Supporting Information

Chemistry, Pharmacology, and Behavioral Studies Identify Chiral Cyclopropanes as Selective α4β2-Nicotinic Acetylcholine Receptor Partial Agonist Exhibiting an Antidepressant Profile. Part II

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In Vitro Functional Studies

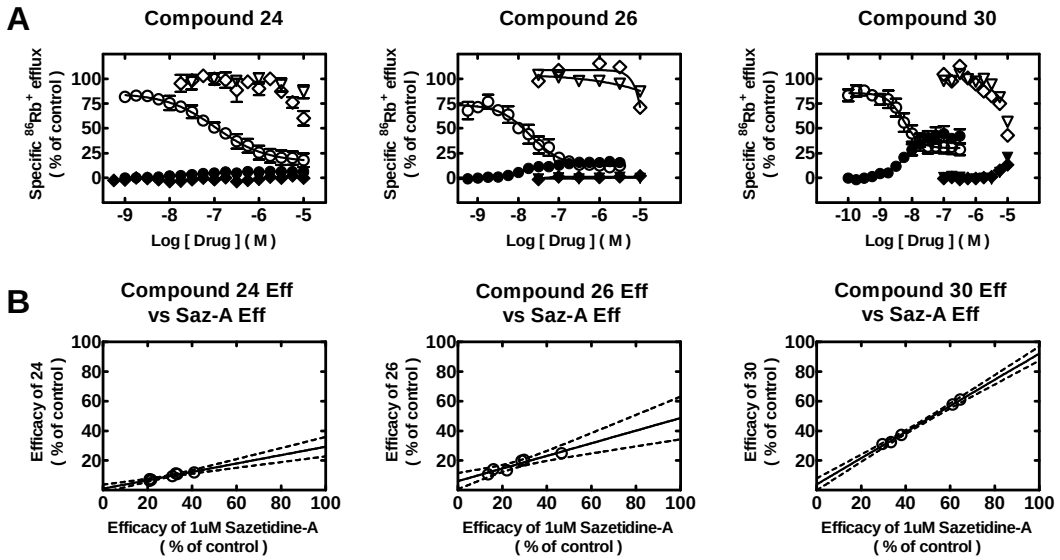


Figure S1. (A) Sensitivities and efficacies of ligand agonism (filled symbols) and inactivation (open symbols) at mixed populations of high sensitivity (HS) and low sensitivity (LS) α4β2-nAChRs (○,●), α3β4*-nAChRs (◇,◆) and α1β1γδ-nAChRs (▽,▼) for compounds **24**, **26**, and **30**. Specific $^{86}Rb^{+}$ efflux (ordinate; percentage of control response to 1 mM carbamylcholine) was determined at the indicated ligand concentration (abscissa, log molar) for 5 min exposure alone to determine agonist effects or at a maximally-efficacious concentration of carbamylcholine following a 10 min pre-exposure to the indicated ligand and its concentration to define receptor inactivation. (B) Efficacies of compound **24**, **26**, or **30** agonism at α4β2-nAChRs. Specific $^{86}Rb^{+}$ efflux (ordinate; percentage of control response to 1 mM carbamylcholine) was determined for human α4β2-nAChRs expressed by different preparations of SH-EP1-hα4β2 cells. Results are plotted against the response to a maximally efficacious concentration of the HS α4β2-nAChR selective ligand, sazetidine-A (1 μM; abscissa, percent of control response to 1 mM carbamylcholine). The latter parameter defines the portion of the carbamylcholine control response due to HS α4β2-nAChRs present in a given preparation of cells. Note that none of the ligands tested appear to have intrinsic activity at LS α4β2-nAChRs (i.e., when the regression lines are extrapolated to an abscissa value of 0%, ordinate values are also ~ 0%), but have apparent efficacies ranging between 29% and 92% at HS α4β2-nAChRs (i.e., when the regression lines are extrapolated to an abscissa value of 100%). Data from an agonist more efficacious at LS than HS α4β2-nAChRs would result in a regression line with a negative slope. The dotted lines represent the 95% confidence intervals of the linear regressions.

$^{86}Rb^{+}$ efflux assays

Function of nAChR subtypes investigated was established based on a proven, routine, $^{86}Rb^{+}$ efflux assay protocol.[23] The assay is specific for nAChR function under the conditions used, for example, giving identical results in the presence of 100 nM atropine to

exclude possible contributions of muscarinic acetylcholine receptors cells harvested at confluence from 100-mm plates under a stream of fresh medium only (SH-SY5Y) or after mild trypsinization (Irvine Scientific, Santa Ana, CA; for TE671/RD or transfected SH-EP1 cells) were then suspended in complete medium and evenly seeded, typically at a density allowing growth to confluence in 2 to 4 days at 37 ^{o}C. Upon reaching confluence, cells were either used immediately for assay or incubated at 29 ^{o}C. Low temperature incubation was used to increase the surface expression of high sensitivity (HS) relative to low sensitivity (LS) α4β2 nAChRs and to enhance surface expression of (α6/3)β2β3-nAChRs.

For assay, the cell culture medium was removed and replaced with 250 μl per well of complete medium supplemented with ~350,000 cpm of $^{86}Rb^{+}$ (NEN; counted at 40% efficiency using Cerenkov counting and the Packard TriCarb 1900 Liquid Scintillation Analyzer). After at least 4 h and typically overnight, $^{86}Rb^{+}$ efflux was measured using the "flip-plate" technique.[23] Briefly, after aspiration of the bulk of $^{86}Rb^{+}$ loading medium from each well of the "cell plate," each well containing cells was rinsed with 2 ml of fresh $^{86}Rb^{+}$ efflux buffer (130 mM NaCl, 5.4 mM KCl, 2 mM $CaCl_2$, 5 mM glucose, 50 mM HEPES, pH 7.4) to remove extracellular $^{86}Rb^{+}$. Following removal of residual rinse buffer by aspiration, the flip-plate technique was used again to simultaneously introduce 1.5 ml of fresh efflux buffer containing drugs of choice at indicated final concentrations from a 24-well "efflux/drug plate" into the wells of the cell plate. After a 9.5-min incubation, the solution was "flipped" back into the efflux/drug plate, and any remaining buffer in the cell plate was removed by aspiration. A second efflux/drug plate was then used to reintroduce the same concentrations of drugs of choice with the addition of an ~EC_{90} concentration of the full agonist carbamylcholine for 5 min (~EC_{90} concentrations were 200 μM for SH-EP1-hα4β2 cells, 100 μM for SH-EP1-h(α6/3)β2β3 cells, 2 mM for SH-SY5Y cells, and 464 μM for TE671/RD cells). The second drug treatment was then flipped back into its drug plate, and the remaining cells in the cell plate were lysed and suspended by addition of 1.5 ml of 0.1 M NaOH, 0.1% sodium dodecyl sulfate to each well. Suspensions in each well were then subjected to Cerenkov counting (Wallac Micobeta Trilux 1450; 25% efficiency) after placement of inserts (Wallac 1450-109) into each well to minimize cross-talk between wells.

For quality control and normalization purposes, the sum of $^{86}Rb^{+}$ in cell plates and efflux/drug plates was defined to confirm material balance (i.e., that the sum of $^{86}Rb^{+}$ released into the efflux/drug plates and $^{86}Rb^{+}$ remaining in the cell plate were the same for each well). Similarly, the sum of $^{86}Rb^{+}$ in cell plates and efflux/drug plates also determined the efficiency of $^{86}Rb^{+}$ loading (the percentage of applied $^{86}Rb^{+}$ actually loaded into cells). Furthermore, the sum of $^{86}Rb^{+}$ in cell plates and the second efflux/drug plates defined the amount of intracellular $^{86}Rb^{+}$ available at the start of the second, 5-min assay and was used to normalize nAChR function thus assessed.

For each experiment, in one set of control samples, total $^{86}Rb^{+}$ efflux was assessed in the presence of a fully efficacious concentration of carbamylcholine (1 mM for SH-EP1-hα4β2, SH-EP1-h(α6/3)β2β3 cells, and TE671/RD cells, or 3 mM for SH-SY5Y cells). Non-specific $^{86}Rb^{+}$ efflux in another set of control samples was measured either in the presence of the fully efficacious concentration of carbamylcholine plus 100 μM

mecamylamine, which gave full block of agonist-induced and spontaneous nAChR-mediated ion flux, or in the presence of efflux buffer alone. Both determinations of non-specific efflux were equivalent. Specific efflux was then taken as the difference in control samples between total and non-specific $^{86}Rb^{+}$ efflux. The same approaches were used to define total, non-specific, and specific ion flux responses in samples subjected to the second, 5-min exposure to test drug when applicable plus either carbamylcholine at its EC_{90} concentration or efflux buffer. Intrinsic agonist activity of test drugs was ascertained during the initial, 9.5-min exposure period using samples containing test drug only at different concentrations and was normalized, after subtraction of non-specific efflux, to specific efflux in test drug-free control samples. Specific $^{86}Rb^{+}$ efflux elicited by test drug as a percentage of specific efflux in the absence of test drug was the same in these samples whether measured in absolute terms or as a percentage of loaded $^{86}Rb^{+}$. Even in samples previously giving an efflux response during the initial, 10-min exposure to a partial or full agonist (9.5-min assay + 30-sec handling), residual intracellular $^{86}Rb^{+}$ was adequate to allow assessment of nAChR function in the secondary, 5-min assay. However, care was taken to ensure that data were normalized to the amount of intracellular $^{86}Rb^{+}$ available at the time of the assay, as absolute levels of total, non-specific, or specific efflux varied in cells partially depleted of intracellular $^{86}Rb^{+}$ due to action of any agonist present during the 10-min drug exposure period. That is, calculations of specific efflux as a percentage of loaded $^{86}Rb^{+}$ corrected for any variation in the electrochemical gradient of $^{86}Rb^{+}$ created by intracellular ion depletion after the first (agonism/pretreatment) drug treatment.

Ion flux assays were fit to the Hill equation, $F = F_{max} / (1 + (X/EC_{50})^{n})$, with F as a percentage of control, F_{max}, for EC_{50} ($n>0$ for agonists) or IC_{50} ($n<0$ for antagonists using Prism (GraphPad). Most ion flux data were fit allowing maximum and minimum ion flux values to be determined by curve fitting, but in some cases where antagonists or agonists had weak functional potency, minimum ion flux was set at 0% of control or maximum ion flux was set at 100% of control, respectively.

Because SH-EP1-hα4β2 cells express a variable mixture of HS and LS hα4β2-nAChRs, determining the efficacies of a compound at each subtype requires a control ligand with differing and defined efficacies at the two subtypes, as well as an agonist such as carbamylcholine that is fully efficacious at both subtypes. Conveniently, sazetidine-A is a full agonist at HS hα4β2-nAChRs while having zero or nearly zero efficacy at LS hα4β2-nAChRs, as measured in the $^{86}Rb^{+}$ ion flux assay. This allows the apparent efficacy of a maximally efficacious 1mM sazetidine-A treatment to be defined as the fraction of the control response to 1mM carbamylcholine due to HS hα4β2-nAChR stimulation in a given experiment ($Frac_{HS}$). The fraction of the carbamylcholine response due to LS hα4β2-nAChRs ($Frac_{LS}$) is simply $Frac_{LS} = 1\text{-}Frac_{HS}$. This allows apparent efficacies of an agonist measured in different experiments to be plotted as a function of the measured efficacies of sazetidine-A controls ($Frac_{HS}$) and fit to the equation, $Eff_t = (Eff_{HS})*(Frac_{HS}) + (Eff_{LS})*(1\text{-}Frac_{HS})$, where Eff_t is the total efficacy of a test compound measured in the experiment. This is a linear equation with two unknowns, the efficacies of the test compound at LS and HS α4β2-nAChRs (Eff_{LS} and Eff_{HS}, respectively). As shown in the lower panels of Figure S1, the ordinate values of the linear regressions at abscissa values of 0% and 100% are the efficacies of test compounds at LS and HS α4β2 nAChRs, respectively.

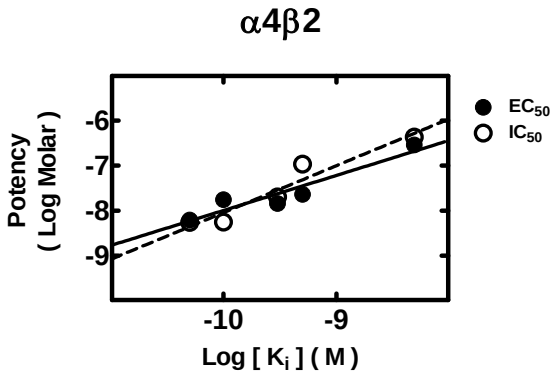


Figure S2. The potencies at α4β2-nAChR of compounds listed in Table 3 correlate linearly with the affinities listed in Table 2. R^2 values for EC_{50} (solid line) and IC_{50} (dashed line) regression lines are 0.90 and 0.93, respectively. Compounds in rank order of affinity (K_i) are **30**, **4**, **26**, **24**, and nicotine.

Mouse Forced Swim Test

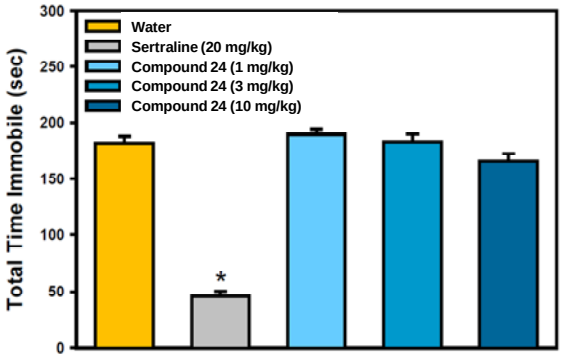
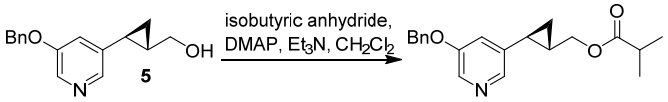


Figure S3. Effects of sertraline and compound **24** in mice on total time immobile in the forced swim test. Data were summed over the 6-min test and represent mean ± SEM. *p < 0.05 indicates statistical significance compared to water.

Chemistry

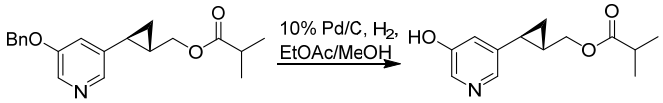
General. All chemicals were purchased from Sigma-Aldrich or Chem-Impex, and solvents were used as obtained from Fisher Scientific or Sigma-Aldrich without further purification. Anhydrous THF and CH_2Cl_2 were obtained by distillation over sodium wire or CaH_2, respectively. All non-aqueous reactions were run under an argon atmosphere with exclusion of moisture from reagents, and all reaction vessels were oven-dried. The progress of the reactions was monitored by TLC on SiO_2. Spots were visualized by their quenching of the fluorescence of an indicator admixed to the SiO_2 layer, or by dipping into I_2/SiO_2 mixture. Products were purified by column chromatography on 230–400 mesh SiO_2. Proton and carbon NMR spectra were recorded at spectrometer frequencies of 400 MHz and 100 MHz, respectively. NMR chemical shifts were reported in δ (ppm) using the δ 7.26 signal of $CDCl_3$ (^{1}H NMR), δ 4.80 signal of HDO (^{1}H NMR), and the δ 77.23 signal of $CDCl_3$ (^{13}C NMR) as internal standards. ^{13}C NMR spectra in D_2O were not adjusted. Optical rotation was detected on an Autopol IV automatic polarimeter. Mass spectra were measured in the ESI mode at an ionization potential of 70 eV with an LC-MS MSD (Hewlett Packard). The final compounds were purified by preparative HPLC, which was carried out on an ACE 5 AQ column (150 × 20 mm), with detection at 254 and 280 nm on a Shimadzu SPD-10A VP detector; flow rate = 17.0 mL/min; gradient of 0 to 50% methanol in water (both containing 0.05 vol% of CF_3COOH) in 30 min. Purities of final compounds were established by analytical HPLC, which was carried out on an Agilent 1100 HPLC system with a Synergi 4 μ Hydro-RP 80A column, with detection at 254 or 280 nm on a variable wavelength detector G1314A; flow rate = 1.4 mL/min; gradient of 0 to 100% methanol in water (both containing 0.05 vol% of CF_3COOH) in 18 min.

(1S,2S)-2-[5-(Benzyloxy)-3-pyridyl]cyclopropylmethyl Isobutyrate



In a 100 mL round-bottom flask, the alcohol **5** (255 mg, 1 mmol) and 4-(dimethyl-amino)pyridine (12 mg, 0.1 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL). Anhydrous Et_3N (0.55 mL, 4 mmol) was added. The solution was cooled in an ice bath before isobutyric anhydride (0.33 mL, 2 mmol) was added dropwise in 5 min. The reaction mixture was then stirred at 0 °C for 2 h. Methanol (0.2 mL) was added, and the mixture was evaporated directly to dryness. The residue was purified by silica gel column chromatography (hexane/EtOAc 1:1) to afford the desired ester (306 mg, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.19 (s, 1H), 8.06 (s, 1H), 7.43-7.33 (m, 5H), 6.90 (s, 1H), 5.08 (s, 2H), 4.11 (m, 2H), 2.57 (m, 1H), 1.89 (m, 1H), 1.47 (m, 1H), 1.17 (d, J = 7.2 Hz, 6H), 1.03 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 177.4, 155.2, 141.0, 138.9, 136.3, 135.1, 128.9, 128.5, 127.8, 119.6, 70.6, 67.4, 34.2, 21.8, 19.3, 19.2, 13.8.

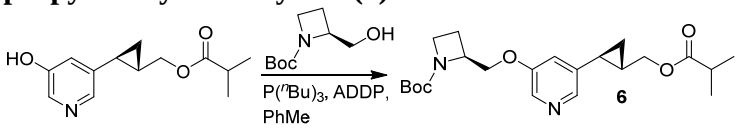
(1S,2S)-2-[5-(Hydroxy)-3-pyridyl]cyclopropylmethyl Isobutyrate



In a 100 mL round-bottom flash, the ester (325 mg, 1 mmol) was dissolved in a mixture of EtOAc (5 mL) and methanol (5 mL), and 10% Pd/C (50 mg, containing 50% water)

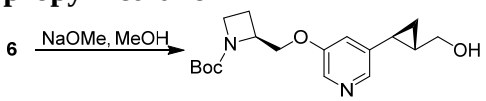
were added. A H_2-filled balloon was connected after the atmosphere was exchanged three times with Ar. The reaction was allowed to proceed at rt for 2 h, then the catalyst was filtered off over Celite. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 9:1) to furnish the hydroxypyridine (221 mg, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 9.08 (br, 1H), 7.96 (s, 1H), 7.80 (s, 1H), 6.85 (s, 1H), 4.05 (m, 1H), 3.95 (m, 1H), 2.48 (m, 1H),1.79 (m, 1H), 1.40, (m, 1H), 1.07 (d, J = 6.4 Hz, 6H), 0.94 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 177.5, 155.1, 139.8, 137.4, 134.2, 121.5, 67.2, 34.0, 21.6, 19.3, 19.0, 13.6.

(1S,2S)-2-[5-[[1-(tert-Butoxycarbonyl)-(2S)-azetidinyl]methoxy]-3-pyridyl]cyclopropylmethyl Isobutyrate (6)



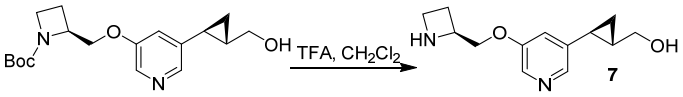
In a 100 mL side-arm flask with stir bar and an Ar balloon, tri-*n*-butylphosphine (0.2 mL, 0.8 mmol) was added dropwise in 5 min to a solution of *N*,*N*'-azodicarbonyldipiperidine (200 mg, 0.8 mmol) in anhydrous toluene (5 mL). Stirring was continued at rt for 30 min to complete the formation of the Mitsunobu reagent. A solution of the hydroxypyridine intermediate (118 mg, 0.5 mmol) and 1-(*tert*-butoxycarbonyl)-(2*S*)-azetidinylmethanol (150 mg, 0.8 mmol) in anhydrous toluene (10 mL) was added to the Mitsunobu reagent at 0 °C for 45 min. The mixture was warmed to rt and stirred overnight. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc 2:1 to 1:1) to furnish the desired product **6** (158 mg, 78%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.04 (s, 1H), 7.95 (s, 1H), 6.78 (s, 1H), 4.41 (m, 1H), 4.20 (m, 1H), 4.02 (m, 3H), 3.79 (m, 2H), 2.47 (m, 1H), 2.31-2.14 (m, 2H), 1.80 (m, 1H), 1.40-1.31 (s, 12H), 1.07 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 177.0, 156.0, 155.0, 141.0, 138.4, 135.2, 118.5, 79.5, 68.6, 67.0, 60.2, 46.7, 33.9, 28.2, 21.5, 20.9, 19.0, 18.9, 13.6.

(1S,2S)-2-[5-[[1-(tert-Butoxycarbonyl)-(2S)-azetidinyl]methoxy]-3-pyridyl]cyclopropylmethanol



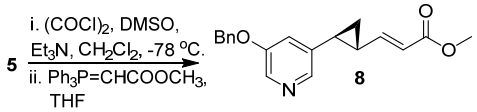
To a solution of compound **6** (203 mg, 0.5 mmol) in anhydrous methanol (10 mL), was added a solution of sodium methoxide in methanol (0.4 mL, 25 wt.%). The reaction mixture was stirred at 40 °C for 6 h and then evaporated to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 10:1) to afford the desired product (152 mg, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.0 (s, 1H), 7.90 (s, 1H), 6.83 (s, 1H), 4.43 (m, 1H), 4.21 (m, 1H), 4.02 (m, 1H), 3.81 (t, J = 7.6 Hz, 2H), 3.61 (m, 1H), 3.49 (m, 1H), 2.22 (m, 2H), 1.73 (m, 1H), 1.37-1.33 (m, 10H), 0.93-0.86 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 156.3, 155.2, 140.6, 139.7, 134.6, 118.9, 79.8, 68.7, 65.3, 60.2, 47.9, 28.4, 25.4, 19.1, 18.6, 13.7.

3-[(2(S)-Azetidinyl)methoxy]-5-[(1S,2S)-2-(hydroxymethyl)cyclopropyl]pyridine Trifluoroacetate (7)



Trifluoroacetic acid (1 mL) was added to a solution of the compound obtained from the previous step (100 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) under Ar. The resulting mixture was stirred at rt overnight, concentrated, and purified by preparative HPLC to give compound **7** (105 mg, 71%) as a colorless oil. ^{1}H NMR (D_2O): δ 8.36 (s, 1H), 8.28 (s, 1H), 7.91 (s, 1H), 4.98 (m, 1H), 4.53 (d, *J* = 3.6 Hz, 2H), 4.12 (m, 2H), 3.69 (m, 1H), 3.54 (m, 1H), 2.70 (q, *J* = 8.4 Hz, 2H), 2.12 (m, 1H), 1.64 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (D_2O): δ 162.3 (TFA), 155.9, 145.2, 132.2, 128.3, 125.7, 115.8 (TFA), 67.2, 64.1, 58.2, 43.3, 25.4, 19.8, 18.1, 14.1; $[\alpha]_D^{20}$ = +27.7 (*c* 0.48, MeOH); Anal. Calcd for $C_{13}H_{18}N_2O_2$•2.15CF_3COOH•0.85H_2O: C, 42.0; H, 4.45; F, 24.77; N, 5.66. Found: C, 41.89; H, 4.18; F, 24.51; N, 5.55. HPLC purity = 99.1%; t_R = 6.1 min.

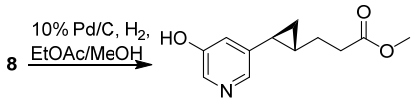
Methyl (E)-3-[(1R,2S)-2-[5-(Benzyloxy)pyridin-3-yl]cyclopropyl]acrylate (8)



A 100 mL three-necked flask with magnetic stirrer, two septa, and an Ar balloon was charged with anhydrous CH_2Cl_2 (10 mL) and oxalyl chloride (0.38 mL, 4.3 mmol). The flask was immersed in an acetone/CO_2 bath, and the solution was stirred. A solution of anhydrous DMSO (0.38 mL, 5.0 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise in 5 min. The Swern reagent solution was stirred at approx. -70 °C for another 15 min. A solution of compound **5** (650 mg, 2.55 mmol) in anhydrous CH_2Cl_2 (15 mL) was added in 25 min. Stirring at approx. -70 °C was continued for another 30 min. Anhydrous triethylamine (2.1 mL, 15 mmol) was added dropwise in 10 min. The reaction mixture was stirred for another 10 min at approx. -70 °C and then allowed to warm to rt. The mixture was subsequently stirred at rt for 25 min, then washed with two 10 mL portions of water. The aqueous phases were back-extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated to furnish the intermediate aldehyde as a yellowish syrup which was directly used for the next step without further purification.

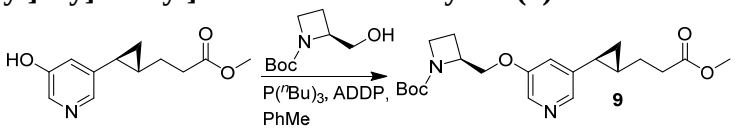
To a mixture of methyl(triphenylphosphoranylidene)acetate (1.7 g, 5.1 mmol) in anhydrous CH_2Cl_2 (20 mL) was added a solution of the aldehyde in anhydrous CH_2Cl_2 (10 mL) at 0 °C in 5 min. The reaction mixture was then warmed to rt and stirred for 3 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (10 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (hexane/acetone 3:1) to afford the desired product **8** (640 mg, 81%, two steps) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 8.17 (s, 1H), 8.0 (s, 1H), 7.38-7.27 (m, 5H), 6.85 (t, *J* = 2.2 Hz, 1H), 6.53 (dd, *J* = 15.4 Hz, *J* = 9.8 Hz, 1H), 5.88 (d, *J* = 15.2 Hz, 1H), 5.02 (s, 2H), 3.67 (s, 3H), 2.08 (m, 1H), 1.77 (m, 1H), 1.36 (m, 1H), 1.27 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 166.7, 154.8, 150.8, 140.8, 137.1, 136.0, 135.6, 128.6, 128.2, 127.4, 119.0, 118.7, 70.2, 51.3, 26.3, 24.0, 17.4.

Methyl 3-[(1S,2S)-2-(5-Hydroxypyridin-3-yl)cyclopropyl]propanoate



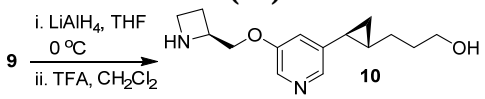
In a 100 mL round-bottom flash, the ester **8** (400 mg, 1.29 mmol) was dissolved in a mixture of EtOAc (5 mL) and methanol (5 mL), and 10% Pd/C (50 mg, containing 50% water) was added. A H_2-filled balloon was connected after the atmosphere was exchanged three times with Ar. The reaction was allowed to proceed at rt for 2 h, then the catalyst was filtered off over Celite. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 9:1) to furnish the hydroxypyridine (272 mg, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.54 (br, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 6.82 (s, 1H), 3.58 (s, 3H), 2.39 (m, 2H), 1.65 (m, 2H), 1.57 (m, 1H), 1.01 (m, 1H), 0.86-0.78 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 174.0, 155.2, 141.1, 138.1, 133.8, 121.1, 51.6, 33.8, 29.5, 23.1, 20.5, 15.9. MS (ESI) *m/z* 222.1 ($M+H^+$).

tert-Butyl (S)-2-[[[5-[(1S,2S)-2-(3-Methoxy-3-oxopropyl)cyclopropyl]pyridin-3-yl]oxy]methyl]azetidine-1-carboxylate (9)



In a 100 mL side-arm flask with stir bar and an Ar balloon, tri-*n*-butylphosphine (0.45 mL, 1.8 mmol) was added dropwise over 5 min to a solution of *N*,*N*'-azodicarbonyldipiperidine (450 mg, 1.8 mmol) in anhydrous toluene (5 mL). Stirring was continued at rt for 30 min to complete the formation of the Mitsunobu reagent. A solution of the hydroxypyridine intermediate (266 mg, 1.2 mmol) and 1-(*tert*-butoxycarbonyl)-(2*S*)-azetidinylmethanol (356 mg, 1.9 mmol) in anhydrous toluene (10 mL) was added to the Mitsunobu reagent at 0 °C over 45 min. The mixture was warmed to rt and stirred overnight. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc 2:1 to 1:1) to furnish the desired product **9** (375 mg, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.0 (s, 1H), 7.90 (s, 1H), 6.72 (s, 1H), 4.39 (m, 1H), 4.19 (m, 1H), 4.01 (m, 1H), 3.78 (m, 2H), 3.55 (s, 3H), 2.35 (t, J = 7.2 Hz, 2H), 2.20 (m, 2H), 1.65-1.55 (m, 3H), 1.33 (s, 9H), 0.98 (m, 1H), 0.83 (m, 1H), 0.75 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 173.6, 156.1, 155.0, 140.9, 139.6, 134.9, 118.2, 79.5, 68.6, 60.2, 51.5, 47.2, 33.7, 29.4, 28.3, 22.9, 20.5, 19.1, 15.7. MS (ESI) *m/z* 391.3 ($M+H^+$).

