Selective and sensitive chromogenic detection of cyanide and hydrogen cyanide in solution and in gas phase

Raul Gotor, Ana M. Costero, Salvador Gil, Margarita Parra, Ramón Matínez-Máñez, Félix Sancenón, and Pablo Gaviña

General Methods

Tetrahydrofurane was distilled over Na prior to use. All other materials were purchased and used as received. The ^{1}H and ^{13}C-NMR spectra were recorded with a Bruker DRX-500 spectrometer (500 MHz for ^{1}H and 126 MHz for ^{13}C) and a Bruker Avance 400MHz (400 MHz for ^{1}H and 100 MHz for ^{13}C). For HRMS an AB SCIEX QTOF mass spectrometer was used. UV-Vis were measured using 1cm path length quartz cuvettes and in a Shimadzu UV-2101PC spectrophotometer.

UV-Vis quantitative analysis were performed by adding aliquots of different anions (as Na^+ or K^+ salts) to 1.0 x 10^{-5} M solutions of compounds **1** and **2** in such a way that the final concentration of the analyte was 9.9 mM. Unless noted, the sensing media was 99:1 H_2O:MeCN pH=10.6 borax/HCl at 293 K. Measurements were made after time enough to ensure complete reaction between the analyte and the chemodosimeter.

Detection limits were calculated by plotting the maximum absorbance of compound **1** and **2** in the presence of the analyte in a 2.5 µM to 9.9 mM concentration. The limit of detection was calculated when $\Delta Abst \geq K \times Sb1/S$, where ΔAbst is the difference of absorbance from the blank at a given time, K=3, Sb1 is the standard deviation of the blank solution and S is the slope of the calibration curve.

Gas phase studies were carried out using aminated silica TLC plates (Merk TLC Silicagel 60 NH_2 F254s) as a solid support, dopped with different ammounts of the chemodosimeter **1** (from 25 nmol/cm^2 to 25 µmol/cm^2). The sensing support was hung inside a 500ml round bottom flask, which was capped with a septum. HCN (g) was generated by injecting H_2SO_4 over a known amount of KCN (s) inside a small vial placed at the bottom of the round bottom flask. H_2S was generated by the addition of H_2SO_4 to NaSH. NH_3 and HCl were added as concentrated aqueous solutions. Detection limits were determined using image processing software, after digitalization on a desktop scanner. Detection was made along with a control strip. Control strip was encapsulated between two microscope slides to avoid reaction with analyte.

Synthesis of 1

To a solution of p-bromophenol (2.71 g, 15.6 mmol), in dry THF (160 ml) at -78 ºC under Ar atmosphere, a 1.4 M solution of BuLi (24.6 ml, 34.4 mmol) was added. The mixture was stirred at -78ºC for 30 min. Then, the reaction mixture was heated during 5 minutes to 0 ºC, and then cooled back again to -78 ºC. At this point, the mixture was transferred via cannula to a round bottom flask containing 4,4'-bis(dimethylamino)benzophenone (4.2 g, 15.6 mmol) in dry THF (225 ml) at -78 ºC. The reaction mixture was allowed to warm up at room temperature for 24 h. After this time, 40 ml of water were added, and the solvents were partially evaporated. The mixture was re-dissolved in EtOAc, and washed 3 times with NH_4Cl 10%. The aqueous layers were re-extracted with EtOAc and the organic phases were combined, washed with NaCl (sat.) and dried with $MgSO_4$. After evaporating the solvents, the red residue was subjected to a column chromatography (Et_3N neutralized Silica, 4:2:1 EtOAc:Hex:MeOH) yielding 2.43 g (45%) of 1 as a deep blue solid. Mp: 194.0-201.0 ºC. R*f* = 0.13 (Et_3N neutralized Silica, EtOAc:Hex:MeOH 4:2:1). IR (cm^{-1}): 3700-3010(b), 2921(w), 2854(w), 2805(w), 1633(w), 1588(s), 1512(w), 1445(w), 1335(s), 1266(w), 1159(s), 1065(w), 944(w), 903(w), 823(m), 733(m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=9.0 Hz, 4H), 7.20 (d, J=8.9 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.82 (d, J=9.3 Hz, 4H), 3.26 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.29, 156.27, 140.61, 138.97, 126.85, 117.73, 117.12, 114.84, 112.62, 40.47. HRMS (ESI): calcd for $C_{23}H_{25}N_2O$ $[M+H]^+$: 345.1971, found: 345.1967.

Synthesis of 2

A 1.4 M solution of BuLi (24.6 ml, 34.4 mmol) was added to a solution of p-bromophenol (2.71 g, 15.6 mmol), in dry THF (160 ml) at -78 ºC under argon atmosphere. The mixture was stirred at -78ºC for 30 min. The reaction mixture was then heated during 5 minutes to 0 ºC. At this point, the mixture was transferred via cannula to a round bottom flask containing 4-dimethylaminobenzophenone (2.8 g, 12.48 mmol) in dry THF (225 ml) at 0 ºC. After 24 h, the reaction was quenched with water (40 ml) and the organic solvents were evaporated. The remanent mixture was re-dissolved in EtOAc and washed three times with with NH_4Cl 10%. The aqueous layers were re-extracted with EtOAc and the organic phases were combined, washed with NaCl (sat.) and dried with $MgSO_4$. After evaporating the solvents, the red residue was subjected to a column chromatography (Silica, EtOAc:Hex 5:5 -> 8:2) yielding 2.04 g (54.2%) of a dark blue solid. Mp: 165.6-167.3 ºC, R*f* = 0.27 (Et_3N neutralized Silica, EtOAc:Hex 8:2). IR (cm^{-1}): 3047(w), 2939(w), 2904(w), 2860(w), 2816(w), 1590(s), 1532(w), 1472(m), 1436(m), 1366(m), 1340(m), 1202(w), 1168(m), 940(w), 892(w), 860(m). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.58–7.53 (m, 2H), 7.51–7.46 (m, 3H), 7.31 (d, J=9.8 Hz, 2H), 7.18 (d, J=8.9 Hz, 2H), 6.75 (d, J=8.9 Hz, 2H), 6.41 (d, J=9.8 Hz, 2H), 3.11 (s, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 186.32, 163.08, 152.21, 140.80, 140.03, 135.13, 132.66, 130.03, 127.97, 127.47, 127.04, 127.03, 111.03, 39.88. HRMS (ESI): calcd for $C_{21}H_{20}NO$, $[M+H]^+$: 302.1545, found: 302.1553.

Synthesis of 3

Compound **1** (1.15 g, 3.34 mmol) was dissolved in MeCN (100 ml). Potassium cyanide (0.65 g, 10 mmol) was added to the solution, and the mixture heated up to 70 ºC with stirring overnight. Then, the unreacted cyanide was filtered off, and the MeCN was evaporated. The remaining solid was purified by means of column chromatograpy (Et_3N neutralized silica, EtOAc:Hex 4:6) yielding 0.69 g (56 %) of a white solid. M.p.: 252.9-256.0 ºC. R*f* = 0,68 (Et_3N neutralized silica, EtOAc:Hex 8:2). IR (cm^{-1}): 3383(m), 3033(w), 2890(w), (2854(w), 2805(w), 2241(m), 1610(s), 1503(s),1440(m), 1355(m), 1266(w), 1217(m), 1176(m), 1105(w), 1051(w), 1011(w), 948(m),818(m), 751(m). ^1H NMR (500 MHz, CD_2Cl_2) δ 7.12 (d, J=8.7 Hz, 2H), 7.05 (d, J=8.9 Hz, 4H), 6.83 (d, J=8.7 Hz, 2H), 6.70 (d, J=8.9 Hz, 4H), 2.98 (s, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.15, 149.99, 133.96, 129.95, 129.18, 128.39, 124.26, 115.06, 111.91, 55.17, 40.14. HRMS (ESI): calcd for $C_{24}H_{26}N_3O$ $[M+H]^+$: 372.2070, found: 372.2064.

Synthesis of 4

Folowing the same procedure as above, from compound **2** (0.95 g, 3.16 mmol) compound **4** **(**0.64 g, 62 %) was isolated as a white solid. M.p.: 230-231ºC. IR (cm^{-1}): 3389(m), 2926(w), 2860(w), 2854(w), 2124(w), 1608(m), 1510(s),1446(m), 1359(m), 1217(m), 1174(m), 833(m), 812(m), 761(s), 700 (s). ^1H NMR (500 MHz, CD_2Cl_2) δ 7.38–7.31 (m, 3H), 7.25–7.21 (m, 2H), 7.07 (d, J=8.8 Hz, 2H), 7.01 (d, J=9.0 Hz, 2H), 6.80 (d, J=8.8 Hz, 2H), 2.94 (s, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.42, 150.09, 141.31, 133.11, 130.06, 129.27, 128.55, 128.47, 127.79, 127.51, 123.90, 115.21, 111.94, 40.11. MS (ESI): $[M+H]^+$: 328.9, 301.9 (M-CN) 225.9 (M-CN-Ph).

