Activity-Directed Expansion of a Series of Antibacterial Agents

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1. **General Experimental**

All reactions were carried out under air and at room temperature unless stated otherwise. Solvents were removed under reduced pressure using a Büchi rotary evaporator and a Vacuubrand PC2001 Vario diaphragm pump. Anhydrous dimethylsulfoxide (DMSO) was obtained from SureSeal bottles from Sigma–Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40-60 °C). Commercially available starting materials were obtained from Alfa Aesar, Enamine BB (EU), Fluorochem or SigmaAldrich.

Flash column chromatography was carried out using silica gel 60 (35-70 μm particles) supplied by Merck. Thin layer chromatography was carried out using commercially available pre-coated aluminium plates (Merck silica gel 60 F254) from Merck. Ultraviolet lamp (λ$_{max}$ = 254 nm) and KMnO$_4$ were used for visualisation. Perkin-Elmer One FT-IR spectrometer was used to analyse the infrared spectra. Melting points (m.p.) were determined using Stuart melting point apparatus SMP3. X-ray measurements were carried out at 120 K on an Agilent SuperNova diffractometer equipped with an Atlas CCD detector and connected to an Oxford Cryostream low temperature device using mirror monochromated Cu Kα radiation (λ = 1.54184 Å) from a Microfocus X-ray source. The structure was solved by intrinsic phasing using SHELXT and refined by a full matrix least squares technique based on F$^2$ using SHELXL2014.

Analytical LC-MS was performed using an Thermo Ultimate 3000 HPLC instrument with a UV diode array detector and an MS detector Bruker Amazon Speeds with electrospray ionisation run positive and negative switching mode. The system used a Phenomenex Kinetex C18 2.1 × 50 mm 2.6 micron column, two solvent systems: MeCN/H$_2$O + 0.1% Formic acid or MeCN/H$_2$O and a run time of 1.7 minutes.

A Bruker Daltonics microOTOF spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS).

Proton (1H) and carbon (13C) NMR data was collected on a Bruker 400 or 500 MHz spectrometer. Data was collected at 300 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (J) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). Many assignments were made using COSY, DEPT, HMQC, HMBC or NOESY experiments.

Preparative LC-MS was performed using an Agilent Technologies Infinity (1260) instrument with a UV diode array detector and an Agilent 6100 series Single Quad MS detector. The system used a Phenomenex Kinetex C18 EVO 21.2 × 250 mm 5 micron column. The general preparation method used a solvent system of MeCN/H$_2$O (5-95%) + 0.1% Formic acid and a run time of 15 minutes.
General Procedure A: Synthesis of 4(3H)-Quinazolinones using Carbonylation Chemistry

By modification of an existing procedure, the appropriate aniline/amine/nitroarene (1.2 equiv.) and 2-iodophenylanilide (1 equiv.) were added to a crimp-top vial containing molybdenum hexacarbonyl (1 equiv.), tri-tert-butylphosphine (0.6 mol%) and tris(dibenzylideneacetone)dipalladium(0) (0.1 mol%) and purged with nitrogen for 5 minutes. The mixture was dissolved in o-xylene (3.0 mL per mmol) and triethylamine (2.5 equiv.) was added at rt. The reaction was stirred vigorously and heated to 105 °C for 48 hours and the resulting mixture was concentrated under reduced pressure to afford the crude product. Reactions were typically performed on a 0.5 mmol scale, and scaled appropriately where necessary.

General Procedure B: Synthesis of iodoanilide substrates

By modification of an existing procedure, the appropriate aniline (1 equiv.) and triethylamine (1.1 equiv.) were dissolved in diethyl ether (4.4 mL per mmol) and cooled to 0 °C. A solution of the appropriate acid chloride (1.1 equiv.) in diethyl ether (2.2 mL per mmol) was added dropwise. The reaction was heated to rt and stirred until complete. The reaction mixture was concentrated under reduced pressure to afford a crude product.

General Procedure C: Implementation of Carbonylation Reaction Array

By modification of an existing procedure, the reaction arrays were carried out in a 96-well plate (8 × 12) custom made out of PTFE in borosilicate glass vials (vial volume = 750 µL, vial dimensions = 8 × 30 mm, CV-2100-0830 Chemglass). 2-Iodophenylanilide substrates were dissolved in THF to give 1.0 M stock solutions. Amine/aniline co-substrates were dissolved in THF to give 1.20 M stock solutions. A stock solution of the catalyst system was prepared that was 2.00 mM in tri-tert-butylphosphine and 0.33 mM in tris(dibenzylideneacetone)dipalladium(0) in o-xylene. 100 µL of the appropriate substrate stock solution was added to the appropriate well and the solvent was evaporated. Then, 100 µL of the appropriate co-substrate stock solution was added and evaporated. This was followed by the addition of 26 mg of molybdenum hexacarbonyl as a solid and 300 µL of the catalyst stock solution. Then, 35 µL of triethylamine was added to each well and the plate was quickly sealed (silica layer and rubber Optibloc™ seal). The final volume of the reaction mixture was 300 µL; with final concentrations of catalyst (0.3 mM), substrate (333 mM), co-substrate (400 mM), ligand (2.0 mM), triethylamine (833 mM) and molybdenum hexacarbonyl (333 mM). The wells were left to react at 105 °C for 48 h and the crude mixture was concentrated under pressure overnight to remove residual o-xylene (EZ-2 Plus Genevac). The wells were re-dissolved in EtOAc (150 µL) and filtered through silica (30 mg) using filter microplates (96-well polypropylene with 0.45 µm polypropylene membrane, 800 µL/well, long drip, Agilent Technologies 200933-100) into new borosilicate glass vials. The crude wells were washed with EtOAc (2 × 150 µL) and the washes also transferred to the corresponding wells. The product mixtures were
left to evaporate under reduced pressure overnight (EZ-2 Plus Genevac). The product mixtures were dissolved in 300 µL of DMSO to give a total product concentration of 333 mM and transferred to a 96-well plate for screening.

2. General Screening Procedure

Evaluation of the Antibacterial Activity of Quinazolinones

Minimum inhibitory concentration (MIC) values for selected compounds were determined by broth microdilution against *S. aureus* strains SH1000, ATCC29213 and USA300 JE2, according to CLSI guidelines for low solubility compounds except for using Iso-Sensitest Broth (ISB) in place of cation-adjusted Mueller-Hinton Broth (MHB-II).

A 2-fold dilution series of the isolated compounds in DMSO was prepared, ranging from 1600–1.6 µg mL⁻¹. Each dilution was transferred into a 96-well format at a final volume of 1 µL and 99 µL of the standardised culture was added to each well to give final antibiotic concentrations of 16–0.016 µg mL⁻¹ (1% DMSO in ISB). Plates were incubated for 16 h at 37 °C (Inkubator 1000, Heidolph) and the minimum inhibitory concentration (MIC) was determined visually as the lowest concentration at which growth was inhibited. Higher concentration ranges (128–0.128 µg mL⁻¹) were used for MIC determinations where no growth inhibition was observed at concentrations up to 16 µg mL⁻¹.

Screening of Carbonylation Reaction Array

Reaction wells were diluted in ISB containing the standardised culture to ensure each screening well contained 1% DMSO and a final total product concentration of 50 µM. Plates were incubated for 10 h at 37 °C (Inkubator 1000, Heidolph) using a growth control (antibacterial free); the optical density was measured using a plate reader (FLUOstar Omega, BMG Labtech, λ = 600 nm). The selection of the incubation time (10 h) was chosen because the control culture reached saturation at that point.

Antifungal Susceptibility Testing

Antifungal susceptibility testing for selected compounds was determined by disk susceptibility testing, against *C. albicans* Ca6 according to CLSI guidelines.

A glycerol stock of Ca6 was swabbed onto a petri-dish of cation-adjusted Mueller-Hinton agar (MHA-II) and incubated at 30°C for 18 h. The fresh culture was added to a vial of MHB-II (10 mL) to obtain an OD > 1 (Novaspec II, Amersham Biosciences, λ = 625 nm) and streaked onto a petri-dish of MHA-II (18 mL).

Stock solutions (16 µg mL⁻¹) of each quinazolinone were prepared in 100% DMSO. Antibiotic discs were prepared by pipetting 20 µL of the stock solutions onto sterile paper discs and placed onto the streaked
Ca6 petri-dish. Fluconazole in DMSO (16 μg mL⁻¹) was used as a positive control and 100% DMSO was used as a negative control. The plates were incubated for 24 h at 37 °C. No growth inhibition was observed for any of the compounds (8b, 8d, 8e, 8f, 8g, 8h, 8i, 8j, 9) tested.

3. Materials

**Mueller-Hinton Agar II (MHA-II):** A stock solution of MHA-II was prepared from MHA-II powder (19 g, BD™BBL™) and purified water (500 mL).

**Iso-Sensitest Broth (ISB):** A 1000 mL stock solution of ISB was prepared from ISB Powder (23 g, Oxoid) and purified water (1000 mL).

**Cation-adjusted Mueller Hinton Broth (MHB-II):** A 1000 mL stock solution of MHBII was prepared from MHB-II Powder (22 g, Sigma Aldrich) and purified water (1000 mL).

**S. aureus strains in ISB:** A glycerol stock of either ATCC29213, SH1000 or USA300 JE2 was streaked onto MHA-II agar and incubated at 37°C for 18 h. An individual colony (using a Sarstedt inoculation loop, 1 µL) was suspended in ISB (5 mL) and incubated at 37°C for 24 h.

4. Compound Synthesis

2-Methyl-3-phenylquinazolin-4-one, 8a

![Chemical Structure](image)

By general procedure A using 2-iodophenylacetamide (0.26 g, 1.00 mmol) and nitrobenzene (0.12 mL, 1.20 mmol) followed by purification by flash column chromatography, eluting with 70:30 petrol–EtOAc gave the quinazolinone¹¹ 8a (0.044 g, 19%) as a colourless amorphous solid, Rf 0.20 (70:30 Petrol–EtOAc); νmax/cm⁻¹ (film): 3270, 1657, 1525 and 1253; δH (400 MHz, CDCl₃); 8.27 (1H, d, d, J 7.9, 1.1, 5-H), 7.77 (1H, td, J 8.3, 1.5, 7-H), 7.68 (1H, br d, J 8.0, 8-H), 7.56 (2H, app t, J 7.3, phenyl 3-H and 5-H), 7.51 (1H, dd, J 6.8, 1.6, phenyl 4-H), 7.46 (1H, app t, J 7.6, 6-H), 7.27 (2H, d, J 6.8, phenyl 2-H and phenyl 6-H), 2.25 (3H, s, 2-methyl); δc (101 MHz, CDCl₃); 162.2 (4-C), 154.3 (2-C), 147.5 (8a-C), 137.8 (phenyl 1-C), 134.7 (7-C), 130.0 (phenyl 3-C and 5-C), 129.4 (phenyl 4-C), 128.1 (phenyl 2-C and 6-C), 127.1 (5-C), 126.8 (8-C), 126.7 (6-C), 120.9 (4a-C), 24.5 (2-methyl); HRMS found MH⁺ 237.1031. C₁₅H₁₂N₂O requires MH⁺ 237.1029.
3-(3-Hydroxyphenyl)-2-(2-phenylethyl)quinazolin-4-one, 8b

By general procedure A using N-(2-iodophenyl)-3-phenylpropanamide, 6b (0.25 g, 1.0 mmol) and 3-aminophenol (0.13 g, 1.2 mmol) followed by purification by flash column chromatography, eluting with 50:50 hexane–EtOAc, gave the quinazolinone \(^{11}\) 8b (0.086 g, 24%) as a colourless amorphous solid, \(R_f\) 0.55 (50:50 hexane–EtOAc); \(\nu_{max}/\text{cm}^{-1}\) (film): 3361, 2945, 1667, 1585 and 1460; \(\delta H\) (501 MHz, \(d_6\)-DMSO); 9.85 (1H, s, \(5\)-H), 8.11 (1H, dd, \(J 7.9, 1.2\), \(5\)-H), 7.86 (1H, ddd, \(J 8.6, 7.3, 1.5\), \(7\)-H), 7.72 (1H, d, \(J 7.8, 8\)-H), 7.53 (1H, td, \(J 8.1, 1.0\), \(6\)-H), 7.33 (1H, app t, \(J 8.0\), hydroxyphenyl \(5\)-H), 7.22 (2H, app t, \(J 7.4\), phenyl \(3\)-H and \(7\)-H), 7.14 (1H, t, \(J 7.3\), phenyl \(4\)-H), 7.07 (2H, d, \(J 7.0\), phenyl \(2\)-H and \(6\)-H), 6.90 (1H, ddd, \(J 8.3, 2.2, 0.9\), hydroxyphenyl \(6\)-H), 6.80–6.78 (2H, m, hydroxyphenyl \(4\)-H and hydroxyphenyl \(2\)-H), 2.98 (2H, t, \(J 7.5\), ethyl \(1\)-H), 2.64 (2H, t, \(J 7.5\), ethyl \(2\)-H); \(\delta C\) (126 MHz, \(d_6\)-DMSO); 161.2 (4\(-\)C), 158.3 (hydroxyphenyl \(5\)-C), 156.0 (2\(-\)C), 147.1 (8\(\alpha\)-C), 140.9 (phenyl \(1\)-C), 138.1 (hydroxyphenyl \(1\)-C), 134.6 (7-C), 130.2 (hydroxyphenyl 3-C), 128.4 (phenyl 3-C and phenyl 5-C), 128.2 (phenyl 2-C and phenyl 6-C), 126.9 (8-C), 126.6 (6-C), 126.3 (5-C), 126.0 (phenyl 4-C), 120.6 (4\(\alpha\)-C), 119.0 (hydroxyphenyl 6-C), 116.0 (hydroxyphenyl 4-C), 115.6 (hydroxyphenyl 2-C), 37.0 (ethyl 1-C), 32.2 (ethyl 2-C); HRMS found \(MH^+\) 343.1441. \(C_{22}H_{18}N_2O_2H\) requires \(MH^+\) 343.1447.

