Multicomponent Reaction through Cooperative Trio Catalysis Incorporating Enamine, Brønsted Acid and Metal Lewis Acid Catalysis: A Concise Route to Access Chromans

Chamini V. Karunaratne, Ryan G. Sarkisian, Jennifer Reeves, Yongming Deng, Kraig A. Wheeler, Hong Wang

SUPPORTING INFORMATION

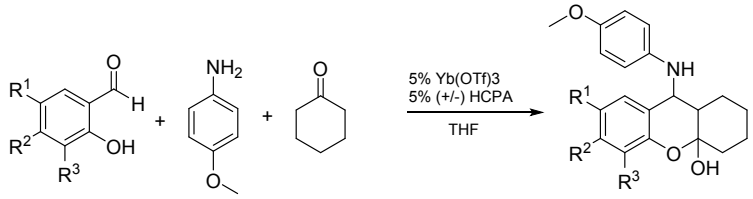
Contents

II. General Information

Unless otherwise noted all commercial materials were used without further purification. Small-scale reactions were conducted in one-dram vials equipped with a magnetic stir bar, fitted with a threaded cap. All NMR spectra were recorded on Bruker and Varian 500 MHz (^{1}H NMR), 125 MHz (^{13}C NMR) spectrometer. Mass spectra were obtained on a Bruker Esquire-LC ion trap instrument with an electrospray ionization source (ESI) operated in either positive or negative mode with direct injection via a syringe pump injecting at 500 μl/hr. HRMS was obtained on positive mode with a resolution of 100,000 on Thermo Fisher Scientific MALDI-LTQ-XL-Orbitrap instrument. IR spectra were taken using PerkinElmer FT-IR spectrometer. Enantiomeric excesses were determined by chiral HPLC analysis Chiralpak AD-H and Chiralcel OD-H and OJ-H in comparison with the authentic racemates. Routine monitoring of the reaction was performed on Silicycle silica gel 60 F254 silica gel plates (TLC). Flash column chromatography was carried out on Silicycle 60 silica gel (40-63 μm). Cyclohexanone and cyclopentanone were ACS reagent pure and dried with molecular sieves. All the solvents were dried on solvent purification system. All the other reagents were purchased from Acros or Aldrich and used directly without further treatment.

III. Substrate Scope

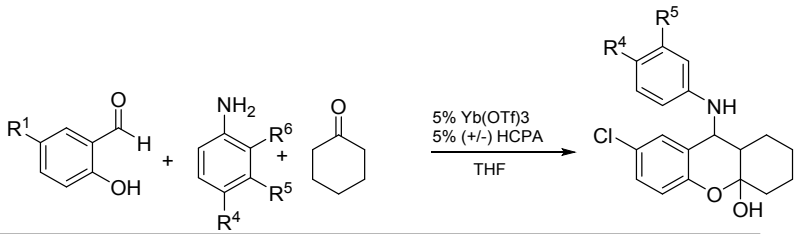
Table 1: Substrate screening of salicylaldehyde with $Yb(OTf)_3$ and (+/-) HCPA



Entry	R^1	R^2	R^3	Name	Time (h)	Yield	dr
1	H	H	H	**4a**	72	92	1:17
2	Cl	H	H	**4b**	24	96	1:14
3	Br	H	H	**4c**	24	91	1:13
4	NO_2	H	H	**4d**	48	94	1:16
5	Br	H	Br	**4e**	72	93	1:10
6	Cl	H	Cl	**4f**	24	67	1:5
7	H	H	OCH_3	**4g**	24	53	1:8
8	H	OCH_3	H	**4i**	20	52	1:7
9	H	H	CH_3	**4s**	36	53	1:10

Reactions were carried out in 1 Dram vials at room temperature using anhydrous THF, with 5% mmol $Yb(OTf)_3$ and 5% mmol (+/-)-HCPA. All transformations were performed on a 1.0 mmol scale. Reaction completion was monitored through TLC. Yields are isolated and dr was calculated from ^{1}H NMR spectroscopy.

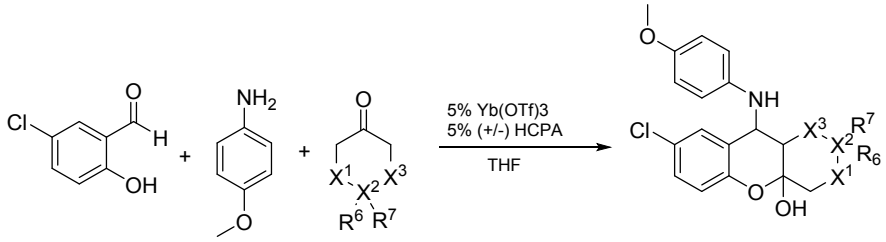
Table 2: Substrate scope of the aryl amines with $Yb(OTf)_3$ and (+/-) HCPA



Entry	R^1	R^4	R^5	R^6	Compound	Yield[a]	dr[b]
1	Cl	H	H	Cl	**4h**	39	1:4
2	Cl	H	H	H	**4j**	96	1:6
3	Cl	H	Cl	H	**4k**	98	1:2.5
4	Cl	Cl	H	H	**4l**	94	1:2
5	Cl	Br	H	H	**4m**	95	1:4
6	Cl	NO_2	H	H	**4n**	-	-

Reactions were carried out in 1 Dram vials at room temperature using anhydrous THF for 20h. [a]Isolated yields. [b]Calculated using ^{1}H NMR spectroscopy.

Table 3: Substrate scope of the cyclic ketone with $Yb(OTf)_3$ and (+/-)-HCPA

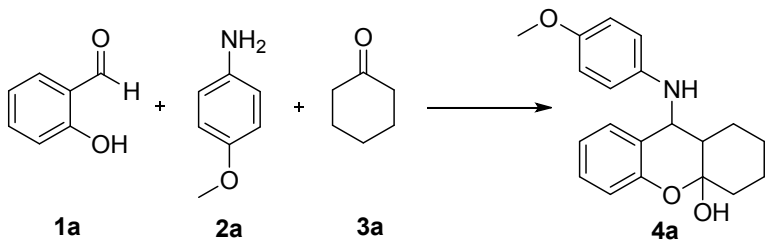


Entry	X^1	X^2	X^3	R^6	R^7	4	Time (h)	Yield[a]	dr[b]
1	CH_2	O	CH_2	-	-	**4o**	18	91	1:16
2	CH_2	S	CH_2	-	-	**4p**	20	96	1:100
3	CH_2	CH	CH_2	CH_3	-	**4q**	18	92	1:4
4	O	C	O	CH_3	CH_3	**4r**	48	90	1:4
5	CH_2	CH_2	-	-	-	-	72	-	-
6	CH_2	-	-	-	-	-	72	-	-
7	CH_2	N	CH_2	CH_3	-	-	72	-	-

Reactions were carried out in 1 Dram vials at room temperature using anhydrous THF. [a]Isolated yields. [b]Calculated using ^{1}H NMR spectroscopy.

IV. Catalytic Asymmetric Synthesis

Table 4: Catalytic asymmetric version of the reaction



1a 2a 3a 4a

Entry	Solvent	Metal (5%)	A:B:C	Brønsted Acid	Time	Yield[a]
1	THF	-	1:1.2:25	(R)HCPA	68h	34
2	Toluene	-	1:1.2:25	(R)HCPA	96h	32
3	Toluene	-	1:1.2:25	(R)TRIP	96h	28
5	THF	$Yb(OTf)_3$	1:1.2:25	(R)HCPA	12h	92[b]

All reactions were set up in small reaction vials with a stir bar at room temperature using anhydrous solvents and 5% chiral phosphoric acid. All transformations were performed on a 1.0 mmol scale. Reaction completion was monitored through TLC. [a]Crude NMR Yields, [b]Isolated Yield.

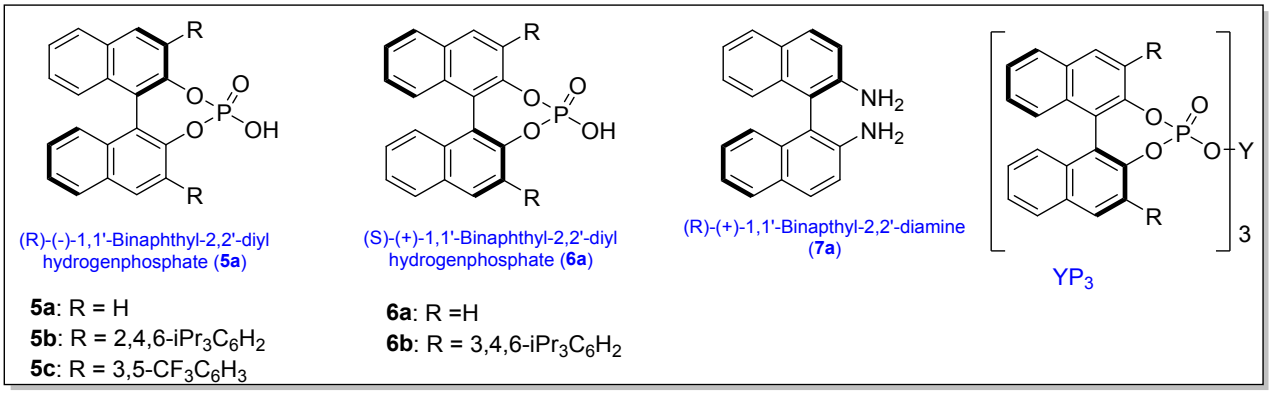
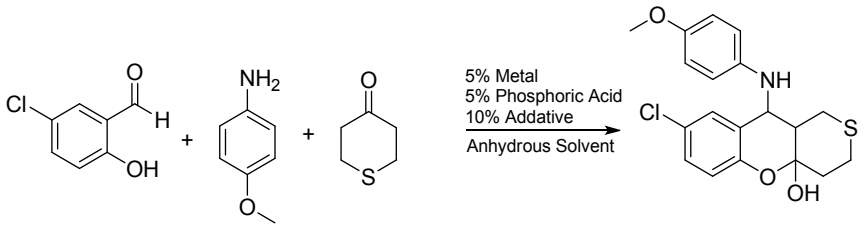


Figure 1: Chiral phosphoric acids and Chiral diamine used in the study

Based on the HPLC data, the ideal substrates for asymmetric exploration are 5-cholosalicylaldehyde, p-methoxyaniline, and the tetrahydrothiopyan-4-one. These three starting reagents produced the high yielding chroman **4p** which is separable on chiral HPLC.

Table 5: Enantiomeric excess and diastereomeric ratio of the three fused ring product

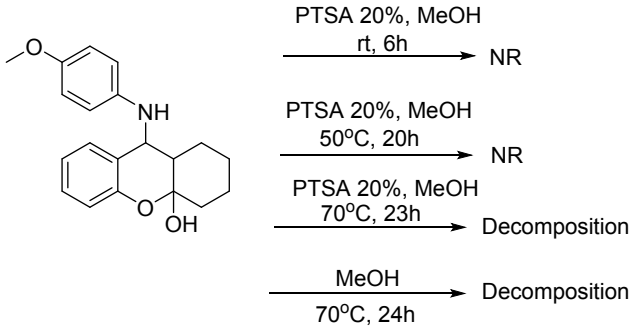


Entry	Solvent	Metal	Phosphoric Acid	Additive	Reaction Time	dr[i]	ee[i]
1	THF	$Y(OTf)_3$	**5b**	-	72h	3:1	15
2	THF	-	**5c**	-	72h	3:1	8
3	Toluene	$Y(OTf)_3$	**5b**	-	72h	3:1	8
4	Methanol	$Y(OTf)_3$	**5b**	-	84h	3:1	Racemic
5	DMF	$Y(OTf)_3$	**5b**	-	96h	-	-
6	Acetonitrile	$Y(OTf)_3$	**5b**	-	84h	4:1	Racemic
7	Dioxane	$Y(OTf)_3$	**5b**	-	96h	-	-
8	Diethyl Ether	$Y(OTf)_3$	**5b**	-	48h	4:1	6
9	Ethyl Acetate	$Y(OTf)_3$	**5b**	-	72h	4:1	Racemic
10	DCM	$Y(OTf)_3$	(+/-)-HCPA	**7a**	48h	5:1	10
11	DCM	$Y(OTf)_3$	**5a**	**7a**	48h	5:1	14
12	DCM	$Y(OTf)_3$	**6a**	**7a**	48h	8:1	42
13	DCM	$Y(OTf)_3$	**5b**	**7a**	48h	5:1	3
14	DCM	$Y(OTf)_3$	**6a**	**7a**	6h	6:1	35
15	DCM	-	**6a**	**7a**	24h	7:1	46
16	DMF	-	**5c**	**7a**	24h	4:1	31
17	DCM	$Y(OTf)_3$		**7a,YP_3**	96h	8:1	24

Reactions were set up in small reaction vials with stir bar at room temperature.
[i]Determined by HPLC analysis.

Reactions were setup using both the sequential and cooperative catalysis conditions. The sequential setup of the reaction was conducted through allowing the transition metal catalyst to activate the iminium ion intermediate formed between the salicylaldehyde and the aryl amine. Next the cyclic ketone and chiral catalytic aryl amine were added and allowed to react. Once this reaction came to completion the chiral phosphoric acid was added allowing for complete transformation to the three fused ring product (Entries 10-14). With this sequence the highest enantiomeric excess 42% was observed with the chiral phosphoric acid, **6a** (Table 6, entry 12). This reaction was then setup cooperatively by adding the transition metal catalyst, the chiral phosphoric acid and the chiral aryl amine allowing to complex first. After complexation the three

components were added. This transformation completed in 6 hours resulting 35% ee (Table 6, entry 14).



Scheme: 1 Attempted dehydration reactions of **4a**

V. NMR Spectroscopic data

4a: Prepared according to the general procedure. Yield 92%, IR (neat) 2938, 2524, 1509, 1232 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.51 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.16 – 7.10 (m, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.80 – 6.75 (m, 4H), 5.19 (d, *J* = 5.4 Hz, 2H), 3.73 (s, 3H), 2.32 – 2.01 (m, 2H), 1.73 – 1.58 (m, 2H), 1.58 – 1.50 (m, *J* = 17.4, 6.3 Hz, 2H), 1.24 – 1.10 (m, 1H), 0.91 (qd, *J* = 13.0, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 152.2, 151.9, 142.2, 127.6, 126.4, 123.5, 120.2, 115.9, 98.0, 54.8, 38.8, 38.4, 24.2, 22.7, 21.6. MS (ESI) m/z calculated 325.2, observed 326.2 $(M+H)^+$. HRMS (MALDI) m/z calculated 325.1678, observed 326.1669.

4b: Prepared according to the general procedure. Yield 96%, IR (neat) 3383, 2934, 1511, 1478, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.13 (d, *J* = 6.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.74 (t, *J* = 8.8 Hz, 3H), 5.22 (d, *J* = 4.7 Hz, 1H), 3.77 (s, 3H), 2.58 (s, 1H), 2.24 (dd, *J* = 8.0, 4.9 Hz, 1H), 2.03 (d, *J* = 10.0 Hz, 1H), 1.76 – 1.42 (m, 3H), 1.17 (d, *J* = 12.9 Hz, 1H), 0.96 – 0.74 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 150.3, 128.3, 126.7, 125.9, 125.0, 117.9, 115.2, 114.6, 98.6, 55.9, 49.9, 49.7, 49.5, 48.2, 39.2, 38.1, 24.2, 22.8, 21.6. MS (ESI) m/z calculated 359.1, observed 382.1 $(M+Na)^+$. HRMS (MALDI) m/z calculated 359.1288, observed 359.1285.

4c: Prepared according to the general procedure. Yield 91%, IR (neat) 3394, 2932, 1512, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 6.84 (t, *J* = 11.3 Hz, 2H), 6.74 (dd, *J* = 15.2, 8.5 Hz, 3H), 5.26 (s, 1H), 3.77 (d, *J* = 24.2 Hz, 3H), 2.32 – 2.18 (m, 1H), 2.05

(d, J = 11.2 Hz, 1H), 1.90 – 1.46 (m, 5H), 1.28 – 1.13 (m, 1H), 0.96 – 0.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 150.8, 140.7, 131.3, 129.7, 125.6, 118.4, 115.2, 114.7, 113.4, 99.1, 55.8, 48.2, 39.2, 37.7, 24.2, 22.8, 21.5. MS (ESI) m/z calculated 403.1, observed 426.1 $(M+Na)^+$. HRMS (MALDI) m/z calculated 403.0783, observed 403.0781.

4d: Prepared according to the general procedure. Yield 94%, IR (neat) 3388, 2916, 2849, 1511, 1238, 1025 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.34 (d, J = 1.8 Hz, 1H), 8.20 – 7.99 (m, 1H), 7.18 (s, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.87 – 6.69 (m, 3H), 5.53 (d, J = 10.8 Hz, 1H), 5.13 (dd, J = 10.3, 5.2 Hz, 1H), 3.65 (s, 3H), 2.17 – 2.09 (m, 2H), 1.69 – 1.49 (m, 4H), 1.36 (dd, J = 25.9, 13.1 Hz, 1H), 1.26 – 1.00 (m, 1H), 0.72-0.65 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 159.7, 152.5, 143.0, 141.9, 126.2, 125.4, 124.5, 118.4, 116.1, 115.4, 101.5, 56.5, 48.7, 39.4, 38.8, 32.0, 24.9, 23.7, 23.0. MS (ESI) m/z caculated 370.1, observed 393.2 $(M+Na)^+$. HRMS (MALDI) m/z caculated 370.1529, observed 370.1526.

4e: Prepared according to the general procedure. Yield 93%, IR (neat) 3388, 2933, 2860, 1703, cm^{-1}; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.71 – 7.53 (m, 1H), 7.50 (s, 1H), 6.72 (d, J = 5.8 Hz, 4H), 5.33 (d, J = 10.5 Hz, 1H), 5.09 (s, 1H), 3.62 (s, 3H), 2.49 (s, 3H), 2.13 (d, J = 12.8 Hz, 1H), 2.00 (d, J = 12.1 Hz, 1H), 1.72 – 1.28 (m, 3H), 1.02 (m, 0.5H), 0.58 (m, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 147.8, 140.6, 134.1, 128.9, 126.9, 115.2, 114.7, 113.0, 111.4, 99.7, 55.6, 48.7, 42.0, 39.0, 37.7, 27.1, 25.0, 23.9, 22.8, 21.5. MS (ESI) m/z calculated 482.9, observed 481.7$(M-H)^-$. HRMS (MALDI) m/z calculated 482.9868, 0bserved 482.9860.

4f: Prepared according to the general procedure. Yield 67%, IR (neat) 3394, 2933, 1510, 1448, 815 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.46 (dd, J = 2.5, 1.1 Hz, 1H), 7.26 (dd, J = 2.6, 0.8 Hz, 1H), 6.82 – 6.76 (m, 4H), 5.20 (d, J = 5.3 Hz, 1H), 3.73 (s, 3H), 3.31 (s, 1H), 2.50 – 2.25 (m, 2H), 2.25 – 2.09 (m, 2H), 1.91 – 1.83 (m, 2H), 1.74 – 1.54 (m, 3H), 0.81 (ddd, J = 26.4, 13.1, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 155.2, 147.0, 141.7, 127.6, 127.2, 125.2, 124.5, 121.6, 114.7, 114.4, 99.3, 54.8, 38.4, 37.9, 24.0, 22.6, 21.5. MS (ESI) m/z calculated 393.0, observed 394.0 $(M+H)^+$. HRMS (MALDI) m/z calculated 393.0898, observed 393.0889.

4g: Prepared according to the general procedure. Yield 53%, IR (neat) 3388, 2916, 2849, 1509, 1234 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 8.34 (t, J = 9.5 Hz, 1H), 8.13 – 8.05 (m, 1H), 7.19 (s, 1H), 7.00 (d, J = 9.0 Hz, 1H), 6.85 – 6.73 (m, 4H), 5.54 (d, J = 10.8 Hz, 1H), 5.14 (dd, J = 10.4,

5.2 Hz, 1H), 3.66 (s, 3H), 2.19 – 2.03 (m, *J* = 35.6, 21.9 Hz, 2H), 1.71 – 1.50 (m, 4H), 1.44 – 1.31 (m, 1H), 1.26 – 1.00 (m, 2H), 0.75 – 0.56 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 158.4, 151.2, 141.7, 140.6, 125.0, 124.1, 123.3, 117.2, 114.8, 114.1, 100.3, 55.3, 47.4, 38.1, 37.5, 23.7, 22.5, 21.7. MS (ESI) m/z calculated 355.2, observed 356.2 $(M+H)^+$. HRMS (MALDI) m/z calculated 355.1784, observed 355.1657.

4h: Prepared according to the general procedure. Yield 39%, IR (neat) 3386, 2928, 2852, 1493, 818 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.41 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.17 – 7.04 (m, 4H), 6.80 – 6.74 (m, 2H), 6.75 – 6.61 (m, 2H), 5.22 (d, *J* = 5.4 Hz, 1H), 2.19 – 2.02 (m, 2H), 1.90 – 1.82 (m, 2H), 1.75 (ddd, *J* = 10.5, 4.8, 2.1 Hz, 1H), 1.73 – 1.50 (m, 3H), 1.36 – 1.14 (m, 2H), 0.89 (qd, *J* = 13.1, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 151.0, 146.8, 128.6, 127.6, 126.3, 125.1, 124.9, 121.0, 117.6, 113.9, 98.3, 41.2, 38.5, 38.1, 26.8, 24.1, 22.6, 21.7. MS (ESI) m/z calculated 393.1 observed 416.1 $(M+Na)^+$. HRMS (MALDI) m/z calculated 393.0898 observed 393.0886.

