

Supporting information

Exploration of [2+2+2] cyclotrimerisation methodology to prepare tetrahydroisoquinoline- based compounds with potential aldo-keto reductase 1C3 target affinity

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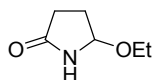
Experimental Protocols

General materials and methods for synthesis

Commercially available reagents were used as received without additional purification. All solvents used in reactions were purchased from Sigma-Aldrich. Petroleum ether refers to the fraction of petroleum spirit boiling in the range of 60 to 80 °C. Where stated, mixtures of solvents are referred to as percentage volume to volume (v/v) ratios. Products were purified by flash column chromatography using Merck 9385 silica gel 60 (40-63 μm). Analytical thin layer chromatography (TLC) was conducted on Merck silica gel 60 F254 aluminium backed plates. Visualisation of the reaction components was accomplished by illumination under short wavelength (254 nm) ultraviolet light or using basic potassium permanganate, phosphomolybdic acid (PMA) or vanillin stain. All melting point (mp) values were determined on a Gallenkamp melting point apparatus and are stated uncorrected. Proton Nuclear Magnetic Resonance (^1H NMR) spectra were recorded using Bruker AMX400 (400 MHz). Carbon Nuclear Magnetic Resonance (^{13}C NMR) spectra were performed in the same instrument operating at 100 MHz. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane. Multiplets are reported as follow: br broad, s singlet, doublet, t triplet, q quartet, qn quintet, dd double doublet, m multiplet. IR spectra were recorded in a PerkinElmer Spectrum 100 FT-IR Spectrometer. Routine mass spectra were run on a Micromass Quattro Ultima spectrometer. The ionisation method (ESI or API), and mode [positive (+) or negative (-)] used are indicated for each compound. High resolution mass spectrometry was performed at the National Mass Spectrometry Centre Swansea using MAT95 or MAT900 in the electrospray ionisation (ESI) mode.

Synthetic procedures

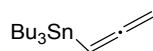
5-Ethoxypyrrolidin-2-one (5)



NaBH_4 (2.9 g, 75.7 mmol) was added over 2 h to a stirred solution of succinimide **4** (5.0 g, 50.5 mmol) in ethanol (225 mL) at 0 °C. 100 μL of HCl solution (2 M in ethanol) was added every 15 min for 5 h before the pH was adjusted to 4 and the resulting slurry was stirred for another 2 h. The reaction mixture was neutralised with KOH (3% in ethanol) and concentrated under vacuum, affording a white solid which was triturated with diethyl ether. The resulting suspension was filtered and the filtrate concentrated under vacuum and purified by flash column chromatography on deactivated (10% w/w H_2O) alumina (Et_2O), affording ethoxy lactam **5** (2.5 g, 41 %) as a white solid.

R_f 0.46 (MeOH/DCM 1:9 v/v); mp = 56 - 60 °C [lit.¹ 56 - 58 °C]; δ_{H} (400 MHz, CDCl_3): 1.22 (t, 3H, J 7.0 Hz, CH_3), 1.96-2.14 (m, 1H, H4), 2.15-2.39 (m, 2H, H3/H4'), 2.49-2.58 (m, 1H, H3), 3.38-3.47 (m, 1H, OCHH'), 3.54-3.61 (m, 1H, OCHH'), 4.98 (d, 1H, J 6.0 Hz, H5), 7.86 (br s, 1H, NH); δ_{C} (100 MHz, CDCl_3): 15.2 (CH_3), 28.3 (CH_2), 28.4 (CH_2), 62.8 (CH_2 , OCH₂), 85.8 (CH, C5), 179.5 (C=O). Data in agreement with literature.¹

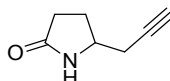
Tributyl(propa-1,2-dien-1-yl)stannane (6)



Tributyltin chloride (5.4 mL, 6.5 g, 20.00 mmol) was added to a stirred suspension of magnesium (631 mg, 26.00 mmol) and lead bromide (366 mg, 1.00 mmol) in THF (20 mL) at room temperature under argon. Propargyl bromide **8** (2.8 mL of an 80 % w/w solution in toluene, 26.00 mmol) was added dropwise to the mixture that was in the following slightly warmed with a heat gun, then stirred for 2.5 h at room temperature. The reaction mixture was quenched with an aq. sat. solution of NH₄Cl (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 40 mL) and the combined organic layers washed with brine (40 mL), dried over Na₂SO₄, concentrated under vacuum and purified by flash column chromatography on deactivated (10 % w/w H₂O) alumina (hexane) affording allenyl tin **6** (21.2 g, 81%) as a colourless liquid.

