Electronic Supplementary Material (ESI) for ChemComm.

Efficient unified synthesis of diverse bridged polycyclic scaffolds using a complexity-generating 'stitching' annulation approach

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Supporting Information

Contents

General Experimental

Commercially available starting materials were obtained from Sigma−Aldrich, Fluorochem and Alfa Aesar. All non-aqueous reactions were performed under nitrogen atmosphere unless otherwise stated. Water-sensitive reactions were performed in anhydrous solvents in oven-dried glassware cooled under nitrogen before use. Anhydrous dichloromethane (DCM), anhydrous tetrahydrofuran (THF), anhydrous toluene, anhydrous ethanol, anhydrous methanol and anhydrous acetonitrile were obtained from a PureSolv MD5 Purification System. Anhydrous dimethylformamide (DMF) was obtained from SureSeal bottles from Sigma-Aldrich. All other solvents used were of chromatography or analytical grade. An IKA RV 10 rotary evaporator was used to remove the solvents under reduced pressure. Thin layer chromatography (TLC) was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualization. Flash column chromatography was performed using silica gel 60 (35-70 µm particles) supplied by Merck. Analytical LC-MS was performed using an Ultimate3000 HPLC instrument with a UV diode array detector and an MS detector Bruker Amazon Speeds with electrospray ionisation run positive and negative switching mode. The system used a Phenomenex Kinetex C18 2.1 × 50 mm 2.6 micron column and two solvent systems: MeCN/H_2O + 0.1% Formic acid or MeCN/H_2O. A Bruker MaXis Impact spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS). A Bruker Alpha-P ATR FR-IR spectrometer was used to analyse the infrared spectra. Proton (^{1}H), carbon (^{13}C) and fluorine (^{19}F) NMR data was collected on a Bruker 500 MHz spectrometer. Data was collected at 300 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Assignments were made using COSY, DEPT, HSQC, HMBC and NOESY experiments.

General Procedures

TDG = 2-hydroxynicotinaldehyde (CAS 36404-89-4)

TDG2 = 2-chloro-6-hydroxybenzaldehyde (CAS 18362-30-6)

L1 = 2-hydroxy-5-trifluoromethylpyridine (CAS 33252-63-0)

General Procedure A

$Pd(OAc)_2$ (5 mol%), 2-hydroxynicotinaldehyde (10 mol%), aryl iodide (2.00 eq) and AgTFA (2.00 eq) were added to HFIP–AcOH 19:1 (0.25 M). Then amine derivative (1.00 eq) and H_2O (10.0 eq) were added and the reaction mixture allowed to stir at rt for 10 mins. The reaction mixture was then stirred at 120 ^oC for 24 h. The dark brown suspension was allowed to cool to rt and filtered through celite, with the celite being subsequently washed with THF (3 x (3 ml per mmol of amine derivative)). The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in THF (0.25 M). 1M HCl (4 ml per mmol of amine derivative) was added and the light brown suspension was left to stir for 1 h at rt. The mixture was basified with 2M NaOH and Boc_2O (3.00 eq) was added with the reaction mixture then being left to stir for 4 h at rt. EtOAc (10 ml per mmol of amine derivative) was added and the layers were separated. The organic layer was passed through a plug of silica, then the aqueous layer was extracted with EtOAc (3 x (4 ml per mmol of amine derivative)). The organic layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General procedure B

$Pd(OAc)_2$ (5 mol%), 2-hydroxynicotinaldehyde (10 mol%), aryl iodide (2.00 eq) and AgTFA (2.00 eq) were added to HFIP–AcOH 19:1 (0.50 M). Then amine derivative (1.00 eq) and H_2O (10.0 eq) were added and the reaction mixture allowed to stir at rt for 10 mins. The reaction mixture was then stirred at 120 ^oC for 24 h. The dark brown suspension was allowed to cool to rt and filtered through celite, with the celite being subsequently washed with THF (3 x (3 ml per mmol of amine derivative)). The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in THF (0.25 M). 1M HCl (4 ml per mmol of amine derivative) was added and the light brown suspension was left to stir for 1 h at rt. The mixture was basified with 2M NaOH and Ac_2O (3.00 eq) was added with the reaction mixture then being left to stir

for 4 h at rt. EtOAc (10 ml per mmol of amine derivative) was added and the layers were separated. The organic layer was passed through a plug of silica, then the aqueous layer was extracted with EtOAc (3 x (4 ml per mmol of amine derivative)). The organic layers were then combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General procedure C

Picolinic acid (1.10 eq) was dissolved in DMF (0.40 M) and CDI (1.10 eq) was subsequently added portionwise. The mixture was then allowed to stir at rt for 90 mins. Amine derivative (1.00 eq) was added and the mixture stirred at rt for a further 16 h. Water (1 ml per mmol of amine derivative) was added followed by 5M NaOH solution (2 ml per mmol of amine derivative). The mixture was then extracted with DCM (3 x (2 ml per mmol of amine derivative)), organic layers combined, washed with water (5 x (2 ml per mmol of amine derivative)), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General procedure D

Picolinamide derivative (1.00 eq) was added to a pressure vial covered with aluminium foil at rt. Then Ag_2CO_3 (1.10 eq), 2,6-dimethylbenzoic acid (0.25 eq), $Pd(OAc)_2$ (10 mol%), aryl iodide (6.00 eq) and DMF (0.27 M) were added sequentially. The vial was then flushed with nitrogen, sealed with a screw-cap and heated to 120 °C for 24 h. Upon cooling to rt, the reaction mixture was filtered through a pad of Celite, eluting with DCM. The filtrate was then concentrated under reduced pressure to give a crude material.

General procedure E

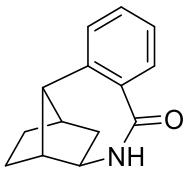
A tube was charged with picolinamide derivative (1.00 eq), $CuBr_2$ (10 mol%), $Pd(OAc)_2$ (5 mol%), CsOAc (4.00 eq), ^{t}AmOH (1.00 M) and aryl iodide (4.00 eq). The tube was sealed and heated at 140 ^{o}C for 24 h. The reaction mixture was allowed to cool to rt, filtered through celite (eluting with EtOAc) then the filtrate was concentrated under reduced pressure to give a crude material.

General procedure F

To a pressure vial was added picolinamide derivative (1.00 eq), PivOH (0.30 eq), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.00 eq), aryl iodide (1.10 eq) and toluene (0.60 M). The mixture was stirred at 130 °C for 18 h. The reaction mixture was cooled to rt then filtered through celite, eluting with EtOAc and MeOH. The filtrate was concentrated under reduced pressure to give a crude material.

Synthesis of scaffolds

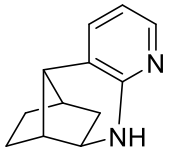
(1*R,3a*R**,4*R**,10b*S**)-2,3,3a,4,5,10b-hexahydro-1,4-methanobenzo[*c*]cyclopenta[*e*]azepin-6(1*H*)-one (7)**



$Pd(OAc)_2$ (51.0 mg, 5 mol%), 2-hydroxynicotinaldehyde (55.0 mg, 10 mol%), methyl-2-iodobenzoate (1.32 ml, 9.00 mmol) and AgTFA (1.99 g, 9.00 mmol) were added to HFIP–AcOH 19:1 (10 ml). Then *exo*-2-aminonorbornane (0.50 g, 4.50 mmol) and H_2O (0.90 ml) were added sequentially and the reaction mixture allowed to stir at rt for 10 mins. The reaction mixture was then stirred at 120 °C for 24 h. The dark brown suspension was allowed to cool to rt and filtered through celite, with the celite being washed with THF (3 x 15 ml). The filtrate was concentrated under reduced pressure and the resulting residue was dissolved in THF (20 ml). 1M HCl (20 ml) was added and the light brown suspension was left to stir for 1 h at rt. The mixture was basified with 2M NaOH and left to stir for 18 h at rt. EtOAc (50 ml) was added and the layers were separated. The organic layer was passed through a plug of silica, then the aqueous layer was extracted with EtOAc (3 x 20 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 35:65 to give *lactam derivative* ***7*** (0.58 g, 60%) as a white solid. R_f 0.21 (EtOAc–hexane 30:70).

ν_{max}/cm^{-1}: 3170, 3055, 2947, 2870, 1639, 1445, 1343, 1251, 1131; δ_H (500 MHz, $CDCl_3$): 8.35 (1H, br. d, *J* 7.2 Hz, NH), 8.30 (1H, d, *J* 8.0 Hz, 7-H), 7.35 (1H, td, *J* 7.8 and 1.2 Hz, 9-H), 7.27-7.21 (2H, m, 8-H and 10-H), 3.30-3.24 (1H, m, 4-H), 2.98 (1H, app. s, 10b-H), 2.37 (1H, d, *J* 3.9 Hz, 3a-H), 2.32 (1H, br. t, *J* 4.0 Hz, 1-H), 1.81-1.61 (4H, m, 11-H_2 and 2-H_2), 1.37-1.30 (1H, m, 3-H_A), 1.22-1.14 (1H, m, 3-H_B); δ_C (125 MHz, $CDCl_3$): 169.2 (C-6), 141.0 (C-10a), 132.0 (C-7), 131.6 (C-6a), 131.1 (C_2-9,10), 125.9 (C-8), 57.4 (C-10b), 54.7 (C-4), 48.1 (C-1), 43.1 (C-3a), 38.0 (C-11), 27.7 (C-2), 27.4 (C-3); HRMS found MNa^+ 236.1050. $C_{14}H_{15}NO$ requires *MNa*, 236.1046.

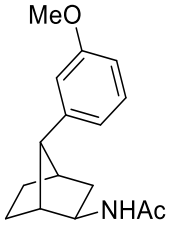
(6*R,6a*R**,9*R**,9a*S**)-6,6a,7,8,9,9a-hexahydro-5*H*-6,9-methanocyclopenta[*c*][1,8]naphthyridine (8)**



$Pd(OAc)_2$ (51.0 mg, 5 mol%), TDG2 (70.0 mg, 10 mol%), L1 (183 mg, 25 mol%), 2-fluoro-3-iodopyridine (2.00 g, 9.00 mmol) and AgTFA (2.00 g, 9.00 mmol) were dissolved in HFIP (10 ml) at rt. Then *exo*-2-aminonorbornane (0.50 g, 4.50 mmol) and H_2O (0.90 ml) were added and the resulting mixture allowed to stir at rt for 10 mins. Then the mixture has stirred at 120 ^oC for 24 h. AcOH (1 ml) was added and the reaction mixture left to stir for a further 24 h at 120 ^oC. The mixture was cooled to rt, filtered through celite (washed with MeOH–$CHCl_3$ 1:4) and the filtrate concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc to give the fused-ring pyridine derivative **8**[1] (0.55 g, 65%) as a light brown oil. R_f 0.19 (EtOAc). δ_H (500 MHz, $CDCl_3$): 7.49 (1H, dd, *J* 6.4 and 1.4 Hz, 3-H), 7.42 (1H, dd, *J* 7.1 and 1.4 Hz, 1-H), 6.54 (1H, app. t, *J* 6.7 Hz, 2-H), 3.65 (1H, app. d, *J* 6.2 Hz, 6-H), 2.71 (1H, br. t, *J* 4.1 Hz, 9a-H), 2.65 (1H, br. t, *J* 1.2 Hz, 6a-H), 2.19 (1H, app. d, *J* 5.0 Hz, 9-H), 1.94-1.86 (1H, m, 8-H_A), 1.86-1.80 (1H, m, 10-H_A), 1.69-1.59 (2H, m, 10-H_B and 7-H_A), 1.42 (1H, ddd, *J* 13.4, 9.1 and 6.3 Hz, 8-H_B), 1.28-1.24 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$): 152.7 (C-4a), 139.4 (C-1), 133.8 (C-3), 126.3 (C-9b), 110.9 (C-2), 54.5

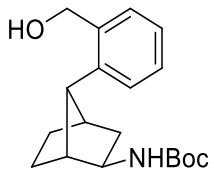
(C-6), 49.2 (C-6a), 48.5 (C-9a), 40.0 (C-10), 36.6 (C-9), 29.9 (C-7), 23.4 (C-8). All data is consistent with known literature values.[1]

_N_-[(1_R_*,2_R_*,4_R_*,7_R_*)-7-(3-methoxyphenyl)bicyclo[2.2.1]heptan-2-yl]acetamide (9)



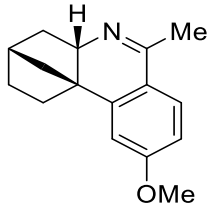
Prepared according to General procedure B, *exo*-2-aminonorbornane (0.50 g, 4.50 mmol) and 3-iodoanisole (1.07 ml, 9.00 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give *arylated derivative* ***9*** (0.81 g, 70%, *dr* >95:<5 by ^{1}H NMR) as an off-white solid. R_f 0.14 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3271, 2961, 2897, 2870, 1637, 1555, 1433, 1294, 1044; δ_H (500 MHz, $CDCl_3$): 7.22 (1H, t, *J* 7.9 Hz, phenyl 5-H), 6.88 (1H, app. d, *J* 7.6 Hz, phenyl 6-H), 6.84-6.82 (1H, m, phenyl 2-H), 6.73 (1H, dd, *J* 8.2 and 2.6 Hz, phenyl 4-H), 4.56 (1H, br. d, *J* 7.2 Hz, NH), 3.83 (1H, td, *J* 8.5 and 4.0 Hz, 2-H), 3.77 (3H, s, OMe), 2.95 (1H, app. s, 7-H), 2.70 (1H, t, *J* 4.0 Hz, 4-H), 2.66 (1H, d, *J* 4.4 Hz, 1-H), 1.85 (1H, dd, *J* 13.4 and 8.5 Hz, 3-H_A), 1.75 (1H, tt, *J* 11.7 and 4.4 Hz, 6-H_A), 1.70-1.61 (1H, m, 5-H_A), 1.55-1.46 (4H, m, 3-H_B and acetyl), 1.40-1.34 (1H, m, 6-H_B), 1.29-1.22 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 168.6 (acetyl C=O), 159.8 (phenyl C-3), 142.3 (phenyl C-1), 129.5 (phenyl C-5), 120.7 (phenyl C-6), 114.3 (phenyl C-2), 111.2 (phenyl C-4), 55.2 (OMe), 53.2 (C-2), 52.8 (C-7), 46.7 (C-1), 37.9 (C-3), 37.6 (C-4), 28.6 (C-5), 27.8 (C-6), 23.3 (acetyl CH_3); HRMS found MH^+ 260.1644. $C_{16}H_{21}NO_2$ requires *MH*, 260.1645.

***tert*-butyl _N_-[(1_R_*,2_R_*,4_R_*,7_R_*)-7-[2-(hydroxymethyl)phenyl]bicyclo[2.2.1]heptan-2-yl]carbamate (10)**



Prepared according to General procedure A, *exo*-2-aminonorbornane (0.50 g, 4.50 mmol) and 2-iodobenzyl alcohol (2.10 g, 9.00 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give *arylated derivative* ***10*** (0.42 g, 30%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.36 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3485, 3433, 2962, 2869, 1693, 1504, 1451, 1346, 1275, 1007; δ_H (500 MHz, $CDCl_3$): 7.46 (1H, app br. d, *J* 4.1 Hz, phenyl 6-H), 7.27-7.18 (3H, m, phenyl 3-H, phenyl 4-H and phenyl 5-H), 4.75-4.64 (2H, m, hydroxymethyl 1-H_2), 3.57-3.46 (2H, m, 2-H and NH), 2.94 (1H, app. s, 7-H), 2.72-2.62 (3H, m, 1-H, 4-H and OH), 1.87 (1H, dd, *J* 13.7 and 8.0 Hz, 3-H_A), 1.82-1.72 (2H, m, 3-H_B and 6-H_A), 1.69-1.61 (1H, m, 5-H_A), 1.39-1.18 (11H, m, 5-H_B, 6-H_B and ^{t}Bu); δ_C (125 MHz, $CDCl_3$): 155.2 (Boc C=O), 140.1 (phenyl C-2), 138.0 (phenyl C-1), 128.4 (phenyl C-6), 127.6 (phenyl C-5), 127.4 (phenyl C-3), 126.6 (phenyl C-4), 78.7 (^{t}Bu C_1), 62.5 (hydroxymethyl C-1), 54.9 (C-2), 50.9 (C-7), 47.0 (C-1), 38.3 (C-4), 38.2 (C-3), 28.6 (C-5), 28.3 (^{t}Bu C_3), 27.6 (C-6); HRMS found MNa^+ 340.1885. $C_{19}H_{27}NO_3$ requires *MNa*, 340.1883.

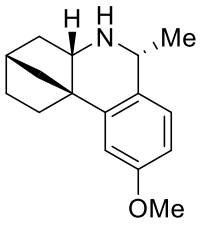
(3*R,4a*R**,10b*S**)-9-methoxy-6-methyl-2,3,4,4a-tetrahydro-1H-3,10b-methanophenanthridine (S1)**



Arylated derivative **9** (100 mg, 0.39 mmol) was dissolved in MeCN (5 ml) at rt. $POCl_3$ (0.28 ml, 3.09 mmol) was added to the solution dropwise over 5 mins. The resulting solution was then stirred and heated at 100 ^{o}C for 4 h. The reaction mixture was allowed to cool to rt and the volatiles removed under reduced pressure. DCM (20 ml) and water (20 ml) were added to the residue and this solution was then basified to pH 12 with 2M NaOH. This was then extracted

with DCM (4 x 20 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–MeOH 95:5 to give the *cyclised imine derivative* ***S1*** (31.0 mg, 33%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.15 (DCM–MeOH 95:5). δ_H (500 MHz, $CDCl_3$): 7.57 (1H, d, *J* 8.6 Hz, 7-H), 7.05 (1H, d, *J* 2.4 Hz, 10-H), 6.80 (1H, dd, *J* 8.6 and 2.4 Hz, 8-H), 3.86 (3H, s, OMe), 3.46 (1H, app. br. s, 4a-H), 2.45 (3H, s, methyl), 2.33 (1H, app. br. t, *J* 3.9 Hz, 3-H), 2.26 (1H, td, *J* 12.3 and 4.1 Hz, 1-H_A), 2.21-2.14 (1H, m, 4-H_A), 2.09-2.03 (1H, m, 4-H_B), 1.83-1.75 (1H, m, 2-H_A), 1.58 (1H, app. d, *J* 9.5 Hz, 11-H_A), 1.40-1.33 (1H, m, 2-H_B), 1.30-1.24 (1H, m, 1-H_B), 1.22 (1H, app. d, *J* 9.5 Hz, 11-H_B); δ_C (125 MHz, $CDCl_3$): 162.4 (C-9), 161.3 (C-6), 142.8 (C-10a), 129.1 (C-6a), 121.2 (C-7), 111.3 (C-8), 111.0 (C-10), 62.6 (C-4a), 55.6 (OMe), 46.3 (C-10b), 44.2 (C-11), 41.7 (C-4), 35.6 (C-3), 31.7 (C-1), 29.4 (C-2), 23.0 (methyl CH_3); HRMS found MH^+ 242.1557. $C_{16}H_{19}NO$ requires *MH*, 242.1539.

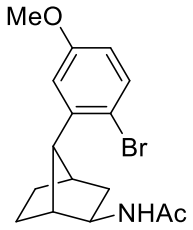
(3*R,4a*R**,6*S**,10b*S**)-9-methoxy-6-methyl-2,3,4,4a,5,6-hexahydro-1*H*-3,10b-methanophenanthridine (5)**



Cyclised imine derivative **S1** (30.0 mg, 0.12 mmol) was dissolved in MeOH (2 ml) and $NaBH_4$ (9.00 mg, 0.24 mmol) was added at rt. The reaction mixture was left to stir at rt for 18 h. 1M HCl (5 ml) was added to quench the reaction and 2M NaOH to basify the reaction mixture to pH 12. This solution was subsequently extracted with DCM (4 x 10 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *amine derivative* ***5*** (21.0 mg, 74%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.63 (DCM–MeOH 80:20). δ_H (500 MHz, $CDCl_3$); 7.13 (1H, d, *J* 8.6 Hz, 7-H), 6.90 (1H, d, *J* 2.7 Hz, 10-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 8-H), 3.99 (1H, q, *J* 6.6 Hz, 6-H), 3.80 (3H, s, OMe), 2.91 (1H, dd, *J* 7.8 and 4.0 Hz, 4a-H), 2.29 (1H, app. br. t, *J* 4.0 Hz, 3-H), 2.01-1.88 (2H, m, 4-H_A and 1-

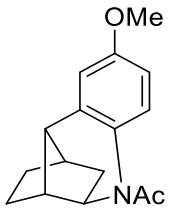
H_A), 1.86-1.78 (1H, m, 2-H_A), 1.63 (1H, dd, *J* 10.0 and 1.6 Hz, 11-H_A), 1.52 (1H, dd, *J* 10.0 and 1.6 Hz, 11-H_B), 1.45 (3H, d, *J* 6.6 Hz, methyl), 1.41-1.24 (4H, m, 4-H_B, 1-H_B, 2-H_B and NH); δ_C (125 MHz, $CDCl_3$): 158.1 (C-9), 140.6 (C-10a), 134.1 (C-6a), 125.9 (C-7), 112.6 (C-10), 111.3 (C-8), 60.8 (C-4a), 55.4 (OMe), 52.4 (C-6), 48.9 (C-10b), 44.8 (C-11), 40.8 (C-4), 36.8 (C-3), 35.2 (C-1), 30.3 (C-2), 21.8 (methyl CH_3); HRMS found MH^+ 244.1708. $C_{16}H_{21}NO$ requires *MH*, 244.1696. The relative configuration was determined from nOe interaction observed between 4a-H and 6-H.

_N_-[(1*R,2*R**,4*R**,7*R**)-7-(2-bromo-5-methoxyphenyl)bicyclo[2.2.1]heptan-2-yl]acetamide (S2)**



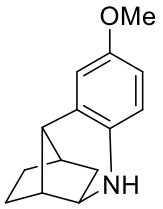
Arylated derivative **9** (100 mg, 0.39 mmol) was dissolved in MeCN (5 ml) at rt. Then NBS (76.0 mg, 0.43 mmol) was added at rt. The resulting solution was stirred at rt for 18 h and then concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *brominated derivative* ***S2*** (118 mg, 89%) as a white powder. R_f 0.20 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3303, 2952, 2906, 2868, 1639, 1533, 1463, 1287, 1175; δ_H (500 MHz, $CDCl_3$); 7.46 (1H, d, *J* 8.7 Hz, phenyl 3-H), 6.90 (1H, d, *J* 2.5 Hz, phenyl 6-H), 6.64 (1H, dd, *J* 8.7 and 2.5 Hz, phenyl 4-H), 4.48 (1H, br. d, *J* 5.4 Hz, NH), 3.82 (1H, td, *J* 8.1 and 2.9 Hz, 2-H), 3.77 (3H, s, OMe), 3.08 (1H, d, *J* 4.3 Hz, 1-H), 2.88 (1H, app. s, 7-H), 2.64 (1H, br. t, *J* 3.9 Hz, 4-H), 1.99-1.91 (1H, m, 3-H_A), 1.89-1.80 (2H, m, 3-H_B and 6-H_A), 1.72-1.64 (1H, m, 5-H_A), 1.48 (3H, s, acetyl), 1.41-1.32 (1H, m, 6-H_B), 1.30-1.22 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 168.7 (acetyl C=O), 158.9 (phenyl C-5), 141.4 (phenyl C-1), 134.2 (phenyl C-3), 116.2 (phenyl C-6), 115.8 (phenyl C-2), 112.5 (phenyl C-4), 55.6 (OMe), 54.1 (C-7), 53.3 (C-2), 46.4 (C-1), 38.8 (C-3), 38.2 (C-4), 28.9 (C-5), 27.4 (C-6), 23.2 (acetyl CH_3); HRMS found MH^+ 338.0748. $C_{16}H_{20}BrNO_2$ requires *MH*, 338.0750.

1-[(1*R,3a*R**,4*R**,9b*S**)-8-methoxy-1,2,3,3a,4,9b-hexahydro-5*H*-1,4-methanocyclopenta[*c*]quinoline-5-yl]ethanone (S3)**



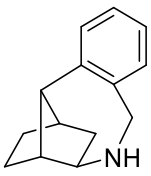
Brominated derivative **S2** (110 mg, 0.33 mmol) was dissolved in toluene (10 ml) and $Pd(OAc)_2$ (3.71 mg, 5 mol%), *rac*-BINAP (15.0 mg, 7.5 mol%) and Cs_2CO_3 (215 mg, 0.66 mmol) were added sequentially at rt. The reaction mixture was then stirred at 100 ^oC for 24 h. The reaction mixture was allowed to cool to rt and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80→50:50 to give *cyclised acetamide derivative* ***S3*** (71.0 mg, 85%, *rotamers* 60:40 by ^1H NMR) as a white solid. R_f 0.54 (EtOAc–hexane 50:50). δ_H (500 MHz, $CDCl_3$, broad peaks due to unresolved rotamers); 8.10 (1H, app. br. s, 6-H^{maj}), 6.95 (1H, app. br. s, 6-H^{min}), 6.71 (2H, app. d, *J* 8.8 Hz, 7-H), 6.65 (2H, app. br. s, 9-H), 5.11 (1H, app. br. s, 4-H^{min}), 4.19-4.01 (1H, m, 4-H^{maj}), 3.77 (6H, s, OMe), 2.71 (2H, app. s, 9b-H), 2.44-2.34 (2H, m, 3a-H), 2.28 (6H, s, acetyl), 2.19 (2H, app. br. s, 1-H), 1.84 (2H, app. br. s, 2-H_A), 1.62 (4H, app. br. s, 10-H_A and 3-H_A), 1.49 (2H, app. br. s, 3-H_B), 1.32 (2H, app. br. s, 2-H_B), 1.31-1.20 (2H, m, 10-H_B); δ_C (125 MHz, $CDCl_3$): 169.7 (acetyl C=O^{min}), 168.5 (acetyl C=O^{maj}), 156.3 (C-8^{min}), 155.7 (C-8^{maj}), 134.3 (C-$9a^{min}$), 132.4 (C-$9a^{maj}$), 130.2 (C-$5a^{min}$), 129.4 (C-$5a^{maj}$), 124.8 (C-6^{maj}), 124.4 (C-6^{min}), 113.9 (C-9), 111.5 (C-7), 60.5 (C-4^{maj}), 59.7 (C-4^{min}), 55.5 (OMe), 50.8 (C-9b), 46.5 (C-3a), 40.1 (C-1^{min}), 39.1 (C-1^{maj}), 34.5 (C-3^{maj}), 32.8 (C-3^{min}), 29.2 (C-10), 25.1 (C-2), 24.5 (acetyl CH_3); HRMS found MNa^+ 280.1312. $C_{16}H_{19}NO_2$ requires *MNa*, 280.1308.

(1*R,3a*R**,4*R**,9b*S**)-8-methoxy-1,2,3,3a,4,9b-hexahydro-5*H*-1,4-methanocyclopenta[*c*]quinoline (11)**



Cyclised acetamide derivative **S3** (70.0 mg, 0.27 mmol) was dissolved in EtOH–HCl 1:1 (10 ml) and stirred at 80 °C for 18 h. The reaction mixture was allowed to cool to rt and concentrated under reduced pressure to give the *aniline derivative **11*** (64.0 mg, 94%) as a white powder. R_f 0.84 (DCM–MeOH 90:10). ν_{max}/cm^{-1}: 3483, 3434, 2961, 2868, 1504, 1446, 1268, 1034; δ_H (500 MHz, MeOD); 7.19 (1H, d, *J* 8.5 Hz, 6-H), 6.97-6.92 (2H, m, 7-H and 9-H), 3.94-3.91 (1H, m, 4-H), 3.83 (3H, s, OMe), 2.97 (1H, app. s, 9b-H), 2.53 (2H, app. d, *J* 3.9 Hz, 3a-H and 1-H), 2.03-1.94 (1H, m, 2-H_A), 1.86-1.77 (1H, m, 3-H_A), 1.77-1.72 (2H, m, 10-H_2), 1.50-1.39 (2H, m, 2-H_B and 3-H_B); δ_C (125 MHz, MeOD): 161.6 (C-8), 136.8 (C-9a), 125.3 (C-6), 120.2 (C-5a), 116.2 (C-9), 115.0 (C-7), 57.6 (C-4), 56.2 (OMe), 49.5 (C-9b), 46.7 (C-3a), 40.8 (C-1), 32.0 (C-10), 30.4 (C-3), 24.8 (C-2); HRMS found MH^+ 216.1394. $C_{14}H_{17}NO$ requires *MH*, 216.1383. The product was isolated as the corresponding HCl salt.

(1*R,3a*R**,4*R**,10b*S**)-1,2,3,3a,4,5,6,10b-octahydro-1,4-methanobenzo[*c*]cyclopenta[*e*]azepine (12)**



Arylated derivative **10** (310 mg, 0.98 mmol), Et_3N (0.27 ml, 1.96 mmol) and MsCl (0.09 ml, 1.17 mmol) were dissolved in DCM (10 ml) at 0 °C. The reaction mixture was then stirred at rt for 18 h. A saturated solution of $NaHCO_3$ (10 ml) was added and the phases separated. The aqueous phase was extracted with DCM (3 x 10 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the mesylate intermediate. This intermediate was then dissolved in DCM (10 ml) and TFA (3 ml) was added dropwise at rt and

the reaction mixture left to stir for 18 h at rt. The TFA and solvent were removed under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc → MeOH–EtOAc 10:90 to give the *cyclised amine derivative* ***12*** (279 mg, 91%) as a colourless hygroscopic solid. R_f 0.08 (EtOAc). ν_{max}/cm^{-1}: 3400, 3254, 2976, 2884, 1669, 1513, 1472, 1398, 1179, 1132; δ_H (500 MHz, $CDCl_3$): 7.43 (1H, app. d, *J* 7.3 Hz, 10-H), 7.34-7.27 (3H, m, 7-H, 8-H and 9-H), 4.80 (1H, d, *J* 11.8 Hz, 6-H_A), 4.62 (1H, d, *J* 11.8 Hz, 6-H_B), 3.28-3.22 (2H, m, 4-H and 10b-H), 2.98 (1H, d, *J* 4.3 Hz, 3a-H), 2.84 (1H, br t. *J* 4.1 Hz, 1-H), 2.19 (1H, dd, *J* 14.7 and 2.8 Hz, 11-H_A), 2.05-1.93 (2H, m, 11-H_B and 3-H_A), 1.81-1.71 (1H, m, 3-H_B), 1.39-1.28 (2H, m, 2-H_2); δ_C (125 MHz, $CDCl_3$): 162.4 (q, *J* 35.2 Hz, TFA C=O), 137.4 (C-10a), 136.7 (C-6a), 132.4 (C-10), 129.9 (C-7), 128.6 (C-9), 128.1 (C-8), 116.5 (q, *J* 290.7 Hz, TFA CF_3), 55.6 (C-4), 50.4 (C-10b), 45.5 (C-3a), 44.2 (C-6), 38.7 (C-1), 35.8 (C-11), 28.3 (C-3), 27.7 (C-2); HRMS found MH^+ 200.1428. $C_{14}H_{17}N$ required *MH*, 200.1434. The product was isolated as the corresponding TFA salt.

tert-butyl _N_-[(1_R_*,3_S_*)-3-(3-methoxyphenyl)cyclohexyl]carbamate (13)

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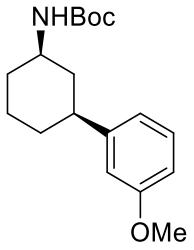
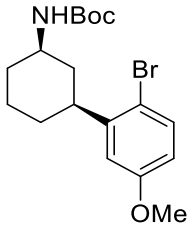


Prepared according to General procedure A, cyclohexylamine (0.50 g, 5.00 mmol) and 3-iodoanisole (1.17 g, 10.0 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give *arylated derivative* ***13*** (1.43 g, 93%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.48 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 3345, 2975, 2929, 2855, 1687, 1584, 1494, 1390, 1266, 1241, 1159, 1049; δ_H (500 MHz, $CDCl_3$): 7.23-7.18 (1H, m, phenyl 5-H), 6.79 (1H, dt, *J* 7.7 and 1.2 Hz, phenyl 4-H), 6.75-6.71 (2H, m, phenyl 2-H and phenyl 6-H), 4.43 (1H, br. s, NH), 3.79 (3H, s, OMe), 3.64-3.54 (1H, m, 1-H), 2.61 (1H, tt, *J* 12.2 and 3.1 Hz, 3-H), 2.19 (1H, d, *J* 12.2 Hz, 2-H_A), 2.08-2.01 (1H, m, 6-H_A), 1.93-1.80 (2H, m, 5-H_A and 4-H_A), 1.54-1.39 (10H, m, ^{t}Bu and 5-H_B), 1.33 (1H, qd, *J* 12.4 and 3.2 Hz, 4-H_B), 1.22 (1H, app. q, *J* 12.2 Hz, 2-H_B), 1.09 (1H, qd, *J* 12.4 and 3.4 Hz, 6-H_B); δ_C (125

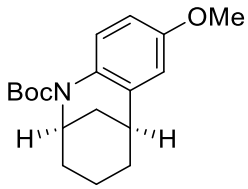
MHz, $CDCl_3$): 159.8 (phenyl C-3), 155.3 (Boc C=O), 148.2 (phenyl C-1), 129.4 (phenyl C-5), 119.3 (phenyl C-4), 112.9 (phenyl C-2), 111.4 (phenyl C-6), 79.3 (^{t}Bu C_1), 55.3 (OMe), 50.1 (C-1), 43.4 (C-3), 41.5 (C-2), 33.4 (C-6), 33.2 (C-4), 28.6 (^{t}Bu C_3), 25.3 (C-5); HRMS found MNa^+ 328.1876. $C_{18}H_{27}NO_3$ requires *MNa*, 328.1883.

tert-butyl _N_-[(1_R_*,3_S_*)-3-(2-bromo-5-methoxyphenyl)cyclohexyl]carbamate (S4)



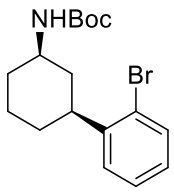
Arylated derivative **13** (100 mg, 0.33 mmol) was dissolved in MeCN (5 ml) then NBS (64.0 mg, 0.36 mmol) was added to the solution at rt. The resulting solution was stirred overnight for 18 h at rt. The solvent was then removed under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give the *brominated derivative **S4*** (101 mg, 79%) as a white solid. R_f 0.50 (EtOAc–hexane 20:80). δ_H (500 MHz, $CDCl_3$): 7.40 (1H, d, *J* 8.7 Hz, phenyl 3-H), 6.75 (1H, d, *J* 3.0 Hz, phenyl 6-H), 6.60 (1H, dd, *J* 8.7 and 3.0 Hz, phenyl 4-H), 4.48 (1H, br. s, NH), 3.75 (3H, s, OMe), 3.66-3.50 (1H, m, 1-H), 3.02 (1H, tt, *J* 11.9 and 2.9 Hz, 3-H), 2.17 (1H, app. d, *J* 11.9 Hz, 2-H_A), 2.06 (1H, app. d, *J* 11.9 Hz, 6-H_A), 1.91-1.82 (2H, m, 4-H_A and 5-H_A), 1.51 (1H, qt, *J* 13.2 and 3.0 Hz, 5-H_B), 1.43 (9H, s, ^{t}Bu), 1.28-1.14 (2H, m, 2-H_B and 4-H_B), 1.09 (1H, qd, *J* 12.7 and 3.6 Hz, 6-H_B); δ_C (125 MHz, $CDCl_3$): 159.2 (phenyl C-5), 155.2 (Boc C=O), 145.8 (phenyl C-1), 133.4 (phenyl C-3), 114.9 (phenyl C-2), 113.7 (phenyl C-6), 112.6 (phenyl C-4), 79.2 (^{t}Bu C_1), 55.5 (OMe), 49.9 (C-1), 42.1 (C-3), 39.8 (C-2), 33.3 (C-6), 32.2 (C-4), 28.5 (^{t}Bu C_3), 25.1 (C-5); HRMS found MNa^+ 406.0984. $C_{18}H_{26}BrNO_3$ requires *MNa*, 406.0988.

***tert*-butyl (2*R**,6*S**)-8-methoxy-3,4,5,6-tetrahydro-2,6-methanobenzo[*b*]azocine-1(2*H*)-carboxylate (4)**



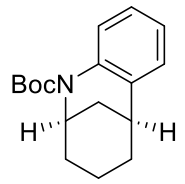
Brominated derivative **S4** (95.0 mg, 0.25 mmol), $Pd(OAc)_2$ (3.00 mg, 5 mol%) and *rac*-BINAP (12.0 mg, 7.5 mol%) were added to toluene (5 ml) and heated until all solids had dissolved. Cs_2CO_3 (163 mg, 0.50 mmol) was then added and the resulting suspension stirred and heated at 100 ^oC for 24 h. The reaction mixture was cooled to rt then filtered through a small plug of silica (washed with EtOAc). The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give *cyclised bridged derivative **4*** (46.0 mg, 62%) as a colourless oil. R_f 0.62 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 2973, 2930, 2852, 1695, 1494, 1325, 1245, 1163, 1048; δ_H (500 MHz, $CDCl_3$): 8.27 (1H, d, *J* 9.2 Hz, 10-H), 6.72 (1H, dd, *J* 9.2 and 3.1 Hz, 9-H), 6.59 (1H, d, *J* 3.1 Hz, 7-H), 4.56 (1H, br. t, *J* 3.1 Hz, 2-H), 3.77 (3H, s, OMe), 2.96-2.92 (1H, m, 6-H), 2.05 (1H app. d, *J* 13.4 Hz, 3-H_A), 1.87 (2H, app. t, *J* 2.6 Hz, 11-H_2), 1.78-1.72 (2H, m, 5-H_2), 1.54 (9H, s, ^{t}Bu), 1.50 (1H, ddd, *J* 13.4, 4.7 and 2.8 Hz, 3-H_B), 1.45-1.37 (1H, m, 4-H_A), 1.33-1.20 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$): 154.2 (C-8), 153.8 (Boc C=O), 133.7 (C-10a), 132.8 (C-6a), 121.5 (C-10), 113.6 (C-7), 111.7 (C-9), 80.6 (^{t}Bu C_1), 55.5 (OMe), 50.0 (C-2), 34.7 (C-6), 33.9 (C-5), 32.1 (C-3), 30.3 (C-11), 28.6 (^{t}Bu C_3), 17.7 (C-4); HRMS found MNa^+ 326.1728. $C_{18}H_{25}NO_3$ requires *MNa*, 326.1727.

***tert*-butyl *N*-[(1*R**,3*S**)-3-(2-bromophenyl)cyclohexyl]carbamate (14)**



Prepared according to General procedure A, cyclohexylamine (0.50 g, 5.00 mmol) and 2-bromoiodobenzene (2.83 g, 10.0 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give arylated derivative **14**[2] (1.00 g, 57%, *dr* >95:<5 by ^{1}H NMR) an off-white solid. R_f 0.50 (EtOAc–hexane 20:80). δ_H (500 MHz, $CDCl_3$): 7.53 (1H, dd, *J* 8.0 and 0.8 Hz, phenyl 3-H), 7.28-7.23 (1H, m, phenyl 5-H), 7.20 (1H, dd, *J* 8.0 and 1.7 Hz, phenyl 6-H), 7.03 (1H, td, *J* 8.0 and 1.7 Hz, phenyl 4-H), 4.45 (1H, br. s, NH), 3.69-3.50 (1H, m, 1-H), 3.10 (1H, t, *J* 11.6 Hz, 3-H), 2.24-2.15 (1H, m, 2-H_A), 2.08 (1H, d, *J* 12.0 Hz, 6-H_A), 1.92-1.83 (2H, m, 4-H_A and 5-H_A), 1.53 (1H, app. qt, *J* 13.2 and 3.2 Hz, 5-H_B), 1.44 (9H, s, ^{t}Bu), 1.32-1.17 (2H, m, 2-H_B and 4-H_B), 1.11 (1H, qd, *J* 12.6 and 3.8 Hz, 6-H_B); δ_C (125 MHz, $CDCl_3$): 155.2 (Boc C=O), 144.8 (phenyl C-1), 133.1 (phenyl C-3), 127.7 (phenyl C-4), 127.6 (phenyl C-5), 127.3 (phenyl C-6), 124.6 (phenyl C-2), 79.3 (^{t}Bu C_1), 50.0 (C-1), 42.0 (C-3), 39.9 (C-2), 33.4 (C-6), 32.3 (C-4), 28.6 (^{t}Bu C_3), 25.2 (C-5). All data is consistent with known literature values.[2]

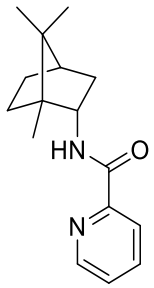
tert-butyl (2*R,6*S**)-3,4,5,6-tetrahydro-2,6-methanobenzo[*b*]azocine-1(2*H*)-carboxylate (15)**



Arylated derivative **14** (100 mg, 0.30 mmol), $Pd(OAc)_2$ (4.00 mg, 5 mol%) and *rac*-BINAP (14.0 mg, 7.5 mol%) were added to toluene (5 ml) and heated until all solids had dissolved. Cs_2CO_3 (194 mg, 0.60 mmol) was then added and the resulting suspension stirred and heated at 100 ^{o}C for 24 h. The reaction mixture was cooled to rt then filtered through a small plug of silica (washed with EtOAc). The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 2:98 to give *cyclised bridged derivative **15*** (33.0 mg, 40%) as a colourless oil. R_f 0.57 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 2973, 2930, 2852, 1705, 1488, 1454, 1366, 1318, 1277, 1254, 1160, 1130; δ_H (500 MHz, $CDCl_3$): 8.32 (1H, d, *J* 8.5 Hz, 10-H), 7.15 (1H, ddd, *J* 8.5, 7.5 and 1.8 Hz, 9-H), 7.03 (1H, dd, *J* 7.5 and 1.8 Hz, 7-H), 6.91 (1H, td, *J* 7.5 and 1.0 Hz, 8-H), 4.60-4.56 (1H, m, 2-H), 3.00-2.95 (1H, m, 6-H), 2.09-2.02 (1H, m, 3-H_A), 1.92-1.84 (2H, m, 11-H_2), 1.76

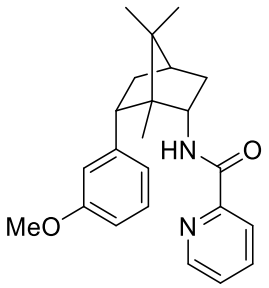
(2H, dt, *J* 10.6 and 3.5 Hz, 5-H_2), 1.55 (9H, s, ^{t}Bu), 1.54-1.50 (1H, m, 3-H_B), 1.45-1.39 (1H, m, 4-H_A), 1.31-1.22 (1H, m, 4-H_B); δ_C (125 MHz, $CDCl_3$): 153.9 (Boc C=O), 140.2 (C-10a), 131.3 (C-6a), 128.6 (C-7), 126.5 (C-9), 121.7 (C-8), 120.3 (C-10), 80.8 (^{t}Bu C_1), 50.3 (C-2), 34.5 (C-6), 33.9 (C-5), 32.1 (C-3), 30.2 (C-11), 28.6 (^{t}Bu C_3), 17.6 (C-4); HRMS found MNa^+ 296.1619. $C_{17}H_{23}NO_2$ requires *MNa*, 296.1621.

_N_-[(1_R_,2_S_,4_R_)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]pyridine-2-carboxamide (S5)



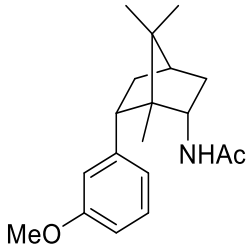
Prepared according to General procedure C, (*R*)-bornylamine (400 mg, 2.61 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 40:60 to give the picolinamide derivative **S5**[3] (604 mg, 90%) as a white solid. R_f 0.41 (EtOAc–hexane 40:60). δ_H (500 MHz, $CDCl_3$): 8.48 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.11 (2H, app. br. d, *J* 7.7 Hz, pyridinyl 3-H and NH), 7.75 (1H, td, *J* 7.7 and 0.9 Hz, pyridinyl 4-H), 7.33 (1H, dd, *J* 7.0 and 4.8 Hz, pyridinyl 5-H), 4.40-4.33 (1H, m, 2-H), 2.38-2.30 (1H, m, 3-H_A), 1.73 (1H, ddd, *J* 16.0, 8.1 and 3.8 Hz, 6-H_A), 1.67-1.59 (2H, m, 4-H and 5-H_A), 1.39-1.31 (1H, m, 5-H_B), 1.27-1.20 (1H, m, 6-H_B), 0.95-0.88 (4H, m, 3-H_B and methyl), 0.82 (3H, s, methyl), 0.80 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 164.1 (C=O), 150.1 (pyridinyl C-1), 147.9 (pyridinyl C-6), 137.2 (pyridinyl C-4), 125.9 (pyridinyl C-5), 122.1 (pyridinyl C-3), 53.7 (C-2), 49.8 (C-7), 48.2 (C-1), 45.0 (C-4), 37.5 (C-3), 28.4 (C-6), 28.1 (C-5), 19.8 (methyl), 18.7 (methyl), 13.7 (methyl). All data is consistent with known literature values.[3]

***N*-[(1*R*,2*S*,4*R*,6*S*)-6-(3-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]pyridine-2-carboxamide (S6)**



Prepared according to General procedure E, picolinamide derivative **S5** (400 mg, 1.55 mmol) and 3-iodoanisole (0.76 ml, 6.20 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give arylated derivative **S6**[3] (276 mg, 50%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.23 (EtOAc–hexane 30:70). δ_H (500 MHz, $CDCl_3$): 8.23 (1H, d, *J* 4.4 Hz, pyridinyl 6-H), 7.95 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 7.85 (1H, br. d, *J* 8.9 Hz, NH), 7.69 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.28-7.25 (1H, m, pyridinyl 5-H), 7.22 (1H, t, *J* 7.9 Hz, methoxyphenyl 5-H), 7.02 (1H, s, methoxyphenyl 2-H), 7.00 (1H, d, *J* 7.9 Hz, methoxyphenyl 6-H), 6.75 (1H, dd, *J* 7.9 and 2.3 Hz, methoxyphenyl 4-H), 4.57-4.50 (1H, m, 2-H), 3.78 (3H, s, OMe), 3.32 (1H, dd, *J* 11.6 and 5.4 Hz, 6-H), 2.59-2.51 (1H, m, 3-H_A), 2.30-2.22 (1H, m, 5-H_A), 2.03 (1H, dd, *J* 13.3 and 5.4 Hz, 5-H_B), 1.93 (1H, t, *J* 4.6 Hz, 4-H), 1.29 (1H, dd, *J* 13.3 and 5.9 Hz, 3-H_B), 1.10 (3H, s, methyl), 1.09 (3H, s, methyl), 1.07 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 164.5 (C=O), 160.3 (methoxyphenyl C-3), 150.1 (pyridinyl C-1), 147.3 (pyridinyl C-6), 143.9 (methoxyphenyl C-1), 136.9 (pyridinyl C-4), 129.9 (methoxyphenyl C-5), 125.6 (pyridinyl C-5), 121.8 (pyridinyl C-3 and methoxyphenyl C-6), 114.2 (methoxyphenyl C-2), 111.6 (methoxyphenyl C-4), 55.2 (OMe), 54.4 (C-2 and C-1), 51.2 (C-7), 47.9 (C-6), 43.7 (C-4), 37.2 (C-3), 32.9 (C-5), 20.3 (methyl), 20.0 (methyl), 13.9 (methyl). All data is consistent with known literature values.[3]

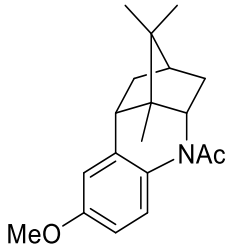
***N*-[(1*R*,2*S*,4*R*,6*S*)-6-(3-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]acetamide (16)**



Water (7.6 ml) and HCl (1.9 ml, 37%) were added to a solution of arylated derivative **S6** (276 mg, 0.76 mmol) in THF (7.6 ml) and the solution was stirred at rt for 5 mins. Zinc dust (741 mg, 11.4 mmol) was then added portionwise over 30 mins and the resulting suspension was stirred at rt for 18 h. The reaction mixture was filtered through celite (eluting with DCM) and then saturated aqueous $NaHCO_3$ (20 ml) was added to the filtrate. The phases were separated and the aqueous phase was extracted with DCM (3 x 20 ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This intermediate was dissolved in THF (10 ml) and the solution was then basified with 2M NaOH. Ac_2O (0.22 ml, 2.28 mmol) was added to this solution and the reaction mixture was then stirred at rt for 4 h. Water (20 ml) was added and the mixture was then extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *acetamide derivative* ***16*** (181 mg, 79%) as a colourless oil. R_f 0.42 (EtOAc–hexane 80:20). $[\alpha_D^{20}]$ +30.2 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3425, 2951, 1661, 1598, 1580, 1518, 1490, 1457, 1378, 1267, 1150, 1041; δ_H (500 MHz, $CDCl_3$): 7.31 (1H, t, *J* 8.0 Hz, methoxyphenyl 5-H), 7.04 (1H, d, *J* 7.4 Hz, methoxyphenyl 6-H), 6.94 (1H, s, methoxyphenyl 2-H), 6.81 (1H, dd, *J* 8.0 and 2.4 Hz, methoxyphenyl 4-H), 5.24 (1H, br. d, *J* 8.3 Hz, NH), 4.28-4.21 (1H, m, 2-H), 3.82 (3H, s, OMe), 3.26 (1H, dd, *J* 11.5 and 5.1 Hz, 6-H), 2.48-2.39 (1H, m, 3-H_A), 2.24-2.15 (1H, td, *J* 13.2 and 4.0 Hz, 5-H_A), 1.96 (1H, dd, *J* 13.2 and 5.8 Hz, 5-H_B), 1.87 (1H, t, *J* 4.7 Hz, 4-H), 1.35 (3H, s, acetyl), 1.07 (1H, dd, *J* 13.4 and 5.8 Hz, 3-H_B), 1.04 (3H, s, methyl) 1.01 (6H, s, dimethyl); δ_C (125 MHz, $CDCl_3$): 169.6 (C=O), 160.1 (methoxyphenyl C-3), 144.8 (methoxyphenyl C-1), 129.8 (methoxyphenyl C-5), 122.2 (methoxyphenyl C-6), 115.4 (methoxyphenyl C-2), 111.6 (methoxyphenyl C-4), 55.4 (OMe), 54.4 (C-2), 54.2 (C-1), 50.9

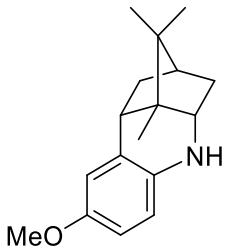
(C-7), 47.7 (C-6), 43.7 (C-4), 37.1 (C-3), 32.3 (C-5), 23.1 (acetyl), 20.2 (methyl), 19.9 (methyl), 13.9 (methyl); HRMS found MH^+ 302.2119. $C_{19}H_{27}NO_2$ requires *MH*, 302.2115.