4i: Prepared according to the general procedure. Yield 52%, IR (neat) 2921, 2850, 1615, 1510, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 12.6, 6.3 Hz, 1H), 6.85 – 6.81 (m, 2H), 6.75 – 6.72 (m, 2H), 6.54 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.42 – 6.39 (m, *J* = 3.7 Hz, 1H), 5.75 (dd, *J* = 6.1, 2.1 Hz, 1H), 5.20 (d, *J* = 5.5 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 2.28 – 2.22 (m, 1H), 2.15 – 2.01 (m, 2H), 2.01-1.97 (m, 1H), 1.89 – 1.78 (m, 2H), 1.74 – 1.65 (m, 2H), 1.63 – 1.57 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 152.6, 152.1, 141.4, 127.6, 115.1, 114.6, 114.5, 107.6, 101.6, 99.0, 67.4, 55.8, 55.3, 47.8, 39.4, 38.4, 29.5, 24.3, 23.8, 22.9, 21.7. MS (ESI) m/z calculated 355.2, observed 356.2 $(M+H)^+$. HRMS (MALDI) m/z calculated 355.1784, observed 355.1775.

4j: Prepared according to the general procedure. Yield 96%, IR (neat) 3155, 1434, 1188, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO) δ 7.33 (d, *J* = 1.7 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.11 (dd, *J* = 15.9, 8.3 Hz, 3H), 6.83 (d, *J* = 9.5 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 2H), 6.57 (t, *J* = 7.2 Hz, 1H), 5.85 (d, *J* = 10.3 Hz, 1H), 5.13 (dd, *J* = 10.0, 5.3 Hz, 1H), 2.24 (t, *J* = 6.7 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.78 – 1.70 (m, *J* = 12.6, 6.3 Hz, 1H), 1.70 – 1.29 (m, 4H), 1.19 – 1.02 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 151.0, 148.0, 129.2, 127.7, 126.4, 125.5, 123.5, 118.2, 116.3, 112.6, 98.7, 46.7, 41.3, 38.4, 37.9, 26.5, 24.3, 23.9, 22.6, 22.0. MS (ESI)

m/z calculated 329.1, observed 328.0 $(M-H)^-$. HRMS (MALDI) m/z calculated 329.1183, observed 329.1171.

4k: Prepared according to the general procedure. Yield 98%, IR (neat) 3369, 2932, 2857, 1493, 812 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) *δ 7.42 (d, *J* = 1.5 Hz, 1H), 7.30 – 7.20 (m, 1H), 7.17 – 7.08 (m, 2H), 7.08 – 7.02 (m, 2H), 6.76 (t, *J* = 6.0 Hz, 2H), 6.74 – 6.68 (m, 1H), 6.62 (t, *J* = 10.7 Hz, 1H), 5.22 (d, *J* = 5.4 Hz, 1H), 4.55 – 4.39 (m, 1H), 2.19 – 1.99 (m, 2H), 1.72 – 1.51 (m, *J* = 27.3, 18.7, 14.4, 6.9 Hz, 3H), 1.37 – 1.12 (m, 3H), 0.95 – 0.80 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 151.0, 146.8, 128.7, 127.6, 127.5, 126.3, 125.1, 124.9, 121.0, 117.7, 113.9, 98.2, 50.3, 38.5, 38.2, 26.3, 25.1, 24.2, 22.6, 21.7. MS (ESI) m/z calculated 363.1, observed 361.8 $(M-H)^-$. HRMS (MALDI) m/z calculated 363.0793, observed 363.0783.

* The spectra exist as a set of diastereomers in a ratio of 1: 2.5. The reported data values are only for the major diastereomer.

4l: Prepared according to the general procedure. Yield 94%, IR (neat) 3387, 2930, 1594, 1476, 933, cm^{-1}; ^1H NMR (500 MHz, CD_3OD) *δ 7.40 (d, *J* = 1.5 Hz, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 7.17 – 7.09 (m, 1H), 7.10 – 7.01 (m, 2H), 6.84 – 6.75 (m, 1H), 6.75 – 6.69 (m, 1H), 6.69 – 6.63 (m, 1H), 6.64 – 6.53 (m, 2H), 5.19 (t, *J* = 29.0 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 2.17 (dt, *J* = 4.6, 3.6 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.98 – 1.80 (m, 1H), 1.73 – 1.52 (m, 3H), 1.38 – 1.13 (m, 2H), 0.96 – 0.82 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 151.1, 149.5, 134.7, 130.1, 127.6, 126.4, 125.1, 124.8, 118.0, 117.7, 116.3, 115.7, 112.2, 111.0, 98.5, 98.4, 50.0, 38.6, 38.1, 37.2, 26.3, 25.1, 24.1, 22.6, 21.8. MS (ESI) m/z calculated 363.1, observed 386.0 $(M+Na)^+$. HRMS (MALDI) m/z calculated 363.0793, observed 363.0784.

* The spectra exist as a set of diastereomers in a ratio of 1: 2.5. The reported data values are only for the major diastereomer.

4m: Prepared according to the general procedure. Yield 95%, IR (neat) 3258, 2932, 1476, 1234, 813 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 7.33 (d, *J* = 1.7 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.17 – 7.09 (m, 1H), 6.85 – 6.75 (m, 2H), 6.72 (t, *J* = 9.4 Hz, 2H), 6.10 (d, *J* = 10.1 Hz, 1H), 5.13 (dd, *J* = 10.0, 5.4 Hz, 1H), 2.13 – 2.01 (m, 2H), 1.86 – 1.71 (m, 1H), 1.71 – 1.46 (m, 4H), 1.38 (ddd, *J* = 17.4, 16.0, 10.8 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 151.6, 147.9, 132.1, 128.3, 126.9, 125.5, 124.3, 118.5, 114.9, 107.2, 98.9, 60.2, 47.4, 38.8, 38.3, 24.3,

23.1, 22.5. MS (ESI) m/z calculated 407.0, observed 388.0 $(M-H_2O)^+$. HRMS (MALDI) m/z calculated 407.0288, observed 407.0278.

4o: Prepared according to the general procedure. Yield 91%, IR (neat) 3370, 1506, 1230, 932 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 7.39 (d, *J* = 1.2 Hz, 1H), 7.24 – 7.19 (m, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.75 (dd, *J* = 27.3, 8.8 Hz, 4H), 5.44 (d, *J* = 10.6 Hz, 1H), 5.07 (dd, *J* = 10.3, 5.7 Hz, 1H), 3.90 – 3.70 (m, 1H), 3.66 (s, 3H), 2.90 (t, *J* = 11.8 Hz, 1H), 2.49 (s, 1H), 2.38 – 2.23 (m, 1H), 2.05 – 1.88 (m, 1H), 1.74 (td, *J* = 13.0, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) *δ* 38.4, 38.4, 45.7, 55.3, 64.6, 96.5, 114.2, 114.9, 118.3, 124.3, 125.2, 126.3, 128.1, 141.8, 150.9, 151.3. MS (ESI) m/z calculated 361.1, observed 384.1 $(M+Na)^+$. HRMS (MALDI) m/z calculated 361.1081, observed 361.1074.

4p: Prepared according to the general procedure. Yield 96%, IR (neat) 3370, 2931, 2858, 1506, 1234 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 7.43 – 7.38 (m, 1H), 7.21 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.05 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.59 (d, *J* = 10.7 Hz, 1H), 5.18 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.65 (s, 3H), 2.73 (t, *J* = 12.3 Hz, 1H), 2.55 – 2.46 (m, *J* = 11.2 Hz, 3H), 2.37 (dd, *J* = 12.0, 9.2 Hz, 2H), 2.30 – 2.20 (m, 1H), 2.07 (t, *J* = 13.0 Hz, 1H), 1.76 (td, *J* = 13.3, 3.6 Hz, 1H), 1.76 (td, *J* = 13.3, 3.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) *δ* 24.6, 24.9, 39.9, 47.7, 55.3, 96.4, 114.1, 114.9, 118.3, 124.4, 125.5, 126.4, 128.0, 141.6, 150.5, 151.2. MS (ESI) m/z calculated 377.0, observed 378.0 $(M+H)^+$. HRMS (MALDI) m/z calculated 377.0852, observed 377.0672.

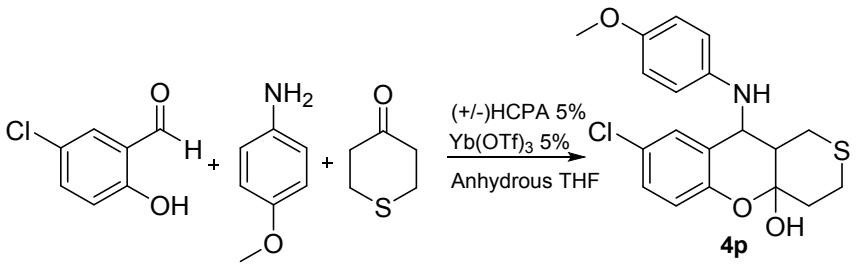
4q: Prepared according to the general procedure. Yield 92%, IR (neat) 2929, 1506, 1228, 818 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 7.39 (d, *J* = 1.9 Hz, 1H), 7.17 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.86 – 6.65 (m, 5H), 5.40 (d, *J* = 10.7 Hz, 1H), 5.06 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.66 (s, 3H), 2.06 (d, *J* = 12.8 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.57 (dd, *J* = 27.2, 13.6 Hz, 1H), 1.47 (td, *J* = 13.1, 3.4 Hz, 1H), 1.37 (dd, *J* = 25.8, 13.0 Hz, 1H), 1.14 – 1.02 (m, 1H), 0.76 – 0.65 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 151.6, 151.4, 142.5, 128.1, 126.9, 126.3, 124.2, 118.4, 115.3, 114.3, 99.0, 55.7, 47.9, 38.8, 38.4, 24.4, 23.1, 22.3. MS (ESI) m/z calculated 373.1, observed 374.1 $(M+H)^+$. HRMS (MALDI) m/z calculated 373.1445, observed 373.1438.

4r: Prepared according to the general procedure. Yield 90%, IR (neat) 3370, 1507, 1229, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 2H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 8.3

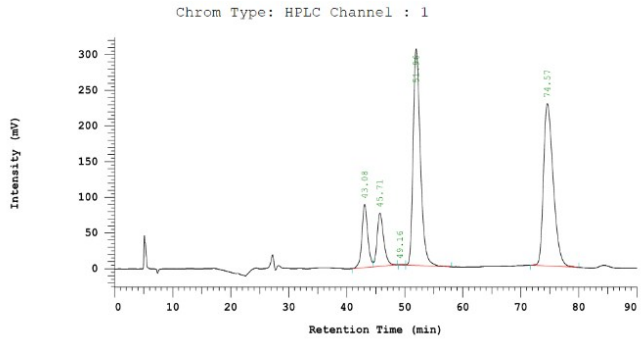
Hz, 2H), 6.88 – 6.77 (m, 3H), 4.42 (s, 1H), 4.31 (s, 1H), 3.91 (s, 2H), 3.82 (s, 3H), 1.57 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 150.1, 138.6, 130.0, 129.7, 126.2, 120.9, 119.4, 117.4, 116.5, 115.1,115.0, 99.6, 90.9, 66.4, 65.5, 55.7, 53.6, 28.8, 18.5. MS (ESI) m/z clculated 391.1, observed 414.1 $(M+Na)^+$. HRMS (MALDI) m/z clculated 391.1187, observed 391.1180.

4s: Prepared according to the general procedure. Yield 53%, IR (neat) 3306, 2939, 1615, 1506, 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.34 – 7.19 (m, 3H), 6.98 – 6.91 (m, 2H), 6.84 (dd, J = 9.4, 5.6 Hz, 1H), 5.70 (dd, J = 5.9, 2.0 Hz, 1H), 4.15 – 4.07 (m, 1H), 4.07 – 4.00 (m, 1H), 3.83 (s, 3H), 2.32 (s, 3H), 2.12 – 1.94 (m, 2H), 1.93 – 1.66 (m, 4H), 1.64 – 1.49 (m, 2H), 1.49 – 1.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 159.3, 133.7, 129.6, 126.1, 122.2, 118.5, 114.5, 106.1, 67.6, 55.5, 30.1, 29.5, 28.8, 25.4, 23.5, 22.6, 22.4, 15.5. HRMS (MALDI) m/z calculated 339.1834, observed 339.1793.

VI. HPLC Chromatography Data



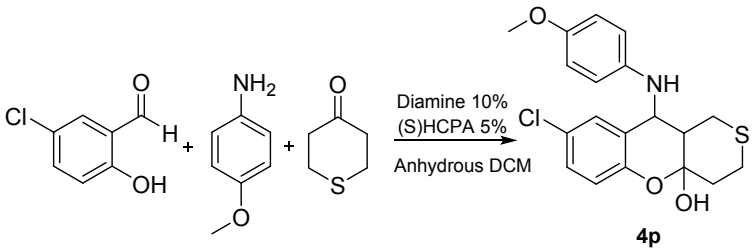
Racemic phosphoric acid, (+/-) HCPA, (0.05mmol, 17.9 mg) and $Yb(OTf)_3$ (0.05mmol, 31.5 mg) were mixed in anhydrous THF at room temperature for one hour. Next, 5-chlorosalicylaldehyde (1.0 mmol, 122.8 mg), p-methoxyaniline (1.2 mmol, 148.7 mg), and tetrahydrothiopyran-4-one (2.5 mmol, 303.2 mg) were added into the solution. After 8 h the reaction was separated using preparative TLC. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5) hexane/2-propanol, 0.5 mL/min, 254 nm, dr: 4:1, ee: racemic.

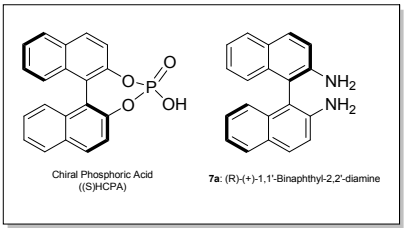


Processing Method: ADH-95Hexane5IPA-0.6-254
Column Type: AD-H Method Developer:
Method Description:

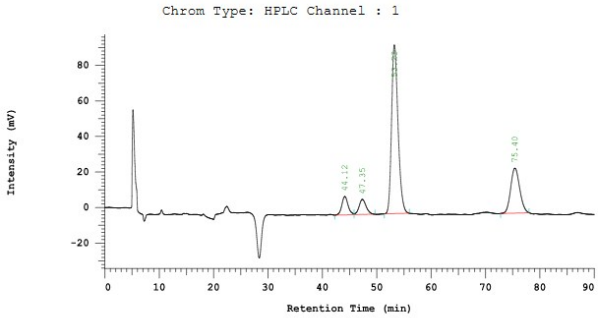
Chrom Type: HPLC Channel : 1
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %
1	43.08	6070733	9.474
2	45.71	5808772	9.066
3	49.16	14647	0.023
4	51.96	25999424	40.576
5	74.57	26181912	40.861





Chiral diamine, (R)-(+)-1,1’-Binaphthyl-2,2’-diamine, and (S)-HCPA (0.005 mmol, 1.8 mg) were dissolved in anhydrous methylene dichloride at room temperature and stirred for two hours. Next, 5-chlorosalicylaldehyde (0.1 mmol, 15.6 mg), p-methoxyaniline (0.1 mmol, 12.3 mg), and tetrahydrothiopyran-4-one (0.25 mmol, 29.0 mg) were mixed into the solution. After 24 h the product was separated using preparative TLC. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5) hexane/2-propanol, 0.5 mL/min, 254 nm, dr: 6:1, ee: 46%.



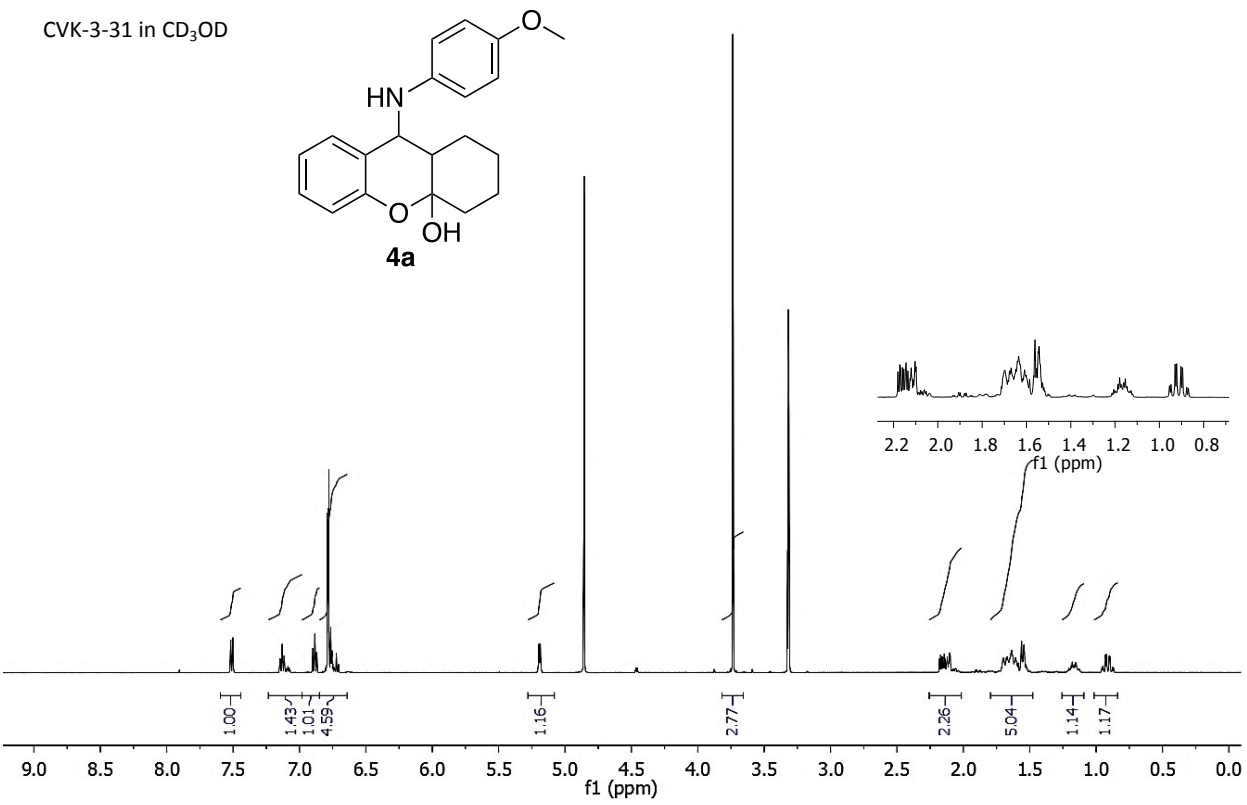
Processing Method: ADH-95Hexane5IPA-0.6-254
Column Type: AD-H Method Developer:
Method Description:

Chrom Type: HPLC Channel : 1
Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area	Area %
1	44.12	820826	6.728
2	47.35	764233	6.264
3	53.23	7736601	63.415
4	75.40	2878350	23.593
		12200010	100.000