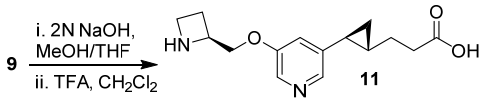
3-[(2(S)-Azetidinyl)methoxy]-5-[(1S,2S)-2-(3-hydroxypropyl)cyclopropyl]pyridine Trifluoroacetate (10)



To a solution of ester **9** (260 mg, 0.67 mmol) in anhydrous THF (10 mL) was added lithium aluminum hydride solution (1.0 mL, 2 mmol, 2 M in THF) slowly at 0 °C under Ar atmosphere. The reaction mixture was stirred at the same temperate for 2 h and quenched by addition of 0.1 mL of H_2O, 0.1 mL of 15% NaOH aqueous solution, and 0.3 mL of H_2O, respectively. The mixture was filtered and the filtrate was evaporated to dryness, followed by purification over a short silica gel column (CH_2Cl_2/MeOH 10:1) to

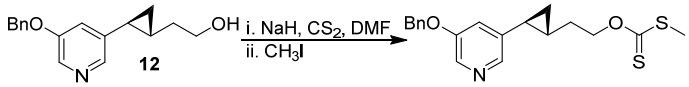
remove baseline impurities. The crude product was taken up in CH_2Cl_2 (5 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at rt overnight. Volatiles were removed, and purification of the residue by preparative HPLC afforded the desired product **10** as a colorless oil (107 mg, 29%, two steps). ^{1}H NMR (D_2O): δ 8.32 (s, 1H), 8.22 (s, 1H), 7.84 (s, 1H), 4.98 (m, 1H), 4.53 (d, *J* = 4.0 Hz, 2H), 4.11 (m, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.70 (q, *J* = 8.4 Hz, 2H), 1.93 (m, 1H), 1.69 (m, 2H), 1.56-1.44 (m, 2H), 1.31 (m, 1H), 1.14 (m, 2H); ^{13}C NMR (D_2O): δ 162.4 (TFA), 155.8, 146.6, 131.9, 127.8, 125.2, 115.8 (TFA), 67.1, 60.9, 58.2, 43.3, 30.4, 29.0, 25.0, 19.8, 19.7, 16.9. $[\alpha]_D^{20}$ = +10.0 (*c* 1.1, MeOH); Anal. Calcd for $C_{15}H_{22}N_2O_2$•2.55CF_3COOH•0.75H_2O: C, 42.61; H, 4.63; F, 25.65, N, 4.94. Found: C, 42.70; H, 4.51; F, 25.55; N, 4.97. HPLC purity = 99.2%; t_R = 6.1 min.

3-[(1S,2S)-2-[5-[((S)-Azetidin-2-yl)methoxy]pyridin-3-yl]cyclopropyl]propanoic Acid Trifluoroacetate (11).



A solution of compound **9** (390 mg, 1.0 mmol) dissolved in THF (5 mL) and methanol (5 mL) was placed in a 50 mL round-bottom flask with stir bar. To this solution was added 2N aqueous NaOH solution (5 mL). The homogeneous solution was stirred at rt for 4 h. 2N aqueous HCl solution was added, and the resulting pH (by indicator paper) was about 5−6. The mixture was extracted with EtOAc (15 mL × 2) and the combined organic layers were washed with H_2O, and brine, dried over anhydrous Na_2SO_4, and evaporated to give the crude carboxylic acid (300 mg, 80%) which was used for the next step without purification. Trifluoroacetic acid (1 mL) was added to a solution of the acid (100 mg, 0.27 mmol) obtained from the previous step dissolved in CH_2Cl_2 (10 mL) under an Ar atmosphere. The mixture was stirred at rt overnight, concentrated, and purified by preparative HPLC to give compound **11** (77 mg, 53%) as a colorless oil. ^{1}H NMR (D_2O): δ 8.34 (s, 1H), 8.22 (s, 1H), 7.85 (s, 1H), 4.98 (m, 1H), 4.52 (d, *J* = 4.0 Hz, 2H), 4.12 (m, 2H), 2.70 (q, *J* = 8.4 Hz, 2H), 2.53 (m, 2H), 1.99 (m, 1H), 1.84 (m, 1H), 1.68 (1H), 1.33 (m, 1H), 1.17 (m, 2H); ^{13}C NMR (D_2O): δ 178.1, 162.4 (TFA), 155.8, 146.1, 132.0, 127.9, 125.4, 115.9 (TFA), 67.1, 58.2, 43.3, 33.1, 28.2, 24.2, 19.8, 19.7, 16.3. $[\alpha]_D^{20}$ = +32.5 (*c* 0.36, MeOH). Anal. Calcd for $C_{15}H_{20}N_2O_3$•2.15CF_3COOH•0.9H_2O: C, 43.11; H, 4.49; F, 22.79, N, 5.21. Found: C, 42.96; H, 4.24; F, 22.53; N, 5.16. HPLC purity = 99.8%; t_R = 7.0 min.

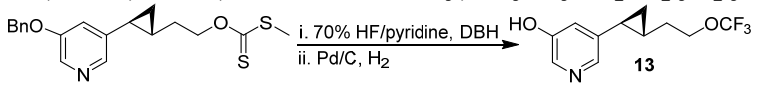
O-[2-[(1R,2S)-2-[5-(Benzyloxy)pyridin-3-yl]cyclopropyl]ethyl] S-Methyl Carbonodithioate



To a stirred solution of alcohol **12** (350 mg 1.3 mmol) in anhydrous DMF (5 mL), NaH (64 mg, 1.6 mmol, 60% dispersion in mineral oil) was slowly added at 0 °C. After the resulting mixture was stirred for 1 h at rt, carbon disulfide (156 μL, 2.6 mmol) was added dropwise at 0 °C and the reaction solution was stirred at rt overnight. After MeI (97 μL, 1.6 mmol) was slowly added, the mixture was stirred for another 1 h at rt, then quenched with saturated NH_4Cl aqueous solution (5 mL) and extracted with EtOAc (15 mL × 2).

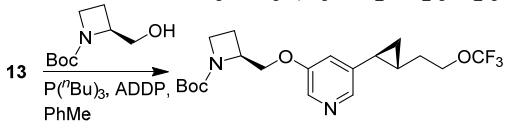
The combined organic layers were washed with H_2O, brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by silica gel column chromatography (hexane/EtOAc 2: 1) to afford the desired product (248 mg, 53%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 8.17 (s, 1H), 8.05 (s, 1H), 7.43-7.31 (m, 5H), 6.87 (s, 1H), 5.07 (s, 2H), 4.71 (m, 2H), 2.60 (s, 3H), 1.88 (m, 2H), 1.71 (m, 1H), 1.12 (m, 1H), 0.97 (m, 1H), 0.89 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 216.0, 154.9, 141.0, 139.4, 136.3, 135.1, 128.7, 128.3, 127.6, 118.7, 73.4, 70.3, 32.9, 20.4, 20.3, 19.1, 15.3.

5-[(1S,2R)-2-[2-(Trifluoromethoxy)ethyl]cyclopropyl]pyridin-3-ol (13)



A polypropylene round bottom flask equipped with a rubber septum, a magnetic stirring bar, was charged with 1,3-Dibromo-5,5-dimethylhydantoin (428 mg, 1.5 mmol) and dry CH_2Cl_2 (15 mL). The suspension was cooled to -78 °C for 10 min, then was slowly added 70% HF/Py (1.0 mL, 20 mmol of HF/mL) over 5 min and stirred vigorously under an Ar atmosphere. To this mixture was added dropwise a solution of the dithiocarbonate (185 mg, 0.51 mmol) in dry CH_2Cl_2 (5 mL) at -78 °C. After the addition was completed, the acetone/dry ice bath was replaced by an ice/NaCl bath. The resulting reaction mixture was stirred at the same temperature for 30 min, and quenched by careful addition of an ice-cold aqueous $NaHSO_3$/$NaHCO_3$/NaOH (pH 10) solution until a red-brownish color of the mixture disappeared at 0 °C. The pH value was readjusted to 10 at 0 °C by the addition of 2N NaOH solution and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, and brine, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was rapidly purified by a short silica column (hexane/EtOAc 2:1) to remove baseline impurities. The crude product was taken up in a mixture of EtOAc (5 mL) and methanol (5 mL), and 10% Pd/C (50 mg, containing 50% water) was added. A H_2-filled balloon was connected after the atmosphere was exchanged three times with Ar. The reaction was allowed to proceed at rt for 2 h, then the catalyst was filtered off over Celite. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 10:1) to furnish the hydroxypyridine **13** (70 mg, 56%, two steps) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 9.97 (br, 1H), 8.00 (s, 1H), 7.85 (s, 1H), 6.90 (s, 1H), 4.05 (m, 2H), 1.81-1.66 (m, 3H), 1.13 (m, 1H), 0.98 (m, 1H), 0.90 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 155.6, 141.1, 137.5, 133.7, 121.9, 121.8 (q, $J_{C\text{-}F}$ = 252.6 Hz), 67.1, 33.4, 20.3, 20.0, 15.5.

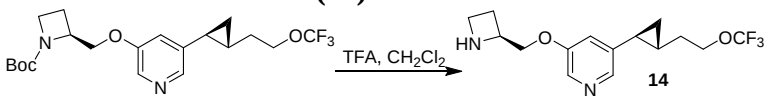
3-[[1-(tert-Butoxycarbonyl)-2(S)-azetidinyl]methoxy]-5-[(1S,2R)-2-(2-trifluoromethoxyethyl)cyclopropyl]pyridine



In a 100 mL side-arm flask with stir bar and an Ar-filled balloon, tri-*n*-butylphosphine (0.1 mL, 0.4 mmol) was added dropwise over 5 min to a solution of *N*,*N*'-azodicarbonyldipiperidine (100 mg, 0.4 mmol) in anhydrous toluene (5 mL). Stirring was continued at rt for 30 min to complete the formation of the Mitsunobu reagent. A solution of the hydroxypyridine intermediate **13** (70 mg, 0.28 mmol) and 1-(*tert*-butoxycarbonyl)-

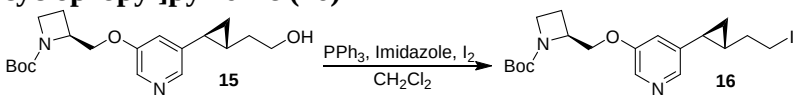
(2*S*)-azetidinylmethanol (100 mg, 0.53 mmol) in anhydrous toluene (5 mL) was added to the Mitsunobu reagent at 0 °C over 45 min. The mixture was warmed to rt and stirred overnight. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc 2:1 to 1:1) to furnish the desired product (87 mg, 75%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.10 (s, 1H), 8.01 (s, 1H), 6.83 (s, 1H), 4.48 (m, 1H), 4.28 (m, 1H), 4.11-4.04 (m, 3H), 3.87 (m, 2H), 2.31 (m, 2H), 1.79-1.68 (m, 3H), 1.39 (s, 9H), 1.12 (m, 1H), 0.99 (m, 1H), 0.87 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 156.4, 155.3, 141.1, 139.4, 135.2, 121.8 (q, $J_{C\text{-}F}$ = 252.5 Hz), 118.6, 79.9, 68.9, 67.1, 60.3, 47.3, 33.4, 28.5, 20.4, 19.8, 19.3, 15.3.

3-[(2(S)-Azetidinyl)methoxy]-5-[(1S,2R)-2-(2-trifluoromethoxyethyl)cyclopropyl]pyridine Trifluoroacetate (14)



Trifluoroacetic acid (1 mL) was added to a solution of compound obtained from the previous step (87 mg, 0.21 mmol) in CH_2Cl_2 (10 mL) under Ar. The resulting mixture was stirred at rt overnight, concentrated, and purified by preparative HPLC to give compound **14** (79 mg, 63%) as a colorless oil. ^{1}H NMR (D_2O): δ 8.33 (s, 1H), 8.22 (s, 1H), 7.85 (s, 1H), 4.96 (m, 1H), 4.51 (d, J = 3.6 Hz, 2H), 4.18-4.03 (m, 4H), 2.68 (q, J = 8.4 Hz, 2H), 2.02 (m, 1H), 1.92 (m, 1H), 1.73 (m, 1H), 1.37 (m, 1H), 1.19 (m, 2H); ^{13}C NMR (D_2O): δ 162.5 (TFA), 156.2, 146.3, 132.4, 128.4, 125.9, 121.5 (q, $J_{C\text{-}F}$ = 251.1 Hz), 116.2 (TFA), 67.7, 67.6, 58.6, 43.6, 32.1, 21.8, 20.2, 19.7, 16.1; ^{19}F NMR (D_2O): δ -60.2, -75.6. $[\alpha]_D^{20}$ = +28.6 (*c* 0.14, MeOH); Anal. Calcd for $C_{15}H_{19}F_3N_2O_2 \bullet 2.4CF_3COOH \bullet 0.5H_2O$: C, 39.7; H, 3.77; F, 32.35; N, 4.68. Found: C, 39.47; H, 3.52; F, 32.14; N, 4.49. HPLC purity = 99.8%; t_R = 9.7 min.

3-[[1-(tert-Butoxycarbonyl)-2(S)-azetidinyl]methoxy]-5-[(1S,2R)-2-(2-iodoethyl)-cyclopropyl]pyridine (16)

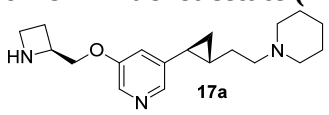


The alcohol **15** (348 mg, 1 mmol), triphenylphosphine (315 mg, 1.2 mmol) and imidazole (88 mg, 1.3 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL) under an Ar atmosphere. Iodine (305 mg, 1.2 mmol) was added in one portion to the flask through a temporarily opened neck with cooling provided by an ice bath. The mixture was stirred at rt for 3 h. After evaporating the solvent, the residue was purified by silica gel column chromatography (hexane/acetone 4:1) to afford the iodide **16** (455 mg, quantitative) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.95 (s, 1H), 6.77 (s, 1H), 4.41 (m, 1H), 4.21 (m, 1H), 4.03 (m, 1H), 3.78 (m, 2H), 3.16 (m, 2H), 2.23 (m, 2H), 1.86 (m, 2H), 1.63 (m, 1H), 1.32 (s, 9H), 0.90 (m, 1H), 0.82-0.78 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 155.7, 154.6, 140.6, 138.8, 134.6, 117.9, 79.1, 68.2, 59.7, 46.7, 37.6, 28.0, 23.9, 19.7, 18.7, 14.8, 4.3. MS (ESI, *m/e*) 459.2 $(M+H)^+$.

Compound **17a**, **17b**, and **17c** were prepared by the same procedure as described below. The iodide **16** (230 mg, 0.5 mmol) and various saturated six-membered heterocycle (2.5 mmol) were dissolved in anhydrous CH_3CN (5 mL) under an Ar atmosphere, and the

resultant mixture was stirred at rt overnight. After evaporating the solvent, the residue was rapidly filtered over a short silica gel column (CH_2Cl_2/MeOH 95:5) to remove baseline impurities. The eluate was evaporated. The residue was taken up in CH_2Cl_2 (5 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature overnight. Volatiles were removed, and purification of the residue by preparative HPLC afforded the desired products as colorless oils.

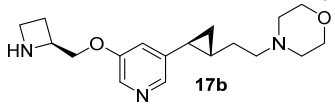
3-[(2(S)-Azetidinyl)methoxy]-5-[(1S,2R)-2-(2-(piperidin-1-yl)ethyl)cyclopropyl]pyridine Trifluoroacetate (17a)



17a

Compound **17a** (230 mg, 68%, two steps) was prepared from piperidine as the starting material. ^{1}H NMR (D_2O): δ 8.37 (s, 1H), 8.25 (s, 1H), 7.87 (s, 1H), 4.99 (m, 1H), 4.54 (s, 2H), 4.18-4.08 (m, 2H), 3.52 (d, *J* = 6.0 Hz, 2H), 3.23 (t, *J* = 8.0 Hz, 2H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.67 (dd, *J* = 12.0, 4.0 Hz, 2H), 2.01 (m, 1H), 1.97–1.70 (m, 7H), 1.49-1.46 (m, 1H), 1.35-1.33 (m, 1H), 1.24-1.19 (m, 2H); ^{13}C NMR (D_2O): δ 162.7 (TFA), 156.2, 145.6, 132.4, 128.5, 126.0, 116.3 (TFA), 67.5, 58.6, 53.1, 27.5, 22.7, 21.5, 21.0, 20.2, 19.8, 16.3. $[\alpha]_D^{20}$ = +43.6 (*c* = 3.4, MeOH). Anal. Calcd for $C_{19}H_{29}N_3O$•3.1CF_3COOH•0.45H_2O: C, 44.71; H, 4.91; F, 26.1; N, 6.21. Found: C, 44.83; H, 4.77; F, 25.97; N, 6.14. HPLC purity = 99.8%; t_R = 4.1 min.

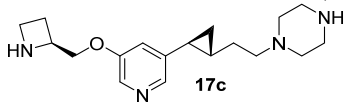
3-[(2(S)-Azetidinyl)methoxy]-5-[(1S,2R)-2-(2-(morpholin-4-yl)ethyl)cyclopropyl]pyridine Trifluoroacetate (17b)



17b

Compound **17b** (221 mg, 62%, two steps) was prepared from morpholine as the starting material. ^{1}H NMR (D_2O) δ 8.33 (s, 1H), 8.21 (s, 1H), 7.82 (s, 1H), 4.96–4.94 (m, 1H), 4.50 (d, *J* = 4.0 Hz, 2H), 4.14–4.05 (m, 4H), 3.78 (t, *J* = 12.4 Hz, 2H), 3.50 (d, *J* = 12.8 Hz, 2H), 3.29 (t, *J* = 8.0 Hz, 2H), 3.16 (dt, *J* = 12.4, 3.2 Hz, 2H), 2.67 (q, *J* = 8.8 Hz, 2H), 2.05–2.03 (m, 1H), 1.91–1.85 (m, 2H), 1.30 (m, 1H), 1.21–1.15 (m, 2H); ^{13}C NMR (D_2O): δ 162.2 (TFA), 155.8, 145.1, 132.0, 128.1, 125.7, 115.9 (TFA), 67.1, 63.3, 58.2, 55.9, 51.2, 43.2, 26.7, 20.8, 19.8, 19.4, 15.9. $[\alpha]_D^{20}$ = +43.5 (*c* = 0.8, MeOH). Anal. Calcd for $C_{18}H_{27}N_3O_2$•3.4CF_3COOH•0.4H_2O: C, 41.82; H, 4.41; F, 27.2; N, 5.9. Found: C, 41.91; H, 4.31; F, 27.09; N, 5.96. HPLC purity = 99.6%; t_R = 3.9 min.

3-[(2(S)-Azetidinyl)methoxy]-5-[(1S,2R)-2-(2-(piperazin-1-yl)ethyl)cyclopropyl]pyridine Trifluoroacetate (17c)

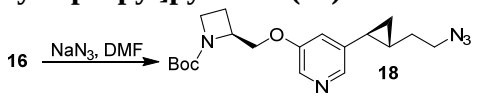


17c

Compound **17c** (283 mg, 72%, two steps) was prepared from 1-Boc-piperazine as the starting material. ^{1}H NMR (D_2O): δ 8.37 (s, 1H), 8.25 (s, 1H), 7.85 (s, 1H), 4.98 (m, 1H), 4.53 (d, *J* = 4.0 Hz, 2H), 4.17-4.05 (m, 2H), 3.65 (br s, 8H), 3.44 (t, *J* = 8.4 Hz, 2H), 2.71 (q, *J* = 8.4 Hz, 2H), 2.09 (m, 1H), 2.02-1.87 (m, 2H), 1.36 (m, 1H), 1.26-1.18 (m, 2H);

^{13}C NMR (D_2O): δ 162.3 (TFA), 155.9, 145.0, 132.1, 128.2, 125.7, 115.9 (TFA), 67.2, 58.2, 55.9, 48.0, 43.3, 40.2, 26.9, 20.6, 19.8, 19.4, 15.9. $[\alpha]_D^{20}$= +36.4 (*c* 1.52, MeOH). Anal. Calcd for $C_{18}H_{28}N_4O$•4.05CF_3COOH•0.45H_2O: C, 39.86; H, 4.22; F, 29.36; N, 7.12. Found: C, 39.97; H, 4.23; F, 29.26; N, 7.03. HPLC purity = 99.7%; t_R = 4.8 min.

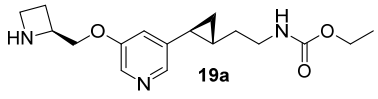
3-[[1-(tert-Butoxycarbonyl)-2(S)-azetidinyl]methoxy]-5-[(1S,2R)-2-(2-azidoethyl)-cyclopropyl]pyridine (18)



The iodide **16** (230 mg, 0.5 mmol) and sodium azide (325 mg, 5 mmol) were dissolved in anhydrous DMF (5 mL) under an Ar atmosphere, and the resultant mixture was stirred at 60 ^oC overnight. H_2O (15 mL) were added to the reaction mixture and then the mixture was extracted with EtOAc (25 mL × 2). The combined organic layers were washed with H_2O and brine, then dried with anhydrous Na_2SO_4. After evaporating the solvent, the residue was purified by silica gel column chromatography (hexane/acetone 3:1) to afford the azide **18** (159 mg, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.09 (s, 1H), 8.00 (s, 1H), 6.81 (s, 1H), 4.46 (m, 1H), 4.26 (m, 1H), 4.08 (m, 1H), 3.85 (m, 2H), 3.36 (m, 2H), 2.28 (m, 2H), 1.66 (m, 3H), 1.38 (s, 9H), 0.96 (m, 1H), 0.94-0.85 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 156.3, 155.2, 141.1, 139.4, 135.2, 118.4, 79.8, 68.8, 60.3, 51.3, 47.2, 33.6, 28.5, 20.9, 20.5, 19.2, 15.6. MS (ESI, *m/e*) 374.3 $(M+H)^+$.

Compounds **19a** and **19b** were prepared by the same procedure as described below. In a 50 mL single-necked flask was placed a solution of the azide **18** (187 mg, 0.5 mmol) in ethanol (10 mL) under an Ar atmosphere, and 10% Pd/C (80 mg, containing 50% water). A H_2-filled balloon was connected to the flask and the atmosphere was exchanged twice. The reaction mixture was stirred at room temperature for 3 h, was and then filtered from the catalyst over a bed of Celite placed in the stem of a funnel. After evaporating the solvent, the filtrate furnished the amine product as a colorless oil which was directly used in next step without further purification. To a solution of the crude amine product and Et_3N (61 mg, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL), various chloroformates (0.6 mmol, 1.2 eqiv) were added at 0 ^oC under an Ar atmosphere. The reaction mixture was stirred at rt for 2 h, then the solvent was removed and the residue was rapidly purified by a short silica column (hexane/acetone 3:1) to remove baseline impurities. The crude product was taken up in CH_2Cl_2 (5 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at rt overnight. Volatiles were removed, and purification of the residue by preparative HPLC afforded the desired product as a colorless oil.

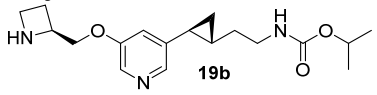
Ethyl [2-[(1R,2S)-2-[5-[((S)-Azetidin-2-yl)methoxy]pyridin-3-yl]cyclopropyl]ethyl]-carbamate Trifluoroacetate (19a)



Compound **19a** (190 mg, 61%) was prepared from ethyl chloroformate as the starting material. ^{1}H NMR (D_2O): δ 8.32 (s, 1H), 8.21 (s, 1H), 7.82 (s, 1H), 4.97 (m, 1H), 4.51 (d, *J* = 4.4 Hz, 2H), 4.12 (m, 2H), 3.94 (m, 2H), 3.23 (m, 2H), 2.68 (q, *J* = 8.4 Hz, 2H), 1.94 (m, 1H), 1.70 (m, 1H), 1.50 (m, 1H), 1.27 (m, 1H), 1.15-1.10 (m, 5H); ^{13}C NMR (D_2O):

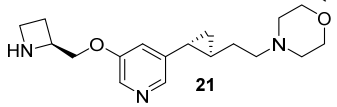
δ 162.6 (TFA), 158.7, 156.2, 146.7, 132.2, 128.2, 125.6, 116.3 (TFA), 67.5, 61.5, 58.6, 43.6, 40.0, 33.1, 23.2, 20.2, 20.0, 16.5, 13.7. $[\alpha]_D^{20}$ = +35.0 (*c* 0.20, MeOH). Anal. Calcd for $C_{17}H_{25}N_3O_3$•2.6CF_3COOH•0.55H_2O: C, 42.61; H, 4.62; F, 23.68, N, 6.71; Found: C, 42.75; H, 4.58; F, 23.55; N, 6.63. HPLC purity = 99.8%; t_R = 6.8 min.

Isopropyl [2-[(1R,2S)-2-[5-[((S)-Azetidin-2-yl)methoxy]pyridin-3-yl]cyclopropyl]-ethyl]carbamate Trifluoroacetate (19b)



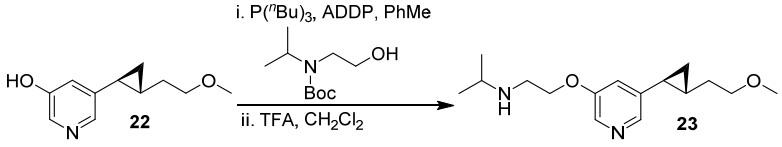
Compound **19b** (176 mg, 58%) was prepared from a solution of isopropyl chloroformate solution (1.0 M in toluene) as the starting material. ^{1}H NMR (D_2O): δ 8.32 (s, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 4.96 (m, 1H), 4.65 (m, 1H), 4.50 (d, *J* = 3.2 Hz, 2H), 4.10 (m, 2H), 3.22 (m, 2H), 2.67 (q, *J* = 8.4 Hz, 2H), 1.93 (m, 1H), 1.69 (m, 1H), 1.50 (m, 1H), 1.26 (m, 1H), 1.12 (m, 8H); ^{13}C NMR (D_2O): δ 162.5 (TFA), 158.3, 156.2, 146.7, 132.2, 128.2, 125.6, 116.2 (TFA), 69.3, 67.5, 58.6, 43.6, 39.9, 33.1, 23.1, 21.1, 20.2, 20.0, 16.6. $[\alpha]_D^{20}$ = +40.0 (*c* 0.24, MeOH). Anal. Calcd for $C_{18}H_{27}N_3O_3$•2.35CF_3COOH•0.2H_2O: C, 45.07; H, 4.96; F, 22.14, N, 6.95; Found: C, 44.99; H, 4.87; F, 22.07; N, 6.95. HPLC purity = 99.7%; t_R = 7.3 min.

3-[(2(S)-Azetidinyl)methoxy]-5-[(1R,2S)-2-(2-(morpholin-4-yl)ethyl)cyclopropyl]py-ridine Trifluoroacetate (21)



Compound **21** was synthesized from the intermediate **20** by the same sequence of steps as described above for compound **17b**. ^{1}H NMR (D_2O) δ 8.37 (s, 1H), 8.26 (s, 1H), 7.87 (s, 1H), 5.00–4.98 (m, 1H), 4.54 (d, 2H, *J* = 4.0 Hz), 4.17–4.08 (m, 4H), 3.82 (t, 2H, *J* = 12.4 Hz), 3.54 (d, 2H, *J* = 12.8 Hz), 3.34 (t, 2H, *J* = 8.0 Hz), 3.20 (dt, 2H, *J* = 12.4, 3.2 Hz), 2.71 (q, 2H, *J* = 8.8 Hz), 2.10–2.08 (m, 1H), 1.97–1.88 (m, 2H), 1.35 (m, 1H), 1.25–1.98 (m, 2H). ^{13}C NMR (D_2O): δ 162.2 (TFA), 155.9, 145.1, 132.1, 128.1, 125.7, 115.9 (TFA), 67.1, 63.3, 58.2, 55.9, 51.2, 43.2, 26.7, 20.8, 19.8, 19.4, 15.9. $[\alpha]_D^{20}$ = -46.4 (*c* 0.78, MeOH). Anal. Calcd for $C_{18}H_{27}N_3O_2$•3.4CF_3COOH•0.05H_2O: C, 42.19; H, 4.35; F, 27.45; N, 5.95. Found: C, 42.22; H, 4.38; F, 27.38; N, 5.97. HPLC purity = 99.9%; t_R = 3.9 min.

