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Supporting Information

Real-Time Biological Annotation of Synthetic Compounds


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1. General Methods

All chemicals and solvents were purchased from Acros Organics, Alfa Aesar, AstaTech, Oakwood Chemical, or Sigma-Aldrich. Chemicals were used without further purification.

Reaction progress was monitored by analytical thin-layer chromatography (TLC) and $^1$H NMR spectroscopy. TLC analyses were performed using E. Merck silica gel 60 F254 pre-coated plates (250 µm). A handheld 254 nm UV lamp and potassium permanganate staining solution (with light heating) were used for detection.

Flash column chromatography was performed using a Teledyne ISCO CombiFlash Rf+ purification system with RediSep Rf Gold Normal-Phase Silica columns (average particle size: 20 – 40 µm; average pore size: 60 Å).

Known compounds were characterized by, at minimum, $^1$H NMR spectroscopy. Novel synthetic intermediates and final compounds were characterized by, at minimum, $^1$H NMR and $^{13}$C NMR spectroscopy and HRMS. Further NMR experiments were performed as needed to confirm structural assignment.

NMR spectra were recorded on Bruker UltraShield 300 MHz and Ascend 400 MHz spectrometers. $^1$H and $^{13}$C NMR chemical shifts are reported using residual non-deuterated solvent as an internal standard – CDCl$_3$: 7.26 ($^1$H), 77.16 ($^{13}$C) ppm. Multiplicity abbreviations are as follows: s = singlet, br s = broad singlet, d = doublet (dd = doublet of doublets, etc.), t = triplet, q = quartet, m = multiplet. All NMR data were collected at 25 °C. All deuterated solvents were purchased from Cambridge Isotope Laboratories.

High-resolution mass spectra were acquired on an Agilent 1290 Infinity separations module coupled to a 6230 time-of-flight (TOF) mass detector operating in ESI+ mode. Masses were confirmed using the “Find by Formula” feature in MassHunter Qualitative Analysis vB.06.00. All values are averages of three independent measurements.

U-2 OS cells were cultured in Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1X GlutaMAX, and 1% penicillin/streptomycin (PS) and maintained in a 37 °C, 5% CO$_2$ humidified incubator.
2. Chemistry Methods

General Synthetic Procedures

Scheme S1. Substrate preparation and overall scheme

Table S1. Influence of solvent on thermal rearrangement

General Procedure A: Tosylation
To a flame-dried round-bottom flask under an atmosphere of N₂ was added tosyl chloride (1.1 equiv.), DMAP (0.15 equiv.), anhydrous DCM (0.2 M), anhydrous NEt₃ (2 equiv.), and the corresponding homoallylic alcohol (1 equiv.). The resulting light yellow solution turned cloudy after 5-10 minutes and was allowed to stir at room temperature for 3 hours. The reaction was quenched with H₂O and diluted with hexanes. The phases were separated and the organic phase was washed twice with saturated aqueous NH₄Cl, dried over Na₂SO₄, and concentrated under reduced pressure. The crude yellow oil was purified via flash column chromatography to afford the desired tosylate.
General Procedure B: Pyrrole alkylation
To a solution of the corresponding pyrrole (1 equiv.) in anhydrous DMF (0.4 M) was added the corresponding tosylate (1.6 equiv.) and cesium carbonate (2.3 equiv.). The reaction mixture was stirred at 85 °C for 16 hours, at which point the reaction vessel was allowed to cool to room temperature and its contents were partitioned between Et₂O and water. The phases were separated and the organic phase was washed an additional 3 times with water, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified via flash column chromatography to afford the desired alkylated pyrrole.

General Procedure C: Photochemical rearrangement of N-substituted pyrroles
To a quartz round-bottom flask was added the corresponding pyrrole and acetonitrile (5 mM), and the resulting colorless solution was sparged with N₂ for 30 minutes. The reaction flask was then placed in a Rayonet photochemical reactor outfitted with a cooling fan and eight low pressure 254 nm (4 W) Hg lamps. The reaction mixture was irradiated until TLC analysis revealed that the reaction had gone to completion (usually 3-12 hours). The solvent was then removed under reduced pressure and the crude oil was purified via flash column chromatography to afford the desired tricyclic aziridine.

General Procedure D: Thermal rearrangement of tricyclic aziridines
To a 1 dram vial was added the corresponding aziridine and CDCl₃ (0.1 M). The vial was tightly capped and placed in a heating block raised to 70 °C. The reaction mixture was allowed to stir until ¹H NMR analysis indicated that the reaction had gone to completion (usually 24-48 hours). The solvent was then removed under reduced pressure and the crude oil was either filtered through activated charcoal or purified via flash column chromatography to afford the desired imine/amine.

Compounds

But-3-en-1-yl 4-methylbenzenesulfonate

General procedure A was followed using but-3-en-1-ol (335 mg, 4.64 mmol) to afford the title compound as a colorless oil (1.04 g, 99% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.67 (ddt, J = 17.1, 10.4, 6.7 Hz, 1H), 5.11 – 5.07 (m, 1H), 5.06 – 5.04 (m, 1H), 4.06 (t, J = 6.7 Hz, 2H), 2.45 (s, 3H), 2.40 (qt, J = 6.7, 1.4 Hz, 2H). Characterization data consistent with those reported in the literature.¹
(±) 2-methylbut-3-en-1-yl 4-methylbenzenesulfonate

General procedure A was followed using 2-methylbut-3-en-1-ol (585 mg, 6.79 mmol) to afford the title compound as a colorless oil (1.53 g, 94% yield). \( ^1{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.78 (d, \( J = 8.2 \) Hz, 2H), 7.34 (d, \( J = 8.2 \) Hz, 2H), 5.63 (ddd, \( J = 17.3, 10.4, 7.0 \) Hz, 1H), 5.08 – 5.01 (m, 2H), 3.92 (dd, \( J = 9.4, 6.4 \) Hz, 1H), 3.84 (dd, \( J = 9.4, 6.9 \) Hz, 1H), 2.56 – 2.47 (m, 1H), 2.45 (s, 3H), 1.01 (d, \( J = 6.9 \) Hz, 3H). Characterization data consistent with those reported in the literature.\(^2\)

3-methylbut-3-en-1-yl 4-methylbenzenesulfonate

General procedure A was followed using 3-methylbut-3-en-1-ol (597 mg, 6.79 mmol) to afford the title compound as a colorless oil (1.52 g, 91% yield). \( ^1{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.78 (d, \( J = 8.1 \) Hz, 2H), 7.33 (d, \( J = 8.1 \) Hz, 2H), 4.77 (br s, 1H), 4.66 (br s, 1H), 4.11 (t, \( J = 6.9 \) Hz, 2H), 2.43 (s, 3H), 2.33 (t, \( J = 6.9 \) Hz, 2H), 1.64 (s, 3H). Characterization data consistent with those reported in the literature.\(^3\)

1-(1-(but-3-en-1-yl)-1H-pyrrol-2-yl)ethan-1-one (1a)

