Supporting Info

Synthesis and biological assessment of 4,1-benzothiazepines with neuroprotective activity on the Ca^{2+} overload for the treatment of neurodegenerative diseases and stroke

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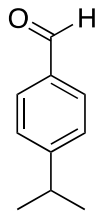
Contents

General procedure for the synthesis of isopropylbenzaldehydes

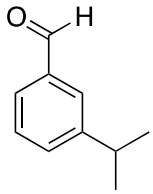
Similar to what has been described, (Anajota, 2015) with slight modifications. To a solution of the corresponding bromoisopropylbenzene (1 equiv) in dry THF (15 mL) at –78 ºC under argon, *n*-butyllithium (2.5 M in hexanes, 1.1 equiv) was added dropwise and the resulting mixture was stirred at –78 ºC for 30 min. Then, *N,N*-dimethylformamide (1.1 equiv) was added and the mixture stirred at –78 ºC for 30 min more, then allowed to warm it up –20 ºC and stirred until the disappearance of reagents monitored by TLC (2–5 h). Reaction was stopped with H_2O (30 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed by vacuum obtaining a colorless oil that did not need further purification.

- p-*isopropylbenzaldehyde*



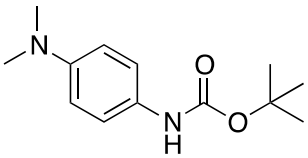
Following the *General procedure for the synthesis of isopropylbenzaldehydes*, reaction of 1-bromo-4-isopropylbenzene (2.51 mmol, 500 mg) [*n*-BuLi (2.76 mmol) and *N,N*-dimethylformamide (2.76 mmol, 202 mg, 214 μL)] yielded *p*-isopropylbenzaldehyde as a yellow oil (372 mg, quantitative yield) with spectral data according to literature [1].

- meta-*isopropylbenzaldehyde*



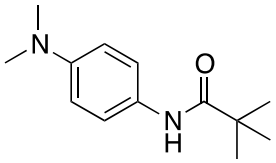
Following the *General procedure for the synthesis of isopropylbenzaldehydes*, reaction of 1-bromo-3-isopropylbenzene (3.07 mmol, 611 mg) [*n*-BuLi (3.38 mmol) and *N,N*-dimethylformamide (3.38 mmol, 247 mg, 261 μL)] yielded *m*-isopropylbenzaldehyde as a yellow oil (453 mg, quantitative yield) with spectral data according to literature [1].

Synthesis of 4-dimethylamino-*N*-tert-butoxycarbonylaniline (19).



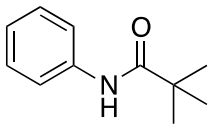
Similar to what we have described for other Boc-protected anilines, (Anajota, 2015) with slight modifications. *N,N*-dimethyl-p-phenylenediamine (1 g, 7.34 mmol) and tert-butyl dicarbonate (1.76 g, 8.08 mmol) were dissolved in dry tetrahydrofurane (THF) under Ar, and triethylamine (810 mg, 1.12 mL, 8.08 mmol) was injected slowly. The reaction mixture was stirred at room temperature for 2 h, after then solvent was evaporated. The crude was dissolved in ethyl acetate (30 mL) and washed with saturated $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and evaporated, obtaining a solid in quantitative yield with spectral data according to the literature [2].

Synthesis of *N*-[4-(dimethylamino)phenyl]-2,2-dimethylpropanamide (22).



N,N-dimethyl-p-phenylenediamine (1 g, 7.34 mmol) was dissolved in dry CH_2Cl_2 (11 mL), and triethylamine (1.28 mL, 928 mg, 9.175 mmol) was slowly added under Ar. The mixture was cooled down to 0 ºC and pivaloyl chloride (0.99 mL, 973 mg, 8.07 mmol) was injected dropwise, allowing the reaction to stir at 0 ºC for 15 min. Then, the reaction mixture was warmed up to rt and stirred for 3 h, monitoring reaction evolution by TLC. Reaction was terminated by addition of water (10 mL) and washed with saturated $NaHCO_3$ (3 × 10 mL). Combined organic layer was dried using anhydrous Na_2SO_4, filtered, and the solvent evaporated under vacuum. Compound **22** (1.53 g, 95%) was obtained as an intense purple-colored solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.0 Hz, 2H, H2, H6), 6.69 (d, *J* = 9.0 Hz, 2H, H3, H5), 7.20 (bs, 1H, NH), 2.90 [s, 6H, $N(CH_3)_2$], 1.29 [s, 9H, $C(CH_3)_3$].

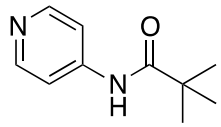
Synthesis of *N*-phenyl-2,2-dimethylpropanamide (29).



Aniline (511 mg, 5.49 mmol) was dissolved in dry CH_2Cl_2 (9 mL), and triethylamine (0.96 mL, 694 mg, 6.86 mmol) was slowly added under Ar. The mixture was cooled down to 0 ºC and pivaloyl chloride (0.67 mL, 662 mg, 5.49 mmol) was injected dropwise, allowing the reaction to stir at 0 ºC for 15 min. Then, the reaction mixture was warmed up to rt and stirred for 3 h, monitoring reaction evolution by TLC. Reaction was terminated by addition of water (10 mL) and washed with saturated $NaHCO_3$ (3 × 10 mL). Combined organic layer was dried using anhydrous Na_2SO_4,

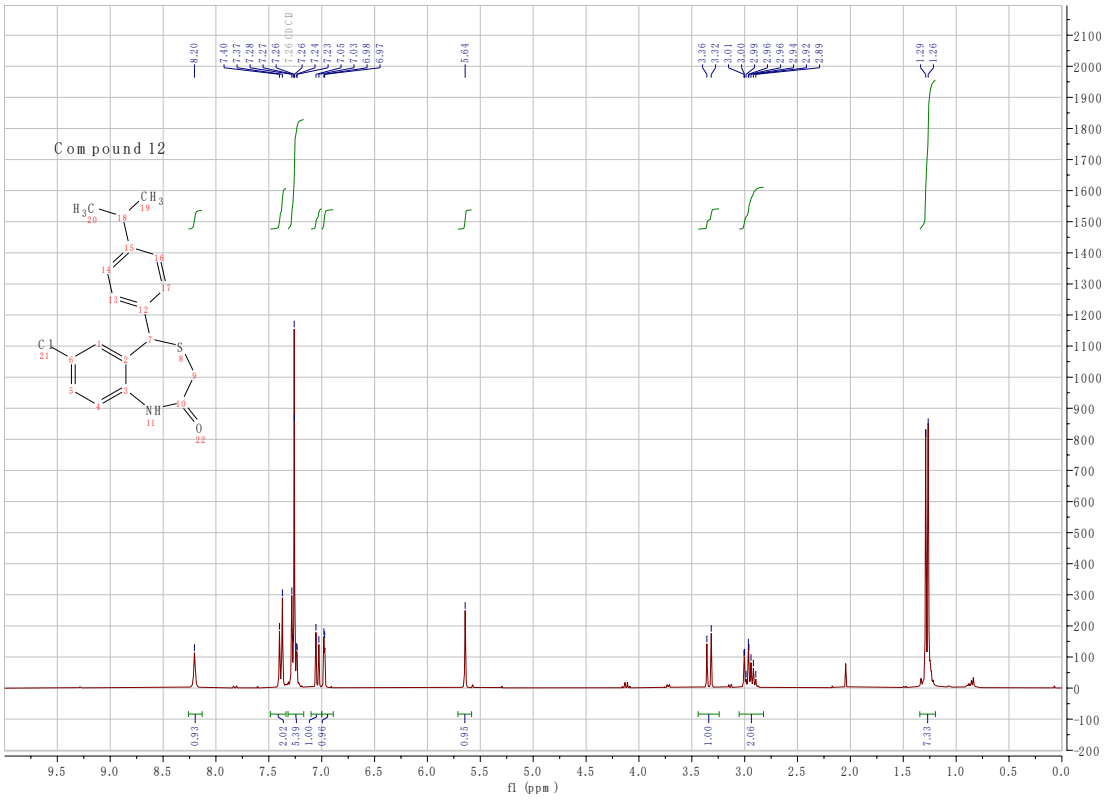
filtered, and the solvent evaporated under vacuum. Compound **29** (974 mg, > 99%) was obtained as a yellow solid, possessing spectral data according with the literature [3].

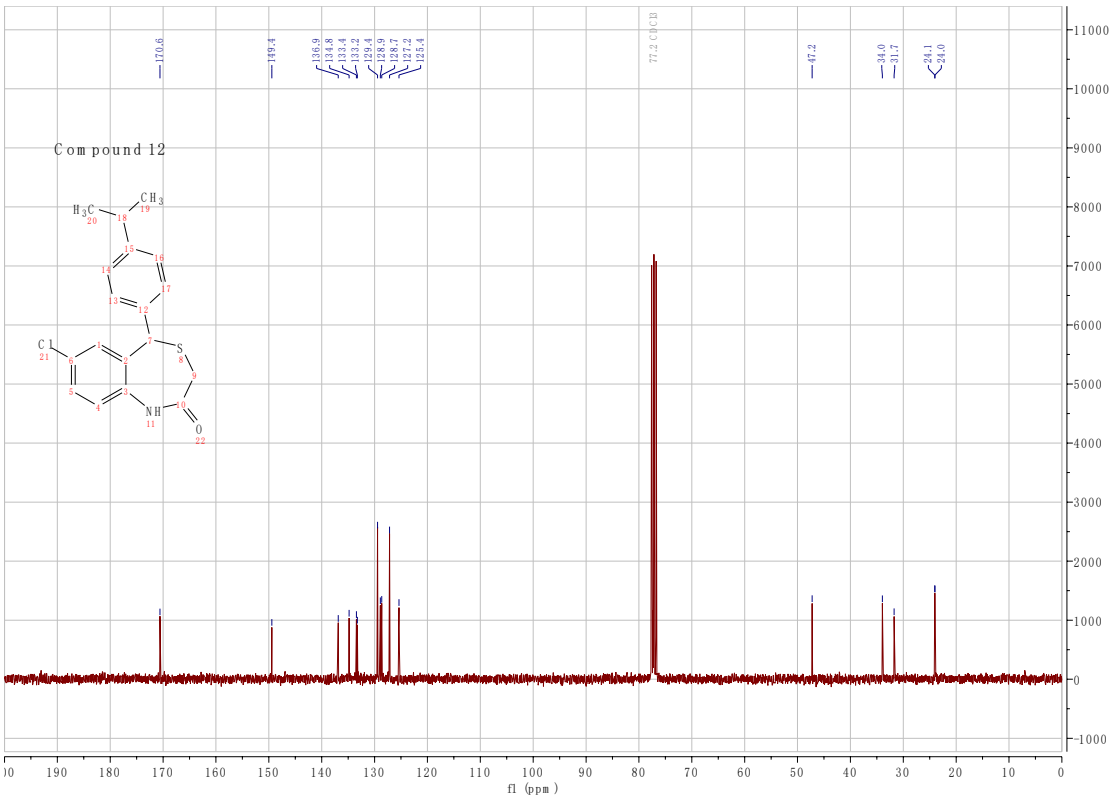
Synthesis of 2,2-dimethyl-*N*-(4-pyridinyl)propanamide (34).