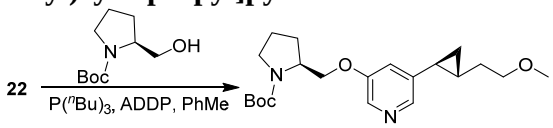
3-[2-(Isopropylamino)ethoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (23)



In a 100 mL side-arm flask with stir bar and an Ar-filled balloon, tri-*n*-butylphosphine (0.23 mL, 0.84 mmol) was added dropwise over 5 min to a solution of *N*,*N*'-azodicarbonyldipiperidine (230 mg, 0.84 mmol) in anhydrous toluene (5 mL). Stirring was continued at rt for 30 min to complete formation of the Mitsunobu reagent. A

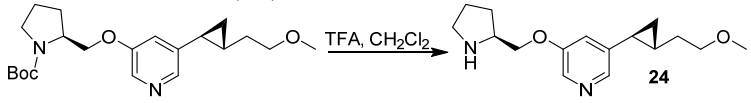
solution of the hydroxypyridine intermediate **22** (110 mg, 0.57 mmol) and *N*-Boc-2-(isopropylamino)ethanol (150 mg, 0.74 mmol) in anhydrous toluene (10 mL) was then added to the Mitsunobu reagent at 0 °C over 45 min. The mixture was warmed to rt and stirred overnight. After removal of the solvent, the residue was rapidly filtered over a short silica gel column (CH_2Cl_2/MeOH 95:5) to remove baseline impurities and the eluate was evaporated to dryness. The residue was taken up in CH_2Cl_2 (5 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature overnight. Volatiles were removed, and purification of the residue by preparative HPLC afforded compound **23** as a colorless oil (268 mg, 87%, two steps). ^{1}H NMR (D_2O): δ 8.14 (s, 1H), 8.07 (s, 1H), 7.66 (s, 1H), 4.35 (t, *J* = 4.0 Hz, 2H), 4.46-4.36 (m, 5H), 3.20 (s, 3H), 1.83 (s, 1H), 1.57 (s, 2H), 1.23 (d, *J* = 6.4 Hz, 6H), 1.16 (m, 1H), 1.02 (m, 2H); ^{13}C NMR (D_2O): δ 162.4 (TFA), 156.1, 146.5, 132.2, 128.2, 125.6, 116.2 (TFA), 71.8, 64.9, 57.7, 51.1, 43.3, 32.6, 22.3, 19.8, 18.0, 16.6. $[\alpha]_D^{20}$ = +33.4 (*c* = 0.9, MeOH). Anal Calcd for $C_{16}H_{26}N_2O_2$•2.15CF_3COOH•0.8H_2O: C, 45.32; H, 5.57; F, 22.78; N, 5.21. Found: C, 45.06; H, 5.24; F, 22.63; N, 5.09. HPLC purity = 99.8%; t_R = 9.3 min.

3-[[1-(*tert*-Butoxycarbonyl)-2(*S*)-pyrrolidinyl]methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine



In a 100 mL side-arm flask with stir bar and an Ar-filled balloon, tri-*n*-butylphosphine (0.2 mL, 0.8 mmol) was added dropwise over 5 min to a solution of *N*,*N*'-azodicarbonyldipiperidine (200 mg, 0.8 mmol) in anhydrous toluene (5 mL). Stirring was continued at rt for 30 min to complete formation of the Mitsunobu reagent. A solution of the hydroxypyridine intermediate **22** (97 mg, 0.5 mmol) and *N*-Boc-L-prolinol (160 mg, 0.8 mmol) in anhydrous toluene (10 mL) was added to the Mitsunobu reagent at 0 °C over 45 min. The mixture was warmed to rt and stirred overnight. After removal of the solvent, the residue was purified by silica gel column chromatography (hexanes/EtOAc 2:1 to 1:1) to furnish the desired product (154 mg, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.0 (s, 1H), 7.94 (s, 1H), 6.76 (m, 1H), 4.04 (m, 2H), 3.86 (m, 1H), 3.41 (t, *J* = 6.6 Hz, 2H), 3.32-3.22 (m, 5H), 1.94 (m, 3H), 1.79 (m, 1H), 1.63-1.54 (m, 3H), 1.39 (s, 9H), 1.07 (m, 1H), 0.87 (m, 1H), 0.78 (m, 1H). MS (ESI) *m/z* 377.3 ($M+H^+$).

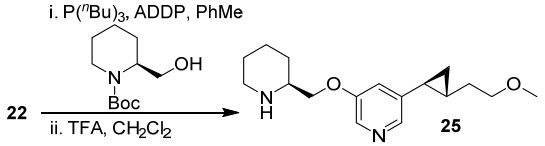
3-[(2(S)-Pyrrolidinyl)methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (24)



Trifluoroacetic acid (1 mL) was added to a solution of the product (151 mg, 0.4 mmol) obtained from the previous step dissolved in CH_2Cl_2 (10 mL) under an Ar atmosphere. The mixture was stirred at rt overnight, concentrated, and purified by preparative HPLC to give compound **24** (133 mg, 65%) as a colorless oil. ^{1}H NMR (D_2O): δ 8.26 (s, 1H), 8.19 (s, 1H), 7.77 (s, 1H), 4.53 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.33 (m, 1H), 4.11 (m, 1H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.39 (t, *J* = 7.2 Hz, 2H), 3.32 (s, 3H), 2.27 (m, 1H), 2.12-2.06 (m, 2H), 1.94 (m, 2H), 1.68 (m, 2H), 1.28 (m, 1H), 1.12 (m, 2H); ^{13}C NMR (D_2O): δ 162.6

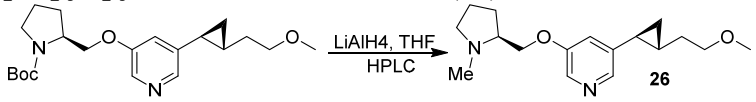
(TFA), 156.1, 146.5, 132.3, 128.2, 125.6, 116.2 (TFA), 71.8, 67.6, 58.3, 57.7, 45.9, 32.6, 25.7, 23.4, 22.3, 19.8, 16.6. $[\alpha]_D^{20}$ = +47.3 (*c* 0.28, MeOH). Anal. Calcd for $C_{16}H_{24}N_2O_2$•2.05CF_3COOH•0.05H_2O: C, 47.24; H, 5.16; F, 22.86; N, 5.48. Found: C, 47.30; H, 5.24; F, 22.75, N, 5.46. HPLC purity = 99.5%; t_R = 7.6 min.

3-[(2(S)-Piperidinyl)methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (25)



Compound **25** was synthesized from (*S*)-*N*-Boc-2-piperidinemethanol by the same sequence of steps as described above for compound **23**. ^{1}H NMR (D_2O): δ 8.22 (s, 1H), 8.16 (s, 1H), 7.74 (s, 1H), 4.39 (m, 1H), 4.24 (m, 1H), 3.61 (m, 1H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.43 (m, 1H), 3.30 (s, 3H), 3.03 (m, 1H), 1.97-1.88 (m, 4H), 1.68-1.58 (m, 5H), 1.25 (m, 1H), 1.10 (m, 2H); ^{13}C NMR (D_2O): δ 162.2 (TFA), 155.7, 146.1, 131.9, 127.8, 125.2, 115.7 (TFA), 71.4, 68.7, 57.3, 54.9, 44.2, 32.2, 23.9, 21.9, 21.2, 20.6, 19.4, 16.2. $[\alpha]_D^{20}$ = +49.3 (*c* 0.53, MeOH). Anal. Calcd for $C_{17}H_{26}N_2O_2$•2.6CF_3COOH•1.05H_2O: C, 44.02; H, 5.11; F, 24.46, N, 4.62. Found: C, 44.04; H, 4.89; F, 24.27; N, 4.78. HPLC purity = 98.7%; t_R = 7.9 min.

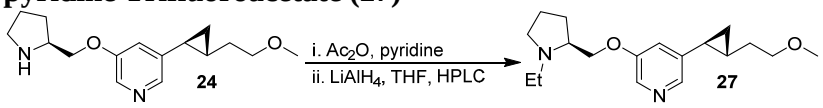
3-[(1-Methyl-2(S)-pyrrolidinyl)methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (26)



Lithium aluminum hydride solution (0.75 mL, 2.0 M in THF) was slowly added to a solution of the product (113 mg, 0.3 mmol) obtained from the previous step in anhydrous THF (5 mL) at 0 °C under Ar. The reaction mixture was heated to 70 °C and stirred for 3 h. After cooling to rt, H_2O (0.06 mL), 15% NaOH solution (0.06 mL), and H_2O (0.18 mL) were added to the reaction mixture sequentially. The resulting suspension was filtered and the filtrate was evaporated to dryness. The residue was purified by preparative HPLC to afford compound **26** as a colorless oil (108 mg, 63%). ^{1}H NMR (D_2O): δ 8.30 (s, 1H), 8.23 (s, 1H), 7.81 (s, 1H), 4.61 (dd, *J* = 10.8, 2.8 Hz, 1H), 4.45 (m, 1H), 3.95 (m, 1H), 3.76 (m, 1H), 3.59 (t, *J* = 6.4 Hz, 2H), 3.34 (s, 3H), 3.25 (m, 1H), 3.04 (s, 3H), 2.40 (m, 1H), 2.18 (m, 1H), 2.09 (m, 2H), 1.98 (m, 1H), 1.71 (m, 2H), 1.31 (m, 1H), 1.15 (m, 2H); ^{13}C NMR (D_2O): δ 162.0 (TFA), 155.6, 146.2, 132.0, 127.8, 125.2, 115.7 (TFA), 71.4, 66.9, 66.0, 57.3, 56.8, 40.2, 32.2, 25.4, 21.9, 21.7, 19.4, 16.2. $[\alpha]_D^{20}$ = +37.0 (*c* 0.27, MeOH). Anal. Calcd for $C_{17}H_{26}N_2O_2$•2.4CF_3COOH•0.4H_2O: C, 45.83; H, 5.15; F, 23.94; N, 4.9. Found: C, 45.64; H, 4.91; F, 23.8, N, 4.9. HPLC purity = 98.9%; t_R = 7.8 min.

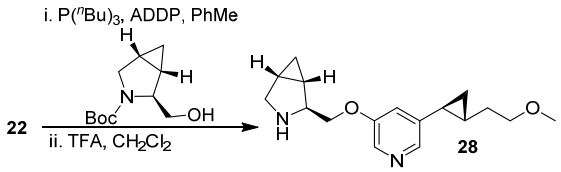
The resulting TFA salt was treated with PL-HCO_3 MP-resin to afford the free amine compound, which then was dissolved in methanol and treated with L-(+)-tartaric acid under argon protection at room temperature. The mixture was stirred for two hours. After the solvent was evaporated, final tartrate salt product could be obtained after lyophilization as a white solid.

3-[(1-Ethyl-2(S)-pyrrolidinyl)methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]-pyridine Trifluoroacetate (27)



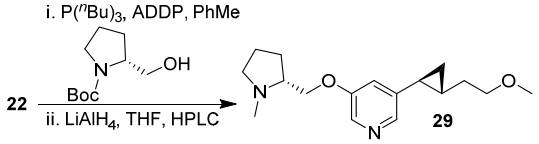
In a 100 mL side-arm flask with stir bar and an Ar-filled balloon, acetic anhydride (1.0 mL) was added dropwise over 5 min to a solution of compound **24** (150 mg, 0.29 mmol) in anhydrous pyridine (1.0 mL) at 0 °C. The mixture was warmed to rt and stirred overnight, and then the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was rapidly filtered over a short silica gel column (CH_2Cl_2/MeOH 95:5) to remove baseline impurities. The eluate was evaporated. The residue was taken up in anhydrous THF (5 mL), and a lithium aluminum hydride solution (0.75 mL, 2.0 M in THF) was slowly added at 0 °C under Ar. The reaction mixture was heated to 70 °C and stirred for 3 h. After cooling to rt, H_2O (0.06 mL), 15% NaOH solution (0.06 mL), and H_2O (0.18 mL) were added to the reaction mixture sequentially. The resulting suspension was filtered and the filtrate was evaporated to dryness. The residue was purified by preparative HPLC to afford compound **27** as a colorless oil (125 mg, 76%). ^{1}H NMR (D_2O): δ 8.30 (s, 1H), 8.23 (s, 1H), 7.80 (s, 1H), 4.57 (m, 1H), 4.44 (m, 1H), 4.05 (m, 1H), 3.73 (m, 1H), 3.61-3.54 (m, 3H), 3.35 (s, 3H), 3.24 (2H), 2.34 (m, 1H), 2.09-1.97 (m, 4H), 1.71 (m, 2H), 1.38-1.32 (m, 4H), 1.15 (m, 2H); ^{13}C NMR (D_2O): δ 161.9 (TFA), 155.6, 146.2, 132.1, 127.8, 125.2, 115.9 (TFA), 71.5, 66.5, 65.5, 57.3, 53.8, 50.1, 32.2, 25.5, 22.0, 21.9, 19.4, 16.2, 9.6. $[\alpha]_D^{20}$ = +39.8 (*c* 0.61, MeOH). Anal. Calcd for $C_{18}H_{28}N_2O_2$•2.1CF_3COOH•0.85H_2O: C, 47.68; H, 5.73; F, 21.4, N, 5.01. Found: C, 47.4; H, 5.42; F, 21.32; N, 4.91. HPLC purity = 99.3%; t_R = 8.0 min.

3-[((1S,2S,5R)-3-Azabicyclo[3.1.0]hexan-2-yl)methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (28)



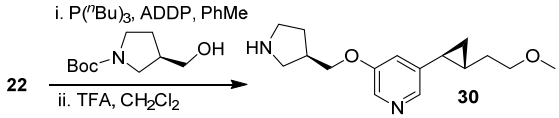
Compound **28** was synthesized from (1*S*,2*S*,5*R*)-3-*tert*-butoxycarbonyl-2-hydroxymethyl-3-azabicyclo[3.1.0]hexane by the same sequence of steps as described above for compound **23** (245 mg, 56%, two steps). ^{1}H NMR (D_2O): δ 8.25 (s, 1H), 8.17 (s, 1H), 7.76 (s, 1H), 4.67 (d, *J* = 14.0 Hz, 1H), 4.35-4.27 (m, 2H), 3.55-3.45 (m, 4H), 3.30 (s, 3H), 1.94-1.88 (m, 3H), 1.66 (m, 2H), 1.26 (m, 1H), 1.10 (m, 2H), 0.84 (m, 1H), 0.59 (m, 1H). ^{13}C NMR (D_2O): δ 162.4 (TFA), 156.2, 146.5, 132.2, 128.2, 125.6, 117.6 (TFA), 71.8, 67.7, 59.3, 57.7, 47.6, 32.6, 22.3, 19.8, 16.6, 15.9, 14.1, 3.9. $[\alpha]_D^{20}$ = +34.3 (*c* = 2.4, MeOH). Anal. Calcd for $C_{17}H_{24}N_2O_2$•2.15CF_3COOH•0.85H_2O: C, 46.61; H, 5.11; F, 22.33; N, 5.1. Found: C, 46.62; H, 4.92; F, 22.14; N, 5.13. HPLC purity = 99.5%; t_R = 12.7 min.

3-[(1-Methyl-2(R)-pyrrolidinyl)methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (29)



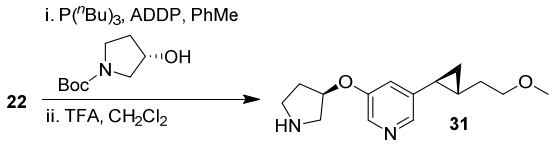
Compound **29** was synthesized from *N*-Boc-D-prolinol by the same sequence of steps as described above for compound **26**. ^{1}H NMR (D_2O): δ 8.29 (s, 1H), 8.21 (s, 1H), 7.79 (s, 1H), 4.60 (dd, *J* = 10.8, 2.8 Hz, 1H), 4.43 (m, 1H), 3.94 (m, 1H), 3.74 (m, 1H), 3.57 (t, *J* = 6.4 Hz, 2H), 3.32 (s, 3H), 3.24 (m, 1H), 3.02 (s, 3H), 2.39 (m, 1H), 2.19 (m, 1H), 2.07 (m, 2H), 1.96 (m, 1H), 1.69 (m, 2H), 1.29 (m, 1H), 1.13 (m, 2H); ^{13}C NMR (D_2O): δ 162.2 (TFA), 155.7, 146.2, 132.1, 127.9, 125.2, 115.8 (TFA), 71.4, 66.9, 66.0, 57.3, 56.8, 40.1, 32.2, 25.4, 22.0, 21.7, 19.4, 16.2. $[\alpha]_D^{20}$ = +39.5 (*c* 0.2, MeOH). Anal. Calcd for $C_{17}H_{26}N_2O_2$•2.1CF_3COOH•0.75H_2O: C, 46.86; H, 5.49; F, 22.03; N, 5.16. Found: C, 46.96; H, 5.14; F, 21.7, N, 5.12. HPLC purity = 99.2%; t_R = 7.4 min.

3-[(3(S)-Pyrrolidinyl)methoxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (30)



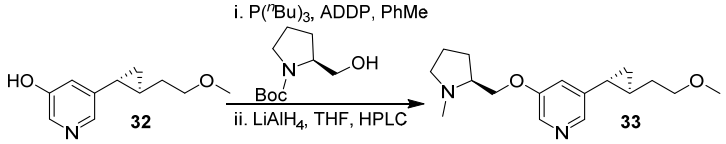
Compound **30** was synthesized from (*R*)-*N*-Boc-3-pyrrolidinemethanol by the same sequence of steps as described above for compound **23**. ^{1}H NMR (D_2O): δ 8.23 (s, 1H), 8.16 (s, 1H), 7.75 (s, 1H), 4.28 (m, 1H), 4.20 (m, 1H), 3.58 (m, 3H), 3.46 (m, 1H), 3.38-3.23 (m, 5H), 2.96 (m, 1H), 2.30 (m, 1H), 1.96 (m, 2H), 1.69 (m, 2H), 1.27 (m, 1H), 1.13 (m, 2H); ^{13}C NMR (D_2O): δ 162.2 (TFA), 156.5, 145.9, 131.4, 127.8, 125.1, 115.8 (TFA), 71.5, 69.6, 57.3, 46.9, 45.1, 36.2, 32.2, 26.0, 21.8, 19.4, 16.1. $[\alpha]_D^{20}$ = +42.0 (*c* 0.70, MeOH). Anal. Calcd for $C_{16}H_{24}N_2O_2$•2.0CF_3COOH•1.05H_2O: C, 45.9; H, 5.41; F, 21.78, N, 5.35. Found: C, 45.52; H, 5.0; F, 21.5; N, 5.31. HPLC purity = 99.4%; t_R = 7.3 min.

3-[(3(R)-Pyrrolidinyl)oxy]-5-[(1S,2R)-2-(2-methoxyethyl)cyclopropyl]pyridine Trifluoroacetate (31)



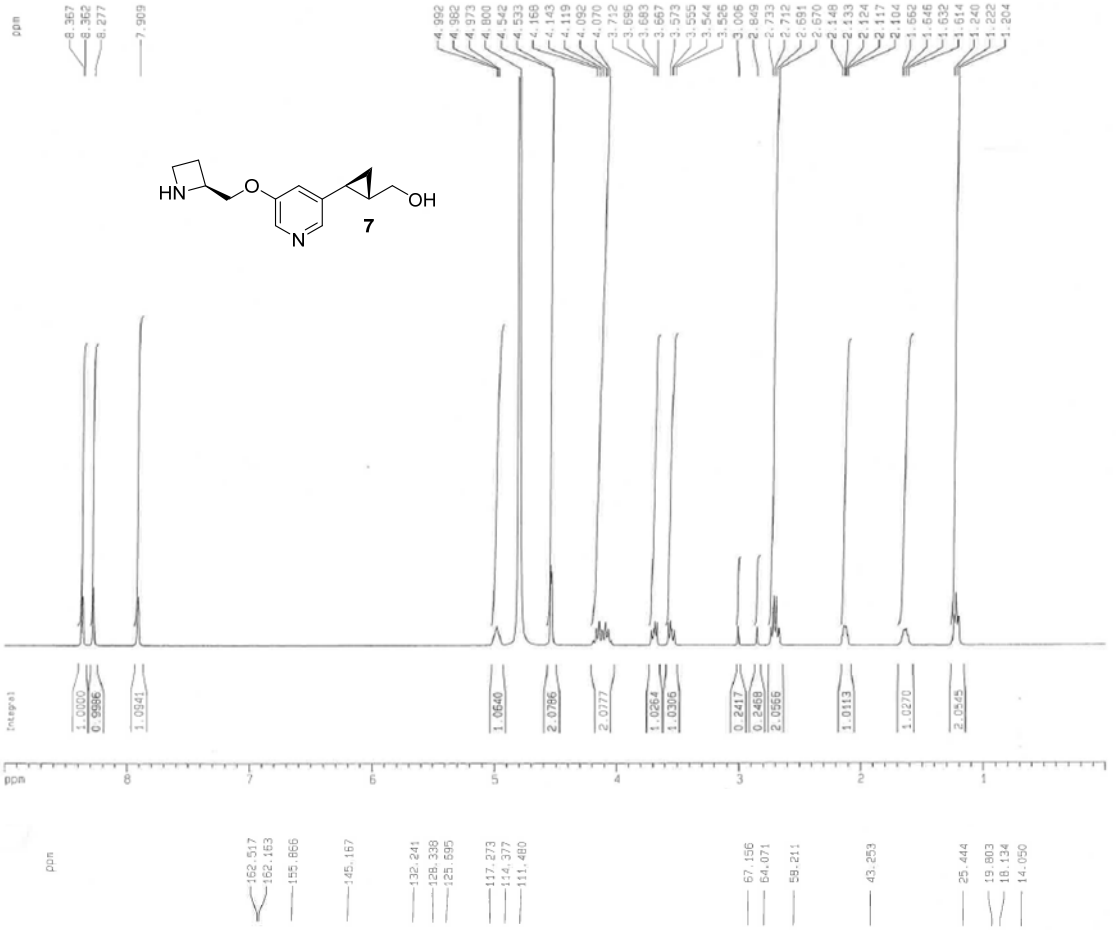
Compound **31** was synthesized from (*R*)-*N*-Boc-3-pyrrolidinemethanol by the same sequence of steps as described above for compound **23** (150 mg, 59%, two steps). ^{1}H NMR (D_2O): δ 8.23 (s, 1H), 8.15 (s, 1H), 7.75 (s, 1H), 5.37 (s, 1H), 3.68-3.46 (m, 6H), 3.29 (s, 3H), 2.34 (m, 2H), 1.91 (m, 1H), 1.66 (m, 2H), 1.24 (m, 1H), 1.09 (m, 2H); ^{13}C NMR (D_2O): δ 162.1 (TFA), 154.5, 146.2, 131.8, 128.7, 126.0, 115.8 (TFA), 77.2, 71.4, 57.3, 50.0, 43.4, 32.2, 29.3, 21.9, 19.4, 16.2. $[\alpha]_D^{20}$ = +34.0 (*c* 0.1, MeOH). Anal. Calcd for $C_{15}H_{22}N_2O_2$•2.15CF_3COOH•0.1H_2O: C, 45.52; H, 4.82; F, 24.06; N, 5.5. Found: C, 45.38; H, 4.72; F, 24.08, N, 5.69. HPLC purity = 99.8%; t_R = 6.4 min.

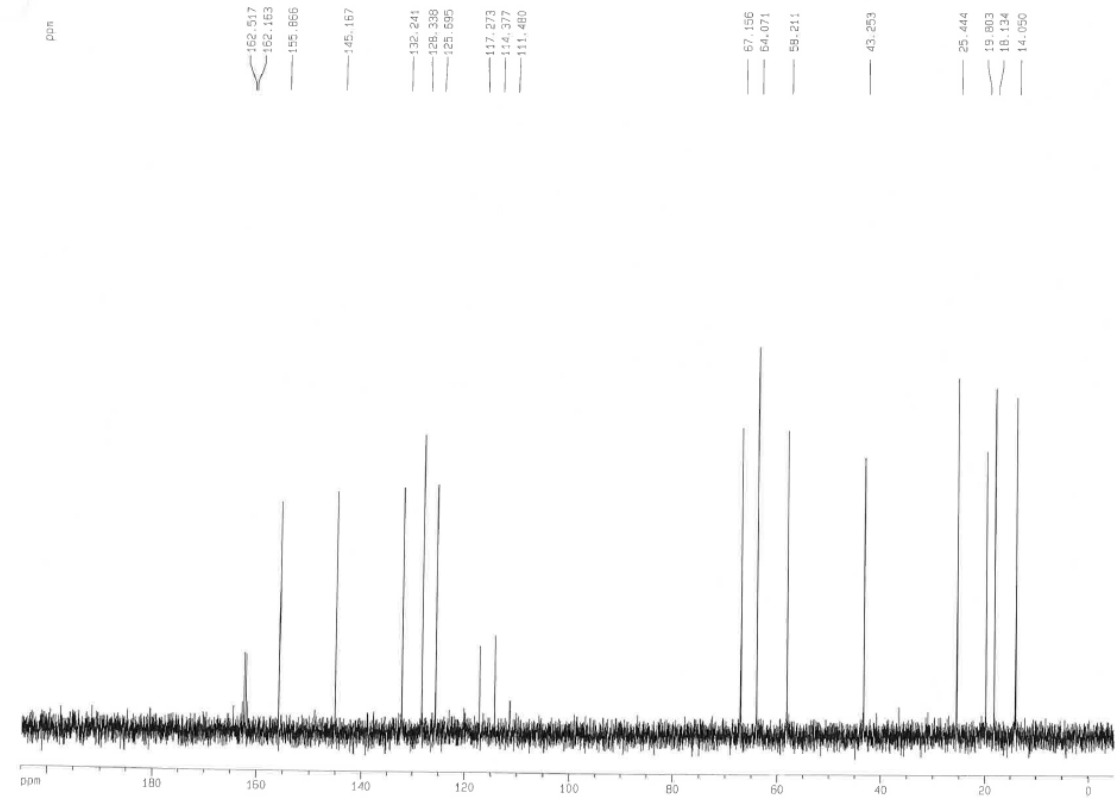
3-[(1-Methyl-2(S)-pyrrolidinyl)methoxy]-5-[(1R,2S)-2-(2-methoxyethyl)cyclo-propyl]pyridine Trifluoroacetate (33)

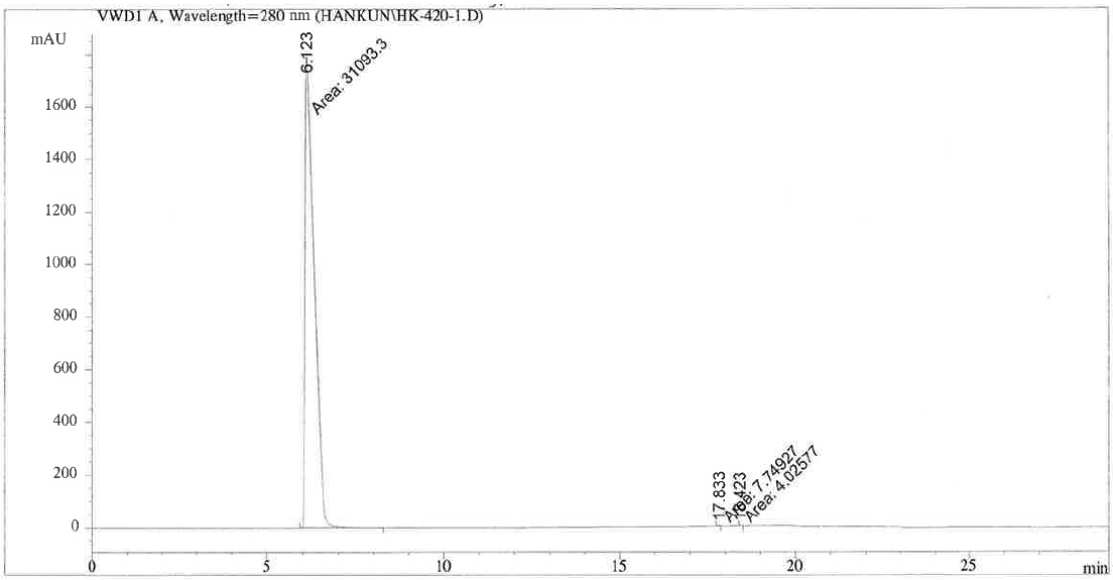


Compound **33** was synthesized from the intermediate **32** by the same sequence of steps as described above for compound **26**. ^{1}H NMR (D_2O): δ 8.30 (s, 1H), 8.22 (s, 1H), 7.80 (s, 1H), 4.60 (dd, *J* = 10.8, 2.8 Hz, 1H), 4.44 (m, 1H), 3.95 (m, 1H), 3.74 (m, 1H), 3.57 (t, *J* = 6.4 Hz, 2H), 3.33 (s, 3H), 3.25 (m, 1H), 3.03 (s, 3H), 2.40 (m, 1H), 2.20 (m, 1H), 2.08 (m, 2H), 1.97 (m, 1H), 1.70 (m, 2H), 1.30 (m, 1H), 1.14 (m, 2H); ^{13}C NMR (D_2O): δ 162.2 (TFA), 155.7, 146.2, 132.1, 127.9, 125.2, 115.9 (TFA), 71.5, 66.9, 66.0, 57.3, 56.8, 40.2, 32.2, 25.4, 22.0, 21.7, 19.4, 16.2. $[\alpha]_D^{20}$ = -33.8 (*c* 0.13, MeOH). Anal. Calcd for $C_{17}H_{26}N_2O_2$•2.05CF_3COOH•0.45H_2O: C, 47.61; H, 5.48; F, 21.95; N, 5.26. Found: C, 47.66; H, 5.24; F, 21.73, N, 5.19. HPLC purity = 99.8%; t_R = 5.8 min.

