

Development of pharmaceutically relevant bio-based intermediates through aldol condensation and Claisen-Schmidt reactions of dihydrolevoglucosenone (Cyrene®)

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Experimental

Gas Chromatography – Flame Ionisation Detector (GC-FID)

Samples were analysed by GC-FID using a Hewlett Packard HP 6890 GC System gas chromatograph fitted with a Rxi-5HT inferno column with dimensions of 30 m x 0.25 mm x 0.25 µm and a helium mobile phase with a flow of 104.1 mLmin⁻¹. Injector temperature, pressure and split ratio were set at 300 °C, 20.2 psi and 50:1 respectively. The initial oven temperature was 50 °C with a ramp rate of 30 °C / min until 300 °C was reached and then held for 5 minutes. The FID was set at 340 °C.

Gas Chromatography – Mass Spectrometry (GC-MS)

Two different GC-MS instruments were used in the analyses of samples. The first was a Perkin Elmer Clarus 500 Gas Chromatograph fitted with a Perkin Elmer Clarus 560S Mass Spectrum which had an Electron Ionisation Detector. The second was an Agilent 7890A Gas Chromatograph fitted with a Waters GCT Premier time of flight mass spectrum. The column and method for both was the same as stated for GC-FID.

IR

Samples were analysed using a Perkin Elmer Spectrum 400 FT-IR/FT-NIR spectrometer. Spectra were recorded from 500 to 4000 cm⁻¹ and 4 background and sample scans were taken.

¹H and ¹³C Nuclear Magnetic Resonance Spectroscopy (¹H and ¹³C NMR)

All NMR spectroscopy was performed using a JEOL 400 ECS MHz Spectrometer with both CDCl₃ and MeOH-d₄ solvents used.

Single-crystal X-ray Crystallography (XRD)

Diffraction data were collected at 110 K on an Oxford Diffraction SuperNova diffractometer with Cu- K_{α} radiation ($\lambda = 1.54184 \text{ \AA}$) using a EOS CCD camera. The crystal was cooled with an Oxford Instruments Cryojet. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement was carried out with "Crysalis".^a Face-indexed absorption corrections were applied using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.^b OLEX2^c was used for overall structure solution, refinement and preparation of computer graphics and publication data. Within OLEX2, the algorithms used for structure solution were "ShelXS direct methods"^d (for structures **2**, **3**, and **4**), "Superflip charge-flipping"^e (for structures **6** & **8**) and "ShelXT dual-space"^f (for structures **1**, **5** and **7**). Refinement by full-matrix least-squares used the SHELXL-97^g algorithm within OLEX2.^c All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a "riding model" and included in the refinement at calculated positions.

References

- a CrysAlisPro, Oxford Diffraction Ltd. Version 1.171.34.41
- b Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm within CrysAlisPro software, Oxford Diffraction Ltd. Version 1.171.34.40
- c "Olex2" crystallography software, J. Appl. Cryst., 2009, 42, 339–341.
- d "SHELXS-97" - program for structure solution.
G.M. Sheldrick, Acta Cryst. 2008, A64, 112-122.
- e SUPERFLIP - a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions,
L. Palatinus & G. J. Chapuis, J. Appl. Cryst. 2007, 40, 786-790.
- f SHELXT – Integrated space-group and crystal-structure determination
G. M. Sheldrick, Acta Cryst. 2015, A71, 3-8
- g "SHELXL-97" - program for the Refinement of Crystal Structures.
G.M. Sheldrick, Acta Cryst. 2008, A64, 112-122.

Synthesis of Cyrene Aldol Condensation Product

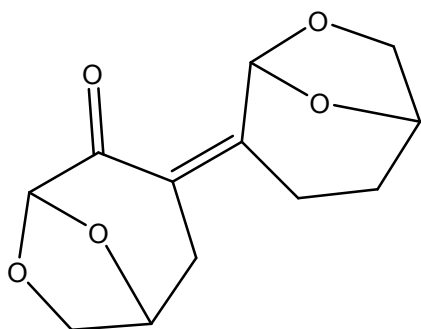


Figure S1: Structure of the self-condensation product of Cyrene

Cyrene (10 mL, 97.6 mMol), K_3PO_4 (1.0 g, 4.87 mMol) and ethanol (5.0 mL) were added to a 50 mL round bottom flask which was charged with a magnetic stirrer bar and fitted with a reflux condenser. The reaction mixture was heated to 120 °C and stirred (550 rpm) for 40 minutes. After this time, the reaction mixture had become a white/brown solid. The solid was washed out of the flask with water and isolated by vacuum filtration and further washed with water then methanol and dried in *vacuo* to yield a white powder (9.51 g, 81.3 %). The product was then recrystallized in hot acetonitrile to give large white crystals which were isolated by vacuum filtration and washed with cold acetonitrile (7.55 g, 64.5 %).

ν_{max} / cm^{-1} : 2963, 2893, 1699, 1618, 1093; 1H NMR (399.78 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.19 (s, 1H), 4.80 (t, $J = 4$ Hz, 1H), 4.61 (t, $J = 4$ Hz, 1H), 3.93 (m, 4H), 2.78 (m, 1H), 2.58 (d, $J = 16$, 1H), 2.37 (m, 2H), 2.13 (m, 1H), 1.77 (m, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 190.75, 151.00, 123.25, 101.50, 97.25, 72.50, 68.75, 34.00, 28.75, 20.25; GC-MS, $gmol^{-1}$: Calculated for $C_{12}H_{14}O_5$ - 238.24 Observed - 238.0834



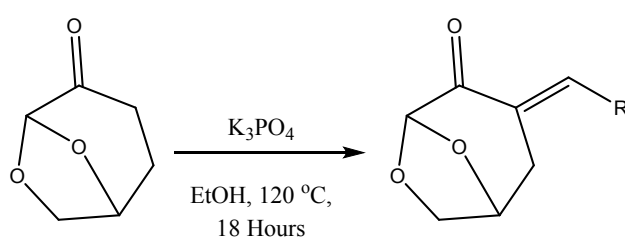
Figure S2: Microscope pictures of the self-condensation product.

Synthesis of Crossed Aldol Condensation Products (General Procedure)

Aldehyde (24.40 mMol), Cyrene (2.50 mL, 24.40 mMol), ethanol (2 mL) and K_3PO_4 (0.25 g, 1.22 mMol) were added to a 25 mL round bottom flask which was charged with a magnetic stirrer bar and fitted with a reflux condenser. The reaction mixture was then heated to 120°C and stirred (550 rpm) for 18 hrs.

For all the following products except LMHTranscinnamaldehyde, LMH4NO and LMH4-FI, the general procedure above was followed and the individual work ups are stated as follows. Experimental data has been provided and where possible crystal structures have been obtained.

Table S1. Claisen-Schmidt reaction between Cyrene and substrate



Entry	Substrate (R)	Product Extracted	Yield (%)	GC-FID Conversion (%)
1	Benzaldehyde	Yes	1.8	12.3
2	4-Cl Benzaldehyde	Yes	30.7	85.7
3	Salicylaldehyde	Yes	83.1	95.0
4	Furfural	Yes	63.2	94.9
5	2-Thiophene Carboxaldehyde	Yes	77.3	97.7
6	Trans-Cinnamaldehyde	No	NA	19.2
7	4-Methylbenzaldehyde	Yes	40.9	93.4
8	4-Nitrobenzaldehyde	Yes	94.7	100.0
9	3-Nitrobenzaldehyde	Yes	43.8	83.7
10	2-Nitrobenzaldehyde	Yes	58.2	62.4
11	4-Fluorobenzaldehyde	Yes	31.5	NA
12	3-Hydroxybenzaldehyde	Yes	8.3	77.9
13	2-Hydroxy - 5-nitrobenzaldehyde	Yes	1.2	60.6
14	4-Pyridine Carboxaldehyde	Yes	13.8	89.7
15	3-Pyridine Carboxaldehyde	Yes	2.7	93.6
16	2-Pyridine Carboxaldehyde	Yes	13.0	91.0
17	2,4-Dichlorobenzaldehyde	No	NA	96.7
18	2,4-Dimethoxybenzaldehyde	No	NA	91.2
19	Benzaldehyde*	Yes	67.3	99.3
20	Trans-Cinnamaldehyde*	Yes	47.2	99.0

* Heated to 120 °C in a closed pressure vessel with stirring (550 rpm) for 18 hours.

Synthesis of Entry 1 (and 19) – Table S1 (aldehyde: Benzaldehyde)

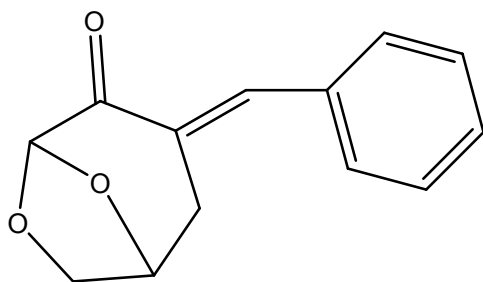


Figure S3: Structure 1 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to yield a sticky orange oil. Hot ethanol (c.a. 10 mL) was added and the resulting mixture added to a glass vial and left to cool to room temperature. From this, square orange plates crystallised which were isolated by vacuum filtration and washed with cold water and ethanol (0.0976 g, 1.8 %). These crystals proved suitable for XRD – see below.

