3, 38.6, 32.6, 31.1, 29.4, 28.9, 26.3, 20.3; m/z (ESI+) found [M+H]+ 363.2050. C_{20}H_{28}FN_{2}O_{3} requires 363.2075.
\end{align*}
\]

Carbamate 36ab[2]
\[ \begin{align*}
\text{H NMR (500 MHz, DMSO)} & \delta 9.80 (s, 1H), 7.49 - 7.35 (m, 4H), 4.02 (t, J = 6.5 Hz, 2H), 3.26 (q, J = 6.8 Hz, 4H), 1.84 (dd, J = 12.2, 5.3 Hz, 2H), 1.79 (dd, J = 13.6, 6.8 Hz, 2H), 1.66 - 1.52 (m, 3H), 1.48 - 1.38 (m, 2H), 1.36 - 1.23 (m, 4H), 1.23 - 1.10 (m, 1H); \\
\text{13C NMR (126 MHz, DMSO)} & \delta 177.9, 153.4, 138.6, 131.5, 120.0, 113.8, 62.1, 44.2, 43.1, 38.8, 32.1, 29.0, 26.3, 25.2, 21.8; m/z (ESI+) found [M+H]^+ 409.0811. C_{19}H_{26}BrN_2O_3 requires 409.1118.
\end{align*} \]

Carbamate 36ab[31]

\[ \begin{align*}
\text{H NMR (500 MHz, DMSO)} & \delta 10.05 (s, 1H), 7.88 (s, 1H), 7.76 - 7.67 (m, 1H), 7.49 (t, J = 7.9, 7.9 Hz, 1H), 7.44 (dt, J = 7.6, 1.3, 1.3 Hz, 1H), 4.05 (t, J = 6.5, 6.5 Hz, 2H), 3.32 - 3.21 (m, 4H), 1.91 - 1.74 (m, 4H), 1.67 - 1.52 (m, 3H), 1.49 - 1.36 (m, 2H), 1.37 - 1.23 (m, 4H), 1.23 - 1.09 (m, 1H); \text{13C NMR (126 MHz, DMSO)} \delta 177.9, 153.4, 140.1, 130.2, 125.8, 122.7, 120.5, 118.7, 111.5, 62.4, 44.2, 43.0, 38.7, 32.1, 29.0, 26.2, 25.2, 21.8; m/z (ESI+) found [M+H]^+ 356.1710. C_{20}H_{26}N_3O_3 requires 356.1965.
\end{align*} \]
C. Sparteine-inspired libraries

General procedures for library preparation and tabulated results.

Carbamates 40

To each reaction tube of a 24-position Bohdan MiniBlock XT was added a solution of carbonate 39 (70 mg, 0.19 mmol) in 1, 2-dichloroethane (2 mL), followed by the appropriate amine (1.26 mmol). The reactions were shaken at 450 rpm for 4 h at 50 °C, then 20% aqueous HCl (3 mL) was added to each tube. The reactions were shaken for 15 additional minutes then passed through hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates 40.

| Compound | Cal. mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|----------|----------|------------|------------------------|-----------|------------|
| 40(1)    | 347.1766 | 347.1798   | 48.5                   | 73.7      | 100.0      |
| 40(2)    | 359.1966 | 359.2099   | 54.2                   | 79.6      | 100.0      |
| 40(3)    | 309.1809 | 309.2050   | 51.2                   | 87.4      | 100.0      |
| 40(4)    | 295.2016 | 295.2288   | 44.8                   | 80.1      | 100.0      |
| 40(5)    | 321.2173 | 321.2421   | 43.0                   | 70.7      | 100.0      |
| 40(6)    | 329.1860 | 329.1831   | 48.7                   | 78.1      | 100.0      |
| 40(7)    | 407.0965 | 407.0986   | 27.9                   | 36.2      | 99.4       |
| 40(8)    | 343.2016 | 343.1972   | 31.0                   | 47.7      | 98.8       |
| 40(9)    | 389.2071 | 389.2049   | 48.2                   | 65.3      | 96.1       |
| 40(10)   | 253.1547 | 253.1495   | 28.1                   | 58.7      | 100.0      |
| 40(11)   | 281.1860 | 281.1848   | 45.6                   | 85.7      | 99.5       |
| 40(12)   | 281.1860 | 281.1858   | 40.0                   | 75.1      | 93.0       |
| 40(13)   | 283.1653 | 283.1595   | 29.1                   | 54.3      | 99.4       |
| 40(14)   | 324.2282 | 324.2248   | 50.5                   | 82.2      | 99.2       |
| 40(15)   | 330.1812 | 330.1796   | 49.3                   | 78.8      | 100.0      |
| 40(16)   | 382.2125 | 382.2110   | 20.1                   | 27.8      | 98.4       |
| 40(17)   | 307.2016 | 307.1973   | 35.0                   | 60.2      | 99.0       |
To each pyrex glass vial placed on a 24 position block was added a solution of alcohol 41 (40 mg, 0.22 mmol) in acetonitrile (1 mL), followed by the appropriate isocyanate (0.66 mmol). The vials were irradiated in a microwave at 110 °C for 1 h and then the contents of each vial were transferred to a phase separator fitted on a 24 position Mini Block. Dichloromethane (3 mL) and saturated aqueous sodium bicarbonate solution (3 mL) were added to each tube. The reactions were shaken for 15 minutes, then passed through hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates 42.

| Compound | Cal. Mass  | Found mass | Recovered | Yield(%) | Purity(%) |
|----------|-----------|------------|-----------|----------|-----------|
| 42(1)    | 329.2224  | 329.2217   | 28.7      | 39.7     | 87.5      |
| 42(2)    | 329.2224  | 329.2185   | 59.1      | 81.8     | 99.0      |
| 42(3)    | 345.2173  | 345.2169   | 57.9      | 76.5     | 91.2      |
| 42(4)    | 307.1475  | 307.1428   | 58.4      | 86.7     | 97.3      |
| 42(5)    | 319.1817  | 319.1777   | 10.6      | 15.1     | 99.9      |
| 42(6)    | 340.2020  | 340.1991   | 62.0      | 83.1     | 41.7      |
| 42(7)    | 343.2300  | 343.2325   | 59.8      | 79.4     | 98.1      |
| 42(8)    | 326.1863  | 326.1801   | 70.1      | 97.9     | 100.0     |
| 42(9)    | 339.2279  | 339.2277   | 39.7      | 53.4     | 95.5      |
| 42(10)   | 315.2067  | 315.2030   | 53.1      | 76.8     | 95.8      |
| 42(11)   | 369.1785  | 369.1769   | 74.2      | 91.6     | 90.4      |
Carbamates 43a

To each reaction tube of a 24-position Bohdan MiniBlock XT was added a solution of alcohol 16a (37 mg, 0.19 mmol) in THF (2 mL), followed by the appropriate isocyanate (0.57 mmol). The reactions were shaken at 450 rpm for 7 h at 50 °C. Saturated aqueous NaHCO₃ (2 mL) and dichloromethane (4 mL) were added to each tube and the reactions shaken for 15 min then passed through Isolute hydrophobic phase separator tubes, which allowed the organic solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates 43a.

| Compound | Cal. Mass  | Found mass | Recovered | Yield(%) | Purity(%) |
|----------|------------|------------|-----------|----------|-----------|
| 43a(1)   | 353.2435   | 353.2427   | 32.0      | 47.8     | 96.6      |
| 43a(2)   | 363.1834   | 363.1796   | 38.6      | 56.1     | 99.6      |
| 43a(3)   | 357.2537   | 357.2525   | 41.7      | 61.6     | 97.6      |
| 43a(4)   | 371.2693   | 371.2697   | 39.3      | 55.9     | 95.1      |
| 43a(5)   | 329.2224   | 329.2212   | 30.9      | 49.6     | 98.4      |
Following the procedure as described for the synthesis of carbamates 43a, reaction of alcohol 16b (45 mg, 0.19 mmol) with the corresponding isocyanate (0.57 mmol) in a 24 well Bohdan MiniBlock XT provided a library of carbamates 43b.
Carbamates 43c

Following the procedure as described for the synthesis of carbamates 43a, reaction of alcohol 16c (51 mg, 0.19 mmol) with the appropriate isocyanate (0.57 mmol) in a 24 well Bohdan MiniBlock XT provided a library of carbamates 43c.

| Compound | Cal. Mass    | Found mass   | Recovered | Yield(%) | Purity(%) |
|----------|--------------|--------------|-----------|----------|-----------|
| 43c(1)   | 371.2693     | 371.2707     | 3.7       | 5.3      | 16.0      |
| 43c(2)   | 371.2693     | 371.2663     | 0.6       | 0.9      | 48.0      |
| 43c(3)   | 429.2748     | 429.2738     | 28.0      | 34.4     | 98.4      |
| 43c(4)   | 405.2537     | 405.2476     | 45.5      | 59.2     | 99.6      |
| 43c(5)   | 405.2537     | 405.2544     | 48.4      | 63.0     | 97.2      |
| 43c(6)   | 416.2333     | 416.2268     | 23.4      | 29.7     | 99.9      |
| 43c(7)   | 416.2333     | 416.2168     | 41.7      | 52.9     | 100.0     |
| 43c(8)   | 391.2380     | 391.2295     | 38.7      | 52.2     | 99.8      |
| 43c(9)   | 405.2537     | 405.2414     | 35.3      | 46.0     | 76.2      |
| 43c(10)  | 433.2850     | 433.2820     | 32.0      | 39.0     | 97.1      |
| 43c(11)  | 447.3006     | 447.3018     | 19.7      | 23.2     | 97.3      |
Characterization data for representative library compounds

