RAPID AND CONVERGENT ASSEMBLY OF NATURAL BENZO[c]PHENANTHRIDINES BY PALLADIUM/NORBORNENE CATALYSIS

Pierre-Alexandre Deyris, Tatiana Cañeque, Filipe Gomes, Vanessa Narbonne, Giovanni Maestri,* and Max Malacria*

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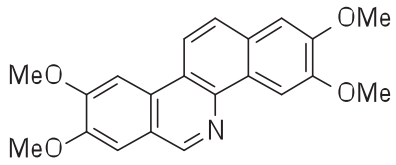
General remarks: Reagents were obtained from commercial sources and used as received. **5-6**[1] and **7-8**[2] were prepared according to reported procedures. Solvents were dried using microwave activated molecular sieves (3 Å for MeCN, 4 Å for DMF), degassed by bubbling argon for at least 30 minutes and stored under an inert atmosphere. Cs_2CO_3 has been dried by heating at 130°C under vacuum for 24 hour and was stored in a Schlenk under argon. Reactions were carried out under argon using standard Schlenk technique. Flash column chromatography was performed on Merck Geduran SI 60 A silica gel (40−63 μm) and thin-layer chromatography on Merck 60F254 plates. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6, $CDCl_3$ and pyridine-d_5 on a Bruker 300 AVANCE spectrometer fitted with a QNP probehead at 300.1 and 75.4 MHz respectively, using the solvent as internal standard (8.74 ppm for ^{1}H NMR and 150.35 ppm for ^{13}C NMR for pyridine and 2.50, 39.51 ppm for ^{1}H and ^{13}C NMR respectively for DMSO).

Synthesis of phenantridines 1-4

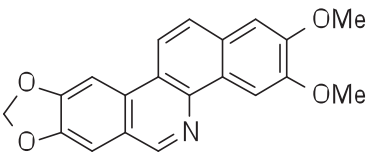
General procedure in DMF: To a Schlenk-type flask were added under argon Cs_2CO_3 (197 mg; 0.6 mmol; 2.3 eq) and triphenylphosphine (12 mg; 0.052 mmol; 0.20 equiv). At least three vacuum/argon cycles were made before addition via cannula of a solution containing the aryl triflate (0.29 mmol; 1.1 equiv), the 2-bromobenzylamine (0.26 mmol; 1 equiv) and norbornene (240 mg, 2.6 mmol; 10 equiv) in 3 mL of MeCN. A solution of $Pd(OAc)_2$ (6 mg, 0.026 mmol; 0.1 equiv) was then eventually added. The same procedure could be adopted when using 2-bromobenzylamines hydrochloric salts by adding 1 more equiv of base in the reaction vessel. The resulting suspension was stirred with a magnetic bar at 90 °C until visible formation of palladium black (16-48 hours). Consumption of starting materials was assessed by ^{1}H NMR. The mixture was then allowed to cool to room temperature, diluted with EtOAc (50 mL), washed with a saturated K_2CO_3 solution (3 × 30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel.

2,3,8,9-Tetramethoxybenzo[*c*]phenanthridine (*O*-methylnorfagaronine) (1)



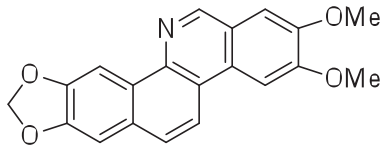
Following the general procedure, from triflate **5** (97 g) and amine **7** (64 mg), 58 mg were obtained as solid. (64%). Spectral data corresponds to those reported in the literature.[3] **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 9.26 (s, 1H, H6), 8.74 (s, 1H), 8.31 (d, 1H, J = 8,9Hz), 7.91 (s, 1H), 7.87 (d, 1H, J = 8,9 Hz), 7.40 (s, 1H), 7.30 (s, 1H), 4.20 (s, 3H), 4.17 ppm (s, 3H), 4.10 (s, 3H), 4.08 (s, 3H). **^{13}C NMR** (75.4 MHz, $CDCl_3$) : δ 153,0, 150.0, 149,9, 149.7, 149.6 (C6), 140,3, 128.9, 128.3, 127.5, 126.1, 122.1, 119.8, 118.0, 107.3, 107.0, 104.2, 101.6, 56.2, 56.1(x2), 56.0.

2,3-dimethoxybenzo[c][1,3]dioxolo[4,5-j]phenanthridine (Norallonitidine) (2)



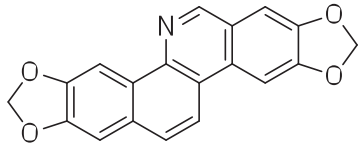
Following the general procedure, from triflate **5** (97 mg) and amine **8** (60 mg), 52 mg were obtained as solid (60%). Spectral data corresponds to those reported in the literature.[4] **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 9.29 (s, 1H), 8.63 (s, 1H), 8.51 (d, 1H, J = 9.0 Hz), 8.33 (s, 1H), 7.96 (d, 1H, J = 9.0 Hz), 7.69 (s, 1H), 7.54 (s, 1H), 6.29 (s, 2H), 4.02 (s, 3H) 3.96 (s, 3H). **^{13}C NMR** (75.4 MHz, $CDCl_3$): δ 151.5, 149.8, 149.5, 147.7, 139.6, 130.4, 128.0, 126.4, 126.1, 123.1, 119.9, 118.8, 107.5, 104.8, 103.7, 102.1, 100.0, 55.5 (x2).

2,3-dimethoxy-[1,3]dioxolo[4',5':4,5]benzo[1,2-c]phenanthridine (Nornitidine) (3)



Following the general procedure, from triflate **6** (93 mg) and amine **7** (64 mg), 62 mg were obtained as solid (72%). Spectral data corresponds to those reported in the literature.[5] **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 9.33 (s, 1H), 8.65 (d, 1H, J = 9.0 Hz), 8.56 (s, 1H), 8.18 (s, 1H), 7.97 (d, 1H, J = 9.0 Hz), 7.73 (s, 1H), 7.53 (s, 1H), 6.22 (s, 2H), 4.10 (s, 3H), 3.99 (s, 3H). **^{13}C NMR** (75.4 MHz, $CDCl_3$): δ 153,3, 149.7, 149,6, 148.0 (x2), 138.4, 129.3, 128.4, 127.9, 126.4, 121.8, 119.8, 119.2, 107.8, 104.5, 102.4, 101.4, 100.9, 56.2, 55,7.

[1,3]dioxolo[4',5':4,5]benzo[1,2-c][1,3]dioxolo[4,5-j]phenanthridine (Noravicine) (4)

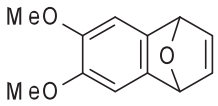


Following the general procedure from the triflate **6** (93 mg) and the amine **8** (60 mg), 61 mg were obtained as solid (74%). Spectral data corresponds to those reported in the literature.[6] **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm) 9.29 (s, 1H), 8.55 (s, 1H), 8.53 (d, 1H, J = 9,2 Hz), 8.34 (s, 1H), 7.95 (d, 1H, J = 9.2 Hz), 7.70 (s, 1H), 7.52 (s, 1H), 6.29 (s, 2H), 6.22 ppm (s, 2H). **^{13}C NMR** (75.4 MHz, $CDCl_3$): δ 151.8, 149.7, 148.1, 147.9, 141.9, 130.5, 129.6, 129.4, 126.7, 123.1, 122.4, 120.3, 119.2, 104.9, 104.6, 102.2, 101.5, 101.0, 100.1.

Synthesis of triflates:

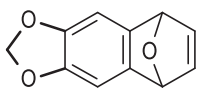
General procedure for the synthesis of epoxynaphtalenes : A dried round-bottom flask was charged with the corresponding dibromoaryl (16.89 mmol, 1 eq) and furane (84.47 mmol, 5 eq) in dry toluene (50 ml) under argon atmosphere. The solution was cooled at -78 ºC and *n*-BuLi 1.6M in THF (18.58 mmol,1.1 eq) was added dropwise to the solution. After complete addition, the solution was warmed up to -40ºC and extracted with EtOAc (3x20 ml), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by chormatography column (EtOAc/heptane).

