Electronic Supplementary Information (ESI)

Green Chemistry

Four–component catalyst–free reaction in water: Combinatorial library synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile derivatives

*Kandhasamy Kumaravel and Gnanasambandam Vasuki**

Department of Chemistry, Pondicherry University, Puducherry-605 014, India.

vasukig@gmail.com & vasuki.che@pondiuni.edu.in

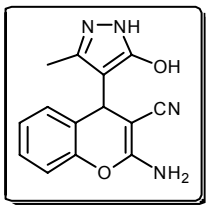
General methods: Hydrazine hydrate, *β*-keto ester and malononitrile were purchased from commercial sources and used without purification. 2-hydroxybenzaldehydes were prepared from standard procedures. All reactions were performed at the room temperature (25-30 ^{o}C) under open atmosphere in a round bottom flask equipped with magnetic stir bar for 5-10 min. The reaction progress and product purity were checked by TLC, using 100-400 mesh silica gel. FT-IR spectra were obtained as potassium bromide pellet with a Varian spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400, and tetramethylsilane (TMS) was used as reference. Data for ^{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad). Data for ^{13}C NMR are reported as ppm. LC-MS were recorded using Atlantis dc18 column on Agilent 6320 Ion Trap LC-MS spectrometer.

General procedure for four–component catalyst–free synthesis of 4-pyrazoyl-4*H*-chromenes (5):

To a stirred aqueous mixture of hydrazine hydrate 98% **1** (0.107 g, 2 mmol) and ethyl acetoacetate **2** (0.260 g, 2 mmol), 2–hydroxy benzaldehyde **3** (2 mmol), malononitrile **4** (0.132 g, 2 mmol) were added successively at ambient temperature under an open atmosphere with vigorous stirring for 5–10 min. The precipitated solid was filtered, washed with water and then with 5 mL of ethyl acetate/hexane mixture (1:1). The product obtained was pure by TLC and spectral techniques.

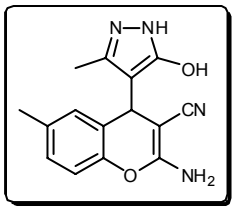
Spectral Characterisation Data (*5a-k)*

2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile



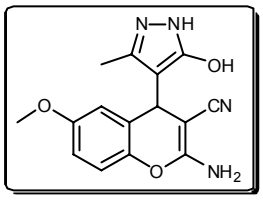
5a White solid; ν_{max}(KBr)/cm^{-1} 3448, 3417, 3351, 2188, 1661, 1610, 1579, 1537, 1487 and 1405; δ_H (400 MHz; DMSO-d_6; TMS) 1.9 (3 H, s, -CH_3), 4.56 (1 H, s, 4-CH), 6.62 (2 H, s, -NH_2), 6.74 (1 H_{arom}, d), 6.93-6.98 (2 H_{arom}, m), 7.08-7.13 (1 H_{arom}, m) and 10.43 (≈ 2 H, br, -OH & -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.8, 28.6, 54.9, 104.9, 115.4, 120.8, 123.4, 124.2, 127.5, 128.9,136.5, 148.3, 159.1 and 160.1; LCMS (*m*/*z*) 269.1 $(M+1)^+$.

2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-6-methyl-4*H*-chromene-3-carbonitrile



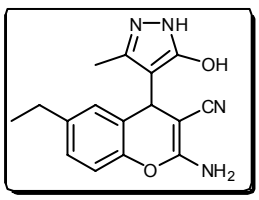
5b White solid; ν_{max}(KBr)/cm^{-1} 3462, 3428, 3356, 2186, 1656, 1595, 1530, 1501 and 1405; δ_H (400 MHz; DMSO-d_6; TMS) 1.9 (3 H, s, -CH_3), 2.17 (3 H, s, -CH_3), 4.57 (1 H, s, 4-CH), 6.62 (2 H, s, -NH_2), 6.7 (1 H_{arom}, s), 6.84 (1 H_{arom}, d), 6.97 (1 H_{arom}, d), 9.6 (≈ 1 H, br, -OH) and 10.78 (≈ 1 H, br, -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.8, 20.2, 28.6, 55, 105, 120.9 123.1, 128.1.128.9, 133.1, 136.5, 146.4, 159 and 160.1; LCMS (*m*/*z*) 283.1 $(M+1)^+$.

2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-6-methoxy-4*H*-chromene-3-carbonitrile



5c White solid; ν_{max}(KBr)/cm^{-1} 3495,3361, 2185, 1655, 1595, 1529, 1499 and 1406; δ_H (400 MHz; DMSO-d_6; TMS) 1.9 (3 H, s, -CH_3), 3.63 (3 H, s, -CH_3), 4.58 (1 H, s, 4-CH), 6.5 (1 H_{arom}, d), 6.51 (2 H, s, -NH_2), 6.75 (1 H_{arom}, d), 6.89 (1 H_{arom}, d), and 10.48 (≈ 2 H, br, -OH & -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.7, 29, 54.4, 104.8, 113, 113.1, 116.4, 120.9, 124.5, 136.5, 142.4, 155.4, 159 and 160.3; LCMS (*m*/*z*) 299.1 $(M+1)^+$.

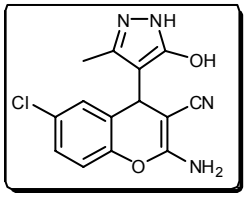
2-amino-6-ethyl-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile



5d White solid; ν_{max}(KBr)/cm^{-1} 3464, 3361, 2185, 1655, 1589, 1573 and 1406; δ_H (400 MHz; DMSO-d_6; TMS) 1.07 (3 H, t, -CH_3), 1.94 (3 H, s, -CH_3), 2.46 (2 H, q, -CH_2), 4.57 (1 H, s, 4-CH), 6.64 (2 H, s, -NH_2), 6.81 (1 H_{arom}, s), 6.85 (1 H_{arom}, d), 7.0 (1 H_{arom}, d), 9.78 (≈ 1 H, br, - OH) and 10.69 (≈ 1 H, br, -NH); δ_C (100 MHz; DMSO-

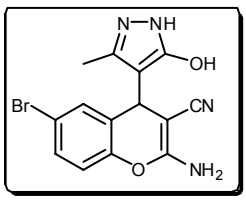
d_6; TMS) 9.9, 15.5, 27.3, 28.7, 54.9, 105.0, 115.4, 120.9,123.2, 126.8, 127.7, 136.0, 139.5, 146.5, 159.0 and 160.2; LCMS (*m*/*z*) 297.1 $(M+1)^+$.

2-amino-6-chloro-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile



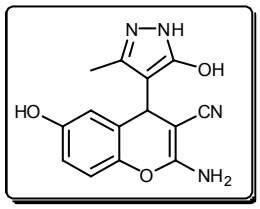
5e White solid; ν_{max}(KBr)/cm^{-1} 3455, 3348, 2190, 1658, 1606, 1531, 1479 and 1405; δ_H (400 MHz; DMSO-d_6; TMS) 2.01 (3 H, s, -CH_3), 4.62 (1 H, s, 4-CH), 6.77 (2 H, s, -NH_2), 6.97-6.99 (2 H_{arom}, m), 7.2-7.23 (1 H_{arom}, m) and 10.58 (≈ 2 H, br, -OH & -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.8, 28.7, 54.6, 104.5, 117.4, 120.5, 125.7, 127.5, 127.6, 128.2,136.0, 147.3, 159.0 and 160.8; LCMS (*m*/*z*) 303.1 $(M+1)^+$.

2-amino-6-chloro-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile



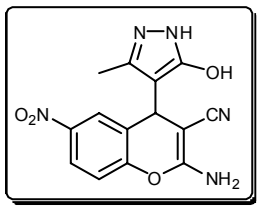
5f White solid; ν_{max}(KBr)/cm^{-1} 3454, 3352, 2188, 1657, 1605, 1529, 1477 and 1405; δ_H (400 MHz; DMSO-d_6; TMS) 2.01 (3 H, s, -CH_3), 4.63 (1 H, s, 4-CH), 6.76 (2 H, s, -NH_2), 6.92 (1 H_{arom}, d), 7.11 (1 H_{arom}, d), 7.32-7.35 (1 H_{arom}, m) and 10.63 (≈ 2 H, br, -OH & -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.8, 28.6, 54.7, 104.5, 115.5, 117.9, 128.5, 126.1, 130.4, 131.1, 136.7, 147.7, 159.0 and 159.7; LCMS (*m*/*z*) 347.05 $(M+1)^+$.

2-amino-6-hydroxy-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile



5g White solid; ν_{max}(KBr)/cm^{-1} 3448, 3344, 2191, 1652, 1596, 1508, 1462 and 1409; δ_H (400 MHz; DMSO-d_6; TMS) 1.93 (3 H, s, -CH_3), 4.56 (1 H, s, 4-CH), 6.39 (1 H_{arom}, d), 6.52 (2 H, s, -NH_2), 6.54-6.57 (1 H_{arom}, m), 6.77 (1 H_{arom}, d), 9.17 (1 H, s, -OH) and 10.43 (≈ 2 H, br, -OH & -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.9, 28.8, 54.6, 104.8, 114.2, 114.5, 116.2, 121.0, 124.3, 136.6, 141.3, 153.6, 159.0 and 160.4; LCMS (*m*/*z*) 285.4 $(M+1)^+$.

