Synthesis of polyhalo 2-aryl-4-aminoquinazolines and 3-aminoindazoles as anticancer agents

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Supporting Information

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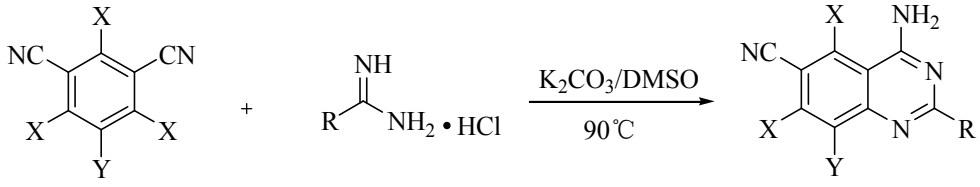
General Information

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, and deuterated DMSO-d_6 was used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMs were performed on a Agllent LC/Msd TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh). Compounds **1~2** were purchased from Aldrich Corporation Limited.

General Procedure for the Preparation of Polyhalo 2-Aryl-4-aminoquinazolines 3



1a: X = F, Y = F
1b: X = F, Y = Cl
1c: X = Cl, Y = Cl

2

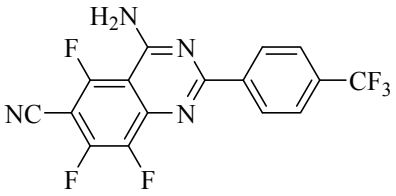
X = F, Cl; Y = F, Cl

3

A 25 mL round-bottom flask was charged with isophthalonitrile derivatives **1** (2 mmol), amidine hydrochlorides **2** (2 mmol) and DMSO (10 mL), then the solution was added to K_2CO_3 (6 mmol), and the mixture was heated 90 °C. The resulting solution was stirred for 2–8 h until the isophthalonitrile derivatives **1** was completely consumed. The reaction mixture was poured into 25 mL of water and filtered to obtain the crude products, which were purified by column chromatography (petroleum ether/EtOAc = 5:1) to afford product **3** with 70–93% yield. The products were further identified by FTIR, NMR and HRMS, being in good agreement with the assigned structures.

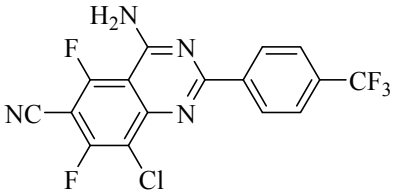
Spectroscopic Data of Polyhalo 2-Aryl-4-aminoquinazolines 3

4-Amino-5,7,8-trifluoro-2-(4-(trifluoromethyl)phenyl)quinazoline-6-carbonitrile (3a)



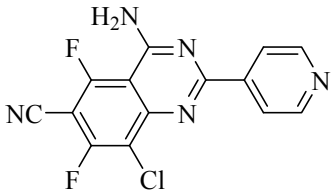
Slight yellow solid, mp: 224–225°C. IR (KBr): 3494, 3388, 2243, 1639, 1554, 1464, 1317, 1134, 930 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.85 (d, J = 8.3 Hz, 2H, ArH), 8.16 (br, 1H, NH_2), 8.48 (d, J = 8.3 Hz, 2H, PhH), 8.90 (br, 1H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.4, 159.3, 158.0 (d, J = 267.5 Hz), 150.5, 146.3, 141.6, 140.5, 131.3–131.8 (m), 129.3, 125.7, 123.4, 109.3, 101.1 (d, J = 11.3 Hz), 87.6 (d, J = 18.8 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): δ -61.3 (s, 3F), -103.4 (s, 1F), -129.2 (d, J = 18.8 Hz, 1F), -153.3 (d, J = 14.1 Hz, 1F). HRMS (TOF ES^-): *m/z* calcd for $C_{16}H_5F_6N_4$ [$(M\text{-}H^+)$], 367.0424; found, 367.0427.

4-Amino-8-chloro-5,7-difluoro-2-(4-(trifluoromethyl)phenyl)quinazoline-6-carbonitrile (3b)



Slight yellow solid, mp: 220–221°C. IR (KBr): 3503, 3401, 2239, 1631, 1554, 1444, 1321, 1134, 738 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.87 (d, J = 7.3 Hz, 2H, PhH), 8.03 (br, 1H, NH_2), 8.52 (d, J = 7.3 Hz, 2H, PhH), 8.93 (br, 1H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.4 (d, J = 50.0 Hz), 160.0, 159.2, 157.1, 152.3, 140.6, 131.8 (t, J = 31.3 Hz), 129.3, 127.7, 127.7, 125.7, 123.4, 109.4, 101.3, 88.2. HRMS (TOF ES^-): *m/z* calcd for $C_{16}H_5ClF_5N_4$ [$(M\text{-}H^+)$], 383.0128; found, 383.0130.

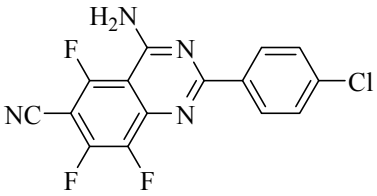
4-Amino-8-chloro-5,7-difluoro-2-(pyridin-4-yl)quinazoline-6-carbonitrile (3c)



Slight yellow solid, mp: 275–276°C. IR (KBr): 3447, 2922, 2235, 1625, 1531, 1452, 1337, 1207, 738 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.27 (d, J = 20.3 Hz, 2H, NH_2), 8.82 (s, 2H,

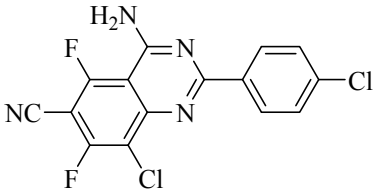
PhH), 9.06 (s, 2H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.4 (d, J = 27.5 Hz), 160.3, 159.4, 157.4, 152.4, 150.7, 144.4, 128.4, 122.5, 109.5, 101.7 (d, J = 11.25 Hz), 88.7. HRMS (TOF ES$^-$): *m/z* calcd for $C_{14}H_5ClF_2N_5$ [(M-H$^+$)], 316.0207; found, 316.0210.

4-Amino-2-(4-chlorophenyl)-5,7,8-trifluoroquinazoline-6-carbonitrile (3d)



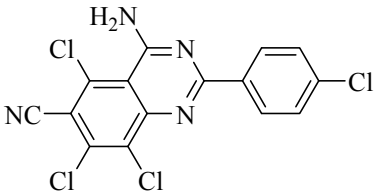
White solid, mp: 235–236°C. IR (KBr): 3457, 3403, 2239, 1623, 1547, 1461, 1349, 1092, 747 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.57 (s, 2H, PhH), 8.35(s, 2H, PhH), 8.00 (t, J = 2.25 Hz, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.0, 159.4, 157.1, 150.7, 146.6, 141.6, 137.1, 135.8, 130.6 129.0, 109.5, 101.1, 86.9. ^{19}F NMR (470 MHz, DMSO-d_6): δ -103.5 (d, J = 14.1 Hz, 1F), -129.5 (d, J = 18.8 Hz, 1F), -153.7 (t, J = 18.8 Hz, 1F). HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_5ClF_3N_4$ [(M-H$^+$)], 333.0160; found, 333.0157.

4-Amino-8-chloro-2-(4-chlorophenyl)-5,7-difluoroquinazoline-6-carbonitrile (3e)



Slight yellow solid, mp: 240–241°C. IR (KBr): 3467, 3397, 2231, 1618, 1537, 1399, 1330, 1088, 673 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60 (s, 2H, PhH), 8.43 (s, 2H, PhH), 7.96 (d, J = 8.7 Hz, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.3, 160.3 (d, J = 37.5 Hz), 157.1, 152.3, 137.1, 135.6 (t, J = 18.8 Hz), 130.5 (t, J = 11.3 Hz), 132.1, 129.0, 126.9, 111.8, 102.9, 97.0. HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_5Cl_2F_2N_4$ [(M-H$^+$)], 348.9865; found, 348.9869.

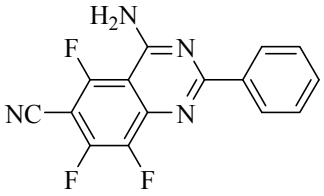
4-Amino-5,7,8-trichloro-2-(4-chlorophenyl)quinazoline-6-carbonitrile (3f)



Slight yellow solid, mp: 275–276°C. IR (KBr): 3441, 3387, 2231, 1618, 1533, 1407, 1321, 1090, 755 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.62 (d, J = 8.2 Hz, 2H, PhH), 8.44 (d, J = 7.9, 2H, PhH), 8.24 (br, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.1, 161.09 (d, J = 50.0 Hz), 152.2, 141.4, 139.6, 137.1, 136.2, 135.6 (d, J = 12.5 Hz), 130.6, 129.1, 114.3, 110.8

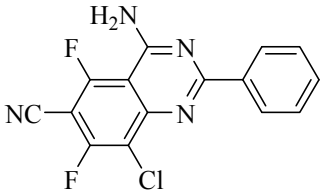
(d, J = 62.5 Hz), 105.6. HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_5Cl_4N_4$ [(M-H$^+$)], 379.9196; found, 379.9193.

4-Amino-5,7,8-trifluoro-2-phenylquinazoline-6-carbonitrile (3g)



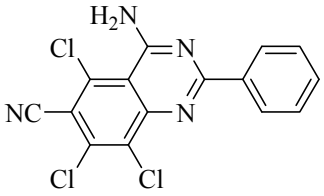
Yellow solid, mp: 220–221°C. IR (KBr): 3507, 3347, 2235, 1618, 1548, 1468, 1352, 1109, 699 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52 (s, 3H, PhH), 8.40 (s, 2H, PhH), 7.89 (br, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.9, 159.3, 157.1, 152.1, 150.5, 148.4, 146.7, 141.6, 139.6, 136.9, 131.9 (d, J = 65.0 Hz), 128.4 (t, J = 86.3 Hz) 109.5, 100.9, 87.0. ^{19}F NMR (470 MHz, DMSO-d_6): δ -103.5 (s, 1F), -129.8 (d, J = 18.8 Hz, 1F), -153.8 (d, J = 18.8 Hz, 1F). HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_6F_3N_4$ [(M-H$^+$)], 299.0550; found, 299.0553.

4-Amino-8-chloro-5,7-difluoro-2-phenylquinazoline-6-carbonitrile (3h)



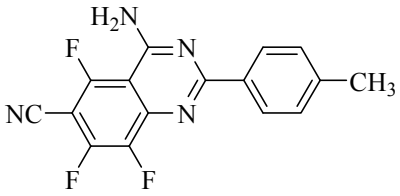
Slight yellow solid, mp: 224–225°C. IR (KBr): 3500, 3343, 2239, 1633, 1550, 1446, 1351, 1207, 690 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.50-7.56 (m, 3H, PhH), 8.41 (d, J = 7.1 Hz, 2H, PhH), 7.91 (br, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.2, 164.5, 162.8, 159.6-160.6, 157.6, 153.0, 137.31, 132.5 (d, J = 26.25 Hz), 129.2 (d, J = 15.0 Hz), 113.6 (d, J = 11.3 Hz), 110.0, 101.5 (d, J = 8.8 Hz), 88.1 (t, J = 22.5 Hz). HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_6ClF_2N_4$ [(M-H$^+$)], 315.0255; found, 315.0254.

4-Amino-5,7,8-trichloro-2-phenylquinazoline-6-carbonitrile (3i)



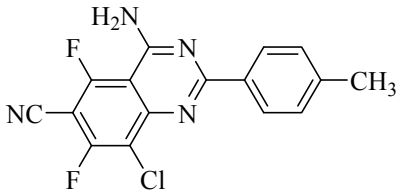
Slight yellow solid, mp: 273–274°C. IR (KBr): 3503, 3380, 2227, 1611, 1537, 1452, 1395, 1207, 683 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.68 (s, 3H, PhH), 8.40 (d, J = 8.6 Hz, 2H, PhH), 7.91 (d, J = 8.7, 2H, NH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 180.0, 163.2, 161.7, 152.3, 141.6, 139.6, 136.8, 132.1, 128.9, 114.4, 110.3-111.0 (d, J = 78.75 Hz), 105.5. HRMS (TOF ES$^-$): *m/z* calcd for $C_{15}H_6Cl_3N_4$ [(M-H$^+$)], 346.9664; found, 346.9662.

4-Amino-5,7,8-trifluoro-2-p-tolylquinazoline-6-carbonitrile (3j)



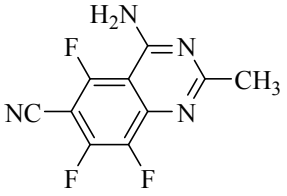
Slight yellow solid, mp: 245–246°C. IR (KBr): 3400, 2924, 2239, 1635, 1556, 1413, 1353, 1090, 745 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.33 (s, 2H, PhH), 8.32 (s, 2H, PhH), 7.83 (br, 2H, NH_2), 2.46 (d, J = 55.5 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.1, 159.4 (d, J = 18.8 Hz), 157.2, 148.5, 146.8, 134.3, 129.7 (d, J = 47.5 Hz), 128.8 (d, J = 40.0 Hz), 109.6, 100.9, 88.6, 21.5. HRMS (TOF ES^-): m/z calcd for $C_{16}H_8F_3N_4$ [$(M-H^+)$], 313.0707; found, 313.0706.

4-Amino-8-chloro-5,7-difluoro-2-p-tolylquinazoline-6-carbonitrile (3k)



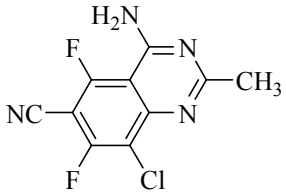
Slight yellow solid, mp: 250–251°C. IR (KBr): 3480, 3060, 2235, 1638, 1557, 1460, 1321, 1089, 726 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34 (s, 2H, PhH), 8.37 (s, 2H, PhH), 7.87 (br, 2H, NH_2), 2.45 (d, J = 51.0 Hz, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.2, 162.3, 160.1 (d, J = 41.3 Hz), 157.1, 152.7, 142.3, 134.2, 129.5, 128.9 (d, J = 31.3 Hz), 124.2, 109.7, 101.1, 87.4, 21.5. HRMS (TOF ES^-): m/z calcd for $C_{16}H_8ClF_2N_4$ [$(M-H^+)$], 329.0411; found, 329.0413.

4-Amino-5,7,8-trifluoro-2-methylquinazoline-6-carbonitrile (3l)



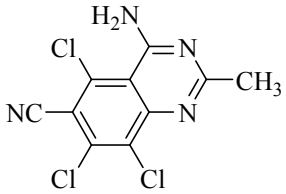
Slight yellow solid, mp: 229–231°C. IR (KBr): 3433, 3123, 2243, 1652, 1554, 1407, 1334, 1019, 787 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.84 (br, 2H, NH_2), 2.48 (d, J = 31.4 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.4, 159.0 (d, J = 55.0 Hz), 151.7, 150.1, 148.1, 146.2, 141.0, 109.4, 100.2, 88.7, 26.4. HRMS (TOF ES^-): m/z calcd for $C_{10}H_4F_3N_4$ [$(M-H^+)$], 237.0394; found, 237.0396.

4-Amino-8-chloro-5,7-difluoro-2-methylquinazoline-6-carbonitrile (3m)



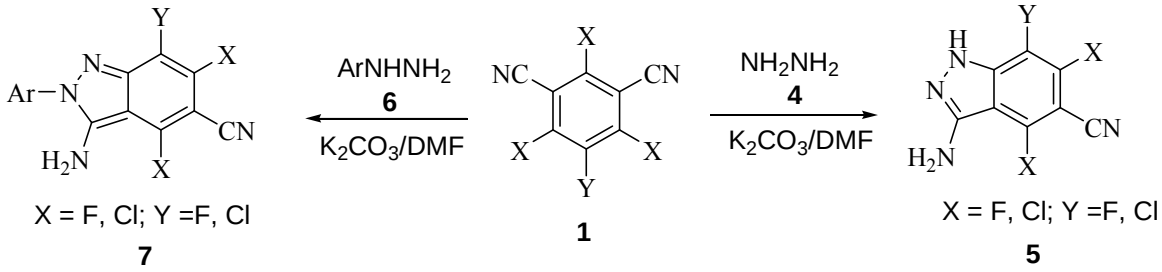
Slight yellow solid, mp: 222–223°C. IR (KBr): 3446, 3128, 2239, 1627, 1558, 1403, 1330, 1199, 828 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.72 (br, 2H, NH2), 2.49 (d, J = 19.9 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.0, 168.8, 160.3, 159.4 (t, J = 27.5 Hz), 157.0, 152.2, 112.3, 109.5, 100.5 (d, J = 10.0 Hz), 87.5 (d, J = 20.0 Hz). HRMS (TOF ES^-): *m/z* calcd for $C_{10}H_4ClF_2N_4$ [$(M-H^+)$], 253.0098; found, 253.0097.

4-Amino-5,7,8-trichloro-2-methylquinazoline-6-carbonitrile (3n)



Slight yellow solid, mp: 249–250°C. IR (KBr): 3464, 2231, 1652, 1539, 1407, 1305, 1041, 730 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.00 (br, 2H, NH_2), 2.50 (d, J = 9.9 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.7, 161.2, 151.9, 139.4, 135.7 (d, J = 38.8 Hz), 130.0, 114.2, 110.2, 103.8, 26.3. HRMS (TOF ES^-): *m/z* calcd for $C_{10}H_4Cl_3N_4$ [$(M-H)^-$], 284.9507; found, 284.9510.

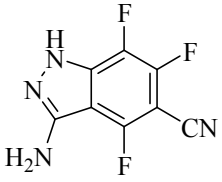
General Procedure for the Preparation of Polyhalo 3-Aminoindazoles 5 and 7



A 25 mL round-bottom flask was charged with isophthalonitrile derivatives **1** (2 mmol), DMF (10 mL) and K_2CO_3 (6 mmol). The solution was cooled to 0 °C by ice bath. The hydrazine hydrate **4** or phenylhydrazine **6** (2.4 mmol) was added. After a few minutes, the resulting solution was stirred for 4 h at room temperature until the isophthalonitrile derivatives **1** was completely consumed. The reaction mixture was poured into 25 mL of ice water and filtered to obtain the crude products, which were purified by column chromatography (petroleum ether/EtOAc = 2:1) to afford product **5** or **7** with 70–87% yield. The products were further identified by FTIR, NMR and HRMS, being in good agreement with the assigned structures.

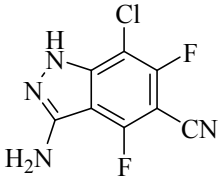
Spectroscopic Data of Polyhalo 3-Aminoindazoles 5 and 7

3-Amino-4,6,7-trifluoro-1*H*-indazole-5-carbonitrile (5a)



Slight yellow solid, mp: 193–194°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.92 (br, 2H, NH_2), 13.12 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 155.5, 153.4, 149.3, 133.8 (d, J = 20.0 Hz), 131.1, 110.7, 102.6, 80.1. IR (KBr): 3499, 2239, 1648, 1574, 1521, 1395, 1268, 901, 820 cm^{-1}. HRMS (TOF ES$^-$): *m/z* calcd for $C_8H_2F_3N_4$ [(M-H)$^-$], 211.0237; found, 211.0239.

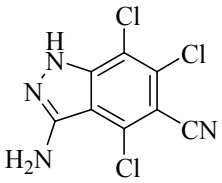
3-Amino-7-chloro-4,6-difluoro-1*H*-indazole-5-carbonitrile (5b)



Deep yellow solid, mp: 225–226°C. IR (KBr): 3494, 2239, 1634, 1436, 1326, 1220, 901, 791

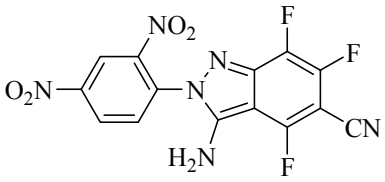
cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.93 (br, 2H, NH_2), 13.07 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.3, 156.1, 149.6, 141.5, 110.6, 101.2, 97.7, 81.0. HRMS (TOF ES$^-$): *m/z* calcd for $C_8H_2ClF_2N_4$ [(M-H$^+$)], 226.9942; found, 226.9942.

3-Amino-4,6,7-trichloro-1*H*-indazole-5-carbonitrile (5c)



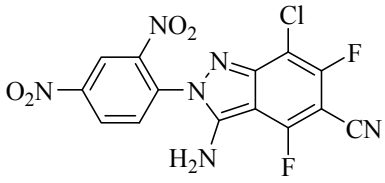
Slight yellow solid, mp: 229–230°C. IR (KBr): 3458, 1603, 1399, 1325, 1183, 1048, 673 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.83 (br, 2H, NH_2), 13.09 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 150.7, 140.5 (d, J = 52.5 Hz), 132.3, 130.0, 128.4, 114.5 (d, J = 90.0 Hz), 110.9, 102.5. HRMS (TOF ES$^-$): *m/z* calcd for $C_8H_2Cl_3N_4$ [(M-H$^+$)], 258.9351, found; 258.9349.

3-Amino-2-(2,4-dinitrophenyl)-4,6,7-trifluoro-2*H*-indazole-5-carbonitrile (7a)



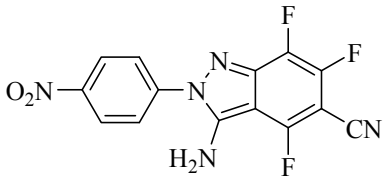
Deep yellow solid, mp: 208–209°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.51 (d, J = 9.4, 1H, PhH), 8.42 (d, J = 9.4, 1H, PhH), 8.98 (d, J = 36.3, 1H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.2, 162.1, 148.8 (d, J = 2.5 Hz), 140.6 (d, J = 13.8 Hz), 138.9, 136.5, 131.4 (d, J = 32.5 Hz), 124.0 (d, J = 26.3 Hz), 116.5, 111.2 (d, J = 28.8 Hz), 101.5, 77.6 (t, J = 20.0 Hz). IR (KBr): 3319, 2231, 1656, 1509, 1342, 1138, 742 cm^{-1}. HRMS (TOF ES$^-$): *m/z* calcd for $C_{14}H_6F_3N_6O_4$ [(M-H$^+$)], 377.0252; found, 377.0250.

3-Amino-7-chloro-2-(2,4-dinitrophenyl)-4,6-difluoro-2*H*-indazole-5-carbonitrile (7b)



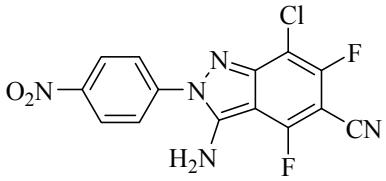
Deep yellow solid, mp: 208–209°C. IR (KBr): 3472, 1639, 1537, 1354, 1081, 759 cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 7.32–7.62 (m, 5H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.9 (d, J = 7.5 Hz), 159.7 (d, J = 6.3 Hz), 155.5, 153.6, 145.8, 144.6, 137.8, 130.2 (d, J = 77.5 Hz), 125.9 (d, J = 66.3 Hz), 111.5, 101.3 (d, J = 20.0 Hz), 97.0 (d, J = 13.8 Hz), 79.1. HRMS (TOF ES$^-$): *m/z* calcd for $C_{14}H_4ClF_2N_6O_4$ [(M-H$^+$)], 392.9956; found, 392.9955.