*R*_f 0.5 (hexane); δ_H (400 MHz, CDCl₃): 0.90 (t, 9H, *J* 7.3 Hz, CH₃), 0.95-0.99 (m, 6H, CH₂), 1.27-1.36 (m, 6H, CH₂), 1.43-1.57 (m, 6H, CH₂), 4.14 (d, 2H, *J* 7.1 Hz, CH₂), 4.97 (t, 1H, *J* 7.1 Hz, CH); δ_C (100 MHz, CDCl₃): 10.3 (CH₂), 13.7 (CH₃), 27.2 (CH₂), 28.9 (CH₂), 63.1 (CH₂), 73.9 (CH), 209.8 (C). NMR in agreement with literature.²

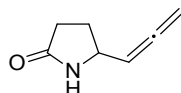
5-(Prop-2-yn-1-yl)pyrrolidin-2-one (7)



Allenyltributyltin **6** (360 μL of a 80 % solution in toluene, 0.97 mmol) was added to a stirred solution of ethoxy lactam **5** (50 mg, 0.39 mmol) in anhydrous DCM (1 mL) at -30 °C under argon. BF₃·OEt₂ (96 μL, 110 mg, 0.77 mmol) was then added dropwise and the reaction was stirred for 7 h at -30 °C. The reaction mixture was quenched with an aq. sat. solution of NaHCO₃ (2 mL) and stirred vigorously for 2 minutes. The layers were separated, the aqueous phase was extracted with DCM (3 x 3 mL) and the combined organic layers were dried over MgSO₄, concentrated under vacuum, and purified by flash column chromatography (ethyl acetate/petroleum ether 1:1 to 1:0 v/v) to afford (S)-5-(propa-1,2-dien-1-yl)pyrrolidin-2-one (0.9 mg, 2 %) as a colourless oil, a mixture of alkyne **7** and allene (9:1, 13.8 mg) and alkyne **7** (22.2 mg, 47 %) as a yellow powder. The overall yield of alkyne **7** was 70 % (35 mg) as a yellow powder.

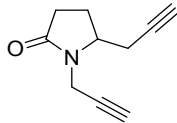
*R*_f 0.23 (Ethyl acetate, 2 elutions); mp = 104 - 106 °C, [lit.³ 109-111 °C]; δ_H (400 MHz, CDCl₃): 1.77-1.94 (m, 1H, H₄), 2.04 (t, 1H, *J* 2.6 Hz, C≡CH), 2.26-2.48 (m, 5H, H₄/H₃/H₃'/CHH'), 3.77-3.88 (dq, 1H, *J* 6.2 Hz, H₅), 6.05 (s, 1H, NH); δ_C (100 MHz, CDCl₃): 26.3 (CH₂, C₄), 26.3 (CH₂), 29.9 (CH₂), 51.0 (CH, C₅), 70.9 (CH, C≡CH), 79.9 (C, C≡C), 177.8 (C=O). Data in agreement with literature.³

(S)-5-(Propa-1,2-dien-1-yl)pyrrolidin-2-one



*R*_f 0.32 (Ethyl acetate 2 elutions); δ_H (400 MHz, CDCl₃): 1.90-1.99 (m, 1H, H₄), 2.26-2.50 (m, 3H, H₄/H₃/H₃'), 4.19-4.21 (m, 1H, H₅), 4.88 (dd, 1H, *J* 2.1 and 6.5 Hz, =CHH'), 4.88 (dd, 1H, *J* 2.1 and 6.5 Hz, =CHH'), 5.16 (ddd, 1H, *J* 6.5 Hz, =CH), 5.63 (s, 1H, NH); δ_C (100 MHz, CDCl₃): 28.4 (CH₂), 29.7 (CH₂), 52.8 (CH, C₅), 78.3 (CH₂, =CH₂), 92.8 (CH, =CH), 178.0 (C=O), 207.4 (=C=). Data in agreement with literature.⁴

1,5-Di(prop-2-yn-1-yl)pyrrolidin-2-one (**9**)



NaH (12 mg of a 60% w/w suspension in mineral oil, 0.51 mmol) was added to a stirred solution of alkyne **7** (48 mg, 0.390 mmol) in anhydrous DMF (1.0 mL) at 0 °C under nitrogen. After 30 minutes, propargyl bromide **8** (91 μ L of a 80 % w/w solution in toluene, 0.82 mmol) was added and the reaction mixture was warmed to rt and stirred for 45 min. The reaction mixture was quenched with water (3 mL) and extracted with ethyl acetate (3 \times 3 mL) and the combined organic layers dried over MgSO₄, concentrated under vacuum and purified by flash column chromatography (ethyl acetate/petroleum ether 7:3 v/v) to afford dialkyne **9** (52 mg, 83 %) as a yellowish oil.

