Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry


# Towards β-Selectivity in Functional Estrogen Receptor Antagonists

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*[e] Institute of Food Science, Food Technology and Nutrition (ICTAN), Spanish National Research Council (CSIC), José Antonio Novais 10, 28040-Madrid, Spain.*

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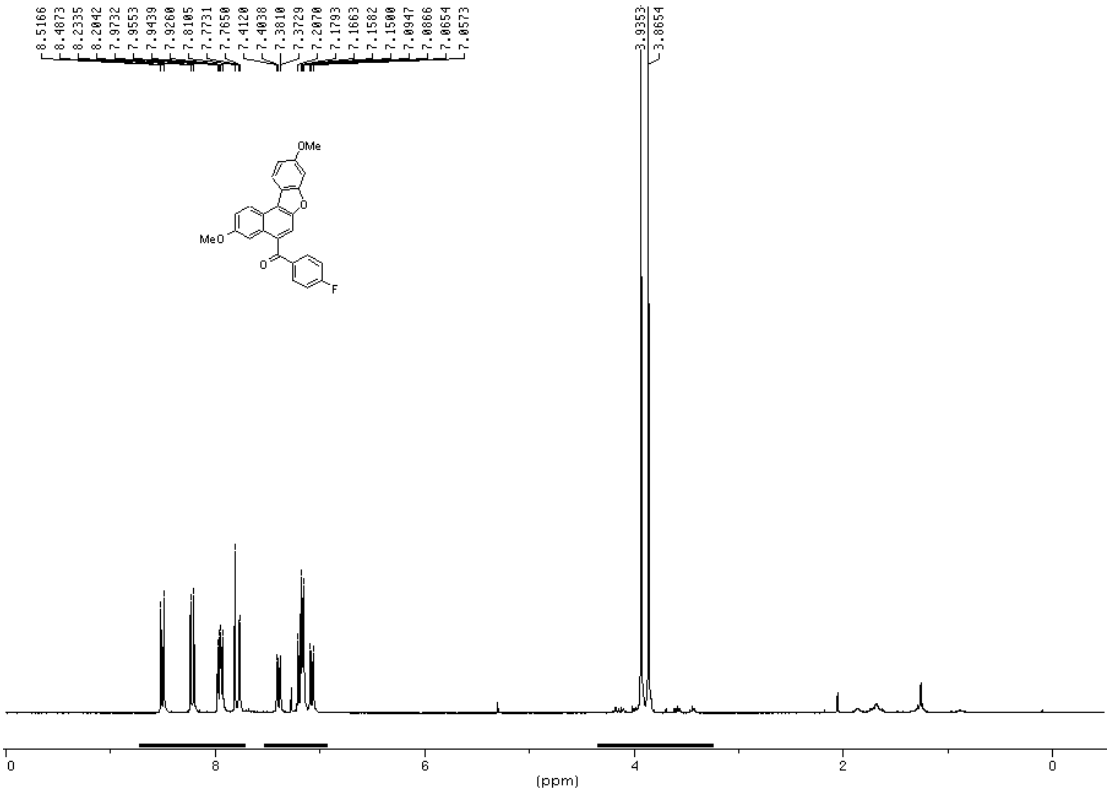


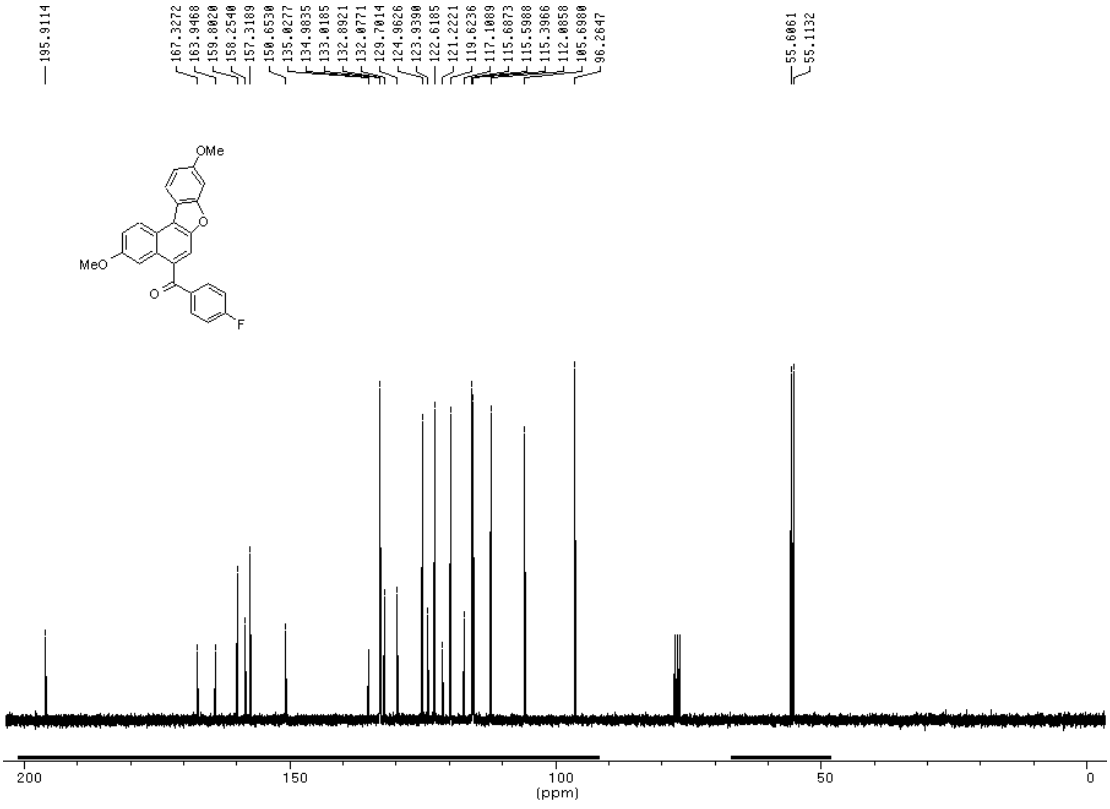

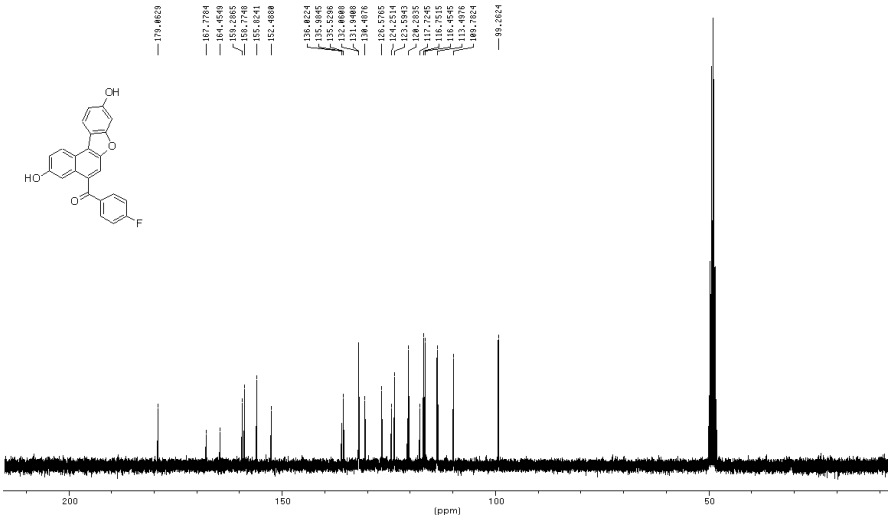
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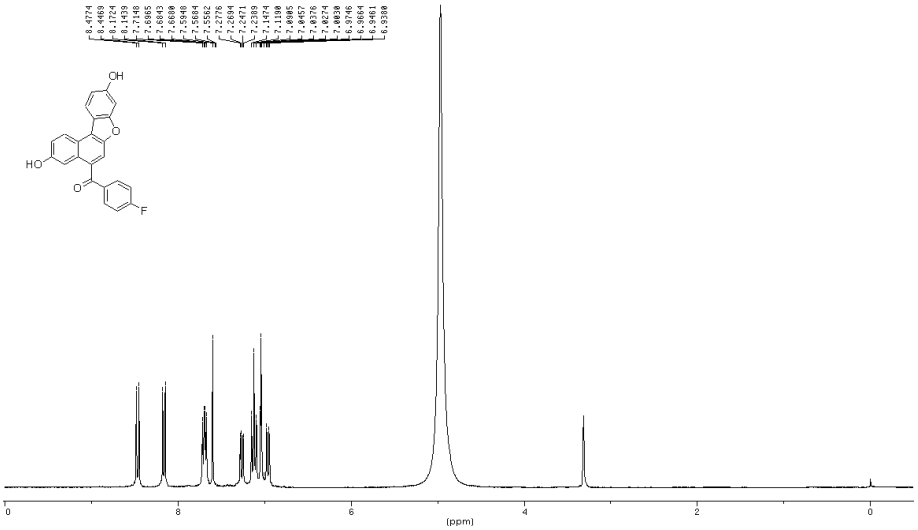
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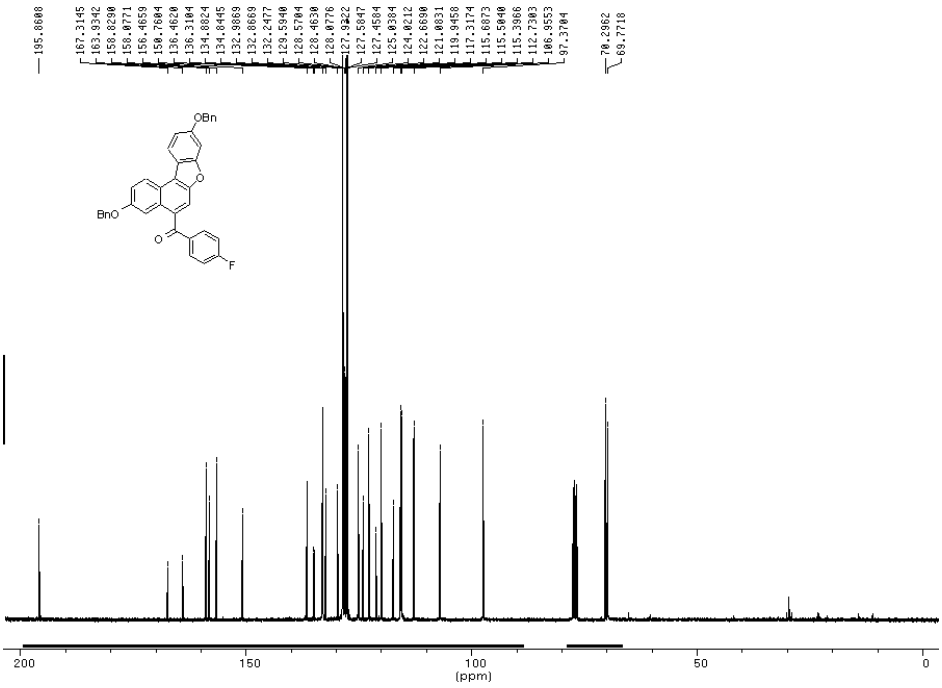
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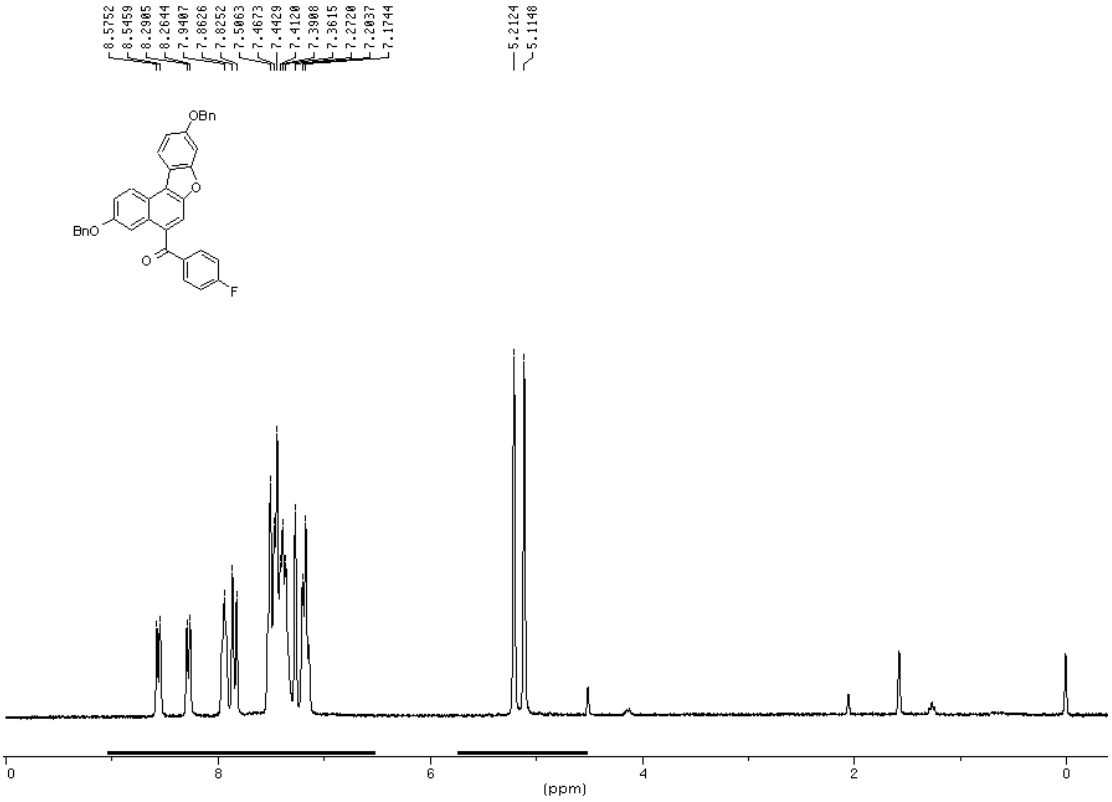