1,4-dihydro-6,7-dimethoxy-1,4-epoxynaphtalene (9)



Following the general procedure, from 4,5-dibromoveratrol (5 g), 1.91 g of **9** (56% yield) were obtained as a white solid, the product is spectroscopically identical to the material described in the literature.[7] **^{1}H-NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.01 (s, 21H), 6.94 (s, 21H), 5.65 (s, 21H), 3.82 (s, 6H).

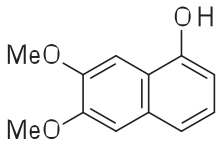
5,8-dihydro-5,8-epoxynaphto[2,3-*d*][1,3]dioxo (10)



Following the general procedure, from 5,6-dibromo-1,3-benzodioxole (4.73 g) were obtained 3.17 g of **10** (81% yield) as a white solid, the product is spectroscopically identical to the material described in the literature.[1] **^{1}H-NMR** (300 MHz, $CDCl_3$): δ (ppm) 7.07 (s, 2H), 6.86 (s, 2H), 5.96 (d, 1H, J = 1.4 Hz), 5.91 (d, 1H, J = 1.4 Hz), 5.66 (s, 2H).

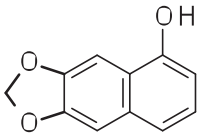
General procedure for the synthesis of alcohols: To a solution of the corresponding epoxynaphtalene (7.35 mmol) in DCE (50 ml) was added at 0°C and dropwise a solution of *p*-toluenesulfonic acid (1.47 mmol, 0.2 eq.) in DCE (2 ml). The reaction mixture was stirred at r.t. overnight. The mixture was diluted with DCM, washed with water and brine, dried over magnesium sulfate and concentrated under vacuum. The products were used for the next step without further purification.

6,7-Dimethoxynaphthalen-1-ol (11)



Following the general procedure, from **9** (1.5 g), was obtained **11** as a white solid. The product is spectroscopically identical to the material described in the literature.[8] **^{1}H-NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.44 (s, 1H), 7.28 (d, 1H, *J* = 8.0 Hz), 7.14 (appt, 1H, *J* = 8.0, 7.4 Hz), 7.08 (s, 1H), 6.68 (d, 1H, *J* = 7.4 Hz), 5.11 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H).

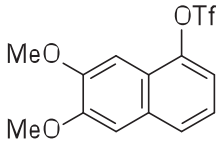
Benzo[f][1,3]benzodioxol-5-ol (12)



Following the general procedure, from **10** (1.38 g), was obtained **12** as a white solid. The product was shown to be spectroscopically identical to the material described in the literature.[1] **^{1}H-NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.50 (s, 1H), 7.32-7.25 (m, 1H), 7.16 (t, 1H, *J* = 7.8 Hz), 7.11 (s, 1H), 6.70 (d, 1H, *J* = 7.4 Hz), 6.05 (s, 2H), 5.04 (s, 1H).

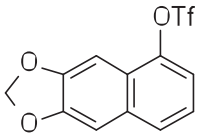
General procedure for the synthesis of triflates: To a solution of the corresponding naphtol (6.86 mmol) and pyridine (13.72 mmol) in DCM (40 ml) at 0 ºC, was slowly added Tf_2O (10.29 mmol). After complete addition the mixture was warmed to r.t. and stirred until complete conversion of the starting material (1h). The mixture then was diluted with Et_2O (20 ml), quenched with 10% aq HCl and washed with sat. $NaHCO_3$ and brine. After drying (Mg_2SO_4), the solvent was removed and the residue was purified by column chromatography (EtOAc/heptane).

6,7-Dimethoxynaphthalen-1-yltrifluoromethanesulfonate (5)



Following the general procedure, from **11** (1.40 g) were obtained 2.04 g (89% yield) of the product as a pale yellow solid. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ (ppm) 7.67 (dd, 1H, *J* = 6.9, 1.6 Hz), 7.32-7.28 (m, 3H), 7.14 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ (ppm) 151.1, 150.5, 144.7, 131.1, 126.6, 123.5, 122.0, 118.7 (q, $J_{C\text{-}F}$ = 319.8 Hz), 116.4, 106.4, 99.3, 56.0, 55.9.

Naphtho[2,3-d][1,3]dioxol-5-yltrifluoromethanesulfonate (6)

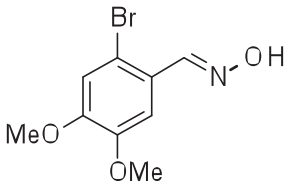


Following the general procedure, from **12** (1.29 g), were obtained 2.19 g (89% yield) of the product as a pale yellow solid, the product is spectroscopically identical to the material described.[1] **^{1}H-NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.66 (dd, 1H, *J* = 5.5, 3.6 Hz), 7.33-7.31 (m, 3H), 7.16 (s, 1H), 6.11 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ (ppm) 149.4, 148.8, 145.3, 132.5, 127.3, 123.8, 123.5, 118.7 (q, $J_{C\text{-}F}$ = 320.5 Hz), 116.4, 104.7, 101.7, 97.4.

Synthesis of amines:

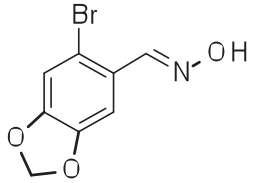
General procedure for the synthesis of oximes : Hydroxylamine hydrochloride (0.775 mg; 11.15 mmol; 1.2 eq.) was added to a solution of $NaHCO_3$ (0.915 g; 10.9 mmol; 1 eq.) in 25 mL of water. The solution was added to a vigorously stirred suspension of a bromobenzylamine (10.9 mmol; 1 eq.) in EtOH (25 mL). The resulting mixture was stirred for 5h and then left at 20 °C overnight. The precipitate formed was filtered, washed with a few mL of cold ethanol and dried under vacuum to give the desired hydroxylamine, which is used without further purification.

2-bromo-4,5-dimethoxy-benzaldehyde oxime (13)



Following the general procedure, from 2-bromo-4,5-dimethoxy-benzaldehyde (2.67 g), 2.72 g (96% yield) of the product were obtained as white crystals. The product is spectroscopically identical to the material described.[9] **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 11.41 (s, 1H), 8.19 (s, 1H), 7.27 (s, 1H), 7.16 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H).

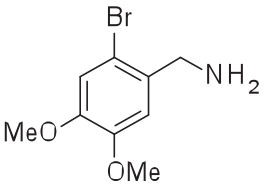
6-bromo-1,3-benzodioxole-5-carbaldehyde oxime (14)



Following the general procedure, from 6-bromo-1,3-benzodioxole-5-carbaldehyde (2.50 g), 1.96 g (72% yield) of the product were obtained as white powder. The product is spectroscopically identical to the material described.[10] **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 8.44 (s, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 6.01 (s, 2H).

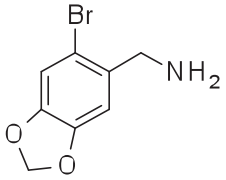
General procedure for the synthesis of amines: To a solution of the corresponding hydroxylamine (7 mmol, 1 eq.) in THF (80 mL) was added a 2N HCl solution (35.3 mL; 70.7 mmol, 10 eq.), followed by zinc (4.62 g, 70.7 mmol, 10 eq.). The mixture was vigorously stirred under reflux until full conversion. The reaction mixture was cooled to room temperature, filtered on a celite pad to remove the excess zinc and condensed under reduce pressure to remove THF. The aqueous layer was extracted with EtOAc (30 mL) and the pH of the aqueous layer was adjusted to >10 by addition of a saturated ammonia solution, then extracted with EtOAc (3x 30mL). These last organic layers were combined and dried over anhydrous K_2CO_3, filtered and evaporated to give a crude, which was purified by flash column chromatography on silica gel (eluent: EtOAc/2% Et_3N).