Carbamate 40[1]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} &\quad 1634, 1709, 2943 \text{ cm}^{-1};
\delta_{\text{n}} \text{ (400 MHz, CDCl}_3\text{)} &\quad 7.38 - 7.11 (m, 2H), 7.10 - 6.88 (m, 2H), 5.35 - 5.00 (m, 2H), 4.62 - 4.44 (m, 1H), 4.36 - 4.27 (m, 2H), 3.40 - 3.25 (m, 1H), 2.75 - 2.60 (m, 2H), 2.52 - 2.25 (m, 2H), 2.00 - 1.50 (m, 7H), 1.45 - 1.03 (m, 2H); \delta_{\text{c}} \text{ (100 MHz, CDCl}_3\text{)} &\quad 174.3, 163.4, 160.9, 156.1, 134.3, 129.3, 129.2, 115.6, 115.4, 62.2, 44.3, 42.0, 41.4, 35.0, 30.2, 25.5, 25.2; m/z \text{ (ESI+) found [M+H]}^+ \quad 347.1762. \text{C}_{19}\text{H}_{24}\text{FN}_{2}\text{O}_3^+ \text{ requires 347.1765.}
\end{align*}
\]

Carbamate 40[2]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} &\quad 1634, 1710, 2941 \text{ cm}^{-1};
\delta_{\text{n}} \text{ (400 MHz, CDCl}_3\text{)} &\quad 7.37 - 7.04 (m, 2H), 6.95 - 6.65 (m, 2H), 5.33 - 4.93 (m, 2H), 4.62 - 4.44 (m, 1H), 4.39 - 4.18 (m, 2H), 3.76 (s, 3H), 3.40 - 3.25 (m, 1H), 2.77 - 2.52 (m, 2H), 2.52 - 2.22 (m, 2H), 2.02 - 1.47 (m, 7H), 1.44 - 1.04 (m, 2H); \delta_{\text{c}} \text{ (100 MHz, CDCl}_3\text{)} &\quad 174.3, 159.0, 156.0, 130.6, 128.9, 114.0, 76.7, 62.1, 55.3, 44.5, 42.0, 41.4, 41.3, 35.0, 31.4, 30.1, 25.5, 25.1; m/z \text{ (ESI+) found [M+H]}^+ \quad 359.4450. \text{C}_{20}\text{H}_{27}\text{N}_{2}\text{O}_4^+ \text{ requires 359.4455.}
\end{align*}
\]
Carbamate 40[3]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} & \quad 1636, 1697, 2943 \text{ cm}^{-1}; \\
\delta_{\text{H}} \text{ (400 MHz, CDCl}_3) & \quad 5.17 (dt, J = 11.1, 5.8 \text{ Hz, 1H}), 4.74 – 4.35 \\
& \quad (m, 1H), 4.00 – 3.10 \text{ (m, 9H), 2.74 – 2.59 \text{ (m, 2H), 2.50 – 2.28 \text{ (m, 2H), 1.89 – 1.53 \text{ (m, 7H), 1.39 – 1.15 \text{ (m, 2H); δ}_C \text{ (100 MHz, CDCl}_3) 174.2, 154.8, 76.7, 66.5, 62.0, 44.3, 43.9, 41.9, 41.4, 41.2, 35.0, 30.2, 25.4, 25.3; \hspace{1em} m/z \text{ (ESI+) found [M+H]^+ 309.1805. C}_{16}H_{25}N_2O_4^+ \text{ requires 309.1809.}}}
\end{align*}
\]

Carbamate 40[4]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} & \quad 1635, 1711, 2938 \text{ cm}^{-1}; \\
\delta_{\text{H}} \text{ (400 MHz, CDCl}_3) & \quad 5.24 – 4.76 \text{ (m, 2H), 4.54 – 4.44 \text{ (m, 1H), 3.35 – 3.20 \text{ (m, 1H), 3.11 – 2.98 \text{ (m, 2H), 2.46 – 2.20 \text{ (m, 4H), 1.95 – 1.50 \text{ (m, 7H), 1.47 – 1.06 \text{ (m, 6H), 0.83 (t, J = 7.3 Hz, 3H); δ}_C \text{ (100 MHz, CDCl}_3) 174.3, 156.0, 76.3, 62.1, 41.9, 41.3, 41.2, 40.6, 34.9, 31.9, 31.4, 29.9, 25.4, 25.1, 19.7, 13.6; \hspace{1em} m/z \text{ (ESI+) found [M+H]^+ 295.2018. C}_{16}H_{27}N_2O_3^+ \text{ requires 295.2016.}}}
\end{align*}
\]

Carbamate 40[5]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} & \quad 1635, 1710, 2936 \text{ cm}^{-1}; \\
\delta_{\text{H}} \text{ (400 MHz, CDCl}_3) & \quad 5.37 – 4.95 \text{ (m, 1H), 4.80 – 4.36 \text{ (m, 2H), 3.60 – 3.20 \text{ (m, 2H), 2.75 – 2.25 \text{ (m, 4H), 2.20 – 1.45 \text{ (m, 12H), 1.45 – 1.00 \text{ (m, 7H); δ}_C \text{ (100 MHz, CDCl}_3) 174.3, 155.2, 76.3, 62.1, 49.8, 42.0, 41.4, 41.3, 34.9, 33.5, 33.2, 31.4, 30.0, 25.5, 25.4, 25.2, 24.8, 24.7; \hspace{1em} m/z \text{ (ESI+) found [M+H]^+ 321.2170. C}_{18}H_{29}N_2O_5^+ \text{ requires 321.2173.}}}
\end{align*}
\]
**Carbamate 40[15]**

\[
\text{\begin{figure}[h]
\begin{center}
\includegraphics[width=0.5\textwidth]{carbamate_40.png}
\end{center}
\end{figure}}
\]

\(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1635, 1712, 2940, 3261 cm\(^{-1}\); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 8.60 – 8.25 \(\text{(m, 2H)}\), 7.61 \(\text{(d, J = 7.8 Hz, 1H)}\), 7.38 – 7.07 \(\text{(m, 1H)}\), 6.11 \(\text{(t, J = 5.8 Hz, 1H)}\), 5.14 \(\text{(dt, J = 10.8, 5.5 Hz, 1H)}\), 4.57 – 4.25 \(\text{(m, 3H)}\), 3.35 – 3.15 \(\text{(m, 1H)}\), 2.36 – 2.29 \(\text{(m, 4H)}\), 1.93 – 1.36 \(\text{(m, 7H)}\), 1.30 – 0.90 \(\text{(m, 2H)}\); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 174.3, 156.2, 148.9, 148.6, 135.4, 134.4, 123.5, 76.7, 62.1, 42.4, 42.0, 41.4, 41.2, 35.1, 31.4, 30.0, 25.4, 25.1; \(m/z\) (ESI+) found \([\text{M+H}]^+\) 330.1810. C\(_{18}\)H\(_{21}\)N\(_3\)O\(_3\) requires 330.1812.

**Carbamate 42[7]**

\[
\text{\begin{figure}[h]
\begin{center}
\includegraphics[width=0.5\textwidth]{carbamate_42.png}
\end{center}
\end{figure}}
\]

\(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1695, 2934 cm\(^{-1}\); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 7.40 – 7.03 \(\text{(m, 5H)}\), 5.25 – 4.75 \(\text{(m, 2H)}\), 3.43 – 2.90 \(\text{(m, 3H)}\), 2.90 – 2.70 \(\text{(m, 2H)}\), 2.70 – 2.30 \(\text{(m, 4H)}\), 2.25 – 1.25 \(\text{(m, 13H)}\), 1.30 – 1.10 \(\text{(m, 1H)}\); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 156.8, 141.5, 128.4, 128.3, 125.9, 67.9, 63.2, 56.6, 42.4, 40.8, 40.4, 37.5, 34.1, 33.9, 33.0, 31.6, 30.6, 25.5, 25.3; \(m/z\) (ESI+) found \([\text{M+H}]^+\) 343.2375. C\(_{21}\)H\(_{31}\)N\(_2\)O\(_2\) requires 343.2380.

**Carbamate 40[9]**

\[
\text{\begin{figure}[h]
\begin{center}
\includegraphics[width=0.5\textwidth]{carbamate_40.png}
\end{center}
\end{figure}}
\]

\(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1715, 2934 cm\(^{-1}\); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 5.21 – 4.90 \(\text{(m, 1H)}\), 4.09 \(\text{(q, J = 7.1 Hz, 2H)}\), 3.50 – 2.80 \(\text{(m, 4H)}\), 2.80 – 2.60 \(\text{(m, 2H)}\), 2.31 \(\text{(t, J = 7.4 Hz, 2H)}\), 2.22 – 1.44 \(\text{(m, 13H)}\), 1.44 – 1.29 \(\text{(m, 2H)}\), 1.21 \(\text{(t, J = 8 Hz, 3H)}\), 1.21 – 0.99 \(\text{(m, 1H)}\); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 173.2, 156.8, 76.7, 67.8, 63.1, 60.4, 56.6, 42.3, 40.9, 40.2, 37.4, 34.0, 33.9, 31.4, 30.6, 25.5, 25.2, 14.1; \(m/z\) (ESI+) found \([\text{M+H}]^+\) 339.2270. C\(_{18}\)H\(_{21}\)N\(_3\)O\(_4\) requires 339.2278.
Carbamate 43a[2]

\[
\begin{align*}
\nu_{\text{max}}\text{ (film)/cm}^{-1} & \quad 1704, 2935 \text{ cm}^{-1}; \\
\delta_{\text{H}}\text{ (400 MHz, CDCl}_3\text{)} & \quad 7.28 (dd, J = 4.7, 3.6 \text{ Hz, 2H}), 7.23 (d, J = 8.3 \text{ Hz, 2H}), 5.35 (\text{br s, 1H}), 5.10 (\text{dt, J = 10.8, 5.4 Hz, 1H}), 4.38 (dd, J = 15.2, 6.4 \text{ Hz, 1H}), 4.28 (dd, J = 15.2, 5.9 \text{ Hz, 1H}), 3.30 - 3.10 (m, 1H), 2.15 - 1.92 (m, 4H), 1.89 - 1.42 (m, 9H), 1.37 (d, J = 12.4 \text{ Hz, 1H}), 1.27 - 1.08 (m, 1H), 1.03 (d, J = 8.0 \text{ Hz, 3H}); \\
\delta_{\text{C}}\text{ (100 MHz, CDCl}_3\text{)} & \quad 156.8, 137.3, 133.0, 128.8, 128.6, 68.3, 63.7, 44.3, 43.1, 41.0, 40.9, 37.7, 31.2, 29.9, 25.9, 25.7, 18.3; \\
m/z \text{ (ESI+) found [M+H]^+} & \quad 368.1830. C_{20}H_{28}ClN_2O_2^+ \text{ requires 363.1834.}
\end{align*}
\]

