One-Pot Formal [3+2] Annulation of 2-Pyridinyl-Substituted *p*-Quinone Methides and Arynes for the Synthesis of 3-Aryl Pyrido[1, 2-*a*]indoles

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Supporting Information

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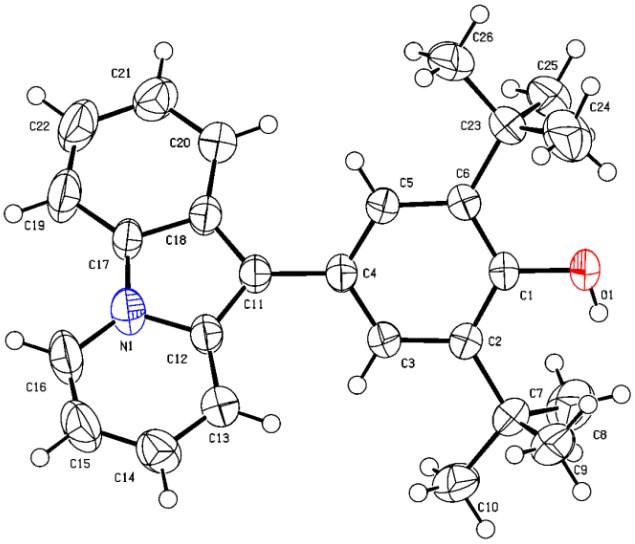
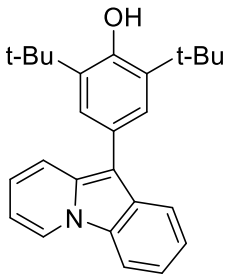
1. X-Ray Data

Crystal structure of the compound **3a**. Thermal ellipsoids are shown at 40% probability level. The crystal of **3a** was achieved by volatilizing a dichloromethane solution of **3a** in the air at room temperature.





3a (CCDC：2306202)

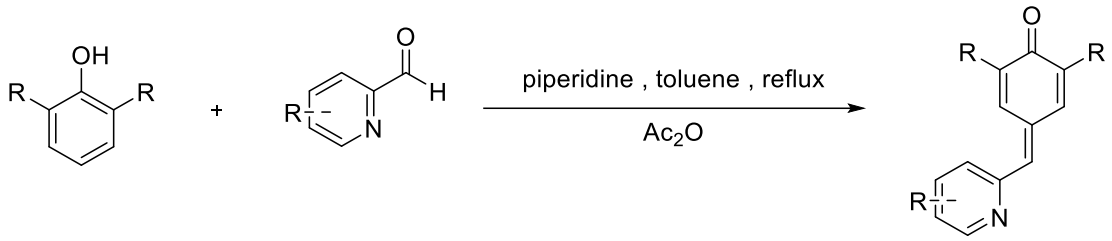
Identification code	cy-2
Empirical formula	$C_{26}H_{29}NO$
Formula weight	371.50
Temperature/K	293.15
Crystal system	triclinic
Space group	P-1
a/Å	9.32650(10)
b/Å	9.32650(10)
c/Å	12.2744(2)
α/°	88.7920(10)
β/°	88.7920(10)
γ/°	80.4880(10)
Volume/Å^3	1052.59(2)
Z	2
ρ_{calc}g/cm^3	1.172
μ/mm^{-1}	0.538
F(000)	400.0
Crystal size/mm^3	0.3 × 0.25 × 0.12
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.204 to 153.058
Index ranges	$-11 \leq h \leq 11$, $-11 \leq k \leq 7$, $-15 \leq l \leq 15$
Reflections collected	13150
Independent reflections	4256 [R_{int} = 0.0255, R_{sigma} = 0.0255]
Data/restraints/parameters	4256/16/260
Goodness-of-fit on F^2	1.110
Final R indexes [I>=2σ (I)]	R_1 = 0.0492, wR_2 = 0.1489
Final R indexes [all data]	R_1 = 0.0557, wR_2 = 0.1572
Largest diff. peak/hole / e Å^{-3}	0.37/-0.26

2. Experimental Section

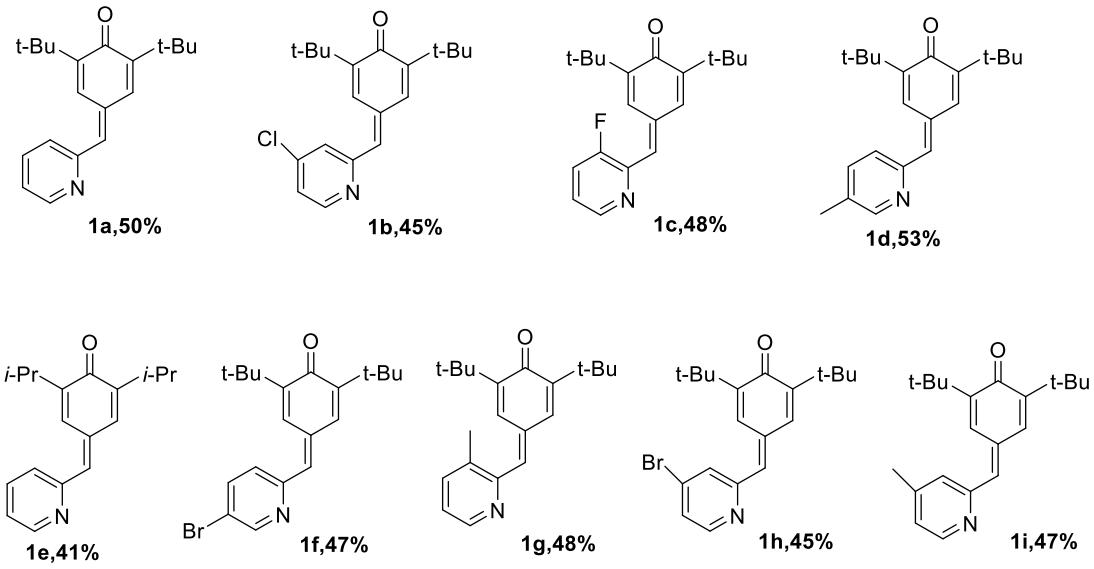
General Information

All reagents including **2a** and all solvents were purchased from commercial suppliers, and were used without further purification. The progress of reactions was monitored by TLC. All heating reactions were carried out in an oil bath. For chromatographic purifications, 200-300 mesh silica gel was used. ^{1}H (400 MHz) and ^{13}C $\{^{1}H\}$ (100 MHz) and ^{19}F (376 MHz) NMR spectra were recorded with tetramethylsilane as an internal standard. HRMS measurements were carried out using the ESI ionization technique with an ESI - FT analyzer. The SC-XRD (Bruker D8 Venture, Germany) was used for the crystal measurement. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. CCDC (for **3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

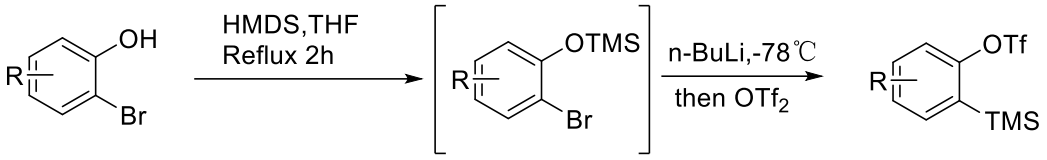
General Procedure for the Synthesis of 2-Pyridinyl-Substituted *p*-Quinone Methides 1a-1i.



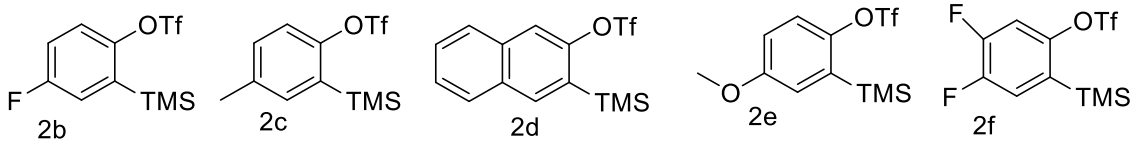
In a Dean-Stark apparatus, a solution of phenols (25.0 mmol) and the corresponding aldehydes (25.0 mmol) in toluene (100 mL) was heated to reflux. Piperidine (50.0 mmol, 4.94 mL) was dropwise added within 1 h. The reaction mixture was continued to reflux for 12 h. After cooling just below the boiling point of the reaction mixture, acetic anhydride (50.0 mmol, 2.55 g) was added and stirring was continued for 15 min. Then the reaction mixture was poured on ice-water (500 mL) and extracted with CH_2Cl_2 (4 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent of the filtrate was removed under reduced pressure. The crude products were purified by flash column chromatography and further recrystallized from n-hexane, affording the desired 2-pyridinyl-substituted *p*-QMs **1a**-**1i**.[1]



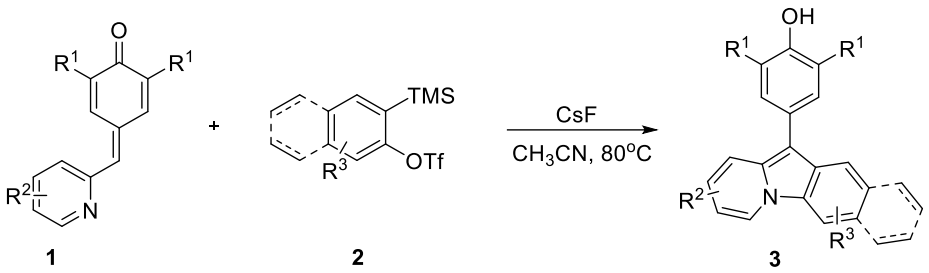
General Procedure for the Synthesis of aryne precursors 2b-2e.



To a solution of *o*-bromophenol (10 mmol) in anhydrous THF (30 mL) was added HMDS (4.2 mL, 2 equiv) under N_2 atmosphere. The reaction mixture was refluxed for 2 h. After cooling to room temperature, the crude product was attained by removing the solvent in vacuo and used for the next step without isolation. The crude product was dissolved in anhydrous THF (30 mL) under N_2 atmosphere and cooled to -78 ℃, then *n*-BuLi (4.4 mL, 1.1 equiv, 2.5 M in hexane) was added dropwise to the mixture and the reaction was stirred for 40 min at -78 ℃. After that, Tf_2O (3.24 mL, 1.2 equiv) was added to the mixture dropwise at -78 °C and the reaction was stirred for another 40 min. The reaction mixture was quenched with cold sat. $NaHCO_3$ aq at -78 °C and warmed to room temperature. Then the aqueous layer was extracted with Et_2O three times. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the residue was purified by silica gel column chromatography to afford aryne precursors **2b-2e**.[2]



General Procedure for the Synthesis of 3a-3af.



Unless otherwise noted, A dried 10 mL round flask was charged with CH_3CN (3 mL), 2-pyridinyl-substituted *p*-QMs **1** (0.3 mmol), aryne precursors **2** (0.45 mmol), CsF (0.137g, 0.9 mmol). The reaction mixture was stirred at 80℃ for 4 h under air. After the completion of reaction monitored by TLC, the mixture was diluted with saturated salt water (5 mL) accompanying by stirring. The organic layer was separated and the aqueous layer were extracted with CH_2Cl_2 (3x15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel to give the desired product **3**.

Gram Scale Synthesis Method of 3a

Unless otherwise noted, A dried 100 mL round flask was charged with CH_3CN (35 mL), 2-pyridinyl-substituted *p*-QMs (1.47 g, 5.0 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2.24 g, 7.5 mmol), CsF (1.52 g, 10 mmol). The reaction mixture was stirred at 80℃ for 4 h under air. After the completion of reaction monitored by TLC, the mixture was diluted with saturated NaCl solution accompanying by stirring. The organic layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel to give the desired product **3a** (1.71 g, 92%).

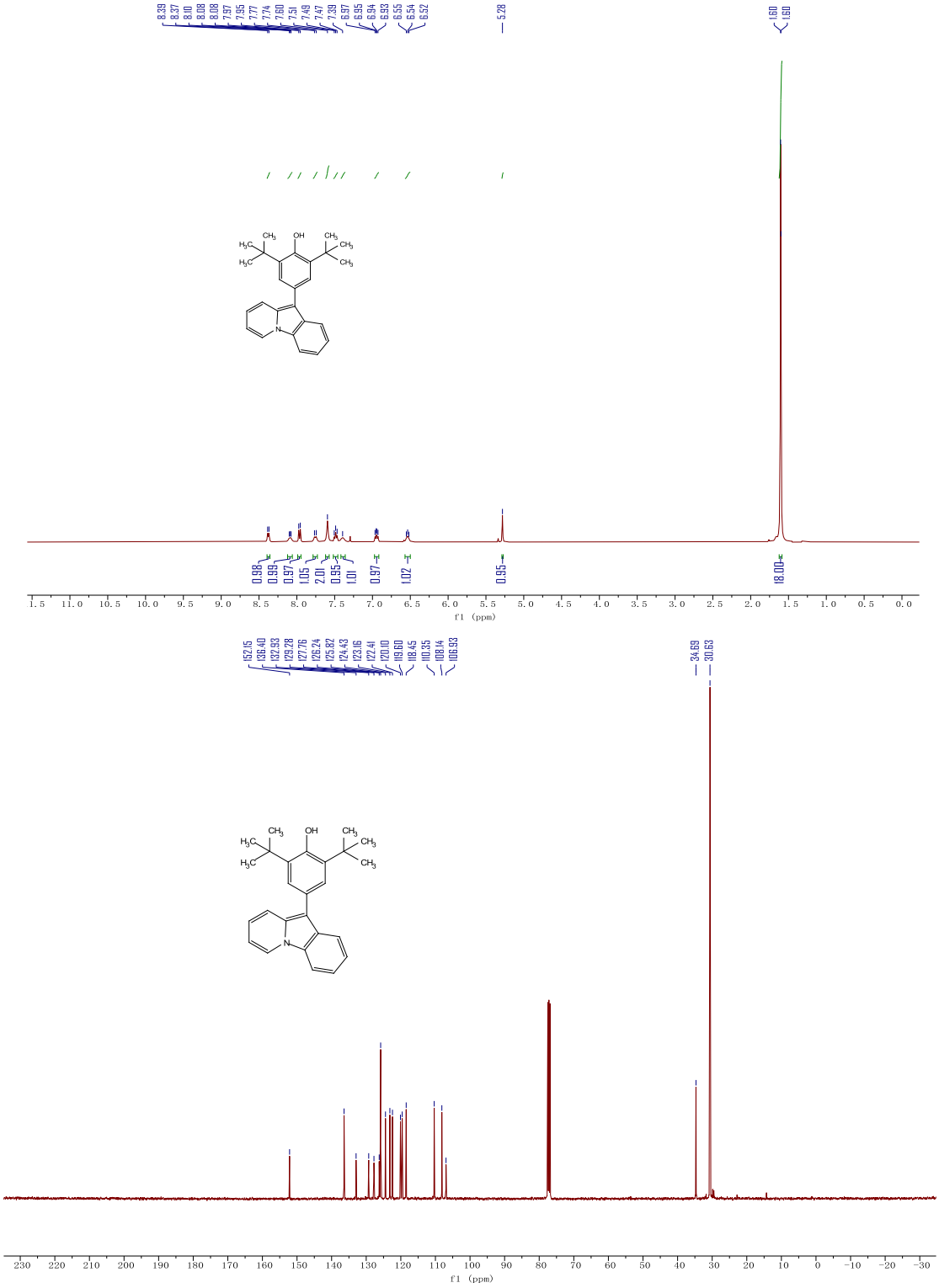
Reference

1 (a) F. Ahmad, P. K. Ranga, Y. A. Pankhade, S. Fatma, A. Gouda and R. V. Anand, *Chem. Commun*., 2022, **58**, 13238–13241; (b) B. Xiong, S. Xu, Y. Liu, K. W. Tang and W. Y. Wong, *J. Org. Chem.*, 2021, **86**, 1516−1527.

2 H.-F. Jiang, Y.-Z. Hang and W.-F. Xiong, *Org. Lett*., 2019, **21**, 345-349.

4. ^{1}H (400 MHz, $CDCl_3$), $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$) and ^{19}F (376 MHz, $CDCl_3$) NMR Spectra of the Products

2,6-di-tert-butyl-4-(pyrido[1,2-a]indol-10-yl)phenol (3a)



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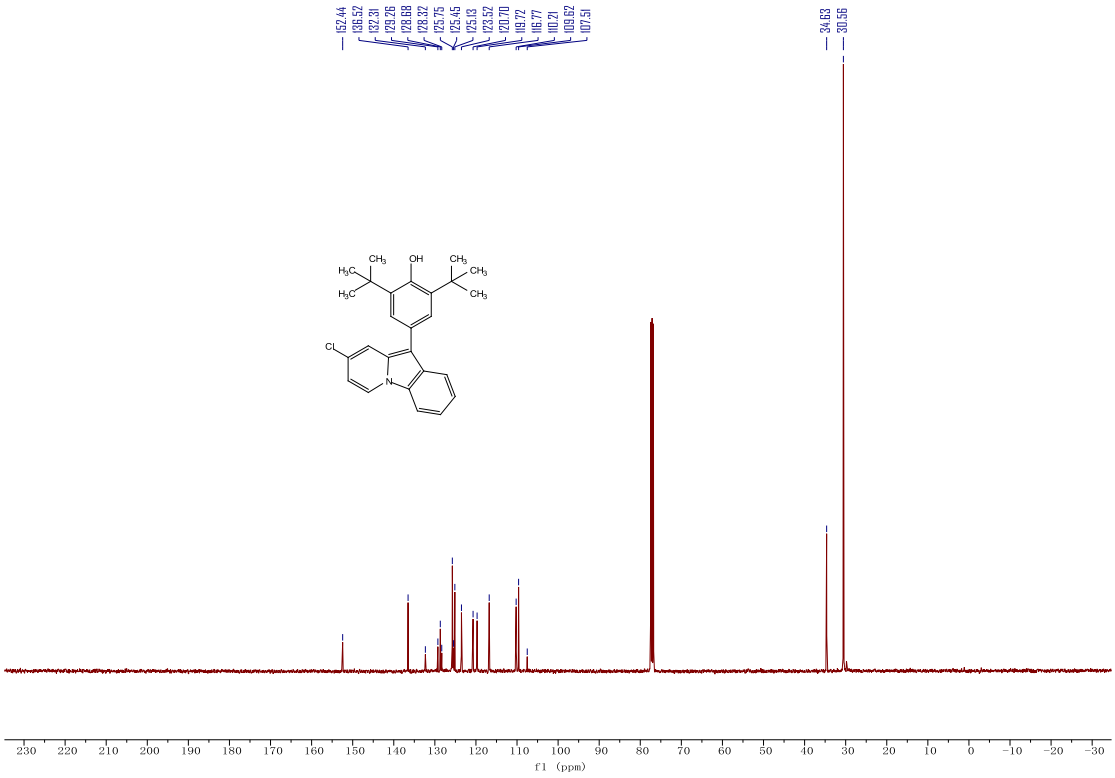
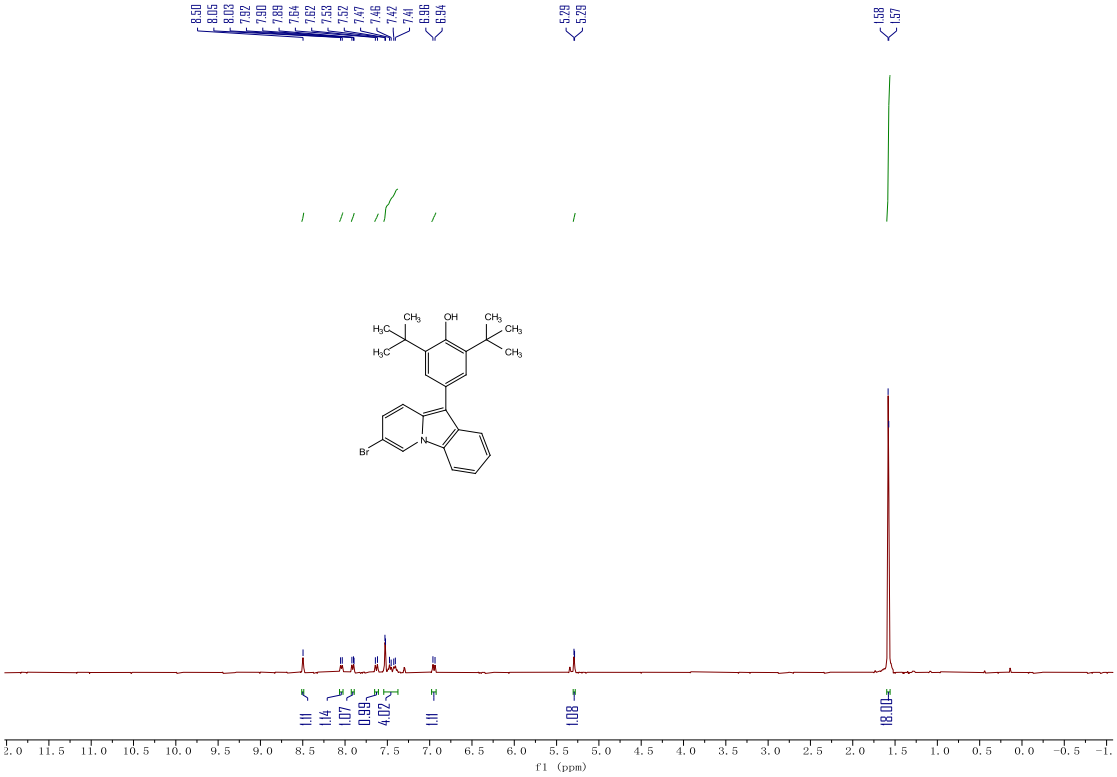
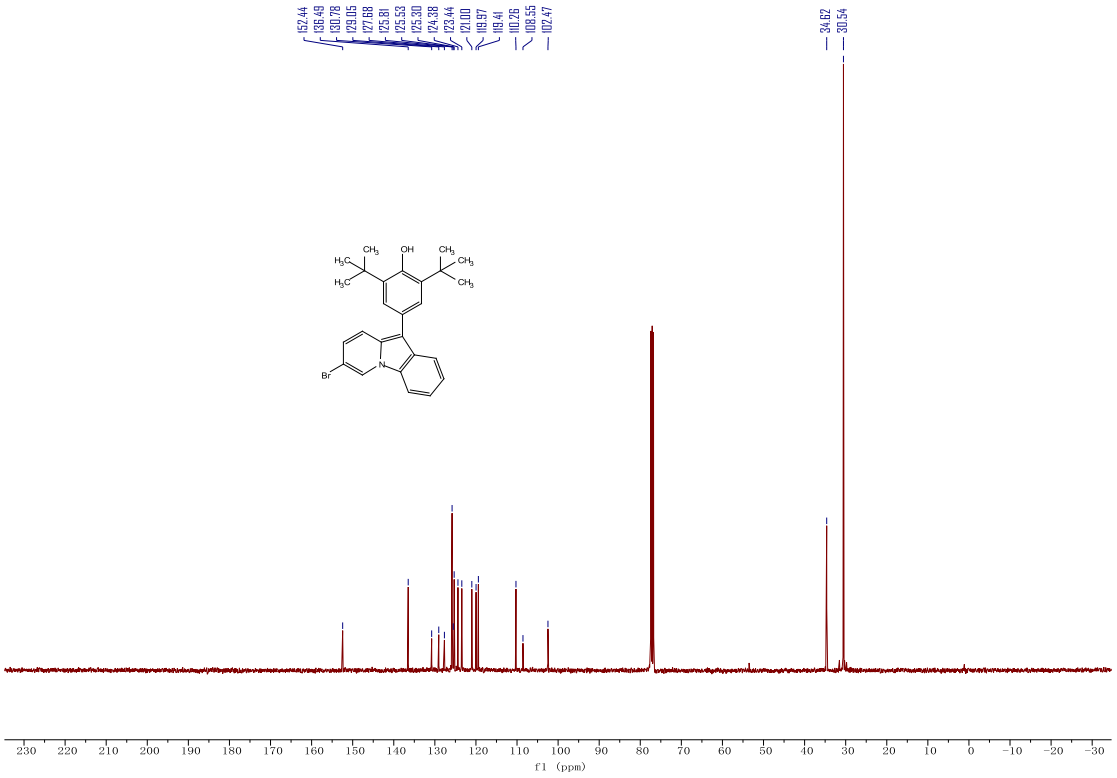


4-(7-bromopyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3c)





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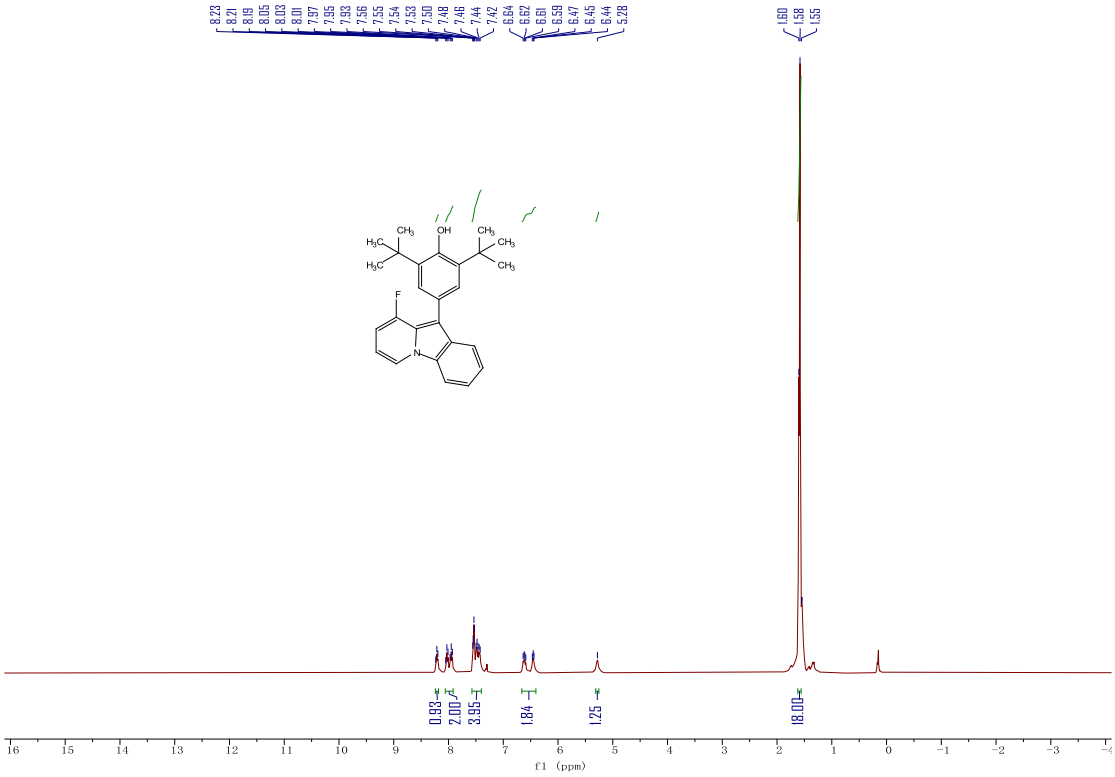