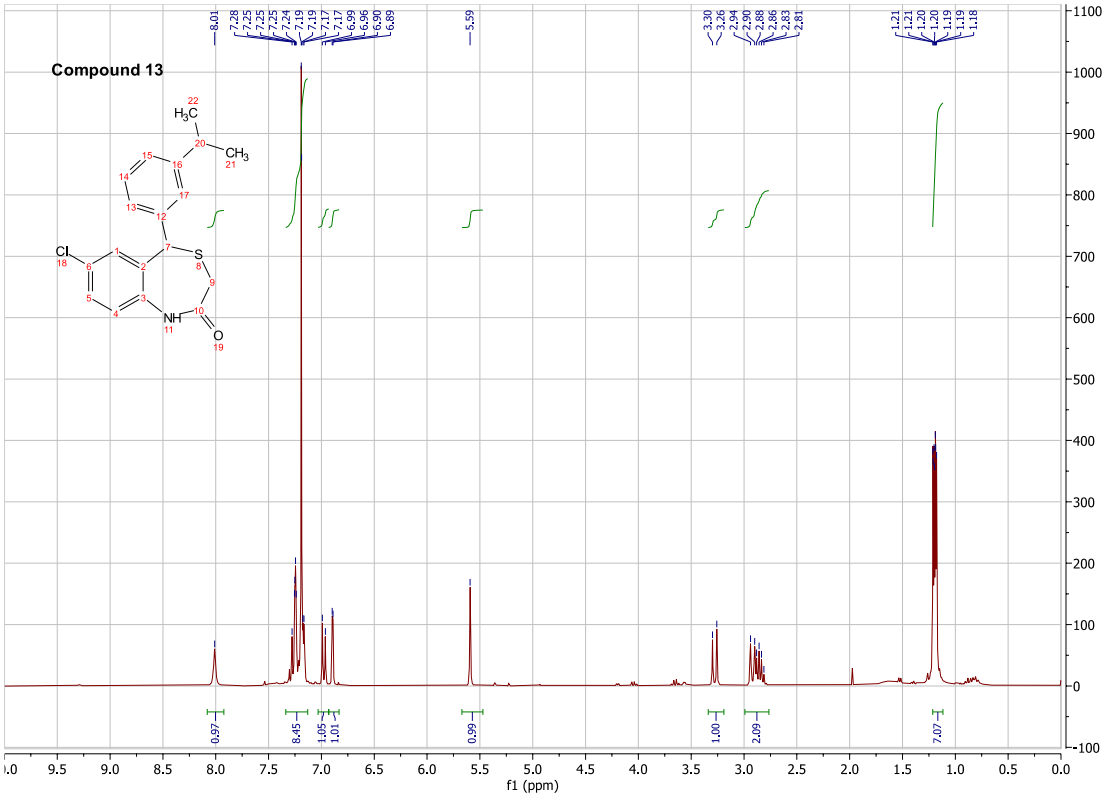


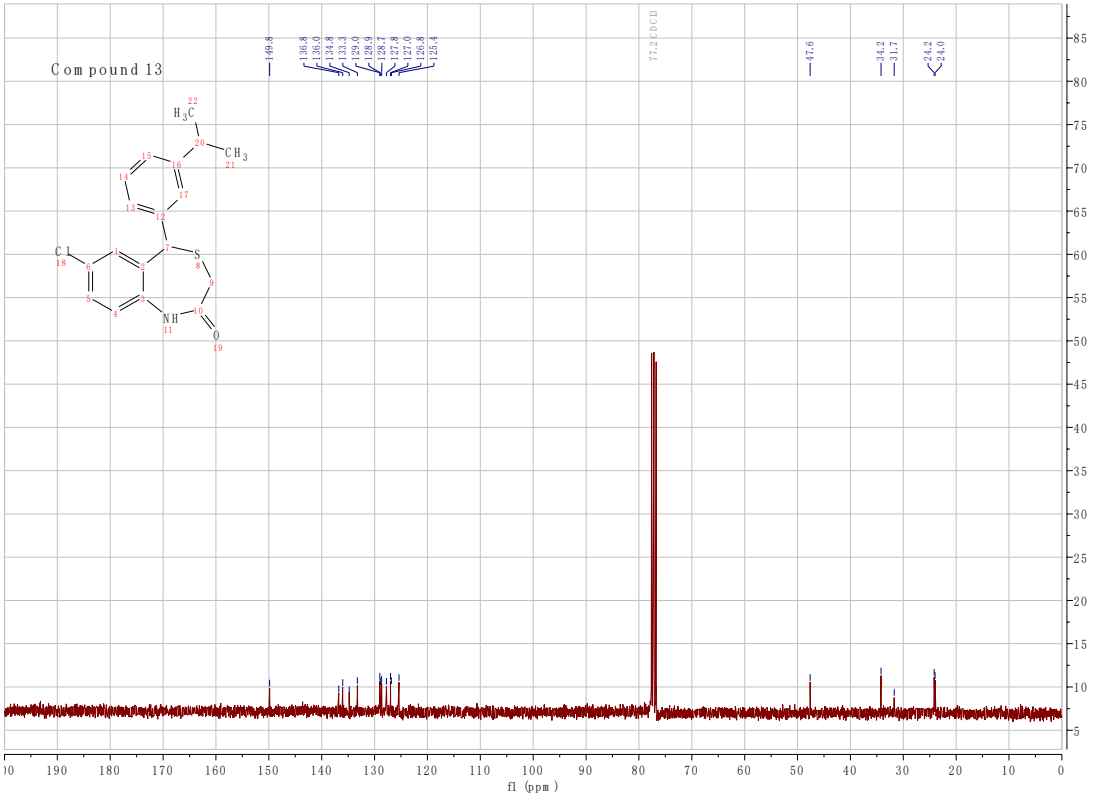
Similarly to what has been described [4] with slight modifications, 4-aminopyridine (2 g, 20.42 mmol) was dissolved in dry CH_2Cl_2 (30 mL), and triethylamine (3.6 mL, 2.6 g, 25.69 mmol) was slowly added under Ar. The mixture was cooled down to –20 ºC and pivaloyl chloride (2.84 mL, 2.78 g, 23.06 mmol) was injected dropwise, allowing the reaction to stir at –20 ºC for 75 min, monitoring reaction evolution by TLC. Reaction was terminated by addition of water (30 mL) and washed with saturated $NaHCO_3$ (3 × 50 mL). Combined organic layer was dried using anhydrous Na_2SO_4, filtered, and the solvent evaporated under vacuum. The crude was purified by automatized flash chromatography (Biotage Isolare One) using ethyl acetate/*n*-hexane mixtures as eluent to give compound **34** (2.2 g, 65%) was obtained as a white solid, possessing spectral data according with the literature [4].