*R*_f: 0.46 (petroleum ether/ethyl acetate 1:1); δ _H (400 MHz, CDCl₃): 1.88-2.00 (m, 1H, H₄), 1.97 (t, 1H, *J* 2.6 Hz, C \equiv CH), 2.20 (t, 1H, *J* 2.3 Hz, C \equiv CH), 2.16-2.26 (m, 2H, H_{4'}), 2.27-2.38 (m, 1H, H₃), 2.44-2.53 (m, 3H, H_{3'}/CCHH'), 3.67 (dd, 1H, *J* 2.3 and 17.8 Hz, NCHH'), 3.92 (dq, 1H, *J* 5.0 and 9.8 Hz, H₅), 4.55 (dd, 1H, *J* 2.3 and 17.8 Hz, NCHH'); δ _C (100 MHz, CDCl₃): 23.1 (CH₂), 23.3 (CH₂), 29.9 (CH₂), 30.0 (CH₂), 55.3 (CH, C₅), 71.3 (C, C \equiv C), 72.4 (C, C \equiv C), 77.5 (CH, C \equiv CH), 78.9 (CH, C \equiv CH), 174.6 (C=O); ν _{max}/cm⁻¹ (neat) 3284, 2960, 2919, 2118, 1676 (C=O), 1416, 1250, 1180; *m/z* (ES⁺) 162 ([M+H]⁺, 100 %); HRMS calc. for C₁₀H₁₂ON 162.0913, found 162.0917 [M+H]⁺.

General procedure for the transition-metal catalysed [2+2+2] cyclotrimerisation reactions:

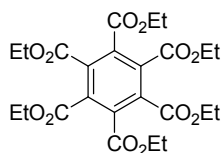
Diethylacetylene dicarboxylate **10a** (355 μ L, 377 mg, 2.26 mmol) was added to a stirred solution of dialkyne **9a** (73 mg, 0.45 mmol), Cp*RuCodCl (17 mg, 0.045 mmol) in anhydrous degassed (three cycles of freeze-pump-thaw) toluene (2.0 mL) under argon. The mixture was heated to reflux for 2.5 h then the solvent removed under vacuum. Purification of the residue by flash column chromatography (petroleum ether/ethyl acetate 9:1 to 0:1 v/v) yielded the tricyclic adduct **14a** (104 mg, 70%) as a brown oil, hexaethyl benzene-1,2,3,4,5,6-hexacarboxylate **11a** (276 mg, 44 %) as a pale yellow solid and 1,5-di(benzyl-1,2,3,4-tetracarboxylic acid tetraethyl ester)-pyrrolidin-2-one **13a** (61 mg, 16 %) as a dark orange oil.

The percentage yield and the appearance of the compounds obtained in these cyclotrimerisation reactions are listed below.

Compound No	% yield	appearance
12a	21	Brown orange oil
11b	22	Orange oil
13b	17	Orange oil
14b	34	Yellow oil
11g	32	White solid
14g	1	Colourless oil

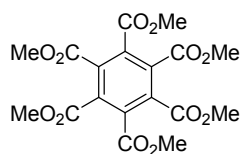
Table S1 – Yield and appearance of compounds obtained through the [2+2+2] cyclotrimerisation of alkynes.

Hexaethyl benzene-1,2,3,4,5,6-hexacarboxylate (**11a**)



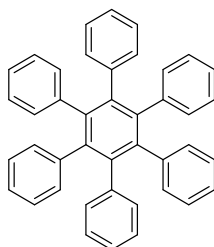
R_f 0.33 (petroleum ether/ethyl acetate 7:3 v/v); mp = 64-67 °C [lit.⁵ 74 °C]; δ_H (400 MHz, $CDCl_3$): 1.28 (t, 18 H, J 7.2 Hz, CH_3), 4.25 (q, 12H, J 7.2 Hz, OCH_2); δ_C (100 MHz, $CDCl_3$): 13.8 (CH_3), 62.6 (CH_2), 133.8 (C), 164.8 (CO). Data in agreement with literature.⁵

Hexamethyl benzene-1,2,3,4,5,6-hexacarboxylate (11b)



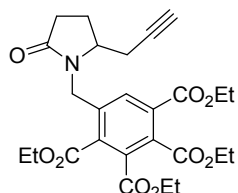
R_f 0.32 (ethyl acetate/petroleum ether 1:1 v/v); mp = 188-190 °C [lit.⁶ 186 °C]; δ_H (400 MHz, $CDCl_3$): 3.82 (s, 18H); δ_C (100 MHz, $CDCl_3$): 52.9 (CH_3), 133.8 (C), 164.8 (CO). Data in agreement with literature.⁶

3',4',5',6'-Tetraphenyl-1,1':2',1''-terphenyl (11g)



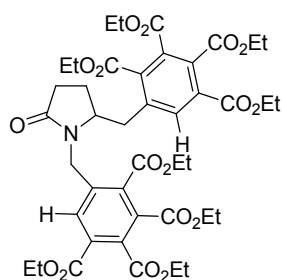
R_f 0.12 (ethyl acetate); mp = 458 °C [lit.⁷ 462 °C]; δ_H (400 MHz, $CDCl_3$): 7.24-7.30 (m, 18H), 7.44-7.49 (m, 12H); δ_C (100 MHz, $CDCl_3$): 128.3, 128.4, 131.6. Data in agreement with literature.⁷

