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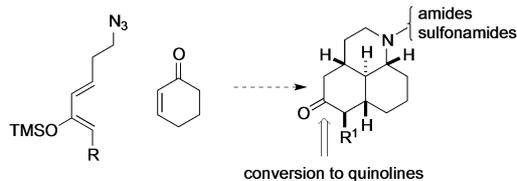
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Efficient access to sp^3 -rich tricyclic amine scaffolds through Diels-Alder reactions of azide-containing silyloxydienes

Michael C. McLeod and Jeffrey Aubé*

Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66047



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Efficient access to sp^3 -rich tricyclic amine scaffolds through Diels-Alder reactions of azide-containing silyloxydienes

Michael C. McLeod and Jeffrey Aubé^{‡}*

The University of Kansas Center of Excellence in Chemical Methodologies and Library Development (KU-CMLD), 2034 Becker Drive, Del Shankel Structural Biology Center, Lawrence, Kansas 66047, United States.

[‡]Current address: UNC Eshelman School of Pharmacy, 125 Mason Farm Road, CB 7363, University of North Carolina, Chapel Hill, NC, 27599-7363

KEYWORDS: Parallel synthesis; Diels-Alder cycloaddition; polycyclic heterocycles

ABSTRACT: The preparation of sp^3 -rich scaffolds to obtain more natural product-like libraries for incorporation into screening decks is challenging. Here, we describe the use of a Diels-Alder reaction between an enone and an azide-containing silyloxydiene to gain efficient access to complex tricyclic amine scaffolds. Derivatization of these scaffolds provided a library of 80 amines, amides, sulfonamides, quinolines and indolenines, all in >20 mg quantities and >90% purities. These library compounds displayed properties more similar to alkaloid natural products

than to drugs and commercial drug-like libraries, as shown by a high proportion of sp^3 carbon centers.

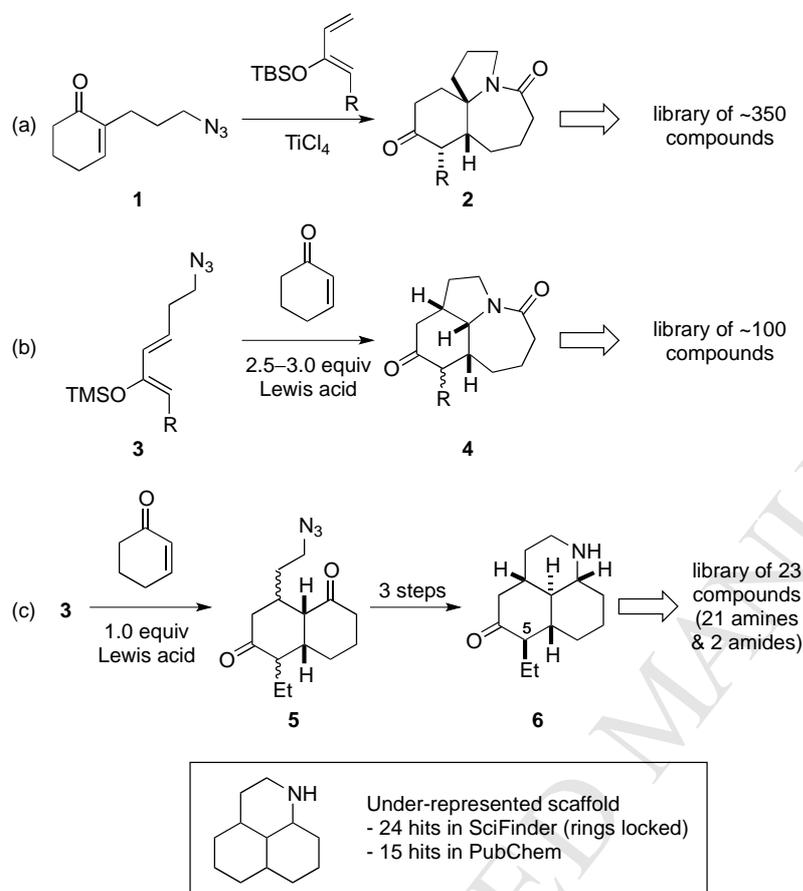
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1. Introduction

A growing movement in the drug discovery community has been the introduction of compounds with greater sp^3 character into screening collections.¹ Such compounds exhibit higher structural complexity than more planar analogs, thereby making them more akin to natural products and better able to probe different regions of chemical space.² As natural products are extensively employed as drugs, the creation of more drug-like libraries has been proposed to increase the likelihood of finding biological hits.³ In order to create such sp^3 -rich collections of molecules, methodology needs to be developed to allow the efficient synthesis of these relatively complex scaffolds. Common approaches to this challenge includes the use of natural products themselves as starting points for diversification,⁴ through diverted total synthesis where advanced intermediates in the synthesis of natural products are repurposed to create analogs of the target molecule,⁵ and by diversity orientated synthesis.⁶ We have recently described an approach to diverse scaffolds that contain similar structural features to biologically active alkaloid natural products.⁷

During this work, we developed a number of enabling technologies to allow access to these complex scaffolds, including a Diels–Alder/Schmidt domino reaction. This combines the most prevalent method for carbocycle formation with a useful method of nitrogen insertion and ring expansion, and allows efficient access to polycyclic amides and lactams.⁸ This methodology permitted the efficient construction of 5,6,7-tricyclic lactam scaffolds **2** through a Lewis acid-promoted Diels–Alder/Schmidt reaction of azidoneone **1** with a number of silyoxydienes (Scheme 1a).^{7b} By simply tethering the azide to the diene rather than the dienophile, the structurally similar, but 3-dimensionally rather different, lactams **4** were obtained (Scheme 1b).^{7a,9} In the latter Diels–Alder/Schmidt reaction, an excess (2.5 to 3 equiv) of Lewis acid is

required for the lactam formation. However, by reducing the Lewis acid loading to 1 equiv, the domino reaction can be interrupted so that the Diels–Alder cycloaddition step occurs without subsequent alkyl azide Schmidt reaction (Scheme 1c). This was previously employed to synthesize a small (23 member) library of amines and amides, the biological testing of which identified a number of compounds as potent and selective Sigma-1 inhibitors ($K_i \geq 2$ nM).^{7a} This promising biological data, as well as the under-representation of this scaffold in the literature prompted us to revisit this chemistry with the goal of creating a ca. 100 member library containing greater structural diversity. In particular, we wanted to obtain scaffolds with different substituents at C-5, and to prepare library compounds containing functional groups other than amines and amides.

Scheme 1. Routes to tricyclic N-containing scaffolds

2. Results and Discussion

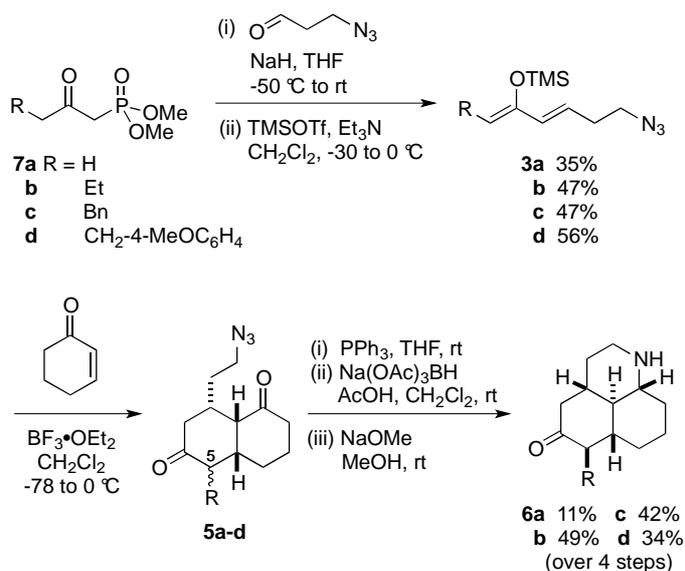
2.1 Scaffold preparation

Our synthetic route to tricyclic amine scaffolds **6a-d** is outlined in Scheme 2, and represents an improved protocol over the previously reported synthesis of **6b** (R = Et).^{7a}

Horner–Wadsworth–Emmons reaction of β -ketophosphonates **7a-d** with 3-azidopropanal and treatment of the resulting enone with TMSOTf and Et₃N afforded silyloxydienes **3a-d**. The key Diels–Alder reaction of cyclohexenone with **3a-d** was then carried out using 1 equiv of BF₃•OEt₂ in the presence of flame-dried molecular sieves to afford the cycloadducts **5a-d** as a

mixture of diastereoisomers. The C-5 chiral center can be epimerized in later transformations, and so this diastereomeric mixture was directly subjected to an aza-Wittig reaction with triphenylphosphine. Reductive amination of the resulting primary amine forms the desired tricyclic scaffold, again as a mixture of diastereoisomers. Under the acid conditions employed, tautomerization of the imine intermediate to its enamine form results in inversion of the C-8a center. Finally, epimerization of the C-5 stereocenter with NaOMe followed by purification by silica gel chromatography allowed the isolation of diastereomerically pure (>9:1 dr) amines **6b-d** in multigram (up to 5.0 g) quantities. Compared to the previous route, this method is advantageous as the difficult separation of isomeric azides **5** is avoided, and epimerization of the C-5 center is carried out prior to scaffold diversification. This chemistry can also be used to install alternative R groups at C-5. The sequence where R = H was not as synthetically useful due to consistently low-yielding steps (mainly caused by difficulties in purification/instability to silica gel), nonetheless 800 mg of **6a** could be obtained along with a diastereoisomer (see Supporting Information).