1-[(2*R*,3a*S*,9*R*,9a*R*)-7-methoxy-1,1,9a-trimethyl-1,2,3,3a,9,9a-hexahydro-4*H*-2,9-methanocyclopenta[*b*]quinilin-4-yl]ethanone (S7)



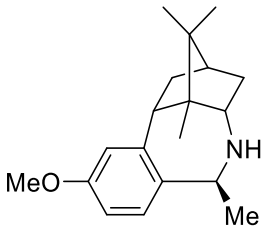
NBS (59 mg, 0.33 mmol) was added to a solution of acetamide derivative **16** (91.0 mg, 0.30 mmol) in MeCN (5 ml) at rt and stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure to give the crude *p*-bromo intermediate. This intermediate was dissolved in toluene (5 ml) and $Pd(OAc)_2$ (3.00 mg, 5 mol%), *rac*-BINAP (14.0 mg, 7.5 mol%) and NaO^tBu (57.6 mg, 0.60 mmol) were then added sequentially at rt. The reaction mixture was then stirred at 100 ^oC for 24 h, cooled to rt and filtered through celite (eluting with DCM). The filtrate was then concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *cyclised acetamide derivative **S7*** (42.0 mg, 47%) as a colourless oil. R_f 0.55 (EtOAc–hexane 50:50). $[\alpha_D^{20}]$ +2.00 (c 0.01, MeOH); ν_{max}/cm^{-1}: 2949, 2878, 1652, 1500, 1462, 1369, 1301, 1273, 1240, 1145, 1110, 1048; δ_H (500 MHz, $CDCl_3$): 6.72 (1H, dd, *J* 9.0 and 2.9 Hz, 6-H), 6.64 (1H, d, *J* 2.9 Hz, 8-H), 3.78 (3H, s, OMe), 2.87 (1H, dt, *J* 9.3 and 2.4 Hz, 9-H), 2.45-2.33 (2H, m, 3-H_A and 10-H_A), 2.32 (3H, s, acetyl), 1.65 (1H, t, *J* 4.2 Hz, 2-H), 1.02 (3H, s, methyl), 1.00-0.93 (5H, m, 3-H_B, 10-H_B and methyl), 0.77 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 171.1 (C=O), 156.3 (C-7), 133.6 (C-4a), 126.7 (C-8a), 124.9 (C-5), 114.3 (C-8), 111.6 (C-6), 56.4 (C-3a), 55.5 (OMe), 48.9 (C-9a), 45.2 (C-1), 42.9 (C-2), 42.4 (C-9), 40.8 (C-3 and C-10), 24.6 (acetyl CH_3), 19.7 (methyl), 18.9 (methyl), 12.4 (methyl); HRMS found MNa^+ 322.1777. $C_{19}H_{25}NO_2$ requires *MNa*, 322.1778. 5-H and 3a-H are not observed by ^1H NMR (500 MHz, $CDCl_3$).

(2*R*,3a*S*,9*R*,9a*R*)-7-methoxy-1,1,9a-trimethyl-1,2,3,3a,9,9a-hexahydro-1*H*-2,9-methanocyclopenta[*b*]quiniline (17)



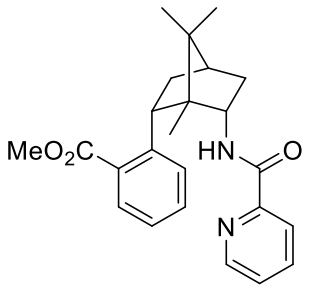
Cyclised acetamide derivative **S7** (40.0 mg, 0.13 mmol) was dissolved in 1:1 HCl–EtOH (10 ml) and stirred at 80 °C for 18 h. The reaction mixture was allowed to cool to rt then concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–MeOH 95:5 to give the *amine derivative **17*** (21.0 mg, 67%) as an off-white solid. R_f 0.67 (EtOAc–MeOH 90:10). [α_D^{20}] +6.00 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3339, 2918, 2850, 1504, 1462, 1256, 1072; δ_H (500 MHz, $CDCl_3$): 6.66-6.60 (2H, m, 5-H and 8-H), 6.51 (1H, d, *J* 8.3 Hz, 6-H), 3.74 (3H, s, OMe), 3.50-3.43 (1H, m, 3a-H), 2.78 (1H, dt, *J* 9.0 and 2.8 Hz, 9-H), 2.45-2.38 (1H, m, 10-H_A), 2.31-2.23 (1H, m, 3-H_A), 1.52 (1H, t, *J* 4.3 Hz. 2-H), 1.24 (1H, br. s, NH), 1.04-0.95 (5H, m, 10-H_B, 3-H_B and methyl), 0.93 (3H, s, methyl), 0.73 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 151.7 (C-7), 143.7 (C-4a), 124.9 (C-8a), 115.3 (C-8), 114.3 (C-6), 113.2 (C-5), 55.9 (OMe), 55.8 (C-3a), 48.9 (C-9a), 42.8 (C-1), 41.7 (C-9), 41.3 (C-2), 40.0 (C-10), 38.8 (C-3), 19.8 (methyl), 19.2 (methyl), 12.8 (methyl); HRMS found MH^+ 258.1867. $C_{17}H_{23}NO$ requires *MH*, 258.1852. The product was isolated as the HCl salt.

(2*R*,3a*S*,5*S*,10*S*,10a*R*)-8-methoxy-1,1,5,10a-tetramethyl-1,2,3,3a,4,5,10,10a-octahydro-2,10-methanobenzo[*e*]cyclopenta[*b*]azepine (18)



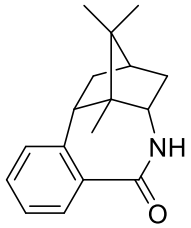
Acetamide derivative **16** (80.0 mg, 0.27 mmol) was dissolved in MeCN (4 ml) and $POCl_3$ (0.25 ml, 2.70 mmol) was added dropwise at rt. The resulting solution was stirred and heated at 100 ^oC for 2 h. The reaction mixture was cooled to rt and then all the volatiles were removed under reduced pressure. The residue was dissolved in DCM (10 ml) then water (5 ml) and 5M NaOH was added to basify the solution. This was then extracted with DCM (3 x 20 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude imine intermediate. This intermediate was dissolved in MeOH (4 ml) and $NaBH_4$ (21.0 mg, 0.54 mmol) was added at rt. The solution was allowed to stir for 2 h then 1M HCl (5 ml) was added to quench the reaction. This solution was basified with 5M NaOH then extracted with DCM (3 x 20 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–MeOH 95:5 to give the *cyclised amine derivative* ***18*** (47.0 mg, 62%, *dr* >95:<5 by ^1H NMR) as a white solid. R_f 0.10 (EtOAc–MeOH 95:5). $[\alpha_D^{20}]$ +39.7 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3332, 2944, 2833, 1606, 1580, 1506, 1461, 1282, 1239, 1147, 1089; δ_H (500 MHz, $CDCl_3$): 7.16 (1H, d, *J* 9.2 Hz, 6-H), 6.70-6.65 (2H, m, 7-H and 9-H), 4.42 (1H, q, *J* 6.5 Hz, 5-H), 3.78 (3H, s, OMe), 3.48 (1H, d, *J* 9.7 Hz, 3a-H), 2.98 (1H, dd, *J* 10.6 and 7.9 Hz, 10-H), 2.35-2.07 (3H, m, 3-H_A, 11-H_A and NH), 1.82 (1H, t, *J* 4.1 Hz, 2-H), 1.72-1.62 (2H, m, 3-H_B and 11-H_B), 1.50 (3H, d, *J* 6.5 Hz, 5-methyl), 1.00 (3H, s, methyl), 0.94 (3H, s, methyl), 0.66 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 157.9 (C-8), 142.9 (C-9a), 138.4 (C-5a), 125.4 (C-6), 119.4 (C-9), 110.1 (C-7), 63.6 (C-3a), 55.3 (OMe), 52.5 (C-10), 49.2 (C-10a), 48.4 (C-1), 45.1 (C-5), 43.3 (C-2), 33.5 (C-3), 32.1 (C-11), 21.6 (methyl C-5), 19.9 (methyl), 19.8 (methyl), 13.0 (methyl); HRMS found MH^+ 286.2171. $C_{19}H_{27}NO$ requires *MH*, 286.2165. The configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 5-H and 3-H_B (500 MHz, $CDCl_3$).

methyl 2-[(1*R*,2*S*,4*R*,6*S*)-6-(pyridine-2-carboxyamidyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]benzoate (19)



Prepared according to General procedure E, picolinamide derivative **S5** (200 mg, 0.78 mmol) and methyl 2-bromobenzoate (670 mg, 3.10 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:60 to give the *arylated ester derivative* ***19*** (160 mg, 53%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.29 (EtOAc–hexane 40:60). [α_D^{20}] +16.2 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3364, 2948, 1713, 1663, 1595, 1569, 1508, 1437, 1428, 1395, 1385, 1255, 1210, 1128, 1040; δ_H (500 MHz, $CDCl_3$): 8.22 (1H, ddd, *J* 4.1, 1.7 and 1.0 Hz, pyridinyl 6-H), 7.95 (1H, dt, *J* 7.8 and 1.0 Hz, pyridinyl 3-H), 7.87 (1H, d, *J* 7.7 Hz, phenyl 6-H), 7.70 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.67 (1H, br. s, NH), 7.63 (1H, dd, J 7.7 and 1.5 Hz, phenyl 3-H), 7.55 (1H, td, *J* 7.7 and 1.5 Hz, phenyl 5-H), 7.30-7.27 (1H, m, phenyl 4-H), 7.27-7.24 (1H, m, pyridinyl 5-H), 4.65 (1H, dd, *J* 11.8 and 5.7 Hz, 2-H), 4.48 (1H, app. dddd, *J* 11.2, 9.2, 6.3 and 1.7 Hz, 6-H), 3.84 (3H, s, CO_2Me), 2.58 (1H, app. dddd, *J* 13.5, 11.2, 4.6 and 3.3 Hz, 5-H_A), 2.35 (1H, tt, *J* 13.1 and 3.8 Hz, 3-H_A), 2.03 (1H, dd, *J* 13.1 and 5.7 Hz, 3-H_B), 1.97 (1H, t, *J* 4.6 Hz, 4-H), 1.39 (1H, dd, *J* 13.5 and 6.3 Hz, 5-H_B), 1.13 (3H, s, methyl), 1.08 (3H, s, methyl), 0.83 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 170.1 (C=O ester), 164.5 (C=O amide), 149.9 (pyridinyl C-2), 147.3 (pyridinyl C-6), 142.4 (phenyl C-1), 137.0 (pyridinyl C-4), 133.4 (phenyl C-2), 132.3 (phenyl C-5), 130.6 (phenyl C-3), 129.5 (phenyl C-6), 125.7 (pyridinyl C-5), 125.6 (phenyl C-4), 121.9 (pyridinyl C-3), 55.8 (C-1), 55.2 (C-6), 52.1 (CO_2Me), 51.4 (C-7), 44.0 (C-4), 41.1 (C-2), 36.7 (C-5), 33.9 (C-3), 20.4 (methyl), 20.1 (methyl), 12.6 (methyl); HRMS found MH^+ 393.2182. $C_{24}H_{28}N_2O_3$ requires *MH*, 393.2173. The configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 2-H and 7-methyl and nOe observed between 6-H and 7-methyl (500 MHz, $CDCl_3$).

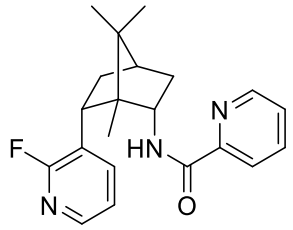
(2*R*,3a*S*,10*S*,10a*R*)-1,1,10a-trimethyl-2,3,3a,4,10,10a-hexahydro-2,10-methanobenzo[*e*]cyclopenta[*b*]azepin-5(1*H*)-one (20)



Water (4.3 ml) and HCl (0.96 ml, 37%) were added to a solution of arylated ester derivative **19** (150 mg, 0.38 mmol) in THF (15 ml). The reaction mixture was stirred at rt for 5 mins then

zinc powder (373 mg, 5.74 mmol) was added portionwise over 30 mins. The resulting suspension was stirred at rt for 18 h. The reaction mixture was filtered through celite (eluting with THF) then the filtrate was basified with 5M NaOH solution and the resulting solution allowed to stir at rt for a further 18 h. This was then extracted with DCM (3 x 30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 40:60 to give the *lactam derivative* ***20*** (69.0 mg, 71%) as a white solid. R_f 0.46 (EtOAc–hexane 70:30). $[\alpha_D^{20}]$ +17.7 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3283, 3050, 2950, 2875, 1645, 1452, 1392, 1372, 1353, 1259, 1208, 1161, 1129, 1029; δ_H (500 MHz, $CDCl_3$): 8.51 (1H, dd, *J* 8.1 and 1.6 Hz, 6-H), 7.41 (1H, td, *J* 7.7 and 1.6 Hz, 8-H), 7.30 (1H, ddd, *J* 8.1, 7.7 and 1.4 Hz, 7-H), 7.18 (1H, dd, *J* 7.7 and 1.4 Hz, 9-H), 6.44 (1H, br. d, *J* 5.7 Hz, NH), 3.71-3.65 (1H, m, 3a-H), 3.48 (1H, ddd, *J* 12.6, 6.2 and 2.6 Hz, 10-H), 2.53 (1H, tt, *J* 12.6 and 4.0 Hz, 11-H_A), 2.45-2.38 (1H, m, 3-H_A), 1.73 (1H, t, *J* 4.7 Hz, 2-H), 1.19 (1H, dd, *J* 13.0 and 5.6 Hz, 3-H_B), 1.14 (1H, dd, *J* 12.6 and 6.2 Hz, 11-H_B), 1.09 (3H, s, methyl), 0.99 (3H, s, methyl), 0.91 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 167.9 (C=O), 143.8 (C-9a), 133.7 (C-6), 132.4 (C-9), 132.1 (C-8), 128.8 (C-5a), 126.1 (C-7), 59.0 (C-3a), 51.5 (C-10), 50.4 (C-10a), 47.8 (C-1), 41.3 (C-2), 40.9 (C-11), 39.5 (C-3), 20.0 (methyl), 19.9 (methyl), 13.1 (methyl); HRMS found MH^+ 256.1692. $C_{17}H_{21}NO$ requires *MH*, 256.1696.

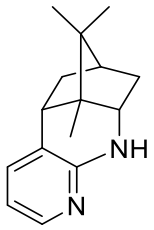
_N_-[(1_R_,2_S_,4_R_,6_R_)-6-(2-fluoropyridin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl]pyridine-2-carboxamide (21)



Prepared according to General procedure E, picolinamide derivative **S5** (200 mg, 0.78 mmol) and 2-fluoro-3-iodopyridine (691 mg, 3.10 mmol) gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 35:65 to give *arylated derivative* ***21*** (118 mg, 42%, *dr* >95:<5 by ^1H NMR) as a colourless oil. R_f 0.17 (EtOAc–hexane 40:60). $[\alpha_D^{20}]$

+2.50 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3387, 3057, 2957, 1676, 1595, 1570, 1517, 1461, 1398, 1345, 1279, 1241, 1163, 1070; δ_H (500 MHz, $CDCl_3$): 8.23 (1H, d, *J* 4.5 Hz, pyridinyl 6-H), 8.06 (1H, d, *J* 4.8 Hz, fluoropyridinyl 6-H), 8.03 (1H, t, *J* 7.9 Hz, fluoropyridinyl 4-H), 7.98 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 7.72 (1H, td, *J* 7.8 and 1.6 Hz, pyridinyl 4-H), 7.69 (1H, br. s, NH), 7.30 (1H, ddd, *J* 7.8, 4.5 and 0.8 Hz, pyridinyl 5-H), 7.22-7.18 (1H, m, fluoropyridinyl 5-H), 4.53-4.47 (1H, m, 2-H), 3.57 (1H, dd, *J* 11.8 and 5.6 Hz, 6-H), 2.66-2.58 (1H, m, 3-H_A), 2.29 (1H, tt, *J* 12.9 and 3.7 Hz, 5-H_A), 2.00-1.93 (2H, m, 5-H_B and 4-H), 1.36 (1H, dd, *J* 13.5 and 6.0 Hz, 3-H_B), 1.12 (3H, s, methyl), 1.11 (3H, s, methyl), 1.06 (3H, d, *J* 4.0 Hz, methyl); δ_C (125 MHz, $CDCl_3$): 164.3 (C=O), 162.5 (d, *J* 239.4 Hz, fluoropyridinyl C-2), 149.6 (pyridinyl C-2), 147.4 (pyridinyl C-6), 144.8 (d, *J* 15.2 Hz, fluoropyridinyl C-6), 141.2 (d, *J* 5.0 Hz, fluoropyridinyl C-4), 137.2 (pyridinyl C-4), 125.9 (pyridinyl C-5), 124.8 (d, *J* 29.0 Hz, fluoropyridinyl C-3), 122.1 (d, *J* 4.1 Hz, fluoropyridinyl 5-H), 121.9 (pyridinyl C-3), 55.5 (C-1), 54.9 (C-2), 51.4 (C-7), 43.8 (C-4), 41.2 (C-6), 36.9 (C-3), 33.2 (C-5), 20.3 (methyl), 19.9 (methyl), 13.5 (methyl); δ_F (470 MHz, $CDCl_3$): -66.3 (pyridinyl CF); HRMS found MH^+ 354.1993. $C_{21}H_{24}FN_3O$ requires *MH*, 354.1976. The configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 2-H and 7-methyl and nOe observed between 6-H and 7-methyl (500 MHz, $CDCl_3$).

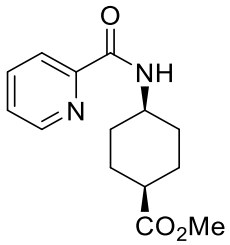
(5*R*,5a*R*,7*R*,8a*S*)-5a,6,6-trimethyl-5a,6,7,8,8a,9-hexahydro-5*H*-5,7-methanocyclopenta[*b*][1,8]naphthyridine (22)



Water (3.5 ml) and HCl (0.78 ml, 37%) were added to a solution of arylated derivative **21** (110 mg, 0.31 mmol) in THF (15 ml) at rt. The solution was stirred at rt for 5 mins then zinc powder (304 mg, 4.67 mmol) was added portionwise over 30 mins. The resulting suspension was stirred at rt for 18 h. The reaction mixture was filtered through celite (eluting with EtOAc) and saturated aqueous $NaHCO_3$ solution (10 ml) was added to the filtrate. This was then extracted

with DCM (3 x 20 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc to give the *fused-ring pyridine derivative* ***22*** (40.0 mg, 55%) as a white solid. R_f 0.26 (EtOAc). [$\alpha_{D^{20}}$] +34.8 (c 0.01, MeOH); ν_{max}/cm^{-1}: 3329, 2948, 2928, 2871, 1602, 1537, 1456, 1389, 1323, 1289, 1162, 1077; δ_H (500 MHz, $CDCl_3$): 7.86 (1H, dd, *J* 5.1 and 1.0 Hz, 2-H), 7.27-7.23 (1H, m, 4-H, overlaps with residual chloroform peak), 6.52 (1H, dd, *J* 6.8 and 5.1 Hz, 3-H), 5.80 (1H, br. s, NH), 3.63-3.56 (1H, m, 8a-H), 2.83 (1H, dt, *J* 8.6 and 3.3 Hz, 5-H), 2.45 (1H, tt, *J* 12.3 and 3.8 Hz, 10-H_A), 2.40-2.33 (1H, m, 8-H_A), 1.56 (1H, t, *J* 4.3 Hz, 7-H), 1.00 (3H, s, methyl), 0.99-0.93 (5H, m, 10-H_B, 8-H_B and methyl), 0.72 (3H, s, methyl); δ_C (125 MHz, $CDCl_3$): 151.7 (C-9a), 144.3 (C-2), 137.7 (C-4), 120.2 (C-4a), 112.4 (C-3), 55.7 (C-8a), 48.9 (C-5a), 42.8 (C-6), 41.3 (C-5), 41.0 (C-7), 39.7 (C-8), 39.3 (C-10), 19.6 (methyl), 19.3 (methyl), 12.7 (methyl); HRMS found MH^+ 229.1705. $C_{15}H_{20}N_2$ requires *MH*, 229.1699.

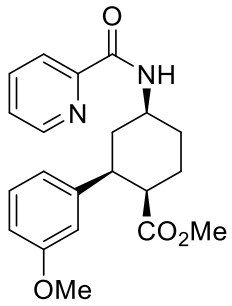
methyl (1*R,4*R**)-4-[(pyridine-2-carbonyl)amino]cyclohexane-1-carboxylate (S8)**



Prepared according to an adapted General procedure C, *cis*-4-amino-cyclohexanecarboxylic acid methyl ester hydrochloride (1.00 g, 5.18 mmol) followed by addition of a saturated aqueous solution of $NaHCO_3$ instead of 5M NaOH gave a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give picolinamide derivative **S8**[4] (1.24 g, 91%) as a colourless oil. R_f 0.20 (EtOAc–hexane 40:60). δ_H (500 MHz, $CDCl_3$): 8.54 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.18 (1H, dt, *J* 7.7 and 1.2 Hz, pyridinyl 3-H), 8.12 (1H, br. d, *J* 6.6 Hz, NH), 7.83 (1H, td, *J* 7.7 and 1.7 Hz, pyridinyl 4-H), 7.41 (1H, ddd, *J* 7.7, 4.8 and 1.2 Hz, pyridinyl 5-H), 4.18-4.11 (1H, m, 4-H), 3.70 (1H, s, CO_2Me), 2.56-2.50 (1H, m, 1-H), 2.02-1.93 (2H, m, 2-H_A and 6-H_A), 1.85-1.69 (6H, m, 2-H_B, 6-H_B, 3-H_2 and 5-H_2); δ_C (125 MHz, $CDCl_3$): 175.7 (C=O ester), 163.6 (C=O amide), 150.2 (pyridinyl C-2), 148.2 (pyridinyl C-6), 137.4 (pyridinyl C-4), 126.2 (pyridinyl C-5), 122.2

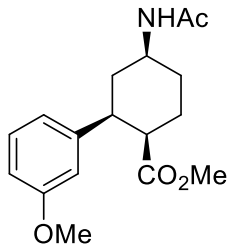
(pyridinyl C-3), 51.8 (CO_2Me), 45.9 (C-4), 40.4 (C-1), 29.6 (C_2-3,5), 25.2 (C_2-2,6). All data is consistent with known literature values.[4]

methyl (1*R,2*S**,4*S**)-4-[(pyridine-2-carbonyl)amino]-2-(3-methoxyphenyl)cyclohexane-1-carboxylate (S9)**



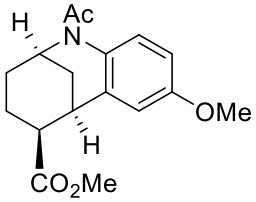
Prepared according to General procedure D, picolinamide derivative **S8** (200 mg, 0.76 mmol) and 3-iodoanisole (0.55 ml, 4.58 mmol) gave a crude material. This was then purified *via* column chromatography eluting with EtOAc–hexane 25:75 to give *arylated derivative **S9*** (243 mg, 87%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.22 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3377, 2944, 2864, 1726, 1669, 1585, 1516, 1433, 1239, 1158; δ_H (500 MHz, $CDCl_3$): 8.56 (1H, d, *J* 4.8 Hz, pyridinyl 6-H), 8.20 (1H, d, *J* 7.7 Hz, pyridinyl 3-H), 8.11 (1H, br. d, *J* 8.4 Hz, NH), 7.84 (1H, td, *J* 7.7 and 1.5 Hz, pyridinyl 4-H), 7.42 (1H, dd, *J* 7.7 and 4.8 Hz, pyridinyl 5-H), 7.19 (1H, t, *J* 7.7 Hz, methoxyphenyl 5-H), 6.80 (1H, d, *J* 7.7 Hz, methoxyphenyl 6-H), 6.78-6.72 (2H, m, methoxyphenyl 2-H and methoxyphenyl 4-H), 4.17 (1H, tdt, *J* 12.2, 8.4 and 4.1 Hz, 4-H), 3.78 (3H, s, OMe), 3.45 (3H, s, CO_2Me), 3.05-2.96 (2H, m, 1-H and 2-H), 2.47 (1H, app. q, *J* 12.2 Hz, 3-H_A), 2.17-2.11 (2H, m, 3-H_B and 5-H_A), 2.03-1.81 (3H, m, 5-H_B and 6-H_2); δ_C (125 MHz, $CDCl_3$): 174.3 (C=O ester), 163.6 (C=O amide), 159.7 (methoxyphenyl C-3), 150.2 (pyridinyl C-2), 148.2 (pyridinyl C-6), 144.6 (methoxyphenyl C-1), 137.5 (pyridinyl C-4), 129.3 (methoxyphenyl C-5), 126.2 (pyridinyl C-5), 122.4 (pyridinyl C-3), 119.8 (methoxyphenyl C-6), 113.3 (methoxyphenyl C-2), 112.1 (methoxyphenyl C-4), 55.3 (OMe), 51.2 (CO_2Me), 48.5 (C-4), 44.8 (C-1), 44.0 (C-2), 32.6 (C-3), 28.2 (C-6), 28.0 (C-5); HRMS found MH^+ 369.1818. $C_{21}H_{24}N_2O_4$ requires *MH*, 369.1809. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between CO_2Me and methoxyphenyl 2-H and nOe observed between 2-H and 4-H (500 MHz, $CDCl_3$).

methyl (1*R,2*S**,4*S**)-4-acetamido-2-(3-methoxyphenyl)cyclohexane-1-carboxylate (23)**



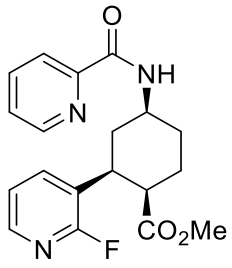
Water (7.40 ml) was added to arylated derivative **S9** (240 mg, 0.65 mmol) in THF (7.40 ml) then HCl (1.64 ml, 37%) was added and the solution stirred for 5 mins at rt. Then zinc powder (636 mg, 9.78 mmol) was added portionwise and the resulting suspension allowed to stir at rt for a further 2 h. The reaction mixture was filtered through celite (eluting with EtOAc) then saturated aqueous $NaHCO_3$ (20 ml) was added to the filtrate. The phases were separated and the aqueous phase extracted with EtOAc (3 x 30 ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This was dissolved in DCM (20 ml) then Et_3N (0.91 ml, 6.50 mmol) and Ac_2O (0.61 ml, 6.50 mmol) were added sequentially. The reaction mixture was then stirred at rt for 18 h then saturated aqueous NH_4Cl (20 ml) was added to the reaction mixture. The phases were separated and the aqueous phase extracted with DCM (3 x 30 ml). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 75:25 → 100% EtOAc to give *acetamide derivative* ***23*** (108 mg, 54%) as a colourless oil. R_f 0.24 (EtOAc). ν_{max}/cm^{-1}: 3277, 2935, 2836, 1728, 1651, 1527, 1434, 1293, 1166; δ_H (500 MHz, $CDCl_3$): 7.19 (1H, t, *J* 7.8 Hz, phenyl 5-H), 6.78-6.72 (3H, m, phenyl 2-H, phenyl 4-H and phenyl 6-H), 5.44 (1H, br. d, *J* 8.1 Hz, NH), 4.10-3.91 (1H, m, 4-H), 3.78 (3H, s, OMe), 3.43 (3H, s, CO_2Me), 2.96-2.91 (2H, m, 1-H and 2-H), 2.27 (1H, app. q, *J* 12.2 Hz, 3-H_A), 2.09-2.01 (2H, m, 3-H_B and 5-H_A), 1.98 (3H, s, acetyl), 1.92-1.86 (1H, m, 6-H_A), 1.83 (1H, dt, *J* 13.5 and 4.1 Hz, 6-H_B), 1.71-1.60 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 174.4 (C=O ester), 169.3 (C=O amide), 159.7 (phenyl C-3), 144.5 (phenyl C-1), 129.3 (phenyl C-5), 119.7 (phenyl C-6), 113.3 (phenyl C-2), 112.0 (phenyl C-4), 55.3 (OMe), 51.2 (CO_2Me), 48.5 (C-4), 44.7 (C-1), 44.0 (C-2), 32.7 (C-3), 28.0 (C-6), 27.9 (C-5), 23.8 (acetyl CH_3); HRMS found MH^+ 306.1700. $C_{17}H_{23}NO_4$ requires *MH*, 306.1700.

methyl (2*R,5*S**,6*R**)-1-acetyl-8-methoxy-1,2,3,4,5,6-hexahydro-2,6-methano-1-benzazocine-5-carboxylate (24)**



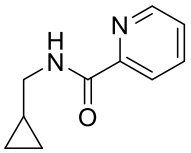
Acetamide derivative **23** (81.0 mg, 0.27 mmol) was dissolved in MeCN (5 ml) then NBS (52.0 mg, 0.29 mmol) was added and the reaction mixture left to stir at rt for 18 h. The volatiles were removed under reduced pressure to give the crude brominated intermediate. This was then dissolved in toluene (2 ml) and added to a pressure vial. Then $Pd(OAc)_2$ (3.00 mg, 5 mol%), *rac*-BINAP (13.0 mg, 7.5 mol%) and Cs_2CO_3 (176 mg, 0.54 mmol) were added sequentially and the resulting reaction mixture stirred at 100 ^oC for 24 h. The reaction mixture was allowed to cool to room temperature, filtered through celite (eluting with DCM) and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 50:50 to give the *cyclised acetamide derivative **24*** (35.0 mg, 43%) as a colourless oil. R_f 0.58 (EtOAc). ν_{max}/cm^{-1}: 2993, 2835, 1730, 1649, 1493, 1434, 1305, 1264, 1176, 1049; δ_H (500 MHz, $CDCl_3$): 6.73 (1H, dd, *J* 9.2 and 3.0 Hz, 9-H), 6.52 (1H, d, *J* 3.0 Hz, 7-H), 4.59 (1H, app. br. s, 2-H), 3.74 (3H, s, OMe), 3.69 (3H, s, CO_2Me), 3.50 (1H, d, *J* 2.8 Hz, 6-H), 2.73 (1H, dt, *J* 12.8 and 3.6 Hz, 5-H), 2.35 (3H, s, acetyl), 2.15 (1H, br. d, *J* 13.5 Hz, 3-H_A), 1.99 (2H, app. s, 11-H_2), 1.76-1.70 (1H, m, 4-H_A), 1.60 (1H, app. t, *J* 13.5 Hz, 3-H_B), 1.38 (1H, qd, *J* 13.7 and 4.0 Hz, 4-H_B); δ_C (125 MHz, $CDCl_3$): 173.7 (C=O ester), 170.7 (C=O amide), 155.1 (C-8), 133.2 (C-10a), 129.7 (C-10), 123.1 (C-6a), 114.1 (C-7), 112.6 (C-9), 55.5 (OMe), 51.7 (CO_2Me), 49.1 (C-2), 48.2 (C-5), 36.7 (C-6), 31.3 (C-11), 31.0 (C-3), 25.1 (acetyl CH_3), 19.5 (C-4); HRMS found MH^+ 304.1544. $C_{17}H_{21}NO_4$ requires *MH*, 304.1543. 10-H is not observed by ^1H NMR (500 MHz, $CDCl_3$).

methyl (1*R,2*S**,4*S**)-2-(2-fluoropyridin-3-yl)-4-[(pyridine-2-carbonyl)amino]cyclohexane-1-carboxylate (25)**



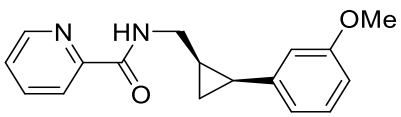
Prepared according to General procedure D, picolinamide derivative **S9** (200 mg, 0.76 mmol) and 2-fluoro-3-iodopyridine (1.02 g, 4.58 mmol) gave a crude material. This was then purified *via* column chromatography eluting with EtOAc–hexane 40:60 to give the *arylated derivative* ***25*** (105 mg, 39%, *dr* >95:<5 by ^{1}H NMR) as a pale-yellow solid. R_f 0.13 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3386, 2845, 1733, 1670, 1520, 1205; δ_H (500 MHz, $CDCl_3$): 8.57 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.20 (1H, dt, *J* 7.8 and 1.2 Hz, pyridinyl 3-H), 8.10 (1H, br. d, *J* 8.4 Hz, NH), 8.07 (1H, dt, *J* 4.7 and 1.5 Hz, fluoropyridinyl 6-H), 7.86 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.73-7.68 (1H, m, fluoropyridinyl 4-H), 7.44 (1H, ddd, *J* 7.8, 4.8 and 1.2 Hz, pyridinyl 5-H), 7.15-7.11 (1H, m, fluoropyridinyl 5-H), 4.19 (1H, tdt, *J* 12.4, 8.4 and 4.1 Hz, 4-H), 3.45 (3H, s, CO_2Me), 3.29 (1H, dt, *J* 13.1 and 3.8 Hz, 2-H), 3.16-3.13 (1H, m, 1-H), 2.46 (1H, q, *J* 12.2 Hz, 3-H_A), 2.23 (1H, dq, *J* 14.0 and 6.1 Hz, 6-H_A), 2.16-2.11 (1H, m, 3-H_B), 2.07-2.01 (1H, m, 5-H_A), 2.01-1.93 (1H, m, 6-H_B), 1.74 (1H, qd, *J* 12.7 and 4.1 Hz, 5-H_B); δ_C (125 MHz, $CDCl_3$): 173.7 (C=O ester), 163.7 (C=O amide), 161.5 (d, *J* 238.1 Hz, fluoropyridinyl C-2), 150.1 (pyridinyl C-2), 148.2 (pyridinyl C-6), 145.6 (d, *J* 15.1 Hz, fluoropyridinyl C-6), 139.4 (d, *J* 5.2 Hz, fluoropyridinyl C-4), 137.6 (pyridinyl C-4), 126.4 (pyridinyl C-5), 124.8 (d, *J* 29.0 Hz, fluoropyridinyl C-3), 122.4 (pyridinyl C-3), 121.4 (d, *J* 4.1 Hz, fluoropyridinyl C-5), 51.3 (CO_2Me), 48.4 (C-4), 42.2 (C-1), 36.6 (d, *J* 2.5 Hz, C-2), 31.7 (C-3), 28.2 (C-5), 28.0 (C-6); δ_F (470 MHz, $CDCl_3$): -72.5 (pyridinyl CF) HRMS found MH^+ 358.1573. $C_{19}H_{20}FN_3O_3$ requires *MH*, 358.1561. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between CO_2Me and fluoropyridinyl 4-H and nOe observed between 2-H and 4-H (500 MHz, $CDCl_3$).

***N*-(cyclopropylmethyl)pyridine-2-carboxamide (S10)**



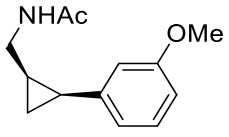
A mixture of picolinic acid (2.08 g, 16.9 mmol), cyclopropanemethylamine (1.00 g, 14.1 mmol) and Et_3N (3.92 ml, 28.2 mmol) were dissolved in DCM (20 ml). $POCl_3$ (2.63 ml, 28.2 mmol) was added dropwise at 0 ^oC then the reaction mixture was stirred at rt for 2 h. DCM (20 ml) and 1M NaOH (30 ml) were added at 0 ^oC, then the phases were separated and the aqueous phase extracted with DCM (3 x 30 ml). The organic phases were combined, washed with water (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the picolinamide derivative **S10**[5] (1.75 g, 71%) as a white solid. R_f 0.30 (EtOAc–hexane 30:70). δ_H (500 MHz, $CDCl_3$): 8.57 (1H, dd, *J* 4.7 and 0.7 Hz, pyridinyl 6-H), 8.21 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 8.13 (1H, br. s, NH), 7.85 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.42 (1H, ddd, *J* 7.2, 4.7 and 0.7 Hz, pyridinyl 5-H), 3.35 (2H, app. t, *J* 6.8 Hz, cyclopropylmethyl 1-H_2), 1.13-1.04 (1H, m, cyclopropylmethyl 2-H), 0.59-0.54 (2H, m, cyclopropylmethyl 3-H_A and cyclopropylmethyl 4-H_A), 0.34-0.26 (2H, m, cyclopropylmethyl 3-H_B and cyclopropylmethyl 4-H_B); δ_C (125 MHz, $CDCl_3$): 164.3 (C=O), 150.3 (pyridinyl C-2), 148.2 (pyridinyl C-6), 137.5 (pyridinyl C-4), 126.2 (pyridinyl C-5), 122.4 (pyridinyl C-3), 44.4 (cyclopropylmethyl C-1), 10.9 (cyclopropylmethyl C-2), 3.7 (cyclopropylmethyl C-3 and cyclopropylmethyl C-4). All data is consistent with known literature values.[5]

***N*-{[(1*R**,2*S**)-2-(3-methoxyphenyl)cyclopropyl]methyl}pyridine-2-carboxamide (26)**



Prepared according to General procedure F, picolinamide derivative **S10** (200 mg, 1.14 mmol) and 3-iodoanisole (0.15 ml, 1.25 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 20:80 to give the *arylated derivative* ***26*** (220 mg, 68%, *dr* >95:<5 by ^{1}H NMR) as a white solid. R_f 0.27 (EtOAc–hexane 30:70). ν_{max}/cm^{-1}: 3354, 3008, 2936, 1659, 1519, 1431, 1238, 1160, 1044; δ_H (500 MHz, $CDCl_3$): 8.53 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.15 (1H, dt, *J* 7.8 and 1.2 Hz, pyridinyl 3-H), 7.96 (1H, br. s, NH), 7.82 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.40 (1H, ddd, *J* 7.8, 4.8 and 1.2 Hz, pyridinyl 5-H), 7.22 (1H, t, *J* 7.9 Hz, methoxyphenyl 5-H), 6.89-6.84 (2H, m, methoxyphenyl 6-H and methoxyphenyl 2-H), 6.76 (1H, dd, *J* 7.9 and 2.5 Hz, methoxyphenyl 4-H), 3.81 (3H, s, OMe), 3.44-3.37 (1H, m, cyclopropylmethyl 1-H_A), 3.05-2.98 (1H, m, cyclopropylmethyl 1-H_B), 2.29 (1H, td, *J* 8.3 and 6.3 Hz, 2-H), 1.55-1.47 (1H, m, 1-H), 1.07 (1H, td, *J* 8.3 and 5.4 Hz, 3-H_A), 0.94 (1H, dd, *J* 11.4 and 5.4 Hz, 3-H_B); δ_C (125 MHz, $CDCl_3$): 164.2 (C=O), 159.8 (methoxyphenyl C-3), 150.2 (pyridinyl C-2), 148.1 (pyridinyl C-6), 139.9 (methoxyphenyl C-1), 137.4 (pyridinyl C-4), 129.4 (methoxyphenyl C-5), 126.1 (pyridinyl C-5), 122.3 (pyridinyl C-3), 121.5 (methoxyphenyl C-6), 114.8 (methoxyphenyl C-2), 112.2 (methoxyphenyl C-4), 55.3 (OMe), 39.6 (cyclopropylmethyl C-1), 21.0 (C-2), 18.4 (C-1), 8.6 (C-3); HRMS found MNa^+ 305.1269. $C_{17}H_{18}N_2O_2$ requires *MNa*, 305.1260. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 1-H and 2-H and nOe observed between cyclopropylmethyl 1-H_2 and methoxyphenyl 2-H (500 MHz, $CDCl_3$).

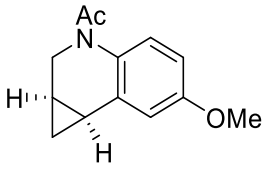
_N_-{[(1*R,2*S**)-2-(3-methoxyphenyl)cyclopropyl]methyl}acetamide (S11)**



Water (7.8 ml) and HCl (1.79 ml, 37%) were added to a solution of arylated derivative **26** (200 mg, 0.71 mmol) in THF (10 ml). The solution was stirred for 5 mins at rt then zinc (689 mg, 10.6 mmol) was added portionwise and the resulting suspension left to stir at rt for 3 h. The mixture was filtered through celite (eluting with DCM) and saturated aqueous $NaHCO_3$ (40 ml) was added to the filtrate. The phases were separated and the aqueous phase extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This intermediate was dissolved in THF

(10 ml), basified with 2M NaOH, then Ac_2O (0.20 ml, 2.13 mmol) was added and the resulting solution stirred at rt for 18 h. Water (20 ml) was added and the mixture was extracted with DCM (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 90:10 to give *acetamide derivative* ***S11*** (94.0 mg, 60%) as a colourless oil. R_f 0.26 (EtOAc–hexane 90:10). ν_{max}/cm^{-1}: 3282, 3070, 2932, 1648, 1580, 1545, 1434, 1370, 1271, 1253, 1150, 1042; δ_H (500 MHz, $CDCl_3$): 7.20 (1H, t, *J* 7.7 Hz, phenyl 5-H), 6.83-6.79 (1H, m, phenyl 6-H), 6.77-6.72 (2H, m, phenyl 2-H and phenyl 4-H), 5.27 (1H, br. s, NH), 3.80 (3H, s, OMe), 3.22 (1H, dt, *J* 13.7 and 6.7 Hz, cyclopropylmethyl 1-H_A), 2.84-2.78 (1H, m, cyclopropylmethyl 1-H_B), 2.22 (1H, td, *J* 8.6 and 6.3 Hz, 2-H), 1.87 (3H, s, acetyl), 1.43-1.35 (1H, m, 1-H), 1.02 (1H, td, *J* 8.6 and 5.4 Hz, 3-H_A), 0.84 (1H, dd, *J* 11.4 and 5.4 Hz, 3-H_B); δ_C (125 MHz, $CDCl_3$): 169.9 (C=O), 159.8 (phenyl C-3), 140.0 (phenyl C-1), 129.5 (phenyl C-5), 121.3 (phenyl C-6), 114.9 (phenyl C-2), 111.6 (phenyl C-4), 55.3 (OMe), 39.7 (cyclopropylmethyl C-1), 23.4 (acetyl), 20.8 (C-2), 18.5 (C-1), 8.6 (C-3); HRMS found MNa^+ 242.1146. $C_{13}H_{17}NO_2$ requires *MNa*, 242.1151.

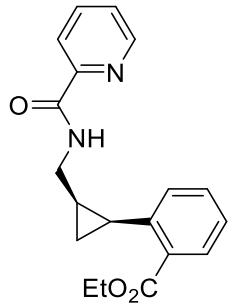
1-[(1a*R,7b*S**)-6-methoxy-1,1a,2,7b-tetrahydro-3*H*-cyclopropa[*c*]quinolin-3-yl]ethanone (27)**



Acetamide derivative **S11** (95.0 mg, 0.43 mmol) was dissolved in MeCN (5 ml) then NBS (85.0 mg, 0.47 mmol) was added and the resulting solution stirred at rt for 4 h. The volatiles were removed under reduced pressure to give the crude brominated intermediate. This was then dissolved in toluene (2 ml) then added to a pressure vial. Then $Pd(OAc)_2$ (5.00 mg, 5 mol%), *rac*-BINAP (20.0 mg, 7.5 mol%) and NaO^tBu (83.0 mg, 0.86 mmol) were added sequentially, the pressure vial sealed then stirred at 100 ^oC for 18 h. The reaction mixture was cooled to rt then filtered through celite (eluting with DCM). The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 25:75 to give the *cyclised acetamide derivative* ***27*** (38.0 mg, 41%) as a colourless oil. R_f 0.31 (EtOAc–hexane 50:50). ν_{max}/cm^{-1}: 3004, 2920, 2836, 1651, 1502, 1385,

1265, 1215, 1139; δ_H (500 MHz, $CDCl_3$): 6.93 (1H, d, *J* 8.7 Hz, 4-H), 6.87 (1H, d, *J* 2.7 Hz, 7-H), 6.68 (1H, dd, *J* 8.7 and 2.7 Hz, 5-H), 5.04 (1H, d, *J* 12.5 Hz, 2-H_A), 3.81 (3H, s, OMe), 2.68 (1H, d, *J* 12.5 Hz, 2-H_B), 2.12 (3H, s, acetyl), 1.93 (1H, td, *J* 8.4 and 4.5 Hz, 7b-H), 1.84-1.78 (1H, m, 1a-H), 1.01 (1H, td, *J* 8.4 and 5.6 Hz, 1-H_A), 0.61 (1H, dd, *J* 10.0 and 5.0 Hz, 1-H_B); δ_C (125 MHz, $CDCl_3$): 170.5 (C=O), 157.6 (C-6), 135.3 (C-3a), 129.4 (C-7a), 126.1 (C-4), 113.8 (C-7), 110.8 (C-5), 55.6 (OMe), 38.4 (C-2), 22.5 (acetyl CH_3), 18.4 (C-1a), 15.2 (C-7b), 9.0 (C-1); HRMS found MH^+ 218.1172. $C_{13}H_{15}NO_2$ requires *MH*, 218.1176.

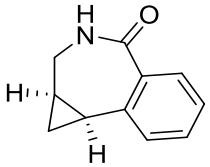
ethyl 2-[(1*R,2*S**)-2-{[(pyridine-2-carbonyl)amino]methyl}cyclopropyl]benzoate (28)**



Prepared according to General procedure F, picolinamide derivative **S10** (200 mg, 1.14 mmol) and ethyl-2-iodobenzoate (345 mg, 1.25 mmol) gave a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 30:70 to give *arylated ester derivative* ***28*** (146 mg, 40%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.23 (EtOAc–hexane 40:60). ν_{max}/cm^{-1}: 3382, 2981, 1712, 1669, 1519, 1488, 1449, 1291, 1253, 1132, 1076; δ_H (500 MHz, $CDCl_3$): 8.51 (1H, ddd, *J* 4.8, 1.7 and 0.9 Hz, pyridinyl 6-H), 8.10 (1H, dt, *J* 7.8 and 1.0 Hz, pyridinyl 3-H), 8.07 (1H, br. s, NH), 7.92 (1H, dd, *J* 7.7 and 1.4 Hz, phenyl 6-H), 7.79 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.44 (1H, td, *J* 7.6 and 1.4 Hz, phenyl 4-H), 7.38 (1H, ddd, *J* 7.8, 4.8 and 1.0 Hz, pyridinyl 5-H), 7.31-7.26 (2H, m, phenyl 3-H and phenyl 5-H), 4.39 (2H, qd, *J* 7.1 and 1.4 Hz, ethyl 1-H_2), 3.34 (1H, dt, *J* 14.0 and 6.5 Hz, cyclopropylmethyl 1-H_A), 2.85 (1H, ddd, *J* 14.0, 8.3 and 4.4 Hz, cyclopropylmethyl 1-H_B), 2.69 (1H, dd, *J* 15.4 and 8.3 Hz, cyclopropyl 1-H), 1.67-1.59 (1H, m, cyclopropyl 2-H), 1.38 (3H, t, *J* 7.1 Hz, ethyl 2-H_3), 1.17 (1H, td, *J* 8.3 and 5.5 Hz, cyclopropyl 3-H_A), 1.04 (1H, dd, *J* 11.9 and 5.5 Hz, cyclopropyl 3-H_B); δ_C (125 MHz, $CDCl_3$): 167.9 (C=O ester), 164.3 (C=O amide), 150.3 (pyridinyl C-2), 148.1 (pyridinyl C-6), 139.4 (phenyl C-2), 137.3 (pyridinyl C-4), 132.0 (phenyl C-4), 131.9

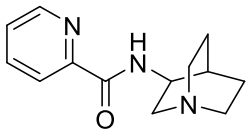
(phenyl C-1), 131.0 (phenyl C-6), 129.9 (phenyl C-5), 126.6 (phenyl C-3), 126.0 (pyridinyl C-5), 122.3 (pyridinyl C-3), 61.1 (ethyl C-1), 40.1 (cyclopropylmethyl C-1), 21.5 (cyclopropyl C-1), 18.9 (cyclopropyl C-2), 14.4 (ethyl C-2), 9.2 (cyclopropyl C-3); HRMS found MH^+ 325.1542. $C_{19}H_{20}N_2O_3$ requires *MH*, 325.1547. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between cyclopropyl 1-H and cyclopropyl 2-H and nOe observed between cyclopropylmethyl 1-H_2 and phenyl 3-H (500 MHz, $CDCl_3$).

(1a*R,8b*S**)-1a,2,3,8b-tetrahydrocyclopropa[*d*][2]benzazepin-4(1*H*)-one (3)**



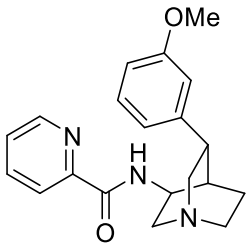
Water (4.73 ml) and HCl (1.08 ml, 37%) were added to a solution of arylated ester derivative **28** (140 mg, 0.43 mmol) in THF (15 ml). The reaction mixture was stirred at rt for 5 mins then zinc powder (419 mg, 6.45 mmol) was added portionwise over 30 mins. The resulting suspension was stirred at rt for 2 h. The reaction mixture was filtered through celite (eluting with THF) then the filtrate was basified with 5M NaOH solution and the resulting solution allowed to stir at rt for a further 18 h. This was then extracted with DCM (3 x 30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 90:10 to give *lactam derivative **3*** (42.0 mg, 57%) as a white solid. R_f 0.36 (EtOAc). ν_{max}/cm^{-1}: 3272, 2995, 2850, 1643, 1598, 1455, 1359, 1153, 1023; δ_H (500 MHz, $CDCl_3$): 7.75 (1H, dd, *J* 7.8 and 1.1 Hz, 5-H), 7.45-7.38 (2H, m, 7-H and 8-H), 7.30 (1H, td, *J* 7.8 and 1.5 Hz, 6-H), 6.39 (1H, br. s, NH), 3.58 (1H, ddd, *J* 14.9, 6.3 and 4.5 Hz, 2-H_A), 2.92-2.81 (1H, m, 2-H_B), 2.13 (1H, td, *J* 8.7 and 5.3 Hz, 8b-H), 1.79-1.70 (1H, m, 1a-H), 1.11 (1H, ddd, *J* 8.7, 7.9 and 5.3 Hz, 1-H_A), 0.78-0.70 (1H, m, 1-H_B); δ_C (125 MHz, $CDCl_3$): 172.4 (C=O), 138.5 (C-8a), 133.2 (C-4a), 132.0 (C-7), 131.1 (C-8), 130.6 (C-5), 126.8 (C-6), 43.5 (C-2), 21.3 (C-1a), 18.3 (C-8b), 11.1 (C-1); HRMS found MH^+ 174.0907. $C_{11}H_{11}NO$ requires *MH*, 174.0913.

***N*-[(1*R**,3*R**,4*R**)-1-azabicyclo[2.2.2]octan-3-yl]pyridine-2-carboxamide (S12)**



Prepared according to General procedure C, 3-aminoquinuclidine dihydrochloride (5.00 g, 25.1 mmol) gave a crude material. This was further purified by stirring in MTBE (60 ml) for 2 h and any solids were subsequently filtered off. The filtrate was concentrated under reduced pressure to give picolinamide derivative **S12**[6] (3.67 g, 63%) as a colourless oil. R_f 0.45 (DCM–MeOH 90:10). δ_H (500 MHz, $CDCl_3$): 8.56 (1H, d, *J* 4.7 Hz, pyridinyl 6-H), 8.26 (1H, br. d, *J* 5.7 Hz, NH), 8.19 (1H, d, *J* 7.8 Hz, pyridinyl 3-H), 7.85 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.43 (1H, ddd, *J* 7.8, 4.7 and 1.2 Hz, pyridinyl 5-H), 4.20-4.14 (1H, m, 3-H), 3.44 (1H, ddd, *J* 14.2, 9.5 and 2.3 Hz, 2-H_A), 3.02-2.95 (1H, m, 6-H_A), 2.95-2.80 (3H, m, 6-H_B and 7-H_2), 2.68 (1H, ddd, *J* 14.2, 4.9 and 2.1 Hz, 2-H_B), 2.07-2.03 (1H, m, 4-H), 1.86-1.80 (1H, m, 5-H_A), 1.76-1.69 (2H, m, 8-H_2), 1.57-1.48 (1H, m, 5-H_B); δ_C (125 MHz, $CDCl_3$): 164.3 (C=O), 150.0 (pyridinyl C-2), 148.2 (pyridinyl C-6), 137.6 (pyridinyl C-4), 126.3 (pyridinyl C-5), 122.3 (pyridinyl C-3), 56.2 (C-2), 47.7 (C-6), 46.9 (C-7) 46.6 (C-3), 26.0 (C-8), 25.9 (C-4), 20.4 (C-5). All data is consistent with known literature values.[6]

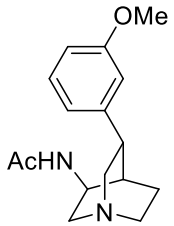
***N*-[(1*R**,3*R**,4*S**,5*S**)-5-(3-methoxyphenyl)-1-azabicyclo[2.2.2]octan-3-yl]pyridine-2-carboxamide (S13)**



To a solution of picolinamide derivative **S12** (0.50 g, 2.16 mmol) and 3-iodoanisole (0.77 ml, 6.49 mmol) in DMF (10 ml) were added pivalic acid (242 mg, 2.38 mmol), $Pd(OAc)_2$ (73.0

mg, 15 mol%) and Ag_2CO_3 (657 mg, 2.38 mmol). The resulting mixture was stirred and heated at 100 °C for 24 h. Then 5M NaOH (20 ml) was added and the resulting solution extracted with DCM (3 x 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 to give *arylated derivative* ***S13*** (0.52 g, 71%, *dr* >95:<5 by ^{1}H NMR) as a dark yellow oil. R_f 0.29 (DCM–sat. NH_3/MeOH 95:5). ν_{max}/cm^{-1}: 3343, 2938, 2872, 1658, 1590, 1515, 1461, 1434, 1319, 1252, 1157, 1040; δ_H (500 MHz, $CDCl_3$): 8.19 (1H, ddd, *J* 4.7, 1.7 and 0.9 Hz, pyridinyl 6-H), 7.96 (1H, dt, *J* 7.8 and 1.2 Hz, pyridinyl 3-H), 7.81 (1H, br. d, *J* 7.9 Hz, NH), 7.70 (1H, td, *J* 7.8 and 1.7 Hz, pyridinyl 4-H), 7.27 (1H, ddd, *J* 7.8, 4.7 and 1.2 Hz, pyridinyl 5-H), 7.18 (1H, t, *J* 7.7 Hz, phenyl 5-H), 6.94 (1H, dd, *J* 7.7 and 0.7 Hz, phenyl 6-H), 6.90 (1H, app. s, phenyl 2-H), 6.65 (1H, dd, *J* 7.7 and 2.5 Hz, phenyl 4-H), 4.20-4.14 (1H, m, 3-H), 3.72 (3H, s, OMe), 3.52-3.36 (3H, m, 2-H_A and 6-H_2), 3.10 (1H, t, *J* 8.7 Hz, 5-H), 2.94-2.86 (2H, m, 7-H_2), 2.78 (1H, dd, *J* 14.1 and 4.6 Hz, 2-H_B), 2.56 (1H, dt, *J* 5.7 and 3.0 Hz, 4-H), 1.93-1.77 (2H, m, 8-H_2); δ_C (125 MHz, $CDCl_3$): 163.7 (C=O), 160.2 (phenyl C-3), 149.6 (pyridinyl C-2), 147.5 (pyridinyl C-6), 144.9 (phenyl C-1), 137.0 (pyridinyl C-4), 130.0 (phenyl C-5), 125.8 (pyridinyl C-5), 121.7 (pyridinyl C-3), 119.6 (phenyl C-6), 112.7 (phenyl C-2), 111.4 (phenyl C-4), 57.0 (C-2), 55.2 (OMe), 52.0 (C-6), 46.7 (C-3), 46.2 (C-7), 38.3 (C-5), 32.7 (C-4), 28.8 (C-8); HRMS found MH^+ 338.1879. $C_{20}H_{23}N_3O_2$ requires *MH*, 338.1863.