3-Amino-4,6,7-trifluoro-2-(4-nitrophenyl)-2*H*-indazole-5-carbonitrile (7c)



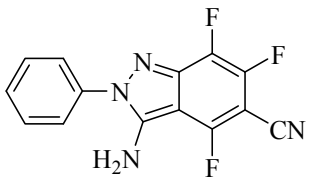
Yellow solid, mp: 227–228°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.64–7.93 (m, 2H, PhH), 8.40 (d, J = Hz, 2H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.6, 156.5, 147.0, 145.8, 144.1 (d, J = 111.3 Hz), 110.8, 98.0 (d, J = 6.3 Hz), 78.1 (t, J = 18.8 Hz). IR (KBr): 3464, 2231, 1660, 1530, 1349, 1183, 1104, 667 cm^{-1}. HRMS (TOF ES^{-}): *m/z* calcd for $C_{14}H_5F_3N_5O_2$ [(M-H^{+})], 332.0401, found; 334.0405.

3-Amino-7-chloro-4,6-difluoro-2-(4-nitrophenyl)-2*H*-indazole-5-carbonitrile (7d)



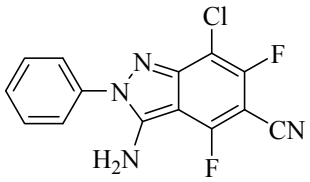
Yellow solid, mp: 227–228°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.68–7.92 (m, 2H, PhH), 8.39 (d, J = 8.6 Hz, 2H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.5, 159.3, 155.4, 153.4, 145.9 (d, J = 138.8 Hz), 142.5, 125.8 (d, J = 118.8 Hz), 110.8, 100.8 (d, J = 20.0 Hz), 96.6 (d, J = 12.5 Hz), 79.1 (d, J = 16.3 Hz). IR (KBr): 3429, 2227, 1639, 1529, 1399, 1342, 1089, 669 cm^{-1}. HRMS (TOF ES^{-}): *m/z* calcd for $C_{14}H_5ClF_2N_5O_2$ [(M-H^{+})], 348.0105; found, 348.0102.

3-Amino-4,6,7-trifluoro-2-phenyl-2*H*-indazole-5-carbonitrile (7e)



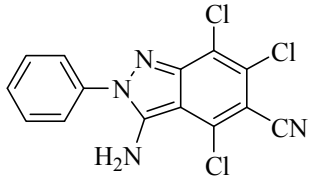
Yellow solid, mp: 246–247°C. IR (KBr): 3383, 2227, 1656, 1529, 1399, 1277, 1179, 763 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.28–7.62 (m, 5H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.5, 156.4, 145.3 (d, J = 10.0 Hz), 143.6 (t, J = 12.5 Hz), 139.7, 137.5 (d, J = 38.8 Hz), 135.4 (d, J = 12.5 Hz), 133.4 (d, J = 12.5 Hz), 129.8, 125.7 (d, J = 35.0 Hz), 111.1 (d, J = 35.0 Hz), 97.8 (t, J = 6.3 Hz), 77.6 (t, J = 20.0 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): δ -109.8 (t, J = 9.4Hz, 1F), -141.8 (d, J = 14.1 Hz, 1F), -162.1 (s, 1F). HRMS (TOF ES^{-}): *m/z* calcd for $C_{14}H_6F_3N_4$ [(M-H^{+})], 287.0550; found, 287.0552.

3-Amino-7-chloro-4,6-difluoro-2-phenyl-2*H*-indazole-5-carbonitrile (7f)



Slight green solid, mp: 221–222°C. IR (KBr): 3471, 2222, 1641, 1529, 1350, 1142, 608 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34–7.62 (m, 5H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.3 (d, J = 7.5 Hz), 159.2, 155.0, 153.1, 145.3, 144.1, 137.32, 129.7 (t, J = 76.3 Hz), 129.4, 125.6, 111.1, 100.8 (d, J = 25.0 Hz), 96.4 (d, J = 13.8 Hz), 78.6 (t, J = 17.5 Hz). HRMS (TOF ES^-): m/z calcd for $C_{14}H_6ClF_2N_4$ [(M-H^+)], 303.0255; found, 303.0255.

3-Amino-4,6,7-trichloro-2-phenyl-2*H*-indazole-5-carbonitrile (7g)



Yellow solid, mp: 227–228°C. IR (KBr): 3482, 2227, 1627, 1492, 1444, 1350, 1036, 722 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.98 (s, 1H, PhH), 7.57-7.64 (d, J = 35 Hz, 4H, PhH) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.2, 145.1 (d, J = 47.5 Hz), 137.4, 135.4, 134.5, 129.8 (d, J = 12.5 Hz), 128.6, 125.9, 122.1, 118.4, 115.1, 105.7, 100.3. HRMS (TOF ES^-): m/z calcd for $C_{14}H_6Cl_3N_4$ [(M-H)$^-$], 334.9664; found, 334.9668.