Carbamate 43a[3]

\[
\begin{align*}
\nu_{\text{max}}\text{ (film)/cm}^{-1} & \quad 1697, 2931 \text{ cm}^{-1}; \\
\delta_{\text{H}}\text{ (400 MHz, CDCl}_3\text{)} & \quad 8.12 (dd, J = 7.6, 2.1 \text{ Hz, 1H}), 7.19 (dd, J = 10.2, 4.5 \text{ Hz, 3H}), 5.10 (\text{dt, J = 10.8, 5.4 Hz, 1H}), 4.96 (\text{br s, 1H}), 3.34 - 3.08 (m, 3H), 2.79 - 2.49 (m, 4H), 2.14 - 1.98 (m, 4H), 1.93 - 1.33 (m, 10H), 1.25 - 1.05 (m, 1H); 1.05 (d, J = 8.0 \text{ Hz, 3H}); \\
\delta_{\text{C}}\text{ (100 MHz, CDCl}_3\text{)} & \quad 153.7, 147.6, 127.9, 122.4, 121.0, 118.1, 109.9, 77.5, 69.4, 68.9, 55.5, 52.9, 43.1, 41.0, 40.9, 40.4, 37.7, 33.0, 31.6, 31.2, 29.9, 26.0, 25.8, 18.3; \\
m/z \text{ (ESI+) found [M+H]^+} & \quad 357.2531. C_{22}H_{33}N_2O_3^+ \text{ requires 357.2537.}
\end{align*}
\]

Carbamate 43b[11]

\[
\begin{align*}
\nu_{\text{max}}\text{ (film)/cm}^{-1} & \quad 1602, 1723, 2935 \text{ cm}^{-1}; \\
\delta_{\text{H}}\text{ (400 MHz, CDCl}_3\text{)} & \quad 8.12 (dd, J = 7.6, 2.1 \text{ Hz, 1H}), 7.34 (\text{br s, 1H}), 7.05 - 6.89 (m, 2H), 6.87 - 6.76 (m, 1H), 5.18 (\text{dt, J = 10.9, 5.6 Hz, 1H}), 3.83 (s, 3H), 3.40 - 3.25 (m, 1H), 2.21 (m, 1H), 2.13 - 1.95 (m, 3H), 1.96 - 1.00 (m, 17H), 0.89 (t, J = 7.1 \text{ Hz, 3H}); \\
\delta_{\text{C}}\text{ (100 MHz, CDCl}_3\text{)} & \quad 153.7, 147.6, 127.9, 122.4, 121.0, 118.1, 109.9, 77.5, 69.4, 68.9, 55.5, 52.9, 43.1, 37.3, 37.1, 31.4, 30.7, 29.8, 29.6, 26.1, 25.8, 23.0, 14.0; \\
m/z \text{ (ESI+) found [M+H]^+} & \quad 287.2635. C_{23}H_{35}N_2O_3^+ \text{ requires 387.2642.}
\end{align*}
\]
Carbamate 43b[9]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} & 1596, 1727, 2222, 2931 \text{ cm}^{-1}; \\
\delta_{\text{H}} \text{ (400 MHz, CDCl}_3) & 7.65 - 7.37 \text{ (m, 5H), 5.15 (dt, } J = 11.0, 5.5 \text{ Hz, 1H), 3.28 (d, } J = 11.2 \text{ Hz, 1H), 2.20 - 2.15 \text{ (m, 1H), 2.11 - 1.95 \text{ (m, 3H), 1.89 (d, } J = 6.7 \text{ Hz, 1H), 1.85 - 1.34 \text{ (m, 11H), 1.34 - 1.05 \text{ (m, 6H), 0.86 (t, } J = 7.1 \text{ Hz, 3H); } \\
\delta_{\text{C}} \text{ (100 MHz, CDCl}_3) & 153.26, 142.6, 133.2, 119.0, 118.2, 105.7, 78.1, 69.2, 68.6, 52.7, 43.0, 40.9, 37.1, 31.5, 30.7, 30.1, 29.5, 26.0, 25.7, 23.0, 14.0. \\
m/z \text{ (ESI+) found } [\text{M+H}^+] & 382.2486. \text{ C}_{23}\text{H}_{32}\text{N}_3\text{O}_2^+ \text{ requires 382.2489.}
\end{align*}
\]

Carbamate 43c[4]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} & 1720, 2935 \text{ cm}^{-1}; \\
\delta_{\text{H}} \text{ (400 MHz, CDCl}_3) & 7.77 \text{ (s, 1H), 7.29 (dd, } J = 8.1, 6.6 \text{ Hz, 2H), 7.25 - 7.10 \text{ (m, 5H), 7.04 (t, } J = 7.3 \text{ Hz, 1H), 6.63 \text{ (s, 1H), 5.17 (dt, } J = 10.9, 5.6 \text{ Hz, 1H), 3.60 - 3.40 \text{ (d, } J = 10.3 \text{ Hz, 1H), 3.20 (dd, } J = 13.3, 2.7 \text{ Hz, 1H), 2.50 - 1.20 \text{ (m, 19H); } \\
\delta_{\text{C}} \text{ (100 MHz, CDCl}_3) & 153.8, 140.2, 136.0, 130.4, 129.5, 128.3, 126.7, 125.9, 124.2, 70.6, 68.7, 52.9, 43.1, 41.0, 37.2, 37.1, 35.8, 31.4, 29.7, 26.1, 25.7, 17.9; m/z \text{ (ESI+) found } [\text{M+H}^+] & 405.2528. \text{ C}_{26}\text{H}_{33}\text{N}_2\text{O}_2^+ \text{ requires 405.2537.}
\end{align*}
\]

Carbamate 43c[5]

\[
\begin{align*}
\nu_{\text{max}} \text{ (film)/cm}^{-1} & 1718, 2935 \text{ cm}^{-1}; \\
\delta_{\text{H}} \text{ (400 MHz, CDCl}_3) & 7.38 - 7.25 \text{ (m, 4H), 7.25-7.21 \text{ (m, 1H), 7.18 - 7.06 \text{ (m, 4H), 6.85 \text{ (s, 1H), 5.19 (dt, } J = 10.9, 5.5 \text{ Hz, 1H), 3.57 (d, } J = 11.1 \text{ Hz, 1H), 3.21 (dd, } J = 13.3, 2.9 \text{ Hz, 1H), 2.63 (s, 3H), 2.40 - 2.35 \text{ (m, 1H), 2.25 - 1.60 \text{ (m, 12H), 1.60 - 1.40 \text{ (m, 1H), 1.37 (dd, } J = 11.6, 2.3 \text{ Hz, 1H), 1.31 - 1.12 \text{ (m, 1H); } \\
\delta_{\text{C}} \text{ (100 MHz, CDCl}_3) & 153.8, 140.21, 135.59, 132.79, 129.5, 128.3, 125.9, 120.0, 118.6, 70.6, 68.9, 53.0, 43.2, 41.0, 37.3, 37.2, 35.8, 31.5, 29.9, 26.1, 25.8, 20.7; m/z \text{ (ESI+) found } [\text{M+H}^+] & 405.2544. \text{ C}_{26}\text{H}_{33}\text{N}_2\text{O}_2^+ \text{ requires 405.2537.}
\end{align*}
\]
Carbamate 43c

\[ \text{Carbamate 43c} \]

\[ \nu_{\text{max}} \text{ (film)/cm}^{-1} 1600, 1702, 2933 \text{ cm}^{-1}; \delta_{\text{H}} (400 MHz, CDCl}_3) 7.45 (dd, J = 8.6, 1.0 Hz, 2H), 7.39 – 7.26 (m, 4H), 7.22 (dd, J = 8.4, 6.3 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.12 – 7.04 (m, 1H), 6.88 (s, 1H), 5.32 – 5.08 (m, 1H), 3.59 – 3.56 (m, 1H), 3.22 (dd, J = 13.3, 3.0 Hz, 1H), 2.41 (dd, J = 13.2, 10.1 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.25 – 2.06 (m, 3H), 2.06 – 1.56 (m, 8H), 1.52 – 1.45 (m, 1H), 1.37 (dd, J = 11.6, 2.4 Hz, 1H), 1.24 (m, 1H); \delta_{\text{C}} (100 MHz, CDCl}_3) 153.6, 140.1, 138.1, 129.5, 129.0, 128.3, 125.9, 123.2, 118.5, 70.6, 68.9, 53.0, 43.2, 41.0, 37.3, 37.2, 35.8, 31.6, 29.9, 26.1, 25.7; m/z (ESI+) found [M+H]+ 391.2387. C_{25}H_{31}N_{2}O_{2} requires 391.2380.

D. Mesembrine-inspired libraries.

General procedures for library preparation and tabulated results.

