Supplementary Information

Synthesis and biological evaluation of N-*alkyl naphthoimidazoles* derived from β-lapachone against *Trypanosoma* cruzi bloodstream trypomastigotes

Ari Miranda da Silva,[a,b] Leonardo Araújo,[a] Ana Cristina Bombaça,[c] Rubem F. S. Menna-Barreto,[c] Claudio Eduardo Rodrigues-Santos,[a] Aurélio B. Buarque Ferreira,[a] and Solange L. de Castro[c,*]

[a]*Programa de Pós-Graduação em Química, UFRRJ, 23890-000, Seropédica, RJ, Brazil*

[b]Instituto de *Pesquisas em Produtos Naturais, UFRJ, 21944-970, Rio de Janeiro, RJ, Brazil*

[c]*Laboratório de Biologia Celular, Instituto Oswaldo Cruz, FIOCRUZ, 21045-900, Rio de Janeiro, RJ, Brazil. Email: solange@ioc.fiocruz.br; Tel: +55 21 25621391*

Contents

1. Spectral data of compounds 5 to 26

2. NMR spectra of compounds 5 to 26

3. Discrimination between N1- alkyl and N3-alkyl regioisomers using NMR data.

4. Structure/trypanocidal activity correlation

1. Spectral data of of compounds 5 to 26

6,6-Dimethyl-2-(2-thienyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazole (5) Using 0.5 mmol 2-thiophenecarboxaldehyde, **5** was obtained in 16% yield (m.p. 183-185°C). IR (KBr) cm^{-1}: 3421, 3212, 3104, 3075, 2974, 2939, 2927, 2850, 1652, 1616, 1604, 1585, 1459, 1444, 1429, 1383, 1367, 1259, 1240, 1159, 1120, 1053, 879, 852, 771, 721, 709. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (s, 6H), 1.98 (t, 2H, J = 6.7 Hz), 3.09 (t, 2H, J = 6.7 Hz), 7.16 (dd, 1H, J = 3.7 and 4.9 Hz), 7.46-7.50 (m, 2H), 7.59 (t, 1H, J = 7.6 Hz), 7.85 (dd, 1H, J = 1.1 and 3.7 Hz), 8.29 (d, 1H, J = 8.3 Hz), 8.44 (d, 1H, J = 8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4, 26.7, 31.7, 75.3, 101.7, 121.9, 122.6, 124.0, 124.5, 125.2, 126.7, 128.0, 128.4, 129.7, 130.6, 147.8, 156.7, 147.4. MS (m/z; (%)): 334 (50), 278 (100). TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 335.1214 $[M+H]^+$, $C_{20}H_{19}N_2OS$. Calculated: 335.1218.

2-(2,6-Dichlorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazole (6) Using 0.5 mmol 2,6-dichlorobenzaldehyde, **6** was obtained in 31% yield (m.p. 159-162°C). IR (KBr) cm^{-1}: 3386, 3070, 3012, 2973, 2927, 2869, 2850, 1631, 1602, 1587, 1560, 1545, 1521, 1481, 1464, 1433, 1379, 1369, 1342, 1333, 1321, 1284, 1259, 1242, 1194, 1161, 1120, 1063, 1053, 968,

953, 883, 791, 777, 766, 739, 719, 663, 648. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (s, 6H), 1.87 (t, 2H**,** J = 6.6 Hz), 2.99 (bs, 2H), 7.22-7.28 (m, 3H), 7.39-7.41 (dd, 2H, J = 3.2 and 6.2 Hz), 8.28-8.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.8, 26.8, 32.1, 74.5, 121.5, 122.6, 123.9, 126.0, 128.1, 130.3, 131.2, 136.5. MS (m/z, (%)): 397 (100). TOF MS ES+ (MeOH-H2O-0.1%-AcOH): m/z: 397.0869 [M+H]+, $C_{20}H_{21}Cl_2N_2O$. Calculated: 397.0874.

2-(2,4-Dichlorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazole (7) Using 0.5 mmol 2,4-dichlorobenzaldehyde, **7** was obtained in 81% yield (m.p. 218-220°C). IR (KBr) cm^{-1}: 3446, 3147, 3066, 3052, 3016, 2973, 2950, 2929, 2850, 2821, 1629, 1600, 1587, 1554, 1520, 1469, 1458, 1444, 1425, 1382, 1376, 1369, 1342, 1333, 1317, 1282, 1266, 1259, 1240, 1159, 1144, 1119, 1105, 1061, 1047, 955, 879, 864, 827, 806, 769, 735, 717, 646, 629. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.43 (s, 6H), 1.97 (t, 2H, J = 6.6 Hz), 3.02 (t, 2H, J = 6.5 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 7.1 Hz), 7.64 (dd, 1H, J = 2.0 and 8.3 Hz), 7.86 (d, 1H, J = 2.0 Hz), 7.89 (d, 1H, J = 8.4 Hz), 8.17 (d, 1H, J = 8.3 Hz), 8.37 (d, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d) δ: 18.7, 26.7, 32.1, 74.7, 122.8, 124.3, 126.3, 127.3, 128.0, 130.3, 130.4, 132.5, 135.1. MS (m/z, (%)): 397 (100). TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 397.0869 $[M+H]^+$, $C_{20}H_{21}Cl_2N_2O$. Calculated: 397.0874.

6,6-Dimethyl-2-(1-naphthyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazole (8) Using 0.5 mmol 1-naphthaldehyde, **8** was obtained in 95% yield (m.p. 210-213°C). IR (KBr) cm^{-1}: 3411, 3050, 3016, 2972, 2929, 2875, 2848, 1635, 1618, 1587, 1541, 1516, 1502, 1444, 1429, 1385, 1367, 1340, 1323, 1282, 1261, 1236, 1159, 1146, 1122, 1074, 1057, 1030, 1016, 968, 951, 941, 883, 800, 773. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (s, 6H), 2.04 (t, 2H, J = 6.6 Hz), 3.05 (bs, 2H), 7.45-7.52 (m, 1H), 7.53-7.64 (m, 4H), 7.87 (d, 1H, J = 6.8 Hz), 7.94 (m, 2H), 8.35 (d, 1H, J = 8.4 Hz), 8.80 (bs, 1H, J = xx Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9, 26.8, 32.2, 74.5, 121.1, 122.8, 123.8, 124.0, 125.0, 126.1, 126.2, 126.3, 127.2, 127.4, 128.4, 129.9, 131.4, 134.0. MS (m/z, (%)): 379 (M^{+1}, 100), 336 (7.5), 323 (42.5). TOF MS ES+ (MeOH-H2O-0.1%-AcOH): m/z: 379.1816 [M+H]+, $C_{26}H_{25}N_2O$. Calculated: 379.1810.

4-(6,6-Dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromene[5,6-*d*]imidazol-2-yl)-2-methoxy-phenol (9) Using 0.5 mmol vanillin, **9** was obtained in 54% yield (m.p. 196199°C). IR (KBr) cm^{-1}: 3421, 3178, 3072, 2971, 2927, 2848, 1655, 1610, 1587, 1549, 1529, 1508, 1493, 1464, 1383, 1367, 1346, 1323, 1282, 1259, 1242, 1223, 1161, 1144, 1120, 1055, 1030, 980, 970, 953, 881, 870, 822, 789, 766, 729, 719, 704, 669, 650. ^{1}H NMR (500 MHz, acetone-D_6) δ: 1.45 (s, 6H), 1.99 (t, 2H, J = 6.7 Hz), 3.11 (t, 2H, J = 6.7 Hz), 3.93 (s, 3H), 6.94 (d, 1H, J = 8.2 Hz), 7.41 (t, 1H, J = 8.1 Hz), 7.51 (t, 1H, J = 7.9 Hz), 7.76 (dd, 1H, J = 1.9 and 7.9 Hz), 7.97 (d, 1H, J = 1.6 Hz), 8.22 (d, 1H, J = 8.3 Hz), 8.51 (d, 1H, J = 8.1 Hz). ^{13}C NMR (125 MHz, acetone-D_6) δ: 19.7, 27.0, 32.8, 56.6, 75.2, 105.0, 110.9, 116.2, 120.6, 122.3, 123.4, 124.4, 124.5, 126.7, 146.0, 148.8, 149.1, 149.8. MS (m/z, (%)): 374 (100), 279 (10). TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 375.1713 $[M+H]^+$, $C_{20}H_{21}Cl_2N_2O$. Calculated: 375.1708.

6,6-Dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromene[5,6-*d*] imidazole (10) Using 3 mmol of paraformaldehyde, **10** was obtained in 85% yield (m.p. 296-298°C). UV (CH_3CN; (ε)) λ_{max} = 332 nm (2700). IR (KBr) cm^{-1}: 3409, 3144, 3083, 3010, 2973, 2924, 2844, 1666, 1652, 1605, 1588, 1486, 1451, 1367, 1257, 1161, 1120, 1056, 948, 770. ^{1}H-NMR (400 MHz, MeOD) δ: 1.46 (s, 6H), 2.00 (t, 2H, J = 6.0 Hz), 3.04 (t, 2H, J = 8.0 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.51 (t, 1H, J = 8.0 Hz), 8.08 (s, 1H), 8.21 (d, 1H, J = 12.0 Hz), 8.29 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, MeOD) δ: 19.8, 27.1, 33.3, 75.7, 106.0, 122.0, 123.8, 124.9, 127.2, 139.2, 146.7. EI MS-70eV (*m/z*, (%)): 252 (100), 196 (80). TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 253.1262 $[M+H]^+$, $C_{16}H_{17}N_2O$. Calculated: 253.1341).

1-Propyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (11): m.p. 134-140 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.04 (t, 3H), 1.48 (s, 6H), 2.01 (t, 2H), 2.01-2.07 (m, 4H), 3.21 (t, 2H, J = 6.6 Hz), 4.52 (t, 2H, J = 7.1 Hz), 7.50 (t, 1H, J = 7.4 Hz), 7.9 (s, 1H), 8.11 (d, 1H, J = 8.2 Hz), 8.43 (d, 1H, J = 8.2 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 11.1, 18.4, 23.4, 26.8, 32.4, 49.5, 74.5, 108.2, 119.8, 121.0, 121.3 (2C), 123.4, 123.5, 124.4, 125.8, 141.5, 144.7. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 295.1801 $[M+H]^+$, $C_{19}H_{22}N_2O$. Calculated: 295.1805.

3-Propyl-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (12): m.p. 159-163°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.02 (t, 3H), 1.48 (s, 6H), 1.90-1.95 (m, 2H), 2.00 (t, 2H, J = 6.6 Hz), 3.21 (t, 2H, J = 6.6 Hz), 4.36 (t, 2H, J = 7.3 Hz), 7.47 (t, 1H, J = 7.6 Hz), 7.60 (t, 1H, J = 7.4 Hz), 7.80 (s, 1H), 8.29 (d, 1H, J = 8.5 Hz), 8.55 (d, 1H, J = 8.2 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 11.2, 20.0, 25.8, 26.5, 32.4, 48.6, 73.6, 101.6, 121.3, 122.4, 123.5 (2C), 123.9, 126.5, 128.8, 133.4, 140.5, 145.9. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 295.1809 $[M+H]^+$, $C_{19}H_{22}N_2O$. Calculated: 295.1805.

1-Butyl-6,6-dimethyl-3,4,5,6- tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (13): m.p. -, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00 (t, 3H), 1.43-1.49 (m, 2H), 1.48 (s, 6H), 1.98-2.02 (m, 4H), 3.22 (t, 2H, J = 7.8 Hz), 4.59 (t, 2H, J = 7.2 Hz), 7.51 (t, 1H, J = 7.2 Hz), 7.59 (t, 1H, J = 8.16 Hz), 8.02 (s, 1H), 8.13 (d, 1H, J = 8.28 Hz), 8.44 (d, 1H, J = 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.6, 18.5, 19.8, 26.7, 32.1, 32.3, 47.9, 74.7, 107.6, 119.9, 120.8, 121.3, 123.5, 123.8, 124.4, 126.0, 140.4, 141.3, 145.1. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 309.1959 $[M+H]^+$, $C_{20}H_{24}N_2O$. Calculated: 309.1961.

3-Butyl-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (14): m.p. 104-107 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00 (t, 3H), 1.40-1.46 (m, 2H), 1.48 (s, 6H), 1.84-1.91 (m, 2H), 2.00 (t, 2H, J = 6.8 Hz), 3.19 (t, 2H, J = 6.7 Hz), 4.40 (t, 2H, J = 7.3 Hz), 7.48 (t, 1H, J = 7.7 Hz), 7.61 (t, 1H, J = 8.0 Hz), 7.92 (s, 1H), 8.29 (d, 1H, J = 8.3 Hz), 8.58 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.7, 19.6, 19.9, 26.5, 32.3, 34.5, 47.0, 73.7, 101.5, 121.4, 122.5, 123.7, 124.2, 125.9, 126.7, 128.7, 132.3, 140.0, 146.2. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): m/z: 309.1960 $[M+H]^+$, $C_{20}H_{24}N_2O$. Calculated: 309.1961.

1-Pentyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (15): m.p. 72-74°C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, 3H, J = 6.9 Hz), 1.37-1.,45 (m, 4H), 1.48 (s, 6H), 1.99-2.07 (m, 4H), 3.25 (t, 2H, J = 6.6 Hz), 4.68 (t, 2H, J = 7.1 Hz), 7.57 (t, 1H, J = 7.7 Hz), 7.64 (t, 1H, J = 7.7 Hz), 8.13 (d, 1H, J = 8.3 Hz), 8.45 (d, 1H, J = 8.3 Hz), 8.58 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 18.7, 22.2, 26.7, 28.6, 29.6, 32.0, 48.9, 75.2, 106.0, 119.9, 120.1, 121.0, 123.7, 124.6, 124.9, 126.7, 136.9, 139.8, 146.4. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z:* 323.2125 $[M+H]^+$, $C_{21}H_{26}N_2O$. Calculated: 323.2118.

3-Pentyl-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (16): m.p. 126-130°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, 3H, J = 6.9 Hz), 1.38-1.42 (m, 4H), 1.48 (s, 6H), 1.91-1.94 (m, 2H), 2.00 (t, 2H, J = 6.6 Hz), 3.17 (t, 2H, J = 6.8 Hz), 4.50 (t, 2H, J = 7.3 Hz), 7.52 (t, 1H, J = 7.3 Hz), 7.65 (t, 1H, J = 8.0 Hz), 8.29 (d, 1H, J = 8.3 Hz), 8.43 (s, 1H), 8.66 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 19.4, 22.3, 26.5, 28.7, 32.0, 32.1, 47.9, 74.1, 101.2, 122.0, 122.6, 124.1, 124.3, 125.1, 127.3, 128.3, 129.0, 19.0, 147.1. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 323.2120 $[M+H]^+$, $C_{21}H_{26}N_2O$. Calculated: 323.2118.

1-Hexyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol (17): m.p. 125-128°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H), 1.27-1.45 (m, 6H), 1.48 (s, 6H), 2.01 (bs, 4H), 3.22 (bs, 2H), 4.57 (t, 2H, J = 6.5 Hz), 7.51 (t, 1H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.1 Hz), 7.98 (s, 1H), 8.12 (d, 1H, J = 8.0 Hz), 8.44 (d, 1H, J = 8.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0, 18.5, 22.5, 26.3, 26.7 (2C), 30.0, 31.3, 32.3, 48.2, 74.7, 107.6, 119.9, 120.8, 121.2, 123.5, 123.8, 124.5, 126.0, 140.3, 141.2, 145.2. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z:* 337.2283 $[M+H]^+$, $C_{22}H_{28}N_2O$. Calculated: 337.2274.

3-Hexyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol (18): m.p. 126-129°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, J = 6.9 Hz), 1.32-1.42 (m, 6H), 1.49 (s, 6H), 1.85-1.92 (m, 2H), 2.01 (t, 2H, J = 6.6 Hz), 3.20 (t, 2H, J = 6.7 Hz), 4.38 (t, 2H, J = 7.3 Hz), 7.47 (t, 1H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.2 Hz), 7.79 (s, 1H), 8.29 (d, 1H, J = 8.3 Hz), 8.55 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0, 19.6, 22.5, 26.4, 26.5 (2C), 31.4, 32.5, 32.4, 47.0, 73.6, 101.6, 121.3, 122.4, 123.6 (2C), 123.9, 126.5, 128.8, 133.4, 140.4, 145.9. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 337.2280 $[M+H]^+$, $C_{22}H_{28}N_2O$. Calculated: 337.2283.

1-Heptyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (19): m.p. 154-160°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 2H, J = 6.6 Hz), 1.25-1.32 (m, 4H), 1.34-1.,37 (m, 2H), 1.40-1.44 (m, 2H), 1.48 (s, 6H), 2.01 (t, 2H, J = 6.8 Hz), 3.21 (t, 2H, J = 6.6 Hz), 4.57 (t, 2H, J = 7.1 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.57 (t, 1H, J = 7.6 Hz), 7.85 (s, 1H), 8.12 (d, 1H, J = 8.5 Hz), 8.43 (d, 1H, J = 8.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0, 18.5, 22.6, 26.7 (2C), 29.7, 31.6 (2C), 32.4, 48.1, 74.6, 107.7, 119.9, 120.8, 123.4, 123.7, 125.8, 141.4, 145.0. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 351.2444 $[M+H]^+$, $C_{23}H_{30}N_2O$. Calculated: 351.2431.

3-Heptyl-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (20): m.p. 115-121°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, 3H, J = 6.5 Hz), 1.25-1.44 (m, 8H), 1.48 (s, 6H), 1.85-1.93 (m, 2H), 2.01 (t, 2H, J = 6.5 Hz), 3.21 (t, 2H, J = 6.5 Hz), 4.48 (t, 2H, J = 7.2 Hz), 7.46 (t, 1H, J = 7.4 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.79 (s, 1H), 8.28 (d, 1H, J = 8.2 Hz), 8.51 (d, 1H, J = 7.9 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.1, 19.6, 22.5, 26.5, 26.7 (2C), 31.6, 32.3, 32.4, 47.5, 73.8, 101.5, 121.4, 122.5, 124.4, 128.7, 131.7, 140.0, 146.4. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 351.2429 $[M+H]^+$, $C_{23}H_{30}N_2O$. Calculated: 351.2431.

1-Octyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (21): m.p. 120-125°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H), 1.25-1.45 (m, 10H), 1.48 (s, 6H), 1.97-2.05 (m, 4H), 3.22 (t, 2H, J = 6.8 Hz), 4.56 (t, 2H, J = 7.3 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 8.2 Hz), 7.92 (s, 1H), 8.12 (d, 1H, J = 8.3 Hz), 8.44 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.5, 22.6, 26.6, 26.8, 29.1, 29.1, 30.1, 31.7, 32.4, 48.1, 74.6, 107.9, 119.9, 120.83, 121.2, 123.4, 123.7, 124.5, 125.9, 140.8, 141.4, 145.0. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z***:** 365.2588 $[M+H]^+$, $C_{24}H_{32}N_2O$. Calculated: 365.2587.

3-Octyl-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol (22): m.p. 204-209°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, J = 6.8 Hz), 1.25-1.43 (m, 10H), 1.48 (s, 6H), 1.87-1.95 (m, 2H), 2.00 (t, 2H, J = 6.6 Hz), 3.17 (t, 2H, J = 6.6.7 Hz), 4.48 (t, 2H, J = 7.4 Hz), 7.52 (t, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 7.0 Hz), 8.29 (d, 1H, J = 8.0 Hz), 8.35 (s, 1H), 8.67 (d, 1H, J = 8.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1, 19.4, 22.6, 26.5, 26.6, 29.1, 29.1, 31.7, 32.1, 32.2, 48.1, 74.1, 101.1, 122.0, 122.6, 124.2, 125.2, 127.4, 128.2 (2C), 129.8, 138.7, 147.3. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 365.576 $[M+H]^+$, $C_{24}H_{32}N_2O$. Calculated: 365.2587

1-Nonyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol (23): m.p. 95-96°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, J = 6.9 Hz), 1.24-1.32 (m, 8H), 1.33-1.38 (m, 2H), 1.39-1.45 (m, 2H), 1.48 (s, 6H), 1.97-2.03 (m, 4H), 3.21 (t, 2H, J = 6.6 Hz), 4.54 (t, 2H, J = 7.1 Hz), 7.50 (t, 1H, J = 7.4 Hz), 7.58 (t, 1H, J = 7.1 Hz), 7.88 (s, 1H), 8.13 (d, 1H, J = 8.3 Hz), 8.43 (d, 1H, J = 8.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.5, 22.6, 26.6, 26.8 (2C), 30.2, 31.8, 32.4, 48.0,

74.5, 108.0, 119.8, 120.9, 121.3, 123.4, 123.5, 124.5, 125.8, 141.2, 141.6, 144.8. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 379.2736 $[M+H]^+$, $C_{26}H_{34}N_2O$. Calculated: 379.2744.

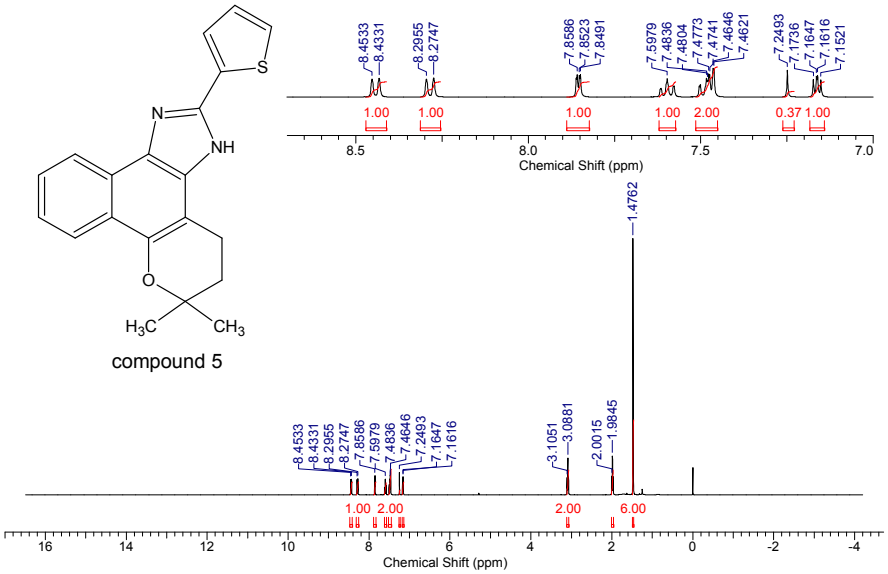
3-Nonyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol (24): m.p. 144-147°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, 3H, J = 6.8 Hz), 1.22-1.42 (m, 12H), 1.48 (s, 6H),1.85-1.92 (m, 2H), 2.01 (t, 2H, J = 6.8 Hz), 3.21 (t, 2H, J = 6.7 Hz), 4.38 (t, 2H, J = 7.3 Hz), 7.47 (t, 1H, J = 7.2 Hz), 7.60 (t, 1H, J = 7.2 Hz), 7.79 (s, 1H), 8.29 (d, 1H, J = 8.5 Hz), 8.55 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1, 19.6, 22.6, 26.5, 26.7, 29.2, 29.4, 31.8, 32.4, 32.6, 47.1, 73.6, 101.6, 121.3, 122.4, 123.6, 124.0, 126.5, 128.8, 133.4, 140.4, 145.9. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 379.2751 $[M+H]^+$, $C_{26}H_{34}N_2O$. Calculated: 379.2744.