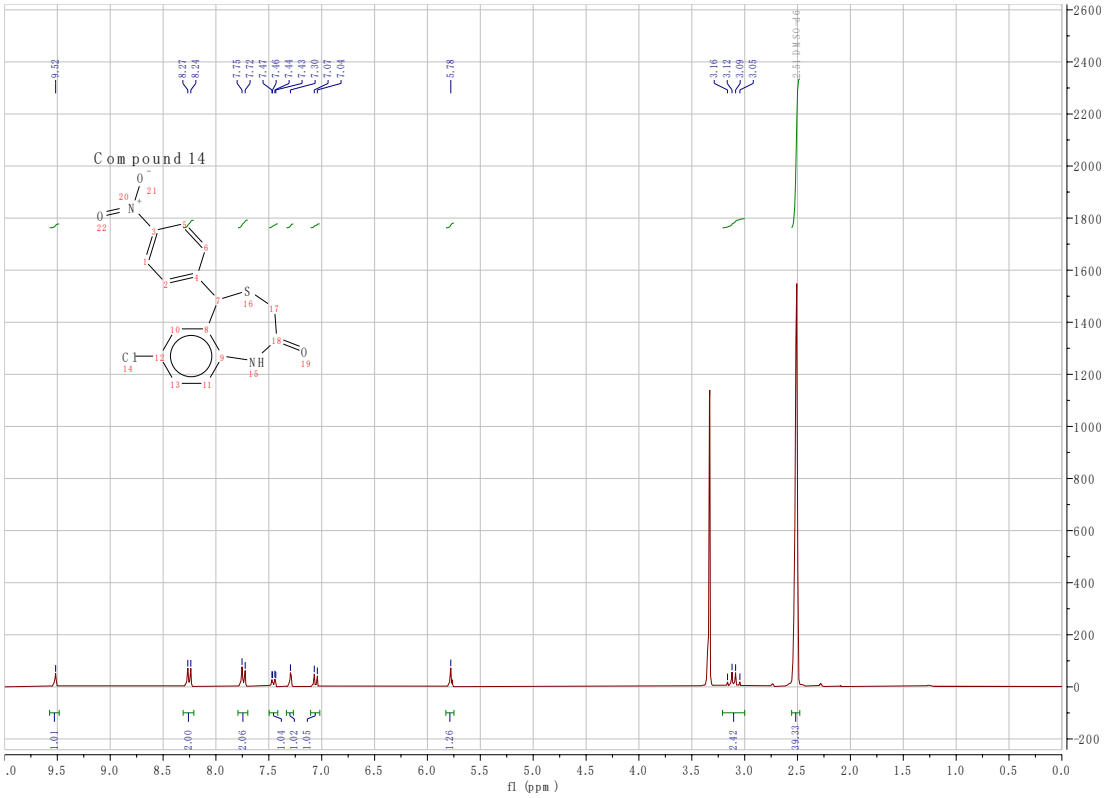
Spectral data

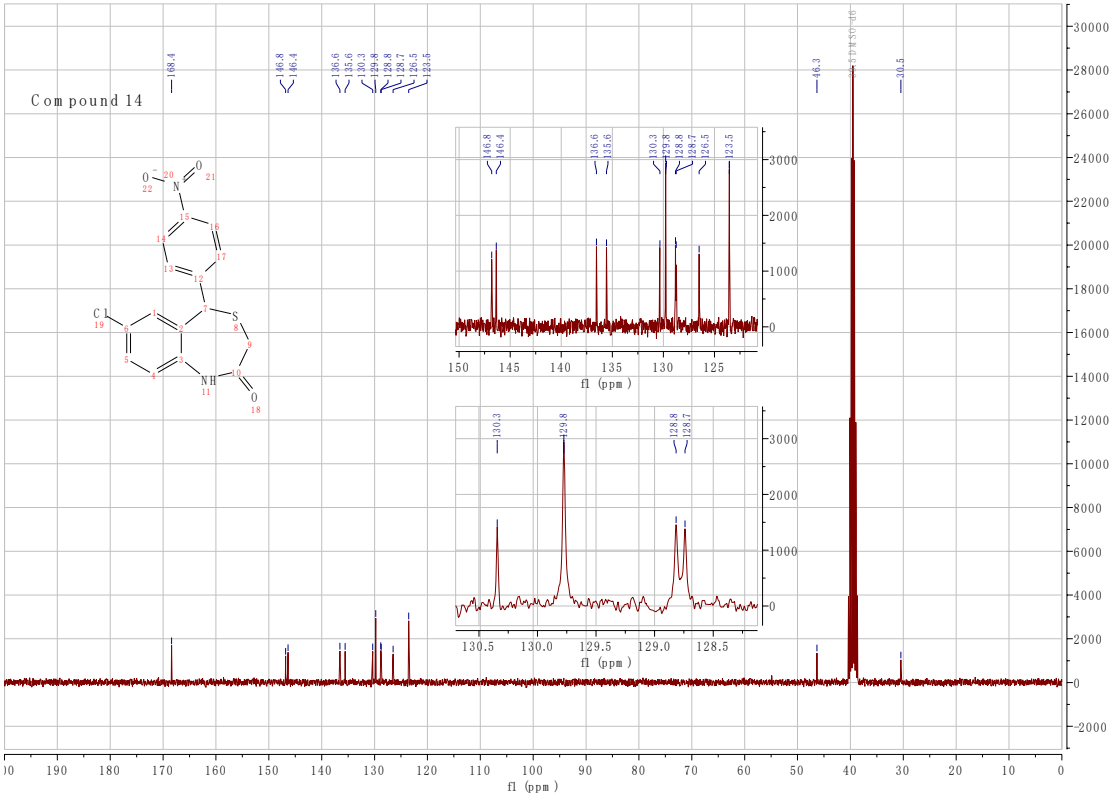


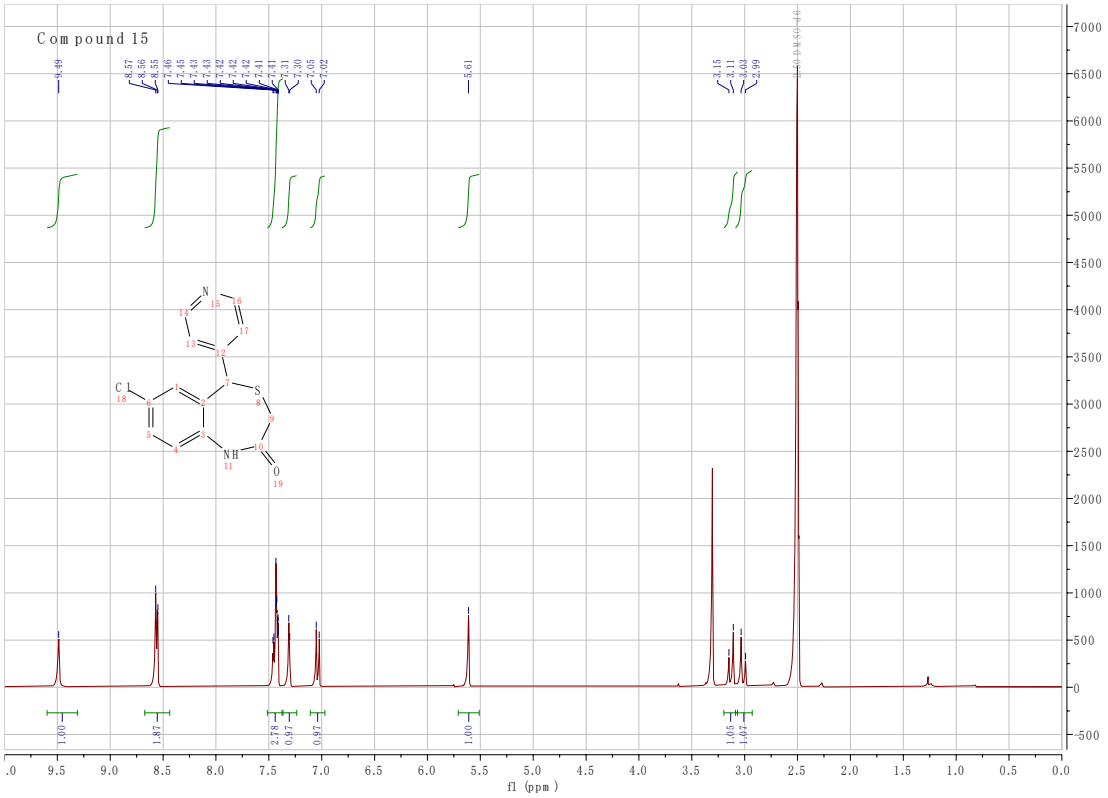


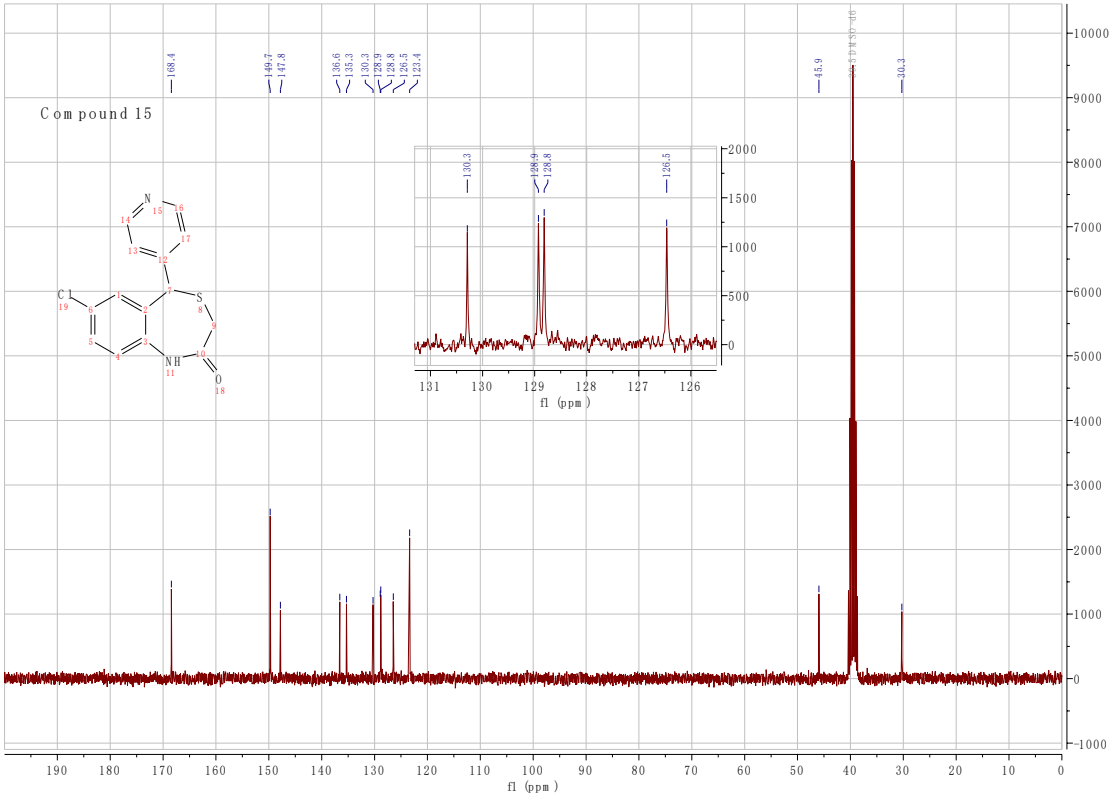

Compound 13
f1 (ppm)

