Supporting Information

Merging Directed C–H Activations with High-throughput Experimentation: Development of Iridium-catalyzed C–H Aminations Applicable to Late-stage Functionalization

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General Information

Reagent Information

Unless otherwise noted, all reagents and solvents were used as received. The \([\text{Cp}^*\text{IrCl}_2]\) catalyst precursor for the preparation of \([\text{Cp}^*\text{Ir(H}_2\text{O)}_3]\text{SO}_4\) was purchased from Strem Chemicals. \(\text{Et}_3\text{N}\) was purchased from Sigma Aldrich. 4-Methoxybenzyloxy carbonyl azide (MozN\(_3\)) was purchased from Sigma Aldrich. All reactions were performed under air atmosphere with no exclusion of moisture. All reagents were used as received from vendors. The SiliaMetS\(^S\) Imidazole (Si-IMI) metal scavenger from SiliCycle was used.

Screening and HTE Information: Reaction set-up and analysis (1.0 nmol – 8.0 nmol scale)

Reagents were dispensed by acoustic dispensing using the Labcyte Echo\(^S\) liquid dispensing system. For the reaction set-up Labcyte Echo\(^S\) qualified 1536-well low dead volume plates were used. As source plates and analytical plates Labcyte Echo\(^S\) qualified 384-well plates were used. LCMS analysis (MS only, no UV) was carried out on a Waters Acquity UPLC system, on a BEH C18 column (basic method: A: H\(_2\)O/MeCN/NH\(_3\) = 95/5/0.2, B: MeCN). MS analysis was also performed on an AMI-MS system as previously described.\(^1\)

Screening and HTE Information: Reaction set-up and analysis (0.2 \(\mu\)mol - 0.8 \(\mu\)mol scale)

For liquid dispensing the Mosquito\(^S\) LV system from SPT Labtech was used. For reaction set-up 384-well Plate\(^+\) glass-coated microplates from Thermo Fisher Scientific were used. For analysis standard 384-well microplates were used. LCMS analysis was carried out on a Waters Acquity UPLC system, on a BEH C18 column (basic method: A: H\(_2\)O/MeCN/NH\(_3\) = 95/5/0.2, B: MeCN).
Screening and HTE information: Reaction set-up and analysis (5 µmol - 0.02 mmol scale)
Solids were weighed in manually or using the Quantos powder dosing system from Mettler Toledo. For liquid dispensing manual pipettes and the TECAN freedom evo liquid handling platform was used. For solvent removal the SP Scientific Genevac HT-6 evaporation system was used. The reactions were set-up in a Para-Dox® 24- or 96-position parallel synthesis plate using 50 µL or 1 mL vials. LCMS analysis was carried out on a Waters Acquity UPLC system, on a BEH C18 column (basic method: A: H2O/MeCN/NH₃ = 95/5/0.2, B: MeCN).

Top: Left: 96-well plate used at 5 µmol scale. Right: 96-well plate used at 0.02 mmol scale.
Bottom: Left: 96-well analytical plate. Right: Analytical plate set-up using the Tecan Freedom EVO® liquid handling system.

Screening and HTE information: Purification (0.02 mmol scale)
Pre-purification analysis of the crude samples was performed on a Waters Acquity System with a Waters QDA Mass Spectrometer using three different columns to evaluate the best method for preparative separation: Waters Acquity UPLC HSS C18 1.8 µm (2.1 x 50 mm) and Waters Acquity UPLC CSH Fluoro-Phenyl 1.7 µm (2.1 x 50 mm) at acidic conditions and Waters Acquity UPLC BEH C18 1.7 µm (2.1 x 50 mm) at basic conditions. A gradient of 2-94% MeCN (10 mM formic acid or 0.2% ammonia) was used with a flow 0.8 mL/min for 2.5 min at 45°C.

Preparative LC was performed on a Waters Fraction Lynx system with a Waters QDA Mass Spectrometer and a 2767 autosampler. The columns used were either Waters SunFire C18 OBD 5 µm (10 x 100 mm) or Waters XSelect CSH Fluoro Phenyl OBD 5 µm (10 x 100 mm) at acidic conditions or Waters XBridge BEH C18 OBD 5 µm (10 x 100 mm) at basic conditions. A focused 50 % MeCN gradient (0.1 M formic acid or 0.2% ammonia) was used with a flow of 8.3 ml/min in 5.2 min at ambient temperature. Fraction collection was triggered using a combination of UV and MS.

The purity of the isolated sample was determined using a Waters Acquity System with a Waters QDA Mass Spectrometer at both acidic and basic conditions, using a Waters Acquity UPLC HSS C18 1.8 µm (2.1 x 50 mm) at low pH and Waters Acquity UPLC BEH C18 1.7 µm (2.1 x 50 mm) at high pH. A
A gradient of 5-94% MeCN (10 mM formic acid or 47 mM NH₃/6.5 mM NH₄HCO₃) was used with a flow 0.8 mL/min for 1.5 min at 50°C.

Purification information: Scale up (0.1 - 0.5 mmol scale)
Flash column chromatography purifications were performed on Biotage ISOLUTE SI 25 g pre-loaded columns, unless otherwise stated. Biotage® Sfär-samplert® (2.5g) were used for sample preparation for flash column chromatography, unless otherwise stated. For HPLC purification of scale-up compounds (0.1 – 0.5 mmol scale), preparative reverse-phase HPLC on a Kromasil C8 column (10 μm, 250x50 ID mm), using gradient elution (acidic method: A: H₂O/MeCN/FA = 95/5/0.2, B: MeCN; or basic method: A: H₂O/MeCN/NH₃ = 95/5/0.2, B: MeCN) was used. The reaction mixtures purified by HPLC were treated with a metal scavenger, SiliaMetS® Imidazole from Silicycle prior to purification. Gilson GX-281 liquid handler/autosampler was used. UV detector Gilson UV/VIS-155 was used for UV-triggered collection of fractions at 254 nm wavelength.

Analytical information
LCMS analysis was carried out on a Waters Acquity UPLC system, on a BEH or HSS C18 column. For SFC-MS analysis a Waters Acquity UPC2 SFC-MS system with a BEH column was used. Conversion quantification in the optimization campaign, informer libraries and functional group tolerance studies were based on UV trace as a ratio of SM:P (starting material : product). Nuclear magnetic resonance spectra (¹H, ¹³C, ¹⁹F, COSY, HSQC, HMBC) were recorded on Bruker ULTRASHIELD 500 and 600 MHz spectrometer with a Bruker CRYO PLATFORM. ¹H NMR spectra were referenced to CD₃OD (3.31 ppm), DMSO-d₆ (2.50) and CDCl₃ (7.26). ¹³C NMR spectra were recorded at 126 and 151 MHz, referenced to in CD₃OD (49.00 ppm), DMSO-d₆ (39.52) and CDCl₃ (77.16 ppm). Coupling constant (J) values were measured in Hertz (Hz) and chemical shift (δ) values in parts per million (ppm). HRMS data was recorded on a Waters Acquity System with a XEVO-QTOF MS spectrometer at either acidic or basic conditions, using Leucine Enkephaline (C28H37N5O7, m/z 556.2771) as lock mass. ESI ionization in positive or negative mode. A gradient of 5-90% MeCN (10 mM formic acid or 47 mM NH₃/6.5 mM NH₄HCO₃) was run with a flow of 0.8 mL/min for 2.5 min at 45°C, using a Waters Acquity UPLC BEH C18 1.7 μm (2.1 x 50 mm) at high pH.

Safety considerations
Organic azides are known high energy compounds and special precautions need to be taken when used. As N₂ gas is formed as a side-product in the reaction, measures to mitigate the pressure build-up should be taken. Keeping a 1:3 reaction volume to head space is recommended.

Catalyst preparation
The [Cp*Ir(H₂O)₃]SO₄ catalyst was prepared according to published procedure.²
Ag₂SO₄ (2.52 mmol, 786 mg) was added to a suspension of [Cp*IrCl₂]₂ (1.255 mmol, 1.00 g) in deionized H₂O (8.0 mL). The mixture was stirred at room temperature for 16 h. The contents were then transferred into a Corning® 15 mL centrifuge tube and centrifuged at 2000rpm for 1 minute to sediment the silver salts. The supernatant was removed and kept. The cake was washed with water (8 mL), centrifuged and filtrate collected two times. The combined aqueous phases were concentrated in vacuo to yield the product [Cp*Ir(H₂O)₃]SO₄ as a yellow solid (1.15 g, 94%).
Reaction optimization

Initial optimization

Screening 1

The initial reaction conditions were based on previously published method. The commercially available MozN₃ was chosen as nitrogen source. Low solubility of the NaOAc and AgNTf₂ additives was noted according to the conditions of entry 1. Highest conversion was observed according to conditions of entry 1. Conditions of entry 8 were chosen for further optimization, as lower reaction concentrations were sought after to facilitate the use of stock solutions.

Reaction scale 0.05 mmol. The reactions were set up in a 24-well Para-doxx block, vials equipped with stirrer bars. The solid additives and catalysts were weighed in manually. N-(tert-butyl)benzamide (8.9 mg, 0.05 mmol) and MozN₃ (15.5 mg, 0.075 mmol) were added, followed by addition of the reaction solvent. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

| Entry | Deviation | Conversion (%) |
|-------|-----------|----------------|
| 1     | None      | 42             |
| 2     | [Cp*Ir(H₂O)₃]SO₄ (10 mol%), no AgNTf₂ | 65             |
| 3     | [Cp*Ir(H₂O)₃]SO₄ (5 mol%), no AgNTf₂ | 31             |
| 4     | [Cp*Ir(H₂O)₃]SO₄ (10 mol%), no AgNTf₂, MozN₃ (2.5 equiv) | 56             |
| 5     | [Cp*Ir(H₂O)₃]SO₄ (10 mol%), no AgNTf₂, room temperature | 0              |
| 6     | [Cp*Ir(H₂O)₃]SO₄ (10 mol%), no AgNTf₂, room temperature, KOAc (0.3 equiv.) | 0              |
| 7     | [Cp*Ir(H₂O)₃]SO₄ (10 mol%), no AgNTf₂, room temperature, nBu₄OAc (0.3 equiv.) | 0              |
| 8     | [Cp*Ir(H₂O)₃]SO₄ (10 mol%), no AgNTf₂, 0.2M concentration | 55             |

Conversion determined by LCMS (UV trace). Entry chosen for next round of optimization highlighted in green.

Entry 1 based on published literature procedure.

Control experiments

A series of control experiments was carried out to prove the observed amination is a result of iridium catalysis. No conversion was observed in absence of [Cp*Ir(H₂O)₃]SO₄ (Entries a-c). Similarly, no conversion was observed in presence of Ag₂SO₄.
The reactions were set up in a 24-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. To each respective vial, the solid reagents, N-phenylacetamide (2.7 mg, 0.02 mmol), N-phenylpyrimidin-2-amine (3.4 mg, 0.02 mmol), MozN₃ (6.2 mg, 0.03 mmol) and Ag₂SO₄ (0.6 mg, 2 µmol) were weighed in manually. DCE (100 µL) was added, followed by addition of 2-(m-tolyl)pyridine (3.4 µL, 0.02 mmol) to respective vials. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

Screening 2
Screening against 2 substrates bearing different directing groups. Further miniaturization was also tested, with the reactions on a 5 µmol scale, 25 µL total volume. Better results obtained with [Cp*Ir(H₂O)₃]SO₄. Significant decrease in conversion observed with [Cp*IrCl₂]₂ in absence of AgNTf₂. Best results obtained with [Cp*Ir(H₂O)₃]SO₄ in absence of any additives.

The reactions were set up in a 96-well Para-dox silver block equipped with stirrer bars. Reaction scale 5 µmol. [Cp*Ir(H₂O)₃]SO₄ (0.05M, 10 µL, 0.5 µmol), NaOAc (0.05M), LiOAc (0.05M) and KOAc (0.05M) were added as solutions in deionized water. [Cp*IrCl₂]₂ (0.025M, 10 µL) was added as stock solution in MeOH. The solvents were then removed using a Genevac HT6 centrifuge evaporator. The substrates and MozN₃ were added as DCE solutions (0.2 M, 25 µL). The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (20 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.
Substrate

\[ \text{[Cp*Ir(H_2O)_3]SO}_4 \quad \text{[CpIrCl}_2 \]

| Substrate | No Additive | NaOAc (0.3 equiv) | LiOAc (0.3 equiv) | KOAc (0.3 equiv) | NaOAc (1.0 equiv) | LiOAc (1.0 equiv) | KOAc (1.0 equiv) |
|-----------|-------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| S1        | 100         | 57                | 93                | 62                | 99                | 97                | 94                |
| S2        | 27          | 21                | 11                | 4                 | 11                | 11                | 8                 |

Converting determined by LCMS (UV trace). Entry chosen for next round of optimization highlighted in green.