1-Dodecyl-6,6-dimethyl-1,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-*d*]imidazol (25): m.p. 75-77°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, J = 6.8 Hz), 1.26-1.43 (m, 18H), 1.48 (s, 6H), 1.97-2.01 (m, 4H), 3.21 (t, 2H, J = 6.6 Hz), 4.54 (t, 2H, J = 7.1 Hz), 7.50 (t, 1H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.86 (s, 1H), 8.12 (d, 1H, J = 8.3 Hz), 8.43 (d, 1H, J = 8.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.4, 22.7, 26.6, 26.8 (2C), 29.1, 30.1, 31.9, 32.4, 39.3, 47.9, 74.5, 108.1, 119.8, 120.9, 123.4, 123.5, 125.8, 141.3, 141.7, 144.8. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 421.3204 $[M+H]^+$, $C_{29}H_{40}N_2O$. Calculated: 421.3213.

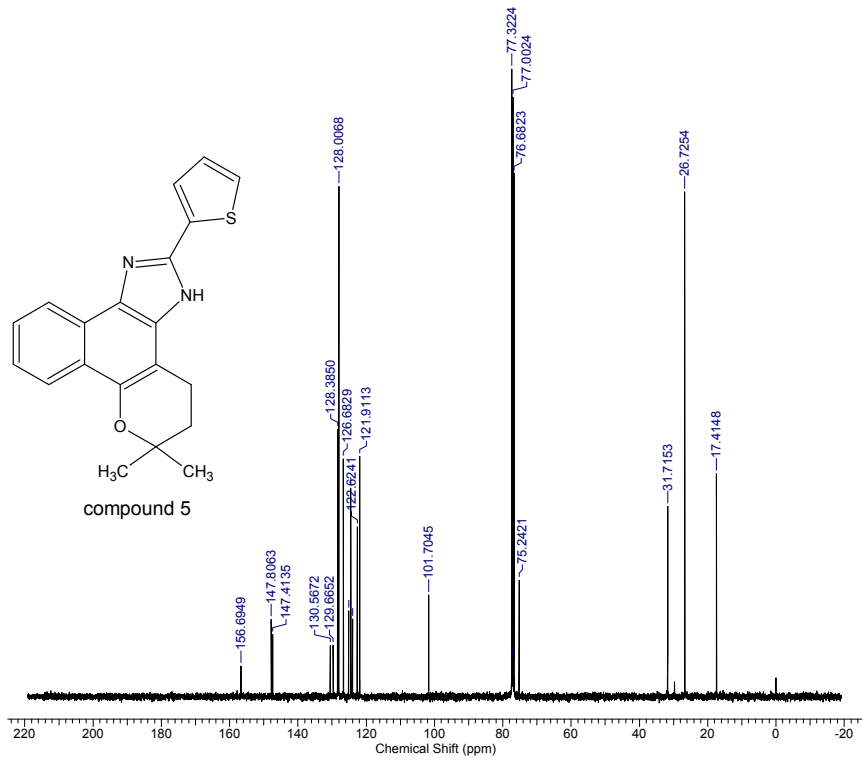
3-Dodecyl-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol (26): m.p. 95-98°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, J = 6.8 Hz), 1.26-1.42 (m, 18H), 1.48 (s, 6H), 1.84-1.91 (m, 2H), 2.00 (t, 2H, J = 6.6 Hz), 3.20 (t, 2H, J = 6.6 Hz), 4.38 (t, 2H, J = 7.3 Hz), 7.47 (t, 1H, J = 7.1 Hz), 7.60 (t, 1H, J = 7.3 Hz), 7.84 (s, 1H), 8.29 (d, 1H, J = 8.3 Hz), 8.56 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.1, 19.6, 22.7, 26.5 (2C), 26.7, 29.2, 29.3, 29.5, 29.6, 31.9, 32.3, 32.5, 47.2, 73.7, 101.5, 121.4, 122.4, 124.1, 126.5, 128.7, 132.9, 140.2, 146.0. TOF MS ES+ (MeOH-H_2O-0.1%-AcOH): *m/z*: 4213217 $[M+H]^+$, $C_{29}H_{40}N_2O$. Calculated: 421.3213.

2. NMR spectra of compounds 5 to 26

2.1. Compound 5:

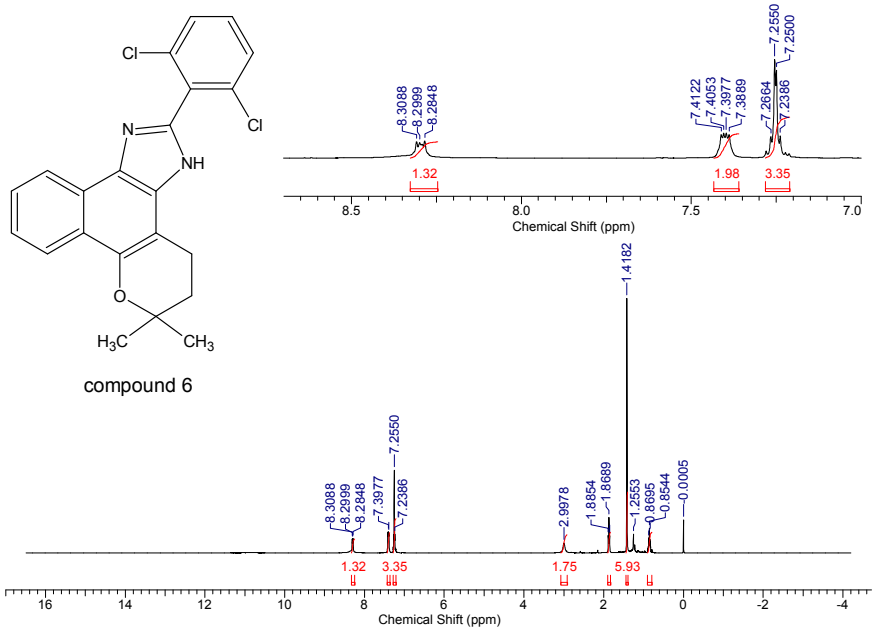


Spectrum 1: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 5.

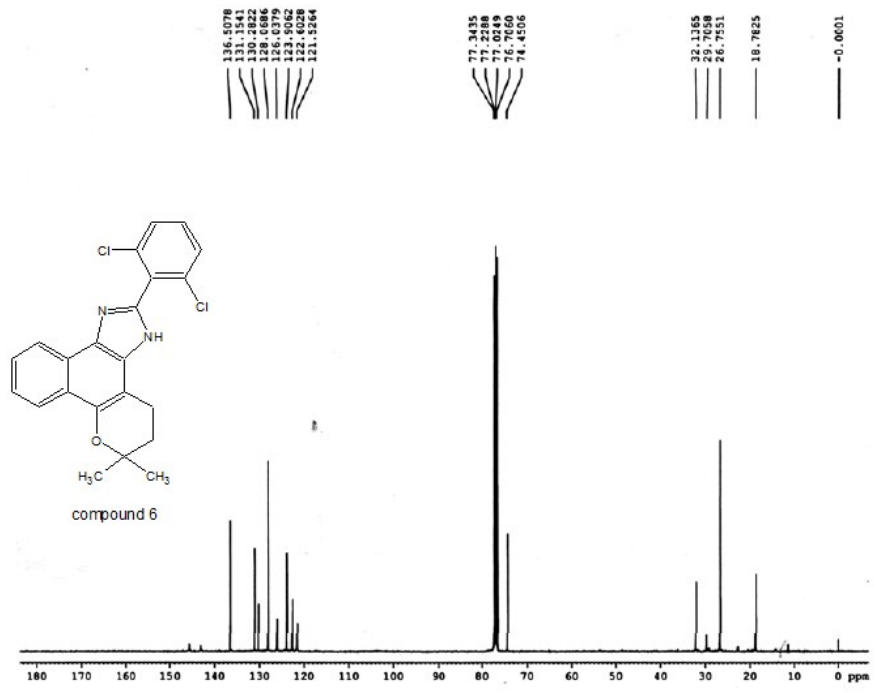


Spectrum 2: ^{13}C-NMR (100 MHz, $CDCl_3$) of compound 5.

2. 2. Compound 6:

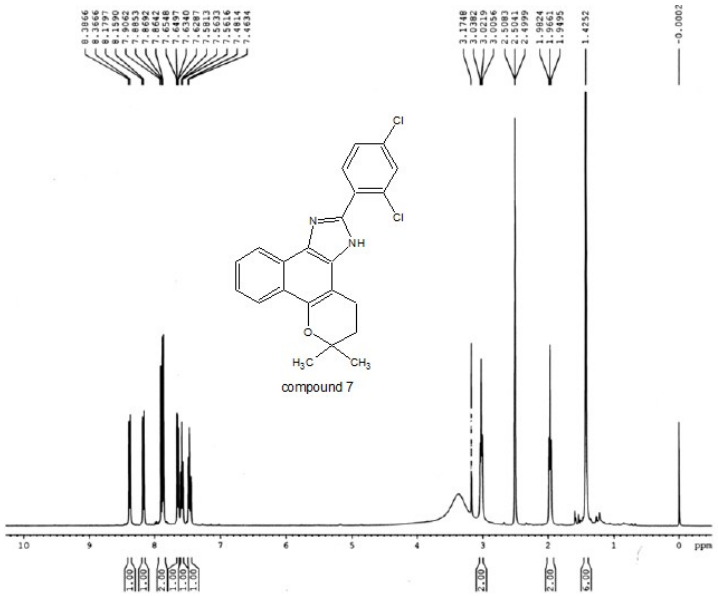


Spectrum 3: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 6.

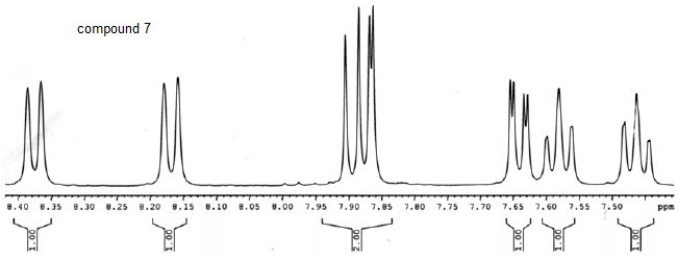


Spectrum 4: ^{13}C-NMR (100 MHz, $CDCl_3$) of compound 6.

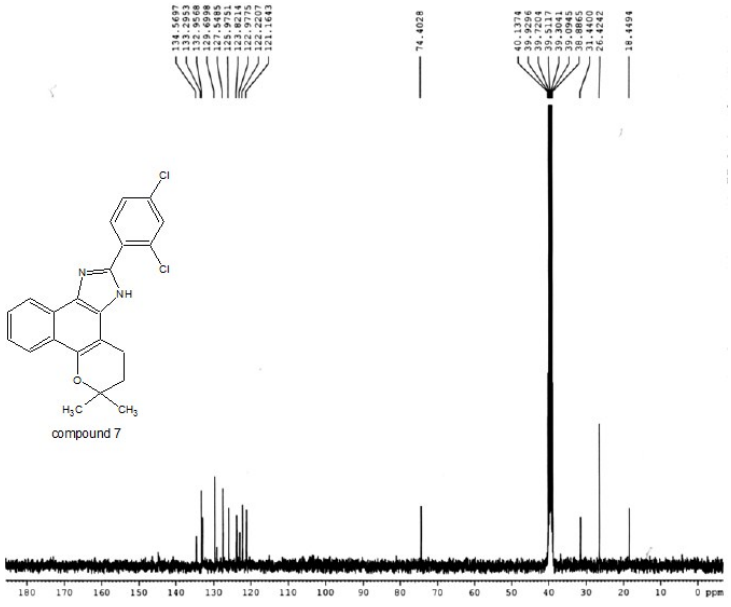
2.3. Compound 7:



Spectrum 5: ^{1}H-NMR (400 MHz, DMDO-d_6) of compound 7.

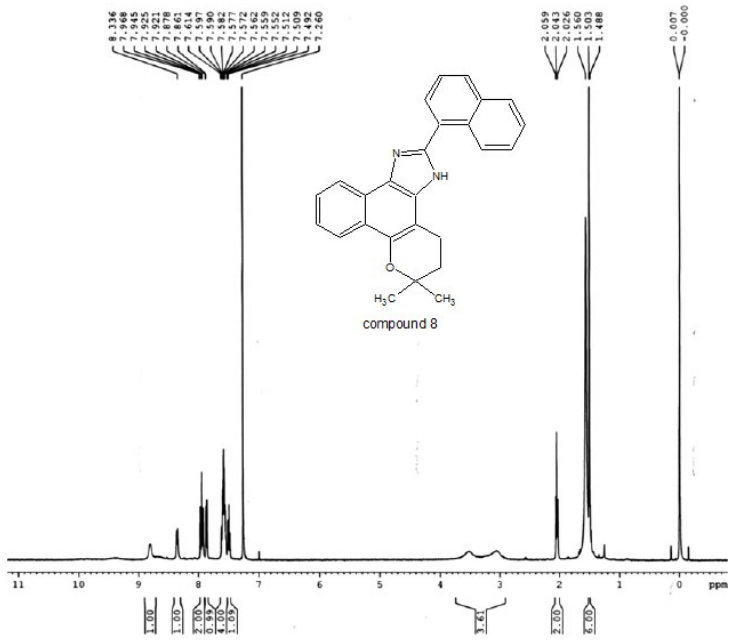


Spectrum 6: Expansion of ^{1}H-NMR (400 MHz, DMDO-d_6) of compound 7.

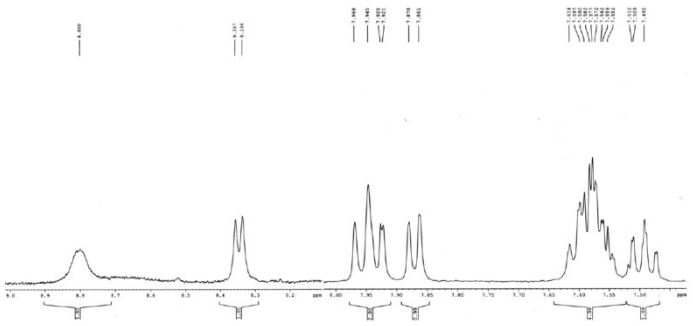


Spectrum 7: ^{13}C-NMR (100 MHz, DMDO-d_6) of compound 7.

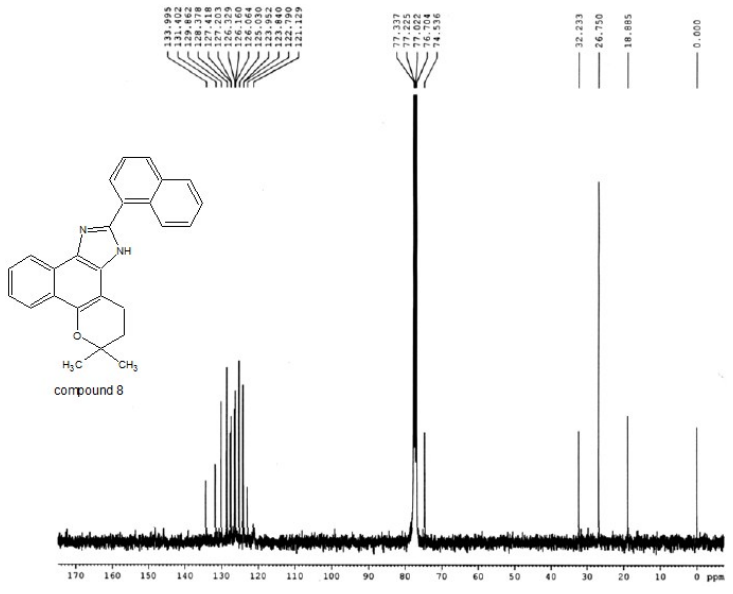
2.4. Compound 8:



Spectrum 8: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 8.

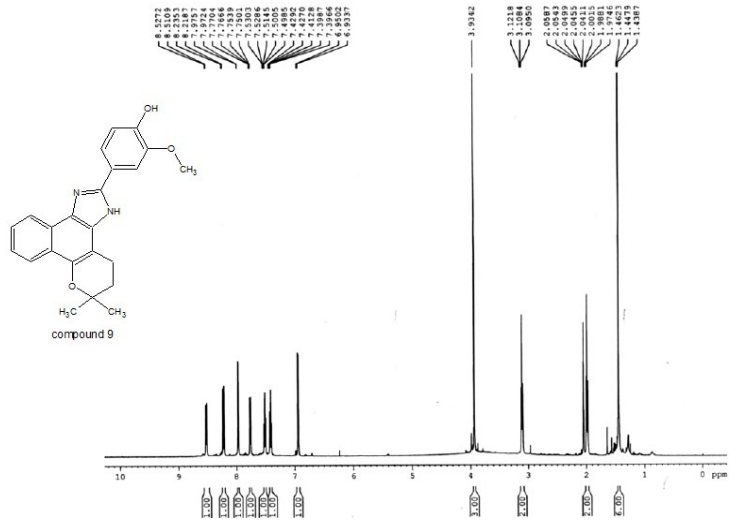


Spectrum 9: Expansion of ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 8.

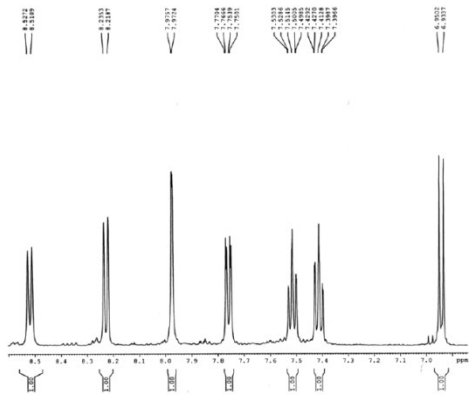


Spectrum 10: ^{13}C-NMR (100 MHz, $CDCl_3$) of compound 8.

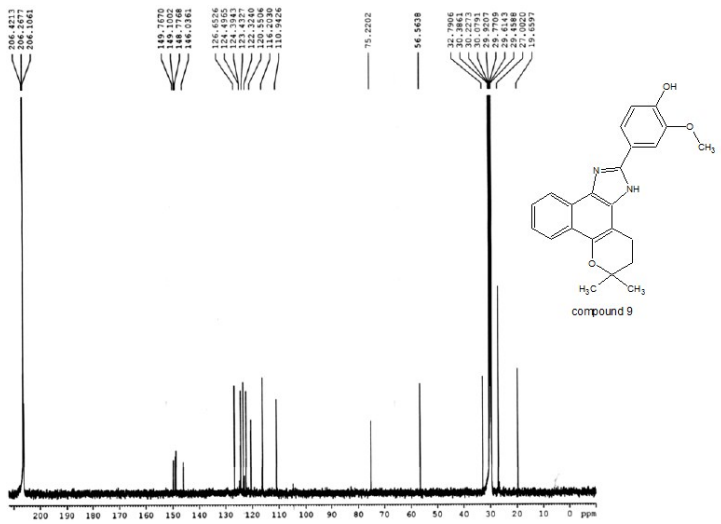
2.5. Compound 9:



Spectrum 11: ^{1}H-NMR (400 MHz, acetone-D_6) of compound 9.

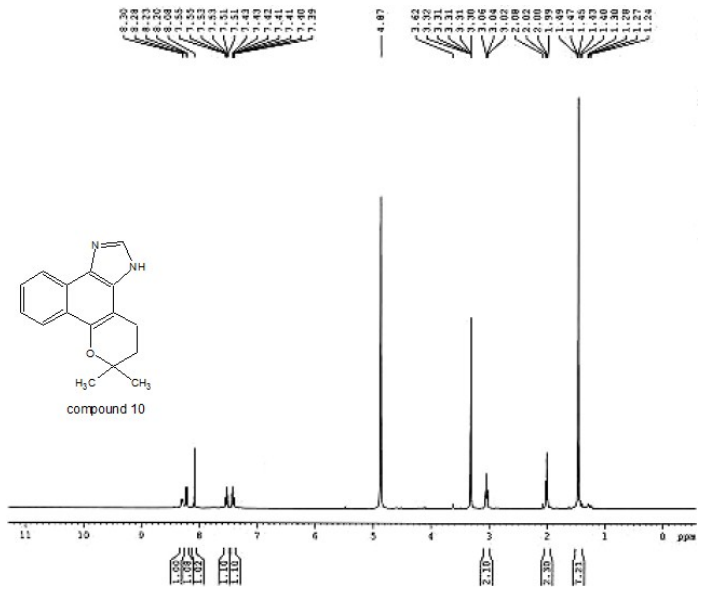


Spectrum 12: Expansion of ^{1}H-NMR (500 MHz, acetone-D_6) of compound 9.

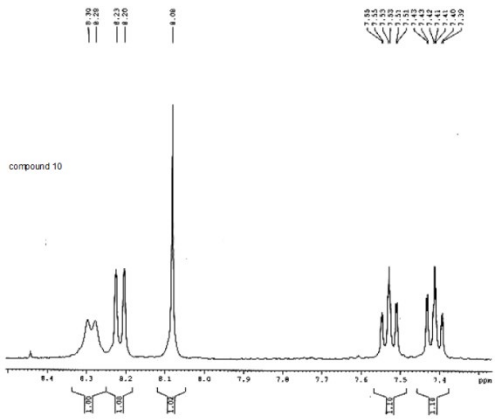


Spectrum 13: ^{13}C-NMR (400 MHz, acetone-D_6) of compound 9.

