Synthesis of Arylethers via a Sulfonyl Transfer Reaction

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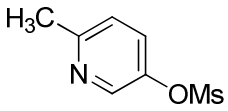
Materials and Methods. Unless stated otherwise, reactions were conducted in air-dried glassware under an atmosphere of nitrogen using commercial solvents without further drying or distilling. All commercially obtained reagents were used as received unless otherwise specified. Commercial reagents, including cesium carbonate (Cs_2CO_3), were obtained from Sigma-Aldrich unless otherwise specified. Sodium tert-butoxide (NaOt-Bu) was obtained from Strem Chemicals in powder form. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, p-anisaldehyde, iodine, and potassium permanganate stains. Biotage and ISCO systems were used for flash column chromatography using compatible silica gel cartridges and eluting with ethyl acetate in heptanes unless otherwise noted. ^{1}H NMR spectra were recorded on Burker spectrometers (at 400 MHz or 500 MHz) and are reported relative to deuterated solvent signals. ^{13}C NMR spectra were recorded on Burker spectrometers (at 75 MHz or 101 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. High resolution mass spectra were obtained using an Agilent Jet Stream 6230 Accurate Mass TOF LC/MS. Chiral supercritical fluid chromatography (SFC) separations were run on a 21.2 mm x 250 mm column at 100 bar, 35 ˚C and 60 – 65 mL/min unless otherwise noted.

Experimental Procedures

A. Preparation of mesylates

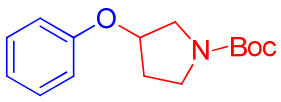
Quinolin-6-yl methanesulfonate[1] phenyl methanesulfonate,[2] o-tolyl methanesulfonate[3] 4-methoxyphenyl methanesulfonate,[4] 4-cyanophenyl methanesulfonate,[5] 4-chlorophenyl methanesulfonate,[3] benzo[d][1,3]dioxol-5-yl methanesulfonate,[3] 2-(pyridin-2-yl)phenyl methanesulfonate,[6] and 4-(chlorocarbonyl)phenyl methanesulfonate,[7] were either purchased or prepared from their corresponding phenols with MsCl in the presence of triethylamine in DCM or 2-methyltetrahydrofuran according to the literature method.[8] Preparation of an example, 6-methylpyridin-3-yl methanesulfonate, not previously described in the literature is shown below as a general procedure.



6-methylpyridin-3-yl methanesulfonate. 6-methylpyridin-3-ol (1.0 g, 9.16 mmol) was dissolved in THF (100 mL). Et_3N (1.4 mL, 10 mmol) was added and the reaction was chilled to 0˚C. Methanesulfonyl chloride (712 uL, 9.16 mmol) was added and the reaction was stirred at 0 ˚C for 30 min. and at room temperature for 1 h longer. LCMS analysis indicated that the reaction was complete. The THF was removed under vacuo and water (50 mL) was added. The product was extracted into 2-MeTHF (x4). The combined organic extract was washed with satd. aqueous NaCl (x2), dried over $MgSO_4$ and concentrated. The product was purified via preparative HPLC using a mass-directed detector to trigger fraction collection. After the pure fractions were combined and concentrated to afford 710 mg (41%) as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.60 (s, 3 H), 3.20 (s, 3 H), 7.22 - 7.29 (m, 1 H), 7.59 (dd, J=8.59, 2.78 Hz, 1 H), 8.47 (d, J=2.78 Hz, 1 H), HRMS Calc. for C13H13NO3S: 263.0616 Found: 263.0619.

B. Representative procedure for Condition A



10
Mitsunobu Ref. 14a

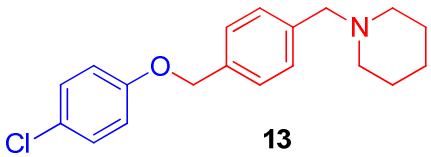
Ether 10. To a solution of 3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (500 mg, 2.67 mmol) and phenyl methanesulfonate (483 mg, 2.80 mmol) in acetonitrile (10 mL) was added NaOtBu (264 mg, 2.67 mmol). The reaction was heated with stirring at 80 ^{o}C for 16 h. The reaction was cooled and the solids were filtered off. The filtrate was concentrated and residue purified via normal phase

chromatography eluting with 15% EtOAc/heptanes. The product was isolated as a colorless oil, contaminated with phenol. The crude mixture was dissolved in EtOAc and washed with 1N NaOH to remove phenol. After the solvent was removed, the product crystallized upon standing to a white solid 390 mg, 55% yield.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.47 (s, 9 H) 2.08 (s, 1 H) 2.19 (s, 1 H) 3.53 (s, 2 H) 3.60 (s, 2 H) 4.88 (s, 1 H) 6.87 (d, J=7.83 Hz,2 H) 6.96 (s, 1 H) 7.29 (d, J=1.26 Hz, 2 H)

^{13}C NMR (101 MHz, CHLOROFORM-d) δ ppm 28.53 (s, 1 C) 31.18 (s, 1 C) 43.90 (s, 1 C) 51.57 (s, 1 C) 77.24 (s, 1 C) 79.43 (s, 1 C) 115.58 (s, 1C) 121.15 (s, 1 C) 129.60 (s, 1 C) 154.55 (s, 1 C) 157.18 (s, 1 C), HRMS calcd. for C15H21NO3: 264.15942 Found: 264.15816

C. Representative procedure for Condition B



13

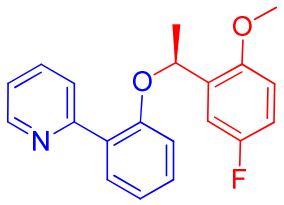
Mitsunobu Ref. 14d

Ether 13. To a solution of (4-piperidin-1-ylmethyl-phenyl)-methanol (220 mg, 1.07 mmol) and 4-chlorophenyl methanesulfonate (244 mg, 1.18 mmol) in DMF (5 mL) was added cesium carbonate (353 mg, 1.07 mmol) and the mixture was stirred at 100° C for 16 h. The reaction was then cooled to ambient temperature, diluted with water and extracted with 10% Heptane/EtOAc. The combined organic extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4. The solvents were removed and the resulting oil was purified on a SiNH2 column eluting with 1:1 EtOAc/heptane. The product was isolated as a colorless oil which crystallized upon standing to give 166 mg (49%) as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.44 (s, 2 H) 1.55 - 1.61 (m, 5 H) 2.38 (s, 4 H) 3.48 (s, 2 H) 5.02 (s, 2 H) 6.89 - 6.93 (m, 2 H) 7.22- 7.26 (m, 2 H) 7.35 (d, J=1.52 Hz, 4 H)

^{13}C NMR (101 MHz, DMSO-d6) δ ppm 23.92 (s, 1 C) 25.48 (s, 1 C) 53.80 (s, 1 C) 62.47 (s, 1 C) 69.34 (s, 1 C) 116.45 (s, 1 C) 124.27 (s, 1 C)127.52 (s, 1 C) 128.70 (s, 1 C) 129.14 (s, 1 C) 135.04 (s, 1 C) 138.41 (s, 1 C) 157.15 (s, 1 C), HRMS calcd. for C19H22ClNO: 316.146268 Found: 316.144792.

D. Representative procedure for Condition C



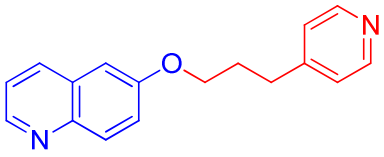
14

Ether 14. To a solution of (*R*)-1-(5-fluoro-2-methoxyphenyl)ethanol (200 mg, 1.18 mmol) in DMF (3.4 mL), sodium hydride 60 % dispersion in mineral oil (106 mg, 2.64 mmol) was added. The reaction mixture was stirred at room temperature. After 30 minutes, 2-(pyridin-2-yl)phenyl methanesulfonate[6] (352 mg, 1.41 mmol) was added, and the reaction was further stirred at 70 °C for 8 h. The reaction was cooled to room temperature and saturated aqueous NH_4Cl (25 mL) was added. The organics were extracted by EtOAc (2x20 mL) and the combined organic extracts were washed with saturated aqueous NaCl (25 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography to afford 156 mg (41%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 - 1.52 (m, 3 H) 3.86 (s, 3 H) 5.71 (d, J=6.32 Hz, 1 H) 6.83 (d, J=8.08 Hz, 1 H) 6.95 - 7.03 (m, 2 H) 7.03 - 7.08 (m, 2 H) 7.22 - 7.30 (m, 1 H) 7.35 (td, J=6.13, 0.88 Hz, 1 H) 7.71 (dd, J=7.58, 1.77 Hz, 1 H) 7.86 (td, J=7.71, 1.77 Hz, 1 H) 8.00 (d, J=8.08 Hz, 1 H) 8.68 (d, J=4.04 Hz, 1 H)

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 22.04, 56.16, 69.91, 112.21, 112.45, 113.66, 114.37, 120.79, 122.00, 124.86, 129.06, 129.84, 130.96, 132.31, 135.86, 149.27, 151.81, 154.45, 155.21, 157.67; HRMS calcd. for C20H18FNO2: 323.1322 Found: 323.1326.

Specific Rotation: $[\alpha]D_{25}$ = +310˚ (c = 0.30, MeOH)
ee = 96% (measured by chiral SFC)

E. Representative procedure for Condition D



3

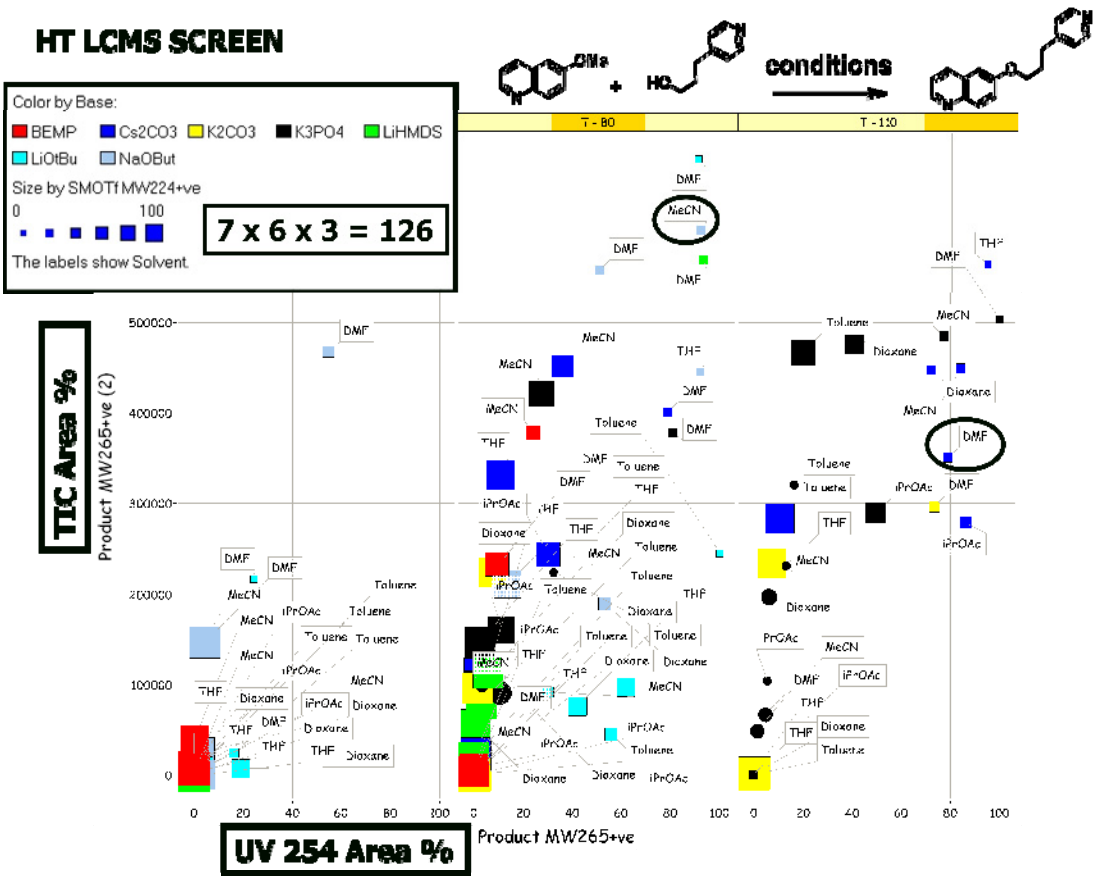
Ether 3. A mixture of 4-pyridinepropanol (151 mg, 1.10 mmol), quinolin-6-yl methanesulfonate (**1c**, 223 mg, 1.00 mmol), lithium tert-butoxide (88 mg, 1.1 mmol) in anhydrous DMSO (3 mL) was stirred at 155° C for 2 h. After cooling to room temperature, the solids were filtered off and the filtrate was purified by supercritical fluid chromatography to afford the title compound as an oil (195 mg, 74% yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm: 8.76 (dd, J=4.29, 1.77 Hz, 1 H), 8.50 (d, J=5.81 Hz, 2 H), 8.01 (d, J=9.60 Hz, 2 H), 7.31 - 7.40 (m, 2 H), 7.16 (d, J=6.06 Hz, 2 H), 7.01 (d, J=2.78 Hz, 1 H), 4.07 (t, J=6.19 Hz, 2 H), 2.82 - 2.90 (m, 2 H), 2.13 - 2.23 (m, 2 H)

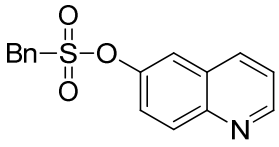
^{13}C NMR (101 MHz, CHLOROFORM-d) δ ppm: 156.89, 150.42, 149.75, 147.95, 144.37, 134.81, 130.87, 129.29, 123.99, 122.37, 121.40, 105.93, 66.75, 31.58, 29.61. HRMS calcd. for C17H16N2O: 265.13354 Found: 265.13369.

