**Author contributions:** C.M.W. conceived the project, wrote the first draft of the paper with subsequent assistance from all authors, and was the principle supervisor of H.X and S.D.H. C.M.W., H.X., S.D.H. and T.F-J. chose the COT/cubane targets. H.X. S.D.H. and T.F-J undertook the synthetic preparation of all COT/cubane analogues, performed the log *P* measurements, and obtained the respective characterisation data. J.-K.T., D.-Y.J. and X.C designed the warfarin study and analyzed results after evaluation of warfarin and related compounds (**6**-**8**) against the VKOR assay and all 27 human VKOR mutation studies. S.G. and M.T.S designed the metabolism study of warfarin and related compounds (**6**-**8**) and analysed the results. T.H.J.B., K.-A.C. and K.N.J. designed and analyzed results after evaluation of moclobemide and related compounds (**9**, **14** and **21**). A.K. and M.T.S. designed the pravadoline and related compounds (**10**, **15** and **22**) study and analysed results. G.M.B. designed and performed the cancer cell assay experiments and analysed results for SAHA and related compounds (**11**, **16** and **23**). C.P. and J.Mc. designed the scabies study and analysed results for benzyl benzoate and related compounds (**12**, **17**-**19** and **24**-**26**). C.-E.M. and G.H.W. designed the diflubenzuron and related compounds (**13**, **20** and **27**) study and analysed results. G.P.S. and J.T. provided cubane expertise, and G.P.S co-supervised H.X, S.D.H and T F-J. J.D.V. provided expertise on P450 metabolism in relation to the metabolism study. P.V.B. performed the X-ray crystallographic structure determination. J.M.B. performed all *in silico* calculations and geometry optimisations, assisted with graphical layouts and manuscript preparation.

# Table of Contents

## Supplementary Information Part 1:
## Synthesis and Physical Property Measurements

Abbreviations

| | |
|---|---|
| °C | degrees Celsius |
| Δ | heat/reflux |
| Δ | chemical shift |
| µL | microliter |
| µm | micrometer |
| Acetone-$d_6$ | deuterated acetone |
| ANOVA | analysis of variance |
| Boc | tert-Butyl carbonate |
| Br. | broad |
| BPU | benzoylphenyl ureas |
| calcd | calculated |
| $CDCl_3$ | deuterated chloroform |
| COT | 1,3,5,7-cyclooctatetraene |
| CSIRO | Commonwealth Scientific and Industrial Research Organisation |
| $D_2O$ | deuterium oxide |
| Da | Dalton(s) |
| dec. | decomposition |
| DCM | dichloromethane |
| DMF | *N*,*N*-dimethylformamide |
| DMAP | *N*,*N*-dimethyl-4-aminopyridine |
| DMSO-$d_6$ | deuterated dimethyl sulfoxide |
| DMSO | dimethyl sulfoxide |
| d | doublet |
| EI | electron ionisation |
| *et al* | et alii / et aliae (and others) |
| EtOAc | ethyl acetate |
| ESI | electrospray ionisation |
| eV | electron volts |
| GCMS | gas chromatography mass spectrometry |
| g | gram |
| HCl | hydrochloric acid |
| h | hour(s) |
| HRMS | high resolution mass spectrometry |
| hυ | photoirradiation |
| Hz | Hertz |
| $IC_{50}$ | 50% maximal inhibitory concentration |
| IGR | insect growth regulator |
| *in vacuo* | in a vacuum |
| *in vitro* | within the glass |
| *in vivo* | within the living |
| *J* | coupling constant |

| | |
|---|---|
| LC-MS/MS | liquid chromatography-mass spectrometry/mass spectrometry |
| Methanol-$d_4$ | deuterated methanol |
| MHz | mega-hertz |
| min | minute(s) |
| mL | millilitre(s) |
| mmol | millimole(s) |
| mm | millimetre |
| m.p. | melting point |
| *m/z* | mass to charge ratio |
| m | multiplet |
| NADPH | nicotinamide adenine dinucleotide phosphate, reduced form |
| nmol | nanomole(s) |
| NMR | nuclear magnetic resonance |
| PBS | phosphate buffered saline |
| *post hoc* | after this |
| ppm | parts per million |
| Prep. | preparative |
| q | quartet |
| rh | relative humidity |
| rpm | revolutions per minute |
| SE/SEM | standard error/standard error of the mean |
| s | singlet |
| TEA | triethylamine |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| *t* | tertiary |
| t | triplet |
| UV | ultraviolet |
| VKOR | vitamin K epoxide reductase |
| wt | weight |

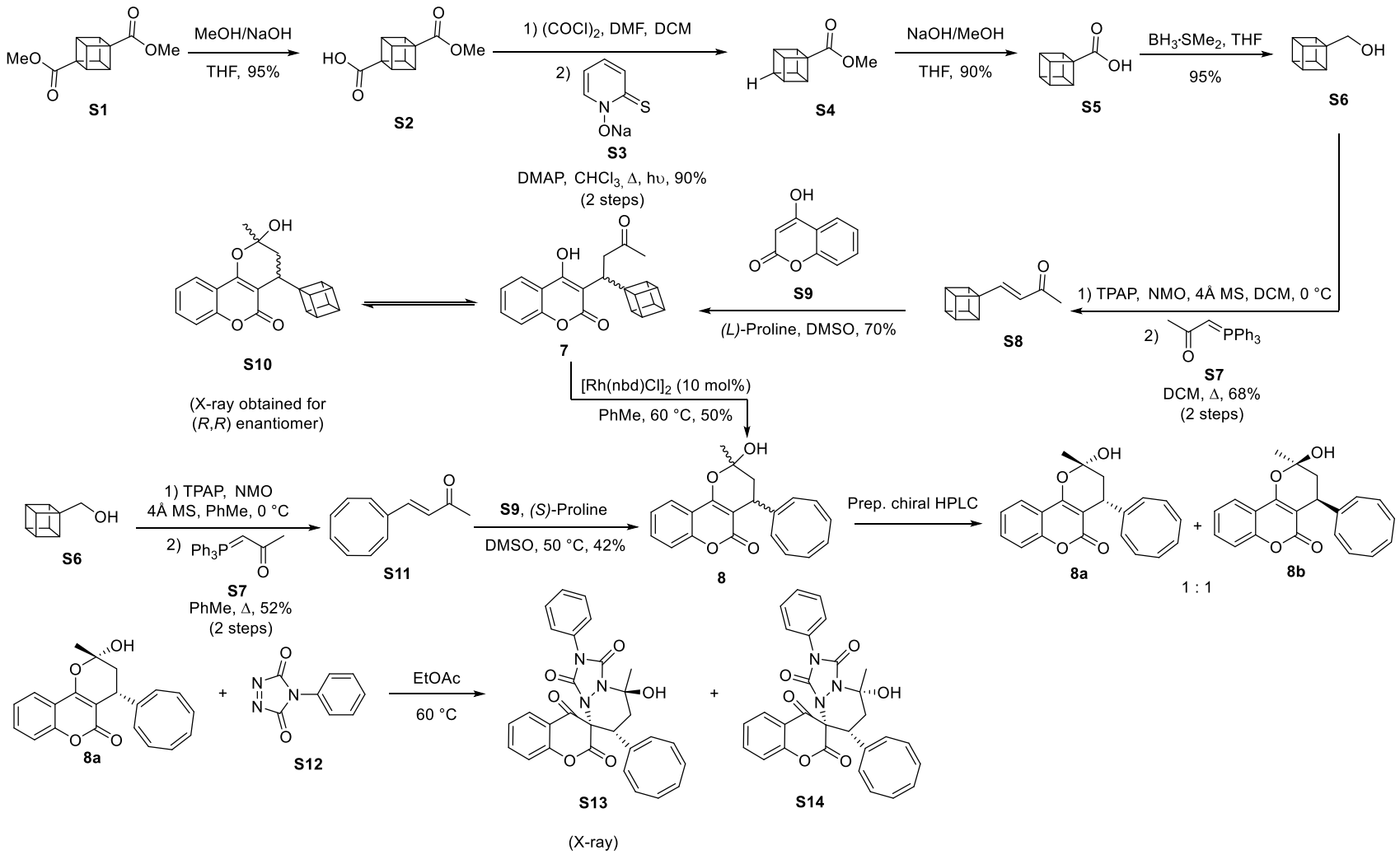
General Experimental

*Synthetic procedures pertaining to warfarin (**6**), moclobemide (**9**), pravadoline (**10**), SAHA (**11**), benzyl benzoate (**12**), diflubenzuron (**13**), and analogues (performed by the group led by Prof. Craig Williams at the School of Chemistry and Molecular Biosciences):*

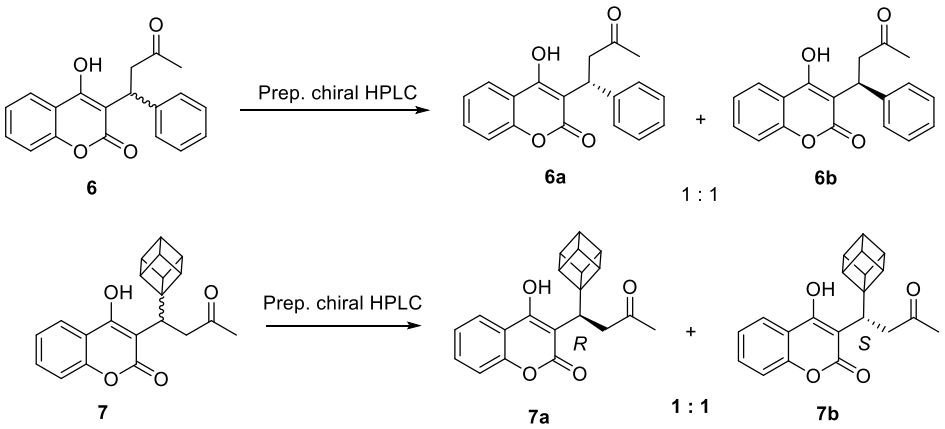
Reactions employing microwave conditions were carried out in a CEM Discover LabMate. Argon was dried by passing through a drying tube containing 4Å molecular sieves and Drierite™. Glassware was oven dried (160 °C) before use with anhydrous solvents and reagents. THF and diethylether were freshly distilled to dryness over elemental sodium/benzophenone under an argon atmosphere. DCM was freshly distilled to dryness over calcium hydride under an argon atmosphere. Unless stated otherwise commercially available chemicals were used without further purification. 2-Mercaptopyridine *N*-oxide sodium salt was concentrated to dryness then washed with ethyl acetate. Diphenylphosphoryl azide (DPPA) was distilled to dryness following known procedures.[41] Acetonitrile, methanol, ethanol, *t*-butanol, *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA), *N*,*N*-dimethylformamide (DMF), triethylamine (TEA), *N*,*N*-diisopropylamine and 2,2,6,6-tetramethylpiperidine were freshly distilled to dryness over calcium hydride under an argon atmosphere or reduced pressure.[42] Chloroform was washed with water, dried over magnesium sulfate then distilled to dryness over $P_2O_5$ under an argon atmosphere. NMR spectra were recorded under standard conditions (unless stated otherwise) using Bruker AV 500, 400 and 300 MHz or Bruker AS 500 MHz spectrometers and were referenced with residual monoprotic solvent peaks (e.g. $CDCl_3$, $C_6D_6$ etc.).[43] Samples run in $D_2O$ were referenced using a dioxane standard ($^1H$ = δ 3.75 ppm, $^{13}C$ = 67.2 ppm). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. The following abbreviations are used to report multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, quin = quintet, sext = sextet, sep = septet, br. = broad. High resolution ESI mass spectra were recorded using a Bruker MicroTOF-Q (quadrupole-Time of Flight) with a Bruker ESI source. Optical rotations were performed on a JASCO P-2000 polarimeter. Melting points were

determined using a Digimelt MPA 160 melting point apparatus and are reported uncorrected. Crystallographic data were collected at 190K on an Oxford Diffraction Gemini Ultra S CCD diffractometer employing graphite monochromated Mo-Kα radiation (0.71073 Å) in the range $2 < 2\theta < 50°$. Data reduction and empirical absorption corrections were performed with CrysAlisPro (version 1.171.38.43). The structure was solved *via* dual space methods with SHELXT. Refinement was performed by full-matrix least-squares analysis against $F^2$ using SHELXL-2014 within the WinGX package. Carbon-bound hydrogen atoms were included at estimated positions using a riding model. The $U_{iso}$(H) of the methyl group were constrained to 1.5 times $U_{eq}$ of the parent carbon atom, while $U_{iso}$(H) of the remaining carbon-bound positions were constrained to 1.2 times $U_{eq}$ of the respective parent carbon atoms. The nitrogen-bound hydrogen atom was located from a difference map; its coordinates were allowed to refine freely, and $U_{iso}$(H) was constrained to 1.5 times $U_{eq}$ of the parent nitrogen atom. Drawings of the molecule were produced with ORTEP-3 with all thermal displacement elipsoids depicted at the 50% probability level. Flash column chromatography was run using Merck silica gel 60 (230–400 mesh). Fractions were initially visualised using UV irradiation and subsequently by heating TLC plates exposed to either ceric ammonium molybdate (Goofy's stain) or 10 % aqueous potassium permanganate. TLC was performed with Merck precoated silica gel plates (silica gel 60 $F_{254}$) 0.2 mm). Preparative Chiral HPLC was performed at the Analytical and Preparative Enantioselective Chromatography facility at the School of Chemistry and Molecular Biosciences, University of Queensland.

## Warfarin

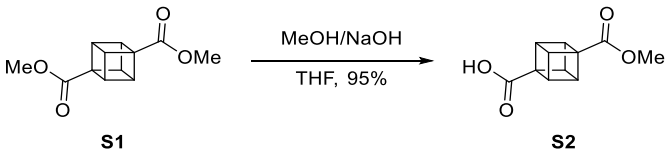



**Scheme S1:** synthesis of cubyl warfarin (**7**), cyclooctatetraenyl warfarin (**8**) and determination of the absolute stereochemistry of enantiomer **8a**.




**Scheme S2:** separation of commercially available racemic warfarin (**6**) and cubyl warfarin (**7**).

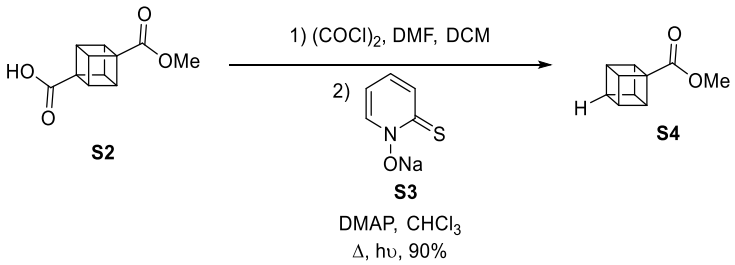
4-(Methoxycarbonyl)cubane-1-carboxylic acid (**S2**)




**S1** **S2**

Following the procedure of Eaton *et al*:[44] dimethyl cubane-1,4-dicarboxylate (**S1**) (6.079 g, 27.60 mmol) was suspended in THF (250 mL). A solution of sodium hydroxide (1.220 g, 30.50 mmol) in methanol (14 mL) was added dropwise and the solution was left to stir for 16 h. The THF was removed *in vacuo* and the residual solid was suspended in water (200 mL), and washed with DCM (3 x 100 mL). The aqueous phase was acidified to pH 2 with hydrochloric acid (10 M) and washed again with DCM (3 x 100 mL). The combined organic phases were dried over magnesium sulfate and concentrated to give the title compound (5.385 g, 95%) as a white solid. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.28 (s, 6H), 3.73 (s, 3H).

Methyl cubane-1-carboxylate (**S4**)

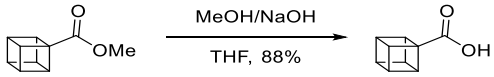



**S2** **S3** **S4**

Following the procedure of Ko *et al*:[45] to a solution of 4-methoxycarbonylcubane-1-carboxylic acid (**S2**) (9.654 g, 46.82 mmol) in anhydrous DCM (500 mL) was added oxalyl chloride (4.81 mL, 56.08 mmol) and anhydrous DMF (0.3 mL) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). Separately, freshly ground 2-mercaptopyridine *N*-oxide sodium salt (**S3**) (10.639 g, 71.33 mmol) and DMAP (59 mg, 0.48 mmol) were suspended in anhydrous chloroform (500 mL) and heated to reflux whilst under irradiation from a 500-W tungsten lamp. [Note: Chloroform (1000 mL) was washed with water (3 x 1000 mL) and dried over molecular sieves prior to use in order to remove the ethanol stabilisier.] The newly

formed acid chloride was suspended in anhydrous chloroform (500 mL) and added slowly over 1 h to the refluxing mixture under an argon atmosphere. After reflux (4 h) the suspension was washed with water (3 x 500 mL), dried over magnesium sulfate and concentrated to give a brown oil. Purification by column chromatography (10% ethyl acetate/petroleum ether v/v) gave the title compound (6.820 g, 90%) as a white sweet smelling solid. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.26–4.24 (m, 3H), 4.04–3.99 (m, 4H), 3.70 (s, 3H).

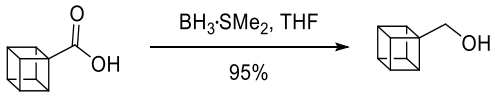
Cubane-1-carboxylic acid (**S5**)




**S4** **S5**

Methyl cubane-1-carboxylate (**S4**) (6.600 g, 0.041 mmol) was suspended in THF (200 mL). A solution of sodium hydroxide (2.004 g, 50.10 mmol) in methanol (12 mL) was added dropwise and the solution was left to stir for 16 h. The THF was removed *in vacuo* and the residual solid was suspended in water (200 mL) and washed with DCM (3 x 100 mL). The aqueous phase was acidified to pH 2 with hydrochloric acid (10 M) and washed again with DCM (3 x 100 mL). The combined organic phases were dried over magnesium sulfate and concentrated to give the title compound (5.324 g, 88%) as a yellow solid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 4.33–4.29 (m, 3H), 4.07–4.00 (m, 4H).

Cubylmethanol (**S6**)

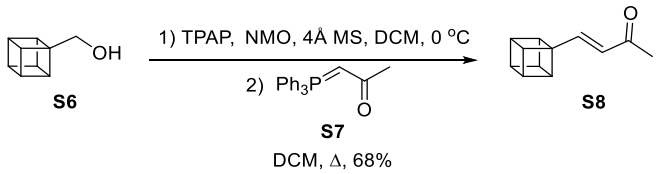



**S5** **S6**

Following the procedure of Priefer *et al*:[46] to a solution of cubane-1-carboxylic acid (**S5**) (100 mg, 0.67 mmol) in anhydrous THF (10 mL) was slowly added borane dimethylsulfide complex (5 M in diethyl ether, 0.40 mL, 2.02 mmol) under an argon atmosphere. The solution was left to stir for 1 h then water (5 mL) was cautiously added. The THF was removed *in vacuo* and the residue was

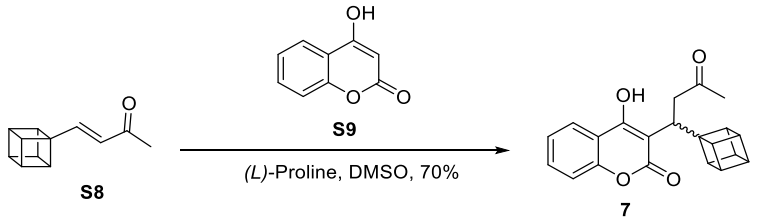
washed with DCM (3 x 10 mL). The combined organic phases were dried over magnesium sulfate, concentrated and purified by column chromatography (50% ethyl acetate/petroleum ether v/v) to give the title compound (85 mg, 95%) as a white solid. $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.08–4.01 (m, 1H), 3.96–3.88 (m, 6H), 3.76 (d, $J$ = 5.5 Hz, 1H).

(Cubanyl) but-3-en-2-one (**S8**)

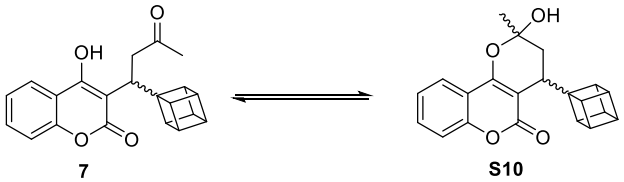



To a solution of cubylmethanol (**S6**) (1.60 g, 11.9 mmol) and *N*-methylmorpholine-*N*-oxide (2.70 g, 23.80 mmol) in anhydrous DCM (20 mL) under an argon atmosphere, was added tetrapropylammonium perruthenate (0.21 g, 0.59 mmol) and 4Å molecular sieves (200 mg). The reaction mixture was stirred at room temperature for 1 hour. The resulting solution was filtered through Celite and eluted with additional anhydrous DCM (20 mL). 1-(Triphenylphosphoranylidene)-2-propanone (**S7**) (7 g, 23.80 mmol) was then added to the eluent and the resulting mixture was heated to reflux in DCM for 12 h. After complete conversion of starting material the solvent was removed and the residue was purified by column chromatography on silica gel (5% ethyl acetate/hexane v/v) to give the title compound (1.35 g, 68% yield, over two steps) as a colorless oil. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 7.00 (d, $J$ = 16.0 Hz, 1H), 5.92 (d, $J$ = 16.0 Hz, 1H), 4.09-4.05 (m, 4H), 3.99- 3.95 (m, 3H), 2.27 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 198.7, 146.5, 127.7, 58.5, 50.1, 48.5, 44.4, 27.0; HRMS-ESI calcd for $C_{12}H_{13}O^{+}$ ($[M+H]^{+}$): 173.0961; found: 173.0960.

Cubyl warfarin (**7**)

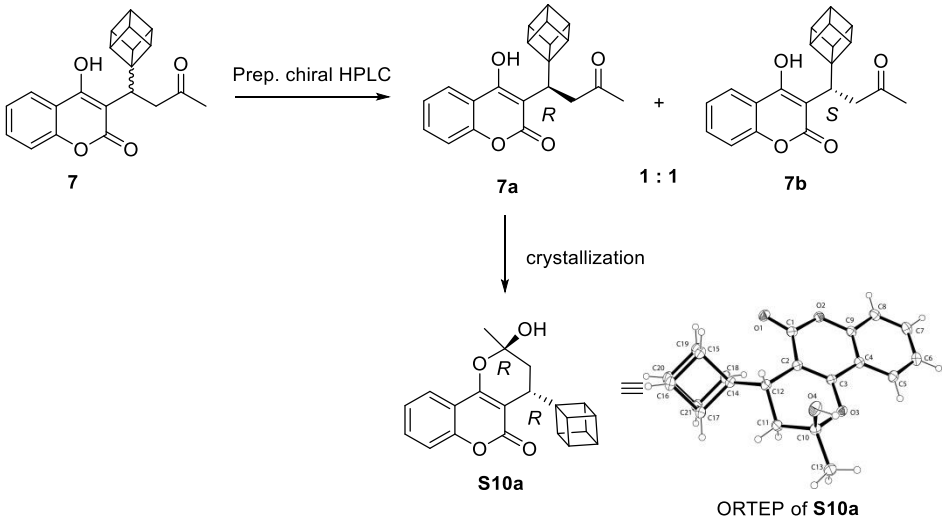



To a solution of 4-(cubanyl) but-3-en-2-one **S8** (45 mg, 0.26 mmol) and 4-hydroxycoumarin (**S9**) (45 mg, 0.27 mmol) in dimethyl sulfoxide (1.5 mL) was added (*L)*-Proline (15 mg, 0.13 mmol) and the mixture was stirred at room temperature for 24 h. Water was added to the mixture and the aqueous layer was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried ($Na_2SO_4$), and the solvent removed *in vacuo* to give the crude product which was purified by column chromatography on silica gel (20 % ethyl acetate/hexane v/v) the title compound (60 mg, 70%) as a white solid. The cubane analogue of warfarin (**7**) existed as an equilibrium in solution with the corresponding cyclic hemiketal (**S10**).




m.p. 170–172°C (dec.); $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 9.77 (s, 1H, -OH, keto), 7.92-7.91 (m, 1H, ArH, keto), 7.79-7.74 (m, 0.48H, ArH, ketal), 7.51-7.46 (m, 1.5H, ArH), 7.30-7.21 (m, 3H, ArH), 3.98-3.81 (m, 10H, cubane), 3.38 (d, $J$ = 10 Hz, 1H, $CH_2$, keto), 3.31-3.22 (m, 1.5H, CH, keto, $CH_2$, CH, ketal), 3.15 (s, 0.2H, -OH, ketal), 3.01 (s, 0.26H, ketal), 2.76 (d, $J$ = 20.0 Hz, 1H, $CH_2$, keto), 2.28-2.20 (m, 0.3 H, $CH_2$, ketal), 2.24 (s, 3H, $CH_3$, keto), 2.00-1.95 (m, 0.26H, $CH_2$, ketal), 1.77 (s, 0.6H, $CH_3$, ketal), 1.76-1.70 (m, 0.2H, $CH_2$, ketal), 1.71 (s, 0.7H, $CH_3$, ketal); $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 124.3, 162.6, 161.8, 158.0, 152.6, 152.5, 131.5, 131.3, 123.7, 123.6, 123.5, 122.6, 116.6, 116.4, 116.1, 115.7, 106.1, 102.5, 99.1, 60.9, 59.6, 49.2, 49.0, 48.9, 48.0, 47.4, 44.2, 44.1, 44.0, 43.3, 34.1, 33.4, 31.5, 29.8, 28.0; HRMS-ESI calcd for $C_{21}H_{18}O_4Na^+$ ($[M+Na]^+$): 357.1097; found: 357.1110.

Enantiomers **7a** and **7b** and cyclic hemiketal **S10a**




Racemic cubyl warfarin (**7**) (200 mg) was separated by preparative chiral HPLC to provide two enantiomers **7a** (90 mg) and **7b** (90 mg). **7a**: $[\alpha]^{24}_{D}$ 29.6 (c 0.06, $CHCl_3$). 7**b**: $[\alpha]^{24}_{D}$ -23.4 (c 0.08, $CHCl_3$). X-ray quality crystals of **S10a** were grown from ethyl acetate and petroleum ether.

**C H R O M A T O G R A M  R E P O R T**

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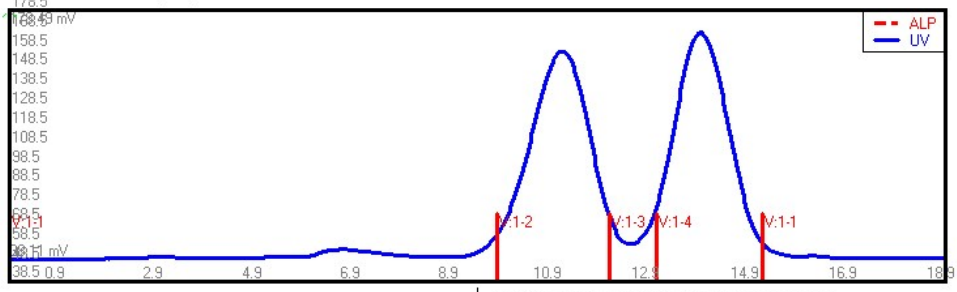


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**Inj Vol µL** :2000

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**Meth. Vol mL** :200
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**Eluent and Gradient**

| Time (min) | Solvent A (%) | Solvent B (%) |
|---|---|---|
| 0.00 | 50.0 | 50.0 |

**P E A K  L I S T  R E P O R T**

| No | Name | Type | Start (min) | End (min) | RT (min) | Height (mV) | Area (mVs) | % Area | Col. Area (mVs) | Plates (#) | Conc (mg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX_1-24_1 | (+) | 9.90 | 12.17 | 11.22 | 88.735 | 6471.409 | 49.31 | 6471.381 | 477.805 | 0.0000 |
| 2 | HX_1-24_2 | (+) | 13.13 | 15.28 | 14.03 | 98.400 | 6652.765 | 50.69 | 6652.756 | 861.424 | 0.0000 |

**Total Peak Area** :13124.173 mVs

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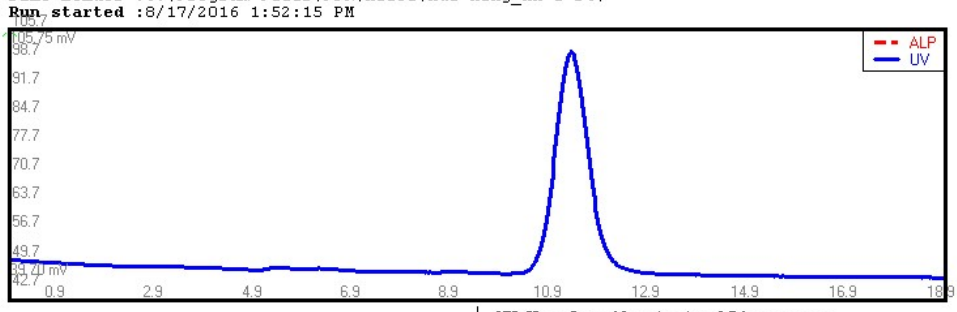


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**Inj Vol µL** :1000

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
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**Meth. Vol mL** :190
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**Eluent and Gradient**

| Time (min) | Solvent A (%) |
|---|---|
| 0.00 | 100.0 |

## P E A K  L I S T  R E P O R T

| No | Name | Type | Start (min) | End (min) | RT (min) | Height (mV) | Area (mVs) | % Area | Col. Area (mVs) | Plates (#) | Conc (mg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX_1-24_1 | (+) | 10.77 | 11.92 | 11.41 | 43.333 | 1615.196 | 100.00 | 1615.171 | 1884.756 | 0.0000 |

**Total Peak Area** :1615.196 mVs

## C H R O M A T O G R A M  R E P O R T

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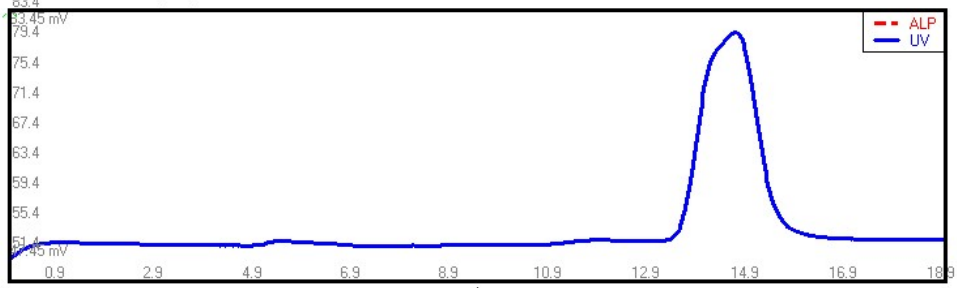


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CSP Density :0.6000
Packed Length :25.0000
Inner Diameter :2.1000
**Inj Vol µL** :1000

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
**Run Time** :19.00 min
**Meth. Vol mL** :190
**Sample ID** :HX_1-24_fr2
**Data Path** :C:\Program Files\PDR\Alice\Hui Xing_HX-1-24

**Eluent and Gradient**

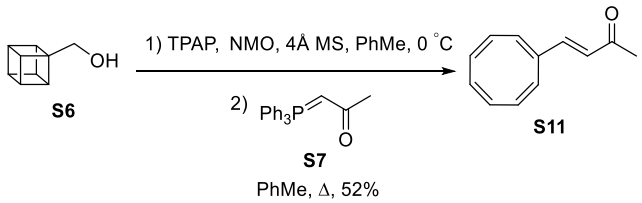
| Time (min) | Solvent A (%) |
|---|---|
| 0.00 | 100.0 |

## P E A K  L I S T  R E P O R T

| No | Name | Type | Start (min) | End (min) | RT (min) | Height (mV) | Area (mVs) | % Area | Col. Area (mVs) | Plates (#) | Conc (mg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX_1-24_2 | (+) | 13.75 | 15.35 | 14.75 | 20.128 | 1302.169 | 100.00 | 1302.157 | 958.435 | 0.0000 |

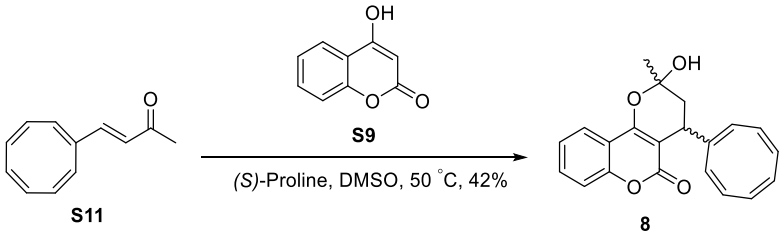
**Total Peak Area** :1302.169 mVs

(*E*)-3-Cyclooctatetraenyl-1-methylprop-2-en-1-one (**S11**)




To a solution of cubylmethanol (**S6**) (52 mg, 0.39 mmol), NMO (141 mg, 1.20 mmol) and 4Å molecular sieves (30 mg) in anhydrous DCM (5 mL) was added TPAP (1 mg, 0.004 mmol) under an argon atmosphere. The mixture was stirred at rt for 20 min until the total consumption of the alcohol. The solvent was removed under reduced pressure to dryness. To the intermediate aldehyde was added toluene (5 mL) and 1-(triphenylphosphoranylidene)-2-propanone (**S7**) (191 mg, 0.60 mmol) and the resulting mixture was stirred at 60 ℃ for 6 h. After cooling, the solvent was removed, and the residue was purified by column chromatography (5% ethyl acetate/hexane v/v) to give the title compound (35 mg, 52%) as a yellow oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 7.17 (d, $J$ = 16.0 Hz, 1H), 6.22-6.21 (m, 1H), 5.98-5.79 (m, 7H), 2.28 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ (ppm) 198.3, 144.7, 140.4, 139.8, 133.7, 131.7, 131.3, 130.9, 129.1, 127.0, 27.5; HRMS-ESI calcd for $C_{12}H_{12}ONa^+$ ([M+Na]$^+$): 195.0780; found: 195.0788.

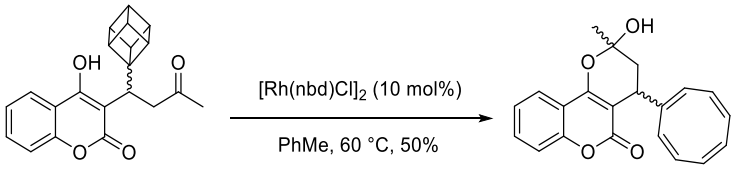
Cyclooctatetraenyl warfarin (**8**)




To a solution of (*E*)-3-cyclooctatetraenyl-1-methylprop-2-en-1-one (**S11**) (60 mg, 0.35 mmol) and 4-hydroxycoumarin (**S9**) (62 mg, 0.38 mmol) in dimethyl sulfoxide (1.5 mL) was added *(D)*-Proline (20 mg, 0.18 mmol) and the mixture was stirred at rt for 24 h. Water was added to the mixture and the aqueous layer was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were dried ($Na_2SO_4$), and the solvent removed *in vacuo* to give the crude product which was purified by column chromatography (15% ethyl acetate/hexane v/v) to give title

compound (51 mg, 42% yield) as a yellow solid. m.p. 98.2–99.8 °C; $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 7.91-7.90 (m, 1H), 7.57-7.53 (m, 1H), 7.34-7.28 (m, 2H), 6.13-5.68 (m, 8H), 4.97 (s, 1H), 3.49 (d, $J$ = 5.5 Hz, 1H), 2.46 (dd, $J$ = 14.5, 1.5 Hz, 1H), 2.03-1.99 (m, 1H), 1.69 (m, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ (ppm) 162.0, 159.5, 153.0, 143.4, 133.9, 132.9, 132.7, 132.0, 131.8, 131.3, 131.2, 128.4, 123.9, 123.2, 116.6, 115.4, 100.8, 99.6, 34.7, 34.0, 28.6; HRMS-ESI calcd for $C_{21}H_{18}O_4Na^+$ ([M+Na]$^+$): 357.1097; found: 357.1094.

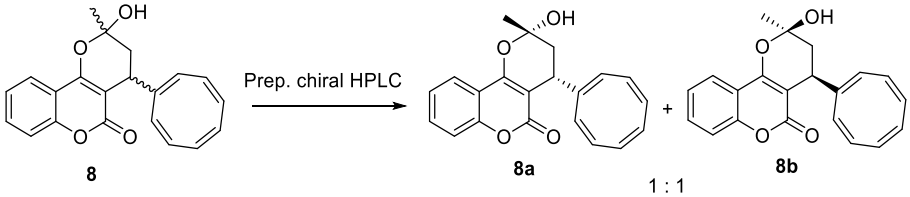
Cyclooctatetraenyl warfarin (**8**) (alternative procedure)




**7** **8**

Cubyl warfarin (**7**) (200 mg, 0.60 mmol) and $[Rh(nbd)Cl]_2$ (27 mg, 0.06 mmol) were suspended in toluene (15 mL) and stirred at 60 °C for 48 h. The solvent was removed and the residue was purified by column chromatography (15% ethyl acetate/hexane v/v) to give the title compound (100 mg, 50%).

Enantiomers **8a** and **8b**




**8** **8a** 1 : 1 **8b**

Racemic cyclooctatetraenyl warfarin (**8**) (150 mg) was separated by chiral preparative HPLC to provide two enantiomers **8a** (70 mg) and **8b** (70 mg). **8a**: $[\alpha]^{24}_D$ 289.3 (c 0.06, $CHCl_3$); **8b**: $[\alpha]^{24}_D$ -307.7 (c 0.08, $CHCl_3$).

**C H R O M A T O G R A M  R E P O R T**

**File name** :20161012_103204.ccf
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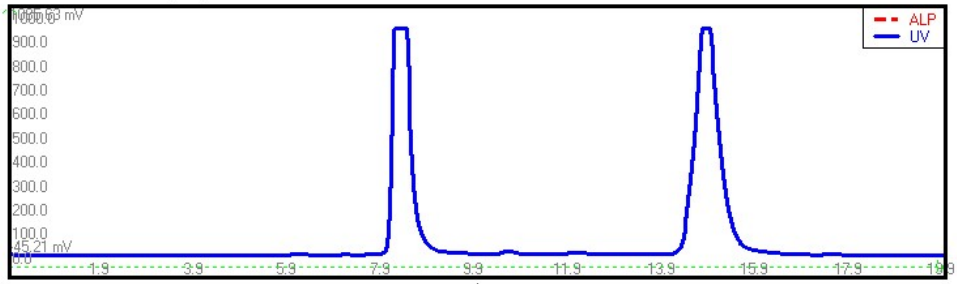
**Run started** :10/12/2016 10:12:04 AM




**Operation Mode** :Standard mode
**Method name** :30IPA_HEX70
**Col Name** :AD
**Column Size**
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Packed Length :25.0000
Inner Diameter :2.1000
**Inj Vol µL** :1500

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
**Run Time** :20.00 min
**Meth. Vol mL** :200
**Sample ID** :HX-5-37
**Data Path** :C:\Program Files\PDR\Alice\Hui Xing_HX-5-37

**Eluent and Gradient**

| Time (min) | Solvent A (%) |
|---|---|
| 0.00 | 100.0 |

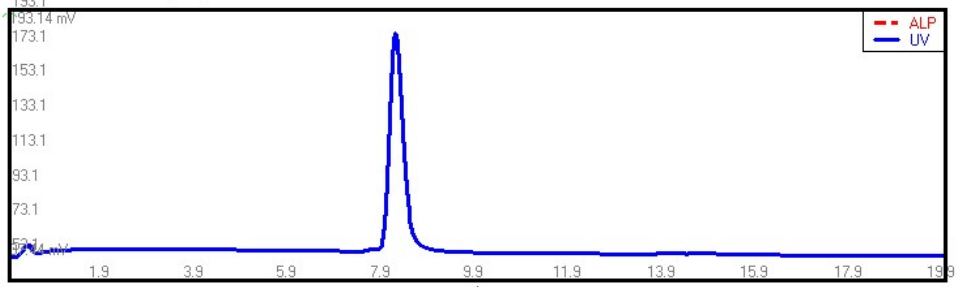
**P E A K  L I S T  R E P O R T**

| No | Name | Type | Start (min) | End (min) | RT (min) | Height (mV) | Area (mVs) | % Area | Col. Area (mVs) | Plates (#) | Conc (mg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX-5-37_1 | (+) | 8.04 | 9.16 | 8.49 | 928.539 | 25239.426 | 43.20 | 25239.406 | 2393.064 | 0.0000 |
| 2 | HX-5-37_2 | (+) | 14.29 | 15.94 | 14.96 | 925.137 | 33186.771 | 56.80 | 33186.755 | 4331.770 | 0.0000 |

**Total Peak Area** :58426.197 mVs

**C H R O M A T O G R A M  R E P O R T**

**File name** :20161019_142824.ccf
**File folder** :C:\Program Files\PDR\Alice\Hui Xing_HX-5-37\
**Run started** :10/19/2016 2:08:23 PM




**Operation Mode** :Standard mode
**Method name** :30IPA_HEX70
**Col Name** :AD
**Column Size**
CSP Density :0.6000
Packed Length :25.0000
Inner Diameter :2.1000
**Inj Vol µL** :1000

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
**Run Time** :20.00 min
**Meth. Vol mL** :300
**Sample ID** :HX-5-37_1
**Data Path** :C:\Program Files\PDR\Alice\Hui Xing_HX-5-37

**Eluent and Gradient**

| Time (min) | Solvent A (%) | Solvent B (%) |
|---|---|---|
| 0.00 | 50.0 | 50.0 |

**P E A K  L I S T  R E P O R T**

| No | Name | Type | Start (min) | End (min) | RT (min) | Height (mV) | Area (mVs) | % Area | Col. Area (mVs) | Plates (#) | Conc (mg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX-5-37_1 | (+) | 8.01 | 8.67 | 8.25 | 116.166 | 2054.890 | 100.00 | 2054.873 | 4807.575 | 0.0000 |

**Total Peak Area** :2054.890 mVs

## C H R O M A T O G R A M  R E P O R T

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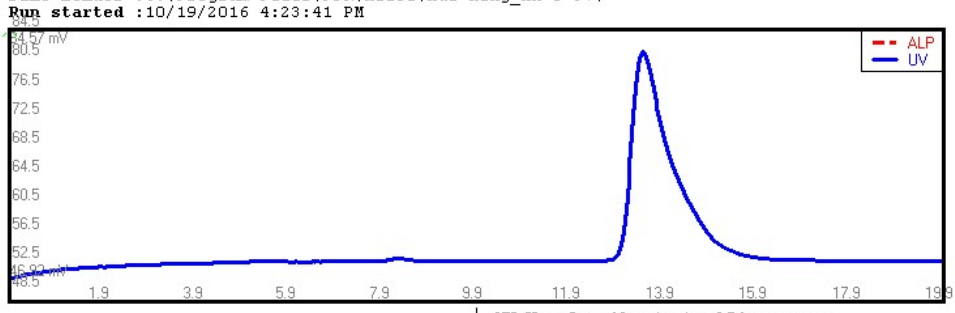



**Operation Mode** :Standard mode
**Method name** :30IPA_HEX70
**Col Name** :AD
**Column Size**
CSP Density :0.6000
Packed Length :25.0000
Inner Diameter :2.1000
**Inj Vol µL** :1000

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
**Run Time** :20.00 min
**Meth. Vol mL** :300
**Sample ID** :HX-5-37_2
**Data Path** :C:\Program Files\PDR\Alice\
Hui Xing_HX-5-37

**Eluent and Gradient**

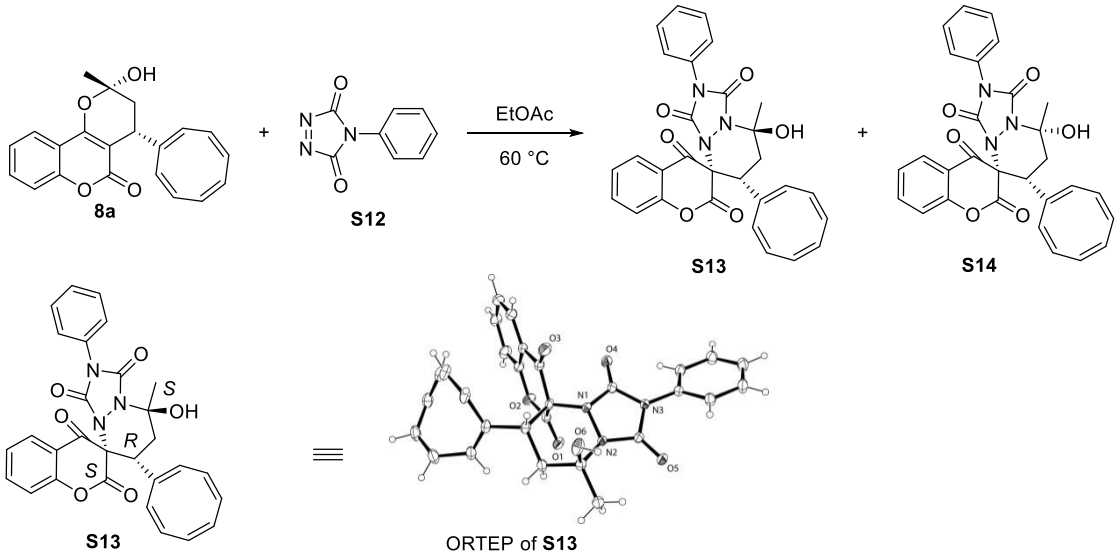
| Time (min) | Solvent A (%) |
|---|---|
| 0.00 | 100.0 |

## P E A K  L I S T  R E P O R T

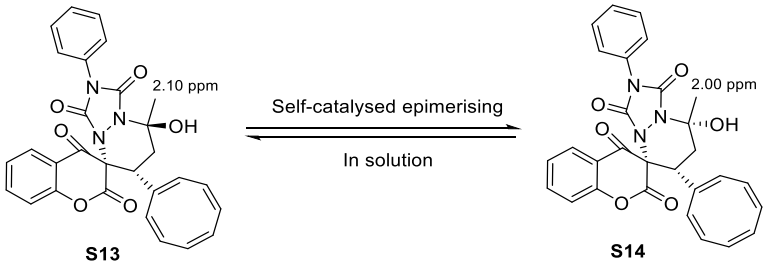
| No | Name | Type | Start (min) | End (min) | RT (min) | Height (mV) | Area (mVs) | % Area (%) | Col. Area (mVs) | Plates (#) | Conc (mg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX-5-37_2 | (+) | 13.23 | 14.52 | 13.57 | 19.917 | 755.578 | 100.00 | 755.574 | 2800.494 | 0.0000 |

**Total Peak Area** :755.578 mVs

Determination of the absolute stereochemistry of **8a**: PTAD adducts **S13** and **S14**




(*R*)-COT warfarin (**8a**) (15 mg, 0.05 mmol) and PTAD (**S12**) (8 mg, 0.05 mmol) were stirred in ethyl acetate (3 mL) at 60 °C for 1 h. The solvent was removed *in vacuo* then purification by column chromatography (20% ethyl acetate/hexane v/v) gave the title compounds (20 mg, 87% yield) as a slight yellow solid. X-ray quality crystals of **S13** (10 mg) were grown from MeOH and MeCN. Isolation of a pure sample of **S14** was not possible due to degradation during crystallization. **S13** and **S14** existed in equilibrium in solution.

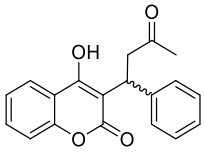



It was not possible to obtain a pure sample of **S14** due to degradation during recrystallisation. Full characterisation of a pure sample of either epimer was not possible due to the rapid equilibrium that exists between **S13** and **S14**.

**S13**: m.p 154 ℃ (dec.) $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.06-7.97 (m, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.46-7.26 (m, 7H), 5.84-5.22 (m, 7H), 3.77-3.61 (m, 1H), 3.44 (s, 1H), 2.66 (br. s, 1H), 2.10 (s, 3H), 1.92 (dd, *J* = 5.0, 15.0 Hz, 1H).

**S13** and **S14** mixture: $^{1}$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 8.06-7.97 (m, 1.7H), 7.71-7.66 (m, 1.8H), 7.47-7.26 (m, 12H), 5.84-5.23 (m, 12.7H), 4.86-4.73 (br m, 1H), 4.23 (br. s, 1H,), 3.74-3.58 (m, 2H, OH and CH, **S13**), 3.31-3.19 (m, 0.84H, CH, **S14**), 2.89 (t, *J* = 15.0 Hz, 0.85H, $CH_2$, **S14**), 2.66 (br. s, 1H, $CH_2$, **S13**), 2.10 (s, 3H, $CH_3$, **S13**), 2.02-1.94 (m, 0.83H, $CH_2$, **S14**), 2.00 (s, 2.5H, $CH_3$, **S14**), 1.92 (dd, *J* = 5.0, 15.0 Hz, 1H, $CH_2$, **S13**); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ (ppm) 190.1, 187.8, 164.9, 164.5, 164.1, 155.0, 154.7, 151.5, 151.1, 150.9, 149.7, 137.6, 137.3, 135.9, 135.5, 135.2, 134.4, 134.2, 134.0, 132.4, 132.0, 131.6, 131.4, 130.5, 130.4, 130.2, 129.1, 128.3, 127.5, 127.1, 125.4, 125.4, 125.2, 120.1, 119.6, 118.3, 118.2, 87.5, 84.5, 70.2, 69.5, 50.5, 48.4, 47.7, 45.5, 39.1, 38.8, 37.6, 27.0, 26.2; HRMS-ESI calcd for $C_{29}H_{23}N_3O_6Na^+$ ([M+Na]$^+$): 532.1479; found: 532.1456.

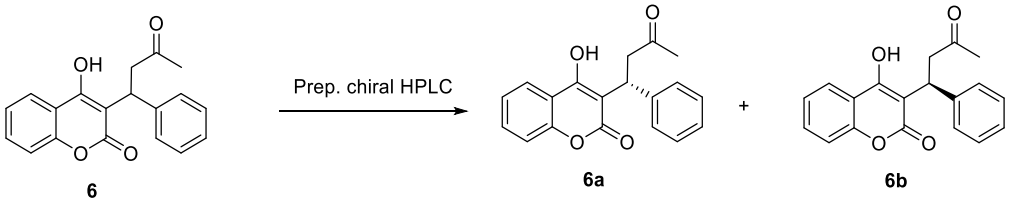
Warfarin (**6**)




**12**

Purchased from Sigma-Aldrich.

Warfarin enantiomers **6a** and 6**b**




**6** **6a** **6b**

Racemic warfarin **6** (200 mg) was separated by chiral preparative HPLC to provide two enantiomers **6a** (90 mg) and **6b** (90 mg). **6a**: $[\alpha]^{24}_{D}$ 17.70 (c 0.14, $CHCl_2$); **6b**: $[\alpha]^{24}_{D}$ -19.46 (c 0.15, $CHCl_2$).