Spectra of 1 to 4

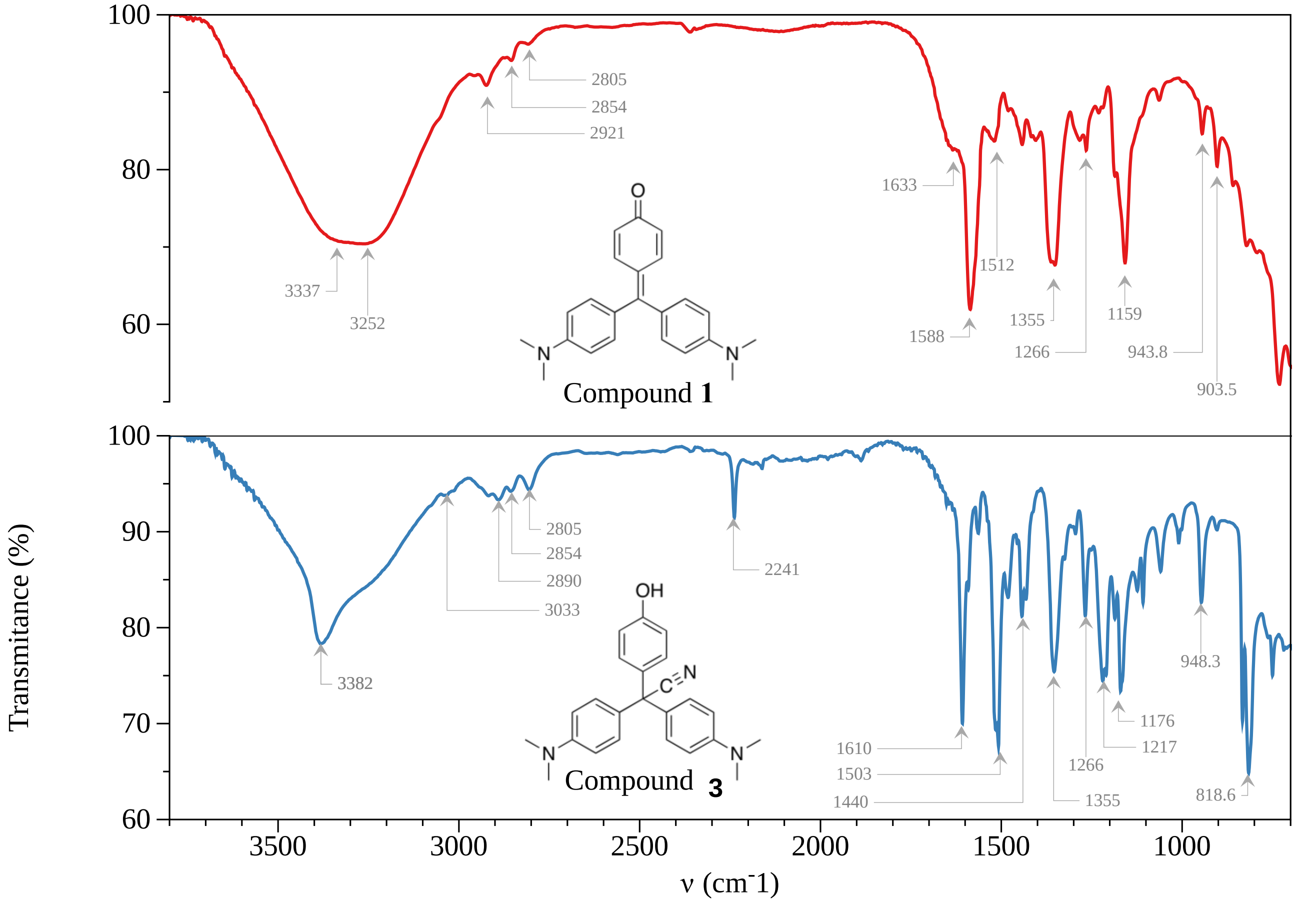
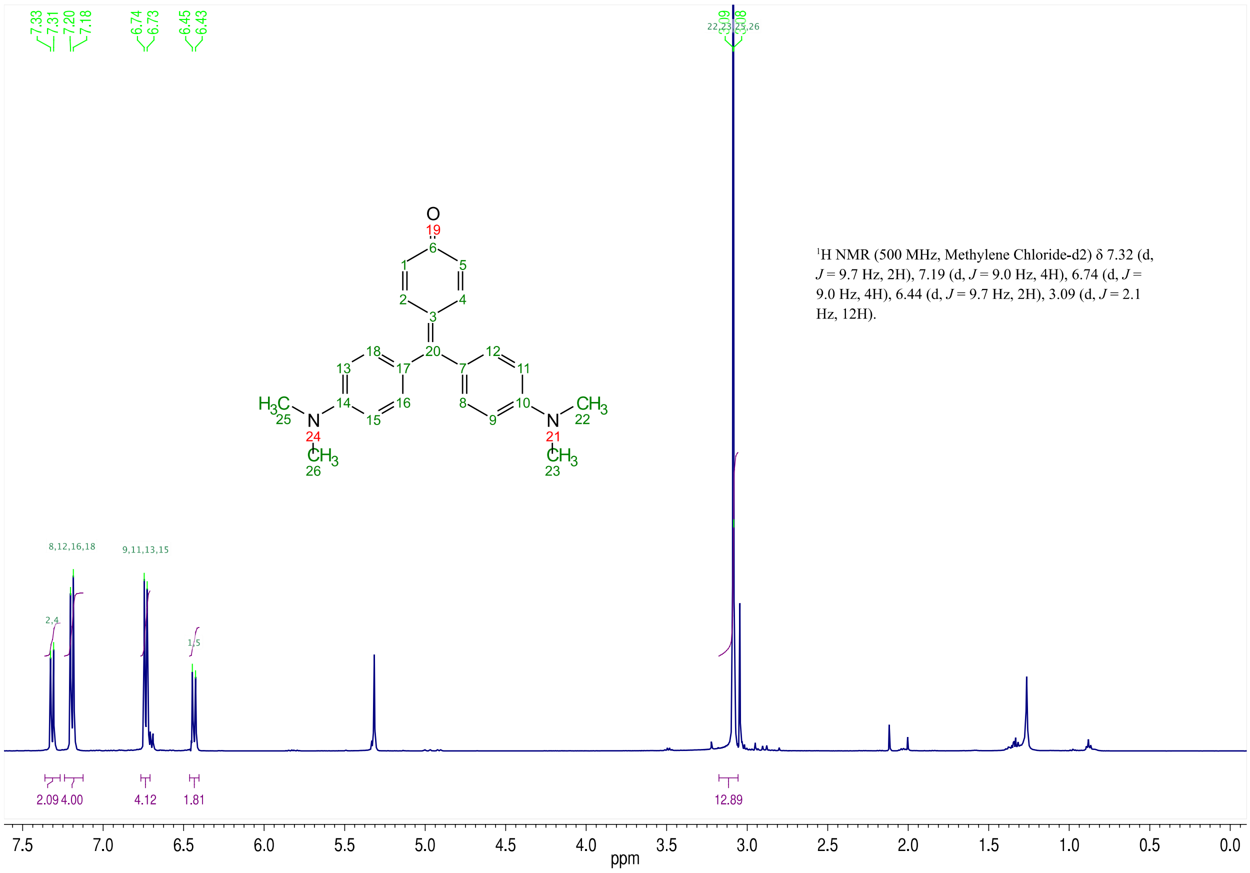
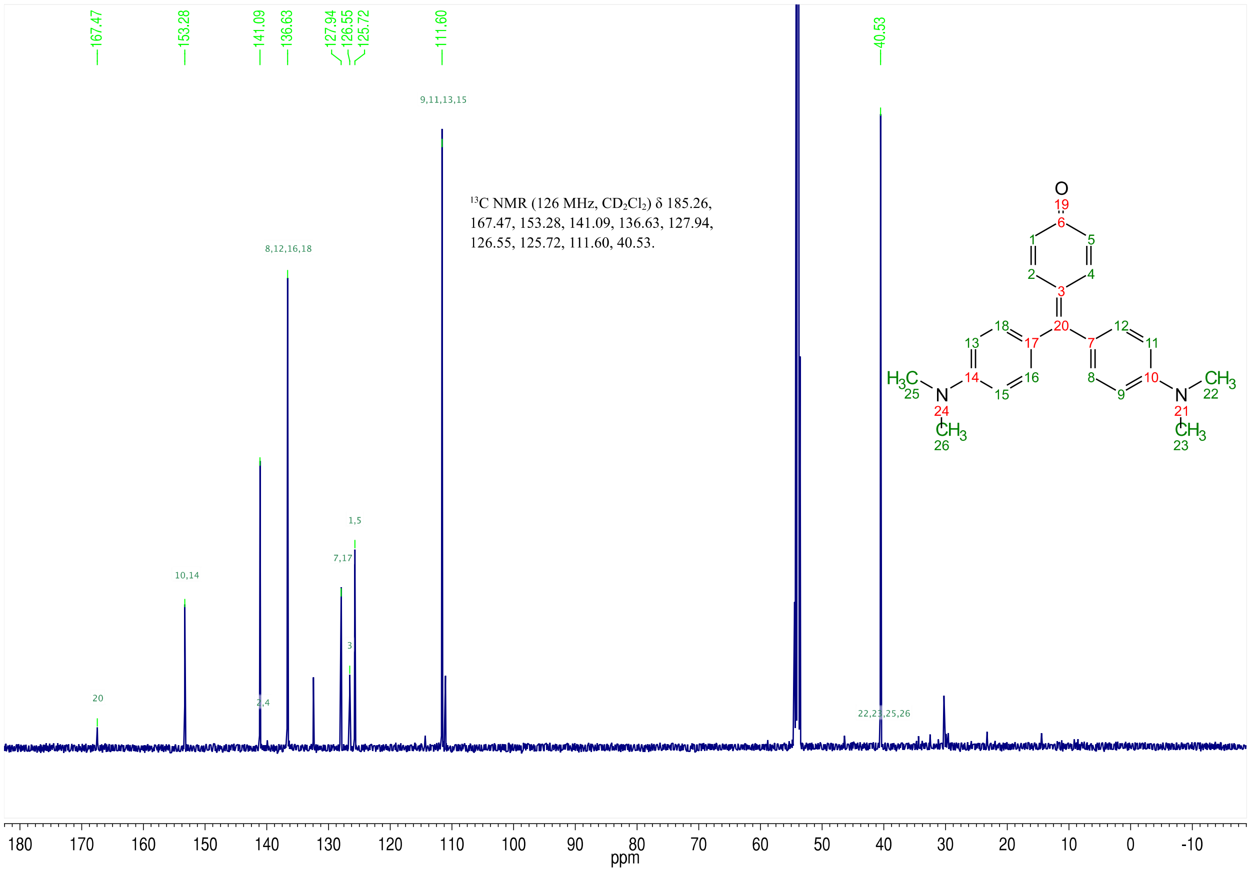


Figure SI-1. ATR-IR spectra of compounds **1** and **3**



^{1}H NMR (500 MHz, Methylene Chloride-d2) δ 7.32 (d, J = 9.7 Hz, 2H), 7.19 (d, J = 9.0 Hz, 4H), 6.74 (d, J = 9.0 Hz, 4H), 6.44 (d, J = 9.7 Hz, 2H), 3.09 (d, J = 2.1 Hz, 12H).

Figure SI-2. ^{1}H-NMR spectra of compound **1** in CD_2Cl_2



^{13}C NMR (126 MHz, CD_2Cl_2) δ 185.26, 167.47, 153.28, 141.09, 136.63, 127.94, 126.55, 125.72, 111.60, 40.53.

