RhIII-Catalyzed C–H Activation of Aryl Hydroxamates for the Synthesis of Isoindolinones

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Table of Contents

Table of Contents ................................................................................................................................................. 1
1. General Information ........................................................................................................................................... 2
2. Reaction Optimization ....................................................................................................................................... 3
  2.1 Solvent Screen ......................................................................................................................................... 3
  2.2 Base Screen .......................................................................................................................................... 3
  2.3 Cyclization step screen ............................................................................................................................... 4
3. General procedures and analytical data ........................................................................................................... 5
  3.1 General Procedure for the synthesis of OBoc-aryl-hydroxamates 1 ....................................................... 5
  3.2 General Procedure for the synthesis of styrenes 2 ..................................................................................... 5
  3.3 General Procedure for the synthesis of 3-Isoindolinones 3 ..................................................................... 8
  3.4 General Procedure for the synthesis of Isoindolobenzazepine scaffolds 4 ............................................. 15
4. X-ray Structure Analyses .............................................................................................................................. 23
5. Biological data ............................................................................................................................................... 25
6. DFT Calculations .......................................................................................................................................... 27
7. References .................................................................................................................................................... 39
8. NMR Spectra ............................................................................................................................................... 40
1. General Information

Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator. Compounds were visualized by irradiation with UV light or potassium permanganate staining. Column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm).

$^1$H-NMR, $^{13}$C-NMR and $^{19}$F-NMR were recorded on a Bruker DRX400 (400 MHz), Bruker DRX500 (500 MHz), INOVA500 (500 MHz) and Bruker DRX700 using CDCl$_3$ or CD$_2$Cl$_2$ as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard (CDCl$_3$: δ = 7.26 ppm for $^1$H, δ = 77.16 ppm for $^{13}$C, CD$_2$Cl$_2$: δ = 5.32 ppm for $^1$H, δ = 54.00 ppm for $^{13}$C). Multiplicities are indicated br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are given in Hertz (Hz).

High resolution mass spectra (HR-MS) were recorded on an LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 μm, ionization method: electron spray ionization). Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm$^{-1}$).

Acid chlorides were either commercially available or made from their corresponding carboxylic acid following the reported procedure. [1] 2-Bromostyrenes were also commercially available or made from their corresponding 2-Bromobenzaldehyde following a modified version of the reported procedure. [2]
2. Reaction Optimization

2.1 Solvent Screen

| Entry | R  | Solvent       | Total yield (%) | Ratio  |
|-------|----|---------------|-----------------|--------|
| 1     | Piv | MeOH          | 84              | 8.3 : 1|
| 2     | Piv | DCM           | 46              | 5.6 : 1|
| 3     | Piv | MeCN          | 27              | 8.0 : 1|
| 4     | Piv | HFIP          | 0               | —      |
| 5     | Piv | Toluene       | 71              | 10.8 : 1|
| 6     | Piv | IPA           | 88              | 8.7 : 1|
| 7     | Piv | Hexafluorobenzene | 48          | 5 : 1  |
| 8     | Piv | MeOH (1.2 styrene) | 86       | 8.6 : 1|
| 9     | Piv | MeOH (1.5 styrene) | 93       | 6.8 : 1|
| 10    | Piv | MeOH (40 °C)  | 69              | 12.8 : 1|
| 11    | Boc | MeOH (2.0 styrene) | 70       | >99:1  |
| 12    | Boc | MeOH (1.5 styrene) | 69b    | >99:1  |
| 13    | Boc | MeOH (40 °C)  | 71              | >99:1  |
| 14    | Boc | TFE           | 73              | >99:1  |
| 15    | Boc | DCM           | 43              | >99:1  |
| 16    | Boc | TFE/DCM (1:1) | 41              | >99:1  |

[a] Determined by NMR using 1,3,5-trimethoxybenzene as internal standard (1.0 equiv). [b] Isolated yield

2.2 Base Screen

| Entry | R  | Solvent | Base       | Yield (%) |
|-------|----|---------|------------|-----------|
| 1     | Boc | MeOH    | CsOPiv     | 63        |
| 2     | Boc | MeOH    | KOPiv      | 60        |
| 3     | Boc | MeOH    | K₂CO₃      | 19        |
| 4     | Boc | MeOH    | CsOAc      | 77        |
| 5     | Boc | MeOH    | KOAc       | 84        |
| 6     | Boc | MeOH    | --         | 0         |
2.3 Cyclization step screen

| Entry | Solvent | Temp. (°C) | Base | Base equiv. | Conc. [M] | Time (mins) | Yield (%)<sup>a</sup> |
|-------|---------|------------|------|-------------|-----------|-------------|-----------------------|
| 1     | THF     | RT         | KOTBu in THF | 2.0      | 0.05      | 10          | 50                    |
| 2     | MeCN    | RT         | KOtBu    | 2.0      | 0.05      | 10          | 28                    |
| 3     | DCM     | RT         | KOtBu    | 2.0      | 0.05      | 10          | 53                    |
| 4     | DMSO    | 50         | KOtBu    | 2.0      | 0.05      | 10          | -                     |
| 5     | THF     | 60         | KOTBu in THF | 2.0      | 0.05      | 10          | 10                    |
| 6     | THF     | RT         | KOTBu in THF | 1.0      | 0.05      | 10          | 29                    |
| 7     | DCM     | RT         | KOtBu    | 1.0      | 0.05      | 10          | 32                    |
| 8     | DCM     | RT         | KOtBu    | 2.0      | 0.10      | 10          | 60                    |
| 9     | DCM     | RT         | KOtBu    | 2.0      | 0.25      | 10          | 63                    |
| 10    | DCM     | RT         | KOTBu    | 3.0      | 0.05      | 30          | 67<sup>b</sup>        |
| 11    | DCM     | RT         | KOTBu    | 4.0      | 0.05      | 10          | 52                    |

[a] Determined by NMR using 1,3,5-trimethoxybenzene as internal standard (1.0 equiv). [b] Isolated yield
3. General procedures and analytical data

3.1 General Procedure for the synthesis of OBoc-aryl-hydroxamates 1

Following a modified procedure by Fagnou et al. [3], a flask was charged with hydroxylamine hydrochloride (1.5 equiv.), potassium carbonate (2.0 equivalent) and solvent (EtOAc/water; 2:1). The reaction was cooled to 0 °C with vigorous stirring before dropwise addition of acid chloride (1 equiv.) dissolved in EtOAc (2 ml). The reaction was stirred at RT for 14 h. The reaction mixture was diluted with water and extracted with EtOAc (2 x 20 ml). The combined organic layers were washed with brine (10 ml), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude hydroxamic acid was used in the next step without further purification.

The hydroxamic acid (1.0 equiv.), NaOtBu (5 mol%) and di-tert-butyl dicarbonate (1.2 equiv.) were dissolved in DCM [0.5 M]. The mixture was stirred at RT for 14 h. The reaction mixture was quenched with saturated NaHCO₃ solution (10 ml) and extracted with DCM (2x 10 ml). The organic layer was dried over Na₂SO₄, concentrated in vacuo, and then purified by silica gel chromatography (Pent/EtOAc, 5:1) to give the title products 1.

All the aryl-hydroxamates are reported and their characterization matches the literature. [4]

3.2 General Procedure for the synthesis of styrenes 2

According to the reported procedure [5], a 100 mL round bottom flask was charged with 2-bromostyrene (1.0 eq.) and THF [0.2M]. The solution was then cooled to -78 °C and n-BuLi (1.2 eq., 1.6 M solution in hexanes) was added dropwise. The resulting mixture was then stirred at -78 °C for 1 h. Ethylene oxide (3.0 eq., 2.5 M solution in THF) was then added to the reaction mixture and stirred for an additional 0.5 h at -78 °C. The reaction was then warmed to RT and stirred for 14 h. A saturated solution of NH₄Cl (10 mL) was added, and the aqueous layer washed with Et₂O (3 x 25 mL). The combined organic layers were
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dried over Na₂SO₄, filtered and concentrated in vacuo to afford the corresponding alcohol which was used in the next step without further purification.

The resulting alcohol (1.0 equiv.) and triethylamine (1.1 equiv.) were dissolved in DCM [0.01M] and cooled to 0°C. Then MsCl (1.1 equiv.) was added dropwise and the reaction was stirred at RT for 12h. The solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography (Pent/EtOAc, 4:1) to afford the title styrenes 2.

Some of the styrenes are reported and our characterization matches the literature. [6]

2-vinylphenethyl methanesulfonate (2a)

![Chemical Structure](attachment:image)

Colourless oil, 78% yield. ¹H-NMR (400 MHz – CDCl₃): δ 7.56 – 7.46 (m, 1H), 7.29 – 7.25 (m, 1H), 7.25 – 7.22 (m, 1H), 7.21 – 7.18 (m, 1H), 6.97 (dd, J = 17.3, 11.0 Hz, 1H), 5.68 (dd, J = 17.3, 1.3 Hz, 1H), 5.37 (dd, J = 11.0, 1.3 Hz, 1H), 4.36 (t, J = 7.2 Hz, 2H), 3.15 (t, J = 7.2 Hz, 2H), 2.83 (s, 3H); ¹³C-NMR (101 MHz – CDCl₃): δ 137.3, 134.0, 133.4, 130.5, 128.2, 127.7, 126.4, 117.0, 69.6, 37.4, 33.1; HR-MS: calc. for [M+H]+ C₁₁H₁₅O₃S: 227.07364, found: 227.07423

5-methyl-2-vinylphenethyl methanesulfonate (2b)

![Chemical Structure](attachment:image)

Colourless oil, 70% yield. ¹H-NMR (500 MHz - CD₂Cl₂): δ 7.43 (d, J = 7.9 Hz, 1H), 7.11 – 7.04 (m, 1H), 7.03 (d, J = 1.7 Hz, 1H), 6.95 (dd, J = 17.3, 10.9 Hz, 1H), 5.65 (dd, J = 17.3, 1.3 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.32 (t, J = 7.2 Hz, 2H), 3.10 (t, J = 7.2 Hz, 2H), 2.82 (s, 3H), 2.32 (s, 3H); ¹³C-NMR (126 MHz - CD₂Cl₂): δ 138.52, 134.71, 134.22, 133.90, 131.57, 128.81, 126.42, 116.00, 70.54, 37.60, 33.38, 21.31; HR-MS: calc. for [M+H]+ C₁₂H₁₇O₃S: 241.08929, found: 241.08939.

2-(6-vinylbenzo[d][1,3]dioxol-5-yl)ethyl methanesulfonate (2c)

![Chemical Structure](attachment:image)

Colourless oil, 40% yield. ¹H-NMR (500 MHz - CD₂Cl₂): δ 6.99 (s, 1H), 6.86 (dd, J = 17.2, 10.9 Hz, 1H), 6.66 (s, 1H), 5.95 (s, 2H), 5.55 (dd, J = 17.2, 1.1 Hz, 1H), 5.26 (dd, J = 10.9, 1.1 Hz, 1H), 4.30 (t, J = 7.2 Hz, 2H), 3.06 (t, J = 7.2 Hz, 2H), 2.89 (s, 3H); ¹³C-NMR (126 MHz - CD₂Cl₂): δ 147.6, 147.4,
133.4, 130.9, 127.3, 115.2, 110.2, 106.0, 101.3, 69.6, 37.5, 33.0; HR-MS: calc. for [M+H]^+ C_{12}H_{15}O_5S: 271.06347, found: 271.06357.