**C H R O M A T O G R A M  R E P O R T**

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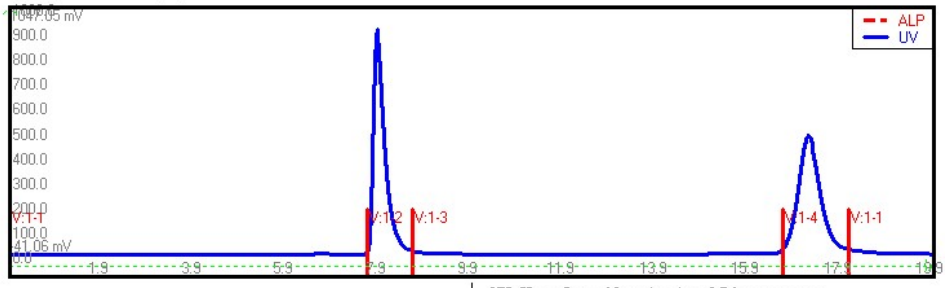
**Run started** :8/4/2016 4:51:15 PM




**Operation Mode** :Standard mode
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**Col Name** :AD
**Column Size**
CSP Density :0.6000
Packed Length :25.0000
Inner Diameter :2.1000
**Inj Vol µL** :1000

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
**Run Time** :20.00 min
**Meth. Vol mL** :200
**Sample ID** :HX_Warfarin
**Data Path** :C:\Program Files\PDR\Alice\
Hui Xing_warfarin

**Eluent and Gradient**

| Time (min) | Solvent A (%) | Solvent B (%) |
|---|---|---|
| 0.00 | 50.0 | 50.0 |

**P E A K  L I S T  R E P O R T**

| No | Name | Type | Start (min) | End (min) | RT (min) | Height (mV) | Area (mVs) | % Area (%) | Col. Area (mVs) | Plates (#) | Conc (mg/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX_WF_1 | (+) | 7.75 | 8.71 | 7.95 | 896.504 | 15702.359 | 51.80 | 15702.338 | 5310.566 | 0.0000 |
| 2 | HX_WF_2 | (+) | 16.73 | 18.15 | 17.28 | 458.640 | 14610.948 | 48.20 | 14610.933 | 1.856 | 0.0000 |

**Total Peak Area** :30313.308 mVs

**C H R O M A T O G R A M  R E P O R T**

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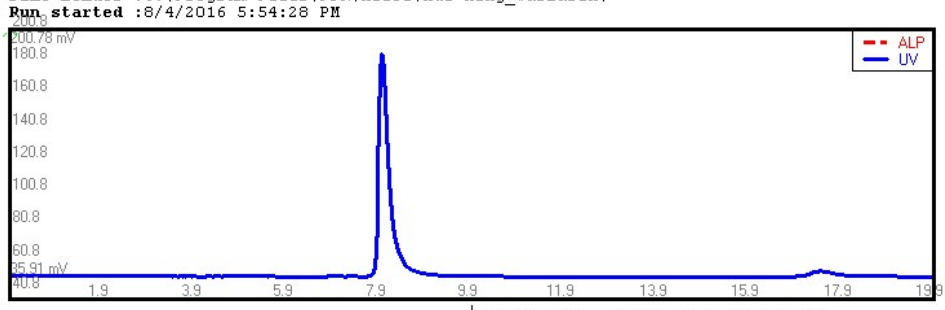


**Operation Mode** :Standard mode
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**Column Size**
CSP Density :0.6000
Packed Length :25.0000
Inner Diameter :2.1000
**Inj Vol µL** :1000

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
**Run Time** :20.00 min
**Meth. Vol mL** :200
**Sample ID** :HX_WF_1
**Data Path** :C:\Program Files\PDR\Alice\
Hui Xing_warfarin

**Eluent and Gradient**

| *Time (min)* | *Solvent A (%)* | *Solvent B (%)* |
|---|---|---|
| 0.00 | 50.0 | 50.0 |

**P E A K  L I S T  R E P O R T**

| *No* | *Name* | *Type* | *Start (min)* | *End (min)* | *RT (min)* | *Height (mV)* | *Area (mVs)* | *% Area (%)* | *Col. Area (mVs)* | *Plates (#)* | *Conc (mg/mL)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX_WF_1 | (+) | 7.91 | 8.46 | 8.07 | 127.377 | 1701.384 | 100.00 | 1701.364 | 8715.681 | 0.0000 |

**Total Peak Area** :1701.384 mVs

**C H R O M A T O G R A M  R E P O R T**

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**File folder** :C:\Program Files\PDR\Alice\Hui Xing_warfarin\
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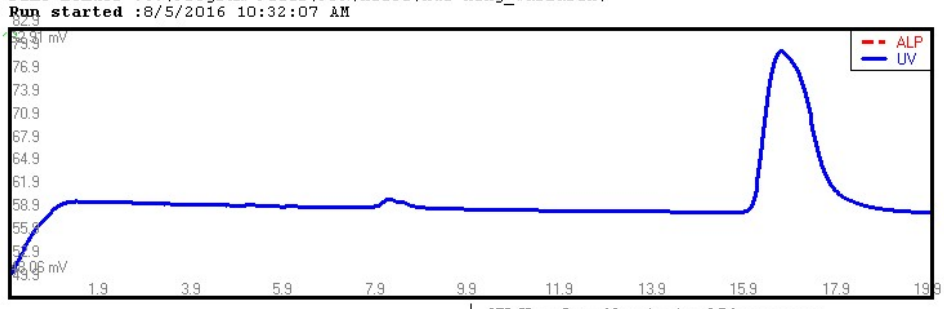


**Operation Mode** :Standard mode
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**Col Name** :AD
**Column Size**
CSP Density :0.6000
Packed Length :25.0000
Inner Diameter :2.1000
**Inj Vol µL** :1000

**UV Wavelengths (nm)** :254,-,-,-,-
**Flow mL/min** :10.00
**Press bar** :150
**Run Time** :20.00 min
**Meth. Vol mL** :200
**Sample ID** :HX_WF_2
**Data Path** :C:\Program Files\PDR\Alice\
Hui Xing_warfarin

**Eluent and Gradient**

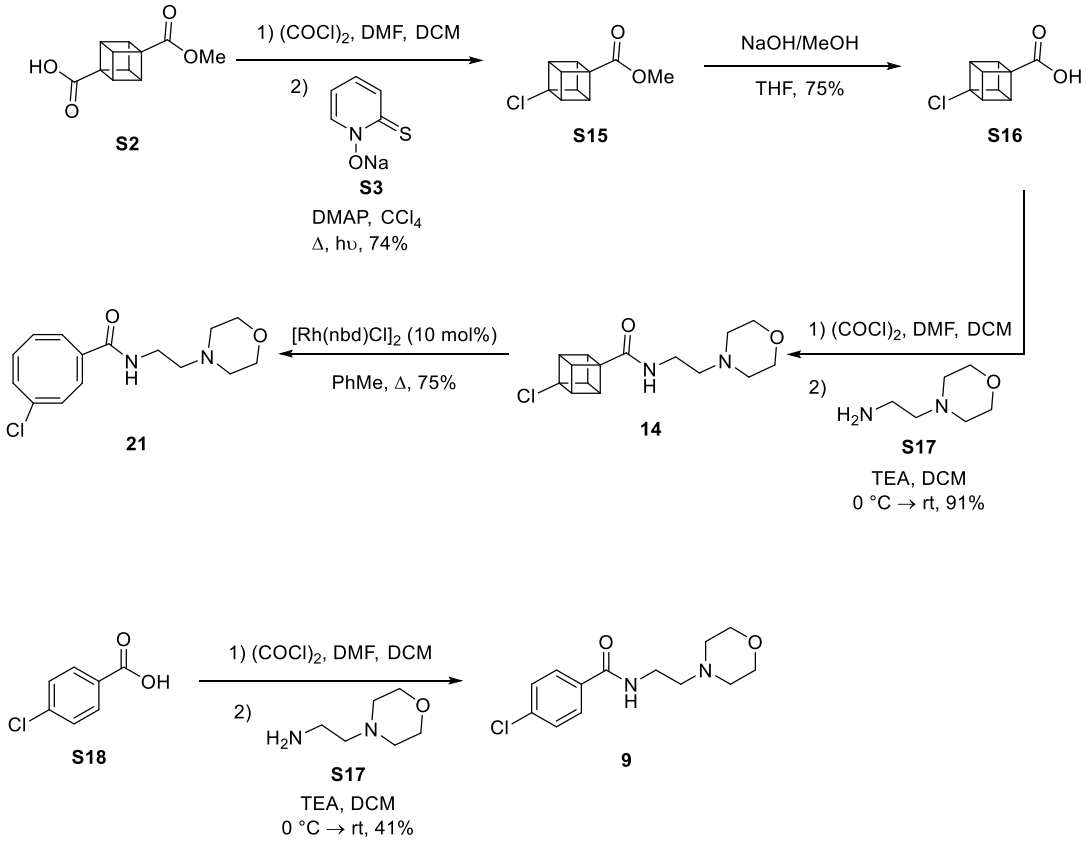
| *Time (min)* | *Solvent A (%)* | *Solvent B (%)* |
|---|---|---|
| 0.00 | 50.0 | 50.0 |

**P E A K  L I S T  R E P O R T**

| *No* | *Name* | *Type* | *Start (min)* | *End (min)* | *RT (min)* | *Height (mV)* | *Area (mVs)* | *% Area (%)* | *Col. Area (mVs)* | *Plates (#)* | *Conc (mg/mL)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HX_WF_2 | (+) | 16.25 | 17.41 | 16.73 | 13.184 | 588.449 | 100.00 | 588.438 | 2452.906 | 0.0000 |

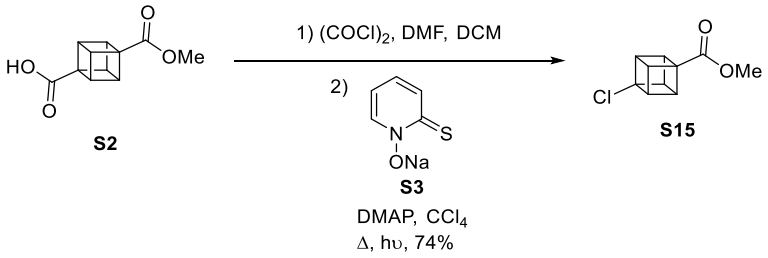
**Total Peak Area** :588.449 mVs

## Moclobemide



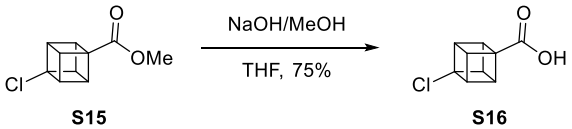

**Scheme S3:** synthesis of moclobemide (**9**) and cubane (**14**) and COT (**21**) analogues.

Methyl 4-chlorocubane-1-carboxylate (**S15**)




To a solution of 4-methoxycarbonylcubane-1-carboxylic acid (**S2**) (2.964 g, 14.37 mmol) in anhydrous DCM (120 mL) was added oxalyl chloride (1.73 mL, 20.12 mmol) and anhydrous DMF (5 drops) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). Separately, freshly ground 2-mercaptopyridine *N*-oxide sodium salt (**S3**) (3.237 g, 21.70 mmol) and DMAP (17 mg, 0.136 mmol) were suspended in carbon tetrachloride (20 mL) and heated to reflux under an argon atmosphere whilst under irradiation from a 500-W tungsten lamp. The newly formed acid chloride was suspended in carbon tetrachloride (20 mL) and added slowly to the refluxing mixture under an argon atmosphere. After reflux (2 h) the carbon tetrachloride was removed by distillation at atmospheric pressure. The resulting residue was suspended in diethyl ether (100 mL) then washed with water (2 x 40 mL), brine (2 x 40 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give an orange oil. Purification by column chromatography (5% ethyl acetate/petroleum ether v/v) gave the title compound (2.104 g, 74%) as a white solid.[47] $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.26–4.12 (m, 3H), 4.20–4.15 (m, 3H), 3.71 (s, 3H).

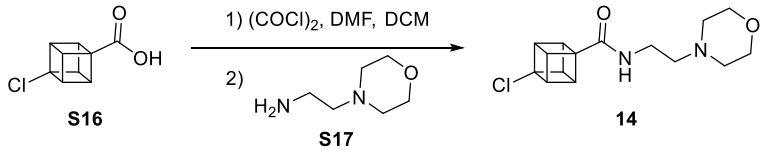
4-Chlorocubane-1-carboxylic acid (**S16**)




Methyl 4-chlorocubane-1-carboxylate (**S16**) (2.091 g, 10.63 mmol) was suspended in THF (50 mL). A solution of sodium hydroxide (444 mg, 11.10 mmol) in methanol (5 mL) was added dropwise and the solution was left to stir for 17 h.

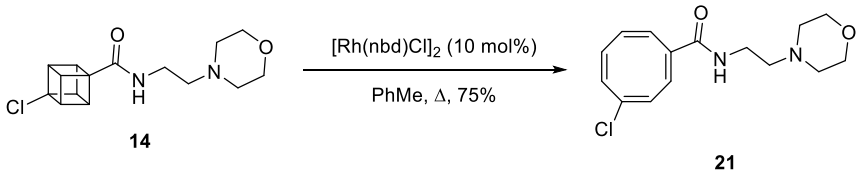
The THF was removed *in vacuo* and the residual solid was suspended in water (50 mL), and washed with chloroform (3 x 25 mL). The aqueous phase was acidified to pH 2 with hydrochloric acid (10 M) and washed again with chloroform (3 x 25 mL). The combined organic phases were dried over magnesium sulfate and concentrated to give the title compound (1.446 g, 75%) as a white solid.[48] $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.31–4.26 (m, 3H), 4.23–4.18 (m, 3H).

Cubane analogue of moclobemide (**14**)




To a solution of 4-chlorocubane-1-carboxylic acid (**S16**) (262 mg, 1.43 mmol) in anhydrous DCM (25 mL) was added oxalyl chloride (0.15 mL, 1.72 mmol) and anhydrous DMF (2 drops) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). The newly formed acid chloride was taken up in anhydrous DCM (25 mL) and cooled to 0 °C under an argon atmosphere. 4-(2-Aminoethyl)morpholine (**S17**) (0.21 mL, 1.72 mmol) was slowly added followed by anhydrous triethylamine (1.00 mL, 7.15 mmol). The solution was allowed to warm to rt, and then left to stir for 17 h before being washed with water (2 x 25 mL) then brine (25 mL). The remaining organic phase was dried over magnesium sulfate, concentrated, and then purified by column chromatography (5% methanol/DCM v/v) to give the title compound (384 mg, 91%) as a white solid. m.p 174.2–175.8 °C; $^1$H-NMR (400 MHz, $C_6D_6$): $\delta$ (ppm) 5.53 (br. s, 1H), 3.82–3.73 (m, 6H), 3.46 (t, $J$ = 4.5 Hz, 4H), 3.18 (q, $J$ = 6.0 Hz, 2H), 1.98–1.93 (m, 6H); $^{13}$C-NMR (100 MHz, $C_6D_6$): $\delta$ (ppm) 170.1, 72.5, 67.0, 58.7, 57.3, 53.9, 53.5, 46.1, 35.5; HRMS-ESI calcd for $C_{15}H_{20}N_2O_2{}^{37}Cl^+$ ($[M+H]^+$): 297.1178; found: 297.1193.

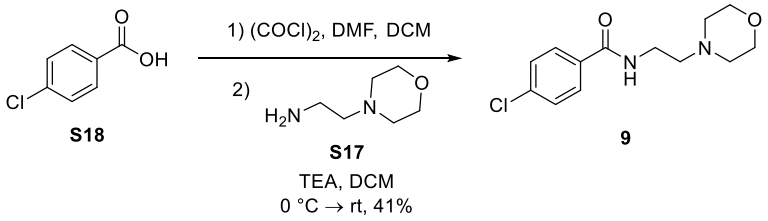
COT analogue of moclobemide (**21**)




**14** **21**

The cubane analogue of moclobemide (**14**) (12 mg, 0.041 mmol) and $[Rh(nbd)Cl]_2$ (2 mg, 0.004 mmol) were suspended in toluene (5 mL) and heated to reflux for 7 h. The solvent was removed and the residue was purified by column chromatography (5% methanol/DCM v/v) to give the title compound (9 mg, 75%) as an orange oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 6.95–6.79 (m, 1H), 6.36–6.26 (m, 1H), 6.17–6.14 (m, 1H), 6.06–6.04 (m, 2H), 6.01–5.95 (m, 1H), 5.83–5.79 (m, 1H), 3.71–3.67 (m, 4H), 3.44–3.36 (m, 2H), 2.54–2.42 (m, 6H); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ (ppm) 165.3, 165.3, 138.0, 136.5, 136.2, 135.9, 134.5, 134.2, 132.6, 132.4, 131.8, 131.2, 131.1, 131.0, 129.8, 129.7, 129.3, 128.3, 67.2, 56.7, 56.5, 53.4, 53.3, 36.2; HRMS-ESI calcd for $C_{15}H_{20}N_2O_2{}^{35}Cl^+$ ($[M+H]^+$): 295.1208; found: 295.1199.

Moclobemide (**9**)

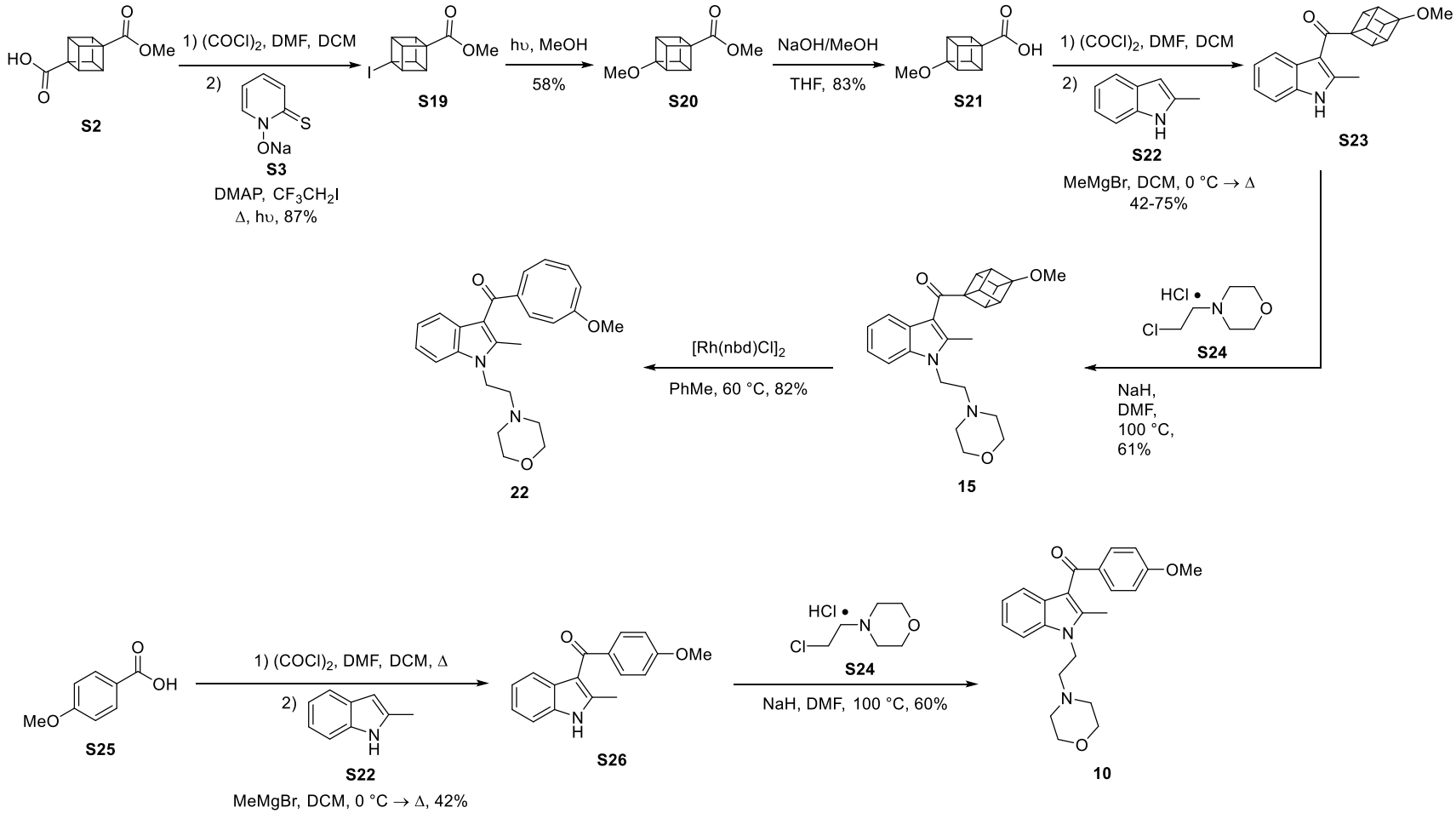



**S18** **S17** **9**

Adapted from the procedure of More *et al*:[49] to a solution of 4-chlorobenzoic acid (**S18**) (307 mg, 1.96 mmol) in anhydrous DCM (60 mL) was added oxalyl chloride (0.25 mL, 2.87 mmol) and anhydrous DMF (5 drops) under an argon atmosphere. The solution was heated to reflux for 1 h. After cooling, the DCM was removed *in vacuo* and the residual brown oil was further dried under high vacuum (1 h). The newly formed acid chloride was taken up in anhydrous DCM (25 mL) and cooled to 0 ℃ under an argon atmosphere. 4-(2-Aminoethyl)morpholine (**S17**) (0.33 mL, 2.30 mmol) and anhydrous triethylamine (0.81 mL, 5.76 mmol) were slowly added. The solution was allowed to warm to rt, and then left to stir for 17 h.

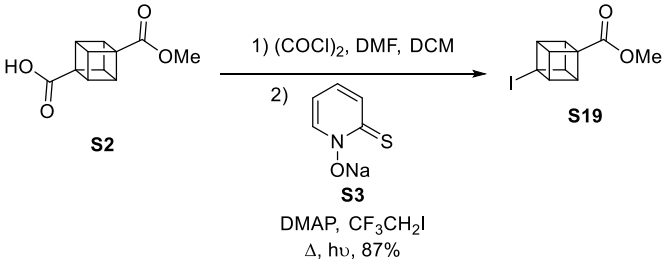
After extensive concentration *in vacuo*, the residual material was taken up in DCM (30 mL) then washed with water (3 x 30 mL). The remaining organic phase dried over magnesium sulfate, concentrated and crystalised from a minimal volume of boiling ethanol to give the title compound (217 mg, 41%) as a white crystaline solid. Data reported are consistent with Allen *et al*.[50] $^1$H-NMR (400 MHz, Acetone-$d_6$): $\delta$ (ppm) 7.89–7.85 (m, 2H), 7.69 (br. s, 1H), 7.50–7.47 (m, 2H), 3.60 (t, $J$ = 4.5 Hz, 4H), 3.51 (q, $J$ = 6.6 Hz, 2H), 2.55 (t, $J$ = 6.6 Hz, 2H), 2.45 (t, $J$ = 4.5 Hz, 4H).

Pravadoline



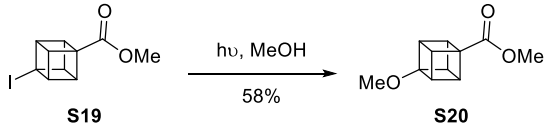

**Scheme S4:** synthesis of pravadoline (**10**) and cubane (**15**) and COT (**22**) analogues.

Methyl 4-iodocubane-1-carboxylate (**S19**)




Following the procedure of Priefer *et al*:[51] to a solution of 4-methoxycarbonylcubane-1-carboxylic acid (**S2**) (1.000 g, 4.84 mmol) in anhydrous DCM (50 mL) was added oxalyl chloride (0.50 mL, 5.82 mmol) and anhydrous DMF (1 drop) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). Separately, freshly ground 2-mercaptopyridine *N*-oxide sodium salt (**S3**) (952 mg, 6.38 mmol), DMAP (6 mg, 0.049 mmol) and 2,2,2-trifluoroiodoethane (2.39 mL, 24.20 mmol) were suspended in anhydrous DCM (50 mL) and heated to reflux under an argon atmosphere whilst under irradiation from a 500-W tungsten lamp. The newly formed acid chloride was suspended in anhydrous DCM (50 mL) and added slowly to the refluxing mixture. After reflux (3 h) the suspension was washed with water (3 x 50 mL) then dried over magnesium sulfate. Concentration and purification by column chromatography (50% ethyl acetate/petroleum ether v/v) gave the title compound (1.210 g, 87%) as an off-yellow solid. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.40–4.36 (m, 3H), 4.30–4.26 (m, 3H), 3.70 (s, 3H).

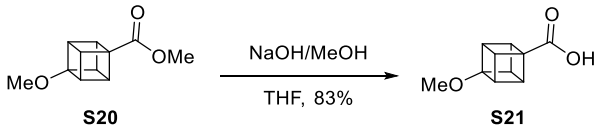
Methyl 4-methoxycubane-1-carboxylate (**S20**)




Methyl 4-iodocubane-1-carboxylate (**S19**) (1080 mg, 3.75 mmol) was suspended in anhydrous methanol (80 mL) in a quartz tube under an argon atmosphere. The tube was placed in a Rayonet (Srinivasen-Griffin) reactor equipped with 2537 Å lamps and irradiated for 17 h. Sodium bicarbonate (5 drops)

was added and the methanol was removed *in vacuo* Purification by column chromatography (DCM) gave the title compound (417 mg, 58%) as a brown oil.[52] $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.18–4.15 (m, 3H), 4.01–3.97 (m, 3H), 3.70 (s, 3H), 3.32 (s, 3H).

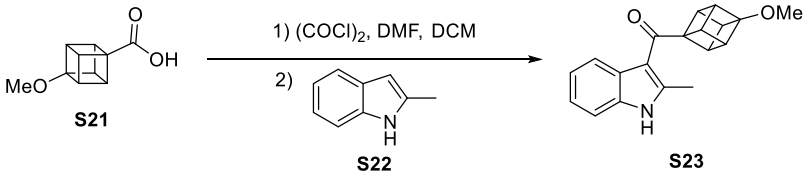
4-Methoxycarbonylcubane-1-carboxylic acid (**S21**)



**S20** **S21**

Methyl 4-methoxycubane-1-carboxylate (**S20**) (407 mg, 2.12 mmol) was suspended in THF (30 mL). A solution of sodium hydroxide (95 mg, 3.96 mmol) in methanol (5 mL) was added dropwise and the solution was left to stir for 21 h. The THF was removed *in vacuo* and the residual solid was suspended in water (20 mL), and washed with DCM (3 x 20 mL). The aqueous phase was acidified to pH 2 with hydrochloric acid (3 M) and washed again with DCM (3 x 20 mL). The combined organic phases were dried over magnesium sulfate and concentrated to give the title compound (315 mg, 83%) as a white solid.[48] m.p 148.7–149.9 ℃; $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 4.21–4.18 (m, 3H), 4.05–4.01 (m, 3H), 3.33 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 177.7, 91.5, 56.4, 51.7, 50.8, 42.7; HRMS-ESI calcd for $C_{10}H_9O_3^-$ ([M-H]$^-$): 177.0557; found: 177.0577.

3-(4-Methoxycubanone)-2-methyl indoline (**S23**)

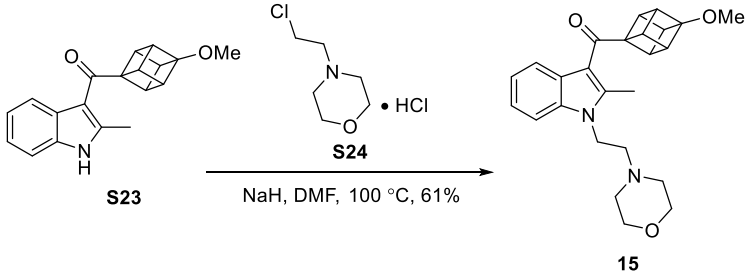


**S21** **S22** **S23**

To a solution of 4-methoxycubane-1-carboxylic acid (**S21**) 28 mg, 0.16 mmol) in anhydrous DCM (5 mL) was added oxalyl chloride (0.02 mL, 0.19 mmol) and anhydrous DMF (1 drop) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). Separately, a

solution of 2-methylindole (**S22**) (22 mg, 0.17 mmol) in anhydrous DCM (5 mL) was added to a solution of methylmagnesium bromide (3 M in diethyl ether, 63 µL, 0.19 mmol) at 0 °C under an argon atmosphere. The solution was warmed to rt, then the newly formed acid chloride was dissolved in anhydrous DCM (5 mL) and slowly added. The mixture was heated to reflux for 2 h. After cooling, saturated ammonium chloride (10 mL) was added and the phases were separated. The aqueous phase was washed with DCM (3 x 10 mL) and the combined organic phases were dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (30% ethyl acetate/petroleum ether v/v) to give the title compound as an orange solid (35 mg, 75%).[53] m.p 161.2–163.8 °C; $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ (ppm) 8.54 (br. s, 1H), 7.82–7.80 (m, 1H), 7.33–7.31 (m, 1H), 7.25–7.18 (m, 2H), 4.30–4.23 (m, 6H), 3.40 (s, 3H), 2.71 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ (ppm) 196.0, 143.6, 134.4, 126.8, 122.5, 122.0, 120.2, 114.3, 110.8, 90.3, 64.5, 51.7, 50.2, 43.4, 15.0; HRMS-ESI calcd for $C_{19}H_{17}O_2NNa^+$ ([M+Na]$^+$): 314.1151; found: 314.1144.

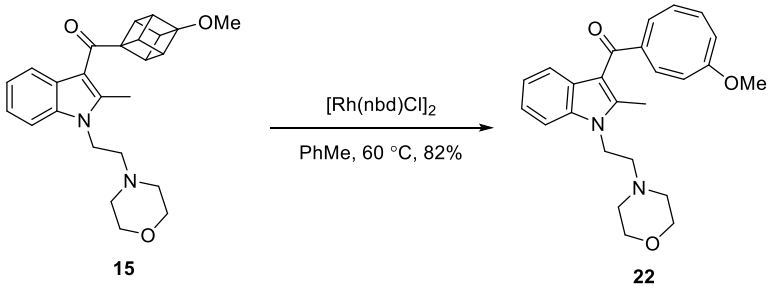
Cubane analogue of pravadoline (**15**)




Sodium hydride (50% dispersion in mineral oil, 40 mg, 0.83 mmol) was suspended in anhydrous DMF (2 mL) under an argon atmosphere. To this was added 3-(4-methoxycubanone)-2-methylindole (**S23**) (20 mg, 0.069 mmol) as a solution in anhydrous DMF (2 mL). The mixture was left to stir for 10 min, then *N*-(2-chloroethyl)-morpholine hydrochloride (**S24**) (21 mg, 0.11 mmol) was slowly added as a solution in anhydrous DMF (2 mL). The mixture was heated to 100 °C. After 17 h the DMF was removed *in vacuo* and the residual material was taken up in water (5 mL) then washed with DCM (3 x 5mL). The combined organic phases were dried over magnesium sulfate, concentrated and purified by column

chromatography (60% ethyl acetate/petroleum ether v/v) to give the title compound (17 mg, 61%) as a yellow solid.[53] m.p 121.5–124.0 ℃; $^1$H-NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.79–7.74 (m, 1H), 7.34–7.31 (m, 1H), 7.25–7.21 (m, 2H), 4.29–4.20 (m, 8H), 3.71 (t, *J* = 4.5 Hz, 4H), 3.39 (s, 3H), 2.73 (s, 3H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.52 (t, *J* = 4.5 Hz, 4H); $^{13}$C-NMR (100 MHz, $CDCl_3$): *δ* (ppm) 196.1, 144.3, 135.7, 126.4, 122.2, 121.9, 120.2, 114.3, 109.4, 90.2, 67.0, 64.7, 57.5, 54.2, 51.7, 50.2, 43.6, 41.1, 12.5; HRMS-ESI calcd for $C_{25}H_{29}O_3N_2^+$ ($[M+H]^+$): 405.2173; found: 405.2176.

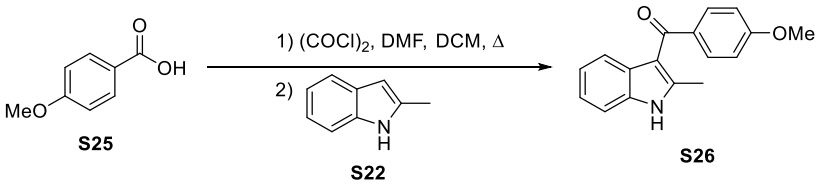
COT analogue of pravadoline (**22**)




**15** **22**

The cubane analogue of pravadoline (**15**) (49 mg, 0.12 mmol) and $[Rh(nbd)Cl]_2$ (6 mg, 0.004 mmol) were suspended in toluene (5 mL) and heated to 60 ℃ for 4 h. The solvent was removed and the residue was purified by column chromatography (ethyl acetate) to give the title compound (40 mg, 82%) as a yellow oil. $^1$H-NMR (500 MHz, $CDCl_3$): *δ* (ppm) 8.11–8.05 (m, 1H), 7.31–7.30 (m, 1H), 7.23–7.16 (m, 2H), 6.54–6.48 (m, 2H), 6.17–5.81 (m, 3H), 5.02–4.97 (m, 1H), 4.24 (t, 2H, *J* = 7.2 Hz), 3.70 (t, 4H, *J* = 4.6 Hz), 3.66–3.63 (m, 3H), 2.72–2.66 (m, 5H), 2.51 (t, 4H, *J* = 4.6 Hz); $^{13}$C-NMR (125 MHz, $CDCl_3$): *δ* (ppm) 191.9, 191.2, 157.5, 156.7, 145.2, 144.0, 143.3, 143.0, 141.2, 140.4, 135.9, 135.9, 134.9, 133.0, 132.3, 131.9, 129.8, 129.1, 128.3, 127.4, 127.4, 122.2, 122.1, 121.6, 121.5, 121.5, 113.6, 113.3, 109.3, 109.2, 99.9, 99.6, 67.0, 57.6, 57.6, 55.6, 55.4, 54.2, 41.2, 12.8, 12.7; HRMS-ESI calcd for $C_{25}H_{29}O_3N_2^+$ ($[M+H]^+$): 05.2173; found: 405.2172.

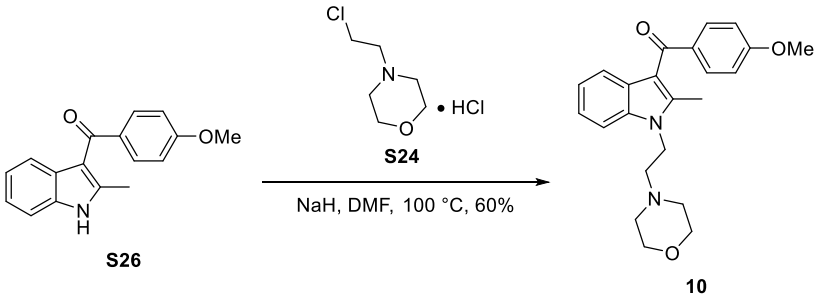
3-(4-Methoxyphenone)-2-methyl indoline (**S26**)




MeMgBr, DCM, 0 °C → Δ, 42%

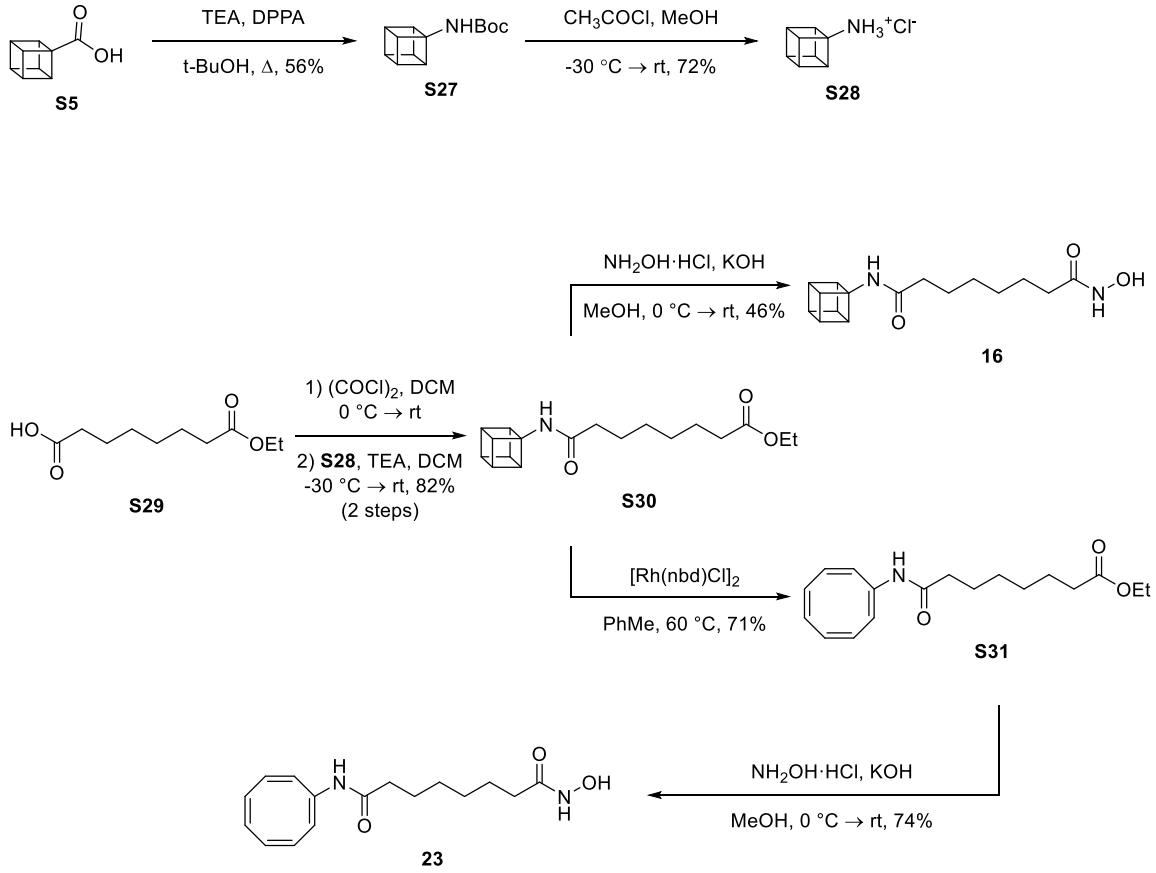
To a solution of p-anisic acid (**S25**) (520 mg, 3.42 mmol) in anhydrous DCM (15 mL) was added oxalyl chloride (0.34 mL, 3.95 mmol) and anhydrous DMF (2 drops) under an argon atmosphere. The solution was heated to reflux. After 2 h, the DCM was removed *in vacuo* and the residual brown solid was further dried under high vacuum (1 h). Separately, a solution of 2-methylindole (**S22**) (455 mg, 3.42 mmol) in anhydrous DCM (15 mL) was added to a solution of methylmagnesium bromide (3M in diethyl ether, 1.32 mL, 3.95 mmol) at 0 ℃ under an argon atmosphere. The solution was warmed to rt, then the newly acid chloride was dissolved in anhydrous DCM (15 mL) and slowly added. The mixture was heated to reflux for 2 h. After cooling, saturated ammonium chloride (10 mL) was added and the phases were separated. The aqueous phase was washed with DCM (3 x 10 mL) and the combined organic phases were dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (30% ethyl acetate/petroleum ether) to give the title compound as a yellow solid (380 mg, 42%). Data reported are consistent with Gong *et al*.[53] $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta$ (ppm) 7.64 (d, $J$ = 8.1 Hz, 2H), 7.39–7.32 (m, 2H), 7.13–6.98 (m, 4H), 3.85 (s, 3H), 2.42 (s, 3H).

Pravadoline (**10**)



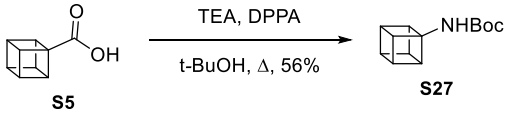

Sodium hydride (50% dispersion in mineral oil, 99 mg, 2.06 mmol) was suspended in anhydrous DMF (1 mL) under an argon atmosphere. To this was added (4-methoxyphenyl)(2-methyl-1H-indol-3-yl)methanone (**S26**) (104 mg, 0.39 mmol) as a solution in anhydrous DMF (3 mL). The mixture was left to stir for 30 min, then *N*-(2-chloroethyl)-morpholine hydrochloride (**S24**) (100 mg, 0.54 mmol) was slowly added as a solution in anhydrous DMF (3 mL) and the mixture was heated to 100 ℃. After 16 h saturated ammonium chloride (10 mL) was added and the mixture was extracted with DCM (2 x 10 mL). The combined organic phases were washed with water (2 x 10 mL), brine (10 mL) then dried over magnesium sulfate and concentrated. Purification by column chromatography (ethyl acetate) gave the title compound (89 mg, 60%) as an orange solid. Data are consistent with Gong *et al*.[53] $^1$H-NMR (500 MHz, Acetone-$d_6$): $\delta$ (ppm) 7.73 (d, $J$ = 9.0 Hz, 2H), 7.50 (d, $J$ = 8.1 Hz, 1H), 7.38 (dt, $J$ = 8.1, 0.9 Hz), 7.19–7.16 (m, 1H), 7.06–7.02 (m, 3H), 4.40 (t, $J$ = 6.8 Hz, 2H), 3.90 (s, 3H), 3.61–3.59 (m, 4H), 2.75 (t, $J$ = 6.8 Hz, 2H), 2.58 (s, 3H), 2.51–2.49 (m, 4H).

SAHA




**Scheme S5:** synthesis of cubane (**16**) and COT (**23**) analogues of SAHA.

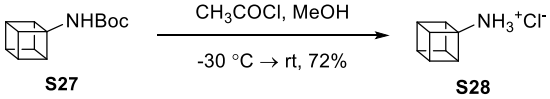
*t*-Butyl cubanylcarbamate (**S27**)




**S5** **S27**

Following the procedure of Chalmers *et al*:[54] a solution of cubanecarboxylic acid (**S5**) (548 mg, 3.70 mmol), anhydrous triethylamine (0.52 mL, 3.73 mmol) and diphenylphosphoryl azide (0.80 mL, 3.72 mmol) in anhydrous tert-butyl alcohol (12 mL) was heated at reflux under an argon atmosphere for 24 h. After cooling to rt, the mixture was concentrated *in vacuo* and purified by column chromatography (40% ethyl acetate / petroleum ether v/v) to give the title compound (453 mg, 56%) as a white solid. $^1$H-NMR (300 MHz, $CDCl_3$): δ (ppm) 5.02 (br. s, 1H), 4.06 (m, 3H), 3.93 (m, 4H), 1.45 (s, 9H).

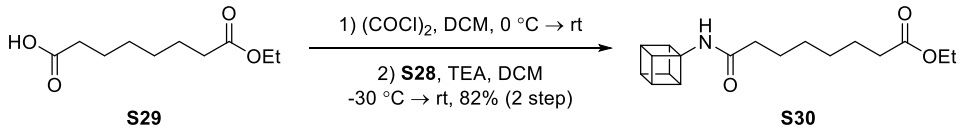
Aminocubane hydrochloride (**S28**)




**S27** **S28**

Adapted from the procedure of Eaton *et al*:[55] acetyl chloride (1.0 mL, 14 mmol) was added slowly dropwise to a vigorously stirring solution of anhydrous methanol (2 mL) at -30 °C under a nitrogen atmosphere. After 15 minutes of stirring, solid tert-butyl cubanylcarbamate (**S27**) (79 mg, 0.36 mmol) was added and the solution continued to stir for 1 h at -30 °C. After warming to rt, the mixture was concentrated *in vacuo* to give a brown solid, which was then filtered and washed (25% acetone / diethyl ether: acetone v/v) to give the title compound (40 mg, 72%) as a white solid. $^1$H-NMR (300 MHz, $D_2O$): δ (ppm) 4.22 (m, 3H), 4.02 (m, 4H).

Ethyl 8-(cubylamino)-8-oxooctanoate (**S30**)

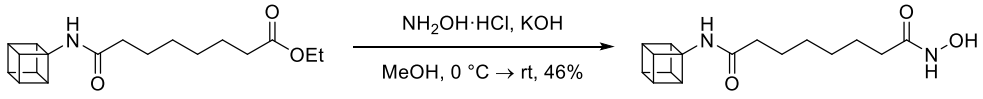



**S29** **S30**

Following the procedure of Chalmers *et al*:[54] dry ethyl hydrogen suberate[56] (**S29**) (286 mg, 1.41 mmol) was dissolved in anhydrous DCM (5 mL) under an

argon atmosphere at 0 °C. Oxalyl chloride (0.15 mL, 1.70 mmol) and anhydrous *N*,*N*-dimethylformamide (1 drop) were added and the solution was left to stir for 2 h. The DCM was removed *in vacuo* and the residual solid was exposed to high vacuum for 1 h to give ethyl 8-chloro-8-oxooctanoate. The nascent acid chloride was dissolved in anhydrous DCM (26 mL, 55 mM) under an argon atmosphere. Separately, aminocubane hydrochloride (**S28**) (30 mg, 0.2 mmol) was suspended in anhydrous DCM (20 mL) and cooled to -30 ℃. A portion of the previously made acid chloride solution (3.69 mL, 0.20 mmol) was added and the solution was stirred for 5 min. Anhydrous triethylamine (0.11 mL, 0.79 mmol) was added dropwise and the solution stirred for 15 min, allowed to warm to rt then concentrated *in vacuo*. The residue was purified by column chromatography (40% ethyl acetate / petroleum ether v/v) to give the title compound (47 mg, 82%) as a white solid. $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.00 (br. s, 1H), 4.13 (m, 5H), 3.93 (m, 4H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.61 (m, 4H), 1.32 (m, 4H), 1.24 (t, *J* = 7.2 Hz, 3H).

Cubane analogue of SAHA (**16**)

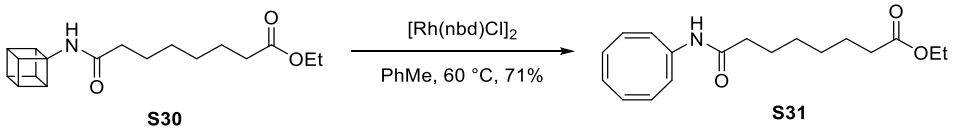



**S30** **16**

Adapted from the procedure of Chalmers *et al*:[54] methanolic potassium hydroxide (2M, 0.89 mL, 1.79 mmol) was slowly added to methanolic hydroxylamine hydrochloride (1M, 0.89 mL, 0.89 mmol) at 0 ℃. The solution was then left to stir for 30 min. Ethyl 8-(cubylamino)-8-oxooctanoate (**S30**) (25 mg, 83 μmol) was dissolved in anhydrous methanol (1.24 mL) and added slowly dropwise under an argon atmosphere. The solution was allowed to stir overnight. The solvent was removed *in vacuo* and water (5 mL) was added followed by glacial acetic acid until pH 6-7 was reached. The mixture was extracted with ethyl acetate (5 x 3 mL) and the combined organic phases were washed with water (3 x 5 mL), concentrated *in vacuo* then crystalised from methanol to give the title compound (11 mg, 46%) as a white solid. $^1$H-NMR (500 MHz, DMSO-$d_6$): δ (ppm) 10.32 (s,

1H), 8.65 (s, 1H), 8.41 (s, 1H), 4.01 (m, 3H), 3.90 (m, 1H), 3.85 (m, 3H), 2.05 (t, *J* = 7.4 Hz, 2H), 1.92 (t, *J* = 7.4 Hz, 2H), 1.46 (m, 4H), 1.22 (m, 4H).

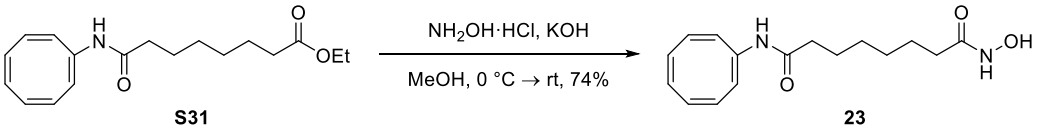
Ethyl 8-((cyclooctatetraenyl)amino)-8-oxooctanoate (**S31**)




**S30** **S31**

Ethyl 8-(cubylamino)-8-oxooctanoate (**S30**) (95 mg, 0.31 mmol) and $[Rh(nbd)Cl]_2$ (14 mg, 30 µmol) were suspended in toluene (5.5 mL) and stirred at 60 ℃ for 3 h. The solvent was removed and the residue was purified by column chromatography (40% ethyl acetate/petroleum ether v/v) to give the title compound (67 mg, 71%) as a yellow oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 6.38-6.34 (m, 1H), 5.98-5.74 (m, 6H), 4.12 (q, *J* =7.2, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 1.68-1.59 (m, 4H), 1.35-1.32 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm) 173.7, 171.3, 134.5, 134.3, 133.0, 131.1, 130.9, 130.5, 129.3, 116.4, 60.2, 37.5, 34.2, 28.8, 28.7, 25.2, 24.7, 14.2; HRMS-ESI calcd for $C_{18}H_{25}NO_3Na^+$ ($[M+Na]^+$): 326.1732, found: 326.1727.

COT analogue of SAHA (**23**)

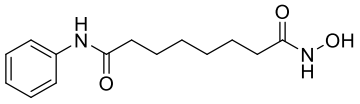



**S31** **23**

Adapted from the procedure of Chalmers *et al*:[54] methanolic potassium hydroxide (2M, 0.75 mL, 1.45 mmol) was slowly added to methanolic hydroxylamine hydrochloride (1M, 0.75 mL, 0.75 mmol) at 0 ℃. The solution was then left to stir for 30 min. Ethyl 8-((cyclooctatetraenyl)amino)-8-oxooctanoate (**S31**) (22 mg, 73 µmol) was dissolved in anhydrous methanol (1.10 mL) and added slowly dropwise under an argon atmosphere. The solution was allowed to stir overnight. The solvent was removed *in vacuo* and water (4 mL) was added followed by glacial acetic acid until pH 6-7 was reached. The mixture was extracted with ethyl acetate (5 x 3 mL) and the combined organic phases were washed with water (3 x 5 mL), concentrated *in vacuo* then crystalised from methanol/ethyl

acetate to give the title compound (16 mg, 74%) as a white solid. m.p. 122.0–124.0 ℃ (dec.); $^{1}$H-NMR (500 MHz, Methanol-$d_4$): $\delta$ (ppm) 6.19 (br. s, 1H), 5.89-5.76 (m, 6H), 2.21 (t, $J$ = 7.4, 2H), 2.08 (t, $J$ = 7.4, 2H), 1.65-1.58 (m, 4H), 1.36-1.33 (m, 4H); $^{13}$C-NMR (125 MHz, Methanol-$d_4$): $\delta$ (ppm) 174.8, 172.9, 136.9, 134.3, 133.4, 132.3, 131.8, 131.7, 130.9, 118.1, 37.7, 33.7, 29.8, 29.8, 26.7, 26.6; HRMS-ESI calcd for $C_{16}H_{22}N_2O_3Na^+$ ([M+Na]$^+$): 313.1528; found: 313.1523.

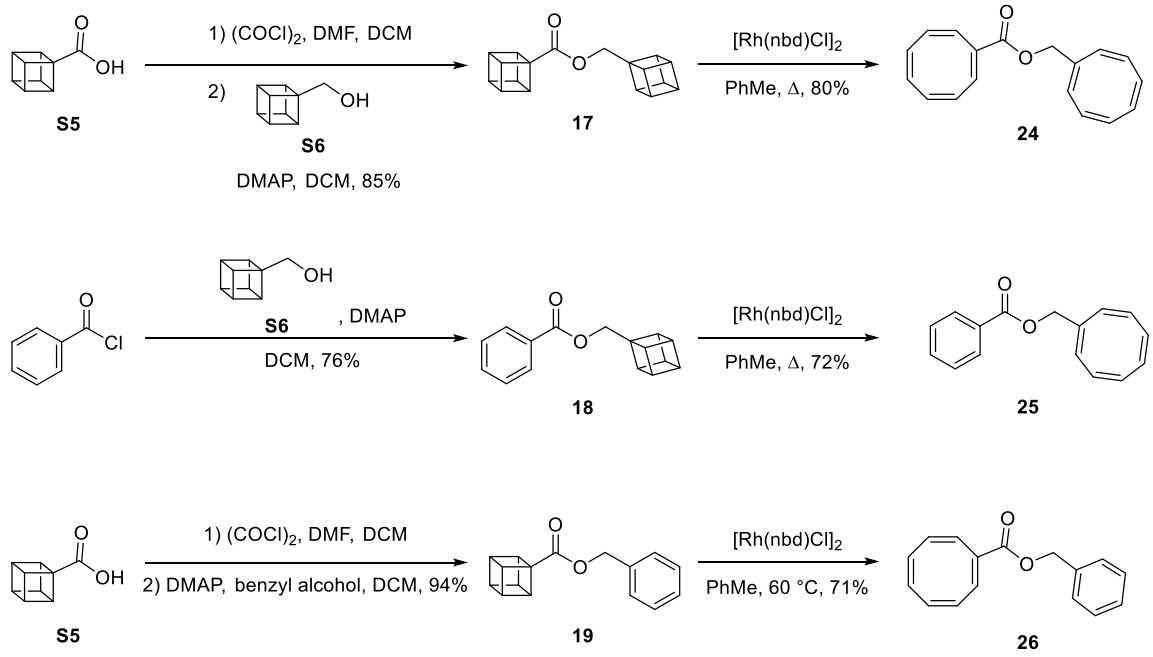
SAHA (**11**)




**11**

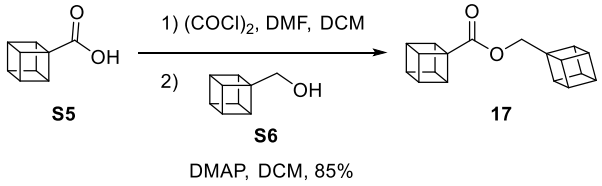
Purchased from Cayman Chemical.

## Benzyl Benzoate



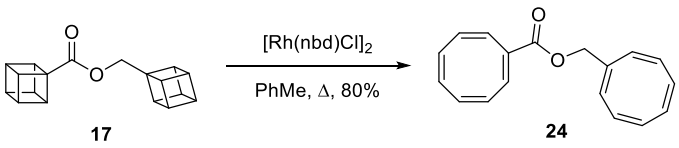

**Scheme S6:** synthesis of cubyl (**17**-**19**) and cyclooctatetraenyl (**24**-**26**) analogues of benzyl benzoate.

Cubylmethyl cubanecarboxylate (**17**)



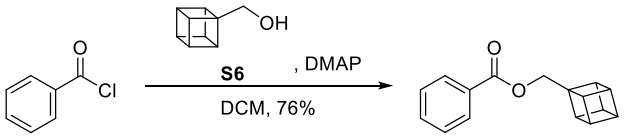

To a solution of cubane-1-carboxylic acid (**S5**) (148 mg, 1.00 mmol) in anhydrous DCM (10 mL) was added oxalyl chloride (0.10 mL, 1.20 mmol) and anhydrous DMF (1 drop) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). The newly formed acid chloride was taken up in anhydrous DCM (6 mL) and a solution of cubylmethanol (**S6**) (134 mg, 1.00 mmol) and DMAP (134 mg, 1.1 mmol) in anhydrous DCM (6 mL) was slowly added under an argon atmosphere. After stirring for 2 h, saturated sodium bicarbonate (10 mL) was added and the phases were separated. The aqueous phase was washed with DCM (2 x 10 mL) then the combined organic phases were dried over magnesium sulfate, concentrated and purified by column chromatography (15% ethyl acetate/petroleum ether v/v) to give the title compound (225 mg, 85%) as a white solid.[54] $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 4.24 (s, 2H), 4.21 (m, 3H), 3.99 (m, 5H), 3.88 (m, 6H).

Cyclooctatetraenylmethyl cyclooctatetraenecarboxylate (**24**)




Cubylmethyl cubanecarboxylate (**17**) (100 mg, 0.38 mmol) and $[Rh(nbd)Cl]_2$ (17 mg, 0.04 mmol) were suspended in toluene (5 mL) and heated to reflux for 4 h. The solvent was removed and the residue was purified by column chromatography (10% ethyl acetate/petroleum ether v/v) to give the title compound (80 mg, 80%) as a yellow oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 7.04 (br. s, 1H), 6.03–5.78 (m, 13H), 4.56 (s, 2H); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ (ppm) 165.4, 142.9, 138.6, 134.2, 133.6, 133.3, 133.2, 132.4, 132.2, 132.0, 131.9, 131.6, 131.3, 131.2, 130.3, 129.8, 129.7, 67.5; HRMS-ESI calcd for $C_{18}H_{16}O_2Na^+$ ($[M+Na]^+$): 287.1043; found: 287.1054.