2-Methyl-4\(H\)-benzo\([d\)]\[1,3\]oxazin-4-one, SI1

Anthranilic acid (8.00 mL, 0.08 mol) was dissolved in triethyl orthoacetate (25.33 mL, 0.14 mol) and the reaction mixture was heated under reflux for 2 h. The crude product was crystallised by cooling the reaction mixture on ice-water for 4 h. The solid precipitate was isolated by vacuum filtration and washed liberally with hexanes to yield the oxazinonone\(^ {11}\) SI1 (5.220 g, 40%) as a colourless amorphous solid, \(R_f\) 0.10 (50:50 Hexane–EtOAc); \(\nu_{max}/\text{cm}^{-1}\) (film): 3070, 2931, 1753 and 1688; \(\delta H\) (400 MHz, CDCl\(_3\)); 8.19 (1H, dd, \(J 7.9, 1.4\), \(5\)-H), 7.79 (1H, ddd, \(J 8.1, 7.4, 1.5\), \(7\)-H), 7.54 (1H, d, \(J 8.1, 8\)-H), 7.50 (1H, td, \(J 7.7, 1.0\), \(6\)-H), 2.47 (3H, s, methyl); \(\delta C\) (101 MHz, CDCl\(_3\)); 160.3 (4-C), 159.8 (2-C), 146.6 (8\(\alpha\)-C), 136.7
(7-C), 128.6 (5-C), 128.3 (8-C), 126.5 (6-C), 116.8 (4a-C), 21.5 (methyl); HRMS found MH+ 162.0543. C₉H₇NO₂H requires MH+ 162.0555.

3-(3-Hydroxyphenyl)-2-methylquinazolin-4-one, SI2

![SI2](image)

2-Methyl-4H-benzo[d][1,3]oxazin-4-one, SI1 (2.10 g, 13.00 mmol) and 3-aminophenol (1.50 g, 13.70 mmol) were suspended in glacial acetic acid (5 mL) and the reaction mixture was heated under reflux for 4 h. The reaction mixture was cooled and water (10 mL) was added. The resulting precipitate was filtered, washed with water, cold EtOH and hexanes to yield the quinazolinone SI2 (1.420 g, 43%) as a colourless amorphous solid, Rf 0.37 (50:50 hexane–EtOAc); ν max/cm⁻¹ (film); 3522, 3164, 1650, 1597 and 1292; δ H (501 MHz, d₆-DMSO); 9.84 (1H, s, OH), 8.09 (1H, dd, J 7.9, 1.2, 5-H), 7.83 (1H, ddd, J 8.6, 7.2, 1.5, 7-H), 7.65 (1H, d, J 7.8, 8-H), 7.51 (1H, ddd, J 8.0, 7.9, 1.0, 6-H), 7.34 (1H, app t, J 8.0, hydroxyphenyl 5-H), 6.91 (1H, ddd, J 8.3, 2.3, 0.8, hydroxyphenyl 6-H), 6.83 (1H, ddd, J 7.8, 1.9, 0.8, hydroxyphenyl 4-H), 6.79 (1H, app t, J 2.1, hydroxyphenyl 2-H), 2.16 (3H, s, methyl); δ c (126 MHz, d₆-DMSO); 161.0 (4-C), 158.1 (hydroxyphenyl 3-C), 154.3 (2-C), 147.2 (8a-C), 138.6 (hydroxyphenyl 1-C), 134.4 (7-C), 130.1 (hydroxyphenyl 5-C), 126.5 (8-C), 126.2 (6-C), 126.1 (5-C), 120.3 (4a-C), 118.6 (hydroxyphenyl 6-C), 115.8 (hydroxyphenyl 4-C), 115.2 (hydroxyphenyl 2-C), 23.6 (methyl); HRMS found MH+ 253.0979. C₁₅H₁₂N₂O₂H requires MH+ 253.0977.

3-(3-Hydroxyphenyl)-2-((1E)-2-(4-cyanophenyl)ethenyl)quinazolin-4-one, 8c

![8c](image)

3-(3-Hydroxyphenyl)-2-methylquinazolin-4-one, 7b (0.50 g, 1.98 mmol) was suspended in glacial acetic acid (5 mL) and dissolved upon heating. 4-Cyano-benzaldehyde (0.26 g, 1.98 mmol) was added and the reaction mixture was heated under reflux for 18 h. The reaction mixture was cooled and water (10 mL) was added. The resulting precipitate was filtered, washed with water, cold EtOH and hexanes to
yield the quinazolinone\textsuperscript{11} 8c (0.475 g, 66\%) as a yellow amorphous solid, R\textsubscript{r} 0.56 (50:50 hexane–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) (film); 3339, 2227, 1655, 1553 and 1286; \(\delta_{\text{H}}\) (501 MHz, \(\text{d}_{6}\)-DMSO); 9.92 (1H, s, OH), 8.14 (1H, dd, J 8.0, 1.2, 5-H), 7.91 (1H, d, J 15.6, ethenyl 2-H), 7.88 (1H, ddd, J 8.6, 7.2, 1.5, 7-H), 7.82 (2H, d, J 8.4, 2-phenyl 2-H and 2-phenyl 6-H), 7.78 (1H, d, J 7.7, 8-H), 7.57–7.54 (3H, m, 2-phenyl 3-H, 2-phenyl 5-H and 6-H), 7.39 (1H, app t, J 8.0, hydroxyphenyl 5-H), 6.97 (1H, ddd, J 8.2, 2.3, 1.0, hydroxyphenyl 6-H), 6.88–6.84 (2H, m, hydroxyphenyl 4-H and hydroxyphenyl 2-H) and 6.53 (1H, d, J 15.6, ethenyl 1-H); \(\delta_{\text{C}}\) (126 MHz, \(\text{d}_{6}\)-DMSO); 161.2 (4-C), 158.5 (2-C), 151.0 (2-phenyl 1-C), 147.4 (8a-C), 139.6 (hydroxyphenyl 3-C), 137.8 (hydroxyphenyl 1-C), 136.8 (ethenyl), 135.0 (8-C), 133.1 (2-phenyl 2-C and 2-phenyl 6-C), 130.6 (hydroxyphenyl 5-C), 128.3 (2-phenyl 3-C and 2-phenyl 6-C), 127.5 (7-C), 127.1 (5-C), 126.7 (6-C), 123.7 (hydroxyphenyl 4-C), 121.0 (4a-C), 119.5 (ethenyl 1-C), 118.8 (CN), 116.6 (hydroxyphenyl 2-C), 116.0 (hydroxyphenyl 6-C), 111.7 (2-phenyl 4-C); HRMS found MH\textsuperscript{+} 366.1232. \(\text{C}_{23}\text{H}_{18}\text{N}_{2}\text{O}_{3}\text{S}\) requires \(\text{MH}^+\) 366.1243.

### Preparation of 2-iodooamide Substrates

\(N\)-(2-iodophenyl)-3-phenylpropanamide, 6b

By general procedure B using 2-iodoaniline (1.50 g, 7.17 mmol) and hydrocinnamoyl chloride (1.17 mL, 7.89 mmol) followed by with recrystallisation using hot EtOH to yield 2-iodoanilide\textsuperscript{12} 6b (0.943 g, 37\%) as a long colourless needles, m.p (from EtOH) 129.2–130.0 °C, R\textsubscript{r} 0.19 (90:10 hexane–EtOAc); \(\nu_{\text{max}}/\text{cm}^{-1}\) (film); 3266, 3024, 1659, 1521 and 1184; \(\delta_{\text{H}}\) (501 MHz, CDCl\textsubscript{3}); 8.22 (1H, d, J 7.4, iodophenyl 3-H), 7.76 (1H, d, J 7.2, iodophenyl 6-H), 7.36–7.27 (5H, m, iodophenyl 4-H, phenyl 2-H, phenyl 3-H, phenyl 5-H and phenyl 6-H), 7.23 (1H, t, J 7.1, phenyl 4-H), 6.84 (1H, app t, J 7.2, iodophenyl 5-H), 3.09 (2H, t, J 7.7, 3-H), 2.75 (2H, t, J 7.7, 2-H); \(\delta_{\text{C}}\) (126 MHz, CDCl\textsubscript{3}); 170.4 (1-C), 140.5 (iodophenyl 1-C), 138.9 (iodophenyl 5-C), 138.2 (phenylpropanamidyl 1-C), 129.4 (iodophenyl 4-C), 128.8 (phenyl 2-C and phenyl 6-C), 128.5 (phenyl 3-C and phenyl 5-C), 126.6 (phenyl 4-C), 126.1 (iodophenyl 6-C), 122.1 (iodophenyl 3-C), 90.1 (iodophenyl 2-C), 39.8 (2-C), 31.6 (3-C); HRMS found MNa\textsuperscript{+} 374.0013. \(\text{C}_{61}\text{H}_{41}\text{N}_{2}\text{O}_{3}\text{Na}\) requires \(\text{MNa}^+\) 374.0019.

\((2\text{E})\)-\(N\)-(2-iodophenyl)-3-phenylprop-2-enamide, 1
By general procedure B using 2-iodoaniline (1.50 g, 7.17 mmol) and cinnamoyl chloride (1.32 g, 7.90 mmol) followed by purification with recrystallisation using hot EtOH to yield 2-iodoanilide\textsuperscript{13} 1 (1.152 g, 46\%) as small colourless needles, m.p (EtOH) 149.1–150.7 °C, R\textsubscript{f} 0.81 (50:50 hexane–EtOAc); \nu\textsubscript{max}/cm\textsuperscript{-1} (film): 3218, 3025, 1657, 1529 and 1182; \delta\textsuperscript{HNMR} (400 MHz, CDCl\textsubscript{3}); 8.19 (1H, d, J 7.7, iodophenyl 3-H), 7.81 (1H, dd, J 7.9, 1.4, iodophenyl 6-H), 7.79 (1H, d, J 15.5, 3-H), 7.59 (2H, dd, J 7.1, 2.4, phenyl 3-H and phenyl 5-H), 7.43–7.36 (4H, m, iodophenyl 4-H, phenyl 2-H, phenyl 4-H and phenyl 6-H), 6.87 (1H, td, J 7.8, 1.6, iodophenyl 5-H), 6.59 (1H, d, J 15.5, 2-H); \delta\textsuperscript{13C} (101 MHz, CDCl\textsubscript{3}); 164.0 (1-C), 143.2 (3-C), 139.0 (iodophenyl 6-C), 138.5 (iodophenyl 1-C), 134.6 (phenyl 1-C), 130.3 (phenyl 4-C), 129.5 (iodophenyl 4-C), 129.1 (phenyl 3-C and phenyl 5-C), 128.2 (phenyl 2-C and phenyl 6-C), 126.2 (iodophenyl 5-C), 122.2 (iodophenyl 3-C), 120.8 (2-C), 83.3 (iodophenyl 2-C); HRMS found MH\textsuperscript{+} 350.0033. C\textsubscript{15}H\textsubscript{12}I2NO requires MH\textsuperscript{+} 350.0042.