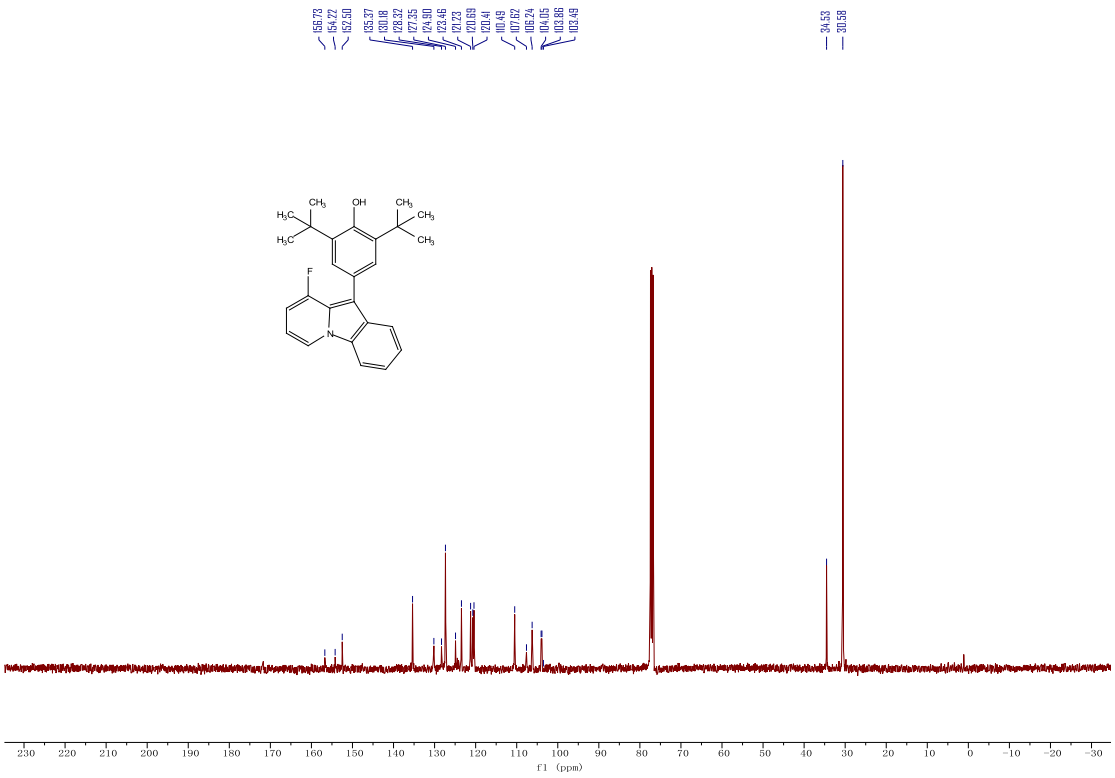

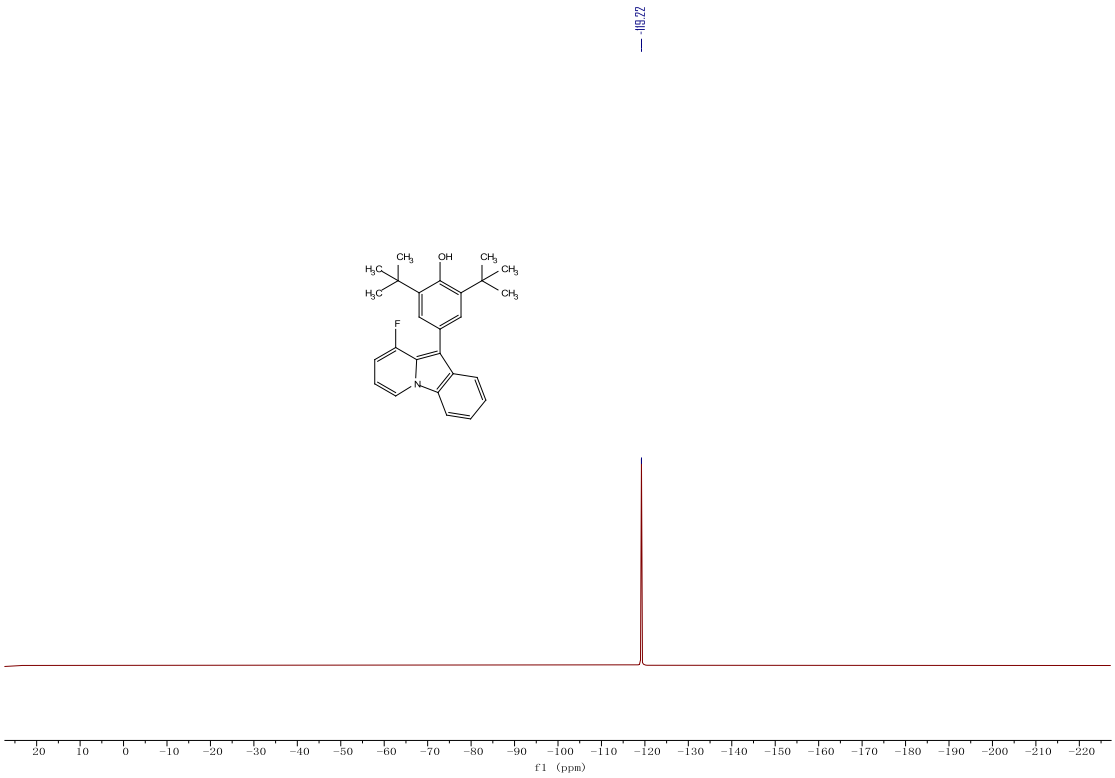
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H3C
CH3
H3C
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F
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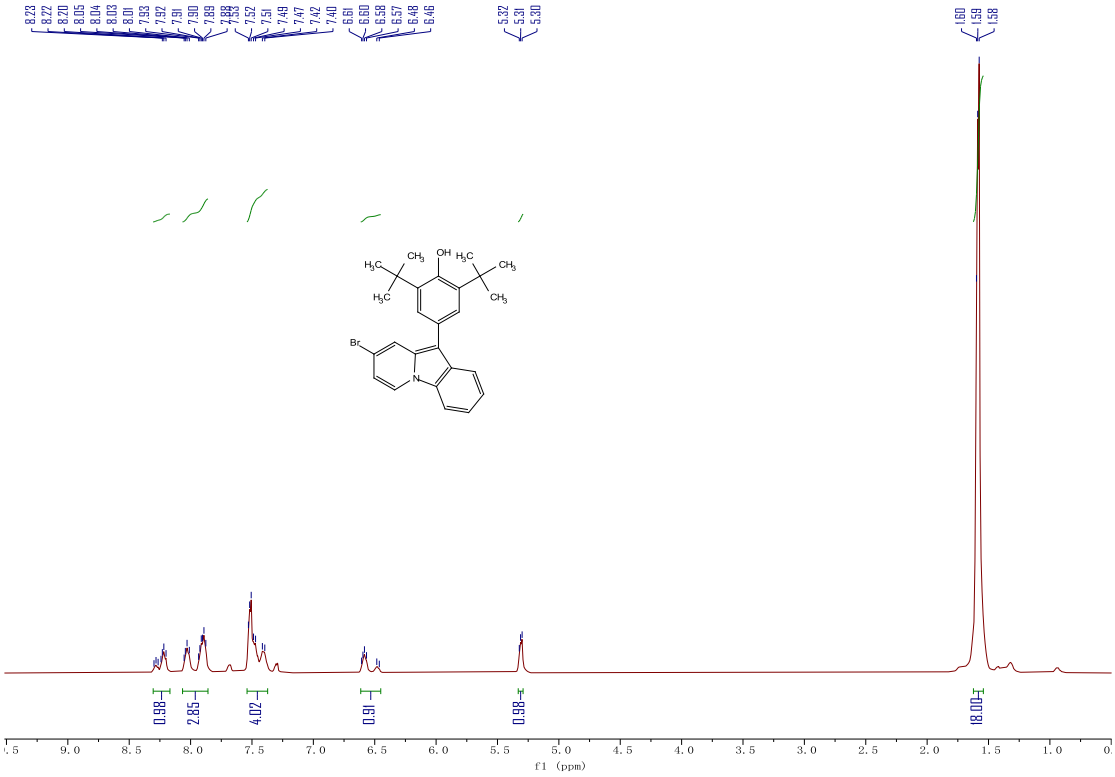
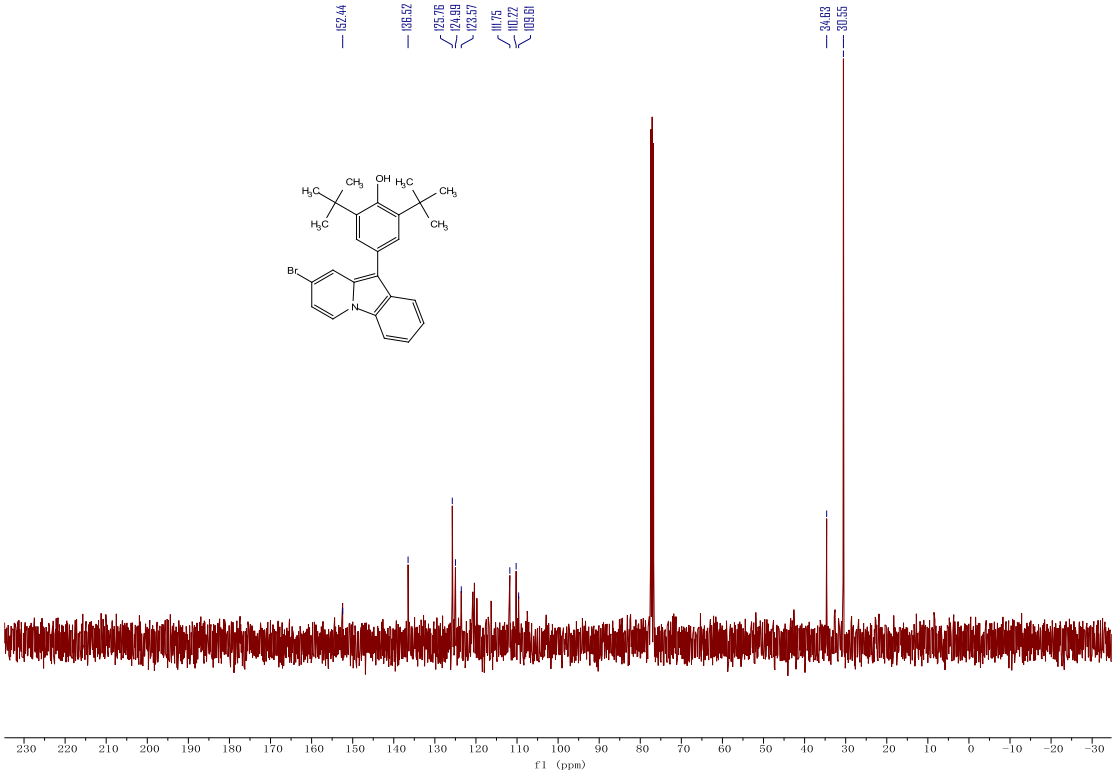
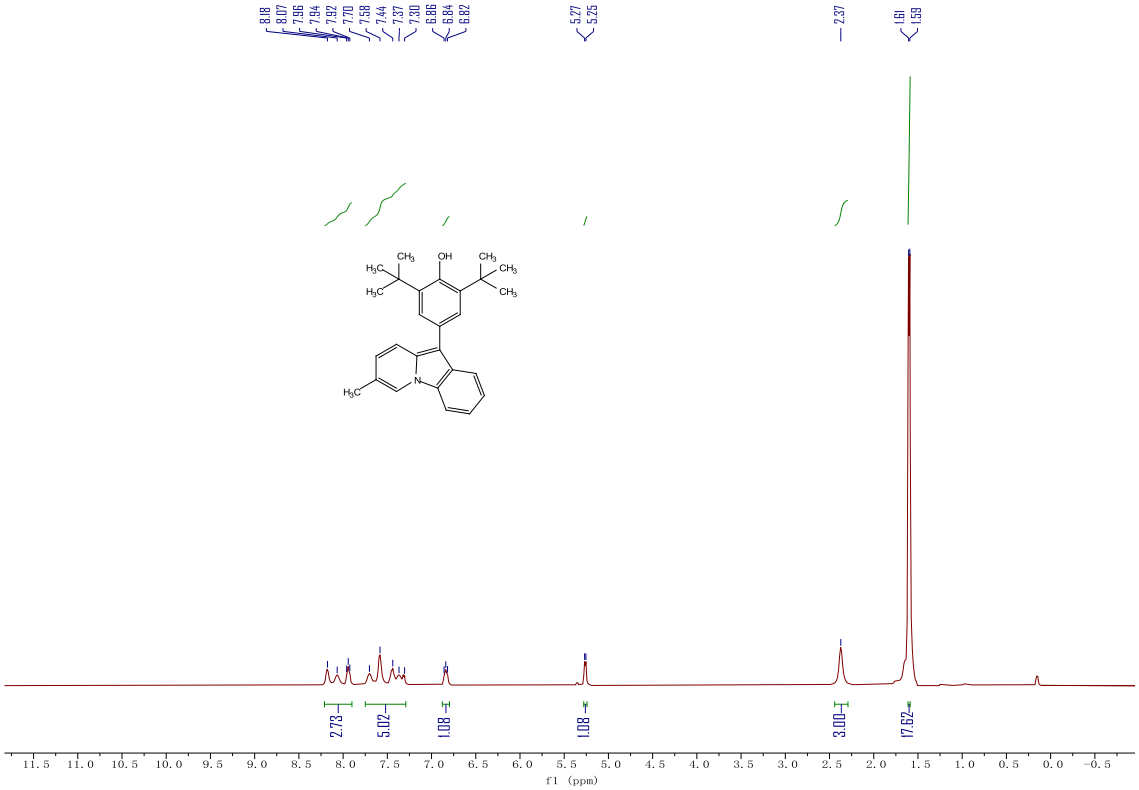
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

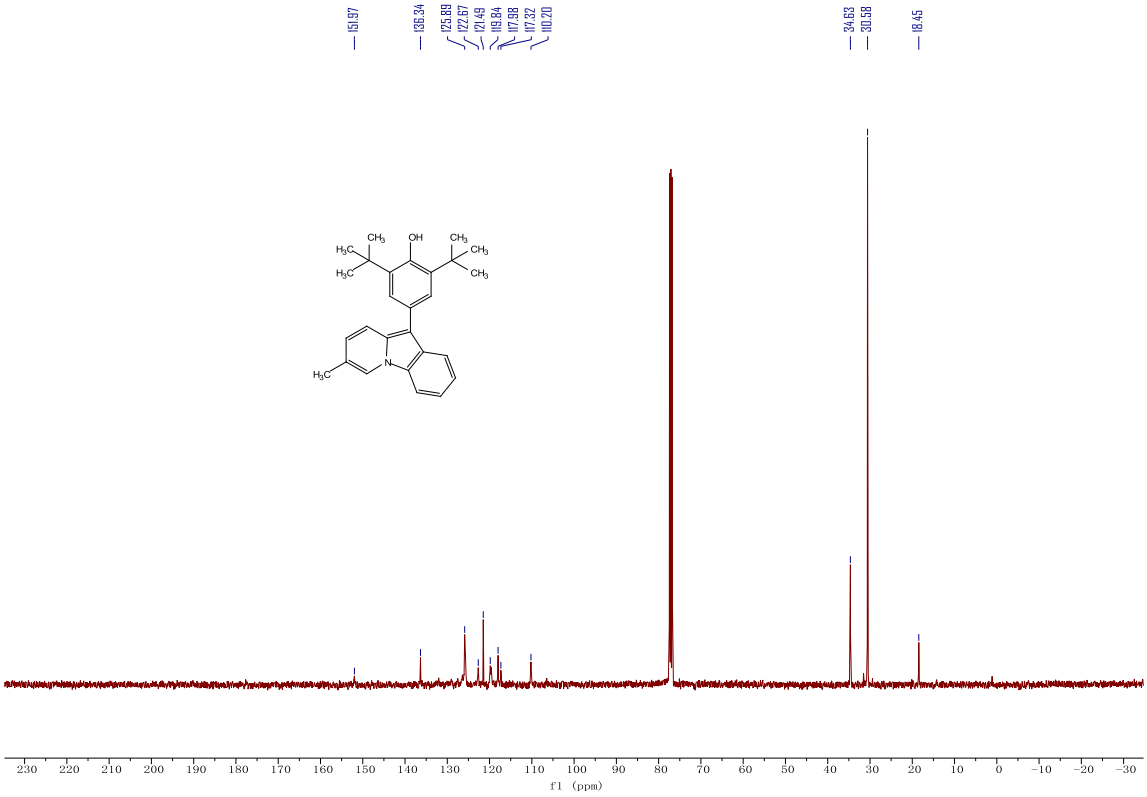
4-(8-bromopyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3e)





2,6-di-tert-butyl-4-(7-methylpyrido[1,2-a]indol-10-yl)phenol(3f)





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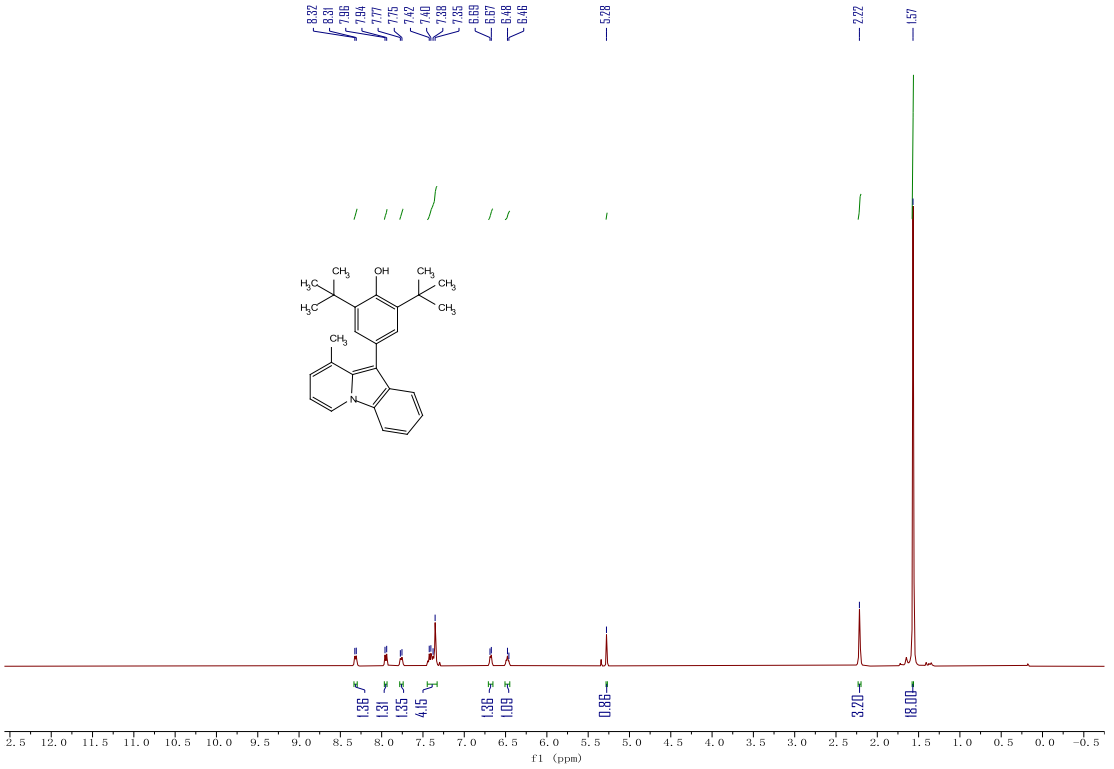
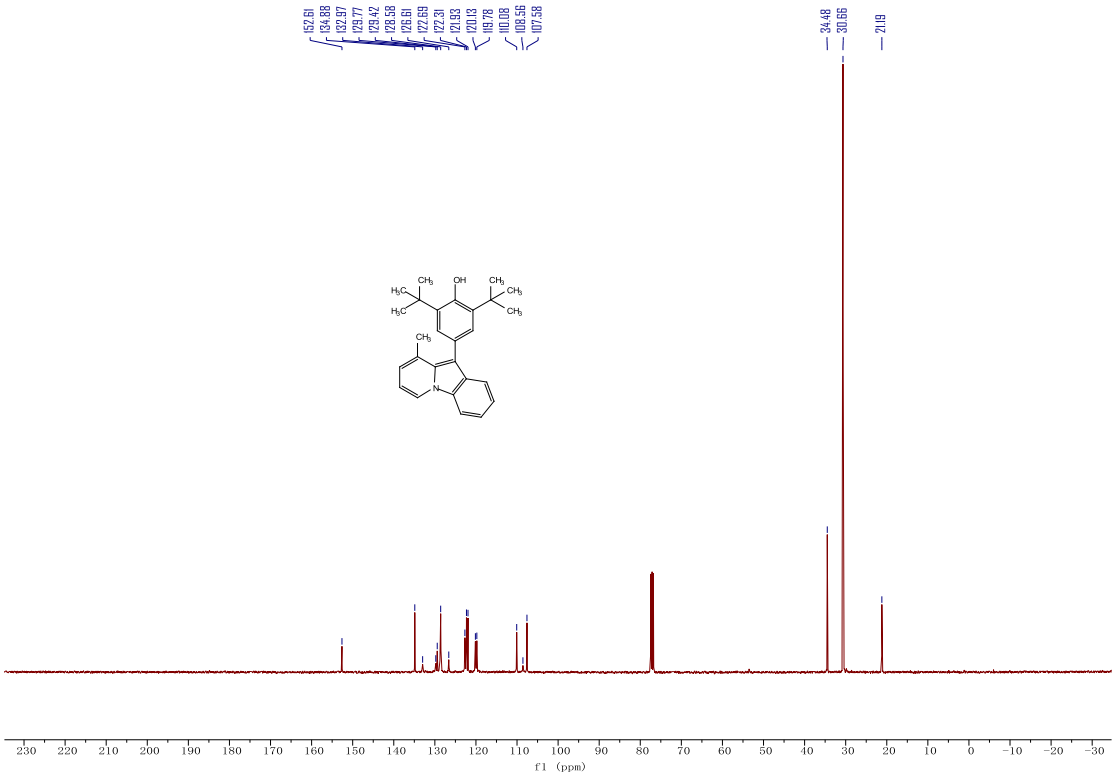
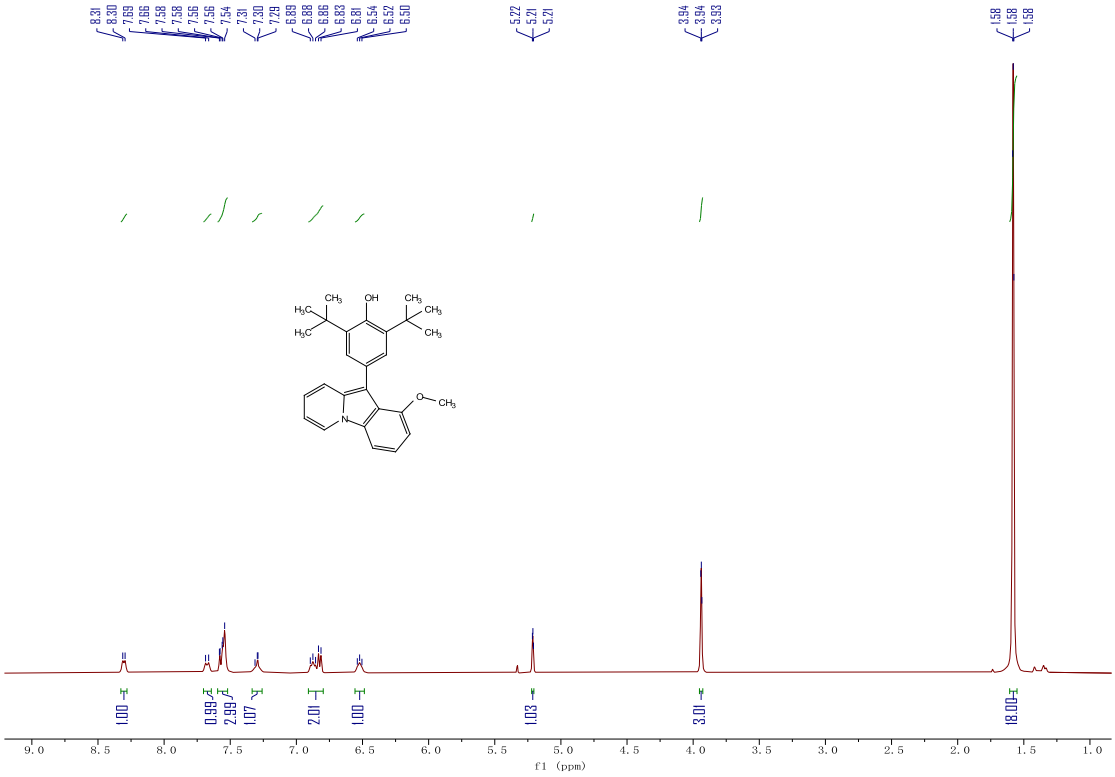
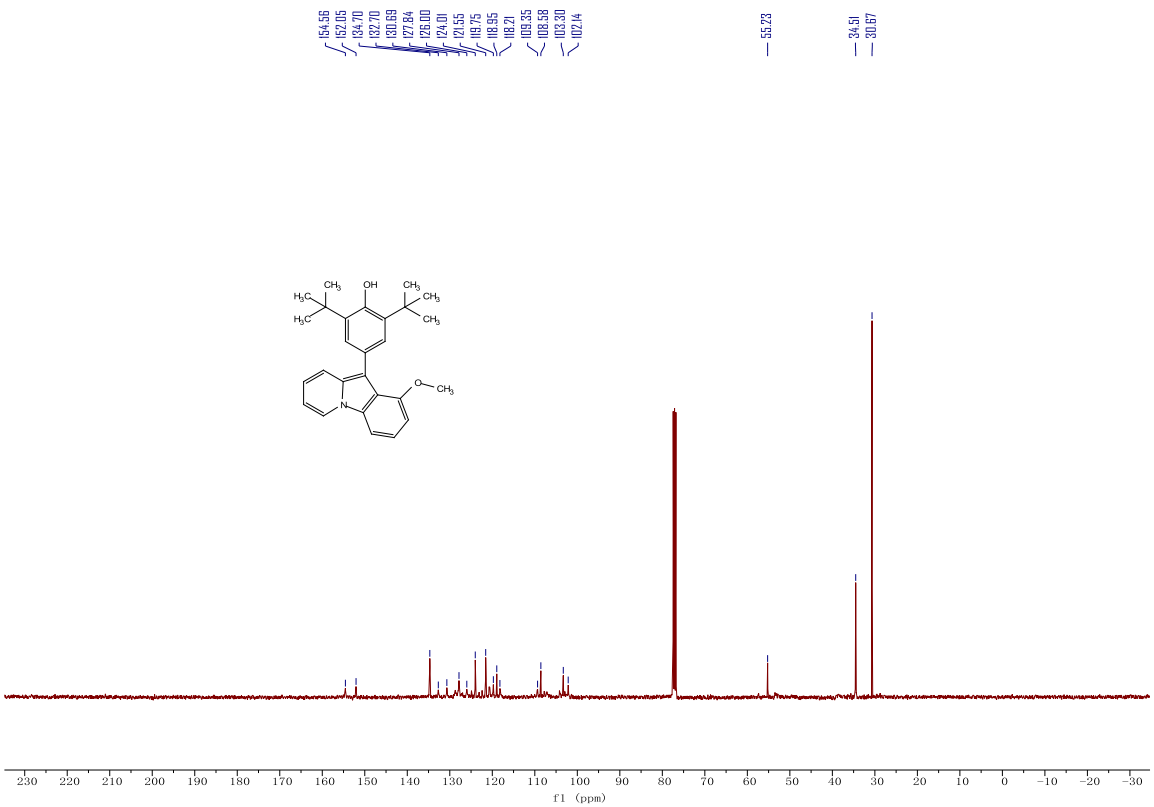


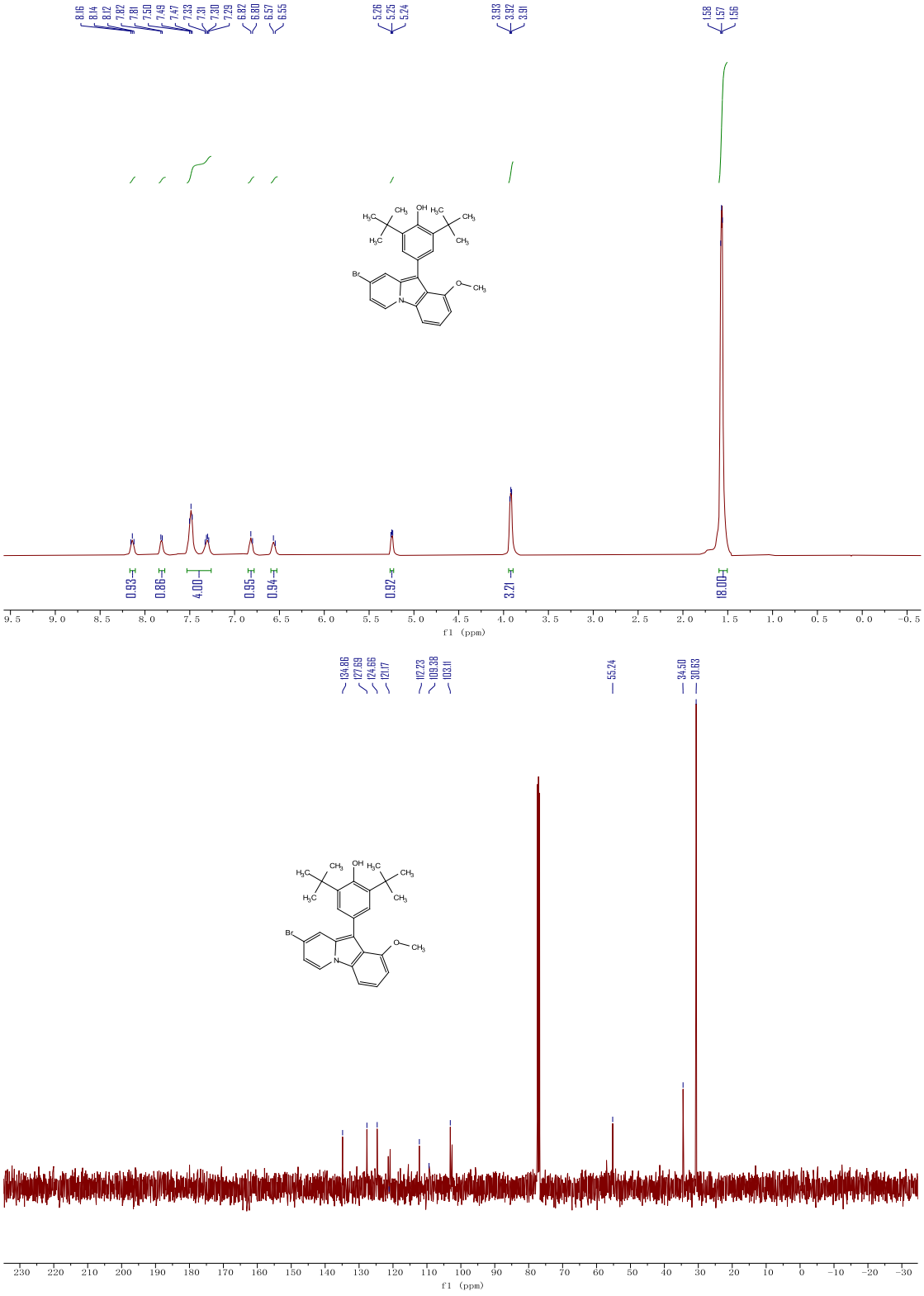


2,6-di-tert-butyl-4-(1-methoxypyrido[1,2-a]indol-10-yl)phenol(3h)

