Supplementary Material

Synthesis and Biological Evaluation of Functionalised Tetrahydro-β-carboline Analogues as Inhibitors of *Toxoplasma gondii* Invasion.

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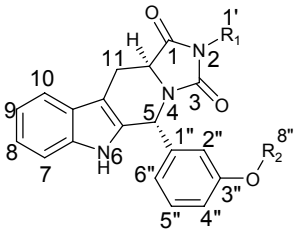
Numbering scheme used for the β-carboline ring system

The following numbering scheme was used throughout the experimental section of the paper.



NOSEY spectrum of *cis*-6b and *trans*-7a

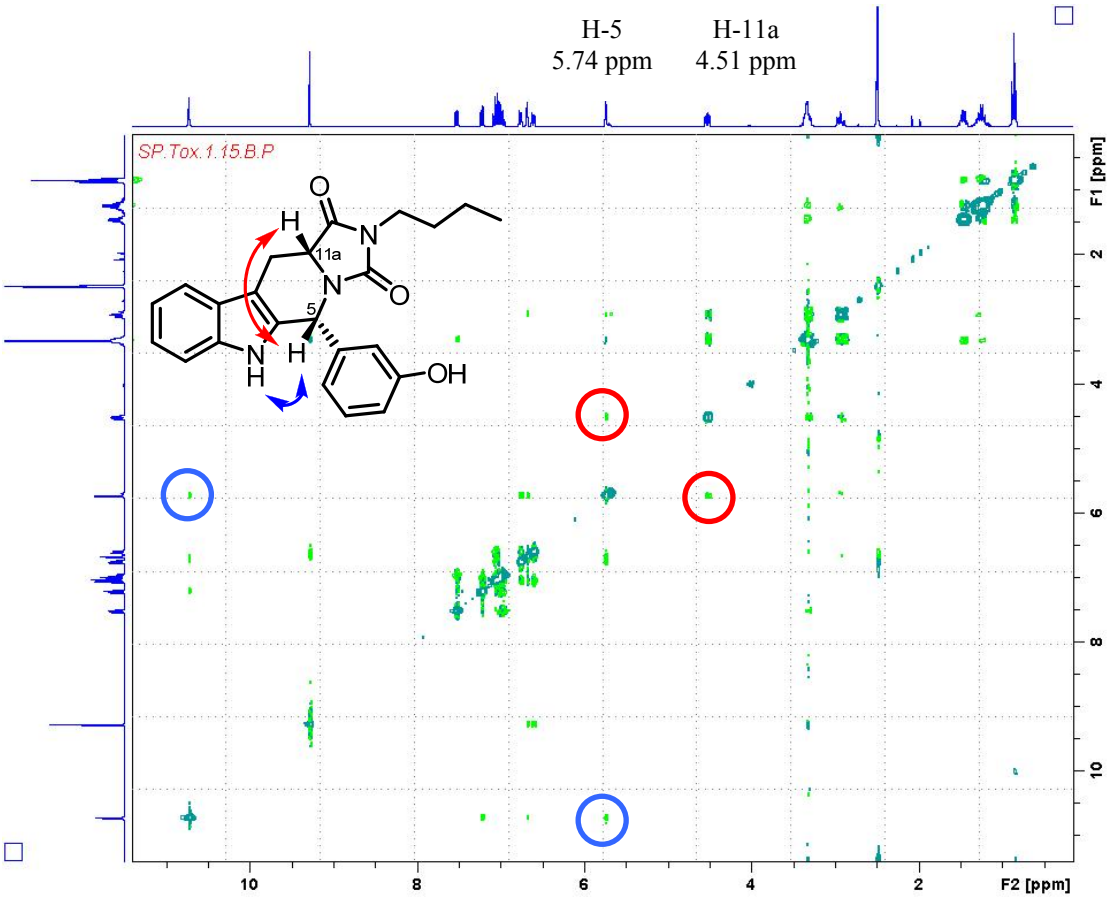


Figure S1. NOESY spectrum of *cis*-**6b**.

Whilst not conclusive, the observed lack of an nOe correlation between the C11a and C5-hydrogens in **7a** was also consistent with these two hydrogens being *trans*-oriented.

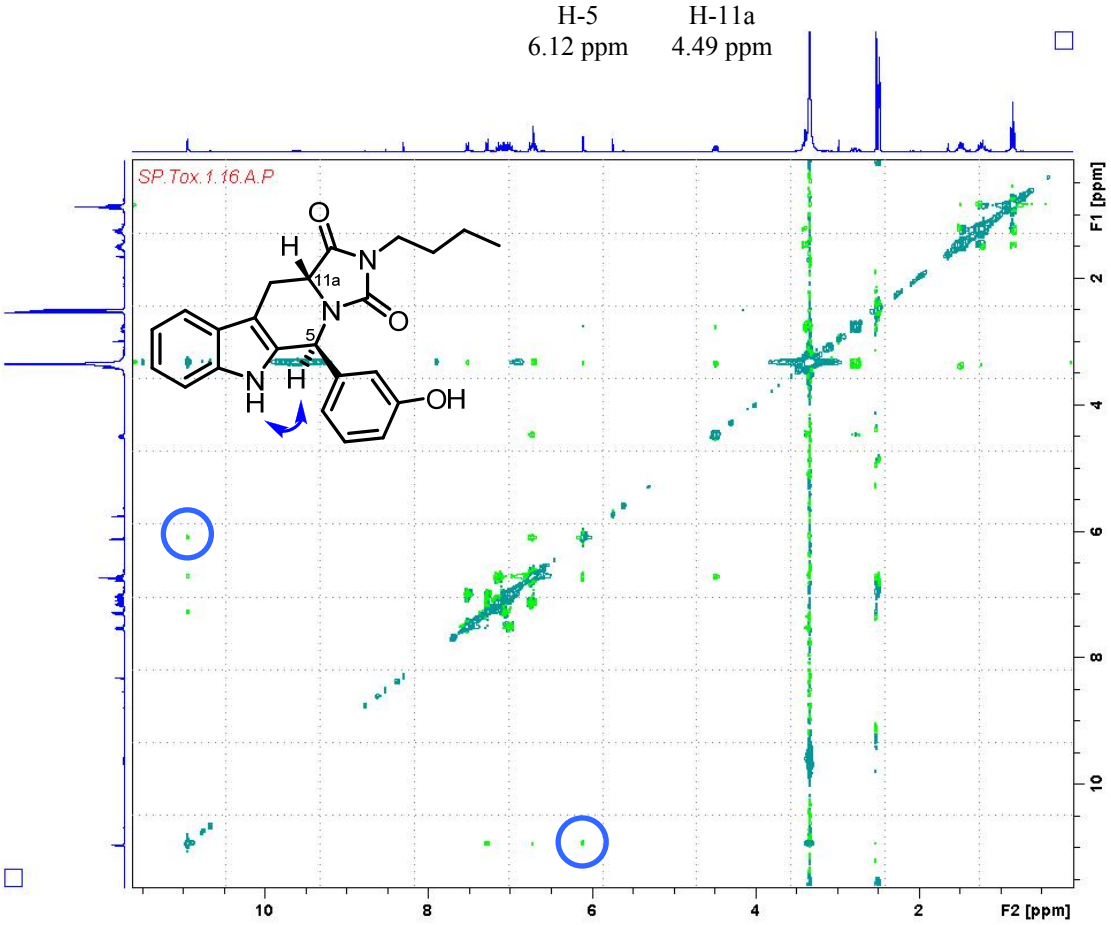


Figure S2. NOESY spectrum of *trans*-**7a**.

Bioinformatic analysis of *T.gondii* kinesins

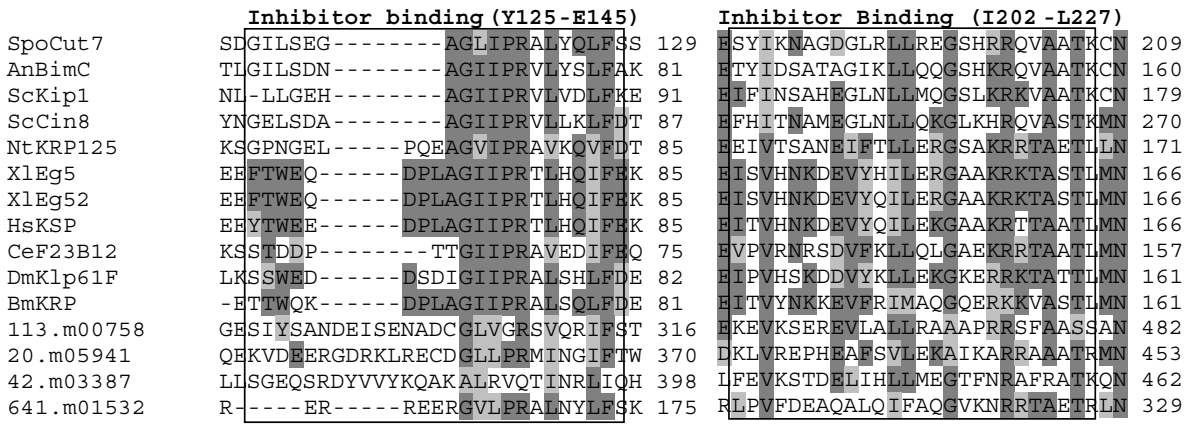


Figure S3 Alignments comparing the two regions of human Eg5 shown to interact with **1** with other family 5 kinesins and the four candidate family 5 kinesins identified in *T. gondii*. The sequences of known family 5 kinesins used in the alignment are; *S. pombe* Cut7, *A. nidulans* BimC, *S. cerevisiae* Kip1 and Cin8, *N. tabacum* KRP125, *X. laevis* Eg5 and Eg52, *H. sapiens* KSP (Eg5), *C. elegans* F23B12, *D. melanogaster* Klp61F, and *B. mori* KRP. The *T. gondii* proteins that were aligned are; 113.m00758, 20.m05941, 42.m03387, and 641.m01532. The regions of human Eg5 that have been shown to interact with 5118793, Tyr125-Glu145 (left) and Ile202-Leu227 (right), and the corresponding regions of the other proteins are shown.

The yeast-3-hybrid approach: Y3H is based on the more familiar yeast two-hybrid (Y2H) assay that allows the detection of protein-protein interactions. In the Y2H assay the two functional domains of a transcriptional activator, the DNA-binding domain (DBD) and the activation domain (AD), are independently fused to 1) a protein of interest, the "bait" and 2) a cDNA library encoding potential interacting proteins, the "prey". A transcriptional read-out is obtained when the bait protein interacts with a prey protein reconstituting the transcriptional activator by bringing the DBD and AD into close proximity. The analogous Y3H assay allows the detection of small molecule-protein interactions by making the transcriptional read-out dependent on the interaction of the bait and prey proteins through a "dimerizing" hybrid small molecule, also known as a chemical inducer of dimerization (CID) (i.e. the bait and prey proteins themselves do not interact) (Fig. S4).

The Y3H system used in this study was developed by the laboratory of Virginia Cornish[S1]. The Cornish Y3H system utilizes two transcriptional reporters of interaction, LEU2 and *lacZ*, each preceded by an array of LexA operator sites. (Figure S4, modified from reference S1). The system is composed of a DHFR-LexA DBD fusion protein and a B42 AD fusion with a cDNA library of putative targets of interest. It relies on DHFR's high affinity interaction with methotrexate (MTX) to anchor a MTX-small molecule CID to the DHFR-LexA DBD fusion (Fig. S4). In this system transcriptional activation is dependent upon binding of the portion of the CID containing the small molecule of interest (the bait), to its putative target-B42 AD fusion.

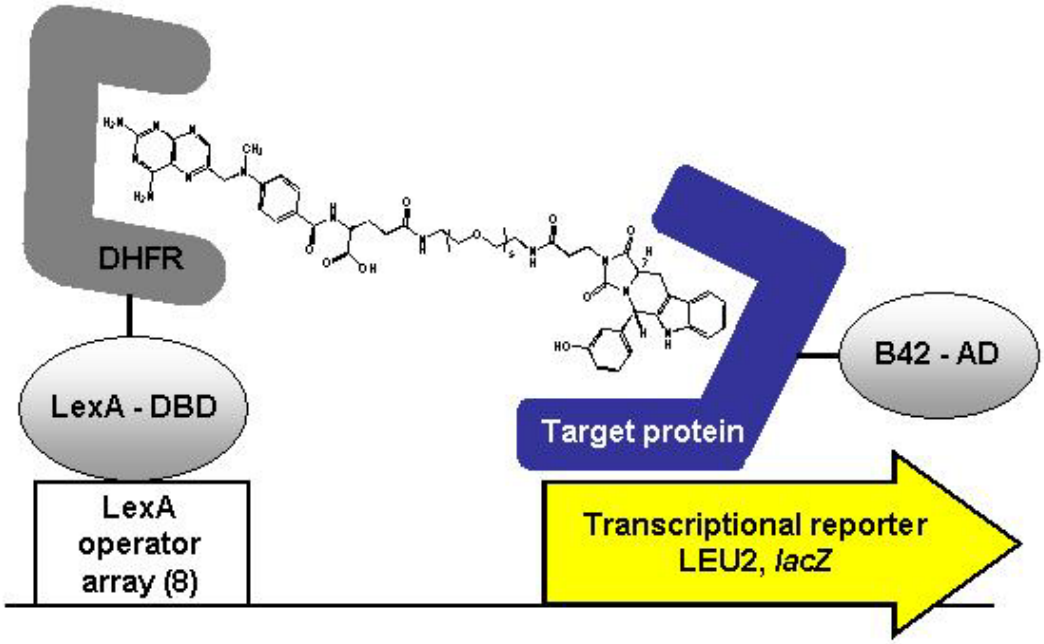


Figure S4. Schematic representation of the yeast-3-hybrid approach adapted from figure in Reference S1.

- **Literature compounds with improved characterisation.**

General procedure for the Pictet-Spengler reaction

D-(**5a**) or **L**-Tryptophan (**5b**) (29 mmol) was suspended in 0.05 M H_2SO_4 (42 mL) and the desired aldehyde (2.0 equiv, 59 mmol) was added. The reaction mixture was stirred at reflux for 4-6 hours and the solid product collected by filtration and thoroughly rinsed with diethyl ether. Whilst **2a** and **2b** are known compounds,[12] optical rotations and melting points have not been previously reported. Previous reports of the synthesis of **2d**[25] described the formation of a diastereomeric mixture only and provided no spectroscopic data.

(1*R*,3*R*)-1-(3-Hydroxy-phenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid (2a)[12] Yield 70%, yellow solid. m.p. 265-266 ºC; ν_{max} (KBr) 3450, 1636, 1560, 1394, 1298 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.44 (1H, d, *J* 8.0, H5), 7.15-7.26 (2H, m, H5', H8), 7.03-7.01 (1H, m, H6), 7.01-6.90 (1H, m, H7), 6.86 (1H, d, *J* 7.6, H6'), 6.81-6.73 (2H, m, H4', H2'), 5.29 (1H, s, H1), 3.75 (1H, dd, *J* 11.4, 4.2, H3), 3.10 (1H, dd, *J* 13.6, 4.2, $H4_{syn}$), 2.84 (1H, dd, *J* 13.6, 12.5, $H4_{anti}$); ^{13}C NMR (100 MHz, DMSO-d_6), δ 172.2 (C=O), 157.3 (C), 140.9 (C), 136.5 (C), 133.4 (C), 129.3 (CH), 126.3 (C), 120.8 (CH), 119.7 (CH), 118.4 (CH), 117.6 (CH), 115.9 (CH), 115.3 (CH), 111.3 (CH), 107.6 (C), 57.6 (CH), 56.8 (CH) 24.5 (CH_2); LRMS (ES^-) *m/z*: 307.20 $[M-H]^-$; $[\alpha]_D^{20} = +147.2$ (*c* = 0.0075, MeOH).