^{1}H NMR and ^{13}C NMR Spectra for Polyhalo 2-Aryl-4-aminoquinazolines 3

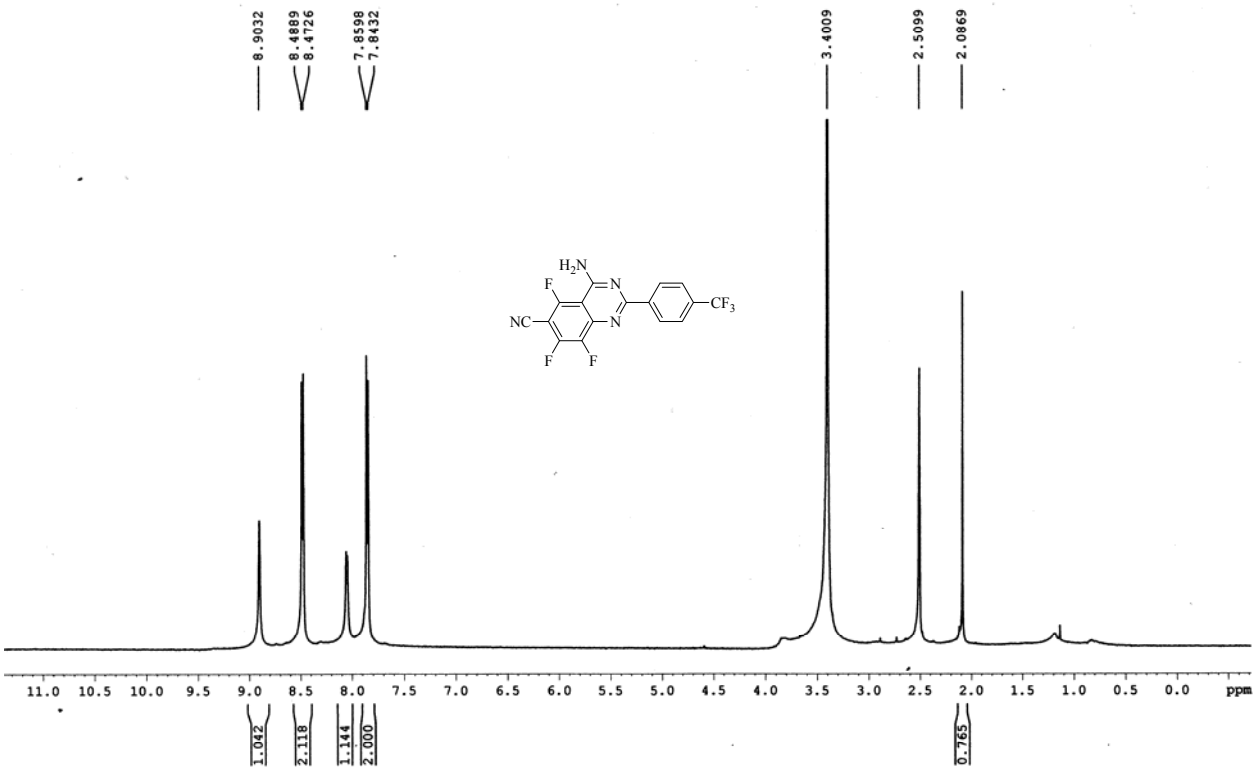


Figure 1. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3a**

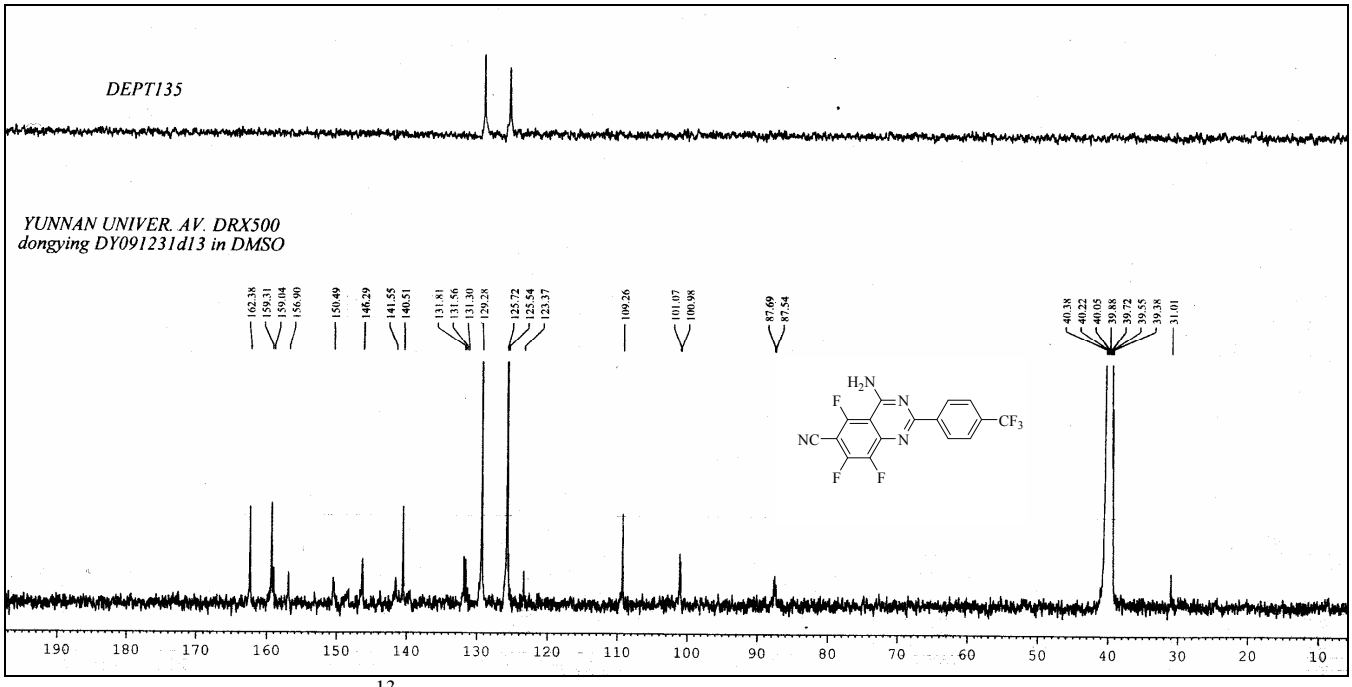


Figure 2. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3a**

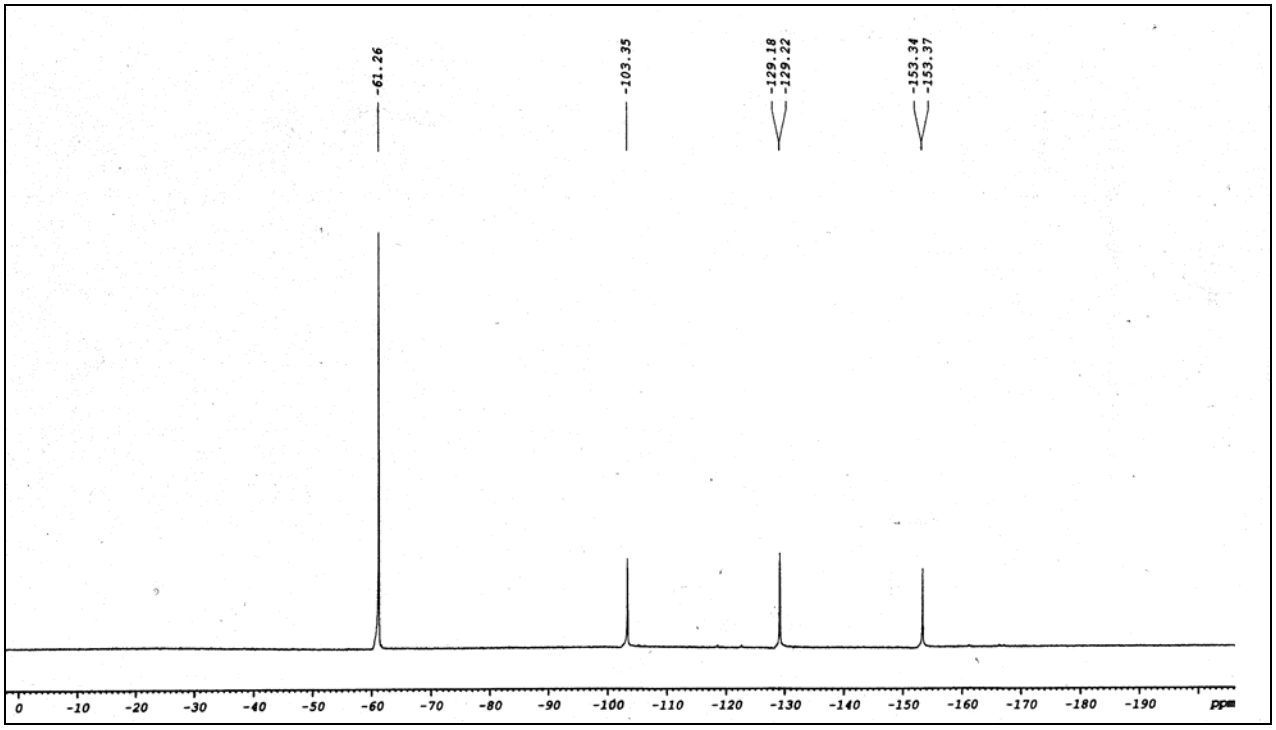


Figure 3. ^{19}F NMR (470 MHz, DMSO-d_6) spectra of compound **3a**

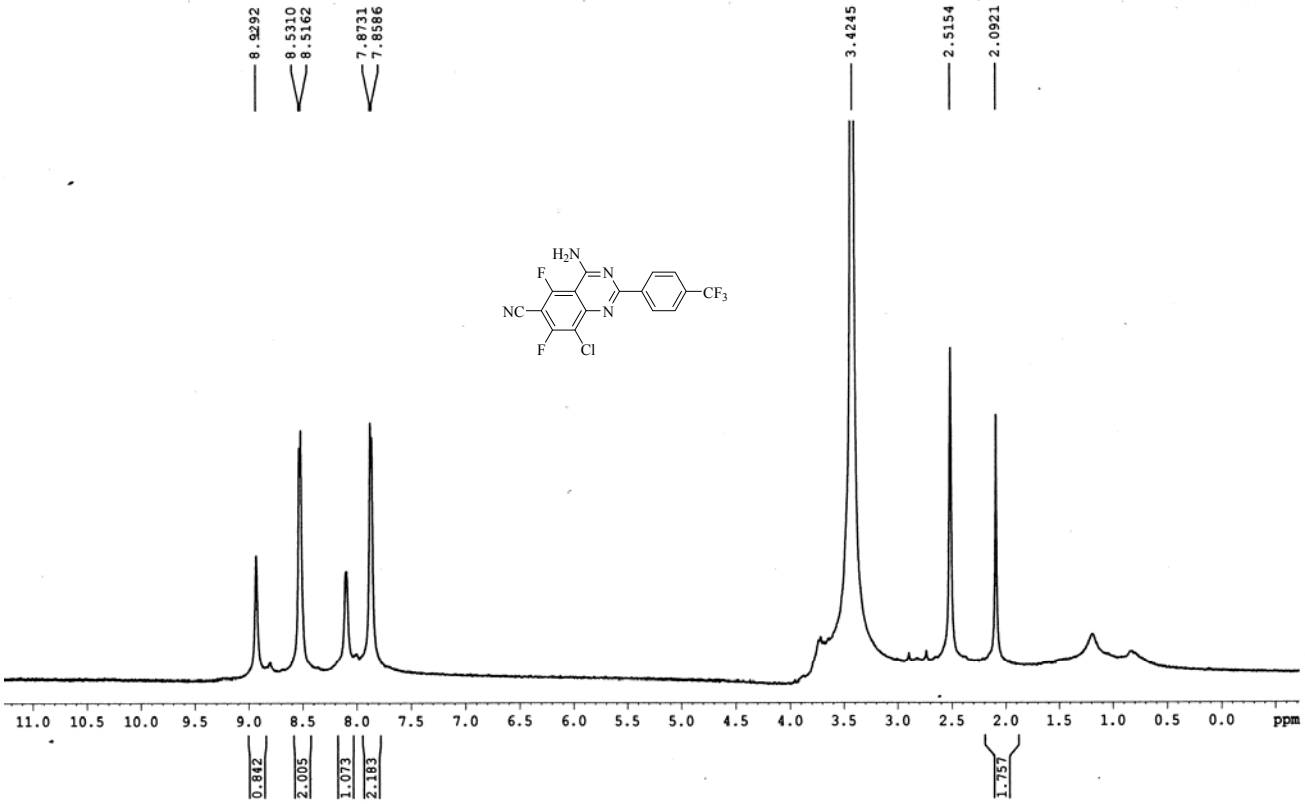


Figure 4. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3b**

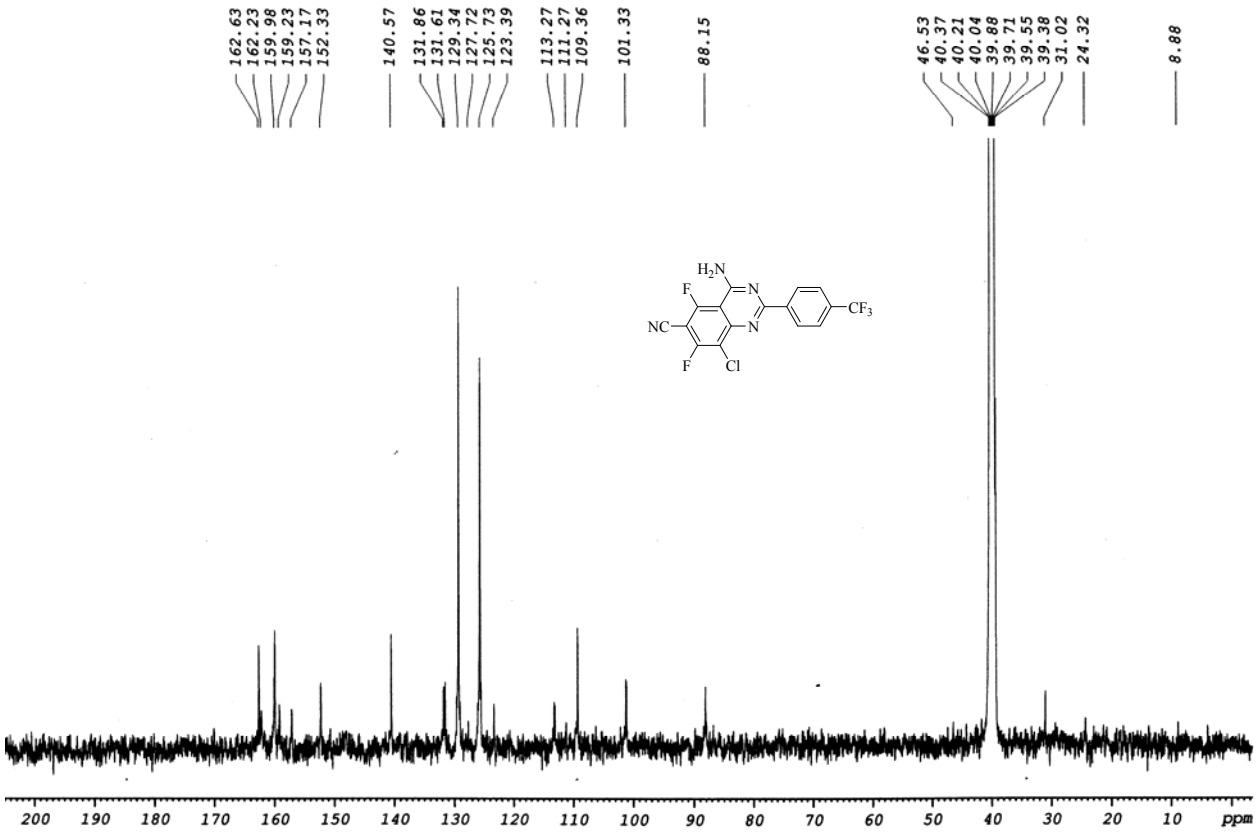


Figure 5. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3b**

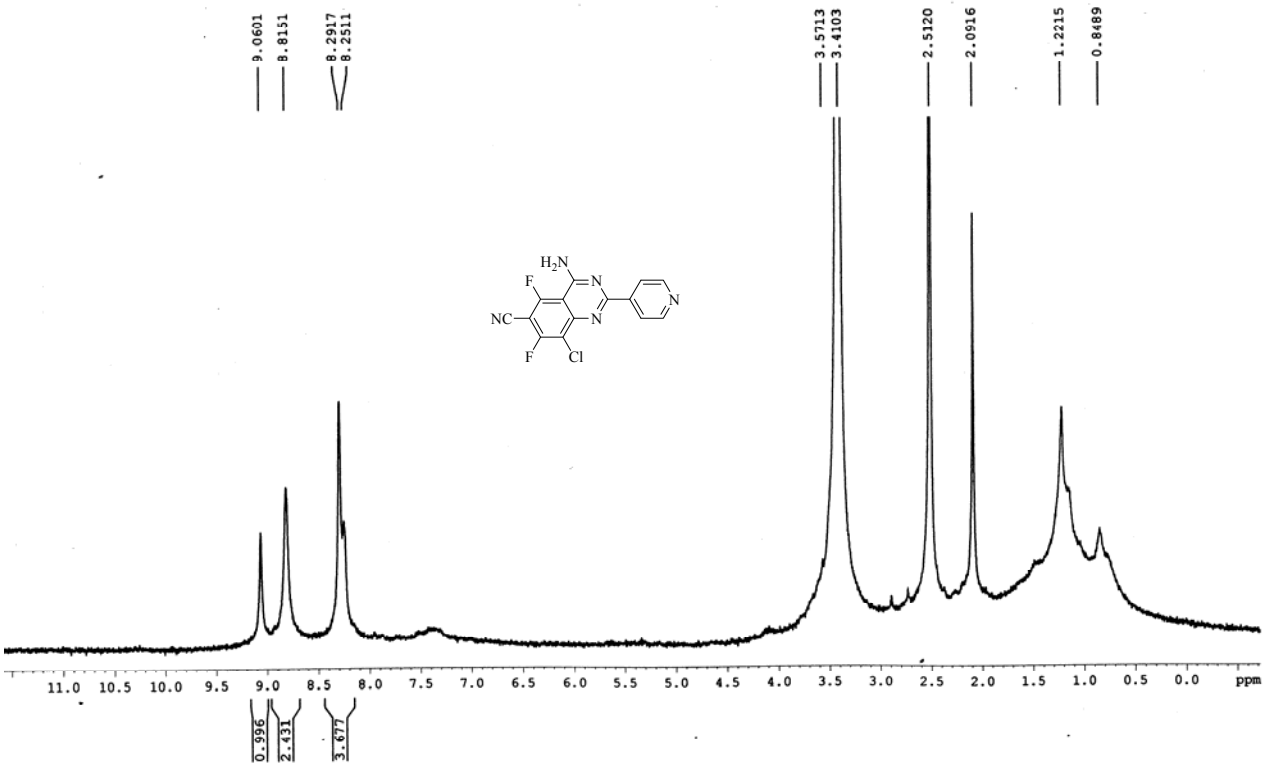


Figure 6. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3c**

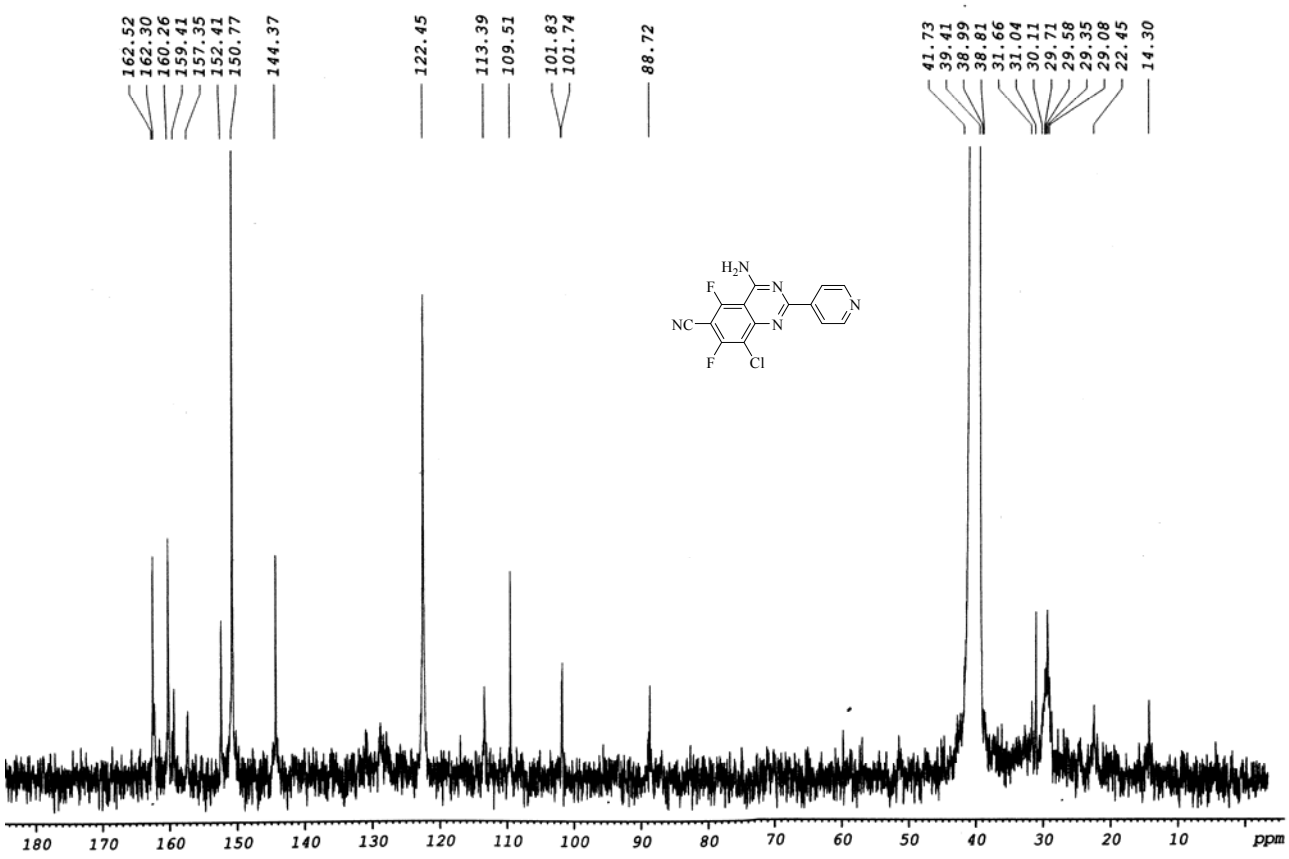


Figure 7. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3c**

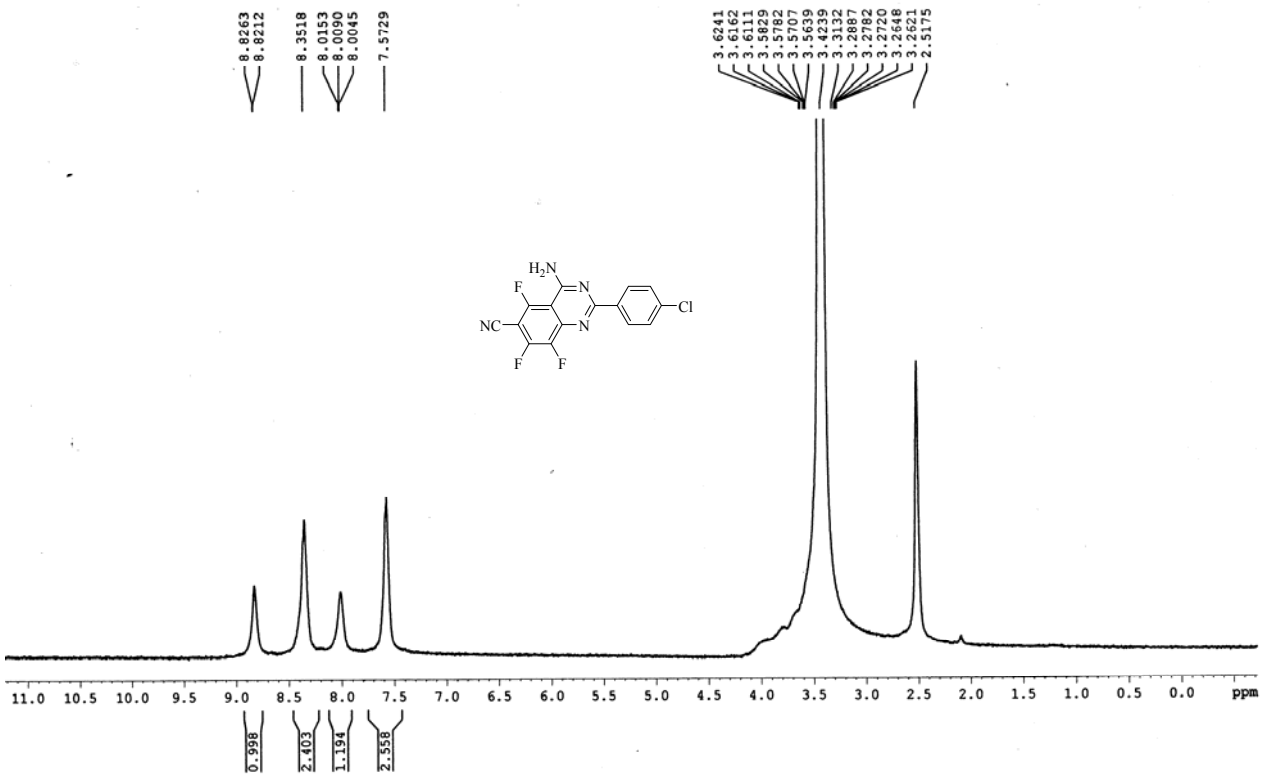


Figure 8. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3d**

