Efficient one-pot synthesis of 2,4-hi(het)aryl and 2,4-diamino pyrido[3,2-*d*]pyrimidines involving regioselective S_NAr and palladium-catalyzed reactions

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Supporting Information

Experimental section

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX 250 or 400 MHz instrument using $CDCl_3$ or DMSO-*d6*. The chemical shifts are reported in ppm (δ scale) and all coupling constants (*J*) values are in hertz (Hz). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet doublet). Melting points are uncorrected. IR absorption spectra were obtained on a Perkin Elmer PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. HMRS were performed by the Centre Commun de Spectrométrie de Masse (Clermont Ferrand, France). Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254). Spots were visualized by UV light at 254 nm and 356 nm. Columns chromatography were performed using silica gel 60 (0.063-0.200 mm, Merck). Microwave irradiation were performed with a Bioatge Initiator Eight EXP Microwave System and temperature are measured by IR.

Compounds **2-9** were described in literature.[1]

4-(3-Methoxyphenyl)-2-(pyridin-3-yl)-pyrido[3,2-*d*]pyrimidi-ne (11). Compound **11** was isolated after flash chromatography (CH_2Cl_2/MeOH, 99/1) as a yellow solid in 78% yield. Mp 136-137°C ; IR (ATR-Ge, cm^{-1}) ν 3002, 2828, 1584, 1538, 1465, 1334, 1257, 1023, 821 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H, CH_3), 7.12 (dd, 1H, *J* = 2.6 Hz, *J* = 7.4 Hz), 7.43 (dd, 1H, *J* = 4.8 Hz, *J* = 7.9 Hz), 7.47 (t, 1H, *J* = 8.0 Hz), 7.72 (dd, 1H, *J* = 4.1 Hz, *J* = 8.6 Hz, H_7), 8.04-8.08 (m, 2H), 8.33 (dd, 1H, *J* = 1.7 Hz, *J* = 8.6 Hz), 8.73 (sl, 1H), 8.88 (d, 1H, *J* = 8.0 Hz), 8.99 (dd, 1H, *J* = 1.7 Hz, *J* = 4.1 Hz, H_6), 9.86 (sl, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4 (CH_3), 116.6 (CH), 117.1 (CH), 123.4 (2CH), 124.4 (CH), 127.9 (CH), 129.1 (CH), 133.1 (Cq), 136.0 (CH), 136.9 (CH), 137.3 (Cq), 137.9 (Cq), 148.0 (Cq), 150.3 (CH), 151.2 (CH), 158.6 (Cq), 159.3 (Cq), 166.2 (Cq); HRMS (EI-MS) : m/z calcd for $C_{19}H_{15}N_4O$: 315.1246, found : 315.1249.

2-Chloro-4-phenylaminopyrido[3,2-*d*]pyrimidine (12). Compound **12** was prepared according the procedure described in literature[2] and was isolated after flash chromatography (CH_2Cl_2) as a yellow solid in 87% yield. Mp 107-108°C ; IR (ATR-Ge, cm^{-1}) ν 3329, 2838,

[1] Tikad, A.; Routier, S.; Akssira, M.; Léger, J. M.; Jarry, C.; Guillaumet, G. *Org. Lett.* 2007, **9**, 4673.
[2] Tikad, A.; Routier, S.; Akssira, M.; Léger, J. M.; Jarry, C.; Guillaumet, G. *Synlett.* 2006, 1938.

1599, 1500, 1456, 1323, 1236, 1092, 954, 826 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.12-7.18 (m, 1H), 7.36-7.43 (m, 2H), 7.66 (dd, 1H, *J* = 4.4 Hz, 8.5 Hz, H_7), 7.84-7.87 (m, 2H), 8.02 (dd, 1H, *J* = 1.6 Hz, 8.5 Hz, H_8), 8.54 (dd, 1H, *J* = 1.6 Hz, 4.4 Hz, H_6), 9.19 (sl, 1H, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 120.5 (2CH), 124.8 (CH), 128.6 (CH), 129.2 (2CH), 130.5 (Cq), 135.3 (CH), 137.4 (Cq), 145.8 (Cq), 148.7 (CH), 157.9 (Cq), 158.0 (Cq); SM (SI) : m/z = 256 (M+H;^{35}Cl), 258 (M+H; ^{37}Cl).

4-*n*Butylamino-2-(4-methoxyphenylamino)-pyrido[3,2-*d*]pyr-imidine (14). The crude material was triturated with Et_2O (2x10 mL), filtered and washed with water (10 mL) to afford **14** a yellow solid in 63% yield. Mp 110-111°C ; IR (ATR-Ge, cm^{-1}) ν 3411, 2935, 1619, 1503, 1414, 1338, 1236, 1174, 1036, 836 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.3 Hz, CH_3), 1.38-1.53 (m, 2H, CH_2), 1.63-1.75 (m, 2H, CH_2), 3.58 (q, 2H, *J* = 6.6 Hz, CH_2), 3.79 (s, 3H, OCH_3), 6.87 (d, 2H, *J* = 8.9 Hz), 7.09 (sl, 1H, NH), 7.31 (sl, 1H, NH), 7.43 (dd, 1H, *J* = 4.2 Hz, *J* = 8.5 Hz, H_7), 7.62 (d, 2H, *J* = 8.9 Hz), 7.75 (d, 1H, *J* = 8.5 Hz, H_8), 8.33 (d, 1H, *J* = 4.2 Hz, H_6) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 20.3 (CH_2), 31.5 (CH_2), 40.6 (CH_2), 55.6 (CH_3), 114.1 (2CH), 121.4 (2CH), 127.6 (CH), 129.8 (Cq), 133.2 (CH), 133.5 (Cq), 143.6 (CH). 146.3 (Cq), 155.2 (Cq), 157.5 (Cq), 160.2 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{18}H_{22}N_5O$: 324.1824, found: 324.1829.

2-*n*Butylamino-4-(4-methoxyphenylamino)-pyrido[3,2-*d*]pyr-imidine (15). Compound **15** was isolated after flash chromatography (CH_2Cl_2/MeOH, 99/1) as a yellow solid in 83% yield. Mp 156-157°C ; IR (ATR-Ge, cm^{-1}) ν 3360, 3247, 2920, 1614, 1538, 1430, 1343, 1239, 1033, 826 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.2 Hz, CH_3), 1.40-1.49 (m, 2H, CH_2), 1.60-1.66 (m, 2H, CH_2), 3.47-3.55 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 5.17 (sl, 1H, NH), 6.92 (d, 2H, *J* = 8.9 Hz), 7.44 (dd, 1H, *J* = 4.2 Hz, *J* = 8.5 Hz, H_7), 7.71 (d, 1H, *J* = 8.5 Hz, H_8), 7.79 (d, 2H, *J* = 8.9 Hz), 8.32-8.34 (m, 1H, H_6), 8.91 (sl, 1H, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.3 (CH_3), 20.7 (CH_2), 32.4 (CH_2), 41.9 (CH_2), 55.9 (CH_3), 114.5 (2CH), 122.2 (2CH), 128.0 (CH), 129.5 (Cq), 132.3 (Cq), 133.1 (CH), 143.3 (CH). 147.4 (Cq), 156.3 (Cq), 157.7 (Cq), 159.9 (Cq) ; HRMS (EI-MS) : m/z calcd for $C_{18}H_{22}N_5O$: 324.1824, found : 324.1822.

4-(4-Methoxybenzylamino)-2-phenylaminopyrido[3,2-*d*]pyri-midine (16). The crude material was triturated with Et_2O (2x10 mL), filtered and washed with water (10 mL) to afford **16** a yellow solid in 89% yield. Mp 196-197°C ; IR (ATR-Ge, cm^{-1}) ν 3237, 2904, 1614, 1555, 1445, 1358, 1238, 1179, 1026, 816 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H, OCH_3), 4.79 (d, 2H, *J* = 5.8 Hz, CH_2), 6.90 (d, 2H, *J* = 8.6 Hz), 7.20 (t, 1H, *J* = 7.4 Hz), 7.28 (d, 2H, *J* = 6.7 Hz), 7.35-7.39 (m, 2H), 7.63-7.66 (m, 3H), 7.98 (d, 1H, *J* = 8.4 Hz, H_8), 8.15 (sl, 1H, NH), 8.51 (dd, 1H, *J* = 1.1 Hz, *J* = 4.4 Hz, H_6), 10.50 (sl, 1H, NH) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.4 (CH_2), 55.5 (CH_3), 114.6 (2CH), 122.3 (2CH), 125.5 (CH), 126.6 (CH), 126.8 (Cq), 127.9 (Cq), 129.0 (2CH), 129.5 (2CH), 129.8 (CH), 136.6 (Cq), 146.5 (CH), 152.7 (Cq), 159.7 (2Cq), 159.8 (Cq) ; HRMS (EI-MS) : m/z calcd for $C_{21}H_{20}N_5O$: 358.1668, found: 358.1674.

2-(4-Methoxyphenylamino)-4-phenylaminopyrido[3,2-*d*]pyri-midine (17). Compound **17** was isolated after flash chromatography (petroleum ether/EtOAc/Et_3N, 7/2/1) as a yellow solid in 60% yield. Mp 233-234°C ; IR (ATR-Ge, cm^{-1}) ν 3056, 1631, 1554, 1509, 1471, 1290, 1248, 1021, 829, 765 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 6.92 (d, 2H, *J* = 8.9 Hz), 7.14 (t, 1H, *J* = 7.3 Hz), 7.34-7.40 (m, 2H), 7.50 (dd, 1H, *J* = 4.3 Hz, *J* = 8.5 Hz, H_7), 7.61 (d, 2H, *J* = 8.5 Hz, H_8), 7.81-7.86 (m, 3H), 8.44 (d, 1H, *J* = 4.3 Hz, H_6), 9.15 (sl, 1H, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.6 (CH_3), 114.1 (2CH), 120.6 (2CH), 122.7 (CH), 124.1 (2CH), 128.2 (CH), 129.0 (2CH), 132.4 (Cq), 132.6 (CH), 138.1 (2Cq), 144.3

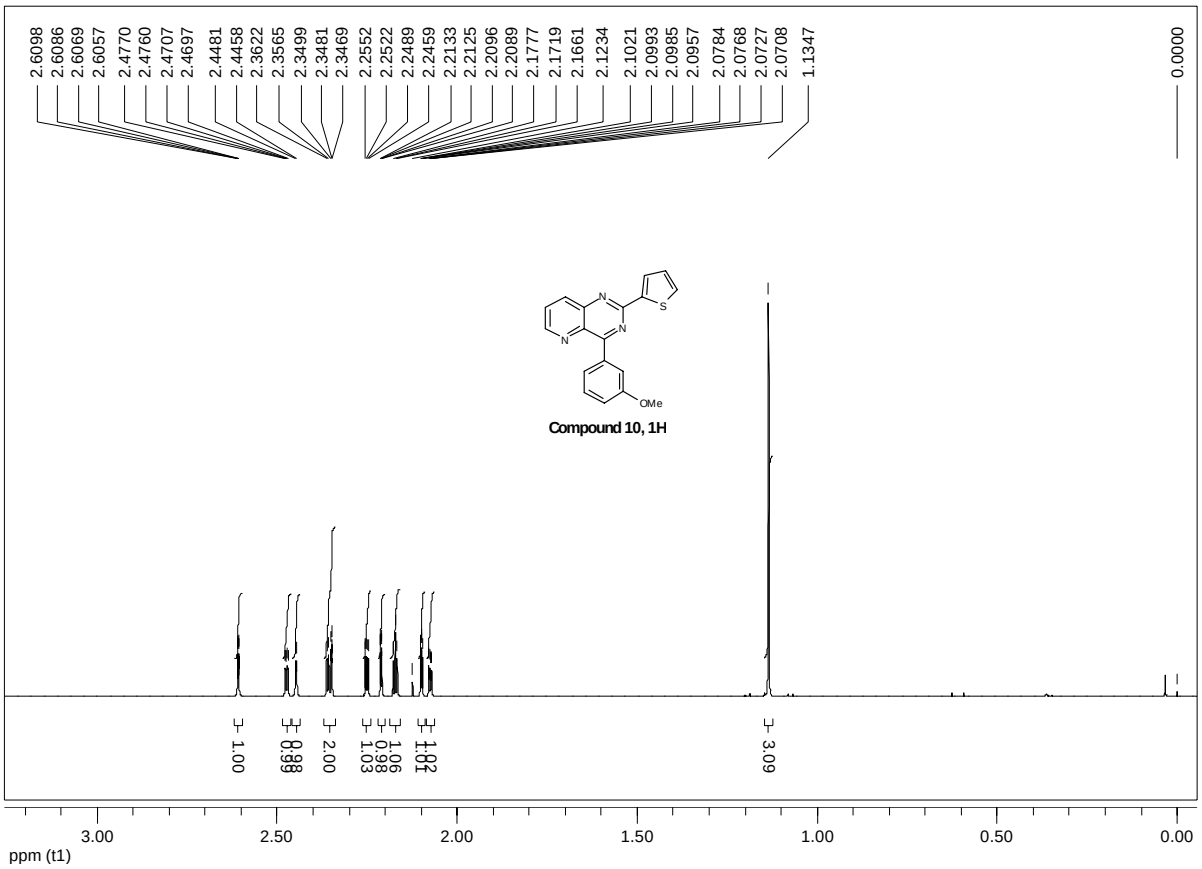
(CH), 145.2 (Cq), 156.0 (Cq), 156.6 (Cq), 157.4 (Cq) ; HRMS (EI-MS) : m/z calcd for $C_{20}H_{18}N_5O$: 344.1511, found : m/z 344.1501.