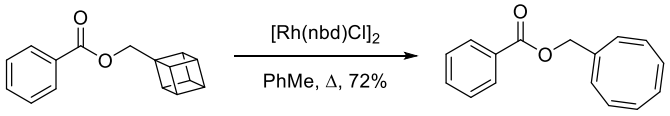
Cubylmethyl benzoate (**18**)




**18**

To a solution of benzoyl chloride (0.31 mL, 2.68 mmol) in anhydrous DCM (3 mL) was slowly added a solution of cubylmethanol (**S6**) **(**300 mg, 2.24 mmol) and DMAP (390 mg, 3.19 mmol) in anhydrous DCM (3 mL) under an argon atmosphere. After stirring for 2 h, saturated sodium bicarbonate (10 mL) was added and the phases were separated. The aqueous phase was washed with DCM (2 x 10 mL) then the combined organic phases were dried over magnesium sulfate, concentrated and purified by column chromatography (10% ethyl acetate/petroleum ether v/v) to give the title compound (410 mg, 76%) as a clear oil.[54] $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 8.06–8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.47–7.41 (m, 2H), 4.48 (s, 2H), 4.08–4.02 (m, 1H), 3.98–3.96 (m, 6H).

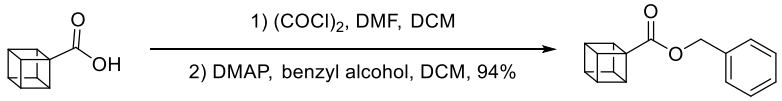
Cyclooctatetraenylmethyl benzoate (**25**)




**18** **25**

Cubylmethyl benzoate (**18**) (126 mg, 0.53 mmol) and $[Rh(nbd)Cl]_2$ (24 mg, 0.05 mmol) were suspended in toluene (5 mL) and heated to reflux for 4 h. The solvent was removed and the residue was purified by column chromatography (10% ethyl acetate/petroleum ether v/v) to give the title compound (91 mg, 72%) as a yellow oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 8.06–8.04 (m, 2H), 7.58–7.55 (m, 1H), 7.46–7.42 (m, 2H), 5.95–5.79 (m, 7H), 4.75 (s, 2H); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ (ppm) 166.3, 138.7, 133.4, 133.1, 132.3, 132.1, 131.9, 131.4, 131.2, 130.3, 130.1, 129.8, 128.5, 67.6; HRMS-ESI calcd for $C_{16}H_{14}O_2Na^+$ ($[M+Na]^+$): 261.0886; found: 261.0898.

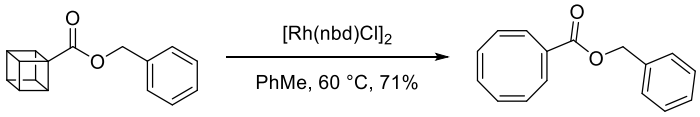
Benzyl cubanecarboxylate (**19**)




**S5** **19**

To a solution of cubane-1-carboxylic acid (**S5**) (206 mg, 1.39 mmol) in anhydrous DCM (10 mL) was added oxalyl chloride (0.15 mL, 1.62 mmol) and anhydrous DMF (1 drop) under an argon atmosphere. After 1 h, the mixture was concentrated *in vacuo* and further dried under high vacuum (1 h). The newly formed acid chloride was taken up in anhydrous DCM (6 mL) and a solution of benzyl alcohol (158 mg, 1.46 mmol) and DMAP (202 mg, 1.65 mmol) in anhydrous DCM (6 mL) was slowly added under an argon atmosphere. After stirring for 2 h, saturated sodium bicarbonate (10 mL) was added and the phases were separated. The aqueous phase was washed with DCM (2 x 10 mL) then the combined organic phases were dried over magnesium sulfate, concentrated and purified by column chromatography (10% ethyl acetate/petroleum ether v/v) to give the title compound (312 mg, 94%) as a clear oil.[54] $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 7.40–7.30 (m, 5H), 5.15 (s, 2H), 4.28–4.26 (m, 3H), 4.03–3.97 (m, 4H).

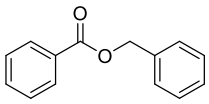
Benzyl cyclooctatetraenecarboxylate (**26**)




**19** **26**

Benzyl cubanecarboxylate (**19**) (97 mg, 0.41 mmol) and $[Rh(nbd)Cl]_2$ (19 mg, 0.04 mmol) were suspended in toluene (5 mL) and heated to 60 ℃ 16 h. The solvent was removed and the residue was purified by column chromatography (10% ethyl acetate/petroleum ether v/v) to give the title compound (69 mg, 71%) as a yellow oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 7.37–7.31 (m, 5H), 7.08 (br. s, 1H), 6.07–5.79 (m, 6H), 5.19 (s, 2H); $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ (ppm) 165.7, 143.0, 136.1, 134.3, 133.6, 133.3, 132.4, 131.6, 130.3, 129.7, 128.7, 128.3, 128.3, 66.7; HRMS-ESI calcd for $C_{16}H_{14}O_2Na^+$ ($[M+Na]^+$): 261.0886; found: 261.0896.

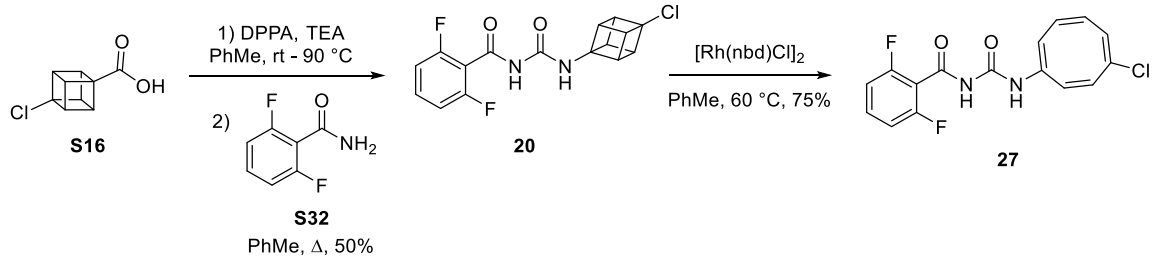
Benzyl benzoate (**12**)



**19**

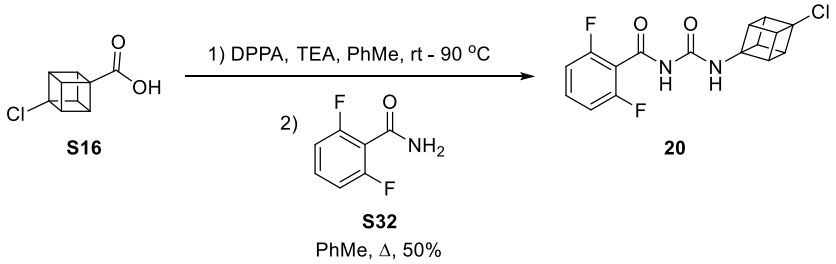
Purchased from Sigma-Aldrich.

Diflubenzuron




**Scheme S7:** synthesis of cubane (**20**) and COT (**27**) analogues of diflubenzuron.

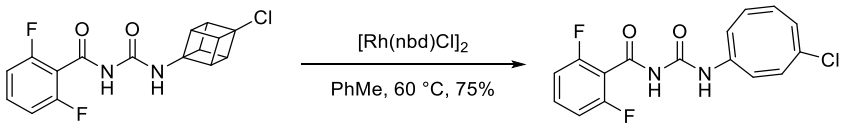
Cubane analogue of diflubenzuron (**20**)




**S16** **S32** **20**

To a solution of 4-chloro-cubane carboxylic acid (**S16**) (1 g, 5.50 mmol) in anhydrous toluene (10 mL), was added triethylamine (0.9 mL, 6.6 mmol) and diphenylphosphorazide (1.50 g, 5.50 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 30 min, and then heated at 90 °C for 2 h to generate the isocyanate. A separate solution of 2,6-difluorobenzamide (**S32**) (0.95 g, 6.05 mmol) in anhydrous toluene (20 mL) under an argon atmosphere was prepared and heated to reflux in toluene. To this solution was added dropwise (10 mins.) the above hot isocyanate solution while maintaining reflux. After addition the reaction mixture was stirred under reflux condition for 12 h. On cooling a precipitate formed, which was filtered and washed with toluene and acetone to afford the title compound as a white solid (924 mg, 50%). Data reported are consistent with Chalmers *et al*.[54] $^1$H NMR (400 MHz, $CDCl_3$) δ: 9.65 (br. s, 1H), 8.83 (br. s, 1H), 7.53-7.45 (m, 1H), 7.03-6.99 (m, 2H), 4.11-4.07 (m, 3H), 4.01-3.98 (m, 3H).

COT analogue of diflubenzuron (**27**)

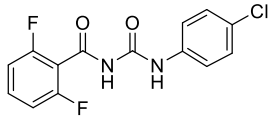



**20** **27**

The cubane analogue of diflubenzuron (**20**) (200 mg, 0.6 mmol) and $[Rh(nbd)Cl]_2$ (27 mg, 0.06 mmol) were suspended in toluene (30 mL) and stirred at 60 °C for 24 h. The solvent was removed and the residue was purified by column chromatography (20% ethyl acetate/petroleum ether v/v) to give the title compound (150 mg, 75%) as a yellow solid. m.p. 146 ℃ (dec.). $^1$H-NMR (500 MHz, $CDCl_3$): δ (ppm) 9.74-9.68 (m, 1H), 9.27-9.24 (m, 1H), 7.51-7.45 (m, 1H), 7.03-6.99 (m, 2H),

6.23-5.68 (m, 6H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ (ppm) 161.8, 161.03, 161.0, 160.9, 159.0, 159.0, 158.9, 150.6, 134.0, 133.6, 133.5, 133.3, 133.1, 132.9, 132.2, 131.6, 130.7, 130.4, 130.3, 130.0, 129.6, 128.9, 128.0, 117.7, 115.7, 115.4, 112.5, 112.3; HRMS-ESI calcd for $C_{16}H_{11}ClF_2N_2O_2Na^+$([M+Na]$^+$): 359.0369; found: 359.0362.

Diflubenzuron (**13**)




**13**

Purchased from AK Scientific.

logP Measurements

*logP measurements pertaining to warfarin (**6**), moclobemide (**9**), pravadoline (**10**), SAHA (**11**), benzyl benzoate (**12**), diflubenzuron (**13**), and analogues (performed by the group led by Prof. Craig Williams at the School of Chemistry and Molecular Biosciences):*

A shake-flask procedure was adapted from several sources.[57] All experiments were conducted at room temperature (*ca* 25 °C). Solvents were saturated before taking measurements: Milli-q water (500 mL) and *n*-octanol (100 mL) were stirred vigorously (24 h) then poured into a separatory funnel and left to partition (3 h). Most of each phase was separated, discarding the phase boundary. The separated phases were used in all subsequent procedures. Measurements of volume were made using a micropipette.

Prior to taking measurements it was useful to estimate the mass expected in the aqueous phase. Estimations can be made using ClogP (calculated using www.molinspiration.com) of the analyte and the following derivation of the standard logP equation:

$$\boldsymbol{y = \frac{B\Sigma_m}{AP + B}}$$

where:

$$A = volume_{octanol}$$

$$B = volume_{water}$$

$$y = mass_{water}$$

$$\Sigma_m = total\ mass$$

$$P = partition\ coefficient$$

A general procedure is as follows:

**Stock solution:** the desired analyte was accurately weighed and *fully dissolved* in a known volume of *n*-octanol.

**Standard solution:** a known volume of stock solution was dissolved in a known volume of suitable HPLC solvent.

**Aqueous 1:** a known volume of water and known volume of stock solution were added to a 10 mL centrifuge tube. Transfer of the stock solution was aided by washing with a known volume of *n*-octanol. The tube was inverted 100 times then centrifuged (20 min). The *n*-octanol and a small volume around the phase boundary were removed. The bottom of the centrifuge tube was pierced with a needle and a known volume of water (≤ 80% of the total volume) was drained into another 10 mL plastic centrifuge tube. The water was extracted with organic solvent (3 x). The combined organic phases were concentrated then dissolved in a known volume of HPLC solvent.

**Aqueous 2-5:** the procedure was repeated four more times, varying the phase ratios (e.g. 1:10, 1:20, 1:40 etc.) for each repeat.

**Quantification:** the standard solution and aqueous 1-5 were each subjected to HPLC. The area under curve (AUC) from the UV (or PDA) trace for each was measured. The concentration of analyte in aqueous 1-5 was calculated using the known concentration of the standard solution.

**logP:** the analyte concentrations were used to calculate a logP for each repeat. The mean of a minimum of three repeats that lay within a range of ± 0.3 was calculated to give the final logP of the analyte.

An example procedure is as follows:

**Warfarin stock solution:** Warfarin (21.2 mg, 0.069 mmol) was dissolved in *n*-octanol (4.000 mL) to give a stock solution of 5.3 mg $mL^{-1}$.

**Warfarin standard solution:** Warfarin stock solution (94 µL, 0.500 mg) was suspended in MeOH (906 µL) to give a standard solution of 0.5 mg $mL^{-1}$. HPLC AUC: 4612006.

**Warfarin aqueous 1:** stock solution (450 µL, 2.385 mg) was washed with *n*-octanol (50 µL) into water (5.000 mL) in a 10 mL plastic centrifuge tube. The tube was inverted 100 times then subjected to centrifugation for (20 min). The *n*-octanol and a small volume around the phase boundary were removed. The bottom of the tube was pierced with a needle and the water layer (4.000 mL) was transferred to another 10 mL plastic centrifuge tube. The aqueous phase was extracted with ethyl acetate (3 x 2 mL). The combined organic phases were concentrated then dissolved in MeOH (300 µL) for HPLC analysis. HPLC AUC: 1272563.

Quantification:

$$HPLC_{Conc.} = \frac{1272563}{4612006} \times 0.5\ mg\ mL^{-1} = 0.14\ mg\ mL^{-1}$$

$$HPLC_{Mass} = 0.14\ mg\ mL^{-1} \times 0.300\ mL\ = 0.041\ mg$$

$$5.000\ mL\ H_2O_{Mass} = \frac{0.041\ mg}{0.8} = 0.051\ mg$$

$$500\ \mu L\ n-octanol_{Mass} = \ 2.39\ mg\ - 0.051\ mg = 2.34\ mg$$

$$logP = log\frac{\left[\frac{2.34\ mg}{0.500\ mL}\right]}{\left[\frac{0.051\ mg}{5.000\ mL}\right]} = 2.66$$

**logP:** the mean of the remaining measurements (excluding outliers i.e. values greater than one standard deviation from the mean) was calculated as 2.73. The logP of Warfarin has previously been measured as 2.70.[58]

The derivation of the standard logP equation is as follows:

$$logP = log\frac{[octanol]}{[water]}$$

$$P = \frac{[octanol]}{[water]}$$

$$P = \frac{\left(\frac{x}{A}\right)}{\left(\frac{y}{B}\right)}$$

$$P = \frac{x}{A} \times \frac{B}{y}$$

$$x + y = \Sigma_m$$

$$x = \Sigma_m - y$$

$$P = \frac{\Sigma_m - y}{A} \times \frac{B}{y}$$

$$P = \frac{B(\Sigma_m - y)}{Ay}$$

$$yAP = B\Sigma_m - yB$$

$$yAP + yB = B\Sigma_m$$

$$y(AP + B) = B\Sigma_m$$

$$\boldsymbol{y = \frac{B\Sigma_m}{AP + B}}$$

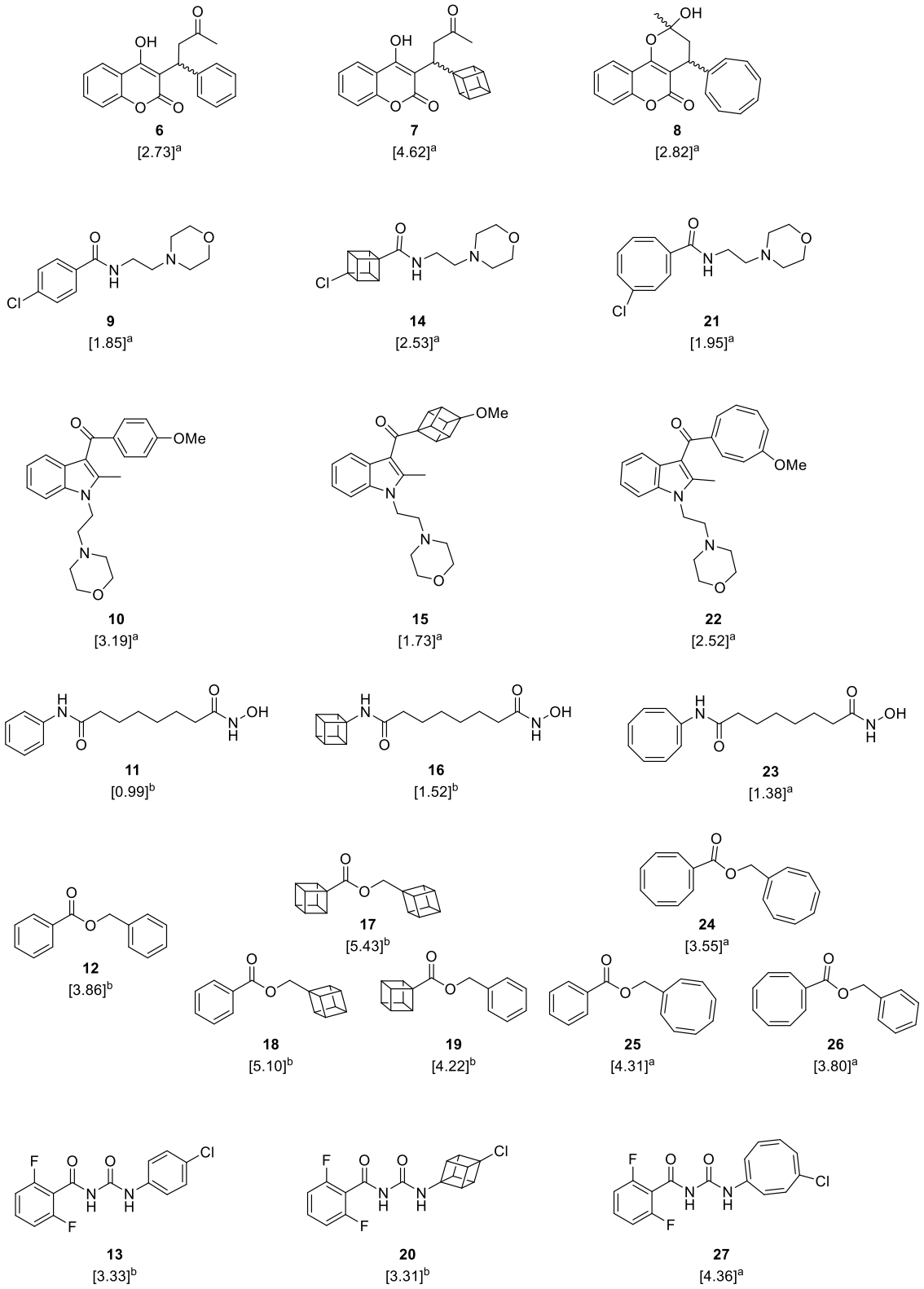



**Figure S1:** summary of logP values. Values in [brackets] denote logP value. 'a' denotes a value measured using the shake-flask procedure. 'b' denotes a value measured using a HPLC calibration curve.[54]

Computational Methods

*Molecular geometry calculations pertaining to cubane (**1**) and cyclooctatetraene (**2**) (performed by Dr Jed Burns at the School of Chemistry and Molecular Biosciences):*

Geometry optimisations were initially conducted using the well-known B3LYP functional with the 6-311+G(d,p) basis set.[59] This level of theory has been used previously to compute reliable structures, especially in the context of NMR prediction of organic compounds.[60] To ensure the validity of the results, computed structures were reoptimised using the modern M06 and M06-2X functionals (6-311+G(d,p) basis set),[61] which are parameterised to include medium range interactions that mimic dispersion. All structures obtained were confirmed as minima by frequency calculations (no imaginary frequencies). Calculations were conducted using the Gaussian 09 (rev. A.02) and 16 (rev. A.03) software packages,[62] chemical figures were generated with CYL view.[63]

In order to confirm the accuracy of the DFT calculations, computed structures were compared with those determined by X-ray crystallography.

Crystal structures for cubane[64] yielded distances of 4.70 (“para”), 3.95 (“meta”) and 2.76 (“ortho”) angstroms (Å), 0.05 – 0.2 shorter than the calculated distances. We observed similar distances in our own crystallographic data for **S10a** (4.706 (“para”), 3.842 (“meta”) and 2.710 (“ortho”) Å).

No unsubstituted or monosubstituted cyclooctatetraene structures could be found in the Cambridge Crystallographic Data Centre (CCDC) database. Equivalent distances from benzocyclooctatetraene[65] were found to be 4.98 (“para”) and 4.33 (“meta”) Å. Our synthesised warfarin COT-analogue **S13** possess “para” and “meta” distances of 4.997 and 4.286 Å. These values are 0.3 – 0.4 Å shorter than the calculated distances.

Discrepancies between the values are likely due to the differences in physical state (calculations were conducted in the gas phase, crystallographic data are solid

state measurements). Nevertheless, the distances are similar and enable meaningful comparisons to be made.

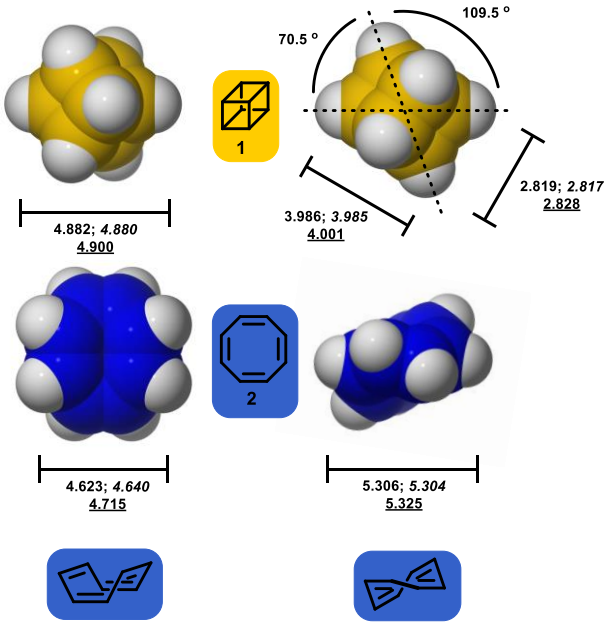



**Figure S2:** Space filled model comparisons of cubane (**1**) and cyclooctatetraene (COT) (**2**). Bond distances are in angstroms [plain text - M06-2X/6-311+G(d,p), *italics* -M06/6-311+G(d,p), underlined -B3LYP/6-311+G(d,p)], angles are in degrees.

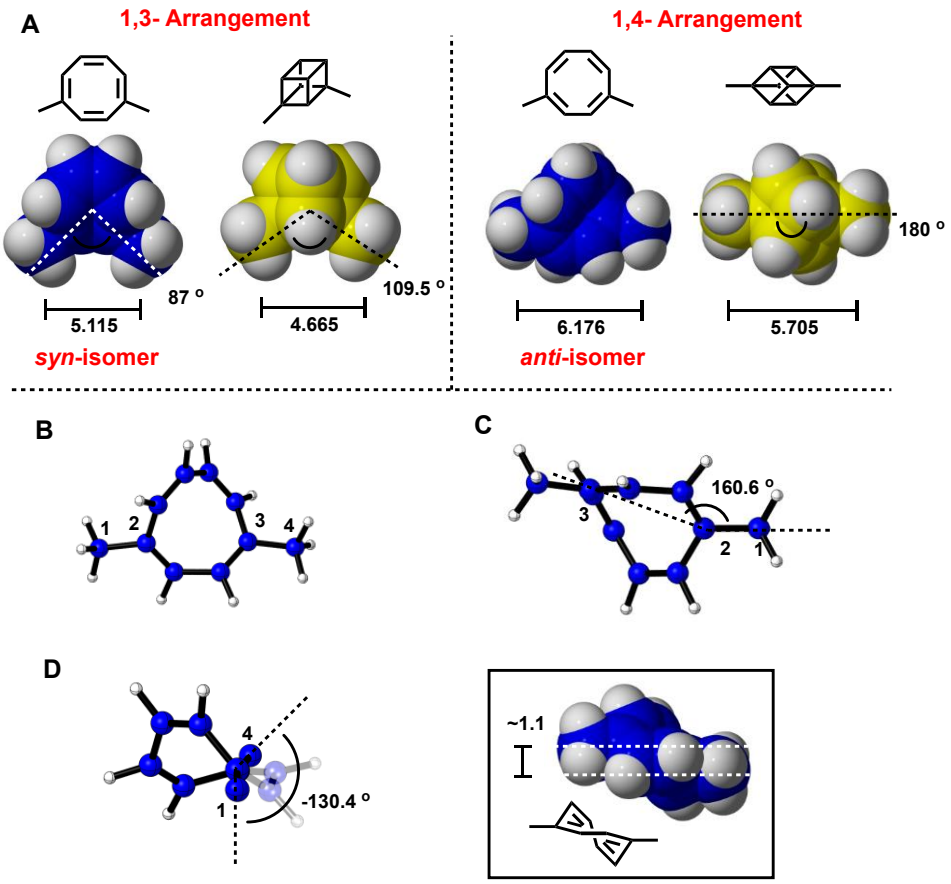



**Figure S3: A)** Energy minimized geometries [M06-2X/6-311+G(d,p)] with selected distances and angles comparing 1,4-disubstituted COT with that of 1,3- and 1,4- disubstituted cubane. Bond distances are in angstroms, angles are in degrees; **B)** Face centered view of 1,4-COT; **C)** Angle between C1-C2-C3; **D)** Dihedral angle of C1 and C4 along the C2-C3 axis. Methyl hydrogen atoms have been omitted for clarity.

Computational data are listed as follows:

Energy (E)
Enthalpy (H)
Gibbs Free Energy (G)

xyz coordinates

Separate data are listed for B3LYP, M06 and M06-2X calculations. All energies are in Hartrees.

**Cubane (1)**

B3LYP
E = -309.5325529
H = -309.394348
G = -309.428088

| | | | |
|---|---|---|---|
| C | -0.78674 | -0.97407 | -0.53303 |
| C | -0.78522 | -0.53335 | 0.97513 |
| C | -0.78642 | 0.53409 | -0.97375 |
| C | -0.78489 | 0.97481 | 0.53441 |
| C | 0.78664 | 0.97406 | 0.53321 |
| H | -1.41293 | 1.75502 | 0.96208 |
| H | -1.41569 | 0.96151 | -1.75312 |
| C | 0.78511 | 0.53353 | -0.97512 |
| C | 0.78631 | -0.53426 | 0.97374 |
| H | -1.41352 | -0.96018 | 1.75560 |
| C | 0.78479 | -0.97480 | -0.53458 |
| H | 1.41692 | 1.75311 | 0.95962 |
| H | -1.41627 | -1.75369 | -0.95961 |

| | | | |
|---|---|---|---|
| H | 1.41633 | -0.96152 | 1.75254 |
| H | 1.41417 | 0.96019 | -1.75502 |
| H | 1.41359 | -1.75444 | -0.96210 |

M06

E = -309.3022645

H = -309.163510

G = -309.197197

| | | | |
|---|---|---|---|
| C | 0.77942 | 0.59637 | -0.92689 |
| C | 0.77844 | 0.92787 | 0.59613 |
| C | 0.78045 | -0.92665 | -0.59540 |
| C | 0.77947 | -0.59516 | 0.92763 |
| C | -0.77934 | -0.59624 | 0.92698 |
| H | 1.40899 | -1.07569 | 1.67684 |
| H | 1.41075 | -1.67508 | -1.07611 |
| C | -0.77836 | -0.92796 | -0.59600 |
| C | -0.78037 | 0.92674 | 0.59526 |
| H | 1.40715 | 1.67726 | 1.07744 |
| C | -0.77940 | 0.59502 | -0.92772 |
| H | -1.40936 | -1.07738 | 1.67534 |
| H | 1.40890 | 1.07786 | -1.67551 |
| H | -1.41121 | 1.67492 | 1.07563 |
| H | -1.40760 | -1.67710 | -1.07695 |
| H | -1.40945 | 1.07521 | -1.67667 |

M06-2X

E = -309.4067648

H = -309.266762

G = -309.300406

| | | | |
|---|---|---|---|
| C | 0.65241 | -0.68866 | 0.96537 |
| C | 0.47981 | 0.86415 | 0.92456 |
| C | -0.85499 | -0.86600 | 0.59249 |
| C | -1.02756 | 0.68683 | 0.55169 |
| C | -0.65251 | 0.68862 | -0.96541 |
| H | -1.85276 | 1.23890 | 0.99493 |
| H | -1.54207 | -1.56136 | 1.06851 |
| C | -0.47978 | -0.86425 | -0.92457 |
| C | 0.85496 | 0.86610 | -0.59252 |
| H | 0.86543 | 1.55818 | 1.66743 |
| C | 1.02765 | -0.68680 | -0.55169 |
| H | -1.17651 | 1.24195 | -1.74098 |
| H | 1.17626 | -1.24199 | 1.74102 |
| H | 1.54202 | 1.56159 | -1.06842 |
| H | -0.86542 | -1.55841 | -1.66732 |
| H | 1.85296 | -1.23887 | -0.99478 |

**COT (2)**

B3LYP

E = -309.6690978

H = -309.529376

G = -309.567551

| | | | |
|---|---|---|---|
| C | 0.67035 | 1.56508 | -0.37512 |
| C | -0.59575 | 1.59477 | 0.37541 |
| H | -0.77933 | 2.51417 | 0.92923 |
| C | -1.56509 | 0.67035 | 0.37513 |
| H | -2.47492 | 0.89728 | 0.92869 |
| C | -1.59479 | -0.59576 | -0.37540 |
| H | -2.51420 | -0.77934 | -0.92922 |

| | | | |
|---|---|---|---|
| C | -0.67035 | -1.56507 | -0.37513 |
| H | -0.89726 | -2.47491 | -0.92871 |
| C | 0.59576 | -1.59477 | 0.37541 |
| H | 0.77931 | -2.51418 | 0.92923 |
| C | 1.56509 | -0.67035 | 0.37513 |
| H | 2.47493 | -0.89727 | 0.92869 |
| H | 0.89728 | 2.47491 | -0.92869 |
| C | 1.59478 | 0.59576 | -0.37541 |
| H | 2.51419 | 0.77932 | -0.92922 |

M06

E = -309.4093751

H = -309.269995

G = -309.308114

| | | | |
|---|---|---|---|
| C | -0.64143 | -1.55571 | -0.38870 |
| C | 0.59955 | -1.57198 | 0.38900 |
| H | 0.77766 | -2.48020 | 0.96575 |
| C | 1.55574 | -0.64144 | 0.38870 |
| H | 2.45908 | -0.84425 | 0.96500 |
| C | 1.57203 | 0.59955 | -0.38900 |
| H | 2.48025 | 0.77768 | -0.96571 |
| C | 0.64144 | 1.55570 | -0.38870 |
| H | 0.84422 | 2.45906 | -0.96499 |
| C | -0.59956 | 1.57199 | 0.38901 |
| H | -0.77764 | 2.48023 | 0.96571 |
| C | -1.55574 | 0.64145 | 0.38870 |
| H | -2.45911 | 0.84424 | 0.96496 |
| H | -0.84425 | -2.45906 | -0.96500 |
| C | -1.57201 | -0.59956 | -0.38900 |
| H | -2.48025 | -0.77765 | -0.96570 |

M06-2X

E = -309.5219292

H = -309.381326

G = -309.419433

| | | | |
|---|---|---|---|
| C | 0.63394 | -1.56035 | 0.39594 |
| C | -0.60874 | -1.56993 | -0.39658 |
| H | -0.78311 | -2.47200 | -0.97905 |
| C | -1.56035 | -0.63394 | -0.39594 |
| H | -2.45958 | -0.82330 | -0.97810 |
| C | -1.56994 | 0.60874 | 0.39658 |
| H | -2.47201 | 0.78312 | 0.97904 |
| C | -0.63395 | 1.56034 | 0.39594 |
| H | -0.82330 | 2.45958 | 0.97809 |
| C | 0.60874 | 1.56994 | -0.39658 |
| H | 0.78311 | 2.47201 | -0.97903 |
| C | 1.56035 | 0.63395 | -0.39594 |
| H | 2.45959 | 0.82330 | -0.97808 |
| H | 0.82330 | -2.45958 | 0.97810 |
| C | 1.56994 | -0.60874 | 0.39658 |
| H | 2.47201 | -0.78312 | 0.97903 |

**Cubane, meta-substituted**

B3LYP

E = -388.1958208

H = -387.999573

G = -388.040253

| | | | |
|---|---|---|---|
| C | -1.10916 | 1.18010 | -0.00011 |

| | | | |
|---|---|---|---|
| C | -1.11586 | -0.39525 | -0.00004 |
| C | 0.00007 | -0.39027 | -1.11148 |
| C | 0.00007 | 1.17936 | -1.11120 |
| C | 1.10925 | 1.18013 | 0.00006 |
| C | -0.00010 | 1.17942 | 1.11114 |
| C | -0.00007 | -0.39021 | 1.11154 |
| C | 1.11582 | -0.39529 | 0.00009 |
| C | 2.34276 | -1.26107 | 0.00001 |
| H | -0.00005 | -1.02385 | 2.00005 |
| H | 0.00009 | -1.02397 | -1.99994 |
| H | 2.00201 | 1.80581 | 0.00009 |
| C | -2.34279 | -1.26103 | -0.00001 |
| H | 0.00008 | 1.80847 | -1.99988 |
| H | -0.00014 | 1.80859 | 1.99979 |
| H | -2.00192 | 1.80575 | -0.00013 |
| H | 2.96083 | -1.07196 | 0.88519 |
| H | 2.07772 | -2.32453 | -0.00015 |
| H | 2.96082 | -1.07168 | -0.88511 |
| H | -2.96091 | -1.07165 | 0.88507 |
| H | -2.96081 | -1.07194 | -0.88523 |
| H | -2.07769 | -2.32447 | 0.00018 |

M06

E = -387.8965152

H = -387.700524

G = -387.741516

| | | | |
|---|---|---|---|
| C | -1.10044 | 1.17063 | -0.00002 |
| C | -1.10466 | -0.39089 | -0.00002 |
| C | 0.00005 | -0.38778 | -1.10345 |
| C | -0.00001 | 1.17016 | -1.10308 |

| | | | |
|---|---|---|---|
| C | 1.10043 | 1.17064 | -0.00001 |
| C | -0.00002 | 1.17020 | 1.10305 |
| C | -0.00002 | -0.38774 | 1.10349 |
| C | 1.10467 | -0.39088 | 0.00005 |
| C | 2.32348 | -1.25042 | 0.00001 |
| H | -0.00002 | -1.02682 | 1.98984 |
| H | 0.00012 | -1.02690 | -1.98977 |
| H | 1.99736 | 1.79265 | -0.00001 |
| C | -2.32348 | -1.25044 | -0.00001 |
| H | -0.00003 | 1.80094 | -1.99199 |
| H | -0.00003 | 1.80101 | 1.99194 |
| H | -1.99734 | 1.79260 | -0.00003 |
| H | 2.94207 | -1.06131 | 0.88587 |
| H | 2.05809 | -2.31466 | -0.00010 |
| H | 2.94207 | -1.06113 | -0.88581 |
| H | -2.94211 | -1.06116 | 0.88578 |
| H | -2.94203 | -1.06133 | -0.88589 |
| H | -2.05807 | -2.31468 | 0.00011 |

M06-2X

E = -388.0274736

H = -387.828797

G = -387.869546

| | | | |
|---|---|---|---|
| C | -1.10334 | 1.17362 | -0.00001 |
| C | -1.10648 | -0.39131 | -0.00001 |
| C | 0.00003 | -0.38897 | -1.10630 |
| C | -0.00002 | 1.17338 | -1.10630 |
| C | 1.10333 | 1.17361 | -0.00002 |
| C | -0.00000 | 1.17341 | 1.10627 |
| C | -0.00002 | -0.38894 | 1.10633 |

| | | | |
|---|---|---|---|
| C | 1.10648 | -0.39130 | 0.00004 |
| C | 2.33227 | -1.25537 | 0.00001 |
| H | -0.00002 | -1.02626 | 1.99033 |
| H | 0.00009 | -1.02633 | -1.99027 |
| H | 1.99783 | 1.79395 | -0.00003 |
| C | -2.33227 | -1.25539 | -0.00001 |
| H | -0.00003 | 1.80260 | -1.99275 |
| H | 0.00000 | 1.80266 | 1.99270 |
| H | -1.99782 | 1.79395 | -0.00000 |
| H | 2.94453 | -1.06172 | 0.88577 |
| H | 2.06087 | -2.31521 | -0.00009 |
| H | 2.94455 | -1.06156 | -0.88571 |
| H | -2.94459 | -1.06159 | 0.88569 |
| H | -2.94451 | -1.06174 | -0.88579 |
| H | -2.06086 | -2.31522 | 0.00010 |

**COT, syn-isomer**

B3LYP

E = -388.3263027

H = -388.128323

G = -388.173558

| | | | |
|---|---|---|---|
| C | 1.56833 | 0.95231 | -0.33804 |
| C | 0.67073 | 1.99209 | 0.18365 |
| H | 1.16789 | 2.89759 | 0.52900 |
| C | -0.67078 | 1.99209 | 0.18364 |
| H | -1.16794 | 2.89759 | 0.52899 |
| C | -1.56837 | 0.95230 | -0.33803 |
| H | -2.35419 | 1.31879 | -0.99844 |
| C | -1.57935 | -0.35512 | -0.03291 |

| | | | |
|---|---|---|---|
| C | -2.62163 | -1.28662 | -0.60439 |
| H | -3.20518 | -1.75688 | 0.19581 |
| H | -3.31058 | -0.76047 | -1.26797 |
| H | -2.15159 | -2.09908 | -1.16921 |
| C | -0.66847 | -0.97671 | 0.95500 |
| H | -1.16948 | -1.55589 | 1.73100 |
| C | 0.66849 | -0.97671 | 0.95499 |
| H | 1.16950 | -1.55590 | 1.73098 |
| H | 2.35415 | 1.31883 | -0.99844 |
| C | 1.57936 | -0.35511 | -0.03293 |
| C | 2.62168 | -1.28657 | -0.60438 |
| H | 3.20529 | -1.75674 | 0.19583 |
| H | 2.15169 | -2.09908 | -1.16914 |
| H | 3.31057 | -0.76040 | -1.26801 |

M06

E = -388.0013364

H = -387.803677

G = -387.848687

| | | | |
|---|---|---|---|
| C | 1.55039 | 0.94731 | -0.35157 |
| C | 0.66796 | 1.98421 | 0.18121 |
| H | 1.16854 | 2.88482 | 0.53945 |
| C | -0.66819 | 1.98419 | 0.18122 |
| H | -1.16879 | 2.88479 | 0.53947 |
| C | -1.55055 | 0.94723 | -0.35155 |
| H | -2.32732 | 1.30196 | -1.03250 |
| C | -1.56034 | -0.35188 | -0.03361 |
| C | -2.57520 | -1.29421 | -0.60278 |
| H | -3.17148 | -1.75330 | 0.19631 |
| H | -3.25566 | -0.78955 | -1.29368 |

| | | | |
|---|---|---|---|
| H | -2.08720 | -2.11791 | -1.13780 |
| C | -0.66589 | -0.95303 | 0.96939 |
| H | -1.17353 | -1.52148 | 1.75221 |
| C | 0.66599 | -0.95303 | 0.96938 |
| H | 1.17363 | -1.52151 | 1.75218 |
| H | 2.32709 | 1.30213 | -1.03256 |
| C | 1.56040 | -0.35179 | -0.03358 |
| C | 2.57538 | -1.29399 | -0.60277 |
| H | 3.17167 | -1.75305 | 0.19633 |
| H | 2.08749 | -2.11771 | -1.13785 |
| H | 3.25582 | -0.78921 | -1.29361 |

M06-2X

E = -388.1386489

H = -387.938792

G = -387.984015

| | | | |
|---|---|---|---|
| C | 1.54655 | 0.94332 | -0.36796 |
| C | 0.66770 | 1.99192 | 0.17561 |
| H | 1.17348 | 2.88365 | 0.54013 |
| C | -0.66839 | 1.99187 | 0.17569 |
| H | -1.17420 | 2.88355 | 0.54024 |
| C | -1.54706 | 0.94308 | -0.36779 |
| H | -2.30511 | 1.28951 | -1.06890 |
| C | -1.55563 | -0.35092 | -0.03121 |
| C | -2.55716 | -1.31535 | -0.61093 |
| H | -3.15666 | -1.76965 | 0.18428 |
| H | -3.22863 | -0.81995 | -1.31292 |
| H | -2.04625 | -2.13085 | -1.13079 |
| C | -0.66624 | -0.93295 | 0.99967 |
| H | -1.17771 | -1.47254 | 1.79593 |

| | | | |
|---|---|---|---|
| C | 0.66651 | -0.93294 | 0.99961 |
| H | 1.17804 | -1.47257 | 1.79580 |
| H | 2.30445 | 1.28999 | -1.06911 |
| C | 1.55570 | -0.35065 | -0.03125 |
| C | 2.55780 | -1.31461 | -0.61076 |
| H | 3.15752 | -1.76841 | 0.18457 |
| H | 2.04741 | -2.13048 | -1.13052 |
| H | 3.22906 | -0.81893 | -1.31276 |

**Cubane, para-substituted**

B3LYP

E = -388.1960872

H = -387.999831

G = -388.040503

| | | | |
|---|---|---|---|
| C | 1.36551 | -0.00007 | 0.00009 |
| C | 0.45179 | -0.77466 | -1.02327 |
| C | -0.45184 | -1.27350 | 0.15919 |
| C | 0.45165 | -0.49889 | 1.18256 |
| C | -0.45179 | 0.77470 | 1.02326 |
| C | 0.45186 | 1.27352 | -0.15920 |
| C | -0.45167 | 0.49891 | -1.18254 |
| C | -1.36550 | 0.00007 | -0.00007 |
| C | -2.86673 | -0.00001 | -0.00002 |
| H | -0.82010 | 0.89773 | -2.12778 |
| H | -0.82032 | -2.29151 | 0.28640 |
| H | -0.82026 | 1.39392 | 1.84124 |
| H | 0.82025 | -1.39386 | -1.84126 |
| H | 0.82006 | -0.89771 | 2.12781 |
| H | 0.82035 | 2.29151 | -0.28642 |

| | | | |
|---|---|---|---|
| C | 2.86673 | -0.00005 | 0.00002 |
| H | -3.26265 | 1.01413 | -0.12686 |
| H | -3.26259 | -0.61699 | -0.81485 |
| H | -3.26247 | -0.39725 | 0.94173 |
| H | 3.26265 | 0.61665 | 0.81504 |
| H | 3.26261 | -1.01424 | 0.12651 |
| H | 3.26247 | 0.39749 | -0.94161 |

M06

E = -387.8967981

H = -387.700817

G = -387.741842

| | | | |
|---|---|---|---|
| C | 1.35106 | -0.00001 | -0.00001 |
| C | 0.44821 | 0.84242 | -0.95590 |
| C | -0.44827 | -0.40665 | -1.20747 |
| C | 0.44827 | -1.24904 | -0.25162 |
| C | -0.44821 | -0.84246 | 0.95587 |
| C | 0.44824 | 0.40662 | 1.20748 |
| C | -0.44825 | 1.24904 | 0.25160 |
| C | -1.35106 | 0.00002 | 0.00003 |
| C | -2.84214 | 0.00002 | 0.00002 |
| H | -0.82392 | 2.25352 | 0.45395 |
| H | -0.82402 | -0.73367 | -2.17852 |
| H | -0.82390 | -1.51994 | 1.72459 |
| H | 0.82391 | 1.51988 | -1.72463 |
| H | 0.82396 | -2.25351 | -0.45398 |
| H | 0.82397 | 0.73363 | 2.17854 |
| C | 2.84214 | 0.00003 | 0.00000 |
| H | -3.23843 | 0.32650 | 0.96930 |
| H | -3.23843 | 0.67618 | -0.76738 |

| | | | |
|---|---|---|---|
| H | -3.23844 | -1.00264 | -0.20187 |
| H | 3.23845 | -0.67632 | 0.76723 |
| H | 3.23844 | -0.32620 | -0.96936 |
| H | 3.23841 | 1.00265 | 0.20215 |

M06-2X

E = -388.0277336

H = -387.829088

G = -387.869785

| | | | |
|---|---|---|---|
| C | 1.35303 | 0.00007 | 0.00007 |
| C | 0.44959 | -1.20461 | -0.42575 |
| C | -0.44953 | -0.97110 | 0.83030 |
| C | 0.44947 | 0.23356 | 1.25617 |
| C | -0.44958 | 1.20460 | 0.42580 |
| C | 0.44950 | 0.97111 | -0.83027 |
| C | -0.44944 | -0.23358 | -1.25615 |
| C | -1.35303 | -0.00006 | -0.00008 |
| C | -2.85245 | -0.00000 | -0.00005 |
| H | -0.82415 | -0.42041 | -2.26084 |
| H | -0.82436 | -1.74779 | 1.49434 |
| H | -0.82447 | 2.16804 | 0.76635 |
| H | 0.82448 | -2.16806 | -0.76627 |
| H | 0.82420 | 0.42038 | 2.26085 |
| H | 0.82431 | 1.74783 | -1.49431 |
| C | 2.85245 | 0.00001 | -0.00001 |
| H | -3.24087 | 0.77740 | -0.66467 |
| H | -3.24085 | -0.96432 | -0.34084 |
| H | -3.24063 | 0.18696 | 1.00557 |
| H | 3.24087 | 0.96425 | 0.34100 |
| H | 3.24088 | -0.77755 | 0.66441 |

| | | | |
|---|---|---|---|
| H | 3.24060 | -0.18671 | -1.00568 |

**COT, anti-isomer**

B3LYP

E = -388.3260108

H = -388.128031

G = -388.173222

| | | | |
|---|---|---|---|
| C | 0.70683 | -1.36461 | 0.20267 |
| C | 1.64539 | -0.43735 | -0.04722 |
| C | 1.40257 | 0.80917 | -0.80585 |
| H | 2.11220 | 1.00026 | -1.61063 |
| C | 0.49404 | 1.75717 | -0.54497 |
| H | 0.51917 | 2.66185 | -1.15106 |
| C | -0.49394 | 1.75718 | 0.54494 |
| C | -1.40253 | 0.80922 | 0.80580 |
| C | -1.64539 | -0.43729 | 0.04719 |
| C | -3.08311 | -0.64813 | -0.36742 |
| H | -3.21981 | -1.60882 | -0.86775 |
| H | -3.41485 | 0.14454 | -1.04672 |
| H | -3.74893 | -0.61589 | 0.50301 |
| H | -2.11219 | 1.00038 | 1.61053 |
| H | -0.51907 | 2.66187 | 1.15102 |
| C | 3.08305 | -0.64816 | 0.36758 |
| H | 3.74909 | -0.61516 | -0.50265 |
| H | 3.21985 | -1.60916 | 0.86729 |
| H | 3.41443 | 0.14412 | 1.04751 |
| C | -0.70688 | -1.36457 | -0.20279 |
| H | -1.03439 | -2.27987 | -0.69635 |
| H | 1.03429 | -2.27995 | 0.69620 |

M06

E = -388.00117

H = -387.803694

G = -387.848806

| | | | |
|---|---|---|---|
| C | -0.70157 | -1.36683 | -0.20640 |
| C | -1.62886 | -0.43724 | 0.04972 |
| C | -1.37628 | 0.78933 | 0.82206 |
| H | -2.07486 | 0.96757 | 1.64252 |
| C | -0.47813 | 1.73786 | 0.55394 |
| H | -0.48960 | 2.63829 | 1.16941 |
| C | 0.47808 | 1.73787 | -0.55393 |
| C | 1.37627 | 0.78935 | -0.82204 |
| C | 1.62886 | -0.43722 | -0.04971 |
| C | 3.05592 | -0.61801 | 0.36884 |
| H | 3.20845 | -1.56663 | 0.89052 |
| H | 3.37581 | 0.19565 | 1.03099 |
| H | 3.72444 | -0.59153 | -0.50136 |
| H | 2.07486 | 0.96763 | -1.64247 |
| H | 0.48956 | 2.63830 | -1.16939 |
| C | -3.05590 | -0.61802 | -0.36891 |
| H | -3.72448 | -0.59135 | 0.50123 |
| H | -3.20844 | -1.56672 | -0.89044 |
| H | -3.37567 | 0.19554 | -1.03123 |
| C | 0.70159 | -1.36681 | 0.20645 |
| H | 1.03571 | -2.27421 | 0.71485 |
| H | -1.03566 | -2.27425 | -0.71479 |

M06-2X

E = -388.1384734

H = -387.938565

G = -387.983471

| | | | |
|---|---|---|---|
| C | 0.70517 | -1.36843 | 0.21207 |
| C | 1.62974 | -0.43936 | -0.05307 |
| C | 1.36757 | 0.78478 | -0.84227 |
| H | 2.04889 | 0.95125 | -1.67547 |
| C | 0.47040 | 1.73317 | -0.56685 |
| H | 0.46238 | 2.62660 | -1.18775 |
| C | -0.47034 | 1.73317 | 0.56684 |
| C | -1.36753 | 0.78480 | 0.84226 |
| C | -1.62975 | -0.43932 | 0.05306 |
| C | -3.06553 | -0.60807 | -0.37269 |
| H | -3.21653 | -1.55056 | -0.89992 |
| H | -3.37036 | 0.21311 | -1.02740 |
| H | -3.72849 | -0.58644 | 0.49806 |
| H | -2.04885 | 0.95132 | 1.67545 |
| H | -0.46233 | 2.62660 | 1.18773 |
| C | 3.06549 | -0.60810 | 0.37276 |
| H | 3.72849 | -0.58655 | -0.49796 |
| H | 3.21645 | -1.55055 | 0.90009 |
| H | 3.37031 | 0.21313 | 1.02742 |
| C | -0.70520 | -1.36841 | -0.21213 |
| H | -1.03133 | -2.26668 | -0.73509 |
| H | 1.03126 | -2.26670 | 0.73505 |

## Supplementary Information Part 2:
## Biological Assay Methods and Results

Warfarin Study: Inhibition of VKOR Activity

*Inhibition of VKOR activity (performed by the group led by Dr Jack Tie at the University of North Carolina at Chapel Hill):*

*Evaluation of the half-maximal inhibition concentration ($IC_{50}$) of warfarin (**6**) and the synthetic compounds (**7** and **8**) to VKOR*: FIXgla-PC/HEK293 reporter cells were plated in a 24-well plate in 1 ml of complete growth medium so that the cells were ~70% confluent at the time for drug treatment, as described previously.[66] Next day, the cell culture medium was replaced with a complete growth medium containing 5 µM vitamin K epoxide (KO) with increasing concentrations of warfarin (**6**) or the synthetic compounds (***7*** *and* ***8***). The cells were cultured for forty-eight hours, and the cell culture medium was collected to determine the efficiency of carboxylation of the reporter protein using ELISA. The $IC_{50}$ of warfarin and the synthetic compounds were determined using GraphPad™ Prism software (version 7.03; GraphPad Software, San Diego, CA, USA).

*Evaluation of the resistance of VKOR and its naturally occurring mutants to warfarin (**6**) and racemic COT warfarin (**8**)*: FIXgla-PC/HEK293 reporter cells with their endogenous VKOR/VKORC1L1 genes knocked out were plated in a 24-well plate in 1 ml of complete growth medium so that the cells will be ~70% confluent at the time for transfection. Wild-type VKOR or its naturally occurring mutants was transiently expressed in these reporter cells using transfection reagent Xfect (Takara Bio USA, Inc., Mountain View, CA, USA). Transfected cells were cultured with 5 µM KO and increasing concentration of warfarin (**6**)/ *racemic COT warfarin (**8**)*. Cell culture medium was collected after a 48-hour incubation and directly used for the determination of reporter protein carboxylation by ELISA. The resistance of VKOR and its naturally occurring mutants to warfarin (**6**) and *racemic COT warfarin (**8**)* was expressed as $IC_{50}$ (**Figure S6**) and normalized resistance (resistance for wild-type VKOR is normalized as 1, **Figure 1**, Main Text).

*ELISA*: A 96-well high binding ELISA microplate was coated with 100 µL/well anti-carboxylated FIXgla mAb (Green Mountain Antibodies, Burlington, VT, USA) overnight at 4°C. The concentration of the coating antibodies was 2 µg/ml in 50 mM carbonate buffer (pH 9.6). After being washed 5 times with TBS-T wash buffer (20 mM Tris-HCl, pH 7.6, 150 mM NaCl, and 0.1% Tween 20), the plate was blocked with 0.2% BSA in TBS-T wash buffer for 2 hours at room temperature. Cell culture medium samples and carboxylated reporter protein standards (0.12-250 ng/mL) containing 5 mM $CaCl_2$ were added at 100 µL/well and incubated for 2 hours at room temperature. After being washed with TBS-T wash buffer containing 5 mM $CaCl_2$, horseradish peroxidase conjugated sheep anti-human protein C IgG (100 µL/well at 1:2500 in TBS-T wash buffer with 5 mM $CaCl_2$) (Affinity Biologicals Inc., Ancaster, Canada) was added to each well and incubated for 45 minutes at room temperature. After the unbound detecting antibody was washed off, 100 µL of ABTS solution was added to each well and the absorbance was determined at 405 nm with a THERMOmax microplate reader (Molecular Devices, Sunnyvale, CA, USA). The concentration of carboxylated FIXgla-PC was determined using the logit (OD)-log (FIXgla-PC) plot.