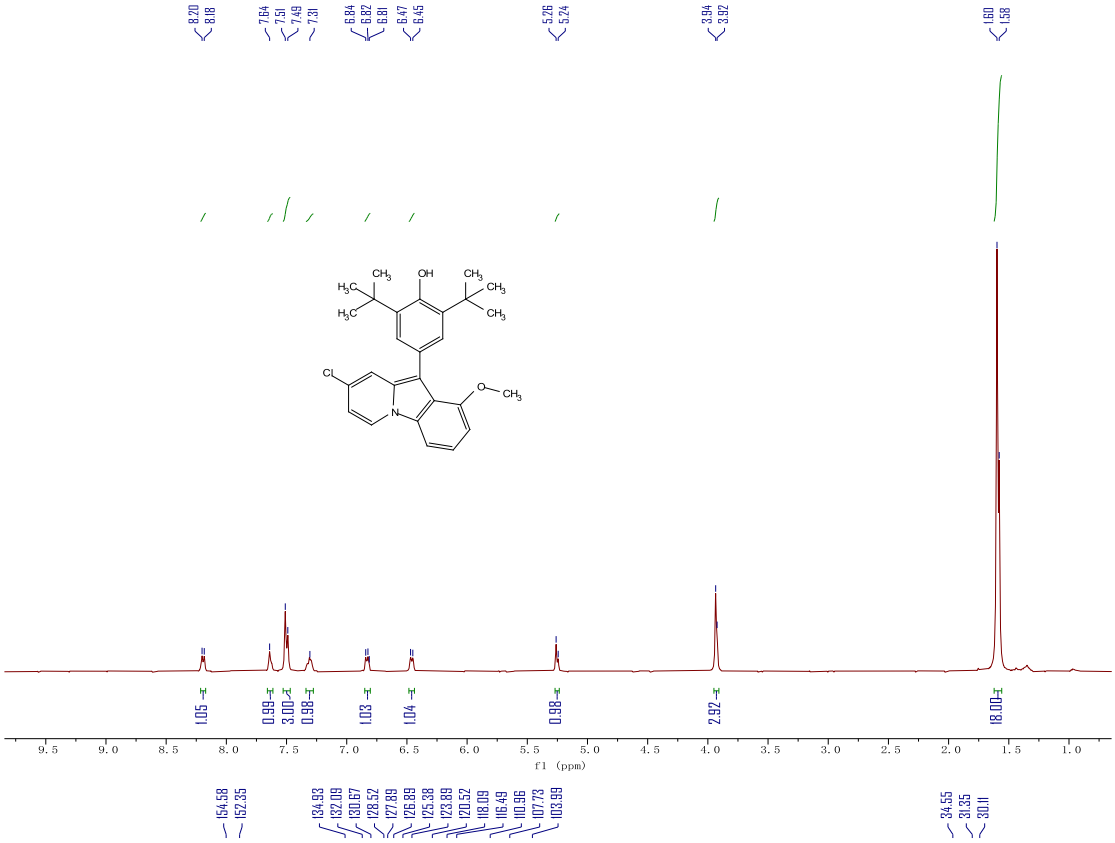


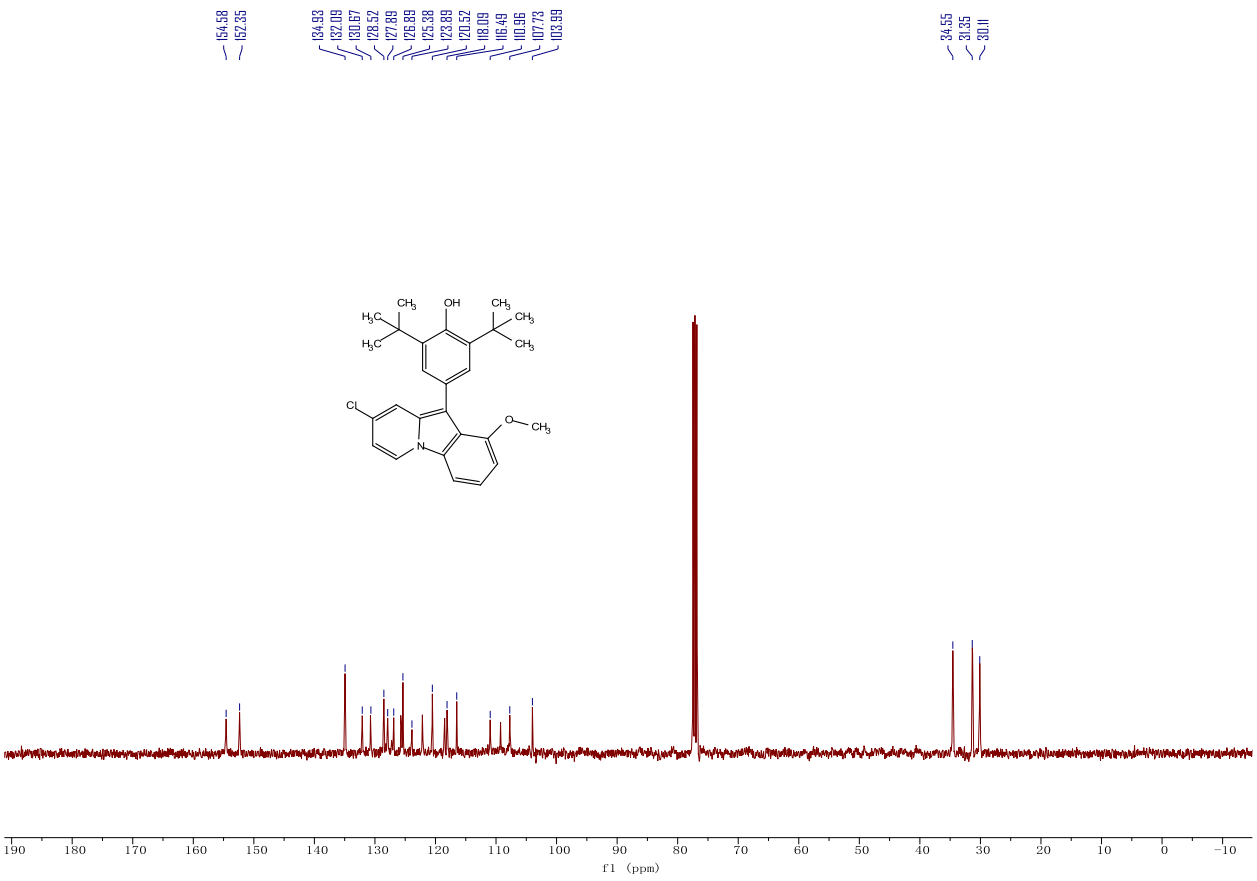


4-(8-bromo-1-methoxypyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3i)

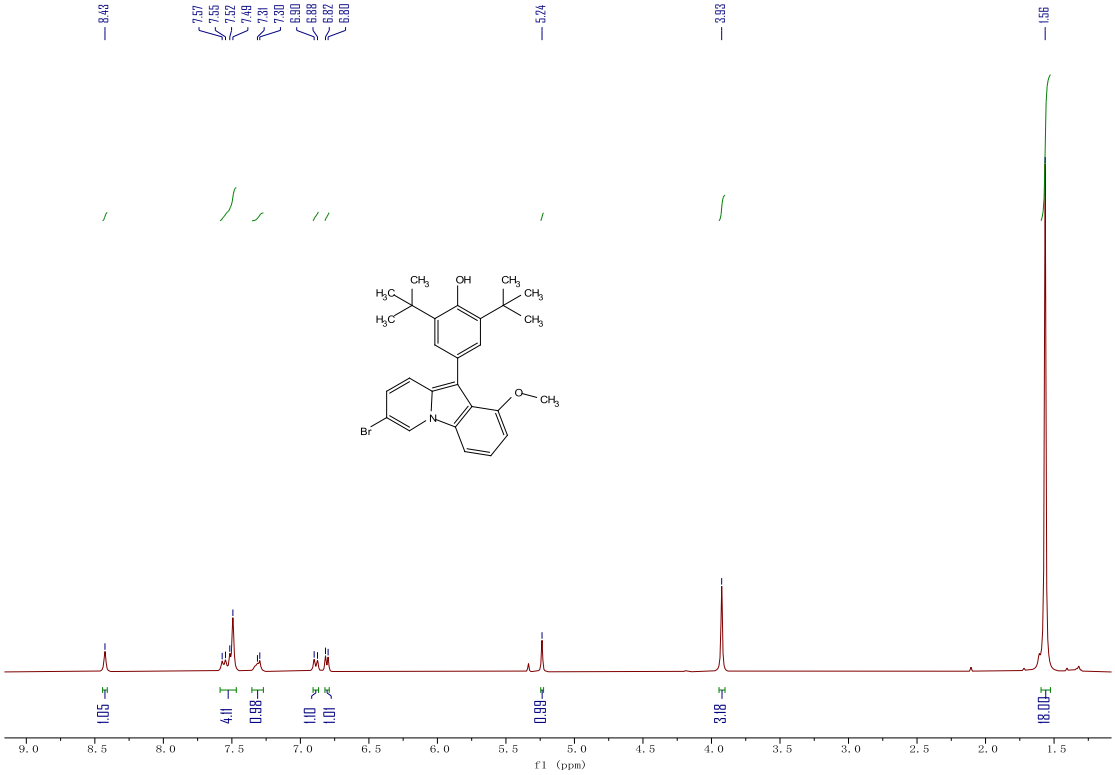


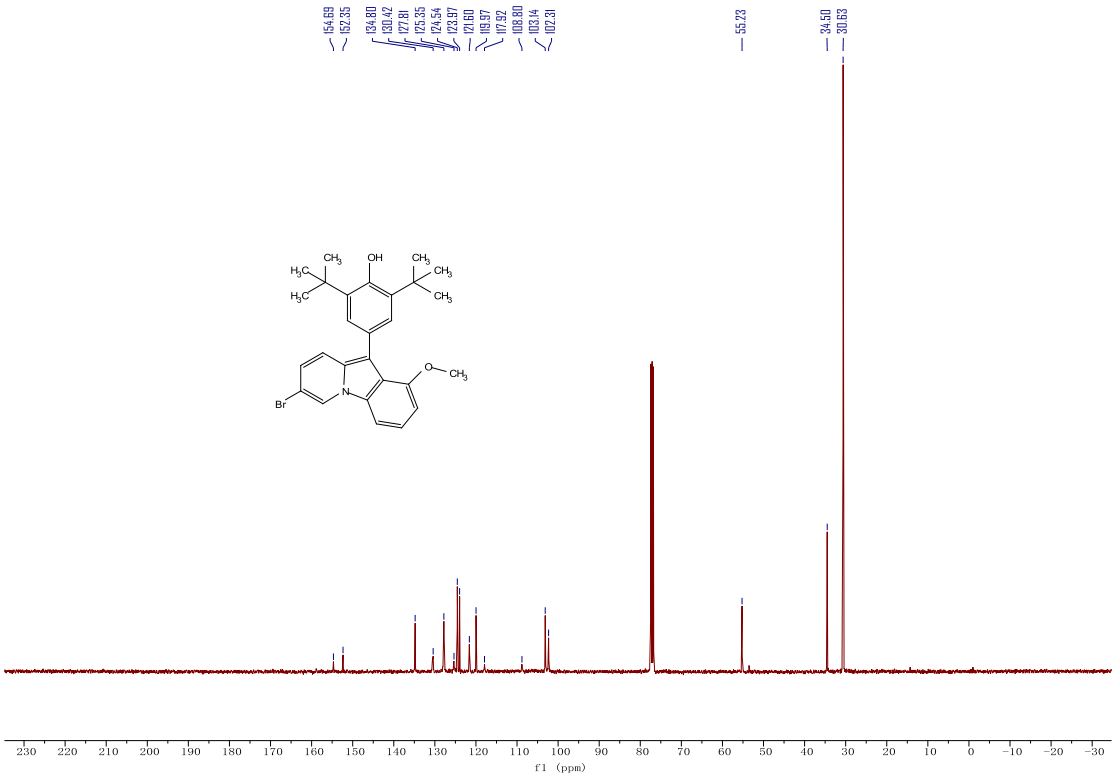
2,6-di-tert-butyl-4-(8-chloro-1-methoxypyrido[1,2-a]indol-10-yl)phenol(3j)



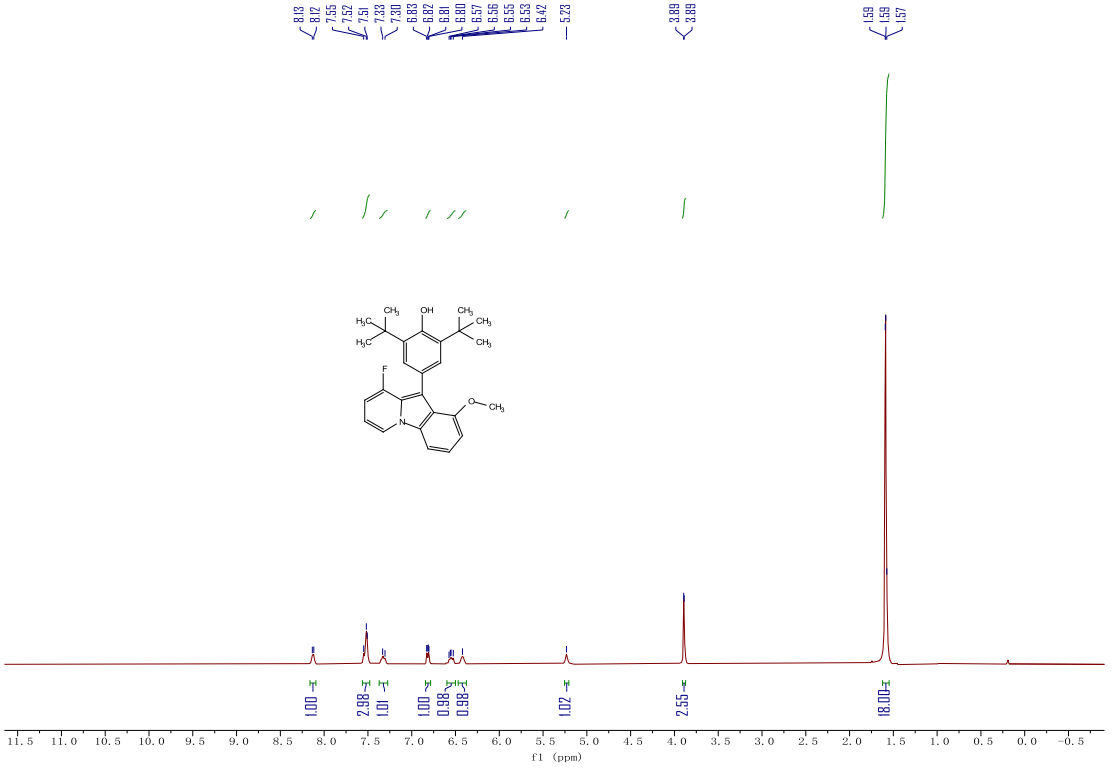


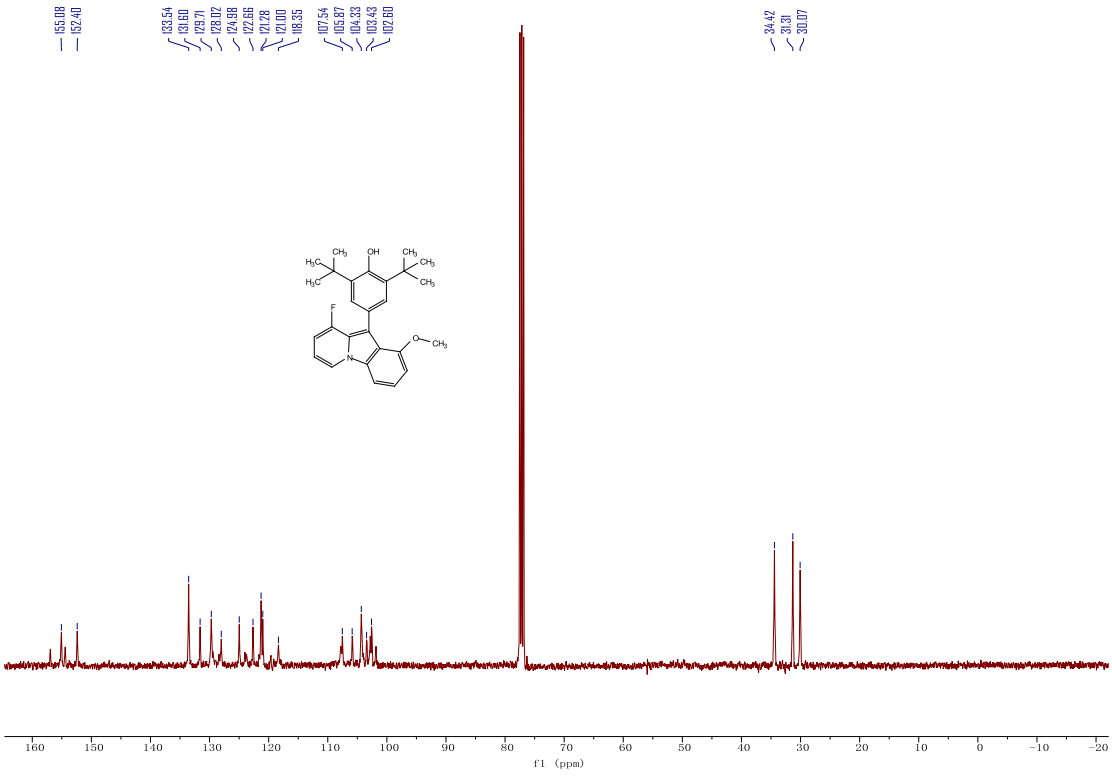
4-(7-bromo-1-methoxypyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3k)

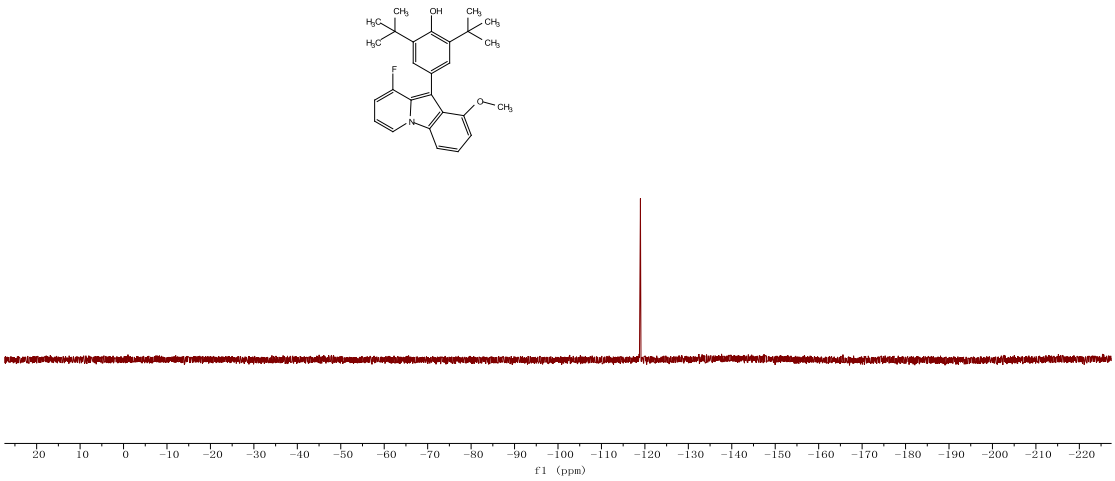




2,6-di-tert-butyl-4-(9-fluoro-1-methoxypyrido[1,2-a]indol-10-yl)phenol(3l)



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H3C
CH3
H3C
CH3
F
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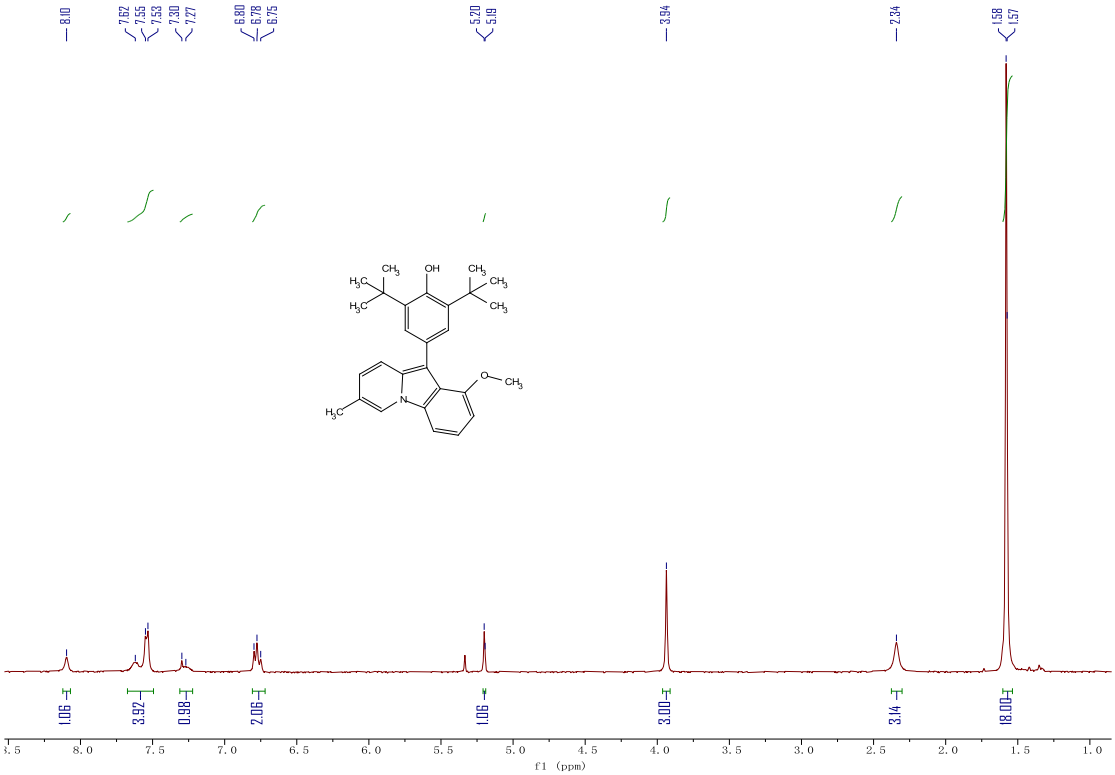
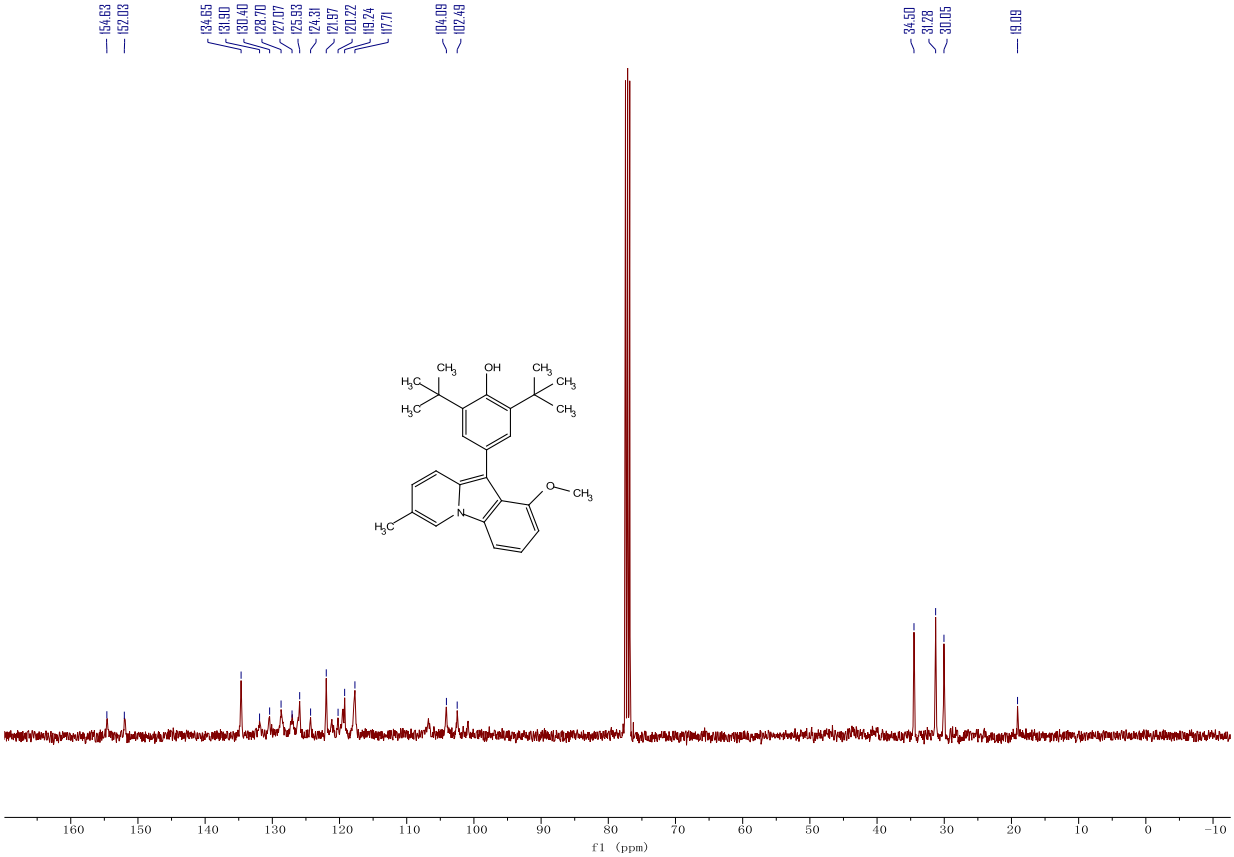
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

2,6-di-tert-butyl-4-(1-methoxy-7-methylpyrido[1,2-a]indol-10-yl)phenol(3m)





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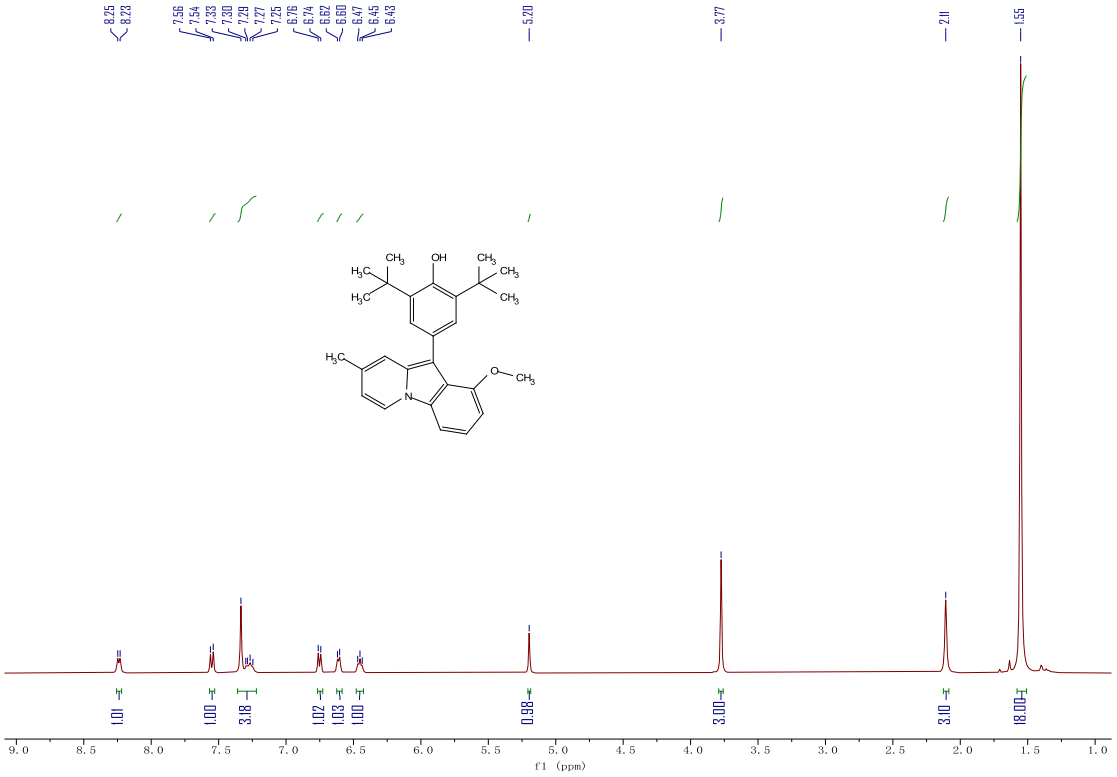