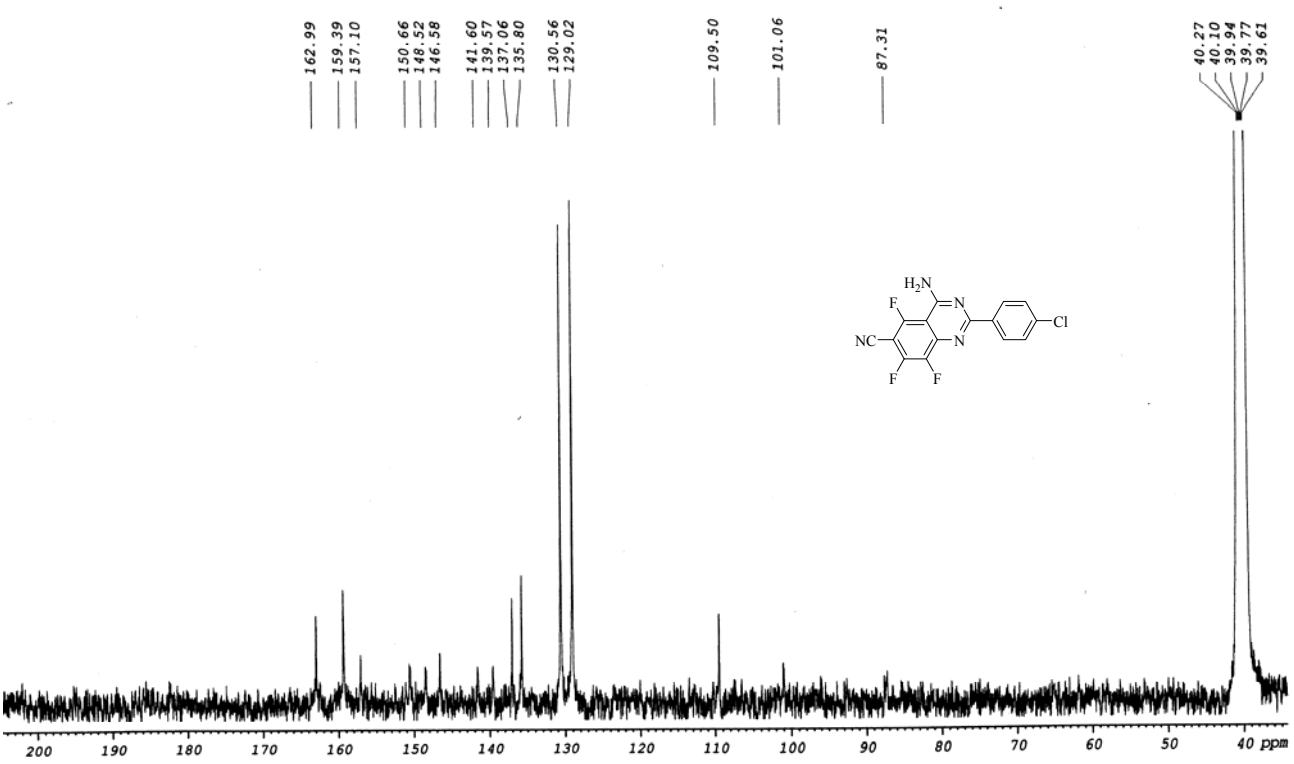


Figure 9. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3d**

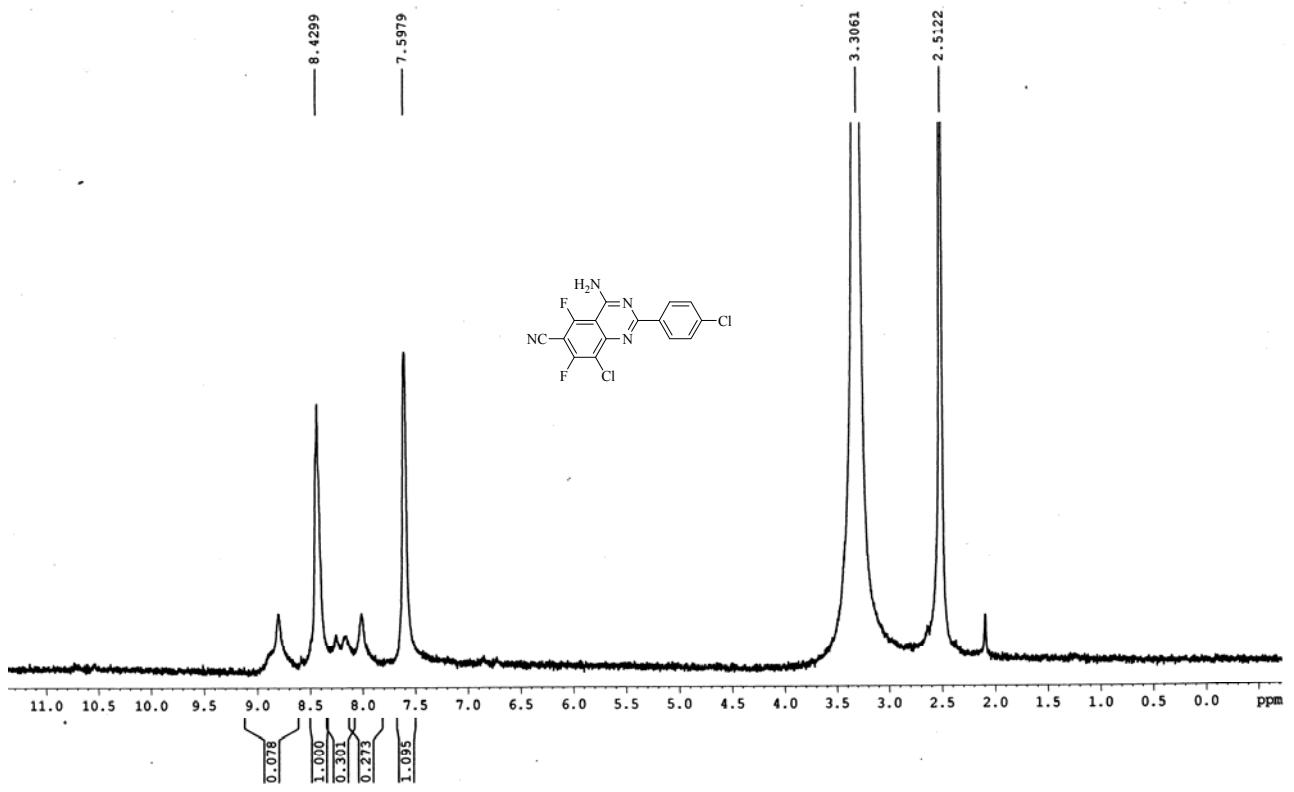


Figure 10. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3e**

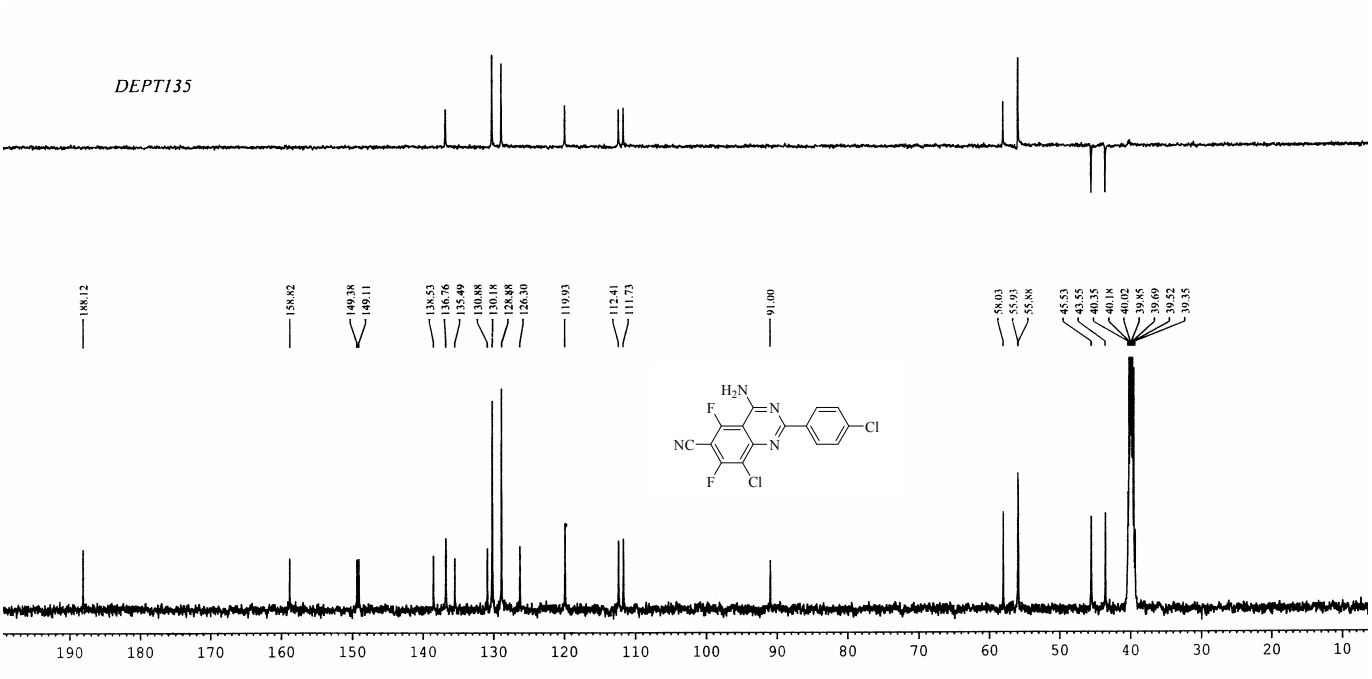


Figure 11. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3e**

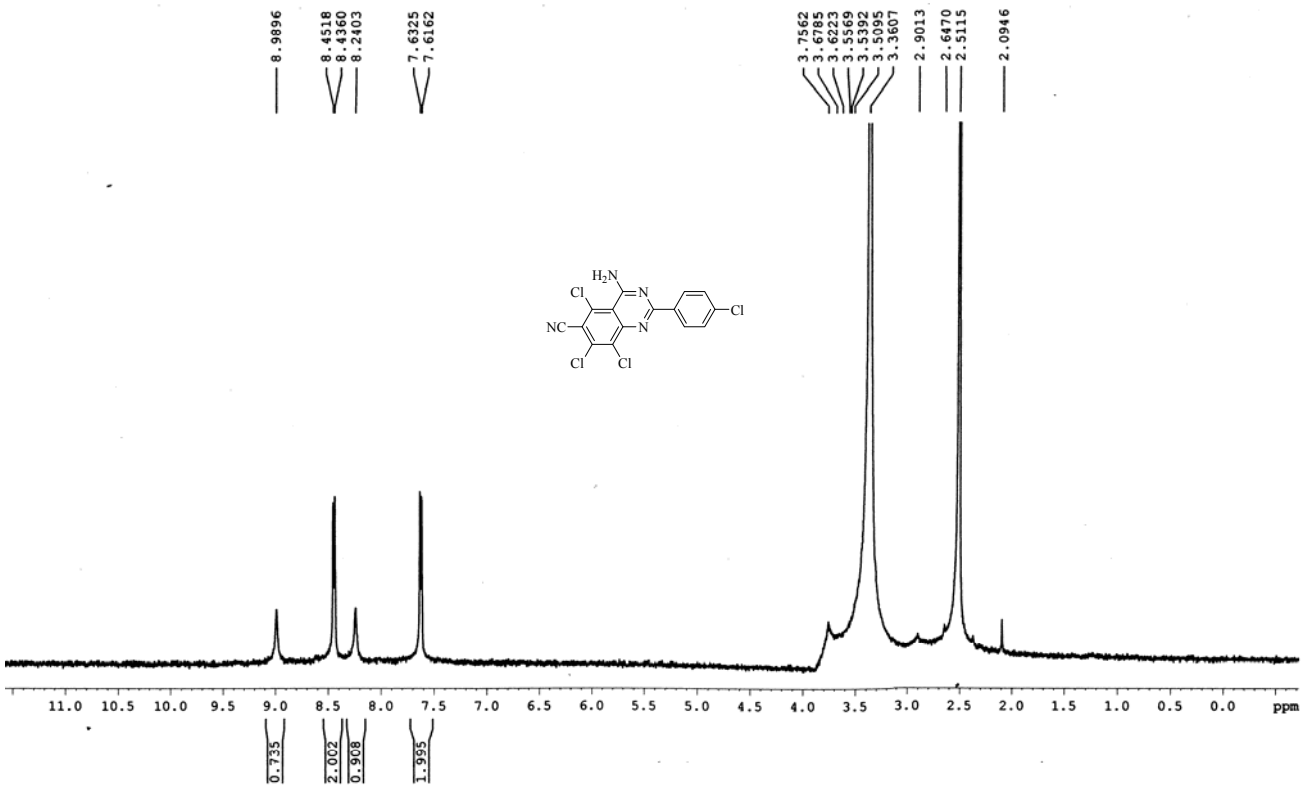


Figure 12. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3f**

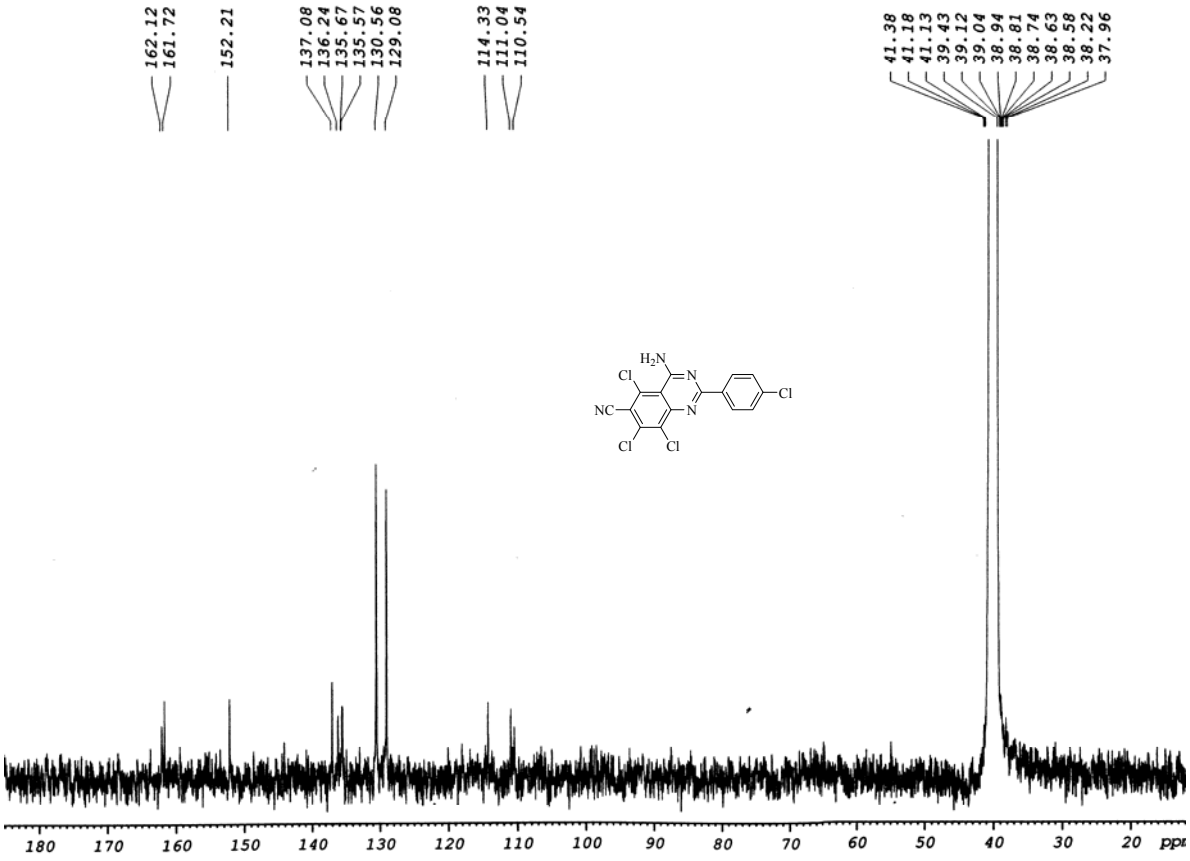


Figure 13. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3f**

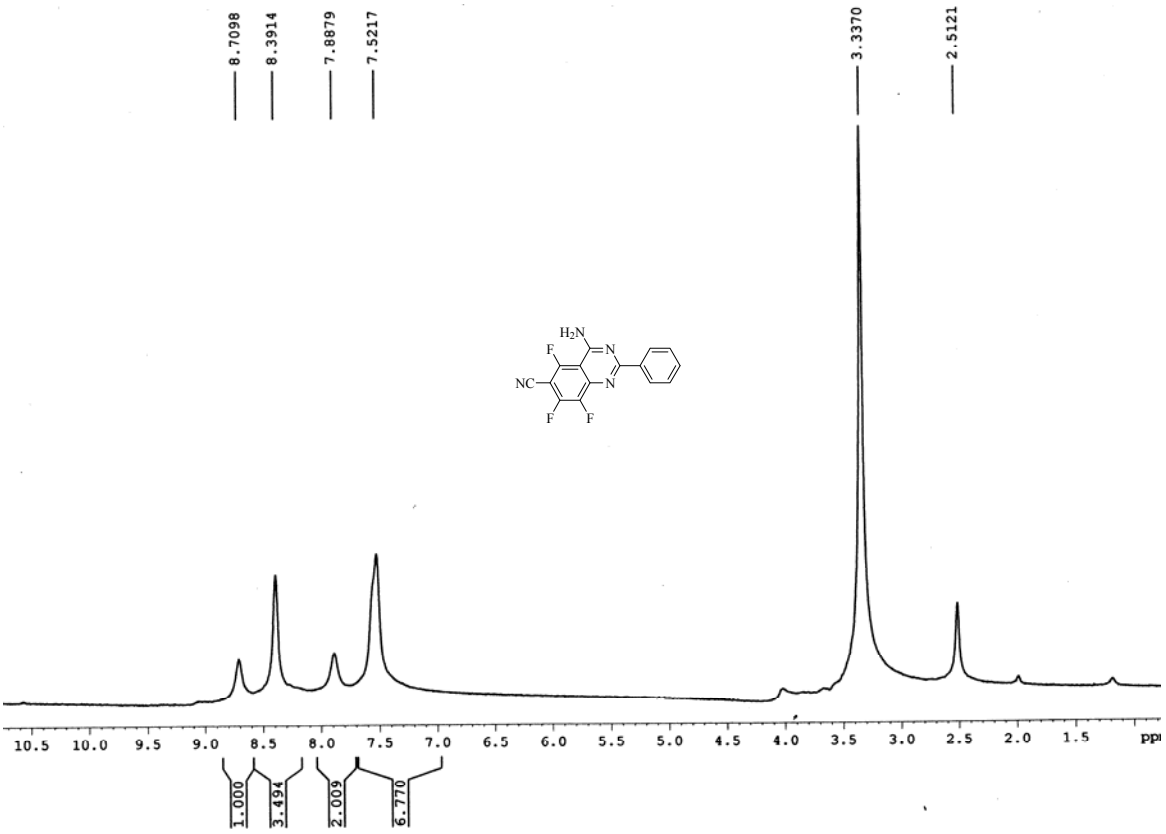


Figure 14. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3g**

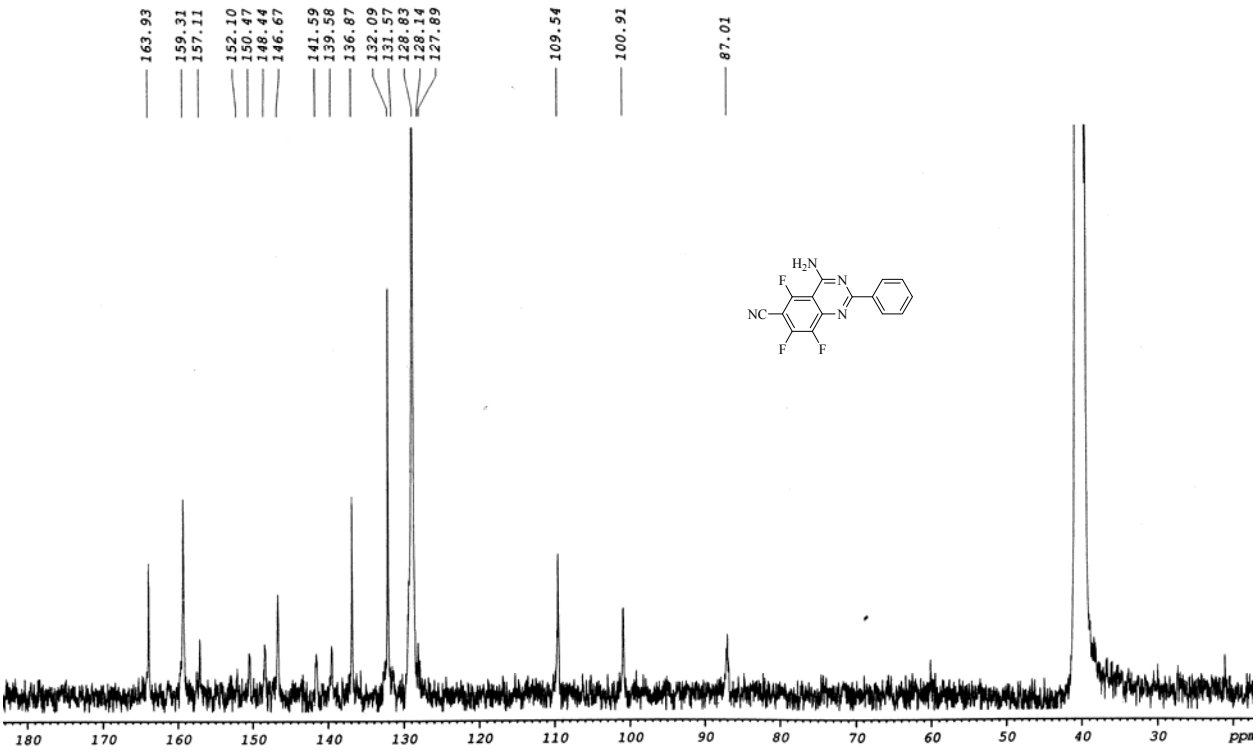


Figure 15. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3g**

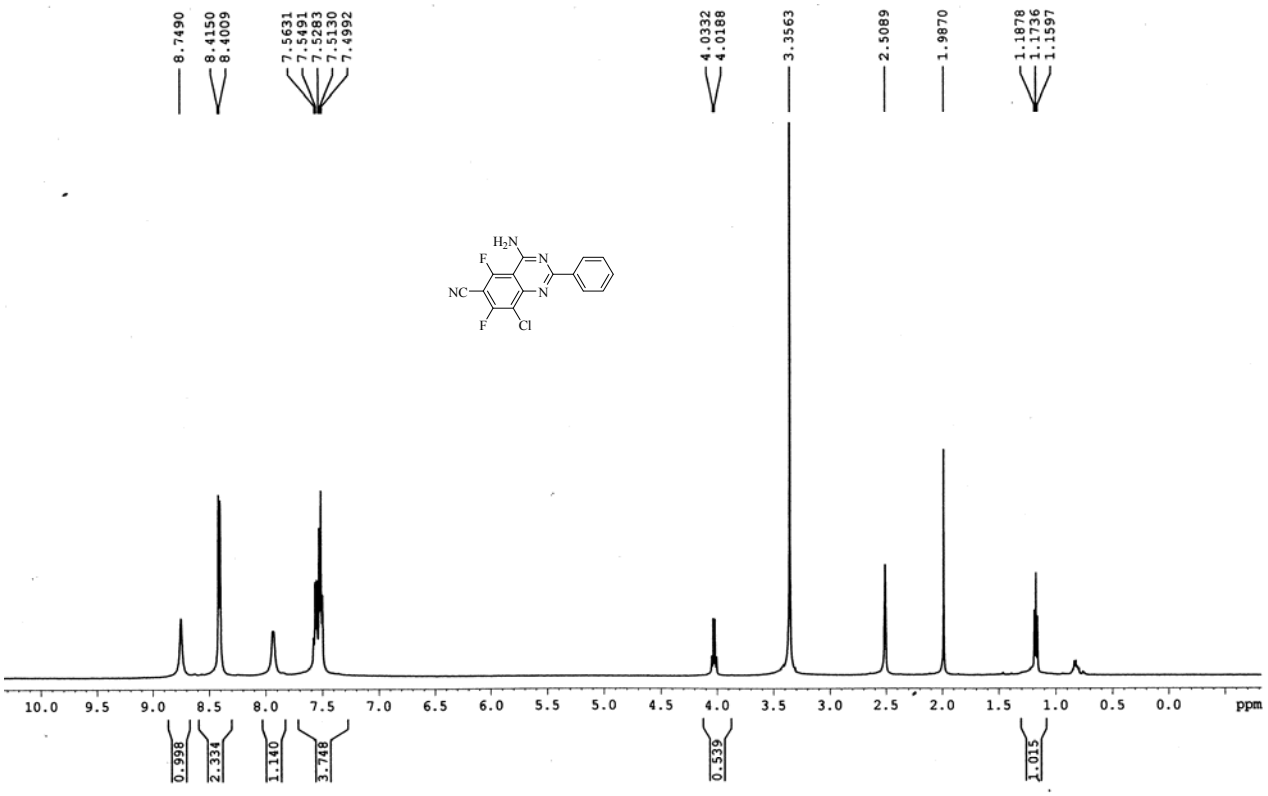


Figure 16. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3h**

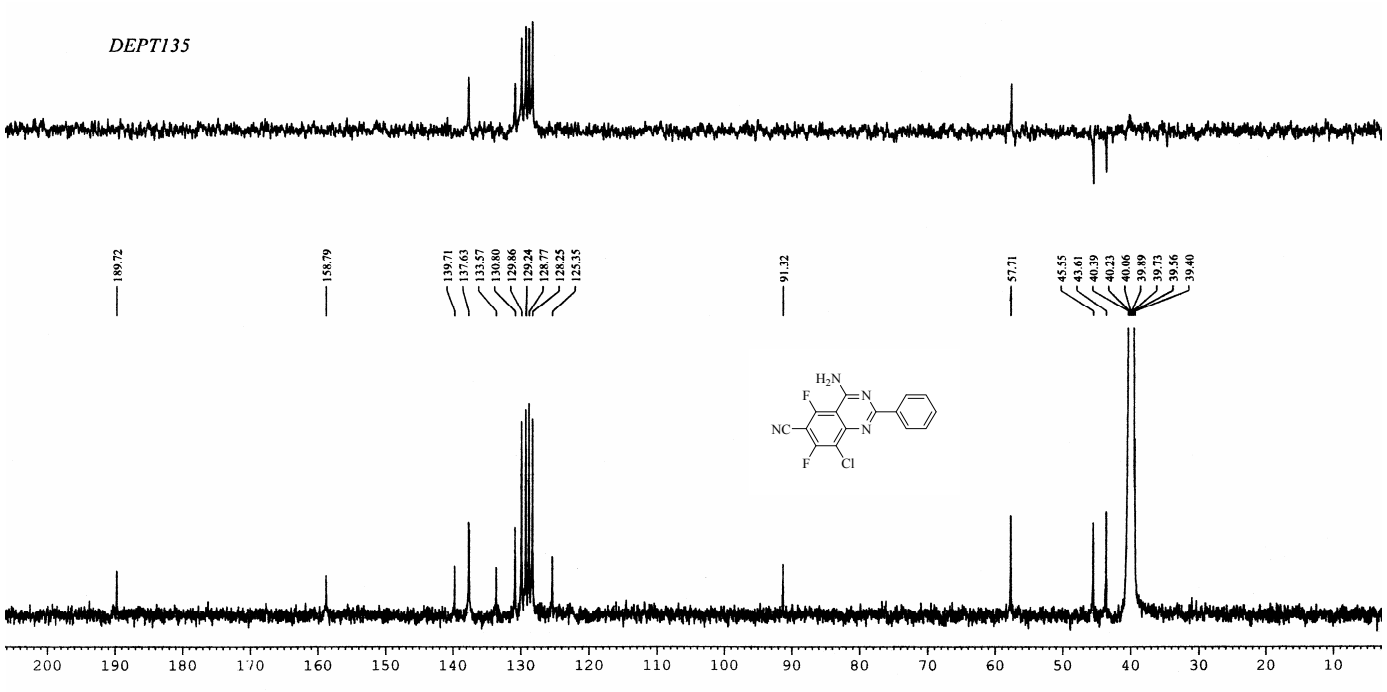