2-Bromo-4,5-dimethoxybenzylamine (7)



Following the general procedure, from **13** (1.82 g), was obtained 1.43 g (83% yield) of the product as white powder. The product is spectroscopically identical to the material described.[11] **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 6.98 (s, 1H), 6.89 (s, 1H), 3.85-3.81 (m, 8H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ (ppm) 148.5, 148.4, 134.2, 115.6, 113.2, 112.0, 56.2, 56.0, 46.6

(6-Bromobenzo[d][1,3]dioxol-5-yl)methanamine (8)



Following the general procedure, from **14** (1.71 g) was obtained **8** (1.28 g, 80%) as a pale yellow solid. The product is spectroscopically identical to the material described.[9] **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 6.99 (s, 1H), 6.88 (s, 1H), 5.96 (s, 2H), 3.80 (s, 2H), 1.56 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ (ppm) 147.5, 147.2, 135.5, 113.6, 112.8, 109.1, 101.7, 46.8

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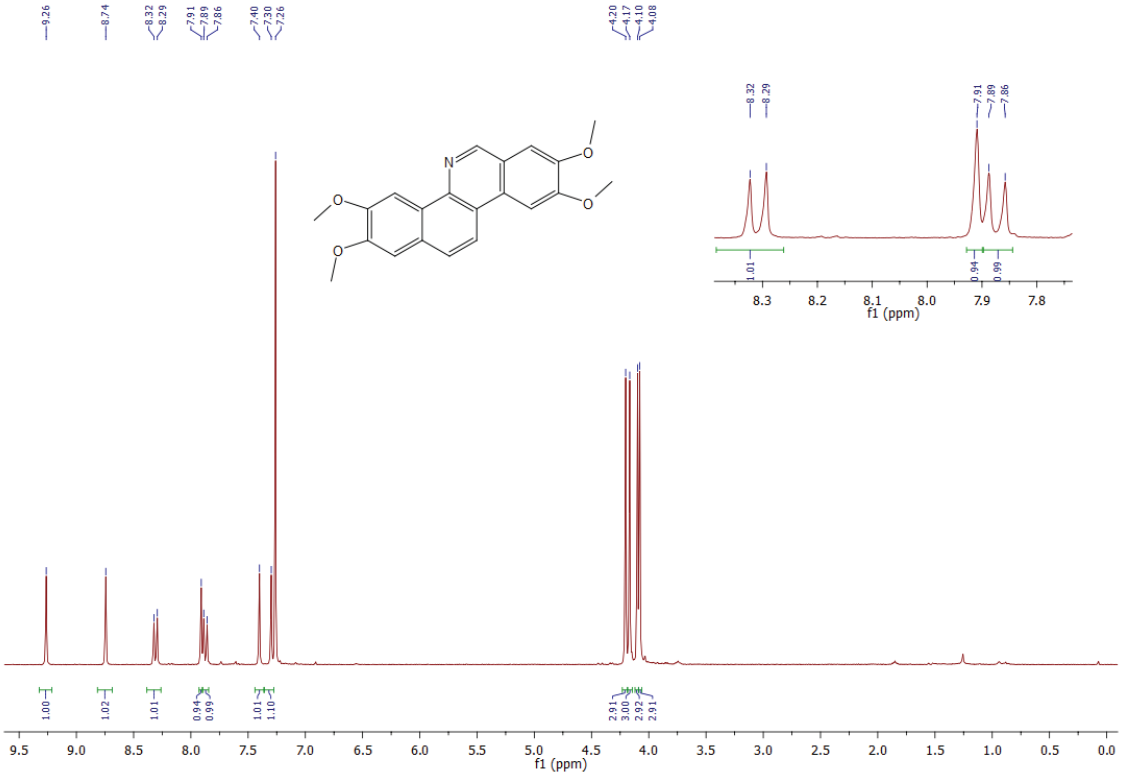
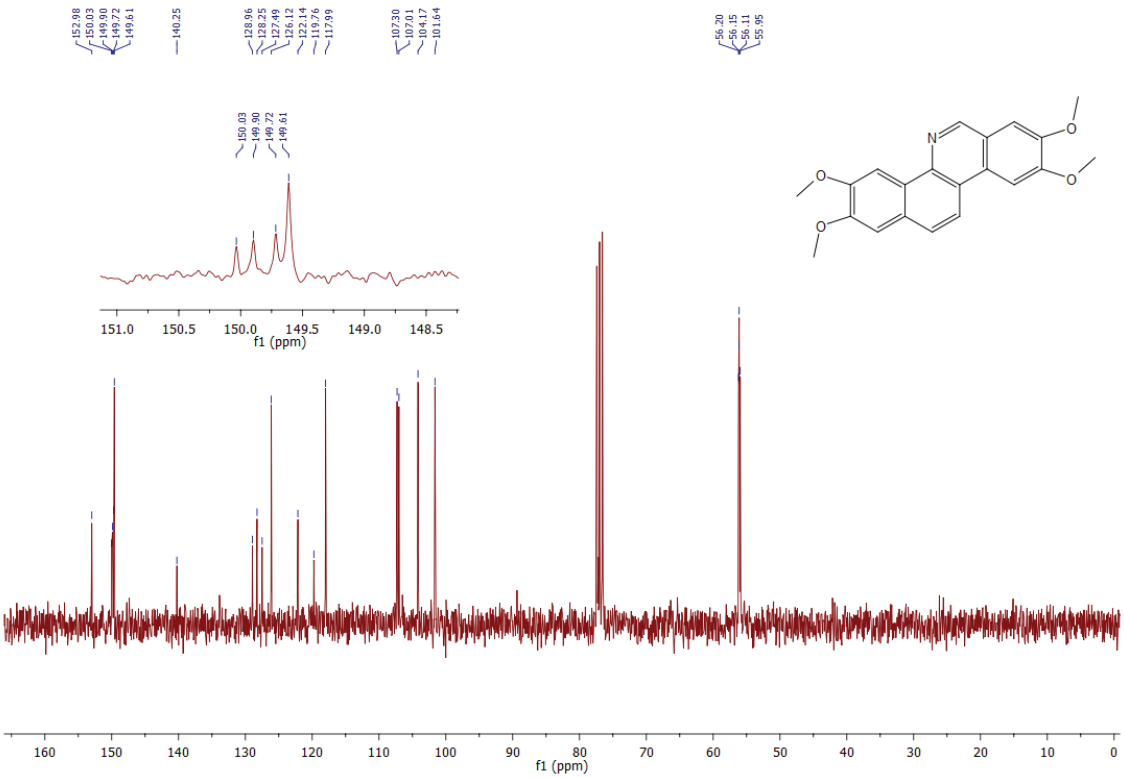
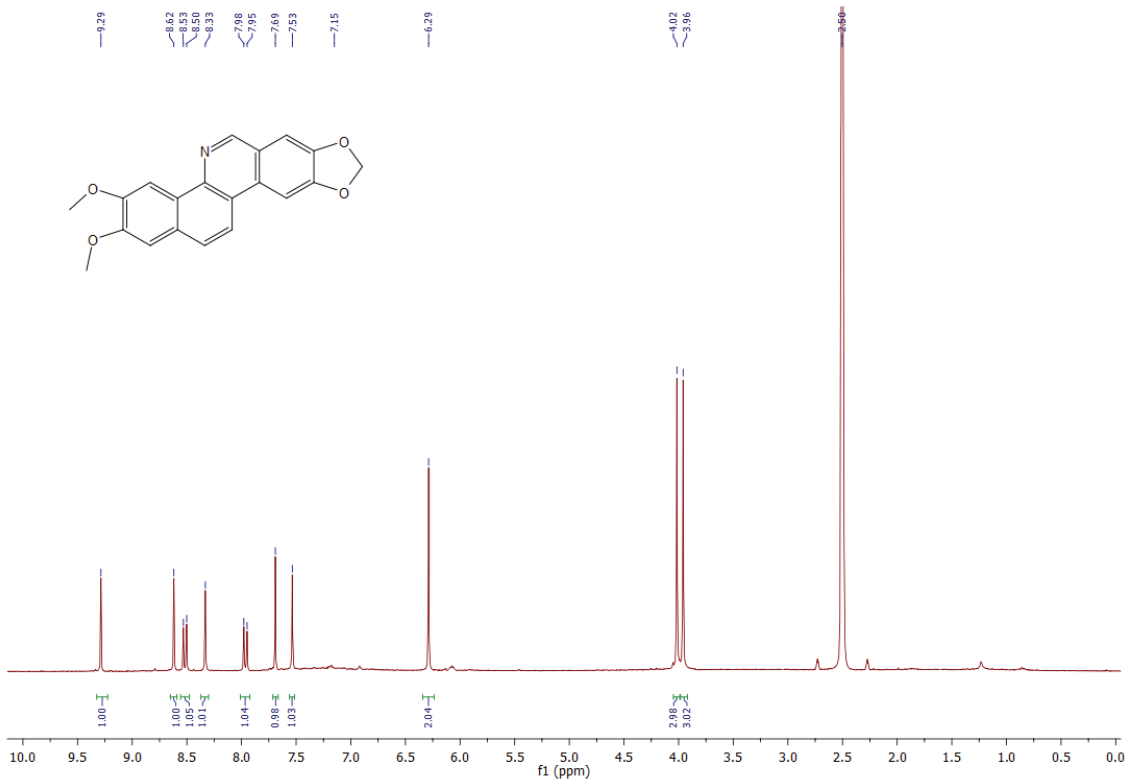
Spectral data for phenantridines