Scheme 2. Preparation of scaffolds



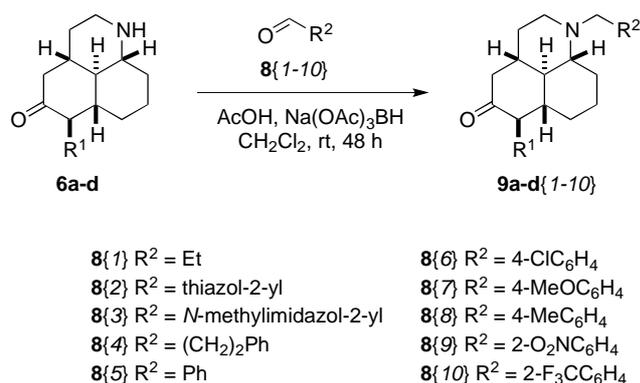
2.2 Library synthesis

During our first foray into tricyclic amine scaffolds **6**, we found that only compounds containing a basic amine displayed significant activity against the Sigma receptors, corresponding amides being inactive at these targets. We therefore wished to add further amines to our screening deck to probe the effect of changing the amine substituent and the R¹ group on the biological activity (Scheme 3). However, we were also interested in the activity of these scaffolds against other biological targets, and so the secondary amine of **6** was also decorated with different functional groups to provide libraries of amides and sulfonamides, thereby expanding the volume of chemical space covered by this collection. We also wanted to incorporate aromatic heterocycles into these scaffolds as not only are such moieties extensively employed in drug molecules,¹⁰ but quinolines derived from related tricyclic scaffolds have been shown to be active at the Sigma-2 receptor.^{7a}

A library of tertiary amines was prepared by reductive amination with scaffolds **6b-d** with ten aldehydes **8** to afford 25 amines **9b-d** (Scheme 3). Of these library members, 20 passed our

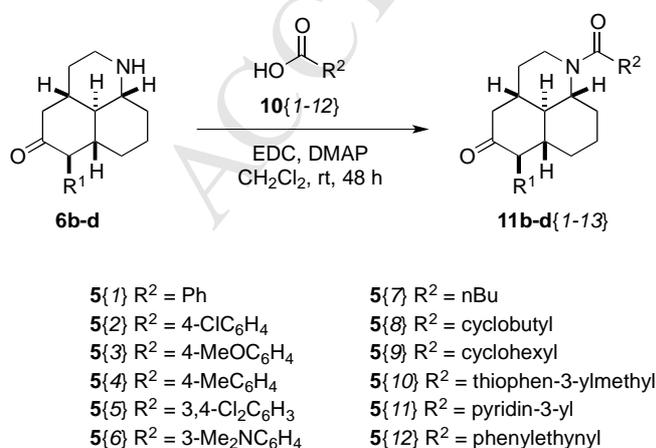
quality hurdles (>20 mg quantities, >90% purity) after mass-directed purification. Scaffold **6a**, along with its diastereoisomer (see Supporting Information) was reacted with propionaldehyde to afford two more amines.

Scheme 3. Synthesis of tertiary amine libraries



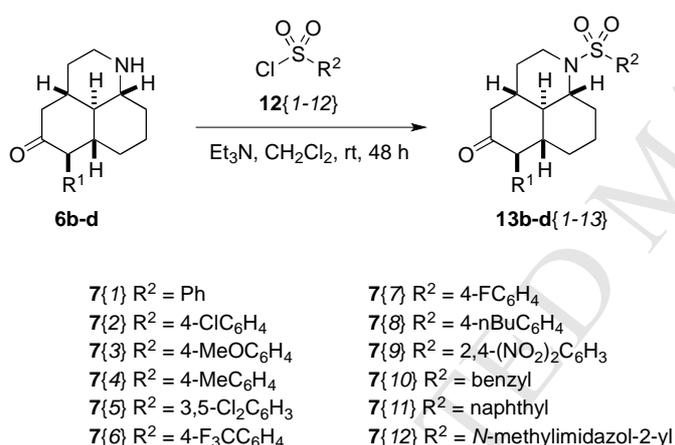
A library of amides was prepared by an EDC-promoted coupling of scaffolds **6b-d** with 12 carboxylic acids (Scheme 4). We were able to employ acyclic and cyclic aliphatic, and aromatic acids in this reaction, to afford 28 new compounds (25 of which passed our quality controls after mass-directed purification).

Scheme 4. Synthesis of amide libraries



Reaction of scaffolds **6b-d** with various sulfonyl chlorides afforded a library of 28 aromatic and heteroaromatic sulfonamides, of which 22 were isolated in >20 mg quantities and >90% purities after mass-directed purification (Scheme 5). We also attempted to incorporate aliphatic sulfonamides into our library by treatment with methylsulfonyl chloride, however this reaction proved unsuccessful, with no desired product isolated. Although we did not carefully examine this, it is possible that mesyl chloride underwent base-mediated elimination before it could react with the relatively hindered amine partner.

Scheme 5. Synthesis of sulfonamide libraries



To prepare compounds containing an indole or quinoline moiety, the synthesis of library member **4b**{2} was scaled up to provide 3 g of this tertiary amine. Fisher indole synthesis of **4b**{2} with aryl hydrazines and *para*-toluenesulfonic acid (PTSA) afforded a library of six indolenines **15** as single diastereoisomers (5/6 in >20 mg and >90% purity, Scheme 6), the relative stereochemistry of which was assigned by consideration of the electrocyclization transition state (Figure 1). A small library of 6 quinolines **17** was also prepared using a one-pot modified Friedländer quinoline synthesis protocol.¹¹ Each 2-nitrobenzaldehyde **16** was reduced *in situ* with Fe⁰

powder before addition of ketone scaffold **4b**{2} and KOH to provide quinolines **17**, all in >20 mg quantities and >90% purities after mass-directed purification.

Scheme 6. Synthesis of indolenine and quinoline libraries

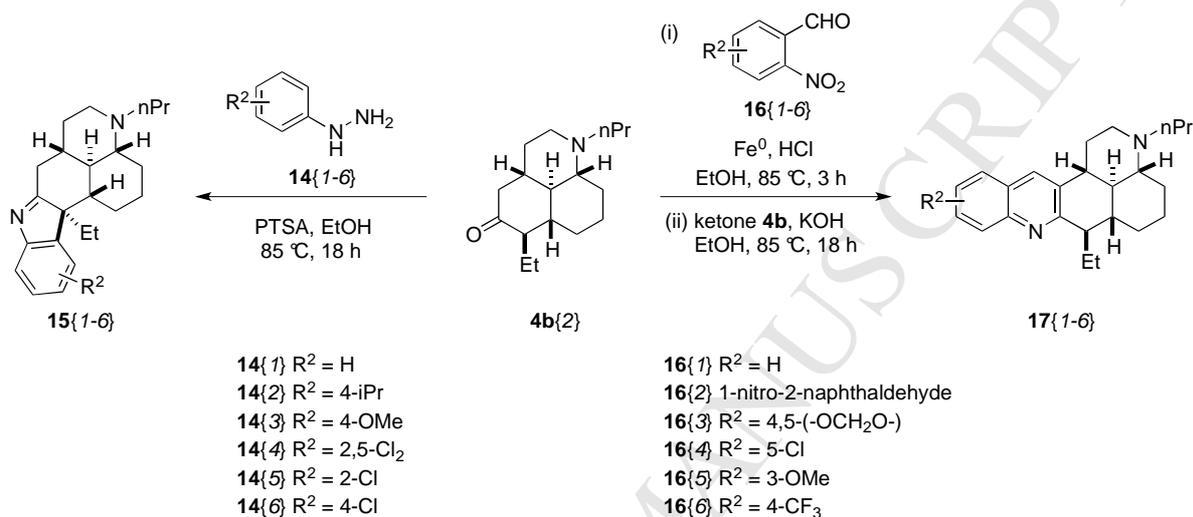
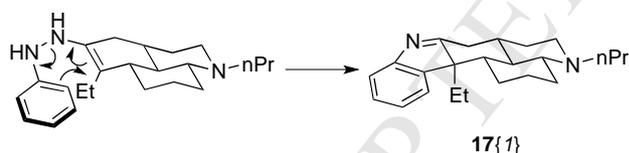


Figure 1. Proposed transition state of electrocyclicization leading to indolenine **17**{1}



2.3 Cheminformatic analysis

In total, 95 library members were prepared, of which 80 (84%) were isolated in >20 mg quantities and >90% purities. As the compounds are to be included in screening decks, it was desirable to gain an insight as to their expected bioavailability properties. To this effect, the molecular weight (m/w), XlogP, number hydrogen bond donors (HBD) and acceptors (HBA), number of rotatable bonds (rotB) and topological polar surface area (tPSA) were calculated

(mean values shown Table 1; see Supporting Information for details). For comparison, the equivalent properties for a set of drugs, natural products (NPs), alkaloid natural products and commercial drug-like libraries are also displayed in Table 1.^{7b,12} The scaffolds and library compounds were all found to be Veber-compliant, while 59% of library members and 100% of scaffolds met all four of Lipinski's rules. Non-compliance of Lipinski's rules for the library compounds was predominantly caused by high XlogP values (average 4.5), presumably arising from the extensive use of aromatic rings used to decorate the scaffolds; the average XlogP of the scaffolds themselves was considerably lower (average 2.5). The XlogP aside, our library compounds were more similar to alkaloid natural products than to the other classes of molecules. In particular they were more rigid and possessed a smaller polar surface area (RotB 4.2, tPSA 43.0) than drugs (6.3, 68.9), and were more akin to alkaloids (2.8, 53.7).

The average degree of carbon atom saturation (fraction sp³ (Fsp³))^{1a} for the scaffolds and library compounds was found to be 0.78 and 0.60 respectively. These values are similar to the reference set of natural products (0.64) and alkaloids (0.65) and considerably higher than those of drugs (0.41) and commercial drug-like libraries (0.23).