ν_{\max} / cm^{-1} : 2975, 2906, 1676, 1579; ^1H NMR (399.78 MHz, CDCl_3) δ 7.73 (s, 1H), 7.45 (m, 5H), 5.37 (s, 1H), 4.89 (t, $J = 8.00$ Hz, 1H), 3.95 (t, $J = 4.00$ Hz, 1H), 3.83 (t, $J = 8.00$, 1H), 3.37 (d, $J = 16$ Hz, 1H), 2.91 (d, $J = 16$ Hz 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 189.66, 139.89, 134.57, 130.35, 129, 128.63, 128.03, 100.93, 72.44, 68.33, 34.56; GC-MS, gmol^{-1} : Calculated for $\text{C}_{13}\text{H}_{12}\text{O}_3$ – 216.23, observed – 216.0790.

Synthesis of Entry 2 – Table S1 (aldehyde: 4-Cl-benzaldehyde)

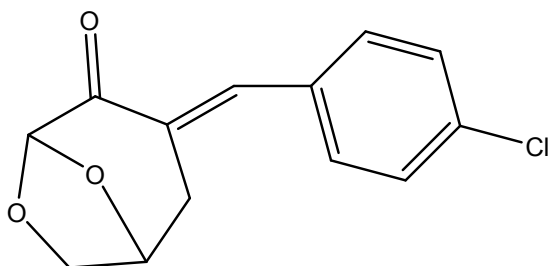


Figure S4: Structure 2 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give a sticky yellow oil. Hot ethanol (c.a. 10 mL) was added and the resulting mixture added to a glass vial and left to cool to room temperature. From this, fluffy white needles crystallised which were isolated by vacuum filtration and washed with cold water and ethanol (1.88 g, 30.8 %). A small amount was then recrystallised in hot ethanol to give needles suitable for XRD – see below.

ν_{\max} / cm^{-1} : 2988, 2904, 1698, 1582, 1099; ^1H NMR (399.78 MHz, CDCl_3) δ 7.66 (s, 1H), 7.39 (m, 4H), 5.37 (s, 1H), 4.89 (t, $J = 4.00$ Hz, 1H), 3.96 (d, $J = 8.00$, 1H), 3.82 (d, $J = 8.00$, 1H), 3.33 (d, $J = 16.00$, 1H), 2.86, $J = 16.00$, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 189.34, 138.40, 134.68, 132.98, 131.51, 128.92, 128.57, 100.86, 72.32, 68.36, 34.49; GC-MS, g mol^{-1} : Calculated for $\text{C}_{13}\text{H}_{11}\text{O}_3\text{Cl}$ – 250.68, observed – 250.0377.

Synthesis of Entry 3 – Table S1 (aldehyde: Salicylaldehyde)

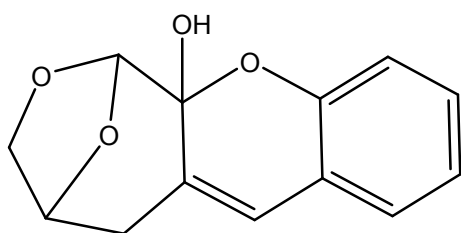


Figure S5: Structure 3 (Table S1)

After this time, the reaction was cooled to room temperature and the mixture turned to a dark solid. This was washed out of the flask with hot ethanol and a yellow powder was isolated by vacuum filtration and washed with further cold ethanol and water and dried in *vacuo* (4.71 g, 83.1 %). A small amount of this was crystallised in hot acetonitrile to give colourless plates suitable for XRD – see below.

ν_{\max} / cm^{-1} : 3418, 2975, 2891, 1663, 1607, 1577, 1041; ^1H NMR (399.78 MHz, CDCl_3) δ 7.17 (t, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.97 (t, $J = 8.0$ Hz, 2H), 6.48 (s, 1H), 5.38 (s, 1H), 4.70 (m, 1H), 3.82 (d, $J = 4.0$ Hz, 1H), 3.08 (d, $J = 16$ Hz, 1H), 2.35 (d, $J = 16$ Hz, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 191.77, 150.40, 128.78, 127.74, 125.97, 123.62, 121.68, 119.95, 116.74, 101.45, 73.50, 67.64, 34.53; GC-MS, g mol^{-1} : Calculated for $\text{C}_{13}\text{H}_{12}\text{O}_4$ - 232.23, observed – 232.0755.

Synthesis of Entry 4 – Table S1 (aldehyde: Furfural)

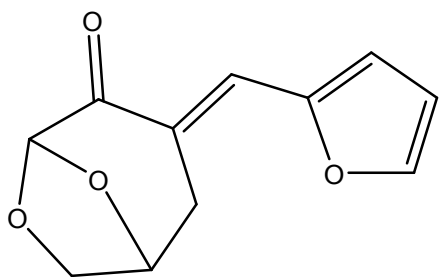


Figure S6: Structure 4 (Table S1)

After this time, the reaction was cooled to room temperature to give brown crystals. These were washed out of the flask with cold ethanol and isolated by vacuum filtration and washed with further cold ethanol and water and dried in *vacuo* (3.18 g, 63.2%). A small amount was then crystallised in hot ethanol to give colourless plates suitable for XRD – see below..

$\nu_{\max} / \text{cm}^{-1}$: 2968, 2905, 2833, 1689, 1593, 1111; $^1\text{H NMR}$ (399.78 MHz, CDCl_3) δ 7.57 (s, 1H), 7.50 (d, $J = 4.00$ Hz, 1H), 6.69 (d, $J = 4.00$ Hz, 1H), 6.52 (t, $J = 4.00$ Hz, 1H), 5.30 (s, 1H), 4.89 (t, $J = 8.00$ Hz, 1H), 3.94 (d, $J = 4.00$ Hz, 1H), 3.83 (d, $J = 4.00$ Hz, 1H), 3.29 (d, $J = 16.00$ Hz, 1H), 3.01 (d, $J = 16.00$ Hz, 1H); $^{13}\text{C NMR}$ (100.53 MHz, CDCl_3) δ 188.87, 151.47, 145.18, 125.56, 123.77, 117.21, 112.23, 100.32, 71.94, 68.39, 33.25; GC-MS, g mol^{-1} : Calculated for $\text{C}_{11}\text{H}_{10}\text{O}_4$ – 206.19, observed – 206.0574.

Synthesis of Entry 5 – Table S1 (aldehyde: 2 thiophene carboxaldehyde)

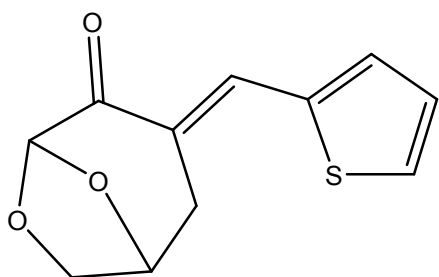


Figure S7: Structure 5 (Table S1)

After this time, the reaction was cooled to room temperature and the mixture turned to a black solid. To this was added hot acetonitrile from which yellow needles crystallised when left to cool. These were then isolated by vacuum filtration and washed with cold acetonitrile and water and dried in *vacuo* to give yellow needles which were suitable for XRD (4.19 g, 77.3 %) – see below..

$\nu_{\max} / \text{cm}^{-1}$: 3104, 2976, 2913, 1692, 1581, 1203; $^1\text{H NMR}$ (399.78 MHz, CDCl_3) δ 7.99 (s, 1H), 7.59 (d, $J = 4.00$ Hz, 1H), 7.38 (d, $J = 4.00$ Hz, 1H), 7.17 (t, $J = 4.00$ Hz, 1H), 5.35 (s, 1H), 4.96 (t, $J = 8.00$ Hz, 1H),

3.97 (t, J = 8.00 Hz, 1H), 3.84 (d, J = 8.00 Hz, 1H), 3.22 (d, J = 20.00 Hz, 1H), 2.82 (d, J = 20.00 Hz, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 188.71, 138.01, 133.62, 132.35, 130.84, 127.63, 123.77, 100.40, 71.79, 68.53, 33.45; GC-MS, g mol^{-1} : Calculated for $\text{C}_{11}\text{H}_{10}\text{O}_3\text{S}$ – 222.26, observed – 222.0363.

Synthesis of Entry 6 (and 20) – Table S1 (aldehyde: trans-cinnamaldehyde)

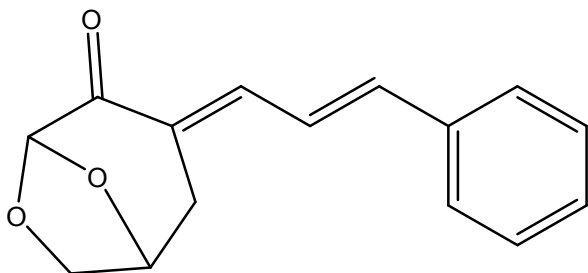


Figure S8: Structure 6 (and 20) (Table S1)

To a high pressure reactor was added trans-cinnamaldehyde (3.07 mL, 24.40 mMol), Cyrene (2.50 mL, 24.40 mMol), K_3PO_4 (0.25 g, 1.22 mMol) and ethanol (2 mL). A magnetic stirrer bar was added and the reactor was heated to 120 °C with stirring (550 rpm) for 18 hours. After this time, the reaction was cooled to room temperature. The yellow reaction mixture was filtered by vacuum filtration and washed with cold ethanol and water and dried in *vacuo* to give a yellow powder (2.79 g, 47.2%). A small amount was crystallised in hot ethanol to give yellow plates for XRD – see below.