F. SpotFire results from micro-scale screening

Micro-scale techniques were used to screen six solvents, seven bases at three temperatures (25˚ C, 80° C and 110° C). Mesylate **1c** and primary alcohol **2** were selected as reactants for this screen based on ease of monitoring disappearance of starting materials and appearance of products by LCMS. The solvents examined included 1,4-dioxane, DMF, CH_3CN, toluene, THF, iPrOAc. The bases screened were BEMP, NaOtBu, LHMDS, Cs_2CO_3, K_3PO_4 and LiOtBu. Results from these 84 reactions were plotted using area % product by UV (254 nm) on the x-axis and total ion current from the MS on the y-axis (both looking at the product peak with MW of 265). Three optimal conditions surfaced from this screen: (1) NaOtBu in CH_3CN at 80° C, (2) LiOtBu in DMF at 80° C and (3) Cs_2CO_3 in DMF at 100° C. NaOtBu in CH_3CN and Cs_2CO_3 in DMF at 100° C were selected for further optimization. LiOtBu in DMF at 80° C was not selected since using alkoxide bases in heated DMF is considered a safety hazard.



G. Experimental procedures for new compounds.

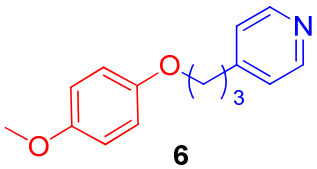


1e

Benzylsulfonate 1e. To a solution of phenylmethanesulfonyl chloride (5.0 g, 26 mmol), and quinolin-6-ol (3.0 g, 21 mmol) in THF (50 mL) was added Et_3N (4.0 g, 40 mmol). The mixture was stirred at room temperature for 16 h. TLC (petroleum/EtOAc = 2:1) showed that most of the starting material was consumed. The mixture was concentrated and EtOAc (50 mL) was added. The organic layer was washed with aq, NaOH (1N, 15 mL), aq. NH_4Cl, and saturated aq. NaCl and dried over Na_2SO_4. After removing the solvents, the crude product was re-crystallized with EtOH to give **1e** (3.1 g, 48%) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ ppm 7.94-7.31 (m, 8H), 7.18-7.16 (d, 2H), 4.72 (s, 2H)

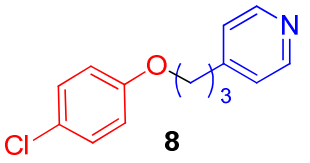
^{13}C NMR (101 MHz, CHLOROFORM-d) δ ppm 57.0, 76.7, 77.3, 119.3, 121.9, 124.3, 127.0, 128.3, 129.0, 129.3, 130.8, 131.6, 135.9, 146.5, 146.7, 150.8; HRMS calcd. for C13H12O3S: 299.0616 Found: 299.0621



6

p-Methoxyphenyl ether 6. General procedure A was ran on a 1 mmol scale to afford 187 mg (77%) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.04 - 2.17 (m, 2 H) 2.77 - 2.88 (m, 2 H) 3.74 - 3.81 (m, 3 H) 3.93 (t, J=6.06 Hz, 2 H) 6.77 - 6.87 (m, 4 H) 7.15 (d, J=6.06 Hz, 2 H) 8.44 - 8.55 (m, 2 H)

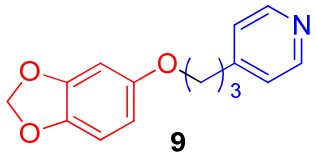
^{13}C NMR (101 MHz, CHLOROFORM-d) δ ppm 29.85 (s, 1 C) 31.59 (s, 1 C) 55.73 (s, 1 C) 67.18 (s, 1 C) 114.69 (s, 1 C) 115.46 (s, 1 C) 123.96 (s, 1 C) 149.76 (s, 1 C) 150.59 (s, 1 C) 152.95 (s, 1 C) 153.92 (s, 1 C); HRMS calcd. for C15H17NO2: 244.1332, Found: 244.1327



8

p-Chlorophenyl ether 8. General procedure A was ran on a 1 mmol scale to afford 156 mg (63%) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.02 - 2.18 (m, 2 H) 2.81 (t, J=7.58 Hz, 2 H) 3.93 (t, J=6.06 Hz, 2 H) 6.76 - 6.85 (m, 2 H) 7.14 (d, J=6.06 Hz, 2 H) 7.20 - 7.26 (m, 2 H) 8.42 - 8.58 (m, 2 H)

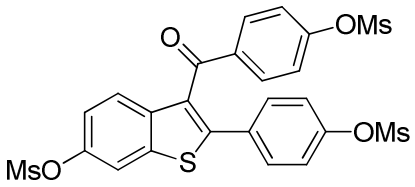
^{13}C NMR (101 MHz, CHLOROFORM-d) δ ppm 29.64 (s, 1 C) 31.50 (s, 1 C) 66.79 (s, 1 C) 115.70 (s, 1 C) 123.91 (s, 1 C) 125.67 (s, 1 C) 129.33 (s, 1 C) 149.79 (s, 1 C) 150.32 (s, 1 C) 157.38 (s, 1 C), HRMS calcd. for C14H14ClNO: 248.0837, Found: 248.0833



9

Dioxolane ether 9. General procedure A was ran on a 1 mmol scale to afford 187 mg (73%) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.00 - 2.16 (m, 2 H) 2.70 - 2.87 (m, 2 H) 3.89 (t, J=6.06 Hz, 2 H) 5.92 (s, 2 H) 6.30 (dd, 1 H) 6.49 (d, J=2.53 Hz, 1 H) 6.70 (d, J=8.34 Hz, 1 H) 7.15 (d, J=5.81 Hz, 2 H) 8.38 - 8.57 (m, 2 H)

^{13}C NMR (101 MHz, CHLOROFORM-d) δ ppm 29.77 (s, 1 C) 31.56 (s, 1 C) 67.45 (s, 1 C) 98.05 (s, 1 C) 101.13 (s, 1 C) 105.66 (s, 1 C) 107.95 (s, 1 C) 123.95 (s, 1 C) 141.71 (s, 1 C) 148.27 (s, 1 C) 149.77 (s, 1 C) 150.51 (s, 1 C) 154.31 (s, 1 C); HRMS calcd. for C15H15NO3: 258.1125, Found: 258.1114.



18

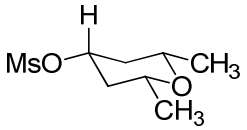
Trismesylate 18. To a solution of 4-(6-((methylsulfonyl)oxy)benzo[b]thiophen-2-yl)phenyl methanesulfonate[9] (581 mg, 1.46 mmol) in 1,2-DCE, was added 4-(chlorocarbonyl)phenyl methanesulfonate[10] (479 mg, 2.04 mmol). $AlCl_3$ (1.75 g, 13 mmol) was added over a period of 15 min. in two portions at room temperature. The reaction progressed nicely over 4 h to afford a 90% conversion with ~10% starting material remaining as measured by LCMS. The reaction was allowed to stir for another 16 h and the mixture was poured onto ice and aqueous NaK-tartrate. $CHCl_3$ (100 mL) was added and the mixture was allowed to stir for 2 h. The aq. layer was extracted with $CHCl_3$ (2 x 50 mL) and the combined organics dried over $MgSO_4$. After removal of the solvents, the product was purified via flash chromatography eluting with a gradient of 12 - 100% EtOAc in heptane. The fractions containing the desired product were pooled and concentrated to afford 540 mg (62%) as a yellow foam. The ^{1}H NMR was consistent with the desired product while the LCMS indicated the ketone-hydrate (M+H = 614).

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 3.10 (s, 3 H), 3.13 (s, 3 H), 3.23 (s, 3 H), 7.13 - 7.23 (m, 4 H), 7.36 (dd, J=8.85, 2.26 Hz, 1 H), 7.39 - 7.47 (m, 2 H), 7.73 - 7.81 (m, 2 H), 7.83 - 7.92 (m, 2 H)

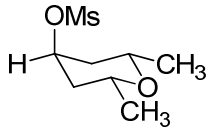
^{13}CNMR (101 MHz, CHLOROFORM-d) δ ppm 37.6, 37.7, 37.9, 115.7, 120.2, 121.8, 122.0, 122.3, 125.0, 125.1, 131.1, 131.8, 131.9, 135.9, 138.1, 139.7, 146.8, 149.7, 152.7, 191.6; HRMS calcd. for C24H20O10S4: 595.9939 Found: unable to obtain a molecular ion using ESI neg or pos mode. The APCI low resolution LCMS showed the ketone-hydrate (M+H = 614).

H. Stereochemical probe experiment:

In an effort to intercept the proposed all cis alkyl mesylate intermediate, isomeric alkylmethanesulfonates were prepared in the 2,6-dimethyl pyran series. The starting pyran alcohols were prepared according to reference 18 of the paper. The corresponding alkylmesylates were prepared using the general procedure for aryl mesylates and the ^{1}H NMRs measured in both DMF d7 and CDCl3 are tabulated below.

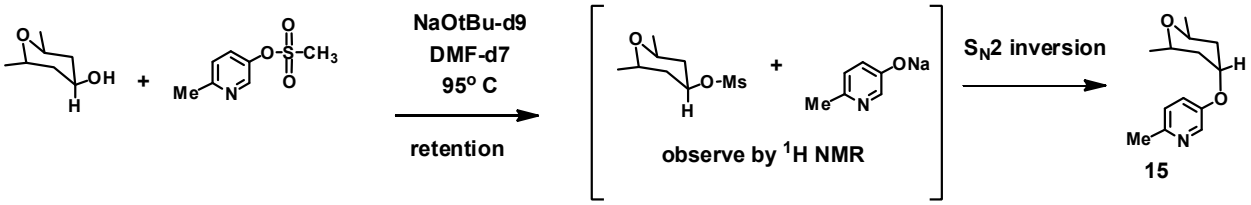


meso-(2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl methanesulfonate: ^{1}H NMR (400 MHz, DMF d7) δ ppm 4.79 - 4.92 (m, 1H), 3.49 - 3.60 (m, 2H), 3.27 (s, 3H), 2.06 - 2.17 (m, 2H), 1.28 (q, J = 11.37 Hz, 2H), 1.13 - 1.18 (m, 6H); ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 4.70-4.87 (m, 1H), 3.42-3.57 (m, 2H), 3.00 (s, 3H), 2.04-2.14 (m, 2H), 1.42 (q, J=11.49 Hz, 2H), 1.22 (d, J=6.24 Hz, 6H); ^{13}CNMR (101 MHz, CHLOROFORM-d) 77.89, 71.21, 39.73, 38.94, 21.56.

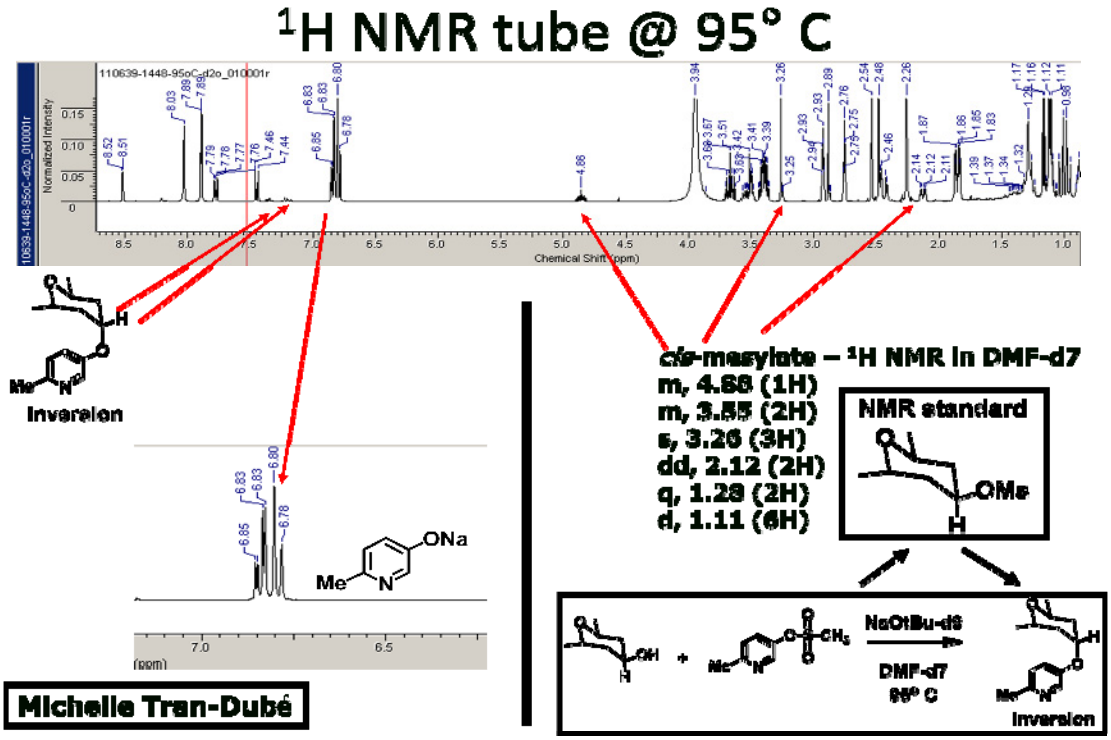


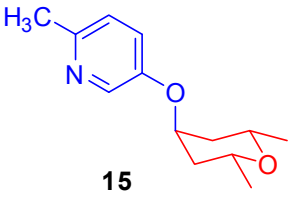
meso-(2R,4s,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl methanesulfonate: ^{1}H NMR (400 MHz, DMF-d7) δ ppm 5.13 (t, J = 2.91 Hz, 1H), 3.77 (ddd, J = 1.52, 6.19, 11.49 Hz, 2H), 3.27 (s, 3H), 1.93 (dd, J = 2.78, 14.91 Hz, 2H), 1.49 (ddd, J = 2.65, 11.62, 14.27 Hz, 2H), 1.11 (d, J = 6.32 Hz, 6H). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 5.13 (t, J=2.81 Hz, 1H), 3.82-3.94 (m, 2H), 3.03 (s, 3H), 1.95 (dd, J=2.32, 14.92 Hz, 2H), 1.45-1.56 (m, 2H), 1.20 (d, J=6.24 Hz, 6H); ^{13}CNMR (101 MHz, CHLOROFORM-d) δ ppm 76.95, 67.75, 38.62, 37.87, 21.64

The VT-NMR reaction was ran in DMF-d6 and upon reaching 95 ˚C, the ^{1}H NMR spectra showed the pyran alkyl mesylate form with retention of configuration.



Shown below is the reaction intercepted at a midpoint showing clear evidence of ^{1}H NMR formation of the all cis-mesylate (**meso-(2R,4r,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl methanesulfonate**) with **15** beginning to form.