Figure 17. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3h**

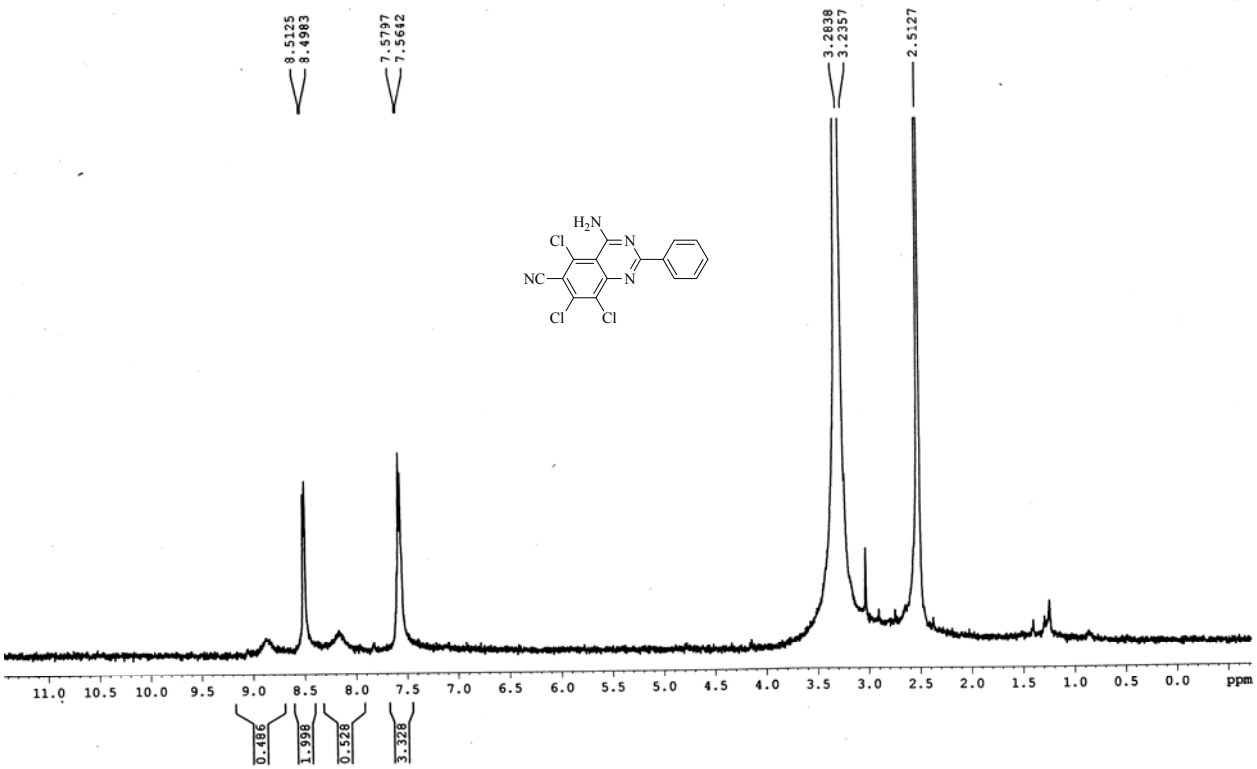


Figure 18. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3i**

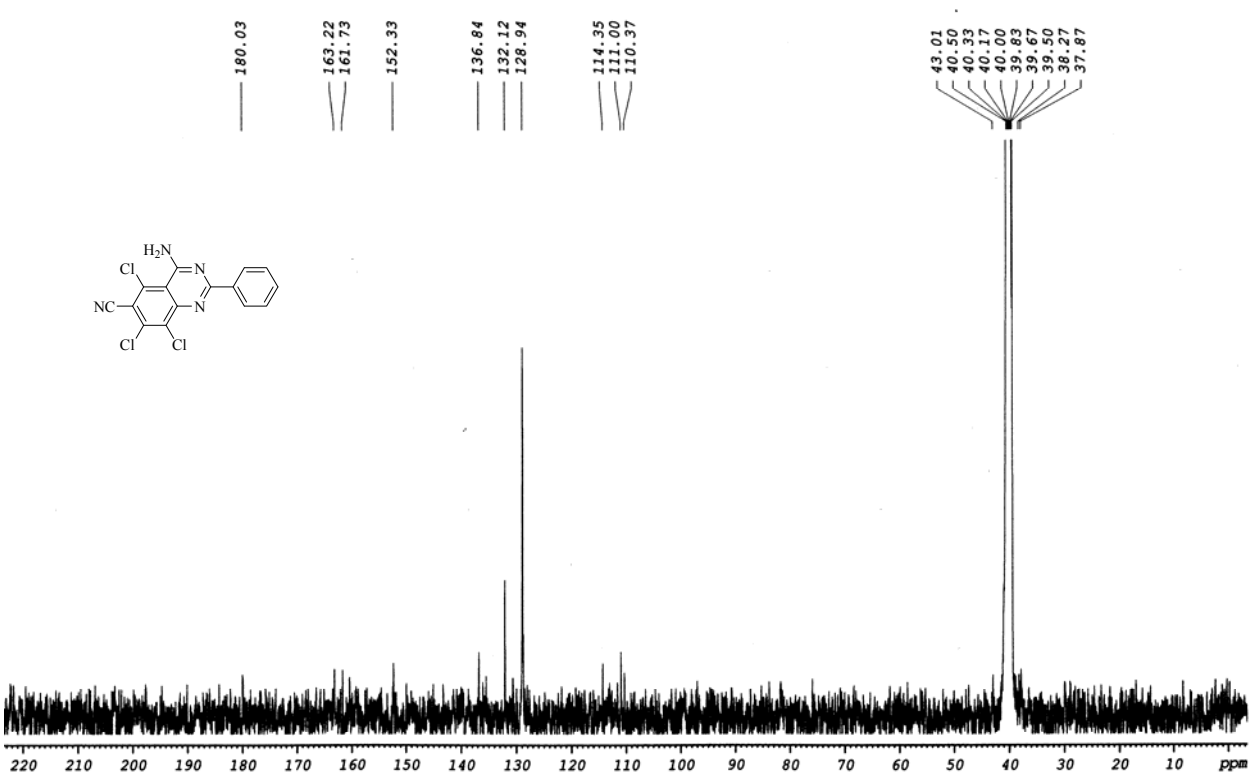


Figure 19. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3i**

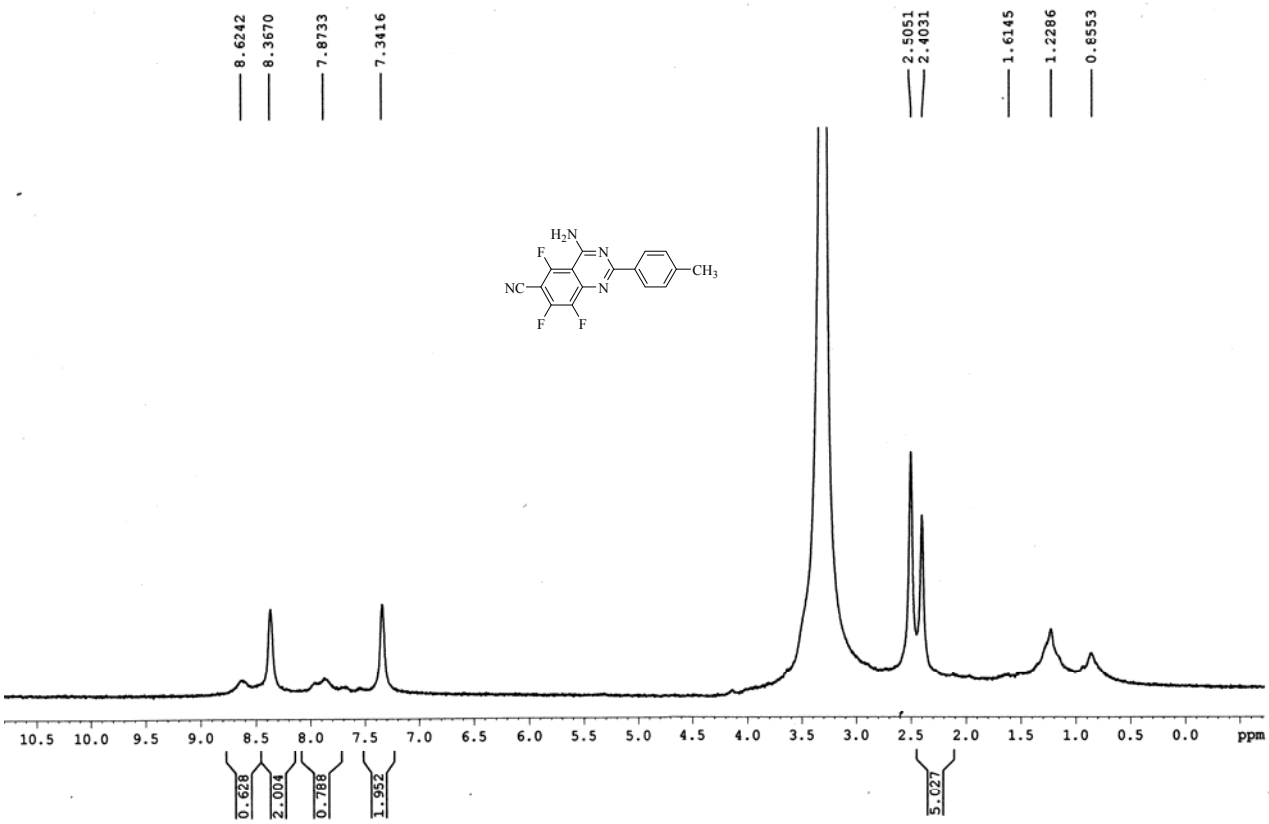


Figure 20. ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compound **3j**

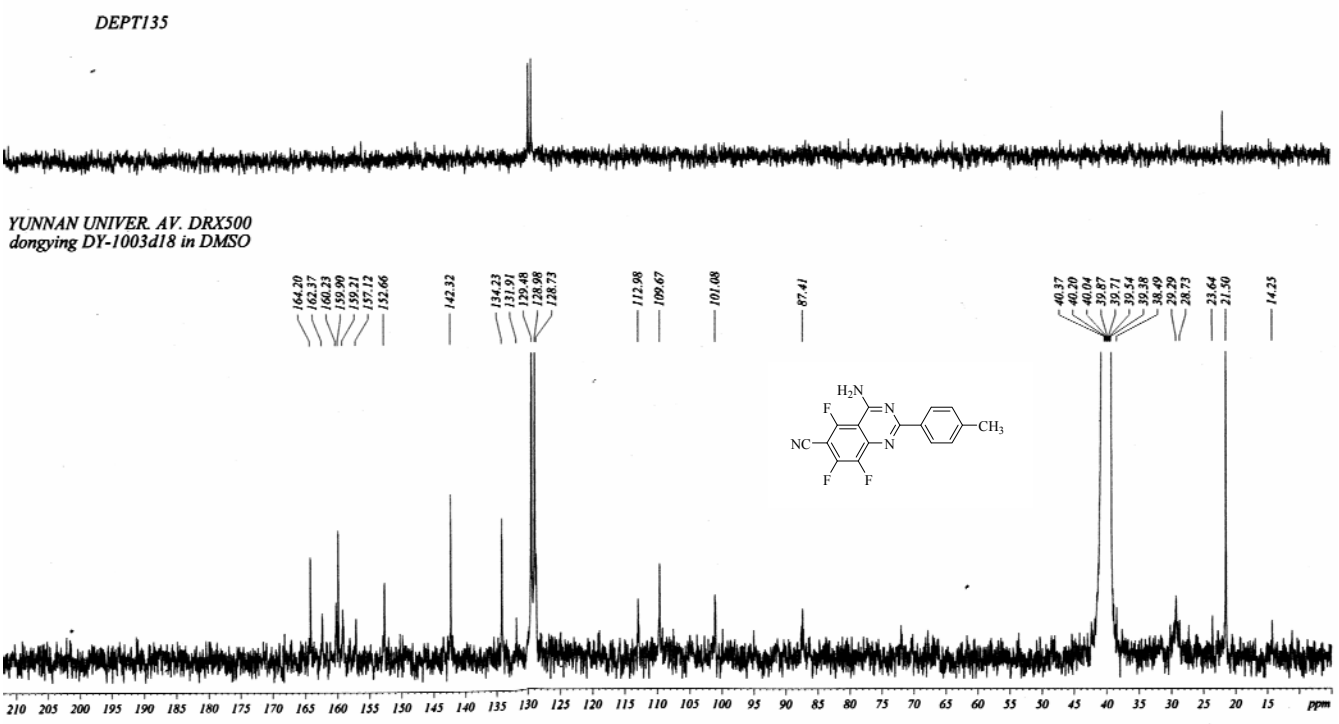


Figure 21. ^{13}C NMR (125 MHz, $CDCl_3$) spectra of compound **3j**

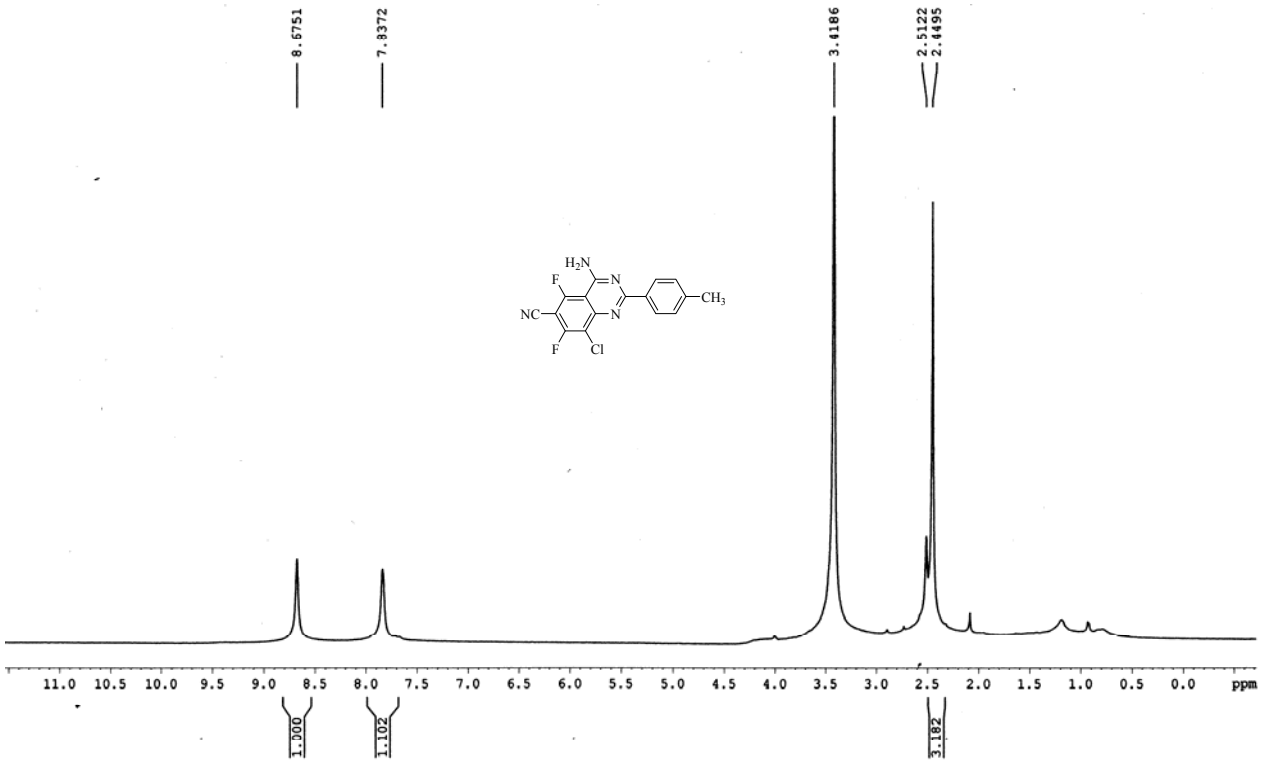


Figure 22. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3k**

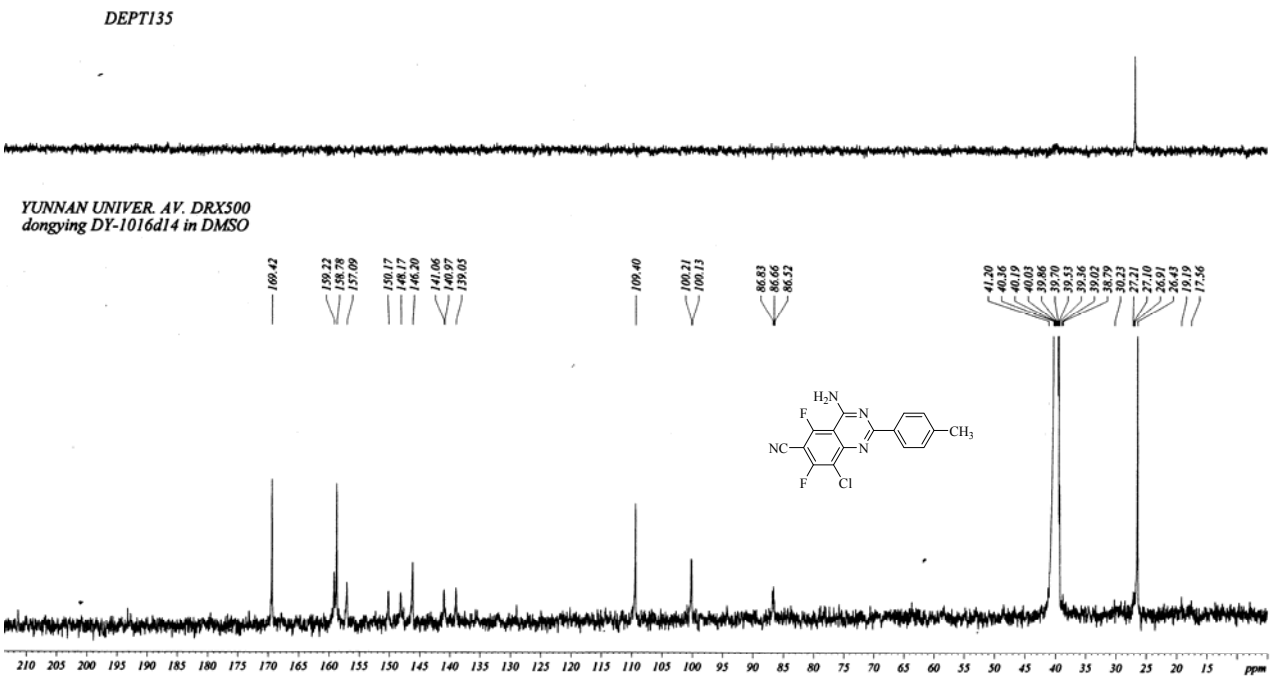


Figure 23. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3k**

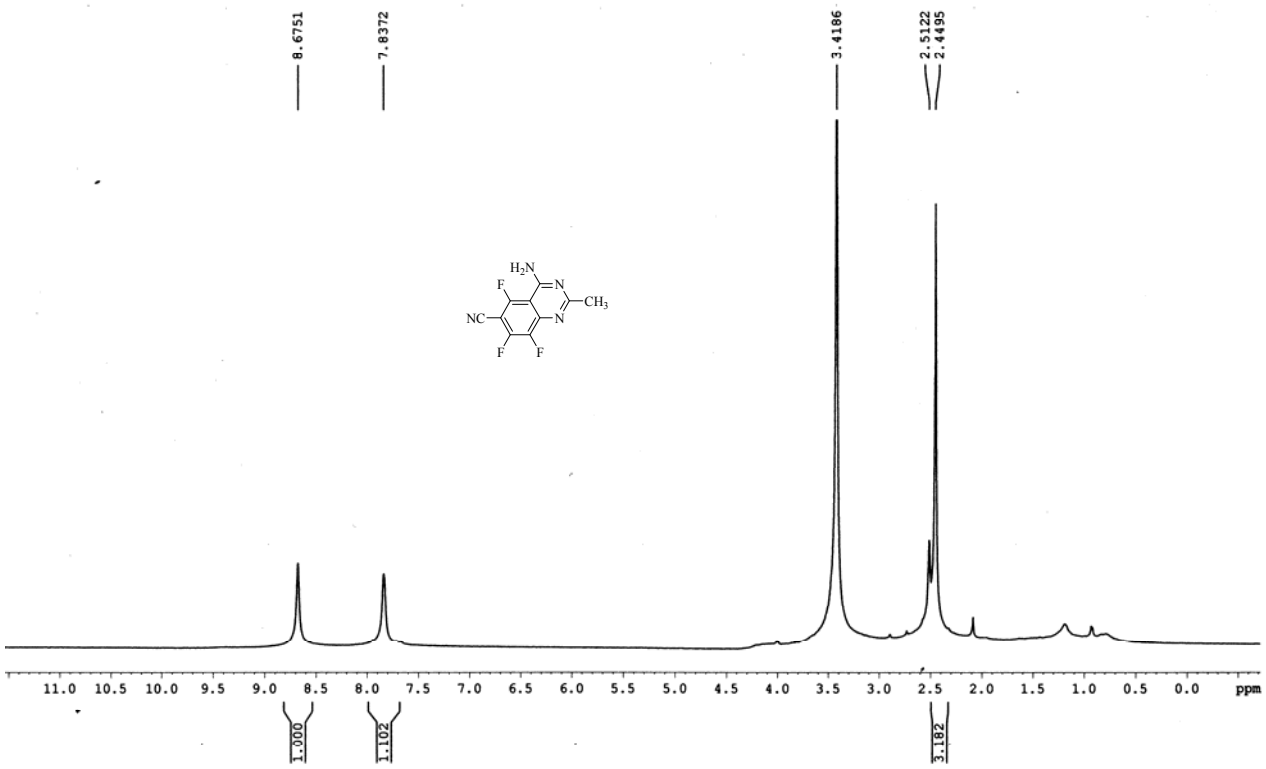


Figure 24. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3l**

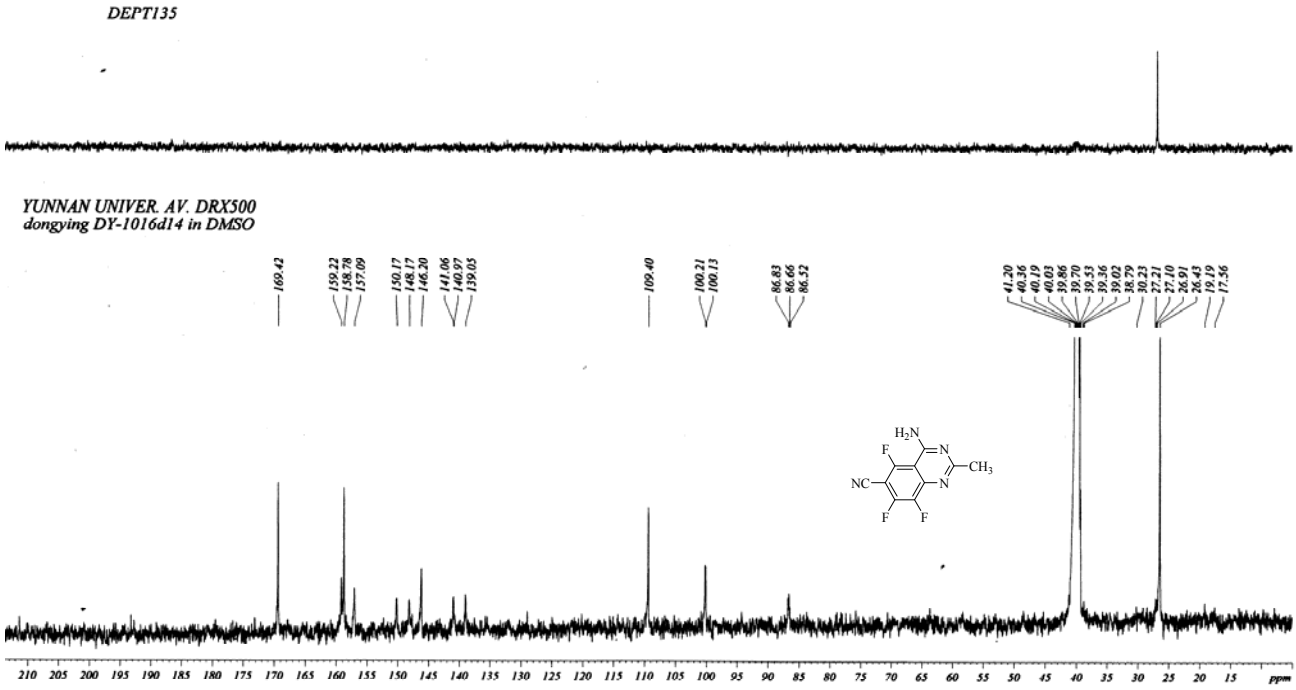