(1*S*,3*S*)-1-(3-Hydroxy-phenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid (2b)[12] Yield 50%, yellow solid. m.p. 262-263ºC ºC; ν_{max} (KBr) 3327 (m), 1638 (s), 1606 (m), 1465 (m) 1396 (m), 1298 cm^{-1} (w); ^1H NMR (500 MHz, DMSO-d_6) δ 10.45 (1H, s, NH), 7.46 (1H, d, *J* 8.0, H5), 7.25-7.15 (2H, m, H5', H8), 7.05-7.02 (1H, m, H6), 7.00-6.96 (1H, m, H7), 6.88 (1H, d, *J* 7.5, H6'), 6.80-6.77 (2H, m, H4', H2'), 5.31 (1H, s, H1), 3.77 (1H, dd, *J* 11.5, 4.5, H3), 3.14-3.10 (1H, m, $H4_{syn}$), 2.89-2.83 (1H, m, $H4_{anti}$); ^{13}C NMR (125 MHz, DMSO-d_6), δ 172.2 (C=O), 157.3 (C), 141.0 (C), 136.5 (C), 133.4 (C), 129.3 (CH), 126.3 (C), 120.9 (CH), 119.8 (CH), 118.5 (CH), 117.7 (CH), 115.9 (CH), 115.3 (CH), 111.3 (CH), 107.6 (C), 57.6 (CH), 56.8 (CH) 24.5 (CH_2); LRMS (ES^+) *m/z*: 331.02 $[M+Na]^+$; HRMS (ES^+) $[M+Na]^+$ m/z expected for $C_{18}H_{16}N_2O_3Na$ 331.1059 found 331.1059; $[\alpha]_D^{20} = -139.5$ (*c* = 0.005, MeOH).

(1*R*,3*R*)-1-(4-Hydroxy-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid (2c)[25] Yield 34%, yellow solid. m.p. 263-264ºC; ν_{max} (KBr) 3417 (m), 1652 (s), 1600 (m), 1400 (m), 1278 cm^{-1} (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.52 (1H, s, NH), 7.47 (1H, d, *J* 8.0, H5), 7.26-7.23 (3H, m, H8, H2'), 7.07-7.04 (1H, m, H7), 7.01-6.98 (1H, m, H6), 6.84-6.81 (2H, AA´BB´, H3'), 5.45 (1H, s, H1), 3.80 (1H, dd, *J* 12.0, 4.5, H3), 3.19 (1H, dd, *J* 15.5, 4.5, $H4_{syn}$), 2.96-2.91 (1H, m, $H4_{anti}$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.1 (C=O), 158.1 (C), 136.6 (C), 132.2 (C), 131.0 (CH), 127.4 (C), 126.2 (C), 121.1 (CH), 118.6 (CH), 117.9 (CH), 115.1 (CH), 111.4 (CH), 108.0 (C), 57.5 (CH), 57.2 (CH), 23.7 (CH_2); LRMS (ES^+) *m/z*: 309.06 $[M+H]^+$; HRMS (ES^+) $[M+H]^+$ m/z expected for $C_{18}H_{17}N_2O_3$ 309.1239 found 309.1239; $[\alpha]_D^{20}$ = +141 (*c* = 0.1, MeOH).

(1*S*,3*S*)-1-(4-Hydroxy-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid (2d)[25] Yield 52%, off white solid. m.p. 263-264ºC; ν_{max} (KBr) 3417 (m), 1653 (s), 1617 (m), 1401 (s), 1278 cm^{-1} (m); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.52 (1H, s, NH), 7.54 (1H, d, *J* 7.2, H5), 7.31-7.26 (3H, m, H2' & H8), 7.13-7.02 (2H, m, H6 & H7), 6.87-6.84 (2H, AA´BB´, H3'), 5.44 (1H, s, H1), 3.82 (1H, dd, *J* 11.5, 4.0, H3), 3.22 (1H, dd, *J* 15.6, 4.0, $H4_{syn}$), 3.00-2.91 (1H, m, $H4_{anti}$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.1 (C=O), 158.0 (C), 136.5 (C), 132.4 (C), 130.9 (CH), 127.8 (C), 126.2 (C), 121.1 (CH), 118.6 (CH), 117.8 (CH), 115.1 (CH), 111.3 (CH), 108.0 (C), 57.4 (CH), 57.1 (CH), 23.8 (CH_2); LRMS (ES^+) *m/z*: 309.06 $[M+H]^+$; HRMS (ES^+) $[M+H]^+$ m/z expected for $C_{18}H_{17}N_2O_3$ 309.1239 found 309.1239; $[\alpha]_D^{20}$ = -141 (*c* = 0.1, MeOH).

General procedure for the synthesis of the *cis*-hydantoins (6a-6d)

To a solution of the desired carboxylic acid **2** (13 mmol) in a mixture of anhydrous acetone (60 mL) and anhydrous DMSO (24 mL) was added the corresponding isocyanate (1.0 eq, 13 mmol). The solution was stirred at reflux for 4 hrs then poured onto H_2O (200 mL). The aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic layers washed with brine (200 mL), dried (Na_2SO_4) and reduced *in vacuo*. Purification of the residue by chromatography on silica gel (EtOAc:Hex 20:80) afforded the desired product. **6a** and **6b** have been reported,

however, the melting points previously associated with these compounds are confusing.[12]

(5*R*,11a*R*)-2-Butyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (6a)[12] Yield 65%, yellow solid. m.p. 186-187 ºC (lit. 134º C)[12]; ν_{max} (KBr) 3433, 2956, 1765, 1701 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (1H, s, NH), 9.28 (1H, s, OH), 7.53 (1H, d, *J* 7.9, H10), 7.30 (1H, d, *J* 7.9, H7), 7.17-7.15 (1H, m, H5"), 7.10-7.08 (1H, m, H9), 7.02-7.01 (1H, m, H8), 6.77 (1H, d, *J* 7.7 H6"), 6.70 (1H, s, H2"), 6.62 (1H, d, *J* 8.0, H4"), 6.13 (1H, s, H5), 4.53 (1H, dd, *J* 11.7, 4.3, H11a), 3.41-3.30 (3H, m, 2 x H1', H11$_{syn}$), 2.90-2.80 (1H, m, H11$_{anti}$), 1.50-1.45 (2H, m, H2'), 1.20-1.10 (2H, m, H3'), 0.86 (3H, t, H4'); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3 (C=O), 158.9 (C), 154.9 (C=O), 142.0 (C), 137.4 (C), 132.0 (C), 130.4 (CH), 126.5 (C), 122.3 (CH), 119.5 (CH), 118.9 (CH), 118.7 (CH), 115.9 (CH), 115.6 (CH), 112.1 (CH), 106.6 (C), 53.5 (CH), 52.1 (CH), 38.4 (CH_2), 32.9 (CH_2), 23.5 (CH_2), 20.1 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z*: 390.40 $[M+H]^+$; $[\alpha]_D^{20}$ = +58.7 (*c* = 0.002, EtOAc).

(5*S*,11a*S*)-2-Butyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (6b)[12] Yield 92%, yellow solid. m.p. 191-192 ºC (lit. 225º C)[12] ν_{max} (KBr) 3340 (m), 2952 (w), 1763 (m), 1694 (s), 1457 cm^{-1} (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.75 (1H, s, NH), 9.31 (1H, s, OH), 7.54 (1H, d, *J* 7.5, H10), 7.24 (1H, d, *J* 7.5, H7), 7.09-7.03 (2H, m, H5' & H8), 7.01-6.98 (1H, m, H9), 6.78 (1H, d, *J* 7.5 H6''), 6.70-6.69 (1H, m, H2''), 6.63 (1H, ddd, *J* 8.0, 2.5, 1.0, H4''), 5.76 (1H, s, H5), 4.54 (1H, dd, *J* 11.5, 4.5, H11a), 3.41-3.31 (3H, m, H11$_{syn}$ & H1'), 2.98-2.92 (1H, m, H11$_{anti}$), 1.51-1.45 (2H, m, H2'), 1.30-1.22 (2H, m, H3'), 0.87 (3H, t, *J* 7.5, H4'); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.7 (C=O), 157.2 (C), 154.1 (C=O), 142.1 (C), 136.6 (C), 134.8 (C), 129.1 (CH), 125.8 (C), 121.3 (CH), 118.8 (CH), 118.1 (CH), 118.08 (CH), 114.4 (CH), 114.1 (CH), 111.3 (CH), 104.8 (C), 57.5 (CH), 55.6 (CH), 37.4 (CH_2), 29.6 (CH_2), 21.8 (CH_2), 19.3 (CH_2), 13.5 (CH_3); LRMS (ES^+) *m/z*: 412.10 $[M+Na]^+$; HRMS (ES^+) $[M+Na]^+$ m/z expected for $C_{23}H_{23}N_3O_3Na$ 412.1637 found 412.1637; $[\alpha]_D^{20}$ = -55.9 (*c* = 0.0054, EtOAc).

General procedure for epimerisation to the *trans*-hydantoins (7a-7m)

A mixture of the desired *cis*-hydantoin **6** (8.00 mmol) and K_2CO_3 (1.3 equiv, 10.4 mmol) in anhydrous MeCN (120 mL) was stirred at reflux for 4 hrs. The solids were removed *via* filtration and the solvent reduced *in vacuo*. Purification of the residue by chromatography on silica gel (EtOAc:Hex 20:80) afforded the desired product. **7a** and **7b** have been reported, however, the m.p. previously associated with these compounds are confusing.[12] For spectroscopic details associated with **7e-7j** see supplementary material.[10]

(5*R*,11a*S*)-2-Butyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (7a)[12] Yield 80%, yellow solid. m.p. 187-189 ºC (lit. 107 ºC)[12]; ν_{max} (KBr) 3433, 2956, 1765, 1701 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.93 (1H, s, NH), 9.46 (1H, s, OH), 7.54 (1H, d, *J* 7.8, H10), 7.30 (1H, d, *J* 8.0, H7), 7.20-6.95 (3H, m, H5", H9, H8), 6.77 (1H, d, *J* 7.7 H6"), 6.72-6.70 (2H, m, H4", H2"), 6.13 (1H, s, H5), 4.49 (1H, dd, *J* 10.9, 5.7, H11a), 3.40 (2H, t, *J* 7.8, H1'), 3.39-3.30 (1H, m, $H11_{syn}$), 2.80 (1H, dd, *J* 15.1, 10.9, $H11_{anti}$), 1.45-1.31 (2H, m, H2'), 1.29-1.10 (2H, m, H3'), 0.86 (3H, t, *J* 7.3, H4'); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4 (C=O), 158.9 (C), 155.0 (C=O), 142.06 (C), 137.40 (C), 132.0 (C), 130.4 (CH), 126.5 (C), 122.4 (CH), 119.5 (CH), 118.8 (CH), 118.7 (CH), 116.0 (CH), 115.6 (CH), 112.1 (CH), 106.7 (C), 53.5 (CH), 52.1 (CH), 38.4 (CH_2), 32.9 (CH_2), 23.5 (CH_2), 20.1 (CH_2), 14.2 (CH_3); LRMS (ES^+) *m/z*: 412.2 $[M+Na]^+$; $[\alpha]_D^{20}$ = -215.5 (*c* = 0.006, EtOAc).

(5*S*,11a*R*)-2-Butyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (7b)[12] Yield 99%, yellow solid. m.p 185-186ºC (lit. 118 ºC)[12]; ν_{max} (KBr) 3338 (m), 2958 (w), 1763 (m), 1700 (s), 1457 cm^{-1} (s); ^1H NMR (500 MHz, DMSO-d_6) δ 11.00 (1H, s, NH), 7.59 (1H, d, *J* 8.0, H10), 7.36 (1H, d, *J* 8.0, H7), 7.20 (1H, dd, *J* 8.0, 8.0, H5''), 7.17-7.13 (1H, m, H8), 7.09-7.06 (1H, m, H9), 6.81-6.76 (3H, m, H2'', H4'' & H6''), 6.18 (1H, s, H5), 4.56 (1H, dd, *J* 10.5, 5.5, H11a), 3.48-3.41 (3H, m, H1' & $H11_{syn}$), 2.88-2.85 (1H, m, $H11_{anti}$), 1.59-1.53 (2H, m, H2'), 1.34-1.27 (2H, m, H3'), 0.92 (3H, t, *J* 7.3, H4'); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.6 (C=O), 158.0 (C), 154.3 (C=O), 141.3 (C), 136.7 (C), 131.3 (C), 129.7 (CH), 125.8 (C), 121.6 (CH), 118.8 (CH), 118.2 (CH), 118.0 (CH), 115.1 (CH), 114.8 (CH), 111.4 (CH), 105.9 (C), 52.7 (CH), 51.4 (CH), 37.7 (CH_2),

29.6 (CH_2), 22.8 (CH_2), 19.4 (CH_2), 13.5 (CH_3); LRMS (ES^+) *m/z*: 412.11 $[M+Na]^+$; HRMS (ES^+) $[M+Na]^+$ m/z expected for $C_{23}H_{23}N_3O_3Na$ 412.1637 found 412.1637; $[\alpha]_D^{20}$ = +204.8 (*c* = 0.007, EtOAc).

General procedure for the synthesis of the *trans*-3-thioxohydantoins (8a & 8b)

To a solution of the desired carboxylic acid **2a** or **2b** (1.0 mmol) in a mixture of anhydrous acetone (3.5 mL) and anhydrous DMSO (1.5 mL) was added the *n*-butylisothiocyante (1.0 eq, 1.0 mmol). The solution was stirred at reflux for 2 hrs, then poured onto H_2O (200 mL). Extracted with DCM (3 x 100 mL) and the combined organic layers washed with brine (200 mL), dried (Na_2SO_4) and reduced *in vacuo*. Purification of the residue by chromatography on silica gel (EtOAc:Hex 20:80) afforded the desired product.

(5*R*,11a*S*)-2-Butyl-5-(3-hydroxyphenyl)-3-thioxo-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1-on *trans* (8a) Yield 56%, orange glass. m.p. 54-55ºC; ν_{max} (KBr) 3338 (m), 1742 (m), 1599(w), 1458 cm^{-1} (s); ^1H NMR (500 MHz, DMSO-d_6) δ 11.05 (1H, s, NH), 9.51 (1H, s, OH), 7.56 (1H, d, *J* 8.0, H10), 7.31 (1H, d, *J* 8.0, H7), 7.17 (1H, dd, *J* 8.0, 8.0, H5''), 7.13-7.10 (1H, m, H8), 7.06-7.03 (1H, m, H9), 6.92-6.90 (1H, m, H6''), 6.88-6.87 (1H, m, H2''), 6.82 (1H, s, H5), 6.74 (1H, ddd, *J* 8.0, 2.5, 0.5, H4''), 4.79 (1H, dd, *J* 10.5, 6.0, H11a), 3.77-3.71 (2H, m, H1'), 3.47 (1H, dd, *J* 15.0, 6.0, $H11_{syn}$), 2.94-2.91 (1H, m, $H11_{anti}$), 1.61-1.55 (2H, m, H2'), 1.32-1.25 (2H, m, H3'), 0.89 (3H, t, *J* 7.5, H4'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5 (C=S), 173.5 (C=O), 156.9 (C), 139.7 (C), 136.7 (C), 131.0 (C), 130.2 (CH), 125.9 (C), 122.8 (CH), 120.2 (CH), 120.1 (CH), 118.3 (CH), 116.2 (CH), 115.5 (CH), 111.3 (CH), 107.0 (C), 55.8 (CH), 55.1 (CH), 41.4 (CH_2), 29.8 (CH_2), 23.8 (CH_2), 20.0 (CH_2), 13.7 (CH_3); LRMS (ES^+) *m/z* 406 $[M+H]^+$; $[\alpha]_D^{20}$ = -216 (*c* = 0.1, DCM).

(5*S*,11a*R*)-2-Butyl-5-(3-hydroxyphenyl)-3-thioxo-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1-on *trans* (8b) Yield 50%, yellow solid. m.p. 57-59ºC; ν_{max} (KBr) 3398 (m), 1726 (m), 1599(w), 1459 cm^{-1} (s); ^1H NMR (500 MHz, DMSO-d_6) δ 11.04 (1H, s, NH), 9.51 (1H, s, OH), 7.56 (1H, d, *J* 8.0, H10), 7.31 (1H, d, *J* 8.0, H7), 7.17 (1H, dd, *J* 8.0, 8.0, H5''), 7.13-7.10 (1H, m, H8), 7.06-7.03 (1H, m, H9), 6.92-6.90 (1H, m, H6''), 6.87-6.86 (1H, m, H2''), 6.81 (1H, s, H5), 6.74-6.72 (1H, m, H4''), 4.79 (1H, dd, *J* 10.5, 6.0, H11a), 3.79-3.69 (2H, m, H1'), 3.47 (1H, dd, *J* 15.0,

6.0, H11$_{syn}$), 2.94-2.89 (1H, m, H11$_{anti}$), 1.62-1.54 (2H, m, H2'), 1.32-1.25 (2H, m, H3'), 0.89 (3H, t, *J* 7.5, H4'); ^{13}C NMR (125 MHz, DMSO-d6) δ 180.6 (C=S), 173.4 (C=O), 156.1 (C), 139.8 (C), 136.7 (C), 130.6 (C), 130.4 (CH), 125.9 (C), 123.0 (CH), 121.0 (CH), 120.3 (CH), 118.5 (CH), 116.2 (CH), 115.5 (CH), 111.3 (CH), 107.5 (C), 55.7 (CH), 55.0 (CH), 41.5 (CH_2), 29.8 (CH_2), 23.8 (CH_2), 20.1 (CH_2), 13.7 (CH_3); LRMS (ES$^+$) *m/z* 406 [M+H]$^+$; $[\alpha]_D^{20}$ = +216 (*c* = 0.1, DCM).