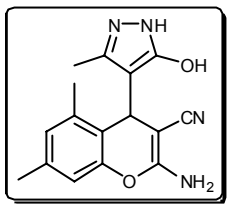
2-amino-6-nitro-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile



5h White solid; ν_{max}(KBr)/cm^{-1} 3425, 3358, 2198, 1665, 1585, 1525 and 1401; δ_H (400 MHz; DMSO-d_6; TMS) 2.08 (3 H, s, -CH_3), 4.77 (1 H, s, 4-CH), 6.96 (2 H, s, -NH_2), 7.21 (1 H_{arom}, d), 6.85 (1 H_{arom}, d), 7.87-7.88 (1 H_{arom}, m), 8.05-8.08 (1 H_{arom}, m), 9.84 (≈ 1 H, br, - OH) and 11.28 (≈ 1 H, br, -NH); δ_C (100 MHz;

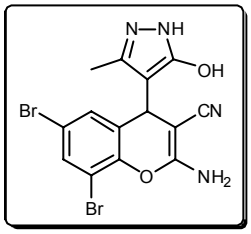
DMSO-d_6; TMS) 9.8, 28.6, 54.9, 104.3, 117.0, 120.1, 123.4, 124.7, 125.0, 136.7, 143.5, 153.0, 159 and 159.2; LCMS (*m*/*z*) 314.2 $(M+1)^+$.

2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-5,7-dimethyl-4*H*-chromene-3-carbonitrile



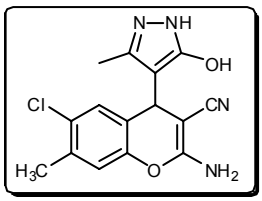
5i White solid; ν_{max}(KBr)/cm^{-1} 3428, 3330, 2189, 1658, 1607, 1525 and 1405; δ_H (400 MHz; DMSO-d_6; TMS) 1.83 (3 H, s, -CH_3), 1.94 (3 H, s, -CH_3), 2.15 (3 H, s, -CH_3), 4.34 (1 H, s, 4-CH), 6.5 (2 H, s, -NH_2), 6.55 (1 H_{arom}, s), 6.64 (1 H_{arom}, s), and 10. 91 (≈ 2 H, br, -OH & -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.6, 18.1, 20.4, 26.9, 56.3, 104.1, 113.4, 118.3, 121.1, 126.7, 136.3, 136.5, 149.3 and 159.9; LCMS (*m*/*z*) 297.1 $(M+1)^+$.

2-amino-6,8-dibromo-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile

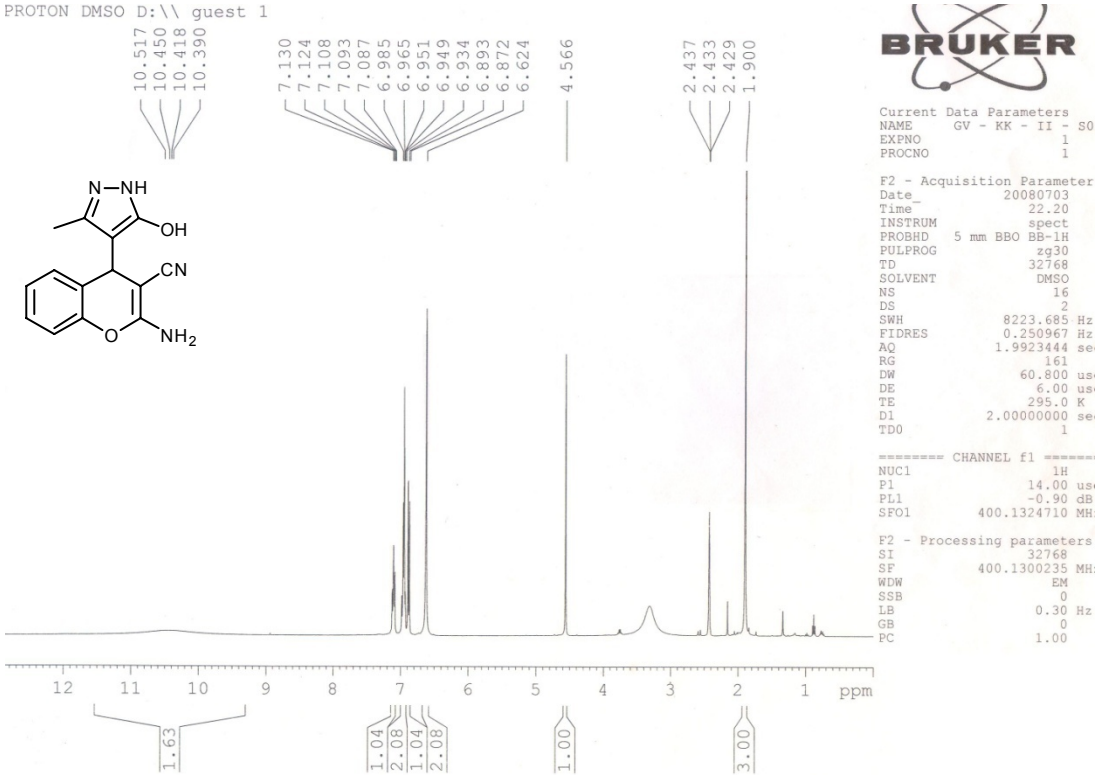


5j White solid; ν_{max}(KBr)/cm^{-1} 3448, 3344, 2191, 1652, 1596, 1508, 1462 and 1408; δ_H (400 MHz; DMSO-d_6; TMS) 2.03 (3 H, s, -CH_3), 4.6 (1 H, s, 4-CH), 6.82 (2 H, s, -NH_2), 7.26 (1 H_{arom}, s), 7.94 (1 H_{arom}, s), 9.75 (≈ 1 H, br, -OH) and 11. 16 (≈ 1 H, br, -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.6, 29.0, 55.2, 104.2, 110.2, 115.7, 120.1, 127.2, 130.6, 132.9, 136.5, 144.9, 158.9 and 159.4; LCMS (*m*/*z*) 427.0 $(M+3)^+$.

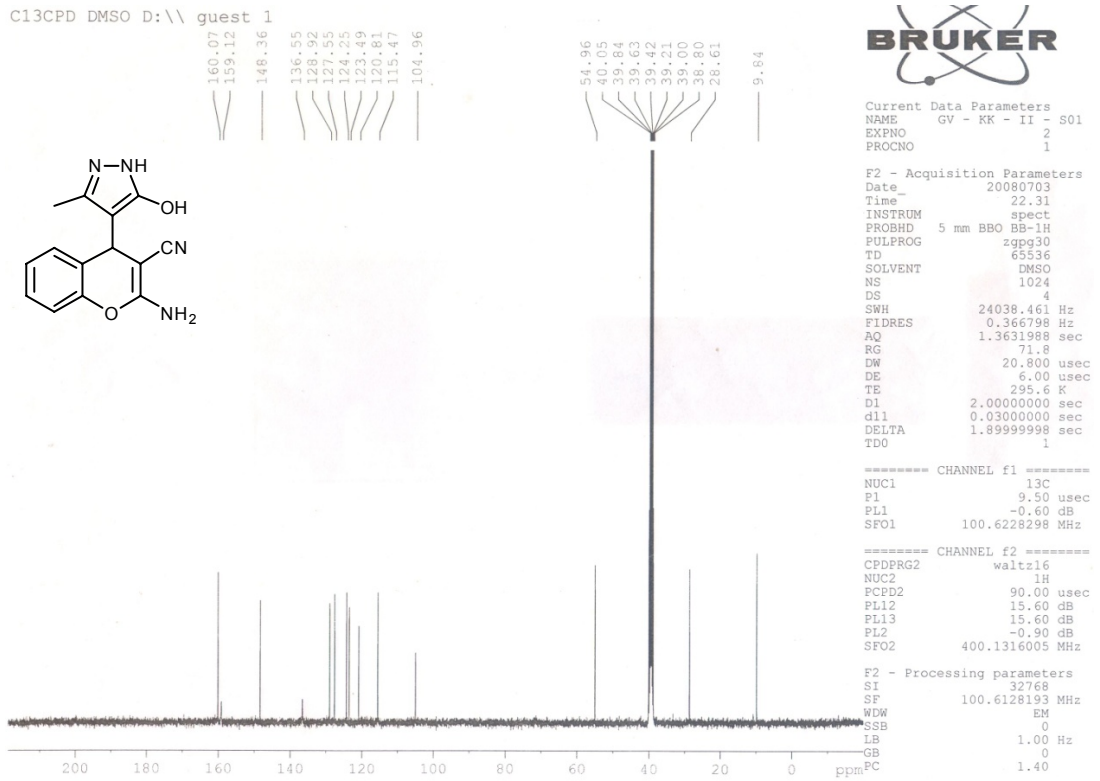
2-amino-6-chloro-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-7-methyl-4*H*-chromene-3-carbonitrile