Figure 25. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3l**

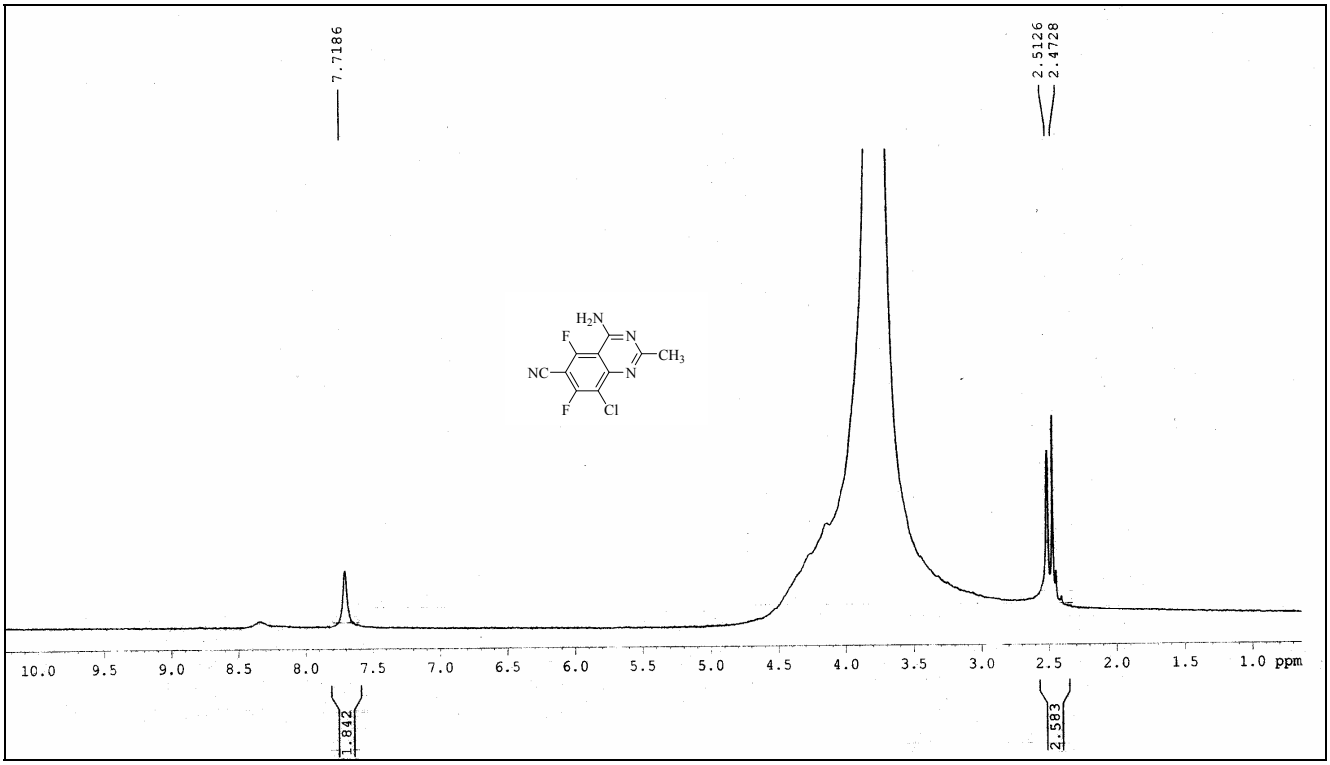


Figure 26. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3m**

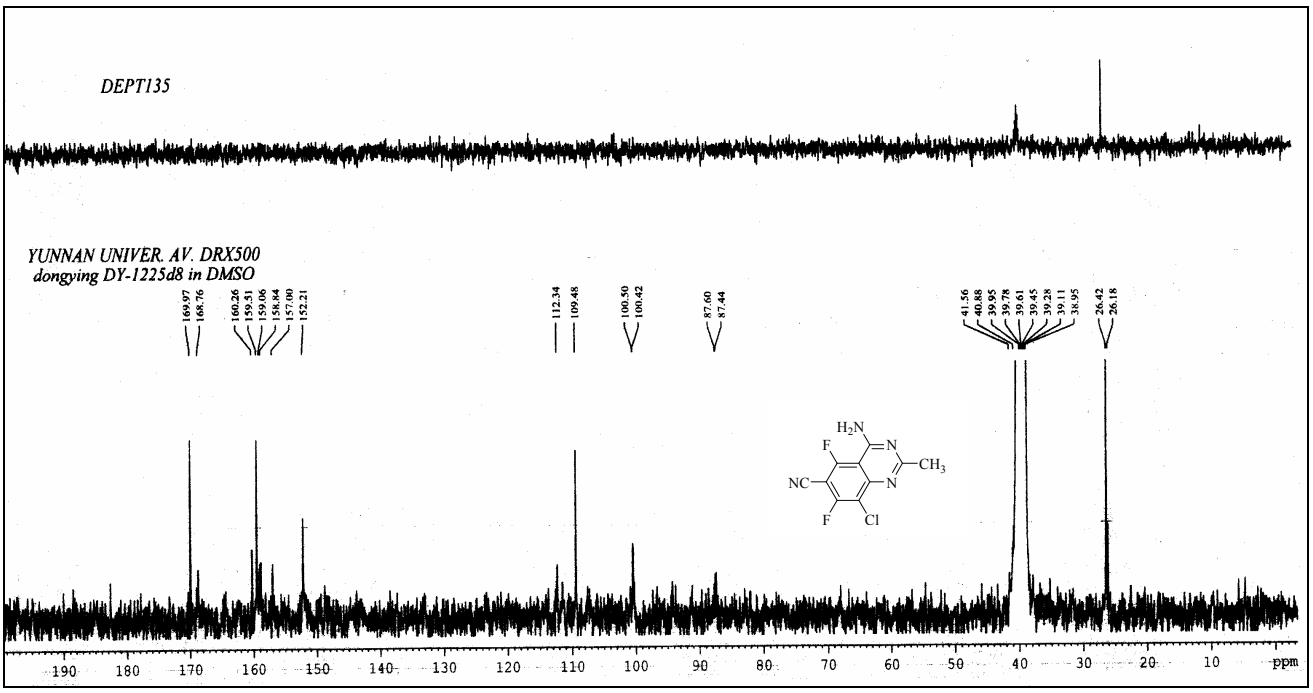


Figure 27. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3m**

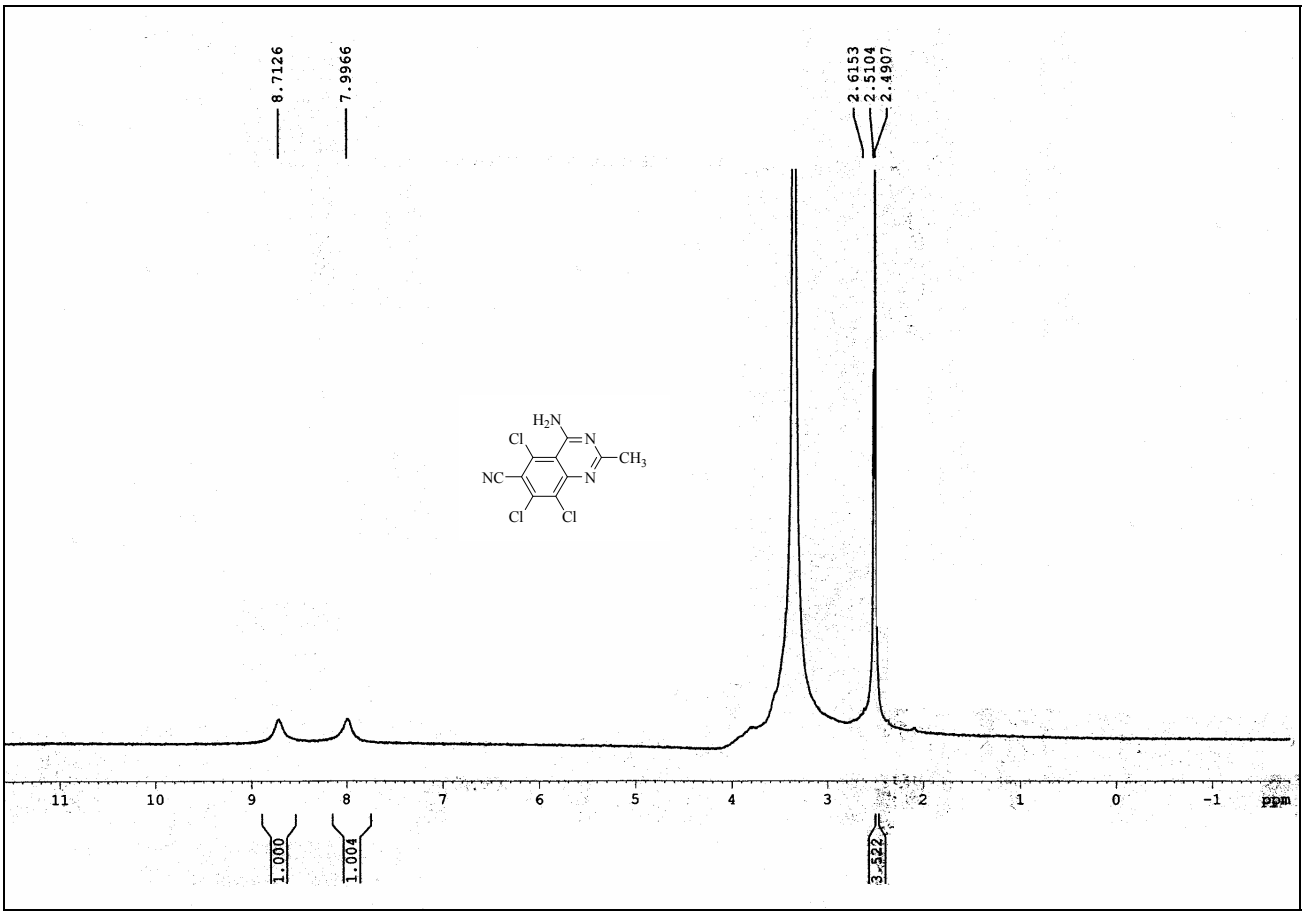


Figure 28. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **3n**

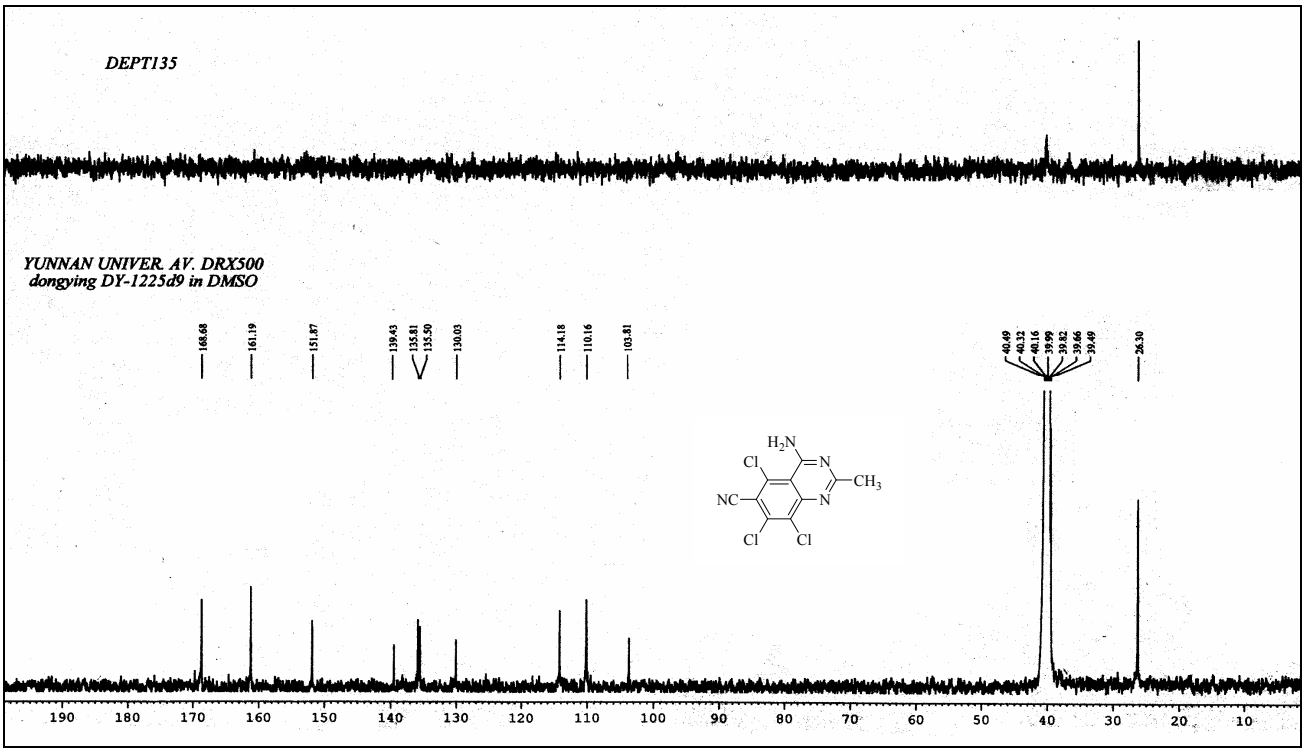


Figure 29. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **3n**

^{1}H NMR and ^{13}C NMR Spectra for Polyhalo 3-Aminoindazoles 5 and 7

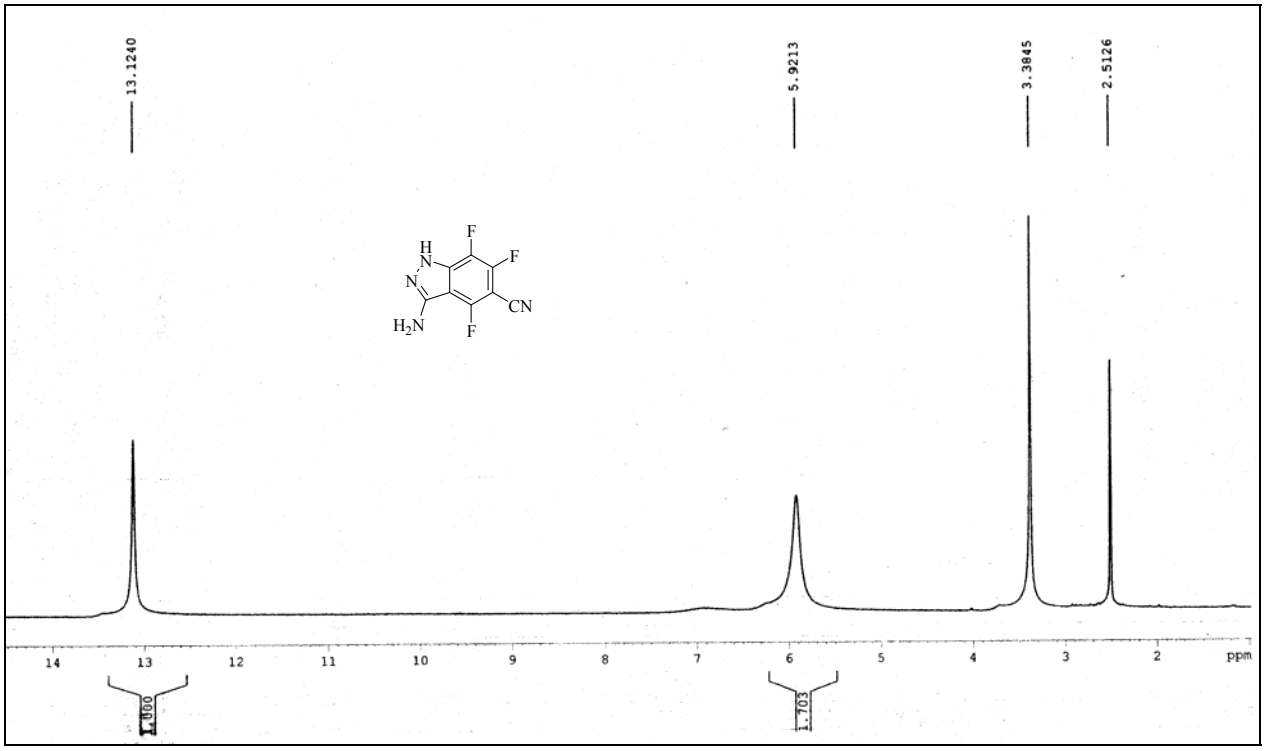


Figure 30. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **5a**

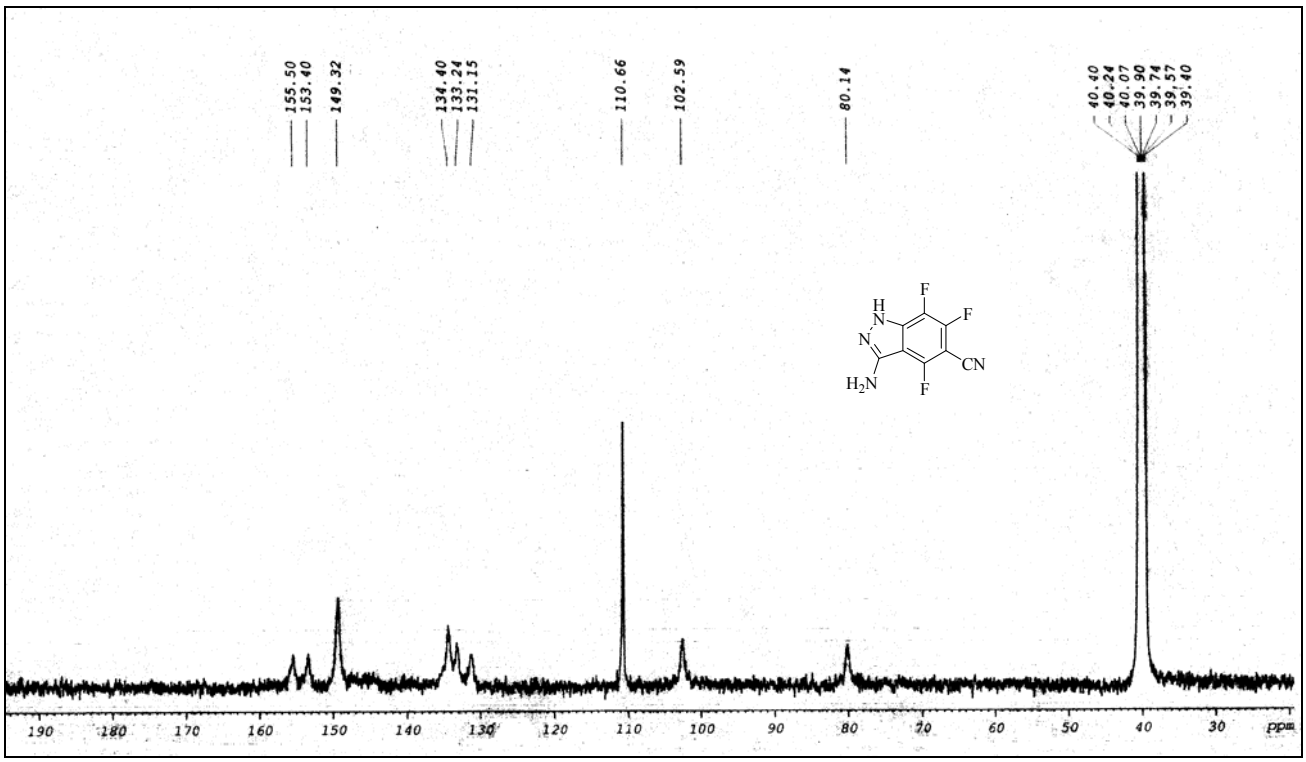


Figure 31. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **5a**

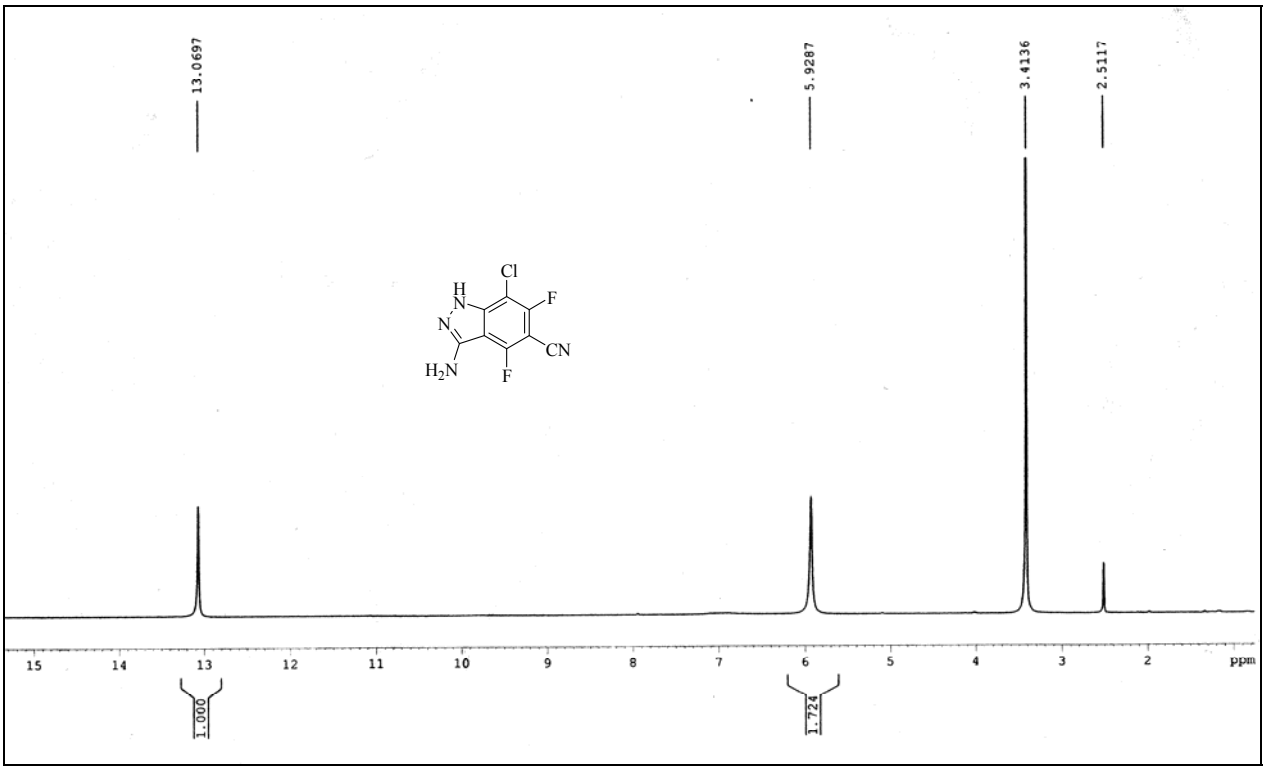


Figure 32. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **5b**

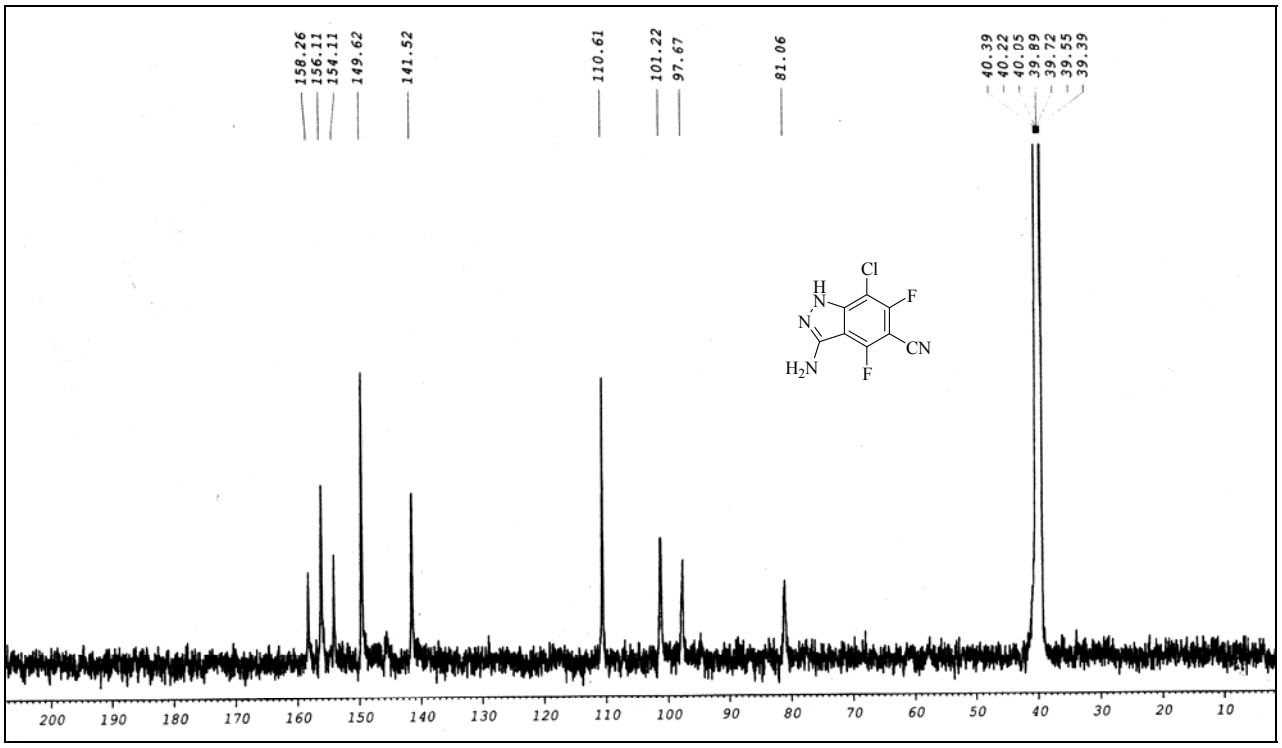