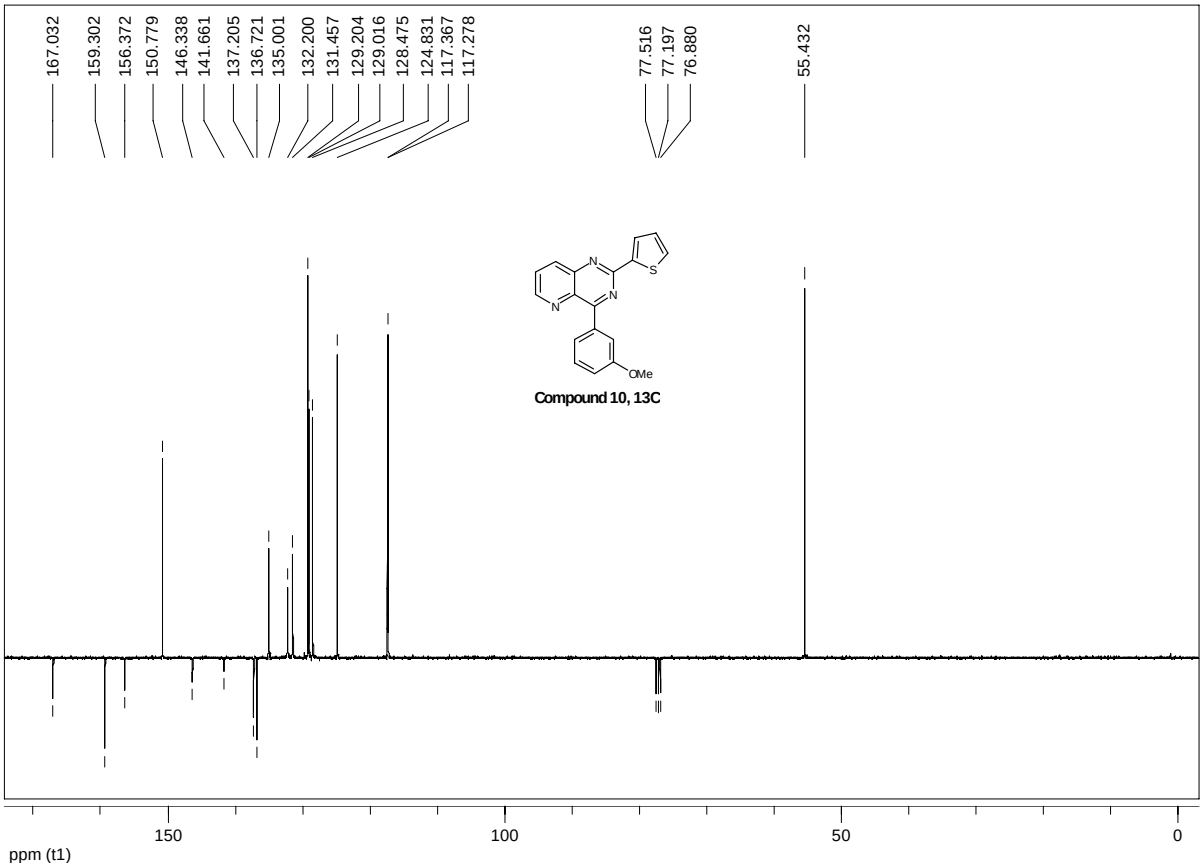
4-(4-Chlorophenylamino)-2-(4-methoxyphenylamino)-pyri-do[3,2-*d*]pyrimidine (18). Compound **18** was isolated after flash chromatography (CH_2Cl_2/MeOH, 99/1) as a yellow solid in 72% yield. Mp 175-176°C ; IR (ATR-Ge, cm^{-1}) ν 3401, 3345, 2828, 1604, 1553, 1489, 1338, 1230, 1041, 831 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 6.92 (d, 2H, *J* = 9.0 Hz), 7.13 (sl, 1H, NH), 7.31 (d, 2H, *J* = 9.0 Hz), 7.52 (dd, 1H, *J* = 4.2 Hz, *J* = 8.5 Hz, H_7), 7.59 (d, 2H, *J* = 8.8 Hz), 7.79-7.83 (m, 3H), 8.43 (dd, 1H, *J* = 1.5 Hz, *J* = 4.2 Hz, H_6), 9.07 (sl, 1H, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.7 (CH_3), 114.2 (2CH), 121.5 (2CH), 122.6 (2CH), 128.1 (CH), 128.6 (Cq), 129.0 (2CH), 129.3 (Cq), 132.7 (Cq), 133.6 (CH), 137.1 (Cq), 144.2 (CH), 146.7 (Cq), 155.9 (Cq), 157.1 (Cq), 157.4 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{20}H_{17}{}^{35}ClN_5O$: 378.1122, found : 378.1125.

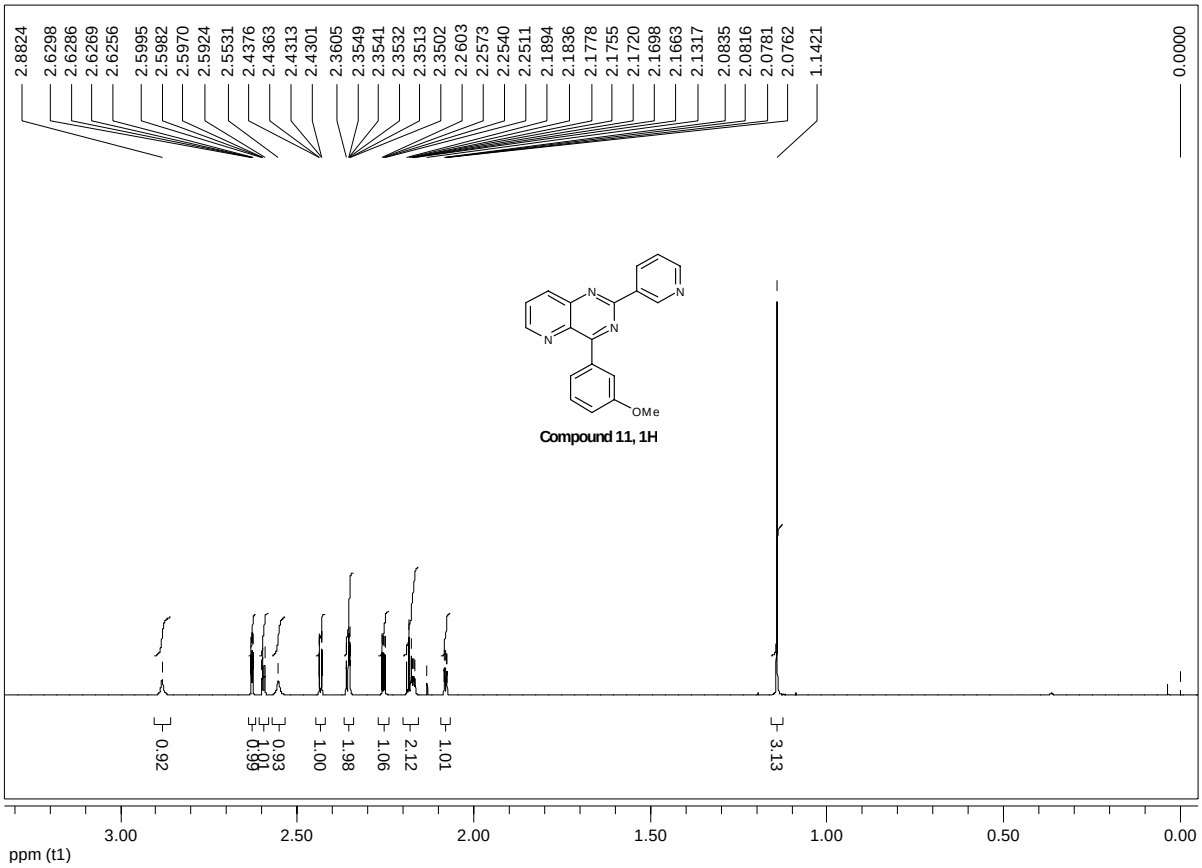
2-(4-Chlorophenylamino)-4-(4-methoxyphenylamino)-pyri-do[3,2-*d*]pyrimidine (19). Compound **19** was isolated after flash chromatography (CH_2Cl_2/MeOH, 99/1) as a white solid in 64% yield. Mp 157-158°C ; IR (ATR-Ge, cm^{-1}) ν 3380, 1604, 1589, 1487, 1420, 1317, 1236, 1179, 1026, 816 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.81 (s, 3H, OCH_3), 6.90 (d, 2H, *J* = 9.0 Hz), 7.24 (d, 2H, *J* = 8.8 Hz), 7.44 (sl, 1H, NH), 7.49 (dd, 1H, *J* = 4.2 Hz, *J* = 8.5 Hz, H_7), 7.63-7.70 (m, 4H), 7.80 (dd, 1H, *J* = 1.1 Hz, *J* = 8.5 Hz, H_8), 8.42 (dd, 1H, *J* = 1.1 Hz, *J* = 4.2 Hz, H_6), 8.94 (sl, 1H, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.6 (CH_3), 114.2 (2CH), 120.8 (2CH), 122.5 (2CH), 127.1 (Cq), 128.0 (CH), 128.7 (2CH), 129.5 (Cq), 131.3 (Cq), 133.6 (CH), 138.6 (Cq), 144.5 (CH), 146.2 (Cq), 156.4 (Cq), 156.6 (Cq), 157.5 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{20}H_{17}{}^{35}ClN_5O$: 378.1122, found: 378.1129.

2-Phenylamino-4-(6-quinolinamino)-pyrido[3,2-*d*]pyrimidine (20). The crude material was triturated with Et_2O (2x10 mL), filtered and washed with water (10 mL) to afford a yellow solid in 68% yield. Mp 241-242°C ; IR (ATR-Ge, cm^{-1}) ν 3365, 2331, 1594, 1522, 1435, 1374, 1271, 1102, 1021, 841 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (t, 1H, *J* = 7.2 Hz), 7.32 (t, 2H, *J* = 7.8 Hz), 7.54 (dd, 1H, *J* = 4.1 Hz, *J* = 8.2 Hz, H_7), 7.75 (dd, 1H, *J* = 4.1 Hz, *J* = 8.4 Hz), 7.92-8.01 (m, 4H), 8.31-8.36 (m, 2H), 8.62 (d, 1H, *J* = 3.2 Hz), 8.81 (d, 1H, *J* = 2.7 Hz), 9.03 (s, 1H, H_6), 9.53 (s, 1H, NH), 10.32 (s, 1H, NH) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.9 (CH), 119.5 (CH), 121.6 (2CH), 125.3 (CH), 128.3 (2Cq), 128.5 (4CH), 129.1 (CH), 133.4 (CH), 135.6 (CH), 137.0 (Cq), 140.6 (Cq), 144.6 (CH), 144.7 (Cq), 146.4 (Cq), 149.0 (CH), 156.4 (Cq), 157.5 (Cq) ; HRMS (EI-MS) : m/z calcd for $C_{22}H_{17}N_6$: 365.1515, found : 365.1510.

