Electronic Supplementary Information (ESI)

An efficient strategy for the general synthesis of 3-aryl substituted pyrazolo[5,1-*c*][1,4]benzoxazines and pyrazolo[1,5-*a*][1,4]benzodiaze-pin-6(4*H*)-ones

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11. NMR Spectra of Compounds 4, 12 and 13

1. General Information:

The palladium catalysed and cycloaddition reactions were carried out under argon atmosphere using dry solvents; otherwise all the reactions were run under open atmosphere using commercial grade solvents. Petroleum ether refers to fraction boiling in the range 60-80 ^{o}C. DMF was dried over CaH_2, distilled, and stored over 3Å molecular sieves in sealed container. THF was distilled over sodium and benzophenone. Analytical thin-layer chromatography (TLC) was performed on silica gel G coated aluminium sheets. Visualization of the developed chromatogram was done by UV absorbance. For purification, column chromatography was performed using silica gel (60-120 or 100- 200 mesh). ^{1}H and ^{13}C NMR spectra were recorded using 300 or 600 MHz NMR instrument using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are given from TMS (δ=0.00) in parts per million (ppm) with the residual signals of deuterated solvent used as standards [$CDCl_3$: ^{1}H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm (t)]. Coupling constants (*J*) are expressed in hertz (Hz) and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), ddd (doublet of double doublet), t (triplet), m (multiplet) and br (broad). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF, EI or FAB ionization mode. Infrared spectra were obtained on FT-IR spectrometer in neat condition or as KBr plate. Melting points were uncorrected.

2. X-Ray Crystallographic Informations of Product 3j:

Single crystal of product **3j** was obtained through slow evaporation (at room temperature) of a solution of dichloromethane-petroleum ether (1:1; v/v). A single crystal of **3j** was attached to a glass fiber with epoxy glue and transferred to a Brüker SHELXL-97 X-ray diffractometer, equipped with a graphite-monochromator. Diffraction data of product **3j** was measured with MoKα radiation (λ = 0.71073 Å) at 296(2) K. Computing cell refinement and data reduction were carried out at APEX 2 Brüker Kappa. The structures were solved by direct methods using the SHELXS-97 program.[1a] Refinements were carried out with a full matrix least squares method against F^2 using SHELXL-97.[1b] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms

were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The important crystal data of product **3j** are given below.

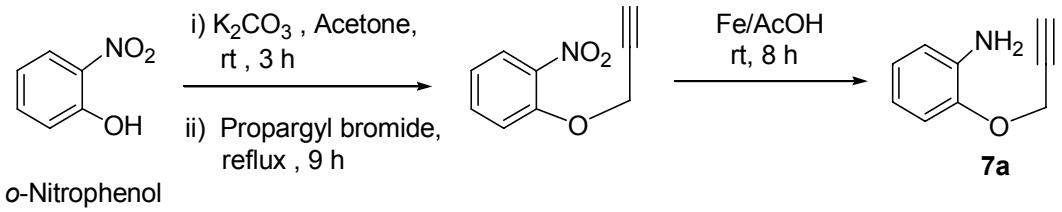
Table 1: Important crystal data of product **3j**

Empirical formula	$C_{20}H_{17}N_3O_5$	
Formula weight	379.37	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.3525(4) Å	α= 113.426(2)°.
	b = 10.0265(5) Å	β= 96.914(2)°.
	c = 10.8420(5) Å	γ = 97.590(2)°.
Volume	907.85(7) $Å^3$	
Z	2	
Density (calculated)	1.388 Mg/m^3	
Absorption coefficient	0.102 mm^{-1}	
F(000)	396	
Crystal size	0.28 x 0.24 x 0.2 mm^3	
Theta range for data collection	2.09 to 25.00°.	
Index ranges	-8<=h<=11, -11<=k<=11, -12<=l<=12	
Reflections collected	13611	
Independent reflections	3186 [R(int) = 0.0219]	
Completeness to theta = 25.00°	99.8%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9949 and 0.9819	
Data / restraints / parameters	3186 / 0 / 255	
Goodness-of-fit on F^2	0.674	
Final R indices [I>2sigma(I)]	R1 = 0.0477, wR2 = 0.1255	
R indices (all data)	R1 = 0.0540, wR2 = 0.1369	
Largest diff. peak and hole	0.434 and -0.280 $e.Å^{-3}$	

For details please see the corresponding CIF file, attached with the supporting information. The crystal data of Product **3j** has already been deposited at Cambridge Crystallographic Data Centre and the CCDC reference no is 838046.

3. Preparation of Starting Materials 7a and 7b:

3.1 Synthesis of 2-(prop-2-ynyloxy)aniline (7a):

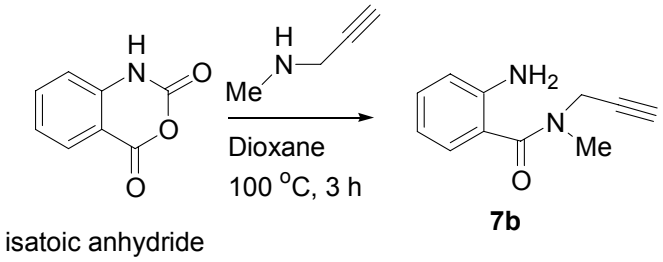


Scheme-1

Synthesis of 2-(prop-2-ynyloxy)aniline (**7a**) was carried out according to the literature procedure,[2] starting with commercially available *o*-nitrophenol (Scheme 1).

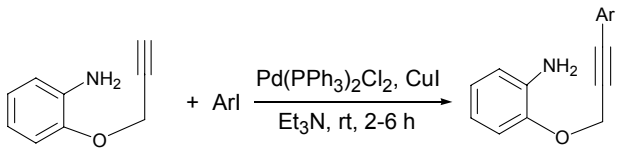
3.2 Synthesis of 2-amino-*N*-methyl-*N*-(prop-2-ynyl)- benzamide (7b)[3]

N-Methylpropargylamine (190 mg, 2.75 mmol) was added to a solution of isatoic anhydride (300 mg, 1.84 mmol) in dioxane (10 mL) and the mixture was heated under reflux for 3 h. It was then poured into ice-water (50 mL), adjusted to pH 9 with 5% NaOH and extracted with ethyl acetate (3 × 150 mL). The organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel (60-120 mesh) column chromatography to furnish the product **7b** (81% yield).



Scheme 2

4. General procedure for the preparation of 2-(3-arylprop-2-ynyloxy)aniline (8) under Sonogashira reaction conditions[4]:

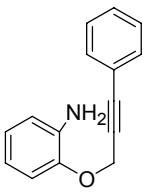


7a **6** **8**

Scheme 3

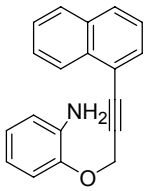
$Pd(PPh_3)_2Cl_2$ (21 mg, 0.03 mmol) and CuI (9.5 mg, 0.05 mmol) were added to aryl iodide **6** (1.0 mmol) dissolved in dry Et_3N (5 mL) and the mixture was stirred under argon atmosphere for 20 minutes. Next, 2-(prop-2-ynyloxy)aniline **7a** (176 mg, 1.2 mmol) dissolved in dry Et_3N (1 mL) was added drop wise to the reaction mixture and flushed carefully with argon. The whole reaction mixture was allowed to stir for 2-6 hours (except the product **8l** for which 15 h stirring was required) at room temperature. After completion of the reaction (TLC), the solvent was removed *in vacuo* and the residue was poured into 30 mL of water. The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography using 3-25% EtOAc in petroleum ether (v/v) as eluent.

4.1 Selected spectral data of alkynes 8 (8a-e, 8h-l):



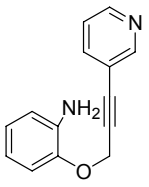
2-(3-Phenylprop-2-ynyloxy)aniline[2] (8a): Yield: 89%; oil; IR (liquid film): 3462, 3375, 2237, 1613 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.84 (br s, 2H), 4.93 (s, 2H), 6.71-6.87 (m, 3H), 6.94-7.00 (m, 1H), 7.25-7.45 (m, 5H) ; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 57.2, 84.2, 87.0, 112.7, 115.4, 118.3, 122.1, 122.3, 128.2, 128.6, 131.7, 136.7, 145.5 ; ESI-MS**:** m/z 246.13 $[M+Na]^+$.

2-[3-(Naphthalene-1-yl)prop-2-ynyloxy]aniline (8b): Yield: 81%; oil; IR (liquid film): 3462, 3376, 2227, 1611 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.87 (br s, 2H), 5.09 (s, 2H),

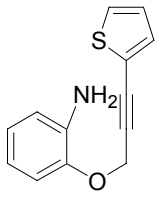


6.78-6.89 (m, 3H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.49-7.52 (m, 2H), 7.67 (d, *J* = 6.9 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 8.21 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 57.4, 85.2, 88.9, 113.0, 115.5, 118.4, 119.9, 122.2, 125.0, 126.0, 126 .4, 126.8, 128.2, 129.1, 130.7, 133.0, 133.2, 136.8, 145.4; ESI-MS**:** m/z 296.13 $[M+Na]^+$**;** Anal. Calcd. for $C_{19}H_{15}NO$**:** C, 83.49; H, 5.53; N, 5.12. Found: C, 83.45; H, 5.51; N, 5.17.

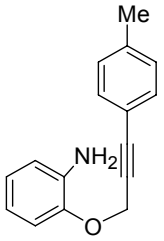
2-[3-(Pyridine-3-yl)prop-2-ynyloxy]aniline (8c): Yield: 92%; oil; IR (liquid film): 3453, 3362, 2240, 1616 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.85 (br s, 2H), 4.95 (s, 2H), 6.72-6.77 (m, 2H), 6.83-6.88 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 7.23-7.26 (m, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 8.54-8.55 (m, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 56.9, 83.7, 87.6, 112.6, 115.5, 118.3, 119.4, 122.2, 122.9, 136.7, 138 .7, 145.3, 148.9, 152.3; ESI-MS**:** m/z 247.13 $[M+Na]^+$**;** Anal. Calcd. for $C_{14}H_{12}N_2O$**:** C, 74.98; H, 5.39; N, 12.49. Found: C, 74.93; H, 5.44; N, 12.56.



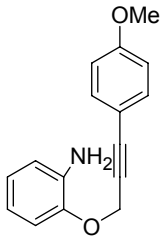
2-[3-(2-Thienyl)prop-2-ynyloxy]aniline (8d): Yield: 83%; oil; IR (liquid film): 3377, 2224, 1606 cm^{-1}; ^1H NMR $CDCl_3$, 300 MHz): δ 3.84 (br s, 2H), 4.93 (s, 2H), 6.69-6.76 (m, 2H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.94-6.98 (m, 2H), 7.22-7.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 57.2, 80.3, 88.1, 112.7, 115.4, 118.3, 122.08, 122.1, 126.9, 127.6, 1 32.7, 136.7, 145.4; ESI-MS**:** m/z 252.09 $[M+Na]^+$**;** Anal. Calcd. for $C_{13}H_{11}NOS$**:** C, 68.09; H, 4.84; N, 6.11. Found: C, 68.13.; H, 4.87; N, 6.08.



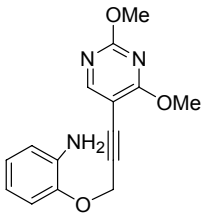
2-[3-(4-Methylphenyl)prop-2-ynyloxy]aniline[2] (8e): Yield: 69%; oil; IR (liquid film): 3482, 3384, 2230, 1609 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz):): δ 2.34 (s, 3H), 3.84 (br s, 2H), 4.92 (s, 2H), 6.71-6.76 (m, 2H), 6.81-6.86 (m, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 57.3, 83.5, 87.2, 112.8, 115.4, 118.3, 119.2, 122.0, 129.0, 131.6, 136.7, 138.8, 145.6 ; ESI-MS**:** m/z 260.13 $[M+Na]^+$.



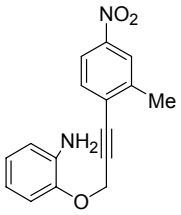
2-[3-(4-Methoxyphenyl)prop-2-ynyloxy]aniline[2] (8h): Yield: 70%; oil; IR (liquid film): 3480, 3375, 2224, 1606 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.80 (s, 3H), 3.84 (br s, 2H), 4.91 (s, 2H), 6.71-6.75 (m, 2H), 6.81-6.86 (m, 3H), 6.97-6.99 (m, 1H), 7.38 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.2, 57.3, 82.8, 86.9, 112.7, 113.8, 114.3, 115.3, 118.2, 121.9, 1 33.2, 136.7, 145.5, 159.8 ; ESI-MS**:** m/z 276.12 $[M+Na]^+$.



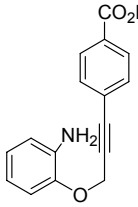
2-[3-(2,4-Dimethoxy-5-pyrimidinyl)prop-2-ynyloxy]aniline[2] (8i): Yield: 84%; sticky oil; IR (liquid film): 3417, 3305, 2233, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.82 (br s, 2H), 3.98 (s, 3H), 4.01 (s, 3H), 4.93 (s, 2H), 6.68-6.73 (m, 2H), 6.79-6.84 (m, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 54.4, 55.1, 57.2, 78.6, 90.5, 99.1, 112.8, 115.4, 118.2, 122.1, 136.6 , 145.3, 161.7, 164.2, 170.6 ; ESI-MS**:** m/z 308.13 $[M+Na]^+$.



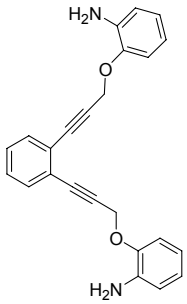
2-[3-(2-Methyl-4-nitrophenyl)prop-2-ynyloxy]aniline (8j): Yield: 96%; sticky oil; IR (liquid film): 3468, 3380, 2250, 1612, 1511, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.46 (s, 3H), 3.84 (br s, 2H), 5.01 (s, 2H), 6.71-6.77 (m, 2H), 6.84-6.89 (m, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.97-8.06 (m, 2H) ; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 20.7, 56.9, 84.3, 93.1, 112.8, 115.6, 118.3, 120.7, 122.4, 124.2, 128.9, 132.7, 136.7, 142.1, 145.2, 147.1 ; ESI-MS**:** m/z 305.11 $[M+Na]^+$ **;**Anal. Calcd. for $C_{16}H_{14}N_2O_3$**:** C, 68.07; H, 5.00; N, 9.92. Found: C, 68.12; H, 5.04; N, 9.86.



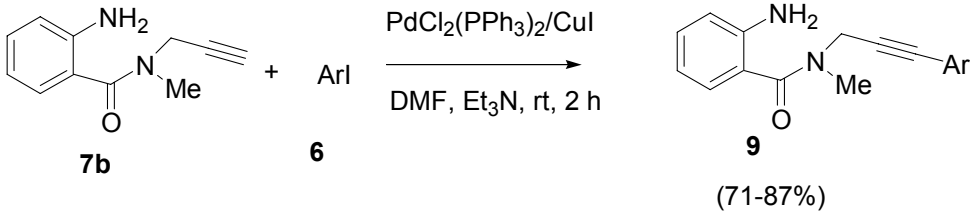
2-[3-(4-Carbomethoxyphenyl)prop-2-ynyloxy]aniline (8k): Yield: 89%; gummy solid, IR (KBr): 3479, 3376, 1716, 1608 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.85 (br s, 2H), 3.91 (s, 3H), 4.95 (s, 2H), 6.72-6.77 (m, 2H), 6.83-6.88 (m, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.98 (d, *J* = 8.1 Hz, 2H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.2, 56.9, 86.2, 87.1, 112.6, 115.4, 118.3, 122.2, 126.8, 129.4, 129.8, 131.6, 136.6, 145.3, 166.3 ; ESI-MS**:** m/z 304.14 $[M+Na]^+$ **;** Anal. Calcd. for $C_{17}H_{15}NO_3$**:** C, 72.58; H, 5.37; N, 4.98. Found: C, 72.53; H, 5.42; N, 4.92.



1,2-Bis[(3′-phenyl-2′-ynyloxy)-2′-amino-phenyl]benzene[2] (8l): Yield 51%, oil, IR(liquid film): 3459, 3371, 1612 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.83 (br s, 4H), 4.84 (s, 4H), 6.73 (t, *J* = 6.9 Hz, 4H), 6.79-6.85 (m, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 7.24-7.27 (m, 2H), 7.40-7.43 (m, 2H) ; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 57.0, 85.3, 88.3, 112.7, 115.4, 118.3, 121.9, 124.9, 128.3, 131.9, 136.6, 145.5 ; ESI-MS**:** m/z 391.15 $[M+Na]^+$.



5. General procedure for the preparation of 2-amino-*N*-methyl-*N*-(3-aryl-prop-2-ynyl)benzamides (9) under Sonogashira reaction conditions[4] :



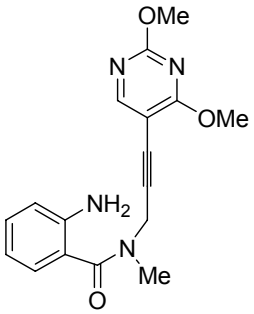
Scheme-4

To a well stirred solution of aryl iodide **6** (1.45 mmol) and Et_3N (10.15 mmol) in DMF (3 mL), $PdCl_2(PPh_3)_2$ (41 mg, 0.058 mmol) was added. The whole reaction mixture was allowed to stir at room temperature for 10 min under argon atmosphere. Next, CuI (16 mg, 0.087 mmol) was added followed by drop wise addition of a solution of amine **7b** (286 mg, 1.52 mmol) in DMF (1.0 mL). The resulting reaction mixture was allowed to stir at room temperature for 2 h. The reaction was monitored through TLC to ensure complete consumption of the starting materials. It was then extracted with ethyl acetate (3 × 50 mL). The combined ethyl acetate extracts were washed successively with brine (30 mL) and water (30 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography over silica gel (100-200 mesh) using 20-30% ethyl acetate in hexane (v/v) to afford the product **9**.

The spectral data of products **9a-f** has been reported[5] earlier.

5.1 Spectral Data of alkynes 9:

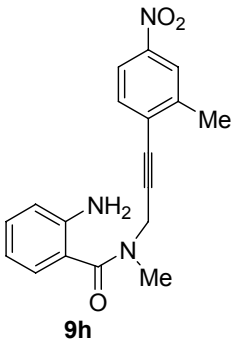
2-Amino-*N*-methyl-*N*-[3-[(2,4-dimethoxy)pyrimidine-5-yl]prop-2-ynyl]benzamide



(9g): Yield 74%; Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (s, 3H), 4.01 (s, 3H), 4.05 (s, 3H), 4.42 (br s, 2H), 4.48 (br s, 2H), 6.71-6.76 (m, 2H), 7.16-7.22 (m, 2H), 8.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.6 (br), 39.9 (br), 54.2, 54.8, 75.6, 90.1, 99.0, 116.3, 116.8, 118.6, 127.7, 130.5, 145.6, 161.2, 163.8, 170.4, 170.6; IR (neat, cm^{-1}) 3460, 3355, 2999, 2956, 1622, 1593, 1550, 1471, 1398, 1323, 1238, 1074; MS (EI) (*m*/*z*) 326, 206, 120. Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.51; H, 5.60; N, 17.12.

2-Amino-*N*-methyl-*N*-[3-(4-nitro-2-methylphenyl)prop-2-ynyl]benzamide (9h):

Yield 80%; Solid, mp 86-88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.20 (s, 3H), 4.43 (s, 2H), 4.53 (s, 2H), 6.71-6.76 (m, 2H), 7.17-7.23 (m, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 35.0 (br), 39.5 (br), 81.2, 93.1, 116.5, 116.9, 118.4, 120.4, 123.9, 127.7, 128.9, 130.8, 132.4, 141.7, 145.7, 146.7, 170.8; IR (KBr, cm^{-1}) 3433, 3347, 3232, 3078, 2923, 1611, 1509, 1339, 1282, 1078; MS (EI) (*m*/*z*) 323, 203, 120. Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.81; H, 5.34; N, 13.06.

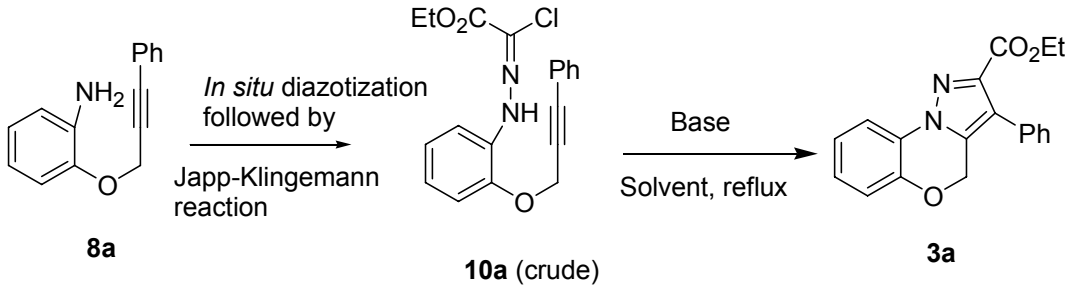


9h

6. Screening Studies about the optimisation of reaction conditions for the synthesis of product 3a (condition A):

Initially, we carried out diazotisation ($NaNO_2$/HCl) followed by Japp-Klingemann reaction (ethyl 2-chloroacetoacetate and sodium acetate) on 2-(3-phenylprop-2-ynyloxy)aniline **8a** in one pot and isolated the crude product **10a** by usual work-up. This crude (without chromatographic purification) intermediate **10a** was used directly for optimisation studies of the cycloaddition reactions (Table 2) varying with different solvents and bases. All the reactions were carried out at reflux temperature of the solvent employed. Our investigation started with earlier reported reaction conditions[6] using Et_3N (10.0 equiv.) in toluene which led to the formation of product **3a** in 46% yield after prolonged (18 h) heating as shown in entry 1 of Table 2. The observation with such sluggish reaction prompted us to screen different bases and high boiling solvents in order to attain the appropriate reaction conditions. Thus, replacement of the solvent from toluene to xylene gave an encouraging result wherein a dropping of the reaction time from 18 h to 6 h with slightly higher yield (49%) was observed (Table 2, entry 2).