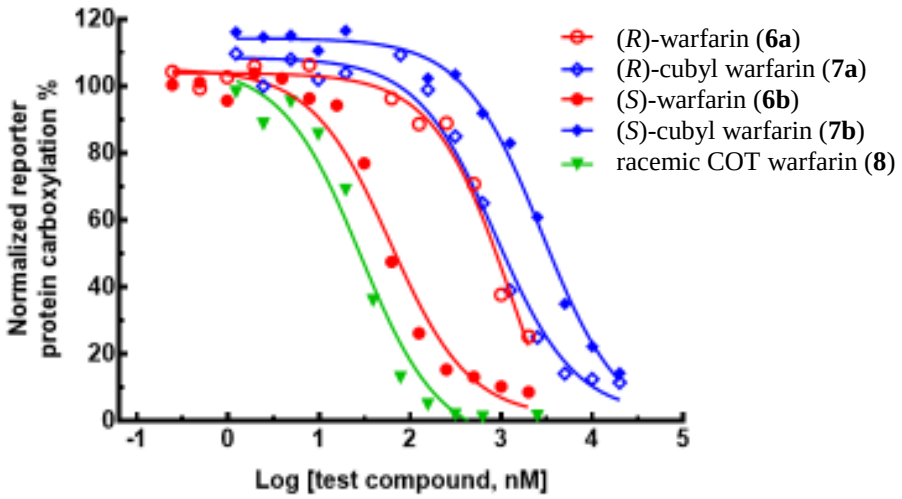



**Figure S4:** (Cubyl and COT Warfarin Combined results). Inhibition of VKOR activity by warfarin enantiomers (**6a** and **6b**), cubyl warfarin enantiomers (**7a** and **7b**) and racemic COT warfarin (**8**).

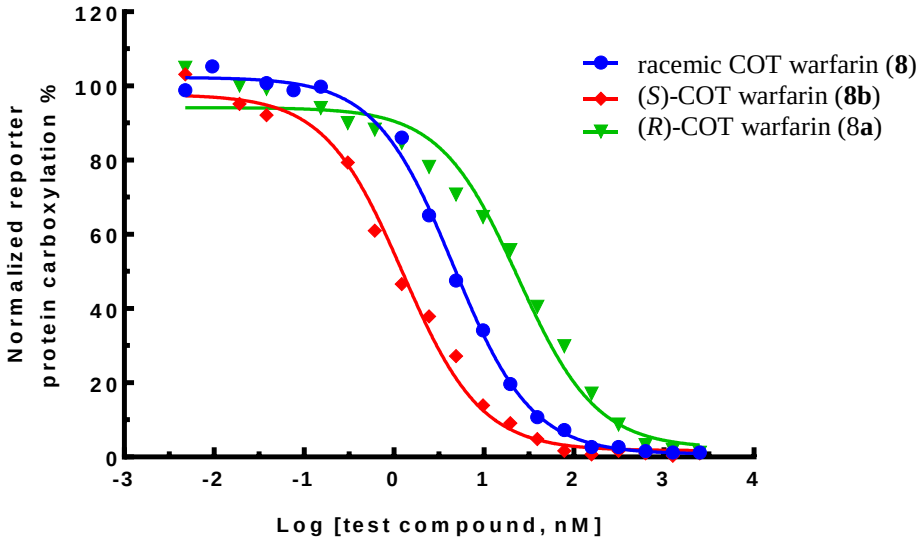



**Figure S5:** Inhibition of VKOR activity by the COT warfarin enantiomers (**8b** and **8a**).

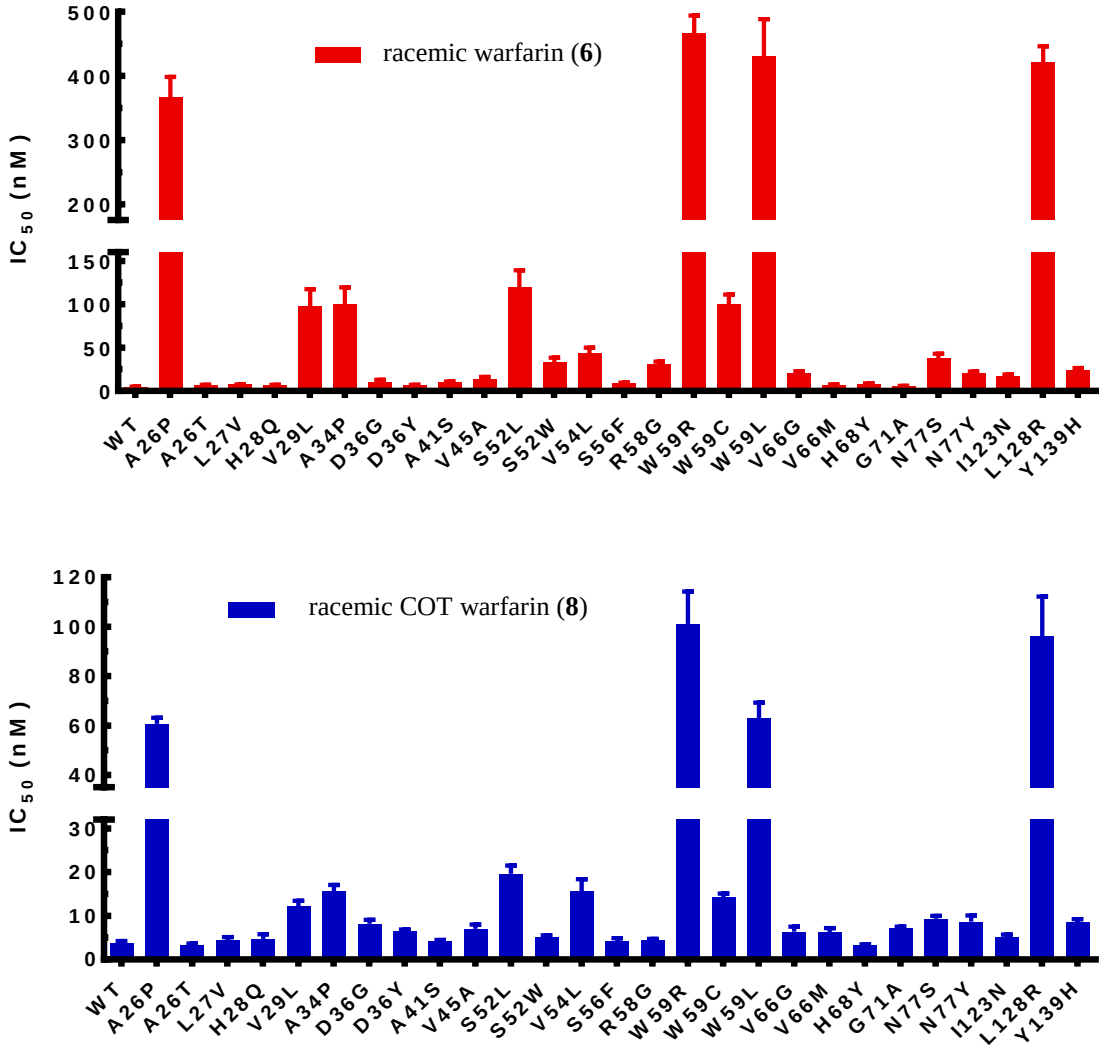



**Figure S6:** Comparison of the resistances of racemic warfarin (**6**) and racemic COT warfarin (**8**) with the 27 naturally occurring VKOR mutants.

Warfarin Study: Human Plasma Protein Binding

*Human plasma protein binding (performed by the group led by Prof. Maree Smith at the Centre for Integrated Preclinical Drug Development):*

## 1. INTRODUCTION

Protein binding was assessed by an ultrafiltration method using Centrifree® Ultrafiltration Devices with a 30000 dalton molecular weight cut-off point. Briefly, known concentrations of analytes were added to human plasmas samples and incubated for 20 min at 37 °C. The samples were then subject to ultrafiltration to separate protein bound and unbound drug. The extent of protein binding was then defined as the percentage difference between the total and unbound concentration of the drug.

## 2. MATERIALS & REAGENTS

| Item | Description |
|---|---|
| (*R*)-warfarin (**6a**) | Racemic warfarin (**6**) was purchased from Sigma-Aldrich and resolved using chiral HPLC (see **Supplementary Information Part 1** for details). Expiry date: 16 Oct 2021, Purity:100% |
| (S)-warfarin (**6b**) | Racemic warfarin (**6**) was purchased from Sigma-Aldrich and resolved using chiral HPLC (see **Supplementary Information Part 1** for details). Expiry date: 16 Oct 2021, Purity: 100% |
| (*R*)-COT warfarin (**8a**) | Expiry date: 16 Oct 2021, Purity: 100% |
| (*S*)-COT warfarin (**8b**) | Expiry date: 16 Oct 2021, Purity: 100% |
| Human plasma | Pooled blank human (Li-Hep as the anticoagulant), pH adjusted to 7.40 using $NaH_2PO_4$ |
| Centrifree® Ultrafiltration Devices | Millipore Item no. 4104 – 30 000 NMWL |

**Table S1:** materials and reagents for warfarin human plasma protein binding study.

## 3. METHOD

### 3.1. LC-MS/MS: Analytical method

| Analyte | Q1 Mass | Q3 Mass | Dwell time | DP | CE | CXP |
|---|---|---|---|---|---|---|
| **(*R*)-warfarin (6a)** | 307.07 | 160.982 | 150 | -205 | -26 | -13 |
| **(*S*)-warfarin (6b)** | 307.07 | 160.982 | 150 | -205 | -26 | -13 |
| **(*R*)-COT warfarin (8a)** | 333.157 | 255.030 | 150 | -30 | -22 | -17 |
| **(*S*)-COT warfarin (8b)** | 333.157 | 255.030 | 150 | -30 | -22 | -17 |

| Parameter Table | Racemic warfarin (6) | Racemic COT warfarin (8) |
|---|---|---|
| CUR | 40.00 | 35.00 |
| CAD | Low | Medium |
| IS | -4500 | -2000 |
| TEM | 600 | 450 |
| GS1 | 30.00 | 60.00 |
| GS2 | 40.00 | 60.00 |
| EP | -10.0 | -10.0 |

| HPLC | |
|---|---|
| **Autosampler Temperature** | 10°C |
| **Column** | Symmetry® C18 3.5 µm 2.1 x 100 mm (Waters®) |
| **Mistral Temperature (Column oven)** | 40°C |
| **Mobile phase A** | 0.1% formic acid in water |
| **Mobile phase B** | 0.1% formic acid in acetonitrile |
| **Needle wash solvent 1 (S1)** | water |
| **Needle wash solvent 2 (S2)** | 0.1 % formic acid in 50% methanol in water |
| **Needle wash solvent 3 (S3)** | 50% acetonitrile in water |

**Gradient**

| Time (min) | Pump flow | Pump fraction B% |
|---|---|---|
| 1:00 | 0.4 | 10 |
| 2:00 | 0.4 | 30 |
| 3:50 | 0.4 | 80 |
| 4:10 | 0.4 | 10 |
| 5:10 | 0.4 | 10 |

**Table S2:** MS/MS Parameters: Q1 – first mass filter; Q3 – mass analyser; Dwell time – amount of time instrument spends at each transition; DP: declustering potential; EP: entrance potential; CE: collision energy, CXP: collision cell exit potential for product ions, GS1: Nebuliser gas pressure (psi), GS2: Heater gas pressure (psi), CUR: Curtain gas pressure, CAD: Collision gas pressure (psi), IS: Spray voltage (V), TEM: Turbo gas temperature (°C).

### 3.2. Sample Preparation

Analyte stock solutions (40 µL) were spiked into solutions of each plasma (1960 µL) as listed below to have a final concentration of 200 ng/mL & 2000 ng/mL.

| Matrix | Analytes concentration in the stock solutions spiked into the matrix (µg/mL) | Analytes final concentration (ng/mL) |
|---|---|---|
| Plasma (human) | 10 | 200 |
| Plasma (human) | 100 | 2000 |

**Table S3:** sample preparation.

Spiked samples were then incubated at 37°C for 20 minutes in a water bath. Aliquots of the samples from each test group (500 µL) were transferred to the ultrafiltration devices (n=3) and centrifuged for 20 minutes at 1000 xg. After centrifugation, aliquots of the ultrafiltrates (50 µL) were transferred to separate test tubes for extraction, alongside triplicate aliquots of the samples prior to ultrafiltration from each test group.

### 3.3. Calibration Curve Preparation

Standard solution aliquots at 100 µg/mL were diluted as shown below.

| Standard ID / Conc. | Preparation Details |
|---|---|
| St A 100 µg/mL | |
| St B 75 µg/mL | mix 150µL of A + 50 µL 50% methanol in water |
| St C 50 µg/mL | mix 120µL of B + 60 µL 50% methanol in water |
| St D 25 µg/mL | mix 100µL of C + 100 µL 50% methanol in water |
| St E 10 µg/mL | mix 80µL of A + 120 µL 50% methanol in water |
| St F 5 µg/mL | mix 100µL of E + 100 µL 50% methanol in water |
| St G 2.5 µg/mL | mix 100µL of F + 100 µL 50% methanol in water |
| St H 1 µg/mL | mix 80µL of F + 120 µL 50% methanol in water |
| St I 0.5 µg/mL | mix 100µL of F + 100 µL 50% methanol in water |

**Table S4:** calibration curve preparation.

Aliquots of the resulting standard solutions (10 µL) were then spiked into 490 µL of the human plasma and mixed well.

### 3.4. Extraction

Aliquots of the spiked standards and samples (50 µL) (before and after incubation and ultrafiltration) were mixed with pure acetonitrile (200 µL) and the samples vortexed immediately. All tubes, were then centrifuged at 14000 xg for 5 minutes. Supernatants were diluted 20 times using 10% acetonitrile in water and 5 µL of diluted solutions were injected into the LC-MS/MS system.

## 4. RESULTS

### *4.1. Plasma Protein Binding*

Plasma protein binding was calculated by comparison of the concentration of each analyte spiked into human plasma, before and after ultrafiltration. The extent of binding was similar for all four analytes in the range of 92.6-99.98%. (see **Table S5**–**Table S8** below).

| **Matrix: Human Plasma** | | | | |
|---|---|---|---|---|
| **Concentrations of (*R*)-warfarin (6a)** | | | | |
| Replicate | 200 ng/mL Pre-filter | 200 ng/mL Post-filter | 2000 ng/mL Pre-filter | 2000 ng/mL Post-filter |
| 1 | 200 | 1.3 | 2060 | 11.8 |
| 2 | 243 | 0.94 | 2020 | 9.8 |
| 3 | 259 | 0.11 | 2210 | 9.1 |
| **Mean** | **234** | **0.78** | **2097** | **10.22** |
| **Calculations: Plasma protein binding** | | | | |
| **Plasma protein binding (%): 100 – [ $\frac{\text{Concentration post-filter}}{\textit{Concentration pre-filter}}$ x 100]** | | | | |
| 200 ng/mL | 100 – [ $\frac{0.78}{234}$ x 100] | | 99.67 | |
| 2000 ng/mL | 100 – [ $\frac{10.22}{2097}$ x 100] | | 99.51 | |

**Table S5:** (*R*)-warfarin (**6a**) binding to human plasma.

| **Matrix: Human Plasma** | | | | |
|---|---|---|---|---|
| **Concentrations of (*S*)-warfarin (6b)** | | | | |
| Replicate | 200 ng/mL Pre-filter | 200 ng/mL Post-filter | 2000 ng/mL Pre-filter | 2000 ng/mL Post-filter |
| 1 | 217 | 0.12 | 2470 | 11.4 |
| 2 | 142 | 0.12 | 1300 | 7.24 |
| 3 | 125 | 0.06 | 1560 | 8.41 |
| **Mean** | **161.3** | **0.1** | **1776.7** | **9.0** |
| **Calculations: Plasma protein binding** | | | | |
| **Plasma protein binding (%): 100 – [ $\frac{\text{Concentration post-filter}}{Concentration\ pre-filter}$ x 100]** | | | | |
| 200 ng/mL | | 100 – [ $\frac{0.1}{161.3}$ x 100] | | 99.94 |
| 2000 ng/mL | | 100 – [ $\frac{9.0}{1776.7}$ x 100] | | 99.49 |

**Table S6:** (*S*)-warfarin (**6b**) binding to human plasma.

| **Matrix: Human Plasma** | | | | |
|---|---|---|---|---|
| **Concentrations of (*R*)-COT warfarin (8a)** | | | | |
| Replicate | 200 ng/mL Pre-filter | 200 ng/mL Post-filter | 2000 ng/mL Pre-filter | 2000 ng/mL Post-filter |
| 1 | 177 | 14.1 | 1810 | 29.1 |
| 2 | 206 | 13.7 | 2360 | 24.5 |
| 3 | 190 | 14.5 | 2360 | 24.6 |
| **Mean** | **191** | **14.1** | **2176.7** | **26.1** |
| **Calculations: Plasma protein binding** | | | | |
| **Plasma protein binding (%): 100 – [ $\frac{\text{Concentration post-filter}}{Concentration\ pre-filter}$ x 100]** | | | | |
| 200 ng/mL | | 100 – [ $\frac{14.1}{191}$ x 100] | | 92.6% |
| 2000 ng/mL | | 100 – [ $\frac{26.1}{2176.7}$ x 100] | | 98.8% |

**Table S7:** (*R*)-COT warfarin (**8a**) binding to human plasma.

| **Matrix: Human Plasma** | | | | |
|---|---|---|---|---|
| **Concentrations of (*S*)-COT warfarin (8b)** | | | | |
| Replicate | 200 ng/mL Pre-filter | 200 ng/mL Post-filter | 2000 ng/mL Pre-filter | 2000 ng/mL Post-filter |
| 1 | 237 | 0.05 | 2360 | 0.48 |
| 2 | 255 | 0.22 | 1620 | 0.39 |
| 3 | 238 | 0.04 | 2030 | 0.41 |
| **Mean** | **243.3** | **0.1** | **2003.3** | **0.43** |
| **Calculations: Plasma protein binding** | | | | |
| **Plasma protein binding (%): 100 – [ $\frac{\text{Concentration post-filter}}{Concentration\ pre-filter}$ x 100]** | | | | |
| 200 ng/mL | | 100 – [ $\frac{0.1}{243.3}$ x 100] | | 99.96 |
| 2000 ng/mL | | 100 – [ $\frac{0.43}{2003.3}$ x 100] | | 99.98 |

**Table S8:** (*S*)-COT warfarin (**8b**) binding to human plasma.

Warfarin Study: Liver Microsome Metabolic Stability

*Human liver microsome metabolic stability (performed by the group led by Prof. Maree Smith at the Centre for Integrated Preclinical Drug Development):*

## 1. Methods

### 1.1 Compounds

| Item | Description |
|---|---|
| (*R*)-warfarin (**6a**) | Racemic warfarin (**6**) was purchased from Sigma-Aldrich and resolved using chiral HPLC (see **Supplementary Information Part 1** for details). Expiry date: 16 Oct 2021, Purity:100% |
| (S)-warfarin (**6b**) | Racemic warfarin (**6**) was purchased from Sigma-Aldrich and resolved using chiral HPLC (see **Supplementary Information Part 1** for details). Expiry date: 16 Oct 2021, Purity: 100% |
| (*R*)-COT warfarin (**8a**) | Expiry date: 16 Oct 2021, Purity: 100% |
| (*S*)-COT warfarin (**8b**) | Expiry date: 16 Oct 2021, Purity: 100% |
| Human liver microsomes | Gibco, 20 mg/mL, Catalogue # HMMCPL, Lot # PL050 B |
| **β-Nicotinamide adenine dinucleotide 2′-phosphate reduced tetrasodium salt hydrate (NADPH)** | Sigma, Catalogue # N-1630-250 mg, Lot # SLBH5704V |

**Table S9:** compounds tested.

### 1.2 Experimental Plan

The reaction conditions for the incubations with substrate and liver microsomes are summarised in **Table S10** and detailed further in sections 1.2.1 to 1.2.4 below.

### 1.2.1 Metabolic stability of w*arfarin enantiomers (6a and 6b) and COT warfarin enantiomers (15a and 15b)* in human liver microsomes

Aliquots (10 µL) of a stock concentration of 250 µM of each of the warfarin enantiomers (**6a** and **6b**) and the COT warfarin enantiomers (**8a** and **8b**) dissolved in 50% methanol in water were added to the reaction tubes. The reaction mixture (final volume of 250 µL) comprised the following: 0.1 M phosphate buffer (pH 7.4), β-Nicotinamide adenine dinucleotide 2´-phosphate (NADPH) (1mM), and pooled human liver microsomes (0.5 mg/mL). The final concentration of warfarin enantiomers (**6a** and **6b**) and COT warfarin enantiomers (**8a** and **8b**) in the incubation medium was 10 µM. Metabolism was started by adding NADPH after a 5 min pre-incubation period to each of the reaction tubes and incubated at 37$^{o}$C in a shaking water bath prior to stopping the reaction with 500 µL aliquots of ice cold acetonitrile added to samples collected at 0, 15, 30, 45 and 60 after metabolism initiation. Two negative controls (no NADPH, and no microsomes) were used in parallel with the study samples. A positive control; midazolam, 10 µM was incubated under the same conditions for 1h. Samples were then vortex-mixed and centrifuged for 5 min at 14,000 rpm. The supernatants were diluted 10 times with 10% acetonitrile in water. Then, aliquots of 50 µL of the diluted samples were mixed with 50 µL of internal standard (mefenamic acid 10 ng/mL in 10% acetonitrile in water) and 400 µL of 10% acetonitrile in water. Samples were transferred to a 96-well plate from which 5 µL aliquots were injected to the HPLC-MS/MS system.

| | Metabolic stability incubation condition |
|---|---|
| Substrate concentrations | 10 µM |
| Incubation volume | 250 µL |
| Incubation medium | Phosphate buffer 100 mM pH 7.4 |
| Incubation total time | 1 h |
| Liver microsome protein concentrations | 0.5 mg/mL |
| Cofactor concentrations | 1 mM (NADPH) |
| Stop reaction solvent | 500 µL acetonitrile |

**Table S10:** summary of human liver microsome incubation conditions.

### 1.2.2 Bioanalysis: Calibration Curves for warfarin enantiomers (6a and 6b) and COT warfarin enantiomers (8a and 8b)

A mix of stock solutions of warfarin enantiomers (**6a** and **6b**)/COT warfarin enantiomers (**8a** and **8b**) (100 µg/mL) and midazolam (100 µg/mL) in 50% methanol in water were diluted to 75, 50, 25, 12.5, 0.25 µg/mL using 50% methanol in water, and aliquots of the working standard solutions (10 µL) were added to plastic tubes. Next, aliquots (190 µL) of phosphate buffer (100 mM, pH 7.4) and microsome solutions in phosphate buffer (100 mM, pH 7.4) (50 µL) were added to the tubes, followed by 500 µL aliquots of acetonitrile. Tubes were vortex-mixed and centrifuged for 5 min at 14,000 rpm. Aliquots of supernatant (50 µL) were diluted 10 times with 10% acetonitrile in water. Then, aliquots of 50 µL of the diluted standards were mixed with 50 µL of internal standard (mefenamic acid 10 ng/mL in 10% acetonitrile in water) and 400 µL of 10% acetonitrile in water. Samples were transferred to a 96-well plate from which 5 µL aliquots were injected to the HPLC-MS/MS system.

#### 1.2.4 Mass spectrometry conditions

The LC-MS/MS parameters used for the analysis of warfarin enantiomers (**6a** and **6b**), COT warfarin enantiomers (**8a** and **8b**) and midazolam are summarized in **Table S11**.

| **HPLC** | |
|---|---|
| Autosampler Temperature | 10°C |
| Column | Symmetry® C18 3.5 µm 2.1 x 100 mm |
| Mistral Temperature (Column oven) | 40°C |
| Mobile phase A | 0.1% Formic acid in water |
| Mobile phase B | 0.1% Formic acid in acetonitrile |
| Needle wash solvent 1 | Water |
| Needle wash solvent 2 | 0.1% formic acid in 50% methanol in water |
| | 50% acetonitrile in water |
| Gradient | |

| **Time (min)** | **Pump flow** | **Pump fraction B%** |
|---|---|---|
| 0.00 | 0.4 | 10 |
| 1:02 | 0.4 | 10 |
| 2:30 | 0.4 | 95 |
| 3:20 | 0.4 | 95 |
| 3:30 | 0.4 | 10 |
| 5:10 | 0.4 | 10 |

| **MS/MS** | | | | | | |
|---|---|---|---|---|---|---|
| Analyte | Q1 Mass | Q3 Mass | Dwell time | DP | CE | CXP |
| Warfarin (**6**) | 307.070 | 160.980 | 150 | -205.0 | -26.0 | -13.0 |
| COT warfarin (**8**) | 333.157 | 255.030 | 150 | -30.0 | -22.0 | -17.0 |
| Midazolam | 325.800 | 291.100 | 150 | 136.0 | 39.0 | 22.0 |
| 1-hydroxymidazolam | 342.300 | 203.046 | 150 | 111.0 | 37.0 | 20.0 |
| 4-hydroxymidazolam | 342.000 | 325.000 | 150 | 106.0 | 31.0 | 28.0 |
| | | | | | | |
| Mefenamic acid | 240.053 | 196.085 | 150 | -135.0 | -24.0 | -11.0 |

**Table S11:** mass spectrometry conditions for the analytes of interest.

| **Parameter Table** | warfarin (**6**) / COT warfarin (**8**) | midazolam |
|---|---|---|
| CUR | 40.0 | 40.0 |
| CAD | LOW | LOW |
| IS | -4500 | 4500 |
| TEM | 600 | 600 |
| GS1 | 30.0 | 30.0 |
| GS2 | 40.0 | 40.0 |
| EP | -10.0 | 10.0 |

MS/MS Parameters: Q1 – first mass filter; Q3 – mass analyser; Dwell time – amount of time instrument spends at each transition; DP- declustering potential; EP – entrance potential; CE – collision energy; CXP: collision cell exit potential for product ions, GS1: Nebuliser gas pressure (psi), GS2: Heater gas pressure (psi), CUR: Curtain gas pressure, CAD: Collision gas pressure (psi), IS: Spray voltage (V), TEM: Turbo gas temperature (°C).

## 2. Results:

### 2.1 (*S*)-warfarin (6b)

| Time (min) | (*S*)-warfarin (**6b**) (μM) | | | Average |
|---|---|---|---|---|
| 0 | 8.5 | 10.7 | 11.5 | **10.2** |
| 15 | 9.0 | 10.7 | 11.0 | **10.2** |
| 30 | 8.9 | 10.8 | 12.7 | **10.8** |
| 45 | 9.3 | 8.2 | 8.5 | **8.7** |
| 60 | 8.5 | 8.6 | | **8.6** |

**Table S12:** concentration of (*S*)-warfarin (**6b**) in incubation medium (μM).

| | (*S*)-warfarin (**6b**) (μM) | | |
|---|---|---|---|
| Negative Control (No NADPH) | 10.9 | 13.0 | 8.5 |
| Negative Control (No Microsome) | 12.0 | 10.8 | 10.0 |

**Table S13:** concentration of (*S*)-warfarin (**6b**) in negative controls.

| | | | |
|---|---|---|---|
| Positive Control (The area of formed metabolite; 1-hydroxymidazolam) | $1.2 \times 10^5$ | $1.4 \times 10^5$ | $1.4 \times 10^5$ |
| Positive Control (The area of formed metabolite; 4-hydroxymidazolam) | $1.2 \times 10^5$ | $1.2 \times 10^5$ | $1.2 \times 10^5$ |

**Table S14:** formation of midazolam metabolites after 1 hour incubation (positive control).

| Time (min) | LN (*S*)-warfarin (**6b**) (μM) | | |
|---|---|---|---|
| 0 | 2.1 | 2.4 | 2.4 |
| 15 | 2.2 | 2.4 | 2.4 |
| 30 | 2.2 | 2.4 | 2.5 |
| 45 | 2.2 | 2.1 | 2.1 |
| 60 | 2.1 | 2.2 | |

**Table S15:** concentration of (*S*)-warfarin (**6b**) in incubation medium (Logarithmic scale).

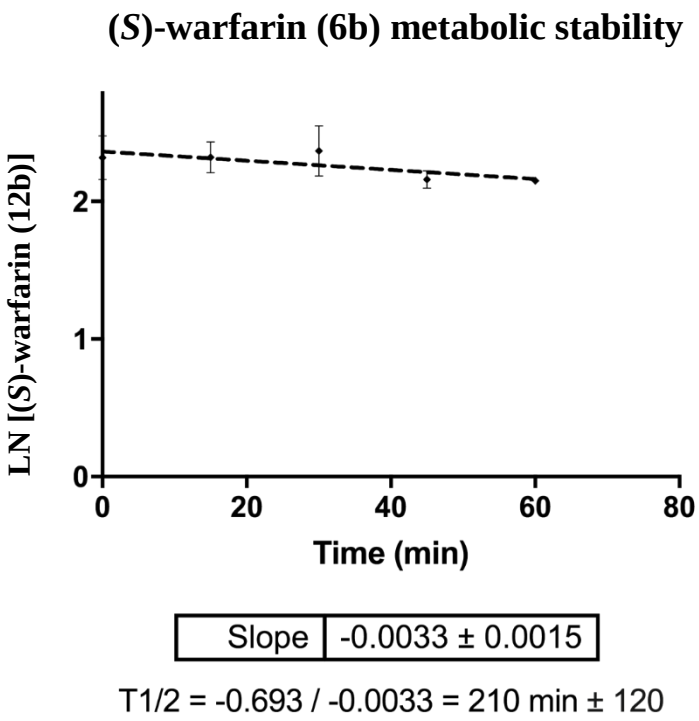



**Figure S7:** (*S*)-warfarin (**6b**) metabolic stability.

**2.2 (*R*)-warfarin (6a)**

| Time (min) | (*R*)-warfarin (**6a**) (uM) | | | Average |
|---|---|---|---|---|
| 0 | 11.4 | 11.0 | 10.9 | **11.1** |
| 15 | 11.2 | 12.1 | | **11.7** |
| 30 | 10.7 | 14.2 | 13.4 | **12.8** |
| 45 | 10.3 | 9.1 | 10.3 | **9.9** |
| 60 | 12.5 | 12.2 | 9.9 | **11.5** |

**Table S16:** concentration of (*R*)-warfarin (**6a**) in incubation medium (μM).

| | (*R*)-warfarin (**6a**) (μM) | | |
|---|---|---|---|
| Negative Control (No NADPH) | 7.8 | 10.4 | 11.7 |
| Negative Control (No Microsome) | 10.5 | 8.6 | 11.4 |

**Table S17:** concentration of (*R*)-warfarin (**6a**) in negative controls.

| | | | |
|---|---|---|---|
| Positive Control (The area of formed metabolite; 1-hydroxymidazolam) | $2.6 \times 10^5$ | $2.9 \times 10^5$ | |
| Positive Control (The area of formed metabolite; 4-hydroxymidazolam) | $7.7 \times 10^3$ | $1.2 \times 10^4$ | |

**Table S18:** formation of midazolam metabolites after 1 hour incubation (positive control).

| Time (min) | LN (*R*)-warfarin (**6a**) (μM) | | |
|---|---|---|---|
| 0 | 2.4 | 2.4 | 2.4 |
| 15 | 2.4 | 2.5 | |
| 30 | 2.4 | 2.7 | 2.6 |
| 45 | 2.3 | 2.2 | 2.3 |
| 60 | 2.5 | 2.5 | 2.3 |

**Table S19:** concentration of (*R*)-warfarin (**6a**) in incubation medium (Logarithmic scale).

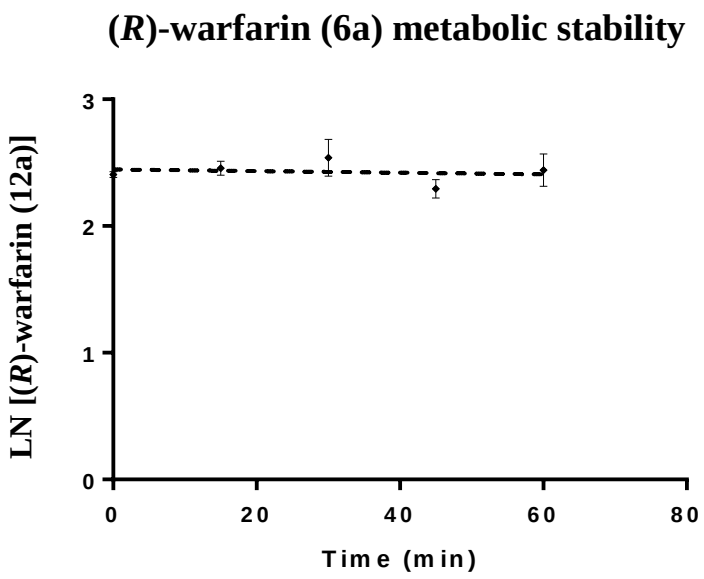



**Figure S8:** (*R*)-warfarin (**6a**) metabolic stability.

**2.3 (*R*)-COT warfarin (8a)**

| Time (min) | (*R*)-COT warfarin (**8a**) (µM) | | | Average |
|---|---|---|---|---|
| 0 | 8.6 | 8.8 | 8.8 | **8.7** |
| 15 | 7.1 | 7.8 | 8.1 | **7.7** |
| 30 | 8.3 | 7.8 | 6.9 | **7.7** |
| 45 | 6.2 | 7.7 | 7.2 | **7.0** |
| 60 | 6.3 | 5.5 | 6.7 | **6.2** |

**Table S20:** concentration of (*R*)-COT warfarin (**8a**) in incubation medium (µM).

| | (*R*)-COT warfarin (**8a**) | | |
|---|---|---|---|
| Negative Control (No NADPH) | 9.2 | 8.9 | 8.7 |
| Negative Control (No Microsome) | 8.0 | 9.6 | 8.0 |

**Table S21:** concentration of (*R*)-COT warfarin (**8a**) in negative controls.

| | | | |
|---|---|---|---|
| Positive Control (The area of formed metabolite; 1-hydroxymidazolam) | $7.7 \times 10^5$ | $6.2 \times 10^5$ | $7.0 \times 10^5$ |
| Positive Control (The area of formed metabolite; 4-hydroxymidazolam) | $2.1 \times 10^5$ | $1.8 \times 10^5$ | $2.0 \times 10^5$ |

**Table S22:** formation of midazolam metabolites after 1 hour incubation (positive control).

| Time (min) | LN (*R*)-COT warfarin (**8a**) (µM) | | |
|---|---|---|---|
| 0 | 2.2 | 2.2 | 2.2 |
| 15 | 2.0 | 2.1 | 2.1 |
| 30 | 2.1 | 2.1 | 1.9 |
| 45 | 1.8 | 2.0 | 2.0 |
| 60 | 1.8 | 1.7 | 1.9 |

**Table S23:** concentration of (*R*)-COT warfarin (**8a**) in incubation medium (Logarithmic scale).

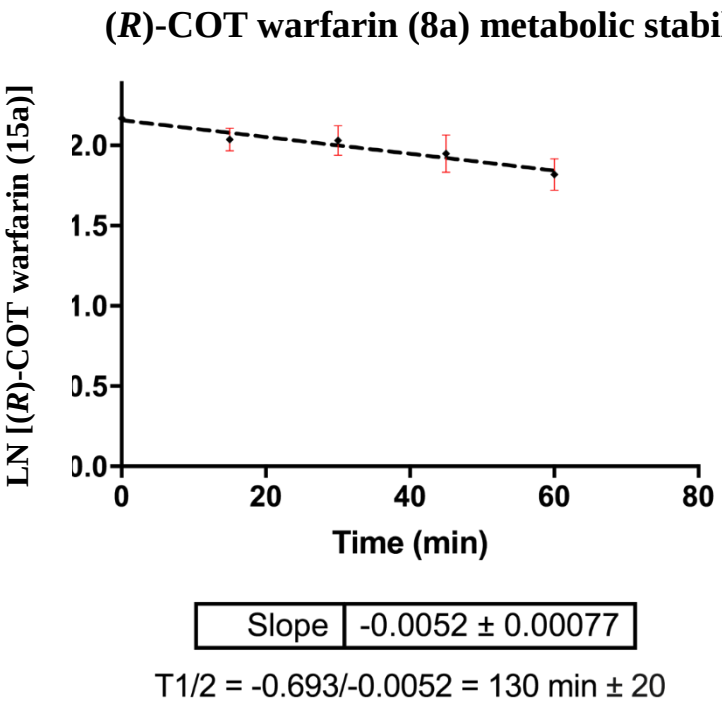



**Figure S9:** (*R*)-COT warfarin (**8a**) metabolic stability.

### 2.4 (*S*)-COT warfarin (8b)

| Time (min) | (*S*)-COT warfarin (**8b**) (µM) | | | Average |
|---|---|---|---|---|
| 0 | 10.2 | 10.0 | 10.3 | **10.2** |
| 15 | 9.6 | 10.1 | 10.1 | **9.9** |
| 30 | 8.0 | 7.6 | 7.0 | **7.5** |
| 45 | 7.4 | 7.2 | | **7.3** |
| 60 | 7.6 | 7.6 | 7.2 | **7.5** |

**Table S24:** concentration of (*S*)-COT warfarin (**8b**) in incubation medium (µM).

| | (*S*)-COT warfarin (**8b**) (µM) | | |
|---|---|---|---|
| Negative Control (No NADPH) | 12.0 | 12.1 | 11.0 |
| Negative Control (No Microsome) | 11.0 | 11.2 | 10.0 |

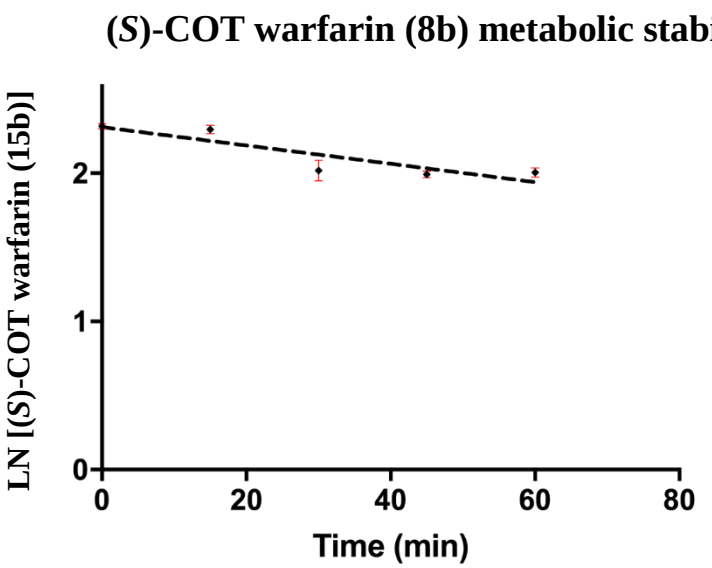
**Table S25:** concentration of (*S*)-COT warfarin (**8b**) in negative controls.

| | | | |
|---|---|---|---|
| Positive Control (The area of formed metabolite; 1-hydroxymidazolam) | $2.8 \times 10^5$ | $2.0 \times 10^5$ | $2.6 \times 10^5$ |
| Positive Control (The area of formed metabolite; 4-hydroxymidazolam) | $2.2 \times 10^4$ | $1.4 \times 10^4$ | $2.5 \times 10^4$ |

**Table S26:** formation of midazolam metabolites after 1 hour incubation (positive control).

| | | | |
|---|---|---|---|
| 0 | 2.3 | 2.3 | 2.3 |
| 15 | 2.3 | 2.3 | 2.3 |
| 30 | 2.1 | 2.0 | 2.0 |
| 45 | 2.0 | 2.0 | |
| 60 | 2.0 | 2.0 | 2.0 |

**Table S27:** concentration of (*S*)-COT warfarin (**8b**) in incubation medium (Logarithmic scale).




| | |
|---|---|
| Slope | -0.0062 ± 0.0019 |

T1/2 = -0.693/ -0.0062 = 110 min ± 38

**Figure S10:** (*S*)-COT warfarin (**8b**) metabolic stability.

## 2.5 Sample Chromatograms

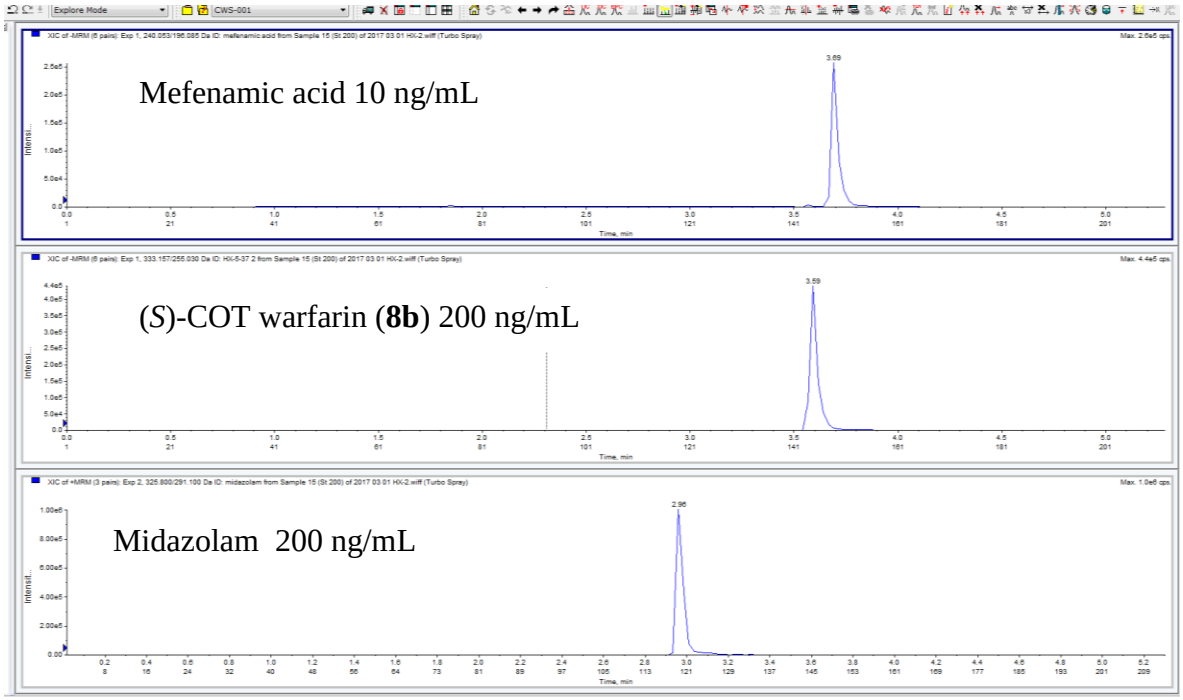



**Figure S11:** representative chromatograms of one of the standards.

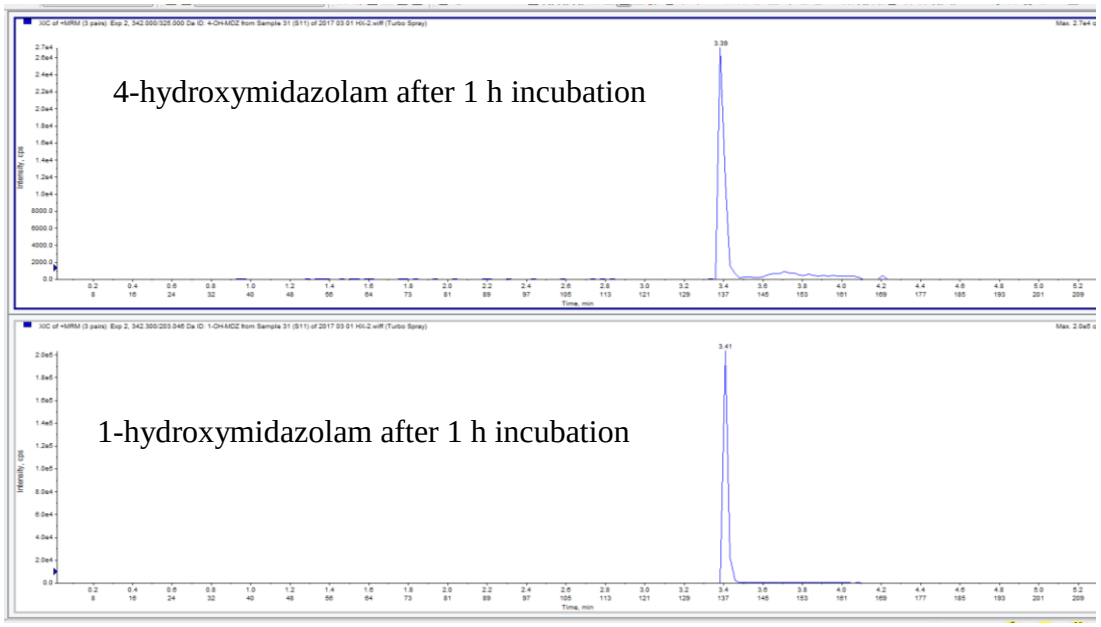



**Figure S12:** representative chromatograms of one of midazolam metabolite formation in positive control samples.

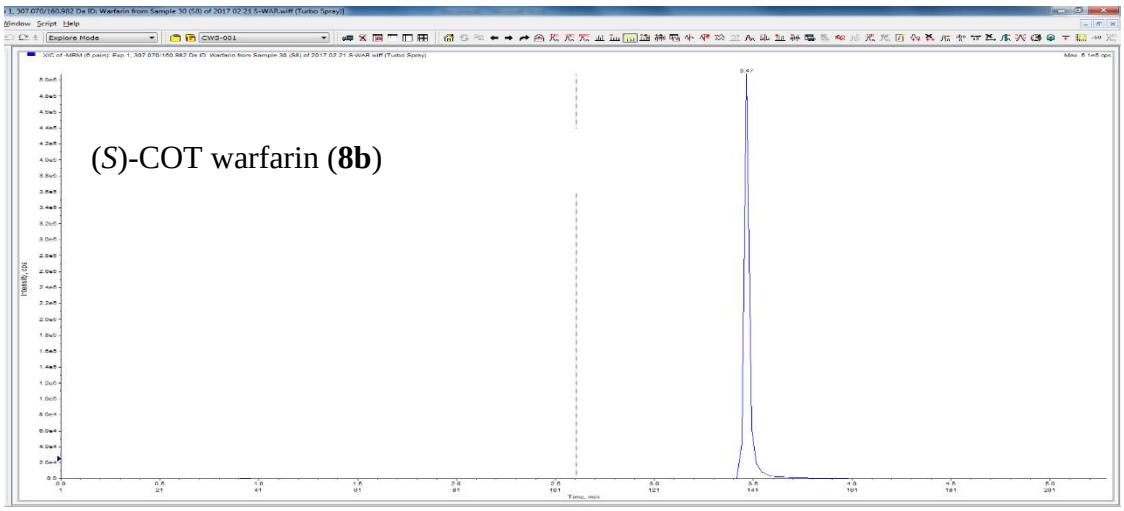



**Figure S13:** representative chromatograms of (*S*)-COT warfarin (**8b**) after 1 h incubation.

## 3. MS Investigation:

The below MS investigation was conducted on (*S*)-warfarin (**6b**), (*S*)-COT warfarin (**8b**) (for [M+16] and [M+34] metabolites) and (*R*)-COT warfarin (**8a**) (for [M+2] and [M+18] metabolites) according to the incubation procedures and MS parameters outlined in subsections **1.2.1** and **1.4.1** respectively.

Using Precursor Ion Scan, the *m/z* [M+16] and [M+34] were identified and using the Multiple Reaction Monitoring (MRM) method, the relative quantity of the metabolites at time 0, and 60 min of the incubation were compared (see below).