\textit{N-(2-iodophenyl)pent-4-enamide, S8}

By general procedure B using 2-iodoaniline (1.50 g, 6.83 mmol) and 4-pentenyl chloride (0.83 mL, 7.51 mmol) followed by purification by flash column chromatography, eluting with 80:20 hexane–EtOAc to yield 2-iodoanilide\textsuperscript{14} S8 (0.906 g, 44\%) as a colourless amorphous solid, R\textsubscript{f} 0.37 (80:20 hexane–EtOAc); \nu\textsubscript{max}/cm\textsuperscript{-1} (film): 3269, 3070, 1657, 1519 and 1287; \delta\textsuperscript{HNMR} (501 MHz, d\textsubscript{6}-DMSO); 10.74 (1H, s, NH), 9.20 (1H, dd, J 7.7, 4.3, iodophenyl 3-H), 8.80–8.64 (2H, m, iodophenyl 5-H and iodophenyl 6-H), 8.37–8.22 (1H, m, iodophenyl 4-H), 7.23 (1H, br ddt, J 16.0, 10.1, 3.6, 4-H), 6.43 (1H, br d, J 16.9, 5-H\textsubscript{a}), 6.33 (1H, br d, J 9.4, 5-H\textsubscript{b}), 3.78–3.74 (2H, m, 2-H), 3.72–3.68 (2H, m, 3-H); \delta\textsuperscript{13C} (126 MHz, d\textsubscript{6}-DMSO); 170.4 (1-C), 139.4 (iodophenyl 1-C), 138.7 (iodophenyl 3-C), 137.4 (4-C), 128.4 (iodophenyl 5-C), 127.4 (iodophenyl 6-C), 127.4 (iodophenyl 4-C), 115.1 (5-C), 96.6 (iodophenyl 2-C), 34.7 (2-C) and 29.0 (3-C); HRMS found MH\textsuperscript{+} 302.0034. C\textsubscript{15}H\textsubscript{13}I2NO requires MH\textsuperscript{+} 302.0042.
2-Iodo-N-(2-iodophenyl)benzamide, S5

By general procedure B using 2-iodoaniline (1.50 g, 6.83 mmol) and 2-iodobenzoyl chloride (2.00 g, 7.51 mmol) followed with purification by flash column chromatography, eluting with 50:50 hexane–EtOAc to yield 2-iodoaniline₁⁵ S5 (0.917 g, 30%) as a colourless amorphous solid, Rᵣ 0.81 (50:50 hexane–EtOAc); νmax/cm⁻¹ (film); 3243, 3017 and 1651; δH (501 MHz, d₆-DMSO); 10.09 (1H, s, NH), 7.94 (2H, m, iodo phenyl 3-H and 3-H), 7.58 (1H, dd, J 7.8, 1.2, iodo phenyl 5-H), 7.54 (1H, app t, J 7.4, iodo phenyl 6-H), 7.52–7.45 (2H, m, 5-H, 6-H), 7.25 (1H, td, J 7.8, 1.5, iodo phenyl 4-H), 7.08 (1H, td, J 8.0, 1.6, 4-H); δc (126 MHz, d₆-DMSO); 167.6 (carbonyl), 142.5 (1-C), 139.4 (iodophenyl 3-C), 139.4 (iodophenyl 1-C), 139.2 (3-C), 131.3 (iodophenyl 4-C), 129.0 (6-C), 128.6 (4-C), 128.3 (iodophenyl 6-C), 128.2 (iodophenyl 5-C), 128.2 (5-C), 98.1 (iodophenyl 2-C) and 93.8 (2-C); HRMS found MH⁺ 449.8841. C₁₃H₉I₂NO requires MH⁺ 449.8846.

(1R*,2R*)-N-(2-iodophenyl)-2-phenylcyclopropane-1-carboxamide, S7

By general procedure B using 2-iodoaniline (1.00 g, 4.57 mmol) and (1R*,2R*)-2-phenylcyclopropane-1-carboxyl chloride (0.75 mL, 5.02 mmol) followed by purification with recrystallisation using hot EtOH to yield 2-iodoanilide S7 (0.200 g, 12%) as long colourless needles, m.p (EtOH) 150.7–151.2 °C, Rᵣ 0.83 (50:50 hexane–EtOAc); νmax/cm⁻¹ (film); 3232, 3025, 1649, 1573 and 1283; δH (501 MHz, MeOD); 9.58 (1H, s, NH), 7.89 (1H, dd, J 7.9, 1.3, iodo phenyl 3-H), 7.49 (1H, d, J 7.7, iodo phenyl 6-H), 7.38 (1H, td, J 7.8, 1.3, iodo phenyl 5-H), 7.28 (2H, app t, J 7.5, phenyl 3-H and phenyl 5-H), 7.22–7.17 (3H, m, phenyl 2-H, phenyl 4-H and phenyl 6-H), 6.98 (1H, td, J 7.8, 1.5, iodo phenyl 4-H), 2.50 (1H, ddd, J 9.4, 6.4, 4.2, cyclopropane 2-H), 2.15 (1H, dt, J 7.0, 4.8 cyclopropane 1-H), 1.61 (1H, ddd, J 9.5, 5.2, 4.4, cyclopropane 3-Hₐ), 1.38 (1H, ddd, J 10.9, 7.3, 4.0, cyclopropane 3-H₉); δc (126 MHz, MeOD);
173.4 (carbonyl), 141.9 (iodophenyl 1-C), 140.6 (phenyl 1-C), 140.5 (iodophenyl 3-C), 129.9 (iodophenyl 5-C), 129.5 (phenyl 3-C and phenyl 5-C), 129.0 (iodophenyl 4-C), 128.4 (iodophenyl 6-C), 127.4 (phenyl 4-C), 127.3 (phenyl 2-C and phenyl 6-C), 27.0 (cyclopropane 1-C), 26.6 (cyclopropane 2-C) and 16.6 (cyclopropane 3-C); HRMS found MH+ 364.0194. C$_{16}$H$_{14}$INO requires MH+ 364.0198.

$N$-(2-iodophenyl)-2-(thiophen-2-yl)acetamide, S6

By general procedure B using 2-idoaniline (1.00 g, 4.57 mmol) and 2-(thiophen-2-yl)acetyl chloride (0.62 mL, 1.1 mmol) followed by purification by flash column chromatography, eluting with 80:20 hexane–EtOAc and recrystallisation using hot EtOH to yield 2-idoanilide S6 (1.067 g, 68%) as a small, brown, flat crystals, m.p (EtOH) 125.1−126.6 °C; $R_f$ 0.33 (80:20 hexane−EtOAc); $\nu_{\text{max}}$/cm$^{-1}$ (film); 3237, 2912, 1660, 1574 and 1282; $\delta_H$ (501 MHz, CDCl$_3$); 8.27 (1H, d, $J$ 8.0, iodophenyl 3-H), 7.75 (1H, s, NH), 7.70 (1H, dd, $J$ 7.9, 0.9, iodophenyl 6-H), 7.35−7.29 (2H, m, iodophenyl 4-H and thiophenyl 3-H), 7.13 (1H, d, $J$ 2.8, thiophenyl 5-H), 7.08 (1H, dd, $J$ 5.0, 3.5, thiophenyl 4-H), 6.81 (1H, td, $J$ 7.9, 1.2, iodophenyl 5-H), 3.99 (2H, s, 2-H$_2$); $\delta_C$ (126 MHz, CDCl$_3$); 168.3 (1-C), 139.0 (iodophenyl 6-C), 138.0 (iodophenyl 1-C), 135.2 (thiophenyl 1-C), 129.4 (thiophenyl 3-C), 128.8 (thiophenyl 5-C), 128.0 (thiophenyl 4-C), 126.6 (iodophenyl 4-C), 126.2 (iodophenyl 5-C), 121.5 (iodophenyl 3-C), 89.3 (iodophenyl 2-C), 38.8 (2-C); HRMS found MH+ 365.9418. C$_{12}$H$_{10}$INOS requires MH+ 365.9425.

1-(3-Amino-4-iodopyrazol-1-yl)-3-phenylpropan-1-one, S9
By general procedure B using 3-amino-4-iodo-1H-pyrazole (2.00 g, 9.57 mmol) and hydrocinnamoyl chloride (1.56 mL, 10.53 mmol) followed by purification by flash column chromatography, eluting with 100% CH$_2$Cl$_2$ and recrystallisation using hot EtOH to yield to yield pyrazole S9 (0.581 g, 18%) as long colourless needles, m.p (EtOH) 110.2-111.5 °C, $R_f$ 0.59 (100% CDCl$_3$); $\nu_{\text{max/cm}^{-1}}$ (film): 3428, 3303, 3124 and 1718; $\delta_{\text{H}}$ (500 MHz, CDCl$_3$): 8.03 (1H, s, pyrazoyl 5-H), 7.23–7.19 (2H, m, phenyl 3-H and 5-H), 7.18–7.15 (2H, m, phenyl 2-H and 6-H), 7.12 (1H, t, $J$ 7.1, phenyl 4-H), 4.01 (2H, br s, NH$_2$), 3.18 (2H, t, $J$ 7.8, 2-H$_2$), 2.98 (2H, t, $J$ 7.8, 3-H$_2$); $\delta_{C}$ (126 MHz, CDCl$_3$): 169.5 (1-C), 157.2 (pyrazoyl 3-C), 140.5 (phenyl 1-C), 134.0 (pyrazoyl 5-C), 128.6 (phenyl 2-C and 6-C), 128.5 (phenyl 3-C and 5-C), 126.4 (phenyl 4-C), 57.6 (pyrazoyl 4-C), 35.01 (3-C), 30.3 (2-C); HRMS found MNa$^+$ 363.9924. C$_{12}$H$_{12}$IN$_2$O requires MNa$^+$ 363.9917. The structure was determined by X-ray crystallography (see Section 6).

3-Cyclopentyl-N-(2-iodophenyl)propanamide, S10

Following known procedure,$^{16}$ 3-Cyclopentylpropanoic acid (1.44 g, 10.04 mmol) was dissolved in DMF (25 mL) and CDI (1.68 g, 10.04 mmol) was added. The reaction mixture was stirred at rt for 90 mins. Afterwards, 2-iodoaniline (2.00 g, 9.13 mmol) was added and the reaction was stirred for a further 16 h at rt. CH$_2$Cl$_2$ (25 mL) was added to the reaction mixture and the resulting solution was washed with water (5 x 30 mL), dried with MgSO$_4$ and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 100% CH$_2$Cl$_2$ to yield 2-iodoanilide S10 (1.399 g, 41%) as a colourless amorphous solid, $R_f$ 0.42 (80:20 hexane–EtOAc); $\nu_{\text{max/cm}^{-1}}$ (film): 3267, 2947 and 1656; $\delta_{\text{H}}$ (501 MHz, CDCl$_3$) 8.24 (1H, d, $J$ 7.7, iodophenyl 3-H), 7.77 (1H, dd, $J$ 8.0, 1.3, iodophenyl 6-H), 7.46 (1H, br s, NH)$_2$, 7.34 (1H, td, $J$ 8.1, 1.3, iodophenyl 4-H), 6.83 (1H, td, $J$ 7.5, 1.3, iodophenyl 5-H), 2.45 (2H, t, $J$ 7.6, 2-H$_2$), 1.90–1.81 (3H, m, cyclopentyl 1-H and cyclopentyl 3-H), 1.81–1.75 (2H, dd, $J$ 14.8, 7.2, 3-H$_2$), 1.67–1.60 (2H, m, cyclopentyl 4-H), 1.58–1.50 (2H, m, cyclopentyl 5-H), 1.20–1.09 (2H, m, cyclopentyl 2-H); $\delta_{C}$ (126 MHz, CDCl$_3$): 171.6 (1-C), 138.9 (iodophenyl 6-C), 138.4 (iodophenyl 1-C), 129.4 (iodophenyl 4-C), 125.9 (iodophenyl 5-C), 122.1 (iodophenyl 3-C), 90.0 (iodophenyl 2-C), 39.7 (cyclopentyl 1-C), 37.5 (2-C), 32.7 (cyclopentyl 2-C), 32.5 (cyclopentyl 3-C), 32.0 (3-C), 25.3 (cyclopentyl 4-C and cyclopentyl 5-C); HRMS found MNa$^+$ 366.0322. C$_{14}$H$_{14}$IN$_2$O requires MNa$^+$ 366.0325.
5. Synthesis of Quinazolinones