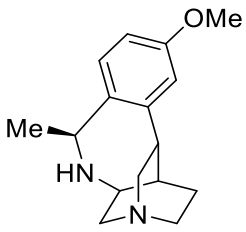
***N*-[(1*R**,3*R**,4*S**,5*S**)-5-(3-methoxyphenyl)-1-azabicyclo[2.2.2]octan-3-yl]acetamide (29)**



Arylated derivative **S13** (0.52 g, 1.54 mmol) was suspended in water (40 ml) to which HCl (5 ml, 37%) was added slowly with stirring. The reaction mixture was stirred for 5 mins at rt then zinc powder (1.50 g, 23.1 mmol) was added slowly. The reaction mixture was left to stir at rt for 16 h. Then DCM (70 ml) and 5M NaOH (100 ml) were added slowly at 0 °C. The mixture

was filtered through celite, with the celite pad being subsequently washed with water (30 ml) and DCM (30 ml). The combined filtrate was extracted with DCM (3 x 50 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This amine intermediate (0.35 g, 1.51 mmol) was dissolved in THF (20 ml) then NaOH (60.0 mg, 1.51 mmol) in water (5 ml) was added at rt. Ac_2O (0.18 ml, 1.89 mmol) was added and the reaction mixture stirred at rt for a further 1 h. 5M NaOH was added to basify the solution to pH 13. This solution was then extracted with DCM (3 x 40 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 to give *acetamide derivative* ***29*** (306 mg, 74%) as a colourless oil. R_f 0.52 (DCM–sat. NH_3/MeOH 90:10). ν_{max}/cm^{-1}: 3291, 3068, 2937, 2870, 2835, 1644, 1546, 1433, 1257, 1043; δ_H (500 MHz, $CDCl_3$): 7.30 (1H, t, *J* 8.0 Hz, phenyl 5-H), 6.96 (1H, dd, *J* 8.0 and 0.7 Hz, phenyl 6-H), 6.88 (1H, s, phenyl 2-H), 6.78 (1H, dd, *J* 8.0 and 2.5 Hz, phenyl 4-H), 5.06 (1H, br. d, *J* 7.2 Hz, NH), 3.98-3.91 (1H, m, 3-H), 3.81 (3H, s, OMe), 3.44-3.25 (3H, m, 2-H_A and 6-H_2), 3.05 (1H, t, *J* 8.6 Hz, 5-H), 2.91-2.77 (2H, m, 7-H_2), 2.57 (1H, ddd, *J* 14.2, 4.9 and 2.1 Hz, 2-H_B), 2.44-2.41 (1H, m, 4-H), 1.87-1.78 (1H, m, 8-H_A), 1.77-1.69 (1H, m, 8-H_B), 1.42 (3H, s, acetyl); δ_C (125 MHz, $CDCl_3$): 169.4 (acetyl C=O), 160.3 (phenyl C-3), 145.7 (phenyl C-1), 130.0 (phenyl C-5), 119.0 (phenyl C-6), 113.5 (phenyl C-2), 111.5 (phenyl C-4), 56.7 (C-2), 55.4 (OMe), 51.8 (C-6), 46.9 (C-3), 46.2 (C-7), 38.2 (C-5), 32.7 (C-4), 28.6 (C-8), 23.0 (acetyl CH_3); HRMS found MH^+ 275.1762. $C_{16}H_{22}N_2O_2$ requires *MH*, 275.1754.

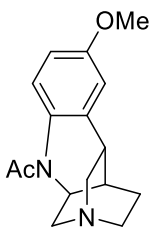
(2*R,4a*S**,5*S**,10*R**,11a*S**)-7-methoxy-10-methyl-1,3,4,4a,5,10,11,11a-octahydro-2,5-methanobenzo[*e*]pyrido[3,4-*b*]azepine (30)**



Acetamide derivative **29** (221 mg, 0.81 mmol) was dissolved in MeCN (10 ml) and $POCl_3$ (0.76 ml, 8.10 mmol) was added dropwise at rt. The reaction mixture was stirred and heated to

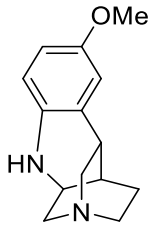
100 °C for 18 h. The reaction mixture was cooled to rt and all volatiles removed under reduced pressure. This residue was dissolved in DCM (10 ml), then water (5 ml) and 5M NaOH were added to basify the reaction mixture. This was then extracted with DCM (3 x 50 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude imine intermediate. This crude intermediate (140 mg, 0.55 mmol) was dissolved in MeOH (5 ml) and $NaBH_4$ (42.0 mg, 1.10 mmol) was added at rt. The resulting solution was allowed to stir at rt for 1 h. Then 1M HCl (15 ml) was added to quench the reaction, followed by 2M NaOH to basify the solution to pH 12. Then this mixture was extracted with DCM (3 x 30 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material (*dr* 68:32 by ^{1}H NMR). This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 → 90:10 to give the *cyclised amine derivative* ***30*** (112 mg, 54%, *dr* 84:16 by ^{1}H NMR) as a colourless oil. R_f 0.25 (DCM–sat. NH_3/MeOH 95:5). ν_{max}/cm^{-1}: 3251, 2947, 2909, 2783, 1602, 1502, 1238, 1038; δ_H (500 MHz, $CDCl_3$): 7.13 (1H, d, *J* 8.6 Hz, 9-H), 6.69-6.62 (2H, m, 6-H and 8-H), 4.19 (1H, q, *J* 6.7 Hz, 10-H), 3.78 (3H, s, OMe), 3.39-3.25 (2H, m, 11a-H and 12-H_A), 3.06-2.80 (5H, m, 12-H_B, 5-H, 1-H_A and 3-H_2), 2.63 (1H, d, *J* 13.8 Hz, 1-H_B), 2.55 (1H, t, *J* 4.5 Hz, 4a-H), 1.76-1.56 (3H, m, 4-H_2 and NH), 1.50 (3H, d, *J* 6.7 Hz, methyl); δ_C (125 MHz, $CDCl_3$): 157.8 (C-7), 144.5 (C-5a), 138.3 (C-9a), 126.8 (C-9), 116.4 (C-6), 110.3 (C-8), 57.3 (C-1), 55.9 (C-12), 55.4 (OMe), 52.0 (C-11a), 49.9 (C-10), 46.6 (C-3), 42.7 (C-5), 29.2 (C-4a), 24.4 (C-4), 22.4 (methyl CH_3); HRMS found MH^+ 259.1808. $C_{16}H_{22}N_2O$ requires *MH*, 259.1805. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 10-H and 4a-H (500 MHz, $CDCl_3$).

1-[(2*R,4a*S**,5*S**,10a*R**)-7-methoxy-1,3,4,4a,5,10a-hexahydro-10*H*-2,5-methanobenzo[*b*][1,7]naphthridin-10-yl]ethanone (S14)**



Acetamide derivative **29** (100 mg, 0.36 mmol) was dissolved in MeCN (5 ml) and NBS (65.0 mg, 0.36 mmol) was added. The reaction mixture was left to stir at rt for 18 h. The solvent was removed under reduced pressure to give the crude *p*-bromo intermediate. This crude intermediate (82.0 mg, 0.23 mmol) was dissolved in toluene (5 ml) and $Pd(OAc)_2$ (3.00 mg, 5 mol%), *rac*-BINAP (11.0 mg, 7.5 mol%) and Cs_2CO_3 (152 mg, 0.47 mmol) were added sequentially. The reaction mixture was heated at 100 °C for 24 h then allowed to cool to rt. The resulting mixture was filtered through celite and concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting DCM–sat. NH_3/MeOH 95:5 to give the *cyclised acetamide derivative* ***S14*** (40.0 mg, 41%) as a pale-yellow oil. R_f 0.61 (DCM–sat. NH_3/MeOH 90:10). ν_{max}/cm^{-1}: 2934, 2871, 1634, 1494, 1243, 1038; δ_H (500 MHz, $CDCl_3$): 6.76 (1H, dd, *J* 9.0 and 2.0 Hz, 8-H), 6.60 (1H, d, *J* 2.0 Hz, 6-H), 3.79 (3H, s, OMe), 3.37-3.26 (2H, m, 1-H_A and 11-H_A), 2.94-2.85 (2H, m, 5-H and 3-H_A), 2.78-2.70 (1H, m, 3-H_B), 2.60 (1H, d, *J* 13.3 Hz, 1-H_B), 2.47-2.42 (1H, m, 11-H_B), 2.33 (3H, s, acetyl), 1.91 (1H, app. s, 4a-H), 1.84-1.72 (2H, m, 4-H_2); δ_C (125 MHz, $CDCl_3$): 170.0 (C=O), 156.8 (C-7), 135.6 (C-9a), 127.5 (C-5a), 125.3 (C-9), 113.3 (C-6), 112.2 (C-8), 57.0 (C-1), 55.6 (OMe), 53.1 (C-11), 46.3 (C-3), 34.6 (C-5), 26.2 (C-4a), 24.8 (acetyl CH_3), 23.0 (C-4); HRMS found MH^+ 273.1606. $C_{16}H_{20}N_2O_2$ requires *MH*, 273.1598. 9-H and 10a-H not observed by ^1H NMR and C-10a not observed by ^{13}C NMR.

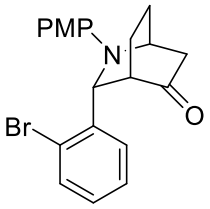
(2*R,4a*S**,5*S**,10a*R**)-7-methoxy-3,4,4a,5,10,10a-hexahydro-1*H*-2,5-methanobenzo[*b*][1,7]naphthridine (31)**



Cyclised acetamide derivative **S14** (40.0 mg, 0.15 mmol) was dissolved in 1:1 HCl–EtOH (10 ml) and stirred at 80 °C for 18 h. The reaction mixture was allowed to cool to rt then concentrated under reduced pressure to give the *amine derivative* ***31*** (36.0 mg, 89%) as an off-white solid. R_f 0.37 (DCM–sat. NH_3/MeOH 90:10). ν_{max}/cm^{-1}: 3151, 3052, 1595, 1238, 1016;

δ_H (500 MHz, MeOD): 7.33 (1H, d, *J* 8.7 Hz, 9-H), 7.08 (1H, d, *J* 8.7 Hz, 8-H), 7.05 (1H, s, 6-H), 4.56-4.48 (1H, m, 10a-H), 4.00-3.93 (1H, m, 1-H_A), 3.86 (4H, app. s, OMe and 11-H_A), 3.64-3.58 (1H, m, 5-H), 3.52-3.44 (1H, m, 3-H_A), 3.40-3.32 (2H, m, 1-H_B and 3-H_B), 3.27 (1H, d, *J* 12.3 Hz, 11-H_B), 2.64 (1H, app. s, 4a-H), 2.34-2.24 (2H, m, 4-H_2); δ_C (125 MHz, MeOD): 162.1 (C-7), 136.6 (C-9a), 126.1 (C-9), 119.9 (C-5a), 117.2 (C-8), 115.8 (C-6), 56.4 (OMe), 54.7 (C-11), 48.8 (C-1), 47.0 (C-3), 46.8 (C-10a), 30.6 (C-5), 23.9 (C-4a), 20.3 (C-4); HRMS found MH^+ 231.1495. $C_{14}H_{18}N_2O$ requires *MH*, 231.1492. The product was isolated as the HCl salt.

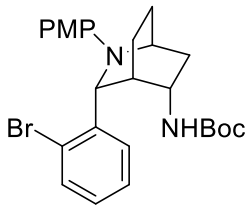
(1*R,3*S**,4*R**)-3-(2-bromophenyl)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one (S15)**



p-anisidine (2.00 g, 16.2 mmol), proline (0.19 g, 30 mol%), 2-cyclohexenone (1.56 ml, 16.2 mmol) and 2-bromobenzaldehyde (1.00 g, 5.41 mmol) were dissolved in MeCN–H_2O 9:1 (15 ml) at rt. The reaction mixture was then stirred at 35 ºC for 3 days. The mixture was filtered through celite, eluting with EtOAc. The filtrate was diluted with EtOAc (20 ml) and subsequently washed with water (2 x 40 ml). The aqueous washings were then back extracted with EtOAc (3 x 30 ml), organic layers combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material (*dr* 80:20 by ^{1}H NMR). This was then purified *via* column chromatography, eluting EtOAc–hexane 15:85 to give *bicyclic ketone derivative* ***S15*** (1.08 g, 53%, *dr* >95:<5 by ^{1}H NMR) as a yellow oil. R_f 0.30 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 3062, 2934, 2868, 2832, 1732, 1508, 1460, 1440, 1293, 1240, 1180, 1110, 1083; δ_H (500 MHz, $CDCl_3$): 7.56 (1H, dd, *J* 7.9 and 1.1 Hz, bromophenyl 3-H), 7.35 (1H, dd, *J* 7.9 and 1.7 Hz, bromophenyl 6-H), 7.20 (1H, td, *J* 7.9 and 1.1 Hz, bromophenyl 5-H), 7.10 (1H, td, *J* 7.9 and 1.7 Hz, bromophenyl 4-H), 6.76 (2H, d, *J* 9.2 Hz, methoxyphenyl 3,5-H), 6.56 (2H, d, *J* 9.2 Hz, methoxyphenyl 2,6-H), 4.90 (1H, d, *J* 1.8 Hz, 3-H), 4.48-4.44 (1H, m, 1-H), 3.71

(3H, s, OMe), 2.88-2.81 (2H, m, 4-H and 6-H_A), 2.51 (1H, dd, *J* 18.8 and 2.2 Hz, 6-H_B), 2.24-2.17 (2H, m, 7-H_A and 8-H_A), 2.03-1.97 (1H, m, 8-H_B), 1.82-1.77 (1H, m, 7-H_B); δ_C (125 MHz, $CDCl_3$): 212.1 (C-5), 152.6 (methoxyphenyl C-4), 141.9 (methoxyphenyl C-1), 140.2 (bromophenyl C-1), 133.5 (bromophenyl C-3), 129.3 (bromophenyl C-4), 128.2 (bromophenyl C-5), 128.0 (bromophenyl C-6), 122.3 (bromophenyl C-2), 115.4 (methoxyphenyl C_2-2,6), 114.9 (methoxyphenyl C_2-3,5), 65.2 (C-3), 55.7 (OMe), 50.6 (C-1), 49.4 (C-4), 46.1 (C-6), 22.7 (C-7), 22.3 (C-8); HRMS found MH^+ 388.0730. $C_{20}H_{20}BrNO_2$ requires *MH*, 388.0730. The relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 3-H and 8-H_A and bromophenyl 6-H and 6-H_A.

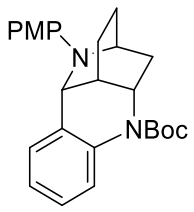
tert-butyl _N_-[(1*R,3*S**,4*S**,5*R**)-3-(2-bromophenyl)-2-(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-yl]carbamate (32)**



Bicyclic ketone **S15** (1.02 g, 2.64 mmol) was dissolved in sat. NH_3/MeOH (50 ml) and $Ti(O^iPr)_4$ (1.59 ml, 5.27 mmol) was added at rt. The solution was allowed to stir for 18 h at rt, then cooled to 0 ^oC and $NaBH_4$ (150 mg, 3.96 mmol) was added portionwise. The resulting reaction mixture was left to stir at rt for 2 h. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in EtOAc (30 ml) and brine (30 ml) was added with vigorous stirring. The phases were separated and the aqueous phase was then extracted with EtOAc (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine intermediate. This intermediate was dissolved in THF (20 ml) and the solution was basified with 2M NaOH. Then Boc_2O (1.73 g, 7.92 mmol) was added and the resulting mixture was allowed to stir at rt for 4 h. Water (20 ml) was added and the mixture was then extracted with EtOAc (3 x 30 ml). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. This was purified *via* column chromatography, eluting EtOAc–hexane 10:90 to

give *carbamate derivative* ***32*** (311 mg, 25%, *dr* 74:26 by ^{1}H NMR) as a colourless oil. R_f 0.54 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 3285, 2937, 2865, 1694, 1510, 1346, 1270, 1225, 1190, 1081; δ_H (500 MHz, $CDCl_3$): 7.64-7.57 (3H, m, bromophenyl 3-H and bromophenyl 6-H^{maj}), 7.57-7.51 (1H, m, bromophenyl 6-H^{min}), 7.29 (1H, td, *J* 7.6 and 1.0 Hz, bromophenyl 5-H^{maj}), 7.23 (1H, td, *J* 7.6 and 1.0 Hz, bromophenyl 5-H^{min}), 7.14 (1H, td, *J* 7.6 and 1.6 Hz, bromophenyl 4-H^{maj}), 7.11 (1H, td, *J* 7.6 and 1.6 Hz, bromophenyl 4-H^{min}), 6.76-6.70 (4H, m, methoxyphenyl 3,5-H), 6.51-6.43 (4H, m, methoxyphenyl 2,6-H), 4.71 (2H, d, *J* 6.2 Hz, NH), 4.56 (2H, d, *J* 2.2 Hz, 3-H), 4.08-4.04 (1H, m, 1-H^{maj}), 4.01-3.97 (1H, m, 1-H^{min}), 3.80-3.73 (2H, m, 5-H), 3.71 (3H, s, OMe^{maj}), 3.70 (3H, s, OMe^{min}), 2.95-2.91 (2H, m, 4-H), 2.42-2.35 (1H, m, 6-H$_A$^{maj}), 2.24-2.16 (1H, m, 6-H$_A$^{min}), 2.12-2.03 (2H, m, 7-H$_A$), 1.82-1.70 (6H, m, 6-H$_B$ and 8-H$_2$), 1.60-1.54 (2H, m, 7-H$_B$, overlap with residual water peak), 1.45 (9H, s, ^{t}Bu^{min}), 1.26 (9H, s, ^{t}Bu^{maj}); δ_C (125 MHz, $CDCl_3$): 155.5 (Boc C=O^{min}), 154.9 (Boc C=O^{maj}), 151.9 (methoxyphenyl C-4^{min}), 151.7 (methoxyphenyl C-4^{maj}), 142.8 (methoxyphenyl C-1^{maj}), 142.2 (methoxyphenyl C-1^{min}), 140.5 (bromophenyl C-1), 134.2 (bromophenyl C-3^{maj}), 133.3 (bromophenyl C-3^{min}), 129.0 (bromophenyl C-4^{min}), 128.7 (bromophenyl C-4^{maj}), 128.5 (bromophenyl C-6), 127.9 (bromophenyl C-5^{maj}), 127.5 (bromophenyl C-5^{min}), 122.1 (bromophenyl C-2), 114.8 (methoxyphenyl C$_2$-3,5^{maj}), 114.7 (methoxyphenyl C$_2$-3,5^{min}), 113.9 (methoxyphenyl C$_2$-2,6), 78.7 (C$_1$ ^{t}Bu), 65.4 (C-3), 55.7 (OMe^{maj}), 55.6 (OMe^{min}), 48.3 (C-5^{min}), 47.5 (C-5^{maj}), 46.8 (C-1^{min}), 46.2 (C-1^{maj}), 36.6 (C-6), 35.2 (C-4), 28.5 (C$_3$ ^{t}Bu^{min}), 28.2 (C$_3$ ^{t}Bu^{maj}), 26.0 (C-8^{min}), 25.7 (C-8^{maj}), 22.6 (C-7^{min}), 21.9 (C-7^{maj}); HRMS found MH$^+$ 489.1583. $C_{25}H_{31}BrN_2O_3$ requires *MH*, 489.1570. The relative configuration of the major diastereomer was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 5-H and 8-H$_A$.

tert-butyl (3*R,4a*R**,9*S**,9a*S**)-11-(4-methoxyphenyl)-2,3,4,4a,9,9a-hexahydro-3,9-epiminoacridine-10(1*H*)-carboxylate (33)**



$Pd(OAc)_2$ (4.00 mg, 5 mol%), *rac*-BINAP (16.0 mg, 7.5 mol%) and NaO^{t}Bu (63.0 mg, 0.66 mmol) were added to a solution of carbamate derivative **32** (160 mg, 0.33 mmol) in toluene (10 ml) at rt. The reaction mixture was then stirred and heated at 100 ^{o}C for 24 h, allowed to cool to rt and then filtered through celite. The filtrate was concentrated under reduced pressure to give a crude material. This was then purified *via* column chromatography, eluting EtOAc–hexane 5:95 to give the *cyclised carbamate derivative* ***33*** (45.0 mg, 32%, *dr* >95:<5 by ^{1}H NMR) as a colourless oil. R_f 0.58 (EtOAc–hexane 20:80). ν_{max}/cm^{-1}: 2990, 2934, 2858, 1692, 1509, 1328, 1273, 1192, 1078; δ_H (500 MHz, $CDCl_3$): 7.97 (1H, d, *J* 8.4 Hz, 5-H), 7.38 (1H, dd, *J* 7.6 and 1.3 Hz, 8-H), 7.21-7.17 (1H, m, 6-H), 7.00 (2H, d, *J* 9.1 Hz, methoxyphenyl 2,6-H), 6.95 (1H, td, *J* 7.6 and 0.9 Hz, 7-H), 6.84 (2H, d, *J* 9.1 Hz, methoxyphenyl 3,5-H), 4.65-4.59 (1H, m, 3-H), 4.54 (1H, d, *J* 2.3 Hz, 9-H), 3.77 (3H, s, OMe), 3.69-3.64 (1H, m, 4a-H), 2.27 (1H, ddd, *J* 13.9, 9.9 and 2.6 Hz, 4-H_A), 2.00-1.92 (2H, m, 9a-H and 2-H_A), 1.87 (1H, ddd, *J* 13.9, 6.5 and 3.4 Hz, 4-H_B), 1.83-1.69 (2H, m, 2-H_B and 1-H_A), 1.57 (9H, s, ^{t}Bu), 1.45-1.36 (1H, m, 1-H_B); δ_C (125 MHz, $CDCl_3$): 153.5 (Boc C=O), 152.2 (methoxyphenyl C-4), 143.5 (methoxyphenyl C-1), 135.9 (C-4b), 131.5 (C-8a), 128.5 (C-8), 127.6 (C-6), 123.2 (C-5), 122.6 (C-7), 116.4 (methoxyphenyl C_2-2,6), 114.9 (methoxyphenyl C_2-3,5), 81.4 (C_1 ^{t}Bu), 55.9 (OMe), 55.3 (C-9), 48.8 (C-3), 46.5 (C-4a), 36.9 (C-4), 30.9 (C-9a), 28.6 (C_3 ^{t}Bu), 21.3 (C-2), 21.2 (C-1); HRMS found MH^+ 407.2338. $C_{25}H_{30}N_2O_3$ requires *MH*, 407.2329. Confirmation of the relative configuration was determined through NOESY (500 MHz, $CDCl_3$). nOe observed between 1-H_B and 4a-H.

Scaffold and Virtual Library Analysis

List of Scaffolds Prepared Including Novelty Assessment

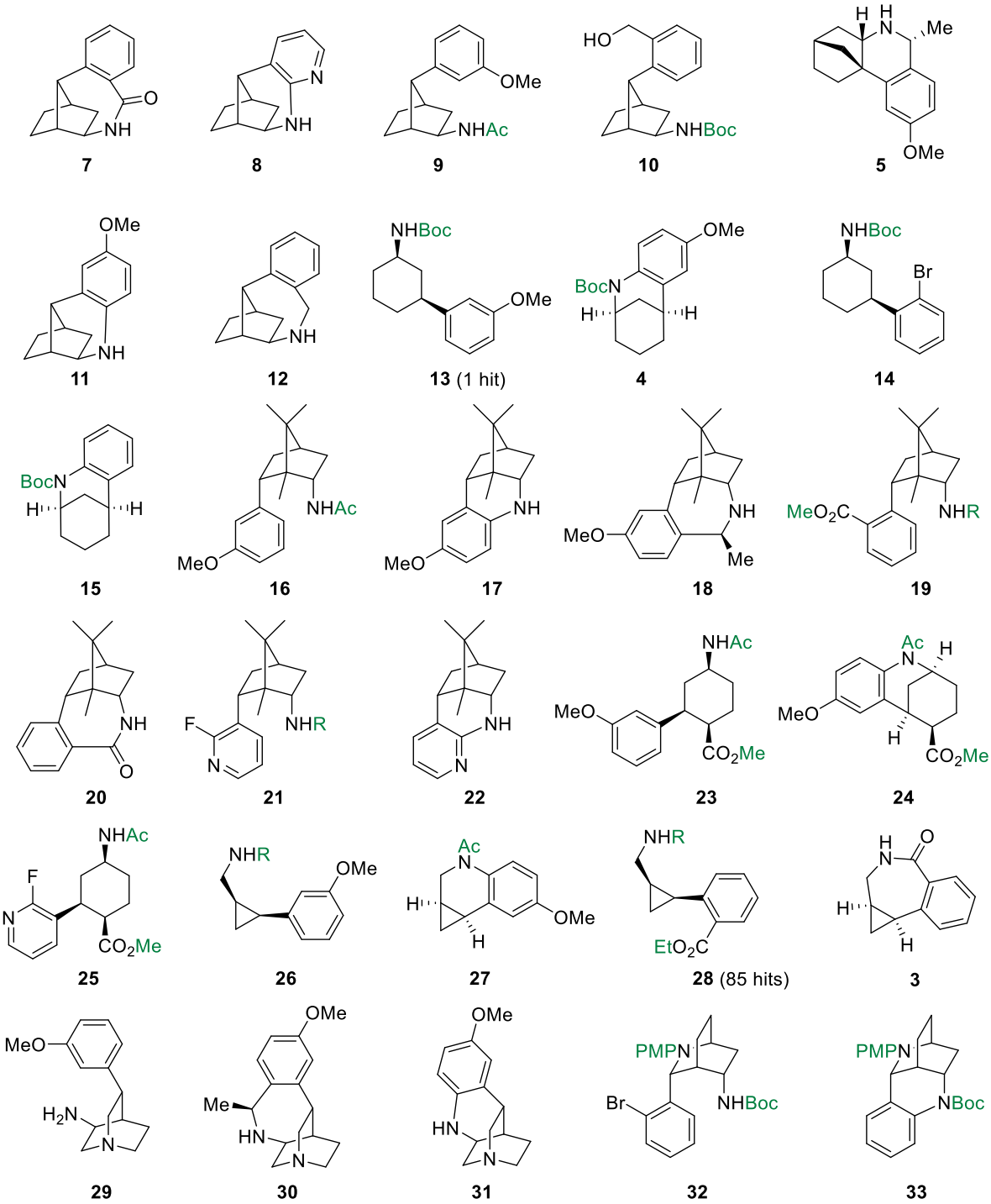


Figure S1: The 30 scaffolds prepared through this unified synthetic approach. The deprotected frameworks (black) are indicated. Number of hits from novelty assessment are shown in brackets where appropriate. R = 2-pyridylcarbonyl.

Scaffold Diversity Assessment

A full version of the hierarchical scaffold tree highlighted in Figure 1 is shown below, including structures of the frameworks at each level of hierarchy.[7]

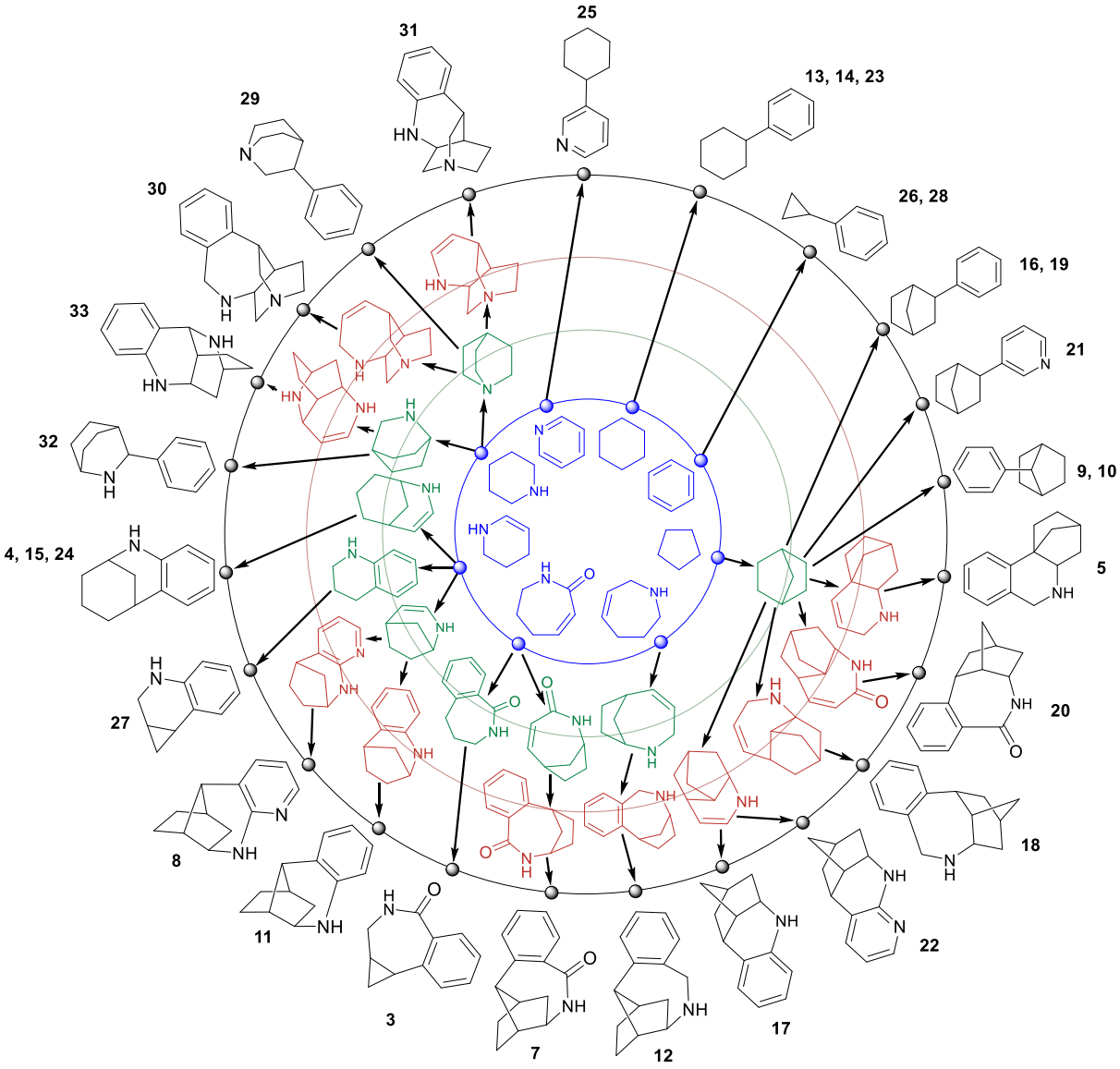


Figure S2: Hierarchical scaffold tree with structures. The twenty-three frameworks (black) at the graph-node-bond level are related hierarchically to eight monocyclic parent (blue) frameworks through iterative removal of rings (red → green). The corresponding scaffolds relating to each framework at the graph-node level are numbered accordingly.

Scaffold Molecular Property Assessment

Computational assessment of the molecular weight and AlogP of the deprotected scaffold library was performed using LLAMA[8] and the data subsequently replotted in Origin. Figure S3 shows a plot of AlogP vs Molecular weight for the deprotected scaffold library.

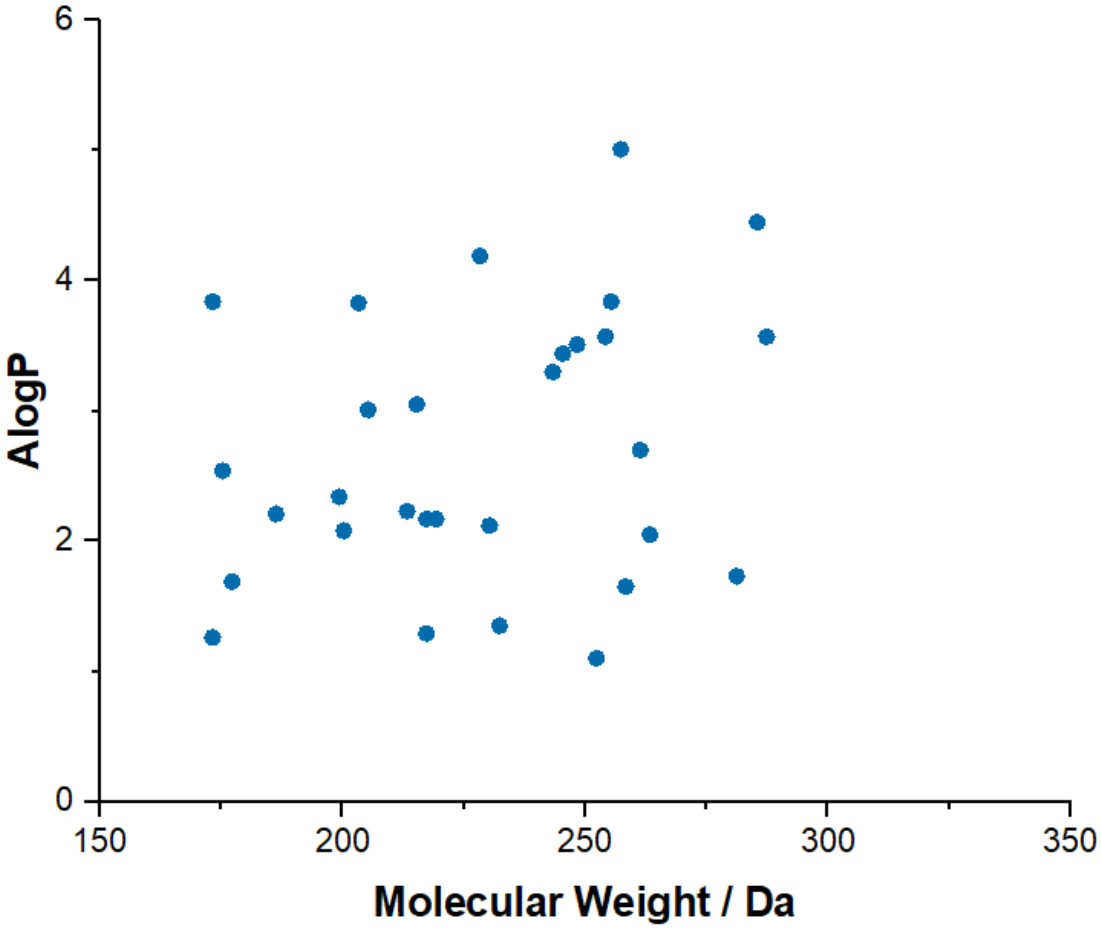


Figure S3: Plot of AlogP vs Molecular weight for the deprotected scaffold library.

Scaffold Shape Diversity Assessment

The principle moments of inertia of the lowest energy conformations of the deprotected scaffold library was performed using LLAMA. Figure S4 shows the PMI plot of the deprotected scaffold library.

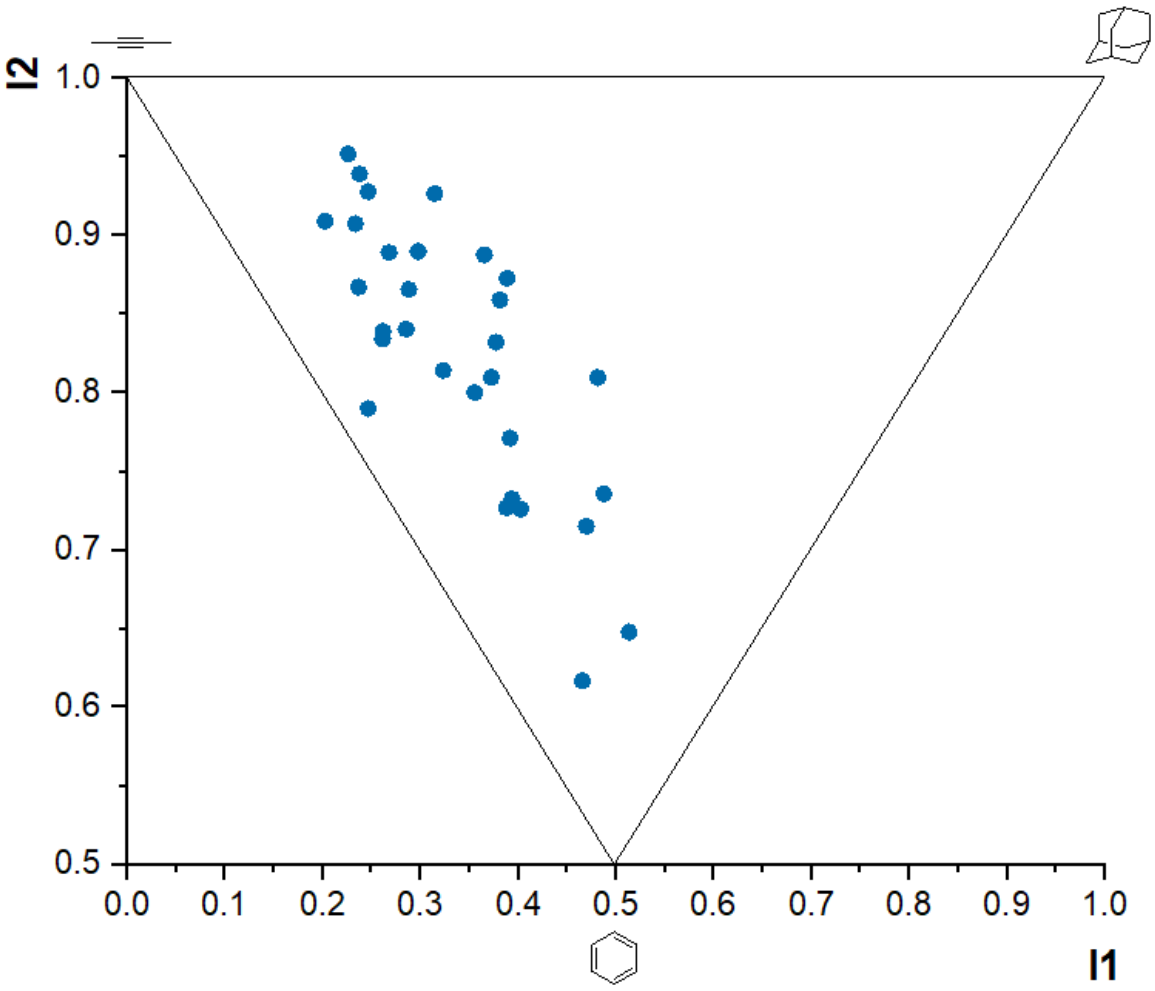


Figure S4: PMI plot of the deprotected scaffold library to highlight shape diversity.

Virtual Library Molecular Property Assessment

Computational assessment of the molecular weight and AlogP of the virtual library was performed using LLAMA, where the scaffolds were decorated once with the set of medicinally relevant capping groups already present within LLAMA. Figure S5 shows a plot of AlogP vs Molecular weight for the virtually decorated library of compounds.

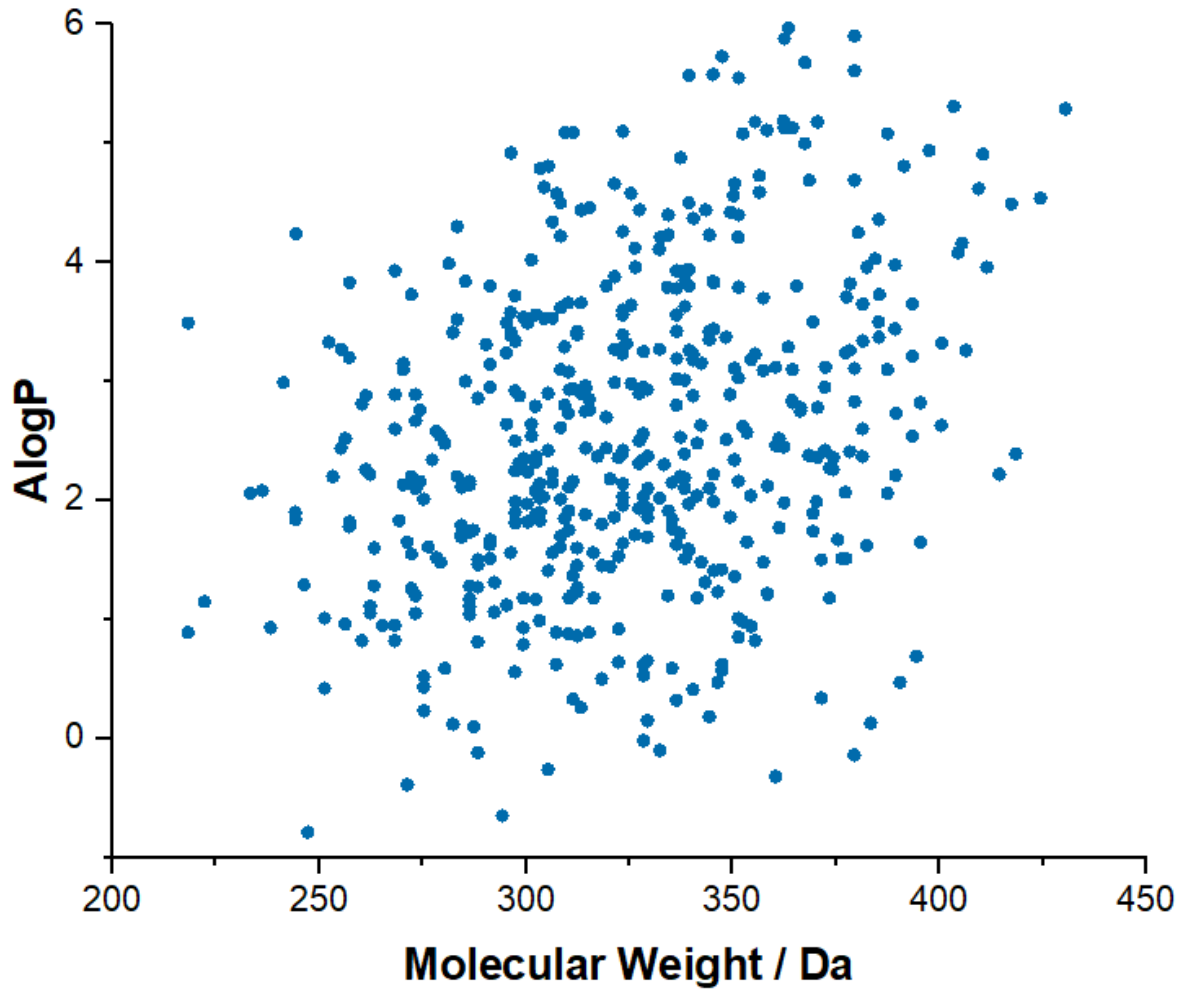


Figure S5: Plot of AlogP vs Molecular weight for the virtual library. The scaffold library was decorated once with medicinally relevant capping groups in LLAMA to provide a virtual mono-decorated library.

Virtual Library Shape Diversity Assessment

The principle moments of inertia of the lowest energy conformations of the virtual library was performed using LLAMA. Figure S6 shows the PMI plot of the virtual library.

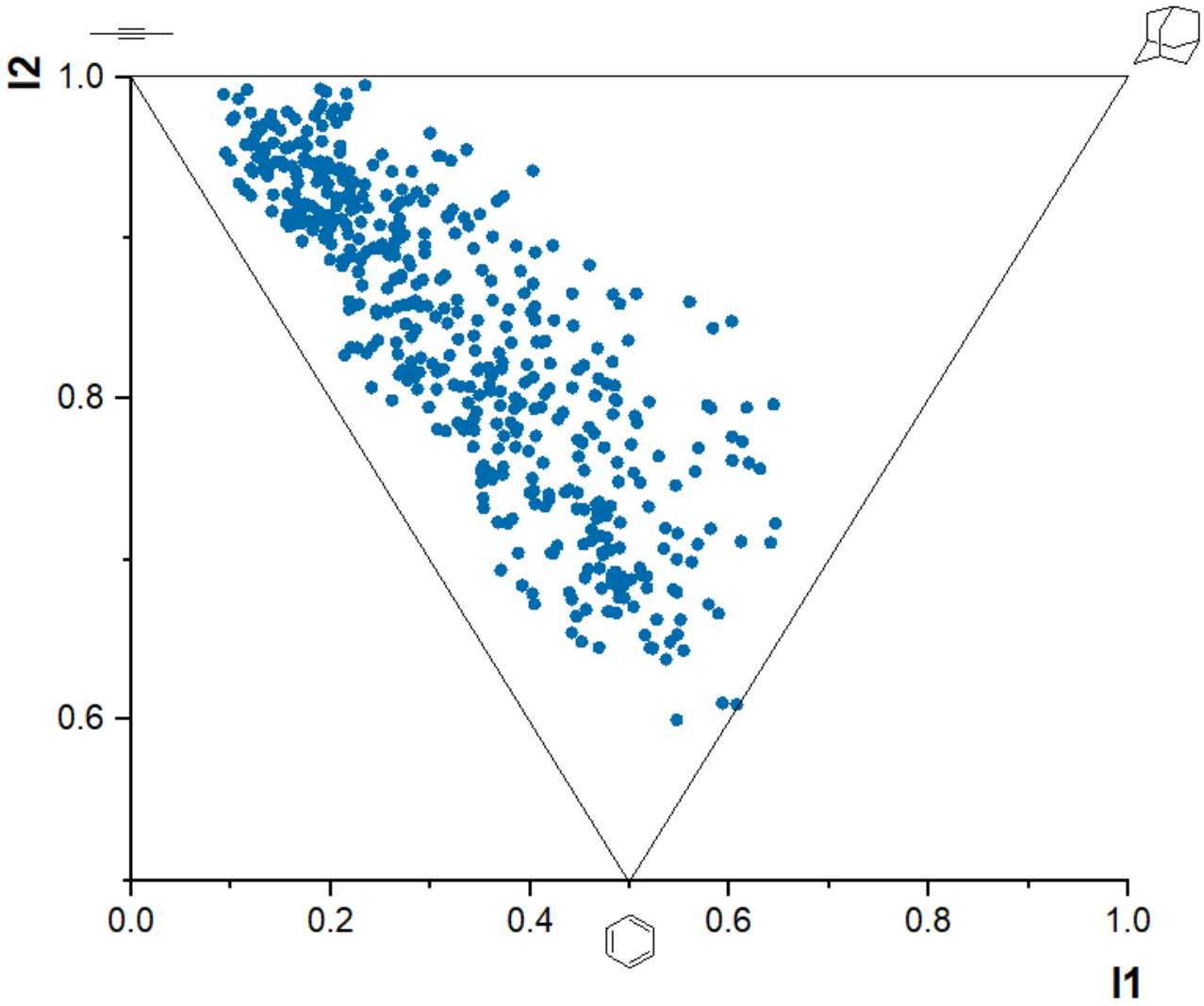


Figure S6: PMI plot of the virtual scaffold library to highlight shape diversity.