4-(trifluoromethyl)-2-vinylphenethyl methanesulfonate (2d)

![Chemical Structure of 2d]

Colourless oil, 52% yield. $^1$H-NMR (400 MHz - CDCl$_3$): $\delta$ 7.66 (s, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.03 (d, J = 1.7 Hz, 1H), 6.95 (dd, J = 17.3, 10.9 Hz, 1H), 5.65 (dd, J = 17.3, 1.3 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.32 (t, J = 7.2 Hz, 2H), 3.10 (t, J = 7.2 Hz, 2H), 2.82 (s, 3H); $^{13}$C-NMR (101 MHz - CDCl$_3$): $\delta$ 137.96, 137.23, 132.85, 130.78, 129.90, 124.55, 124.52, 123.29, 123.26, 118.80, 68.54, 37.48, 32.93.; $^{19}$F-NMR (470 MHz, CDCl$_3$): $\delta$ = -62.68.

2-(vinyl-2,2-d$_2$)phenethyl-d$_2$ 4-methylbenzenesulfonate (2')

![Chemical Structure of 2']

Colourless oil, 75% yield (90% D). $^1$H-NMR (500 MHz - CDCl$_3$): $\delta$ 7.66 – 7.59 (m, 2H), 7.34 (dd, J = 7.6, 1.5 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.14 (td, J = 7.5, 1.4 Hz, 1H), 7.10 (td, J = 7.4, 1.5 Hz, 1H), 7.01 (dd, J = 7.5, 1.4 Hz, 1H), 6.76 – 6.70 (m, 1H), 4.12 – 4.01 (m, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.37 (s, 3H); $^{13}$C-NMR (126 MHz - CDCl$_3$): $\delta$ 144.66, 144.62, 137.09, 133.72, 133.69, 133.61, 133.37, 133.17, 132.98, 130.27, 129.83, 129.82, 129.77, 127.97, 127.88, 127.84, 127.44, 127.17, 126.20, 126.19, 70.19, 69.78, 66.80, 32.80, 32.10, 21.63, 14.73.
3.3 General Procedure for the synthesis of 3-Isoindolinones 3

In a dram vial equipped with a stirring bar was added \([\text{RhCp}^*\text{Cl}_2\text{]}_2\) (1.0 mol%), KOAc (0.025 mmol, 0.25 eq.), \(N-((\text{tert}-\text{butylocarbonyl})\text{oxy})\text{aryl-hydroxamate substrate (1)}\) (0.1 mmol, 1.0 eq.) and dry MeOH [0.1 M]. The mixture was stirred for 30 seconds before the addition of the alkene substrate (2), (0.15 mmol, 1.5 eq.). The reaction was left to stir at room temperature for 16 h. The solvent was then evaporated under reduced pressure and the crude mixture was purified by silica gel chromatography using DCM to DCM: DMA* (10:1) as eluent to afford the title 3-Isoindolinones 3.

*DMA: is a mixture of DCM:MeOH:NH₃ (100:5:0.15).

2-((3-oxoisooindolin-1-yl)methyl)phenethyl methanesulfonate (3a)

Colourless oil, 74% yield. \(^1\)H-NMR (500 MHz - CDCl₃): \(\delta\) 7.86 (d, \(J = 7.3\), 1.0 Hz, 1H), 7.58 (td, \(J = 7.5, 1.2\) Hz, 1H), 7.51 (t, 1H), 7.39 (d, \(J = 7.6\), 0.9 Hz, 1H), 7.30 – 7.26 (m, 4H), 6.40 (br s, 1H, NH), 4.80 (dd, \(J = 9.7, 4.9\) Hz, 1H), 4.43 – 4.29 (m, 2H), 3.36 (dd, \(J = 14.0, 4.9\) Hz, 1H), 3.13 (t, 2H), 2.91 (s, 3H), 2.81 (dd, \(J = 9.2, 4.8\) Hz, 1H); \(^13\)C-NMR (125 MHz - CDCl₃): \(\delta\) 170.36, 146.80, 135.87, 134.68, 132.18, 131.73, 130.66 (2C), 128.74, 128.00, 127.98, 124.16, 122.91, 69.71, 57.64, 38.18, 37.60, 32.75; FT-IR: \(\tilde{\nu} = 3245, 2514, 2159, 2030, 1976, 1690, 1468, 1346, 1168, 947\) cm\(^{-1}\); HR-MS: calc. for [M+H]\(^+\) C\(_{18}\)H\(_{20}\)O\(_4\)NS 346.1107, found: 346.1108.

3-(2-(2-hydroxyethyl)benzyl)isoindolin-1-one (3b)

Red solid, 49% yield. \(^1\)H-NMR (400 MHz - CDCl₃): \(\delta\) 7.80 (dt, \(J = 7.5, 1.0\) Hz, 1H), 7.60 – 7.40 (m, 2H), 7.34 (d, \(J = 7.6\) Hz, 1H), 7.26 – 7.13 (m, 4H), 7.11 (s, 1H), 4.77 (dd, \(J = 9.6, 4.7\) Hz, 1H), 3.86 (tp, \(J = 7.7, 3.6\) Hz, 2H), 3.27 (dd, \(J = 14.0, 4.7\) Hz, 1H), 2.98 – 2.75 (m, 3H); \(^13\)C-NMR (100 MHz - CDCl₃): \(\delta\) 161.51, 147.07, 137.32, 135.97, 131.90, 130.52, 130.38, 130.15, 128.84, 128.46, 127.55, 127.43,
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126.96, 123.98, 122.68, 63.17, 58.25, 38.16, 35.14; **FT-IR**: \( \tilde{\nu} = 3059, 2348, 1680, 1542, 1492, 1449, 1153, 1094, 1062, 1011, 856 \text{ cm}^{-1}; \)** **LC-MS**: calc. for [M+H]^+ C_{17}H_{17}O_2N 268.1, found: 268.1.

2-((3-oxoisoindolin-1-yl)methyl)phenethyl acetate (3c)

Red oil, 63% yield. **\(^1\)H-NMR (400 MHz - CDCl\(_3\))**: \( \delta 7.79 \) (d, \( J = 7.3, 1.0 \text{ Hz}, 1\text{H} \)), 7.48 (td, \( J = 7.5, 1.2 \text{ Hz}, 1\text{H} \)), 7.42 (t, 1\text{H} ), 7.30 (d, \( J = 7.7 \text{ Hz}, 1\text{H} \)), 7.20 – 7.11 (m, 4\text{H} ), 6.47 (br s, 1\text{H}, NH), 4.73 (dd, \( J = 9.5, 4.9 \text{ Hz}, 1\text{H} \)), 4.17 – 4.11 (m, 2\text{H} ), 3.32 (dd, \( J = 14.0, 4.9 \text{ Hz}, 1\text{H} \)), 2.91 (t, 2\text{H} ), 2.75 (dd, \( J = 9.2, 4.8 \text{ Hz}, 1\text{H} \)), 1.93 (s, 3\text{H} ); \(^{13}\)C-NMR (101 MHz - CDCl\(_3\)): \( \delta 171.08, 170.33, 146.88, 135.92, 135.70, 131.95, 131.73, 130.46, 130.40, 128.83, 128.51, 127.64, 127.44, 127.39, 124.01, 122.78, 119.50, 64.50, 57.62, 38.16, 31.94, 20.98; **FT-IR**: \( \tilde{\nu} = 3045, 2486, 2159, 1976, 1690, 1468, 1289, 1163, 973 \text{ cm}^{-1}; \)** **LC-MS**: calc. for [M+H]^+ C_{19}H_{19}O_3N 309.3, found: 309.3.

3-((2-((triisopropylsilyl)oxy)ethyl)benzyl)isoindolin-1-one (3d)

Red oil, 58% yield. **\(^1\)H-NMR (500 MHz - CDCl\(_3\))**: \( \delta 7.83 – 7.78 \) (m, 1\text{H} ), 7.57 – 7.3 (m, 3\text{H} ), 7.39 – 7.11 (m, 4\text{H} ), 6.31 (s, 1\text{H} ), 4.76 (dd, \( J = 10.1, 4.9 \text{ Hz}, 1\text{H} \)), 3.81 (t, 1\text{H}, J = 7.0 Hz, 2\text{H} ), 3.32 (dd, \( J = 13.8, 4.8 \text{ Hz}, 1\text{H} \)), 2.86 (td, 1\text{H}, J = 6.9, 2.1 Hz, 2\text{H} ), 2.71 (dd, \( J = 13.9, 10.1 \text{ Hz}, 1\text{H} \)), 1.05 – 0.96 (m, 3\text{H} ), 0.99 – 0.78 (m, 18\text{H} ); \(^{13}\)C-NMR (125 MHz - CDCl\(_3\)): \( \delta 170.21, 147.00, 137.74, 135.64, 131.97, 131.57, 130.68, 130.02, 129.17, 128.85, 128.51, 127.47, 126.89, 124.06, 122.66, 64.50, 57.79, 38.41, 36.15, 17.93, 17.71, 13.67, 11.89.; **FT-IR**: \( \tilde{\nu} = 3023, 2861, 1683, 1545, 1294, 1175, 1065, 1013, 849 \text{ cm}^{-1}; \)** **LC-MS**: calc. for [M+H]^+ C_{26}H_{37}O_2NSi 432.2, found: 432.2.

4-methyl-N-((3-oxoisoindolin-1-yl)methyl)phenethyl)benzenesulfonamide (3e)
Red oil, 87% yield. $^1$H-NMR (400 MHz - CDCl$_3$): $\delta$ 7.74 (dd, $J = 7.0$, 1.3 Hz, 1H), 7.64 – 7.52 (m, 2H), 7.41 (dd, $J = 22.8$, 7.4, 1.2 Hz, 3H), 7.21 (d, $J = 7.4$ Hz, 1H), 7.16 – 7.08 (m, 2H), 7.12 – 7.01 (m, 3H), 6.88 (s, 1H), 5.56 (t, $J = 6.2$ Hz, 1H), 4.62 (dd, $J = 8.9$, 5.6 Hz, 1H), 3.12 (dd, $J = 13.8$, 5.6 Hz, 1H), 3.09 – 2.96 (m, 2H), 2.91 – 2.75 (m, 2H), 2.28 (s, 3H); $^{13}$C-NMR (101 MHz - CDCl$_3$): $\delta$ 170.65, 146.91, 143.36, 137.04, 136.57, 135.48, 132.09, 131.90, 131.66, 130.61, 130.10, 129.71, 128.11, 128.44, 127.65, 127.42, 127.24, 127.00, 123.91, 122.95, 57.68, 53.47, 43.86, 38.01, 33.17, 21.49; FT-IR: $\tilde{\nu} = 3592$, 3057, 1681, 1486, 1320, 1152, 1017, 866, 815 cm$^{-1}$; LC-MS: calc. for [M+H]$^+$ C$_{24}$H$_{24}$O$_3$N$_2$S 421.1, found: 421.1.