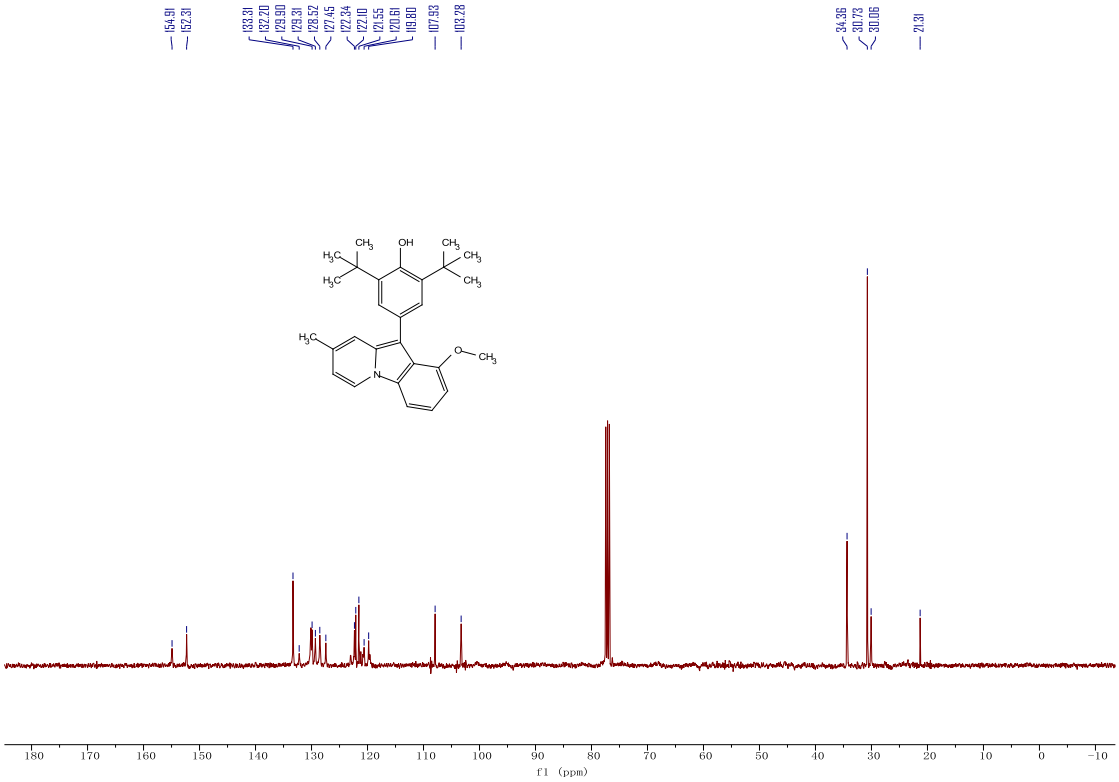

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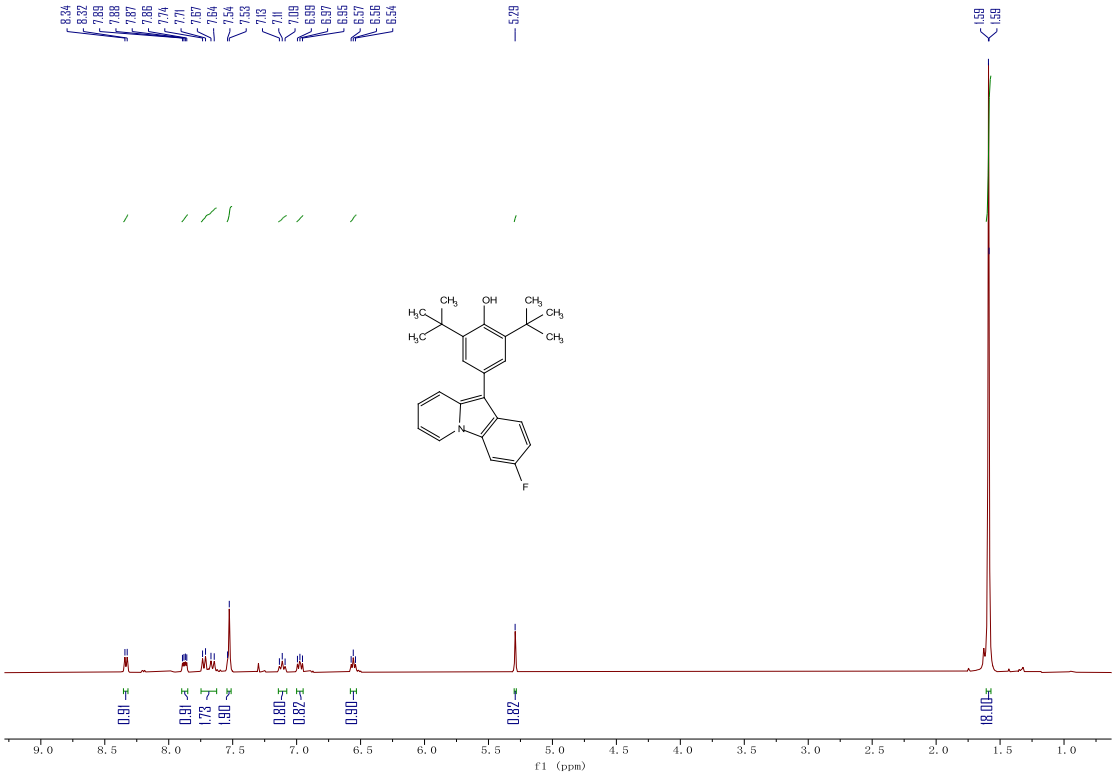

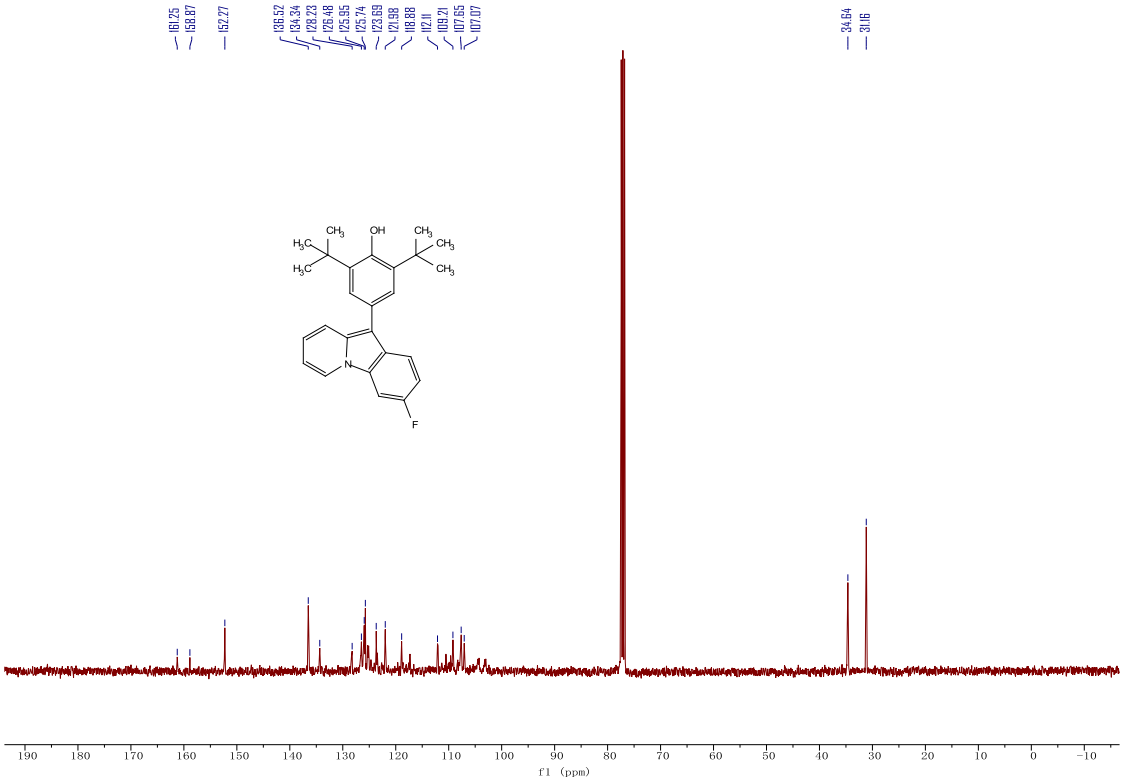

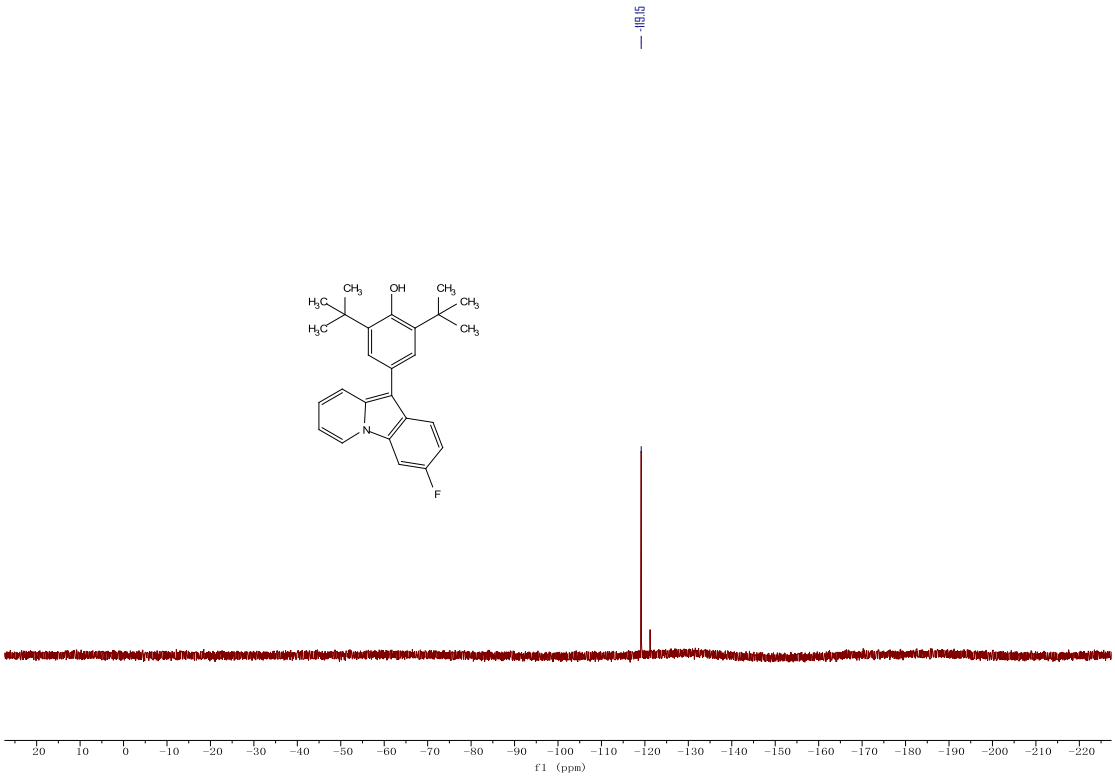
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CH3
H3C
CH3
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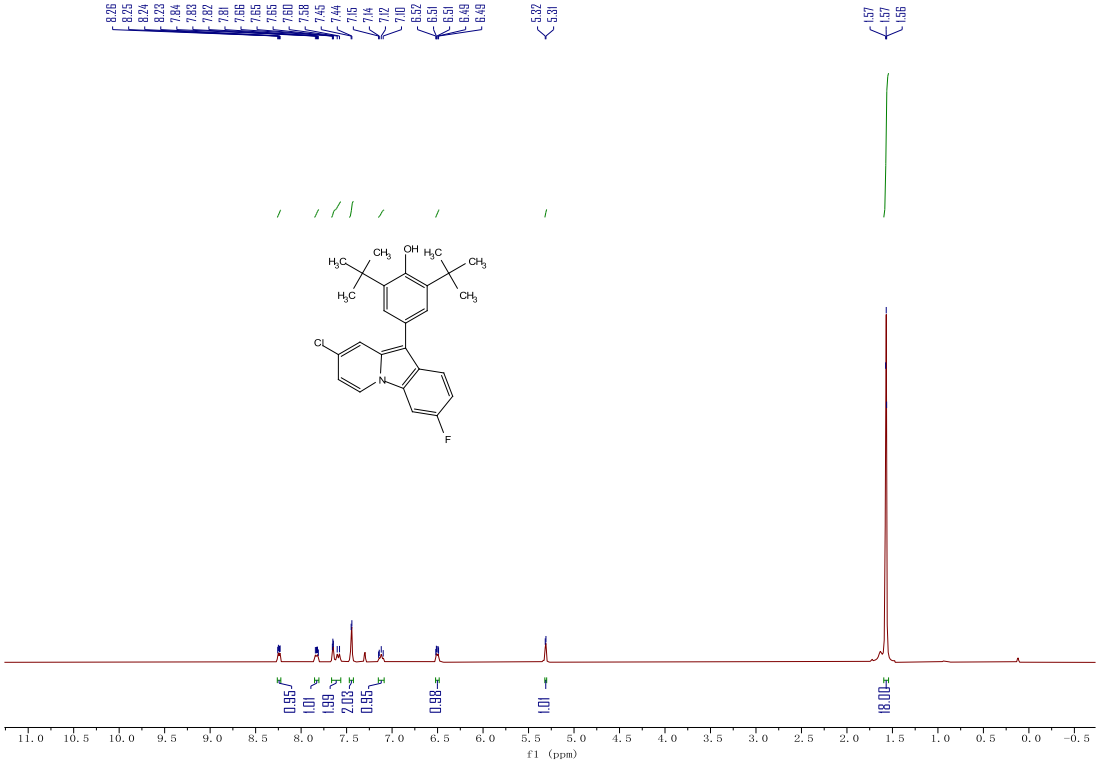
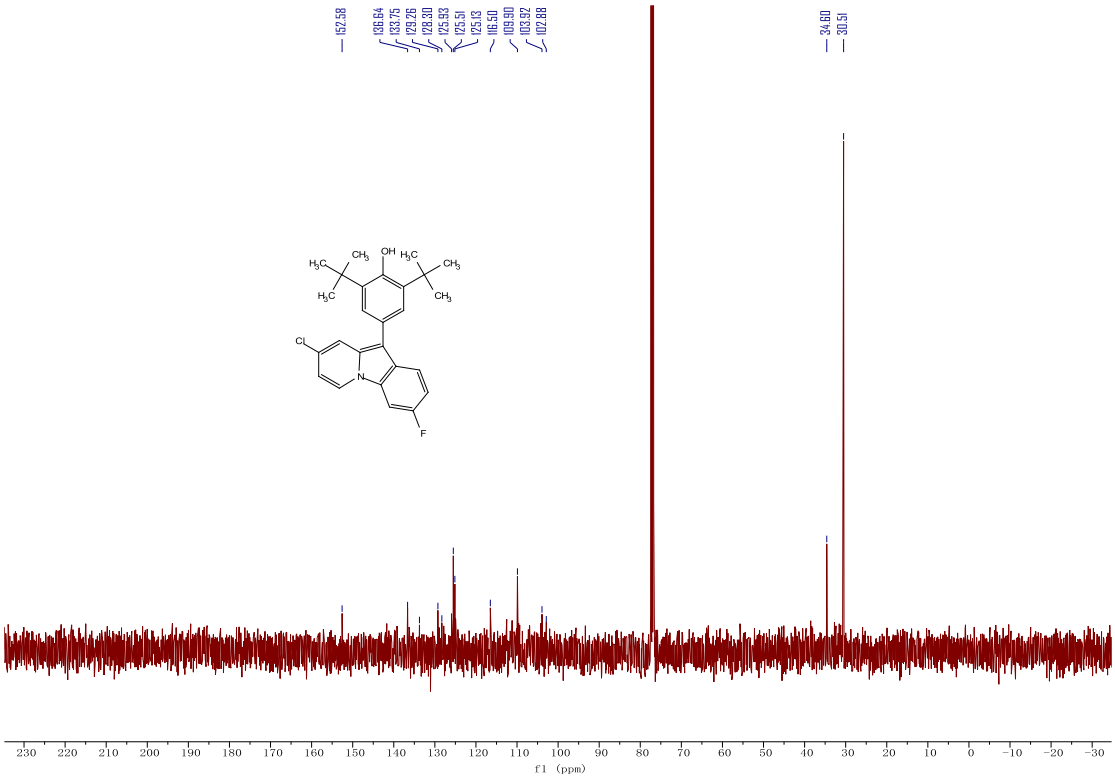
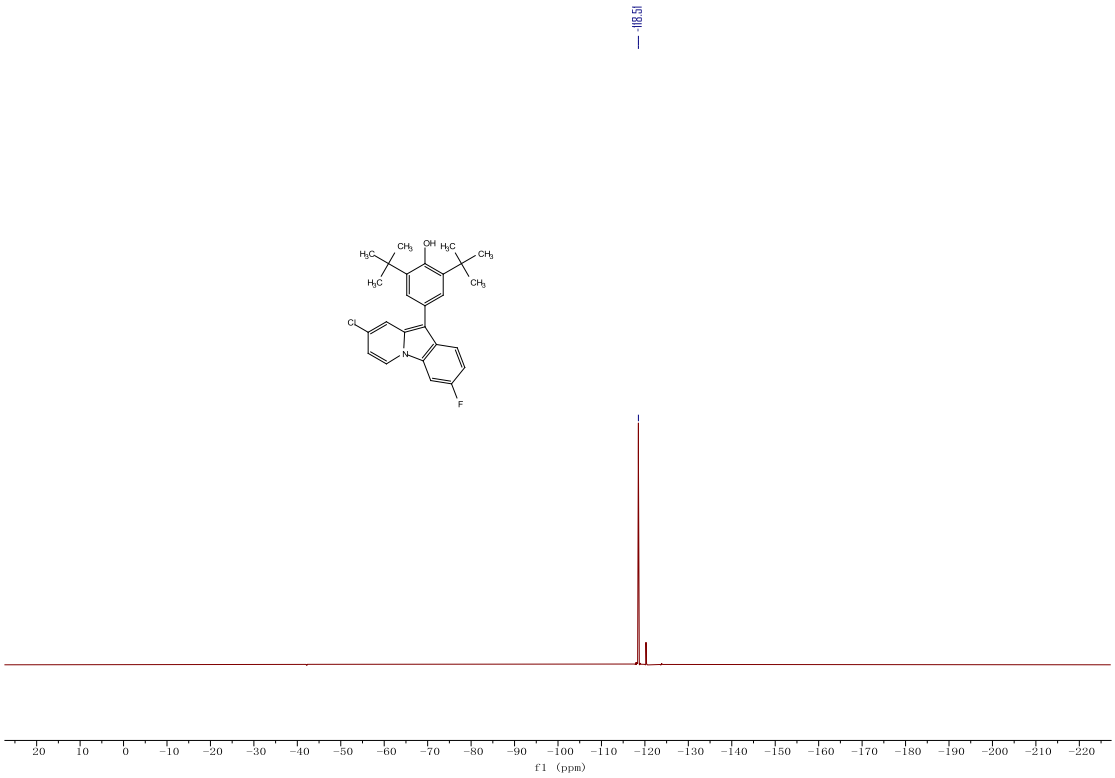
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

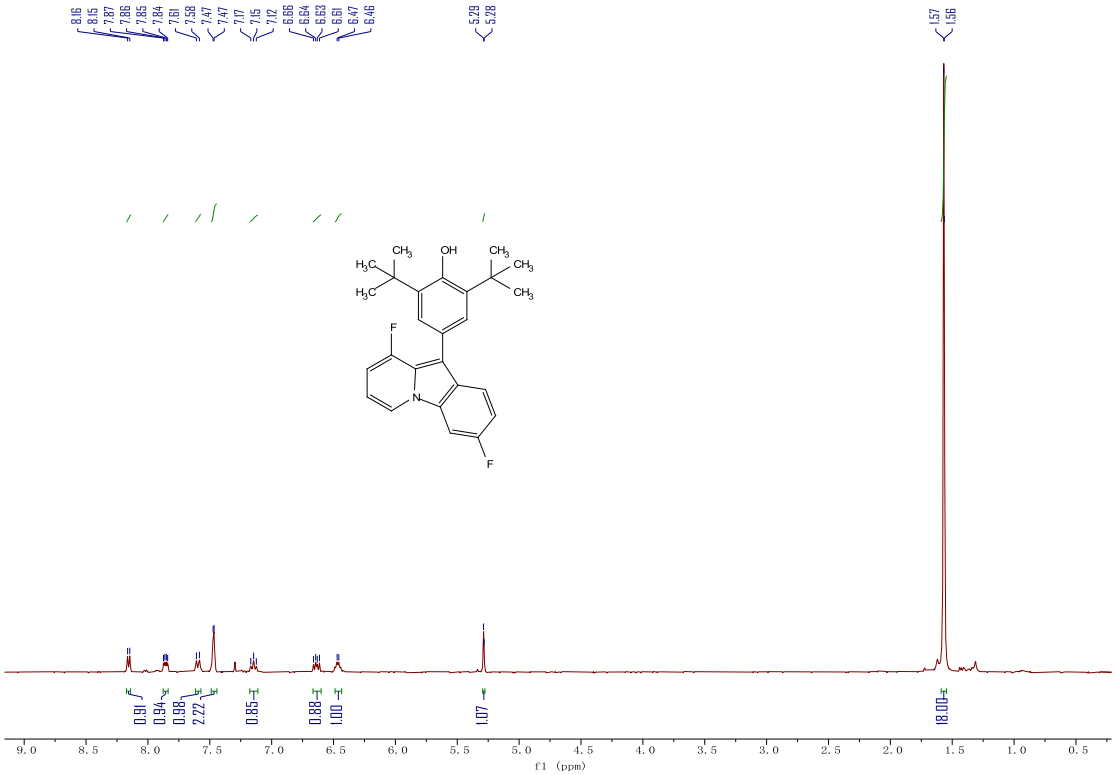
2,6-di-tert-butyl-4-(8-chloro-3-fluoropyrido[1,2-a]indol-10-yl)phenol(3p)

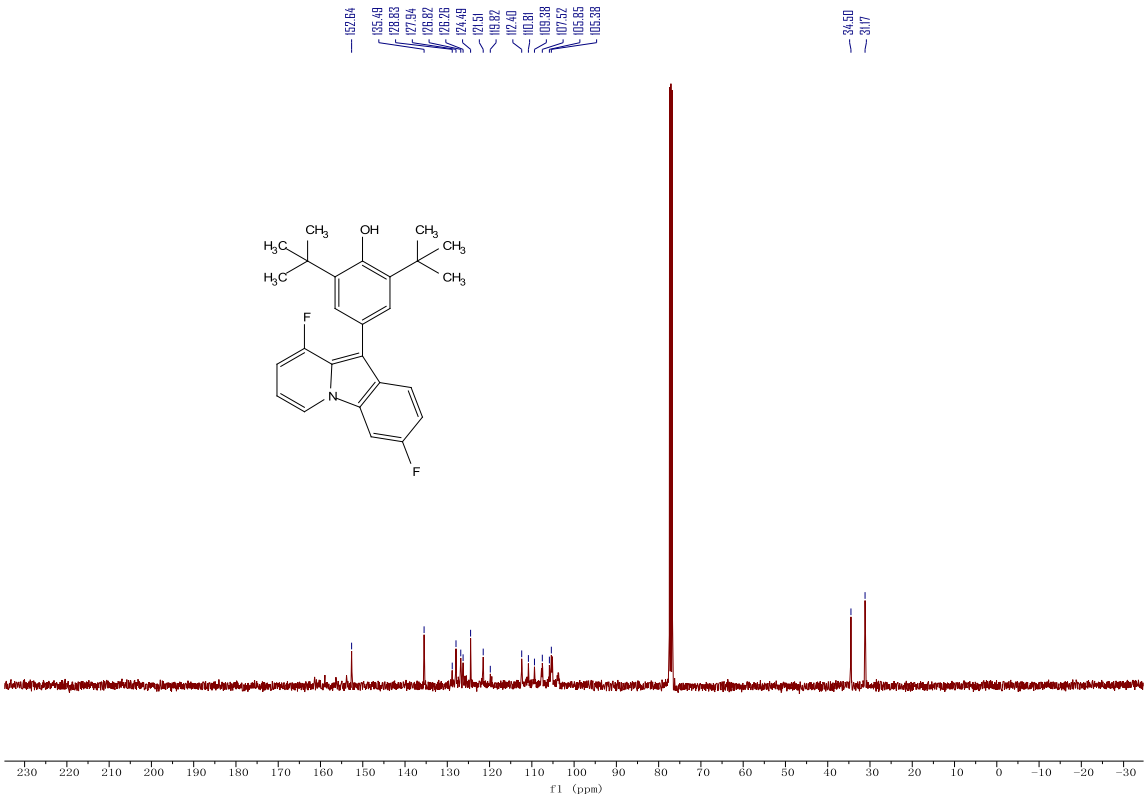


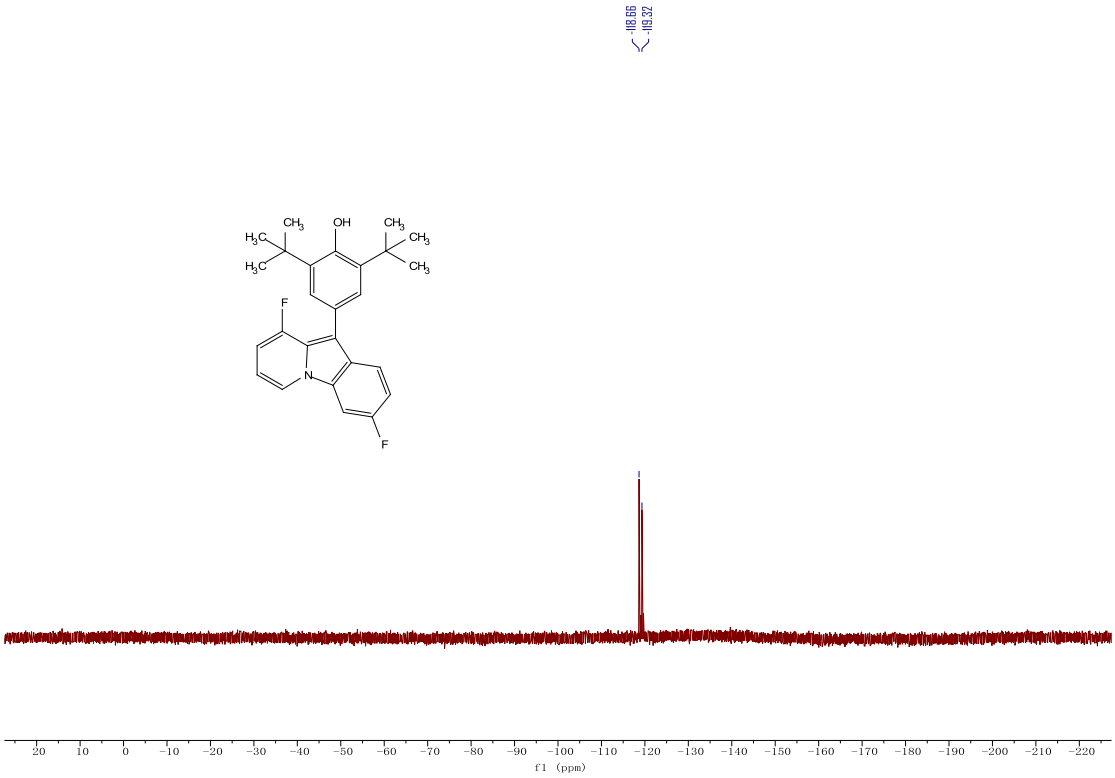



-118.51
OH
CH3
H3C
H3C
H3C
CH3
CH3
Cl
N
F
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

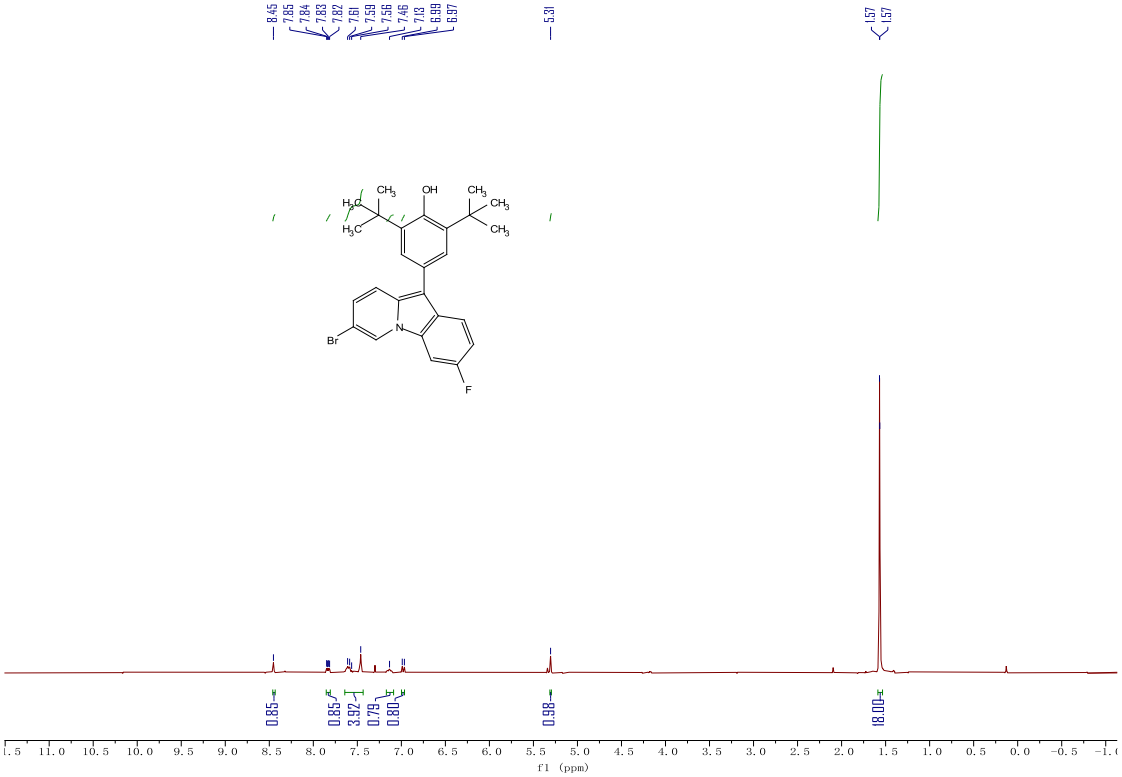
2,6-di-tert-butyl-4-(3,9-difluoropyrido[1,2-a]indol-10-yl)phenol(3q)