^{1}H NMR and ^{13}C NMR spectra:



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Compound 11, 1H
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1.00
1.98
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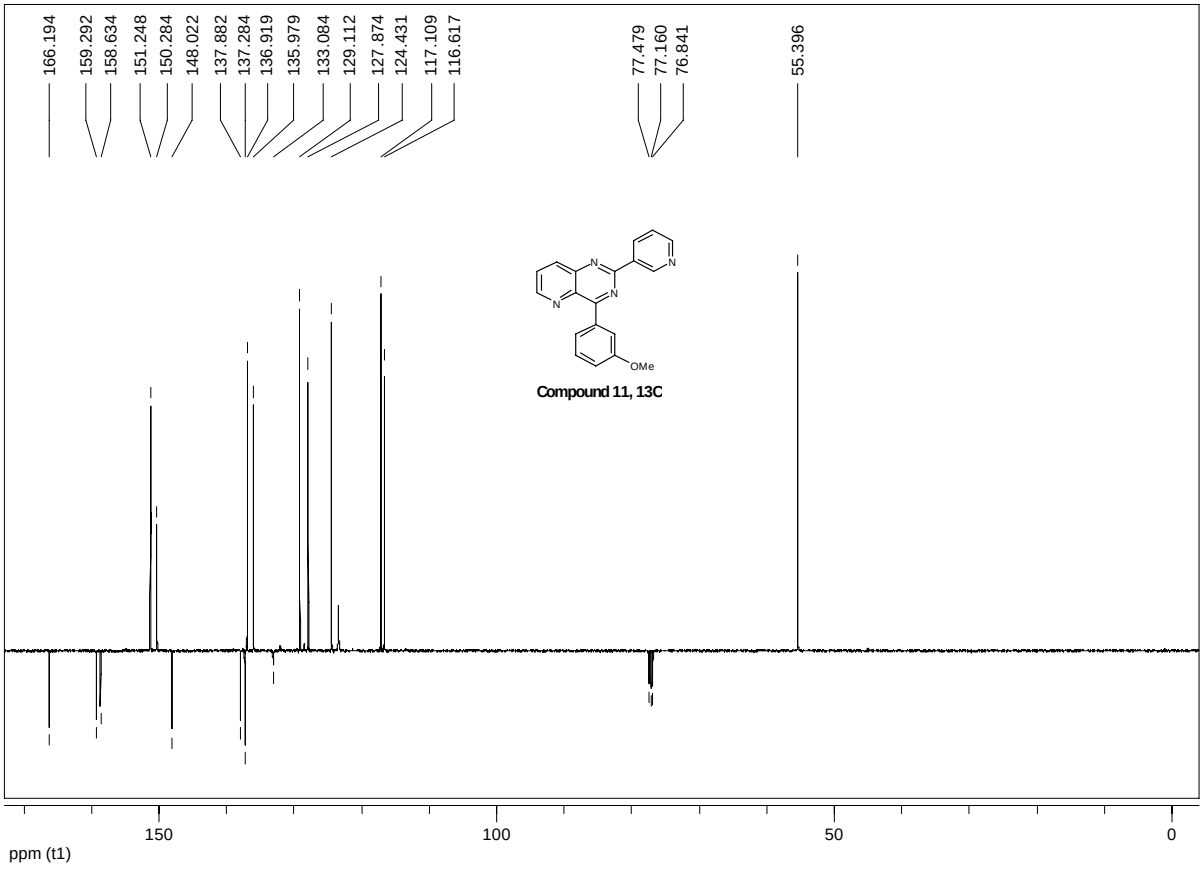
ppm (t1)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100
50
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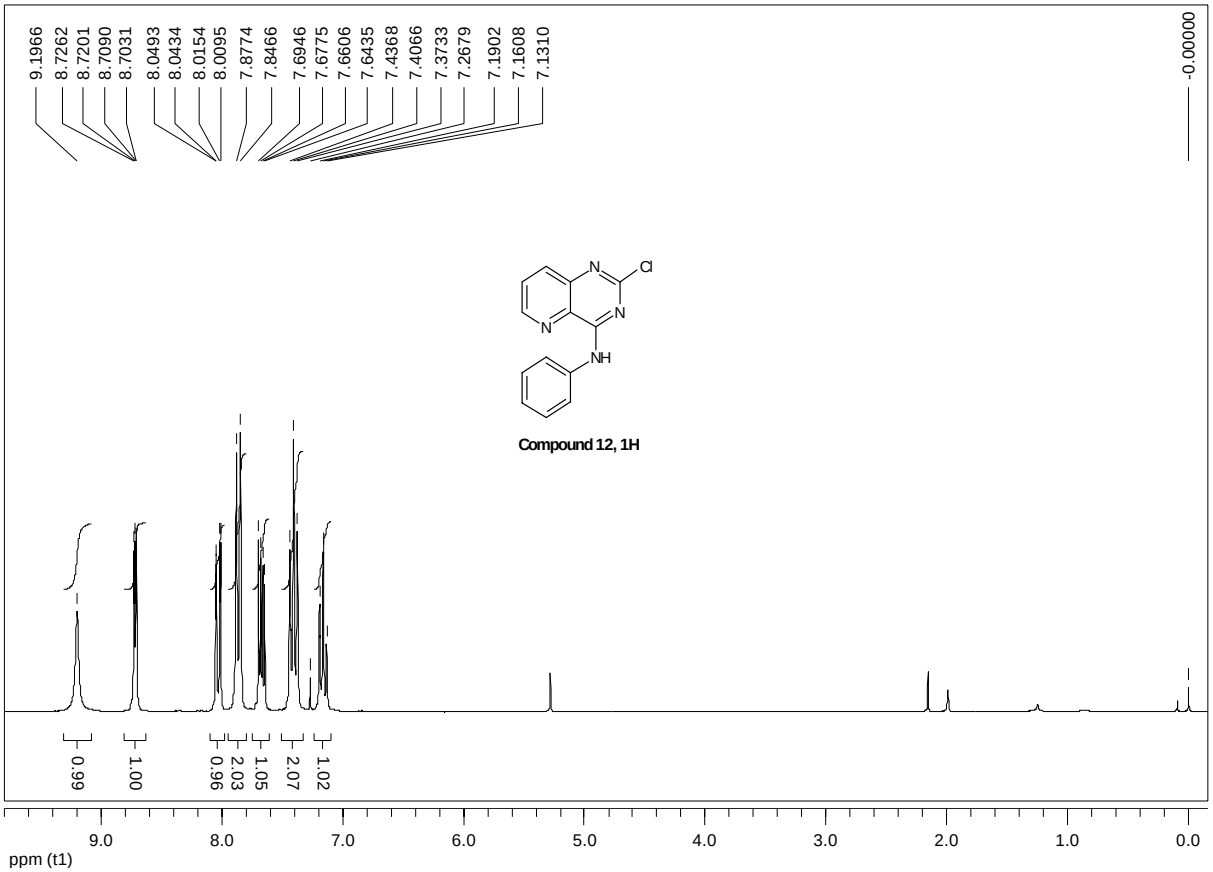
ppm (t1)



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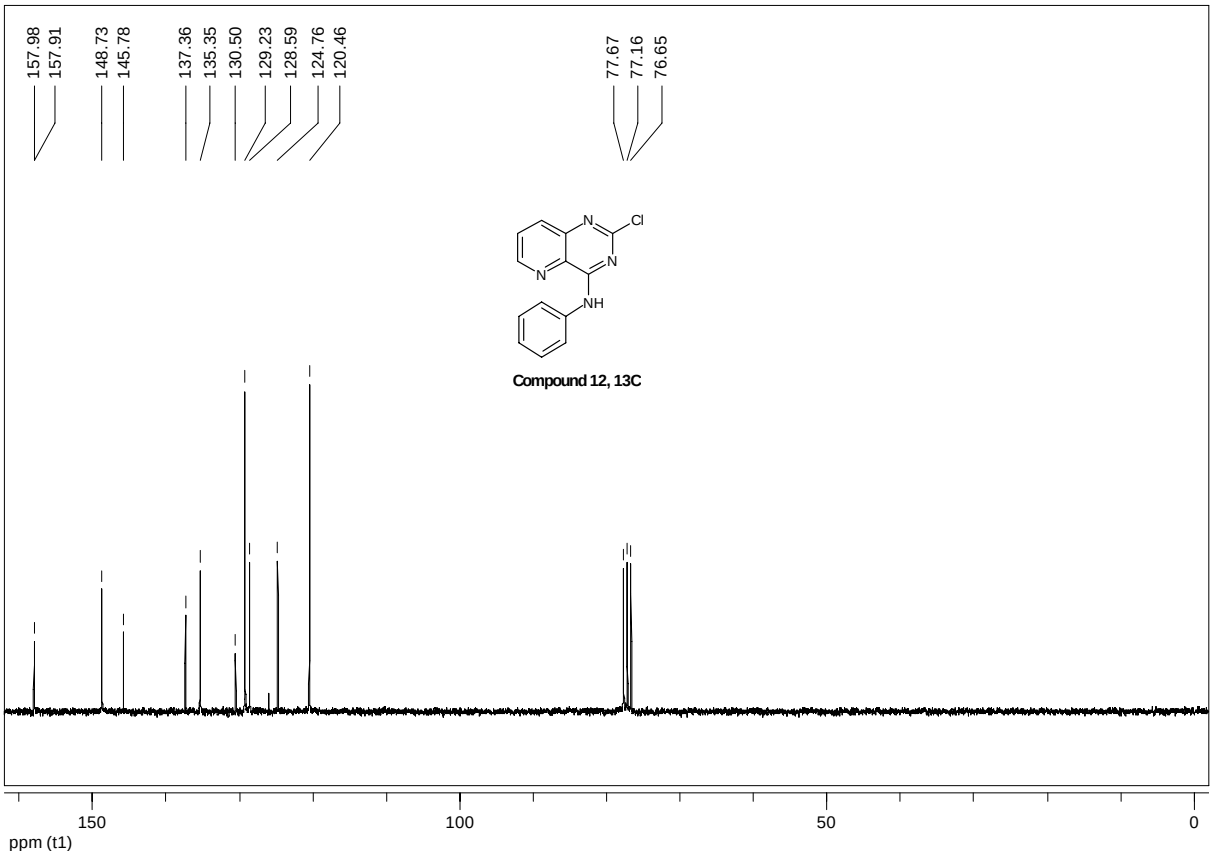