Figure SI-3. ^{13}C-NMR spectra of compound **1** in CD_2Cl_2

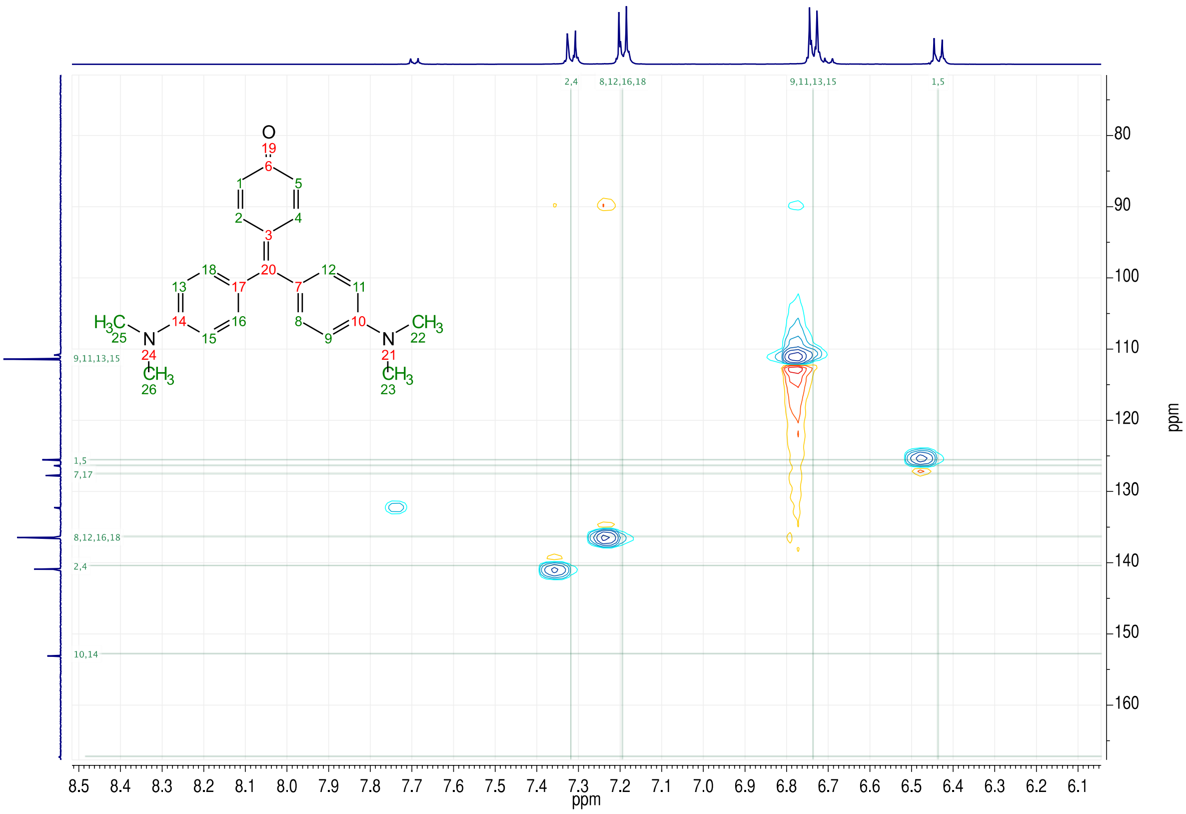


Figure SI-4. HSQC spectra (selected regions) of compound **1** in CD_2Cl_2

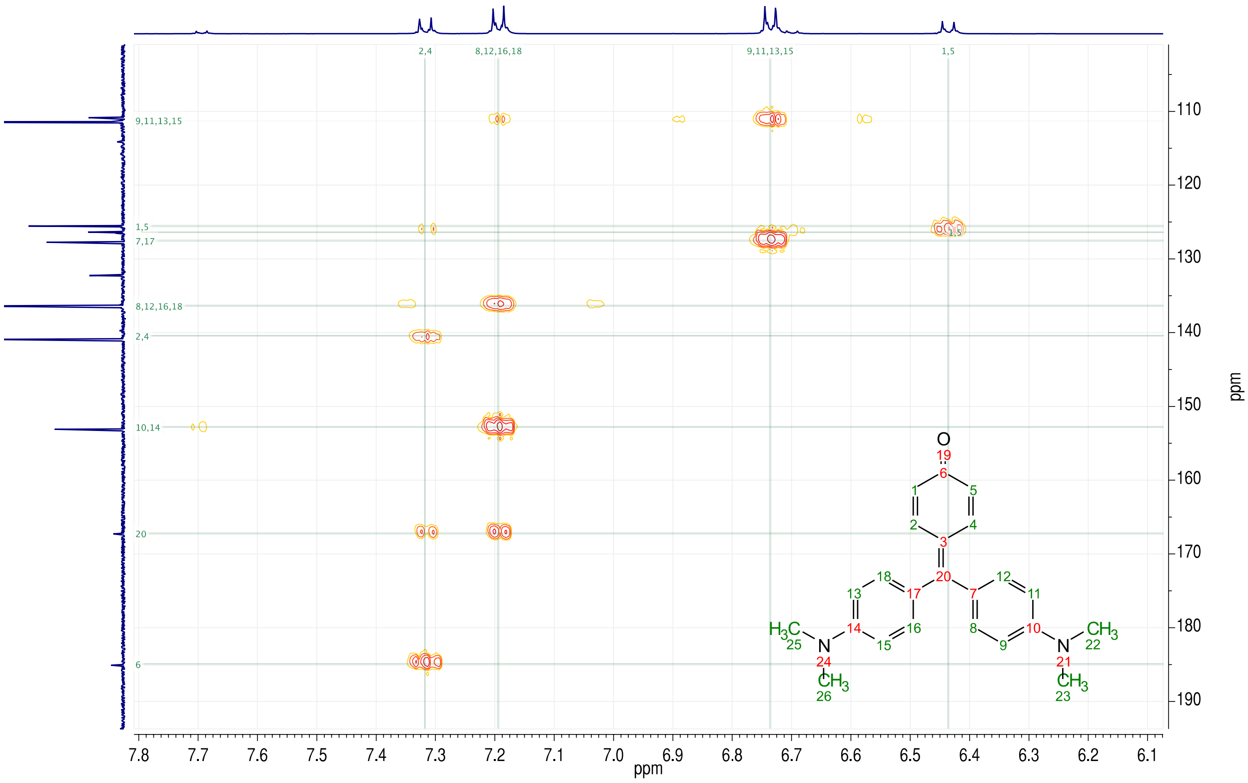
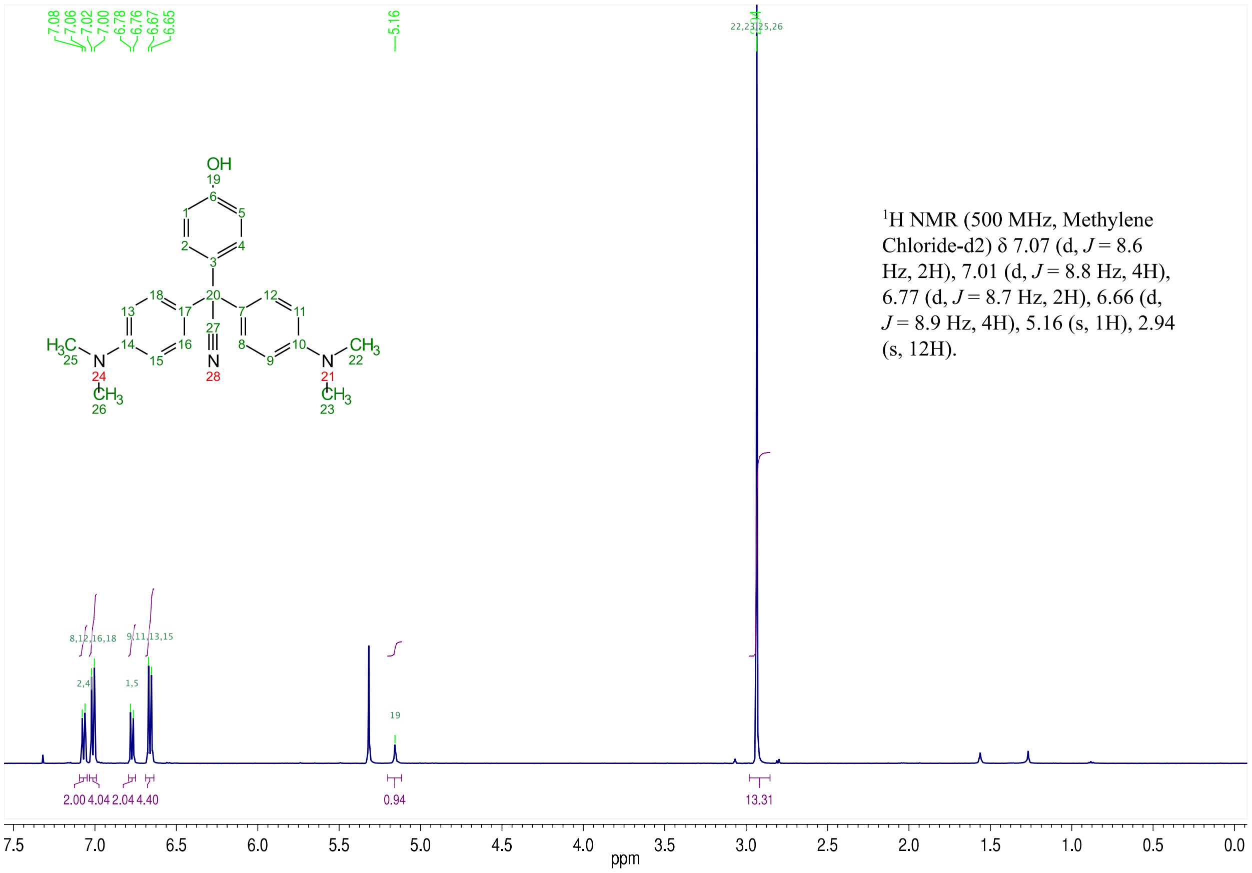
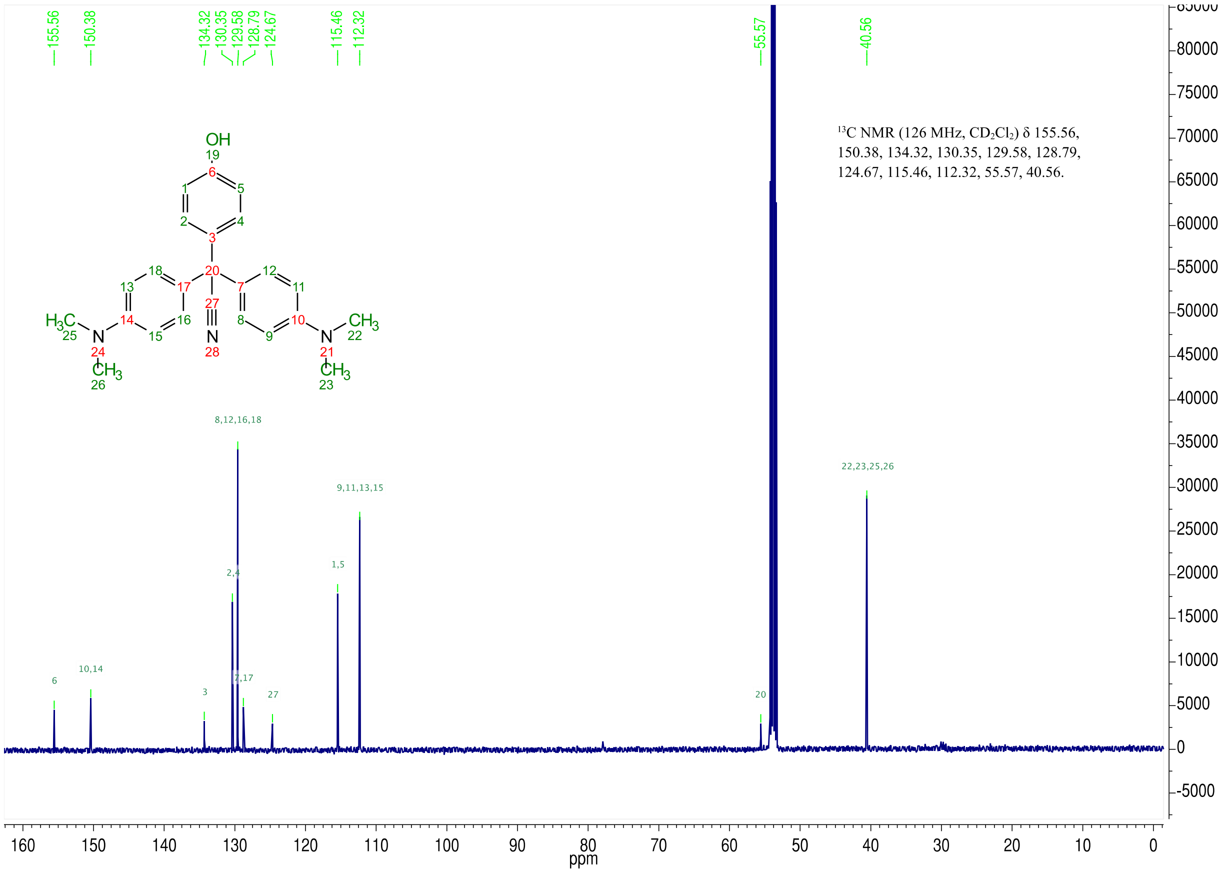


Figure SI-5. HMBC spectra (selected regions) of compound **1** in CD_2Cl_2



^{1}H NMR (500 MHz, Methylene Chloride-d2) δ 7.07 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 4H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 4H), 5.16 (s, 1H), 2.94 (s, 12H).