Table 2: Optimisation of the reaction conditions (*condition A*) for the cycloaddition of crude intermediate **10a**[a]



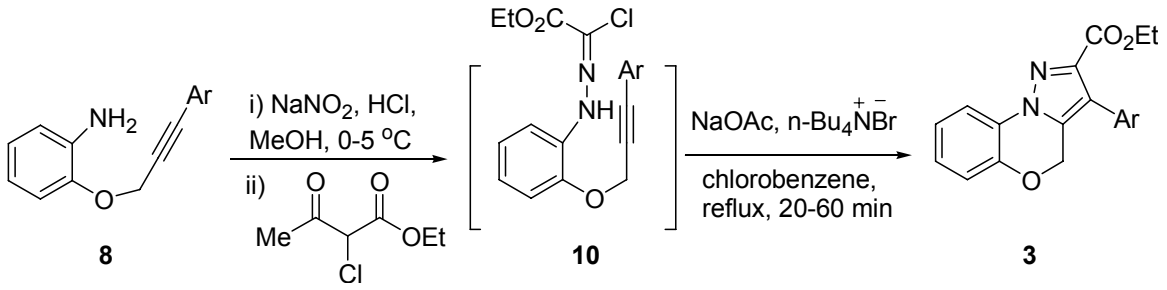
8a **10a** (crude) **3a**

Entry	**Base**	Amount of base[b] (equiv.)	Solvent	Time (h)	Yield(%)[c] **3a**
1	Et_3N	10.0	Toluene	18.0	46
2	Et_3N	5.0	Xylene	6.0	49
3	2,6-Lutidine	2.0	Xylene	5.0	No reaction
4	DMAP	2.5	Xylene	1.0	26
5[d]	K_2CO_3	4.0	Xylene	3.0	44
6[d]	Cs_2CO_3	4.0	Xylene	1.5	33
7[d]	NaOAc	4.0	Xylene	2.0	52
8[e]	NaOAc	4.0	Xylene	8.0	51
9[d]	**NaOAc**	**4.0**	**Chlorobenzene**	**0.5**	**53**
10	DBU	2.0	Xylene	3.0	No reaction

[a]Reaction conditions: Crude hydrazonoyl chloride **10a** (205 mg derived from 0.5 mmol of **8a**) and base (2.0-10.0 equiv.) in dry solvent (6 mL) was heated under reflux until the complete consumption of the starting materials (TLC). [b]Base (equiv.) was employed with respect to starting amine **8a**. [c]Chromatographically isolated pure products and yields were calculated based on the amine **8a**. [d]Tetrabutylammonium bromide (0.1 equiv.) was used as phase transfer catalyst. [e]No phase transfer catalyst (tetrabutylammonium bromide) was used.

Next, we used 2, 6-lutidine as base and to our surprise, it did not yield any desired product **3a**; starting materials were only recovered in this case. We then examined a variety of bases (DMAP, K_2CO_3, Cs_2CO_3, NaOAC etc.) in refluxing xylene (Table 2, entries 4-8). Pleasingly, reaction was found to be complete within two hours (52% yield) by the employment of NaOAC and catalytic amount of n-tetrabutylammonium bromide (TBAB) as shown in entry 7 of Table 2. Interestingly, omission of TBAB made the cycloaddition slower moving (Table 2, entry 8). Gratifyingly, replacement of xylene by chlorobenzene led to completion of the cycloaddition within 30 min only (Table 2, entry 9). Further, change of bases like DBU resulted in a tarry mixture with no sign of the product formation. Thus, reaction conditions of entry 9 of Table 2 appeared to be the optimum and therefore, we decided to employ chlorobenzene and NaOAc as solvent and base (*condition A*) in the following cycloaddition reactions of crude intermediate **10**.

7. General procedure (condition A) for the synthesis of 2-carbethoxy-4*H*-pyrazolo[5, 1-*c*][1,4]benzoxazines 3:

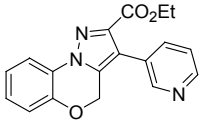


To an ice-cooled (0-5°C) solution of **8** (0.85 mmol) in MeOH (1.5 mL), 6 M hydrochloric acid (0.5 mL) and $NaNO_2$ (117 mg, 1.70 mmol) were added successively and the reaction mixture was allowed to stir at this temperature for one hour. The acidity of the medium was then adjusted to pH 5 by careful addition of sodium acetate. Next, a solution of ethyl 2-chloroacetoacetate (0.12 mL, 0.85 mmol) in MeOH (1 mL) was added drop wise and the reaction mixture was allowed to stir vigorously at room temperature. After completion (4 h) of the reaction the solvent was removed under reduced pressure and the residue was extracted with EtOAc (2×15 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution (15 mL) followed by water (15 mL), dried over anhydrous

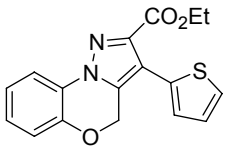
Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude intermediate **10** was then used directly. Thus, a solution of the product **10** in chlorobenzene (4 mL) was refluxed in the presence of NaOAc (278 mg, 3.39 mmol) and n-Bu_4NBr (27 mg, 0.085 mmol) until complete consumption of the starting material (TLC). After removal of the solvent, it was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Finally, the crude residue was purified by silica gel (100-200 mesh) column chromatography using 4-30% EtOAc in petroleum ether (v/v) as eluent.

7.1 Spectral Data of 3-aryl substituted 2-carbethoxy-4*H*-pyrazolo-[5,1-*c*][1,4]benz-oxazines 3:

2-Carbethoxy-3-(pyridine-3-yl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3c): Yield: 45%; solid, m.p.: 170-172 °C; IR (KBr): 2981, 1715, 1604, 1479, 1365, 1233, 1162, 861 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, *J* = 7.2 Hz, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 5.25 (s, 2H), 7.08-7.17 (m, 2H), 7.21-7.27 (m, 1H), 7.36-7.40 (m, 1H), 7.76-7.79 (m, 1H), 8.05 (dd, *J* = 1.4, 7.7 Hz, 1H), 8.53 (s, 1H), 8.61-8.63 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 61.3, 61.8, 116.7, 117.6, 117.9, 122.91, 122.97, 125.7, 126.6, 127.9, 132.6, 137.4, 141 .8, 146.4, 148.9, 149.9, 161.8 ; ESI-MS**:** m/z 344.15 $[M+Na]^+$ **;** HRMS (EI, 70 eV) calcd for $C_{18}H_{15}N_3O_3$ $[M^+]$ 321.1113, found 321.1103.

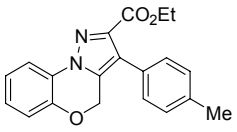


2-Carbethoxy-3-(2-thienyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3d): Yield: 46%; solid, m.p.: 119-122 °C; IR (KBr): 2985, 1721, 1603, 1506, 1364, 1235, 1179, 862 cm^{-1}; ^1H NMR



($CDCl_3$, 300 MHz): δ 1.37 (t, *J* = 7.1 Hz, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 5.34 (s, 2H), 7.06-7.26 (m, 5H), 7.39 (d, *J* = 4.8 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 61.2, 62.1, 114.3, 116.5, 117.4, 122.7, 125.6, 126.2, 127.0, 127.8, 128.4, 130.3, 132.5, 141.7, 146.3, 161.8 ; ESI-MS**:** m/z 349.07 $[M+Na]^+$ **;** Anal. Calcd. for $C_{17}H_{14}N_2O_3S$**:** C, 62.56; H, 4.32; N, 8.58. Found: C, 62.52; H, 4.37; N, 8.64.

2-Carbethoxy-3-(4-methylphenyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3e): Yield: 43%



; solid, m.p.: 105-108 °C; IR (KBr): 2976, 1720, 1601, 1497, 1360, 1215, 1152, 820 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 5.23 (s, 2H), 7.05-7.15 (m, 2H), 7.18-7.23 (m, 5H), 8.04 (dd, *J* = 1.1, 7.9 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 21.2, 60.9, 62.0, 116.5, 117.4, 121.6, 122.7, 125.9, 127.1, 127.5, 128.8, 129.5, 131.9, 137.5, 141.6, 146.4, 162.1 ; ESI-MS**:** m/z 357.10 $[M+Na]^+$**;** Anal. Calcd. for $C_{20}H_{18}N_2O_3$**:** C, 71.84; H, 5.43; N, 8.38. Found: C, 71.90; H, 5.37; N, 8.32.

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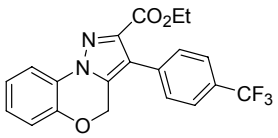
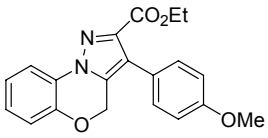
2-Carbethoxy-3-(4-trifluoromethylphenyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3f):

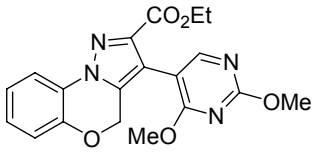


Yield: 51% ; solid, m.p.: 133-135 °C; IR (KBr): 2990, 1716, 1618, 1502, 1447, 1391, 1324, 1229, 864 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, *J* = 7.2 Hz, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 5.23 (s, 2H), 7.09 (td, *J* = 1.3, 7.4 Hz, 1H), 7.16 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.22 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 8.05 (dd, *J* = 1.4, 7.9 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.1, 61.4, 61.9, 116.8, 117.6, 120.4, 123.1, 124.1 (q, *J* = 270.4 Hz), 125.1 (q, *J* = 3.75 Hz), 125.8, 128.0, 129.9 (q, *J* = 32.3 Hz), 130.2, 132.5, 134.2, 141.7, 146.5, 161.9 ; ESI-MS **:** m/z 411.18 $[M+Na]^+$**;** HRMS (EI, 70 eV) calcd for $C_{20}H_{15}F_3N_2O_3$ $[M^+]$ 388.1035, found 388.1017.

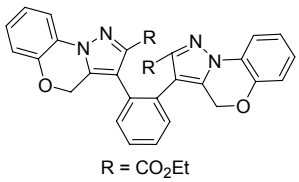
2-Carbethoxy-3-(4-methoxyphenyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3h): Yield: 47 %; solid, m.p.: 134-136 °C; IR (KBr): 2976, 1717, 1606, 1493, 1383, 1250, 1172, 858 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (t, *J* = 7.1 Hz, 3H), 3.85 (s, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 5.23 (s, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.08 (td, *J* = 1.2, 7.1 Hz, 1H), 7.12-7.15 (m, 1H), 7.19 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.23-7.28 (m, 2H), 8.04 (dd, *J* = 1.4, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz),δ 14.1, 55.2, 61.0, 62.1, 113.5, 116.6, 117.5, 121.4, 122.4, 122.8, 125.9, 127.6, 130.9, 131.9, 141.6, 146.4, 159.1, 162.1; ESI-MS**:** m/z 373.05 $[M+Na]^+$; HRMS (EI, 70 eV) calcd for $C_{20}H_{18}N_2O_4$ $[M^+]$ 350.1267, found 350.1283.



2-Carbethoxy-3-(2,4-dimethoxy-5-pyrimidinyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3i): Yield: 44%; solid, m.p.: 200-202 °C; IR (KBr): 2990, 1713, 1565, 1467, 1378, 1228, 1181, 861 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, *J* = 7.1 Hz, 3H), 3.97 (s, 3H), 4.05 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 5.15 (s, 2H), 7.08 (td, *J* = 1.2, 7.1 Hz, 1H), 7.14 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.22 (td, *J* = 1.4, 7.7 Hz, 1H), 8.03 (dd, *J* = 1.5, 7.8 Hz, 1H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 14.2, 54.1, 54.9, 61.2, 62.4, 105.3, 111.9, 116.7, 117.5, 122.9, 125.9, 127.9, 133.2, 142.5, 146.3, 159.2, 161.9, 165.1, 168.2 ; ESI-MS**:** m/z 405.14 $[M+Na]^+$ **;** HRMS (EI, 70 eV) calcd for $C_{19}H_{18}N_4O_5$ $[M^+]$ 382.1277, found 382.1269.

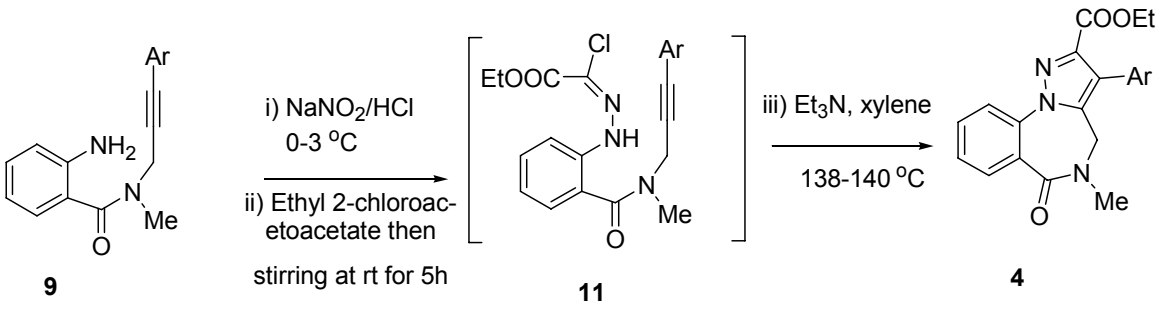


1,2-Bis[2′-carbethoxy-3′-phenyl-4′*H*-pyrazolo[5′,1′-*c*][1,4]benzoxazinyl]benzene (3l):



Yield: 36%; solid, m.p.: 186-188 °C; IR (KBr): 2991, 1720, 1604, 1490, 1380, 1226, 1160, 1021, 864 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, *J* = 7.1 Hz, 6H), 4.29 (q, *J* = 6.9 Hz, 4H), 4.83 (d, *J* = 14.1 Hz, 2H), 5.06 (d, *J* = 14.1 Hz, 2H), 6.99-7.08 (m, 4H), 7.16 (t, *J* = 7.4 Hz, 2H), 7.31-7.34 (m, 2H), 7.44-7.47 (m, 2H), 7.91 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.9, 61.1, 62.0, 116.6, 117.5, 120.3, 122.7, 125.8, 127.8, 128.1, 130.7, 130.8, 133.1, 141.7, 146.5, 161. 9 ; ESI-MS**:** m/z 585.27 $[M+Na]^+$ **;** Anal. Calcd. for $C_{32}H_{26}N_4O_6$**:** C, 68.32; H, 4.66; N, 9.96. Found: C, 68.37; H, 4.63; N, 9.99.

8. General procedure (condition B) for the synthesis of 2-carbethoxy-5-methyl-3-aryl-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-ones 4 :

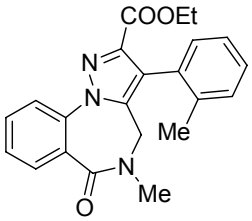


To a well stirred and cooled (0-3 °C) solution of **9** (0.50 mmol) in 2 M hydrochloric acid (8.0 mL) was added a solution of $NaNO_2$ (48 mg, 0.70 mmol) in 2 mL H_2O drop wise during 45 min and the reaction mixture was allowed to stir for another 30 min at the same temperature. Ethyl 2-chloroacetoacetate (90 mg, 0.55 mmol) was added drop wise during 2-3 min at 0-3 °C. The temperature of the reaction mixture was then allowed to attain room temperature (rt) and stirred for another 5 h. It was then extracted with ethyl acetate (2 × 20 mL). The organic extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude product was refluxed (138-140 °C) in xylene (5.0 mL) in the presence of triethylamine (0.42 mL, 3.0 mmol) for few hours. Upon completion of the reaction (TLC), the solvent was removed *in vacuo* and extracted

with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over Na_2SO_4, filtered and concentrated. The resulting crude product was purified through silica gel (100-200 mesh) column chromatography (40-50% ethyl acetate in hexane, v/v) to furnish the desired product **4**.

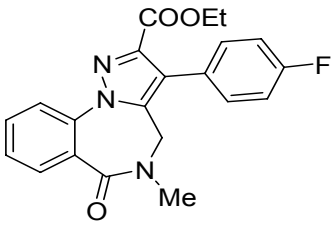
8.1 Spectral data of the products 4:

2-Carbethoxy-5-methyl-3-(2-methylphenyl)-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (4c): Yield 45%; Solid, mp 180-182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, J = 7.05 Hz, 3H), 2.15 (s, 3H), 3.10 (s, 3H), 4.12-4.32 (m, 4H), 7.14 (d, J = 7.2 Hz, 1H), 7.24-7.37 (m, 3H), 7.50 (t, J = 7.65 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 8.04 (t, J = 8.1 Hz, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.1, 35.6, 42.1, 60.8, 121.9, 122.8, 125.4, 127.4, 127.9, 128.3, 129.7, 130.0, 130.3, 131.6, 132.3, 135.3, 137.6, 139.5, 142.4, 161.6, 166.6; IR (KBr, cm^{-1}) 2982, 2931, 1724, 1643, 1479, 1346, 1274, 1171; MS (ESI) (*m*/*z*) 398.13 (M+Na$^+$). Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.43; H, 5.67; N, 11.14.



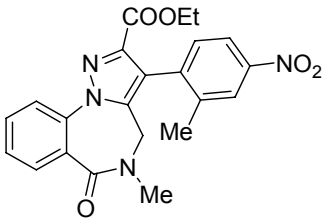
4c

2-Carbethoxy-5-methyl-3-(4-fluorophenyl)-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (4e): Yield 40%; Solid, mp 76-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 3.14 (s, 3H), 4.24 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 7.17 (t, J = 8.55 Hz, 2H), 7.31-7.44 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.69 (td, J = 7.8 Hz, 1H), 8.02 (t, J = 8.1 Hz, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 35.6, 42.2, 61.0, 115.2 (d, J = 21.75 Hz), 121.8, 122.8, 126.5 (d, J = 6.0 Hz), 127.4, 128.0, 131.6, 131.7 (d, J = 8.25 Hz), 132.4, 135.2, 139.6, 142.2, 161.7, 162.4 (d, J = 246 Hz), 166.5; IR (KBr, cm^{-1}) 2983, 2936, 1723, 1643, 1481, 1388, 1289, 1225, 1167; MS (ESI) (*m*/*z*) 402.09 (M+Na$^+$). Anal. Calcd. for $C_{21}H_{18}FN_3O_3$: C, 66.48; H, 4.78; N, 11.08. Found: C, 66.44; H, 4.80; N, 11.03.



4e

2-Carbethoxy-5-methyl-3-(4-nitro-2-methylphenyl)-pyrazolo[l,5-*a*][1,4]benzodiazepine-6(4*H*)-one (4h): Yield 37%; Solid, mp 85-87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.05 Hz, 3H), 2.28 (s, 3H), 3.10 (s, 3H), 4.15 (br s, 2H), 4.24-4.34 (m, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.54 (td, *J* = 7.5 Hz, 1H), 7.70 (td, *J* = 7.8 Hz, 1H), 8.02-8.06 (m, 2H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.21 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.3, 35.7, 42.1, 61.2, 119.8, 120.6, 122.8, 124.5, 127.4, 128.3, 131.1, 131.7, 132.5, 134.9, 137.7, 139.5, 140.0, 142.3, 147.7, 161.3, 166.5; IR (KBr, cm^{-1})2986, 2932, 1723, 1643, 1518, 1479, 1386, 1346, 1289, 1173; MS (ESI) (*m*/*z*) 443.15 ($M+Na^{+}$). Anal. Calcd. for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.79; N, 13.33; Found: C, 62.89; H, 4.77; N, 13.37.



4h

9. References:

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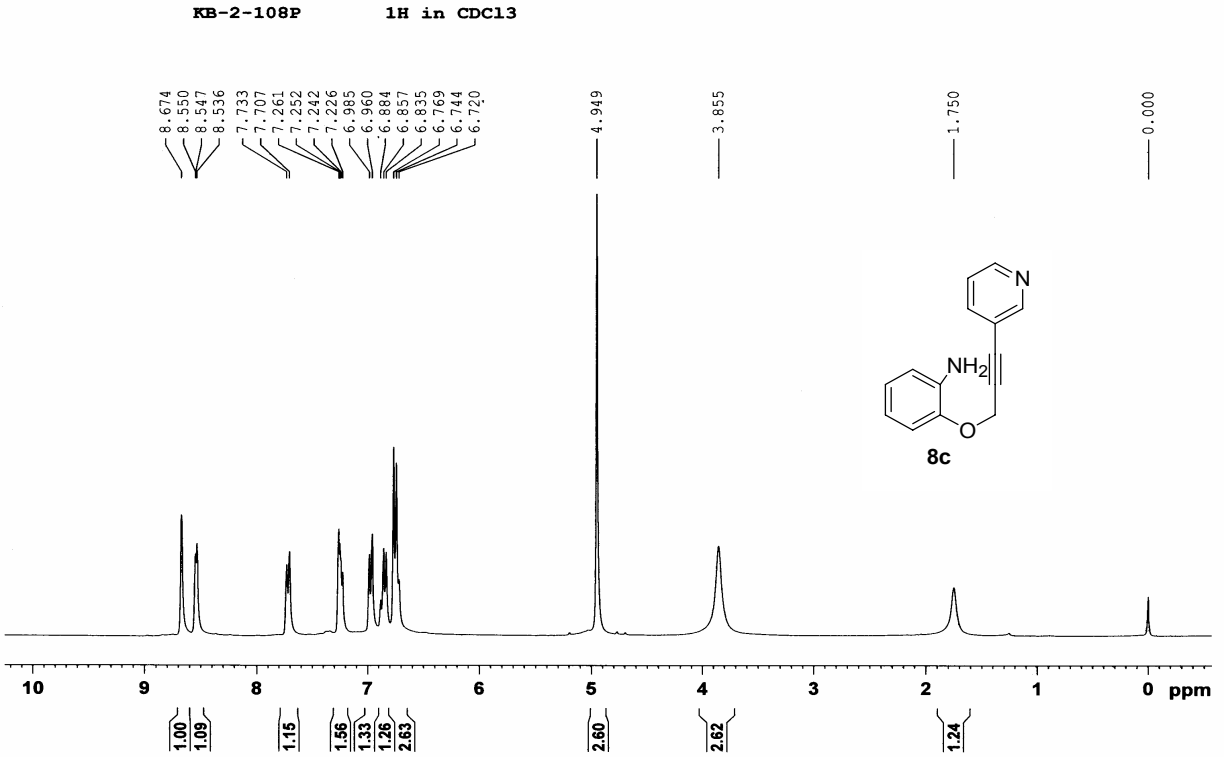
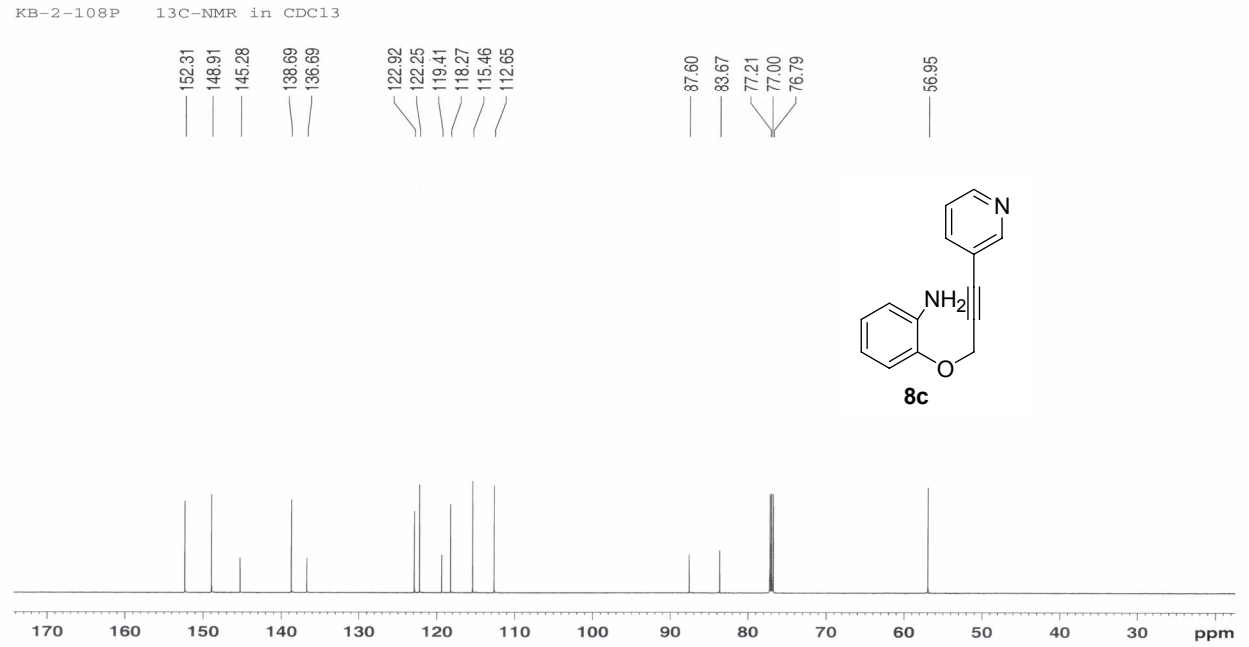
10. NMR Spectra of Compounds 8 and 3:

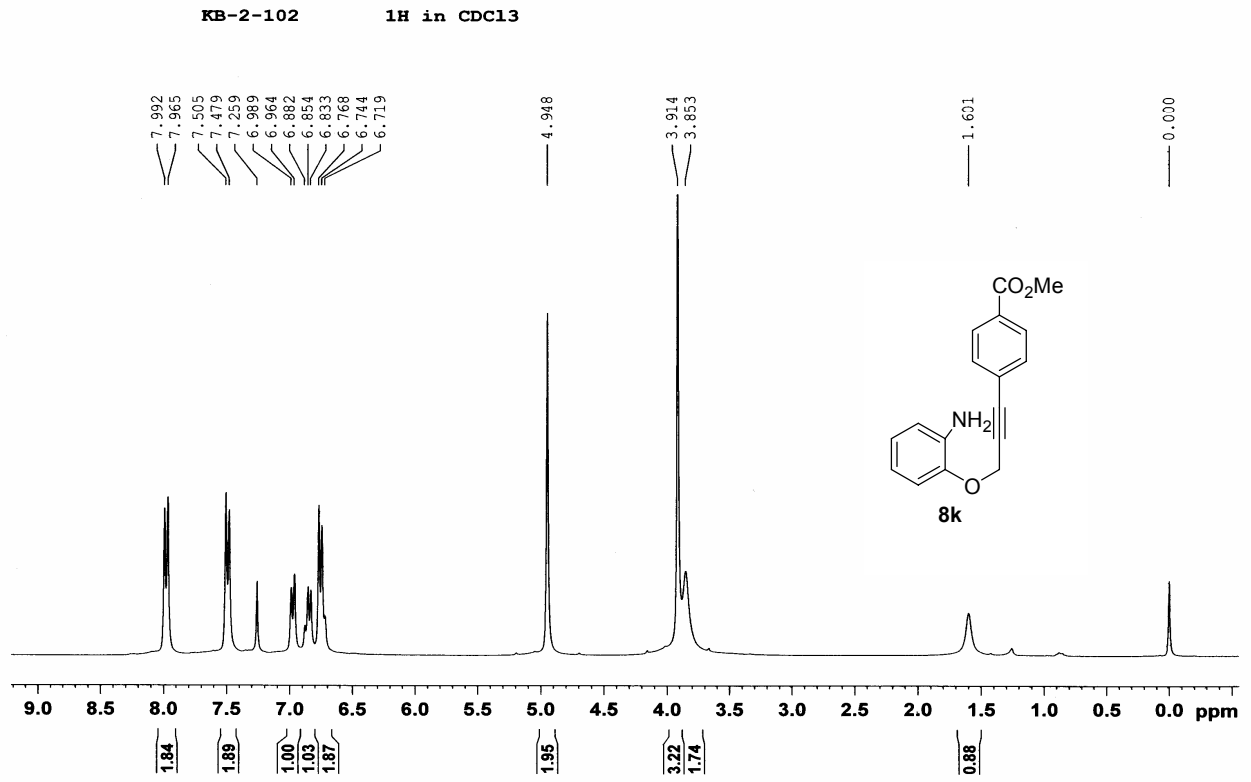
^{1}H NMR (300 MHz) SPECTRUM of 8c:



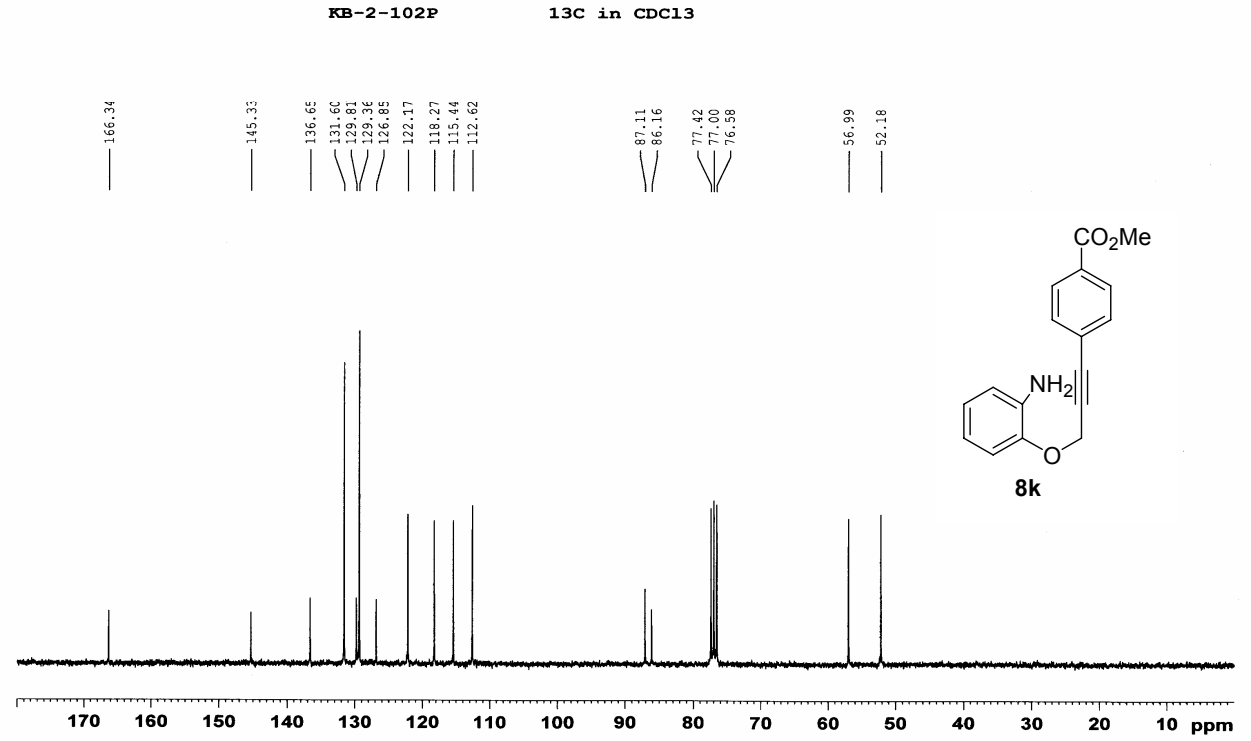
^{13}C NMR (150 MHz) SPECTRUM of 8c:



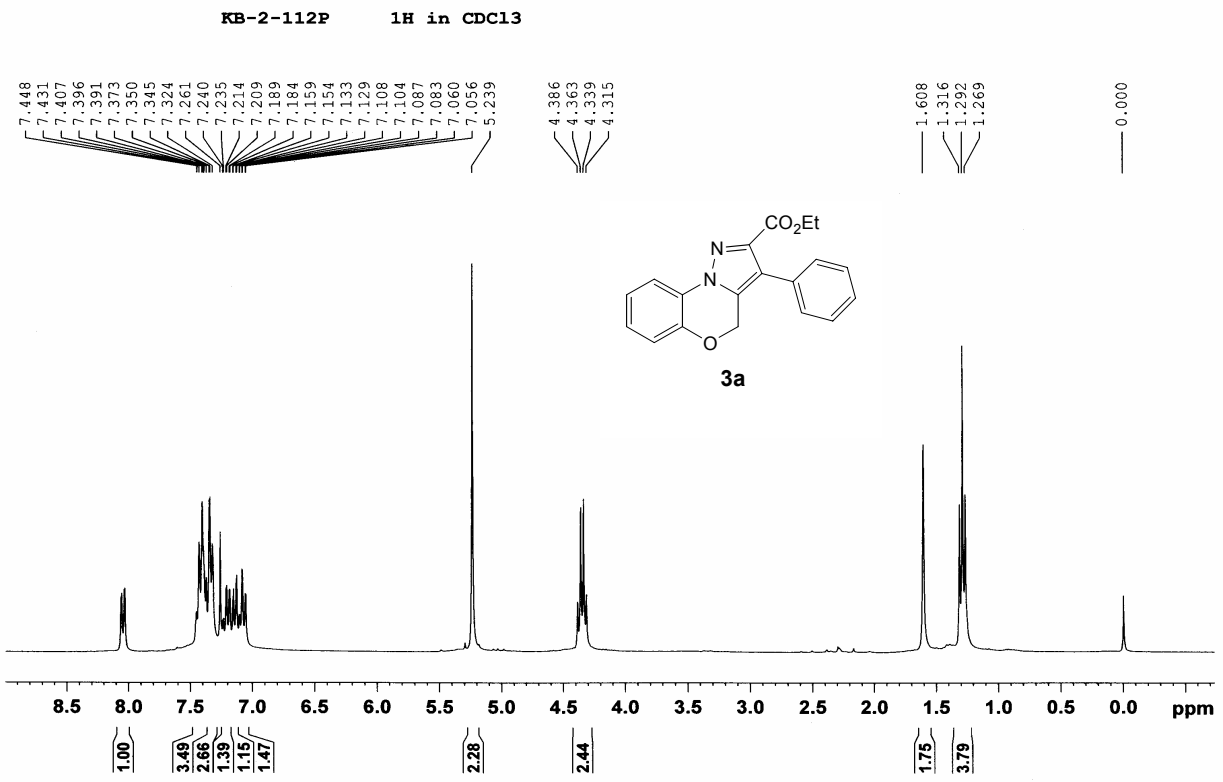
^{1}H NMR (300 MHz) SPECTRUM of 8k:



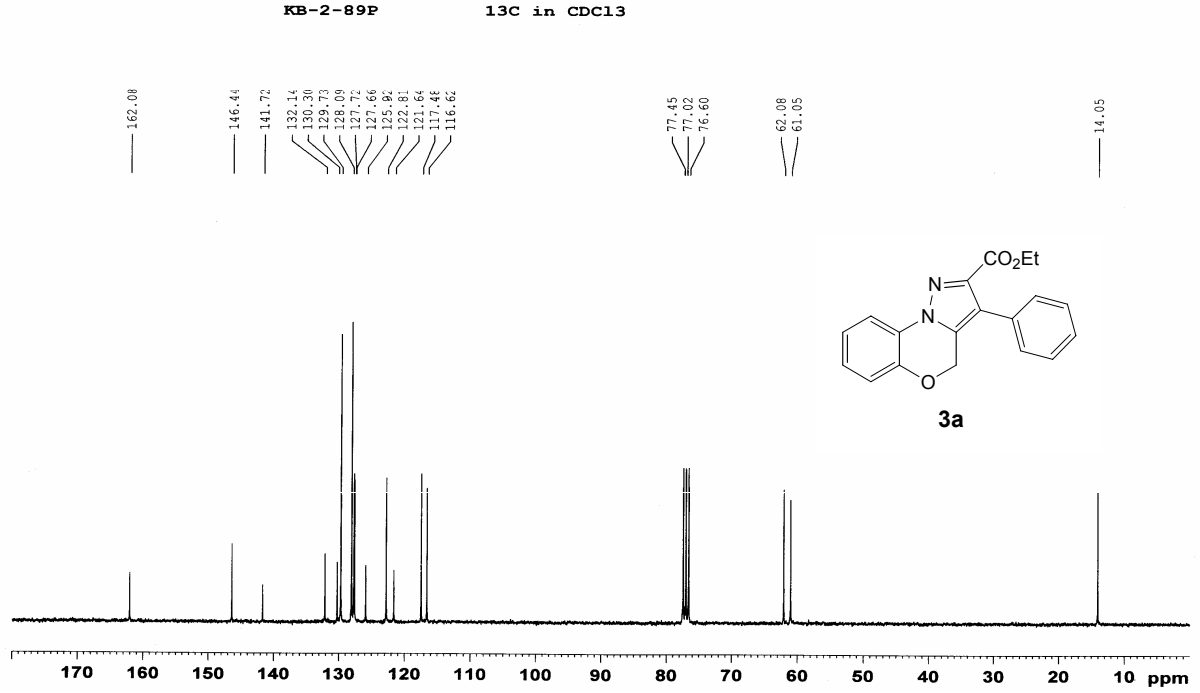
^{13}C NMR (75 MHz) SPECTRUM of 8k:



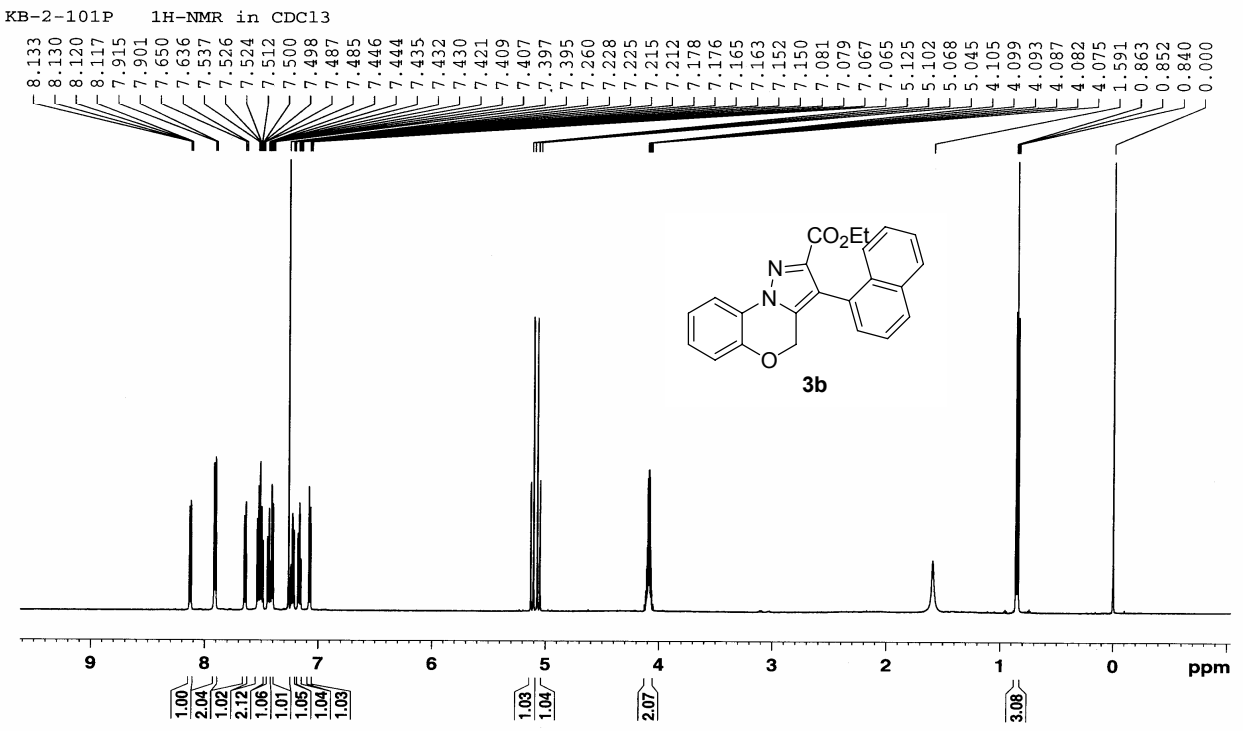
^{1}H NMR (300 MHz) SPECTRUM of 3a:



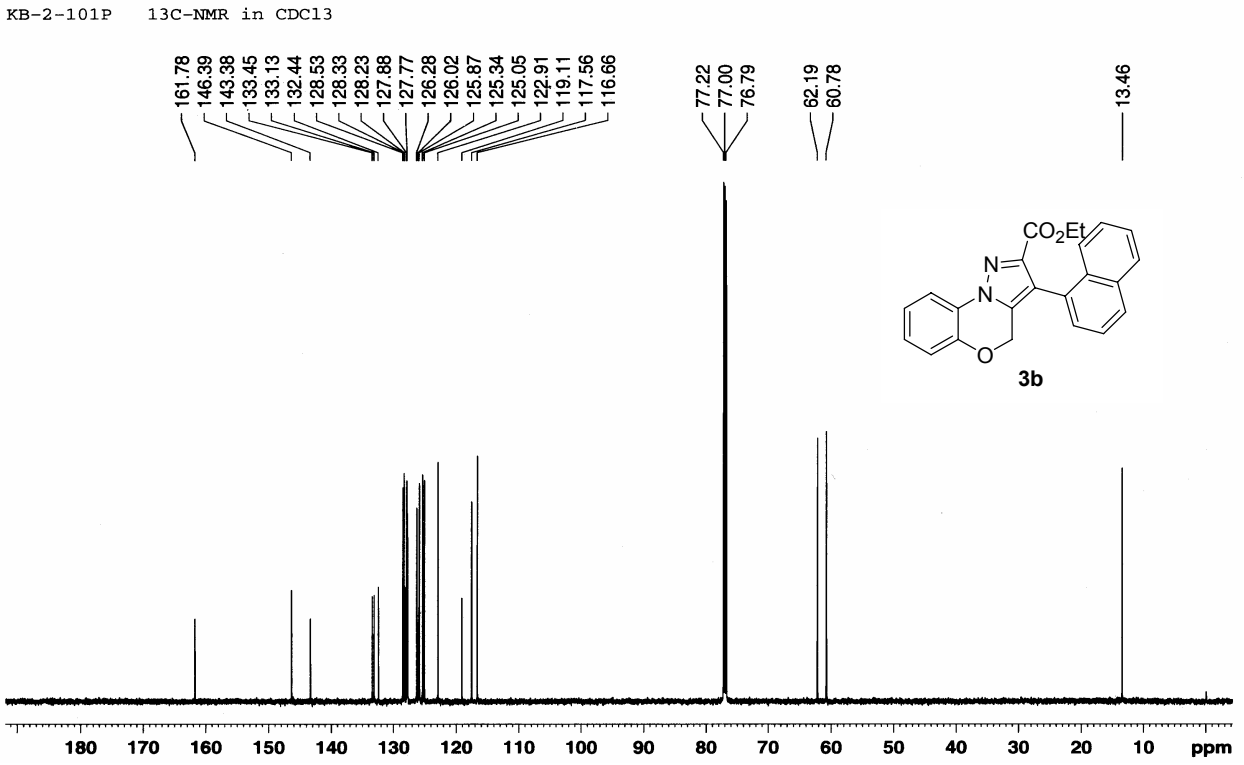
^{13}C NMR (75 MHz) SPECTRUM of 3a:



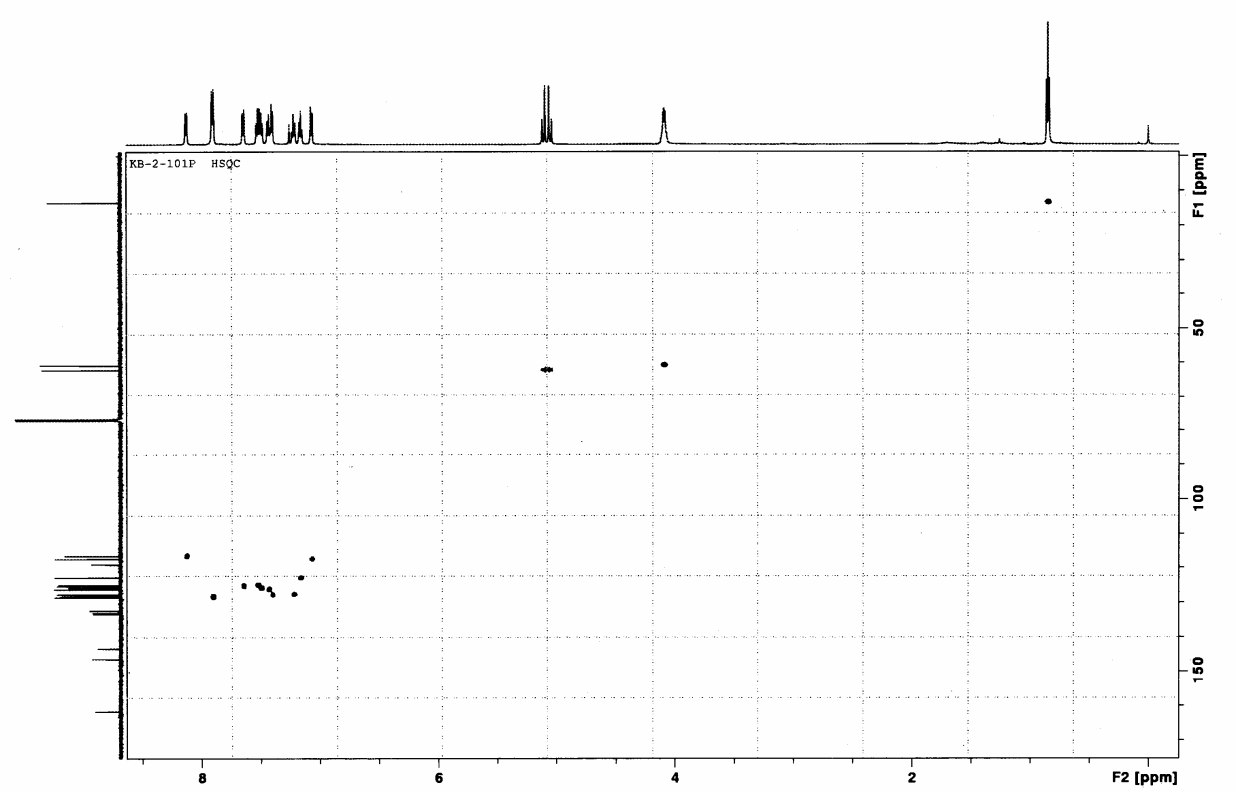
^{1}H NMR (600 MHz) SPECTRUM of 3b:



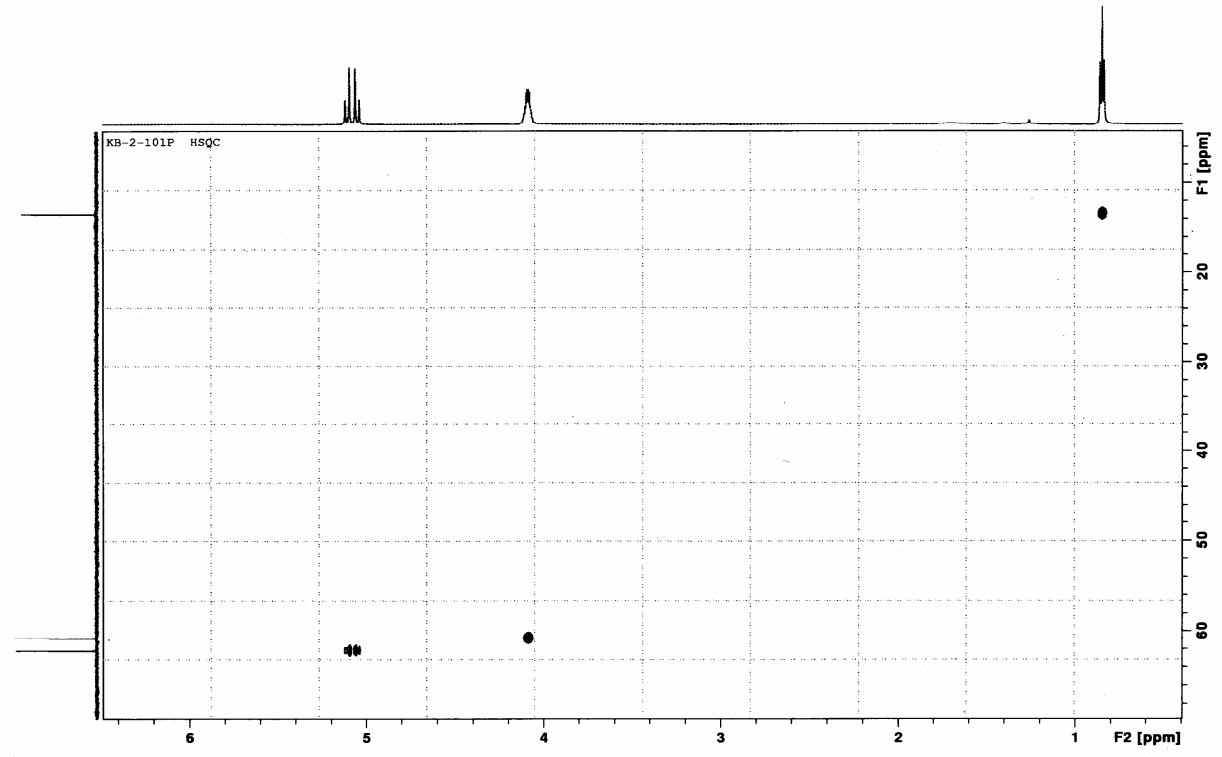
^{13}C NMR (150 MHz) SPECTRUM of 3b:



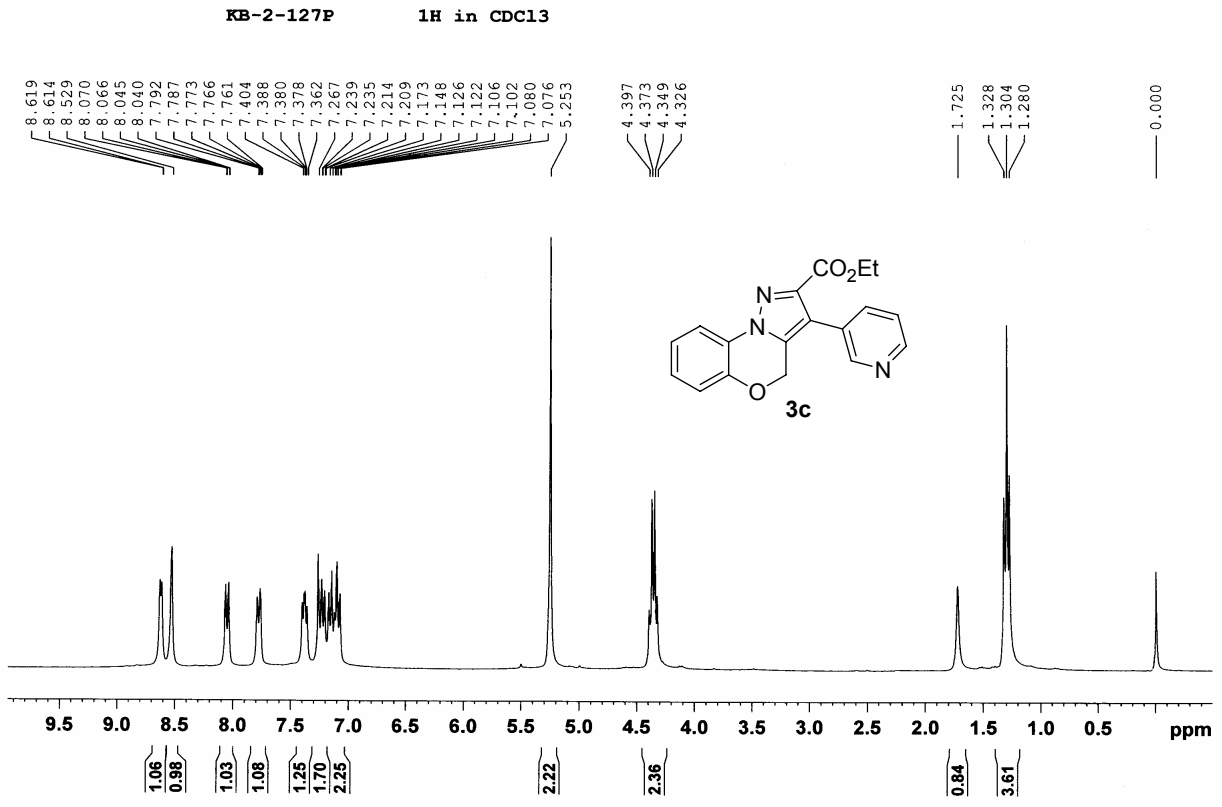
HSQC SPECTRUM of 3b:



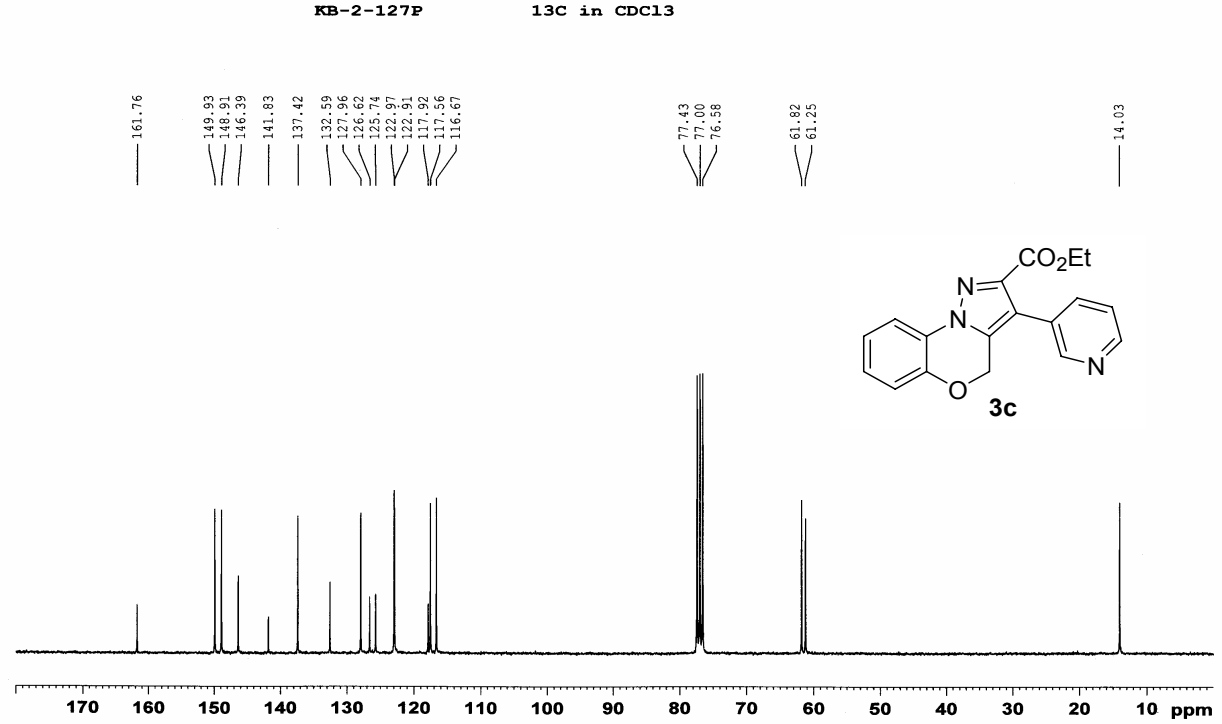
A Part of HSQC Spectrum of 3b:



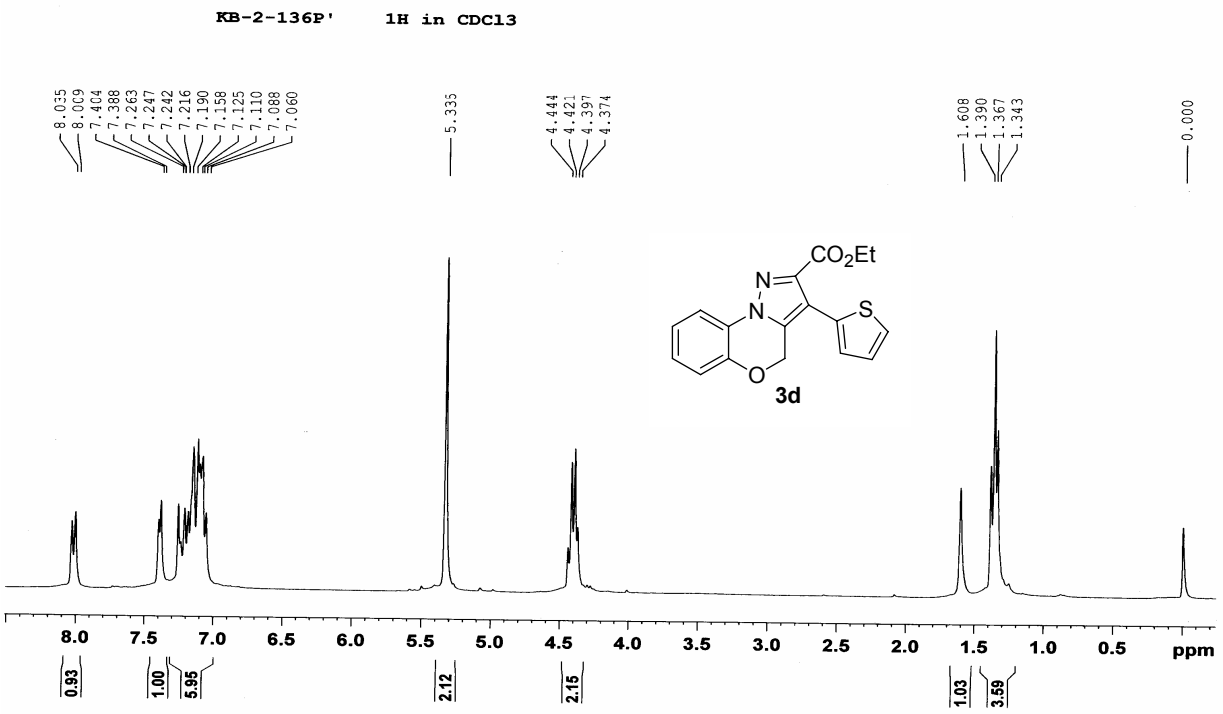
^{1}H NMR (300 MHz) SPECTRUM of 3c:



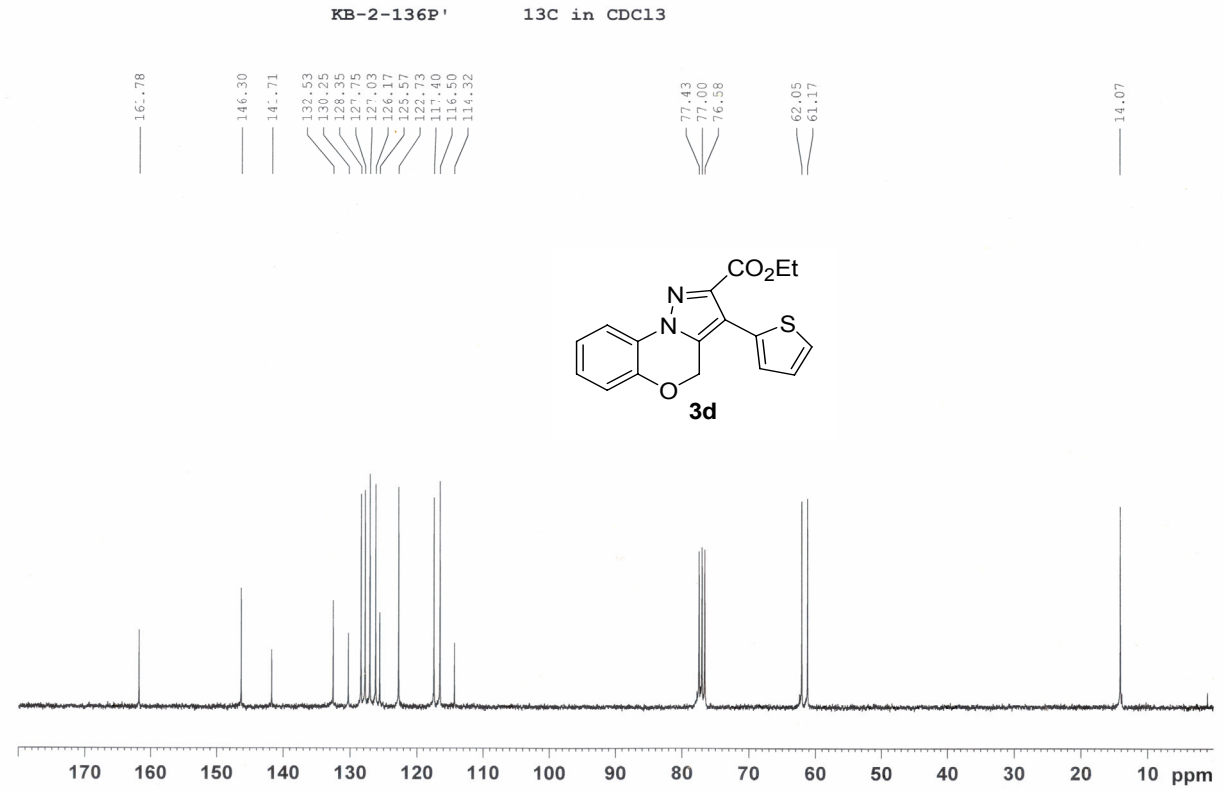
^{13}C NMR (75 MHz) SPECTRUM of 3c:



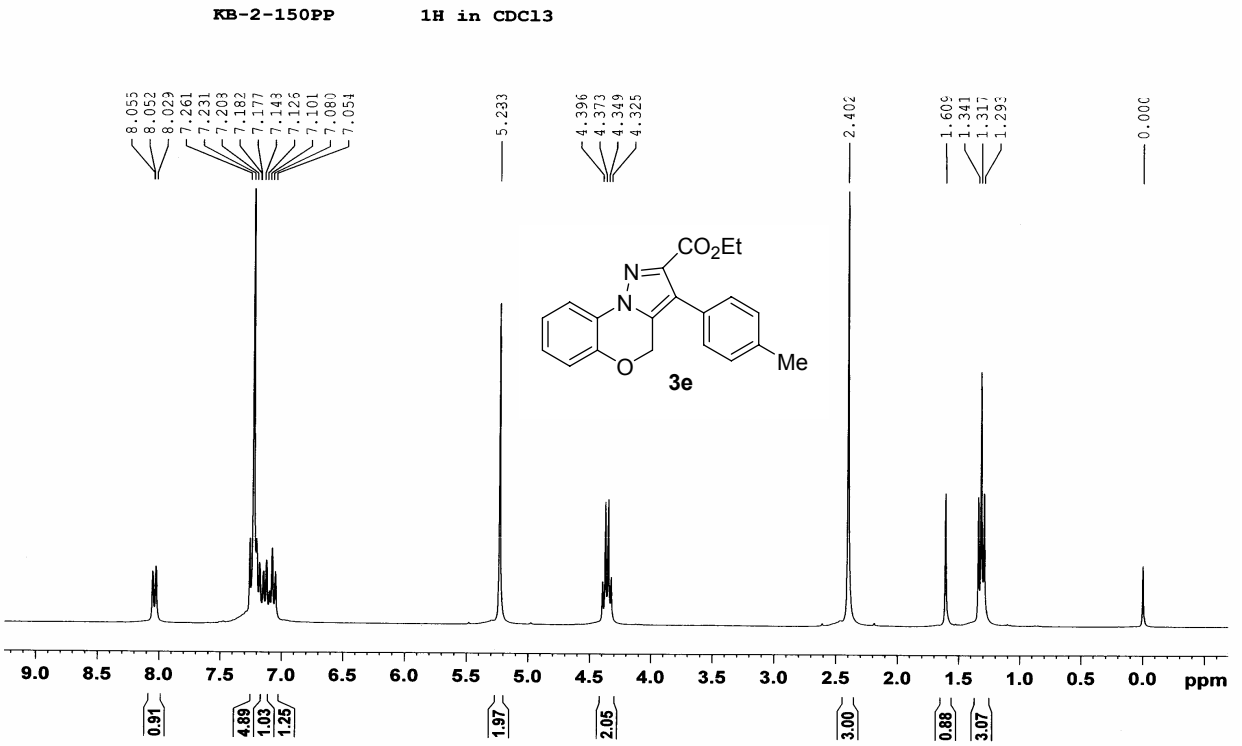
^{1}H NMR (300 MHz) SPECTRUM of 3d:



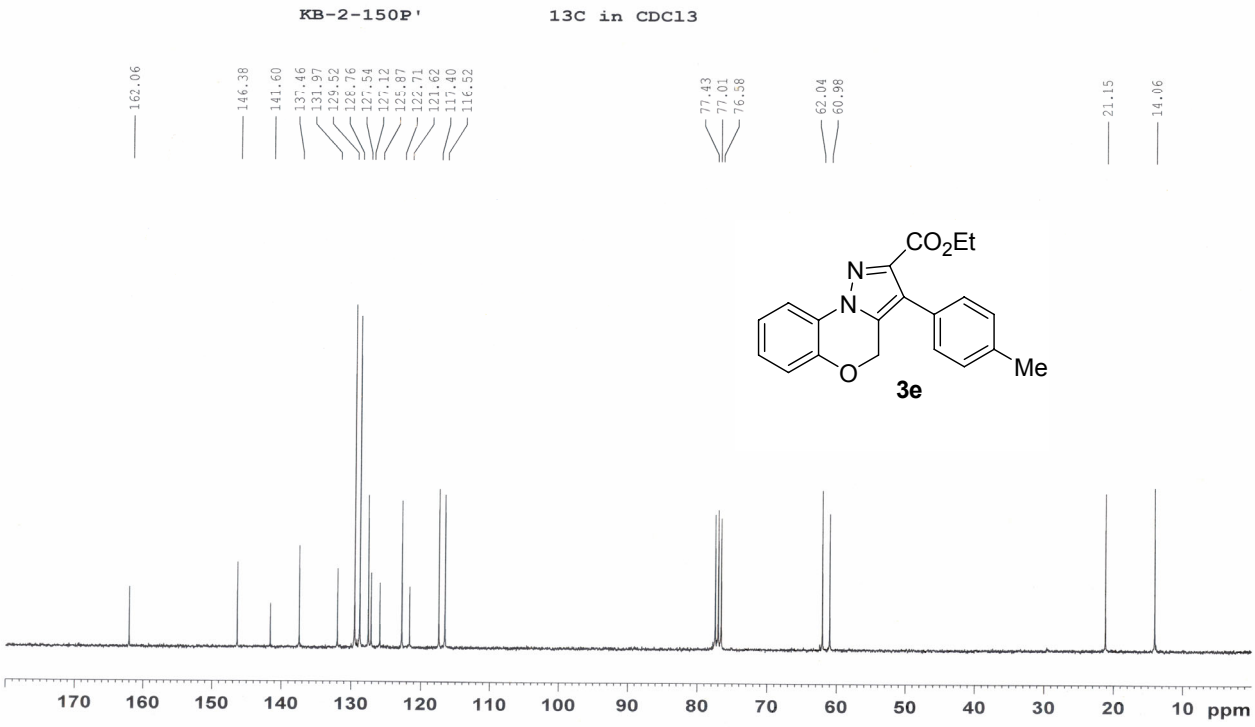
^{13}C NMR (75 MHz) SPECTRUM of 3d:



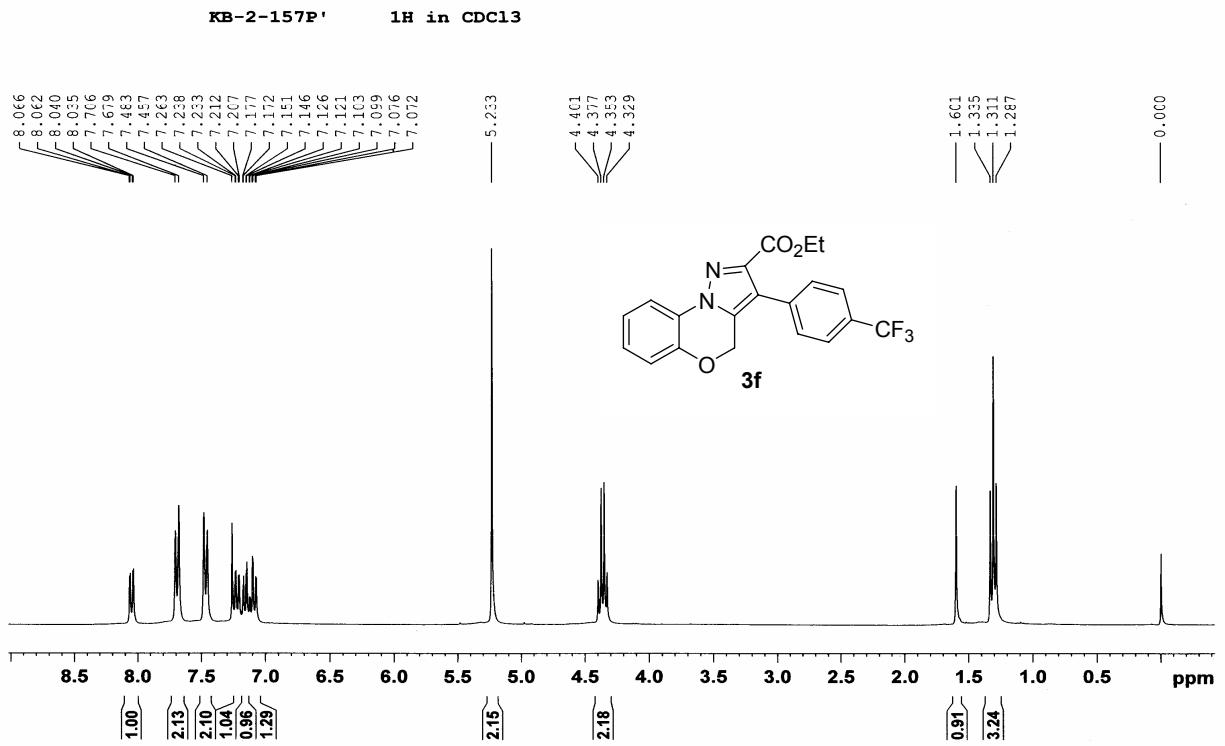
^{1}H NMR (300 MHz) SPECTRUM of 3e:



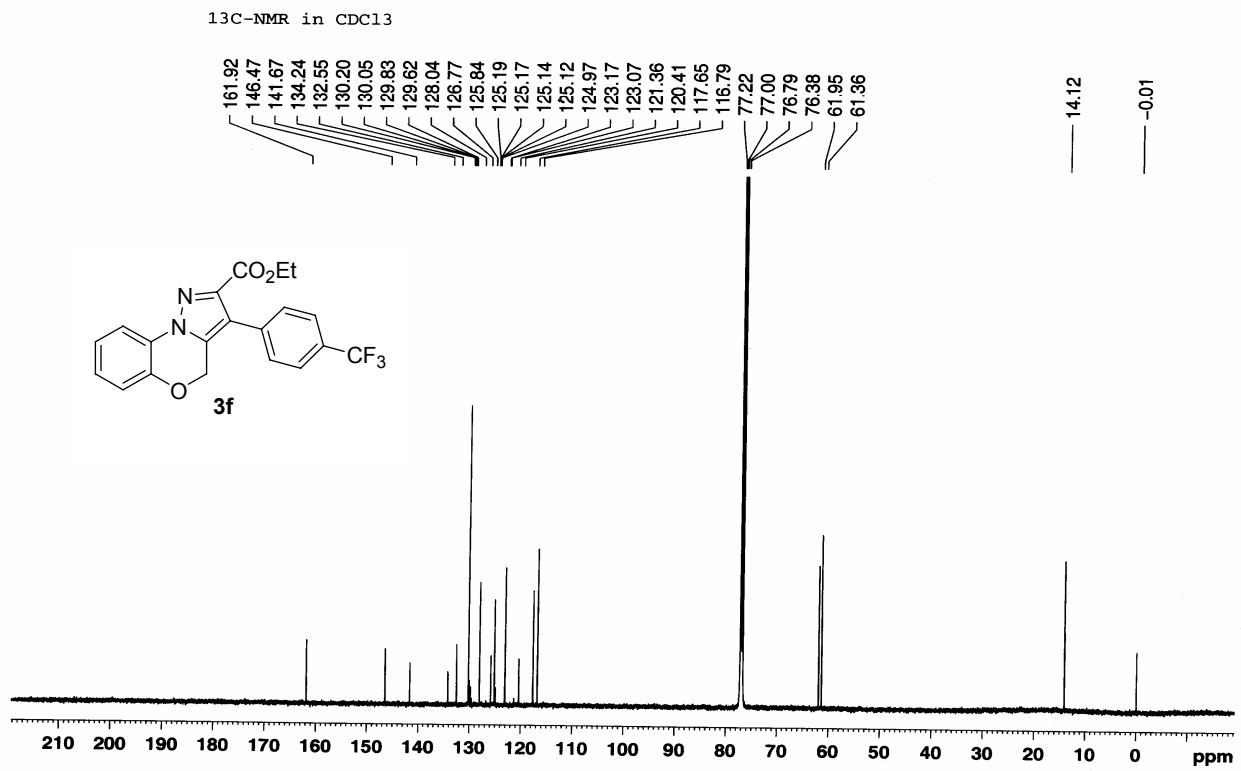
^{13}C NMR (75 MHz) SPECTRUM of 3e:



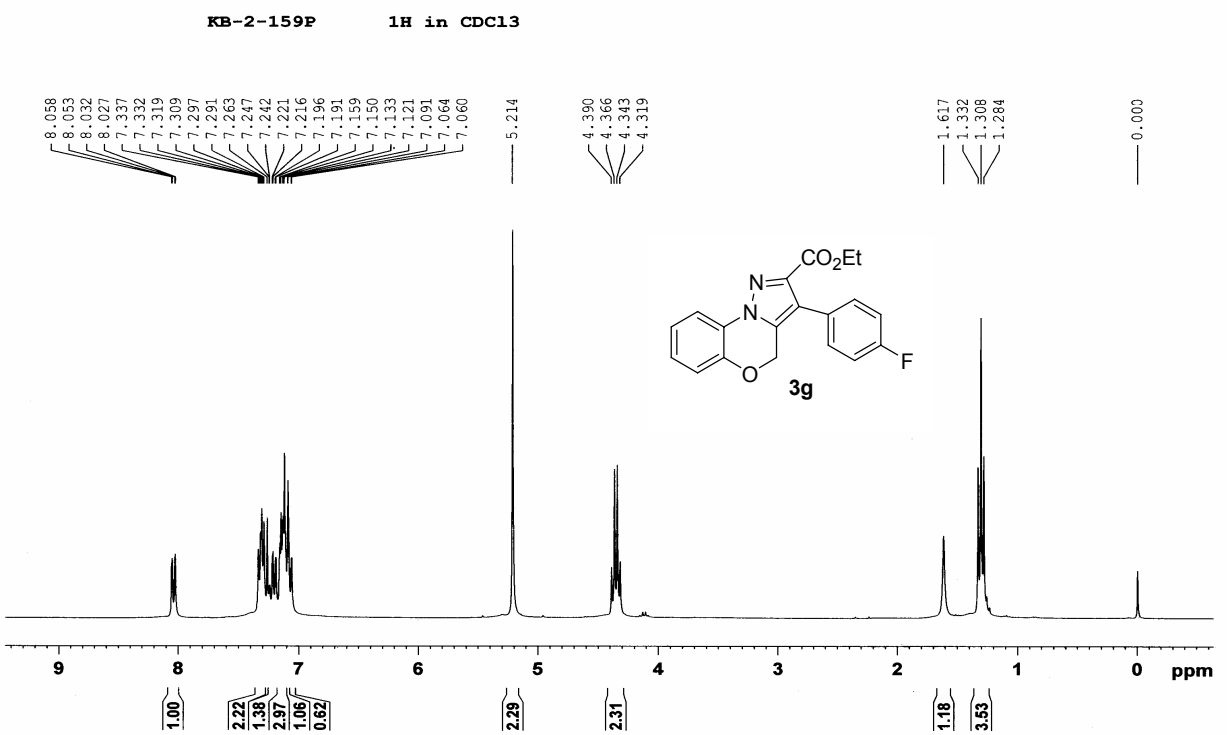
^{1}H NMR (300 MHz) SPECTRUM of 3f:



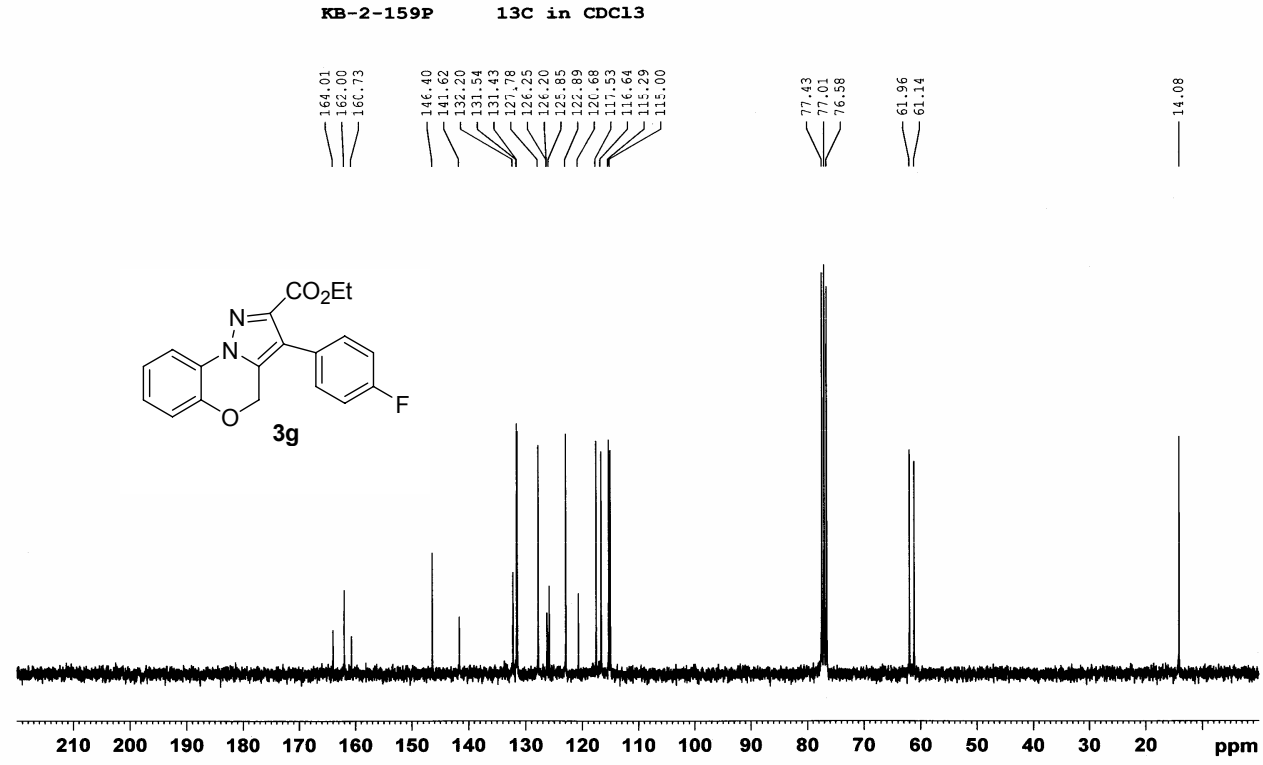
^{13}C NMR (150 MHz) SPECTRUM of 3f:



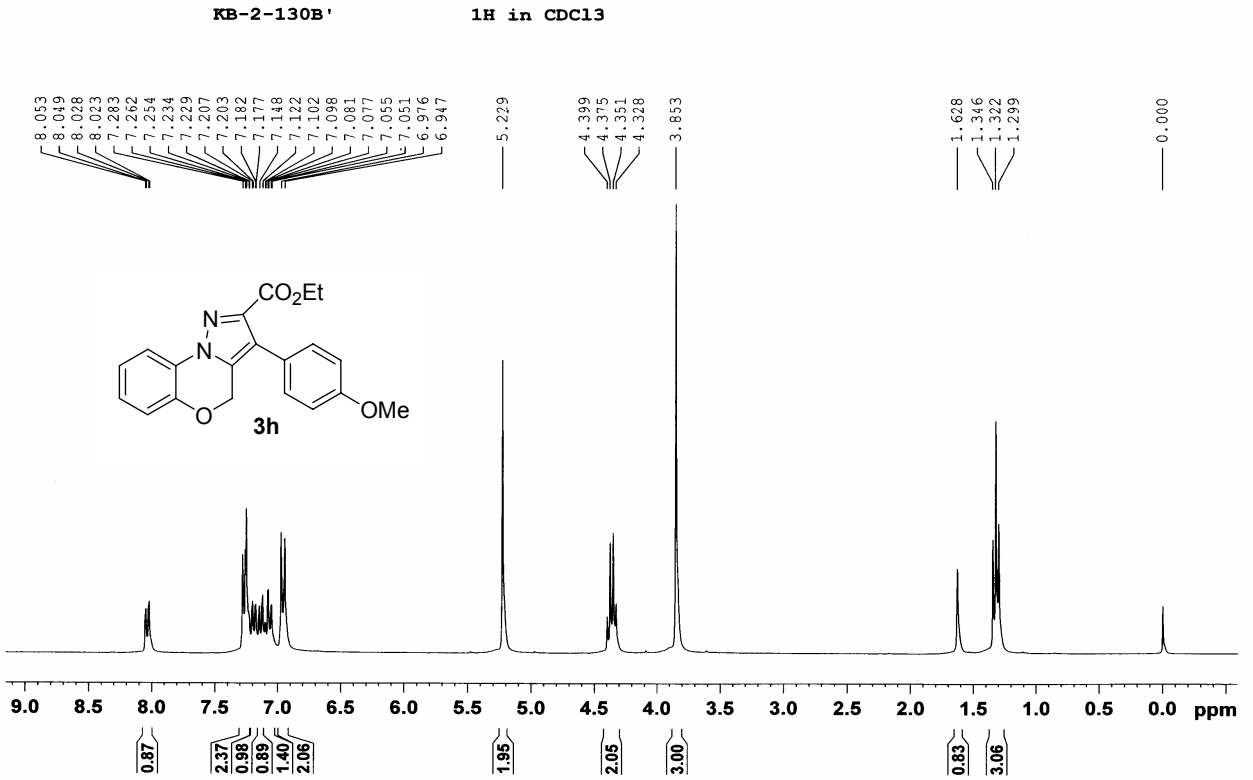
^{1}H NMR (300 MHz) SPECTRUM of 3g:



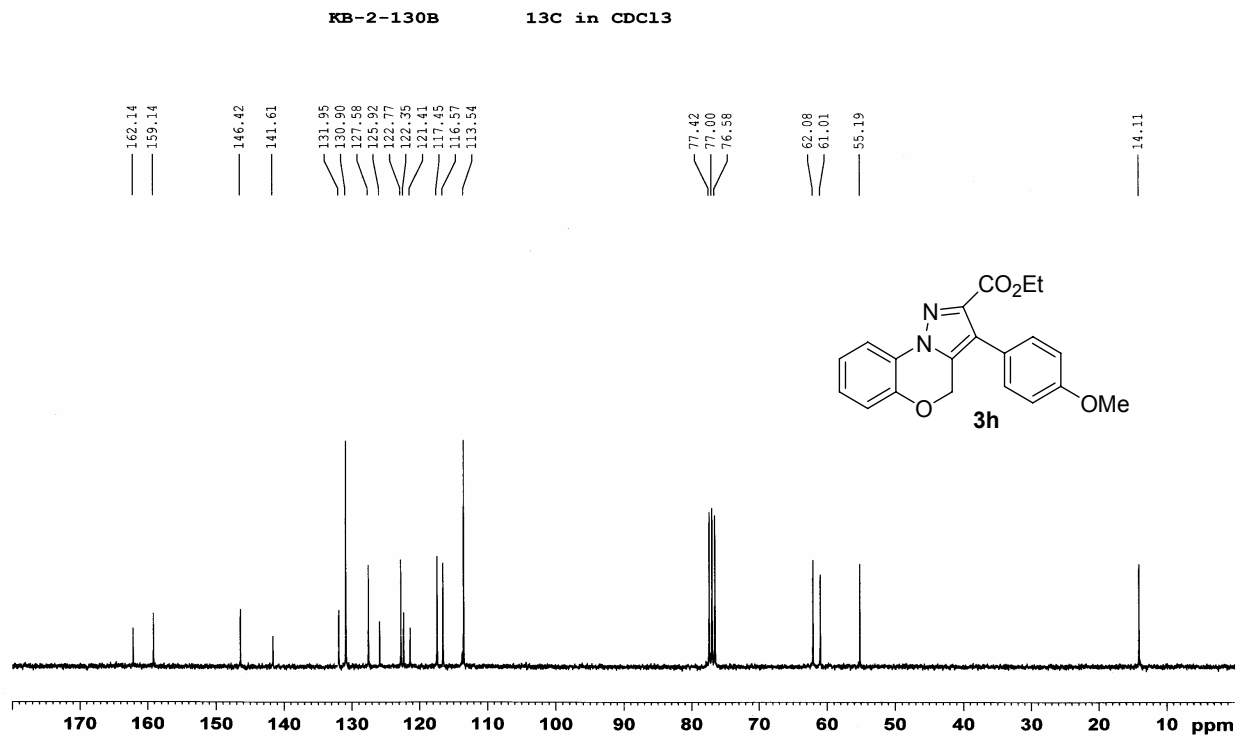
^{13}C NMR (75 MHz) SPECTRUM of 3g:



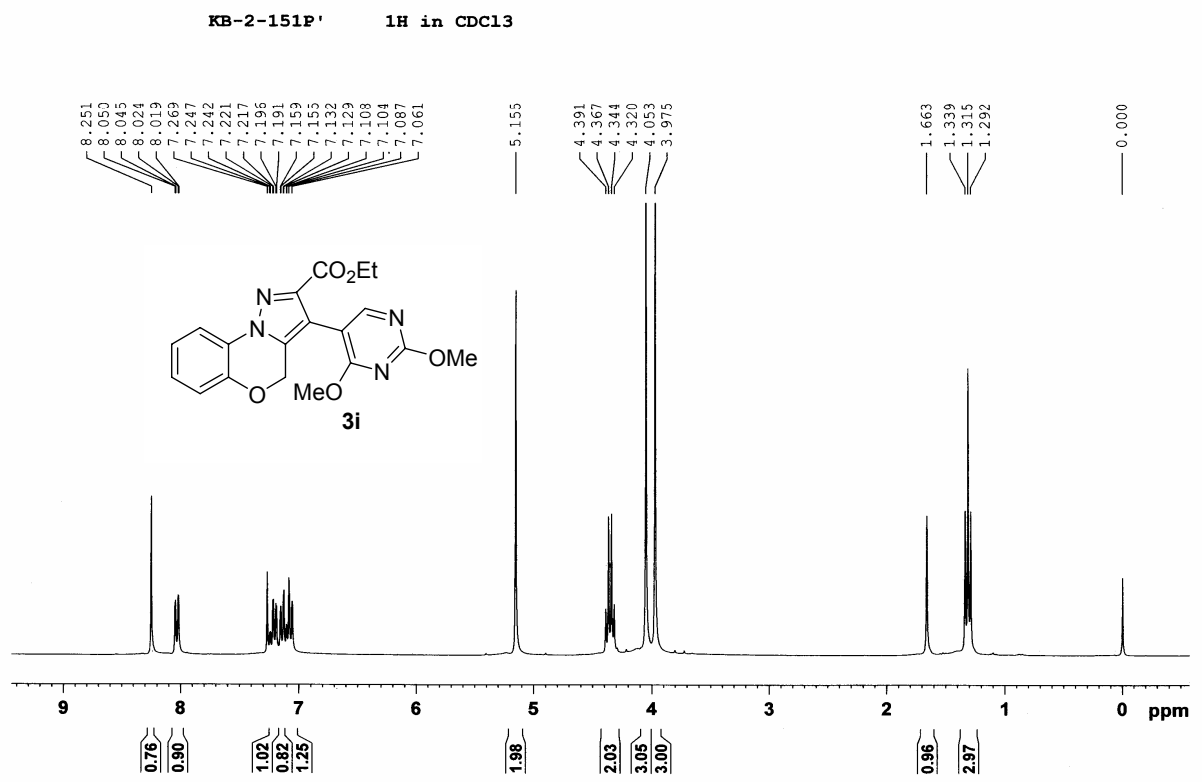
^{1}H NMR (300 MHz) SPECTRUM of 3h:



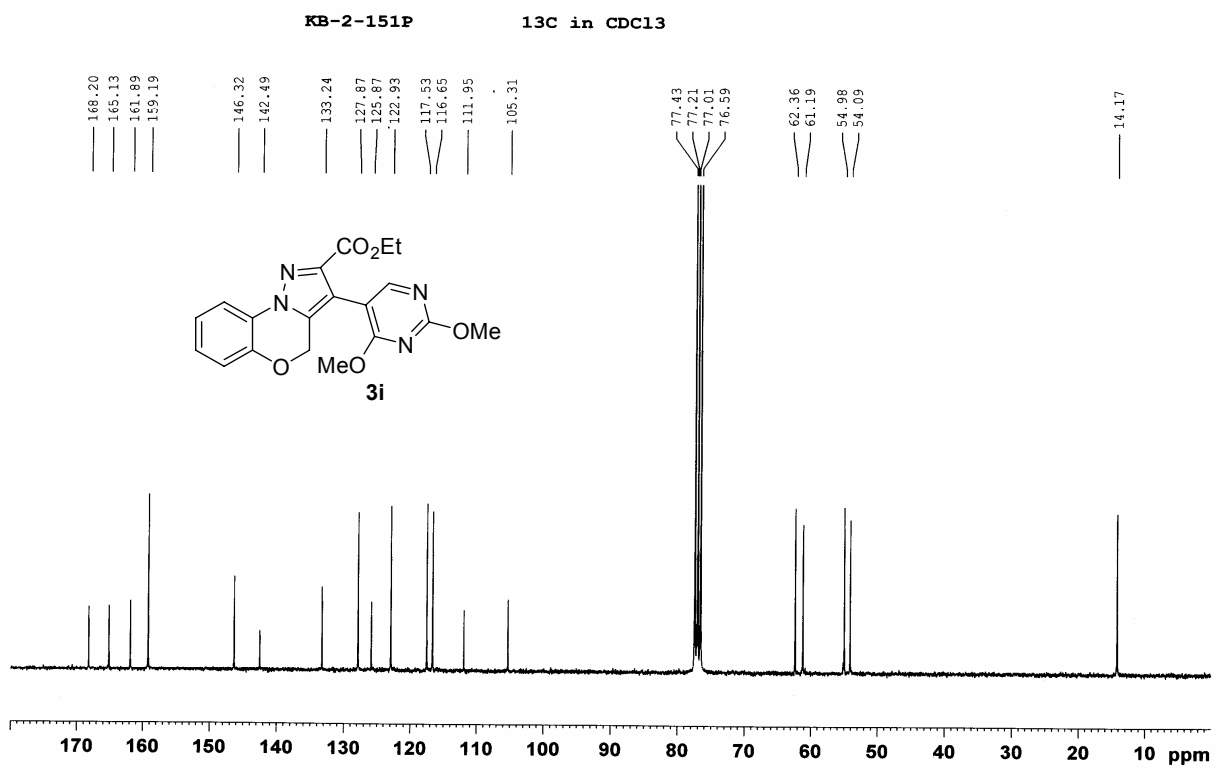
^{13}C NMR (75 MHz) SPECTRUM of 3h:



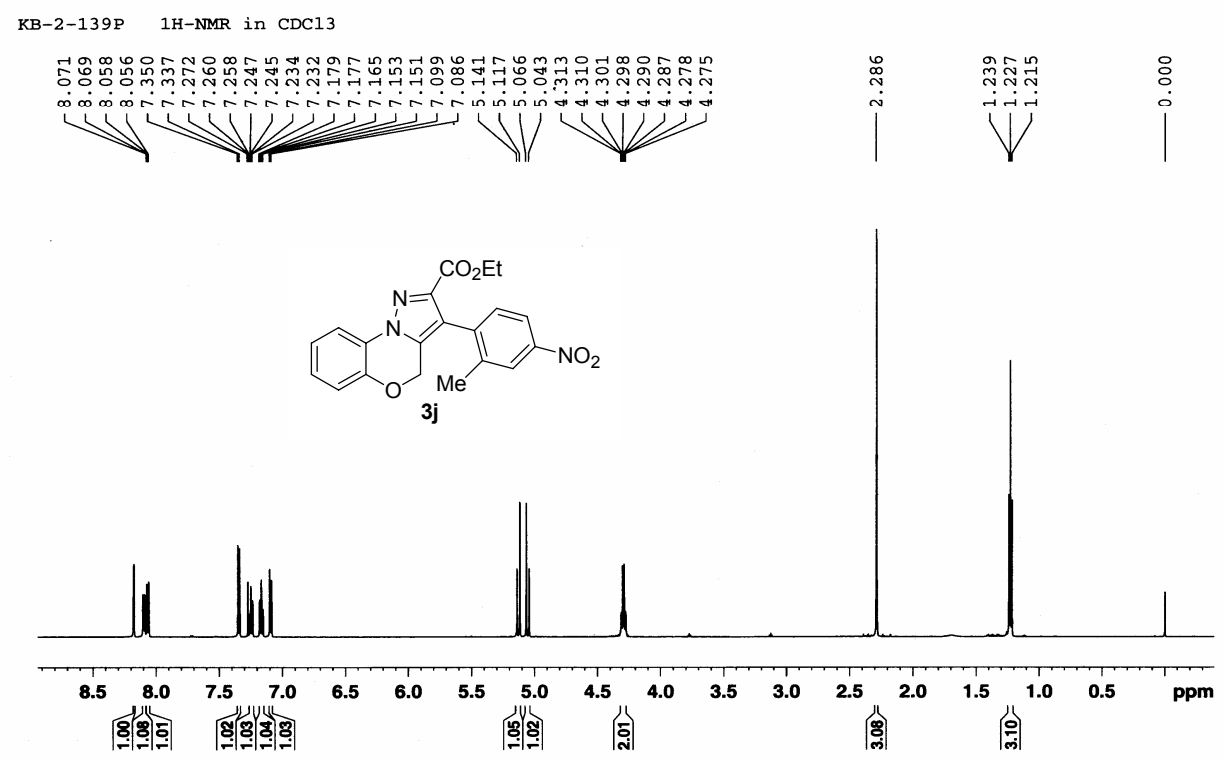
^{1}H NMR (300 MHz) SPECTRUM of 3i:



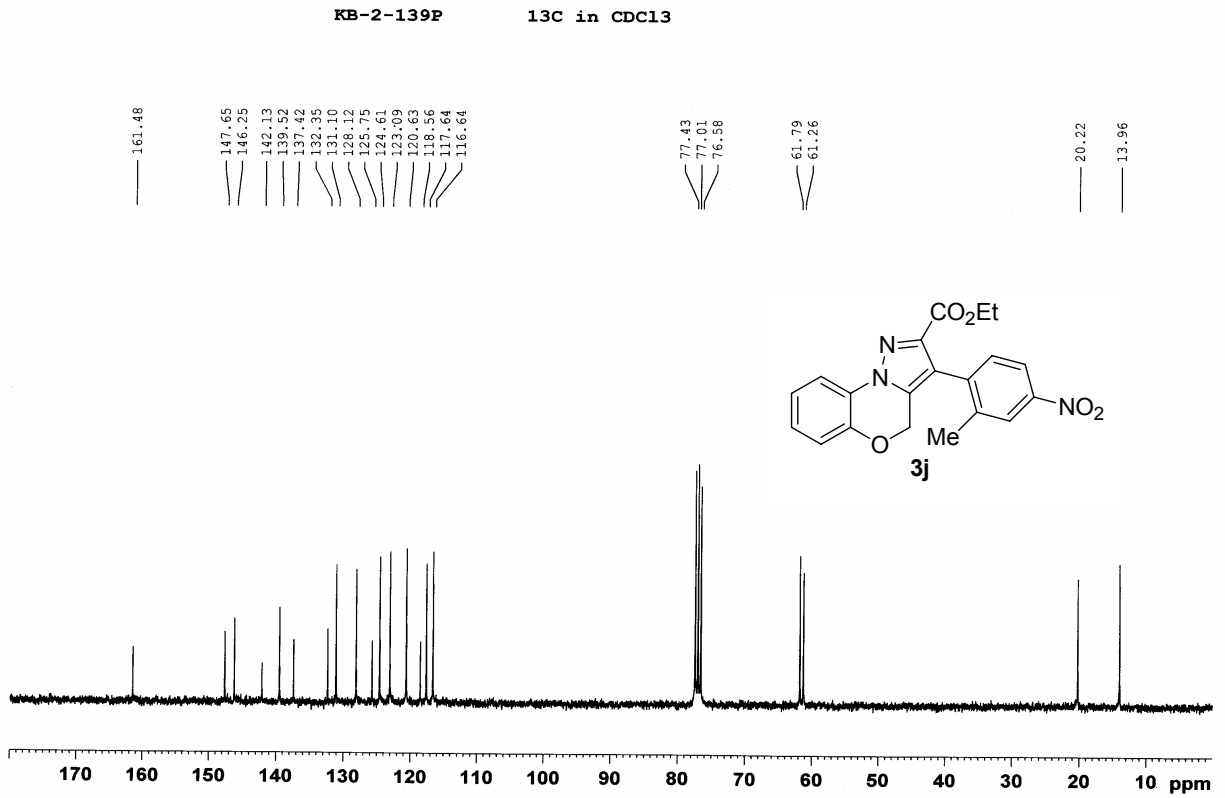
^{13}C NMR (75 MHz) SPECTRUM of 3i:



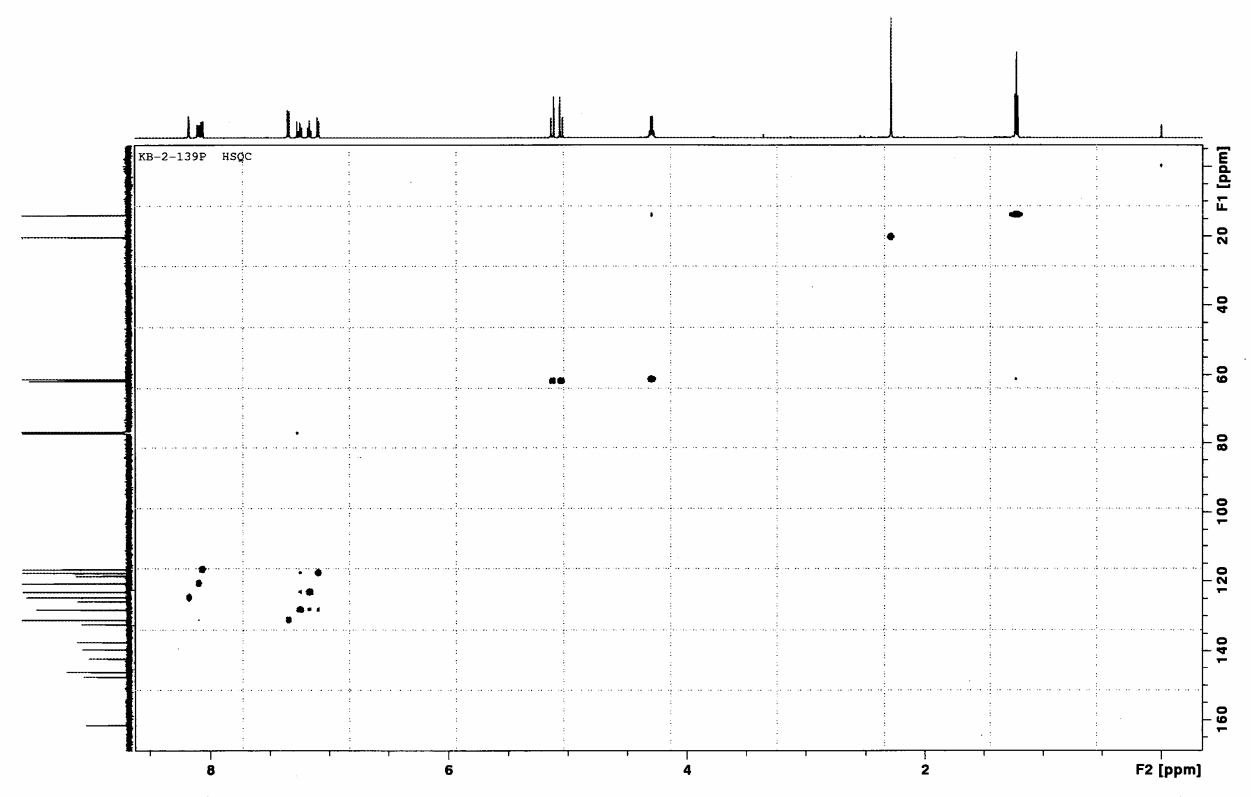
^{1}H NMR (600 MHz) SPECTRUM of 3j:



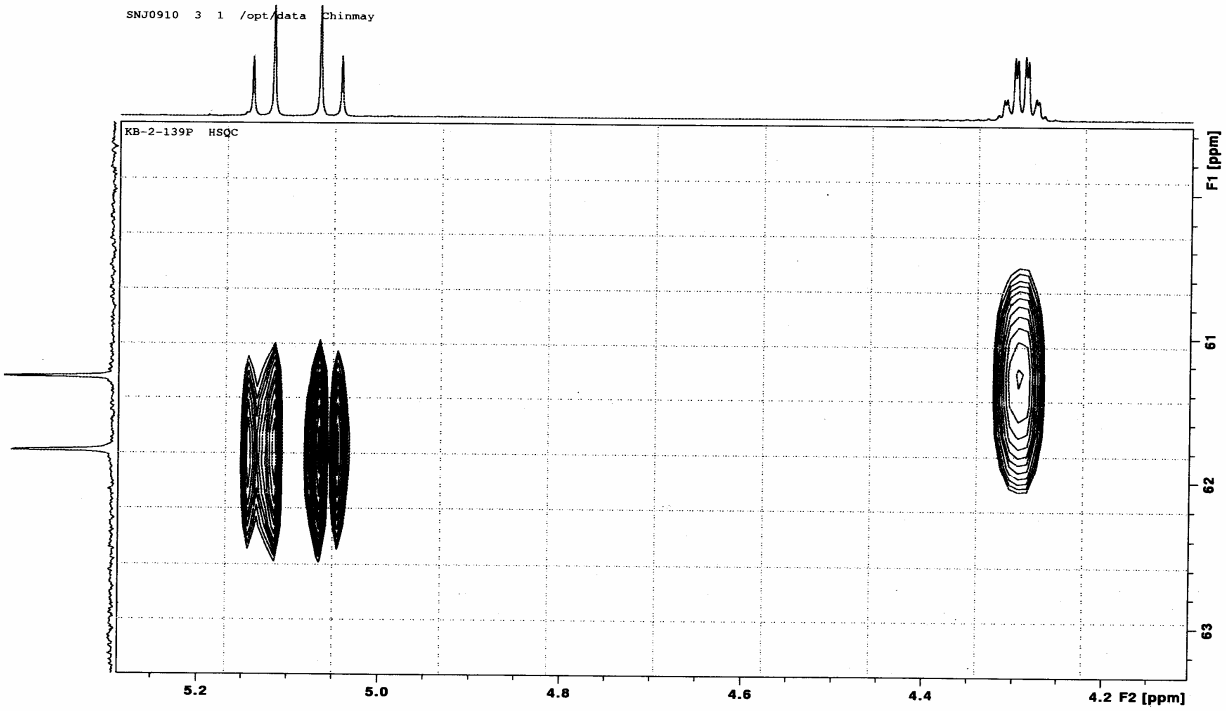
^{13}C NMR (75 MHz) SPECTRUM of 3j:



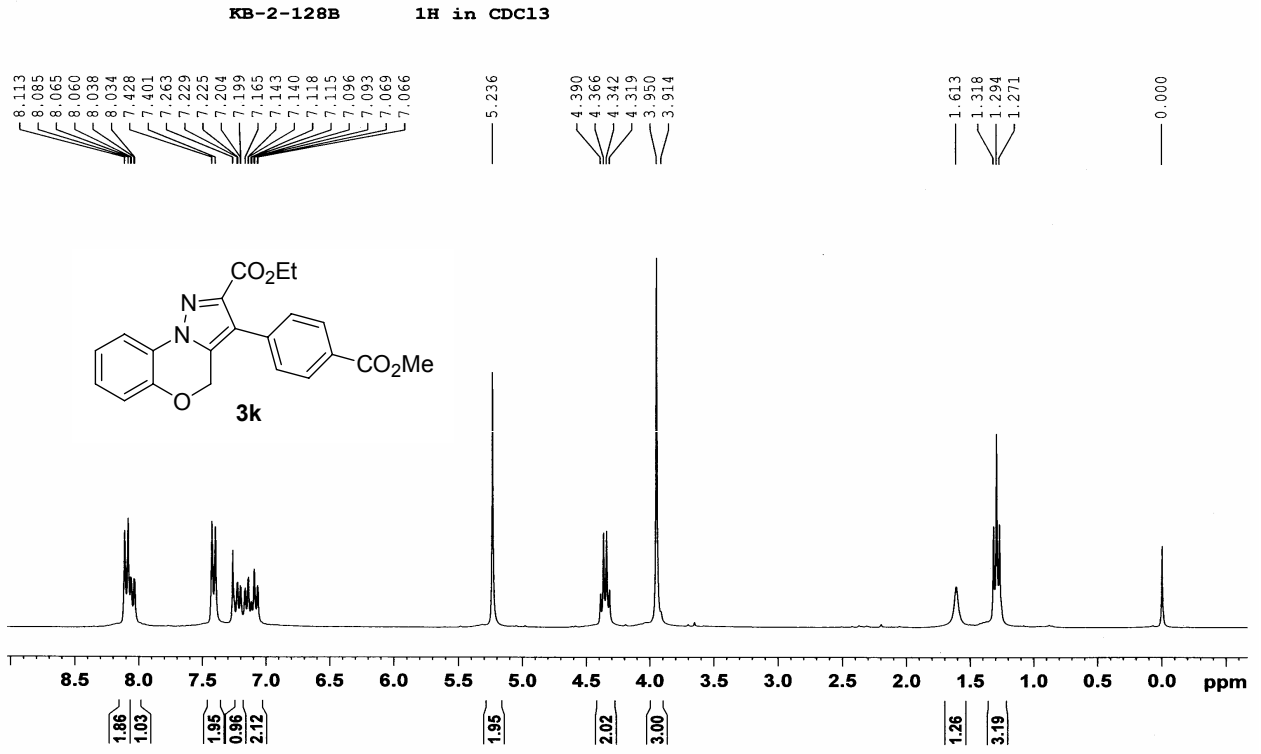
HSQC SPECTRUM of 3j:



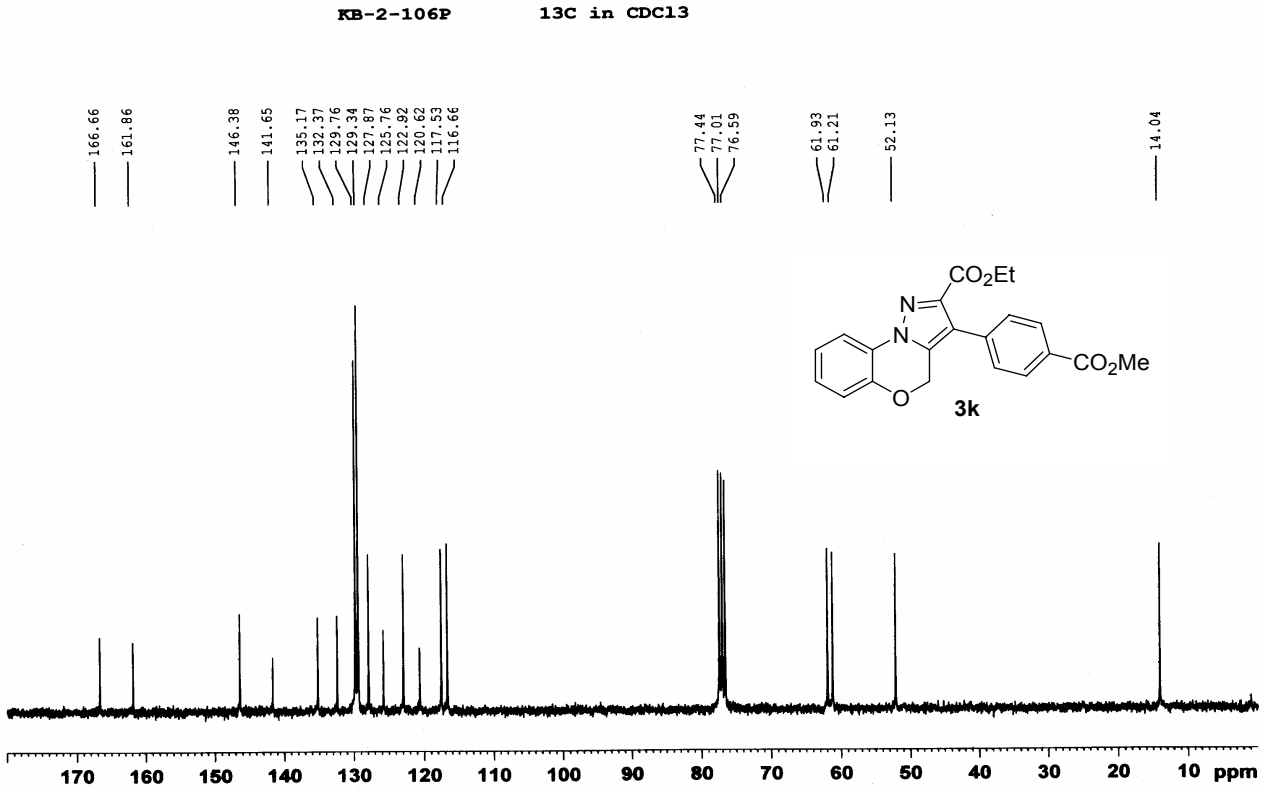
A Part of HSQC SPECTRUM of 3j:



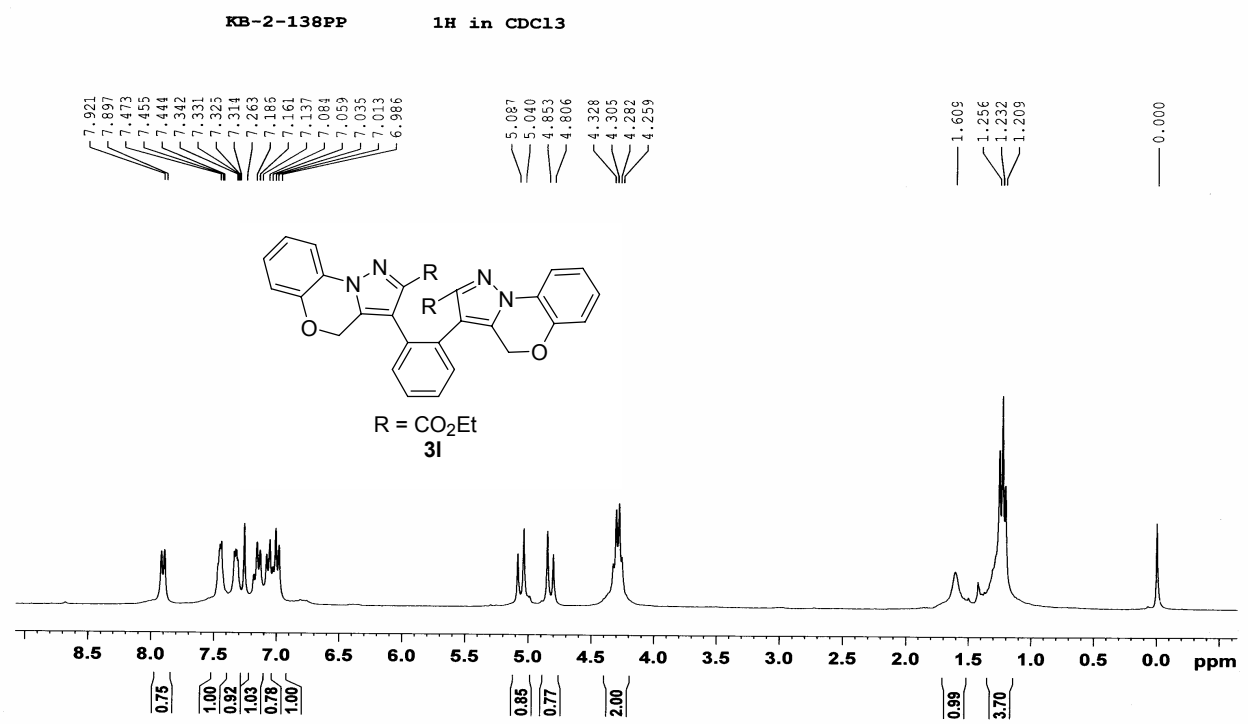
^{1}H NMR (300 MHz) SPECTRUM of 3k:



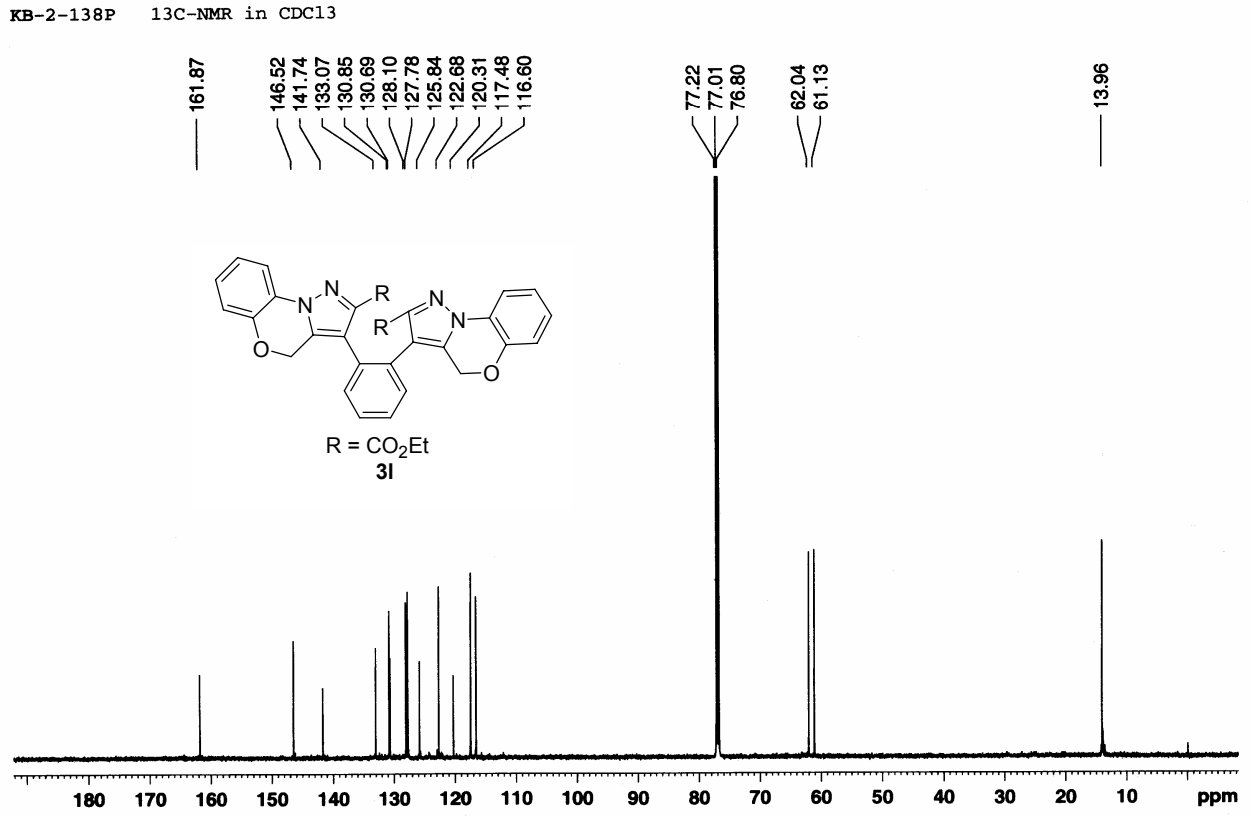
^{13}C NMR (75 MHz) SPECTRUM of 3k:



^{1}H NMR (300 MHz) SPECTRUM of 3l:

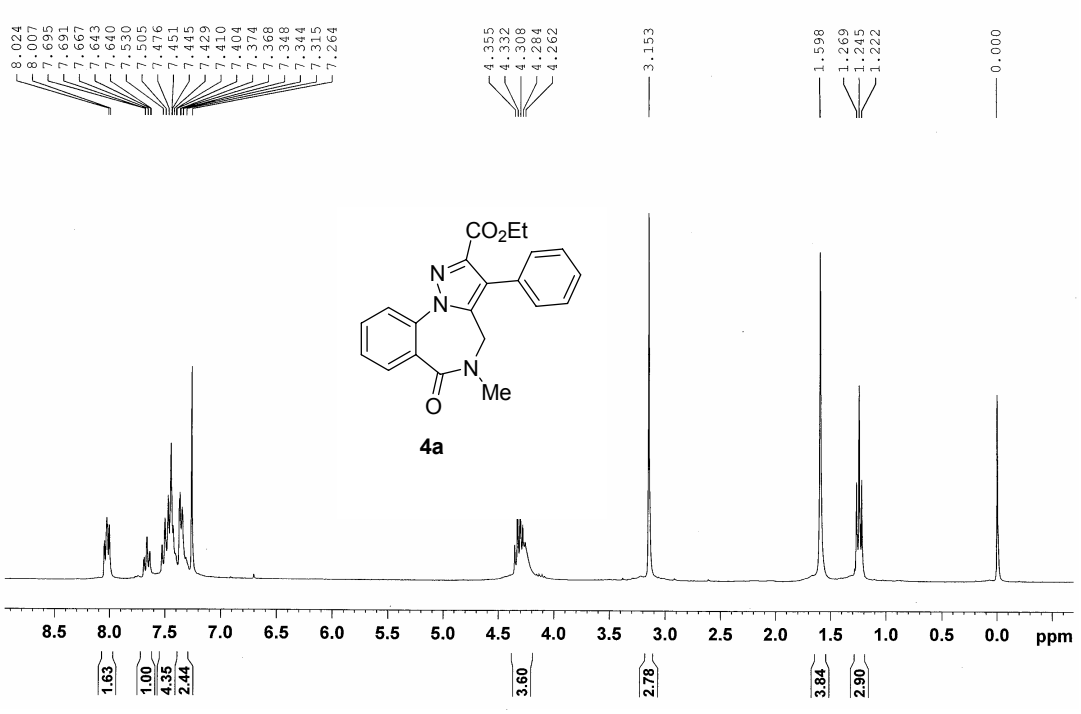


^{13}C NMR (150 MHz) SPECTRUM of 3l:

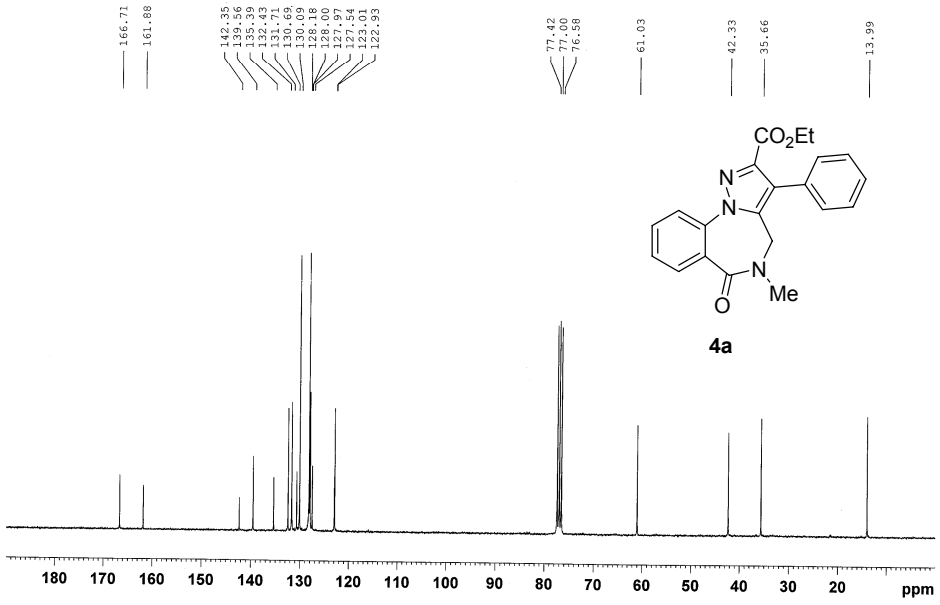


11. NMR Spectra of Compounds 4, 12 and 13:

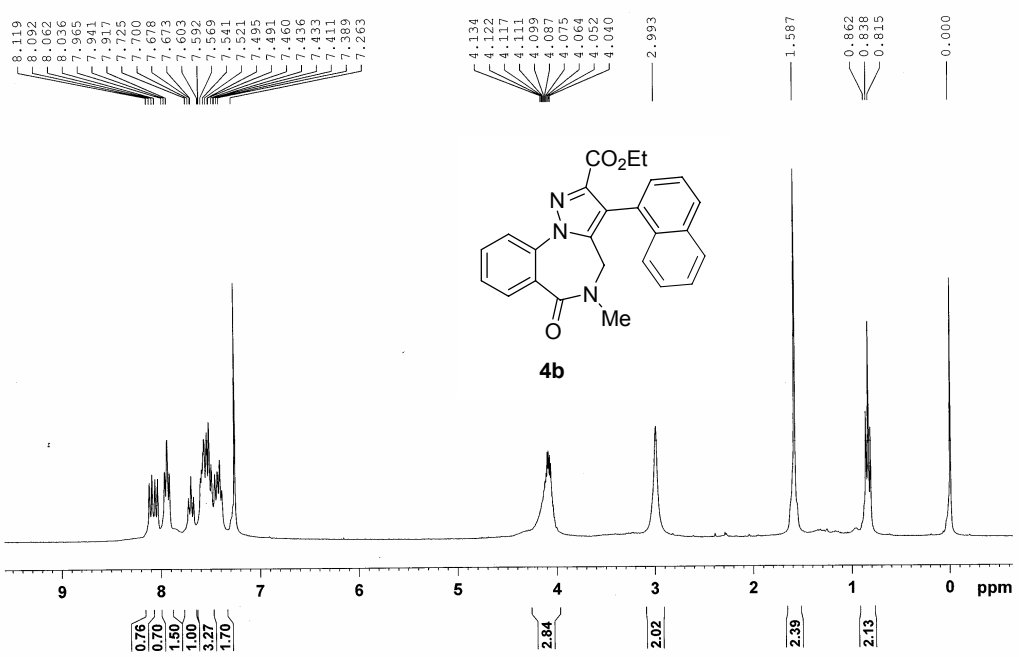
^{1}H NMR (300 MHz, $CDCl_3$) of **4a**



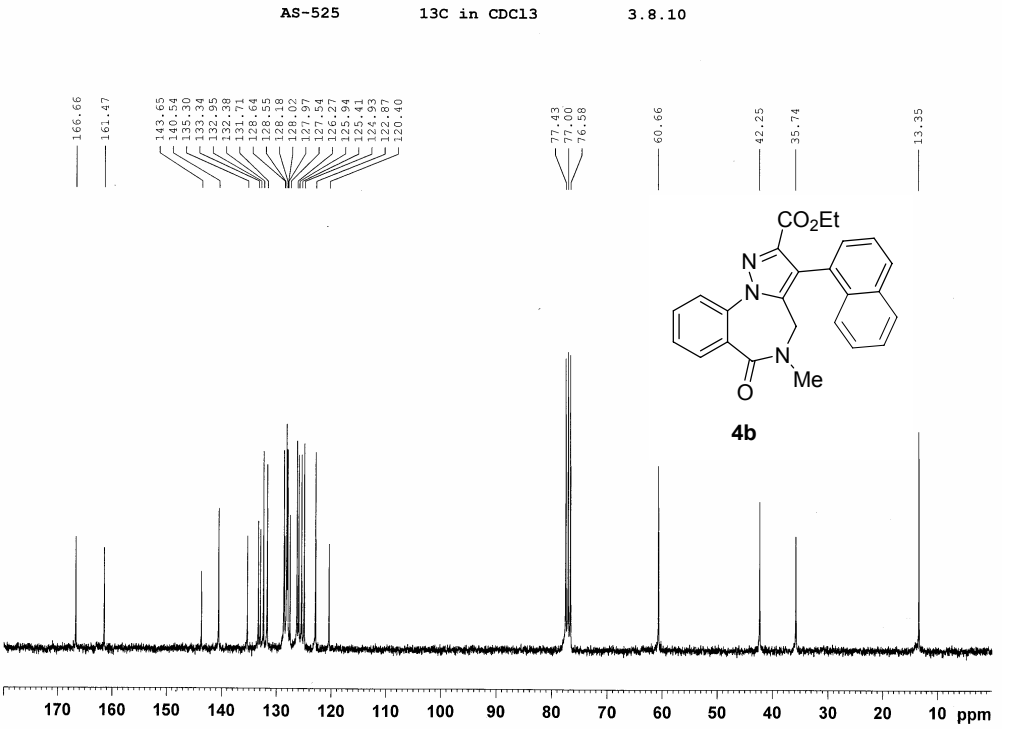
^{13}C NMR (75 MHz, $CDCl_3$) of **4a**



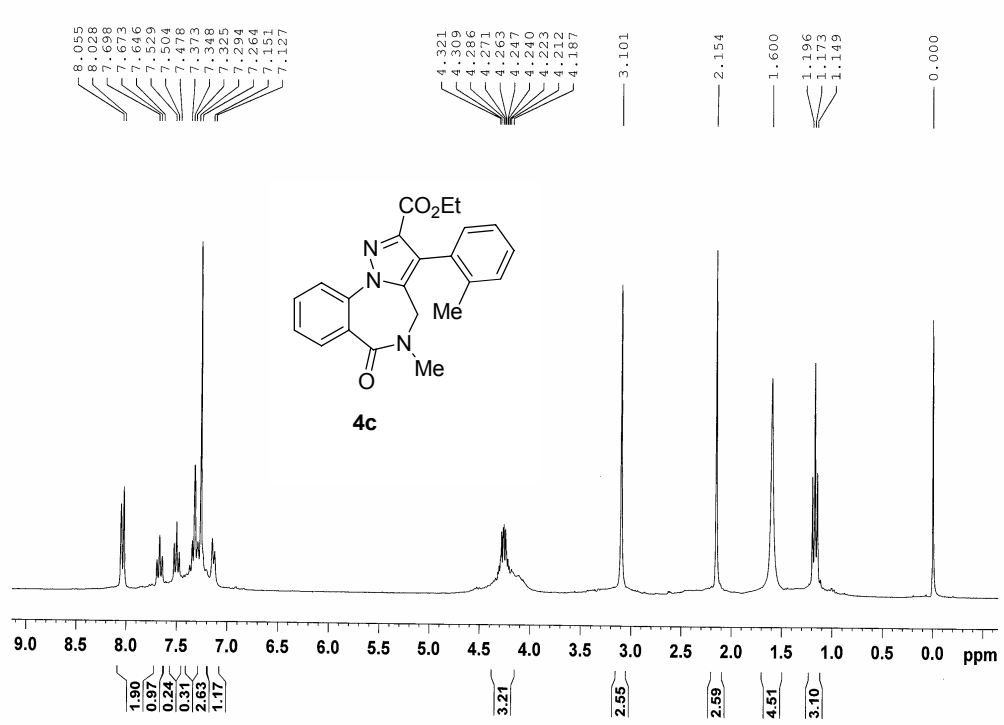
^{1}H NMR (300 MHz, $CDCl_3$) of **4b**



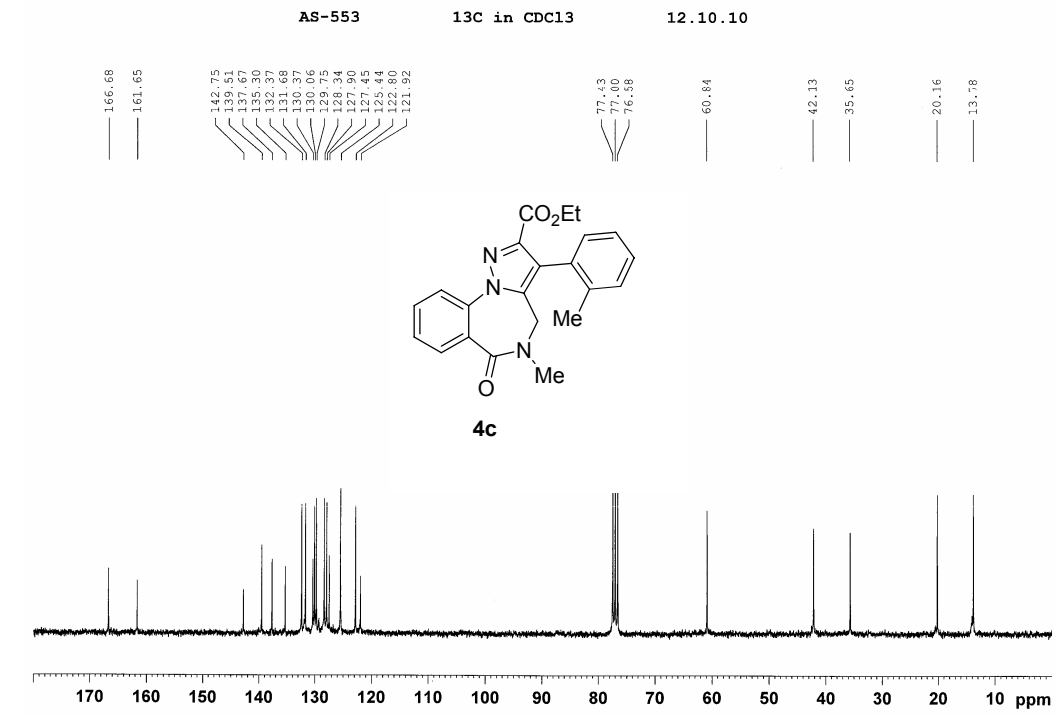
^{13}C NMR (75 MHz, $CDCl_3$) of **4b**



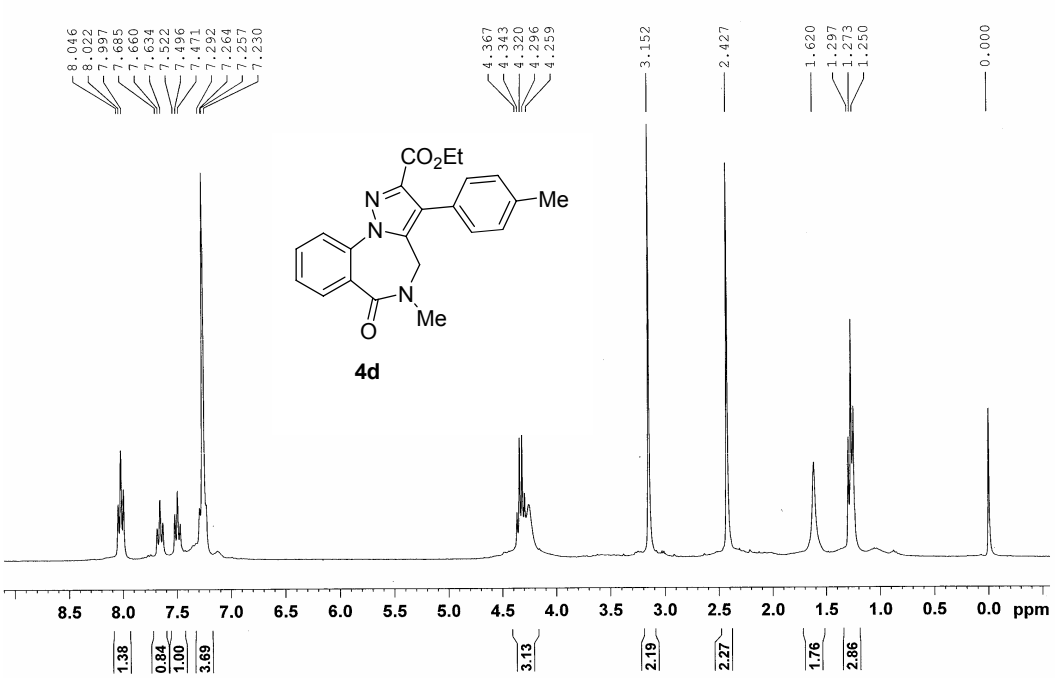
^{1}H NMR (300 MHz, $CDCl_3$) of **4c**



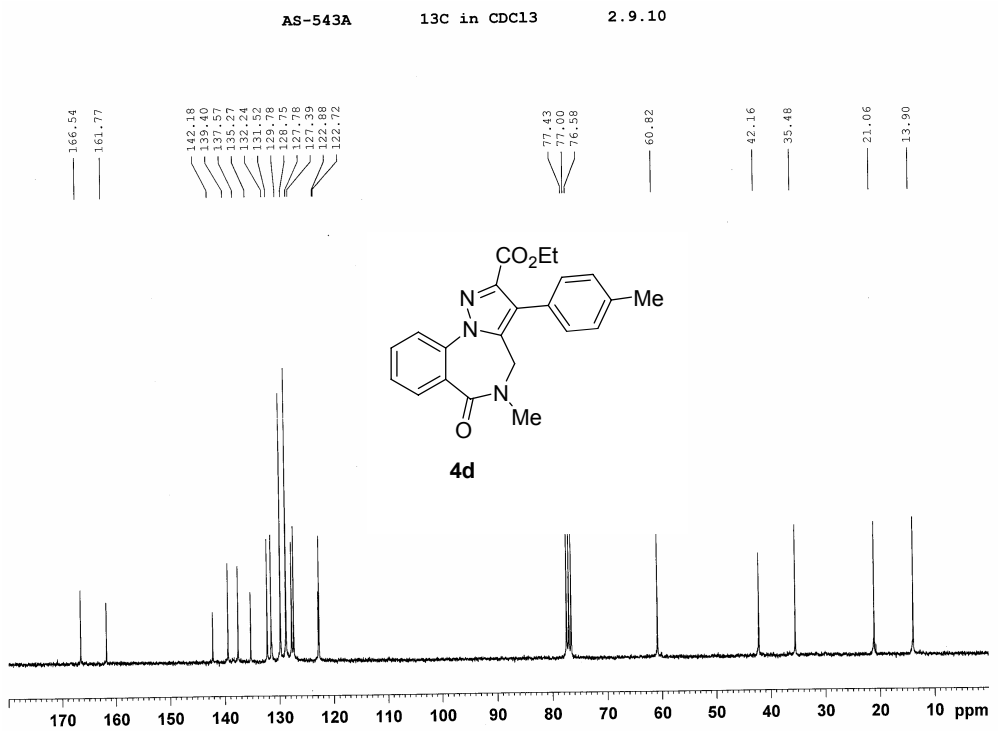
^{13}C NMR (75 MHz, $CDCl_3$) of **4c**



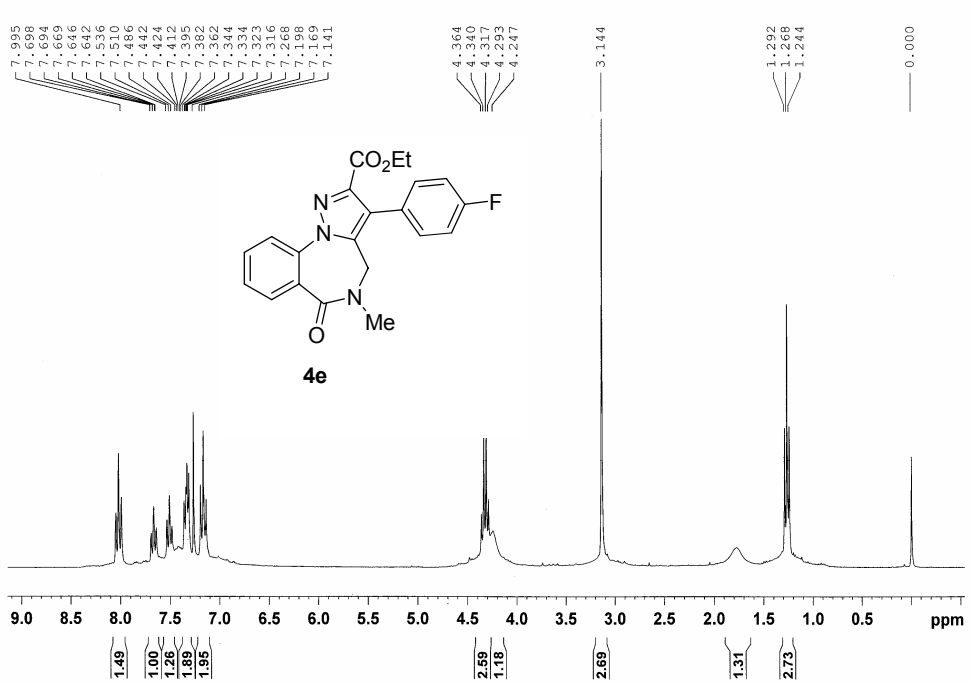
^{1}H NMR (300 MHz, $CDCl_3$) of **4d**



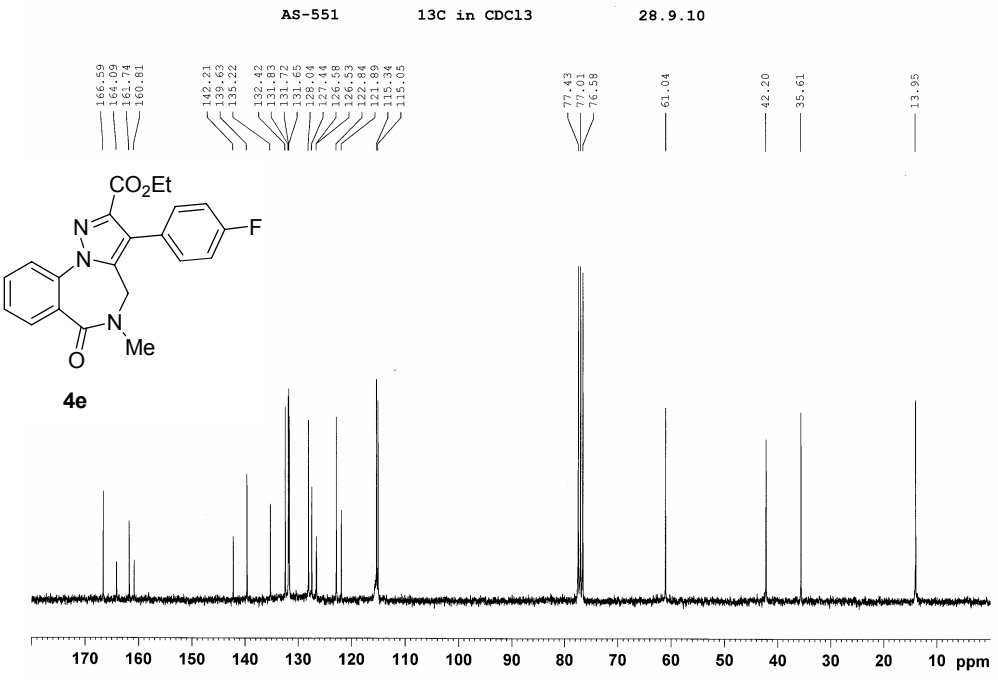
^{13}C NMR (75 MHz, $CDCl_3$) of **4d**



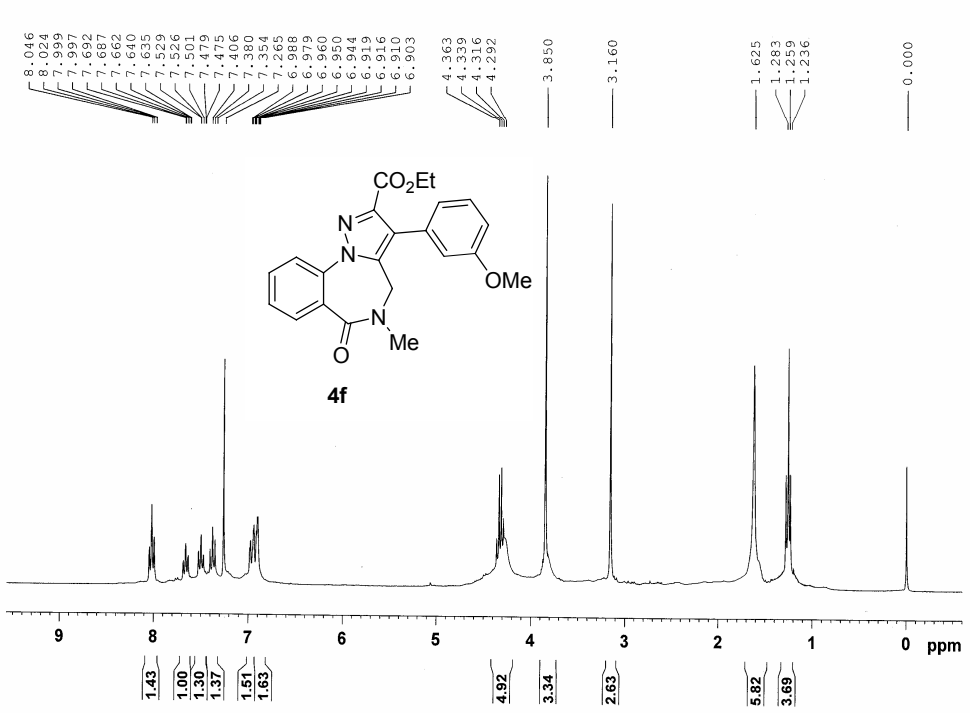
^{1}H NMR (300 MHz, $CDCl_3$) of **4e**



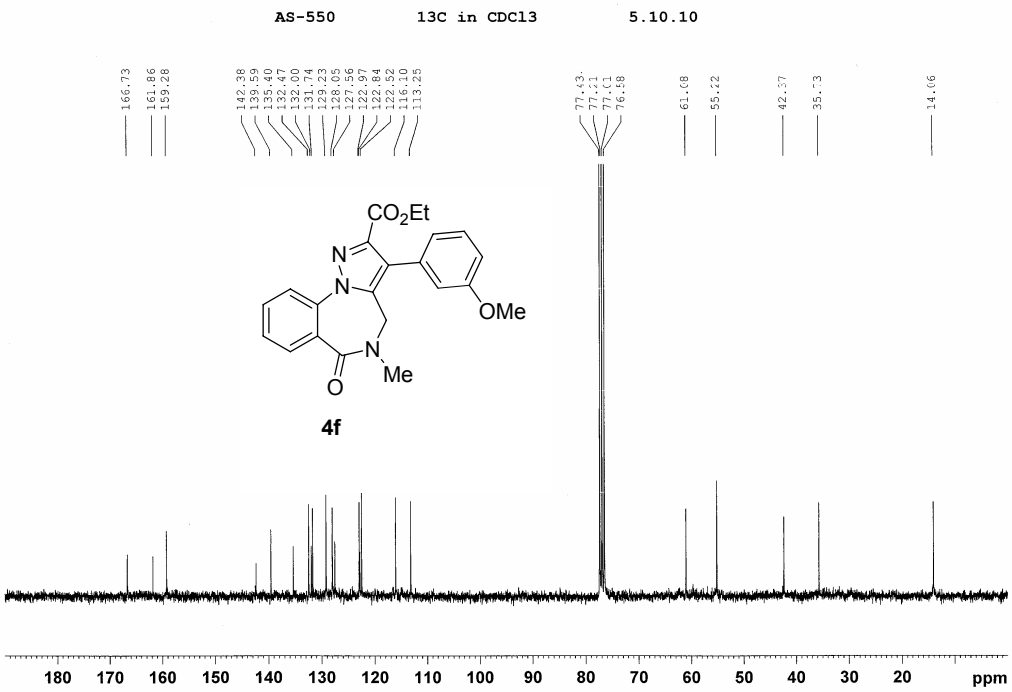
^{13}C NMR (75 MHz, $CDCl_3$) of **4e**



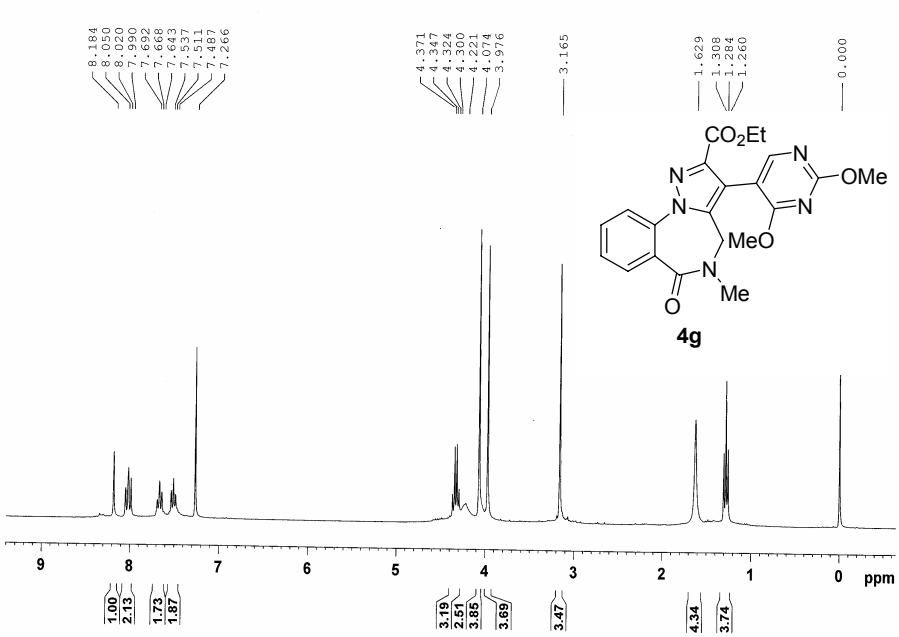
^{1}H NMR (300 MHz, $CDCl_3$) of **4f**



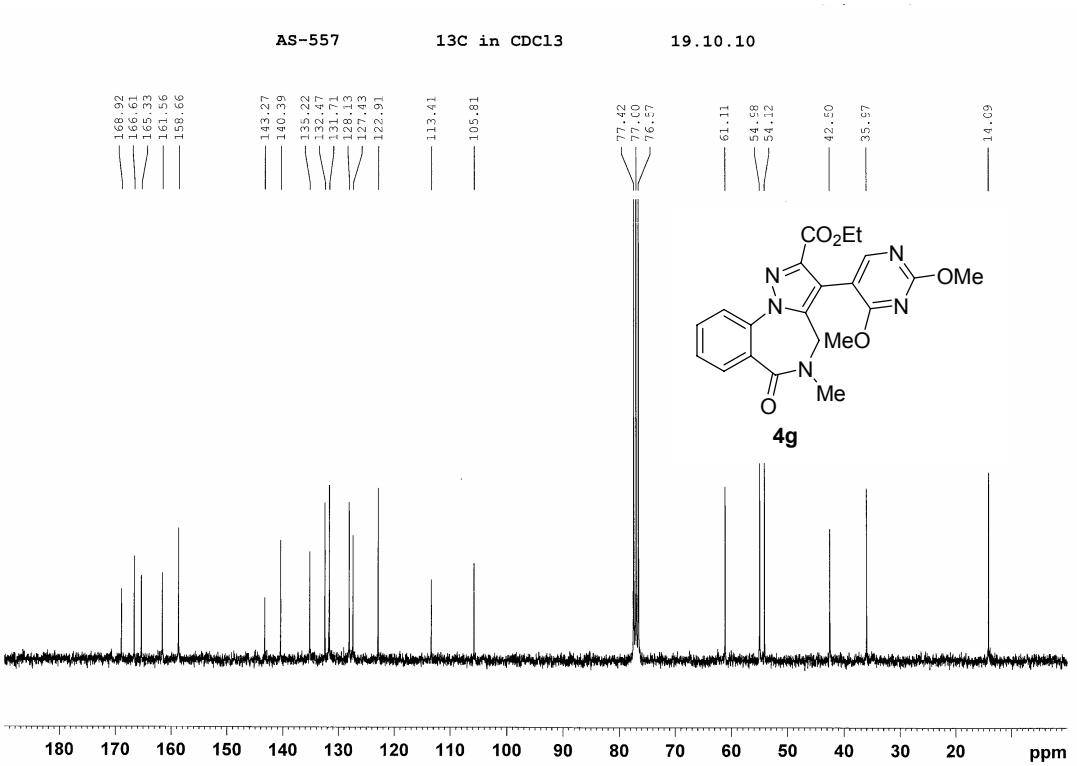
^{13}C NMR (75 MHz, $CDCl_3$) of **4f**



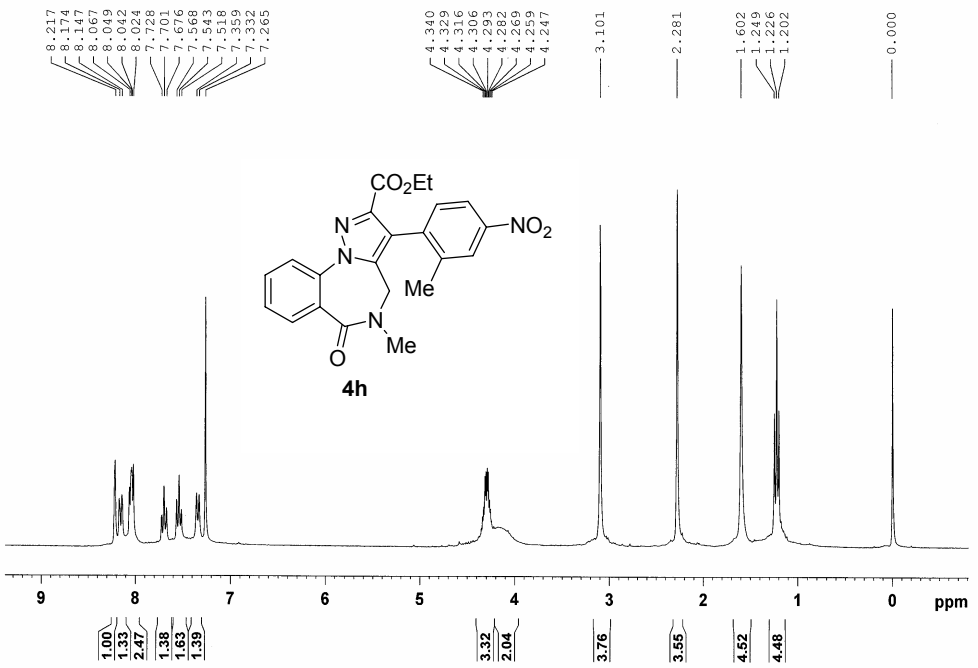
^{1}H NMR (300 MHz, $CDCl_3$) of **4g**



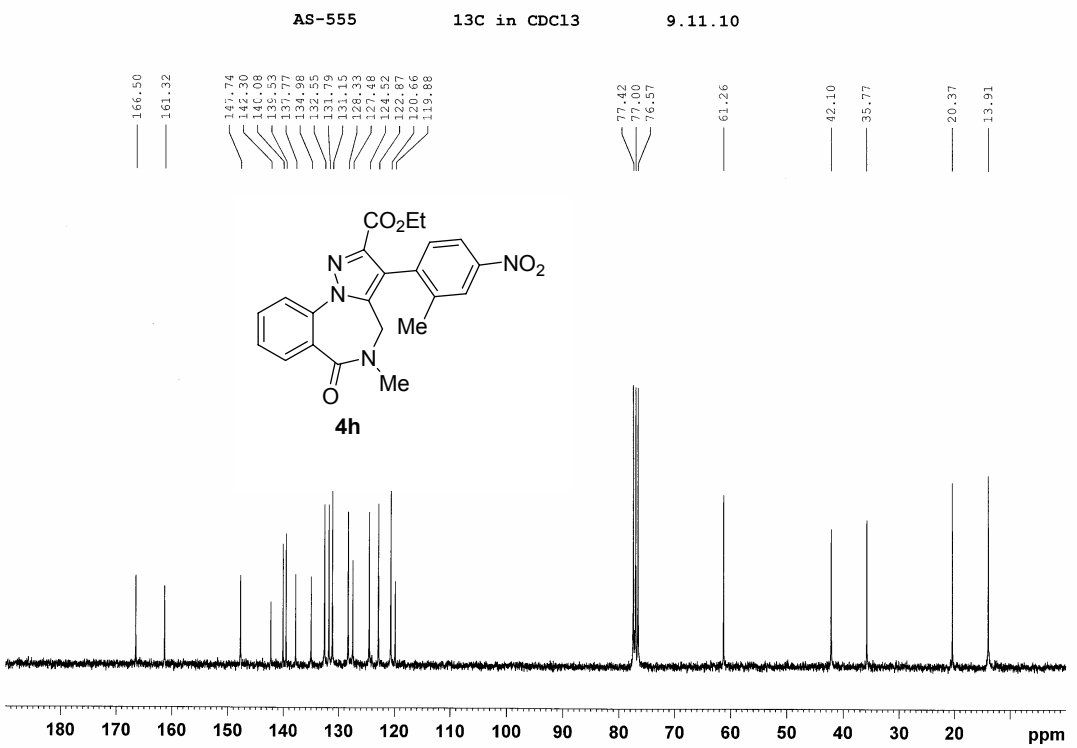
^{13}C NMR (75 MHz, $CDCl_3$) of **4g**



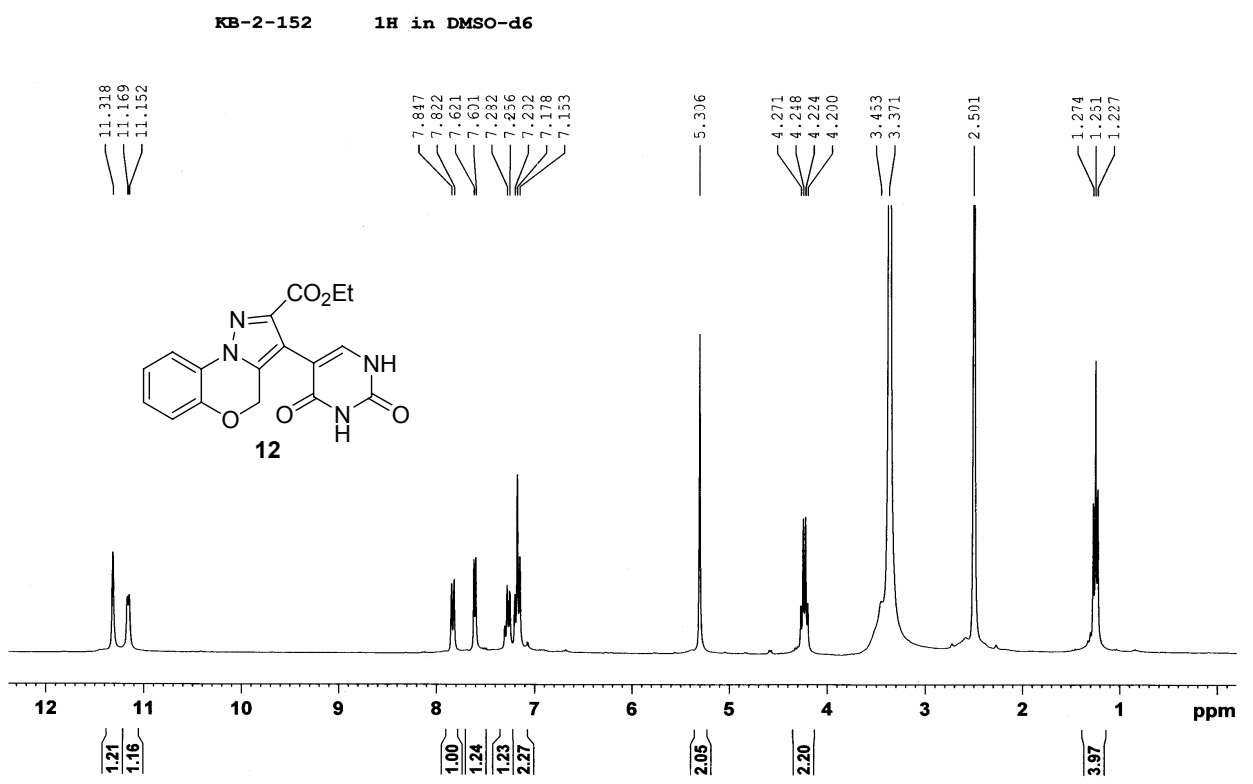
^{1}H NMR (300 MHz, $CDCl_3$) of **4h**



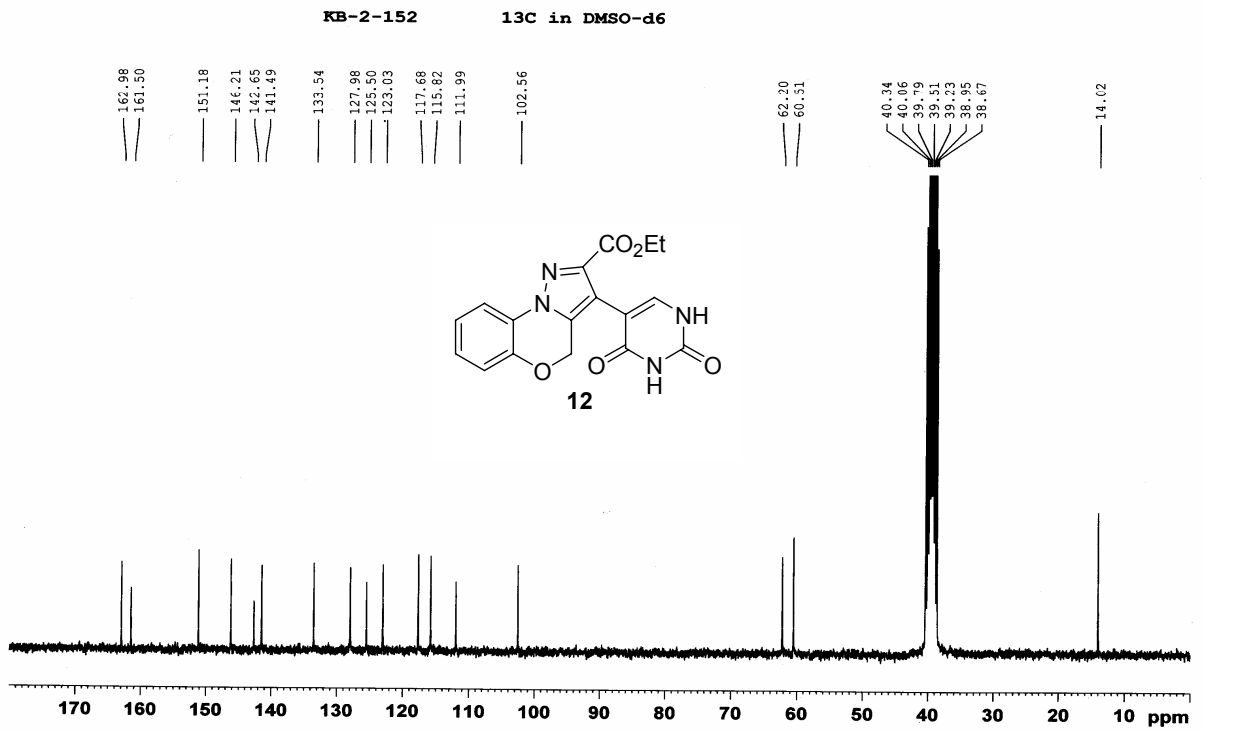
^{13}C NMR (75 MHz, $CDCl_3$) of **4h**



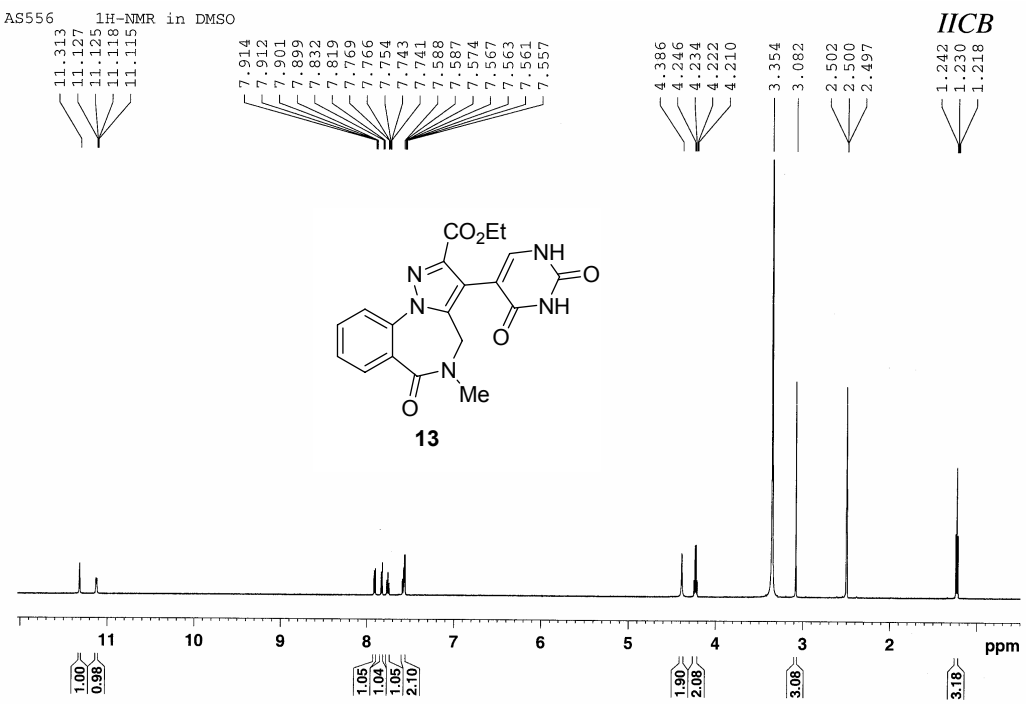
^{1}H NMR (300 MHz) SPECTRUM of 12:



^{13}C NMR (75 MHz) SPECTRUM of 12:



^{1}H NMR (600 MHz, DMSO-d_6) of **13**



^{13}C NMR (150 MHz, DMSO-d_6) of **13**