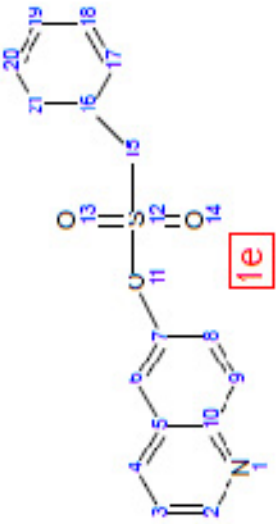
15

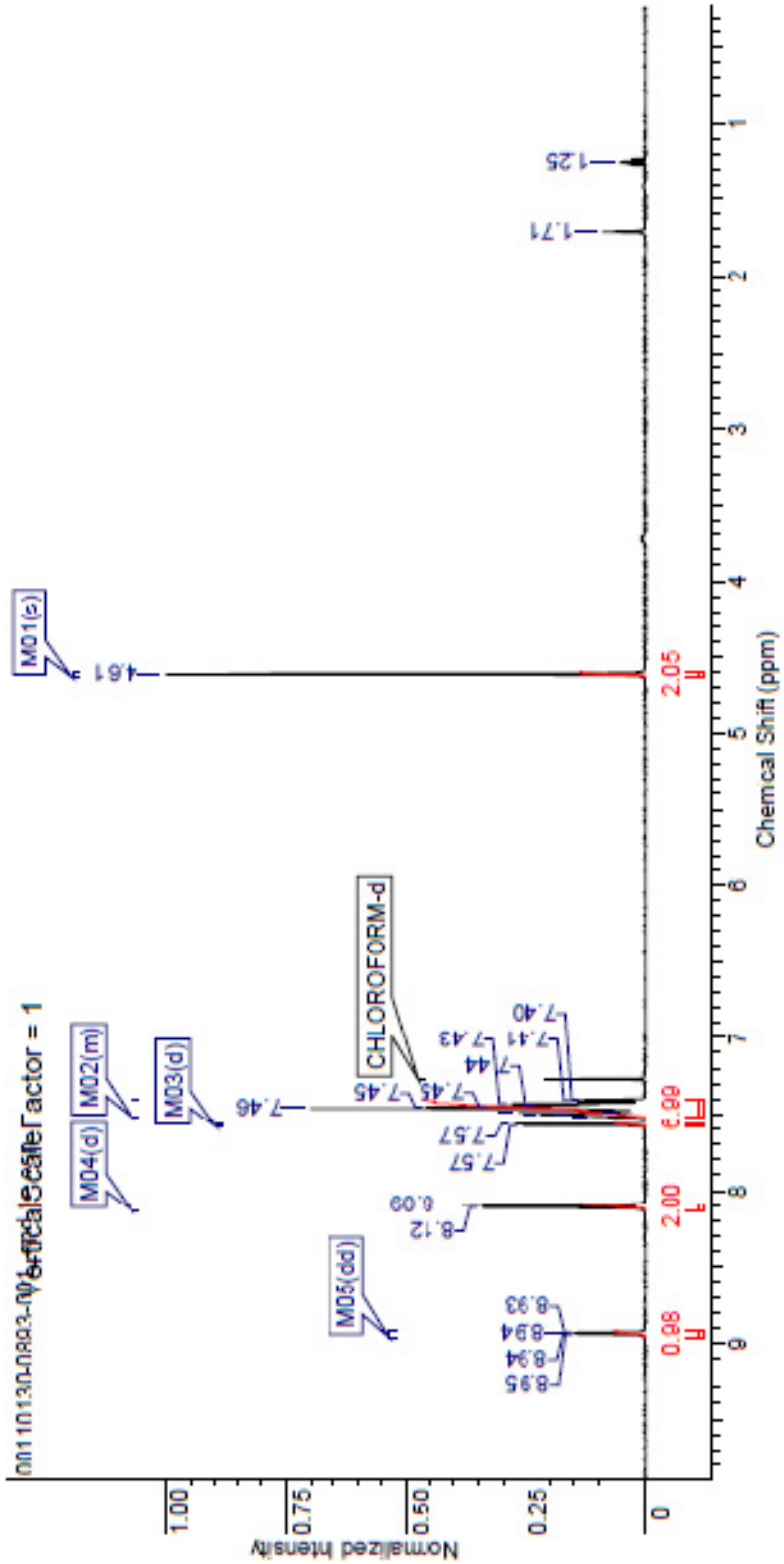
Compound 15. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.19 (d, J = 2.69 Hz, 1H), 7.07 - 7.18 (m, 2H), 4.65 - 4.76 (m, 1H), 3.90 - 4.00 (m, 2H), 2.52 (s, 3H), 1.90 (dd, J = 2.45, 14.43 Hz, 2H), 1.48 (ddd, J = 2.69, 11.55, 14.00 Hz, 2H), 1.14 - 1.23 (m, 6H); ^{13}CNMR (75 MHz, CHLOROFORM-d) δ ppm 151.37, 150.38, 138.07, 123.38, 123.31, 71.04, 67.75, 36.44, 23.21, 21.74; HRMS Calcd. for C13H19NO2: 221.1416 Found: 221.1423

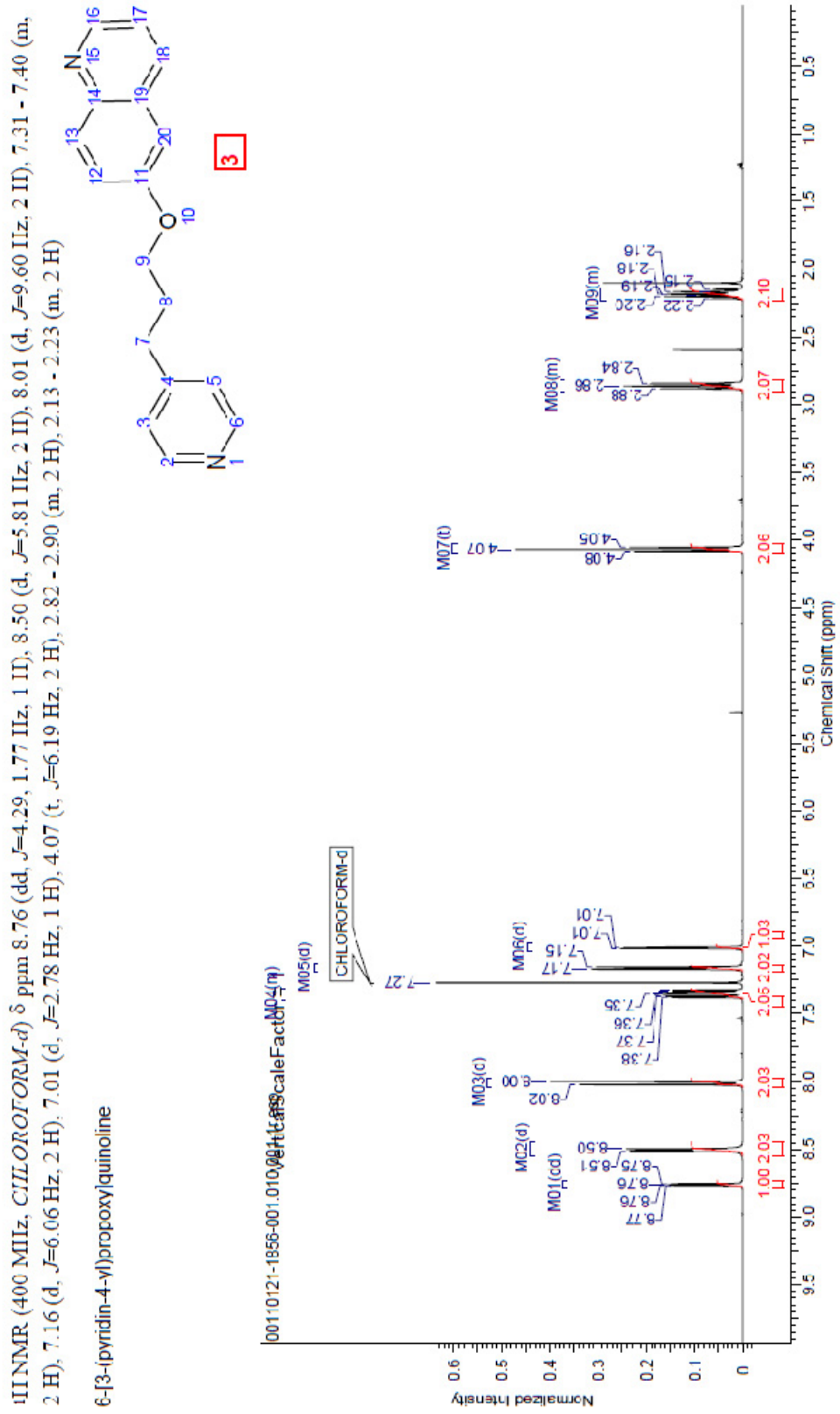
^{1}H NMR Spectra of new compounds and those used to demonstrate representative procedures:

1e, 3, 6, 8, 9, 10, 13, 14, 15, 18

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.61 (s, 2 H) 7.40 - 7.52 (m, 7 H) 7.57 (d, *J*=2.69 Hz, 1 H) 8.10 (d, *J*=8.93 Hz, 2 H) 8.94 (dd, *J*=4.16, 1.71 Hz, 1 H)