Amines 44:

\[ \text{A solution of ketone scaffold 19 (50 mg, 0.27 mmol) in anhydrous THF (2 mL) was added to a 4-dram vial flushed with argon. The appropriate amine (0.54 mmol) was added, followed by acetic acid (21 \muL, 0.36 mmol). The reaction was stirred at room temperature for 1 h, then sodium triacetoxyborohydride (150 mg, 0.72 mmol) added. The reactions were shaken for a further 13 h, then quenched by addition of 2M NaOH (0.5 mL) and shaken for an additional 10 min. Dichloromethane (2 mL) was added to each tube and the reactions passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were} \]
evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines 44a and 44b.

| Product | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|---------|-----------------|------------|-----------------------|-----------|------------|
| 44a(1) | 273.1967        | 273.1966   | 15.5                  | 20        | 100        |
| 44a(2) | 307.1577        | 307.1600   | 30.0                  | 35        | 100        |
| 44a(3) | 307.1577        | 307.1602   | 30.5                  | 35        | 100        |
| 44a(4) | 307.1577        | 307.1589   | 2.0                   | 02        | 99         |
| 44a(5) | 291.1873        | 277.1695   | 5.6                   | 07        | 83         |
| 44a(6) | 291.1873        | 291.1875   | 7.6                   | 10        | 100        |
| 44a(7) | 291.1873        | 291.1879   | 5.2                   | 07        | 100        |
| 44a(8) | 351.1072        | 351.1096   | 26.1                  | 27        | 100        |
| 44a(9) | 341.1187        | 341.1198   | 33.2                  | 35        | 100        |
| 44a(10)| 341.1841        | 341.1850   | 30.9                  | 33        | 100        |
| 44a(11)| 287.2123        | 287.2129   | 24.1                  | 35        | 100        |
| 44a(12)| 287.2123        | 287.2156   | 26.1                  | 33        | 100        |
| 44a(13)| 287.2123        | 287.2120   | 3.1                   | 04        | 100        |
| 44a(14)| 303.2073        | 303.2083   | 13.4                  | 16        | 98         |
| 44a(15)| 303.2073        | 303.2075   | 25.3                  | 32        | 100        |
| 44a(16)| 333.2178        | 333.2188   | 28.6                  | 31        | 100        |
| 44a(17)| 289.1916        | 289.1940   | 2.7                   | 04        | 100        |
| 44a(18)| 375.1451        | 375.1464   | 31.1                  | 30        | 98         |
| 44a(19)| 279.1531        | 279.1556   | 22.3                  | 29        | 100        |
| 44a(20)| 263.1760        | 263.1783   | 16.8                  | 23        | 100        |
| 44a(21)| 277.1916        | 277.1955   | 23.7                  | 31        | 100        |
| 44a(22)| 274.1919        | 274.1931   | 20.8                  | 28        | 100        |
| 44a(23)| 288.2076        | 288.2100   | 18.1                  | 23        | 86         |
| 44a(24)| 265.2280        | 265.2302   | 9.9                   | 13        | 94         |
| 44b(1) | 273.1967        | 273.1983   | 7.0                   | 09        | 100        |
| 44b(2) | 307.1577        | 307.1599   | 12.8                  | 15        | 100        |
| 44b(3) | 307.1577        | 307.1586   | 14.3                  | 17        | 100        |
| 44b(4) | 291.1873        | 277.1680   | 2.7                   | 03        | 97         |
| 44b(5) | 351.1072        | 351.1075   | 14.5                  | 15        | 100        |
| 44b(6) | 287.2123        | 287.2148   | 10.4                  | 13        | 100        |
| 44b(7) | 287.2123        | 287.2134   | 10.2                  | 13        | 100        |
| 44b(8) | 303.2073        | 303.2091   | 9.6                   | 12        | 100        |
| 44b(18)| 375.1451        | 375.1466   | 19.6                  | 19        | 100        |
| 44b(19)| 279.1531        | 279.1551   | 10.2                  | 13        | 100        |
| 44b(20)| 263.1760        | 263.1783   | 10.2                  | 10        | 86         |
| 44b(21)| 277.1916        | 277.1950   | 10.1                  | 13        | 100        |
| 44b(22)| 274.1919        | 274.1939   | 8.7                   | 12        | 84         |
Quinolines 45 from 2-nitrobenzaldehydes

Fe\(^0\) powder (90 mg, 1.6 mmol) was added to a solution of the appropriate 2-nitrobenzaldehyde (0.41 mmol) in ethanol (2 mL) in a microwave vial, followed by 0.1 M HCl (210 μL). The vial was sealed, then heated in an oil bath at 85 °C until complete by TLC (~2 h). The mixture was cooled to room temperature, then a solution of ketone scaffold 19 (50 mg, 0.27 mmol) in EtOH (1 mL) added, followed by powdered KOH (22 mg, 0.38 mmol). The mixture was heated at 85 °C until complete by TLC (~3 h), then cooled to room temperature, passed through a celite plug, eluting with dichloromethane, and concentrated under reduced pressure. The residues were subjected to mass-directed preparative HPLC purification to afford pure quinolines 45.

| Product | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|---------|----------------|------------|-----------------------|-----------|------------|
| 45[1]   | 267.1497       | 267.1496   | 27.1                  | 51        | 93         |
| 45[2]   | 301.1108       | 301.1130   | 30.0                  | 46        | 100        |
| 45[3]   | 297.1603       | 297.1613   | 36.5                  | 60        | 92         |
| 45[4]   | 335.1371       | 335.1383   | 39.0                  | 58        | 100        |
| 45[5]   | 283.1447       | 283.1438   | 41.0                  | 73        | 100        |
| 45[6]   | 301.1108       | 301.1117   | 39.4                  | 66        | 100        |
| 45[7]   | 317.1654       | 317.1667   | 9.7                   | 15        | 88         |

Quinolines 45 from 2-aminoacetophenones and 2-aminobenzophenones

Ketone scaffold 19 (50 mg, 0.27 mmol) was placed in a 2-dram vial containing a magnetic stir bar. The appropriate 2-amino benzophenone or 2-amino acetophenone (0.30 mmol) was then added, followed by p-toluenesulphonic acid (0.27 mmol). The vial was sealed shut and heated at 100 °C in
an oil bath for 12 h, then cooled to room temperature, diluted with dichloromethane (2 ml) and quenched with 0.1M NaOH (5 ml). The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure quinolines 45.

| Product | Calculated mass | Found mass | Recovered weight (mg) | Yield (%) | Purity (%) |
|---------|-----------------|------------|-----------------------|-----------|------------|
| 45[8]   | 281.1654        | 281.1662   | 28.7                  | 45        | 100        |
| 45[9]   | 341.1865        | 341.1891   | 13.0                  | 10        | 100        |
| 45[10]  | 325.1552        | 325.1565   | 42.8                  | 60        | 86         |
| 45[12]  | 377.1414        | 377.1414   | 49.6                  | 60        | 100        |
| 45[12]  | 388.1661        | 388.1677   | 35.2                  | 41        | 100        |

Characterization data for representative library compounds

Quinoline 45[2]

δ_H (400 MHz, CDCl_3) At ambient temperature, a 5:1 mixture of rotamers was observed. Major rotamer: 7.96 – 7.80 (m, 2H), 7.72 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 9.0, 2.3 Hz, 1H), 4.25 (dd, J = 16.2, 4.7 Hz, 1H), 3.77 – 3.38 (m, 4H), 3.04 – 2.77 (m, 2H), 2.32 – 2.16 (m, 2H), 2.12 (s, 3H), 1.83 – 1.71 (m, 1H). Minor rotamer (characteristic signals): 4.02 (dd, J = 11.9, 8.1 Hz, 1H), 3.08 – 2.97 (m, 1H), 2.13 (s, 3H); δ_C (125 MHz, CDCl_3) Major rotamer: 170.9, 157.9, 145.2, 136.1, 131.8, 130.4, 130.1, 127.7, 125.9, 60.3, 49.1, 42.9, 38.3, 35.6, 30.3, 23.4; m/z (ESI+) found [M+H]^+ 301.1130. C_{17}H_{18}ClN_2O^+: requires 301.1108.

Quinoline 45[8]

δ_H (400 MHz, CDCl_3) At ambient temperature, a 5:1 mixture of rotamers was observed. Major rotamer: 7.98 (dd, J = 18.3, 8.3 Hz, 2H), 7.74 – 7.57 (m, 1H), 7.49 (m, 1H), 4.29 (dd, J = 16.3, 5.0 Hz, 1H), 3.83 – 3.33 (m, 4H), 3.01 (dd, J = 16.8, 12.7 Hz, 1H), 2.68 – 2.60 (m, 4H), 2.35 – 2.09 (m, 5H), 1.75 (dd, J = 11.6, 8.6 Hz, 1H). Minor rotamer (characteristic signals): 4.18 – 4.05 (m, 1H), 2.89 (d, J = 16.4 Hz, 1H), 2.17 (s, 3H); δ_C (125 MHz, CDCl_3) Major rotamer: 171.0, 156.9, 146.2, 143.4, 129.1, 128.7, 127.4, 126.8, 125.8, 123.6, 61.0, 49.3, 42.3, 38.9, 33.7, 30.3, 23.5, 14.3; m/z (ESI+) found [M+H]^+ 281.1662. C_{18}H_{21}N_2O^+: requires 281.1654.
δ\text{H} (500 MHz, CDCl\textsubscript{3}) At ambient temperature, a 5:1 mixture of rotamers was observed. Major rotamer: 7.97 – 7.92 (m, 1H), 7.58 – 7.51 (m, 2H), 7.49 – 7.44 (m, 2H), 7.29 – 7.24 (m, 2H), 7.16 – 7.09 (m, 1H), 3.89 – 3.77 (dd, J = 16.8, 4.8 Hz, 1H), 3.74 – 3.63 (m, 1H), 3.62 – 3.41 (m, 2H), 3.14 – 2.99 (m, 1H), 2.50 – 2.39 (dd, J = 16.8, 11.4 Hz, 1H), 2.29 – 2.12 (m, 2H), 2.07 – 1.94 (s, 3H), 1.80 – 1.67 (m, 2H). Minor rotamer (characteristic signals): 4.04 (dd, J = 11.8, 8.0 Hz, 1H), 3.28 – 3.20 (m, 1H). δ\text{C} (125 MHz, CDCl\textsubscript{3}) Major rotamer: 170.7, 157.8, 148.0, 144.9, 136.0, 131.7, 130.2, 129.8, 128.5, 128.0, 127.4, 124.9, 60.8, 49.2, 42.5, 39.0, 34.4, 30.3, 23.4; m/z (ESI+) found [M+H]\textsuperscript{+} 377.1414. C\textsubscript{23}H\textsubscript{22}ClN\textsubscript{2}O\textsubscript{2}: requires 377.1421.