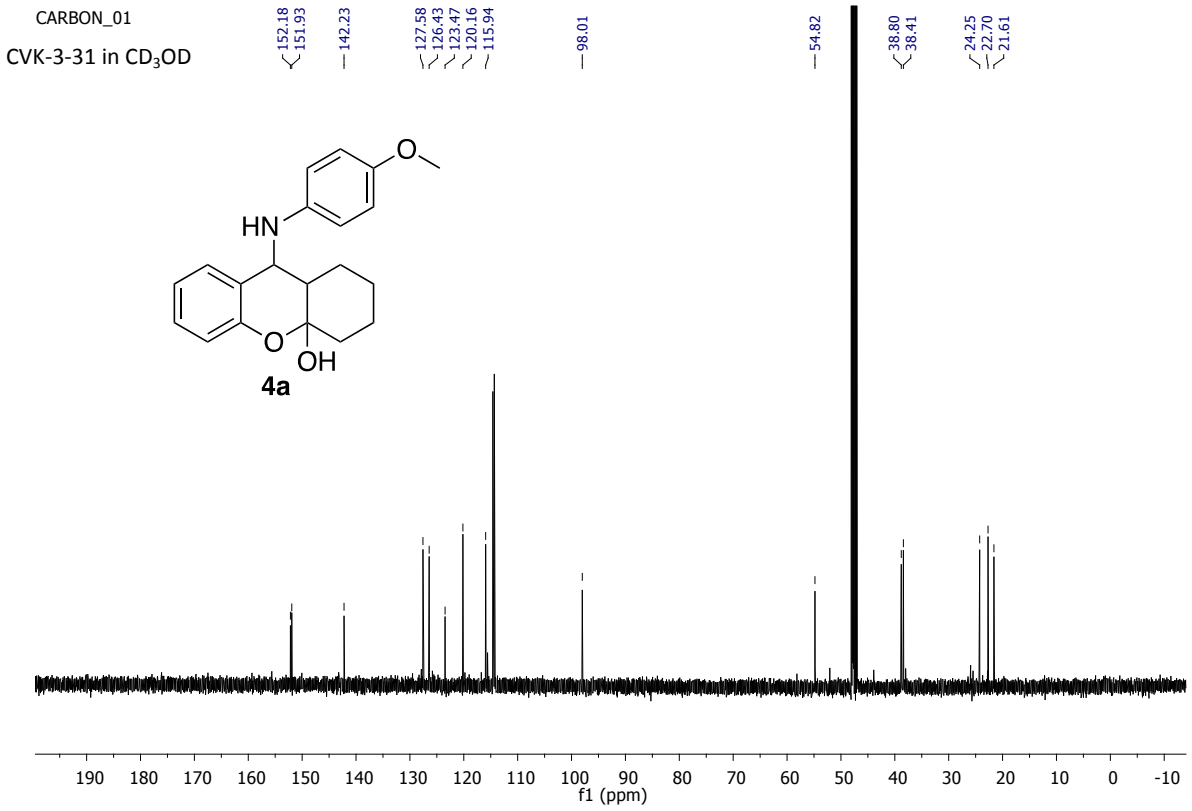
VII. ^{1}H and ^{13}C NMR Spectra

CVK-3-31 in CD_3OD

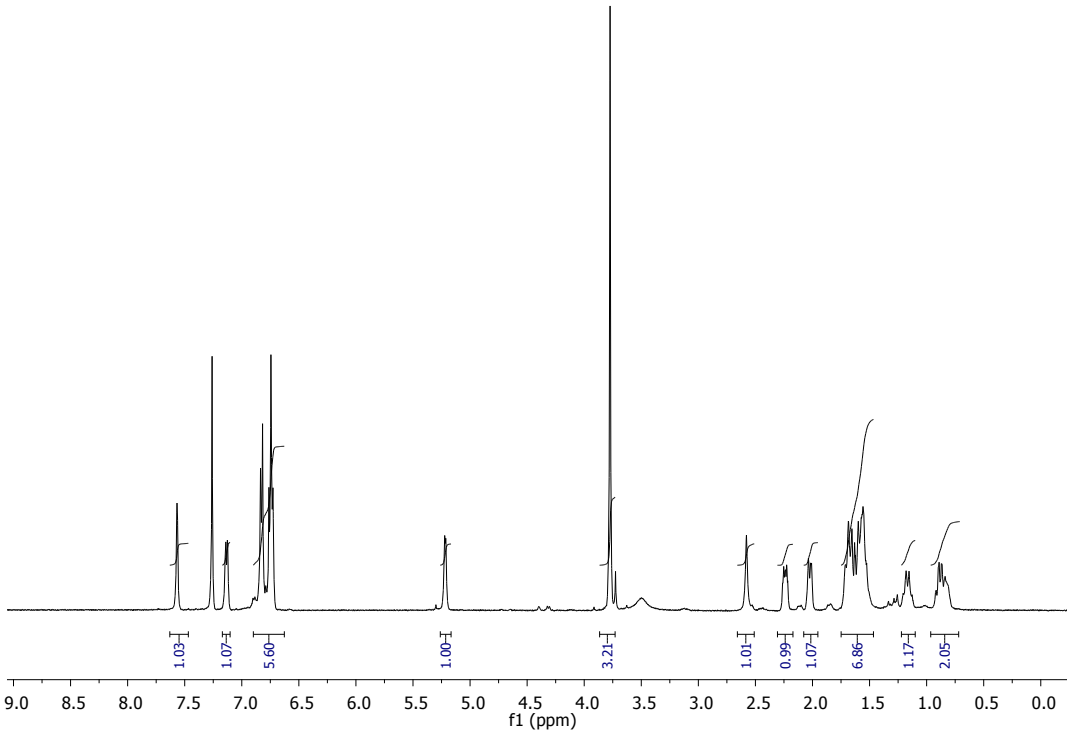


CARBON_01

CVK-3-31 in CD_3OD

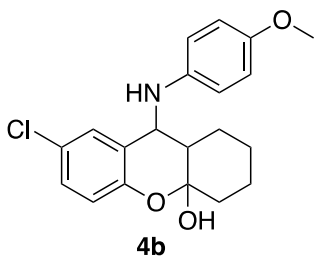


RS-1-185
RS-1-185 H



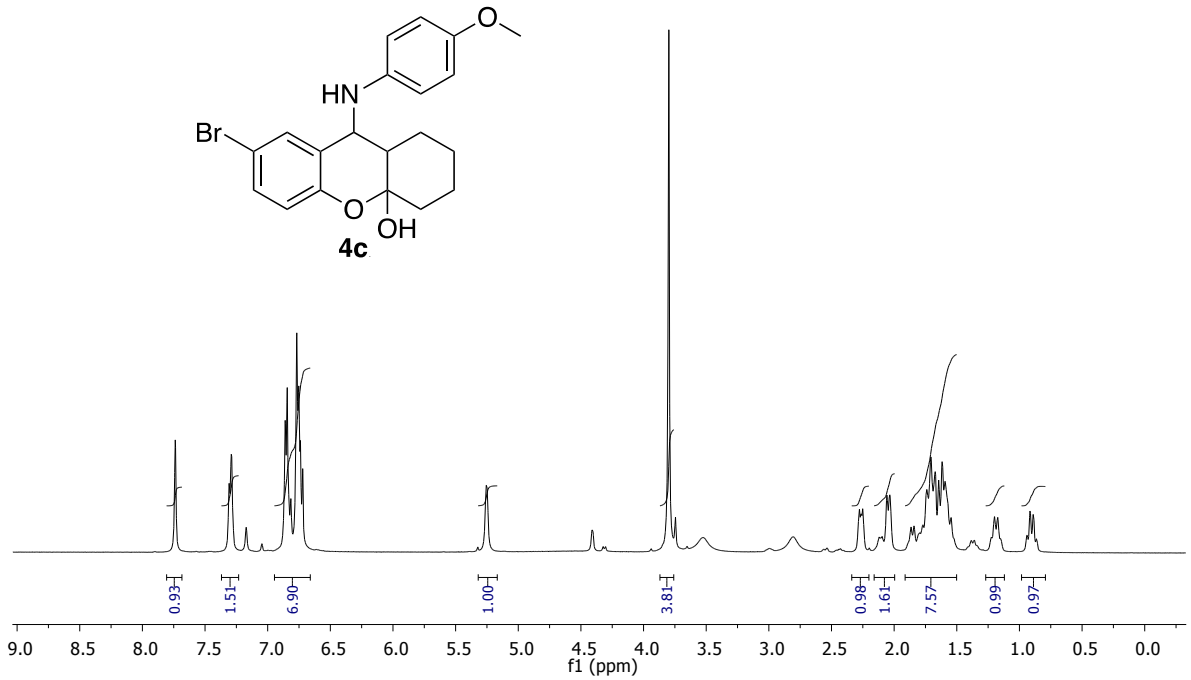
RGS-1-1984bJAR
RGS-1-1984bJAR More concentrated

RS-1-85 in $CDCl_3$

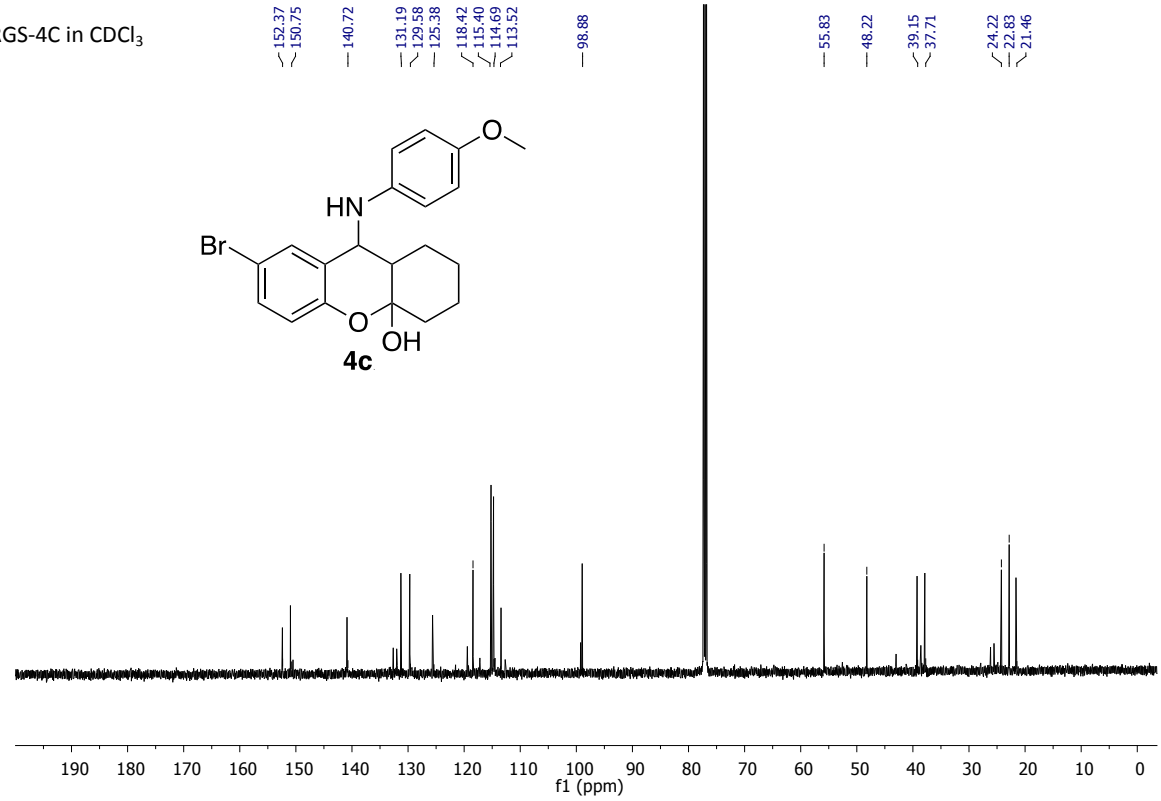


4b

RGS-4C in $CDCl_3$

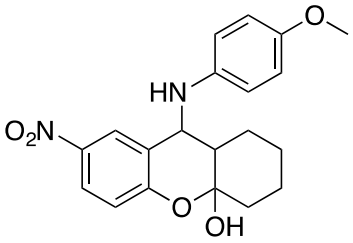


RGS-4C in $CDCl_3$



PROTON_01

CVK-3-133 in DMSO

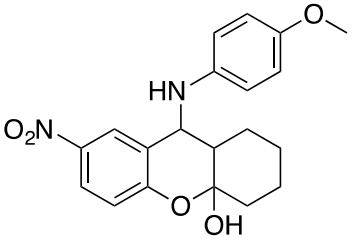


4d

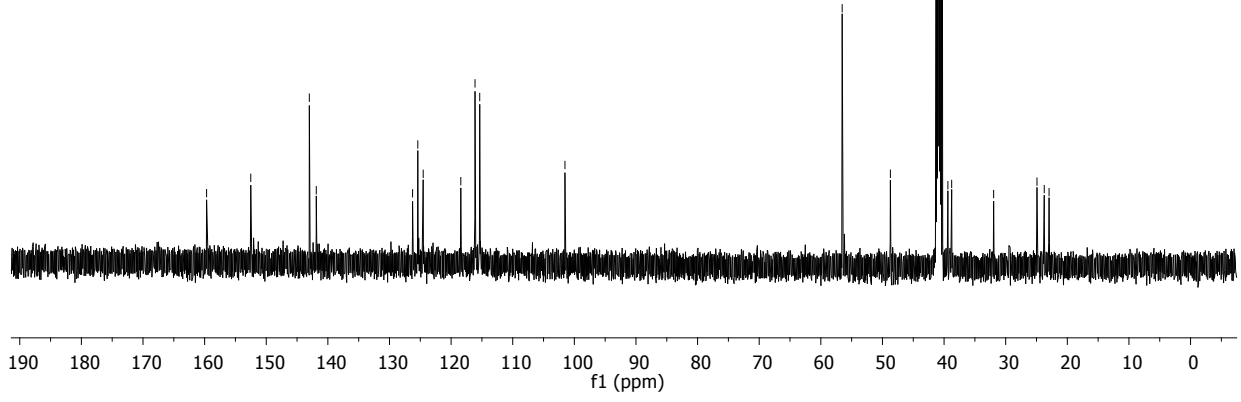
CARBON_01

CVK-3-133 in DMSO

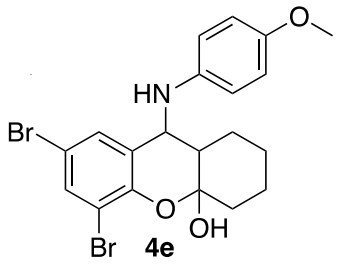
159.68 152.51 143.01 141.88 126.25 125.40 124.53 118.43 116.12 115.36 101.52 56.54 48.71 39.50 38.77 31.96 24.92 23.74 22.96