Tetraethyl 5-((2-oxo-5-(prop-2-yn-1-yl)pyrrolidin-1-yl)methyl)benzene-1,2,3,4-tetracarboxylate (12a)



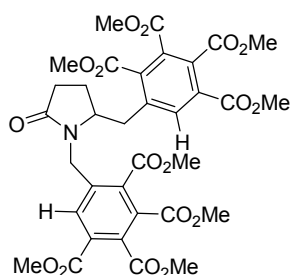
R_f 0.42 (ethyl acetate/petroleum ether 7:3 v/v); δ_H (400 MHz, $CDCl_3$): 1.31-1.37 (m, 12H, CH_3), 1.93-2.01 (m, 1H, H4), 1.97 (t, 1H, J 2.6 Hz, $C\equiv CH$), 2.13-2.23 (m, 1H, H4'), 2.32-2.45 (m, 3H, H3, CHH'), 2.57-2.66 (m, 1H, H3'), 3.53-3.58 (m, 1H, H5), 4.17 (d, 1H, J 15.8 Hz, $NCHH$), 4.15-4.39 (m, 8H, OCH_2), 5.10 (d, 1H, J 15.8 Hz, $NCHH'$), 7.96 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 13.9 (CH_3), 13.9 (CH_3), 14.1 (CH_3), 23.1 (CH_2 , C4), 23.4 (CH_2), 29.8 (CH_2 , C3), 41.3 (CH_2), 55.4 (CH, C5), 62.1 (CH_2 , OCH_2), 62.2 (CH_2 , OCH_2), 62.5 (CH_2 , OCH_2), 62.6 (CH_2 , OCH_2), 71.5 (C, $C\equiv C$), 79.0 (CH, $C\equiv CH$), 130.8 (CAr), 131.2 (CAr), 132.7 (CHAr), 134.4 (CAr), 136.2 (CAr), 136.4 (CAr), 164.6 (C=O), 165.3 (C=O), 166.5 (C=O), 166.6 (C=O), 175.5 (C=O); ν_{max}/cm^{-1} (neat) 3309, 3059, 2985, 1727 (C=O), 1690 (C=O), 1420, 1368, 1266, 1244; m/z (AP⁺) 502 ([M+H]⁺, 100%); HMRS calc. for $C_{26}H_{32}NO_9$ 502.2072, found 502.2068 [M+H]⁺.

1,5-Di(benzyl-2,3,4,5-tetracarboxylic acid tetraethyl ester)-pyrrolidin-2-one (13a)



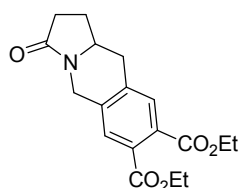
R_f 0.36 (ethyl acetate/petroleum ether 7:3 v/v); δ_H (400 MHz, $CDCl_3$): 1.24-1.31 (m, 24 H, CH_3), 1.69-1.86 (m, 2H, H_4/H_4'), 2.26-2.34 (m, 1H, H_3), 2.41 (dd, 1H, J 8.7 and 17.3 Hz, H_3'), 2.49 (dd, 1H, J 10.3 and 13.2 Hz, $CCHH'$), 3.15 (dd, 1H, J 3.9 and 13.2 Hz, $CCHH'$), 3.70 (m, 1H, H_5), 4.25 (d, 1H, J 13.7 Hz, $NCHH'$), 4.21-4.31 (m, 16H, OCH_2), 5.00 (d, 1H, J 13.7 Hz, $NCHH'$), 7.82 (s, 1H, H_{Ar}), 7.88 (s, 1H, H_{Ar}); δ_C (100 MHz, $CDCl_3$): 13.8 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 14.0 (CH_3), 23.1 (CH_2 , C4), 29.2 (CH_2 , C3), 35.8 (CH_2), 41.5 (CH_2), 58.1 (CH , C5), 62.1 (CH_2 , OCH_2), 62.2 (CH_2 , OCH_2), 62.4 (CH_2 , OCH_2), 62.4 (CH_2 , OCH_2), 62.5 (CH_2 , OCH_2), 130.9 (CAr), 131.1 (CAr), 131.2 (CAr), 131.3 (CAr), 132.1 (CHAR), 133.7 (CAr), 133.8 (CHAR), 134.3 (CAr), 135.8 (CAr), 136.8 (CAr), 137.0 (CAr), 137.2 (CAr), 164.5 (C=O), 164.5 (C=O), 165.4 (C=O), 165.4 (C=O), 166.4 (C=O), 166.4 (C=O), 166.6 (C=O), 166.7 (C=O), 175.3 (C=O); ν_{max}/cm^{-1} (neat) 2983, 2940, 2908, 1722 (C=O), 1694 (C=O), 1445, 1415, 1233, 1196, 1177, 1156, 1101, 1018; m/z (AP+) 843 ($[M+2H]^+$, 50 %), 842 ($[M+H]^+$, 100 %); HMRS calc. for $C_{42}H_{55}N_2O_{17}$ 859.3495, found 859.3497 $[M+NH_4]^+$.