Figure SI-6. ^{1}H-NMR spectra of compound **3** in CD_2Cl_2



^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.56, 150.38, 134.32, 130.35, 129.58, 128.79, 124.67, 115.46, 112.32, 55.57, 40.56.

Figure SI-7. ^{13}C-NMR spectra of compound **3** in CD_2Cl_2

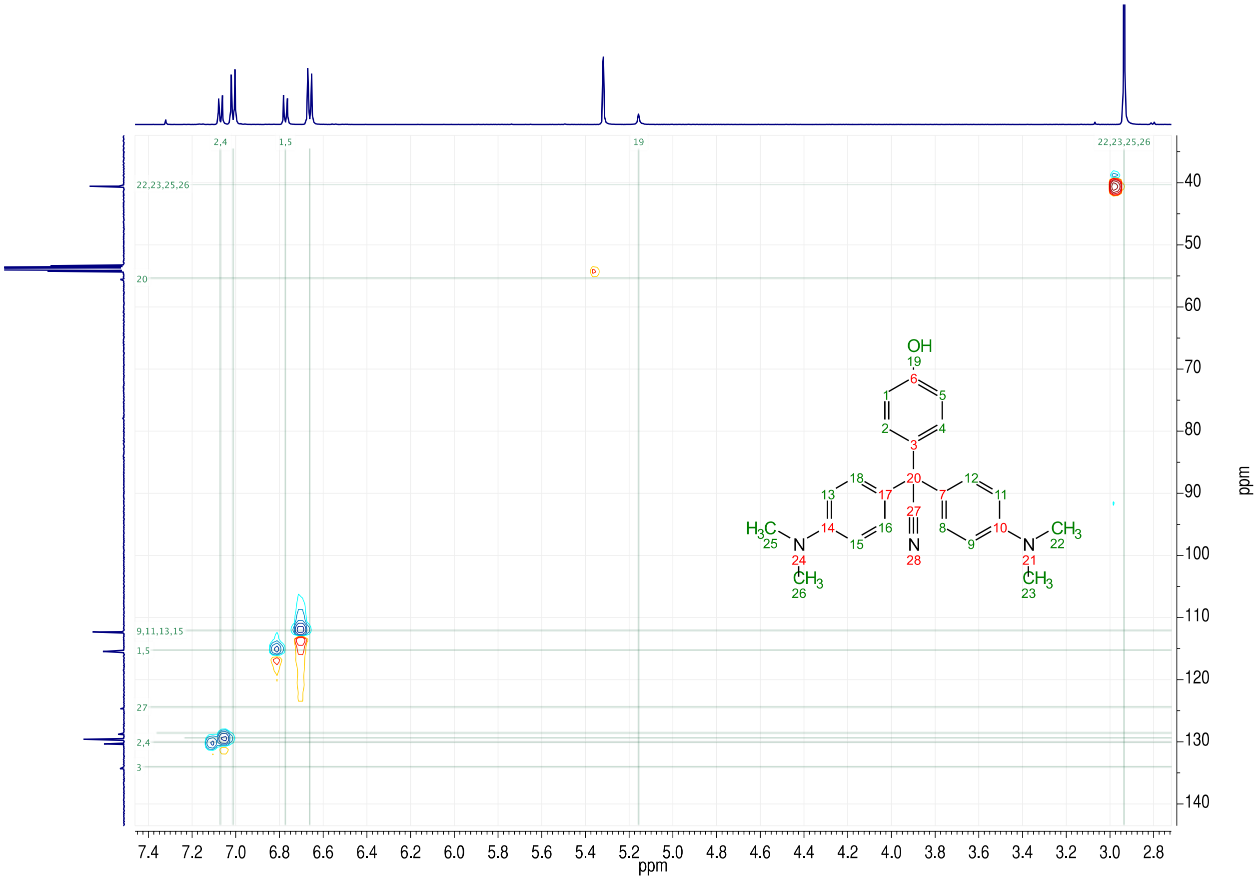


Figure SI-8. HSQC spectra (selected regions) of compound **3** in CD_2Cl_2

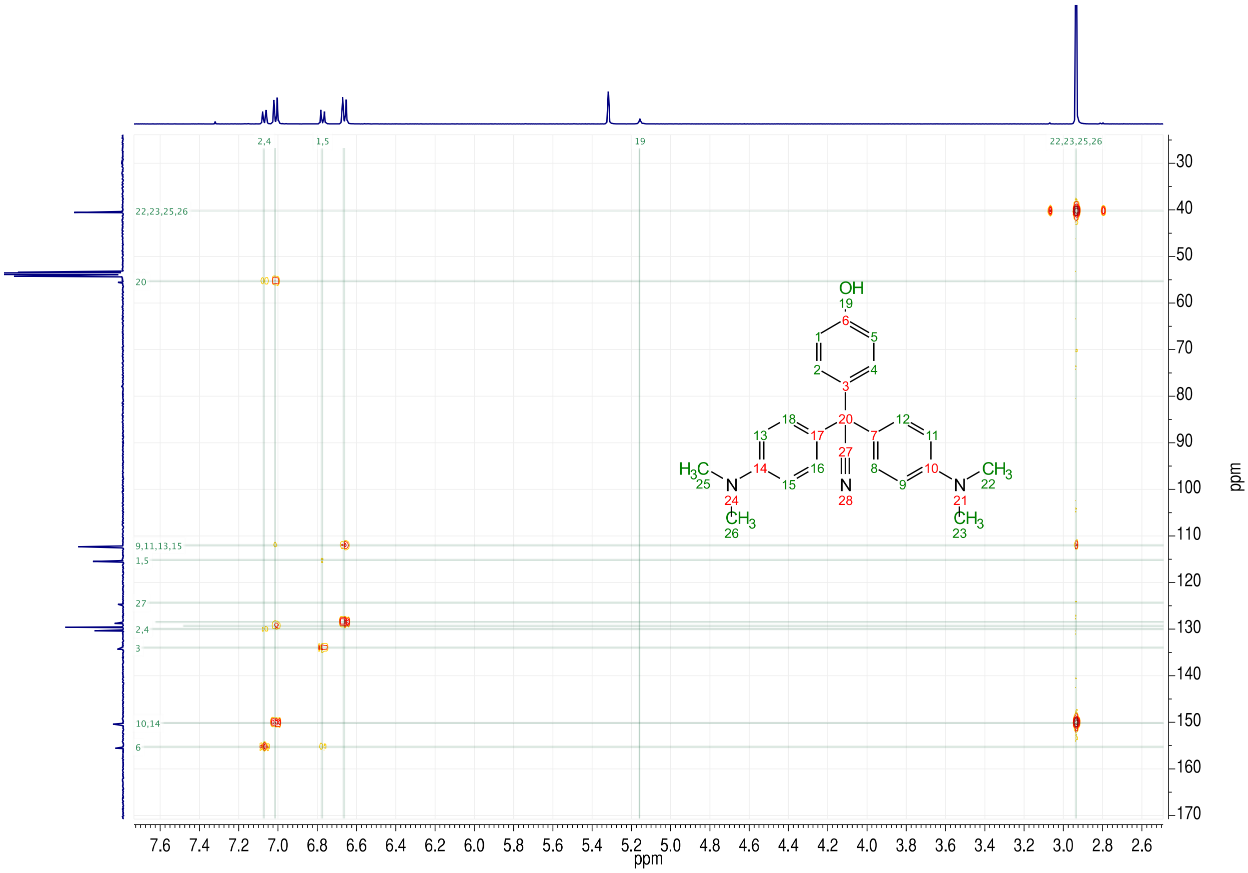