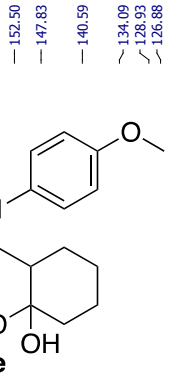
4d



RS-1-193 in $CDCl_3$

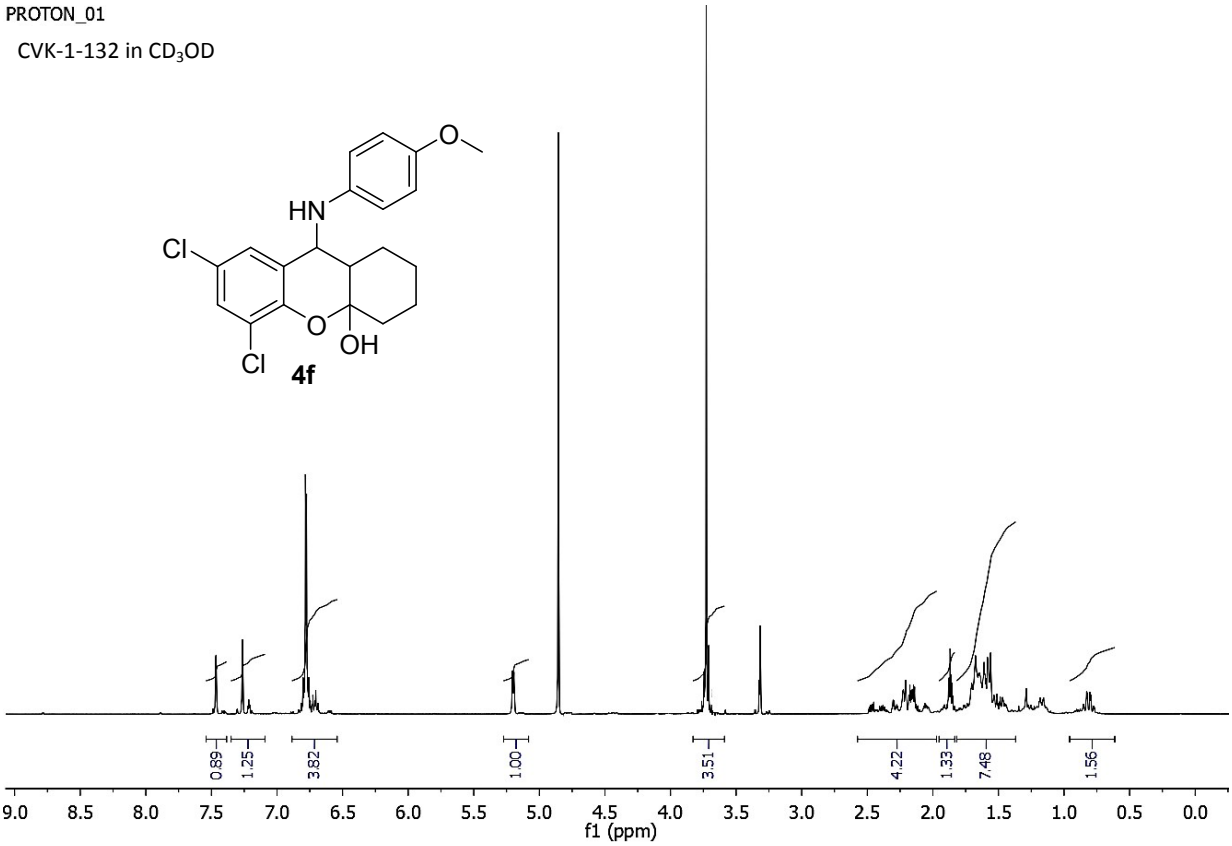


RS-1-193 in $CDCl_3$



PROTON_01

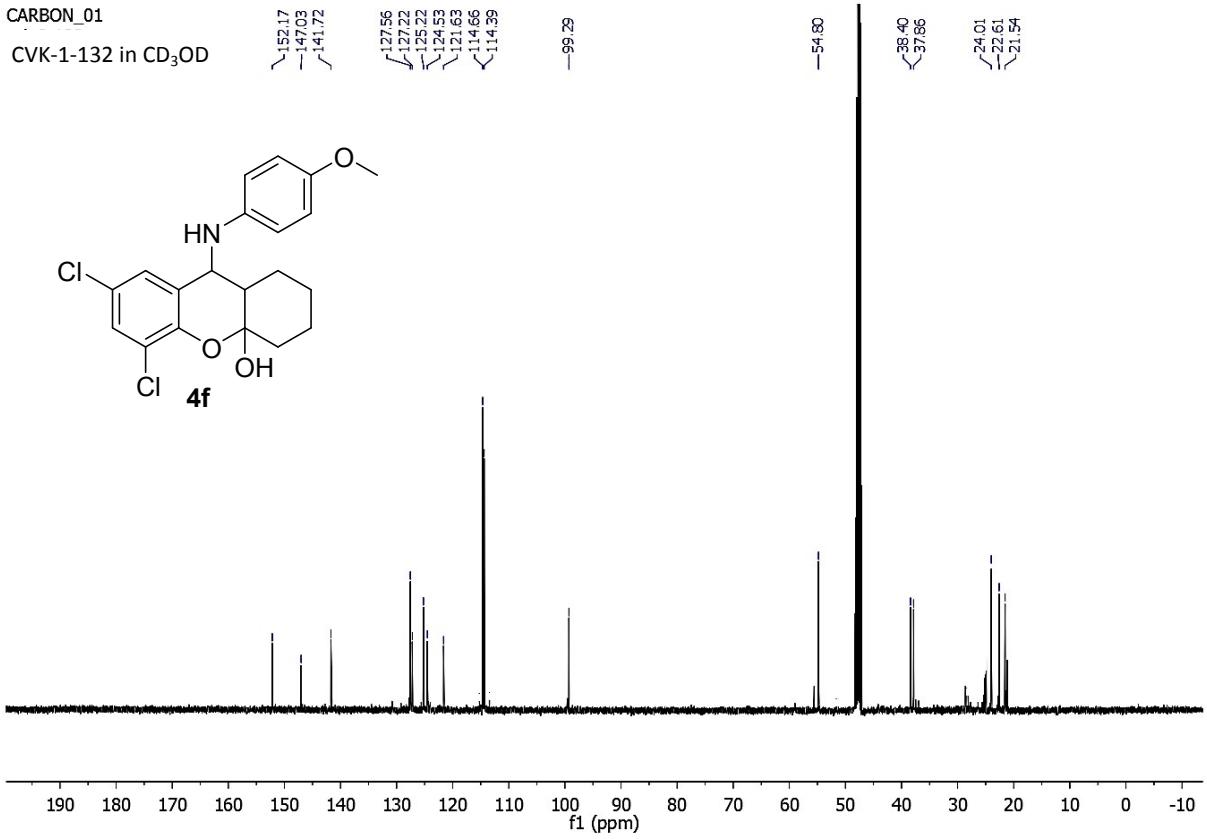
CVK-1-132 in CD_3OD



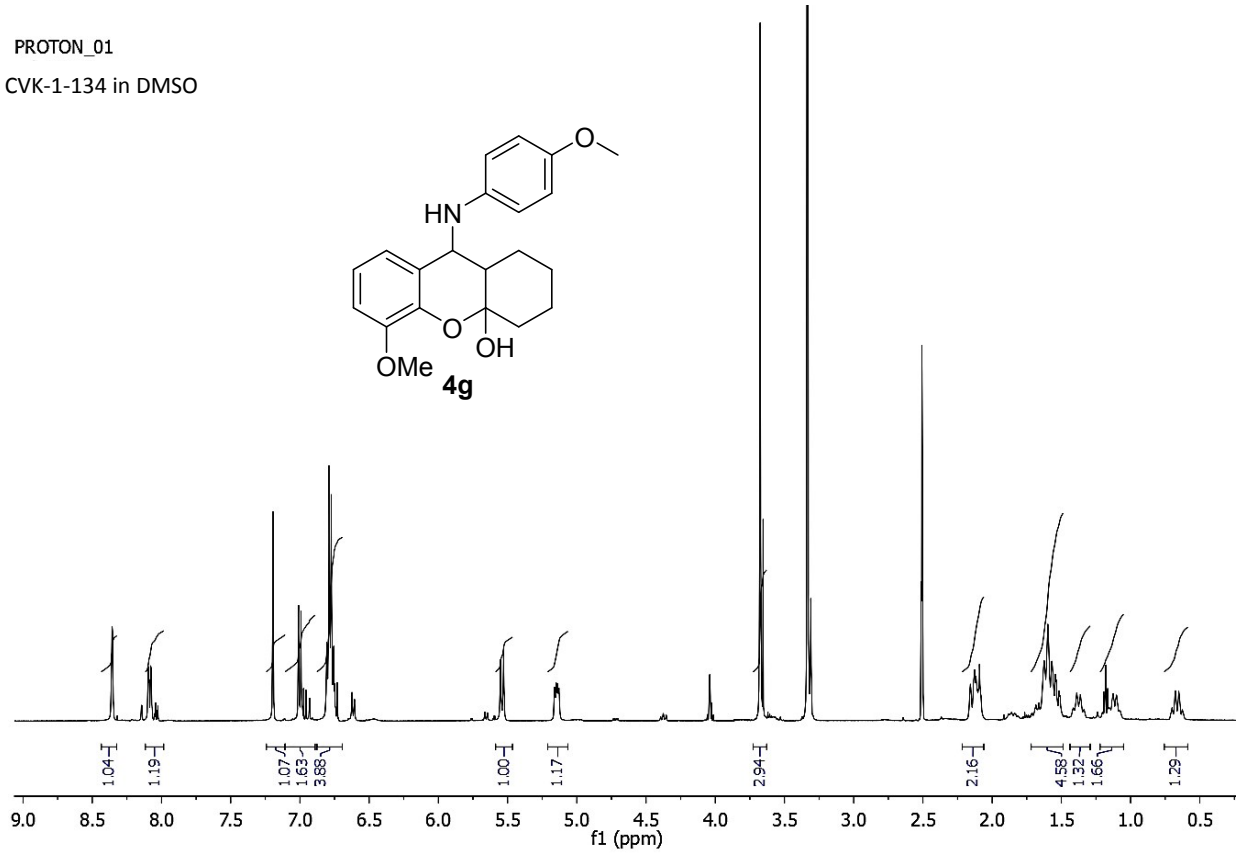
4f

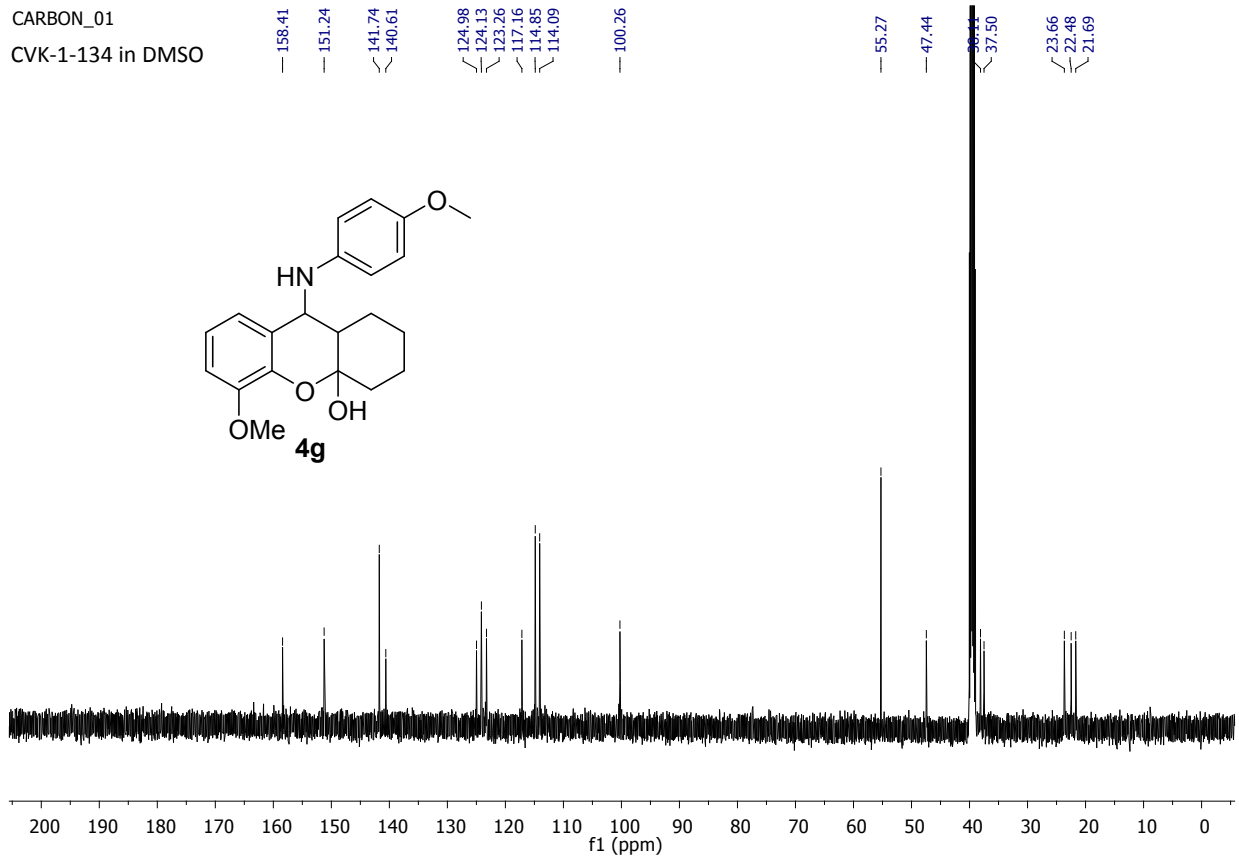
CARBON_01

CVK-1-132 in CD_3OD



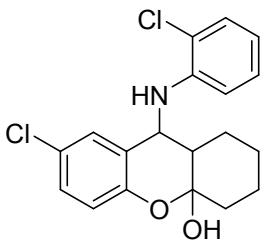
4f


PROTON_01
CVK-1-134 in DMSO
HN
O
O
OH
OMe
4g
1.04
1.19
1.07
1.63
3.88
1.00
1.17
2.94
2.16
4.58
1.32
1.66
1.29
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


CARBON_01
CVK-1-134 in DMSO
158.41
151.24
141.74
140.61
124.98
124.13
123.26
117.16
114.85
114.09
100.26
55.27
47.44
38.11
37.50
23.66
22.48
21.69
HN
O
O
OH
OMe
4g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

PROTON_01

CVK-4H in CD_3OD

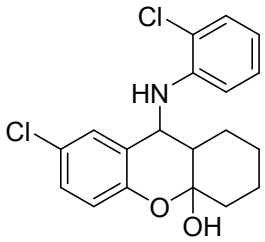


4h

CARBON_01

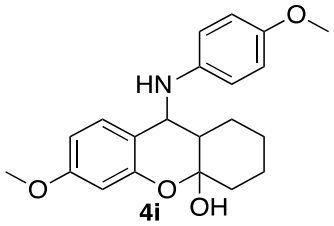
CVK-4H in CD_3OD

151.03
146.85
128.64
127.62
126.29
125.05
124.93
120.96
117.65
113.90
107.62
98.34
41.24
38.48
38.13
26.80
24.14
22.60
21.72



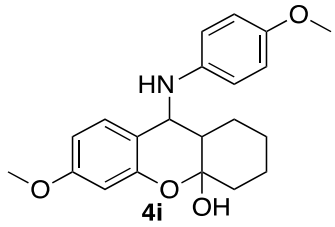
4h

PROTON_01
cvk-3-136(4i) in CDCl3

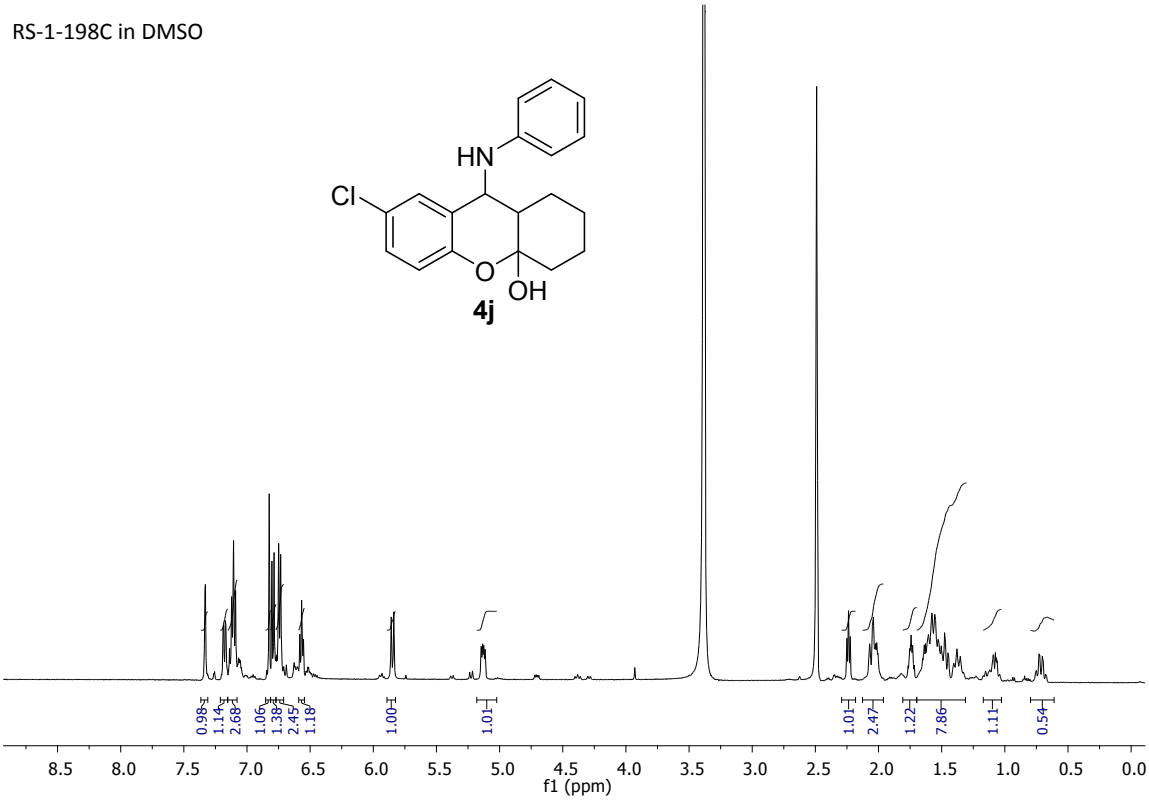


CARBON_01
cvk-3-136(4i) in CDCl3

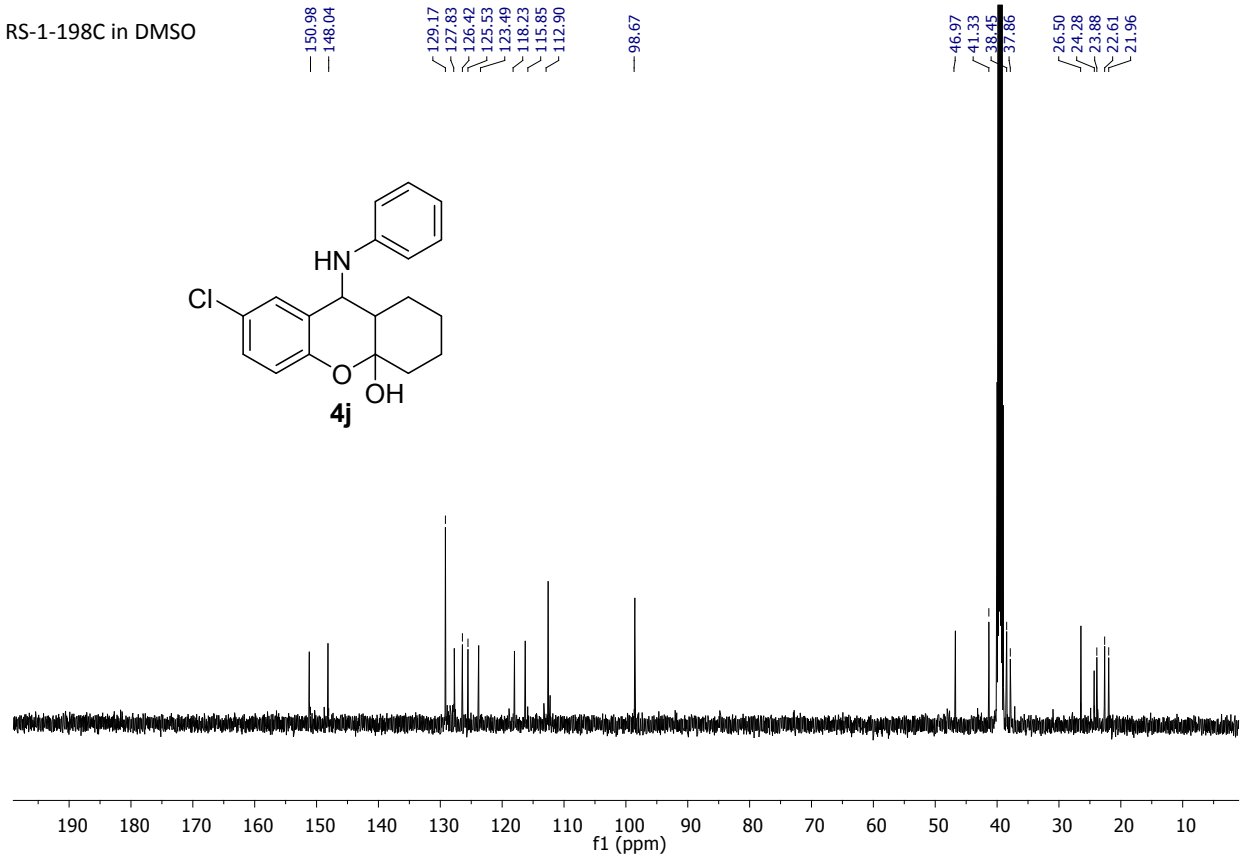
159.96
152.57
152.08
141.39
127.60
115.13
114.56
114.53
107.63
101.56
98.97
67.43
55.82
55.32
47.78
39.42
38.38
29.50
24.31
23.84
22.92
21.68

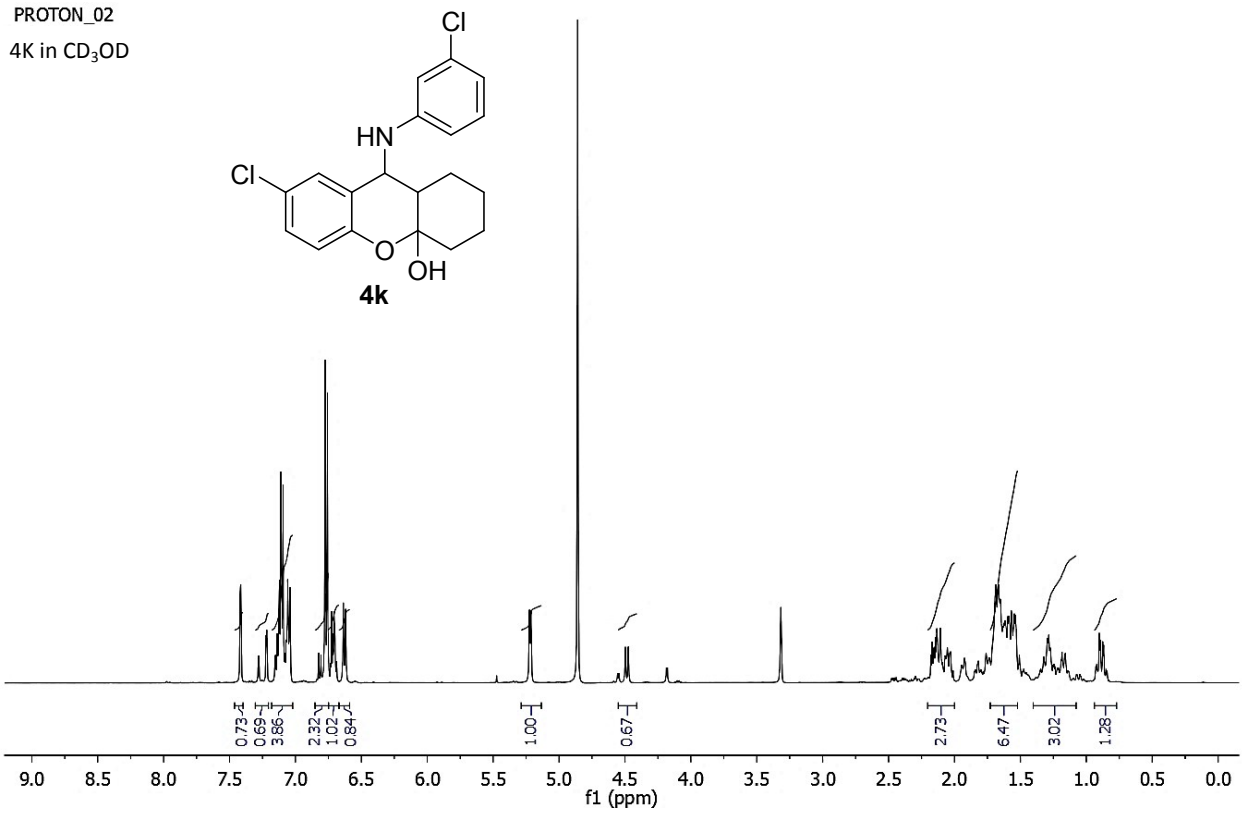


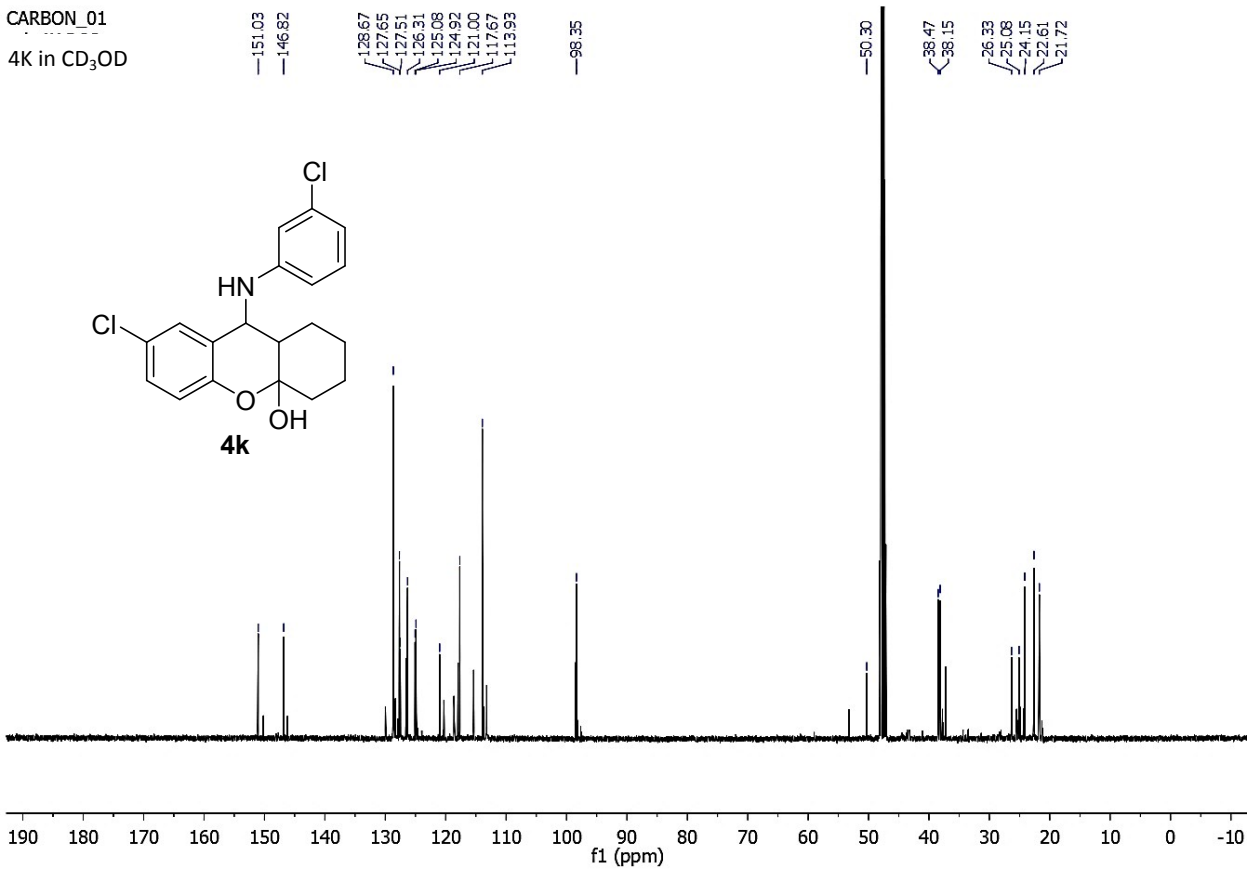
RS-1-198C in DMSO



RS-1-198C in DMSO

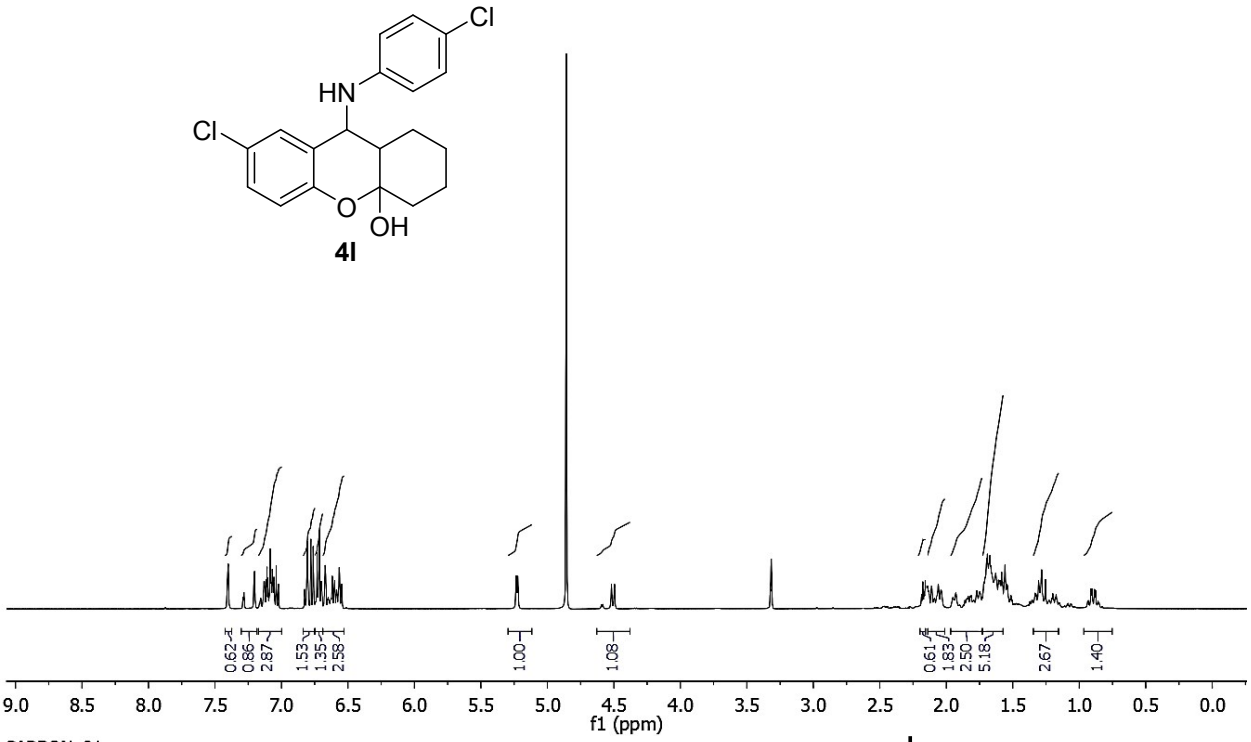



PROTON_02
4K in CD3OD
Cl
HN
Cl
O
OH
4k
0.73
0.69
3.86
2.32
1.02
0.84
1.00
0.67
2.73
6.47
3.02
1.28
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CARBON_01
4K in CD3OD
151.03
146.82
128.67
127.65
127.51
126.31
125.08
124.92
121.00
117.67
113.93
98.35
50.30
38.47
38.15
26.33
25.08
24.15
22.61
21.72
Cl
HN
Cl
O
OH
4k
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