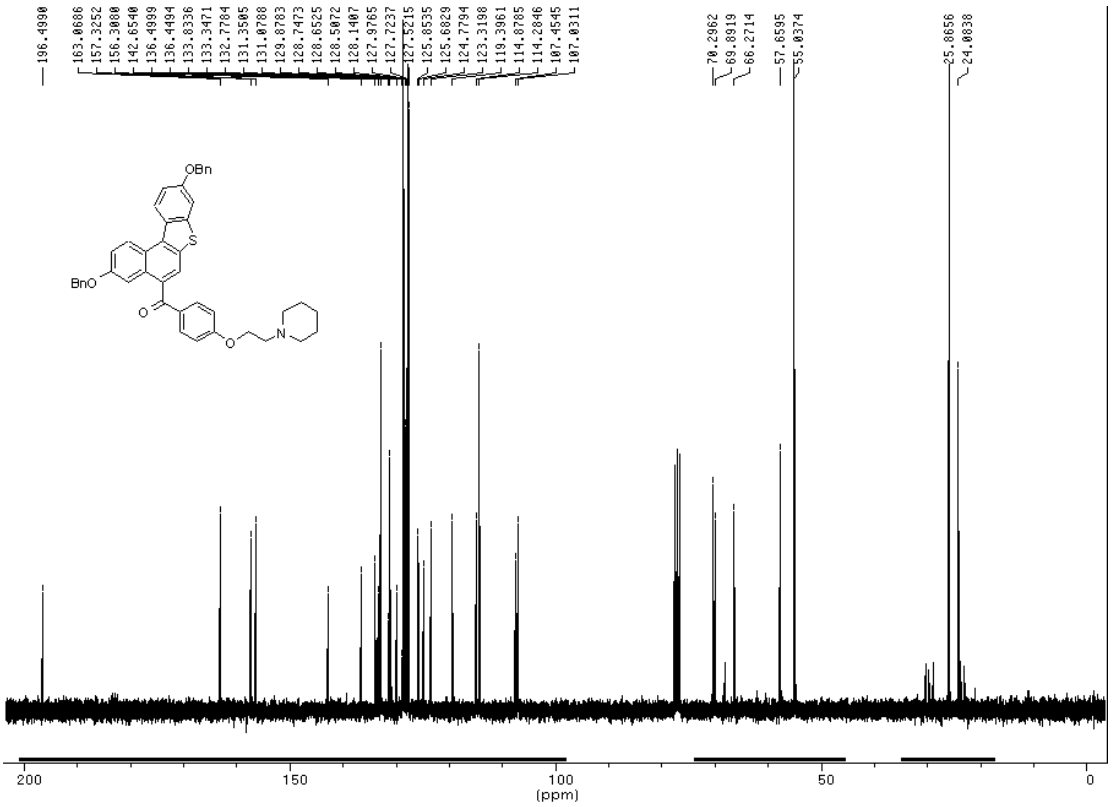

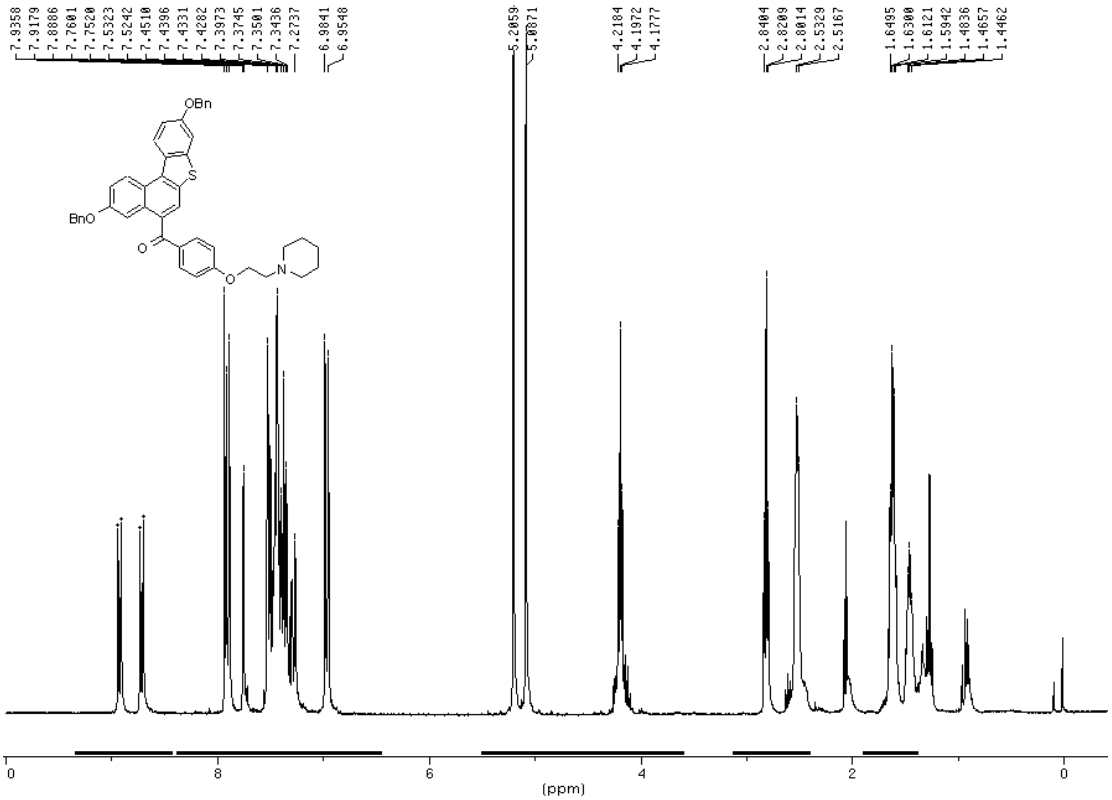


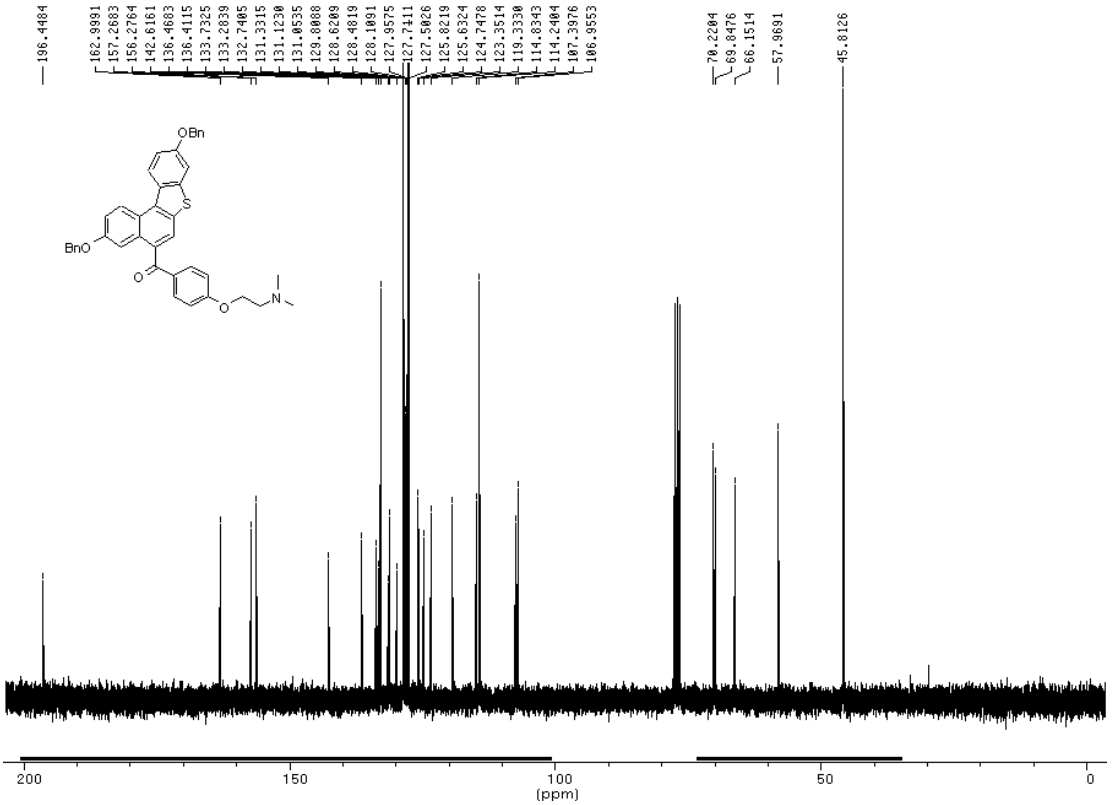

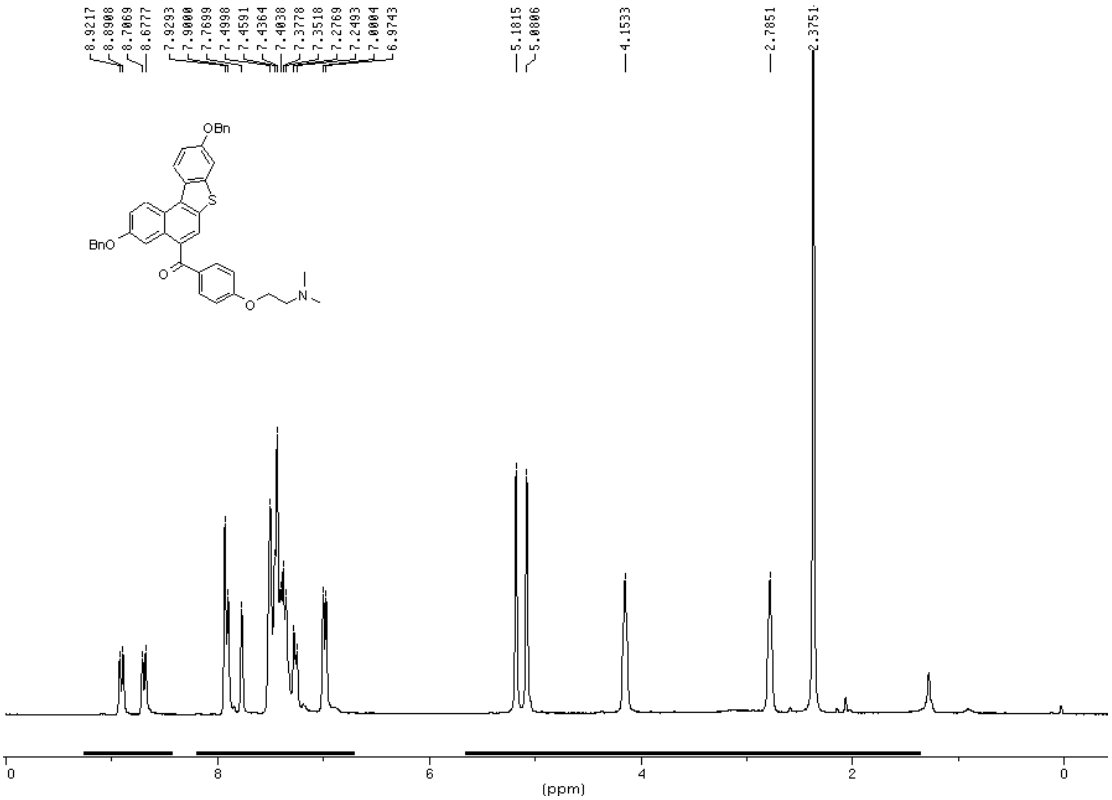


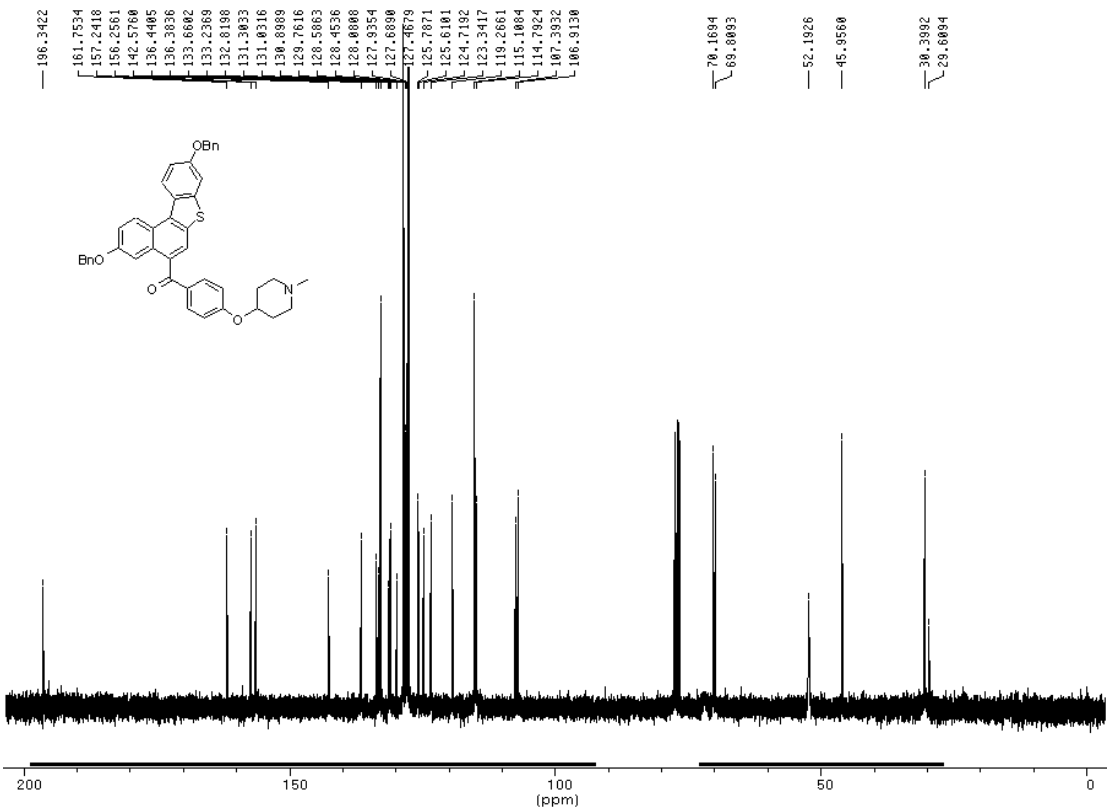

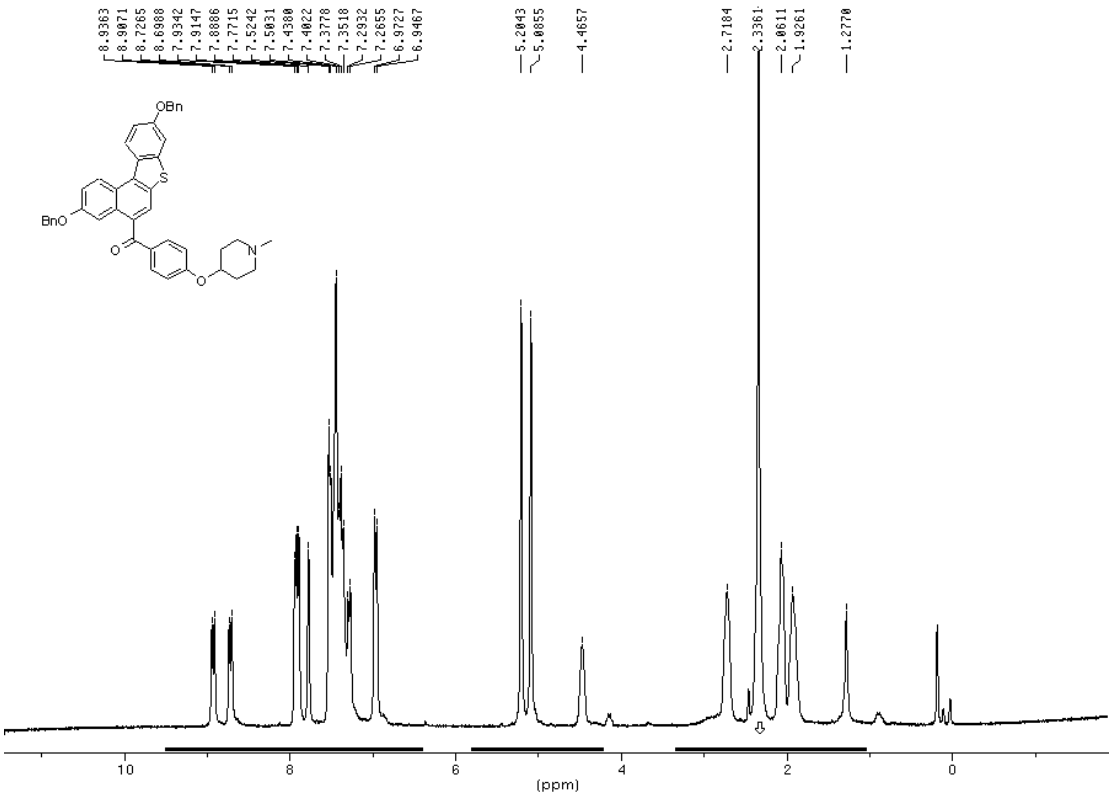


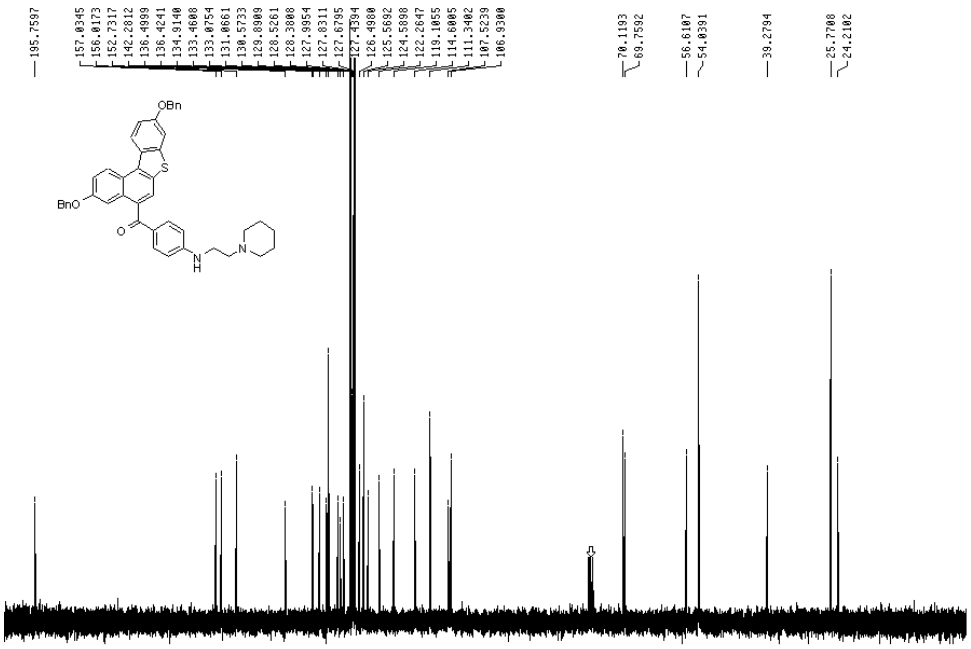

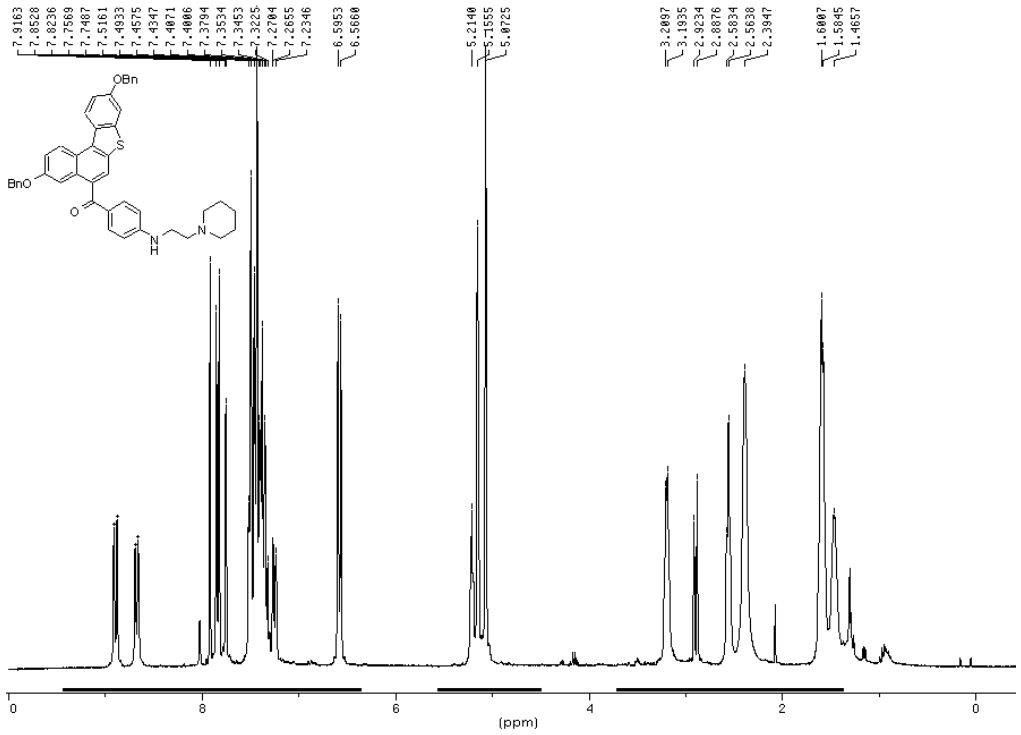
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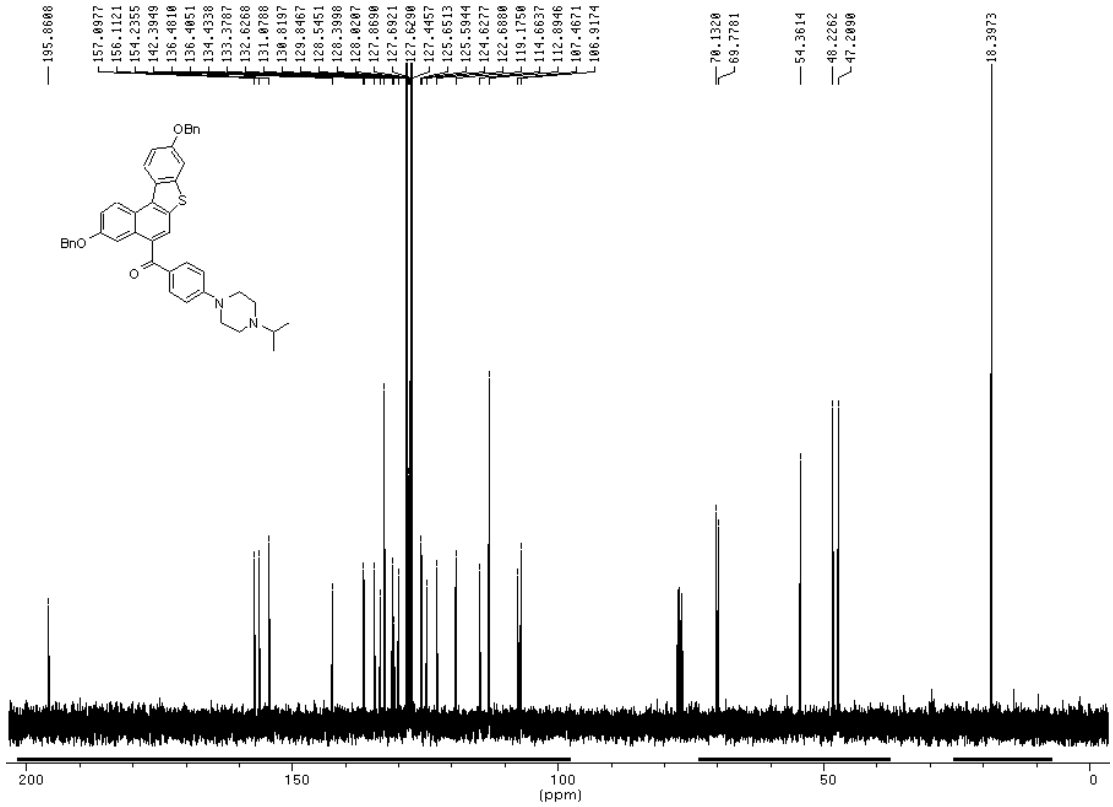
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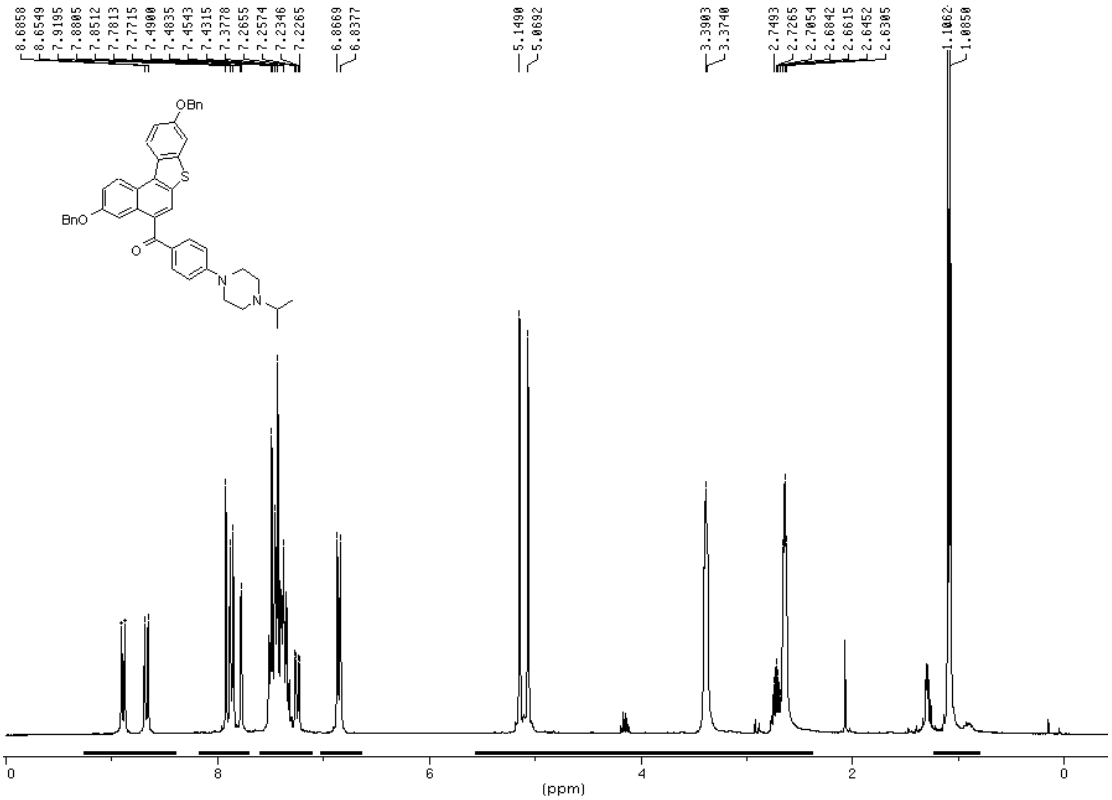
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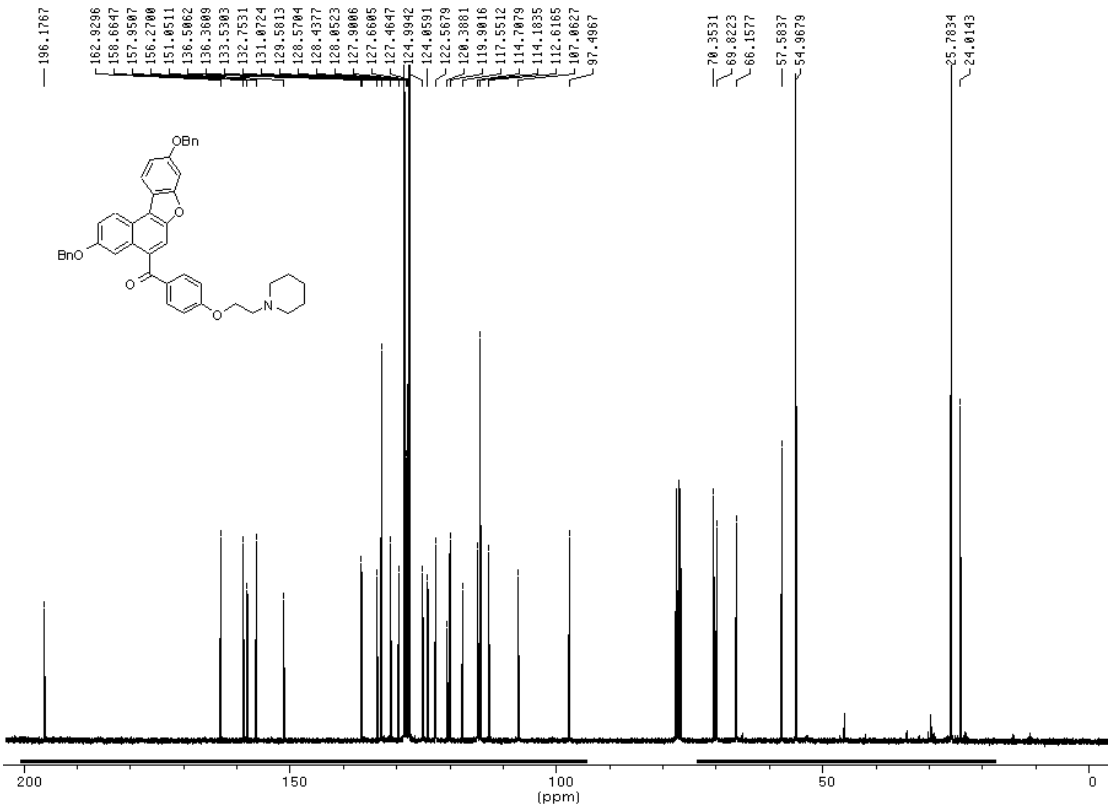
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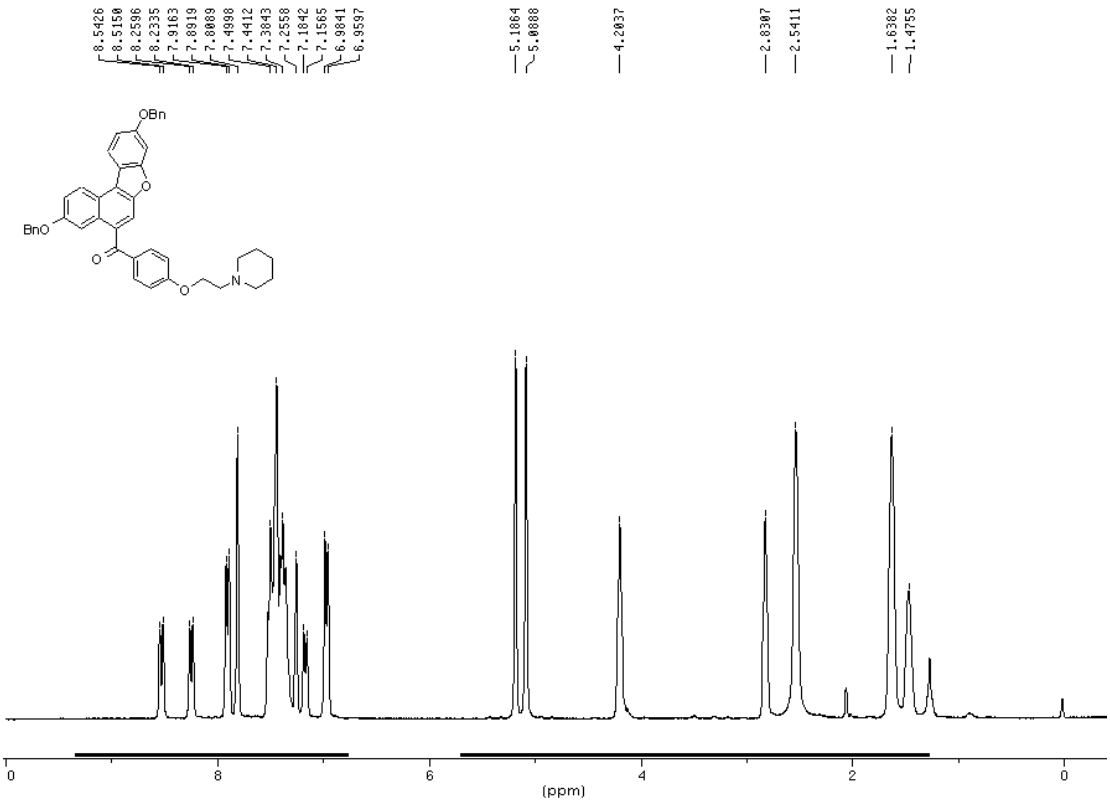