NMR Spectra and HPLC Traces



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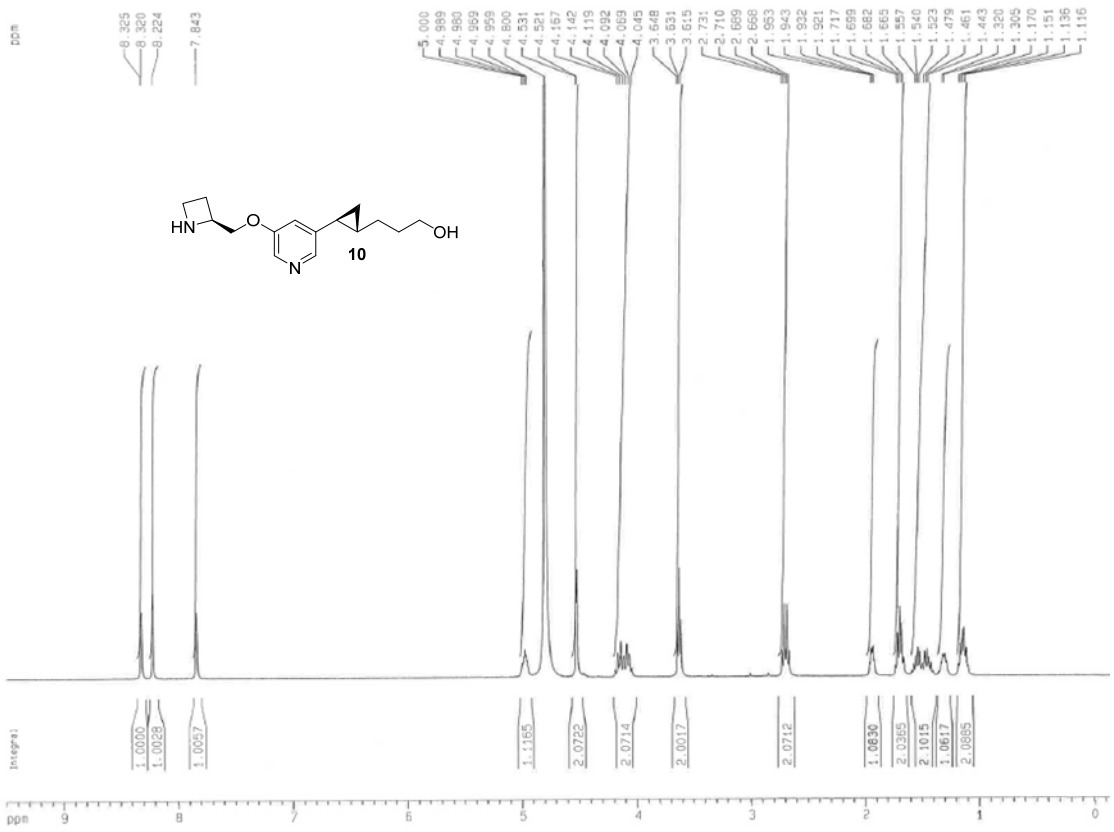
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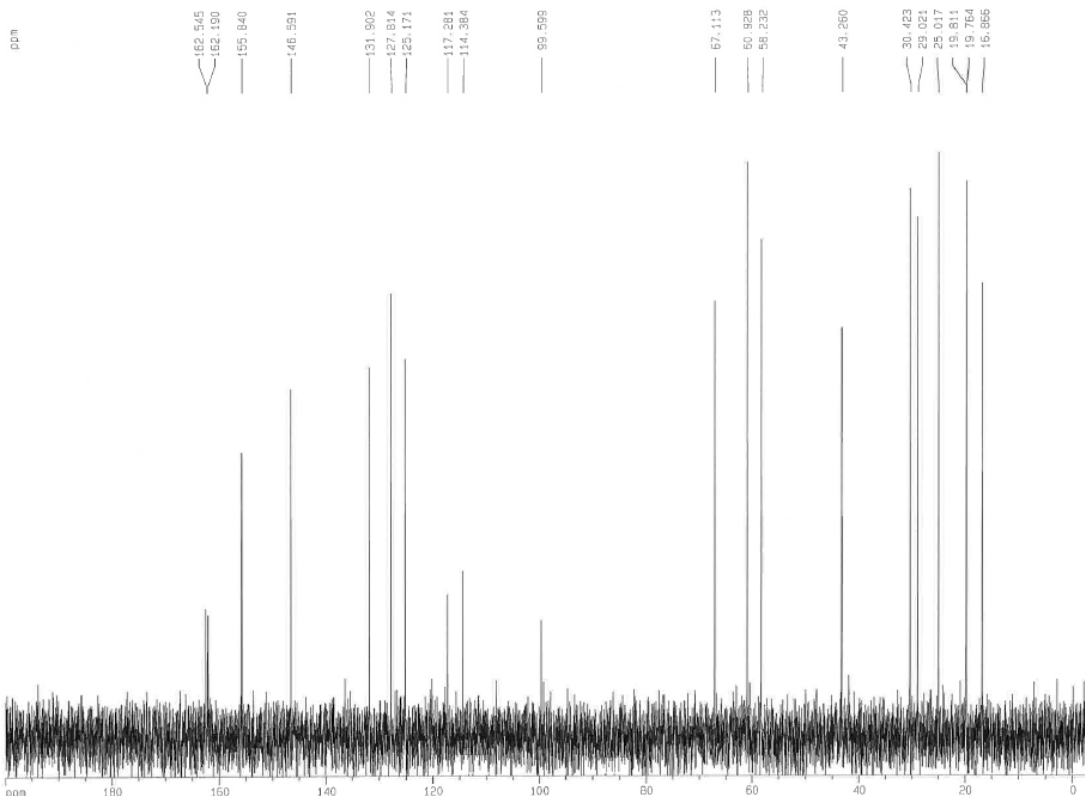
OH
N
10
ppm
Integral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43.260
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19.764
15.866
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140
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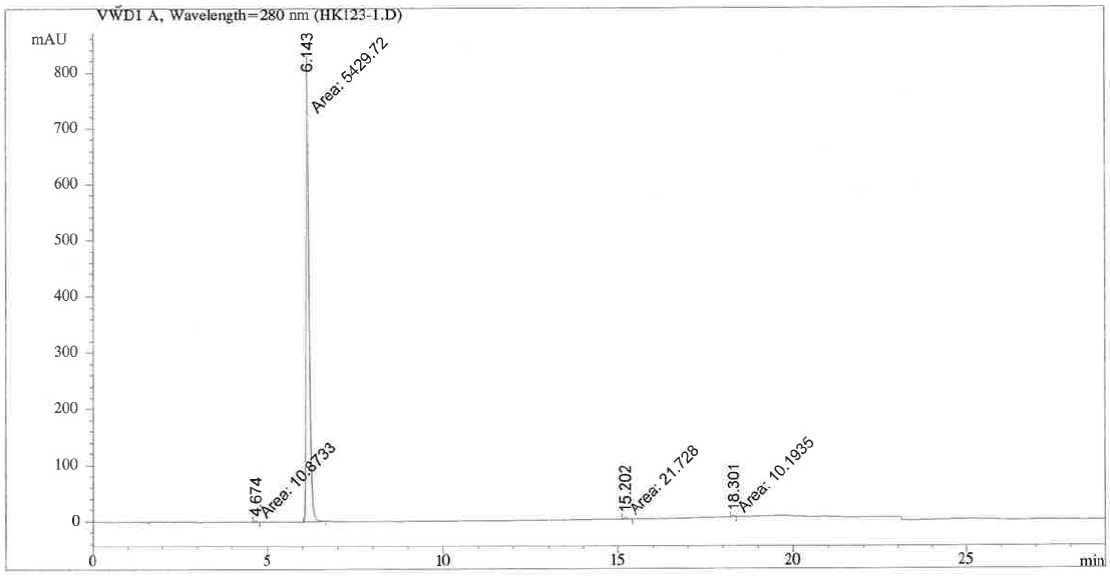
100
80
60
40
20
0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400
300
200
100
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4.674
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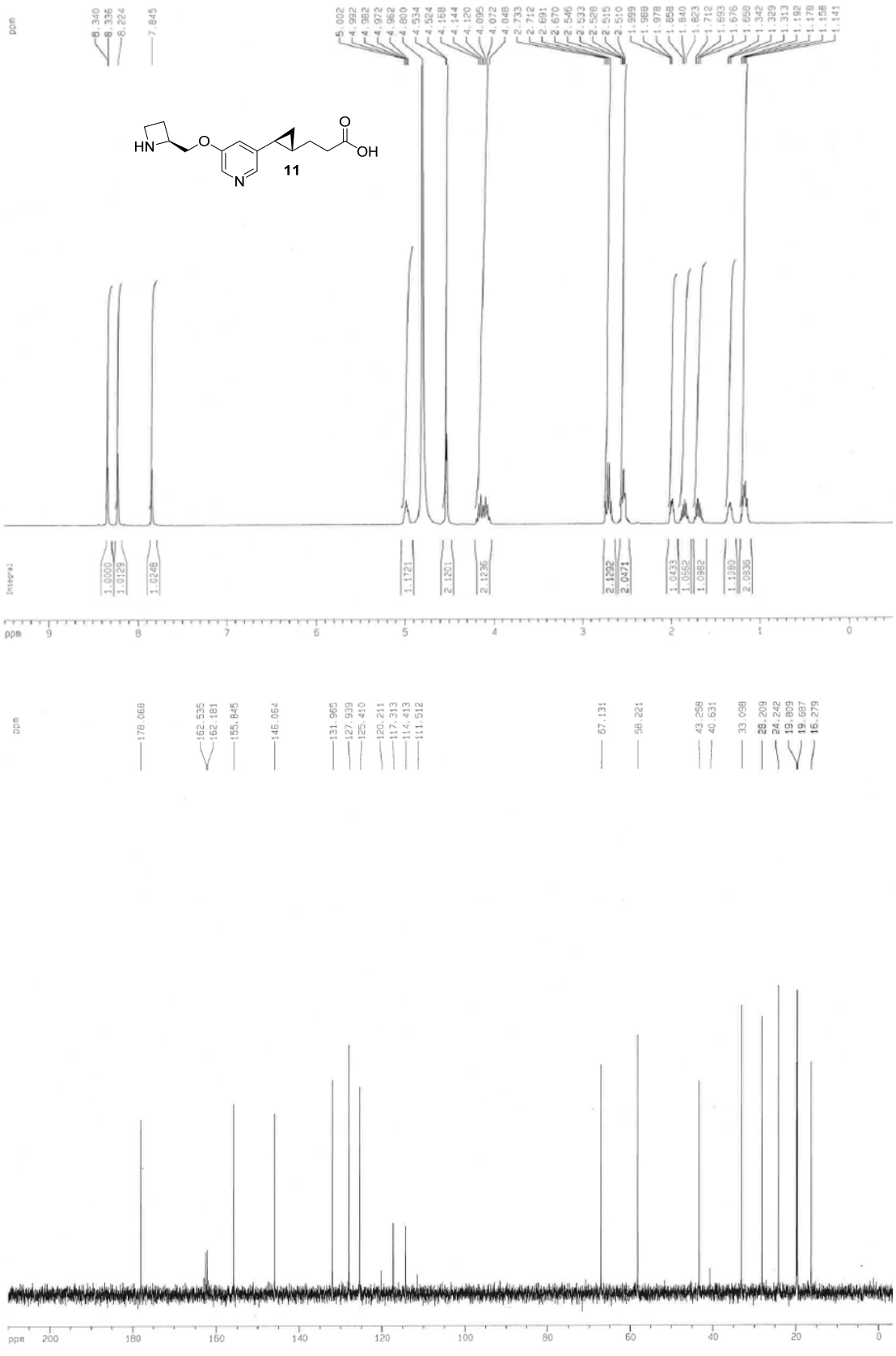
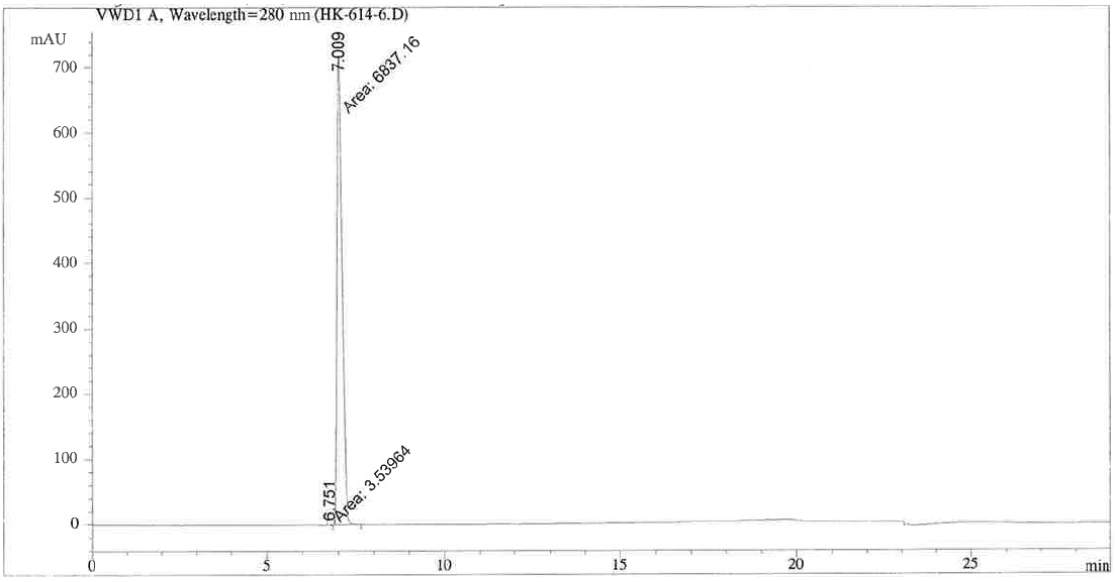
15.202
Area: 21.728
18.301
Area: 10.1935
0
5
10
15
20
25
min


11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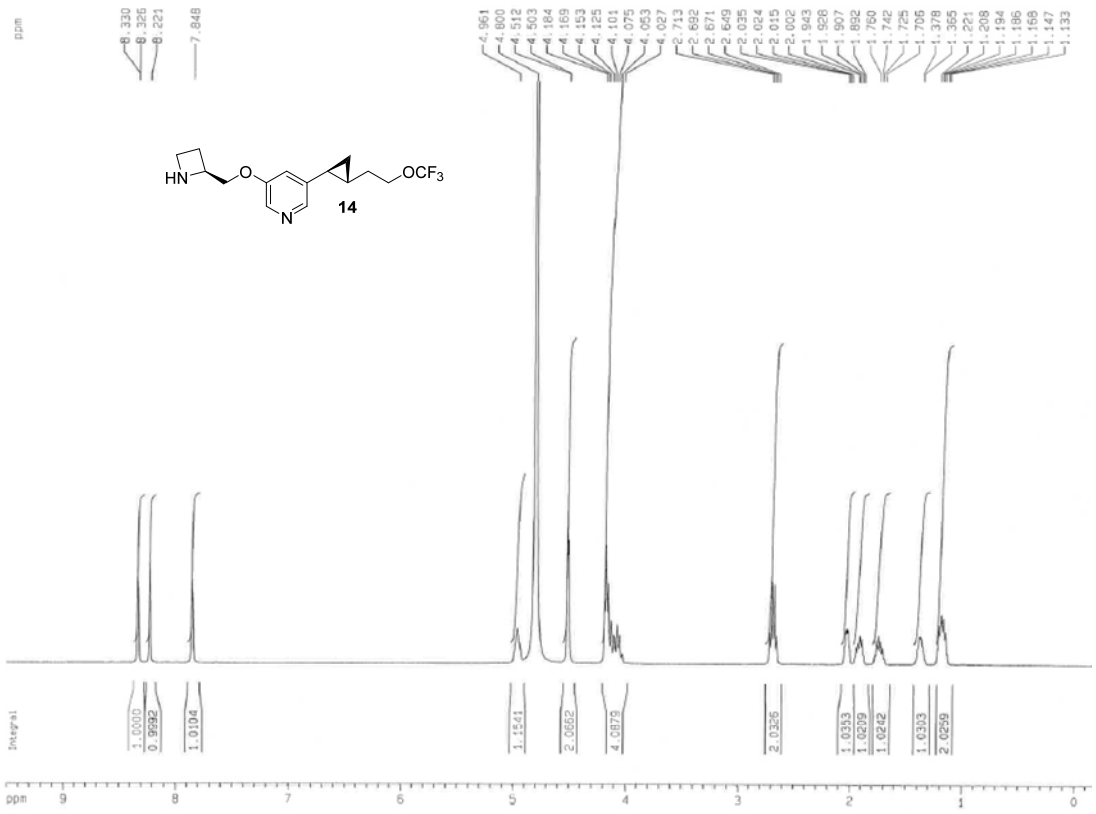
Area: 3.53964
0
5
10
15
20
25
min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4.075
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2.692
2.671
2.649
2.035
2.024
2.015
2.002
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1.892
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1.742
1.725
1.706
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1.168
1.147
1.133
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O
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1.0209
1.0242
1.0303
2.0259
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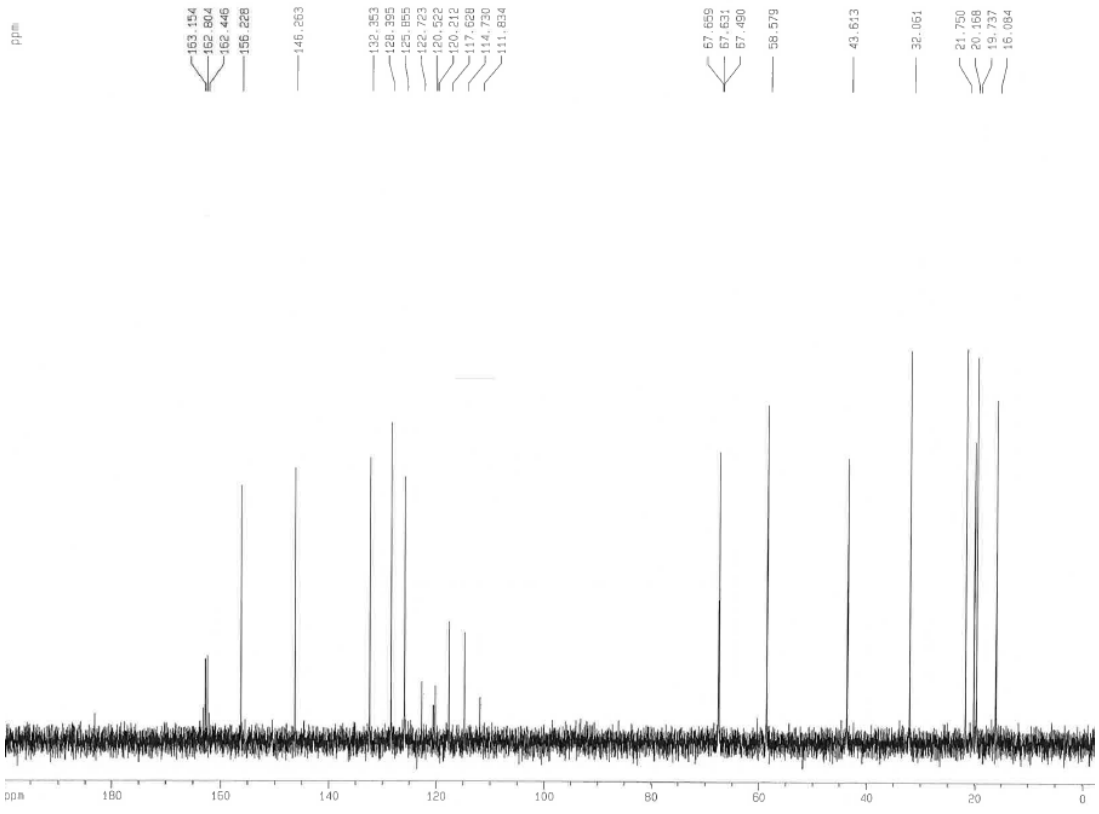
8
7
6
5
4
3
2
1
0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111.834
67.659
67.631
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16.084
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20
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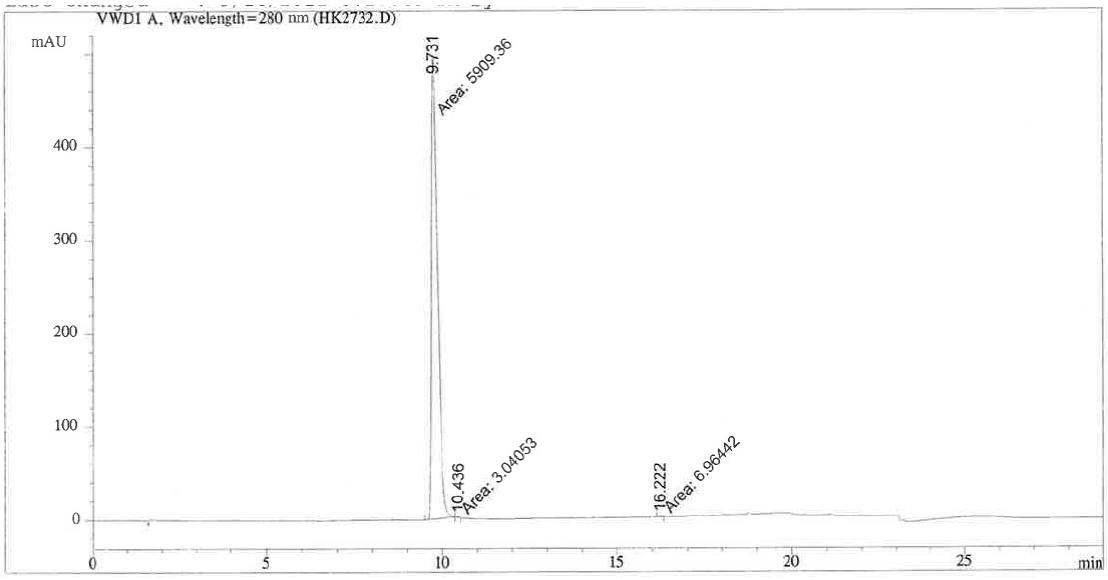
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Area: 6.96442
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0
0
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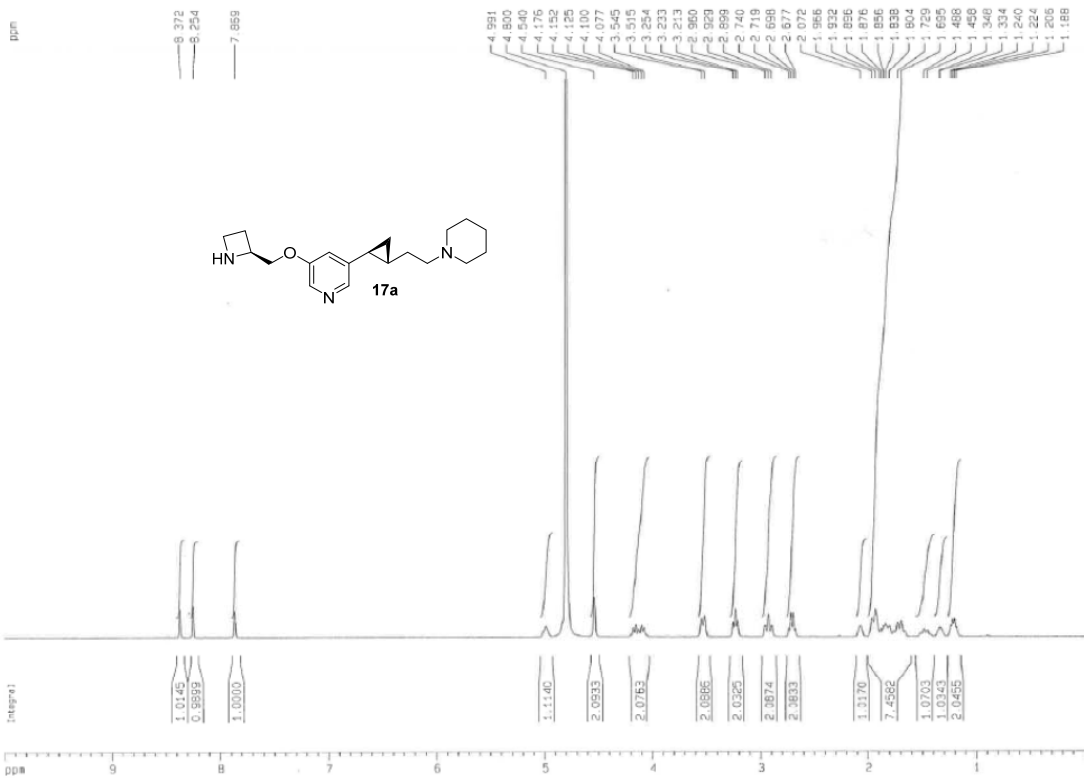
10
15
20
25
min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3.254
3.233
3.213
2.960
2.929
2.899
2.740
2.719
2.698
2.677
2.072
1.966
1.932
1.856
1.876
1.856
1.838
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1.729
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1.456
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1.334
1.240
1.224
1.206
1.188
HN
O
N
N
17a
Integral
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2.0886
2.0325
2.0874
2.0833
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1.0703
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2.0456
ppm
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8
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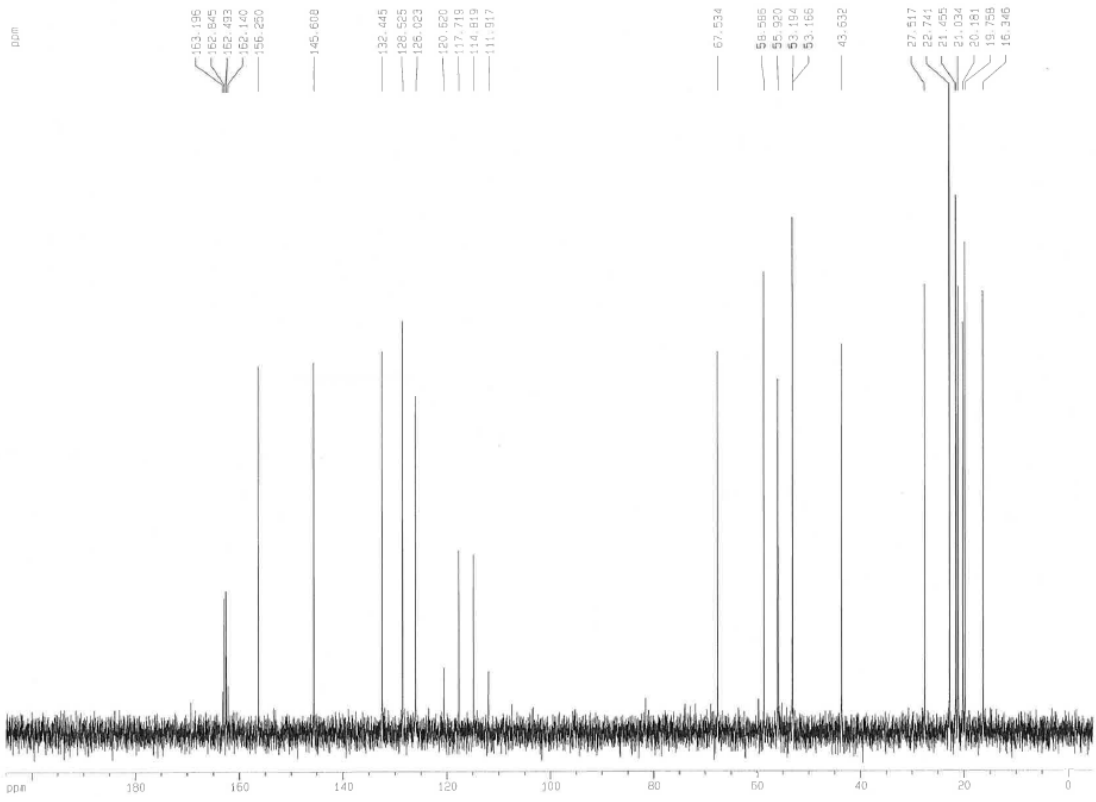
6
5
4
3
2
1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111.917
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58.566
55.920
53.194
53.166
43.632
27.517
22.741
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16.346
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60
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20
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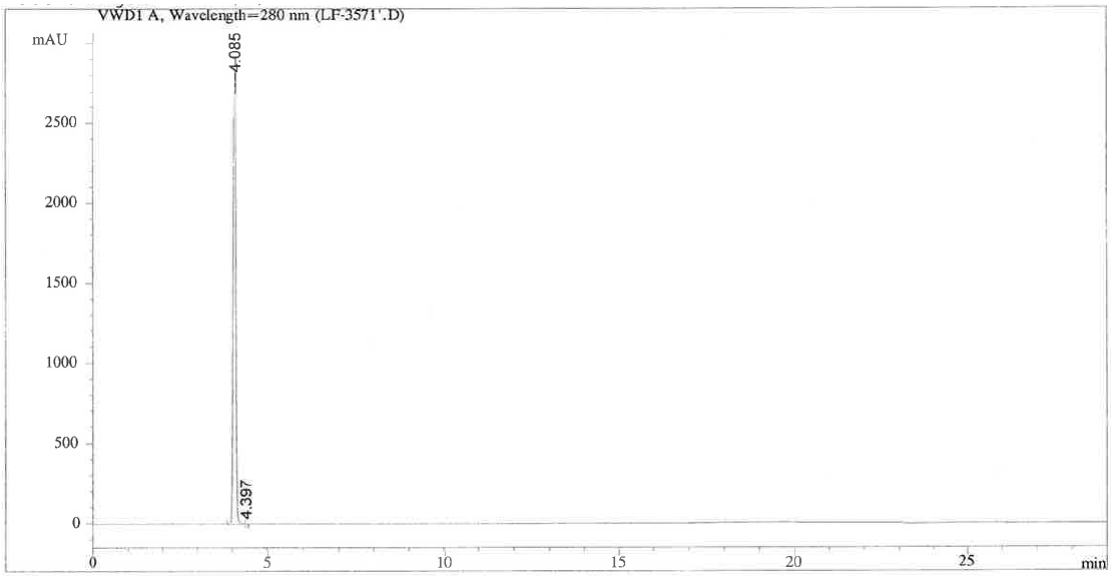
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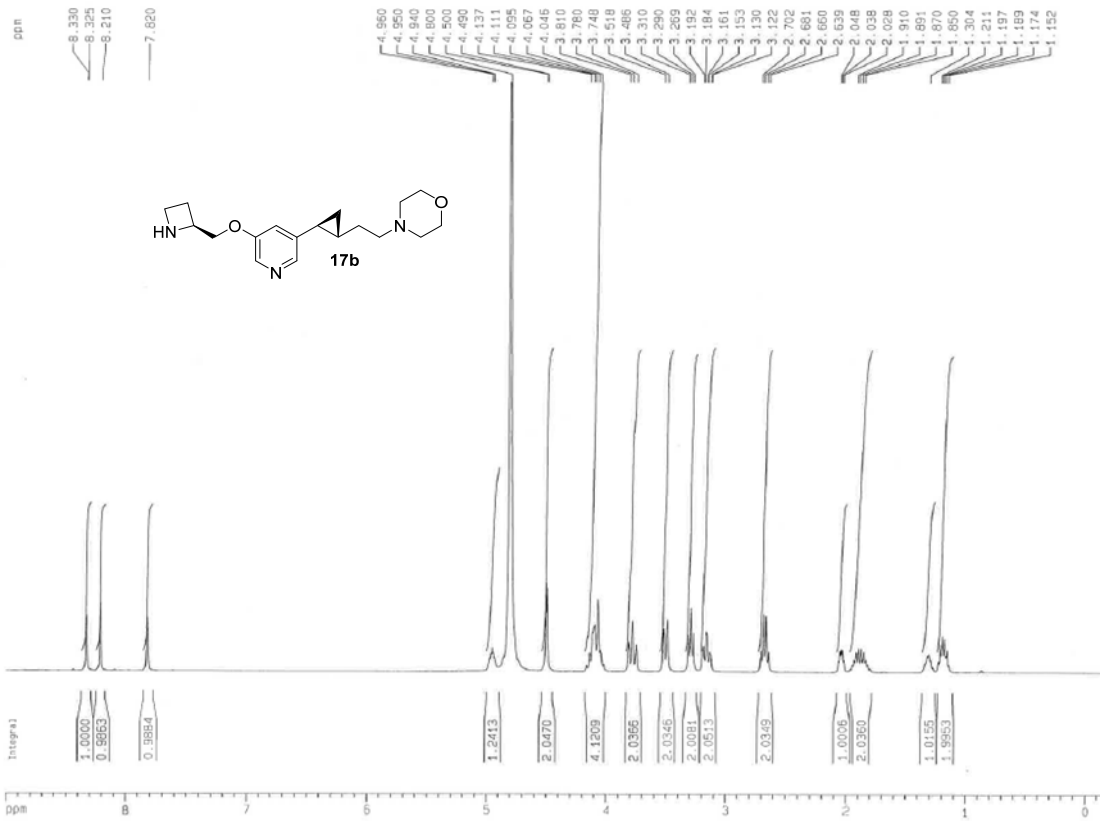
10
15
20
25
min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3.780
3.748
3.518
3.486
3.310
3.290
3.269
3.192
3.184
3.161
3.153
3.130
3.122
2.702
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2.660
2.639
2.048
2.038
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1.891
1.870
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1.197
1.189
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1.152
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N
O
N
17b
Integral
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0.9884
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2.0365
2.0346
2.0081
2.0513
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2.0360
1.0155
1.9953
ppm
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7
6
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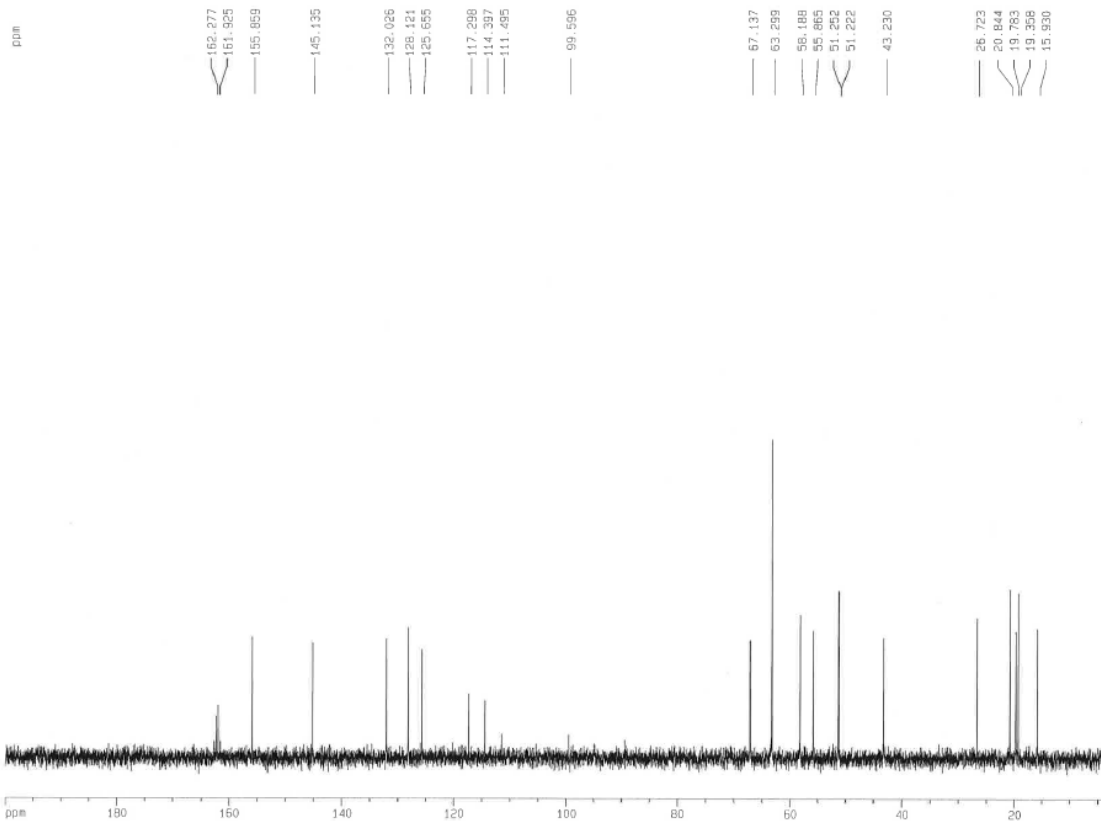
4
3
2
1
0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58.188
55.865
51.252
51.222
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120
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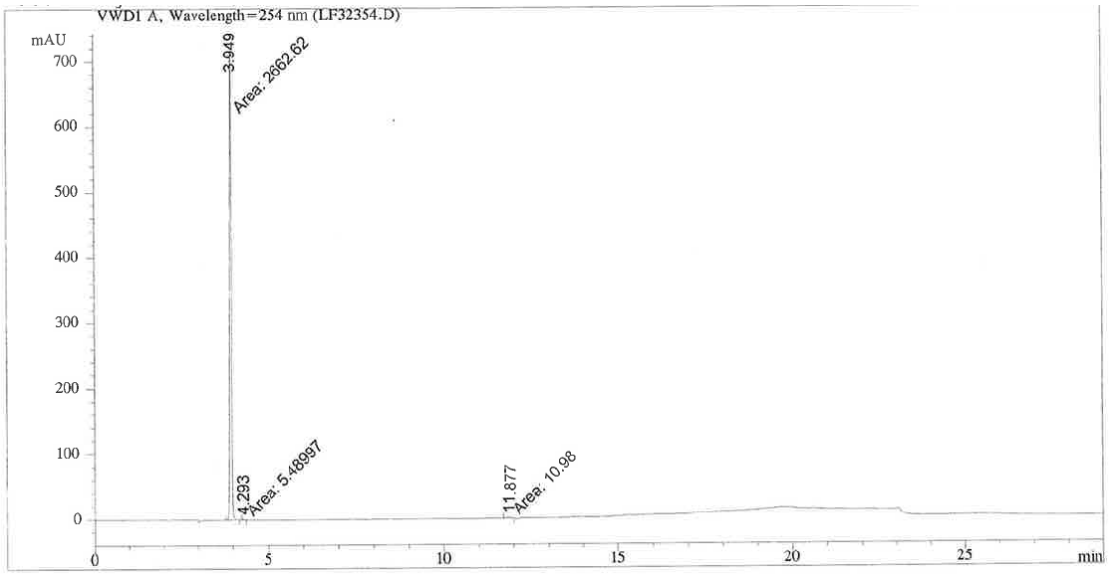
80
60
40
20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600
500
400
300
200
100
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4.293
Area: 5.48997
11.877
Area: 10.98
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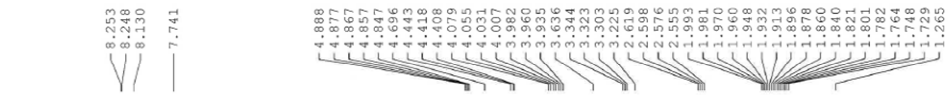
5
10
15
20
25
min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4.418
4.408
4.079
4.055
4.031
4.007
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3.960
3.935
3.636
3.344
3.323
3.303
3.225
2.619
2.598
2.576
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1.981
1.970
1.960
1.948
1.932
1.913
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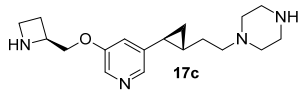
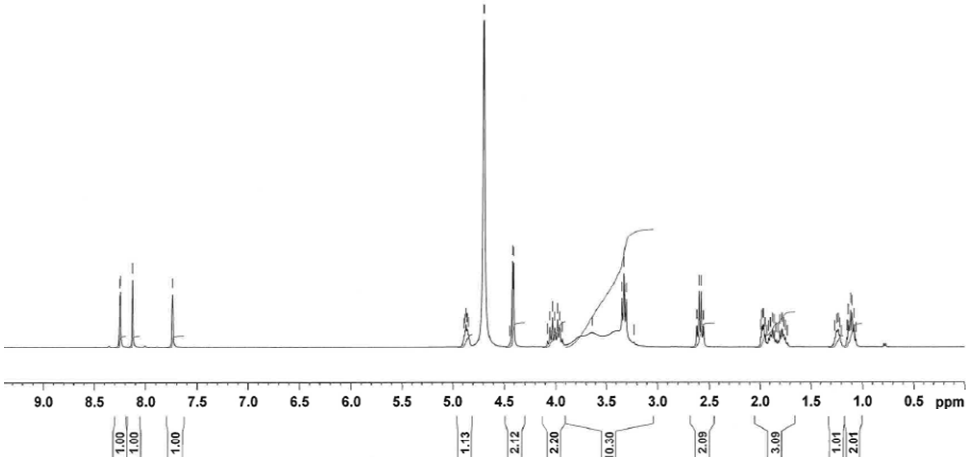
1.764
1.748
1.729
1.265