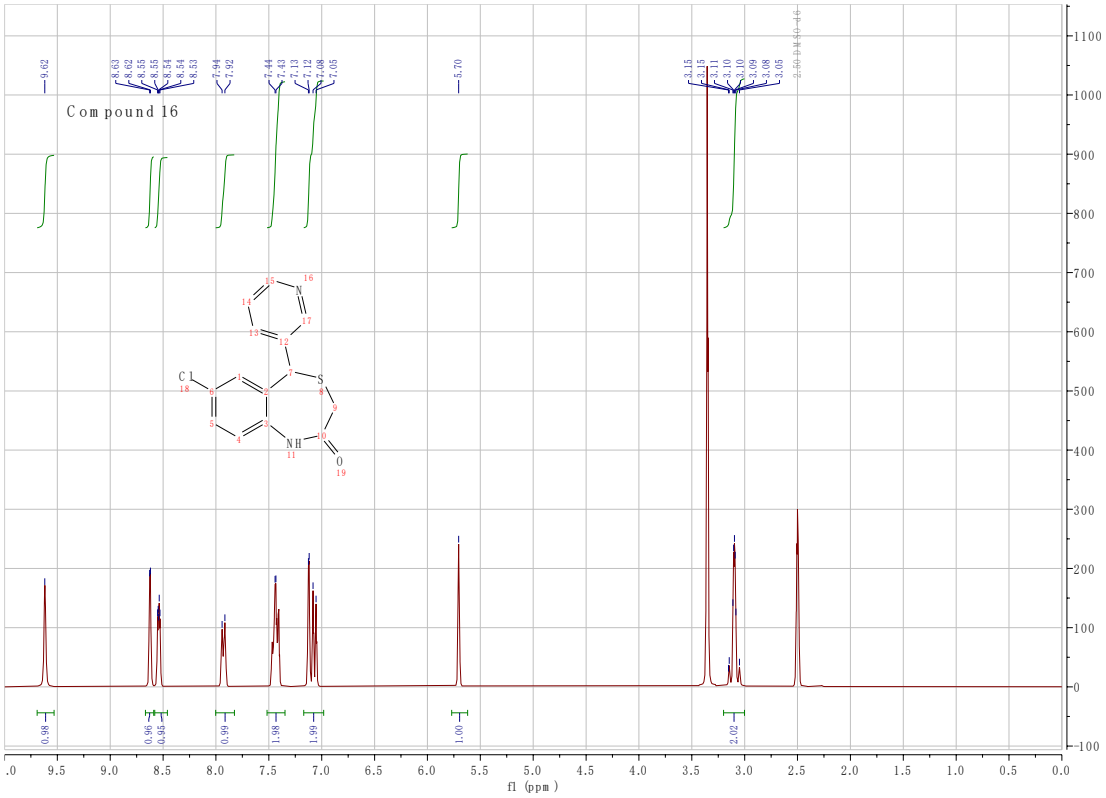

Compound 13
f1 (ppm)

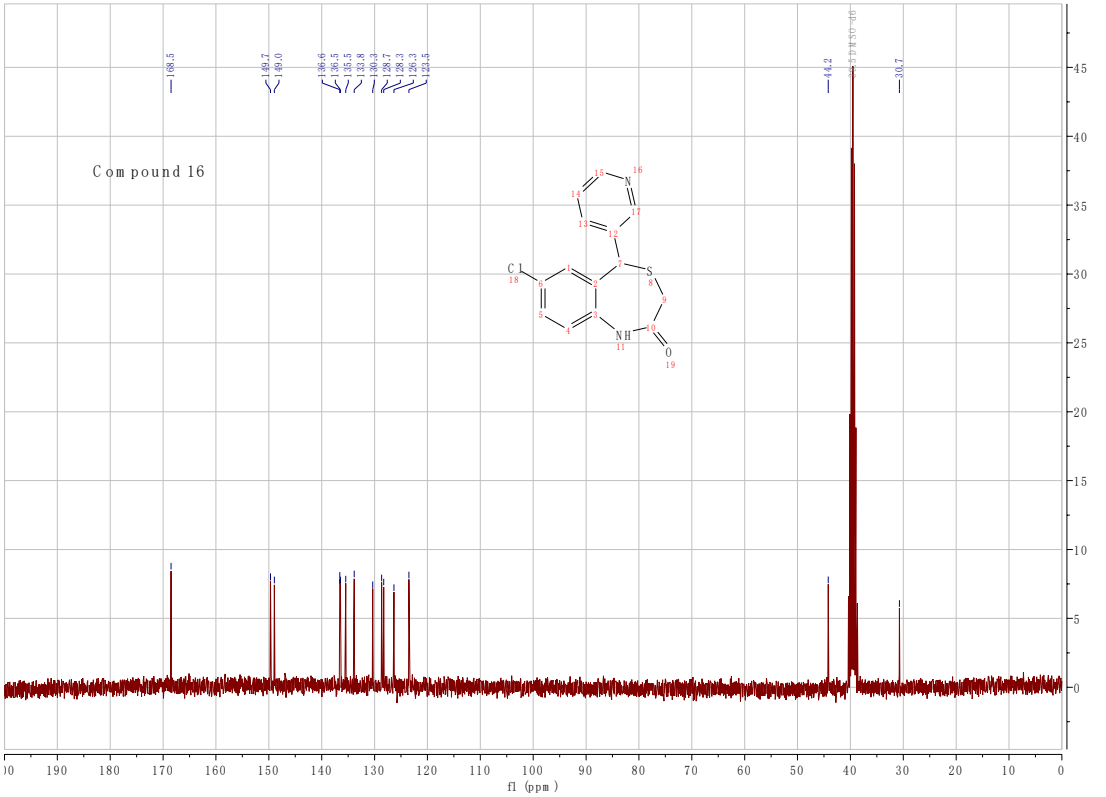

Compound 14
f1 (ppm)

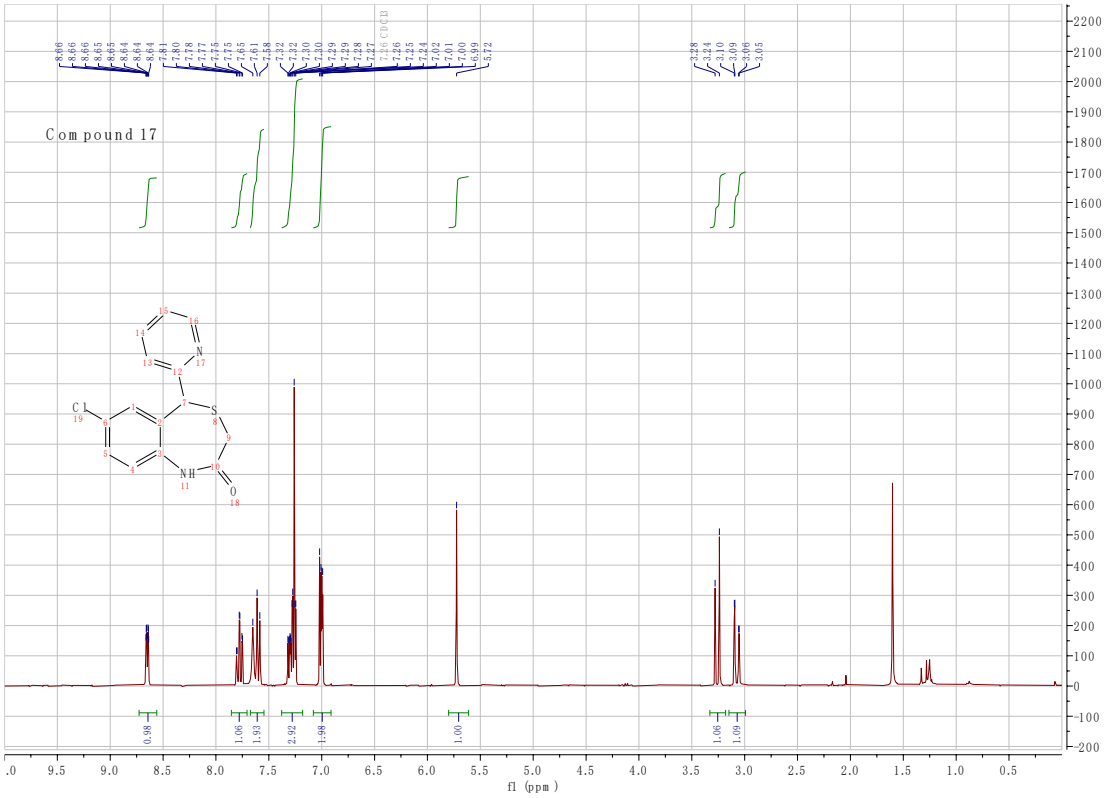

Compound 14
f1 (ppm)

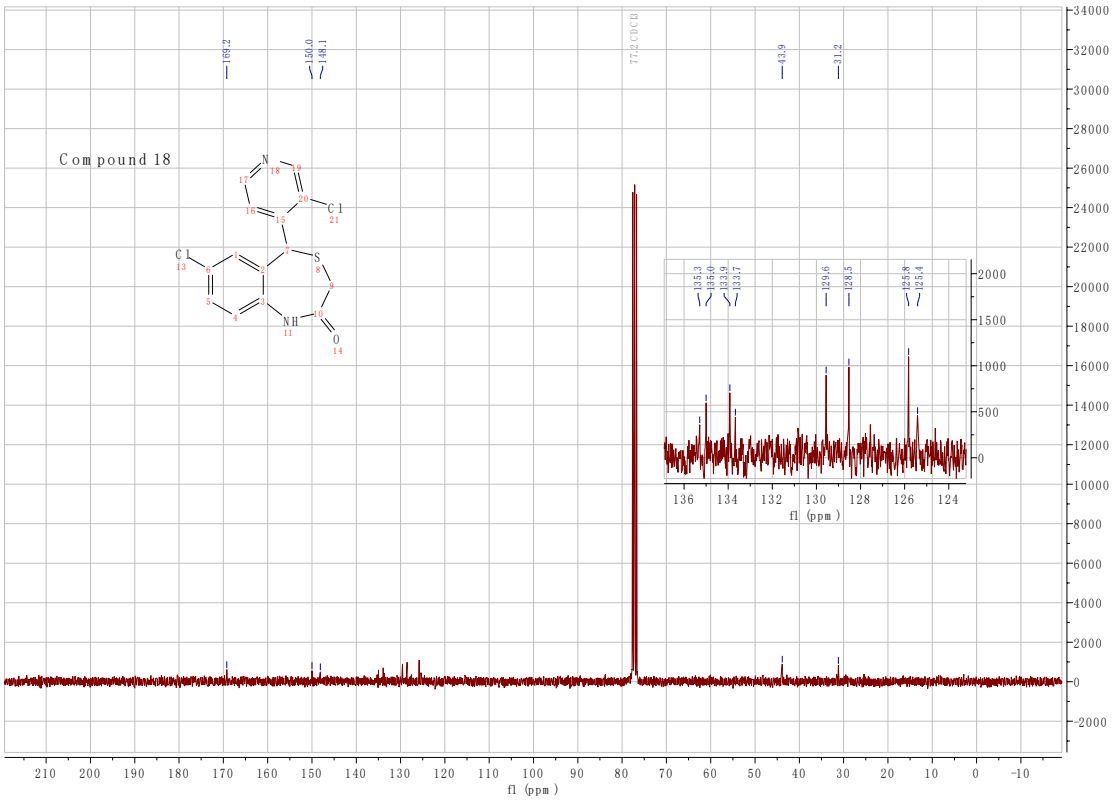

Compound 15
fl (ppm)