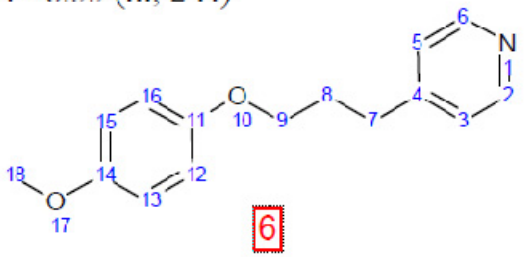


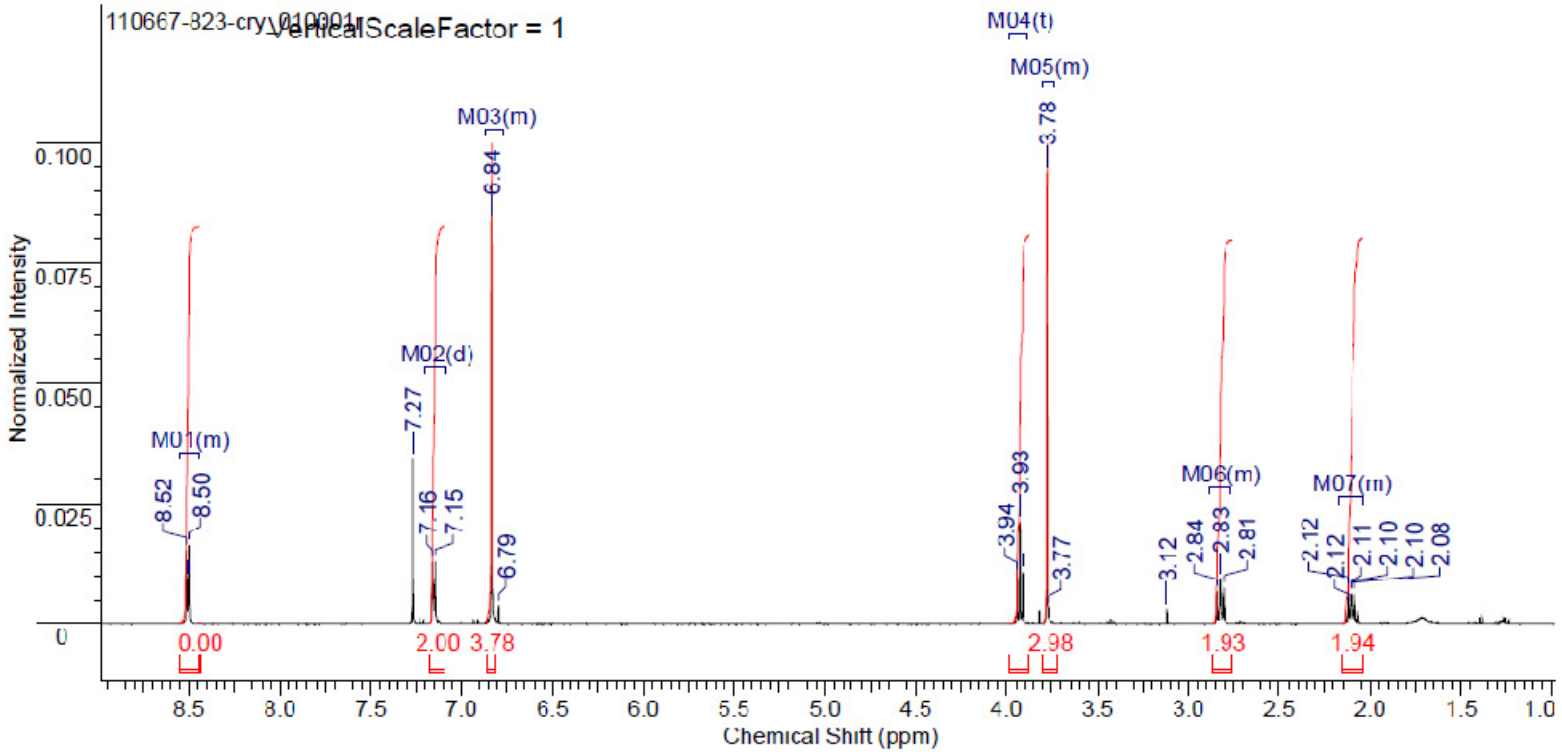


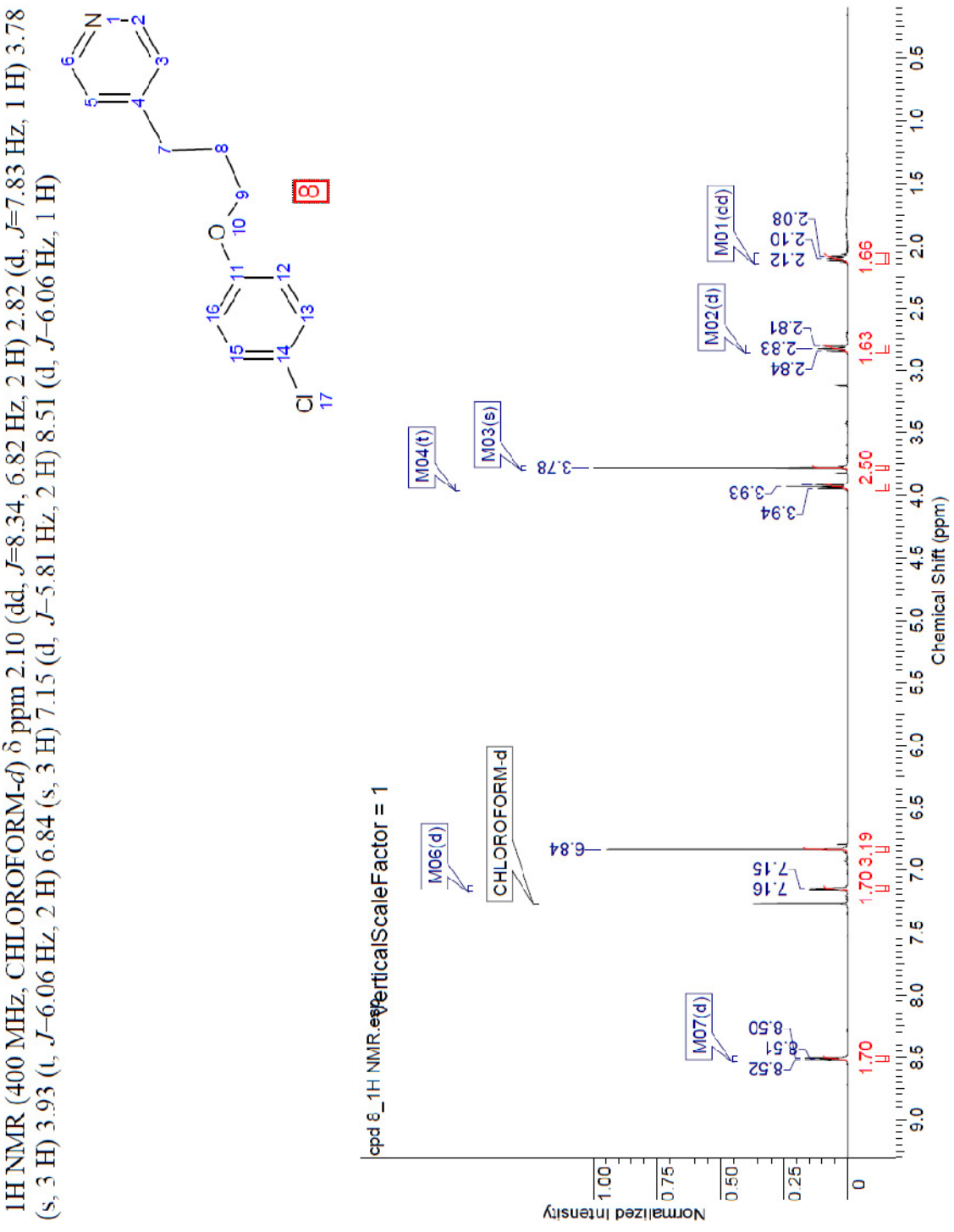
6-[3-(pyridin-4-yl)propoxy]quinoline

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.76 (dd, *J*=4.29, 1.77 Hz, 1 H), 8.50 (d, *J*=5.81 Hz, 2 H), 8.01 (d, *J*=9.60 Hz, 2 H), 7.31 - 7.40 (m, 2 H), 7.16 (d, *J*=6.06 Hz, 2 H), 7.01 (d, *J*=2.78 Hz, 1 H), 4.07 (t, *J*=6.19 Hz, 2 H), 2.82 - 2.90 (m, 2 H), 2.13 - 2.23 (m, 2 H)

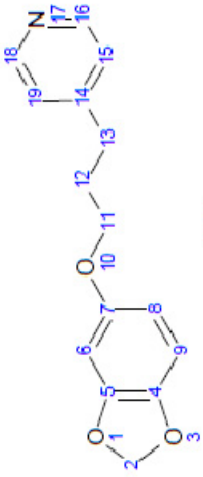
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.04 - 2.17 (m, 2 H) 2.77 - 2.88 (m, 2 H) 3.74 - 3.81 (m, 3 H) 3.93 (t, *J*=6.06 Hz, 2 H) 6.77 - 6.87 (m, 4 H) 7.15 (d, *J*=6.06 Hz, 2 H) 8.44 - 8.55 (m, 2 H)



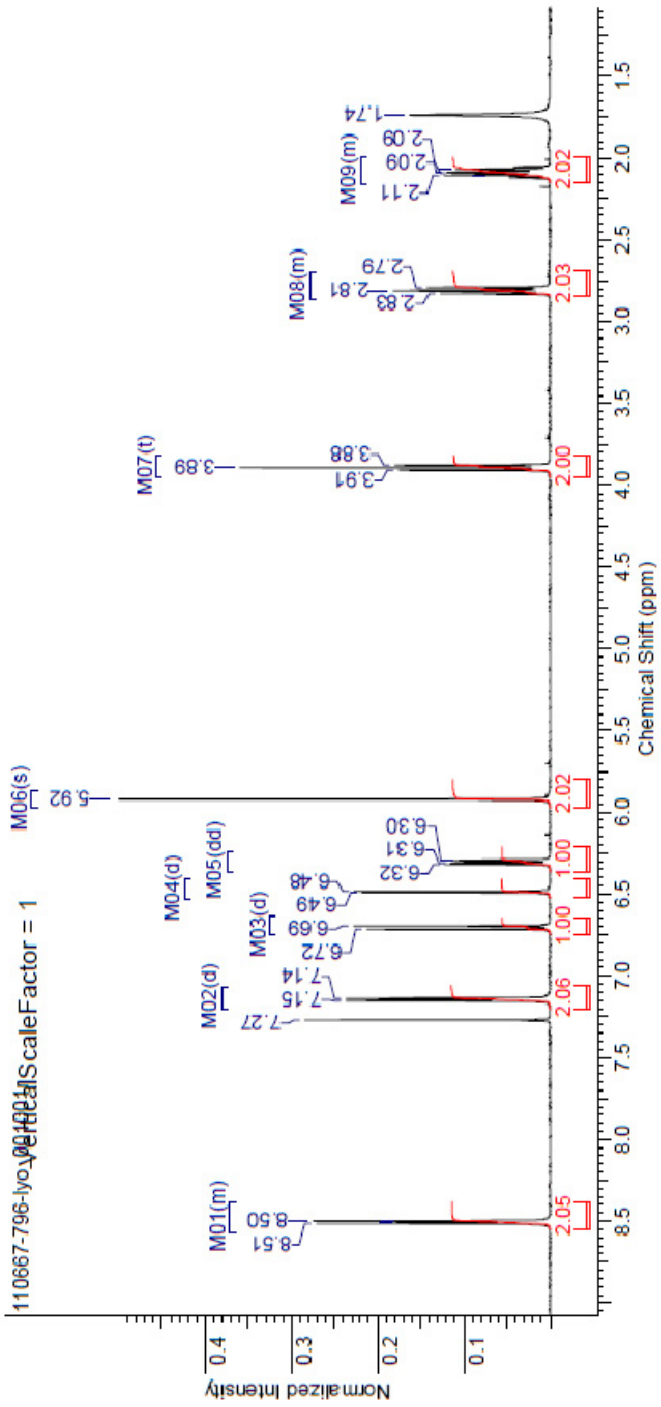


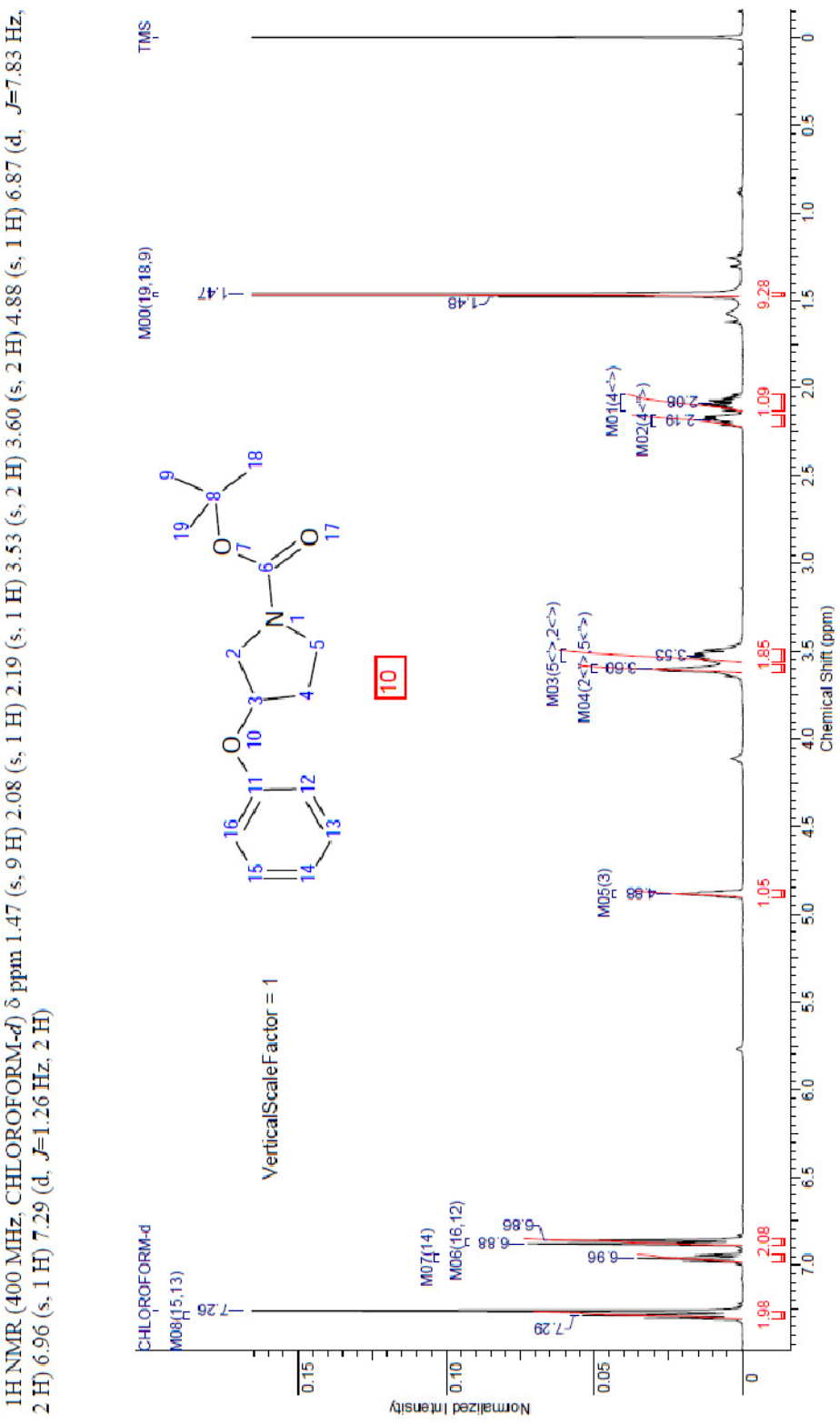

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 2.10 (dd, J=8.34, 6.82 Hz, 2 H) 2.82 (d, J=7.83 Hz, 1 H) 3.78 (s, 3 H) 3.93 (t, J=6.06 Hz, 2 H) 6.84 (s, 3 H) 7.15 (d, J=5.81 Hz, 2 H) 8.51 (d, J=6.06 Hz, 1 H)
8
cpd 8_1H NMR.esp VerticalScaleFactor = 1
Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
M01(cd)
M02(d)
M03(s)
M04(t)
M06(d)
M07(d)

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.00 - 2.16 (m, 2 H) 2.70 - 2.87 (m, 2 H) 3.89 (t, *J*=6.06 Hz, 2 H) 5.92 (s, 2 H) 6.30 (dd, 1 H) 6.49 (d, *J*=2.53 Hz, 1 H) 6.70 (d, *J*=8.34 Hz, 1 H) 7.15 (d, *J*=5.81 Hz, 2 H) 8.38 - 8.57 (m, 2 H)