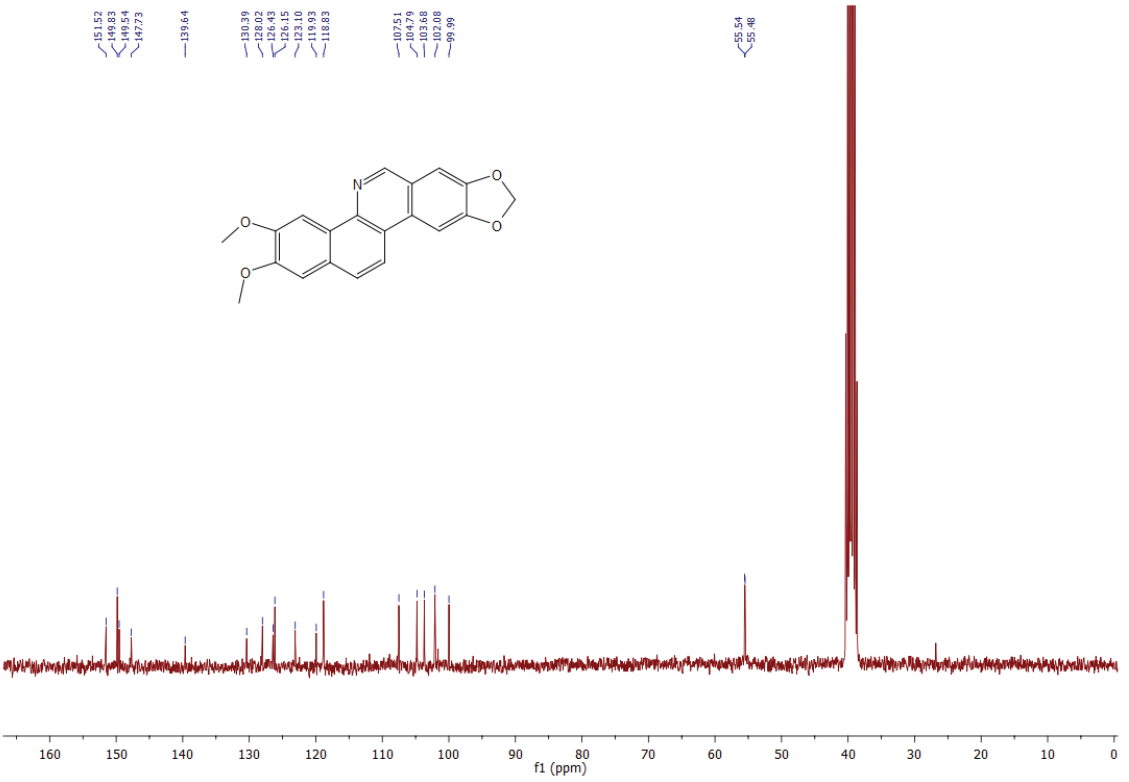
2,3,8,9-Tetramethoxybenzo[*c*]phenanthridine (*O*-methylnorfagaronine) (1)