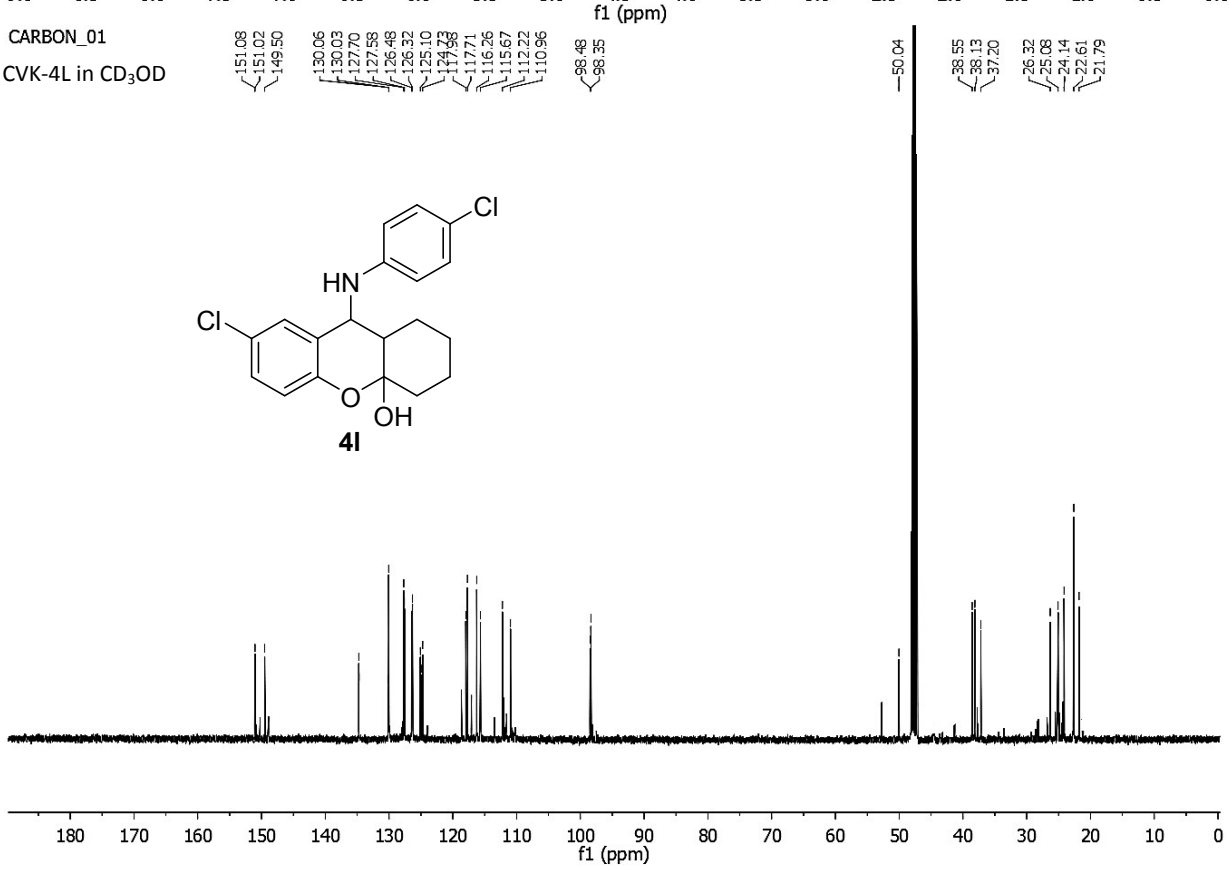
PROTON_02

CVK-4L in CD_3OD



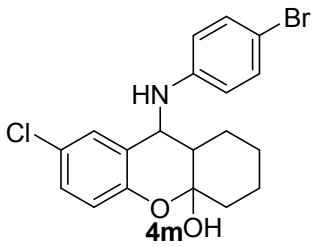
CARBON_01

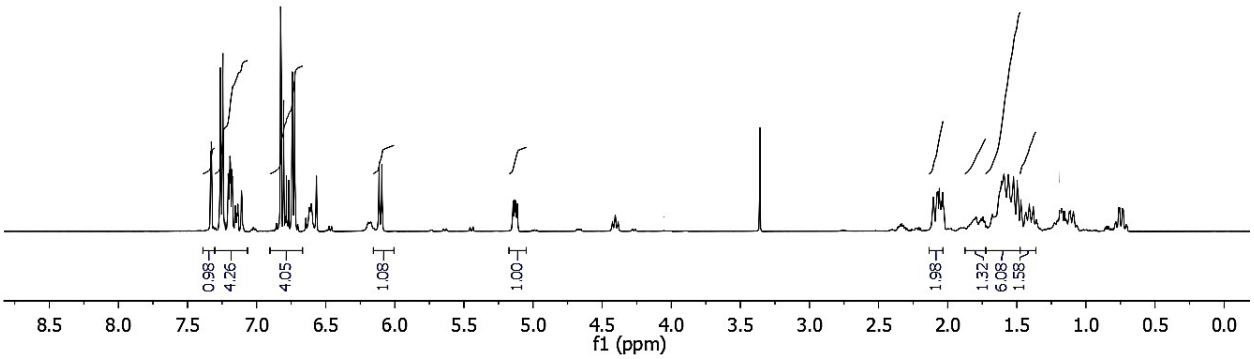
CVK-4L in CD_3OD



PROTON_01

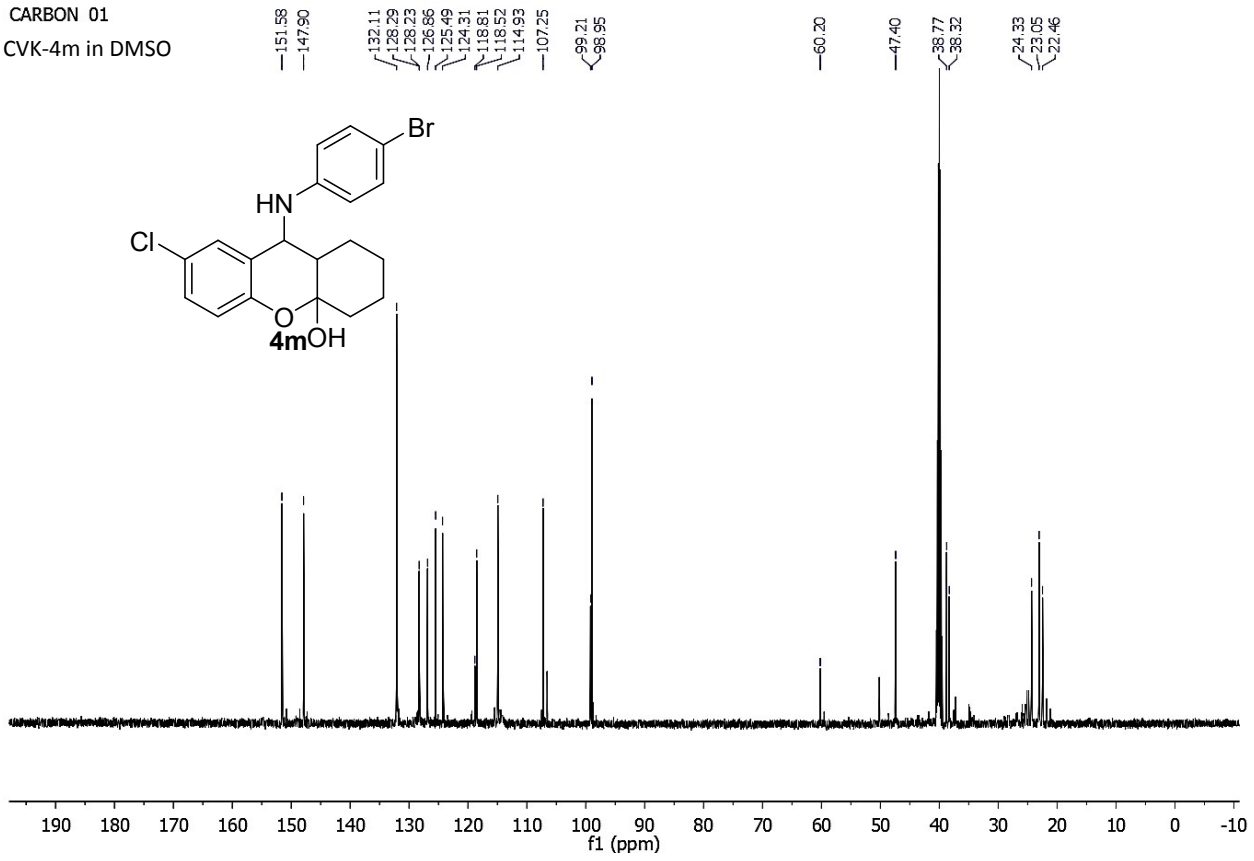
CVK-4m in DMSO



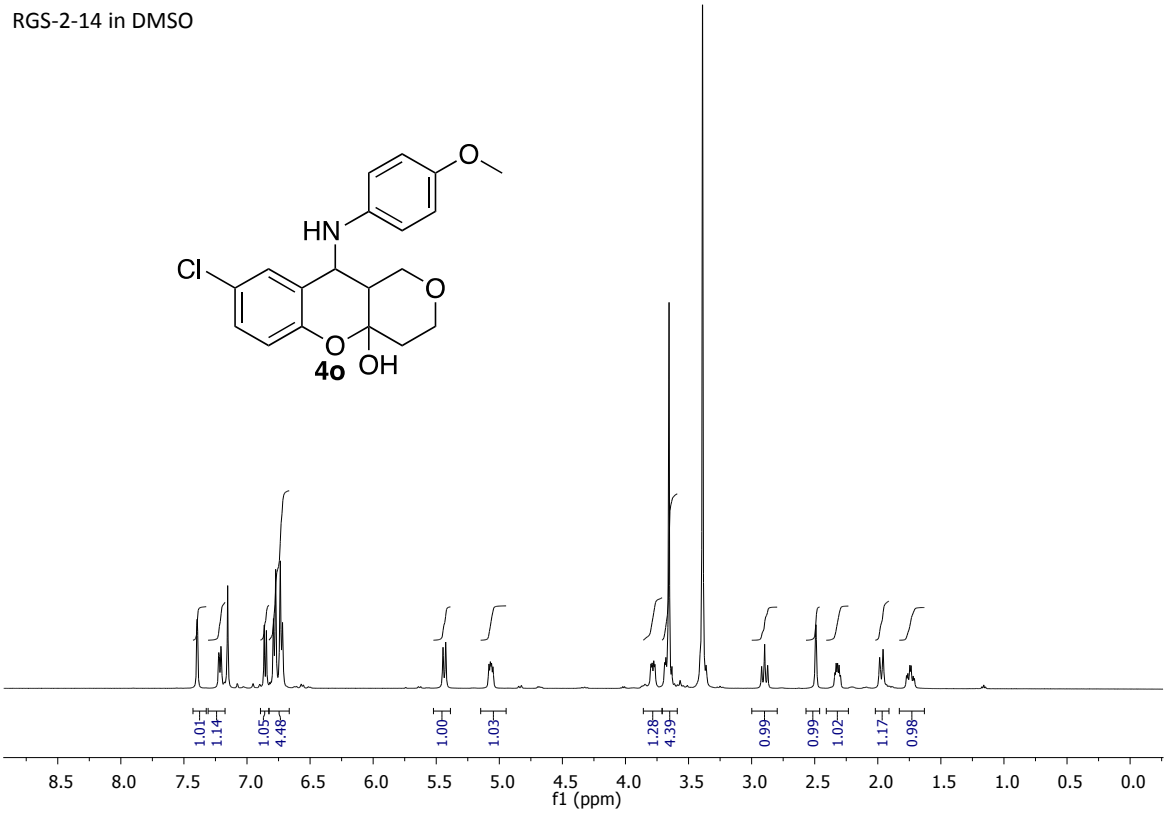


CARBON 01

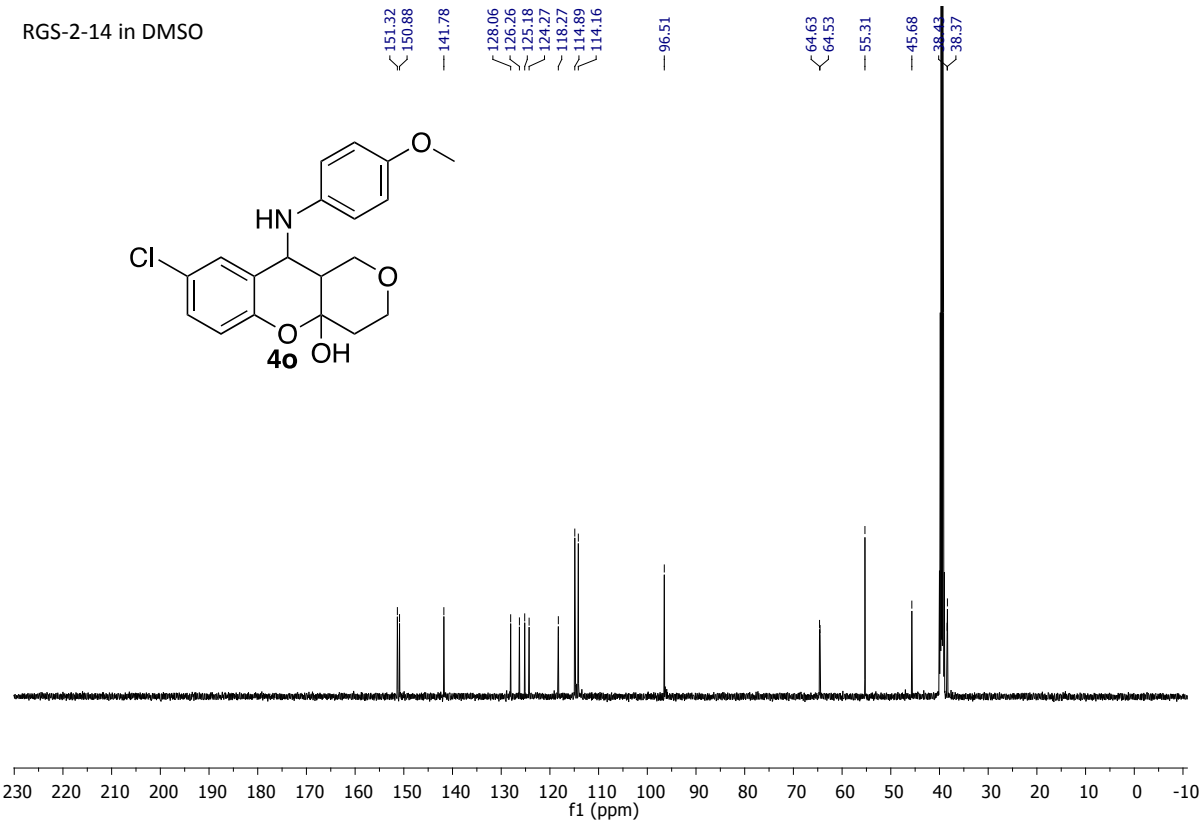
CVK-4m in DMSO



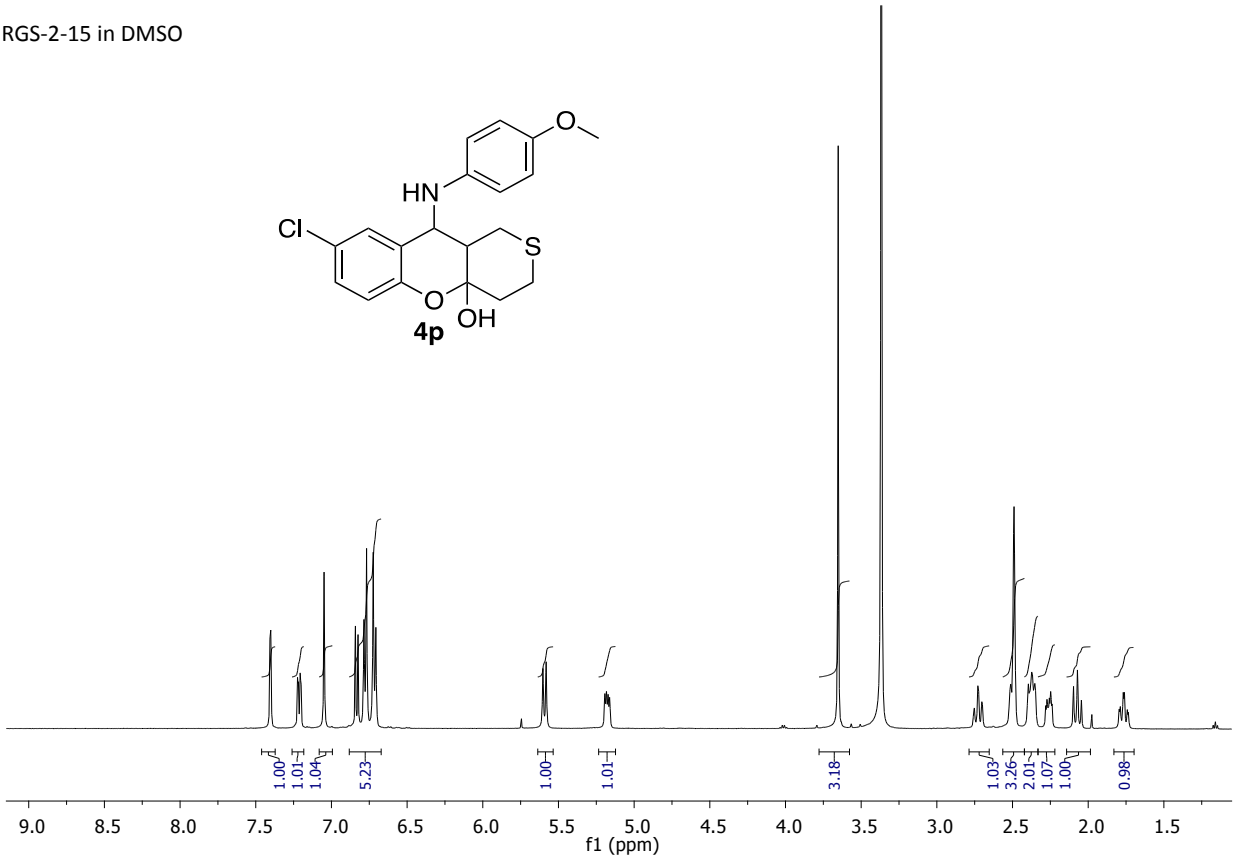
RGS-2-14 in DMSO



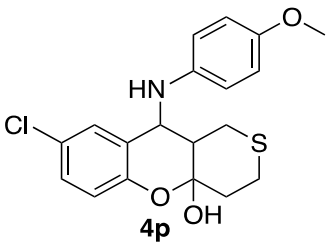
RGS-2-14 in DMSO

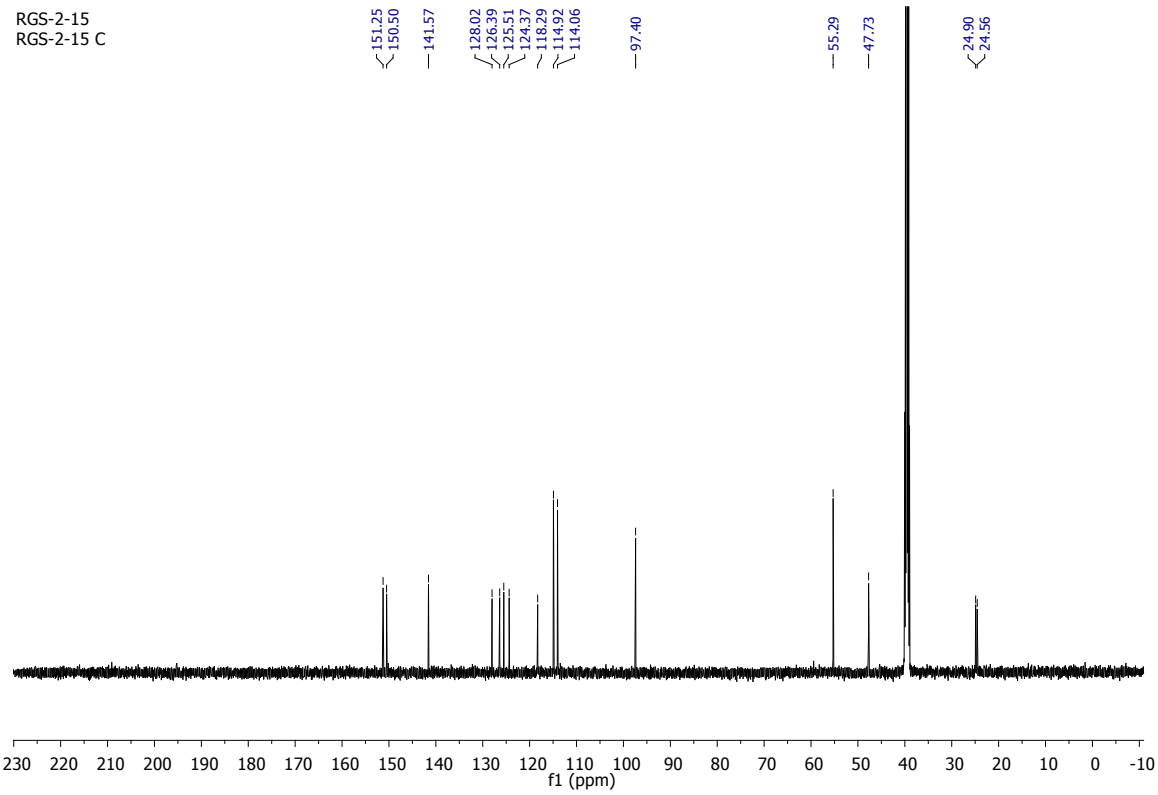


RGS-2-15 in DMSO



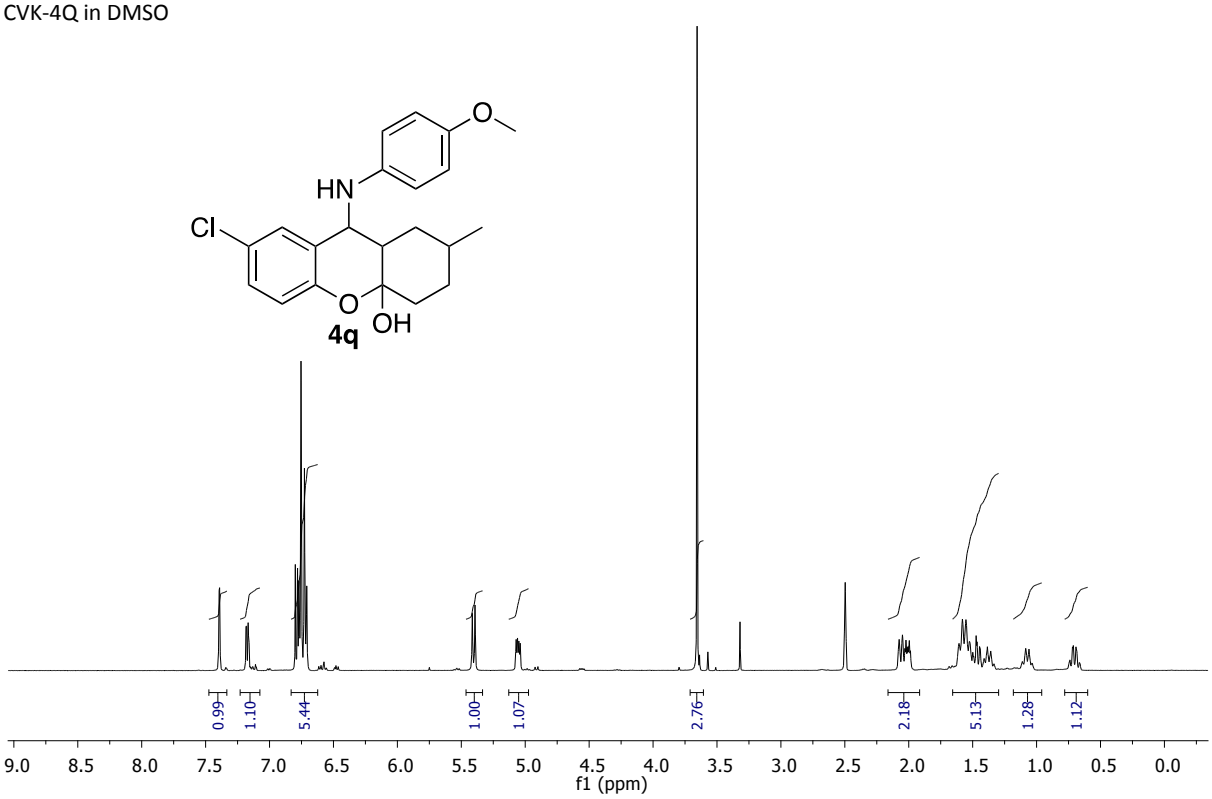
RGS-2-15 in DMSO




RGS-2-15
RGS-2-15 C
151.25
150.50
141.57
128.02
126.39
125.51
124.37
118.29
114.92
114.06
97.40
55.29
47.73
24.90
24.56
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

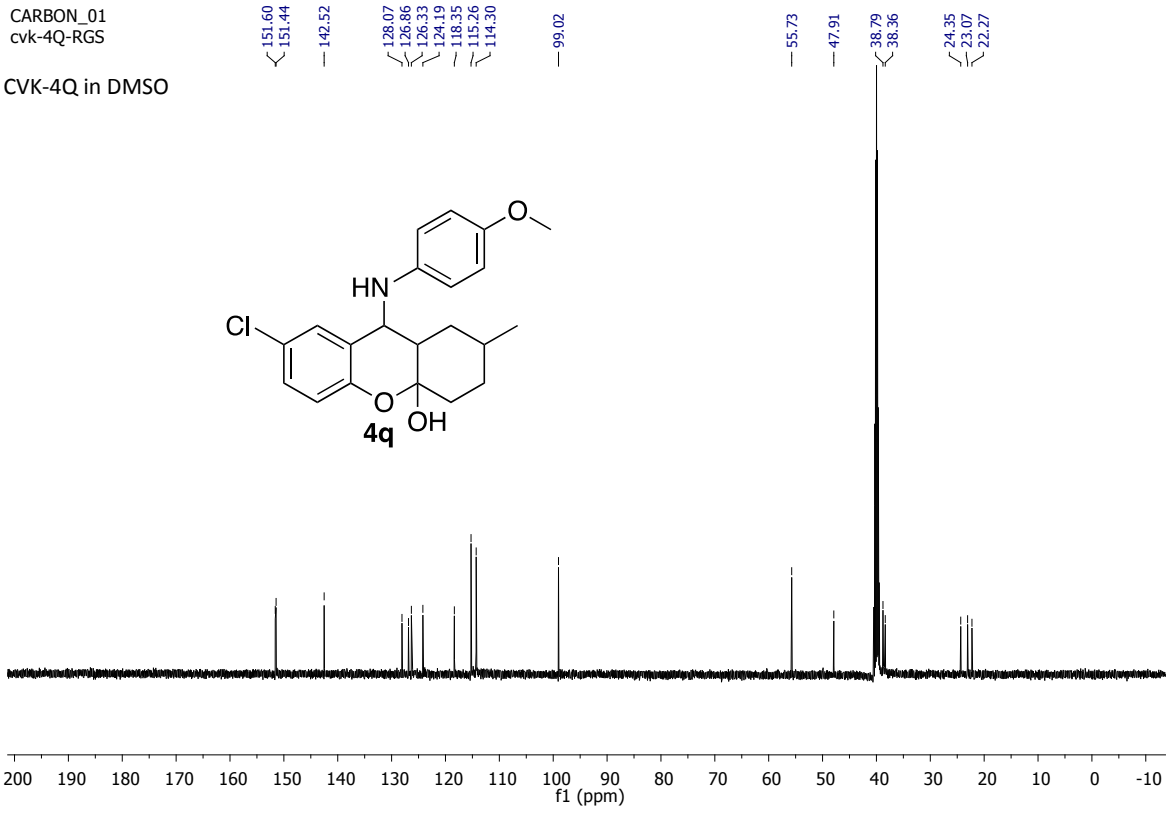