Screening 3

The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. \([\text{Cp*Ir(H}_2\text{O)}_3]\text{SO}_4 \) (0.05M, 40 µL, 2 µmol) and NaOAc (0.1M, 60 µL, 6 µmol) were added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. \(N-(\text{tert-butyl})\text{benzamide} \) (S2, 3.5 mg, 0.02 mmol) was added as solid using the Quantos powder dosing system. MozN\(_3\) (6.2 mg, 0.03 mmol) was weighed in manually. The respective solvents (100 µL) were added, followed by the addition of 2-(3-methylphenyl)pyridine (S1, 3.4 µL, 0.02 mmol). The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

Substrate

| Substrate | NMP | IPA | 2MeTHF | EtOAc | Acetone | DCE | Toluene | CPME |
|-----------|-----|-----|--------|-------|---------|-----|---------|------|
| S1        | 100 | 100 | 100    | 100   | 100     | 100 | 86      | 100  |
| No Additive |     |     |        |       |         |     |         |      |
| NaOAc (0.3 equiv) | 0   | 7   | 0      | 0     | 0       | 3   | 0       | 0    |
| S2        |     |     |        |       |         |     |         |      |
| No Additive |     |     |        |       |         |     |         |      |
| NaOAc (0.3 equiv) | 0   | 12  | 12     | 16    | 11      | 21  | 19      | 21   |

Conversion determined by LCMS (UV trace). Entry chosen for next round of optimization highlighted in green.
Catalyst loading and solvent effect study
The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. [Cp*Ir(H₂O)]SO₄(0.05M) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. N-(2-Pyrimidyl)indole (3.9 mg, 0.02 mmol) was added as solid using the Quantos powder dosing system. To the same vials MozN₃ (0.3M, 100 µL, 0.03 mmol) was added in respective solvents. 2-(3-methylphenyl)pyridine (0.02 mmol) and MozN₃ (0.03 mmol) were added together as stock solution (100 µL per vial) in respective solvents. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

![Substrate and solvent effect study](image)

| Substrate | Solvent | 2c | 2h |
|-----------|---------|----|----|
|           |         | NMP | DCE | EtOAc | CPME | NMP | DCE | EtOAc | CPME |
| 10        | 90.9    | 99.1 | 99.5 | 99.5 | 100 | 100 | 100 | 93.6 |
| 8         | 92.7    | 99.2 | 100 | 99.4 | 98.0 | 100 | 100 | 83.9 |
| 6         | 88.1    | 99.1 | 64.4 | 98.6 | 87.0 | 100 | 96.0 | 66.3 |
| 4         | 57.4    | 99.5 | 25.1 | 65.4 | 38.9 | 100 | 81.6 | 35.2 |
| 2         | 13.1    | 83.2 | 11.1 | 21.8 | 6.9  | 55.0 | 54.7 | 7.6  |

Ir (mol%)
- Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.

MozN₃ and catalyst loading effect study
The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. [Cp*Ir(H₂O)]SO₄(0.05M) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The substrates were weighed in manually. N-(2-Pyrimidyl)indole (3.9 mg, 0.02 mmol) was added as solid using the Quantos powder dosing system. To the same vials MozN₃ (0.3M, 100 µL, 0.03 mmol) was added in respective solvents. 2-(3-methylphenyl)pyridine (0.02 mmol) and MozN₃ (0.03 mmol) were added together as stock solution (100 µL per vial) in respective solvents. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.
Overall lower yield for the desired product from the functionalization of 2-(3-methylphenyl)pyridine were obtained in NMP due to regioisomer formation, as well as difunctionalization (see below).

Single substrate reoptimizations

For a series of substrates catalyst loading and MozN₃ loading were optimized.

The reactions were set up in a 24- or 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. [Cp*Ir(H₂O)₃]SO₄ (0.05M) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The substrate (0.02 mmol) and MozN₃ (6.2 mg, 0.03 mmol) were together added as stock solutions in DCE (100 µL). The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.
Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.

Single substrate optimization (2f)
The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. \([\text{Cp}^*\text{Ir(H}_2\text{O)}_3]\text{SO}_4\) (0.05M) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The substrate (0.02 mmol) and MozN\(_3\) (6.2 mg, 0.03 mmol) were together added as stock solutions in DCE (100 µL). The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

Single substrate optimization (2q)
The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. \([\text{Cp}^*\text{Ir(H}_2\text{O)}_3]\text{SO}_4\) (0.05M) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The substrate (0.02 mmol) and MozN\(_3\) (6.2 mg, 0.03 mmol) were together added as stock solutions in DCE (100 µL). The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.
Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.

**Single substrate optimization (2e)**

The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. [Cp*Ir(H₂O)₃]SO₄ (0.05M) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The substrate (0.02 mmol) and MozN₃ (6.2 mg, 0.03 mmol) were together added as stock solutions in DCE (100 µL). The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

| Ir (mol%) | 2  | 4  | 6  |
|-----------|----|----|----|
| Mono      | Di | Mono | Di | Mono | Di |
| 1.0       | 22.5 | 2.5 | 36.8 | 10.2 | 42.4 | 21.1 |
| 1.1       | 23.5 | 3.1 | 37.7 | 9.8  | 40.2 | 15.6 |
| 1.3       | 22.2 | 2.2 | 33.6 | 7.9  | 38.5 | 13.6 |
| 1.5       | 32.2 | 2.4 | 33.1 | 7.6  | 38.0 | 12.9 |
| 2.0       | 14.7 | 0.9 | 25.5 | 5.1  | 35.1 | 10.7 |

**Single substrate optimization (2d)**

Note: Optimization not conducted in plate format. Scale 0.1 mmol. Experiments set up in 3 consecutive rounds, round 1 (Entries 1-4), round 2 (Entries 5 and 6), Round 3 (Entries 7 and 8). Conditions of entry 8 chosen for scale up. Automatic peak integration and processing used.

[Cp*Ir(H₂O)₃]SO₄ was weighed in a 2 mL glass screw top vial, followed by addition of MozN₃. DCE (0.5 mL) was added, followed by addition of 2-phenylpyridine (14.3 µL, 0.1 mmol). The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. Analyzed by LCMS.

| Ir (mol%) | Product | 2  | 4e | 2e | 2e' |
|-----------|---------|----|----|----|-----|
| 1.0       | 86.4 | 9.5 | 86.9 | 10.2 |
| 1.1       | 85.9 | 10.4 | 86.8 | 7.7  | 85.6 | 13.0 |
| 1.3       | 78.0 | 21.2 | 77.6 | 22.1 | 73.7 | 26.3 |
| 1.5       | 81.1 | 17.5 | 53.9 | 45.8 | 49.6 | 50.1 |
| 2.0       | 84.3 | 10.6 | 53.4 | 46.0 | 22.7 | 76.4 |

Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.
| Entry | Ir (mol%) | MozN$_3$ (equiv) | % Mono | % Di |
|-------|-----------|-----------------|--------|------|
| 1     | 2         | 1.0             | 75.0   | 2.0  |
| 2     | 2         | 1.1             | 76.4   | 2.5  |
| 3     | 4         | 3.0             | 59.7   | 4.0  |
| 4     | 6         | 3.0             | 52.7   | 13.5 |
| 5     | 4         | 1.1             | 92.7   | 7.3  |
| 6     | 4         | 1.3             | 88.5   | 11.5 |
| 7     | 4         | 1.0             | 82.9   | 2.9  |
| 8     | 4         | 1.05            | 92.4   | 3.3  |

Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.

**Single substrate optimization (2k and 2u)**

The reactions were set up in a 24- or 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol, 100 µL total volume. [Cp*Ir(H$_2$O)$_3$]SO$_4$ was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The substrate and MozN$_3$ were added as stock solutions in DCE. C$_5$H$_9$COOH (2.2 µL) was added with a multichannel pipette. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

**Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.**

### Experiment Details

- **Solvent Options**
  - DCE
  - CPME
  - EtOAc

| Solvent | DCE | CPME | EtOAc |
|---------|-----|------|-------|
| Ir (mol%) | 2   | 4    | 6     |
| MozN$_3$ (equiv) | 1.1 | 1.3  | 1.5   |

**Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.**
Single substrate optimization (3a and 3a’)

The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. \([\text{Cp}*\text{Ir(H}_2\text{O})_3]\text{SO}_4 (0.05M)\) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. Atazanavir (14.1 mg, 0.02 mmol) was added as solid using the Quants powder dosing system. MozN\(_3\) (0.3M, 100 µL, 0.03 mmol) was added as stock solutions in respective solvents. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

| Ir (mol%) | DCE | NMP |
|----------|-----|-----|
|          | P1  | P2  | P1  | P2  | P1  | P2  | P1  | P2  | P1  | P2  |
| 1.0      | 86.5| 3.3 | 90.2| 3.7 | 92.0| 4.0 | 73.4| 8.6 | 77.4| 9.3 | 81.9| 11.2|
| 1.1      | 89.2| 4.5 | 92.1| 7.9 | 94.2| 5.8 | 76.8| 13.6| 78.3| 19.5| 80.6| 19.4|
| 1.3      | 83.3| 16.7| 80.0| 20.0| 80.9| 19.1| 74.9| 13.0| 76.2| 23.8| 67.8| 32.2|
| 1.5      | 63.0| 37.0| 63.9| 36.1| 65.0| 35.0| 73.8| 11.9| 64.8| 35.2| 65.2| 34.8|
| 2.0      | 43.5| 56.5| 14.3| 85.7| 13.0| 87.0| 72.6| 11.6| 58.4| 32.5| 46.9| 53.1|
| 3.0      | 61.4| 38.6| 21.9| 21.9| 0.0 | 100 | 74.8| 8.9 | 76.0| 24.0| 60.0| 40.0|

*Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.*
Single substrate optimization (3e)

The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. \([\text{Cp}^*\text{Ir(H}_2\text{O})_3]\text{SO}_4 (0.05M)\) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. Telmisartan (10.3 mg, 0.02 mmol) was added as solid using the Quantos powder dosing system. \(\text{MozN}_3\) (0.3M, 100 µL, 0.03 mmol) was added as stock solution in respective solvent. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

\[
\begin{array}{cccc|cccc|cccc}
\text{Ir} & \text{DCE} & \text{NMP} \\
\text{(mol%)} & 2 & 4 & 6 & & 4 & 6 & 8 & \\
& P1 & P2 & P1 & P2 & P1 & P2 & P1 & P2 & P1 & P2 \\
1.0 & 2.4 & 1.3 & 4.6 & 1.8 & 6.7 & 2.4 & 4.9 & 0.3 & 7.6 & 0.3 & 14.2 & 0.6 \\
1.1 & 2.7 & 1.1 & 4.6 & 2.7 & 5.5 & 3.9 & 5.7 & 0.3 & 10.3 & 0.4 & 15.2 & 0.5 \\
1.3 & 2.8 & 0.8 & 5.0 & 1.6 & 6.2 & 3.4 & 5.8 & 0.3 & 8.3 & 0.3 & 15.4 & 0.4 \\
1.5 & 2.1 & 0.9 & 6.0 & 1.6 & 6.8 & 2.8 & 5.9 & 0.3 & 9.4 & 0.4 & 16.7 & 0.7 \\
2.0 & 2.5 & 0.8 & 5.6 & 1.7 & 7.7 & 1.8 & 6.2 & 0.2 & 11.5 & 0.4 & 18.2 & 0.7 \\
3.0 & 2.2 & 0.4 & 5.8 & 1.0 & 8.4 & 1.7 & 6.7 & 0.3 & 12.8 & 0.4 & 16.7 & 0.6 \\
\end{array}
\]

Conversion determined by LCMS (UV trace). Color gradient: lowest → highest conversion, red → green.
Functional group tolerance study

The reactions were set up in a 96-well Para-doX gold block equipped with stirrer bars. Reaction scale 0.02 mmol. 48 additives screened against 2 solvents (NMP, DCE). [Cp*Ir(H$_2$O)$_3$]SO$_4$ (0.05 M, 40 µL, 2 µmol) was added as solution in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The solid additives (0.02 mmol) were weighed in manually. 2-(3-methylphenyl)pyridine (0.02 mmol) and MozN$_3$ (0.03 mmol) were added together as stock solution in respective solvents (100 µL per vial). The liquid additives (0.02 mmol) were added manually using a single channel pipette. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20 h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

Conversion determined by LCMS (UV trace). Top bars NMP, bottom bars DCE. Color coding: green >50%; orange 25-50%, red <25%.
The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. \([\text{Cp}^*\text{Ir}(\text{H}_2\text{O})_3\text{SO}_4\text{]}(0.05\text{M, }40\ \mu\text{L, }2\ \mu\text{mol})\] was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The solid substrates were weighed in manually. After this, \(\text{MozN}_3\) (0.3M, 100 µL, 0.03 mmol) was added as stock solution in respective solvents. Addition of liquid substrates (0.02 mmol) followed. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS.

Below: successful examples

Successful examples, identity confirmed by NMR analysis at screening scale. Conversion determined by LCMS (UV trace).

Below: Purification was not attempted due to low conversion (top row) or insufficient separation in analytical LCMS (bottom row).
Conversion determined by LCMS (UV trace).