3-(3-(N-Phenylmethanesulfonamide))-2-(2-phenylethyl)quinazolin-4-one, 8d

By general procedure A using N-(2-iodophenyl)-3-phenylpropanamide, 6b (0.13 g, 0.50 mmol) and N-(3-aminophenyl)methanesulfonamide (0.11 g, 0.60 mmol) followed by purification by flash column chromatography, eluting with 50:50 hexane−EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN−water to yield quinazolinone 8d (0.008 g, 4%) as a colourless amorphous solid. Rf 0.36 (50:50 petrol−EtOAc); νmax/cm−1 (film): 3241, 3018, 1651, 1570 and 1302; δH (501 MHz, CDCl3); δC (126 MHz, CDCl3); 8.26 (1H, dd, J 8.0, 1.1, 5-H), 7.81 (1H, ddd, J 8.4, 7.0, 1.5, 7-H), 7.76 (1H, dd, J 8.1, 0.7, 8-H), 7.49 (1H, ddd, J 8.1, 7.1, 1.3, 6-H), 7.46 (1H, br d, J 8.3, 3-phenyl 6-H), 7.28 (1H, ddd, J 8.3, 2.0, 0.9, 3-phenyl 5-H), 7.22 (2H, app t, J 7.2, 2-phenyl 3-H and 2-phenyl 5-H), 7.17 (1H, t, J 7.3, 2-phenyl 4-H), 7.05–7.01 (2H, m, 2-phenyl 2-H and 2-phenyl 6-H), 6.95–6.93 (2H, m, 3-phenyl 4-H and 3-phenyl 2-H), 3.07 (2H, t, J 7.5, 2-ethyl 1-H), 2.97 (3H, s, Me) and 2.72 (2H, t, J 7.5, 2-ethyl 2-H); δc (126 MHz, CDCl3); 162.8 (4-C), 155.6 (2-C), 147.6 (8r-C), 140.7 (2-phenyl 1-C), 138.9 (3-phenyl 3-C), 138.3 (3-phenyl 1-C), 135.0 (7-C), 131.3 (3-phenyl 6-C), 128.7 (2-phenyl 2-C and 2-phenyl 6-C), 128.6 (2-phenyl 3-C and 2-phenyl 5-C), 127.4 (8-C), 127.1 (5-C), 127.1 (6-C), 126.5 (2-phenyl 4-C), 124.7 (3-phenyl 4-C), 120.7 (4r-C), 120.1 (3-phenyl 2-C and 5-C), 39.9 (Me), 37.6 (2-ethyl 2-C) and 33.3 (2-ethyl 1-C); HRMS found MH+ 420.1387. C23H21N3O3S requires MH+ 420.1376.

3-(3-(N-Phenylmethanesulfonamide))-2-((1R*, 2R*)-2-phenylcyclopropyl)quinazolin-4-one, 8e
By general procedure A using (1R*, 2R*)-N-(2-iodophenyl)-2-phenylcyclopropane-1-carboxamide, S7 (0.18 g, 0.50 mmol) and N-(3-aminophenyl)methanesulfonamide (0.11 g, 0.60 mmol) followed by purification by flash column chromatography, eluting with 50:50 hexane–EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN–water to yield quinazolinone 8e (0.004 g, 2%, rotamers 56:44 by 1H NMR) as a colourless amorphous solid. R\_f 0.11 (50:50 hexane–EtOAc); \( \nu_{\text{max}}/\text{cm}^{-1} \) (film): 3213, 2926, 1662, 1584 and 1153; \( \delta \text{H} \) (501 MHz, CDCl3); 8.25 (2H, ddd, \( J = 7.9, 3.7, 1.3 \), 5-H\text{maj} and 5-H\text{min}), 7.77 (2H, td, \( J = 8.4, 1.4 \), 7-H\text{maj} and 7-H\text{min}), 7.66 (2H, d, \( J = 8.1 \), 8-H\text{maj} and 8-H\text{min}), 7.51–7.46 (2H, m, 3-phenyl 5-H\text{maj} and 3-phenyl 5-H\text{min}), 7.47–7.43 (2H, m, 6-H\text{maj} and 6-H\text{min}), 7.25–7.20 (4H, m, 2-phenyl 4-H\text{maj}, 2-phenyl 4-H\text{min}, 3-phenyl 6-H\text{maj} and 3-phenyl 6-H\text{min}), 7.20–7.18 (4H, m, 2-phenyl 3-H\text{maj}, 2-phenyl 3-H\text{min}, 2-phenyl 5-H\text{maj} and 2-phenyl 5-H\text{min}), 7.17–7.14 (2H, m, 3-phenyl 4-H\text{maj} and 3-phenyl 4-H\text{min}), 6.95–6.88 (6H, m, 2-phenyl 2-H\text{maj}, 2-phenyl 2-H\text{min}, 2-phenyl 6-H\text{maj}, 2-phenyl 6-H\text{min}, 3-phenyl 2-H\text{maj} and 3-phenyl 2-H\text{min}), 3.02 (3H, s, methyl\text{min}), 2.66 (3H, s, methyl\text{maj}), 2.59 (1H, ddd, \( J = 9.2, 6.4, 4.4 \), cyclopropane 2-H\text{maj}), 2.53 (ddd, \( J = 9.2, 6.4, 4.4 \), cyclopropane 2-H\text{min}), 2.16 (1H, ddd, \( J = 9.1, 5.5, 4.7 \), cyclopropane 3-H\text{maj} and 3-H\text{min}), 2.07 (1H, ddd, \( J = 9.2, 5.4, 4.7 \), cyclopropane 3-H\text{min}, 1.65 (2H, m, cyclopropane 1-H\text{maj} and cyclopropane 1-H\text{min}) and 1.34 (2H, m, cyclopropane 3-H\text{maj} and cyclopropane 3-H\text{min}); \( \delta \text{C} \) (126 MHz, CDCl3): 162.6 (4-C\text{maj}), 162.5 (4-C\text{min}), 156.1 (2-C\text{maj}), 156.0 (2-C\text{min}), 147.9 (8\text{a}-C\text{min}), 147.9 (8\text{a}-C\text{maj}), 140.4 (2-phenyl 1-C\text{maj}), 140.2 (2-phenyl 1-C\text{min}), 138.5 (3-phenyl 3-C\text{maj}), 138.4 (3-phenyl 3-C\text{min}), 138.3 (3-phenyl 1-C\text{maj}), 138.3 (3-phenyl 1-C\text{min}), 134.5 (7-C), 131.1 (3-phenyl 5-C\text{maj}), 131.0 (3-phenyl 5-C\text{min}), 128.8 (2-phenyl 3-C\text{maj} and 2-phenyl 5-C\text{maj}), 128.5 (2-phenyl 3-C\text{min} and 2-phenyl 5-C\text{min}), 127.3 (5-C\text{maj}), 127.3 (5-C\text{min}), 127.2 (8-C\text{maj}), 127.2 (8-C\text{min}), 126.8 (2-phenyl 4-C\text{maj}), 126.6 (2-phenyl 4-C\text{min}), 126.6 (6-C\text{maj}), 126.5 (6-C\text{min}), 126.0 (2-phenyl 2-C\text{maj} and 2-phenyl 2-C\text{min}), 125.2 (3-phenyl 4-C\text{maj}), 125.1 (3-phenyl 4-C\text{min}), 120.8 (3-phenyl 2-C\text{maj}), 120.7 (4\text{a}-C\text{maj}), 120.6 (4\text{a}-C\text{min}), 120.5 (3-phenyl 2-C\text{maj}), 120.3 (3-phenyl 6-C\text{maj}), 120.0 (3-phenyl 6-C\text{min}), 39.9 (methyl\text{min}), 39.3 (methyl\text{maj}), 29.7 (cyclopropane 2-C\text{maj}), 29.3 (cyclopropane 2-C\text{min}), 26.6 (cyclopropane 1-C\text{maj}), 26.4 (cyclopropane 1-C\text{min}), 18.1 (cyclopropane 3-C\text{min}), 17.9 (cyclopropane 3-C\text{maj}); HRMS found MH\text{+} 432.1378. C_{12}H_{17}N_{2}O_{3}S requires MH\text{+} 432.1376. It was noted that two diastereomeric rotamers were observed.

3-(3-(N-Phenylmethanesulfonamide))-2-(2-cyclopentylethyl)quinazolin-4-one, 8f

![8f](image-url)
By general procedure A using 3-cyclopentyl-N-(2-iodophenyl)propenamide, **S10** (0.17 g, 0.50 mmol) and N-(3-aminophenyl)methanesulfonylamine (0.11 g, 0.60 mmol) followed by purification followed by purification by flash column chromatography, eluting with 50:50 hexane–EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN–water to yield quinazolinone **8f** (0.029 g, 14%) as a colourless amorphous solid. \( R \_f 0.31 \) (50:50 hexane–EtOAc); \( \nu_{\text{max}} / \text{cm}^{-1} \) (film): 3221, 2944, 1656, 1570 and 1472; \( \delta_{\text{H}} \) (501 MHz, CDCl\(_3\)): 8.25 (1H, dd, J 8.0, 1.3, 5-H), 7.92 (1H, s, NH), 7.78 (1H, td, J 8.3, 1.5, 7-H), 7.71 (1H, d, J 8.0, 8-H), 7.47 (1H, app t, J 8.0, 3-phenyl 5-H), 7.47 (1H, td, J 8.0, 1.0, 6-H), 7.28 (1H, dd, J 8.2, 1.4, 3-phenyl 4-H), 7.08 (1H, br t, J 2.0, 3-phenyl 2-H), 7.06–7.02 (1H, m, 3-phenyl 6-H), 2.98 (3H, s, Me), 2.43 (2H, t, J 7.5, ethyl 1-H), 1.70–1.62 (3H, m, cyclopentyl 1-H and cyclopentyl 2-H), 1.61–1.57 (2H, m, ethyl 2-H), 1.53–1.46 (2H, m, cyclopentyl 4-H), 1.46–1.39 (2H, m, cyclopentyl 5-H), 0.96–0.82 (2H, m, cyclopentyl 2-H); \( \delta_{\text{C}} \) (126 MHz, CDCl\(_3\)): 163.1 (4-C), 156.9 (2-C), 147.6 (8\(_2\)-C), 139.1 (3-phenyl 3-C), 138.2 (3-phenyl 1-C), 135.0 (7-C), 131.2 (3-phenyl 5-C), 127.2 (6-C), 127.1 (8-C), 126.9 (5-C), 124.4 (3-phenyl 6-C), 120.9 (3-phenyl 4-C), 120.4 (4\(_4\)-C), 120.3 (3-phenyl 2-C), 39.7 (cyclopentyl 1-C), 39.6 (ethyl 1-C), 35.3 (cyclopentyl 2-C), 33.7 (cyclopentyl 3-C), 32.4 (ethyl 2-C), 32.3 (cyclopentyl 5-C), 25.1 (cyclopentyl 4-C); HRMS found MH\(^+\) 412.1691. C\(_{22}\)H\(_{25}\)N\(_3\)O\(_3\)S requires MH\(^+\) 412.1689.