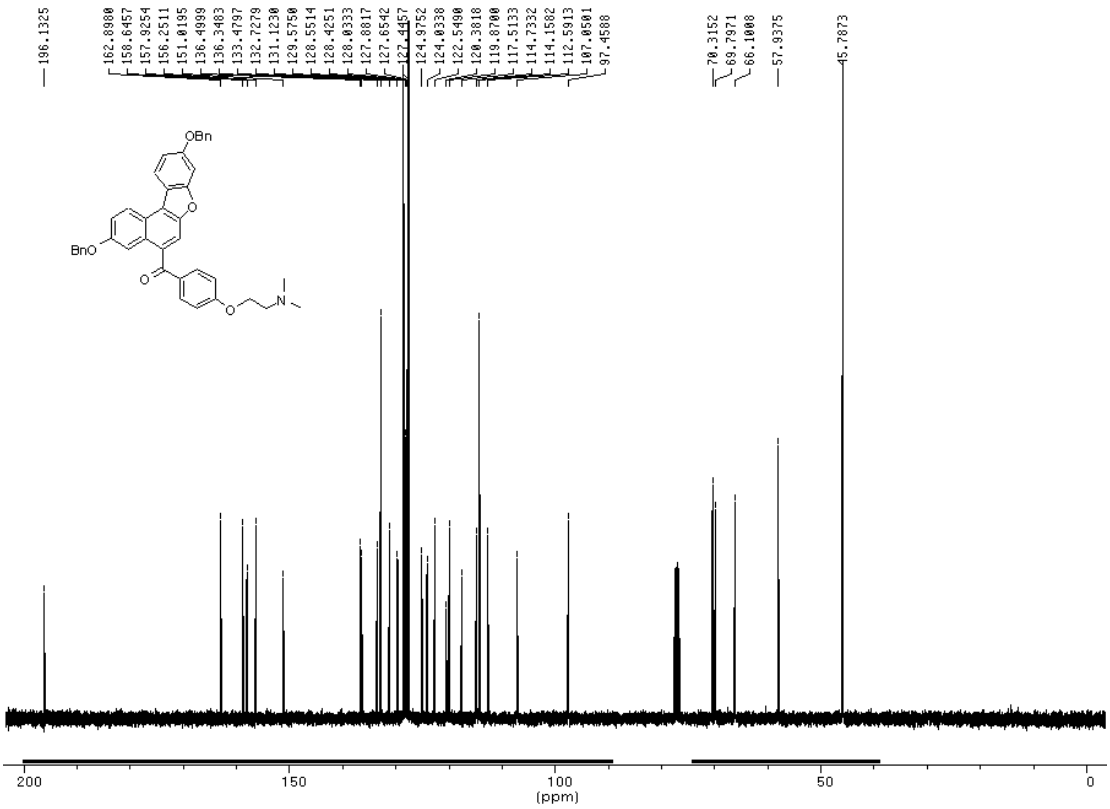

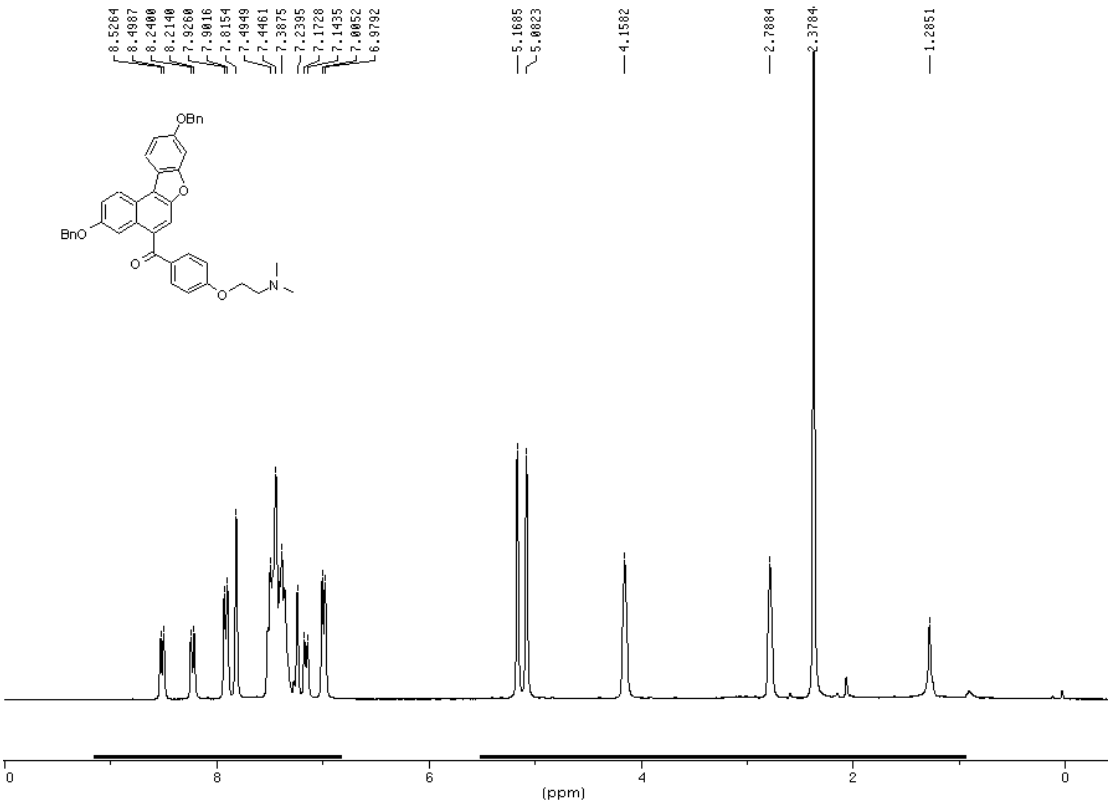


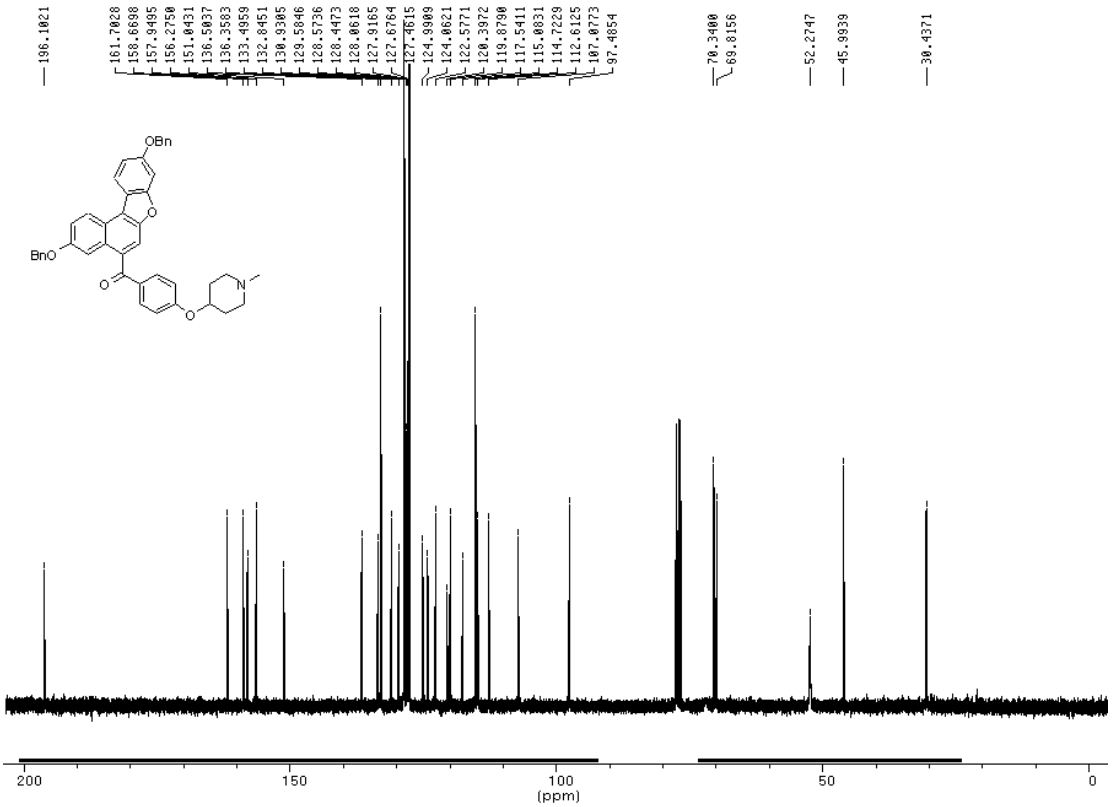

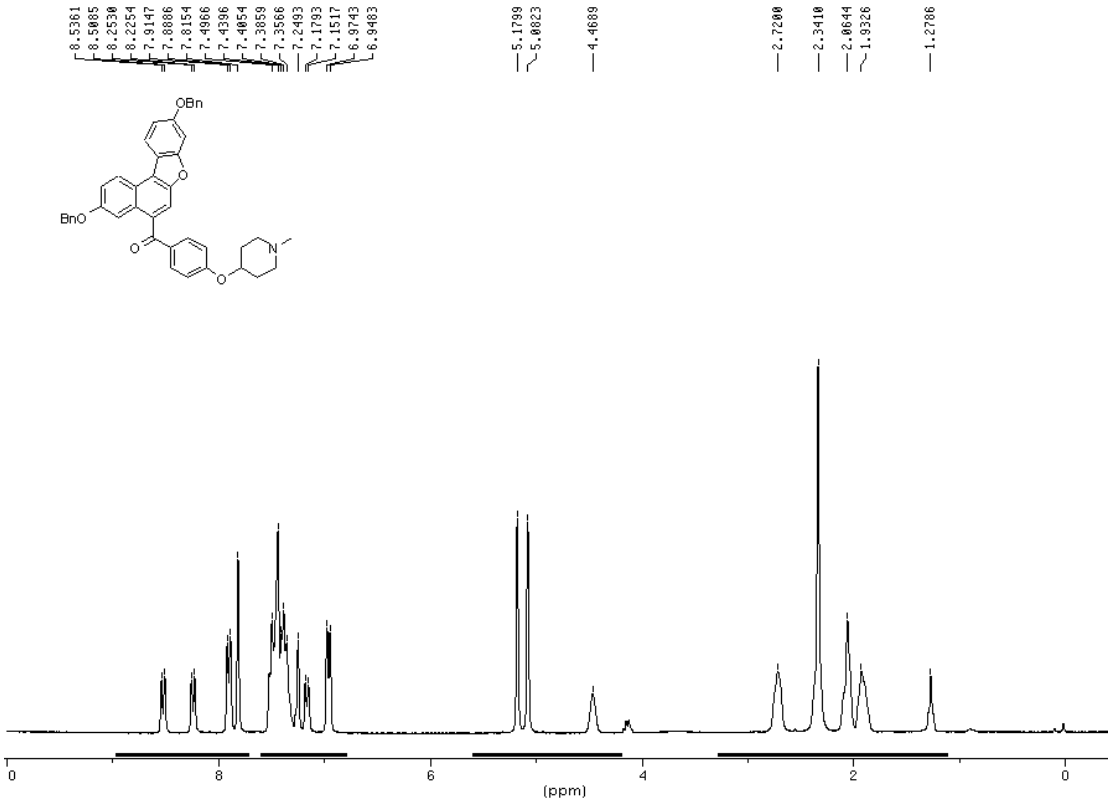


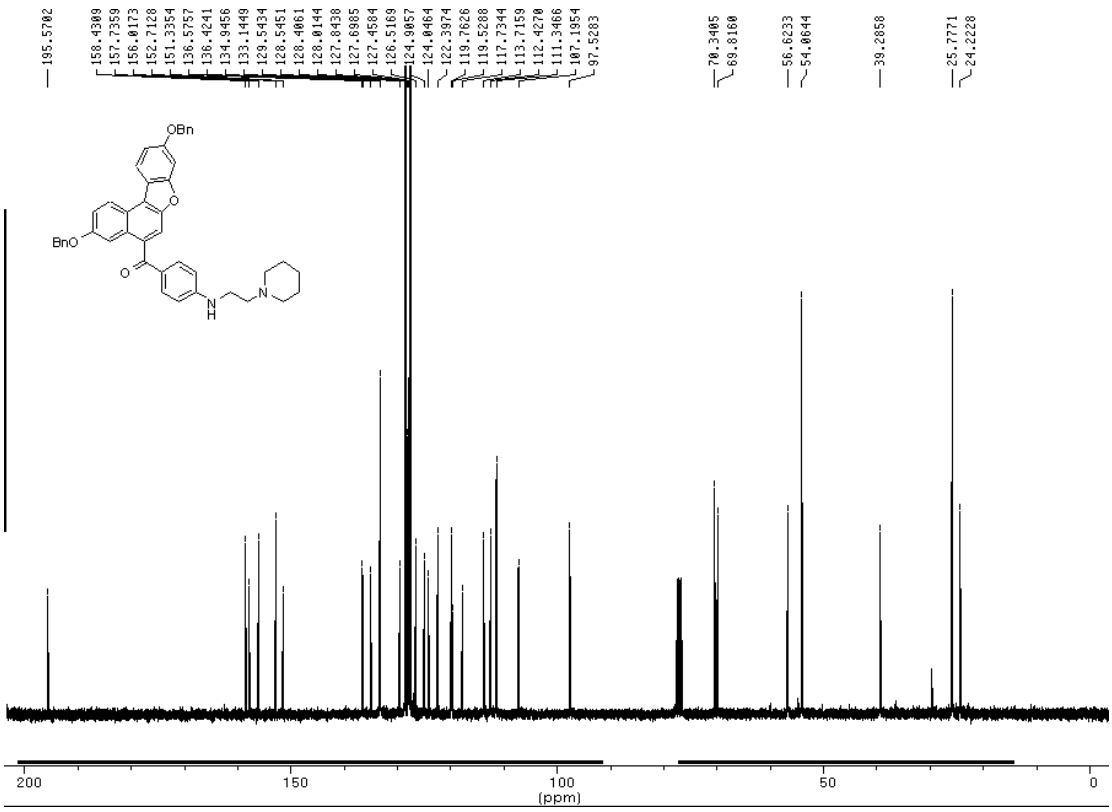

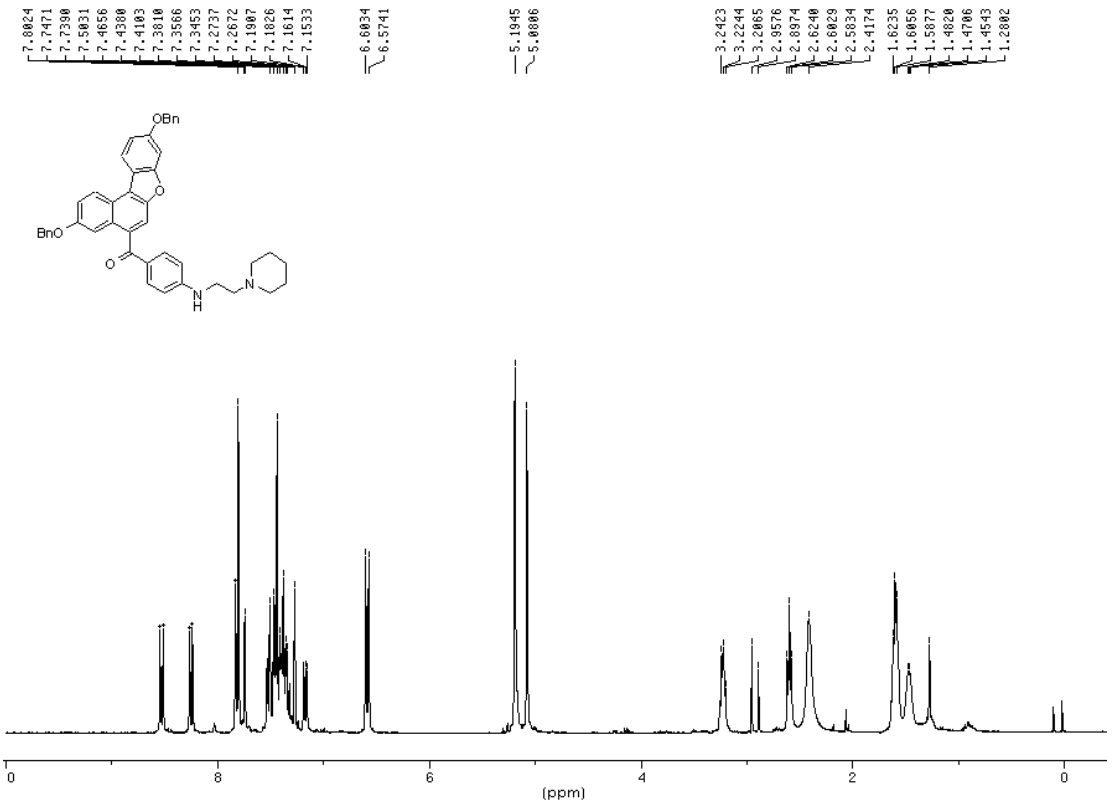


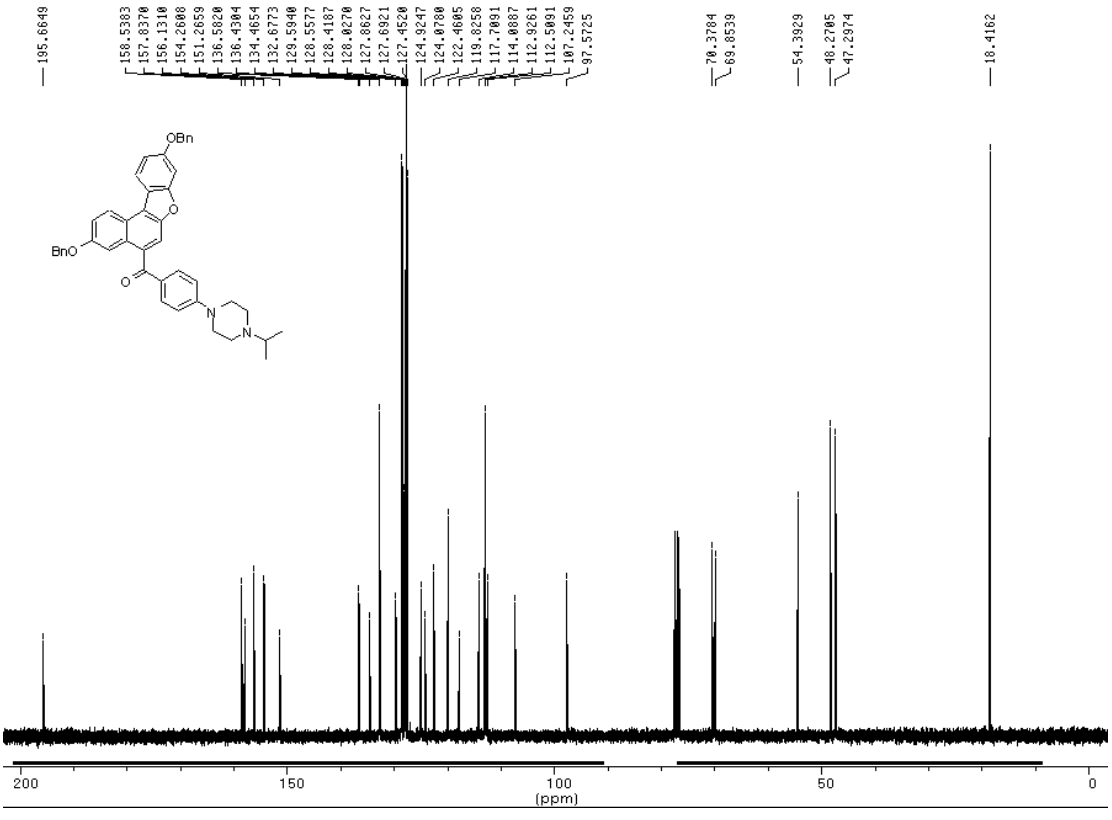

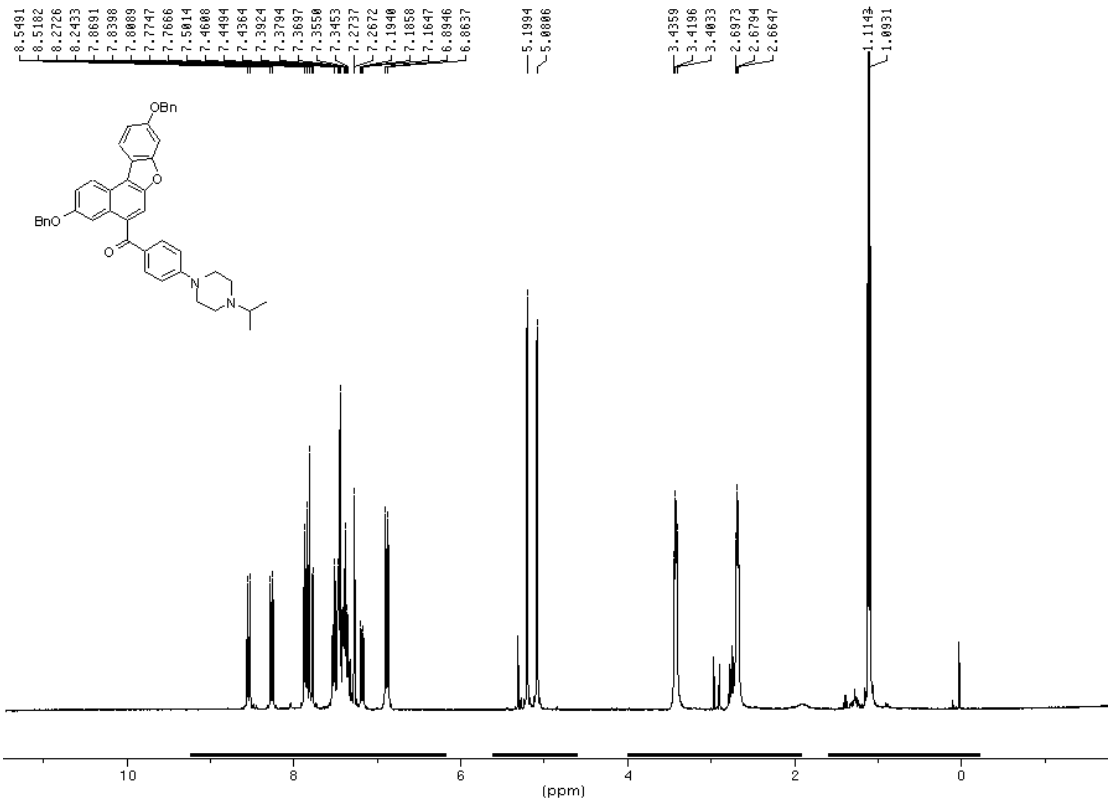


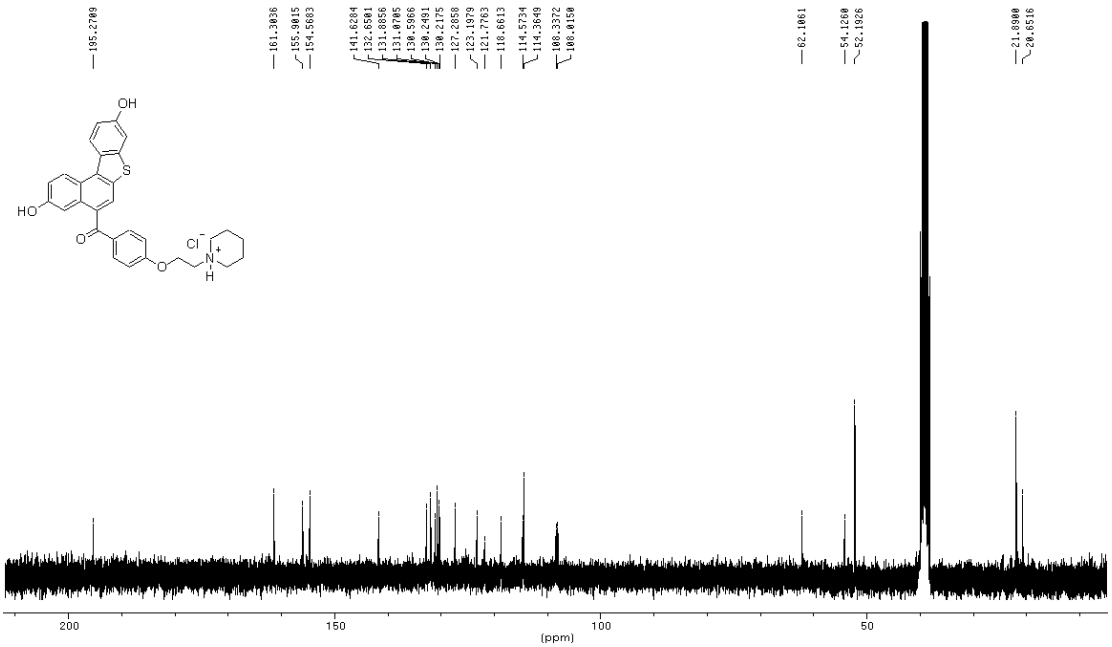

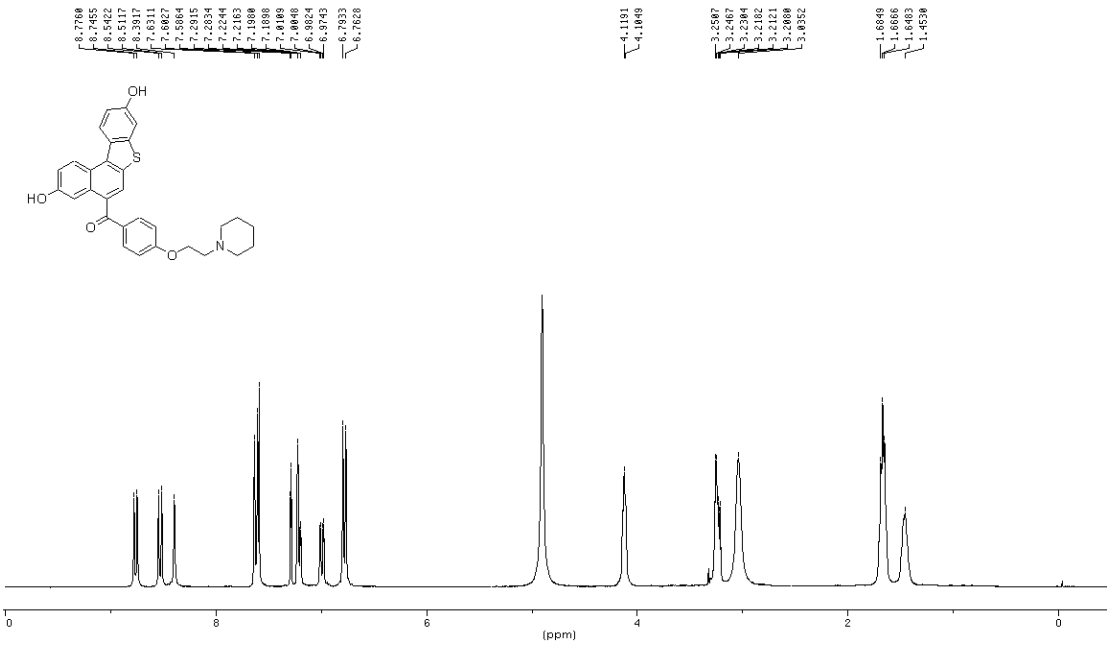


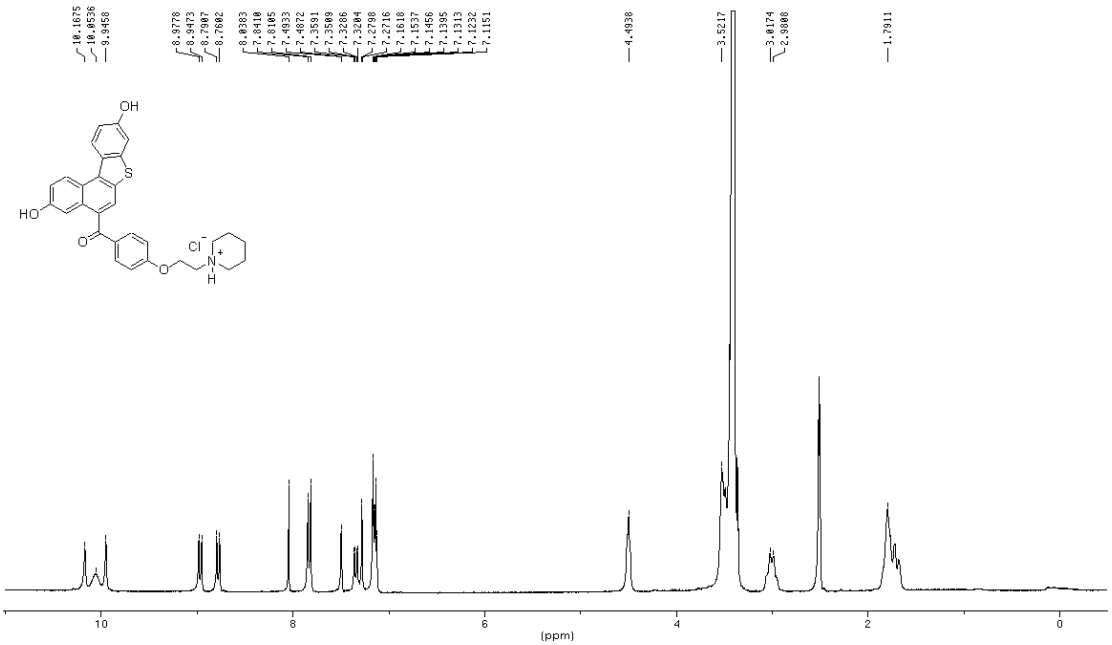

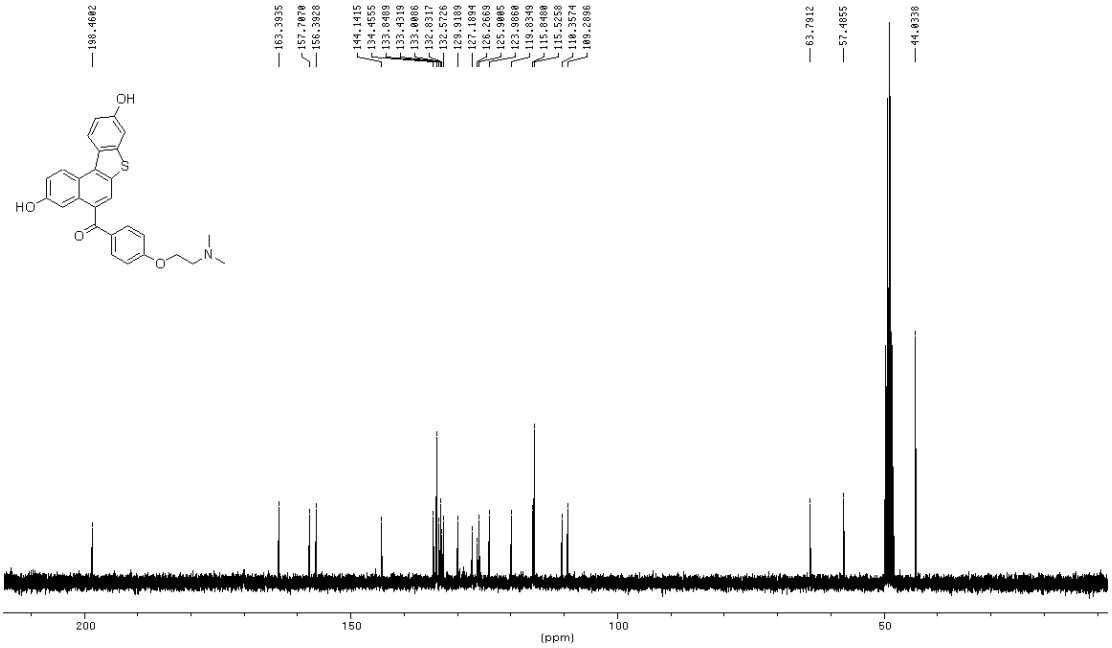


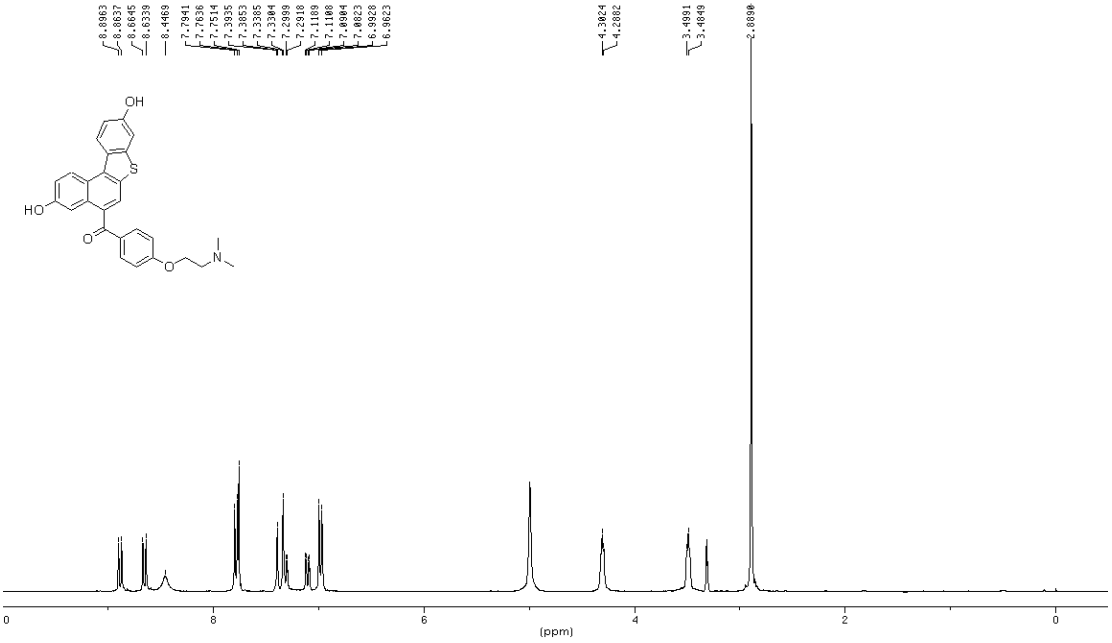