HN
O
N
NH
N

17c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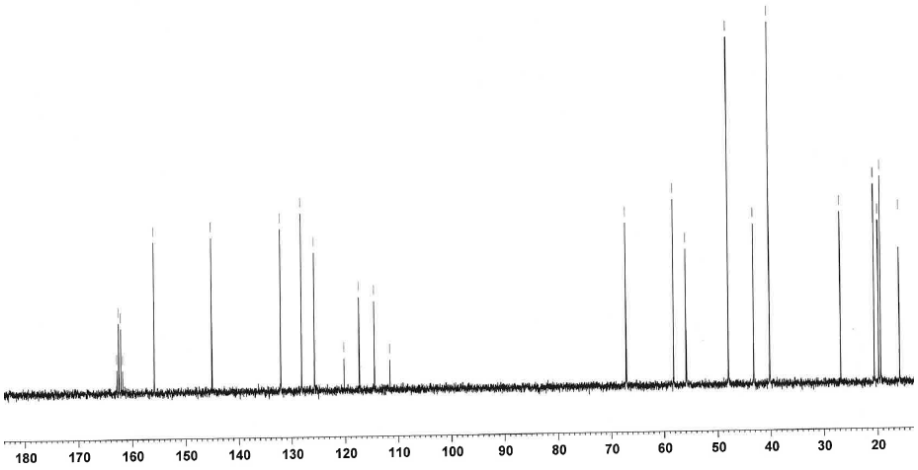
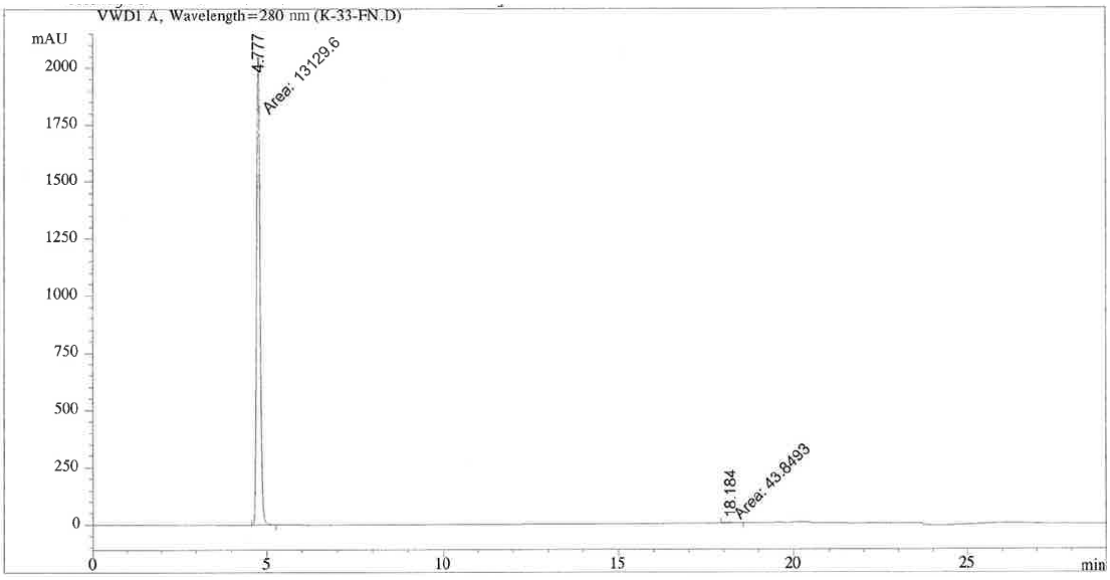
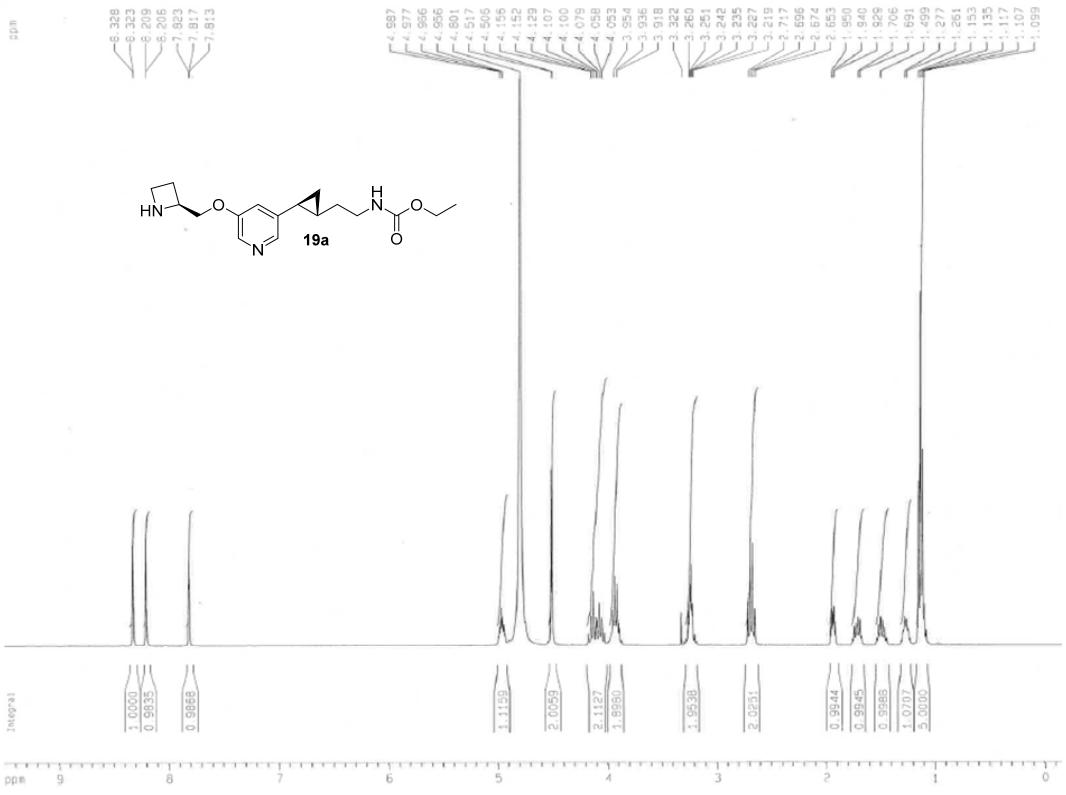
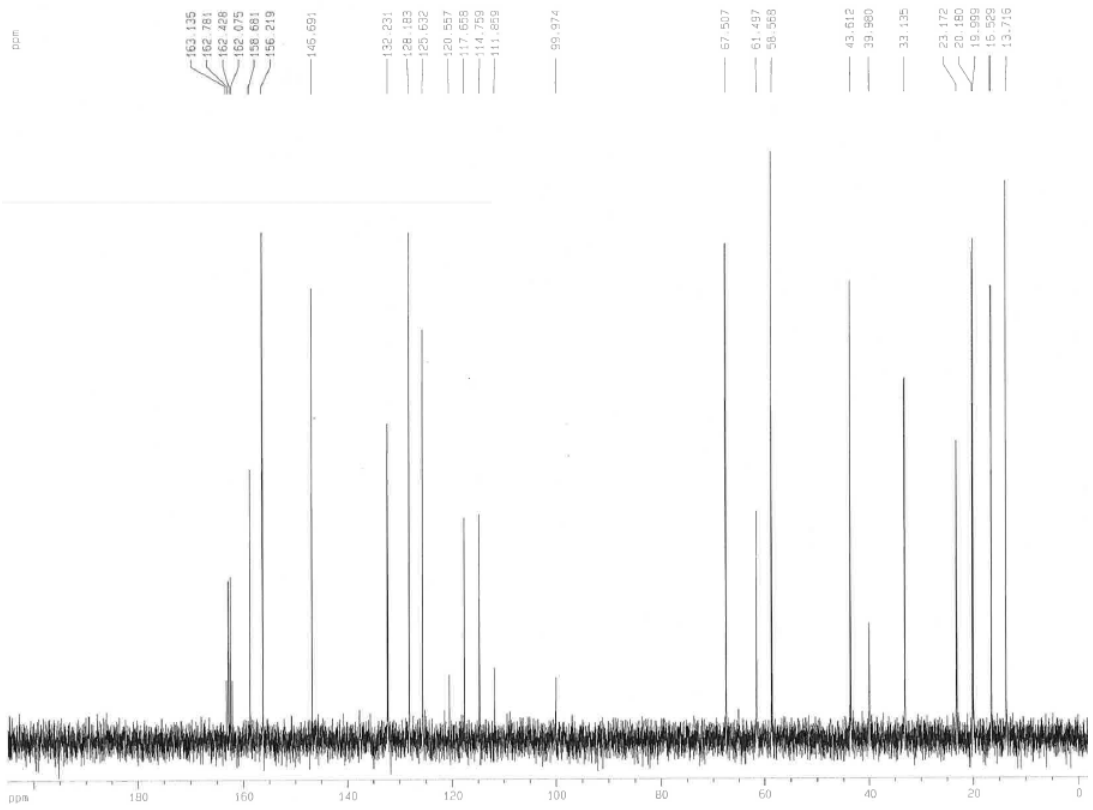
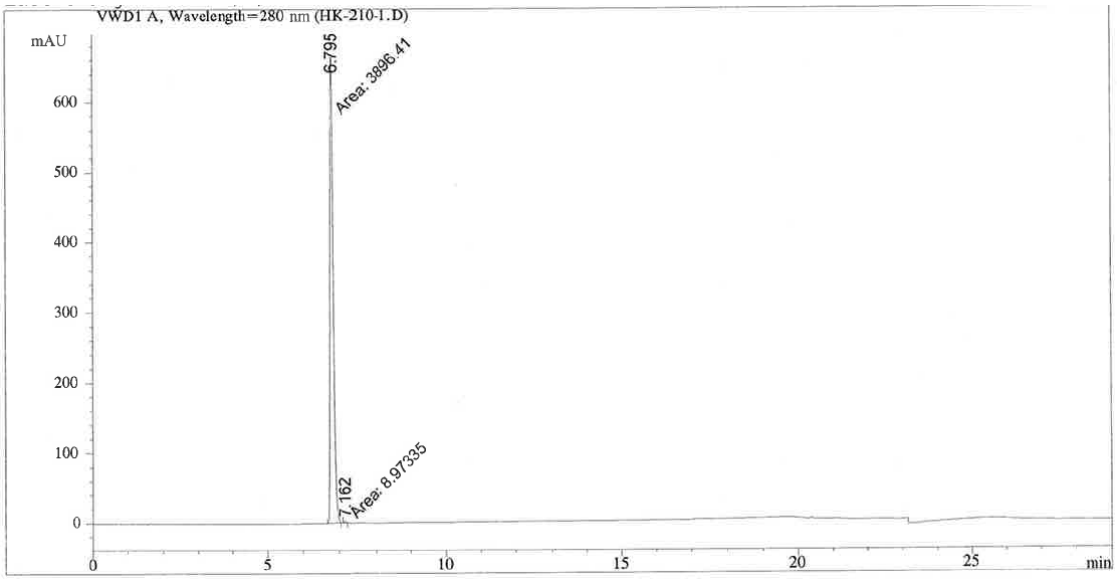
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.00
1.00
1.13
2.12
2.20
0.30
2.09
3.09
1.01
2.01

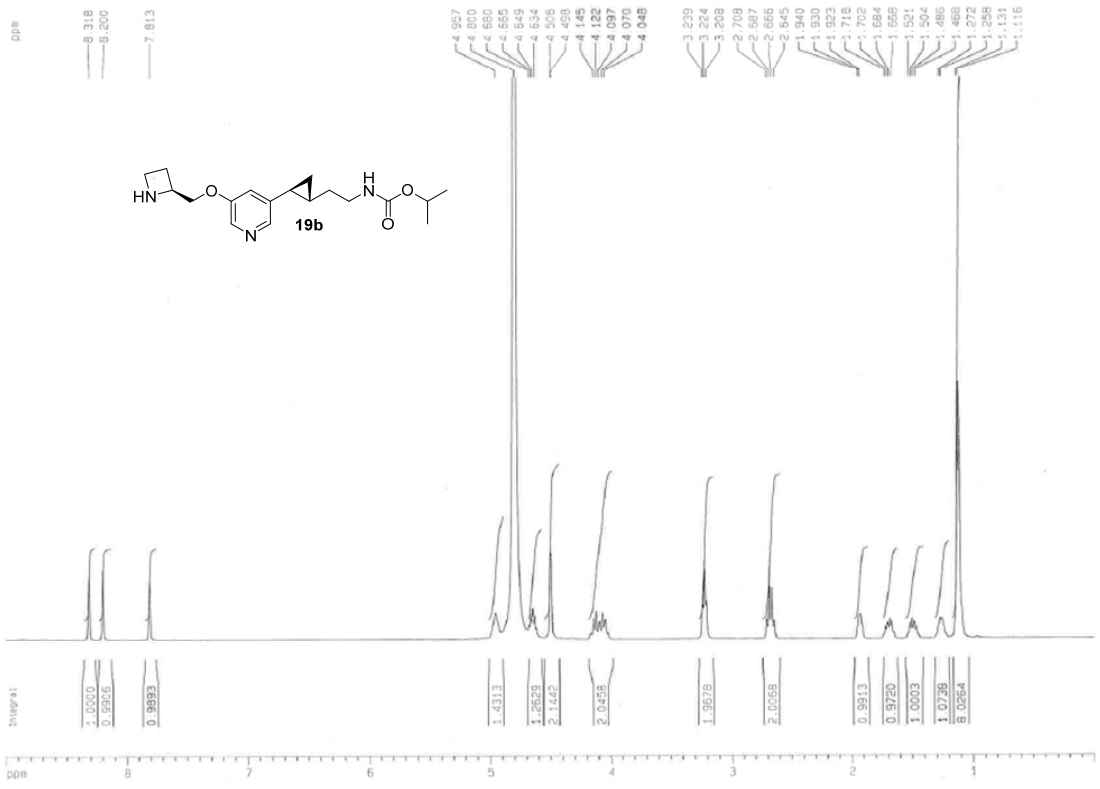

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

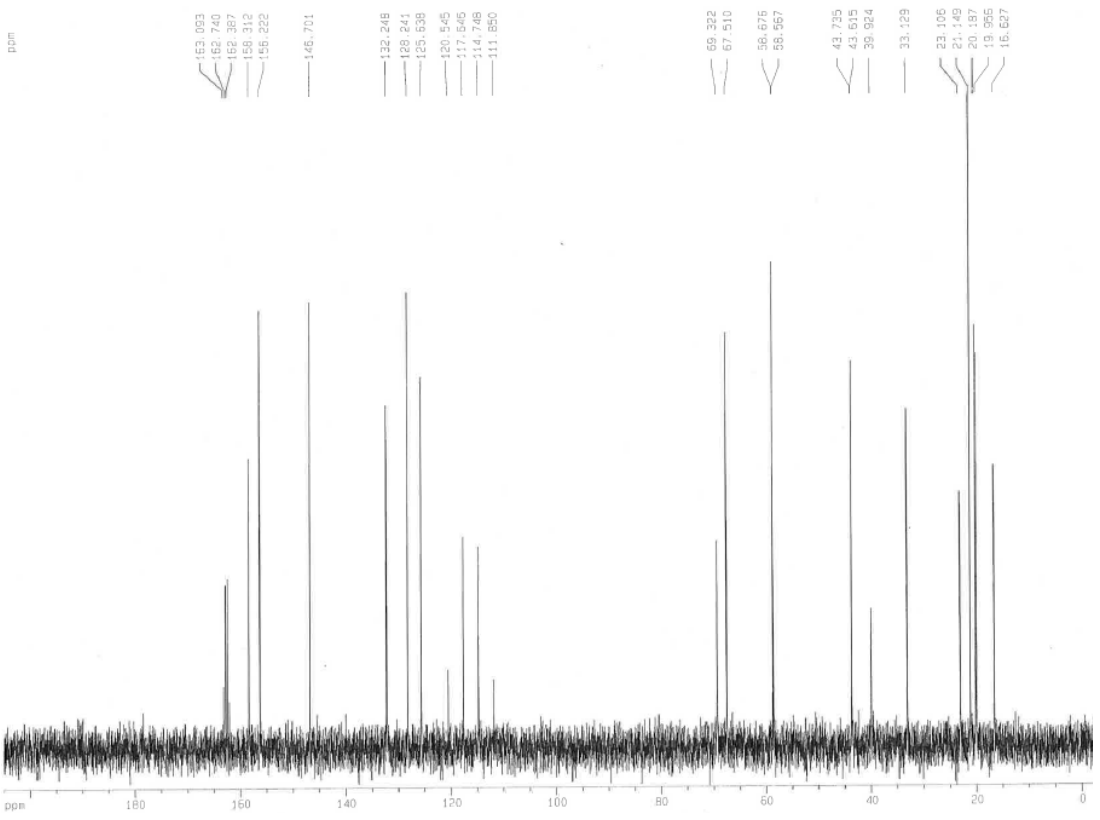

VWD1 A, Wavelength=280 nm (K-33-FN.D)
mAU
4.777
Area: 13129.6
18.184
Area: 43.8493
min