$\nu_{\text{max}} / \text{cm}^{-1}$: 2955, 2901, 1684, 1575, 1111; ^1H NMR (399.78 MHz, CDCl_3) δ 7.50 (m, 3H), 7.36 (m, 3H), 6.94 (m, 2H), 5.32 (s, 1H), 4.91 (t, J = 8.00 Hz, 1H), 3.97 (t, J = 4.00 Hz, 1H), 3.84 (d, J = 8.00 Hz, 1H), 3.15 (d, J = 20.00 Hz, 1H), 2.80 (d, J = 20.00 Hz, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 189.34, 143.01, 139.69, 136.21, 129.63, 129.05, 127.56, 126.91, 122.29, 100.93, 72.60, 68.85, 32.09; GC-MS, g mol^{-1} : Calculated for $\text{C}_{15}\text{H}_{14}\text{O}_3$ – 242.27, observed – 242.0933.

Synthesis of Entry 7 – Table S1 (aldehyde: 4-methylbenzaldehyde)

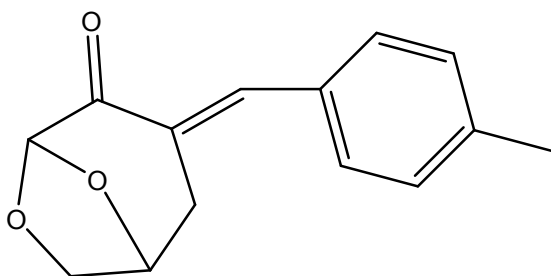


Figure S9: Structure 7 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give a red sticky oil. To this was added hot acetonitrile from which off white powder precipitated. This was then isolated by vacuum filtration and washed with cold water and acetonitrile and dried in *vacuo* to give a white powder (2.30 g, 40.9 %). A small amount was then crystallised in hot ethanol to give needles for XRD – see below..

ν_{\max} / cm^{-1} : 2985, 2920, 1698, 1599, 1110; ^1H NMR (399.78 MHz, CDCl_3) δ 7.69 (s, 1H), 7.36 (d, J = 8.00 Hz, 2H), 7.22 (d, J = 8.00 Hz, 2H), 5.34 (s, 1H), 4.88 (t, J = 8.00 Hz, 1H), 3.93 (t, J = 4.00 Hz, 1H), 3.79 (d, J = 4.00 Hz, 1H), 3.34 (d, J = 16.00 Hz, 1H), 2.88 (d, J = 16.00 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 190.06, 140.38, 140.27, 132.10, 130.82, 129.69, 127.26, 101.22, 72.71, 68.66, 34.83, 21.66; GC-MS, gmol^{-1} : Calculated for $\text{C}_{14}\text{H}_{14}\text{O}_3$ – 230.26, observed – 230.0936.

Synthesis of Entry 8 – Table S1 (aldehyde: 4-nitrobenzaldehyde)

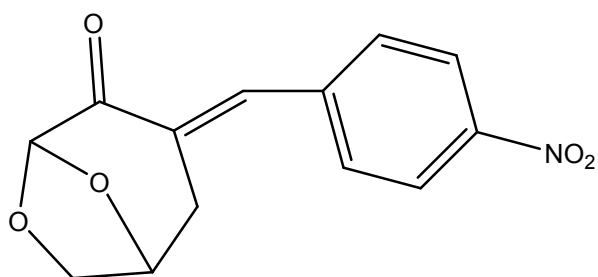


Figure S10: Structure 8 (Table S1)

4-Nitrobenzaldehyde (1.52 g, 10.00 mMol), Cyrene (1.03 mL, 10.00 mMol), K_3PO_4 (0.10 g, 0.50 mMol) and ethanol (1.00 mL) were added to a 25 mL round bottom flask charged with a magnetic stirrer bar and fitted with a reflux condenser and heated to 120 °C with stirring (550 rpm) for 20 mins. After this time, the reaction mixture had become a brown solid which was washed out of the flask with ethanol and isolated by vacuum filtration and washed with further ethanol and water and dried in *vacuo*. This gave a brown powder (2.49 g, 95.4 %). A small amount was then crystallised in hot toluene for XRD – see below.

ν_{\max} / cm^{-1} : 2972, 1699, 1604, 1590, 1512, 1344, 1107; ^1H NMR (399.78 MHz, CDCl_3) δ 8.26 (d, J = 8.00 Hz, 2H), 7.70 (s, 1H), 7.58 (d, J = 12.00 Hz, 2H), 5.38 (s, 1H), 4.91 (t, J = 4.00 Hz, 1H), 3.96 (d, J = 4.00 Hz, 1H), 3.82 (d, J = 4.00 Hz, 1H), 3.37 (d, J = 16.00 Hz, 1H), 2.89 (d, J = 16.00 Hz, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 188.66, 147.36, 140.57, 136.51, 131.72, 130.51, 123.60, 100.54, 72.07, 68.19, 34.34; GC-MS, gmol^{-1} : Calculated for $\text{C}_{13}\text{H}_{11}\text{O}_5\text{N}$ – 261.23, observed – 261.0652

Synthesis of Entry 9 – Table S1 (aldehyde: 3-nitrobenzaldehyde)

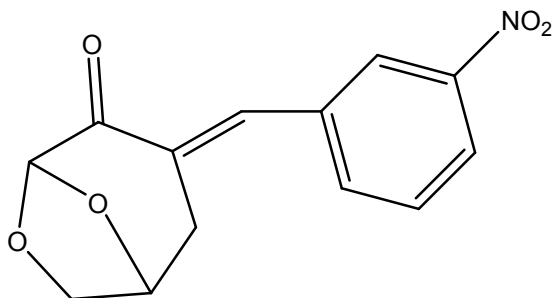


Figure S11: Structure 9 (Table S1)

After this time, the reaction was left to cool to room temperature and the sticky mixture became a black solid. This was solubilised in hot ethanol and filtered which isolated hard brown clumps of solid which were washed with ethanol and water and dried in *vacuo* (2.79 g, 43.8 %).

ν_{\max} / cm^{-1} : 2971, 2912, 1701, 1600, 1528, 1351, 1103; ^1H NMR (399.78 MHz, CDCl_3) δ 8.26 (s, 1H), 8.20 (d, $J = 8.00$ Hz, 1H), 7.73 (d, $J = 8.00$, 1H), 7.67 (s, 1H), 7.60 (t, $J = 4.00$ Hz, 1H), 5.34 (s, 1H), 4.91 (t, $J = 8.00$ Hz, 1H), 3.94 (m, 1H), 3.81 (d, $J = 8.00$ Hz, 1H), 2.89 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 189.28, 148.50, 136.97, 136.44, 131.30, 130.07, 124.41, 124.13, 100.98, 72.54, 68.70, 50.82, 34.61; GC-MS, g mol^{-1} : Calculated for $\text{C}_{13}\text{H}_{11}\text{O}_5\text{N}$ – 261.23, observed – 261.0634.

Synthesis of Entry 10 – Table S1 (aldehyde: 2-nitrobenzaldehyde)

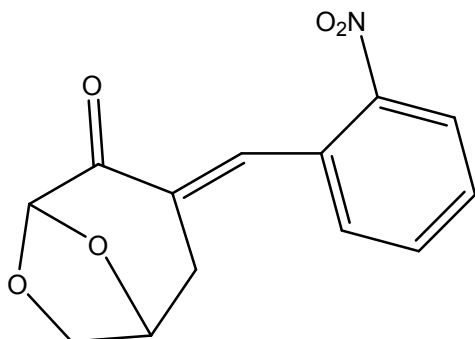


Figure S12: Structure 10 (Table S1)

After this time, the reaction was left to cool to room temperature and the sticky mixture became a black solid. This was solubilised in hot ethanol and filtered which isolated sticky brown clumps of solid which were washed with ethanol and water and dried in *vacuo* (3.71 g, 58.24 %).

ν_{\max} / cm^{-1} : 2943, 2831, 1698, 1615, 1520, 1023 ; ^1H NMR (399.78 MHz, CDCl_3) δ 8.16 (d, $J = 8.00$ Hz, 1H), 7.90 (s, 1H), 7.68 (t, $J = 8.00$ Hz, 1H), 7.56 (t, $J = 8.00$ Hz, 1H), 7.36 (d, $J = 8.00$ Hz, 1H), 5.36 (s, 1H), 4.79 (t, $J = 8.00$ Hz, 1H), 3.93 (m, 1H), 3.83 (d, $J = 8.00$ Hz, 1H), 3.07 (d, $J = 16.00$ Hz, 1H), 2.55 (d, $J = 16.00$ Hz, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 188.83, 148.01, 136.49, 133.47, 131.40, 130.32, 129.66, 125.17, 100.88, 72.61, 68.26, 33.75; GC-MS, g mol^{-1} : Calculated for $\text{C}_{13}\text{H}_{11}\text{O}_5\text{N}$ – 261.23, observed – 261.0648.

Synthesis of Entry 11 – Table S1 (aldehyde: 4-fluorobenzaldehyde)

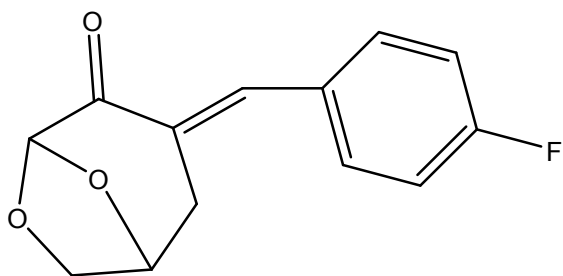


Figure S13: Structure 11 (Table S1)

4-fluoro benzaldehyde (1.58 g, 12.73 mMol), Cyrene (1.30 mL, 12.73 mMol), ethanol (1.00 mL) and K_3PO_4 (0.13 g, 0.64 mMol) were added to a 25 mL round bottom flask which was charged with a magnetic stirrer bar and fitted with a reflux condenser. The reaction mixture was then heated to 120°C and stirred (550 rpm) for 18 hrs. After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give a sticky orange oil. This was then dissolved in hot methanol and placed in the freezer overnight. From this crystallised white fluffy needles which were isolated by vacuum filtration and washed with ice cold methanol and dried in *vacuo* (0.94 g, 31.54 %). Attempts to grow crystals suitable for XRD were unsuccessful.

