A Novel and Convenient Protocol for Synthesis of Pyridazines: toward Analogues of GABA-A Receptor Antagonists

Orazio A. Attanasi, Gianfranco Favi,* Paolino Filippone, Francesca R. Perrulli, and Stefania Santeusanio

Istituto di Chimica Organica, Università degli Studi di Urbino "Carlo Bo", Via I Maggetti 24, 61029 Urbino, Italy

E-mail: gianfranco.favi@uniurb.it

Università degli Studi di Urbino

SUPPORTING INFORMATION

Table of Contents

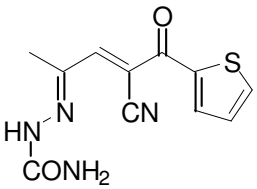
1. General Remarks.

All reactions requiring anhydrous conditions were carried out using oven-dried glassware. All the commercially available reagents and solvents were used without further purification. 1,2-Diaza-1,3-butadienes **1a**,**b** were synthesized as a mixture of *E/Z* isomers as previously reported[1],[2].

Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Proton and carbon spectra were referenced internally to solvent signals, using values of δ = 2.49 ppm for proton (middle peak) and δ = 39.50 ppm for carbon (middle peak) in DMSO-d_6 and δ = 7.26 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet q = quartet, m = multiplet and br = broad signal. All coupling constants (*J*) are given in Hz. FT-IR spectra were obtained as Nujol mulls. Mass spectra were recorded in the EI mode (70eV). Melting points were determined in open capillary tubes and are uncorrected.

2. Experimental procedures and spectral data.

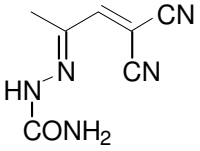
General Procedure for the Synthesis of 3a–f and 4a–d, f, g, k, l: To a solution of **2a–n** (1 mmol) and DIPEA (1.1 mmol) in $CHCl_3$ (5 mL) 4-chloro-1,2-diaza-1,3-butadiene **1a,b** was added and the reaction mixture was allowed to stand at room temperature for the appropriate time (checked by TLC, 1-24 h). Pure derivatives **3a–f** were obtained by spontaneous crystallization from the reaction medium or by flash chromatography of the crude on silica gel column, eluting with cyclohexane-ethyl acetate mixtures.



3a

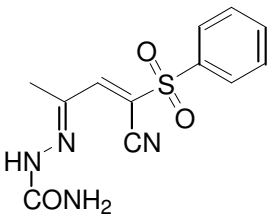
2-[3-Cyano-1-methyl-4-oxo-4-(2-thienyl)-2-butenylidene]-1-hydrazinecarboxamide (3a): Yellow powder from $CHCl_3$; mp 147-9 °C. ^1H NMR (DMSO-d_6): δ = 2.18 (s, 3H, CH_3), 6.70 and 6.92 (2 br, 2H, NH_2), 7.30 (t, *J* = 4.4 Hz, 1H, Het), 7.75 (s, 1H, CH), 8.05 (d, *J* = 4.0 Hz, 1H, Het), 8.16 (d, *J* = 4.8 Hz, 1H, Het), 10.38 (s, 1H, NH.). ^{13}C NMR (DMSO-d_6): δ = 14.8 (q), 107.4 (s), 117.1 (s), 128.2 (d), 134.3 (d), 135.6 (d), 138.9 (s), 140.8 (s), 153.9 (d), 156.0 (s), 178.6 (s). IR: ν_{max}= 3442, 3200, 3103, 2207, 1701, 1587, 1408, 1248, 834 cm^{-1}. MS: m/z (%) =

262 [M^+] (1), 219 (67), 190 (27), 176 (17), 163 (14), 149 (11), 135 (12), 125 (17), 111 (100). Anal calcd for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.49; H, 3.97; N, 21.15.



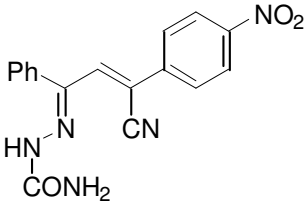
3b

2-[3,3-Dicyano-1-phenyl-2-propenylidene]-1-hydrazinecarboxamide (3b): Light yellow powder from $CHCl_3$; mp 148-50 °C. ^{1}H NMR (DMSO-d_6): δ = 2.08 (s, 3H, CH_3), 6.48 and 7.10 (2 br, 2H, NH_2) 7.86 (s, 1H, CH), 10.60 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 14.9 (q), 79.4 (q), 114.3 (s), 114.4 (s), 139.0 (s), 155.9 (s), 159.8 (d). IR: ν_{max}= 3451, 3214, 3152, 2361, 2227, 1727, 1581, 1526, 1414, 1201 cm^{-1}. MS: m/z (%) = 177 [M^+] (7), 134 (46), 105 (27), 79 (29), 66 (47), 44 (100). Anal calcd for $C_7H_7N_5O$: C, 47.46; H, 3.98; N, 39.53. Found: C, 47.29; H, 3.85; N, 39.71.