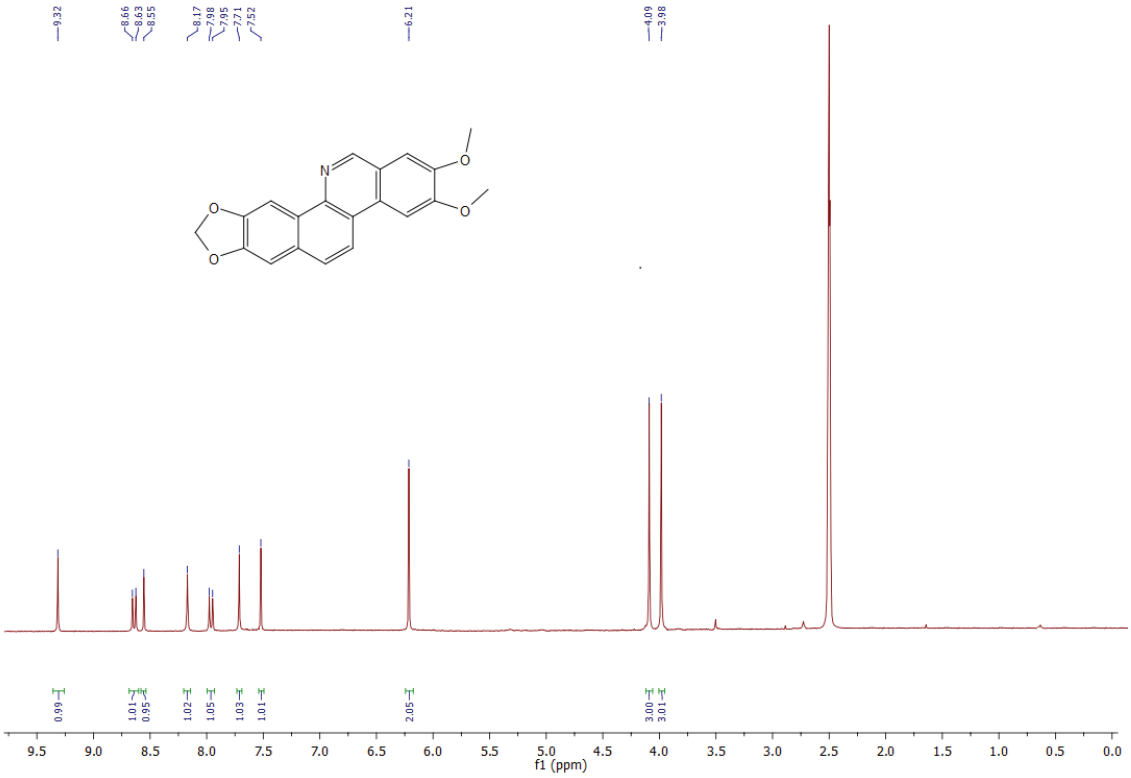


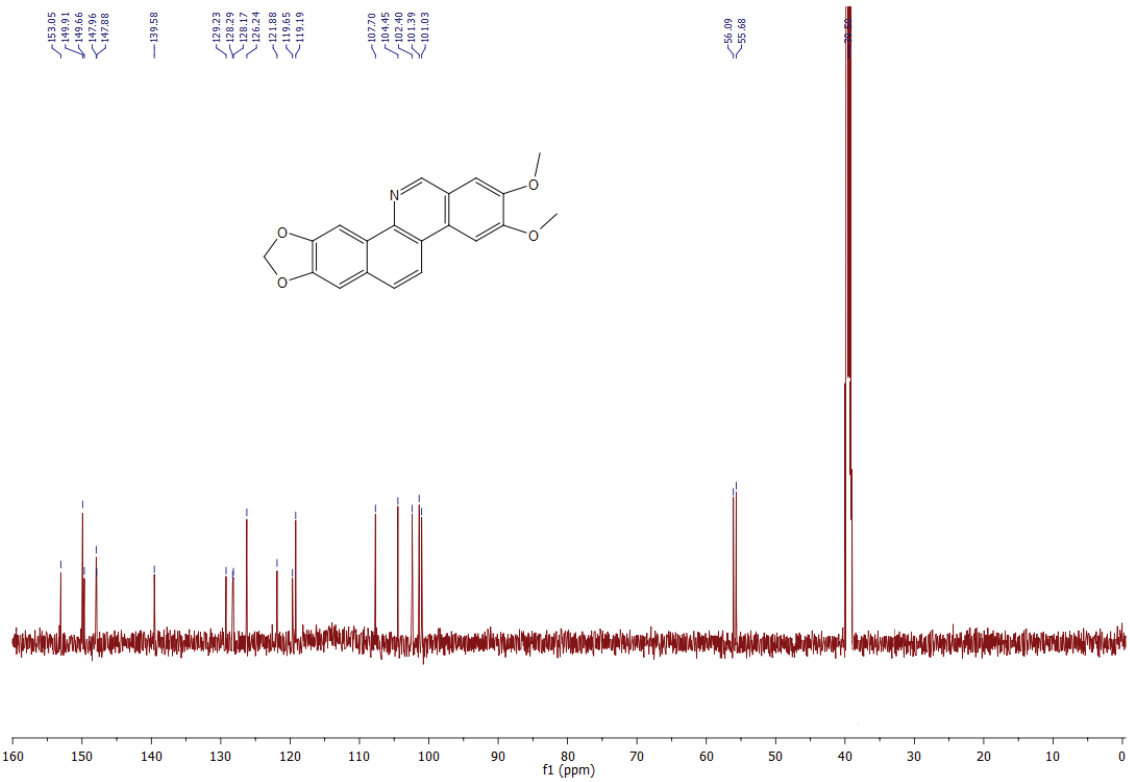
2,3-dimethoxybenzo[c][1,3]dioxolo[4,5-j]phenanthridine (Norallonitidine) (2)



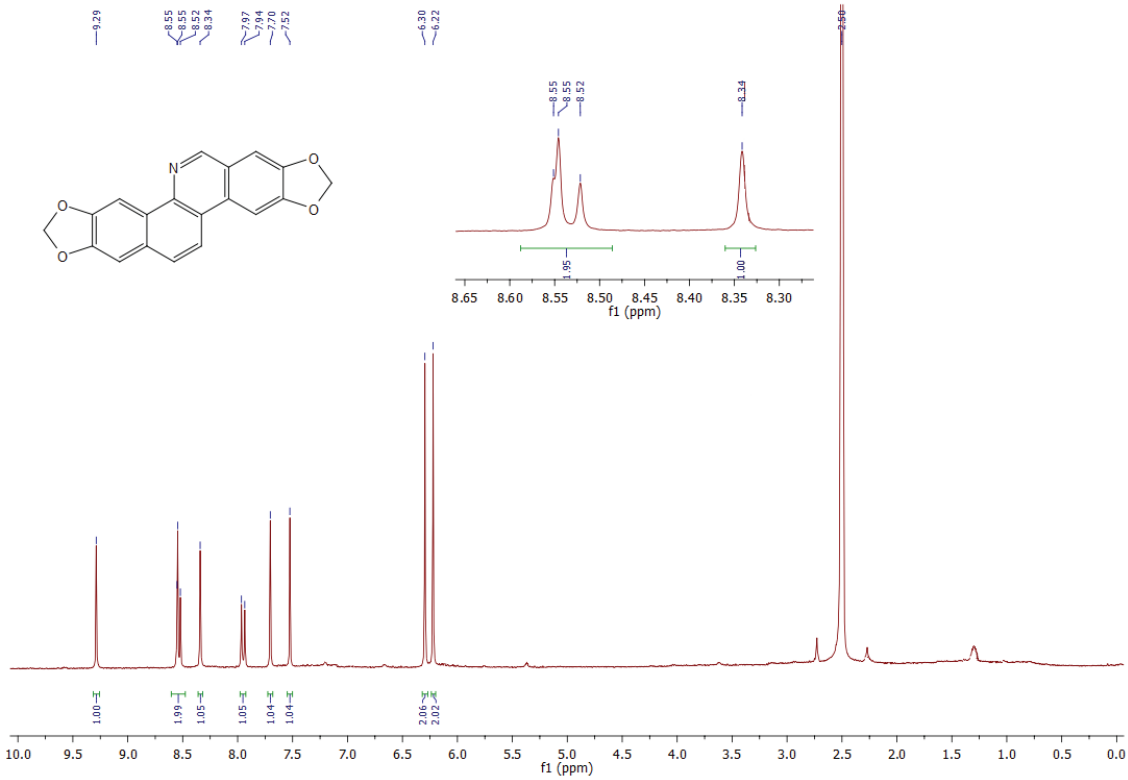


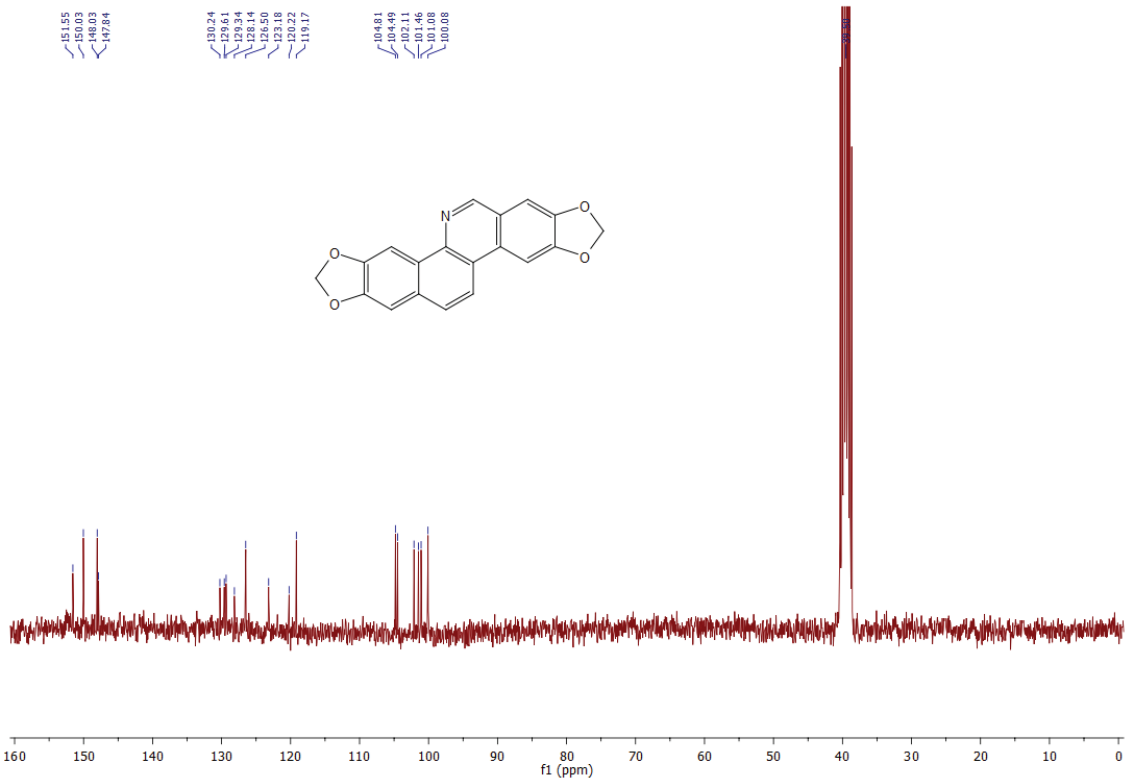
2,3-dimethoxy-[1,3]dioxolo[4',5':4,5]benzo[1,2-c]phenanthridine (Nornitidine) (3)