General procedure B was followed using 2-acetyl-1H-pyrrole (678 mg, 6.21 mmol) and but-3-en-1-yl 4-methylbenzenesulfonate (2.25 g, 9.94 mmol) to afford the title compound as a colorless oil (950 mg, 94% yield). \( ^1{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 6.95 (dd, \( J = 4.1, 1.7 \) Hz, 1H), 6.84 – 6.80 (m, 1H), 6.10 (dd, \( J = 4.1, 2.6 \) Hz, 1H), 5.74 (ddt, \( J = 17.0, 10.2, 6.8 \) Hz, 1H), 5.06 – 4.98 (m, 2H), 4.36 (t, \( J = 7.1 \) Hz, 2H), 2.50 – 2.43 (m, 2H), 2.42 (s, 3H). \( ^{13}{C} \text{NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 188.2, 134.7, 130.3, 130.0, 120.4, 117.2, 107.9, 49.3, 35.8, 27.3. \( \text{HRMS (ESI+)} \) C\(_{10}\)H\(_{13}\)NO – calculated: 163.0997, found: 163.0999. Characterization data consistent with those reported in the literature.\(^4\)
General procedure B was followed using 2-acetyl-1H-pyrrole (227 mg, 2.08 mmol) and 2-methylbut-3-en-1-yl 4-methylbenzenesulfonate (800 mg, 3.33 mmol) to afford the title compound as a colorless oil (234 mg, 64% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.95 (dd, $J = 4.1, 1.7$ Hz, 1H), 6.82 – 6.76 (m, 1H), 6.08 (dd, $J = 4.1, 2.5$ Hz, 1H), 5.69 (ddd, $J = 16.9, 10.6, 7.4$ Hz, 1H), 4.97 – 4.88 (m, 2H), 4.23 (dd, $J = 13.1, 7.0$ Hz, 1H), 4.17 (dd, $J = 13.1, 7.6$ Hz, 1H), 2.69 – 2.57 (m, 1H), 2.42 (s, 3H), 0.97 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 188.4, 140.8, 131.1, 130.2, 120.5, 114.9, 107.6, 55.3, 39.4, 27.4, 17.1. HRMS (ESI+) C$_{11}$H$_{15}$NO – calculated: 177.1154, found: 177.1155.

General procedure B was followed using 2-acetyl-1H-pyrrole (97 mg, 0.892 mmol) and 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (343 mg, 1.43 mmol) to afford the title compound as a colorless oil (145 mg, 92% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.93 (dd, $J = 4.1, 1.7$ Hz, 1H), 6.84 – 6.79 (m, 1H), 6.09 (dd, $J = 4.1, 2.5$ Hz, 1H), 4.77 – 4.74 (m, 1H), 4.68 – 4.61 (m, 1H), 4.44 – 4.35 (m, 2H), 2.43 – 2.38 (m, 5H), 1.74 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 188.1, 142.4, 130.2, 130.0, 120.3, 112.3, 107.9, 48.6, 39.6, 27.3, 22.5. HRMS (ESI+) C$_{11}$H$_{15}$NO – calculated: 177.1154, found: 177.1153.

General procedure B was followed using 2-acetyl-1H-pyrrole (147 mg, 1.89 mmol) and but-3-en-1-yl 4-methylbenzenesulfonate (684 mg, 3.02 mmol) to afford the title compound as a colorless oil (249 mg, 90% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.83 (dd, $J = 2.7, 1.6$ Hz, 1H), 6.76 (dd, $J = 4.0, 1.6$ Hz, 1H), 6.15 (dd, $J = 4.0, 2.7$ Hz, 1H), 5.73 (ddd, $J = 17.3, 10.6, 6.9$ Hz, 1H), 5.10 – 5.03 (m, 2H), 4.09 (t, $J = 7.0$ Hz, 2H), 2.59 – 2.52 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 133.4, 126.5, 120.1, 118.4, 114.0, 109.4, 103.6, 48.5, 35.5. HRMS (ESI+) C$_9$H$_{16}$N$_2$ –
calculated: 146.0844, found: 146.0849. Characterization data consistent with those reported in the literature.4

(±) 1-(2-methylbut-3-en-1-yl)-1H-pyrrole-2-carbonitrile (5a)

General procedure B was followed using 1H-pyrrole-2-carbonitrile (128 mg, 1.40 mmol) and 2-methylbut-3-en-1-yl 4-methylbenzenesulfonate (540 mg, 2.24 mmol) to afford the title compound as a colorless oil (186 mg, 83% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.80 (dd, $J = 2.7, 1.6$ Hz, 1H), 6.75 (dd, $J = 4.0, 1.6$ Hz, 1H), 6.14 (dd, $J = 4.0, 2.7$ Hz, 1H), 5.68 (ddd, $J = 17.1, 10.4, 7.5$ Hz, 1H), 5.04 – 4.95 (m, 2H), 3.98 – 3.88 (m, 2H), 2.75 – 2.62 (m, 1H), 1.02 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 139.5, 127.0, 119.9, 116.1, 114.1, 109.3, 104.0, 54.4, 39.8, 17.2. HRMS (ESI+) C$_{10}$H$_{12}$N$_2$ – calculated: 160.1000, found: 160.1002.

1-(3-methylbut-3-en-1-yl)-1H-pyrrole-2-carbonitrile (6a)

General procedure B was followed using 1H-pyrrole-2-carbonitrile (164 mg, 1.78 mmol) and 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (684 mg, 2.85 mmol) to afford the title compound as a colorless oil (276 mg, 97% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.83 (dd, $J = 2.6, 1.6$ Hz, 1H), 6.76 (dd, $J = 4.0, 1.6$ Hz, 1H), 6.14 (dd, $J = 4.0, 2.6$ Hz, 1H), 4.84 – 4.78 (m, 1H), 4.69 – 4.64 (m, 1H), 4.14 (t, $J = 7.3$ Hz, 2H), 2.50 (t, $J = 7.3$ Hz, 2H), 1.76 (s, 3H). HRMS (ESI+) C$_{10}$H$_{12}$N$_2$ – calculated: 160.1000, found: 160.0999. Characterization data consistent with those reported in the literature.5

Ethyl 4-acetyl-1-(but-3-en-1-yl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (7a)

General procedure B was followed using ethyl 4-acetyl-3,5-dimethyl-1H-pyrrole-2-carboxylate (396 mg, 1.89 mmol) and but-3-en-1-yl 4-methylbenzenesulfonate (684 mg, 3.02 mmol) to afford
the title compound as a colorless oil (474 mg, 95% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.73 (ddt, $J$ = 17.1, 10.2, 6.9 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.32 – 4.23 (m, 4H), 2.48 (s, 3H), 2.43 (s, 3H), 2.42 – 2.34 (m, 5H), 1.34 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.1, 161.7, 139.3, 134.0, 129.1, 123.3, 119.5, 117.2, 59.9, 44.5, 34.9, 31.6, 14.3, 13.3, 12.1. HRMS (ESI+) C$_{15}$H$_{21}$NO$_3$ – calculated: 263.1521, found: 263.1527. Characterization data consistent with those reported in the literature.$^4$