Proposed Mechanism for Rearrangement Process (Compound 5)

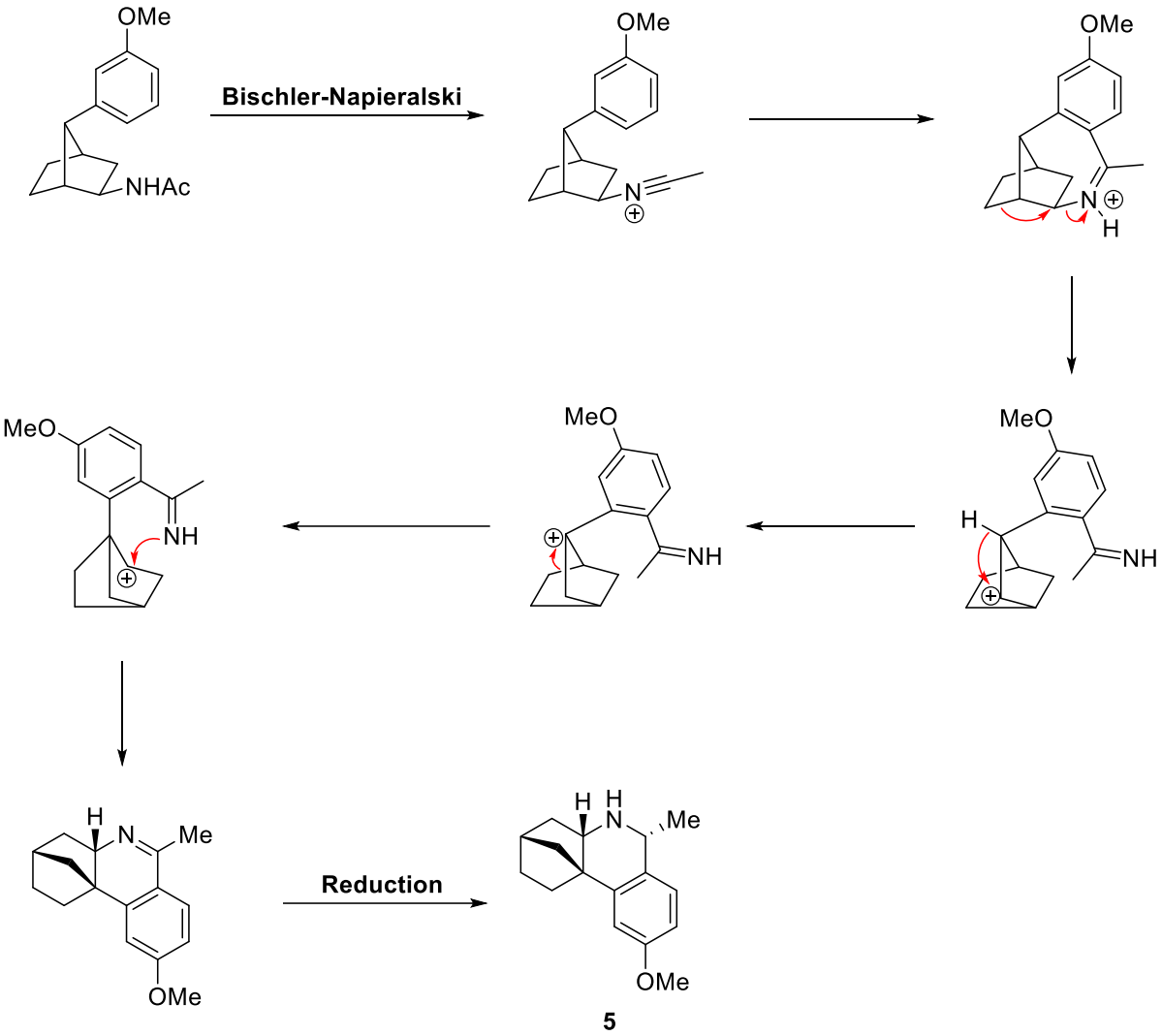
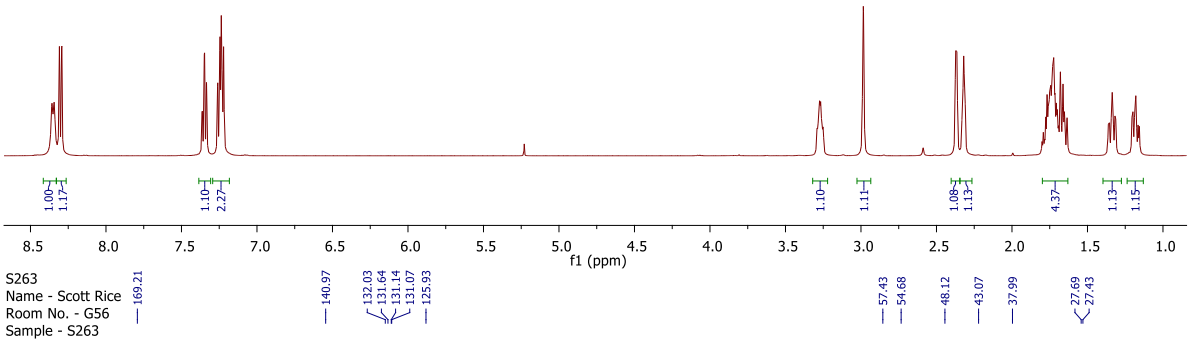


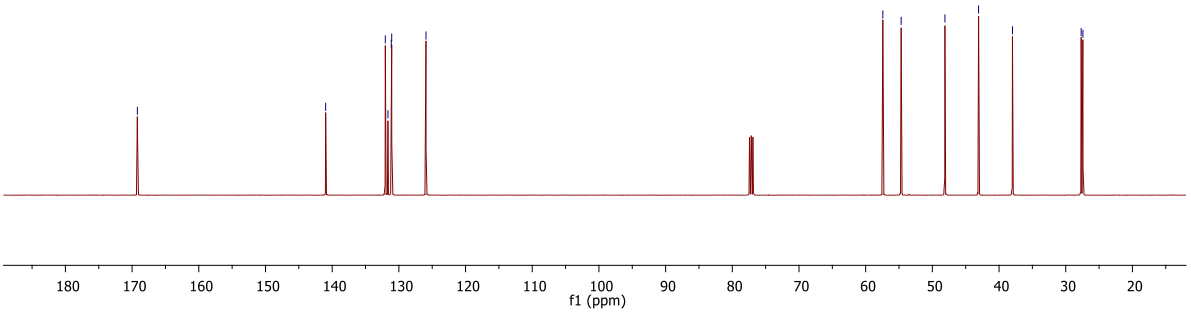
Figure S7: Proposed mechanism for the rearrangement process observed in the synthesis of compound **5**.

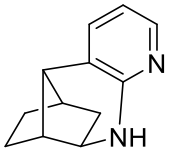
NMR Spectra

^{1}H NMR



^{13}C NMR

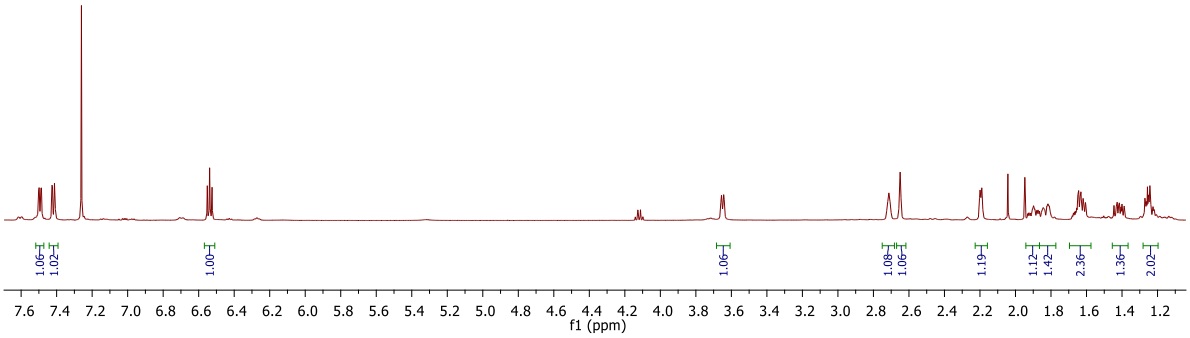




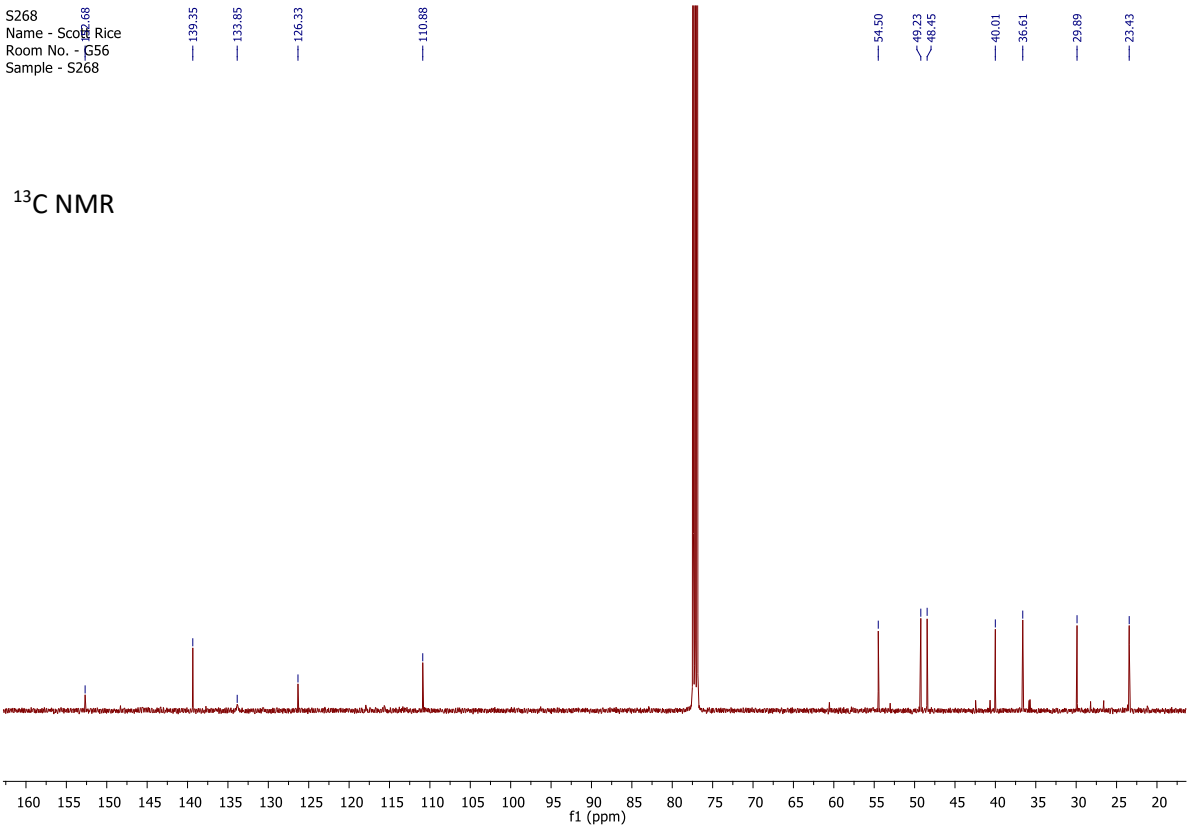
8

S268
Name - Scott Rice
Room No. - G56
Sample - S268

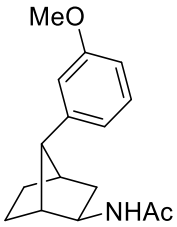
^{1}H NMR



S268
Name - Scott Rice
Room No. - G56
Sample - S268



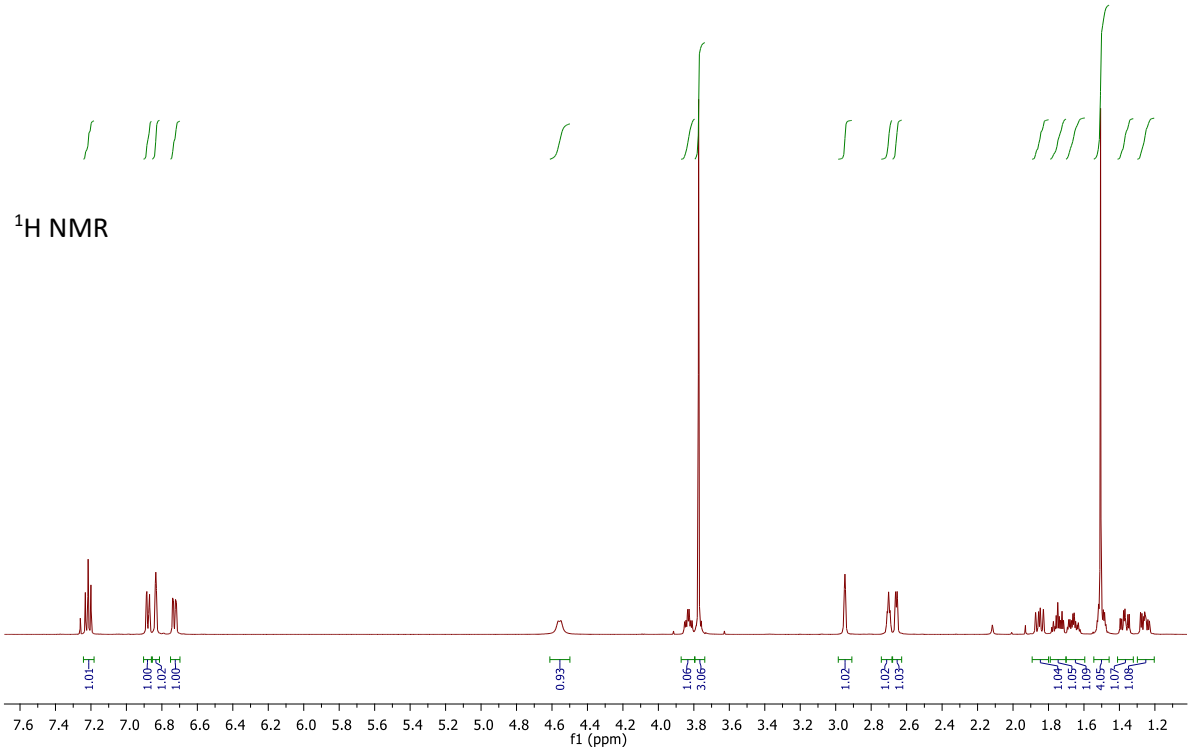
^{13}C NMR



9

S252
Name - Scott Rice
Room No. - G56
Sample - S252

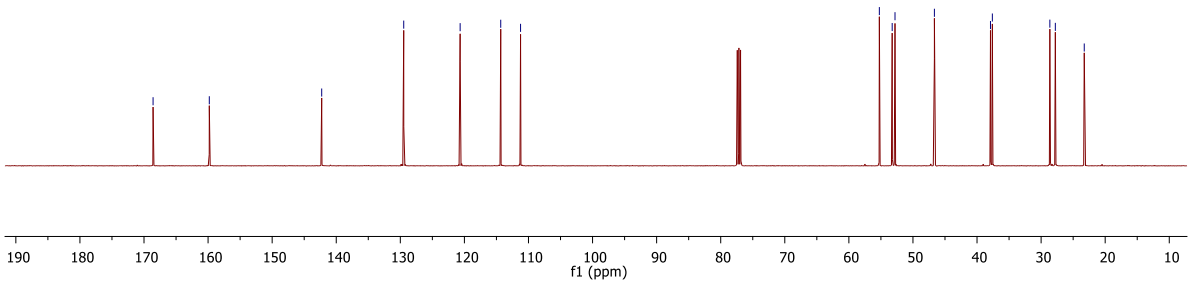
^{1}H NMR

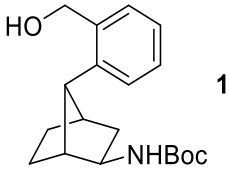


S252
Name - Scott Rice
Room No. - G56
Sample - S252

168.58 159.81 142.27 129.47 120.66 114.33 111.24 55.24 53.24 52.80 46.65 37.90 37.61 28.64 27.78 23.27

^{13}C NMR

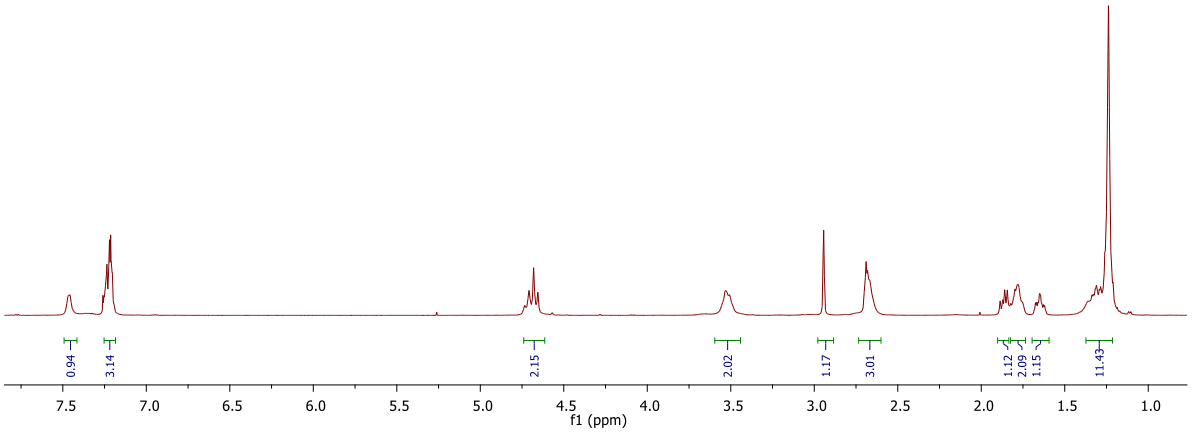




10

sample14216
Name - Scott Rice
Room No. - G56
Sample - S265

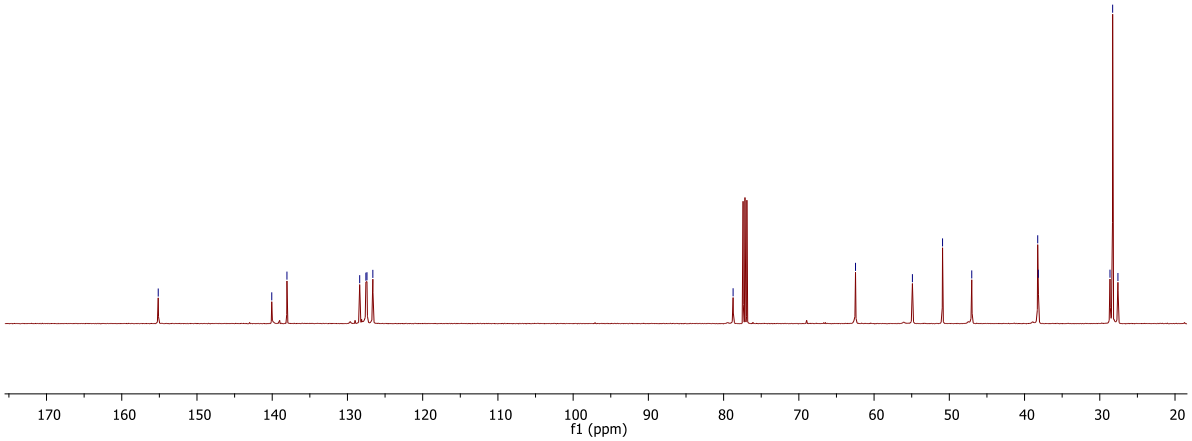
^{1}H NMR

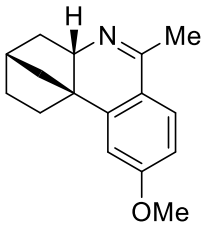


sample14216
Name - Scott Rice
Room No. - G56
Sample - S265

155.15
140.06
138.04
128.37
127.55
127.40
126.63
78.74
62.47
54.90
50.90
47.02
38.25
38.17
28.64
28.29
27.59

^{13}C NMR

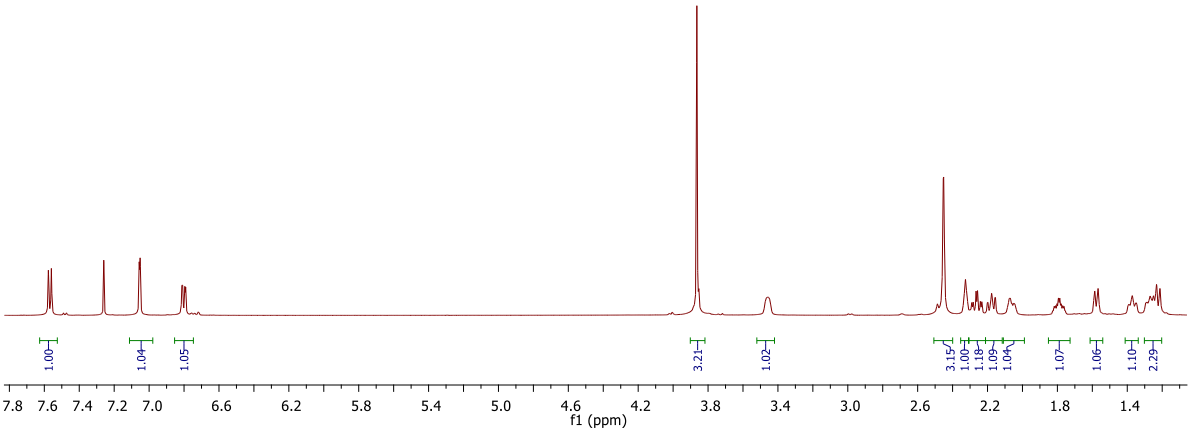




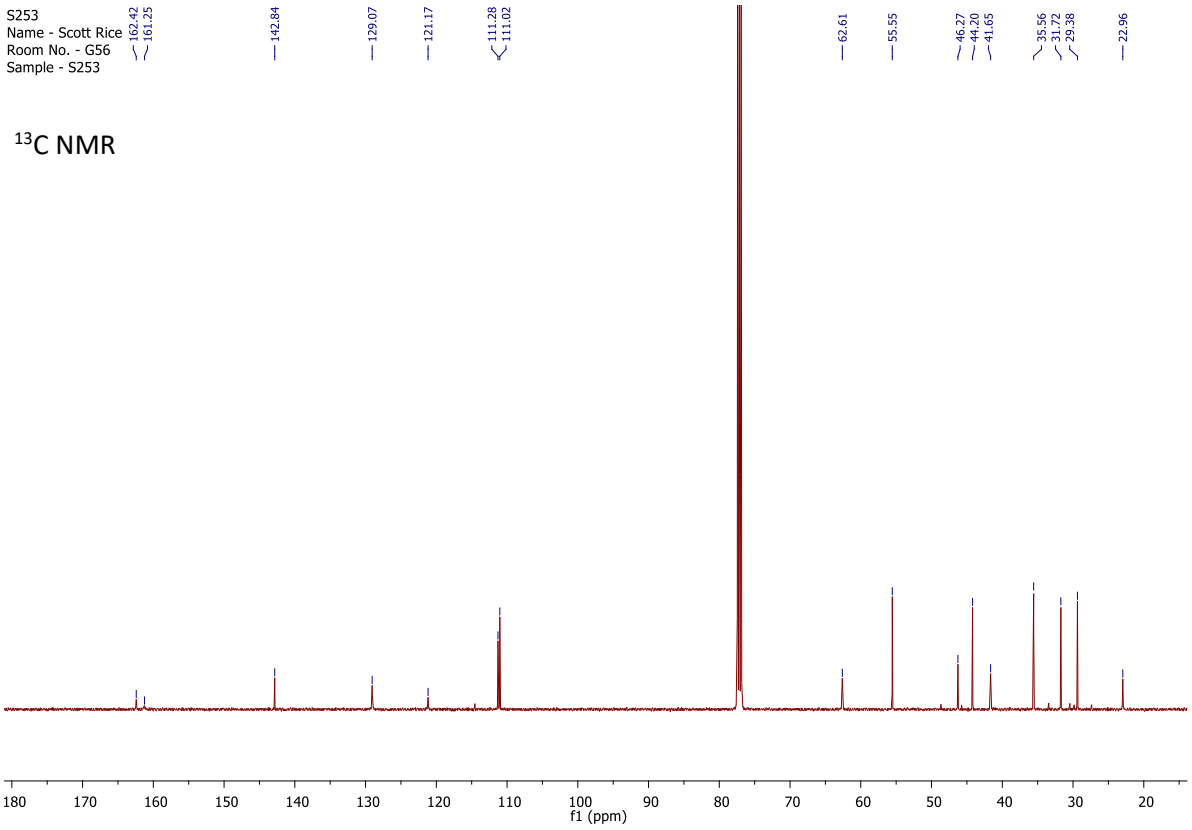
S1

S253
Name - Scott Rice
Room No. - G56
Sample - S253

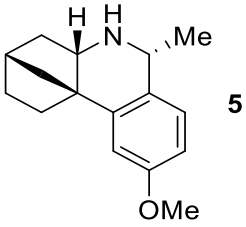
^{1}H NMR



S253
Name - Scott Rice
Room No. - G56
Sample - S253



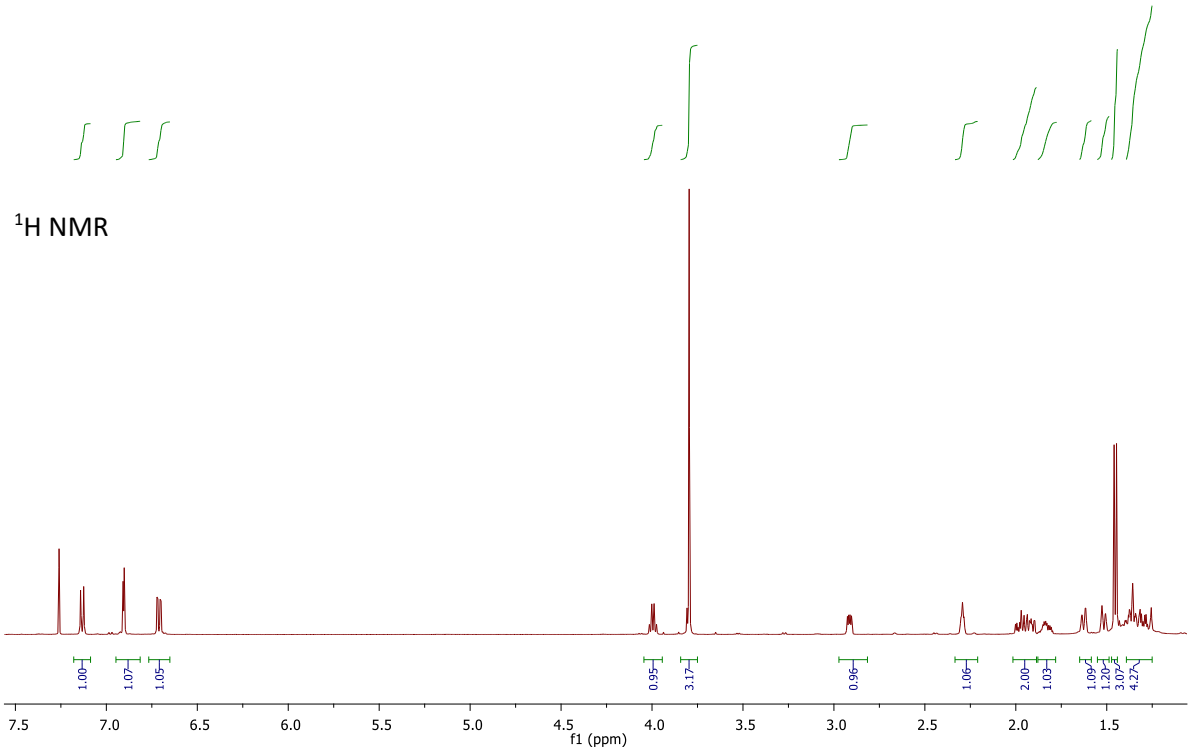
^{13}C NMR



5

S254c
Name - Scott Rice
Room No. - G56
Sample - S254c

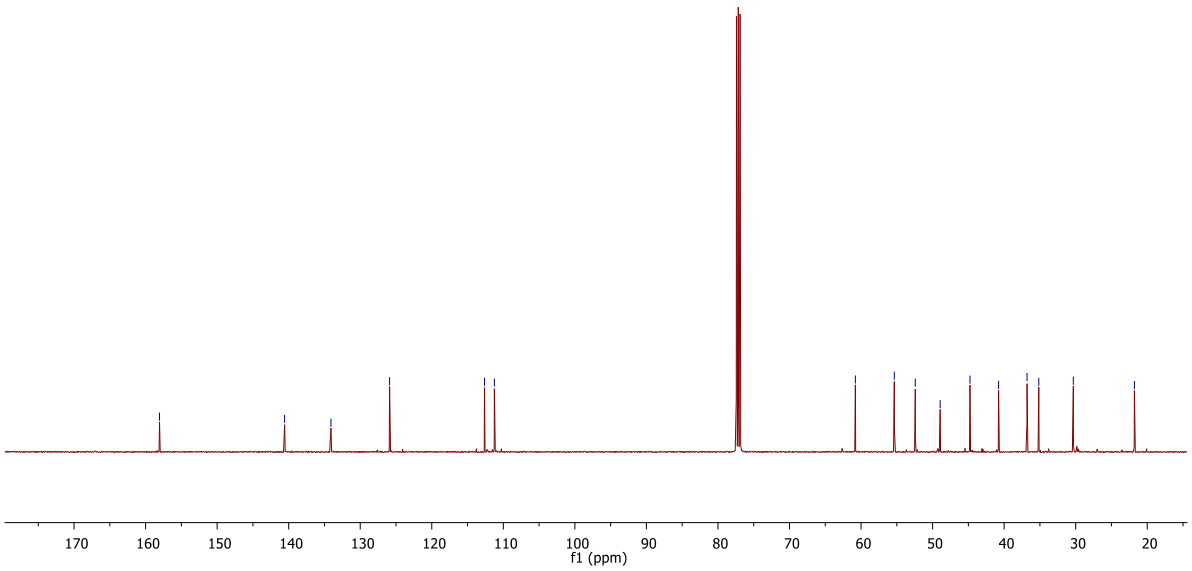
^{1}H NMR

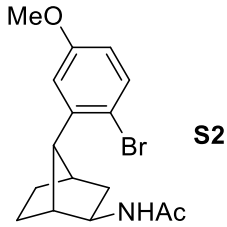


S254c
Name - Scott Rice
Room No. - G56
Sample - S254c

158.05
140.57
134.09
125.90
112.63
111.25
60.79
55.35
52.42
48.94
44.78
40.78
36.80
35.16
30.33
21.79

^{13}C NMR

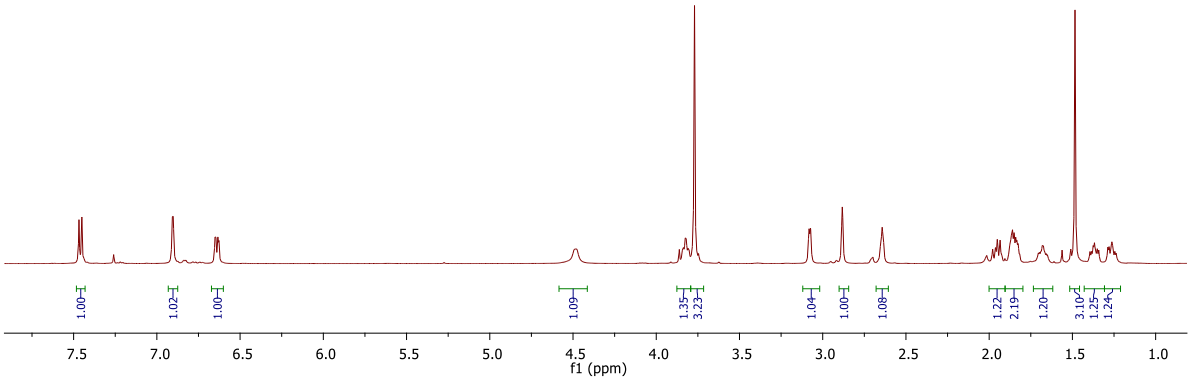




S2

S260
Name - Scott Rice
Room No. - G56
Sample - S260

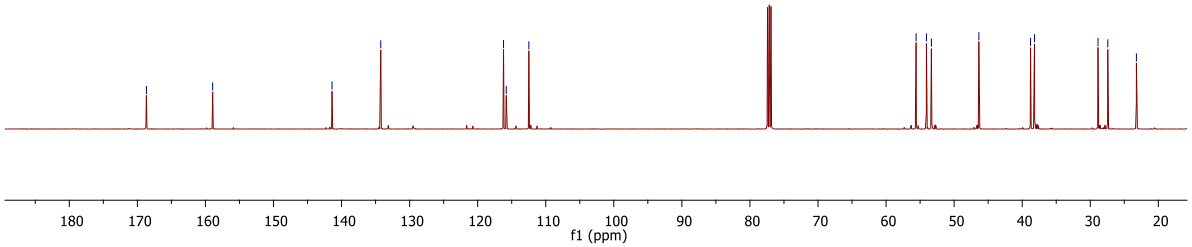
^{1}H NMR

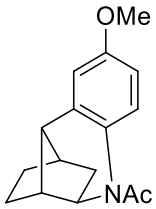


S260
Name - Scott Rice
Room No. - G56
Sample - S260

168.67
158.94
141.40
134.24
116.20
115.80
112.48
55.59
54.07
53.34
46.37
38.77
38.19
28.86
27.42
23.22

^{13}C NMR

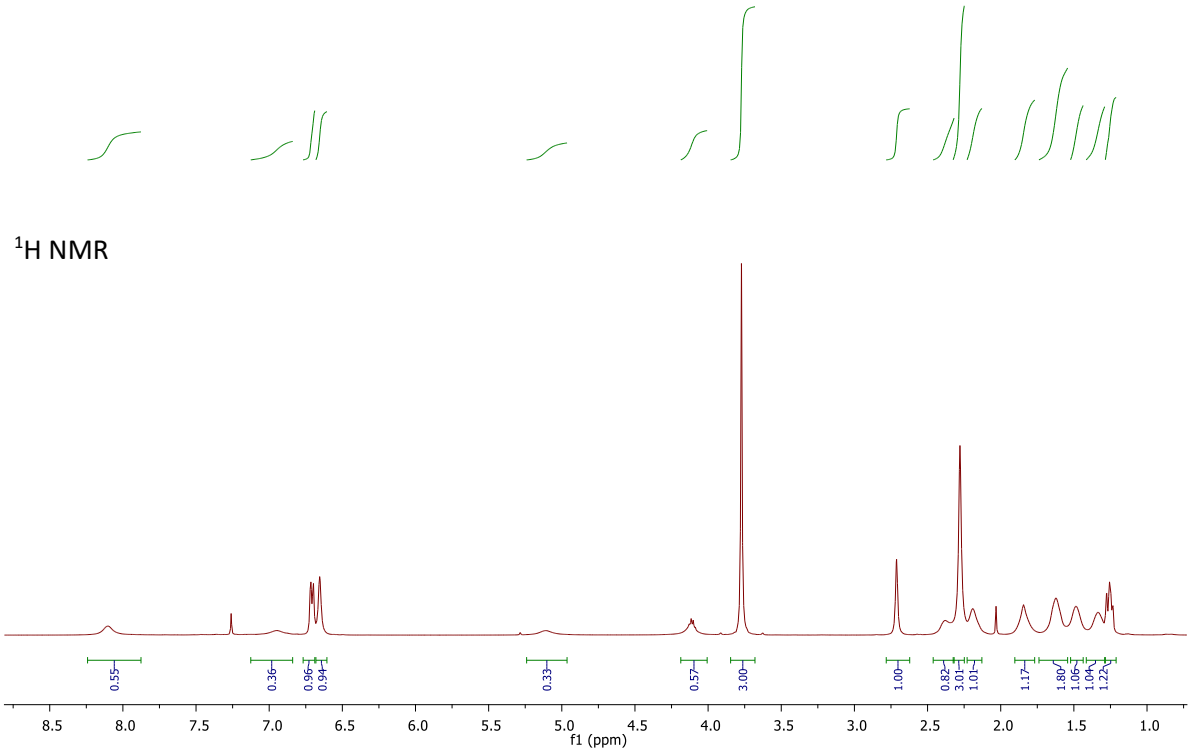




S3

S261
Name - Scott Rice
Room No. - G56
Sample - S261

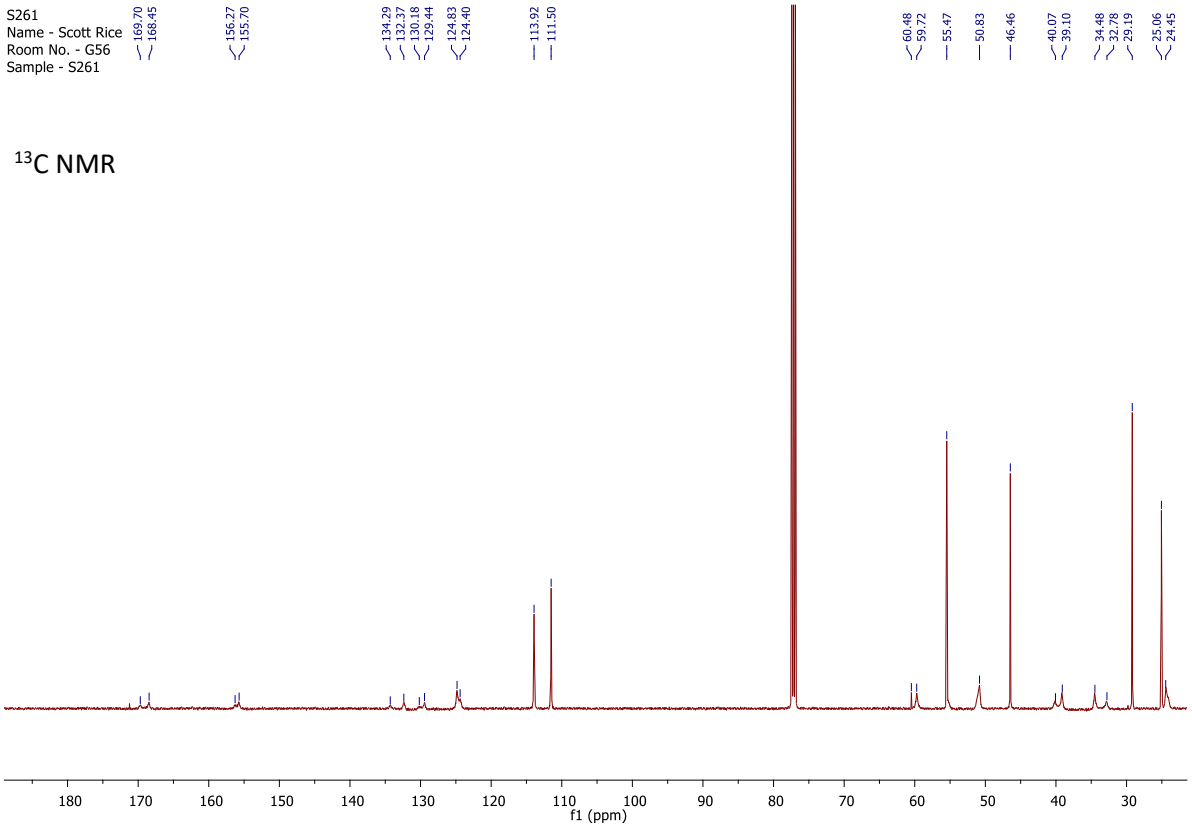
^{1}H NMR

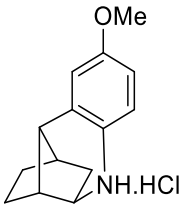


S261
Name - Scott Rice
Room No. - G56
Sample - S261

169.70
168.45
156.27
155.70
134.29
132.37
130.18
129.44
124.83
124.40
113.92
111.50
60.48
59.72
55.47
50.83
46.46
40.07
39.10
34.48
32.78
29.19
25.06
24.45

^{13}C NMR

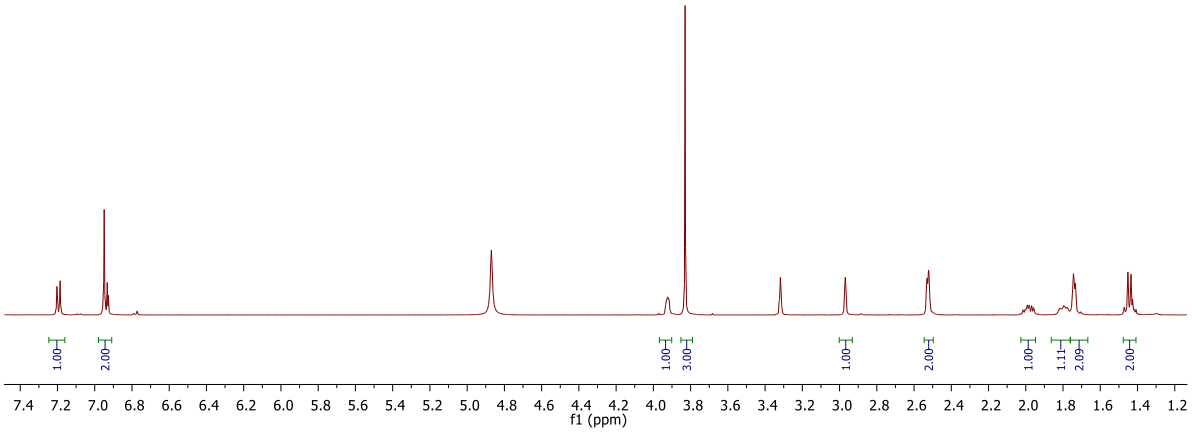




11

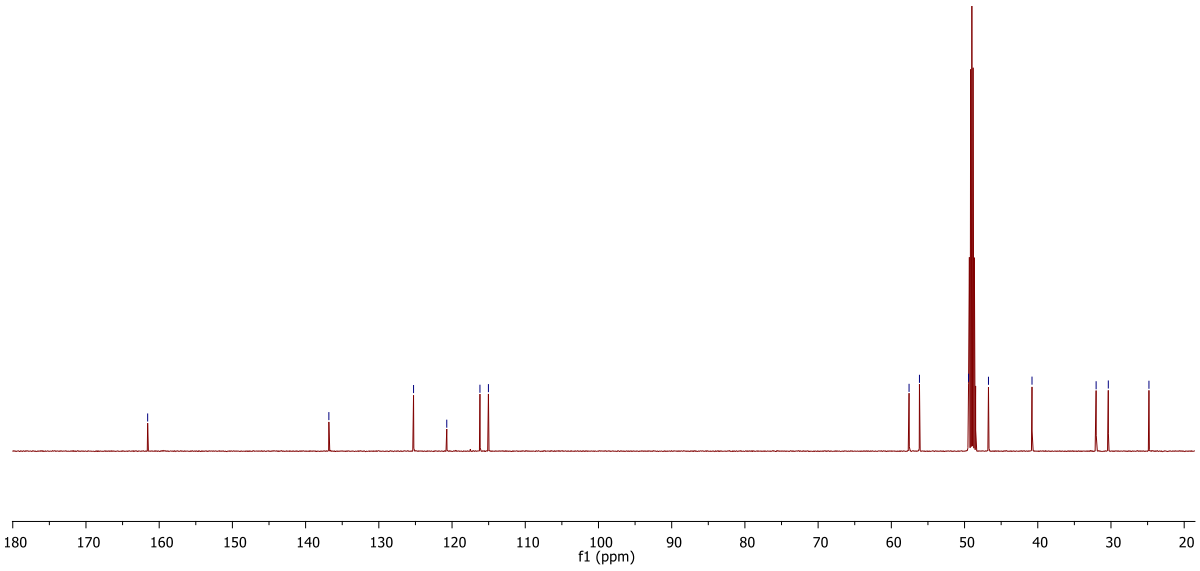
S262
Name - Scott Rice
Room No. - G56
Sample - S262

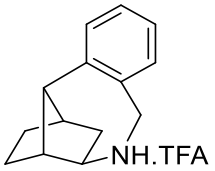
^{1}H NMR



S262
Name - Scott Rice
Room No. - G56
Sample - S262

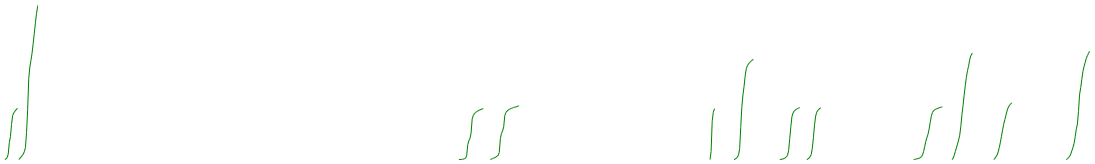
^{13}C NMR



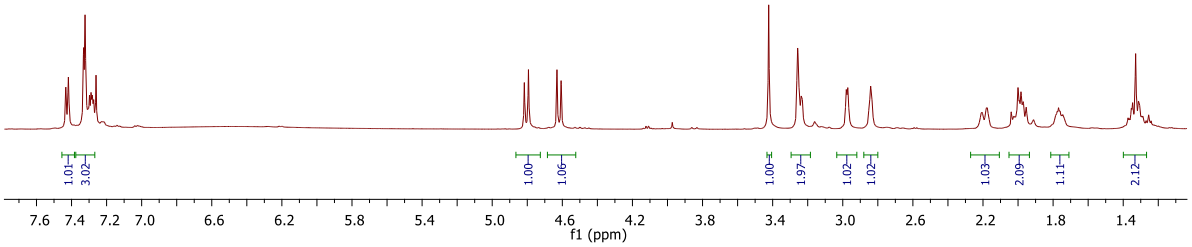


12

S266
Name - Scott Rice
Room No. - G56
Sample - S266



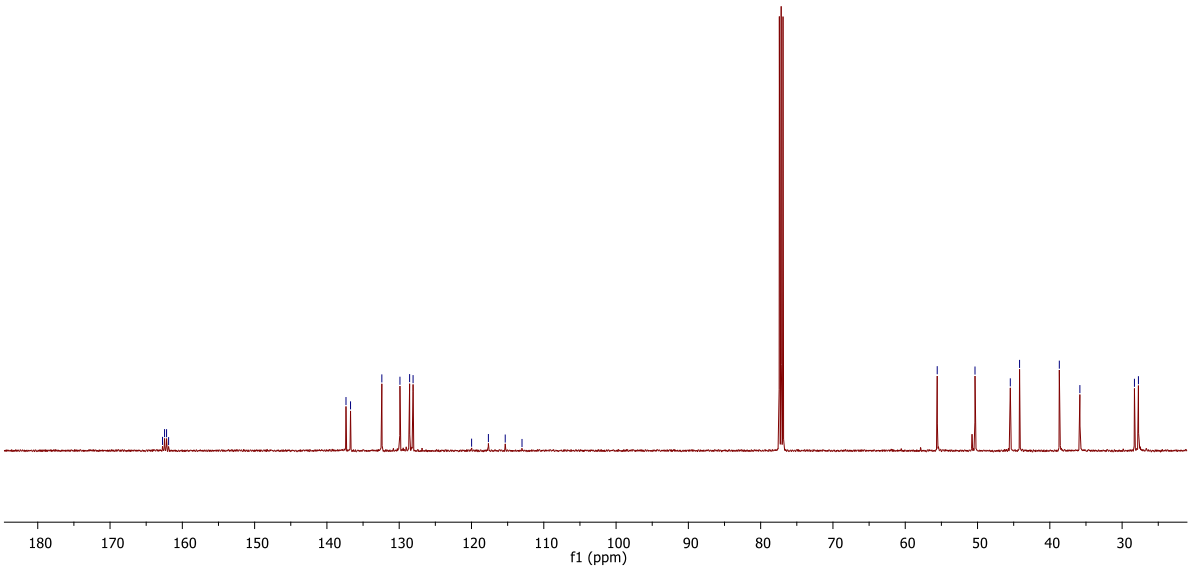
^{1}H NMR

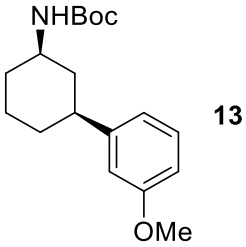


S266
Name - Scott Rice
Room No. - G56
Sample - S266

162.74
162.46
162.18
161.90
137.36
136.73
132.40
129.90
128.56
128.08
119.99
117.66
115.33
113.01
55.58
50.35
45.47
44.19
38.69
35.84
28.30
27.74

^{13}C NMR

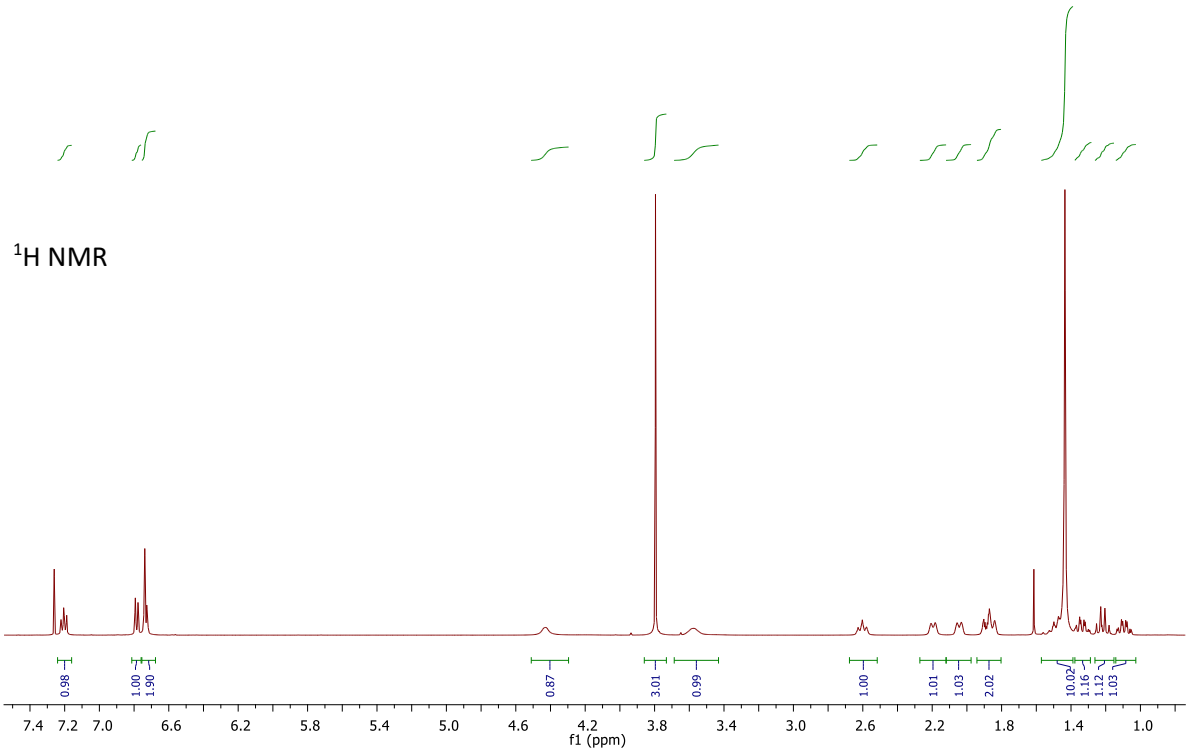




13

S244
Name - Scott Rice
Room No. - G56
Sample - S244

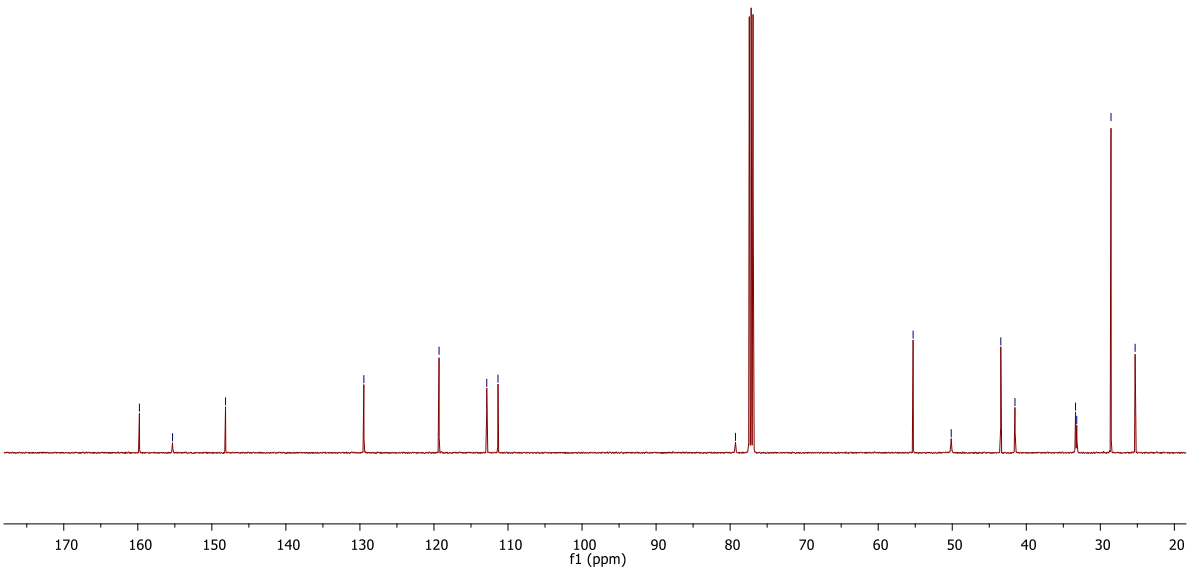
^{1}H NMR

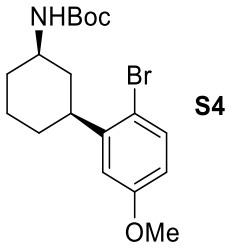


S244
Name - Scott Rice
Room No. - G56
Sample - S244

159.78 155.31 148.15 129.47 119.31 112.87 111.35 79.28 55.29 50.14 43.44 41.53 33.35 33.18 28.56 25.30