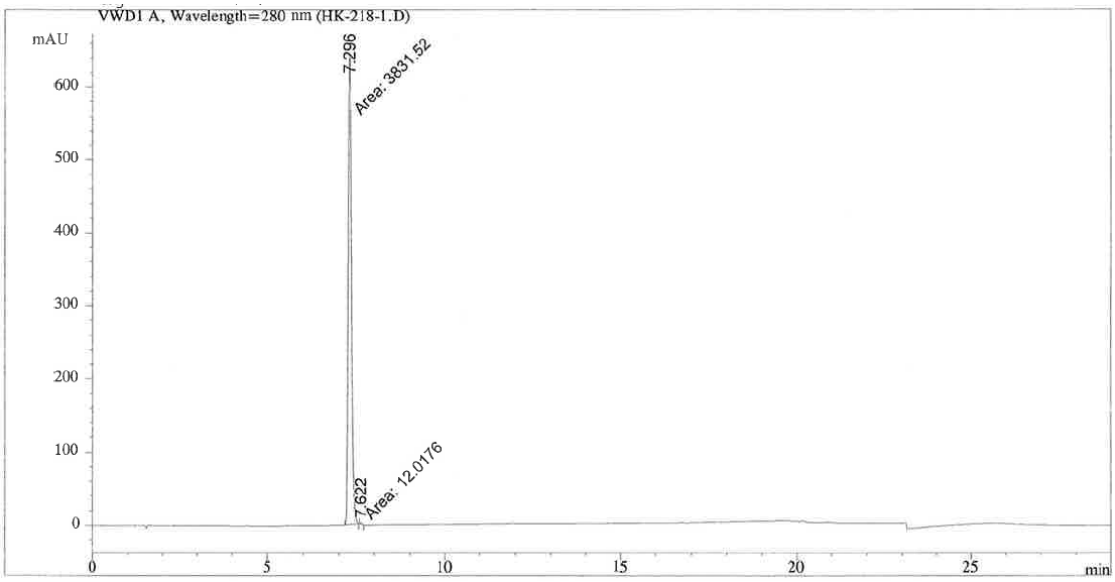

19a
ppm
Integral

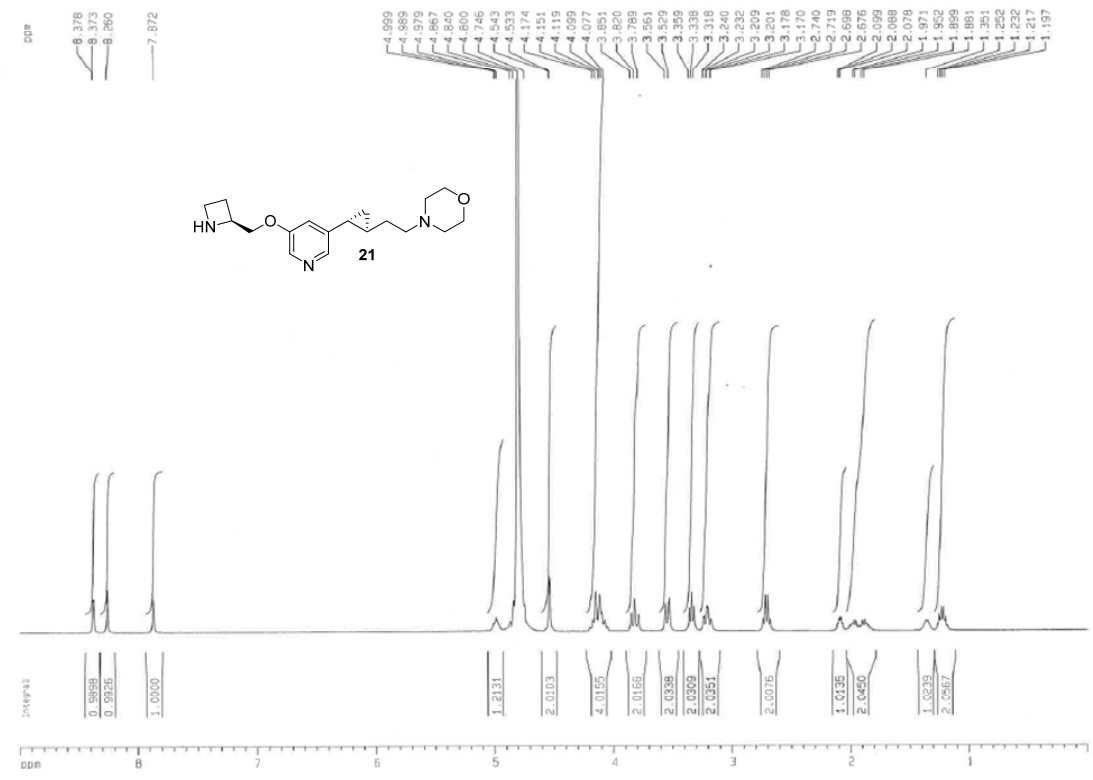

ppm
163.135
162.781
162.428
162.075
158.681
156.219
145.691
132.231
128.183
125.632
120.557
117.658
114.759
111.859
99.974
67.507
61.497
58.568
43.612
39.980
33.135
23.172
20.180
19.999
15.529
13.716
ppm
180
160
140
120
100
80
60
40
20
0

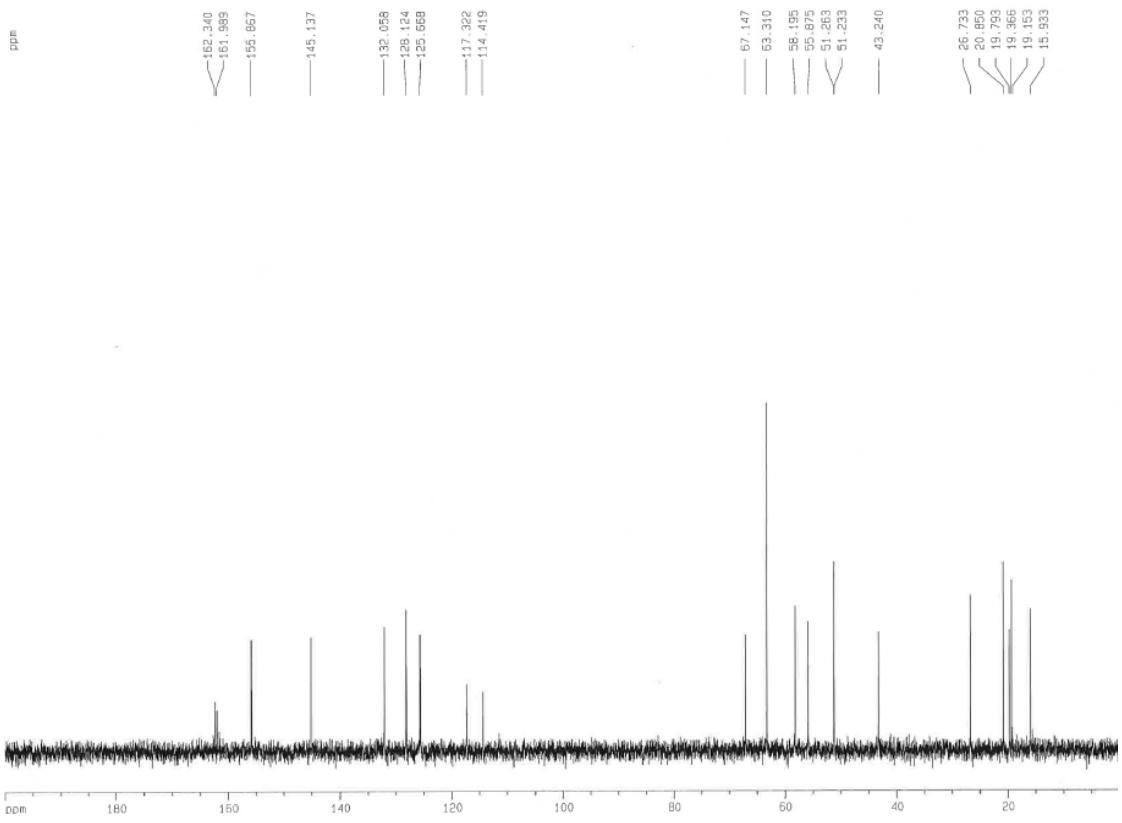

VWD1 A, Wavelength=280 nm (HK-210-1.D)
mAU
600
500
400
300
200
100
0
6.795
Area: 3896.41
7.162
Area: 8.97335
0
5
10
15
20
25
min

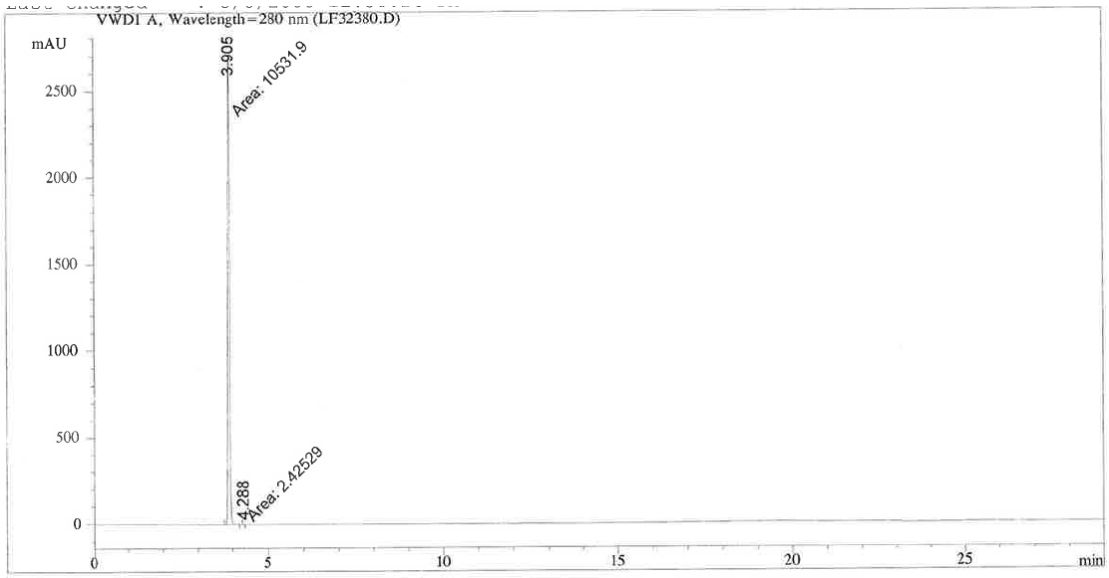

19b

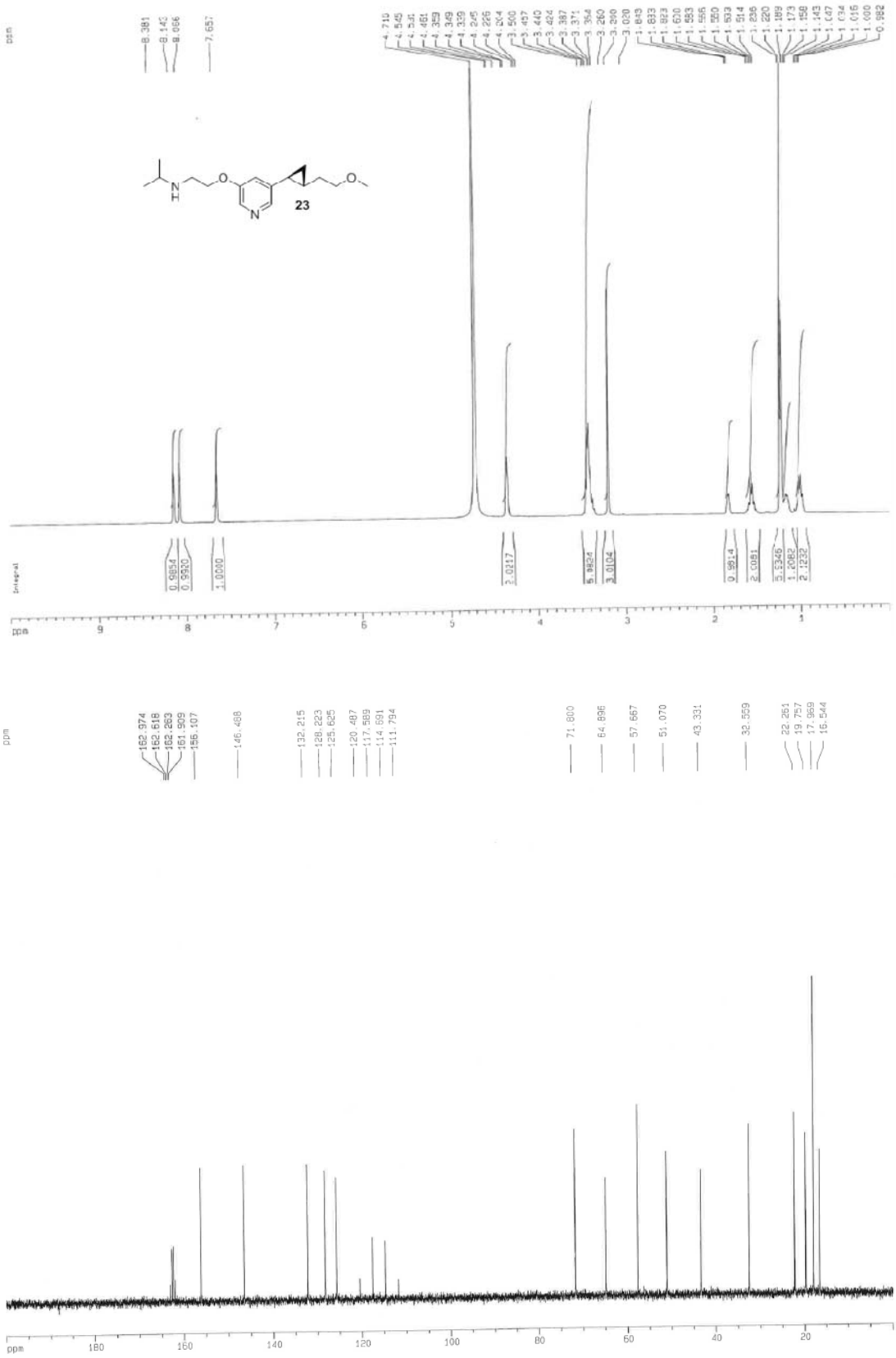


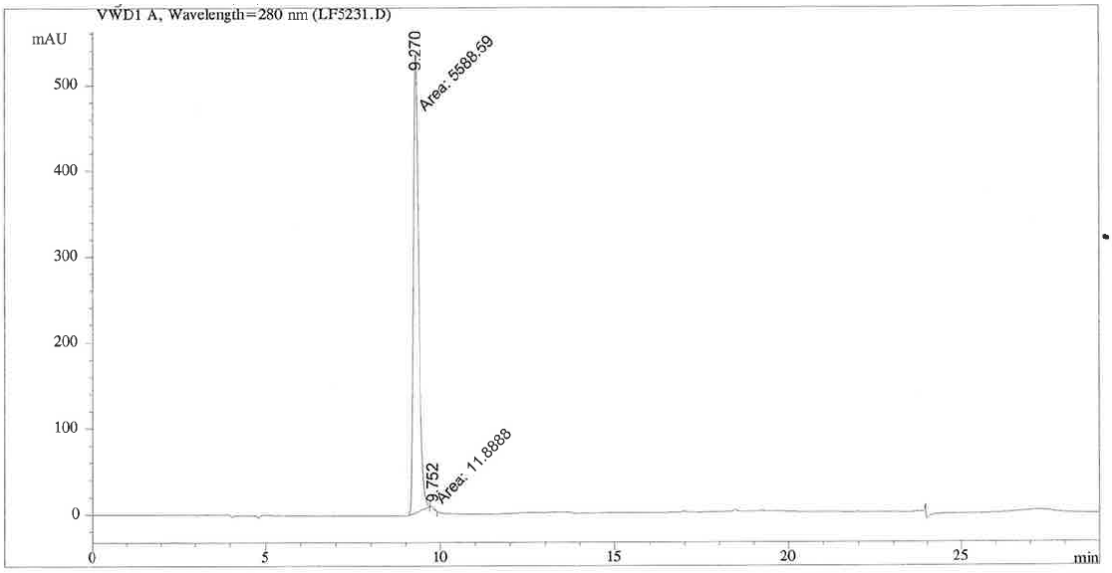

VWD1 A, Wavelength=280 nm (HK-218-1.D)
mAU
600
500
400
300
200
100
0
7.296
Area: 3831.52
7.622
Area: 12.0176
0
5
10
15
20
25
min

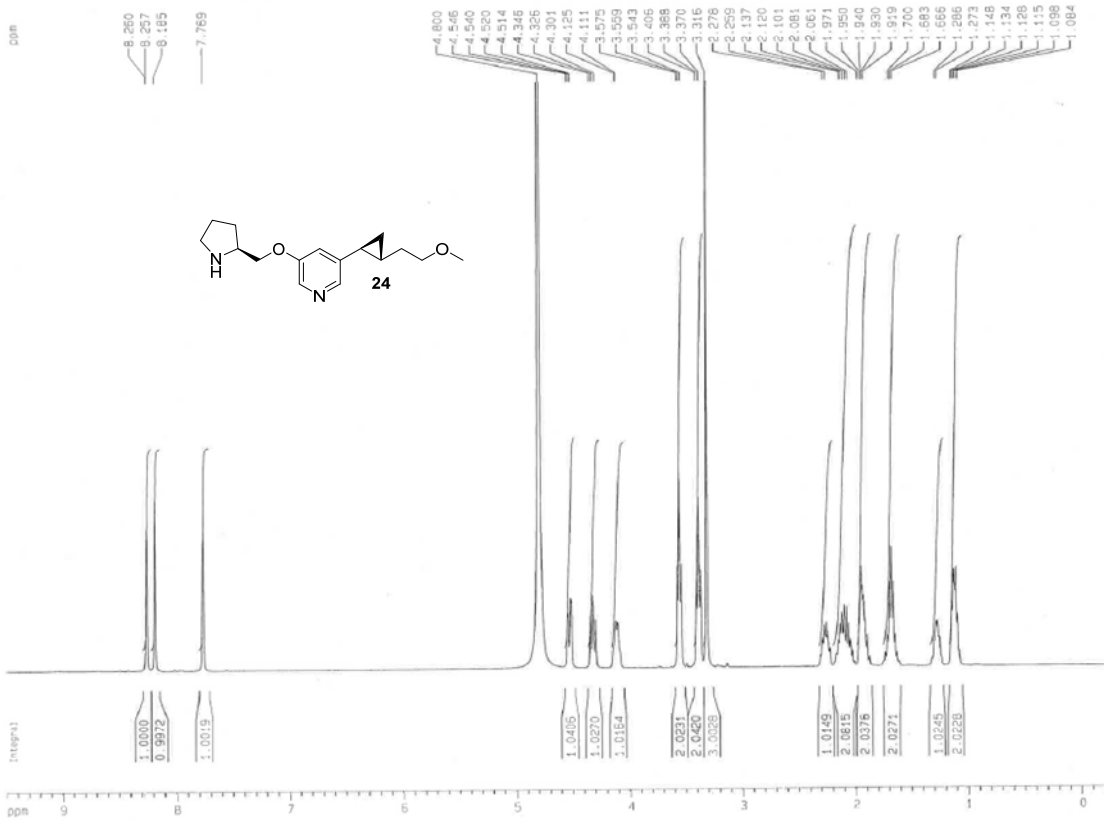

HN
O
O
N
N
21
ppm
8.378
8.373
8.260
7.872
4.999
4.989
4.979
4.867
4.840
4.800
4.746
4.643
4.533
4.174
4.151
4.119
4.099
4.077
3.851
3.820
3.789
3.561
3.529
3.359
3.338
3.318
3.240
3.232
3.209
3.201
3.178
3.170
2.740
2.719
2.698
2.676
2.099
2.089
2.078
1.971
1.952
1.899
1.881
1.351
1.252
1.232
1.217
1.197
Integral
0.5898
0.9926
1.0000
1.2131
2.0103
4.0155
2.0166
2.0338
2.0909
2.0951
2.0076
1.0135
2.0450
1.0039
2.0567
ppm
8
7
6
5
4
3
2
1

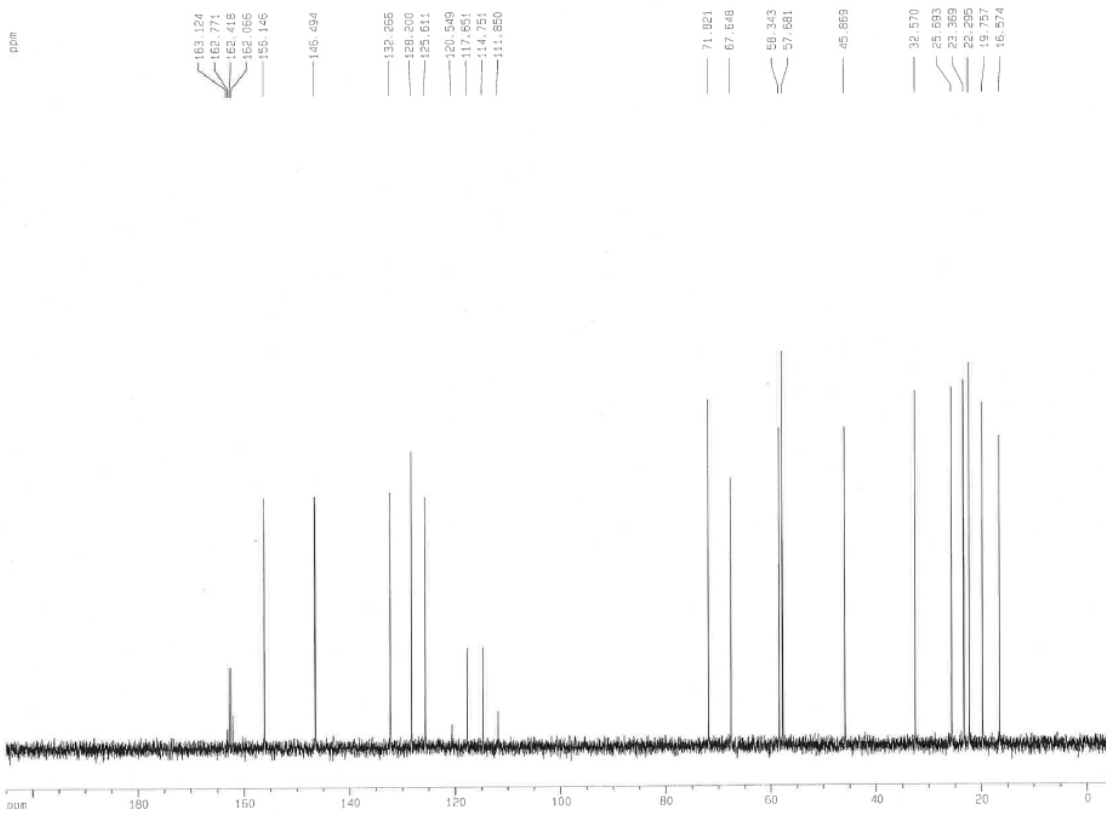

ppm
162.340
161.989
155.867
145.137
132.058
126.124
125.668
117.322
114.419
67.147
63.310
58.195
55.875
51.263
51.233
43.240
26.733
20.850
19.793
19.366
19.153
15.933
ppm
180
160
140
120
100
80
60
40
20

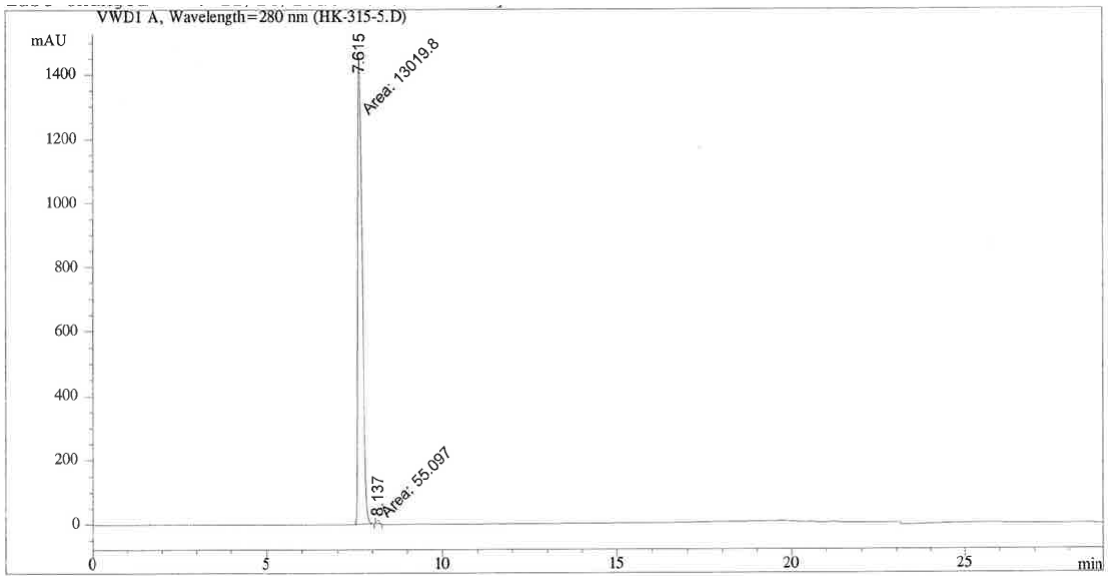

VWD1 A, Wavelength=280 nm (LF32380.D)
mAU
2500
2000
1500
1000
500
0
3.905
Area: 10531.9
4.288
Area: 2.42529
0
5
10
15
20
25
min

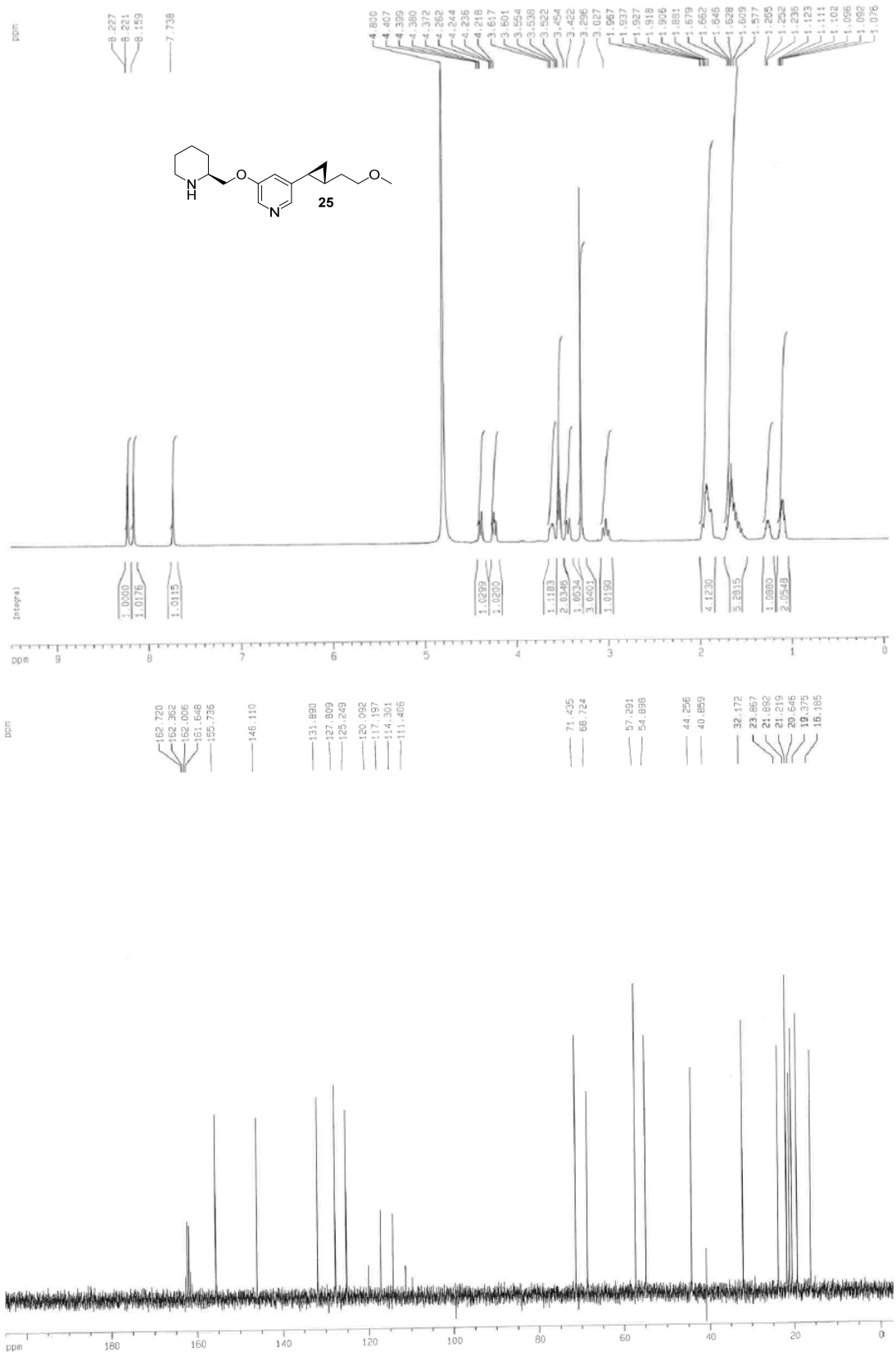

23

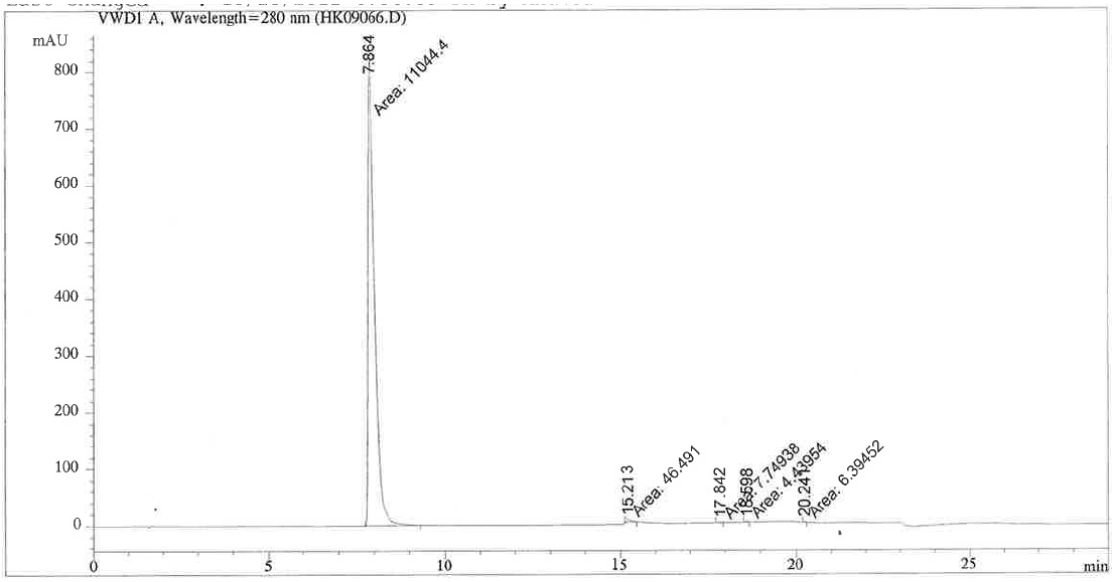

VWD1 A, Wavelength=280 nm (LF5231.D)
mAU
500
400
300
200
100
0
9.270
Area: 5588.59
9.752
Area: 11.8888
0
5
10
15
20
25
min