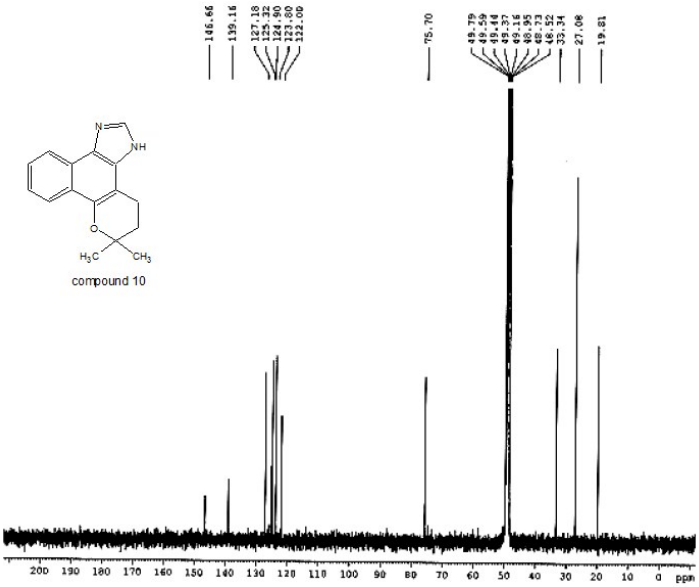
2.6. Compound 10:



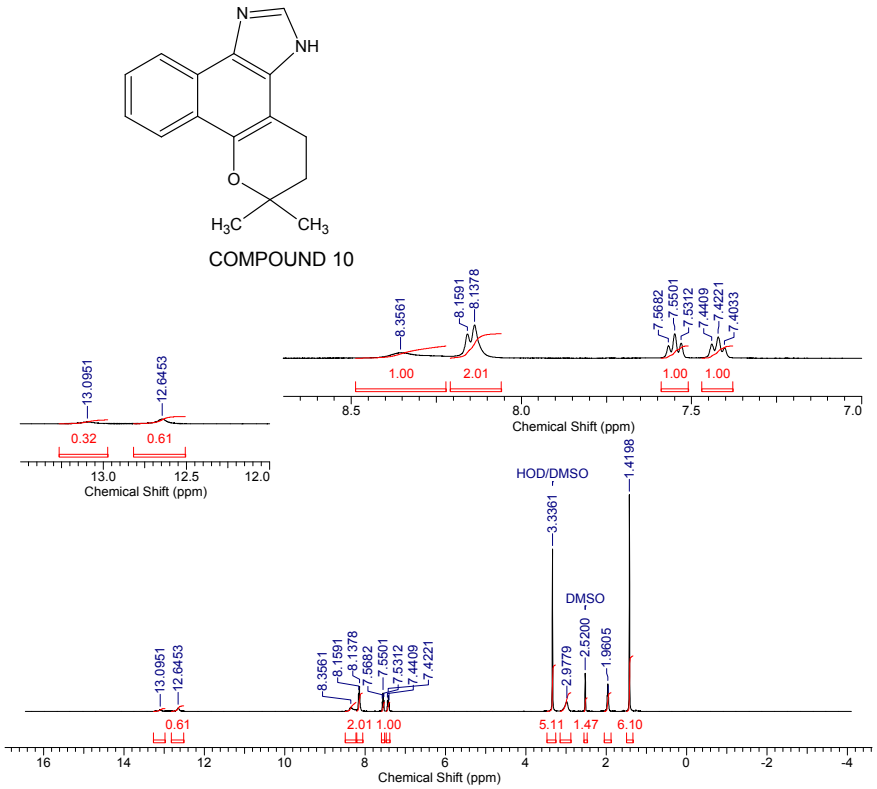
Spectrum 14: ^{1}H-NMR (400 MHz, MeOD) of compound 10.



Spectrum 15: Expansion of ^{1}H-NMR (400 MHz, MeOD) of compound 10.

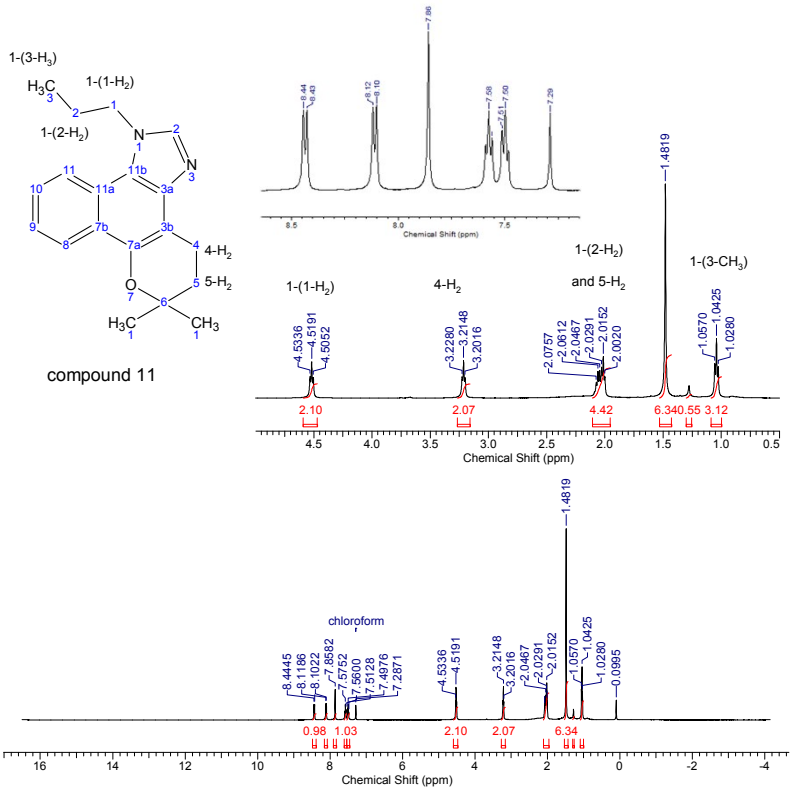


Spectrum 16: ^{13}C-NMR (100 MHz, MeOD) of compound 10.

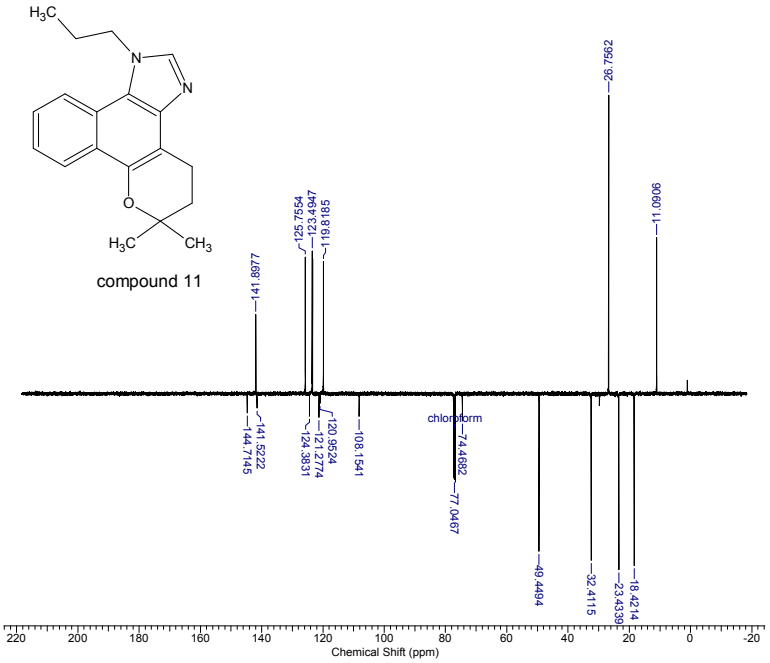


Spectrum 17: ^{1}H-NMR (400 MHz, DMDO-d_6) of compound 10.

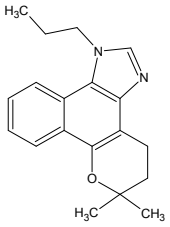
2.7. Compound 11:



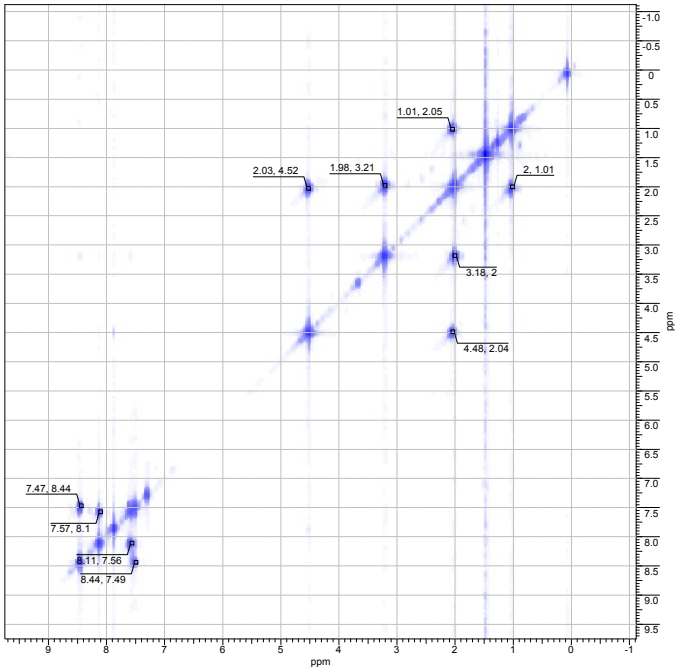
Spectrum 18: ^{1}H-NMR (500 MHz, $CDCl_3$) of compound 11.



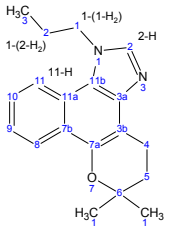
Spectrum 19: DEPTQ (125 MHz, $CDCl_3$) of compound 11.



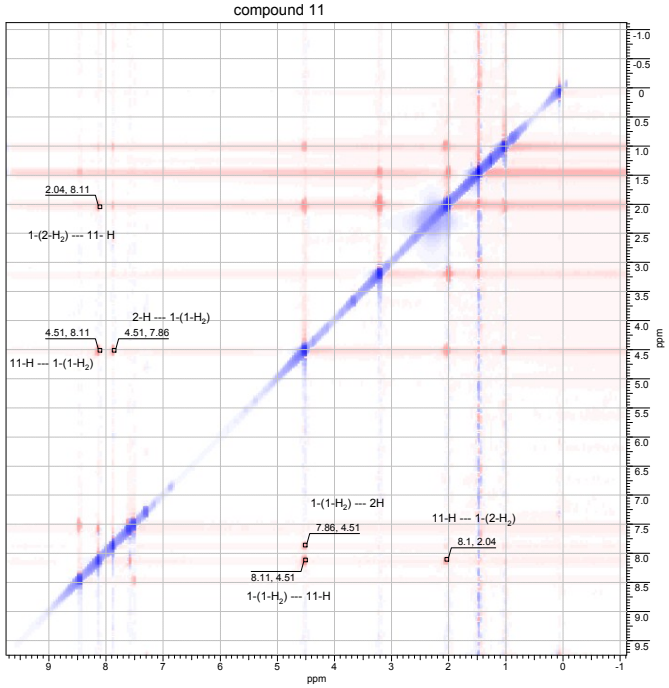
compound 11



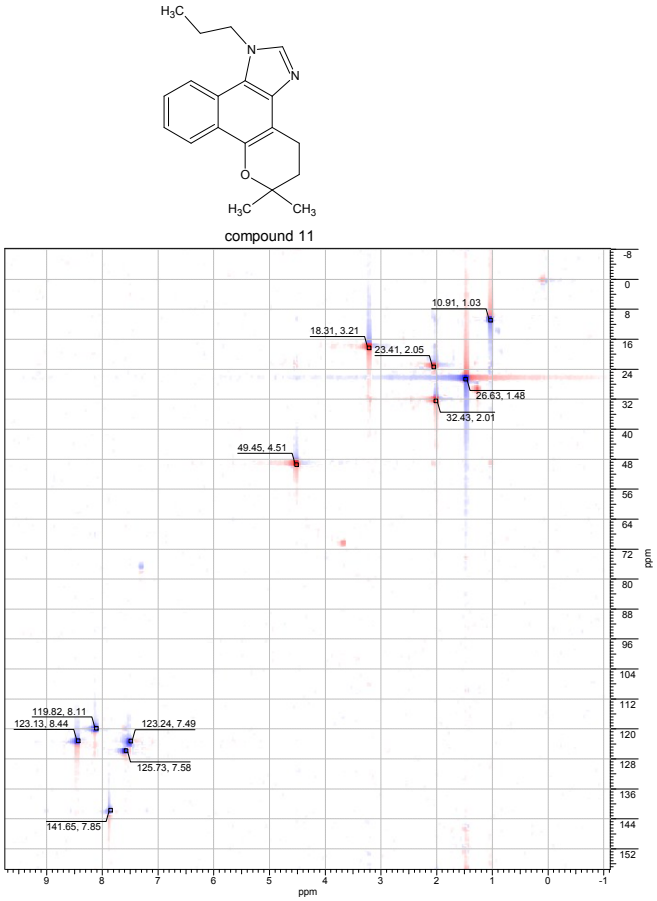
Spectrum 20: ^{1}H-HOMOCOSY (500 MHz, $CDCl_3$) of compound 11.



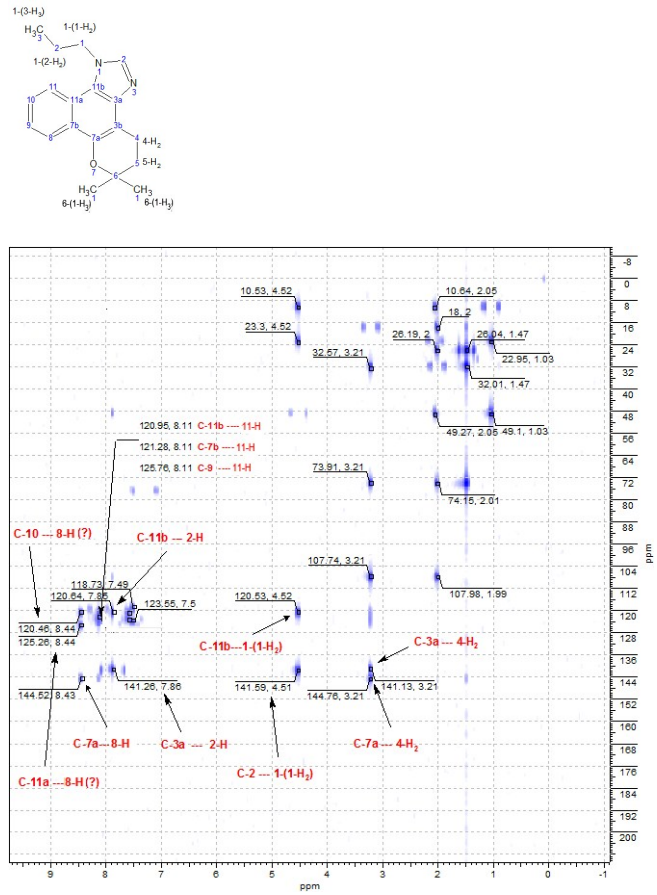
compound 11



Spectrum 21: NOESY (500 MHz, $CDCl_3$) of compound 11.

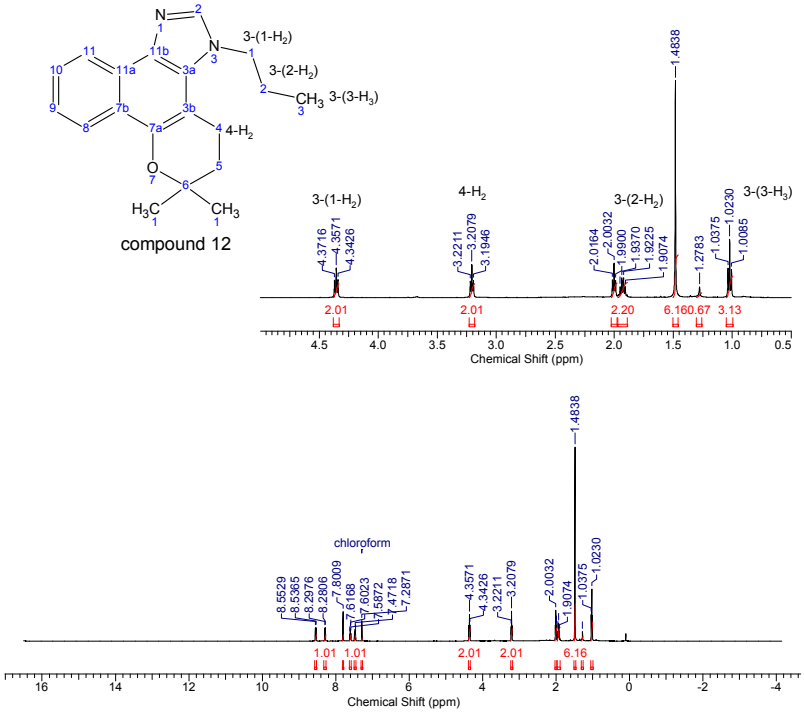


Spectrum 22: HSQC (125 MHz, $CDCl_3$) of compound 11.

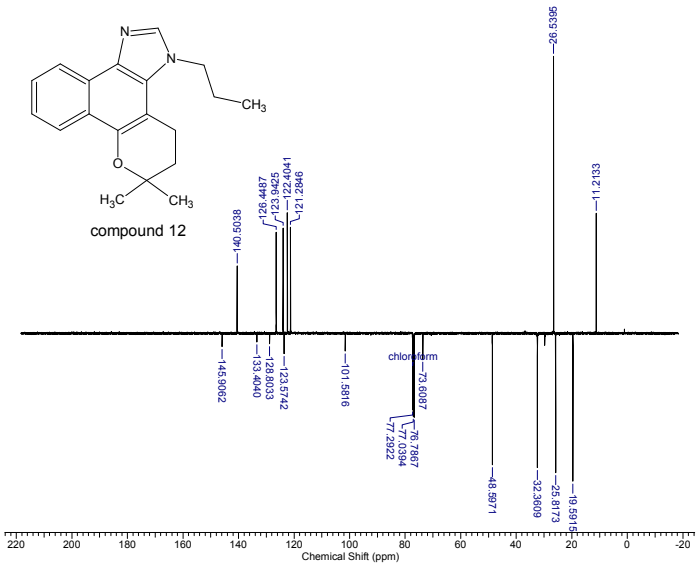


Spectrum 23: HMBC (125 MHz, $CDCl_3$) of compound 11.

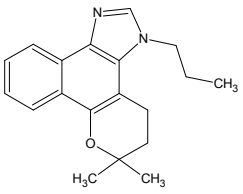
2.8. Compound 12:



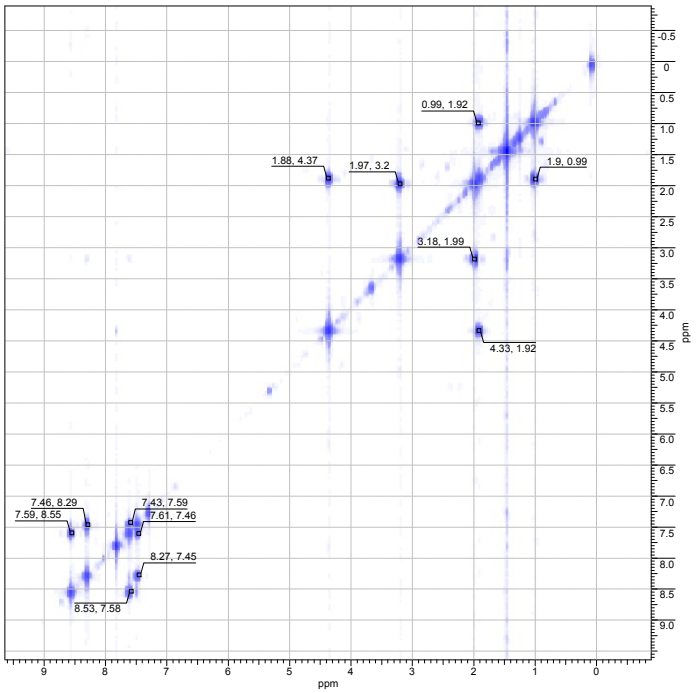
Spectrum 24: ^{1}H-NMR (500 MHz, $CDCl_3$) of compound 12.



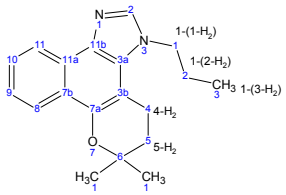
Spectrum 25: DEPTQ (125 MHz, $CDCl_3$) of compound 12.



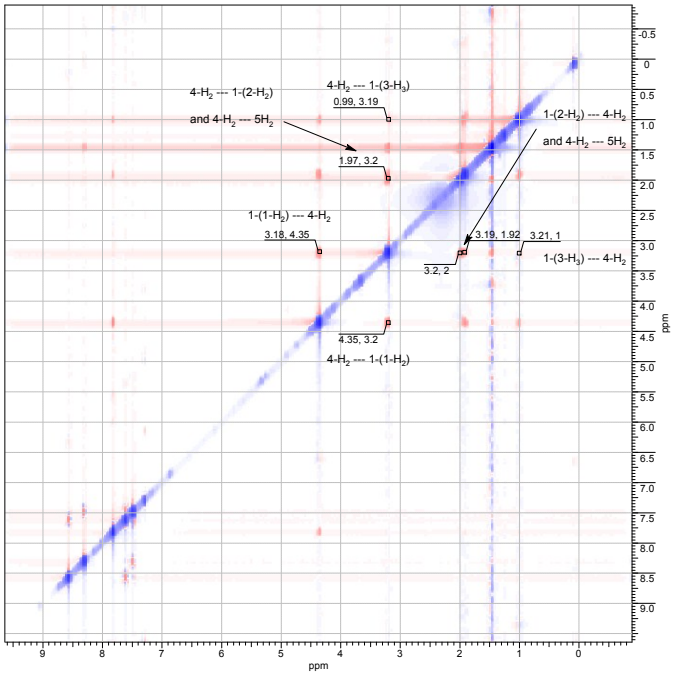
compound 12



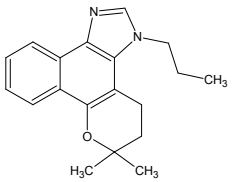
Spectrum 26: ^{1}H-HOMOCOSY (500 MHz, $CDCl_3$) of compound 12.