ν_{\max} / cm^{-1} : 2827, 1672, 1602, 1157; ^1H NMR (399.78 MHz, CDCl_3) δ 8.39 (m, 2H), 7.41 (m, 2H), 5.37 (s, 1H), 4.97 (t, $J = 4.00$ Hz, 1H), 4.31 (d, $J = 8.00$ Hz, 1H), 4.22 (m, 1H), 2.89 (m, 1H), 2.29 (m, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 190.89, 170.48, 133.08, 132.45, 125.88, 116.71, 116.01, 101.70, 73.36, 67.77, 31.32; GC-MS (EI), g mol^{-1} : Calculated for $\text{C}_{13}\text{H}_{11}\text{O}_3\text{F}$ – 234.22, observed – 234.0674.

Synthesis of Entry 12 – Table S1 (aldehyde: 3-hydroxybenzaldehyde)

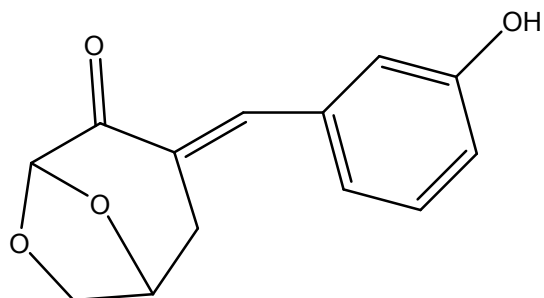


Figure S14: Structure 12 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give a dark brown sticky oil. This was solubilised in hot methanol and left overnight in the freezer. The solution was then filtered and a brown powder was isolated which was washed in ethyl acetate and dried in *vacuo* (0.47 g, 8.30 %).

ν_{\max} / cm^{-1} : 3245, 2975, 2906, 1676, 1579, 1114; ^1H NMR (399.78 MHz, CDCl_3) δ 7.66 (s, 1H), 7.28 (t, J = 8.00 Hz, 1H), 7.01 (d, J = 8.00 Hz, 1H), 6.93 (s, 1H), 6.89 (d, J = 8.00 Hz, 1H), 6.15 (s, 1H), 5.37 (s, 1H), 4.87 (t, J = 8.00 Hz, 1H), 3.95 (m, 1H), 3.82 (d, J = 8.00 Hz, 1H), 3.33 (d, J = 16.00 Hz, 1H), 2.90 (d, J = 16.00 Hz, 1H); ^{13}C NMR (100.53 MHz, CDCl_3) δ 190.24, 156.02, 140.16, 135.98, 129.95, 128.27, 122.88, 117.16, 100.92, 72.55, 68.46, 34.59; GC-MS, g mol^{-1} : Calculated for $\text{C}_{13}\text{H}_{12}\text{O}_4$ – 232.23, observed – 232.0747.

Synthesis of Entry 13 – Table S1 (aldehyde: 2-Hydroxy, 5-Nitro benzaldehyde. Note: Reaction carried out at scale of 0.5.)

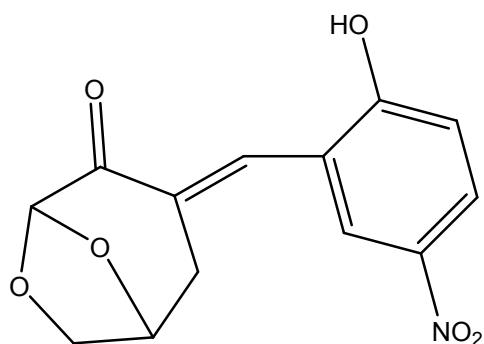


Figure S15: Structure 13 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give an orange sticky oil. This was solubilised in ethyl acetate and left over night. The solution was then filtered and a yellow solid was isolated which was washed in ethyl acetate and dried in *vacuo* (0.0388 g, 1.15 %).

ν_{\max} / cm^{-1} : 3387, 2972, 1626, 1576, 1512, 1074; ^1H NMR (399.78 MHz, CDCl_3) δ 8.11 (d, J = 8.00 Hz, 1H), 8.04 (s, 1H), 7.09 (d, J = 8.00 Hz, 1H), 6.58 (s, 1H), 5.42 (s, 1H), 4.79 (m, 1H), 3.90 (m, 1H), 3.87 (m, 1H), 3.17 (d, J = 12.00 Hz, 1H), 2.46 (d, J = 12.00 Hz, 1H). ; GC-MS (EI), g mol^{-1} : Calculated for $\text{C}_{13}\text{H}_{11}\text{O}_6\text{N}$ – 277.23, observed – 280.9693.

Synthesis of Entry 14 – Table S1 (aldehyde: 4-Pyridine carboxaldehyde)

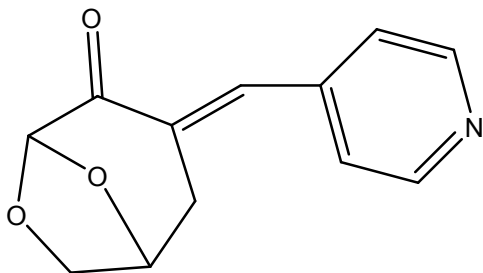


Figure S16: Structure 14 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give an orange sticky oil. This was solubilised in hot methanol and filtered to isolate a white powder which was washed with methanol and dried in *vacuo* (0.7312 g, 13.80 %).

ν_{\max} / cm^{-1} : 2969, 1672, 1604, 1089; ^1H NMR (399.78 MHz, CDCl_3) δ 8.57 (d, J = 4.00 Hz, 2H), 7.13 (d, J = 4.00 Hz, 2H), 5.39 (s, 1H), 5.26 (s, 1H), 4.57 (d, J = 28.00 Hz, 2H), 3.93 (t, J = 8.00 Hz, 2H), 3.78 (s, 2H), 3.65 (d, J = 8.00 Hz, 1H), 3.20 (d, J = 12.00 Hz, 1H), 2.35 (d, J = 16.00 Hz, 1H), 2.21 (m, 1H), 1.43 (d, J = 16.00 Hz, 1H), 1.24 (m, 2H); GC-MS (EI) of reaction mixture, g mol^{-1} : Calculated for $\text{C}_{12}\text{H}_{11}\text{O}_3\text{N}$ – 217.22, observed – 217.1891.

Synthesis of Entry 15 – Table S1 (aldehyde: 3-Pyridine carboxaldehyde)

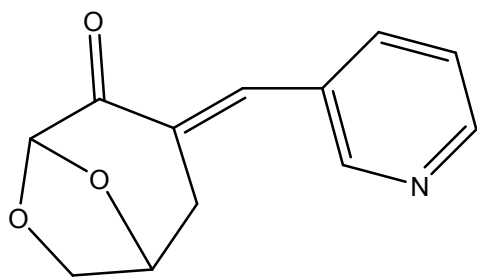


Figure S17: Structure 15 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give a red sticky oil. This was solubilised in hot methanol and placed in the freezer overnight. This was then filtered to isolate an orange powder which was washed with cold methanol and dried in *vacuo* (0.1438 g, 2.71 %).

ν_{\max} / cm^{-1} : 2905, 1705, 1661, 1643, 1273; ^1H NMR not possible; GC-MS (EI) of reaction mixture, gmol^{-1} : Calculated for $\text{C}_{12}\text{H}_{11}\text{O}_3\text{N}$ – 217.22, observed – 217.2176.

Synthesis of Entry 16 – Table S1 (aldehyde: 2-Pyridine carboxaldehyde)

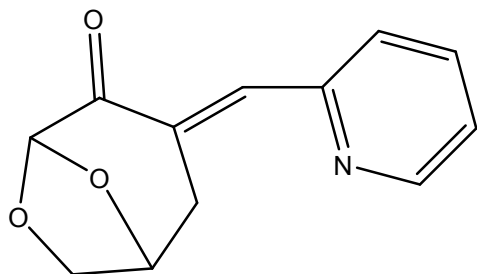


Figure S18: Structure 16 (Table S1)

After this time, the reaction was cooled to room temperature and the ethanol removed in *vacuo* to give a dark orange sticky oil. This was solubilised in hot methanol and placed in the freezer overnight. This was then filtered to isolate a brown powder which was washed with cold methanol and dried in *vacuo* (0.6913 g, 13.04 %).

ν_{\max} / cm^{-1} : 3046, 1608, 1584, 1563, 1386; ^1H NMR not possible; GC-MS (EI) of reaction mixture, gmol^{-1} : Calculated for $\text{C}_{12}\text{H}_{11}\text{O}_3\text{N}$ – 217.22, observed – 217.2529.

The following reactions were also attempted, however following cooling and ethanol removal, no product could be extracted from the resulting sticky oil residue.