(5*R*,11a*S*)-2-Butyl-5-(3-methoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9i)

Diethyl azidocarboxylate (60.16 μL, 0.38 mmol) was added dropwise to a solution of triphenylphosphine (101 mg, 0.38 mmol) in anhydrous THF (10 mL) and stirred for 30 minutes. A solution of **7a** (100 mg, 0.25 mmol) and anhydrous MeOH (104.1 μL, 2.5 mmol) in anhydrous THF (10 mL) was added, and the mixture stirred for 48 hrs. The solvent was reduced, and the residue partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organics were dried over Na_2SO_4 and reduced. Purification of the residue by chromatography on silica gel (EtOAc:Hex 1:9) afforded **9i** as a white solid (85 mg, 0.21 mmol, 85 %). m.p. 115.1-115.5 ºC; ν_{max} (KBr) 2960, 1713, 1490, 1222 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* 7.8, H10), 7.25-7.07 (4H, 4H, H8, 9, 5", 7), 6.87-6.78 (3H, m, H4", 2", 6"), 6.19 (1H, s, H5), 4.25 (1H, dd, *J* 11.0, 5.58, H11a), 3.69 (3H, s, H8"), 3.52-3.38 (3H, m, H1', H11$_{syn}$), 2.81 (1H, dd, *J* 15.4, 11.0, H11$_{anti}$), 1.56-1.49 (2H, m, H2'), 1.29-1.21 (2H, m, H3'), 0.88 (3H, t, *J* 7.6, H4'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C=O), 160.2 (C), 155.0 (C=O), 140.7 (C), 136.6 (C), 130.2 (CH), 130.4 (C), 126.2 (C), 122.9 (CH), 120.3 (CH), 120.2 (CH), 118.4 (CH), 114.1 (CH), 114.0 (CH), 111.2 (CH), 108.1 (C), 55.3 (CH_3), 53.4 (CH), 51.9 (CH), 38.6 (CH_2), 30.2 (CH_2), 23.5 (CH_2), 20.0 (CH_2), 13.6 (CH_3); LRMS (ES$^+$) *m/z*: 404.31 [M+H]$^+$; HRMS (ES$^+$) [M+H]$^+$ m/z expected for $C_{24}H_{26}N_3O_3$ 404.1896 obtained 404.1906; $[\alpha]_D^{20}$ = -207.5 (*c* = 0.00342, DCM).

Diamino PEG Linker (16)

To a solution of **18** (1.17 g, 3.07 mmol) in anhydrous DCM (15 mL) at 0 ºC was added DIPEA (1.10 mL, 6.13 mmol) and methane sulfonyl chloride (0.31 mL, 3.98 mmol). After stirring at 0 ºC for 20 minutes, the reaction mixture was allowed to

warm to room temperature and stirred overnight. The mixture was washed with H_2O (30 mL), sat $NaHCO_3$ (30 mL), dried (Na_2SO_4) and reduced *in vacuo*. Purification of the residue by chromatography on silica gel (DCM:MeOH 97:3) afforded the mesylate as a yellow oil (1.18g, 2.30 mmol, 75%). ν_{max} (Nujol) 2873, 1700, 1517, 1391, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (2H, t, *J* 4.6, CH_2-OH), 3.76-3.59 (20H, m, CH_2-O), 3.48-3.33 range (2H, m, CH_2-NH), 2.93 (3H, s, CH_3-S), 1.45 (9H, s, $(CH_3)C$); ^{13}C NMR (75 MHz $CDCl_3$), δ 157.5 (C=O), 70.6 (C), 71.5-62.2 (CH_2 x10), 45.3 (CH_2), 33.9 (CH_3), 28.7 (CH_3); LRMS (ES^+) *m/z*: 460.35 $[M+H]^+$.

The above mesylate (1.12 g, 2.18 mmol) and sodium azide (0.24 g, 3.27 mmol) were dissolved in anhydrous DMF (20 mL) and heated at 110°C for 4 h. Upon cooling the solvent was reduced *in vacuo*. Purification of the residue by chromatography on silica gel (DCM: MeOH 97: 3) afforded the azide as a yellow oil (0.76 g, 1.94 mmol, 89%). ν_{max} (Nujol) 2922, 2113, 1720, 1301, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79-3.61 (20H, m, CH_2-O), 3.42 (2H, t, *J* 7.3, CH_2-N_3), 3.45-3.33 (2H, m, CH_2-NH), 1.45 (9H, s, $(CH_3)C$); ^{13}C NMR (75 MHz $CDCl_3$) δ 157.5 (C=O), 71.4-70.0 (CH_2 x10), 70.5 (C), 50.7 (CH_2), 40.4 (CH_2), 28.4 (CH_3); LRMS (ES^+) *m/z*: 429.32 $[M+Na]^+$.

The azide (0.70 g 1.7 mmol) was dissolved in anhydrous THF (5 mL) and cooled to 0°C, PS-PPh_3 (2g, 1.83 mmol/g) was added and mixture was allowed to warm to room temperature overnight. H_2O (0.5 mL) was added into mixture stirred for 4 hours. The reaction was filtered and the solvent was reduced *in vacuo* to afford the desired product without the need for purification (0.64 g, 1.6 mmol, 99%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.72-3.50 (20H, m, (CH_2)x10), 3.43 (2H, t, *J* 8.0, CH_2-OH), 2.82 (2H, t, *J* 7.5, CH_2-NH), 1.45 (9H, s, $(CH_3)C$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5 (C=O), 71.4-70.0 (CH_2 x10), 70.5 (C) 41.78 (CH_2), 40.33 (CH_2), 28.41 (CH_3); LRMS (ES^+) *m/z*: 381.29 $[M+H]^+$.

- Unknown enantiomers synthesised using well established literature route.

(5*R*,11a*R*)-2-Butyl-5-(4-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (6c) Yield 74%, white solid. m.p. 272-273ºC; ν_{max} (KBr) 3401 (m), 2960 (w), 1765 (m), 1699 (s), 1454 cm^{-1} (m); ^1H NMR (300 MHz, DMSO-d_6) δ 10.67 (1H, s, NH), 9.33 (1H, s, OH), 7.53 (1H, d, *J* 7.1, H10), 7.22 (1H, d, *J* 7.3, H7), 7.11-6.96 (4H, m, H8, H9, H2''), 6.67-6.64 (2H, AA′BB′, H3''), 5.76 (1H, s, H5), 4.52 (1H, dd, *J* 11.4, 4.3, H11a), 3.33-3.27 (3H, m, $H11_{syn}$ &

H1'), 3.00-2.91 (1H, m, H11^{anti}), 1.52-1.42 (2H, m, H2'), 1.31-1.18 (2H, m, H3'), 0.86 (3H, t, *J* 7.2, H4'); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7 (C=O), 156.7 (C), 154.0 (C=O), 136.6 (C), 135.2 (C), 130.9 (C), 128.6 (CH), 125.9 (C), 121.2 (CH), 118.7 (CH), 118.1 (CH), 114.9 (CH), 111.2 (CH), 104.8 (C), 57.6 (CH), 55.3 (CH), 37.3 (CH_2), 29.6 (CH_2), 21.8 (CH_2), 19.3 (CH_2), 13.5 (CH_3); LRMS (ES$^+$) *m/z* 390 $[M+H]^+$; $[\alpha]_D^{20}$ = +54 (*c* = 0.1, MeOH).

(5*S*,11a*S*)-2-Butyl-5-(4-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (6d) Yield 64%, white solid. m.p. 274-275ºC; ν_{max} (KBr) 3324 (m), 2957 (w), 1760 (m), 1694 (s), 1458 cm^{-1} (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.68 (1H, s, NH), 9.34 (1H, s, OH), 7.53 (1H, d, *J* 7.5, H10), 7.23 (1H, d, *J* 8.0, H7), 7.11-7.09 (2H, AA´BB´, H2''), 7.06-7.03 (1H, m, H8), 7.01-6.98 (1H, m, H9), 6.68-6.65 (2H, AA´BB´, H3''), 5.77 (1H, s, H5), 4.53 (1H, dd, *J* 11.5, 4.5, H11a), 3.38-3.29 (3H, m, H11$_{syn}$ & H1'), 2.99-2.93 (1H, m, H11$_{anti}$), 1.50-1.44 (2H, m, H2'), 1.29-1.21 (2H, m, H3'), 0.87 (3H, t, *J* 7.0, H4'); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.8 (C=O), 156.8 (C), 154.1 (C=O), 136.7 (C), 135.3 (C), 130.9 (C), 128.7 (CH), 126.0 (C), 121.3 (CH), 118.8 (CH), 118.2 (CH), 115.0 (CH), 111.3 (CH), 104.9 (C), 57.7 (CH), 53.4 (CH), 37.4 (CH_2), 29.7 (CH_2), 21.9 (CH_2), 19.4 (CH_2), 13.6 (CH_3); LRMS (ES$^+$) *m/z* 296 (10) $[M-C_6H_5O]^+$, 390 (100) $[M+H]^+$; $[\alpha]_D^{20}$ = -54 (*c* = 0.1, MeOH).

(5*R*,11a*S*)-2-Butyl-5-(4-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (7c) Yield 53%, off-white solid. m.p. 145-146ºC; ν_{max} (KBr) 3399 (m), 2958 (w), 1762 (m), 1700 (s), 1457 cm^{-1} (s); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (1H, s, NH), 9.52 (1H, s, OH), 7.54 (1H, d, *J* 8.0, H10), 7.29 (1H, d, *J* 8.0, H7), 7.15-7.13 (2H, AA´BB´, H2''), 7.11-7.08 (1H, m, H8), 7.04-7.01 (1H, m, H9), 6.76-6.74 (2H, AA´BB´, H3''), 6.12 (1H, s, H5), 4.53 (1H, dd, *J* 11.0, 5.5, H11a), 3.44-3.38 (3H, m, H11$_{syn}$ & H1'), 2.81-2.76 (1H, m, H11$_{anti}$), 1.53-1.48 (2H, m, H2'), 1.29-1.21 (2H, m, H3), 0.87 (3H, t, *J* 7.3, H4); ^{13}C NMR (125 MHz, DMSO-d6) δ 172.7 (C=O), 157.3 (C), 154.1 (C=O), 136.6 (C), 131.7 (C), 130.5 (C), 129.1 (CH), 125.8 (C), 121.6 (CH), 118.7 (CH), 118.1 (CH), 115.3 (CH), 111.3 (CH), 105.8 (C), 52.6 (CH), 51.0 (CH), 37.6 (CH_2), 29.6 (CH_2), 22.8 (CH_2), 19.4 (CH_2), 13.5 (CH_3); LRMS (ES$^+$) *m/z*: 412.11 $[M+Na]^+$; HRMS (ES$^+$) $[M+Na]^+$ m/z expected for $C_{23}H_{23}N_3O_3Na$ 412.1637 found 412.1637; $[\alpha]_D^{20}$ = -207 (*c* = 0.2, DCM).

(5*S*,11a*R*)-2-Butyl-5-(4-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (7d) Yield 77%, white solid. m.p. 142-143ºC; ν_{max} (KBr) 3344 (m), 2959 (w), 1761 (m), 1699 (s), 1457 cm^{-1} (s); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.89 (1H, s, NH), 9.52 (1H, s, OH), 7.54 (1H, d, *J* 8.0, H10), 7.29 (1H, d, *J* 8.0, H7), 7.15-7.13 (2H, AA´BB´, H2''), 7.11-7.08 (1H, m, H8), 7.04-7.01 (1H, m, H9), 6.76-6.73 (2H, AA´BB´, H3''), 6.13 (1H, s, H5), 4.53 (1H, dd, *J* 11.0, 5.5, H11a), 3.44-3.38 (3H, m, H11$_{syn}$ & H1'), 2.81-2.76 (1H, m, H11$_{anti}$), 1.54-1.48 (2H, m, H2'), 1.29-1.21 (2H, m, H3'), 0.89 (3H, t, *J* 7.0, H4'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (C=O), 156.5 (C), 155.1 (C=O), 136.7 (C), 131.0 (C), 130.7 (C), 129.6 (CH), 126.0 (C), 122.7 (CH), 120.0 (CH), 118.4 (CH), 116.0 (CH), 111.3 (CH), 107.6 (C), 53.2 (CH), 51.6 (CH), 38.7 (CH_2), 30.2 (CH_2), 23.3 (CH_2), 20.0 (CH_2), 13.6 (CH_3); LRMS (ES^+) *m/z*: 412.11 $[M+Na]^+$; HRMS (ES^+) $[M+Na]^+$ m/z expected for $C_{23}H_{23}N_3O_3Na$ 412.1637 found 412.1637; $[\alpha]_D^{20}$ = +207 (*c* = 0.2, DCM).

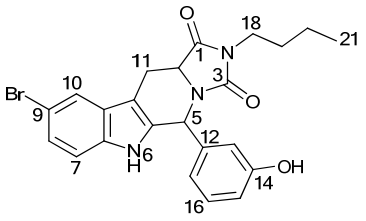
(5*R*,11a*S*)-2-Octyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (7k) Yield 87%, yellow solid. m.p. 93.5-95 ºC; ν_{max} (KBr) 3344 (m), 2927 (m), 1764 (m), 1699 (s), 1457 cm^{-1} (s); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.0 (1H, s, NH), 9.52 (1H, s, OH), 7.60 (1H, d, *J* 7.7, H10), 7.36 (1H, d, *J* 7.9, H7), 7.24-7.05 (3H, m, H8, H9, H5''), 6.84-6.77 (3H, m, H2', H4', H6'), 6.19 (1H, s, H4), 4.54 (1H, dd, *J* 10.8, 5.7, H11a), 3.47-3.40 (3H, m, H11$_{syn}$ & H1'), 2.89-2.81 (1H, m, H11$_{anti}$), 1.62-1.53 (2H, m, H2'), 1.32-1.24 (10H, m, H3'-H7'), 0.88 (3H, t, *J* 6.7, H8'); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5 (C=O), 157.6 (C), 154.2 (C=O), 141.3 (C), 136.6 (C), 131.1 (C), 129.7 (CH), 125.7 (C), 121.6 (CH), 118.8 (CH), 118.4 (CH), 118.1 (CH), 115.0 (CH), 114.7 (CH), 111.3 (CH), 105.9 (C), 52.7 (CH), 51.3 (CH), 37.9 (CH_2), 31.1 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 26.0 (CH_2), 22,7 (CH_2), 22.0 (CH_2), 13.9 (CH_3); LRMS (ES^+) *m/z* 446 $[M+H]^+$; $[\alpha]_D^{20}$ = -244 (*c* = 0.05, DCM).