1,5-Di(benzyl-2,3,4,5-tetracarboxylic acid tetramethyl ester)-pyrrolidin-2-one (13b)



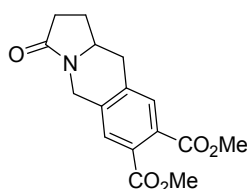
R_f 0.3 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.76 (m, 1H, H_4), 1.88 (m, 1H, H_4'), 2.34 (m, 1H, H_3), 2.46 (dd, 1H, J 8.7 and 17.3 Hz, H_3'), 2.54 (dd, 1H, J 9.9 and 13.4 Hz, CHH'), 3.15 (dd, 1H, J 4.3 and 13.4 Hz, CHH'), 3.69-3.75 (m, 1H, H_5), 3.75 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.89 (s, 6H, CH_3), 4.18 (d, 1H, J 15.9 Hz, $NCHH'$), 5.02 (d, 1H, J 15.9 Hz, $NCHH'$), 7.88 (s, 1H, H_{Ar}), 7.92 (s, 1H, H_{Ar}); δ_C (100 MHz, $CDCl_3$): 23.3 (CH_2 , C4), 29.1 (CH_2 , C3), 36.1 (CH_2), 41.7 (CH_2), 53.0 (CH_3), 53.1 (CH_3), 53.1 (CH_3), 53.2 (CH_3), 58.0 (C5), 130.3 (CAr), 130.5 (CAr), 130.6 (CAr), 130.7 (CAr), 132.8 (CHAR), 134.0 (CAr), 134.2 (CHAR), 134.7 (CAr), 136.1 (CAr), 137.0 (CAr), 137.1 (CAr), 137.4 (CAr), 164.6 (C=O), 164.6 (C=O), 165.5 (C=O), 165.6 (C=O), 166.8 (C=O), 166.9 (C=O), 167.2 (C=O), 167.2 (C=O), 175.3 (C=O); ν_{max}/cm^{-1} (neat) 2950, 2850, 1723 (C=O), 1694 (C=O), 1420, 1375, 1237, 1175, 1017; m/z (AP+) 748 ($[M+NH_4]^+$, 100 %), 731 ($[M+H]^+$, 10 %); HMRS calc. for $C_{34}H_{39}N_2O_{17}$ 747.2243, found 747.2243 $[M+NH_4]^+$.

Diethyl 3-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline-7,8-dicarboxylate (14a)



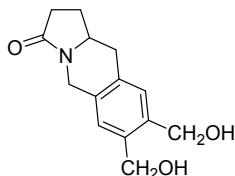
R_f 0.18 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.34 (t, 3H, J 7.1 Hz, CH_3), 1.34 (t, 3H, J 7.1 Hz, CH_3), 1.78-1.86 (m, 1H, H1), 2.37-2.49 (m, 3H, H1', H2, H2'), 2.70 (dd, 1H, J 11.4 and 15.7 Hz, H10), 3.02 (dd, 1H, J 3.7 and 15.7 Hz, H10'), 3.72-3.79 (m, 1H, H10a), 4.26 (d, 1H, J 18.2 Hz, H5), 4.33 (q, 2H, J 7.1 Hz, OCH_2), 4.33 (q, 2H, J 7.1 Hz, OCH_2), 4.97 (d, 1H, J 18.2 Hz, H5'), 7.47 (s, 1H, HAr), 7.49 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 14.1 (CH_3), 14.1 (CH_3), 25.1 (CH_2 , C1), 29.9 (CH_2 , C2), 36.6 (CH_2 , C10), 42.3 (CH_2 , C5), 53.4 (CH, C10a), 61.7 (CH_2 , OCH_2), 61.7 (CH_2 , OCH_2), 127.4 (CHAr), 129.8 (CHAr), 130.6 (CAr), 130.7 (CAr), 135.2 (CAr), 136.7 (CAr), 167.1 (C=O), 167.3 (C=O), 174.2 (C=O); ν_{max}/cm^{-1} (neat) 2982, 2940, 2908, 1718 (C=O), 1686 (C=O), 1442, 1419, 1285, 1255, 1180, 1129, 1018; m/z (AP+) 332 ($[M+H]^+$, 100%), 286 ($[M-OCH_2CH_3]^+$, 90 %); HMRS calc. for $C_{18}H_{22}O_9N$ 332.1492, found 332.1496 $[M+H]^+$.