Below: Compounds with failed purification. The four examples presented are counted as unsuccessful reactions.

Conversion determined by LCMS (UV trace). Potential reasons for failed purification: Decomposition during sample preparation and/or purification, lack of ionization and detection of predicted product mass during the purification run, or observation of false positives by LCMS.

Below: Compounds with no conversion observed.

Analyzed by LCMS (UV trace).
LSF informer library

The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol. [Cp*Ir(H_2O)_3]SO_4 (0.05M, 40 µL, 2 µmol) was added as solutions in deionized water. The solvent was then removed using a Genevac HT6 centrifuge evaporator. The substrates (0.02 mmol) were weighed in manually. After this, MozN_3 (0.3M, 100 µL, 0.03 mmol) was added as stock solution in respective solvents. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS. Selected examples (highlighted in colored squares) were submitted for purification by HPLC.

Below: Successful isolated examples

Conversion determined by LCMS (UV trace). * Only difunctionalization observed.

Below: Substrate not chosen for purification due to low conversion or product decomposition. Counted as unsuccessful reactions.
Conversion determined by LCMS (UV trace). Product with O-deacetylation under reaction conditions.

LSF Scope: side reaction

In all depicted cases formation of a new species (% conversion in parentheses) was observed, in all cases with a MW lower by 15 Dalton then for the expected products. In the case of Mirabegron the product was isolated and confirmed as the addition product depicted. As the common feature of the compounds with which this mass difference was observed was the presence of highly nucleophilic functional groups, at this point we speculate that the same side reaction occurred in all presented cases.
Conversion determined by LCMS (UV trace). Potential reasons for failed purification: Decomposition during sample preparation and/or purification, lack of ionization and detection of predicted product mass during the purification run, or observation of false positives by LCMS.

Unsuccessful substrates (no conversion)
Miniaturization studies

Reaction scale 0.2 - 0.8 µmol

The reactions were set up in a 384-well Plate+™ glass-coated microplate. Stock solutions S1 were prepared with the respective substrates (0.256 mmol) and MozN₃ (0.256 mmol) in 640 µL NMP. Stock solution S2 was prepared from [Cp*Ir(H₂O)₃]SO₄ (0.04 mmol) in 1 mL NMP. Reactions were run at three distinct volumes: 1, 2 and 4 µL. A column control experiments with no catalyst was also set up for each substrate. The stock solutions were dispensed to the reaction plate using the Mosquito liquid dispensing system, with S1 added first, followed by S2. The plate was sealed and heated at 60 °C in a Genevac centrifuge at atmospheric pressure (Note: Using the centrifuge for the reaction minimized solvent loss). The plate was allowed to reach ambient temperature, centrifuged for 5 min at 2500 rpm, seal removed. Metal scavenger (Si-IMI, 2 equiv) was added in NMP. The reactions were diluted with NMP to a total of 40 µL. The plate was sealed and heated at 50 °C on an orbital shaker. An analytical plate was made, with 2 mM concentration, solvent DMSO. Analyzed by LCMS. Reactions were successful throughout the plate, including the lowest reaction volume (1 µL, see manuscript).

Reaction scale 1.0 – 8.0 mmol

The reactions were set up in a 1536-well echo plate. Stock solutions S1 were prepared with the respective substrates (0.1 mmol) and MozN₃ (0.1 mmol) in 233 µL NMP. Stock solution S2 was prepared from [Cp*Ir(H₂O)₃]SO₄ (8 µmol) in 200 µL NMP. Reactions were run at four distinct volumes: 5, 10, 20 and 40 nL. The stock solutions were dispensed to the reaction plate using the Echo acoustic liquid handling system, with S1 added first, followed by S2. The plate was sealed and heated at 60 °C in a Genevac centrifuge at atmospheric pressure (Note: Using the centrifuge for the reaction minimized solvent loss). An analytical plate was made, with 2 mM concentration, solvent water. Analyzed by LCMS and AMI-MS. Product detection by MS was observed throughout the plate, even at the lowest reaction volumes (5 nL).

General experimental procedures

General Procedure A

[Cp*Ir(H₂O)₃]SO₄ (9.7 mg, 0.02 mmol, 4 mol%) was weighed in a glass screw-top vial (16 mL). MozN₃ (134.7 mg, 0.65 mmol) was added, followed by addition of substrate (0.5 mmol). The vial was
equipped with a stirrer bar, followed by addition of DCE (2.5 mL). The sealed vial was placed in a heating block at 60 °C and stirred for 20 hours.

**General Procedure B**

[Cp*Ir(H₂O)₃]SO₄ (3.9 mg, 8.0 µmol, 4 mol%) was weighed in a glass screw-top vial (4 mL). MozN₃ (41.4 mg, 0.2 mmol) was added, followed by addition of substrate (0.2 mmol). The vial was equipped with a stirrer bar, followed by addition of solvent (1.0 mL). The sealed vial was placed in a heating block at 60 °C and stirred for 20 hours.

**General Procedure C**

Based on screening conditions. [Cp*Ir(H₂O)₃]SO₄ (4.9 mg, 0.01 mmol, 10 mol%) was weighed in a glass screw-top vial (2 mL). MozN₃ (31.1 mg, 0.15 mmol) was added, followed by addition of substrate (0.1 mmol). The vial was equipped with a stirrer bar, followed by addition of solvent (0.5 mL). The sealed vial was placed in a heating block at 60 °C and stirred for 20 hours.

**General Procedure D**

Reaction set-up according to Directing group and LSF informer library chapters.

**General Procedure E**

Screening format, selected examples isolated. The reactions were set up in a 96-well Para-dox gold block equipped with stirrer bars. Reaction scale 0.02 mmol, 100 µL total volume. [Cp*Ir(H₂O)₃]SO₄ was added as solutions in deionized water (final loading 1.0mg, 2 µmol per vial). The solvent was then removed using a Genevac HT6 centrifuge evaporator. The solid substrates were weighed in manually (0.02 mmol). MozN₃ (per vial 6.2 mg, 0.03 mmol) was added as stock solution in respective solvents. Liquid substrates (0.02 mmol) were added. The reaction mixtures were stirred at 500 rpm and heated at 60 °C for 20h. After this DMSO (200 µL) and metal scavenger were added to the vials and stirred for additional 2 hours at room temperature. Analyzed by LCMS. Purified by preparative reverse phase HPLC.
4-methoxybenzyl (3-methyl-2-(pyridin-2-yl)phenyl)carbamate (2a) was prepared according to General Procedure A. Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO$_2$). Compound 2a was obtained as a colorless solid (132.7 mg, 76%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.72 (ddd, $J = 4.9, 1.7, 0.9$ Hz, 1H), 7.96 (s, 1H), 7.78 (td, $J = 7.7, 1.8$ Hz, 1H), 7.72 (s, 1H), 7.27 – 7.34 (m, 5H), 7.02 (d, $J = 7.6$ Hz, 1H), 6.84 – 6.88 (m, 2H), 5.04 (s, 2H), 3.79 (s, 3H), 2.15 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 159.7, 156.7, 153.7, 149.8, 137.0, 136.2, 135.7, 130.2, 130.0, 128.9, 128.4, 126.2, 125.8, 122.5, 114.0, 66.7, 55.4, 20.9. HRMS (ESI) m/z calcd. for C$_{21}$H$_{20}$N$_2$O$_3$ [M+H]$^+$: 349.1552, found 349.1554.

4-methoxybenzyl (3-bromo-2-(pyridin-2-yl)phenyl)carbamate (2b) was prepared according to General Procedure A. Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO$_2$). Compound 2b was obtained as a colorless wax (76.1 mg, 37%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.71 (ddd, $J = 4.9, 1.8, 0.9$ Hz, 1H), 8.13 (d, $J = 7.5$ Hz, 1H), 7.95 (s, 1H), 7.82 (td, $J = 7.7, 1.8$ Hz, 1H), 7.54 (dt, $J = 7.9, 1.0$ Hz, 1H), 7.40 (dd, $J = 8.1, 1.1$ Hz, 1H), 7.33 (ddd, $J = 7.6, 4.9, 1.2$ Hz, 1H), 7.26 – 7.3 (m, 2H), 7.22 – 7.26 (m, 1H), 6.85 – 6.89 (m, 2H), 5.04 (s, 2H), 3.80 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 159.8, 156.0, 153.5, 149.5, 137.6, 137.0, 130.4, 130.3, 130.1, 128.2, 127.3 (2C), 123.2, 122.7, 120.1, 114.0, 67.0, 55.4. HRMS (ESI) m/z calcd. for C$_{20}$H$_{17}$BrN$_2$O$_3$ [M+H]$^+$: 413.0501, found 413.0513.
4-methoxybenzyl (3-methyl-2-(pyridin-2-yl)phenyl)carbamate (2c) was prepared according to General Procedure A. Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO\textsubscript{2}). Compound 2c was obtained as a colorless solid (152.5 mg, 88%).

The same compound was also prepared using CPME (2.5 mL) as solvent and increased [Cp*Ir(H\textsubscript{2}O)\textsubscript{3}]SO\textsubscript{4} (14.6 mg, 0.03 mmol, 6 mol%) according to otherwise standard conditions. Compound 2c was obtained as a colorless solid (153.0 mg, 88%).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 11.22 (s, 1H), 8.62 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.79 (td, J = 7.8, 1.9 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.34 – 7.38 (m, 2H), 7.2 – 7.24 (m, 2H), 6.88 – 6.91 (m, 2H), 5.12 (s, 2H), 3.81 (s, 3H), 2.36 (s, 3H). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 159.6, 158.4, 154.2, 147.9, 137.6, 135.2, 132.1, 130.8, 130.2, 129.6, 128.9, 125.8, 123.0, 121.8, 120.8, 114.0, 66.4, 55.4, 21.0. HRMS (ESI) m/z calcd. for C\textsubscript{21}H\textsubscript{20}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: 349.1552, found 349.1550.

4-methoxybenzyl (2-(pyridin-2-yl)phenyl)carbamate (2d) was prepared according to modified General Procedure A, MozN\textsubscript{3} (108.8 mg, 0.525 mmol). Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO\textsubscript{2}). Compound 2d was obtained as a colorless solid (143.2 mg, 86%).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 11.48 (s, 1H), 8.63 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.35 (d, J = 8.2 Hz, 1H), 7.78 – 7.82 (m, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.61 (dd, J = 7.8, 1.5 Hz, 1H), 7.35 – 7.42 (m, 3H), 7.24 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.12 (td, J = 7.8, 1.2 Hz, 1H), 6.88 – 6.92 (m, 2H), 5.14 (s, 2H), 3.81 (s, 3H). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 159.6, 158.4, 154.1, 147.9, 137.6, 135.2, 132.1, 130.8, 130.2, 129.6, 128.9, 125.8, 123.0, 121.8, 120.8, 114.0, 66.5, 55.4. HRMS (ESI) m/z calcd. for C\textsubscript{20}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: 335.1396, found 335.1401.
4-methoxybenzyl (2-(pyridin-2-yl)phenyl)carbamate (2d) and bis(4-methoxybenzyl) (2-(pyridin-2-yl)-1,3-phenylene)dicarbamate (2d') were prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2d (2.5 mg, 37%, >95% purity) was obtained as a colorless solid. Compound 2d' (0.8 mg, 8%, >95% purity) was obtained as a colorless solid.

2d'

$^1$H NMR (500 MHz, DMSO) δ 9.18 (s, 2H), 8.67 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.80 (td, J = 7.8, 1.8 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.35 – 7.4 (m, 3H), 7.22 (d, J = 8.7 Hz, 4H), 6.88 – 6.92 (m, 4H), 4.92 (s, 4H), 3.74 (s, 6H).

$^{13}$C NMR (151 MHz, DMSO) δ 159.1, 154.4, 153.7, 148.8, 137.0, 136.1, 129.8, 129.0, 128.5, 125.8, 122.5, 120.4, 113.8, 65.6, 55.1. HRMS (ESI) m/z calcd. For C$_{29}$H$_{27}$N$_3$O$_6$ [M+H]$^+$: 514.1978, found 514.1995.

4-methoxybenzyl (2-(1H-pyrazol-1-yl)phenyl)carbamate (2e) was prepared according to modified General Procedure A, [Cp$^*$Ir(H$_2$O)$_3$]SO$_4$ (4.9 mg, 0.01 mmol, 2 mol%), MozN$_3$ (103.6 mg, 0.5 mmol). Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO$_2$). Compound 2e was obtained as a colorless solid (116.7 mg, 72%).