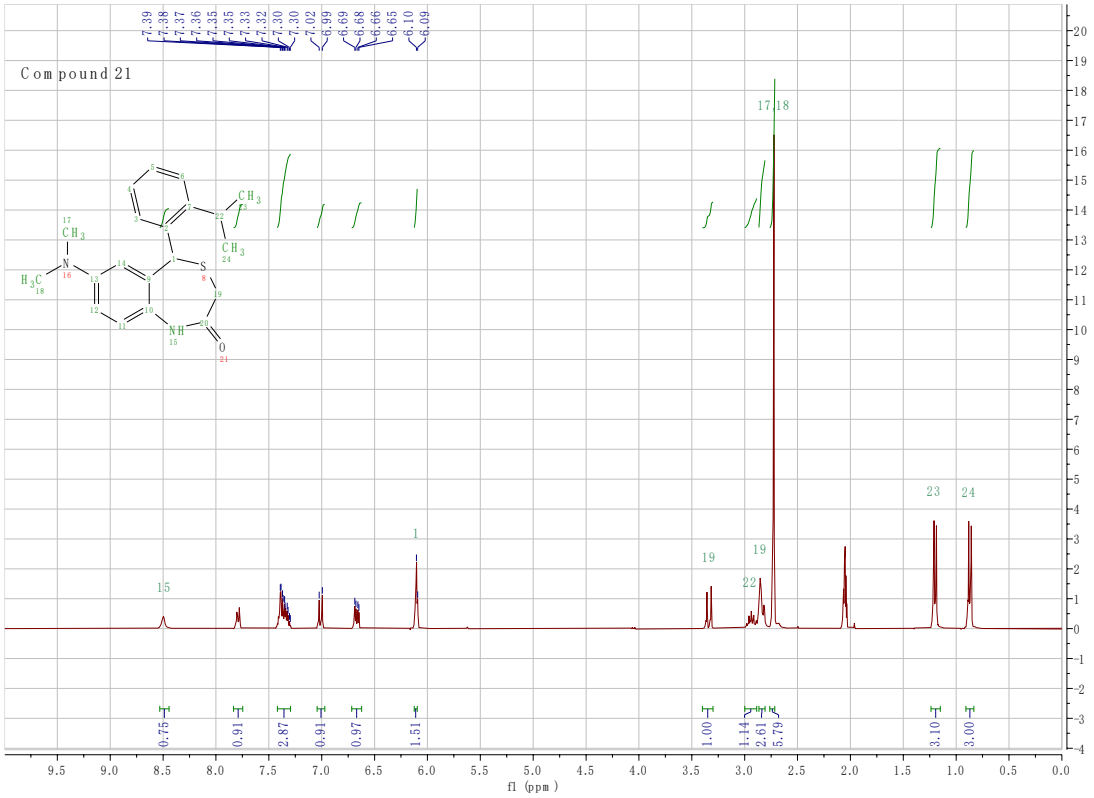

Compound 15
fl (ppm)

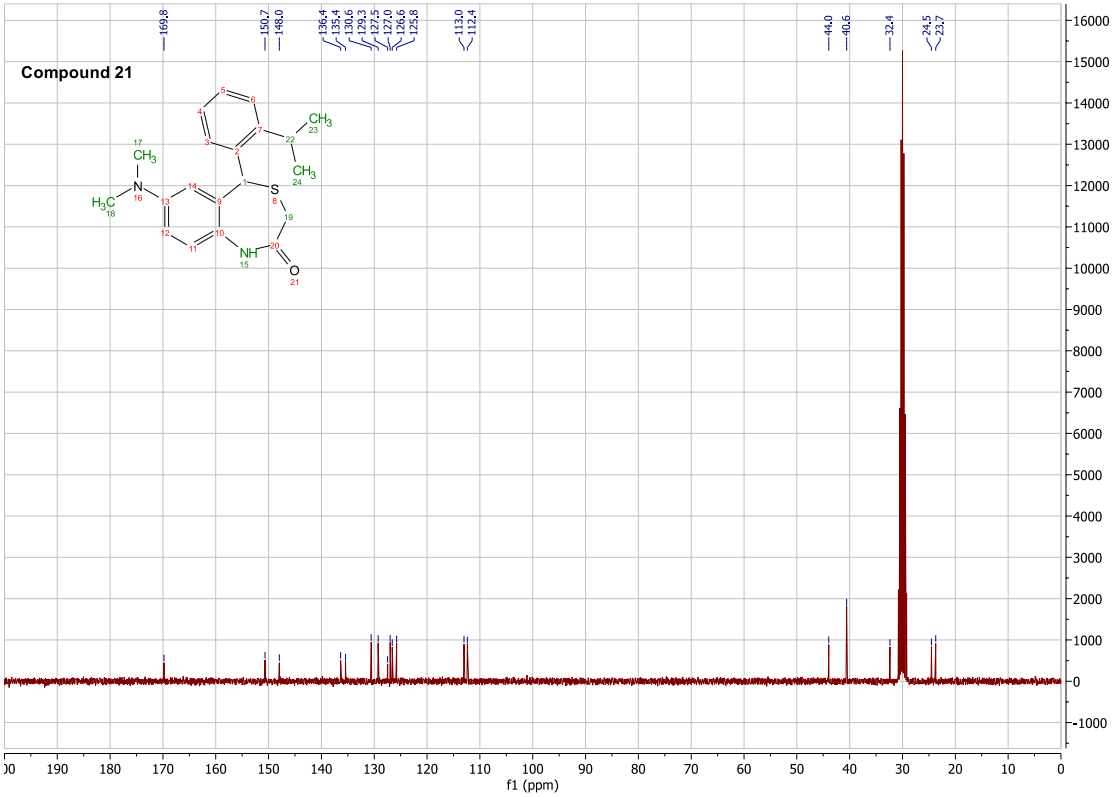

Compound 16
9.62
8.63
8.62
8.55
8.54
8.54
8.53
7.94
7.92
7.44
7.43
7.13
7.12
7.08
7.05
5.70
3.15
3.15
3.11
3.10
3.10
3.09
3.08
3.05
0.98
0.96
0.65
0.99
1.68
1.99
1.00
2.02
fl (ppm)

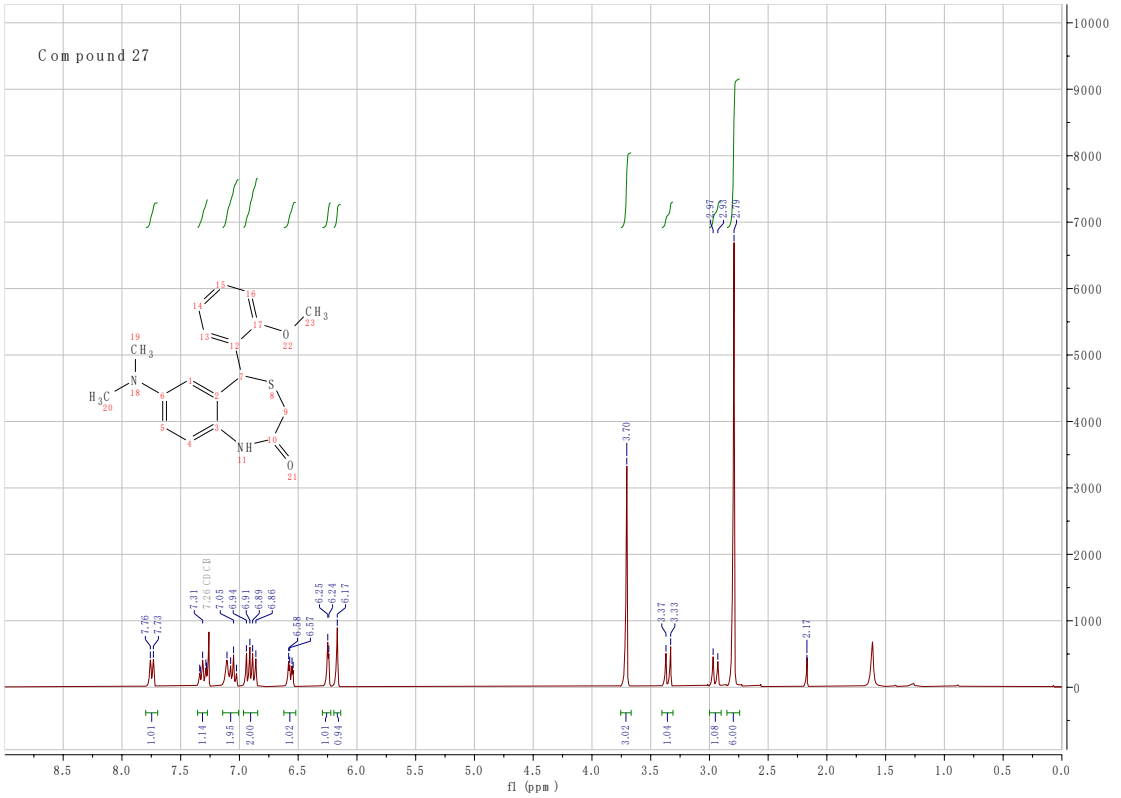

Compound 16
168.5
149.7
149.0
136.6
136.5
135.5
133.8
130.3
129.7
128.3
126.3
123.5
44.2
30.7
fl (ppm)