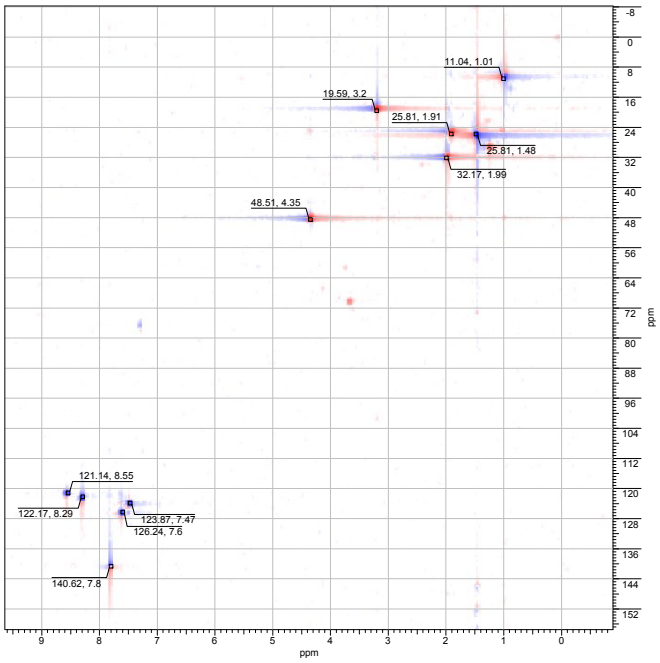
compound 12



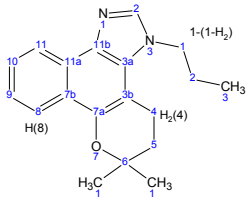
Spectrum 27: NOESY (500 MHz, $CDCl_3$) of compound 12.



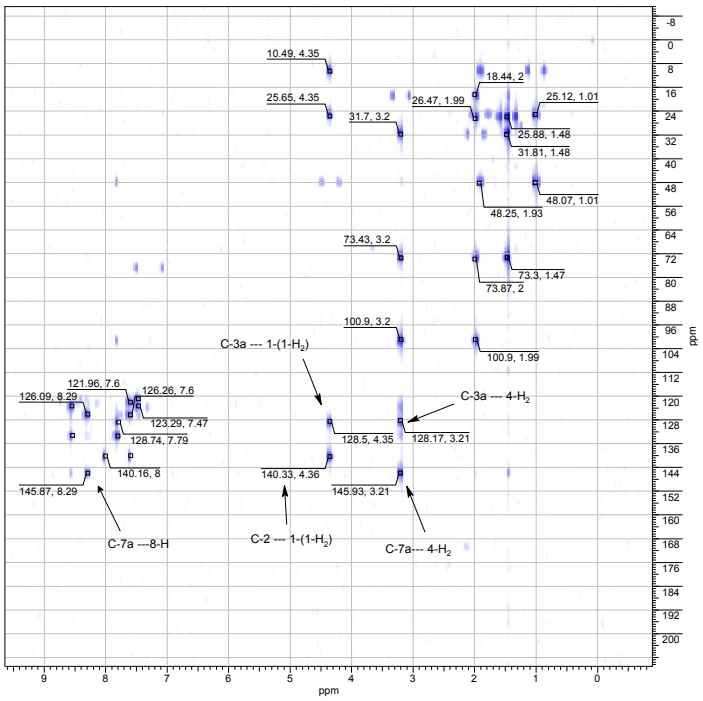
compound 12



Spectrum 28: HSQC (125 MHz, $CDCl_3$) of compound 12.

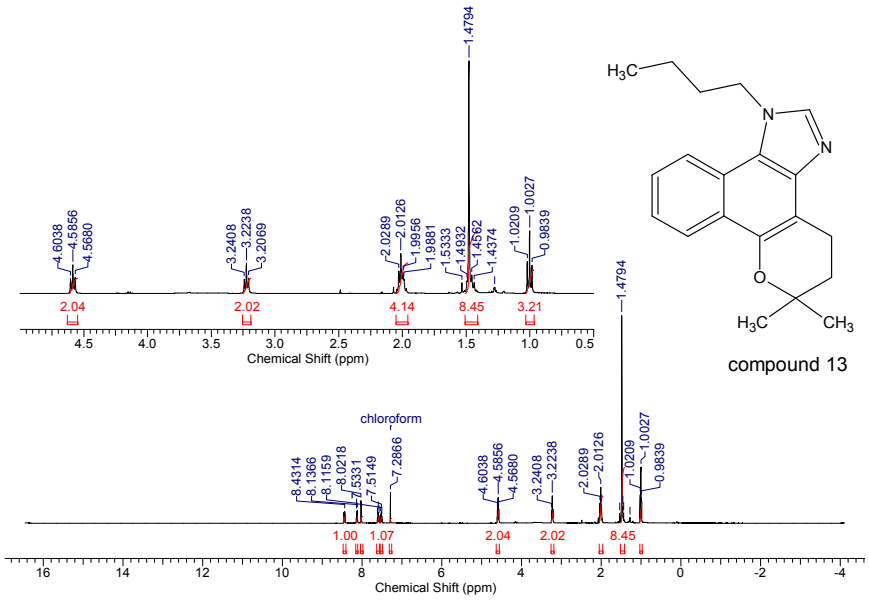


compound 12

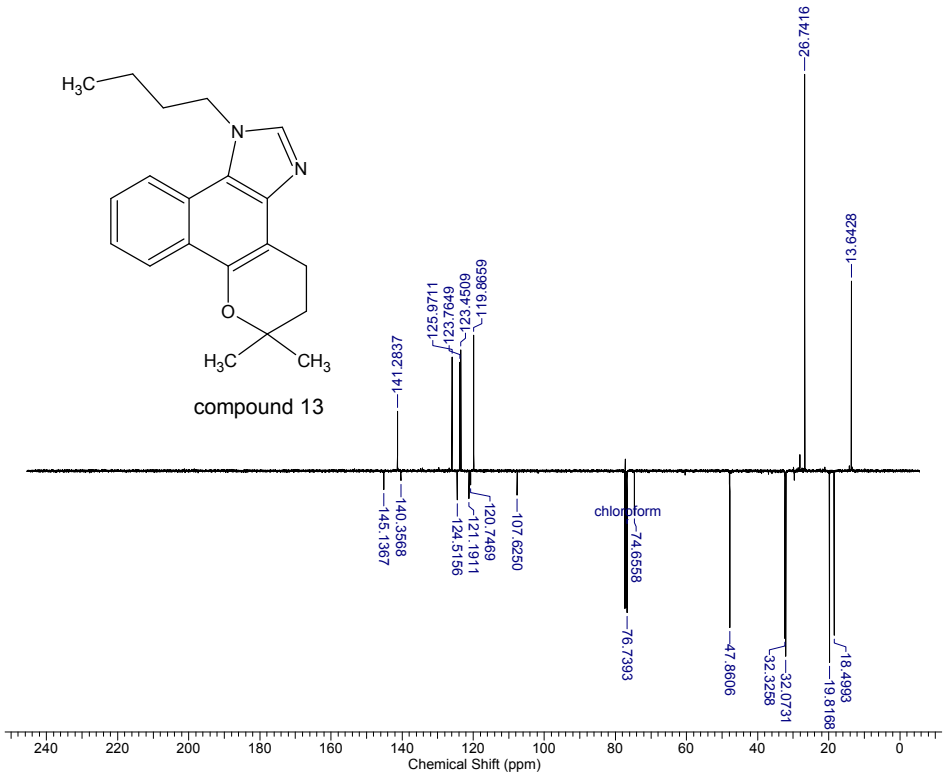


Spectrum 29: HMBC (125 MHz, $CDCl_3$) of compound 12.

2.9. Compound 13:

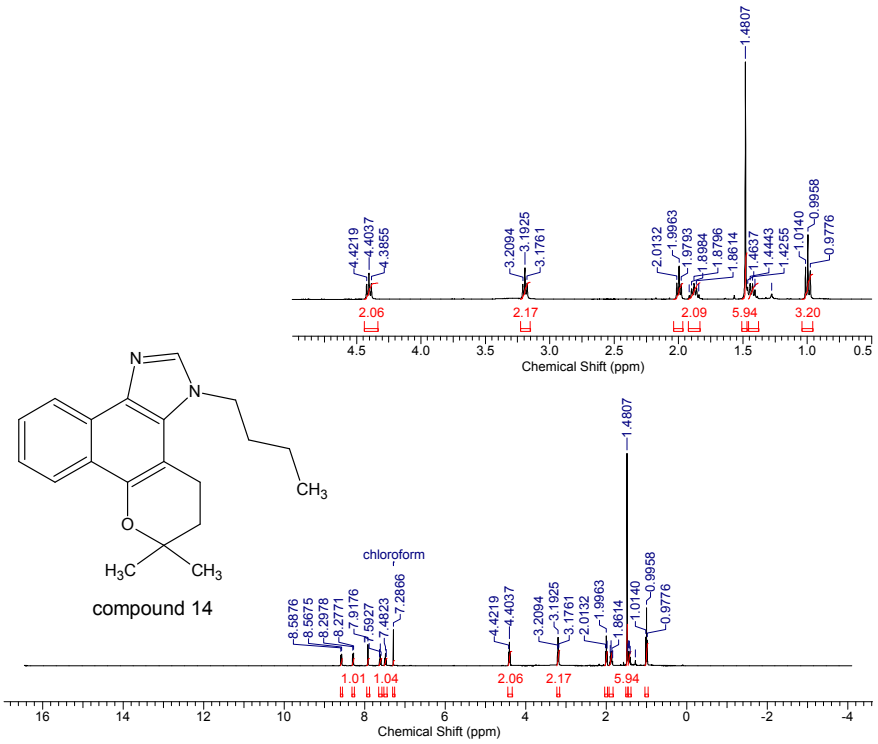


Spectrum 30: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 13.

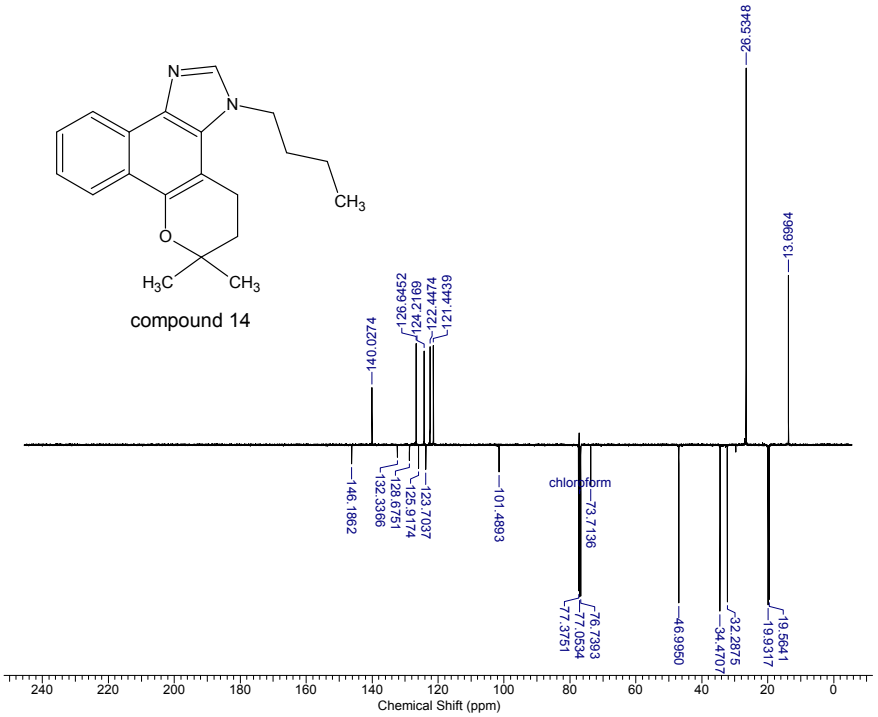


Spectrum 31: DEPTQ (100 MHz, $CDCl_3$) of compound 13.

2.10. Compound 14:

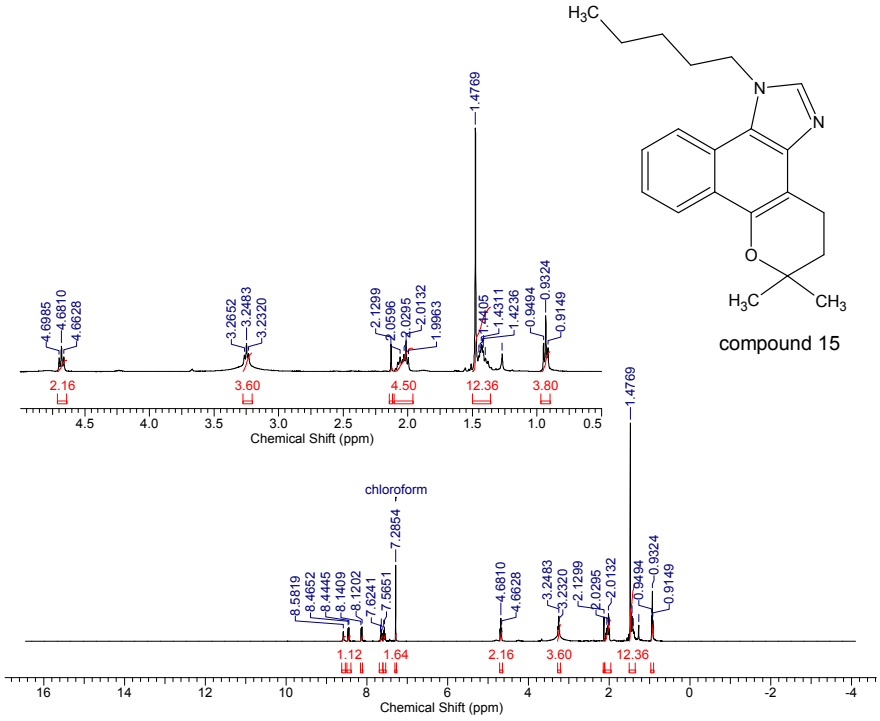


Spectrum 32: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 14.

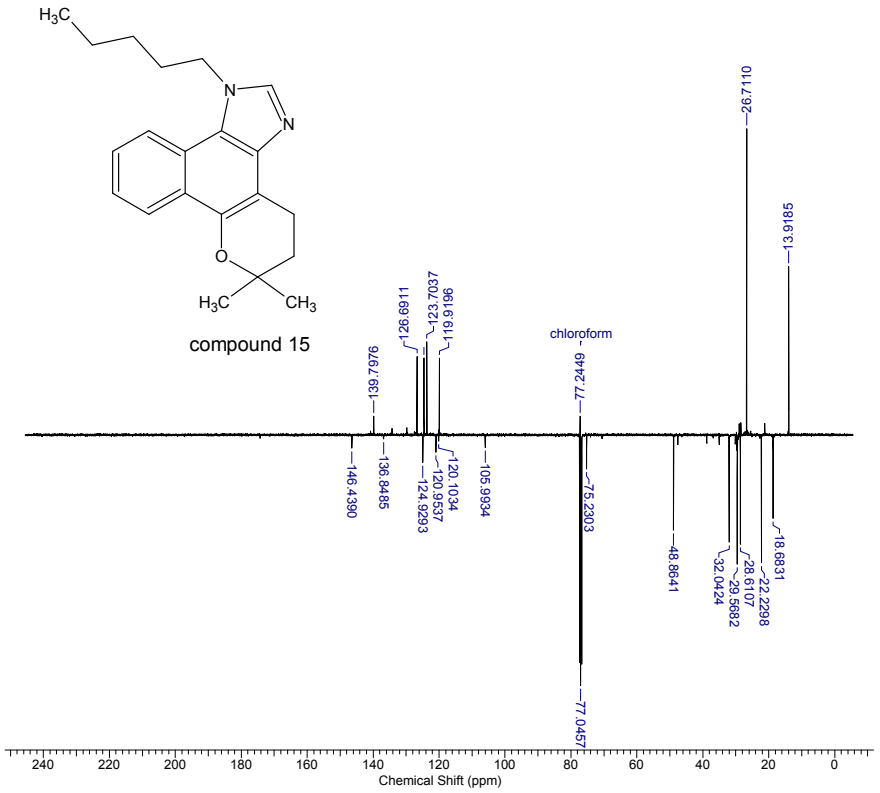


Spectrum 33: DEPTQ (100 MHz, $CDCl_3$) of compound 14.

2.11. Compound 15:

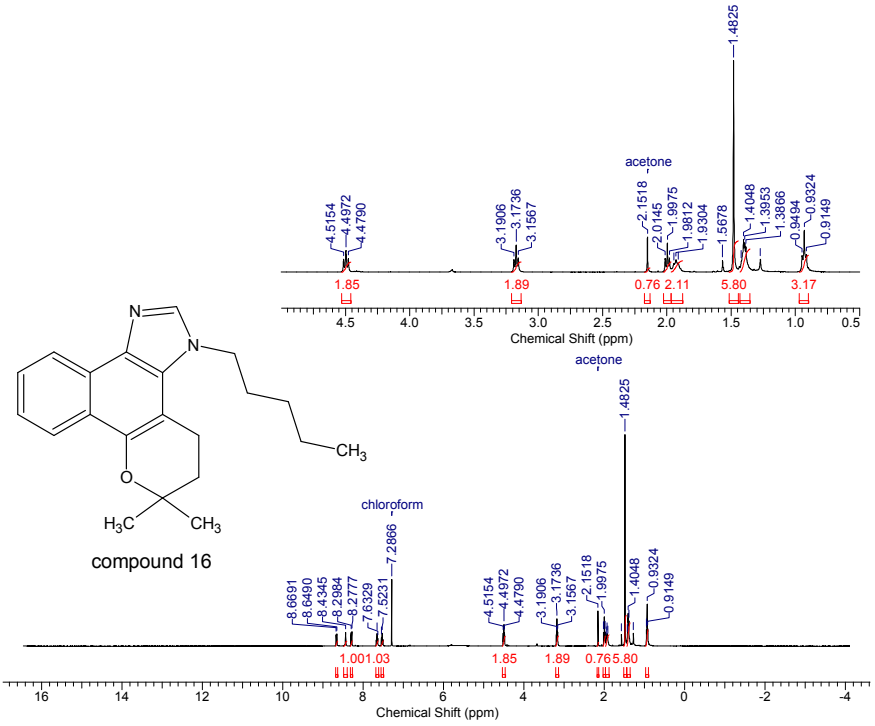


Spectrum 34: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 15.

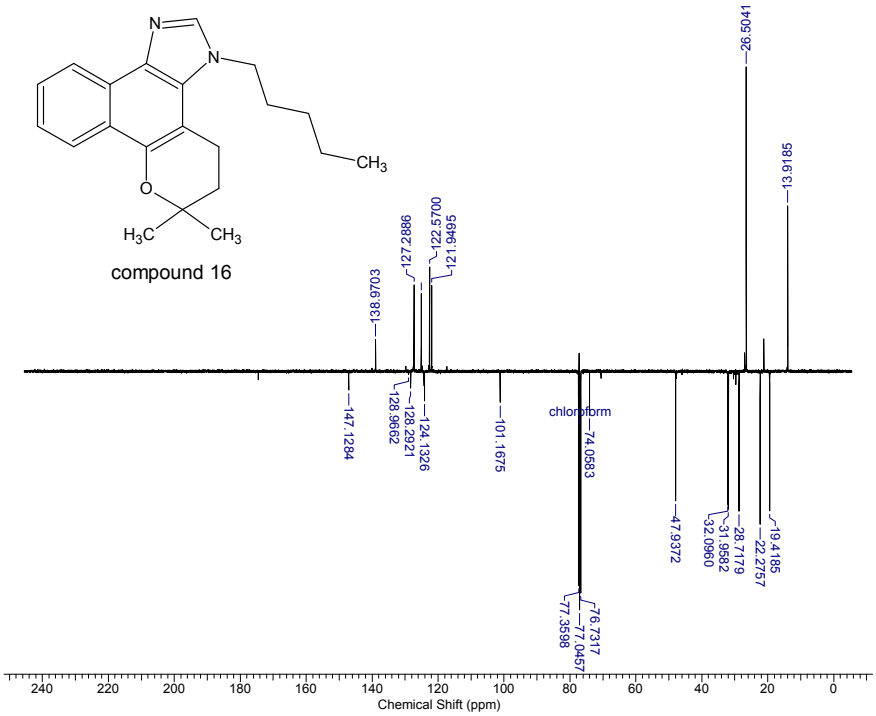


Spectrum 35: DEPTQ (100 MHz, $CDCl_3$) of compound 15.

2.12. Compound 16:

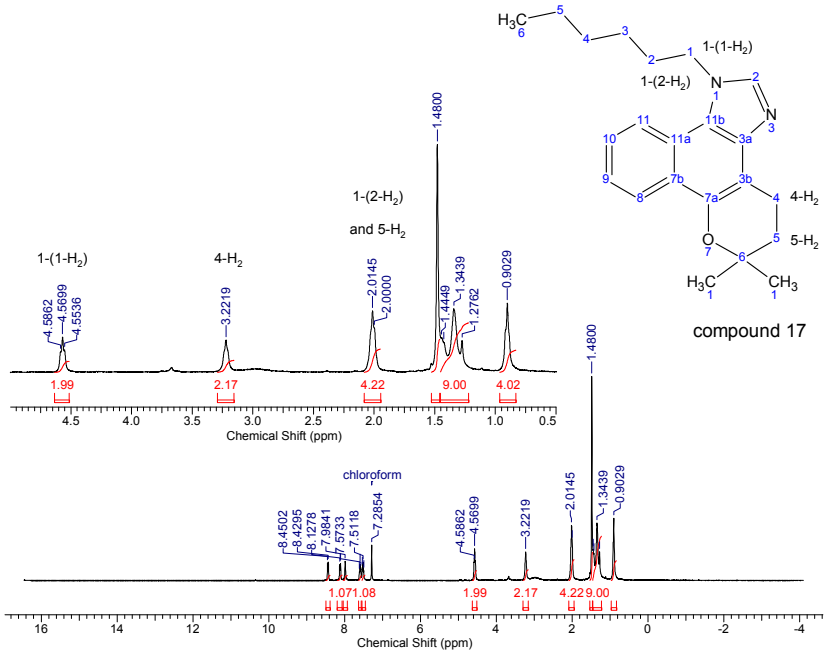


Spectrum 36: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 16.