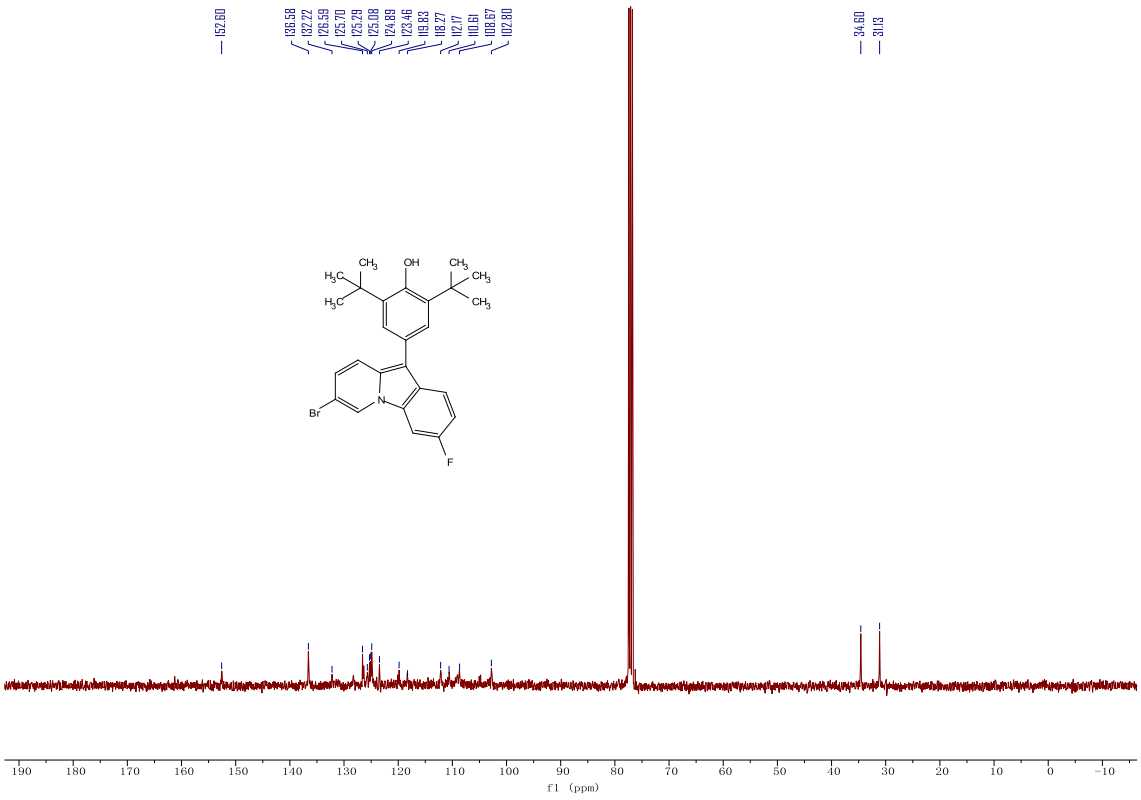


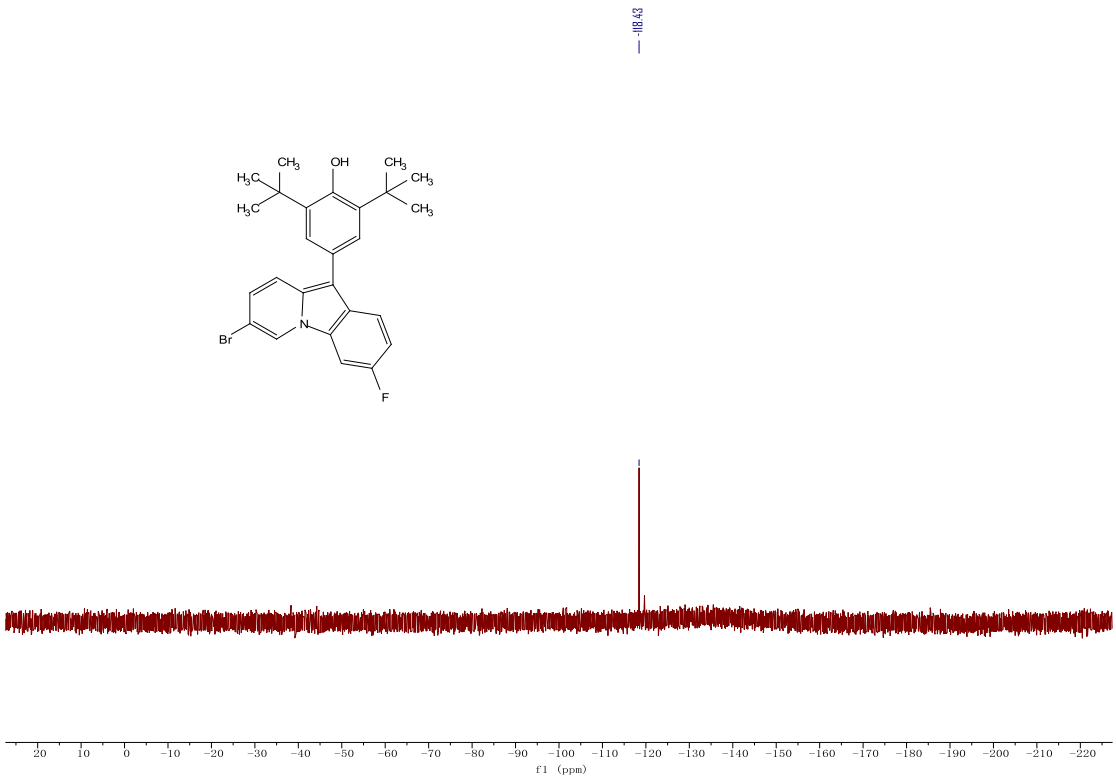



-118.65
-119.32
CH3
OH
CH3
H3C
CH3
H3C
CH3
F
N
F
20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210 −220
f1 (ppm)

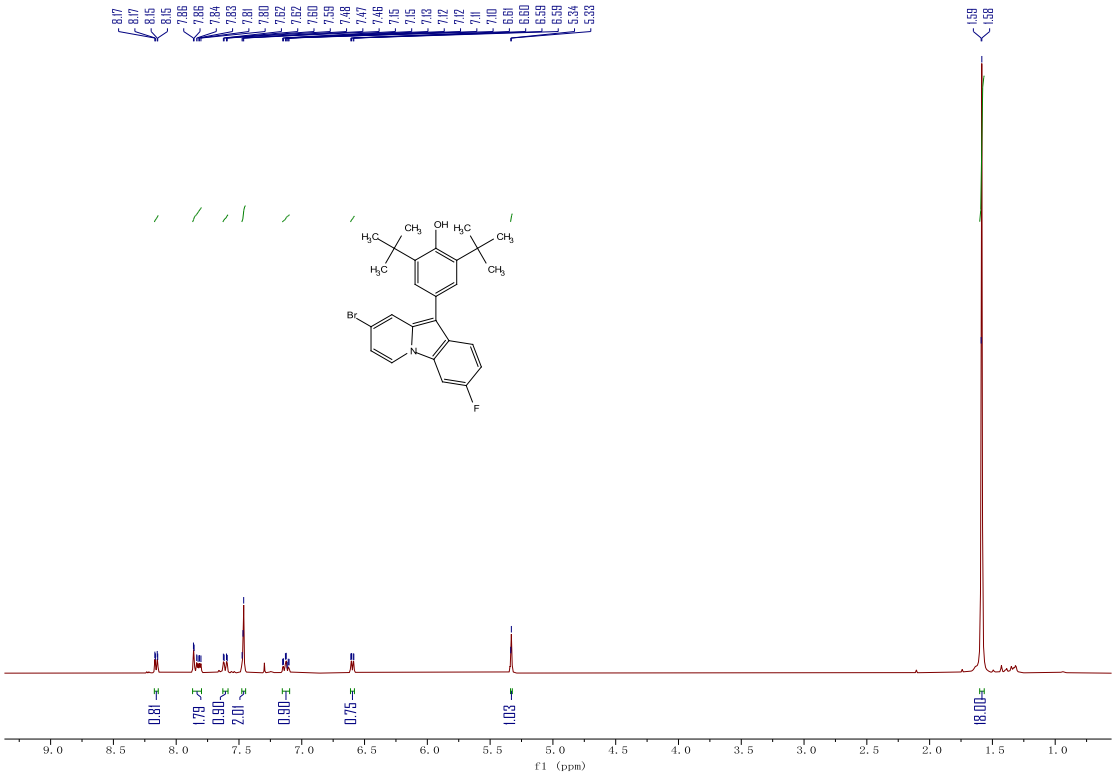
4-(7-bromo-3-fluoropyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3r)

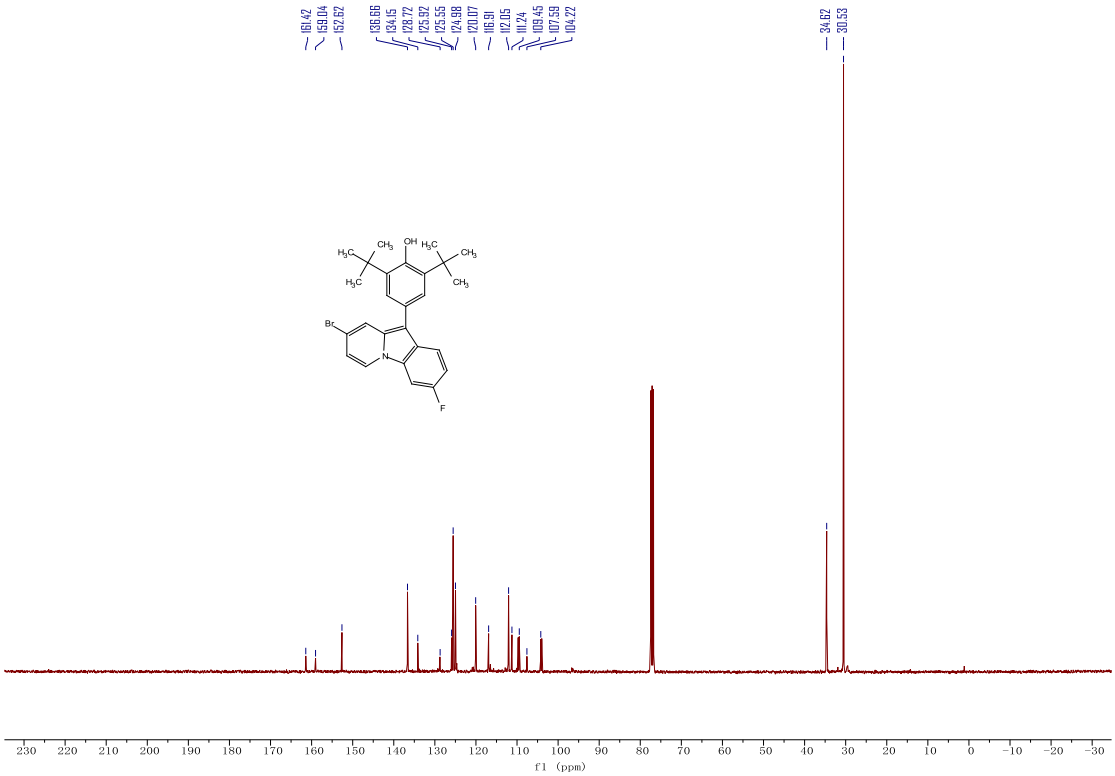


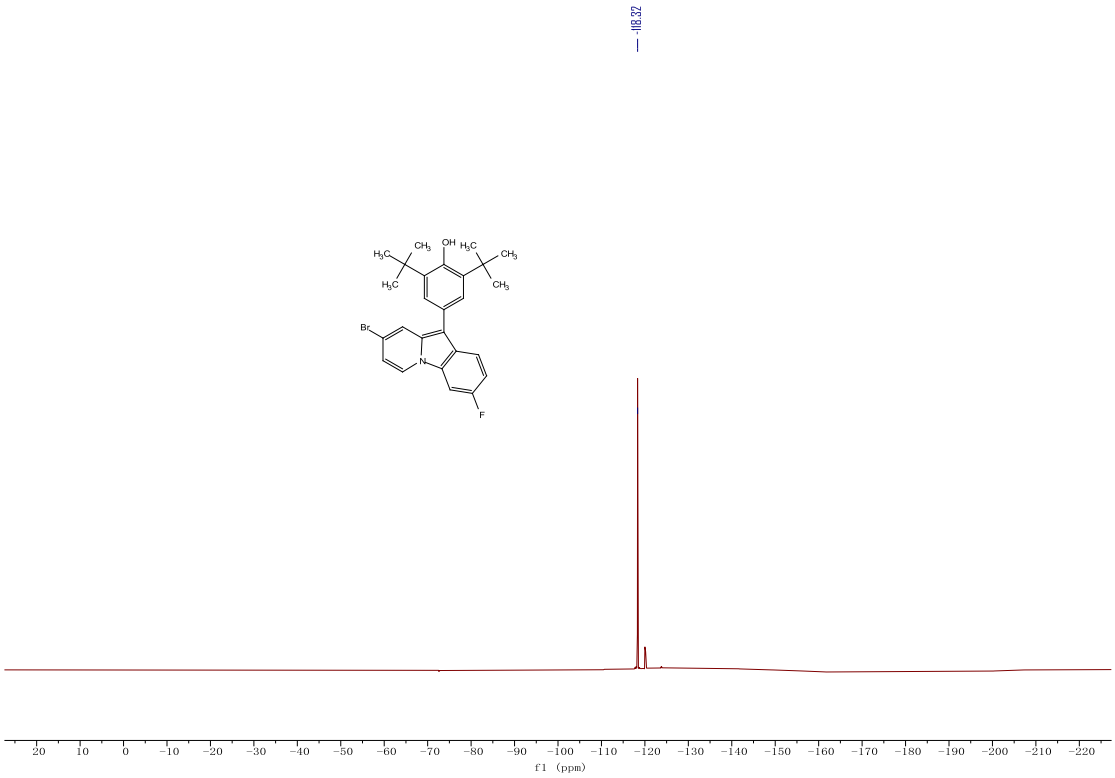



-118.43
CH3
OH
CH3
CH3
H3C
CH3
H3C
Br
N
F
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

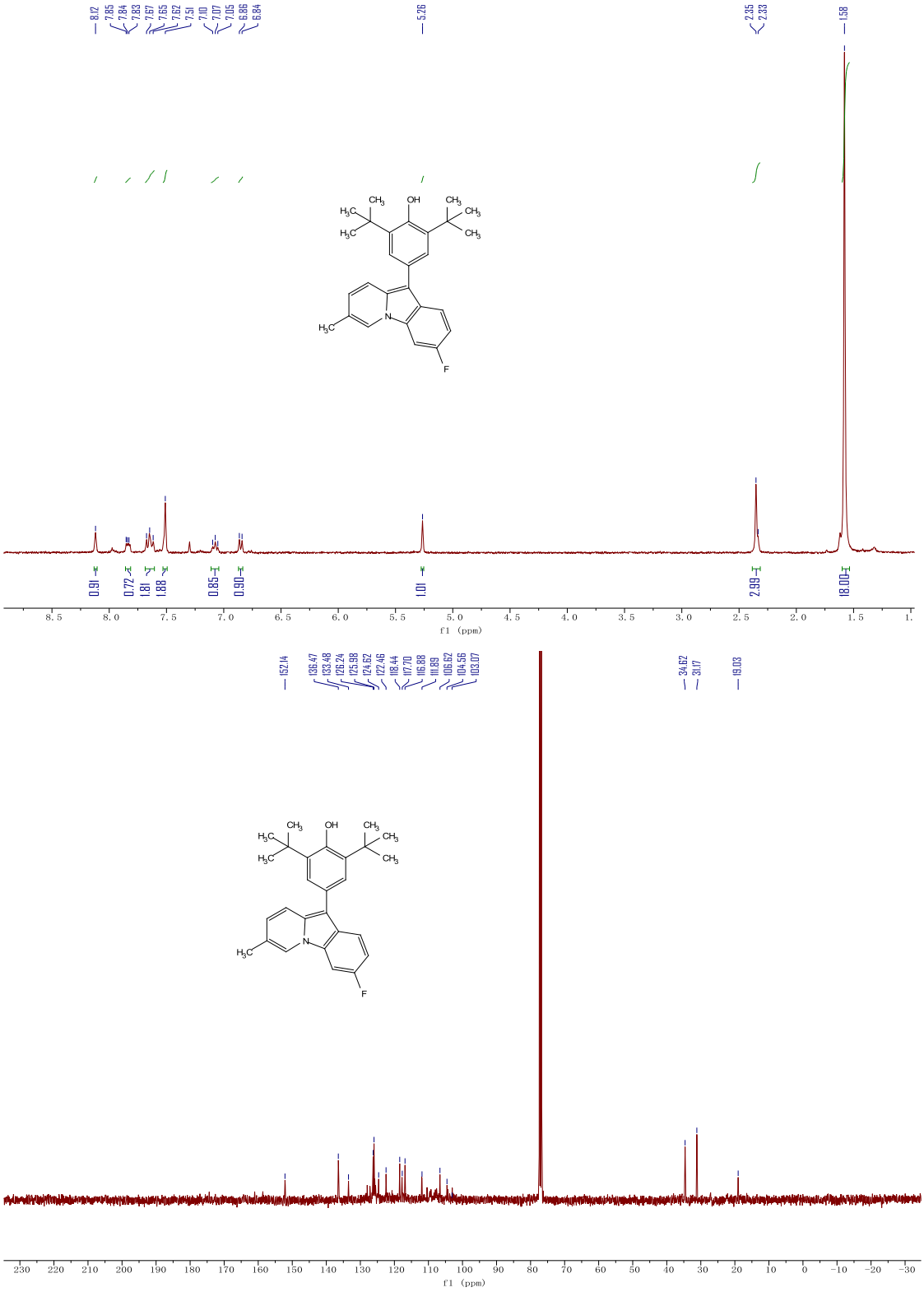
4-(8-bromo-3-fluoropyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3s)

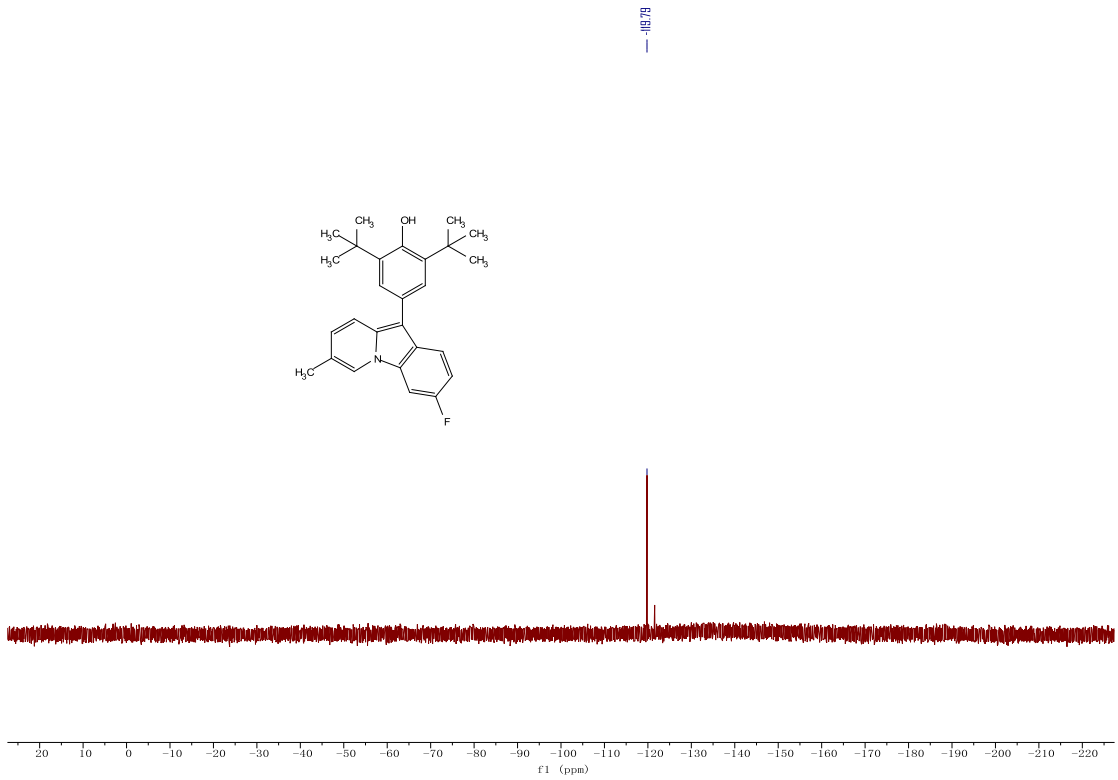




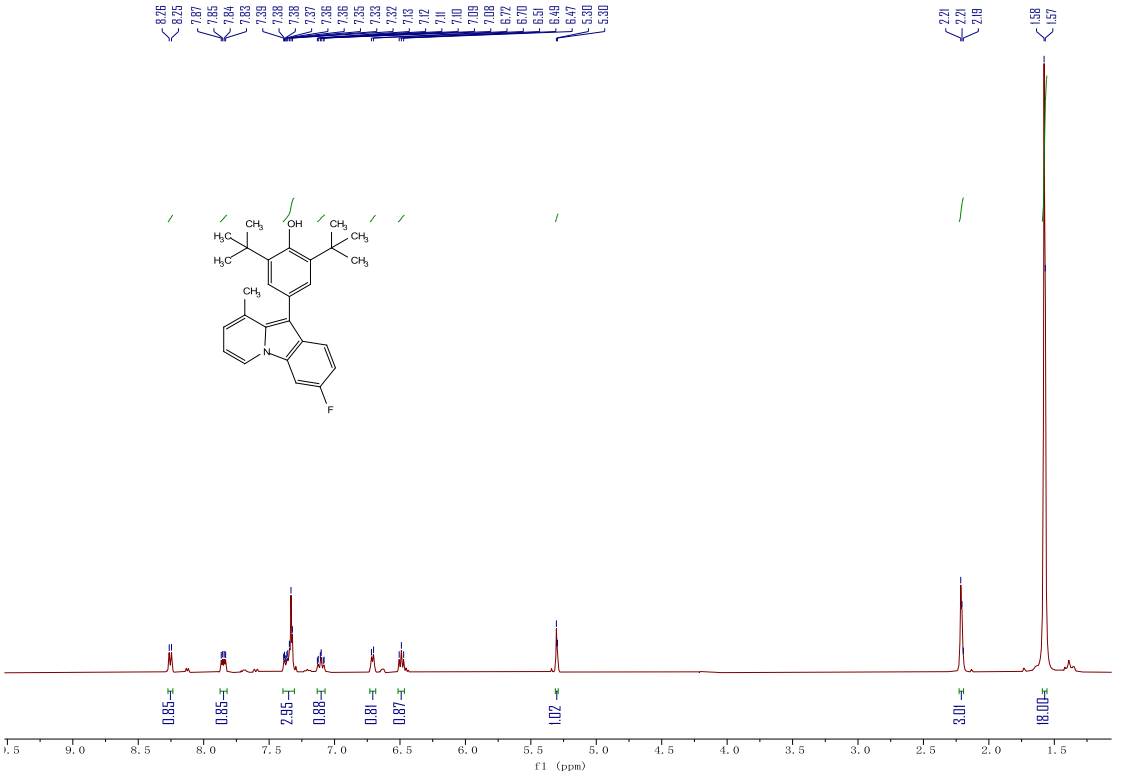

-118.32
OH
CH3
H3C
H3C
H3C
CH3
CH3
Br
N
F
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

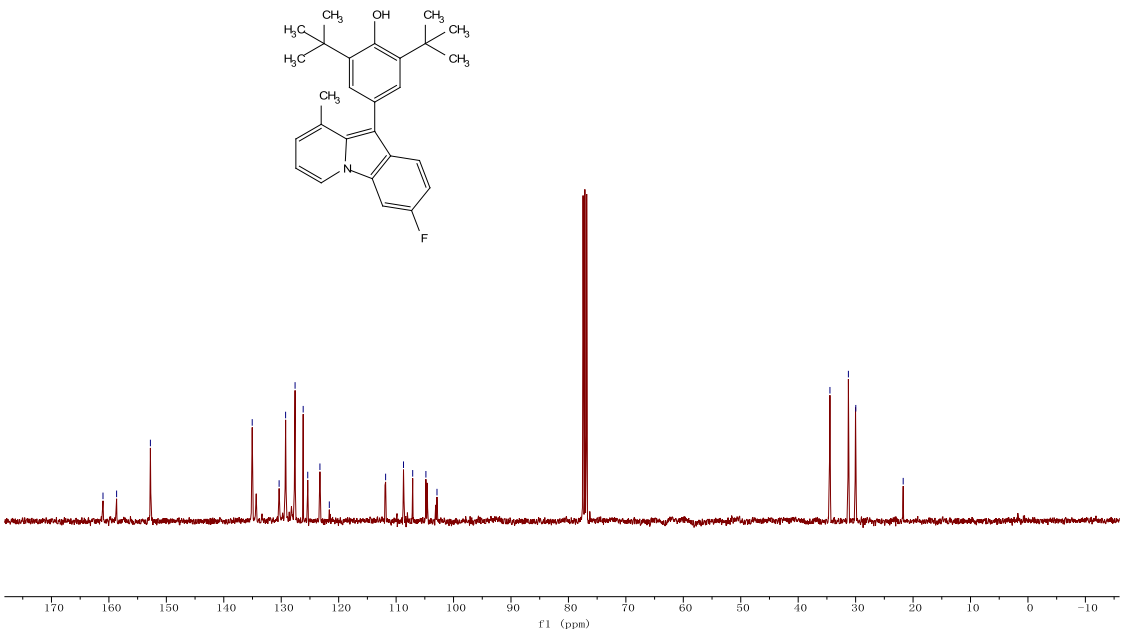
2,6-di-tert-butyl-4-(3-fluoro-7-methylpyrido[1,2-a]indol-10-yl)phenol(3t)

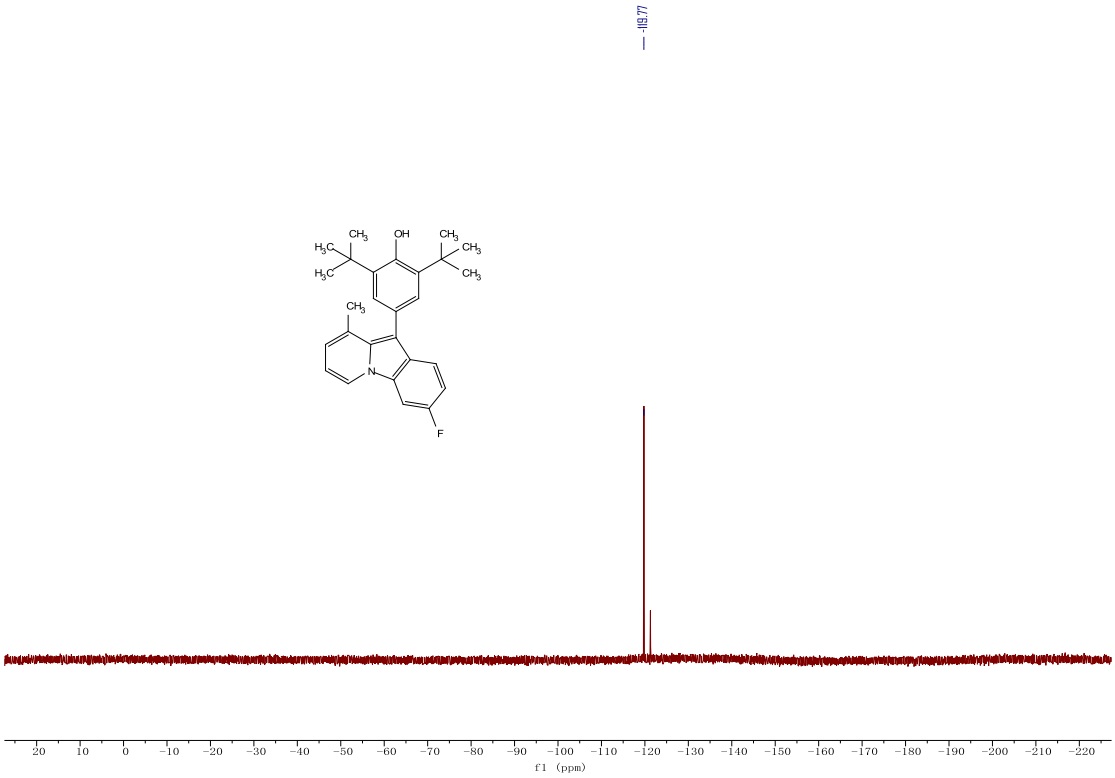



-119.79
CH3
OH
CH3
H3C
CH3
H3C
CH3
N
H3C
F
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