^{13}C NMR

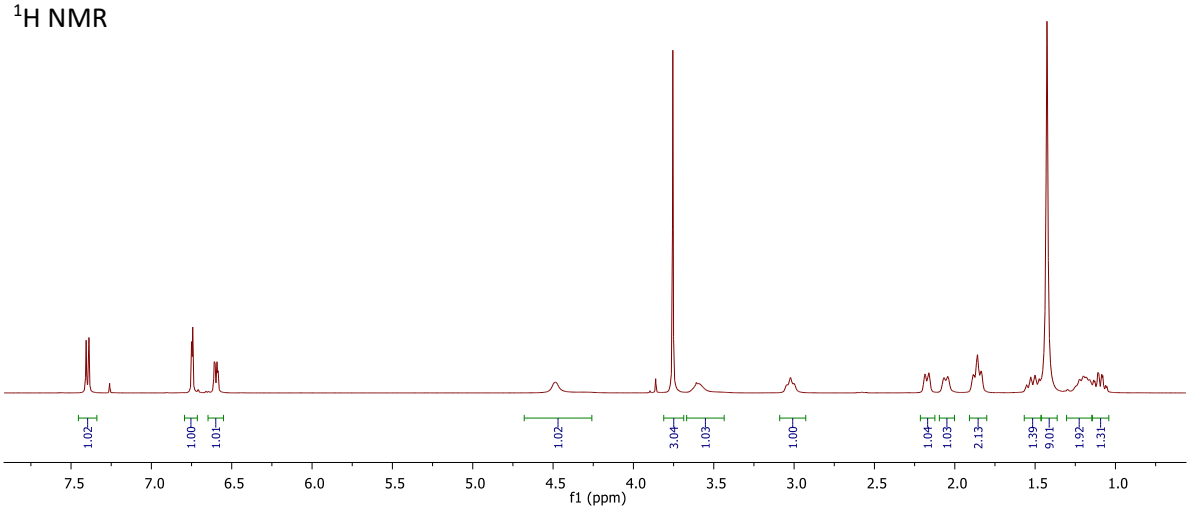




S4

S236
Name - Scott Rice
Room No. - G56
Sample - S236

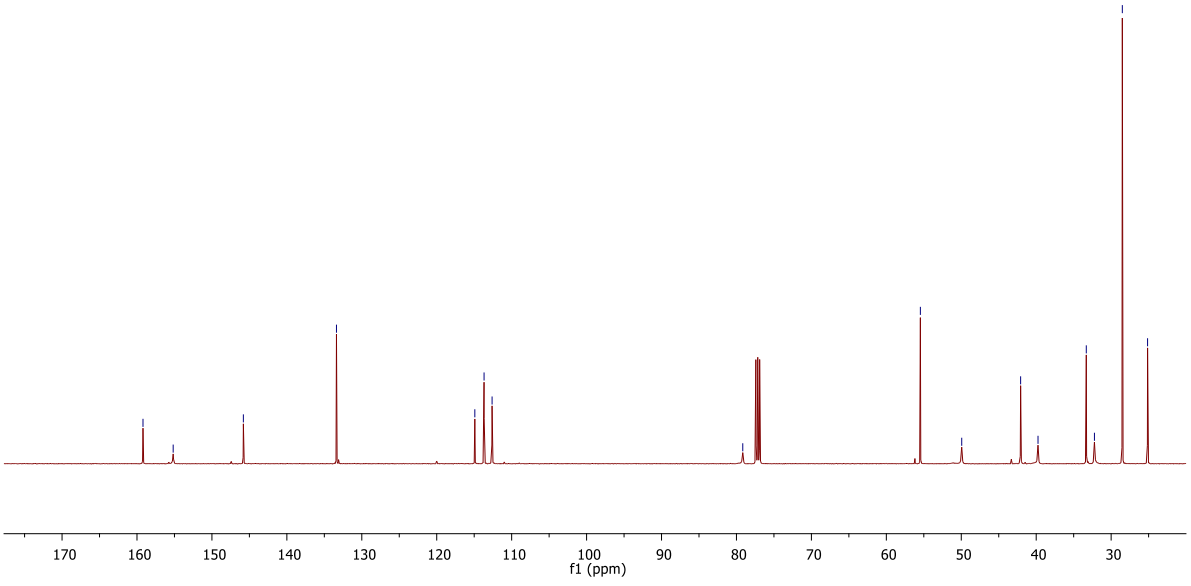
^{1}H NMR

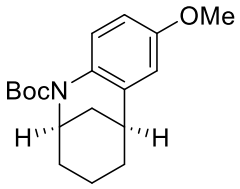


S236
Name - Scott Rice
Room No. - G56
Sample - S236

159.20
155.17
145.80
133.38
114.92
113.68
112.61
79.16
55.46
49.94
42.08
39.76
33.32
32.23
28.51
25.14

^{13}C NMR

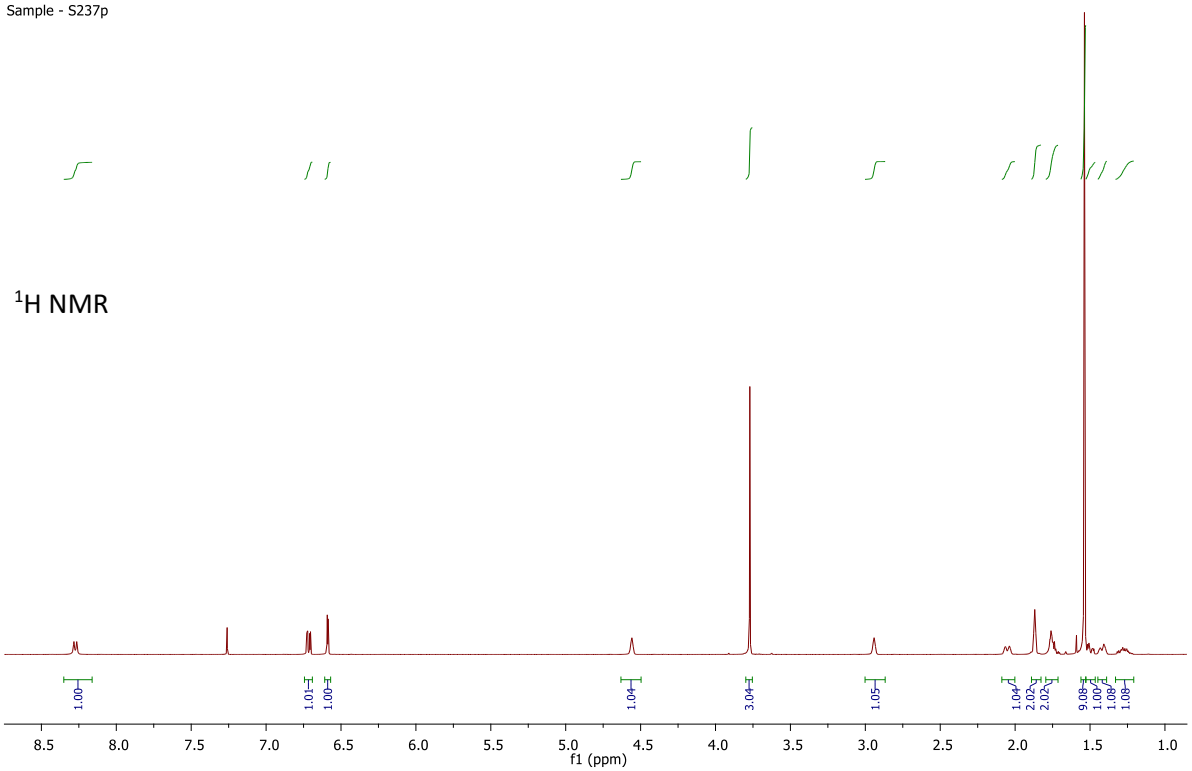




4

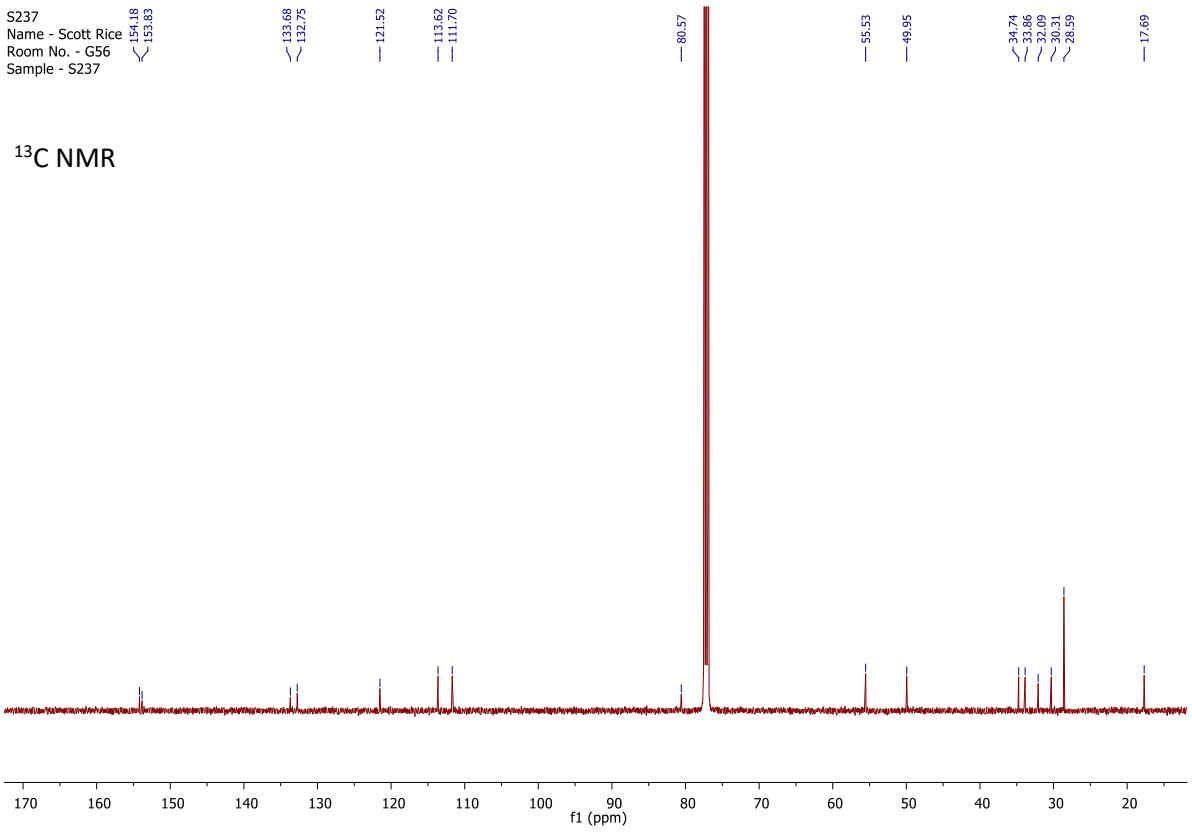
S237p
Name - Scott Rice
Room No. - G56
Sample - S237p

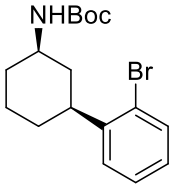
^{1}H NMR



S237
Name - Scott Rice
Room No. - G56
Sample - S237

^{13}C NMR

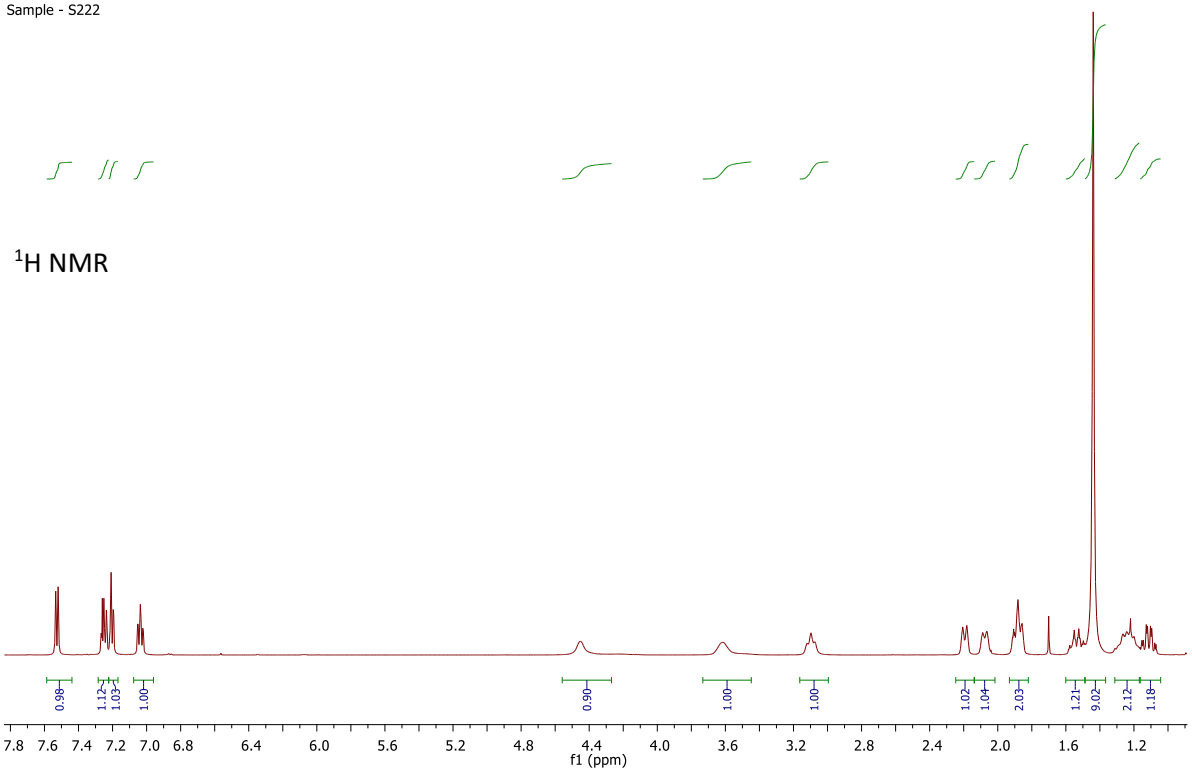




14

S222
Name - Scott Rice
Room No. - G56
Sample - S222

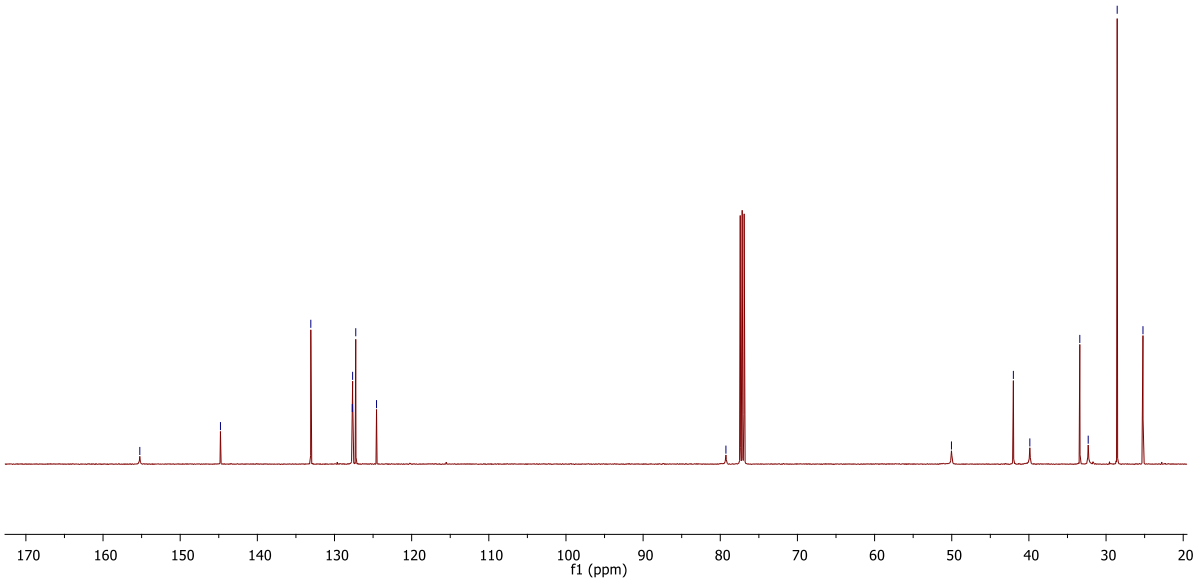
^{1}H NMR

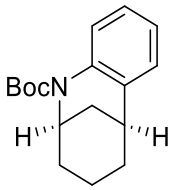


S222
Name - Scott Rice
Room No. - G56
Sample - S222

155.23 144.78 133.07 127.69 127.65 127.25 124.55 79.27 50.04 42.01 39.88 33.40 32.31 28.56 25.21

^{13}C NMR

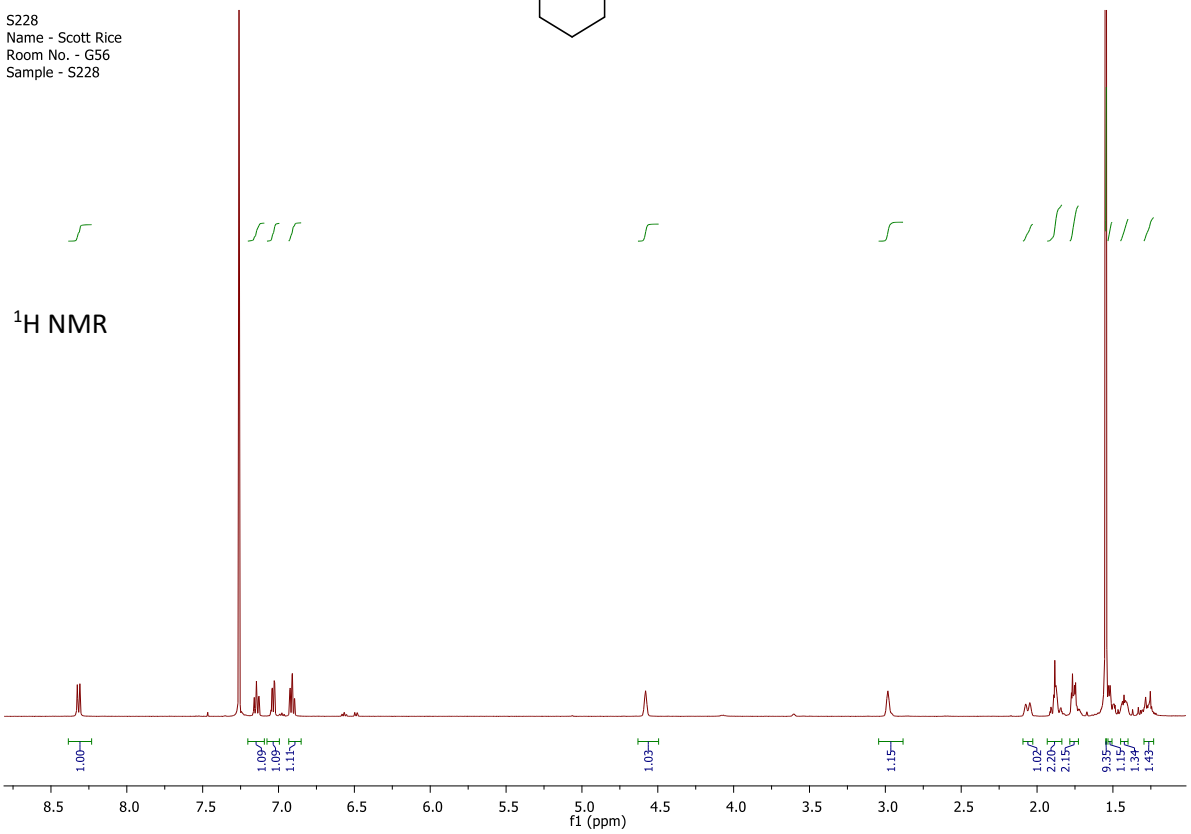




15

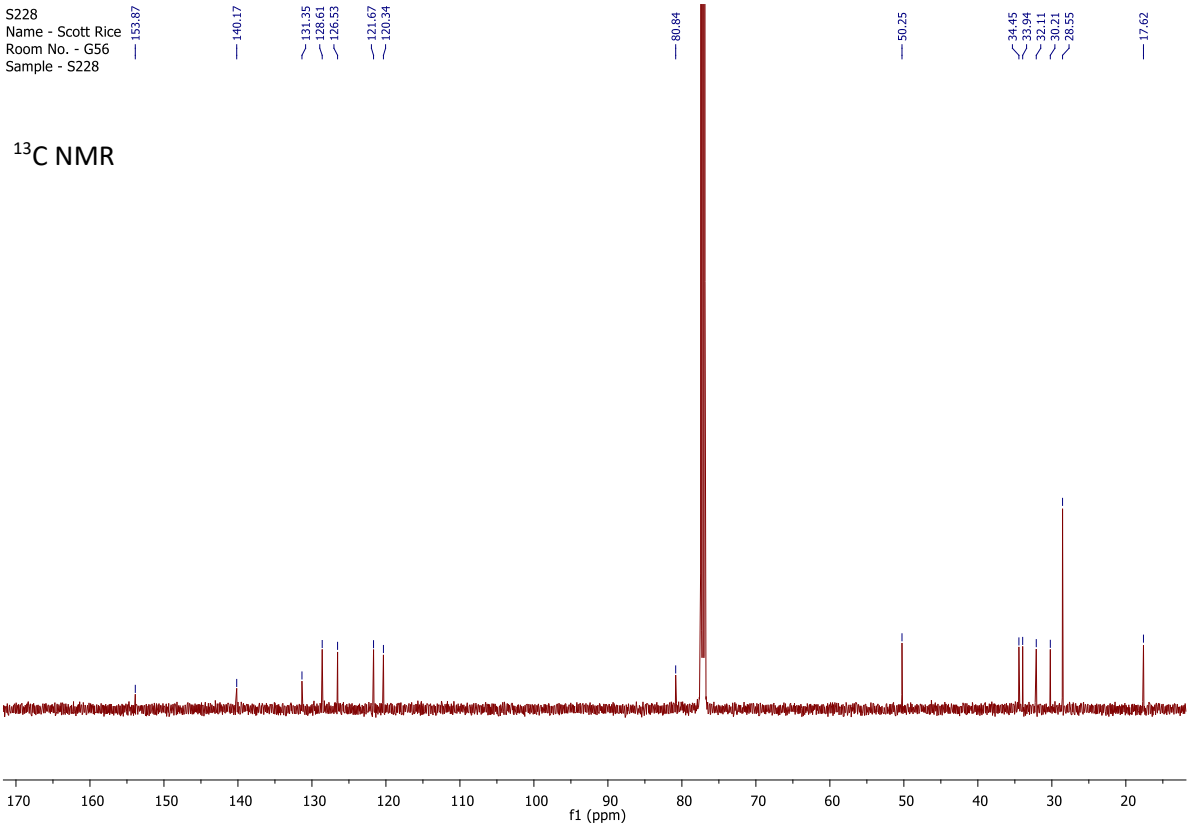
S228
Name - Scott Rice
Room No. - G56
Sample - S228

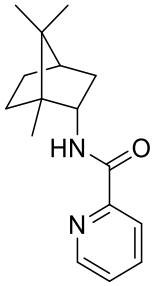
^{1}H NMR



S228
Name - Scott Rice
Room No. - G56
Sample - S228

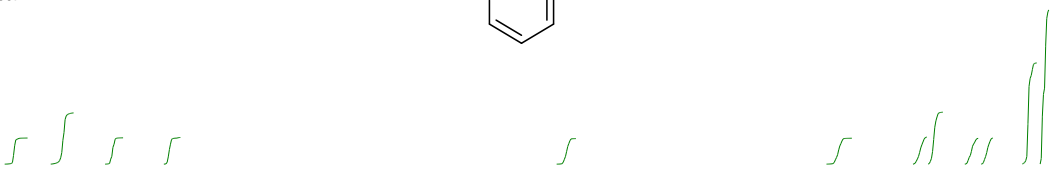
^{13}C NMR



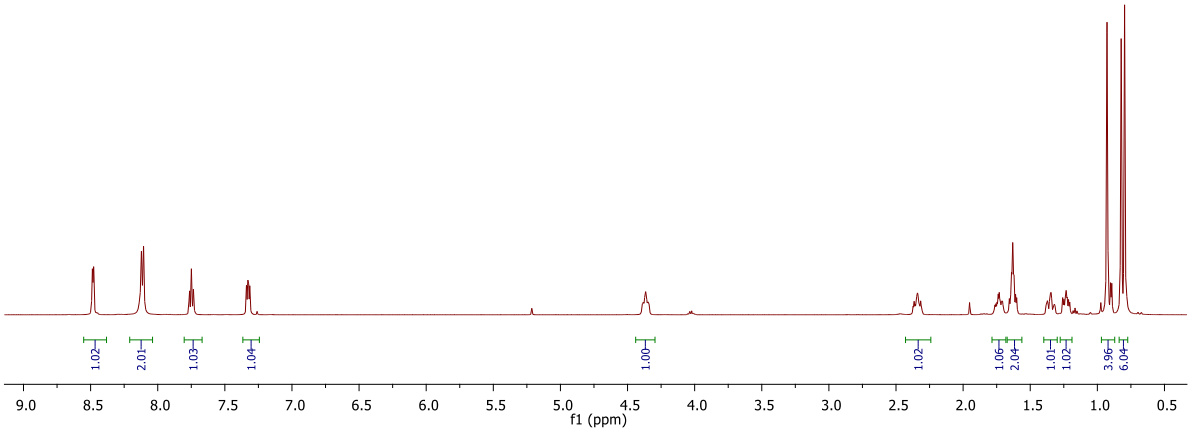


S5

S387
Name - Scott Rice
Room No. - G56
Sample - S387



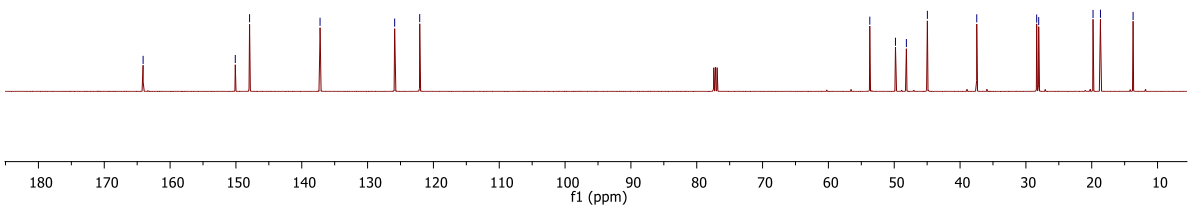
^{1}H NMR

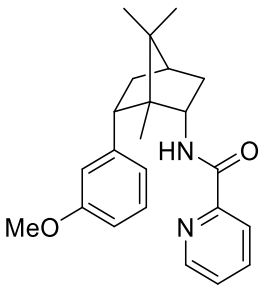


S387
Name - Scott Rice
Room No. - G56
Sample - S387

164.10
150.10
147.93
137.22
125.89
122.08
53.71
49.81
48.15
44.96
37.46
28.36
28.05
19.80
18.67
13.72

^{13}C NMR

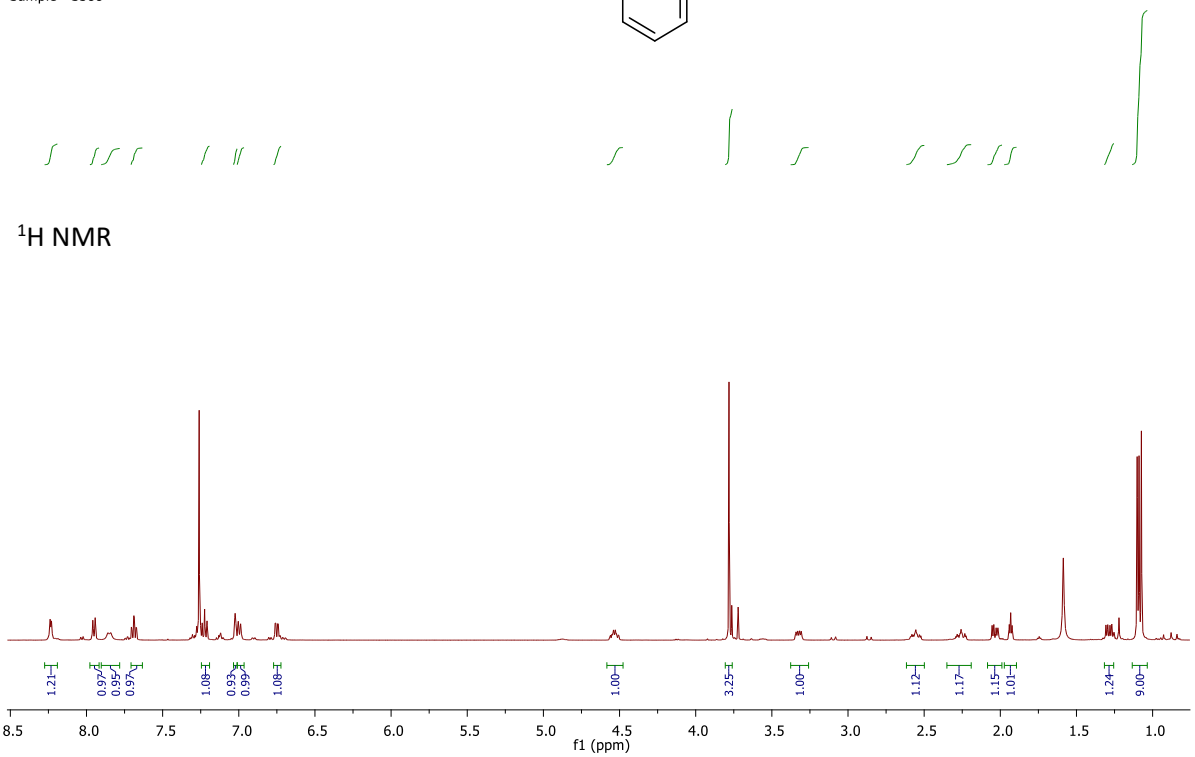




S6

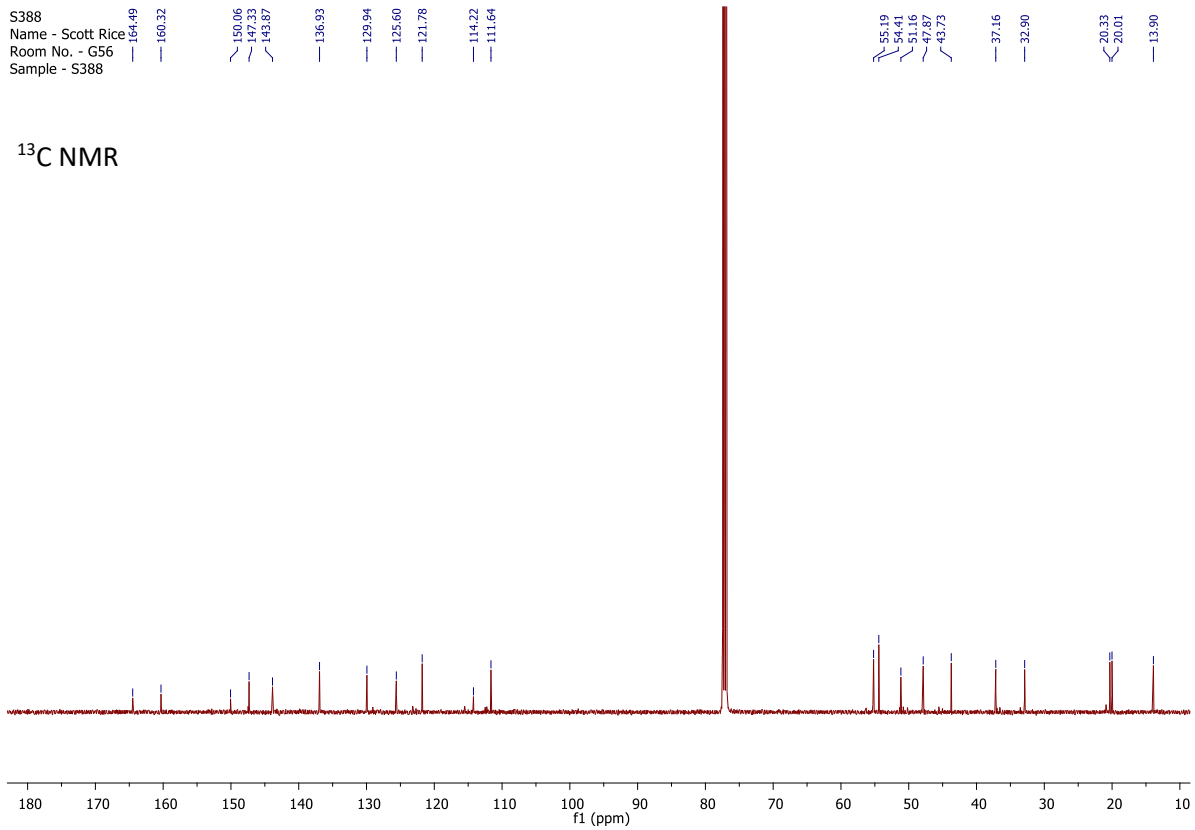
S388
Name - Scott Rice
Room No. - G56
Sample - S388

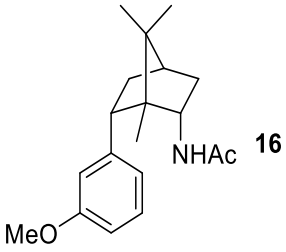
^{1}H NMR



S388
Name - Scott Rice
Room No. - G56
Sample - S388

^{13}C NMR

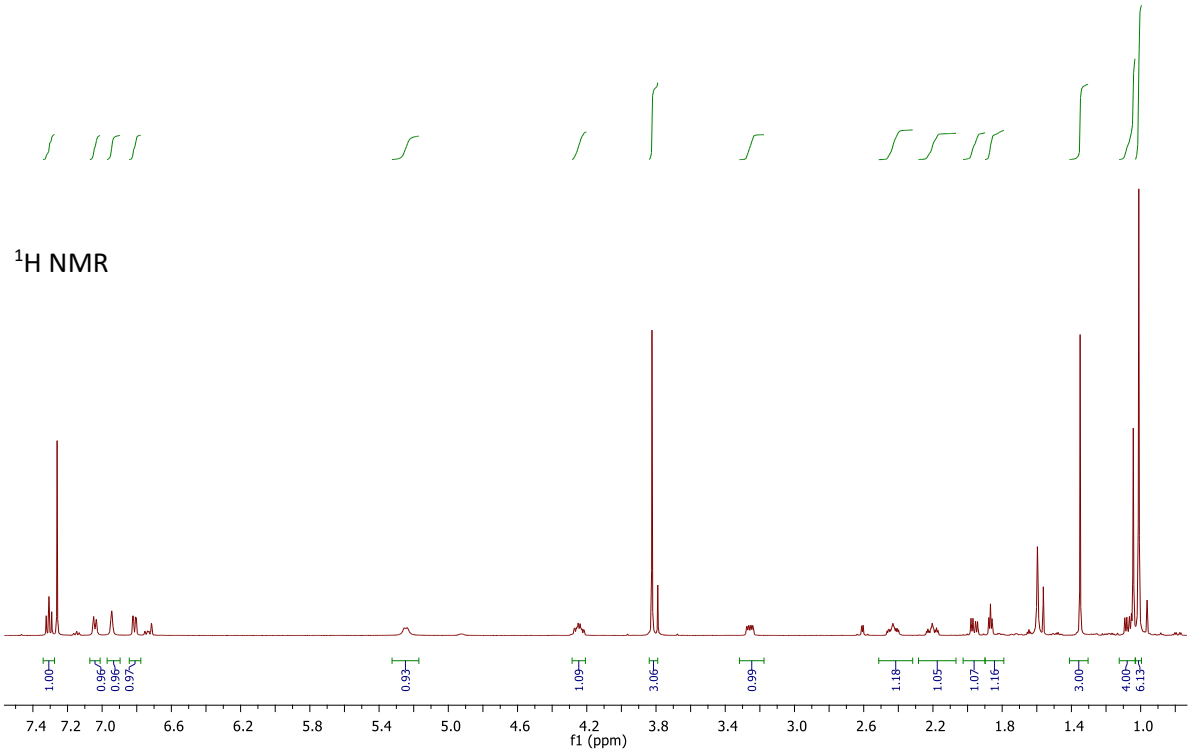




16

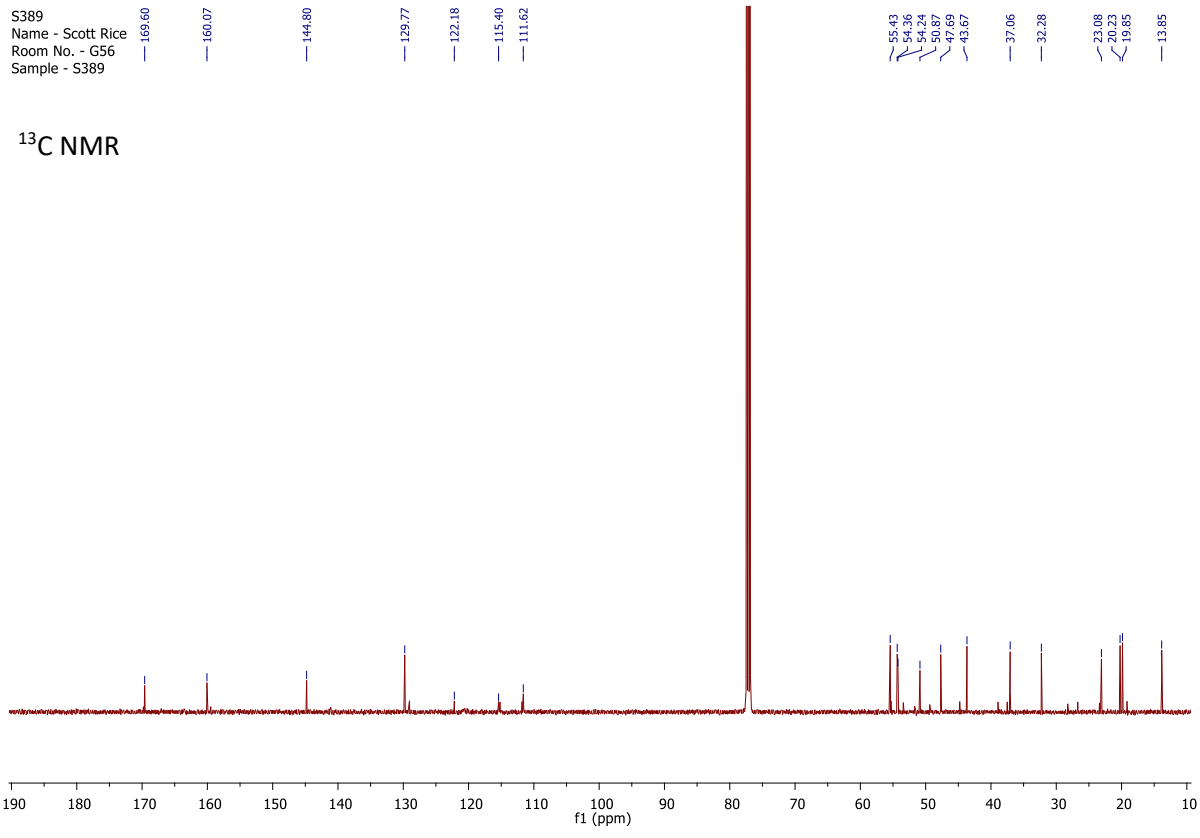
S389
Name - Scott Rice
Room No. - G56
Sample - S389

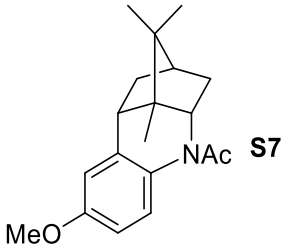
^{1}H NMR



S389
Name - Scott Rice
Room No. - G56
Sample - S389

^{13}C NMR

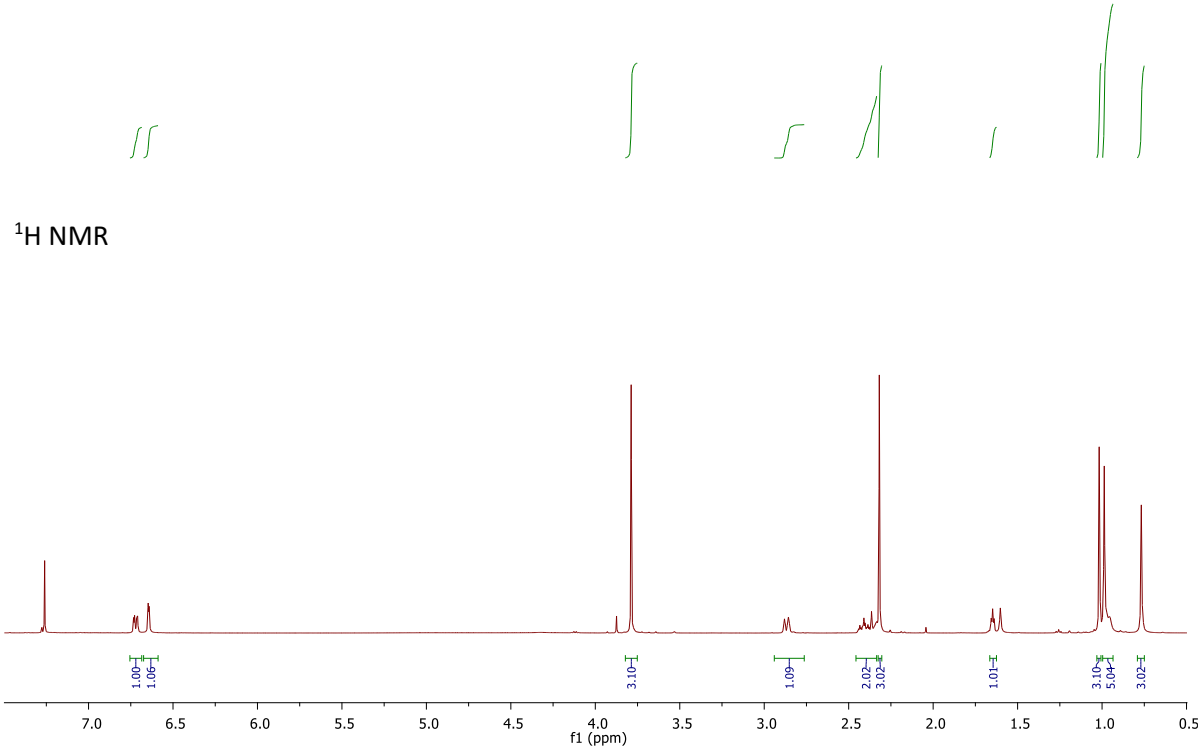




S7

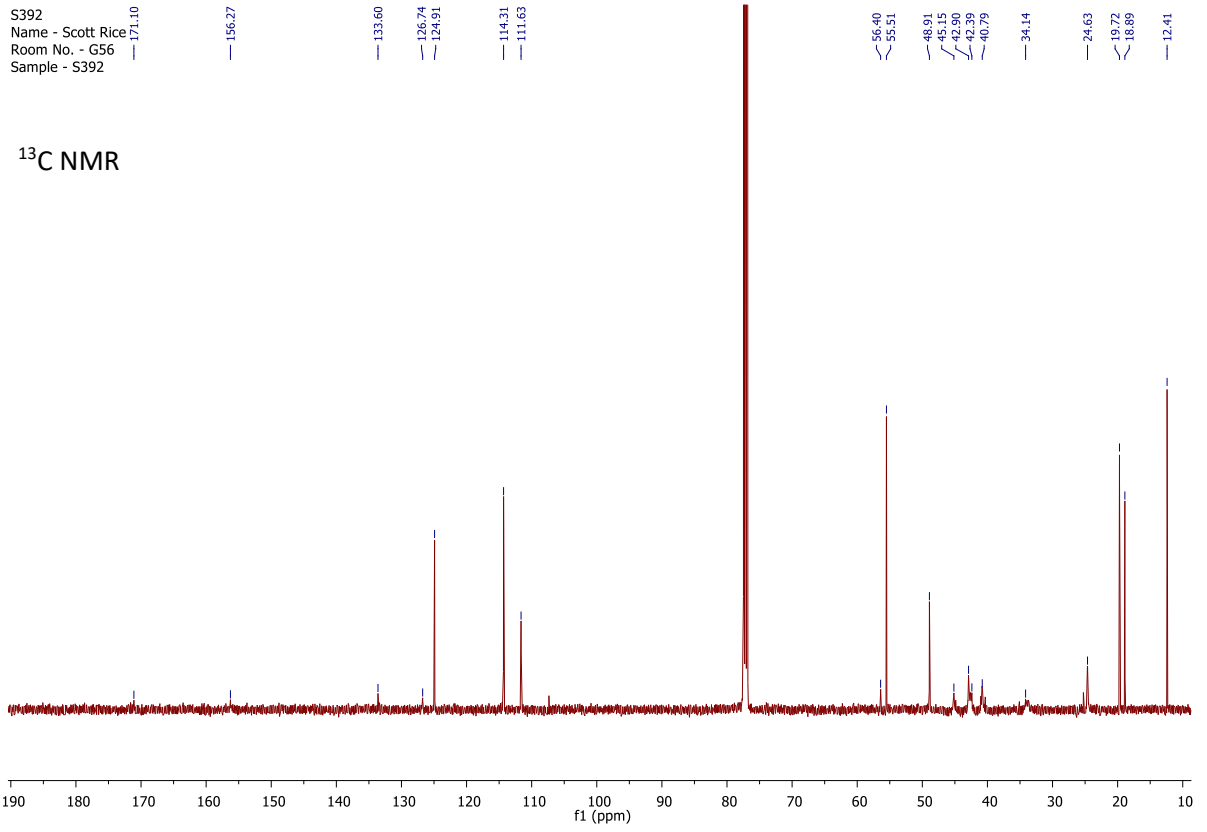
S392
Name - Scott Rice
Room No. - G56
Sample - S392

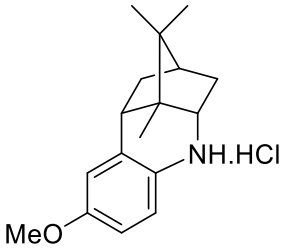
^{1}H NMR



S392
Name - Scott Rice
Room No. - G56
Sample - S392

^{13}C NMR

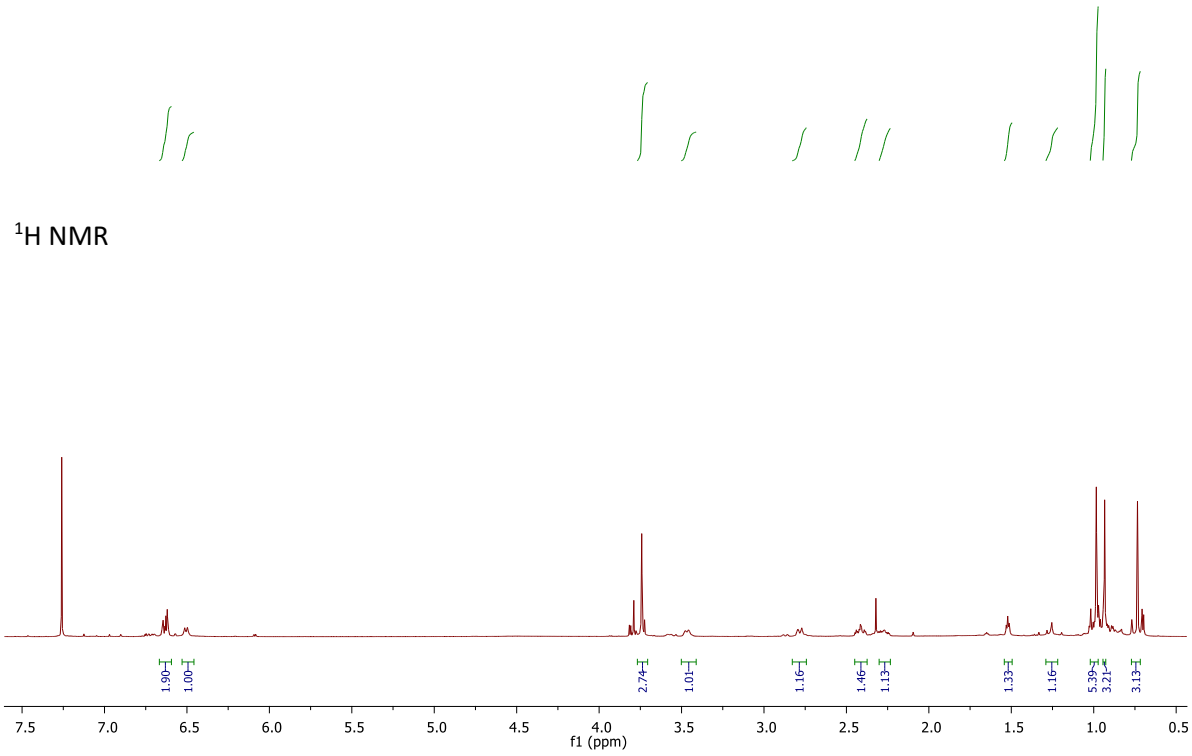




17

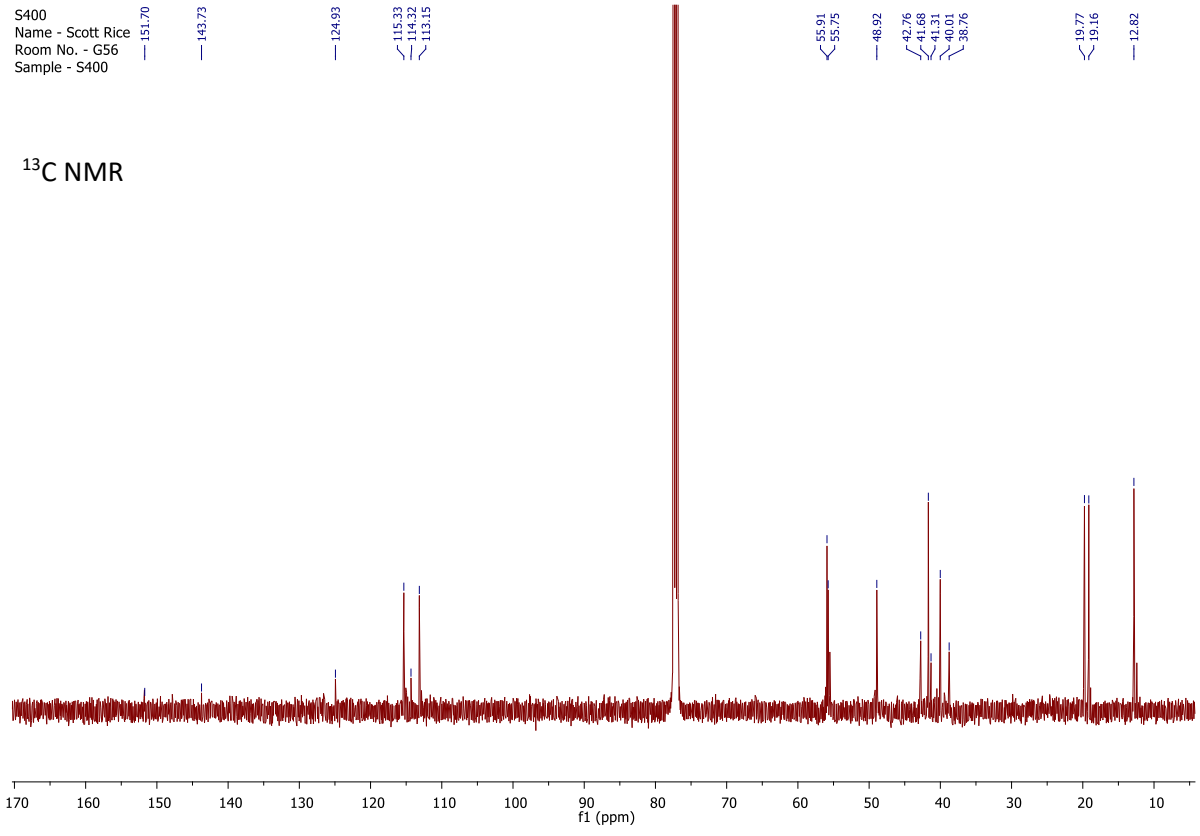
S400
Name - Scott Rice
Room No. - G56
Sample - S400