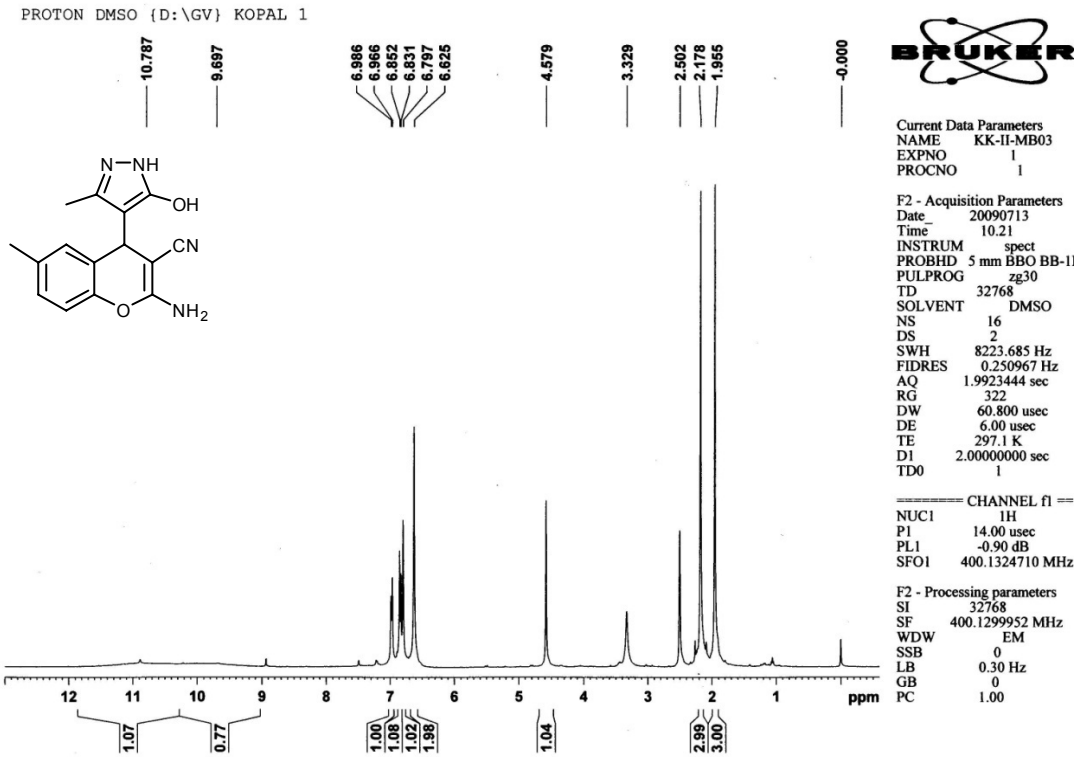
5k White solid; ν_{max}(KBr)/cm^{-1} 3449, 3372, 3174, 2186, 1659, 1610, 1530, 1487 and 1404; δ_H (400 MHz; DMSO-d_6; TMS) 1.99 (3 H, s, -CH_3), 2.25 (3 H, s, -CH_3), 4.58 (1 H, s, 4-CH), 6.74 (2 H, s, -NH_2), 6.96 (2 H_{arom}, s), 10.02 (≈ 1 H, br, -OH) and 10. 80 (≈ 1 H, br, -NH); δ_C (100 MHz; DMSO-d_6; TMS) 9.8, 19.1, 54.7, 104.5, 117.8, 120.6, 123.0, 128.0, 128.4, 134.9, 136.6, 147.0, 159.0 and 159.8; LCMS (*m*/*z*) 317.1 $(M+1)^+$.