4-methyl-N-(2-((3-oxo-2,3-dihydro-1H-benzo[f]isoindol-1-yl)methyl)phenethyl)benzenesulfonamide (3f)

Red solid, 48% yield. $^1$H-NMR (500 MHz - CDCl$_3$): $\delta$ 8.33 (d, $J = 4.8$ Hz, 1H), 7.94 (d, $J = 8.2$ Hz, 1H), 7.81 (d, $J = 8.2$ Hz, 1H), 7.76 (s, 1H), 7.70 – 7.61 (m, 4H), 7.59 – 7.48 (m, 3H), 7.19 – 7.03 (m, 5H), 4.89 (d, $J = 7.0$ Hz, 1H), 3.21 (dd, $J = 13.7$, 5.8 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.92 (dt, $J = 55.9$, 7.9 Hz, 3H), 2.27 (s, 3H); $^{13}$C-NMR (125 MHz - CDCl$_3$): $\delta$ 170.61, 143.35, 141.50, 136.97, 136.72, 135.27, 132.94, 130.83, 130.17, 129.70, 129.63, 128.96, 128.26, 128.09, 127.79, 127.22, 127.01, 126.61, 124.63, 122.15, 58.03, 43.95, 38.54, 33.18, 29.73, 21.47; FT-IR: $\tilde{\nu} = 3630$, 3057, 2549, 2148, 1685, 1492, 1321, 1207, 1073, 1017, 956, 905, 814 cm$^{-1}$; LC-MS: calc. for [M+H]$^+$ C$_{28}$H$_{26}$O$_3$N$_2$S 471.1, found: 471.1.

N-(2-((6-chloro-3-oxoisooindolin-1-yl)methyl)phenethyl)-4-methylbenzenesulfonamide (3g)

Yellow oil, 28% yield. $^1$H-NMR (500 MHz - CDCl$_3$): $\delta$ 7.74 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 8.1$ Hz, 2H), 7.46 (dd, $J = 8.0$, 1.7 Hz, 1H), 7.32 (d, $J = 1.7$ Hz, 1H), 7.25 – 7.19 (m, 4H), 7.16 (ddd, $J = 15.4$, 6.8, 2.1 Hz, 2H), 6.70 (s, 1H), 5.07 (s, 1H), 4.70 (dd, $J = 9.4$, 5.4 Hz, 1H), 3.21 (dd, $J = 14.0$, 5.4 Hz, 1H), 3.15 (dt, $J = 9.8$, 7.3 Hz, 2H), 2.88 (t, $J = 7.4$ Hz, 2H), 2.78 (dd, $J = 14.0$, 9.3 Hz, 1H), 2.38 (s, 3H); $^{13}$C-NMR (125 MHz - CDCl$_3$): $\delta$ 168.34, 147.35, 142.51, 137.43, 135.94, 135.41, 134.01, 129.54, 129.17, 129.02, 128.73 (2C), 128.13, 126.92, 126.42, 125.97 (2C), 124.20, 122.40, 56.29, 42.79, 36.86, 32.19,
Supporting Information

20.47; FT-IR: \(\tilde{\nu} = 3182, 2514, 2360, 2159, 2030, 1977, 1692, 1327, 1155, 925\) cm\(^{-1}\); HR-MS: calc. for [M+H]\(^+\) C\(_{24}\)H\(_{22}\)O\(_3\)N\(_2\)SCl 455.1190, found: 455.1189.

2-((6-fluoro-3-oxoisoindolin-1-yl)methyl)phenethyl methanesulfonate (3h)

![Chemical structure of 3h](image)

Colourless oil, 61% yield. \(^1\)H-NMR (500 MHz - CDCl\(_3\)): \(\delta 7.83 (dd, J = 8.4, 5.0\) Hz, 1H), 7.33 – 7.23 (m, 4H), 7.19 (td, J = 8.7, 2.2 Hz, 1H), 7.06 (dd, J = 8.2, 2.2 Hz, 1H), 6.39 (br s, 1H, NH), 4.77 (dd, J = 9.6, 5.0 Hz, 1H), 4.43 – 4.31 (m, 2H), 3.32 (dd, J = 14.0, 5.1 Hz, 1H), 3.13 (t, J = 7.8, 6.8 Hz, 2H), 2.93 (s, 3H), 2.87 – 2.77 (m, 1H); \(^13\)C-NMR (125 MHz - CDCl\(_3\)): \(\delta 169.29, 166.46, 164.46, 149.23, 135.45, 134.68, 130.70, 128.15, 128.07, 127.80, 126.24, 116.57, 110.43, 69.64, 57.26, 38.07, 37.66, 32.81; \(^19\)F-NMR (470 MHz, CDCl\(_3\)): \(\delta = -106.13\) (q, J = 7.6); HR-MS: calc. for [M+H]\(^+\) C\(_{18}\)H\(_{19}\)O\(_4\)NFS 364.1013, found: 364.1013.

2-((6-chloro-3-oxoisoindolin-1-yl)methyl)phenethyl methanesulfonate (3i)

![Chemical structure of 3i](image)

Yellow solid, 77% yield. \(^1\)H-NMR (500 MHz - CDCl\(_3\)): \(\delta 7.78 (d, J=8.1\) Hz, 1H), 7.48 (dd, J=8.1, 1.7 Hz, 1H), 7.39 (d, J=1.7 Hz, 1H), 7.34 – 7.27 (m, 4H), 6.27 (br s, 1H, NH), 4.78 (dd, J=9.9, 4.9 Hz, 1H), 4.43 – 4.35 (m, 2H), 3.34 (dd, J=14.0, 4.9 Hz, 1H), 3.14 (t, J=7.3 Hz, 2H), 2.94 (s, 3H), 2.84 – 2.78 (m, 1H); \(^13\)C-NMR (125 MHz - CDCl\(_3\)): \(\delta 169.04, 148.21, 138.50, 135.31, 134.59, 130.58, 130.52, 130.12, 129.26, 128.07, 127.97, 125.32, 123.34, 69.48, 57.13, 37.97, 37.56, 32.65; FT-IR: \(\tilde{\nu} = 3199, 2507, 2360, 2159, 2029, 1977, 1708, 1376, 1162, 946\) cm\(^{-1}\); HR-MS: calc. for [M+H]\(^+\) C\(_{18}\)H\(_{19}\)O\(_4\)NSCl 382.0685, found: 382.0688.

2-((6-methyl-3-oxoisoindolin-1-yl)methyl)phenethyl methanesulfonate (3j)
Colourless oil, 61% yield. \(^1\)H-NMR (500 MHz - CDCl\(_3\)): \(\delta\) 7.73 (d, J=7.8 Hz, 1H), 7.33 – 7.30 (d, 1H), 7.28 (m, 4H), 7.21 (d, J=1.6 Hz, 1H), 6.25 (br s, 1H, NH), 4.74 (dd, J=10.0, 4.6 Hz, 1H), 4.37 (m, 2H), 3.35 (dd, J=14.0, 4.6 Hz, 1H), 3.13 (t, J=7.3 Hz, 2H), 2.91 (s, 3H), 2.75 (dd, J=14.0, 10.0 Hz, 1H), 2.47 (s, 3H); \(^13\)C-NMR (125 MHz - CDCl\(_3\)): \(\delta\) 170.47, 147.27, 142.97, 136.02, 134.68, 130.63, 130.59, 129.74, 129.11, 127.99, 127.94, 123.35, 69.73, 57.48, 38.26, 37.57, 32.69, 22.13; FT-IR: \(\tilde{\nu}\) = 3232, 2513, 2159, 2029, 1977, 1690, 1618, 1346, 1168, 947 cm\(^{-1}\); HR-MS: calc. for [M+H]\(^+\) C\(_{19}\)H\(_{22}\)O\(_4\)NS 360.1264, found: 360.1264.

2-((3-oxo-2,3-dihydro-1H-benzo[f]isoindol-1-yl)methyl)phenethyl methanesulfonate (3k)

Yellow oil, 74% yield. \(^1\)H-NMR (500 MHz - CDCl\(_3\)): \(\delta\) 8.40 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.62 (td, J = 8.2, 6.8, 1.4 Hz, 1H), 7.58 (td, J = 8.1, 6.8, 1.4 Hz, 1H), 7.31 (d, J = 2.5 Hz, 4H), 6.56 (br s, 1H, NH), 4.97 (dd, J = 9.7, 4.9 Hz, 1H), 4.47 – 4.30 (m, 2H), 3.46 (dd, J = 14.0, 4.9 Hz, 1H), 3.23 – 3.11 (m, 2H), 2.92 (dd, 1H), 2.91 (s, 3H); \(^13\)C-NMR (125 MHz - CDCl\(_3\)): \(\delta\) 170.13, 141.45, 135.67, 135.32, 134.64, 133.08, 130.63, 130.58, 129.67, 129.18, 128.26, 128.09, 127.96 (2C), 126.68, 124.64, 121.93, 69.62, 57.56, 38.78, 37.49, 32.67; FT-IR: \(\tilde{\nu}\) = 3189, 2928, 2522, 2362, 2159, 2029, 1977, 1690, 1639, 1342, 1178 cm\(^{-1}\); HR-MS: calc. for [M+H]\(^+\) C\(_{22}\)H\(_{22}\)O\(_4\)NS 396.1264, found: 396.1260.

2-((5-methyl-3-oxoisooindolin-1-yl)methyl)phenethyl methanesulfonate (3l)

Colourless oil, 80% yield. \(^1\)H-NMR (500 MHz - CDCl\(_3\)): \(\delta\) 7.64 (d, J = 1.7 Hz, 1H), 7.36 (dd, J = 7.7, 1.6 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.23 (m, 3H), 7.21 (d, J = 7.7 Hz, 1H), 6.58 (br s, 1H, NH), 4.75 (dd, J = 9.5, 5.2 Hz, 1H), 4.34 (m, 2H), 3.28 (dd, J = 14.0, 5.2 Hz, 1H), 3.10 (t, J = 7.3 Hz, 2H), 2.89 (s, 3H), 2.81 (dd, J = 14.0, 9.4 Hz, 1H); \(^13\)C-NMR (125 MHz - CDCl\(_3\)): \(\delta\) 170.61, 144.15, 138.82, 135.93, 134.72, 133.16, 131.82, 130.65, 130.60, 127.94, 127.89, 124.32, 122.64, 69.71, 57.57, 38.24, 37.57, 32.72, 21.48; FT-IR: \(\tilde{\nu}\) = 3189, 2522, 2362, 2159, 2029, 1977, 1690, 1343, 1168, 947 cm\(^{-1}\); HR-MS: calc. for [M+H]\(^+\) C\(_{19}\)H\(_{22}\)O\(_4\)NS 360.1264, found: 360.1264.

2-((5-chloro-3-oxoisooindolin-1-yl)methyl)phenethyl methanesulfonate (3m)
A mixture of regioisomers (1:1.3) were isolated as a colourless oil (81%).

Major isomer: $^1$H-NMR (500 MHz - CDCl$_3$): δ 7.75 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.27 (m, 3H), 7.24 (m, 1H), 6.47 (br s, 1H, NH), 4.83 (dd, J = 10.4, 3.1 Hz, 1H), 4.43 (t, J = 7.1 Hz, 2H), 3.98 (dd, J = 14.2, 3.1 Hz, 1H), 3.22 (m, 2H), 2.92 (s, 3H), 2.56 (dd, J = 14.1, 10.3 Hz, 1H); $^{13}$C-NMR (125 MHz - CDCl$_3$): δ 167.75, 142.53, 134.60, 133.80, 133.17, 132.48, 131.69, 129.52, 129.29, 128.42, 126.87, 126.82, 121.64, 68.63, 56.31, 36.37, 34.61, 31.36; FT-IR: ν = 3198, 2515, 2360, 2159, 2028, 1977, 1693, 1344, 1166, 947 cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{18}$H$_{18}$O$_4$NSCl 382.0685, found: 382.0688.