3-(3-Aminophenyl)-2-(2-cyclopentylethyl)quinazolin-4-one, 8g

![3-(3-Aminophenyl)-2-(2-cyclopentylethyl)quinazolin-4-one](image)

By general procedure A using 3-cyclopentyl-N-(2-iodophenyl)propenamide, **S10** (0.09 g, 0.26 mmol) and m-phenylenediamine (0.03 g, 0.31 mmol) followed by purification by flash column chromatography, eluting with 50:50 hexane–EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN–water to yield quinazolinone **8g** (0.007 g, 8%) as a colourless amorphous solid. \( R\_f 0.50 \) (50:50 hexane–EtOAc); \( \nu_{\text{max}} / \text{cm}^{-1} \) (film): 3267, 2947, 2920 and 1656; \( \delta_{\text{H}} \) (501 MHz, CDCl\(_3\)): 8.27 (1H, dd, J 7.9, 0.9, 5-H), 7.77–7.73 (1H, m, 7-H), 7.69 (1H, d, J 8.1, 8-H), 7.44 (1H, td, J 7.8, 0.8, 6-H), 7.30 (1H, app t, J 7.9, 3-phenyl 5-H), 6.79 (1H, dd, J 8.1, 2.1, 3-phenyl 6-H), 6.62 (1H, dd, J 7.7, 1.0, 3-phenyl 4-H), 6.54 (1H, br t, J 2.0, 3-phenyl 2-H), 3.87 (2H, s, NH\(_2\)), 2.51 (2H, t, J 7.5, ethyl 1-H), 1.74–1.67 (3H, m, cyclopentyl 1-H and cyclopentyl 3-H), 1.67–1.59 (2H, m, ethyl 2-H), 1.56–1.51 (2H, m, cyclopentyl 4-H), 1.48–1.41 (2H, m, cyclopentyl 5-H), 1.00–0.90 (2H, m, cyclopentyl 2-H); \( \delta_{\text{C}} \) (126 MHz, CDCl\(_3\)): 162.9 (4-C), 158.0 (2-C), 148.3 (3-phenyl 3-C), 148.0 (8\(_4\)-C), 138.7 (3-phenyl 1-C), 134.8
(7-C), 130.9 (3-phenyl 5-C), 127.4 (8-C), 127.3 (5-C), 126.8 (6-C), 121.1 (4-C), 118.4 (3-phenyl 4-C), 116.2 (3-phenyl 2-C), 115.0 (3-phenyl 6-C), 40.1 (cyclopentyl 1-C), 35.4 (ethyl 1-C), 34.2 (cyclopentyl 2-C), 32.7 (cyclopentyl 3-C), 32.7 (ethyl 2-C), 25.5 (cyclopentyl 4-C and cyclopentyl 5-C); HRMS found MH+ 334.1912. C_{21}H_{32}N_{2}O requires MH+ 334.1914.

2-(2-Cyclopentylethyl)-3-(3-hydroxyphenyl)quinazolin-4-one, 8h

![8h](image)

By general procedure A using 3-cyclopentyl-N-(2-iodophenyl)propenamide, S10 (0.17 g, 0.50 mmol) and 3-aminophenol (0.07 g, 0.60 mmol) followed by purification by preparative LC-MS followed by purification by flash column chromatography, eluting with 50:50 hexane–EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN–water to yield quinazolinone 8h (0.014 g, 8%) as a colourless amorphous solid. R_{f} 0.60 (50:50 hexane–EtOAc); 3244, 2946 and 1655; δ_{H} (501 MHz, CDCl{3}); 8.28 (1H, dd, J 7.9, 0.9, 5-H), 7.78 (1H, td, J 8.0, 1.4, 7-H), 7.73 (1H, d, J 8.0, 8-H), 7.47 (1H, td, J 8.3, 1.1, 6-H), 7.32 (1H, app t, J 8.1, 3-phenyl 5-H), 6.83 (1H, dd, J 8.3, 1.7, 3-phenyl 4-H), 6.71–6.68 (1H, m, 3-phenyl 6-H), 6.56 (1H, br t, J 2.1, 3-phenyl 2-H), 5.48 (2H, t, J 7.5, ethyl 1-H), 1.72–1.54 (5H, m, cyclopentyl i-H, ethyl 2-H and cyclopentyl 3-H), 1.55–1.48 (2H, m, cyclopentyl 4-H), 1.46–1.38 (2H, m, cyclopentyl 5-H), 0.97–0.85 (2H, m, cyclopentyl 2-H); δ_{C} (126 MHz, CDCl{3}); 163.3 (4-C), 158.8 (2-C), 157.8 (3-phenyl 3-C), 147.6 (8a-C), 137.3 (3-phenyl 1-C), 135.2 (7-C), 130.9 (6-C), 127.2 (8-C), 127.0 (5-C and 3-phenyl 5-C), 120.2 (4a-C), 118.9 (3-phenyl 6-C), 117.5 (3-phenyl 4-C), 115.8 (3-phenyl 2-C), 39.8 (cyclopentyl 1-C), 35.0 (ethyl 1-C), 33.9 (cyclopentyl 2-C), 32.4 (cyclopentyl 3-C), 32.3 (ethyl 2-C), 25.1 (cyclopentyl 5-C), 25.1 (cyclopentyl 4-C); HRMS found MH+ 335.1757. C_{21}H_{32}N_{2}O requires MH+ 335.1754.
3-Phenyl-2-[(1R*,2R*)-2-phenylcyclopropyl]quinazolin-4-one, 8j

By general procedure A using (1R*,2R*)-N-(2-iodophenyl)-2-phenylcyclopropane-1-carboxamide, S7 (0.13, 0.31 mmol) and aniline (0.03 mL, 0.37 mmol) followed by purification by flash column chromatography, eluting with 50:50 hexane−EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN−water to yield quinazolinone 8j (0.019 g, 18%) as a colourless amorphous solid. $R_f$ 0.19 (80:20 hexane−EtOAc); $v_{	ext{max}}$/cm$^{-1}$ (film): 3306, 3056, 1674, and 1586; $\delta$H (501 MHz, CDCl$_3$); 8.28 (1H, d, $J_{8.0}$, 1.1, 5-H), 7.76 (1H, td, $J_{8.3}$, 1.4, 7-H), 7.67 (1H, d, $J_{8.1}$, 8-H), 7.52 (1H, app t, $J_{7.7}$, 3-phenyl 5-H), 7.44 (1H, app t, $J_{7.5}$, 6-H), 7.38 (1H, d, $J_{7.5}$, 3-phenyl 4-H), 7.35 (1H, br d, $J_{7.8}$, 3-phenyl 2-H), 7.30−7.26 (1H, m, 3-phenyl 3-H), 7.22−7.15 (4H, m, 3-phenyl 2-H, 2-phenyl 3-H, 2-phenyl 4-H and 2-phenyl 5-H), 6.89 (2H, d, $J_{7.0}$, 2-phenyl 2-H and 2-phenyl 6-H), 2.67−2.61 (1H, m, cyclopropane 2-H), 2.05 (1H, dt, $J_{9.7}$, 5.0, cyclopropane 3-H), 1.69 (1H, dt, $J_{8.5}$, 4.9, cyclopropane 1-H), 1.29 (1H, ddd, $J_{8.2}$, 6.3, 4.5, cyclopropane 3-H); $\delta$C (126 MHz, CDCl$_3$); 162.5 (4-C), 156.7 (2-C), 148.0 (8a-C), 140.3 (2-phenyl 1-C), 137.2 (3-phenyl 1-C), 134.6 (7-C), 129.8 (3-phenyl 3-C and 3-phenyl 5-C), 129.1 (3-phenyl 4-C), 128.8 (3-phenyl 6-C), 128.5 (3-phenyl 2-C), 128.4 (2-phenyl 3-C and 2-phenyl 5-C), 127.2 (5-C), 127.1 (8-C), 126.5 (2-phenyl 4-C), 126.3 (6-C), 126.1 (2-phenyl 2-C and 2-phenyl 6-C), 120.9 (4-C), 29.1 (cyclopropane 2-C), 25.9 (cyclopropane 1-C), 18.3 (cyclopropane 3-C); HRMS found MH$^+$ 339.1504. C$_{23}$H$_{19}$N$_2$O requires MH$^+$ 339.1497. The two sides of the N-phenyl ring were revealed to be diastereotopic, indicating slow rotation around the N-phenyl bond.

3-(3-Hydroxyphenyl)-2-[(1R*,2R*)-2-phenylcyclopropyl]quinazolin-4-one, 8i

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By general procedure A using (1R*,2R*)-N-(2-iodophenyl)-2-phenylcyclopropane-1-carboxamide, S7 (0.12 g, 0.28 mmol) and 3-aminophenol (0.04 g, 0.33 mmol) followed by purification by flash column chromatography, eluting with 50:50 hexane–EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN–water to yield quinazolinone 8I (0.021 g, 21%, rotamers 55:45 by 1H NMR) as a colourless amorphous solid. δH (501 MHz, CDCl3): 8.29 (2H, dd, J 7.2, 1.5, 5-H^maj and 5-H^min), 7.76 (2H, td, J 8.5, 1.4, 7-H^maj and 7-H^min), 7.67 (2H, dd, J 8.0, 2.8, 8-H^maj and 8-H^min), 7.44 (2H, app t, J 7.5, 6-H^maj and 6-H^min), 7.29 (1H, br d, J 8.0, 3-phenyl 5-H^min), 7.24–7.13 (6H, m, 2-phenyl 3-H^maj, 2-phenyl 3-H^min, 2-phenyl 4-H^maj, 2-phenyl 4-H^min, 2-phenyl 5-H^maj and 2-phenyl 5-H^min), 7.03 (1H, app t, J 8.0, 3-phenyl 5-H^maj), 6.94 (2H, d, J 7.3, 2-phenyl 2-H^min and 2-phenyl 6-H^min), 6.88 (2H, d, J 7.1, 2-phenyl 2-H^maj and 2-phenyl 6-H^maj), 6.76 (1H, dd, J 7.7, 0.9, 3-phenyl 4-H^min), 6.72–6.65 (3H, m, 3-phenyl 6-H^min, 3-phenyl 4-H^maj and 3-phenyl 2-H^maj), 6.60–6.57 (2H, m, 3-phenyl 6-H^maj and 3-phenyl 2-H^min), 2.67 (1H, ddd, J 11.1, 7.8, 4.7, cyclopropane 2-H^min), 2.58 (1H, ddd, J 9.4, 6.3, 4.4, cyclopropane 2-H^maj), 2.03 (1H, dd, J 9.4, 5.1, cyclopropane 3-H^maj), 1.94 (1H, dt, J 9.4, 4.9 cyclopropane 3-H^min), 1.77 (2H, td, J 9.8, 4.7, cyclopropane 1-H^maj and cyclopropane 1-H^min), 1.30 (2H, dddd, J 16.9, 8.2, 6.4, 4.4, cyclopropane 3-H^maj and cyclopropane 3-H^min); δC (126 MHz, CDCl3): 163.3 (4-C^maj), 163.3 (4-C^min), 158.5 (3-phenyl 3-C^min), 158.5 (3-phenyl 3-C^maj), 156.8 (2-C^maj), 156.8 (2-C^min), 148.2 (8a-C^maj), 148.1 (8a-C^min), 140.2 (2-phenyl 1-C^maj), 140.1 (2-phenyl 1-C^min), 137.2 (3-phenyl 1-C^min), 137.2 (3-phenyl 1-C^maj), 135.0 (7-C^maj), 135.0 (7-C^min), 130.8 (3-phenyl 5-C^min), 130.8 (3-phenyl 5-C^maj), 128.5 (2-phenyl 2-C^maj), 2-phenyl 2-C^min, 2-phenyl 6-C^maj, 2-phenyl 6-C^min), 127.3 (8-C^maj), 127.2 (8-C^min), 126.6 (5-C^maj), 126.5 (5-C^min), 126.5 (6-C^maj), 126.4 (6-C^min), 126.4 (2-phenyl 4-C^min), 126.4 (2-phenyl 4-C^maj), 126.1 (2-phenyl 3-C^maj), 2-phenyl 3-C^min, 2-phenyl 5-C^maj and 2-phenyl 5-C^min), 120.4 (4a-C^min), 120.3 (4a-C^maj), 119.5 (3-phenyl 4-C^maj), 119.0 (3-phenyl 4-C^min), 117.4 (3-phenyl 6-C^maj), 117.2 (3-phenyl 6-C^min), 116.2 (3-phenyl 2-C^maj), 115.8 (3-phenyl 2-C^min), 29.7 (cyclopropane 2-C^maj), 28.9 (cyclopropane 2-C^min), 25.6 (cyclopropane 1-C^min), 25.5 (cyclopropane 1-C^maj), 18.5 (cyclopropane 3-C^maj), 18.5 (cyclopropane 3-C^min); HRMS found MH+ 355.1437. C29H19N2O2 requires MH+ 355.1441. It was noted that two rotamers were observed.

\[ N(2,6\text{-dimethoxypyrimidin-4-yl})\text{-2-}(pent-4-enamido)benzamide , 9 \]

![Chemical structure of 9](attachment:image.png)