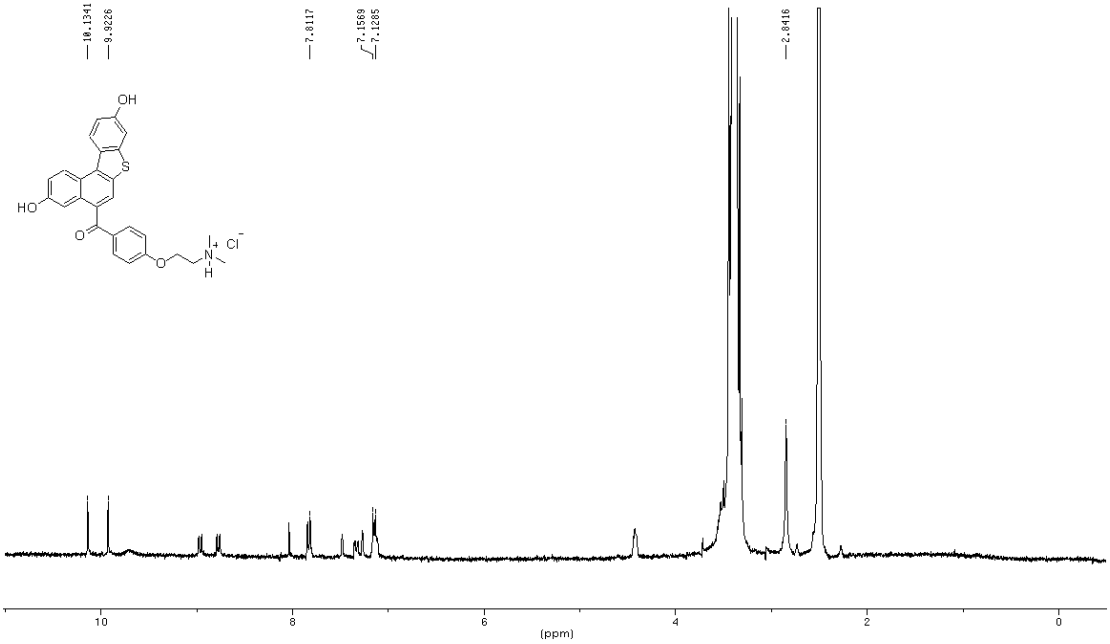


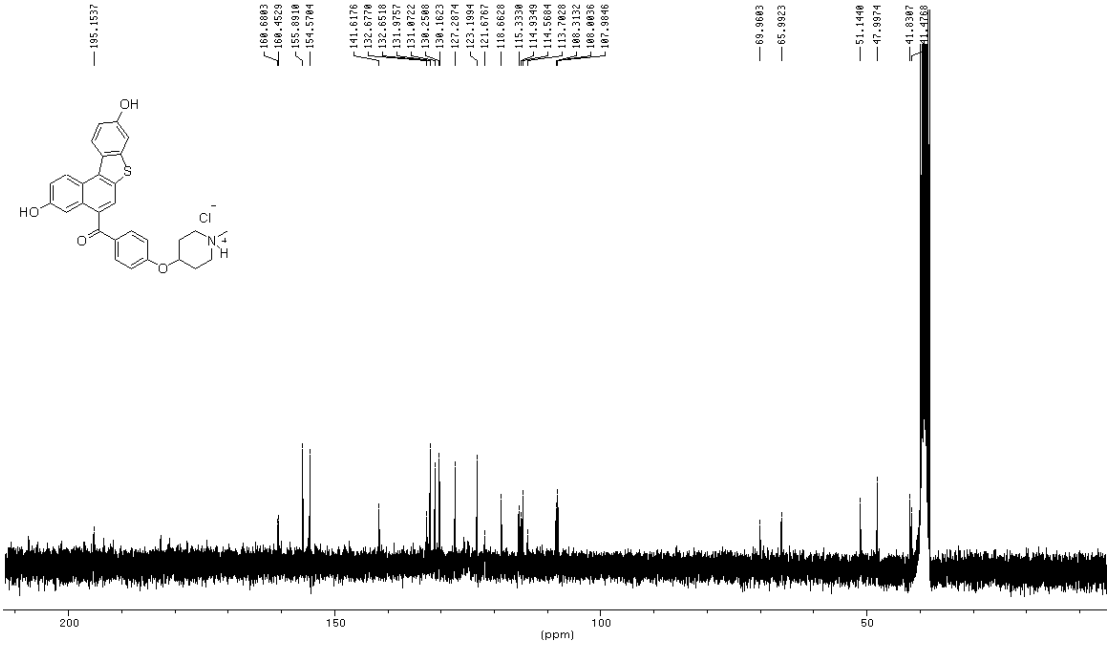

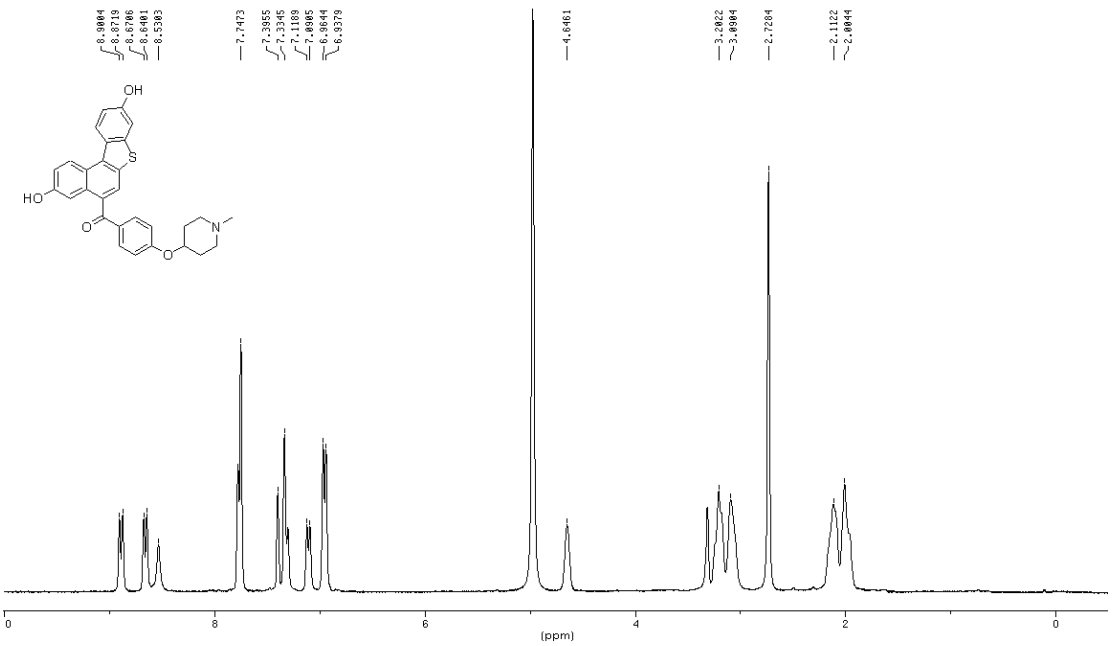


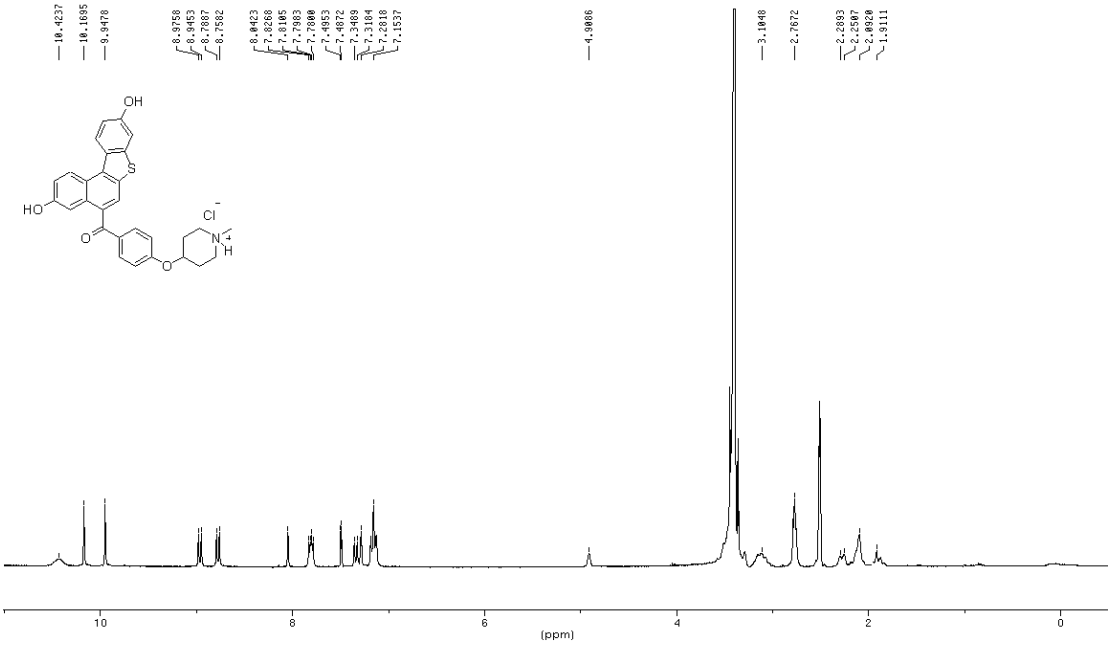

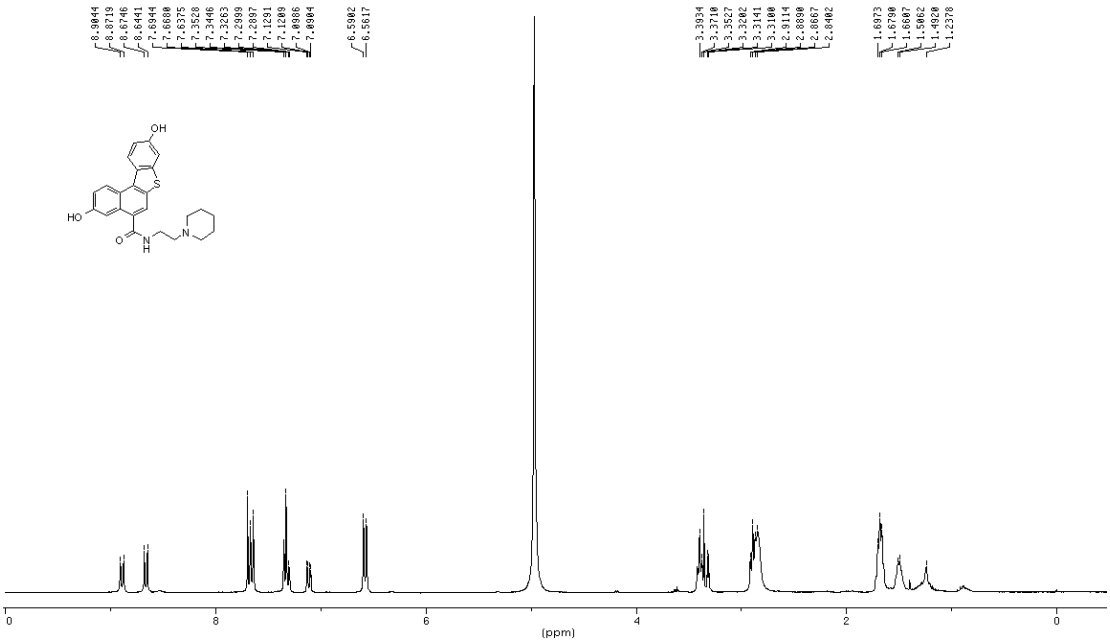


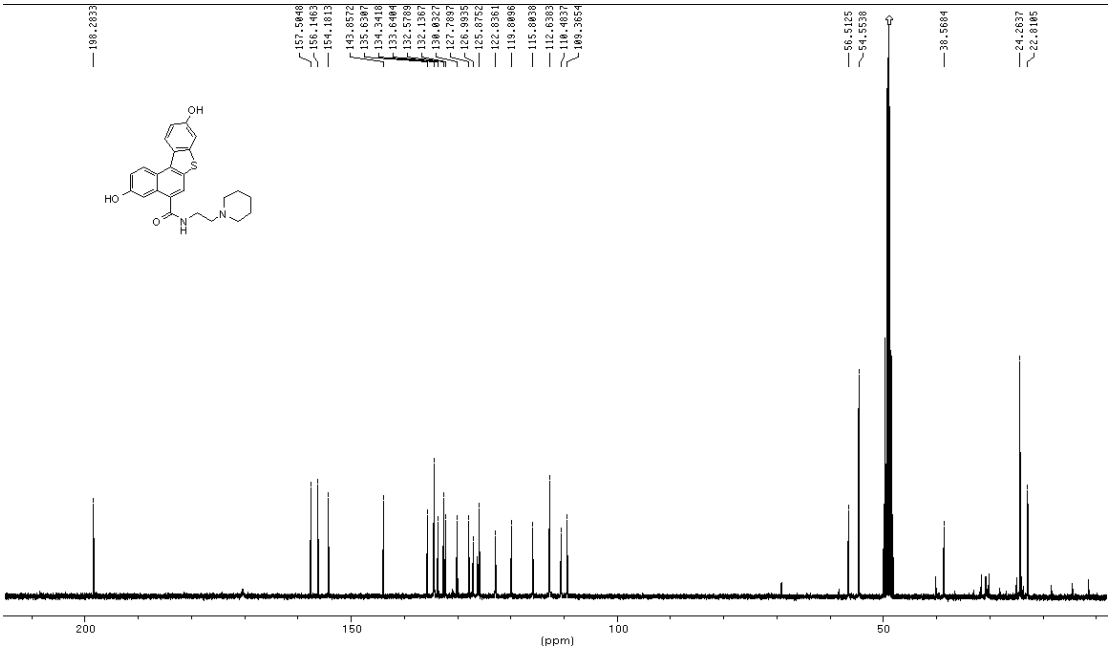

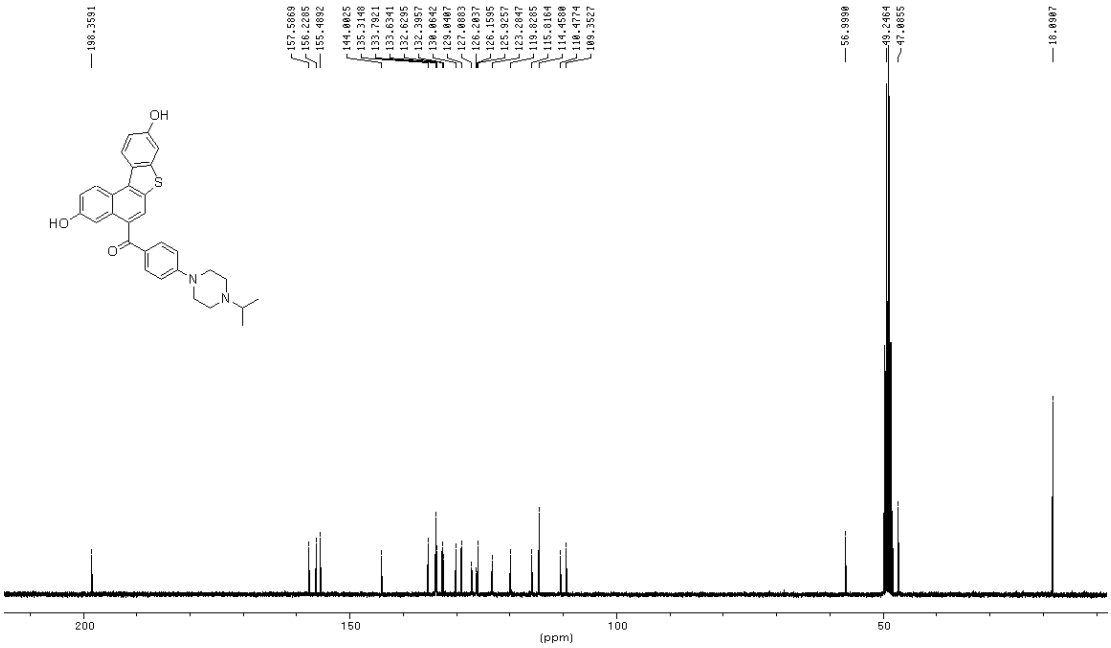


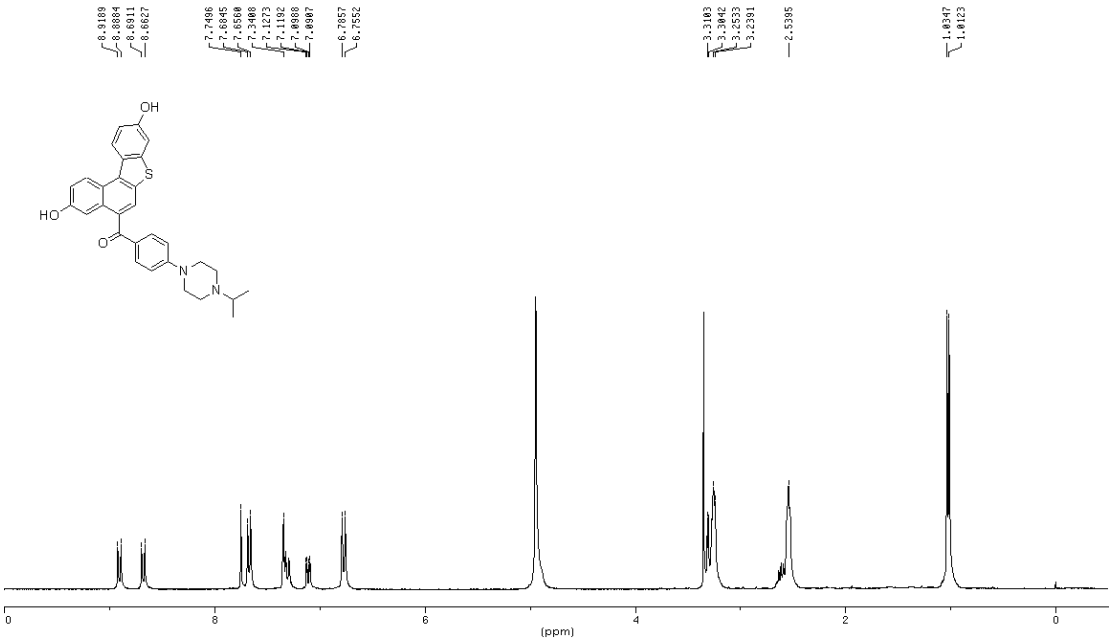

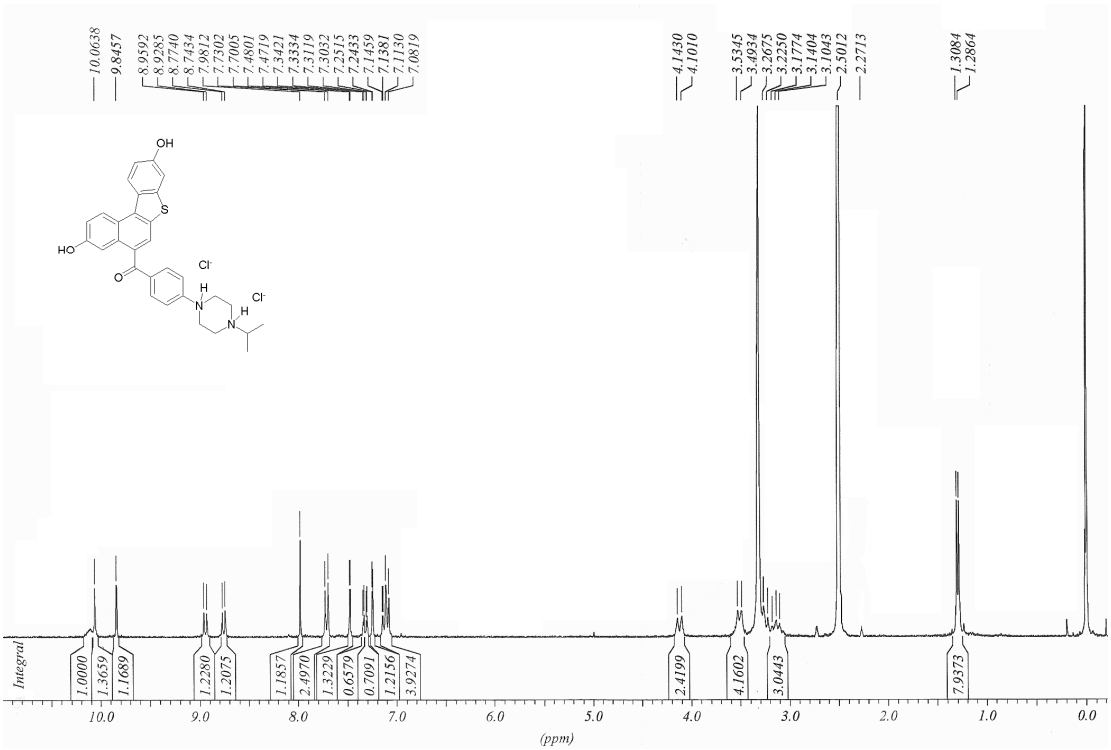
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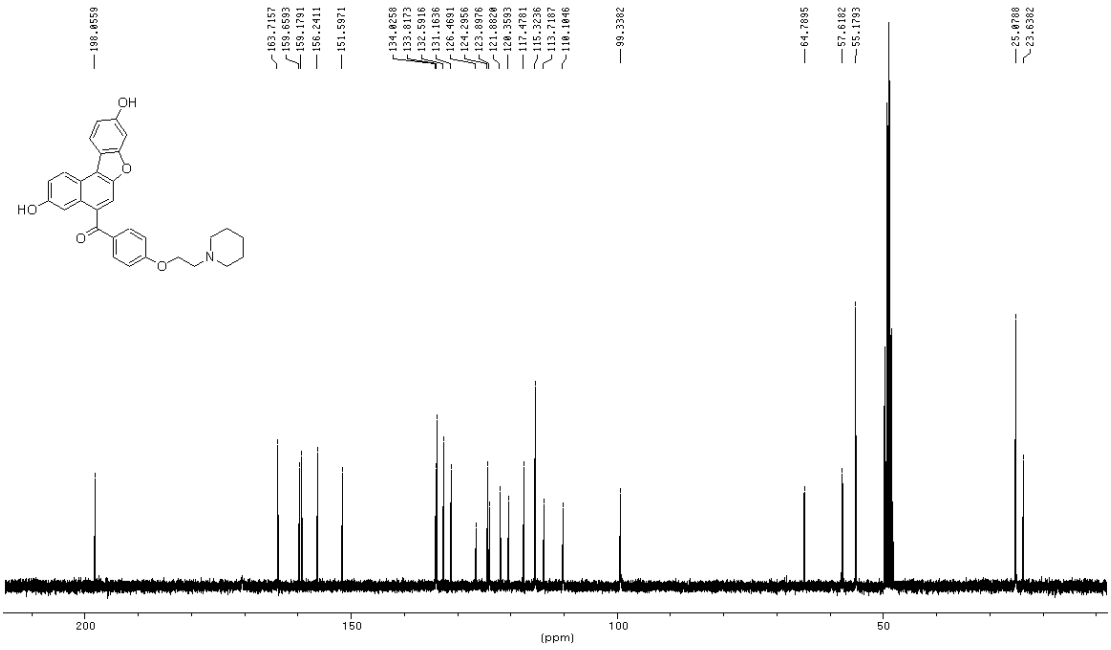
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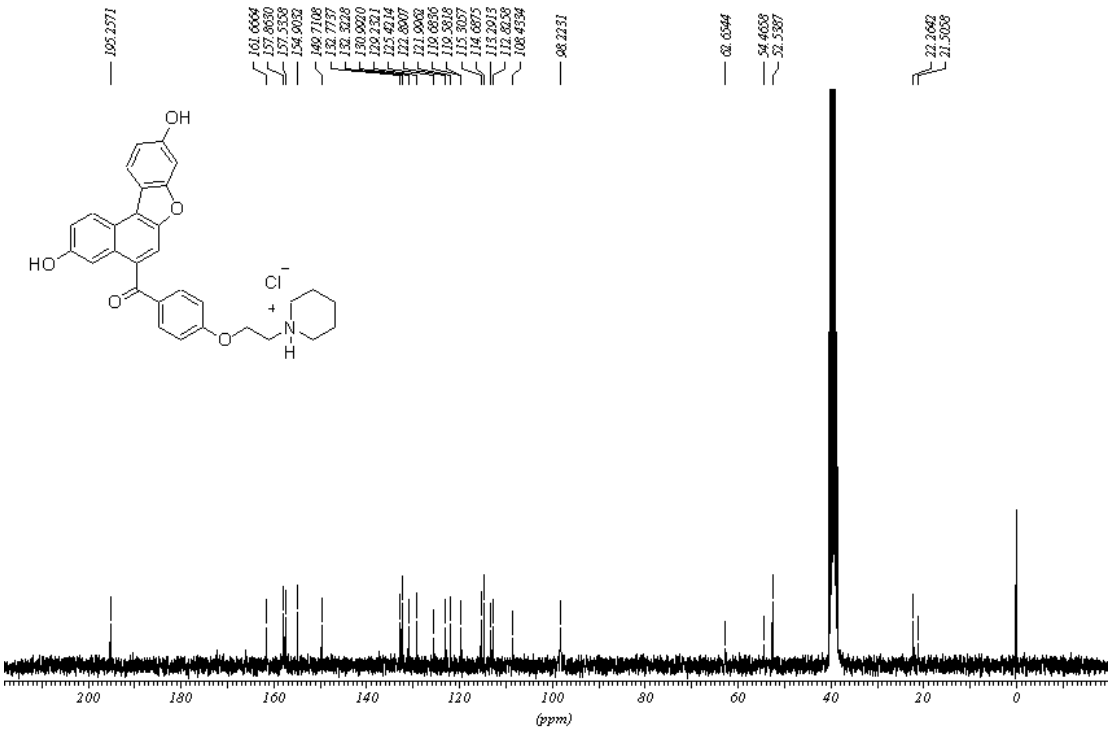