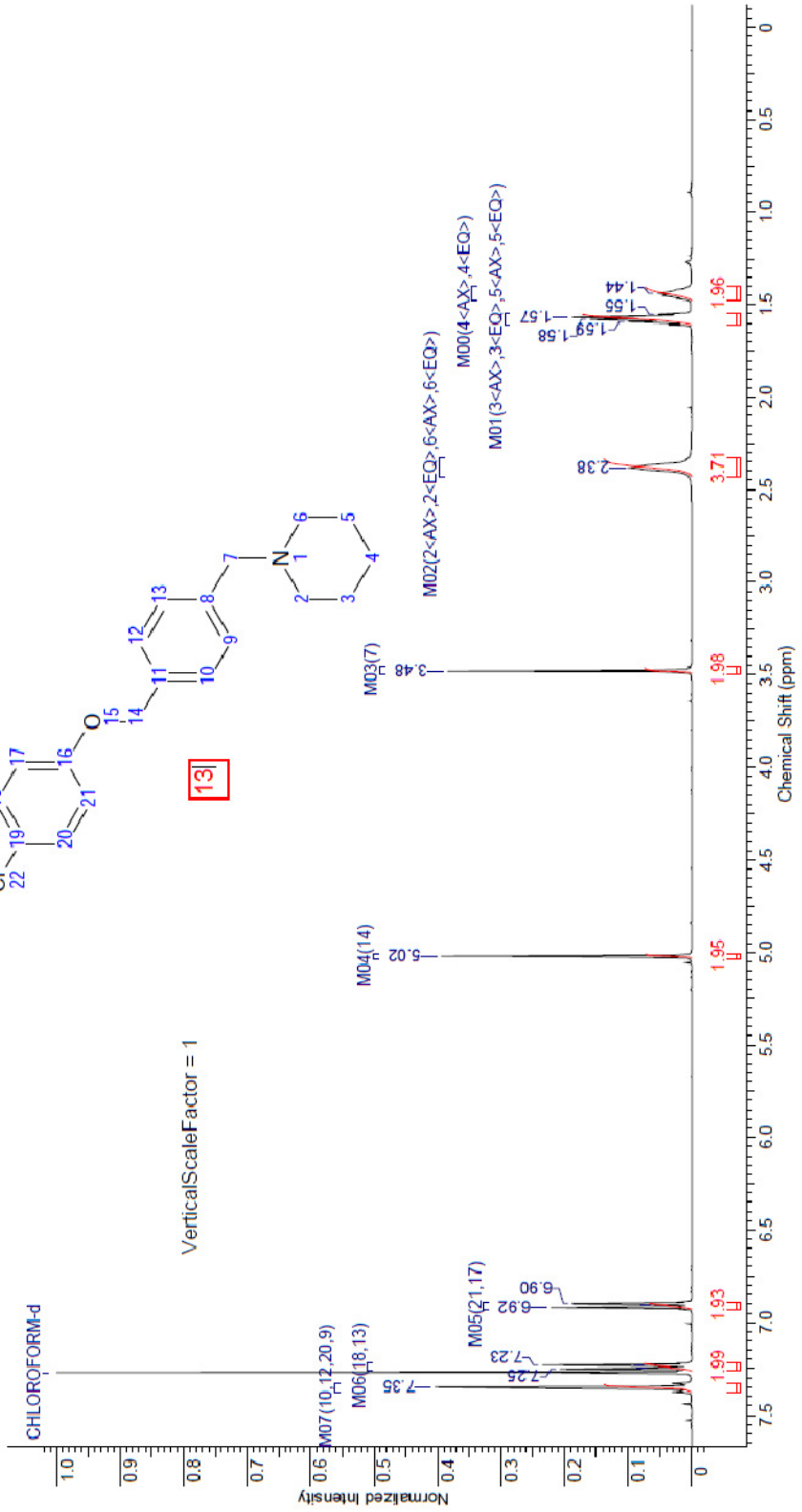


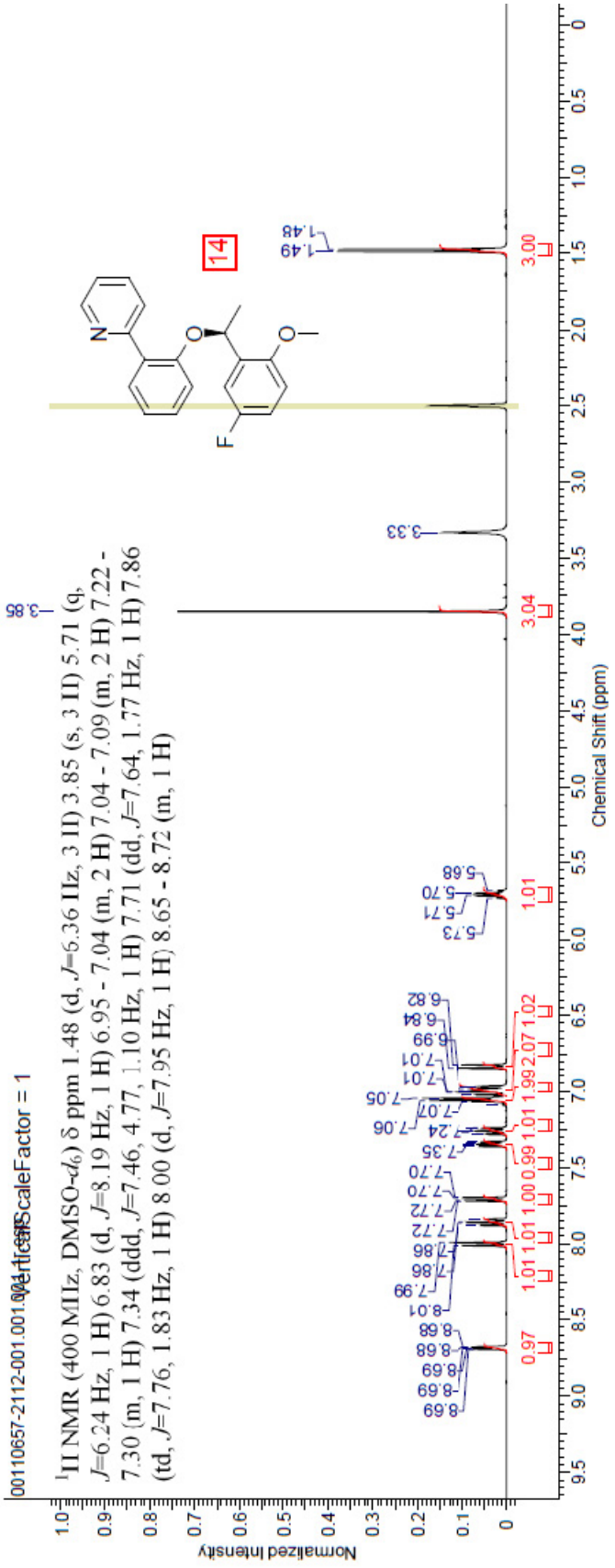
9



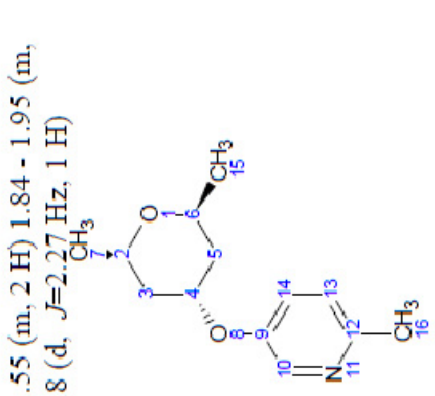

1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.47 (s, 9 H) 2.08 (s, 1 H) 2.19 (s, 1 H) 3.53 (s, 2 H) 3.60 (s, 2 H) 4.88 (s, 1 H) 6.87 (d, J=7.83 Hz, 2 H) 6.96 (s, 1 H) 7.29 (d, J=1.26 Hz, 2 H)
VerticalScaleFactor = 1
10
Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
TMS

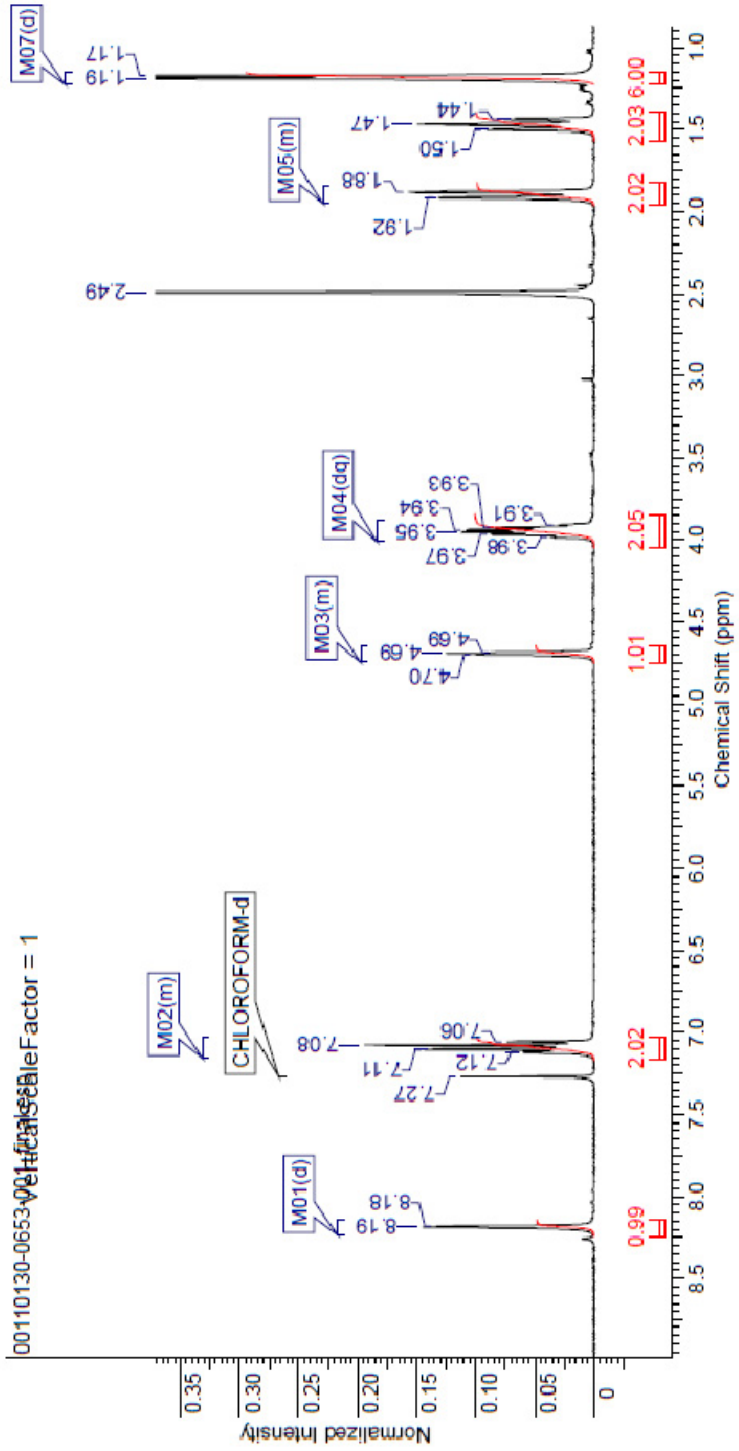
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.44 (s, 2 H) 1.55 - 1.61 (m, 5 H) 2.38 (s, 4 H) 3.48 (s, 2 H) 5.02 (s, 2 H) 6.89 - 6.93 (m, 2 H) 7.22 - 7.26 (m, 2 H) 7.35 (d, *J*=1.52 Hz, 4 H)

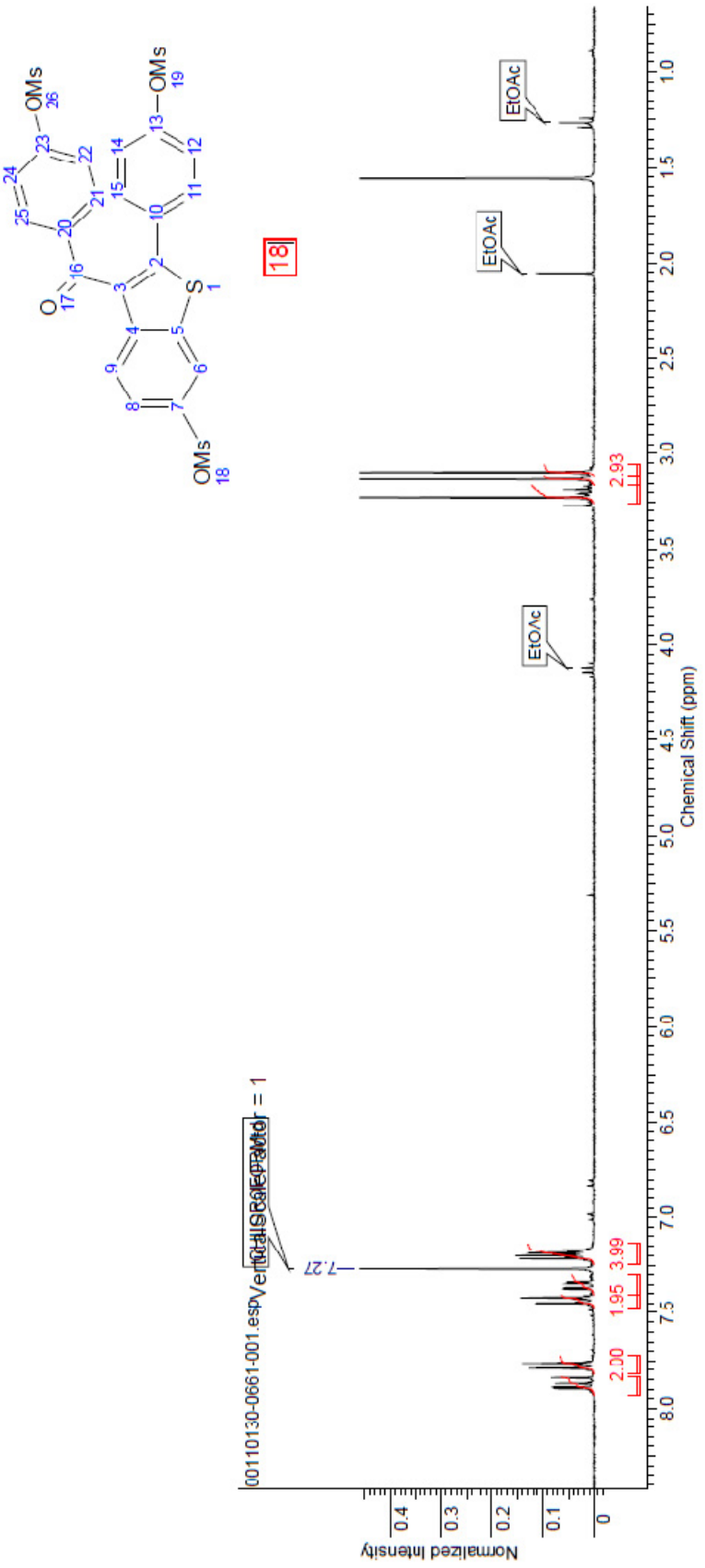



00110657-2112-001.001.001.001.1r.esp
VerticalScaleFactor = 1
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 (d, J=6.36 Hz, 3 H) 3.85 (s, 3 H) 5.71 (q, J=6.24 Hz, 1 H) 6.83 (d, J=8.19 Hz, 1 H) 6.95 - 7.04 (m, 2 H) 7.04 - 7.09 (m, 2 H) 7.22 - 7.30 (m, 1 H) 7.34 (ddd, J=7.46, 4.77, 1.10 Hz, 1 H) 7.71 (dd, J=7.64, 1.77 Hz, 1 H) 7.86 (td, J=7.76, 1.83 Hz, 1 H) 8.00 (d, J=7.95 Hz, 1 H) 8.65 - 8.72 (m, 1 H)
14
Normalized Intensity
Chemical Shift (ppm)

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.18 (d, *J*=6.32 Hz, 6 H) 1.40 - 1.55 (m, 2 H) 1.84 - 1.95 (m, 2 H) 3.95 (dq, *J*=11.46, 5.86 Hz, 2 H) 4.65 - 4.74 (m, 1 H) 7.03 - 7.16 (m, 2 H) 8.18 (d, *J*=2.27 Hz, 1 H)