(5*R*,11a*S*)-2-(3-Propionic acid ethyl ester)-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (7l) Yield 82%, yellow solid. m.p. 128-130 ºC; ν_{max} (KBr) 3398 (m), 1707 (s), 1458 cm^{-1} (m); ^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.06 (1H, s, NH), 9.59 (1H, s, OH), 7.66 (1H, d, *J*

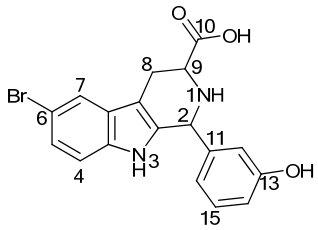
7.5, H10), 7.41 (1H, d, *J* 8.0, H7), 7.29-7.26 (1H, m, H5''), 7.22-7.19 (1H, m, H8), 7.15-7.12 (1H, m, H9), 6.69-6.82 (3H, m, H2'', H4'' & H6''), 6.23 (1H, s, H5), 4.59 (1H, dd, *J* 11, 5.5, H11a), 4.13-4.08 (2H, m, $OC\underline{H_2}CH_3$), 3.79-3.76 (2H, m, H1'), 3.5-3.48 (1H, m, $H11_{syn}$), 2.93 (1H, dd, *J* 14, 11, $H11_{anti}$), 2.73-2.70 (2H, m, H2'), 1.21 (3H, t, *J* 7.0, $OCH_2C\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (C=O), 171.2 (C=O), 156.6 (C), 154.6 (C=O), 140.5 (C), 136.6 (C), 130.3 (CH), 130.2 (C), 126.0 (C), 122.8 (CH), 120.0 (CH), 119.6 (CH), 118.4 (CH), 116.1 (CH), 115.3 (CH), 111.2 (CH), 107.6 (C), 61.0 (CH_2), 53.4 (CH), 52.0 (CH), 34.6 (CH_2), 32.5 (CH_2), 23.2 (CH_2), 14.0 (CH_3); LRMS (ES^+) *m/z*: 456.06 $[M+Na]^+$; HRMS (ES^+) $[M+Na]^+$ m/z expected for $C_{24}H_{23}N_3O_5Na$ 456.1535 found 456.1535; $[\alpha]_D^{20}$ = -94 (*c* = 0.1, DCM).

Synthesis of C9-substituted analogues 7e-7j

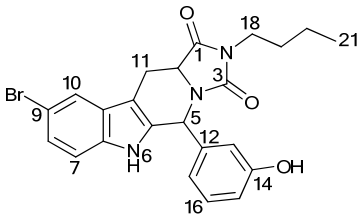
Synthesis of 7e via S1 and S2



7e



S1



S2

To a suspension of DL-5-bromotryptophan (**5c)** (1.02 g, 3.60 mmol) in 0.1 M H_2SO_4 (10 ml) was added 3-hydroxybenzaldehyde (0.88 g, 7.20 mmol). The mixture was heated at reflux for 6 hours, cooled to ambient temperature at which point a solid crashed out. The solid was collected by filtration and then washed with water (3 x 25ml) and ether (4 x 50 ml) to give the carboxylic acid **S1** as a white solid (1.08 g, 77%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.68 (s, 1H, H7), 7.12-7.33 (m, 3H, H5, H4, H15), 6.89 (d, 1H, H16, ^3J= 7.5) 6.72-6.85 (m, 2H, H14, H12), 5.32 (s, 1H, H2), 3.80 (dd, 1H, H9, ^3J= 4.0, 12.5), 3.11 (dd, 1H, H8*syn*, ^3J= 13.5, 4.0), 2.86 (dd, 1H, H8*anti*, ^3J= 13.5, 12.5). 13C NMR (100 MHz, $(CD_3)_2SO$), δ 172.4(C10), 157.4(C13), 140.9(C11), 135.5(C2a), 135.1(C3a), 129.3(C15), 128.1(C7a), 120.1(C7), 119.7(C16), 115.8(C12), 115.5(C4), 115.3(C14), 113.2(C5), 111.1(C6), 107.5(C7b), 57.5(C2), 56.6(C9), 24.4(C8); LRMS *m/z*, ES- 385.15 (100%) $[M-H]^-$. To a suspension of **s1** (1.05 g, 2.70 mmol) in anhydrous DMSO (4 ml) was added *n*-

butylisocyanate (0.268 g, 2.70 mmol) and anhydrous acetone (10 ml). The mixture was heated to reflux for 4 hours before cooling. Solvent was removed *in vacuo* to give an orange that was purified by column chromatography (eluting with EtOAc: petrol ether 30-100%) to give ***cis*-S2** as an off white solid (0.820 g, 65%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.98 (s, 1H, NH), 9.35 (s, 1H, OH), 7.79 (s, 1H, H10), 7.24 (d, 1H, H7, ^3J= 8.5), 7.11 (dd, 1H, H16, ^3J= 7.50, 8.0), 6.80 (d, 1H, H17, ^3J= 7.5), 6.73 (s, 1H, H13), 6.67 (d, 1H, H15, ^3J= 8.0), 5.80 (s, 1H, H5), 4.56 (dd, 1H, H11a, ^3J= 4.5, 11.5), 3.32-3.48 (m, 3H, H18, H11*syn*), 2,95 (m, 1H, H11*anti*), 1,46-1.56 (m, 2H, H19), 1.23-1.34 (m, 2H, H20), 0.90 (t, 3H, H21, ^3J= 7.5). 13C NMR (100 MHz, $(CD_3)_2SO$), δ 171.5(C1), 157.2(C14), 154.0(C3), 141.7(C12), 136.4(C6a), 135.3(C5a), 129.2(C16), 127.6(C10a), 123.8(C7), 120.6(C10), 118.0(C15), 114.5(C17), 114.1(C13), 113.2(C8), 111.4(C9), 104.8(C10b), 57.3(C11a), 55.5(C5), 37.4(C18), 29.6(C19), 29.6(C19), 21.7(C11), 19.3(C20), 13.4(C21), *m/z*, ES- 466.44 (100%) $[M-H]^-$. K_2CO_3 (0.117 g, 0.85 mmol) and ***cis*-S2** (0.263 g, 0.56 mmol) were then suspended in anhydrous MeCN (3 ml) and refluxed under N_2 for 4 hrs. The crude reaction mixture was filtered and the solvent removed *in vacuo* to give a yellow solid. This solid was purified by column chromatography (eluting with EtOAc: petrol ether 30-100%) to yield the desired product **7e** as a pale yellow solid (0.261 g, 0.56 mmol, 99%). m.p: 236-237 ºC (dec). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.20 (s, 1H, H6), 9.53 (s, 1H, OH), 7.80 (s, 1H, H10), 7.30 (d, 1H, ^3J= 8.5, H7), 7.24 (d, 1H, ^3J= 8.5, H8), 7.20 (m, 1H, H16), 6.74-6.80 (m, 3H, H15, H13, H17), 6.18 (s, 1H, H5), 4.53 (dd, 1H, ^3J= 5.5, 15.5, H11a), 3.40-3.47 (m, 3H, H18, H11*syn*), 2.80 (dd, 1H, H11*anti*), 1.54 (m, 2H, H19), 1.29 (m, 2H, H10), 0.90 (t, 3H, ^3J= 7.5, H21). ^{13}C NMR (100 MHz, $(CD_3)_2SO$), δ 172.4 (C1), 157.6(C14), 154.2(C3), 141.1(C12), 135.3(C6a), 132.9(C5a), 129.8(C16), 127.5(C10a), 124.1(C15), 120.6(C10), 118.3(C17), 115.1(C13), 114.7(C7), 113.3(C8), 111.4(C9), 105.9(C10b), 52.6(C11a), 51.2(C5), 37.6(C18), 29.6(C19), 22.5(C11), 19.3(C2). 13.4(C21), *m/z*, ES- 466.01 (100%) $[M-1]^-$.

Conversion of 7e to 7g-7j

General procedure for Suzuki coupling: sodium carbonate (0.048 g, 0.45 mmol), the required boronic acid (0.23 mmol) and $Pd(PPh_3)_4$ (0.012 g, 7 mol%) were added to a sealed tube under argon. Water (1ml) was added, followed by **7e** (0.070 g, 0.15mmol) as a solution in DME (3ml). The reaction mixture was then heated at 70 ºC for 24 hrs. The crude reaction mixture was concentrated *in vacuo* and the residue filtered through a silica column (eluting with 40% EtOAc/petrol ester) to yield the desired compound **7g-7j**.

7g (0.039 g, 55%). Mp: 150 ºC (dec) ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.00 (s, 1H, H6), 9.52 (s, 1H, OH), 7.91 (s, 1H, H10), 7.76 (d, 2H, ^3J= 8.5, H24), 7.53 (d, 2H, ^3J= 8.5, H23), 7.40-7.47 (m, 2H, H7, H8), 7.19-7.24 (m, 1H, H16), 6.74-6.85 (m, 3H, H15, H13, H17), 6.19 (s, 1H, H5), 4.54 (dd, 1H, ^3J= 5.5, 11.0, H11a), 3.43-3.53 (m, 3H, H18, H11*syn*), 2.86 (dd, 1H, ^3J= 5.5, 15.5, H11*anti*), 1.54 (m, 2H, H19), 1.29 (m, 2H, H20), 0.90 (t, 3H, ^3J= 7.5, H21). ^{13}C NMR (100 MHz, $(CD_3)_2SO$), δ 172.5(C1), 157.6(C14), 154.2(C3), 141.2(C12), 140.5(C9), 136.4(C6a), 132.2(C5a), 131.0(C10a) 129.9(C22), 129.8(C16), 128.6(C24), 128.3(C23), 126.4(C25), 120.7(C15), 118.4(C17), 116.5(C13), 115.1(C10), 114.7(C8), 111.8(C7), 106.6(C10b), 52.6(C11a), 51.3(C5), 37.6(C18), 29.6(C19), 22.7(C11), 19.3(C20), 13.4(C21), *m/z*, ES- 498.13 (100%) $[M-1]^-$.

7h (0.029 g, 41%). m.p.: 135 ºC (dec). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.00 (s, 1H, H6), 9.52 (s, 1H, OH), 7.85 (s, 1H, H10), 7.62 (d, 2H, ^{3}J= 8.0, H23), 7.37-7.45 (m, 2H, H7, H8), 7.29 (d, 2H, ^{3}J= 8.0, H24), 7.21 (m, 1H, H16)), 6.73-6.85 (m, 3H, H13, H15, H17), 6.19 (s, 1H, H5), 4.54 (dd, 1H, ^{3}J= 5.5, 11.0, H11a), 3.40-3.53 (m, 3H, H18, H11*syn*), 2.86 (dd, 1H, ^{3}J= 5.5, 15.5, H11*anti*), 2.38 (s, 3H, H26), 1.54 (m, 2H, H19), 1.29 (m, 2H, H20), 0.90 (t, 3H, ^{3}J= 7.5, H21). ^{13}C NMR (100 MHz, $(CD_3)_2SO$), δ 172.5(C1), 157.6(C14), 154.2(C3), 141.3(C12), 138.8(C22), 136.1(C6a), 135.3(C25), 131.9(C5a), 131.3(C10a), 129.7(C24), 129.3(C16), 126.4(C23), 126.3(C9), 120.8(C15), 118.4(C17), 116.0(C10), 115.0(C13), 114.7(C8), 111.7(C7), 106.4(C10b), 52.6(C11a), 51.3(C5), 37.6(C18), 29.6(C19), 22.7(C11), 20.6(C26), 19.3(C20), 13.4(C21), *m/z*, ES- 478.18 (100%) $[M-1]^-$.

7i (21 mg, 84%) m.p.: 215 ºC (dec) ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.00 (s, 1H, H6), 9.52 (s, 1H, OH), 7.81 (s, 1H, H10), 7.65 (d, 2H, ^{3}J= 9.0, H24), 7.40 (m, 2H, H7, H8), 7.21 (m, 1H, H16), 7.05 (d, 2H, ^{3}J= 9.0, H23), 6.72-6.84 (m, 3H, H15, H13, H17), 6.18 (s, 1H, H5), 4.54 (dd, 1H, ^{3}J= 5.5, 11.0, H11a), 3.8 (s, 3H, H26), 3.43-3.53 (m, 3H, H18, H11*syn*), 2.86 (dd, 1H, ^{3}J= 15.5, 5.5, H11*anti*), 1.54 (m, 2H, H19), 1.29 (m, 2H, H20), 0.90 (t, 3H, ^{3}J= 7.5, H21). ^{13}C NMR (100 MHz, $(CD_3)_2SO$), δ 172.6(C1), 158.0(C25), 157.6(C14), 154.2(C3), 141.3(C12), 135.8(C6a), 134.1(C5a), 131.8(C16), 131.1(C10a), 129.7(C15), 127.6(C24), 126.3(C9), 120.7(C10), 118.4(C17), 115.8(C13), 115.0(C7), 114.7(C8), 114.2(C23), 111.6(C22), 106.4(C10b), 55.1(C26), 52.7(C11a), 51.3(C5), 37.6(C18), 29.6(C19), 22.7(C11), 19.3(C20), 13.4(C21), *m/z*, ES- 494.18 (100%) $[M-1]^-$.

7j (44mg, 63%) m.p.: 135 ºC (dec) ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.12 (s, 1H, H6), 9.52 (s, 1H, OH), 8.02 (m, 2H, H10, H23), 7.75 (d, 1H, ^{3}J= 8.5, H27), 7.72 (d, 1H, ^{3}J= 8.5, H26), 7.50 (d, 1H, ^{3}J= 9.0, H7), 7.42 (d, 1H, ^{3}J= 9.0, H8), 7.21 (m, 1H, H16), 6.74-6.85 (m, 3H, H15, H13, H17), 6.19 (s, 1H, H5), 4.54 (dd, 1H, ^{3}J= 5.5, 11.0, H11a), 3.40-3.53 (m, 3H, H18, H11*syn*), 2.86 (dd, 1H, ^{3}J= 5.5, 15.5, H11*anti*), 1.54 (m, 2H, H19), 1.29 (m, 2H, H20), 0.90 (t, 3H, ^{3}J= 7.5, H21). ^{13}C NMR (100 MHz, $(CD_3)_2SO$), δ 172.5(C1), 157.6(C14), 154.2(C3), 142.3(C12), 141.2(C9), 136.6(C6a), 132.3(C5a), 131.5(C10a), 130.8(C26), 129.8(C16), 128.7(C24), 128.4(C25), 128.1(C23), 126.6(C27), 126.4(C22), 120.7(C15), 118.4(C17), 116.9(C13), 115.1(C10), 114.7(C7), 111.9(C8), 106.8(C10b), 52.6(C11a), 51.30(C5), 37.6(C18), 29.6(C19), 22.8(C11), 19.3(C20), 13.4(C21), *m/z*, ES- 532.08 (100%) $[M-1]^-$.

Synthesis of analogues 9ii, 9iv, 9x-xvii

During the course of this work additional analogues of **9** were prepared. The spectroscopic analysis and biological data relating to these additional are given below (see Table S1). In addition spectroscopic analysis for compounds included in Table 2 of the paper but not discussed specifically in the text of the paper are included here to reduce the size of the experimental section.

Representative procedure for the alkylation of 7a

To a solution of **7a** (50 mg) in anyhdrous MeCN (2 mL) was added K_2CO_3 (27 mg) and alkyl bromide (1.05 eq). After stirring at 50 ºC for 48 hours, the reaction mixture diluted with water (3 mL). The aqueous layer was extracted with DCM (2 x 2 mL) and the combined extracts were dried and concentrated *in vacuo*. Purification of the residue by filtration through a plug of silica (EtOAc:Hex 1:9) afforded the desired product.

(5*R*, 11a*S*)-2-Butyl-5-(3-ethoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9ii) Yield 71%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s, NH), 7.56 (1H, d, *J* 7.5, H10), 7.31-7.15 (4H, m, H8, 9, 5", 7), 6.91 (1H, d, *J* 7.7, H6"), 6.88-6.85 (2H, m, H4", 2"), 6.26 (1H, d, *J* 1.3, H5), 4.32 (1H, dd, *J* 11.0, 5.5, H11a), 3.98 (2H, q, *J* 7.0, H8"), 3.57-3.48 (3H, m, H1', 11_{syn}), 2.88 (1H, ddd, *J* 15.3, 11.0, 1.8, $H11_{anti}$), 1.65-1.57 (2H, m, H2'), 1.39-1.30 (5H, m, H9", H3'), 0.92 (3H, t, *J* 7.4 Hz, H4'); LRMS (ES^+) *m/z*: 440.20 (100%) $[M+Na]^+$.

(5*R*, 11a*S*)-2-Butyl-5-(3-butoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9iv) Yield 89%, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, s, NH), 7.56 (1H, d, *J* 7.5, H10), 7.31-7.16 (4H, m, H8, 9, 5", 7), 6.91-6.86 (3H, m, H4", 2", 6"), 6.27 (1H, d, *J* 1.2, H5), 4.33 (1H, dd, *J* 11.1, 5.4, H11a), 3.88 (2H, t, *J* 6.5, H8"), 3.57-3.49 (3H, m, H1', 11_{syn}), 2.88 (1H, ddd, *J* 15.2, 11.1, 1.8, $H11_{anti}$), 1.81-1.73 (2H, m, H9"), 1.65-1.58 (2H, m, H2'), 1.38-1.28 (2H, m, H3'), 1.26-1.25 (2H, m, H12"), 1.00 (3H, t, *J* 7.5, H11"), 0.93 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 468.18 (100%) $[M+Na]^+$.