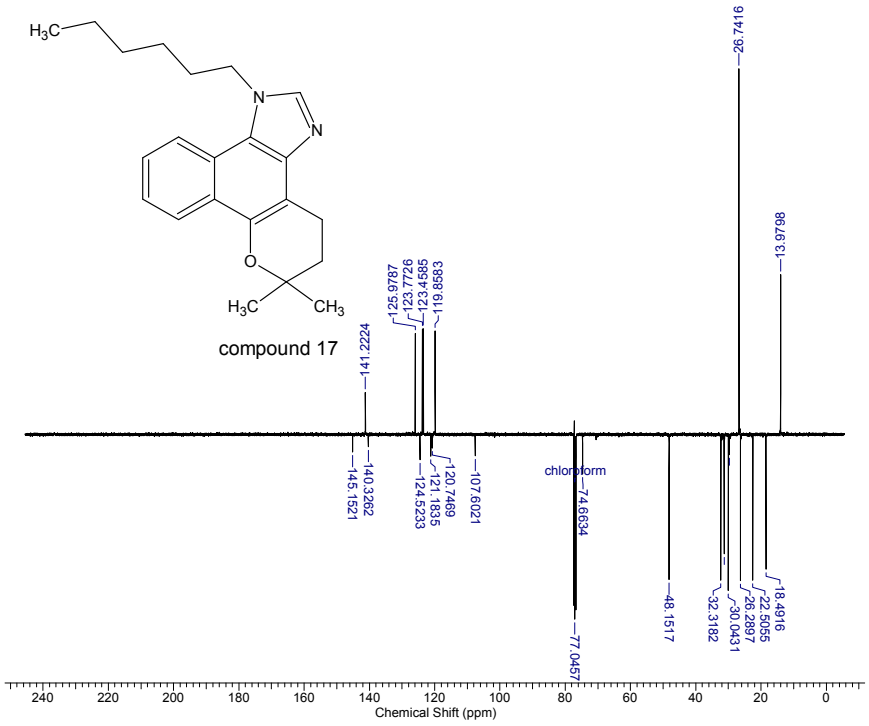


Spectrum 37: DEPTQ (100 MHz, $CDCl_3$) of compound 16.

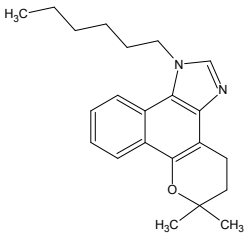
2.13. Compound 17:



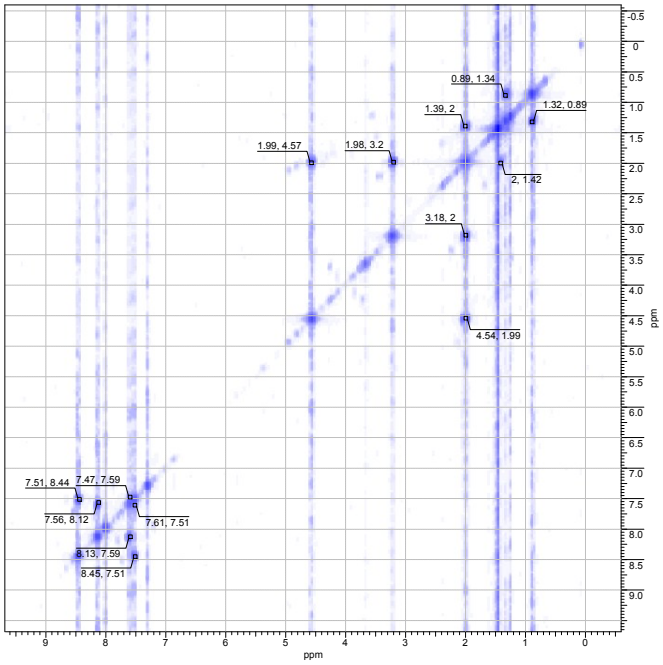
Spectrum 38: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 17.



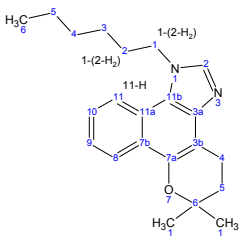
Spectrum 39: DEPTQ (100 MHz, $CDCl_3$) of compound 17.



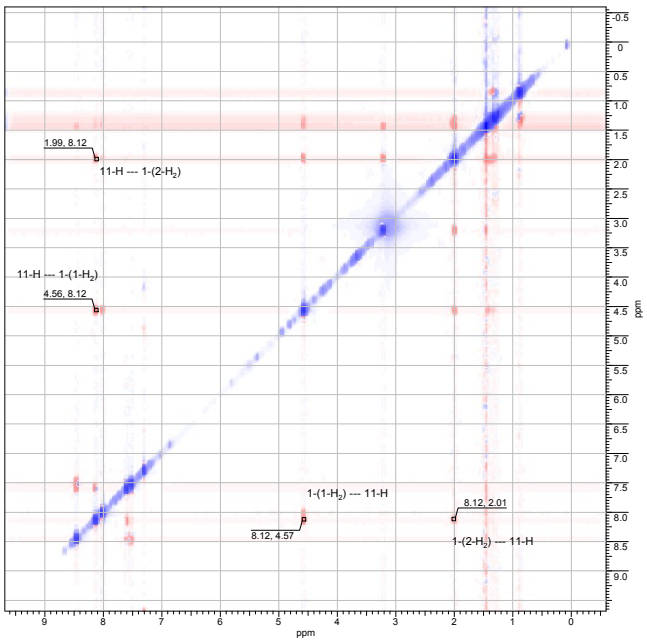
compound 17



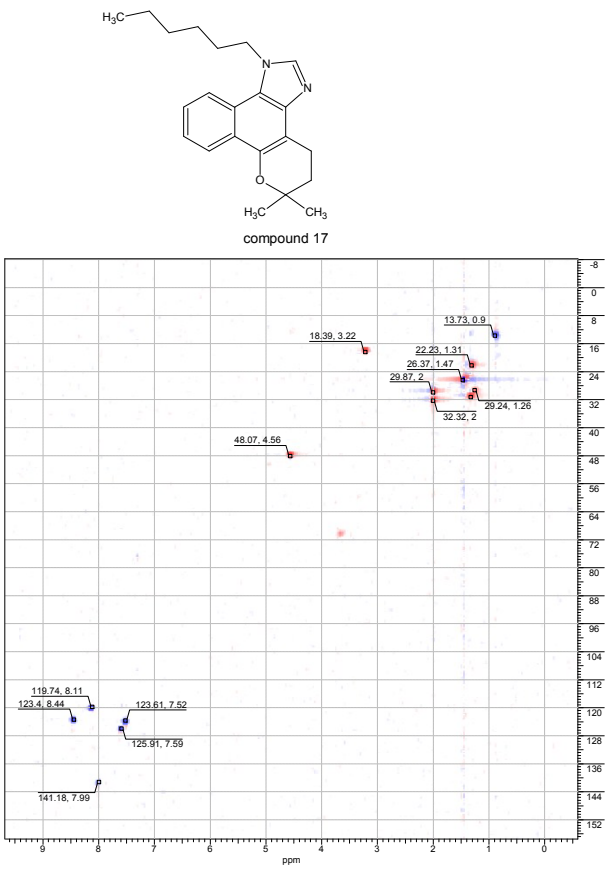
Spectrum 40: ^{1}H-HOMOCOSY (400 MHz, $CDCl_3$) of compound 17.



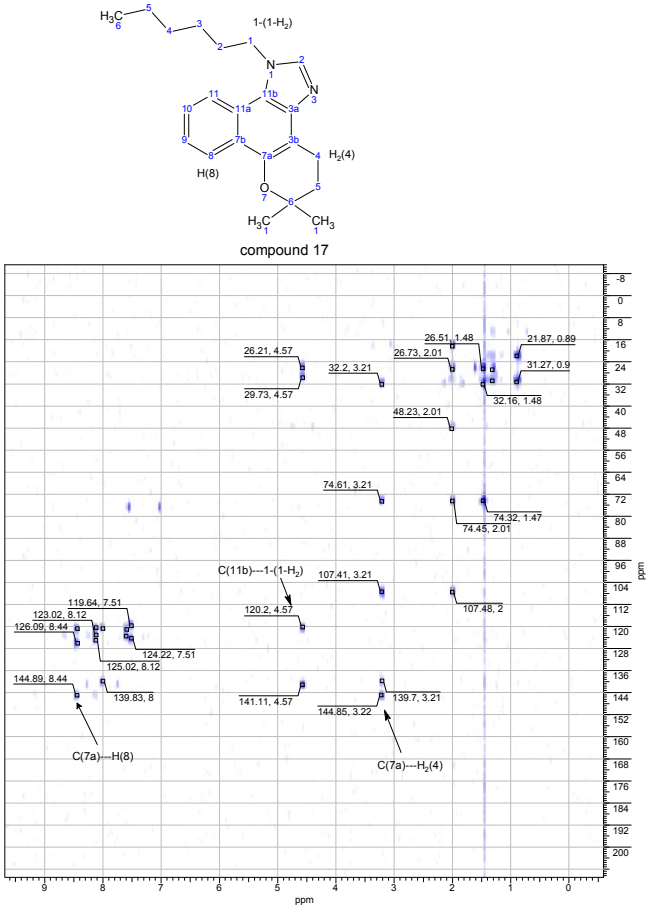
compound 17



Spectrum 41: NOESY (400 MHz, $CDCl_3$) of compound 17.

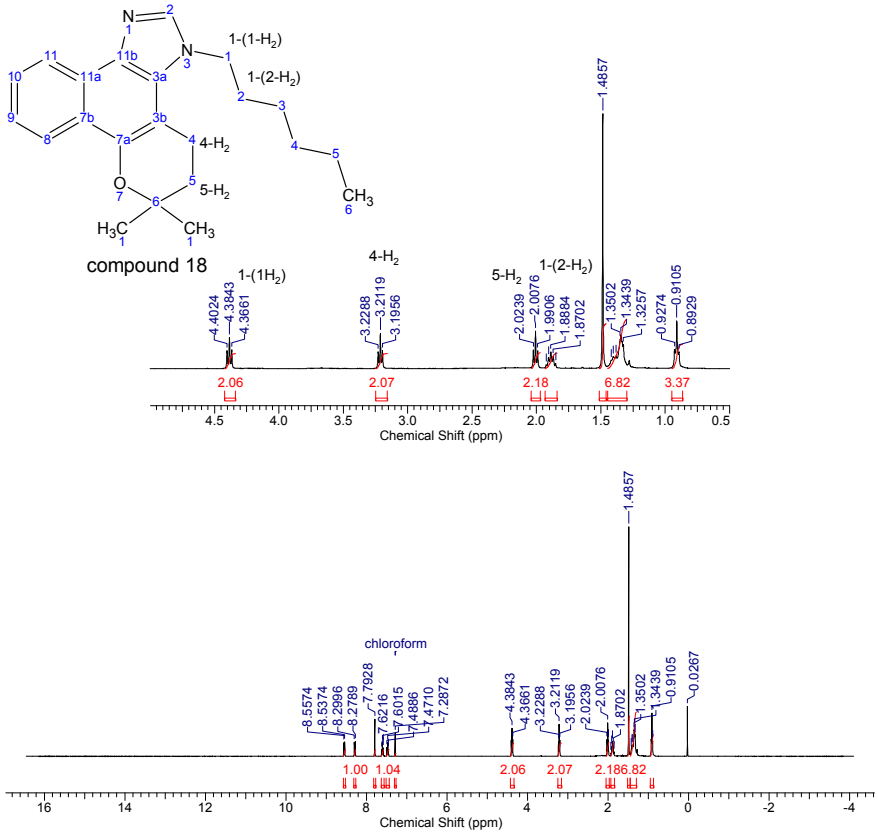


Spectrum 42: HSQC (100 MHz, $CDCl_3$) of compound 17.

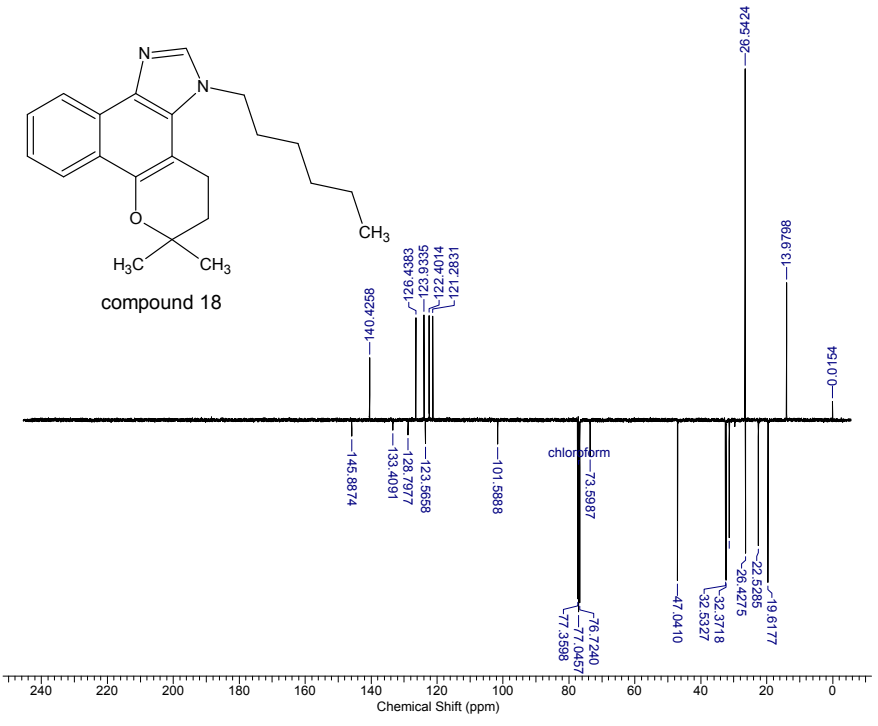


Spectrum 43: HMBC (100 MHz, $CDCl_3$) of compound 17.

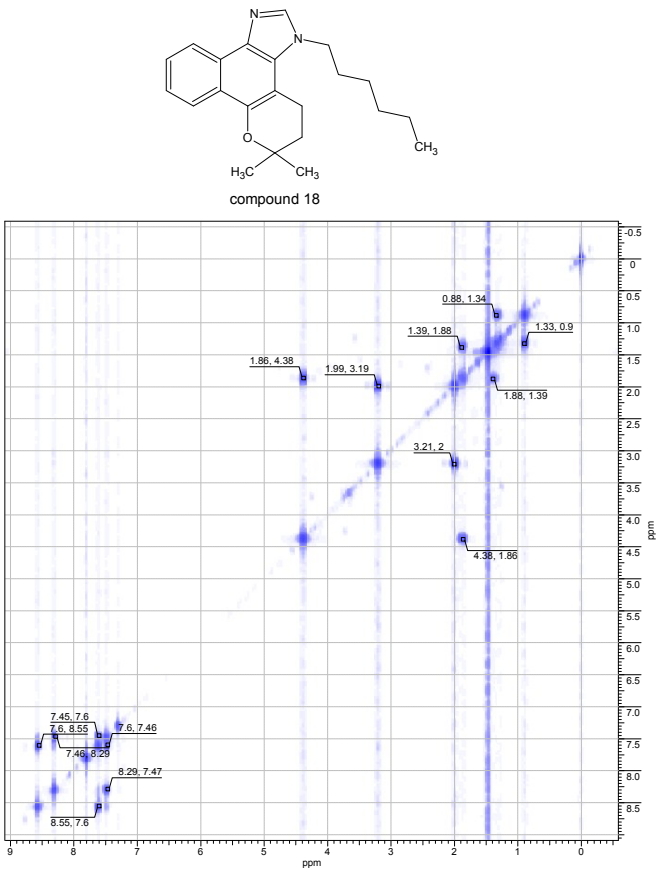
2.14. Compound 18:



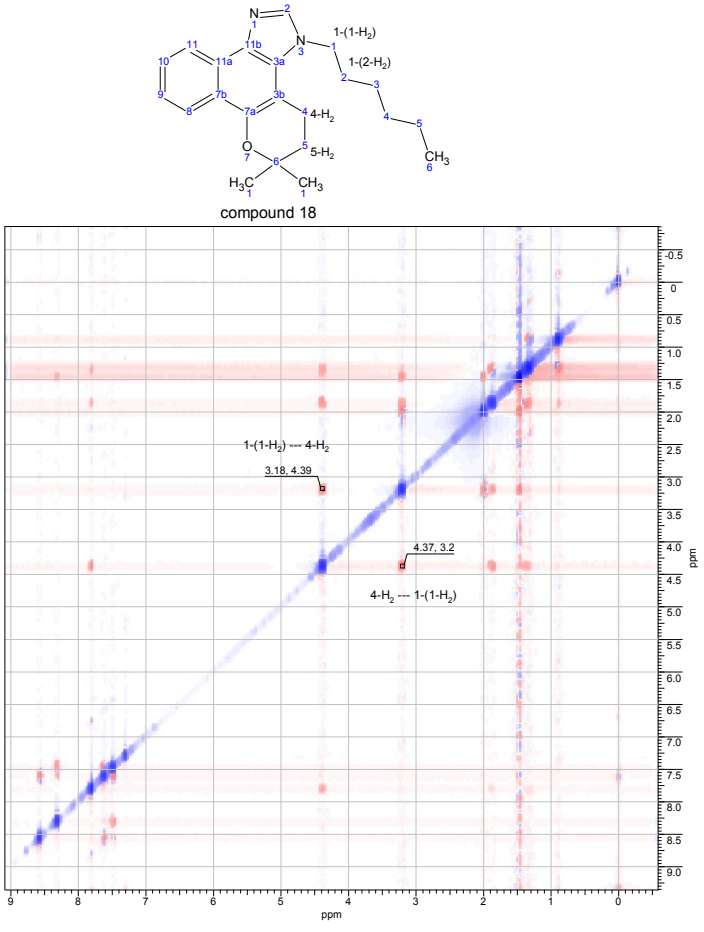
Spectrum 44: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 18.



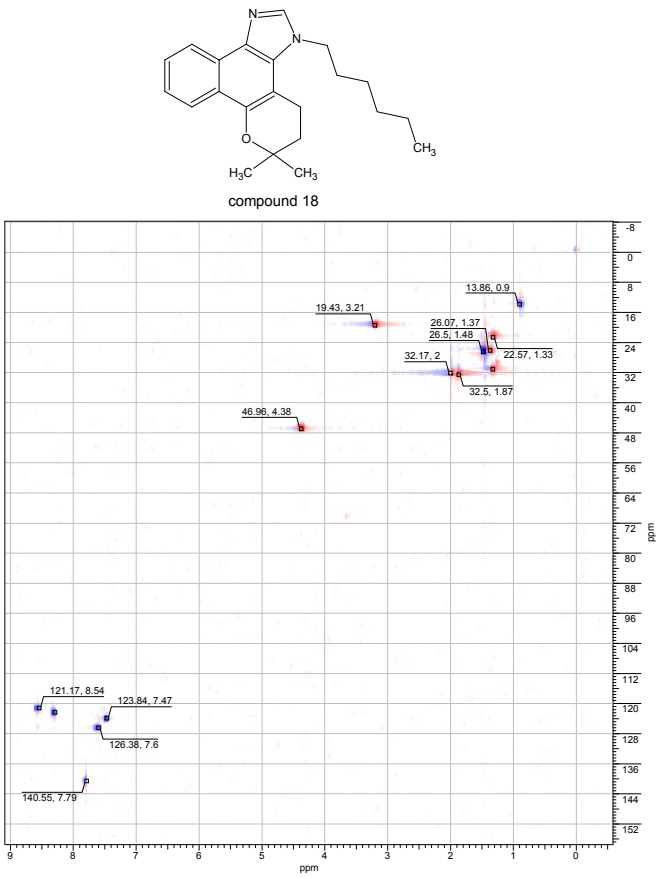
Spectrum 45: DEPTQ (100 MHz, $CDCl_3$) of compound 18.



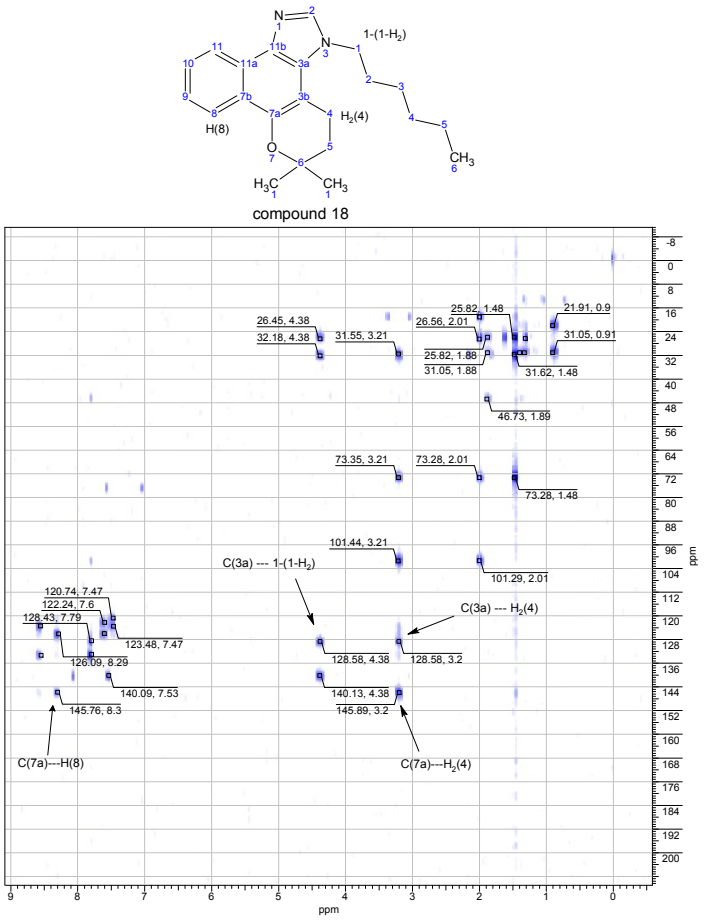
Spectrum 46: ^{1}H-HOMOCOSY (400 MHz, $CDCl_3$) of compound 18.



Spectrum 47: NOESY (400 MHz, $CDCl_3$) of compound 18.

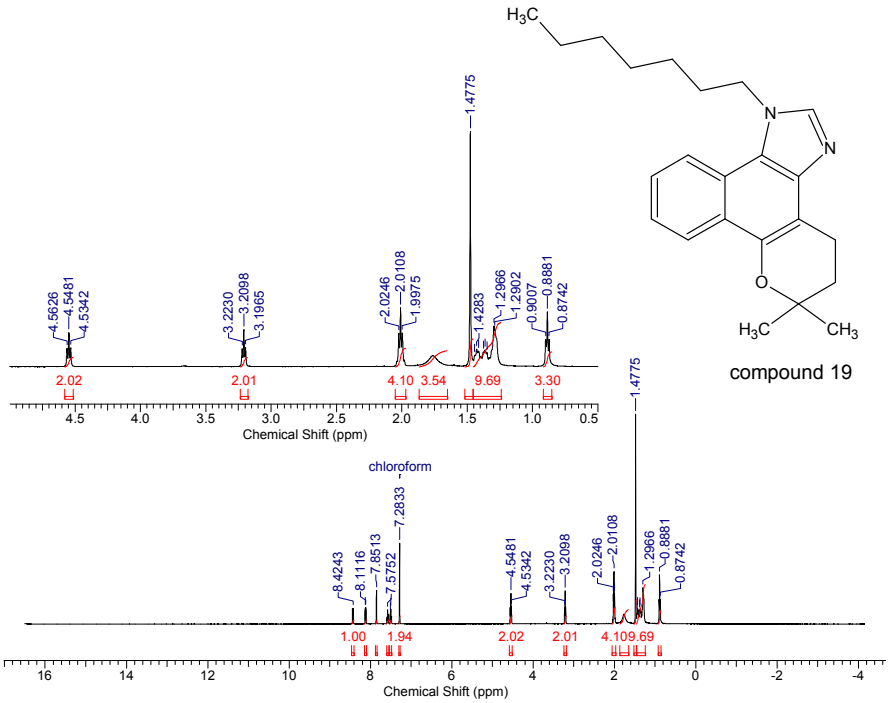


Spectrum 48: HSQC (100 MHz, $CDCl_3$) of compound 18.