Dimethyl 3-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline-7,8-dicarboxylate (14b)



R_f 0.12 (ethyl acetate); δ_H (400 MHz, $CDCl_3$): 1.78-1.86 (m, 1H, H1), 2.37-2.49 (m, 3H, H1', H2, H2'), 2.70 (dd, 1H, J 11.2 and 15.6 Hz, H10), 3.01 (dd, 1H, J 3.7 and 15.6 Hz, H10'), 3.73-3.80 (m, 1H, H10a), 3.87 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.25 (d, 1H, J 18.3 Hz, H5), 4.97 (d, 1H, J 18.3 Hz, H5'), 7.47 (s, 1H, HAr), 7.49 (s, 1H, HAr); δ_C (100 MHz, $CDCl_3$): 25.1 (CH_2 , C1), 29.9 (CH_2 , C2), 36.6 (CH_2 , C10), 42.3 (CH_2 , C5), 52.7 (CH_3), 52.7 (CH_3), 53.4 (CH, C10a), 127.4 (CHAr), 129.8 (CHAr), 130.3 (CAr), 130.3 (CAr), 135.3 (CAr), 136.9 (CAr), 167.6 (C=O), 167.8 (C=O), 174.2 (C=O); ν_{max}/cm^{-1} (neat) 2954, 2845, 1719(C=O), 1675 (C=O), 1432, 1247, 1210, 1157, 1125; m/z (AP+) 304 ($[M+H]^+$, 100 %); HMRS calc. for $C_{16}H_{16}O_5N$ 302.1023, found 302.1029 $[M-H]^+$.

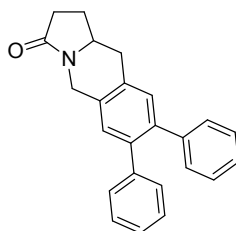
7,8-bis(hydroxymethyl)-1,2,10,10a-tetrahydropyrrolo[1,2-b]isoquinolin-3(5H)-one (14e)



$LiAlH_4$ (3.0 eq.) suspended in dry THF (5 mL) was added in small batches under a N_2 blanket to a stirred solution of compound **14a** (50 mg, 1.0 eq.) in dry THF (3.0 mL) at $-80^\circ C$. The reaction mixture was allowed to warm up to $0^\circ C$ over a period of 2 hours before H_2O (2 ml) was carefully added to remove the excess of the reagent. The product was then extracted by CH_2Cl_2 (3 X 10 mL), and the combined organic layers were dried by magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using a gradient eluent ($CH_2Cl_2:CH_3OH:NH_3$, 95:5:0 \rightarrow 90:9:1 v/v/v) to obtain the desired target compounds as a white solid (25.3 mg, 72.0 % yield).

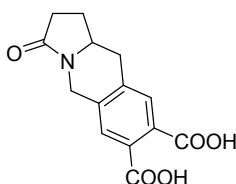
δ_{H} (400 MHz, DMSO:CD₃OD (1:1)): 1.49-1.53 (m, 1H), 1.75-1.86 (m, 1H), 2.09-2.22 (m, 1H), 2.29-2.35 (q, 1H), 2.58-2.66 (m, 1H), 2.92-3.01 (dd, 1H), 3.20-3.30 (m, 1H), 3.42 (d, 1H), 4.03 (d, 1H), 4.58 (s, 4H), 7.23 (s, 1H, HAr), 7.25 (s, 1H, HAr); δ_{C} (100 MHz, DMSO: CD₃OD (1:1)): 21.3, 30.5, 34.8, 54.6, 55.1, 60.9, 63.0, 127.4 (CHAr), 129.8 (CHAr), 133.7 (CAr), 134.1 (CAr), 137.0 (CAr), 138.0 (CAr), 173.6 (C=O); m/z (AP+) 248 ([M+H]⁺, 100%); HMRS calc. for C₁₄H₁₇O₃N 247.1208, found 247.1291 [M-H]⁺.

7,8-Diphenyl-1,2,10,10a-tetrahydropyrrolo[1,2-b]isoquinolin-3(5H)-one (14g)



R_f 0.24 (ethyl acetate); δ_{H} (400 MHz, CDCl₃): 1.82-1.91 (m, 1H, H1), 2.40-2.54 (m, 3H, H1, H2, H2'), 2.79 (dd, 1H, *J* 11.3 and 15.3 Hz, H10), 3.05 (dd, 1H, *J* 3.7 and 15.3 Hz, H10'), 3.85-3.92 (m, 1H, H10a), 4.35 (d, 1H, *J* 17.6 Hz, H5), 5.04 (d, 1H, *J* 17.6 Hz, H5'), 7.10-7.13 (m, 4H, HAr), 7.19-7.23 (m, 8H, HAr); δ_{C} (100 MHz, CDCl₃): 25.4 (CH₂, C1), 30.2 (CH₂, C2), 36.6 (CH₂, C10), 42.4 (CH₂, C5), 54.1 (CH, C10a), 126.6 (CHAr), 126.6 (CHAr), 127.9 (CHAr), 128.0 (CHAr), 128.7 (CHAr), 129.8 (CHAr), 131.1 (CAr), 131.2 (CHAr), 132.5 (CAr), 139.1 (CAr), 139.4 (CAr), 140.8 (CAr), 140.9 (CAr), 174.3 (C=O); ν_{max} /cm⁻¹ (neat) 2974, 2843, 1657 (C=O), 1444, 1335, 1264; m/z (AP+) 340 ([M+H]⁺, 100 %); HMRS calc. for C₂₄H₂₂ON 340.1696, found 340.1699 [M+H]⁺.