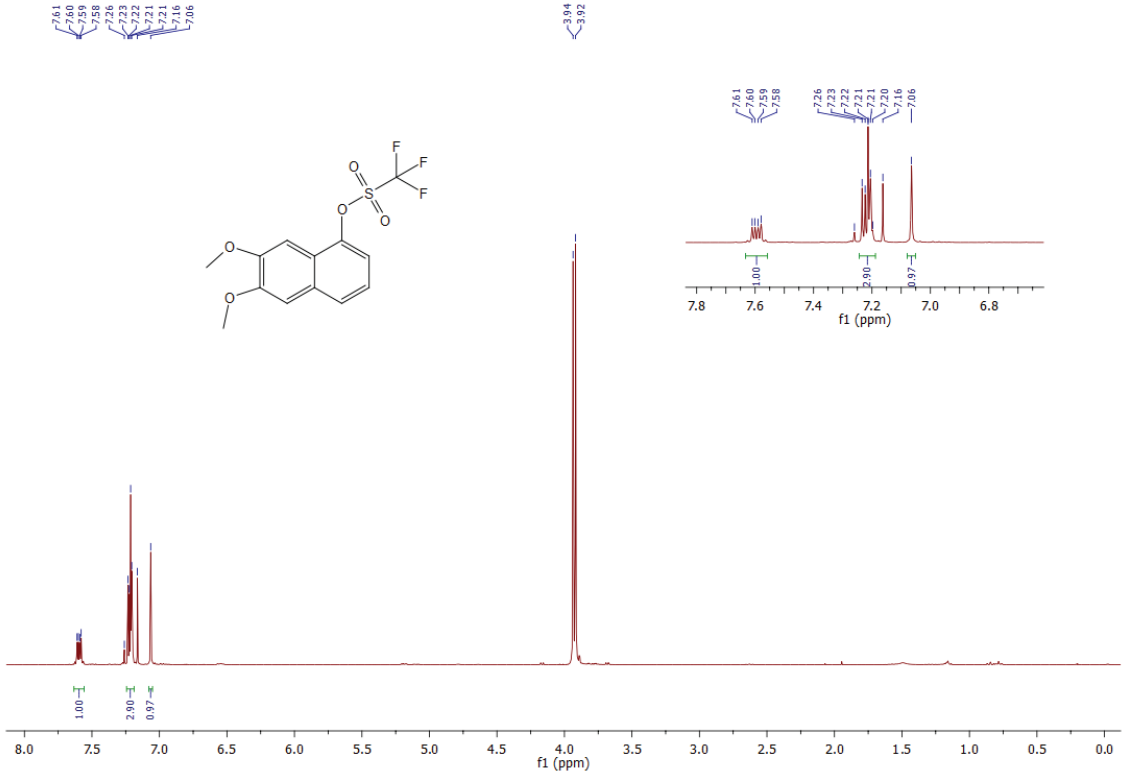
[1,3]dioxolo[4',5':4,5]benzo[1,2-c][1,3]dioxolo[4,5-j]phenanthridine (Noravicine) (4)