Figure 33. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **5b**

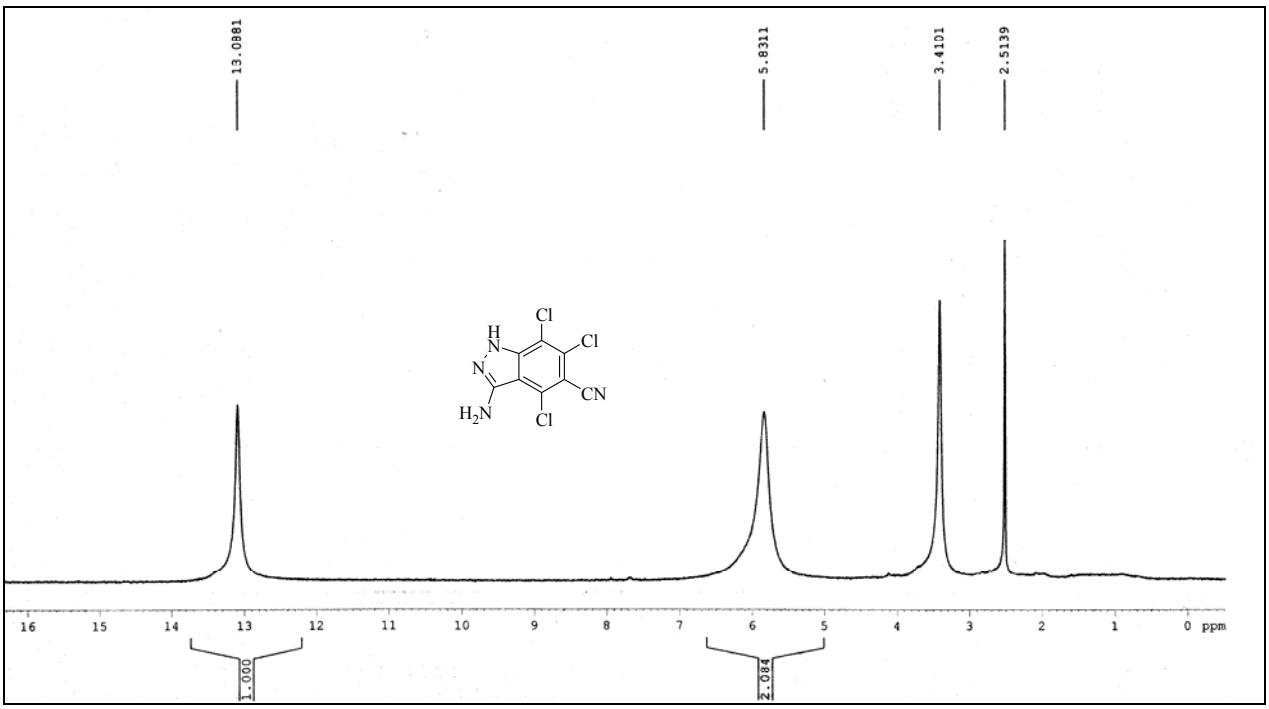


Figure 34. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **5c**

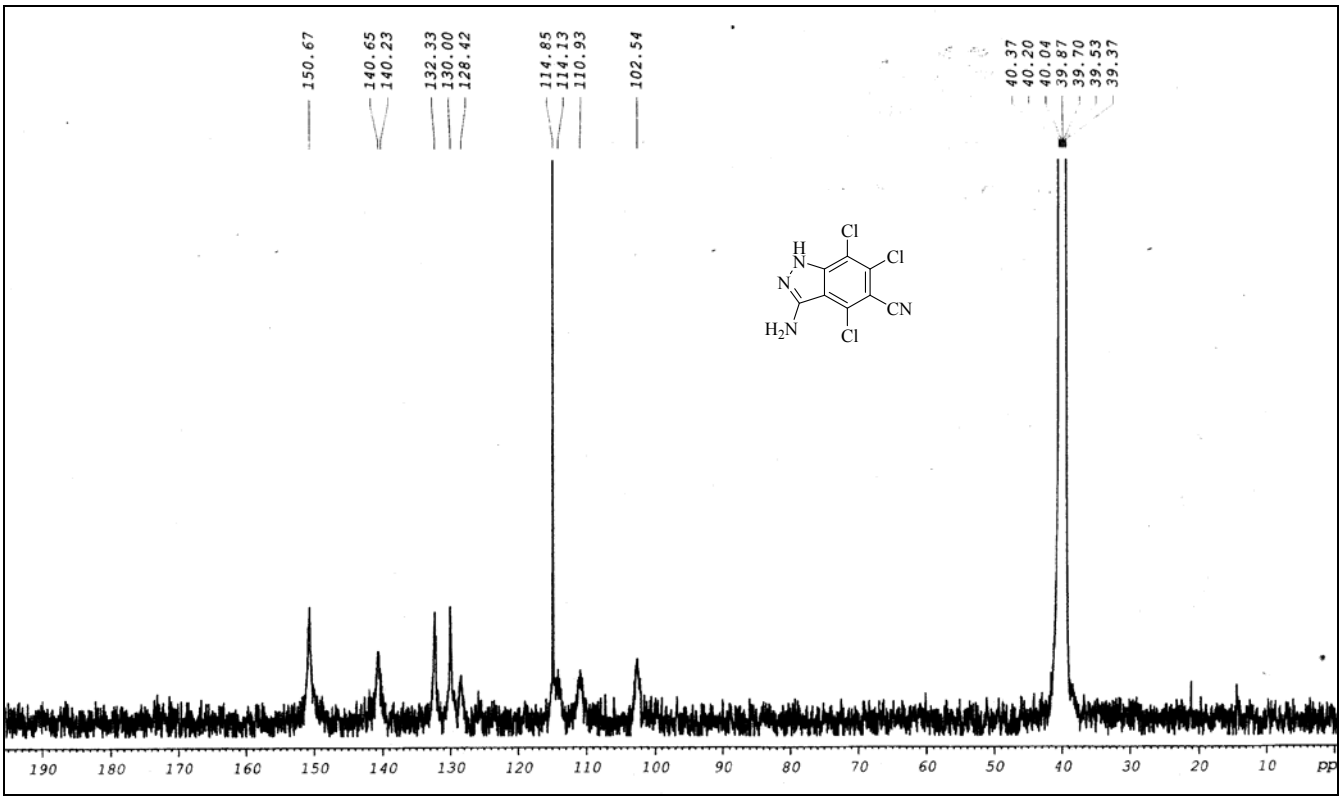


Figure 35. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **5c**

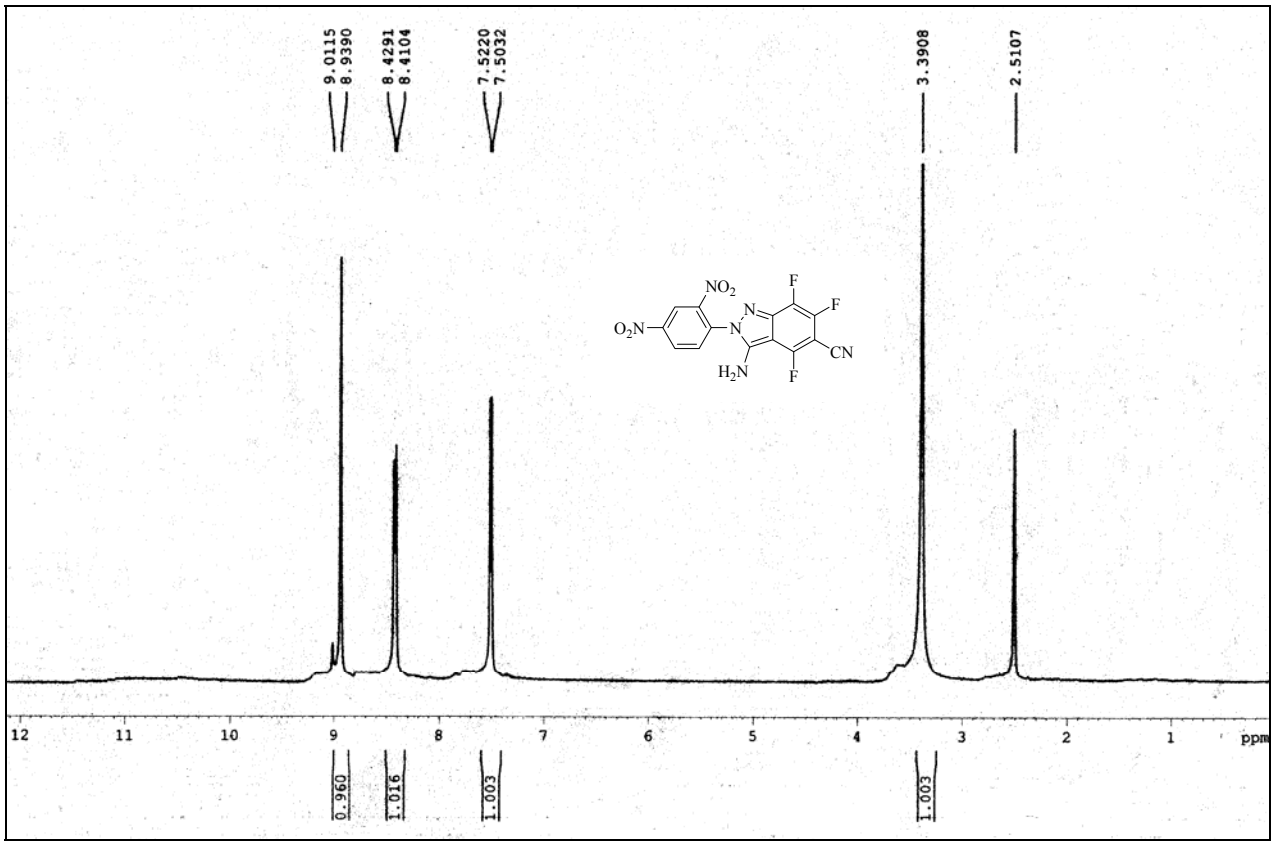


Figure 36. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **7a**

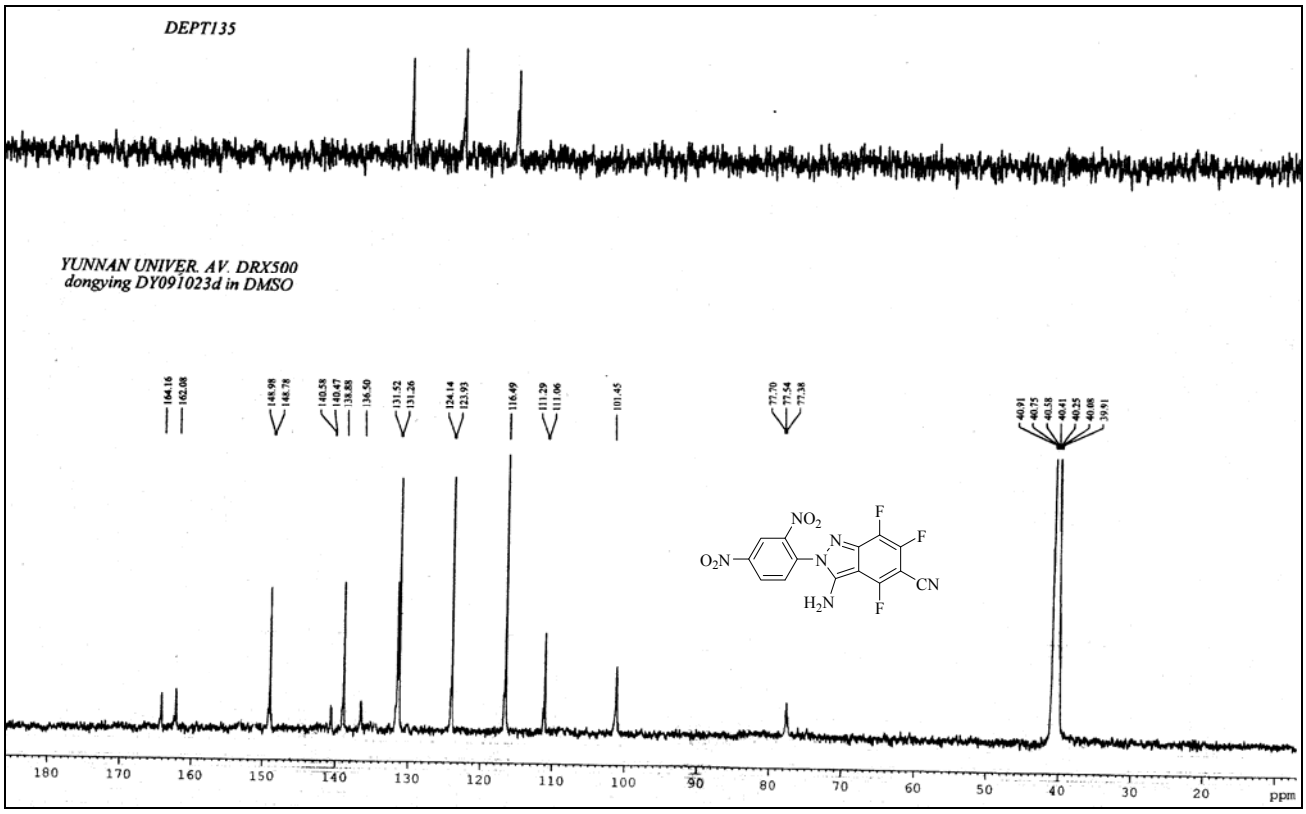


Figure 37. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **7a**

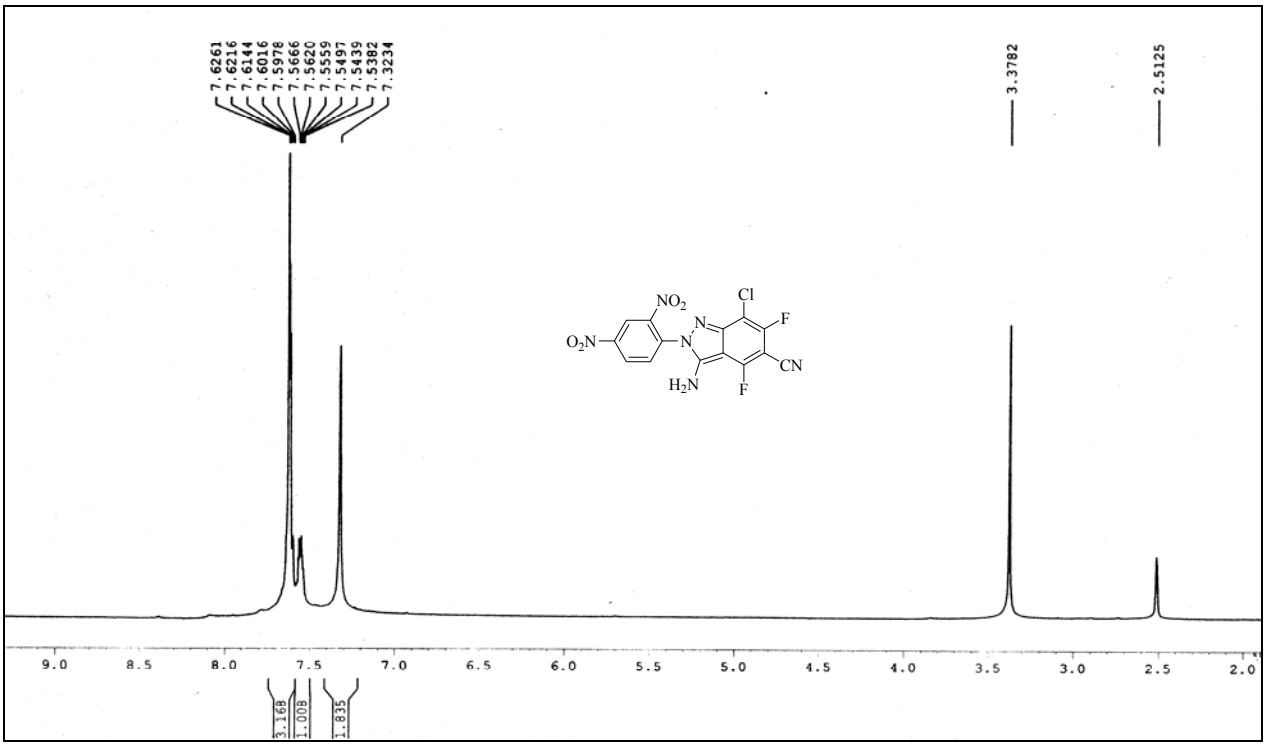


Figure 38. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **7b**

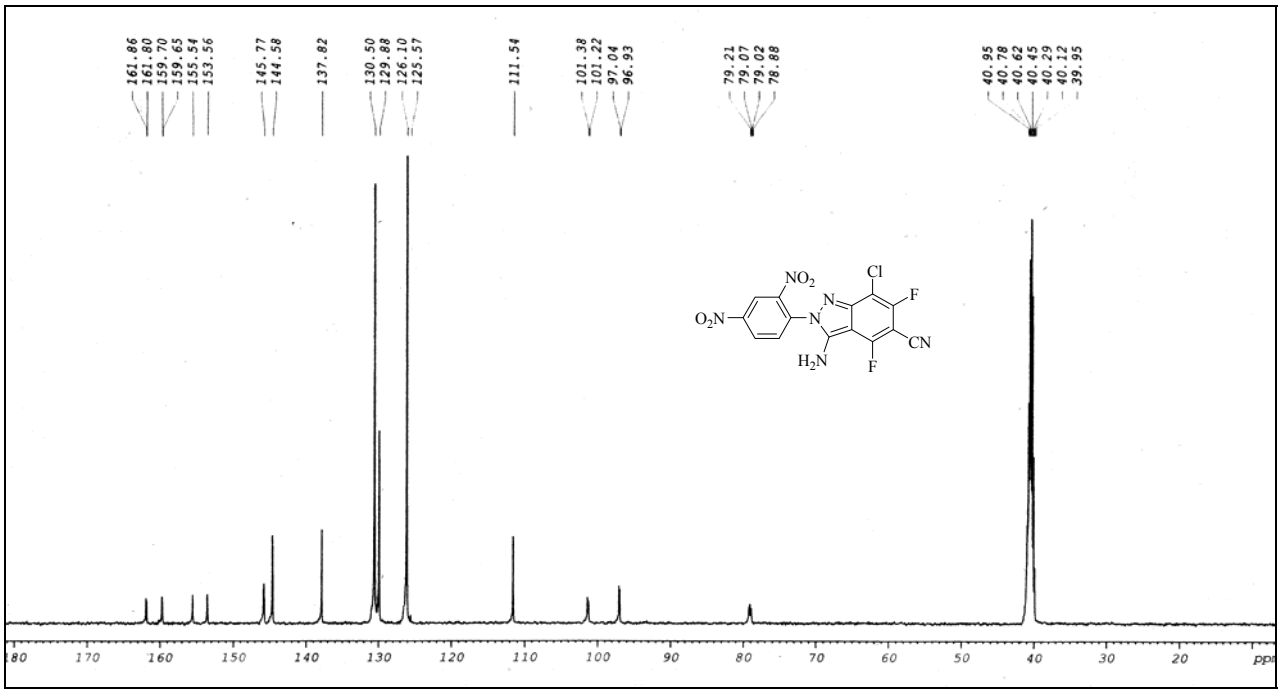


Figure 39. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **7b**

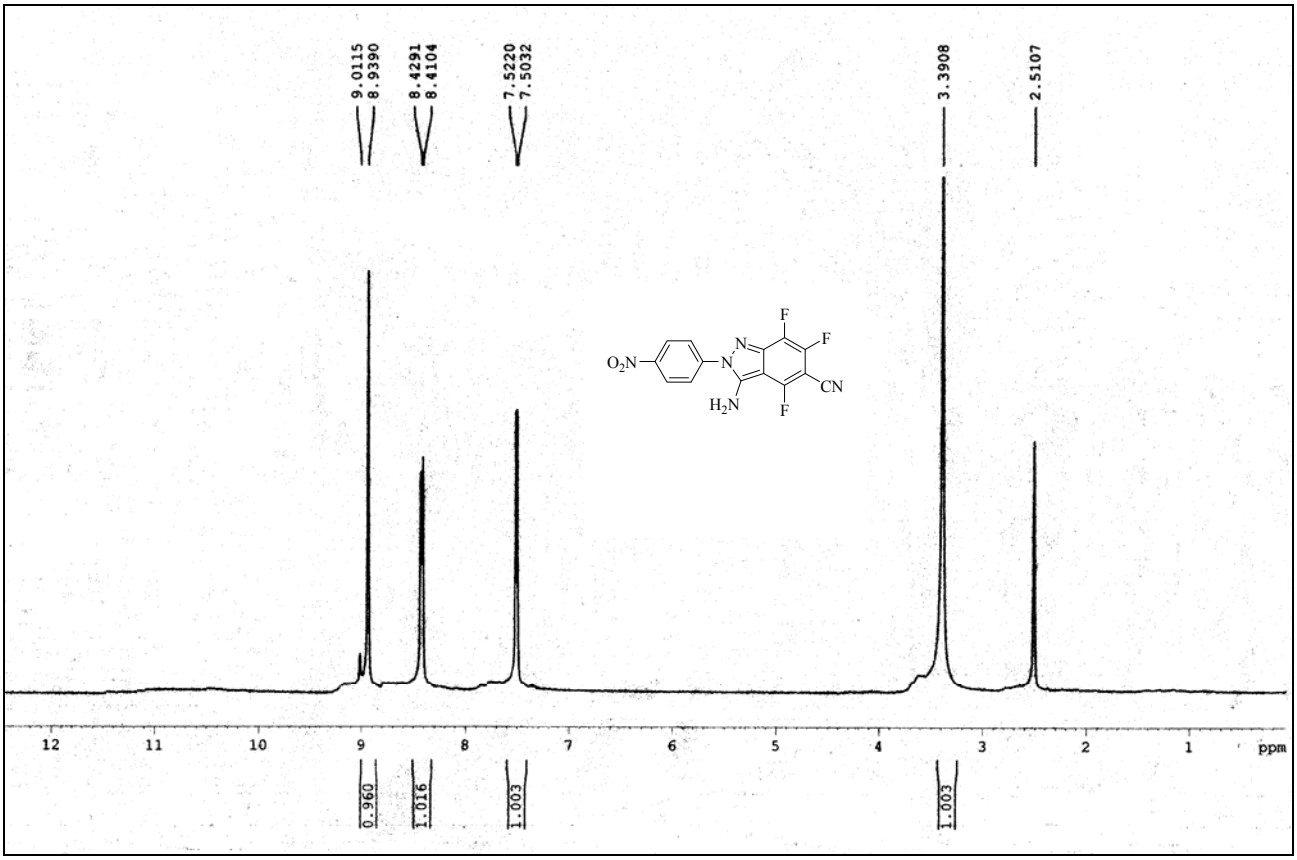


Figure 40. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **7c**

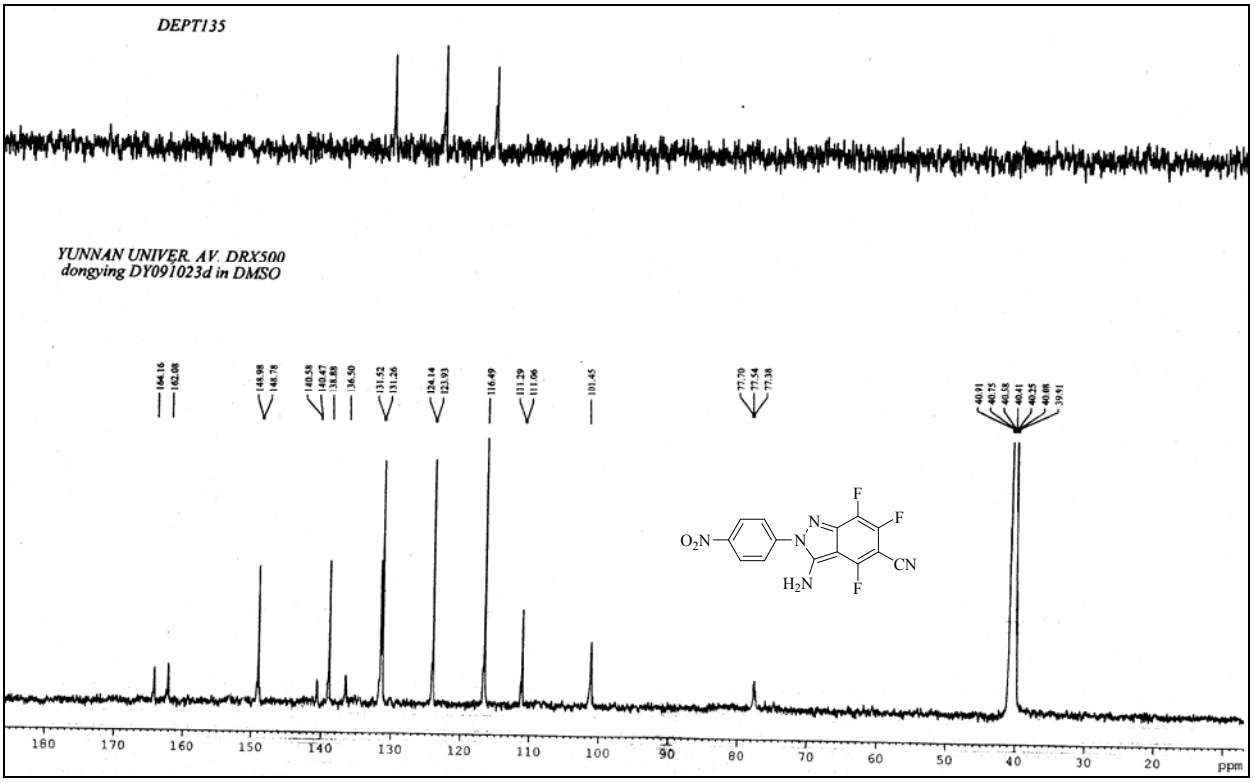