PROTON_01

CVK-4Q in DMSO

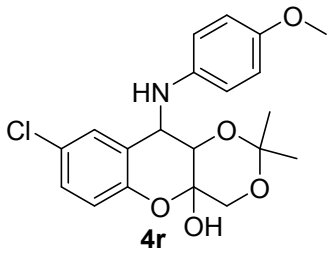


CARBON_01
cvk-4Q-RGS

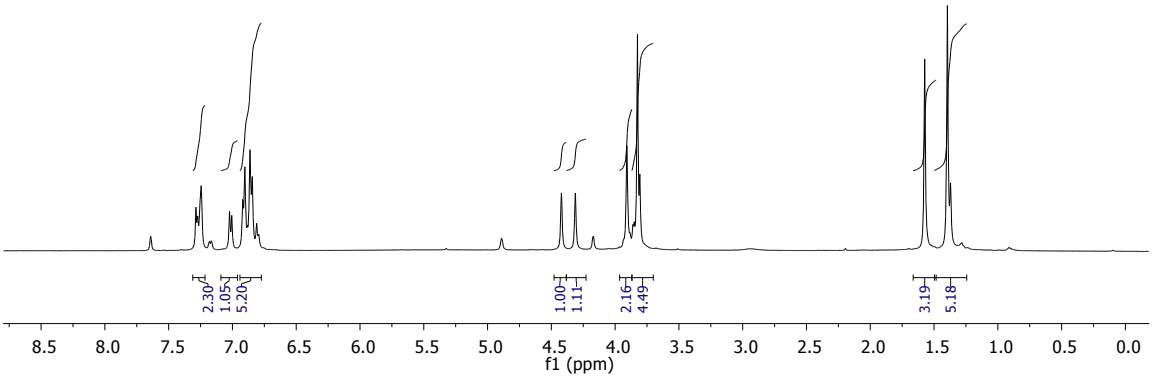
CVK-4Q in DMSO



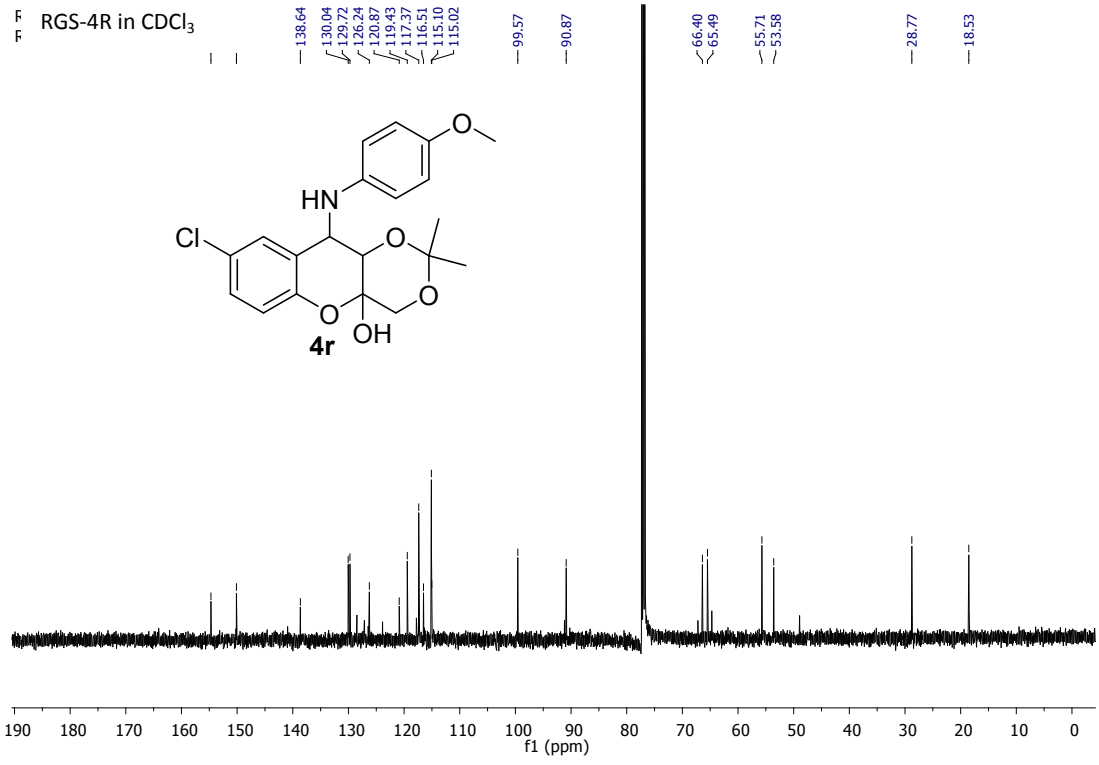
RGS-4R in $CDCl_3$



4r



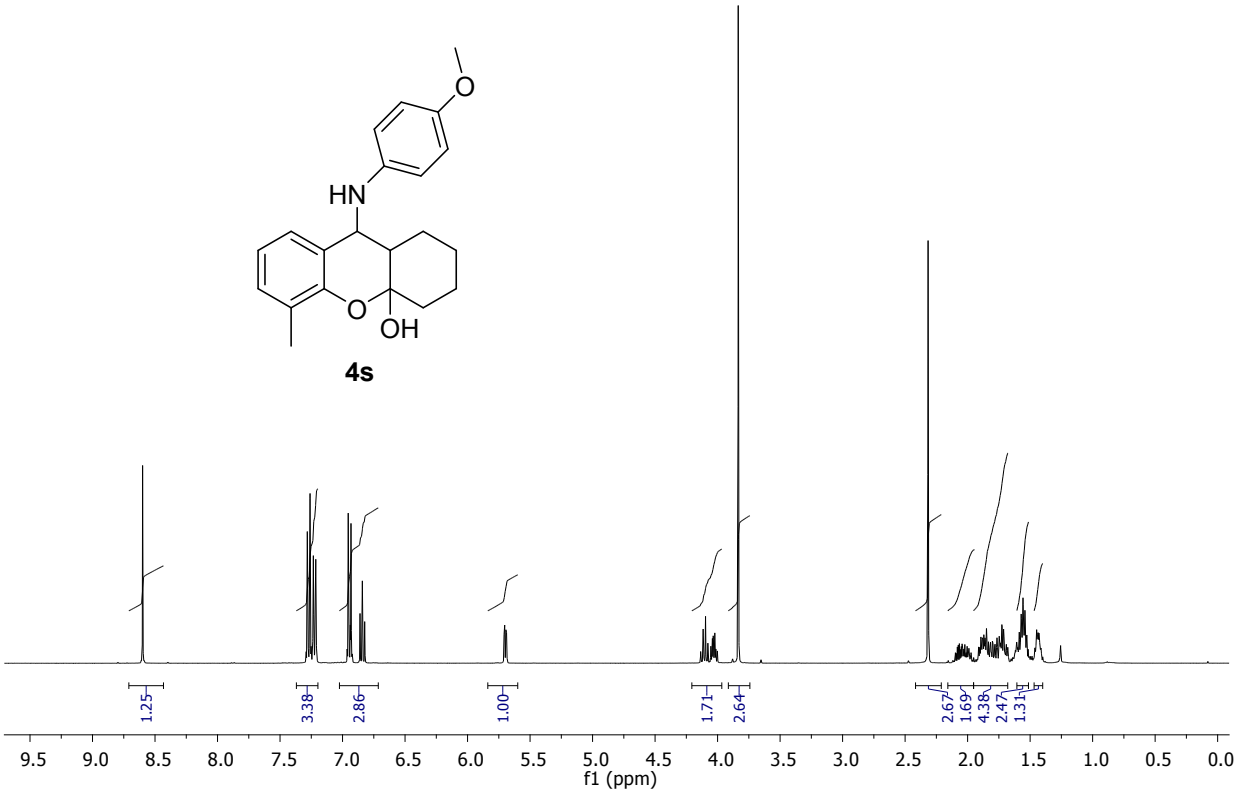
RGS-4R in $CDCl_3$



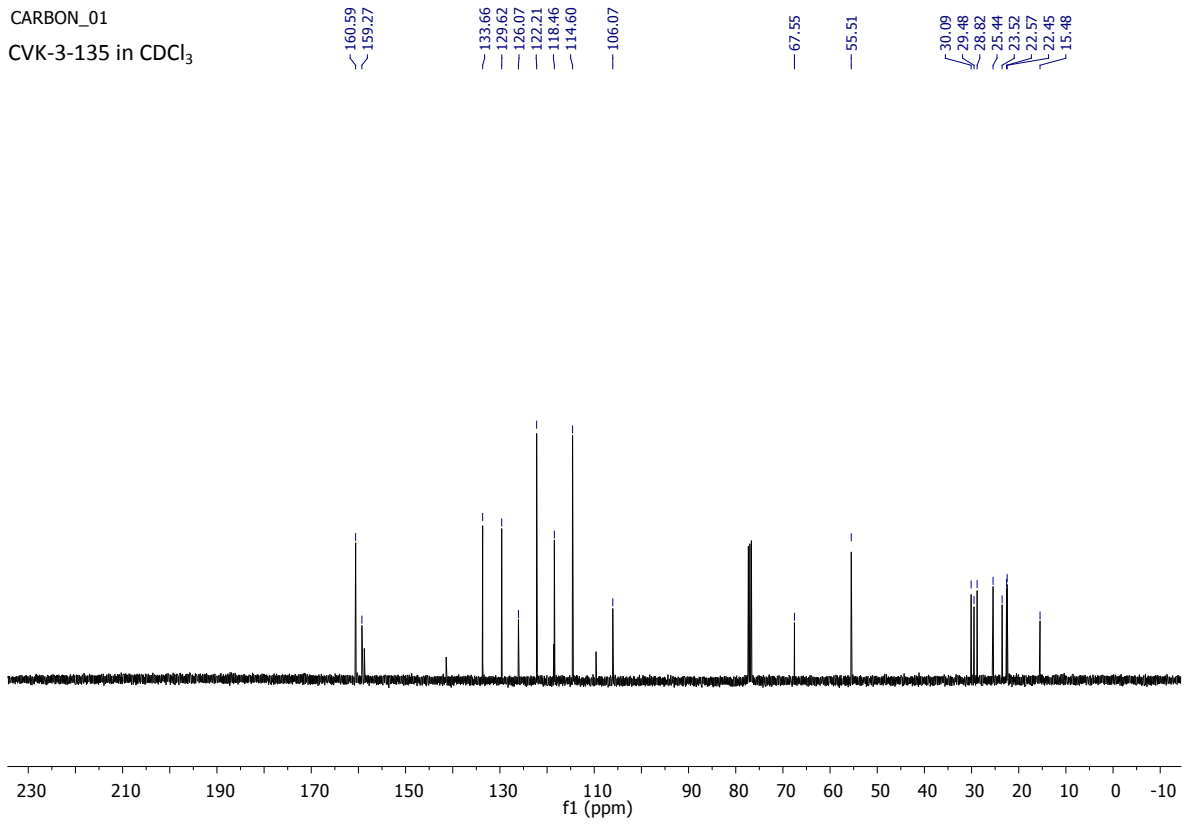
4r

PROTON_02

CVK-3-135 in $CDCl_3$



4s



VIII. X-Ray crystal Structure of 4a

X-ray crystallographic data of **4a** complex (CCDC,1518410): crystals were grown through slow vapor diffusion of cyclohexane into the chloroform solution of the **4a**; color of the crystal: colorless plates; T: 173 K; molecular formula: C20H23NO3; space group: P21/n; unit cell parameters: a = 11.6820 (6), b = 7.2674 (4), c = 20.0741 (10); alpha = 90, beta = 103.443 (4), gamma = 90; R = 0.0634 (2206), wR2 = 0.1652 (2980).