(±) Ethyl 4-acetyl-3,5-dimethyl-1-(2-methylbut-3-en-1-yl)-1H-pyrrole-2-carboxylate (8a)

General procedure B was followed using ethyl 4-acetyl-3,5-dimethyl-1H-pyrrole-2-carboxylate (184 mg, 0.881 mmol) and 2-methylbut-3-en-1-yl 4-methylbenzenesulfonate (340 mg, 1.41 mmol) to afford the title compound as a colorless oil (214 mg, 88% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.62 (ddd, $J$ = 17.4, 10.4, 7.4 Hz, 1H), 4.94 – 4.85 (m, 2H), 4.29 (q, $J$ = 7.1 Hz, 2H), 4.19 (br s, 2H), 2.57 – 2.48 (m, 4H), 2.45 – 2.39 (m, 6H), 1.35 (t, $J$ = 7.1 Hz, 3H), 0.94 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.6, 162.2, 140.2, 140.0, 129.4, 123.5, 120.1, 115.3, 60.1, 50.1, 39.5, 32.0, 17.0, 14.5, 13.7, 12.9. HRMS (ESI+) C$_{16}$H$_{23}$NO$_3$ – calculated: 277.1678, found: 277.1683.

Ethyl 4-acetyl-3,5-dimethyl-1-(3-methylbut-3-en-1-yl)-1H-pyrrole-2-carboxylate (9a)

General procedure B was followed using ethyl 4-acetyl-3,5-dimethyl-1H-pyrrole-2-carboxylate (373 mg, 1.78 mmol) and 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (684 mg, 3.02 mmol) to afford the title compound as a colorless oil (483 mg, 98% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.80 (s, 1H), 4.73 – 4.70 (m, 1H), 4.38 – 4.27 (m, 4H), 2.51 (s, 3H), 2.47 (s, 3H), 2.44 (s, 3H), 2.36 – 2.29 (m, 2H), 1.78 (s, 3H), 1.37 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 196.5, 161.9, 142.2, 139.5, 129.2, 123.6, 119.8, 112.2, 60.1, 44.3, 38.7, 31.9, 22.7, 14.5, 13.6, 12.1. HRMS (ESI+) C$_{16}$H$_{23}$NO$_3$ – calculated: 277.1678, found: 277.1685.
To a flame-dried round-bottom flask under an atmosphere of N₂ was added 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (300 mg, 1 equiv.), triphenylphosphine (0.926 g, 2.5 equiv.), anhydrous THF (8 ml, 0.16 M), and but-3-en-1-ol (305 mg, 3 equiv.). The resulting colorless solution was cooled to 0 °C. Once cool, DIAD (0.686 ml, 2.5 equiv.) was added dropwise via syringe over the course of 30 minutes to afford a yellow solution. The ice bath was allowed to melt slowly and the reaction mixture stirred for 24 hours. Solvent was removed under reduced pressure and the resulting yellow oil was partitioned between 25 mL Et₂O and 2 mL H₂O. The phases were separated and the organic phase was washed with an additional 2 x 2 mL H₂O, dried over Na₂SO₄, and concentrated under reduced pressure. The crude reaction product was purified via flash column chromatography (ISCO, Silica 24 g, 0-10% EtOAc in hexanes) to afford the title compound as a colorless oil (230 mg, 61% yield).

**1H NMR** (400 MHz, CDCl₃) δ 7.54 (dd, J = 4.4, 1.6 Hz, 1H), 7.00 (dd, J = 2.4, 1.6 Hz, 1H), 6.22 (dd, J = 4.4, 2.4 Hz, 1H), 5.76 (ddt, J = 16.9, 9.8, 7.0 Hz, 1H), 5.08 – 5.02 (m, 2H), 4.39 (t, J = 7.1 Hz, 2H), 2.50 (qt, J = 7.0, 1.3 Hz, 2H). Characterization data consistent with those reported in the literature.⁴

1-(but-3-en-1-yl)-N-(adamantan-1-ylmethyl)-1H-pyrrole-2-carboxamide (10a)

To a solution of 1-(1-(but-3-en-1-yl)-1H-pyrrol-2-yl)-2,2,2-trichloroethan-1-one (140 mg, 0.525 mmol) in acetonitrile (1.0 mL, 0.42 M) was added triethylamine (0.110 ml, 0.788 mmol, 1.5 equiv.) and adamantan-1-ylmethanamine (0.140 ml, 0.788 mmol, 1.5 equiv.). The resulting colorless solution was allowed to stir at 50 °C for 5 hours, during which time the reaction mixture turned bright orange. The reaction vial was then allowed to cool to room temperature and its contents were diluted with 75 mL hexanes, washed with 2 x 5 mL saturated aqueous NH₄Cl and 5 mL H₂O, dried over Na₂SO₄, and concentrated under reduced pressure. The crude light yellow oil was purified via flash column chromatography (ISCO, Silica 12g, 0-10% EtOAc in hexanes) to afford the title compound as a colorless oil (160 mg, 97% yield). **1H NMR** (400 MHz, CDCl₃) δ 6.75 (dd, J = 2.5, 1.7 Hz, 1H), 6.52 (dd, J = 3.9, 1.7 Hz, 1H), 6.07 (dd, J = 3.9, 2.5 Hz, 1H), 5.94 (br s, 1H), 5.76 (ddt, J = 17.2, 10.2, 6.9 Hz, 1H), 5.06 – 4.97 (m, 2H), 4.39 (t, J = 7.1 Hz, 2H), 3.07 (d, J = 6.5 Hz, 2H), 2.55 – 2.48 (m, 2H), 2.00 – 1.96 (m, 3H), 1.74 – 1.69 (m, 3H), 1.65 – 1.60 (m, 3H), 1.54 (d, J = 2.9 Hz, 6H). **13C NMR** (101 MHz, CDCl₃) δ 162.1, 135.1, 126.8, 125.6, 117.0, 111.3, 107.1, 50.6, 48.5, 40.4, 37.1, 36.3, 34.2, 28.4. **HRMS** (ESI+) C₂₀H₂₈N₂O – calculated: 312.2202, found: 312.2208.
(±) 1-((31R,3aS,6aS)-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indol-3(2H)-yl)ethan-1-one (1b)

General procedure C was followed using pyrrole 1a (230 mg, 1.40 mmol) to afford the title compound as a yellow oil (149 mg, 65% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.18 (dddd, $J$ = 10.0, 6.1, 2.0, 0.9 Hz, 1H), 5.74 (dddd, $J$ = 10.0, 4.1, 3.3, 0.9 Hz, 1H), 3.22 (ddd, $J$ = 9.7, 4.3, 2.0 Hz, 1H), 3.16 – 3.06 (m, 1H), 2.80 (d, $J$ = 3.8 Hz, 1H), 2.52 (ddd, $J$ = 11.4, 10.0, 8.0 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.25 – 2.18 (m, 1H), 2.03 (s, 3H), 1.93 – 1.85 (m, 1H), 1.50 – 1.42 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 208.5, 135.7, 120.1, 59.5, 49.9, 44.0, 41.1, 31.9, 29.8, 24.3. HRMS (ESI+) C$_{10}$H$_{13}$NO – calculated: 163.0997, found: 163.0998. Characterization data consistent with those reported in the literature.$^4$