Table 1. Bioavailability properties and Fsp³ analysis

	Drugs	NPs	Commercial	Alkaloid NPs	Scaffolds	Library Cmpds
m/w	361	629	414	319	253	396
XlogP	2.7	1.5	2.4	2.0	2.5	4.5
HBD	1.5	4.9	1.5	1.3	1.0	0.0
HBA	5.4	10.8	6.8	4.4	2.3	3.1
% Pass Lipinski (4/4)	85	42	95	90	100	59
% Pass Lipinski (3/4)	98	53	100	100	100	100
RotB	6.3	9.7	5.7	2.8	1.5	4.2
tPSA	68.9	183.2	98.3	53.7	31.4	43.0
% Pass Veber (2/2)	88	33	95	95	100	99

F_{sp}^3		0.41	0.64	0.23	0.65	0.78	0.60
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3. Conclusion

We have prepared a library of 95 previously unreported compounds from four tricyclic amine scaffolds, of which 80 were obtained in useful quantities (>20 mg) and purities (>90%) for incorporation into multiple screening decks. The chemical properties of these compounds were found to be more similar to natural products, in particular alkaloid natural products, than to drugs and commercial drug-like libraries, due to their relatively small polar surface area, rigid structure and high proportion of sp^3 carbon centers. One global lesson from our studies and those of similarly minded laboratories^{4a,13} is that complex-looking molecules, prepared by total synthesis, need not be considered beyond the reach of chemists in studying the biological properties of such molecules. Conversely, we are convinced that the continuing need for precisely targeted compounds represents an important contemporary motivation for continued advances in synthetic methodology.

These compounds will be screened against the Sigma 1 and 2 receptors and/or deposited with the NIH MLSMR (molecular libraries small molecule repository), and their biological activities will be reported in due course.

4. Experimental Section

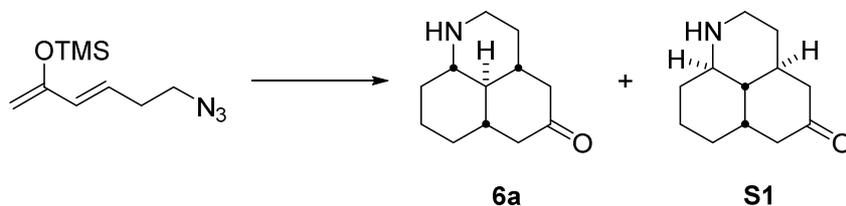
4.1 General experimental

Unless stated, all solvents and reagents were used as supplied from commercial sources. Dichloromethane and tetrahydrofuran were dried by being passed through two packed columns of neutral ammonia using a commercial solvent purification system prior to use. Parallel library syntheses were performed on a Bohdan Miniblock XT parallel solution phase synthesiser

obtained from Mettler-Toledo Auto Chem. Parallel evaporation was performed on a GeneVac EZ-2 plus evaporation system. Purification of the libraries was performed by mass-directed preparative HPLC: the HPLC analysis was carried out using a Waters Acquity system with UV and mass detection with a linear gradient of 5% acetonitrile in pH 9.8 buffered aqueous NH_4HCO_2 to 100% MeCN at a flow rate of 0.6 mL/min. Preparative reverse-phase purification was carried out using a Waters 2767 preparative system with UV detection (Waters 2996 PAD) and mass detection (Waters Micromass ZQ) with a Waters X-Bridge C18 column (19 x 150 mm, with 19 x 10 mm guard column) eluting with a water (or pH 9.8 aqueous NH_4OH)/ acetonitrile gradient with a flow rate of 20 mL/min, and sample dilution in DMSO. Flash chromatography was performed using Sorbent Technologies standard grade silica gel (40-63 μm particle size, 230 Å 400 mesh). Automated column chromatography was performed on a Teledyne CombiFlashRf system with pre-packed RediSepRf columns for normal phase, and RediSepRf C18 high performance Gold columns for reverse phase separations. Infrared spectra were acquired on a PerkinElmer Spectrum 100 FT-IR spectrophotometer. NMR spectra were recorded at the frequencies stated using a Bruker AM 400 or Bruker 500 MHz AVIII with ^{13}C -observe cryogenically-cooled probe spectrometer. Chemical shifts were referenced to δ 7.26 and 77.0 ppm from chloroform for ^1H and ^{13}C respectively. The multiplicities of ^1H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. All ^{13}C NMR spectra were acquired using broadband decoupled mode and assignments were determined using DEPT sequences. Mass spectra were obtained by electrospray ionization in positive ion mode.

4.2 Experimental procedures for scaffold synthesis

4.2.1 Amine scaffolds **6a** and **S1**

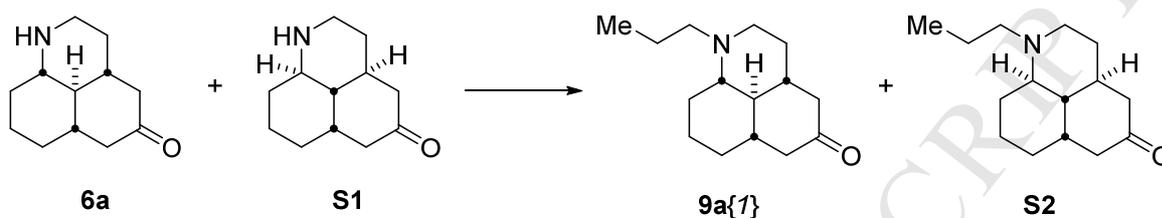


$\text{BF}_3 \cdot \text{OEt}_2$ (4.60 mL, 37.1 mmol) was added to a solution of cyclohexenone (3.60 mL, 37.1 mmol) in anhydrous CH_2Cl_2 (300 mL) with 4Å MS (~8.5 g) at -78°C under argon. The mixture was stirred at -78°C for 5 min, then a solution of silyloxydiene **3a**⁹ (11.8 g, 55.6 mmol) in CH_2Cl_2 (50 mL) was added over 10 min. The reaction was allowed to warm from -78°C to rt and stirred for 18 h. The reaction was quenched with H_2O (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown oil. The crude product was purified by automated chromatography (2 x 40 g silica columns, 0 to 10% MeOH in CH_2Cl_2 over 20 min). All of the fractions containing the correct mass were combined to afford an orange oil (4.00 g).

The diastereomeric mixture of above azides was dissolved in anhydrous THF (200 mL) and PPh_3 (8.90 g, 34.0 mmol) added. The reaction mixture was stirred at rt for 18 h, then 2M NaOH (50 mL) added and the mixture extracted with EtOAc (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown oil. The residue was dissolved in CH_2Cl_2 (200 mL) and acetic acid (970 μL , 17.0 mmol) added, followed by sodium triacetoxyborohydride (7.20 g, 34.0 mmol). The reaction was stirred at rt for 18 h, then quenched with 2M NaOH (50 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown solid. The crude product was purified by

chromatography (silica gel, 90:9:1 CH₂Cl₂:MeOH:NH₄OH) to afford the title compound (800 mg, 7% from diene **3a**, inseparable mixture of diastereoisomers) as a brown oil.

4.2.2 Amines **9a{1}** and **S2**



Propionaldehyde (450 μ L, 6.21 mmol) was added to a solution of the diastereomeric mixture of amines **6a** and **S1** (800 mg, 4.14 mmol) in anhydrous CH₂Cl₂ (30 mL) at rt under argon. Acetic acid (240 μ L, 4.14 mmol) was then added, followed by sodium triacetoxyborohydride (1.75 g, 8.28 mmol). The reaction mixture was stirred at rt for 18 h, then quenched with 2 M NaOH (10 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a brown oil (850 mg). The crude product was purified by automated reverse-phase chromatography (50 g C18 column, 10% MeCN in basic H₂O to 100% over 20 min), to afford **9a{1}** (286 mg, 29%) and **S2** (152 mg, 16%) as pale yellow solids. **9a{1}**: IR 2926, 1711 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 2.95 – 2.90 (m, 1H), 2.66 – 2.58 (m, 1H), 2.45 – 2.38 (m, 1H), 2.33 – 2.24 (m, 3H), 2.12 – 2.00 (m, 3H), 1.88 – 1.77 (m, 2H), 1.65 – 1.59 (m, 2H), 1.51 – 1.26 (m, 6H), 1.18 – 1.04 (m, 3H), 0.82 (t, $J = 7.4$ Hz, 3H); δ_{C} (125 MHz, CDCl₃) 210.2 (C), 63.8 (CH), 55.1 (CH₂), 52.6 (CH₂), 50.5 (CH), 48.5 (CH₂), 48.4 (CH₂), 41.01 (CH), 40.99 (CH), 33.8 (CH₂), 33.3 (CH₂), 30.0 (CH₂), 24.5 (CH₂), 17.5 (CH₂), 12.0 (CH₃); m/z (ESI⁺) found [M+H]⁺ 236.2001. C₁₅H₂₆NO⁺ requires 236.2009. **S2**: IR 2926, 1710 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 2.96 – 2.90 (m, 1H), 2.60 – 2.53 (m, 2H), 2.49 – 2.37 (m, 2H), 2.28 – 2.21 (m, 2H), 2.19 – 1.99 (m, 5H), 1.75 – 1.62 (m, 2H), 1.62 – 1.50 (m, 2H),

1.48 – 1.24 (m, 5H), 1.14 (ddd, $J = 16.5, 12.5, 4.0$ Hz, 1H), 0.85 (t, $J = 7.4$ Hz, 3H); δ_C (125 MHz, $CDCl_3$) 211.5 (C), 59.2 (CH), 54.4 (CH_2), 53.1 (CH_2), 48.6 (CH_2), 47.6 (CH_2), 45.1 (CH), 39.1 (CH), 34.9 (CH_2), 32.6 (CH), 29.7 (CH_2), 28.1 (CH_2), 19.8 (CH_2), 17.1 (CH_2), 12.0 (CH_3); m/z (ESI+) found $[M+H]^+$ 236.1999. $C_{15}H_{26}NO^+$ requires 236.2009.

4.2.3 Amine scaffold **6c**

$BF_3 \cdot OEt_2$ (5.20 mL, 42.4 mmol) was added to a solution of cyclohexenone (4.10 mL, 42.4 mmol) in anhydrous CH_2Cl_2 (350 mL) with 4Å MS (~20 g) at -78 °C under argon. The mixture was stirred at -78 °C for 5 min, then a solution of silyloxydiene **3c**⁹ (17.9 g, 59.4 mmol) in CH_2Cl_2 (50 mL) was added over 10 min. The reaction was allowed to warm from -78 °C to rt and stirred for 18 h. The reaction was quenched with H_2O (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown oil (19.5 g). The crude product was purified by automated chromatography (40 g silica column, 0 to 10% MeOH in CH_2Cl_2 over 20 min). All of the fractions containing the correct mass were combined to afford an orange oil (6.60 g).