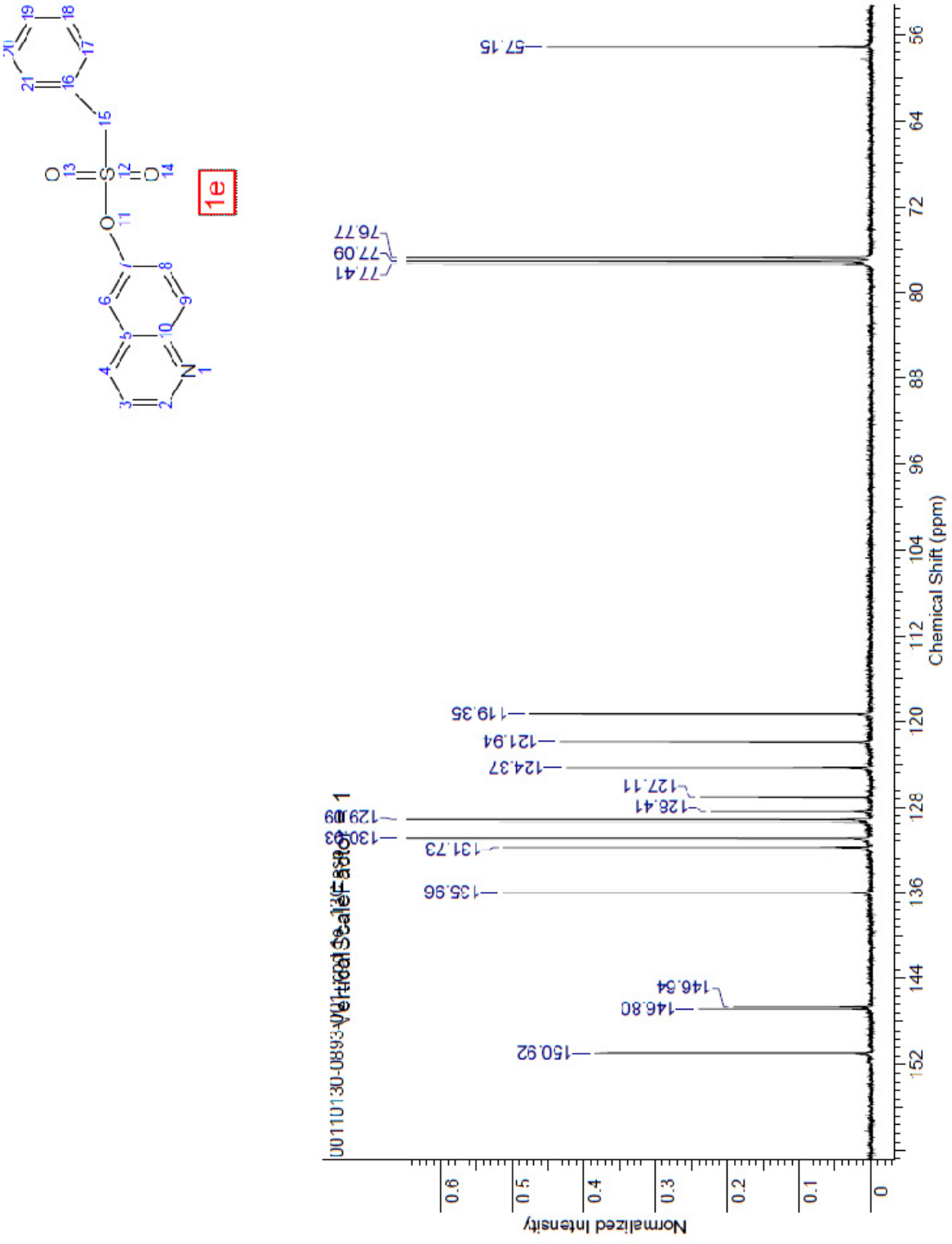


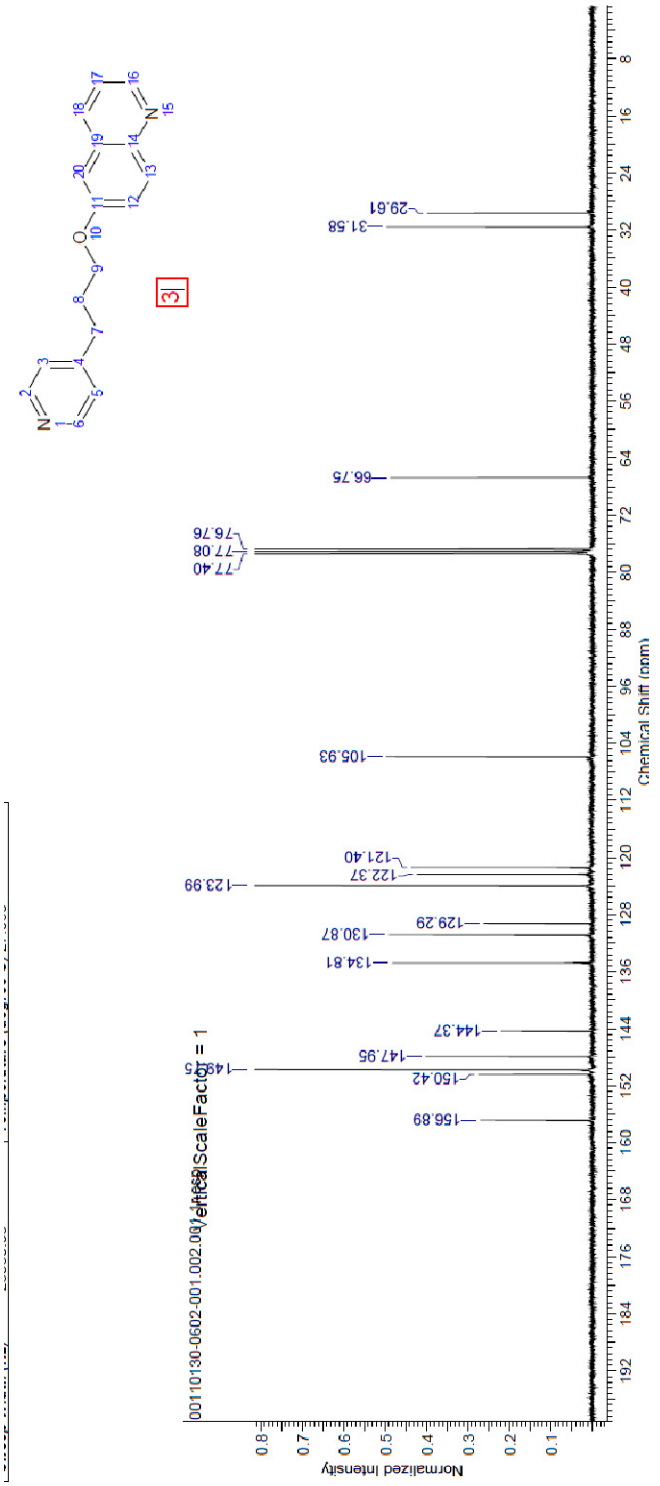



18
OMs
OMs
OMs
O
S
EtOAc
EtOAc
EtOAc
7.27
2.00
1.95
3.99
2.93
Normalized Intensity
Chemical Shift (ppm)

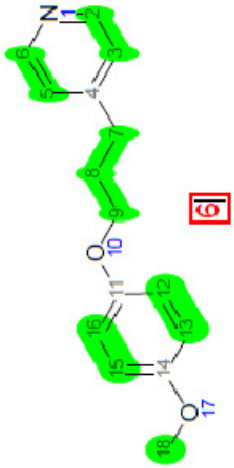
^{13}C NMR Spectra of new compounds and those used to demonstrate representative procedures:

1e, 3, 6, 8, 9, 10, 13, 14, 15, 18

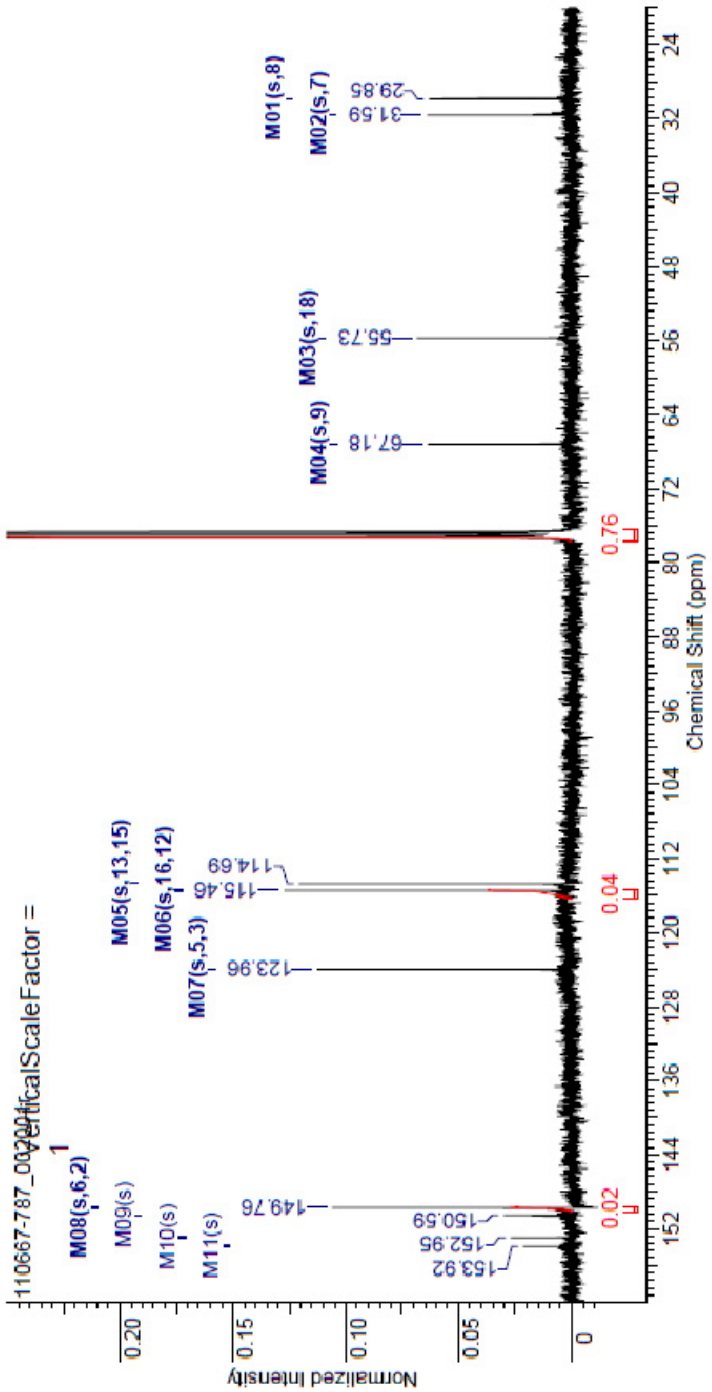

1e
57.15
76.77
77.09
77.41
119.35
121.94
124.37
127.11
128.41
129.09
130.33
131.73
135.96
146.54
146.80
150.92
Chemical Shift (ppm)
Normalized Intensity

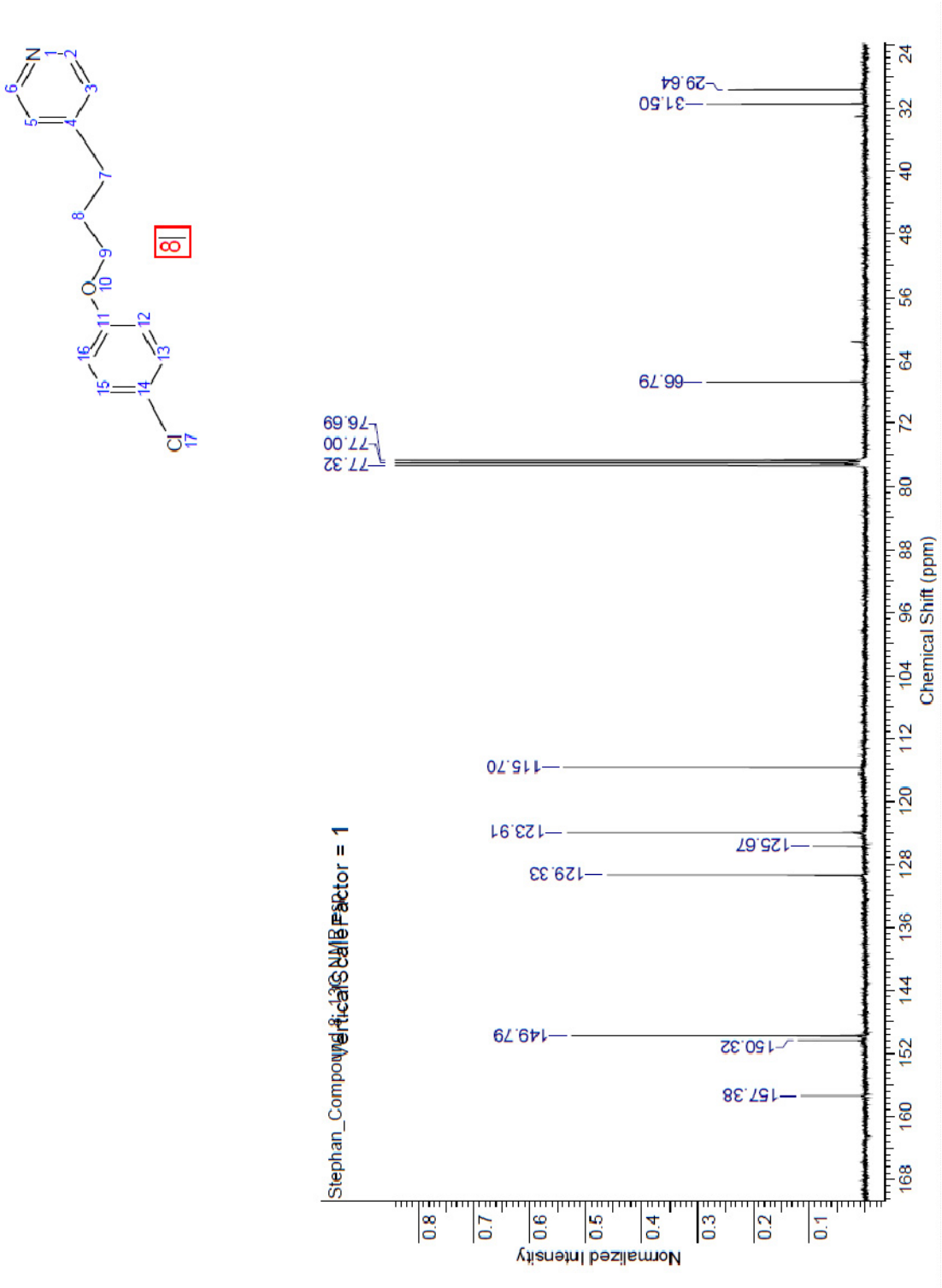

3l
29.61
31.58
66.75
76.76
77.08
77.40
105.93
121.40
122.37
123.99
129.29
130.87
134.81
144.37
147.95
149.75
150.42
156.89
Chemical Shift (ppm)
Normalized Intensity
00110130-0602-001.002.001 (1668)
VerticalScaleFactor = 1