Figure 41. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **7c**

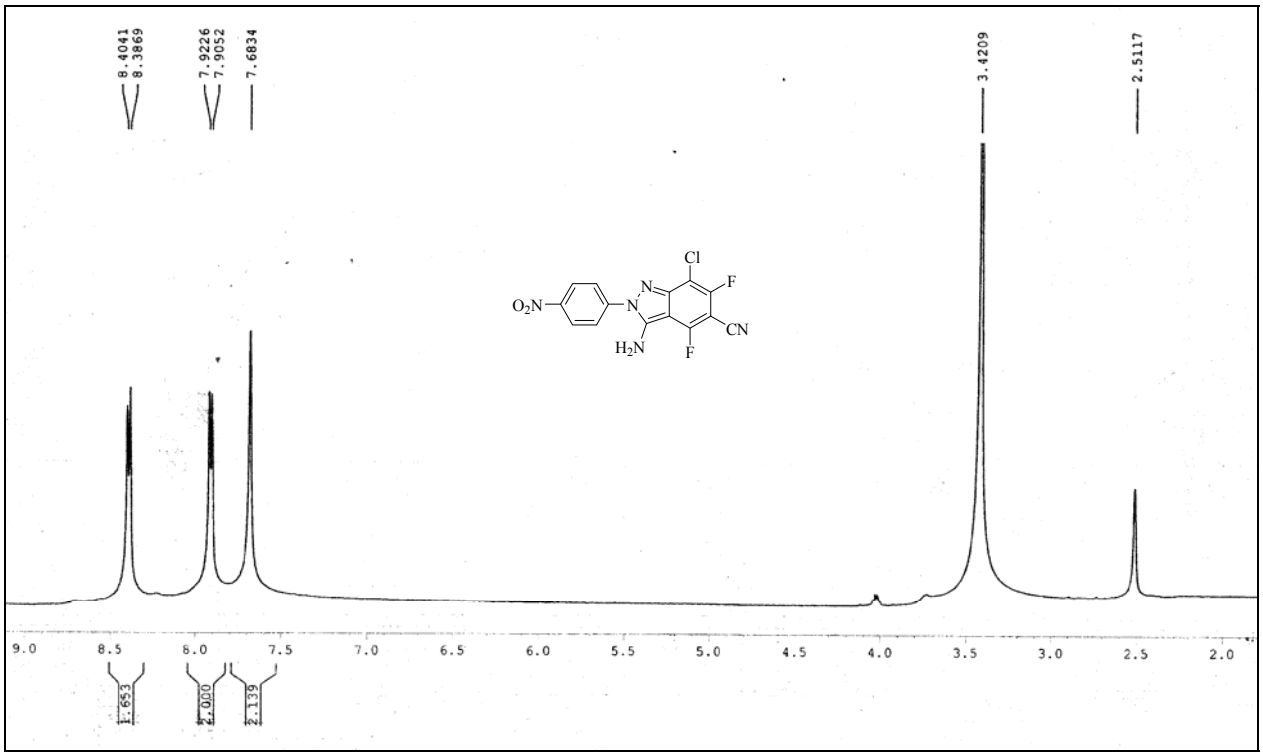


Figure 42. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **7d**

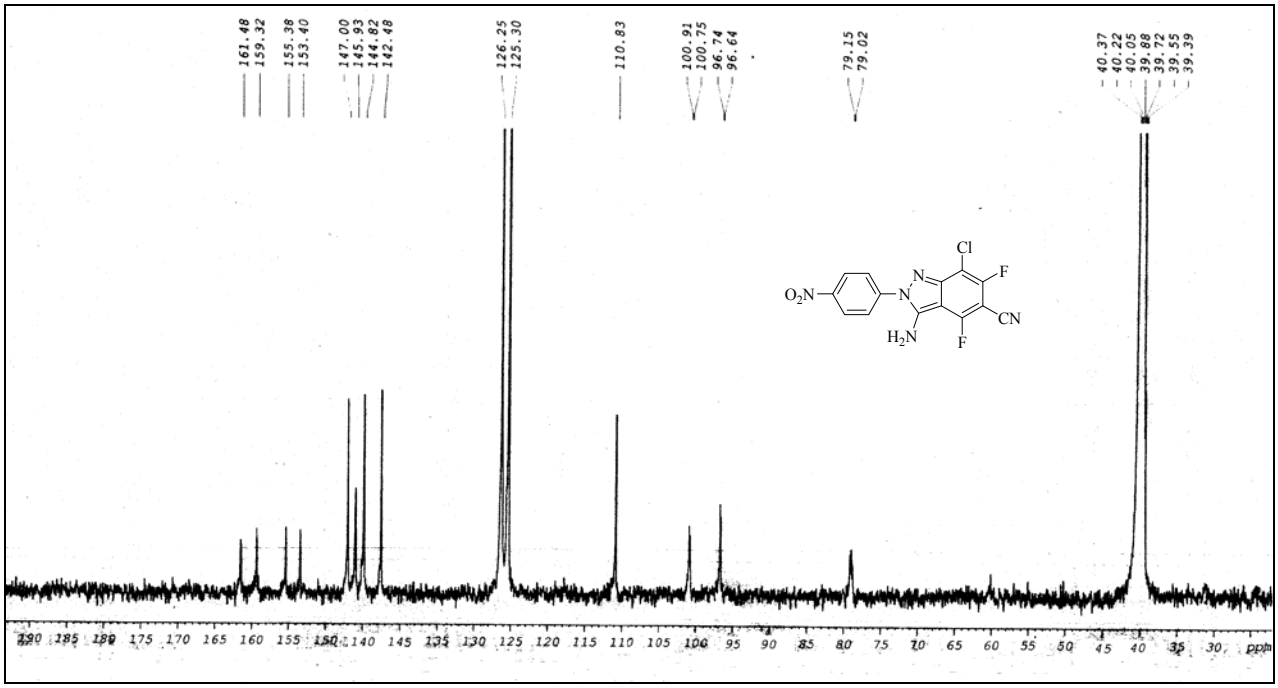


Figure 43. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **7d**

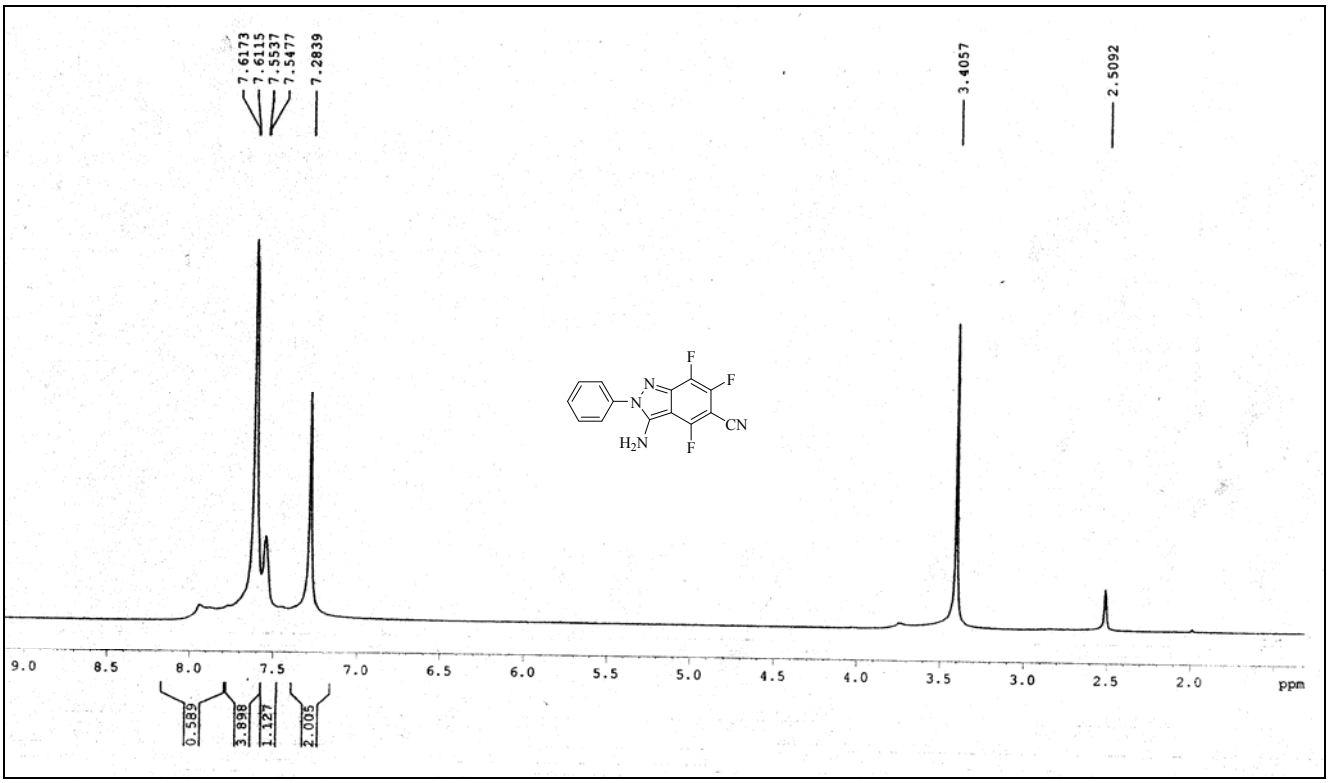


Figure 44. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **7e**

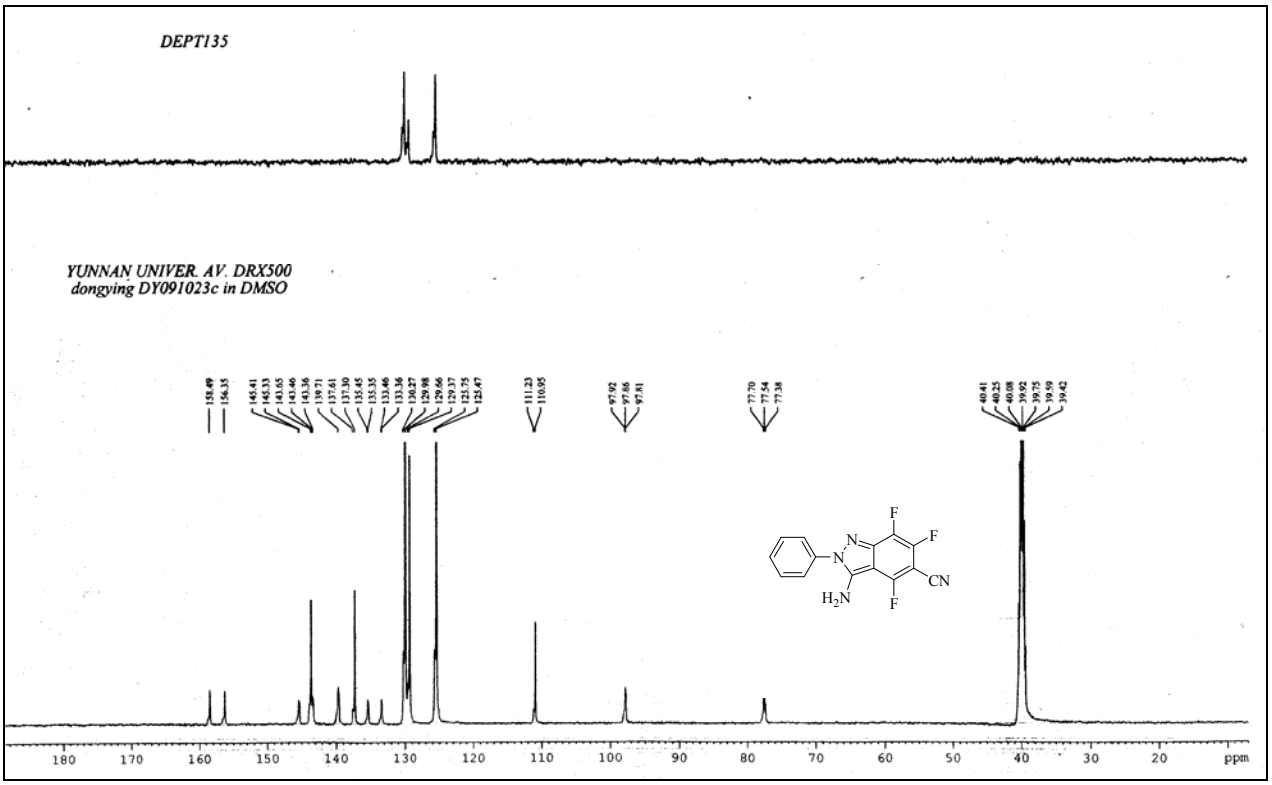


Figure 45. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **7e**

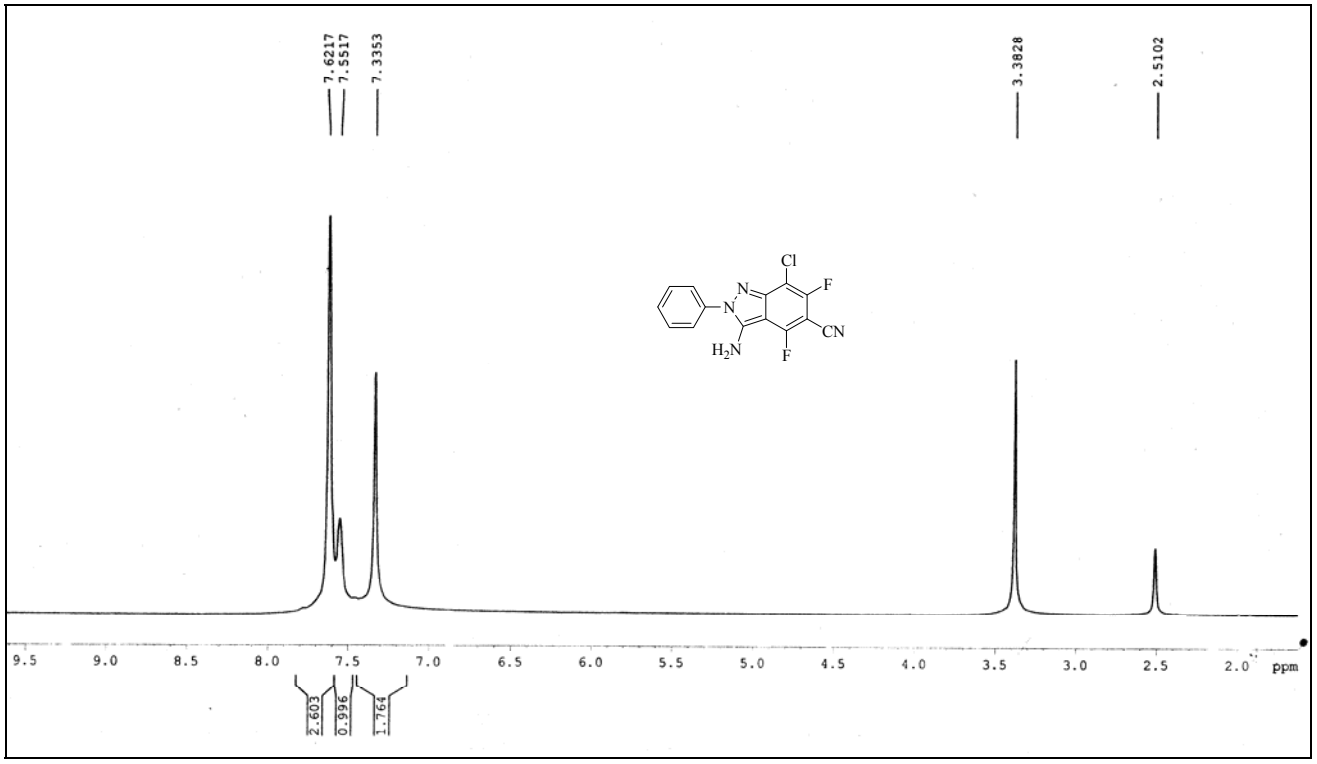


Figure 46. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **7f**

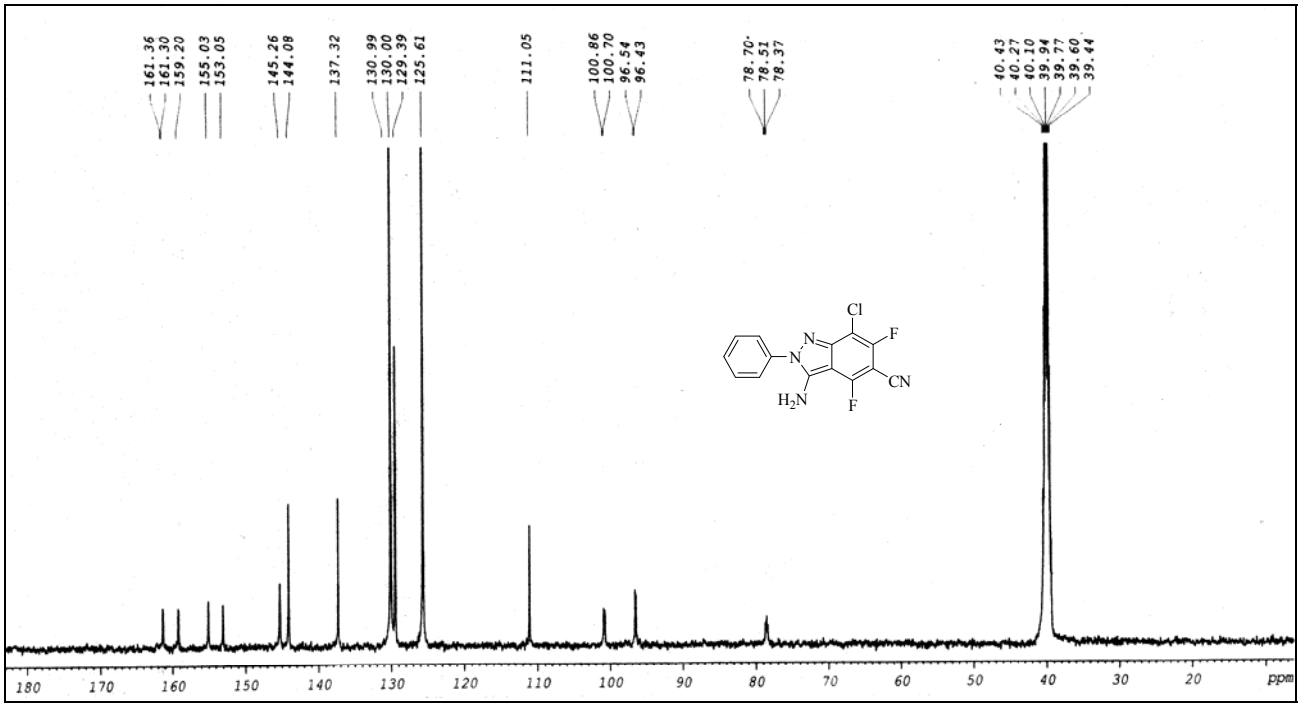


Figure 47. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **7f**

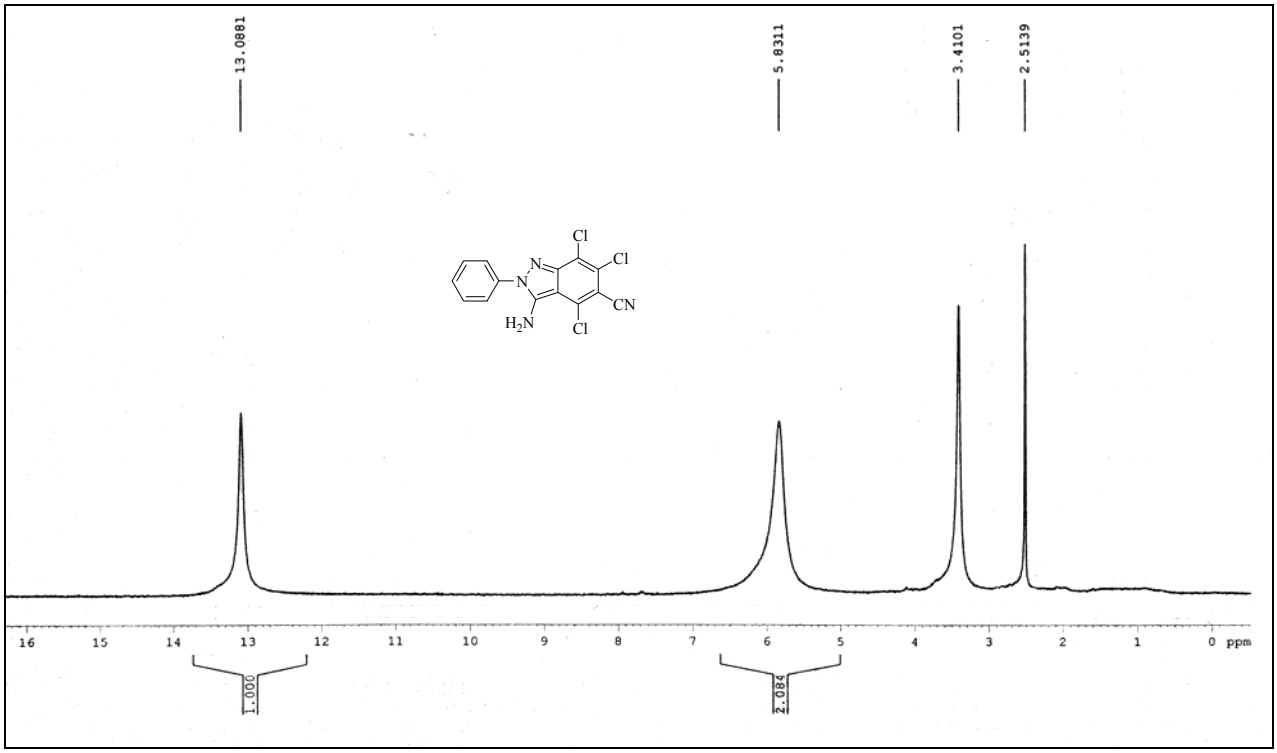


Figure 48. ^{1}H NMR (500 MHz, DMSO-d_6) spectra of compound **7g**

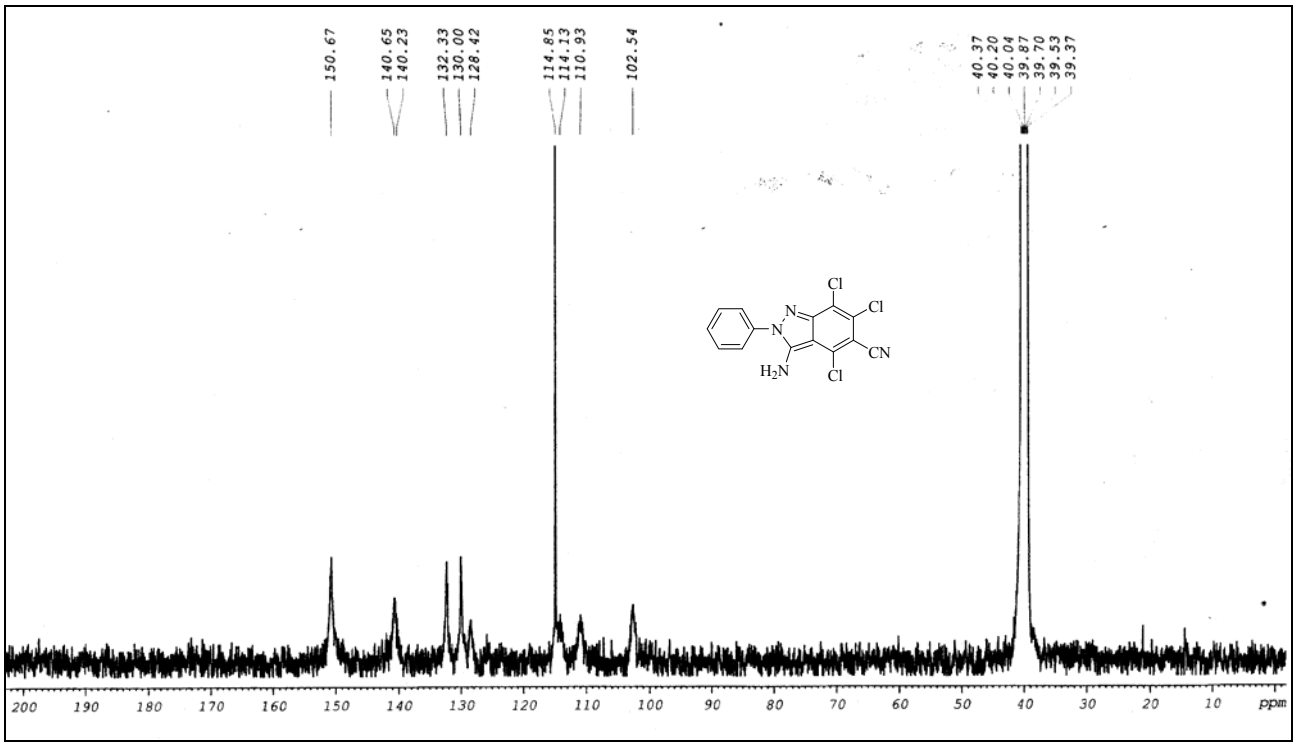


Figure 49. ^{13}C NMR (125 MHz, DMSO-d_6) spectra of compound **7g**