(ppm)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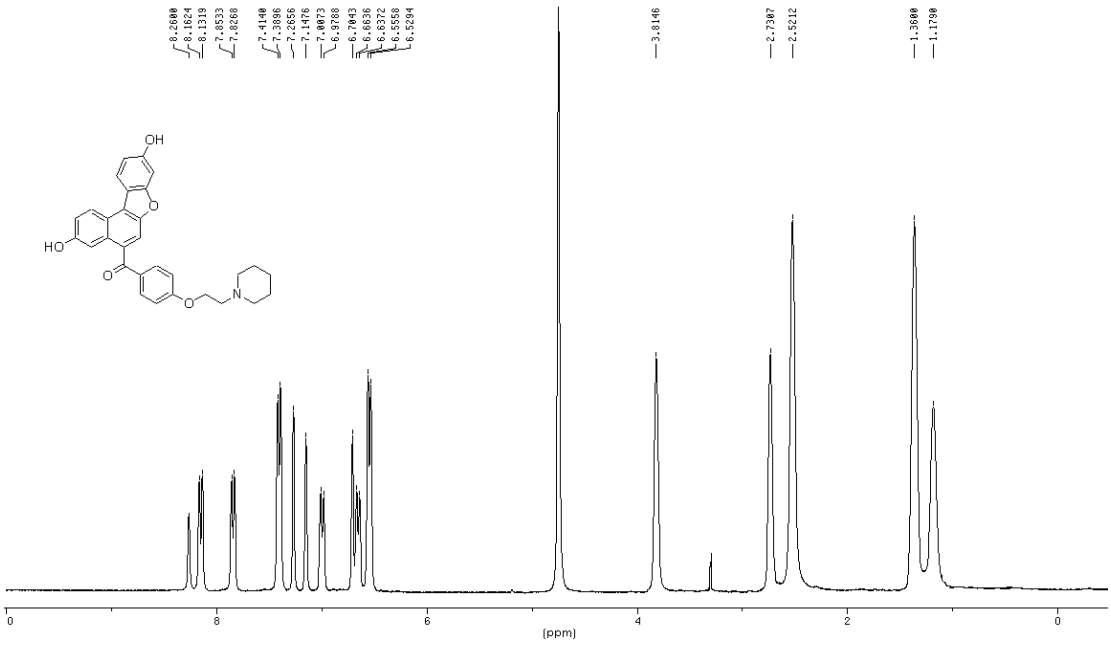
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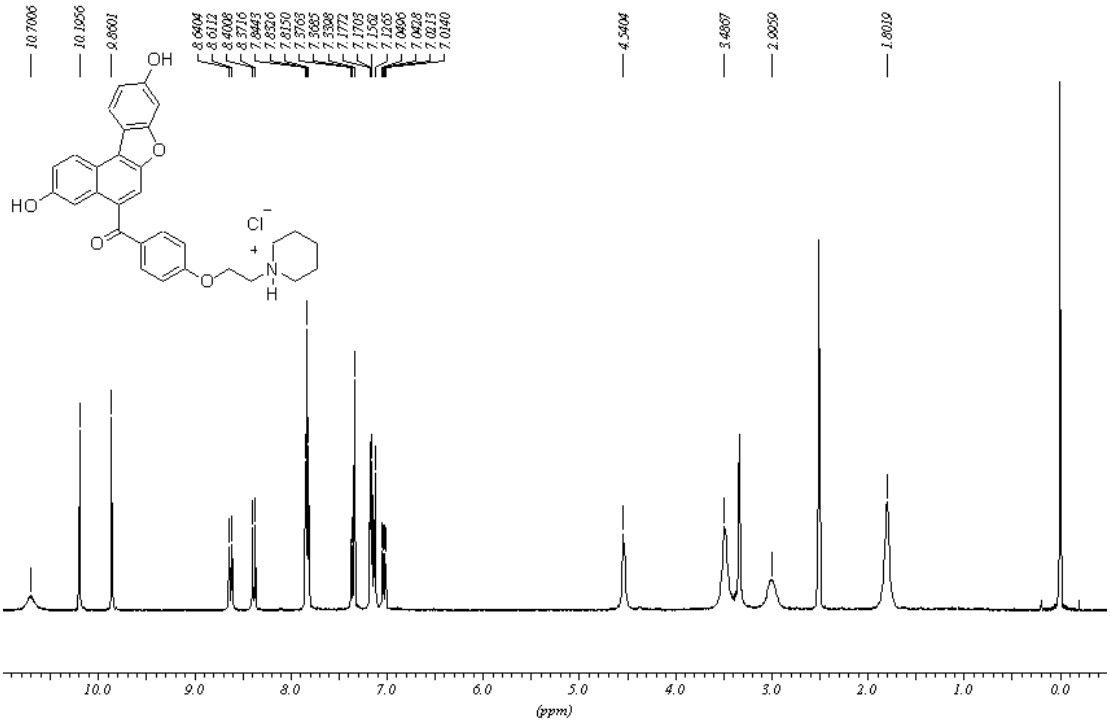
(ppm)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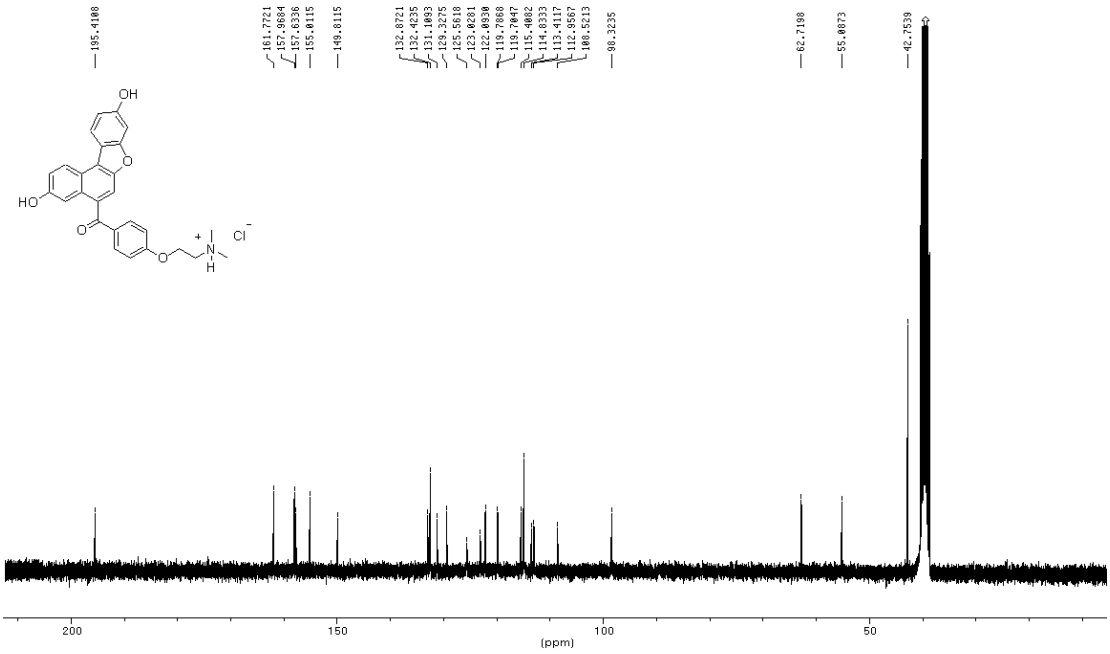
10.1956
9.8601
8.6404
8.6112
8.4008
8.3716
7.8443
7.8326
7.8150
7.3763
7.3685
7.3308
7.1772
7.1703
7.1562
7.1265
7.0496
7.0428
7.0213
7.0140
4.5404
3.4867
2.9959
1.8019
OH
HO
O
Cl
N