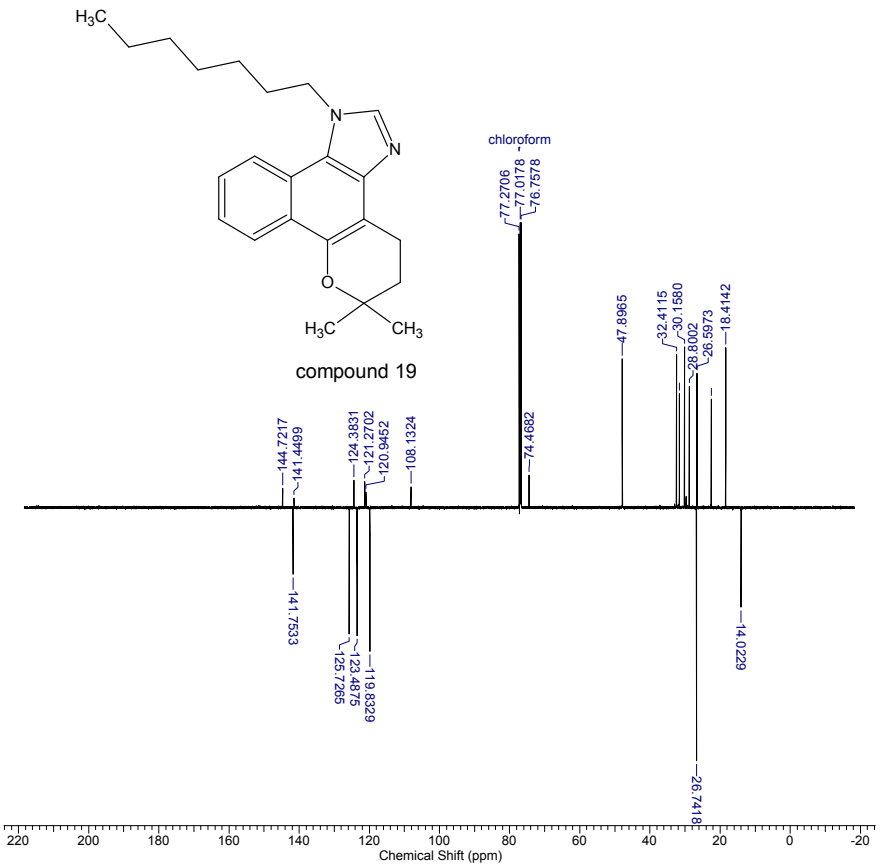


Spectrum 49: HMBC (100 MHz, $CDCl_3$) of compound 18.

2.15. Compound 19:

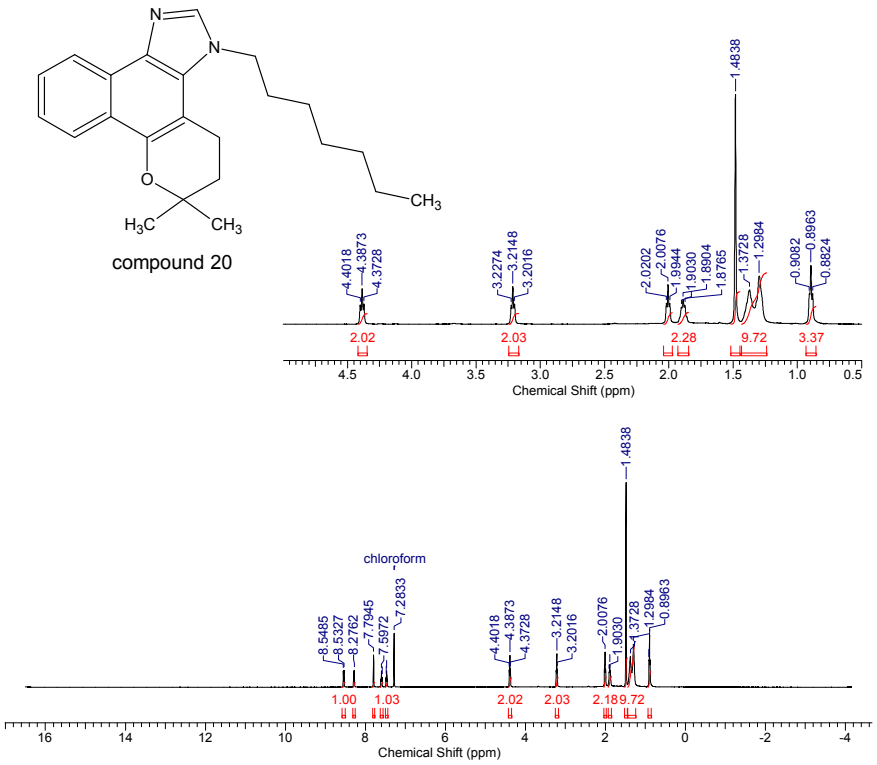


Spectrum 50: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 19.

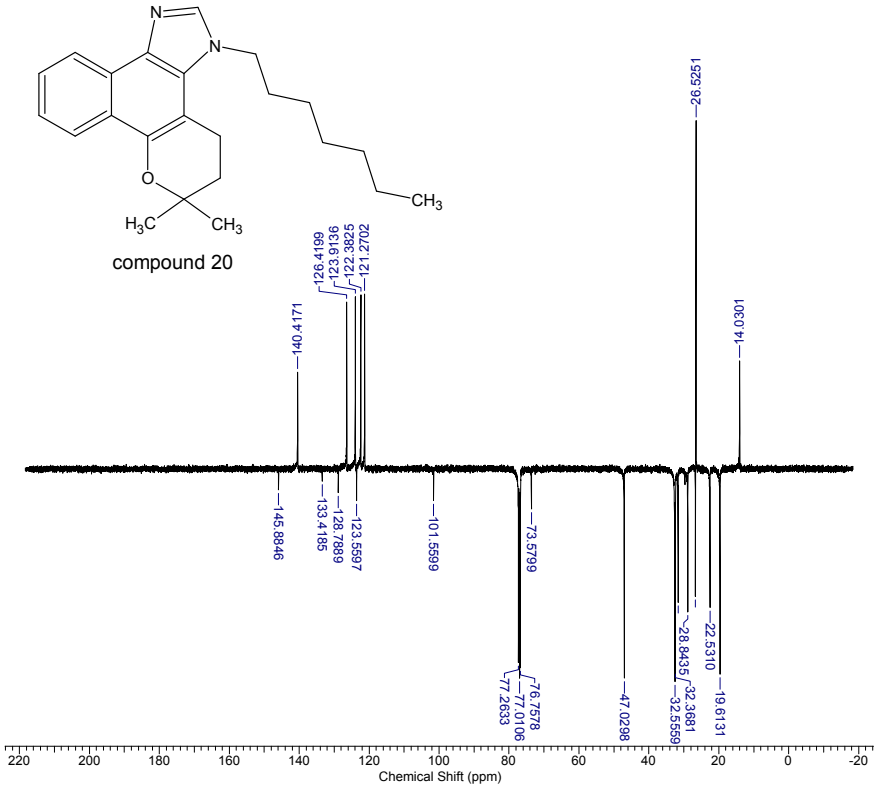


Spectrum 51: DEPTQ (100 MHz, $CDCl_3$) of compound 19.

2.16. Compound 20:

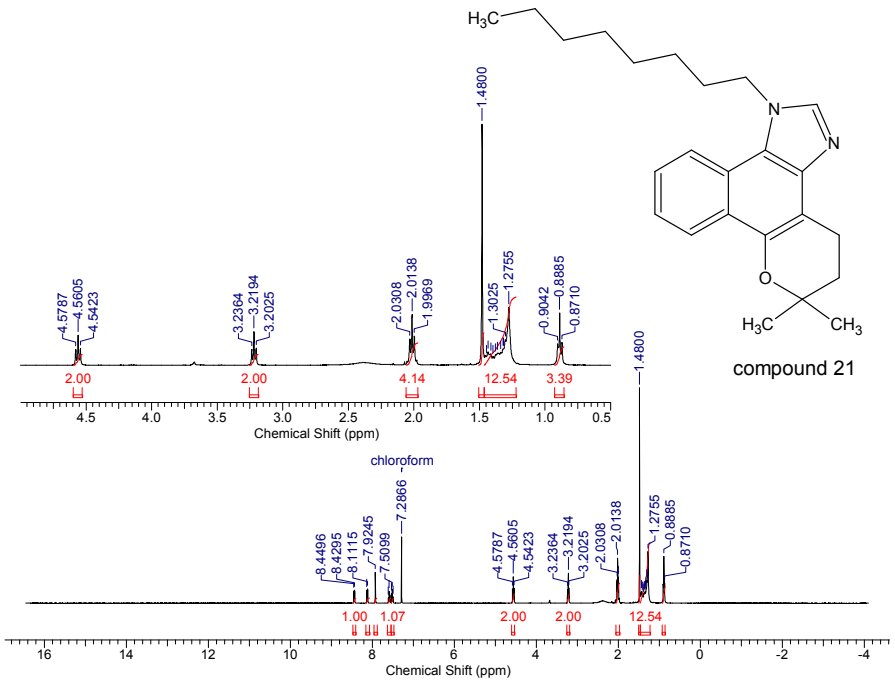


Spectrum 52: ^{1}H-NMR (500 MHz, $CDCl_3$) of compound 20.

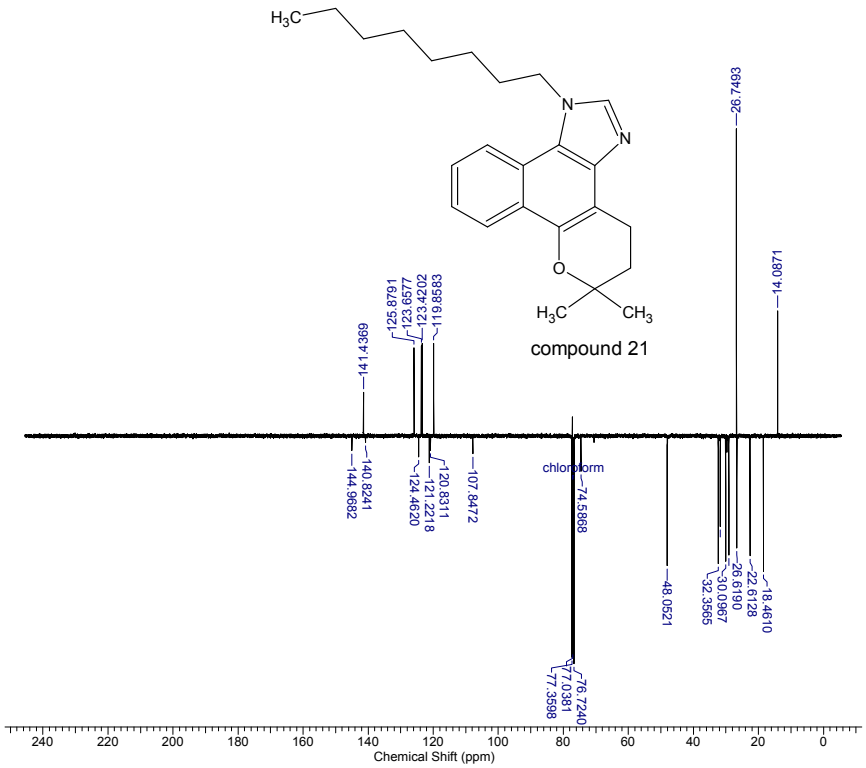


Spectrum 53: DEPTQ (125 MHz, $CDCl_3$) of compound 20.

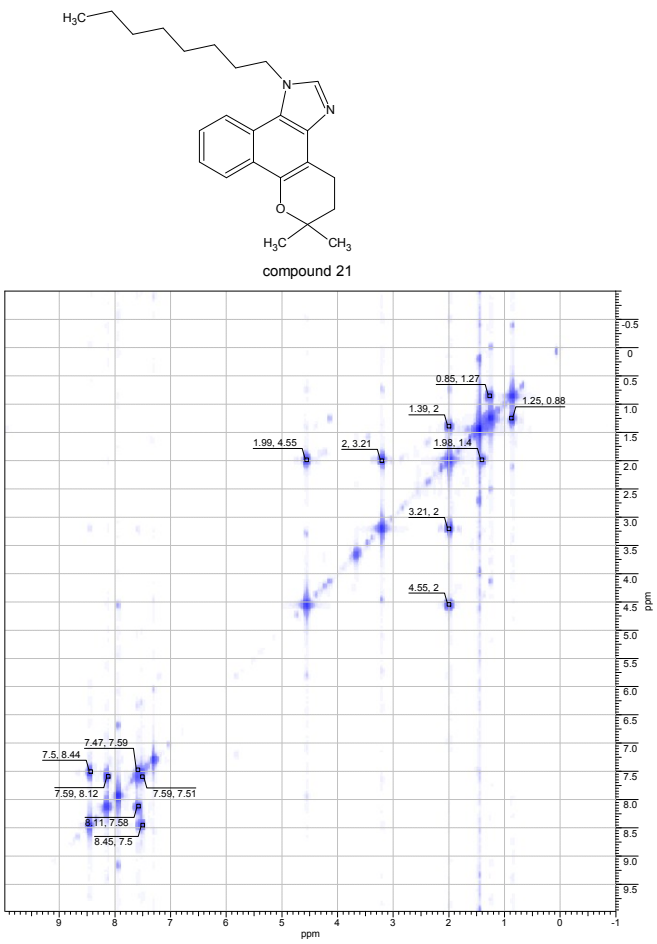
2.17. Compound 21:



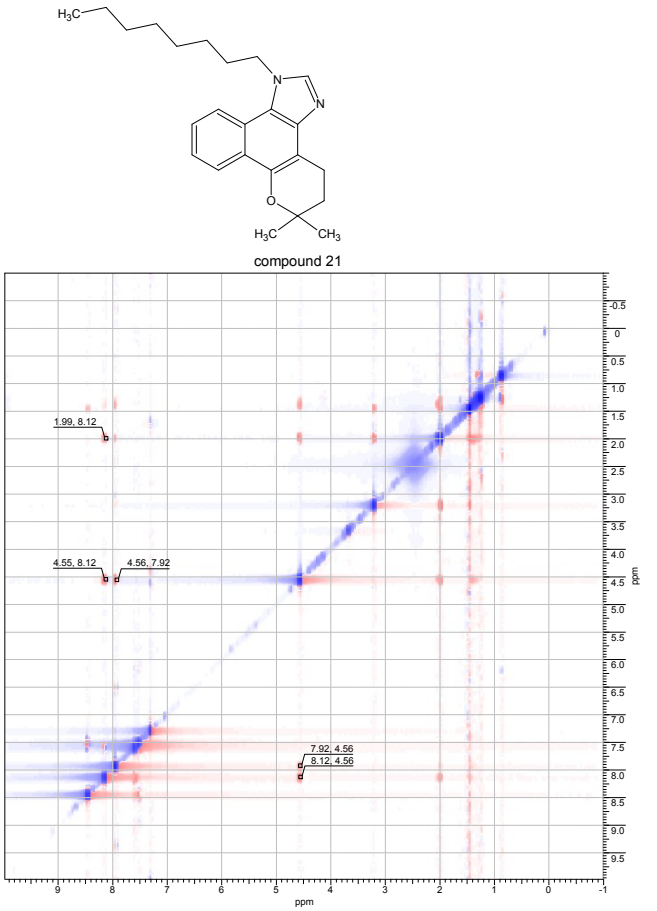
Spectrum 54: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 21.



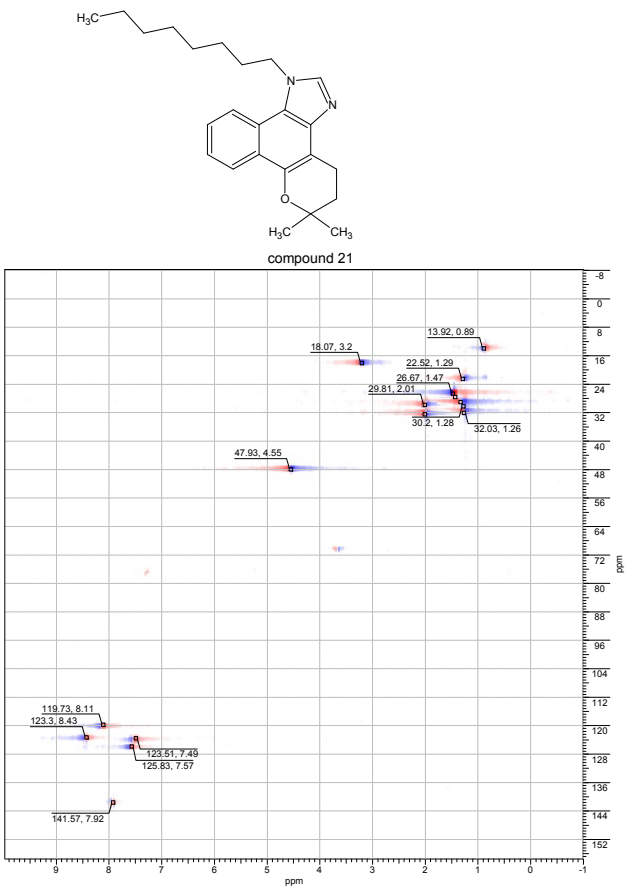
Spectrum 55: DEPTQ (100 MHz, $CDCl_3$) of compound 21.



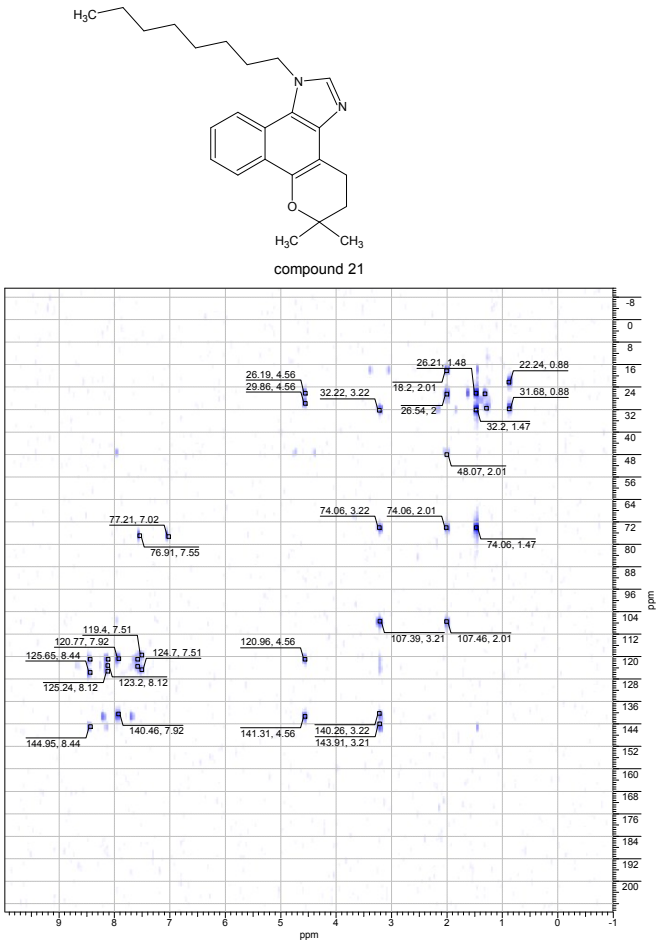
Spectrum 56: ^{1}H-HOMOCOSY (400 MHz, $CDCl_3$) of compound 21.



Spectrum 57: NOESY (400 MHz, $CDCl_3$) of compound 21.

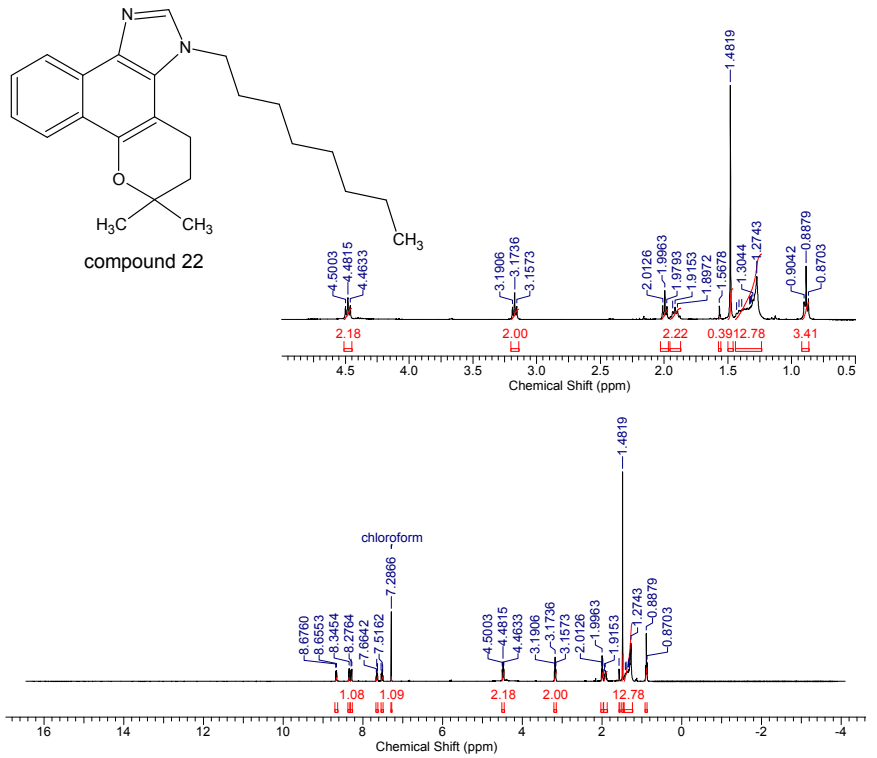


Spectrum 58: HSQC (100 MHz, $CDCl_3$) of compound 21.