$^1$H NMR (500 MHz, DMSO) δ 9.81 (s, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.8 – 7.91 (m, 1H), 7.57 (dd, J = 8.0, 1.4 Hz, 1H), 7.39 (td, J = 8.0, 1.5 Hz, 1H), 7.29 – 7.36 (m, 2H), 7.23 (td, J = 7.9, 1.4 Hz, 1H), 6.86 – 7 (m, 2H), 6.55 – 6.61 (m, 1H), 5.04 (s, 2H), 3.75 (s, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 159.2, 153.2, 141.1, 131.2, 130.7, 130.1, 129.9, 128.2, 127.8, 124.2, 123.5, 122.5, 113.9, 107.3, 66.1, 55.1. HRMS (ESI) m/z calcd. For C$_{18}$H$_{12}$N$_3$O$_3$ [M+H]$^+$: 324.1348, found 324.1343.
4-methoxybenzyl (2-(1H-pyrazol-1-yl)phenyl)carbamate (2e) and bis(4-methoxybenzyl) (2-(1H-pyrazol-1-yl)-1,3-phenylene)dicarbamate (2e') were prepared according to general conditions E. Purification by preparative LC (pH 3, FP column, acidic method). Compound 2e (3.0 mg, 46%, >95% purity) was obtained as a colorless solid. Compound 2e' (1.0 mg, 10%, >95% purity) was obtained as a colorless wax.

**2e**

$^1$H NMR (500 MHz, DMSO) $\delta$ 8.61 (s, 2H), 7.78 – 7.85 (m, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.42 (t, $J = 8.2$ Hz, 1H), 7.24 – 7.27 (m, 4H), 6.89 – 6.93 (m, 4H), 6.48 – 6.51 (m, 1H), 4.96 (s, 4H), 3.74 (s, 6H).

$^{13}$C NMR (151 MHz, DMSO) $\delta$ 159.2, 153.6, 141.2, 133.9, 133.1, 129.9, 128.8, 128.2, 113.8, 106.7, 65.9, 55.1. HRMS (ESI) m/z calcd. For C$_{27}$H$_{26}$N$_4$O$_6$ [M+H]$^+$: 503.1931, found 503.1952.

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4-methoxybenzyl (2-(benzo[d]oxazol-2-yl)phenyl)carbamate (2f) was prepared according to modified General Procedure B. [Cp*Ir(H$_2$O)$_3$SO$_4$ (5.8 mg, 12.0 µmol, 6 mol%), solvent DCE (1.0 mL). Purification by automated flash column chromatography (0-40% EtOAc in heptane, 25g SiO$_2$). Compound 2f was obtained as a colorless solid (30.2 mg, 40%).

$^1$H NMR (500 MHz, DMSO) $\delta$ 11.12 (s, 1H), 8.41 (d, $J = 8.1$ Hz, 1H), 8.19 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.8 – 7.86 (m, 2H), 7.63 (td, $J = 8.7$, 8.1, 1.5 Hz, 1H), 7.48 (td, $J = 7.8$, 1.4 Hz, 1H), 7.4 – 7.45 (m, 3H), 7.25 – 7.29 (m, 1H), 6.95 – 6.98 (m, 2H), 5.19 (s, 2H), 3.76 (s, 3H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 161.3, 159.3, 153.1, 148.7, 140.2, 138.5, 133.0, 130.2, 128.6, 128.2, 126.1, 125.2, 122.7, 119.6, 118.7, 113.9, 112.4, 111.0, 66.3, 55.1. HRMS (ESI) m/z calcd. For C$_{22}$H$_{18}$N$_2$O$_4$ [M+H]$^+$: 375.1345, found 375.1342.
4-methoxybenzyl (2-(pyrimidin-2-ylamino)phenyl)carbamate (2g) and bis(4-methoxybenzyl) (2-(pyrimidin-2-ylamino)-1,3-phenylene)dicarbamate (2g’) were prepared according to General Procedure C. Purification by preparative reverse phase HPLC (36-76% MeCN in NH₃ buffer) to give 2g (16.2 mg, 46%) as a colorless solid, and 2g’ (3.5 mg, 7%) as a colorless solid.

2g

¹H NMR (500 MHz, DMSO) δ 8.98 (d, J = 23.1 Hz, 1H), 8.66 (s, 1H), 8.40 (d, J = 4.8 Hz, 2H), 7.71 (dd, J = 7.8, 1.7 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.07 – 7.14 (m, 2H), 6.91 – 6.94 (m, 2H), 6.81 (t, J = 4.8 Hz, 1H), 5.06 (s, 2H), 3.75 (s, 3H).

¹³C NMR (151 MHz, DMSO) δ 160.4, 159.2, 158.2, 154.3, 131.8, 130.2, 130.0, 128.4, 124.4, 123.9, 113.8, 112.6, 65.9, 55.1.

HRMS (ESI) m/z calcd. For C₁₉H₁₈N₄O₃ [M+H]⁺: 351.1457, found 351.1443.

2g’

¹H NMR (500 MHz, CDCl₃) δ 8.28 (d, J = 4.8 Hz, 2H), 7.62 (s, 2H), 7.27 – 7.32 (m, 5H), 6.97 (s, 2H), 6.87 (d, J = 8.6 Hz, 4H), 6.84 (s, 1H), 6.67 (t, J = 4.8 Hz, 1H), 5.08 (s, 4H), 3.80 (s, 6H).

¹³C NMR (151 MHz, CDCl₃) δ 161.3, 159.8, 158.7, 153.8, 135.4, 130.3, 128.1, 128.0, 114.0, 113.1, 77.2, 77.0, 76.8, 67.1, 55.3.

HRMS (ESI) m/z calcd. For C₂₈H₂₇N₅O₆ [M+H]⁺: 530.2039, found 530.2052.

4-methoxybenzyl (2-(pyrimidin-2-ylamino)phenyl)carbamate (2g) and bis(4-methoxybenzyl) (2-(pyrimidin-2-ylamino)-1,3-phenylene)dicarbamate (2g’) were prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2g (2.3 mg, 33%, >95% purity) was obtained as a colorless solid. Compound 2e’ (0.5 mg, 5%, >95% purity) was obtained as a colorless wax.

4-methoxybenzyl (1-(pyrimidin-2-yl)-1H-indol-7-yl)carbamate (2h) was prepared according to General Procedure B. Solvent DCE. Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO₂). Compound 2h was obtained as a colorless solid (30.2 mg, 40%).

The same compound was also prepared using EtOAc (1.0 mL) as solvent and increased [Cp*Ir(H₂O)₃]SO₄ (5.9 mg, 12.0 µmol, 6 mol%) according to otherwise standard conditions. Compound 2h (30.7 mg, 41%) was obtained as a colorless solid.
**1H NMR** (500 MHz, CDCl₃) δ 11.23 (s, 1H), 8.72 (d, J = 4.8 Hz, 2H), 8.59 – 8.65 (m, 1H), 7.48 – 7.51 (m, 1H), 7.39 – 7.43 (m, 2H), 7.17 – 7.23 (m, 2H), 7.09 (t, J = 4.8 Hz, 1H), 6.97 (s, 1H), 6.91 – 6.94 (m, 2H), 5.21 (s, 2H), 3.82 (s, 3H).

**13C NMR** (126 MHz, CDCl₃) δ 159.9, 158.8, 157.8, 152.8, 135.6, 132.9, 130.6, 130.0, 128.3, 123.1, 122.1, 119.6, 116.3, 116.1, 114.1, 93.8, 67.2, 55.4.

**HRMS** (ESI) m/z calcd. For C₂₁H₁₈N₄O₃ [M+H]+: 375.1457, found 375.1469.

4-methoxybenzyl (1-(pyridin-2-yl)-1H-indol-7-yl)carbamate (2i) was prepared according to General Procedure B. Solvent DCE. Purification by automated flash column chromatography (0-70% EtOAc in heptane, 25g SiO₂). Compound 2i (61.9 mg, 83%) was obtained as a light yellow wax.

**1H NMR** (500 MHz, CDCl₃) δ 9.75 (s, 1H), 8.56 (ddd, J = 5.0, 1.9, 0.7 Hz, 1H), 7.89 (ddd, J = 8.2, 7.5, 2.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.55 – 7.59 (m, 1H), 7.5 – 7.52 (m, 1H), 7.36 – 7.39 (m, 2H), 7.23 (ddd, J = 7.4, 5.0, 0.9 Hz, 1H), 7.12 – 7.2 (m, 2H), 6.71 – 6.99 (m, 3H), 5.18 (s, 2H), 3.81 (s, 3H).

**13C NMR** (126 MHz, CDCl₃) δ 159.9, 152.9, 151.5, 148.9, 139.2, 134.8, 132.3, 130.5, 129.4, 121.9, 121.4, 121.0, 120.3, 118.4, 114.1, 110.3, 92.0, 67.3, 55.4. **HRMS** (ESI) m/z calcd. For C₂₂H₂₀N₃O₄ [M+H]+: 374.1504, found 374.1499.

4-methoxybenzyl (5-bromo-2-(N,N,N’-trimethylsulfamidimidoyl)phenyl)carbamate (2j) was prepared according to General Procedure C. Solvent DCE, 0.2 mmol scale. Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO₂). Compound 2j (31.4 mg, 34%) was obtained as a colorless oil.

**1H NMR** (500 MHz, CDCl₃) δ 11.65 (s, 1H), 8.64 (d, J = 1.8 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.32 – 7.36 (m, 2H), 7.23 (dd, J = 8.6, 1.9 Hz, 1H), 6.87 – 6.92 (m, 2H), 5.14 (d, J = 2.1 Hz, 2H), 3.81 (s, 3H), 2.87 (s, 3H), 2.61 (s, 6H).

**13C NMR** (126 MHz, CDCl₃) δ 159.8, 153.3, 138.9, 130.1, 129.7, 128.4, 128.3, 125.0, 123.0, 119.5, 114.0, 66.9, 55.4, 38.4, 27.7. **HRMS** (ESI) m/z calcd. For C₁₈H₂₀BrN₃O₄S [M+H]+: 456.0593, found 456.0598.
4-methoxybenzyl (2-acetamidophenyl)carbamate (2k) was prepared according to modified General Procedure C. Solvent DCE, 0.2 mmol scale, MozN$_3$ (41.4 mg, 0.2 mmol). Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25 g SiO$_2$). Compound 2k (15.5 mg, 25%) was obtained as a colorless solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.12 (s, 1H), 7.39 – 7.53 (m, 2H), 7.34 – 7.37 (m, 2H), 7.26 (d, $J = 7.5$ Hz, 1H), 7.15 (td, $J = 7.9$, 1.4 Hz, 1H), 7.05 – 7.09 (m, 1H), 6.89 – 6.94 (m, 2H), 5.14 (s, 2H), 3.82 (s, 3H), 2.07 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.9, 159.8, 154.9, 130.9, 130.4, 129.6, 128.2, 126.6, 125.5, 125.3, 124.5, 114.0, 67.2, 55.4, 23.8. HRMS (ESI) m/z calcd. For C$_{17}$H$_{18}$N$_2$O$_4$ [M+H]$^+$: 315.1345, found 315.1360.

4-methoxybenzyl (2-(dimethylcarbamoyl)phenyl)carbamate (2l) was prepared according to General Procedure D. Purification by automated flash column chromatography (10-100% EtOAc in heptane, 25 g SiO$_2$). Compound 2l (35.1 mg, 53%) was obtained as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.30 (s, 1H), 8.15 (d, $J = 8.1$ Hz, 1H), 7.33 – 7.4 (m, 3H), 7.18 – 7.21 (m, 1H), 7.03 (td, $J = 7.5$, 1.1 Hz, 1H), 6.87 – 6.92 (m, 2H), 5.11 (s, 2H), 3.81 (s, 3H), 3.08 (s, 3H), 2.99 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.2, 159.7, 153.7, 137.1, 130.8, 130.4, 128.3, 127.7, 123.7, 122.2, 121.0, 114.0, 66.8, 55.4, 40.0, 35.49. HRMS (ESI) m/z calcd. For C$_{18}$H$_{20}$N$_2$O$_4$ [M+H]$^+$: 329.1501, found 329.1508.
4-methoxybenzyl (2-(methoxy(methyl)carbamoyl)phenyl)carbamate (2m) was prepared according to General Procedure D. Purification by automated flash column chromatography (0-80% EtOAc in heptane, 25g SiO₂). Compound 2m (19.5 mg, 28%) was obtained as a colorless wax.

\[ ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3) \delta 8.63 (s, 1H), 8.18 (d, J = 8.1 \text{ Hz, } 1H), 7.47 - 7.51 (m, 1H), 7.39 - 7.43 (m, 1H), 7.35 (d, J = 8.7 \text{ Hz, } 2H), 7.03 (td, J = 7.8, 1.0 \text{ Hz, } 1H), 6.88 - 6.91 (m, 2H), 5.12 (s, 2H), 3.81 (s, 3H), 3.52 (s, 3H), 3.34 (s, 3H). \]

\[ ^{13}C \text{ NMR} (126 \text{ MHz, CDCl}_3) \delta 168.9, 159.8, 153.7, 137.7, 131.6, 130.4, 128.9, 128.3, 122.1, 121.4, 120.6, 114.0, 66.9, 61.5, 55.4, 34.1. \]

\[ \text{HRMS (ESI)} \text{ m/z calcd. For C}_{18}H_{20}N_2O_5 [M+H]^+ : 345.1450, \text{ found 345.1460}. \]