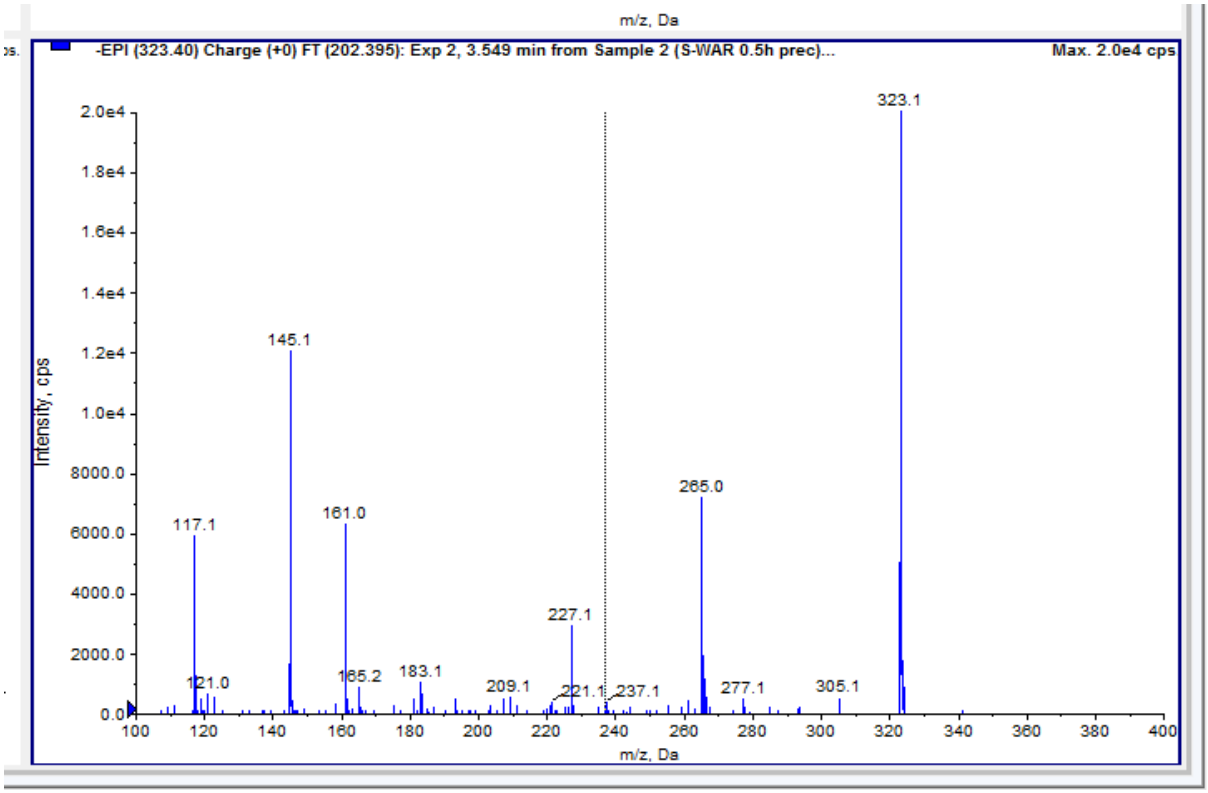



**Figure S14:** (*S*)-warfarin (**6b**) potential hydroxy metabolite (323.1 = [M + 16]) fragmentation pattern.

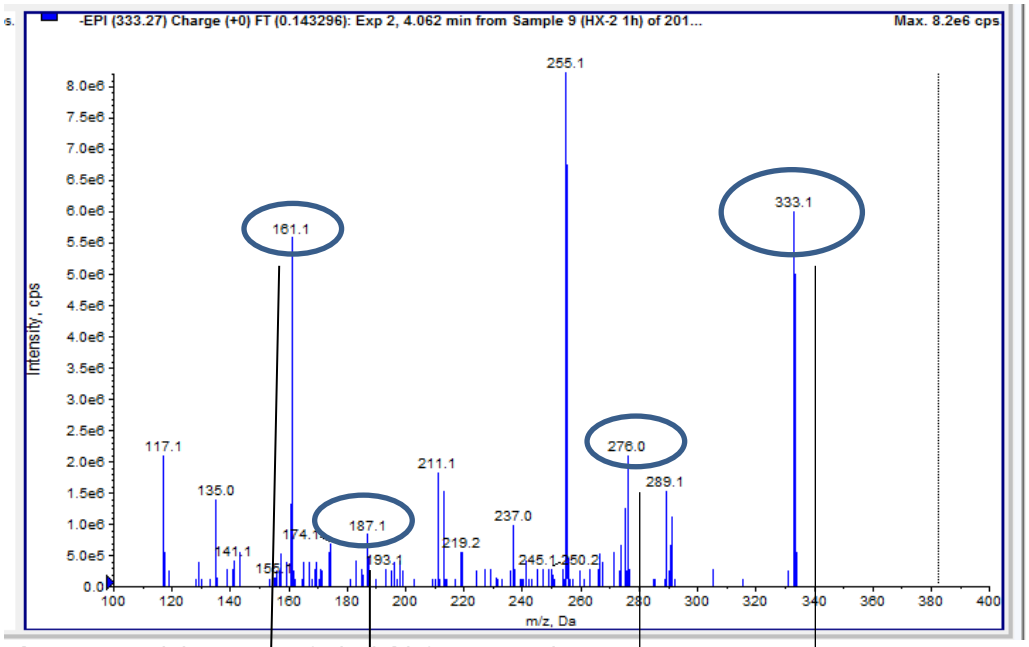



**Figure S15:** (*S*)-COT warfarin (**8b**) fragmentation pattern.

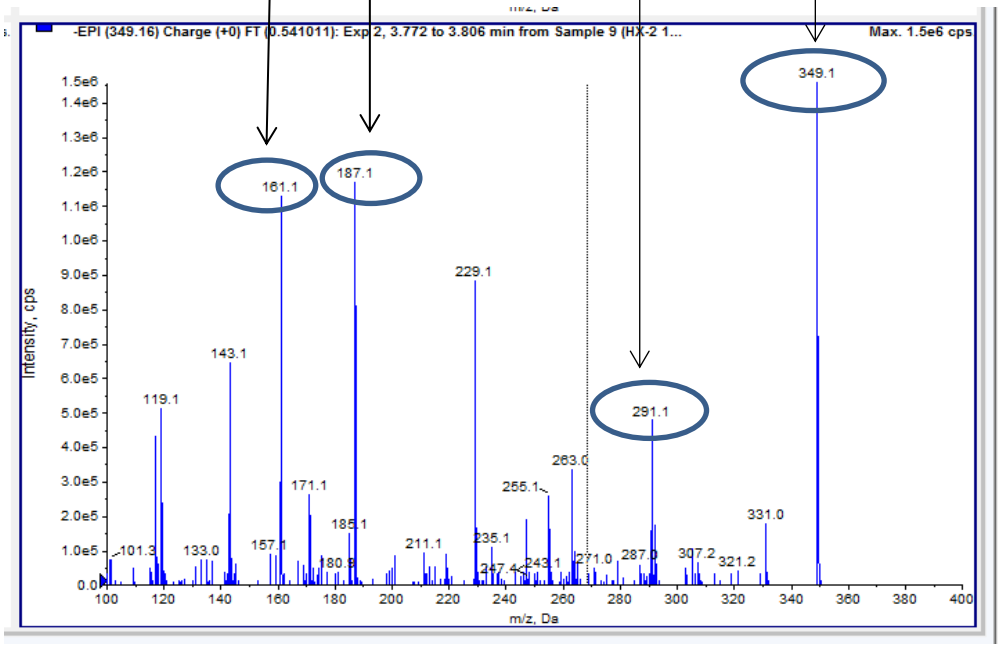



**Figure S16:** Potential hydroxy metabolite of (*S*)-COT warfarin (**8b**) [M + 16] fragmentation pattern.

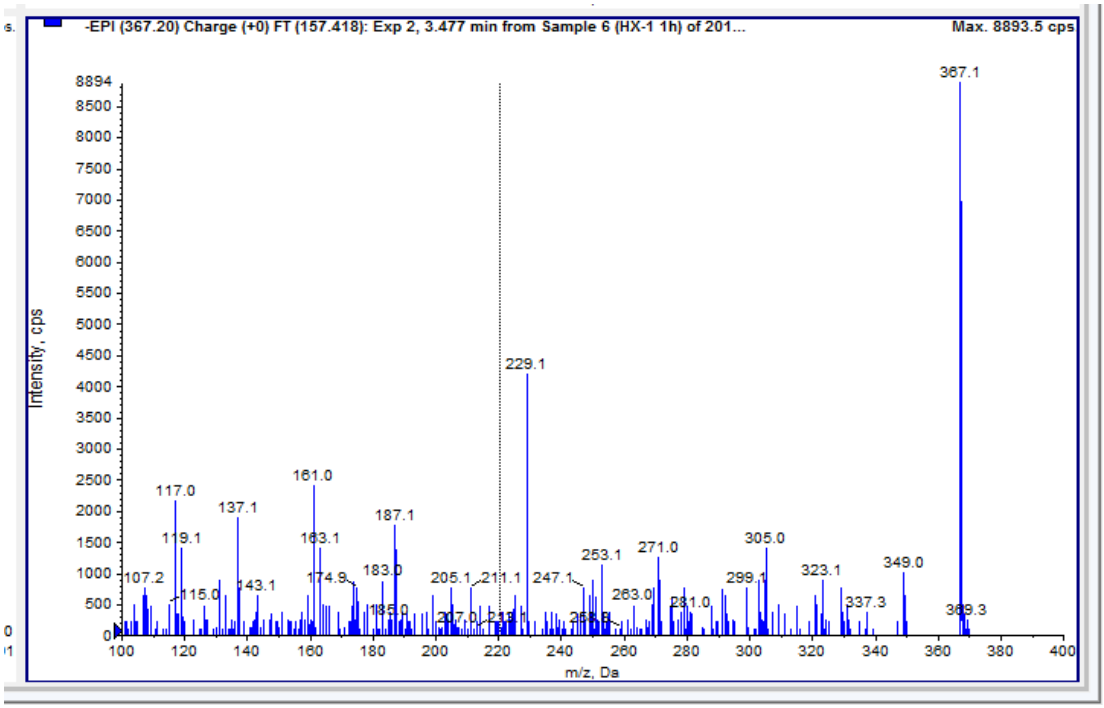



**Figure S17:** Potential hydrated epoxy metabolite of (*S*)-COT warfarin (**8b**) [M + 34] fragmentation pattern.

## MRM peaks

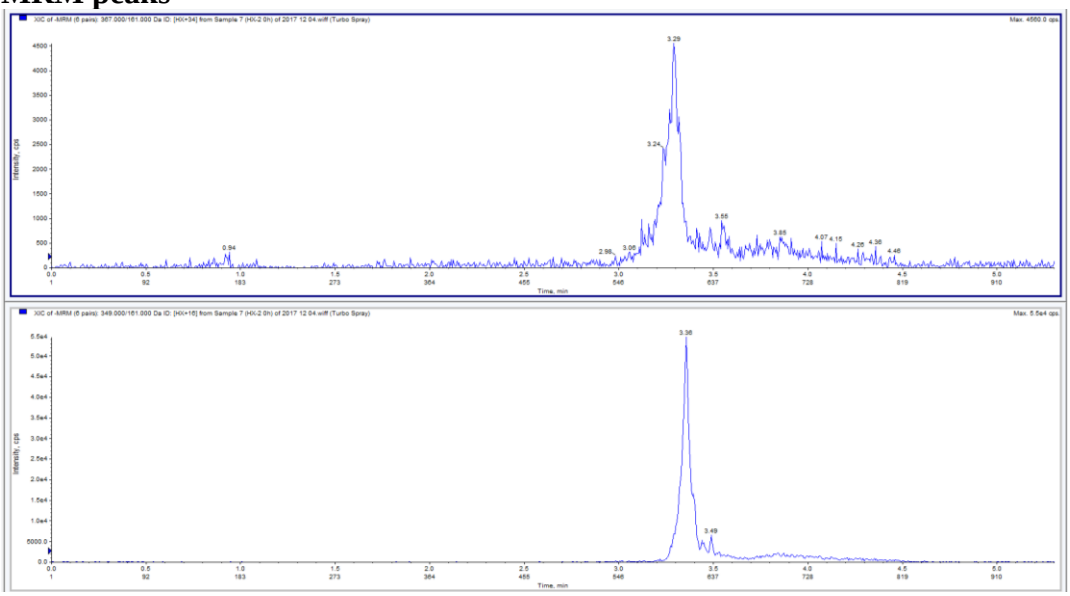


**Figure S18:** Comparison of [M+34] and [M+16] metabolites for (*S*)-COT warfarin (**8b**) after 0 h. **Top:** Potential hydrated epoxy metabolite of (*S*)-COT warfarin (**8b**) [M+34] chromatogram after 0 h incubation (intensity: $6.4e^3$). **Bottom:** Potential hydroxy metabolite of (*S*)-COT warfarin (**8b**) [M+16] chromatogram after 0 h incubation (intensity: $5.2e^4$).

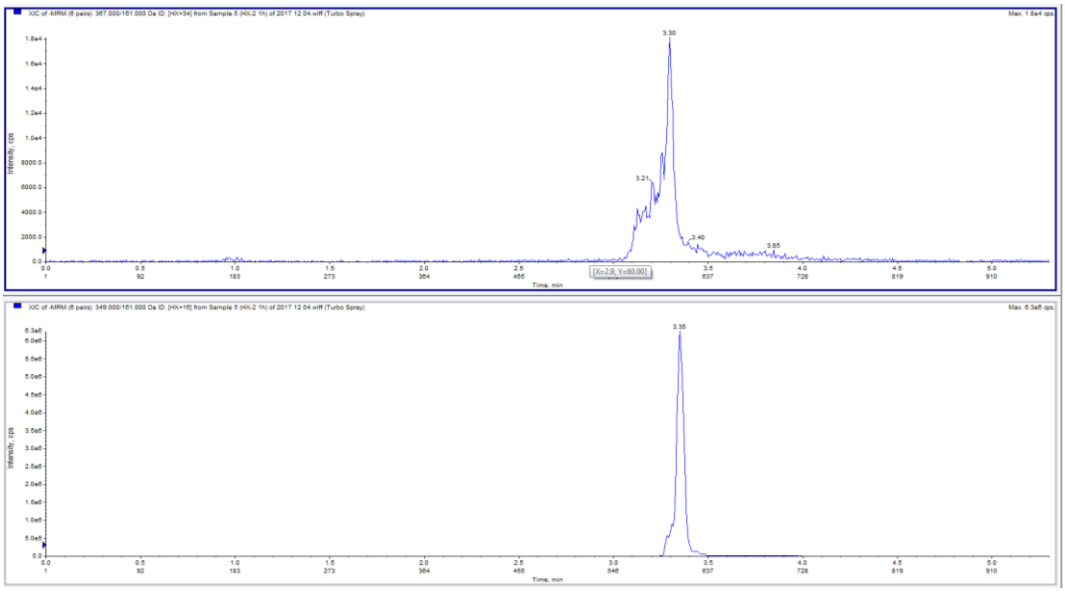


**Figure S19:** Comparison of [M+34] and [M+16] metabolites for (*S*)-COT warfarin (**8b**) after 1 h. **Top:** Potential hydrated epoxy metabolite of (*S*)-COT warfarin (**8b**) [M+34] chromatogram after 1 h incubation (intensity: $2.1e^4$). **Bottom:** Potential hydroxy metabolite of (*S*)-COT warfarin (**8b**) [M+16] chromatogram after 1 h incubation (intensity: $5.5e^6$).

Using Precursor Ion Scan, the *m/z* [M+2] and [M+18] were identified and using Multiple Reaction Monitoring (MRM) method, the relative quantity of the metabolites at time 0, and 60 min of the incubation were compared.

No M+2 or M+18 with similar fragmentation pattern were found in the Precursor Ion Scan from (*R*)- and (*S*)-warfarin (**6a** and **6b**). However, [M+2] and [M+18] for COT-warfarin (**15**) were detected. Data for (*R*)-COT warfarin (**8a**) is shown below.

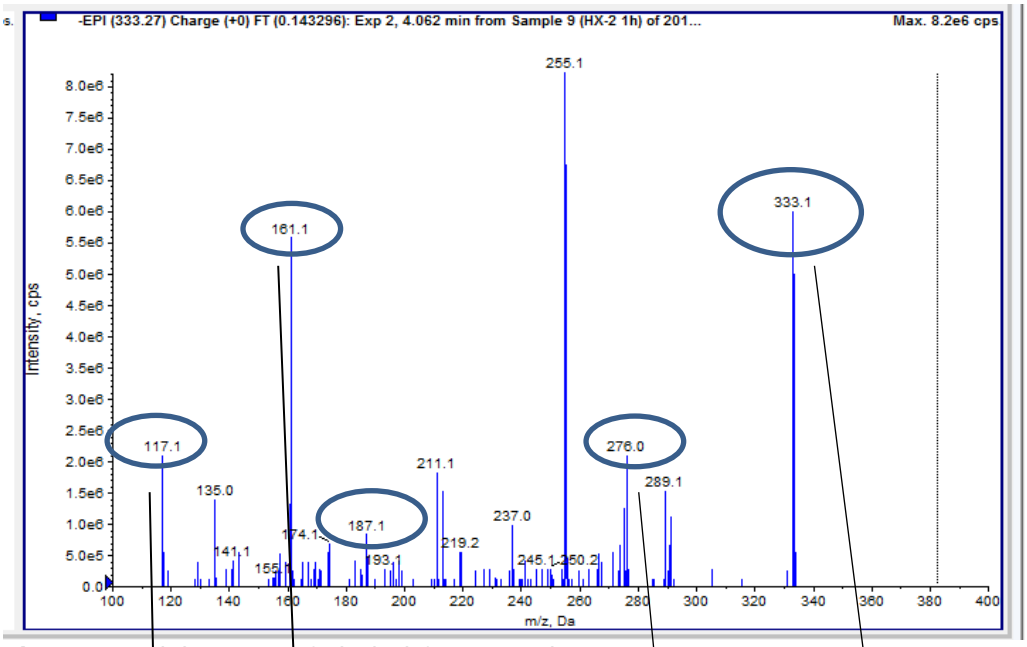



**Figure S20:** (*R*)-COT warfarin (**8a**) fragmentation pattern.

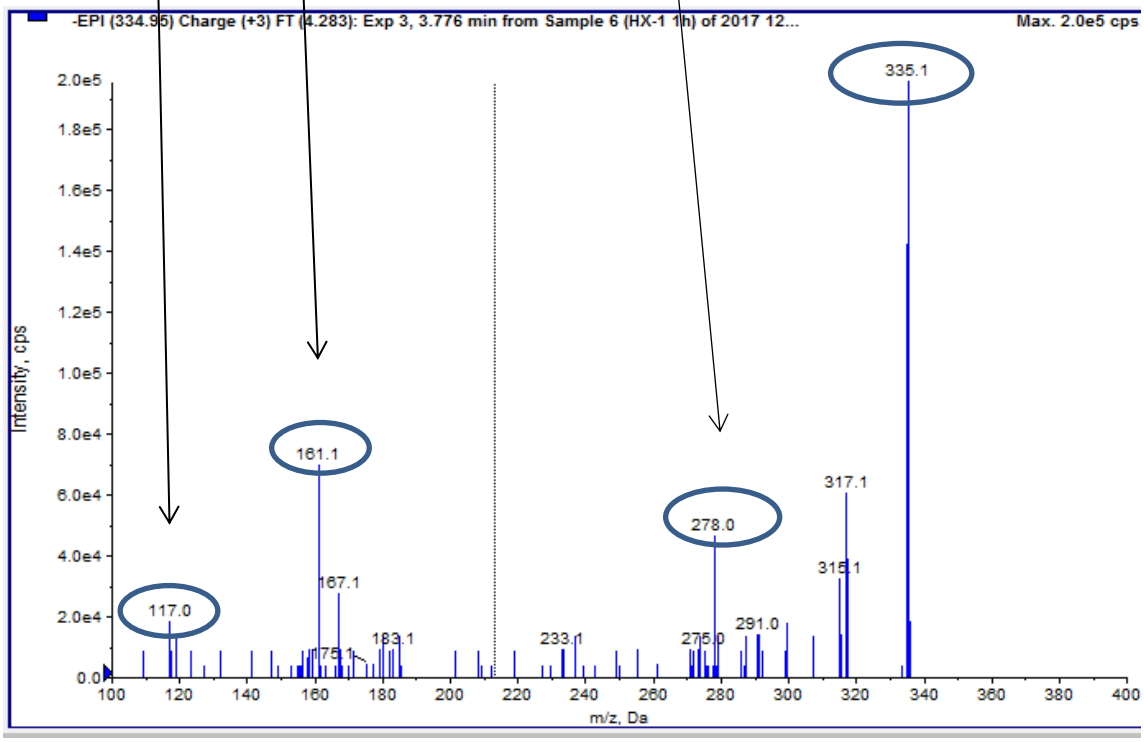



**Figure S21:** Potential carbonyl reduction metabolite [M + 2] of (*R*)-COT warfarin (**8a**) fragmentation pattern.

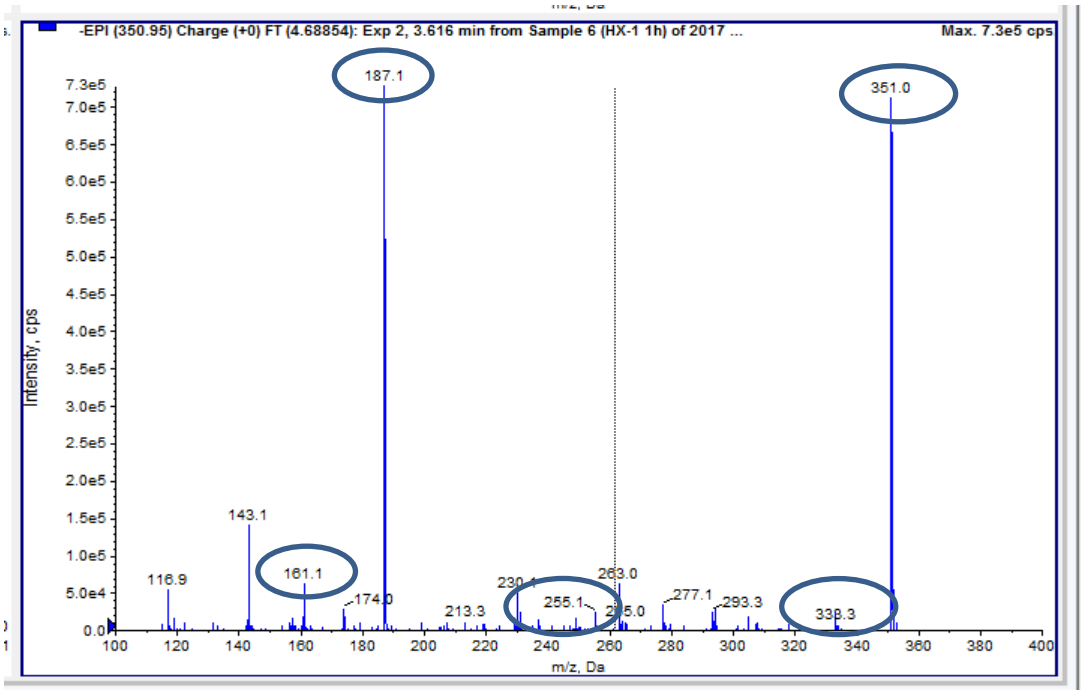



**Figure S22:** Potential carbonyl reduction and hydroxy/epoxy metabolites [M + 18] of (*R*)-COT warfarin (**8a**) fragmentation pattern.

## MRM peaks

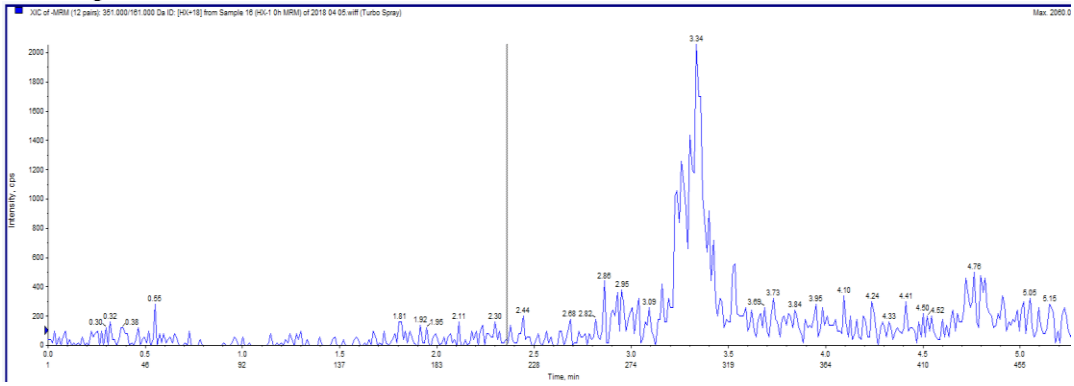


**Figure S23:** Potential carbonyl reduction and hydroxy/epoxy metabolites [M+18] of (*R*)-COT warfarin (**8a**) chromatogram. Time 0 h; intensity: $2e^3$.

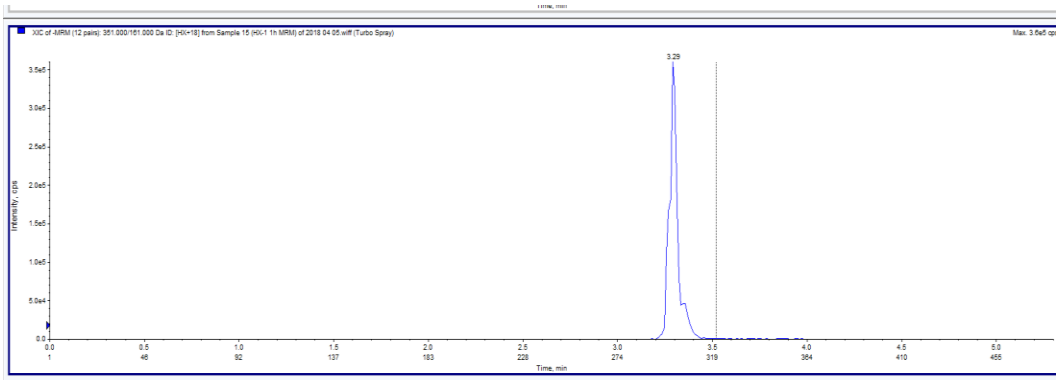


**Figure S24:** Potential carbonyl reduction and hydroxy/epoxy metabolites [M+18] of (*R*)-COT warfarin (**8a**) chromatogram. Time 1 h; intensity: $3.5e^5$.

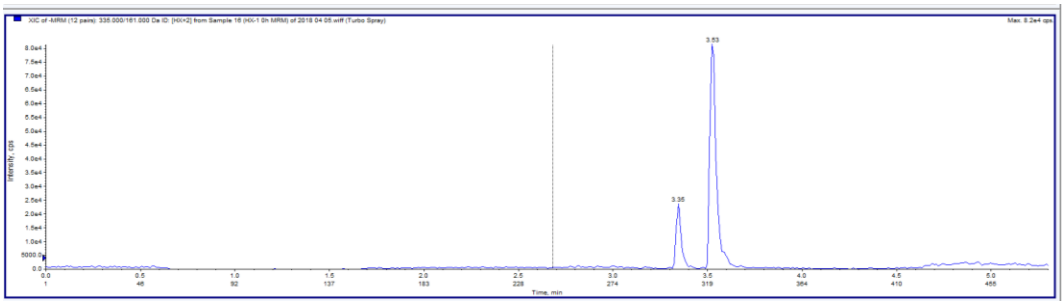


**Figure S25:** Potential carbonyl reduction metabolite of (*R*)-COT warfarin (**8a**) [M+2] chromatogram (left hand peak), Time 0 h (intensity: 2.5e4).

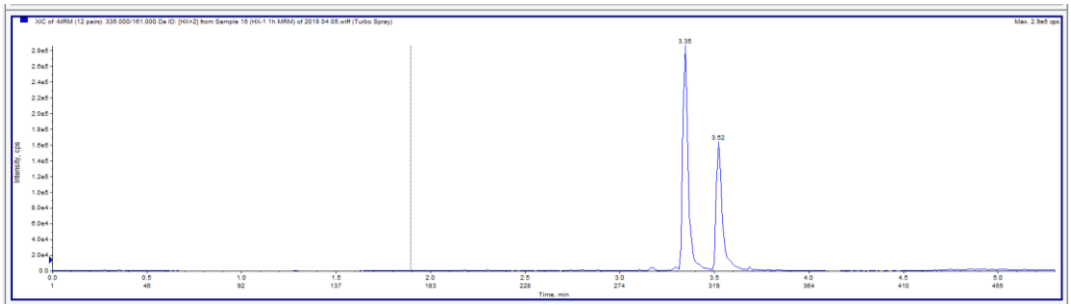



**Figure S26:** Potential carbonyl reduction metabolite of (*R*)-COT warfarin (**8a**) [M+2] chromatogram (left hand peak). Time 1 h; intensity: $2.8e^5$ after 1 h incubation.

Moclobemide Study

*Behavioural evaluation in mice (performed by the group led by A/ Prof. Tom Burne at the Queensland Brain Institute):*

**Experimental Animals**

All animal care and experimental procedures complied with the Australia Code of Practice for the Care and Use of Animals for Scientific Purposes (8th edition, 2013). Ethics approval was obtained from the Animal Ethics Committee of The University of Queensland (Brisbane, Australia).

Sixty-four adult male C57BL6/J mice were purchased from the Animal Resources Centre (Perth, WA, Australia). Mice weighed 34 g ( ± 4g ) upon arrival and they were housed in a purpose-built Physical Containment Level 2 (PC2) animal holding facility in groups of four in individually ventilated cages (OptiMice cages, Animal Care Systems, CO, USA) at 21°C, 40–60% humidity and 12/12 h light/dark cycle (lights on 0700 h) with ad libitum access to pelleted food (Specialty Feeds, WA) and water. The mice were habituated to the QBI animal house for 4–5 days prior to testing. One mouse became unwell and was euthanised prior to the experiment.

**Test Compounds Preparation and Administration**

Working solutions of each of moclobemide (**9**), the cubane (**14**) and COT (**21**) analogues were prepared at concentrations of 3.15mg/ml – made up in 50% EtOH and Saline, 25mg/ml – made up in 100% EtOH and 8mg/ml – made up in 100% EtOH , respectively. Working solutions were then diluted in sterile water for injection (Pfizer, West Ryde, NSW, Australia) to the final concentration of 5 mg/ml, and stored refrigerated and protected from light the day before the experiment.

**Open Field activity monitoring**

Each mouse was injected via the intraperitoneal route with 5 mg/ml (10ml/kg) and returned to its home cage 30 minutes prior to open field activity monitoring. The mouse was then placed in a clear open field (27.5 x 27.5 x 30cm, Med

Associates Inc, USA) within a sound attenuated chamber and activity levels were recorded for 30 minutes. The light level was set at 18 lux. As a measure of spontaneous activity, distance travelled was calculated using activity monitor tracking software based on beam breaks from three 16 beam infrared arrays and was sampled in 1 min time bins.

**Data analysis**

Results were analysed for statistical significance using the SPSS statistics software package (ver. 24, SPSS Inc., Chicago, Illinois). Data were pooled into 5 minute time bins and analysed using ANOVA to assess the difference between three groups, with a main effect of test compound and repeated measure on time bin. A p value of <0.05 was considered to be statistically significant.

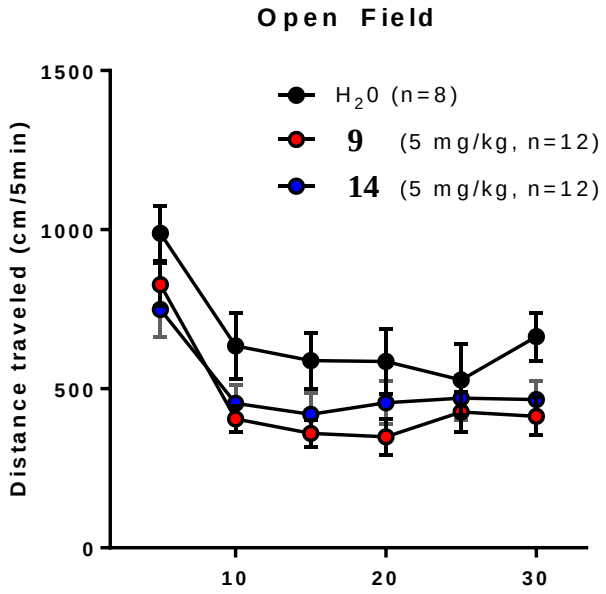



**Figure S27:** Average distance travelled values for moclobemide (**9**) vs. the cubane analogue (**14**). Single bolus i.p. injections of water (vehicle), **9** or **14** were administered to adult male C57BL6/J mice at doses of 5 mg / kg. After a wait period of thirty minutes, the mice were individually placed in the center of an enclosure (“open field”) surrounded by walls that prevented escape. The total distance travelled by each mouse in thirty minutes was measured. There was a significant main effect of Time ($F_{5,145}$=27.67, p<0.001) and test compound ($F_{1,29}$=3.35, p<0.05).

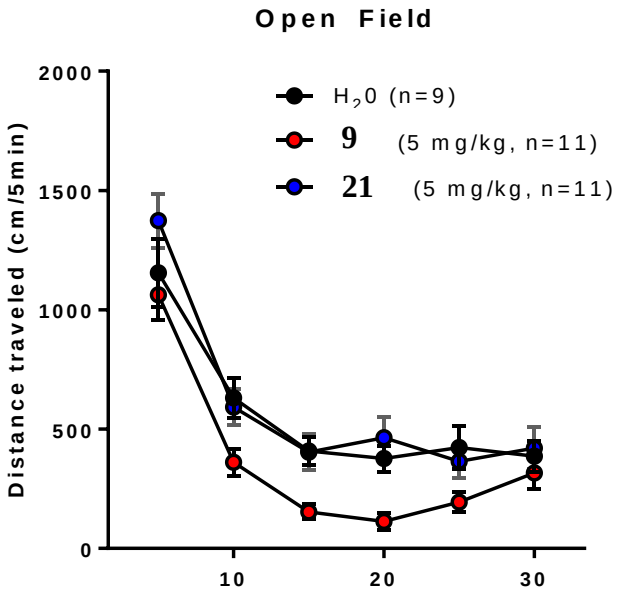



**Figure S28:** Average distance travelled values for moclobemide (**9**) vs. the COT analogue (**21**). Single bolus i.p. injections of water (vehicle), **9** or **21** were administered to adult male C57BL6/J mice at doses of 5 mg / kg. After a wait period of thirty minutes, the mice were individually placed in the center of an enclosure ("open field") surrounded by walls that prevented escape. The total distance travelled by each mouse in thirty minutes was measured. There was a significant main effect of Time ($F_{5,140}$=22.65, p<0.001) and test compound ($F_{1,28}$=4.77, p<0.01).

Pravadoline Study

*Antinociception evaluation (performed by the group led by Prof. Maree Smith at the Centre for Integrated Preclinical Drug Development):*

**Experimental Animals**

All animal care and experimental procedures complied with the Australia Code of Practice for the Care and Use of Animals for Scientific Purposes (8th edition, 2013). Ethics approval was obtained from the Animal Ethics Committee of The University of Queensland (Brisbane, Australia).

Male Sprague-Dawley (SD) rats were purchased from the Animal Resources Centre (Perth, WA, Australia). Rats weighed 180-200 g upon arrival and they were housed in a purpose-built Physical Containment Level 2 (PC2) animal holding facility in groups of three to four in individually ventilated cages (BioZone, Thorne Hill, Ramsgate, Kent, UK). Rat chow (Specialty Feeds, Glen Forrest, WA, Australia) and tap water were available *ad libitum* throughout the housing period. Rats were maintained in cages that contained recycled paper bedding material (FibreCycle Pty Ltd, Yatala, QLD, Australia) and environmental enrichment comprising Kimwipes (Kimberly-Clark Professional, Milsons Point, NSW, Australia), a rodent hutch (red Perspex hutch) and Rat Chewsticks (Able Scientific, Welshpool, WA, Australia) in each cage. The animal holding facility had a 12 h/12 h light/dark cycle and a mean (±SEM) room temperature of 23 (±3) °C. Animals were acclimatised for at least four days in the animal holding facility prior to initiation of any experimentation.

**Rat model of Freund's Complete Adjuvant (FCA) induced Inflammatory Pain**

Rats, whilst anaesthetised with 3% isoflurane (Abbott Australasia Pty Ltd, Botany, NSW, Australia) delivered in oxygen, received an intraplantar (i.pl.) injection of 150 µL of Freund's Complete Adjuvant (FCA; Sigma-Aldrich, MO, USA) into the plantar aspect of the left hindpaws. Clinical observations were performed post-FCA injection and at least once weekly until study completion (≤ day 14).

**Test Compounds Preparation and Administration**

Working solutions of each of pravadoline (**10**), cubane (**15**) and COT (**22**) analogues were prepared at concentrations of 300 ug/100-150 µL, 321 ug/150 µL and 321 ug/150 µL respectively. Working solutions were prepared using pure DMSO and then diluted with 40% Captisol (CyDex Pharmaceuticals Inc, KS, USA) in sterile water for injection (Pfizer, West Ryde, NSW, Australia) so that the final vehicle concentrations were 10% DMSO/40% Captisol. Working solutions were stored refrigerated and protected from light with a one week expiry date from the date of preparation.

Rats were anaesthetised briefly with 3% isoflurane (Abbott Australasia Pty Ltd, Botany, NSW, Australia) delivered in oxygen to facilitate intraplantar (i.pl.) drug administration. The i.pl. injection volumes were fixed at 150 µL and injections were made using a Hamilton syringe (SGE Analytical Science Pty Ltd, Ringwood, VIC, Australia) with a 25G x 5/8 needle (Terumo Corporation, Shibuya-ku, Tokyo, Japan). Each rat received a maximum of three doses according to a 'washout' protocol in the inflamed hindpaw with at least 3 days between each successive dose.

**Rat model of acute pain: Noxious mechanical stimuli to the hindpaws**

The Randall Sellito apparatus was used to apply acute noxious mechanical stimuli (Ugo Basile, Comerio, Italy) to the hindpaws of rats. As previously described,[67] a noxious mechanical stimulus with increasing force was applied to the medial portion of the hindpaw until a withdrawal response was evoked. A cut-off force of 250 g was used to prevent tissue damage. Baseline Paw Pressure Thresholds (PPTs) were determined in both hindpaws prior to i.pl. FCA. Baseline PPTs were the mean of three readings for the corresponding hindpaw, with a 5-min interval between consecutive measurements. Following dose administration, inflamed hindpaw PPTs were measured at the following post-dosing times 30, 45, 60, 75, 90, 120 and 180 min.

**Data Analysis**

For individual rats, delta (Δ) PPTs were calculated by subtracting the pre-dosing PPT from the corresponding post-dosing PPTs and any negative Δ PPTs were arbitrarily assigned a value of 0. For each rat, the extent and duration of antinociception (pain relief) was determined by using trapezoidal integration to estimate the area under the ΔPPT versus time curve (Δ PPT AUC values) using GraphPad™ Prism software (version 7.03; GraphPad Software, San Diego, CA, USA).

Analysis of variance (ANOVA) with a post-hoc Dunn's Multiple Comparison test was performed on the mean (±SEM) ΔPPT AUC values for groups of SD-rats administered single i.pl. bolus doses of the cubane (**15**) and COT (**22**) analogues or the positive control item, pravadoline (**10**) relative to animals administered vehicle (10%DMSO/40% Captisol). Microsoft Excel (version 16.0.4549.1000; Microsoft Corporation, Redmond, WA, USA) and GraphPad™ Prism software (version 7.03; GraphPad Software, San Diego, CA, USA).were used for all data and statistical analysis. The statistical significance criterion was $p \leq 0.05$.

Only responder-rats were included for the data plotting and analysis. Responders were defined as FCA-rats that received a test or positive control item that evoked a ΔPPT AUC response that was > 2 standard deviations above that of vehicle (i.e. mean vehicle + 2 SD).

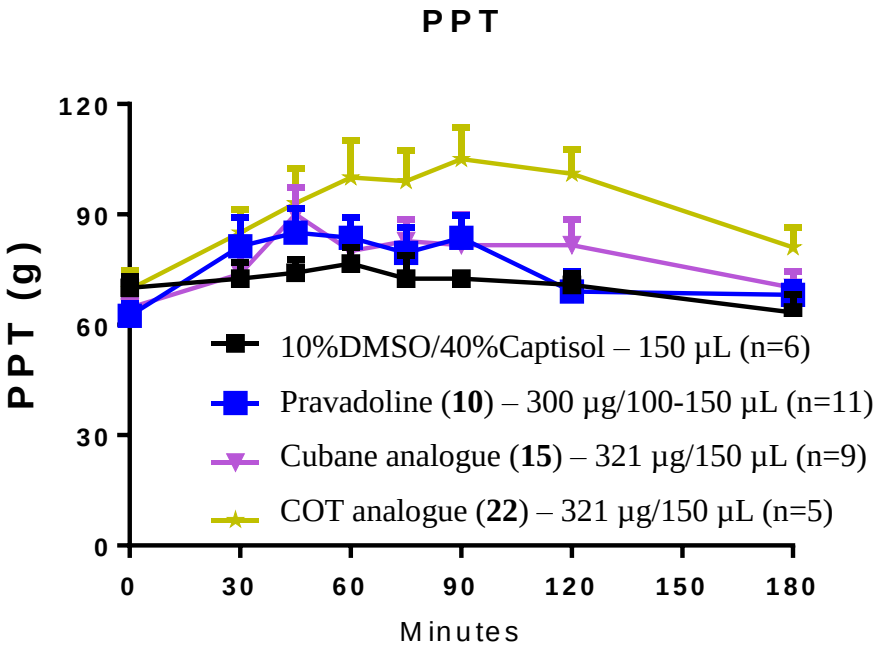



**Figure S29:** Mean (±SEM) paw pressure threshold (PPT) versus time curves for the ipsilateral hindpaws of FCA-rats that responded[1] following administration of single intraplantar bolus doses of vehicle (10%DMSO/40% Captisol; n=6) at 150 µL, pravadoline (**10**) at 300 µg/100-150 µL (n=11), pravadocube (**15**) at 321 µg/150 µL (n=9) and pravadocot (**22**) at 321 µg/150 µL (n=5) at time 0 (pre-dosing) and at 30, 45, 60, 75, 90, 120 and 180 min post-dosing.

[1] Responders were defined as FCA-rats that received a test item (pravadoline (**10**), cubane (**15**) or COT (**22**) analogues) that evoked a ΔPPT AUC response that was > 2 standard deviations above that of vehicle (i.e. mean vehicle + 2 SD; refer to **Figure S30**). N=6, n=2 and n=4 were excluded from pravadoline (**10**), cubane (**15**) and COT (**22**) analogues respectively using the above mentioned exclusion criteria.

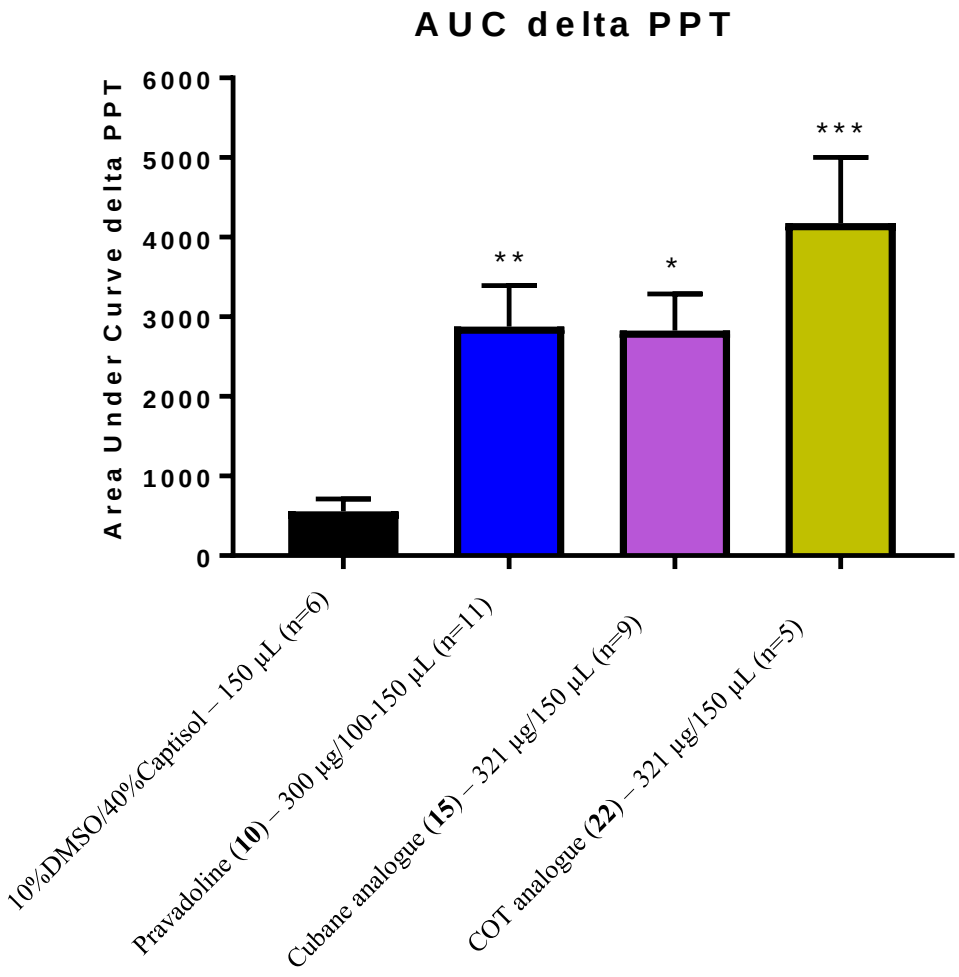



**Figure S30:** Mean (±SEM) extent and duration of action quantified as the mean (±SEM) areas under the Δ PPT versus time curves (Δ PPT AUC values) for the ipsilateral (FCA injected) hindpaws of FCA-rats that responded[1] following administration of single intraplantar bolus doses of vehicle (10%DMSO/40% Captisol; n=6) at 150 µL, pravadoline (**10**) at 300 µg/100-150 µL (n=11), cubane analogue (**15**) at 321 µg/150 µL (n=9) and COT analogue (**22**) at 321 µg/150 µL (n=5) at time 0 (pre-dosing) and at 30, 45, 60, 75, 90, 120 and 180 min post-dosing.

[1] Responders were defined as FCA-rats that received a test item (pravadoline (**10**), cubane (**15**) or COT (**22**) analogues) that evoked a ΔPPT AUC response that was > 2 standard deviations above that of vehicle (i.e. mean vehicle + 2 SD).

* $p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$; one-way ANOVA (post-hoc Dunn's multiple comparisons test).

| | 10%DMSO/40%Captisol - 150uL (n=6) | Pravadoline - 300µg/100-150µL (n=11) | Cubane-Pravadoline - 321ug/150uL (n=9) | COT-Pravadoline - 321ug/150uL (n=5) |
|---|---|---|---|---|
| **Number of values** | 6 | 11 | 9 | 5 |
| | | | | |
| **Minimum** | 313 | 1600 | 1275 | 1763 |
| **25% Percentile** | 341 | 1725 | 1494 | 2544 |
| **Median** | 431.3 | 1913 | 3088 | 3774 |
| **75% Percentile** | 712.2 | 4875 | 3901 | 6019 |
| **Maximum** | 1312 | 6188 | 5151 | 6238 |
| | | | | |
| **Mean** | 558.3 | 2875 | 2827 | 4180 |
| **Std. Deviation** | 377.4 | 1721 | 1382 | 1844 |
| **Std. Error of Mean** | 154.1 | 518.9 | 460.7 | 824.5 |
| | | | | |
| **Lower 95% CI of mean** | 162.3 | 1719 | 1764 | 1890 |
| **Upper 95% CI of mean** | 954.4 | 4031 | 3889 | 6469 |
| | | | | |
| **Sum** | 3350 | 31628 | 25441 | 20898 |
| | | | | |
| **D'Agostino & Pearson normality test** | | | | |
| **K2** | N too small | 3.436 | 1.014 | N too small |
| **P value** | | 0.1794 | 0.6022 | |
| **Passed normality test (alpha=0.05)?** | | Yes | Yes | |
| **P value summary** | | ns | ns | |
| | | | | |
| **Shapiro-Wilk normality test** | | | | |
| **W** | 0.6835 | 0.7298 | 0.9106 | 0.9383 |
| **P value** | 0.0041 | 0.0011 | 0.3199 | 0.6536 |
| **Passed normality test (alpha=0.05)?** | No | No | Yes | Yes |
| **P value summary** | ** | ** | ns | ns |
| | | | | |
| **KS normality test** | | | | |
| **KS distance** | 0.382 | 0.3246 | 0.2157 | 0.2101 |
| **P value** | 0.0065 | 0.0019 | >0.1000 | >0.1000 |
| **Passed normality test (alpha=0.05)?** | No | No | Yes | Yes |
| **P value summary** | ** | ** | ns | ns |

**Table S28:** summary table of normality test results for the vehicle and three test items.

SAHA Study

*Inhibition of cancer cell growth in culture (performed by the group led by Dr Glen Boyle at the QIMR Berghofer Medical Research Institute):*

**Materials and Methods**

SAHA (**11**) was purchased from Cayman Chemical (Ann Arbor, Michigan 48108 USA; Catalogue #10009929). The cubane (**16**) and COT (**23**) analogues were synthesized as detailed **Supplementary Information Part 1**. Both compounds were dissolved in DMSO. MM96L and MCF7 are human tumor cell lines derived from melanoma and breast cancer respectively. NFF are early passage neonatal foreskin fibroblasts.

Sulforhodamine B assay for cell survival assessment of cultured cells.

Cells were seeded at 2,500 per microtitre well (96-well plate) in 10% FCS-RPMI 1640 culture medium, treated, and allowed to grow until the controls were nearly confluent (6 days). Culture media was removed; the wells were then washed twice with phosphate buffered solution (PBS), fixed with ethanol for a minimum of 5 min. and washed with water. Sulforhodamine B (SRB) solution (50 µL of 0.4% in 1% acetic acid) was added and the mixture left at room temperature for a minimum of 15 min. The plate was washed rapidly with tap water and then twice with 0.1-1% acetic acid, the liquid being removed by tapping each time. After addition of 100 µL/well of 10 mM Tris base (unbuffered, pH > 9), plates were left for a minimum of 5 min, then the absorbance was read at 564 nm on an Biotek Synergy H4 Multi Mode Plate Reader, with a 3 second prior shaking operation. Data were exported to an Excel spreadsheet. After subtraction of a blank (i.e. wells with no cells, A564 typically ~0.04), growth inhibition was calculated as a percentage of the untreated control and plotted against dose.[68] Non-linear regression was performed using GraphPad™ Prism version 7.02 for Windows (GraphPad Software, La Jolla California USA).

| Compound | NFF | MCF-7 | MM96L |
|---|---|---|---|
| SAHA (**11**) | 32 ± 5 | 17 ± 1 | 26 ± 5 |
| Cubane analogue (**16**) | 142 ± 21 | 53 ± 4 | 137 ± 5 |
| COT analogue (**23**) | 77 ± 11 | 37 ± 3 | 73 ± 8 |

**Table S29:** $IC_{50}$ Values (ng/ml).

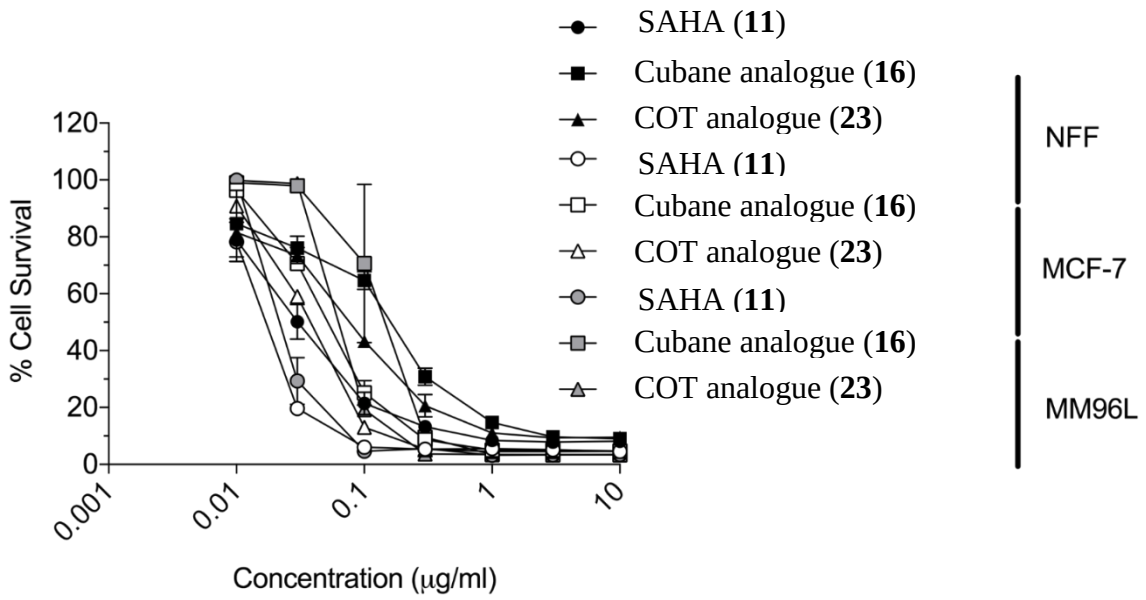



**Figure S31:** Cell survival of NFF, MCF-7 and MM96L cells following treatment with SAHA (**11**), and cubane (**16**) or COT (**23**) analogues for 6 days.

SAHA (**11**)

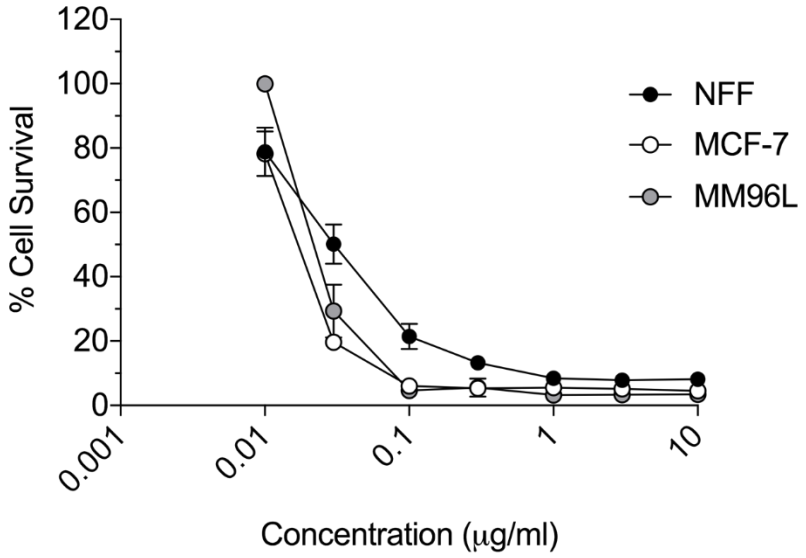



**Figure S32:** Cell survival of NFF, MCF-7 and MM96L cells following treatment with SAHA (**11**) for 6 days.

Cubane analogue (**16**)

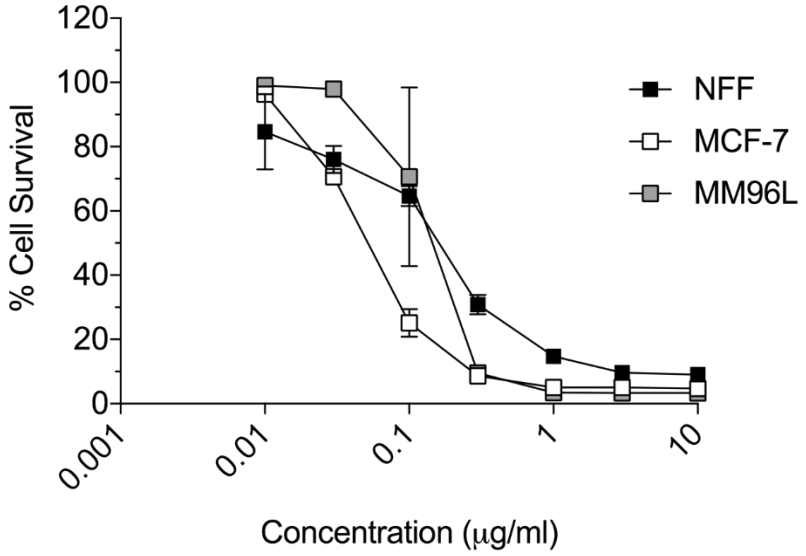



**Figure S33:** Cell survival of NFF, MCF-7 and MM96L cells following treatment with cubane analogue (**16**) for 6 days.

COT analogue (**23**)

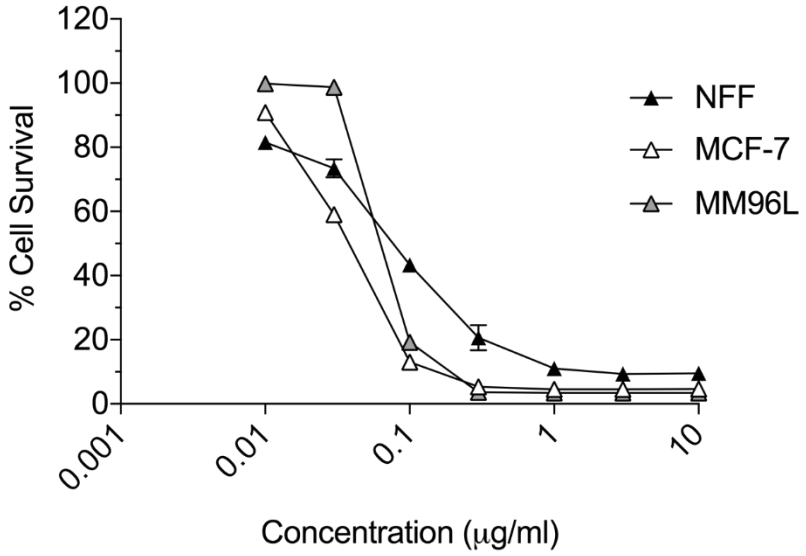



**Figure S34:** Cell survival of NFF, MCF-7 and MM96L cells following treatment with COT analogue (**23**) for 6 days.

Benzyl Benzoate Study

*Acaricidal activity of scabies mites (performed by the group led by Professor James McCarthy at the QIMR Berghofer Medical Research Institute):*

**Method**

Three concentrations (100mM, 50mM, 25mM) of each compound for testing were prepared using mineral oil as diluent. Each compound concentration was spread thinly in each duplicate dish and live mites (at least 10) were placed to allow contact with compounds. Mite status was observed under the microscope within one hour of contact and hourly thereafter, for up to 7 hours. Mite status was again observed after 24 hours. (Mortality was described as absence of leg movement or gut peristalsis when touched with needle). Benzyl Benzoate (**12**) (25mM) was used as the positive control acaricide and mineral oil as negative control. The bioassay was performed twice.

Data was analysed using Survival Analysis in Graph Pad Prism™ (v7) and statistical significance between survival curves compared by the Log Rank Test. Results are expressed as median survival time.