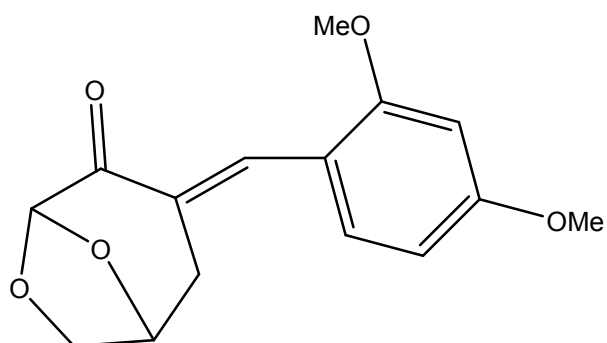


Figure S19: Structure 17 (Table S1)

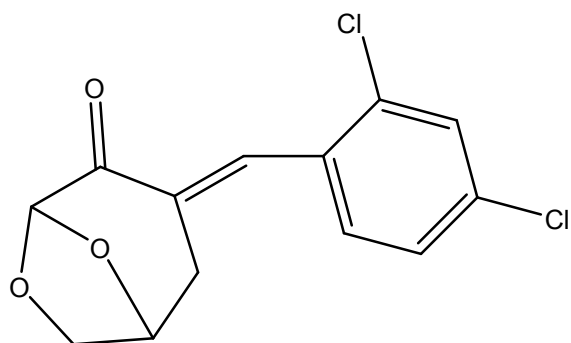


Figure S20: Structure 18 (Table S1)

X-Ray Crystal data

Table S2: Crystal data and structure refinement for structure 1.

Identification code	CCDC 1837709
Empirical formula	C ₁₃ H ₁₂ O ₃
Formula weight	216.23
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	11.11016(10)
b/Å	9.04172(9)
c/Å	15.58673(13)
α/°	90
β/°	95.3028(8)
γ/°	90
Volume/Å ³	1559.06(2)
Z	6
Z'	3
ρ _{calc} /g/cm ³	1.382
μ/mm ⁻¹	0.804
F(000)	684.0
Crystal size/mm ³	0.207 × 0.172 × 0.038
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.992 to 142.298
Index ranges	-13 ≤ h ≤ 13, -10 ≤ k ≤ 10, -18 ≤ l ≤ 19
Reflections collected	28119

Independent reflections 5845 [$R_{\text{int}} = 0.0258$, $R_{\text{sigma}} = 0.0201$]
Data/restraints/parameters 5845/1/434
Goodness-of-fit on F^2 1.060
Final R indexes [$I \geq 2\sigma(I)$] $R_1 = 0.0277$, $wR_2 = 0.0673$
Final R indexes [all data] $R_1 = 0.0300$, $wR_2 = 0.0692$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$ 0.21/-0.15
Flack parameter -0.05(5)

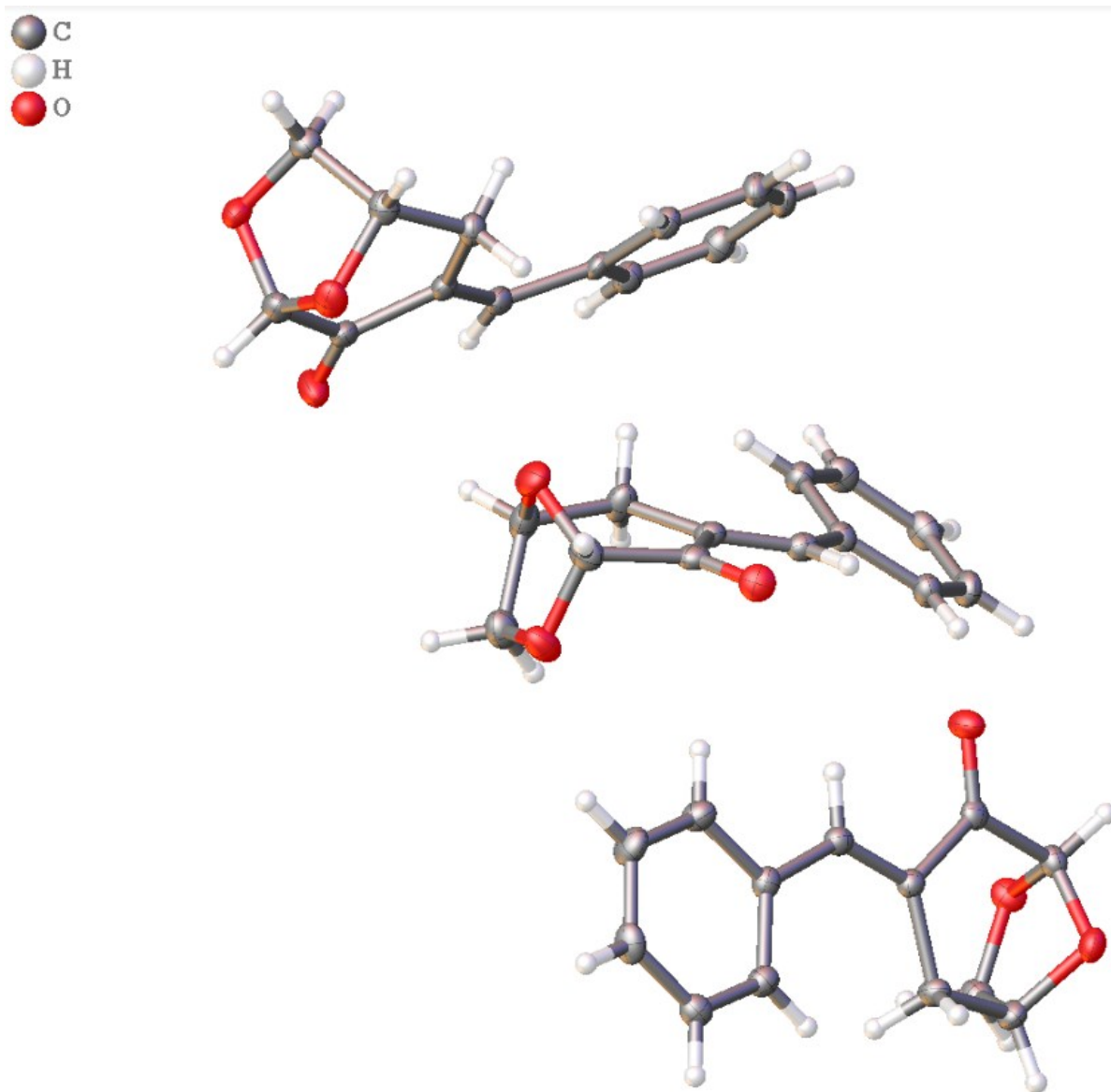


Figure S21: X-ray crystal structure for Structure 1.

Table S3: Crystal data and structure refinement for Structure 2.

Identification code	CCDC 1837711
Empirical formula	$C_{13}H_{11}O_3Cl$
Formula weight	250.67
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.94601(13)
b/Å	5.17983(13)
c/Å	18.2456(5)
$\alpha/^\circ$	90
$\beta/^\circ$	94.739(2)
$\gamma/^\circ$	90
Volume/Å ³	560.03(2)
Z	2
Z'	1
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.487
μ/mm^{-1}	2.974
F(000)	260.0
Crystal size/mm ³	0.152 × 0.069 × 0.019
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$	9.728 to 134.15
Index ranges	$-4 \leq h \leq 7, -6 \leq k \leq 6, -21 \leq l \leq 21$
Reflections collected	3274

Independent reflections	1995 [$R_{\text{int}} = 0.0269$, $R_{\text{sigma}} = 0.0411$]
Data/restraints/parameters	1995/1/154
Goodness-of-fit on F^2	1.038
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0358$, $wR_2 = 0.0920$
Final R indexes [all data]	$R_1 = 0.0371$, $wR_2 = 0.0934$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.25/-0.22
Flack parameter	-0.03(2)

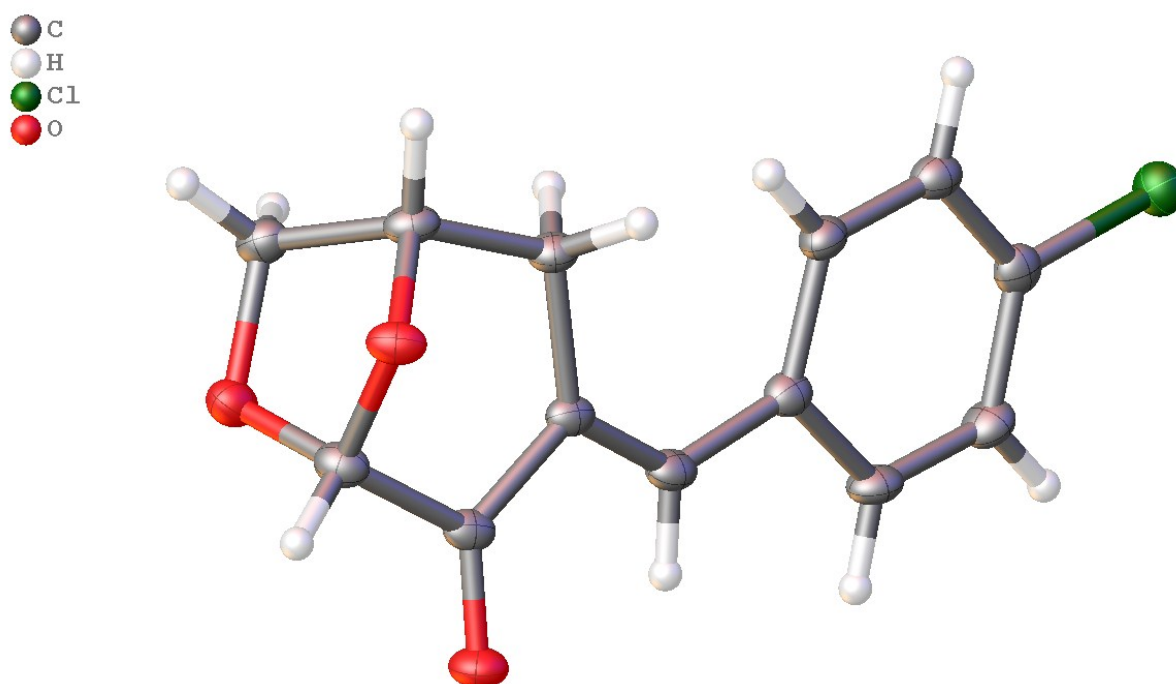


Figure S22: X-ray crystal structure for Structure 2.