Minor isomer: $^1$H-NMR (500 MHz - CDCl$_3$): δ 7.80 (d, J = 1.9 Hz, 1H), 7.52 (dd, J = 9.4, 5.3 Hz, 1H), 7.27 (m, 3H), 7.24 (m, 2H), 6.63 (br s, 1H, NH), 4.78 (dd, J = 9.7, 4.9 Hz, 1H), 4.36 (m, 2H), 3.30 (dd, J = 14.2, 5.0 Hz, 1H), 3.11 (t, J = 7.3 Hz, 2H), 2.92 (s, 3H), 2.84 (dd, J = 14.4, 9.1 Hz, 1H); $^{13}$C-NMR (125 MHz - CDCl$_3$): δ 167.81, 143.75, 134.36, 133.87, 133.56, 131.13, 129.59 (2C), 129.56, 126.96, 126.89 – 126.88 (m), 123.16, 123.15, 68.53, 56.27, 36.94, 36.50, 31.67; FT-IR: ν = 3198, 2515, 2360, 2159, 2028, 1977, 1693, 1344, 1166, 947 cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{18}$H$_{19}$O$_6$NS 390.1007, found: 390.1005.

2-(6-((3-oxoisooindolin-1-yl)methyl)benzo[d][1,3]dioxol-5-yl)ethyl methanesulfonate (3n)

Colourless oil, 40% yield. $^1$H-NMR (500 MHz - CDCl$_3$): δ 7.86 (d, J = 7.5, 1.2 Hz, 1H), 7.59 (t, J = 7.5, 1.2 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.6, 1.0 Hz, 1H), 6.73 (d, J = 2.0 Hz, 2H), 6.41 (br s, 1H, NH), 5.98 – 5.96 (m, 2H), 4.75 (dd, J = 9.7, 4.9 Hz, 1H), 4.35 – 4.23 (m, 2H), 3.25 (dd, J = 14.2, 5.0 Hz, 1H), 3.02 (t, J = 7.3 Hz, 2H), 2.96 (s, 3H), 2.71 (dd, J = 14.2, 9.7 Hz, 1H); $^{13}$C-NMR (125 MHz - CDCl$_3$): δ 169.24, 146.21, 146.19, 145.55, 131.14, 130.46, 127.81, 127.64, 126.65, 123.08, 121.73, 109.19, 109.14, 100.35, 68.50, 56.82, 36.94, 36.55, 31.64; FT-IR: ν = 3182, 2516, 2159, 2030, 1977, 1694, 1502, 1485, 1367, 1276, 1166, 1039, 976 cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{19}$H$_{20}$O$_6$NS 390.1007, found: 390.1005.
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4-methoxy-2-((3-oxoisooindolin-1-yl)methyl)phenethyl 4-methylbenzenesulfonate (3o)

![Chemical Structure](image)

Pink oil, 55% yield. $^{1}$H-NMR (600 MHz - CDCl$_3$): δ 7.81 (d, J = 7.5, 1.2 Hz, 1H), 7.60 (d, J = 7.4 Hz, 2H), 7.52 (t, J = 7.5, 1.2 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.29 – 7.18 (m, 1H), 7.16 – 6.99 (m, 2H), 6.81 (d, J = 2.0 Hz, 2H), 6.73, (d, J = 7.5 Hz, 1H), 6.66 (br s, 1H, NH), 4.69 (dd, J = 9.7, 4.9 Hz, 1H), 4.07 – 4.05 (m, 2H), 3.72 (s, 3H), 3.58 (dd, J = 14.2, 5.0 Hz, 1H), 3.02 (t, J = 7.3 Hz, 1H), 2.89 – 2.68 (m, 2H), 2.32 (s, 3H); $^{13}$C-NMR (167 MHz - CDCl$_3$): δ 170.52, 158.90, 146.68, 144.86, 136.67, 132.91, 132.41, 131.59, 131.04, 129.83, 128.85, 128.74, 127.76, 127.44, 126.49, 124.18, 122.84, 115.80, 113.20, 70.21, 68.12, 58.12, 55.35, 38.07, 31.65, 31.45, 29.71, 21.63; FT-IR: ν = 2923, 1684, 1609, 1466, 1291, 1188, 1096, 1010, 897, 814 cm$^{-1}$; LC-MS: calc. for [M+H]$^+$ C$_{25}$H$_{25}$O$_5$NS 452.3, found: 452.3.

2-((6-nitro-3-oxoisooindolin-1-yl)methyl)phenethyl methanesulfonate (3p)

![Chemical Structure](image)

Yellow solid, 18% yield. $^{1}$H-NMR (500 MHz - CDCl$_3$): δ 8.39 (dd, J = 8.2, 2.0 Hz, 1H), 8.29 – 8.25 (m, 1H), 8.01 (d, J = 8.3, 0.6 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.26 – 7.23 (m, 1H), 6.50 (br s, 1H, NH), 4.91 (dd, J = 9.7, 5.0 Hz, 1H), 4.45 – 4.37 (m, 2H), 3.43 (dd, J = 14.0, 5.1 Hz, 1H), 3.16 (t, J = 7.3 Hz, 2H), 2.97 (s, 3H), 2.89 – 2.85 (m, 1H); $^{13}$C-NMR (125 MHz - CDCl$_3$): δ 167.60, 150.44, 147.44, 137.06, 134.80, 134.61, 128.10, 125.24, 124.32, 118.67, 69.44, 57.41, 37.83, 37.62, 32.73; FT-IR: ν = 3192, 2929, 2523, 2360, 2159, 2030, 1977, 1715, 1690, 1525, 1342, 1163, 976 cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{18}$H$_{19}$O$_6$S$_2$ 391.0959, found: 391.0958.

2-((3-oxoisooindolin-1-yl-1-d)methyl-d2)phenethyl-d2 4-methylbenzenesulfonate (3q)
SUPPORTING INFORMATION

Colorless oil, 67% yield. $^1$H-NMR (600 MHz - CDCl$_3$): $\delta$ 7.76 (d, $J = 7.5$, 1.2 Hz, 1H), 7.59 (d, $J = 7.4$ Hz, 2H), 7.49 – 7.39 (m, 2H), 7.19 – 7.08 (m, 6H), 6.57 (br s, 1H, NH), 4.14 – 4.04 (m, 2H), 3.12 (s, 1H), 2.96 – 2.92 (m, 2H), 2.35 (dd, $J = 14.2$, 5.0 Hz, 1H), 2.32 (s, 3H); $^{13}$C-NMR (151 MHz - CDCl$_3$): $\delta$ 170.47, 146.67, 144.90, 144.66, 135.62, 134.64, 133.59, 133.16, 132.90, 132.82, 131.97, 131.70, 130.45, 130.38, 130.27, 129.86, 129.79, 128.78, 128.55, 127.97, 127.87, 127.82, 127.75, 127.73, 127.65, 127.44, 126.19, 123.97, 122.82, 119.31, 77.29, 69.99, 69.81, 66.84, 32.78, 32.28, 21.63, 14.73; FT-IR: $\tilde{\nu} = 3061, 1684, 1692, 1597, 1493, 1354, 1188, 1095, 1010, 960, 815$ cm$^{-1}$; LC-MS: calc. for [M+H]$^+$ C$_{24}$H$_{21}$D$_2$O$_2$NS 424.1, found: 424.1.

3.4 General Procedure for the synthesis of Isoindolobenzazepine scaffolds 4

In a dram vial equipped with a stirring bar was added [RhCp$^\ast$Cl$_2$]$_2$ (1.0 mol%), KOAc (0.0025 mmol, 0.25 eq.), N-((tert-butoxycarbonyl)oxy)aryl-hydroxamate substrate (1) (0.1 mmol, 1.0 eq.) and dry MeOH [0.1 M]. The mixture was stirred for 30 seconds before the addition of the alkene substrate (2), (0.15 mmol, 1.5 eq.). The reaction was left to stir at room temperature for 16 h. The solvent was then evaporated under reduced pressure. Dry DCM [0.05 M] was added to the crude mixture followed by rBuOK (0.30 mmol, 3.0 eq.). The reaction mixture was stirred for 30 minutes at room temperature. The reaction was then quenched with H$_2$O and extracted with DCM (2 x 5 mL). The organic layer was washed with brine, dried over MgSO$_4$, filtered, and the solvent was evaporated. The crude material was purified by silica gel chromatography (Pent/EtOAc, 4:1) to afford the title compounds 4.

8,13-dihydro-6,13-methanodibenzo[c,f]azonin-5(7H)-one (4a)

White solid, 79% yield. $^1$H-NMR (500 MHz - CDCl$_3$): 7.82 (d, $J = Hz$, 1H), 7.55-7.48 (m, 2H), 7.43 (t, $J = Hz$, 1H), 7.62-7.22 (m, 1H), 7.19-7.13 (m, 3H), 4.80-4.72 (m, 1H), 4.38 (d, $J = Hz$, 1H), 3.22 (d, $J = Hz$, 1H), 3.00-2.81 (m, 4H); $^{13}$C-NMR (125 MHz - CDCl$_3$): 167.1, 144.9, 141.4, 137.8, 131.9, 131.6, 129.9 (2C), 128.4, 127.4, 123.8, 122.2, 61.3, 42.3, 41.3, 36.2; FT-IR: $\tilde{\nu} = 2910, 2508, 2159, 2029, 1976, 1679, 1451$ cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{17}$H$_{16}$ON = 250.1226 found: 250.1227.
2-methyl-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4b)

White solid, 62% yield. $^1$H-NMR (500 MHz - CDCl$_3$): 7.77 (d, $J = 7.7$ Hz, 1H), 7.36 (s, 1H), 7.32 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 4.86 – 4.74 (m, 1H), 4.42 – 4.35 (d, 1H), 3.27 (dd, $J = 14.6$, 1.7 Hz, 1H), 3.05 – 2.88 (m, 4H), 2.50 (s, 3H); $^{13}$C-NMR (125 MHz - CDCl$_3$): 167.20, 145.28, 142.19, 141.50, 137.94, 129.88 (2C), 129.42, 127.43, 127.05, 123.59, 122.63, 60.99, 42.68, 41.17, 36.38, 21.98; FT-IR: $\tilde{\nu} = 2921$, 2513, 2159, 2030, 1976, 1676, 1415 cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{18}$H$_{18}$ON = 264.1382 found: 264.1384.

2-isopropyl-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4c)

White solid, 69% yield. $^1$H-NMR (500 MHz - CDCl$_3$): 7.80 (d, $J = 7.8$ Hz, 1H), 7.39 (d, $J = 1.4$ Hz, 1H), 7.34 – 7.31 (m, 1H), 7.26 – 7.21 (m, 3H), 4.81 (dd, $J = 11.6$, 5.5 Hz, 1H), 4.44 – 4.35 (m, 1H), 3.29 (dd, $J = 14.6$, 1.7 Hz, 1H), 3.04 – 2.98 (m, 3H), 2.96 – 2.88 (m, 2H), 1.33 (d, $J = 6.9$ Hz, 6H); $^{13}$C-NMR (125 MHz - CDCl$_3$): 167.18, 153.26, 145.27, 141.53, 137.99, 129.90, 129.87, 129.82, 127.42, 127.04, 127.00, 123.70, 119.93, 61.13, 42.69, 41.18, 36.42, 34.69, 24.09 (2C); FT-IR: $\tilde{\nu} = 2962$, 2514, 2159, 2029, 1977, 1671, 1417 cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{20}$H$_{22}$ON = 292.1695 found: 292.1697.