**Results**

No solubility issues were identified; all three compounds dissolved well in mineral oil at room temperature. Of the three concentrations tested, the highest concentration (100mM) showed discriminatory activity against scabies mites within 7 hours of observation with benzyl cyclooctatetraenecarboxylate (**26**) giving the fastest killing effect (Median survival of mites= 4 hrs). At lower concentrations (50 mM and 25mM) of benzyl cyclooctatetraenecarboxylate (**26**), median survival of mites (7 hours) was the same. On the other hand, mites remained alive within 7 hours of exposure to cyclooctatetraenemethyl benzoate (**25**) of the same lower concentrations. Median survival of mites in cyclooctatetraenylmethyl cyclooctatetraenecarboxylate (**24**) was the same (7 hrs) in all concentrations (100mM, 50mM, 25mM) tested. Structure -activity relationship was evident in the mites bioassay performed.

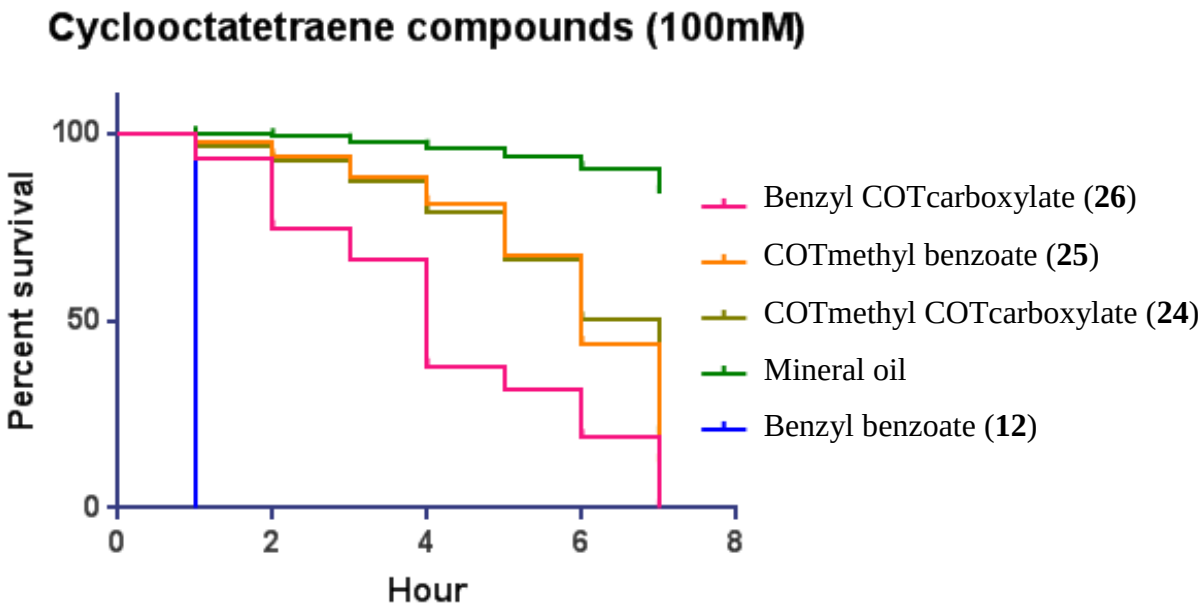
| | **26** | **25** | **24** | Benzyl Benzoate (**12**) | Mineral Oil |
|---|---|---|---|---|---|
| Concentration(mM) | (hour) | (hour) | (hour) | (hour) | (hour) |
| 100 | 4 | 6 | 7 | - | * |
| 50 | 7 | >7 | 7 | - | * |
| 25 | 7 | >7 | 7 | 1 | * |

**Table S30:** median survival time of scabies mites in cycloctatetraene derivatives **24**-**26** in contact bioassays. *mites remained alive >24hrs

When mites were checked after 24 hrs of exposure to test compounds, % mortality was observed to be dose-dependent with all three compounds demonstrating acaricidal activity with longer exposure time. This is in comparison to mites in contact with mineral oil (negative control) that remained alive (39/42=93%), after 24 hours. Data as shown in **Table S31** below:

| | **26** | **25** | **24** |
|---|---|---|---|
| Concentration (mM) | * | * | * |
| 100 | 38/40(95%) | 39/40(98%) | 30/40(75%) |
| 50 | 36/40(90%) | 31/40(78%) | 27/40(68%) |
| 25 | 26/40(65%) | 26/40(65%) | 23/40(58%) |

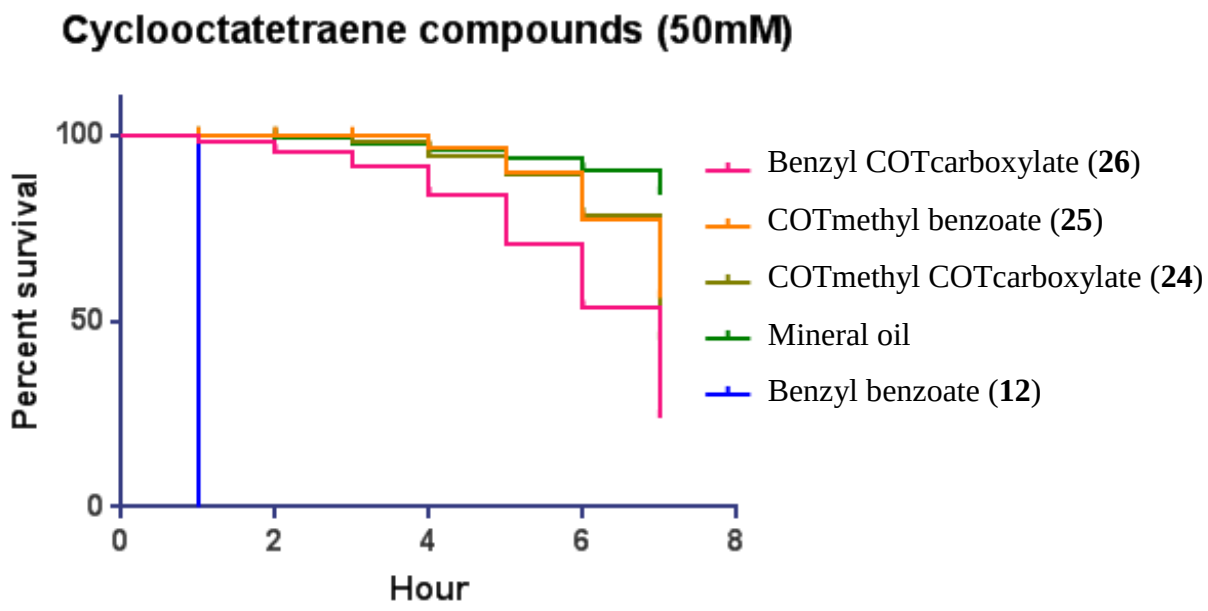
**Table S31:** proportion of dead mites after 24 hours of contact with compounds. *no. of dead mites/total no. of mites exposed (percentage).




Comparison of survival curves:

| | |
|---|---|
| Log-rank (Mantel-Cox) test | |
| Chi square | 835.8 |
| df | 4 |
| P value | <0.0001 |
| P value summary | **** |
| Are the survival curves sig different? | Yes |

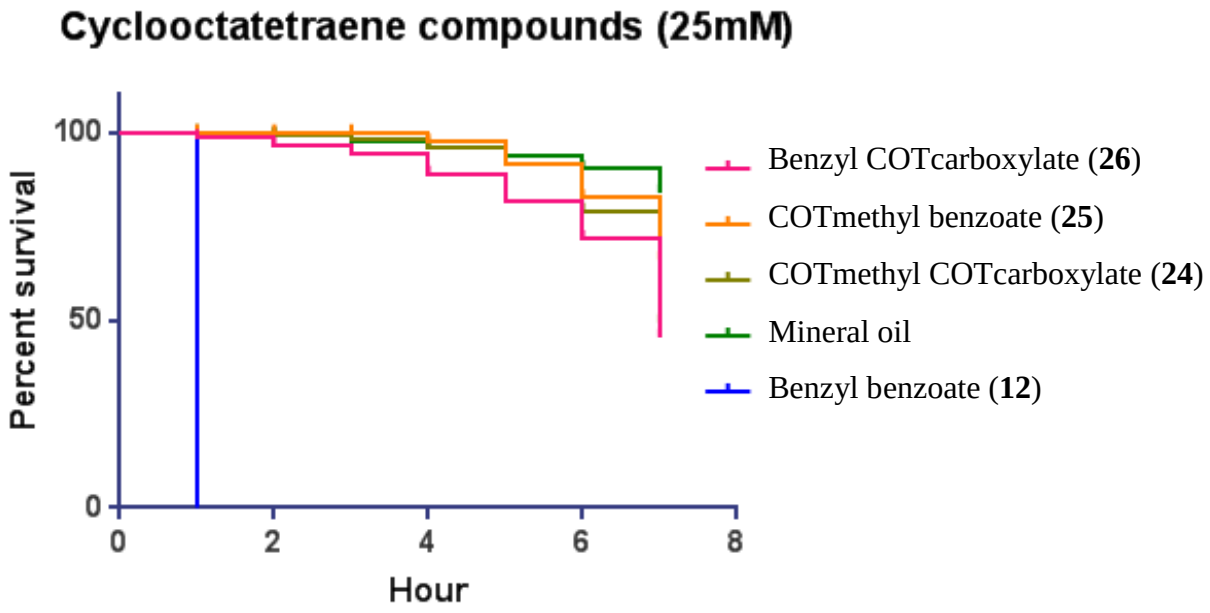
**Figure S35:** survival of scabies mites in 100mM. Cyclooctatetraene compounds (**24**-**26**) compared to survival in mineral oil (negative control) and benzyl benzoate (**12**) (positive acaricidal control).




Comparison of survival curves:

| | |
|---|---|
| Log-rank (Mantel-Cox) test | |
| Chi square | 1138 |
| df | 4 |
| P value | <0.0001 |
| P value summary | **** |
| Are the survival curves sig different? | Yes |

**Figure S36:** survival of scabies mites in 50mM. Cyclooctatetraene compounds (**24**-**26**) compared to survival in mineral oil (negative control) and benzyl benzoate (**12**) (positive acaricidal control).




Comparison of survival curves:

| | |
|---|---|
| Log-rank (Mantel-Cox) test | |
| Chi square | 1079 |
| df | 4 |
| P value | <0.0001 |
| P value summary | **** |
| Are the survival curves sig different? | Yes |

**Figure S37:** survival of scabies mites in 25mM. Cyclooctatetraene compounds (**24**-**26**) compared to survival in mineral oil (negative control) and benzyl benzoate (**12**) (positive acaricidal control).

Diflubenzuron Study

*Tribolium castaneum (rust-red flour beetle) evaluation (performed by the group led by Prof. Gimme Walter at the School of Biological Sciences, The University of Queensland):*

**Introduction**

*Tribolium* has often been used in investigations of the mode of action of insecticides, using insect growth regulators (IGRs) such as benzoylphenyl ureas (BPUs), including diflubenzuron (**13**), an inhibitor of chitin formation.[69] Diflubenzuron (**13**) is considered most effective on the larval stages of arthropods, inducing abortive molting.[70] We tested the mortality imposed on field strain *T. castaneum* larvae by diflubenzuron (**13**) at different doses relative to that caused by the COT analogue (**27**). In general, methods are similar to those we used previously.[54]

**Materials and Methods - Rearing *T. castaneum***

Three hundred *T. castaneum* adults (collected from the field at Dalby, Queensland [27° 11' S 151° 16' E]) were placed in a 400 g whole-wheat flour enriched with 5% (20 g) torula yeast mixture at 25 °C and ~70% rh overnight. The following day the adults were sieved from the medium, which was retained so as to culture the larvae that hatched from the eggs deposited in it. After three weeks these larvae were ~6 mm long, so were close to pupation, and were used in experiments.

**Experimental methods**

The treatment doses and application methods for testing chitin inhibition in insects using IGR's vary considerably in the literature (e.g. direct application to larval and adult insects, and direct or acetone dissolved application to food sources).[71] We used the following method, which is fairly representative.[71] Controls comprised a Petri dish containing 10 late instar larvae in a 10 g organic

whole wheat flour/yeast medium prepared as described above. The diflubenzuron (**13**) and COT analogue (**27**) treatments were conducted in the same manner as the controls, with the appropriate weight of the relevant compound (53, 35, 18, 9 and 4 μmol) added to the flour medium and mixed thoroughly, 30 seconds clockwise then 30 seconds anticlockwise, before adding the larvae. All treatments were held at 25 °C and 70% rh for 10 days. The larvae were sieved from the medium to record mortality. Data were analysed by means of ANOVA's. No significance was determined from the ANOVA's, so post hoc tests were unnecessary.

**Comparison with equimolar doses of (13) and (27)**

The efficacy of the COT analogue (**27**) and diflubenzuron (**13**) at equimolar doses were tested on a field strain of *T. castaneum* (see above). Three replicates of each dose level were run, plus three blank controls.

## Results

None of the treatments imposed mortality that was significantly higher than that recorded in the control tests. The culture medium could have imposed stresses on insects adapted to field conditions and led to an increase in the variance in recorded mortality. Similar levels of variance were also seen in a previous study[54] that tested the cubane analogue of diflubenzuron (i.e. **20**) against field strain beetle larvae. However, the controls for laboratory strain tests returned lower levels of mortality.

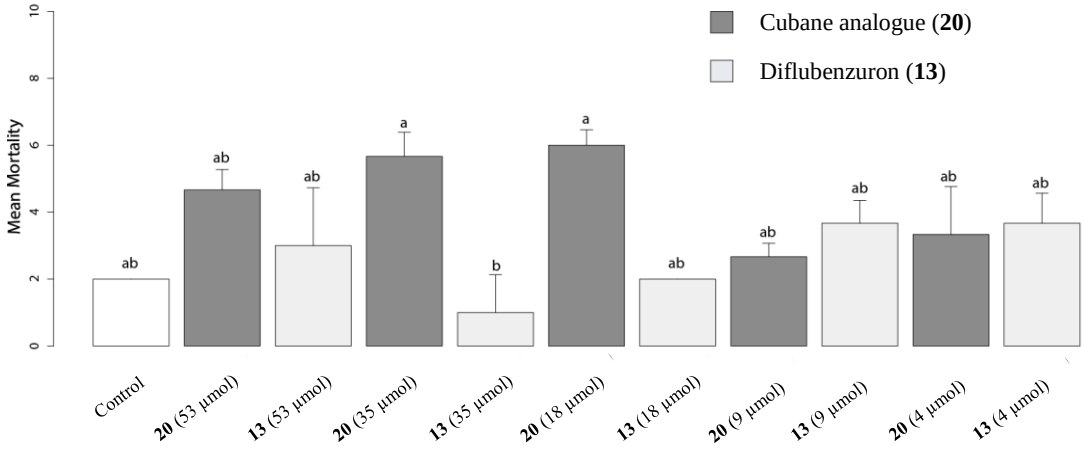



**Figure S38:** mean mortality for the cubane analogue (**20**) and diflubenzuron (**13**) at different concentrations.

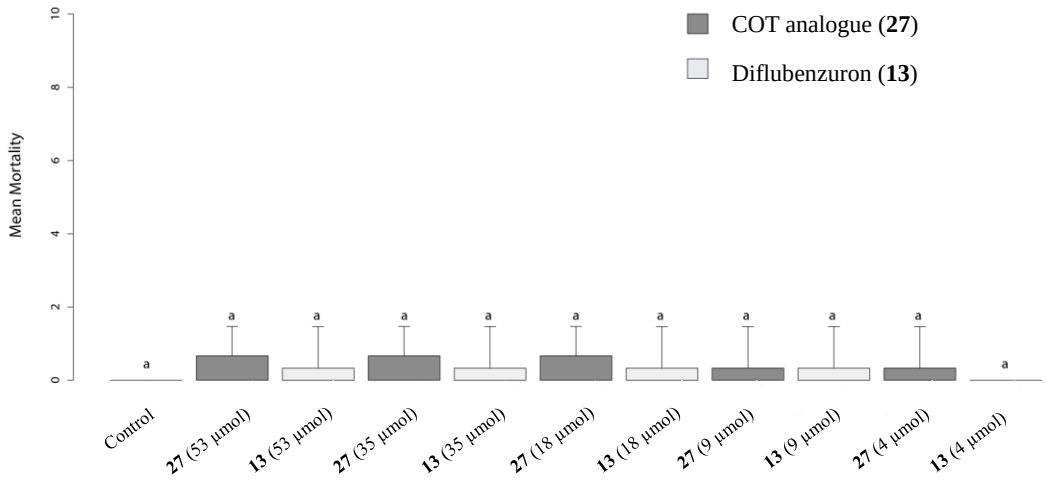



**Figure S39:** mean mortality for COT analogue(**27**) and diflubenzuron (**20**) at different concentrations.

**Comparing the efficacy of equimolar doses of the cubane (20) and COT (27) analogues against that of diflubenzuron (13)**

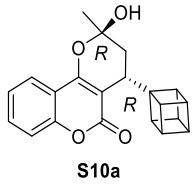
Tests comparing diflubenzuron (**13**) against the cubane (**20**) and COT (**27**) analogues were conducted separately, so the data could not be combined for statistical analysis. However, comparison of the efficiency of compounds **20** and **27** against diflubenzuron (**13**) is valid because field strain beetles from the same locality (Dalby) were used in both experiments.

In neither study were the mortalities associated with the cubane (**20**) and COT (**27**) analogues significantly different from the mortality levels recorded in the untreated controls. Nevertheless, in one experiment using a mid-range concentration of the cubane analogue (**20**) significantly higher mortality was recorded than with diflubenzuron (**13**),[54] although this could be attributed to chance. Results from the COT analogue (**27**) experiment were generally similar in that no significant differences from the controls were recorded.

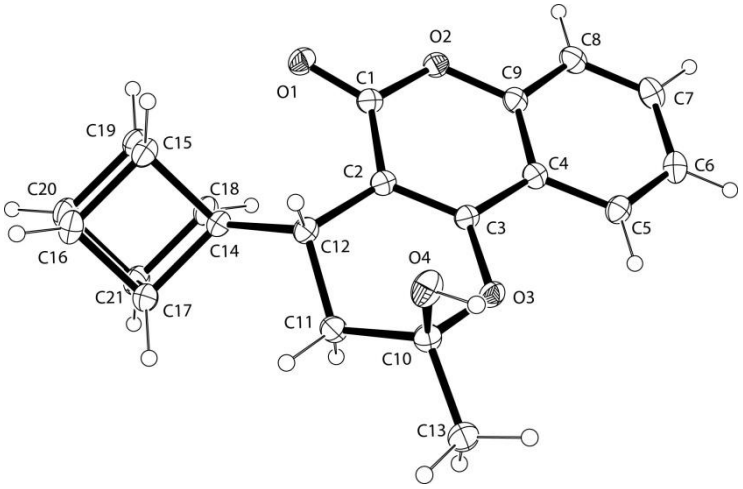
**Supplementary Information Part 3: Crystallographic Data**

*Crystallographic information for compounds **S10a**, **S13** and **23** (collection and analysis by Prof. Paul Bernhardt at the School of Chemistry and Molecular Biosciences):*

CCDC 1847176 (for compound **S10a**), 1847177 (for compound **S13**) and 1847178 (for compound **23**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.




**S10a**



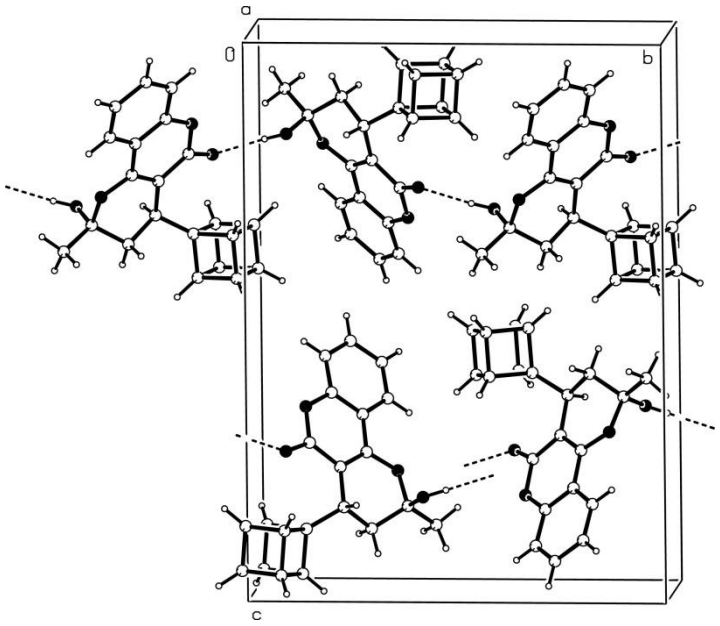
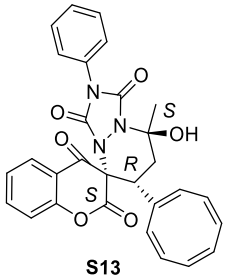

a
0
b
c

**Table S32:** crystal data and structure refinement for **S10a**

| | | |
|---|---|---|
| CCDC | 1847176 | |
| Identification code | **S10a** | |
| Empirical formula | $C_{21}\ H_{18}\ O_4$ | |
| Formula weight | 334.35 | |
| Temperature | 190(2) K | |
| Wavelength | 1.54184 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P\ 2_1\ 2_1\ 2_1$ | |
| Unit cell dimensions | a = 5.4085(2) Å | α= 90°. |
| | b = 14.7083(4) Å | β= 90°. |
| | c = 19.7970(7) Å | γ = 90°. |
| Volume | 1574.85(9) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.410 $Mg/m^3$ | |
| Absorption coefficient | 0.791 $mm^{-1}$ | |
| F(000) | 704 | |
| Crystal size | 0.6 x 0.15 x 0.15 $mm^3$ | |
| Theta range for data collection | 3.74 to 62.45°. | |
| Index ranges | -6<=h<=5, -16<=k<=12, -21<=l<=22 | |
| Reflections collected | 5483 | |
| Independent reflections | 2481 [R(int) = 0.0169] | |
| Completeness to theta = 62.45° | 99.7 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 1 and 0.73628 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2481 / 0 / 228 | |
| Goodness-of-fit on $F^2$ | 1.068 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0287, wR2 = 0.0753 | |
| R indices (all data) | R1 = 0.0293, wR2 = 0.0760 | |
| Absolute structure parameter | -0.01(15) | |
| Largest diff. peak and hole | 0.147 and -0.250 $e.Å^{-3}$ | |




**S13**

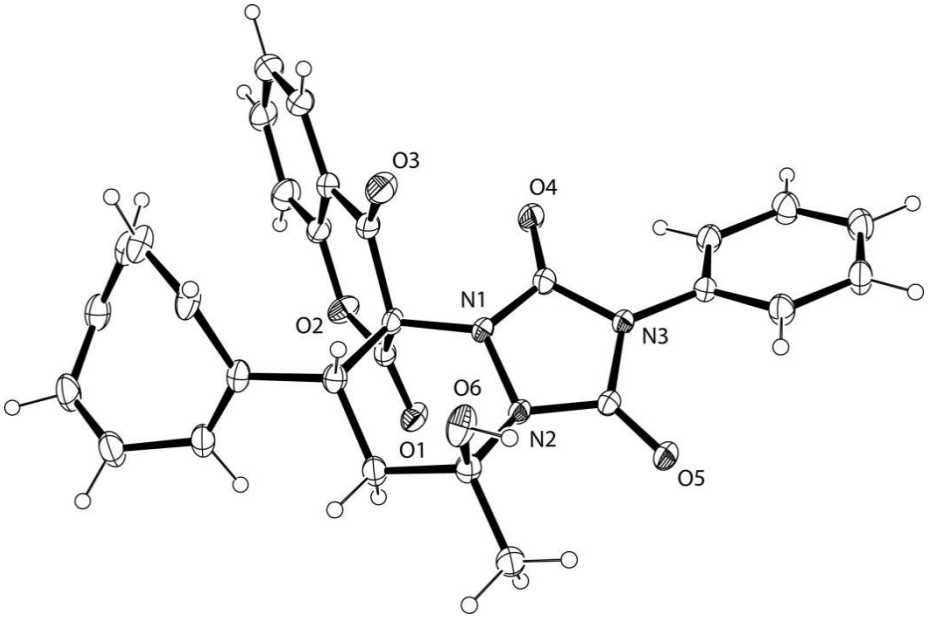
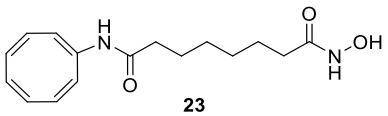



**Table S33:** crystal data and structure refinement for **S13.**

| | | |
|---|---|---|
| CCDC | 1847177 | |
| Identification code | **S13** | |
| Empirical formula | $C_{29}$ $H_{23}$ $N_3$ $O_6$ | |
| Formula weight | 509.50 | |
| Temperature | 190(2) K | |
| Wavelength | 1.54184 Å | |
| Crystal system | Orthorhombic | |
| Space group | P $2_1$ $2_1$ $2_1$ | |
| Unit cell dimensions | a = 9.4892(1) Å | α= 90°. |
| | b = 10.7010(1) Å | β= 90°. |
| | c = 23.5032(3) Å | γ = 90°. |
| Volume | 2386.61(5) $Å^3$ | |

| | |
|---|---|
| Z | 4 |
| Density (calculated) | 1.418 $Mg/m^3$ |
| Absorption coefficient | 0.832 $mm^{-1}$ |
| F(000) | 1064 |
| Crystal size | 0.4 x 0.1 x 0.1 $mm^3$ |
| Theta range for data collection | 3.76 to 62.42°. |
| Index ranges | -9<=h<=10, -12<=k<=11, -26<=l<=27 |
| Reflections collected | 10005 |
| Independent reflections | 3772 [R(int) = 0.0200] |
| Completeness to theta = 62.42° | 99.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 1 and 0.89725 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3772 / 0 / 345 |
| Goodness-of-fit on $F^2$ | 1.057 |
| Final R indices [I>2sigma(I)] | R1 = 0.0284, wR2 = 0.0711 |
| R indices (all data) | R1 = 0.0291, wR2 = 0.0718 |
| Absolute structure parameter | 0.01(15) |
| Largest diff. peak and hole | 0.229 and -0.198 e.Å-3 |




**23**

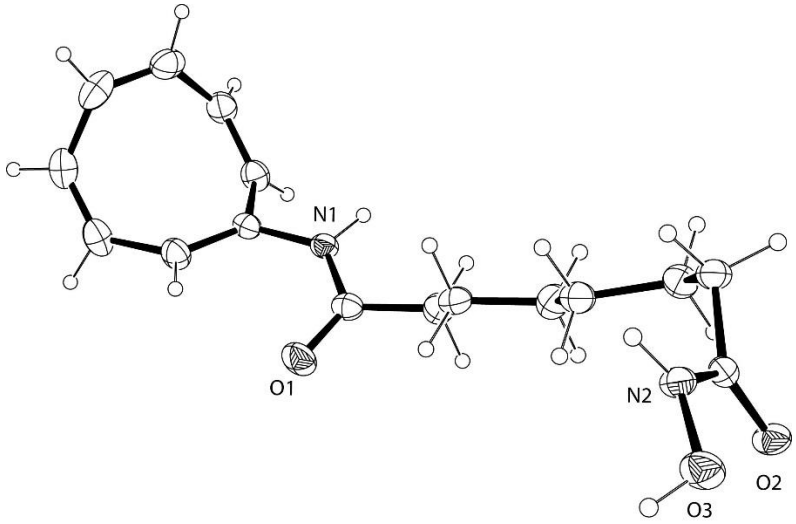


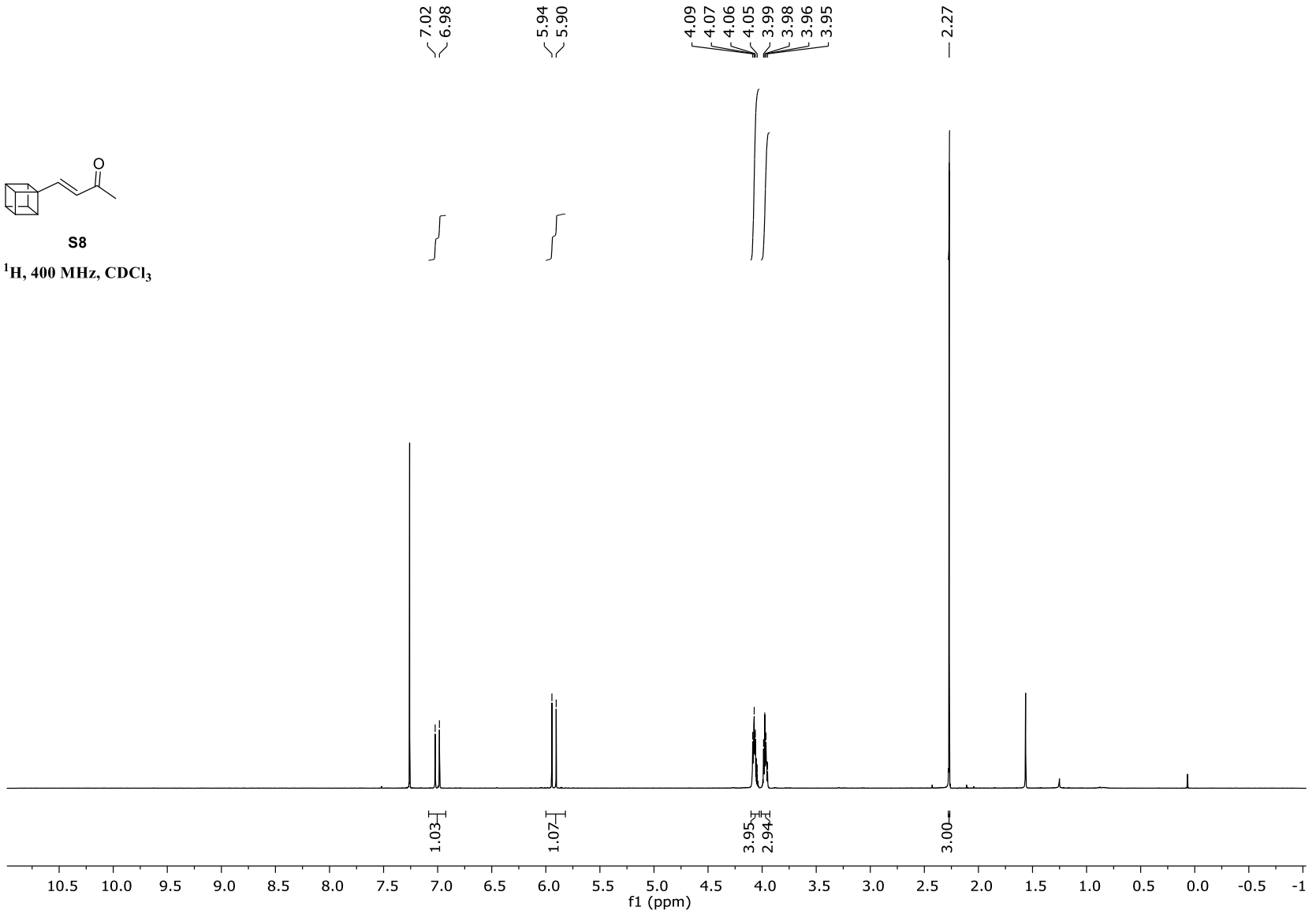

**Table S34:** crystal data and structure refinement for **23**

| | | |
|---|---|---|
| CCDC | 1847178 | |
| Identification code | **23** | |
| Empirical formula | $C_{16}$ $H_{22}$ $N_2$ $O_3$ | |
| Formula weight | 290.36 | |
| Temperature | 190(2) K | |
| Wavelength | 1.54184 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1/c$ | |
| Unit cell dimensions | a = 18.325(5) Å | α= 90°. |
| | b = 9.2693(8) Å | β= 90.000(9)°. |
| | c = 9.2733(8) Å | γ = 90°. |
| Volume | 1575.2(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.224 $Mg/m^3$ | |
| Absorption coefficient | 0.688 $mm^{-1}$ | |
| F(000) | 624 | |
| Crystal size | 0.2 x 0.08 x 0.02 $mm^3$ | |
| Theta range for data collection | 4.83 to 62.40°. | |
| Index ranges | -21<=h<=19, -10<=k<=10, -10<=l<=10 | |
| Reflections collected | 4181 | |
| Independent reflections | 4181 [R(int) = 0.0000] | |

| | |
|---|---|
| Completeness to theta = 62.40° | 98.3 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 1 and 0.7873 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4181 / 0 / 192 |
| Goodness-of-fit on $F^2$ | 0.986 |
| Final R indices [I>2sigma(I)] | R1 = 0.0511, wR2 = 0.1466 |
| R indices (all data) | R1 = 0.0771, wR2 = 0.1631 |
| Largest diff. peak and hole | 0.213 and -0.245 e.$Å^{-3}$ |

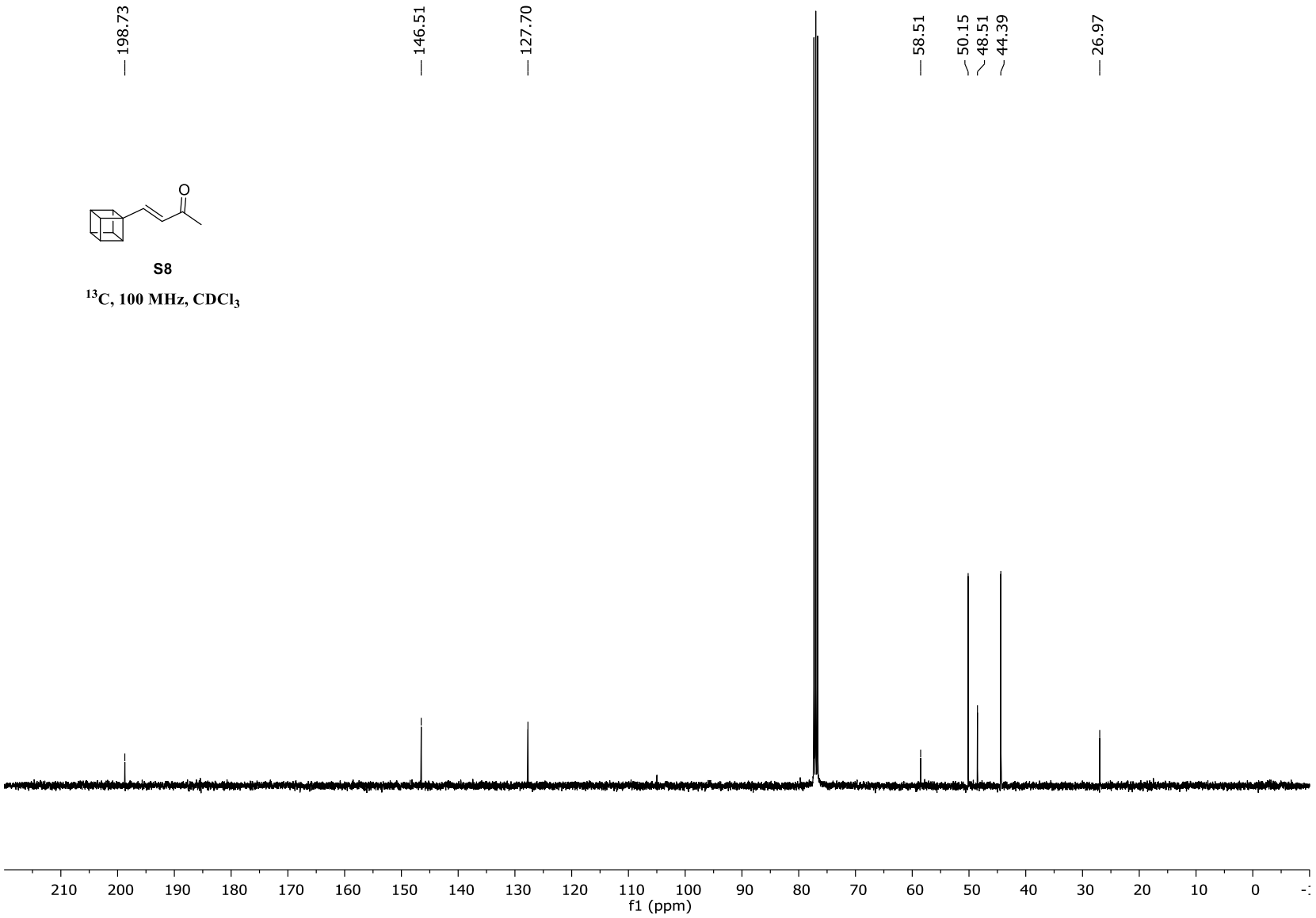
## Supplementary Information Part 4: $^{1}H$ and $^{13}C$ Spectra

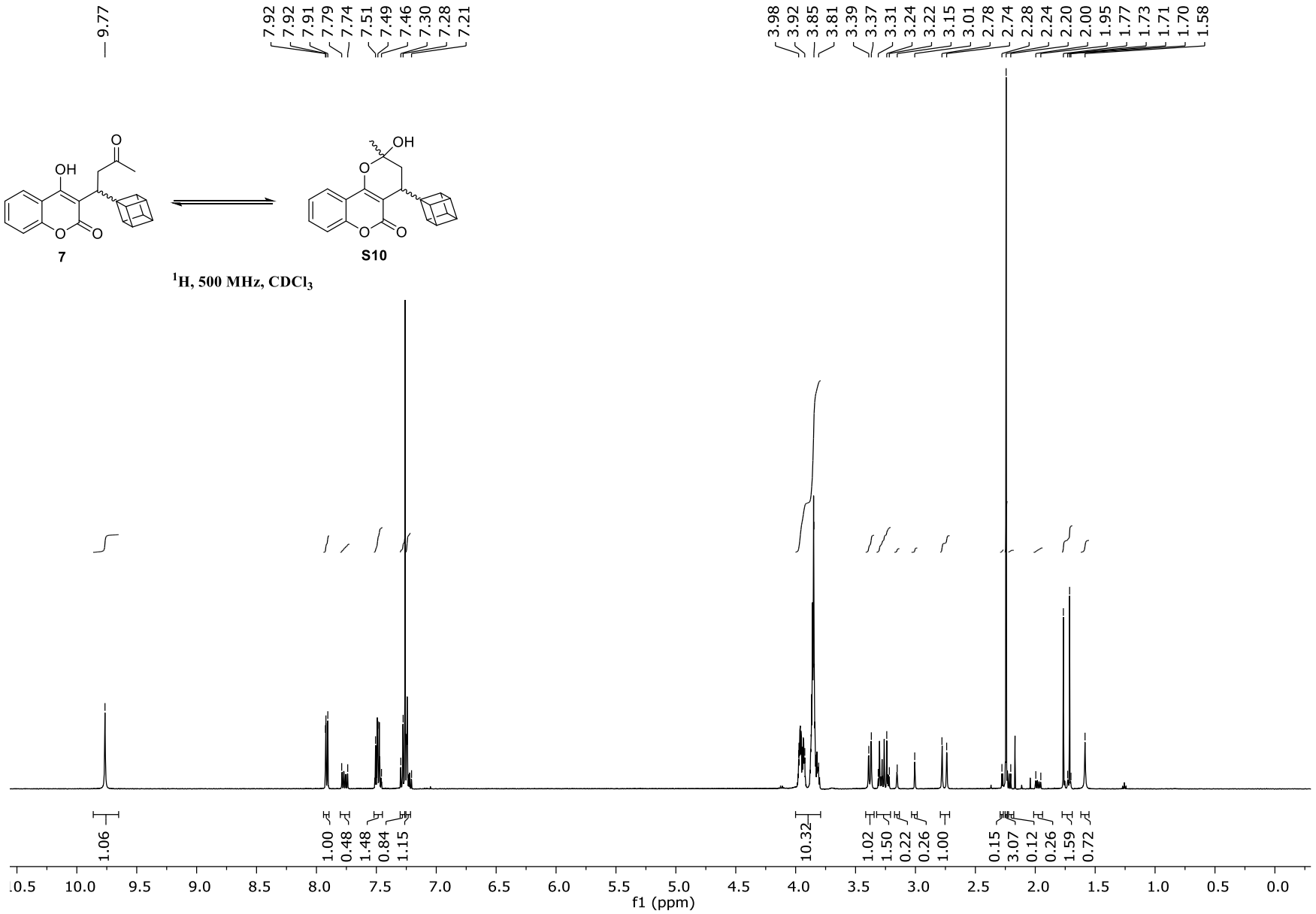
*Spectroscopic data pertaining to warfarin (**6**), moclobemide (**9**), pravadoline (**10**), SAHA (**11**), benzyl benzoate (**12**), diflubenzuron (**13**), and analogues (performed by the group led by Prof. Craig Williams at the School of Chemistry and Molecular Biosciences):*

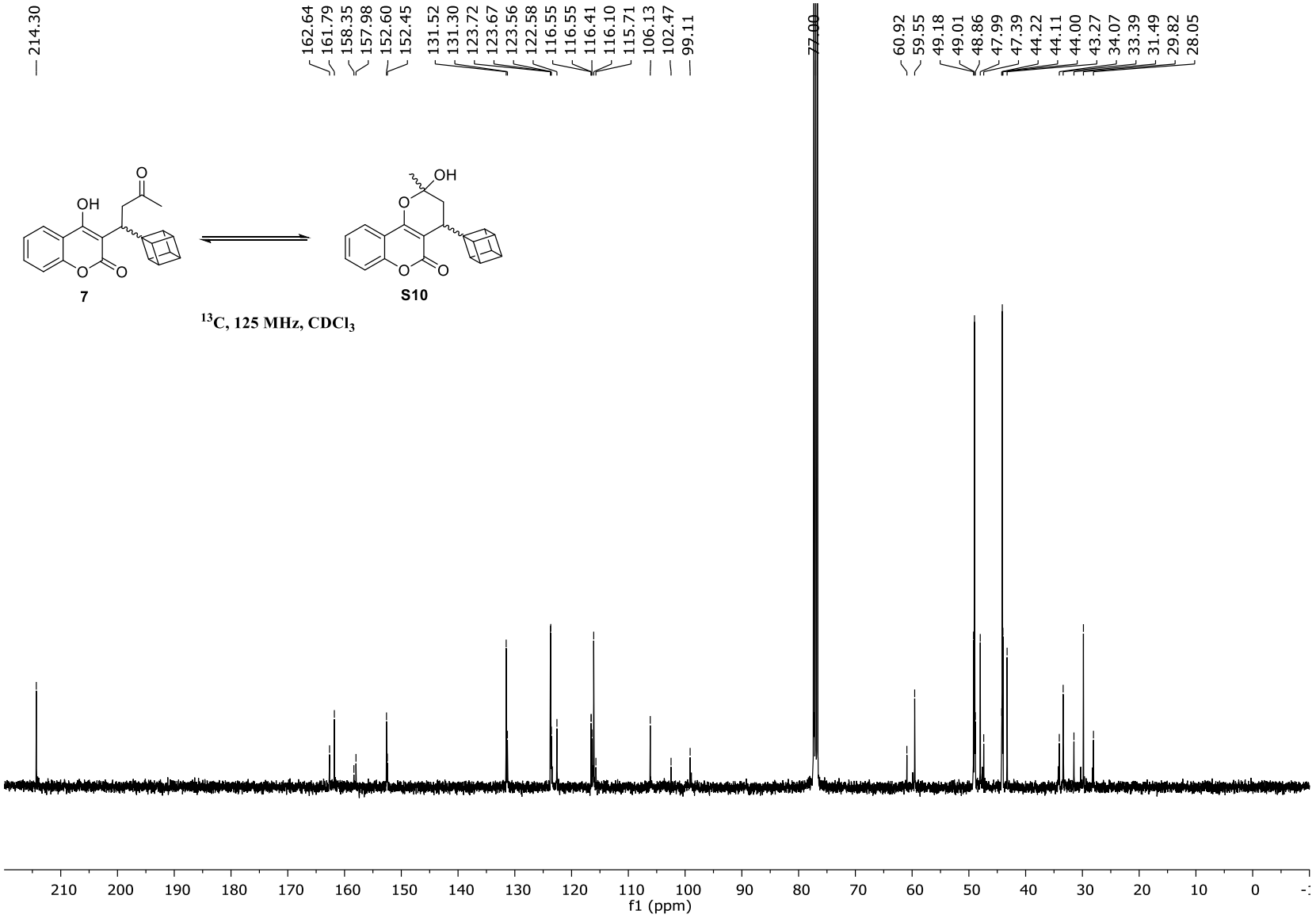


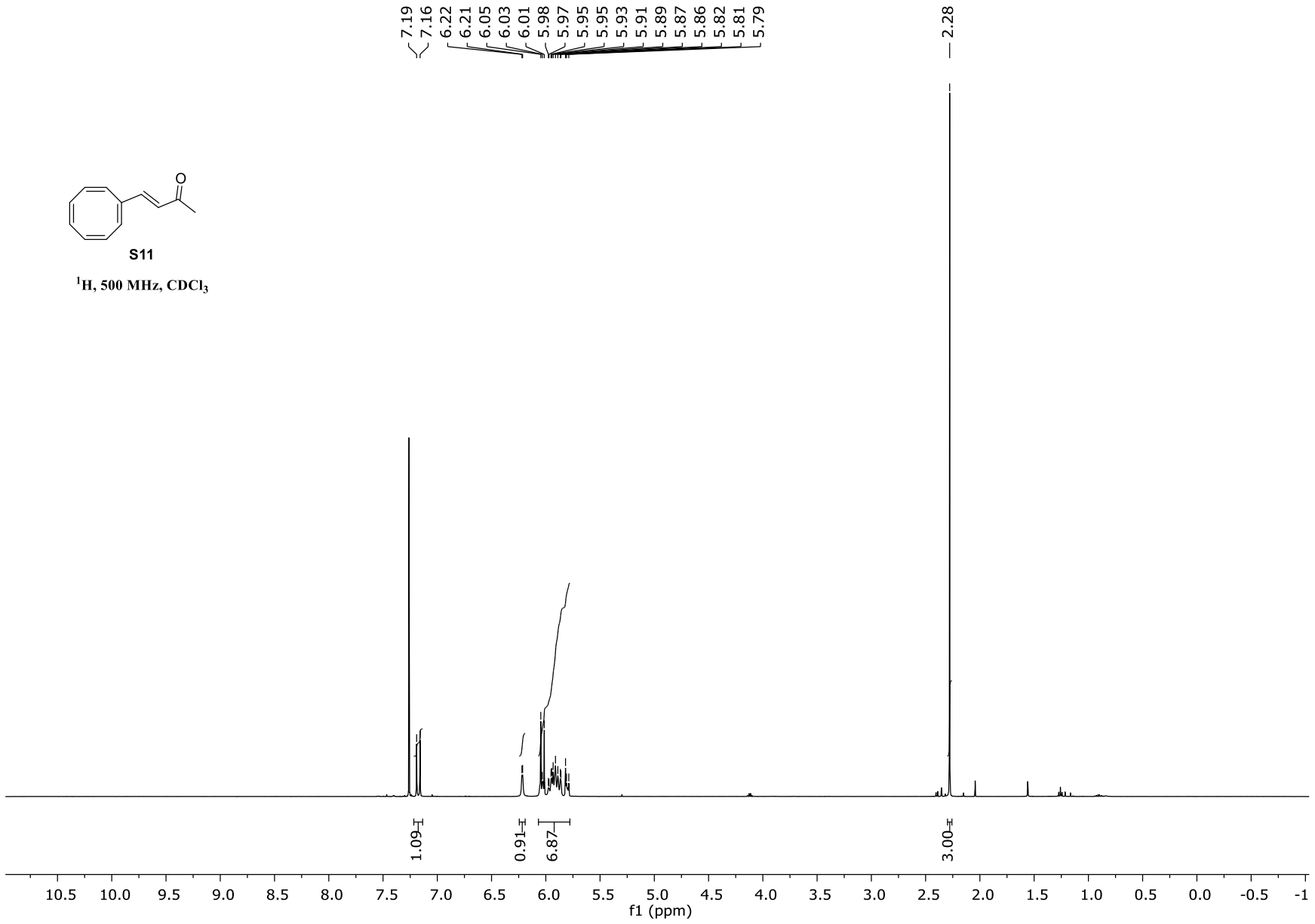

**S8**

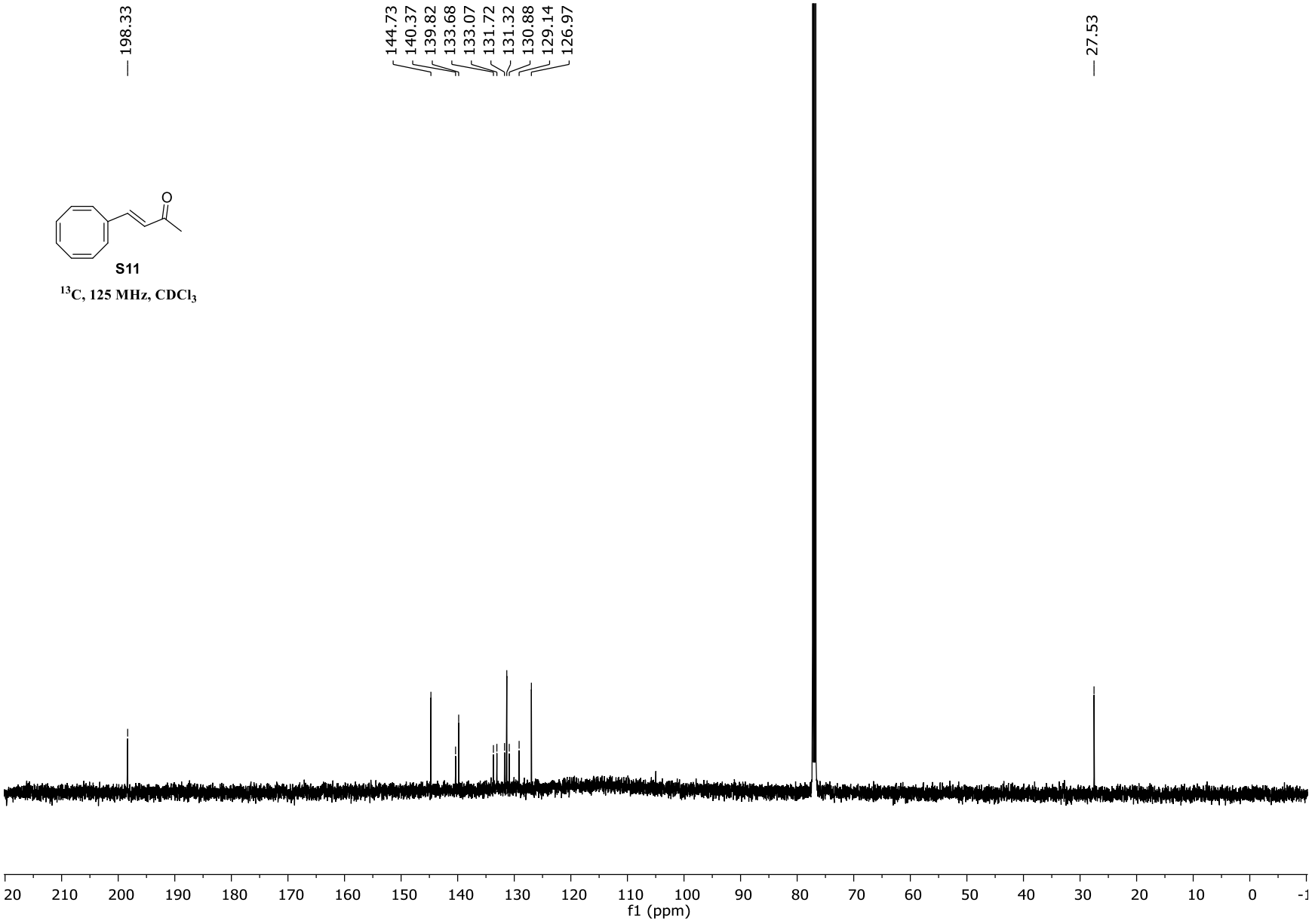
**$^1$H, 400 MHz, $CDCl_3$**


198.73
146.51
127.70
58.51
50.15
48.51
44.39
26.97
O
S8
13C, 100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9.77
7.92
7.92
7.91
7.79
7.74
7.51
7.49
7.46
7.30
7.28
7.21
3.98
3.92
3.85
3.81
3.39
3.37
3.31
3.24
3.22
3.15
3.01
2.78
2.74
2.28
2.24
2.20
2.00
1.95
1.77
1.73
1.71
1.70
1.58
OH
O
O
O
7
OH
O
O
O
S10
1H, 500 MHz, CDCl3
1.06
1.00
0.48
1.48
0.84
1.15
10.32
1.02
1.50
0.22
0.26
1.00
0.15
3.07
0.12
0.26
1.59
0.72
f1 (ppm)