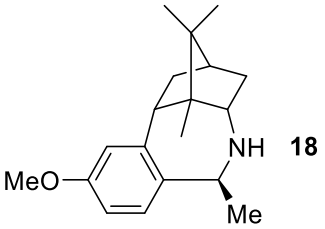
^{1}H NMR



S400
Name - Scott Rice
Room No. - G56
Sample - S400

^{13}C NMR

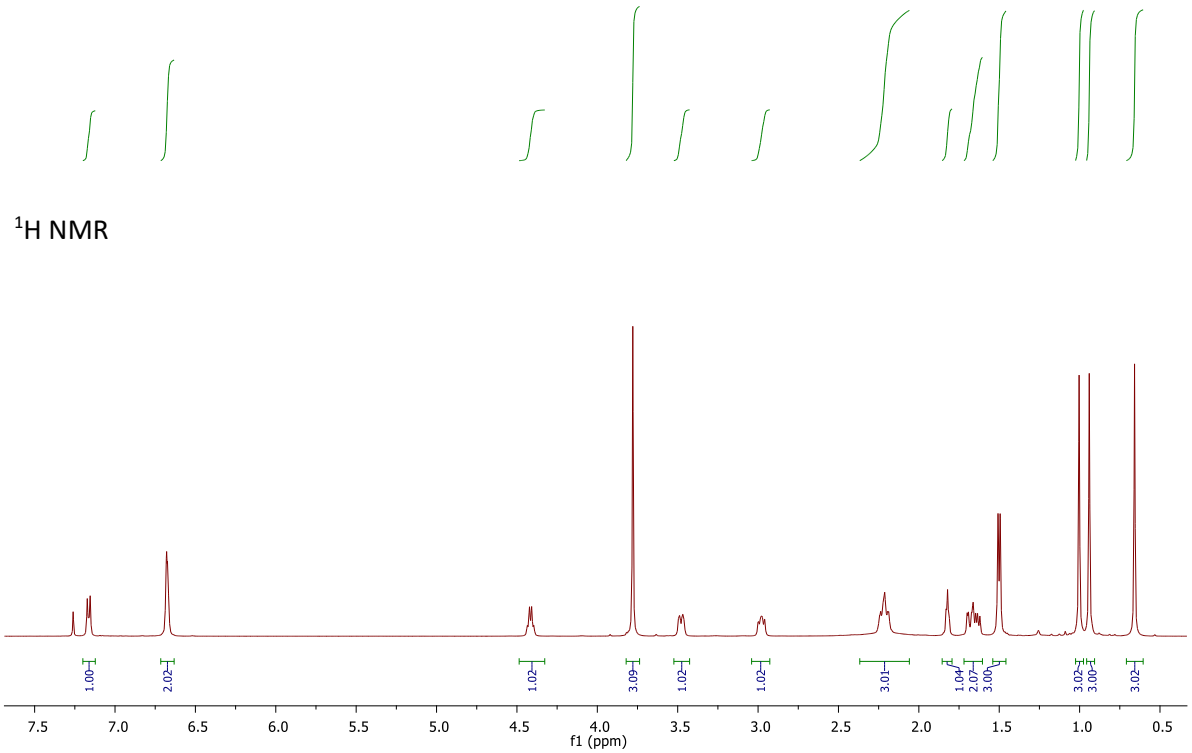




18

S390
Name - Scott Rice
Room No. - G56
Sample - S390

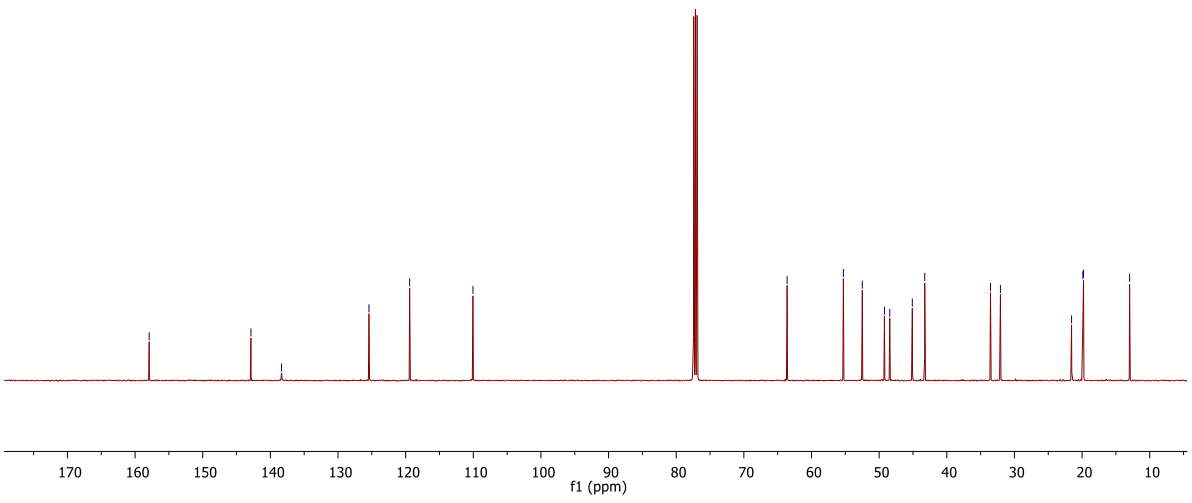
^{1}H NMR

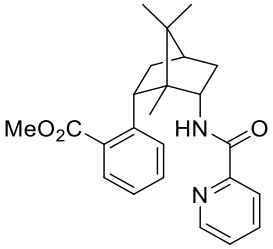


S390
Name - Scott Rice
Room No. - G56
Sample - S390

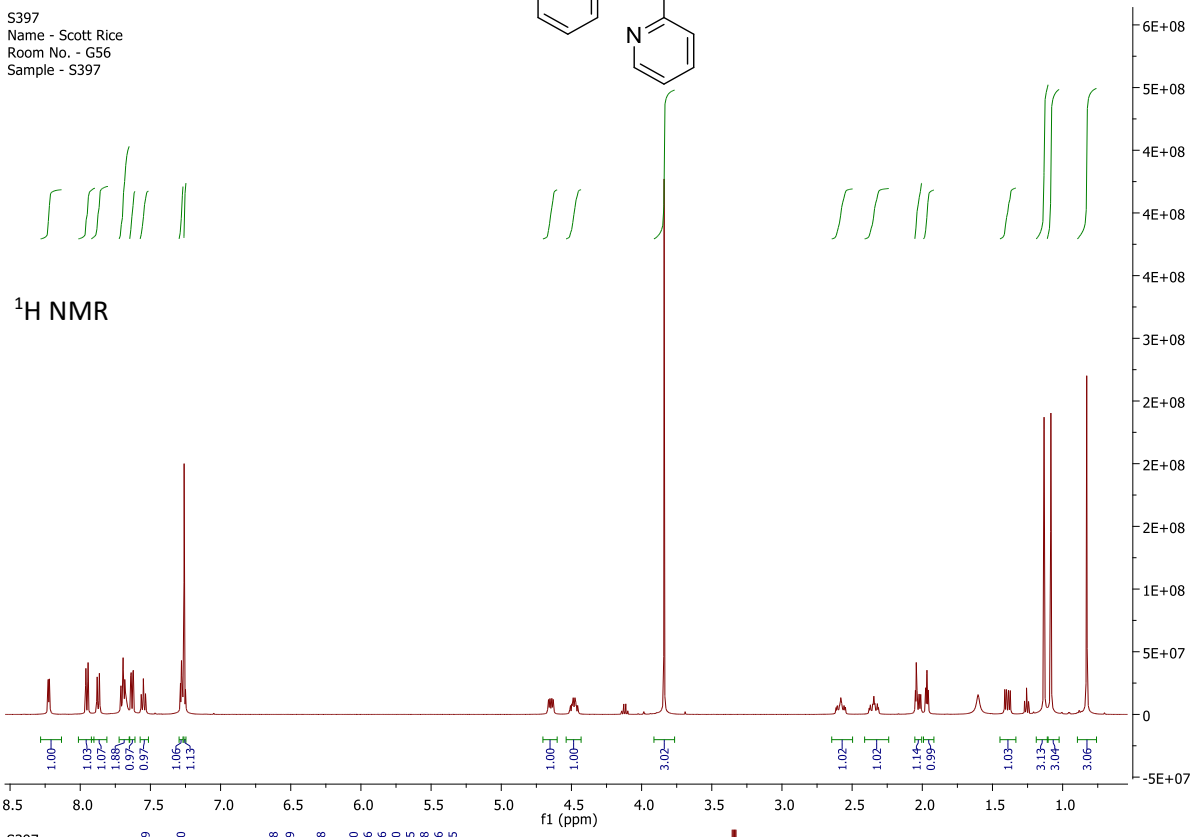
157.92
142.87
138.35
125.42
119.41
110.05
63.60
55.28
52.49
49.22
48.43
45.10
43.26
33.54
32.07
21.55
19.88
19.79
12.98

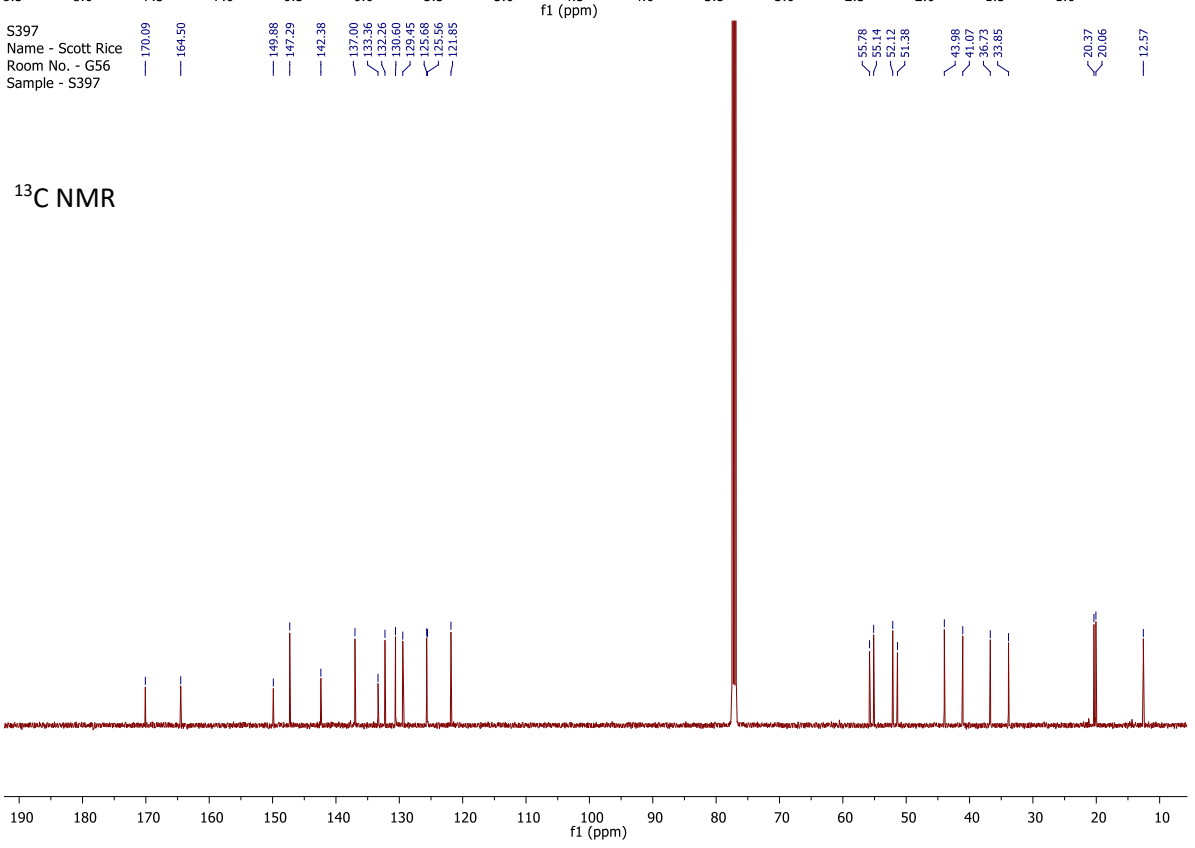
^{13}C NMR

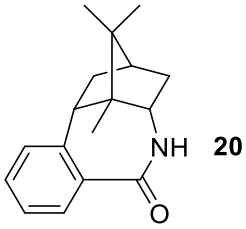



MeO2C
HN
O
N

19


S397
Name - Scott Rice
Room No. - G56
Sample - S397
1H NMR
f1 (ppm)

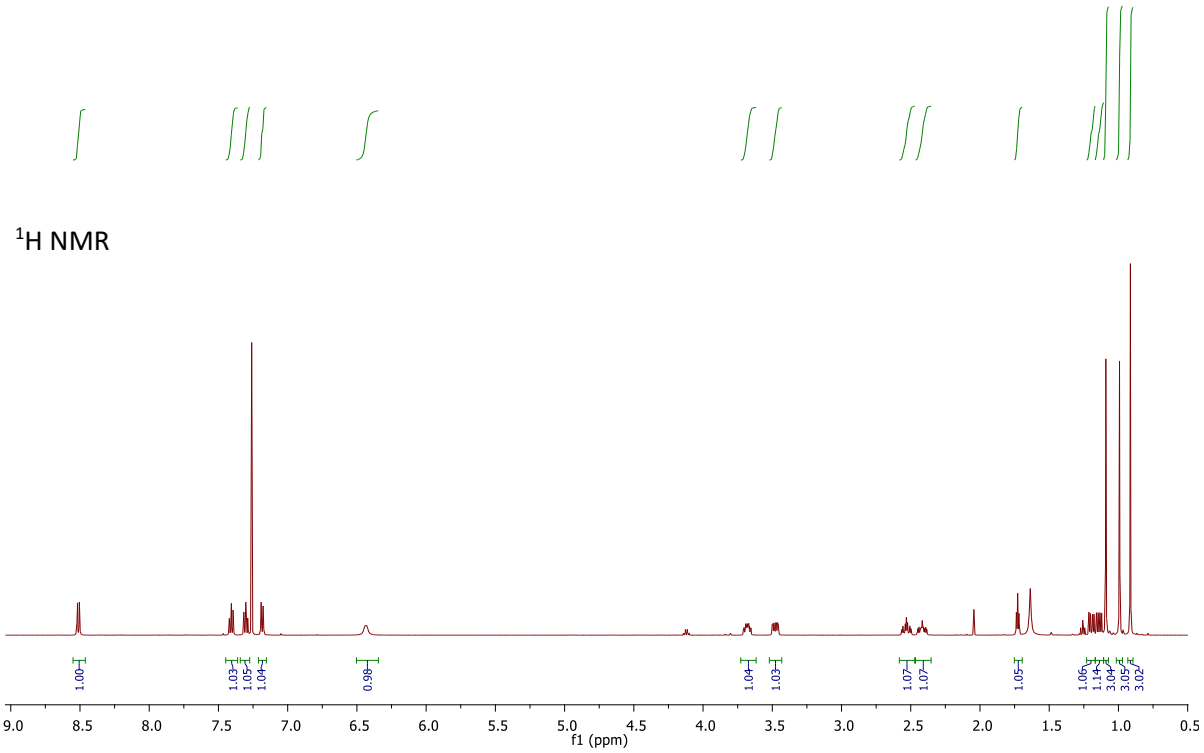

S397
Name - Scott Rice
Room No. - G56
Sample - S397
13C NMR
f1 (ppm)



20

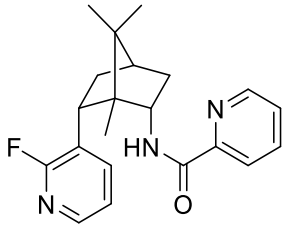
S398
Name - Scott Rice
Room No. - G56
Sample - S398

^{1}H NMR



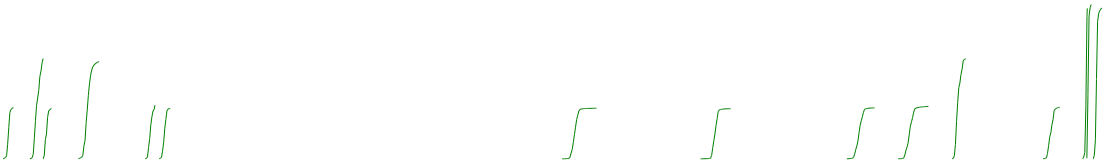
S398
Name - Scott Rice
Room No. - G56
Sample - S398

^{13}C NMR

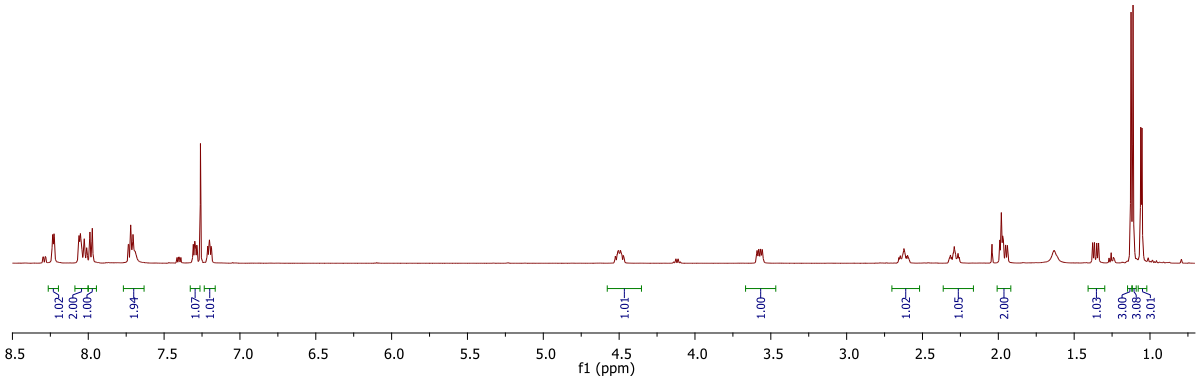


21

S395
Name - Scott Rice
Room No. - G56
Sample - S395



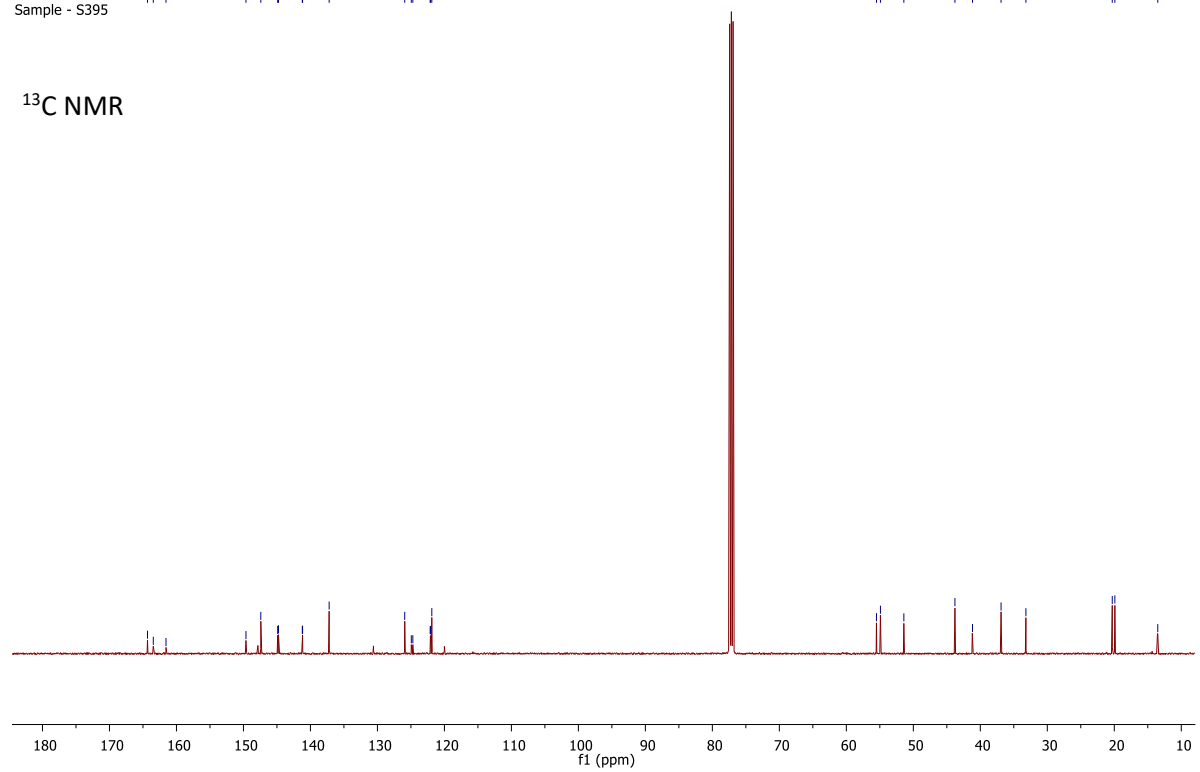
^{1}H NMR



S395
Name - Scott Rice
Room No. - G56
Sample - S395

164.33
163.46
161.56
149.63
147.41
144.89
144.77
141.21
141.17
137.21
125.92
124.94
124.71
122.12
122.08
121.88
55.50
54.91
51.41
43.79
41.16
36.90
33.19
20.30
19.91
13.51

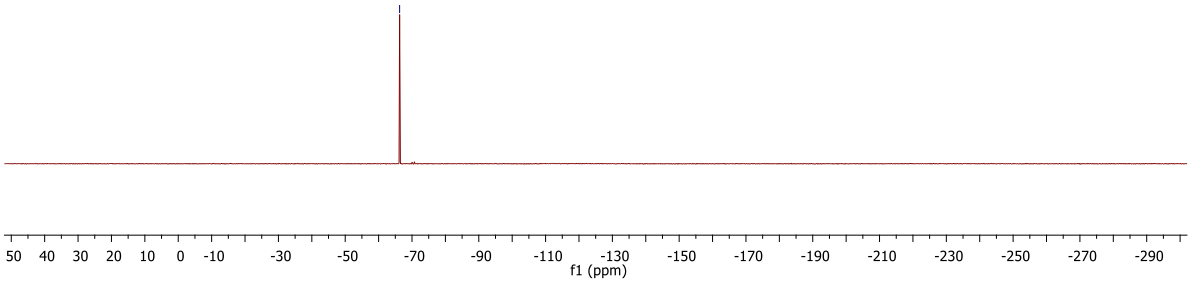
^{13}C NMR

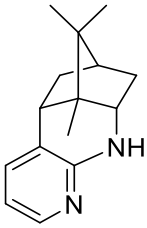


S395
Name - Scott Rice
Room No - G56
Sample S395

-66.29

^{19}F NMR

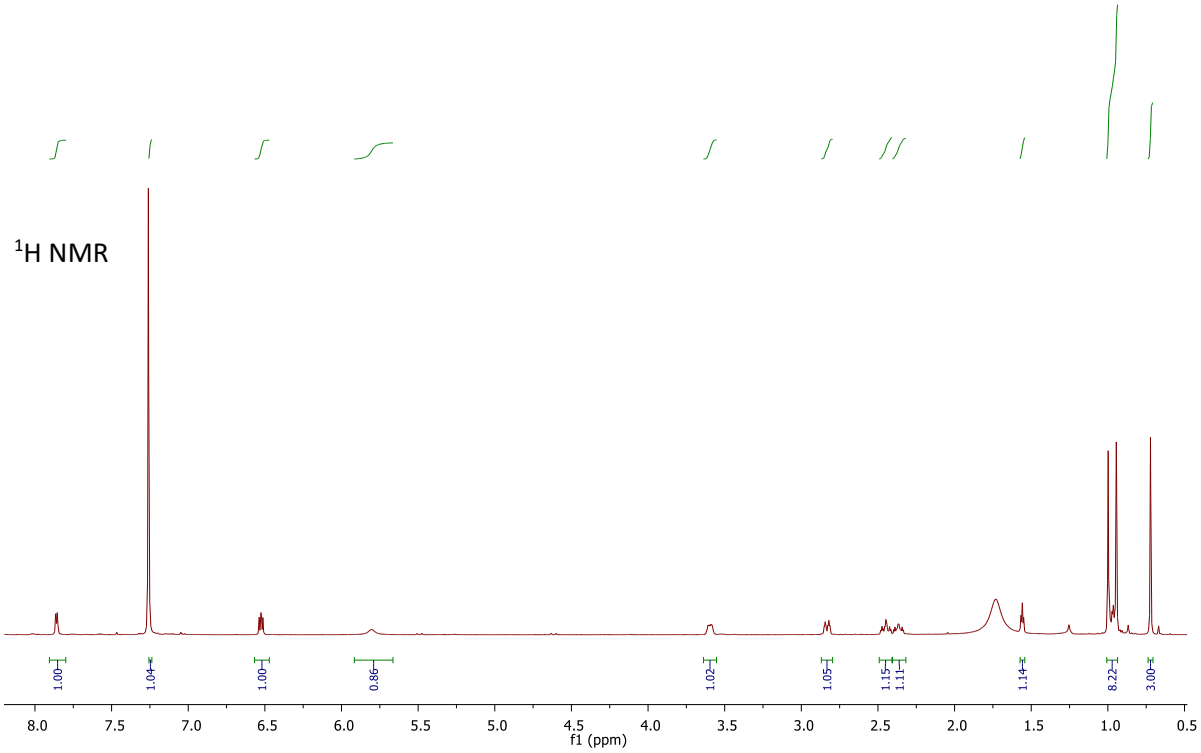




22

S396
Name - Scott Rice
Room No. - G56
Sample - S396

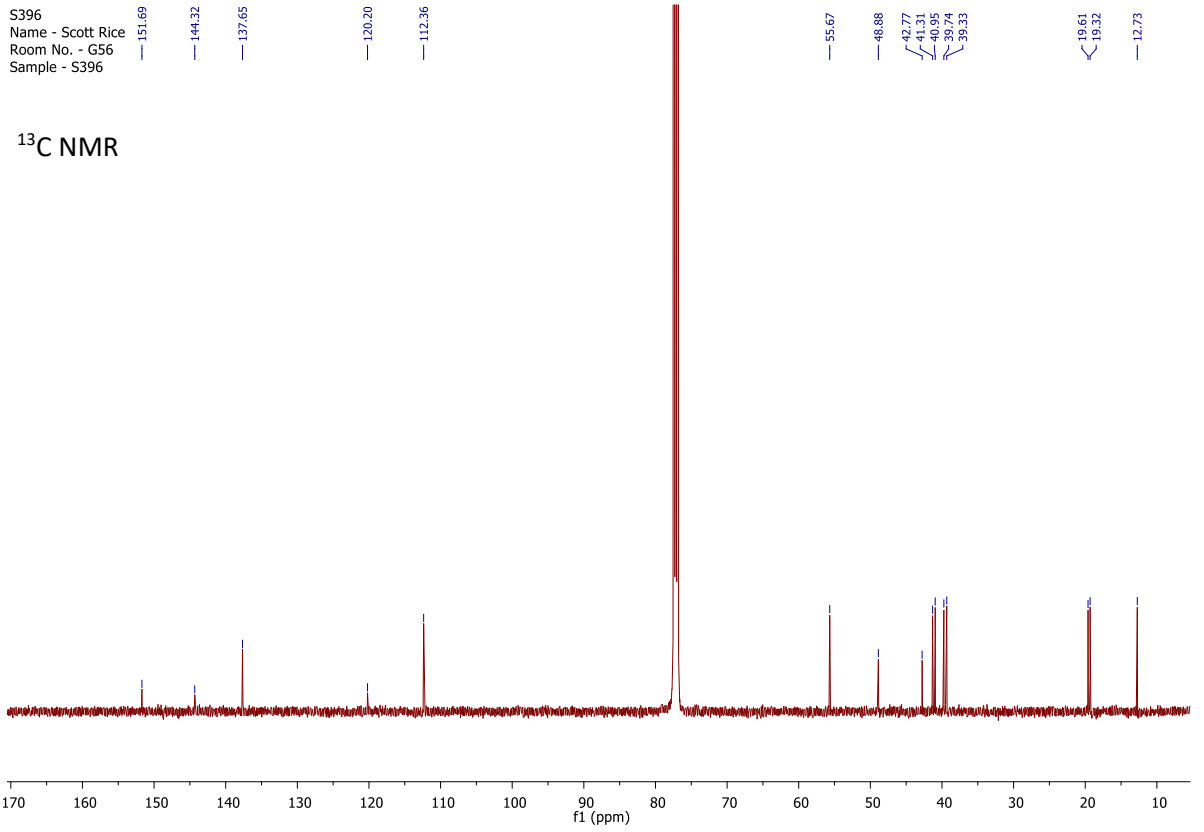
^{1}H NMR

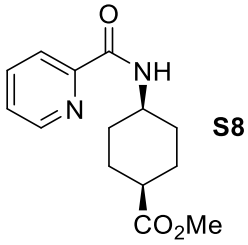


S396
Name - Scott Rice
Room No. - G56
Sample - S396

151.69
144.32
137.65
120.20
112.36
55.67
48.88
42.77
41.31
40.95
39.74
39.33
19.61
19.32
12.73

^{13}C NMR

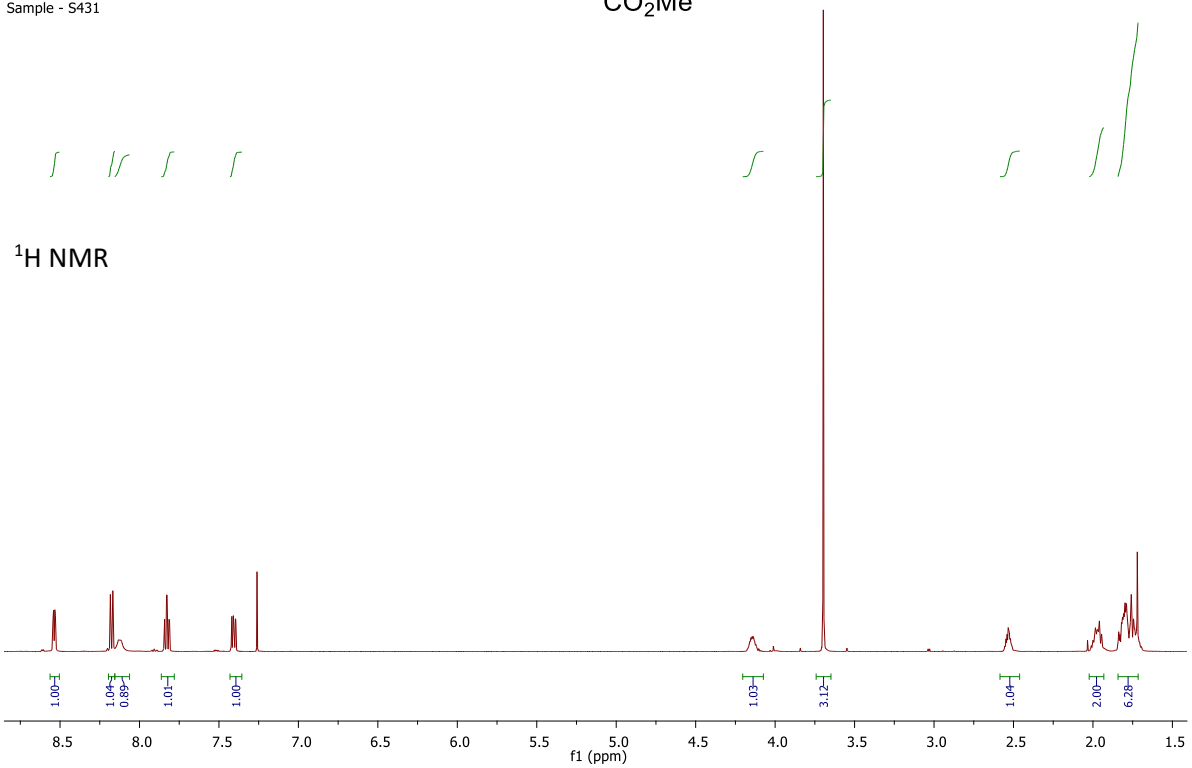




S8

S431
Name - Scott Rice
Room No. - G56
Sample - S431

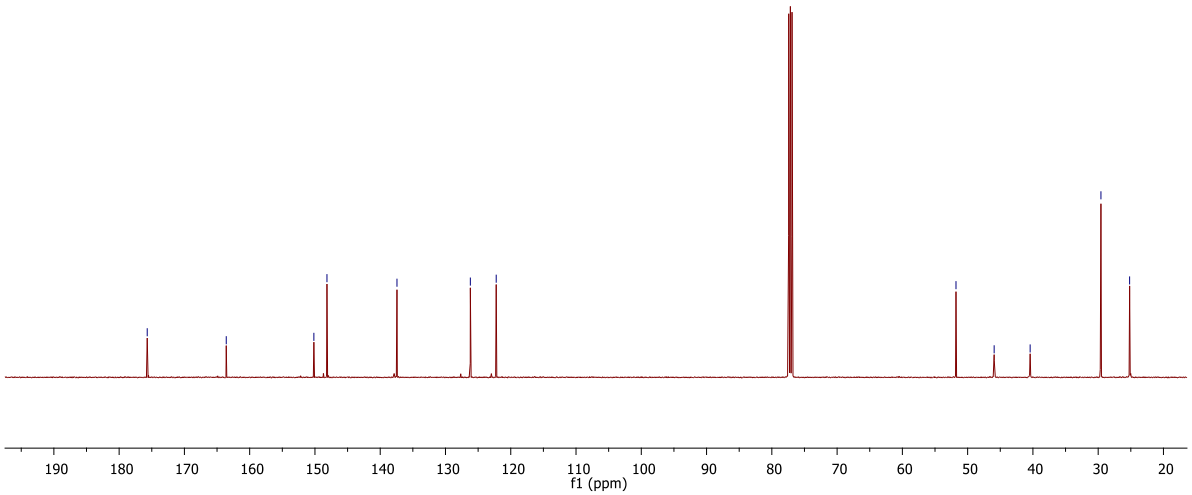
^{1}H NMR

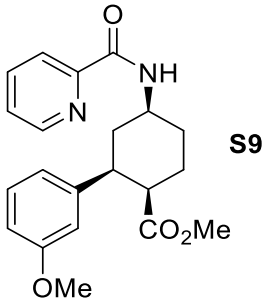


S431
Name - Scott Rice
Room No. - G56
Sample - S431

175.70
163.59
150.16
148.16
137.43
126.19
122.23
51.78
45.94
40.42
29.58
25.18

^{13}C NMR

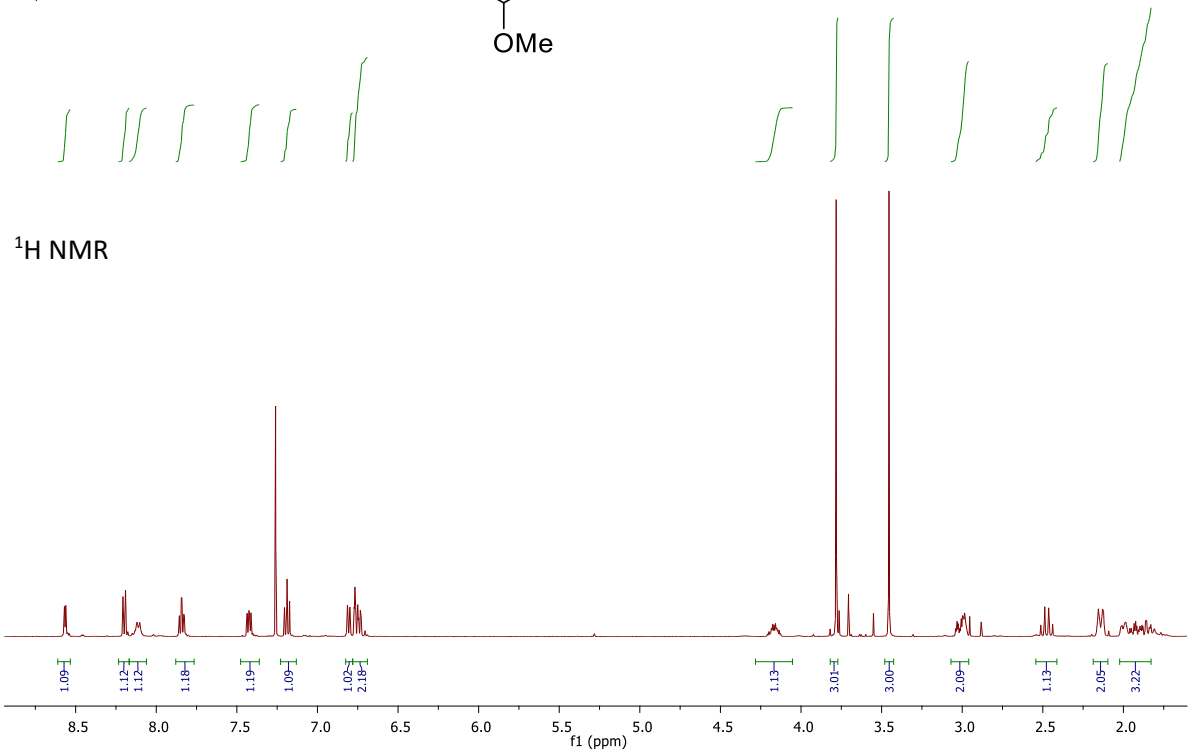




S9

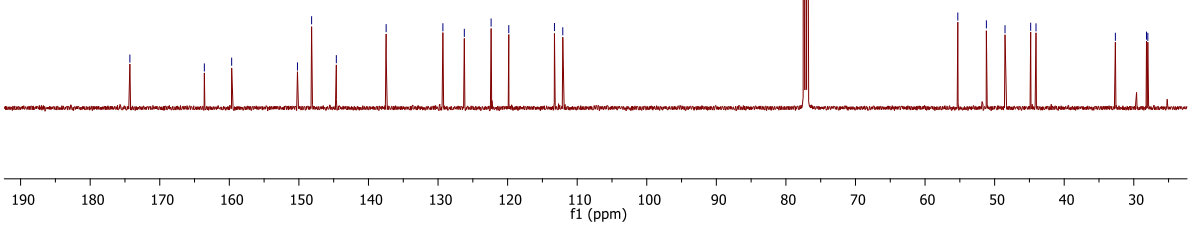
S432
Name - Scott Rice
Room No. - G56
Sample - S432

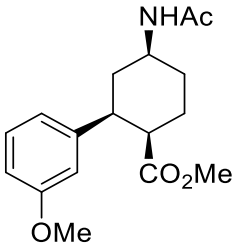
^{1}H NMR



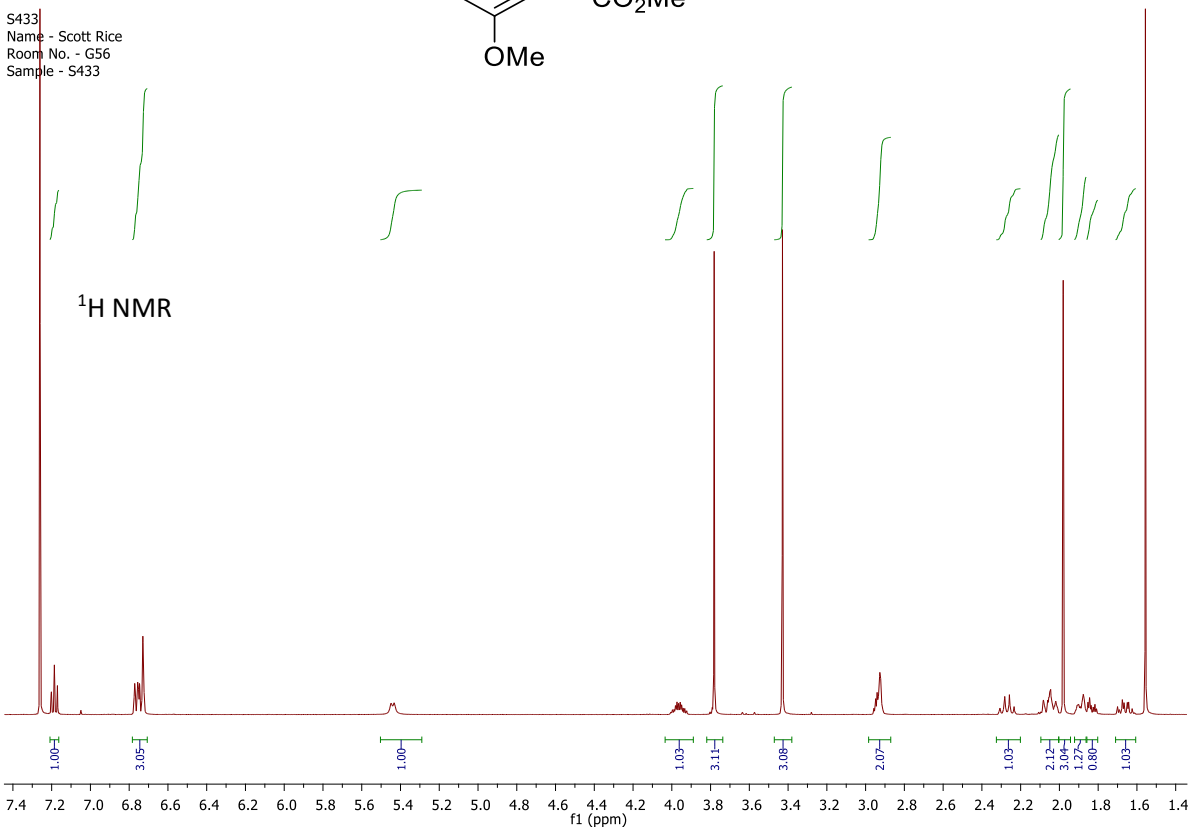
S432
Name - Scott Rice
Room No. - G56
Sample - S432

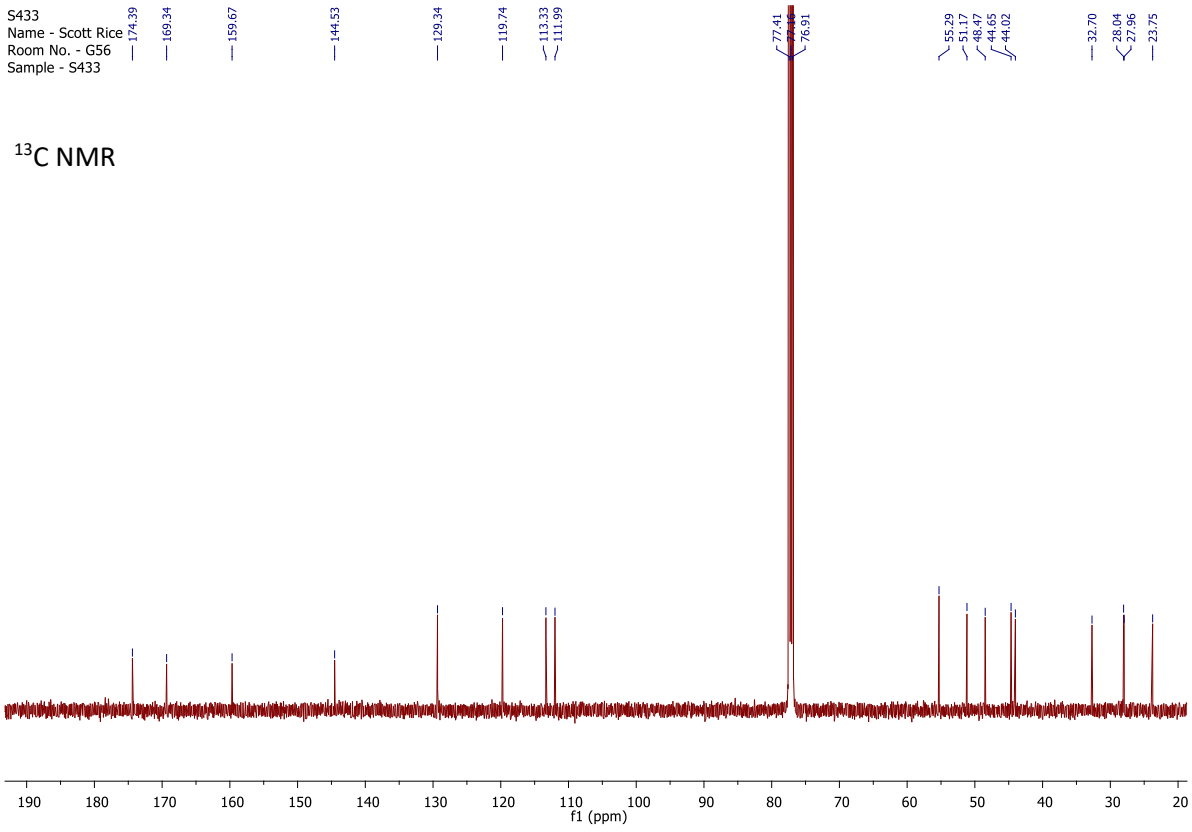
^{13}C NMR

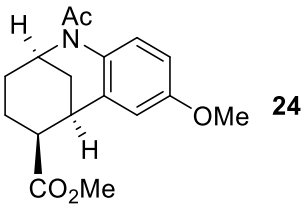



NHAc
CO2Me
OMe

23


S433
Name - Scott Rice
Room No. - G56
Sample - S433
1H NMR
1.00
3.05
1.00
1.03
3.11
3.08
2.07
1.03
2.12
3.04
1.27
0.80
1.03
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
f1 (ppm)

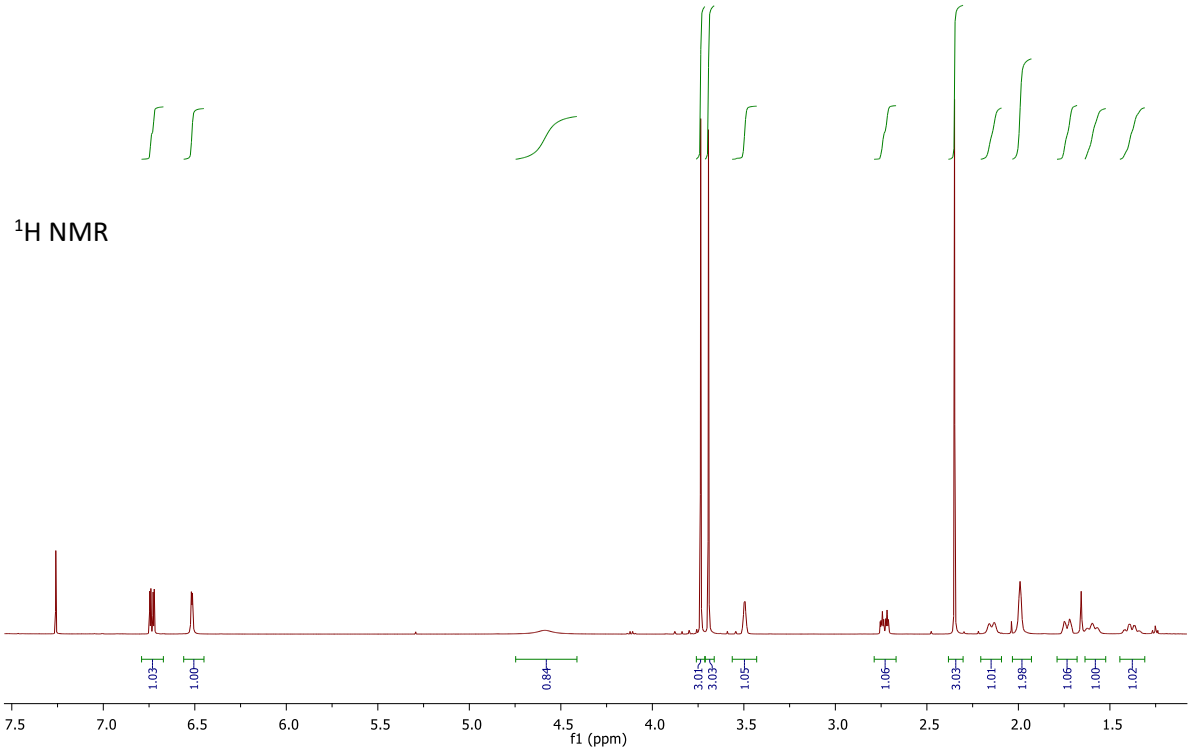

S433
Name - Scott Rice
Room No. - G56
Sample - S433
174.39
169.34
159.67
144.53
129.34
119.74
113.33
111.99
77.41
77.16
76.91
55.29
51.17
48.47
44.65
44.02
32.70
28.04
27.96
23.75
13C NMR
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)



24

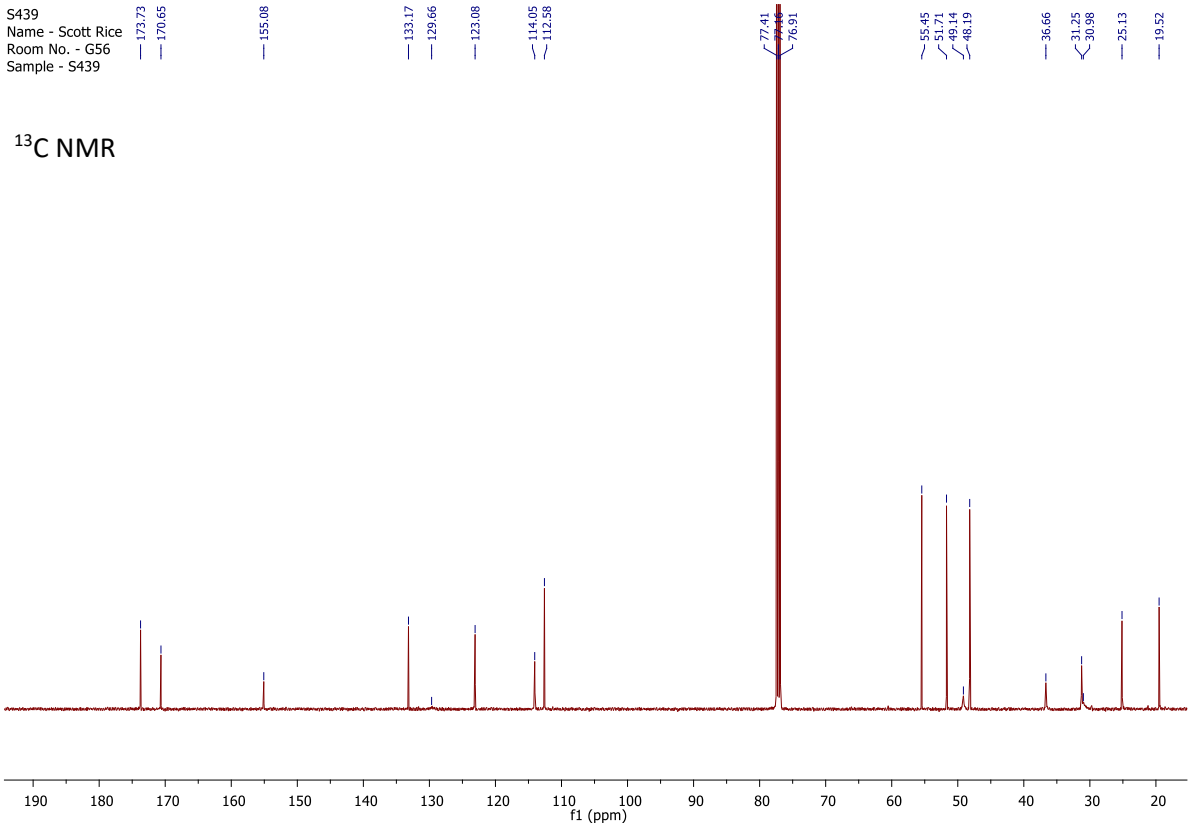
S439
Name - Scott Rice
Room No. - G56
Sample - S439