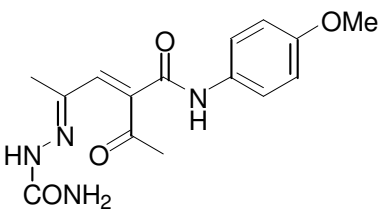
3c

2-[3-Cyano-1-methyl-3-(phenysulfonyl)-2-propenylidene]-1-hydrazinecarboxamide (3c): White powder from ethyl acetate/cyclohexane; mp 156-9 °C (dec). ^{1}H NMR (DMSO-d_6): δ = 2.12 (s, 3H, CH_3), 6.70 and 6.99 (2 br, 2H, NH_2), 7.76 (t, *J* = 7.6 Hz, 2H, Ar), 7.84 (t, *J* = 7.6 Hz, 1H, Ar), 7.94-7.98 (m, 3H, CH and Ar), 10.53 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 14.4 (q), 111.8 (s), 113.9 (s), 128.0 (d), 130.1 (d), 135.0 (d), 137.7 (s), 138.6 (s), 153.0 (d), 155.9 (s). IR: ν_{max}= 3480, 3365, 3200, 3091, 3055, 2213, 1700, 1585, 1529, 1428, 1331, 1154, 1085, 703 cm^{-1}. MS: m/z (%) = 292 [M^+] (0.4), 249 (100), 205 (25), 184 (57). Anal calcd for $C_{12}H_{12}N_4O_3S$: C, 49.31; H, 4.14; N, 19.17. Found: C, 49.53; H, 4.32; N, 19.01.



3d

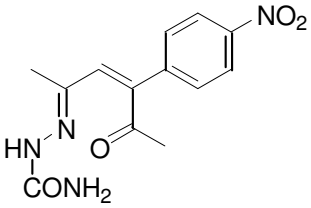
2-[3-Cyano-3-(4-nitrophenyl)-1-phenyl-2-propenylidene]-1-hydrazinecarboxamide (3d): Yellow powder from $CHCl_3$; mp 271-3 °C. ^{1}H NMR (DMSO-d_6): δ = 6.82 (br, 2H, NH_2), 7.39-7.42 (m, 2H, Ar), 7.53-7.58 (m, 3H, Ar), 7.81 (s, 1H, CH), 7.94 (d, *J* = 9.2 Hz, 2H, Ar), 8.30 (d, *J* = 9.2 Hz, 2H, Ar), 9.21 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 109.3 (s), 116.1 (s), 124.3 (d), 127.1 (d), 128.5 (d), 129.5 (d), 130.2 (d), 130.6 (s), 140.1 (s), 143.1 (s), 144.2 (d), 147.4 (s), 155.2 (s). IR: ν_{max}= 3416, 3340, 3292, 3154, 2210, 1709, 1602, 1518, 1344, 1168, 1084, 854, 701 cm^{-1}. MS: m/z (%) = 335 [M^+] (4), (292 (100), 275 (20), 245 (42), 189 (19), 162 (35). Anal calcd for $C_{17}H_{13}N_5O_3$: C, 60.89; H, 3.91; N, 20.89. Found: C, 60.71; H, 3.79; N, 21.01.



3e

2-{-3[(4-Methoxyanilino)carbonyl]-1-methyl-4-oxo-2-pentylidene}-1-hydrazinecarboxamide (3e): White powder from hot ethanol/ethyl acetate; mp 167 °C (dec.). ^{1}H NMR (DMSO-d_6): δ = 1.94 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.54 (br, 2H), 6.89 (d, *J* = 9.2 Hz, 2H, Ar), 7.15 (s, 1H, CH), 7.52 (d, *J* = 9.2 Hz, 2H, Ar), 9.86 (s, 1H, NH) 10.19 (s, 1H, NH). ^{13}C NMR

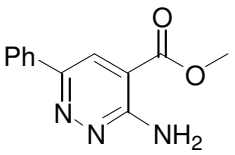
(DMSO-d_6): δ = 13.8 (q), 26.3 (q), 55.1 (q), 113.9 (d), 120.7 (d), 131.9 (s), 137.3 (s), 139.3 (d), 141.1 (s), 155.5 (s), 156.4 (s), 164.8 (s), 195.9 (s). IR: ν_{max} = 3256, 3130, 1726, 1676, 1513, 1239, 1146, 837 cm^{-1}. MS: m/z (%) = 318 [M^+] (0.4), 257 (100), 122 (83). Anal calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.46; H, 5.85; N, 17.83.