2-methoxy-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4d)

White solid, 40% yield. $^1$H-NMR (500 MHz - CDCl$_3$): 7.80 (d, $J = 8.3$ Hz, 1H), 7.31 (dd, $J = 5.3$, 3.5 Hz, 1H), 7.25 (dd, $J = 5.6$, 3.3 Hz, 2H), 7.24 – 7.20 (m, 1H), 7.03 (d, $J = 2.1$ Hz, 1H), 7.01 (dd, $J = 8.3$, 2.2 Hz, 1H), 4.83 – 4.75 (m, 1H), 4.38 (d, $J = 10.9$ Hz, 1H), 3.92 (s, 3H), 3.24 (dd, $J = 14.7$, 1.7 Hz, 1H), 3.06 – 2.97 (m, 2H), 2.96 – 2.89 (m, 2H); $^{13}$C-NMR (125 MHz - CDCl$_3$): 165.92, 161.85, 146.08, 140.47, 136.80, 128.86 (2C), 126.43, 126.00, 124.14, 123.56, 113.61, 106.32, 59.88, 54.72, 41.77, 40.16, 35.42;
FT-IR: $\tilde{\nu} = 2919, 2515, 2159, 2027, 1666, 1610, 1414$ cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{18}$H$_{18}$O$_2$N = 280.1332 found: 280.1334.

8,9,14,14a-tetrahydro-6H-benzo[f]benzo[4,5]azepino[2,1-a]isoindol-6-one (4e)

Yellow powder, 72% yield. $^1$H-NMR (500 MHz - CDCl$_3$): 8.40 (s, 1H), 8.03 (d, 1H), 7.99 (s, 1H), 7.96 (d, $J = 8.2$, 1.3 Hz, 1H), 7.64 – 7.52 (m, 2H), 7.38 – 7.32 (m, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.21 (m, 2H), 4.95 – 4.79 (m, 1H), 4.60 (d, $J = 11.1$, 1.4 Hz, 1H), 3.40 (dd, $J = 14.7$, 1.8 Hz, 1H), 3.13 – 2.92 (m, 4H); $^{13}$C-NMR (125 MHz - CDCl$_3$): 165.87, 140.34, 139.15, 136.86, 134.14, 132.16, 128.91, 128.81, 128.75, 128.53, 127.07, 126.64, 126.43, 126.05, 125.40, 122.96, 120.09, 60.01, 42.44, 40.44, 35.32; FT-IR: $\tilde{\nu} = 2923, 2519, 2031, 1976, 1686, 1418$ cm$^{-1}$; HR-MS: calc. for [M+H]$^+$ C$_{21}$H$_{18}$ON = 300.1382 found: 300.1386.

2-bromo-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4f)

White solid, 55% yield. $^1$H-NMR (700 MHz - CDCl$_3$): $\delta$ 7.68 – 7.64 (m, 2H), 7.56 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.22 (dd, $J = 5.3$, 3.5 Hz, 1H), 7.20 – 7.12 (m, 3H), 4.76 – 4.68 (m, 1H), 4.38 – 4.33 (m, 1H), 3.18 (dd, $J = 14.7$, 1.8 Hz, 1H), 2.98 – 2.91 (m, 2H), 2.91 – 2.82 (m, 2H); $^{13}$C-NMR (167 MHz - CDCl$_3$): $\delta$ 166.21, 146.67, 141.25, 137.33, 131.92, 130.95, 129.92, 127.64, 127.21, 126.26, 125.65, 125.28, 60.76, 42.43, 41.31, 36.16, 29.71; FT-IR: $\tilde{\nu} = 3053, 2913, 2159, 1683, 1493, 1363, 1277, 1166, 1050, 994, 893, 828$ cm$^{-1}$; LC-MS: calc. for [M+H]$^+$ C$_{17}$H$_{14}$ONBr = 330.1 found: 331.1.

2-chloro-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4g)

Yellow solid, 74% yield. $^1$H-NMR (600 MHz - CDCl$_3$): $\delta$ 7.74 (d, $J = 8.1$ Hz, 1H), 7.52 – 7.48 (m, 1H), 7.41 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.27 – 7.10 (m, 4H), 4.73 (ddt, $J = 11.1$, 9.3, 4.6 Hz, 1H), 4.40 – 4.34 (m, 1H), 3.19 (dd, $J = 14.6$, 1.7 Hz, 1H), 3.00 – 2.80 (m, 4H); $^{13}$C-NMR (151 MHz - CDCl$_3$): $\delta$ 166.13,
SUPPORTING INFORMATION

Yellow solid, 58% yield. **1H-NMR** (500 MHz - CDCl₃): δ 7.93 (d, J = 7.8 Hz, 1H), 7.77 (s, 1H), 7.71 (dd, J = 7.9, 1.5 Hz, 1H), 7.44 (td, J = 7.0, 1.7 Hz, 1H), 7.26 (dd, J = 5.3, 3.6 Hz, 3H), 4.81 – 4.70 (m, 1H), 4.45 (dd, J = 11.0, 1.8 Hz, 1H), 3.26 (dd, J = 14.6, 1.8 Hz, 1H), 3.04 – 2.79 (m, 4H); **13C-NMR** (125 MHz - CDCl₃): δ 165.81, 145.22, 141.15, 137.15, 135.17, 133.97, 133.85, 133.71, 133.45, 129.99, 129.96, 128.11, 127.74, 127.68, 127.30, 125.88, 125.86, 124.93, 124.47, 122.76, 119.48, 119.45, 119.41, 116.99, 61.18, 42.30, 41.47, 37.29, 36.06; **19F-NMR** (470 MHz - CDCl₃): δ -62.20; **LC-MS**: calc. for [M+H]⁺ C₁₈H₁₄OF₃N = 318.1 found: 318.1.

2-(trifluoromethyl)-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4h)

White solid, 68% yield. **1H-NMR** (600 MHz - CDCl₃): δ 7.96 – 7.93 (m, 1H), 7.84 (dd, J = 8.0, 1.4 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.26 – 7.20 (m, 3H), 4.85 – 4.73 (m, 1H), 4.45 – 4.36 (m, 1H), 3.25 (dd, J = 14.7, 1.8 Hz, 1H), 3.06 – 2.97 (m, 2H), 2.97 – 2.88 (m, 2H); **13C-NMR** (151 MHz - CDCl₃): δ 166.38, 146.71, 141.26, 137.75, 137.36, 131.56, 131.53, 129.92 (2C), 127.63, 127.20, 125.32, 98.37, 60.61, 42.41, 41.25, 36.16; **FT-IR**: ν = 2896, 2352, 2115, 1997, 1674 cm⁻¹; **LC-MS**: calc. for [M+H]⁺ C₁₈H₁₄OF₃N = 376.1 found: 376.1.

1,3-dichloro-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4k)

Yellow solid, 58% yield. **1H-NMR** (700 MHz - CDCl₃): 7.69 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 1.7 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.20 – 7.12 (m, 3H), 4.76 – 4.68 (m, 1H), 4.41 (dd, J = 10.3, 1.7 Hz, 1H), 3.70
19

**SUPPORTING INFORMATION**

(dd, J = 14.5, 1.7 Hz, 1H), 3.01 – 2.94 (m, 2H), 2.91 – 2.83 (m, 1H), 2.66 (dd, J = 14.5, 10.3 Hz, 1H); 13C-NMR (176 MHz - CDCl3): 164.71, 141.02, 140.05, 137.31, 135.70, 135.61, 131.96, 130.07, 129.80, 129.77, 127.69, 127.25, 122.80, 60.89, 53.43, 41.65, 39.47, 35.94, 29.71; FT-IR: \( \tilde{\nu} = 3042, 2917, 1688, 1450, 1319, 1230, 1102, 959, 890 \) cm\(^{-1}\); LC-MS: calc. for [M+H]+ \( \text{C}_{17}\text{H}_{13}\text{OCl}_2\text{N} = 318.2 \) found: 318.2.

3-(fluoro)-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4l)

Off-white solid, 44% yield. \(^1\)H-NMR (700 MHz - CDCl3): 7.69 (d, J = 7.4 Hz, 1H), 7.49 (td, J = 7.8, 4.5 Hz, 1H), 7.33 (dd, J = 5.3, 3.5 Hz, 1H), 7.26 – 7.23 (m, 3H), 7.24 – 7.20 (m, 1H), 4.82 (ddd, J = 9.9, 5.5, 1.5 Hz, 1H), 4.59 (dd, J = 10.9, 1.7 Hz, 1H), 3.55 (dd, J = 14.6, 1.7 Hz, 1H), 3.07 – 3.00 (m, 2H), 2.99 – 2.92 (m, 1H), 2.89 (dd, J = 14.6, 10.8 Hz, 1H); 13C-NMR (176 MHz - CDCl3): 164.96 (d, J = 2.3 Hz), 156.69 (d, J = 250.6 Hz), 140.21, 136.57, 134.13 (d, J = 4.2 Hz), 129.63 (d, J = 6.7 Hz), 129.46 (d, J = 16.0 Hz), 129.20, 128.76, 126.54, 126.14, 118.76 (d, J = 3.7 Hz), 117.51 (d, J = 20.1 Hz), 58.20 (d, J = 2.6 Hz), 40.43, 39.73, 35.14; \(^{19}\)F NMR (470 MHz, CDCl3) \( \delta = -120.59 \) (dd, J = 9.3, 4.4 Hz); HR-MS: calc. for [M+H]+ \( \text{C}_{18}\text{H}_{15}\text{OFN} = 268.1132 \) found: 268.1134.

3-(chloro)-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4m)

White solid, 36% yield. \(^1\)H-NMR (500 MHz - CDCl3): 7.74 (dd, J = 7.4, 1.0 Hz, 1H), 7.54 (dd, J = 7.9, 1.0 Hz, 1H), 7.45 (dt, 1H), 7.34 (dd, J = 5.0, 3.7 Hz, 1H), 7.26 – 7.20 (m, 3H), 4.89 – 4.77 (m, 1H), 4.52 (dd, J = 10.3, 1.4 Hz, 1H), 3.84 (dd, J = 14.5, 1.5 Hz, 1H), 3.12 – 2.99 (m, 2H), 2.99 – 2.88 (m, 1H), 2.75 (dd, J = 14.4, 10.3 Hz, 1H); 13C-NMR (126 MHz - CDCl3): 165.80, 142.99, 141.21, 137.36, 134.74, 133.77, 131.70, 129.90, 129.75, 127.59, 127.14, 123.98, 123.36, 60.88, 42.41, 41.33, 36.11; FT-IR: \( \tilde{\nu} = 2918, 2159, 2027, 1977, 1675 \) cm\(^{-1}\); HR-MS: calc. for [M+H]+ \( \text{C}_{18}\text{H}_{15}\text{ONCl} = 284.0836 \) found: 284.0839.

1-(chloro)-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4m')

White solid, 36% yield. \(^1\)H-NMR (500 MHz - CDCl3): 7.74 (dd, J = 7.4, 1.0 Hz, 1H), 7.48 (dd, J = 7.9, 1.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.28 (dd, J = 5.2, 3.6 Hz, 1H), 7.21 – 7.14 (m, 3H), 4.82 – 4.70 (m,
1H), 4.46 (dd, J = 10.4, 1.5 Hz, 1H), 3.77 (dd, J = 14.5, 1.6 Hz, 1H), 3.09 – 2.93 (m, 2H), 2.93 – 2.82 (m, 1H), 2.69 (dd, J = 14.4, 10.3 Hz, 1H); \textsuperscript{13}C-NMR (126 MHz - CDCl\textsubscript{3}): 165.88, 141.71, 141.16, 137.69, 134.44, 132.18, 130.11, 130.06, 129.73, 129.10, 127.53, 127.15, 122.39, 61.07, 41.47, 39.53, 36.06; FT-IR: $\tilde{\nu}$ = 2929, 2159, 2028, 1976, 1686 cm\textsuperscript{-1}; HR-MS: calc. for [M+H]\textsuperscript{+} C\textsubscript{17}H\textsubscript{15}ONCl = 284.0836 found: 284.0840.