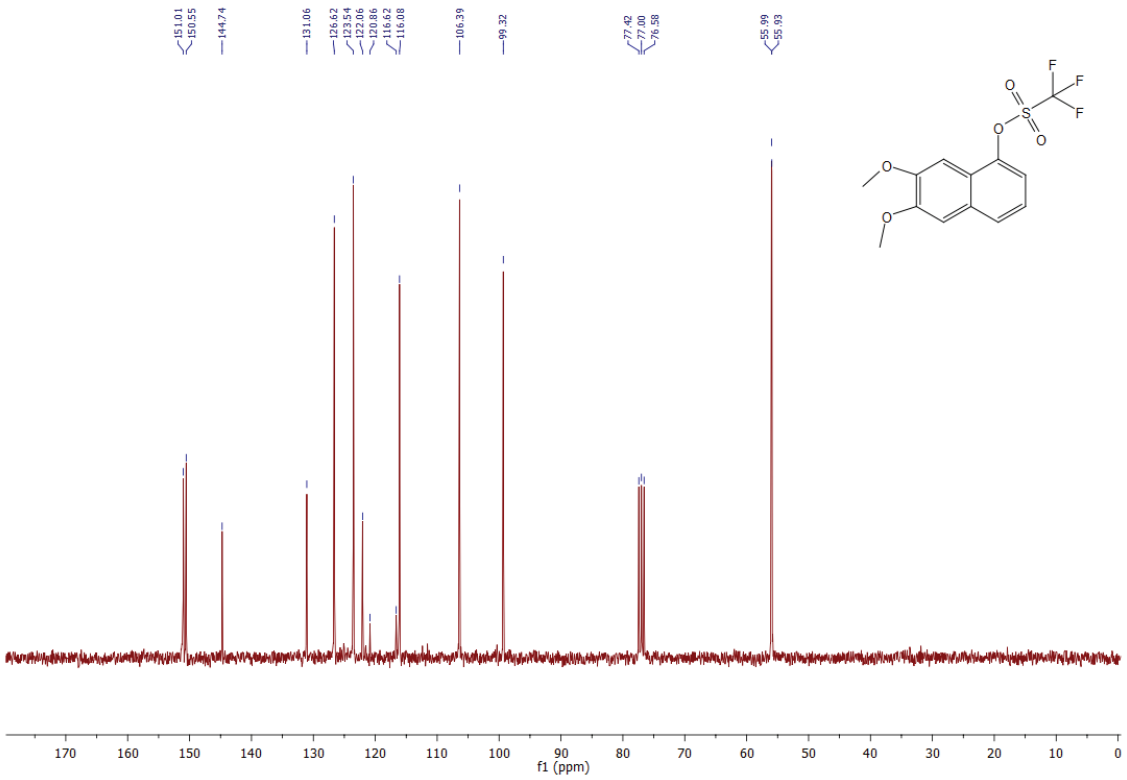




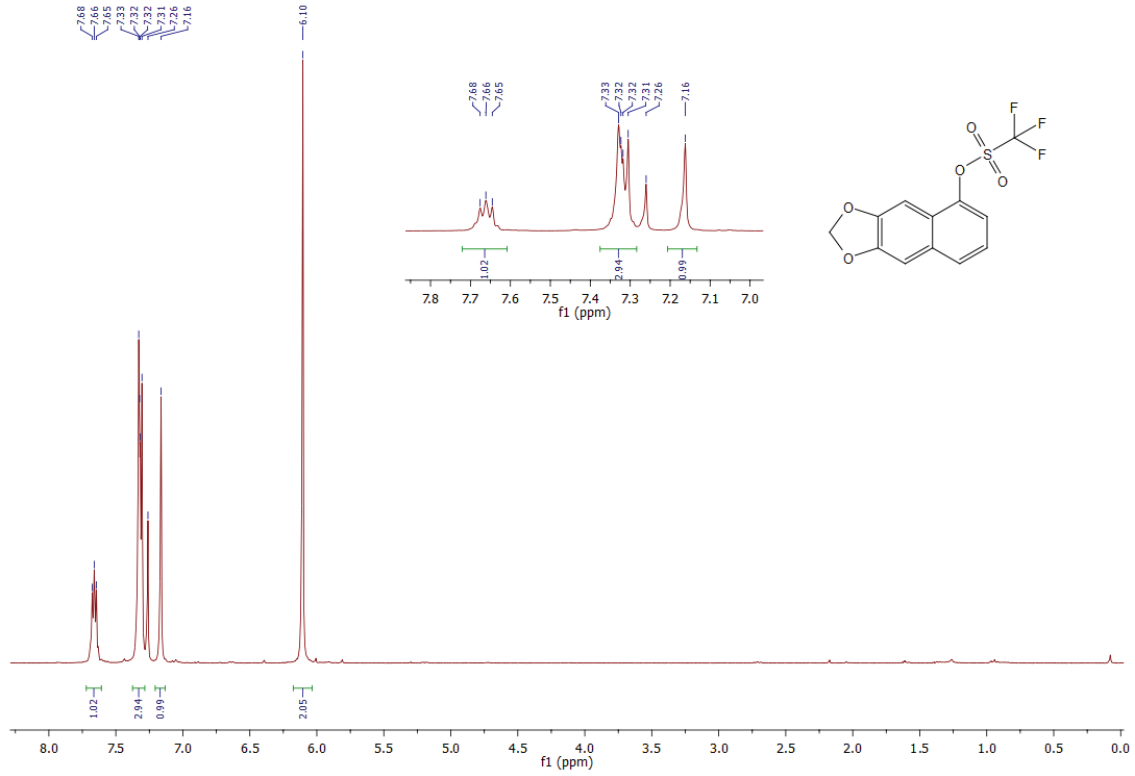
Spectral data for triflates

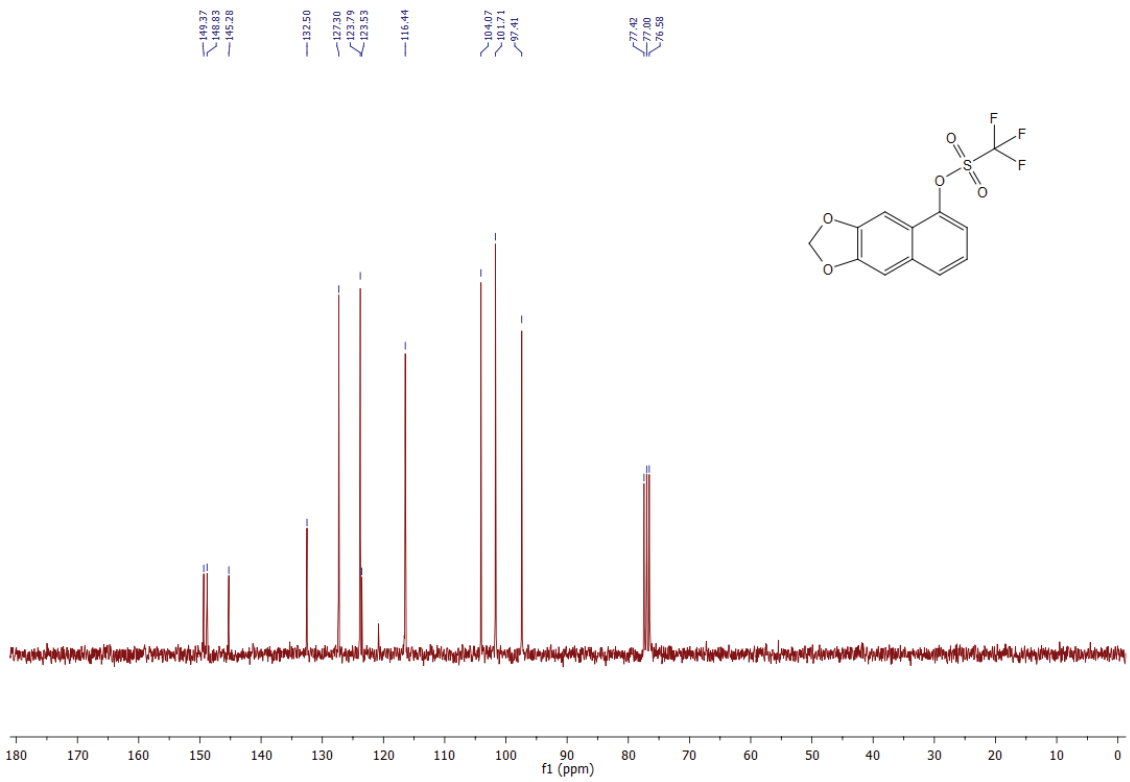
6,7-Dimethoxynaphthalen-1-yltrifluoromethanesulfonate (5)





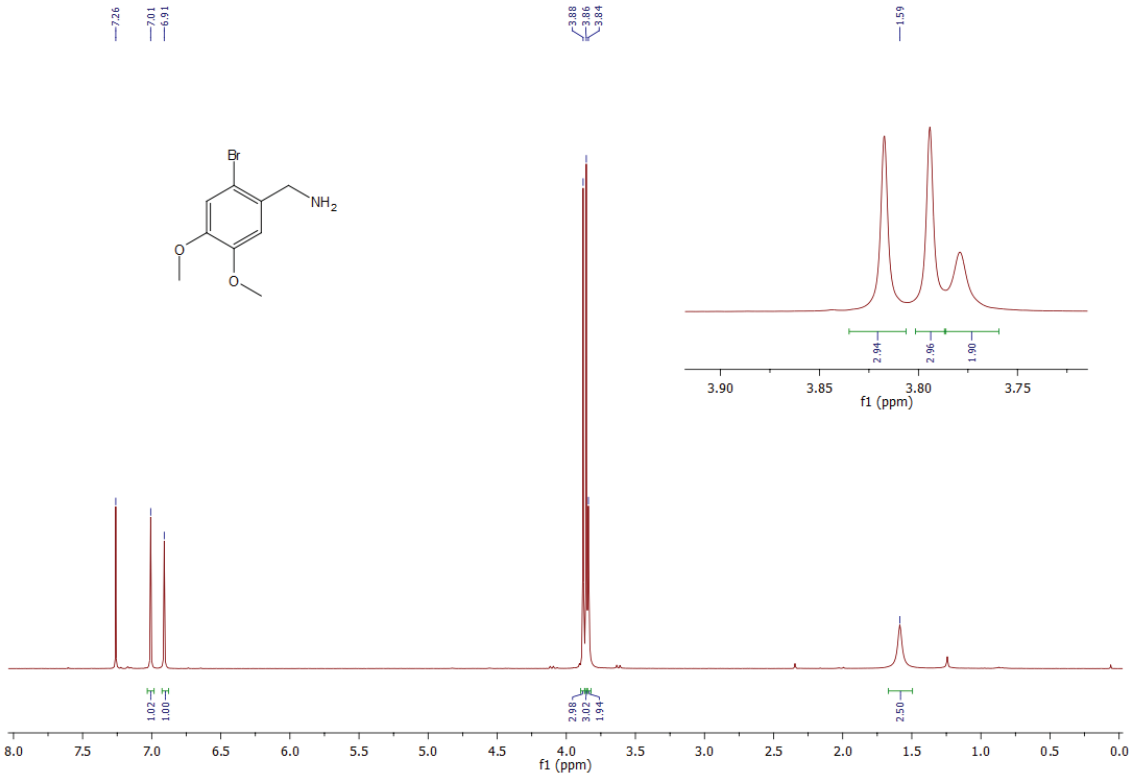
Naphtho[2,3-d][1,3]dioxol-5-yltrifluoromethanesulfonate (6)