4-methoxybenzyl (2-(4,5-dihydrooxazol-2-yl)phenyl)carbamate (2n) was prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2n (3.1 mg, 47%, 90% purity) was obtained as a colorless solid.

\[ ^1H \text{ NMR} (500 \text{ MHz, DMSO}) \delta 11.76 (s, 1H), 8.34 - 8.38 (m, 1H), 7.81 (dd, J = 7.9, 1.5 \text{ Hz, } 1H), 7.52 - 7.55 (m, 1H), 7.36 - 7.39 (m, 2H), 7.11 (td, J = 7.9, 1.1 \text{ Hz, } 1H), 6.93 - 6.96 (m, 2H), 5.11 (s, 2H), 4.38 (t, J = 9.6 \text{ Hz, } 2H), 4.07 (t, J = 9.6 \text{ Hz, } 2H), 3.75 (s, 3H). \]

\[ ^{13}C \text{ NMR} (151 \text{ MHz, DMSO}) \delta 163.6, 159.3, 153.0, 139.4, 132.7, 130.4, 129.1, 128.2, 121.7, 117.4, 113.9, 112.2, 66.3, 66.1, 55.2, 54.3. \]

\[ \text{HRMS (ESI)} \text{ m/z calcd. For C}_{18}H_{18}N_2O_4 [M+H]^+ : 327.1345, \text{ found 327.1348}. \]

4-methoxybenzyl (2-(thiazol-2-yl)phenyl)carbamate (2o) was prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2o (1.7 mg, 25%, >95% purity) was obtained as a colorless solid.

\[ ^1H \text{ NMR} (500 \text{ MHz, DMSO}) \delta 11.51 (s, 1H), 8.30 (d, J = 8.3 \text{ Hz, } 1H), 8.02 (d, J = 3.4 \text{ Hz, } 1H), 7.90 (dd, J = 7.9, 1.4 \text{ Hz, } 1H), 7.86 (d, J = 3.4 \text{ Hz, } 1H), 7.48 (ddd, J = 8.6, 7.4, 1.5 \text{ Hz, } 1H), 7.36 - 7.39 (m, 2H), 7.16 - 7.19 (m, 1H), 6.93 - 6.96 (m, 2H), 5.12 (s, 2H), 3.75 (s, 3H). \]

\[ ^{13}C \text{ NMR} (151 \text{ MHz, DMSO}) \delta 167.6, 159.3, 153.3, 142.8, 136.3, 131.0, 130.3, 129.1, 128.3, 123.2, 120.4, 119.5, 119.4, 113.9, 66.1, 55.2. \]

\[ \text{HRMS (ESI)} \text{ m/z calcd. For C}_{18}H_{16}N_2O_3S [M+H]^+ : 341.0960, \text{ found 341.0966}. \]
4-methoxybenzyl (2-(benzo[d]thiazol-2-yl)-5-bromophenyl)carbamate (2p) and bis(4-methoxybenzyl) (2-(benzo[d]thiazol-2-yl)-5-bromo-1,3-phenylene)dicarbamate (2p’) were prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2p (1.1 mg, 12%, >95% purity) was obtained as a colorless solid. Compound 2p’ (0.9 mg, 7%, >95% purity) was obtained as a colorless solid.

2p

$^1$H NMR (500 MHz, DMSO) δ 11.66 (s, 1H), 8.53 (d, $J = 1.9$ Hz, 1H), 8.18 (d, $J = 7.7$ Hz, 1H), 7.99 (d, $J = 7.8$ Hz, 1H), 7.93 (d, $J = 8.5$ Hz, 1H), 7.56 – 7.6 (m, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.38 – 7.45 (m, 3H), 6.94 – 6.97 (m, 2H), 5.17 (s, 2H), 3.76 (s, 3H).

$^{13}$C NMR (151 MHz, DMSO) δ 167.0, 159.3, 152.0, 133.0, 131.8, 130.0, 128.2, 127.1, 126.2, 125.2, 122.3, 122.1, 113.9, 66.4, 55.1. HRMS (ESI) m/z calcd. For C$_{22}$H$_{17}$BrN$_2$O$_5$ [M+H]$^+$: 469.0221, found 469.0221.

2p’

$^1$H NMR (500 MHz, DMSO) δ 10.57 (s, 2H), 8.12 (d, $J = 7.4$ Hz, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.87 (s, 2H), 7.58 (td, $J = 8.2$, 7.7, 1.2 Hz, 1H), 7.5 – 7.53 (m, 1H), 7.29 (d, $J = 8.5$ Hz, 4H), 6.88 (d, $J = 8.6$ Hz, 4H), 5.05 (s, 4H), 3.73 (s, 6H).

$^{13}$C NMR (151 MHz, DMSO) δ 159.1, 153.8, 150.4, 134.3, 129.9, 128.2, 126.7, 126.0, 123.7, 122.3, 122.0, 113.8, 66.2, 55.1. HRMS (ESI) m/z calcd. For C$_{31}$H$_{26}$BrN$_3$O$_6$S [M+H]$^+$: 648.0804, found 648.0828.

4-methoxybenzyl (2-(pyrimidin-2-yl)phenyl)carbamate (2q) and bis(4-methoxybenzyl) (2-(pyrimidin-2-yl)-1,3-phenylene)dicarbamate (2q’) were prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2q (0.5 mg, 7%, 90% purity in pH10, >95%...
purity at pH 3) was obtained as a yellow wax. Compound \(2q\) (3.3 mg, 32%, >95% purity) was obtained as a yellow solid.

**2q**

\[^1\text{H}~\text{NMR}\] (500 MHz, DMSO) \(\delta\) 12.00 (s, 1H), 8.98 (d, \(J = 4.9\) Hz, 2H), 8.50 (dd, \(J = 8.1, 1.5\) Hz, 1H), 8.32 (dd, \(J = 8.4, 0.9\) Hz, 1H), 7.48 – 7.54 (m, 2H), 7.36 – 7.4 (m, 2H), 7.18 (ddd, \(J = 8.1, 7.2, 1.2\) Hz, 1H), 6.93 – 6.96 (m, 2H), 5.12 (s, 2H), 3.75 (s, 3H).

\[^{13}\text{C}~\text{NMR}\] (151 MHz, DMSO) \(\delta\) 163.7, 159.2, 157.3, 153.1, 139.1, 131.9, 130.4, 128.4, 122.3, 119.5, 119.1, 113.9, 65.9, 55.1.

HRMS (ESI) m/z calcd. For \(\text{C}_{19}\text{H}_{17}\text{N}_{3}\text{O}_{3}\) [M+H]~: 336.1348, found 336.1352.

**2q´**

\[^1\text{H}~\text{NMR}\] (500 MHz, DMSO) \(\delta\) 10.00 (s, 2H), 8.93 (d, \(J = 5.0\) Hz, 2H), 7.61 (d, \(J = 8.2\) Hz, 1H), 7.46 (t, \(J = 8.2\) Hz, 1H), 7.26 – 7.3 (m, 4H), 6.89 – 6.93 (m, 4H), 4.97 (s, 4H), 3.74 (s, 6H).

\[^{13}\text{C}~\text{NMR}\] (151 MHz, DMSO) \(\delta\) 163.11, 159.14, 157.19, 153.33, 137.45, 130.15, 129.92, 128.41, 119.51, 119.02, 117.49, 113.81, 65.71, 55.12.

HRMS (ESI) m/z calcd. For \(\text{C}_{28}\text{H}_{26}\text{N}_{4}\text{O}_{6}\) [M+H]~: 515.1931, found 515.1944.

4-methoxybenzyl (2-\((6\text{-chloropyridazin-3-yl})\)phenyl)carbamate (\(2r\)) and bis(4-methoxybenzyl) (2-\((6\text{-chloropyridazin-3-yl})\)-1,3-phenylene)dicarbamate (\(2r´\)) were prepared according to general conditions E. Purification by preparative LC (pH 3, FP column, acidic method). Compound \(2r\) (0.6 mg, 8%, 82% purity at pH 10, 87% purity at pH 3) was obtained as a light yellow wax. Compound \(2r´\) (3.2 mg, 29%, >95% purity) was obtained as a yellow solid.

**2r**

\[^1\text{H}~\text{NMR}\] (500 MHz, DMSO) \(\delta\) 10.10 (s, 1H), 8.07 (d, \(J = 9.0\) Hz, 1H), 7.99 (d, \(J = 9.0\) Hz, 1H), 7.85 (d, \(J = 8.8\) Hz, 1H), 7.71 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.5 – 7.54 (m, 1H), 7.31 (dd, \(J = 7.6, 1.1\) Hz, 1H), 7.26 – 7.29 (m, 2H), 6.91 – 6.93 (m, 2H), 4.99 (s, 2H), 3.75 (s, 3H).

\[^{13}\text{C}~\text{NMR}\] (151 MHz, DMSO) \(\delta\) 159.8, 159.2, 154.8, 153.6, 136.5, 130.7, 130.36, 130.0, 129.50, 129.47, 129.4, 128.4, 124.4, 113.8, 65.8, 55.1.

HRMS (ESI) m/z calcd. For \(\text{C}_{19}\text{H}_{16}\text{ClN}_{3}\text{O}_{3}\) [M+H]+ : 370.0958, found 370.0965.

**2r´**

\[^1\text{H}~\text{NMR}\] (500 MHz, DMSO) \(\delta\) 9.06 (s, 2H), 7.85 (d, \(J = 8.9\) Hz, 1H), 7.61 (d, \(J = 8.9\) Hz, 1H), 7.44 – 7.48 (m, 1H), 7.37 – 7.43 (m, 2H), 7.16 – 7.2 (m, 4H), 6.89 – 6.92 (m, 4H), 4.91 (s, 4H), 3.75 (s, 6H).

\[^{13}\text{C}~\text{NMR}\] (151 MHz, DMSO) \(\delta\) 159.1, 157.5, 154.6, 154.0, 136.6, 132.8, 130.4, 129.7, 129.4, 128.5, 125.5, 121.9, 113.8, 65.6, 55.1.

HRMS (ESI) m/z calcd. For \(\text{C}_{28}\text{H}_{25}\text{ClN}_{4}\text{O}_{6}\) [M+H]+ : 547.1384, found 547.1373.
4-methoxybenzyl (E)-(2-(((4-methoxyphenyl)imino)methyl)phenyl)carbamate (2s) was prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2s (1.2 mg, 16%, 90% purity at pH 10, 88% purity at pH 3) was obtained as yellow wax.

**1H NMR** (500 MHz, DMSO) δ 12.27 (s, 1H), 8.82 (s, 1H), 8.26 (d, J = 8.3 Hz, 1H), 7.74 (dd, J = 7.7, 1.6 Hz, 1H), 7.47 – 7.52 (m, 1H), 7.36 – 7.4 (m, 2H), 7.3 – 7.33 (m, 2H), 7.18 (td, J = 7.5, 1.1 Hz, 1H), 7.01 – 7.04 (m, 2H), 6.93 – 6.96 (m, 2H), 5.14 (s, 2H), 3.79 (s, 3H), 3.75 (s, 3H). **13C NMR** (126 MHz, DMSO) δ 161.0, 159.2, 158.5, 153.3, 142.1, 139.4, 134.1, 131.9, 129.9, 128.4, 122.5, 122.2, 121.2, 117.9, 114.7, 113.9, 65.9, 55.4, 55.1. **HRMS (ESI) m/z calcd.** For C_{23}H_{22}N_{2}O_{4}[M+H]^+ : 391.1658, found 391.1659.

4-methoxybenzyl (1-acetyllindolin-7-yl)carbamate (2t) was prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2t (1.2 mg, 16%, >95% purity) was obtained as colorless solid.

**1H NMR** (500 MHz, DMSO) δ 9.86 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.32 – 7.36 (m, 2H), 7.11 – 7.15 (m, 1H), 7.01 (dd, J = 7.3, 1.1 Hz, 1H), 6.92 – 6.95 (m, 2H), 5.03 (s, 2H), 4.10 (t, J = 7.9 Hz, 2H), 3.75 (s, 3H), 3.04 (t, J = 7.9 Hz, 2H), 2.27 (s, 3H). **13C NMR** (151 MHz, DMSO) δ 170.0, 159.2, 153.0, 135.9, 132.6, 132.0, 130.2, 128.5, 127.5, 125.8, 119.8, 113.9, 65.7, 55.1, 51.2, 28.5, 24.3. **HRMS (ESI) m/z calcd.** For C_{19}H_{20}N_{2}O_{4}[M+H]^+ : 339.1345, found 339.1349.

4-methoxybenzyl (2-(methylcarbamoyl)phenyl)carbamate (2u) was prepared according to general conditions E. Purification by preparative LC (pH 10, basic method). Compound 2u (0.7 mg, 11%, >95% purity) was obtained as colorless solid.