Figure SI-9. HMBC spectra (selected regions) of compound **3** in CD_2Cl_2

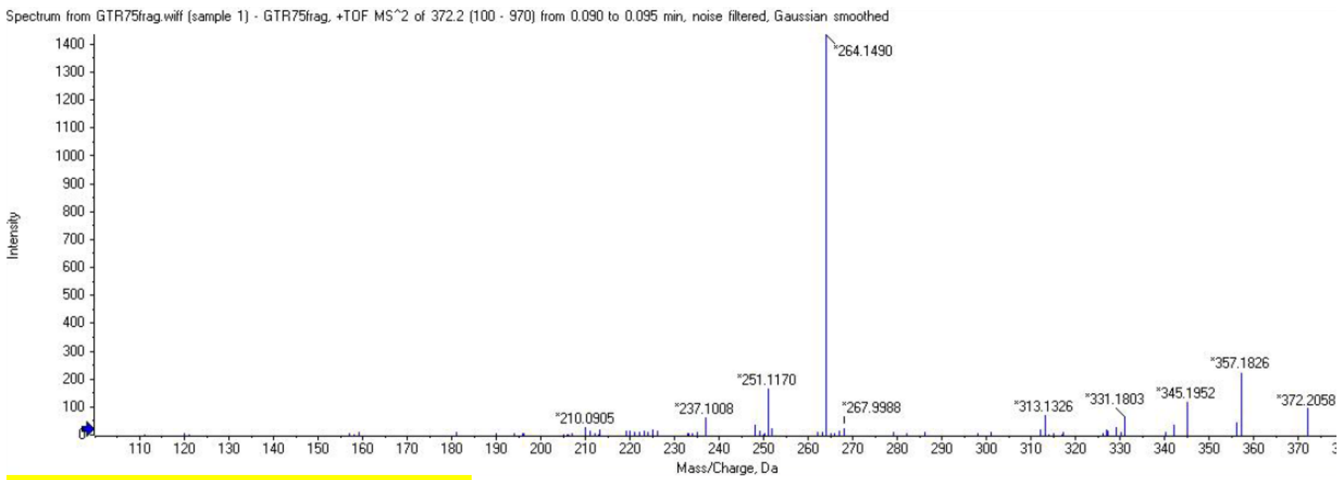


Figure SI-10. EI-HRMS spectra of compound **3**

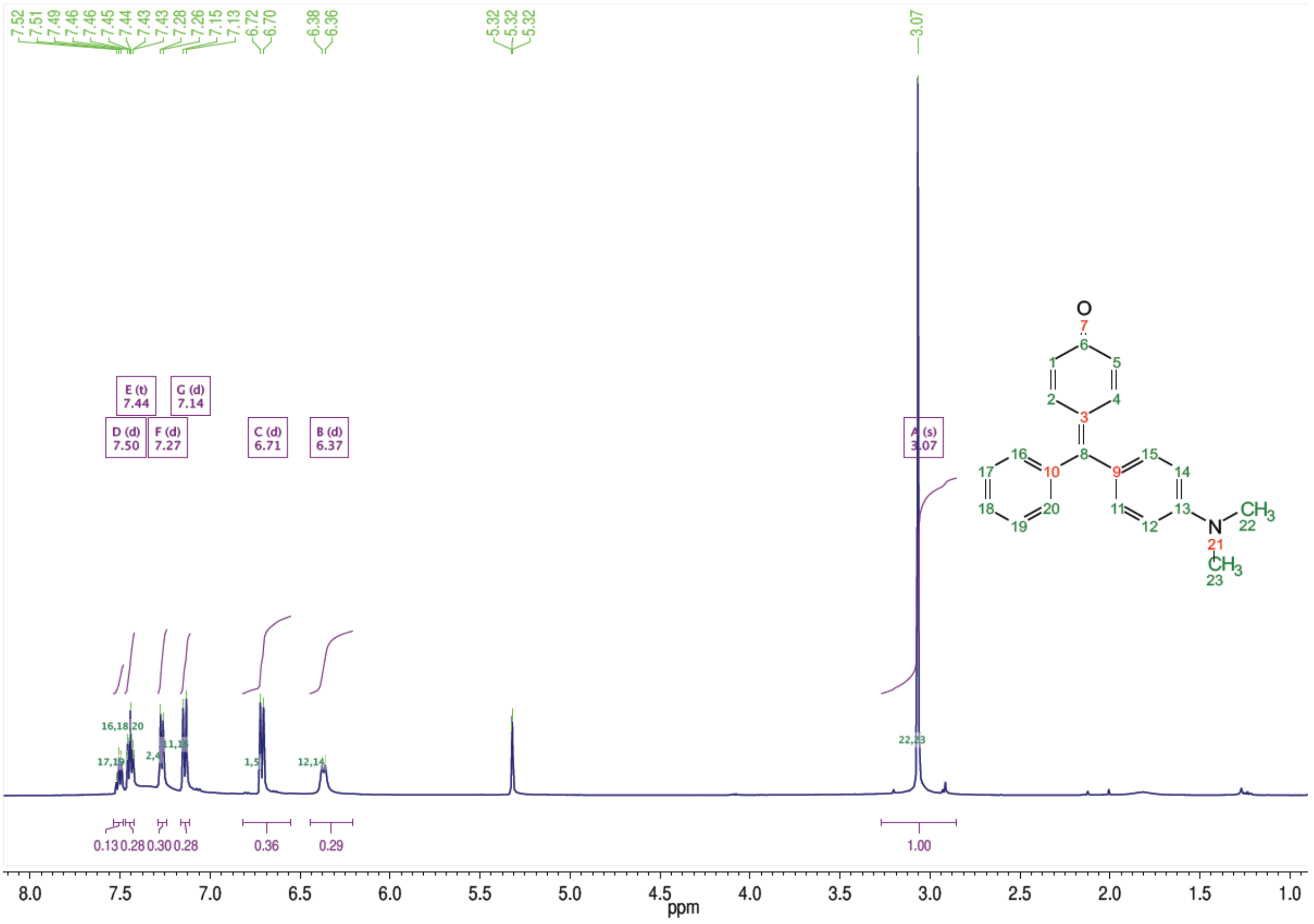


Figure SI-11. ^{1}H-NMR spectra of compound **2** in CD_2Cl_2

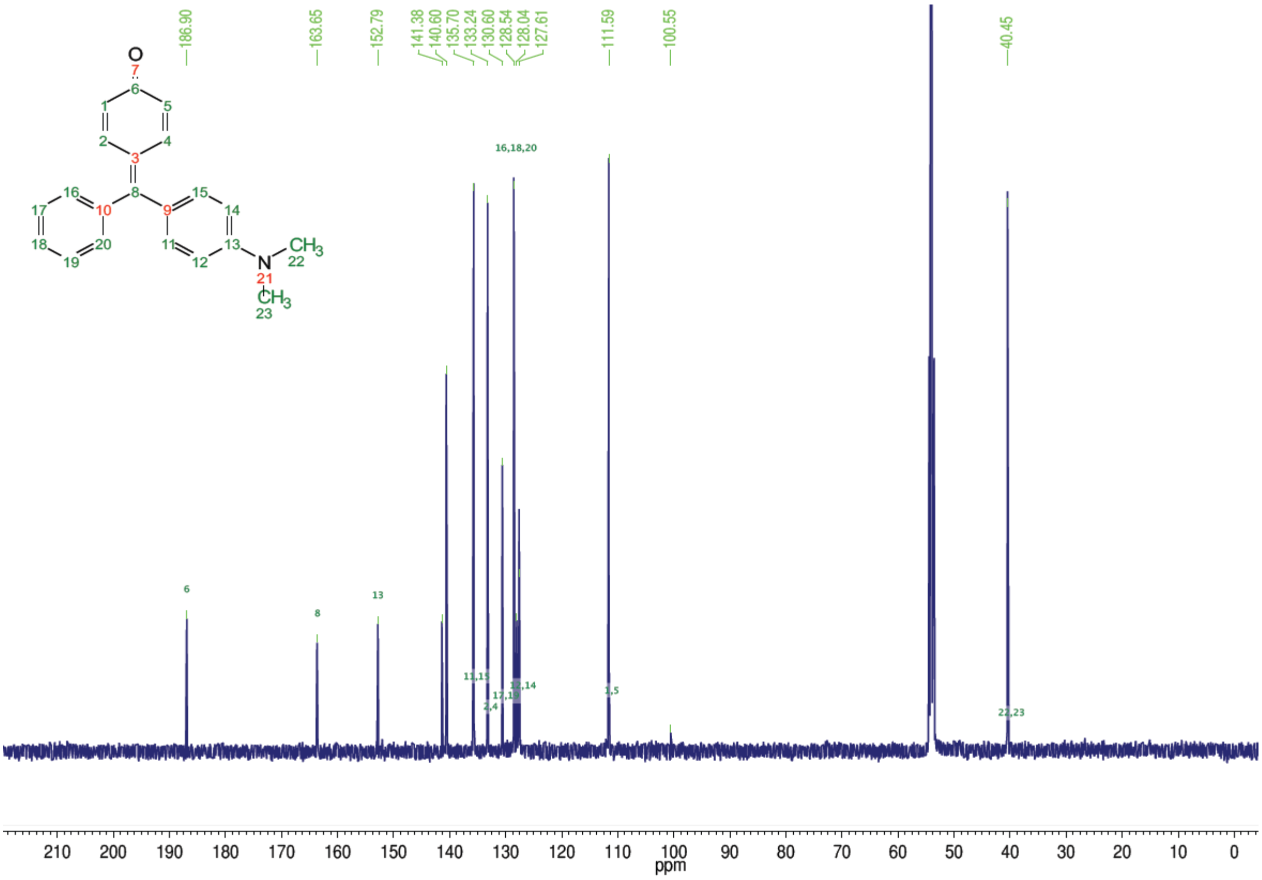


Figure SI-12. ^{13}C-NMR spectra of compound **2** in CD_2Cl_2