(±) 1-((31R,3aS,6aS)-6a-methyl-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indol-3(2H)-yl)ethan-1-one (2b)

General procedure C was followed using pyrrole 2a (158 mg, 0.891 mmol) to afford the title compound as a light yellow oil (81 mg, 51% yield, d.r. = 6:1). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.21 (dddd, $J$ = 10.0, 6.0, 2.0, 0.8 Hz, 1H), 5.74 (dddd, $J$ = 10.0, 4.1, 3.2, 1.1 Hz, 1H), 2.83 – 2.78 (m, 2H), 2.76 – 2.71 (m, 2H), 2.29 – 2.20 (m, 1H), 2.08 (s, 3H), 2.01 – 1.92 (m, 2H), 0.99 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 208.6, 135.6, 119.7, 58.5, 56.8, 50.3, 43.6, 40.1, 29.2, 24.1, 22.7. HRMS (ESI+) C$_{11}$H$_{15}$NO – calculated: 177.1154, found: 177.1153.

(±) 1-((31R,3aS,6aS)-6a-methyl-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indol-3(2H)-yl)ethan-1-one (3b)

General procedure C was followed using pyrrole 3a (131 mg, 0.739 mmol) to afford the title compound as a light yellow oil (63 mg, 48% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.19 (ddd, $J$ = 10.0, 6.2, 2.0 Hz, 1H), 5.78 (ddd, $J$ = 10.0, 4.0, 3.2, 1.0 Hz, 1H), 3.15 (td, $J$ = 11.6, 3.2 Hz, 1H), 2.49 (dt, $J$ = 12.1, 9.0 Hz, 1H), 2.41 (d, $J$ = 3.7 Hz, 1H), 2.33 – 2.23 (m, 1H), 2.13 – 2.02 (m, 4H), 1.88 (dd, $J$ = 17.2, 6.1 Hz, 1H), 1.70 – 1.59 (m, 1H), 1.26 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 208.5, 136.1, 120.8, 59.7, 48.6, 48.2, 42.1, 42.0, 38.5, 27.6, 26.9. HRMS (ESI+) C$_{11}$H$_{15}$NO – calculated: 177.1154, found: 177.1154.
(±) (3'R,3aS,6aS)-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indole-3'(2H)-carbonitrile (4b)

General procedure C was followed using pyrrole 4a (241 mg, 1.65 mmol) to afford the title compound as an orange oily solid (67 mg, 28% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.25 – 6.16 (m, 1H), 5.77 (dtd, $J = 10.2, 3.6, 1.0$ Hz, 1H), 3.21 (td, $J = 11.1, 2.4$ Hz, 1H), 2.97 – 2.91 (m, 1H), 2.85 (d, $J = 3.7$ Hz, 1H), 2.74 – 2.61 (m, 1H), 2.47 (dd, $J = 11.7, 10.0, 7.8$ Hz, 1H), 2.41 – 2.33 (m, 1H), 1.98 – 1.90 (m, 1H), 1.62 – 1.54 (m, 1H). HRMS (ESI+) C$_9$H$_{10}$N$_2$ – calculated: 146.0844, found: 146.0844. Characterization data consistent with those reported in the literature.$^4$

(±) (1S,3'R,3aS,6aS)-1-methyl-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indole-3'(2H)-carbonitrile (5b)

General procedure C was followed using pyrrole 5a (234 mg, 1.46 mmol) to afford the title compound as a yellow-orange oil (98 mg, 42% yield, d.r. = 4:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.22 (dd, $J = 10.2, 4.1, 3.3, 1.1$ Hz, 1H), 5.77 (ddd, $J = 10.2, 4.1, 3.3, 1.1$ Hz, 1H), 2.89 – 2.77 (m, 2H), 2.68 (dd, $J = 12.0, 6.8$ Hz, 1H), 2.50 (d, $J = 5.0$ Hz, 1H), 2.43 – 2.33 (m, 1H), 2.13 – 1.95 (m, 2H), 1.22 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 134.6, 121.4, 119.2, 56.6, 51.9, 45.8, 42.8, 37.6, 28.4, 22.9. HRMS (ESI+) C$_{10}$H$_{12}$N$_2$ – calculated: 160.1000, found: 160.1000.

(±) (3'R,3aS,6aS)-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indole-3'(2H)-carbonitrile (6b)

General procedure C was followed using pyrrole 6a (200 mg, 1.25 mmol) to afford the title compound as a light yellow oil (58 mg, 29% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.22 (ddd, $J = 10.1, 6.2, 2.1$ Hz, 1H), 5.80 (dtd, $J = 10.1, 3.4, 1.0$ Hz, 1H), 3.21 (td, $J = 11.5, 2.7$ Hz, 1H), 2.87 (d, $J = 3.6$ Hz, 1H), 2.48 (dd, $J = 11.9, 9.8, 8.3$ Hz, 1H), 2.27 (ddddd, $J = 12.7, 11.1, 9.8, 1.5$ Hz, 1H), 2.21 – 2.14 (m, 1H), 1.98 (dd, $J = 17.6, 6.2$ Hz, 1H), 1.81 – 1.73 (m, 1H), 1.46 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 135.3, 119.7, 119.4, 49.4, 48.9, 44.2, 43.3, 41.5, 37.2, 27.7. HRMS (ESI+) C$_{10}$H$_{12}$N$_2$ – calculated: 160.1000, found: 160.1000.
(±) Ethyl (31R,3aS,6aS)-4-acetyl-3a,5-dimethyl-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indole-31(2H)-carboxylate (7b)

General procedure C was followed using pyrrole 7a (100 mg, 0.380 mmol) to afford the title compound as an orange oil (75 mg, 75% yield). 1H NMR (400 MHz, CDCl3) δ 4.31–4.16 (m, 2H), 3.46–3.34 (m, 1H), 3.03–2.95 (m, 1H), 2.77–2.64 (m, 2H), 2.55–2.41 (m, 1H), 2.27 (s, 3H), 1.94 (s, 3H), 1.90 (dd, J = 17.1, 2.4 Hz, 1H), 1.43 (ddt, J = 13.5, 8.6, 2.4 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 203.3, 171.2, 144.1, 132.4, 61.3, 59.7, 51.6, 47.8, 38.8, 37.6, 36.9, 30.0, 21.8, 18.9, 14.5. HRMS (ESI+) C15H21NO3 – calculated: 263.1521, found: 263.1526. Characterization data consistent with those reported in the literature.4

(±) Ethyl (1S,31R,3aS,6aS)-4-acetyl-1,3a,5-trimethyl-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indole-31(2H)-carboxylate (8b)

General procedure C was followed using pyrrole 8a (177 mg, 0.638 mmol) to afford the title compound as a light yellow oil (67 mg, 38% yield, d.r. > 10:1). 1H NMR (400 MHz, CDCl3) δ 4.22 (q, J = 7.1 Hz, 2H), 2.95 (dd, J = 12.5, 2.4 Hz, 1H), 2.84 (dd, J = 12.5, 7.2 Hz, 1H), 2.62 (ddd, J = 17.3, 4.8, 1.4 Hz, 1H), 2.49–2.43 (m, 1H), 2.21 (s, 3H), 1.95–1.83 (m, 5H), 1.25 (t, J = 7.1 Hz, 3H), 1.19 (s, 3H), 1.05 (d, J = 7.2 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 203.4, 171.4, 143.7, 132.2, 61.3, 58.9, 58.7, 48.4, 47.3, 45.6, 36.8, 29.9, 23.0, 21.4, 18.9, 14.4. HRMS (ESI+) C16H23NO3 – calculated: 277.1678, found: 277.1683.