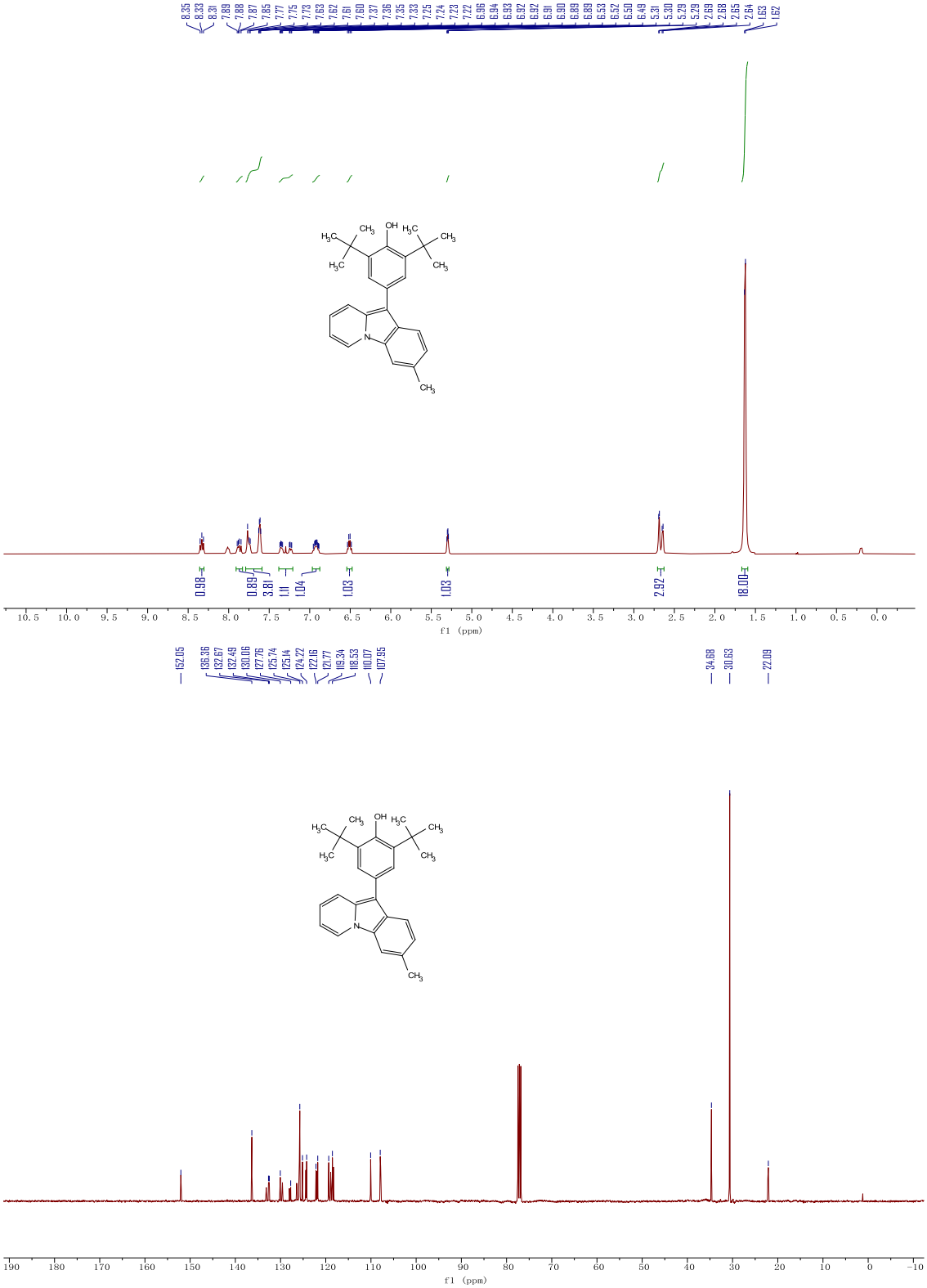
2,6-di-tert-butyl-4-(3-fluoro-9-methylpyrido[1,2-a]indol-10-yl)phenol(3u)



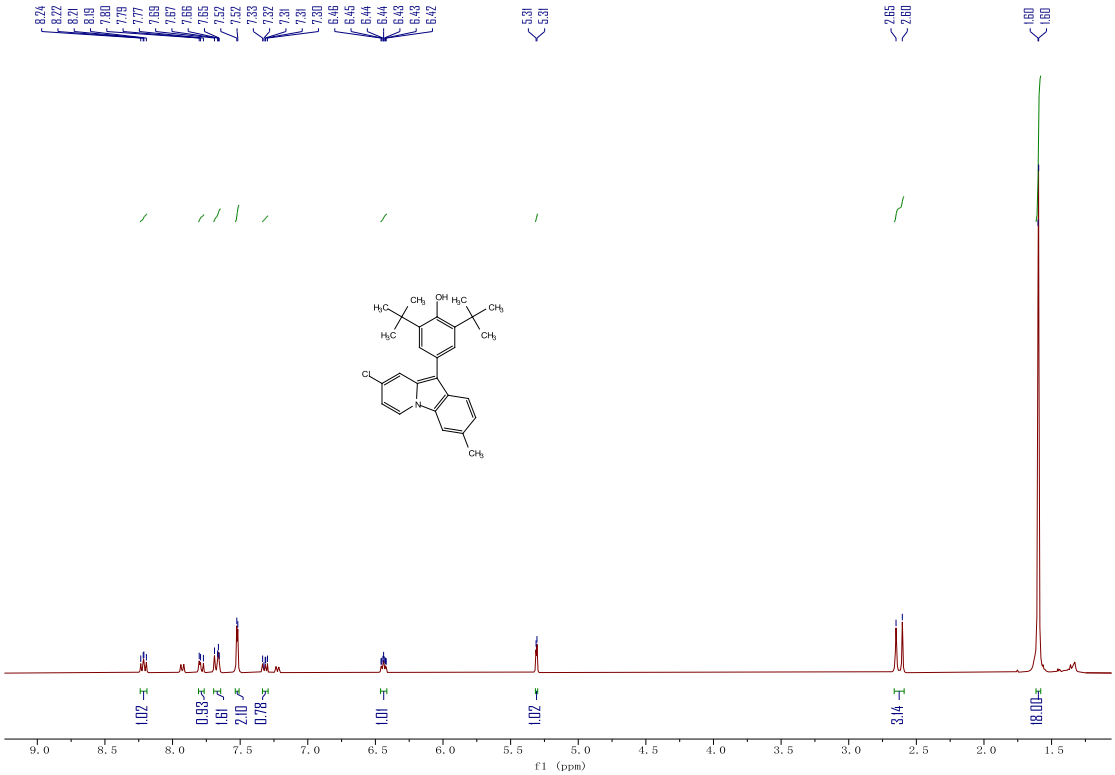


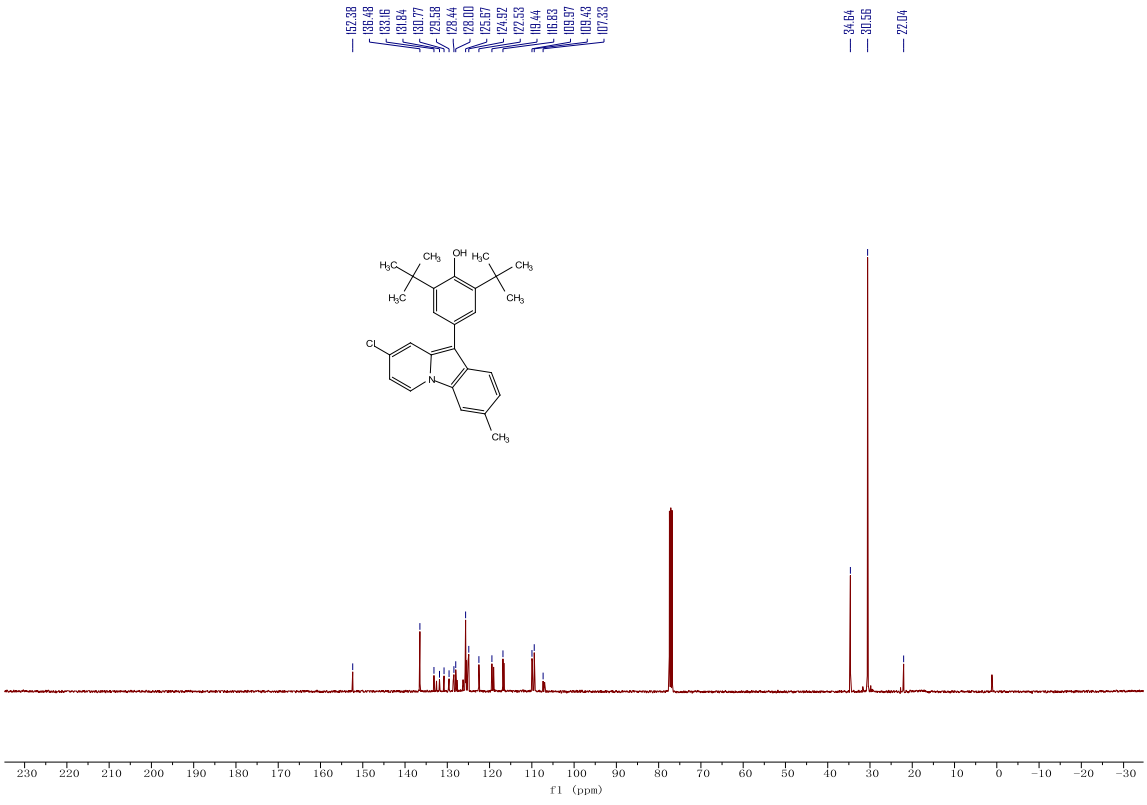

-119.77
CH3
OH
CH3
H3C
CH3
H3C
CH3
CH3
N
F
20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210 −220
f1 (ppm)

2,6-di-tert-butyl-4-(3-methylpyrido[1,2-a]indol-10-yl)phenol(3v)

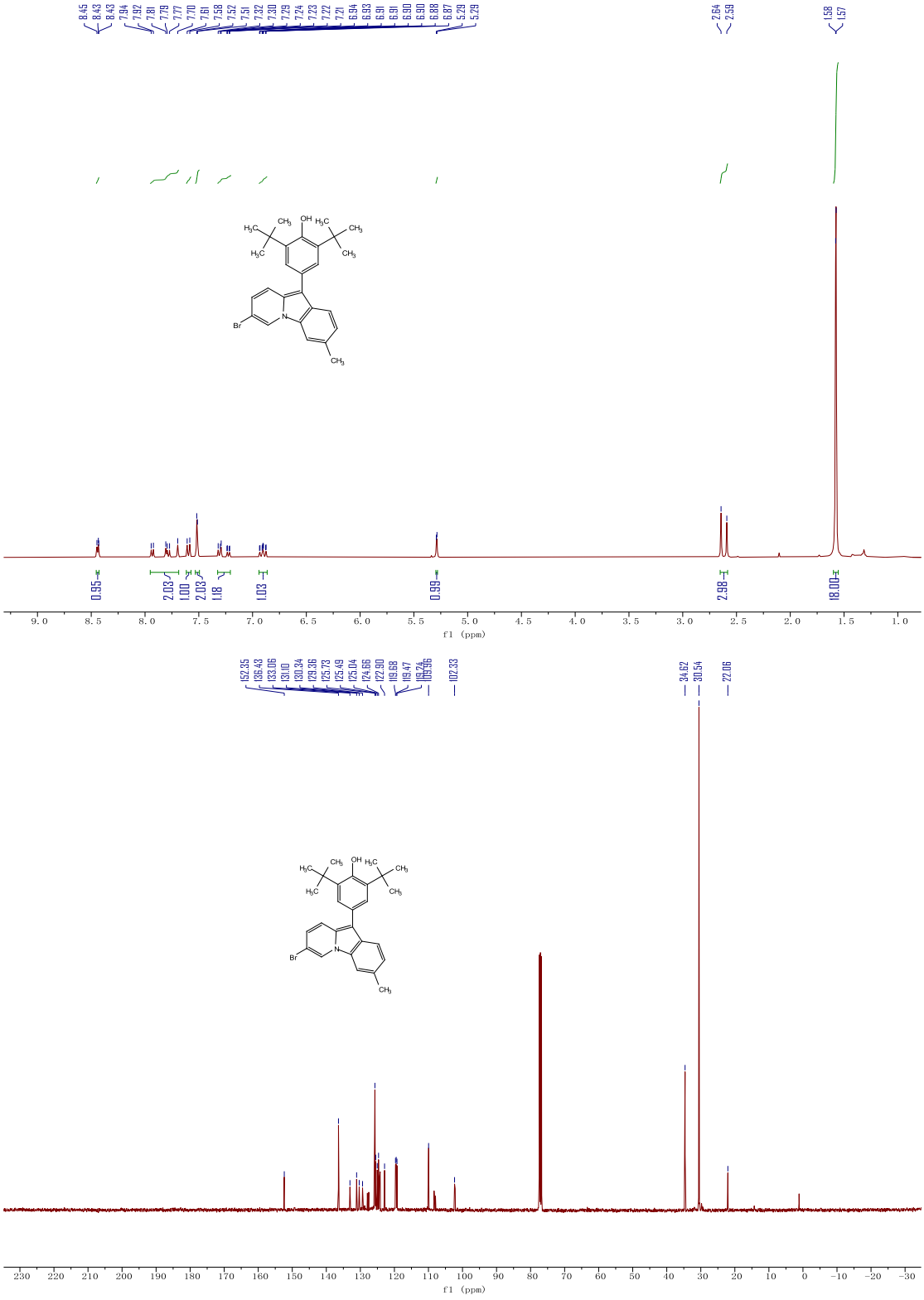


2,6-di-tert-butyl-4-(8-chloro-3-methylpyrido[1,2-a]indol-10-yl)phenol(3w)

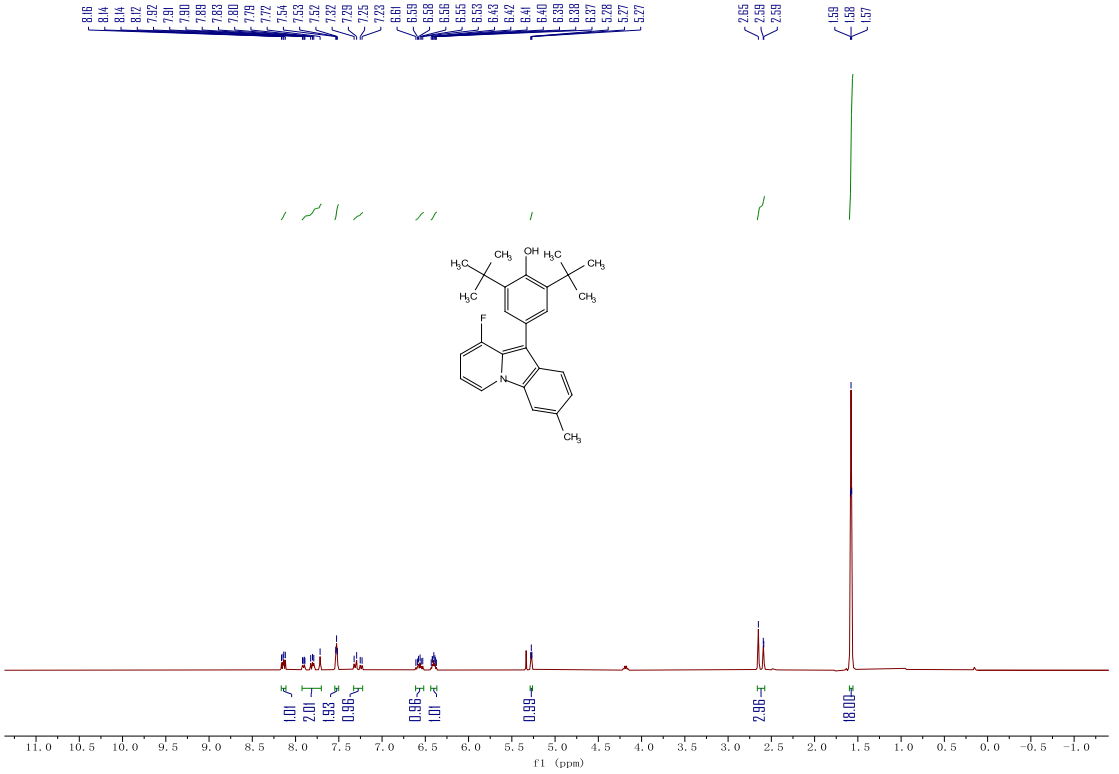


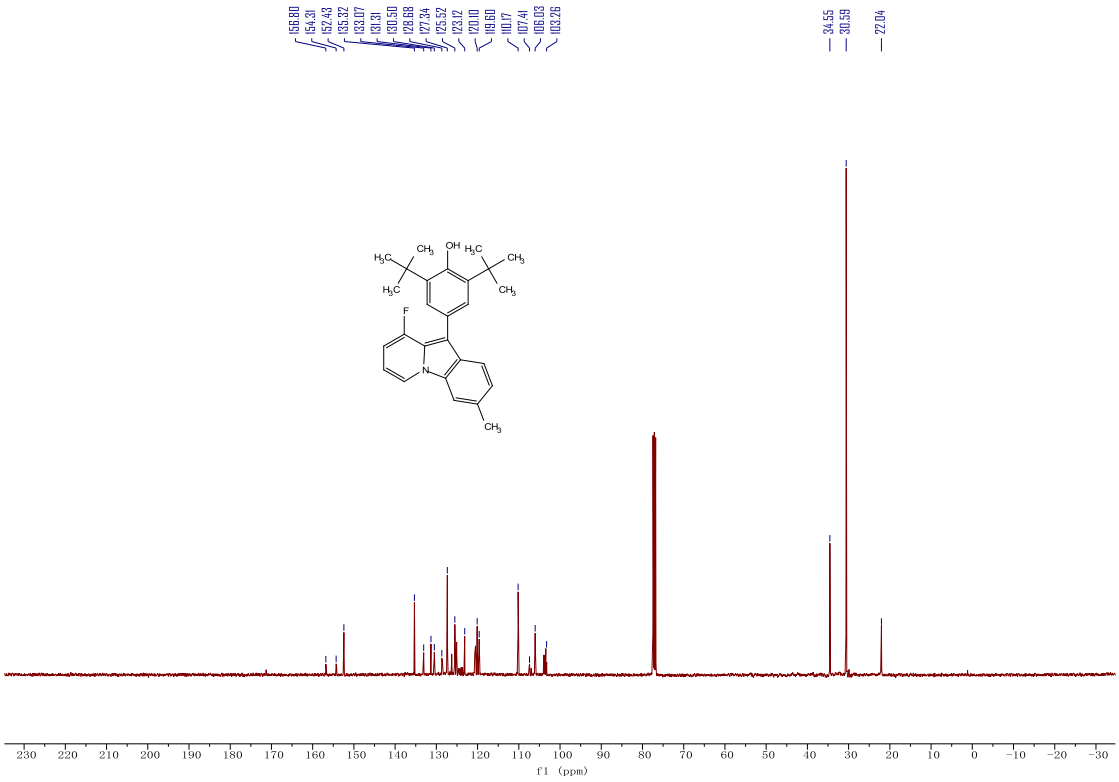


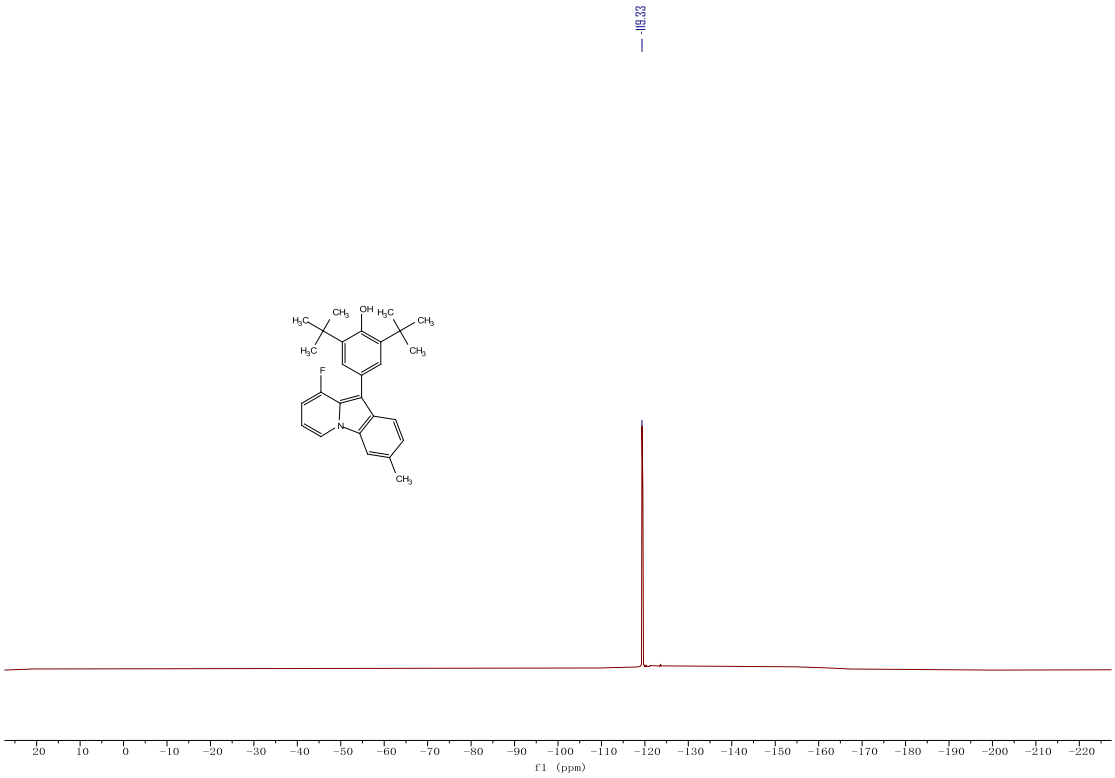
4-(7-bromo-3-methylpyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3x)



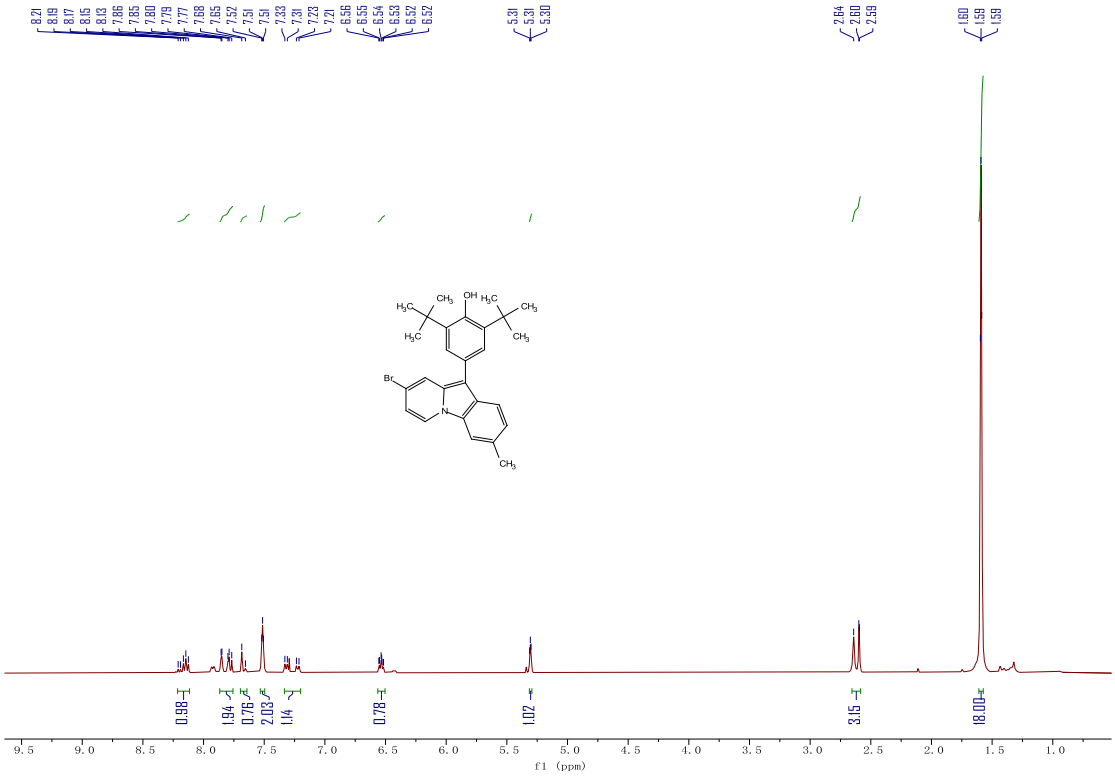
2,6-di-tert-butyl-4-(9-fluoro-3-methylpyrido[1,2-a]indol-10-yl)phenol(3y)

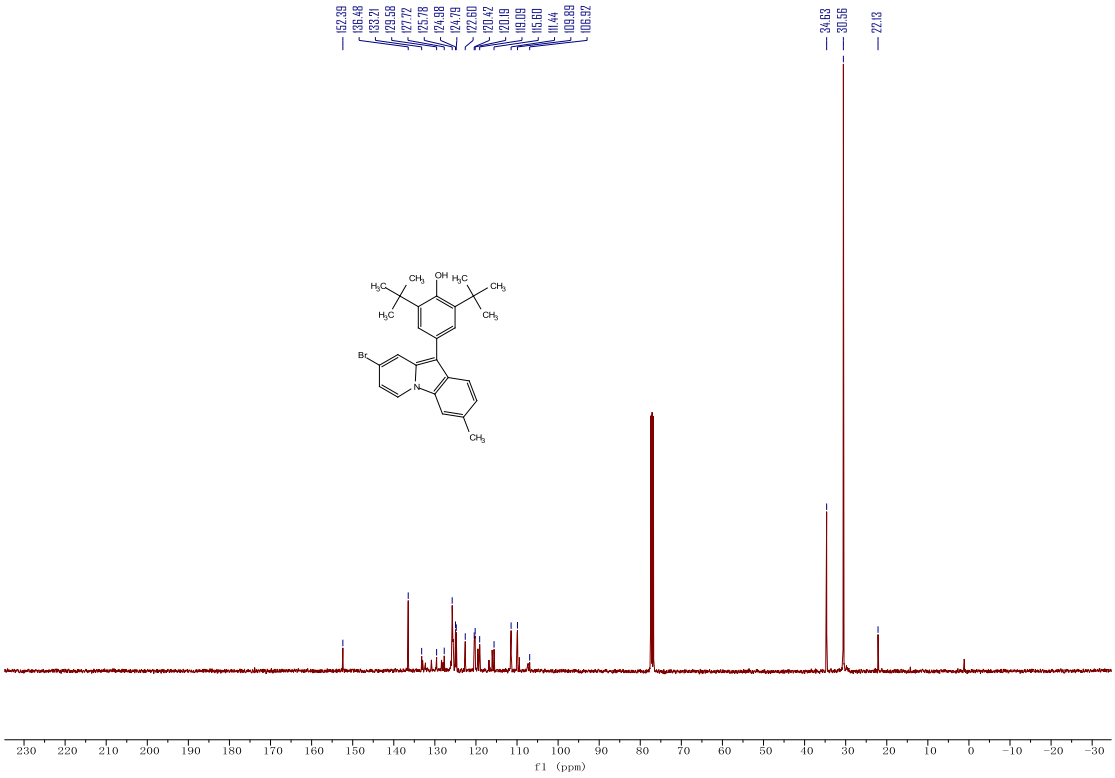




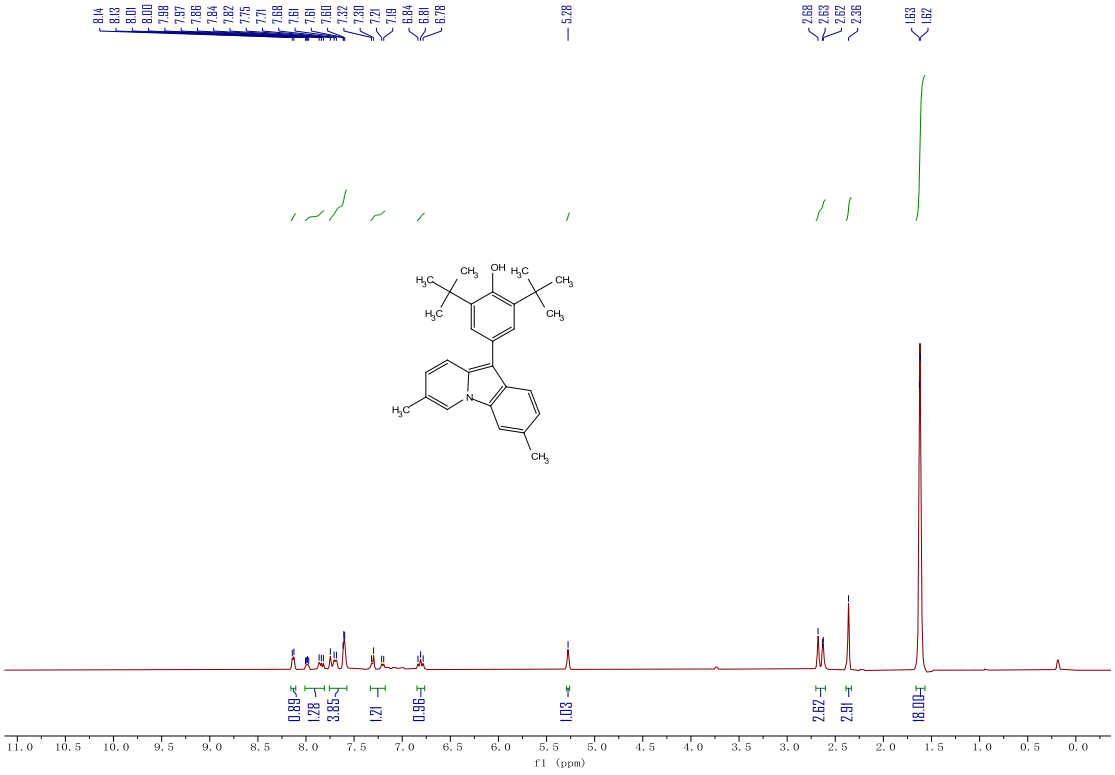

-119.33
OH
CH3
H3C
H3C
CH3
H3C
CH3
F
N
CH3
20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210 −220
f1 (ppm)