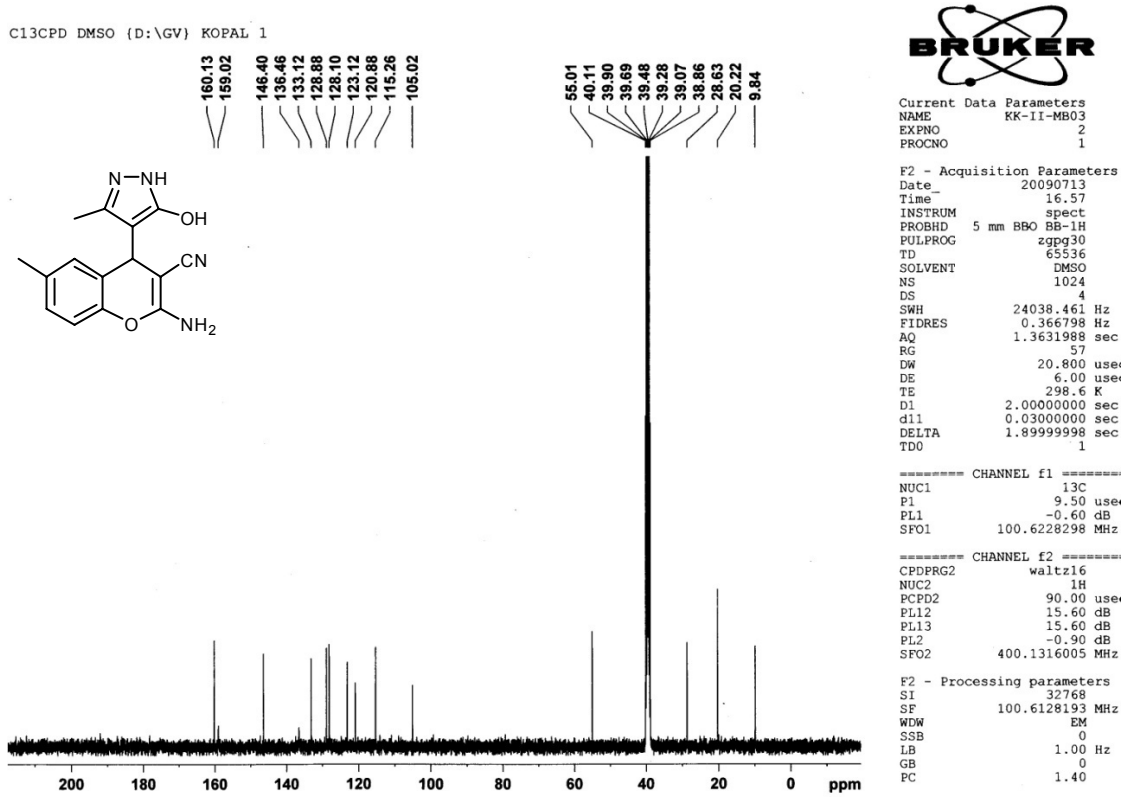
^{1}H NMR Spectrum of *5a*



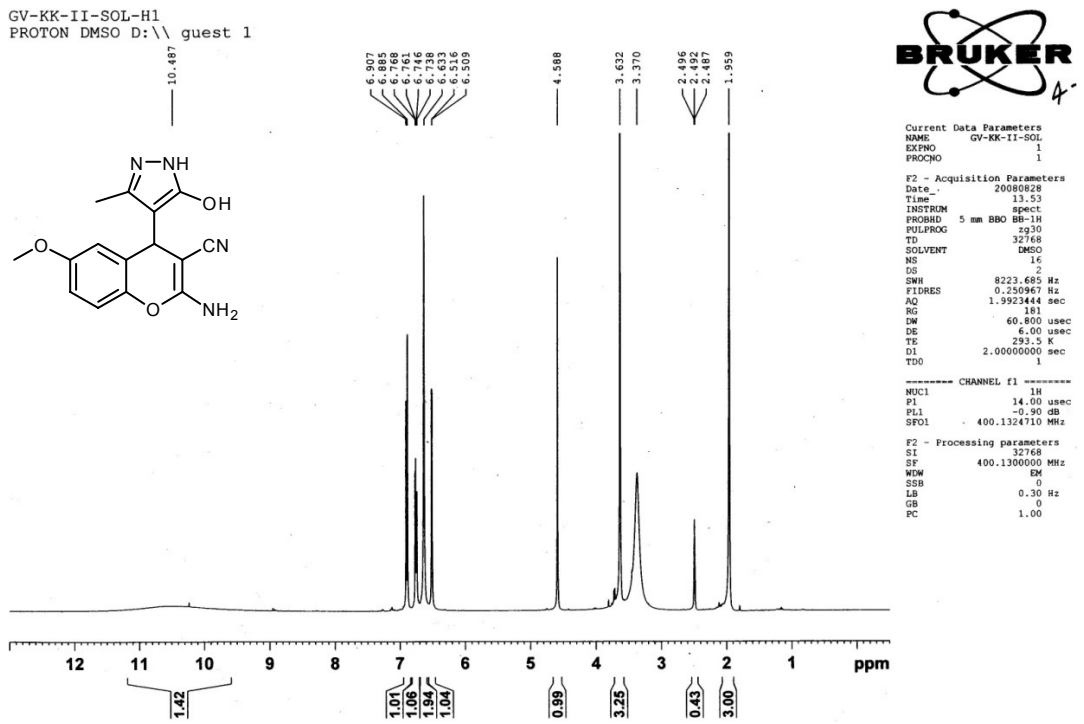
^{13}C NMR Spectrum of *5a*



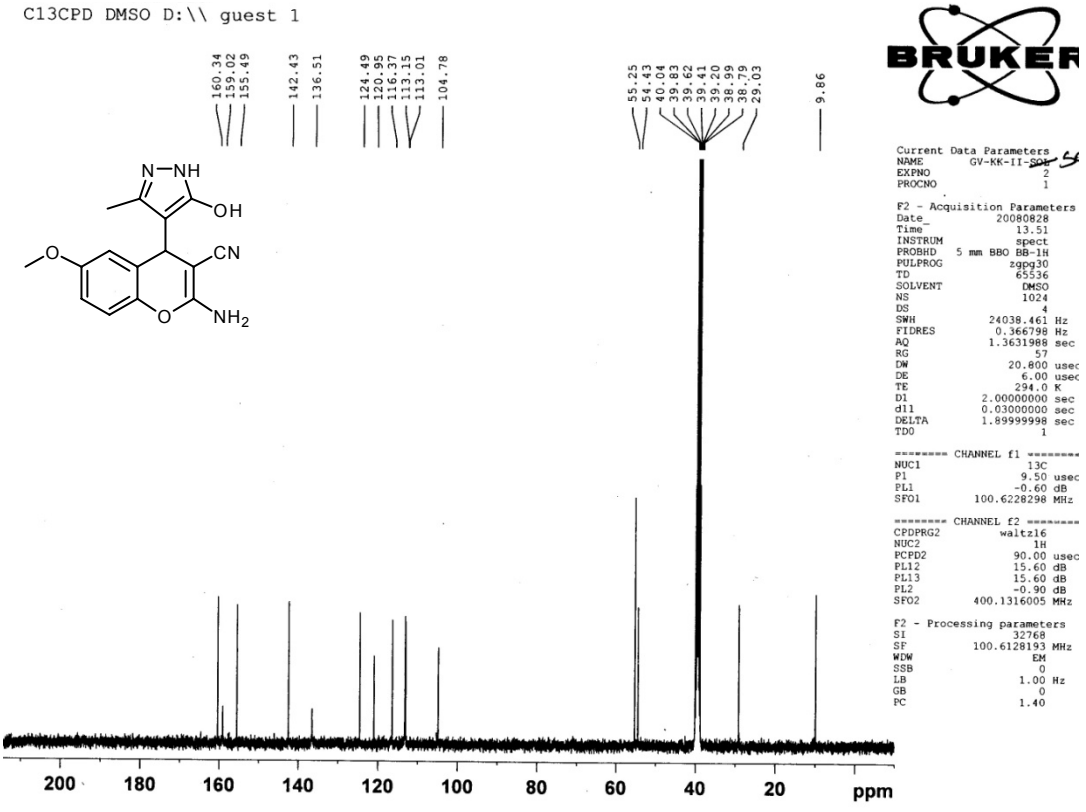
^{1}H NMR Spectrum of *5b*



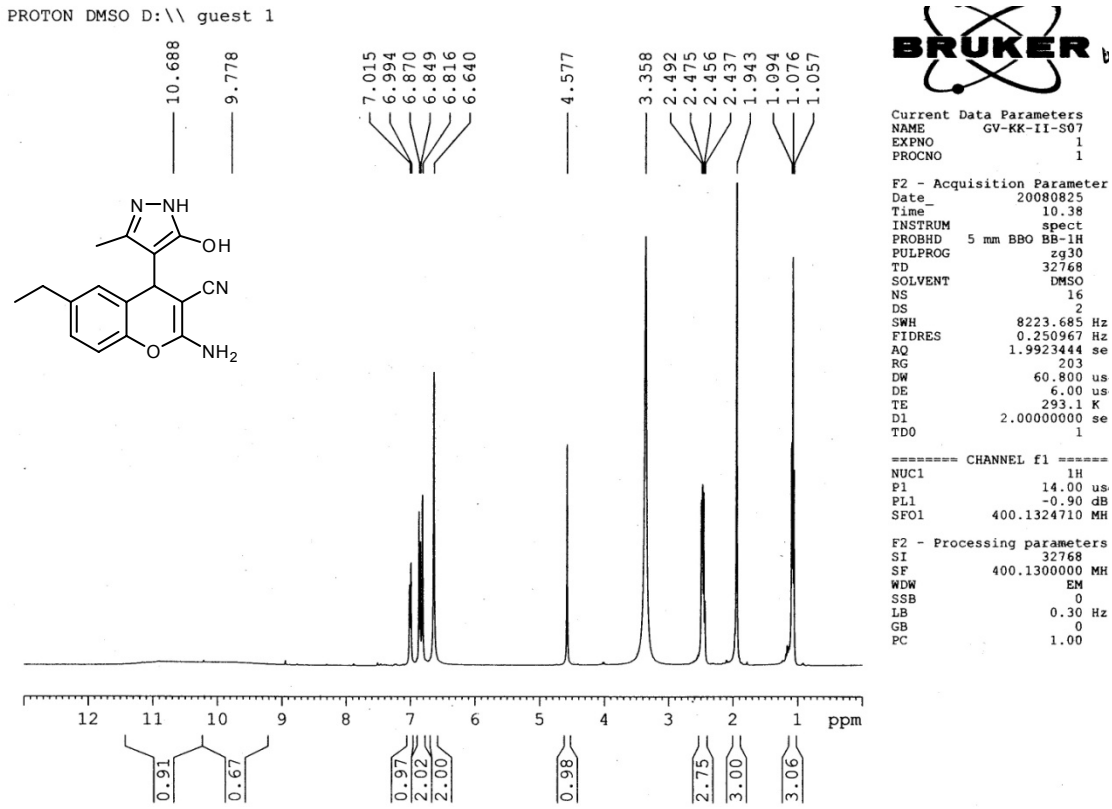
^{13}C NMR Spectrum of *5b*



^{1}H NMR Spectrum of *5c*



^{13}C NMR Spectrum of *5c*



Current Data Parameters
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PROCNO 1

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TD 32768
SOLVENT DMSO
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DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 se
RG 203
DW 60.800 us
DE 6.00 us
TE 293.1 K
D1 2.00000000 se
TD0 1

======== CHANNEL f1 ======
NUC1 1H
P1 14.00 us
PL1 -0.90 dB
SFO1 400.1324710 MH

F2 - Processing parameters
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SF 400.1300000 MH
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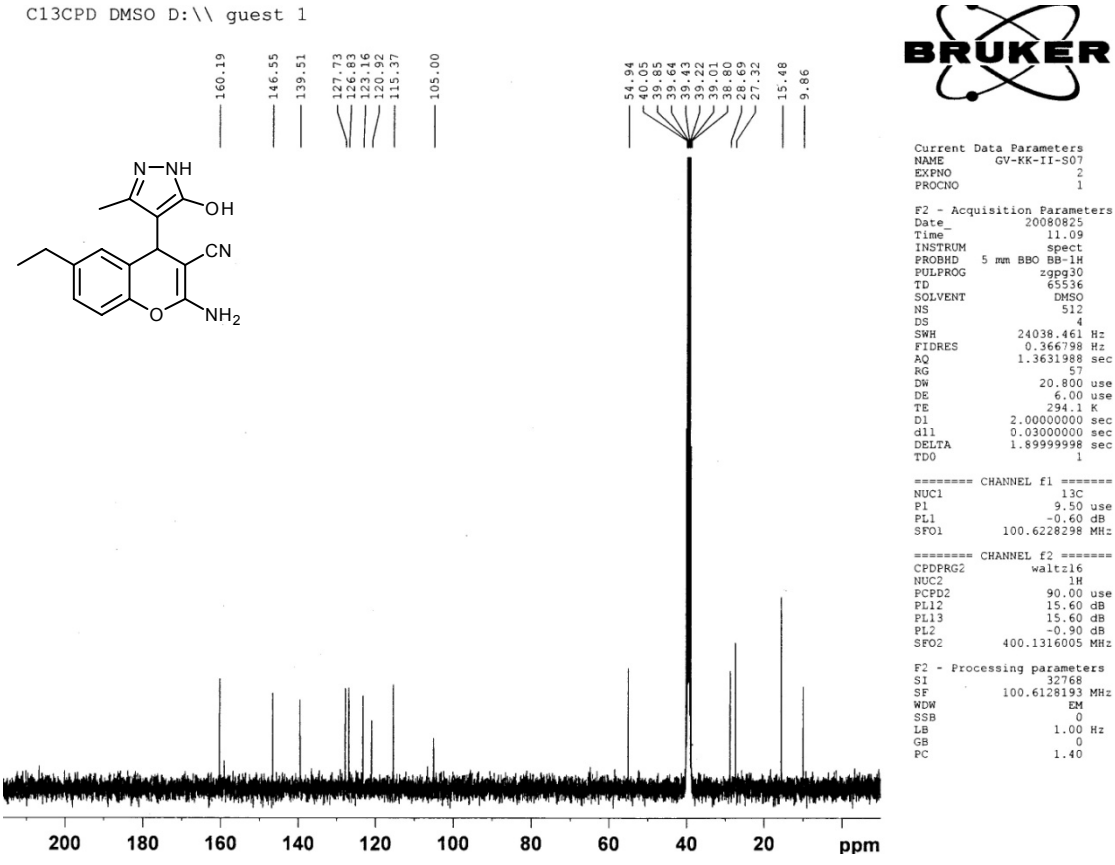
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

^{1}H NMR Spectrum of *5d*



Current Data Parameters
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EXPNO 2
PROCNO 1