(±) Ethyl (31R,3aS,6aS)-4-acetyl-3a,5,6a-trimethyl-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indole-31(2H)-carboxylate (9b)

General procedure C was followed using pyrrole 9a (151 mg, 0.544 mmol) to afford the title compound as a light yellow oil (62 mg, 41% yield). 1H NMR (400 MHz, CDCl3) δ 4.31–4.16 (m, 2H), 3.39 (ddd, J = 12.7, 11.2, 3.5 Hz, 1H), 2.65 (dt, J = 12.7, 8.9 Hz, 1H), 2.58 (d, J = 16.9 Hz, 1H), 2.27 (s, 3H), 2.19–2.09 (m, 1H), 1.93 (d, J = 1.2 Hz, 3H), 1.82 (d, J = 16.9 Hz, 1H), 1.69–1.59 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.26 (s, 3H), 1.16 (s, 3H). 13C NMR (101 MHz, CDCl3) δ
203.4, 169.8, 145.2, 132.4, 62.8, 61.0, 50.2, 47.1, 46.8, 45.9, 42.7, 30.2, 26.0, 21.7, 20.3, 14.5.

HRMS (ESI+) C_{16}H_{23}NO_{3} – calculated: 277.1678, found: 277.1682.

(±) (3^{1}R,3aS,6aS)-N-(((3S)-adamantan-1-yl)methyl)-1,3a,6,6a-tetrahydroazirino[2,3,1-hi]indole-3^{1}(2H)-carboxamide (10b)

General procedure C was followed using pyrrole 10a (156 mg, 0.499 mmol) to afford the title compound as a colorless oily solid (78 mg, 50% yield). \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.68 (br s, 1H), 6.23 (ddd, \(J = 10.1, 6.1, 1.9\) Hz, 1H), 5.73 (dt, \(J = 10.1, 3.4\) Hz, 1H), 3.14 – 3.03 (m, 3H), 2.68 (dd, \(J = 13.4, 5.3\) Hz, 1H), 2.57 – 2.39 (m, 4H), 1.97 – 1.91 (m, 4H), 1.68 (d, \(J = 12.3\) Hz, 3H), 1.59 (d, \(J = 12.3\) Hz, 3H), 1.47 – 1.38 (m, 7H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.6, 135.8, 120.0, 53.4, 50.4, 49.2, 44.8, 41.2, 40.4, 37.1, 34.2, 33.9, 30.2, 28.4. HRMS (ESI+) C\(_{20}\)H\(_{28}\)N\(_{2}\)O – calculated: 312.2202, found: 312.2207.

(±) 1-((3aS,7aR)-3,3a,4,5-tetrahydro-7aH-indol-7a-yl)ethan-1-one (1c)

General procedure D was followed using aziridine 1b (47 mg, 0.288 mmol) to afford the title compound as a colorless oil (33 mg, 70% yield). \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.60 (s, 1H), 6.03 (ddd, \(J = 10.1, 4.4, 3.4\) Hz, 1H), 5.95 (dt, \(J = 10.1, 1.9\) Hz, 1H), 2.77 – 2.64 (m, 2H), 2.36 (ddd, \(J = 16.7, 4.5, 1.3\) Hz, 1H), 2.27 (s, 2H), 2.07 – 1.94 (m, 2H), 1.88 – 1.79 (m, 1H), 1.40 – 1.30 (m, 1H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 207.6, 167.5, 131.9, 125.9, 86.7, 42.6, 35.1, 26.4, 24.9, 22.0. HRMS (ESI+) C\(_{10}\)H\(_{13}\)NO – calculated: 163.0997, found: 163.0997.

(±) 1-((3S,3aS,7aS)-3-methyl-3,3a,4,5-tetrahydro-7aH-indol-7a-yl)ethan-1-one (2c)

General procedure D was followed using aziridine 2b (90 mg, 0.508 mmol) to afford the title compound as a colorless oil (54 mg, 60% yield). \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 (s, 1H), 5.94 (dt, \(J = 10.2, 3.6\) Hz, 1H), 5.82 – 5.77 (m, 1H), 2.76 – 2.67 (m, 1H), 2.35 (s, 3H), 2.25 (dt, \(J = 9.3, 4.8\) Hz, 1H), 2.07 – 1.92 (m, 3H), 1.71 – 1.63 (m, 1H), 1.15 (d, \(J = 7.2\) Hz, 3H). \(^{13}C\) NMR (101
MHz, CDCl3) δ 208.9, 172.4, 130.8, 125.7, 86.5, 47.3, 43.7, 26.5, 21.6, 21.1, 15.4. HRMS (ESI+) C11H15NO – calculated: 177.1154, found: 177.1156.

(±) (3aS,7aS)-3a-methyl-3a,4,5,7a-tetrahydro-3H-indole (3c)

General procedure D was followed using aziridine 3b (95 mg, 0.536 mmol) to afford the title compound as a colorless oil (57 mg, 60% yield). 1H NMR (400 MHz, CDCl3) δ 7.68 (s, 1H), 5.90 (dt, J = 10.1, 3.7 Hz, 1H), 5.58 (dt, J = 10.1, 2.2 Hz, 1H), 2.62 (d, J = 17.5 Hz, 1H), 2.28 (s, 3H), 2.23 (dd, J = 17.2, 1.3 Hz, 1H), 2.14 – 2.09 (m, 2H), 1.88 (dt, J = 13.7, 7.8 Hz, 1H), 1.64 (dt, J = 13.8, 4.8 Hz, 1H), 0.93 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 210.6, 168.2, 128.6, 126.6, 86.6, 48.1, 42.5, 30.1, 29.7, 24.3, 21.6. HRMS (ESI+) C11H15NO – calculated: 177.1154, found: 177.1156.

(±) (3aS,7aR)-3,3a,4,5-tetrahydro-7aH-indole-7a-carbonitrile (4c)

General procedure D was followed using aziridine 4b (50 mg, 0.342 mmol) to afford the title compound as a colorless oil (19 mg, 38% yield). 1H NMR (400 MHz, CDCl3) δ 7.72 (s, 1H), 6.09 (dt, J = 10.0, 4.0 Hz, 1H), 5.97 (dt, J = 10.0, 2.1 Hz, 1H), 2.94 (ddd, J = 17.7, 8.2, 1.1 Hz, 1H), 2.81 (tt, J = 8.4, 4.9 Hz, 1H), 2.52 (ddd, J = 17.7, 4.9, 1.2 Hz, 1H), 2.09 – 2.03 (m, 2H), 1.88 (ddt, J = 13.7, 6.3, 5.0 Hz, 1H), 1.40 (ddddd, J = 14.0, 8.7, 7.0, 5.6 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 170.4, 132.5, 123.7, 120.6, 69.8, 42.5, 40.2, 23.4, 21.5. HRMS (ESI+) C9H10N2 – calculated: 146.0844, found: 146.0843.