\textsuperscript{2,3}-(dimethoxy)-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4n)

White solid, 27% yield. \textsuperscript{1}H-NMR (700 MHz - CDCl\textsubscript{3}): 7.36 (s, 1H), 7.31 (m, 1H), 7.23 (m, 3H), 7.00 (s, 1H), 4.82 – 4.74 (m, 1H), 4.36 (dd, J = 11.0, 1.8 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 3.25 (dd, J = 14.7, 1.8 Hz, 1H), 3.06 – 2.98 (m, 2H), 2.97 – 2.87 (m, 2H); \textsuperscript{13}C-NMR (176 MHz - CDCl\textsubscript{3}): 167.39, 152.68, 149.96, 141.50, 138.40, 137.77, 129.91, 129.86, 127.46, 127.05, 124.22, 105.47, 104.36, 60.88, 56.38, 56.33, 42.75, 41.31, 36.38; FT-IR: $\tilde{\nu}$ = 2924, 2159, 2029, 1977, 1663, 890 cm\textsuperscript{-1}; HR-MS: calc. for [M+H]\textsuperscript{+} C\textsubscript{19}H\textsubscript{20}O\textsubscript{3}N = 310.1437 found: 310.1441.

\textsuperscript{1,2}-(dimethoxy)-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4n’)

White solid, 39% yield. \textsuperscript{1}H-NMR (700 MHz - CDCl\textsubscript{3}): 7.59 (d, J = 8.2 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.25 – 7.19 (m, 3H), 7.05 (d, J = 8.2 Hz, 1H), 4.81 – 4.74 (m, 1H), 4.50 (dd, J = 10.6, 1.6 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.64 (dd, J = 14.5, 1.7 Hz, 1H), 3.08 – 2.97 (m, 2H), 2.91 (dd, J = 13.3, 5.5 Hz, 1H), 2.80 (dd, J = 14.4, 10.6 Hz, 1H); \textsuperscript{13}C-NMR (176 MHz - CDCl\textsubscript{3}): 166.66, 155.36, 143.93, 141.48, 138.40, 136.91, 130.14, 129.73, 127.34, 127.01, 125.61, 119.65, 113.03, 60.68, 59.84, 56.25, 41.37, 40.75, 36.40; FT-IR: $\tilde{\nu}$ = 2925, 2159, 2029, 1977, 1689 cm\textsuperscript{-1}; HR-MS: calc. for [M+H]\textsuperscript{+} C\textsubscript{19}H\textsubscript{20}O\textsubscript{3}N = 310.1437 found: 310.1439.

\textsuperscript{11}-methoxy-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4o)
White solid, 50% yield. ¹H-NMR (600 MHz - CDCl₃): 7.88 (d, J = 7.6, 1.2 Hz, 1H), 7.60 (td, J = 7.3, 1.2 Hz, 1H), 7.56 (dd, J = 7.6, 1.1 Hz, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 2.7 Hz, 1H), 6.77 (dd, J = 8.2, 2.7 Hz, 1H), 4.83 – 4.74 (m, 1H), 4.44 (d, 1H), 3.84 (s, 3H), 3.23 (dd, J = 14.6, 1.7 Hz, 1H), 3.04 – 2.83 (m, 4H); ¹³C-NMR (151 MHz - CDCl₃): 166.08, 157.44, 143.81, 137.98, 132.48, 130.94, 130.50, 129.82, 127.41, 122.77, 121.03, 115.14, 110.62, 60.14, 54.32, 41.75, 40.57, 34.32; FT-IR: ʋ = 2923, 2360, 2159, 2030, 1977, 1689 cm⁻¹; HR-MS: calc. for [M+H]+ C₁₈H₁₈O₂N = 280.1332 found: 280.1333.

11-(trifluoromethyl)-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4p)

Yellow solid, 80% yield. ¹H-NMR (500 MHz - CDCl₃): 7.83 (dt, J = 7.6, 1.0 Hz, 1H), 7.55 (td, J = 7.4, 1.2 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.48 – 7.36 (m, 2H), 7.27 (d, J = 7.8 Hz, 1H), 4.83 – 4.73 (m, 1H), 4.39 (dd, J = 11.1, 1.8 Hz, 1H), 3.30 (dd, J = 14.8, 1.8 Hz, 1H), 3.04 – 2.85 (m, 4H); ¹³C-NMR (126 MHz - CDCl₃): 167.15, 145.41, 144.46, 138.58, 131.85, 131.74, 130.32, 129.51, 129.25, 128.70, 126.90, 126.66, 125.17, 124.39, 124.36, 123.98, 122.10, 60.72, 42.48, 40.76, 36.25; ¹⁹F-NMR (470 MHz, CDCl₃): δ = -62.34; LC-MS: calc. for [M+H]+ C₁₈H₁₄OF₃N = 318.1 found: 318.1.

5,6,12b,13-tetrahydro-8H-[1,3]dioxolo[4',5':4,5']benzo[1',2':4,5]azepino[2,1-a]isoindol-8-one (4q)

White solid, 31% yield. ¹H-NMR (500 MHz - CDCl₃): 7.88 (d, J = 7.5, 1.0 Hz, 1H), 7.59 (td, J = 7.4, 1.2 Hz, 1H), 7.54 (dd, J = 7.5, 1.0 Hz, 1H), 7.49 (t, 1H), 6.80 (s, 1H), 6.72 (s, 1H), 5.96 (dd, 2H), 4.83 – 4.73 (m, 1H), 4.41 (d, 1H), 3.18 (dd, J = 14.8, 1.8 Hz, 1H), 3.04 – 2.90 (m, 2H), 2.89 – 2.80 (m, 2H); ¹³C-NMR (126 MHz - CDCl₃): 167.10, 146.43, 146.16, 144.73, 134.82, 131.98, 131.56, 130.90, 128.46, 123.81, 122.06, 110.42, 110.40, 101.11, 61.19, 42.19, 41.31, 35.96; FT-IR: ʋ = 2930, 2522, 2363, 2159, 2028, 1977, 1698, 1038 cm⁻¹; LC-MS: calc. for [M+H]+ C₁₈H₁₅O₃N = 294.0 found: 294.0.

11-methyl-7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (4r)
White solid, 39% yield.  

$^1$H-NMR (600 MHz - CDCl$_3$): 7.88 (d, J = 7.5, 1.0 Hz, 1H), 7.59 (td, J = 7.4, 1.1 Hz, 1H), 7.55 (d, J = 7.5, 1.1 Hz, 1H), 7.49 (t, J = 7.4, 0.8 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 4.82 (d, J = 1.2 Hz, 1H), 4.42 (d, 1H), 3.27 (dd, J = 14.7, 1.8 Hz, 1H), 3.06 – 2.95 (m, 2H), 2.94 – 2.82 (m, 2H), 2.35 (s, 3H);  

$^{13}$C-NMR (151 MHz - CDCl$_3$): 167.11, 144.94, 141.26, 137.11, 134.74, 132.01, 131.52, 130.74, 129.87, 128.40, 127.55, 123.79, 122.08, 61.39, 42.15, 41.28, 36.29, 20.98;  

FT-IR: $\tilde{\nu}$ = 2920, 2159, 2029, 1977, 1680 cm$^{-1}$;  

HR-MS: calc. for [M+H]$^+$ C$_{18}$H$_{18}$ON = 264.1382 found: 264.1385.
Data collection was conducted on a Bruker D8 Venture four-circle diffractometer by Bruker AXS GmbH using a PHOTON II CPAD detector by Bruker AXS GmbH. X-ray radiation was generated by microfocus sources IμS and IμS 3.0 Cu or Mo by Incoatec GmbH with HELIOS mirror optics and a single-hole collimator by Bruker AXS GmbH.

For the data collection, the programs APEX 3 Suite (v.2018.7-2) with the integrated programs SAINT (integration) and SADABS (adsorption correction) by Bruker AXS GmbH were used. Using Olex2, the structures were solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimization.

Crystal data and structure refinement for compound 3p (CCDC 1990749) and 4g (CCDC 1990750) with 50% ellipsoid probability level.

| Compound | 3q | 4g* |
|----------|----|-----|
| Empirical formula | C_{18}H_{18}N_{2}O_{6}S | C_{17}H_{14}ClNO |
| Formula weight | 390.40 | 283.74 |
| Temperature/K | 100.0 | 100.0 |
| Crystal system | monoclinic | monoclinic |
| Space group | P2_1/n | P2_1/c |
| a/Å | 14.8594(8) | 12.3505(13) |
| b/Å | 5.4431(3) | 9.3353(9) |
| c/Å | 21.6605(12) | 12.2839(11) |
| α/° | 90 | 90 |
| β/° | 90.003(2) | 105.592(4) |
| γ/° | 90 | 90 |
| Volume/Å³ | 1751.93(17) | 1364.2(2) |
| Z | 4 | 4 |
### SUPPORTING INFORMATION

| Property                        | Value 1          | Value 2          |
|--------------------------------|------------------|------------------|
| $\rho_{calc}$ g/cm$^3$         | 1.480            | 1.382            |
| $\mu$/mm$^1$                   | 2.002            | 0.274            |
| $F(000)$                       | 816.0            | 592.0            |
| Crystal size/mm$^3$            | $0.542 \times 0.107 \times 0.04$ | $0.466 \times 0.311 \times 0.1$ |
| Radiation                      | CuKα ($\lambda = 1.54178$) | MoKα ($\lambda = 0.71073$) |
| $2\theta$ range for data collection/° | 7.214 to 159.562 | 5.548 to 59.998 |
| Index ranges                   | $-18 \leq h \leq 18$, $-6 \leq k \leq 6$, $-27 \leq l \leq 26$ | $-17 \leq h \leq 17$, $-13 \leq k \leq 13$, $-17 \leq l \leq 16$ |
| Reflections collected          | 28346            | 29747            |
| Independent reflections        | 3739 ($R_{int} = 0.0493$, $R_{sigma} = 0.0288$) | 3982 ($R_{int} = 0.0313$, $R_{sigma} = 0.0210$) |
| Data/restraints/parameters     | 3739/0/245       | 3982/0/245       |
| Goodness-of-fit on $F^2$       | 1.064            | 1.062            |
| Final R indexes [$I>=2\sigma(I)$] | $R_1 = 0.0714$, $wR_2 = 0.2227$ | $R_1 = 0.0456$, $wR_2 = 0.1121$ |
| Final R indexes [all data]     | $R_1 = 0.0748$, $wR_2 = 0.2263$ | $R_1 = 0.0531$, $wR_2 = 0.1175$ |
| Largest diff. peak/hole / e Å$^3$ | 0.67/-0.81       | 0.39/-0.41       |

*Disorder omitted for clarity.*
5. Biological data

Reagents

Purmorphamine was purchased from Cayman Chemical (#10009634) and DMSO from (Sigma Aldrich, #67685). The compound collection was synthesized as described in the paper. All other reagents used are mentioned in the respective protocols below, with the corresponding sources.

Cell lines

The murine mesenchymal stem cell line C3H10T1/2 (ATCC, CCL-226) was cultured in Dulbecco’s Modified Eagle’s medium (DMEM, high glucose, PAN, #P04-03550) supplemented with 10% of fetal calf serum (FCS, Fisher Scientific, #10136253, heat inactivated), 1 mM sodium pyruvate (PAN, #P04-43100) and 2 mM L-glutamine (PAN, #P0480100). The cells were cultured at 37°C and 5% CO₂ in a humidified atmosphere. Checks for mycoplasma contaminations were performed regularly and cells were always found to be free of any contaminations.