The diastereomeric mixture of above azides was dissolved in anhydrous THF (400 mL) and PPh_3 (10.6 g, 40.6 mmol) added. The reaction mixture was stirred at rt for 18 h, then 2M NaOH (60 mL) added and the mixture extracted with EtOAc (3 x 200 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown oil. The residue was dissolved in CH_2Cl_2 (350 mL) and acetic acid (1.20 mL, 20.3 mmol) added, followed by sodium triacetoxyborohydride (8.60 g, 40.6 mmol). The reaction was stirred at rt for 18 h, then quenched with 2M NaOH (70 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown oil. The crude product was purified by

chromatography (silica gel, 90:9:1 CH₂Cl₂:MeOH:NH₄OH) to afford the title compound (3.30 g, 20% from diene **3c**, mixture of diastereoisomers) as a brown oil.

The diastereomeric mixture was dissolved in MeOH (150 mL) and K₂CO₃ (7.20 g, 52.4 mmol) added. The reaction was stirred at rt for 18 h, then concentrated to a brown oil, which was dissolved in CH₂Cl₂ (100 mL) and H₂O (30 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 100 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford the title compound (2.44 g, 74%, >9:1 dr) as a yellow solid foam. δ_{H} (500 MHz, CDCl₃) 7.26 – 7.12 (m, 5H), 3.11 – 3.05 (m, 2H), 2.79 (dd, $J = 14.5, 2.6$ Hz, 1H), 2.72 (ddd, $J = 12.2, 12.2, 2.7$ Hz, 1H), 2.43 (ddd, $J = 10.8, 8.1, 1.9$ Hz, 1H), 2.37 (dd, $J = 12.8, 3.8$ Hz, 1H), 2.31 – 2.22 (m, 1H), 2.18 – 2.12 (m, 2H), 1.89 – 1.83 (m, 2H), 1.81 – 1.76 (m, 1H), 1.66 (ddd, $J = 12.9, 5.9, 2.5$ Hz, 1H), 1.58 – 1.49 (m, 1H), 1.42 – 1.23 (m, 4H), 1.19 – 1.05 (m, 2H); δ_{C} (125 MHz, CDCl₃) 209.9 (C), 141.5 (C), 129.3 (CH), 128.2 (CH), 125.7 (CH), 59.9 (CH), 58.0 (CH), 52.3 (CH), 48.9 (CH₂), 46.2 (CH₂), 46.0 (CH), 41.5 (CH), 34.3 (CH₂), 33.2 (CH₂), 31.9 (CH₂), 31.2 (CH₂), 24.3 (CH₂); m/z (ESI+) found [M+H]⁺ 284.1991. C₁₉H₂₆NO⁺ requires 284.2009.

4.2.4 Dimethyl (4-(4-methoxyphenyl)-2-oxobutyl)phosphonate **7d**

n-Butyllithium (2.5 M in hexanes, 22.0 mL, 55.1 mmol) was added slowly to a solution of dimethyl methylphosphonate (6.00 mL, 55.1 mmol) in anhydrous THF (100 mL) at –78 °C under argon. The reaction mixture was stirred at –78 °C for 1 h, then a solution methyl 3-(4-methoxyphenyl)propanoate¹⁴ (10.7 g, 55.1 mmol) in THF (50 mL) was added dropwise. The mixture was stirred at –78 °C for 5 min, then at rt for 30 min, after which the reaction was quenched with saturated aqueous NH₄Cl (100 mL) and extracted with Et₂O (3 x 100 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a pale yellow oil (15.8 g).

The crude product was purified by chromatography (silica gel, 100% EtOAc) to afford the title compound (9.00 g, 57%) as a colourless oil. IR 2956, 1712 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.23 – 7.06 (m, 2H), 6.93 – 6.76 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.09 (d, $J = 22.7$ Hz, 2H), 2.98 – 2.84 (m, 4H); δ_{C} (100 MHz, CDCl_3) 201.1 (C, d, $J = 6.1$ Hz), 158.0 (C), 132.6 (C), 129.3 (CH), 113.9 (CH), 55.3 (CH_3), 53.1 (CH_3), 53.0 (CH_3), 45.8 (CH_2), 41.5 (CH_2 , d, $J = 128$ Hz), 28.6 (CH_2); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 287.1049. $\text{C}_{13}\text{H}_{20}\text{O}_5\text{P}^+$ requires 287.1043.

4.2.5 (E)-7-Azido-1-(4-methoxyphenyl)hept-4-en-3-one **S3**

Sodium hydride (60% dispersion in oil, 1.54 g, 38.6 mmol) was added portionwise to a solution of **7d** (8.50 g, 29.7 mmol) in anhydrous THF (100 mL) at -50 °C under argon. The resulting suspension was warmed from -78 °C to 0 °C over 2.5 h, then cooled to -10 °C and a solution of 3-azidopropanal¹⁵ (3.82 g, 38.6 mmol) in THF (20 mL) was added over 5 min. The reaction mixture was stirred between 0 and -10 °C for 1 h, then at rt for 45 min. Water (50 mL) was then added and extracted with Et_2O (2 x 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to afford a brown oil (10.1 g). The crude product was purified by automated chromatography (2 x 40 g columns, 0 to 25% EtOAc in hexanes over 15 min) to afford the title compound (4.5 g, 58%) as a yellow oil. IR 2935, 2094, 1511 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.17 – 7.05 (m, 2H), 6.86 – 6.81 (m, 2H), 6.76 (dt, $J = 15.9$, 6.9 Hz, 1H), 6.19 (dt, $J = 15.9$, 1.5 Hz, 1H), 3.79 (s, 3H), 3.42 (t, $J = 6.7$ Hz, 2H), 3.04 – 2.80 (m, 4H), 2.49 (dtd, $J = 6.9$, 6.9, 1.5 Hz, 2H); δ_{C} (100 MHz, CDCl_3) 199.1 (C), 158.0 (C), 142.0 (CH), 133.1 (C), 132.3 (CH), 129.3 (CH), 113.9 (CH), 55.3 (CH_3), 49.7 (CH_2), 42.2 (CH_2), 31.8 (CH_2), 29.1 (CH_2); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 260.1421. $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}_2^+$ requires 260.1394.

4.2.6 (((2Z,4E)-7-azido-1-(4-methoxyphenyl)hepta-2,4-dien-3-yl)oxy)trimethylsilane **3d**

TMSOTf (4.65 mL, 25.7 mmol) was added dropwise to a solution of azide **S3** (4.45 g, 17.2 mmol) and Et₃N (7.18 mL, 51.5 mmol) in anhydrous CH₂Cl₂ (150 mL) at -30 °C under argon. The resulting yellow solution was stirred at -30 °C for 15 min then at 0 °C for 15 min, then quenched with sat. aq. NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a brown oil, which was dissolved in 4:1 hexanes: EtOAc and passed through a Florisil plug with 4:1 hexanes: EtOAc washings. The filtrate was concentrated to afford the title compound (5.50 g, 96%) as a yellow oil that was used immediately in the next step. δ_{H} (400 MHz, CDCl₃) 6.93 – 6.88 (m, 2H), 6.65 – 6.60 (m, 2H), 5.80 (d, $J = 15.4$ Hz, 1H), 5.55 (dt, $J = 15.0, 7.1$ Hz, 1H), 4.71 (t, $J = 7.1$ Hz, 1H), 3.58 (s, 3H), 3.20 (d, $J = 7.1$ Hz, 2H), 3.12 (t, $J = 7.1$ Hz, 2H), 2.19 (dt, $J = 7.1, 7.1$ Hz, 2H), 0.05 (s, 9H).

4.2.7 Amine scaffold **6d**

BF₃·OEt₂ (1.47 mL, 11.9 mmol) was added to a solution of cyclohexenone (1.15 mL, 11.9 mmol) in anhydrous CH₂Cl₂ (100 mL) with 4Å MS (~5 g) at -78 °C under argon. The mixture was stirred at -78 °C for 5 min, then a solution of silyloxydiene **3d** (5.50 g, 16.6 mmol) in CH₂Cl₂ (20 mL) was added over 10 min. The reaction was allowed to warm from -78 °C to rt and stirred for 18 h. The reaction was quenched with H₂O (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a brown oily solid (5.72 g). The crude product was purified by automated chromatography (40 g silica column, 0 to 10% MeOH in CH₂Cl₂ over 20 min). All of the fractions containing the correct mass were combined to afford a brown oil (4.85 g).

The diastereomeric mixture of above azides was dissolved in anhydrous THF (200 mL) and PPh₃ (7.16 g, 27.3 mmol) added. The reaction mixture was stirred at rt for 18 h, then 2M NaOH (50 mL) added and the mixture extracted with EtOAc (3 x 100 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a brown oil. The residue was dissolved in CH₂Cl₂ (200 mL) and acetic acid (780 μ L, 13.6 mmol) added, followed by sodium triacetoxyborohydride (5.79 g, 27.3 mmol). The reaction was stirred at rt for 18 h, then quenched with 2M NaOH (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a brown oil (15 g). The crude product was purified by chromatography (silica gel, 90:9:1 CH₂Cl₂:MeOH:NH₄OH) to afford the title compound (1.70 g, 46% from silyloxydiene **3d**, 4:1 dr) as a brown oil.