(5*R*,11a*S*)-2-Butyl-5-(3-(4-methoxy-benzyloxy)phenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9x) Yield 91%, yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (1H, s, NH), 7.55 (1H, d, *J* 7.5, H10), 7.28-7.14 (6H, m, H8, 9, 5", 7, 10"), 6.94-6.85 (5H, m, H6", 4", 2", 11"), 6.22 (1H, s, H5), 4.88 (2H, s, H8"), 4.23 (1H, dd, *J* 11.0, 5.5, H11a), 3.80 (3H, s, H14"), 3.57-3.42 (3H, m, H1', 11_{syn}), 2.86 (1H, ddd, *J* 15.3, 11.0, 1.8, $H11_{anti}$), 1.66-1.56 (2H, m, H2'), 1.40-1.26 (2H, m, H3'), 0.92 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 532.22 (100%) $[M+Na]^+$.

(5*R*,11a*S*)-2-Butyl-5-(3-(3,4-Dichloro-benzyloxy)phenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9xi) Yield 87%, yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, s, NH), 7.57 (1H, d, *J* 7.5, H10), 7.48 (1H, d, *J* 2.0, H10"), 7.39 (1H, d, *J* 8.2, H12"), 7.30-7.16 (5H, m, H8, 9, 5", 7, 13"), 6.95-6.89 (3H, m, H6", 4", 2"), 6.26 (1H, d, *J* 1.0, H5), 4.94 (2H, s, H8"), 4.28 (1H, dd, *J* 11.0, 5.5, H11a), 3.58-3.46 (3H, m, H1', 11_{syn}), 2.88 (1H, ddd, *J* 15.3, 11.0, 1.8, $H11_{anti}$), 1.66-1.55 (2H, m, H2'), 1.40-1.24 (2H, m, H3'), 0.93 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 570.13 $[M+Na]^+$.

(5*R*,11a*S*)-2-Butyl-5-(3-carbamoylmethoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9xii) Yield 55%, yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (1H, s, NH), 7.58 (1H, d, *J* 7.5, H10), 7.34-7.16 (4H, m, H8, 9, 5", 7), 7.01 (1H, d, *J* 7.9, H6"), 6.96-6.95 (1H, m, H2"), 6.86 (1H, dd, *J* 8.1, 2.5, H4"), 6.57-6.47 (1H, br s, NH), 6.29 (1H, d, *J* 1.4, H5), 5.72-5.59 (1H, br s, NH), 4.41 (2H, s, H8"), 4.30 (1H, dd, *J* 11.0, 5.5, H11a), 3.56-3.48 (3H, m, H1', 11_{syn}), 2.89 (1H, ddd, *J* 15.3, 11.0, 1.8, $H11_{anti}$), 1.66-1.56 (2H, m, H2'), 1.39-1.25 (2H, m, H3'), 0.92 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 469.18 (100%) $[M+Na]^+$.

(5*R*,11a*S*)-2-Butyl-5-(3-cyanomethoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9xiii) Yield 54%, yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, s, NH), 7.57 (1H, d, *J* 7.5, H10), 7.37-7.16 (4H, m, H8, 9, 5", 7), 7.06-6.95 (3H, m, H6", 4", 2"), 6.31 (1H, d, *J* 1.4, H5), 4.74 (2H, s, H8"), 4.30 (1H, dd, *J* 11.0, 5.5, H11a), 3.58-3.46 (3H, m, H1', 11_{syn}), 2.88 (1H, ddd, *J* 15.3, 11.0, 1.8, $H11_{anti}$), 1.66-1.56 (2H, m, H2'), 1.40-1.25 (2H, m, H3'), 0.93 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 451.18 (100%) $[M+Na]^+$.

(5*R*,11a*S*)-2-Butyl-5-(3-but-2-enyloxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9xiv) Yield 64%, yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, s, NH), 7.56 (1H, d, *J* 7.5, H10), 7.31-7.14 (4H, m, H8, 9, 5", 7), 6.92 (1H, d, *J* 7.7, H6"), 6.90-6.87 (2H, m, H4", 2"), 6.27 (1H, s, H5), 5.88-5.76 (1H, m, H10"), 5.71-5.61 (1H, m, H9"), 4.40 (2H, d, *J* 6.0, H8"), 4.31 (1H, dd, *J* 11.0, 5.5, H11a), 3.56-3.47 (3H, m, H1', 11_{syn}), 2.88 (1H, ddd, *J* 15.3, 11.0, 1.8 Hz, $H11_{anti}$), 1.72 (3H, dd, *J* 6.3, 1.3, H11"), 1.68-1.59 (2H, m, H2'), 1.40-1.27 (2H, m, H3'), 0.92 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 466.28 (100%) $[M+Na]^+$.

(5R,11aS,)-2-Butyl-5-(3-but-3-enyloxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9xv) Yield 72%, yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, s, NH), 7.55 (1H, d, *J* 7.5, H10), 7.28-7.13 (4H, m, H8, 9, 5", 7), 6.90-6.79 (3H, m, H6", 4", 2"), 6.23 (1H, d, *J* 1.3, H5), 5.88-5.78 (1H, m, H10"), 5.14-5.04 (2H, m, H11"), 4.30 (1H, dd, *J* 11.0, 5.5, H11a), 3.93 (2H, pseudo t, *J* 8.7, H8"), 3.53-3.43 (3H, m, H1', 11_{syn}), 2.88 (1H, ddd, *J* 15.3, 11.0, 1.8 Hz, $H11_{anti}$), 2.50-2.44 (2H, m, H9"), 1.65-1.55 (2H, m, H2'), 1.40-1.27 (2H, m, H3'), 0.92 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 466.21 (100%) $[M+Na]^+$.

(5*R*,11a*S*)-2-Butyl-5-(3-(3-Methyl-but-2-enyloxy)phenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9xvi) Yield 51%, yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, s, NH), 7.55 (1H, d, *J* 7.5, H10), 7.30-7.14 (4H, m, H8, 9, 5", 7), 6.95 (1H, d, *J* 7.7, H6"), 6.93-6.84 (2H, m, H4", 2"), 6.27 (1H, d, *J* 1.3, H5), 5.44-5.38 (1H, m, H9"), 4.45 (2H, d, *J* 6.8, H8"), 4.31 (1H, dd, *J* 11.0, 5.5, H11a), 3.56-3.46 (3H, m, H1', 11_{syn}), 2.88 (1H, ddd, *J* 15.3, 11.0, 1.8, $H11_{anti}$), 1.74 (3H, s, H11"), 1.67 (3H, s, H12"), 1.64-1.56 (2H, m, H2'), 1.40-1.25 (2H, m, H3'), 0.92 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 480.23 (100%) $[M+Na]^+$.

(5*R*,11a*S*)-2-Butyl-5-(3-cyclopentyloxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione (9xvii) Yield 72%, yellow oil, ^{1}H NMR (400 MHz, MeOD) δ 7.50 (1H, d, *J* = 7.7 Hz, H10), 7.25 (1H, d, *J* = 7.9 Hz, H7), 7.20 (1H, dd, *J* 7.9, H5'), 7.11-7.07 (1H, m, H9), 7.04-7.00 (1H, m, H8), 6.88-6.85 (1H, m, H6"), 6.82-6.78 (2H, m, H4", 2"), 6.23 (1H, s, H5), 4.74-4.70 (1H, m, H8"), 4.39 (1H, dd, *J* 11.1, 5.5, H11a), 3.49 (2H, t, *J* 7.2, H1'), 3.42 (1H, dd, *J* 15.1, 5.5, 11_{syn}), 2.79 (1H, ddd, *J* 15.1, 11.1, 1.7, $H11_{anti}$), 1.89-1.70 (6H, m, H9", H2'), 1.60-1.53 (4H, m, H10"), 1.35-1.26 (2H, m, H3'), 0.91 (3H, t, *J* 7.4, H4'); LRMS (ES^+) *m/z*: 480.23 (100%) $[M+Na]^+$.

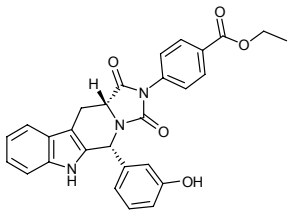
Entry #	Cpd #	C5	C11a	R^1	R^3	R^4	MIC (μM)
1	**9i**	*R*	*S*	OMe	^{n}Butyl	H	12.5
2	**9ii**	*R*	*S*	Oet	^{n}Butyl	H	6.25
3	**9iii**	*R*	*S*	O^{n}Pr	^{n}Butyl	H	12.5
4	**9iv**	*R*	*S*	O^{n}Bu	^{n}Butyl	H	6.25
5	**9v**	*R*	*S*	Oallyl	^{n}Butyl	H	12.5
6	**9vi**	*R*	*S*	O^{i}Pr	^{n}Butyl	H	1.6
7	**9vii**	*R*	*S*	$OCH_2C(CH_3)=CH_2$	^{n}Butyl	H	3.1
8	**9viii**	*R*	*S*	Opropargyl	^{n}Butyl	H	3.1
9	**9ix**	*R*	*S*	OBn	^{n}Butyl	H	12.5
10	**9x**	*R*	*S*	OCH_2*p*-C_6H_4-OMe	^{n}Butyl	H	100
11	**9xi**	*R*	*S*	OCH_2*m,p*-C_6H_3-Cl_2	^{n}Butyl	H	100
12	**9xii**	*R*	*S*	CH_2CONH_2	^{n}Butyl	H	25

13	**9xiii**	*R*	*S*	OCH_2CN	^{n}Butyl	H	6.25
14	**9xiv**	*R*	*S*	$OCH_2CH{=}CHCH_3$	^{n}Butyl	H	3.1
15	**9xv**	*R*	*S*	$OCH_2CH_2CH{=}CH_2$	^{n}Butyl	H	1.6
16	**9xvi**	*R*	*S*	$OCH_2CH{=}C(CH_3)_2$	^{n}Butyl	H	3.1
17	**9xvii**	*R*	*S*	O^{c}Pentyl	^{n}Butyl	H	1.6

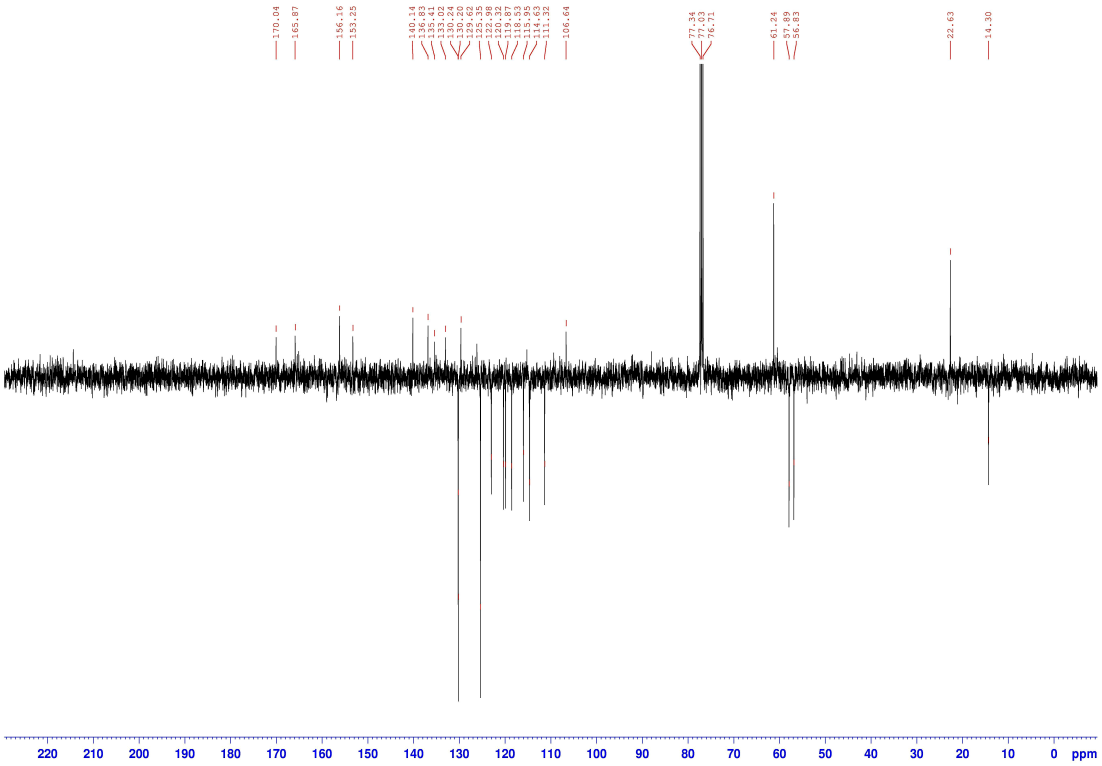
Table S1. Minimum inhibitory concentrations (MIC) in the *T. gondii* cell invasion assay for analogues of **1**.

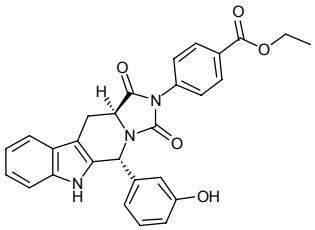
References

S1 Baker K.; Sengupta D.; Salazar-Jimenez G.; Cornish V.W. *Anal Biochem.* **2003**, *315(1)*, 124-137