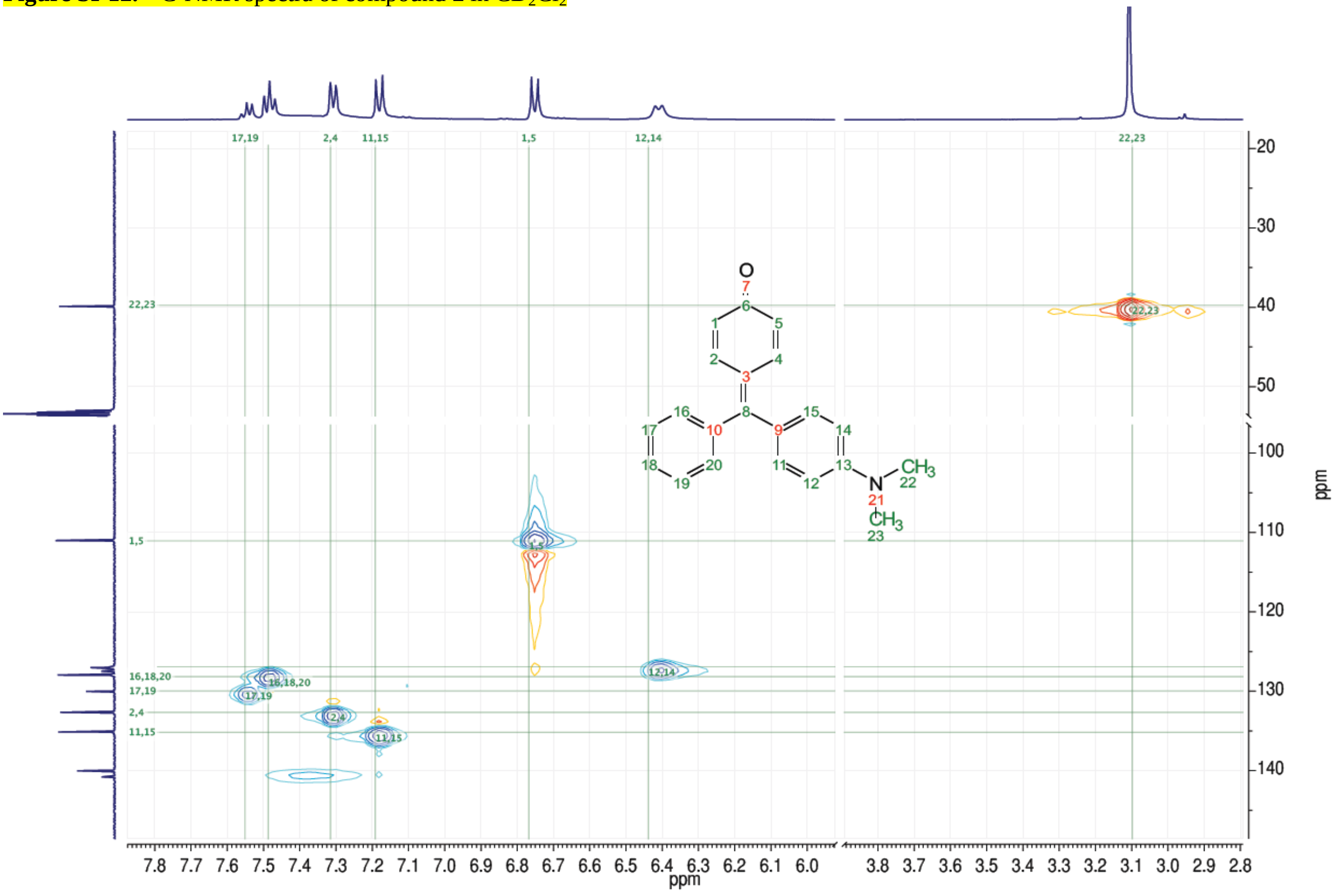


Figure SI-13. HC-HSQC spectra of compound **2** in CD_2Cl_2

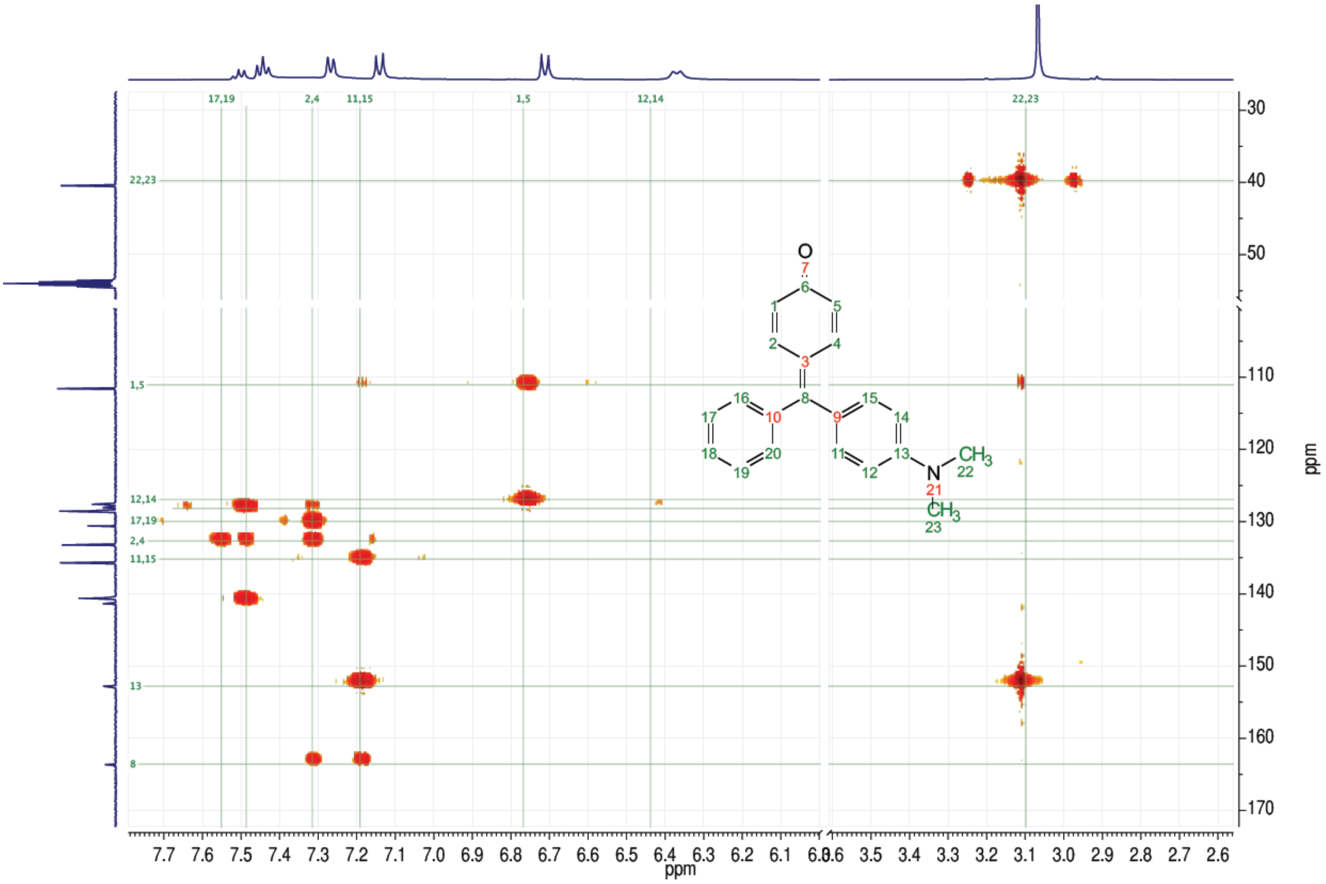
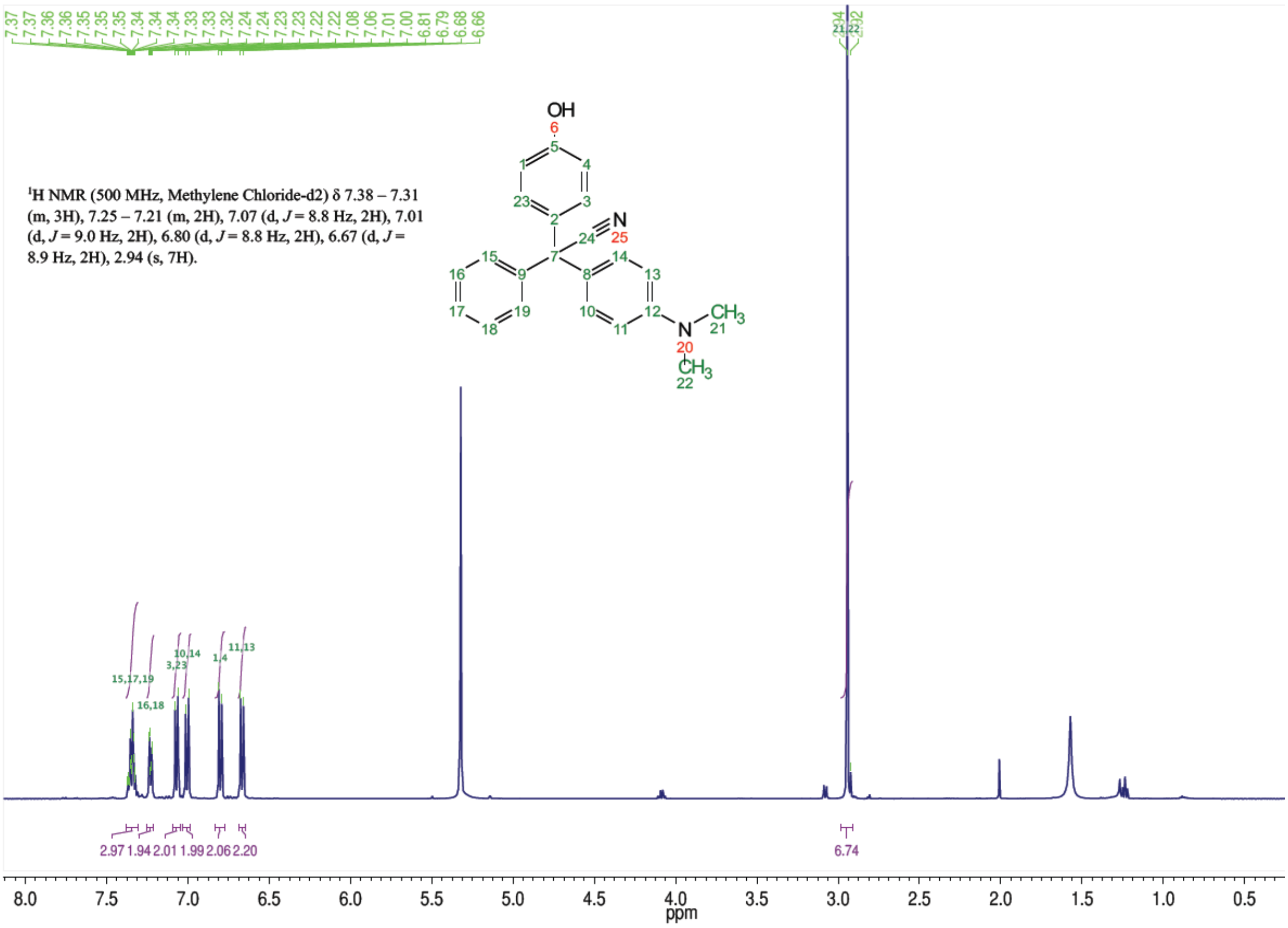


Figure SI-14. HC-HMBC spectra of compound **2** in CD_2Cl_2



^{1}H NMR (500 MHz, Methylene Chloride-d2) δ 7.38 – 7.31 (m, 3H), 7.25 – 7.21 (m, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.9 Hz, 2H), 2.94 (s, 7H).