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TD 65536
SOLVENT DMSO
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 57
DW 20.800 use
DE 6.00 use
TE 294.1 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 =======
NUC1 13C
P1 9.50 use
PL1 -0.60 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 use
PL12 15.60 dB
PL13 15.60 dB
PL2 -0.90 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
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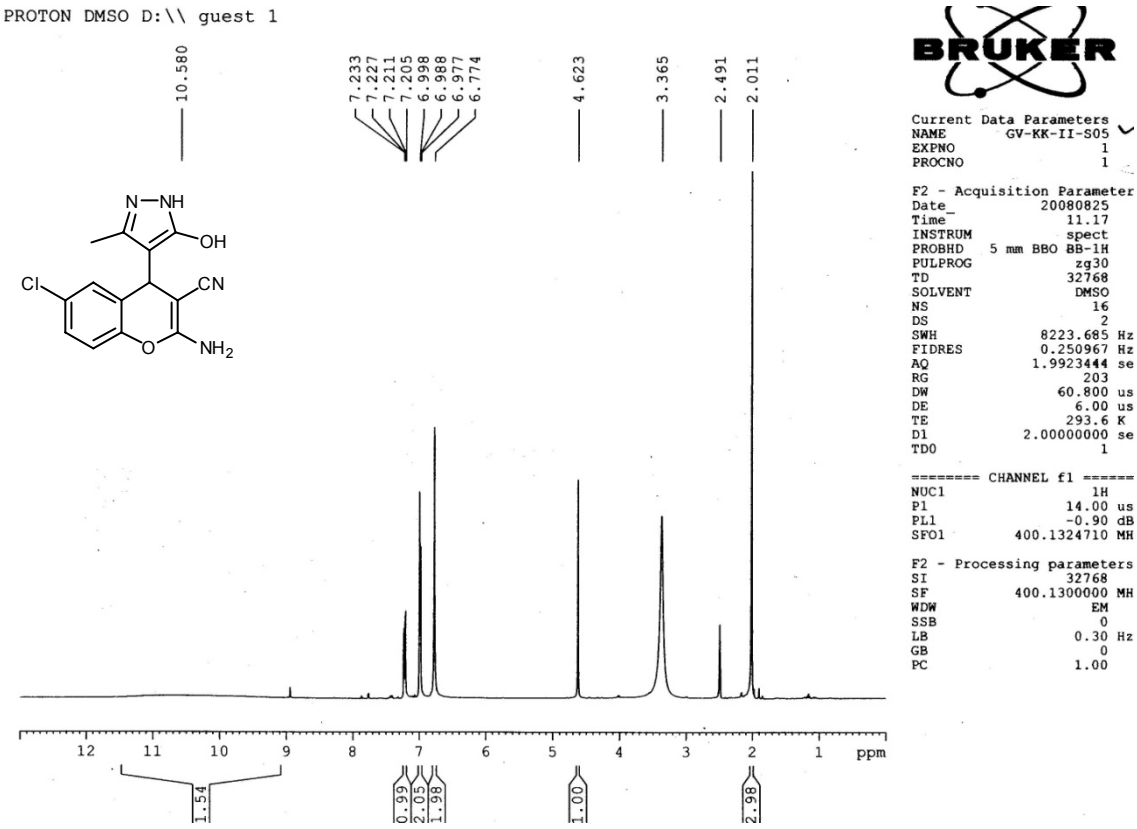
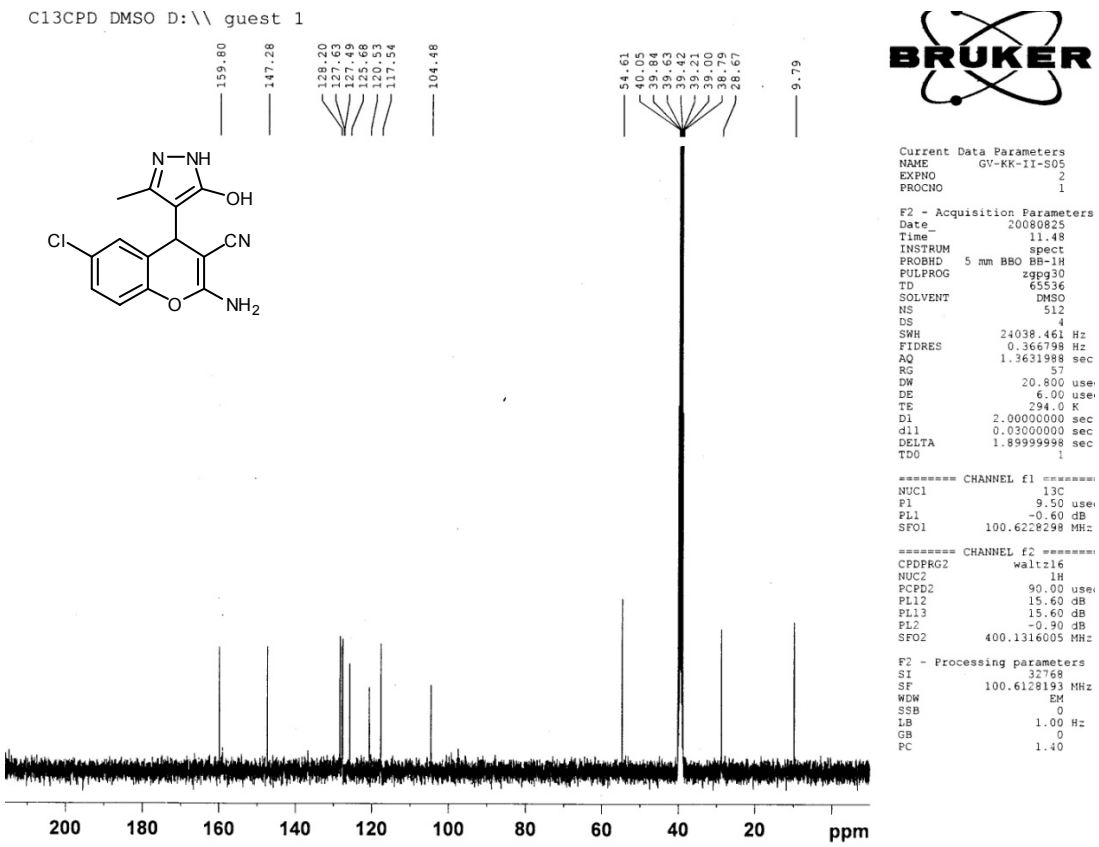
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