By general procedure A using N-(2-iodophenyl)pent-4-enamide, S8 (0.15 g, 0.5 mmol) and 4-amino-2,6-dimethoxypyrimidine (0.09 g, 0.6 mmol) followed by purification by flash column chromatography,
eluting with 50:50 hexane–EtOAc and purification using mass-directed HPLC eluting with gradient elution: 5:95 → 95:5 MeCN–water to yield benzamide 9 (0.08 g, 4%) as a colourless amorphous solid; 

\[ \nu_{\text{max}}/\text{cm}^{-1} \text{ (film)}: 3540, 2920, 1708, 1669, 1583 \text{ and } 1384; \delta_{\text{H}} (501 \text{ MHz, CDCl}_3): 10.72 (1H, s, N-H), 8.66 (1H, d, \text{ J } 8.4, 6-H), 8.50 (1H, s, pyrimidinyl N-H), 7.63 (1H, d, \text{ J } 7.7, 3-H), 7.54 (1H, app t, \text{ J } 7.7, 5-H), 7.30 (1H, s, pyrimidinyl 3-H), 7.14 (1H, app t, \text{ J } 7.6, 4-H), 5.88 (1H, ddt, \text{ J } 17.1, 10.3, 4.0, \text{ pentenyl 4-H}), 5.11 (1H, d, \text{ J } 17.1, \text{ pentenyl 5-Ha}), 5.02 (1H, d, \text{ J } 10.3, \text{ pentenyl 5-Hb}), 4.00 (3H, s, 6-methoxy methyl), 3.96 (3H, s, 2-methoxy methyl), 2.56–2.47 (4H, m, \text{ pentenyl 2-C and pentenyl 3-C}); \delta_{\text{c}} \text{ (126 MHz, CDCl}_3): 173.60 \text{ (pyrimidinyl 5-C)}, 171.36 \text{ (pentenyl 1-C)}, 167.97 \text{ (carbonyl)}, 164.82 \text{ (pyrimidinyl 3-C)}, 158.61 \text{ (pyrimidinyl 1-C)}, 140.34 \text{ (1-C)}, 136.81 \text{ (pentenyl 4-C)}, 134.05 \text{ (5-C)}, 126.85 \text{ (3-C)}, 123.09 \text{ (4-C)}, 122.17 \text{ (6-C)}, 119.51 \text{ (2-C)}, 115.87 \text{ (pentenyl 5-C)}, 89.28 \text{ (pyrimidinyl 3-C)}, 54.98 \text{ (2-methoxyl methyl)}, 54.45 \text{ (6-methoxyl methyl)}, 37.68 \text{ (pentenyl 2-C)}, 29.42 \text{ (pentenyl 3-C)}; \text{ HRMS found } \text{MH}^+ \text{ 357.1566. } \text{C}_{18}\text{H}_{21}\text{N}_{4}\text{O}_{4} \text{ requires } \text{MH}^+ \text{ 357.1563.} \]
6. X-Ray Structures

**Figure S1**: ORTEP diagram of S9, CCDC 1991665

| Crystal data and structure refinement for S9 |
|---------------------------------------------|
| Empirical formula                         | C_{12}H_{12}IN_{3}O                        |
| Formula Weight                            | 341.15                                     |
| Temperature/K                              | 120.00(10)                                 |
| Crystal system                             | triclinic                                  |
| Space group                                | P-1                                        |
| a/Å                                        | 4.1678(4)                                  |
| b/Å                                        | 10.6544(9)                                 |
| c/Å                                        | 14.6694(12)                                |
| α/°                                        | 73.012(7)                                  |
| β/°                                        | 84.892(7)                                  |
| γ/°                                        | 78.774(8)                                  |
| Volume/Å^{3}                               | 610.70(10)                                 |
| Z                                          | 2                                           |
| ρcalc/g/cm^{3}                             | 1.855                                      |
| µ/mm^{-1}                                  | 20.504                                     |
| F(000)                                     | 332.0                                      |
| Crystal size/mm^{3}                        | 0.22 × 0.11 × 0.07                         |
| Radiation                                  | CuKα (λ = 1.54184)                         |
| 2Θ range for data collection/°             | 8.818 to 146.602                            |
| Index ranges                               | -3 ≤ h ≤ 4, -11 ≤ k ≤ 13, -18 ≤ l ≤ 17    |
| Reflections collected                      | 3920                                       |
| Independent reflections                    | 2275 [R_{int} = 0.0278, R_{sigma} = 0.0360]|
| Data/restraints/parameters                 | 2275/0/162                                 |
| Goodness-of-fit on F^{2}                   | 1.093                                      |
| Final R indexes [I>=2σ (I)]                | R_{1} = 0.0329, wR_{2} = 0.0868             |
| Final R indexes [all data]                 | R_{1} = 0.0337, wR_{2} = 0.0880             |
| Largest diff. peak/hole / e Å^{-3}         | 1.31/-1.17                                 |
7. LCMS Analysis of Reductive Heck Reaction

LCMS analysis was performed on a crude reaction mixture containing (2E)-N-(2-iodophenyl)-3-phenylprop-2-enamide, 1 and 3-aminophenol to identify the mass of the products formed. The mass of a product formed from an intramolecular Heck reaction was identified within the crude mixture.

![Figure S1: LCMS analysis of reductive Heck reaction. Peak 4 corresponds to the mass of the reductive Heck product, SI3 and peak 5 corresponds to the mass of the intramolecular Heck product before reduction, SI4.](image)

8. Configuration of the Assay for ADS

To demonstrate that any unreacted starting material would not interfere with the assay, mock microreactions with each individual component were performed separately. Individual components were tested at the concentrations they would be used within each reaction mixture during the final array screen. One mock reaction was performed for each component and four screening concentrations were investigated to inform the selection of an appropriate final screening concentration.

The following stock solutions were prepared: 2-iodophenylaniline substrates 6b (= S1) and 6a (= S4) (1.0 M in THF); co-substrate 7b (= C1) (1.20 M in THF); tri-tert-butylphosphine (2.00 mM in o-xylene); and tris(dibenzylideneacetone)dipalladium(0) (0.33 mM in o-xylene).
Into well 1, 100 µL of the substrate 6b stock solution was added and evaporated. Then, 300 µL of o-xylene was added. The final volume of the reaction mixture was 300 µL; with final concentration of 6b (333 mM).

Into well 2, 100 µL of the substrate 6a stock solution was added and evaporated. Then, 300 µL of o-xylene was added. The final volume of the reaction mixture was 300 µL; with final concentration of 6a (333 mM).

Into well 3, 100 µL of the co-substrate 7b stock solution was added and evaporated. Then, 300 µL of o-xylene was added. The final volume of the reaction mixture was 300 µL; with final concentration of 7b (400 mM).

Into well 4, 300 µL of the tris(dibenzylideneacetone)dipalladium(0) stock solution was added. The final volume of the reaction mixture was 300 µL; with final concentration of catalyst (0.33 mM).

Into well 5, 300 µL of the tri-tert-butyphosphine stock solution was added. The final volume of the reaction mixture was 300 µL; with final concentration of ligand (2.00 mM).

Into well 6, 265 µL of o-xylene was added followed by the addition of 35 µL of concentrated triethylamine. The final volume of the reaction mixture was 300 µL; with final concentration of triethylamine (833 mM).

Into well 7, 26 mg of molybdenum hexacarbonyl was added as a solid followed by 300 µL of o-xylene. The final volume of the reaction mixture was 300 µL; with final concentration of molybdenum hexacarbonyl (333 mM).

The positive control was screened as a mixture and contained the crude product of the reaction between substrate 6b and co-substrate 7b. All reaction components were present within this mixture and the reaction was performed as described in general procedure C.

The negative control was screened as a mixture and contained the crude product of the reaction between substrate 6a and co-substrate 7b. All reaction components were present within this mixture and the reaction was performed as described in general procedure C.

All microreaction wells were sealed and left for 48 h at 105 °C. After evaporating the o-xylene, dissolving in EtOAc and filtering the crude mixtures through silica, the solutions were left to evaporate, and the crude dissolved in dimethyl sulfoxide (300 µL) to correspond to a final total product concentration of 333 mM.

These stock solutions were subsequently further diluted with DMSO and screened at total product concentrations of 100 µM, 50 µM, 25 µM and 12.5 µM (1% DMSO in ISB) following the General Screening Procedure against ATCC29213. Each reaction mixture/component was screened in triplicate against one colony of ATCC29213 and the average value was plotted.

8b, a pure, S. aureus active quinazolinone11, was also screened at the respective concentrations.
Figure S3: Growth inhibition values of individual reaction components, a reaction that forms a positive control and a reaction that forms a negative control against ATCC29213. Reaction concentrations were based on the limiting reagent of the reaction mixtures, 333 mM. Screening concentrations were as follows: A = total product concentration, 100 µM, B = total product concentration, 50 µM, C = total product concentration, 25 µM and D = total product concentration, 12.5 µM.
9. Reaction Array Table

Reaction array data: Percentage growth inhibition of product mixtures prepared in carbonylation array. Product mixtures were assayed at a total product concentration of 50 μM following the general screening procedure for the screening of the Carbonylation Reaction Array.