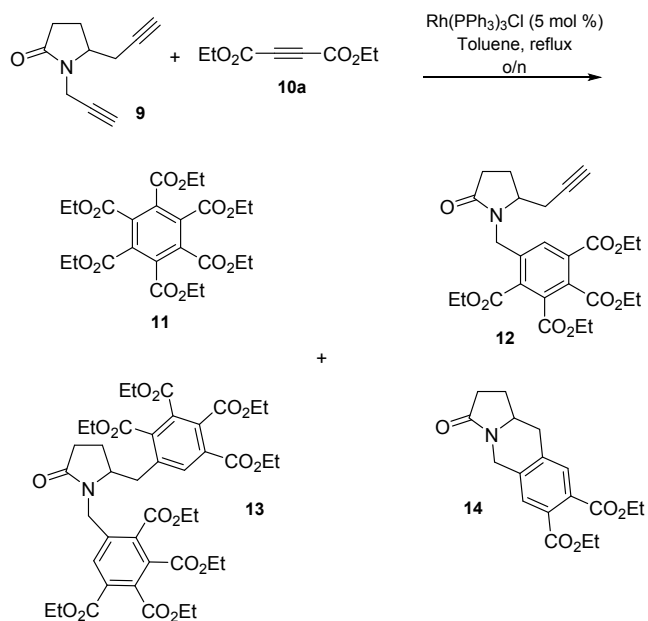
3-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline-7,8-dicarboxylic acid 15



To compound **14a** (50 mg, 0.151 mmol) in 50 ml round bottom flask was added sodium hydroxide aqueous solution (20%, 20 ml) and the mixture was refluxed for 4 hours. After the reaction mixture had cooled down, it was neutralised by diluted HCl aqueous solution. The formed solid was filtered, dried and purified by column chromatography using CH₂Cl₂:CH₃OH (95:5) to afford the title compound as an off-white solid (37.4 mg, 90 % yield)

δ_{H} (400 MHz, DMSO:CD₃OD (9:1)): 1.71-1.86 (m, 1H), 2.45-2.51 (m, 3H), 2.77 (dd, 1H), 3.08 (dd, 1H), 3.84-3.90 (m, 1H), 4.30 (d, 1H), 4.93 (d, 1H), 7.55 (s, 1H, HAr), 7.59 (s, 1H, HAr); δ_{C} (100 MHz, DMSO:CD₃OD (9:1)): 23.7, 27.6, 28.6, 34.9, 41.1, 53.2, 126.1 (CHAr), 128.6 (CHAr), 130.2 (CAr), 130.3 (CAr), 133.9 (CAr), 136.1 (CAr), 158.6 (C=O), 168.8 (C=O), 174.7 (C=O); m/z (AP+) 276 ([M+H]⁺, 100 %); HMRS calc. for C₁₄H₁₃O₅N 275.0794, found 275.0154 [M-H]⁺.

Optimisation of the reaction described in Scheme 3:



Entry	Catalyst (mol %)	Temp (°C)	Solvent	Time (h)	yield (%)			
					11 ^a	12	13	14
1	A 5	reflux	Toluene	18	24	21	22	30
2	A 5	reflux	Toluene ^b	7	--- ^c	--- ^c	--- ^c	--- ^c
3	A 5	reflux	Toluene ^d	5.5	7	e	e	17
4	A 10	reflux	Toluene	2.5	--- ^c	--- ^c	--- ^c	--- ^c
5	B 10	reflux	Toluene	4	11	4	8	42
6	B 10	rt	DCE	24	--- ^f	--- ^f	--- ^f	--- ^f
7 ^g	B 10	reflux	Toluene	4	11	3	7	44
8 ^g	B 5	reflux	Toluene	8.5	14	2	8	15
9 ^g	B 10	50	Toluene	Incomplete after 3 days				
10 ^g	B 10	100	Toluene	24	10	1	7	15

11^g	B 10	reflux	Dioxane	8.5	7	6	5	29
12^g	B 10	reflux	Benzene	9	8	3	4	2
13^g	B 10	reflux	THF	24	10	2	4	14
14^{g,h}	B 10	reflux	Toluene	24	8	trace	3	27

Table S2 – Optimisation of tricyclic adduct 14 synthesis. Reactions performed with 0.310 mmol of dialkyne **9**, 5 eq. of diethyl acetylenedicarboxylate **10a** in 2 mL of solvent. Catalyst: A - RhCl(PPh₃)₃, B – CpCo(CO)₂, C - [Ir(cod)Cl]₂, D – Cp*Ru(cod)Cl. ^a yield based on the amount of diethyl acetylenedicarboxylate **10a** used, ^b Pre-mixing of RhCl(PPh₃)₃ with dialkyne **9** followed by syringe addition of diethyl acetylenedicarboxylate **10a**, ^c degradation, ^d syringe addition of diethyl acetylenedicarboxylate **10a**, ^e mixture **12:13** 1:15, ^f did not react, ^g stock solution of catalyst (0.23 M), ^h 2.5 eq. diethyl acetylenedicarboxylate **10a**.