Table S4: Crystal data and structure refinement for Structure 3.

Identification code	CCDC 1837713
Empirical formula	$C_{13}H_{12}O_4$
Formula weight	232.23
Temperature/K	110.10(14)

Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.50457(13)
b/Å	9.59528(11)
c/Å	11.47760(13)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å ³	1046.75(2)
Z	4
Z'	1
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.474
μ/mm^{-1}	0.914
F(000)	488.0
Crystal size/mm ³	0.226 × 0.133 × 0.102
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$	12.022 to 134.152
Index ranges	$-11 \leq h \leq 9, -11 \leq k \leq 11, -13 \leq l \leq 13$
Reflections collected	9461
Independent reflections	1872 [$R_{\text{int}} = 0.0200, R_{\text{sigma}} = 0.0145$]
Data/restraints/parameters	1872/0/202
Goodness-of-fit on F ²	1.084
Final R indexes [$ I \geq 2\sigma(I)$]	$R_1 = 0.0244, wR_2 = 0.0604$
Final R indexes [all data]	$R_1 = 0.0257, wR_2 = 0.0615$
Largest diff. peak/hole / e Å ⁻³	0.15/-0.18

Flack parameter 0.10(6)

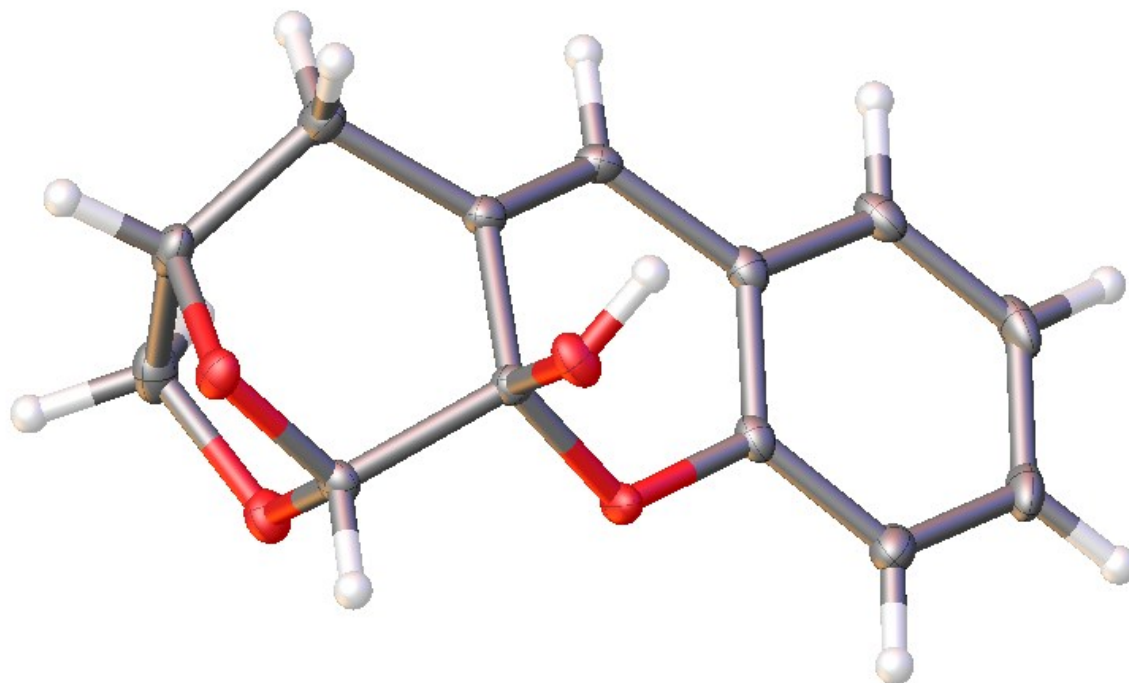


Figure S23: X-ray crystal structure for Structure 3.

Table S5: Crystal data and structure refinement for Structure 4.

Identification code	CCDC 1837708
Empirical formula	$C_{11}H_{10}O_4$
Formula weight	206.19
Temperature/K	109.95(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.22158(15)
b/Å	9.60997(16)
c/Å	13.4791(3)

$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/ \AA^3	935.44(3)
Z	4
Z'	1
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.464
μ/mm^{-1}	0.946
F(000)	432.0
Crystal size/ mm^3	$0.261 \times 0.221 \times 0.083$
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$ 11.308 to 134.044	
Index ranges	$-8 \leq h \leq 8, -11 \leq k \leq 7, -11 \leq l \leq 16$
Reflections collected	2614
Independent reflections	1484 [$R_{\text{int}} = 0.0109, R_{\text{sigma}} = 0.0176$]
Data/restraints/parameters	1484/0/176
Goodness-of-fit on F^2	1.075
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0247, wR_2 = 0.0639$
Final R indexes [all data]	$R_1 = 0.0256, wR_2 = 0.0646$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.20/-0.22
Flack parameter	0.09(8)

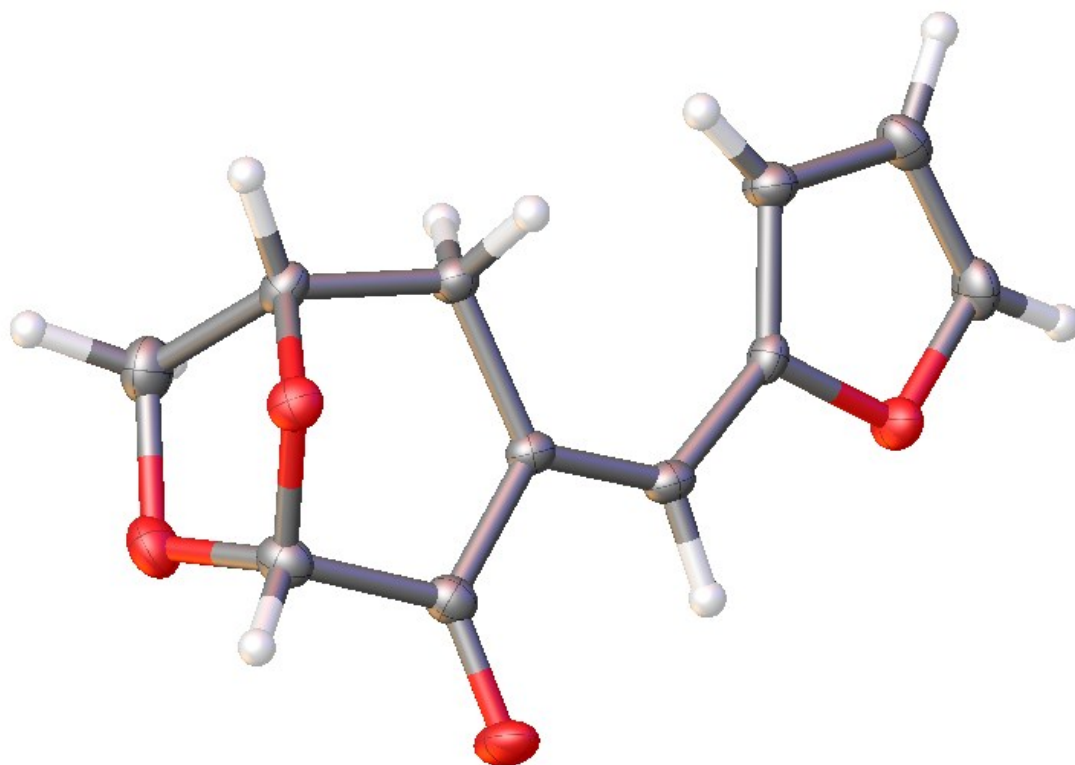


Figure S24: X-ray crystal structure for Structure 4.

Table S6: Crystal data and structure refinement for Structure 5.