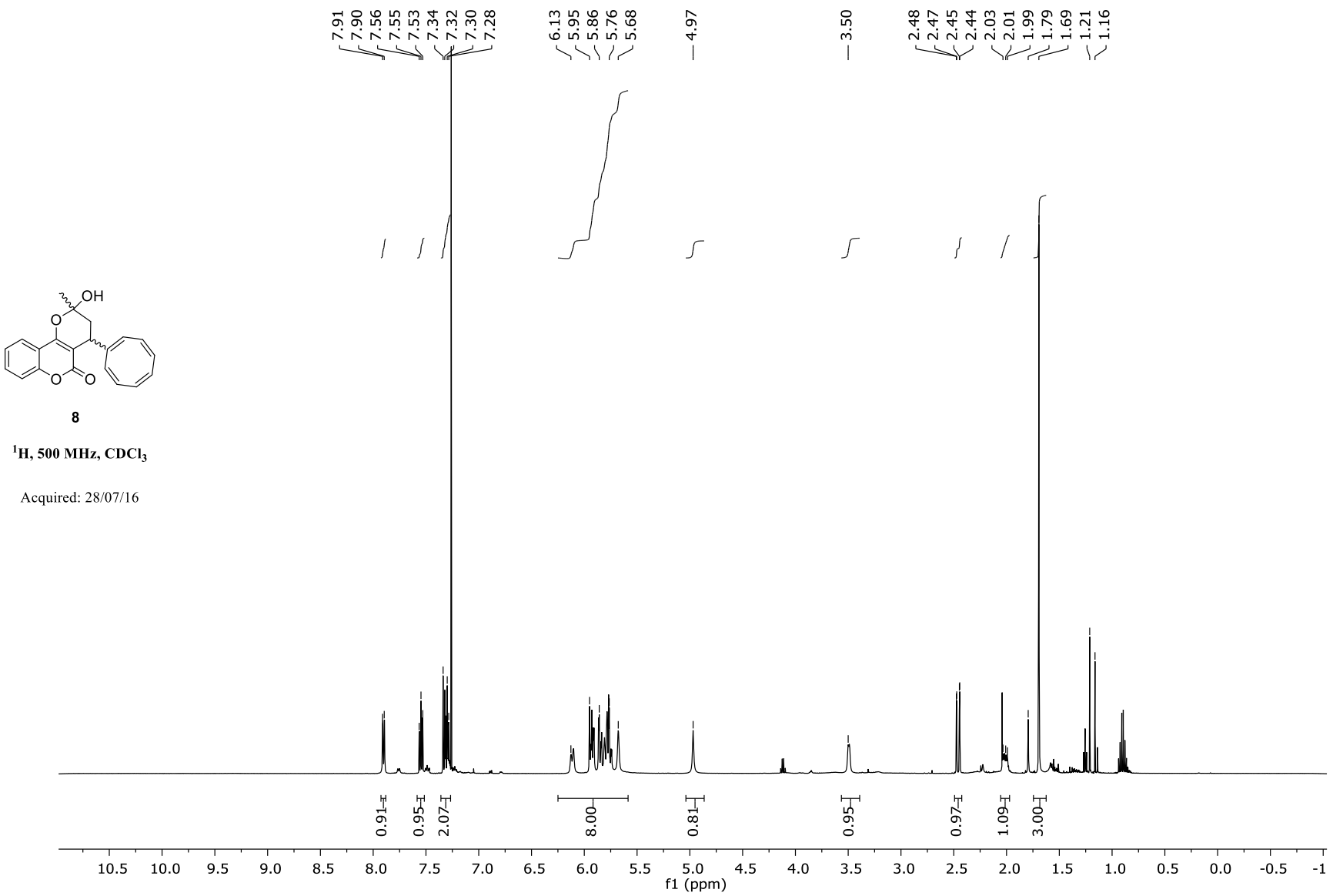

214.30
162.64
161.79
158.35
157.98
152.60
152.45
131.52
131.30
123.72
123.67
123.56
122.58
116.55
116.55
116.41
116.10
115.71
106.13
102.47
99.11
77.00
60.92
59.55
49.18
49.01
48.86
47.99
47.39
44.22
44.11
44.00
43.27
34.07
33.39
31.49
29.82
28.05
OH
O
O
O
7
OH
O
O
O
S10
$^{13}$C, 125 MHz, CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.19
7.16
6.22
6.21
6.05
6.03
6.01
5.98
5.97
5.95
5.95
5.93
5.91
5.89
5.87
5.86
5.82
5.81
5.79
2.28
O
S11
$^1$H, 500 MHz, CDCl$_3$
1.09
0.91
6.87
3.00
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 -1
f1 (ppm)




**S11**

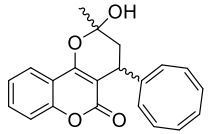
**$^{13}$C, 125 MHz, $CDCl_3$**




**8**

**$^{1}$H, 500 MHz, $CDCl_3$**

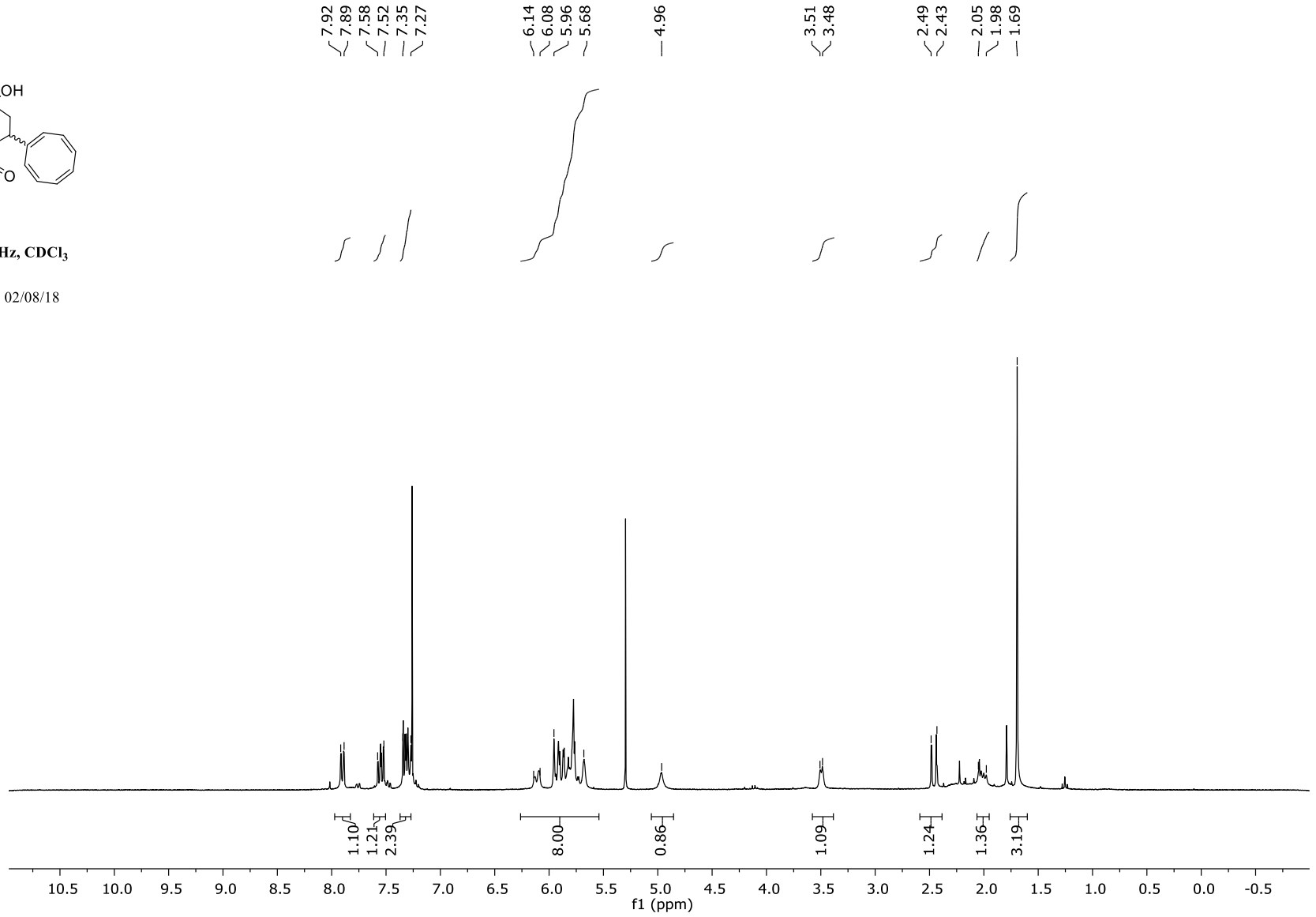
Acquired: 28/07/16

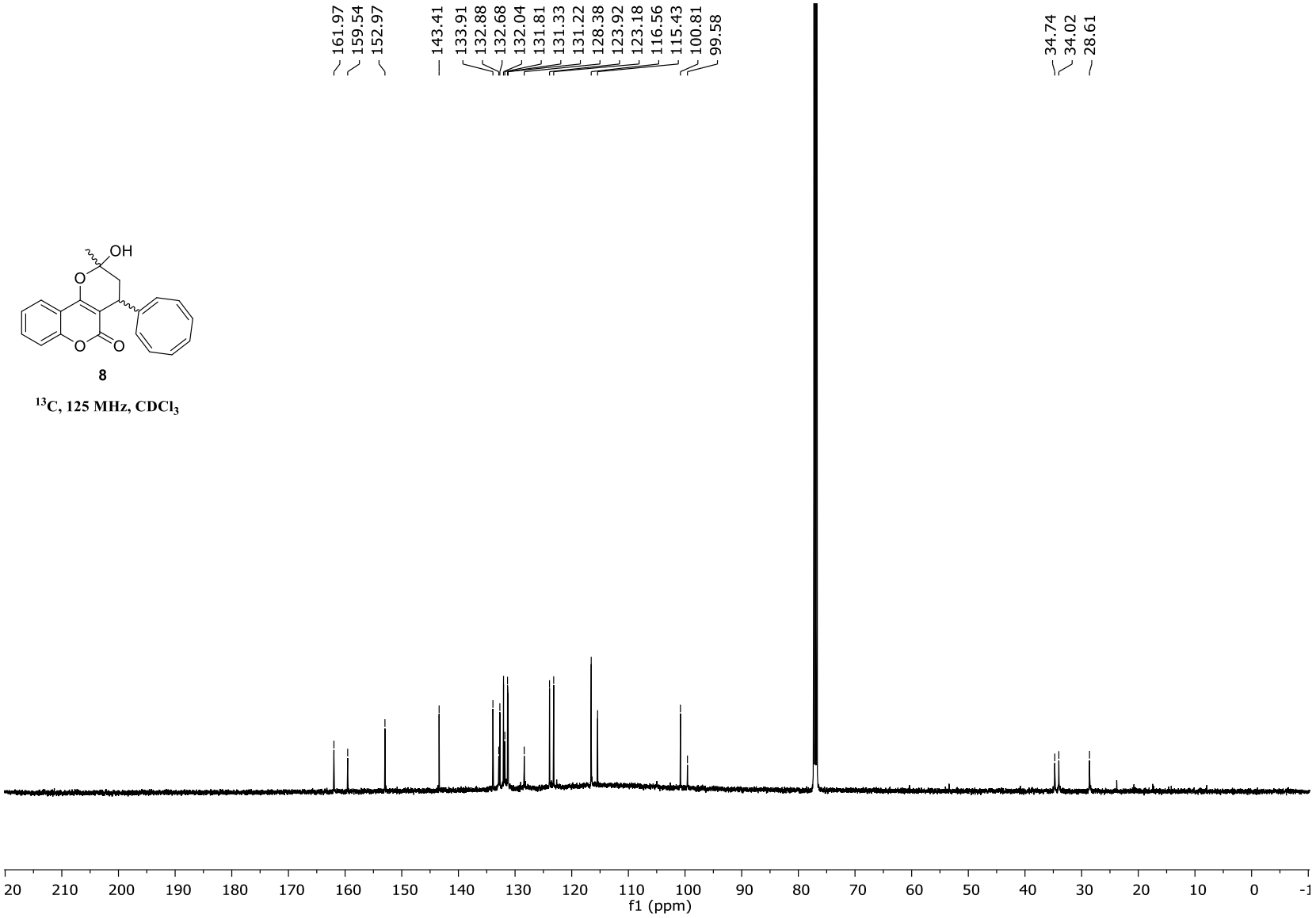


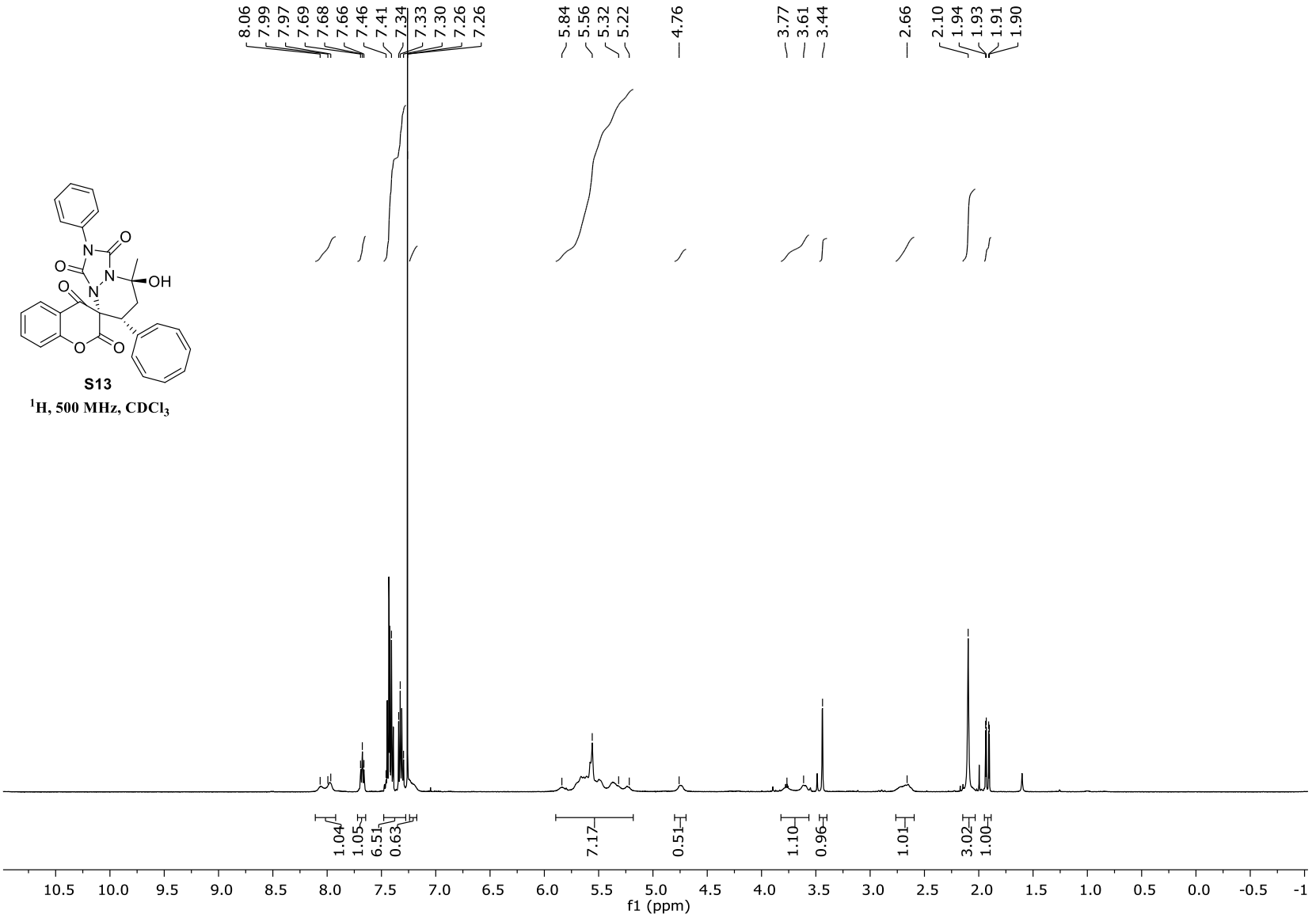

**8**

**$^1$H, 300 MHz, $CDCl_3$**

Acquired: 02/08/18

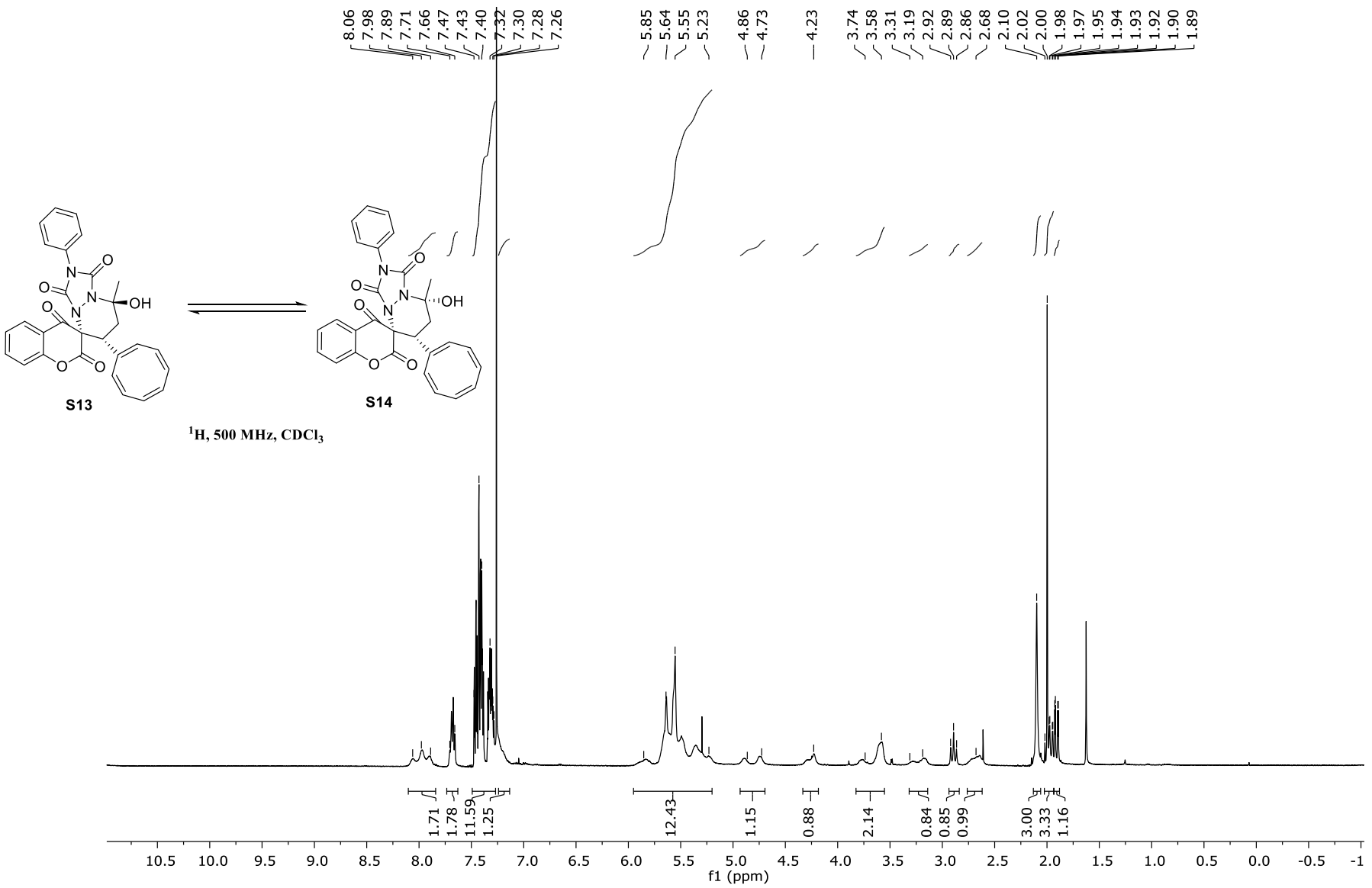


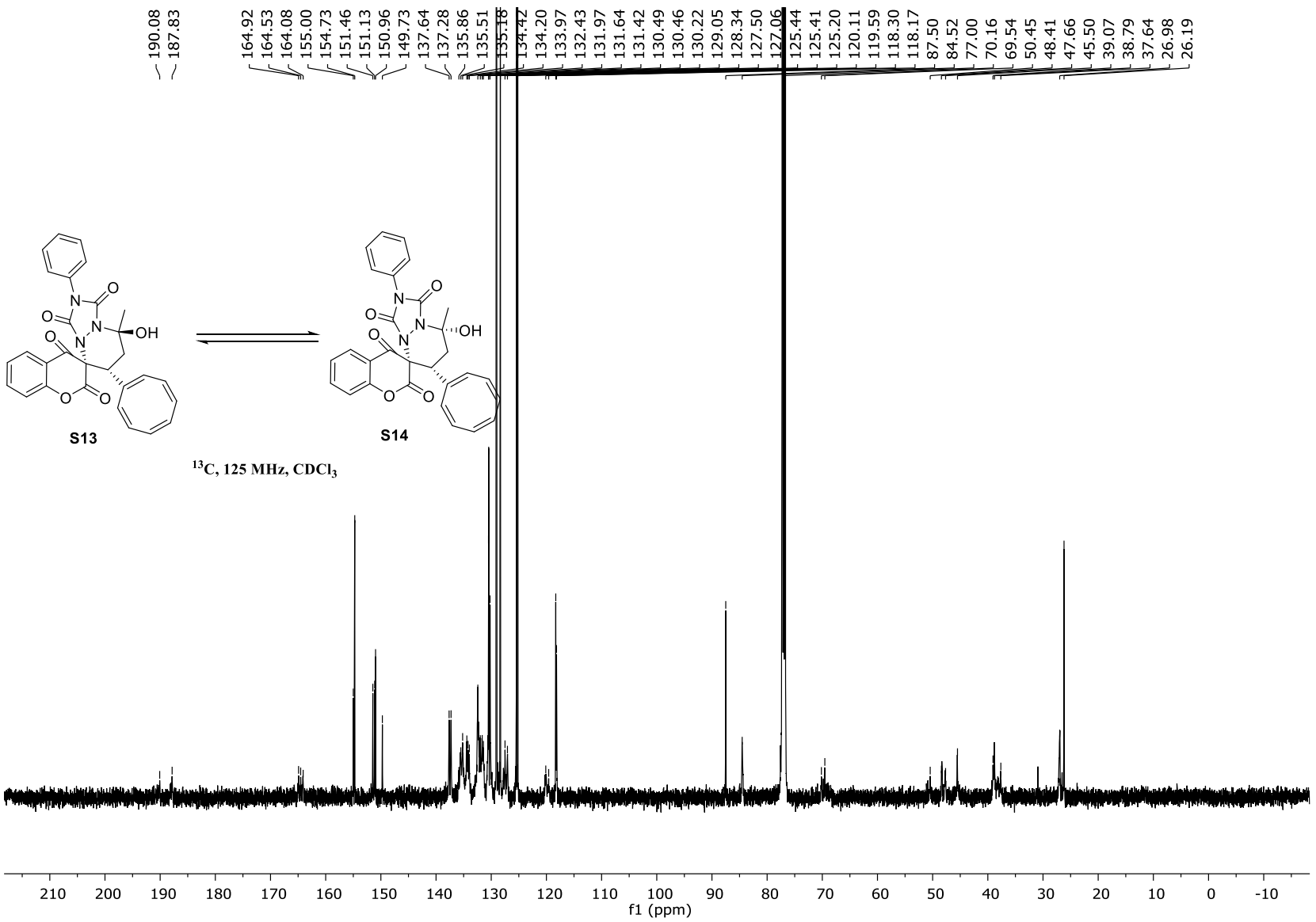

161.97
159.54
152.97
143.41
133.91
132.88
132.68
132.04
131.81
131.33
131.22
128.38
123.92
123.18
116.56
115.43
100.81
99.58
34.74
34.02
28.61
OH
O
O
O
8
$^{13}$C, 125 MHz, CDCl$_3$
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

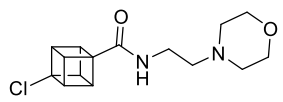



**S13**

**$^1$H, 500 MHz, $CDCl_3$**

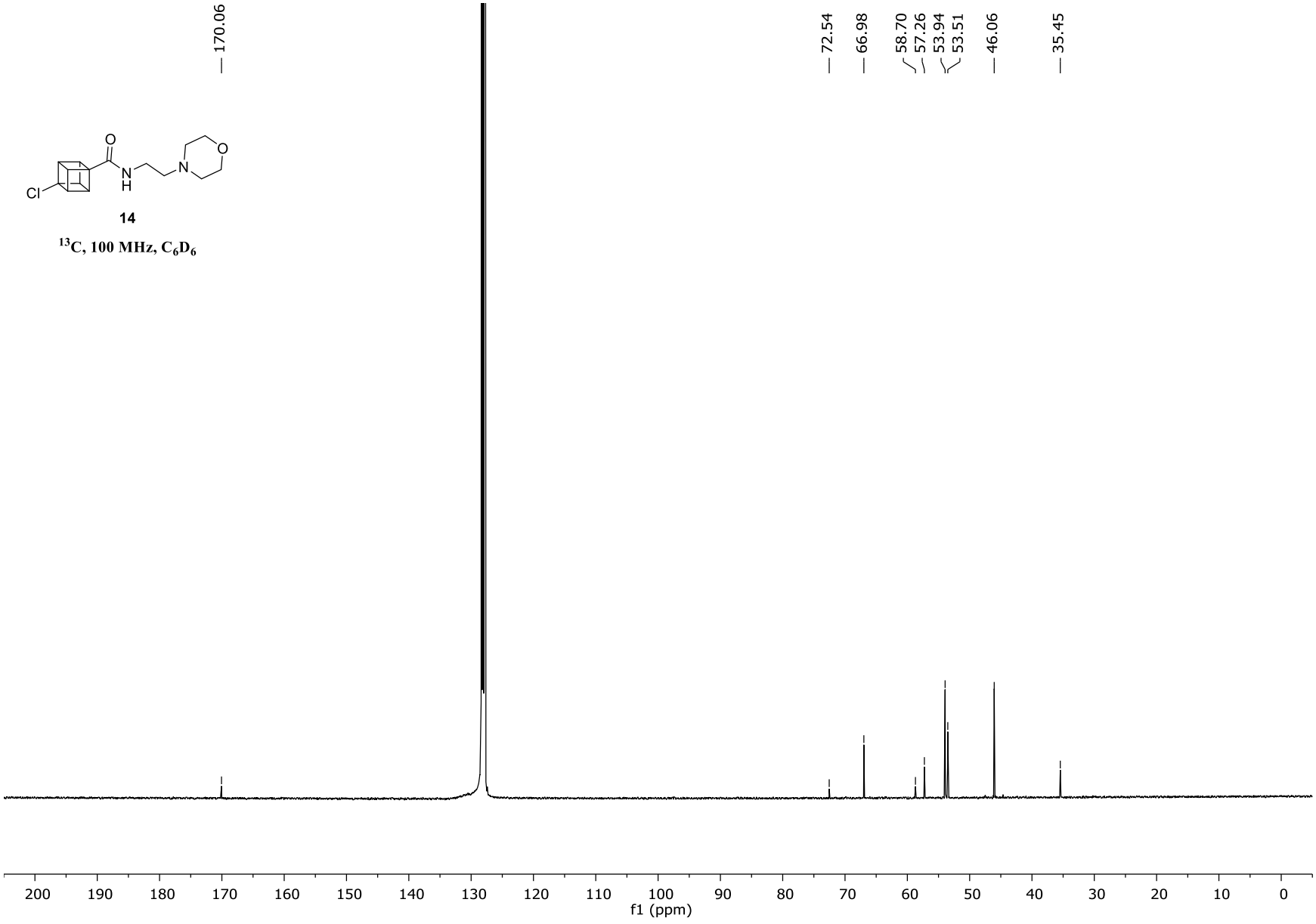

8.06
7.98
7.89
7.71
7.66
7.47
7.43
7.40
7.32
7.30
7.28
7.26
5.85
5.64
5.55
5.23
4.86
4.73
4.23
3.74
3.58
3.31
3.19
2.92
2.89
2.86
2.68
2.10
2.02
2.00
1.98
1.97
1.95
1.94
1.93
1.92
1.90
1.89
S13
S14
1H, 500 MHz, CDCl3
1.71
1.78
11.59
1.25
12.43
1.15
0.88
2.14
0.84
0.85
0.99
3.00
3.33
1.16
f1 (ppm)


190.08
187.83
164.92
164.53
164.08
155.00
154.73
151.46
151.13
150.96
149.73
137.64
137.28
135.86
135.51
135.18
134.42
134.20
133.97
132.43
131.97
131.64
131.42
130.49
130.46
130.22
129.05
128.34
127.50
127.06
125.44
125.41
125.20
120.11
119.59
118.30
118.17
87.50
84.52
77.00
70.16
69.54
50.45
48.41
47.66
45.50
39.07
38.79
37.64
26.98
26.19
OH
OH
S13
S14
$^{13}$C, 125 MHz, CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



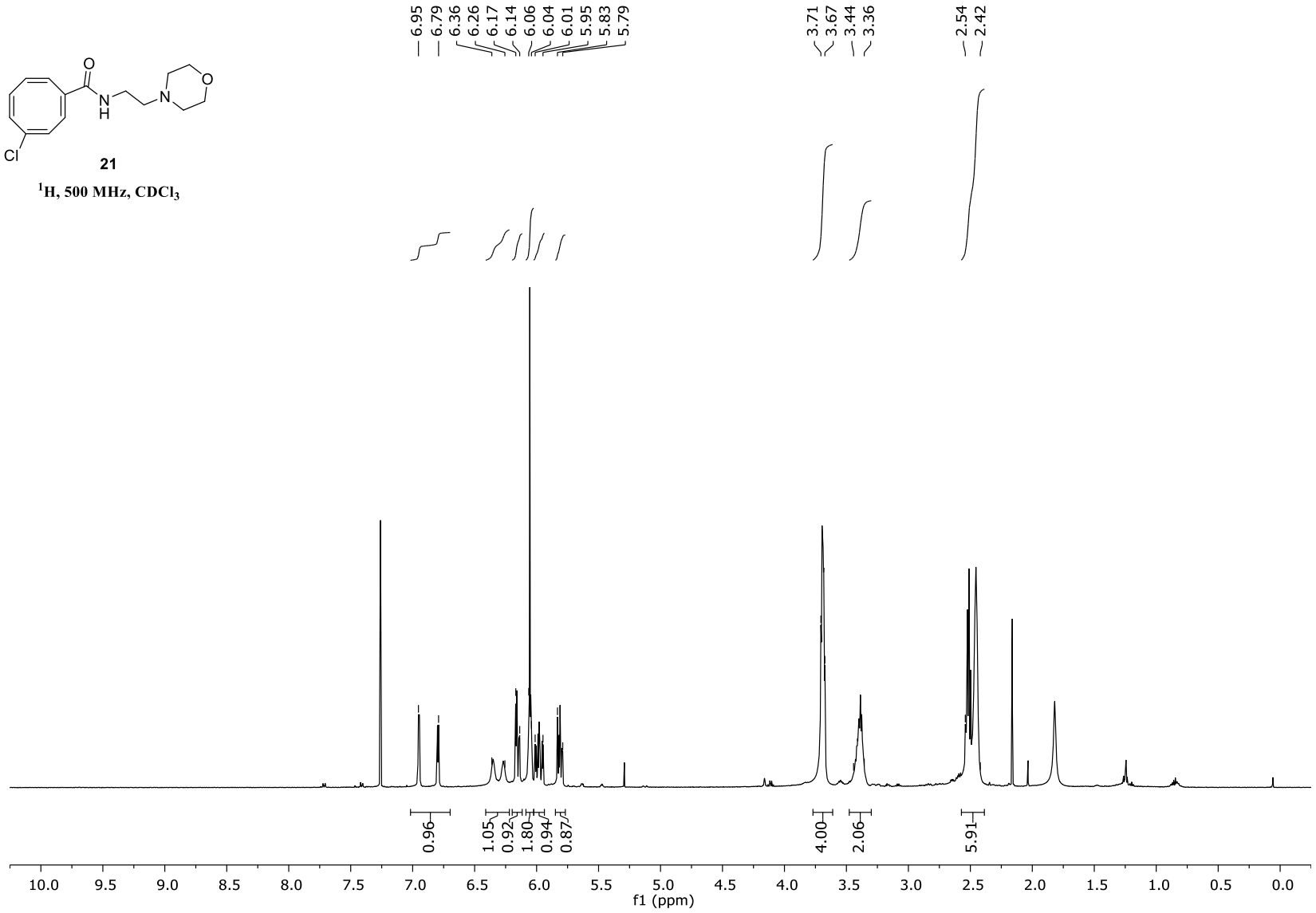
**14**

**$^1$H, 400 MHz, $C_6D_6$**



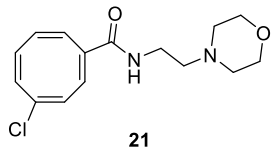

**14**

**$^{13}$C, 100 MHz, $C_6D_6$**




**21**

**$^1$H, 500 MHz, $CDCl_3$**

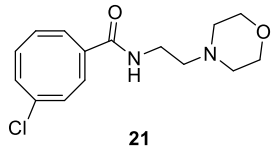


**21**

**$^{1}$H, 500 MHz, $CDCl_3$**

(Crude sample)

Acquired: 25/11/16

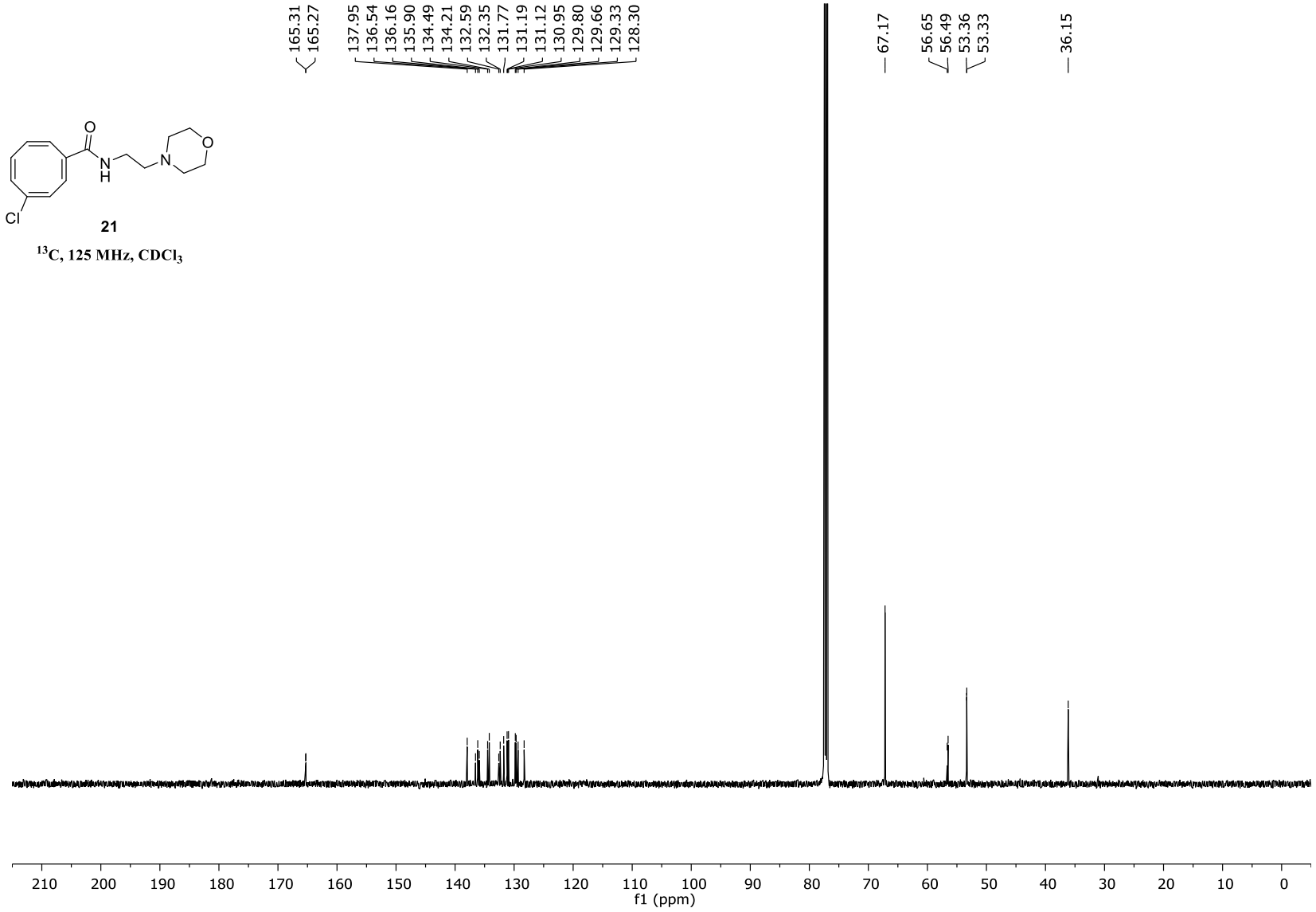


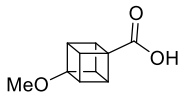
**21**

**$^{1}$H, 300 MHz, $CDCl_3$**

(Crude sample)

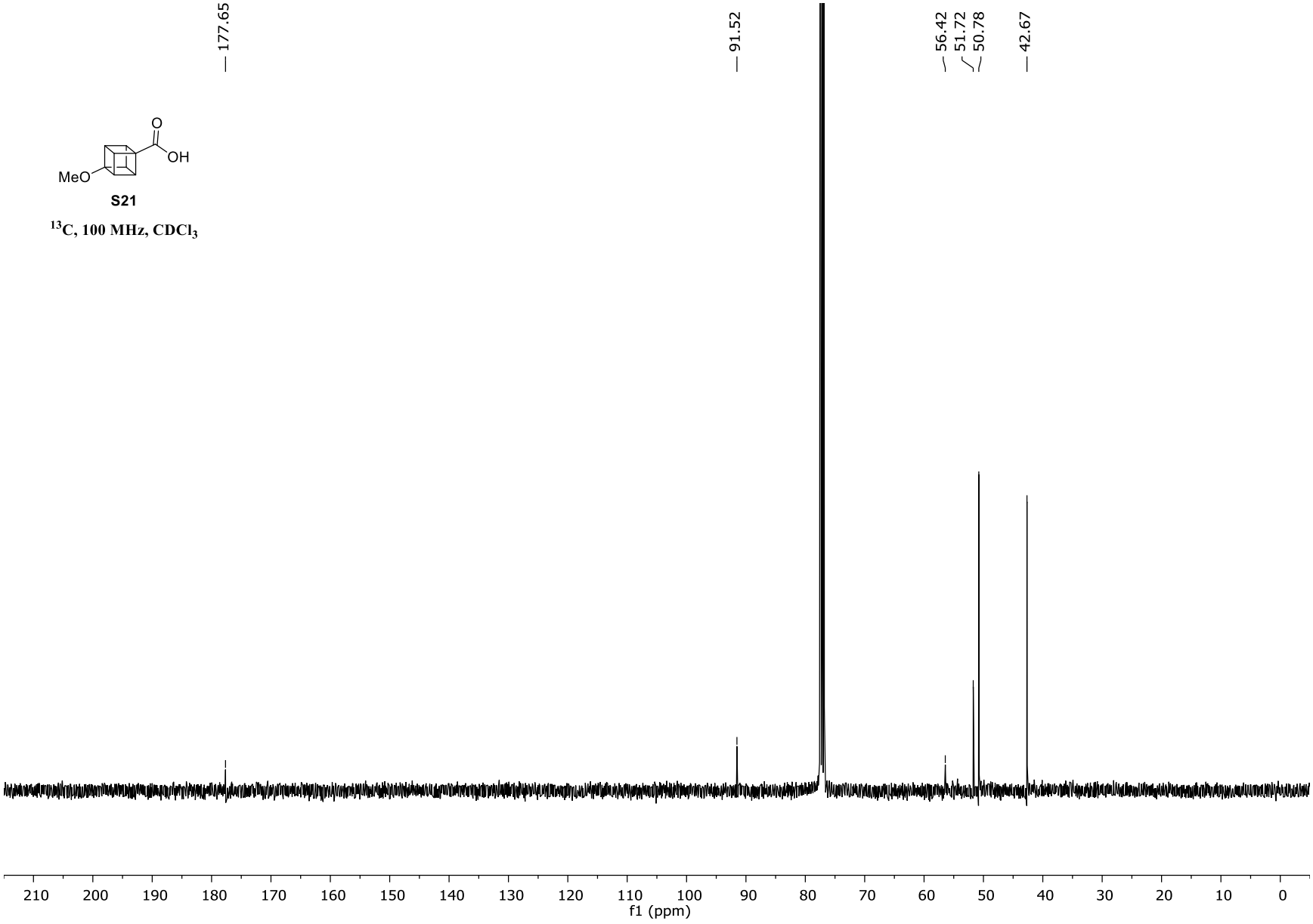
Acquired: 02/08/18


165.31
165.27
137.95
136.54
136.16
135.90
134.49
134.21
132.59
132.35
131.77
131.19
131.12
130.95
129.80
129.66
129.33
128.30
67.17
56.65
56.49
53.36
53.33
36.15
O
N
H
N
O
Cl
21
$^{13}$C, 125 MHz, CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