**1H NMR** (500 MHz, DMSO) δ 11.05 (s, 1H), 8.73 (s, 1H), 8.20 (d, J = 7.7 Hz, 1H), 7.70 (dd, J = 7.9, 1.4 Hz, 1H), 7.47 – 7.51 (m, 1H), 7.34 – 7.37 (m, 2H), 7.09 (td, J = 7.8, 1.2 Hz, 1H), 6.93 – 6.96 (m, 2H), 5.07 (s, 2H), 3.75 (s, 3H), 2.76 (d, J = 4.5 Hz, 3H). **13C NMR** (151 MHz, DMSO) δ 169.12, 159.71, 153.26, 139.59, 135.29, 132.57, 130.64, 128.70, 128.43, 120.03, 119.05, 114.34, 66.40, 55.59, 26.67. **HRMS (ESI) m/z calcd.** For C_{17}H_{18}N_{2}O_{4}[M+H]^+ : 315.1345, found 315.1351.
Methyl ((S,S,10S,11S,14S)-11-benzyl-5-(tert-butyl)-10-hydroxy-8-(((4-methoxybenzyl)oxy)carbonyl)amino)-4-(pyridin-2-yl)benzyl)-15,15-dimethyl-3,6,13-trioxo-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (3a) was prepared based on modified General Procedure A. [Cp*Ir(H₂O)₃]SO₄ (4.9 mg, 0.01 mmol, 2 mol%), MozN₃ (103.6 mg, 0.5 mmol). Purification by preparative reverse phase HPLC (44-84% MeCN in NH₃ buffer) to give compound 3a (356.6 mg, 81%) as a yellow solid.

¹H NMR (500 MHz, DMSO) δ 11.61 (s, 1H), 9.14 (s, 1H), 8.64 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.10 (s, 1H), 7.96 (td, J = 7.8, 1.8 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.39 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 7.32 – 7.36 (m, 2H), 7.16 – 7.24 (m, 6H), 7.1 – 7.15 (m, 1H), 7.00 (d, J = 9.5 Hz, 1H), 6.91 – 6.95 (m, 2H), 6.86 (d, J = 9.4 Hz, 1H), 5.06 (s, 2H), 5.02 (s, 1H), 3.9 – 3.99 (m, 2H), 3.64 (d, J = 9.4 Hz, 1H), 3.74 (d, J = 1.3 Hz, 3H), 3.64 (d, J = 9.4 Hz, 1H), 3.49 – 3.55 (m, 6H), 2.69 – 2.84 (m, 3H), 0.74 (s, 9H), 0.62 (s, 9H).

¹³C NMR (126 MHz, DMSO) δ 170.2, 170.0, 159.2, 157.1, 156.5, 153.0, 147.7, 139.6, 139.0, 138.3, 136.9, 130.0, 129.8, 129.1, 129.0, 128.6, 128.0, 125.8, 124.1, 123.2, 122.9, 122.3, 120.3, 113.9, 113.8, 68.0, 65.6, 63.1, 61.3, 61.1, 60.7, 55.1, 51.6, 51.4, 40.4, 37.7, 33.6, 33.4, 26.7, 26.2. HRMS (ESI) m/z calcd. For C₄₇H₆₁N₇O₁₀ [M+H]⁺: 884.4558, found 884.4525.

Bis(4-methoxybenzyl) (5-((S,S,8S,9S)-8-benzyl-5-(tert-butyl)-11-hydroxy-11-((S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanamido)-3,6-dioxo-2-oxa-4,7,11-triazadodecan-12-yl)-2-(pyridin-2-yl)-1,3-phenylene)dicarbamate (3a') was prepared according to modified General Procedure B. [Cp*Ir(H₂O)₃]SO₄ (5.9 mg, 12.0 µmol, 6 mol%), MozN₃ (124.3 mg, 0.6 mmol), DCE solvent. Purification by preparative reverse phase HPLC (55-95% MeCN in NH₃ buffer) to give compound 3a' (154.3 mg, 73%) as a yellow solid.
$^1$H NMR (500 MHz, DMSO) δ 9.30 (s, 2H), 9.19 (s, 1H), 8.67 (d, $J = 4.6$ Hz, 1H), 7.78 (td, $J = 7.8$, 1.7 Hz, 1H), 7.57 (d, $J = 8.9$ Hz, 1H), 7.47 (s, 2H), 7.32 – 7.38 (m, 2H), 7.18 – 7.24 (m, 8H), 7.12 – 7.15 (m, 1H), 7.02 (d, $J = 9.3$ Hz, 1H), 6.85 – 6.92 (m, 5H), 5.05 (s, 1H), 4.91 (s, 4H), 3.96 – 4.01 (m, 1H), 3.89 – 3.96 (m, 2H), 3.86 (d, $J = 9.4$ Hz, 1H), 3.74 (s, 6H), 3.66 (d, $J = 9.3$ Hz, 1H), 3.57 – 3.62 (m, 1H), 2.71 – 2.85 (m, 3H), 2.61 (d, $J = 9.9$ Hz, 1H), 0.76 (s, 9H), 0.64 (s, 9H). $^{13}$C NMR (126 MHz, DMSO) δ 170.3, 170.1, 159.1, 156.6, 154.7, 153.5, 148.7, 139.0, 138.7, 137.0, 135.9, 129.8, 129.51, 129.49, 129.1, 128.5, 128.0, 125.9, 125.6, 122.3, 120.6, 119.9, 114.8, 113.82, 113.78, 68.8, 67.8, 65.5, 63.1, 61.3, 61.1, 60.7, 55.1, 51.8, 51.5, 51.5, 37.7, 33.7, 33.4, 26.6, 26.3. HRMS (ESI) m/z calcd. For C$_{58}$H$_{78}$N$_{10}$O$_{13}$ [M+H]$^+$: 1063.5140, found 1063.5129.

4-methoxybenzyl (5-(2-(methyl(4-methyl-5-sulfamoylthiazol-2-yl)amino)-2-oxoethyl)-2-(pyridin-2-yl)phenyl)carbamate (3b) was prepared based on General Procedure B. [Cp*Ir(H$_2$O)$_3$]SO$_4$ (5.9 mg, 12.0 µmol, 6 mol%), MozN$_2$ (45.6 mg, 0.22 mmol), solvent DCE. Purification by preparative reverse phase HPLC (36-76% MeCN in HCOOH buffer) to give compound 3b (56.9 mg, 49%) as a colorless solid.

$^1$H NMR (500 MHz, DMSO) δ 11.62 (s, 1H), 8.67 (ddd, $J = 4.9$, 1.8, 0.9 Hz, 1H), 8.10 (s, 1H), 7.98 (td, $J = 7.8$, 1.8 Hz, 1H), 7.93 (d, $J = 8.2$ Hz, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.66 (s, 2H), 7.41 (ddd, $J = 7.4$, 4.9, 1.2 Hz, 1H), 7.31 – 7.36 (m, 2H), 7.09 (dd, $J = 8.1$, 1.7 Hz, 1H), 6.91 – 6.95 (m, 2H), 5.06 (s, 2H), 4.23 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 2.48 (s, 3H). $^{13}$C NMR (151 MHz, DMSO) δ 171.6, 159.2, 158.5, 156.9, 153.1, 148.2, 147.8, 138.3, 137.1, 136.1, 136.0, 129.4, 128.5, 128.3, 124.6, 124.1, 123.0, 122.5, 121.4, 113.9, 65.8, 55.1, 40.5, 34.3, 16.2. HRMS (ESI) m/z calcd. For C$_{27}$H$_{29}$N$_2$O$_5$ [M+H]$^+$: 582.1481, found 582.1475.

4-methoxybenzyl (2-(3-carbamoyl-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridin-1-yl)-5-methoxynitrophenyl)carbamate (3c) was prepared based on General Procedure C. MozN$_2$ (20.7 mg, 0.1 mmol), solvent NMP. Purification by preparative reverse phase HPLC (34-74% MeCN in NH$_3$ buffer) to give compound 3c (14.6 mg, 23%) as a yellow solid, as well as recovered starting material (28.4 mg, 62%).

$^1$H NMR (500 MHz, DMSO) δ 8.91 (s, 1H), 7.77 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.23 – 7.3 (m, 7H), 6.89 – 6.93 (m, 2H), 6.73 (dd, $J = 8.8$, 2.8 Hz, 1H), 5.00 (s, 2H), 3.96 (t, $J = 6.5$ Hz, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.57 (t, $J = 5.6$ Hz, 2H), 3.17 (t, $J = 6.6$ Hz, 2H), 2.37 (t, $J = 6.4$ Hz, 2H), 1.84 (qt, $J = 10.8$, 5.3 Hz,
$^{13}$C NMR (126 MHz, DMSO) δ 168.8, 163.3, 159.5, 159.2, 156.6, 153.7, 141.9, 141.2, 139.7, 135.2, 134.7, 130.0, 129.2, 128.3, 126.3, 125.7, 124.7, 124.5, 113.8, 108.3, 65.8, 55.5, 55.1, 50.9, 50.8, 32.6, 23.0, 21.1, 20.9. HRMS (ESI) m/z calcd. For C$_{34}$H$_{34}$N$_{6}$O$_{7}$ [M-H$^{-}$]: 637.2411, found 637.2383.

4-methoxybenzyl (2-((4-aminophenyl)sulfonamido)-1H-pyrazol-1-yl)phenylcarbamate (3d) was prepared based on General Procedure B. MozN$_3$ (45.6 mg, 0.22 mmol), solvent DCE. Purification by preparative reverse phase HPLC (38-78% MeCN in HCOOH buffer) to give compound 3d (46.6 mg, 47%) as a colorless solid, as well as recovered starting material (16.8 mg, 27%).

$^1$H NMR (500 MHz, DMSO) δ 9.88 (s, 1H), 8.02 (s, 1H), 7.98 (d, $J$ = 8.2 Hz, 1H), 7.65 (d, $J$ = 2.0 Hz, 1H), 7.44 – 7.48 (m, 1H), 7.29 – 7.34 (m, 4H), 7.17 (td, $J$ = 7.7, 1.3 Hz, 1H), 7.11 (dd, $J$ = 7.9, 1.5 Hz, 1H), 6.9 – 6.94 (m, 2H), 6.56 – 6.6 (m, 2H), 6.10 (s, 2H), 5.88 (d, $J$ = 1.9 Hz, 1H), 5.03 (s, 2H), 3.74 (s, 3H).

$^{13}$C NMR (126 MHz, DMSO) δ 159.2, 153.3, 152.8, 140.7, 137.0, 133.9, 130.1, 129.2, 128.9, 128.1, 127.4, 124.0, 123.4, 121.5, 113.9, 112.6, 101.6, 66.1, 55.1. HRMS (ESI) m/z calcd. For C$_{24}$H$_{23}$N$_{5}$O$_{5}$S [M+H$^+$]: 494.1498, found 494.1497.

$^1$H NMR (500 MHz, MeOD) δ 7.72 (dd, $J$ = 7.7, 1.1 Hz, 1H), 7.66 (d, $J$ = 7.6 Hz, 1H), 7.45 – 7.49 (m, 2H), 7.32 – 7.4 (m, 4H), 7.27 – 7.31 (m, 3H), 7.11 (d, $J$ = 8.2 Hz, 2H), 6.88 – 6.94 (m, 2H), 6.61 (d, $J$ = 8.2 Hz, 2H), 5.55 (s, 2H), 4.83 (s, 2H), 3.75 (s, 3H), 3.45 (s, 3H), 2.99 – 3.03 (m, 2H), 2.60 (s, 3H), 1.83 (h, $J$ = 7.4 Hz, 2H), 1.04 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, MeOD) δ 173.4, 160.8, 159.5, 157.3, 153.5, 144.5, 142.7, 142.1, 141.0, 136.3, 135.0, 134.3, 131.6, 131.4, 130.7, 130.5, 130.0, 128.3, 127.4, 124.6, 124.3, 118.9, 114.7, 112.0, 111.8, 67.3, 64.9, 55.7, 48.1, 30.3, 22.8, 14.2, 12.6. HRMS (ESI) m/z calcd. For C$_{42}$H$_{39}$N$_{5}$O$_{5}$S [M-H$^{-}$]: 692.2873, found 692.2854.
4-methoxybenzyl (2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)phenyl)carbamate (3f) and bis(4-methoxybenzyl) (2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-1,3-phenylene)dicarbamate (3f') were prepared based on General Procedure E. Solvent DCE. Purification by preparative LC (pH 3, HSS column, acidic method).

Compound 3f (3.2 mg, 34%, 90% purity) was obtained as a colorless solid, and compound 3f' (3.2 mg, 25%, >95% purity) was obtained as a colorless solid.

3f

$^1$H NMR (500 MHz, DMSO) δ 10.28 (s, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.66 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.29 (dd, $J = 8.7$, 2H), 7.18 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.13 – 7.16 (m, 1H), 7.11 (d, $J = 2.5$, 1H), 6.9 – 6.95 (m, 2H), 4.97 (s, 2H), 4.53 (d, $J = 11.1$, 1H), 3.81 (d, $J = 11.0$, 1H), 3.75 (s, 6H), 3.29 (s, 3H). $^{13}$C NMR (151 MHz, DMSO) δ 169.2, 168.8, 159.2, 153.4, 142.4, 137.8, 132.2, 131.4, 131.0, 130.2, 129.9, 128.3, 127.9, 127.8, 123.8, 123.2, 122.1, 113.8, 65.7, 56.3, 55.1, 34.4. HRMS (ESI) m/z calcd. For C$_{25}$H$_{22}$ClN$_3$O$_4$ [M+H]$^+$: 464.1377, found 464.1385.