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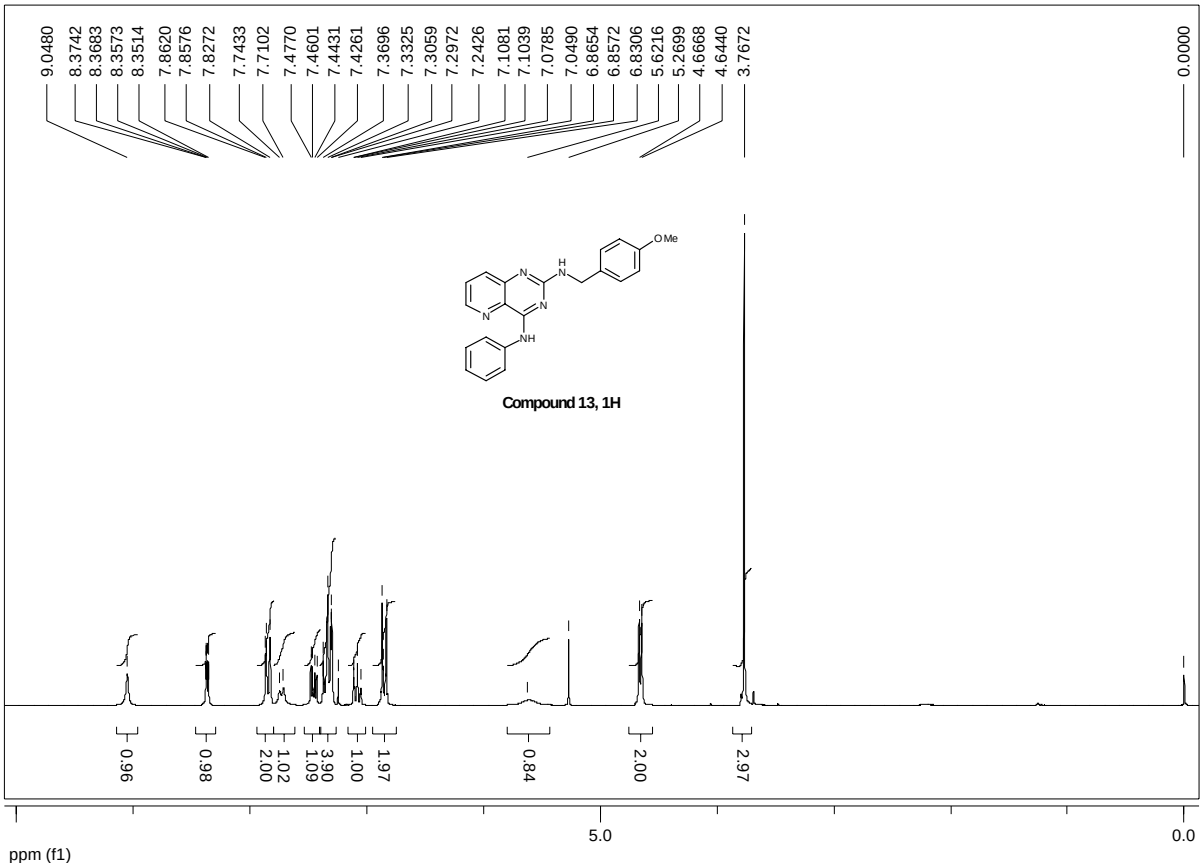
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Compound 13, 1H
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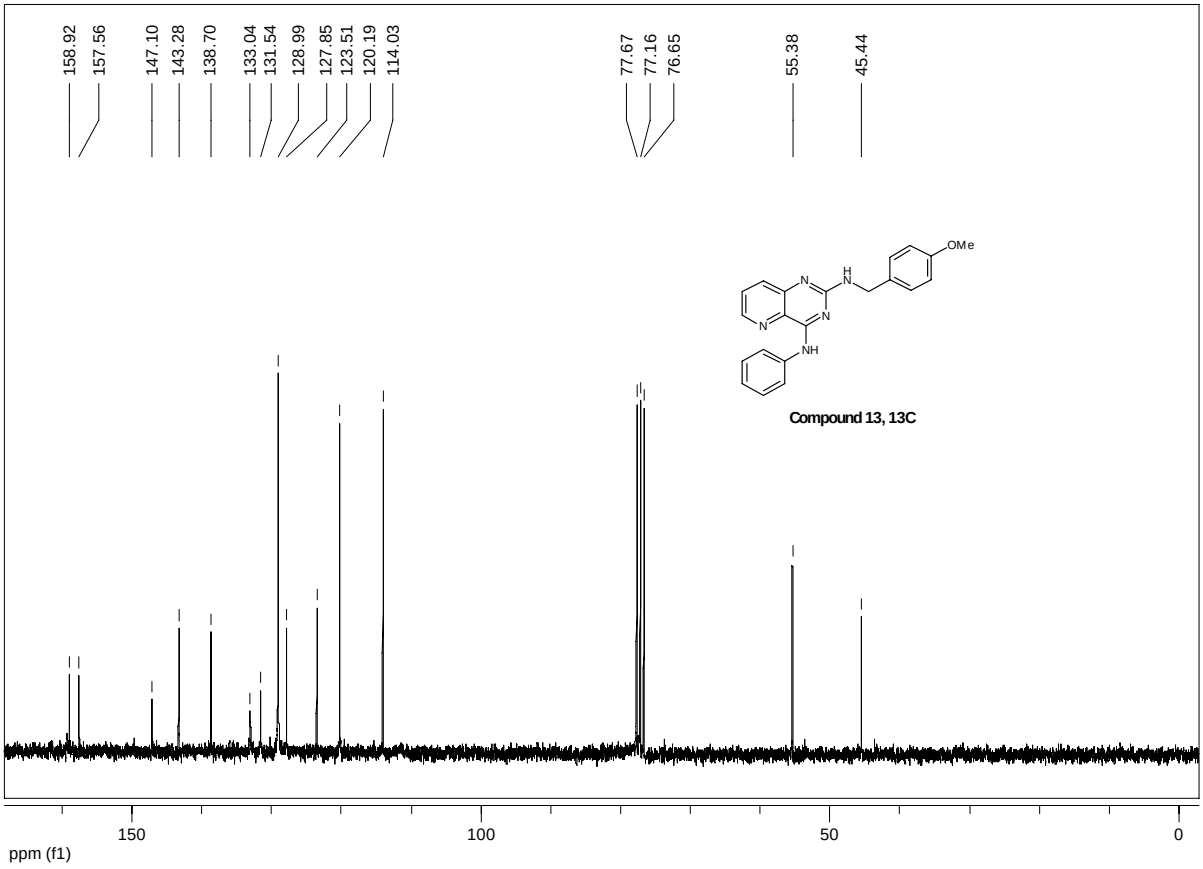
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Compound 13, 13C
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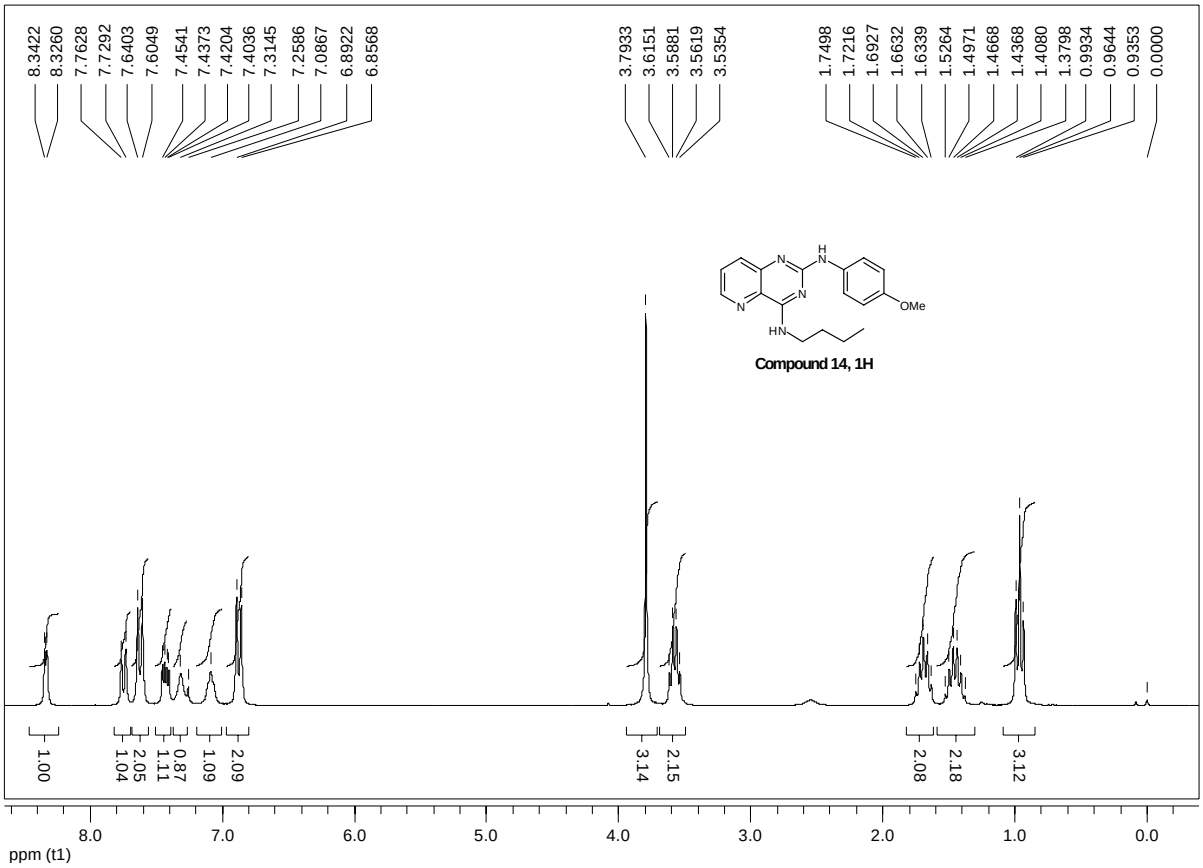