General proposed mechanism for the transition-metal mediated [2+2+2] cyclotrimerisation of alkynes:

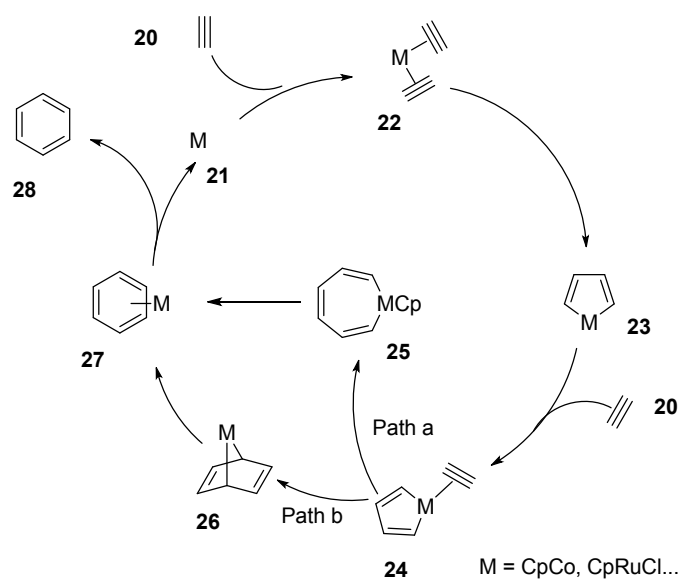


Figure S1

The absence of reaction of dialkyne **9** with diphenylacetylene **10g** may be due to a steric clash associated with the insertion of this alkyne to the metallacycle adduct during the catalytic cycle (Figure S1). Regardless of whether the insertion happens via path a or path b, there is a repulsion between the phenyl group and the Cp* group (Figure S2).

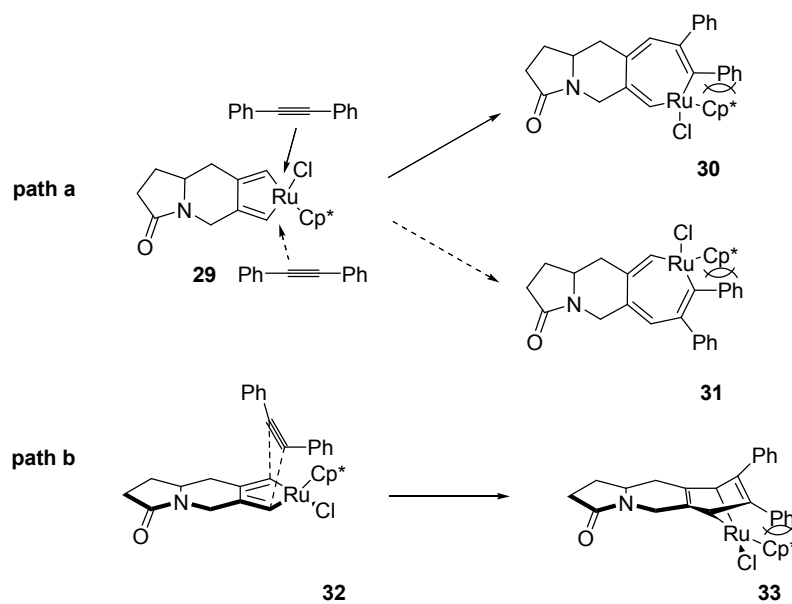


Figure S2

Computational chemistry

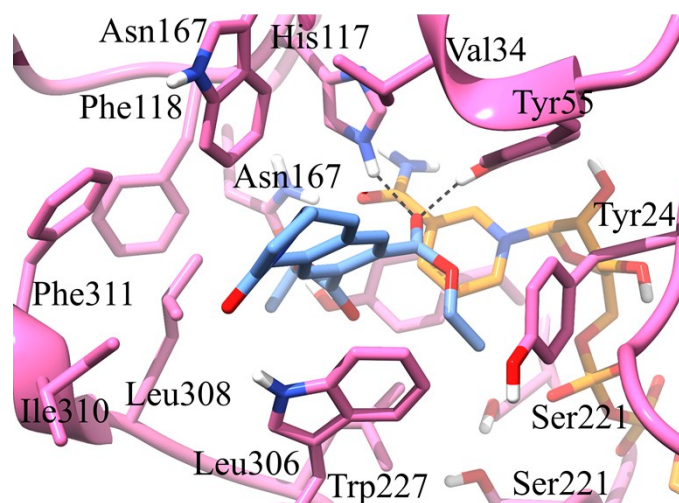


Figure S3 Compound 14a (Blue) docked in the AKR1C2 binding site. Dash lines represent H-bond. NADP+ is coloured in orange.

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