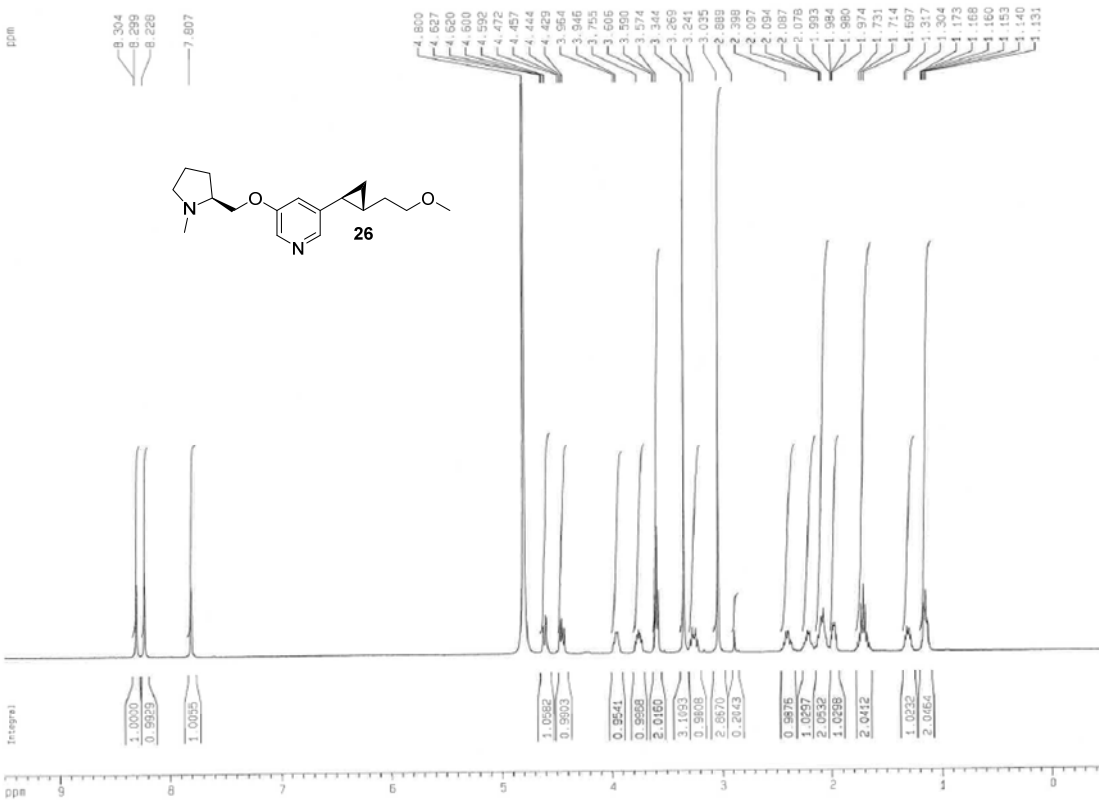

ppm
8.260
8.257
8.185
7.769
4.800
4.546
4.540
4.520
4.514
4.346
4.326
4.301
4.125
4.111
3.575
3.559
3.543
3.406
3.388
3.370
3.316
2.276
2.259
2.137
2.120
2.101
2.081
2.061
1.971
1.950
1.940
1.930
1.919
1.700
1.683
1.666
1.286
1.273
1.148
1.134
1.128
1.115
1.098
1.084
N
H
O
N
O
24
Integral
1.0000
0.9972
1.0019
1.0496
1.0270
1.0164
2.0231
2.0420
3.0028
1.0149
2.0615
2.0376
2.0271
1.0245
2.0228
ppm
9
8
7
6
5
4
3
2
1
0

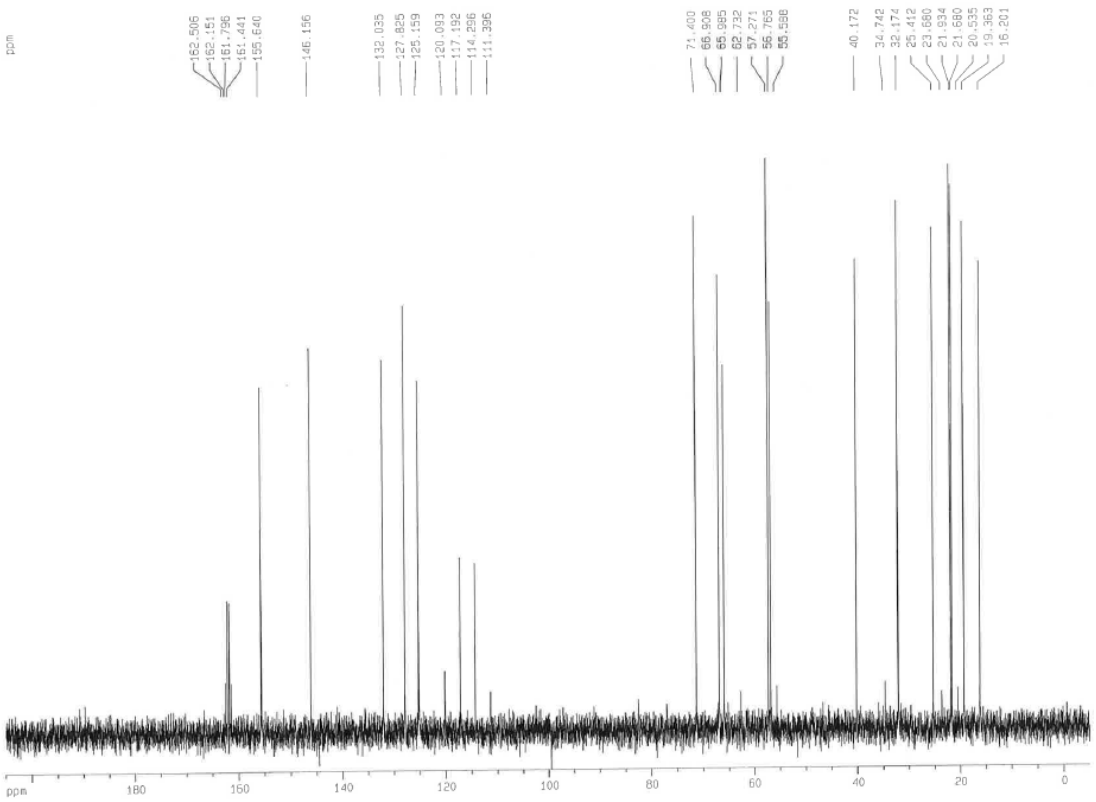

ppm
163.124
162.771
162.418
162.066
156.146
146.494
130.266
128.200
125.611
120.549
117.651
114.751
111.850
71.921
67.648
58.343
57.681
45.869
32.570
25.693
23.369
22.295
19.757
16.574
ppm
180
160
140
120
100
80
60
40
20
0

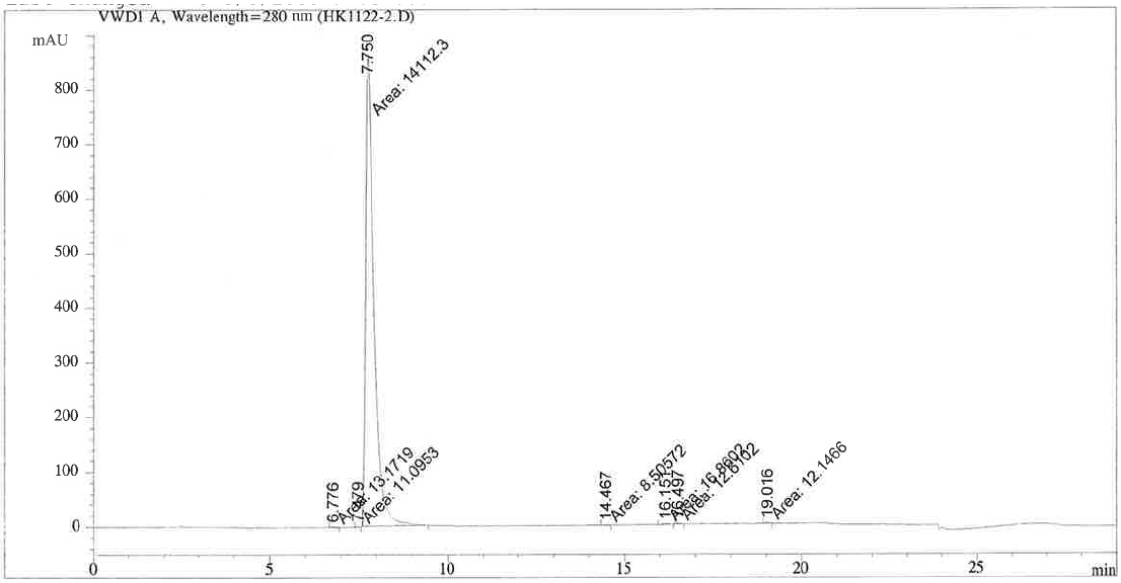

VWD1 A, Wavelength=280 nm (HK-315-5.D)
mAU
1400
1200
1000
800
600
400
200
0
7.615
Area: 13019.8
8.137
Area: 55.097
0
5
10
15
20
25
min

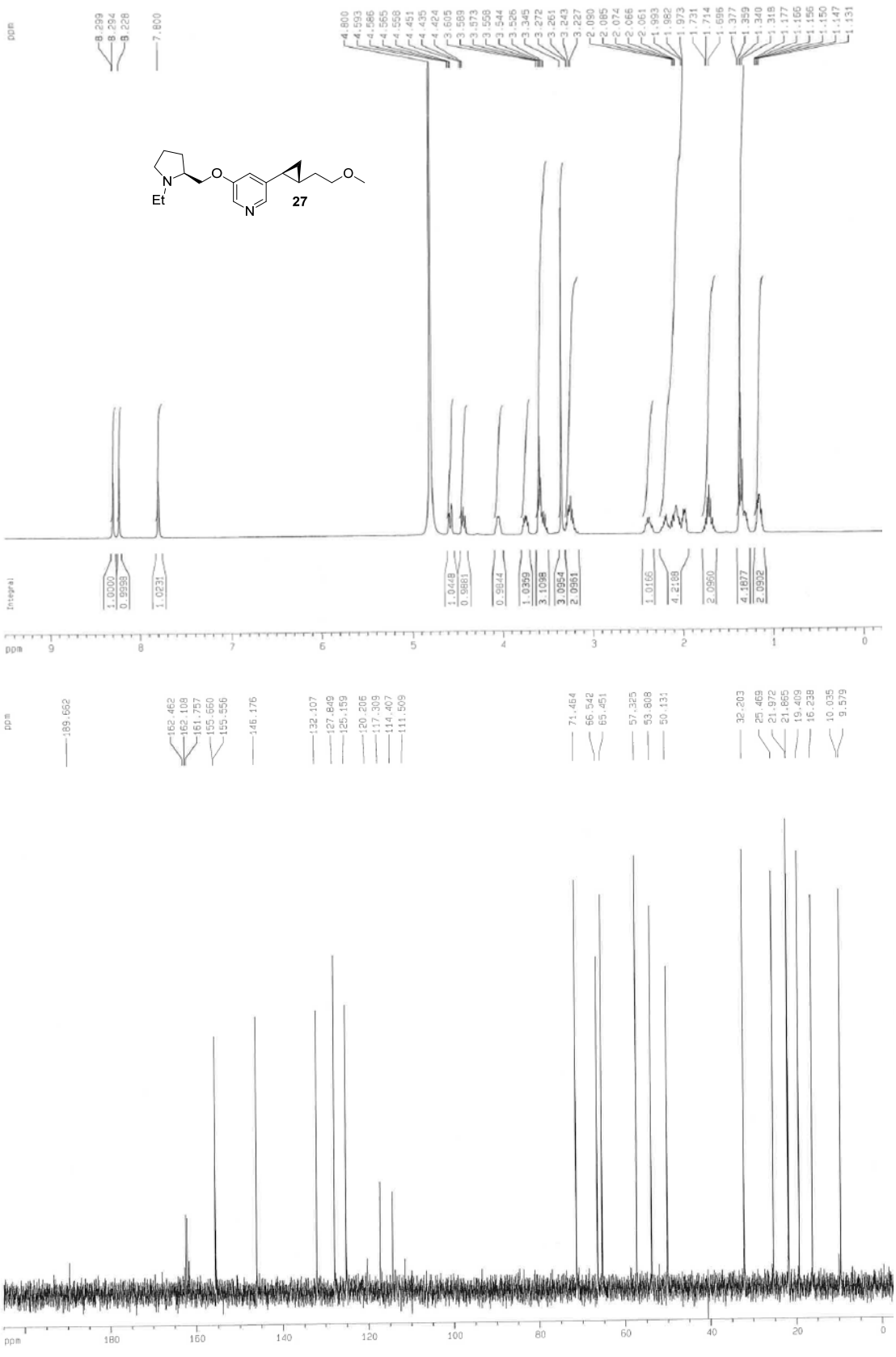

25

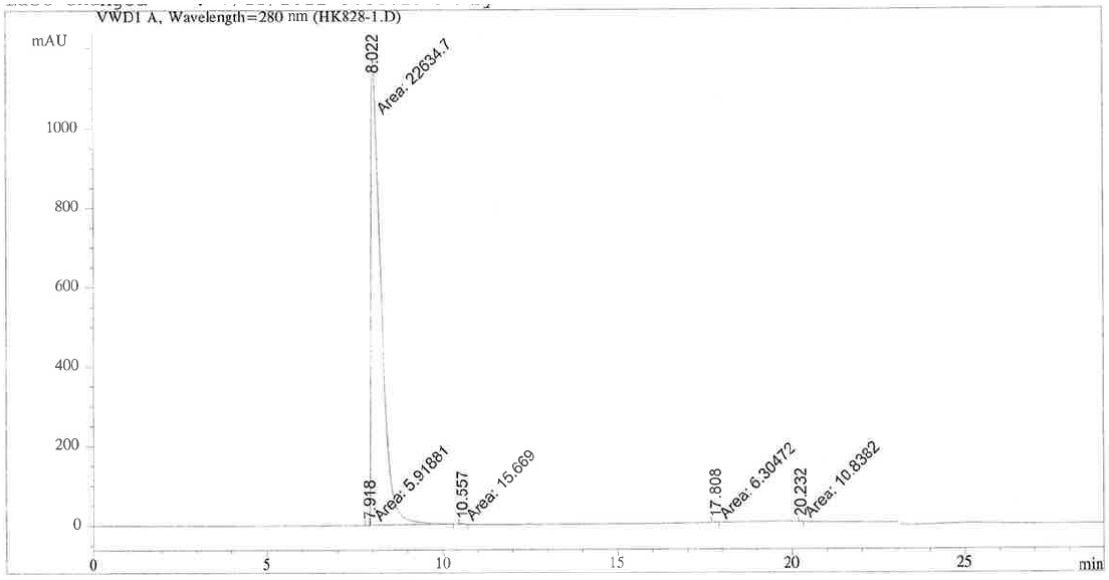

VWDI A, Wavelength=280 nm (HK09066.D)
mAU
7.864
Area: 11044.4
15.213
Area: 46.491
17.842
Area: 74938
Area: 4.43954
20.243
Area: 6.39452
min

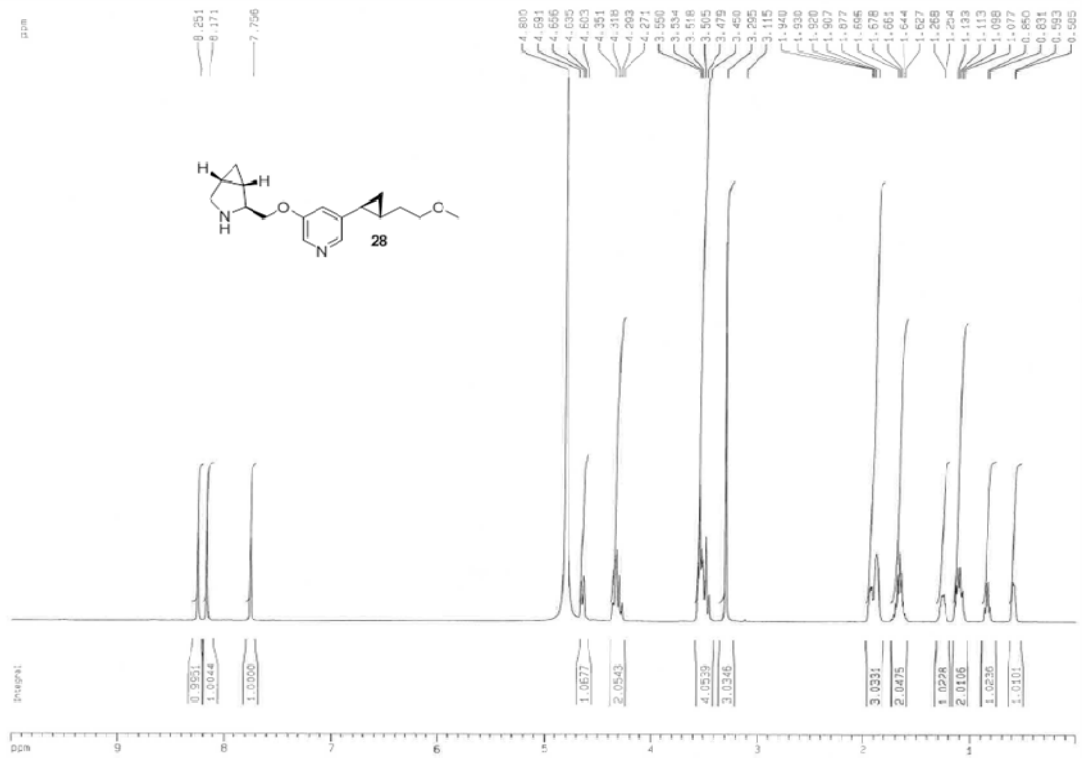

ppm
26

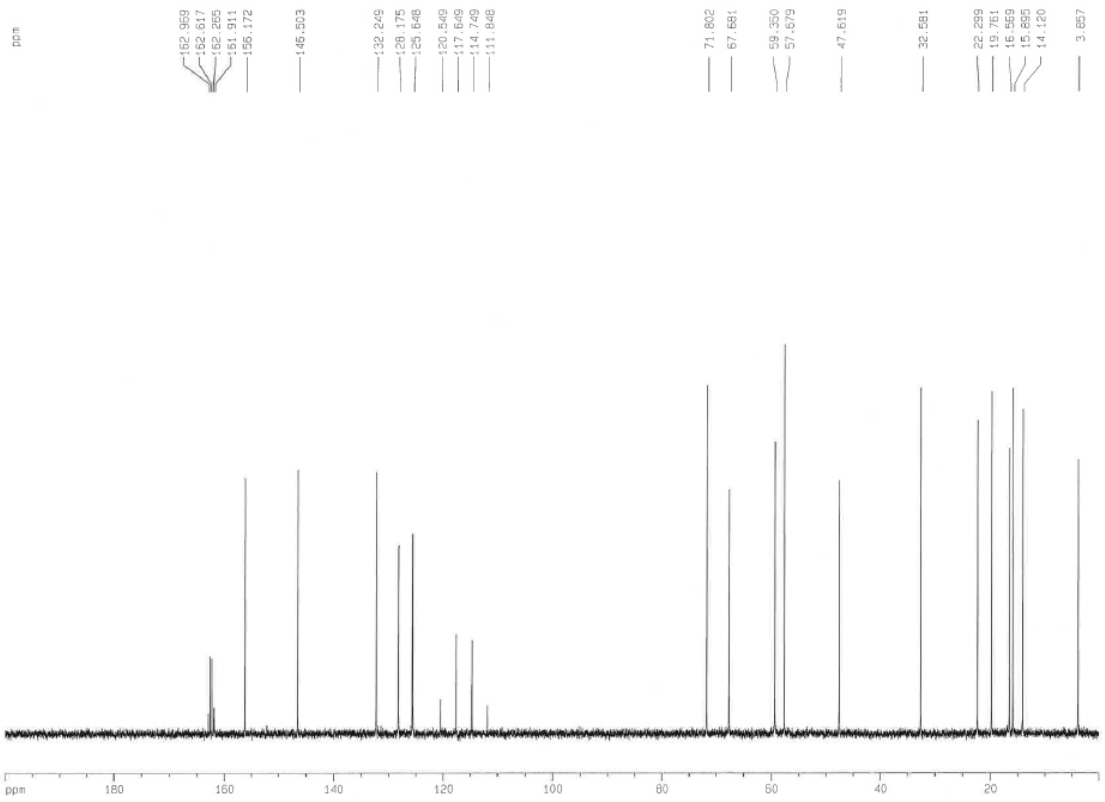

ppm
162.506
162.151
161.796
161.441
155.640
146.156
132.035
127.825
125.159
120.093
117.192
114.256
111.396
71.400
66.908
65.985
62.732
57.271
56.765
55.598
40.172
34.742
32.174
25.412
23.660
21.934
21.680
20.535
19.363
16.201
ppm
180
160
140
120
100
80
60
40
20
0

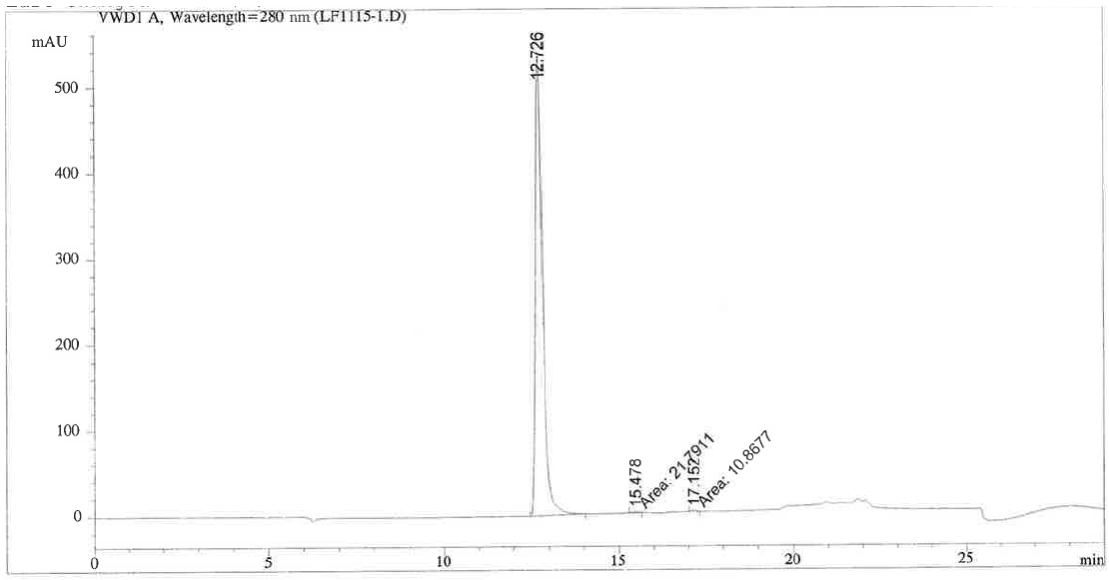

VWD1 A, Wavelength=280 nm (HK1122-2.D)
mAU
800
700
600
500
400
300
200
100
0
7.750
Area: 14112.3
6.776
13.1719
Area: 11.0953
14.467
Area: 8.50572
19.016
Area: 12.1466
0
5
10
15
20
25
min

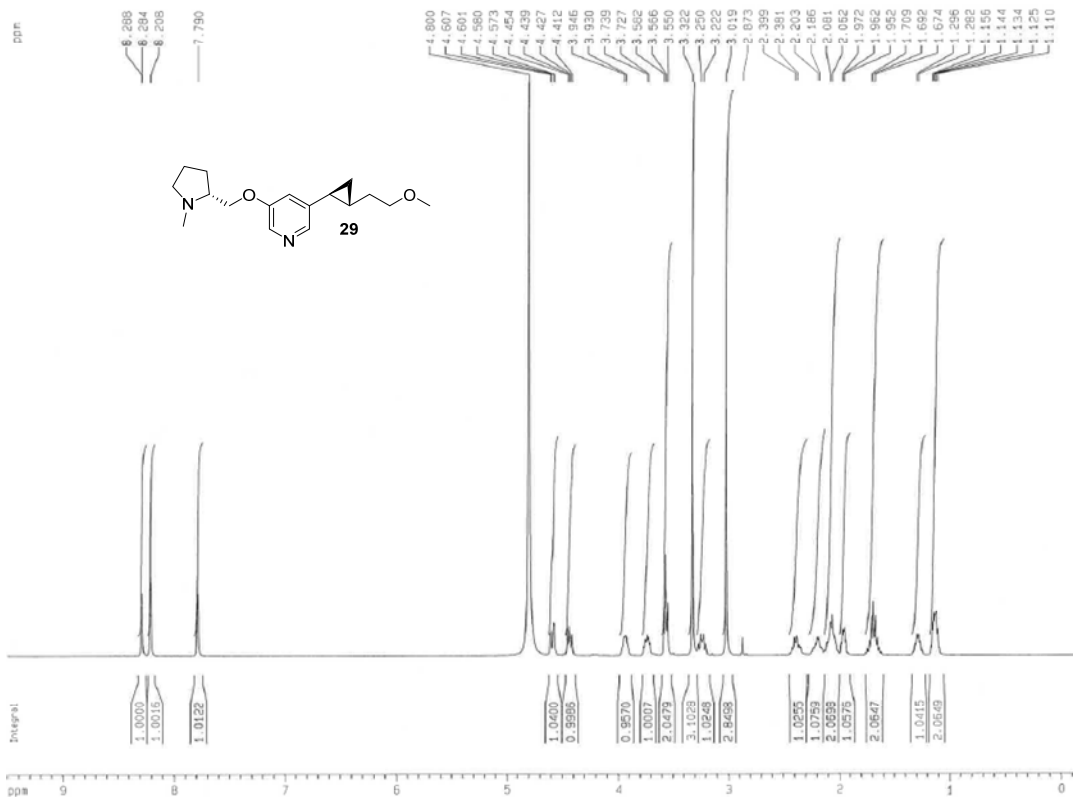

8.299
8.294
8.228
7.800
4.800
4.593
4.586
4.565
4.558
4.451
4.435
4.424
3.605
3.569
3.573
3.558
3.544
3.526
3.345
3.272
3.261
3.243
3.227
2.090
2.085
2.074
2.066
2.061
1.993
1.982
1.973
1.731
1.714
1.696
1.377
1.359
1.340
1.318
1.177
1.166
1.156
1.150
1.147
1.131
Et
N
O
O
N
27
Integral
1.0000
0.9998
1.0231
1.0448
0.9861
0.9844
1.0399
3.1098
3.0954
2.0961
1.0166
4.2188
2.0960
4.1677
2.0902
ppm
189.662
162.462
162.108
161.757
155.660
155.556
146.176
132.107
127.849
125.159
120.206
117.309
114.407
111.509
71.464
66.542
65.451
57.325
53.808
50.131
32.203
25.469
21.972
21.665
19.409
16.238
10.035
9.579

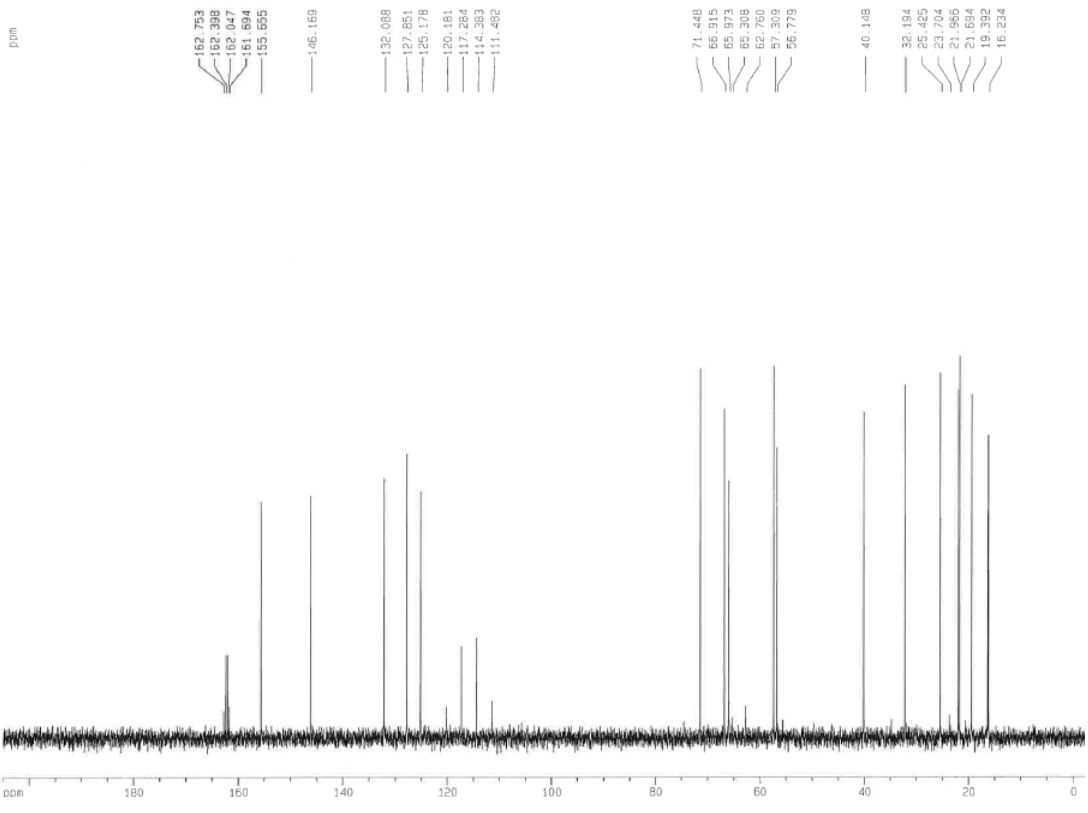

VWD1 A, Wavelength=280 nm (HK828-1.D)
mAU
1000
800
600
400
200
0
8.022
Area: 22634.7
7.918
Area: 5.91881
10.557
Area: 15.669
17.808
Area: 6.30472
20.232
Area: 10.8382
0
5
10
15
20
25
min

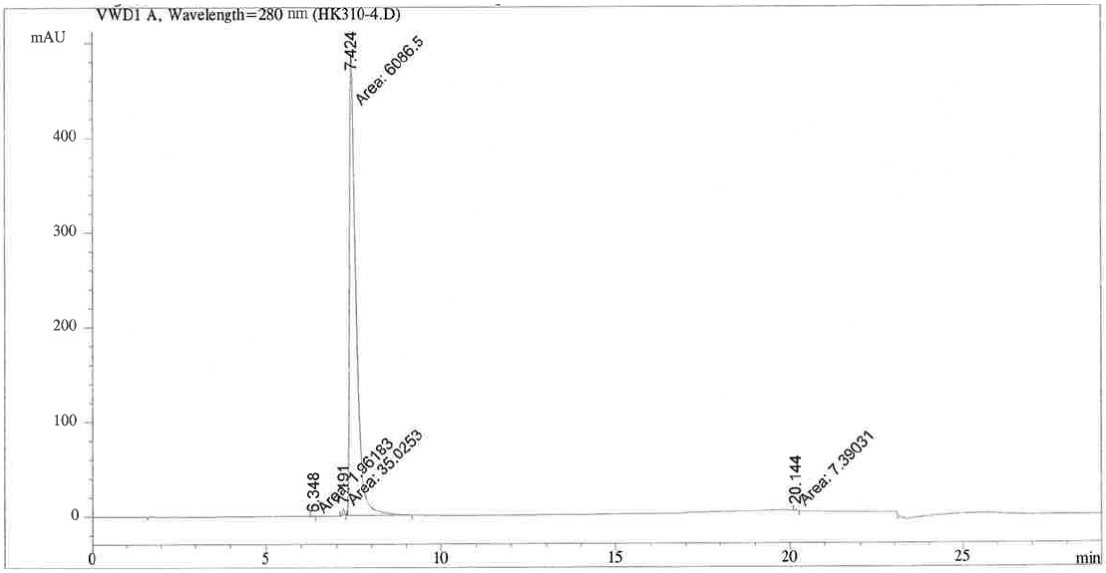

28

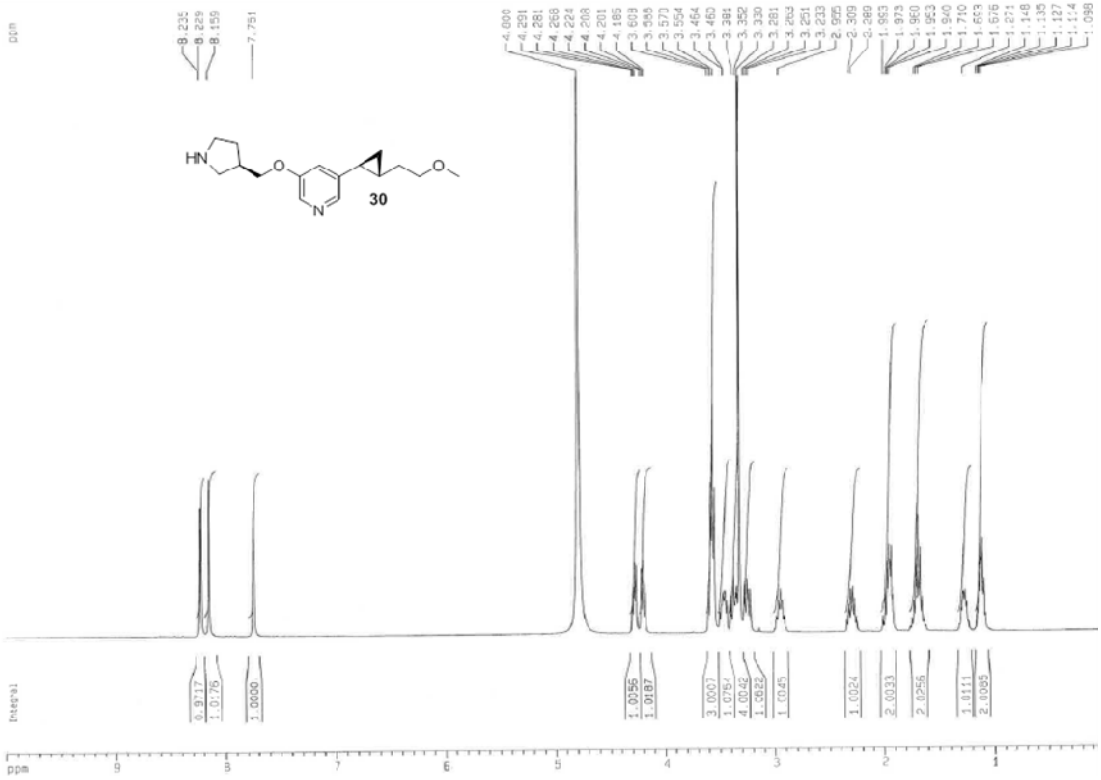

ppm
162.959
162.617
162.265
161.911
156.172
146.503
132.249
128.175
125.648
120.549
117.649
114.749
111.848
71.802
67.681
59.350
57.679
47.619
32.581
22.299
19.761
16.569
15.895
14.120
3.857
ppm
180
160
140
120
100
80
60
40
20

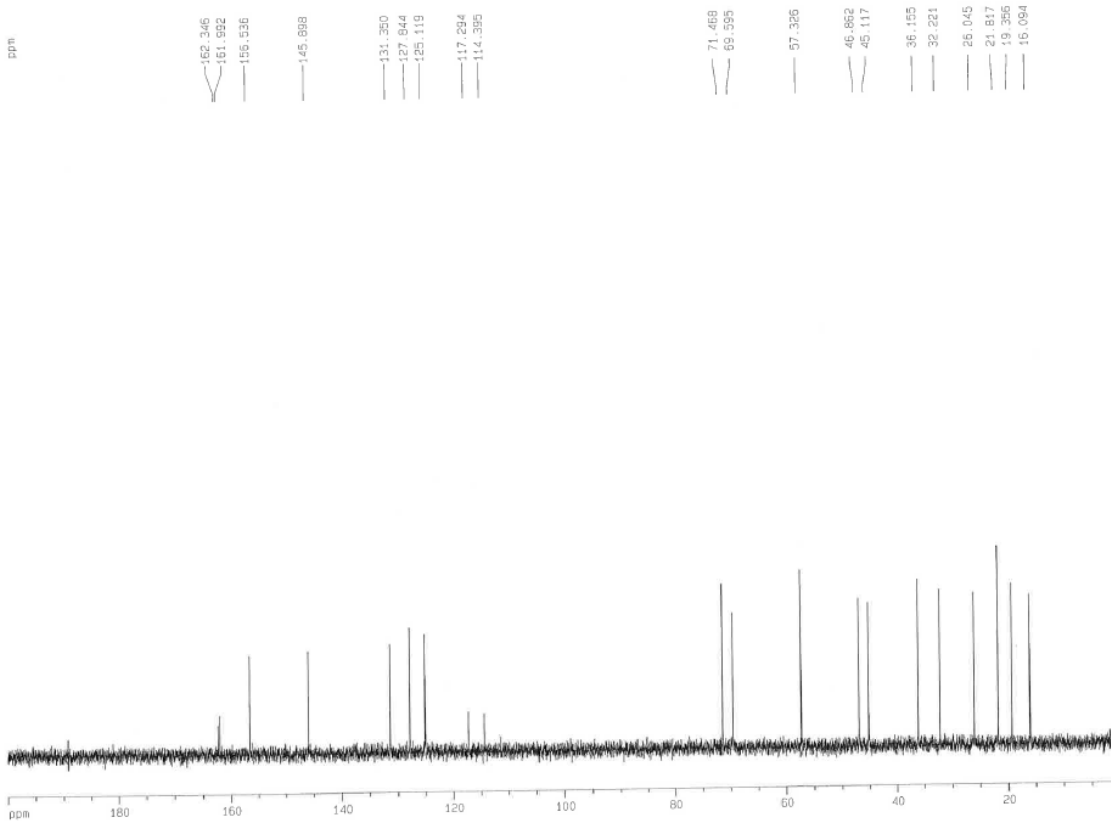

VWD1 A, Wavelength=280 nm (LF1115-1.D)
mAU
500
400
300
200
100
0
12.726
15.478
Area: 21.7911
17.152
Area: 10.8677
0
5
10
15
20
25
min

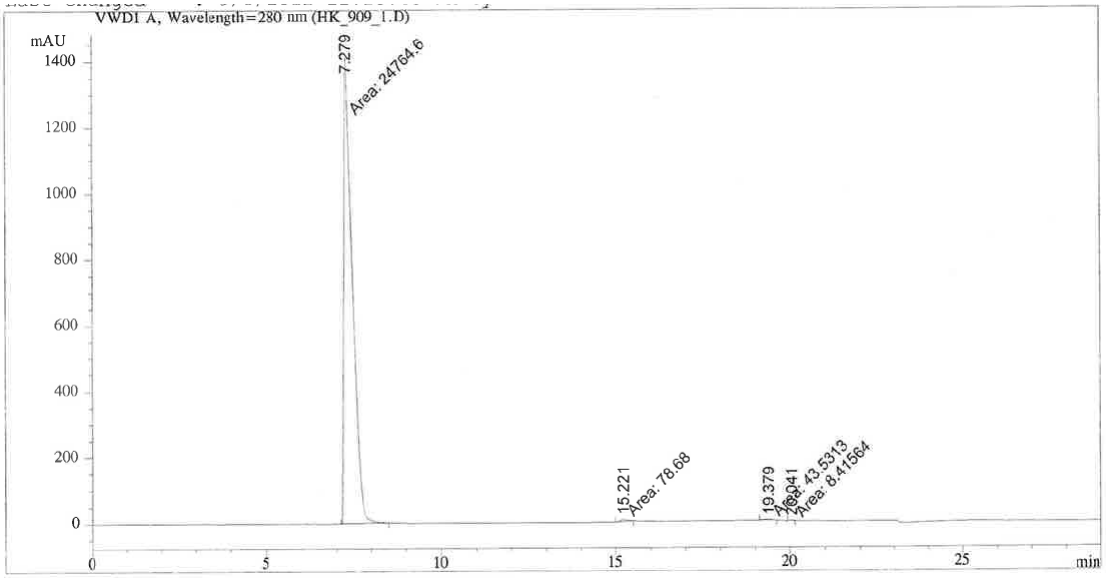

ppm
8.288
8.284
8.208
7.790
4.800
4.607
4.601
4.580
4.573
4.454
4.439
4.427
4.412
3.946
3.930
3.739
3.727
3.562
3.556
3.550
3.322
3.250
3.222
3.019
2.873
2.399
2.381
2.203
2.186
2.081
2.052
1.972
1.962
1.952
1.709
1.692
1.674
1.296
1.282
1.156
1.144
1.134
1.125
1.110
29
Integral
1.0000
1.0016
1.0122
1.0400
0.9986
0.9570
1.0007
2.0479
3.1029
1.0248
2.8498
1.0255
1.0759
2.0698
1.0575
2.0647
1.0415
2.0649
ppm

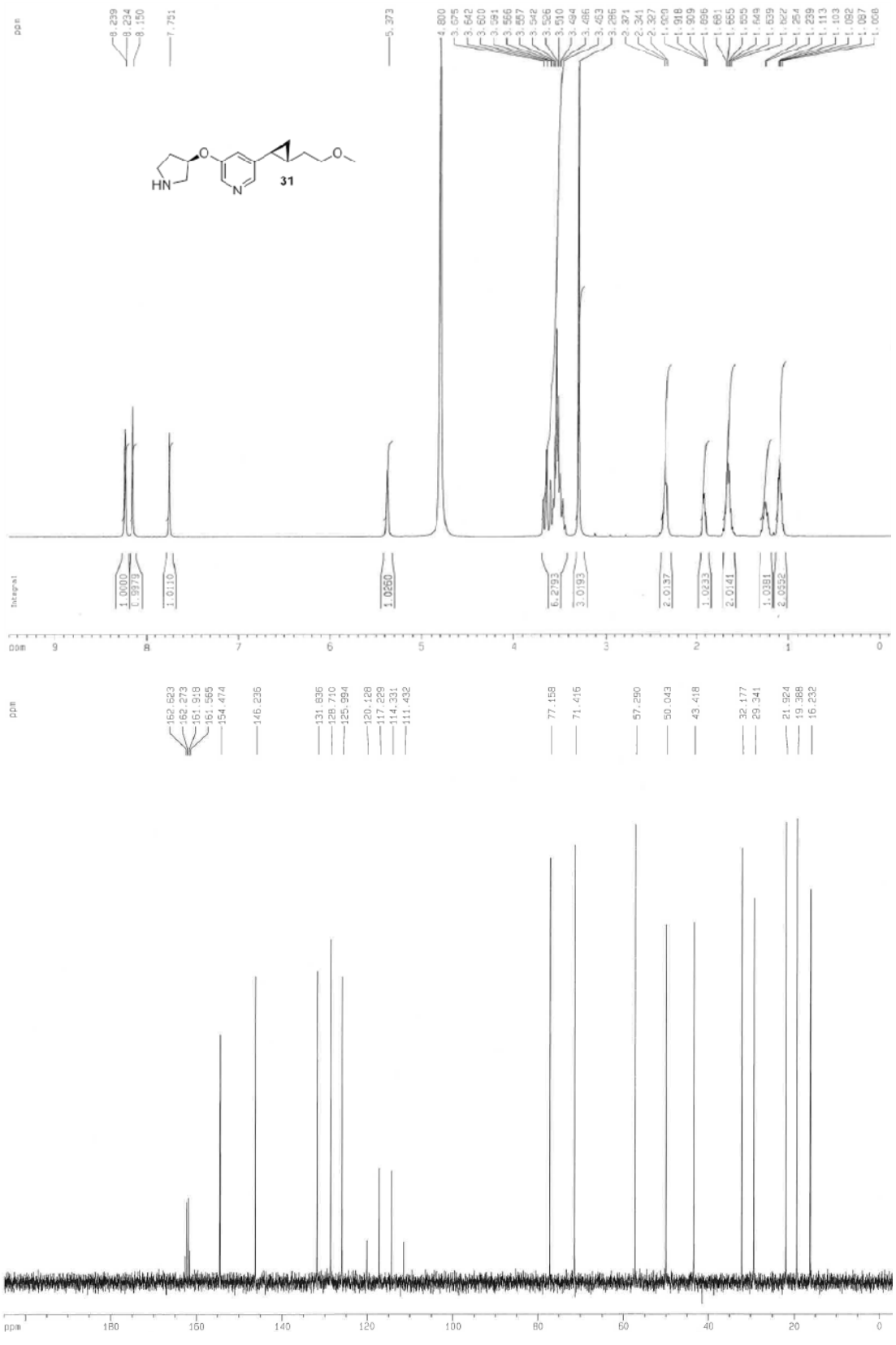

ppm
162.753
162.398
162.047
161.694
155.655
146.169
132.088
127.851
125.178
120.181
117.284
114.383
111.482
71.448
66.915
65.973
65.308
62.760
57.309
56.779
40.148
33.194
25.425
23.704
21.966
21.694
19.392
16.234
ppm

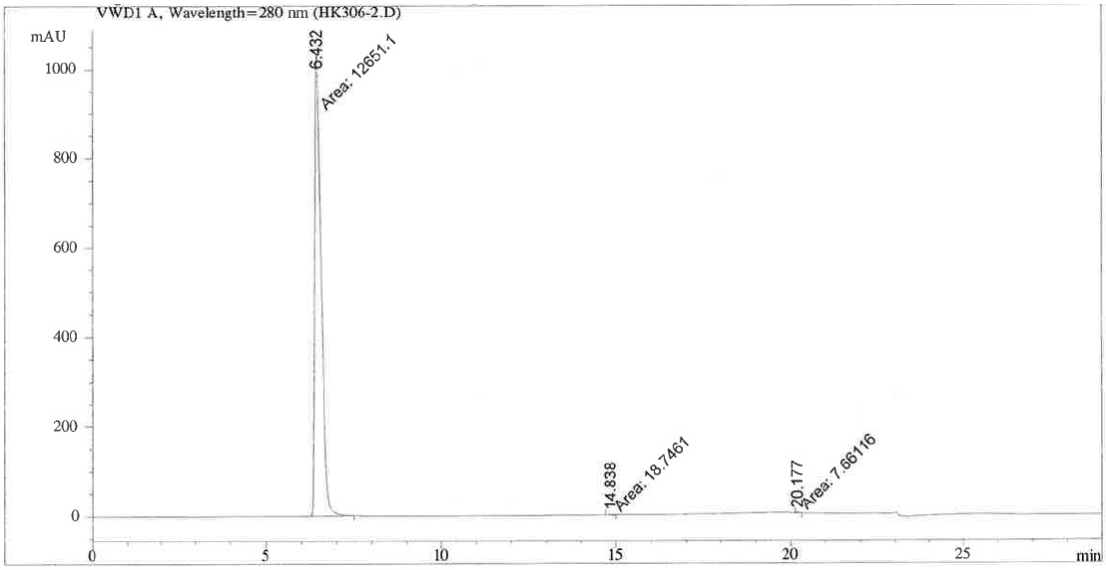

VWD1 A, Wavelength=280 nm (HK310-4.D)
mAU
7.424
Area: 6086.5
6.348
Area: 1.96183
Area: 35.0253
20.144
Area: 7.39031
min

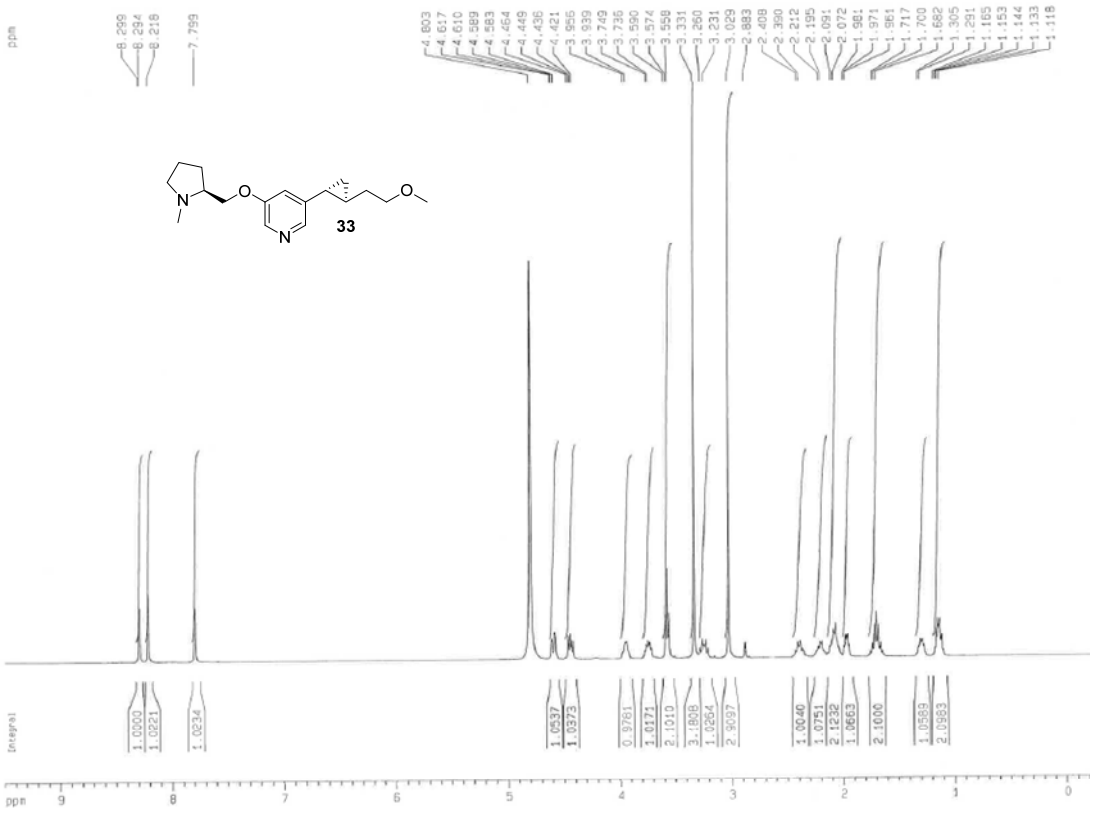

ppm
HN
O
N
O
30
Integral
ppm

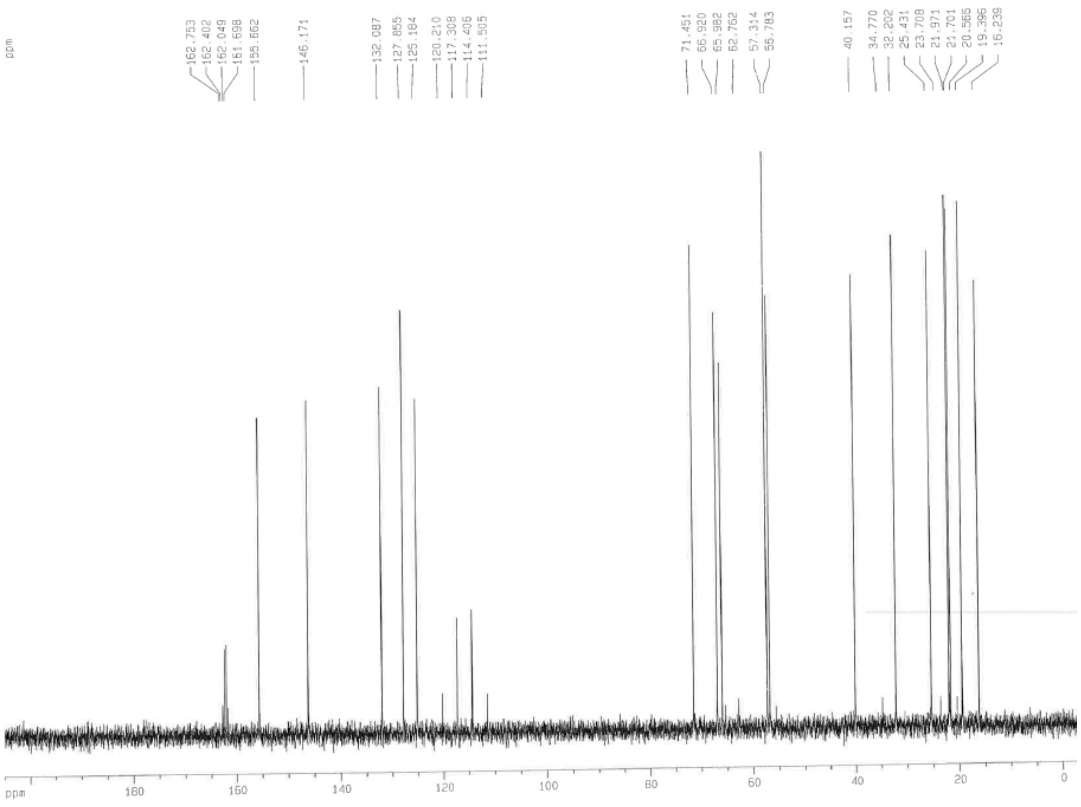

ppm
162.346
161.992
156.536
145.898
131.350
127.844
125.119
117.294
114.395
71.468
69.595
57.326
46.862
45.117
36.155
32.221
26.045
21.817
19.356
16.094
ppm
180
160
140
120
100
80
60
40
20

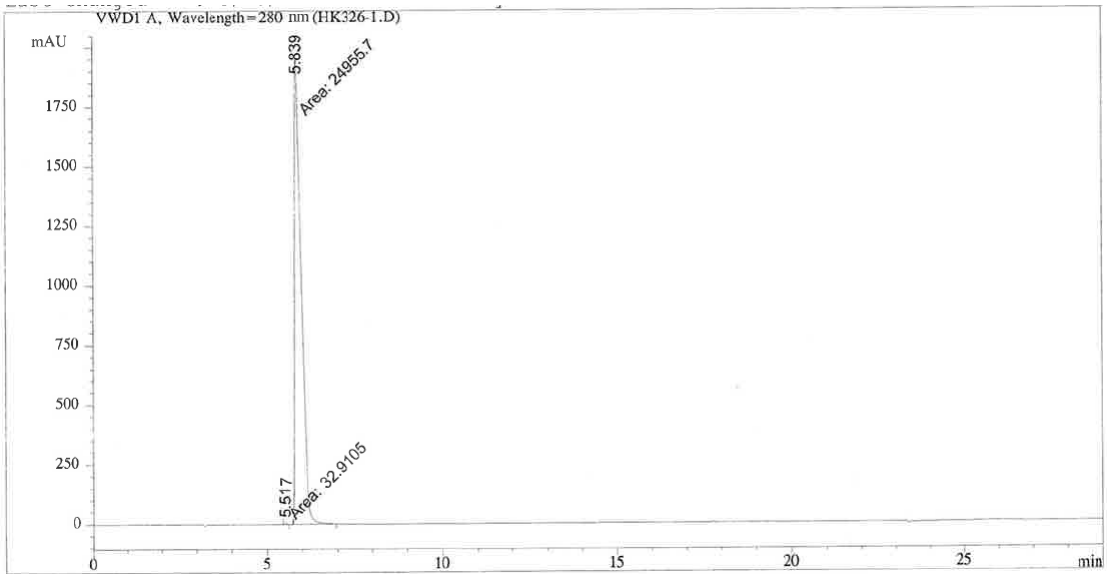

VWDI A, Wavelength=280 nm (HK_909_1.D)
mAU
1400
1200
1000
800
600
400
200
0
7.279
Area: 24764.6
15.221
Area: 78.68
19.379
19.641
Area: 43.5313
Area: 8.41564
0
5
10
15
20
25
min


31


VWD1 A, Wavelength=280 nm (HK306-2.D)
mAU
1000
800
600
400
200
0
6.432
Area: 12651.1
14.838
Area: 18.7461
20.177
Area: 7.66116
0
5
10
15
20
25
min


ppm
8.299
8.294
8.218
7.799
4.603
4.617
4.610
4.589
4.583
4.464
4.449
4.436
4.421
3.956
3.939
3.749
3.736
3.590
3.574
3.558
3.331
3.260
3.231
3.029
2.883
2.408
2.390
2.212
2.195
2.091
2.072
1.981
1.971
1.961
1.717
1.700
1.682
1.305
1.291
1.165
1.153
1.144
1.133
1.118
33
Integral
1.0000
1.0221
1.0234
1.0537
1.0373
0.9761
1.0172
2.1010
3.1808
1.0264
2.9097
1.0040
1.0751
2.1232
1.0663
2.1000
1.0583
2.0983
ppm
9
8
7
6
5
4
3
2
1
0


ppm
162.753
162.402
162.049
161.698
155.662
146.171
132.087
127.855
125.164
120.210
117.308
114.406
111.505
71.451
66.920
65.982
62.762
57.314
56.783
40.157
34.770
32.202
25.431
23.708
21.971
21.701
20.565
19.396
16.238
ppm
180
160
140
120
100
80
60
40
20
0


VWD1 A, Wavelength=280 nm (HK326-1.D)
mAU
1750
1500
1250
1000
750
500
250
0
5.839
Area: 24955.7
5.517
Area: 32.9105
0
5
10
15
20
25
min