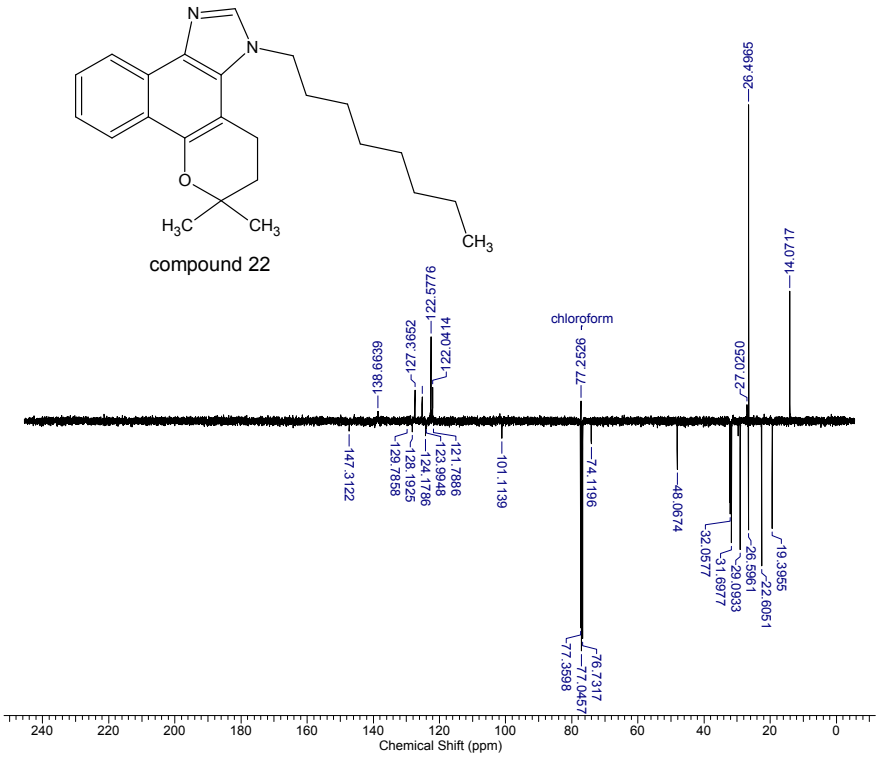


Spectrum 59: HMBC (100 MHz, $CDCl_3$) of compound 21.

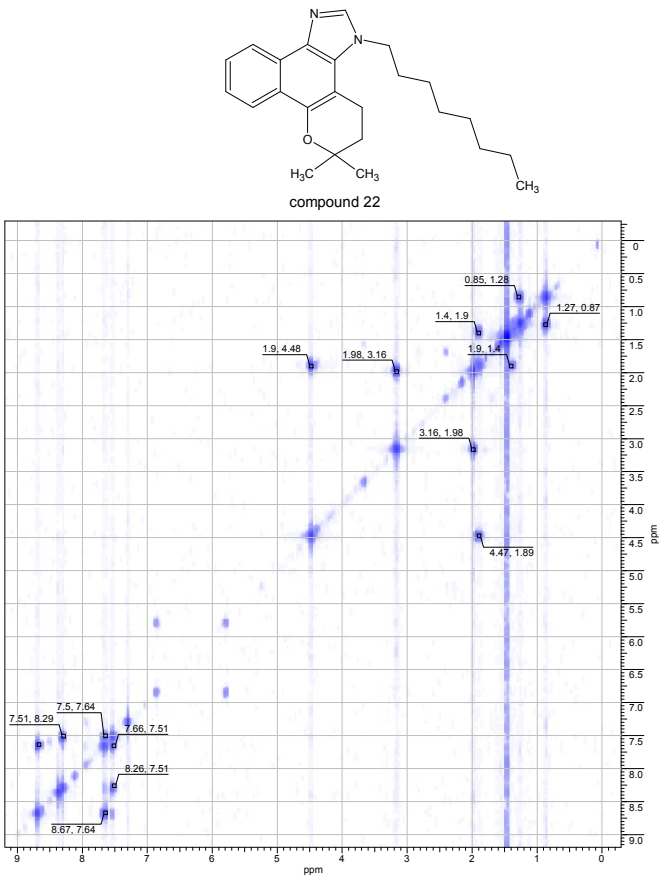
2.18. Compound 22:



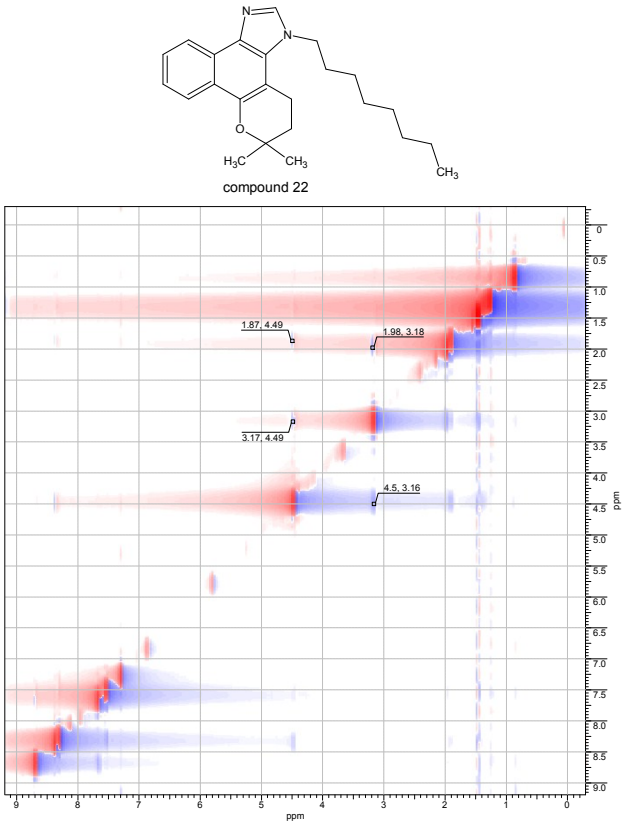
Spectrum 60: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 22.



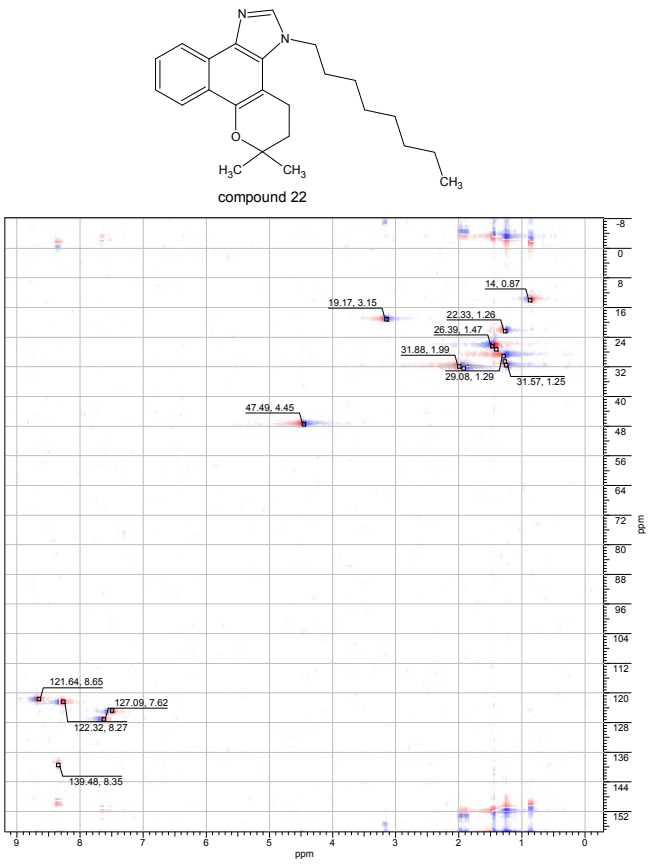
Spectrum 61: DEPTQ (100 MHz, $CDCl_3$) of compound 22.



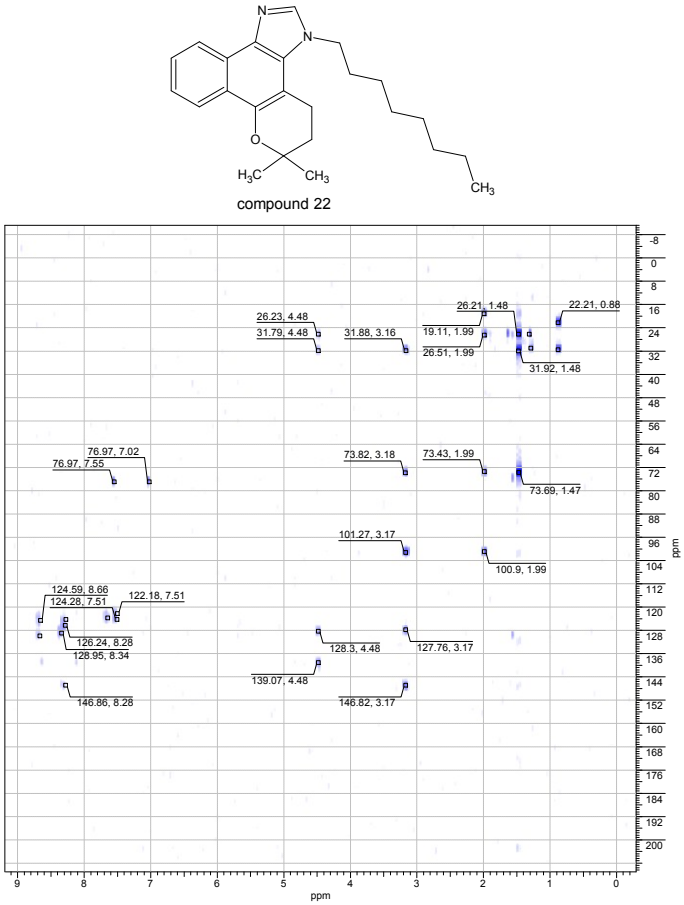
Spectrum 62: ^{1}H-HOMOCOSY (400 MHz, $CDCl_3$) of compound 22.



Spectrum 63: NOESY (400 MHz, $CDCl_3$) of compound 22.

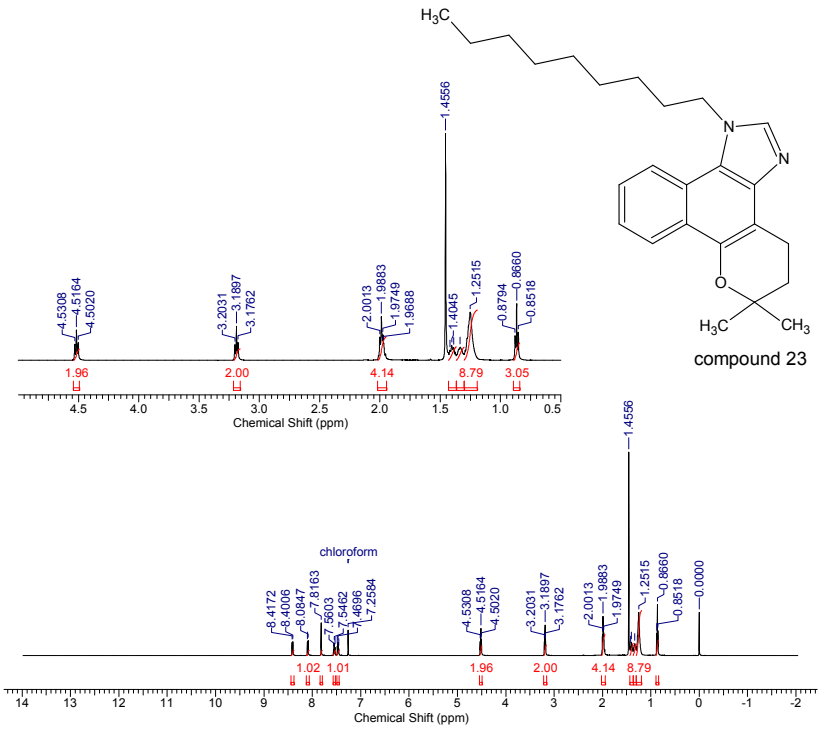


Spectrum 64: HSQC (100 MHz, $CDCl_3$) of compound 22.

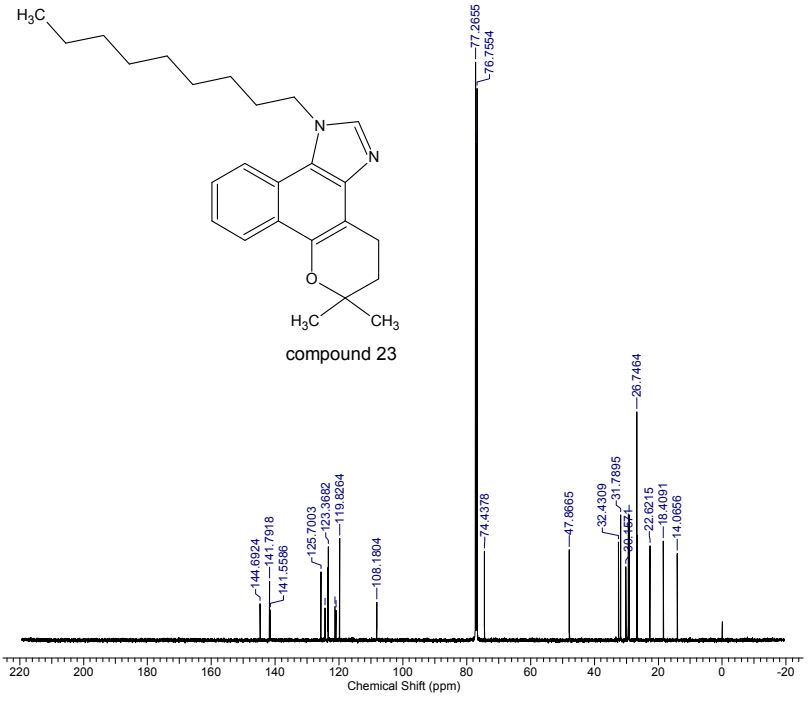


Spectrum 65: HMBC (100 MHz, $CDCl_3$) of compound 22.

2.19. Compound 23:

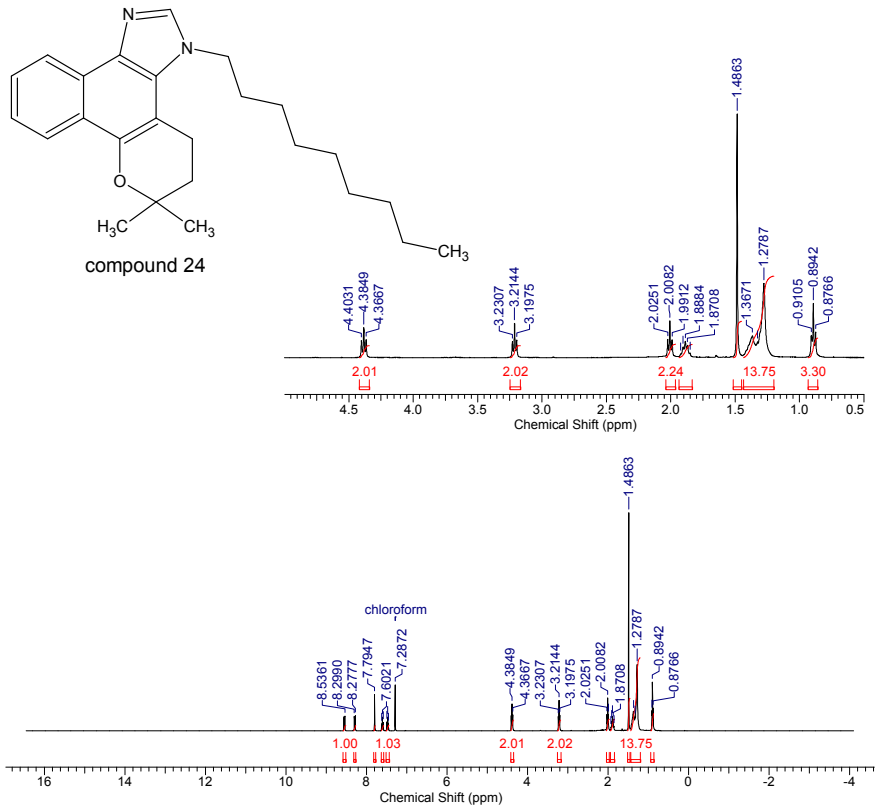


Spectrum 66: ^{1}H-NMR (500 MHz, $CDCl_3$) of compound 23.

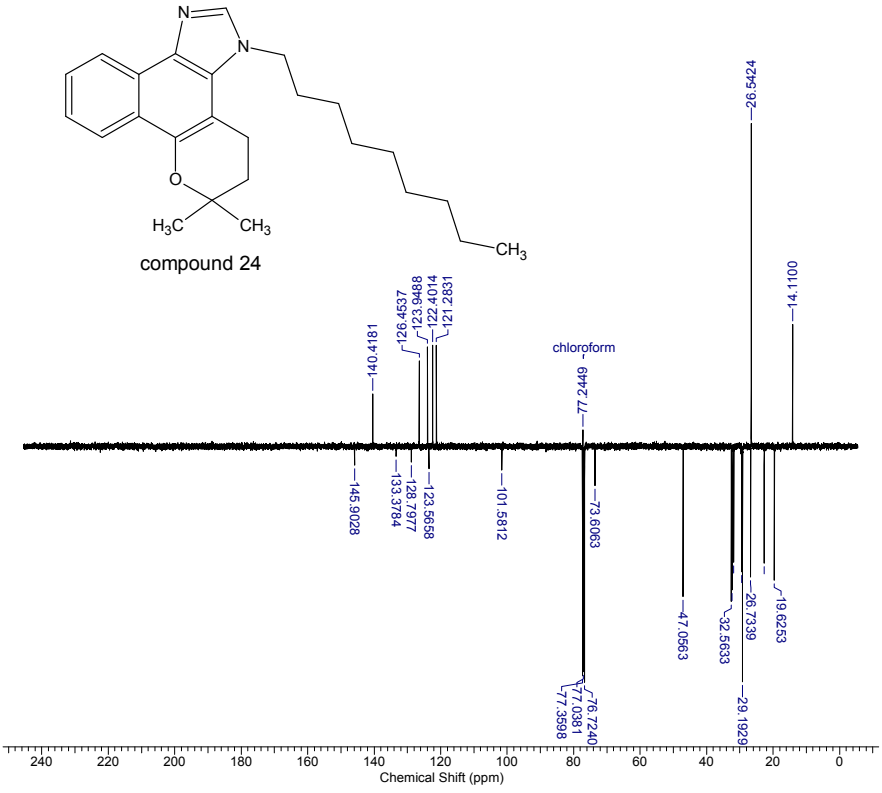


Spectrum 67: ^{13}C-NMR (125 MHz, $CDCl_3$) of compound 23.

2.20. Compound 24:

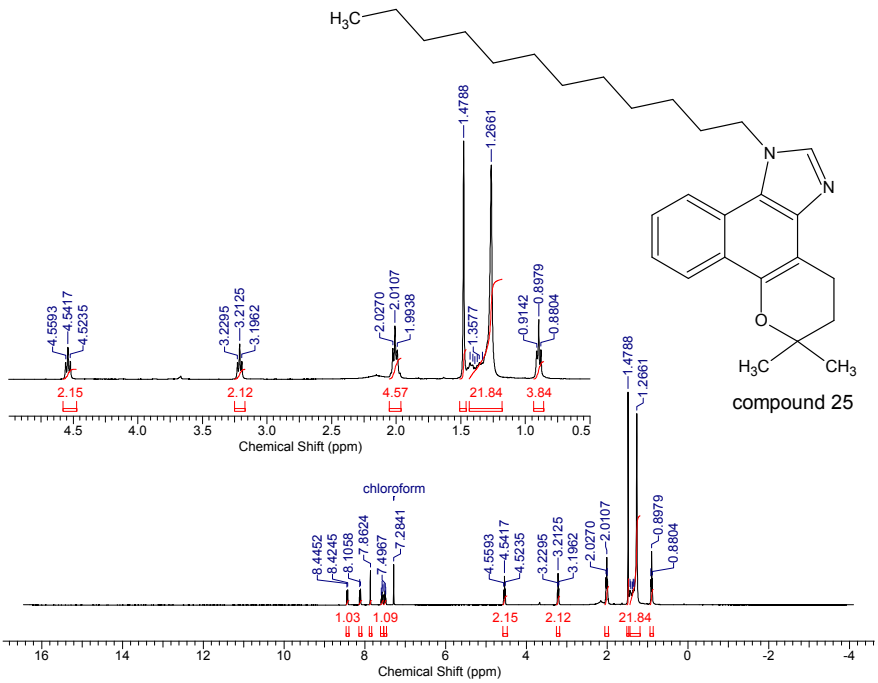


Spectrum 68: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 24.

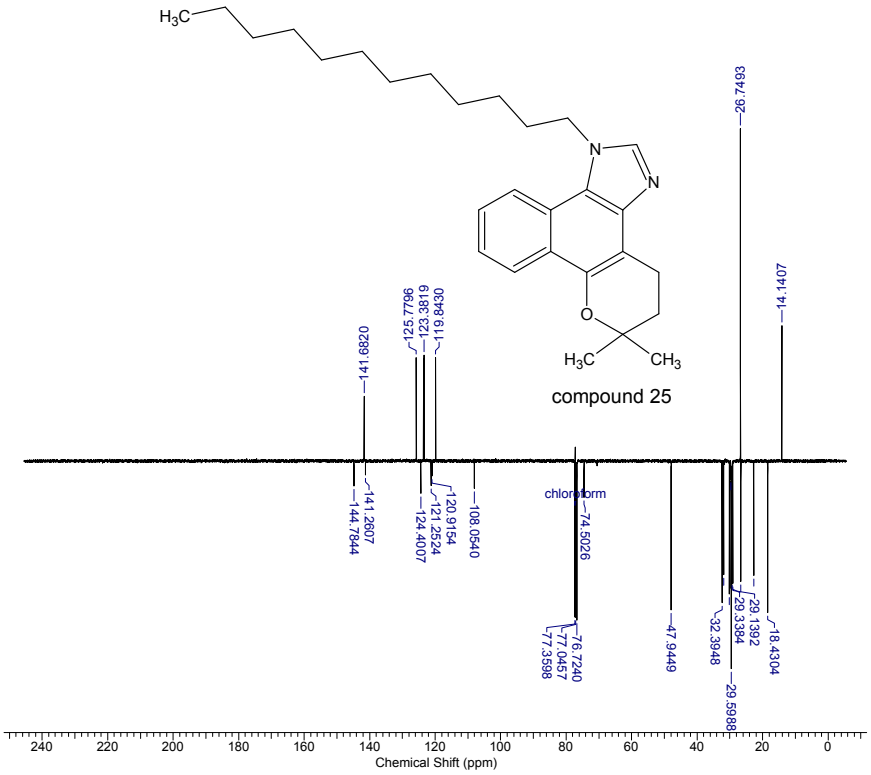


Spectrum 69: DEPTQ (100 MHz, $CDCl_3$) of compound 24.