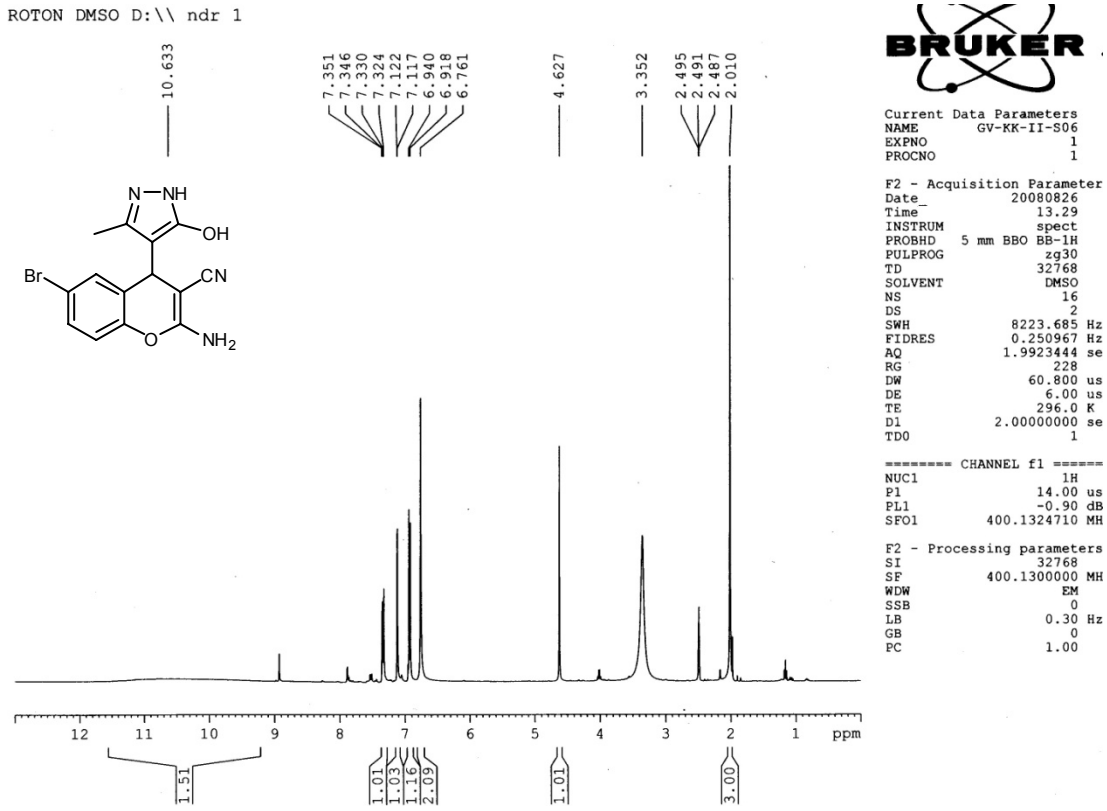
^{13}C NMR Spectrum of *5d*



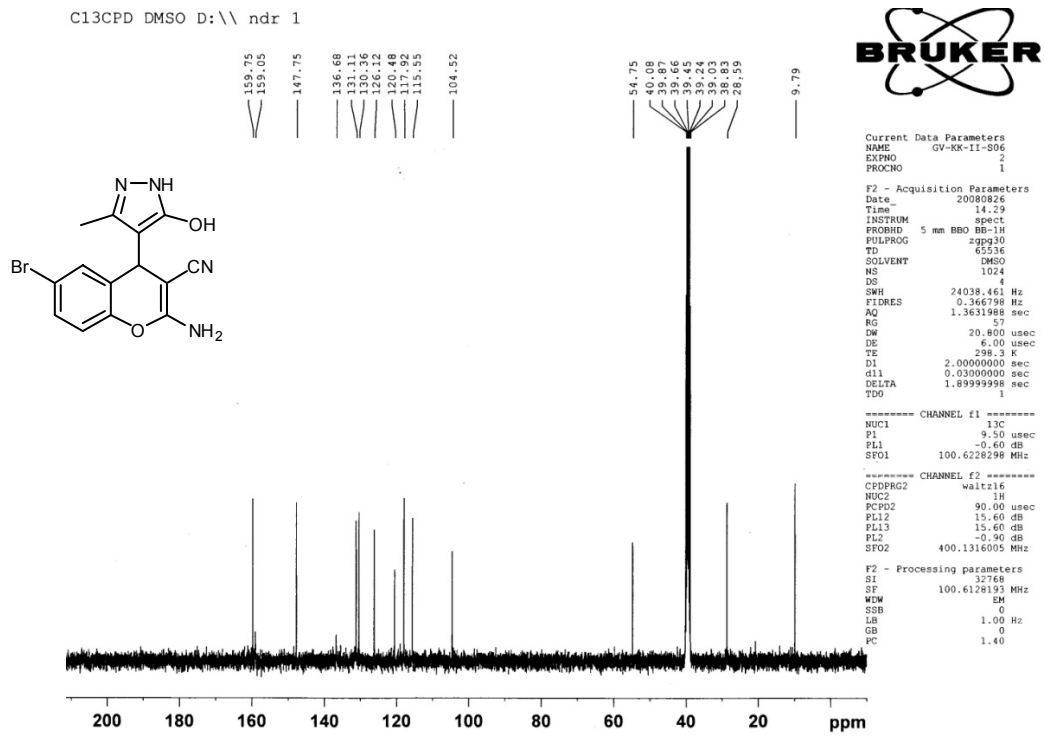
^{1}H NMR Spectrum of *5e*



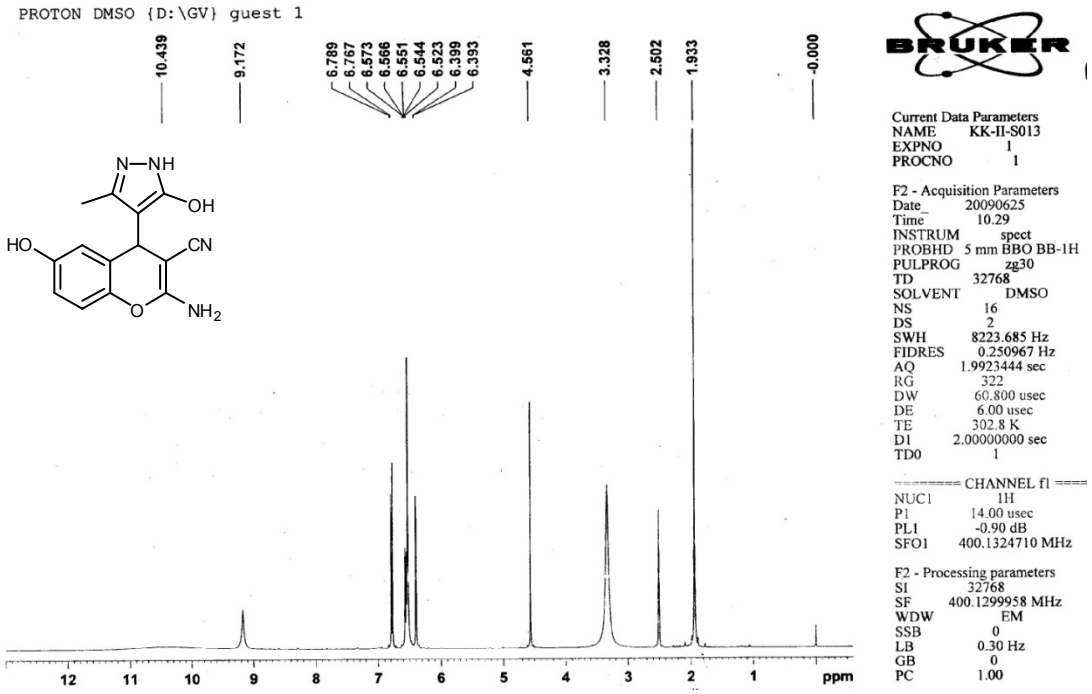
^{13}C NMR Spectrum of *5e*



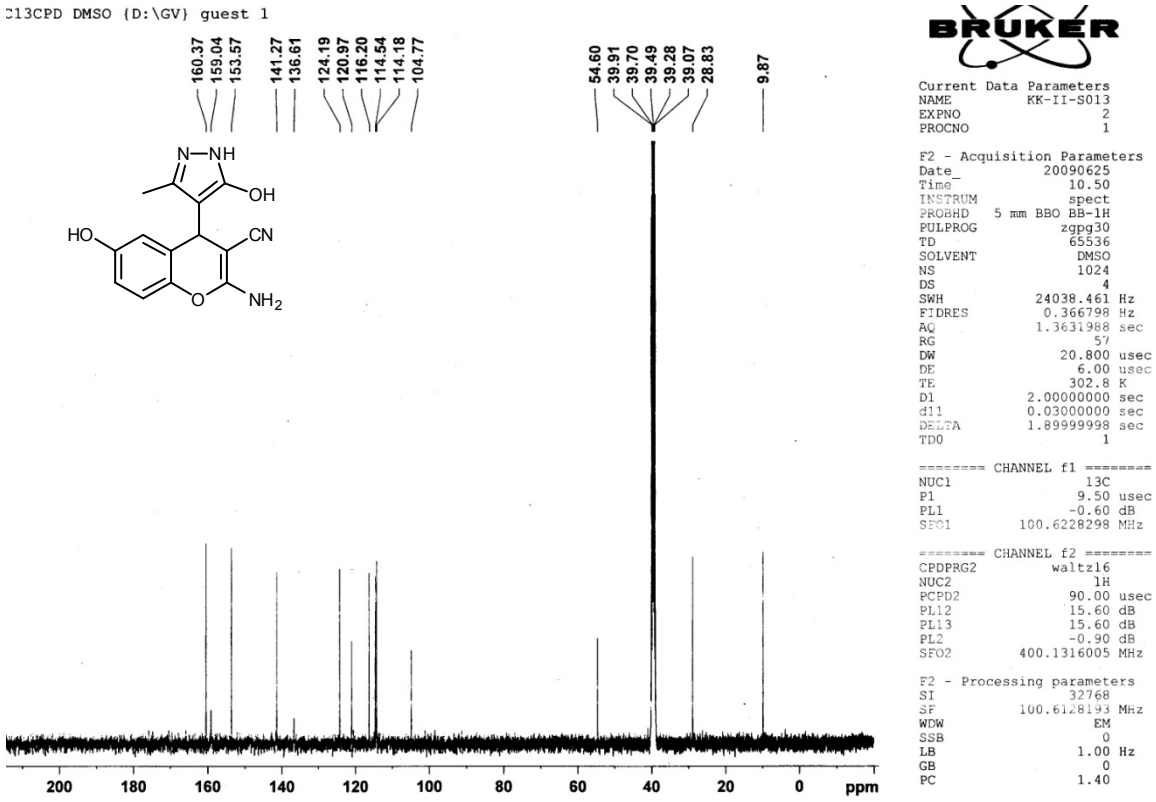
^{1}H NMR Spectrum of *5f*



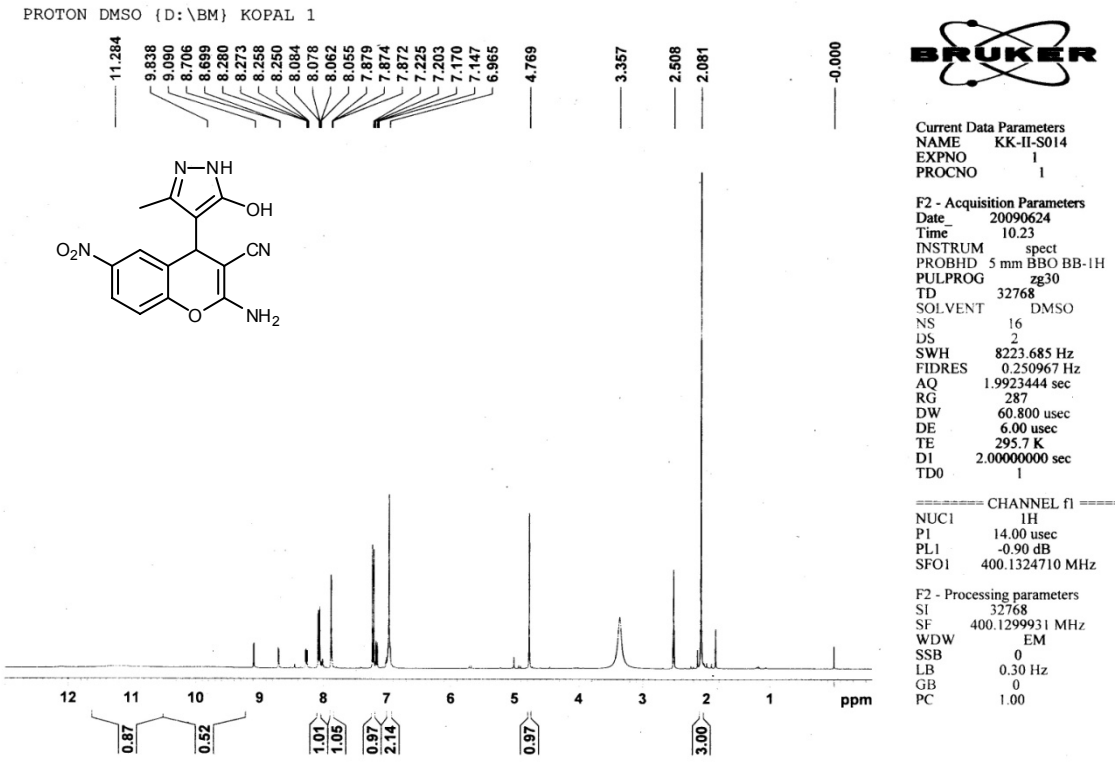