| Iodoanilide substrate | Co-substrate | Catalyst     | Solvent  | Growth Inhibition / % ATCC29213 A | ATCC29213 B |
|-----------------------|--------------|--------------|----------|-----------------------------------|-------------|
| S1                    | C1           | Pd₂(dba)₃    | o-xylene | 88                                | 78          |
| S1                    | C2           | Pd₂(dba)₃    | o-xylene | 4                                 | 19          |
| S1                    | C3           | Pd₂(dba)₃    | o-xylene | 12                                | 10          |
| S1                    | C4           | Pd₂(dba)₃    | o-xylene | 10                                | 27          |
| S1                    | C5           | Pd₂(dba)₃    | o-xylene | 4                                 | 39          |
| S1                    | C6           | Pd₂(dba)₃    | o-xylene | 0                                 | 1           |
| S1                    | C7           | Pd₂(dba)₃    | o-xylene | 28                                | 0           |
| S1                    | C8           | Pd₂(dba)₃    | o-xylene | 1                                 | 0           |
| S1                    | C9           | Pd₂(dba)₃    | o-xylene | 18                                | 38          |
| S1                    | C10          | Pd₂(dba)₃    | o-xylene | 33                                | 0           |
| S1                    | C11          | Pd₂(dba)₃    | o-xylene | 0                                 | 39          |
| S1                    | C12          | Pd₂(dba)₃    | o-xylene | 6                                 | 0           |
| S1                    | C13          | Pd₂(dba)₃    | o-xylene | 0                                 | 45          |
| S1                    | C14          | Pd₂(dba)₃    | o-xylene | 0                                 | 52          |
| S1                    | C15          | Pd₂(dba)₃    | o-xylene | 0                                 | 45          |
| S1                    | C16          | Pd₂(dba)₃    | o-xylene | 3                                 | 0           |
| S1                    | C17          | Pd₂(dba)₃    | o-xylene | 0                                 | 35          |
| S1                    | C18          | Pd₂(dba)₃    | o-xylene | 79                                | 78          |
| S1                    | C19          | Pd₂(dba)₃    | o-xylene | 0                                 | 16          |
| S1                    | Blank        | Pd₂(dba)₃    | o-xylene | 19                                | 1           |
| S2                    | C1           | Pd₂(dba)₃    | o-xylene | 0                                 | 18          |
| S2                    | C2           | Pd₂(dba)₃    | o-xylene | 3                                 | 9           |
| S2                    | C3           | Pd₂(dba)₃    | o-xylene | 0                                 | 6           |
| S2                    | C4           | Pd₂(dba)₃    | o-xylene | 0                                 | 13          |
| S2                    | C5           | Pd₂(dba)₃    | o-xylene | 0                                 | 10          |
| S2                    | C6           | Pd₂(dba)₃    | o-xylene | 1                                 | 6           |
| S2                    | C7           | Pd₂(dba)₃    | o-xylene | 2                                 | 2           |
| S2 | C8  | Pd₂(dba)₃ | o-xylene | 2  | 0  |
| S2 | C9  | Pd₂(dba)₃ | o-xylene | 0  | 29 |
| S2 | C10 | Pd₂(dba)₃ | o-xylene | 3  | 0  |
| S2 | C11 | Pd₂(dba)₃ | o-xylene | 0  | 31 |
| S2 | C12 | Pd₂(dba)₃ | o-xylene | 3  | 0  |
| S2 | C13 | Pd₂(dba)₃ | o-xylene | 0  | 27 |
| S2 | C14 | Pd₂(dba)₃ | o-xylene | 0  | 35 |
| S2 | C15 | Pd₂(dba)₃ | o-xylene | 0  | 41 |
| S2 | C16 | Pd₂(dba)₃ | o-xylene | 9  | 0  |
| S2 | C17 | Pd₂(dba)₃ | o-xylene | 0  | 15 |
| S2 | C18 | Pd₂(dba)₃ | o-xylene | 14 | 0  |
| S2 | C19 | Pd₂(dba)₃ | o-xylene | 0  | 4  |
| S2 | Blank | Pd₂(dba)₃ | o-xylene | 10 | 0  |
| S3 | C1  | Pd₂(dba)₃ | o-xylene | 0  | 20 |
| S3 | C2  | Pd₂(dba)₃ | o-xylene | 0  | 6  |
| S3 | C3  | Pd₂(dba)₃ | o-xylene | 0  | 0  |
| S3 | C4  | Pd₂(dba)₃ | o-xylene | 4  | 2  |
| S3 | C5  | Pd₂(dba)₃ | o-xylene | 0  | 0  |
| S3 | C6  | Pd₂(dba)₃ | o-xylene | 0  | 1  |
| S3 | C7  | Pd₂(dba)₃ | o-xylene | 8  | 0  |
| S3 | C8  | Pd₂(dba)₃ | o-xylene | 1  | 0  |
| S3 | C9  | Pd₂(dba)₃ | o-xylene | 0  | 12 |
| S3 | C10 | Pd₂(dba)₃ | o-xylene | 0  | 0  |
| S3 | C11 | Pd₂(dba)₃ | o-xylene | 0  | 16 |
| S3 | C12 | Pd₂(dba)₃ | o-xylene | 0  | 0  |
| S3 | C13 | Pd₂(dba)₃ | o-xylene | 0  | 24 |
| S3 | C14 | Pd₂(dba)₃ | o-xylene | 0  | 27 |
| S3 | C15 | Pd₂(dba)₃ | o-xylene | 0  | 28 |
| S3 | C16 | Pd₂(dba)₃ | o-xylene | 0  | 6  |
| S3 | C17 | Pd₂(dba)₃ | o-xylene | 0  | 14 |
| S3 | C18 | Pd₂(dba)₃ | o-xylene | 90 | 24 |
| S3 | C19 | Pd₂(dba)₃ | o-xylene | 0  | 3  |
| S3 | Blank | Pd₂(dba)₃ | o-xylene | 13 | 0  |
|   |   |   |   |
|---|---|---|---|
|S4| C1| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C2| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C3| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C4| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C5| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C6| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C7| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C8| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C9| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C10| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C11| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C12| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C13| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C14| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C15| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C16| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C17| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C18| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| C19| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S4| Blank| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C1| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C2| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C3| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C4| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C5| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C6| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C7| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C8| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C9| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C10| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C11| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C12| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|S5| C13| Pd$_2$(dba)$_3$| o-xylene |
|  |  |  | 0 |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| S5 | C14 | Pd$_2$(dba)$_3$ | o-xylene | 4 | 22 |
| S5 | C15 | Pd$_2$(dba)$_3$ | o-xylene | 0 | 18 |
| S5 | C16 | Pd$_2$(dba)$_3$ | o-xylene | 12 | 5 |
| S5 | C17 | Pd$_2$(dba)$_3$ | o-xylene | 0 | 19 |
| S5 | C18 | Pd$_2$(dba)$_3$ | o-xylene | 13 | 1 |
| S5 | C19 | Pd$_2$(dba)$_3$ | o-xylene | 0 | 0 |
| S5 | Blank | Pd$_2$(dba)$_3$ | o-xylene | 33 | 8 |
| S6 | C1  | Pd$_2$(dba)$_3$ | o-xylene | 1 | 13 |
| S6 | C2  | Pd$_2$(dba)$_3$ | o-xylene | 0 | 0 |
| S6 | C3  | Pd$_2$(dba)$_3$ | o-xylene | 0 | 0 |
| S6 | C4  | Pd$_2$(dba)$_3$ | o-xylene | 15 | 0 |
| S6 | C5  | Pd$_2$(dba)$_3$ | o-xylene | 21 | 0 |
| S6 | C6  | Pd$_2$(dba)$_3$ | o-xylene | 18 | 15 |
| S6 | C7  | Pd$_2$(dba)$_3$ | o-xylene | 23 | 26 |
| S6 | C8  | Pd$_2$(dba)$_3$ | o-xylene | 11 | 7 |
| S6 | C9  | Pd$_2$(dba)$_3$ | o-xylene | 33 | 11 |
| S6 | C10 | Pd$_2$(dba)$_3$ | o-xylene | 13 | 5 |
| S6 | C11 | Pd$_2$(dba)$_3$ | o-xylene | 0 | 0 |
| S6 | C12 | Pd$_2$(dba)$_3$ | o-xylene | 1 | 0 |
| S6 | C13 | Pd$_2$(dba)$_3$ | o-xylene | 18 | 6 |
| S6 | C14 | Pd$_2$(dba)$_3$ | o-xylene | 17 | 95 |
| S6 | C15 | Pd$_2$(dba)$_3$ | o-xylene | 19 | 99 |
| S6 | C16 | Pd$_2$(dba)$_3$ | o-xylene | 0 | 0 |
| S6 | C17 | Pd$_2$(dba)$_3$ | o-xylene | 12 | 8 |
| S6 | C18 | Pd$_2$(dba)$_3$ | o-xylene | 0 | 20 |
| S6 | C19 | Pd$_2$(dba)$_3$ | o-xylene | 2 | 97 |
| S6 | Blank | Pd$_2$(dba)$_3$ | o-xylene | 19 | 3 |
| S7 | C1  | Pd$_2$(dba)$_3$ | o-xylene | 26 | 37 |
| S7 | C2  | Pd$_2$(dba)$_3$ | o-xylene | 0 | 0 |
| S7 | C3  | Pd$_2$(dba)$_3$ | o-xylene | 14 | 0 |
| S7 | C4  | Pd$_2$(dba)$_3$ | o-xylene | 0 | 5 |
| S7 | C5  | Pd$_2$(dba)$_3$ | o-xylene | 0 | 0 |
| S7 | C6  | Pd$_2$(dba)$_3$ | o-xylene | 19 | 99 |
|   |   |   |   |
|---|---|---|---|
| S7 | C7 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 24 |
| S7 | C8 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 23 |
| S7 | C9 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 41 |
| S7 | C10 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S7 | C11 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S7 | C12 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 5 |
| S7 | C13 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S7 | C14 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 40 |
| S7 | C15 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 43 |
| S7 | C16 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 25 |
| S7 | C17 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 20 |
| S7 | C18 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 96 |
| S7 | C19 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 46 |
| S7 | Blank | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 19 |
| S8 | C1 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C2 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C3 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C4 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C5 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C6 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 20 |
| S8 | C7 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 20 |
| S8 | C8 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 16 |
| S8 | C9 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 16 |
| S8 | C10 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C11 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C12 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C13 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 6 |
| S8 | C14 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
| S8 | C15 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 24 |
| S8 | C16 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 18 |
| S8 | C17 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 100 |
| S8 | C18 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 12 |
| S8 | C19 | Pd$_2$(dba)$_3$ | o-xylene |
|   |   |   | 0 |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| S8 | Blank | Pd$_2$(dba)$_3$ | o-xylene | 1 | 3 |
| S9 | C1 | Pd$_2$(dba)$_3$ | o-xylene | 14 | 12 |
| S9 | C2 | Pd$_2$(dba)$_3$ | o-xylene | 14 | 12 |
| S9 | C3 | Pd$_2$(dba)$_3$ | o-xylene | 24 | 32 |
| S9 | C4 | Pd$_2$(dba)$_3$ | o-xylene | 18 | 26 |
| S9 | C5 | Pd$_2$(dba)$_3$ | o-xylene | 23 | 33 |
| S9 | C6 | Pd$_2$(dba)$_3$ | o-xylene | 20 | 40 |
| S9 | C7 | Pd$_2$(dba)$_3$ | o-xylene | 22 | 45 |
| S9 | C8 | Pd$_2$(dba)$_3$ | o-xylene | 13 | 22 |
| S9 | C9 | Pd$_2$(dba)$_3$ | o-xylene | 15 | 24 |
| S9 | C10 | Pd$_2$(dba)$_3$ | o-xylene | 8 | 20 |
| S9 | C11 | Pd$_2$(dba)$_3$ | o-xylene | 6 | 19 |
| S9 | C12 | Pd$_2$(dba)$_3$ | o-xylene | 22 | 7 |
| S9 | C13 | Pd$_2$(dba)$_3$ | o-xylene | 20 | 22 |
| S9 | C14 | Pd$_2$(dba)$_3$ | o-xylene | 23 | 24 |
| S9 | C15 | Pd$_2$(dba)$_3$ | o-xylene | 23 | 29 |
| S9 | C16 | Pd$_2$(dba)$_3$ | o-xylene | 16 | 36 |
| S9 | C17 | Pd$_2$(dba)$_3$ | o-xylene | 16 | 25 |
| S9 | C18 | Pd$_2$(dba)$_3$ | o-xylene | 6 | 17 |
| S9 | C19 | Pd$_2$(dba)$_3$ | o-xylene | 15 | 15 |
| S9 | Blank | Pd$_2$(dba)$_3$ | o-xylene | 17 | 36 |
| S10 | C1 | Pd$_2$(dba)$_3$ | o-xylene | 95 | 97 |
| S10 | C2 | Pd$_2$(dba)$_3$ | o-xylene | 27 | 27 |
| S10 | C3 | Pd$_2$(dba)$_3$ | o-xylene | 15 | 24 |
| S10 | C4 | Pd$_2$(dba)$_3$ | o-xylene | 42 | 47 |
| S10 | C5 | Pd$_2$(dba)$_3$ | o-xylene | 38 | 44 |
| S10 | C6 | Pd$_2$(dba)$_3$ | o-xylene | 96 | 95 |
| S10 | C7 | Pd$_2$(dba)$_3$ | o-xylene | 51 | 59 |
| S10 | C8 | Pd$_2$(dba)$_3$ | o-xylene | 16 | 46 |
| S10 | C9 | Pd$_2$(dba)$_3$ | o-xylene | 49 | 55 |
| S10 | C10 | Pd$_2$(dba)$_3$ | o-xylene | 11 | 16 |
| S10 | C11 | Pd$_2$(dba)$_3$ | o-xylene | 17 | 30 |
| S10 | C12 | Pd$_2$(dba)$_3$ | o-xylene | 16 | 27 |
|     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|
| S10 | C13 | Pd_2(dba)_3 | o-xylene | 25  | 57  |
| S10 | C14 | Pd_2(dba)_3 | o-xylene | 40  | 54  |
| S10 | C15 | Pd_2(dba)_3 | o-xylene | 32  | 64  |
| S10 | C16 | Pd_2(dba)_3 | o-xylene | 18  | 40  |
| S10 | C17 | Pd_2(dba)_3 | o-xylene | 28  | 32  |
| S10 | C18 | Pd_2(dba)_3 | o-xylene | 94  | 98  |
| S10 | Blank | Pd_2(dba)_3 | o-xylene | 51  | 57  |
| Blank | C1 | Pd_2(dba)_3 | o-xylene | 30  | 45  |
| Blank | C2 | Pd_2(dba)_3 | o-xylene | 11  | 5   |
| Blank | C3 | Pd_2(dba)_3 | o-xylene | 0   | 0   |
| Blank | C4 | Pd_2(dba)_3 | o-xylene | 0   | 3   |
| Blank | C5 | Pd_2(dba)_3 | o-xylene | 0   | 0   |
| Blank | C6 | Pd_2(dba)_3 | o-xylene | 20  | 0   |
| Blank | C7 | Pd_2(dba)_3 | o-xylene | 30  | 5   |
| Blank | C8 | Pd_2(dba)_3 | o-xylene | 6   | 0   |
| Blank | C9 | Pd_2(dba)_3 | o-xylene | 0   | 14  |
| Blank | C10 | Pd_2(dba)_3 | o-xylene | 5   | 9   |
| Blank | C11 | Pd_2(dba)_3 | o-xylene | 0   | 16  |
| Blank | C12 | Pd_2(dba)_3 | o-xylene | 7   | 5   |
| Blank | C13 | Pd_2(dba)_3 | o-xylene | 0   | 29  |
| Blank | C14 | Pd_2(dba)_3 | o-xylene | 0   | 24  |
| Blank | C15 | Pd_2(dba)_3 | o-xylene | 0   | 30  |
| Blank | C16 | Pd_2(dba)_3 | o-xylene | 8   | 0   |
| Blank | C17 | Pd_2(dba)_3 | o-xylene | 0   | 11  |
| Blank | C18 | Pd_2(dba)_3 | o-xylene | 21  | 4   |
| Blank | C19 | Pd_2(dba)_3 | o-xylene | 0   | 4   |
| Blank | Blank | Pd_2(dba)_3 | o-xylene | 25  | 7   |
10. Reinvestigation of Reactions that were Hits against One Colony

A number of reactions resulted in hits against only one of the two colonies. We therefore retested these samples against two more colonies of ATCC29213 to reinvestigate their activity. Reaction mixtures were screened at a total product concentration of 50 µM in ISB containing 1% DMSO. None of the reaction mixtures inhibited bacterial growth greater than 75% and growth inhibition was no visually observed.