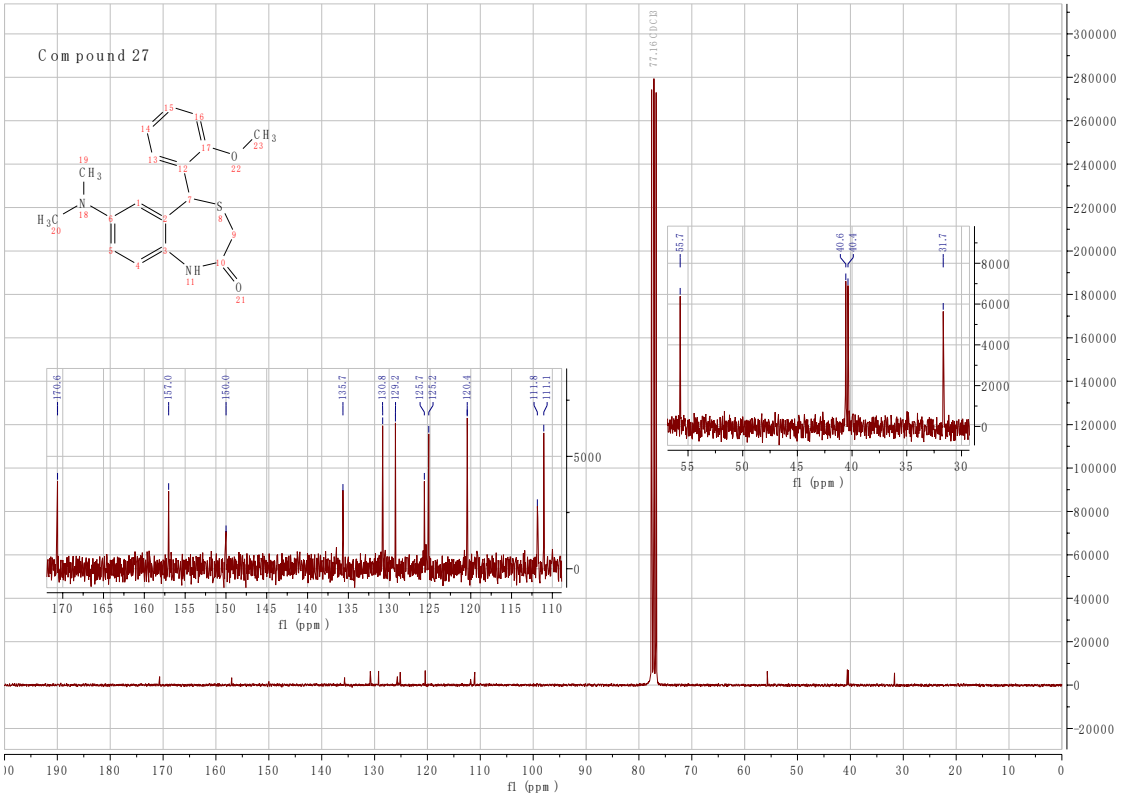

Compound 17
f1 (ppm)

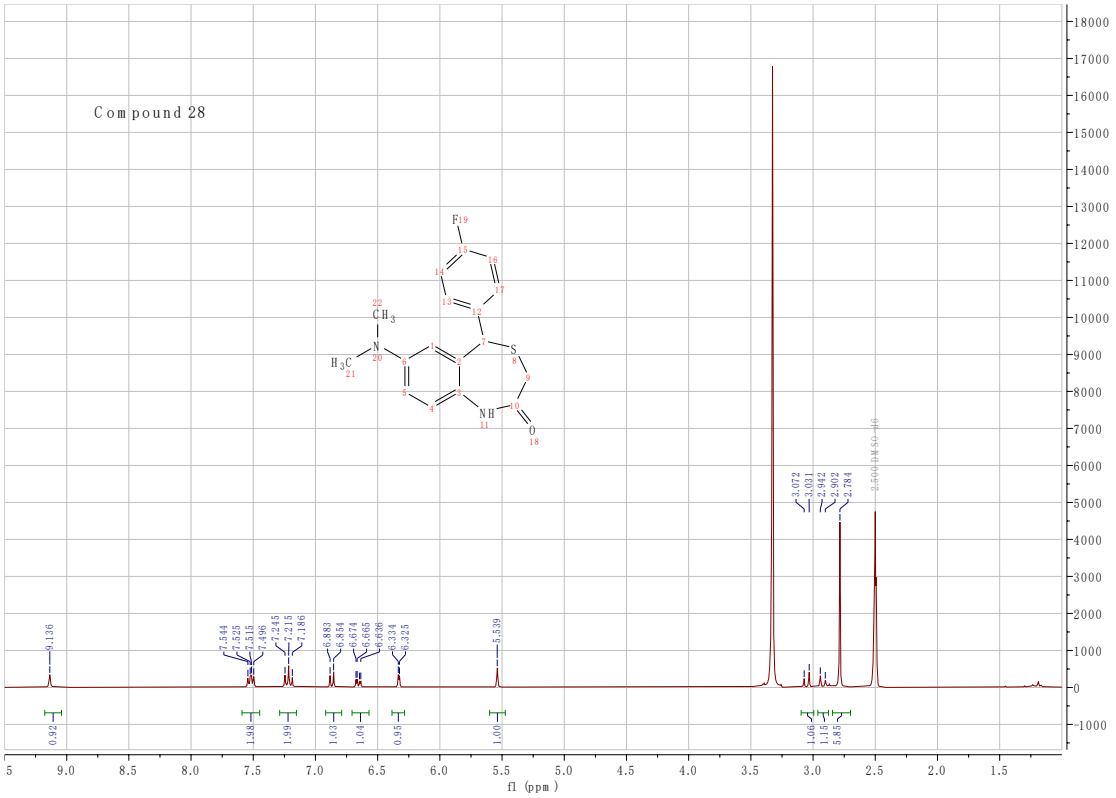

Compound 18
f1 (ppm)

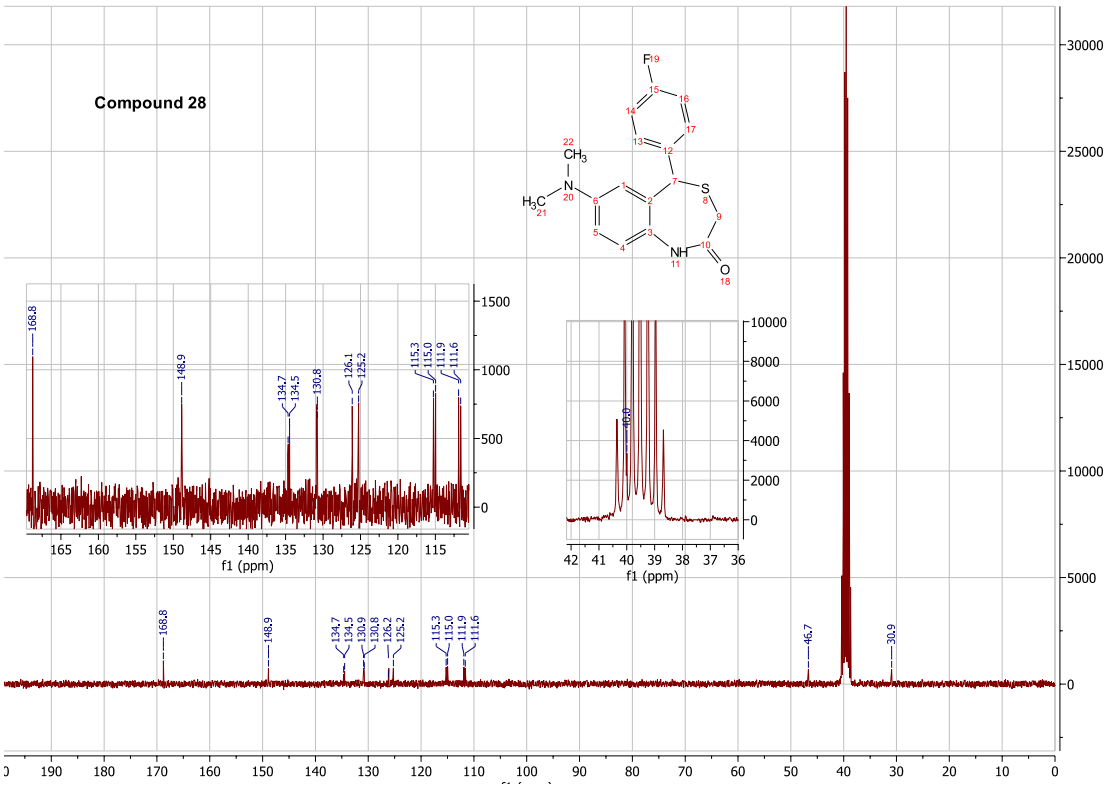

Compound 21
7.39
7.38
7.37
7.36
7.35
7.35
7.33
7.32
7.30
7.30
7.02
6.99
6.69
6.68
6.66
6.65
6.10
6.09
17,18
23
24
1
19
19
22
15
0.75
0.91
2.87
0.91
0.97
1.51
1.00
1.14
2.61
5.79
3.10
3.00
f1 (ppm)