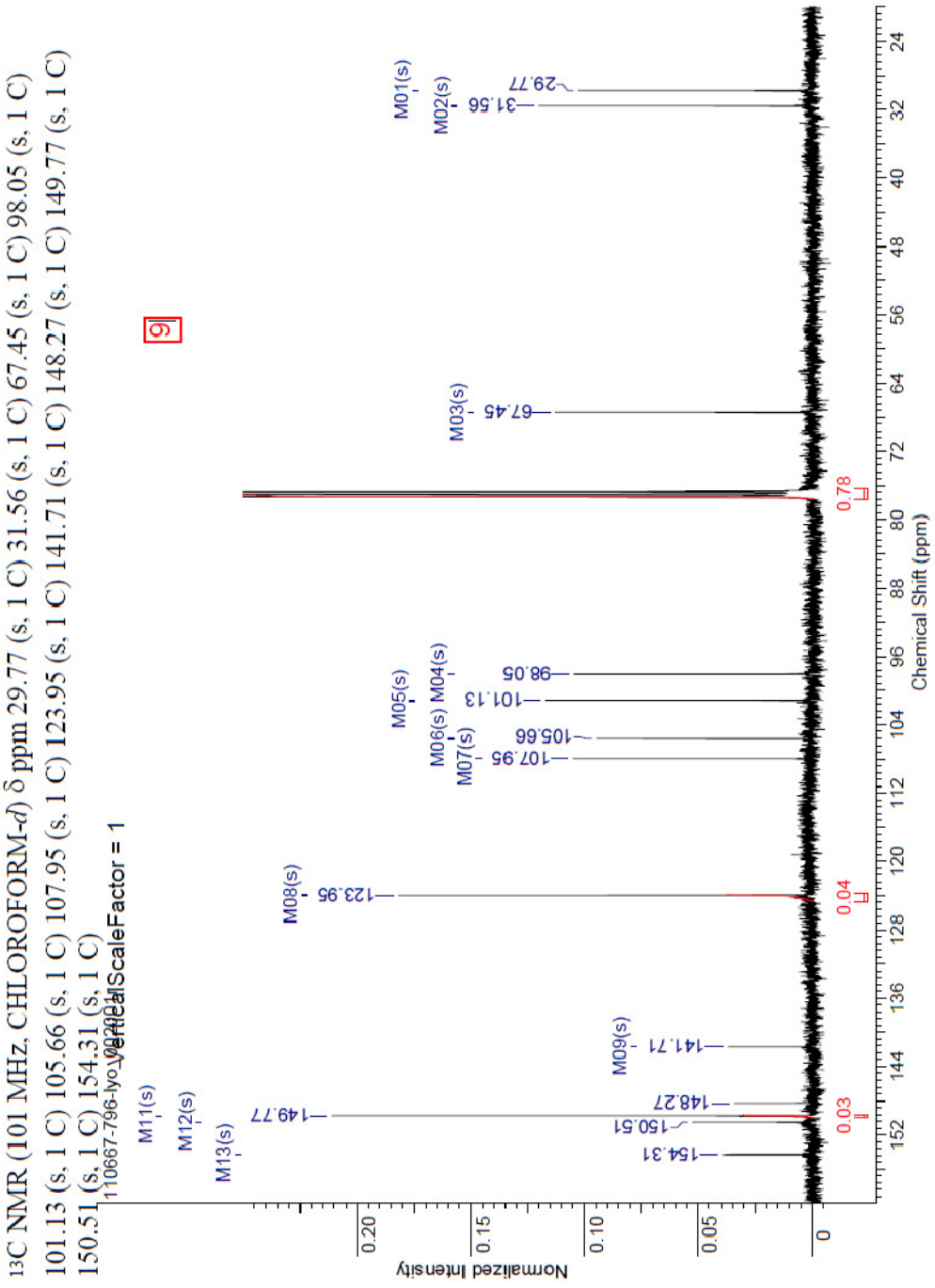
^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 29.85 (s, 1 C) 31.59 (s, 1 C) 55.73 (s, 1 C) 67.18 (s, 1 C) 114.69 (s, 1 C) 115.46 (s, 1 C) 123.96 (s, 1 C) 149.76 (s, 1 C) 150.59 (s, 1 C) 152.95 (s, 1 C) 153.92 (s, 1 C)