Identification code	CCDC 1837712
Empirical formula	$C_{11}H_{10}O_3S$
Formula weight	222.25
Temperature/K	110.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.32713(7)
b/Å	10.32552(10)
c/Å	15.23806(18)
$\alpha/^\circ$	90
$\beta/^\circ$	90

$\gamma/^\circ$	90
Volume/ \AA^3	995.516(18)
Z	4
Z'	1
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.483
μ/mm^{-1}	2.763
F(000)	464.0
Crystal size/ mm^3	$0.293 \times 0.245 \times 0.189$
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$	10.348 to 133.742
Index ranges	$-7 \leq h \leq 7, -12 \leq k \leq 12, -18 \leq l \leq 18$
Reflections collected	8921
Independent reflections	1777 [$R_{\text{int}} = 0.0170, R_{\text{sigma}} = 0.0111$]
Data/restraints/parameters	1777/0/137
Goodness-of-fit on F^2	1.046
Final R indexes [$ I \geq 2\sigma(I)$]	$R_1 = 0.0209, wR_2 = 0.0563$
Final R indexes [all data]	$R_1 = 0.0210, wR_2 = 0.0563$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.20/-0.18
Flack parameter	-0.014(5)

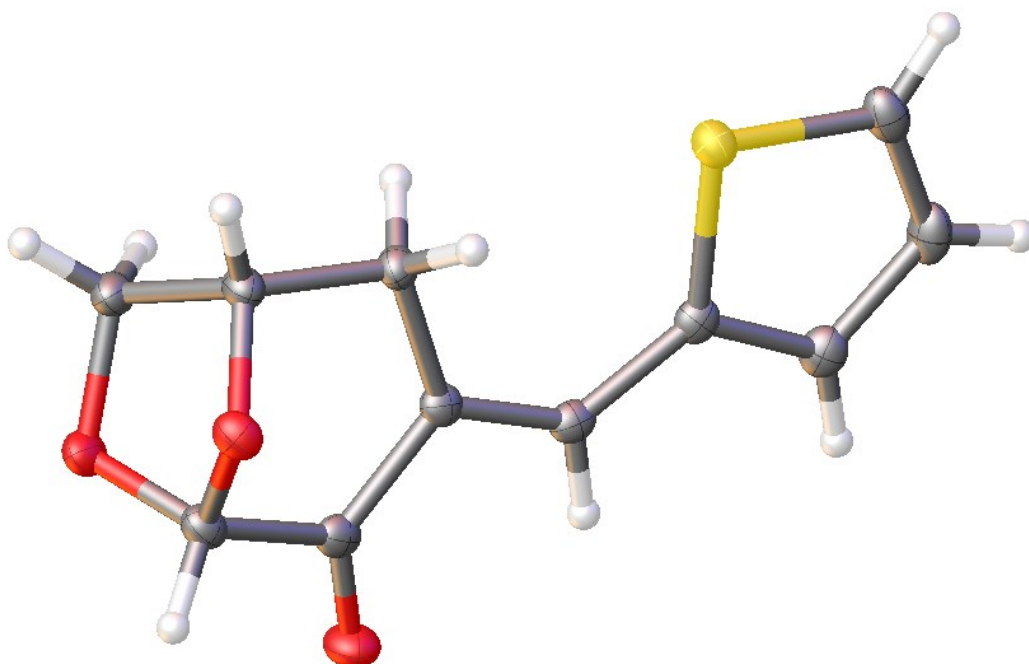
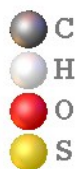


Figure S25: X-Ray crystal structure of Structure 5.

Table S7: Crystal data and structure refinement for Structure 6.

Identification code	CCDC 1837710
Empirical formula	C ₁₅ H ₁₄ O ₃
Formula weight	242.26
Temperature/K	110.05(10)
Crystal system	hexagonal
Space group	P6 ₅
a/Å	13.5583(2)
b/Å	13.5583(2)
c/Å	45.7998(6)
α/°	90

$\beta/^\circ$	90
$\gamma/^\circ$	120
Volume/ \AA^3	7291.3(2)
Z	24
Z'	4
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.324
μ/mm^{-1}	0.747
F(000)	3072.0
Crystal size/ mm^3	$0.287 \times 0.142 \times 0.088$
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$ 7.53 to 134.112	
Index ranges	$-16 \leq h \leq 16, -16 \leq k \leq 14, -54 \leq l \leq 54$
Reflections collected	86742
Independent reflections	8674 [$R_{\text{int}} = 0.1146, R_{\text{sigma}} = 0.0425$]
Data/restraints/parameters	8674/1/602
Goodness-of-fit on F^2	1.072
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0909, wR_2 = 0.2298$
Final R indexes [all data]	$R_1 = 0.0914, wR_2 = 0.2302$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.59/-0.47
Flack parameter	0.06(10)

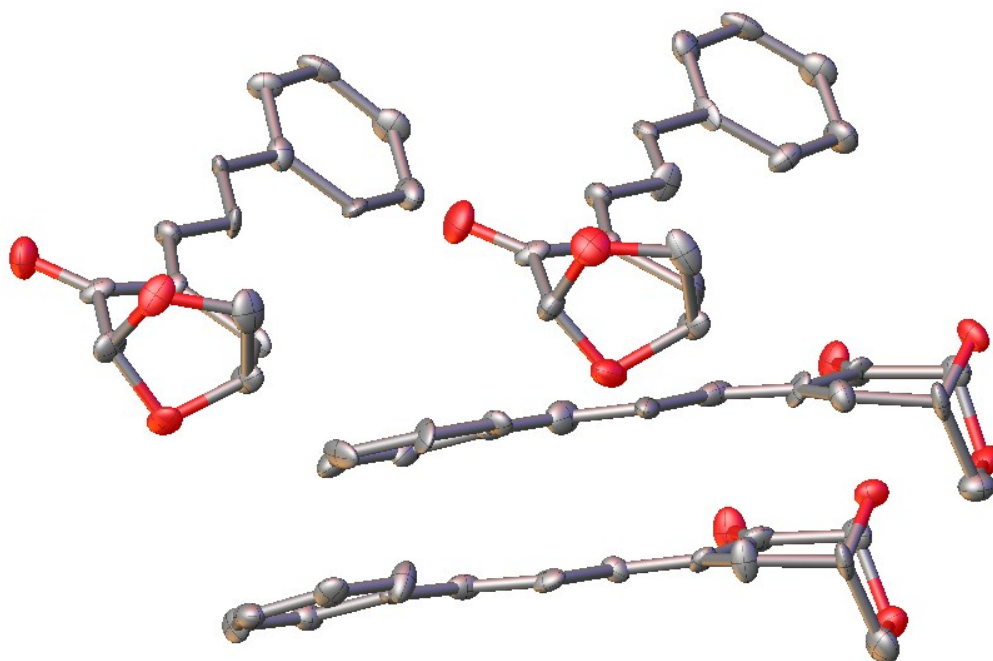


Figure S26: X-ray crystal structure for Structure 6.

Table S8: Crystal data and structure refinement for structure 7.

Identification code	CCDC 1837792
Empirical formula	C ₁₄ H ₁₄ O ₃
Formula weight	230.25
Temperature/K	109.9(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	6.47958(16)
b/Å	7.89044(19)
c/Å	22.4589(6)

$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/ \AA^3	1148.25(5)
Z	4
Z'	1
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.332
μ/mm^{-1}	0.759
F(000)	488.0
Crystal size/ mm^3	$0.524 \times 0.135 \times 0.086$
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$ 7.874 to 142.216	
Index ranges	$-7 \leq h \leq 6, -8 \leq k \leq 9, -26 \leq l \leq 27$
Reflections collected	5107
Independent reflections	2057 [$R_{\text{int}} = 0.0270, R_{\text{sigma}} = 0.0316$]
Data/restraints/parameters	2057/0/155
Goodness-of-fit on F^2	1.067
Final R indexes [$ I \geq 2\sigma(I)$]	$R_1 = 0.0334, wR_2 = 0.0839$
Final R indexes [all data]	$R_1 = 0.0360, wR_2 = 0.0864$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.16/-0.19
Flack parameter	0.06(13)

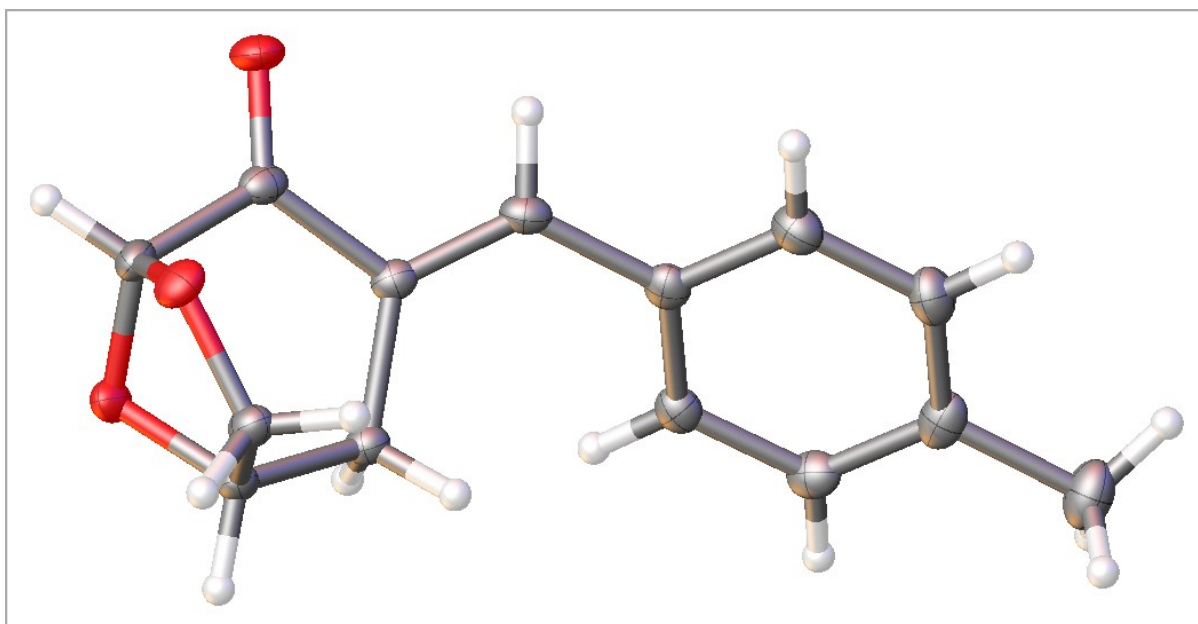


Figure S27: X-ray crystal structure for Structure 7

Table 1 Crystal data and structure refinement for structure 8.