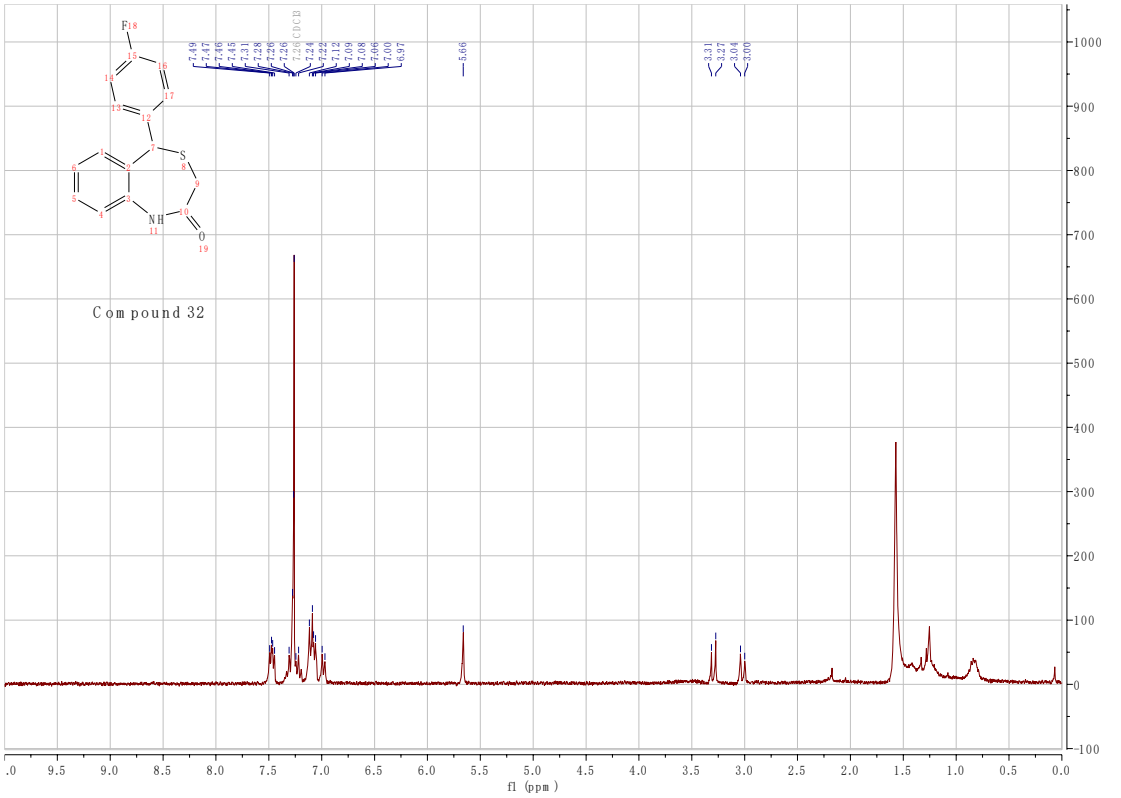

Compound 21
169.8
150.7
148.0
136.4
135.4
130.6
129.3
127.5
127.0
126.6
125.8
113.0
112.4
44.0
40.6
32.4
24.5
23.7
f1 (ppm)

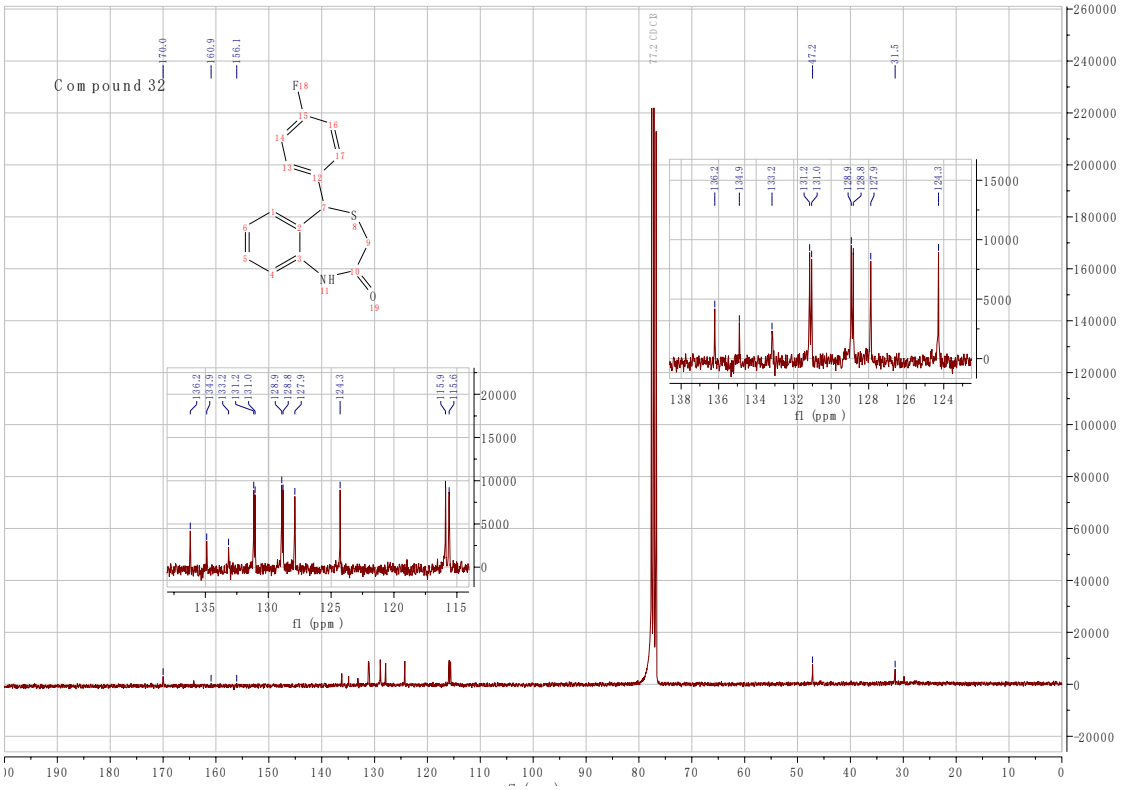

Compound 27
f1 (ppm)

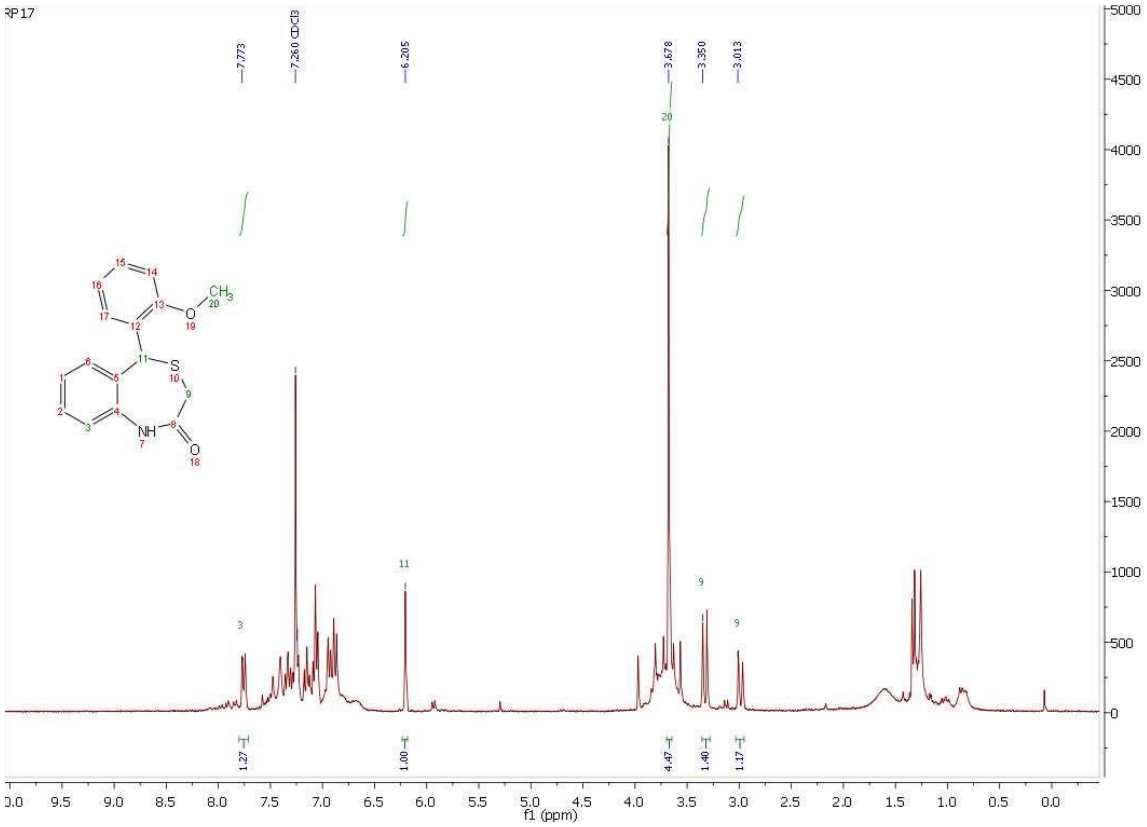

Compound 27
77.16(CDCl3)
f1 (ppm)

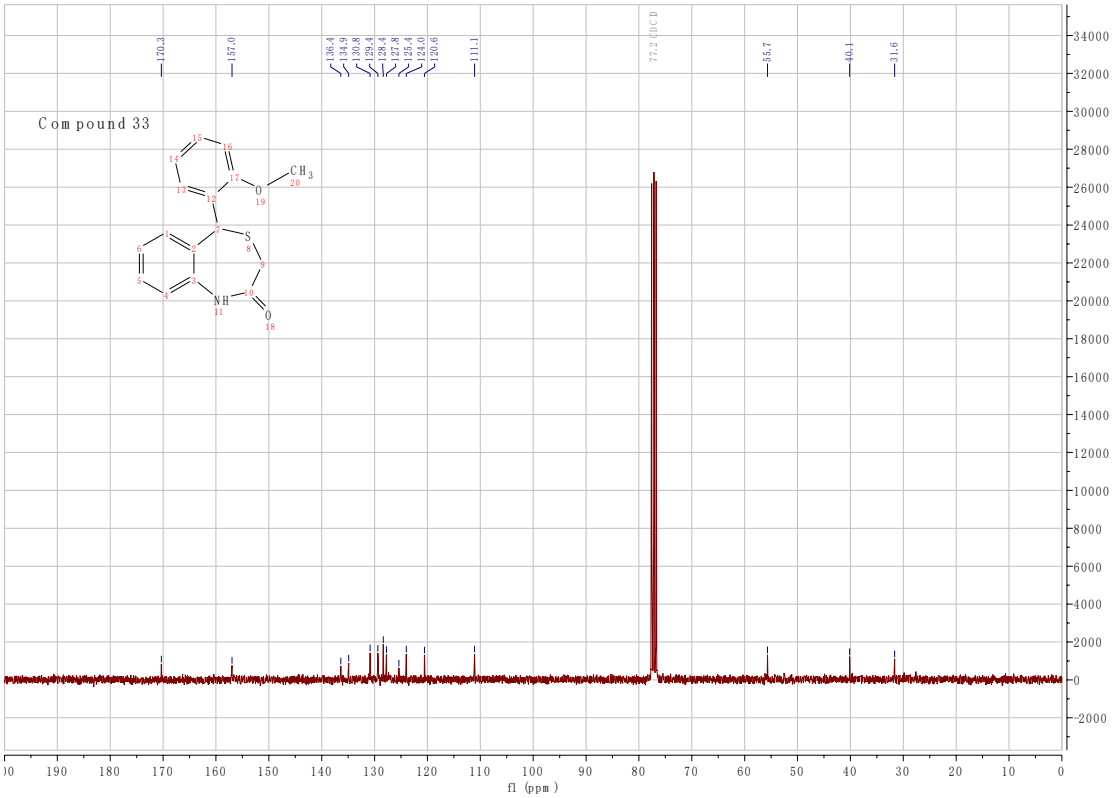

Compound 28
f1 (ppm)