Figure SI-15. H-NMR spectra of compound **4** in CD_2Cl_2

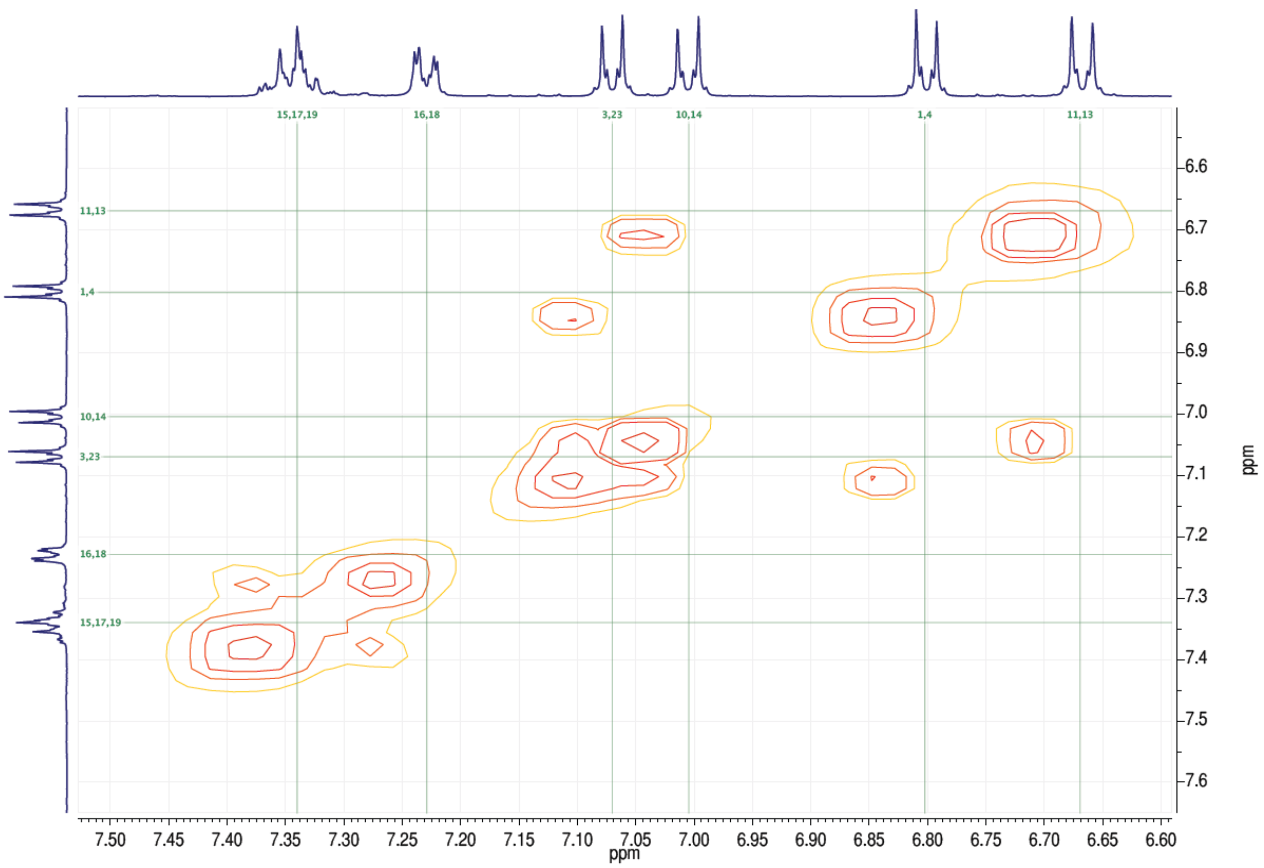
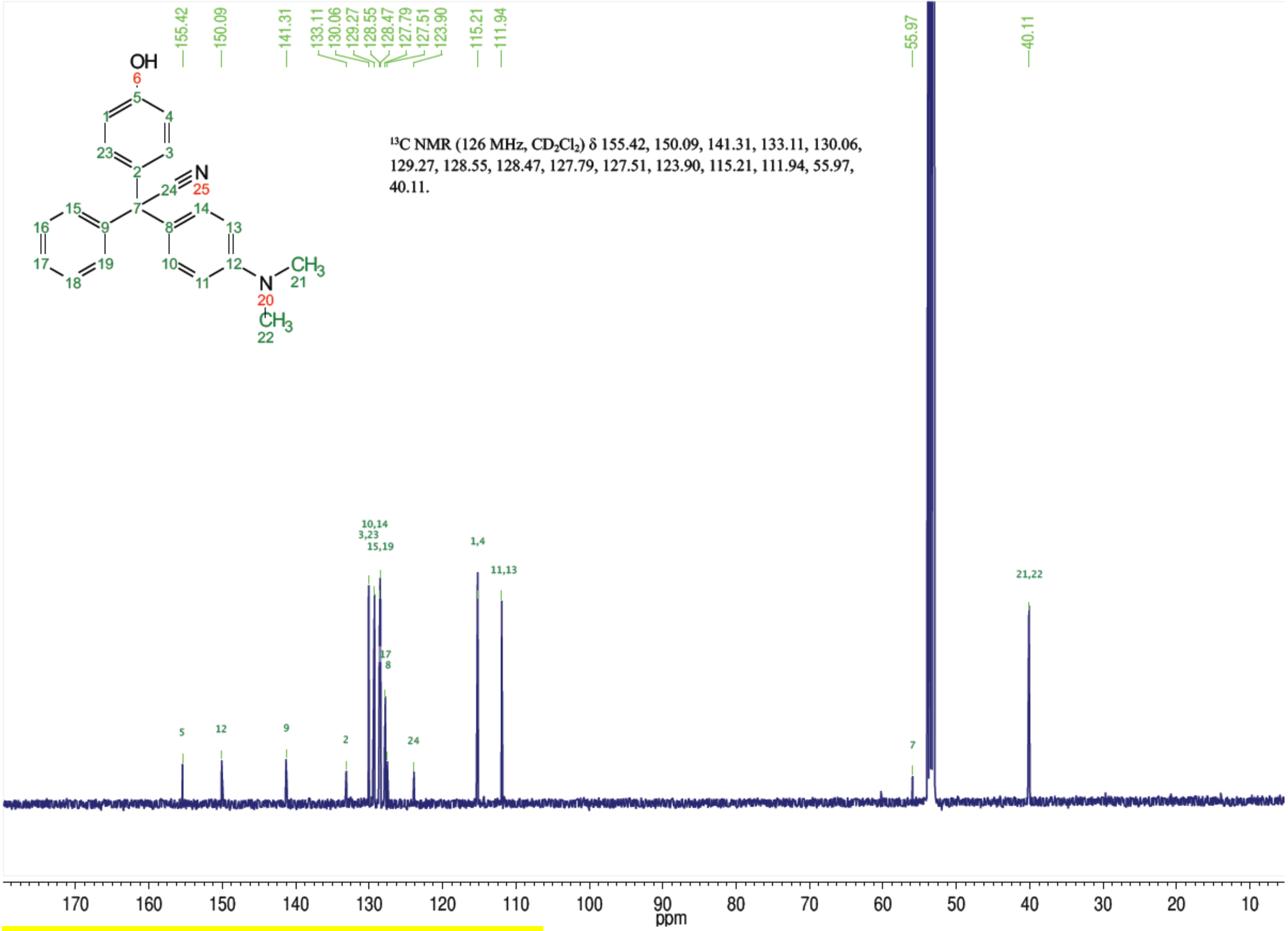


Figure SI-16. HH-COSY spectra (expansion) of compound **4** in CD_2Cl_2



^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.42, 150.09, 141.31, 133.11, 130.06, 129.27, 128.55, 128.47, 127.79, 127.51, 123.90, 115.21, 111.94, 55.97, 40.11.

Figure SI-17. C-NMR spectra of compound **4** in CD_2Cl_2

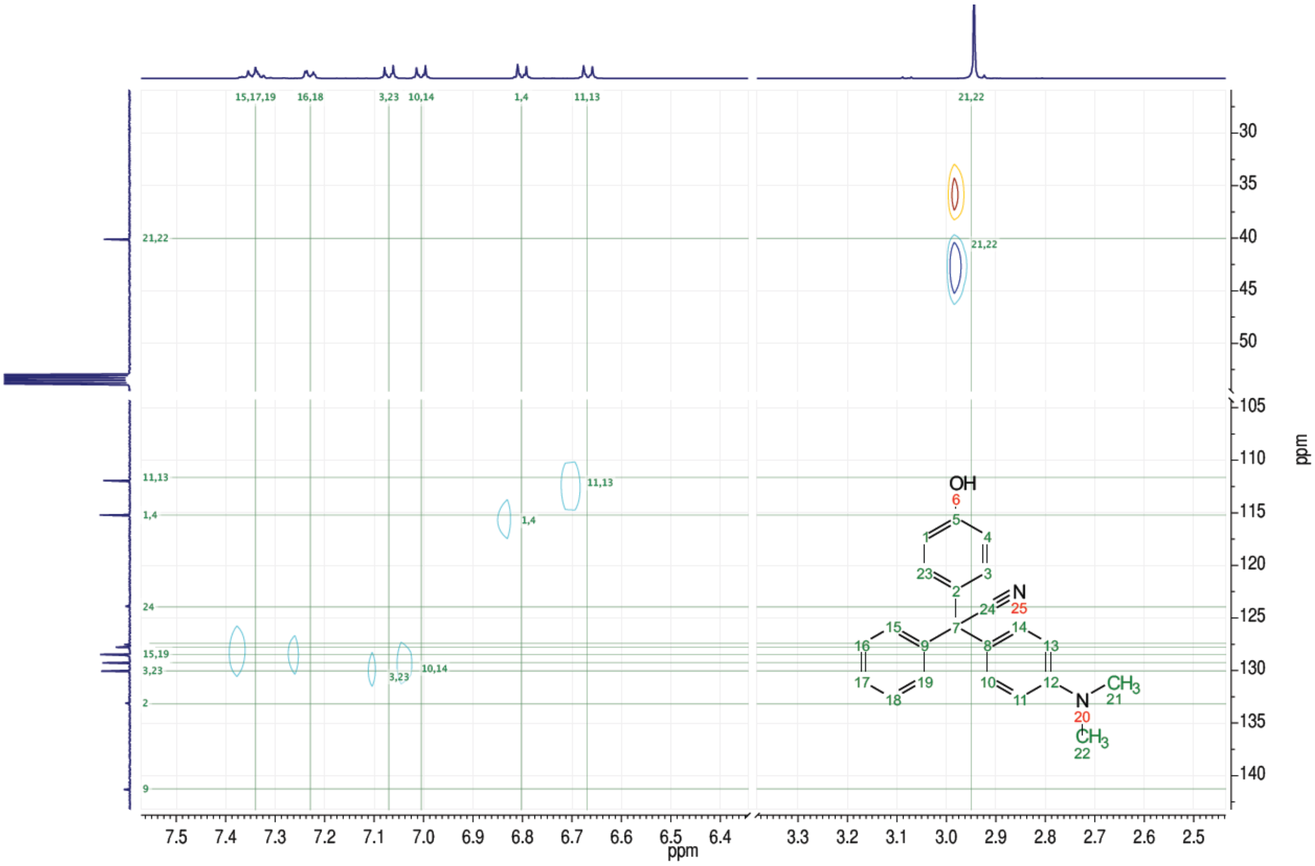


Figure SI-18. HC-HSQC spectra of compound **4** in CD_2Cl_2

Chromogenic detection of cyanide anion

1000 equivalents of F^-, Cl^-, Br^-, CN^-, HS^-, SCN^-, AcO^-, and HPO_4^{2-} anions were added to 2 ml aliquots of a 1.0 x 10^{-5} M water:acetonitrile (99:1) solution of **1** (pH 10.6 Borax/HCl), and the mixtures were allowed to react at 293 K. Then, the absorption intensity of the samples at 563 nm was measured. While cyanide anion is able to complete bleach of the solution, other anions (F^-, Cl^-, Br^-, OAc^-, HPO_4^{2-}) induced negligible changes in the visible band (less than 6% decrease). The only potential interferent was HS^- (27% of decrease) (see Figure SI-1).

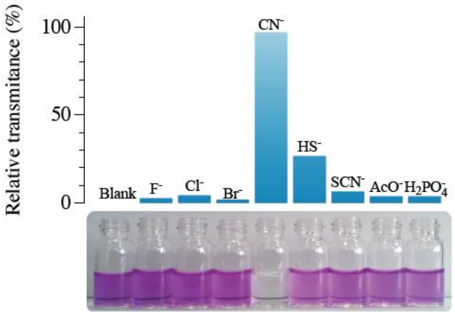


Figure SI-19. (Bottom) color changes of **1** (2 ml, 1.0 x 10^{-5} M, borax buffer, pH 10.6, 1% acetonitrile), after addition of 1000 equivalents of cyanide or other possible interferent anions. From left to right: **(1), (1)** + F^-, **(1)** + Cl^-, **(1)** + Br^-, **(1)** + CN^-, **(1)** + HS^-, **(1)** + SCN^-, **(1)** + AcO^-, and **(1)** + HPO_4^{2-}. Anions were added as 20 μL aliquots of 1 M aqueous solutions. F^-, Cl^-, HS^-, HPO_4^{2-}, and AcO^- where added as Na^+ salts, the rest were added as K^+ salts. (Top) relative transmitance $((A_0-A)/A_0)\cdot 100$ of the different samples. Temperature 293 K.