^{13}C NMR Spectrum of *5f*



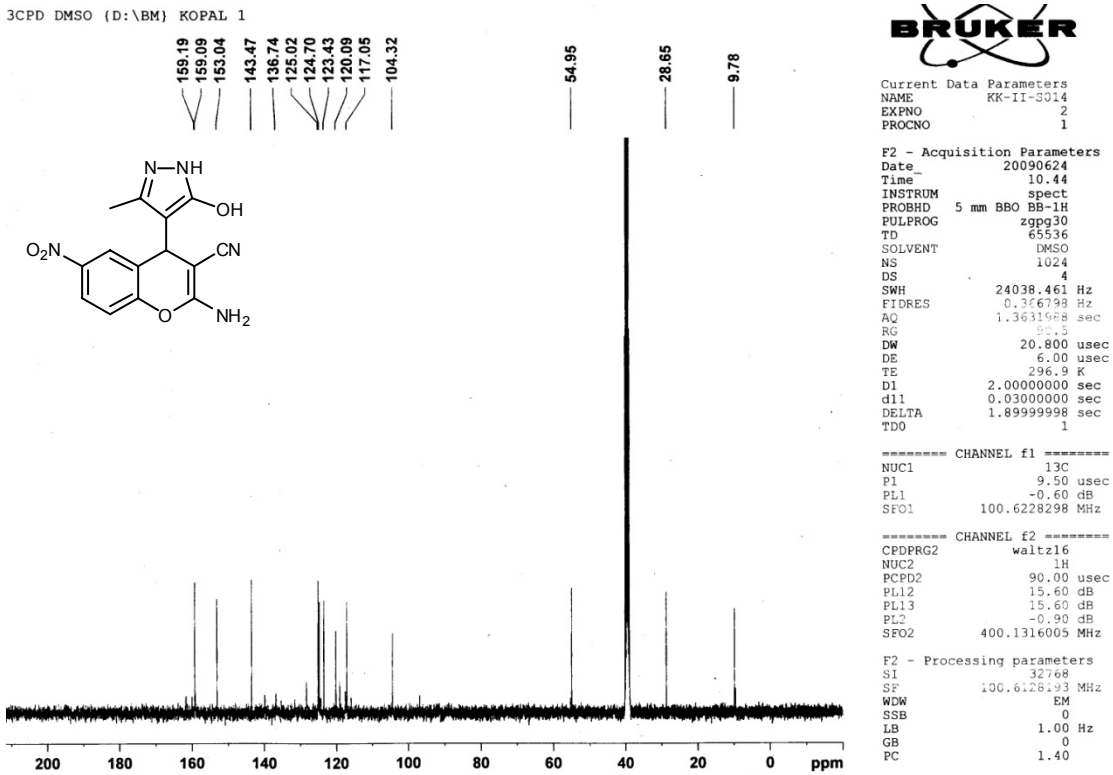
^{1}H NMR Spectrum of *5g*



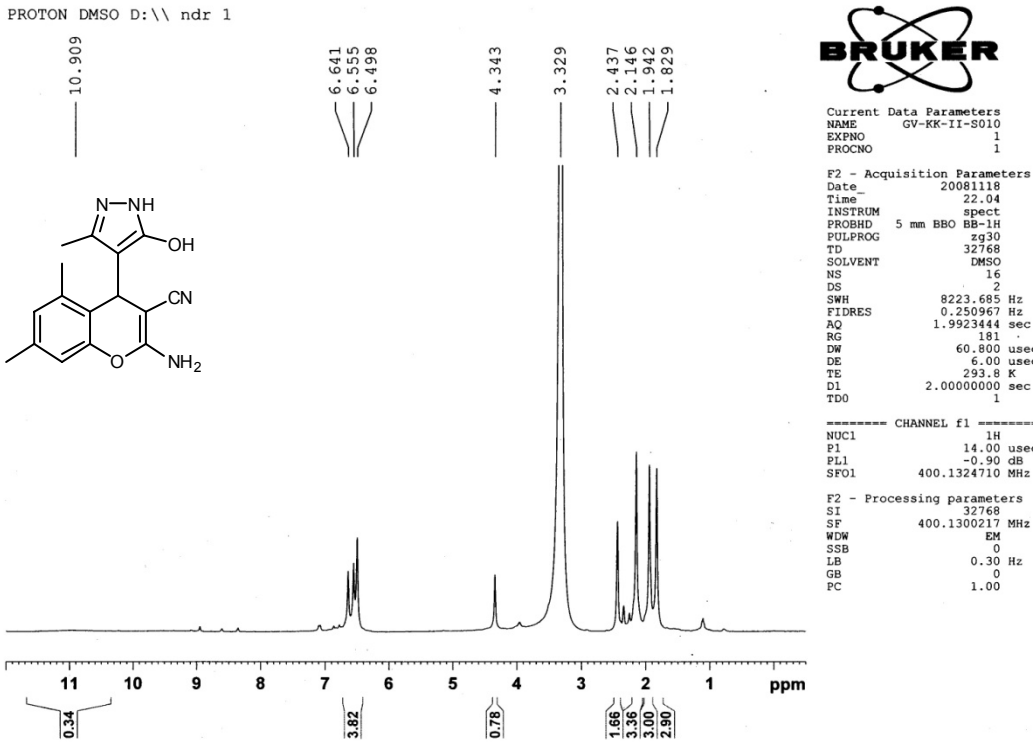
^{13}C NMR Spectrum of *5g*



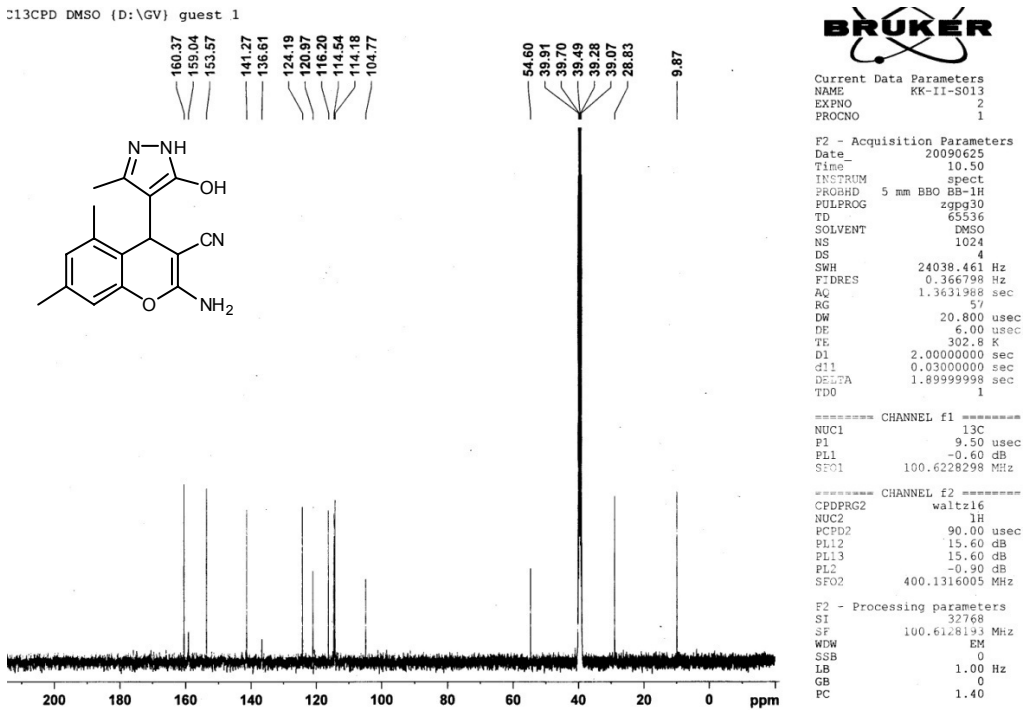
^{1}H NMR Spectrum of *5h*



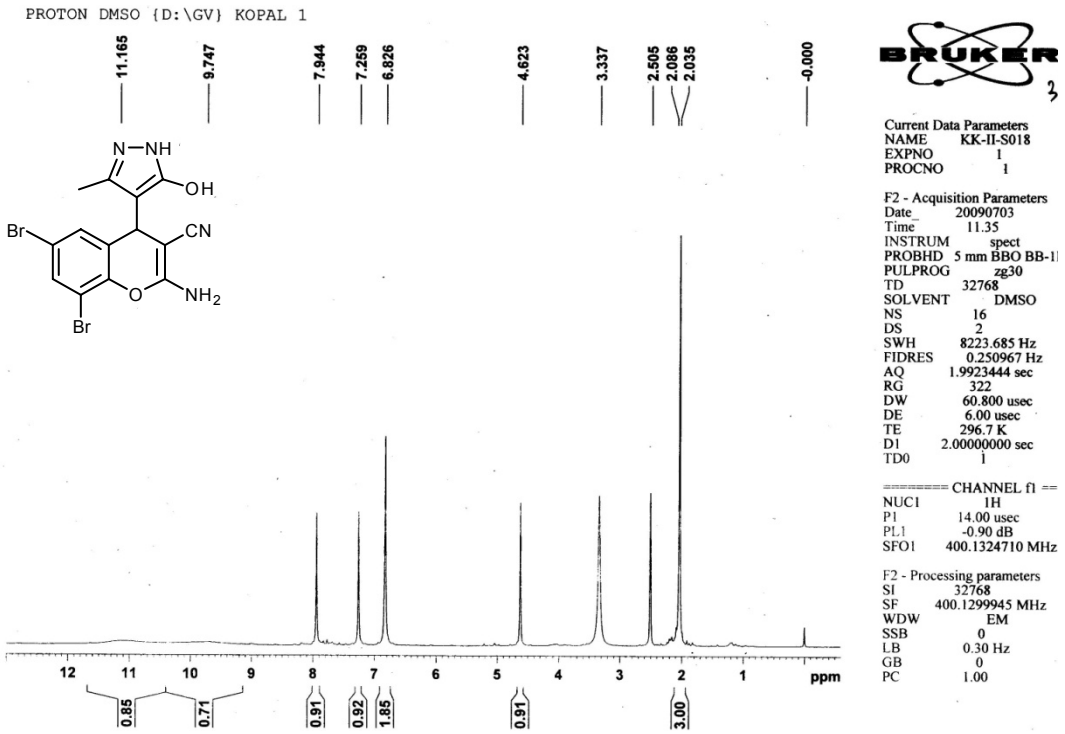
^{13}C NMR Spectrum of *5h*