H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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157.6336
155.8115
149.8115
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132.4235
131.1093
129.3275
125.5618
123.8281
122.4930
119.7868
119.7047
115.4082
114.8333
113.4117
112.9567
108.5213
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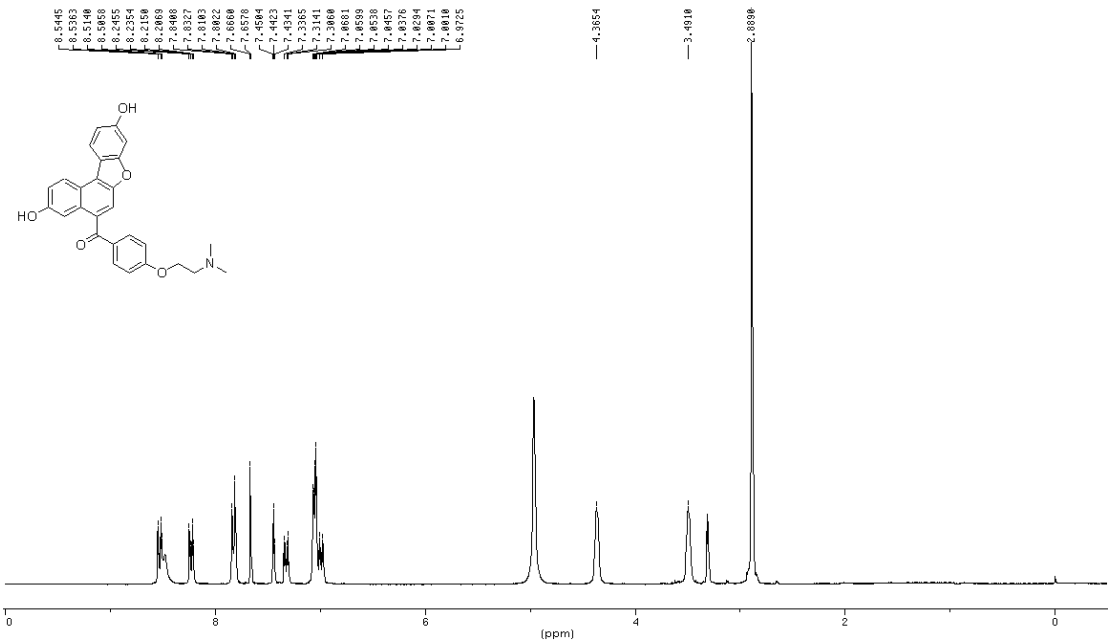
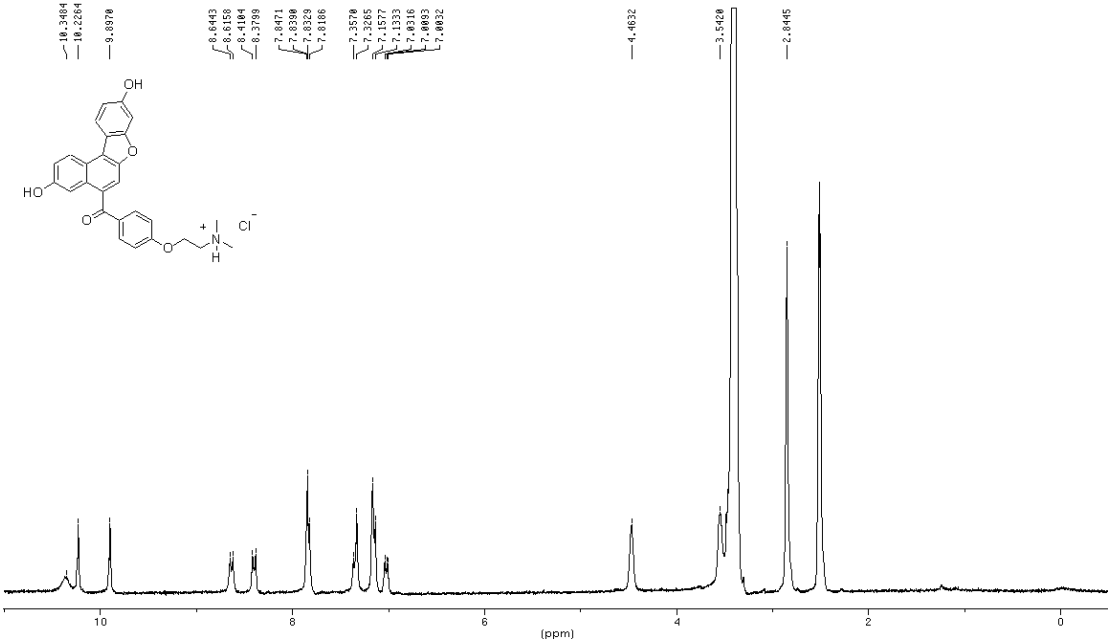
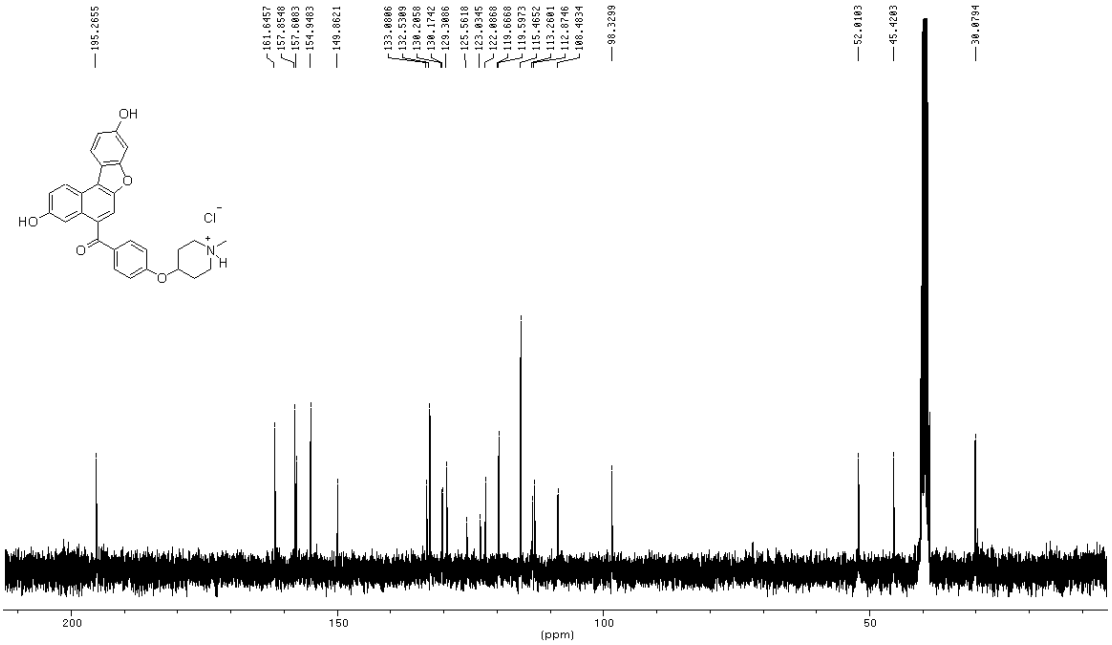
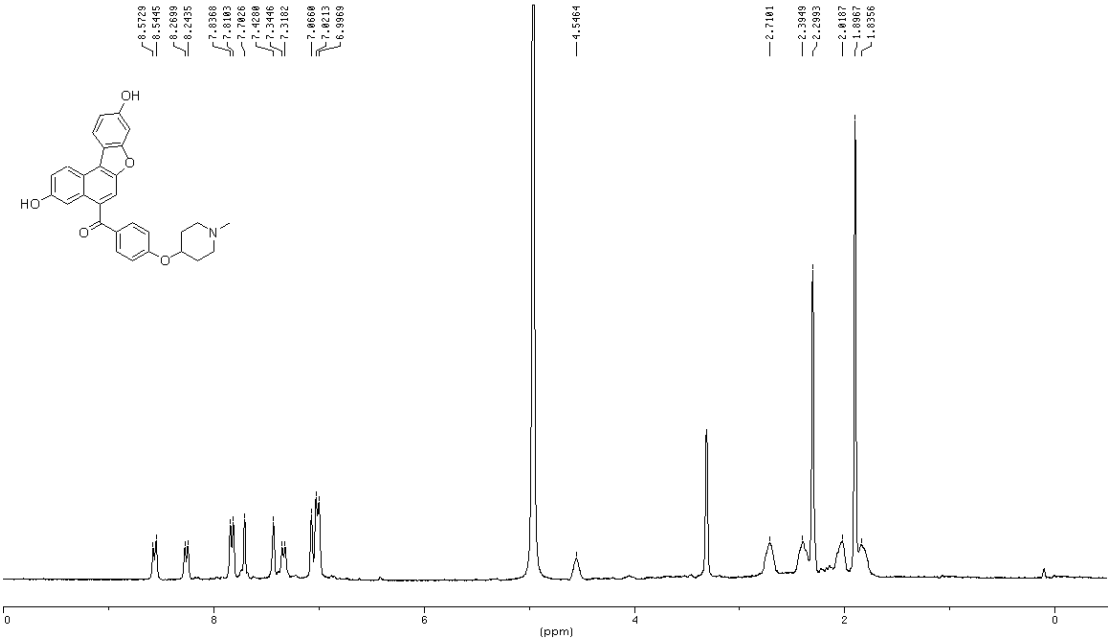
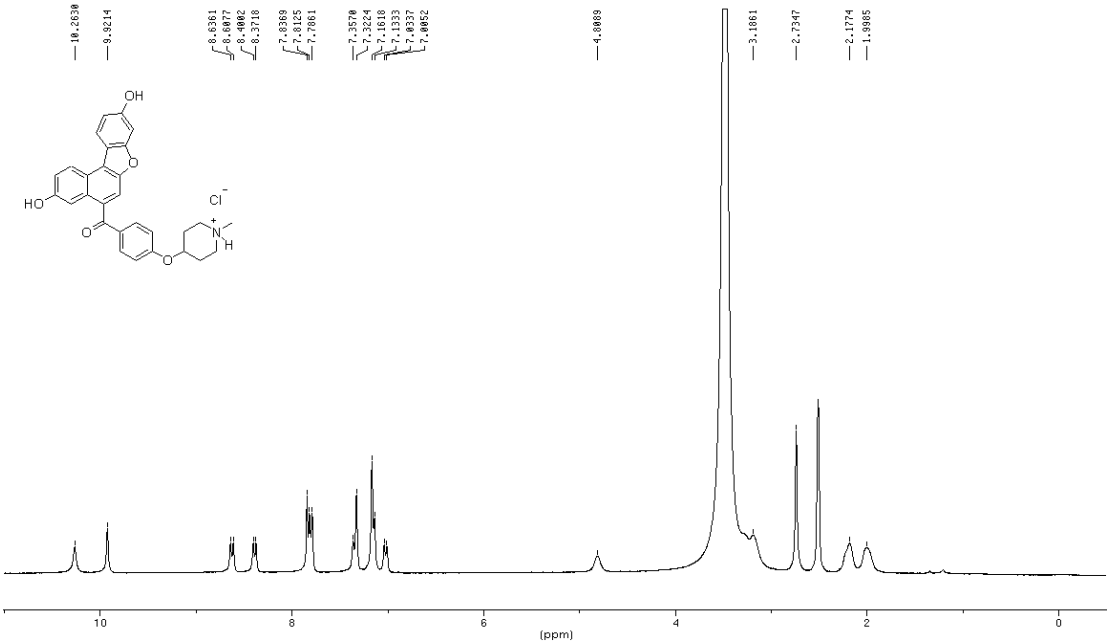
OH
HO
O
Cl
N
H
200
150
100
50
(ppm)