The diastereomeric mixture was dissolved in MeOH (50 mL) and K₂CO₃ (3.37 g, 24.4 mmol) added. The reaction was stirred at rt for 18 h, then concentrated to a brown oil, which was dissolved in CH₂Cl₂ (100 mL) and H₂O (30 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 100 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford the title compound (1.65 g, 97%, 9:1 dr) as a brown solid foam. IR 2925, 1707, 1511 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.12 – 7.07 (m, 2H), 6.81 – 6.75 (m, 2H), 3.77 (s, 3H), 3.32 (d, J = 12.4 Hz, 1H), 2.96 (dd, J = 14.3, 7.9 Hz, 1H), 2.88 – 2.78 (m, 2H), 2.65 – 2.58 (m, 1H), 2.49 – 2.39 (m, 2H), 2.25 – 2.07 (m, 3H), 1.94 – 1.87 (m, 1H), 1.80 – 1.52 (m, 5H), 1.42 – 1.26 (m, 2H), 1.24 – 1.13 (m, 1H); δ_{C} (100 MHz, CDCl₃) 208.4 (C), 157.7 (C), 132.6 (C), 130.2 (CH), 113.7 (CH), 59.0 (CH), 57.4 (CH), 55.2 (CH₃), 48.0 (CH), 47.7 (CH₂), 45.2 (CH), 43.7 (CH₂), 39.5 (CH), 30.9 (CH₂), 30.1 (CH₂), 30.1 (CH₂), 29.7 (CH₂), 23.8 (CH₂); m/z (ESI+) found [M+H]⁺ 314.2137. C₂₀H₂₈NO₂⁺ requires 314.2115.

4.2.8 Amine **9b**{1}

Propionaldehyde (1.22 mL, 16.8 mmol) was added to a solution of amine **6b** (2.48 g, 11.2 mmol) in anhydrous CH₂Cl₂ (100 mL) at rt under argon. Acetic acid (640 μL, 11.2 mmol) was then added, followed by sodium triacetoxyborohydride (4.75 g, 22.4 mmol). The reaction mixture was stirred at rt for 48 h, then quenched with 2 M NaOH (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford the title compound (2.94 g, 100%) as a yellow oil, which was used without further purification. IR 2929, 1711 cm⁻¹; δ_H (400 MHz, CDCl₃) 3.04-2.99 (1H, m), 2.74-2.66 (1H, m), 2.58-2.51 (1H, m), 2.40-2.32 (2H, m), 2.17-1.87 (6H, m), 1.70-1.41 (7H, m), 1.36-1.19 (4H, m), 1.10-1.00 (1H, m), 0.87 (3H, t, *J* 7.2), 0.85 (3H, t, *J* 7.6); δ_C (100 MHz, CDCl₃) 210.8 (C), 63.9 (CH), 56.1 (CH), 54.8 (CH₂), 52.4 (CH₂), 50.4 (CH), 48.8 (CH₂), 44.7 (CH), 41.4 (CH), 32.9 (CH₂), 31.2 (CH₂), 29.5 (CH₂), 24.6 (CH₂), 17.9 (CH₂), 17.1 (CH₂), 12.0 (CH₃), 11.2 (CH₃); *m/z* (ESI+) found [M+H]⁺ 264.2314. C₁₇H₃₀NO⁺ requires 264.2322.

4.2.9 Alcohol **S4**

L-Selectride (1 M in THF, 8.10 mL) was added dropwise to a solution of **9b**{1} (850 mg, 3.23 mmol) in anhydrous THF (20 mL) at -78 °C under argon. The reaction mixture was allowed to warm slowly to rt and stirred for 18 h, then quenched with 30% aq H₂O₂ (5.1 mL) and 2 M NaOH (6.8 mL). The mixture was stirred at rt for 1 h, then extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were dried (Na₂SO₄) and concentrated to afford a yellow oil. The crude product was purified by chromatography (silica gel, 90:9:1 CH₂Cl₂:MeOH:NH₄OH) to afford the title compound (825 mg, 96%) as a yellow oil. δ_H (500 MHz, CDCl₃) 4.03 (br s, 1H), 2.93 (ddd, *J* = 11.3, 3.8, 3.8 Hz, 1H), 2.70 – 2.56 (m, 1H), 2.55 – 2.40 (m, 1H), 2.32 (ddd, *J* =

12.0, 12.0, 2.5 Hz, 1H), 2.14 – 2.00 (m, 1H), 1.96 – 1.76 (m, 4H), 1.68 – 1.60 (m, 1H), 1.53 (ddd, $J = 12.6, 2.7, 2.7$ Hz, 1H), 1.50 – 1.40 (m, 3H), 1.41 – 0.94 (m, 7H), 0.94 – 0.87 (m, 3H), 0.84 (t, $J = 7.4$ Hz, 3H), 0.81 – 0.71 (m, 2H); δ_C (125 MHz, $CDCl_3$) 66.5 (CH), 63.5 (CH), 55.3 (CH₂), 52.7 (CH₂), 51.4 (CH), 47.6 (CH), 40.3 (CH₂), 38.6 (CH), 33.3 (CH), 32.8 (CH₂), 29.9 (CH₂), 29.8 (CH₂), 24.5 (CH₂), 21.4 (CH₂), 17.1 (CH₂), 12.0 (CH₃), 11.7 (CH₃); m/z (ESI+) found $[M+H]^+$ 266.2480. $C_{17}H_{32}NO^+$ requires 266.2478

4.3. Experimental procedures for library synthesis

4.3.1 General procedure for the preparation of amines.

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold **6b-d** (70 mg) in anhydrous dichloromethane (2 mL) was added, followed by the appropriate aldehyde (1.5 equiv), acetic acid (1 equiv) and $Na(OAc)_3BH$ (2 equiv). The reactions were shaken at 500 rpm at rt for 48 h, then 2 M NaOH (1 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 amines **9b-d**{1-10} in average yields of 43% (range 4–76%) and purities of 97.9% (range 94.1–100%), excluding three compounds that did not meet quantity or purity requirements (**9b**{9}, **9d**{2}, and **9d**{5}). Full data are provided in Supporting Information.

4.3.2 General procedure for the preparation of amides.

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold **6b-d** (70 mg) in anhydrous dichloromethane (2 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 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 amides **11b-d**{1-13} in average yields of 39% (range 20–57%) and purities of 97.3% (range 85.9–100%), excluding two compounds that did not meet quantity or purity requirements (**11b**{9} and **11b**{11}). Full data are provided in Supporting Information.

4.3.3 General procedure for the preparation of sulfonamides.

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold **6b-d** (70 mg) in anhydrous dichloromethane (2 mL) was added, followed by the appropriate sulfonyl chloride (1.5 equiv) and Et₃N (1.5 equiv). 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 sulfonamides **13b-d**{1-13} in average yields of 39% (range 6–63%) and purities of 98.0% (range 87.8–100%), excluding three compounds that did not meet quantity or purity requirements (**13b**{9}, **13c**{8}, and **13c**{9}). Full data are provided in Supporting Information.

4.3.4 General procedure for the preparation of 3H-indoles

PTSA (510 mg, 2.3 mmol) was added to a solution of amine scaffold **4b{2}** (60 mg, 0.23 mmol) in EtOH (1.5 mL) in a microwave vial, followed by the appropriate hydrazine (hydrochloride) (2.5 equiv). The vial was sealed then heated in an oil bath at 90 °C for 4 h, then cooled to rt, 2 M NaOH (2 mL) added and the mixture extracted with CH₂Cl₂ (3 x 5 mL). The combined organics were dried (Na₂SO₄) and concentrated under reduced pressure. The residues were subjected to mass-directed preparative HPLC purification to afford pure 3H-indoles **15{1-6}** in average yields of 40% (range 27–57%) and purities of 99.4% (range 87.8–100%), excluding compound **15{4}**, which was not obtained in sufficient purity for screening. Full data are provided in Supporting Information.

4.3.5 General procedure for the preparation of quinolines.

Fe⁰ powder (77 mg, 1.4 mmol) was added to a solution of nitrobenzaldehyde **16{1-6}** (0.35 mmol) in ethanol (1 mL) in a microwave vial, followed by 0.1 M HCl (180 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 **4b{2}** (0.27 mmol) in EtOH (2 mL) added, followed by powdered KOH (18 mg, 0.32 mmol). The mixture was heated at 85 °C for 18 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 **17{1-6}** in average yields of 42% (range 26–62%) and purities of 97.0% (range 91.7–100%). Full data are provided in Supporting Information.

4.4. Characterization for representative library examples

4.4.1 Amine **9b**{2}

δ_{H} (500 MHz, CDCl_3) 7.72 (d, $J = 3.3$ Hz, 1H), 7.26 (d, $J = 3.3$ Hz, 1H), 4.23 (d, $J = 15.8$ Hz, 1H), 3.94 (d, $J = 15.8$ Hz, 1H), 3.05 – 2.93 (m, 1H), 2.53 – 2.40 (m, 1H), 2.34 (dd, $J = 13.1$, 3.3 Hz, 1H), 2.30 – 2.20 (m, 1H), 2.20 – 2.10 (m, 1H), 2.10 – 1.99 (m, 2H), 1.99 – 1.91 (m, 1H), 1.91 – 1.82 (m, 1H), 1.70 – 1.45 (m, 5H), 1.40 – 1.14 (m, 4H), 1.05 (qd, $J = 13.0$, 3.6 Hz, 1H), 0.84 (t, $J = 7.4$ Hz, 3H); δ_{C} (125 MHz, CDCl_3) 210.7 (C), 170.7 (C), 142.4 (CH), 119.1 (CH), 64.3 (CH), 56.1 (CH), 54.3 (CH_2), 53.9 (CH_2), 50.9 (CH), 48.7 (CH_2), 44.4 (CH), 41.3 (CH), 33.2 (CH_2), 31.4 (CH_2), 30.3 (CH_2), 24.4 (CH_2), 17.9 (CH_2), 11.1 (CH_3); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 319.1847. $\text{C}_{18}\text{H}_{27}\text{N}_2\text{OS}^+$ requires 319.1839.