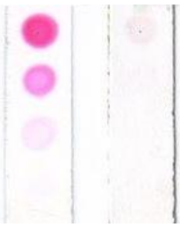


Figure SI-20. Fotography of sensing strips containing different amounts of **1** (from top to bottom: 5.00, 0.50, 0.05 and 0.005 nmol) adsorbed onto an aminated silica support before (left) and after (right) exposure to 50 ppm of HCN.

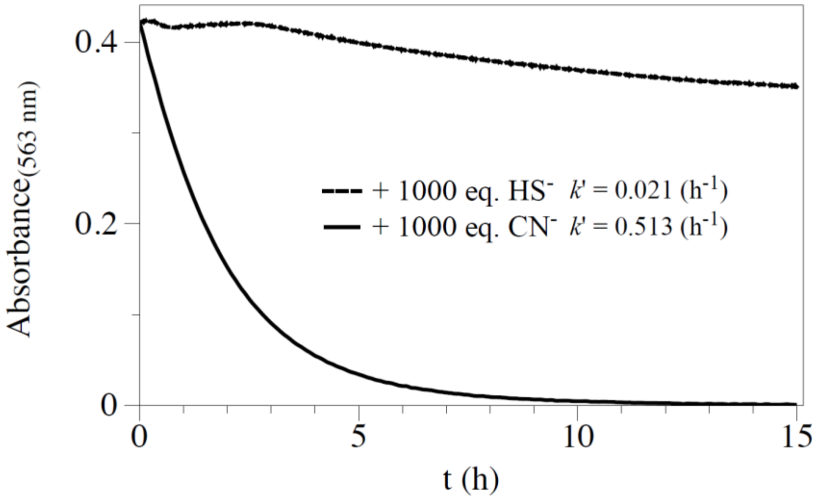


Figure SI-21. Kinetic plot of the absorption band at 563 nm of compound **1** (1.0 x 10^{-5} M, borax buffer, pH 10.6, 1% acetonitrile) in the presence of a)1000 equivalents of KCN and b) 1000 equivalents of NaSH

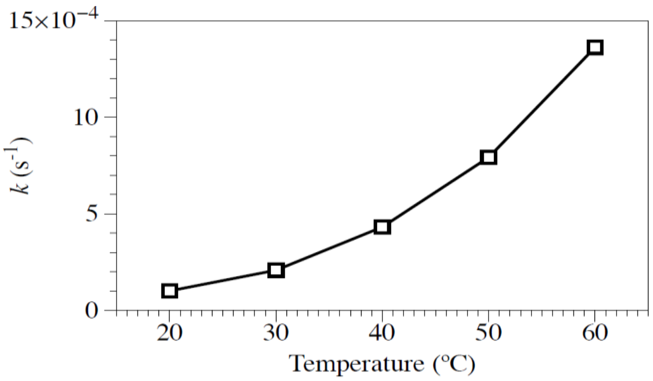


Figure SI-22. Kinetic plot of **1** with 1000 equivalents of KCN at diverse temperatures At pH=10.6, compound **1** has a half life time of $t_{1/2}$=1.89 hr at 293 K in the presence of cyanide. In order to decrease detection times, kinetic experiments at different temperatures were carried out. Following a similar procedure under thermostated conditions the rate constants at different temperatures were determined. From the Arrhenius plot (ln(k_r) *vs* T^{-1}) of this data its activation energy E_a= 23.029 kJ·mol^{-1}was obtained.

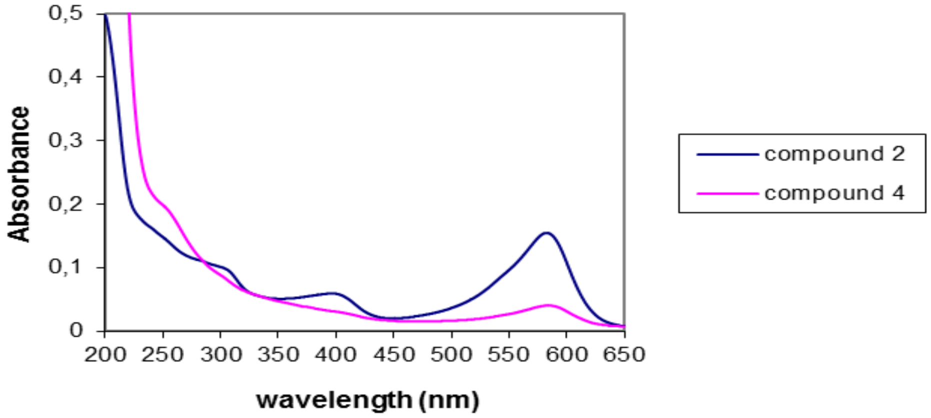


Figure SI-23. UV-vis spectra of compound **2** (1.0 x 10^{-5} M, borax buffer, pH 10.6, 1% acetonitrile), (in blue) and after addition of 100 equivalents of KCN (in magenta, Compound **4**).

Chemodosimeter regeneration

As published in the literature, most leuco cyanides undergo photoionic dissociation under ultraviolet light. Numerous physicochemical studies about the nature of the mechanism of this photonic driven reaction have been carried out. In these studies the heterolytic rupture of the C-C bond, that linked the cyano moety with the leuco form, is the key step. Therefore, we studied the possibility of using this photochemicaly driven reaction to develop a simple and fast chemodosimeter regeneration method. Samples using chemodosimeter **2** were prepared as decribed before, and treated with potassium cyanide and other selected anions. After complete bleaching, the sample was placed under the radiation of a 50 watt UV lamp at 254 nm. Under these conditions, the sample got colored after 2 minutes irradiation (see Figure SI-24). The UV-vis spectrum of these colored samples was identical to the UV of compound **2**. Based on the absorbance values (see Figure SI-25), around a 95% recovery was calculated. In addition, in the mass spectrum of the recovered compound a molecular peak compatible with structure **2** was detected**.** These data demonstrate the success of the regeneration process.

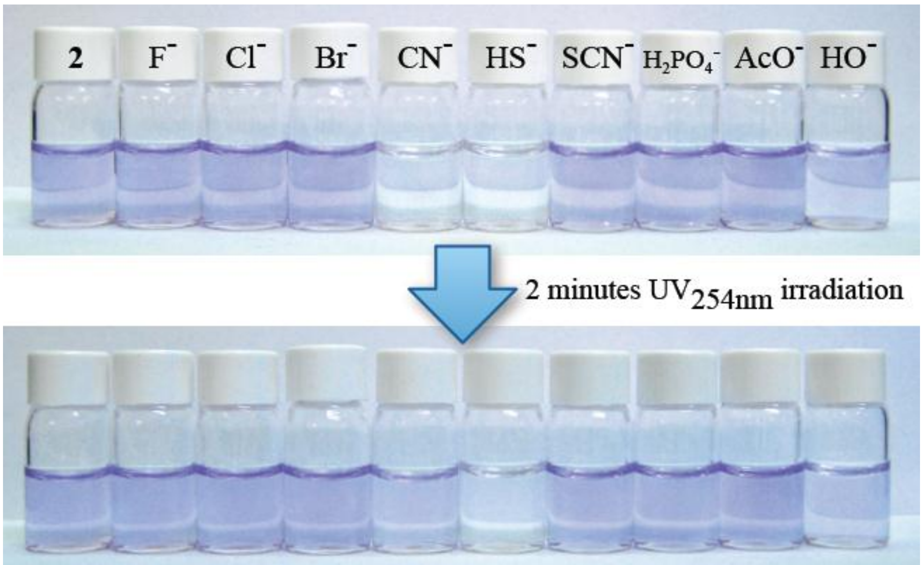


Figure SI-24. Top: color changes of **2** (2 ml, 1.0 x 10^{-5} M, borax buffer, pH 10.6, 1% acetonitrile), after addition of 1000 equivalents of cyanide and other possible interfering anions. From left to right: **(2), (2)** + F$^-$, **(2)** + Cl$^-$, **(2)** + Br$^-$, **(2)** + CN$^-$, **(2)** + SH$^-$, **(2)** + SCN$^-$, **(2)** + OAc$^-$, **(2)** + HPO_4^{2-}, **(2)** + OH$^-$. Anions were added as 20 µL aliquots of 1 M solutions. F$^-$, Cl$^-$, SH$^-$, HPO_4^{2-}, AcO$^-$ and OH$^-$ where added as Na$^+$ salts, the rest was added as K$^+$ salts. Bottom: same samples after 2 minutes exposure to 50 W of UV$_{254nm}$ light.

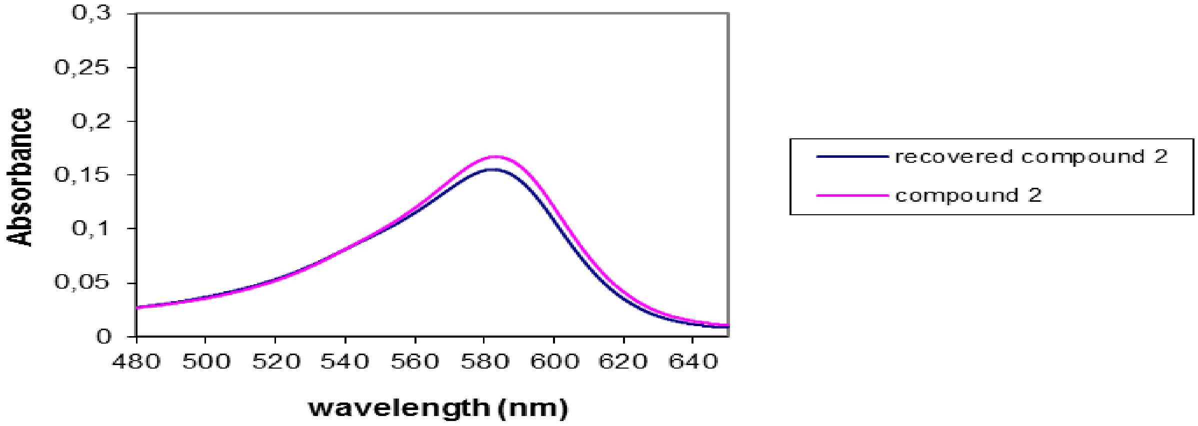


Figure SI-25. Vis spectra of compound **2** (1.0 x 10^{-5} M, borax buffer, pH 10.6, 1% acetonitrile) (in magenta), and after addition of 100 equivalents of KCN followed by 2 minutes irradiation under a 50 W of UV$_{254nm}$ light (in blue).