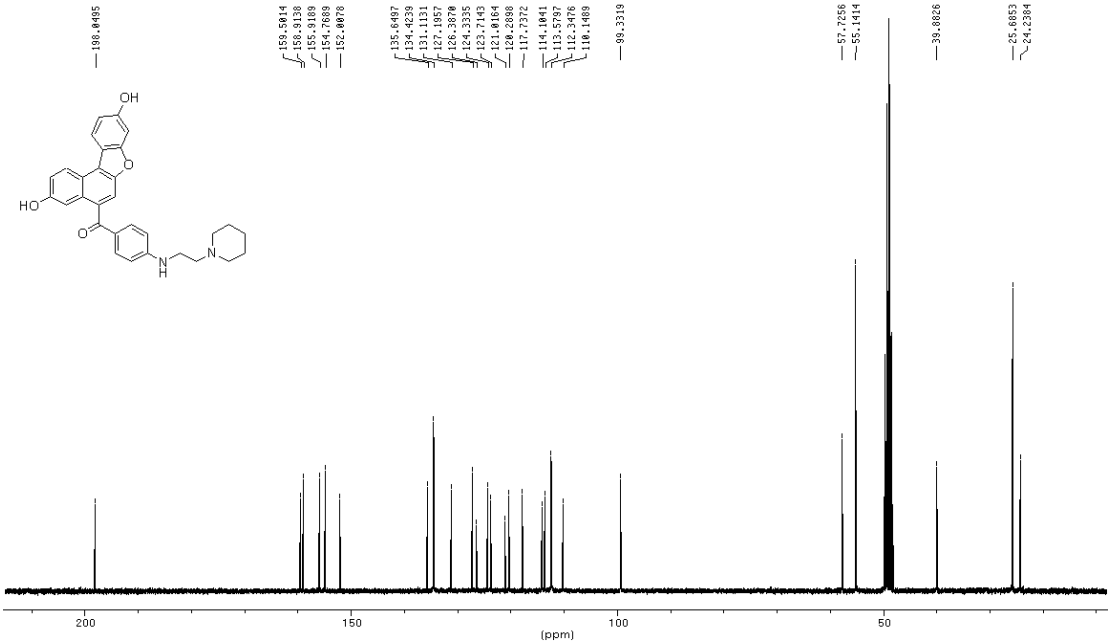


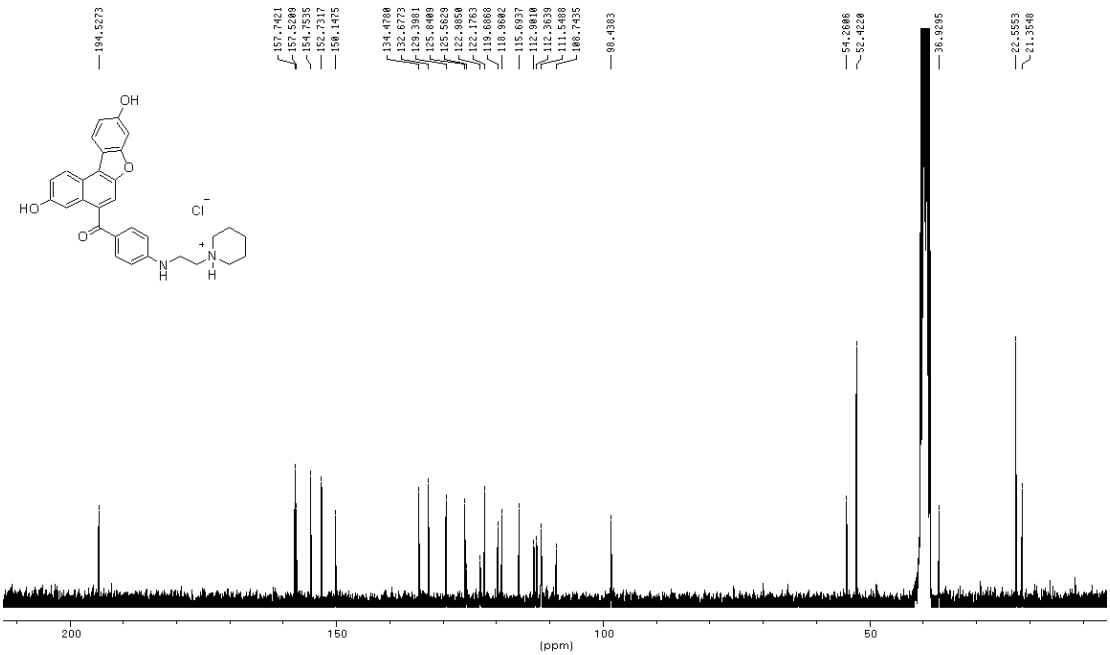



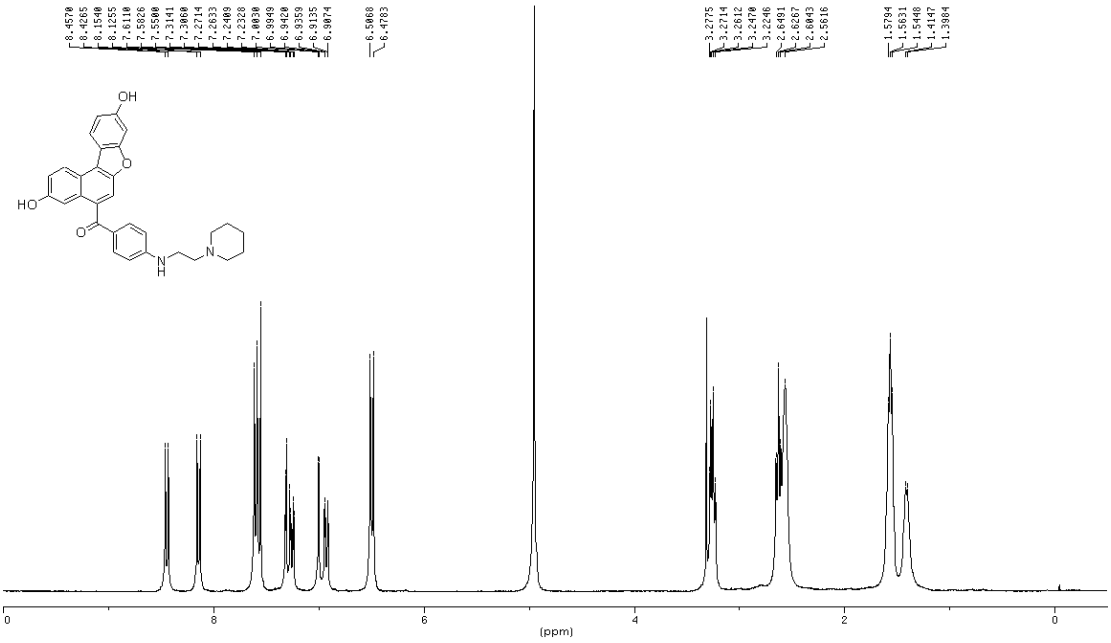


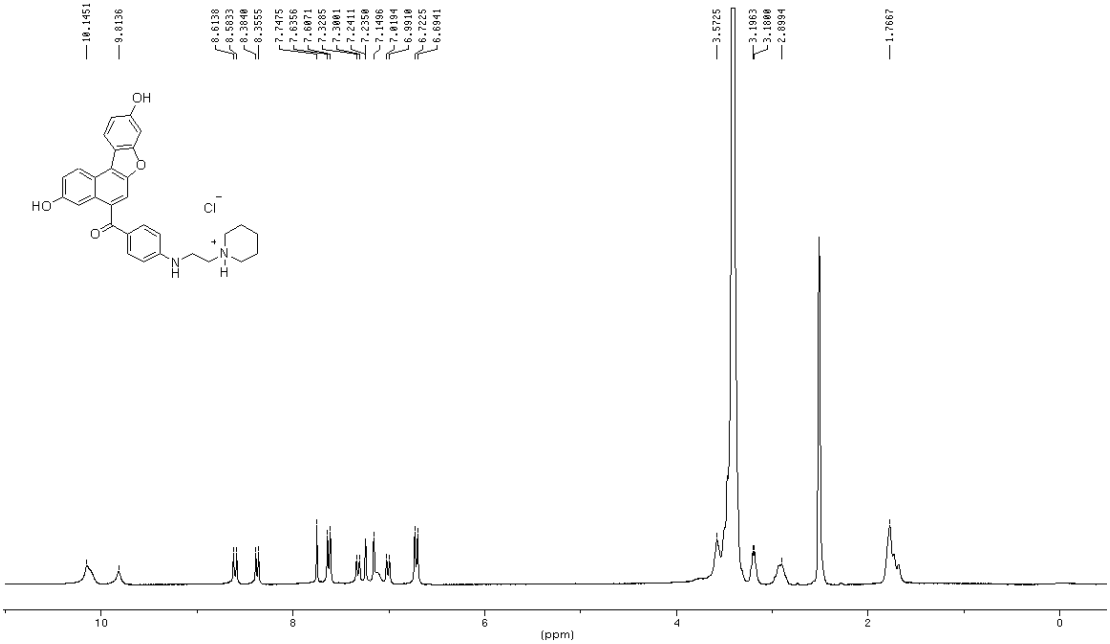



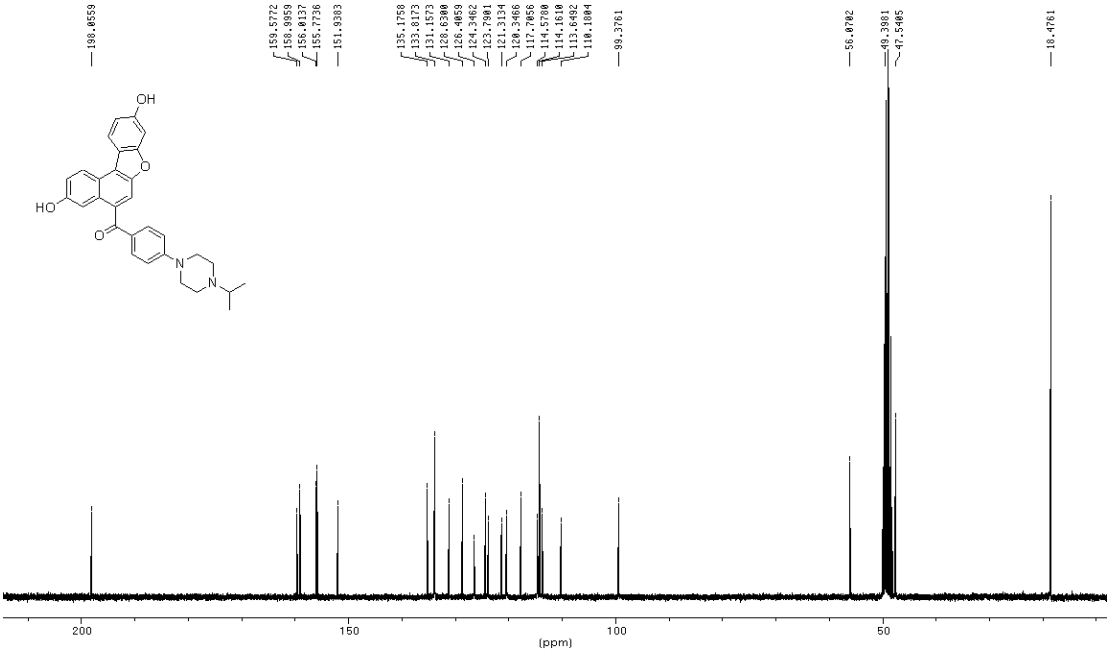


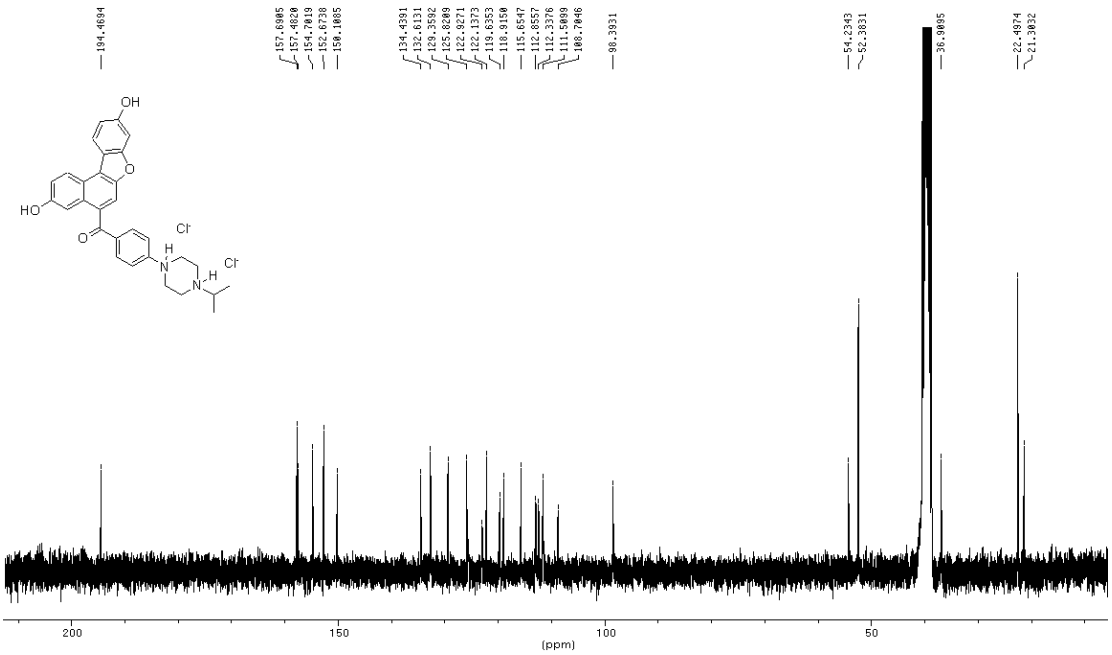



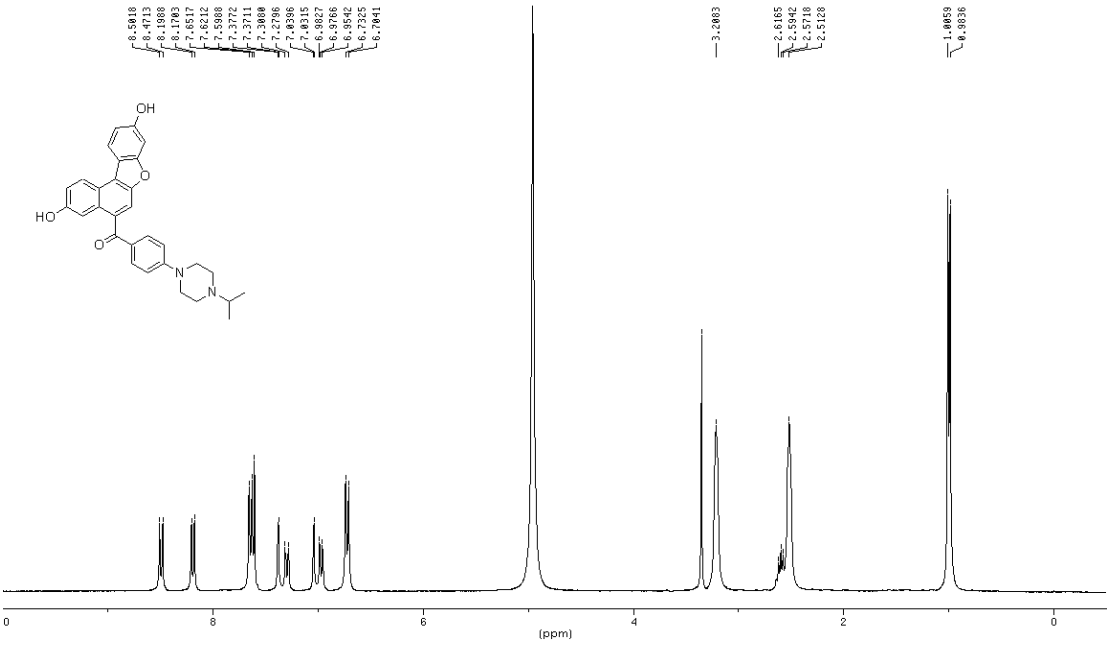


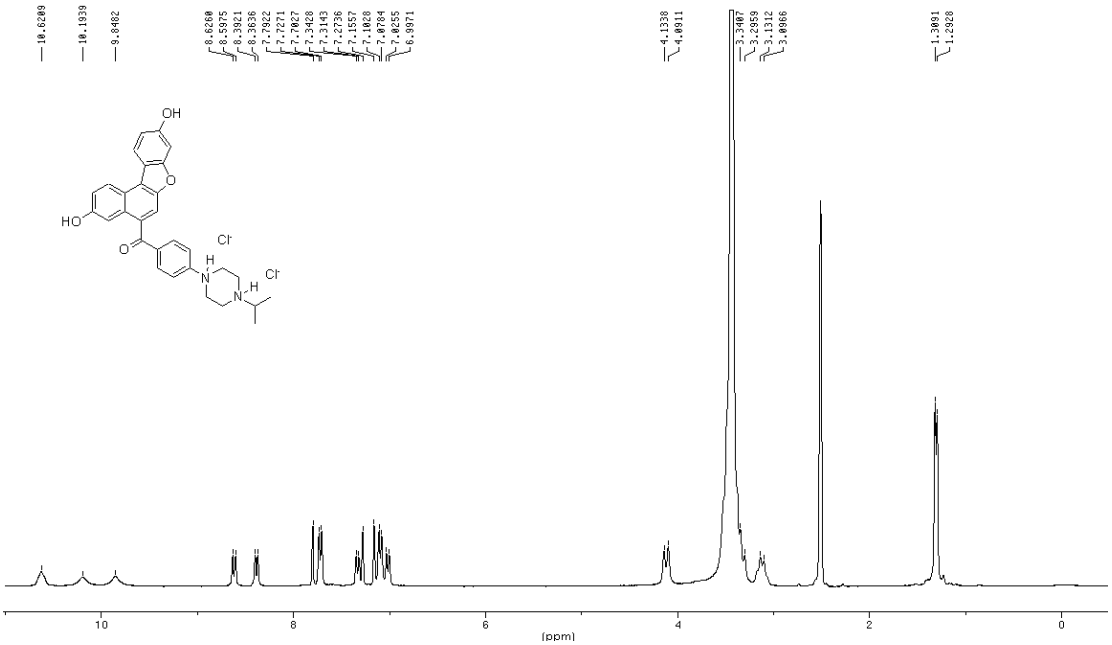



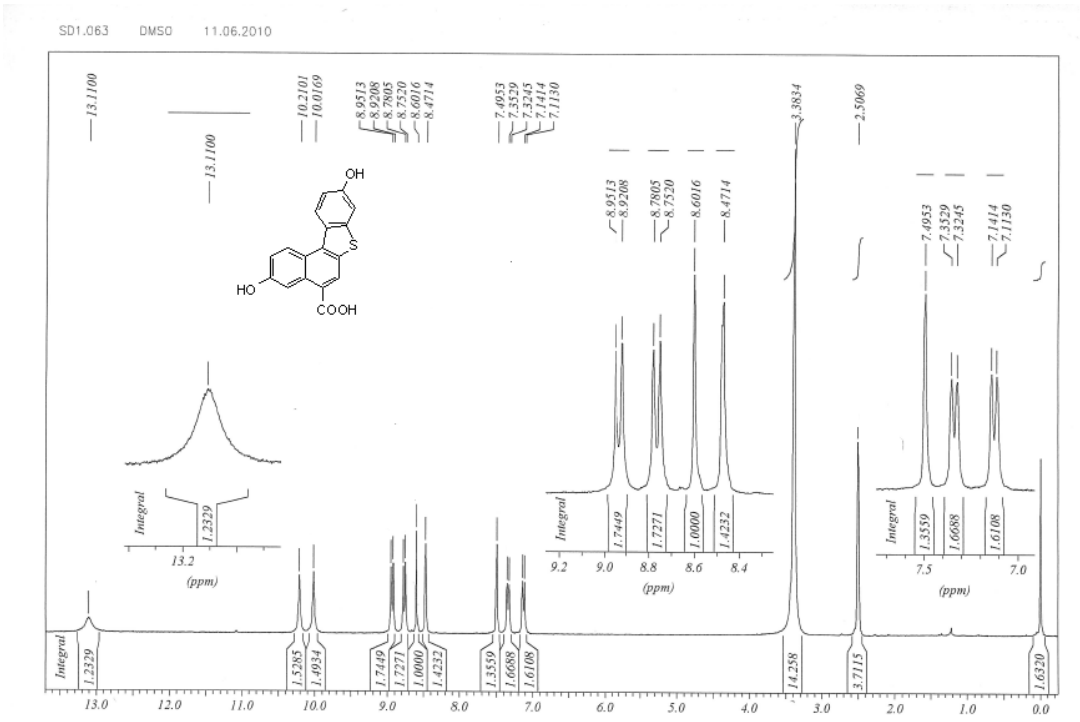


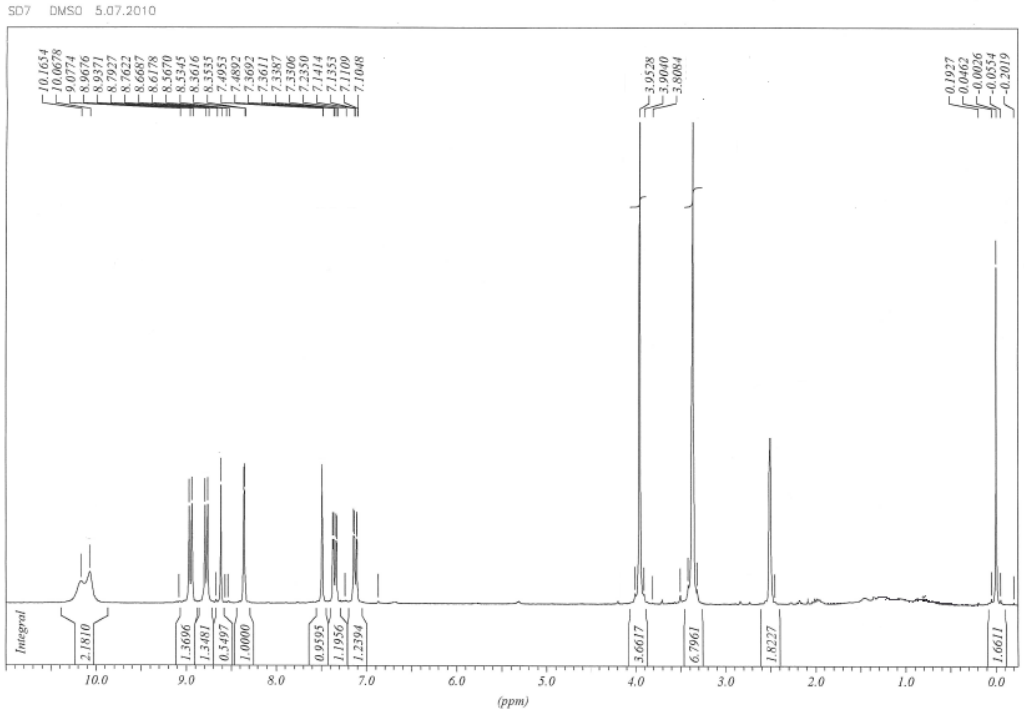





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10.0678
9.0774
8.9676
8.9371
8.7927
8.7622
8.6687
8.6178
8.5670
8.5345
8.3616
8.3535
7.4953
7.4892
7.3692
7.3611
7.3387
7.3306
7.2350
7.1414
7.1353
7.1109
7.1048
3.9528
3.9040
3.8084
0.1927
0.0462
-0.0026
-0.0554
-0.2019
Integral
2.1810
1.3696
1.3481
0.5497
1.0000
0.9595
1.1956
1.2394
3.6617
6.7961
1.8227
1.6611
(ppm)

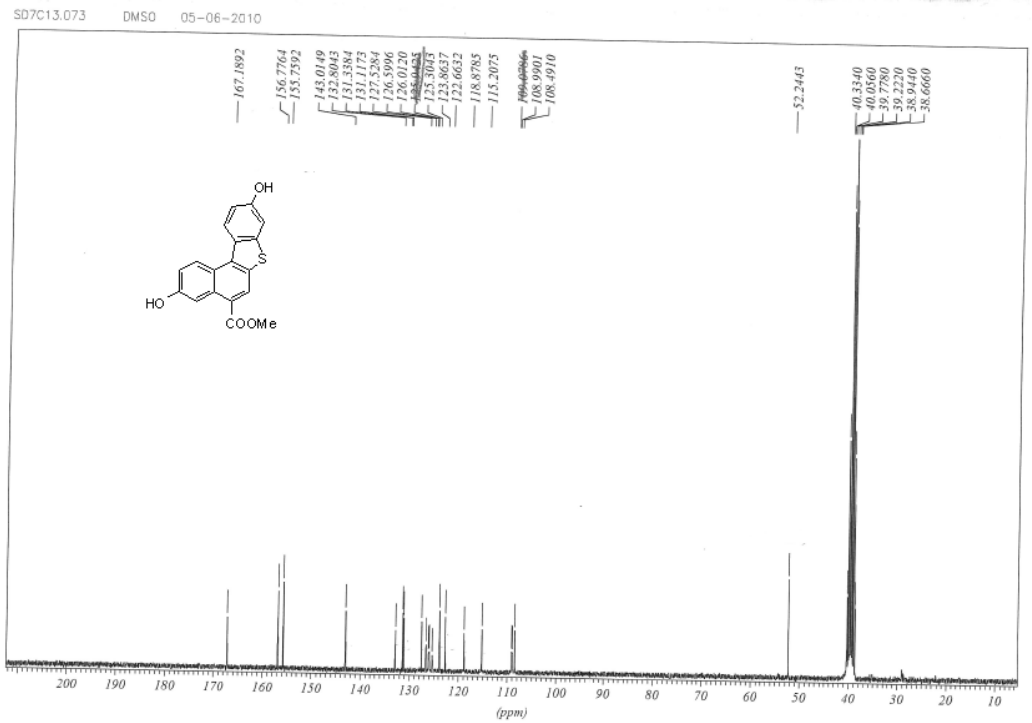
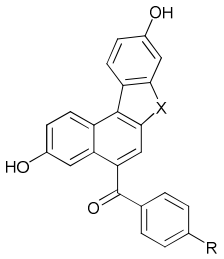
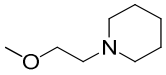
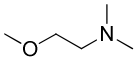
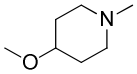
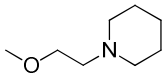
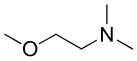
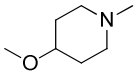
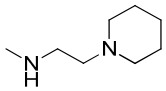
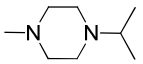

SD7C13.073 DMSO 05-06-2010
167.1892
156.7764
155.7592
145.0149
132.8043
131.3384
131.1173
127.5284
126.5996
126.0120
125.3043
123.8637
122.6632
118.8765
115.2075
108.9901
108.4910
52.2443
40.3340
40.0560
39.7780
39.2220
38.9440
38.6660
OH
HO
S
COOMe
(ppm)

**Table S1**. Predicted binding energy from the docking studies with **Glide** and *AutoDock*, corresponding to estradiol-like binding modes within the LBD. No value provided means that the docking calculation did not yield any binding pose within the LBD.




| **Comp.** | X | R | Binding energy in ERα (kcal/mol$^{-1}$) | Binding energy in ERβ (kcal/mol$^{-1}$) |