Identification code	CCDC 1837793
Empirical formula	C ₁₃ H ₁₁ NO ₅
Formula weight	261.23
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	8.36693(18)
b/Å	7.08624(14)
c/Å	19.5336(4)
α/°	90
β/°	93.2815(18)
γ/°	90
Volume/Å ³	1156.25(4)

Z	4
Z'	2
$\rho_{\text{calc}}/\text{cm}^3$	1.501
μ/mm^{-1}	0.992
F(000)	544.0
Crystal size/ mm^3	$0.163 \times 0.086 \times 0.025$
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$	9.07 to 134.138
Index ranges	$-9 \leq h \leq 7, -8 \leq k \leq 8, -20 \leq l \leq 23$
Reflections collected	12361
Independent reflections	4125 [$R_{\text{int}} = 0.0258, R_{\text{sigma}} = 0.0289$]
Data/restraints/parameters	4125/1/343
Goodness-of-fit on F^2	1.051
Final R indexes [$ I \geq 2\sigma(I)$]	$R_1 = 0.0334, wR_2 = 0.0811$
Final R indexes [all data]	$R_1 = 0.0381, wR_2 = 0.0846$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.18/-0.18
Flack parameter	0.08(9)

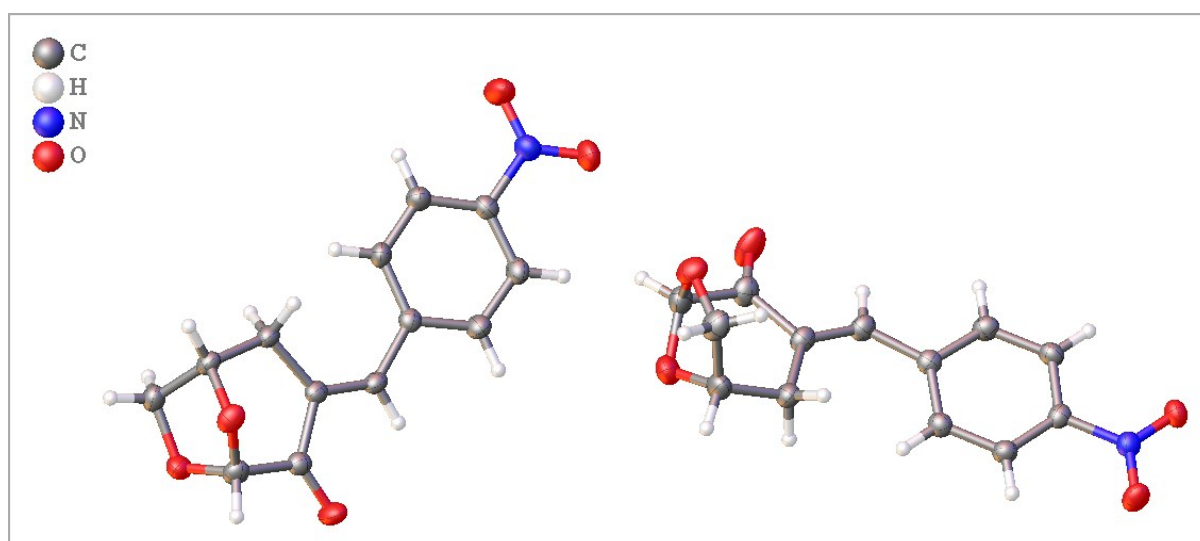


Figure S28: X-ray crystal structure for Structure **8LLAMA** Analysis

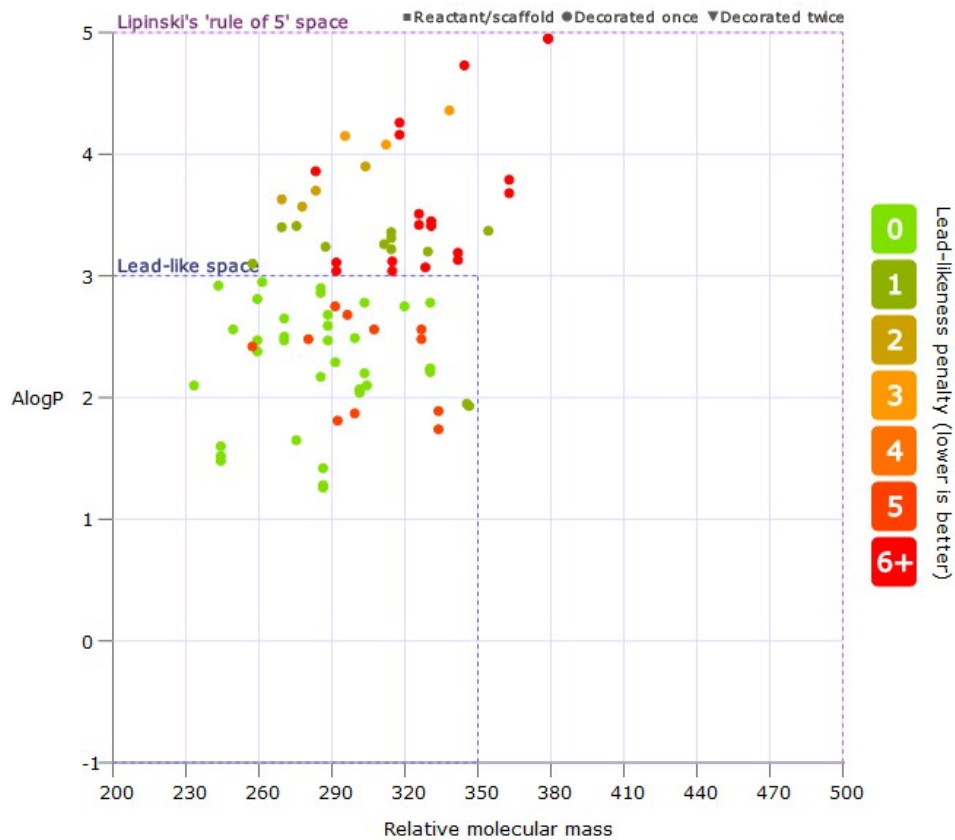


Figure S29: Lead-like plot for 1 decoration

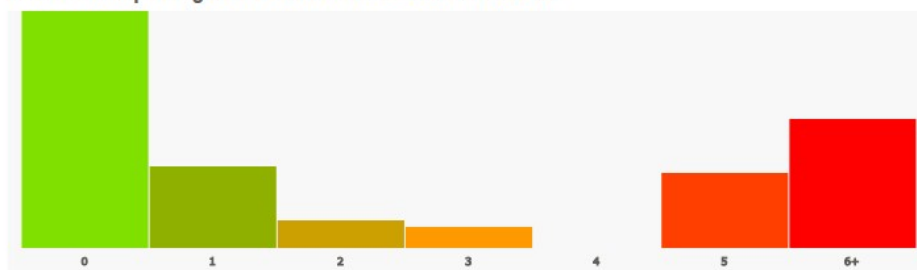


Figure S30: Lead-like distribution for 1 decoration

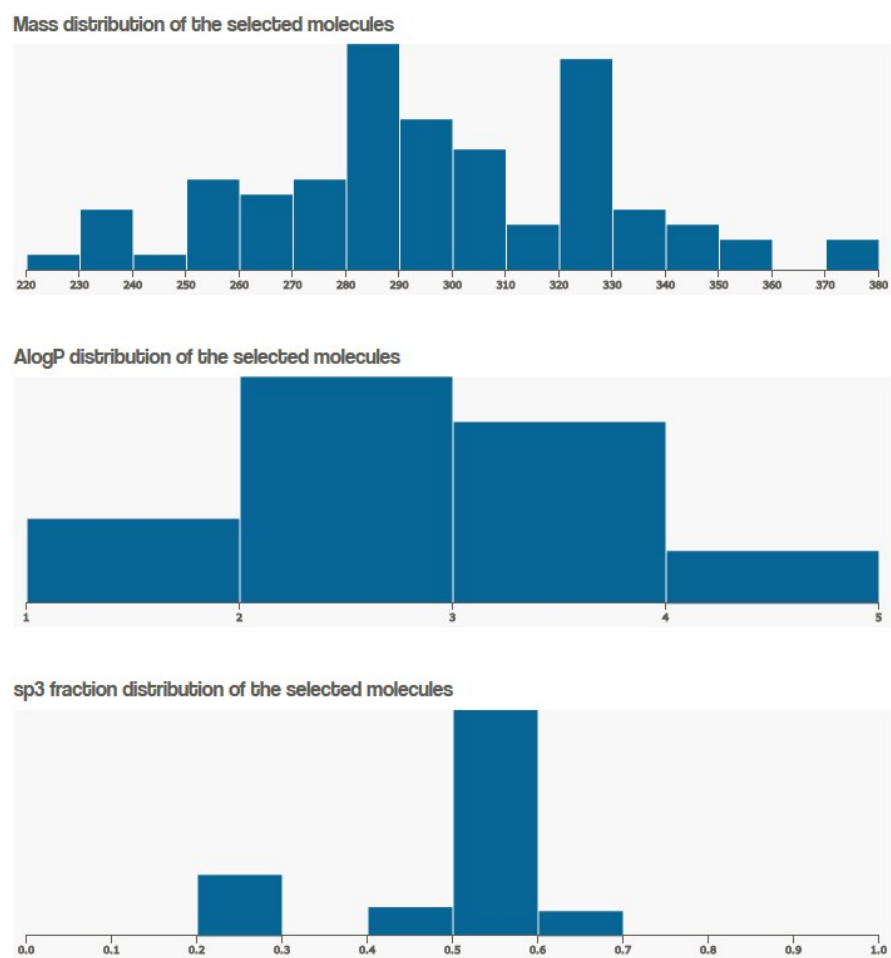


Figure S31: MW, AlogP and sp3 distributions for 1 decoration