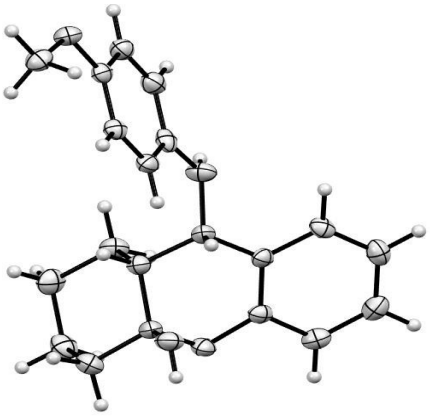
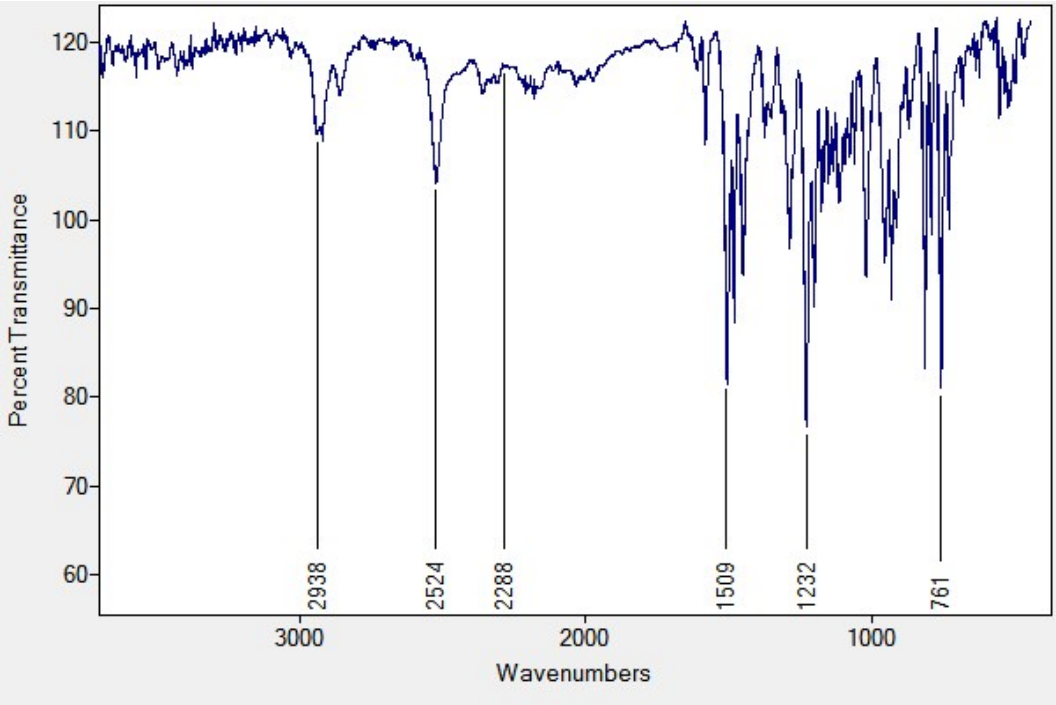


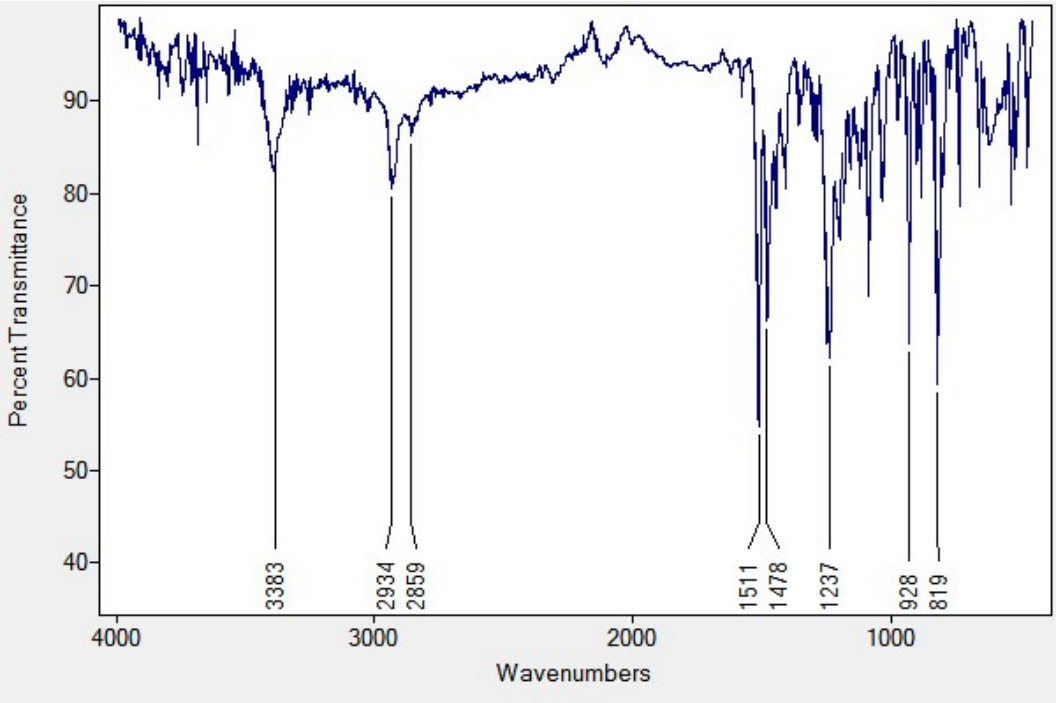
Figure 2: X-ray crystal structure of **4a**