ppm (f1)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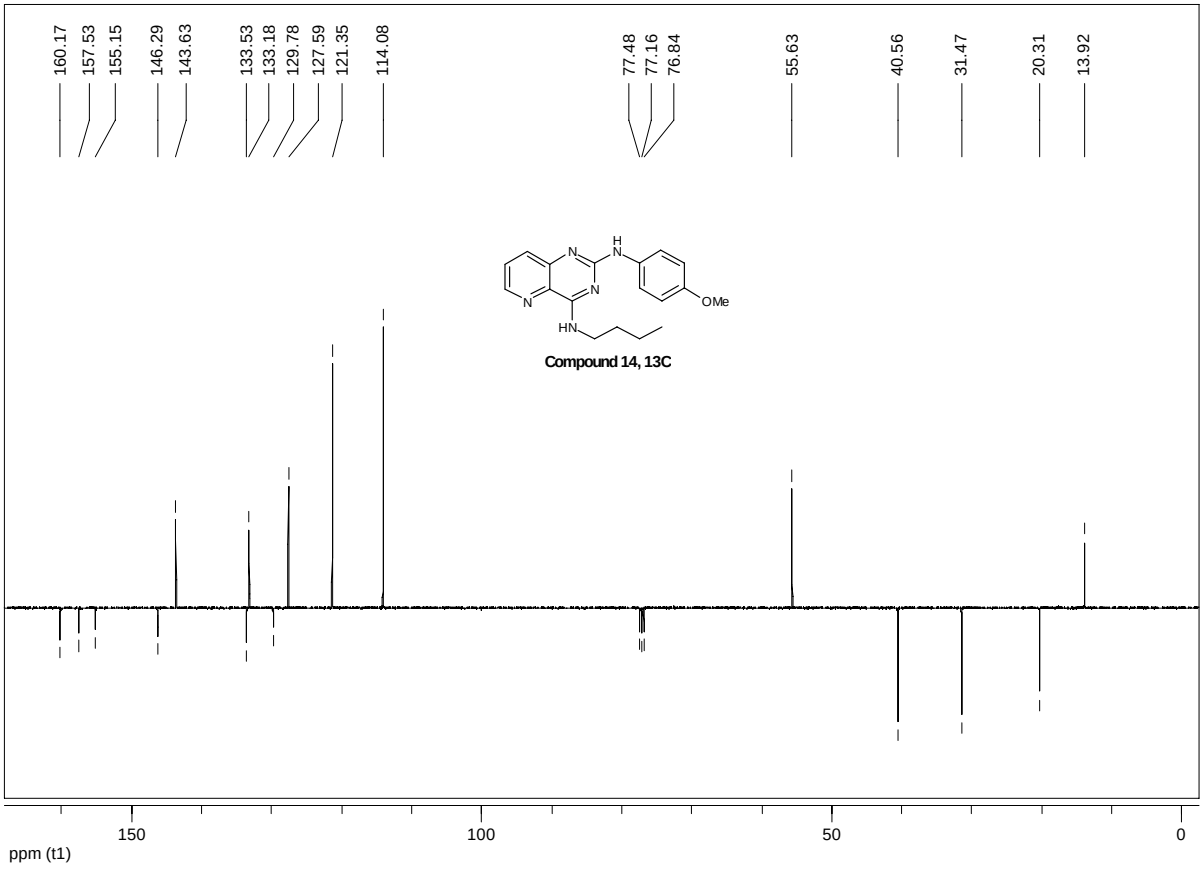
ppm (t1)
Compound 14, 1H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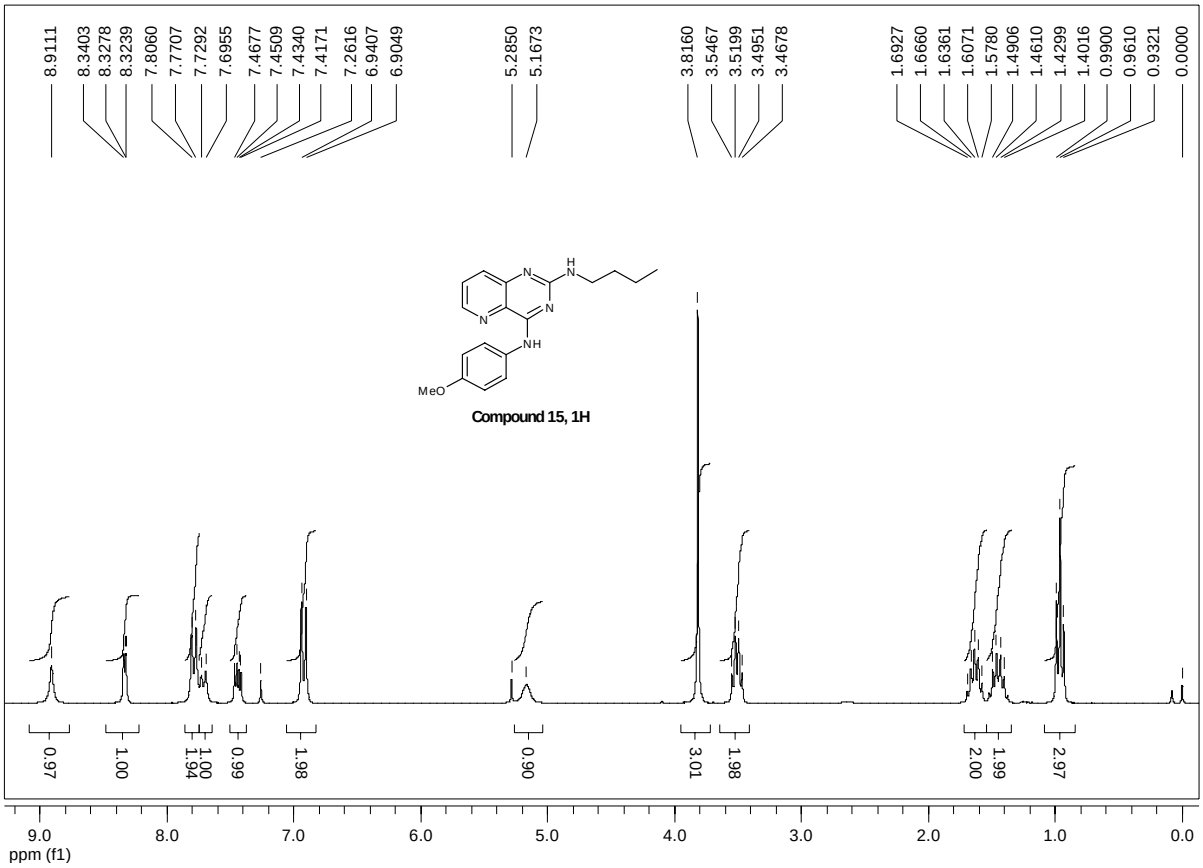
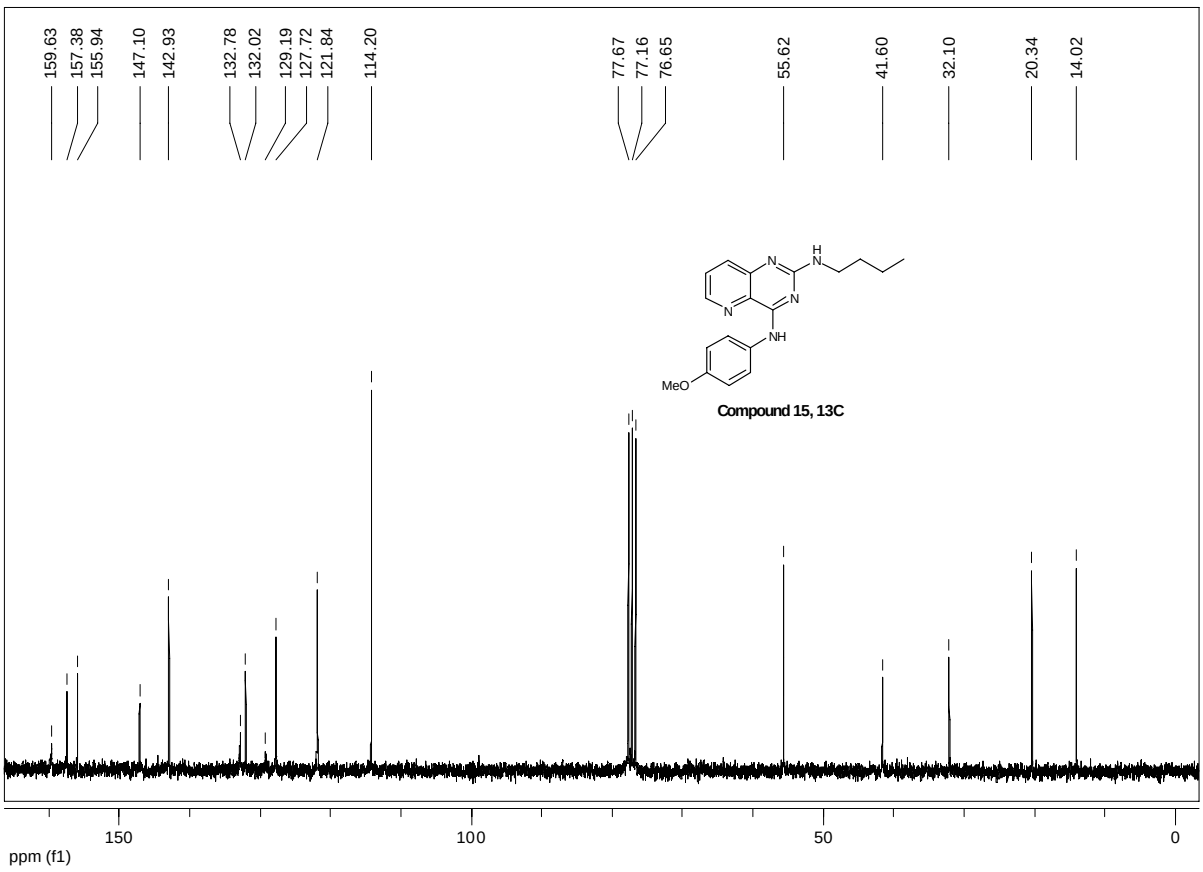
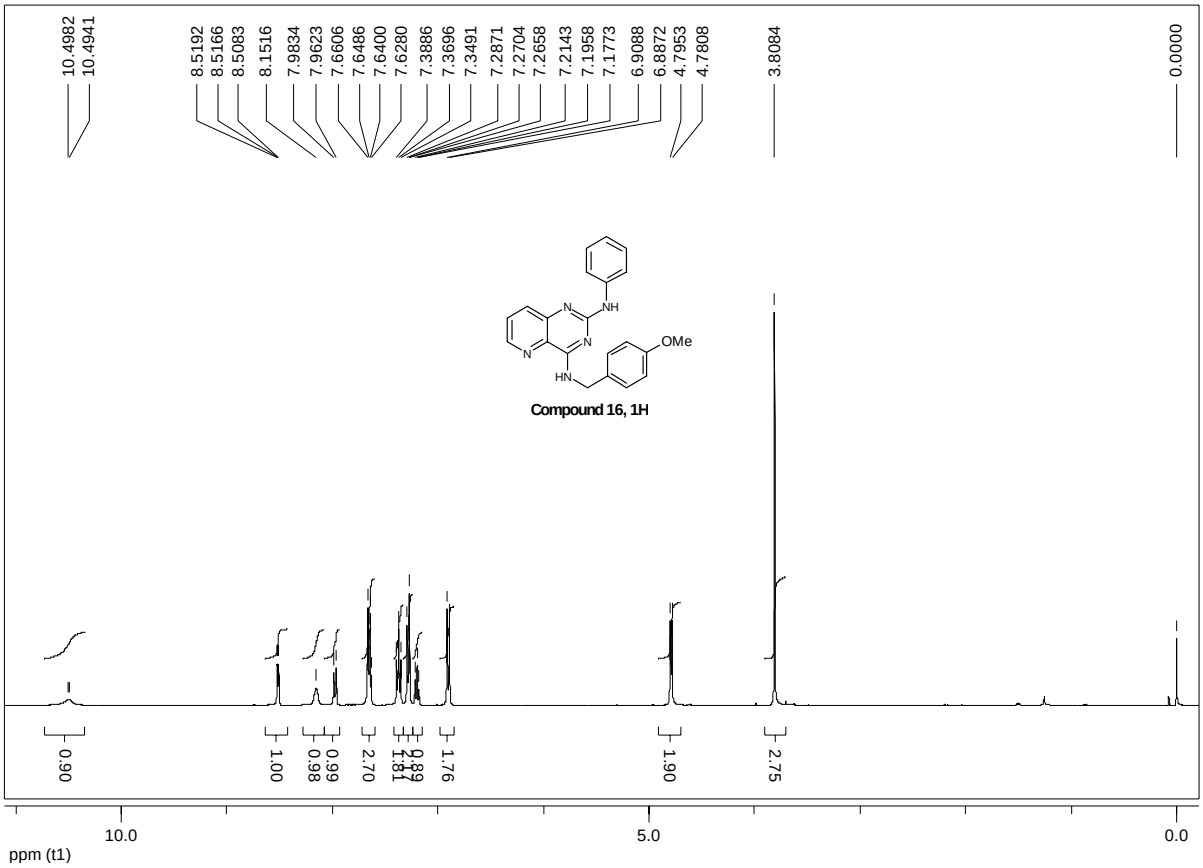
ppm (t1)
Compound 14, 13C