(±) (3S,3aS,7aS)-3-methyl-3a,4,5-tetrahydro-7aH-indole-7a-carbonitrile (5c)

General procedure D was followed using aziridine 5b (18 mg, 0.112 mmol) to afford the title compound as a light yellow oil (10 mg, 55% yield). 1H NMR (400 MHz, CDCl3) δ 7.53 (s, 1H), 6.00 (dt, J = 10.0, 3.9 Hz, 1H), 5.81 (dt, J = 10.0, 2.0 Hz, 1H), 2.84 – 2.74 (m, 1H), 2.45 – 2.37 (m, 1H), 2.10 – 1.98 (m, 3H), 1.75 – 1.65 (m, 1H), 1.26 (d, J = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ
174.8, 131.4, 123.8, 121.3, 69.8, 48.4, 47.3, 20.7, 20.7, 15.1. **HRMS** (ESI+) C\textsubscript{10}H\textsubscript{12}N\textsubscript{2} – calculated: 160.1000, found 160.1001.

(±) (3aS,7aS)-3a-methyl-3,3a,4,5-tetrahydro-7H-indole-7a-carbonitrile (6c)

General procedure D was followed using aziridine 6b (21 mg, 0.131 mmol) to afford the title compound as a colorless oil (14 mg, 67% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.69 (s, 1H), 5.99 (dt, \(J = 10.0, 3.8\) Hz, 1H), 5.85 (dt, \(J = 10.0, 2.1\) Hz, 1H), 2.64 (dd, \(J = 17.6, 1.1\) Hz, 1H), 2.48 (dd, \(J = 17.6, 1.3\) Hz, 1H), 2.14 – 2.06 (m, 2H), 1.73 – 1.62 (m, 2H), 1.33 (s, 3H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 170.6, 130.8, 124.3, 118.8, 74.4, 48.3, 42.3, 29.6, 24.8, 21.3. **HRMS** (ESI+) C\textsubscript{10}H\textsubscript{12}N\textsubscript{2} – calculated: 160.1000, found 160.1001.

(±) Ethyl (3aS,7aR)-6-acetyl-7-methyl-5-methylene-1,2,3,3a,4,5-hexahydro-7H-indole-7a-carboxylate (7c)

General procedure D was followed using aziridine 7b (24 mg, 0.0911 mmol) to afford the title compound as a colorless oil (18 mg, 75% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 4.95 (s, 1H), 4.72 (s, 1H), 4.21 (q, \(J = 7.1\) Hz, 2H), 3.06 (dt, \(J = 10.1, 7.6\) Hz, 1H), 2.90 (ddd, \(J = 10.1, 8.0, 4.8\) Hz, 1H), 2.74 (ddt, \(J = 14.1, 4.6, 2.0\) Hz, 1H), 2.64 (br s, 1H), 2.44 – 2.33 (m, 2H), 2.31 (s, 3H), 1.88 (dtd, \(J = 12.6, 7.6, 4.8\) Hz, 1H), 1.67 – 1.59 (m, 4H), 1.26 (t, \(J = 7.1\) Hz, 3H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 206.5, 175.0, 139.7, 137.3, 132.0, 112.5, 70.1, 61.8, 44.7, 42.6, 33.0, 31.1, 30.4, 15.6, 14.4. **HRMS** (ESI+) C\textsubscript{15}H\textsubscript{21}NO\textsubscript{3} – calculated: 263.1521, found 263.1526.

(±) Ethyl (3S,3aS,7aR)-6-acetyl-3,7-dimethyl-5-methylene-1,2,3,3a,4,5-hexahydro-7H-indole-7a-carboxylate (8c)

General procedure D was followed using aziridine 8b (50 mg, 0.180 mmol) to afford the title compound as a light yellow oil (22 mg, 44% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 4.92 (d, \(J = 2.1\) Hz, 1H), 4.74 (d, \(J = 2.1\) Hz, 1H), 3.07 (dt, \(J = 10.0, 7.6\) Hz, 1H), 2.91 (dt, \(J = 10.0, 2.1\) Hz, 1H), 2.63 (dd, \(J = 17.6, 1.1\) Hz, 1H), 2.43 – 2.36 (m, 2H), 2.32 (s, 3H), 1.94 – 1.78 (m, 4H), 1.34 (t, \(J = 7.1\) Hz, 3H). **HRMS** (ESI+) C\textsubscript{15}H\textsubscript{21}NO\textsubscript{3} – calculated: 263.1521, found 263.1526.
Hz, 1H), 4.69 (d, J = 2.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.03 (dd, J = 9.4, 6.9 Hz, 1H), 2.80 (ddt, J = 14.6, 5.0, 2.3 Hz, 1H), 2.63 (t, J = 9.4 Hz, 1H), 2.54 (br s, 1H), 2.36 (dd, J = 14.6, 2.8 Hz, 1H), 2.30 (s, 3H), 1.98 – 1.86 (m, 1H), 1.77 (ddd, J = 10.4, 5.0, 2.8 Hz, 1H), 1.59 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 206.5, 175.1, 138.6, 136.9, 132.8, 112.2, 70.1, 61.8, 53.2, 49.8, 36.6, 31.1, 31.0, 16.2, 15.3, 14.4. HRMS (ESI+) C16H23NO3 – calculated: 277.1678, found 277.1682.

(±) Ethyl (3aS,7aR)-6-acetyl-3a,7-dimethyl-5-methylene-1,2,3,3a,4,5-hexahydro-7aH-indole-7a-carboxylate (9c)

General procedure D was followed using aziridine 9b (30 mg, 0.108 mmol) to afford the title compound as a colorless oil (17 mg, 57% yield). 1H NMR (400 MHz, CDCl3) δ 4.93 (d, J = 2.1 Hz, 1H), 4.71 (d, J = 2.1 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.10 (q, J = 7.1 Hz, 2H), 3.10 (q, J = 7.1 Hz, 2H), 3.10 (q, J = 7.1 Hz, 2H), 3.10 (q, J = 7.1 Hz, 2H), 2.81 (dd, J = 10.3, 9.0, 3.5 Hz, 1H), 2.70 (dt, J = 14.4, 2.2 Hz, 1H), 2.47 (br s, 1H), 2.34 – 2.28 (m, 4H), 1.89 (dt, J = 12.6, 9.0 Hz, 1H), 1.60 (s, 3H), 1.46 (dd, J = 12.6, 8.0, 3.5 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.94 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 206.8, 173.1, 139.1, 137.8, 133.3, 112.3, 74.0, 61.6, 44.0, 42.8, 40.1, 36.7, 31.1, 24.8, 15.6, 14.4. HRMS (ESI+) C16H23NO3 – calculated: 277.1678, found 277.1682.