4.4.2 Amine **9c**{1}

δ_{H} (500 MHz, CDCl_3) 7.26 – 7.11 (m, 5H), 3.08 (dd, $J = 14.2$, 8.1 Hz, 1H), 2.97 – 2.92 (m, 1H), 2.80 (dd, $J = 14.2$, 2.6 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.52 – 2.45 (m, 1H), 2.45 – 2.38 (m, 1H), 2.38 – 2.28 (m, 2H), 2.17 – 2.10 (m, 3H), 1.92 – 1.86 (m, 2H), 1.66 – 1.61 (m, 1H), 1.52 – 1.41 (m, 4H), 1.37 – 1.07 (m, 5H), 0.85 (t, $J = 7.4$ Hz, 3H); δ_{C} (125 MHz, CDCl_3) 210.1 (C), 141.6 (C), 129.3 (CH), 128.2 (CH), 125.6 (CH), 63.8 (CH), 57.8 (CH), 55.2 (CH_2), 52.5 (CH_2), 51.2 (CH), 48.9 (CH_2), 46.5 (CH), 41.6 (CH), 33.4 (CH_2), 32.0 (CH_2), 31.2 (CH_2), 30.0 (CH_2), 24.6 (CH_2), 17.4 (CH_2), 12.0 (CH_3); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 326.2516. $\text{C}_{22}\text{H}_{32}\text{NO}^+$ requires 326.2478.

4.4.3 Amine **9c**{2}

δ_{H} (400 MHz, CDCl_3) 7.72 (d, $J = 3.3$ Hz, 1H), 7.28 – 7.12 (m, 6H), 4.23 (d, $J = 15.8$ Hz, 1H), 3.94 (d, $J = 15.4$ Hz, 1H), 3.08 (dd, $J = 14.2, 8.1$ Hz, 1H), 3.03 – 2.95 (m, 1H), 2.82 (dd, $J = 14.2, 2.6$ Hz, 1H), 2.51 – 2.40 (m, 2H), 2.37 (dd, $J = 12.9, 3.2$ Hz, 1H), 2.29 – 2.23 (m, 1H), 2.20 – 2.01 (m, 3H), 1.94 – 1.87 (m, 1H), 1.67 – 1.61 (m, 1H), 1.57 – 1.42 (m, 2H), 1.40 – 1.20 (m, 4H), 1.19 – 1.08 (m, 1H); δ_{C} (100 MHz, CDCl_3) 209.8 (C), 170.9 (C), 142.5 (CH), 141.4 (C), 129.3 (CH), 128.2 (CH), 125.7 (CH), 119.1 (CH), 64.2 (CH), 57.7 (CH), 54.4 (CH_2), 53.9 (CH_2), 51.2 (CH), 48.7 (CH_2), 46.2 (CH), 41.3 (CH), 33.3 (CH_2), 32.0 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 24.4 (CH_2); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 381.2039. $\text{C}_{23}\text{H}_{29}\text{N}_2\text{OS}^+$ requires 381.1995.

4.4.4 Amine **9d**{1}

δ_{H} (500 MHz, CDCl_3) 7.15 – 7.10 (m, 2H), 6.80 – 6.76 (m, 2H), 3.77 (s, 3H), 3.01 – 2.91 (m, 2H), 2.78 (dd, $J = 14.2, 2.5$ Hz, 1H), 2.70 – 2.61 (m, 1H), 2.54 – 2.44 (m, 1H), 2.39 – 2.27 (m, 3H), 2.17 – 2.08 (m, 3H), 1.93 – 1.85 (m, 2H), 1.67 – 1.60 (m, 1H), 1.54 – 1.38 (m, 4H), 1.36 – 1.05 (m, 5H), 0.85 (t, $J = 7.4$ Hz, 3H); δ_{C} (125 MHz, CDCl_3) 210.2 (C), 157.6 (C), 133.4 (C), 130.3 (CH), 113.5 (CH), 63.8 (CH), 57.9 (CH), 55.21 (CH_3), 55.18 (CH_2), 52.5 (CH_2), 51.1 (CH), 48.9 (CH_2), 46.2 (CH), 41.5 (CH), 33.3 (CH_2), 31.9 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 24.6 (CH_2), 17.4 (CH_2), 12.0 (CH_3); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 356.2596. $\text{C}_{23}\text{H}_{34}\text{NO}_2^+$ requires 356.2584.

4.4.5 Amine **9d**{4}

δ_{H} (500 MHz, CDCl_3) 7.32 – 7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 7.15 – 7.12 (m, 2H), 6.81 – 6.77 (m, 2H), 3.78 (s, 3H), 3.01 – 2.95 (m, 2H), 2.84 – 2.77 (m, 2H), 2.65 – 2.53 (m, 3H), 2.40 – 2.32 (m, 3H), 2.18 – 2.04 (m, 3H), 1.97 – 1.74 (m, 4H), 1.67 – 1.62 (m, 1H), 1.61 – 1.41 (m, 2H), 1.39 – 1.08 (m, 5H); δ_{C} (125 MHz, CDCl_3) 210.1 (C), 157.6 (C), 141.9 (C), 133.3 (C),

130.3 (CH), 128.4 (CH), 128.3 (CH), 125.9 (CH), 113.5 (CH), 63.9 (CH), 57.8 (CH), 55.2 (CH₃), 52.5 (CH₂), 52.4 (CH₂), 50.8 (CH), 48.7 (CH₂), 46.1 (CH), 41.3 (CH), 33.8 (CH₂), 33.0 (CH₂), 31.8 (CH₂), 30.2 (CH₂), 29.7 (CH₂), 26.0 (CH₂), 24.5 (CH₂); m/z (ESI+) found $[M+H]^+$ 432.2902. C₂₉H₃₈NO₂⁺ requires 432.2897.

4.4.6 Amine **9d**{6}

δ_H (500 MHz, CDCl₃) 7.29 – 7.23 (m, 4H), 7.15 – 7.12 (m, 2H), 6.81 – 6.77 (m, 2H), 4.09 (d, $J = 13.7$ Hz, 1H), 3.78 (s, 3H), 3.16 (d, $J = 13.5$ Hz, 1H), 2.98 (dd, $J = 14.2, 8.1$ Hz, 1H), 2.84 – 2.77 (m, 2H), 2.41 – 2.31 (m, 2H), 2.29 – 2.23 (m, 1H), 2.19 – 2.10 (m, 2H), 2.06 – 2.00 (m, 1H), 1.95 – 1.87 (m, 2H), 1.57 – 1.52 (m, 1H), 1.50 – 1.10 (m, 7H); δ_C (125 MHz, CDCl₃) 210.1 (C), 157.6 (C), 138.1 (C), 132.4 (C), 133.4 (C), 130.3 (CH), 130.2 (CH), 128.3 (CH), 113.5 (CH), 65.2 (CH), 57.9 (CH), 56.7 (CH₂), 55.2 (CH₃), 52.9 (CH₂), 51.1 (CH), 48.8 (CH₂), 46.1 (CH), 41.5 (CH), 33.0 (CH₂), 32.0 (CH₂), 30.6 (CH₂), 30.3 (CH₂), 24.5 (CH₂); m/z (ESI+) found $[M+H]^+$ 438.2191. C₂₇H₃₃ClNO₂⁺ requires 438.2194.

4.4.7 Amide **11b**{1}

δ_H (500 MHz, CDCl₃) 7.43 – 7.35 (m, 5H), 3.56 – 3.46 (m, 2H), 3.41 (ddd, $J = 13.9, 6.1, 4.1$ Hz, 1H), 2.46 (dd, $J = 13.1, 4.4$ Hz, 1H), 2.31 – 2.24 (m, 1H), 2.17 – 2.06 (m, 2H), 2.03 – 1.98 (m, 1H), 1.95 – 1.86 (m, 2H), 1.82 – 1.52 (m, 5H), 1.51 – 1.33 (m, 2H), 1.26 – 1.19 (m, 1H), 1.18 – 1.08 (m, 1H), 0.86 (t, $J = 7.4$ Hz, 3H); δ_C (125 MHz, CDCl₃) 210.0 (C), 171.7 (C), 137.2 (C), 129.6 (CH), 128.5 (CH), 126.9 (CH), 60.2 (CH), 55.9 (CH), 49.0 (CH₂), 46.4 (CH), 45.7 (CH), 43.0 (CH₂), 37.0 (CH), 32.1 (CH₂), 31.4 (CH₂), 29.7 (CH₂), 24.7 (CH₂), 17.9 (CH₂), 11.3 (CH₃); m/z (ESI+) found $[M+H]^+$ 326.2130. C₂₁H₂₈NO₂⁺ requires 326.2115.

4.4.8 Amide **11b**{4}

δ_{H} (500 MHz, CDCl_3) 7.30 (d, $J = 7.8$ Hz, 2H), 7.18 (d, $J = 7.8$ Hz, 2H), 3.54 – 3.46 (m, 2H), 3.43 (ddd, $J = 13.8, 6.1, 4.3$ Hz, 1H), 2.45 (dd, $J = 13.1, 4.4$ Hz, 1H), 2.36 (s, 3H), 2.28 – 2.23 (m, 1H), 2.17 – 2.06 (m, 2H), 2.03 – 1.97 (m, 1H), 1.94 – 1.85 (m, 2H), 1.81 – 1.51 (m, 5H), 1.50 – 1.33 (m, 2H), 1.25 – 1.18 (m, 1H), 1.17 – 1.08 (m, 1H), 0.86 (t, $J = 7.4$ Hz, 3H); δ_{C} (125 MHz, CDCl_3) 210.1 (C), 172.0 (C), 139.7 (C), 134.3 (C), 129.0 (CH), 127.0 (CH), 60.2 (CH), 55.9 (CH), 49.0 (CH_2), 46.4 (CH), 45.7 (CH), 43.3 (CH_2), 37.1 (CH), 32.2 (CH_2), 31.4 (CH_2), 29.7 (CH_2), 24.7 (CH_2), 21.4 (CH_3), 17.9 (CH_2), 11.3 (CH_3); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 340.2284. $\text{C}_{22}\text{H}_{30}\text{NO}_2^+$ requires 340.2271.