δ\text{H} (500 MHz, CDCl\textsubscript{3}) At ambient temperature, a 3.5:1 mixture of rotamers was observed. Major rotamer: 8.38 (dd, J = 9.2, 2.5 Hz, 1H), 8.29 (d, J = 2.5 Hz, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.59 (tt, J = 7.4, 3.4 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.31 – 7.27 (m, 1H), 7.19 – 7.14 (m, 1H), 3.89 (dd, J = 16.9, 4.7 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.58 (dt, J = 17.2, 4.8 Hz, 2H), 3.48 (td, J = 11.1, 4.7 Hz, 1H), 3.11 (dd, J = 17.3, 12.8 Hz, 1H), 2.49 (dd, J = 16.9, 11.4 Hz, 1H), 2.30 – 2.17 (m, 2H), 2.03 (s, 3H), 1.82 – 1.70 (m, 1H). Minor rotamer (characteristic signals): 3.35 – 3.25 (m, 1H), 2.72 (dd, J = 16.1, 11.4 Hz, 1H), 2.43 – 2.30 (m, 1H); δ\text{C} (125 MHz, CDCl\textsubscript{3}) Major rotamer: 170.8, 161.8, 150.7, 148.5, 145.3, 135.0, 130.4, 129.5, 129.4, 129.2, 129.1, 129.0, 128.8, 125.8, 123.3, 122.4, 60.6, 49.2, 42.3, 39.3, 34.5, 30.3, 23.4; m/z (ESI+) found [M+H]\textsuperscript{+} 388.1677. C\textsubscript{23}H\textsubscript{22}N\textsubscript{3}O\textsubscript{3}: requires 388.1661.

δ\text{H} (500 MHz, CDCl\textsubscript{3}) At ambient temperature, a 2:1 mixture of rotamers was observed. Major rotamer: 7.54 – 7.35 (m, 2H), 6.28 – 6.25 (m, 1H), 6.09 (s, 1H), 4.40 (dd, J = 16.0, 5.0 Hz, 1H), 3.99 –
3.88 (m, 1H), 3.80 (td, \( J = 10.7, 10.2, 6.1 \text{ Hz}, 1\text{H} \)), 3.68 (tq, \( J = 11.5, 6.4, 5.6 \text{ Hz}, 1\text{H} \)), 3.57 – 3.46 (m, 1H), 3.21 – 3.06 (m, 1H), 2.84 – 2.73 (m, 1H), 2.73 – 2.61 (m, 4H), 2.49 – 2.38 (m, 1H), 2.37 – 2.25 (m, 3H), 1.99 – 1.85 (m, 1H). Minor rotamer (characteristic signals): 4.30 – 4.26 (m, 1H), 3.64 – 3.59 (m, 1H), 3.02 – 2.97 (m, 1H); \( \delta_C \) (125 MHz, CDCl\(_3\)) Major rotamer: 170.9, 154.4, 149.9, 147.6, 125.7, 123.5, 109.1, 105.4, 101.6, 99.3, 96.8, 61.0, 49.3, 42.4, 38.5, 33.4, 30.3, 23.5, 14.7; m/z (ESI+) found [M+H]\(^+\) 325.1565. C\(_{19}\)H\(_{21}\)N\(_2\)O\(_3\)\(^+\): requires 325.1552.

Amine 44a\(^3\)

\[ \text{δ}_H (500 \text{ MHz, CDCl}_3) \] At ambient temperature, a 2.6:1 mixture of rotamers was observed. Major rotamer: 7.32 (s, 1H), 7.27 – 7.17 (m, 3H), 3.86 – 3.76 (m, 2H), 3.52 (dd, \( J = 9.7, 8.4 \text{ Hz}, 1\text{H} \)), 3.42 (td, \( J = 10.5, 6.4 \text{ Hz}, 1\text{H} \)), 3.05 – 2.90 (m, 2H), 2.70 – 2.54 (m, 1H), 2.26 – 2.13 (m, 1H), 2.12 – 1.97 (m, 4H), 1.94 – 1.80 (m, 2H), 1.67 – 1.36 (m, 2H), 1.36 – 1.04 (m, 2H). Minor rotamer (characteristic signals): 3.79 – 3.65 (m, 1H), 3.16 (td, \( J = 11.7, 6.3 \text{ Hz}, 1\text{H} \)), 2.27 (dq, \( J = 11.8, 3.3 \text{ Hz}, 1\text{H} \)); \( \delta_C \) (125 MHz, CDCl\(_3\)) Major rotamer: 170.8, 142.8, 134.3, 129.8, 128.2, 126.2, 64.0, 56.3, 50.8, 49.1, 44.9, 36.3, 32.2, 29.7, 29.4, 23.4; m/z (ESI+) found [M+H]\(^+\) 307.1586. C\(_{17}\)H\(_{24}\)ClN\(_2\)O\(^+\): requires 307.1577.

Amine 44b\(^3\)

\[ \text{δ}_H (500 \text{ MHz, CDCl}_3) \] At ambient temperature, a 3:1 mixture of rotamers was observed. Major rotamer: 7.32 (s, 1H), 7.25 – 7.16 (m, 3H), 3.78 – 3.66 (m, 2H), 3.53 – 3.34 (m, 2H), 3.01 – 2.85 (m, 2H), 2.82 – 2.71 (m, 1H), 2.12 – 1.70 (m, 7H), 1.61 – 1.29 (m, 4H). Minor rotamer (characteristic signals): 3.83 (dd, \( J = 11.8, 8.1 \text{ Hz}, 1\text{H} \)), 3.30 (td, \( J = 11.6, 6.3 \text{ Hz}, 1\text{H} \)), 2.07 (s, 3H); \( \delta_C \) (125 MHz, CDCl\(_3\)) Major rotamer: 170.8, 143.2, 134.3, 129.7, 128.1, 127.1, 126.2, 64.4, 51.8, 51.3, 48.6, 39.7, 34.2, 30.0, 29.6, 26.3, 23.5; m/z (ESI+) found [M+H]\(^+\) 307.1602. C\(_{17}\)H\(_{24}\)ClN\(_2\)O\(^+\): requires 307.1577.
Amine 44b\{11\}

\[
\begin{align*}
\delta_\text{H} (500 \text{ MHz, CDCl}_3) \text{ At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: } & 7.27 (d, J = 1.9 \text{ Hz, 1H}), 7.20 - 7.12 (m, 3H), 3.79 (s, 2H), 3.58 - 3.38 (m, 2H), 3.05 - 2.89 (m,
\end{align*}
\]

Minor rotamer (characteristic signals): 3.91 - 3.82 (m, 1H), 3.31 (td, J = 11.6, 6.3 Hz, 1H), 2.42 (ddd, J = 11.2, 7.4, 4.0 Hz, 1H), 2.07 (s, 3H); \(\delta_\text{C} (125 \text{ MHz, CDCl}_3)\) 170.8, 138.6, 136.3, 130.4, 128.4, 127.1, 126.1, 64.2, 57.0, 49.3, 49.1, 45.0, 36.4, 32.4, 29.7, 29.5, 23.5, 19.1; \(m/z\) (ESI+) found [M+H]\(^+\) 287.2148. \(\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}^+\): requires 287.2123.

Amine 44b\{9\}

\[
\begin{align*}
\delta_\text{H} (500 \text{ MHz, CDCl}_3) \text{ At ambient temperature, a 2.7:1 mixture of rotamer was observed. Major rotamer: } & 7.45 (d, J = 1.7 \text{ Hz, 1H}), 7.42 - 7.34 (m, 1H), 7.17 (dd, J = 8.2, 1.8 \text{ Hz, 1H}), 3.79 - 3.63 (m, 2H), 3.57 - 3.36 (m, 2H), 3.07 - 2.87 (m, 2H), 2.87 - 2.71 (m, 1H), 2.15 - 1.68 (m, 7H), 1.63 - 1.20 (m, 4H). \text{Minor rotamer (characteristic signals): } & 3.82 (dd, J = 11.8, 8.2 \text{ Hz, 1H}), 3.32 - 3.26 (m, 1H), 2.06 (s, 3H); \delta_\text{C} (125 \text{ MHz, CDCl}_3) \text{ Major rotamer: } 170.8, 141.5, 132.4, 130.4, 130.0, 127.5, 127.4, 64.4, 51.9, 50.7, 48.6, 39.8, 34.2, 30.0, 29.6, 26.4, 23.5; \text{m/z (ESI+) found [M+H]\(^+\) 341.1198. C}_{17}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}^+\): requires 341.1187.
\end{align*}
\]

Amine 44a\{6\}

\[
\begin{align*}
\delta_\text{H} (500 \text{ MHz, CDCl}_3) \text{ At ambient temperature, a 2.3:1 mixture of rotamer was observed. Major rotamer: } & 7.30 - 7.23 (m, 1H), 7.12 - 7.03 (m, 2H), 6.92 (td, J = 8.4, 2.4 \text{ Hz, 1H}), 3.81 - 3.70 (m, 2H), 3.52 - 3.36 (m, 2H), 3.04 - 2.88 (m, 2H), 2.82 - 2.73 (m, 1H), 2.14 - 1.71 (m, 7H), 1.62 - 1.28 (m, 4H). \text{Minor rotamer (characteristic signals): } & 3.87 - 3.78 (m, 1H), 3.32 - 3.23 (m, 1H), 2.06 (s, 3H); \delta_\text{C} (125 \text{ MHz, CDCl}_3) \text{ Major rotamer: } 170.8, 163.1 (d, J_{cd} = 245 \text{ Hz}), 143.7, 129.9 (d, J_{cd} = 9 \text{ Hz}), 123.6 (d, J_{cd} =
\end{align*}
\]
3 Hz), 114.9 (d, $^2J_{cd} = 21$ Hz), 113.8 (d, $^2J_{cd} = 21$ Hz), 64.5, 51.8, 51.2, 48.6, 39.8, 34.2, 30.0, 29.6, 26.3, 23.5; m/z (ESI+) found [M+H]$^+$ 291.1879. C$_{17}$H$_{24}$FN$_2$O$^+$: requires 291.1873.