(±) (3aS,7aR)-N-(((3R,5R,7R)-adamantan-1-yl)methyl)-3a,4,5-tetrahydro-7aH-indole-7a-carboxamide (10c)

General procedure D was followed using aziridine 10b (35 mg, 0.112 mmol) to afford the title compound as a colorless oil (29 mg, 83% yield). 1H NMR (400 MHz, CDCl3) δ 7.62 (s, 1H), 6.72 (br s, 1H), 5.98 (dt, J = 10.0, 4.0 Hz, 1H), 5.74 (dt, J = 10.0, 2.1 Hz, 1H), 3.01 (dd, J = 13.4, 6.9 Hz, 1H), 2.83 (dd, J = 13.4, 6.1 Hz, 1H), 2.75 – 2.63 (m, 2H), 2.48 – 2.38 (m, 1H), 2.22 – 2.13 (m, 1H), 2.09 – 2.01 (m, 2H), 1.95 (s, 3H), 1.69 (d, J = 12.6 Hz, 3H), 1.60 (d, J = 12.6 Hz, 3H), 1.53 – 1.44 (m, 7H). 13C NMR (101 MHz, CDCl3) δ 174.3, 168.0, 131.0, 127.1, 80.7, 50.8, 41.9, 40.4, 37.3, 37.1, 34.0, 28.3, 24.0, 21.0. HRMS (ESI+) C20H28N2O – calculated: 312.2202, found 312.2205.
$^1$H NMR (CDCl$_3$, 400 MHz)

$^1$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)

S22
$^1$H NMR (CDCl$_3$, 400 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^13$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

13C NMR (CDCl$_3$, 101 MHz)

S27
$^1$H NMR (CDCl₃, 400 MHz)

$^{13}$C NMR (CDCl₃, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl₃, 300 MHz)

3b

$^{13}$C NMR (CDCl₃, 101 MHz)
$^1$H COSY NMR (CDCl$_3$, 400 MHz)

$^1$H-$_{13}$C HSQC NMR (CDCl$_3$, 400/101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

4b
$^{1}H$ NMR (CDCl$_3$, 400 MHz)

$^{13}C$ NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
\[\text{\textsuperscript{1}H NMR (CDCl}_3, 400 MHz)\]

\[\begin{array}{c}
\text{8b}
\end{array}\]

\[\text{\textsuperscript{13}C NMR (CDCl}_3, 101 MHz)\]
$^1$H NMR (CDCl$_3$, 400 MHz)

13C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H COSY NMR (CDCl$_3$, 400 MHz)

DEPT-135 NMR (CDCl$_3$, 101 MHz)
$^1$H-$^{13}$C HSQC NMR (CDCl$_3$, 400/101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H COSY NMR (CDCl$_3$, 400 MHz)
$^1$H NMR (CDCl₃, 400 MHz)

$^{13}$C NMR (CDCl₃, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^1$H NMR (CDCl$_3$, 101 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H COSY NMR (CDCl$_3$, 400 MHz)

DEPT-135 NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

![$^1$H NMR spectrum](image)

$^{13}$C NMR (CDCl$_3$, 101 MHz)

![$^{13}$C NMR spectrum](image)
$^1$H COSY NMR (CDCl$_3$, 400 MHz)

DEPT-135 NMR (CDCl$_3$, 101 MHz)
$^{1}H-^{13}C$ HSQC NMR (CDCl$_3$, 400/101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
$^1$H COSY NMR (CDCl$_3$, 400 MHz)

DEPT-135 NMR (CDCl$_3$, 101 MHz)
$^1$H-$^{13}$C HSQC NMR (CDCl$_3$, 400/101 MHz)
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$^13$C NMR (CDCl$_3$, 101 MHz)
$^1$H-$^{13}$C HSQC NMR (CDCl$_3$, 400/101 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
X-Ray Crystallography Data

**Scheme S2.** Chemical derivatization of aziridine 5b to afford a regioisomeric mixture of crystalline amides 5b' and 5b'"
Figure S1. Summary of X-ray diffraction data of amides 5b’ and 5b’’

Empirical formula: $\text{C}_{23}\text{H}_{21}\text{ClN}_{2}\text{O}$

Formula weight: 376.885 g/mol

a: 9.444 Å  
b: 9.392 Å  
c: 44.328 Å  
α (alpha): 90.00°  
β (beta): 90.00°  
γ (gamma): 90.00°  
Volume: 3931.81 Å³  
Space group: Pbca  
Calculated density: 1.273 g/cm³  
Color, habit: colorless blade  
Z: 8  
Temperature: 100 K  
R(F): 0.0570  
Rw(F²): 0.1183  
S: 1.129

Data deposited into the Cambridge Crystallographic Data Center (CCDC 1472245)
3. Biological Annotation Methods

Multiplexed cellular morphology (“Cell Painting”) imaging assay protocol

We adapted our protocol from the one outlined by Gustafsdottir et al. and Wawer et al. 1,000-2,000 U-2 OS cells (ATCC, #HTB-96) were seeded in 50 µL media per well in 384-well clear-bottom imaging plates. After incubating for 24 hours at 37 °C, compounds (6-point dose, 2-fold dilution, range: 3.125-100 µM assay concentration) were pin-transferred to the assay plates via a CyBi-Well robot. Treatments were performed in quadruplicate. Following transfer, the cells were allowed to incubate at 37 °C for an additional 24 hours.

A 1 mM DMSO solution of MitoTracker Deep Red (Thermo Fisher, #M22426) and a 1 mg/mL dH₂O solution of Wheat Germ Agglutinin (WGA), Alexa Fluor 594 conjugate (Thermo Fisher, #W11262) were prepared and combined in pre-warmed media to afford a staining solution (SS1) of 500 nM MitoTracker and 60 µg/mL WGA. After 40 µL of media were removed from each well of the assay plates (~10 µL remaining), 30 µL of SS1 were added to each well (~12 mL/plate). After incubating for 30 minutes at 37 °C, cells were fixed for 20 minutes at room temperature with 16% aqueous paraformaldehyde (10 µL/well). Wells were then washed with 70 µL 1X HBSS (Thermo Fisher, #14065-056 [as 1X]).

A 0.1% HBSS solution of Triton X-100 (Sigma-Aldrich, #T8787) was added to each well (30 µL/well) to permeabilize the cells. After incubating for 15 minutes at room temperature, wells were washed with 70 µL 1X HBSS.

A 1 mg/mL solution in 0.1 M aqueous sodium bicarbonate of Concanavalin A, Alexa Fluor 488 conjugate (Thermo Fisher, #C11252) and a 1.5 mL/vial methanol solution of Phalloidin, Alexa Fluor 594 conjugate (Thermo Fisher, #A12381) were combined with a 10 mg/mL aqueous solution of Hoechst 33342 (Thermo Fisher, #H3570) and a 5 mM DMSO solution of SYTO 14 Green Fluorescent Nucleic Acid Stain (Thermo Fisher, #S7576) in 1X HBSS supplemented with 1% bovine serum albumin to afford a staining solution (SS2) of 0.025 mL Phalloidin/mL, 100 µg/mL Concanavalin, 5 µg/mL Hoechst, and 3 µM SYTO 14. 30 µL of SS2 were then added to each of the wells and the fixed cells were allowed to incubate at room temperature for 30 minutes. Wells were then washed with 70 µL 1X HBSS (no final aspiration) and the plates were thermally sealed with foil at 171 °C (4 seconds) for imaging.