Compound 15, 1H



Compound 15, 13C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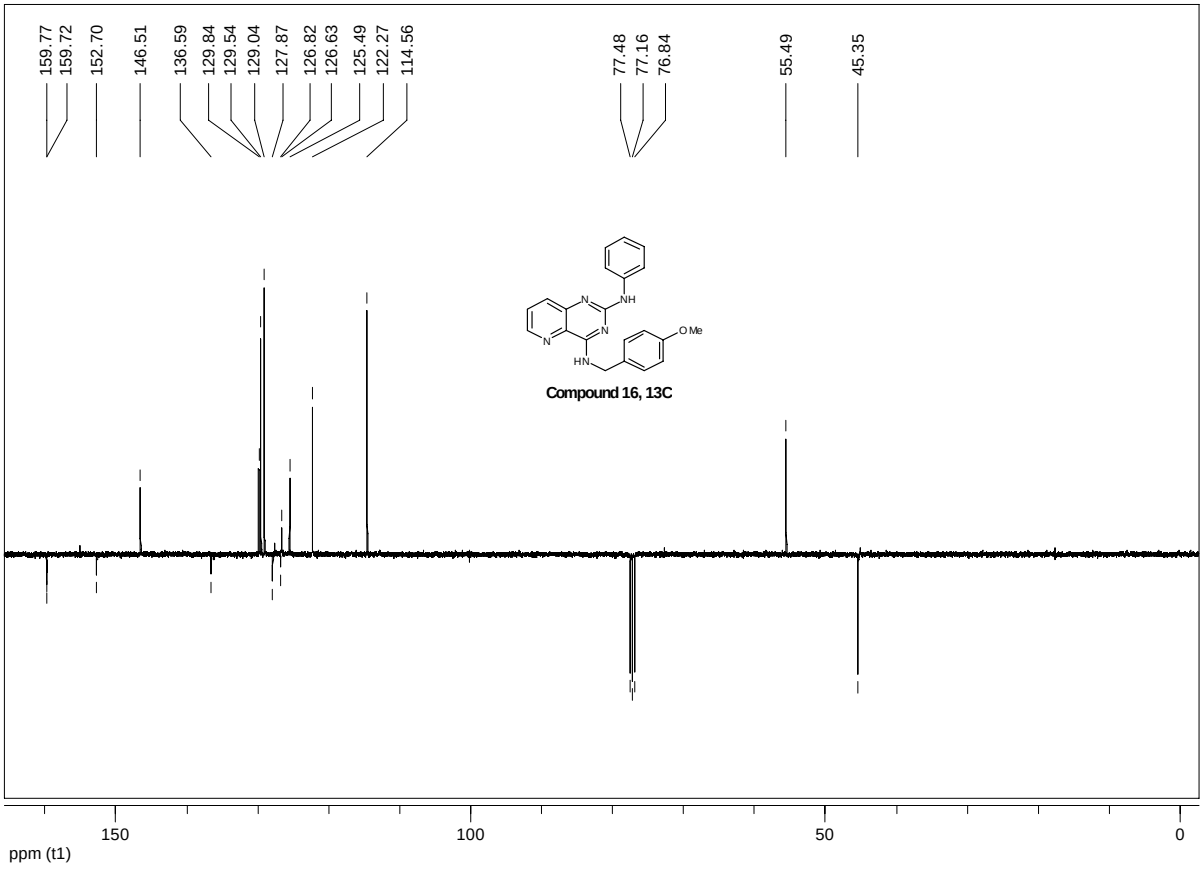
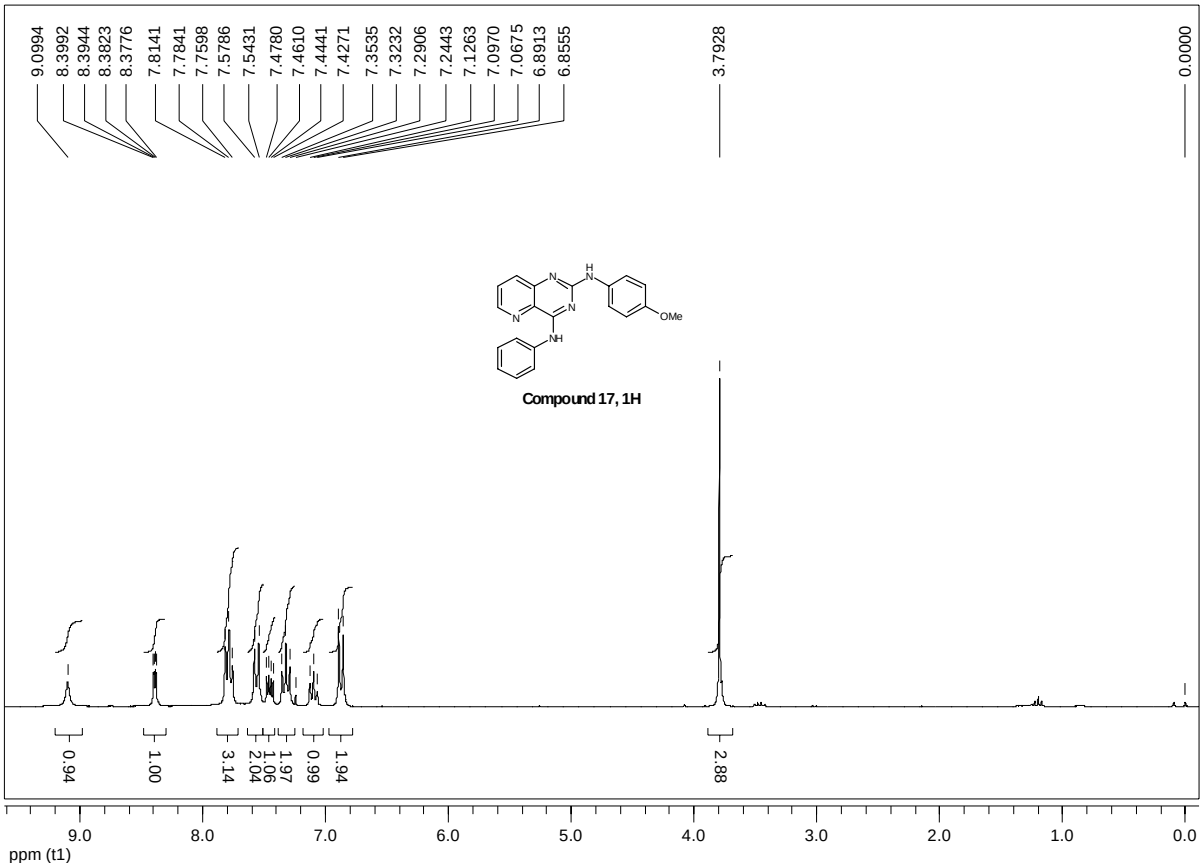
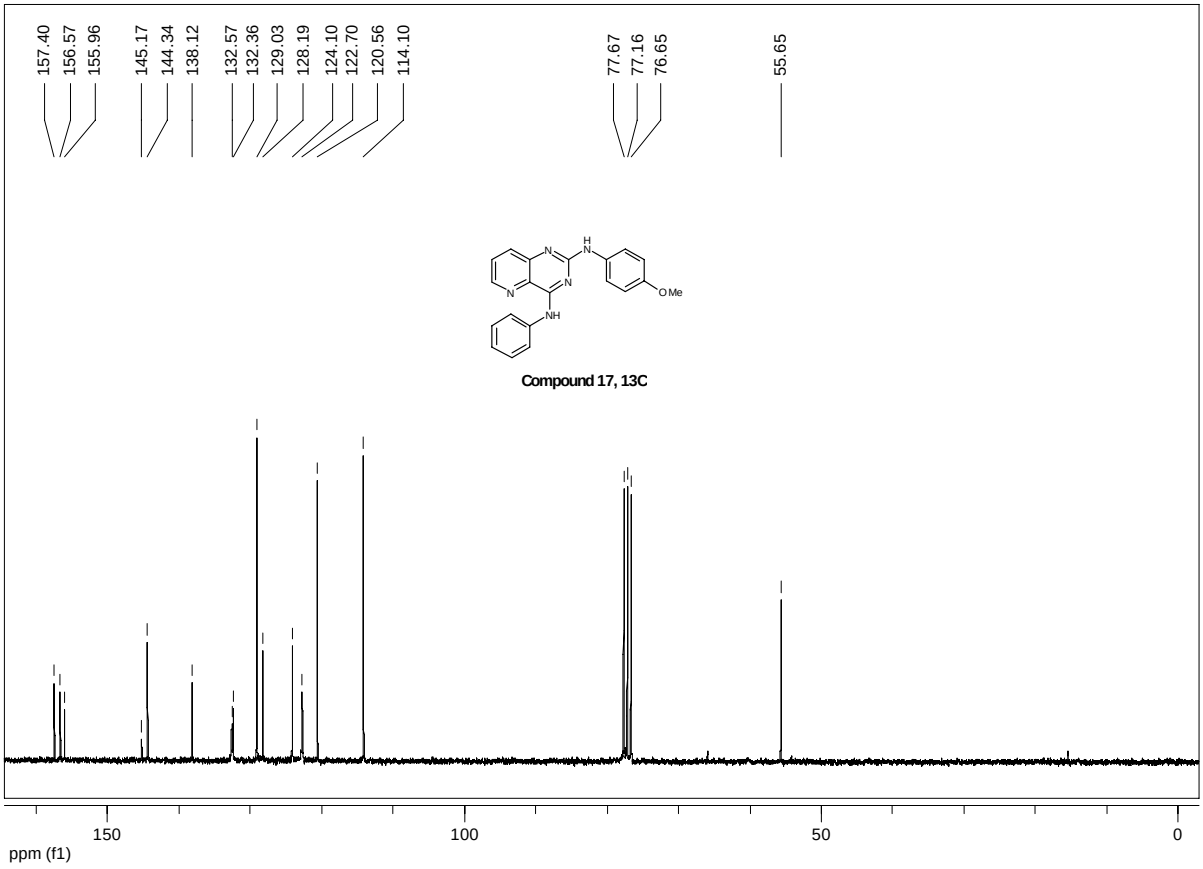
7.9623
7.6606
7.6486
7.6400
7.6280
7.3886
7.3696
7.3491
7.2871
7.2704
7.2658
7.2143
7.1958
7.1773
6.9088
6.8872
4.7953
4.7808
3.8084
0.0000
0.90
1.00
0.98
0.99
2.70
1.81
0.87
1.76
1.90
2.75
10.0
5.0
0.0
ppm (t1)
Compound 16, 1H

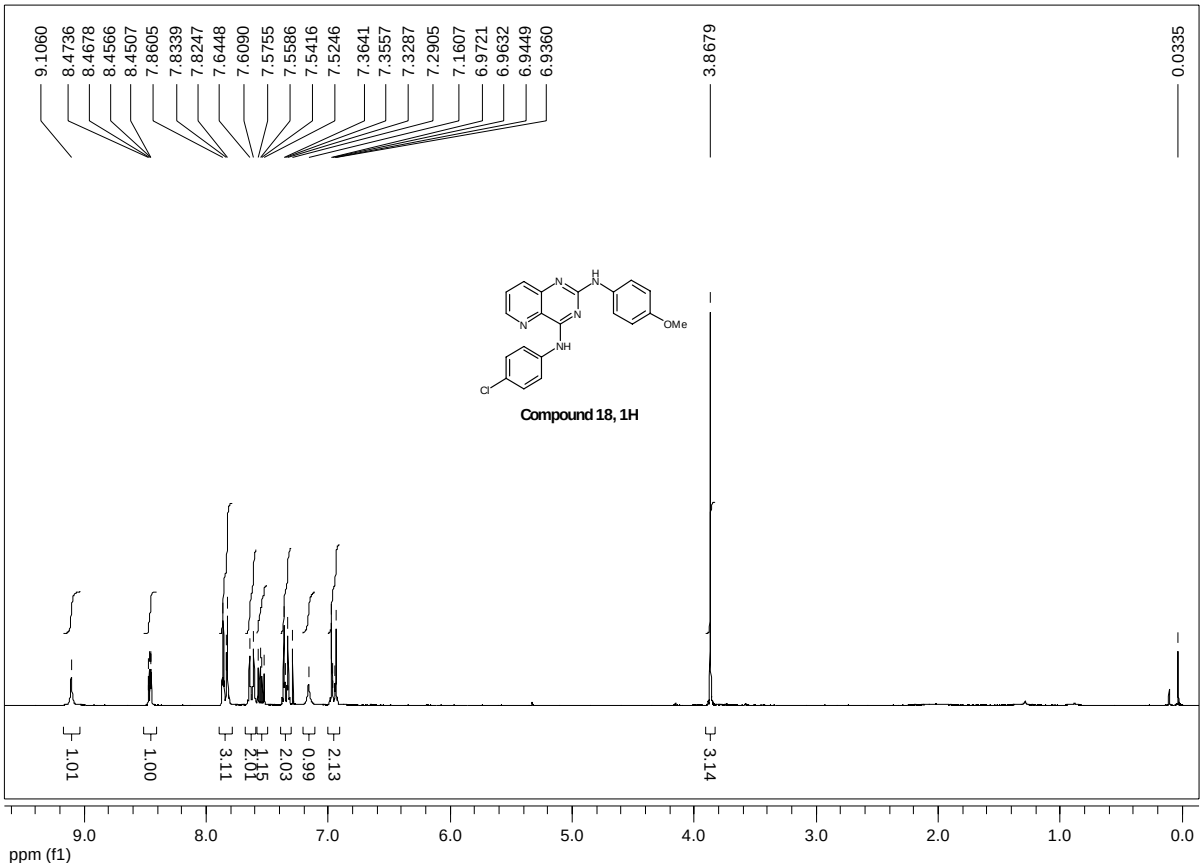

159.77
159.72
152.70
146.51
136.59
129.84
129.54
129.04
127.87
126.82
126.63
125.49
122.27
114.56
77.48
77.16
76.84
55.49
45.35
150
100
50
0
ppm (t1)
Compound 16, 13C