Amine 44b[8]

\[
\begin{array}{c}
\text{Br} \\
\text{A} \\
\text{H} \\
\text{N} \\
\text{H} \\
\text{O}
\end{array}
\]

$\delta_{ii}$ (500 MHz, CDCl$_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.48 – 7.40 (m, 2H), 7.19 (m, 2H), 3.84 – 3.73 (m, 2H), 3.59 – 3.49 (m, 1H), 3.42 (td, $J = 10.4$, 6.4 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.69 – 2.53 (m, 1H), 2.26 – 2.13 (m, 1H), 2.13 – 1.97 (m, 4H), 1.95 – 1.81 (m, 1H), 1.66 – 1.04 (m, 5H). Minor rotamer (characteristic signals): 3.89 – 3.79 (m, 1H), 3.28 (td, $J = 11.7$, 6.3 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.05 (s, 3H); $\delta_{c}$ (125 MHz, CDCl$_3$) Major rotamer: 170.8, 139.8, 131.6, 129.8, 120.8, 64.1, 56.3, 50.8, 49.1, 45.0, 36.3, 32.3, 29.7, 29.5, 23.5; m/z (ESI+) found [M+H]$^+$ 351.1075. C$_{17}$H$_{24}$BrN$_2$O$^+$: requires 351.1072.

Amine 44a[8]

\[
\begin{array}{c}
\text{Br} \\
\text{A} \\
\text{H} \\
\text{N} \\
\text{H} \\
\text{O}
\end{array}
\]

$\delta_{ii}$ (500 MHz, CDCl$_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.45 – 7.39 (m, 2H), 7.18 (m, 2H), 3.75 – 3.66 (m, 2H), 3.50 – 3.44 (m, 1H), 3.43 – 3.35 (m, 1H), 3.01 – 2.86 (m, 2H), 2.80 – 2.72 (m, 1H), 2.11 – 1.98 (m, 4H), 1.98 – 1.67 (m, 3H), 1.60 – 1.27 (m, 4H). Minor rotamer (characteristic signals): 3.86 – 3.75 (m, 1H), 3.35 – 3.27 (m, 1H), 2.25 – 2.13 (m, 2H), 2.05 (s, 3H); $\delta_{c}$ (125 MHz, CDCl$_3$) Major rotamer: 170.8, 140.1, 131.5, 129.8, 120.6, 64.5, 51.8, 51.1, 48.6, 39.8, 34.2, 30.0, 29.6, 26.3, 23.5; m/z (ESI+) found [M+H]$^+$ 351.1096. C$_{17}$H$_{24}$BrN$_2$O$^+$: requires 351.1072.

Amine 44b[15]

\[
\begin{array}{c}
\text{MeO} \\
\text{A} \\
\text{H} \\
\text{N} \\
\text{H} \\
\text{O}
\end{array}
\]
δ_H (500 MHz, CDCl₃) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.26 – 7.19 (m, 1H), 6.92 – 6.85 (m, 2H), 6.82 – 6.76 (m, 1H), 3.86 – 3.73 (m, 5H), 3.56 – 3.48 (m, 1H), 3.41 (td, J = 10.5, 6.4 Hz, 1H), 3.03 – 2.91 (m, 2H), 2.70 – 2.57 (m, 1H), 2.28 – 2.14 (m, 1H), 2.12 – 1.96 (m, 4H), 1.91 – 1.80 (m, 1H), 1.74 – 1.36 (m, 3H), 1.35 – 1.04 (m, 2H). Minor rotamer (characteristic signals): 3.29 (td, J = 11.7, 6.3 Hz, 1H), 2.46 – 2.37 (m, 1H), 2.06 (s, 2H); δ_C (125 MHz, CDCl₃) Major rotamer: 170.8, 159.9, 142.3, 129.6, 120.4, 113.7, 112.5, 64.1, 56.3, 55.3, 51.4, 49.1, 45.0, 36.3, 32.3, 29.7, 29.5, 23.5; m/z (ESI+) found [M+H]^+ 303.2091. C₁₈H₂₇N₂O₂⁺: requires 303.2073.

Amine 44a[15]

δ_H (500 MHz, CDCl₃) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.25 – 7.20 (m, 1H), 6.91 – 6.85 (m, 2H), 6.80 – 6.74 (m, 1H), 3.79 (s, 3H), 3.73 (s, 2H), 3.50 – 3.33 (m, 2H), 3.04 – 2.85 (m, 2H), 2.80 – 2.70 (m, 1H), 2.14 – 1.71 (m, 6H), 1.59 – 1.25 (m, 5H). Minor rotamer (characteristic signals): 3.27 (td, J = 11.6, 6.3 Hz, 1H), 2.05 (s, 3H); δ_C (125 MHz, CDCl₃) Major rotamer: 170.8, 159.8, 142.7, 129.4, 120.4, 113.8, 112.1, 64.5, 55.3, 51.7, 51.6, 48.6, 39.8, 34.2, 30.0, 29.6, 26.4, 23.5; m/z (ESI+) found [M+H]^+ 303.2075. C₁₈H₂₇N₂O₂⁺: requires 303.2073.

Amine 44a[14]

δ_H (500 MHz, CDCl₃) At ambient temperature, a 2.3:1 mixture of rotamer was observed. Major rotamer: 7.25 – 7.19 (m, 1H), 6.94 – 6.81 (m, 3H), 3.89 – 3.79 (s, 3H), 3.75 (s, 2H), 3.52 – 3.33 (m, 2H), 2.98 – 2.86 (m, 2H), 2.80 – 2.70 (m, 1H), 2.14 – 1.94 (m, 5H), 1.93 – 1.70 (m, 2H), 1.59 – 1.27 (m, 4H). Minor rotamer (characteristic signals): 3.27 (td, J = 11.6, 6.2 Hz, 1H), 2.20 (ddd, J = 15.0, 10.0, 3.2 Hz, 2H), 2.05 (s, 3H); δ_C (125 MHz, CDCl₃) Major rotamer: 170.7, 157.7, 129.9, 128.2, 120.5, 110.4, 64.5, 55.4, 51.2, 48.7, 47.1, 39.9, 34.2, 30.1, 29.6, 26.6, 23.6; m/z (ESI+) found [M+H]^+ 303.2083. C₁₈H₂₇N₂O₂⁺: requires 303.2073.
Amine 44a\{16\}

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) \text{ At ambient temperature, a 2.6:1 mixture of rotamer was observed. Major rotamer: } & 6.88 - 6.77 (m, 3H), 3.86 (m, 6H), 3.72 - 3.63 (m, 2H), 3.51 - 3.32 (m, 2H), 3.02 - 2.86 (m, 2H), 2.82 - 2.70 (m, 1H), 2.11 - 1.69 (m, 7H), 1.58 - 1.26 (m, 4H). \text{Minor rotamer (characteristic signals): } & 3.26 (td, J = 11.7, 6.3 \text{ Hz, 1H}), 2.25 - 2.13 (m, 2H), 2.04 (s, 3H); \\
\delta_C (125 \text{ MHz, CDCl}_3) \text{ Major rotamer: } & 170.8, 149.0, 148.0, 133.6, 120.1, 111.4, 111.1, 64.5, 56.1, 56.0, 51.7, 51.6, 48.6, 39.8, 34.3, 30.0, 29.5, 26.4, 23.5; \text{ m/z (ESI+) found } [M+H]^+ 333.2188. \text{ C}_{19}H_{29}N_2O_3^+: \text{ requires } 333.2178.
\end{align*}
\]

Amine 44a\{11\}

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) \text{ At ambient temperature, a 2.3:1 mixture of rotamer was observed. Major rotamer: } & 7.31 - 7.26 (m, 1H), 7.19 - 7.11 (m, 3H), 3.77 - 3.66 (m, 2H), 3.53 - 3.32 (m, 2H), 3.09 - 2.99 (m, 1H), 2.97 - 2.87 (m, 1H), 2.82 - 2.73 (m, 1H), 2.36 (s, 3H), 2.16 - 1.72 (m, 7H), 1.64 - 1.31 (m, 4H). \text{Minor rotamer (characteristic signals): } & 3.82 (dd, J = 11.9, 8.2 \text{ Hz, 1H}), 3.27 (td, J = 11.7, 6.3 \text{ Hz, 1H}), 2.07 (s, 3H); \\
\delta_C (125 \text{ MHz, CDCl}_3) \text{ Major rotamer: } & 170.8, 138.9, 136.6, 130.4, 128.7, 127.1, 126.0, 64.6, 52.6, 50.0, 48.7, 39.9, 34.6, 30.0, 29.7, 26.5, 23.6, 19.1; \text{ m/z (ESI+) found } [M+H]^+ 287.2129. \text{ C}_{18}H_{27}N_2O^{3-}: \text{ requires } 287.2123.
\end{align*}
\]

Amine 44b\{19\}

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) \text{ At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: } & 7.23 - 7.17 (m, 1H), 6.98 - 6.87 (m, 2H), 4.02 (s, 2H), 3.59 - 3.35 (m, 2H), 3.06 - 2.89 (m, 2H), 2.76 - 2.56 (m, 1H), 2.27 - 1.94 (m, 4H), 1.93 - 1.80 (m, 1H), 1.68 - 1.00 (m, 6H). \text{Minor rotamer (characteristic signals): } & 3.84 (dd, J = 11.8, 8.2 \text{ Hz, 1H}), 3.29 (td, J = 11.7, 6.3 \text{ Hz, 1H}), 2.45 - 2.37 (m, 1H), 2.05 (s, 3H); \\
\delta_C (125 \text{ MHz, CDCl}_3) \text{ Major rotamer: } & 170.8, 144.5, 126.8, 124.8, 124.4, 64.1, 55.9, 49.1, 45.9, 45.0, 36.2, 32.2, 29.7, 29.5, 23.5; \text{ m/z (ESI+) found } [M+H]^+ 279.1556. \text{ C}_{18}H_{22}N_2OS^{3-}: \text{ requires } 279.1531.
\end{align*}
\]
Amine 44b\[21\]

![Amine 44b](image)

$\delta_{n}$ (500 MHz, CDCl$_3$) At ambient temperature, a 2.6:1 mixture of rotamer was observed. Major rotamer: 6.02 (s, 1H), 5.86 (s, 1H), 3.74 (s, 2H), 3.57 – 3.48 (m, 1H), 3.41 (td, $J = 10.5$, 6.4 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.71 – 2.49 (m, 1H), 2.26 (s, 3H), 2.11 – 1.95 (m, 4H), 1.94 – 1.77 (m, 2H), 1.77 – 1.04 (m, 6H). Minor rotamer (characteristic signals): 3.84 (dd, $J = 11.9$, 8.2 Hz, 1H), 3.29 (td, $J = 11.7$, 6.3 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.05 (s, 3H); $\delta_{C}$ (125 MHz, CDCl$_3$) Major rotamer: 170.8, 152.1, 151.6, 107.7, 106.0, 64.1, 55.9, 49.1, 44.9, 43.9, 36.0, 32.0, 29.7, 29.4, 23.5, 13.7; m/z (ESI+) found [M+H]$^+$ 277.1955. C$_{16}$H$_{25}$N$_2$O$_2$: requires 277.1916.