We captured images on an ImageXpress Micro epi fluorescent microscope at 20x magnification over 5 fluorescent channels: DAPI (387/447 nm), GFP (472/520 nm), Cy3 (531/593 nm), TexasRed (562/642 nm), and Cy5 (628/692 nm). 9 sites were imaged per well. The first site of each well was used for lased-based auto-focus (DAPI channel).

Table S2. Stains used in cell-painting experiment

<table>
<thead>
<tr>
<th>Stain</th>
<th>Channel Name</th>
<th>Excitation/Emission Wavelength (nm)</th>
<th>Cellular Compartment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoechst</td>
<td>DAPI</td>
<td>387/447</td>
<td>Nucleus</td>
</tr>
<tr>
<td>Concanavalin A</td>
<td>GFP</td>
<td>472/520</td>
<td>Endoplasmic reticulum</td>
</tr>
<tr>
<td>SYTO 14</td>
<td>Cy3</td>
<td>531/593</td>
<td>Nucleolus</td>
</tr>
<tr>
<td>WGA</td>
<td>TexasRed</td>
<td>562/642</td>
<td>Golgi/plasma membrane</td>
</tr>
<tr>
<td>Phalloidin</td>
<td>TexasRed</td>
<td>562/642</td>
<td>F-actin</td>
</tr>
<tr>
<td>MitoTracker DR</td>
<td>Cy5</td>
<td>628/692</td>
<td>Mitochondria</td>
</tr>
</tbody>
</table>
Assay materials

- U-2 OS cells (ATCC, #HTB-96)
- Aurora 384-well black/clear bottom plates, imaging quality (Brooks, #1022-11330)
- DMEM (Fisher Scientific, #MT10017CV)
- FBS (Thermo Fisher, #10437028)
- Penicillin/streptomycin (Fisher Scientific, #MT30002CI)
- Hank’s Balanced Salt Solution, HBSS (Thermo Fisher, #14065-056)
- MitoTracker Deep Red (Thermo Fisher, #M22426)
- Wheat Germ Agglutinin, Alexa Fluor 594 conjugate (Thermo Fisher, #W11262)
- Concanavalin A, Alexa Fluor 488 conjugate (Thermo Fisher, #C11252)
- Phalloidin, Alexa Fluor 594 conjugate (Thermo Fisher, #A12381)
- Hoechst33342 (Thermo Fisher, #H3570)
- SYTO 14 green fluorescent nucleic acid stain (Thermo Fisher, #S7576)
- Paraformaldehyde 16%, methanol free (Electron Microscopy Sciences, #15710-S)
- Triton X-100 (Sigma-Aldrich, #T8787)
- Bovine serum albumin
- DMSO (Molecular Biology grade)
- Methanol
- Sodium bicarbonate
- ImageXpress Micro (Molecular Devices)

Assay timeline/overview

| Day One | • Plate cells at 1,000-2,000 cells/50 µL per well (~30,000 cells/mL) in DMEM/10% FBS/1% PS  
• Grow overnight at 37 °C |
| Day Two | • Prepare reagents and stock solutions  
• Pin compounds  
• Treat for 24 hours at 37 °C |
| Day Three | • Prepare SS1 and SS2  
• Remove media from assay plates and add SS1; incubate for 30 minutes at 37 °C  
• Fix cells for 20 minutes at room temperature  
• Wash; permeabilize cells for 15 minutes at room temperature  
• Wash and add SS2; incubate for 30 minutes at room temperature  
• Wash (no final aspiration) and seal plates  
• Capture images (several hours per plate) |
4. Data Processing and Analysis

Image analysis and data processing

We used the CellProfiler® software pipelines provided by the Broad Institute Imaging Platform to process the raw images and obtain the morphological features used in subsequent analyses. First, the images were corrected for uneven illumination. Then, CellProfiler software (version 2.1.1) was used to locate and segment cells into nuclei and cytoplasm, after which the size, shape, texture, intensity, local density, and radial distribution were measured for nuclei, cytoplasm, and entire cells. To obtain profiles for each compound, these cell-morphology features of compound-treated cells were averaged per well and then normalized by calculating robust z-scores based on the population of individual DMSO-treated cells found on the same plate. That is, the feature values were subtracted by the median value of the DMSO-treated cells, and then divided by the median absolute deviation of the DMSO-treated population.

Biological profiles

The “spectra” provided below are graphical representations of the biological profiles (i.e., vector of z-scores corresponding to the 1,140 cellular features) for each compound treatment condition (e.g. 5c at 50 μM) compared to DMSO. Each point on the spectrum represents a single cellular feature and its associated z-score (depicted by its y-value). Adjacent points are connected by a line for ease of viewing. Each replicate (4 per treatment condition) is represented by a different color (orange, blue, green, and gray).
cellular feature
cellular feature
Compound activity calculation

To determine the compound activities, we calculated the Mahalanobis distances of each compound profile from the associated populations of vehicle-treated well profiles. The profiles for all replicates of a compound were first combined with the corresponding DMSO-control wells into a matrix of dimensions $m \times n$, where the rows $m$ represent the individual wells and the columns $n$ represent the profiling features. Principal component analysis was performed on this matrix to obtain a new matrix $P$ with the principal components as the columns. For each of these matrices, the first $q$ principal components were taken that were capable of explaining at least 90% of the variance. This matrix $P$ was separated into treatment and control matrices and for each part a covariance matrix was calculated. Each of the two covariance matrices (treatment and control) was weighted by the number of samples in each matrix, and the sum of the resulting matrices was used to calculate the Mahalanobis distance.

Principal moment-of-inertia (PMI) calculations

To calculate the principal moments of inertia, we first used Pipeline Pilot (version 8.5)\textsuperscript{10} to determine the most stable conformations (up to 5 each) for each of the 30 compounds using Dreiding force field for conformer calculation (ChemAxon 3D Conformers plugin).\textsuperscript{11} The PMIs were then calculated using the R package “Rcpi” (version 1.4.0)\textsuperscript{12} and the values were ordered from smallest to greatest as $I_1$, $I_2$, and $I_3$. The ratios $I_1/I_3$ and $I_2/I_3$ were taken as the coordinates of the PMI plot.

Heat map generation and clustering

The heat map was generated using the pairwise Pearson correlations between each compound profile-compound profile pair. The profile for each compound was taken to be the average of each of its doses for all replicates. The correlation distance between each pair of compounds was taken to be $(1 − \text{Pearson coefficient})$. These distances were used to hierarchically cluster the compounds (using complete linkage) to provide the dendrograms shown on the correlation heat map.

Supplementary References

(7) Wawer, M. J.; Li, K.; Gustafsdottir, S. M.; Ljosa, V.; Bodycombe, N. E.; Marton, M. A.;