|---|---|---|---|---|
| **6b** | O | F | **-7.6**/*-5.7* | **-10.0**/*-6.0* |
| **9a** | S |  | --/-- | **-6.5**/-- |
| **9b** | S |  | **--**/-5.1 | **--**/*-4.7* |
| **9c** | S |  | --/-- | **-6.6**/-- |
| **9f** | O |  | **-6.3**/-- | **-6.8**/*-6.6* |
| **9g** | O |  | **-6.1**/*-6.9* | **-6.7**/*-6.5* |
| **9h** | O |  | **-6.5**/-- | **-6.8**/*-5.4* |
| **9i** | O |  | **-6.6**/*-7.0* | **-6.7**/*-7.8* |
| **9j** | O |  | **--**/-- | **-7.8**/*-6.6* |

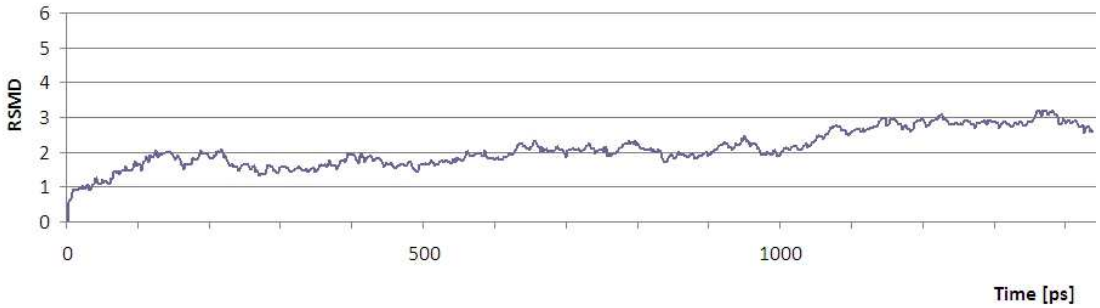



**Figure S1.** Evolution of the root-mean-square deviation (rmsd) of the Cα atoms of ERβ-**9f** complex with respect to the initial structure during the MD simulation (initial 500 ps with distance restriction).

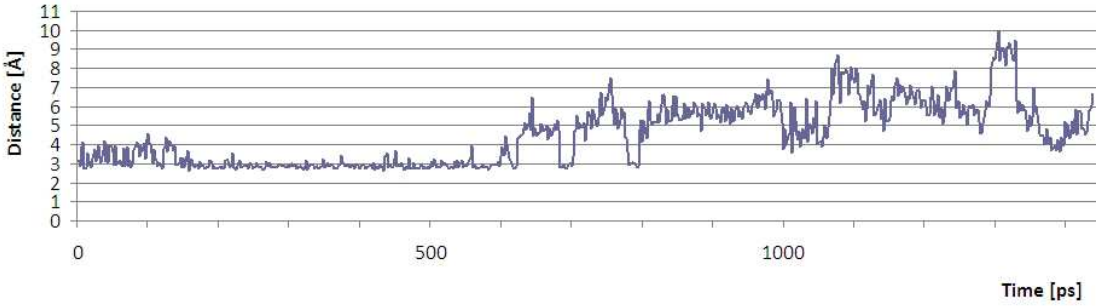



**Figure S2.** Evolution of the Asp303 $COO^{-}\cdots NH^{+}$ piperidinium distance (Å) of ERβ-**9f** complex during the MD simulation (initial 500 ps with distance restriction).

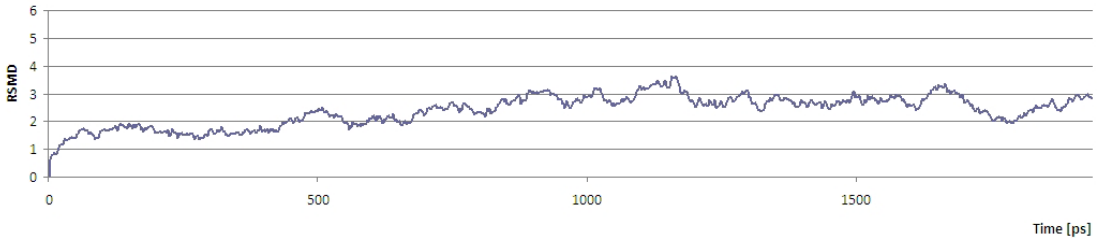



**Figure S3.** Evolution of the root-mean-square deviation (rmsd) of the Cα atoms of ERβ-**9f** complex with respect to the initial structure during the MD simulation (with no restrictions).

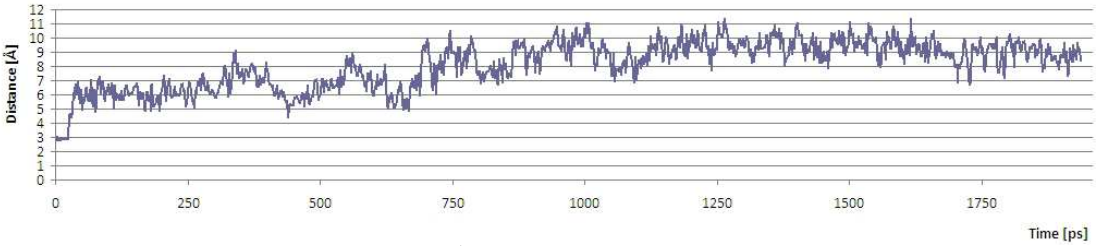



**Figure S4.** Evolution of the Asp303 $COO^{-}\cdots NH^{+}$ piperidinium distance (Å) of ERβ-**9f** complex during the MD simulation (with no restrictions).

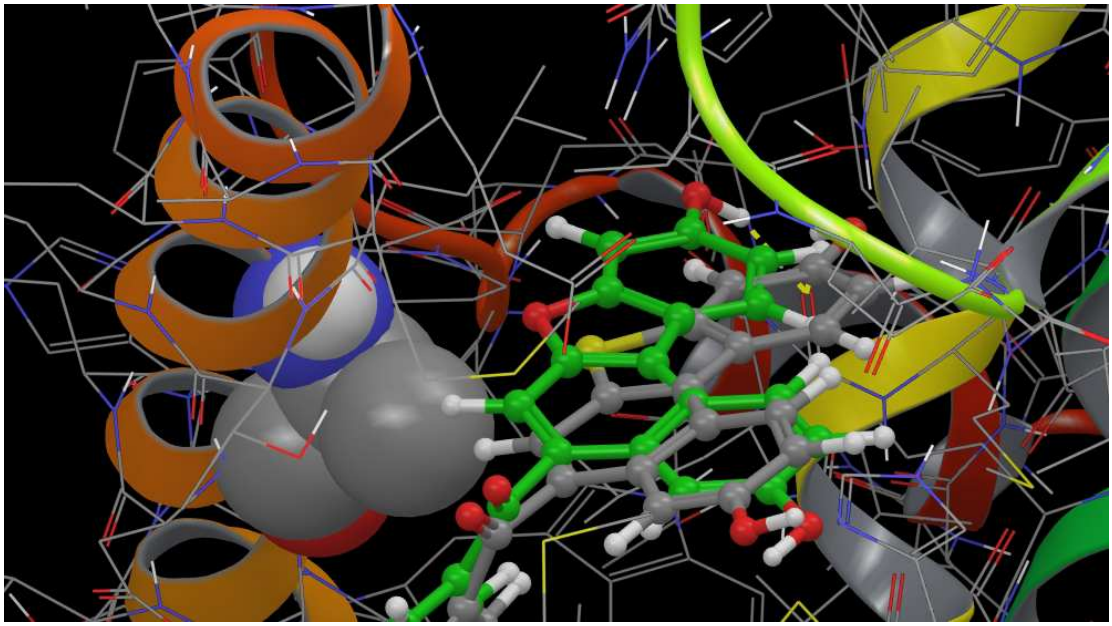


**Figure S5.** Superimposition of docked poses of compound **9f** (green) and the thioderivative **9a** (grey).