2.21. Compound 25:

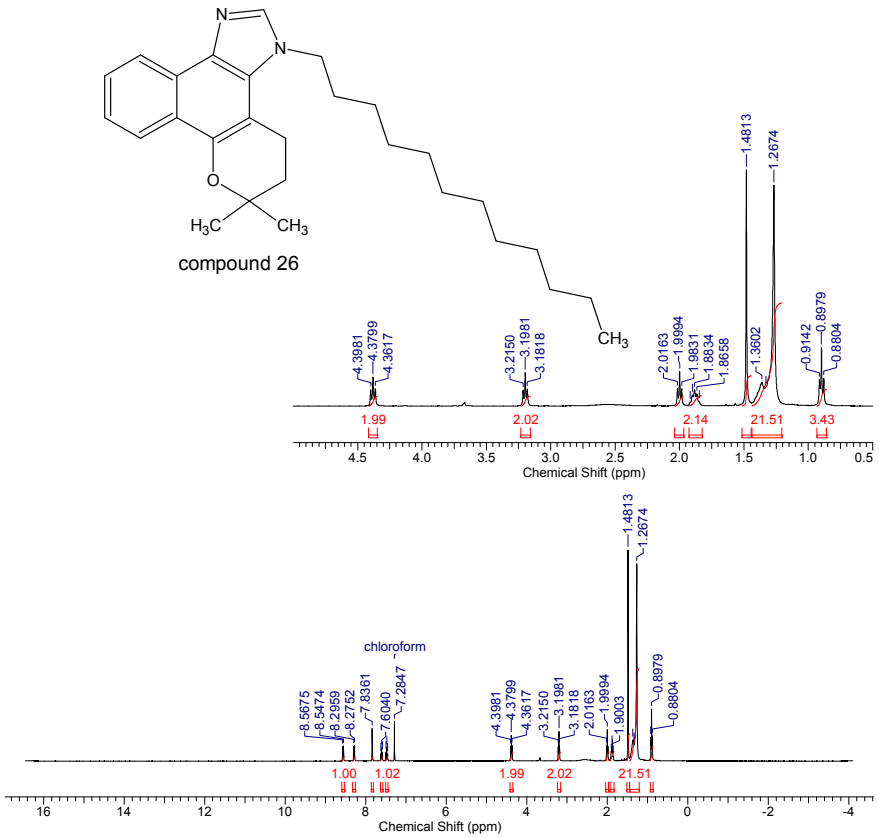


Spectrum 70: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 25.

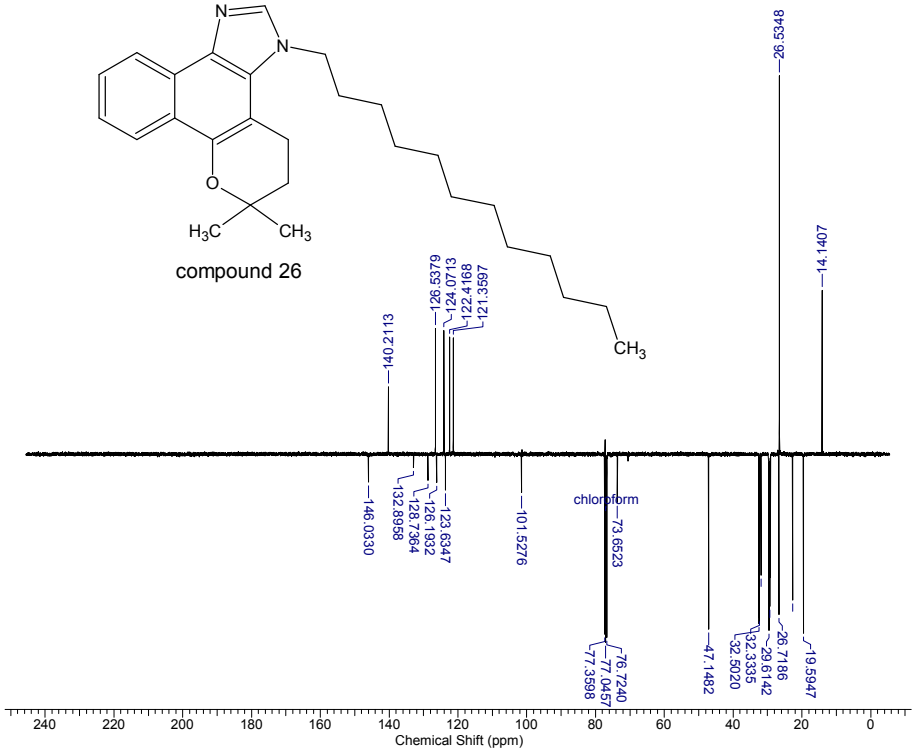


Spectrum 71: DEPTQ (100 MHz, $CDCl_3$) of compound 25.

2.22. Compound 26:



Spectrum 72: ^{1}H-NMR (400 MHz, $CDCl_3$) of compound 26.

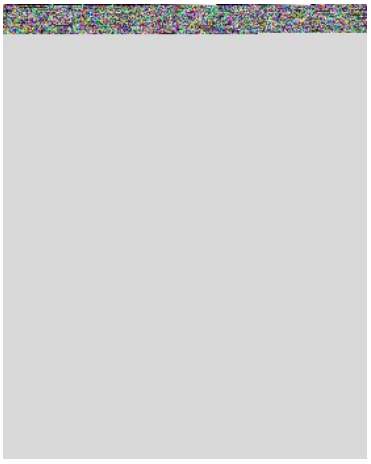


Spectrum 73: DEPTQ (100 MHz, $CDCl_3$) of compound 26.

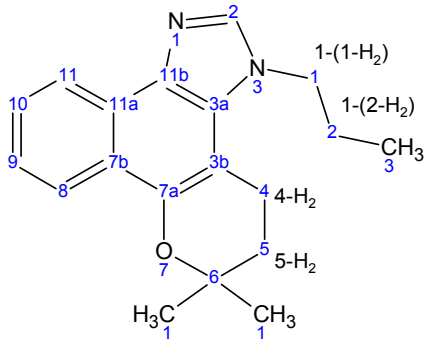
3. Discrimination between N1- alkyl and N3-alkyl regioisomers using NMR data.

To discriminate between each pair of N1-*n*-alkyl and N3-*n*-alkyl naphthoimidazole derivatives (exemplified by compounds **11** and **12** (below) the strategy adopted will be:

11



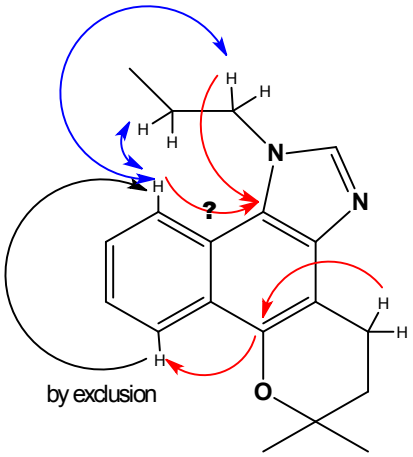
12



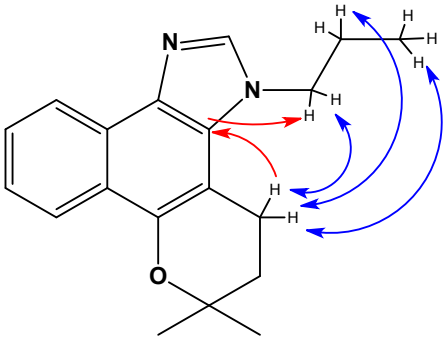
a) the N1-*n*-alkyl will show HMBC $^3J_{CH}$ correlation between C-11b and the hydrogens attached to the first carbon in the alkyl chain (1-(1-H_2)); it should also show NOESY correlation between 11-H and 1-(1-H_2) and, probably, other hydrogens in the side chain. The N3-*n*-alkyl compound should show HMBC $^3J_{CH}$ correlation between C-3a and the hydrogens attached to the first carbon in the alkyl chain (3-(1-H_2)) and it should show NOESY correlation between 4-H_2 and 3-(1-H_2) and, probably, other hydrogens in the side chain. (HMBC correlation of 1-(1-H_2) or 3-(1-H_2) with C-2 is not elucidative.)

b) The methylene at carbon 4 (4-H_2) is a convenient starting point, since it´s position at δ ~3.2- 3.1 ppm (triplet) is quite constant, for all compounds, **10** to **26**. The two doublets at ~8,1 and 8.4 ppm, corresponding to hydrogens 8-H and 11-H (attributions undetermined as yet) are also important and their position quite constant.

Regiochemistry of the N1-*n*-alkyl series (**11**, **13**, … **25**): HMBC $^3J_{CH}$ correlations 4-H_2 --- C-7a and C-7a --- H-8 are clearly seen in the spectra. (Attributions are shown for **11**, as an example, in Spectrum 23). This establishes δ 8.4 for H-8, so H-11 must be at δ 8,1. It is not possible attribute the correlation H-11 --- C-11b precisely (and from C-11b proceed to 1-(1-H_2)), because this and H-11 --- C-7b and H-11 --- C-9 are jumbled into a single oblong blob. But the inverse correlation, 1-(1-H_2) --- C-11b is clearly seen. The proposed N-1-*n*-alkyl is confirmed by NOESY (for **11**, Spectrum 21): clearly seen correlations H-11 --- 1-(1-H_2) and H-11 --- 1-(2-H_2), no sign of involvement of 4-H_2 (δ 3.2 ppm). (See figure below.)



Regiochemistry for the N3-*n*-alkyl series (**12**, **14**, … **26**), the important HMBC $^{3}J_{CH}$ correlations are 4-H_2 --- C-3a and C-3a --- 1-(1-H_2) (Spectrum **29**, for HMBC of **12** as example); besides 1-(1-H_2) --- C-2, no other correlation of 1-(1-H_2) with low field signal is seen. NOESY (Spectrum **27**) confirms the regiochemistry: correlations of 4-H_2 with 1-(1-H_2), 1-(2-H_2) and 1-(3-H_3) are clearly present. (See figure below.)



(HMBC and NOESY spectra for compounds **17** and **18** (1-*n*- and 3-*n*-hexyl) and **21** and **22** (1-*n*- and 3-*n*-octyl) can also be found in the NMR Spectra, **item 2 of Supplementary Information**.)

Observing the ^{1}H NMR spectra of compounds **11** to **26**, it can be noticed that peaks for 1-(1-H_2) and 3-(1-H_2) are always within the region δ = 4.3 to 4.6 ppm (doublets), but for the *n*-alkyl group, 1-(1-H_2) is <u>always</u> more deshielded than 3-(1-H_2):

Cs in alkyl	3	4	5	6	7	8	9	12	mean
1-(1-H_2)	4.52	4.58	4.68	4.57	4.55	4.56	4.52	4.54	**4.57**
3-(1-H_2)	4.35	4.40	4.49	4.38	4.34	4.48	4.39	4.38	**4.40**
Δ (N1-N3)	0.17	0.18	0.19	0.19	0.21	0.08	0.13	0.16	**0.16**

This deshielding effect is due to the aromatic system which is closer to the alkyl group for the N1-alkyl series. [The relative positions (but not the absolute values) are also observed using the ACD Labs HNMR DB simulator: for *n*-propyl, 1-(1-H_2) = 4.3 and 3-(1-H_2) = 4.1 ppm.]

4. Structure/trypanocidal activity correlation

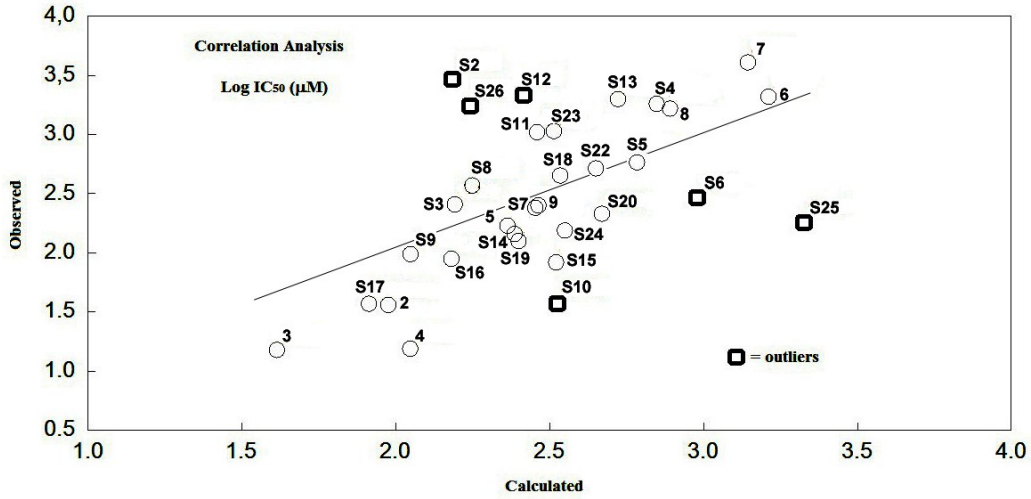


Figure 1S. Plot relating the values of trypanocidal activity, IC_{50} (µM), observed and calculated with **Eq. 1** (log $1/IC_{50}$ = - 10.271 (± 2.667) σ_i - 0.0716 (± 0.032) MR + 1.399 (± 1.170)), for data in **Table 2S.** (Outliers: entries **S2**, **S6**, **S10**, **S12**, **S25** and **S26**, (**Table 2S**) excluded from correlation; line shows best fit).

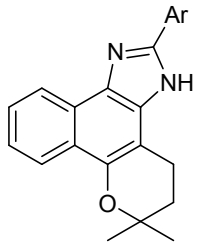
Table 1S Activity of 2-aryl-naphthoimidazoles against trypomastigote forms of *T. cruzi*

Cpd	2-Aryl-naphthoimidazole	IC_{50}/24 h[a] (μM)
2	4,5-Dihydro-6,6-dimethyl-6H-2-phenyl-pyran[b-4,3]naphth[1,2-d] imidazole	37.0±0.7[b]
3	3,4-Dihydro-6,6-dimethyl-6H-2-(3´-indolyl)-pyran[b-4,3]naphth[1,2-d] imidazole	15.4±0.2[c]
4	4,5-Dihydro-6,6-dimethyl-6H-2-(4´-methylphenyl)-pyran[b-4,3]naphth[1,2-d] imidazole	15.5±2.9[d]
5	6,6-Dimethyl-2-(2-thienyl)-3,4,5,6-tetrahydrobenzo[7,8]chromene[5,6-d]imidazole	170.2±20.4
6	2-(2,6-Dichlorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromene[5,6-d]imidazole	2118.8±546.1
7	2-(2,4-Dichlorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromene[5,6-d]imidazole	> 4000
8	6,6-Dimethyl-2-(1-naphthyl)-3,4,5,6-tetrahydrobenzo[7,8]chromene[5,6-d]imidazole	1680.7±47.5
9	4-(6,6-Dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromene[5,6-d]imidazol-2-yl)-2-methoxy-phenol	251.8±28.0
S1	6,6-Dimethyl-2-(2-methoxyphenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	> 6500
S2	6,6-Dimethyl-2-(3-methoxyphenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	3057.8±836.7
S3	6,6-Dimethyl-2-(4-methoxyphenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	259.3±40.4
S4	6,6-Dimethyl-2-(2-nitrophenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	1858.1±366.7
S5	6,6-Dimethyl-2-(3-nitrophenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	579.3±52.5
S6	6,6-Dimethyl-2-(4-nitrophenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	303.6±12.2
S7	2-(2-Fluorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	243.3±24.6
S8	2-(3-Fluorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	372.0±38.7
S9	2-(4-Fluorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	98.0±4.8
S10	2-(2-Chlorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	39.4±8.1
S11	2-(3-Chlorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	1064.2±261.6
S12	2-(4-Chlorophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	2286.3±21.1
S13	2-(2-Bromophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	2004.0±22.9
S14	2-(3-Bromophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	147.8±12.5
S15	2-(4-Bromophenyl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	84.9±3.2
S16	6,6-Dimethyl-2-(2-methylphenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	90.8±5.8
S17	6,6-Dimethyl-2-(3-methylphenyl)-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	37.5±12.8

S18	6,6-Dimethyl-2-[2-(trifluoromethyl)phenyl]-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	448.0±55.7
S19	6,6-Dimethyl-2-[3-(trifluoromethyl)phenyl]-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	128.7±29.4
S20	6,6-Dimethyl-2-[4-(trifluoromethyl)phenyl]-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	227.5±58.0
S21	2-(6,6-Dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol-2-yl)benzonitrile	>8000
S22	3-(6,6-Dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol-2-yl)benzonitrile	518.5±78.9
S23	4-(6,6-Dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazol-2-yl)benzonitrile	1095.9±92.9
S24	6,6-Dimethyl-2-pyridin-3-yl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	154.9±10.4
S25	6,6-Dimethyl-2-quinolin-3-yl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	190.5±30.3
S26	2-(1,3-Benzodioxol-5-yl)-6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,6-d]imidazole	1850.5±241.1

[a] Mean ± SD of at least three independent experiments; [b] Ref. 10a;[c] Ref. 10b; [d] Ref. 10c

Table 2S Data for QSAR. [Compounds **2**-**9**, **S2**-**S20** and **S22**-**S26**: see **Table 1S**; compounds **S1** and **S21** were not included due to very large (> 6500 μM) IC_{50}. Parameters: frontier orbital energies (LUMO and HOMO); hardness ($\eta(E_{LUMO}-E_{HOMO})/2$); inductive effect constant (σ_I); lipophilicity (Log *P*, calculated for the whole molecule); molar refractivity (MR).]



Cpd	Ar from	IC_{50} (μM)	Log IC_{50} (μM)	LUMO	HOMO	η	σ_I	Log *P*	MR
2	Benzaldeyde	37±0.7	1.56	-0.615	-8.082	3.73	0.00	6.15	25.73
3	Indole-3-carboxaldehyde	15.4±0.2	1.18	-0.483	-7.755	3.64	-0.01	6.07	37.21
4	4-Methylbenzaldehyde	15.5±2.9	1.19	-0.603	-8.049	3.72	0.10	6.61	30.35
5	Thiophene-2-carboxaldehyde	170.2±20.4	2.23	-0.808	-8.077	3.63	0.19	5.57	23.87
6	2.6-Diclorobenzaldeyde	2118.8±546.1	3.32	-0.719	-8.146	3.71	0.24	6.51	35.38
7	2.4- Diclorobenzaldeyde	4116±281.7	3.61	-0.842	-8.162	3.66	0.23	6.93	35.38
8	1-Naphthaldehyde	1680.7±47.5	3.22	-0.708	-8.087	3.69	0.14	7.38	43.28
9	2-Methoxy-4-hydroxybenzaldehyde	251.8±28	2.4	-0.621	-8.058	3.72	0.14	5.74	33.62
S2	3-Methoxybenzaldeyde	3057.8±836.7	3.48	-0.599	-8.072	3.74	0.10	6.31	0.11

S3	4-Methoxybenzaldeyde	259.3±40.4	2.41	-0.572	-8.015	3.72	0.11	6.39	32.09
S4	2-Nitrobenzaldeyde	1858.1±366.7	3.26	-1.110	-8.271	3.58	0.21	5.64	31.76
S5	3-Nitrobenzaldeyde	579.3±52.5	2.76	-1.273	-8.336	3,53	0,22	5.88	0.20
S6	4-Nitrobenzaldeyde	303.6±12.2	2.48	-1.470	-8.418	3.47	0.23	6.11	31.76
S7	2- Fluorobenzaldeyde	243.3±24.6	2.38	-0.721	-8.117	3.70	0.19	5.78	25.84
S8	3-Fluorobenzaldeyde	372±38.7	2.57	-0.792	-8.180	3.69	0.16	6.40	25.84
S9	4-Fluorobenzaldeyde	98±4.8	1.99	-0.780	-8.164	3.93	0.13	6.20	25.84
S10	2-Chlorobenzaldeyde	39.4±8.1	1.59	-0.695	-8.116	3.71	0.17	6.32	30.55
S11	3-Chlorobenzaldeyde	1064.2±261.6	3.02	-0.729	-8.144	3.71	0.16	6.94	30.55
S12	4-Chlorobenzaldeyde	2286.3±21.1	3.35	-0.755	-8.130	3.69	0.15	6.74	30.55
S13	2-Bromobenzaldeyde	2004±22.9	3.3	-0.697	-8.097	3.70	0.18	6.50	33.45
S14	3-Bromobenzaldeyde	147.8±12.5	2.16	-0.765	-8.159	3.70	0.13	7.12	33.45
S15	4-Bromobenzaldeyde	84.9±3.2	1.92	-0.778	-8.171	3.70	0.15	7.09	33.45
S16	2-Methylbenzaldeyde	90.8±5.8	1.95	-0.413	-8.142	3.86	0.12	6.61	30.35
S17	3-Methylbenzaldeyde	37.5±12.8	1.57	-0.592	-8.069	3.74	0.08	6.61	30.35
S18	2-Trifluoromethylbenzaldehyde	448±55.7	2.65	-0.745	-8.230	3.74	0.17	7.12	30.72

S19	3-Trifluoromethylbenzaldehyde	128.7±29.4	2.1	-0.949	-8.257	3.65	0.15	7.20	30.72
S20	4-Trifluoromethylbenzaldehyde	227.5±58.0	2.33	-1.088	-8.297	3.60	0.19	7.12	30.72
S22	3-Cyanobenzaldeyde	518±78.9	2.71	-0.954	-8.253	3.65	0.19	5.77	30.29
S23	4-Cyanobenzaldeyde	1095.9±92.9	3.03	-1.103	-8.271	3.58	0.17	5.80	30.29
S24	3-Pyridine carboxylaldehyde	154.9±10.4	2.19	-0.862	-8.173	3.66	0.22	5.07	23.52
S25	3-Quinoline carboxylaldehyde	190.5±30.3	2.27	-0.995	-8.123	3.56	0.22	6.43	41.08
S26	3.4-Methylenedioxybenzaldehyde	1850.5±241.1	3.26	-0.683	-8.099	3.71	0.12	5.56	31.78