Osteoblast differentiation and viability assay

The osteoblast differentiation assay and the viability assay were performed using C3H10T1/2 cells. For the screening and IC₅₀ determinations 800 C3H10T1/2 cells per well were seeded in white 384-well plates. After incubation overnight, cells were treated with 1.5 μM purmorphamine and different concentrations of the compounds or DMSO as a control. After 96 h the cell culture medium was aspirated and the commercial luminogenic ALP substrate CDP-Star (Roche, #11685627001) was added. The cells were incubated for one hour at room temperature and in absence of light. Afterwards the luminescence signal was read. To identify and exclude toxic compounds, which would also lead to a reduced luminescent signal, cell viability measurements were conducted in parallel. For this purpose, C3H10T1/2 cells were seeded and treated as described above. The cellular ATP content was determined as a measure of cell viability using the Cell Titer Glo reagent (Promega). Compounds were considered as hit compounds if they caused at least 50% reduction in the luminescent signal in the osteoblast differentiation assay while retaining cell viability ≥ 80% at a concentration of 10 μM. To determine IC₅₀ curves for hit compounds, three-fold dilution curves starting from 10 μM, were used. Calculations of the IC₅₀ values were conducted, using GraphPad Prism 7. (GraphPad Software, USA).
Figure 1: Hh-dependent osteoblast differentiation of C3H10T1/2 cells. A/B: C3H10T1/2 cells were treated with 1.5 μM purmorphamine or DMSO as a control (A) or with 1.5 μM purmorphamine and different concentrations of the known Hh inhibitor vismodegib (B). After 96 h, the activity of alkaline phosphatase was detected using a chemiluminescent substrate. The purmorphamine control was set to 100%. Data are mean values ± SD and representative of three biological replicates, each performed in three technical replicates. C: Chemical structure of the known Hh inhibitor Vismodegib.
6. DFT Calculations

Geometry optimizations and frequency analysis were carried out using Gaussian 16 Rev. B\textsuperscript{[11]} employing tight convergence criteria using the M06-2X functional. \textsuperscript{[12]} The 6-31G(2d,p) basis set was used for all elements except for Rh, for which LabL2DZ including pseudo potentials was used. The solvent environment was simulated by the IEFPCM of methanol as implemented in the software package.

Cartesian coordinates

*Structure II*

\begin{verbatim}
C    -1.61797100  -1.77769800    2.33470600
C    -1.33605000  -0.39123300    2.55196900
C    -0.49547900  -2.34232600    1.69196800
C     0.53203400  -1.33640400    1.59338900
C     0.01267600  -0.14723700    2.12719300
H    -0.41510200   -3.36029900    1.33658600
H     1.50230200  -1.46399400    1.13421800
H     0.50249300    0.81405300    2.12528400
C    -3.64462100    0.98435200   -0.25669700
C    -3.34696400  -0.29535900    0.21621700
C    -4.39413900  -1.13835900    0.57906000
C    -5.71232600  -0.68575200    0.49058300
C    -5.99825400    0.60042500    0.03712400
C    -4.95642900    1.43835700   -0.34334300
C    -2.49605600    1.83031800   -0.68999300
H    -4.20226200   -2.15053900    0.92107000
H    -6.52199000  -1.34883800    0.77848900
H    -7.02594500    0.94038900   -0.02464500
H    -5.13622100    2.44303900   -0.71334600
O    -2.57247300    3.00050000   -1.04649600
N    -1.37657500    1.07300600   -0.65143700
O    -0.21779000    1.76518400   -0.99856800
\end{verbatim}
|  | X       | Y       | Z       |
|---|---------|---------|---------|
| C | 0.07953 | -3.96387 | -1.30256 |
| C | 2.75099 | -3.26855 | -1.15369 |
| C | 1.02923 | -4.94838 | -1.06543 |
| H | -0.96522 | -4.24539 | -1.37702 |
| C | 2.37050 | -4.59598 | -0.97982 |
| H | 3.80312 | -3.02066 | -1.07792 |
| H | 0.72202 | -5.98164 | -0.95076 |
| H | 3.12478 | -5.35037 | -0.78611 |
| H | -2.54306 | -2.28438 | 2.56364 |
| H | -1.99661 | 0.33185 | 3.00719 |
| C | 1.15811 | 3.68706 | -0.73669 |
| C | 2.07945 | 3.01257 | -1.75571 |
| H | 2.70786 | 2.27013 | -1.25966 |
| H | 1.51389 | 2.52656 | -2.55322 |
| H | 2.73051 | 3.76951 | -2.20357 |
| C | 1.98085 | 4.35557 | 0.36405 |
| H | 2.61190 | 5.13344 | -0.07602 |
| H | 1.32876 | 4.81456 | 1.11003 |
| H | 2.62212 | 3.62375 | 0.86155 |
| C | 0.27396 | 4.73234 | -1.44429 |
| H | -0.37129 | 4.25657 | -2.18587 |
| H | -0.36364 | 5.24935 | -0.72188 |
| H | 0.91359 | 5.46946 | -1.93891 |
| C | 2.22334 | -0.82585 | -1.62372 |
| H | 1.59649 | -0.15378 | -1.02503 |
| H | 2.04989 | -0.55091 | -2.67276 |
| Element | X         | Y         | Z         |
|--------|-----------|-----------|-----------|
| C      | 0.51493600| 1.31475500| -3.67337700|
| H      | -1.17261000| -1.83459000| 4.37030000|
| H      | -1.59219800| 0.09810500| 3.94659500|
| O      | 0.61796100| 0.97986200| 3.84256300|
| O      | 1.52817900| 0.58179500| 4.87987700|
| O      | 1.09726800| 0.94097300| 2.48304600|
| C      | -0.09990000| 2.54760600| 4.19265100|
| H      | 2.65917000| 3.26591700| 4.17441000|
| H      | 2.76948500| 2.50209000| 3.41384900|
| H      | 2.15265000| -2.03922600| 5.17847400|
| C      | 0.37483500| 2.09863600| -0.23804100|
| H      | 1.59176000| 1.87289400| -1.29030300|
| C      | 2.04009100| 2.39018500| 1.40246000|
| C      | 2.09863600| 2.39018500| 1.40246000|
| C      | 2.04009100| 2.39018500| 1.40246000|
| C      | 2.09863600| 2.39018500| 2.76948500|
| C      | 2.39018500| 2.39018500| 2.76948500|
| C      | 2.39018500| 2.39018500| 2.76948500|
| C      | 2.39018500| 2.39018500| 2.76948500|

*Structure III*
SUPPORTING INFORMATION

H  6.11681800  -1.29760100  0.12477300
H  5.16818900  -3.53480700  0.65753900
H  2.82334700  -4.05524200  0.00001300
O  0.71691000  -3.64051300  -1.52256400
N  0.21052000  -1.52210100  -0.75768100
O  -1.14481700  -1.84388200  -0.84823600
C  -1.57244500  -2.75435200  0.05963800
O  -0.90778400  -3.12953300  0.98689300
Rh 1.15650300  -0.18284500  0.56987300
C  1.17846500  0.99122100  -1.13178500
H  0.19116600  0.89244300  -1.57614400
C  2.20469400  0.19370000  -1.96097800
H  1.68159700  -0.32527500  -2.76724800
H  2.93310300  0.86932400  -2.41839500
C  1.52281500  2.42010100  -0.86298500
C  0.58519100  3.45932100  -1.03207700
C  2.80695500  2.75815100  -0.41112300
C  0.95300000  4.77222800  -0.72488100
C  3.16145800  4.06563500  -0.11364600
H  3.53383000  1.96574500  -0.26363900
C  2.22609500  5.08525500  -0.26704500
H  0.21997200  5.56298000  -0.85618900
H  4.16263600  4.28742500  0.23961800
H  2.48597000  6.11246900  -0.03755700
H  2.47315300  -1.25011800  3.17700800
H  -0.13156600  -1.74497000  2.85938600
C  -2.95868200  -3.27145800  -0.29422800
C  -3.86620700  -2.15307400  -0.81649700
H  -3.98739100  -1.36683800  -0.06653000
H  -3.45929400  -1.70676700  -1.72699200
H  -4.85130700  -2.57027000  -1.04700300
C  -3.57190600  -3.92066200  0.94581200
H  -4.54581900  -4.34768200  0.69034400
SUPPORTING INFORMATION

Structure A'

C  -2.84676300  2.79123800  1.00644200
C  -1.49340400  3.12972900  1.40579800
C  -3.36743800  1.88283700  1.93098100
C  -2.28503200  1.52260700  2.80939000
C  -1.17466500  2.40512300  2.54957000
H   -4.35569200  1.44646000  1.92789100
H   -2.35046600  0.82321200  3.63205600
H    -0.23163800  2.40810400  3.07823100
C   -1.95294900 -1.49558700  -2.26280000
|  |   |   |   |
|---|---|---|---|
| C | -1.31357700 | -2.59360600 | -1.68216500 |
| C | -1.95243600 | -3.82956000 | -1.70240600 |
| C | -3.21032000 | -3.95531600 | -2.28456900 |
| C | -3.83878500 | -2.85385800 | -2.86531900 |
| C | -3.20220700 | -1.62003200 | -2.86676900 |
| C | -1.23905700 | -0.19723100 | -2.30631200 |
| H | -1.46690300 | -4.69141800 | -1.25647800 |
| H | -3.70521700 | -4.92024400 | -2.28618200 |
| H | -4.81764700 | -2.96131600 | -3.31762700 |
| H | -3.65963200 | -0.74902100 | -3.32315800 |
| O | -1.29095600 | 0.57093100 | -3.23011800 |
| N | 0.47140500 | 0.09761400 | -1.13938800 |
| O | 0.56998900 | 0.99242700 | -1.44729000 |
| C | 0.23189700 | 2.31092000 | -1.52179100 |
| O | -0.89188000 | 2.71363300 | -1.48033300 |
| Rh | -1.61271500 | 0.76428500 | 0.87788200 |
| C | 0.14147000 | -1.03030800 | -0.34991300 |
| H | 1.18988800 | -0.74689000 | -0.28183700 |
| C | 0.05274300 | -2.36997300 | -1.09232300 |
| H | 0.80261200 | -2.38442100 | -1.89290900 |
| H | 0.30632300 | -3.17226300 | -0.39367800 |
| C | -0.48580100 | -1.04078400 | 1.03624200 |
| C | 0.35435900 | -1.07758800 | 2.21608600 |
| C | -1.86921500 | -1.39666900 | 1.16824300 |
| C | -0.18239100 | -1.45130700 | 3.41741300 |
| C | -2.36565300 | -1.80745400 | 2.44948700 |
| H | -2.44654400 | -1.70075000 | 0.30410700 |
| C | -1.54800500 | -1.83575100 | 3.53967900 |
| H | 0.45138400 | -1.45317800 | 4.29962000 |
| H | -3.39968800 | -2.12855300 | 2.52672700 |
| H | -1.92608400 | -2.15714300 | 4.50419200 |
| H | -3.36219400 | 3.20904500 | 0.15323500 |
| H | -0.85270100 | 3.82291800 | 0.88016400 |
|    |     C       |     H       |     C       |     H       |     H       |     C       |     H       |     H       |     H       |     H       |     C       |     H       |     H       |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
|    | 1.49841800 | 3.14614200 | -1.61538900|            |            |            |            |            |            |            |            |            |            |
| C  | 2.25570300 | 2.97678900 | -0.28647100|            |            |            |            |            |            |            |            |            |            |
| H  | 1.61281700 | 3.21409500 | 0.56833900 | -1.7962100 |            |            |            |            |            |            |            |            |            |
| H  | 2.62251700 | 1.95273000 | -0.27103200|            |            |            |            |            |            |            |            |            |            |
| H  | 3.11125500 | 3.65836100 | -0.28647100|            |            |            |            |            |            |            |            |            |            |
| C  | 1.09696200 | 4.60461200 | -1.82539800|            |            |            |            |            |            |            |            |            |            |
| H  | 1.99738200 | 5.22069700 | -1.89558900|            |            |            |            |            |            |            |            |            |            |
| H  | 0.51962700 | 4.72428000 | -2.74575900|            |            |            |            |            |            |            |            |            |            |
| H  | 0.49022900 | 4.97083900 | -0.99319600|            |            |            |            |            |            |            |            |            |            |
| C  | 2.37136000 | 2.65125400 | -2.77726700|            |            |            |            |            |            |            |            |            |            |
| H  | 2.69826800 | 1.62293000 | -2.61024300|            |            |            |            |            |            |            |            |            |            |
| H  | 1.83033900 | 2.70125600 | -3.72681400|            |            |            |            |            |            |            |            |            |            |
| H  | 3.25702200 | 3.28862300 | -2.85380300|            |            |            |            |            |            |            |            |            |            |
| C  | 1.81070800 | -0.68923500| 2.12770800 |            |            |            |            |            |            |            |            |            |            |
| H  | 2.16068700 | -0.34456100| 3.10449900 |            |            |            |            |            |            |            |            |            |            |
| H  | 1.95198600 | 0.13497400 | 1.42031600 |            |            |            |            |            |            |            |            |            |            |
| C  | 2.67487000 | -1.86823400| 1.69876400 |            |            |            |            |            |            |            |            |            |            |
| H  | 2.69151400 | -2.64292500| 2.46674700 |            |            |            |            |            |            |            |            |            |            |
| H  | 2.31693300 | -2.31775400| 0.76707600 |            |            |            |            |            |            |            |            |            |            |
| O  | 4.05131500 | -1.45709200| 1.54164600 |            |            |            |            |            |            |            |            |            |            |
| S  | 4.52815800 | -1.03042500| 0.08467500 |            |            |            |            |            |            |            |            |            |            |
| O  | 3.42537900 | -0.41501200| -0.60973300|            |            |            |            |            |            |            |            |            |            |
| O  | 5.74066000 | -0.29955900| 0.29218400 |            |            |            |            |            |            |            |            |            |            |
| C  | 4.88596000 | -2.58279500| -0.67403800|            |            |            |            |            |            |            |            |            |            |
| H  | 5.23655800 | -2.36601500| -1.68313200|            |            |            |            |            |            |            |            |            |            |
| H  | 5.65967600 | -3.07364300| -0.08608000|            |            |            |            |            |            |            |            |            |            |
| H  | 3.97229800 | -3.17617800| -0.70796900|            |            |            |            |            |            |            |            |            |            |