4.4.9 Amide **IIc**{8}

δ_{H} (500 MHz, CDCl_3) 7.26 – 7.12 (m, 5H), 3.56 – 3.38 (m, 2H), 3.30 – 3.16 (m, 2H), 3.05 (dd, $J = 14.2, 8.5$ Hz, 1H), 2.76 (dd, $J = 14.2, 2.6$ Hz, 1H), 2.51 – 2.44 (m, 2H), 2.38 – 2.27 (m, 2H), 2.22 – 2.07 (m, 5H), 2.06 – 1.80 (m, 4H), 1.75 – 1.64 (m, 1H), 1.61 – 1.33 (m, 4H), 1.29 – 1.13 (m, 2H); δ_{C} (125 MHz, CDCl_3) 209.3 (C), 173.8 (C), 141.2 (C), 129.2 (CH), 128.2 (CH), 125.8 (CH), 59.3 (CH), 57.3 (CH), 49.1 (CH_2), 47.4 (CH), 46.4 (CH), 37.8 (CH), 35.9 (CH), 32.3 (CH_2), 31.7 (CH_2), 31.1 (CH_2), 30.2 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 24.5 (CH_2), 18.0 (CH_2); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 366.2454. $\text{C}_{24}\text{H}_{32}\text{NO}_2^+$ requires 366.2428.

4.4.10 Amide **IIc**{10}

δ_{H} (500 MHz, CDCl_3) 7.29 – 7.27 (m, 1H), 7.25 – 7.21 (m, 2H), 7.19 – 7.12 (m, 3H), 7.05 – 7.03 (m, 1H), 6.99 (dd, $J = 4.9, 1.3$ Hz, 1H), 3.69 (s, 1H), 3.64 (br s, 1H), 3.52 – 3.45 (m, 1H), 3.30 – 3.21 (m, 1H), 3.04 (dd, $J = 14.2, 8.5$ Hz, 1H), 2.75 (dd, $J = 14.2, 2.6$ Hz, 1H), 2.49 – 2.41 (m, 2H), 2.22 – 2.15 (m, 2H), 2.08 (t, $J = 12.3$ Hz, 2H), 1.93 – 1.86 (m, 1H), 1.84 – 1.73 (m, 1H), 1.67 – 1.31 (m, 5H), 1.22 – 1.12 (m, 2H); δ_{C} (125 MHz, CDCl_3) 209.2 (C), 169.8 (C), 141.2

(C), 135.1 (C), 129.2 (CH), 128.2 (CH), 128.0 (CH), 126.0 (CH), 125.8 (CH), 121.7 (CH), 59.4 (CH), 57.1 (CH), 48.9 (CH₂), 47.4 (CH), 46.3 (CH), 39.0 (CH₂), 36.7 (CH₂), 35.7 (CH), 32.2 (CH₂), 31.2 (CH₂), 31.1 (CH₂), 30.1 (CH₂), 24.5 (CH₂); m/z (ESI+) found $[M+H]^+$ 408.2026. C₂₅H₃₀NO₂S⁺ requires 408.1992.

4.4.11 Amide **11d**{7}

δ_H (500 MHz, CDCl₃) 7.13 – 7.09 (m, 2H), 6.80 – 6.76 (m, 2H), 3.76 (s, 3H), 3.76 – 3.67 (m, 1H), 3.44 (dt, $J = 10.7, 5.5$ Hz, 1H), 3.31 – 3.21 (m, 1H), 2.96 (dd, $J = 14.2, 8.5$ Hz, 1H), 2.73 (dd, $J = 14.2, 2.5$ Hz, 1H), 2.48 (dd, $J = 12.8, 4.6$ Hz, 1H), 2.42 (ddd, $J = 11.0, 8.6, 2.0$ Hz, 1H), 2.34 – 2.16 (m, 3H), 2.15 – 2.03 (m, 3H), 1.91 – 1.85 (m, 1H), 1.75 – 1.65 (m, 1H), 1.63 – 1.55 (m, 3H), 1.54 – 1.24 (m, 6H), 1.23 – 1.13 (m, 1H), 0.92 (t, $J = 7.4$ Hz, 3H); δ_C (125 MHz, CDCl₃) 209.5 (C), 172.4 (C), 157.7 (C), 133.1 (C), 130.2 (CH), 113.6 (CH), 59.3 (CH), 57.4 (CH), 55.2 (CH₃), 49.1 (CH₂), 47.2 (CH), 46.4 (CH), 38.1 (CH₂), 35.7 (CH), 33.6 (CH₂), 32.3 (CH₂), 31.5 (CH₂), 30.4 (CH₂), 30.1 (CH₂), 27.6 (CH₂), 24.5 (CH₂), 22.6 (CH₂), 14.0 (CH₃); m/z (ESI+) found $[M+H]^+$ 398.2692. C₂₅H₃₆NO₃⁺ requires 398.2690.

4.4.12 Sulfonamide **13b**{12}

δ_H (500 MHz, CDCl₃) 7.46 (d, $J = 1.2$ Hz, 1H), 7.39 (d, $J = 1.2$ Hz, 1H), 4.15 (dt, $J = 13.1, 3.9$ Hz, 1H), 3.75 (s, 3H), 2.97 – 2.91 (m, 1H), 2.70 (ddd, $J = 11.8, 9.5, 3.8$ Hz, 1H), 2.47 – 2.42 (m, 1H), 2.33 (dd, $J = 13.4, 3.1$ Hz, 1H), 2.17 – 2.10 (m, 1H), 2.07 – 2.02 (m, 1H), 1.90 – 1.82 (m, 2H), 1.80 – 1.61 (m, 3H), 1.57 – 1.42 (m, 4H), 1.31 – 1.14 (m, 2H), 1.07 – 0.98 (m, 1H), 0.80 (t, $J = 7.4$ Hz, 3H); δ_C (125 MHz, CDCl₃) 210.0 (C), 140.9 (C), 138.8 (CH), 123.6 (CH), 63.6 (CH), 55.8 (CH), 49.8 (CH), 48.6 (CH₂), 48.5 (CH₂), 44.8 (CH), 40.9 (CH), 34.1

(CH₃), 32.8 (CH₂), 31.0 (CH₂), 30.6 (CH₂), 24.8 (CH₂), 17.8 (CH₂), 10.9 (CH₃); *m/z* (ESI+) found [M+H]⁺ 366.1856. C₁₈H₂₈N₃O₃S⁺ requires 366.1846.

4.4.13 Sulfonamide **13b**{11}

δ_{H} (500 MHz, CDCl₃) 8.38 – 8.36 (m, 1H), 7.99 – 7.95 (m, 2H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.77 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.67 – 7.60 (m, 2H), 4.35 (dt, *J* = 13.0, 3.7 Hz, 1H), 2.96 – 2.89 (m, 1H), 2.73 – 2.67 (m, 1H), 2.36 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.20 – 2.13 (m, 2H), 2.09 – 2.03 (m, 1H), 1.88 – 1.73 (m, 4H), 1.70 – 1.46 (m, 5H), 1.29 – 1.22 (m, 1H), 1.17 – 0.98 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); δ_{C} (125 MHz, CDCl₃) 209.6 (C), 138.4 (C), 134.7 (C), 132.2 (C), 129.3 (CH), 129.2 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 122.4 (CH), 63.8 (CH), 55.9 (CH), 49.8 (CH), 48.7 (CH₂), 48.5 (CH₂), 44.8 (CH), 41.2 (CH), 33.2 (CH₂), 30.7 (CH₂), 30.5 (CH₂), 24.8 (CH₂), 17.8 (CH₂), 10.9 (CH₃); *m/z* (ESI+) found [M+H]⁺ 412.1971. C₂₄H₃₀NO₃S⁺ requires 412.1941.

4.4.14 Sulfonamide **13c**{7}

δ_{H} (500 MHz, CDCl₃) 7.73 – 7.69 (m, 2H), 7.24 – 7.20 (m, 2H), 7.18 – 7.11 (m, 3H), 6.98 – 6.94 (m, 2H), 4.20 (dt, *J* = 12.9, 3.8 Hz, 1H), 3.87 (s, 3H), 3.01 (dd, *J* = 14.3, 7.9 Hz, 1H), 2.84 – 2.76 (m, 2H), 2.57 (ddd, *J* = 11.9, 9.7, 3.7 Hz, 1H), 2.45 (ddd, *J* = 10.8, 8.0, 2.3 Hz, 1H), 2.37 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.20 – 2.13 (m, 2H), 2.07 – 2.03 (m, 1H), 1.86 – 1.81 (m, 1H), 1.75 – 1.66 (m, 2H), 1.57 – 1.43 (m, 3H), 1.29 – 1.21 (m, 1H), 1.18 – 1.05 (m, 2H); δ_{C} (125 MHz, CDCl₃) 208.9 (C), 162.6 (C), 141.0 (C), 132.5 (C), 129.2 (CH), 129.1 (CH), 128.2 (CH), 125.8 (CH), 114.2 (CH), 63.4 (CH), 57.4 (CH), 55.6 (CH₃), 49.9 (CH), 48.4 (CH₂), 48.2 (CH₂), 46.4 (CH), 41.0 (CH), 32.9 (CH₂), 31.1 (CH₂), 31.1 (CH₂), 30.9 (CH₂), 24.7 (CH₂); *m/z* (ESI+) found [M+H]⁺ 454.2046. C₂₆H₃₂NO₄S⁺ requires 454.2047.