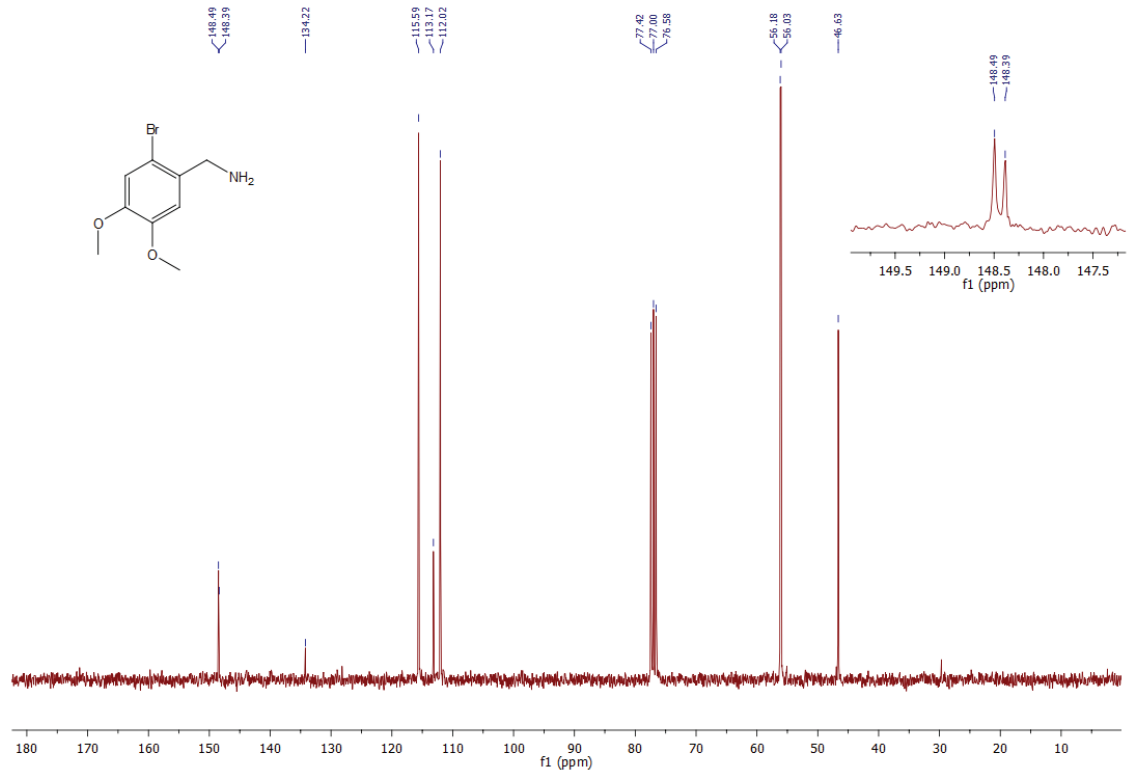




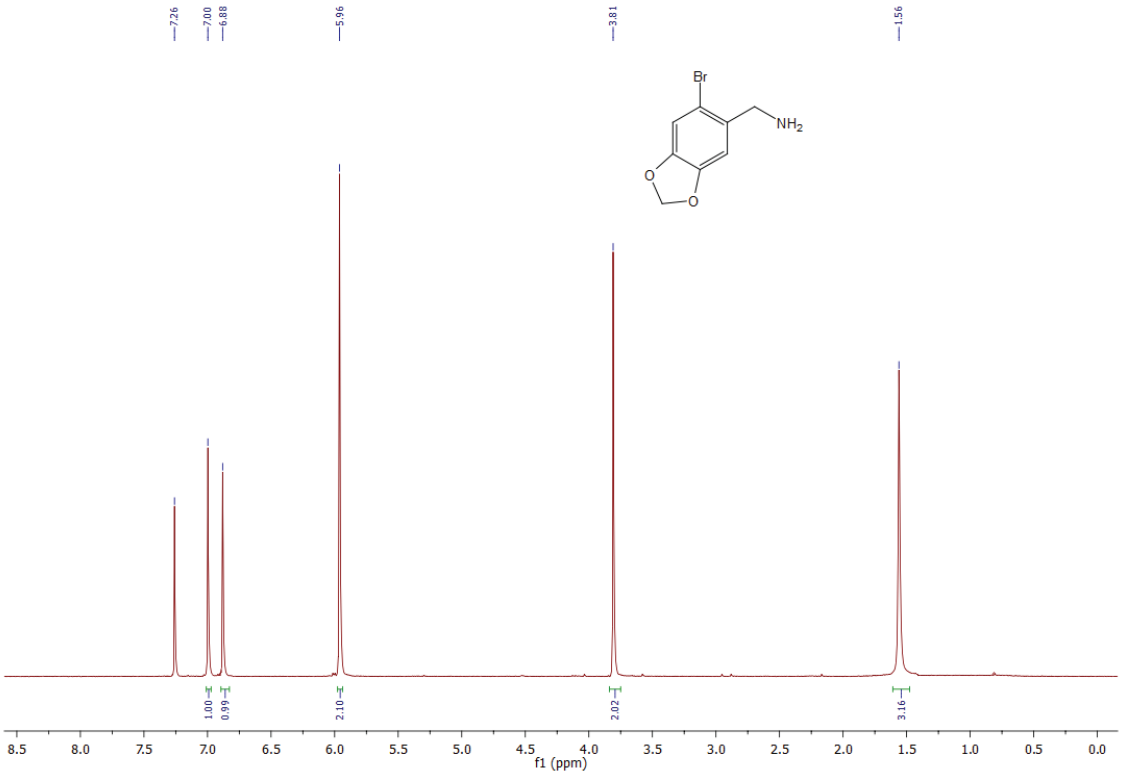
Spectral data for bromides

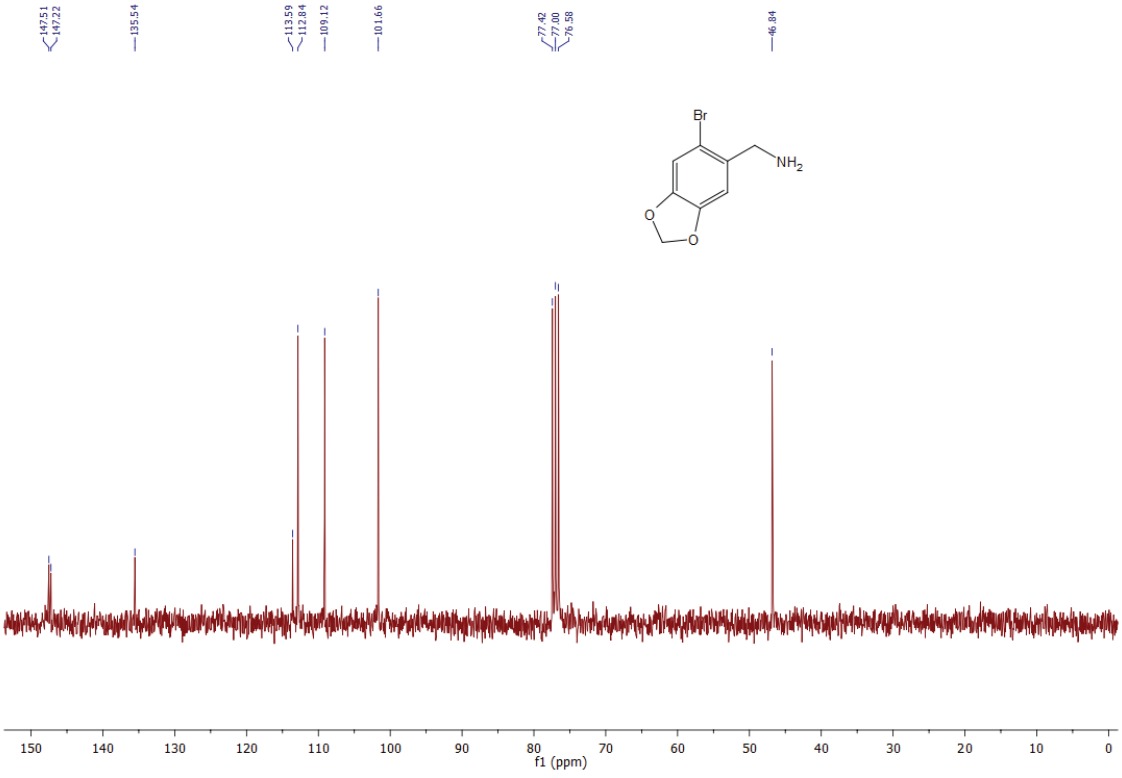
2-Bromo-4,5-dimethoxybenzylamine (7)





(6-Bromobenzo[d][1,3]dioxol-5-yl)methanamine (8)


7.26
7.00
6.88
5.96
3.81
1.56
Br
NH2
O
O
1.00
0.99
2.10
2.02
3.16
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)


147.51
147.22
135.54
113.59
112.84
109.12
101.66
77.42
77.00
76.58
46.84
Br
NH2
O
O
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)