3f'

$^1$H NMR (500 MHz, DMSO) δ 9.36 (s, 1H), 8.52 (s, 1H), 7.73 (s, 1H), 7.50 (d, $J = 7.4$, 1H), 7.37 – 7.45 (m, 2H), 7.31 (d, $J = 6.9$, 2H), 7.14 (s, 2H), 6.95 (s, 1H), 6.90 (d, $J = 8.3$, 4H), 6.85 (d, $J = 2.3$, 1H), 5.03 (s, 2H), 4.62 (s, 2H), 4.48 (d, $J = 10.4$, 1H), 3.80 (d, $J = 10.5$, 1H), 3.74 (s, 6H), 3.17 (s, 3H). $^{13}$C NMR (151 MHz, DMSO) δ 168.4, 166.1, 159.1, 153.8, 153.7, 141.7, 137.1, 131.4, 130.6, 130.1, 130.0, 128.4, 128.3, 127.5, 123.3, 119.8, 113.8, 65.8, 65.4, 56.4, 55.1, 34.6. HRMS (ESI) m/z calcd. For C$_{34}$H$_{31}$ClN$_4$O$_7$ [M+H]$^+$: 643.1959, found 643.1971.

5-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carboxamido)-3-methylpyridin-2-yl)-2-(((4-methoxybenzyl)oxy)carbonyl)amino)benzoic acid (3g) was prepared according to General Procedure C. Scale 0.2 mmol, MozN$_3$ (41.4 mg, 0.2 mmol), NMP solvent. Purification by preparative reverse phase HPLC (28-68% MeCN in NH$_3$ buffer) to give compound 3g (20.0 mg, 16%) as a light brown solid, as well as recovered starting material (66.6 mg, 74%).
\[ ^1H\text{NMR}\ (500\ MHz,\ MeOD)\ \delta\ 8 - 8.03\ (m,\ 2H),\ 7.88\ (d,\ J = 8.6\ Hz,\ 1H),\ 7.81\ (d,\ J = 2.0\ Hz,\ 1H),\ 7.70\ (d,\ J = 8.7\ Hz,\ 1H),\ 7.29\ (d,\ J = 1.6\ Hz,\ 1H),\ 7.2 - 7.25\ (m,\ 3H),\ 7.13\ (d,\ J = 8.2\ Hz,\ 1H),\ 6.87 - 6.89\ (m,\ 2H),\ 5.00\ (s,\ 2H),\ 3.79\ (s,\ 3H),\ 2.07\ (s,\ 3H),\ 1.64\ (q,\ J = 3.9\ Hz,\ 2H),\ 1.20\ (q,\ J = 4.0\ Hz,\ 2H).\ \]

\[ ^{13}C\text{NMR}\ (126\ MHz,\ MeOD)\ \delta\ 174.0,\ 170.2,\ 161.2,\ 155.6,\ 154.6,\ 150.2,\ 145.3,\ 144.8,\ 142.7,\ 140.7,\ 136.5,\ 132.7,\ 131.5,\ 131.1,\ 130.0,\ 129.7,\ 129.0,\ 128.2,\ 123.1,\ 114.9,\ 113.5,\ 111.2,\ 67.8,\ 55.7,\ 40.4,\ 32.3,\ 18.3,\ 17.6.\ \]

\[ ^{19}F\text{NMR}\ (471\ MHz,\ MeOD)\ \delta\ -51.83.\ \]

\[ \text{HRMS (ESI) m/z calcd. For } C_{33}H_{27}F_2N_3O_8 [M+H]^+: 632.1844,\ \text{found 632.1871.} \]

\[ (S)-2-ethoxy-6-(((4-methoxybenzyl)oxy)carbonylamino)-4-{2-((3-methyl-1-{2-(piperidin-1-yl)phenyl}butyl)amino)-2-oxoethyl}benzoic acid (3h) was prepared according to General Procedure E. Solvent NMP. Purification by preparative LC (pH 10, basic method). Compound 3h (2.9 mg, 23%, >95% purity) was obtained as a light brown solid. \]

\[ ^1H\text{NMR}\ (500\ MHz,\ DMSO)\ \delta\ 9.38\ (s,\ 1H),\ 8.45\ (d,\ J = 8.5\ Hz,\ 1H),\ 7.32 - 7.35\ (m,\ 2H),\ 7.31\ (dd,\ J = 7.7, 1.5\ Hz,\ 1H),\ 7.27\ (s,\ 1H),\ 7.13 - 7.16\ (m,\ 1H),\ 7.08\ (dd,\ J = 7.9, 1.1\ Hz,\ 1H),\ 6.99 - 7.03\ (m,\ 1H),\ 6.91 - 6.95\ (m,\ 2H),\ 6.69\ (s,\ 1H),\ 5.35\ (td,\ J = 9.4, 4.8\ Hz,\ 1H),\ 5.04\ (s,\ 2H),\ 3.97\ (q,\ J = 6.9\ Hz,\ 2H),\ 3.75\ (s,\ 3H),\ 3.41\ (s,\ 2H),\ 3.08\ (s,\ 2H),\ 2.54\ (s,\ 2H),\ 1.62 - 1.72\ (m,\ 2H),\ 1.44 - 1.62\ (m,\ 6H),\ 1.26 - 1.34\ (m,\ 4H),\ 0.88 - 0.91\ (m,\ 6H).\ \]

\[ ^{13}C\text{NMR}\ (151\ MHz,\ DMSO)\ \delta\ 168.7,\ 167.7,\ 159.2,\ 156.7,\ 153.3,\ 151.5,\ 140.5,\ 140.1,\ 137.2,\ 129.9,\ 128.4,\ 127.2,\ 126.0,\ 124.0,\ 120.5,\ 114.5,\ 113.8,\ 109.0,\ 65.8,\ 64.2,\ 55.1,\ 46.5,\ 46.0,\ 42.8,\ 26.3,\ 24.9,\ 23.9,\ 23.2,\ 21.8,\ 14.6.\ \text{HRMS (ESI) m/z calcd. For } C_{36}H_{45}N_3O_7 [M+H]^+: 632.3336,\ \text{found 632.3359.} \]

\[ (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12-(benzoyloxy)-4,11-dihydroxy-9-(((2R,3S)-2-hydroxy-3-(((4-methoxybenzyl)oxy)carbonylamino)benzamido)-3-phenylpropanoyloxy)-4a,8,13,13-tetramethyl-5-oxo-3,4,4a,5,6,9,10,11,12,12a-decahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxete-6,12b(2H)-diyl diacetate (3i) was prepared according to General Procedure C. MozN_3 (20.7
mg, 0.1 mmol), solvent DCE. Purification by preparative reverse phase HPLC (43-83% MeCN in HCOOH buffer) to give compound 3i (20.7 mg, 20%) as a colorless solid, as well as recovered starting material (33.3 mg, 39%).

Compound 3i was also prepared according to General Procedure D, 0.1 mmol scale. Purification by preparative reverse phase HPLC (43-83% MeCN in HCOOH buffer) to give compound 3i (74.8 mg, 72%) as a colorless solid.

\[ \text{1H NMR (500 MHz, DMSO)} \delta 10.58 (s, 1H), 9.30 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.92 – 7.97 (m, 2H), 7.87 (dd, J = 7.9, 1.3 Hz, 1H), 7.69 – 7.74 (m, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.51 – 7.57 (m, 1H), 7.37 – 7.41 (m, 4H), 7.32 – 7.36 (m, 2H), 7.16 – 7.25 (m, 2H), 6.9 – 6.94 (m, 2H), 6.34 (d, J = 7.3 Hz, 1H), 6.28 (s, 1H), 5.86 (t, J = 8.7 Hz, 1H), 5.40 (d, J = 7.2 Hz, 1H), 5.30 (t, J = 8.6 Hz, 1H), 5 – 5.09 (m, 2H), 4.93 (d, J = 7.1 Hz, 1H), 4.90 (d, J = 10.9 Hz, 1H), 4.69 (s, 1H), 4.51 – 4.58 (m, 1H), 4.09 (dt, J = 11.0, 7.0 Hz, 1H), 3.96 – 4.05 (m, 2H), 3.73 (s, 3H), 3.59 (d, J = 7.2 Hz, 1H), 2.31 (tt, J = 9.0, 4.6 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 1.75 – 1.83 (m, 4H), 1.63 (dd, J = 15.0, 9.3 Hz, 2H), 1.50 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H). \]

\[ \text{13C NMR (126 MHz, DMSO)} \delta 202.4, 172.7, 169.9, 168.8, 168.1, 165.2, 159.3, 139.1, 138.9, 138.5, 133.5, 133.4, 132.4, 130.2, 130.0, 129.5, 128.7, 128.5, 128.4, 128.2, 127.7, 127.6, 121.9, 120.0, 118.7, 113.9, 83.6, 80.2, 76.7, 75.4, 74.8, 74.5, 73.5, 70.5, 69.5, 66.0, 57.4, 56.6, 55.1, 46.1, 43.0, 36.6, 34.6, 26.3, 22.6, 21.3, 20.7, 13.8, 9.8. \]

\[ \text{HRMS (ESI) m/z calcd. For C}_{56}\text{H}_{60}\text{N}_{2}\text{O}_{17}[\text{M+H}]^{+}: 1033.3970, \text{found 1033.3960}. \]

2-(4-(2-(4-chloro-2-(((4-methoxybenzyl)oxy)carbonyl)amino)benzamido)ethyl)phenoxy)-2-methylpropanoic acid (3j) was prepared according to General Procedure C, 0.2 mmol scale. Purification by preparative reverse phase HPLC (53-93% MeCN in HCOOH buffer) to give compound 3j (59.9 mg, 55%) as a colorless solid.

\[ \text{1H NMR (500 MHz, DMSO)} \delta 13.01 (s, 1H), 11.18 (s, 1H), 8.94 (t, J = 5.5 Hz, 1H), 8.28 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.35 – 7.39 (m, 2H), 7.18 (dd, J = 8.5, 2.2 Hz, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.92 – 6.97 (m, 2H), 6.72 – 6.77 (m, 2H), 5.09 (s, 2H), 3.75 (s, 3H), 3.38 – 3.44 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 1.47 (s, 6H). \]

\[ \text{13C NMR (126 MHz, DMSO)} \delta 175.1, 167.4, 159.3, 153.7, 152.7, 140.7, 136.7, 132.3, 130.3, 129.8, 129.4, 128.0, 121.6, 118.5, 117.9, 117.9, 113.9, 78.3, 66.3, 55.1, 41.0, 33.8, 25.1. \]

\[ \text{HRMS (ESI) m/z calcd. For C}_{28}\text{H}_{25}\text{ClN}_{2}\text{O}_{7}[\text{M+H}]^{+}: 541.1741, \text{found 541.1760}. \]
Bis(4-methoxybenzyl) (2-(2,3,5,6-tetrahydroimidazo[2,1-b]thiazol-6-yl)-1,3-phenylene)(S)-dicarbamate (3k) was prepared according to General Procedure C. Purification by preparative reverse phase HPLC (44-84% MeCN in NH₃ buffer) to give compound 3k (18.1 mg, 32%) as a yellow solid.

1H NMR (500 MHz, DMSO) δ 8.37 (s, 1H), 7.26 – 7.36 (m, 6H), 7.07 – 7.11 (m, 2H), 6.88 – 6.92 (m, 2H), 6.81 – 6.85 (m, 2H), 5.16 (dd, J = 9.4, 3.4 Hz, 1H), 4.95 – 5.01 (m, 4H), 3.85 – 3.93 (m, 1H), 3.73 (s, 6H), 3.39 – 3.47 (m, 1H), 3.3 – 3.38 (m, 3H), 3.23 (dd, J = 9.3, 3.3 Hz, 1H), 2.76 (t, J = 7.1 Hz, 2H).

13C NMR (151 MHz, DMSO) δ 159.2, 159.0, 157.6, 153.0, 151.0, 141.9, 129.9, 129.3, 128.7, 128.3, 127.7, 125.7, 113.8, 113.6, 66.7, 66.5, 55.1, 54.9, 49.9, 41.5, 36.3.

HRMS (ESI) m/z calcd. For C₃₀H₃₂N₄O₅S [M+H]⁺: 561.2172, found 561.2181.

4-methoxybenzyl (R)-(4-(2-(2-aminothiazol-4-yl)acetamido)phenethyl)(2-hydroxy-2-phenylethyl)carbamate (3l) was prepared according to General Procedure E. Solvent NMP. Purification by preparative LC (pH 10, basic method). Compound 3l (6.8 mg, 61%, >95% purity) was obtained as a colorless solid.