7m, before epimerisation

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O
O
H
N
N
O
N
H
OH

7m

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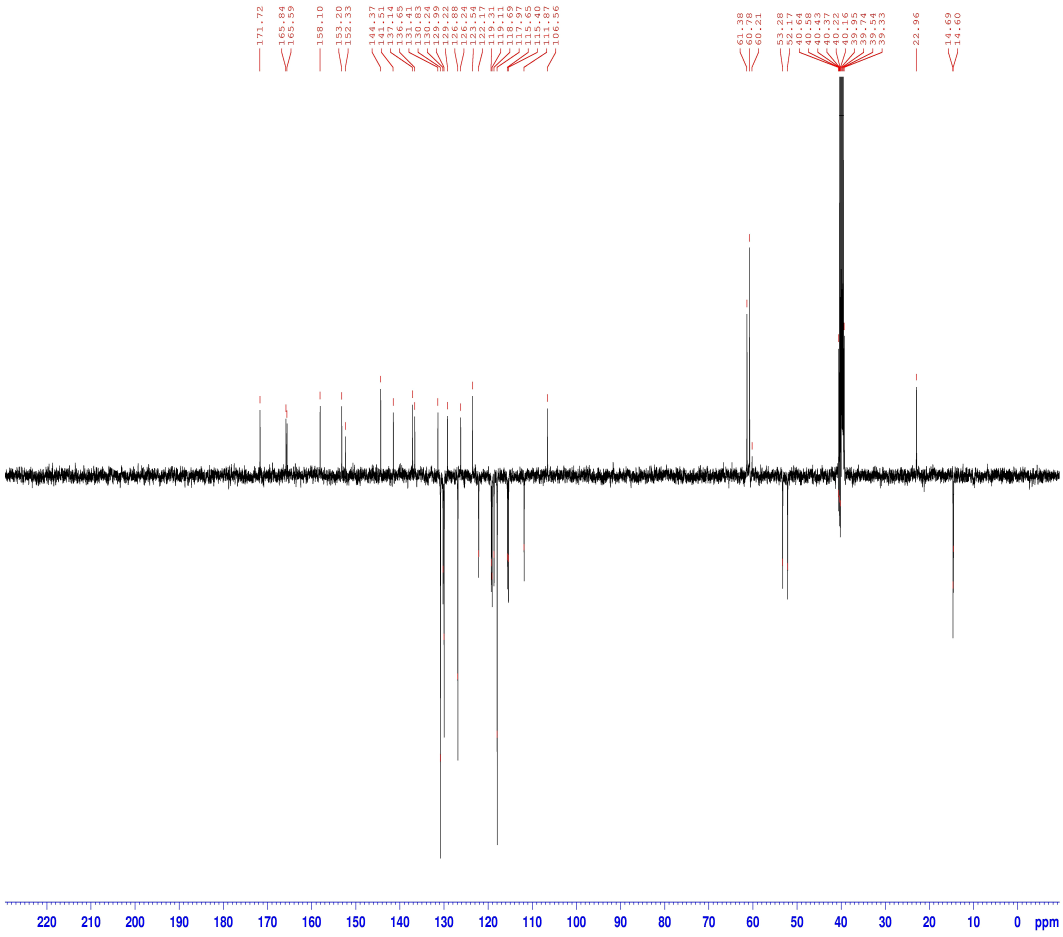
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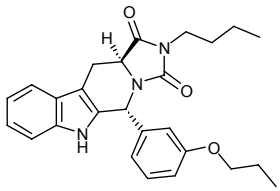
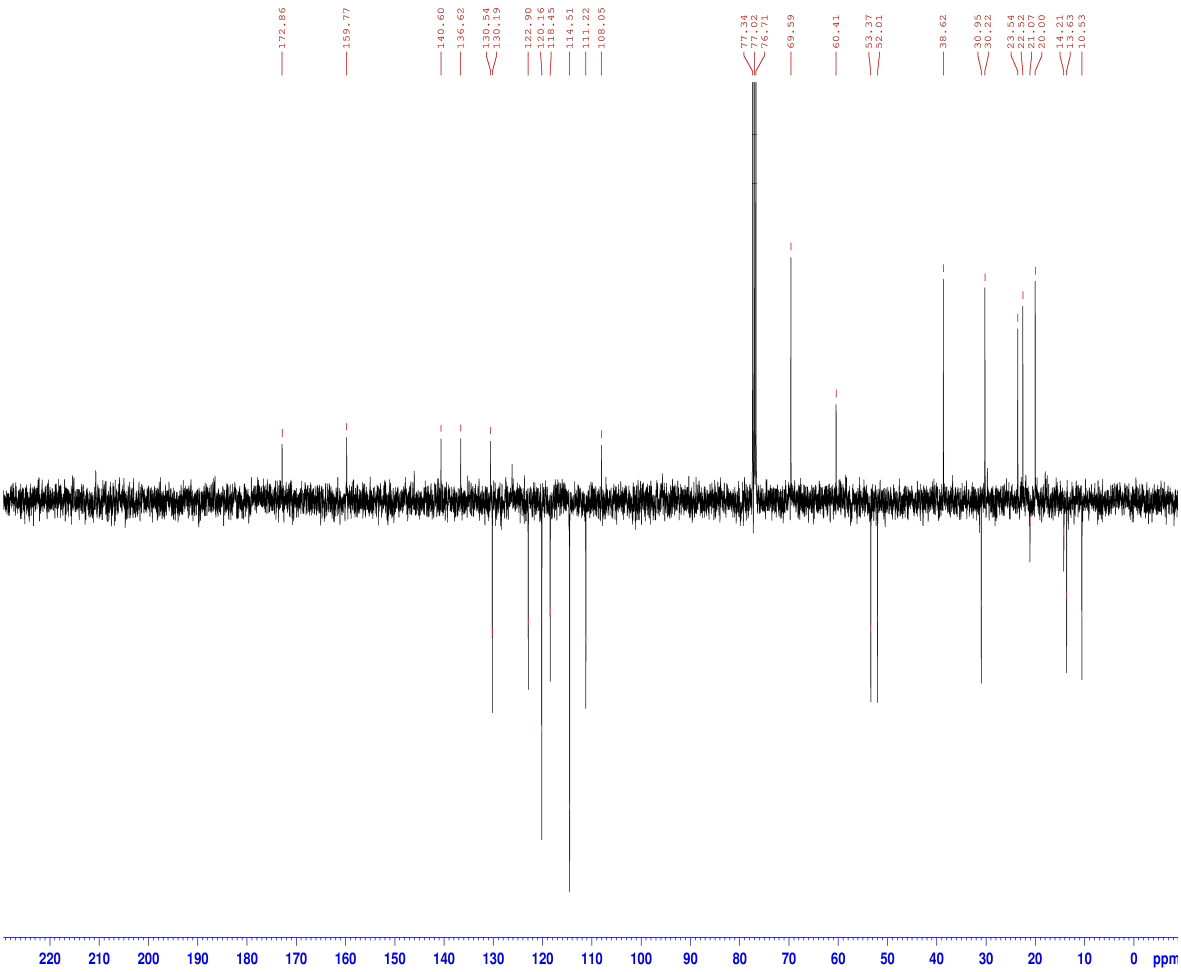
129.99
129.28
128.80
126.24
123.57
123.17
119.31
118.71
118.69
117.97
115.65
115.40
111.87
106.56
61.38
61.08
60.21
53.28
52.17
40.64
40.48
40.43
40.37
40.22
40.16
39.95
39.74
39.54
39.33
22.96
14.69
14.60
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



9ii

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm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159.77
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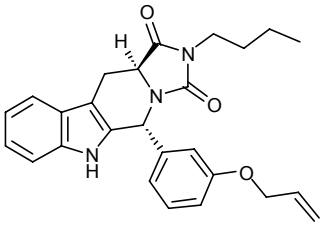
130.54
130.19
122.90
120.16
118.45
114.51
111.22
108.05
77.34
77.02
76.71
69.59
60.41
53.37
52.01
38.62
30.95
30.22
23.54
22.52
21.07
20.00
14.21
13.63
10.53
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



9v

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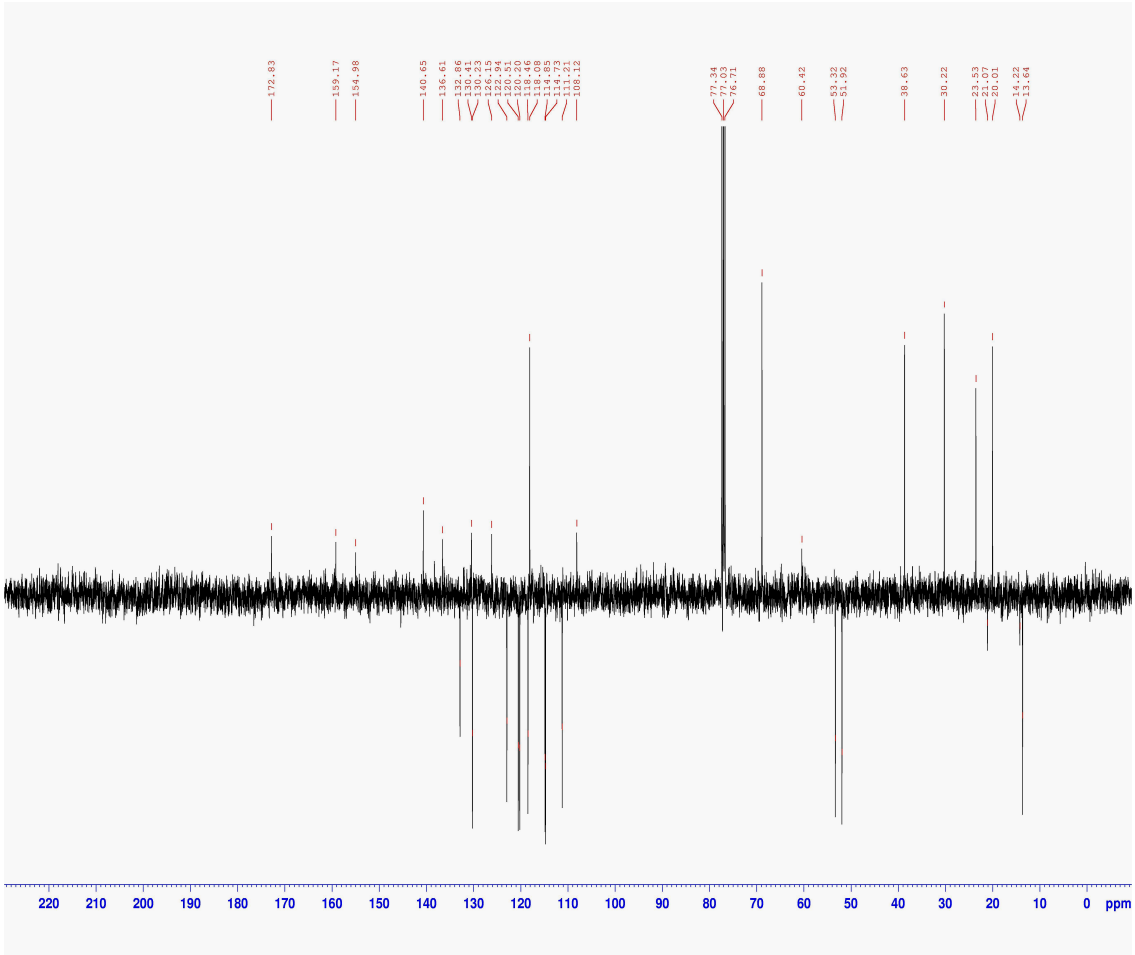
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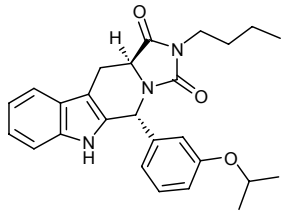
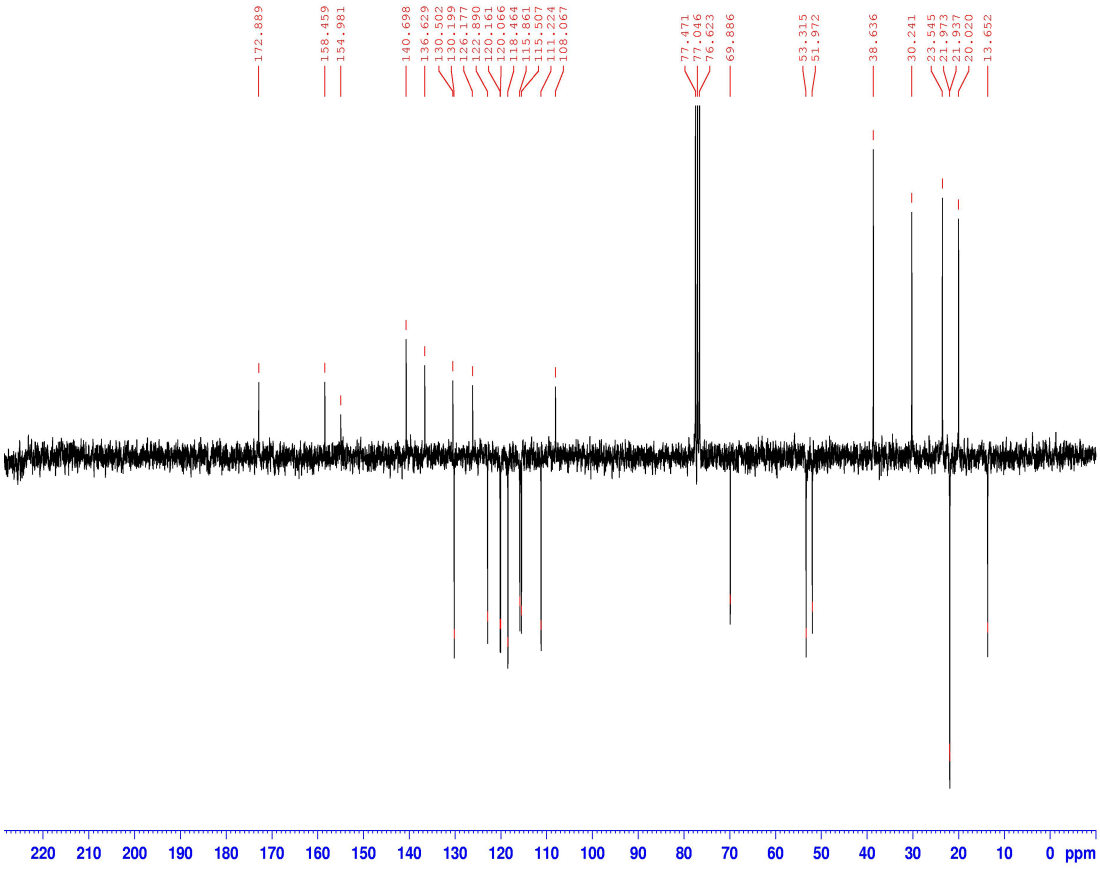
118.08
114.85
114.73
111.21
108.12
77.34
77.03
76.71
68.88
60.42
53.32
51.92
38.63
30.22
23.53
21.07
20.01
14.22
13.64
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



9vi

12
11
10
9
8
7
6
5
4
3
2
1
0
ppm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118.464
115.861
115.507
111.224
108.067
77.471
77.046
76.623
69.886
53.315
51.972
38.636
30.241
23.545
21.973
21.937
20.020
13.652
220
210
200
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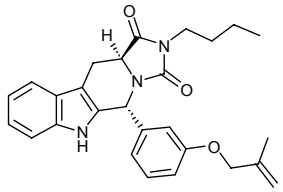
ppm



9vii

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8
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6
5
4
3
2
1
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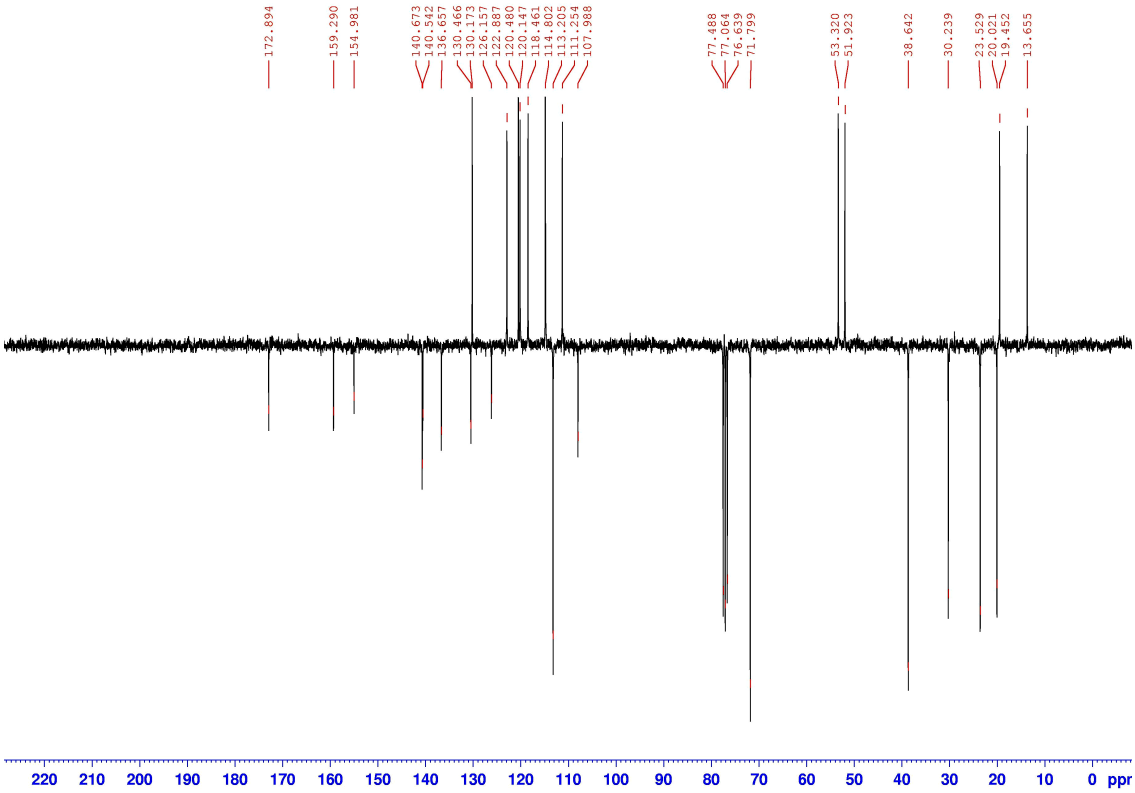
ppr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38.642
30.239
23.529
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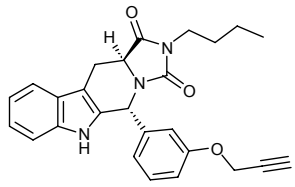