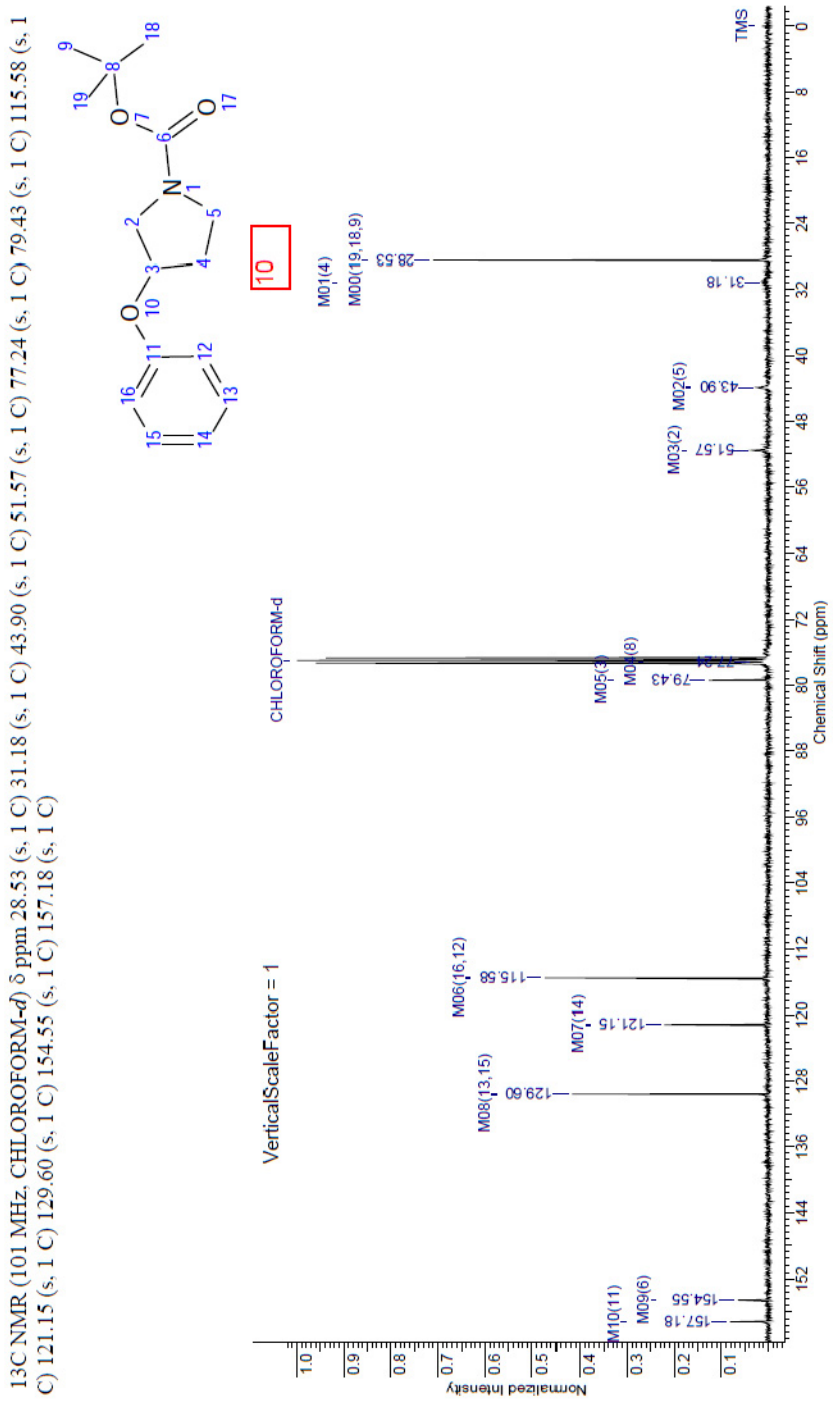


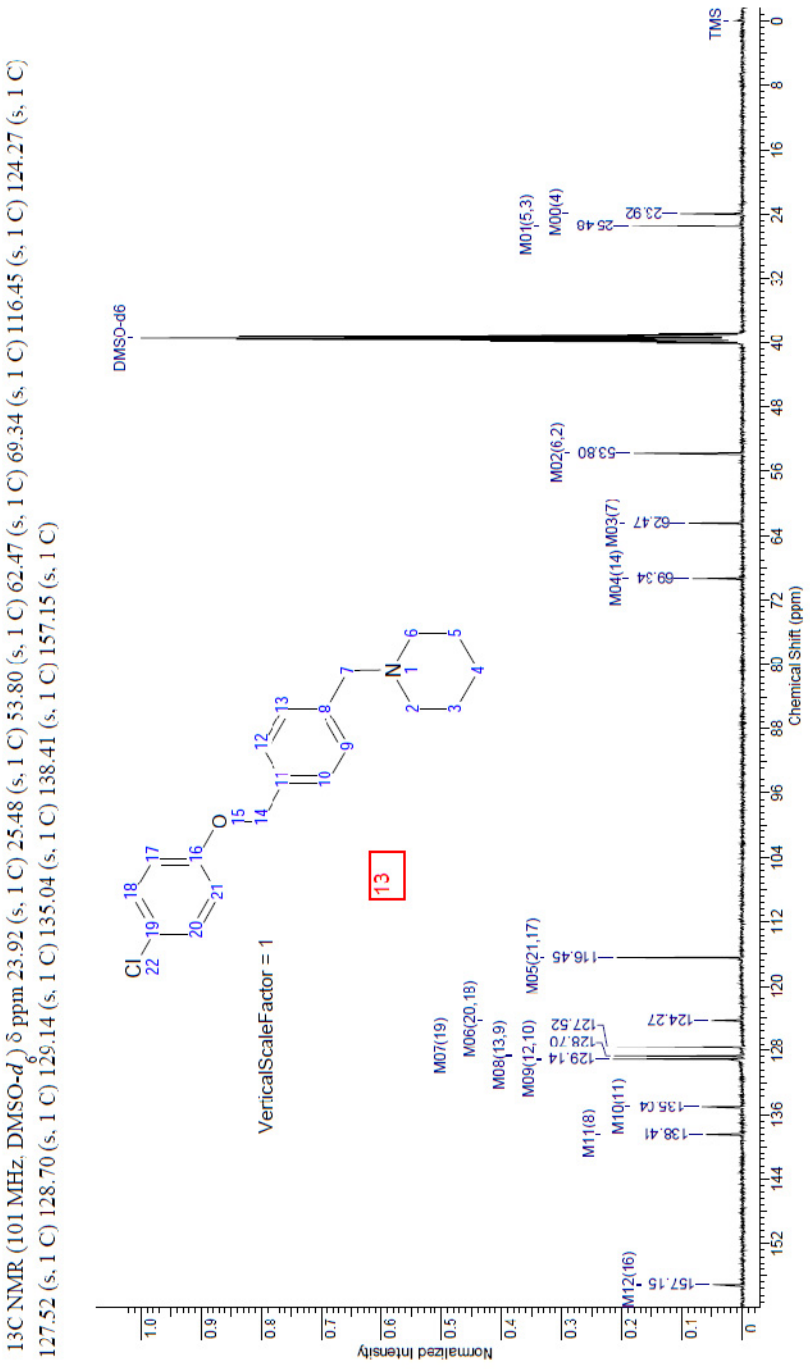
6l

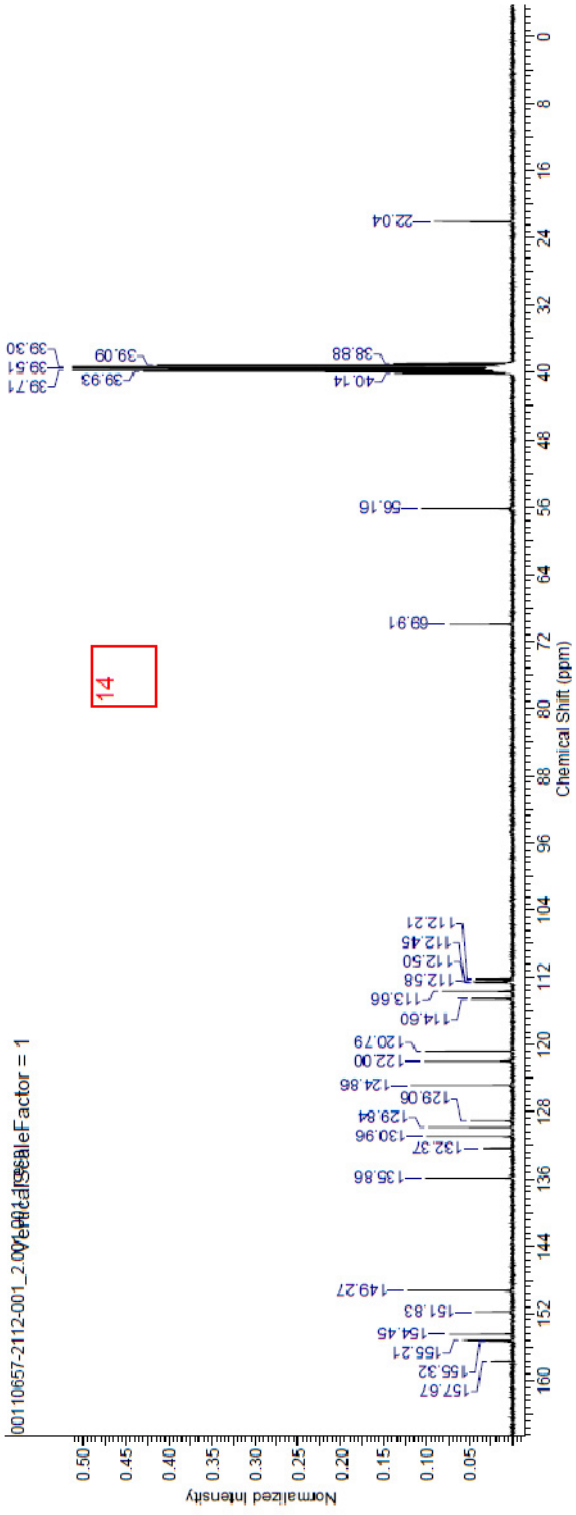


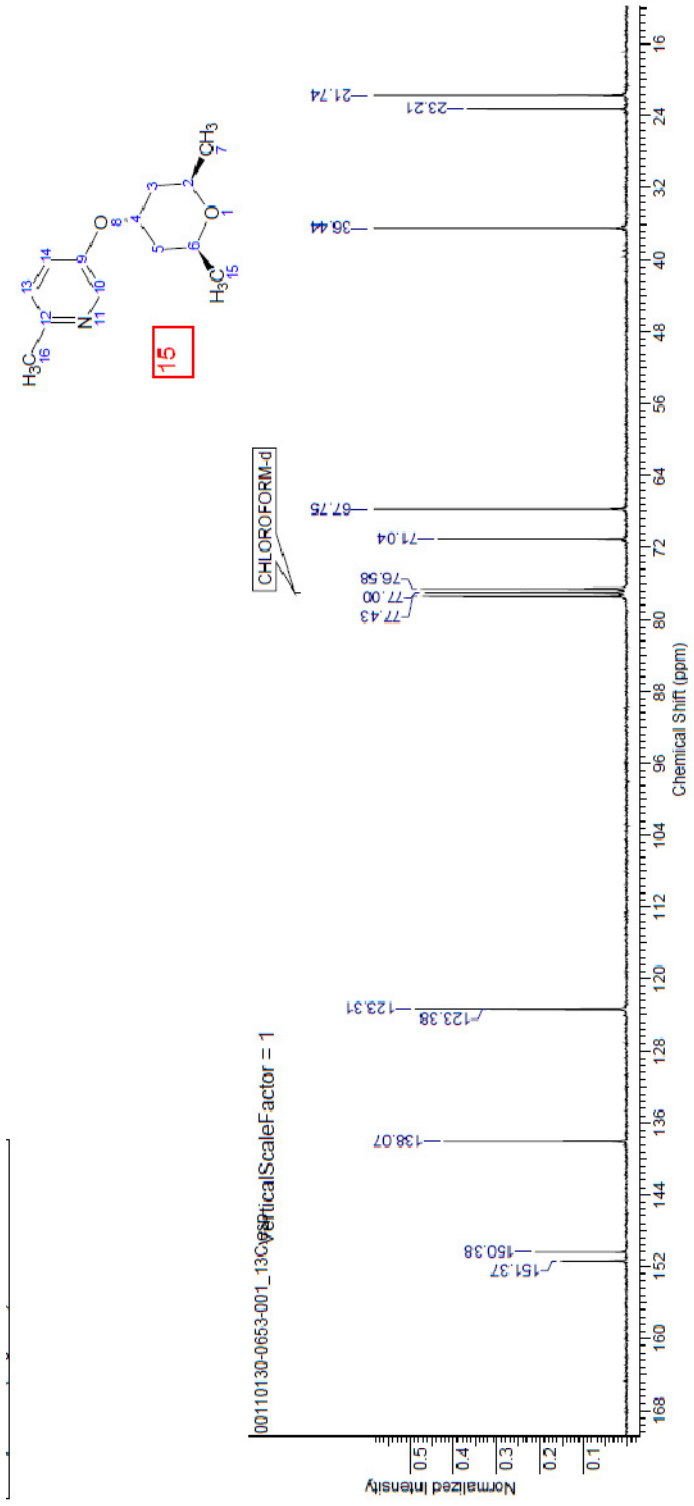

8l
Cl
Stephan_Compound_8l_13C_NMR_PSD
Vertical Scale Factor = 1
Normalized Intensity
Chemical Shift (ppm)
157.38
150.32
149.79
129.33
125.67
123.91
115.70
77.32
77.00
76.69
66.79
31.50
29.64

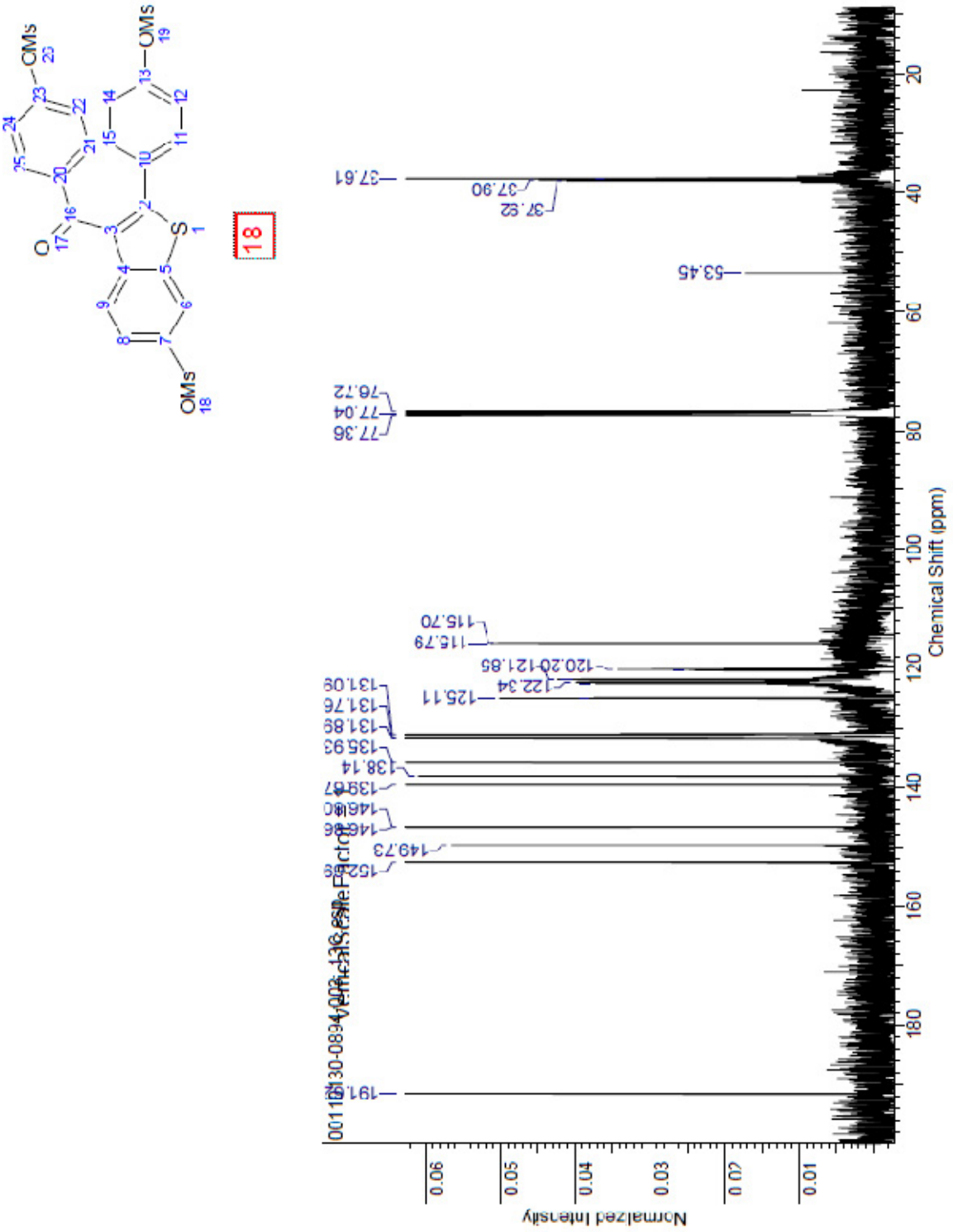

^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 29.77 (s, 1 C) 31.56 (s, 1 C) 67.45 (s, 1 C) 98.05 (s, 1 C)
101.13 (s, 1 C) 105.66 (s, 1 C) 107.95 (s, 1 C) 123.95 (s, 1 C) 141.71 (s, 1 C) 148.27 (s, 1 C) 149.77 (s, 1 C)
150.51 (s, 1 C) 154.31 (s, 1 C)
110667-796-lyo-VerticalScaleFactor = 1
6
M01(s)
M02(s)
M03(s)
M04(s)
M05(s)
M06(s)
M07(s)
M08(s)
M09(s)
M11(s)
M12(s)
M13(s)
29.77
31.56
67.45
98.05
101.13
105.66
107.95
123.95
141.71
148.27
149.77
150.51
154.31
0.78
0.04
0.03
Normalized Intensity
0.20
0.15
0.10
0.05
0
Chemical Shift (ppm)
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24


13C NMR (101 MHz, CHLOROFORM-d) δ ppm 28.53 (s, 1 C) 31.18 (s, 1 C) 43.90 (s, 1 C) 51.57 (s, 1 C) 77.24 (s, 1 C) 79.43 (s, 1 C) 115.58 (s, 1 C) 121.15 (s, 1 C) 129.60 (s, 1 C) 154.55 (s, 1 C) 157.18 (s, 1 C)
10
CHLOROFORM-d
TMS
VerticalScaleFactor = 1
Normalized Intensity
Chemical Shift (ppm)
M00(19,18,9)
M01(4)
M02(5)
M03(2)
M04(8)
M05(3)
M06(16,12)
M07(14)
M08(13,15)
M09(6)
M10(11)
28.53
31.18
43.90
51.57
79.43
115.58
121.15
129.60
154.55
157.18


13C NMR (101 MHz, DMSO-d_6) δ ppm 23.92 (s, 1 C) 25.48 (s, 1 C) 53.80 (s, 1 C) 62.47 (s, 1 C) 69.34 (s, 1 C) 116.45 (s, 1 C) 124.27 (s, 1 C) 127.52 (s, 1 C) 128.70 (s, 1 C) 129.14 (s, 1 C) 135.04 (s, 1 C) 138.41 (s, 1 C) 157.15 (s, 1 C)
DMSO-d6
TMS
M01(5,3)
M00(4)
M02(6,2)
M04(14)
M03(7)
M07(19)
M06(20,18)
M08(13,9)
M09(12,10)
M05(21,17)
M11(8)
M10(11)
M12(16)
23.92
25.48
53.80
62.47
69.34
116.45
124.27
127.52
128.70
129.14
135.04
138.41
157.15
VerticalScaleFactor = 1
13
Cl
O
N
Normalized Intensity
Chemical Shift (ppm)


14
Chemical Shift (ppm)
Normalized Intensity
00110657-2112-001_2.001.1r
VerticalScaleFactor = 1
22.04
38.88
39.09
39.30
39.51
39.71
40.14
56.16
69.91
112.21
112.45
112.50
112.58
113.66
114.60
120.79
122.00
124.86
129.06
129.84
130.96
132.37
135.86
149.27
151.83
154.45
155.21
155.32
157.67


15
CHLOROFORM-d
00110130-0653-001_13C.esp
VerticalScaleFactor = 1
Normalized Intensity
Chemical Shift (ppm)
151.37
150.38
138.07
123.38
123.31
77.43
77.00
76.58
71.04
67.75
36.44
23.21
21.74


OMs
OMs
OMs
O
S
18
Normalized Intensity
Chemical Shift (ppm)

References for Supporting Information

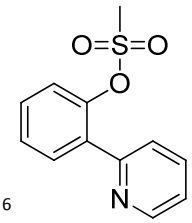
[1] *Org. Lett.* **2009**, *11(2),* 317.

[2] Phenyl methanesulfonate was purchased from Sigma-Aldrich.

[3] *o*-tolyl methanesulfonate, *p*-chlorophenyl methanesulfonate and 1,3-benzodioxol-5-ol, 5-methanesulfonate were purchased from Princeton Building Blocks.

[4] *p*-methoxyphenyl methanesulfonate was purchased from CombiBlocks.

[5] See *J. Am. Chem. Soc.,* **2010**, *132(6),* 1800 for the preparation of *p*-cyanophenyl methanesulfonate.



[6]

2-(pyridin-2-yl)phenyl methanesulfonate. To a mixture of 2-(pyridin-2-yl)phenol (4.0 g, 23 mmol) and DIEA (8.5 mL, 49 mmol) in CH_2Cl_2 (50 mL) at 0° C was added methanesulfonyl chloride (1.8 mL, 23 mmol). The mixture was slowly warmed to room temperature and stirred at room temperature for 2 hr. The organic layer was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$. After drying over MgSO4 and removing the solvents, the mesylate was purified via flash chromatography, eluting with a gradient of 5 – 50% EtOAc in heptanes. After concentrating the fractions containing the desired product, 5.5 g (96%) was obtained as a white solid. TLC EtOAc: Heptane = 1:1 Rf = 0.38**,** ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.12 - 3.19 (m, 3 H) 7.41 (ddd, J=7.49, 4.85, 0.76 Hz, 1 H) 7.46 - 7.59 (m, 3 H) 7.73 (d, J=8.06 Hz, 1 H) 7.78 (dd, J=7.43, 1.64 Hz, 1 H) 7.91 (td, J=7.68, 1.76 Hz, 1 H) 8.71 (d, J=4.78 Hz, 1 H), LCMS M+H = 250.

[7] See *J. Org. Chem.* **1954**, *19*, 784 for the preparation of 4-(chlorocarbonyl)phenyl methanesulfonate.

[8] *J. Am. Chem. Soc.* **2004**, *126*, 3058.

[9] U.S. 4418068, 29 Nov 1983

[10] *J. Org. Chem.* **1954**, *19*, 784