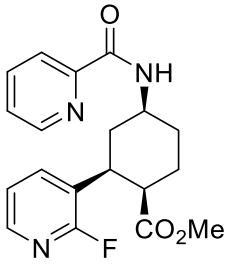
^{1}H NMR



S439
Name - Scott Rice
Room No. - G56
Sample - S439

^{13}C NMR

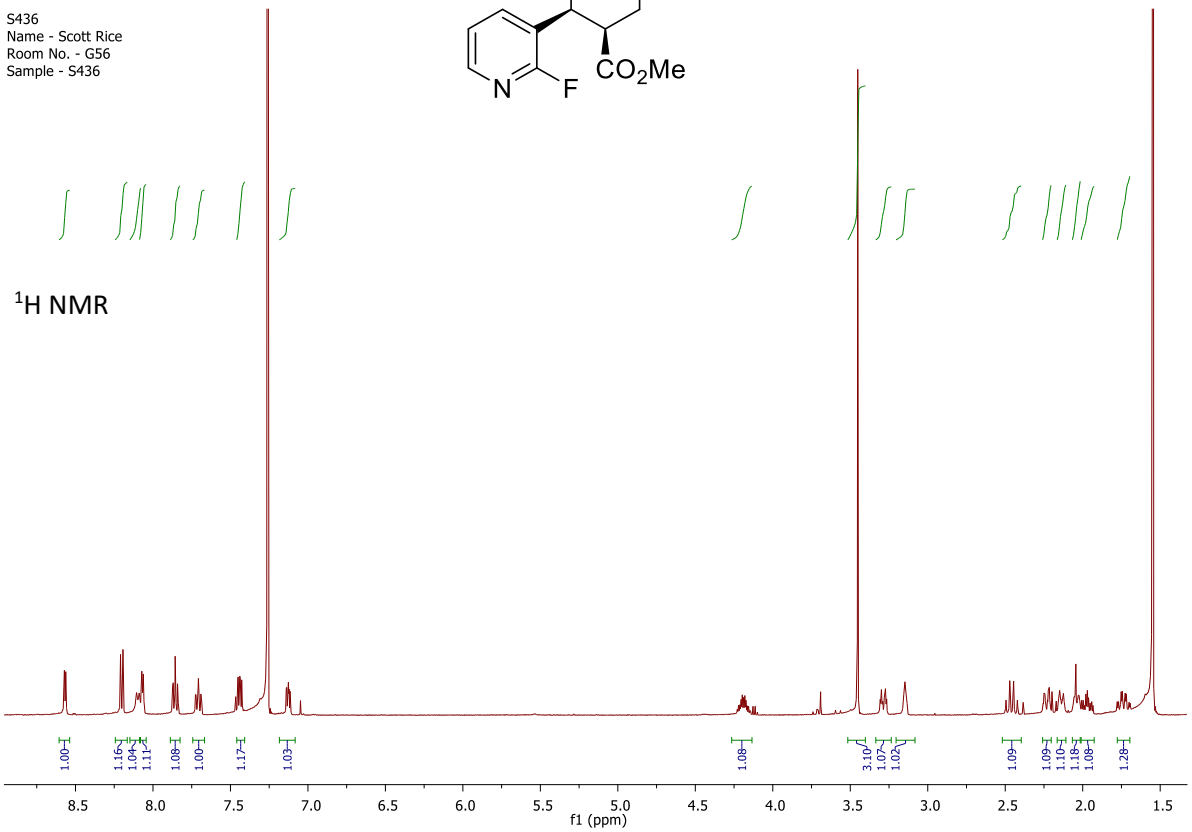




25

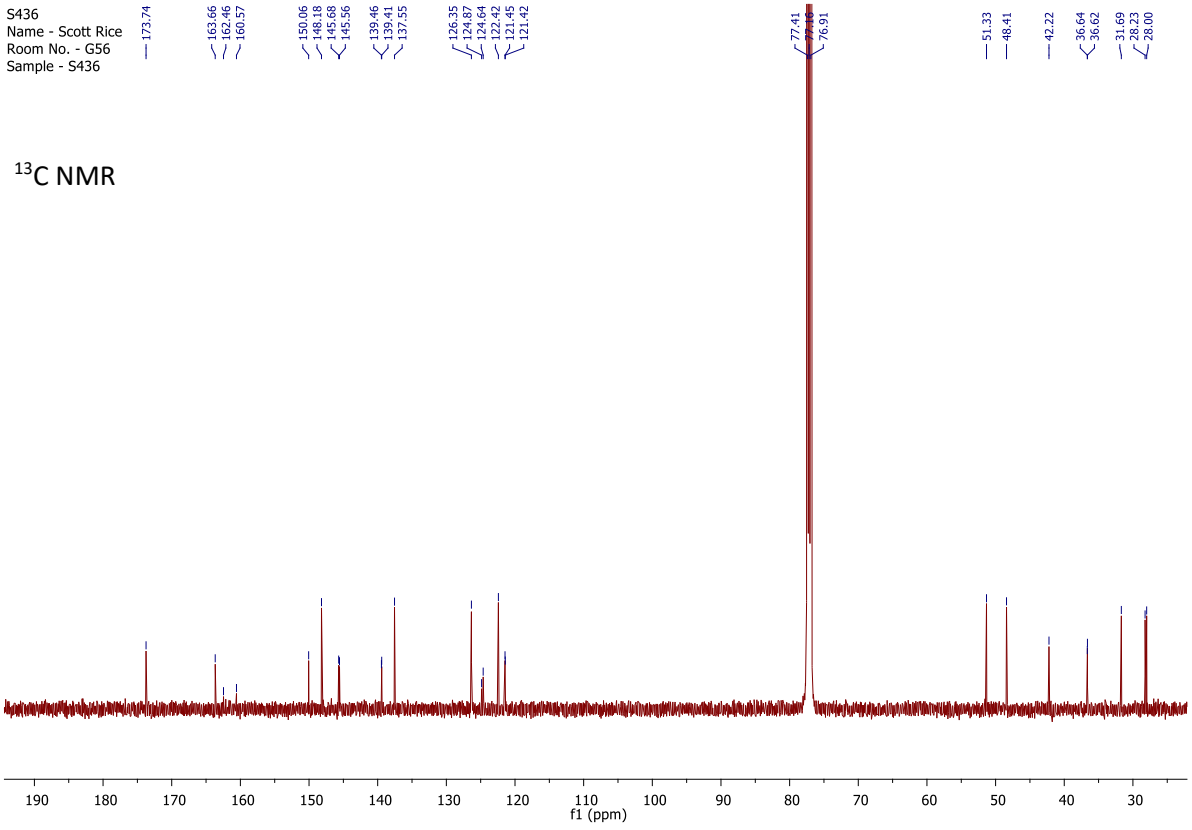
S436
Name - Scott Rice
Room No. - G56
Sample - S436

^{1}H NMR



S436
Name - Scott Rice
Room No. - G56
Sample - S436

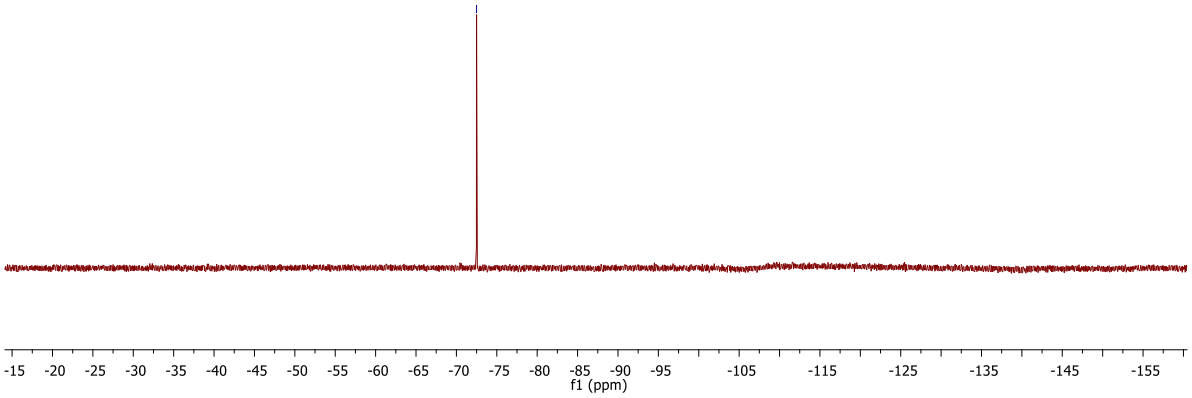
^{13}C NMR

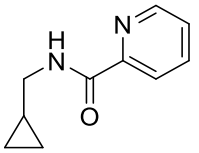


S436
Name - Scott Rice
Room No - G56
Sample S436

-72.50

^{19}F NMR

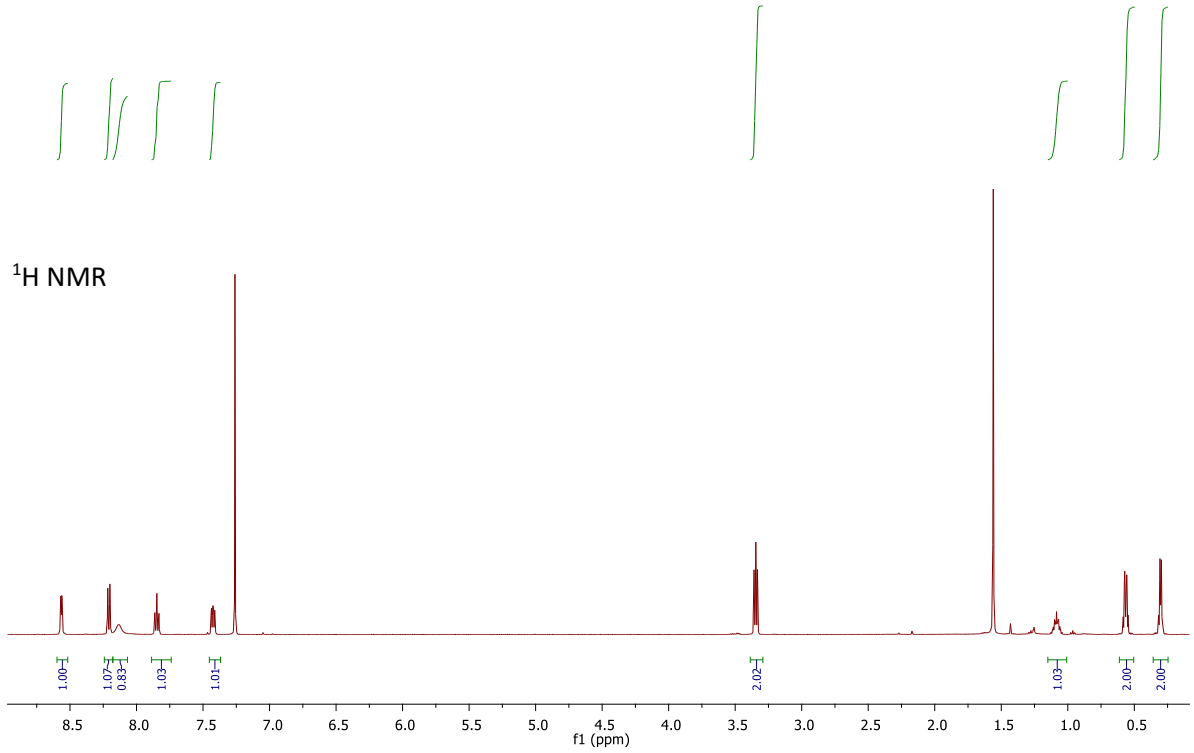




S10

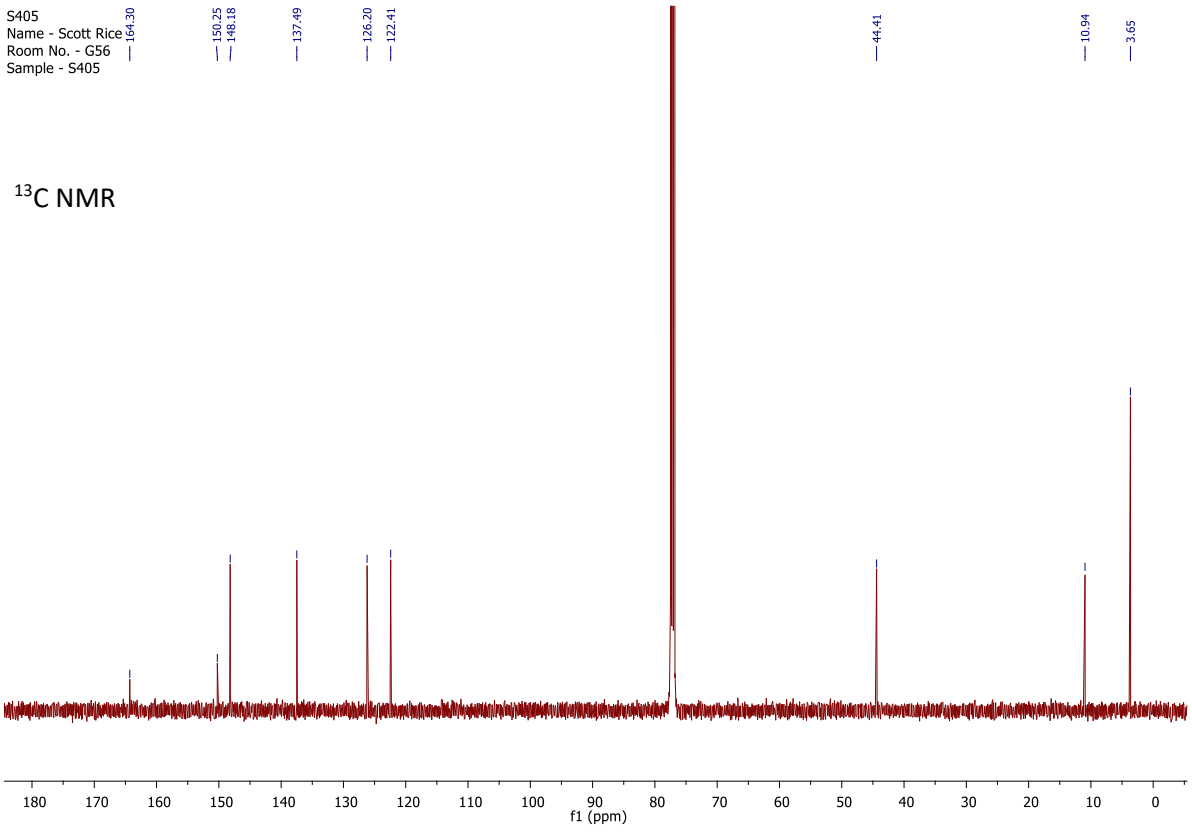
S405
Name - Scott Rice
Room No. - G56
Sample - S405

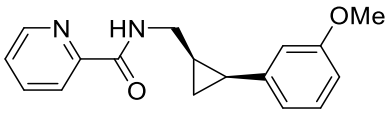
^{1}H NMR



S405
Name - Scott Rice
Room No. - G56
Sample - S405

^{13}C NMR

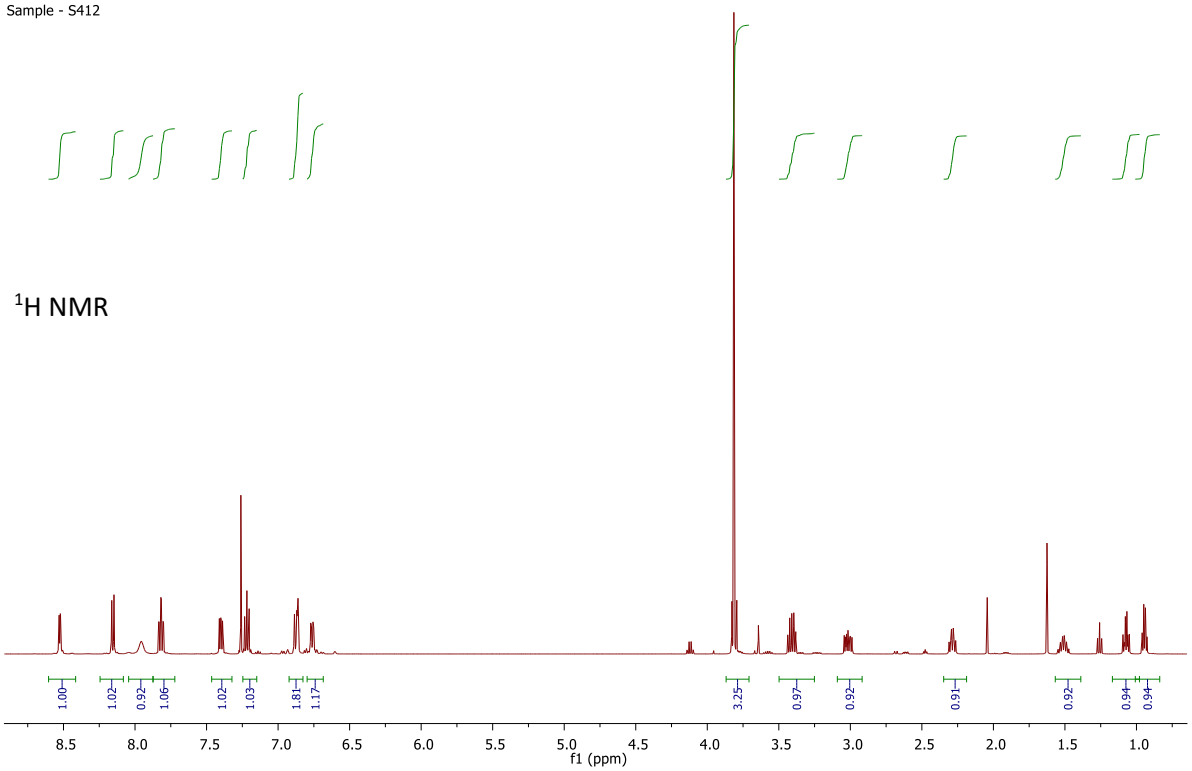




26

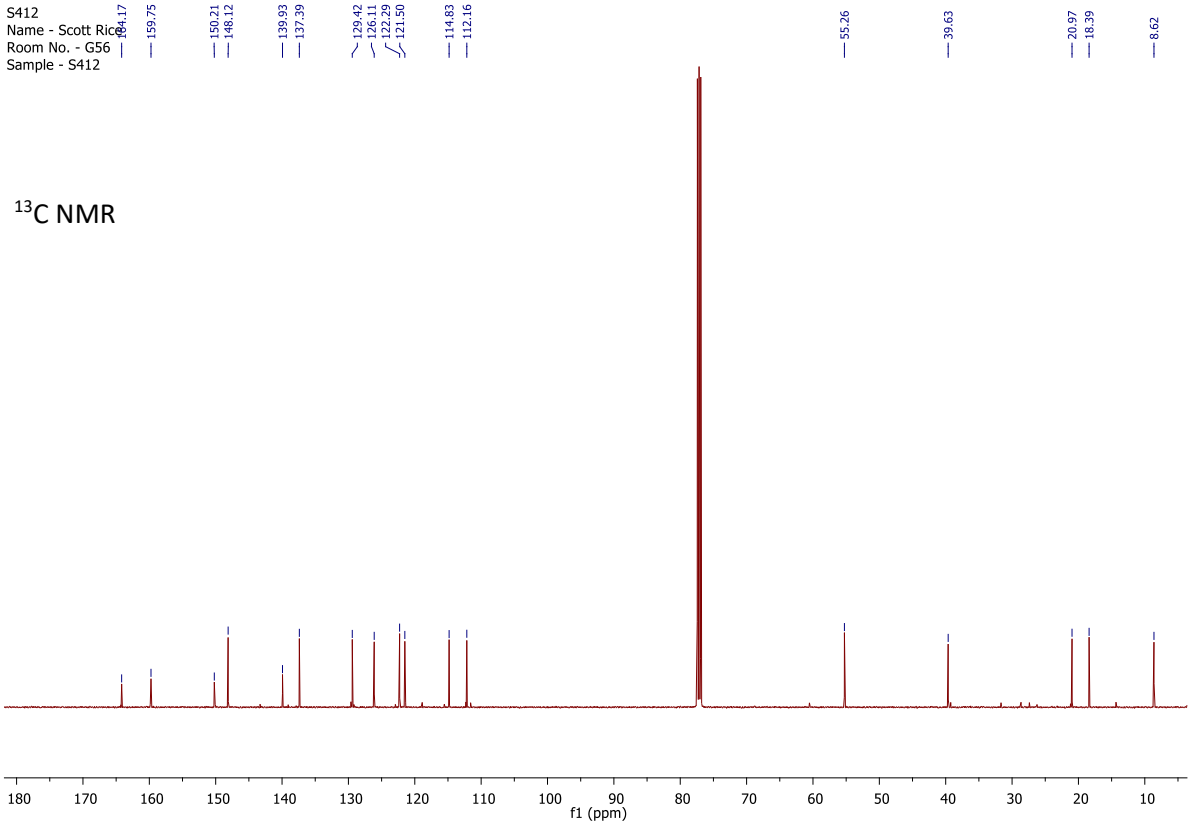
S412
Name - Scott Rice
Room No. - G56
Sample - S412

^{1}H NMR

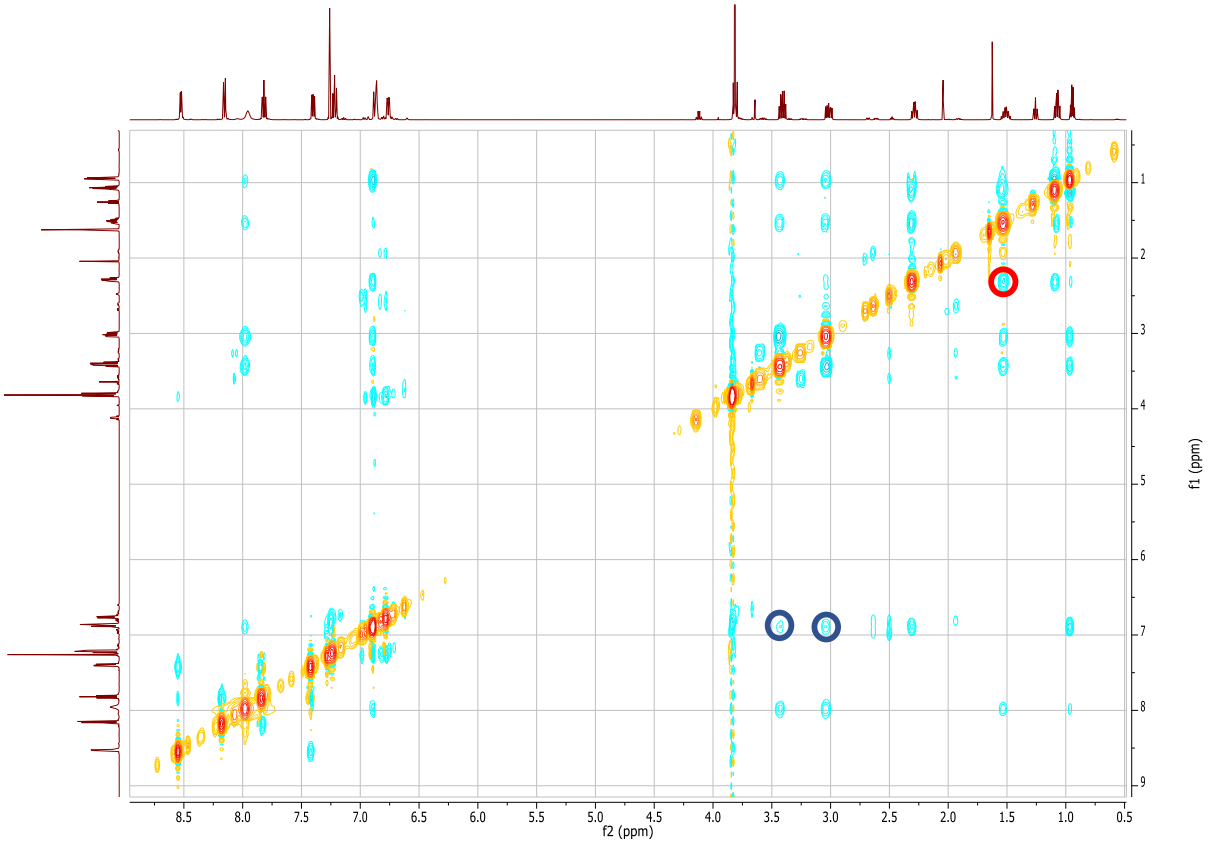


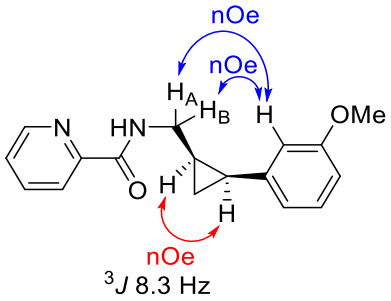
S412
Name - Scott Rice
Room No. - G56
Sample - S412

^{13}C NMR

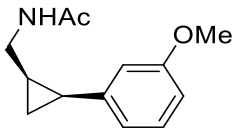


NOESY





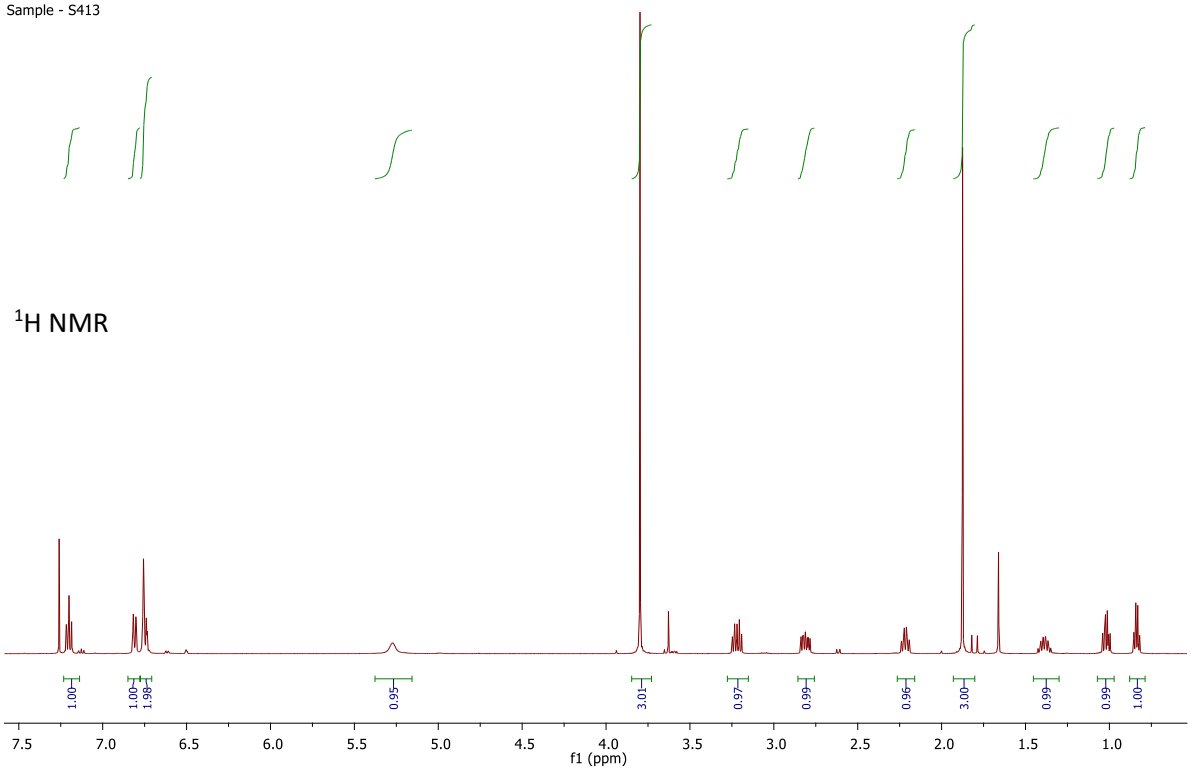
^{3}J 8.3 Hz



S11

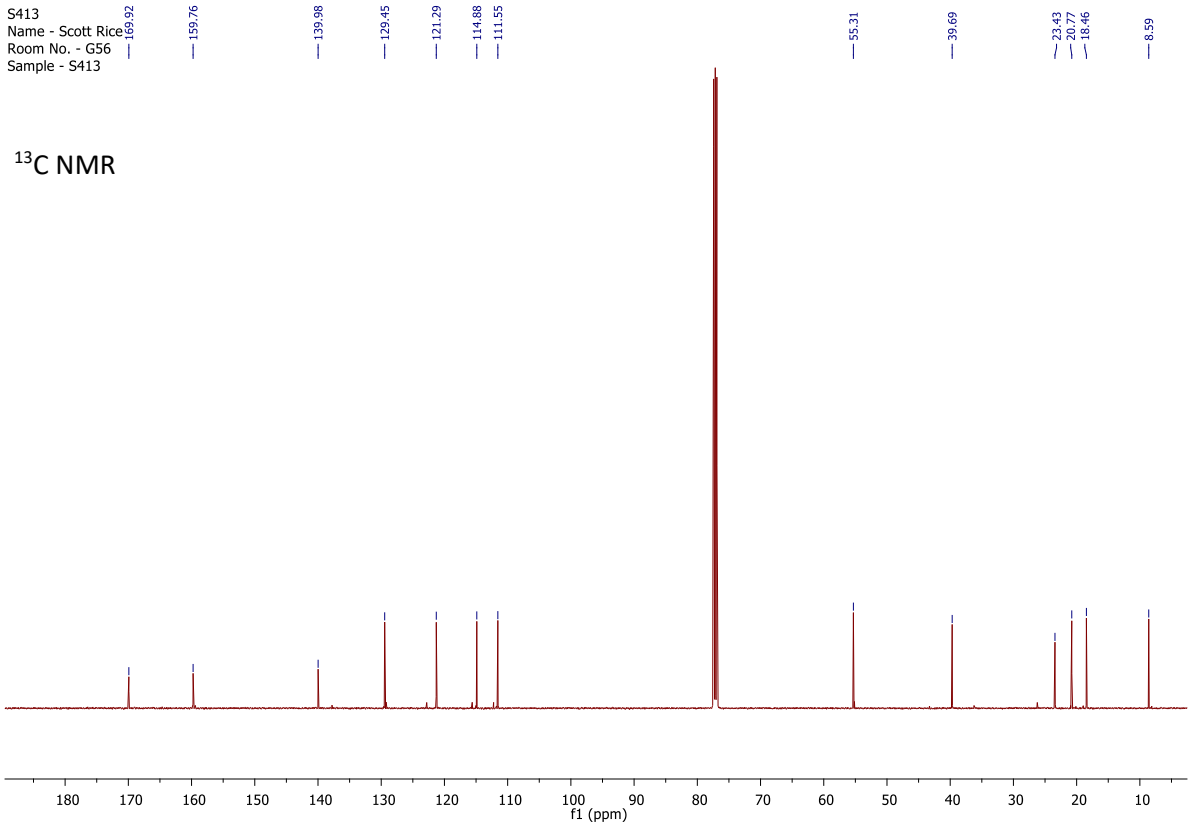
S413
Name - Scott Rice
Room No. - G56
Sample - S413

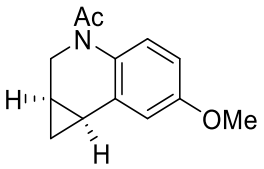
^{1}H NMR



S413
Name - Scott Rice
Room No. - G56
Sample - S413

^{13}C NMR

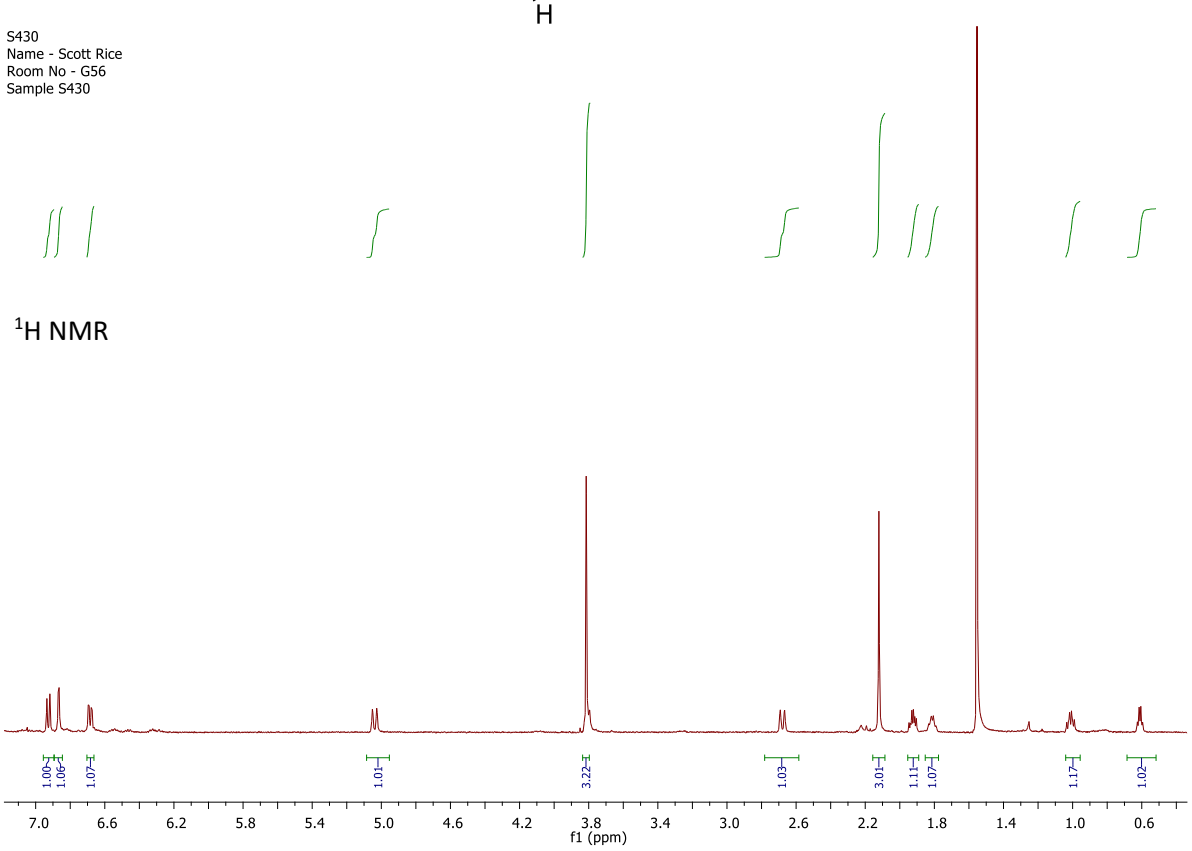




27

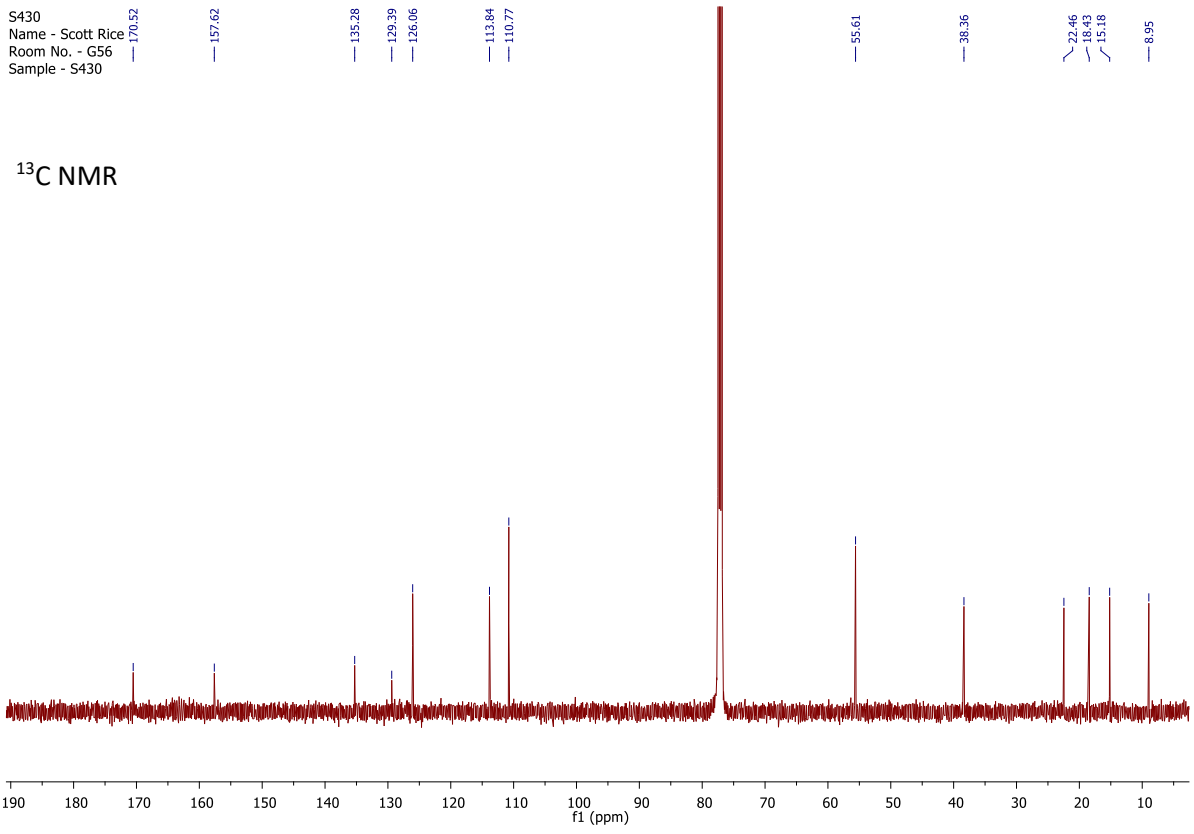
S430
Name - Scott Rice
Room No - G56
Sample S430

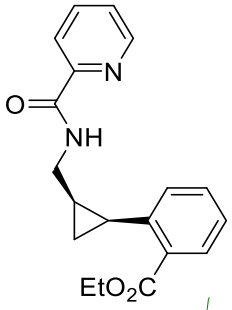
^{1}H NMR



S430
Name - Scott Rice
Room No. - G56
Sample - S430

^{13}C NMR

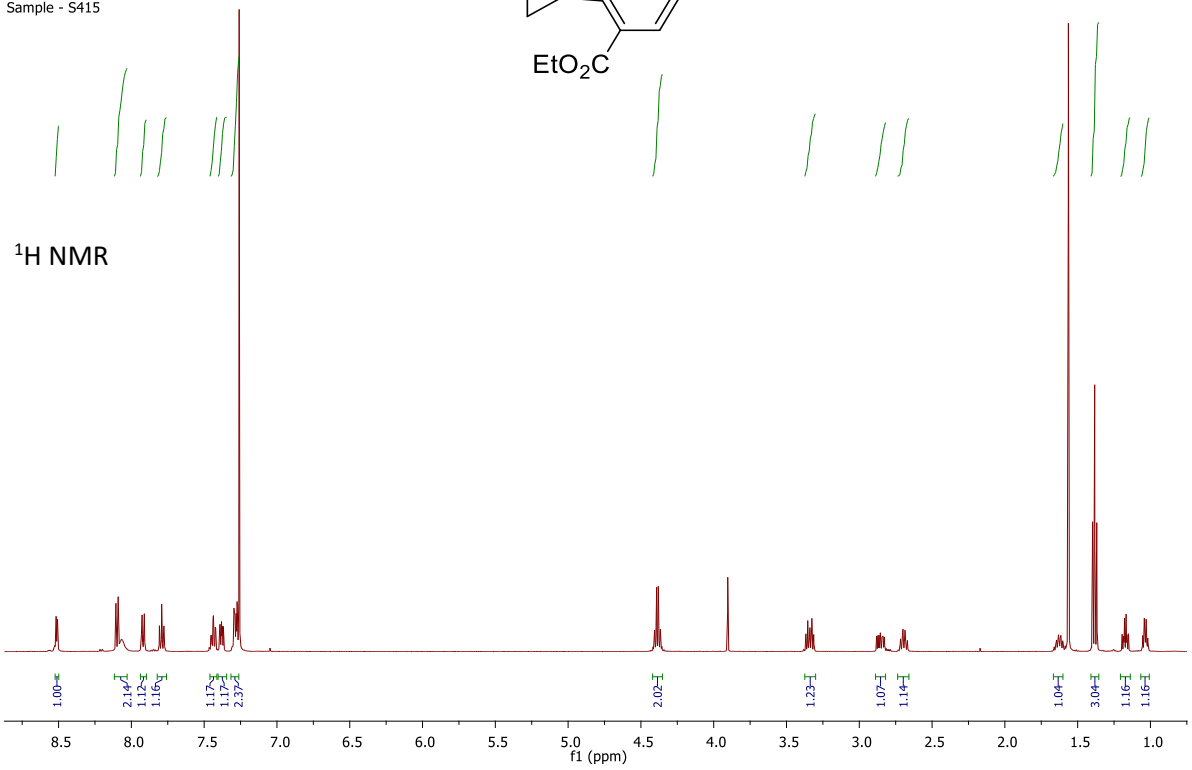




28

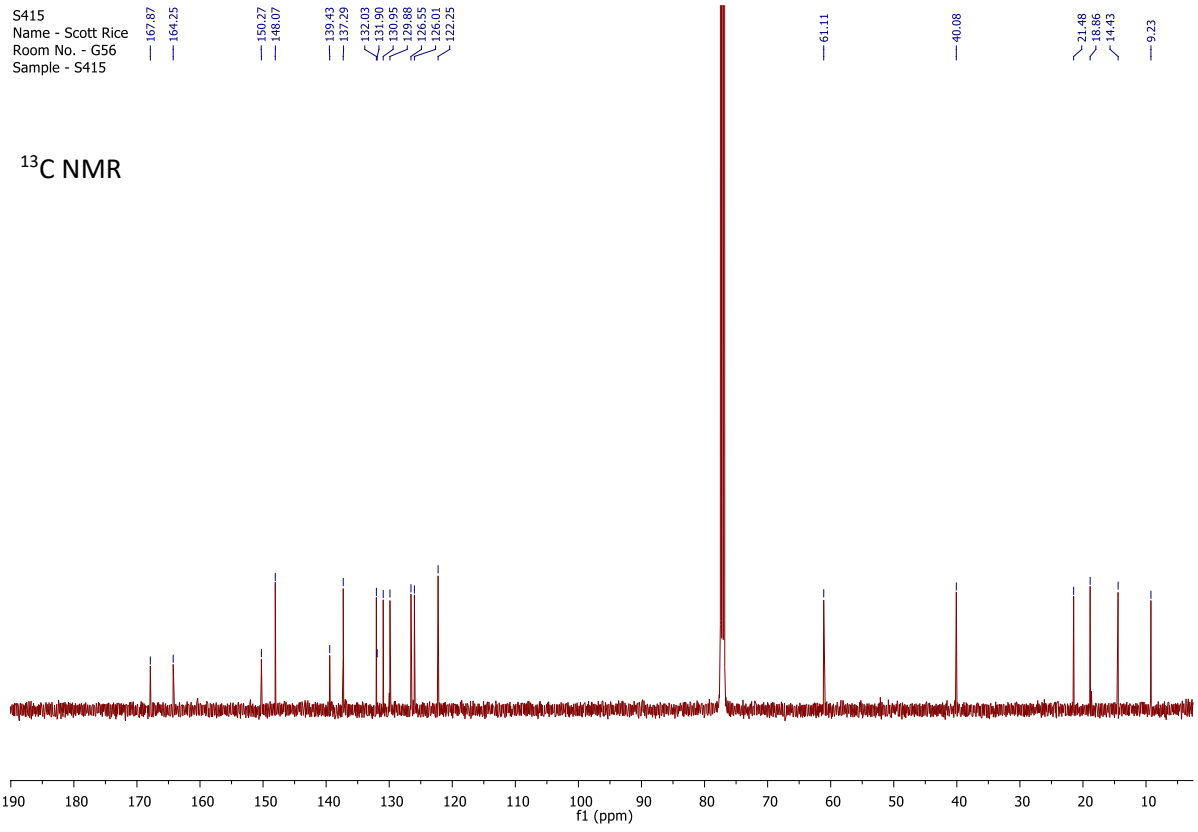
S415
Name - Scott Rice
Room No. - G56
Sample - S415

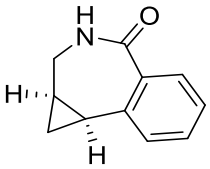
^{1}H NMR



S415
Name - Scott Rice
Room No. - G56
Sample - S415

^{13}C NMR

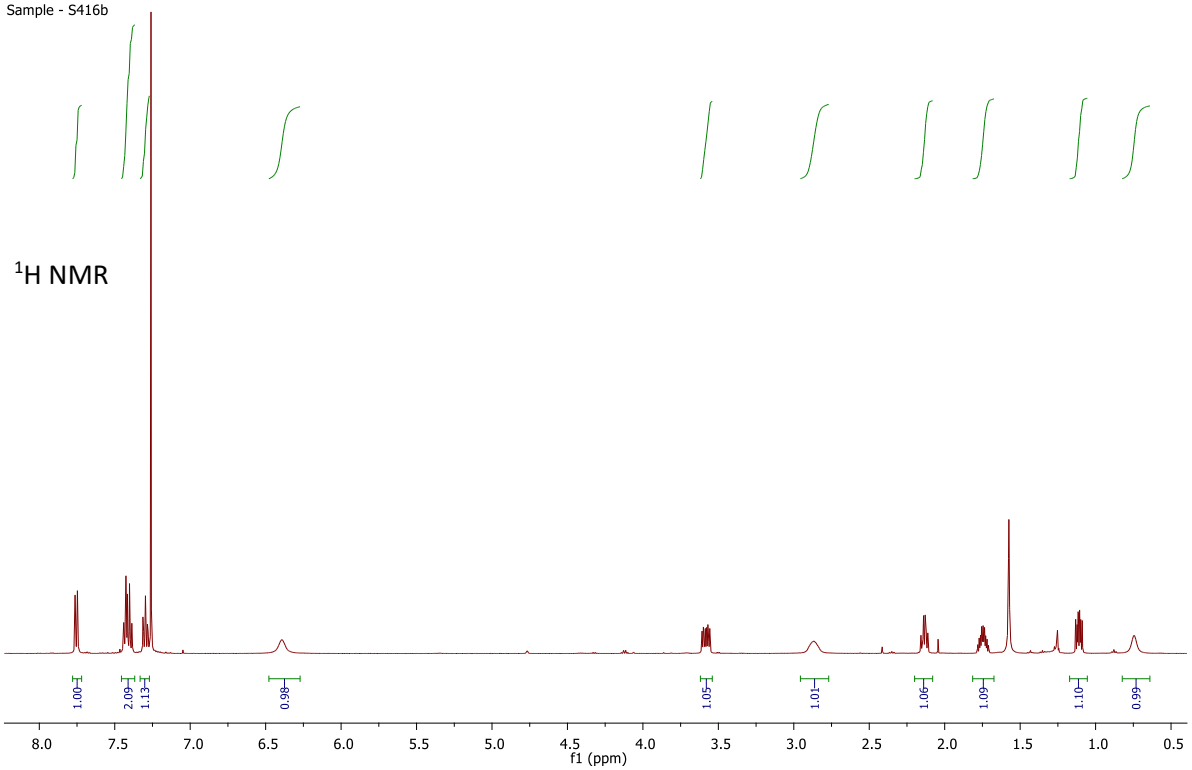




3

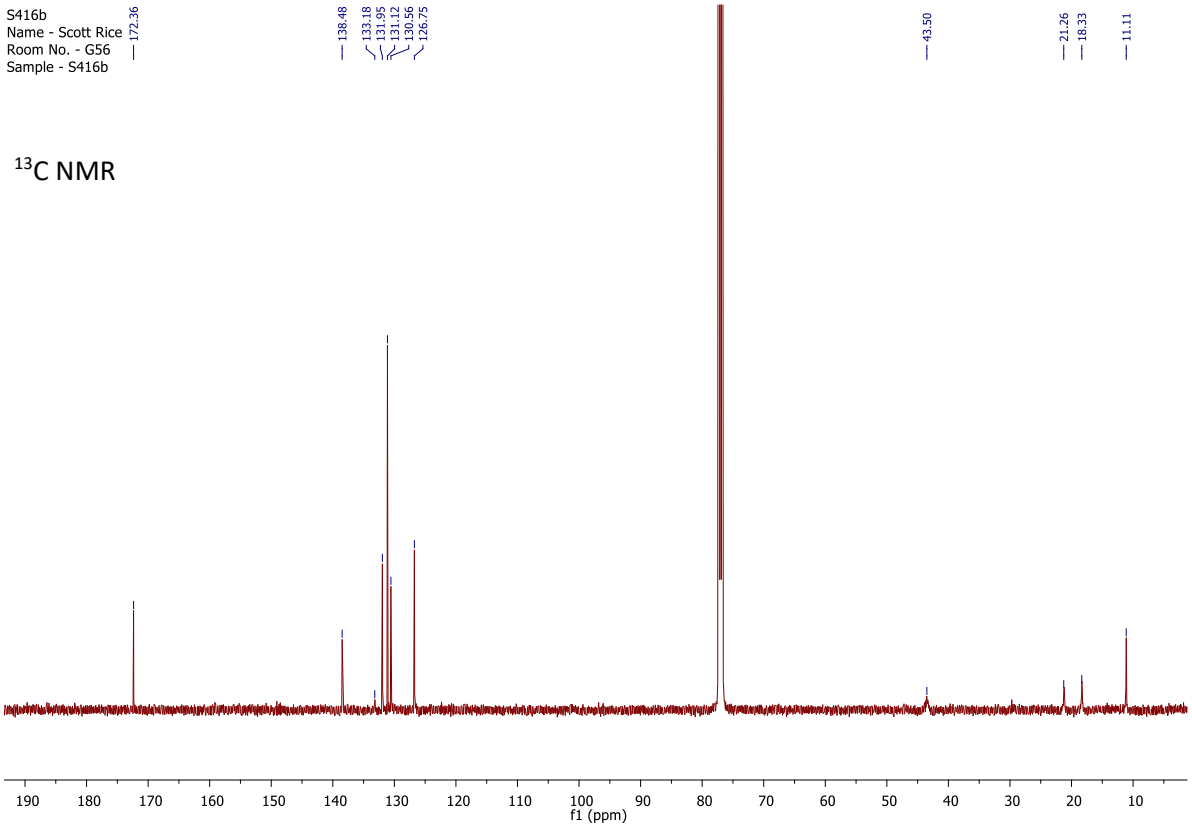
S416b
Name - Scott Rice
Room No. - G56
Sample - S416b

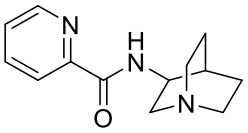
^{1}H NMR



S416b
Name - Scott Rice
Room No. - G56
Sample - S416b

^{13}C NMR

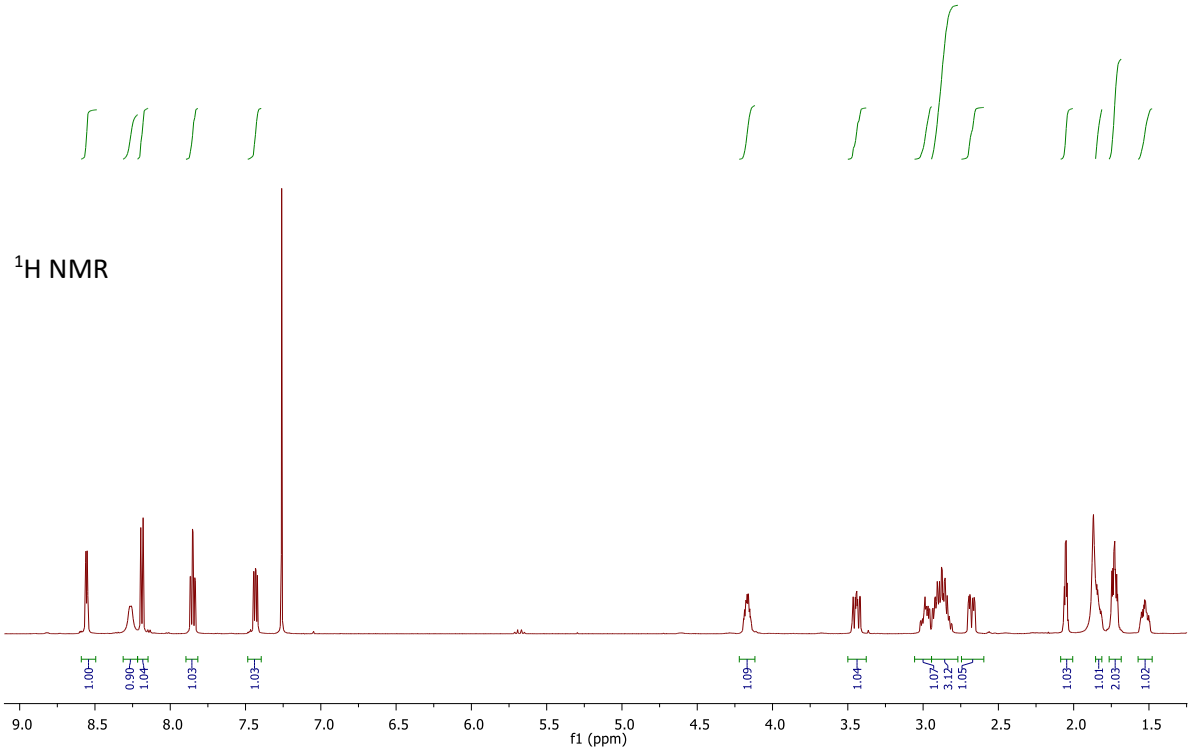




S12

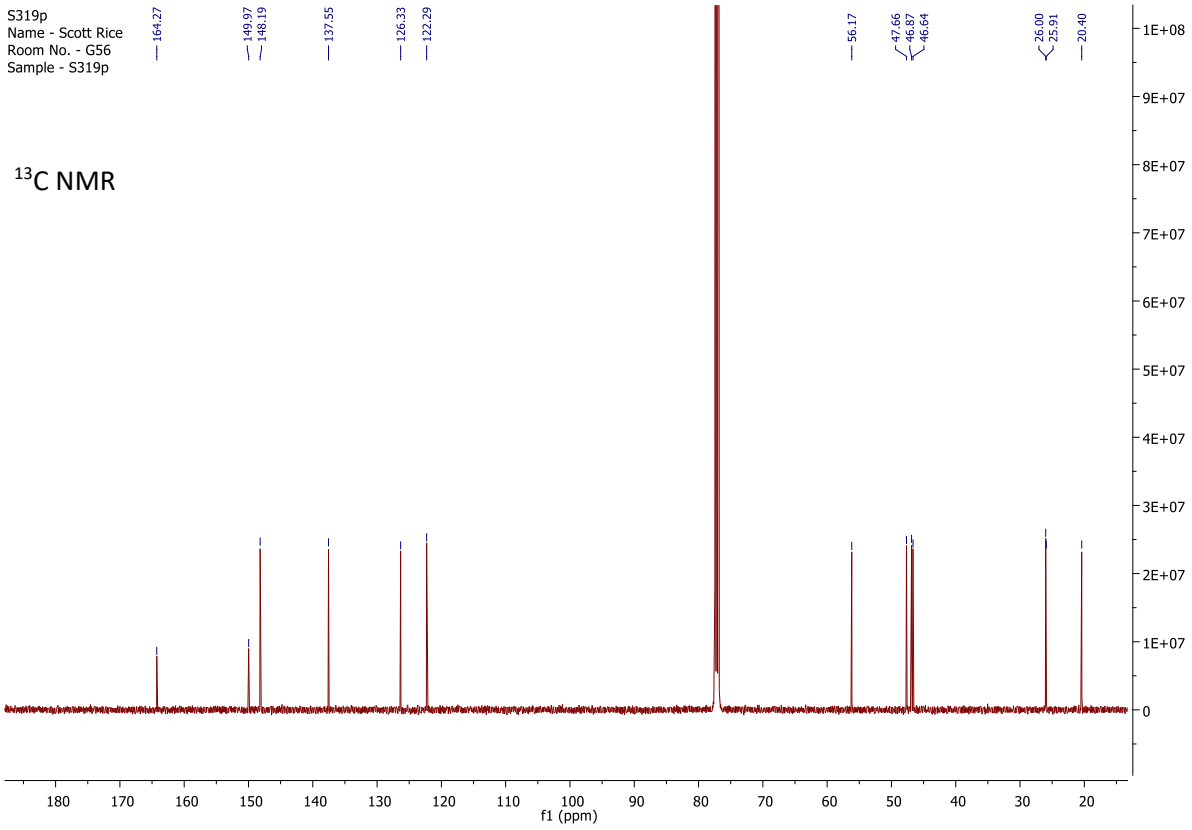
S319p
Name - Scott Rice
Room No. - G56
Sample - S319p