1H NMR (500 MHz, DMSO) δ 10.01 (d, J = 3.5 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.26 – 7.32 (m, 5H), 7.18 – 7.25 (m, 2H), 7.07 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.93 – 6.96 (m, 2H), 6.90 (s, 2H), 6.29 (s, 1H), 5.46 (dd, J = 8.9, 4.6 Hz, 1H), 4.93 – 4.98 (m, 2H), 4.70 (ddt, J = 36.2, 8.5, 4.5 Hz, 1H), 3.76 (s, 3H), 3.14 – 3.31 (m, 3H), 2.58 – 2.73 (m, 2H).

13C NMR (151 MHz, DMSO) δ 168.3, 167.9, 159.0, 155.6, 155.2, 145.9, 143.7, 143.6, 137.4, 133.9, 133.8, 129.6, 128.9, 128.08, 128.05, 127.1, 126.0, 125.9, 119.0, 113.8, 102.6, 71.6, 71.0, 66.01, 65.97, 55.4, 55.1, 54.9, 50.1, 49.8, 33.7, 32.9. HRMS (ESI) m/z calcd. For C₃₉H₃₉N₄O₆S [M+H]⁺: 561.2172, found 561.2181.
4-methyl-2-(pyridin-2-yl)aniline (4a) was prepared with 3 distinct protocols.

**Conditions A: Acidic deprotection**
4-methoxybenzyl (4-methyl-2-(pyridin-2-yl)phenyl)carbamate (2c, 70.0 mg, 0.2 mmol) was added into a 4 mL screw top vial, followed by addition of CH$_2$Cl$_2$ (1 mL) and TFA (0.5 mL). The resulting mixture was stirred at room temperature for 10 minutes, followed by removal of volatiles in vacuo. The residue was redissolved in CH$_2$Cl$_2$ (2 mL) and washed with saturated aq. NaHCO$_3$ (2 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 2 mL). The combined organic phases were concentrated in vacuo. Purification by automated flash column chromatography (0-60% EtOAc in heptane, 25g SiO$_2$). Compound 4a was obtained as a yellow solid (35.1 mg, 93%).

**Conditions B: Basic deprotection**
4-methoxybenzyl (4-methyl-2-(pyridin-2-yl)phenyl)carbamate (2c, 70.0 mg, 0.2 mmol) was added into a 4 mL screw top vial, followed by addition of powdered KOH (157.0 mg, 2.8 mmol), EtOH (95%, 1 mL). The resulting mixture was heated at 80 °C for 1 hour, followed by removal of volatiles in vacuo. The residue was redissolved in CH$_2$Cl$_2$ (4 mL) and washed with saturated aq. NH$_4$Cl (8 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 4 mL). Purification by automated flash column chromatography (0-60% EtOAc in heptane, 25g SiO$_2$). Compound 4a was obtained as a yellow solid (27.9 mg, 74%).

**Conditions C: Hydrogenolysis**
4-methoxybenzyl (4-methyl-2-(pyridin-2-yl)phenyl)carbamate (2c, 70.0 mg, 0.2 mmol) was added into a 4 mL screw top vial, followed by addition of Pd/C (22.7 mg, 10 mol%, Pd 10% wt.), EtOAc (0.5 mL), MeOH (0.5 mL) and AcOH (50 μL). The resulting mixture was stirred under an H$_2$ atmosphere (1.2 bar) at room temperature for 5 hours. Solids were removed by filtration, and the filtrate concentrated in vacuo. The residue was redissolved in CH$_2$Cl$_2$ (2 mL) and washed with saturated aq. NaHCO$_3$ (2 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 2 mL). The combined organic phases were concentrated in vacuo. Purification by automated flash column chromatography (0-60% EtOAc in heptane, 25g SiO$_2$). Compound 4a was obtained as a yellow solid (30.8 mg, 82%).

$^1$H NMR (500 MHz, DMSO) δ 8.55 – 8.63 (m, 1H), 7.85 (td, $J = 8.0$, 1.9 Hz, 1H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.34 (s, 1H), 7.26 (ddd, $J = 7.3$, 4.9, 0.9 Hz, 1H), 6.92 (dd, $J = 8.1$, 1.6 Hz, 1H), 6.68 (d, $J = 8.2$ Hz, 1H), 6.32 (s, 2H), 2.21 (s, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 158.98, 147.74, 145.25, 137.13, 130.43, 129.24, 124.17, 121.75, 120.89, 120.31, 116.73, 20.18. HRMS (ESI) m/z calcd. For C$_{12}$H$_{12}$N$_2$ [M+H]$^+$: 185.1078, found 185.1071.

2-(4-(2-(2-amino-4-chlorobenzamido)ethyl)phenoxy)-2-methylpropanoic acid (4b) was prepared from commercially available Bezofibrate (72.4 mg, 0.2 mmol) utilizing a sequential one pot protocol. The
substrate was weighed in a 4 mL screw top glass vial, followed by addition of MozN₃ (62.2 mg, 0.3 mmol), [Cp*Ir(H₂O)]SO₄ (9.7 mg, 0.02 mmol, 10 mol%) and DCE (1.0 mL). The sealed vial was placed in a heating block at 60 °C and stirred for 20 hours. After this, the reaction mixture was let to cool to room temperature, followed by addition of TFA (0.5 mL). The Mixture was let to stir at room temperature for 10 minutes, followed by removal of volatiles in vacuo. Purification by preparative reverse phase HPLC (36-76% MeCN in HCOOH buffer) to give compound 4b (44.9 mg, 60%) as a light brown solid.

¹H NMR (500 MHz, DMSO) δ 8.36 (t, J = 5.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.09 – 7.12 (m, 2H), 6.73 – 6.76 (m, 3H), 6.66 (s, 2H), 6.51 (dd, J = 8.5, 2.2 Hz, 1H), 3.36 – 3.4 (m, 2H), 2.7 – 2.76 (m, 2H), 1.47 (s, 6H).

¹³C NMR (126 MHz, DMSO) δ 175.2, 168.0, 153.7, 151.0, 136.0, 132.7, 129.9, 129.4, 118.5, 115.0, 114.2, 113.5, 78.3, 40.7, 34.2, 25.1. HRMS (ESI) m/z calcd. For C₁₉H₂₁ClN₂O₄ [M+H]+ : 377.1268, found 377.1264.
NMR Spectra

4-methoxybenzyl (3-methyl-2-(pyridin-2-yl)phenyl)carbamate (2a)
4-methoxybenzyl (3-bromo-2-(pyridin-2-yl)phenyl)carbamate (2b)
4-methoxybenzyl (3-methyl-2-(pyridin-2-yl)phenyl)carbamate (2c)
α-4-methoxybenzyl (2-(pyridin-2-yl)phenyl)carbamate (2d)
bis(4-methoxybenzyl) (2-(pyridin-2-yl)-1,3-phenylene)dicarbamate (2d')
4-methoxybenzyl (2-(1H-pyrazol-1-yl)phenyl)carbamate (2e)
bis(4-methoxybenzyl) (2-(1H-pyrazol-1-yl)-1,3-phenylene)dicarbamate (2e')
4-methoxybenzyl (2-(benzo[d]oxazol-2-yl)phenyl)carbamate (2f)
4-methoxybenzyl (2-(pyrimidin-2-ylamino)phenyl)carbamate (2g)
bis(4-methoxybenzyl) (2-(pyrimidin-2-ylamino)-1,3-phenylene)dicarbamate (2g')
4-methoxybenzyl (1-(pyrimidin-2-yl)-1H-indol-7-yl)carbamate (2h)
4-methoxybenzyl (1-(pyridin-2-yl)-1H-indol-7-yl)carbamate (2i)
4-methoxybenzyl (5-bromo-2-(N,N,N'-trimethylsulfamidimido)phenyl)carbamate (2j)
4-methoxybenzyl (2-acetamidophenyl)carbamate (2k)
4-methoxybenzyl (2-(dimethylcarbamoyl)phenyl)carbamate (21)
o’-4-methoxybenzyl (2-(methoxy(methyl)carbamoyl)phenyl)carbamate (2m)
4-methoxybenzyl (2-(4,5-dihydrooxazol-2-yl)phenyl)carbamate (2n)
4-methoxybenzyl (2-(thiazol-2-yl)phenyl)carbamate (2o)
4-methoxybenzyl (2-(benzo[d]thiazol-2-yl)-5-bromophenyl)carbamate (2p)
bis(4-methoxybenzyl) (2-(benzo[d]thiazol-2-yl)-5-bromo-1,3-phenylene)dicarbamate (Zp')
4-methoxybenzyl (2-(pyrimidin-2-yl)phenyl)carbamate (2q)
bis(4-methoxybenzyl) (2-(pyrimidin-2-yl)-1,3-phenylene)dicarbamate (2q')
4-methoxybenzyl (2-(6-chloropyridazin-3-yl)phenyl)carbamate (2r)
bis(4-methoxybenzyl) (2-(6-chloropyridazin-3-yl)-1,3-phenylene)dicarbamate (2r')
4-methoxybenzyl (E)-(2-(((4-methoxyphenyl)imino)methyl)phenyl)carbamate (2s)
4-methoxybenzyl (1-acetyllindolin-7-yl)carbamate (2t)
4-methoxybenzyl (2-(methylcarbamoyl)phenyl)carbamate (2u)
Methyl ((5S,10S,11S,14S)-11-benzyl-5-(tert-butyl)-10-hydroxy-8-(3-(((4-methoxybenzyl)oxy)carbonyl)amino)-4-(pyridin-2-yl)benzyl)-15,15-dimethyl-3,6,13-trioxo-2-oxa-4,7,8,12-tetraazahexadecan-14-yl)carbamate (3a)
Bis(4-methoxybenzyl) (5-((S,5S,8S)-8-benzyl-5-(tert-butyl)-9-hydroxy-11-((S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanamido)-3,6-dioxo-2-oxa-4,7,11-triazadodecan-12-yl)-2-(pyridin-2-yl)-1,3-phenylene)dicarbamate (3a')
4-methoxybenzyl (5-(2-(methyl(4-methyl-5-sulfamoylthiazol-2-yl)amino)-2-oxoethyl)-2-(pyridin-2-yl)phenyl)carbamate (3b)
4-methoxybenzyl \((2\text{-}(3\text{-carbamoyl-7-oxo-6-(4-oxopiperidin-1-yl)phenyl})-4,5,6,7\text{-tetrahydro-1H-pyrazolo[3,4-c]pyridin-1-yl})-5\text{-methoxyphenyl})\text{carbamate (3c)}\)
4-methoxybenzyl (2-(5-((4-aminophenyl)sulfonamido)-1H-pyrazol-1-yl)phenyl)carbamate (3d)
$4'(4'(((4\text{-methoxybenzyl})\text{oxy})\text{carbonyl})\text{amino})-1,7'\text{-dimethyl-2'}\text{-propyl-1H,3'H-[2,5'}\text{-bibenzo[d]imidazol}-3'-yl)methyl]-[1,1'-biphenyl]-2\text{-carboxylic acid (3e)}$
4-methoxybenzyl (2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)phenyl)carbamate (3f)
bis(4-methoxybenzyl) (2-(7-chloro-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-1,3-phenylene)dicarbamate (3f')
5-[(6-(1,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane-1-carboxamido)-3-methylpyridin-2-yl)-2-(((4-methoxybenzyl)oxy)carbonyl)amino]benzoic acid (3g)
(S)-2-ethoxy-6-(((4-methoxybenzyl)oxy)carbonyl)amino)-4-(2-((3-methyl-1-(2-{(3-methyl-1-yl)phenyl}butyl)amino)-2-oxoethyl)benzoic acid (3h)
(2aR,4S,4aS,6R,9S,12S,12aR,12bS)-12-{benzoyloxy}-4,11-dihydroxy-9-(((2R,3S)-2-hydroxy-3-{2-{(((4-methoxybenzyl)oxy)carbonyl)amino}benzamido)-3-phenylpropanoyl)oxy)-4a,8,13,13-tetramethyl-5-oxo-3,4,4a,5,6,9,10,11,12,12a-decahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxete-6,12b(2aH)-diyl diacetate (3i)
2-((4-(2-(4-chloro-2-(((4-methoxybenzyl)oxy)carbonyl)amino)benzamido)ethyl)phenoxy)-2-methylpropanoic acid (3j)
Bis(4-methoxybenzyl) (2-(2,3,5,6-tetrahydroimidazo[2,1-b]thiazol-6-yl)-1,3-phenylene)(S)-dicarbamate (3k)
4-methoxybenzyl (R)-(4-(2-aminothiazol-4-yl)acetamido)phenethyl)(2-hydroxy-2-phenylethyl)carbamate (3l)
4-methyl-2-(pyridin-2-yl)aniline (4a)

Frequency: 500.12MHz
Experiment Name: Proton, d8
Spectrum: 18
Solvent: CDCl3
2-(4-(2-amino-4-chlorobenzamido)ethyl)phenoxy)-2-methylpropanoic acid (4b)
References

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