Structure IV*
| Element | X          | Y          | Z          |
|---------|------------|------------|------------|
| C       | 0.40202800 | -1.39749800| 2.86950800 |
| C       | 1.36005800 | -0.69091300| 2.05784700 |
| H       | -1.33168700| -0.65744000| 4.06770900 |
| H       | 0.41769900 | -2.45477600| 3.09041000 |
| H       | 2.17434200 | -1.13967900| 1.50479900 |
| C       | -3.44017100| -0.60202400| -1.09059500|
| C       | -3.06053200| -1.85444600| -0.56613800|
| C       | -3.98462500| -2.90399800| -0.60032200|
| C       | -5.24796300| -2.74934100| -1.15649900|
| C       | -5.61231200| -1.52176600| -1.69462500|
| C       | -4.70974300| -0.46724400| -1.65523600|
| C       | -2.62919700| 0.67982600  | -1.09880900 |
| H       | -3.69521300| -3.86626300| -0.18952400|
| H       | -5.93850000| -3.58525000| -1.16781800|
| H       | -6.59325200| -1.38117800| -2.13418400|
| H       | -4.97048500| 0.50264600  | -2.06040700 |
| O       | -2.96092700| 1.61226700  | -1.82977000 |
| N       | -1.58506200| 0.72553200  | -0.25831100 |
| O       | -0.88425500| 1.93251900  | -0.35955100 |
| C       | -1.44565000| 2.97561500  | 0.29687000  |
| O       | -2.41466800| 2.87730900  | 0.99667300  |
| Rh      | -0.84472700| -0.53979900| 1.18062700  |
| C       | -0.52331600| -1.88203000| -0.61000300 |
| C       | -1.72883200| -2.20931900| 0.00079500  |
| C       | 0.75675200 | -2.60679000| -0.46072700 |
| C       | 1.88140400 | -2.20066000| -1.20472400 |
| C       | 0.88152700 | -3.68441000| 0.42634600  |
| C       | 3.10033200 | -2.84854900| -0.99217600 |
| C       | 2.09820700 | -4.31956800| 0.62185000  |
| H       | 0.01717300 | -4.02416500| 0.98686400  |
| C       | 3.22050900 | -3.89200500| -0.08295400 |
| H       | 3.96800100 | -2.51659600| -1.55457500 |
| H       | 2.16964800 | -5.14512100| 1.32094200  |
| Atom | X       | Y       | Z       |
|------|---------|---------|---------|
| H    | 4.1793200 | -4.3756200 | 0.06572700 |
| H    | -0.73189100 | 1.74250200 | 2.98971900 |
| H    | 1.47616800 | 1.43013200 | 1.44676800 |
| C    | -0.67244100 | 4.25439000 | 0.00921200 |
| C    | 0.81612200 | 4.04588200 | 0.32274100 |
| H    | 0.96795900 | 3.81798300 | 1.38304300 |
| H    | 1.23677000 | 3.23364300 | -0.27666100 |
| C    | 1.36641100 | 4.96335900 | 0.09381900 |
| C    | -1.24496800 | 5.37642400 | 0.87258400 |
| H    | -0.70336500 | 6.30483700 | 0.67104400 |
| H    | -2.30362700 | 5.53464800 | 0.65450700 |
| H    | -1.14835300 | 5.14065600 | 1.93575000 |
| C    | -0.85148500 | 4.58028100 | -1.48225600 |
| H    | -0.42822000 | 3.79039900 | -2.10648300 |
| H    | -1.91051500 | 4.68741800 | -1.73290300 |
| H    | -0.34338700 | 5.52174500 | -1.71063200 |
| H    | -2.29976700 | -0.71321700 | 1.54903400 |
| H    | -0.58231600 | -1.19481900 | -1.44644600 |
| H    | -1.76099800 | -3.06909500 | 0.66310900 |
| C    | 1.85268400 | -1.06994300 | -2.20959400 |
| H    | 0.97226100 | -1.12446700 | -2.85792400 |
| H    | 2.72709200 | -1.16352800 | -2.85478000 |
| C    | 1.86254100 | 0.31947500 | -1.57346300 |
| H    | 0.90243000 | 0.57435500 | -1.12069200 |
| H    | 2.10678700 | 1.08380700 | -2.31753100 |
| O    | 2.78754800 | 0.39758600 | -0.46660100 |
| S    | 4.33652400 | 0.63206100 | -0.75221000 |
| C    | 4.43743100 | 2.39232100 | -0.83356500 |
| H    | 3.82489000 | 2.74007000 | -1.66548900 |
| H    | 4.08799300 | 2.79282200 | 0.11737200 |
| H    | 5.48516800 | 2.64154800 | -1.00245000 |
| O    | 4.99413100 | 0.16665900 | 0.43193500 |
| O    | 4.67481900 | 0.07764500 | -2.03430500 |
Structure V*

C   1.04187800  0.12986600  3.02642200
C  -0.15174400 -0.69640100  2.85191000
C    0.67049800  1.49340000  2.79380200
C   -0.63619800  1.47082700  2.27588200
C   -1.16593800  0.11633500  2.38313000
H    1.31717800  2.35525800  2.86400300
H   -1.17662000  2.32145100  1.87964800
H   -2.14808700 -0.18578600  2.04561000
C    3.37434900  -0.69896800 -1.00659000
C    3.39481700  0.58849300 -0.44241200
C    4.62899300  1.24719400 -0.36490900
C    5.80226700  0.66899600 -0.83178200
C    5.76683500 -0.59926600 -1.40347300
C    4.55602200 -1.27082300 -1.48458300
C    2.15871700 -1.57943300 -1.10299100
H    4.65835900  2.24352800  0.06759600
H    6.73971000  1.20880900 -0.75056900
H    6.67424800 -1.06233400 -1.77442900
H    4.49498500 -2.26345700 -1.91445200
O    2.18384500 -2.62563300 -1.74114300
N    1.07678900 -1.14452800 -0.41210700
O    0.01002000 -2.05355400 -0.50992100
C    0.05943800 -3.09121700  0.35083400
O    0.95972800 -3.27731700  1.12398100
Rh   0.69109200  0.30807600  0.95534900
C    1.49030800  2.07010300 -1.16730700
C    2.18339300  1.34831600  0.01868400
C    0.33517400  2.94256800 -0.71185500
C   -0.97932900  2.79760200 -1.18395700
C    0.60010200  3.92606500  0.24912600
SUPPORTING INFORMATION

C  -1.98975400  3.58936800  -0.62269700
C  -0.40584000  4.71921600  0.78357100
H   1.62397000  4.07127600  0.58285200
C  -1.71875300  4.53466000  0.35810400
H  -3.00526900  3.46042900  -0.98291700
H  -0.16728600  5.47291900  1.52609200
H  -2.52143400  5.13653500  0.76972200
H   1.99442400  -0.21851800  3.39890500
H  -0.16968000  -1.77161900  2.95724200
C  -1.21999700  -3.91013700  0.25800500
C  -2.99646000  -3.10115900  0.99866900
H  -2.06904100  -3.01661500  2.06564500
H  -2.38046600  -2.09268600  0.58071700
H  -3.26639500  -3.60649800  0.90473900
C  -1.00079400  -5.25650500  0.94429700
H  -1.93350500  -5.82737000  0.93601900
H  -0.23399700  -5.83903900  0.42615100
H  -0.68313900  -5.11771400  1.97979800
C  -1.62983900  -4.10714100  -1.20626000
H  -1.83801800  -3.15065100  -1.69140200
H  -0.83953600  -4.61042400  -1.77080400
H  -2.53135700  -4.72566200  -1.24933800
H   2.52482000  2.10894700  0.72512100
H   1.16788100  1.33167800  -1.90684900
H   2.24814400  2.69559500  -1.66139000
C  -1.36447500  1.89031100  -2.33625700
H  -0.60988800  1.93671400  -3.12917100
H  -2.29446800  2.26887500  -2.76345300
C  -1.54499100  0.40986300  -2.01015200
H  -0.59158300  -0.09332300  -1.84909800
H  -2.06144200  -0.09732200  -2.83085600
O  -2.25205900  0.17297000  -0.77087500
S  -3.83637900  0.27833500  -0.73512400
|   | X (Å) | Y (Å) | Z (Å) |
|---|-------|-------|-------|
| C | -4.37835000 | -1.20149200 | -1.53349300 |
| H | -4.01889600 | -1.20764400 | -2.56194400 |
| H | -4.00717600 | -2.05686600 | -0.97159200 |
| H | -5.46814000 | -1.16974000 | -1.51776000 |
| O | -4.15061700 | 0.20844800 | 0.66355800 |
| O | -4.26913800 | 1.40162800 | -1.51936900 |
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8. NMR Spectra