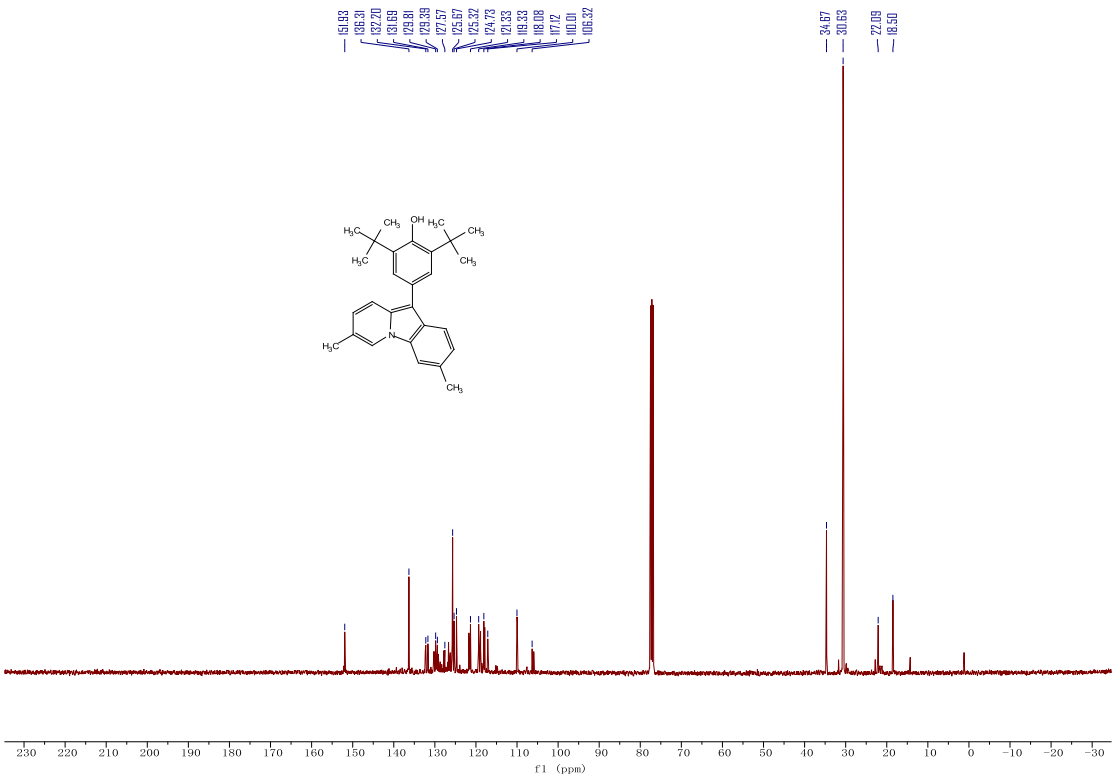
4-(8-bromo-3-methylpyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol(3z)



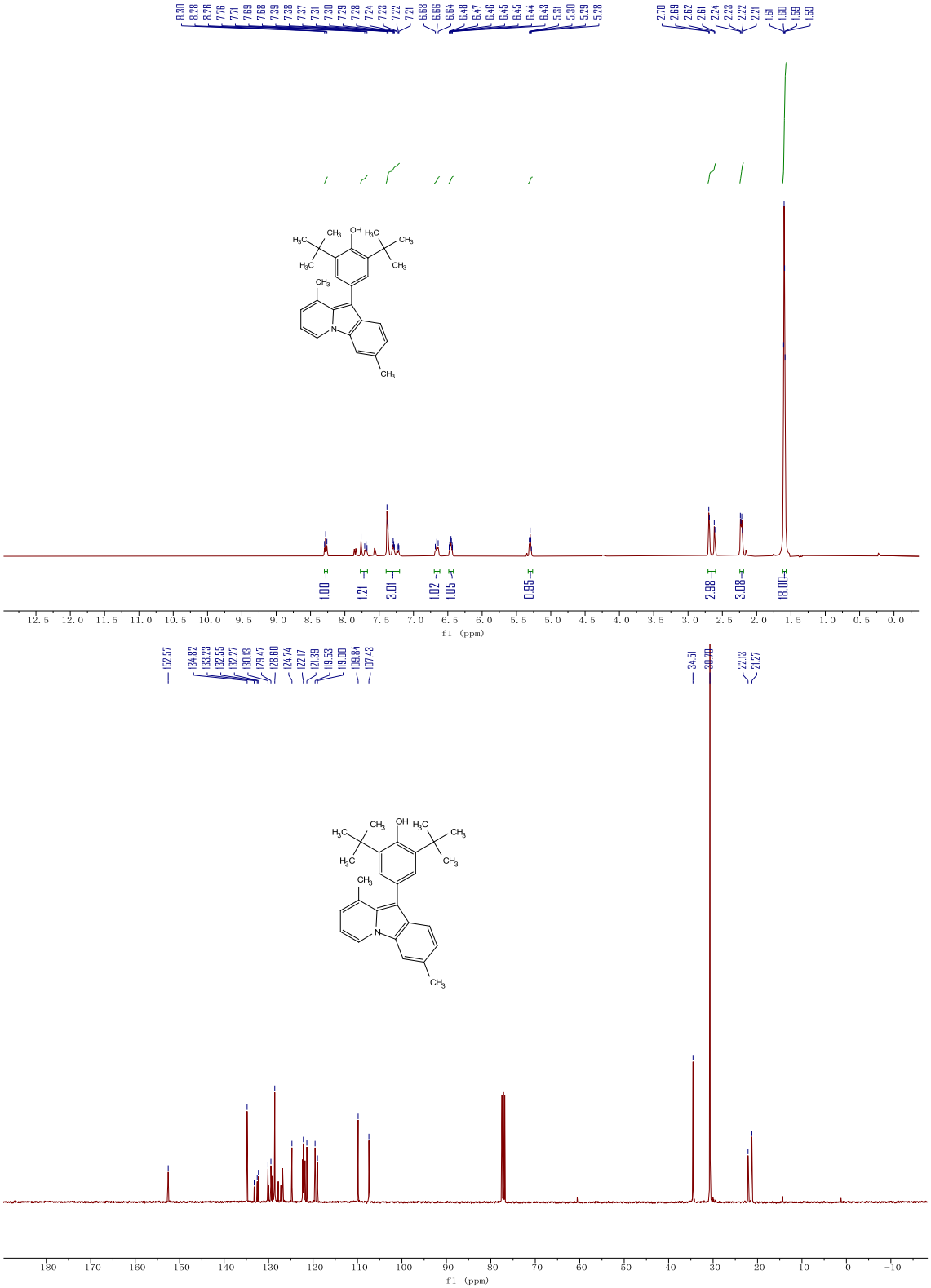


2,6-di-tert-butyl-4-(3,7-dimethylpyrido[1,2-a]indol-10-yl)phenol(3aa)

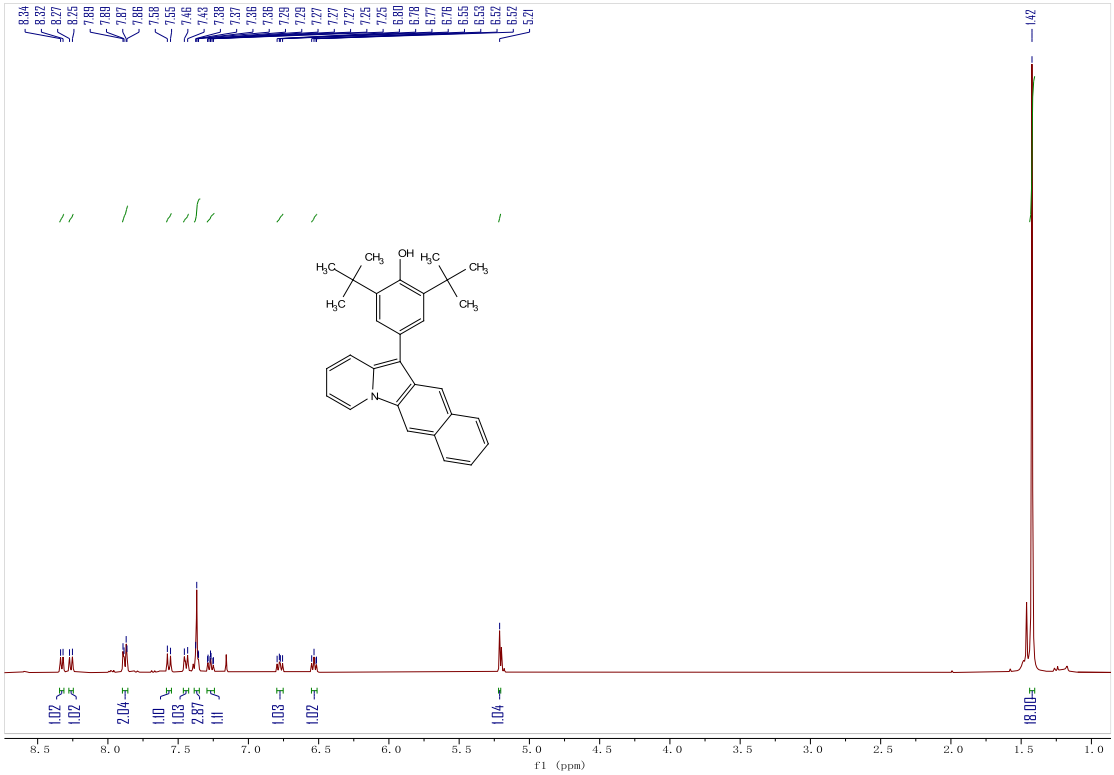


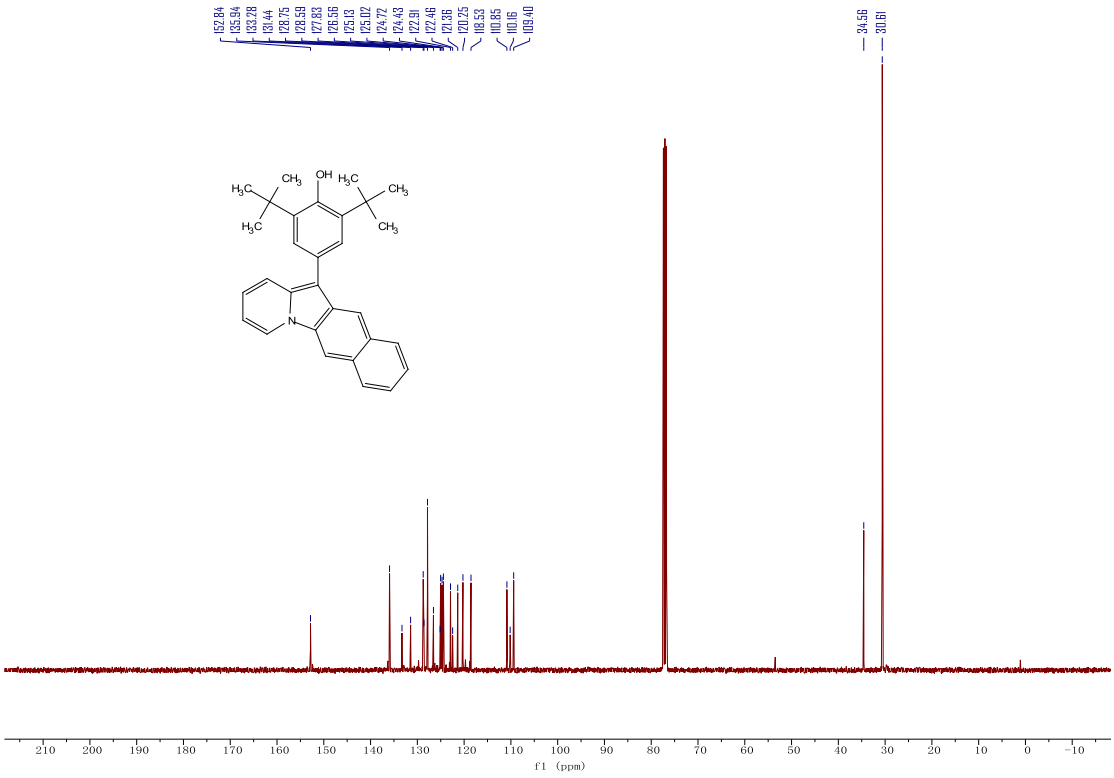


2,6-di-tert-butyl-4-(3,9-dimethylpyrido[1,2-a]indol-10-yl)phenol(3ab)

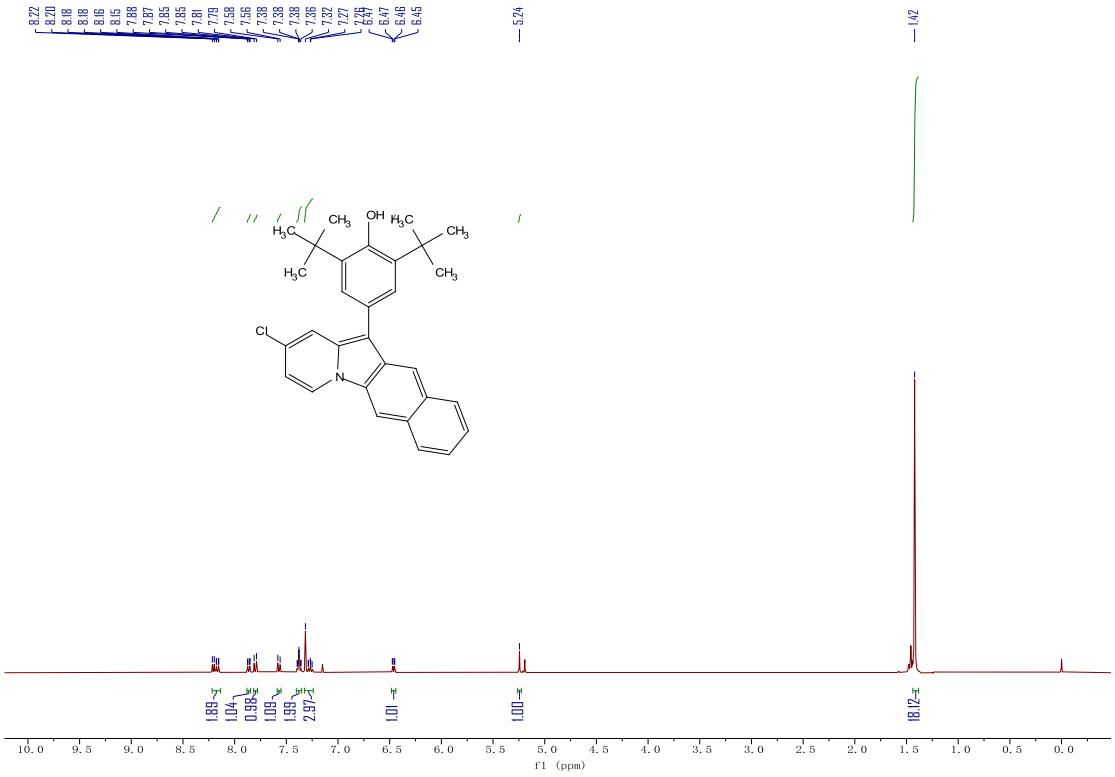


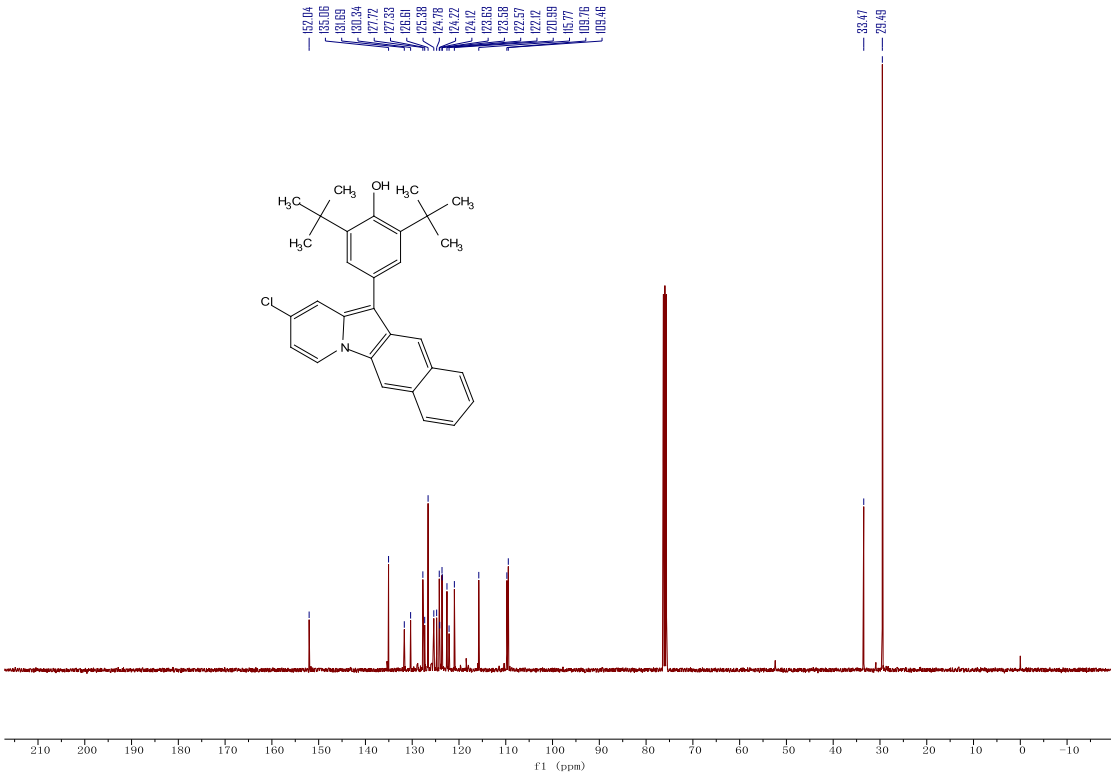
4-(benzo[f]pyrido[1,2-a]indol-12-yl)-2,6-di-tert-butylphenol(3ac)



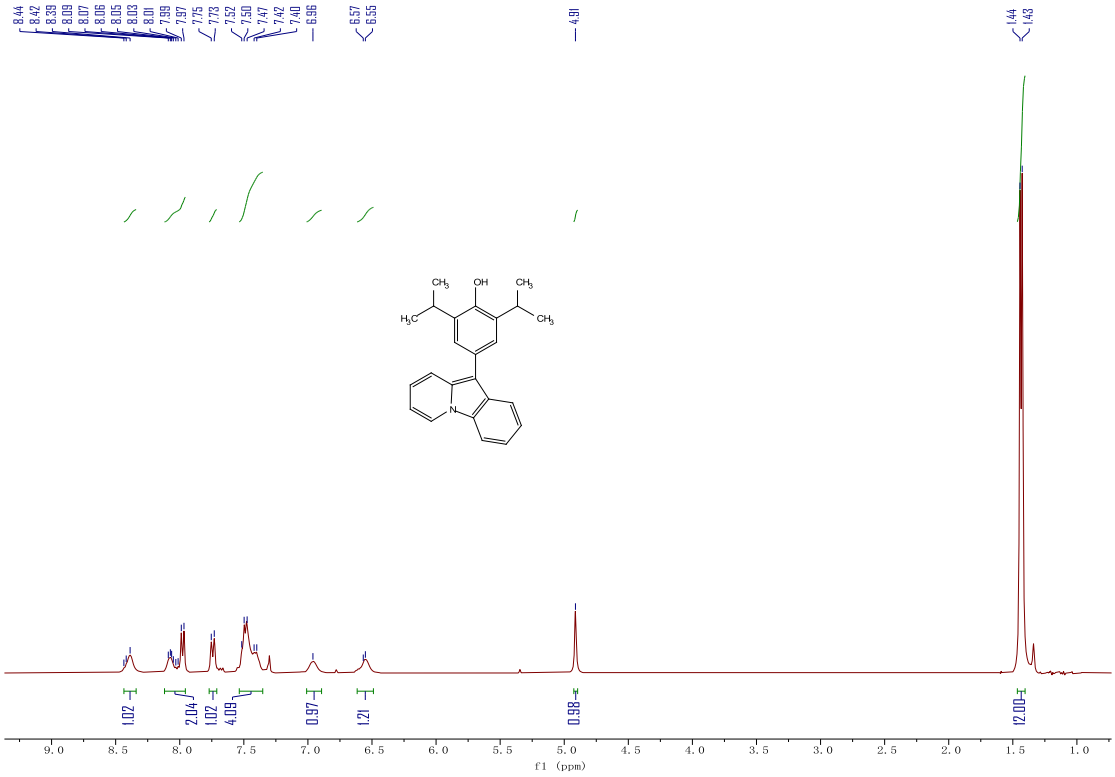


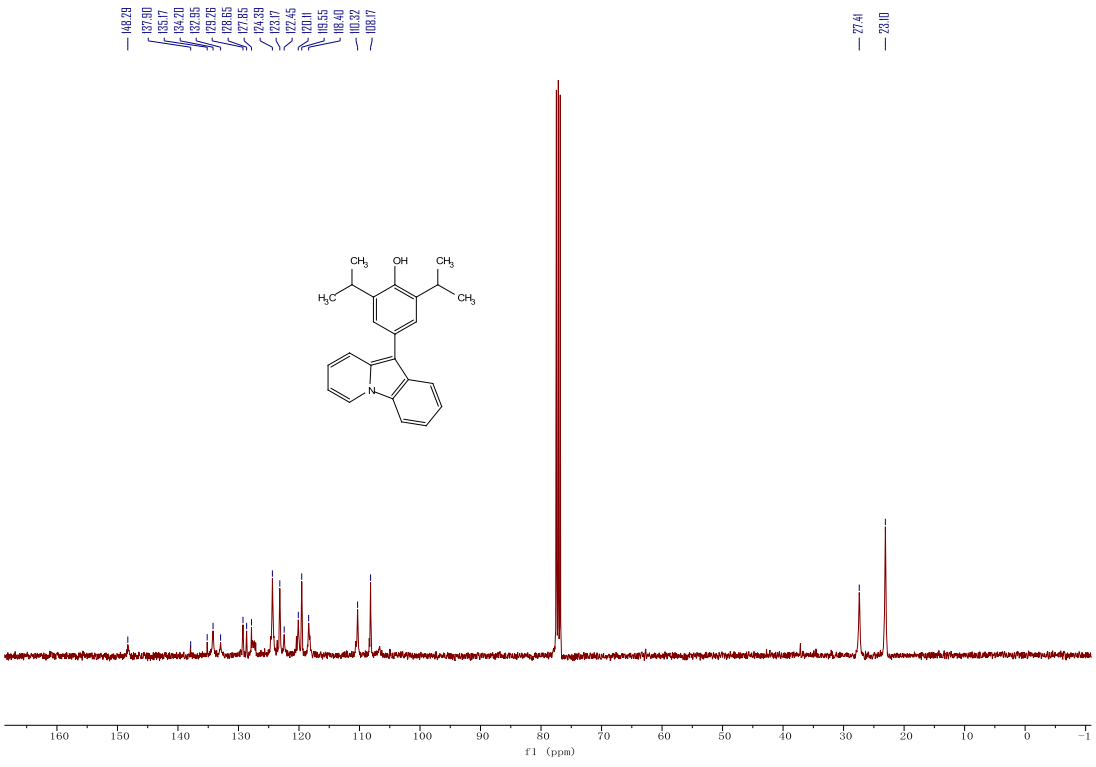
2,6-di-tert-butyl-4-(2-chlorobenzo[f]pyrido[1,2-a]indol-12-yl)phenol(3ad)



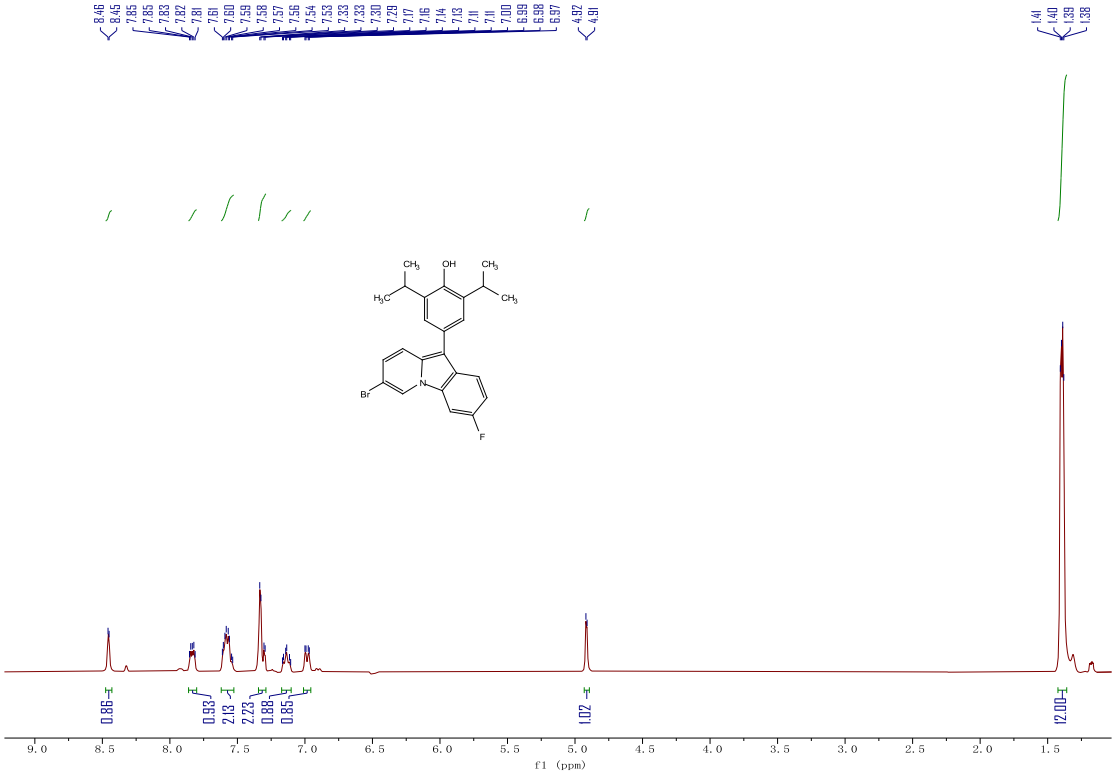


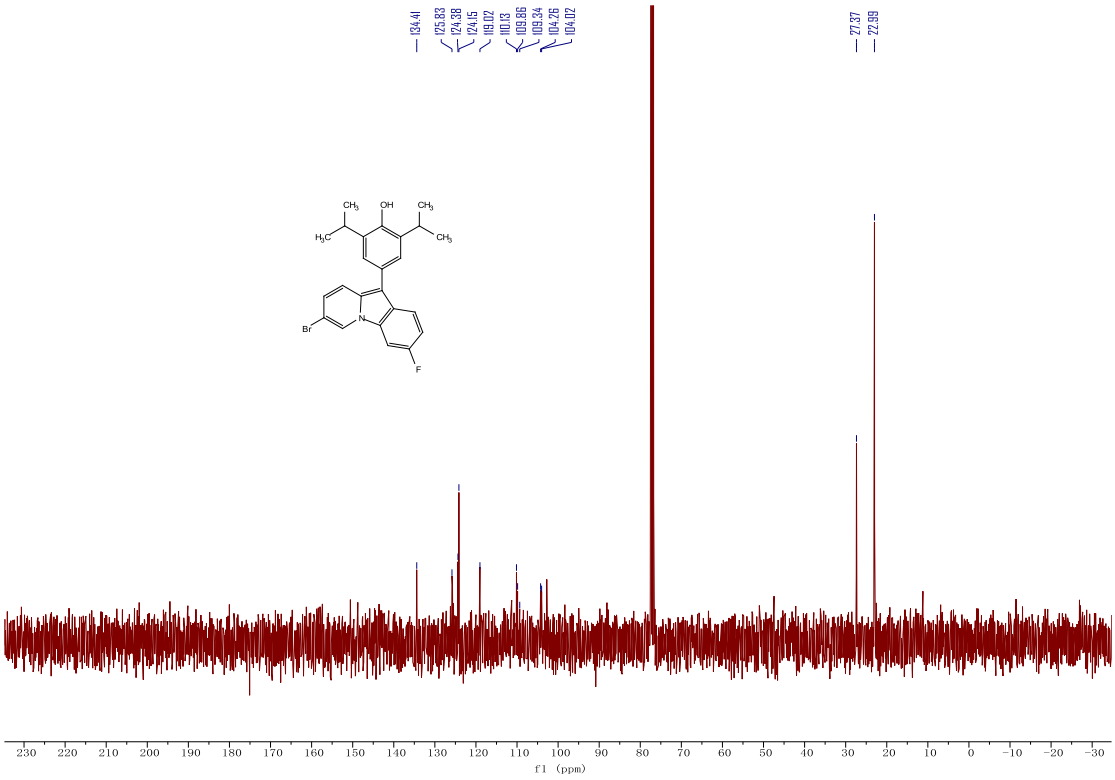
2,6-diisopropyl-4-(pyrido[1,2-a]indol-10-yl)phenol(3ae)