Amine 44a\[23\]

![Amine 44a](image)

$\delta_{n}$ (500 MHz, CDCl$_3$) At ambient temperature, a 3:1 mixture of rotamer was observed. Major rotamer: 8.53 (s, 1H), 8.50 – 8.39 (m, 1H), 7.74 – 7.57 (m, 1H), 7.26 – 7.17 (m, 1H), 3.81 – 3.69 (m, 2H), 3.53 – 3.32 (m, 2H), 3.04 – 2.83 (m, 2H), 2.80 – 2.68 (m, 1H), 2.12 – 1.67 (m, 7H), 1.59 – 1.28 (m, 4H). Minor rotamer (characteristic signals): 3.25 (td, $J = 11.6$, 6.3 Hz, 1H), 2.03 (s, 3H); $\delta_{C}$ (125 MHz, CDCl$_3$) Major rotamer: 170.8, 149.6, 148.4, 136.3, 135.8, 123.4, 64.4, 51.9, 49.1, 48.6, 39.7, 34.1, 29.9, 29.5, 26.3, 23.5; m/z (ESI+) found [M+H]$^+$ 274.1931. C$_{16}$H$_{24}$N$_3$O$: requires 274.1919.
IV. Supplementary Note: Cheminformatic analysis

Principal Component Analysis

The plots shown in Fig 6a-c were generated from principal component analysis (PCA) of a total of 183 compounds:

- Tan’s established reference set consisting of 40 small molecule drugs, 20 drug-like compounds from commercial vendors (ChemBridge and Chem Div) and 60 diverse natural products (Suppl. Table 3),
- 20 alkaloid natural products (Suppl. Fig. 1),
- 14 representative scaffolds (Suppl. Fig. 2),
- 29 representative library members (Suppl. Fig. 3).

The 20 structural and physiochemical properties (Supplementary Table 4) introduced by Tan were determined by SYBYL, free online cheminformatic tools (VCC Lab), ChemDraw and manual inspection. For a discussion on the relevance of the 20 selected parameters, see Tan’s earlier paper. This property data for all the compounds was assembled in a Microsoft Excel spreadsheet (Supplementary Dataset 1 PCA.xls). The mean average value for each parameter was calculated for each compound series (Supplementary Table 5). This hypothetical average structure for each series was also included in the PCA analysis.
Supplementary Table 4. Parameters employed in PCA.

| Parameter | Description | Method of Determination |
|-----------|-------------|-------------------------|
| MW | molecular weight | SYBYL |
| N | number of nitrogen atoms | SYBYL |
| O | number of oxygen atoms | SYBYL |
| XLogP | calc n-octanol/water partition coefficient | http://www.vcclab.org |
| HBD | number of hydrogen bond donors | SYBYL |
| HBA | number of hydrogen bond acceptors | SYBYL |
| RotB | number of rotatable bonds | SYBYL |
| tPSA | topological polar surface area | SYBYL |
| nStereo | number of stereocenters | SYBYL |
| R | number of R stereocentres | ChemDraw Show Stereochemistry |
| S | number of S stereocentres | ChemDraw Show Stereochemistry |
| nStMW | | Microsoft Excel |
| RSdelta | nStereo / MW (stereochemical density) | Microsoft Excel |
| Rings | number of rings | Manual inspection |
| RngAr | number of aromatic rings | Manual inspection |
| RngSys | number of ring systems | Manual inspection |
| RngLg | number of atoms in largest ring outline | Manual inspection |
| RRsys | Rings / RngSys (ring complexity) | Microsoft Excel |
| ALOGPs | calc n-octanol/water partition coefficient (alt) | http://www.vcclab.org |
| ALOGpS | calc aqueous solubility | http://www.vcclab.org |

Supplementary Table 5. Average parameters by compound series.

| Parameter | Drugs | NPs | Commercial | Alkaloid NPs | Scaffolds | Libraries |
|-----------|-------|-----|------------|--------------|-----------|-----------|
| m/w       | 361   | 629 | 414        | 319          | 243       | 355       |
| N         | 2.2   | 2.6 | 4.5        | 1.7          | 0.9       | 1.9       |
| O         | 2.9   | 9.7 | 3.3        | 2.8          | 1.6       | 1.8       |
| XLogP     | 2.7   | 1.5 | 2.4        | 2.0          | 2.3       | 4.0       |
| HBD       | 1.5   | 4.9 | 1.5        | 1.3          | 0.7       | 0.8       |
| HBA       | 5.4   | 10.8| 6.8        | 4.4          | 2.5       | 4.3       |
| RotB      | 6.3   | 9.7 | 5.7        | 2.8          | 1.7       | 4.1       |
| tPSA      | 69    | 183 | 98         | 54           | 33        | 42        |
| ALOGPs    | 2.8   | 2.1 | 3.0        | 2.3          | 2.4       | 4.0       |
| ALOGpS    | -3.9  | -3.8| -3.9       | -2.7         | -2.5      | -4.5      |
| nStereo   | 1.4   | 9.1 | 0.5        | 4.0          | 3.1       | 3.3       |
| R         | 0.6   | 4.1 | 0.3        | 1.7          | 1.6       | 1.6       |
| S         | 0.8   | 5.0 | 0.3        | 2.3          | 1.6       | 1.6       |
| nStMW*    | 3.7   | 13.9| 1.1        | 12.7         | 13.5      | 9.4       |
| RSdelta   | -0.2  | -0.9| 0.0        | -0.6         | 0.0       | 0.0       |
| Rings     | 2.9   | 3.8 | 3.7        | 3.9          | 3.0       | 3.8       |
| RngAr     | 2.1   | 1.0 | 2.9        | 0.9          | 0.5       | 1.1       |
| RngSys    | 2.1   | 2.0 | 3.1        | 1.4          | 1.5       | 2.0       |
| RngLg     | 8.4   | 15.8| 7.9        | 13.4         | 10.9      | 11.9      |
| RRsys     | 1.4   | 2.3 | 1.2        | 3.2          | 2.2       | 2.1       |

*nStMW x 1000
Principal component analysis was then carried out using the procedure outlined by Tan. This resulted in the construction of 3 plots of PC1 v PC2, PC1 v PC3 and PC2 v PC3 (Supplementary Fig. 1a-c). Summary information from R (the open source statistical computing package used for the PCA analysis) is shown below in Supplementary Table 6.

**Supplementary Table 6. Standard deviation and proportion of variance for each component in PCA plot (R Summary).**

| Component | PC1 | PC2 | PC3 | PC4 | PC5 | PC6 | PC7 | PC8 | PC9 | PC10 |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Standard deviation | 2.871 | 1.856 | 1.747 | 1.384 | 1.094 | 0.844 | 0.575 | 0.568 | 0.468 | 0.374 |
| Proportion of Variance | 0.412 | 0.172 | 0.153 | 0.096 | 0.060 | 0.036 | 0.017 | 0.016 | 0.011 | 0.007 |
| Cumulative Proportion | 0.412 | 0.584 | 0.737 | 0.833 | 0.893 | 0.928 | 0.945 | 0.961 | 0.972 | 0.979 |

This data shows that of the 20-dimensional dataset, >90% of the variance is accounted for within the first 6 principal components (PC1 – PC6). In order to simplify the interpretation of this data, the first 3 principal components (accounting for ~74% of the variation) were used to generate the PCA plots shown in Fig. 6a-c.

The R program was used to plot the weightings of the original 20 parameters for each of the three 2-dimensional PCA plots (Supplementary Fig. 8). The parameters that have the greatest influence on PC1 are MW, O, HBA and tPSA, which move compounds to the right for plots PC1 v PC2 and PC1 v PC3. The descriptors with the largest loading on PC2 are N, RingAr and RingSys, which shift compounds up in plots PC1 v PC2 and PC2 v PC3, as well as nStMW, which shifts compounds down in these plots. Finally, PC3 is affected to the greatest degree by XLogP, Rings and ALOGPs, shifting compounds in a negative direction along the PC3 axis in plots PC1 v PC3 and PC2 v PC3, in addition to ALOGpS, which shifts compounds in a positive direction in these plots.
Supplementary Figure 8. Biplots and component loadings for PCA of alkaloid-inspired scaffolds and libraries, and reference sets. The biplots for (a) PC1 v PC2. (b) PC1 v PC3. (c) PC2 v PC3. (d) Component loadings of each of the 20 structural and physiochemical descriptors for the first 3 principal components (PC1 – PC3). The four descriptors with the highest weightings are highlighted for each principal component.

Principal Moment of Inertia Analysis

Principal moment of inertia analysis was carried out by calculation of the lowest energy conformation of each representative scaffold and library compound, and each compound from the above reference set. The conformation calculation was performed using the MOE molecular modelling software package\(^7\) in a similar manner to that reported by Tan\(^7\), with the only difference being the selection of parameters employed for conformation generation:

- maxConfs: 1000
• RMSD: ≤0.15
• Failure limit: 100
• Energy cutoff: 7 kcal/mol
• Iteration limit: 1000
• MM iteration limit: 500

Once the lowest energy conformer was calculated, the three principal moments of inertia (lxx, lyy, lzz) and normalized principal moments of inertia, npr1 (lxx/lzz) and npr2 (lyy/lzz) were determined using MOE. These PMI ratios were calculated for our representative scaffolds and library members, in addition to the reference sets47 of alkaloids, drugs, commercial drug-like library compounds and natural products. The ratios were plotted on a triangular graph where the vertices (0,1), (0.5,0.5) and (1,1) represent a perfect rod, disc and sphere, respectively (Fig. 6d).74
V. Supplementary Note: 1H and 13C NMR spectra for intermediates, scaffolds and representative library compounds

*Stemona* alkaloid-inspired series

S1c
S2d
3c

[Chemical structure diagram and NMR spectra]
S4d
27b[1]

![Chemical Structure](image)

---

S140
$27d(19)$
28c(8)
$28c(13)$
28d[11]
29b[2]

S147
29d[19]
$29d_{22}$
$30d^{(21)}$
Cylindricine-inspired series

Ketone 6b
Ketone 6c
Ketone 6d
Ketone 6e
Ketone 6g
Ketone 6h
Lactam 8ca

\[ \text{Structural formula of lactam 8ca} \]
Lactam 8ea
Lactam 8ga
Lactam 8ha
Lactam 8ab
Lactam 8bb
Lactam 9bb
Amine 10ca
Amine 10da
Amine 10db

![Chemical Structure of Amine 10db](image)

![NMR Spectroscopy of Amine 10db](image)
Lactam 8dd
Lactam 8fd
Lactam 9ga

3 \{1\}

\begin{align*}
\text{δ ppm} & : 1.74, 2.02, 2.35, 2.37, 2.54, 3.13, 3.15, 3.27, 3.39, 3.50, 3.62, 3.64, 3.81, 3.83, 3.95, 4.12, 4.14, 4.25, 4.27, 4.38, 4.40, 4.51, 4.53, 4.64, 4.66, 4.77, 4.79, 4.90, 4.92, 5.03, 5.05, 5.16, 5.18, 5.29, 5.31, 5.42, 5.44, 5.55, 5.57, 5.68, 5.70, 5.81, 5.83, 5.94, 5.96, 6.07, 6.09, 6.20, 6.22, 6.33, 6.35, 6.46, 6.48, 6.59, 6.61, 6.72, 6.74, 6.85, 6.87, 6.98, 6.99, 7.07, 7.09, 7.14, 7.16, 7.23, 7.25, 7.32, 7.34, 7.41, 7.43, 7.50, 7.52, 7.59, 7.61, 7.68, 7.70, 7.77, 7.79, 7.86, 7.88, 7.95, 7.97, 8.04, 8.06, 8.13, 8.15, 8.22, 8.24, 8.31, 8.33, 8.40, 8.42, 8.49, 8.51, 8.58, 8.60, 8.67, 8.69, 8.76, 8.78, 8.85, 8.87, 8.94, 8.96, 9.03, 9.05, 9.12, 9.14, 9.21, 9.23, 9.30, 9.32, 9.39, 9.41, 9.48, 9.50, 9.57, 9.59, 9.69, 9.71, 9.79, 9.81, 9.88, 9.89, 9.96, 9.98, 10.05, 10.07, 10.14, 10.16.
\end{align*}
Lactam 9ha

\[
\text{Chemical structure of Lactam 9ha}
\]
Lactam 9dd
Lactam 9fd
Alcohol S9a
Alcohol S9c
Carbamate 36db[21]
Carbamate \textbf{36db}[18]
Carbamate 36bb\(^{[16]}\)
Carbamate 36db[12]
Carbamate 34a(6)
Carbamate 34d[17]
Carbamate 36bb{15}
Carbamate 36bb (5)
Carbamate 36bb[22]
Carbamate 36ab(2)
Carbamate 36ab (31)
Sparteine-inspired series
15a
15b
16c
40[2]
43a(3)
43b[9]
43c(4)
Mesembrine-inspired series:
Hydroxyketone S15
Enone S16a
Enone S16b
Enone S16c
Enone S16d

\[
\begin{align*}
\text{OPMB} & \quad \text{OMe} \\
\end{align*}
\]
Silyloxydiene 22a
Silyloxydiene 22b
Silyloxydiene 22c
Silyloxydiene 22d
Hydroxy enone S17a
Hydroxy enone S17b
Hydroxy enone S17c
Hydroxy enone S17d
Azidoketone S18a
Azidoketone S18b
Azidoketone S18c
Azidoketone S18d
Silyl enol ether 23a
Silyl enol ether 23d
Silyl enol ether 23c
Silyl enol ether 23b
Tetrahydroisochromenone 24a
Tetrahydroisochromenone 24d
Tetrahydroisochromenone 24c
Tetrahydroisochromenone 24b
Amide 18a
Amide 18d
Amide 18c
Amide 18b
Quinoline 45[2]
Quinoline 45[11]

[Chemical structure image]
Quinoline 45[12]
Quinoline 45[10]
Amine 44a(3)
Amine 44b\(^3\)
Amine 44b[11]
Amine 44b[9]
Amine 44a(6)
Amine 44a(8)
Amine 44b\[15\]
Amine 44a{14}
Amine 44a{16}
Amine 44a\{11\}
Amine 44b{19}
Amine 44b{21}
Amine 44a[23]
VI. Supplementary Note: X-ray crystallography data.

Structure of 3b (Deposition number: CCDC 945414):

Structure of 3c (Deposition number: CCDC 945415):

Structure of 3d (Deposition number: CCDC 945419):
Structure of **S3b** (Deposition number: CCDC 945416):

Structure of **S3c** (Deposition number: CCDC 945417):

Structure of **S3d** (Deposition number: CCDC 945421):
Structure of **29d** (Deposition number: CCDC 945418):

Structure of **29c** (Deposition number: CCDC 945420):

Structure of **S6** (Deposition number: CCDC 945413):
Structure of **S14** (Deposition number: CCDC 946099):

![Structure of S14](image1)

Structure of **42{13}** (Deposition number: CCDC 946100):

![Structure of 42{13}](image2)

Structure of **43b{23}** (Deposition number: CCDC 946101):

![Structure of 43b{23}](image3)
Level A & B alerts encountered during IUCR’s CheckCIF routine:

| Compound name | CCDC reference | A/B level alerts |
|---------------|----------------|------------------|
| 3b            | 945414         | PLAT029_ALERT_3_B_diffrn_measured_fraction_theta_full_Low ....... 0.952 |
| 3c            | 945415         | PLAT222_ALERT_3_B Large Non-Solvent H Uiso(max)/Uiso(min) .. 8.6 Ratio |
| 3d            | 945419         | PLAT029_ALERT_3_B_diffrn_measured_fraction_theta_full_Low ....... 0.952 |
| S3b           | 945416         | None |
| S3c           | 945417         | PLAT089_ALERT_3_B Poor Data / Parameter Ratio (Zmax < 18) ..... 5.13 |
| S3d           | 945421         | PLAT029_ALERT_3_B_diffrn_measured_fraction_theta_full_Low ....... 0.950 |
|               |                | PLAT031_ALERT_4_B Refined Extinction Parameter within Range ..... 1.000 Sigma |
| S6            | 945413         | PLAT410_ALERT_2_B Short Intra H...H Contact H9B .. H11D .. 1.89 Ang. |
|               |                | PLAT431_ALERT_2_B Short Inter HL..A Contact Br .. O3 . 3.06 Ang. |
| 29d[2]        | 945418         | PLAT029_ALERT_3_B_diffrn_measured_fraction_theta_full_Low ....... 0.953 |
| 29c[8]        | 945420         | None |
| S14           | 946099         | PLAT431_ALERT_2_B Short Inter HL..A Contact Br .. O1 . 3.03 Ang. |
| 42[13]        | 946100         | None |
| 43b[23]       | 946101         | None |

Justification for alerts:

- The checkCIF B-alerts for the crystal structures reported in this manuscript are principally due to the fact that Cu radiation, instead of the more traditional Mo radiation, was used to collect the diffraction data or that hydrogen atom parameters were actually refined instead of being fixed at idealized values. Most of the crystals (10 of 12) used in the present studies were too small to use with the in-house instrument that uses a Mo sealed-tube x-ray source. Since it is physically difficult to get close to full coverage at high diffraction angles with Cu radiation on a CCD diffractometer, four of the twelve structures (Compounds 3b, 3d, S3d and 29d[2]; CCDC reference numbers 945414, 945419, 945421, and 945418) have PLAT029_ALERT_3_B_diffrn_measured_fraction_theta_full_Low alerts because their coverage was between 95% and 96% at a resolution of 0.844 Å. The alert B “threshold” value is 96% at this resolution.

- The PLAT222_ALERT_3_BLarge Non-Solvent H Uiso(max)/Uiso(min) alert for Compound 3c (CCDC reference # 945415) is due to the fact that hydrogen atom thermal parameters were actually refined instead of being fixed at a multiplier of the nonhydrogen atom to which it is covalently bonded. The ability to actually refine hydrogen atom parameters to reasonable values is an indication of high quality data. Some of the hydrogen isotropic thermal parameters refined to low (but positive) values.
The PLAT089_ALERT_3_B Poor Data/Parameter Ratio alert for compound \textit{S3c} (CCDC reference # 945417) is due to the facts that Cu radiation was used, hydrogen atom parameters were actually refined instead of being fixed at idealized values and the crystal utilized a noncentrosymmetric space group.

The PLAT431_ALERT_2B Short Inter HL..A Contact Br..O alerts for Compounds \textit{S6} and \textit{S14} (CCDC Reference Nos. 945413 and 946099) are due to checkCIF’s choice of van der Waals radii for Br and O. A contact of 3.03- 3.06 Å is not unreasonable.

The PLATT410_ALERT_2_B Short Intra H...H Contact for Compound \textit{S6} (CCDC Reference # 945413) alert is caused by disorder.

The PLAT031_ALERT_4_B Refined Extinction Parameter with Range...1.000 Sigma for compound \textit{S3d} (CCDC Reference 945421) just informs you that the s.u. of the extinction parameter is the nearly the same as its value.
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