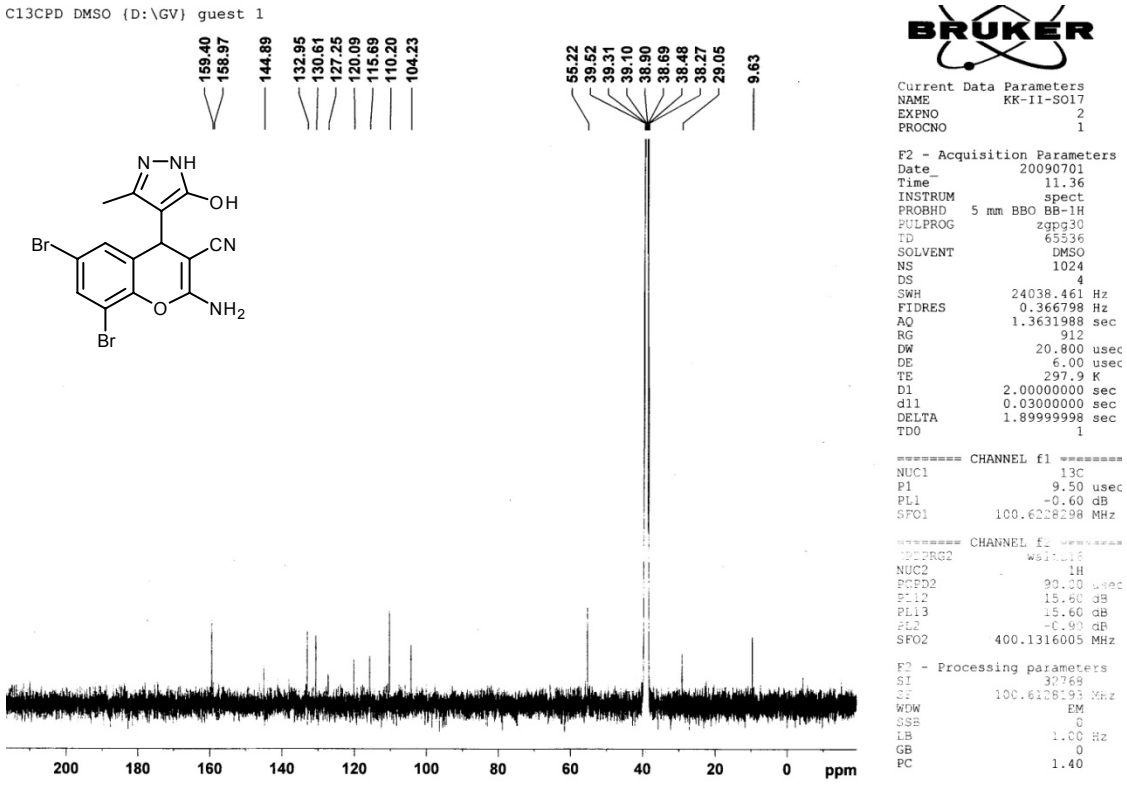
^{1}H NMR Spectrum of *5i*



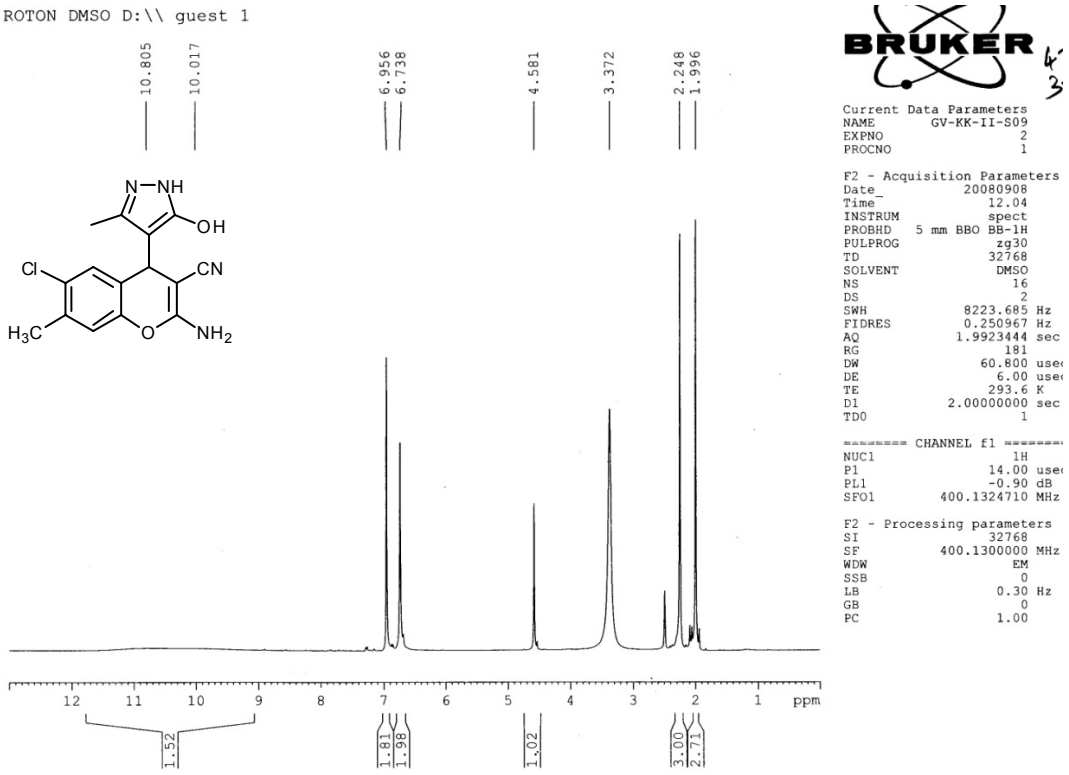
^{13}C NMR Spectrum of *5i*



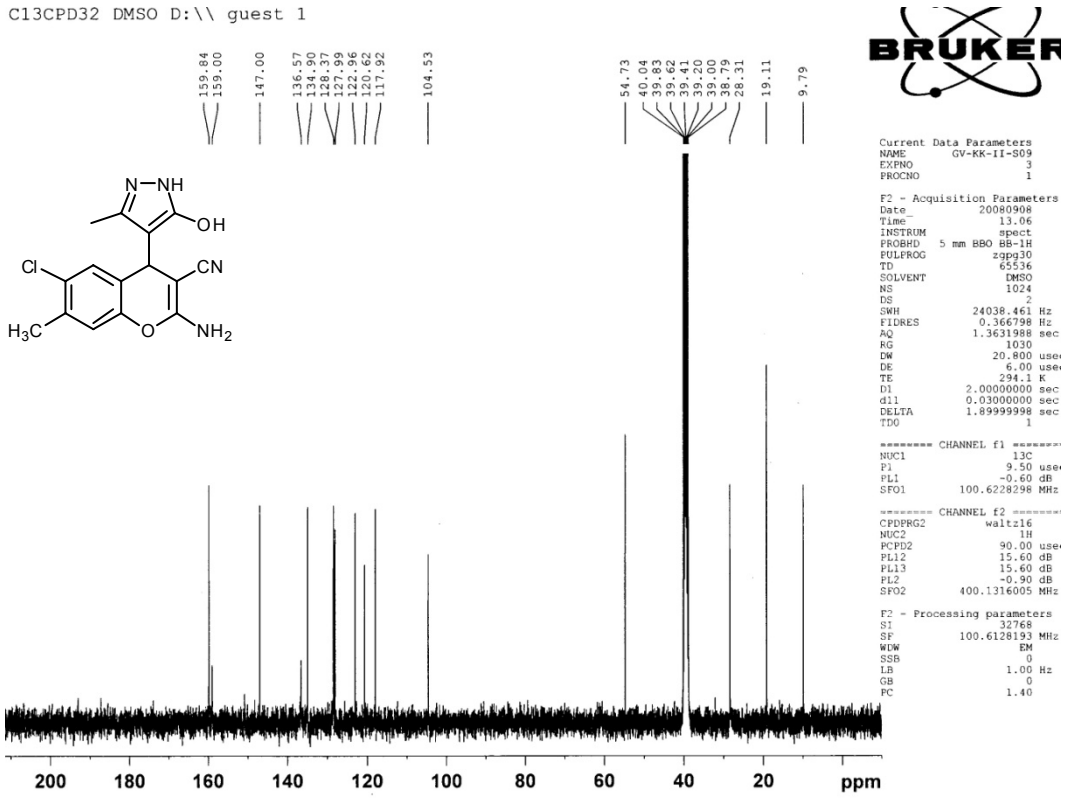
^{1}H NMR Spectrum of *5j*



^{13}C NMR Spectrum of *5j*



^{1}H NMR Spectrum of *5k*



^{13}C NMR Spectrum of *5k*