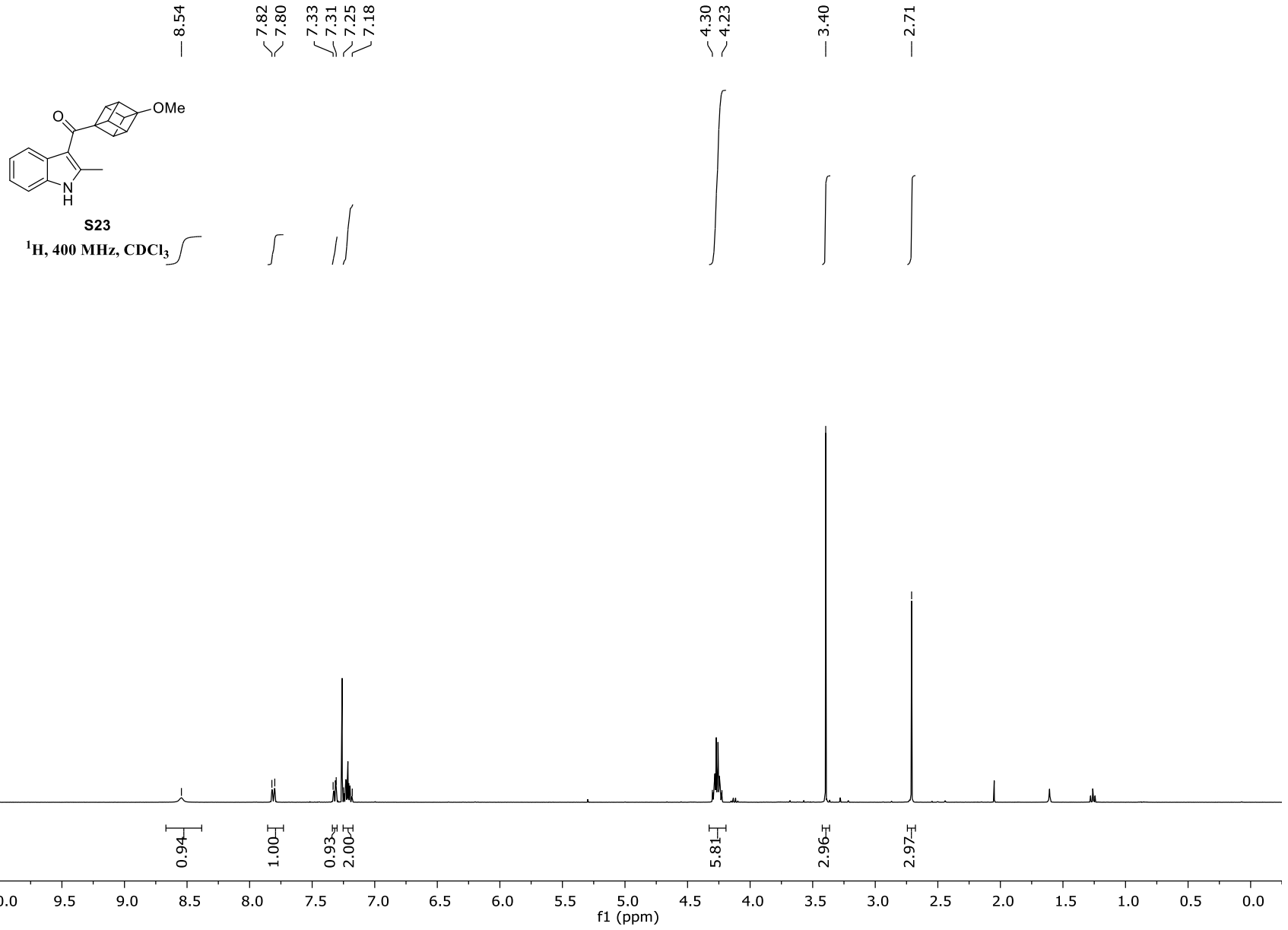

**S21**

**$^1$H, 400 MHz, $CDCl_3$**



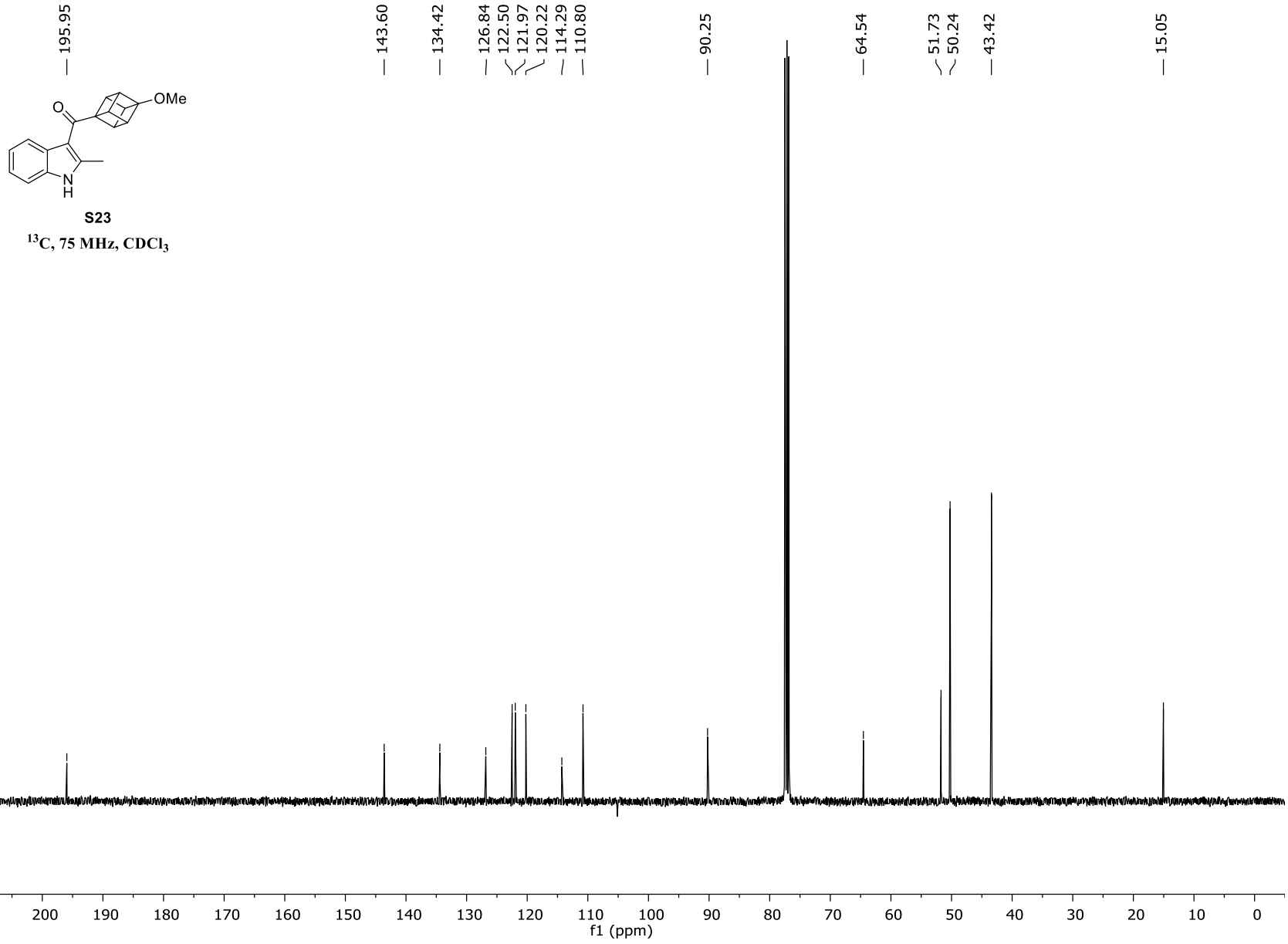

**S21**

**$^{13}$C, 100 MHz, $CDCl_3$**



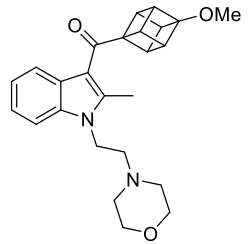

**S23**

**$^1$H, 400 MHz, $CDCl_3$**



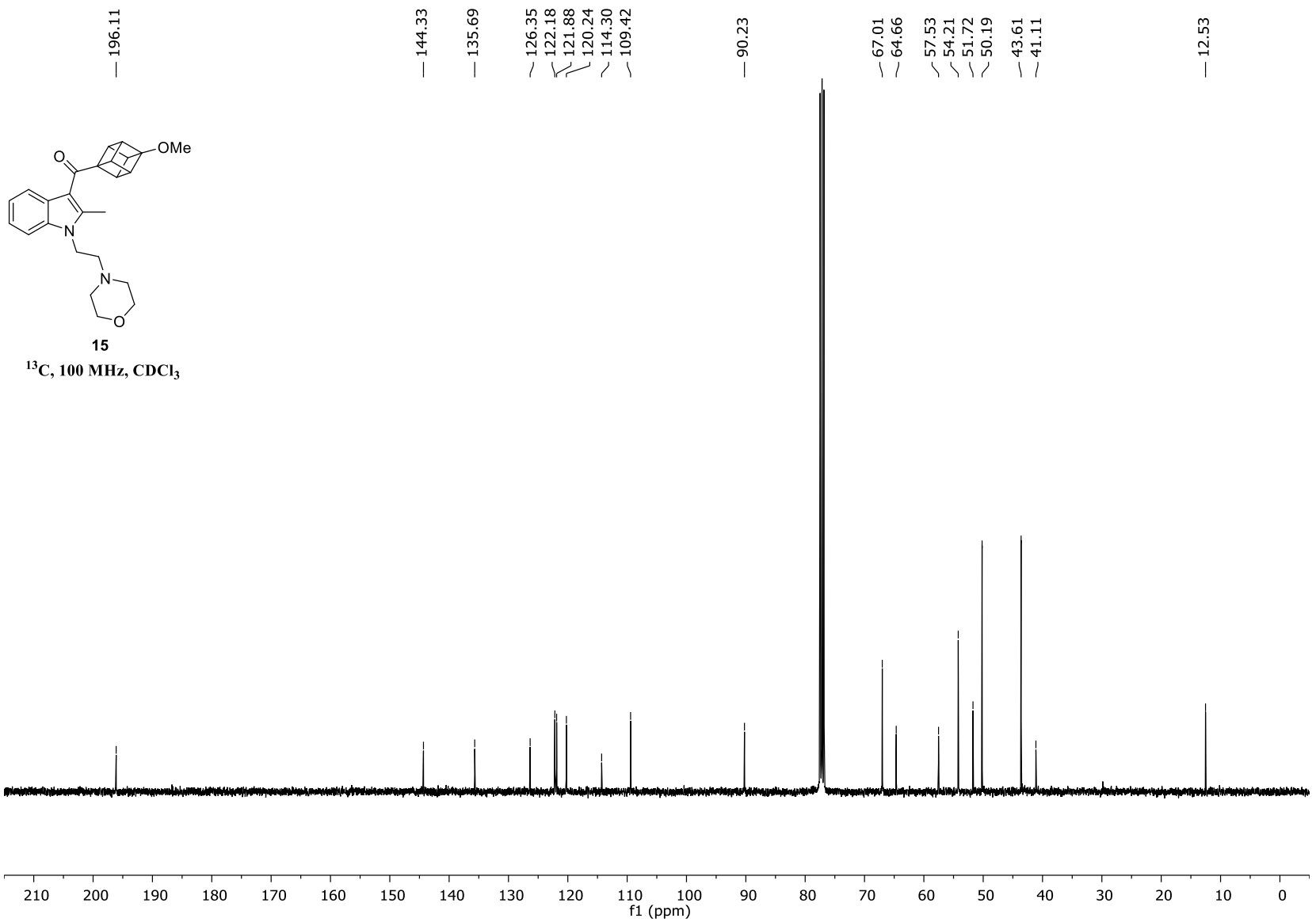

**S23**

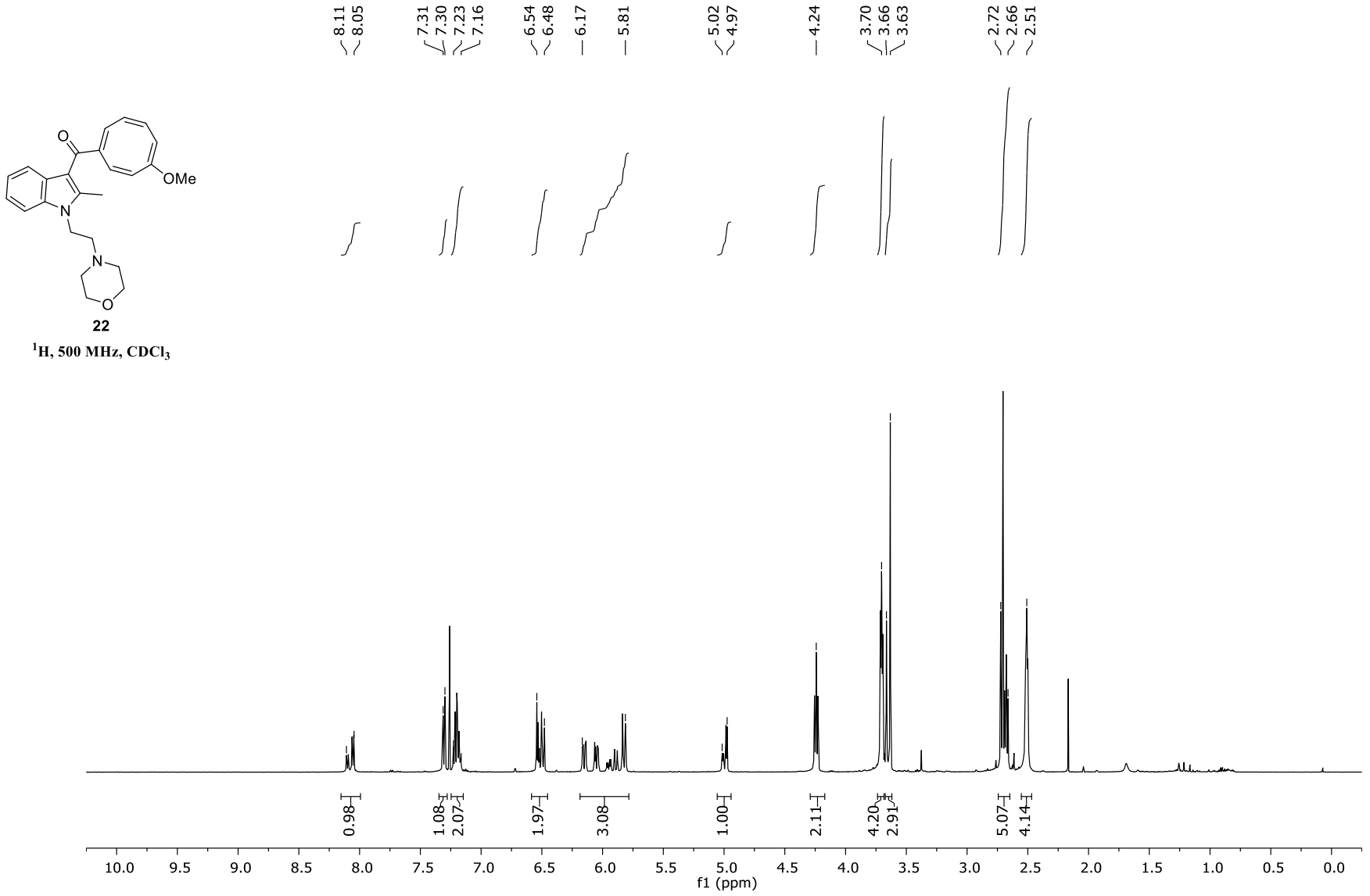
**$^{13}$C, 75 MHz, $CDCl_3$**




**15**

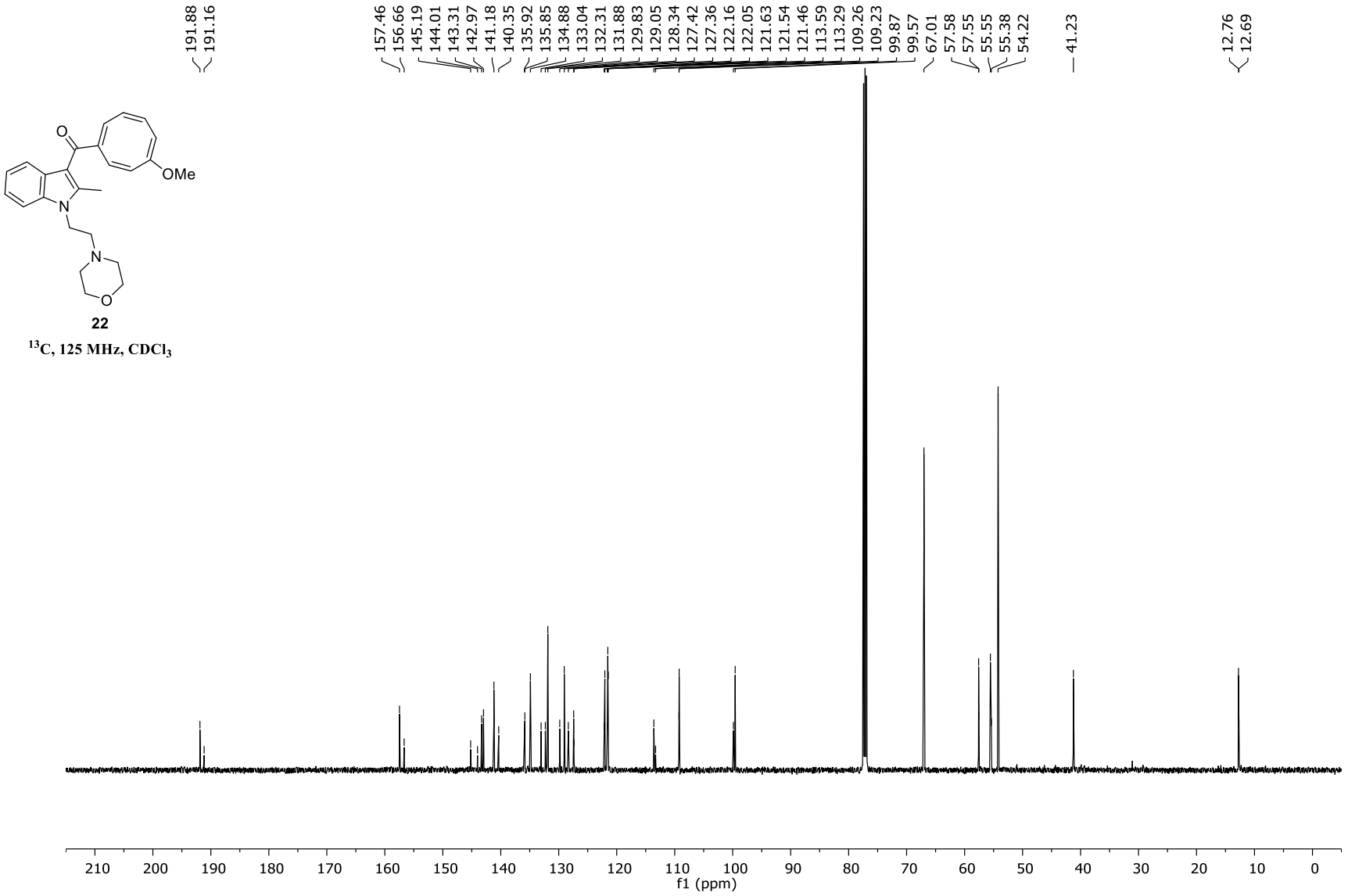
**$^1$H, 400 MHz, $CDCl_3$**

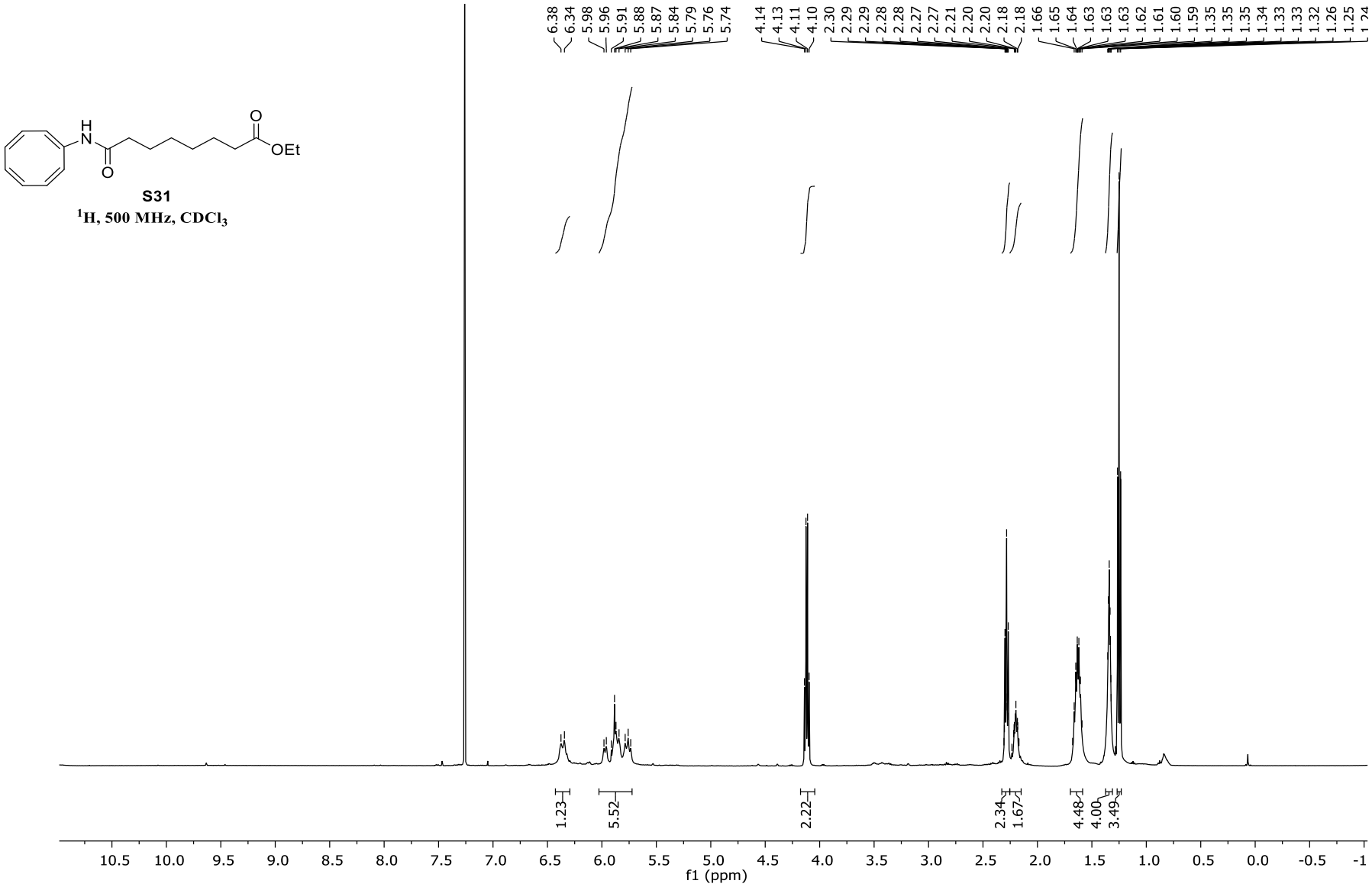

196.11
144.33
135.69
126.35
122.18
121.88
120.24
114.30
109.42
90.23
67.01
64.66
57.53
54.21
51.72
50.19
43.61
41.11
12.53
OMe
O
N
N
O
15
$^{13}$C, 100 MHz, CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

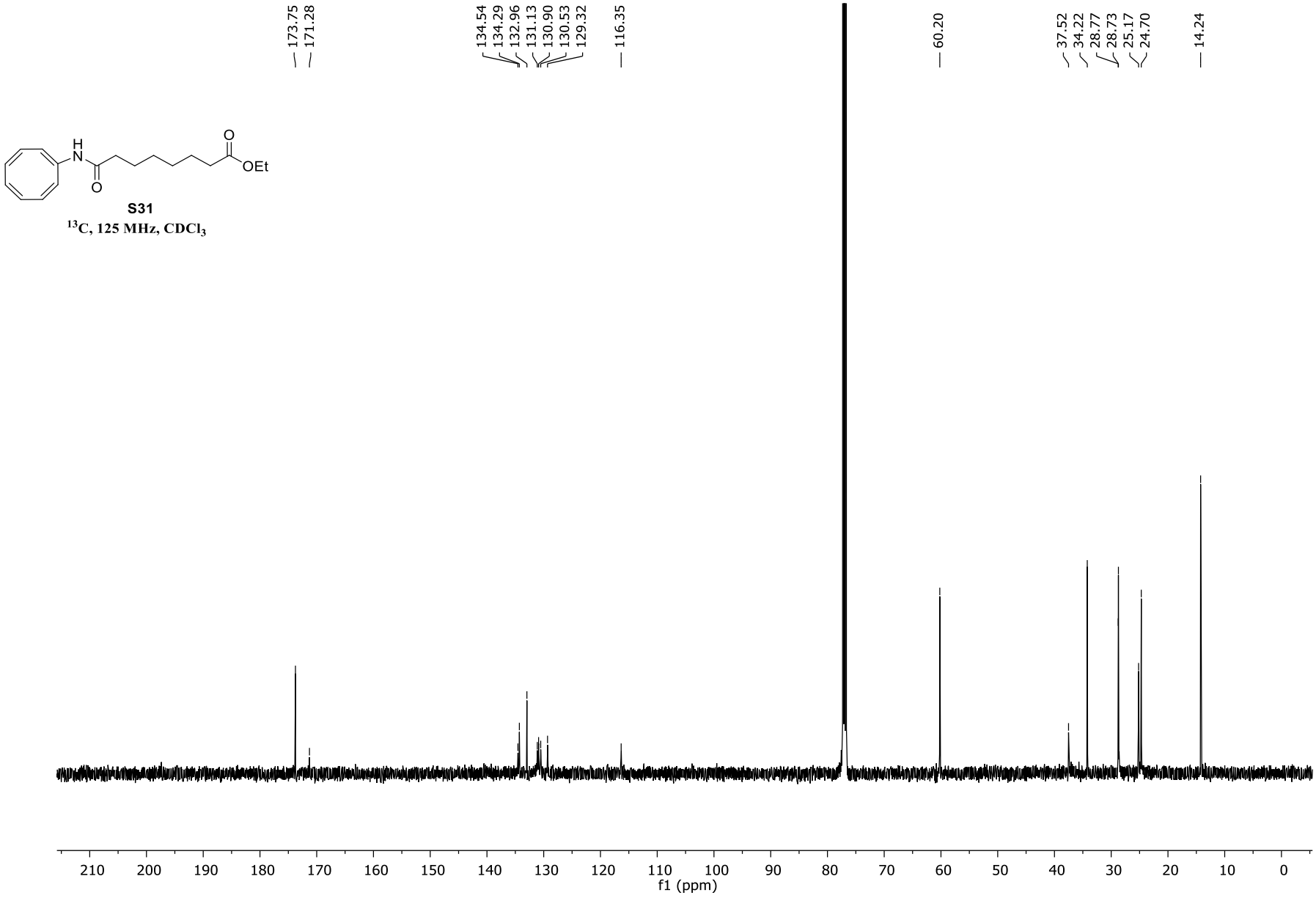



**22**

**$^{1}$H, 500 MHz, $CDCl_3$**

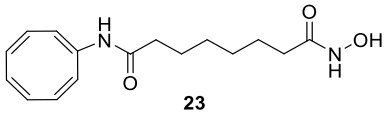

191.88
191.16
157.46
156.66
145.19
144.01
143.31
142.97
141.18
140.35
135.92
135.85
134.88
133.04
132.31
131.88
129.83
129.05
128.34
127.42
127.36
122.16
122.05
121.63
121.54
121.46
113.59
113.29
109.26
109.23
99.87
99.57
67.01
57.58
57.55
55.55
55.38
54.22
41.23
12.76
12.69
O
OMe
N
N
O
22
$^{13}$C, 125 MHz, CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


S31
$^1$H, 500 MHz, CDCl$_3$
f1 (ppm)



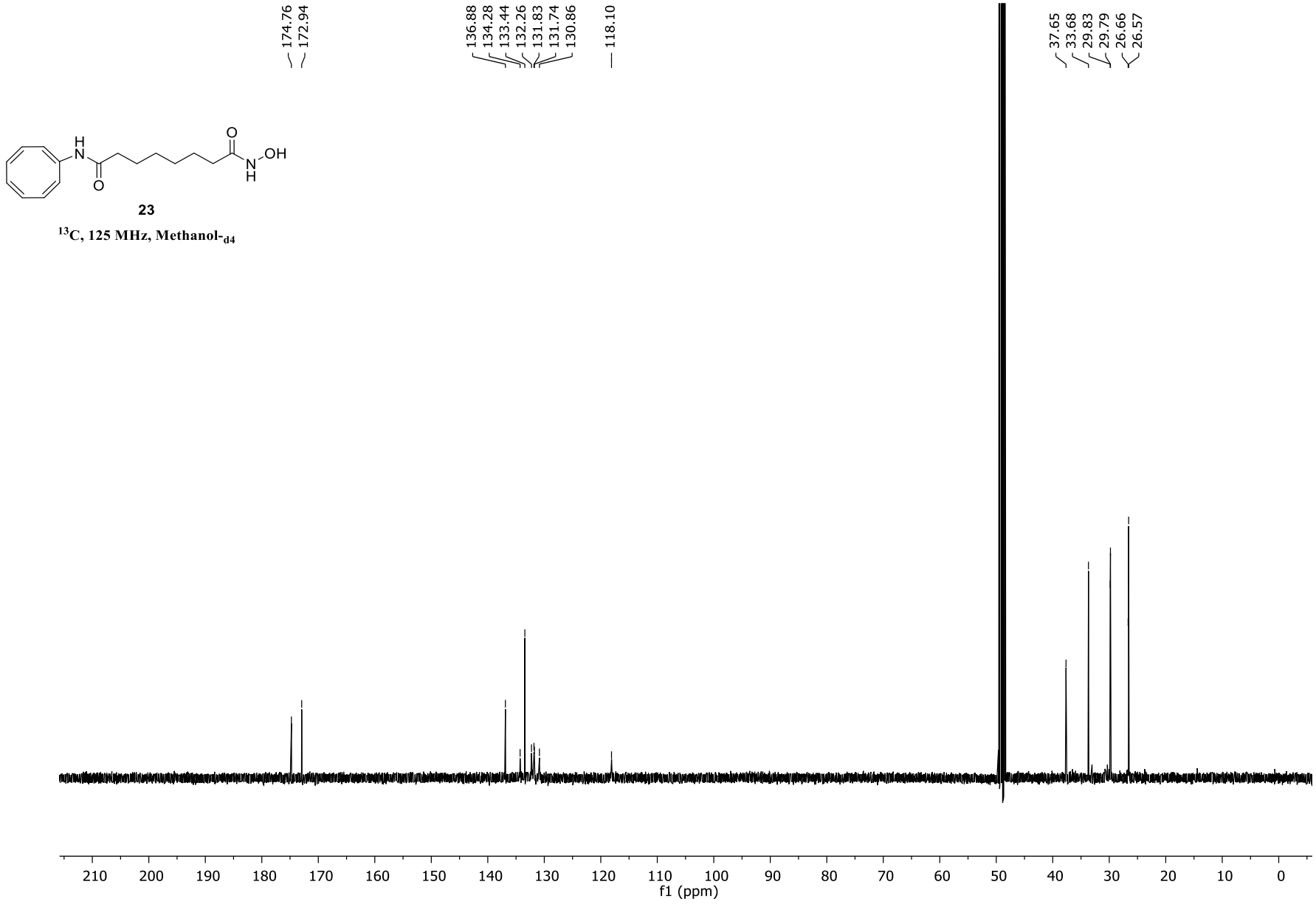

**S31**

**$^{13}$C, 125 MHz, $CDCl_3$**



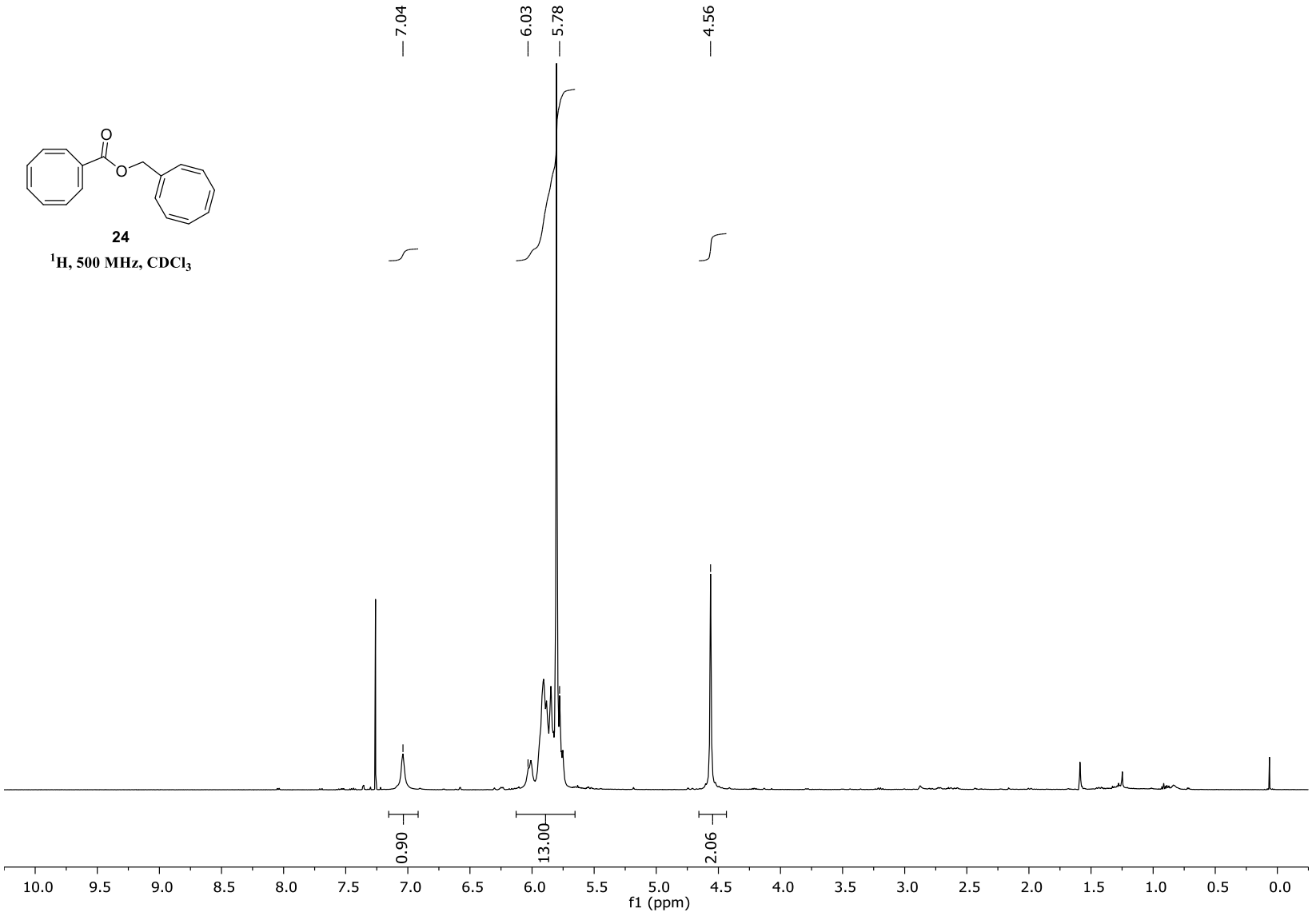
**23**

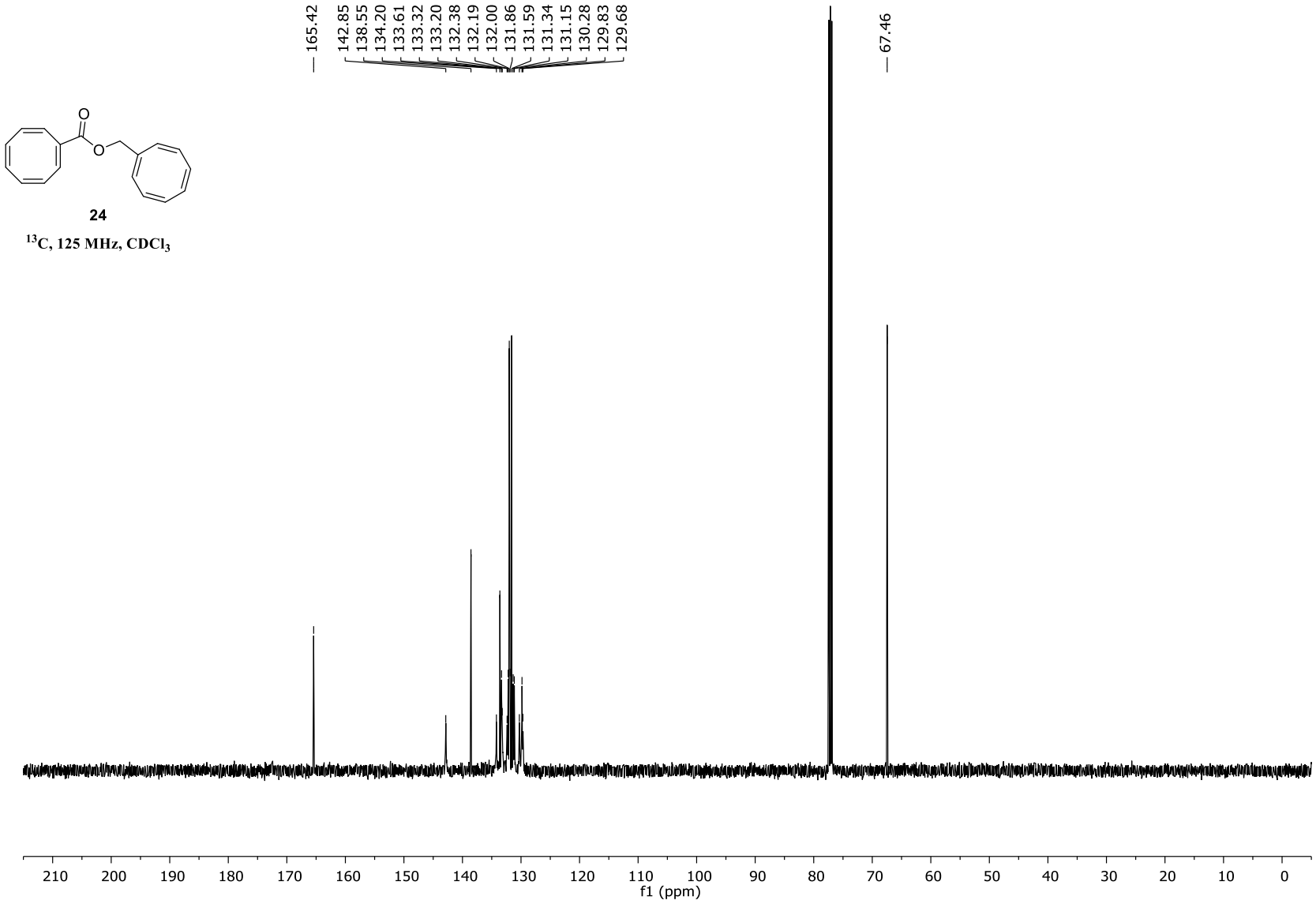
**$^{1}$H, 500 MHz, Methanol-$_{d4}$**

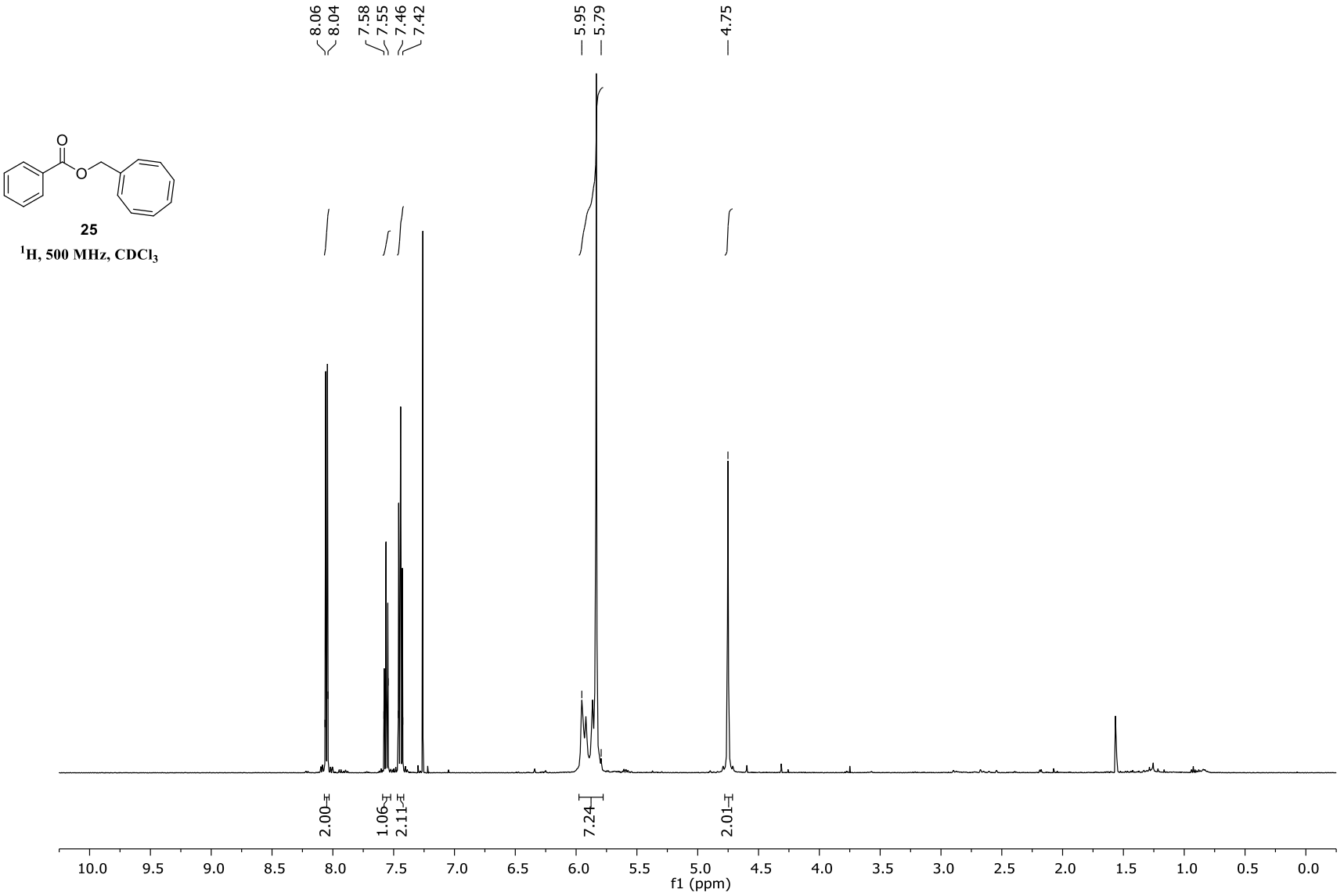


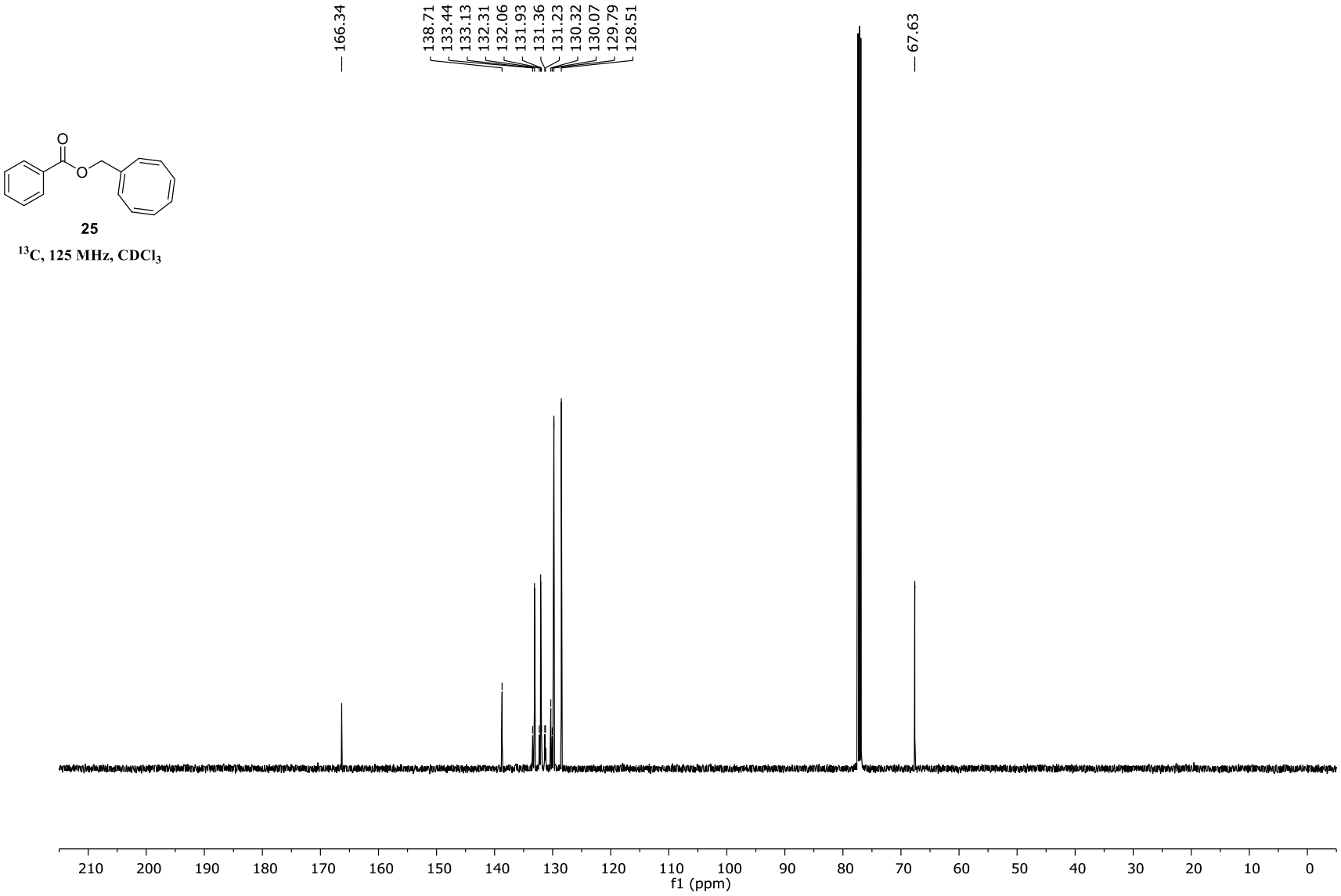

**23**

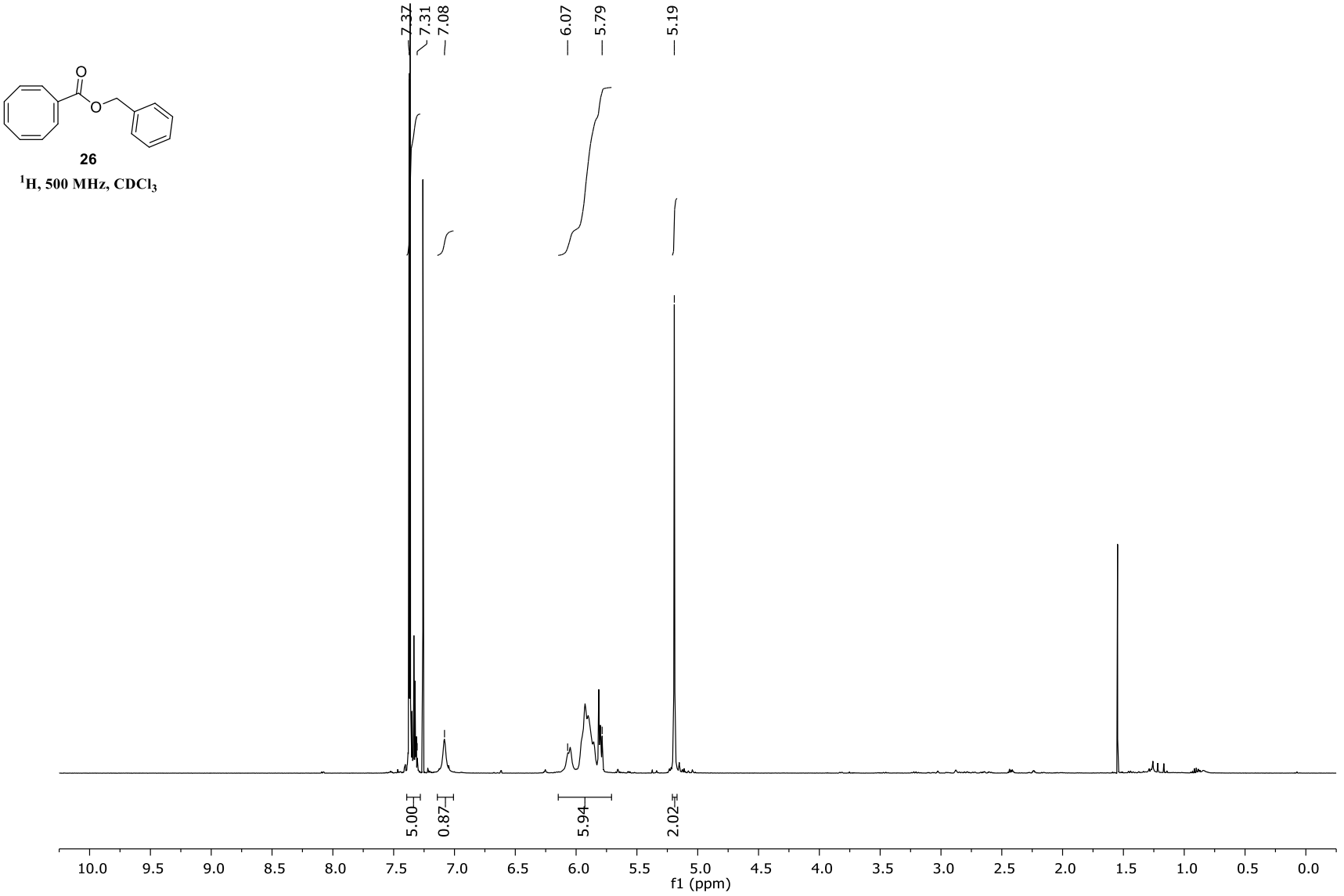
**$^{13}$C, 125 MHz, Methanol-$_{d4}$**


7.04
6.03
5.78
4.56
O
O
24
$^1$H, 500 MHz, $CDCl_3$
0.90
13.00
2.06
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
f1 (ppm)


165.42
142.85
138.55
134.20
133.61
133.32
133.20
132.38
132.19
132.00
131.86
131.59
131.34
131.15
130.28
129.83
129.68
67.46
O
O
24
$^{13}$C, 125 MHz, CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

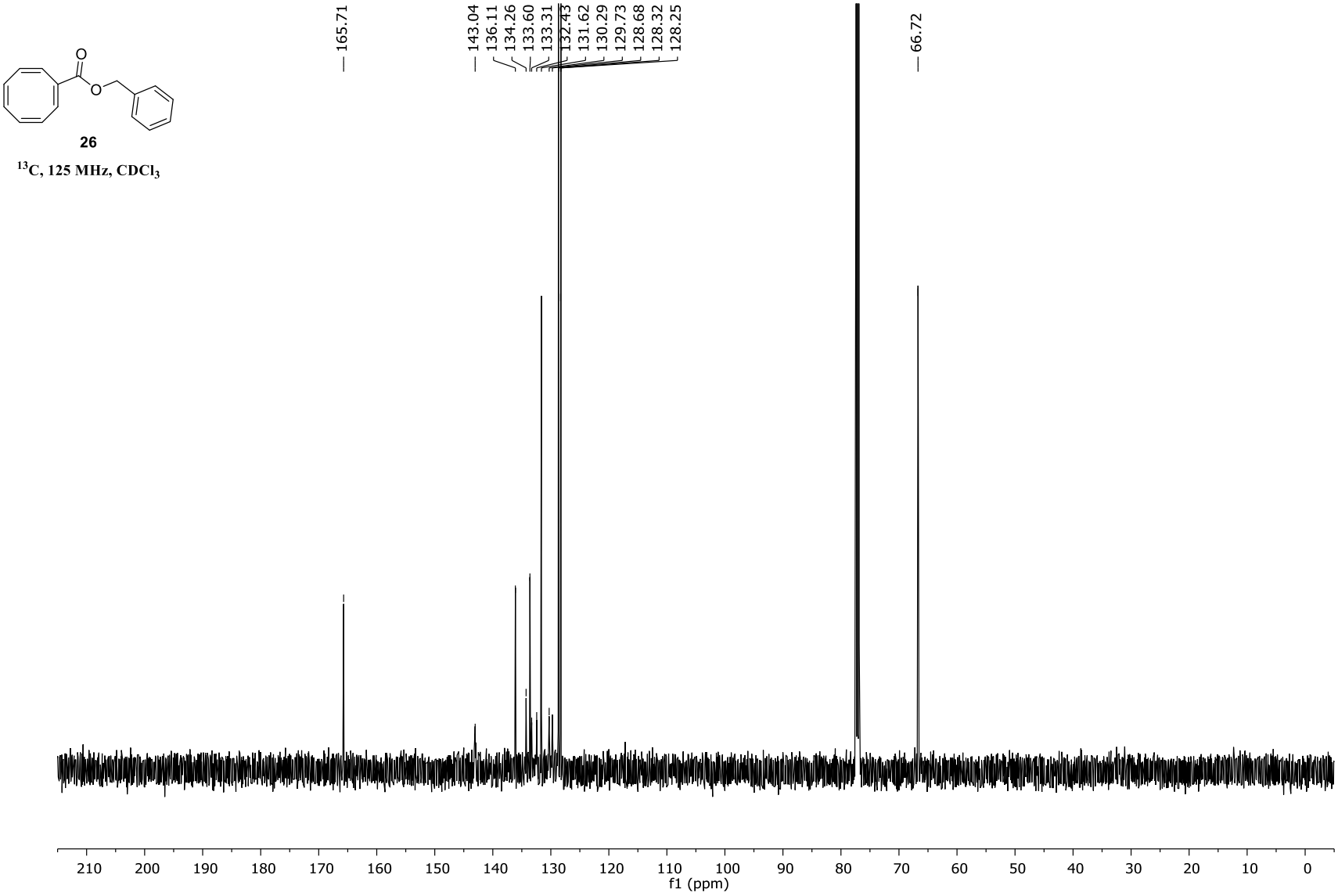

8.06
8.04
7.58
7.55
7.46
7.42
5.95
5.79
4.75
25
1H, 500 MHz, CDCl3
2.00
1.06
2.11
7.24
2.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


166.34
138.71
133.44
133.13
132.31
132.06
131.93
131.36
131.23
130.32
130.07
129.79
128.51
67.63
O
O
25
$^{13}$C, 125 MHz, CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



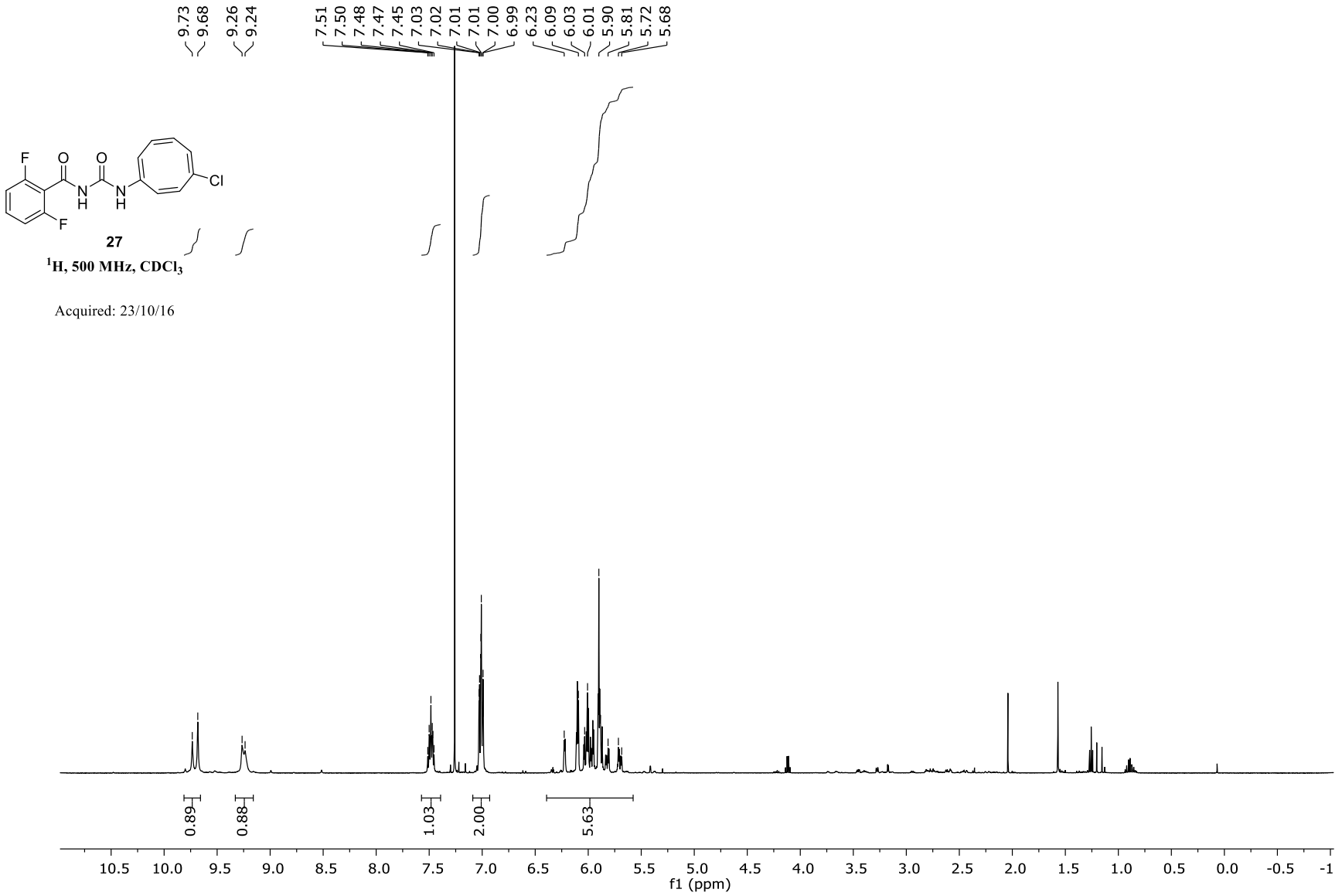

**26**

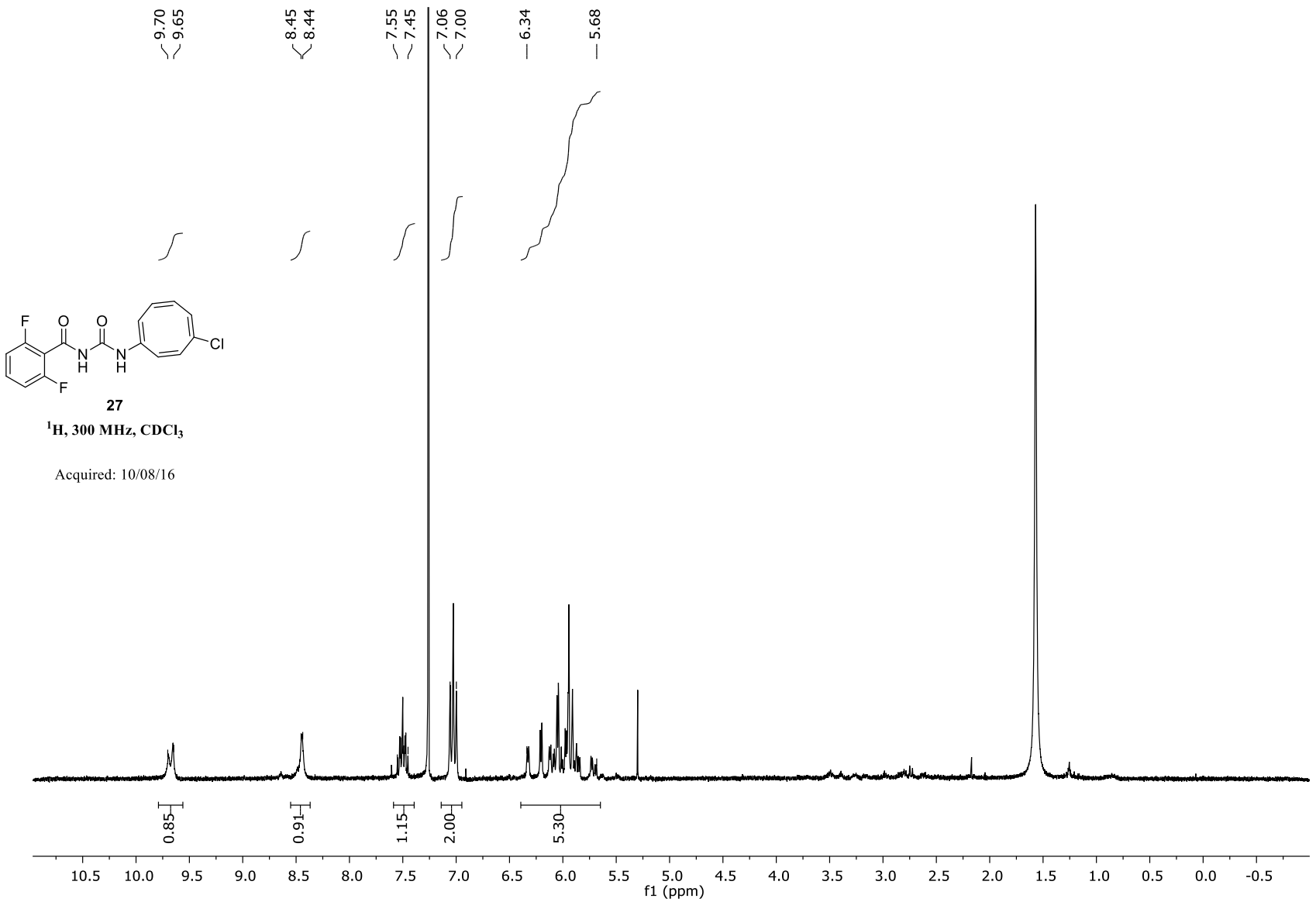
**$^1$H, 500 MHz, $CDCl_3$**




**26**

**$^{13}$C, 125 MHz, $CDCl_3$**

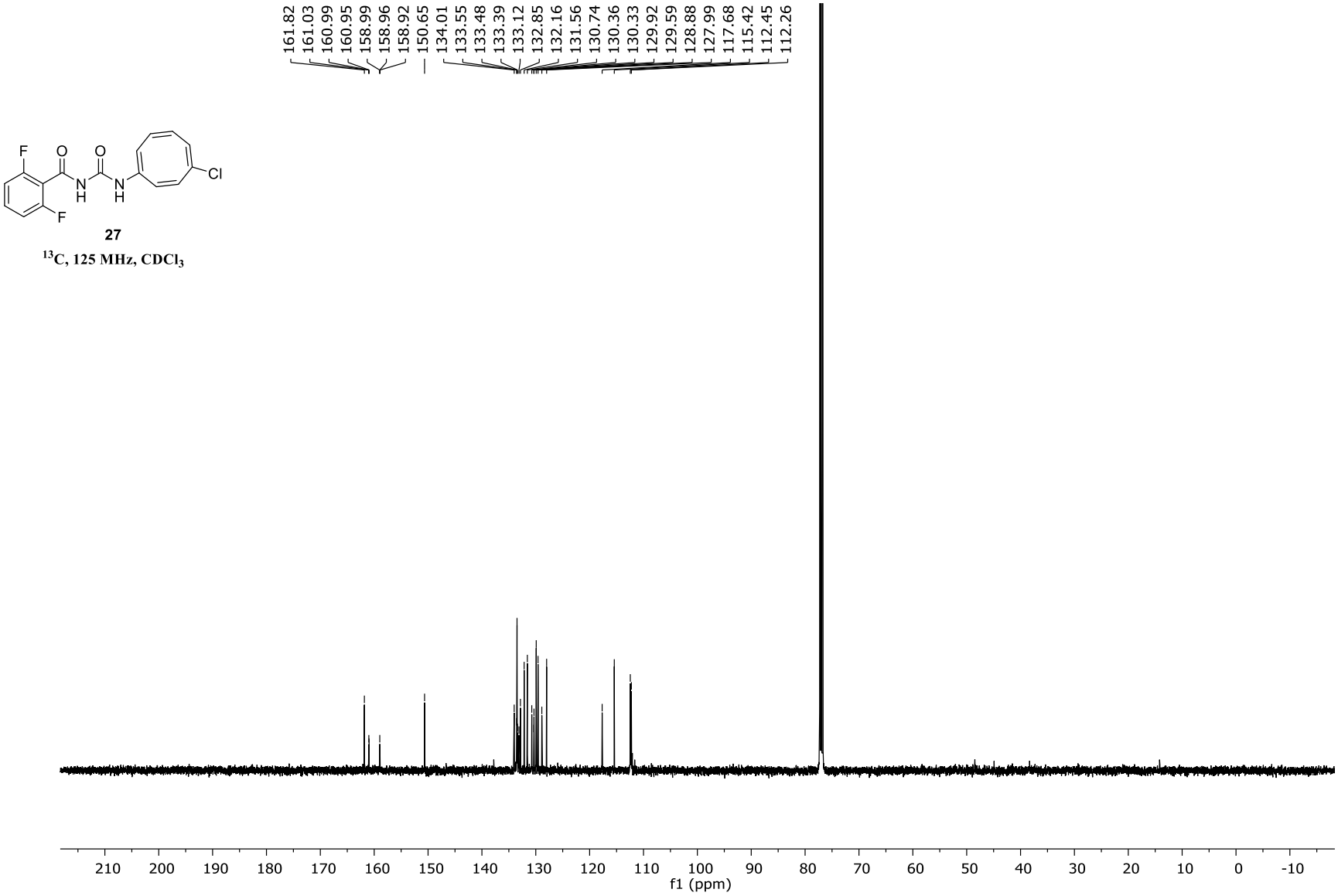

9.73
9.68
9.26
9.24
7.51
7.50
7.48
7.47
7.45
7.03
7.02
7.01
7.01
7.00
6.99
6.23
6.09
6.03
6.01
5.90
5.81
5.72
5.68
F
O
O
N
H
N
H
Cl
F
27
1H, 500 MHz, CDCl3
Acquired: 23/10/16
0.89
0.88
1.03
2.00
5.63
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)




**27**

**$^1$H, 300 MHz, $CDCl_3$**

Acquired: 10/08/16




**27**

**$^{13}$C, 125 MHz, $CDCl_3$**

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