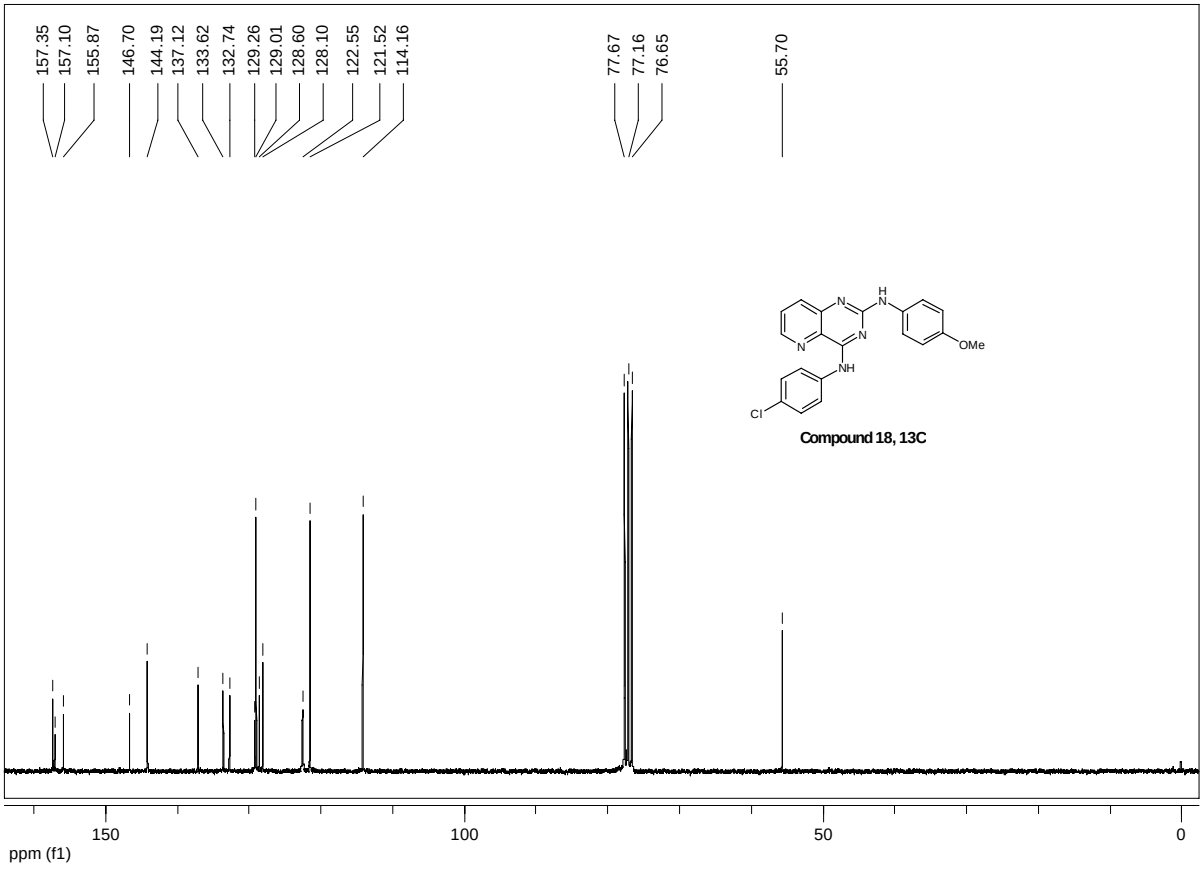
Compound 17, 1H



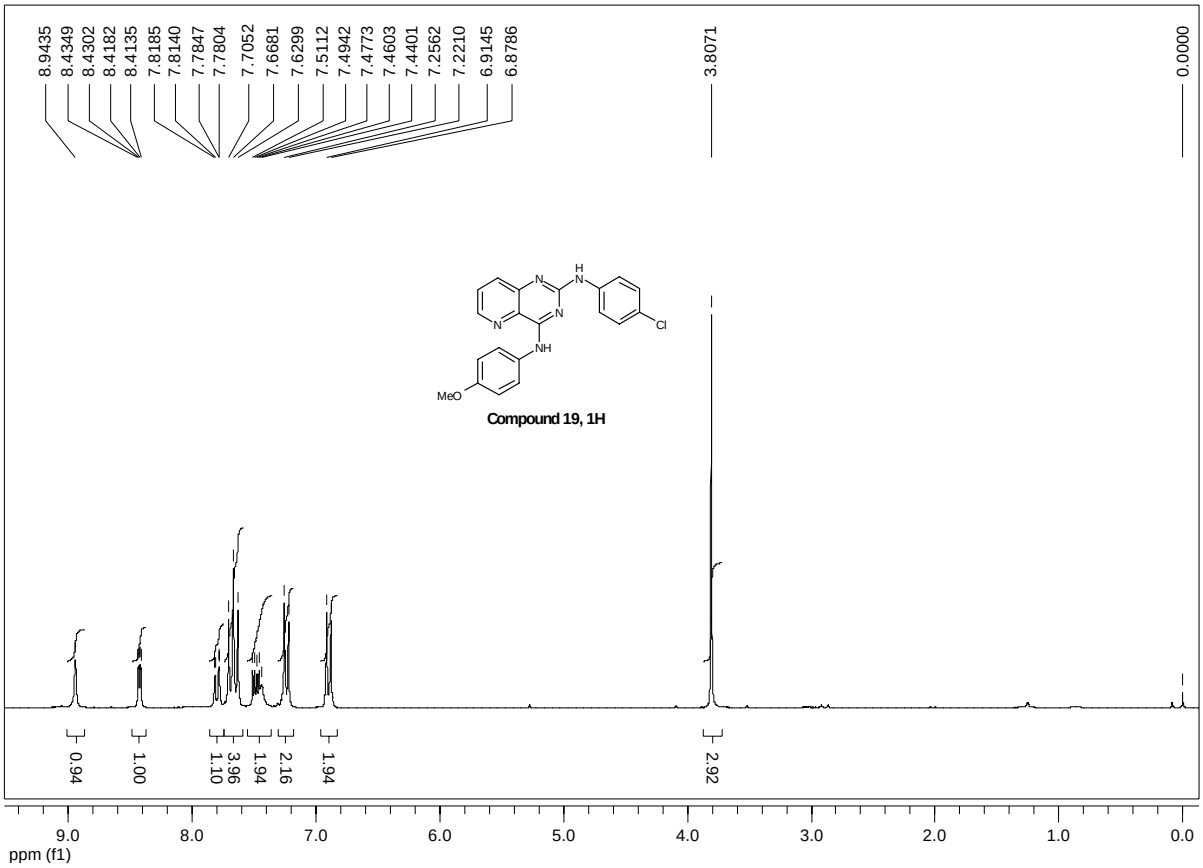
Compound 17, 13C



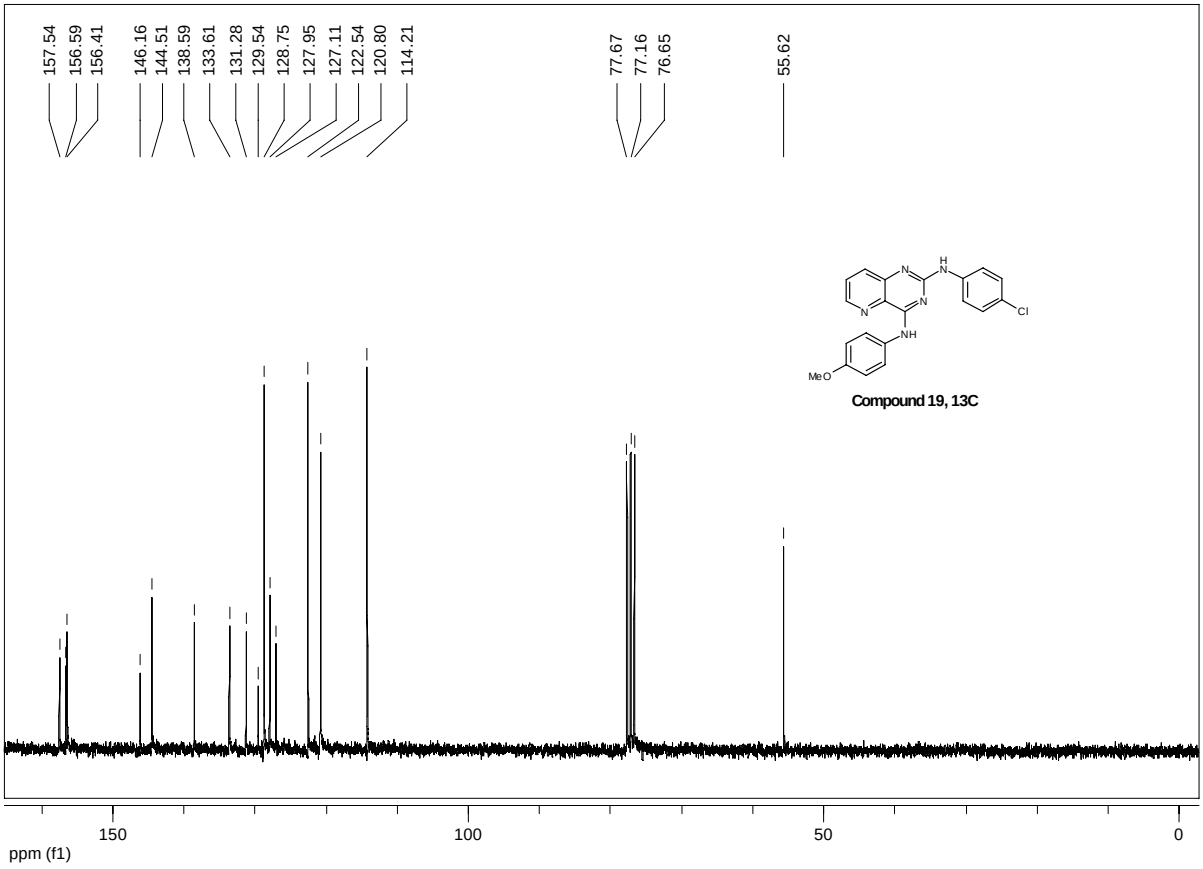
Compound 18, 1H



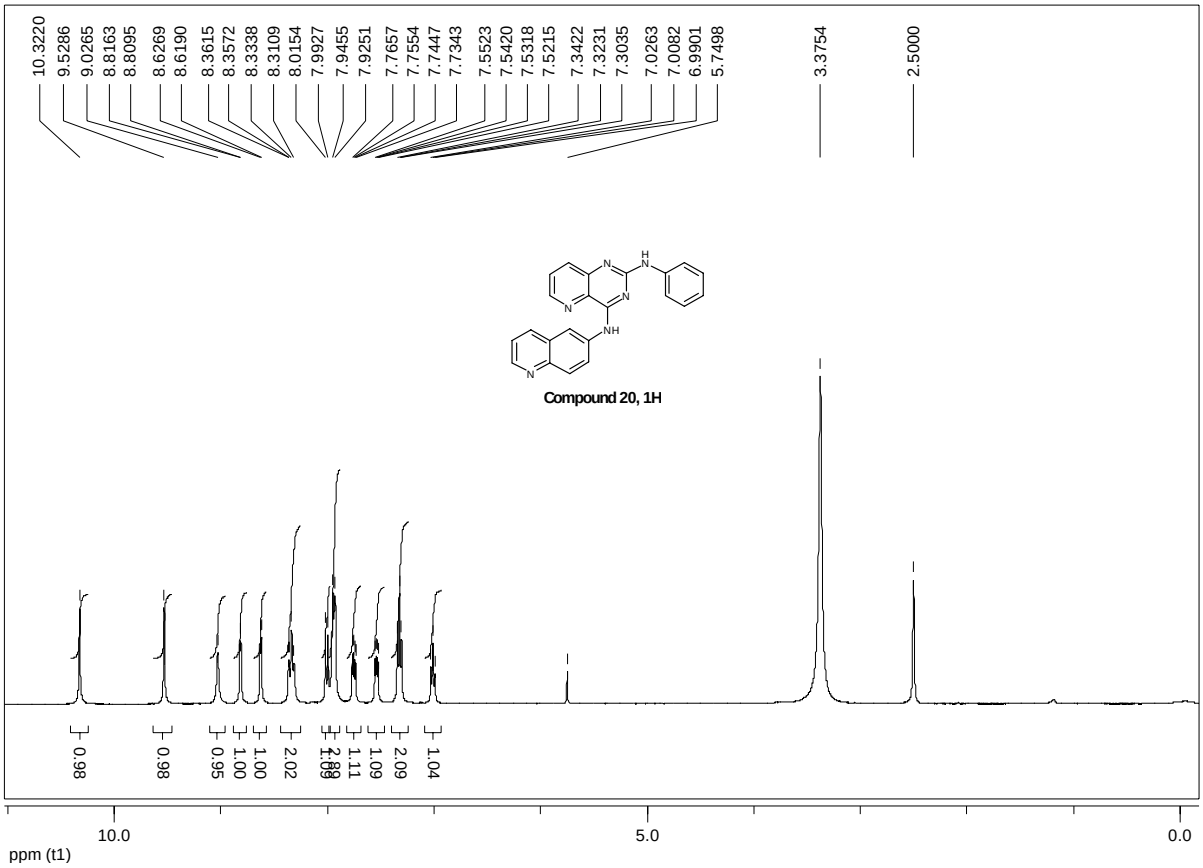
Compound 18, 13C

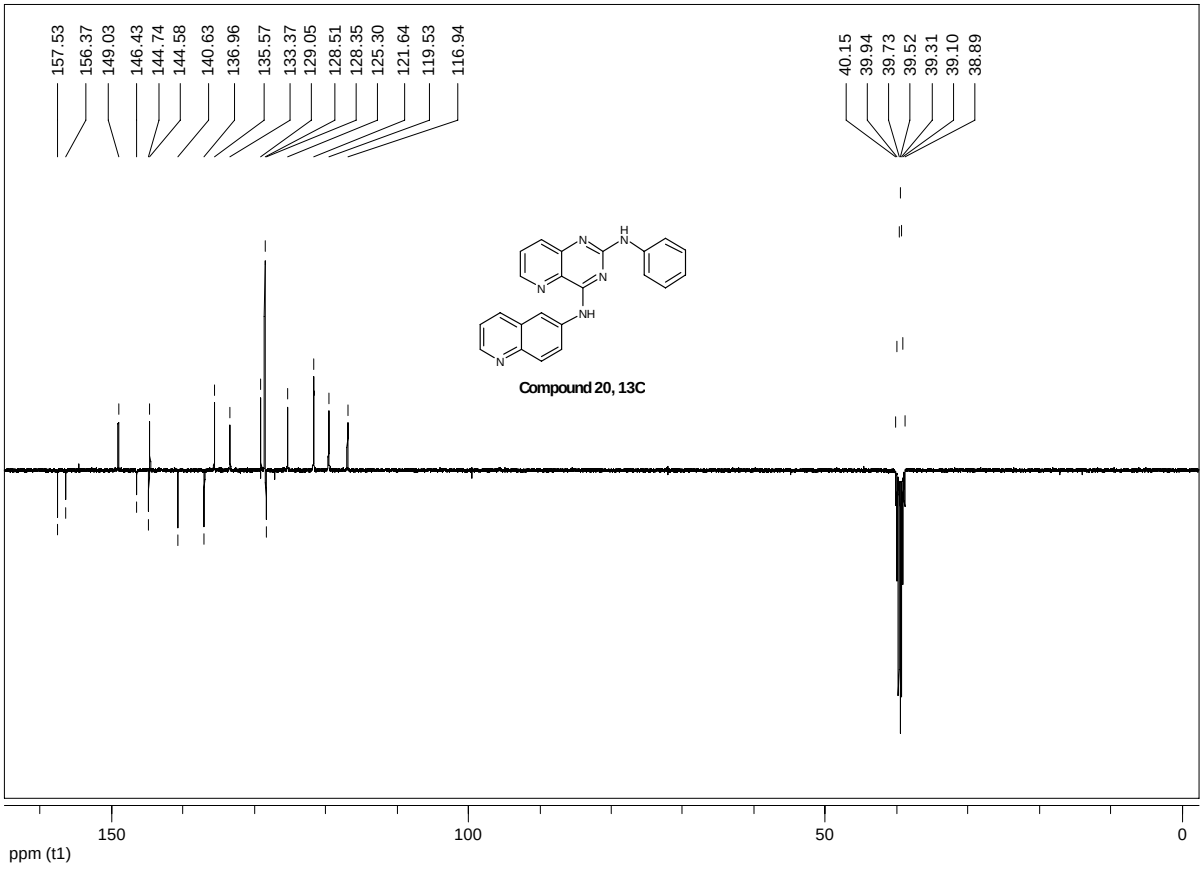


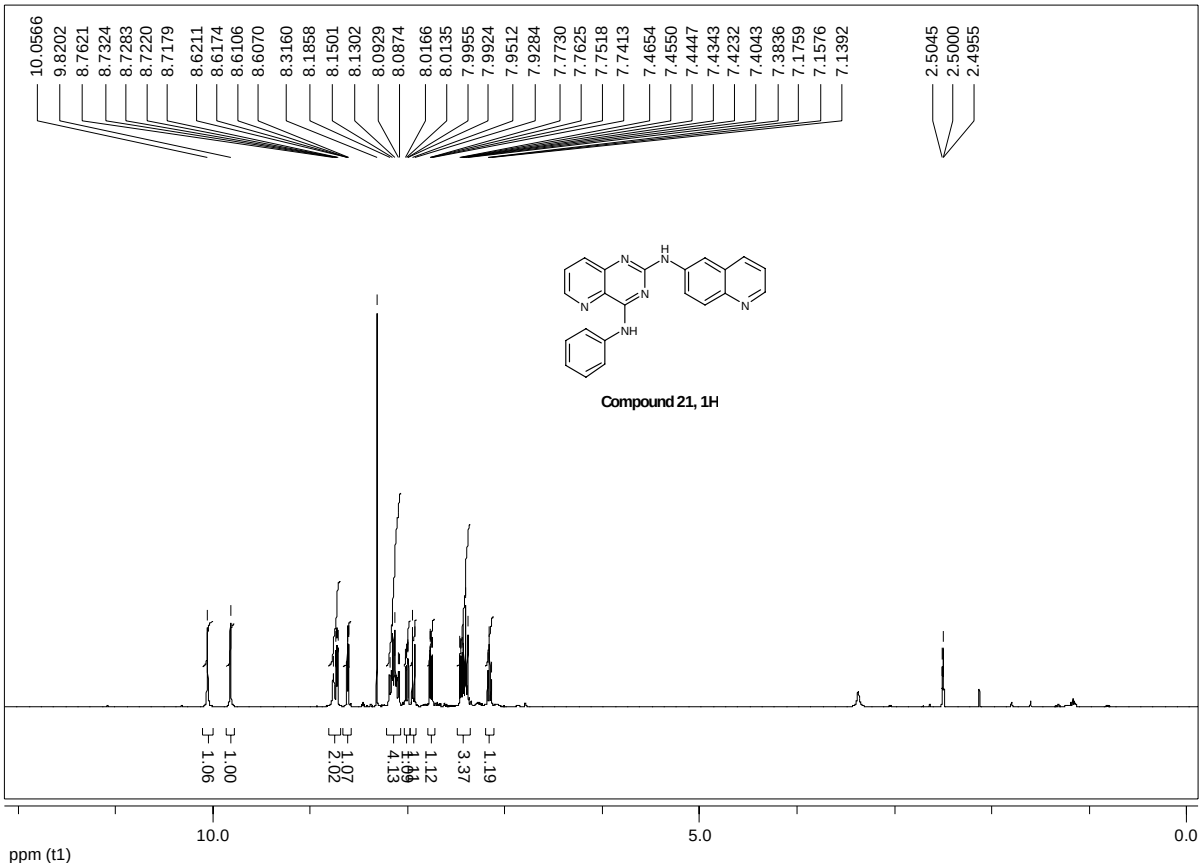
Compound 19, 1H

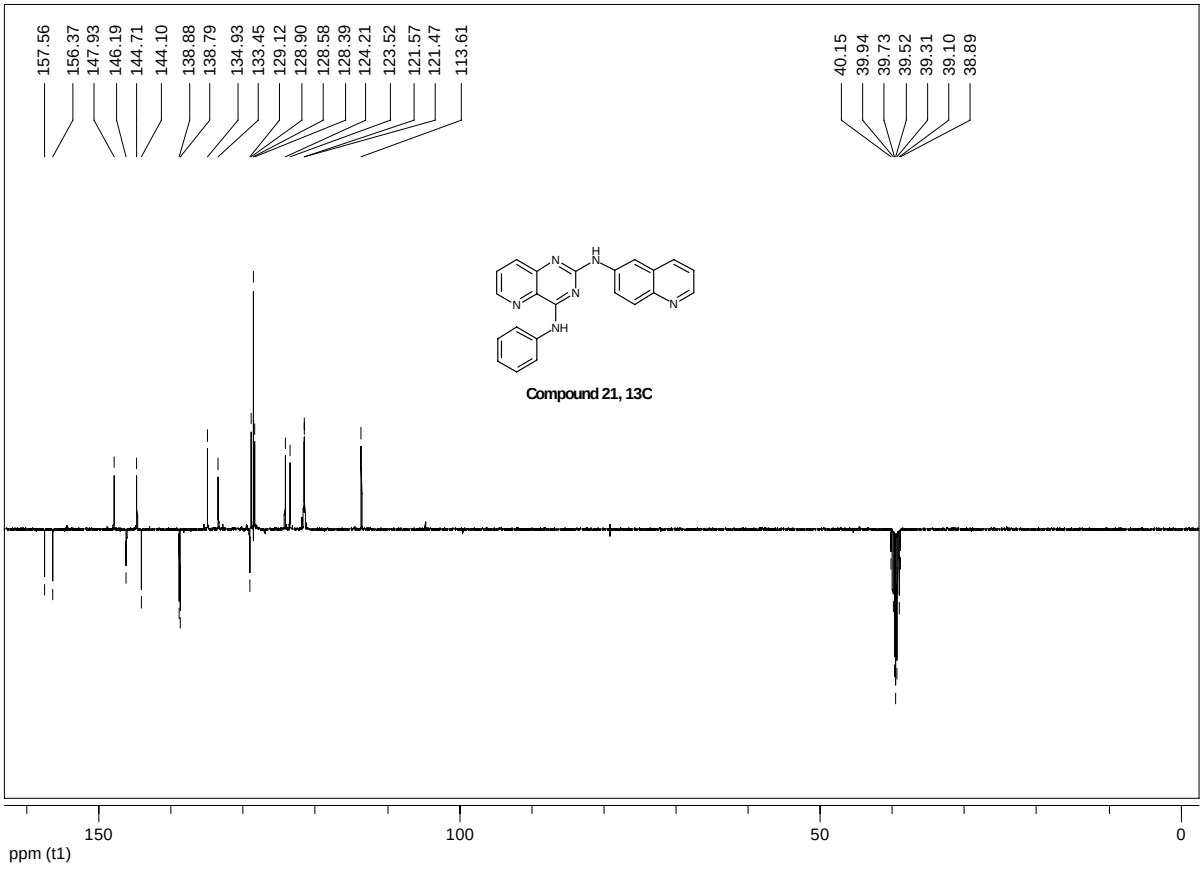


Compound 19, 13C


10.3220
9.5286
9.0265
8.8163
8.8095
8.6269
8.6190
8.3615
8.3572
8.3338
8.3109
8.0154
7.9927
7.9455
7.9251
7.7657
7.7554
7.7447
7.7343
7.5523
7.5420
7.5318
7.5215
7.3422
7.3231
7.3035
7.0263
7.0082
6.9901
5.7498
3.3754
2.5000
0.98
0.98
0.95
1.00
1.00
2.02
2.08
1.11
1.09
2.09
1.04
Compound 20, 1H
10.0
5.0
0.0
ppm (t1)


157.53
156.37
149.03
146.43
144.74
144.58
140.63
136.96
135.57
133.37
129.05
128.51
128.35
125.30
121.64
119.53
116.94
40.15
39.94
39.73
39.52
39.31
39.10
38.89
Compound 20, 13C
150
100
50
0
ppm (t1)


10.0566
9.8202
8.7621
8.7324
8.7283
8.7220
8.7179
8.6211
8.6174
8.6106
8.6070
8.3160
8.1858
8.1501
8.1302
8.0929
8.0874
8.0166
8.0135
7.9955
7.9924
7.9512
7.9284
7.7730
7.7625
7.7518
7.7413
7.4654
7.4550
7.4447
7.4343
7.4232
7.4043
7.3836
7.1759
7.1576
7.1392
2.5045
2.5000
2.4955
Compound 21, 1H
1.06
1.00
2.02
1.07
4.13
1.09
1.12
3.37
1.19
10.0
5.0
0.0
ppm (t1)


157.56
156.37
147.93
146.19
144.71
144.10
138.88
138.79
134.93
133.45
129.12
128.90
128.58
128.39
124.21
123.52
121.57
121.47
113.61
40.15
39.94
39.73
39.52
39.31
39.10
38.89
Compound 21, 13C
150
100
50
0
ppm (t1)