9viii

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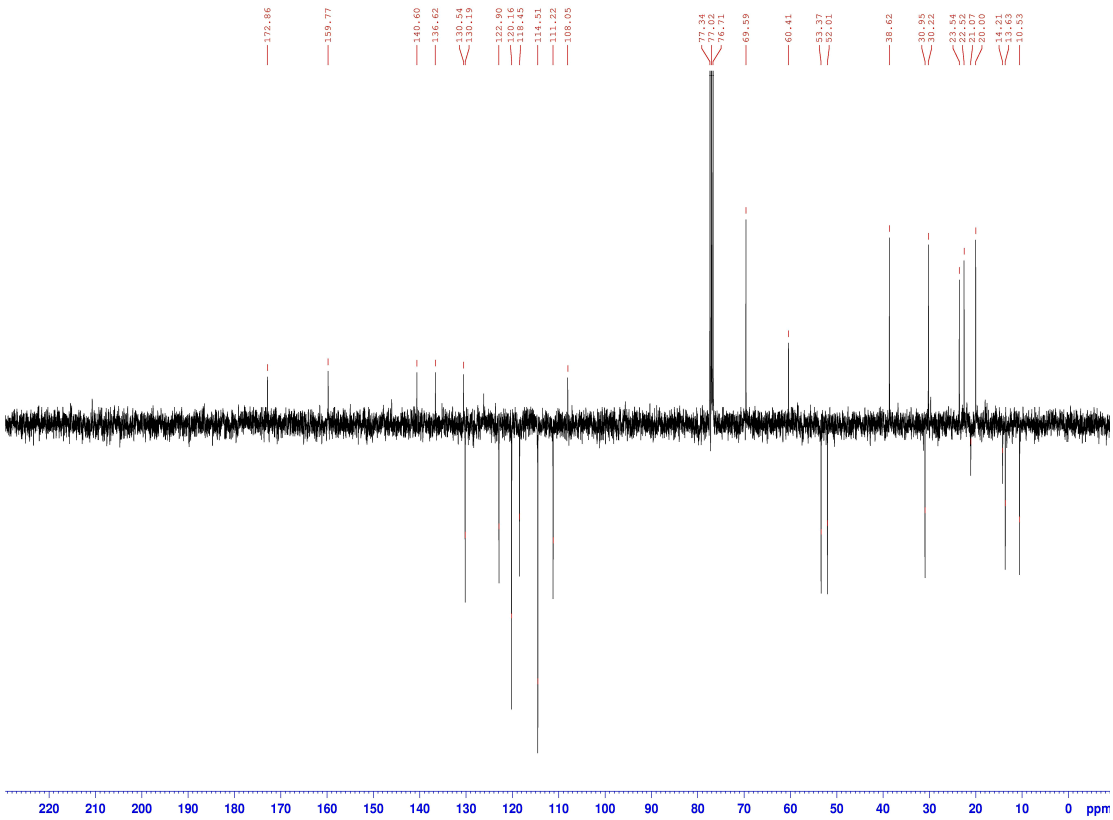
10
9
8
7
6
5
4
3
2
1
0
ppm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130.19
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114.51
111.22
108.05
77.34
77.02
76.71
69.59
60.41
53.37
52.01
38.62
30.95
30.22
23.54
22.52
21.07
20.00
14.21
13.63
10.53
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200
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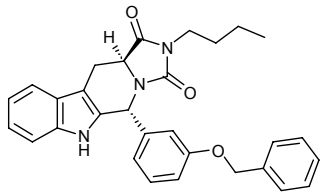
ppm



9ix

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8
7
6
5
4
3
2
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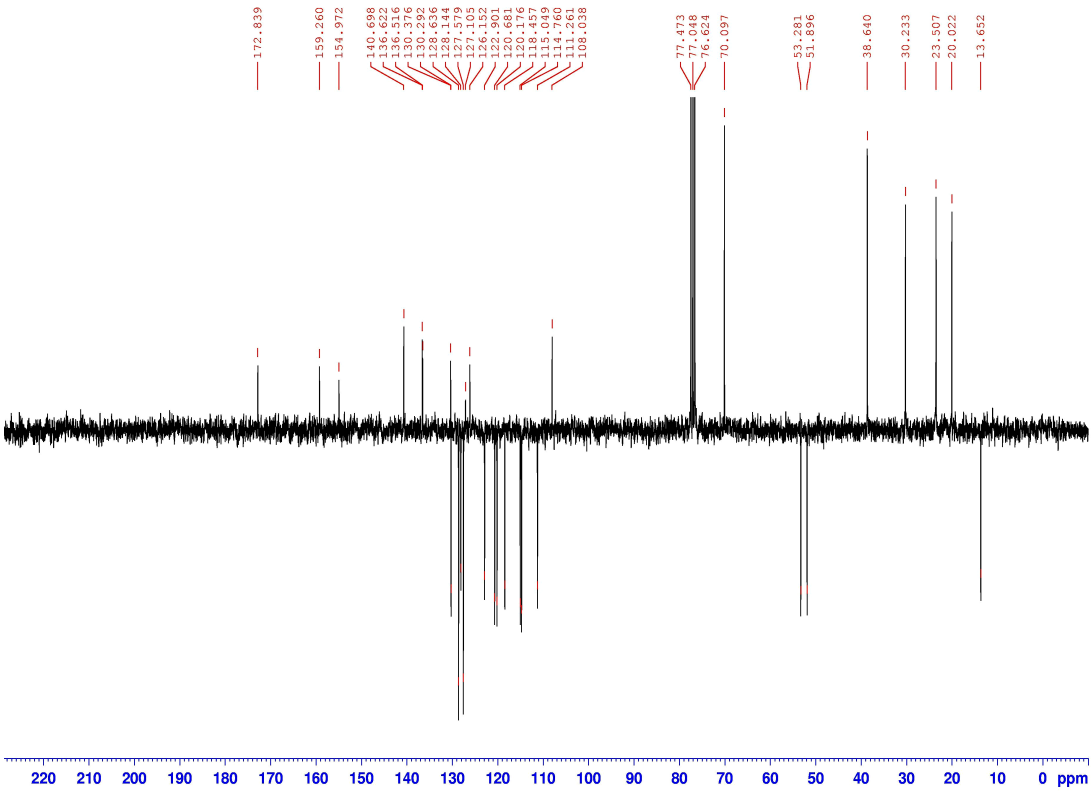
0
ppm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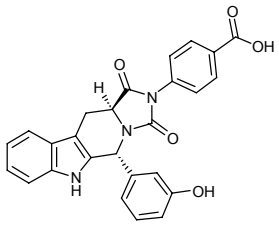
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OH
O
H
N
N
O
N
H
OH

19

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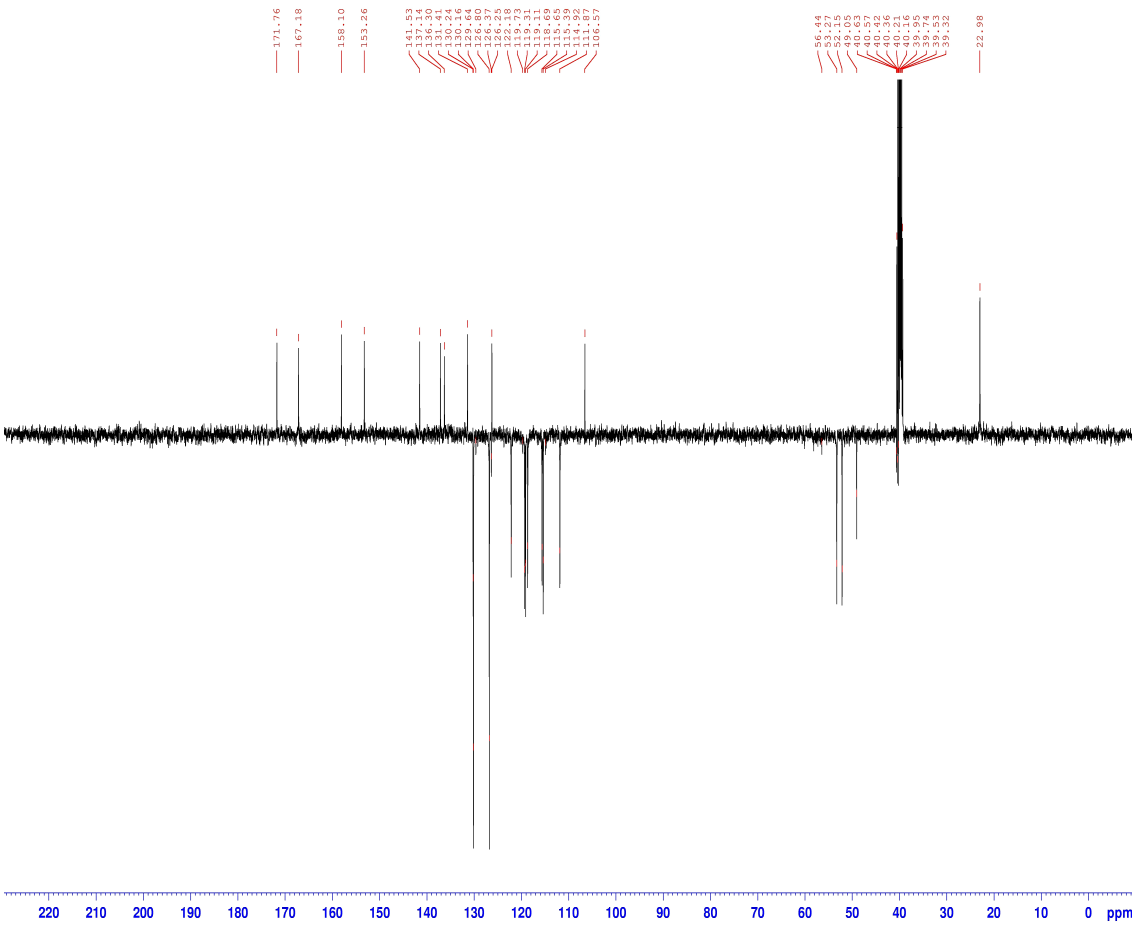
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106.57
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49.05
40.57
40.53
40.42
40.36
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39.32
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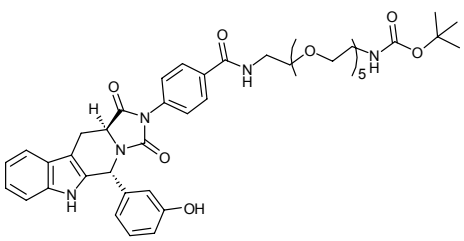

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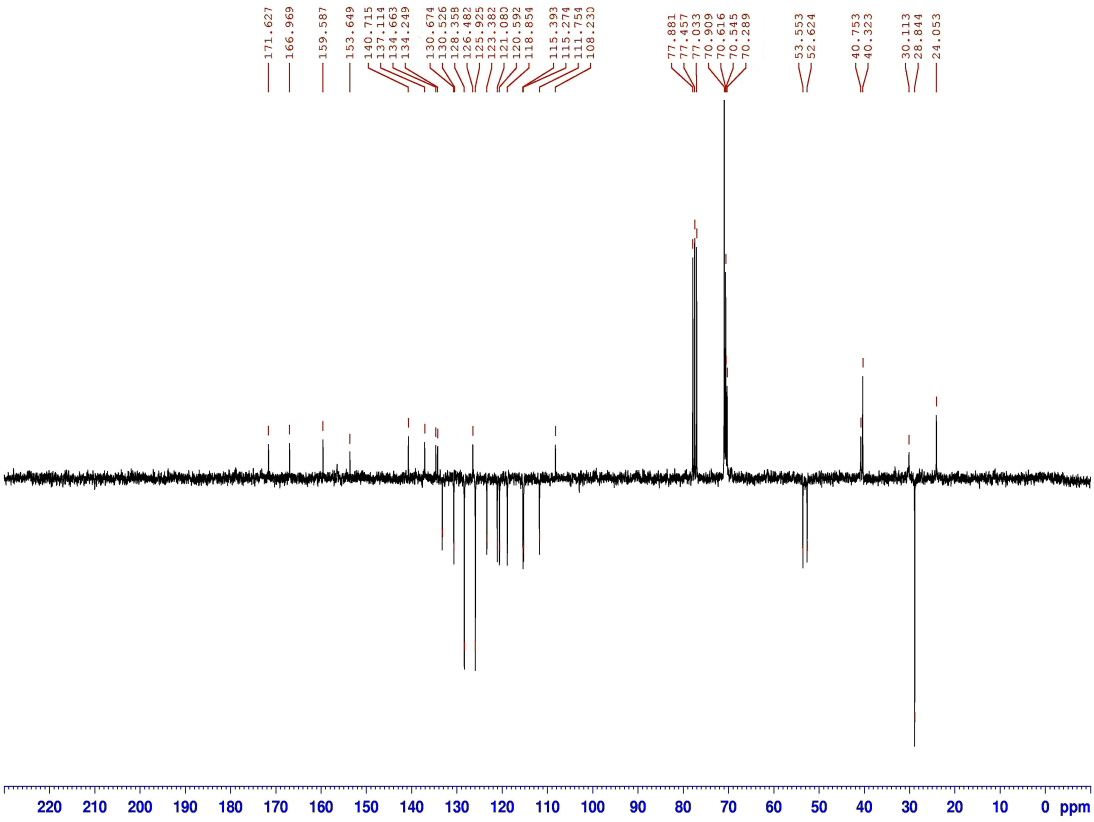
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123.332
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120.592
118.854
115.393
115.274
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77.033
70.909
70.616
70.545
70.289
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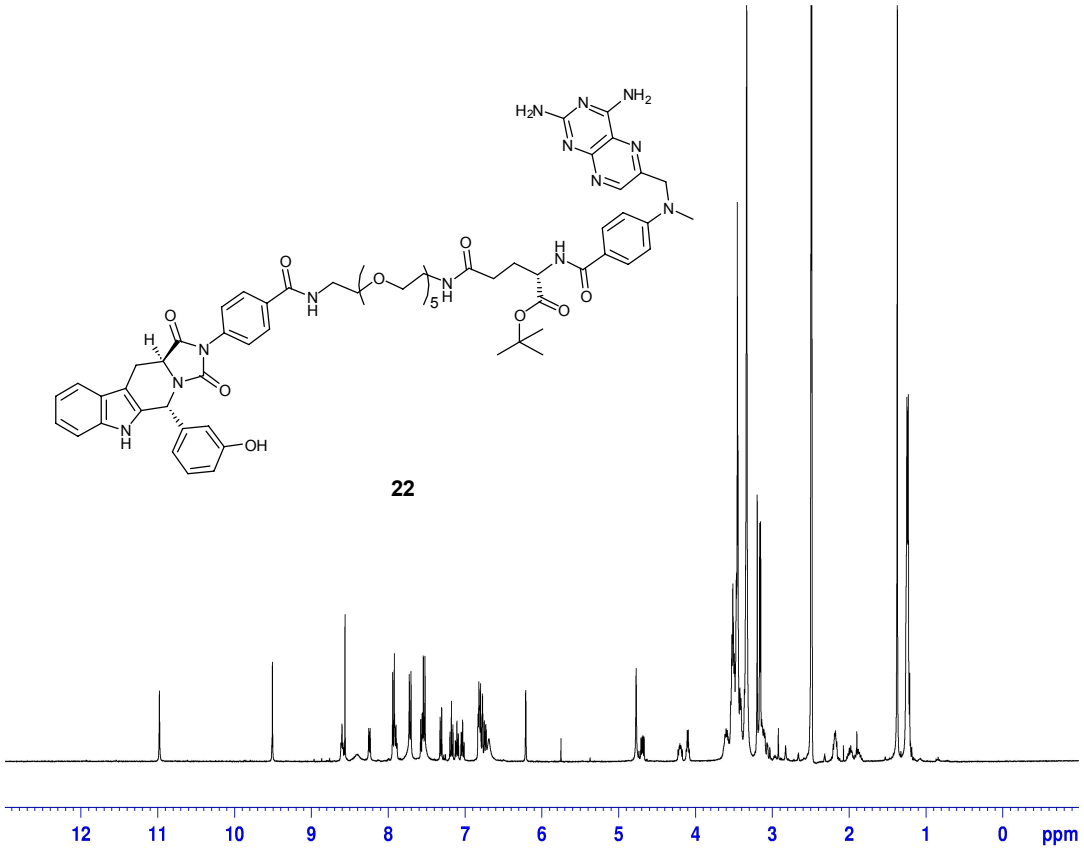
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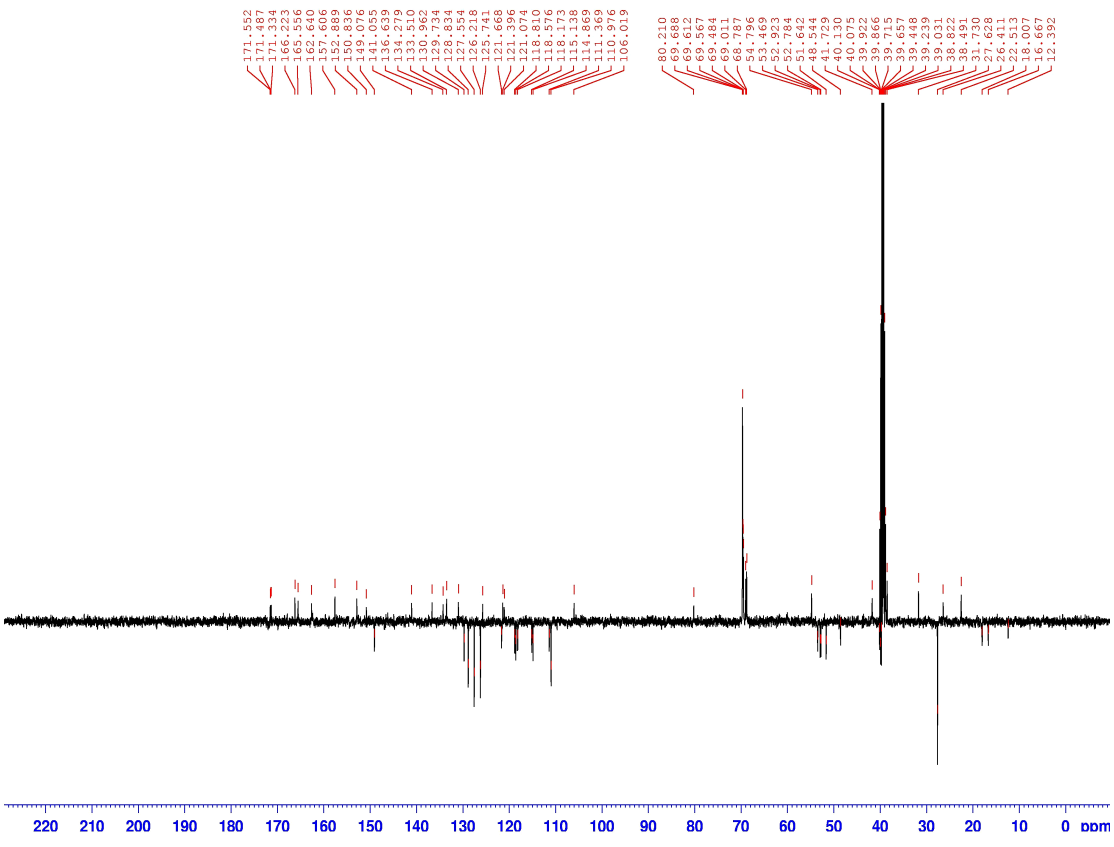
8
7
6
5
4
3
2
1
0
ppm