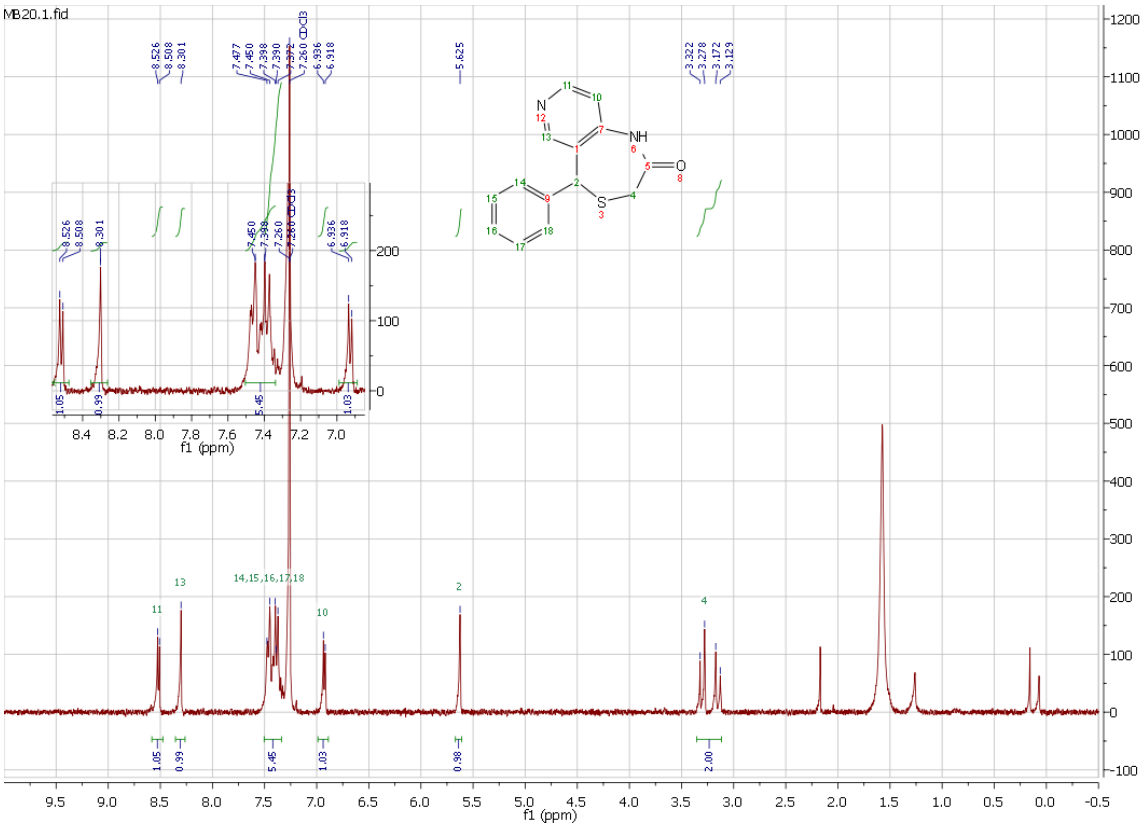

Compound 28
f1 (ppm)
f1 (ppm)


Compound 32
fl (ppm)


Compound 32
fl (ppm)


RP17
7.773
7.260 CDCl3
6.205
3.678
3.350
3.013
1.27
1.00
4.47
1.40
1.17
f1 (ppm)


Compound 33
170.3
157.0
136.4
134.9
130.8
129.4
128.4
127.8
125.4
124.0
120.6
111.1
77.2 CDCl3
55.7
40.1
31.6
f1 (ppm)


MB20.1.fid
f1 (ppm)

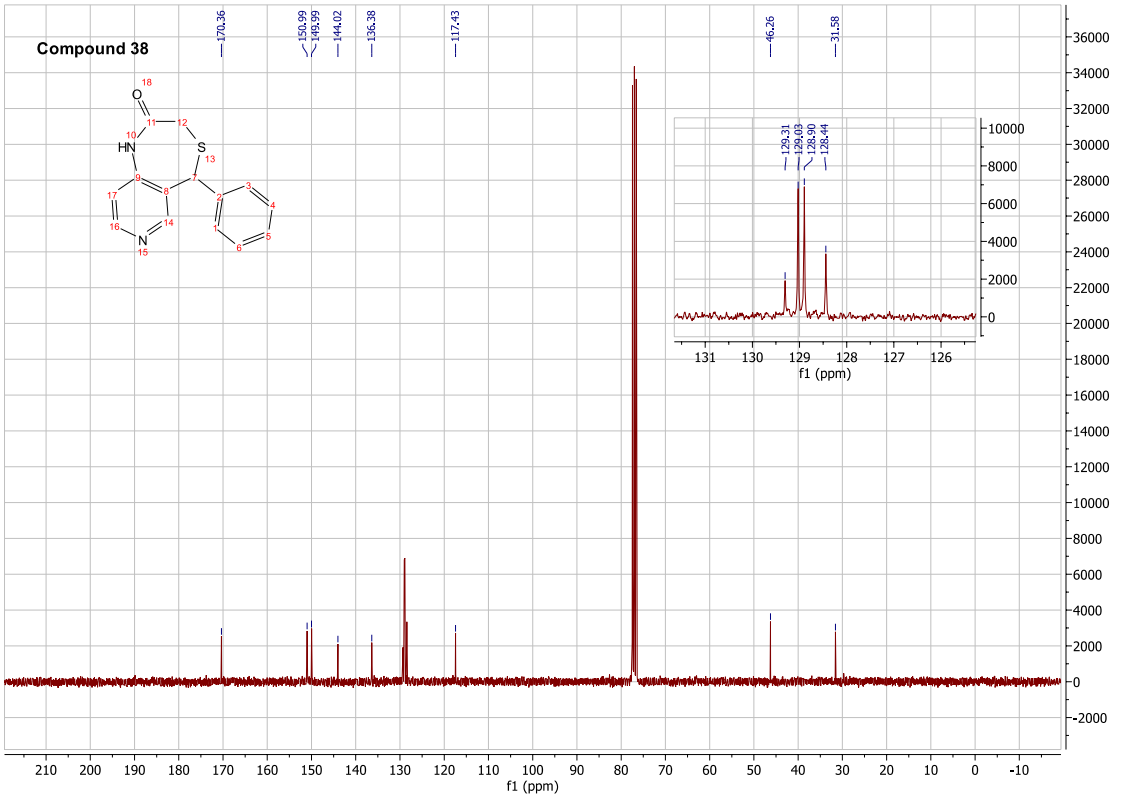
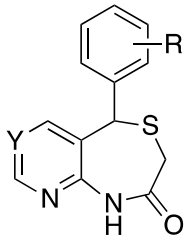
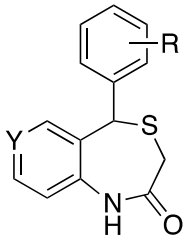

Compound 38
f1 (ppm)

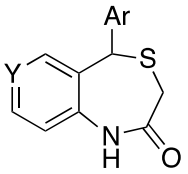
Table S1. Prediction of log P and other Lipinski's parameters.



ITH12662



12–14, 21, 26–28, 32, 33, 38



15–18

COMPOUNDS	Y	R	AR	DON.[A]	ACC.[B]	PSA (Å^2)[C]	CLOG P
CGP37157	C–Cl	2-Cl	-	1	2	54.4	4.36
ITH12575	C–Cl	2-^{i}Pr	-	1	2	54.4	5.00
12	C–Cl	4-^{i}Pr	-	1	2	54.4	5.00
13	C–Cl	3-^{i}Pr	-	1	2	54.4	5.00
14	C–Cl	4-NO_2	-	1	4	100.2	3.70
21	C–NMe_2	2-^{i}Pr	-	1	3	57.6	4.51
26	C–NMe_2	2-Cl	-	1	3	57.6	3.86
27	C–NMe_2	2-OMe	-	1	4	66.9	3.10
28	C–NMe_2	4-F	-	1	3	57.6	3.40
32	C–H	4-F	-	1	2	54.4	3.30
33	C–H	2-OMe	-	1	3	63.6	2.99
38	N	H	-	1	3	67.3	1.93
15	C–Cl	H	4-y	1	3	67.3	2.54
16	C–Cl	H	3-y	1	3	67.3	2.54
17	C–Cl	H	2-y	1	3	67.3	2.67
18	C–Cl	2-Cl	4-y	1	3	67.3	3.14
ITH12662	C–Cl	4-F	-	1	3	67.3	3.28

[a] Number of H-bonds-donating groups; [b] Number of H-bonds-accepting groups; [c] Polar surface Area (according to the Hopkins-modified Lipinski's rules of five, PSA of drug-like compounds should be below 150).

References and notes

[1] Han, C.; Buchwald, S.L. Negishi Coupling of Secondary Alkylzinc Halides with Aryl Bromides and Chlorides. J Am Chem Soc **2009***, 131*, 7532-7533.

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[3] Gowda, B.T.; Usha, K.M.; Jayalakshmi, K.L. H and 13 C NMR Spectral Studies on N-(Aryl)-Substituted Acetamides, C 6 H 5 NHCOCH 3-i X i and 2/4-XC 6 H 4 NHCOCH 3-i X i (Where X = Cl Or CH 3 and i = 0, 1, 2 Or 3). Z. Naturforsch **2003***, 58*, 801.

[4] Turner, J.A. Regiospecific Electrophilic Substitution of Aminopyridines: Ortho Lithiation of 2-, 3-, and 4-(Pivaloylamino)Pyridines. J. Org. Chem. **1983***, 48*, 3401-3408.