4.4.15 Sulfonamide **13c**{5}

δ_{H} (500 MHz, CDCl_3) 7.65 (d, $J = 1.8$ Hz, 2H), 7.54 (t, $J = 1.8$ Hz, 1H), 7.26 – 7.22 (m, 2H), 7.19 – 7.13 (m, 3H), 4.24 (dt, $J = 13.2, 3.6$ Hz, 1H), 3.03 (dd, $J = 14.3, 7.9$ Hz, 1H), 2.94 – 2.83 (m, 2H), 2.76 (ddd, $J = 13.0, 9.4, 3.7$ Hz, 1H), 2.48 (ddd, $J = 10.9, 7.9, 2.4$ Hz, 1H), 2.42 (dd, $J = 13.4, 2.7$ Hz, 1H), 2.25 – 2.17 (m, 1H), 2.11 – 2.05 (m, 1H), 1.98 – 1.92 (m, 1H), 1.90 – 1.75 (m, 3H), 1.65 – 1.52 (m, 3H), 1.33 – 1.25 (m, 1H), 1.21 – 1.07 (m, 2H); δ_{C} (125 MHz, CDCl_3) 208.5 (C), 144.7 (C), 140.9 (C), 136.0 (C), 132.4 (CH), 129.2 (CH), 128.2 (CH), 125.8 (CH), 125.2 (CH), 63.8 (CH), 57.3 (CH), 49.8 (CH), 48.8 (CH_2), 48.3 (CH_2), 46.3 (CH), 41.0 (CH), 33.2 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 30.4 (CH_2), 24.7 (CH_2); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 492.1176. $\text{C}_{25}\text{H}_{28}\text{Cl}_2\text{NO}_3\text{S}^+$ requires 492.1161.

4.4.16 Sulfonamide **13d**{2}

δ_{H} (500 MHz, CDCl_3) 7.74 – 7.70 (m, 2H), 7.49 – 7.46 (m, 2H), 7.11 – 7.07 (m, 2H), 6.79 – 6.75 (m, 2H), 4.23 (dt, $J = 13.0, 3.6$ Hz, 1H), 3.76 (s, 3H), 2.92 (dd, $J = 14.3, 7.8$ Hz, 1H), 2.86 – 2.79 (m, 2H), 2.67 – 2.60 (m, 1H), 2.43 – 2.36 (m, 2H), 2.20 – 2.14 (m, 1H), 2.08 – 2.02 (m, 2H), 1.88 – 1.79 (m, 1H), 1.78 – 1.69 (m, 2H), 1.59 – 1.45 (m, 3H), 1.28 – 1.20 (m, 1H), 1.18 – 1.04 (m, 2H); δ_{C} (125 MHz, CDCl_3) 208.9 (C), 157.7 (C), 139.9 (C), 138.9 (C), 132.8 (C), 130.2 (CH), 129.4 (CH), 128.4 (CH), 113.6 (CH), 63.6 (CH), 57.5 (CH), 55.2 (CH_3), 49.8 (CH), 48.5 (CH_2), 48.4 (CH_2), 46.0 (CH), 40.9 (CH), 33.0 (CH_2), 31.0 (CH_2), 30.7 (CH_2), 30.1 (CH_2), 24.7 (CH_2); m/z (ESI+) found $[\text{M}+\text{H}]^+$ 488.1643. $\text{C}_{26}\text{H}_{31}\text{ClNO}_4\text{S}^+$ requires 488.1657.

4.4.18 Indolenine **15**{1}

δ_{H} (500 MHz, CDCl_3) 7.64 (d, $J = 7.7$ Hz, 1H), 7.32 (td, $J = 7.6, 1.4$ Hz, 1H), 7.25 – 7.16 (m, 2H), 3.37 (d, $J = 11.4$ Hz, 1H), 2.98 – 2.63 (m, 4H), 2.36 (td, $J = 11.5, 3.2$ Hz, 1H), 2.30 –

2.14 (m, 3H), 2.11 – 1.94 (m, 2H), 1.94 – 1.74 (m, 4H), 1.73 – 1.35 (m, 5H), 1.26 (h, $J = 14.3$, 13.2 Hz, 1H), 1.11 – 1.00 (m, 1H), 0.95 (t, $J = 7.3$ Hz, 3H), 0.37 (q, $J = 8.2$, 7.8 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 188.5 (C), 155.0 (C), 144.0 (C), 127.8 (CH), 125.1 (CH), 121.4 (CH), 120.5 (CH), 64.5 (CH), 58.3 (C), 53.3 (CH₂, br), 51.9 (CH₂, br), 51.5 (CH, br), 42.7 (CH₂), 41.6 (CH), 35.0 (CH), 29.6 (CH₂, br), 28.1 (CH₂), 27.9 (CH₂), 26.1 (CH₂), 23.6 (CH₂), 16.3 (CH₂), 11.5 (CH₃), 8.0 (CH₃); m/z (ESI+) found $[M+H]^+$ 337.2645. $C_{23}H_{33}N_2^+$ requires 337.2638.

4.4.19 Quinoline 17{6}

δ_H (500 MHz, $CDCl_3$) 8.31 (s, 1H), 7.94 (s, 1H), 7.85 (d, $J = 8.5$ Hz, 1H), 7.61 (dd, $J = 8.5$, 1.5 Hz, 1H), 3.23 – 3.17 (m, 1H), 2.91 – 2.86 (m, 1H), 2.73 (dt, $J = 13.4$, 7.8 Hz, 1H), 2.60 – 2.47 (m, 4H), 2.34 – 2.26 (d, 1H), 2.20 – 2.11 (m, 2H), 2.09 – 2.03 (m, 1H), 1.95 – 1.82 (m, 2H), 1.75 – 1.59 (m, 2H), 1.56 – 1.43 (m, 3H), 1.29 – 1.11 (m, 3H), 0.89 (t, $J = 7.3$ Hz, 3H), 0.73 (t, $J = 7.4$ Hz, 3H); δ_C (125 MHz, $CDCl_3$) 163.3 (C), 145.6 (C), 136.9 (C), 130.6 (CH), 130.2 (C, q, $J = 32$ Hz), 128.4 (CH), 128.2 (C), 126.4 (CH, q, $J = 4.2$ Hz), 124.2 (C, q, $J = 270$ Hz), 121.1 (CH, q, $J = 3.1$ Hz), 65.4 (CH), 54.8 (CH₂), 52.3 (CH₂), 48.9 (CH), 47.0 (CH), 40.3 (CH), 39.4 (CH), 33.3 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 27.0 (CH₂), 24.8 (CH₂), 17.5 (CH₂), 12.0 (CH₃), 9.7 (CH₃); m/z (ESI+) found $[M+H]^+$ 417.2518. $C_{25}H_{32}F_3N_2^+$ requires 417.2512.

4.4.20 Quinoline 17{5}

δ_H (500 MHz, $CDCl_3$) 7.85 (s, 1H), 7.37 – 7.30 (m, 2H), 6.96 (d, $J = 7.4$ Hz, 1H), 4.05 (s, 3H), 3.21 (d, $J = 11.3$ Hz, 1H), 3.08 – 3.03 (m, 1H), 2.77 – 2.70 (m, 1H), 2.62 – 2.45 (m, 4H), 2.27 – 2.13 (m, 3H), 2.05 – 1.99 (m, 1H), 1.94 – 1.81 (m, 2H), 1.74 – 1.42 (m, 5H), 1.30 – 1.12 (m, 3H), 0.90 (t, $J = 7.3$ Hz, 3H), 0.73 (t, $J = 7.4$ Hz, 3H); δ_C (125 MHz, $CDCl_3$) 160.6 (C), 154.9 (C), 138.8 (C), 135.1 (C), 130.7 (CH), 127.9 (C), 125.5 (CH), 119.3 (CH), 106.9 (CH), 65.5

(CH), 56.1 (CH₃), 54.7 (CH₂), 52.3 (CH₂), 48.5 (CH), 47.1 (CH), 40.7 (CH), 39.1 (CH), 33.4 (CH₂), 29.7 (CH₂), 28.1 (CH₂), 25.0 (CH₂), 17.5 (CH₂), 12.0 (CH₃), 9.8 (CH₃); m/z (ESI+) found $[M+H]^+$ 379.2762. C₂₅H₃₅N₂O⁺ requires 379.2744.

4.4.21 Quinoline 17{4}

δ_H (500 MHz, CDCl₃) 7.91 (d, $J = 9.0$ Hz, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 7.55 (d, $J = 9.0$, 1.5 Hz, 1H), 3.30 (d, $J = 11.4$ Hz, 1H), 2.90 – 2.85 (m, 1H), 2.84 – 2.73 (m, 1H), 2.71 – 2.61 (m, 2H), 2.57 – 2.44 (m, 2H), 2.31 – 2.22 (m, 2H), 2.20 – 2.14 (m, 1H), 2.05 (d, $J = 12.9$ Hz, 1H), 1.97 – 1.91 (m, 1H), 1.89 – 1.72 (m, 2H), 1.65 – 1.43 (m, 4H), 1.38 – 1.12 (m, 3H), 0.92 (t, $J = 7.3$ Hz, 3H), 0.72 (t, $J = 7.4$ Hz, 3H); δ_C (125 MHz, CDCl₃) 161.7 (C), 145.2 (C), 135.2 (C), 131.1 (C), 130.1 (CH), 130.0 (CH), 129.5 (CH), 127.3 (C), 125.9 (CH), 65.3 (CH), 54.2 (CH₂), 51.9 (CH₂), 48.7 (CH), 46.3 (CH), 40.5 (CH), 39.1 (CH), 33.1 (CH₂), 29.2 (CH₂), 29.1 (CH₂), 27.1 (CH₂), 24.8 (CH₂), 17.1 (CH₂), 11.9 (CH₃), 9.7 (CH₃); m/z (ESI+) found $[M+H]^+$ 383.2255. C₂₄H₃₂ClN₂⁺ requires 383.22

Supporting Information. Experimental procedures for the synthesis of scaffolds, tabulated results for all libraries, characterization data and ¹H and ¹³C NMR spectra for scaffolds and representative library compounds.

Author Contributions

M.C.M. and J.A. conceived and designed the experiments, M.C.M. carried out the experiments, and M.C.M and J.A. co-wrote the manuscript and Supporting Information.

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ABBREVIATIONS

PTSA, *para*-toluenesulfonic acid; NP, natural product; Fsp³, fraction sp³; HBD, hydrogen bond donors; HBA, hydrogen bond acceptors; tPSA, topological polar surface area; rotB, rotatable bonds.

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