22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128.834
127.554
126.218
125.741
121.668
121.396
121.074
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118.576
118.173
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114.869
111.369
110.976
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80.210
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69.612
69.567
69.484
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52.784
51.642
48.544
41.729
40.130
40.075
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39.866
39.715
39.657
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39.239
39.031
38.822
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27.628
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22.513
18.007
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220
210
200
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60
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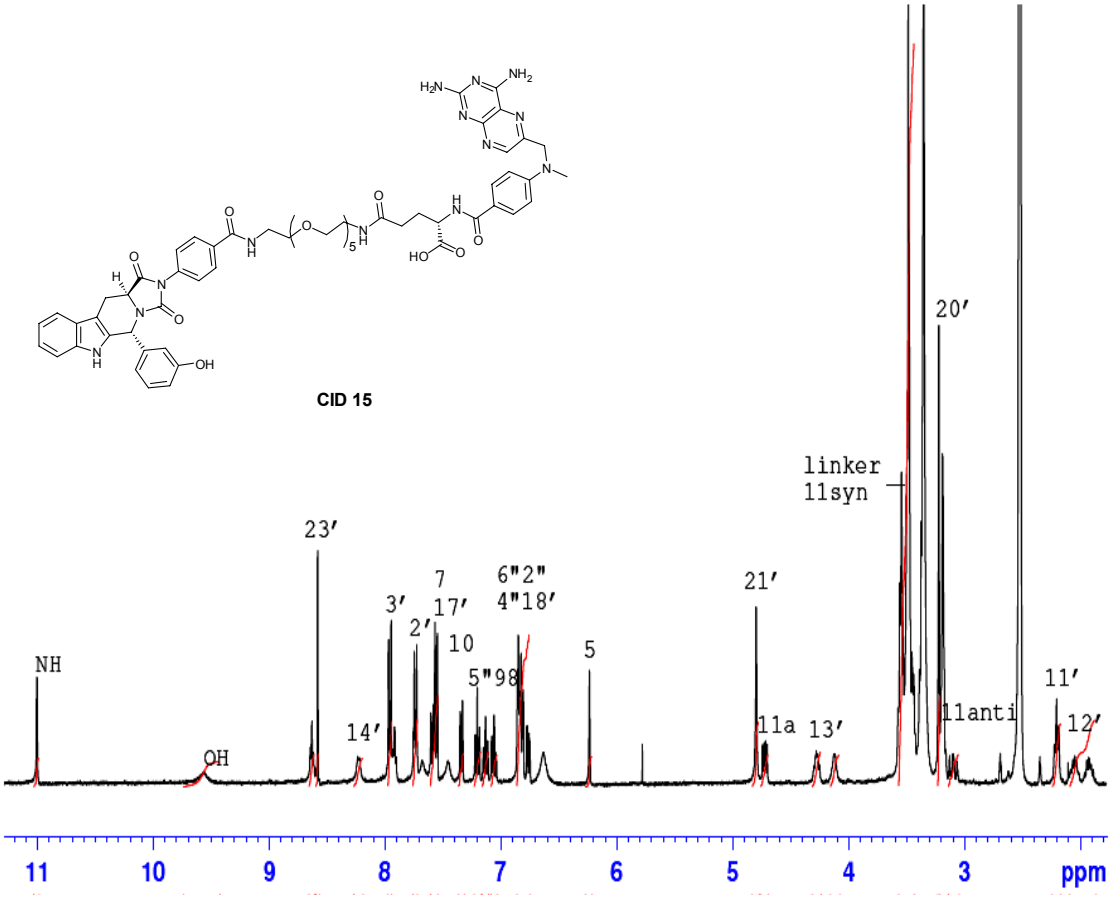
10
0
ppm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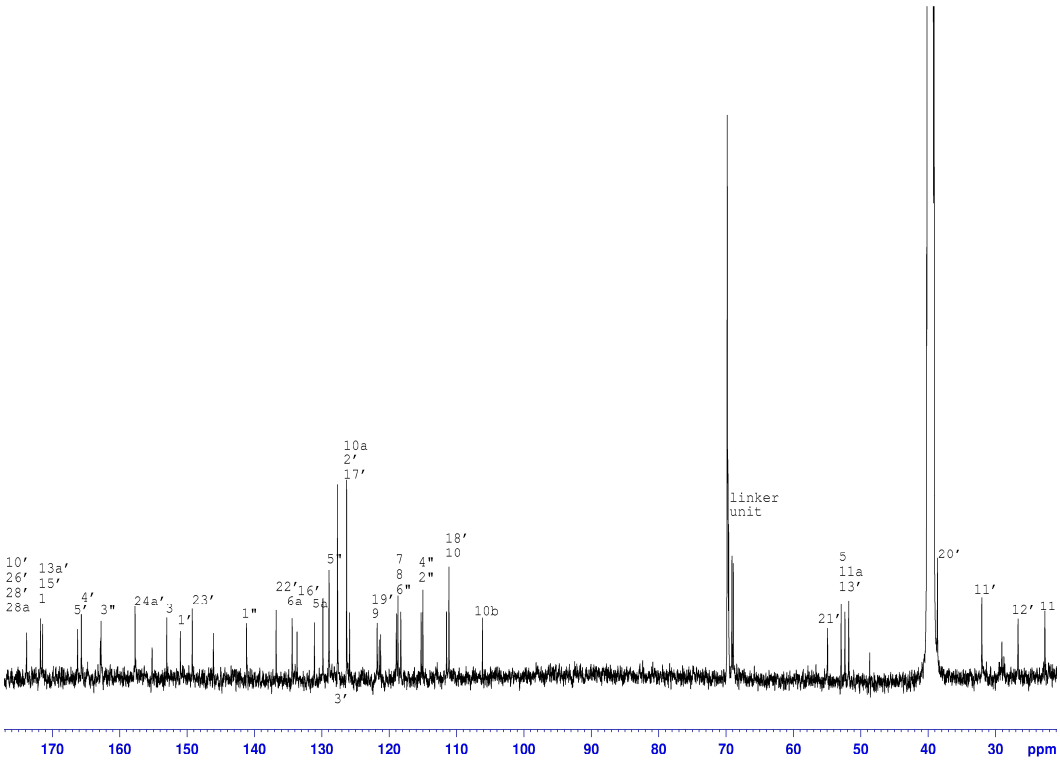
23′
14′
3′
2′
7
17′
10
6"2"
4"18′
5"98
5
21′
11a
13′
linker
11syn
20′
11anti
11′
12′
11
ppm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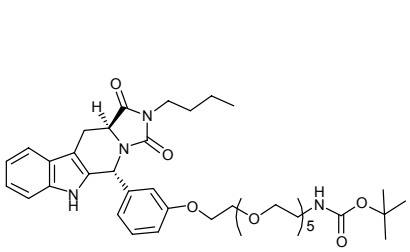
26′
28′
28a
13a′
15′
1
5′
4′
3"
24a′
3
1′
23′
1"
22′
6a
16′
5a
10a
2′
17′
5"
3′
19′
9
7
8
6"
4"
2"
18′
10
10b
linker
unit
21′
5
11a
13′
20′
11′
12′
11
ppm



24

12
11
10
9
8
7
6
5
4
3
2
1
0
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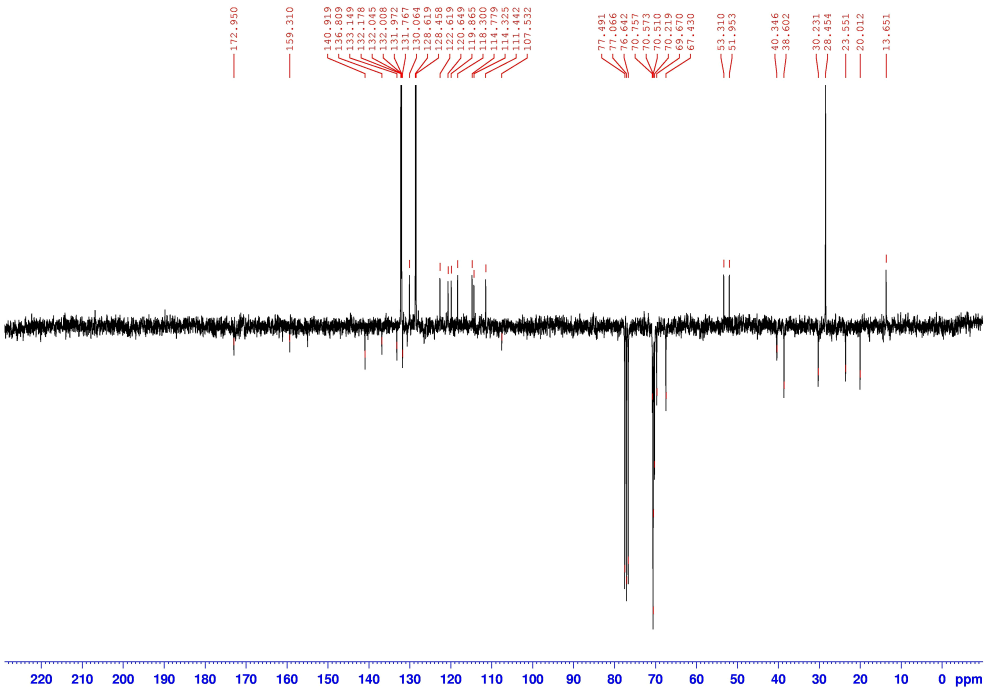
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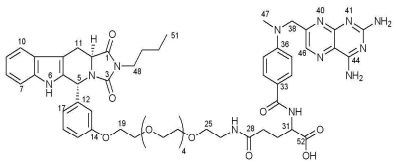
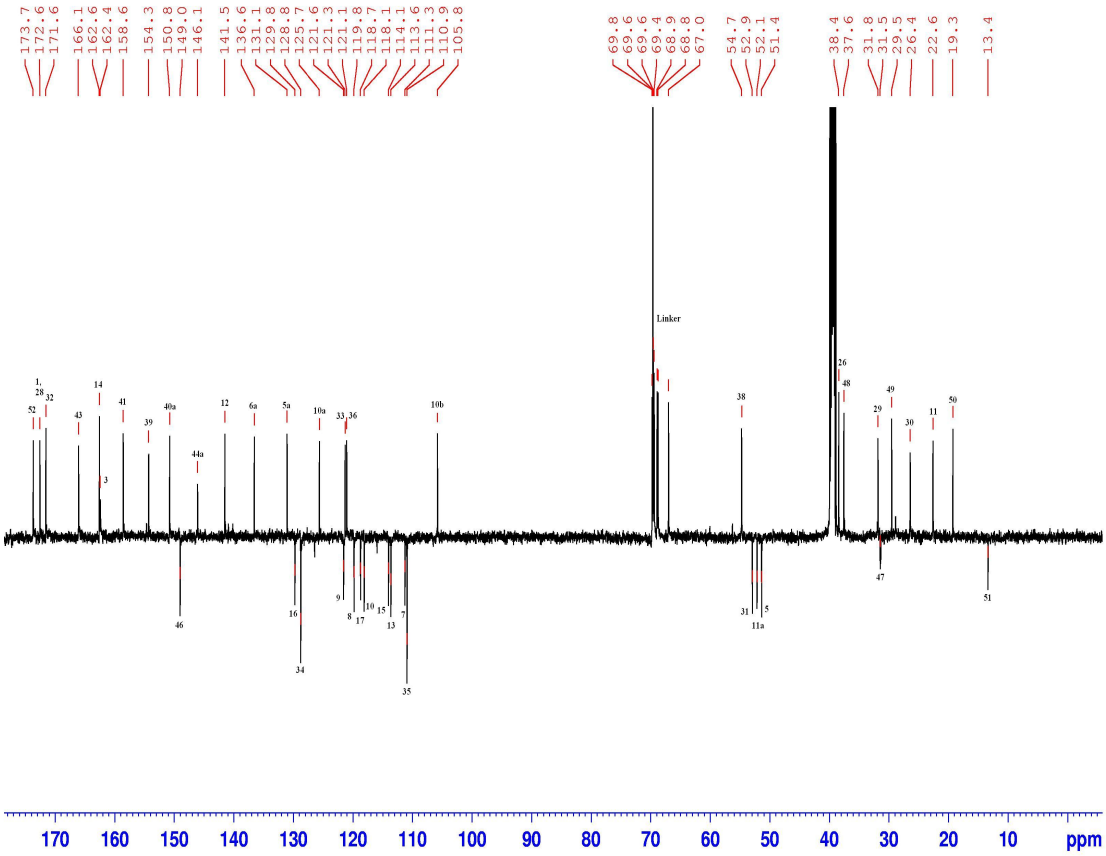
140.919
136.809
133.149
132.178
132.045
132.000
131.972
131.767
130.064
128.619
128.458
122.619
120.649
119.865
119.300
114.779
114.325
111.442
107.532
77.491
77.066
76.642
70.797
70.573
70.510
70.219
69.670
67.430
53.310
51.953
40.346
38.602
30.231
28.454
23.551
20.012
13.651
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



23

NH
NH
NH
NH
OH
NH
7, 15
10
9
16
8, 17, 13
34
35
5
46
38
11a
31
Linker
Linker
11syn
47
48
11anti
29
30
49
50
51
11
10
9
8
7
6
5
4
3
2
1
ppm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171.6
166.1
162.6
162.4
158.6
154.3
150.8
149.0
146.1
141.5
136.6
131.1
129.8
128.8
125.7
121.6
121.3
121.1
119.8
118.7
118.1
114.1
113.6
111.3
110.9
105.8
69.8
69.6
69.6
69.4
68.9
68.8
67.0
54.7
52.9
52.1
51.4
38.4
37.6
31.8
31.5
29.5
26.4
22.6
19.3
13.4
Linker
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm