Late-stage *N*-Me Selective Arylation of Trialkylamines Enabled by Ni/Photoredox Dual Catalysis

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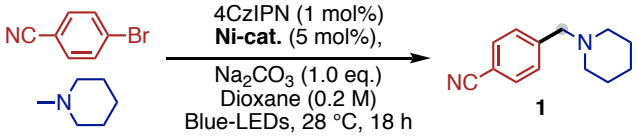
I. General considerations

Reagents: Unless otherwise noted, all reactions were carried out in reaction tubes with screw cap. Anhydrous solvents were purchased from Sigma Aldrich and used without further purification. All other reagents were purchased from commercial sources and used as received. For the pharmaceuticals received in salt form, a simple treatment with ethyl acetate and K_2CO_3 (aq.) or KOH (1 M) offered pure enough sample in the organic phase for the reactions. Purification of the product was conducted manually on SiliCycle® SilicaFlash® P60 (230-400 mesh) silica gel columns. Thin layer chromatography (TLC) was performed on Silicycle 250 μm silica gel 60 Å plates. Visualization was accomplished with UV lamp (254 nm), $KMnO_4$ or Iodine. A Kessil blue LED (34W maximum, 24 VDC, 440 nm) was used as the light source for the photoredox catalyzed reactions. The procedures described in this section are representative. Thus, the yields may differ slightly from those given in the tables of the manuscript.

Analytical Methods: ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra are included for all new compounds. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Varian 300/400 MHz or Bruker 400/500 MHz at ambient temperature. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77.16 ppm) and were obtained with ^{1}H decoupling. Coupling constants, *J*, are reported in hertz (Hz). In the case of diastereomeric mixtures, isolated NMR was recorded to determine the ratio. High resolution mass spectra (HRMS) were obtained from the Columbia University Chemistry Department Mass Spectrometry Facility on a Waters XEVO G2XS QToF mass spectrometer equipped with a UPC2 SFC inlet and a LockSpray source with one of the following three probes: electrospray ionization (ESI) probe, atmospheric pressure chemical ionization (APCI) probe, or atmospheric pressure solids analysis probe (ASAP).

II. Optimization details and control experiments

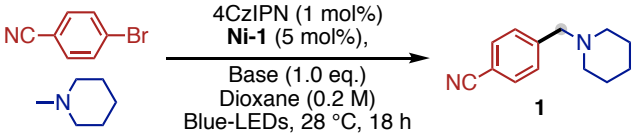
Table S1. Screening of Ni-catalysts



entry	Ni-cat.	Conv. (%)	Ar-H (%)[a]	**1** (%)[a]
1	**Ni-1**	100	12	49
2	$Ni(COD)_2$[b]	100	27	5
3	$NiCl_2(H_2O)_6$[b]	100	19	48
4	$Ni(OAc)_2(H_2O)_4$[b]	20	12	4
5	$Ni(acac)_2$[b]	100	36	45
6	$Ni(PPh_3)Cl_2$[b]	83	17	40

0.2 mmol scale, amine (2.0 equiv), mass balance acounts for homocoupling of ArBr. [a] GC-MS yield with ethyl benzoate as internal standard. [b] dtbbpy (6 mol%) as ligand.

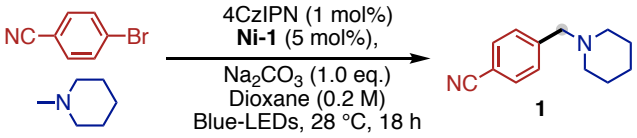
Table S2. Screening of Bases



entry	Base	Conv. (%)	Ar-H (%)[a]	**1** (%)[a]
1	Na_2CO_3	100	12	49
2	K_2CO_3	100	12	44
3	Cs_2CO_3	100	11	43
4	$NaHCO_3$	83	7	40
5	K_2HPO_4	100	16	44
6	K_3PO_4	100	12	46
7	DABCO	48	11	15
8	2,4,6-Collidine	100	4	43
9	Barton's base	100	10	33
10	LiOPiv	100	39	47
11	NaOPiv	100	94	5
12	CsOPiv	100	96	4
13	NaO_2CAd	100	86	11
14	KO_2CAd	100	91	6
15	CsO_2CAd	100	83	8

0.2 mmol scale, amine (2.0 equiv), mass balance acounts for homocoupling of ArBr. [a] GC-MS yield with ethyl benzoate as internal standard.

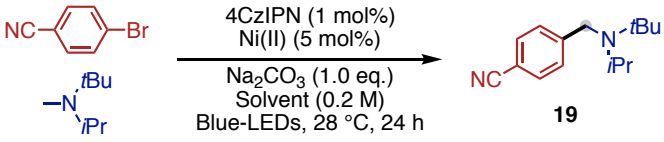
Table S3. H_2O Titration



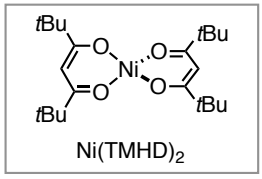
entry	H_2O (x eq.) as add.	Conv. (%)	Ar-H (%)[a]	**1** (%)[a]
1	0	100	12	49
2	5	100	16	38
3	10	100	31	38
4	20	100	59	29
5	50	100	90	3
6	100	55	54	0
7	200	81	77	0

0.2 mmol scale, amine (2.0 equiv), mass balance accounts for homocoupling of ArBr. [a] GC-MS yield with ethyl benzoate as internal standard.

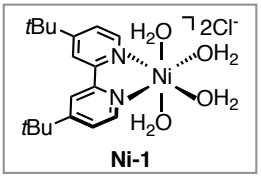
Table S4. Conditions for Hindered Amine Substrate



entry	Ni-cat.	Solvent	Ar-H (%)[a]	**19** (%)[a]
1	**Ni-1**	DME	13	4
2[b]	$Ni(TMHD)_2$	DMA	16	25
3[c]	$NiCl_2(H_2O)_6$	ACN	12	90 (86)[d]
4[c]	$NiCl_2(H_2O)_6$	Dioxane	12	62
5[b,c]	$NiCl_2(H_2O)_6$	DMA	21	30
6[b,c]	$NiCl_2(H_2O)_6$	DMF	35	53



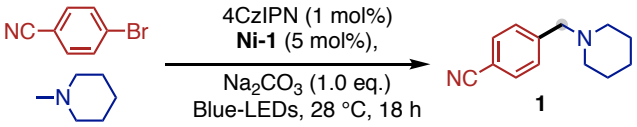
$Ni(TMHD)_2$



Ni-1

0.2 mmol scale, amine (2.0 equiv), mass balance acounts for homocoupling of ArBr, full conversion. [a] GC-MS yield with ethyl benzoate as inter standard. [b] Dimerization of amine was detected. [c] 10 mol% of dipivaloyl methane was used as ligand. [d] isolated yield.

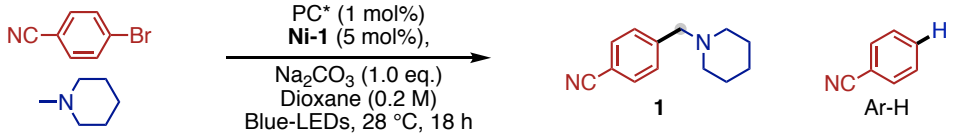
Table S5. Ratio and Concentration of Starting Materials

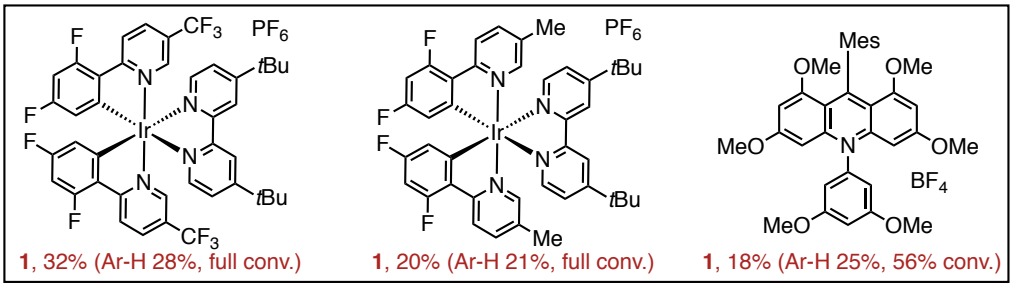


entry	amine: ArBr	Dioxane	Ar-H (%)[a]	**1** (%)[a]
1	2: 1	0.2 M	12	49 (50)[b]
2	1: 1	0.2 M	23	33
3	2: 1	0.1 M	25	46
4	2: 1	0.067 M	28	44
5[c]	2: 1	0.05 M	29	43

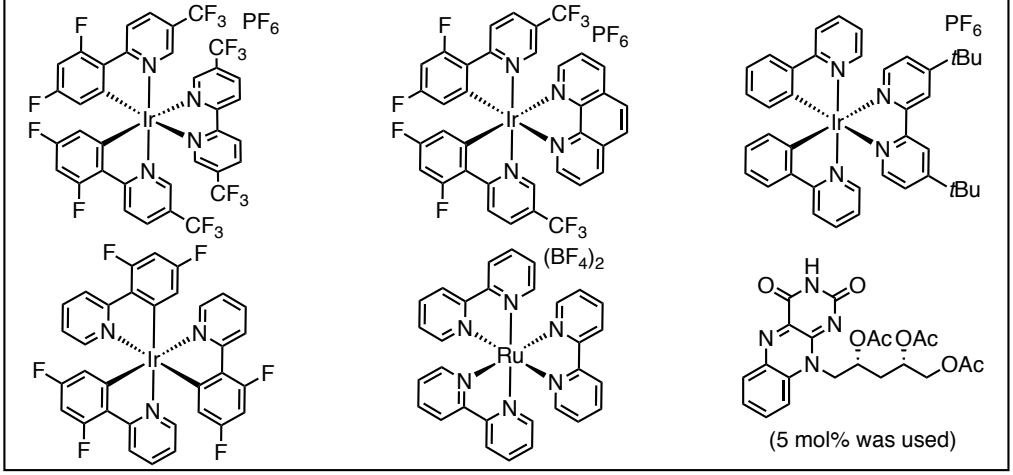
0.2 mmol scale, amine (2.0 equiv), full conversion of ArBr, mass balance acounts for homocoupling of ArBr. [a] GC-MS yield with ethyl benzoate as inter standard. [b] isolated yield. [c] 87% conversion.

Table S6. Photocatalysts Screening





0 < yield < 10%, < 20% conversion



0.2 mmol scale, amine (2.0 equiv), mass balance acounts for homocoupling of ArBr. [a] GC-MS yield with ethyl benzoate as inter standard.

III. Deuteration studies

α- and β- deuterated tributylamines were synthesized according to reported literatures.[1-3]

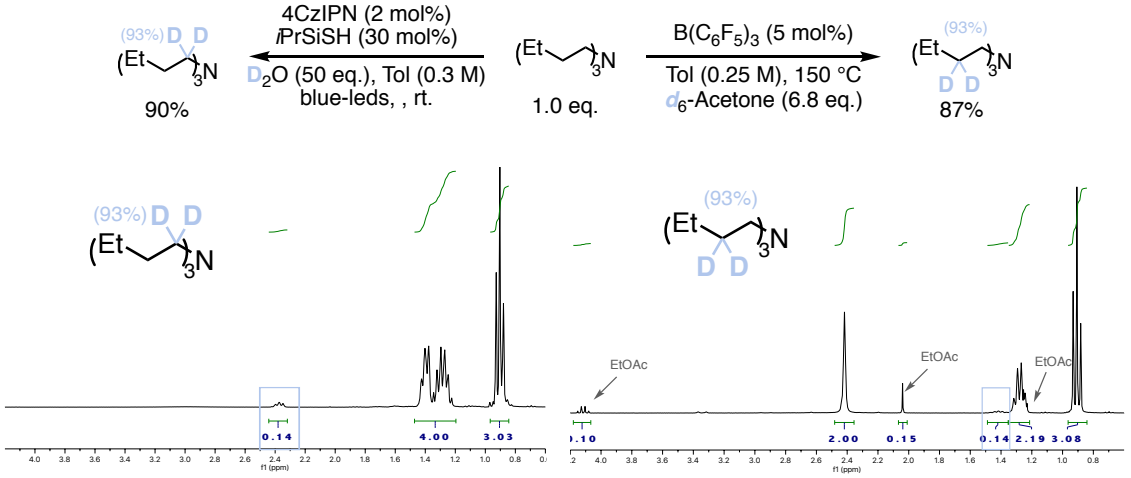


Figure S1. Synthesis of deuterated tributylamine

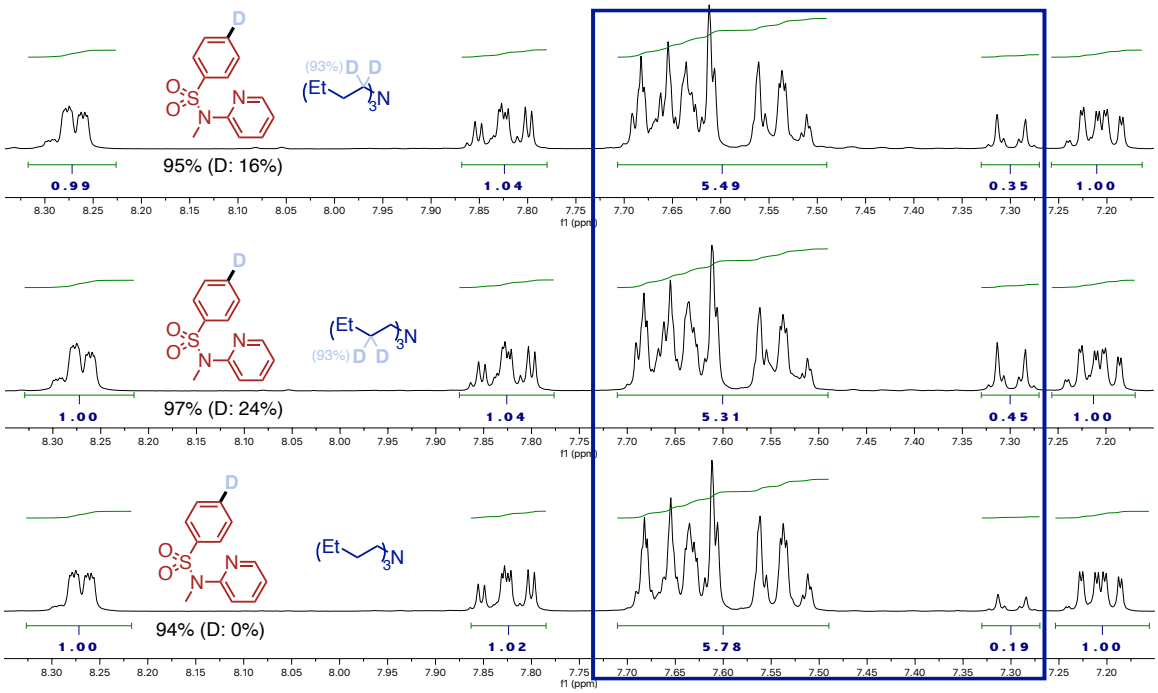


Figure S2. ^{1}H-NMR of hydrodebromination with tributylamine

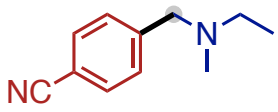
IV. *N*-Me selective arylation

General Procedure A for the *N*-Me arylation of simple trialkylamines. A 8.0 mL disposable borosilicate glass tube with screw cap containing a stir bar was charged with 4CzIPN (1 mol%, 1.6 mg, 0.002 mmol), $NiCl_2(dtbbpy)(H_2O)_4$ (5 mol%, 4.7 mg, 0.01 mmol), Na_2CO_3 (21.2 mg, 0.2 mmol), trialkylamine (0.4 mmol, added after solvent if volatile) and aryl bromide (0.2 mmol, added after solvent if liquid). The tube was transferred to a nitrogen-filled glove-box where the dry 1,4-Dioxane (1.0 mL, 0.2 M) was added. Then the reaction was stirred for 1 minute and transferred outside, placing ~10 cm away from a Kessil blue LED (34W maximum, 24 VDC, 440 nm) and vigorously stirred for 18h with cooling by fan. After completion of the reaction, the mixture was filter through a short pad of celite and purified by flash column chromatography on silica gel with EtOAc/Hexane.

Note: for the arylation of complex trialkylamines, the reaction scale is 0.1 mmol in Dioxane (0.1 M) for 24h.

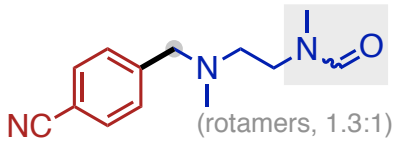
General Procedure B for the *N*-Me arylation of sterically hindered trialkylamines. A 8.0 mL disposable borosilicate glass tube with screw cap containing a stir bar was charged with 4CzIPN (1 mol%, 1.6 mg, 0.002 mmol), $NiCl_2(H_2O)_6$ (5 mol%, 2.4 mg, 0.01 mmol), Na_2CO_3 (21.2 mg, 0.2 mmol) and aryl bromide (0.2 mmol, added after solvent if liquid). The tube was transferred to a nitrogen-filled glove-box where the dry 1,4-Dioxane (1.0 mL, 0.2 M), *N*-isopropyl-*N*-methyl-*tert*-butylamine (0.4 mmol, 67.4 μL) and dipivaloylmethane (10 mol%, 4.2 μL, 0.02 mmol) were added. Then the reaction was stirred for 1 minute and transferred outside, placing ~10 cm away from a Kessil blue LED (34W maximum, 24 VDC, 440 nm) and vigorously stirred for 18h with cooling by fan. After completion of the reaction, the mixture was filter through a short pad of celite and purified by flash column chromatography on silica gel with EtOAc/Hexane.

*Both ^{1}H-NMR and ^{13}C-NMR of Products **1**[6], **3**[11e] and **4**[6] are in good consistency with reported data in literatures.*

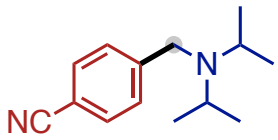


4-((ethyl(methyl)amino)methyl)benzonitrile (2). Following the general procedure A, the

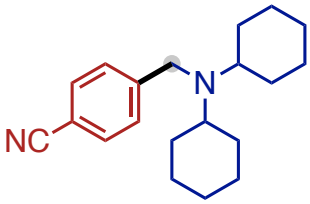
title compound was obtained in 72% yield (25.1 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 3.52 (s, 2H), 2.45 (q, J = 7.1 Hz, 2H), 2.18 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.46, 132.21, 129.57, 119.15, 110.87, 61.66, 51.56, 41.87, 12.58. HRMS *calcd*. for $C_{11}H_{14}N_2$ $[M+H]^+$: 175.1235, *found* 175.1246.



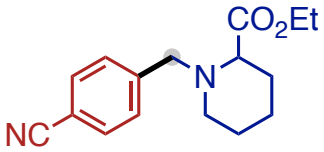
***N*-(2-((4-cyanobenzyl)(methyl)amino)ethyl)-*N*-methylformamide (5)**. Following the general procedure A, the title compound was obtained in 78% yield (36.1 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ [8.01 (s) + 8.00(s), 1H], 7.58-7.55 (m, 2H), 7.41-7.36 (m, 2H), [3.56 (s) + 3.55 (s), 2H], [3.46 (t, J = 6.5 Hz, 0.88H) + 3.29 (t, J = 6.0 Hz, 1.12H)], [2.92 (s, 1.3H) + 2.74 (s, 1.7H)], [2.55 (t, J = 6.5 Hz, 0.9H) + 2.49 (t, J = 6.0 Hz, 1.1H)], [2.22 (s) + 2.21 (s), 3H]. ^{13}C NMR (101 MHz, $CDCl_3$) δ (163.03, 162.67), (144.85, 144.61), (132.26, 132.13), (129.42, 129.31), (118.96, 118.87), (111.08, 110.91), (62.30, 61.77), (54.75, 54.21), (47.54, 42.32), (41.91, 35.00), (29.86, 29.71). HRMS *calcd*. for $C_{13}H_{17}N_3O$ $[M+H]^+$: 232.1450, *found* 232.1462.



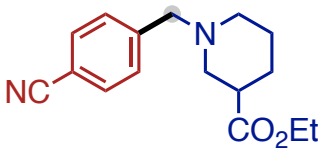
4-((diisopropylamino)methyl)benzonitrile (6). Following the general procedure A, the title compound was obtained in 77% yield (33.3 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 3.71 (s, 2H), 3.02 (m, 2H), 1.04 (d, J = 6.6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.78, 132.03, 128.52, 119.43, 110.07, 49.14, 48.59, 20.89. HRMS *calcd*. for $C_{14}H_{20}N_2$ $[M+H]^+$: 217.1705, *found* 217.1717.



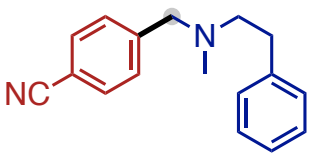
4-((dicyclohexylamino)methyl)benzonitrile (7). Following the general procedure A, the title compound was obtained in 75% yield (44.5 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 3.78 (s, 2H), 2.53-2.47 (m, 2H), 1.75-1.55 (m, 10H), 1.27-0.97 (m, 10 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.23, 131.99, 128.41, 119.51, 109.93, 58.32, 50.22, 32.07, 26.49, 26.32. HRMS *calcd*. for $C_{20}H_{28}N_2$ $[M+H]^+$: 297.2331, *found* 297.2343.



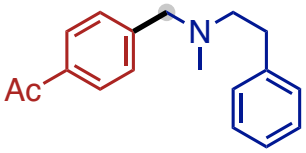
ethyl 1-(4-cyanobenzyl)piperidine-2-carboxylate (8). Following the general procedure A, the title compound was obtained in 51% yield (27.8 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 4.4-4.12 (m, 2H), 3.83 (d, *J* = 14.2 Hz, 1H), 3.44 (d, *J* = 14.2 Hz, 1H), 3.18 (dd, *J* = 7.1, 4.6 Hz, 1H), 2.87 (dt, *J* = 10.5, 4.6 Hz, 1H), 2.19-2.13 (m, 1H), 1.89-1.79 (m, 2H), 1.63-1.51 (m, 3H), 1.45-1.37 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.72, 144.90, 132.14, 129.52, 119.15, 110.88, 64.45, 60.52, 60.23, 50.25, 29.65, 25.41, 22.38, 14.43. HRMS *calcd*. for $C_{16}H_{20}N_2O_2$ $[M+H]^+$: 273.1603, *found* 273.1615.



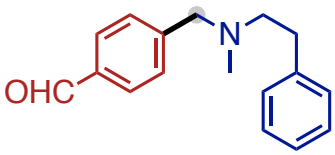
ethyl 1-(4-cyanobenzyl)piperidine-3-carboxylate (9). Following the general procedure A, the title compound was obtained in 55% yield (30.0 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 4.10 (qd, *J* = 7.1, 2.2 Hz, 2H), 3.58-3.49 (m, 2H), 2.88-2.83 (m, 1H), 2.66-2.52 (m, 2H), 2.27 (t, *J* = 10.4 Hz, 1H), 2.11-2.06 (m, 1H), 1.93-1.89 (m, 1H), 1.76-1.70 (m, 1H), 1.61-1.45 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.12, 144.63, 132.18, 129.44, 119.11, 110.90, 62.79, 60.44, 55.56, 53.91, 41.93, 26.85, 24.60, 14.32. HRMS *calcd*. for $C_{16}H_{20}N_2O_2$ $[M+H]^+$: 273.1603, *found* 273.1614.



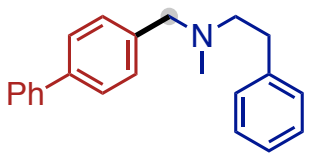
4-((methyl(phenethyl)amino)methyl)benzonitrile (10). Following the general procedure A, the title compound was obtained in 88% yield (44.1 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.37-7.35 (m, 2H), 7.30-7.25 (m, 2H), 7.22-7.15 (m, 3H), 3.58 (s, 2H), 2.81 (dd, *J* = 8.8, 6.5 Hz, 2H), 2.64 (dd, *J* = 8.8, 6.3 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.25, 140.35, 132.18, 129.41, 128.86, 128.47, 126.18, 119.14, 110.83, 61.92, 59.28, 42.35, 34.06. HRMS *calcd*. for $C_{17}H_{18}N_2$ $[M+H]^+$: 251.1548, *found* 251.1561.



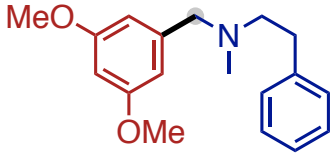
1-(4-((methyl(phenethyl)amino)methyl)phenyl)ethan-1-one (11). Following the general procedure A, the title compound was obtained in 68% yield (36.4 mg) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.30-7.26 (m, 2H), 7.22-7.17 (m, 3H), 3.61 (s, 2H), 2.83 (dd, *J* = 9.3, 6.3 Hz, 2H), 2.67 (dd, *J* = 9.2, 6.3 Hz, 2H), 2.60 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.99, 145.06, 140.44, 136.15, 129.01, 128.84, 128.46, 126.12, 61.97, 59.32, 42.37, 34.03, 26.71. HRMS *calcd*. for $C_{18}H_{21}NO$ $[M+H]^+$: 268.1701, *found* 268.1718.



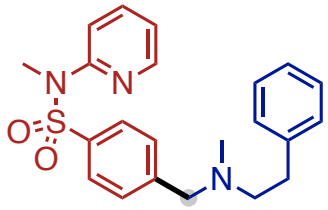
4-((methyl(phenethyl)amino)methyl)benzaldehyde (12). Following the general procedure A, the title compound was obtained in 70% yield (35.5 mg) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.30-7.26 (m, 2H), 7.22-7.17 (m, 3H), 3.63 (s, 2H), 2.83 (dd, *J* = 9.3, 6.1 Hz, 2H), 2.67 (dd, *J* = 9.0, 6.2 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.16, 146.86, 140.46, 135.60, 129.91, 129.42, 128.88, 128.49, 126.18, 62.12, 59.38, 42.43, 34.10. HRMS *calcd*. for $C_{17}H_{19}NO$ $[M+H]^+$: 254.1545, *found* 254.1544.



***N*-([1,1'-biphenyl]-4-ylmethyl)-*N*-methyl-2-phenylethan-1-amine (13)**. Following the general procedure A, the title compound was obtained in 66% yield (39.8 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.52 (m, 4H), 7.44-7.41 (m, 2H), 7.37-7.24 (m, 5H), 7.20-7.17 (m, 3H), 3.61 (s, 2H), 2.85 (dd, *J* = 9.5, 6.2 Hz, 2H), 2.69 (dd, *J* = 9.5, 6.1 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.16, 140.61, 140.05, 138.11, 129.57, 128.91, 128.87, 128.47, 127.28, 127.19, 127.11, 126.10, 61.94, 59.28, 42.31, 34.02. HRMS *calcd*. for $C_{22}H_{23}N$ $[M+H]^+$: 302.1909, *found* 302.1921.

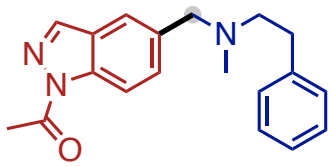


***N*-(3,5-dimethoxybenzyl)-*N*-methyl-2-phenylethan-1-amine (14)**. Following the general procedure A, the title compound was obtained in 71% yield (40.5 mg) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.19-7.16 (m, 3H), 6.47 (d, *J* = 2.3 Hz, 2H), 6.35 (t, *J* = 2.3 Hz, 1H), 3.76 (s, 6H), 3.49 (s, 2H), 2.82 (dd, *J* = 9.2, 6.3 Hz, 2H), 2.65 (dd, *J* = 9.3, 6.3 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.85, 141.90, 140.70, 128.90, 128.42, 126.04, 106.74, 99.31, 62.53, 59.21, 55.43, 42.46, 34.02. HRMS *calcd*. for $C_{18}H_{23}NO_2$ $[M+H]^+$: 286.1807, *found* 286.1820.

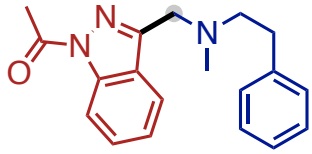


***N*-methyl-4-((methyl(phenethyl)amino)methyl)-*N*-(pyridin-2-yl)benzenesulfonamide (15)**. Following the general procedure A, the title compound was obtained in 53% yield (41.9 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dt, *J* = 4.8, 1.5 Hz, 1H), 7.70-7.69 (m, 2H), 7.51-7.49 (m, 2H), 7.33-7.08 (m, 8H), 3.56 (s, 2H), 3.28 (s, 3H), 2.79 (dd, *J* = 8.9, 6.4 Hz, 2H), 2.63 (dd, *J* = 9.0, 6.3 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.84, 148.01, 145.26, 140.35, 137.62, 135.75, 129.14, 128.83, 128.44, 127.59,

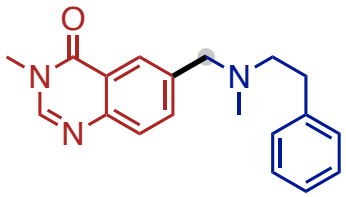
126.13, 121.12, 120.75, 61.73, 59.28, 42.36, 35.62, 34.03. HRMS *calcd*. for $C_{22}H_{25}N_3O_2S$ $[M+H]^+$: 396.1746, *found* 396.1785.



1-(5-((methyl(phenethyl)amino)methyl)-1*H*-indazol-1-yl)ethan-1-one (16). Following the general procedure A, the title compound was obtained in 57% yield (35.0 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 8.05 (s, 1H), 7.58 (s, 1H), 7.50 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.29-7.26 (m, 2H), 7.22-7.16 (m, 3H), 3.67 (s, 2H), 2.83 (dd, *J* = 9.1, 6.4 Hz, 2H), 2.78 (s, 3H), 2.67 (dd, *J* = 9.1, 6.3 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.00, 140.44, 139.75, 138.41, 135.82, 130.77, 128.78, 128.34, 126.52, 126.00, 120.62, 115.21, 61.95, 59.06, 42.15, 33.94, 23.00. HRMS *calcd*. for $C_{19}H_{21}N_3O$ $[M+H]^+$: 308.1763, *found* 308.1777.

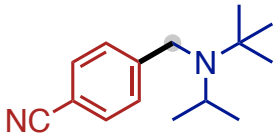


1-(3-((methyl(phenethyl)amino)methyl)-1*H*-indazol-1-yl)ethan-1-one (17). Following the general procedure A, the title compound was obtained in 53% yield (32.6 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.51 (ddd, *J* = 8.3, 7.1, 1.1 Hz, 1H), 7.29-7.24 (m, 3H), 7.21-7.17 (m, 3H), 3.92 (s, 2H), 2.89 (dd, *J* = 8.9, 5.8 Hz, 2H), 2.80-2.76 (m, 5H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.08, 150.07, 140.41, 140.09, 129.47, 128.85, 128.49, 126.15, 126.10, 124.27, 121.60, 115.59, 59.51, 54.70, 42.56, 33.98, 23.24. HRMS *calcd*. for $C_{19}H_{21}N_3O$ $[M+H]^+$: 308.1763, *found* 308.1783.

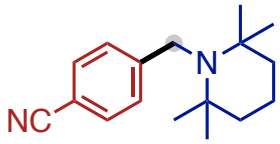


3-methyl-6-((methyl(phenethyl)amino)methyl)quinazolin-4(3*H*)-one (18). Following the general procedure A, the title compound was obtained in 40% yield (24.6 mg) as brown

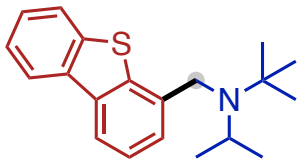
oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.5 Hz, 1H), 8.01 (s, 1H), 7.72 (dd, *J* = 8.4, 1.9 Hz, 0H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 3.67 (s, 2H), 3.03 (s, 3H), 2.83 (dd, *J* = 9.3, 6.2 Hz, 1H), 2.68 (dd, *J* = 9.2, 6.1 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.73, 147.63, 146.56, 140.52, 139.13, 135.23, 128.85, 128.45, 127.63, 126.31, 126.10, 121.73, 61.81, 59.32, 42.25, 34.15, 34.10. HRMS *calcd*. for $C_{19}H_{21}N_3O$ $[M+H]^+$: 308.1763, *found* 308.1790.



4-((*tert*-butyl(isopropyl)amino)methyl)benzonitrile (19). Following the general procedure B, the title compound was obtained in 86% yield (39.6 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.51 (m, 4H), 3.79 (s, 2H), 3.50 (hept, *J* = 6.6 Hz, 1H), 1.05 (s, 9H), 0.99 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.77, 131.89, 131.87, 127.65, 119.53, 109.47, 55.88, 47.01, 46.14, 28.93, 22.46. HRMS *calcd*. for $C_{15}H_{22}N_2$ $[M+H]^+$: 231.1861, *found* 231.1874.

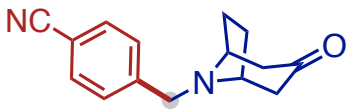


4-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)benzonitrile (20). Following the general procedure B, the title compound was obtained in 91% yield (46.6 mg) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.53 (m, 4H), 3.83 (s, 2H), 1.62 (br, 2H), 1.54-1.51 (d, *J* = 10.8 Hz, 4H), 0.97 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.33, 131.80, 127.57, 119.56, 109.35, 55.01, 48.16, 41.28, 17.84. HRMS *calcd*. for $C_{17}H_{24}N_2$ $[M+H]^+$: 257.2018, *found* 257.2024.

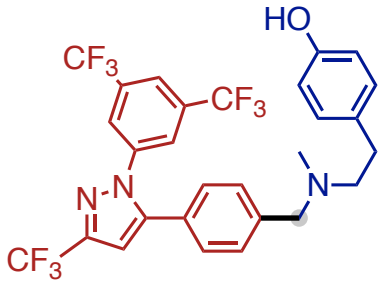


***N*-(dibenzo[*b*,*d*]thiophen-4-ylmethyl)-*N*-isopropyl-2-methylpropan-2-amine (21)**. Following the general procedure B, the title compound was obtained in 61% yield (38.0 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.92-7.89 (m, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.48-7.45 (m, 3H), 4.01 (s, 2H), 3.60

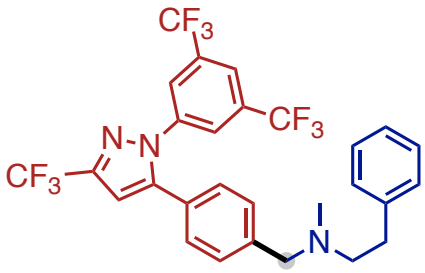
(hept, J = 6.7 Hz, 1H), 1.17 (s, 9H), 1.10 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.30, 139.79, 136.49, 136.04, 135.54, 126.50, 125.60, 124.58, 124.34, 122.88, 121.66, 119.23, 56.06, 47.32, 45.40, 28.71, 22.45. HRMS *calcd*. for $C_{20}H_{25}NS$ $[M+H]^+$: 312.1786, *found* 312.1783.



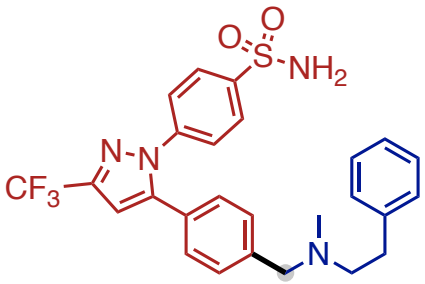
4-(((1*R*,5*S*)-3-oxo-8-azabicyclo[3.2.1]octan-8-yl)methyl)benzonitrile (22). Following the general procedure A, the title compound was obtained in 61% yield (29.3 mg) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.53 (m, 4H), 3.79 (s, 2H), 3.45 (d, J = 5.3 Hz, 2H), 2.66 (dd, J = 16.0, 4.4 Hz, 2H), 2.22 (d, J = 15.9 Hz, 2H), 2.16-2.03 (m, 2H), 1.65 (d, J = 7.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.63, 145.22, 132.34, 129.02, 118.98, 111.08, 59.03, 55.19, 48.47, 27.89. HRMS *calcd*. for $C_{15}H_{16}N_2O$ $[M+H]^+$: 241.1341, *found* 241.1345.



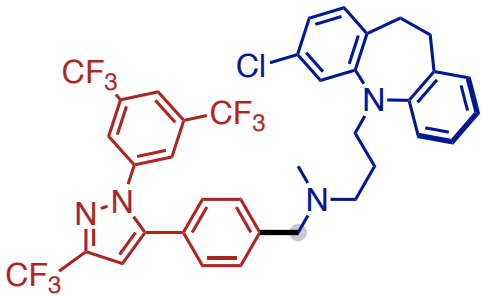
4-(2-((4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)(methyl)amino)ethyl)phenol (23). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 74% yield (43.4 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.78 (s, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 6.79 (s, 1H), 6.71 (d, J = 8.5 Hz, 2H), 3.62 (s, 2H), 2.77 (dd, J = 9.6, 5.9 Hz, 2H), 2.65 (dd, J = 9.6, 5.8 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.34, 145.35, 144.72 (q, J = 38.9 Hz), 140.37, 132.73 (q, J = 34.2 Hz), 131.98, 130.07, 129.90, 129.00, 127.18, 125.10, 125.06, 122.65 (q, J = 273.0 Hz), 121.65, 121.03 (q, J = 269.3 Hz), 115.50, 106.93, 61.69, 59.53, 41.77, 32.82. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.55, -63.15. HRMS *calcd*. for $C_{28}H_{22}N_3OF_9$ $[M+H]^+$: 588.1697, *found* 588.1683.



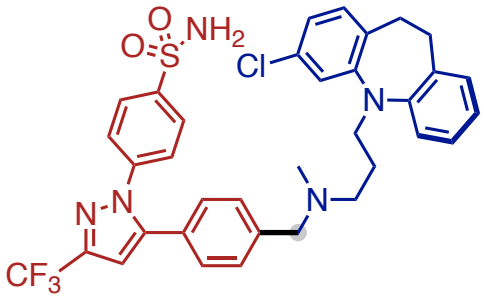
***N*-(4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)-*N*-methyl-2-phenylethan-1-amine (24)**. Following the general procedure A (0.1 mmol scale), the title compound was obtained in 84% yield (48.0 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.78 (s, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.28-7.24 (m, 2H), 7.20-7.13 (m, 5H), 6.78 (s, 1H), 3.58 (s, 2H), 2.85-2.81 (m, 2H), 2.66 (dd, *J* = 9.0, 6.3 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.49, 144.74 (q, *J* = 38.9 Hz), 141.81, 140.53, 140.47, 132.77 (q, *J* = 34.1 Hz), 129.75, 128.95, 128.89, 128.46, 126.97, 126.15, 125.10, 122.69 (q, *J* = 273.2 Hz), 121.61, 121.07 (q, *J* = 269.2 Hz), 106.90, 61.83, 59.38, 42.04, 34.10. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.57, -63.17. HRMS *calcd*. for $C_{28}H_{22}N_3F_9$ $[M+H]^+$: 572.1748, *found* 572.1742.



4-(5-(4-((methyl(phenethyl)amino)methyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (25). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 65% yield (33.4 mg) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.30-7.25 (m, 4H), 7.20-7.14 (m, 5H), 6.76 (s, 1H), 5.14 (br, 1H), 3.57 (s, 2H), 2.81 (dd, *J* = 9.2, 6.2 Hz, 2H), 2.66 (dd, *J* = 9.3, 6.2 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.20, 144.25 (q, *J* = 38.6 Hz), 142.56, 141.66, 140.87, 140.34, 129.70, 128.90, 128.84, 128.52, 127.59, 127.43, 126.22, 125.60, 121.16 (q, *J* = 269.3 Hz), 106.64, 61.72, 59.27, 42.31, 33.86. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.39. HRMS *calcd*. for $C_{26}H_{25}N_4O_2SF_3$ $[M+H]^+$: 515.1729, *found* 515.1731.

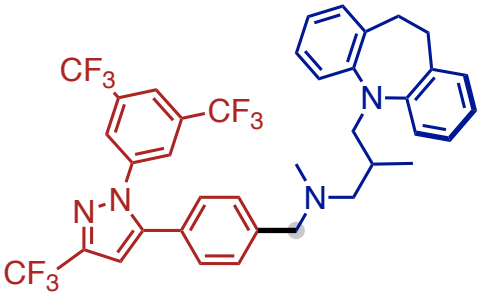


***N*-(4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)-3-(3-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*-methylpropan-1-amine (26)**. Following the general procedure A (0.1 mmol scale), the title compound was obtained in 68% yield (50.1 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.79 (s, 2H), 7.29-7.27 (m, 2H), 7.16-7.05 (m, 6H), 6.97-6.94 (m, 2H), 6.85 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.80 (s, 1H), 3.77 (t, *J* = 6.7 Hz, 2H), 3.47 (s, 2H), 3.10-3.03 (m, 4H), 2.44 (t, *J* = 6.6 Hz, 2H), 2.12 (s, 3H), 1.80-1.74 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.21, 148.01, 145.45, 144.74 (q, *J* = 38.9 Hz), 140.46, 135.24, 132.75 (q, *J* = 34.1 Hz), 131.69, 131.63, 131.32, 129.74, 129.57, 128.94, 126.95, 126.70, 125.10, 123.37, 122.69 (q, *J* = 273.1 Hz), 122.07, 121.64, 121.07 (q, *J* = 269.5 Hz), 120.68, 119.96, 106.84, 61.98, 55.10, 48.75, 41.98, 32.35, 31.68, 25.76. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.53, -63.13. HRMS *calcd*. for $C_{37}H_{30}N_4ClF_9$ $[M+H]^+$: 737.2094, *found* 737.2083.

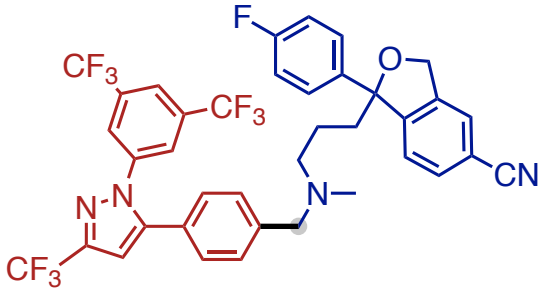


4-(5-(4-(((3-(3-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)propyl)(methyl)amino)methyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (27). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 51% yield (34.6 mg) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.24-7.22 (m, 2H), 7.12-7.02 (m, 6H), 6.96-6.92 (m, 2H), 6.84 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.77 (s, 1H), 5.10 (br, 2H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.45 (s, 2H), 3.04 (s, 4H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.14 (s, 3H), 1.75

(p, J = 6.5 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.39. ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.99, 147.77, 145.07, 144.13 (q, J = 38.6 Hz), 142.44, 141.58, 135.10, 131.49, 131.25, 129.54, 129.46, 128.82, 128.74, 127.50, 127.43, 127.26, 126.60, 125.53, 123.30, 121.96, 121.06 (q, J = 269.2 Hz), 120.53, 119.76, 106.47, 61.75, 54.94, 48.60, 42.18, 32.18, 31.48, 25.41. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.36. HRMS *calcd*. for $C_{35}H_{33}N_5O_2SClF_3$ $[M+H]^+$: 680.2074, *found* 680.2067.

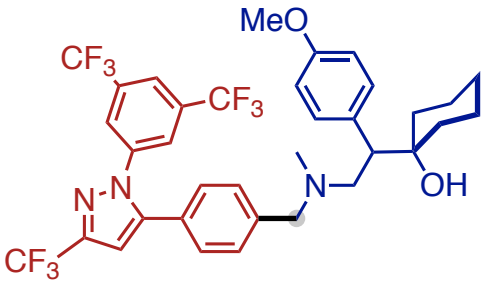


***N*-(4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)-3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*,2-dimethylpropan-1-amine (28)**. Following the general procedure A (0.1 mmol scale), the title compound was obtained in 47% yield (34.0 mg) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.79 (s, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.10-7.08 (m, 6H), 6.92-6.88 (m, 2H), 6.81 (s, 1H), 3.99-3.94 (m, 1H), 3.49-4.40 (m, 2H), 3.29-3.14 (m, 2H), 3.18 (s, 2H), 2.39-2.32 (m, 1H), 2.18-2.01 (m, 5H), 0.93 (d, J = 5.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.60, 145.34, 144.60 (d, J = 38.8 Hz), 142.08, 140.32, 134.14, 132.61 (d, J = 34.3 Hz), 129.88, 129.55, 128.79, 126.26, 124.95, 124.92, 122.55 (d, J = 273.1 Hz), 122.34, 121.50, 120.94 (d, J = 269.3 Hz), 119.87, 106.80, 106.79, 63.14, 62.40, 56.00, 42.74, 32.30, 29.44, 17.51. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56, -63.13. HRMS *calcd*. for $C_{38}H_{33}N_4F_9$ $[M+H]^+$: 717.2640, *found* 717.2653.

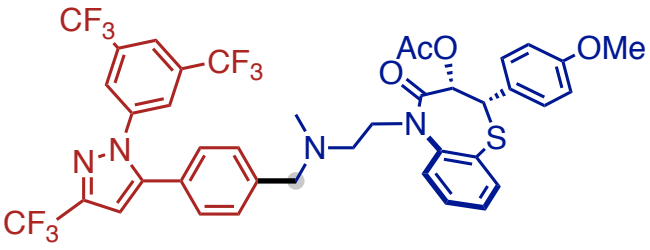


1-(3-((4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)(methyl)amino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-

carbonitrile (29). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 45% yield (31.9 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.77 (s, 2H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.51 (s, 1H), 7.44-7.37 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 2.36 (t, *J* = 6.8 Hz, 2H)., 7.69 (s, 1H), 5.21-5.13 (m, 2H), 3.45 (s, 2H), 2.27-2.10 (m, 2H), 2.08 (s, 3H), 1.58-1.48 (m, 1H), 1.44-1.35 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.41, 160.96, 149.59, 145.33, 144.71 (q, *J* = 38.8 Hz), 140.50, 140.38, 139.66, 132.68 (q, *J* = 34.2 Hz), 131.99, 129.82, 128.97, 126.90, 126.82, 125.38, 125.03, 125.00, 122.83, 122.65 (d, *J* = 273.1 Hz), 121.58, 121.01 (d, *J* = 269.2 Hz), 118.73, 115.59, 115.37, 111.92, 106.91, 91.23, 71.39, 61.87, 57.27, 41.77, 38.98, 21.98, 14.32. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56, -63.14, -115.31. HRMS *calcd*. for $C_{38}H_{28}N_4OF_{10}$ $[M+H]^+$: 747.2181, *found* 747.2181.

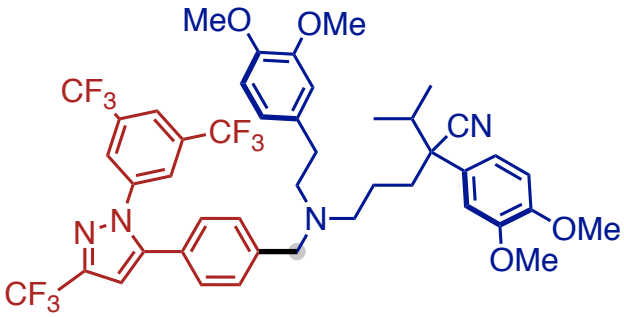


1-(2-((4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)(methyl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexan-1-ol (30). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 83% yield (58.0 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.78 (s, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 10.1 Hz, 3H), 3.79-3.78 (m, 4H), 3.47-3.37 (m, 2H), 3.07-3.04 (m, 1H), 2.47-2.43 (m, 1H), 2.26 (s, 3H), 1.71-0.83 (m, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 74.40, 62.31, 59.37, 55.18, 51.55, 41.93, 37.95, 31.25, 25.84, 21.48, 21.34. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.40, 145.04, 144.61 (q, *J* = 38.8 Hz), 140.24, 140.05, 132.67 (q, *J* = 34.3 Hz), 132.53, 130.10, 129.01, 127.40, 125.06, 125.03, 122.51 (q, *J* = 273.2 Hz),121.65 (m), 120.87 (q, *J* = 269.3 Hz), 113.39, 106.85, 74.40, 62.31, 59.37, 55.18, 51.55, 41.93, 37.95, 31.25, 25.84, 21.48, 21.34. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56, -63.16. HRMS *calcd*. for $C_{35}H_{34}N_3O_2F_9$ $[M+H]^+$: 700.2585, *found* 700.2574.



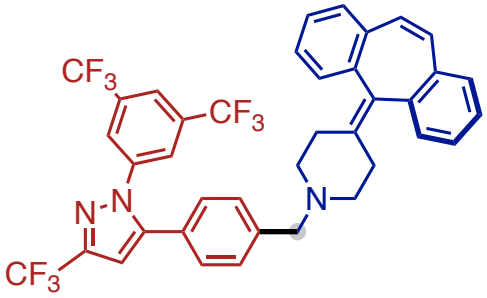
(*contains 19% oxidized diltiazem impurity, likely the formamide*)

(2S,3S)-5-(2-((4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)benzyl)(methyl)amino)ethyl)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl acetate (31). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 77% yield (64.0 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.78 (s, 2H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.48-7.47 (m, 2H), 7.44-7.41 (m, 2H), 7.28-7.24 (3H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.80 (s, 1H), 5.18 (d, *J* = 7.6 Hz, 1H), 5.03 (d, *J* = 7.6 Hz, 1H), 4.51 (dt, *J* = 13.7, 6.8 Hz, 1H), 3.83-3.79 (m, 1H), 3.81 (s, 3H), 3.63-3.54 (m, 2H), 2.92-2.85 (m, 1H), 2.75-2.68 (m, 1H), 2.17 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.02, 167.09, 159.86, 145.82, 145.41, 144.64 (q, *J* = 38.8 Hz), 140.86, 140.37, 135.53, 132.68 (q, *J* = 34.2 Hz), 131.10, 130.91, 129.82, 128.85, 127.40, 126.78, 125.04, 125.00, 124.70, 123.23, 122.62 (q, *J* = 273.1 Hz), 121.58, 121.02 (q, *J* = 269.3 Hz), 113.84, 106.86, 71.21, 61.79, 55.63, 55.28, 54.57, 47.88, 41.82, 20.59. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.55, -63.16. HRMS *calcd*. for $C_{40}H_{33}N_4O_4SF_9$ $[M+H]^+$: 837.2157, *found* 837.2169.

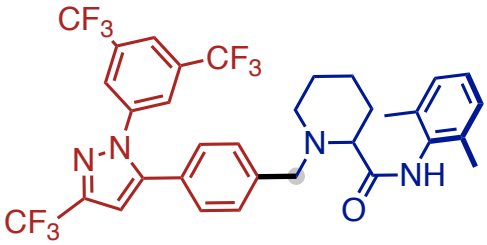


5-((4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)(3,4-dimethoxyphenethyl)amino)-2-(3,4-dimethoxyphenyl)-2-isopropylpentanenitrile (32). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 64% yield (56.1 mg) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.78 (s, 2H), 7.28-7.26 (m, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 6.87-6.80

(m, 4H), 6.76 (d, J = 8.3 Hz, 1H), 6.63-6.61 (m, 2H), 3.89 (d, J = 2.9 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 6H), 3.81 (s, 3H), 3.57 (br, 1H), 2.64-1.50 (m, 11H), 1.15 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.20, 148.99, 148.52, 147.54, 145.39, 144.63 (q, J = 39.3 Hz), 142.31, 140.44, 133.09, 132.58 (q, J = 34.6, 34.0 Hz), 130.80, 129.52, 128.86, 126.88, 125.05, 122.54 (q, J = 273.0 Hz), 121.54, 120.88 (q, J = 269.2 Hz), 120.74, 118.75, 112.34, 111.45, 111.30, 110.00, 106.95, 58.07, 56.13, 56.07, 55.98, 55.54, 53.45, 53.05, 38.10, 35.62, 33.17, 23.20, 19.02, 18.65. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.57, -63.08. HRMS *calcd*. for $C_{45}H_{45}N_4O_4F_9$ $[M+H]^+$: 877.3375, *found* 877.3352.

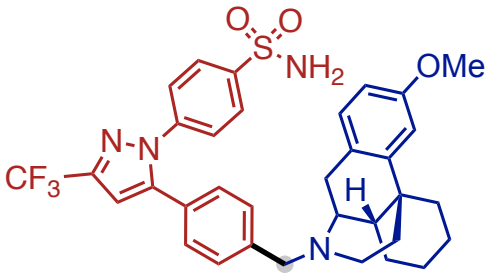


1-(4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)-4-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)piperidine (33). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 45% yield (31.9 mg) as red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.68 (s, 2H), 7.30-7.22 (m, 6H), 7.18-7.07 (m, 6H), 6.85 (s, 2H), 6.71 (s, 1H), 3.43 (s, 2H), 2.54-2.39 (m, 2H), 2.36-2.23 (m, 2H), 2.12-2.03 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.36, 144.72 (q, J = 38.9 Hz), 140.38, 139.21, 134.92, 132.73 (q, J = 34.3 Hz), 131.14, 130.03, 128.95, 128.62, 128.35, 127.91, 126.44, 125.07, 125.04, 122.64 (q, J = 273.1 Hz), 121.63, 121.04 (d, J = 269.3 Hz), 106.90, 62.36, 55.16, 30.05. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56, -63.20. HRMS *calcd*. for $C_{39}H_{28}N_3F_9$ $[M+H]^+$: 710.2218, *found* 710.2220.



1-(4-(1-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide (34). Following the

general procedure A (0.1 mmol scale), the title compound was obtained in 37% yield (24.7 mg) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.82 (s, 1H), 7.77 (s, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.12-7.05 (m, 3H), 6.80 (s, 1H), 4.24 (d, *J* = 14.2 Hz, 1H), 3.42 (d, *J* = 14.2 Hz, 1H), 3.06 (dd, *J* = 10.2, 3.4 Hz, 1H), 2.93 (dt, *J* = 11.7, 3.3 Hz, 1H), 2.23-2.18 (m, 1H), 2.18 (s, 6H), 2.08-2.01 (m, 1H), 1.88-1.78 (m, 2H), 1.71-1.67 (m, 1H), 1.54-1.37 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.59, 145.11, 144.79 (q, *J* = 38.8 Hz), 140.34, 135.60, 133.56, 132.78 (q, *J* = 34.2 Hz), 129.30, 128.59, 127.53, 127.42, 125.05, 125.02, 122.64 (q, *J* = 273.0 Hz), 121.72, 121.00 (q, *J* = 269.4 Hz), 106.98, 68.57, 60.86, 51.96, 31.04, 24.94, 23.61, 18.84. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.57, -63.20. HRMS *calcd*. for $C_{33}H_{29}N_4OF_9$ $[M+H]^+$: 669.2276, *found* 669.2272.

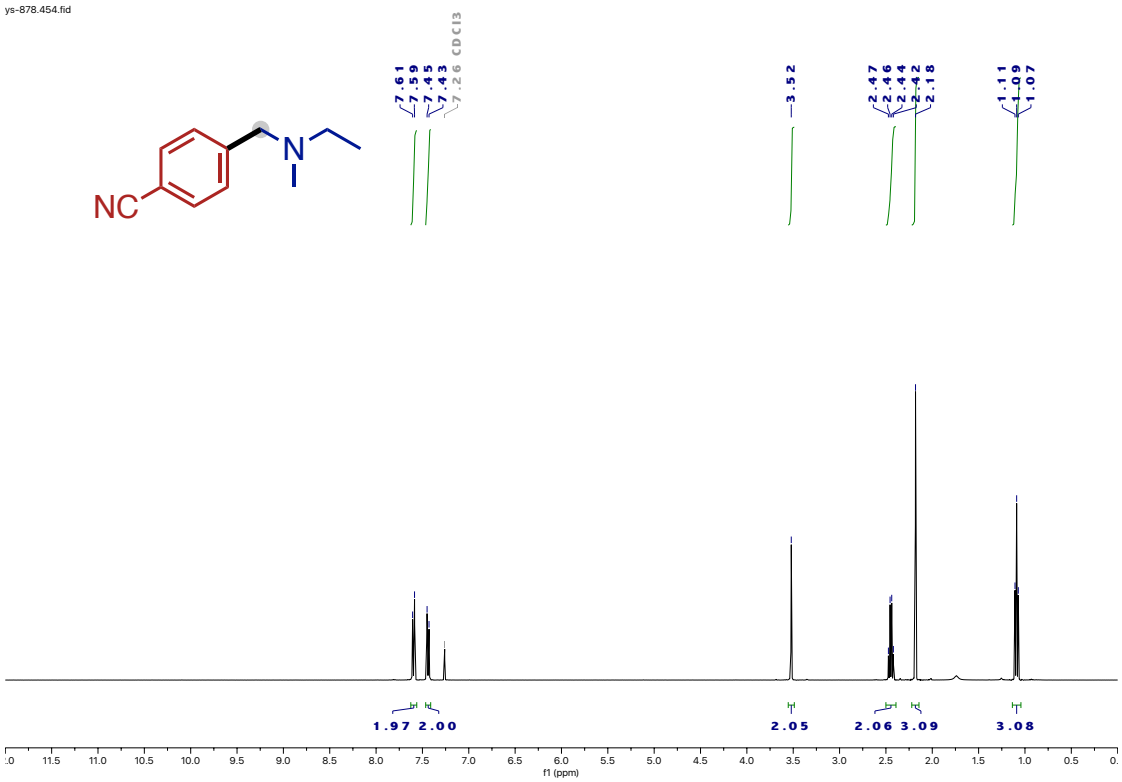


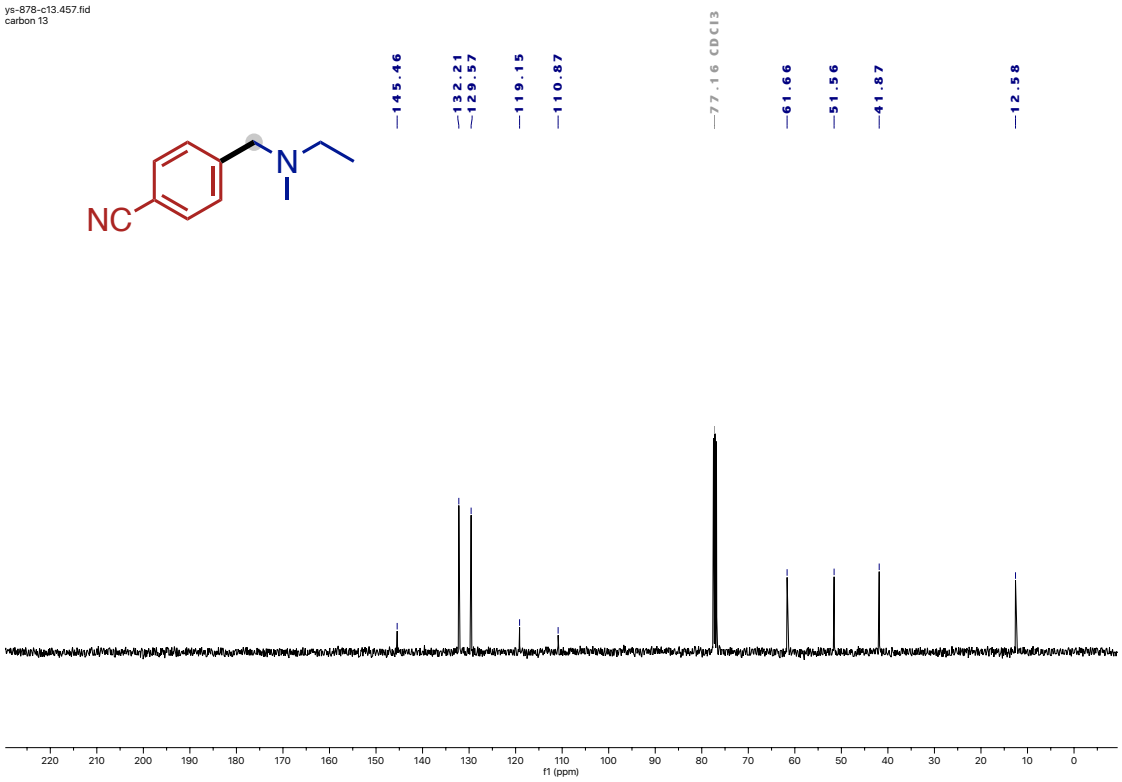
4-(5-(4-(((4b*S*,8a*S*)-3-methoxy-6,7,8,8a,9,10-hexahydro-5*H*-9,4b-(epiminoethano)phenanthren-11-yl)methyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35). Following the general procedure A (0.1 mmol scale), the title compound was obtained in 72% yield (45.8 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.87 (m, 2H), 7.48-7.44 (m, 2H), 7.39-7.37 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.76 (s, 1H), 6.71 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.10 (br, 2H), 3.78 (s, 3H), 3.77-3.60 (m, 2H), 3.03-3.63 (m, 3H), 2.42-2.11 (m, 3H), 1.89-1.50 (m, 4H), 1.37-1.24 (m, 5H), 1.16-1.07 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.39, 145.29, 144.24 (q, *J* = 38.6 Hz), 142.63, 141.94, 141.61, 129.89, 129.39, 128.88, 128.66, 127.62, 127.18, 125.64, 121.17 (q, *J* = 269.2 Hz), 111.28, 110.91, 106.60, 59.02, 56.75, 55.34, 45.52, 45.29, 42.08, 37.89, 36.74, 26.94, 26.68, 24.91, 22.37. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.41. HRMS *calcd*. for $C_{34}H_{35}N_4O_3SF_3$ $[M+H]^+$: 637.2460, *found* 637.2471.

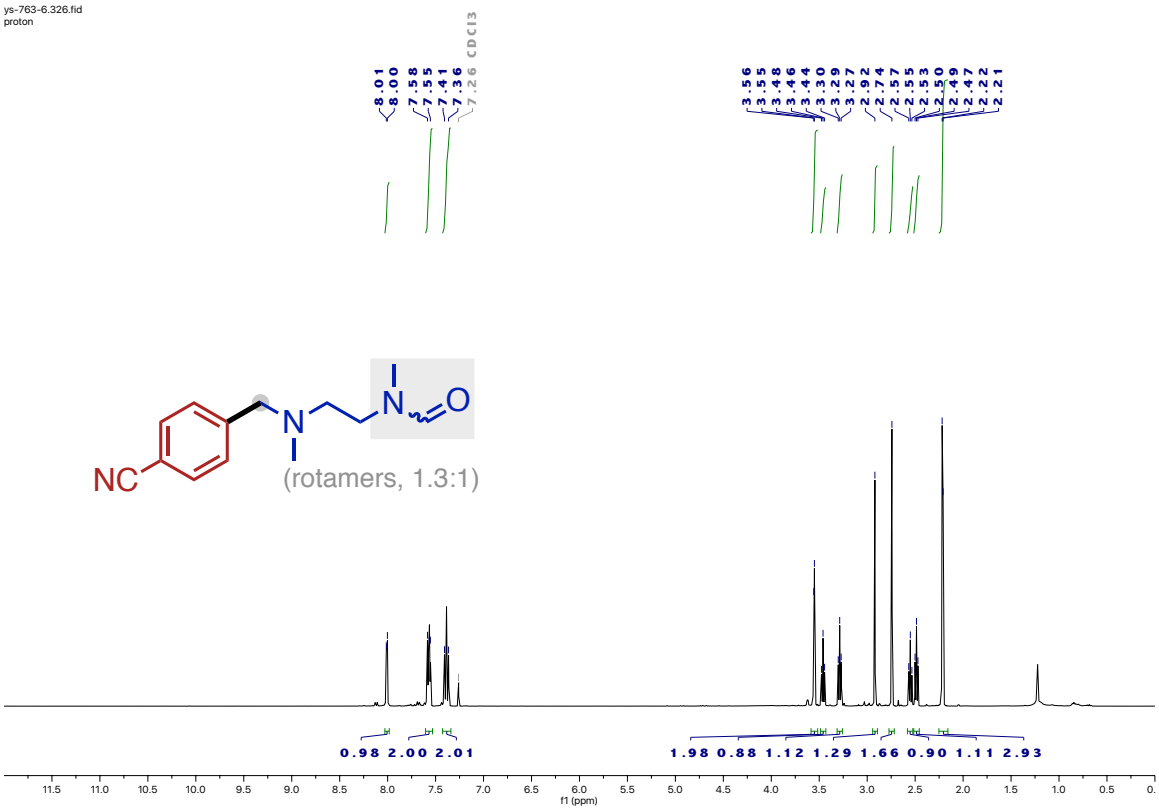
IV. References

1. Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C. Photoredox-Catalyzed Deuteration and Tritiation of Pharmaceutical Compounds. *Science* **2017**, *358*, 1182–1187.
2. Shen, Y.; Funes-Ardoiz, I.; Schoenebeck, F.; Rovis, T. Site-selective α-C–H Functionalization of Trialkylamines via Reversible Hydrogen Atom Transfer Catalysis. *ChemRxiv* **2021**, DOI: 10.26434/chemrxiv.14442290.v1.
3. Chang, Y.; Yesilcimen, A.; Cao, M.; Zhang, Y.; Zhang, B.; Chan, J. Z.; Wasa, M. Catalytic Deuterium Incorporation within Metabolically Stable β-Amino C–H Bonds of Drug Molecules. *J. Am. Chem. Soc.* **2019**, *141*, 14570–14575.

V. ^{1}H, ^{13}C and ^{19}F NMR spectra



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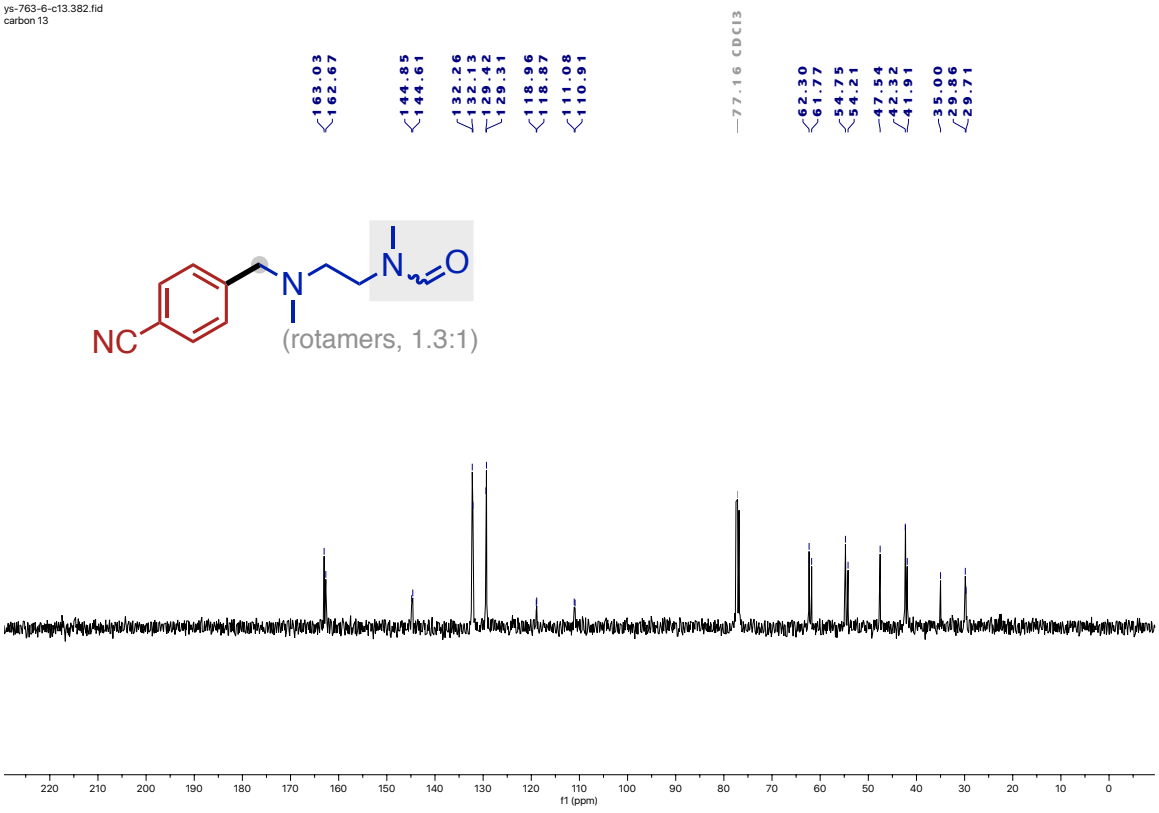
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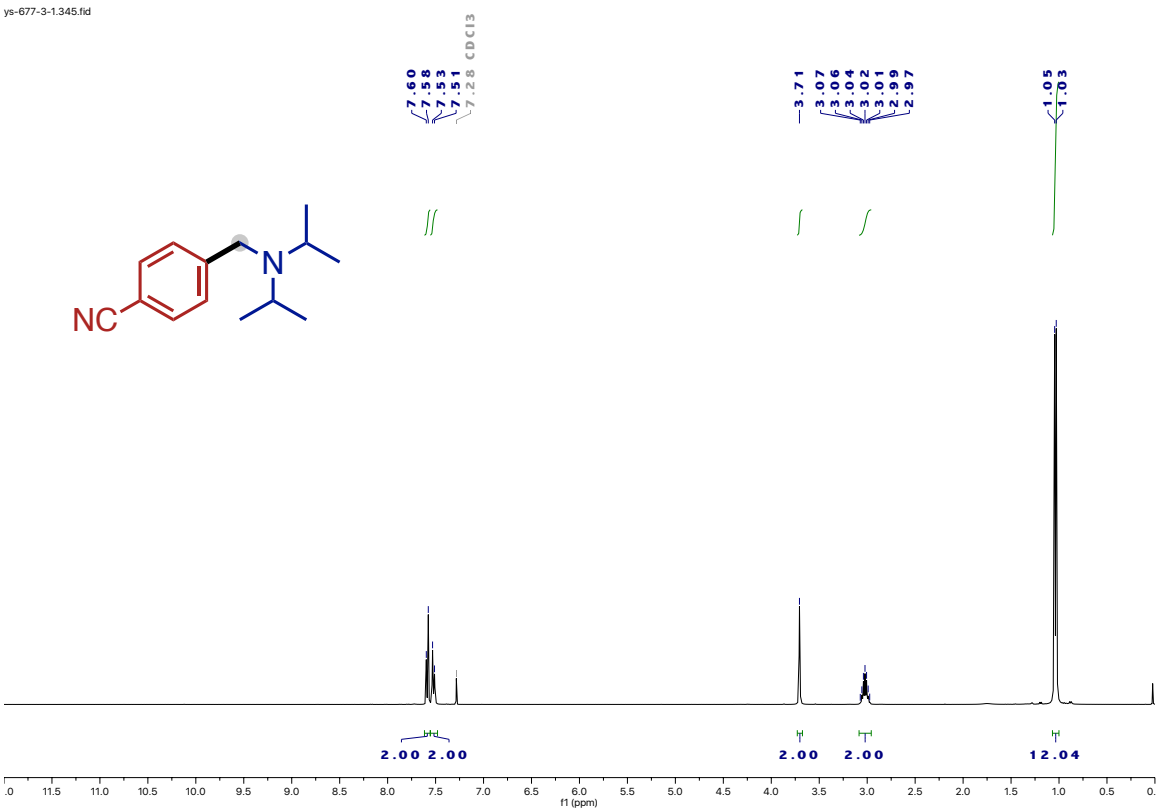
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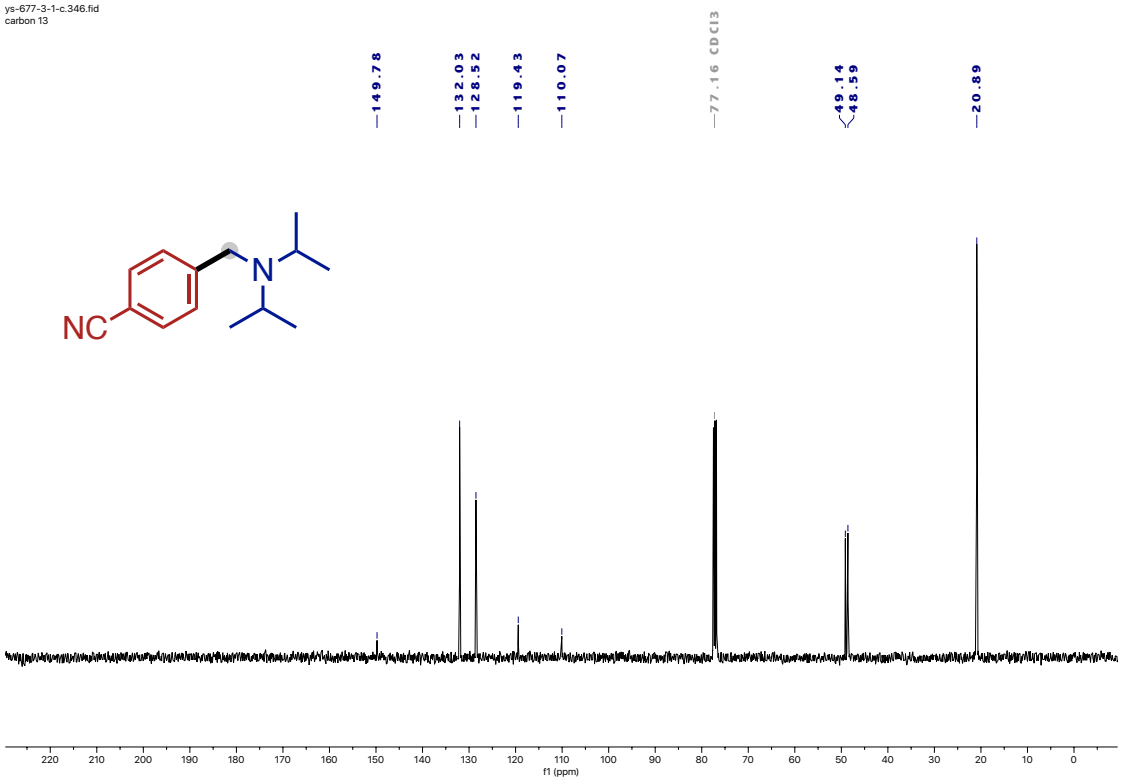
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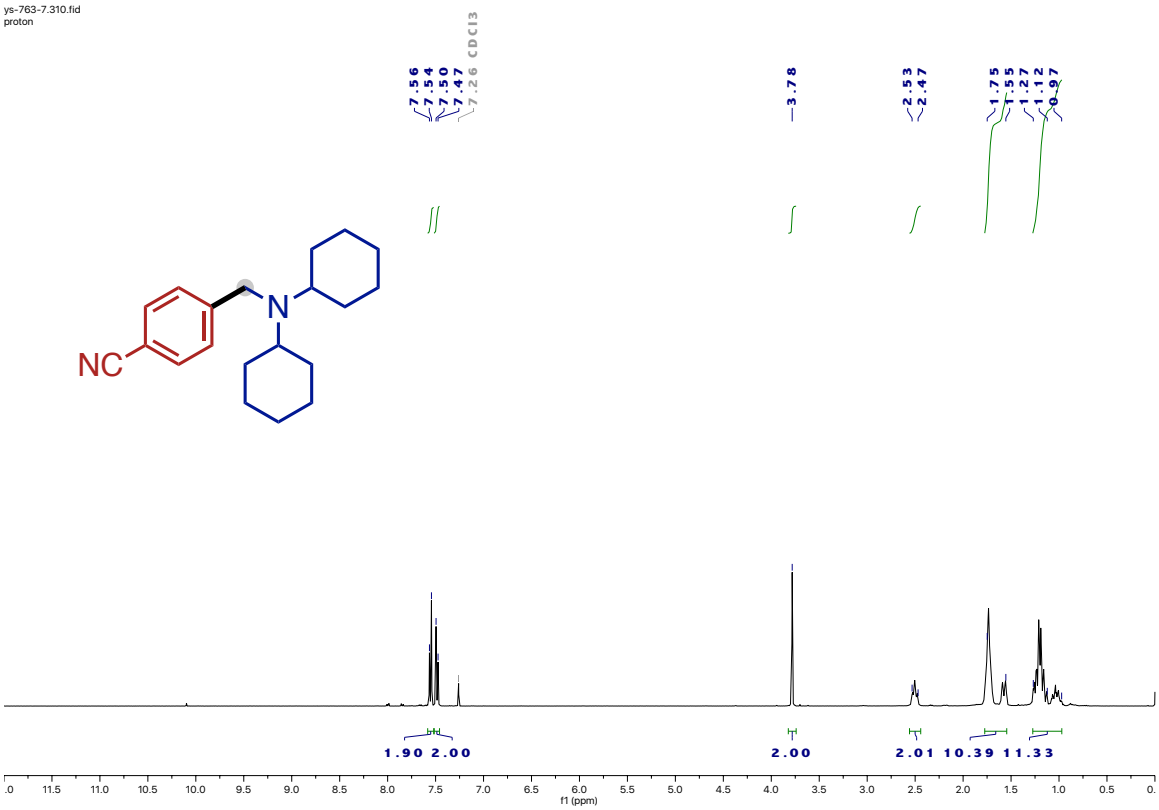
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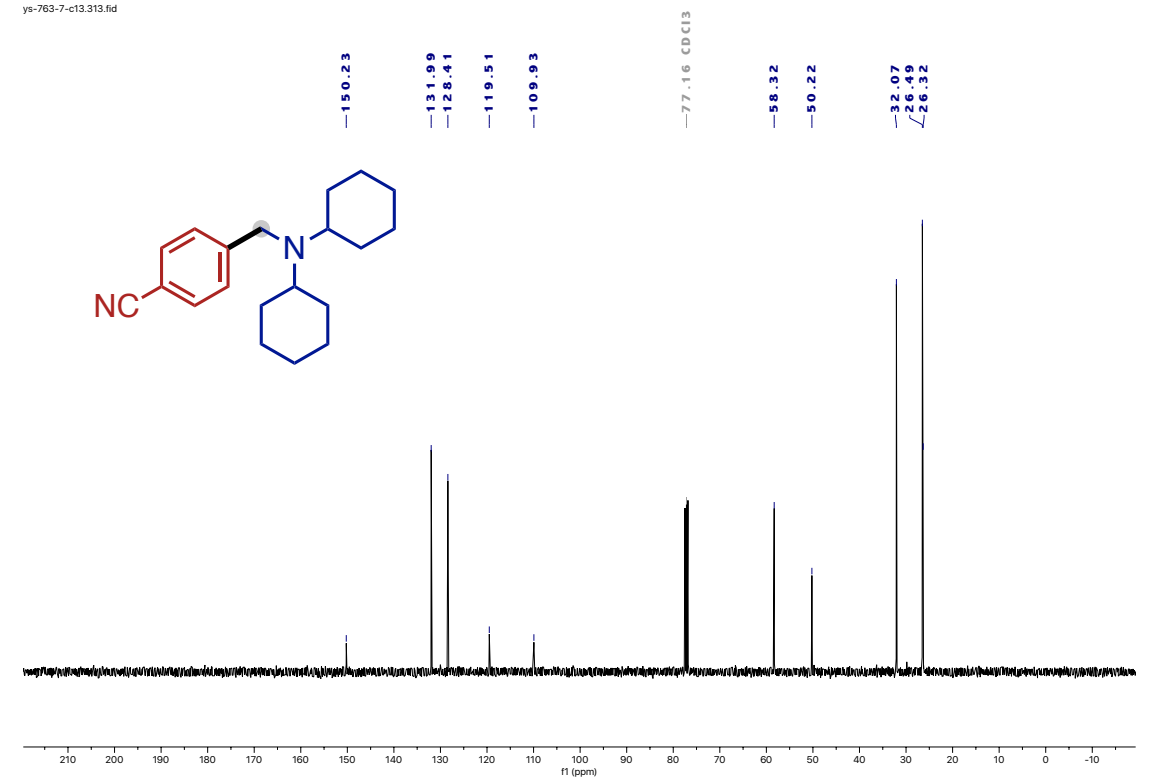
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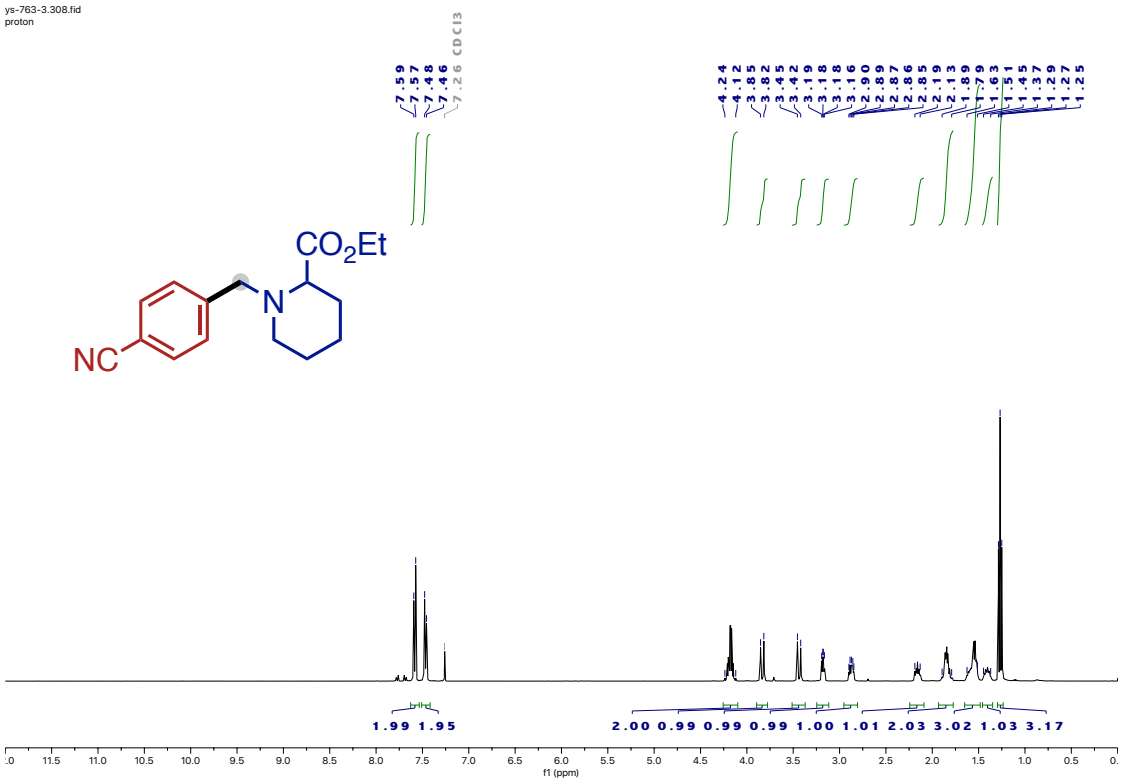
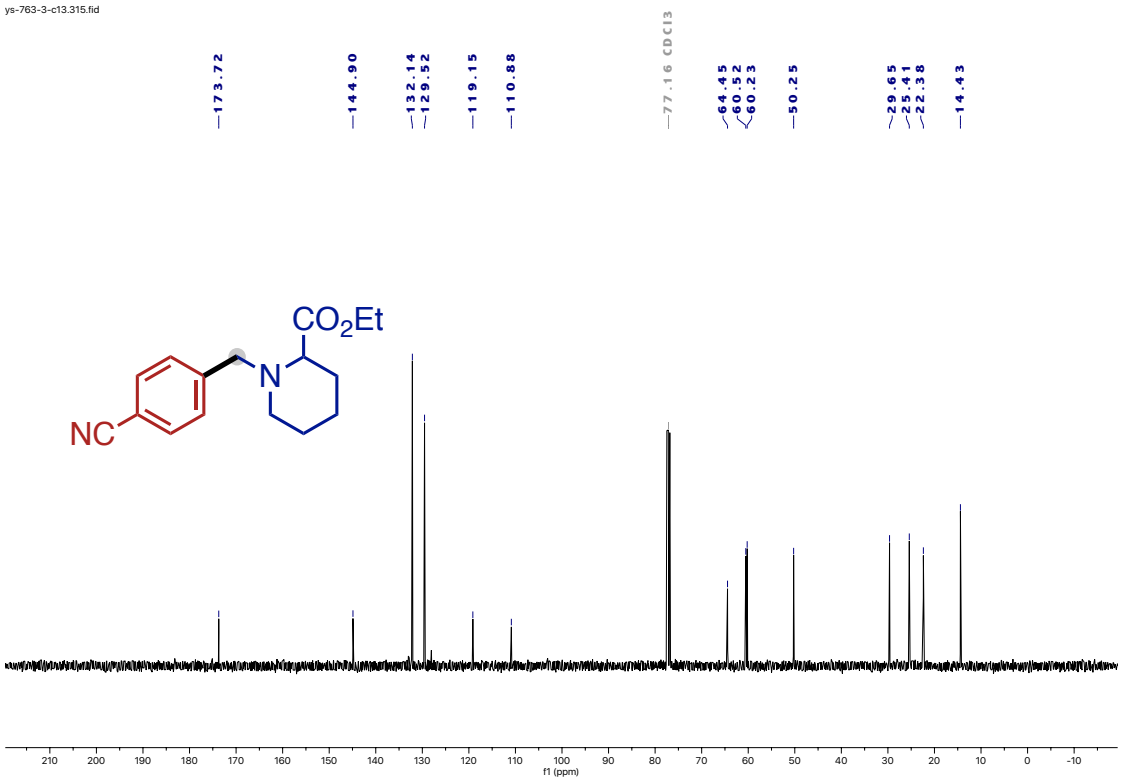
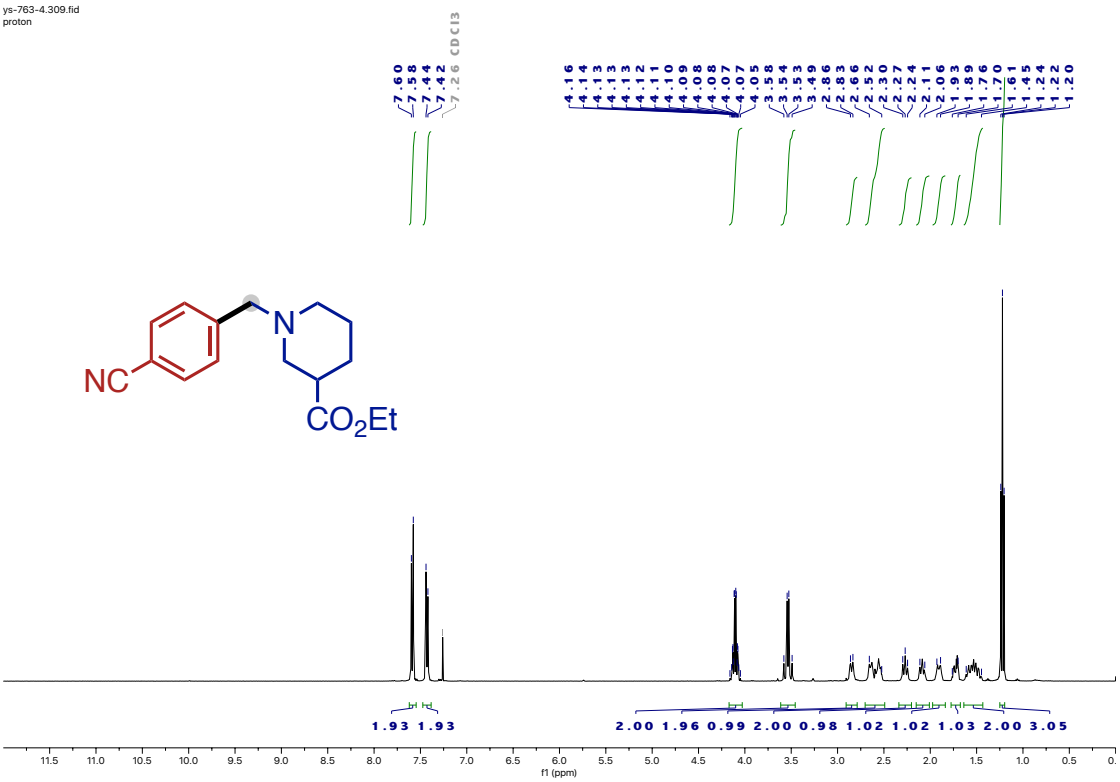
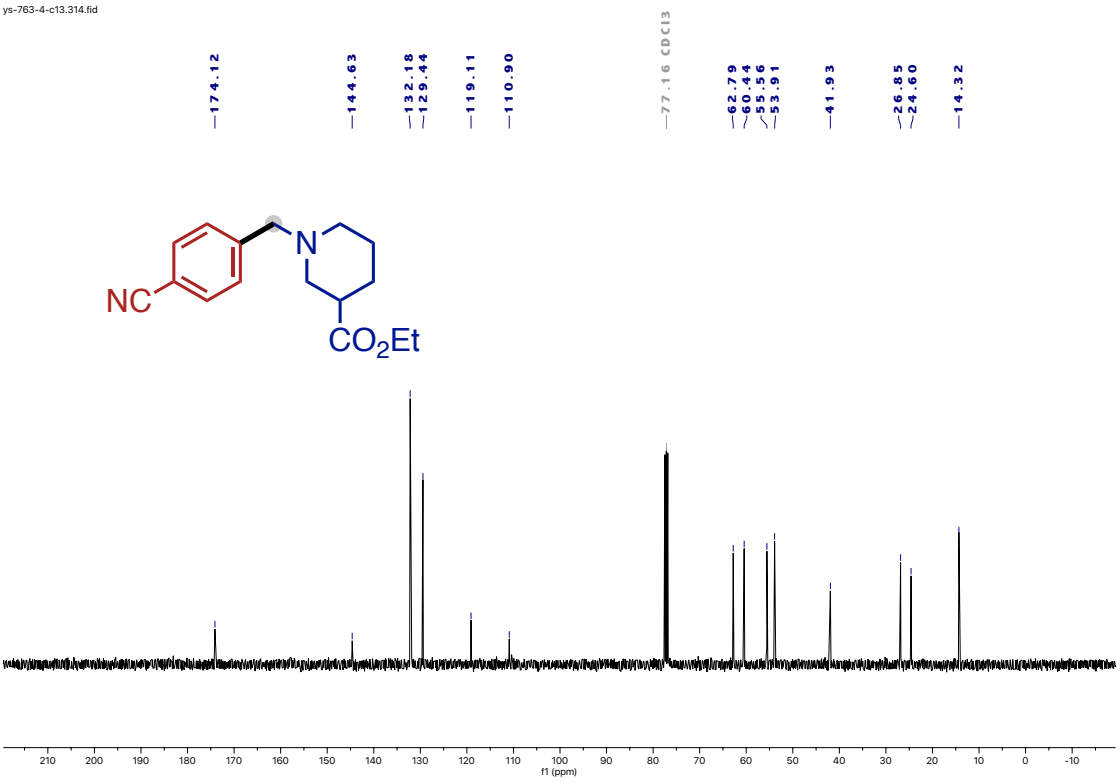
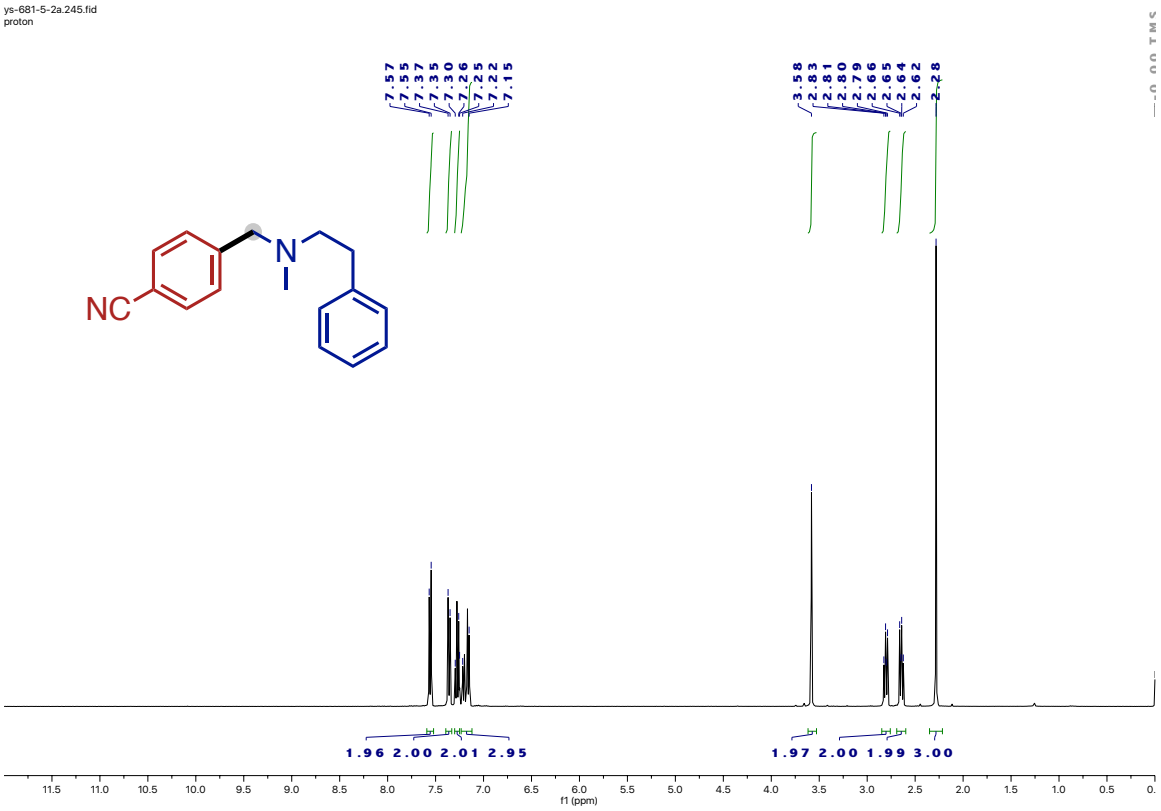
N
f1 (ppm)


ys-763-3.308.fid
proton
7.59
7.57
7.48
7.46
7.26 CDCl3
4.24
4.12
3.85
3.82
3.45
3.42
3.18
3.16
3.00
2.89
2.87
2.86
2.85
2.19
2.13
1.89
1.79
1.63
1.51
1.45
1.37
1.29
1.27
1.25
CO2Et
N
NC
1.99 1.95
2.00 0.99 0.99 0.99 1.00 1.01 2.03 3.02 1.03 3.17
f1 (ppm)


ys-763-3-c13.315.fid
173.72
144.90
132.14
129.52
119.15
110.88
77.16 CDCl3
64.45
60.52
60.23
50.25
29.65
25.41
22.38
14.43
CO2Et
N
NC
f1 (ppm)


ys-763-4.309.fid
proton
7.60
7.58
7.44
7.42
7.26 CDCl3
4.16
4.14
4.13
4.13
4.12
4.11
4.10
4.09
4.08
4.08
4.07
4.07
4.05
3.58
3.54
3.53
3.49
2.86
2.83
2.66
2.52
2.30
2.27
2.24
2.11
2.06
1.93
1.89
1.76
1.70
1.61
1.45
1.24
1.22
1.20
NC
N
CO2Et
1.93 1.93
2.00 1.96 0.99 2.00 0.98 1.02 1.02 1.03 2.00 3.05
f1 (ppm)


ys-763-4-c13.314.fid
174.12
144.63
132.18
129.44
119.11
110.90
77.16 CDCl3
62.79
60.44
55.56
53.91
41.93
26.85
24.60
14.32
NC
N
CO2Et
f1 (ppm)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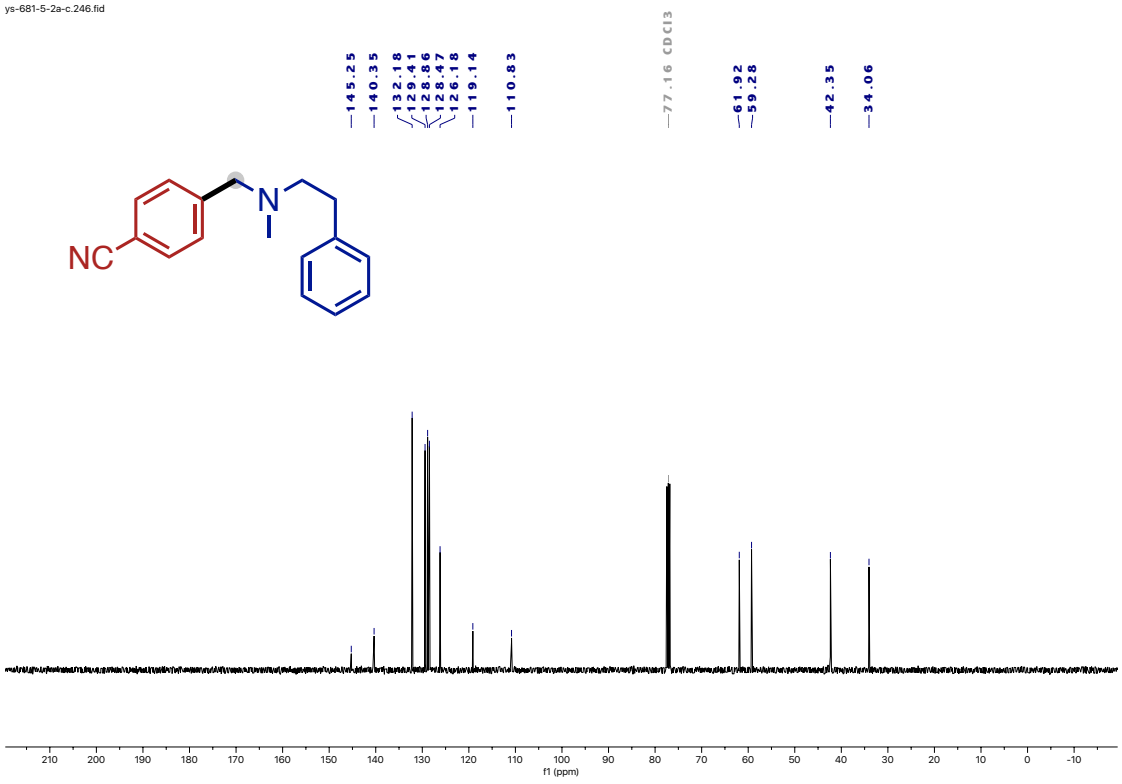
proton
7.57
7.55
7.37
7.35
7.30
7.26
7.25
7.22
7.15
3.58
2.83
2.81
2.80
2.79
2.66
2.65
2.64
2.62
2.28
TMS
NC
N
1.96 2.00 2.01 2.95
1.97 2.00 1.99 3.00
f1 (ppm)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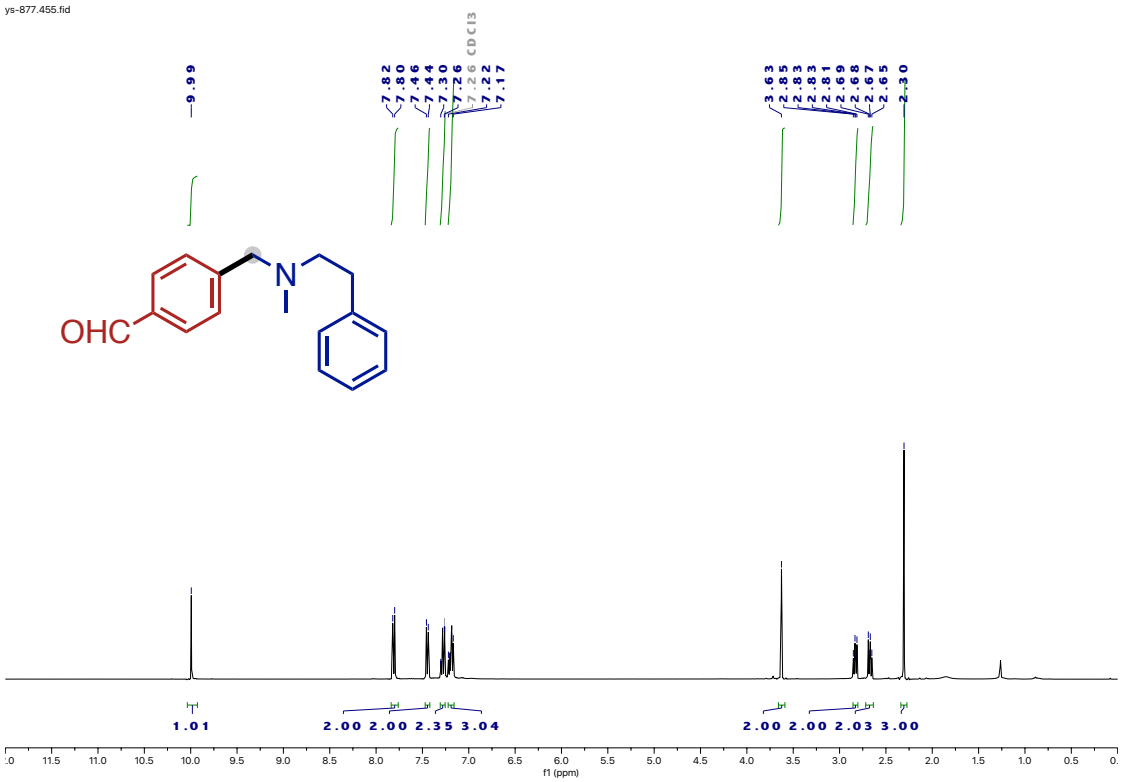
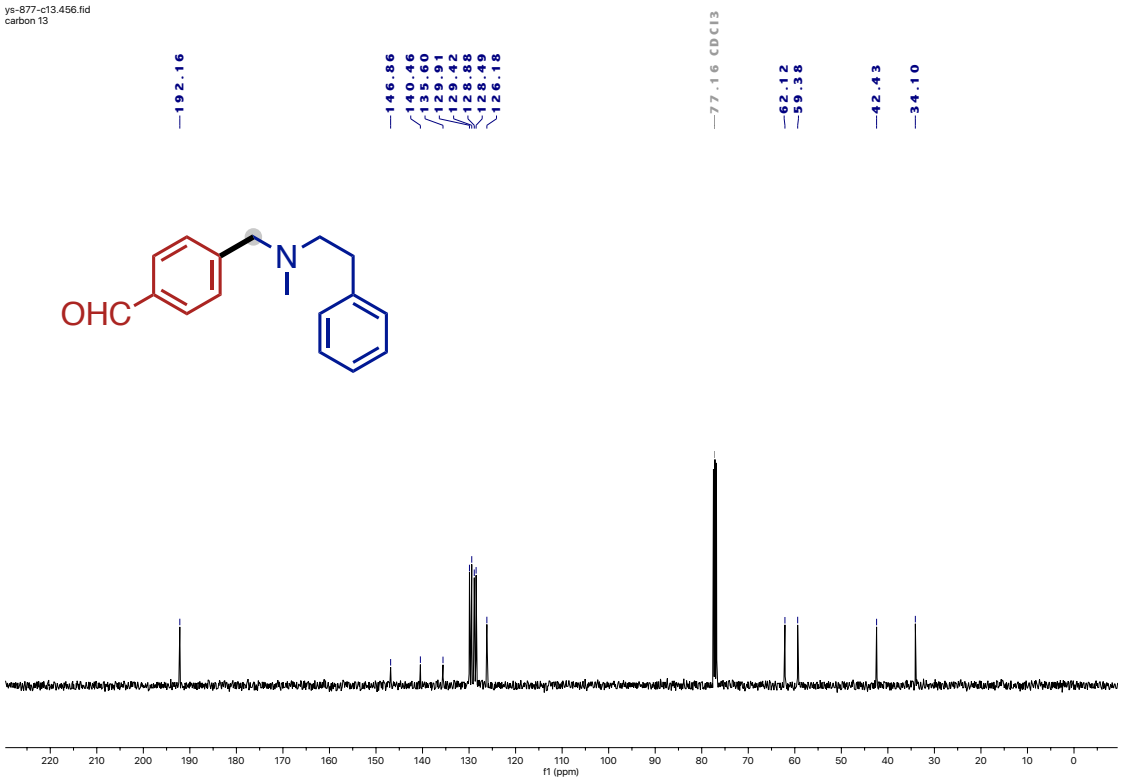
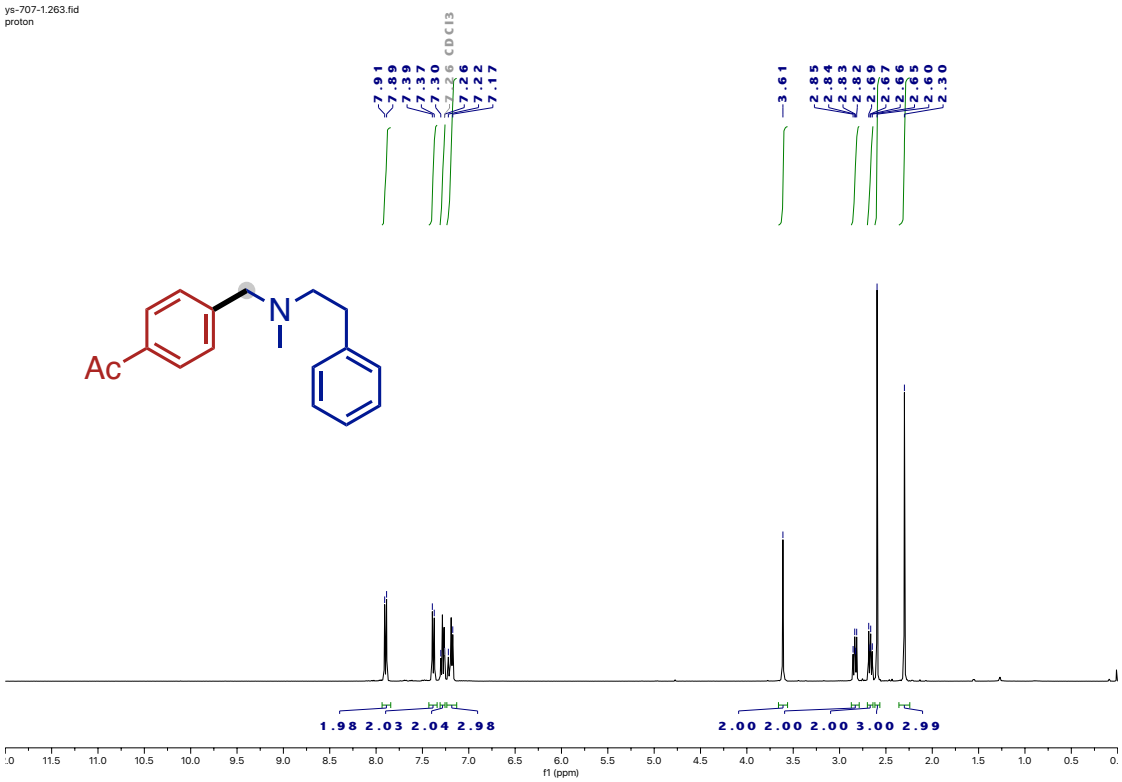
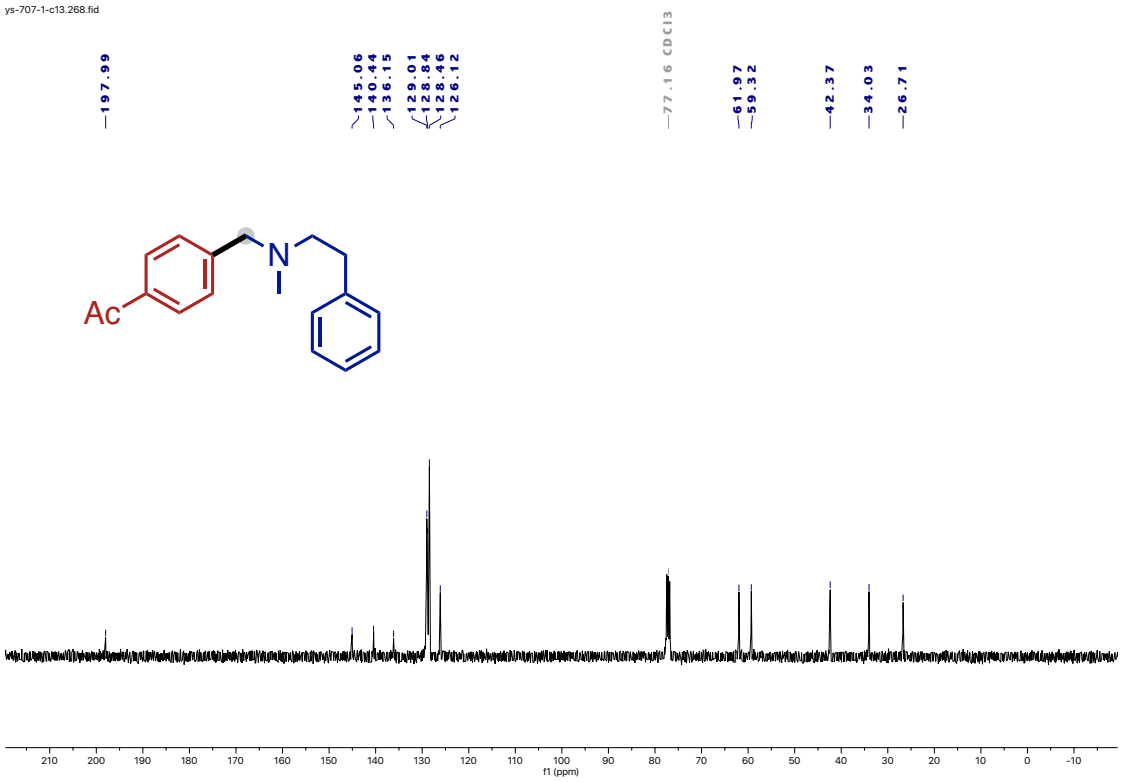
145.25
140.35
132.18
129.41
128.86
128.47
126.18
119.14
110.83
77.16 CDCl3
61.92
59.28
42.35
34.06
NC
N
f1 (ppm)


ys-877.455.fid
9.99
7.82
7.80
7.46
7.44
7.30
7.26 CDCl3
7.22
7.17
3.63
2.85
2.83
2.81
2.69
2.68
2.67
2.65
2.30
OHC
N
1.01
2.00 2.00 2.35 3.04
2.00 2.00 2.03 3.00
f1 (ppm)


ys-877-c13.456.fid
carbon 13
192.16
146.86
140.46
135.60
129.91
129.42
128.88
128.49
126.18
77.16 CDCl3
62.12
59.38
42.43
34.10
OHC
N
f1 (ppm)


ys-707-1.263.fid
proton
7.91
7.89
7.39
7.37
7.30
7.26
CDCl3
7.26
7.22
7.17
3.61
2.85
2.84
2.83
2.82
2.69
2.67
2.66
2.65
2.60
2.30
Ac
N
1.98 2.03 2.04 2.98
2.00 2.00 2.00 3.00 2.99
f1 (ppm)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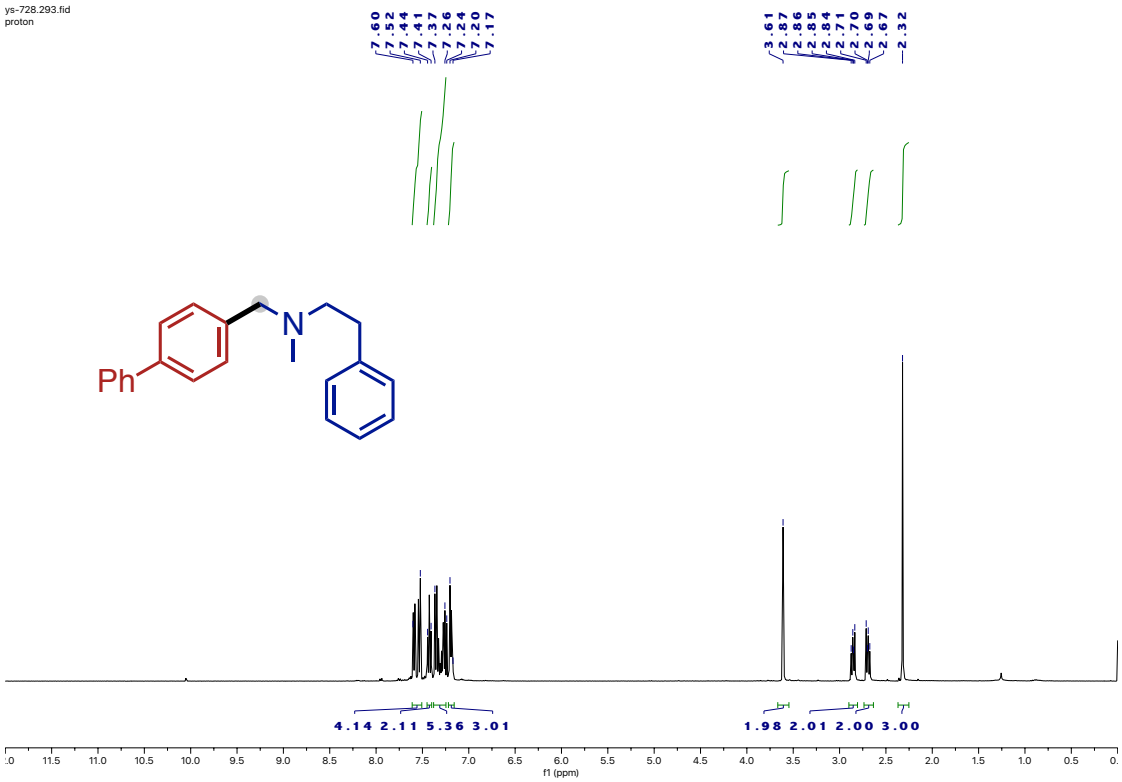
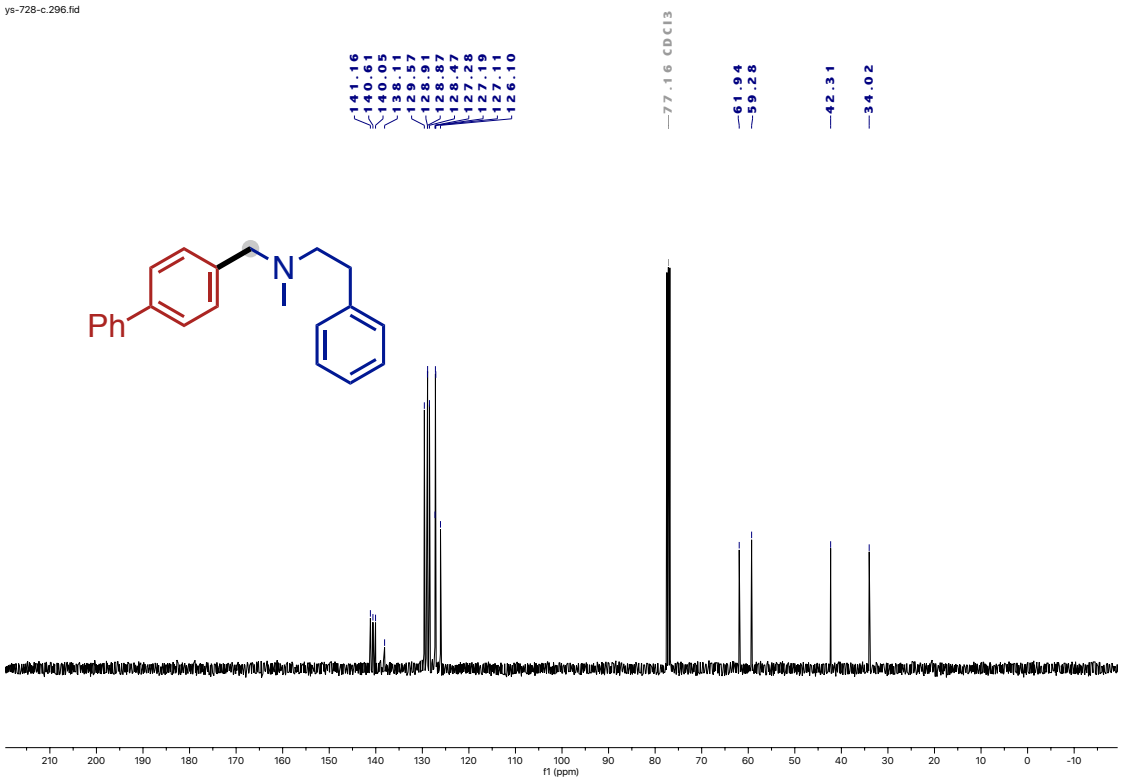
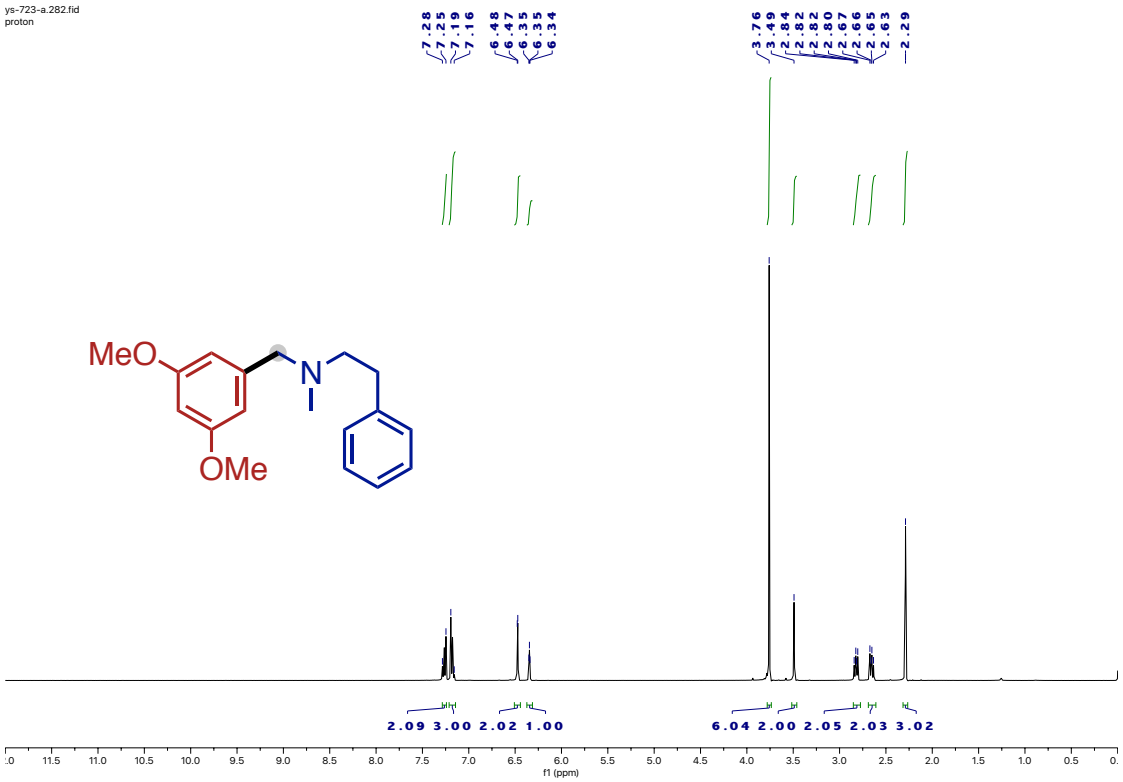
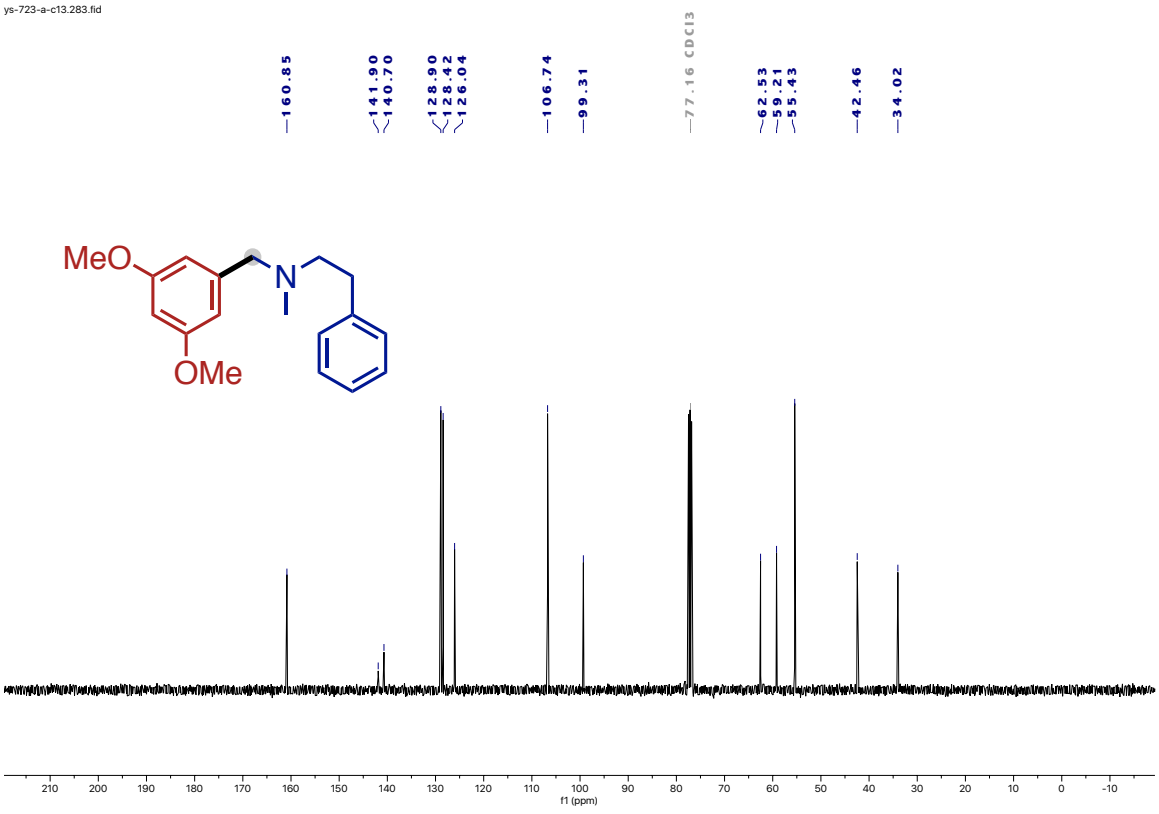
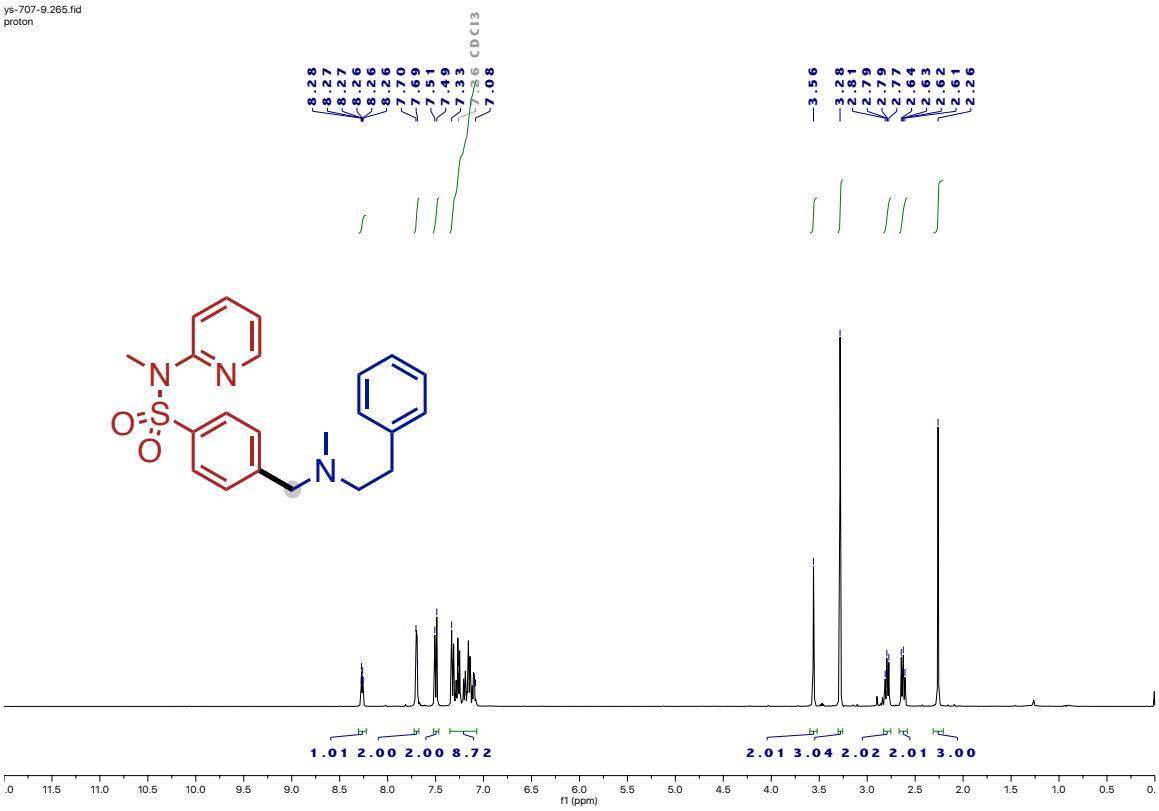
197.99
145.06
140.44
136.15
129.01
128.84
128.46
126.12
77.16 CDCl3
61.97
59.32
42.37
34.03
26.71
Ac
N
f1 (ppm)

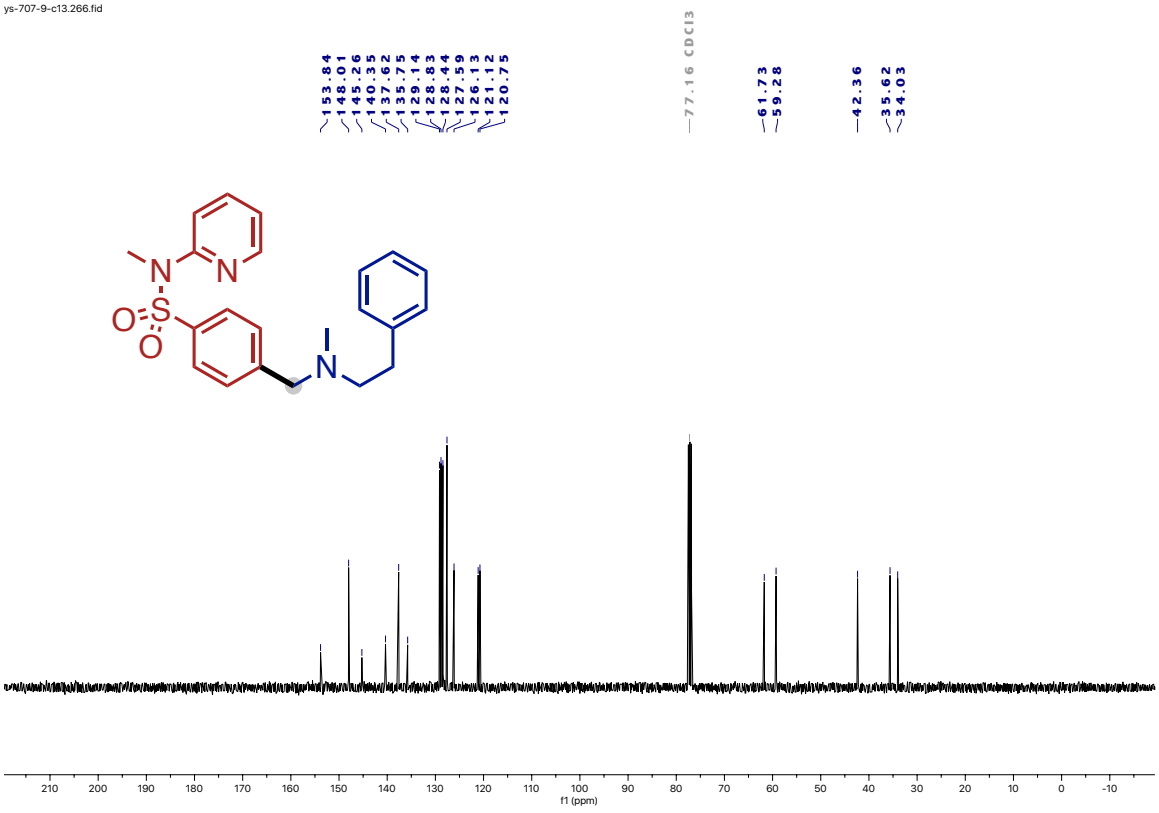

ys-728.293.fid
proton
7.60
7.52
7.44
7.41
7.37
7.26
7.24
7.20
7.17
3.61
2.87
2.86
2.85
2.84
2.71
2.70
2.69
2.67
2.32
Ph
N
4.14 2.11 5.36 3.01
1.98 2.01 2.00 3.00
f1 (ppm)


ys-728-c.296.fid
141.16
140.61
140.05
138.11
129.57
128.91
128.87
128.47
127.28
127.19
127.11
126.10
77.16 CDCl3
61.94
59.28
42.31
34.02
Ph
N
f1 (ppm)


ys-723-a.282.fid
proton
7.28
7.25
7.19
7.16
6.48
6.47
6.35
6.35
6.34
3.76
3.49
2.84
2.82
2.82
2.80
2.67
2.66
2.65
2.63
2.29
MeO
N
OMe
2.09 3.00 2.02 1.00
6.04 2.00 2.05 2.03 3.02
f1 (ppm)


ys-723-a-c13.283.fid
160.85
141.90
140.70
128.90
128.42
126.04
106.74
99.31
77.16 CDCl3
62.53
59.21
55.43
42.46
34.02
MeO
N
OMe
f1 (ppm)


ys-707-9.265.fid
proton
8.28
8.27
8.27
8.26
8.26
8.26
7.70
7.69
7.51
7.49
7.33
7.08
CDCl3
3.56
3.28
2.81
2.79
2.79
2.77
2.64
2.63
2.62
2.61
2.26
1.01 2.00 2.00 8.72
2.01 3.04 2.02 2.01 3.00
f1 (ppm)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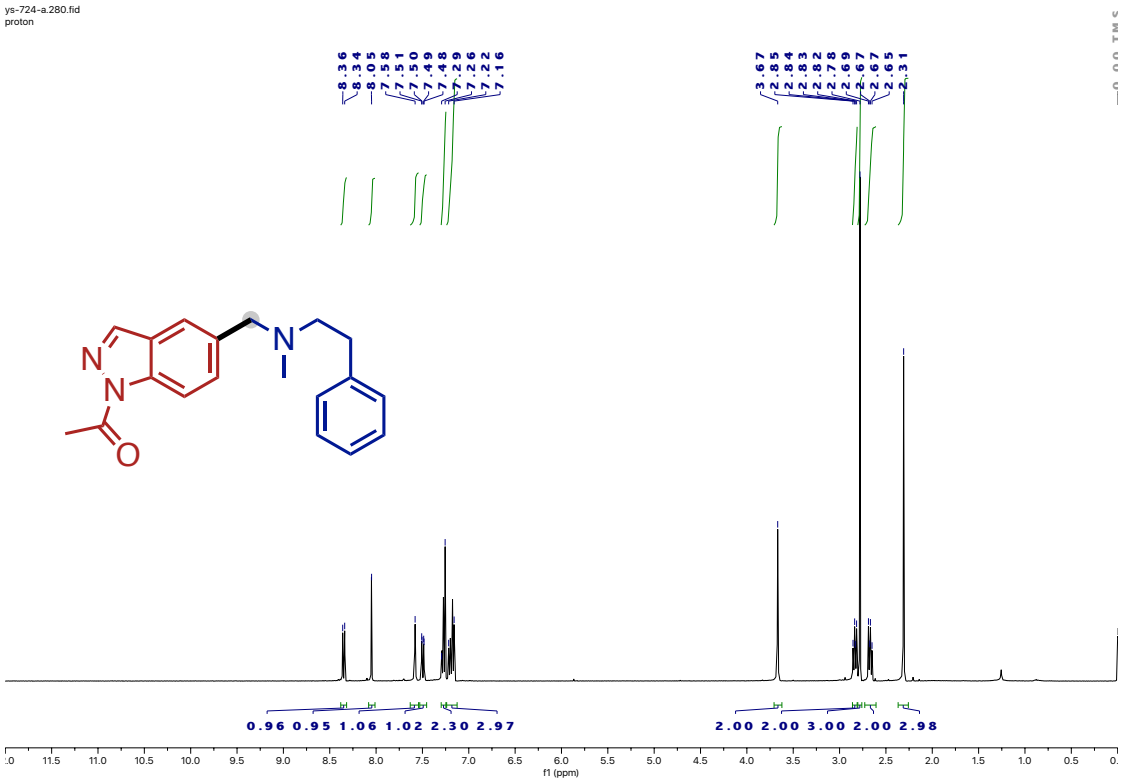
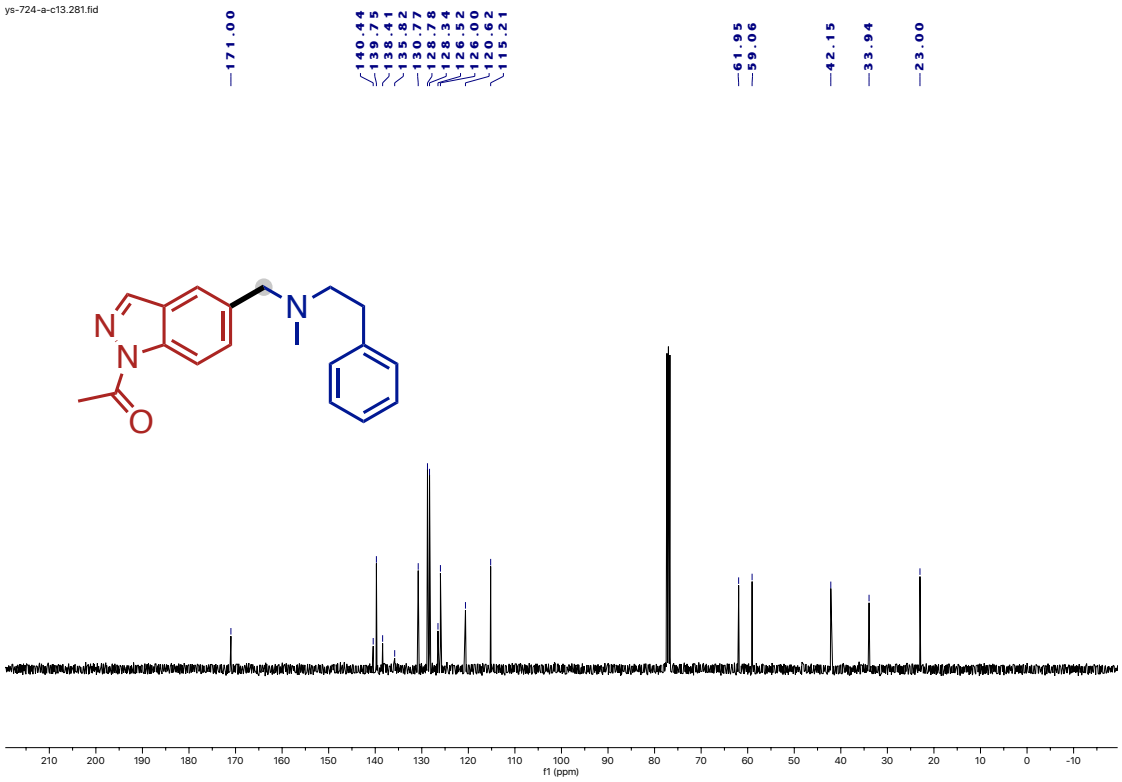
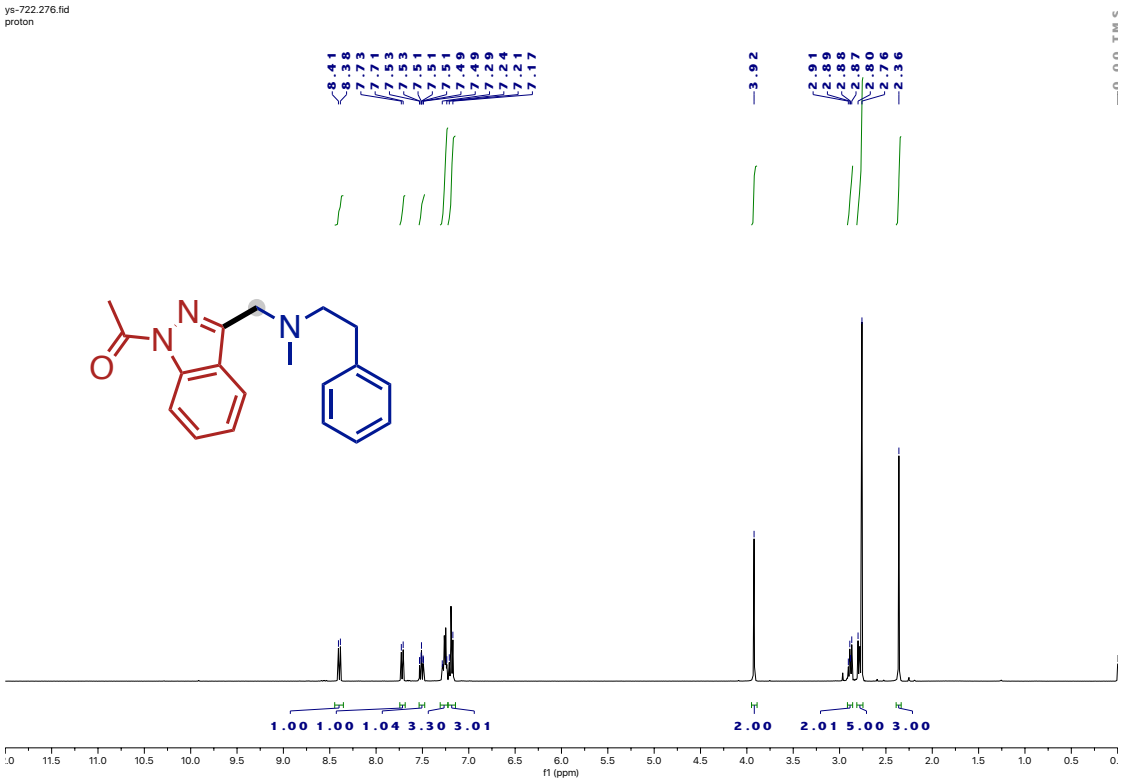
153.84
148.01
145.26
140.35
137.62
135.75
129.14
128.83
128.44
127.59
126.13
121.12
120.75
77.16 CDCl3
61.73
59.28
42.36
35.62
34.03
f1 (ppm)


ys-724-a.280.fid
proton
8.36
8.34
8.05
7.58
7.51
7.50
7.49
7.48
7.29
7.26
7.22
7.16
3.67
2.85
2.84
2.83
2.82
2.78
2.69
2.67
2.67
2.65
2.31
0.96 0.95 1.06 1.02 2.30 2.97
2.00 2.00 3.00 2.00 2.98
f1 (ppm)


ys-724-a-c13.281.fid
171.00
140.44
139.75
138.41
135.82
130.77
128.78
128.34
126.52
126.00
120.62
115.21
61.95
59.06
42.15
33.94
23.00
f1 (ppm)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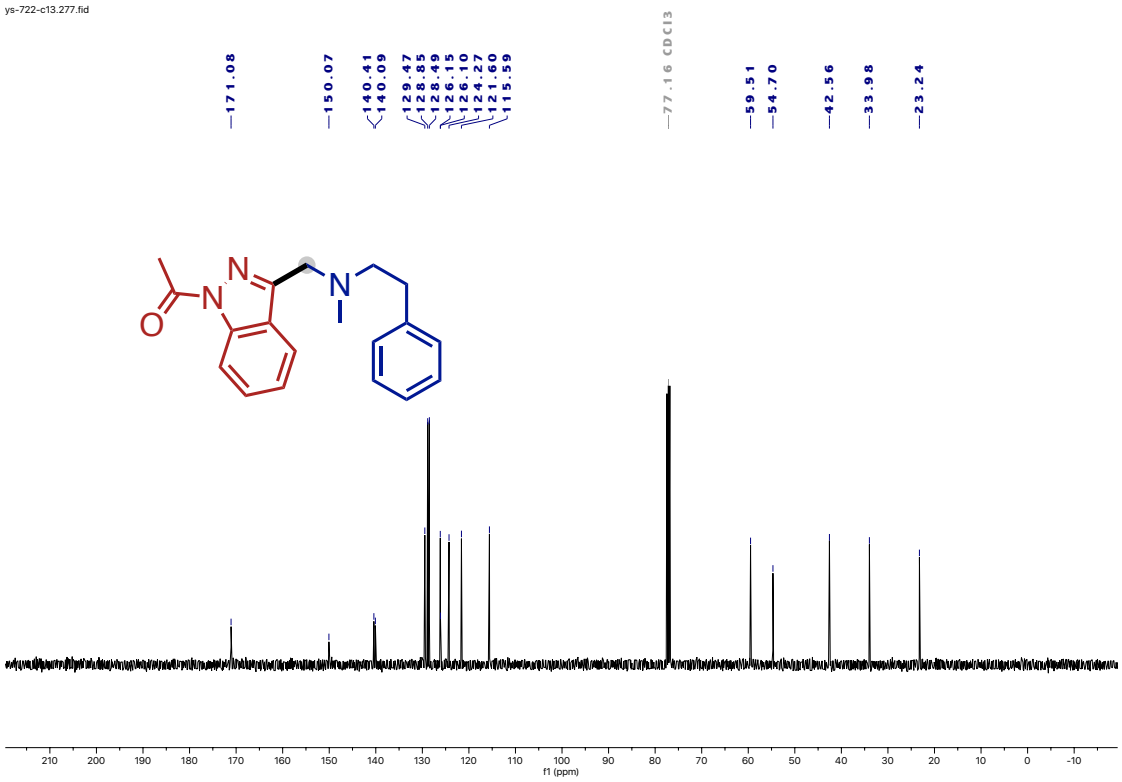
proton
8.41
8.38
7.73
7.71
7.53
7.53
7.51
7.51
7.49
7.49
7.29
7.24
7.21
7.17
3.92
2.91
2.89
2.88
2.87
2.80
2.76
2.36
1.00 1.00 1.04 3.30 3.01
2.00
2.01 5.00 3.00
f1 (ppm)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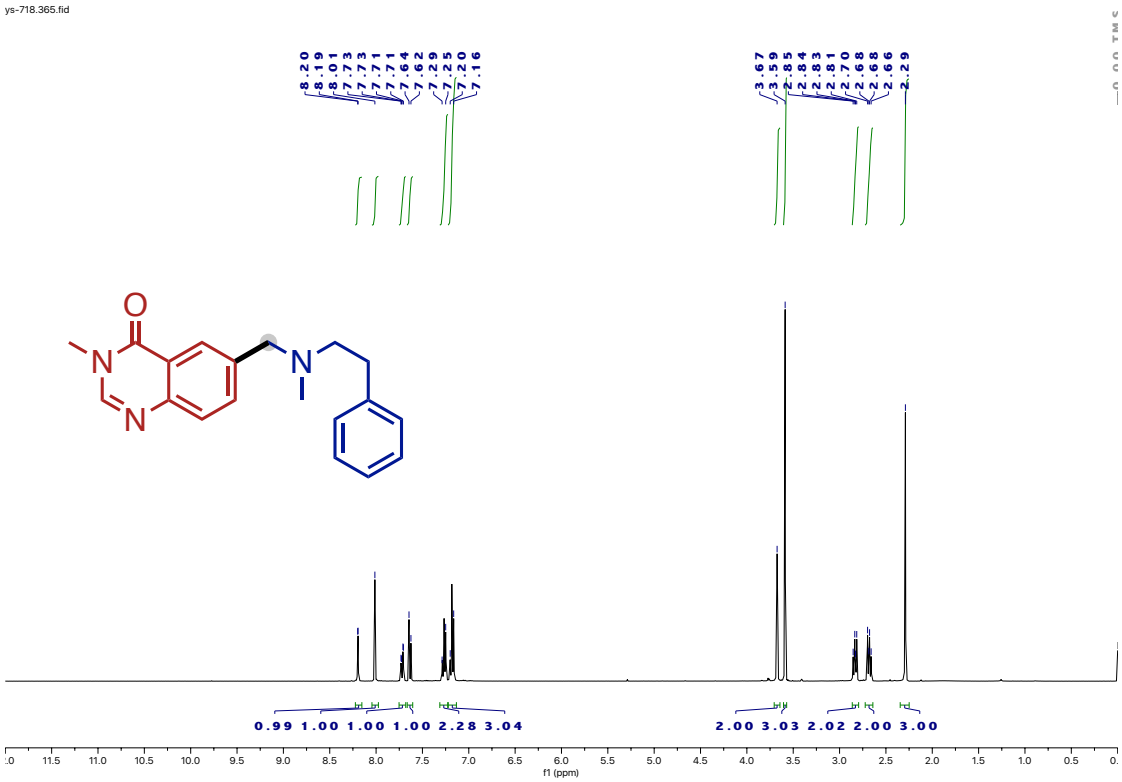
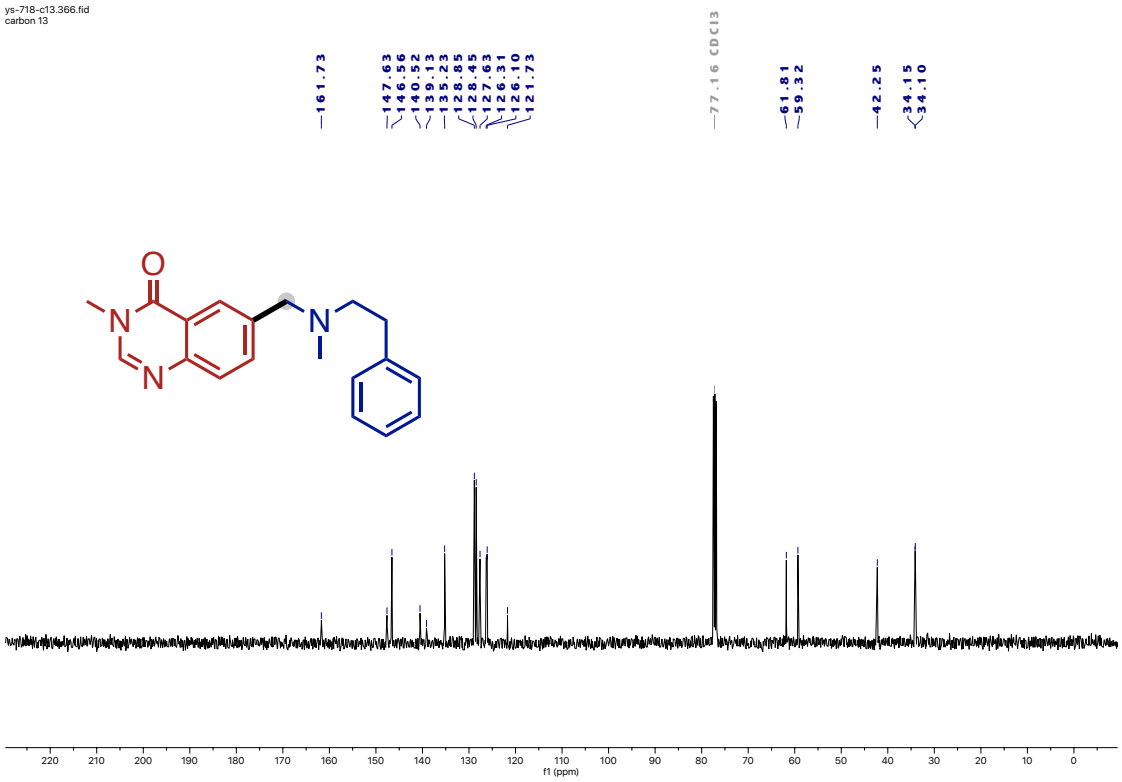
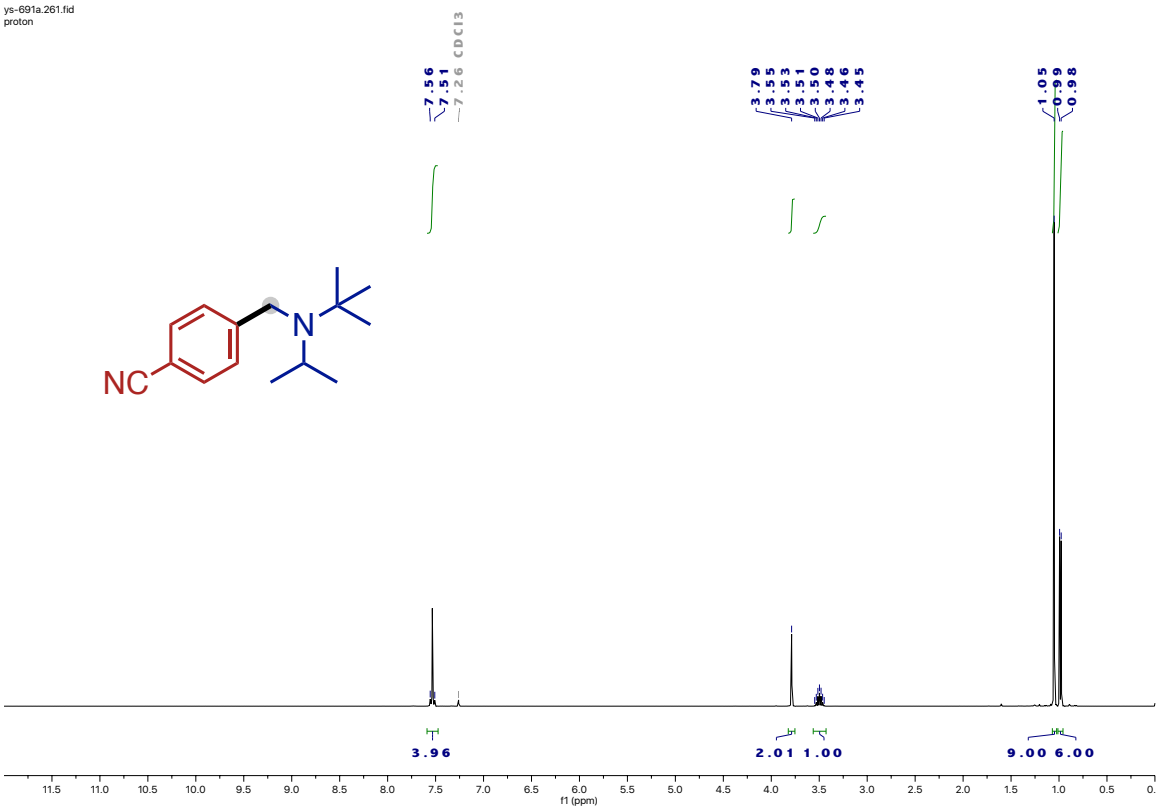
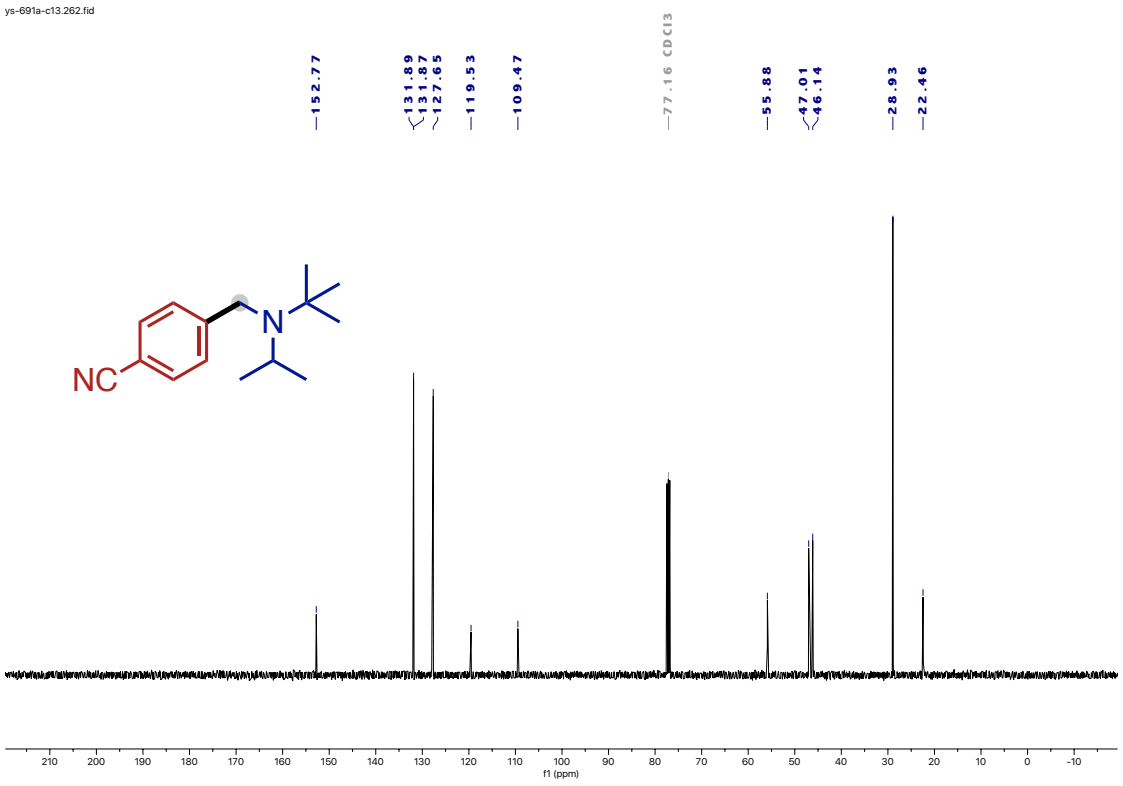
171.08
150.07
140.41
140.09
129.47
128.85
128.49
126.15
126.10
124.27
121.60
115.59
77.16 CDCl3
59.51
54.70
42.56
33.98
23.24
f1 (ppm)


ys-718.365.fid
8.20
8.19
8.01
7.73
7.73
7.71
7.71
7.64
7.62
7.29
7.25
7.20
7.16
3.67
3.59
2.85
2.84
2.83
2.81
2.70
2.68
2.68
2.66
2.29
0.99 1.00 1.00 1.00 2.28 3.04
2.00 3.03 2.02 2.00 3.00
f1 (ppm)


ys-718-c13.366.fid
carbon 13
161.73
147.63
146.56
140.52
139.13
135.23
128.85
128.45
127.63
126.31
126.10
121.73
77.16 CDCl3
61.81
59.32
42.25
34.15
34.10
f1 (ppm)


ys-691a.261.fid
proton
7.56
7.51
7.26 CDCl3
3.79
3.55
3.53
3.51
3.50
3.48
3.46
3.45
1.05
0.99
0.98
NC
N
3.96
2.01
1.00
9.00
6.00
f1 (ppm)


ys-691a-c13.262.fid
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131.89
131.87
127.65
119.53
109.47
77.16 CDCl3
55.88
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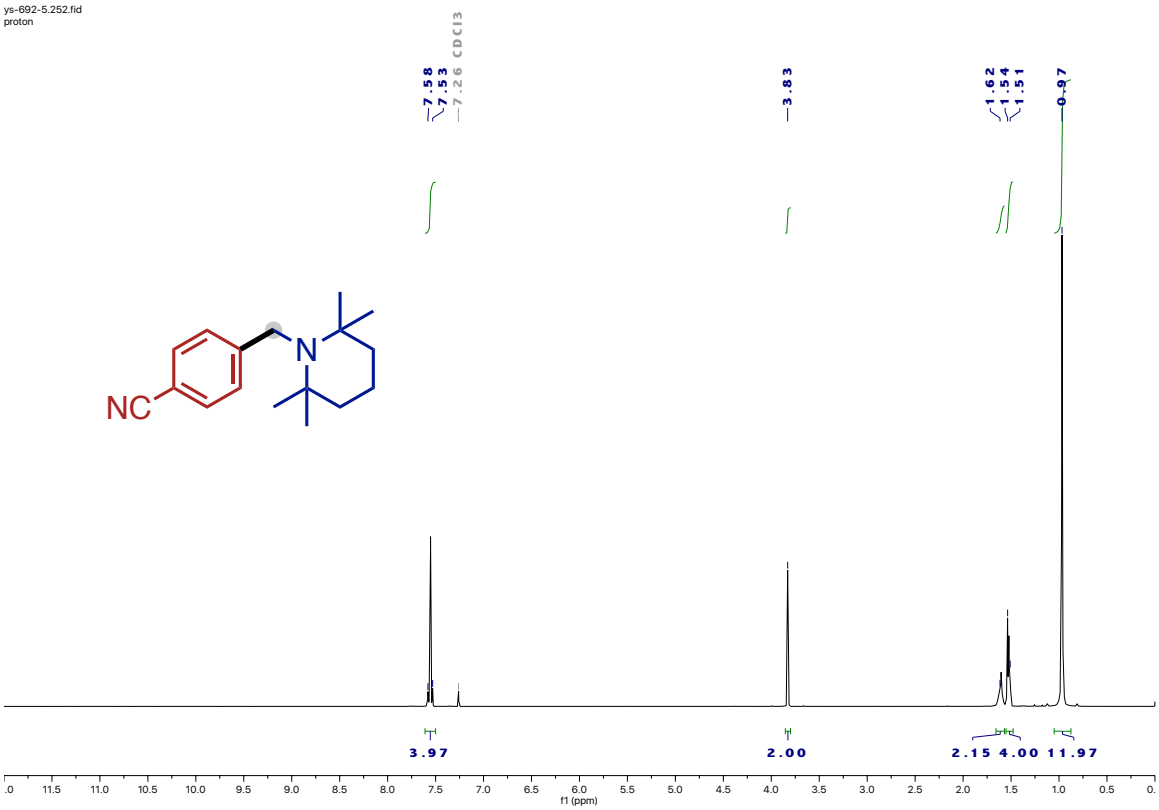
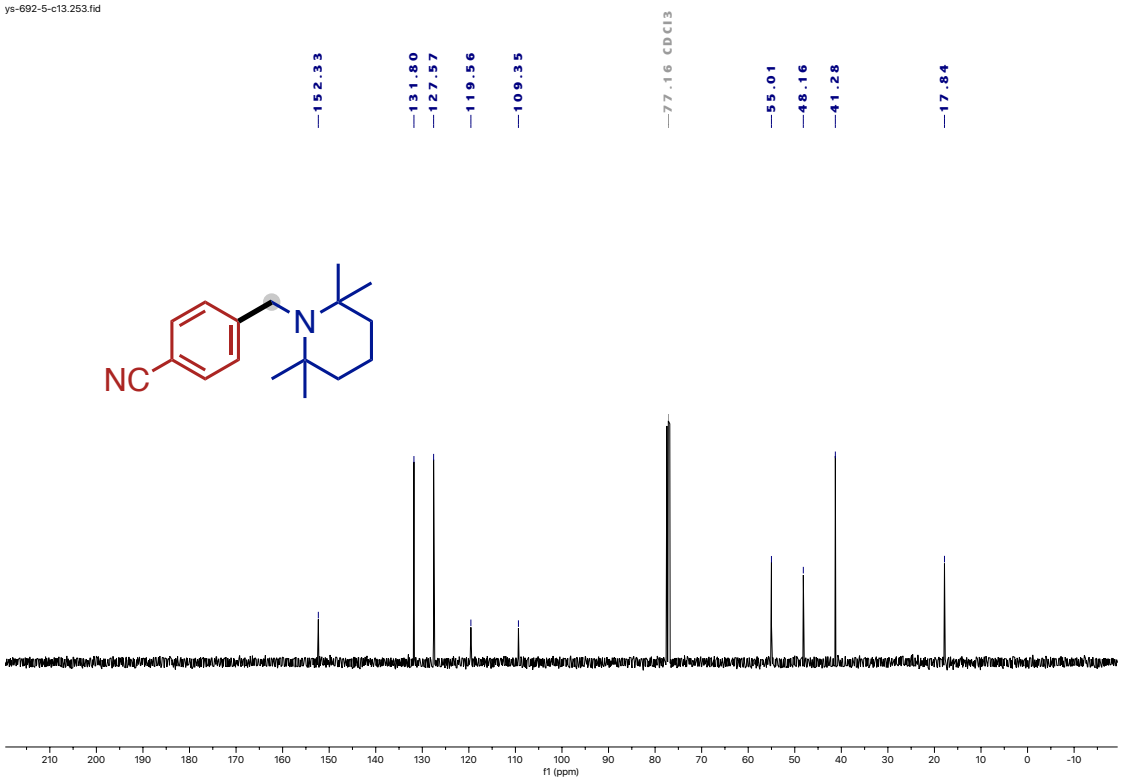
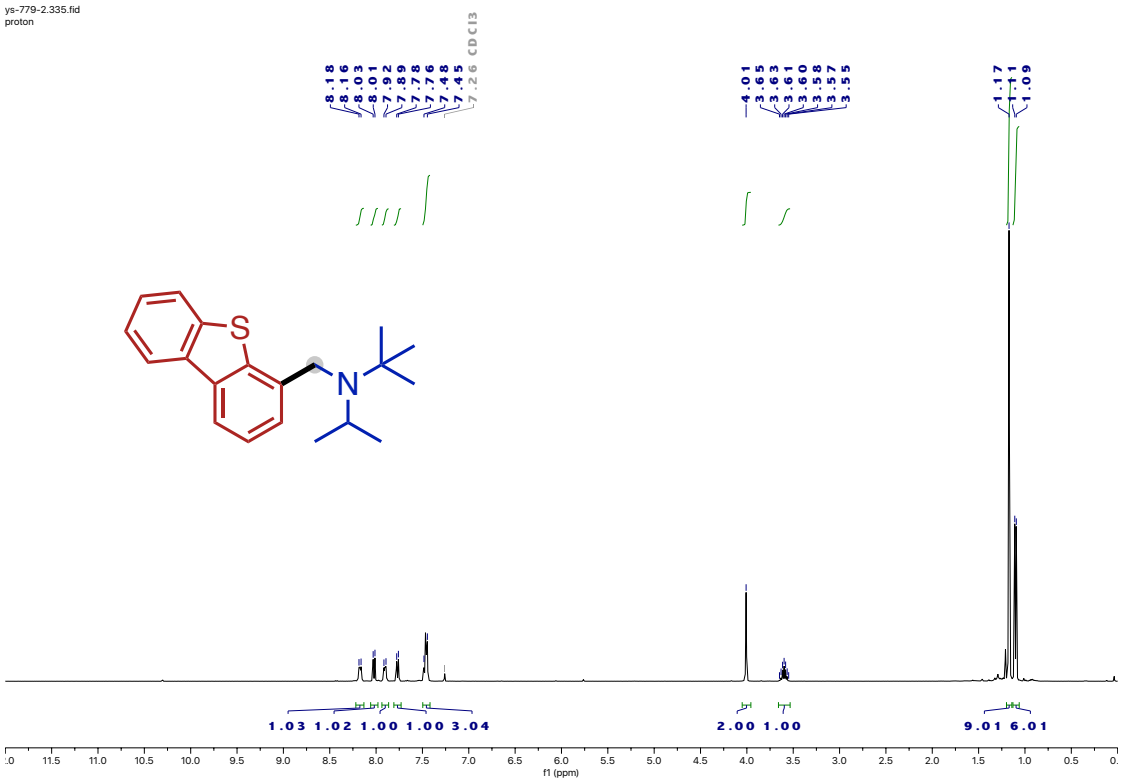
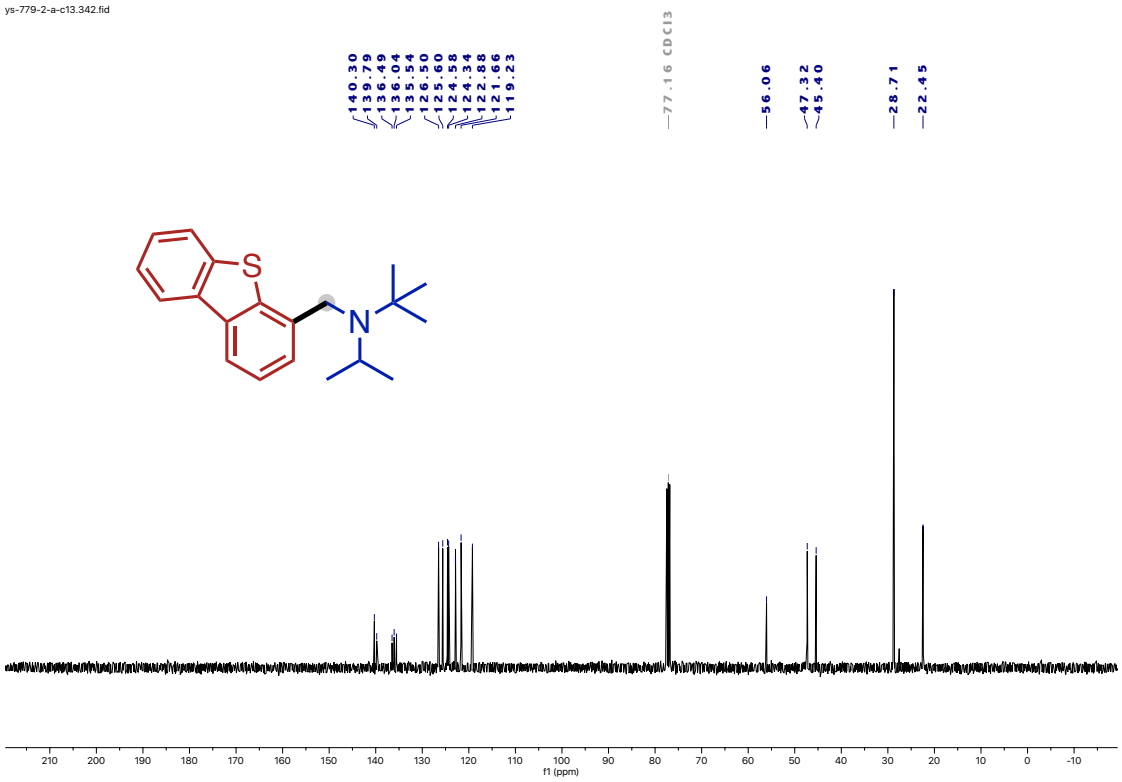
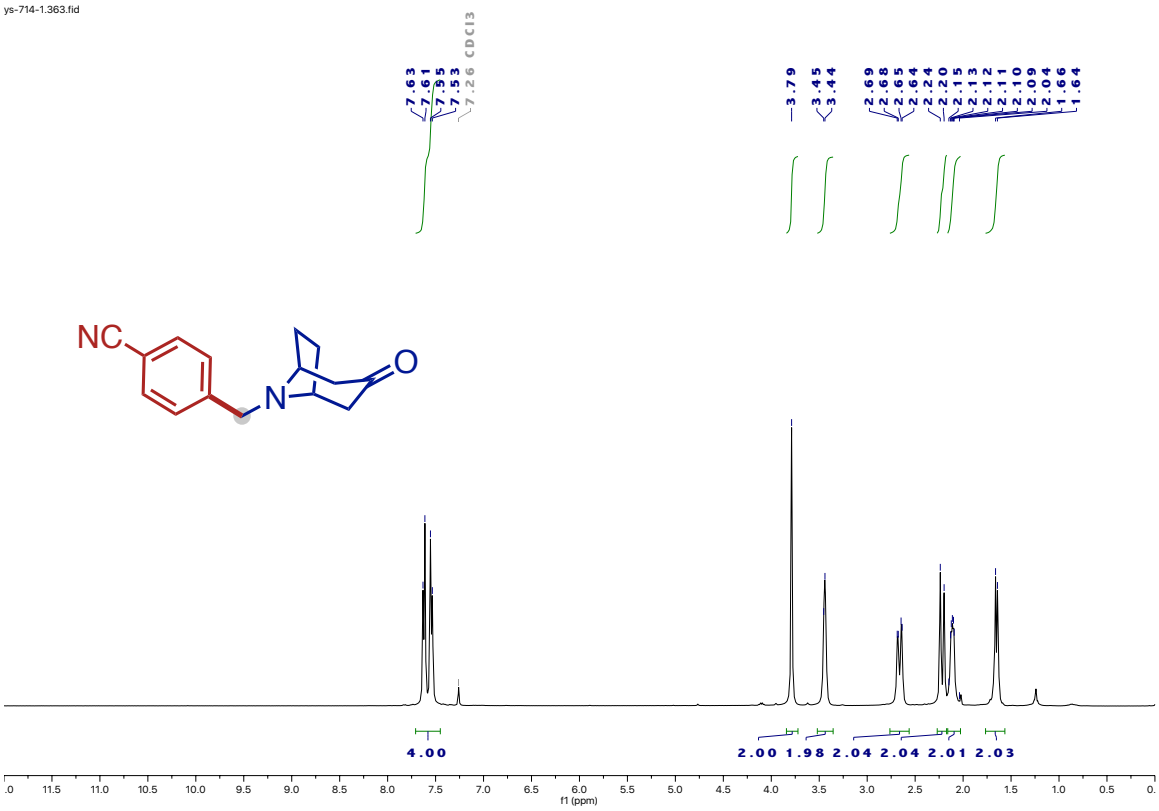
46.14
28.93
22.46
NC
N
f1 (ppm)

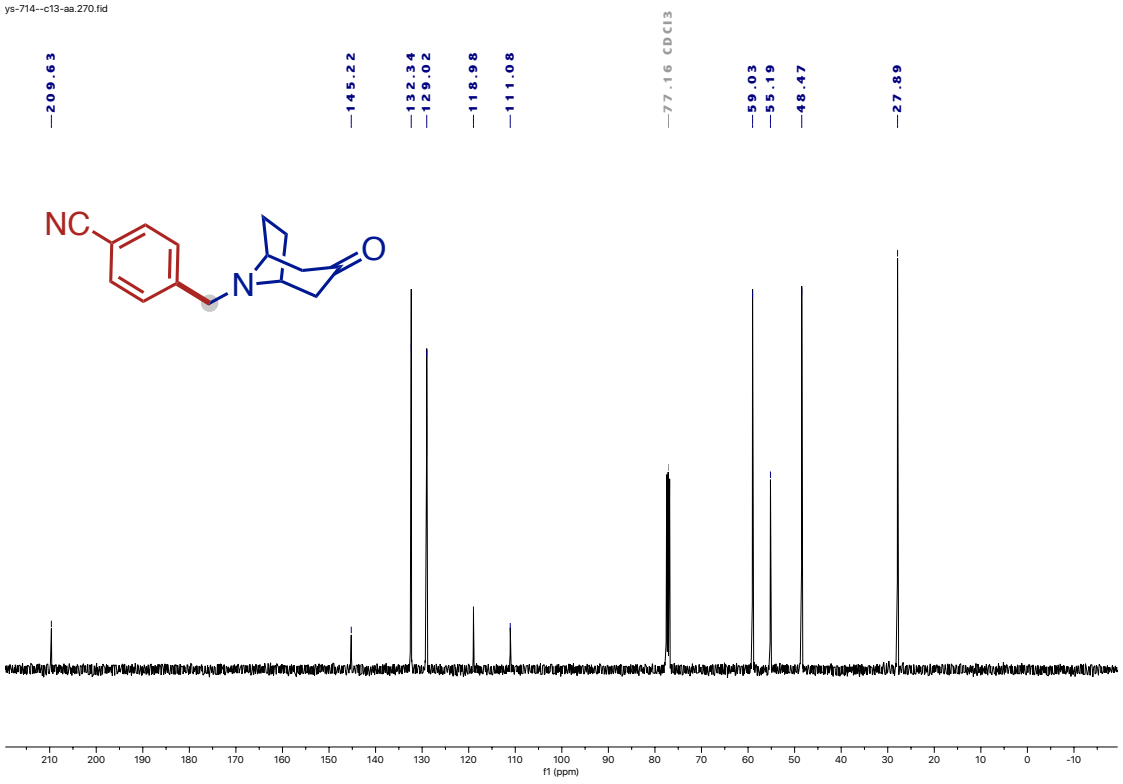

ys-692-5.252.fid
proton
7.58
7.53
7.26 CDCl3
3.83
1.62
1.54
1.51
0.97
NC
N
3.97
2.00
2.15
4.00
11.97
f1 (ppm)

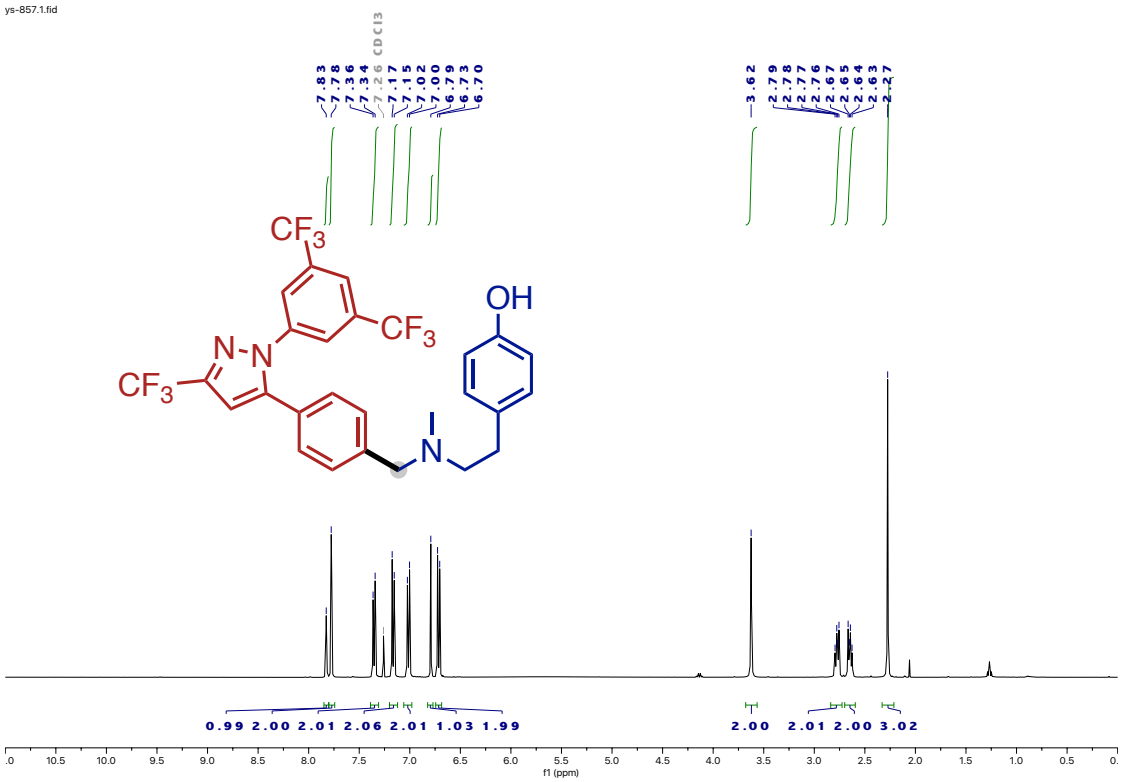

ys-692-5-c13.253.fid
152.33
131.80
127.57
119.56
109.35
77.16 CDCl3
55.01
48.16
41.28
17.84
NC
N
f1 (ppm)

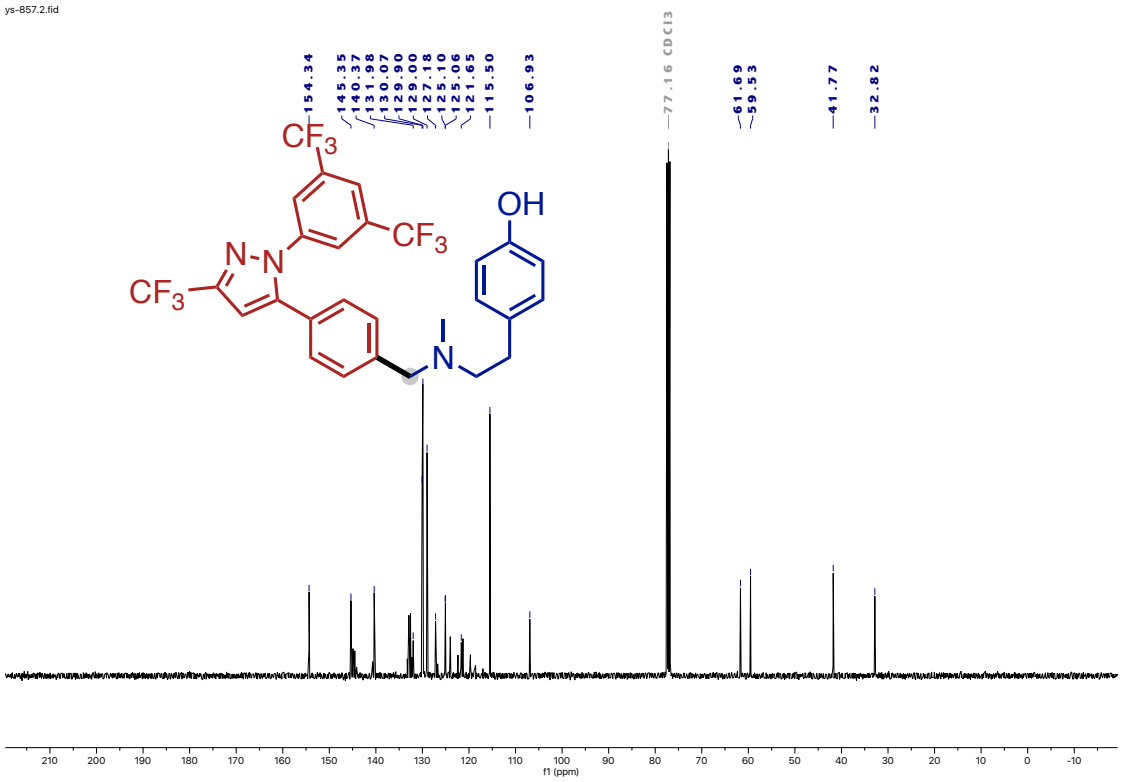

ys-779-2.335.fid
proton
8.18
8.16
8.03
8.01
7.92
7.89
7.78
7.76
7.48
7.45
7.26 CDCl3
4.01
3.65
3.63
3.61
3.60
3.58
3.57
3.55
1.17
1.11
1.09
S
N
1.03 1.02 1.00 1.00 3.04
2.00 1.00
9.01 6.01
f1 (ppm)

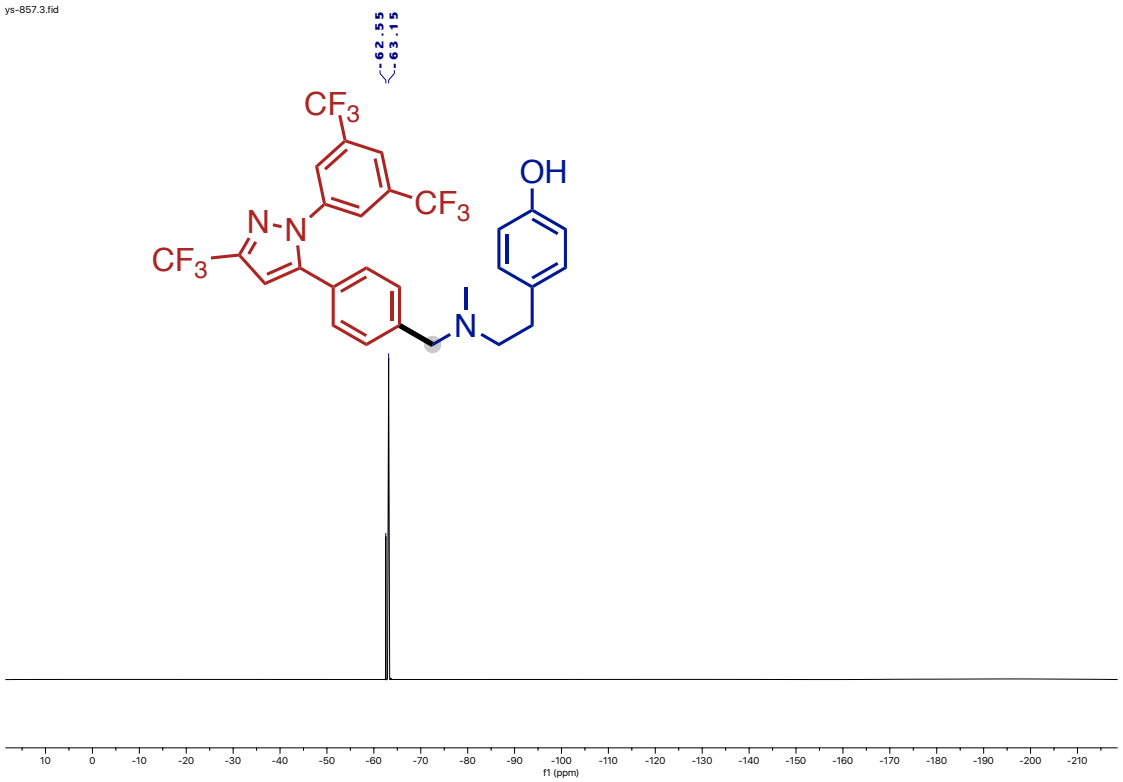

ys-779-2-a-c13.342.fid
140.30
139.79
136.49
136.04
135.54
126.50
125.60
124.58
124.34
122.88
121.66
119.23
77.16 CDCl3
56.06
47.32
45.40
28.71
22.45
S
N
f1 (ppm)

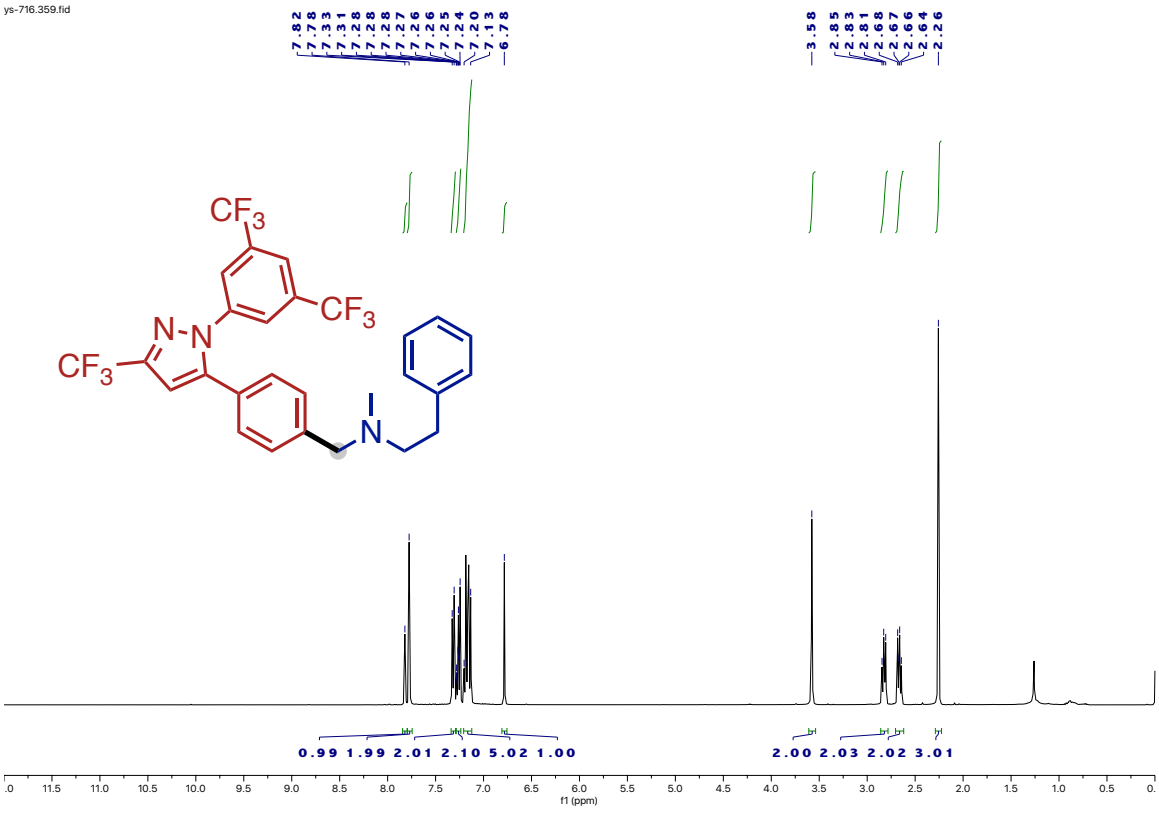

ys-714-1.363.fid
7.63
7.61
7.55
7.53
7.26 CDCl3
3.79
3.45
3.44
2.69
2.68
2.65
2.64
2.24
2.20
2.15
2.13
2.12
2.11
2.10
2.09
2.04
1.66
1.64
NC
O
N
4.00
2.00 1.98 2.04 2.04 2.01 2.03
f1 (ppm)

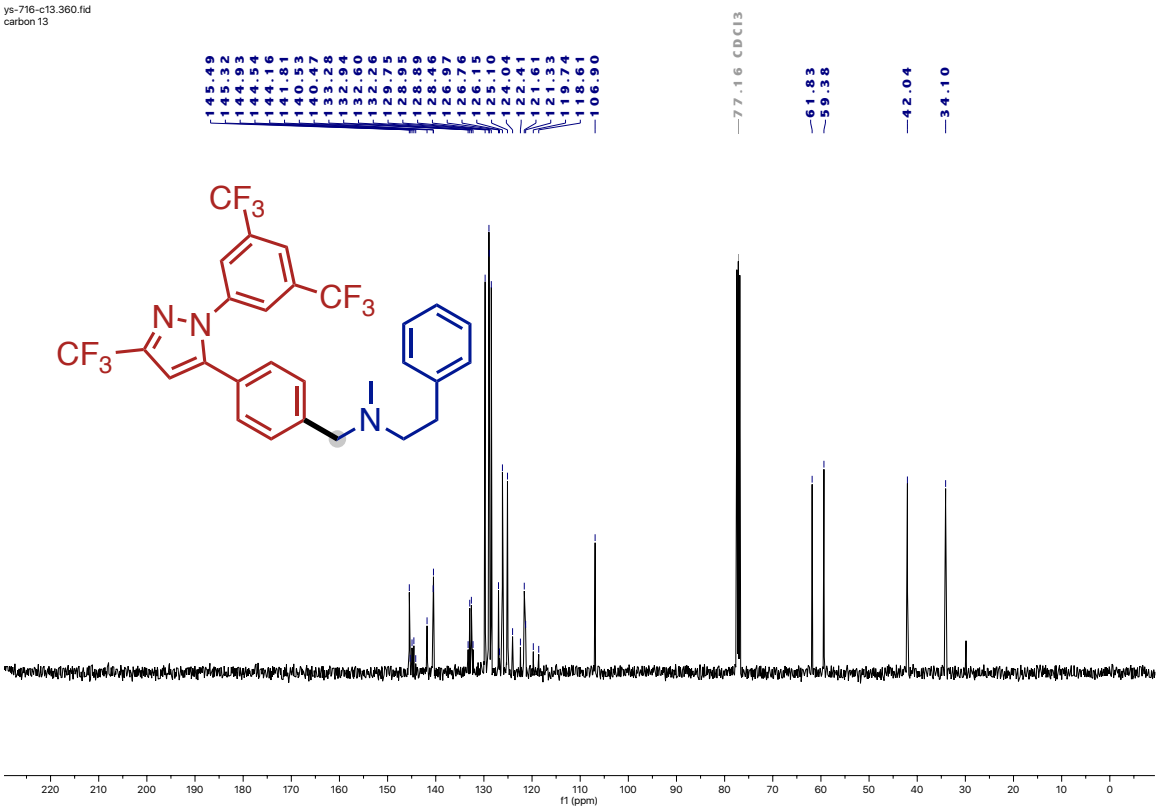

ys-714--c13-aa.270.fid
209.63
145.22
132.34
129.02
118.98
111.08
77.16 CDCl3
59.03
55.19
48.47
27.89
NC
O
N
f1 (ppm)

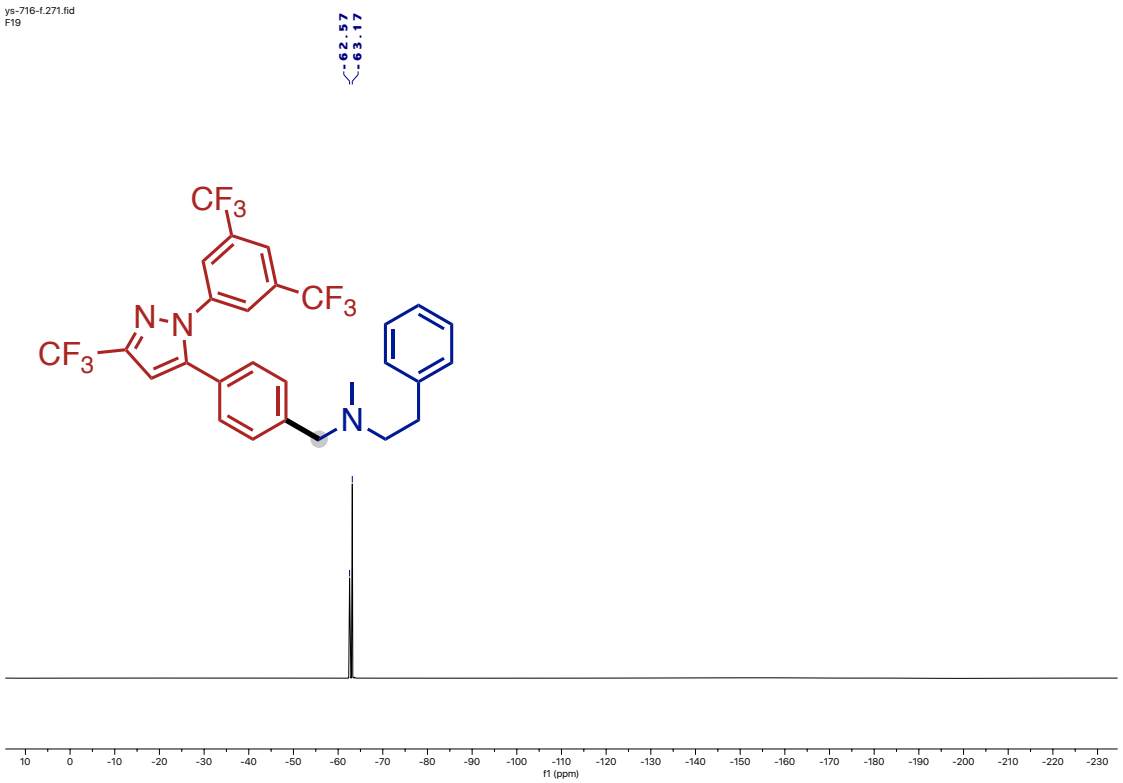

ys-857.1.fid
7.83
7.78
7.36
7.34
7.26 CDCl3
7.17
7.15
7.02
7.00
6.79
6.73
6.70
3.62
2.79
2.78
2.77
2.76
2.67
2.65
2.64
2.63
2.27
CF3
CF3
CF3
N-N
OH
N
0.99 2.00 2.01 2.06 2.01 1.03 1.99
2.00 2.01 2.00 3.02
f1 (ppm)

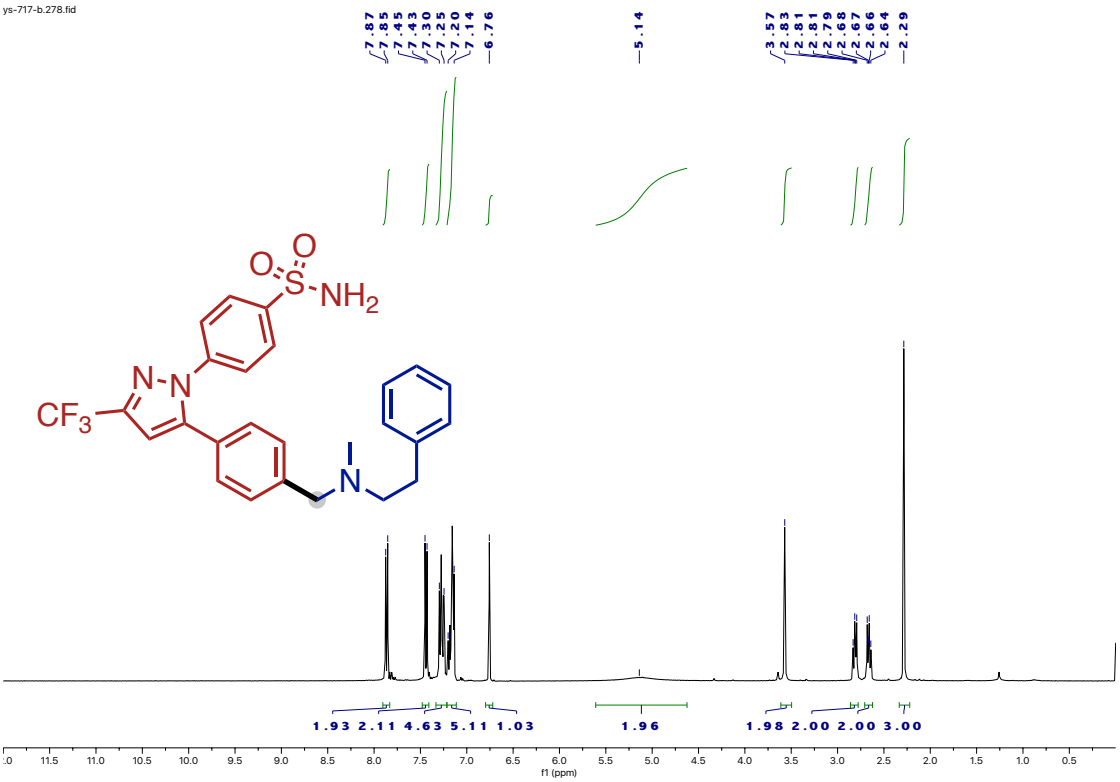

ys-857.2.fid
154.34
145.35
140.37
131.98
130.07
129.90
129.00
127.18
125.10
125.06
121.65
115.50
106.93
77.16 CDCl3
61.69
59.53
41.77
32.82
CF3
CF3
CF3
N-N
OH
N
f1 (ppm)

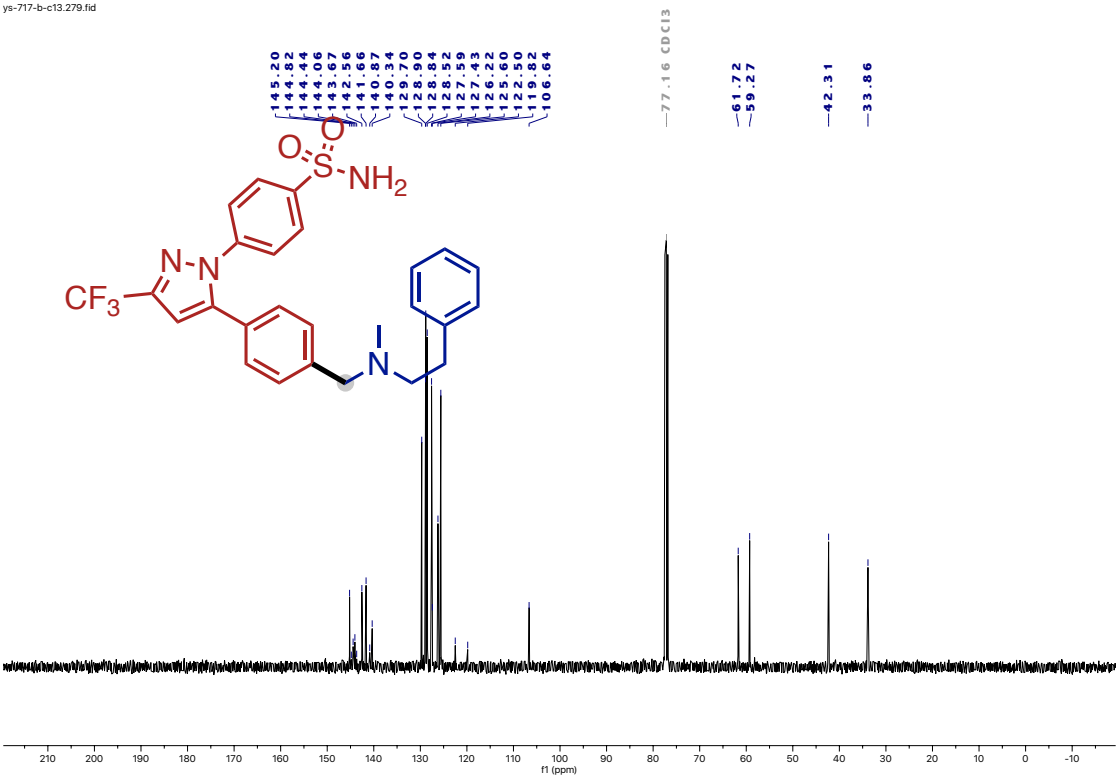

ys-857.3.fid
-62.55
-63.15
CF3
CF3
CF3
N-N
OH
N
f1 (ppm)

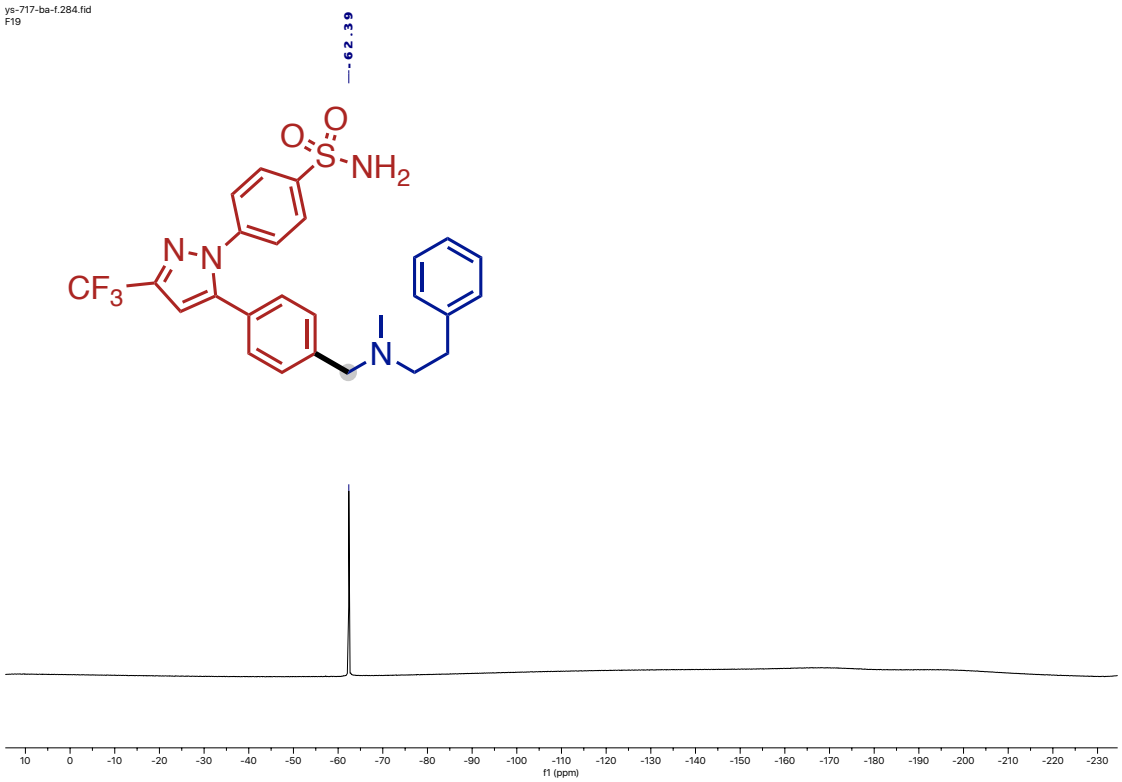

ys-716.359.fid
7.82
7.78
7.33
7.31
7.28
7.28
7.28
7.27
7.26
7.26
7.25
7.24
7.20
7.13
6.78
3.58
2.85
2.83
2.81
2.68
2.67
2.66
2.64
2.26
CF3
CF3
CF3
N-N
N
0.99 1.99 2.01 2.10 5.02 1.00
2.00 2.03 2.02 3.01
f1 (ppm)

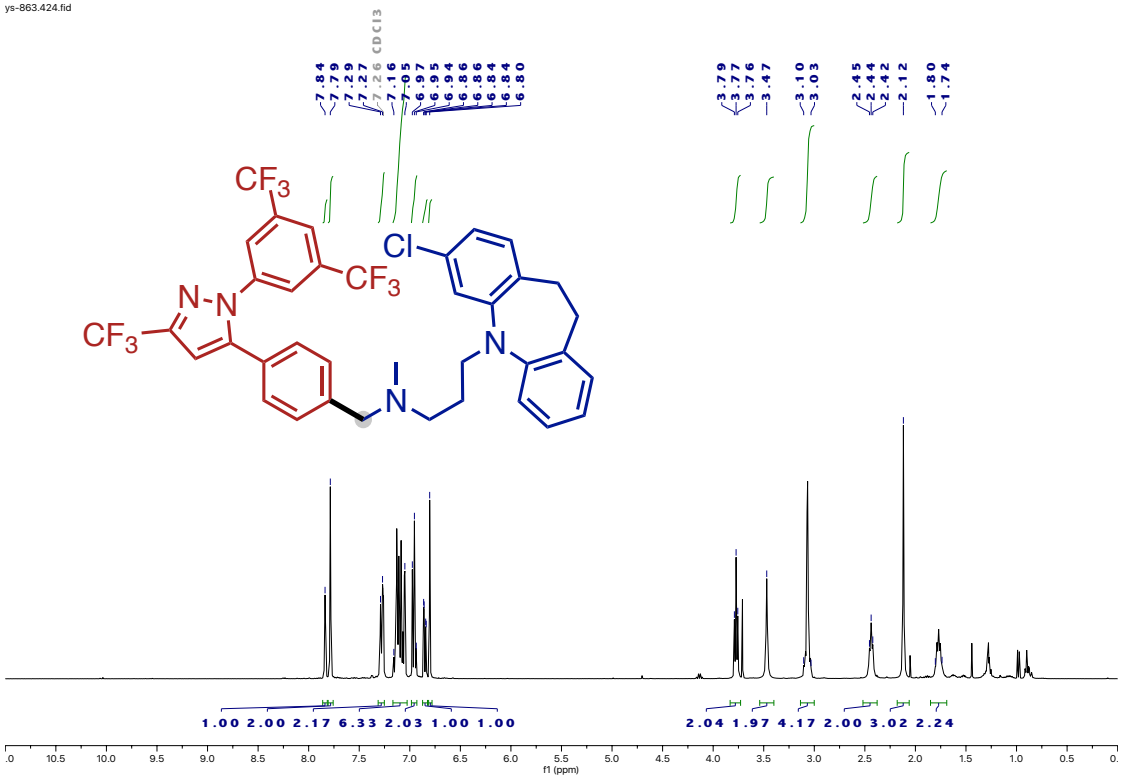

ys-716-c13.360.fid
carbon 13
145.49
145.32
144.93
144.54
144.16
141.81
140.53
140.47
133.28
132.94
132.60
132.26
129.75
128.95
128.89
128.46
126.97
126.76
126.15
125.10
124.04
122.41
121.61
121.33
119.74
118.61
106.90
77.16 CDCl3
61.83
59.38
42.04
34.10
CF3
CF3
CF3
N-N
N
f1 (ppm)


ys-716-f.271.fid
F19
-62.57
-63.17
CF3
CF3
CF3
N-N
N
f1 (ppm)


ys-717-b.278.fid
7.87
7.85
7.45
7.43
7.30
7.25
7.20
7.14
6.76
5.14
3.57
2.83
2.81
2.81
2.79
2.68
2.67
2.66
2.64
2.29
O
O
S
NH2
N
N
CF3
N
1.93 2.11 4.63 5.11 1.03
1.96
1.98 2.00 2.00 3.00
f1 (ppm)


ys-717-b-c13.279.fid
145.20
144.82
144.44
144.06
143.67
142.56
141.66
140.87
140.34
129.70
128.90
128.84
128.52
127.59
127.43
126.22
125.60
122.50
119.82
106.64
77.16 CDCl3
61.72
59.27
42.31
33.86
O
O
S
NH2
N
N
CF3
N
f1 (ppm)


ys-717-ba-f.284.fid
F19
-62.39
f1 (ppm)


ys-863.424.fid
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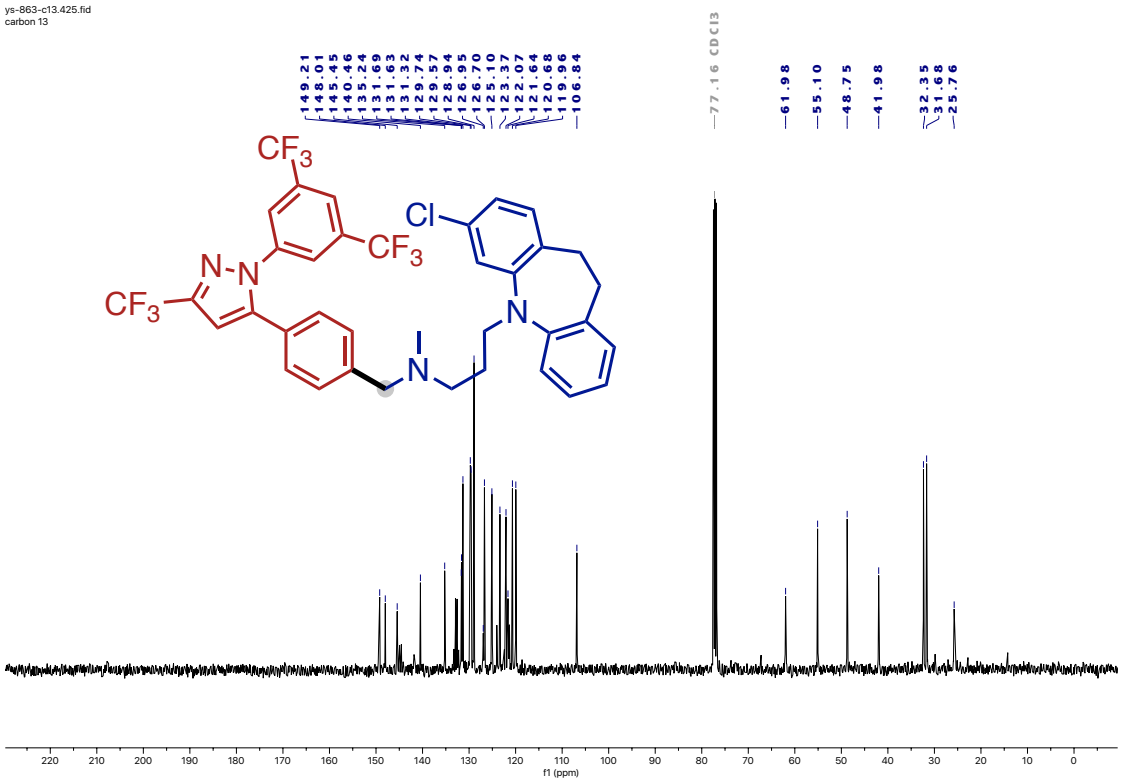
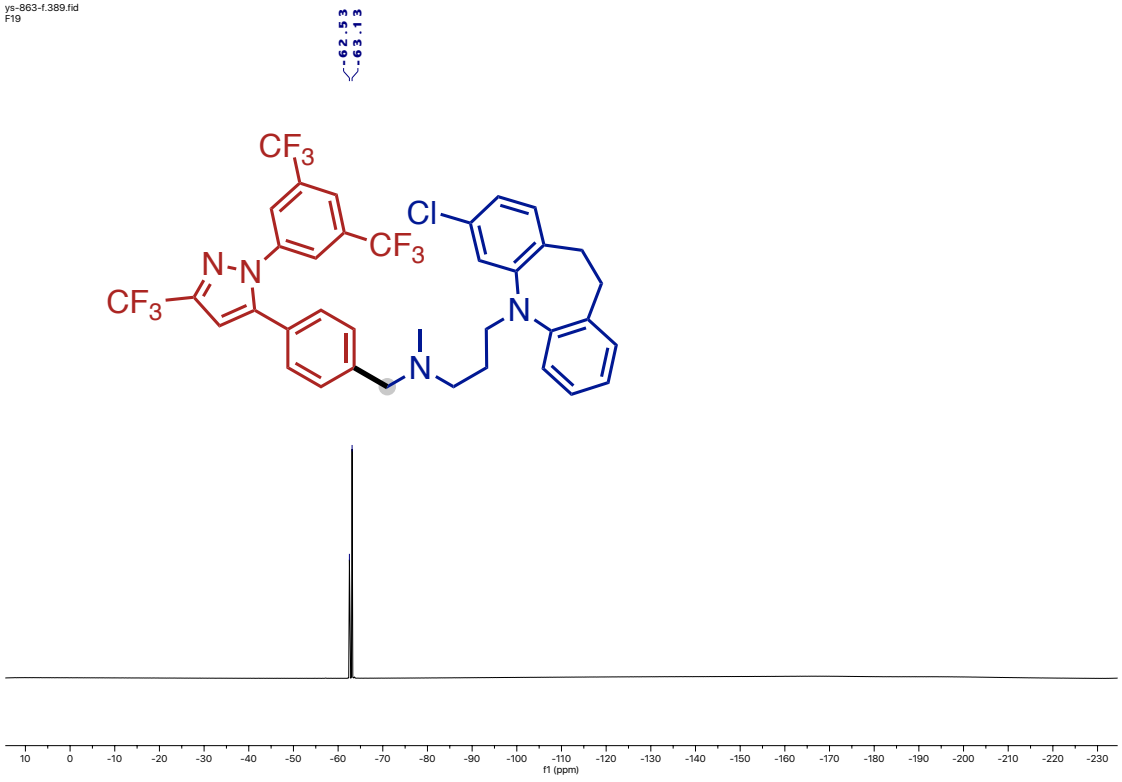
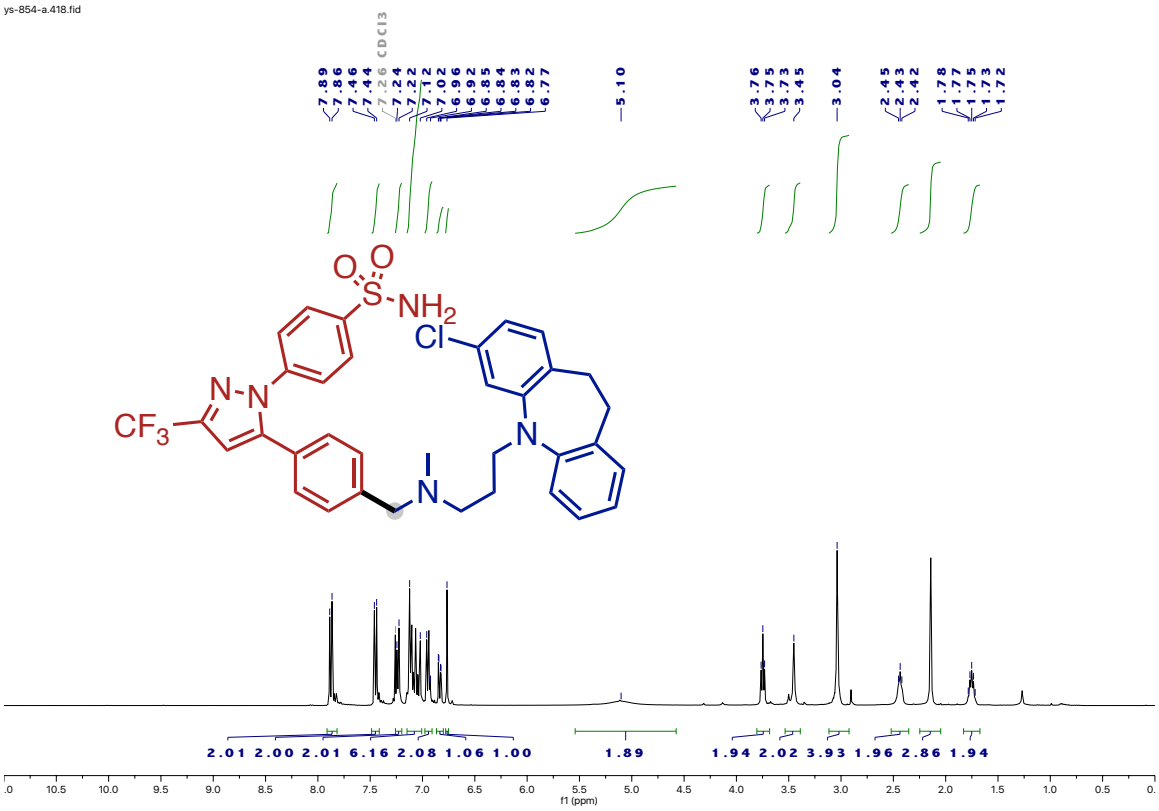
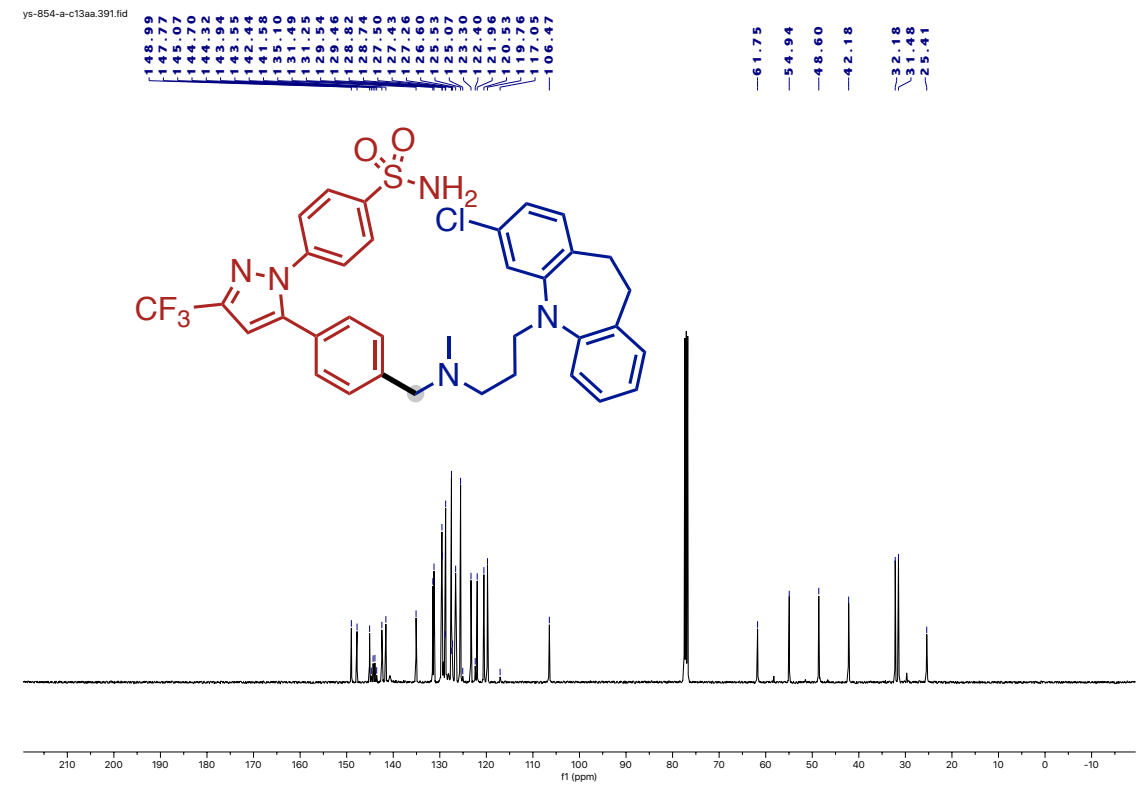
7.79
7.29
7.27
7.26 CDCl3
7.16
7.05
6.97
6.95
6.94
6.86
6.84
6.84
6.80
3.79
3.77
3.76
3.47
3.10
3.03
2.45
2.44
2.42
2.12
1.80
1.74
1.00 2.00 2.17 6.33 2.03 1.00 1.00
2.04 1.97 4.17 2.00 3.02 2.24
f1 (ppm)


ys-863-c13.425.fid
carbon 13
149.21
148.01
145.45
140.46
135.24
131.69
131.63
131.32
129.74
129.57
128.94
126.95
126.70
125.10
123.37
122.07
121.64
120.68
119.96
106.84
77.16 CDCl3
61.98
55.10
48.75
41.98
32.35
31.68
25.76
CF3
CF3
CF3
N-N
Cl
N
N
f1 (ppm)


ys-863-f.389.fid
F19
-62.53
-63.13
CF3
CF3
CF3
N-N
Cl
N
N
f1 (ppm)


ys-854-a.418.fid
7.89
7.86
7.46
7.44
7.26 CDCl3
7.24
7.22
7.12
7.02
6.96
6.92
6.85
6.84
6.83
6.82
6.77
5.10
3.76
3.75
3.73
3.45
3.04
2.45
2.43
2.42
1.78
1.77
1.75
1.73
1.72
O
O
S
NH2
Cl
N
N
CF3
N
2.01 2.00 2.01 6.16 2.08 1.06 1.00
1.89
1.94 2.02 3.93 1.96 2.86 1.94
f1 (ppm)


ys-854-a-c13aa.391.fid
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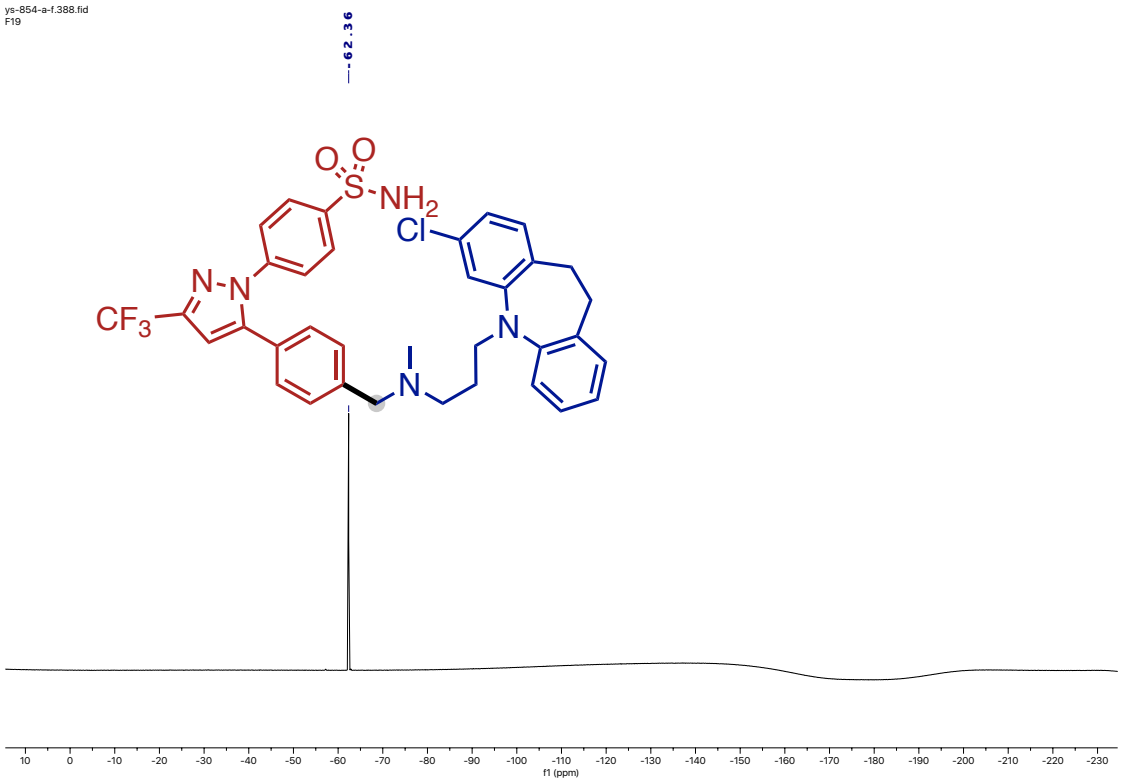
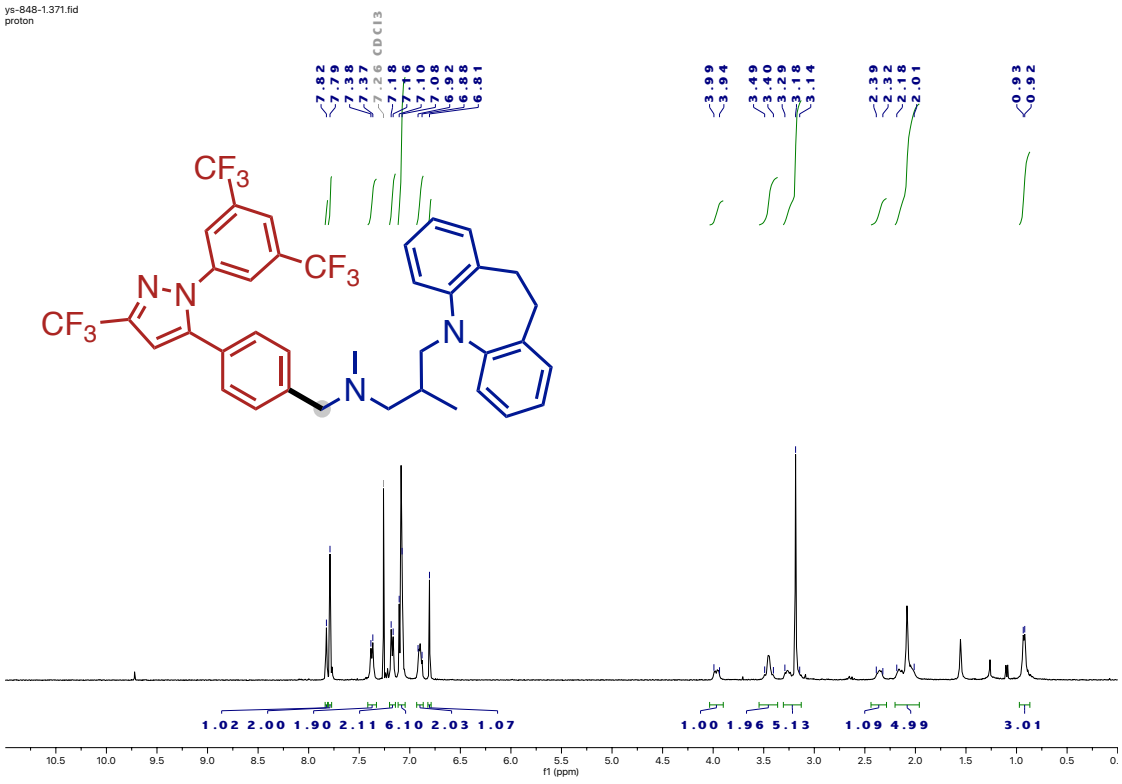
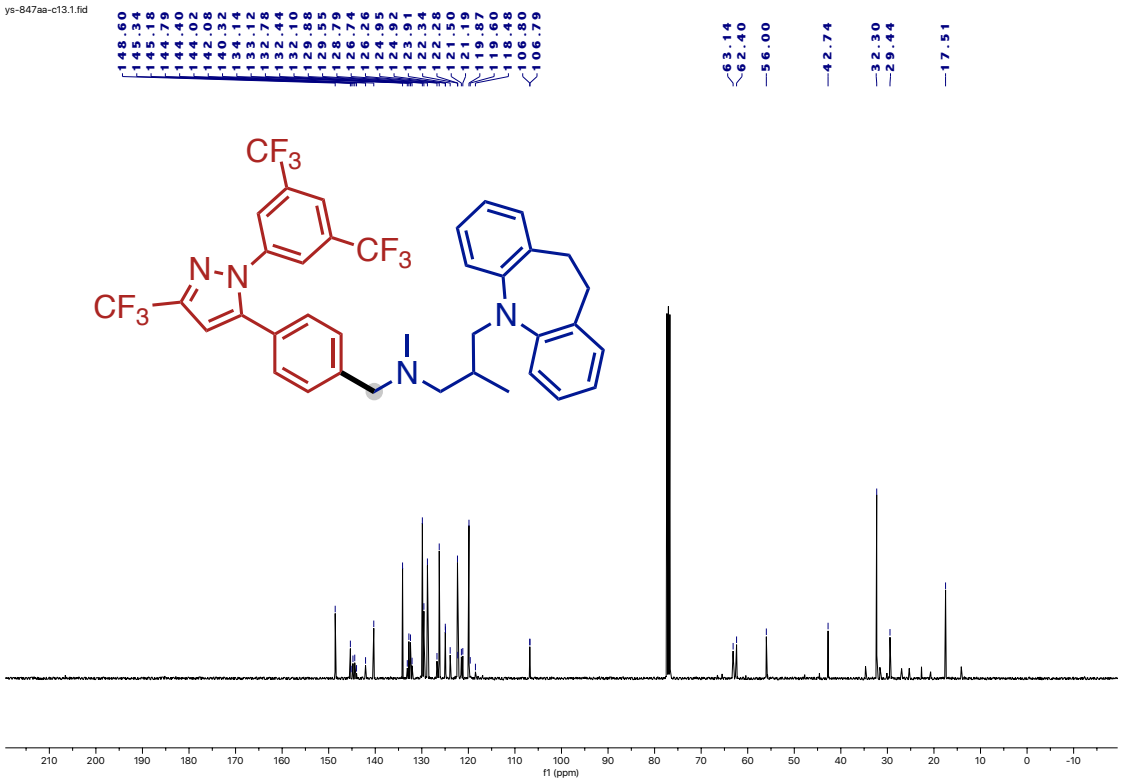
147.77
145.07
144.70
144.32
143.94
143.55
142.44
141.58
135.10
131.49
131.25
129.54
129.46
128.82
128.74
127.50
127.43
127.26
126.60
125.53
125.07
123.30
122.96
122.40
120.53
119.76
117.05
106.47
61.75
54.94
48.60
42.18
32.18
31.48
25.41
O
O
S
NH2
Cl
N
N
CF3
N
f1 (ppm)


ys-854-a-f.388.fid
F19
-62.36
f1 (ppm)


ys-848-1.371.fid
proton
7.82
7.79
7.38
7.37
7.26 CDCl3
7.18
7.16
7.10
7.08
6.92
6.88
6.81
3.99
3.94
3.49
3.40
3.29
3.18
3.14
2.39
2.32
2.18
2.01
0.93
0.92
1.02 2.00 1.90 2.11 6.10 2.03 1.07
1.00 1.96 5.13
1.09 4.99
3.01
f1 (ppm)


ys-847aa-c13.1.fid
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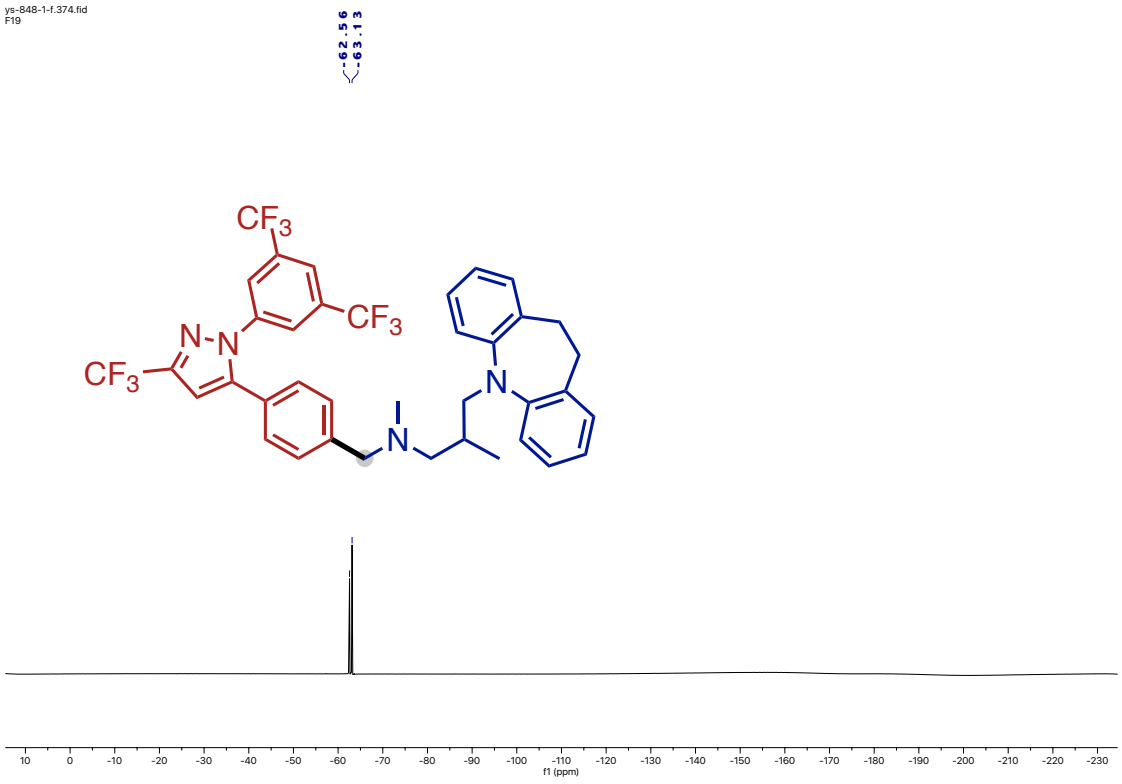
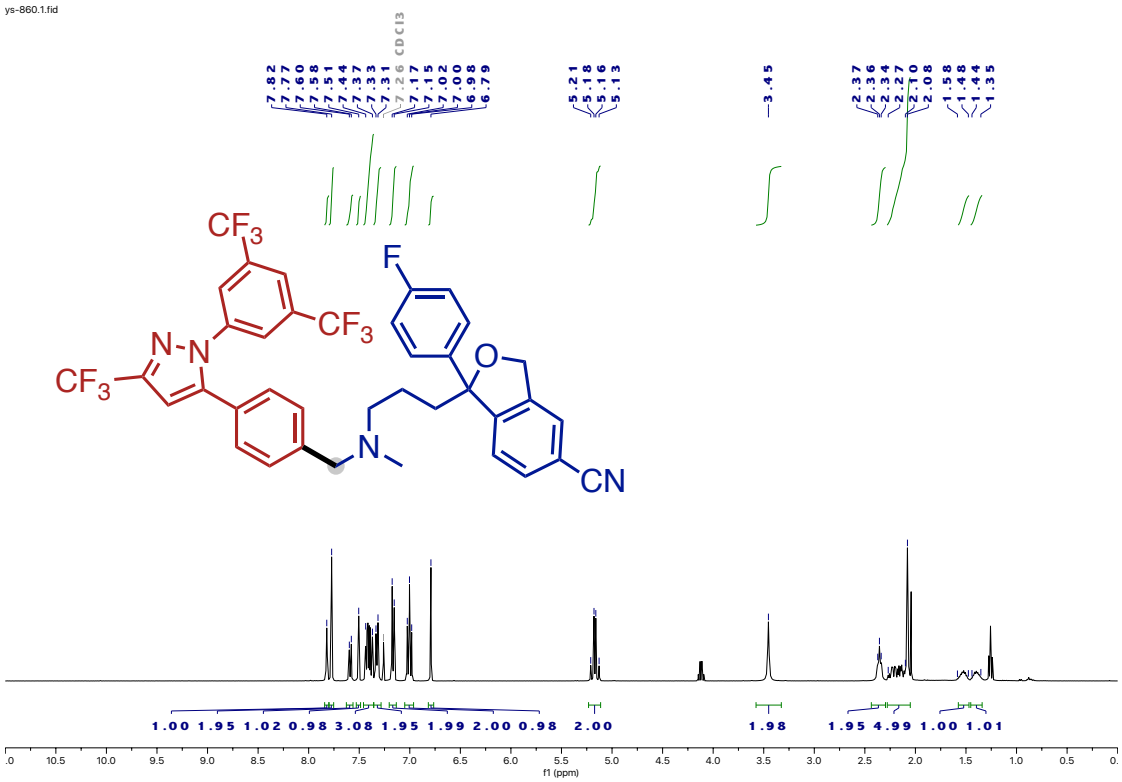
145.34
145.18
144.79
144.40
144.02
142.08
140.32
134.14
133.12
132.78
132.44
132.10
129.88
129.55
128.79
126.74
126.26
124.95
124.92
123.91
122.34
122.28
121.50
121.19
119.87
119.60
118.48
106.80
106.79
63.14
62.40
56.00
42.74
32.30
29.44
17.51
CF3
CF3
CF3
N-N
N
N
f1 (ppm)


ys-848-1-f.374.fid
F19
-62.56
-63.13
CF3
CF3
CF3
N-N
N
N
f1 (ppm)


ys-860.1.fid
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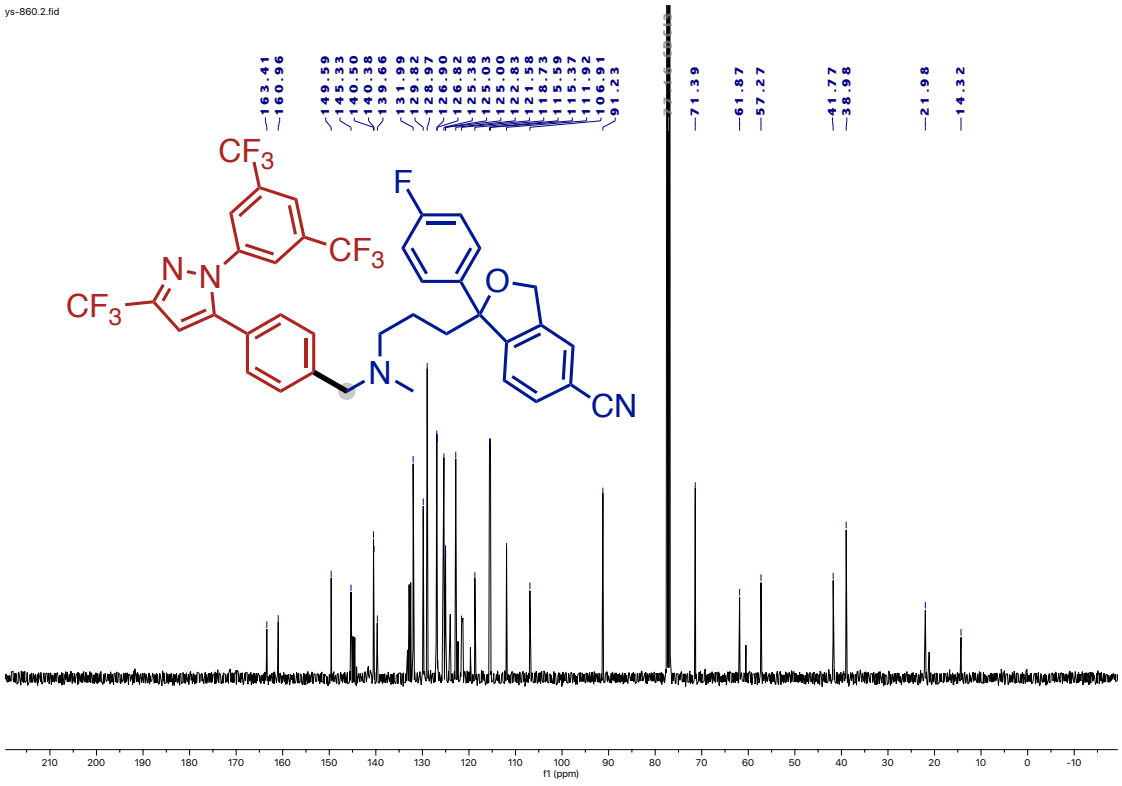
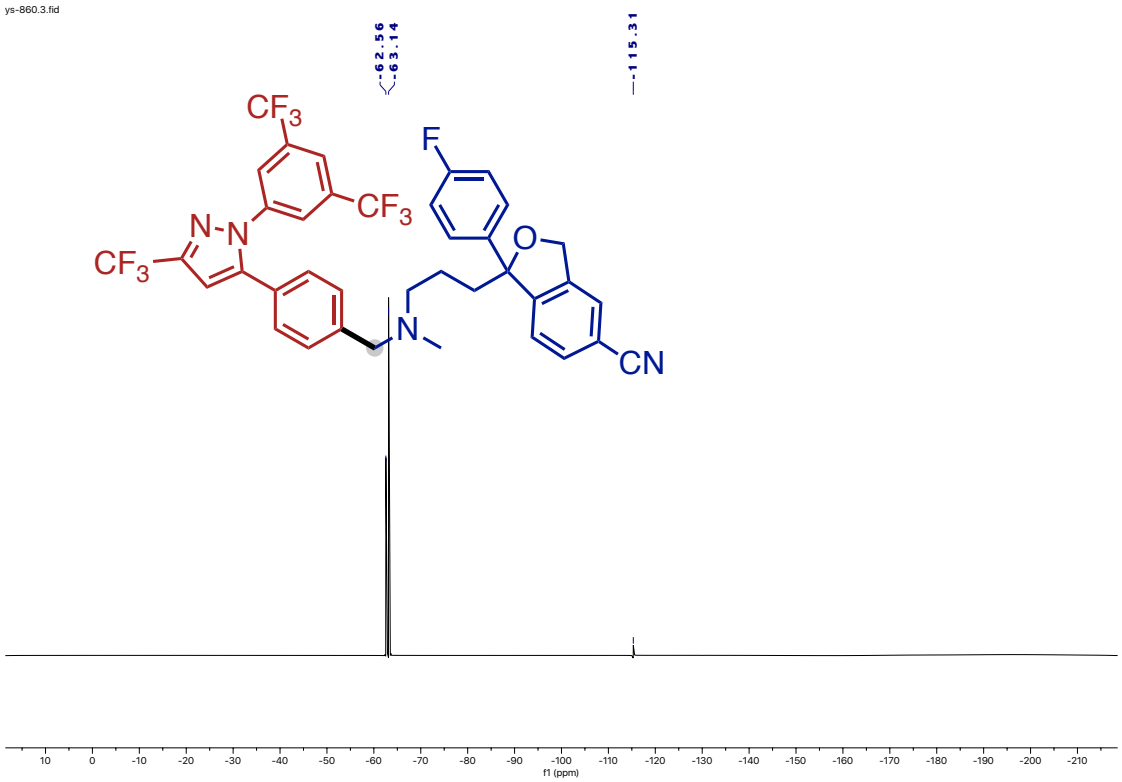
7.77
7.60
7.58
7.51
7.44
7.37
7.33
7.31
7.26
CDCl3
7.17
7.15
7.02
7.00
6.98
6.79
5.21
5.18
5.16
5.13
3.45
2.37
2.36
2.34
2.27
2.10
2.08
1.58
1.48
1.44
1.35
CF3
CF3
CF3
N-N
F
O
N
CN
1.00 1.95 1.02 0.98 3.08 1.95 1.99 2.00 0.98 2.00 1.98 1.95 4.99 1.00 1.01
f1 (ppm)


ys-860.2.fid
163.41
160.96
149.59
145.33
140.50
140.38
139.66
131.99
129.82
128.97
126.90
126.82
125.38
125.03
125.00
122.83
121.58
118.23
115.59
115.37
111.92
106.91
91.23
71.39
61.87
57.27
41.77
38.98
21.98
14.32
CF3
CF3
CF3
N-N
F
O
N
CN
f1 (ppm)


ys-860.3.fid
-62.56
-63.14
-115.31
CF3
CF3
CF3
N-N
F
O
N
CN
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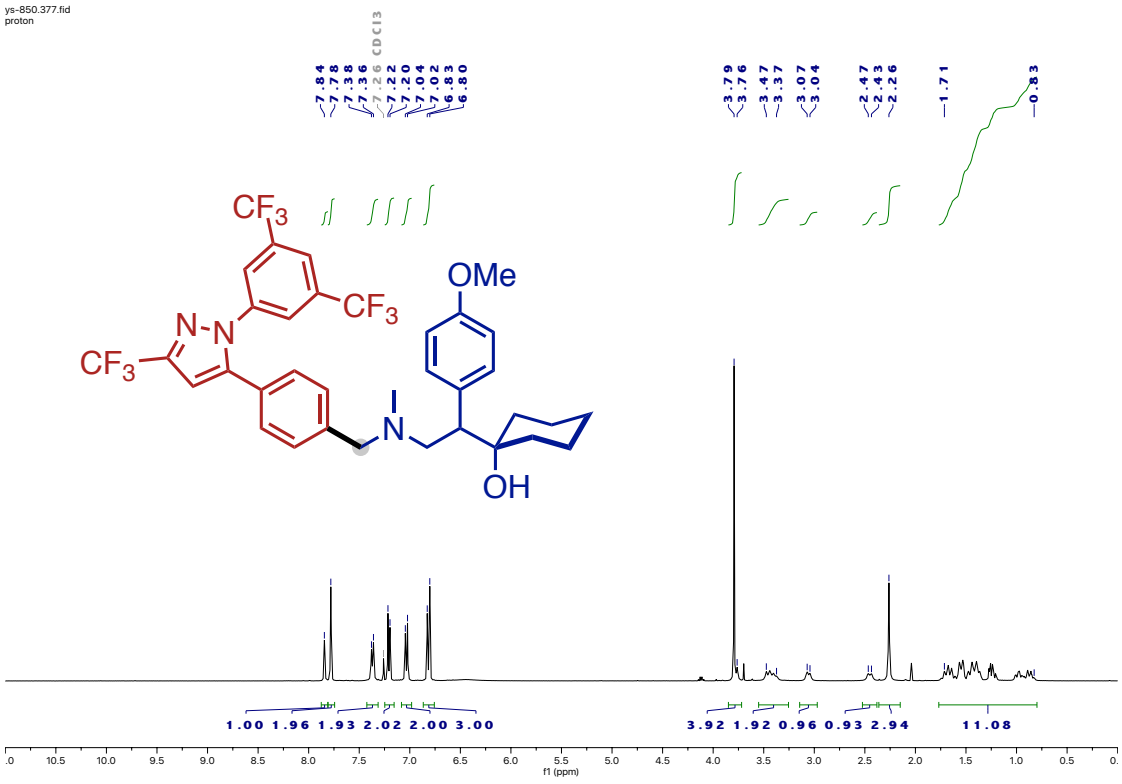
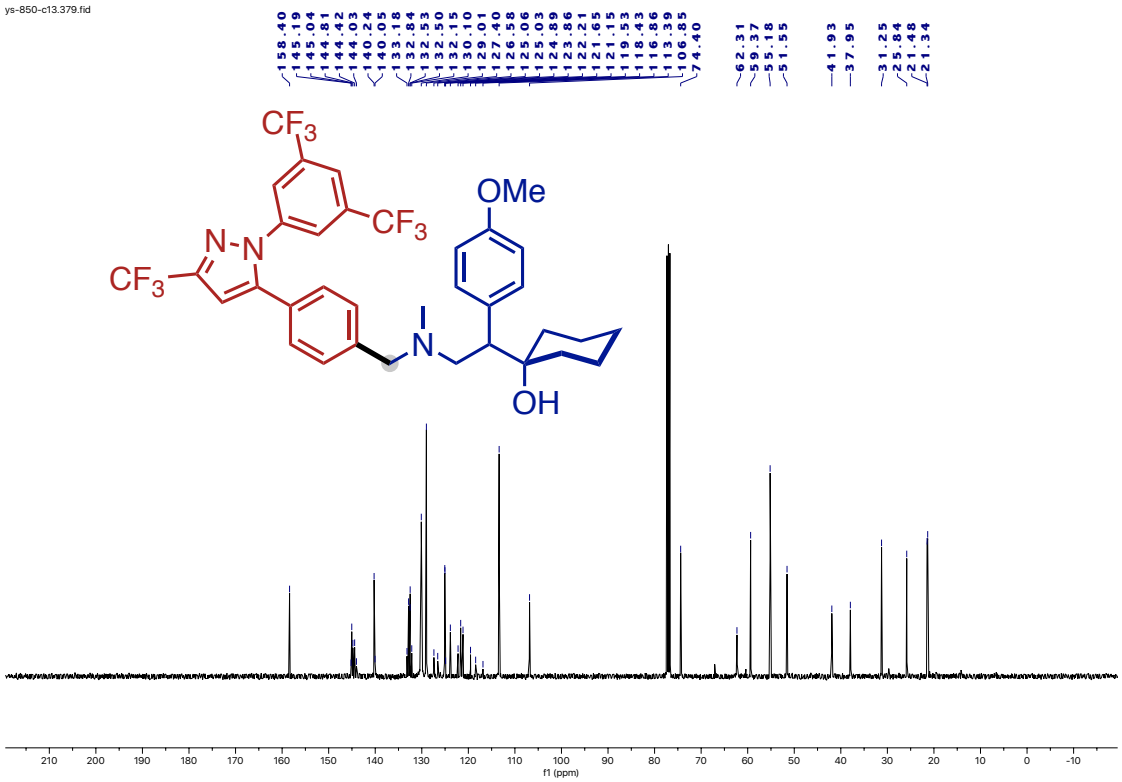
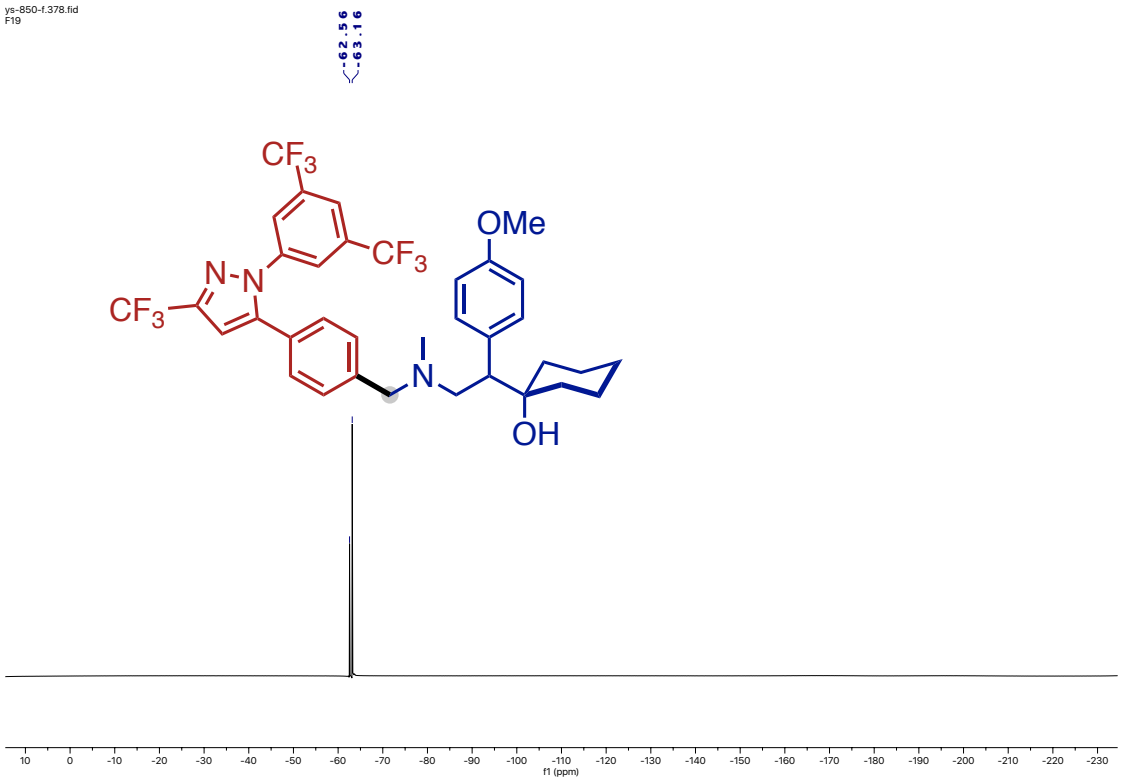
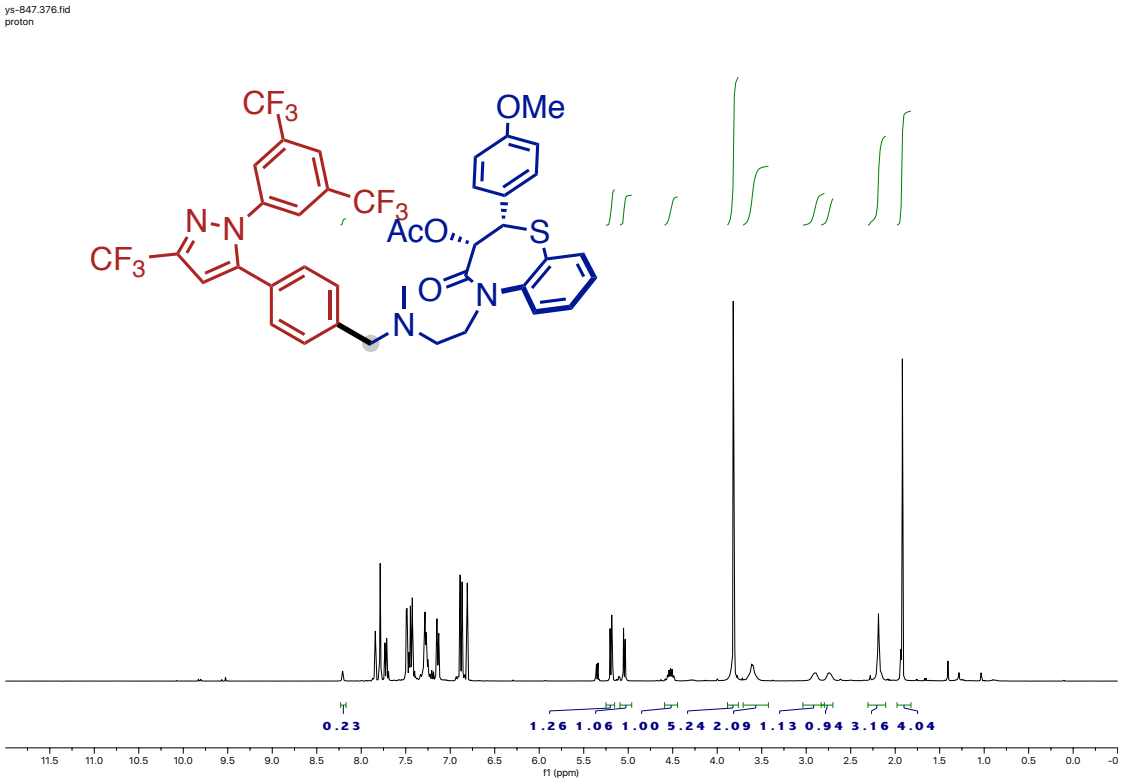
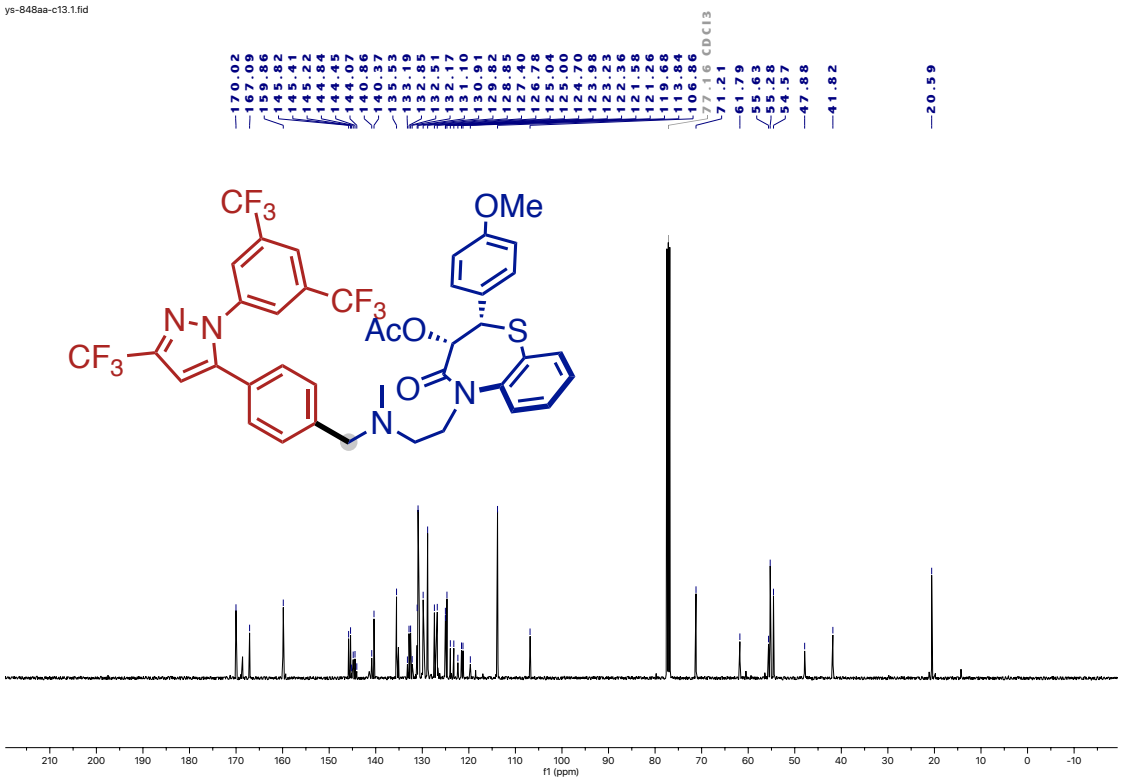
f1 (ppm)

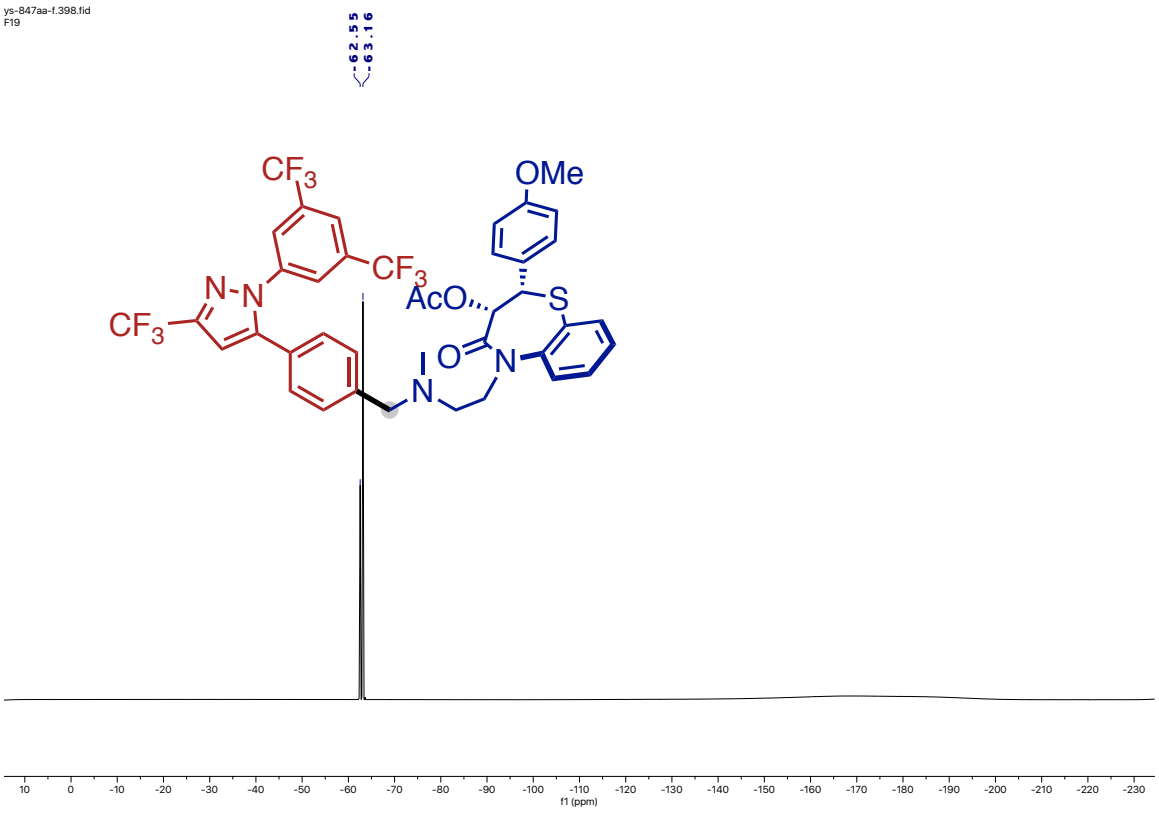

ys-850.377.fid
proton
7.84
7.78
7.38
7.36
CDCl3
7.22
7.20
7.04
7.02
6.83
6.80
3.79
3.76
3.47
3.37
3.07
3.04
2.47
2.43
2.26
1.71
0.83
CF3
CF3
CF3
N-N
OMe
N
OH
1.00 1.96 1.93 2.02 2.00 3.00
3.92 1.92 0.96 0.93 2.94 11.08
f1 (ppm)

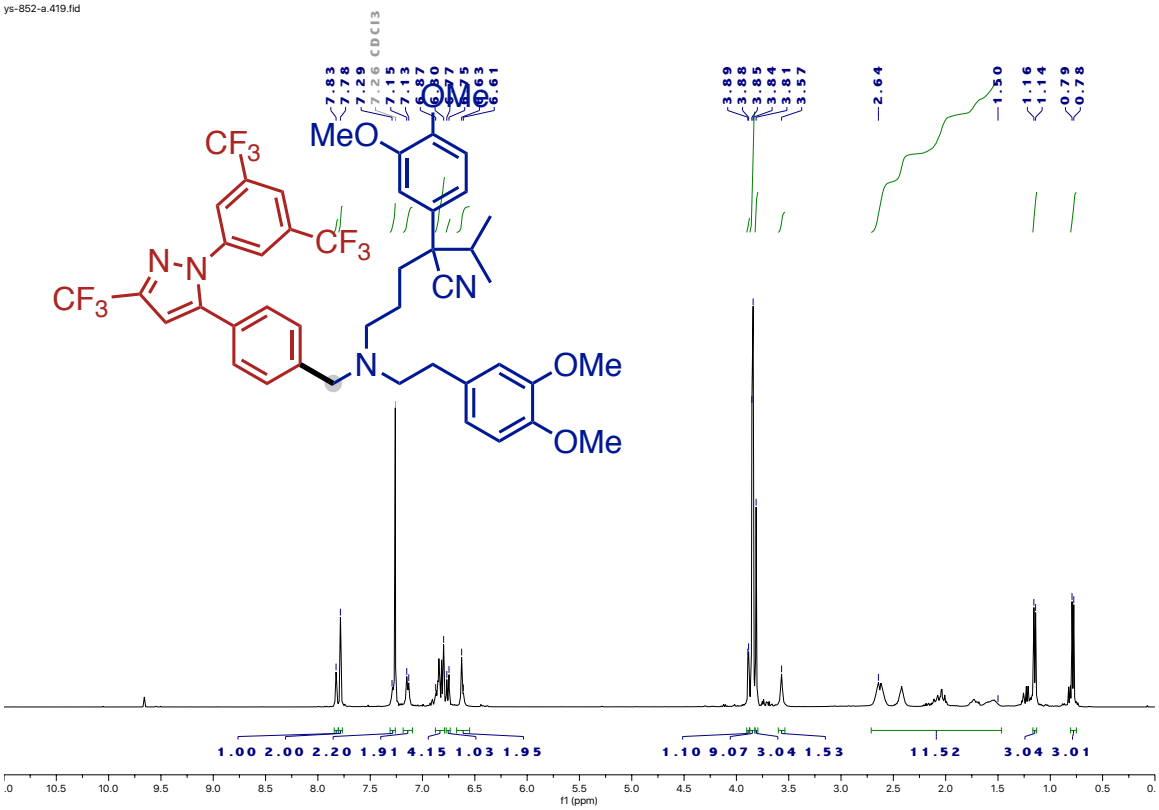

ys-850-c13.379.fid
158.40
145.19
145.04
144.81
144.42
144.03
140.24
140.05
133.18
132.84
132.53
132.50
132.15
130.10
129.01
127.40
126.58
125.06
125.03
124.89
123.86
122.21
121.65
121.15
119.53
118.43
116.86
113.39
106.85
74.40
62.31
59.37
55.18
51.55
41.93
37.95
31.25
25.84
21.48
21.34
CF3
CF3
CF3
N-N
OMe
N
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

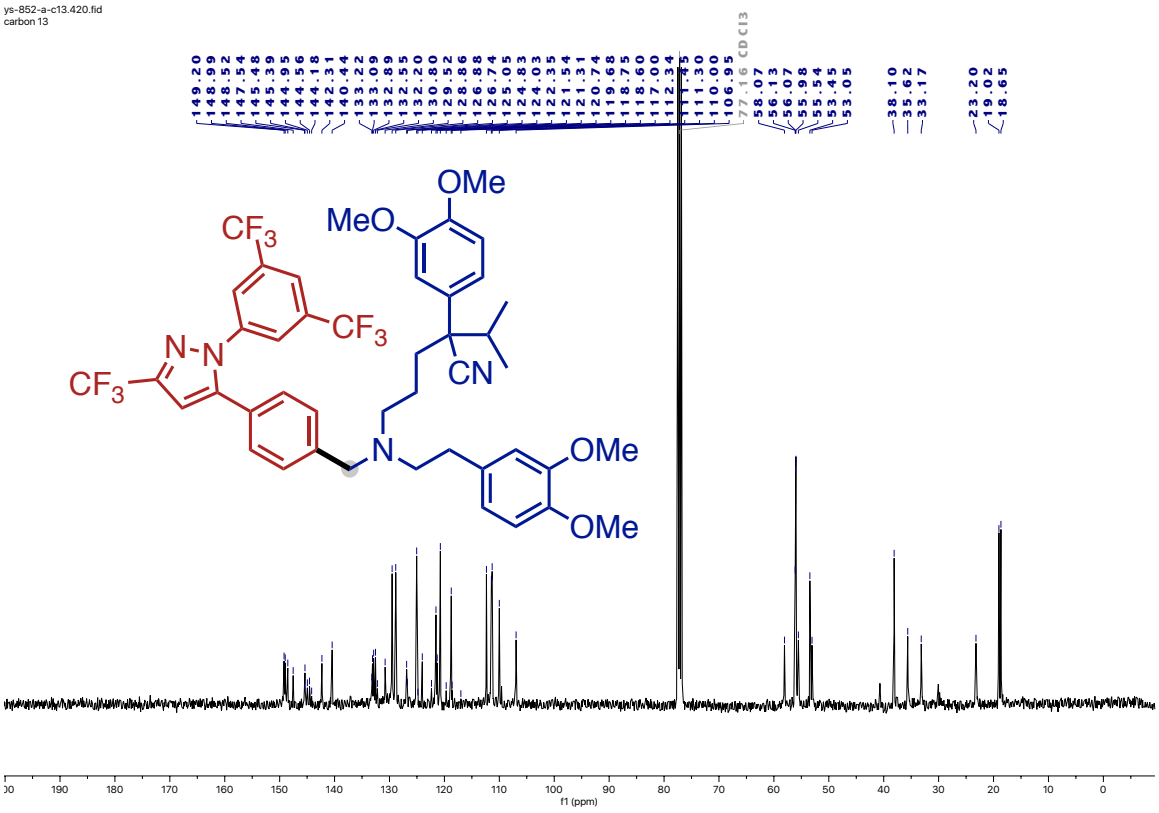

ys-850-f.378.fid
F19
-62.56
-63.16
CF3
CF3
CF3
N-N
OMe
N
OH
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

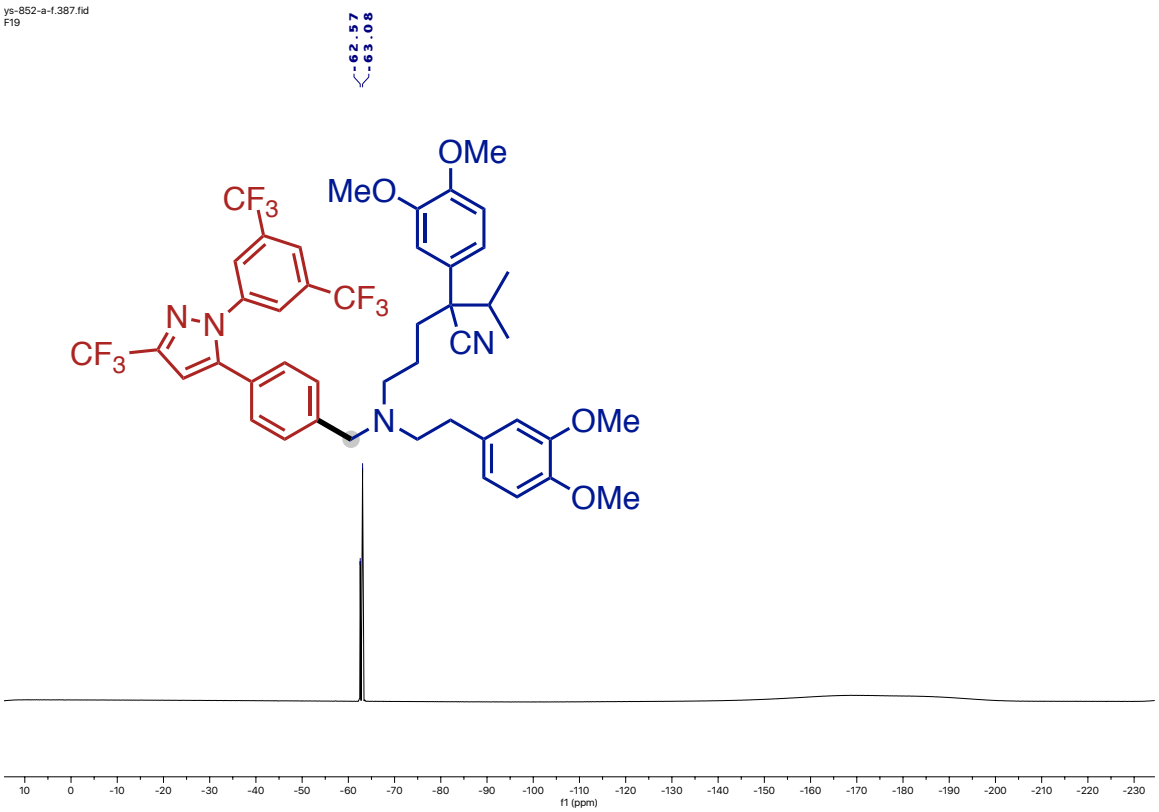

ys-847.376.fid
proton
CF3
CF3
CF3
N-N
OMe
AcO
S
O
N
N
0.23
1.26 1.06 1.00 5.24 2.09 1.13 0.94 3.16 4.04
f1 (ppm)

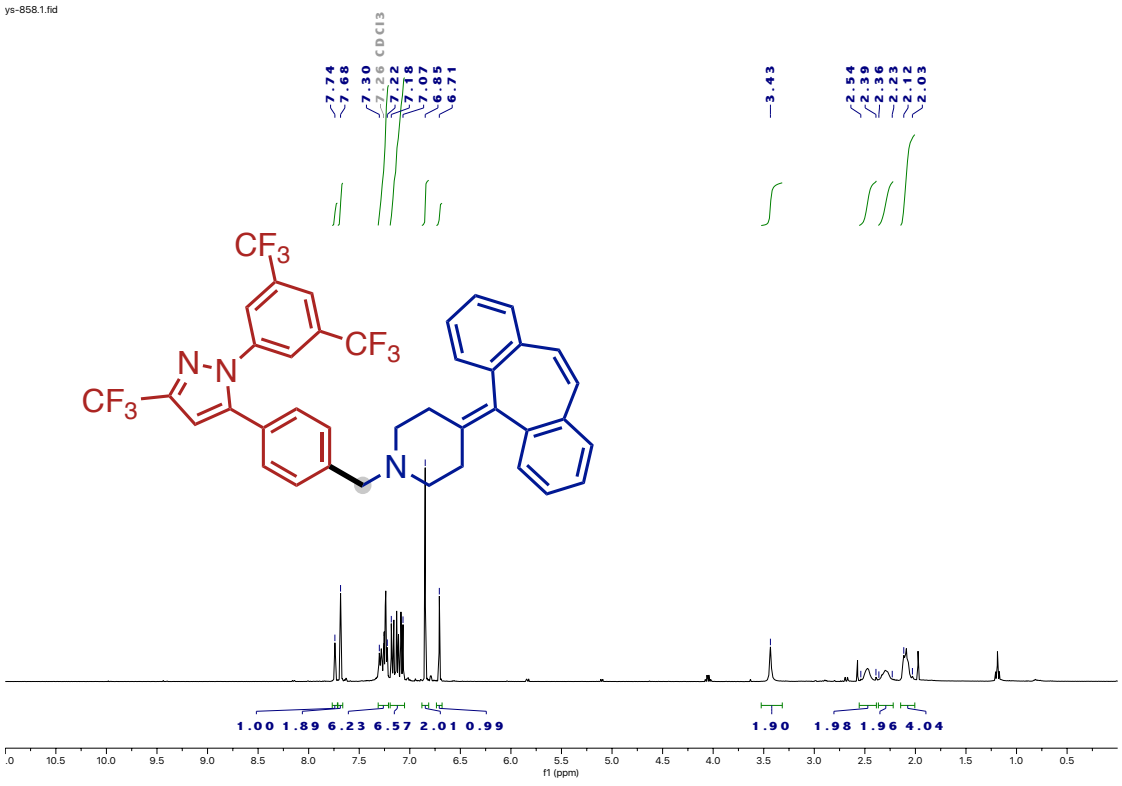

ys-848aa-c13.1.fid
170.02
167.09
159.86
145.82
145.41
145.22
144.84
144.45
144.07
140.86
140.37
135.53
133.19
132.85
132.51
132.17
131.10
130.91
129.82
128.85
127.40
126.78
125.04
125.00
124.70
123.98
123.23
122.36
121.58
121.26
119.68
113.84
106.86
77.16 CDCl3
71.21
61.79
55.63
55.28
54.57
47.88
41.82
20.59
CF3
CF3
CF3
N-N
OMe
AcO
S
O
N
N
f1 (ppm)

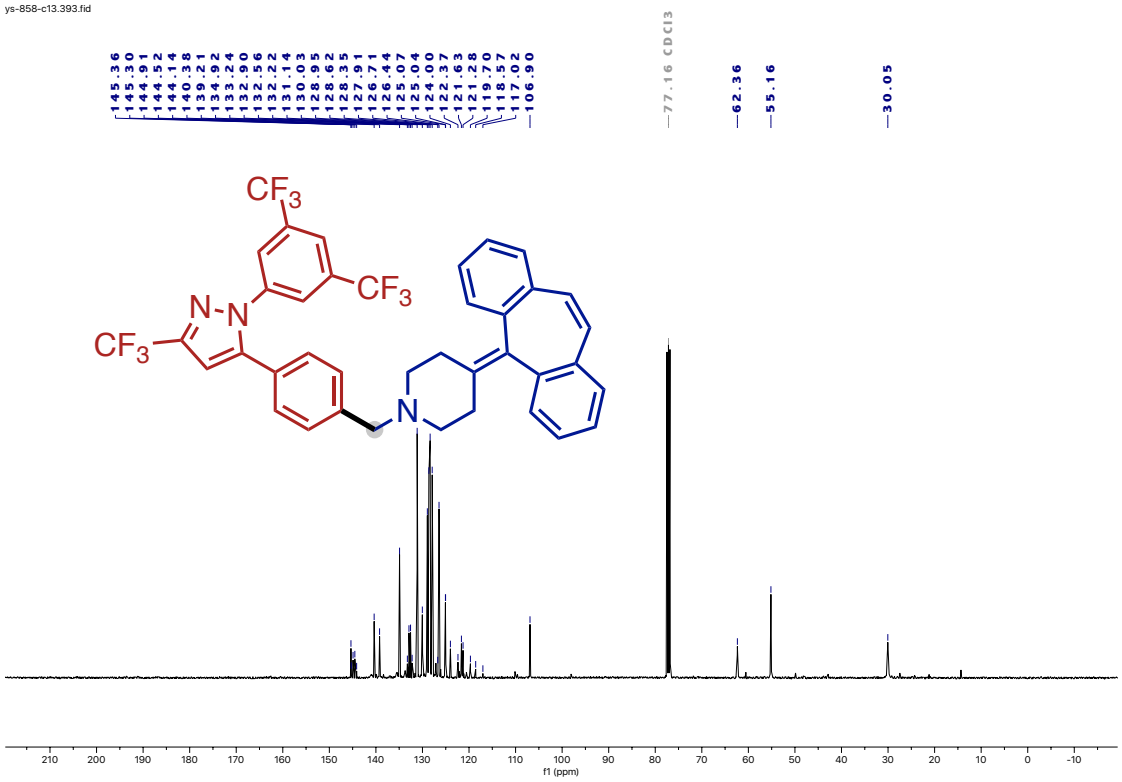

ys-847aa-f.398.fid
F19
-62.55
-63.16
CF3
CF3
CF3
N
N
OMe
AcO
S
O
N
N
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)

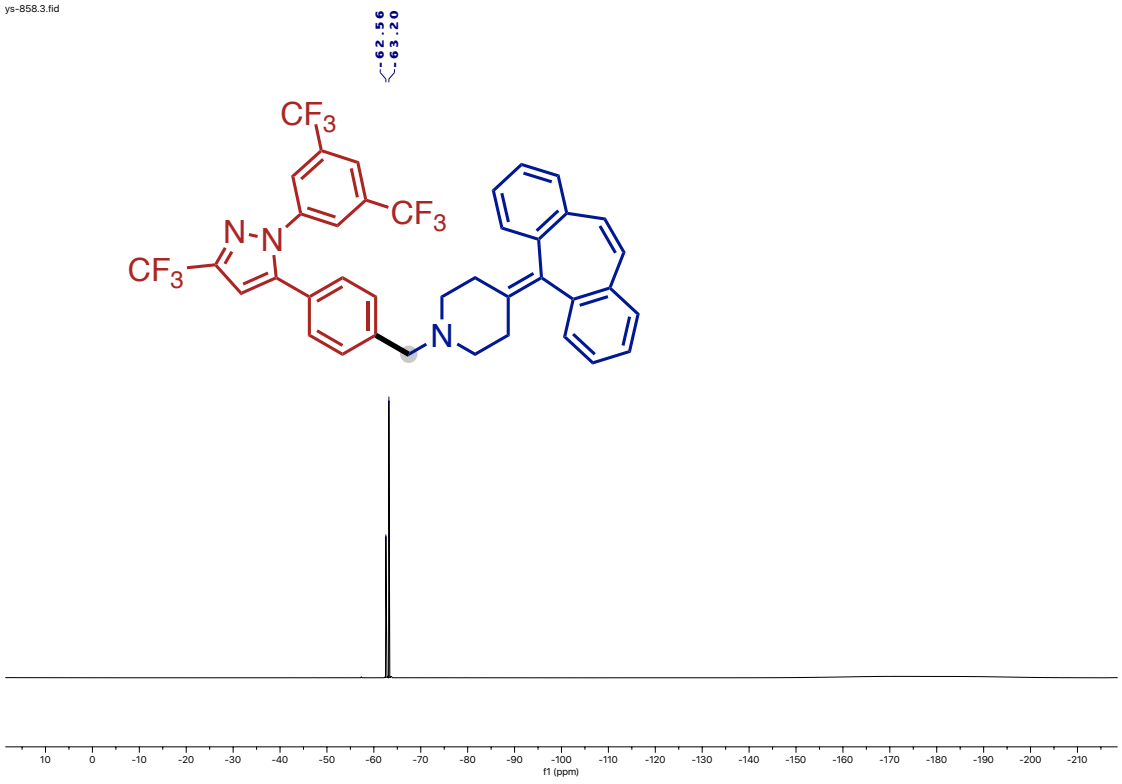

ys-852-a.419.fid
CDCl3
MeO
OMe
CF3
CF3
CF3
N-N
CN
N
OMe
OMe
1.00 2.00 2.20 1.91 4.15 1.03 1.95
1.10 9.07 3.04 1.53
11.52
3.04 3.01
f1 (ppm)

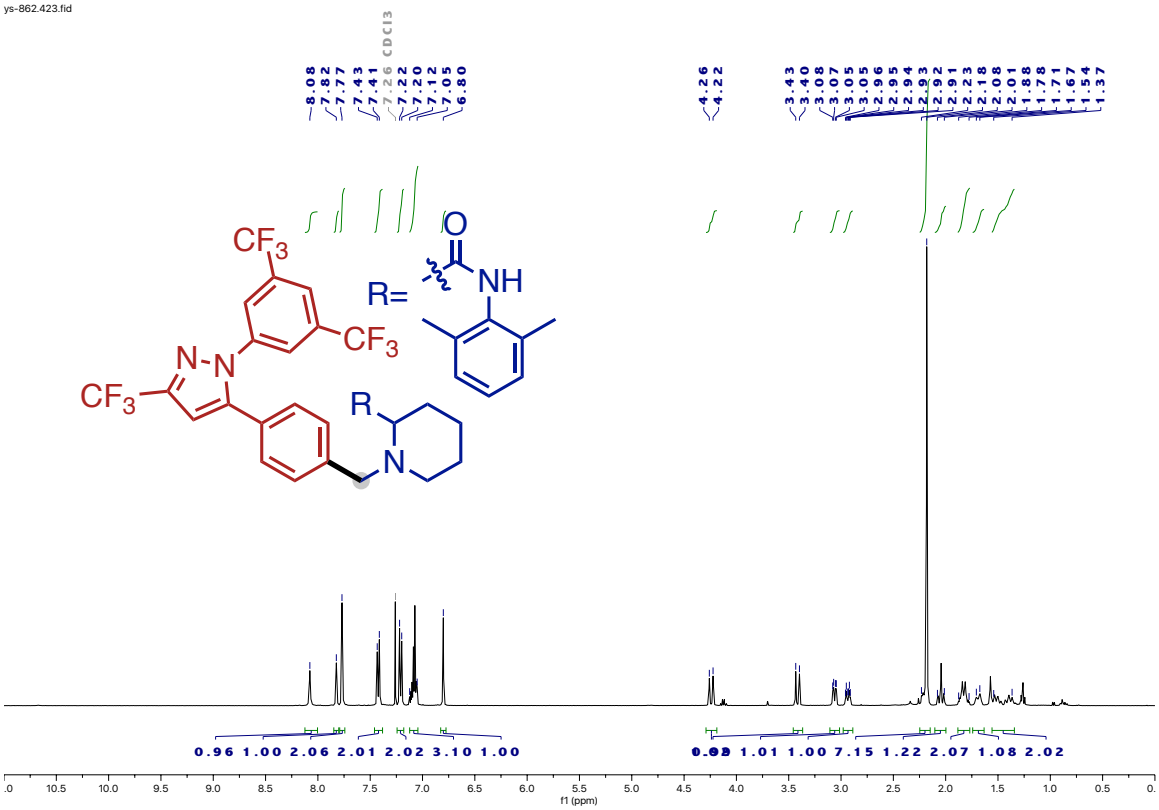

ys-852-a-c13.420.fid
carbon 13
CDCl3
OMe
MeO
CF3
CF3
CF3
N-N
CN
N
OMe
OMe
f1 (ppm)

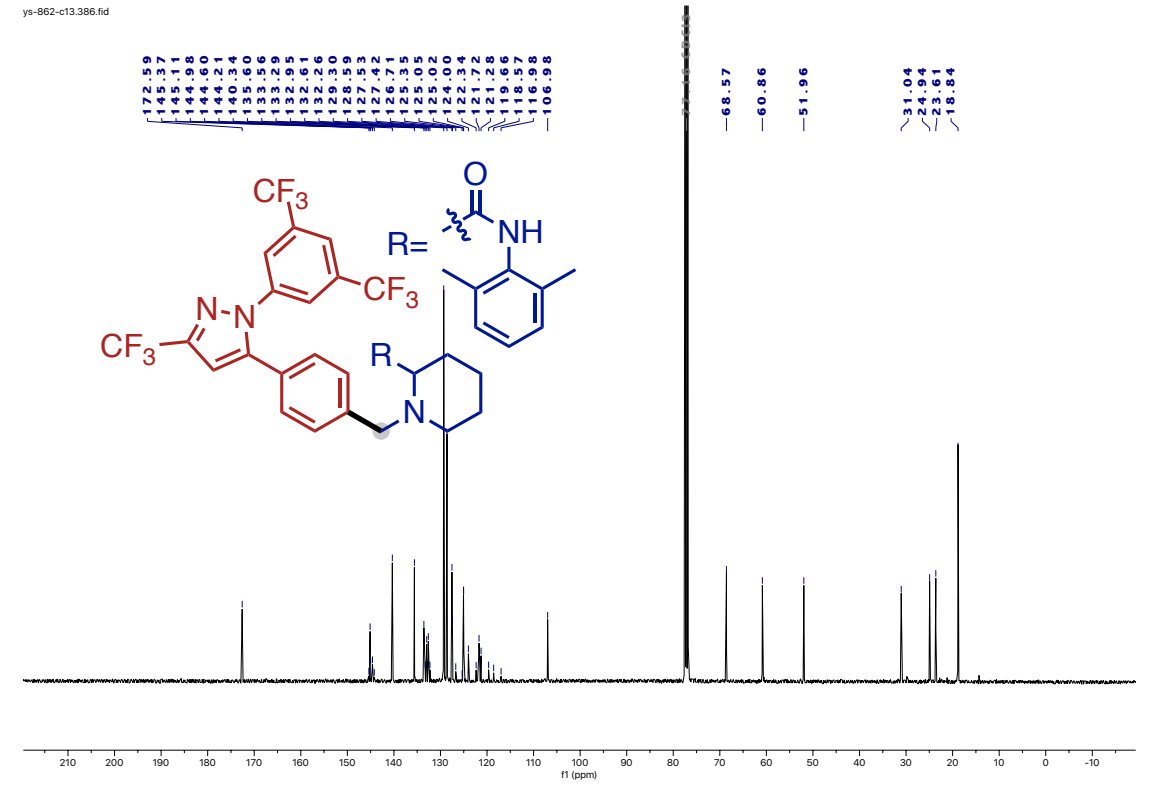

ys-852-a-f.387.fid
F19
-62.57
-63.08
OMe
MeO
CF3
CF3
N-N
CF3
CN
N
OMe
OMe
f1 (ppm)

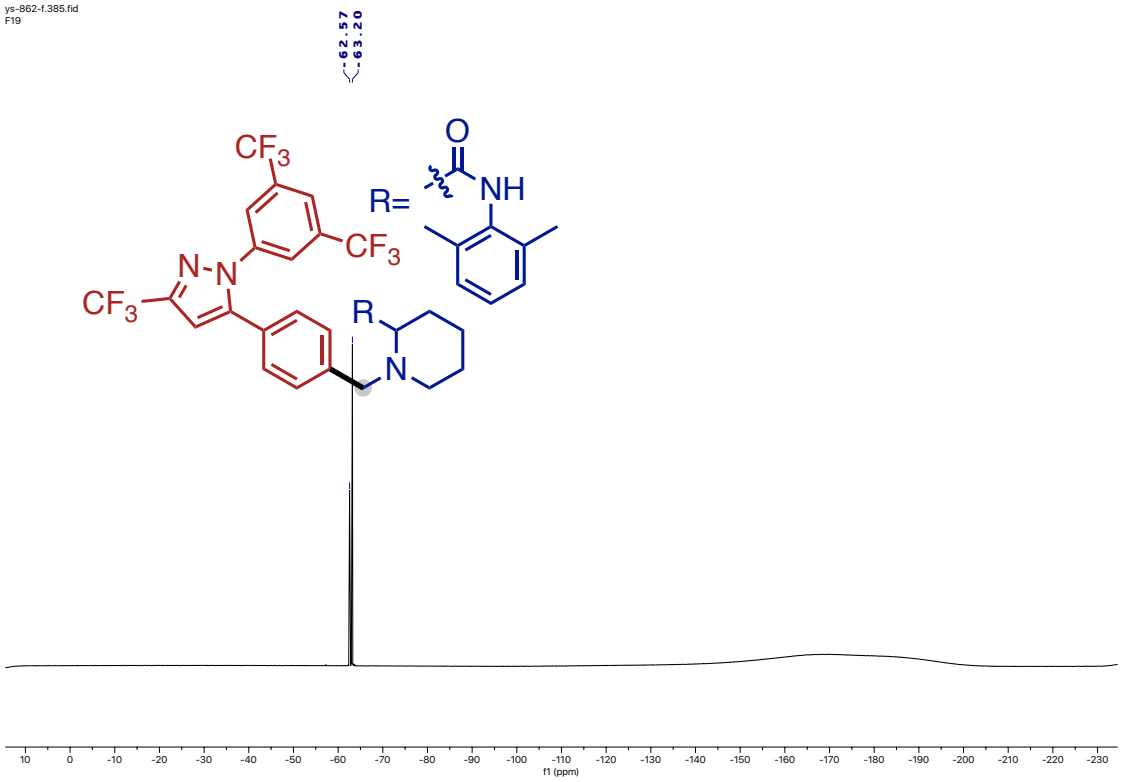

ys-858.1.fid
7.74
7.68
7.30
7.26 CDCl3
7.22
7.18
7.07
6.85
6.71
3.43
2.54
2.39
2.36
2.23
2.12
2.03
CF3
CF3
N-N
CF3
N
1.00 1.89 6.23 6.57 2.01 0.99
1.90
1.98 1.96 4.04
f1 (ppm)

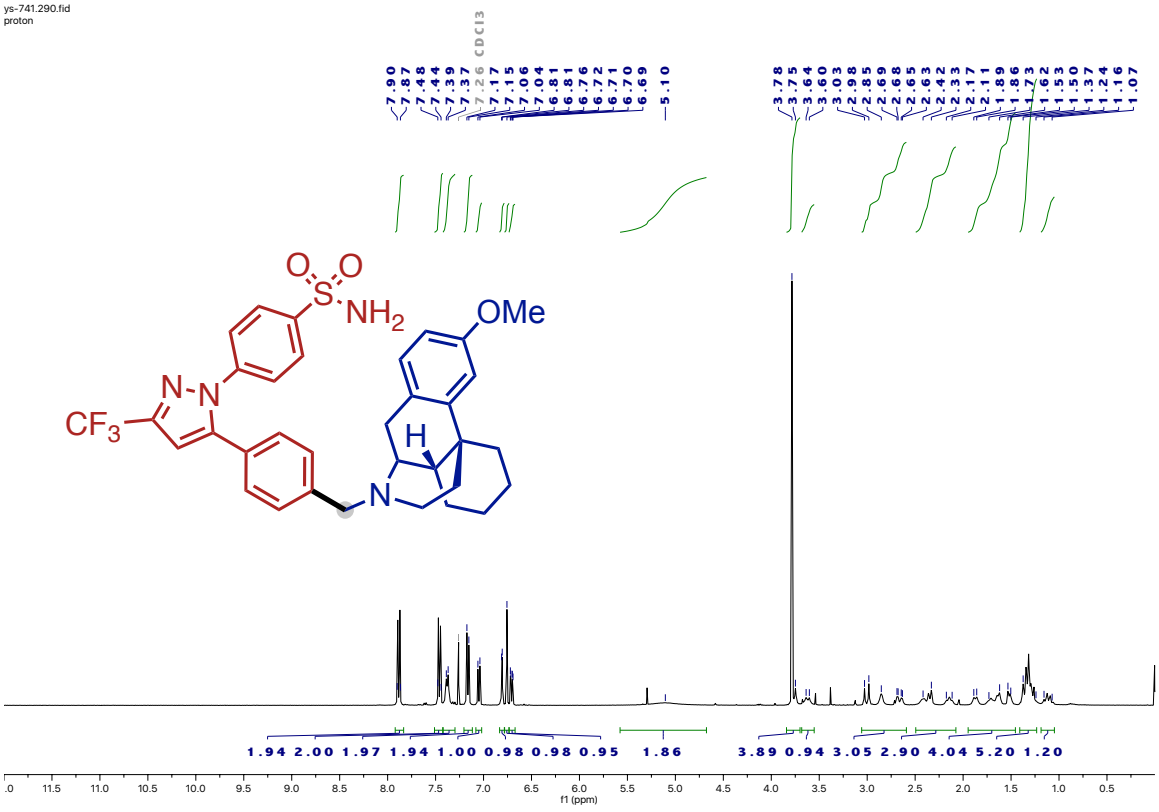

ys-858-c13.393.fid
145.36
145.30
144.91
144.52
144.14
140.38
139.21
134.92
133.24
132.90
132.56
132.22
131.14
130.03
128.95
128.62
128.35
127.91
126.71
126.44
125.07
125.04
124.00
122.37
121.63
121.28
119.70
118.57
117.02
106.90
77.16 CDCl3
62.36
55.16
30.05
CF3
CF3
N-N
CF3
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

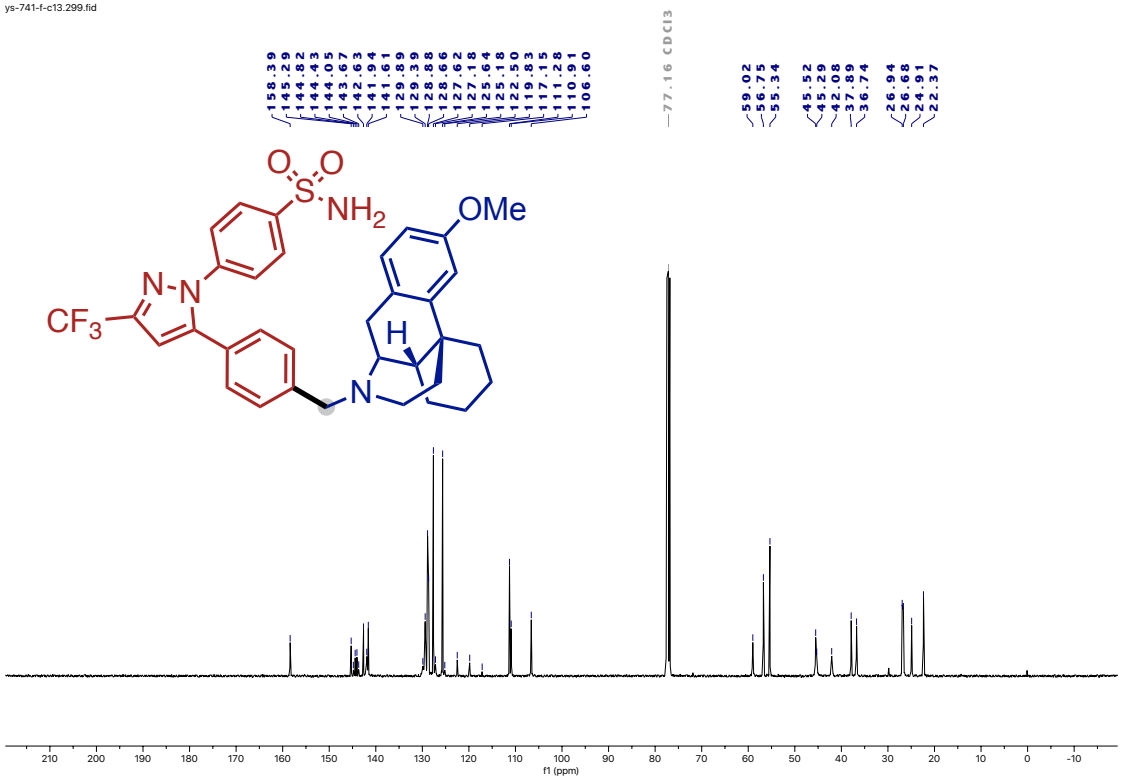

ys-858.3.fid
-62.56
-63.20
CF3
CF3
N-N
CF3
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


ys-862.423.fid
8.08
7.82
7.77
7.43
7.41
7.26 CDCl3
7.22
7.20
7.12
7.05
6.80
4.26
4.22
3.43
3.40
3.08
3.07
3.05
2.96
2.95
2.94
2.93
2.92
2.91
2.23
2.18
2.08
2.01
1.88
1.78
1.71
1.67
1.54
1.37
CF3
CF3
CF3
N-N
R=
O
NH
R
N
0.96 1.00 2.06 2.01 2.02 3.10 1.00
1.01 1.00 7.15 1.22 2.07 1.08 2.02
f1 (ppm)


ys-862-c13.386.fid
172.59
145.37
145.11
144.98
144.60
144.21
140.34
135.60
133.56
133.29
132.95
132.61
132.26
129.30
128.59
127.53
127.42
126.71
125.35
125.05
125.02
124.00
122.34
121.72
121.28
119.66
118.57
116.98
106.98
68.57
60.86
51.96
31.04
24.94
23.61
18.84
CF3
CF3
CF3
N-N
R=
O
NH
R
N
f1 (ppm)


ys-862-f.385.fid
F19
-62.57
-63.20
CF3
CF3
CF3
N-N
R=
O
NH
R
N
f1 (ppm)


ys-741.290.fid
proton
CDCl3
7.90
7.87
7.48
7.44
7.39
7.37
7.17
7.15
7.06
7.04
6.81
6.76
6.72
6.71
6.70
6.69
5.10
3.78
3.75
3.64
3.60
3.03
2.98
2.85
2.69
2.68
2.65
2.63
2.42
2.33
2.17
2.11
1.89
1.86
1.73
1.62
1.53
1.50
1.37
1.24
1.16
1.07
O
S
O
NH2
OMe
N-N
CF3
H
N
1.94 2.00 1.97 1.94 1.00 0.98 0.98 0.95 1.86 3.89 0.94 3.05 2.90 4.04 5.20 1.20
f1 (ppm)


ys-741-f-c13.299.fid
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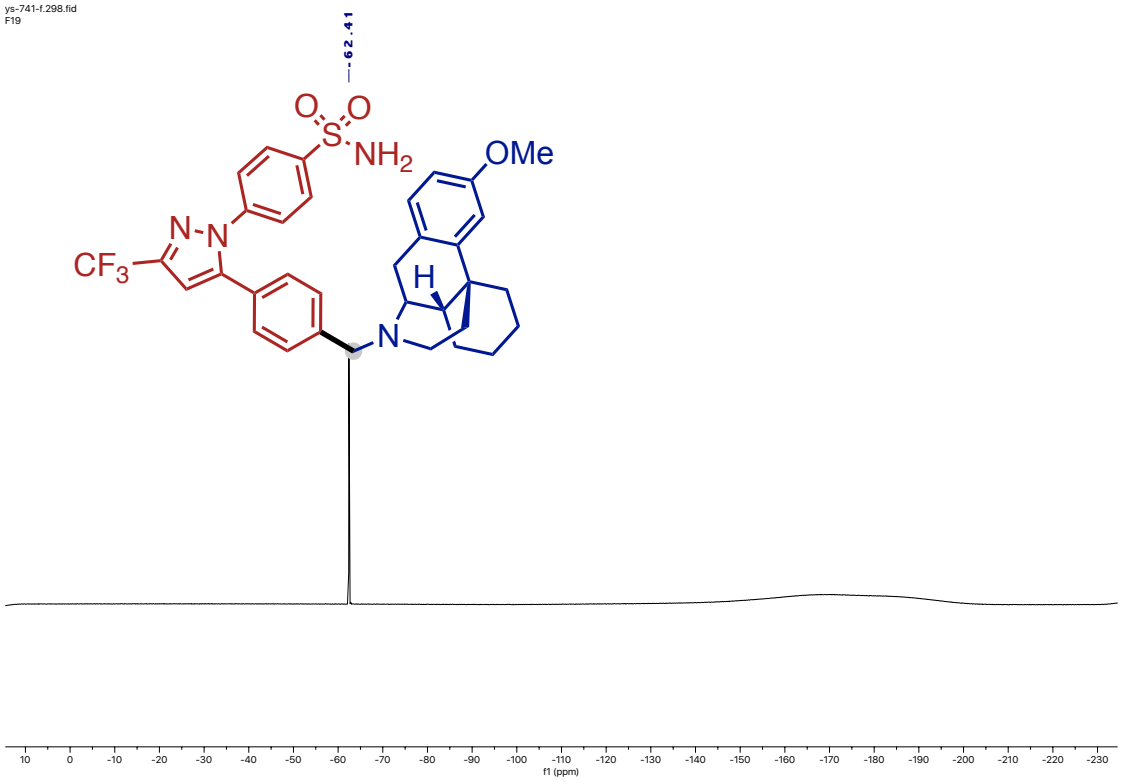
145.29
144.82
144.43
144.05
143.67
142.63
141.94
141.61
129.89
129.39
128.88
128.66
127.62
127.18
125.64
125.18
122.50
119.83
117.15
111.28
110.91
106.60
77.16 CDCl3
59.02
56.75
55.34
45.52
45.29
42.08
37.89
36.74
26.94
26.68
24.91
22.37
O
S
O
NH2
OMe
N
N
CF3
H
N
f1 (ppm)


ys-741-f.298.fid
F19
-62.41
O
S
O
NH2
OMe
N
N
CF3
H
N
f1 (ppm)