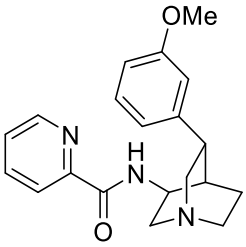
^{1}H NMR



S319p
Name - Scott Rice
Room No. - G56
Sample - S319p

^{13}C NMR

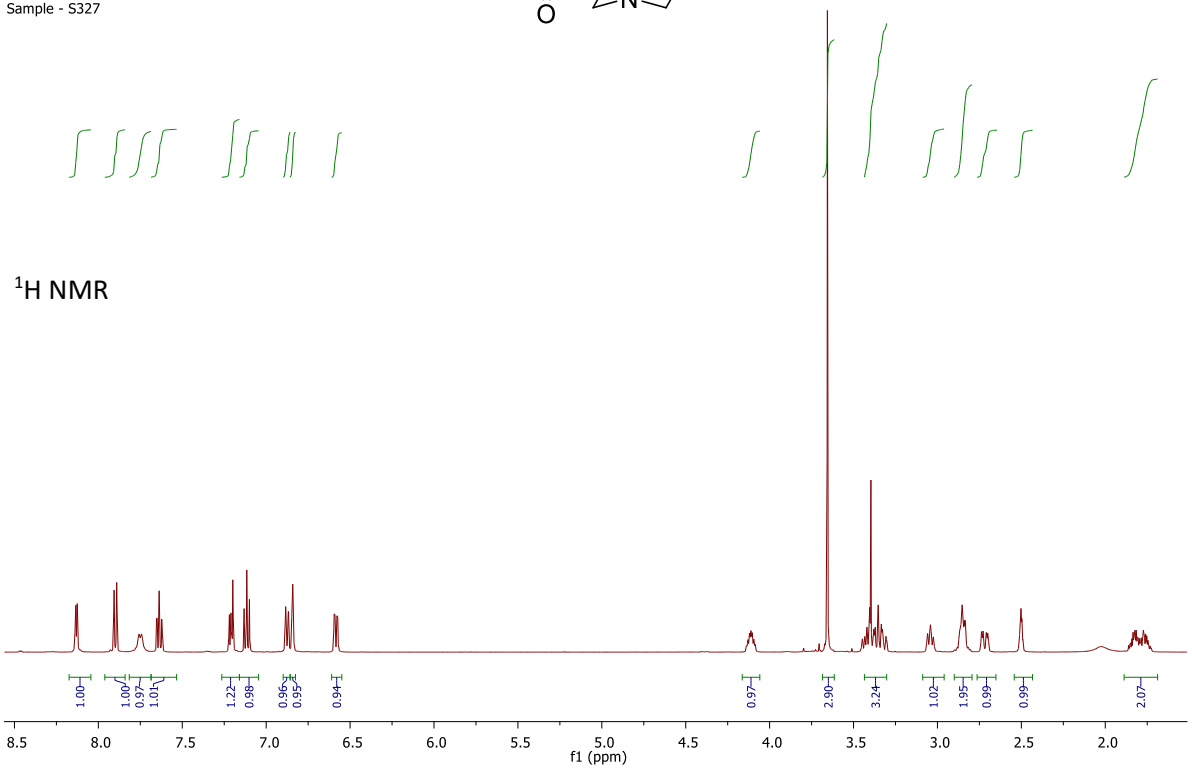




S13

S327
Name - Scott Rice
Room No. - G56
Sample - S327

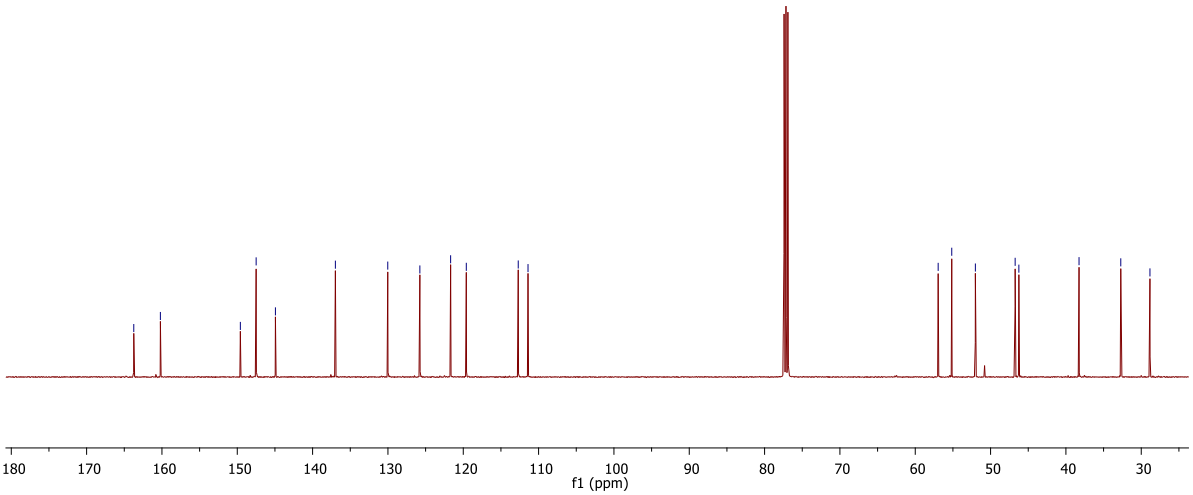
^{1}H NMR

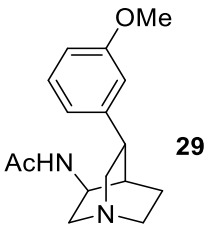


S327
Name - Scott Rice
Room No. - G56
Sample - S327

163.74
160.21
149.59
147.49
144.94
136.98
130.02
125.76
121.68
119.60
112.70
111.40
56.96
55.15
52.02
46.74
46.24
38.26
32.72
28.84

^{13}C NMR

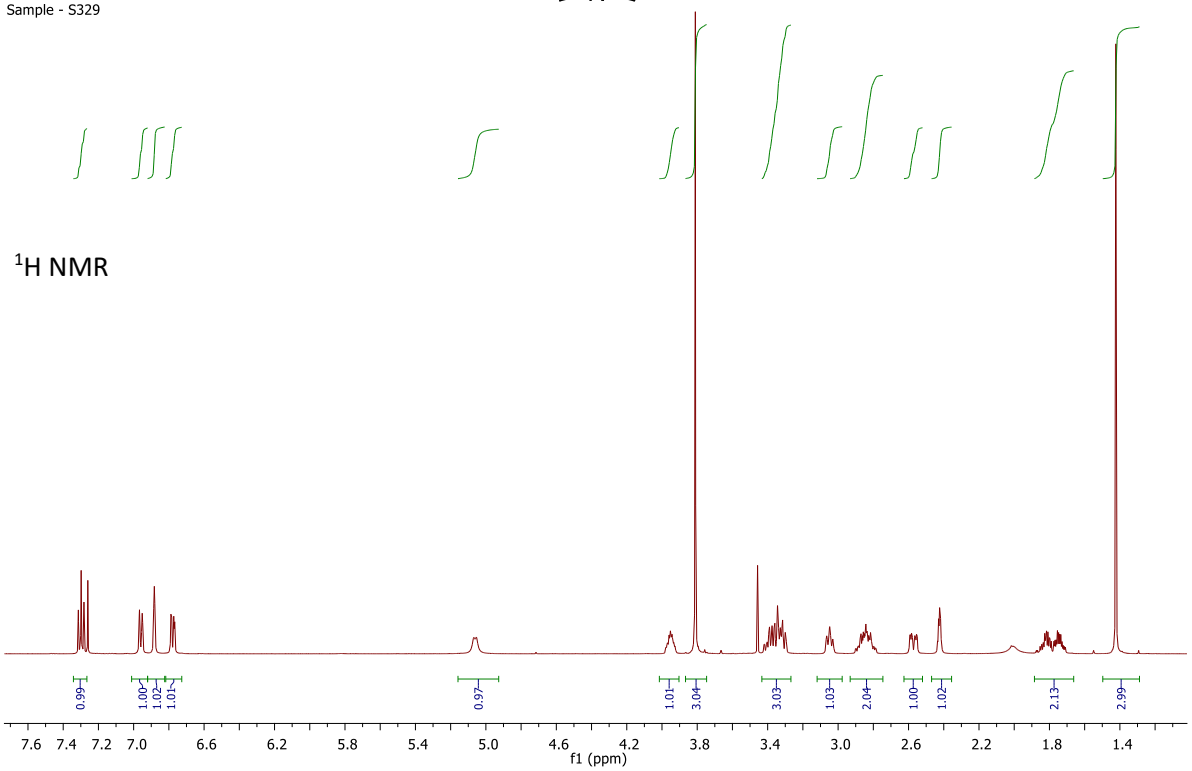




29

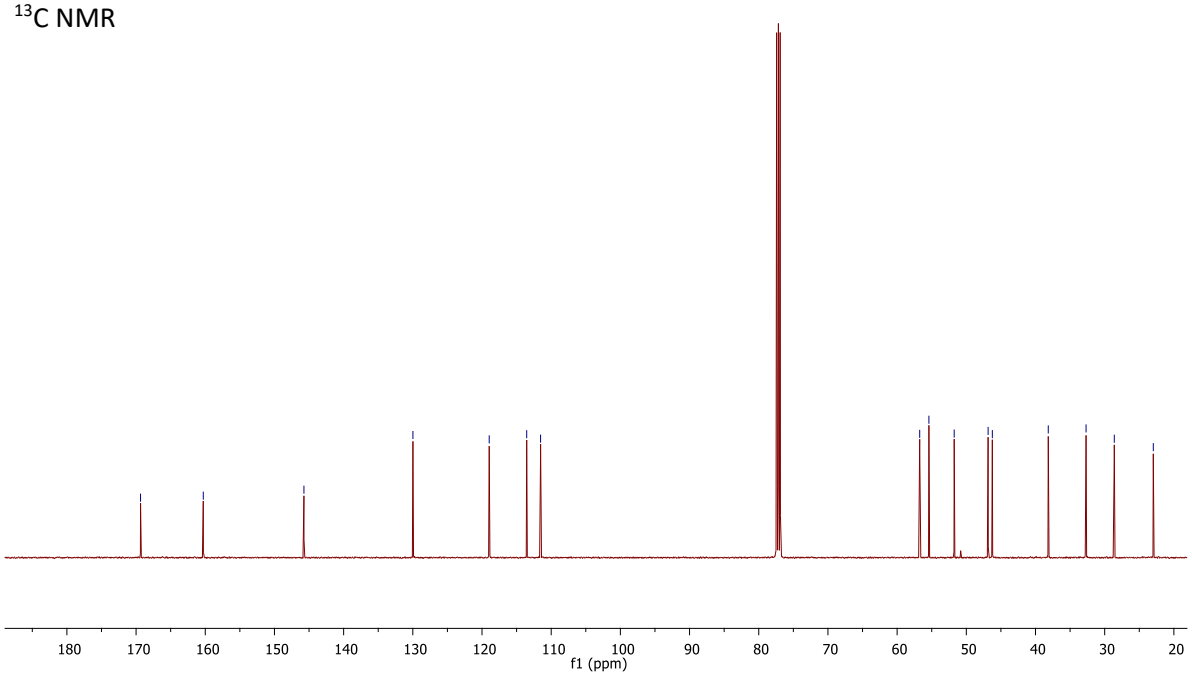
S329
Name - Scott Rice
Room No. - G56
Sample - S329

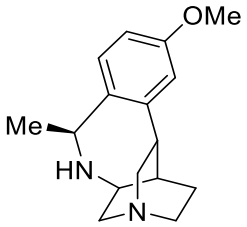
^{1}H NMR



S329
Name - Scott Rice
Room No. - G56
Sample - S329

^{13}C NMR

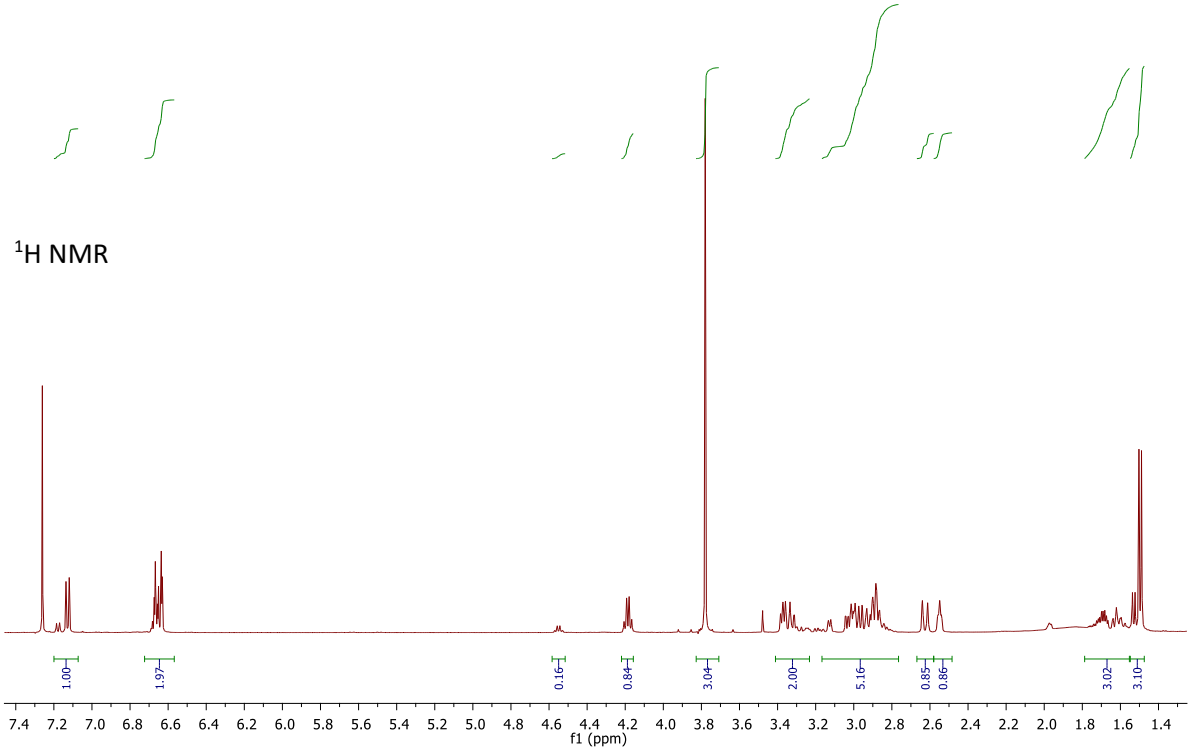




30 (*dr* 84:16)

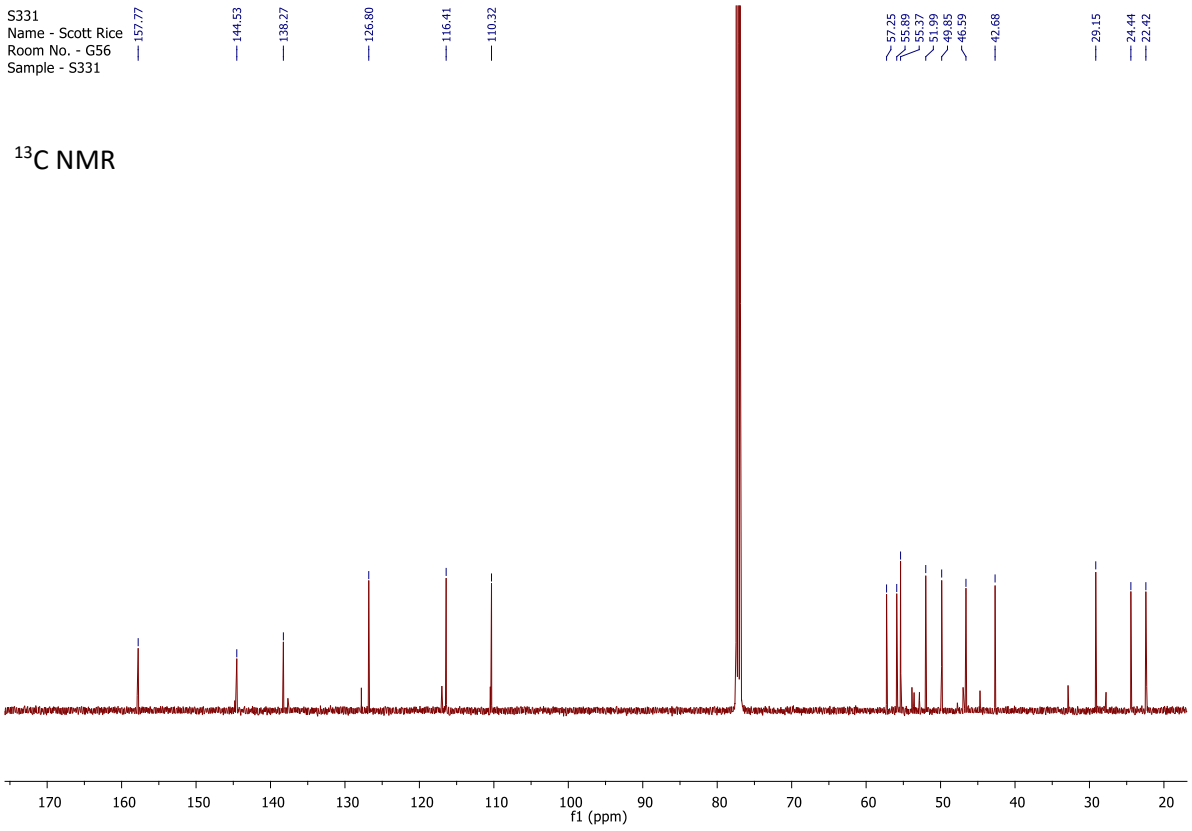
S331
Name - Scott Rice
Room No. - G56
Sample - S331

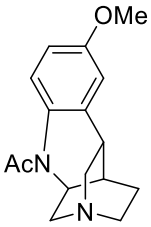
^{1}H NMR



S331
Name - Scott Rice
Room No. - G56
Sample - S331

^{13}C NMR

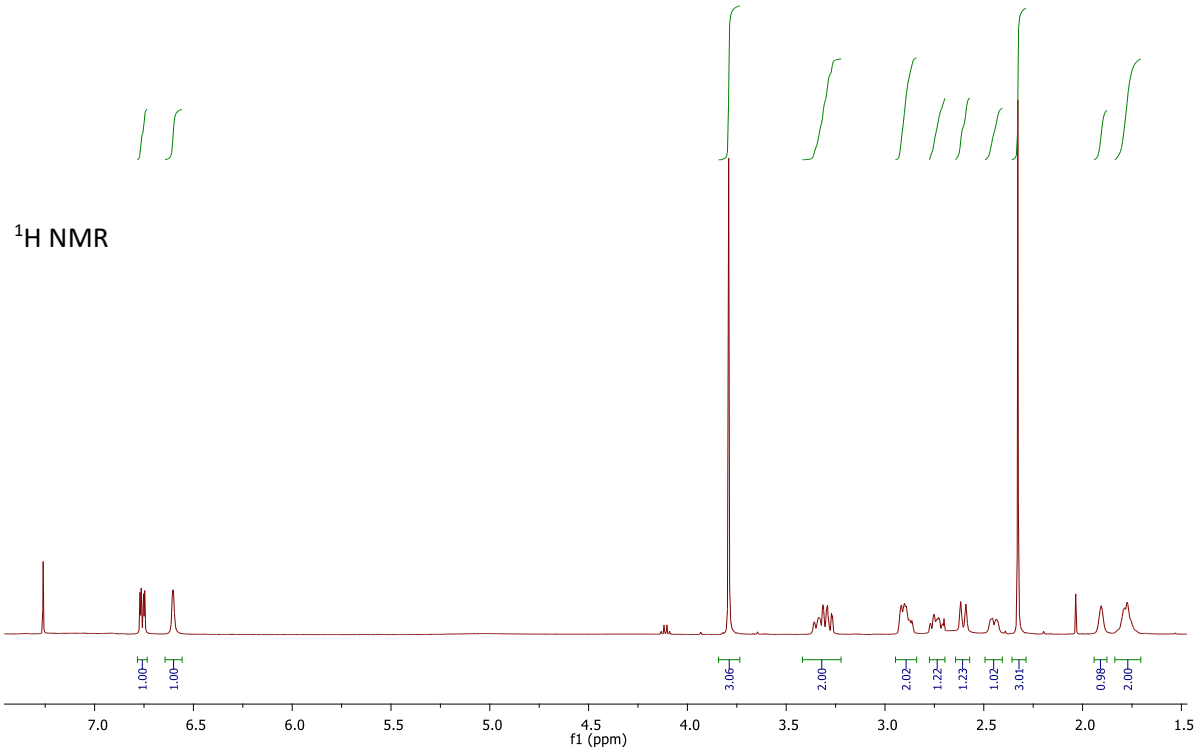




S14

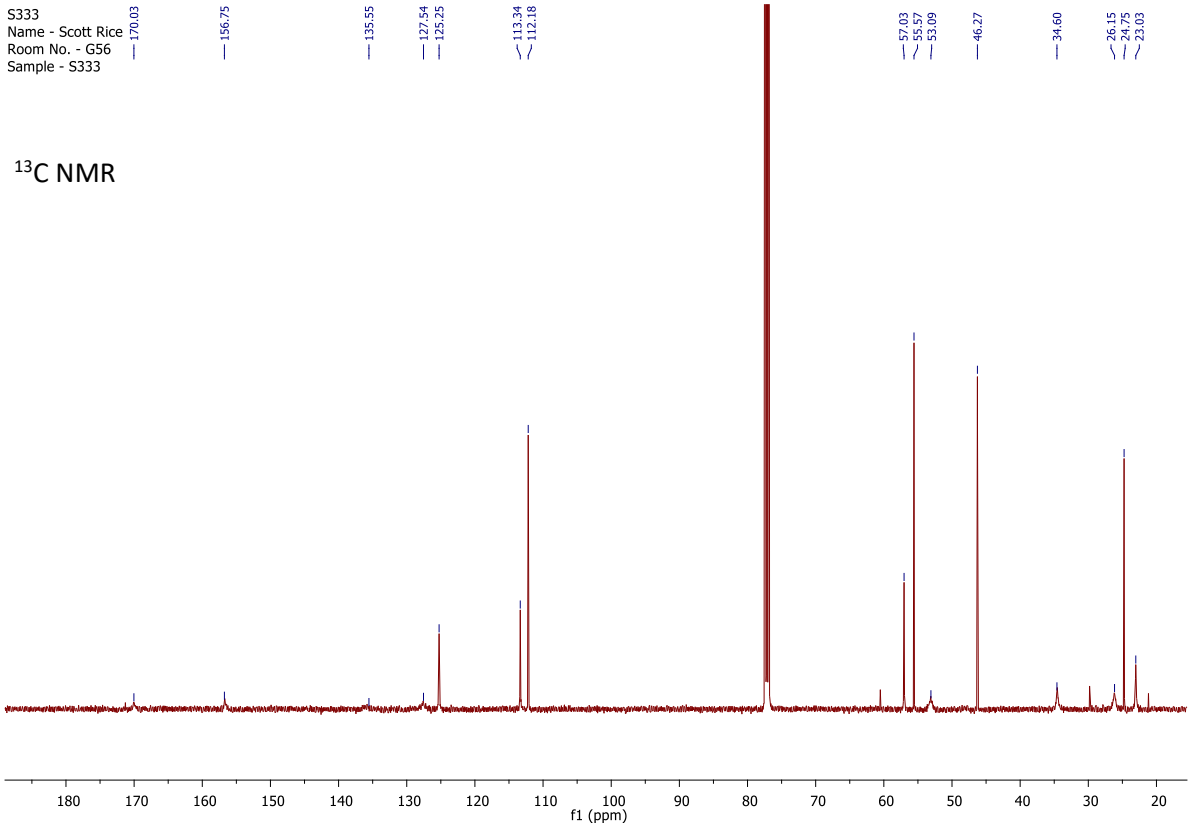
S333
Name - Scott Rice
Room No. - G56
Sample - S333

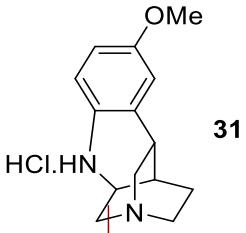
^{1}H NMR



S333
Name - Scott Rice
Room No. - G56
Sample - S333

^{13}C NMR

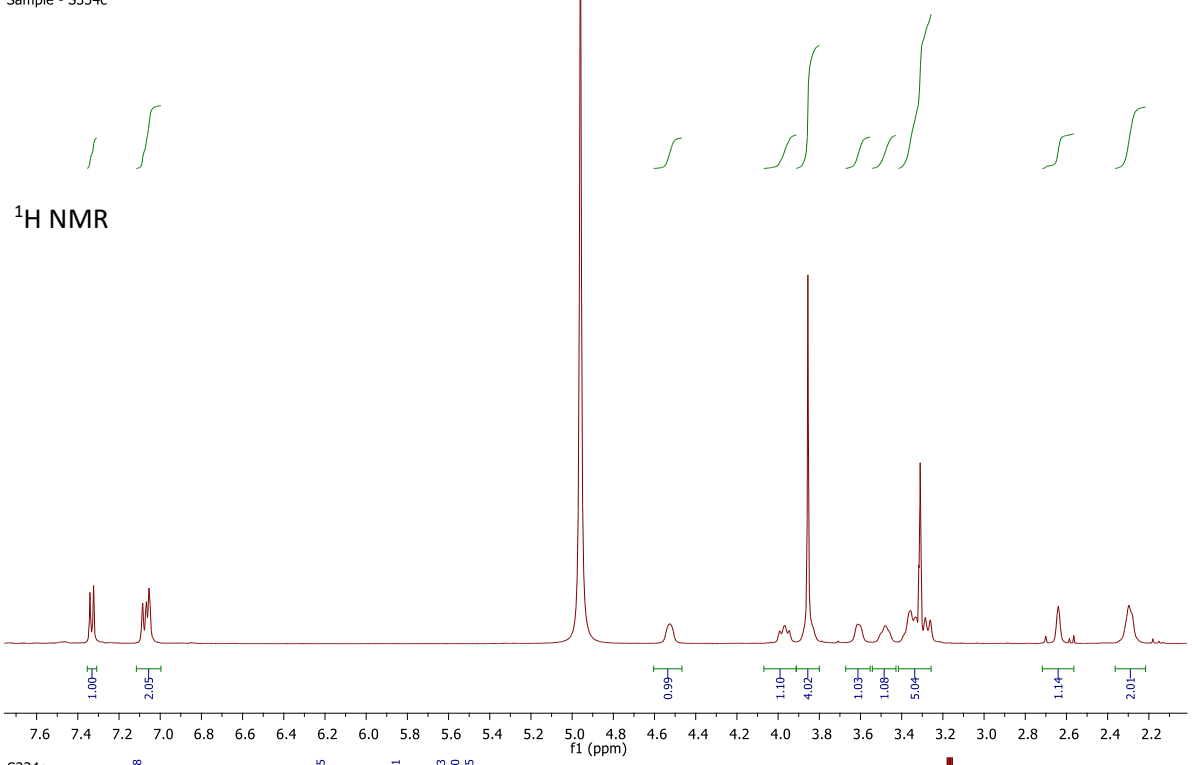




31

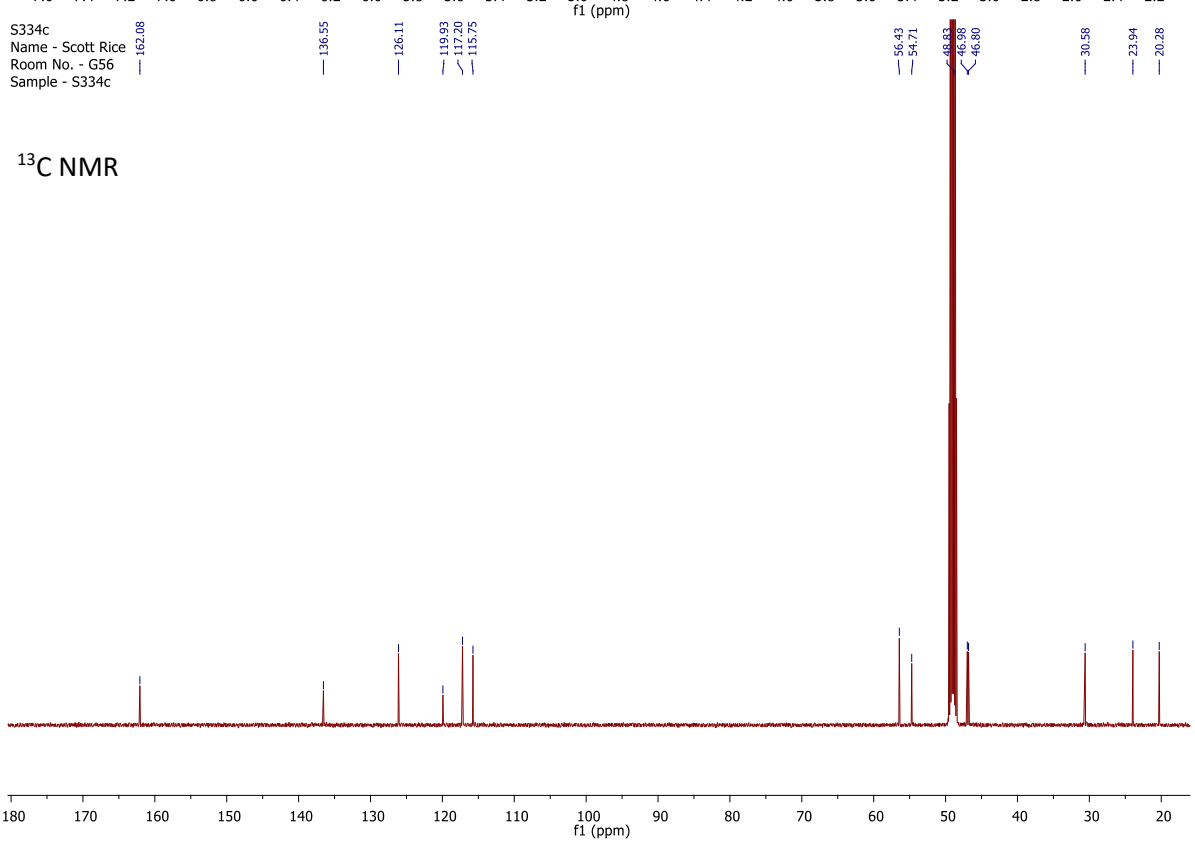
S334c
Name - Scott Rice
Room No. - G56
Sample - S334c

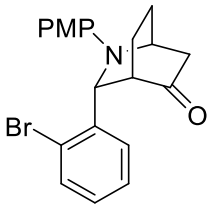
^{1}H NMR



S334c
Name - Scott Rice
Room No. - G56
Sample - S334c

^{13}C NMR

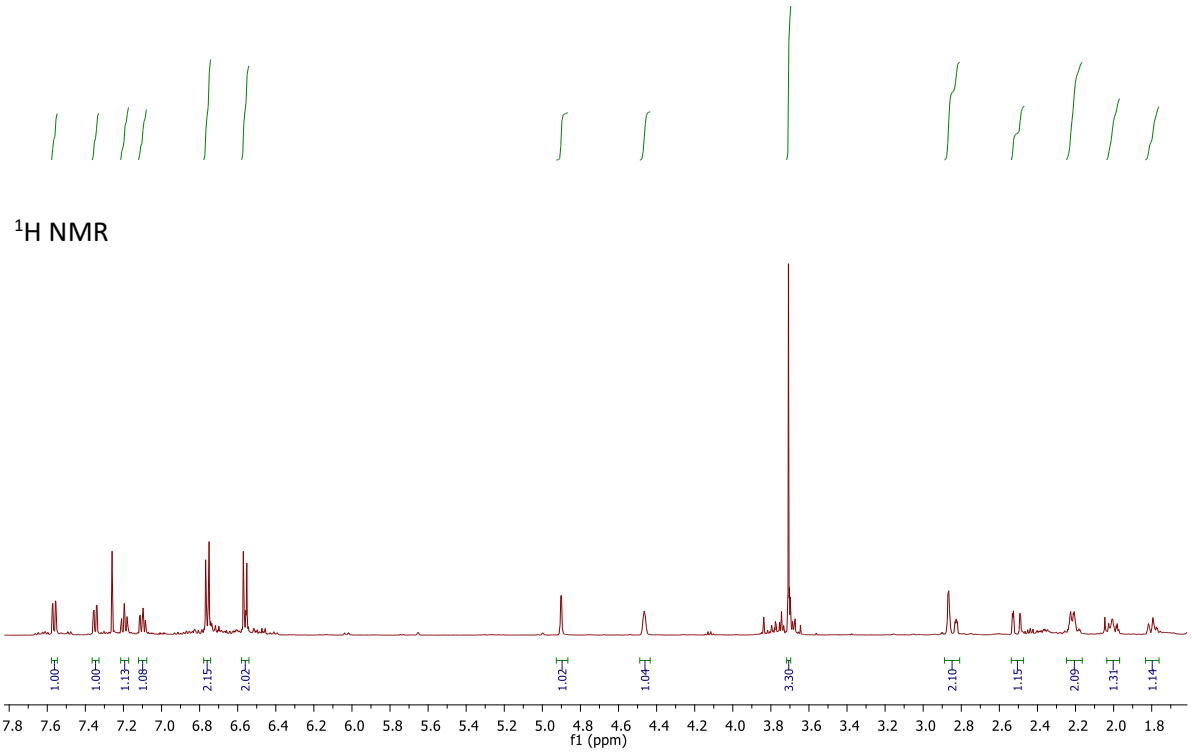




S15

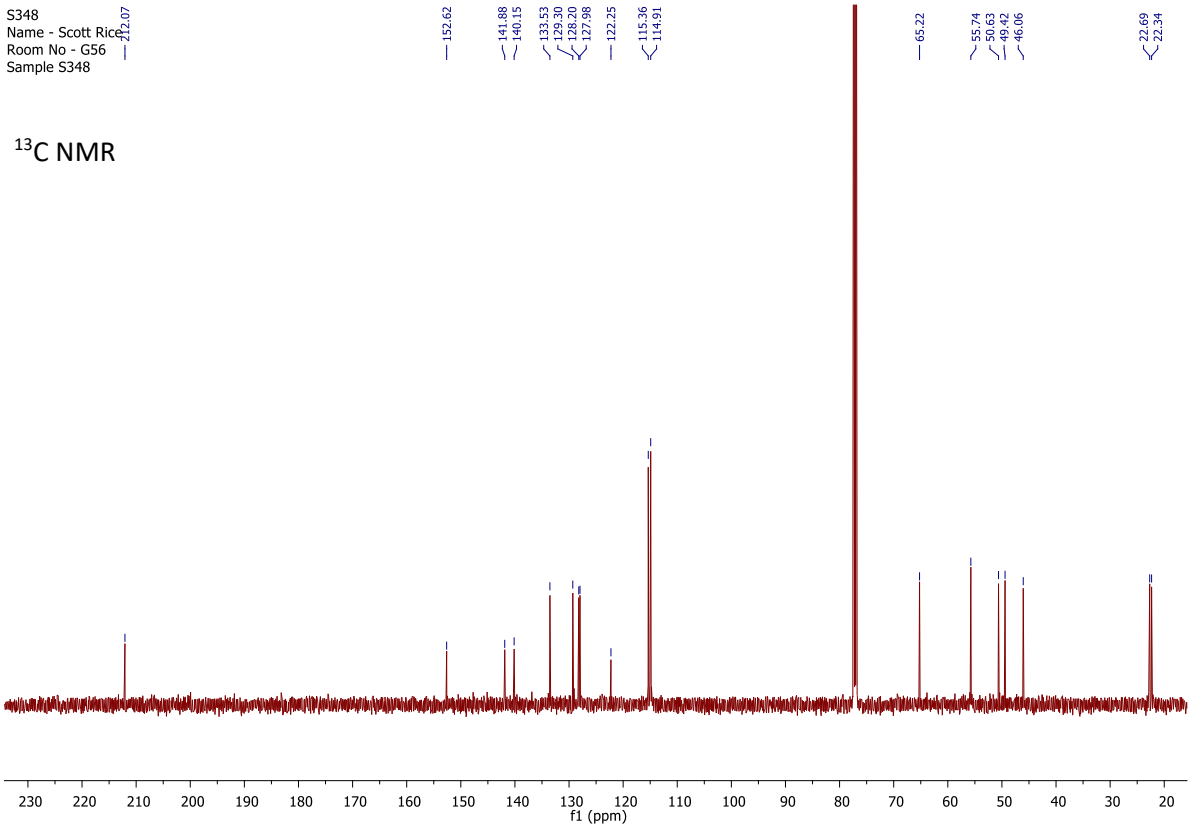
S348
Name - Scott Rice
Room No - G56
Sample S348

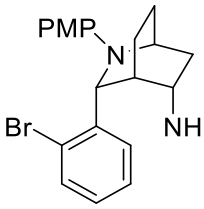
^{1}H NMR



S348
Name - Scott Rice
Room No - G56
Sample S348

^{13}C NMR

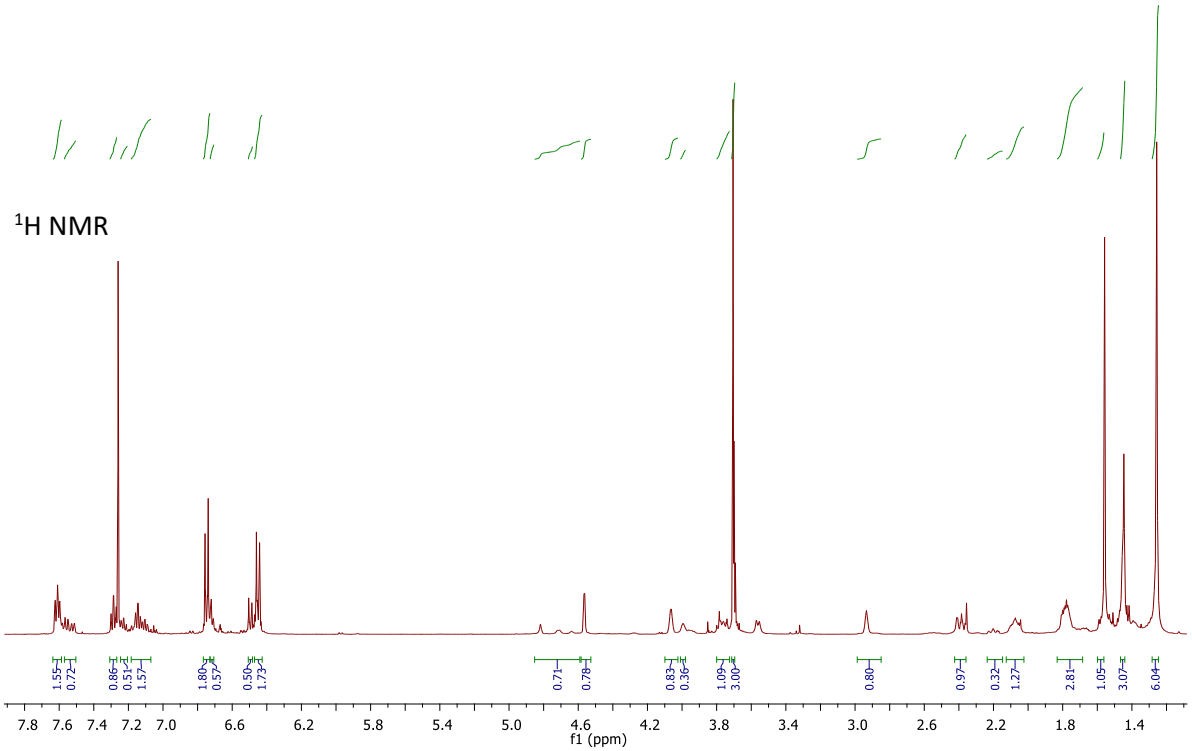




32 (*dr* 74:26)

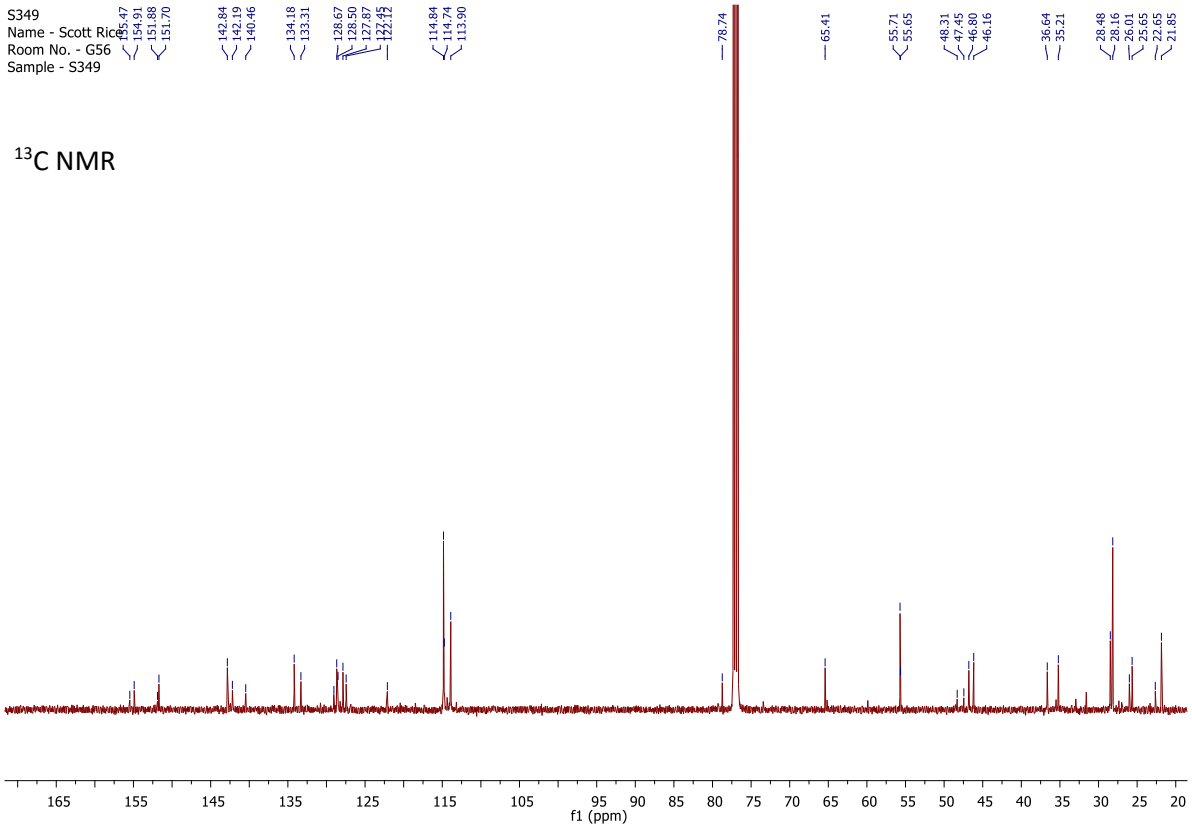
S349
Name - Scott Rice
Room No. - G56
Sample - S349

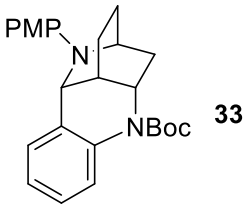
^{1}H NMR



S349
Name - Scott Rice
Room No. - G56
Sample - S349

^{13}C NMR

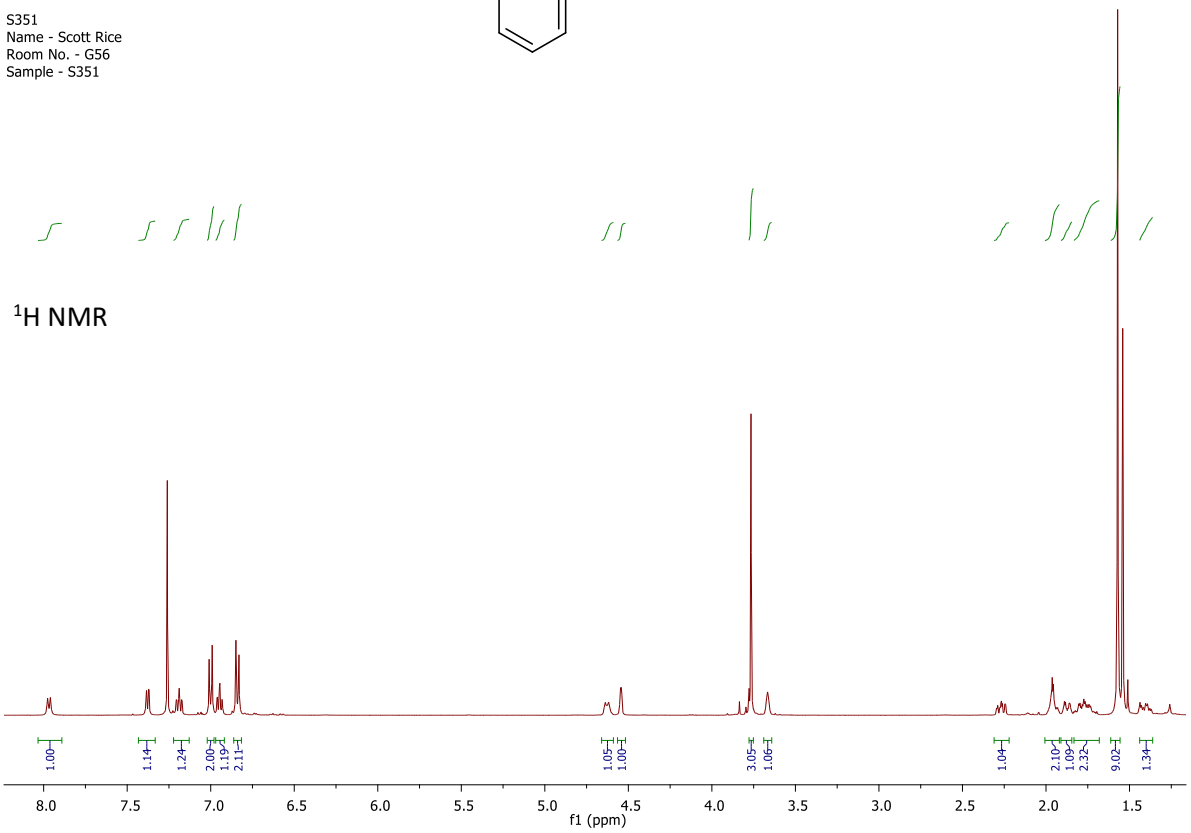




33

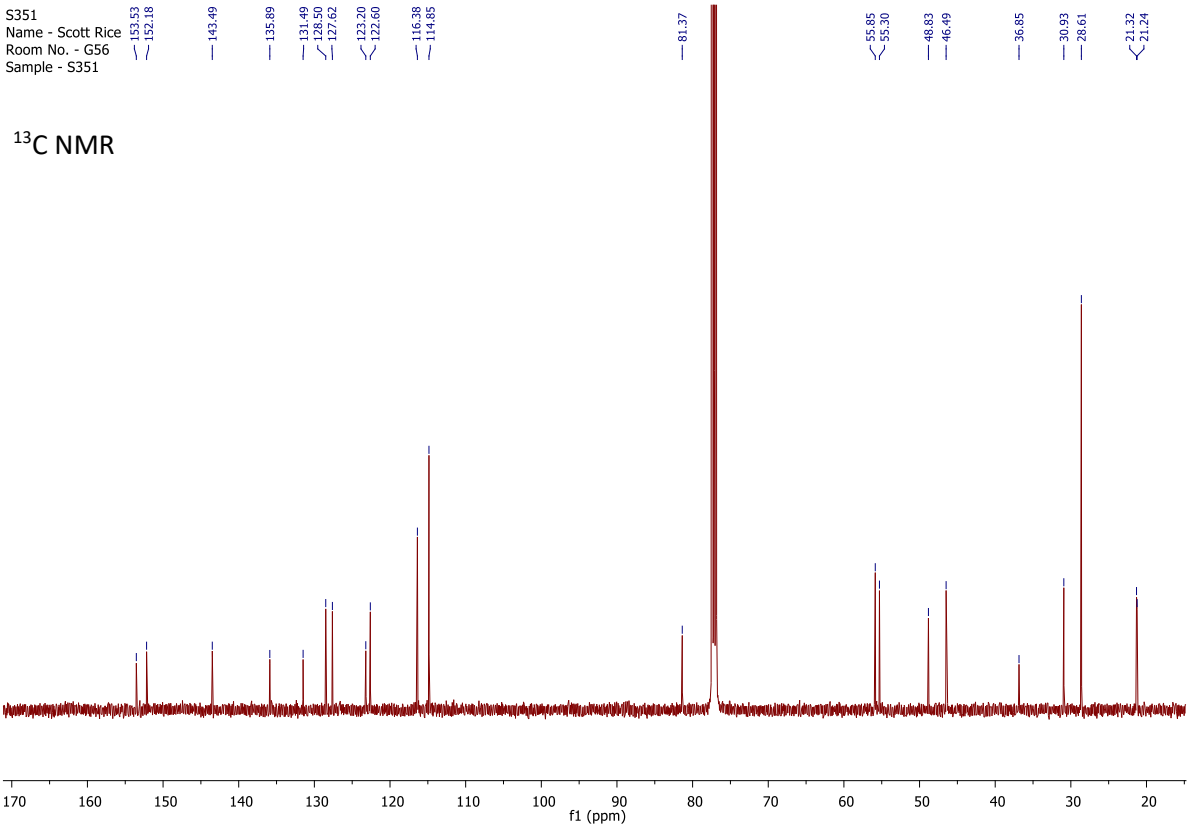
S351
Name - Scott Rice
Room No. - G56
Sample - S351

^{1}H NMR



S351
Name - Scott Rice
Room No. - G56
Sample - S351

^{13}C NMR



References

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