Figure S5: Reinvestigation of reaction hits that had been active against one colony. Reaction combinations that did not show duplicated biological activity (see Figure 2, main paper) at total product concentration: 50 µM against ATCC29213 were were re-screened in duplicate.
| Iodoanilide substrate | Co-substrate | Catalyst     | Solvent    | Growth Inhibition / % |
|-----------------------|--------------|--------------|------------|-----------------------|
|                       |              |              |            | ATCC29213 A | ATCC29213 B |
| S3                    | C19          | Pd$_2$(dba)$_3$ | o-xylene   | 46         | 6          |
| S8                    | C17          | Pd$_2$(dba)$_3$ | o-xylene   | 0          | 0          |
| S7                    | C6           | Pd$_2$(dba)$_3$ | o-xylene   | 32         | 45         |
| S7                    | C9           | Pd$_2$(dba)$_3$ | o-xylene   | 0          | 17         |
| S7                    | C19          | Pd$_2$(dba)$_3$ | o-xylene   | 16         | 24         |
| S6                    | C14          | Pd$_2$(dba)$_3$ | o-xylene   | 9          | 7          |
| S6                    | C15          | Pd$_2$(dba)$_3$ | o-xylene   | 0          | 31         |
| S6                    | C19          | Pd$_2$(dba)$_3$ | o-xylene   | 9          | 0          |

11. LCMS Analysis of Product Mixtures from Array

Analytical LCMS was performed on twenty-three product mixtures (ca. 10% of the total number of reactions) to identify intermolecular mass and estimate the success of the reaction. Analytical LCMS was performed using an Thermo Ultimate 3000 HPLC instrument with a UV diode array detector and an MS detector Bruker Amazon Speeds with electrospray ionisation run positive and negative switching mode. The system used a Phenomenex Kinetex C18 2.1 × 50 mm 2.6 micron column and two solvent systems: MeCN/H$_2$O + 0.1% Formic acid or MeCN/H$_2$O.

Masses that matched that of the respective the quinazolinone and intermolecular carbonylation product were identified and recorded below.

| Substrate | Co-Substrate | Quinazolinone product$^a$ | Intermolecular carbonylation product$^b$ |
|-----------|--------------|---------------------------|----------------------------------------|
| S5        | 7b (= C1)    |                           |                                        |
| S5        | C18          |                           |                                        |
| S2        | C12          |                           | ✓                                      |
| 6a (=S4)  | C8           |                           |                                        |
| 1 (=S3)   | C6           | ✓                         |                                        |
| 6b (=S1)  | C18          | ✓                         |                                        |
| S2        | C17          |                           |                                        |
| 6a (=S4)  | C9           | ✓                         |                                        |
| 6b (=S1)  | C4           | ✓                         |                                        |
| S5        | C13          | ✓$^c$                     |                                        |
Table S1 Results of the LCMS screen performed on a random ~10% of wells. aTick indicates that the mass corresponding to a quinazolinone product was observed. bTick indicates that the mass corresponding to an intermolecular carbonylation product was observed. cThe observed mass corresponded to a quinazolinone in which the second iodo group in the product had undergone a carbonylation reaction to form a carboxylic acid.

12. Evaluation of Activity of Quinazolinones against S. aureus

| Hit? | Substrates | Product (Yield) | MIC (µg mL⁻¹) | ATCC29213 | USA300 JE2 | SH1000 |
|------|------------|----------------|----------------|-----------|------------|--------|
| ✓    | S1, C1     | 8b (19%)       | 0.5–1 (1.5–2.9 µM) | 0.5 (1.5 µM) | 4 (11.7 µM) |
| ✓    | S1, C18    | 8d (4%)        | 0.016 (0.038 µM) | 0.016 (0.038 µM) | 0.5–1 (1.2–2.4 µM) |
| ✗    | S7, C18    | 8e (2%)        | 1–2 (2.3–4.6 µM) | 2 (4.6 µM) | 32–64 (74–148 µM) |
| ✓    | S10, C1    | 8f (8%)        | 1 (2.4 µM) | 0.5–1 (1.2–2.4 µM) | 4–8 (9.7–19.5 µM) |
| ✓    | S10, C6    | 8g (8%)        | 2–4 (6.0–12.0 µM) | 2–4 (6.0–12.0 µM) | 16 (48 µM) |
| ✓    | S10, C18   | 8h (14%)       | 0.5 (1.5 µM) | 0.5 (1.5 µM) | 1–2 (3.0–6.0 µM) |
| ✗    | S7, C1     | 8i (21%)       | 4–8 (11.8–22.6 µM) | 4–8 (11.8–22.6 µM) | 16 (45 µM) |
| ✗    | S4, C9     | 9 (5%)         | >128 (>379 µM) | 64 (189 µM) | 32–64 (95–189 µM) |
| ✗    | S7, aniline | 8j (18%)       | >128 (>359 µM) | >128 (>359 µM) | >128 (>359 µM) |

Table S2 Extended table of the scale-up of reactions and evaluation of the activity against three S. aureus strains (ATCC29213, USA300 JE2, SH1000). The range of MICs observed obtained in duplicate on three different days. MIC values have been converted to µM using the molecular mass of each product and reported in brackets next to the appropriate MIC value.
13. $^1$H and $^{13}$C NMR Spectra

2-Methyl-3-phenylquinazolin-4-one, 8a

400 MHz $^1$H NMR spectrum

101 MHz $^{13}$C NMR spectrum
3-(3-Hydroxyphenyl)-2-(2-phenylethyl)quinazolin-4-one, 8b

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
2-Methyl-4H-benzo[d][1,3]oxazin-4-one, SI1

400 MHz $^1$H NMR spectrum

101 MHz $^{13}$C NMR spectrum
3-(3-hydroxyphenyl)-2-methylquinazolin-4-one, SI2

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-(3-Hydroxyphenyl)-2-(((1E)-2-(4-cyanophenyl)ethenyl)quinazolin-4-one, 8c

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
N-(2-iodophenyl)-3-phenylpropanamide, 6b

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
(2E)-N-(2-iodophenyl)-3-phenylprop-2-enamide, 1

400 MHz $^1$H NMR spectrum

101 MHz $^{13}$C NMR spectrum
N-(2-iodophenyl)pent-4-enamide, S8

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
2-Iodo-N-(2-iodophenyl)benzamide, S5

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
(1R*,2R*)-N-(2-iodophenyl)-2-phenylcyclopropane-1-carboxamide, S7

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
N-(2-iodophenyl)-2-(thiophen-2-yl)acetamide, S6

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
1-(3-Amino-4-iodopyrazol-1-yl)-3-phenylpropan-1-one, S9

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-Cyclopentyl-N-(2-iodophenyl)propenamide, S10

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-(3-(N-phenylmethanesulfonamide))-2-(2-phenylethyl)quinazolin-4-one, 8d

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-(3-(N-phenylmethanesulfonamide))-2-((1R*, 2R*)-2-phenylcyclopropyl)quinazolin-4-one, 8e

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-(3-(N-phenylmethanesulfonamide))-2-(2-cyclopentylethyl)quinazolin-4-one, 8f

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-(3-Aminophenyl)-2-(2-cyclopentylethyl)quinazolin-4-one, 8g

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
2-(2-Cyclopentylethyl)-3-(3-hydroxyphenyl)quinazolin-4-one, 8h

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-Phenyl-2-[(1R*,2R*)-2-phenylcyclopropyl]quinazolin-4-one, 8j

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
3-(3-Hydroxyphenyl)-2-[(1R',2R')-2-phenylcyclopropyl]quinazolin-4-one, 8i

501 MHz $^1$H NMR spectrum

126 MHz $^{13}$C NMR spectrum
**N-(2,6-dimethoxypyrimidin-4-yl)-2-(pent-4-enamido)benzamide, 9**

501 MHz $^1$H NMR spectrum

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

126 MHz $^{13}$C NMR spectrum

![126 MHz $^{13}$C NMR spectrum](image)
14. References

1. J. B. Peng, H. Q. Geng, W. Wang, X. Qi, J. Ying and X. F. Wu. Palladium-catalyzed four-component carbonylation of allenes, alcohols and nitroarenes, *J. Catal.*, 2018, **365**, 10-13.

2. C. Gimbert and A. Vallribera. A Straightforward Synthesis of Benzothiazines, *Org. Lett.* 2009, **11**, 2, 269-271.

3. G. Karageorgis, M. Dow, A. Aimon, S. Warriner and A. Nelson. Activity-Directed Synthesis with Intermolecular Reactions: Development of a Fragment into a Range of Androgen Receptor Agonists, *Angew. Chemie. Int. Ed.*, 2015, **54**, 13538-13544.

4. A. J. O’Neill. *Staphylococcus aureus* SH1000 and 8325-4: comparative genome sequences of key laboratory strains in staphylococcal research. *Lett Appl Microbiol*, 2010, **51**, 358 –361.

5. I. Soni, H. Chakrapani and S. Chopra. Draft genome sequence of Methicillin-Sensitive *Staphylococcus aureus* ATCC 29213, 2015, *Genome Announc.* **3**, 1.

6. B. A. Diep, S. R. Gill, R. F. Chang, T. H. Phan, J. H. Chen, M. G. Davidson, F. Lin, J. Lin, H. A. Carleton, E. F. Mongodin, G. F. Sensabaugh and F. Perdreau-Remington. Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2006. **367**, 731–739

7. CLSI, M07-A9: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 9th ed. *Clinical and Laboratory Standards Institute*. 2012.

8. CLSI, M100-S23: Performance standards for antimicrobial susceptibility testing; Twenty-third informational supplement. *Clinical and Laboratory Standards Institute*. 2013.

9. C.M. Martel, J.E. Parker, O. Bader, M. Weig, Y. Gross, A.G.S. Warrilow, N. Rolley, D.E. Kelly and S.L. Kelly. *Antimicrobial Agents and Chemotherapy*, 2010, **54**, 4527-4533.

10. CLSI, M44-A2: Method for antifungal disk diffusion susceptibility testing of yeasts; approved guideline, 2nd ed. *Clinical and Laboratory Standards Institute*. 2009.

11. R. Bouley, D. Ding, Z. Peng, M. Bastian, E. Lastochkin, W. Song, M. A. Suckow, V. A. Schroeder, W. R. Wolter, S. Mobashery and M. Chang. *J. Med. Chem*, 2016, **59**, 5011-5021.

12. S. Redon, Y. Kabri, M. Crozet and P. Vanelle. *Tet. Lett*. 2014, **55**, 5052-5054.

13. W. Dong, Y. Liu, B. Hu, K. Ren, Y. Li, X. Xie, Y. Jiang and Z. Zhang. *Chem. Comm.* 2015, **51**, 4587-4590.

14. K. C. Nicolaou, P. S. Baran, Y. L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich and J. A. Vega. *J. Am. Chem. Soc.* **124**, 2233-2244.

15. S. J. Balkrishna and S. Kumar. *Synthesis*. 2012, **44**, 1417-1426.
16 D. H. O’Donovan, P. Aillard, M. Berger, A. Torre, D. Petkova, C. Knittl-Frank, D. Geerdink, M. Kaiser and N. Maulide. Angew. Chem. Int. Ed. 2018, 57, 10737–10741.

17 B. Li, Y. Park and S. Chang, Regiodivergent Access to Five- and Six-Membered Benzo-Fused Lactams: Ru-Catalyzed Olefin Hydrocarbamoylation, J. Am. Chem. Soc. 2014, 136, 1125-1131.