IX. IR Spectroscopy Data

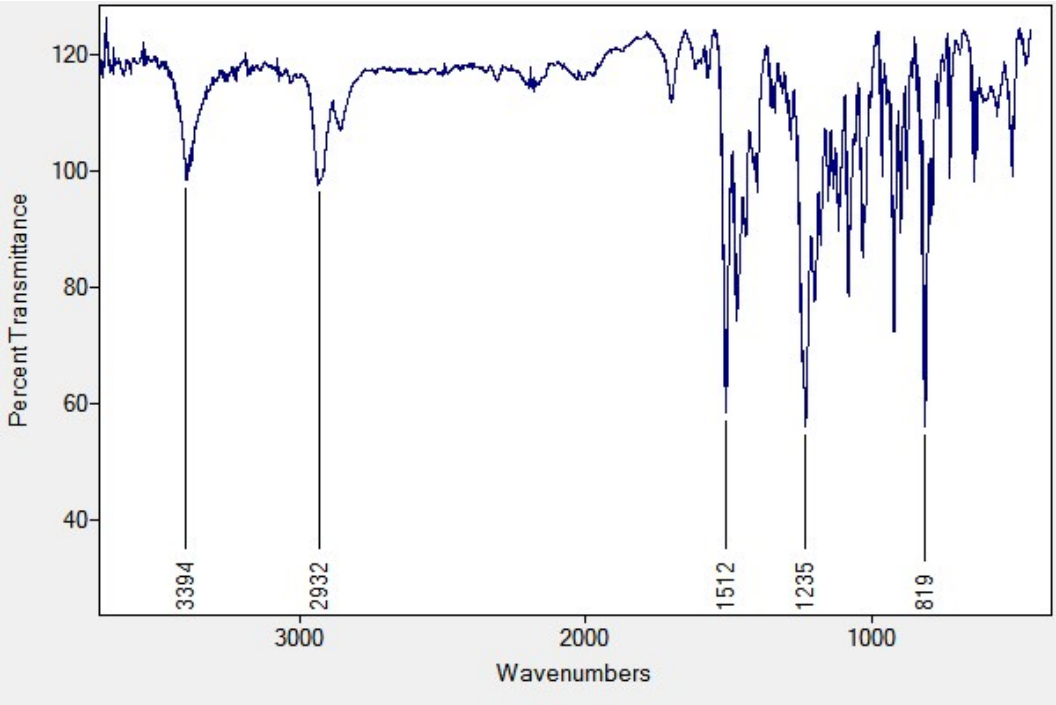
Compound 4a



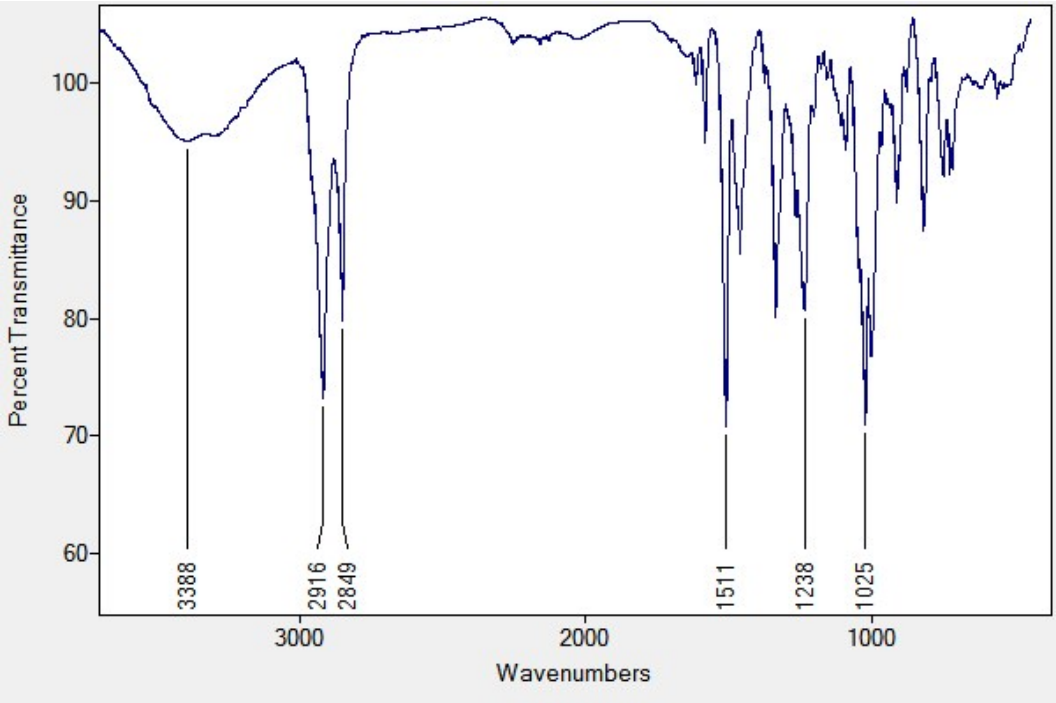
Compound 4b



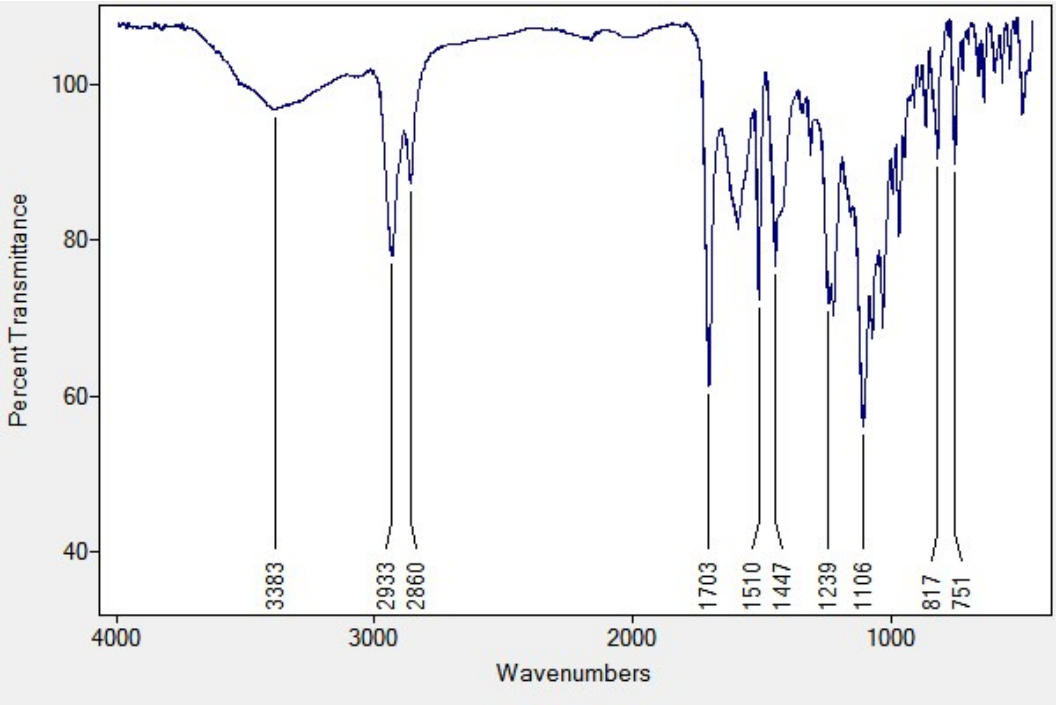
Compound 4c



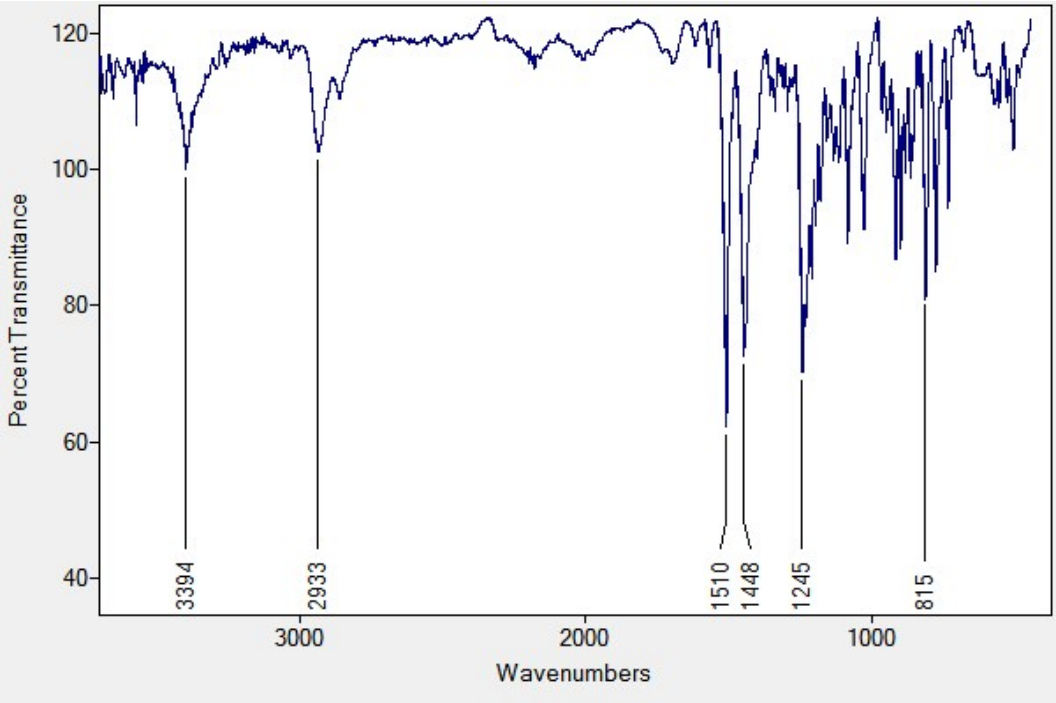
Compound 4d



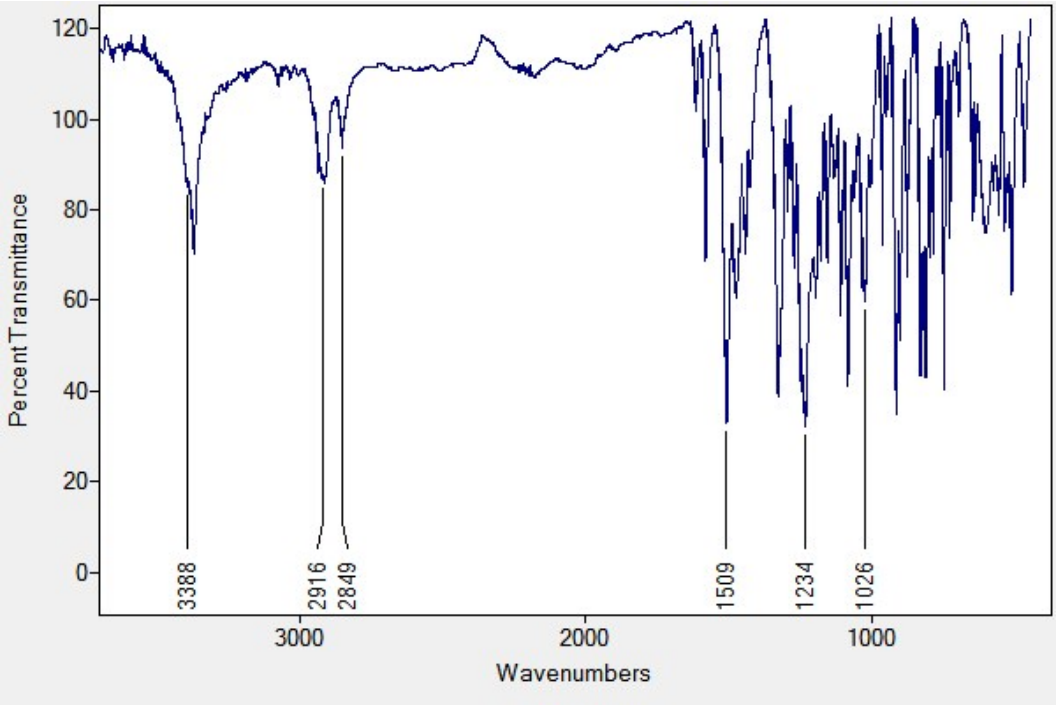
Compound 4e



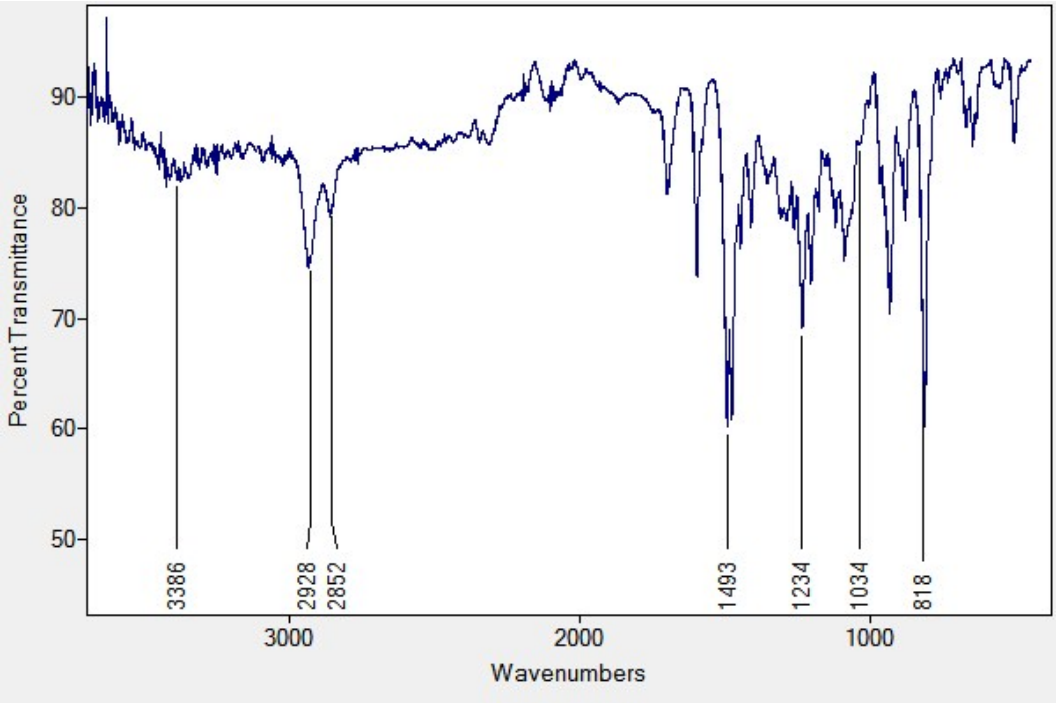
Compound 4f



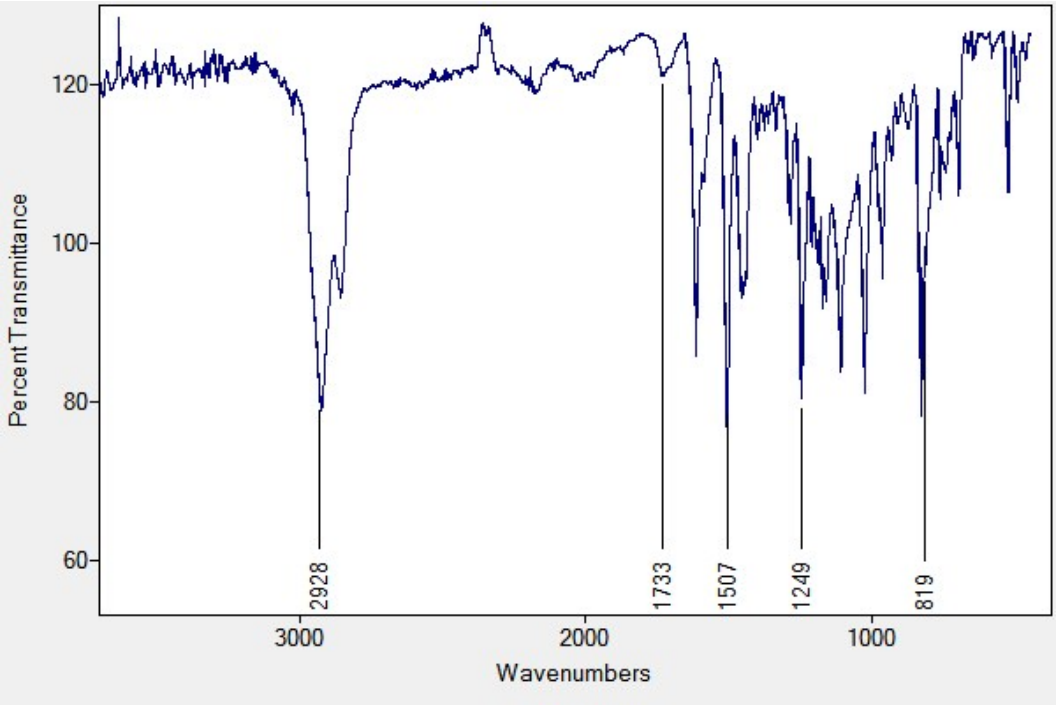
Compound 4g



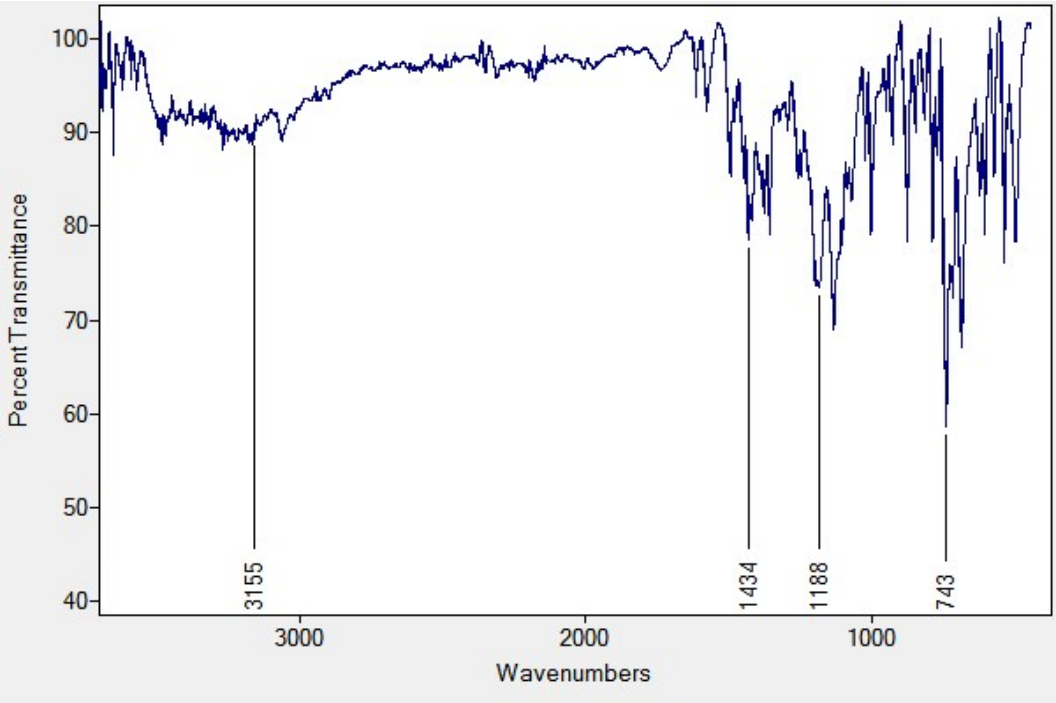
Compound 4h



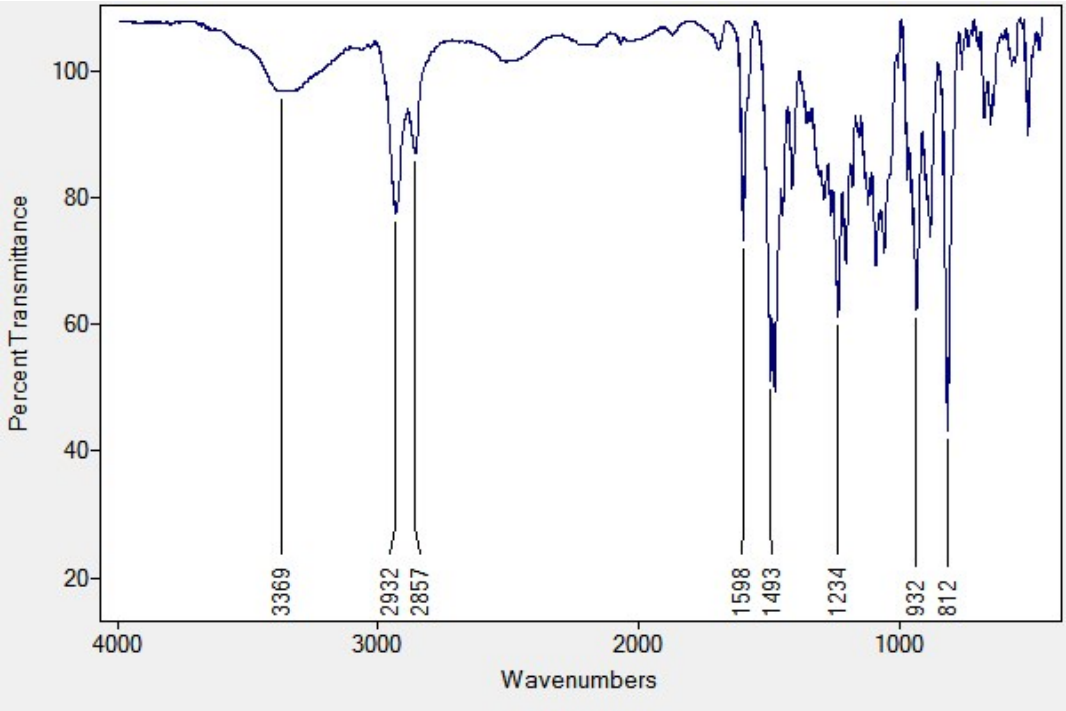
Compound 4i



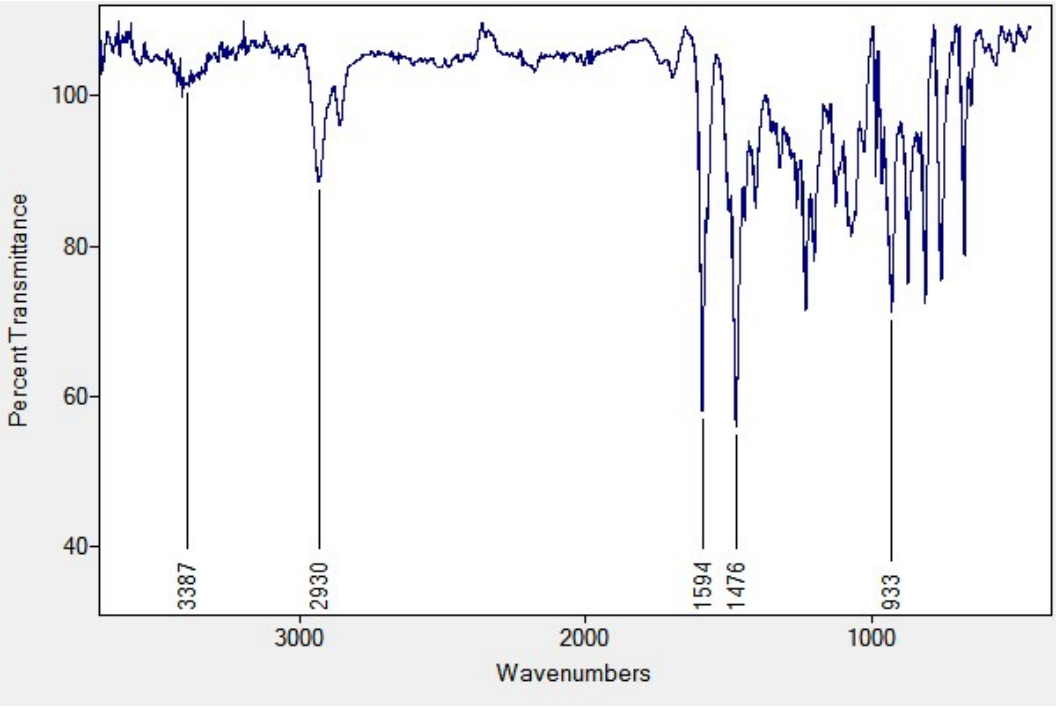
Compound 4j



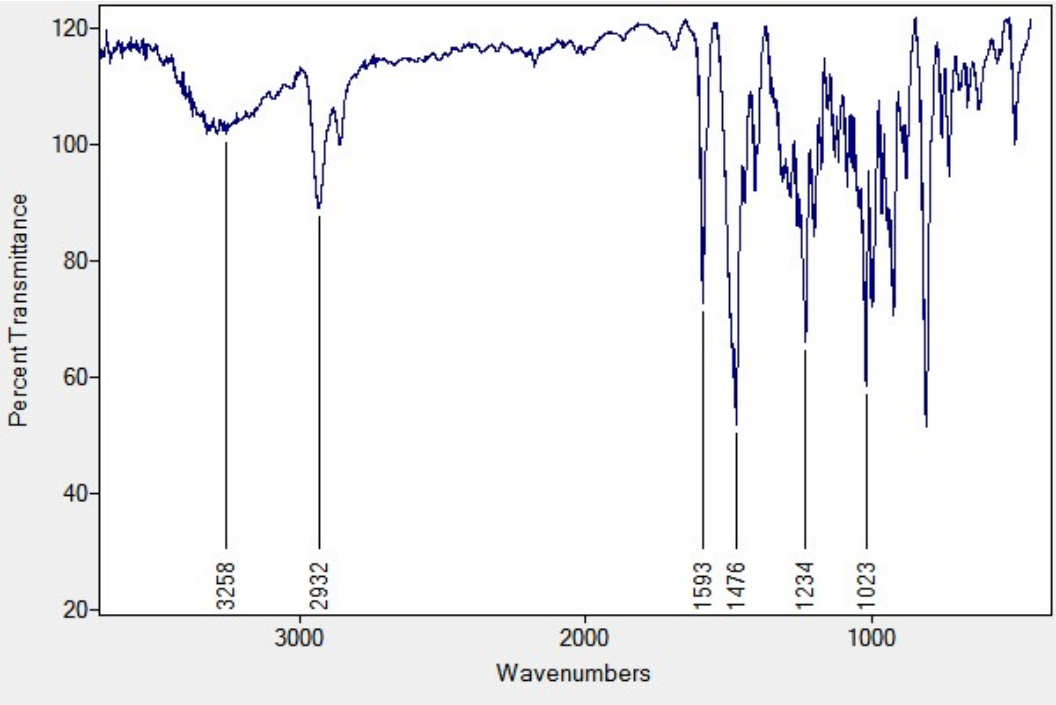
Compound 4k



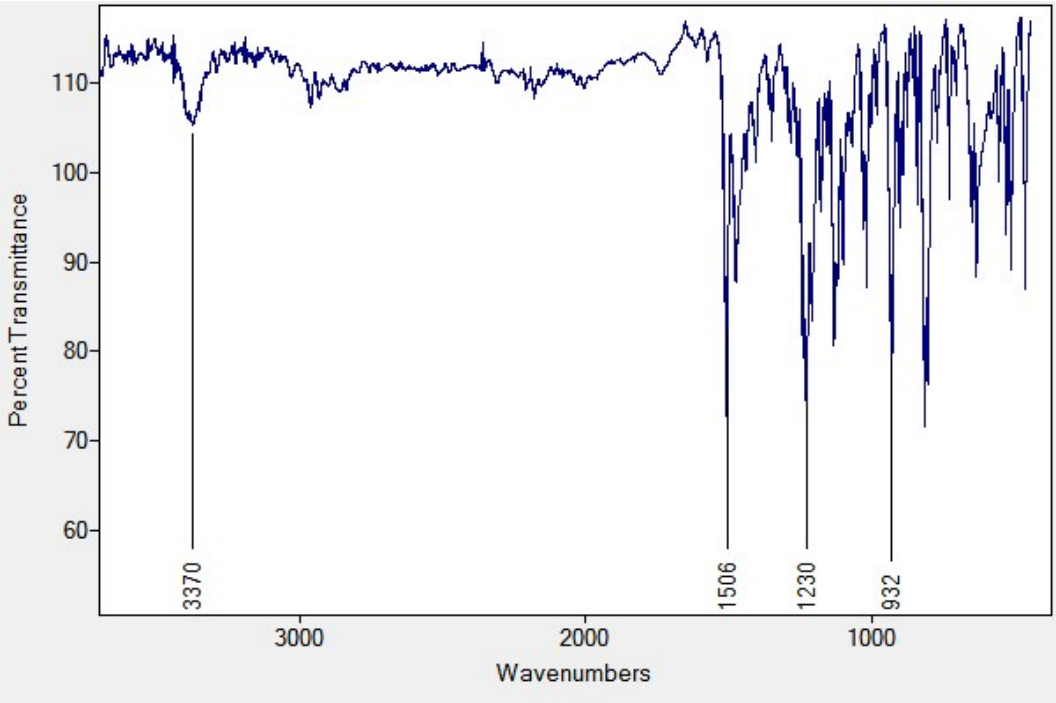
Compound 4l



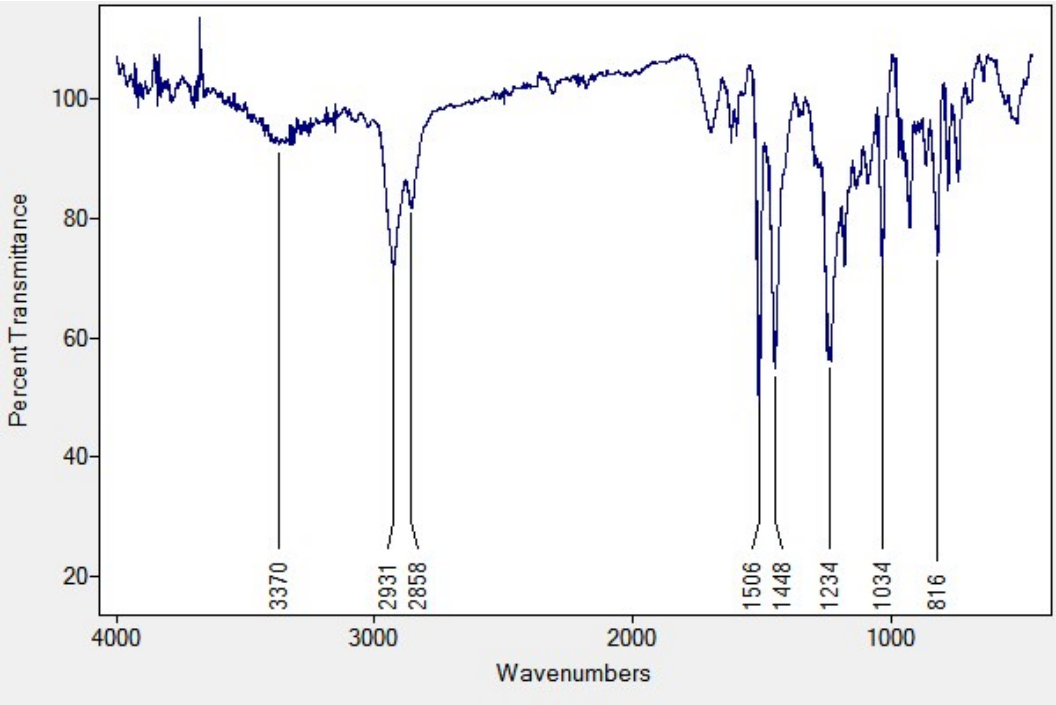
Compound 4m



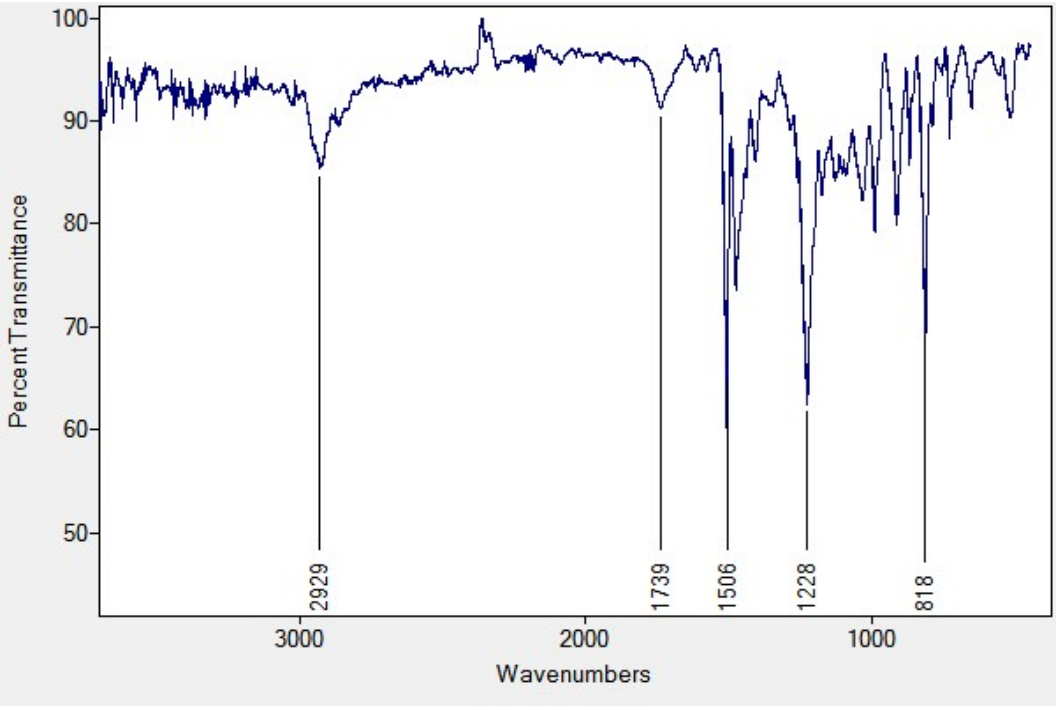
Compound 4o



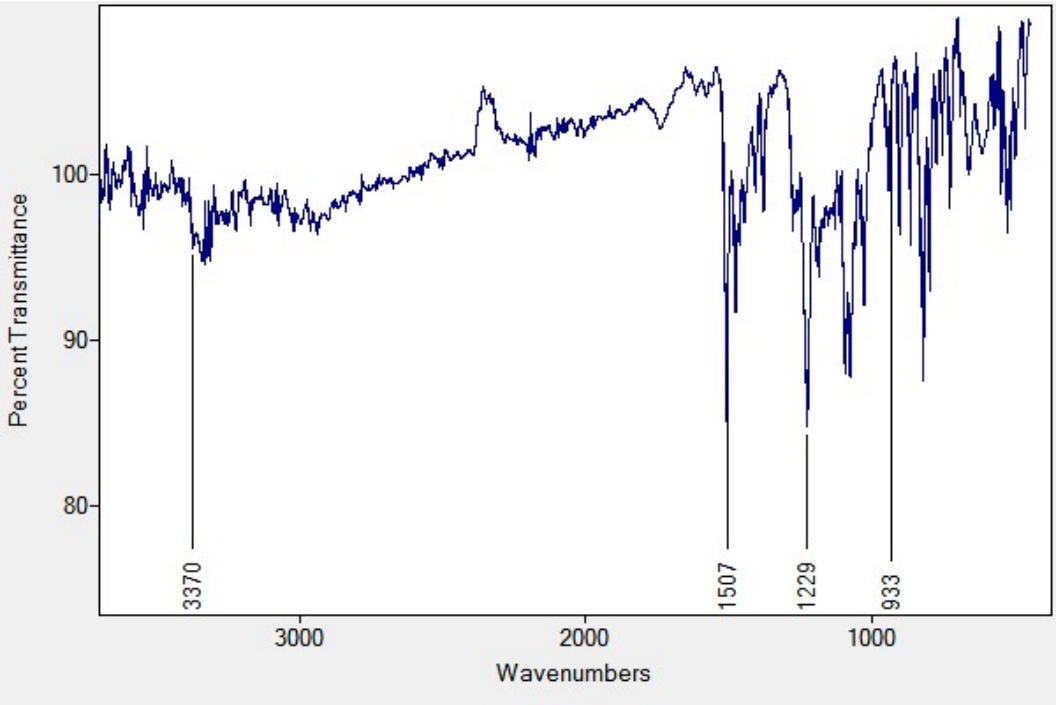
Compound 4p



Compound 4q



Compound 4r



Compound 4s