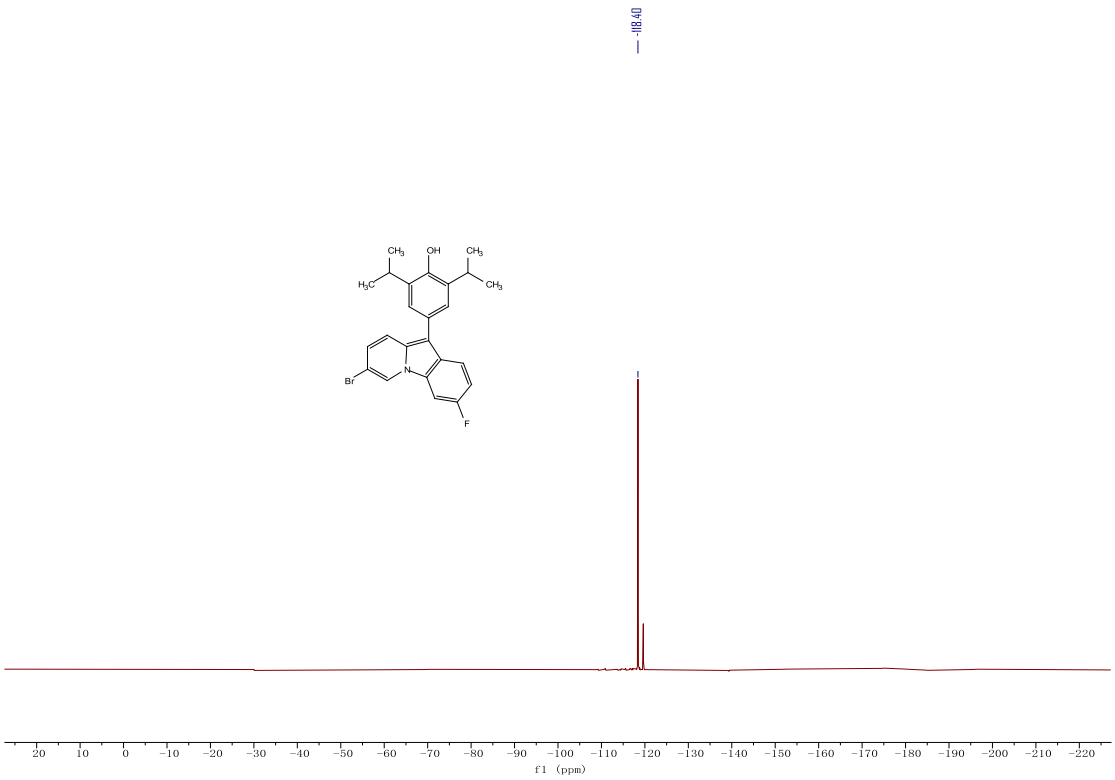




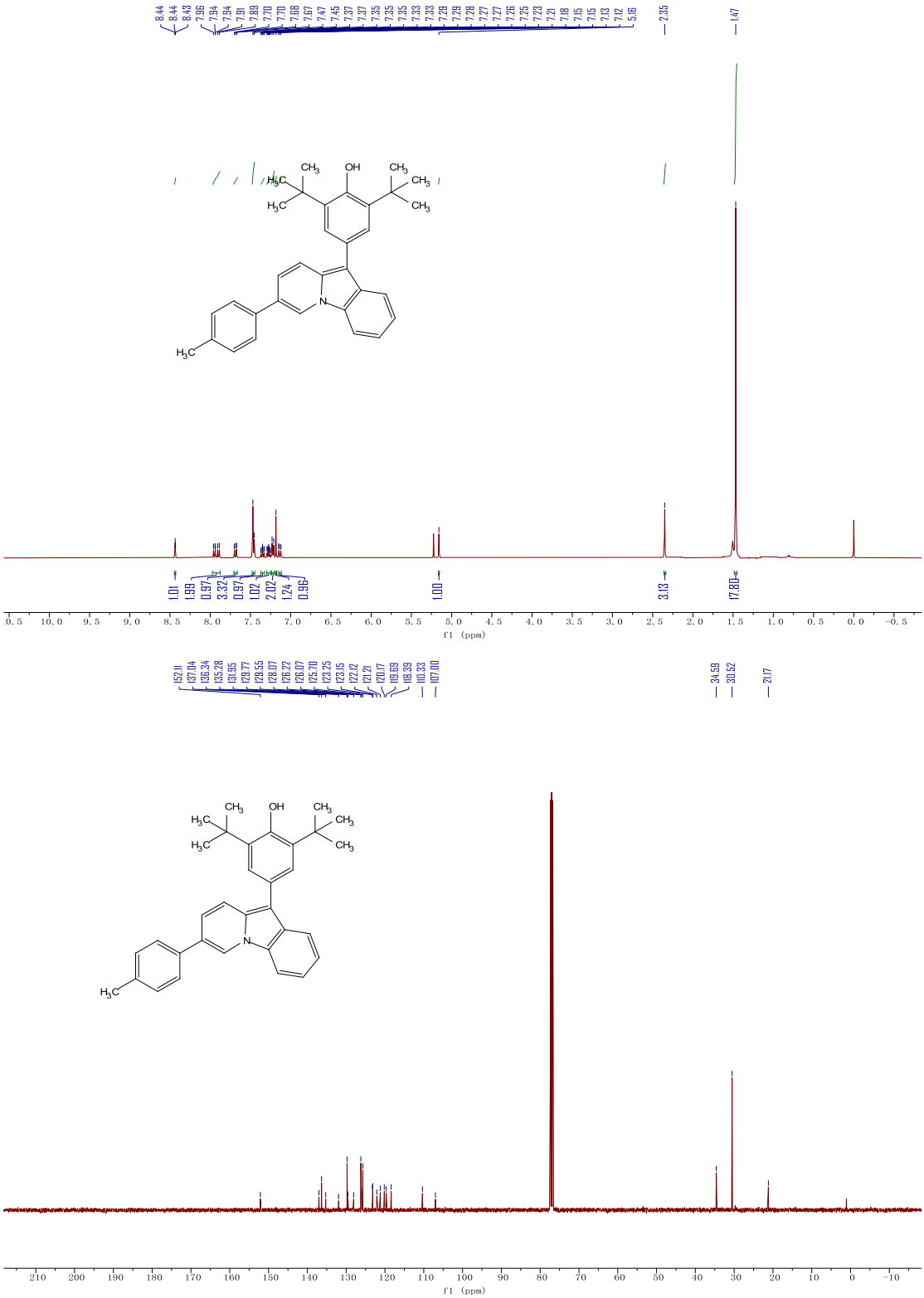
4-(7-bromo-3-fluoropyrido[1,2-a]indol-10-yl)-2,6-diisopropylphenol(3af).



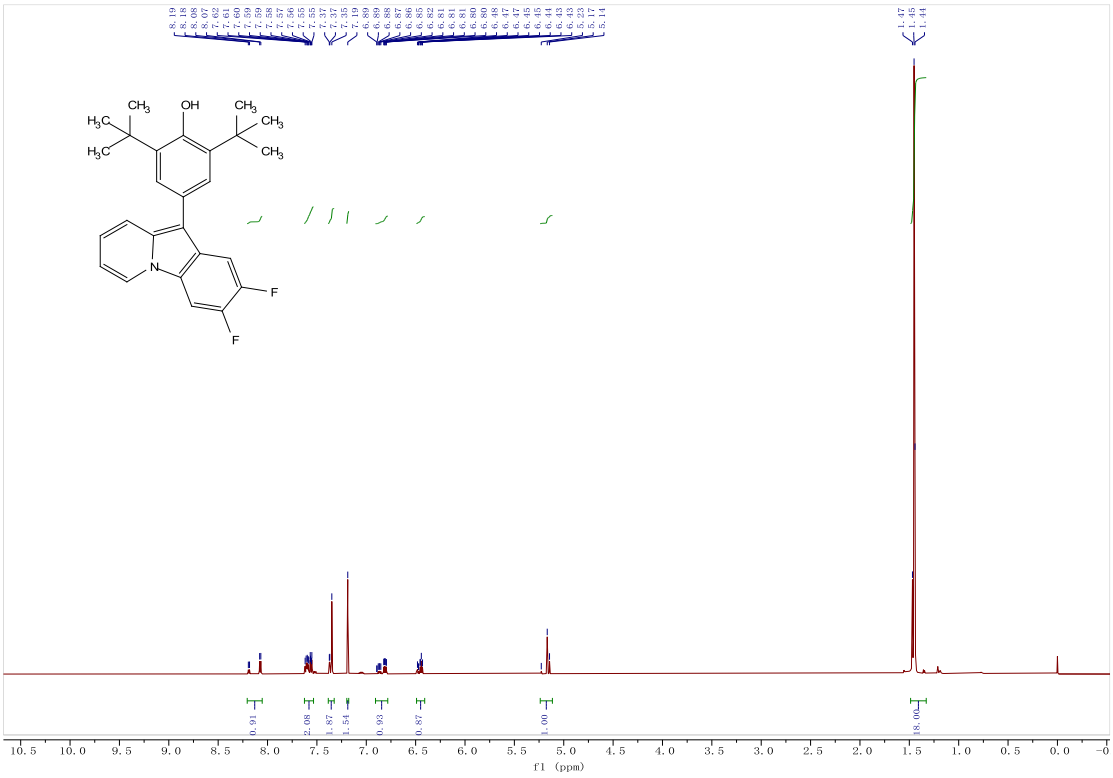


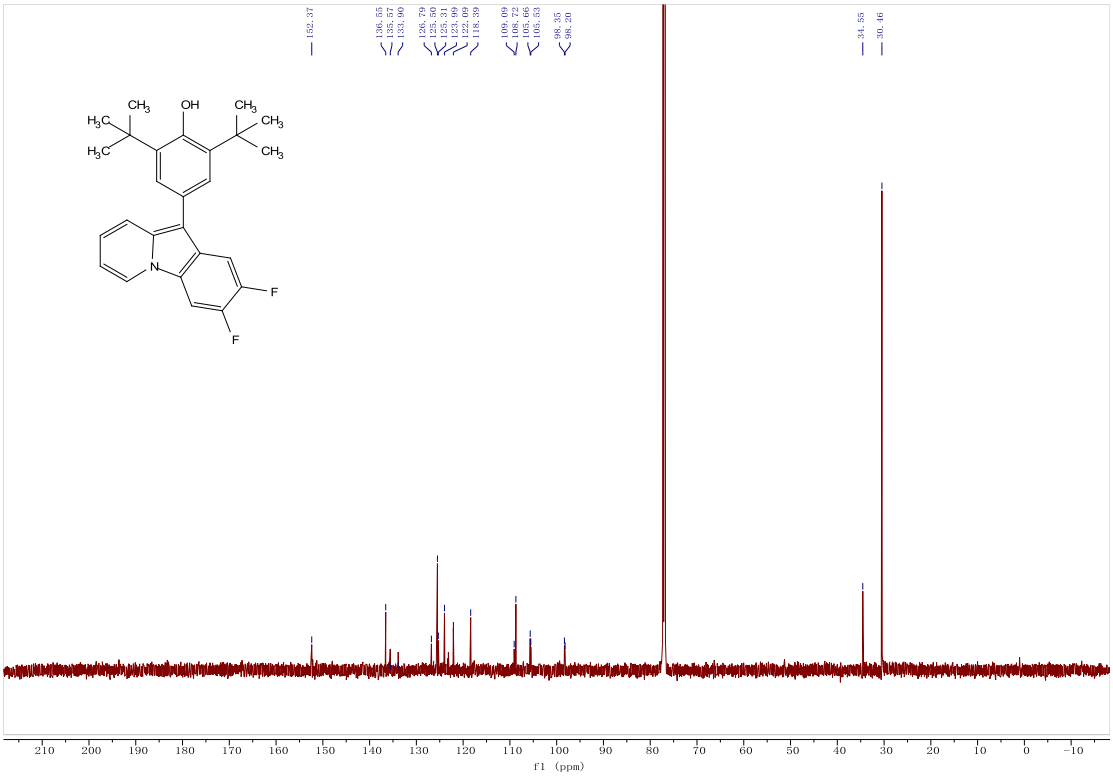

-118.40
CH3
OH
CH3
H3C
CH3
Br
N
F
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
−220
f1 (ppm)

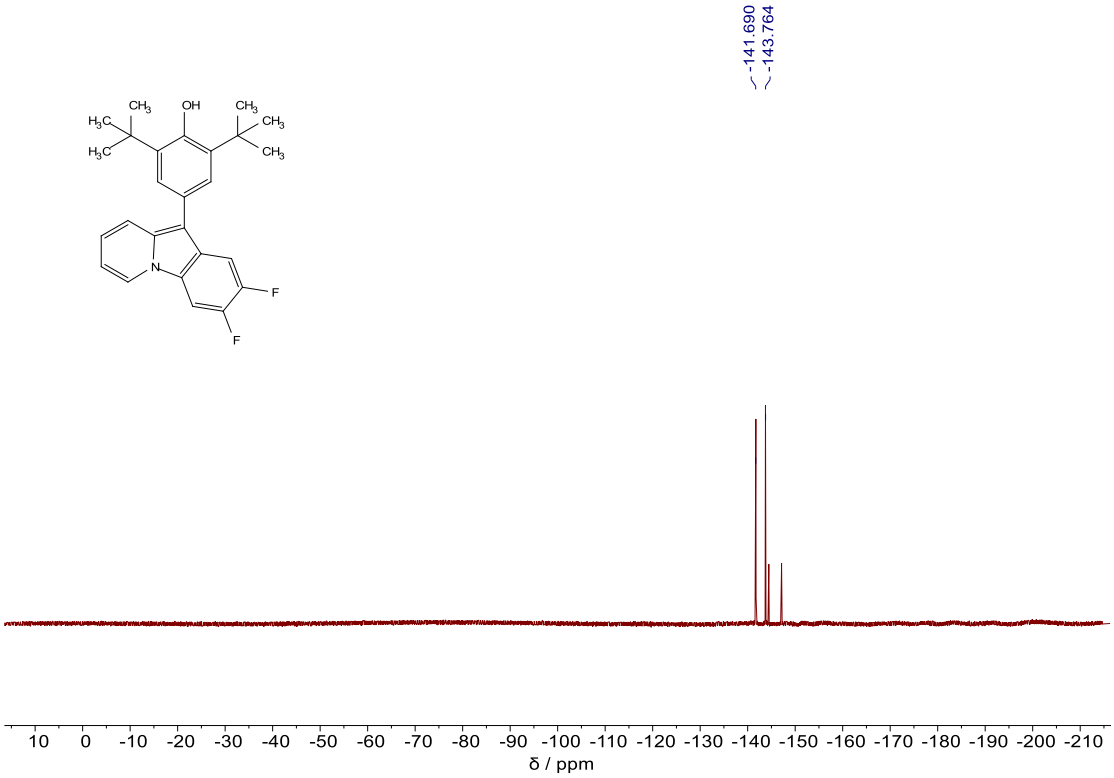
2,6-di-tert-butyl-4-(7-(p-tolyl)pyrido[1,2-a]indol-10-yl)phenol(3ag).



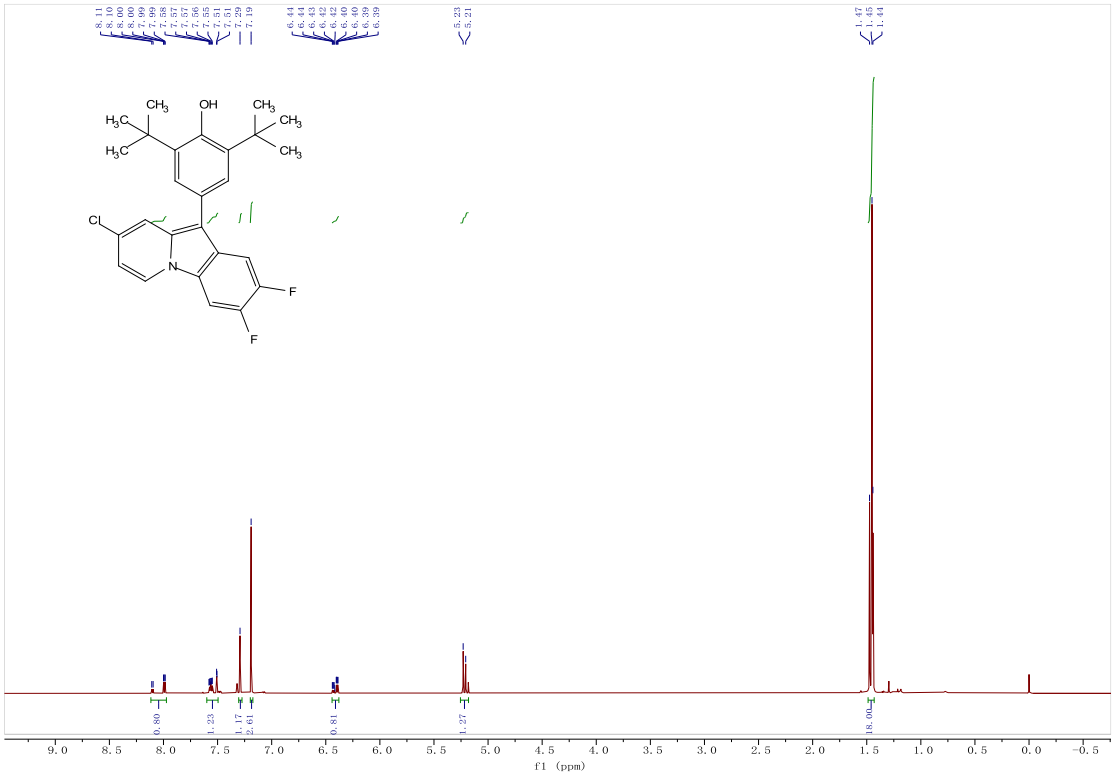
2,6-di-tert-butyl-4-(2,3-difluoropyrido[1,2-a]indol-10-yl)phenol(3ah).

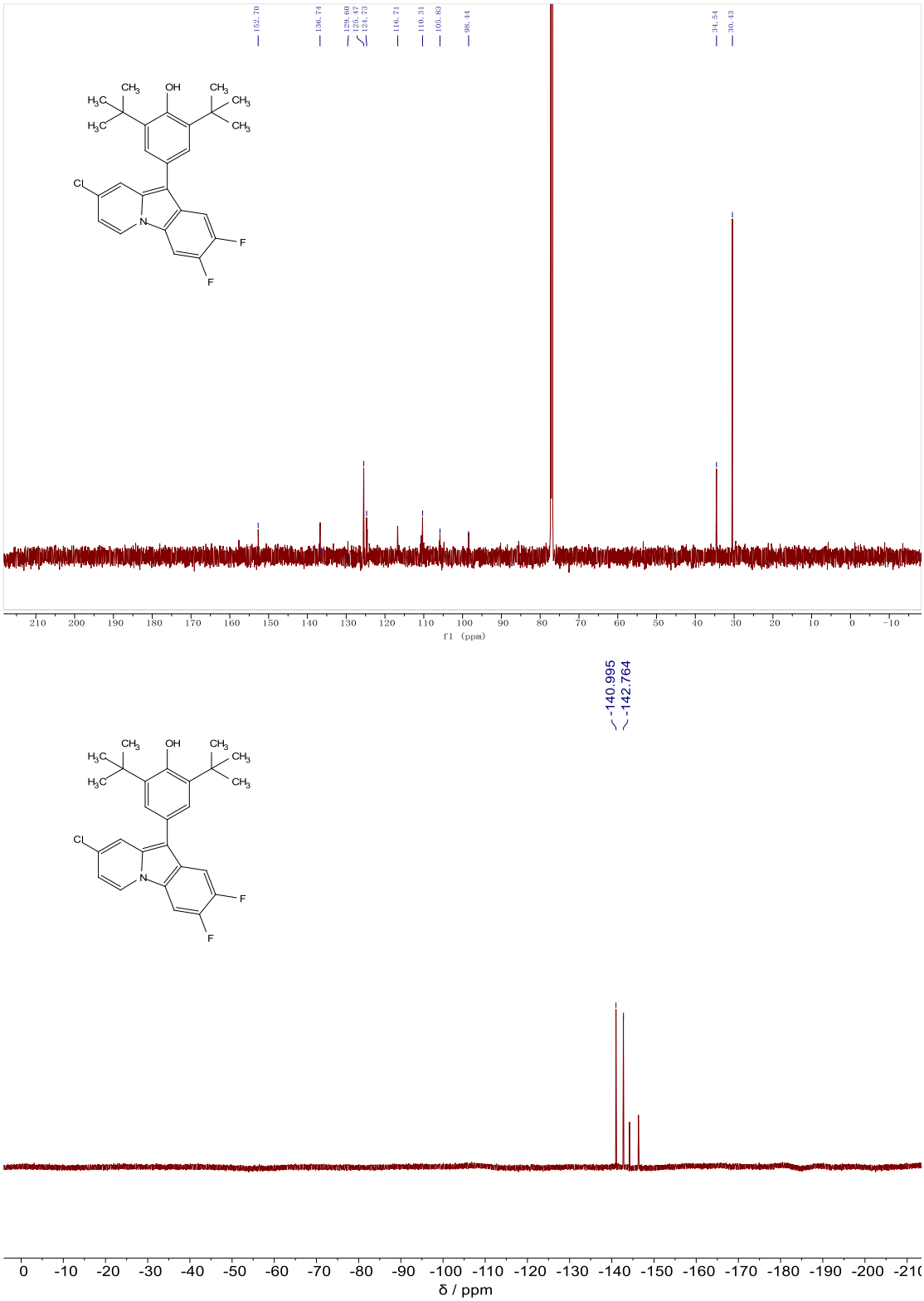

CH3
OH
CH3
H3C
CH3
H3C
CH3
N
F
F
f1 (ppm)


CH3
OH
CH3
H3C
CH3
H3C
CH3
N
F
F
f1 (ppm)

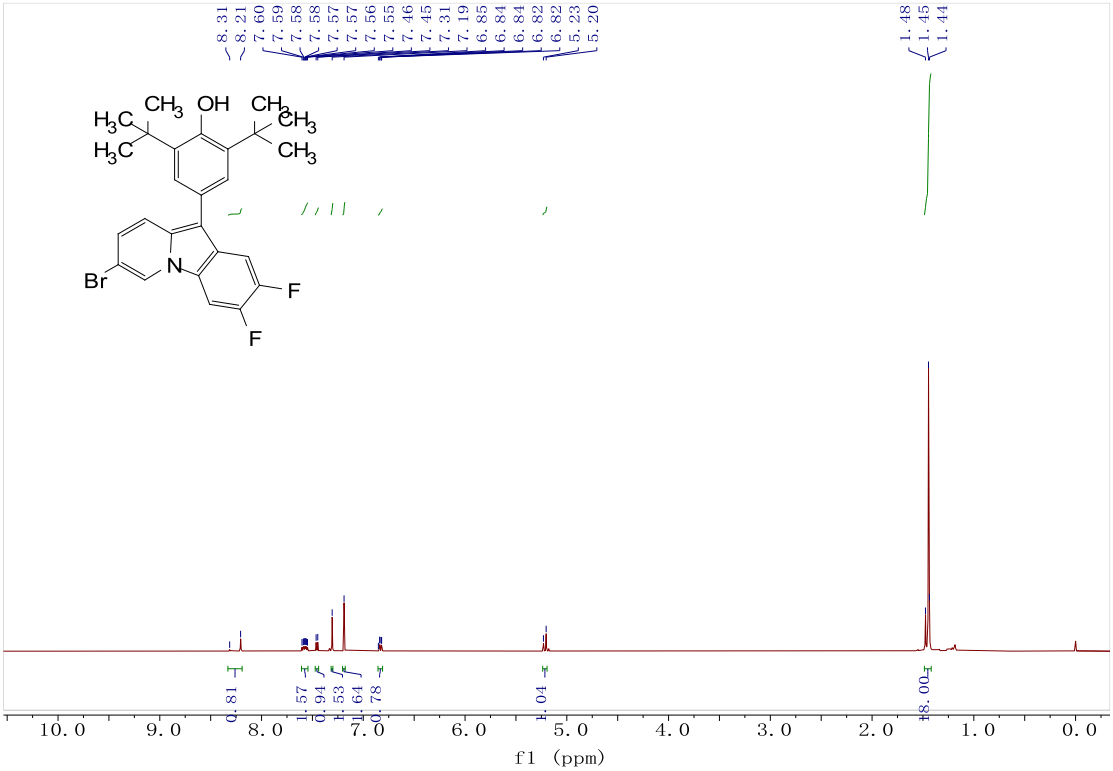


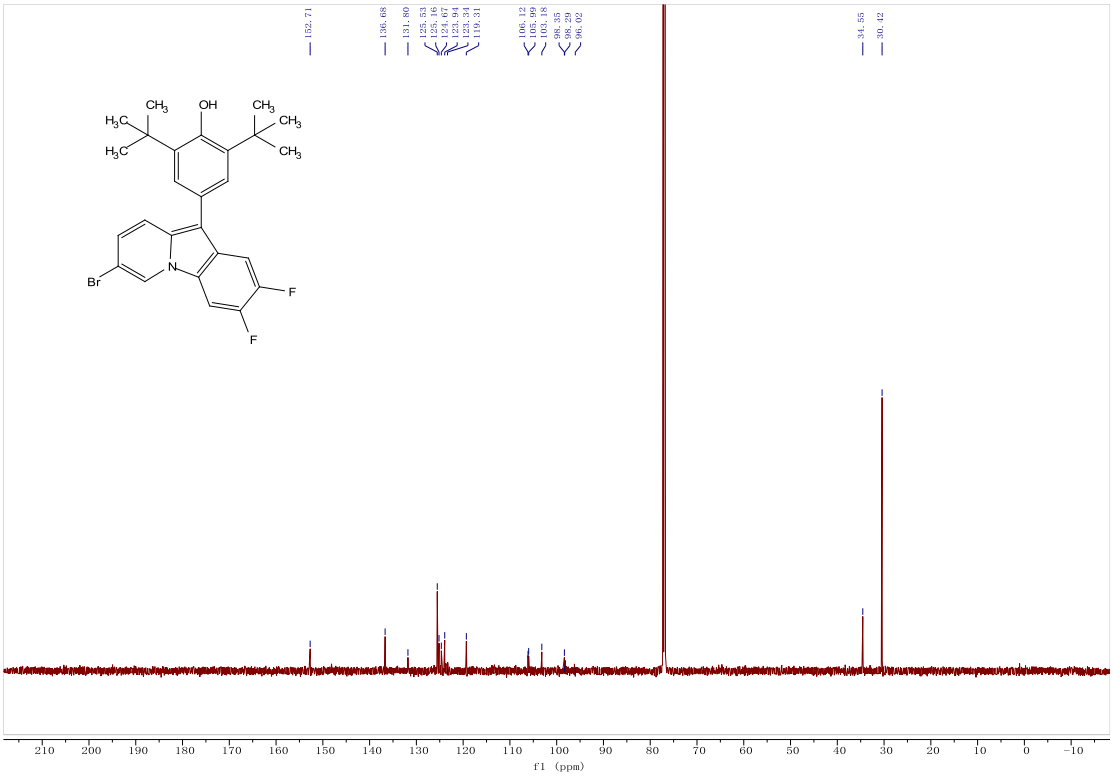
2,6-di-tert-butyl-4-(8-chloro-2,3-difluoropyrido[1,2-a]indol-10-yl)phenol (3ai).

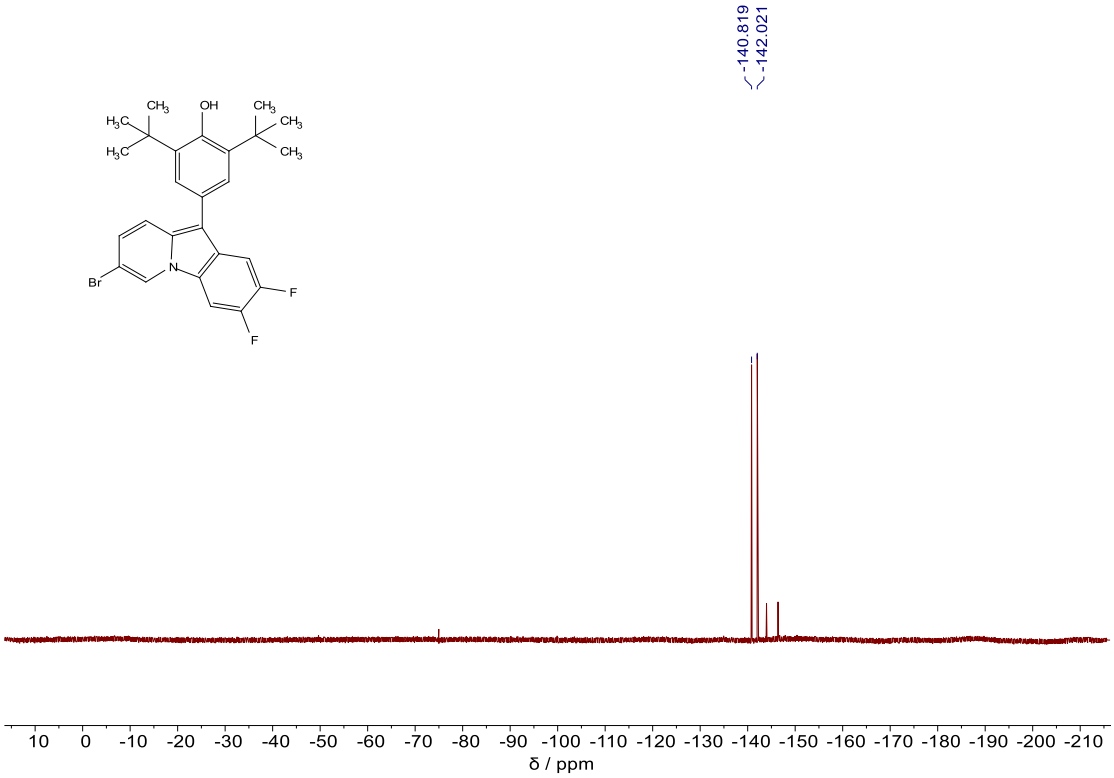




4-(7-bromo-2,3-difluoropyrido[1,2-a]indol-10-yl)-2,6-di-tert-butylphenol (3aj).


8.31
8.21
7.60
7.59
7.58
7.58
7.57
7.57
7.56
7.55
7.46
7.45
7.31
7.19
6.85
6.84
6.84
6.82
6.82
5.23
5.20
1.48
1.45
1.44
CH3
OH
CH3
H3C
CH3
H3C
CH3
N
Br
F
F
0.81
1.57
0.94
1.53
1.64
0.78
1.04
18.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


152.71
136.68
131.89
125.53
125.16
124.67
123.94
123.34
119.31
106.12
105.99
103.18
98.35
98.29
96.02
34.55
30.42
CH3
OH
CH3
H3C
CH3
H3C
CH3
N
Br
F
F
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)


-140.819
-142.021
CH3
OH
CH3
H3C
CH3
H3C
CH3
N
Br
F
F
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
δ / ppm