3f

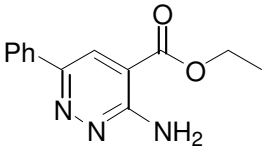
2-[1-Methyl-3-(4-nitrophenyl)-4-oxo-2-pentenylidene]-1-hydrazinecarboxamide (3f) Yellow powder from $CHCl_3$; mp 208-9 °C (dec.). ^{1}H NMR (DMSO-d_6): δ = 1.43 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.34 (br, 2H, NH_2), 7.41 (m, 3H, CH and Ar), 8.22 (d, J = 7.2 Hz, 2H, Ar), 9.70 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 9.3 (q), 20.7 (q), 116.7 (d), 125.0 (d), 132.6 (s), 135.2 (d), 135.7 (s), 138.1 (s), 140.6 (s), 150.1 (s), 191.6 (s). IR: ν_{max}= 3460, 3326, 3255, 3185, 1692, 1654, 1512, 1345, 1236, 1161, 849, 703 cm^{-1}. MS: m/z (%) = 290 [M^+] (0.4), 272 (4), 229 (100). Anal calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.96; H, 4.67; N, 19.14.

General Procedure for the Synthesis of 4e, h–j, m, n: Derivative **3a–f** (0.5 mmol) was solved or suspended in methanol (5 mL) in the presence of NaOMe (0.5 mmol) and the reaction mixture was refluxed for the appropriate time (checked by TLC, 1-6 h). Pure derivatives **4e, h–j, m, n** were isolated by spontaneous crystallization from the reaction medium or by treatment of the crude with appropriate solvents.



4a

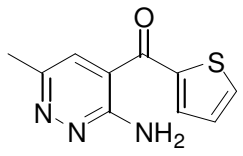
Methyl 3-amino-6-phenyl-4-pyridazinecarboxylate (4a): Yellow powder from ethyl acetate/cyclohexane; mp 156-7 °C. ^{1}H NMR (DMSO-d_6): δ = 3.91 (s, 3H, CH_3), 7.38-7.52 (m. 5H, Ar and NH_2), 8.00 (d, J = 8.4 Hz, 2H, Ar), 8.17 (s, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 52.8 (q), 109.9 (s), 124.7 (d), 125.4 (d), 128.6 (d), 128.9 (d), 136.1 (s), 150.2 (s), 157.5 (s), 166.1 (s). IR: ν_{max}= 3421, 3260, 1713, 1624, 1242, 1160, 1100, 773, 702 cm^{-1}. MS: m/z (%) = 229 [M^+] (100), 168 (27), 141 (34), 115 (33). Anal calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.64; H, 4.63; N, 18.47.



4b

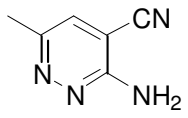
Ethyl 3-amino-6-phenyl-4-pyridazinecarboxylate (4b): Yellow powder from ethyl acetate/cyclohexane; mp 138-9 °C. ^{1}H NMR (DMSO-d_6): δ = 1.36 (t, J = 7.2 Hz, 3H, CH_3), 4.37 (q, J = 7.2 Hz, 2H, CH_2), 7.39-7.52 (m. 5H, Ar and NH_2), 8.00 (d, J = 8.4 Hz, 2H, Ar), 8.16 (s, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 13.9 (q), 61.7 (t), 110.0 (s), 124.6 (d), 125.4 (d), 128.6 (d),

128.9 (d), 136.1 (s), 150.2 (s), 157.6 (s), 165.6 (s). IR: ν_{max}= 3437, 3264, 1712, 1625, 1242, 1169, 1101, 783, 698 cm^{-1}. MS: m/z (%) = 243 [M^+] (25), 97 (100). Anal calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.37; H, 5.21; N, 17.08.



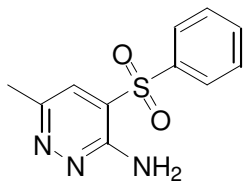
4c

(3-Amino-6-methyl-4-pyridazinyl)(2-thienyl)methanone (4c) Yellow powder from methanol/water; mp 170-3 °C. ^{1}H NMR (DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 6.65 (s, 2H, NH_2), 7.30 (dd, *J* = 4.4 Hz, *J* = 3.6 Hz, 1H, Het), 7.49 (s, 1H, CH), 7.78 (d, *J* = 3.6 Hz, 1H, Het), 8.19 (d, *J* = 4.4 Hz, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 20.6 (q), 118.3 (s), 127.1 (d), 129.0 (d), 136.4 (d), 136.9 (d), 142.4 (s), 150.0 (s), 155.5 (s), 186.7 (s). IR: ν_{max}= 3440, 3263, 3110, 3039, 1723, 1626, 1577, 1414, 1287, 1155, 807, 772 cm^{-1}. MS: m/z (%) = 219 [M^+] (72), 190 (30), 176 (19), 163 (15), 149 (16), 135 (12), 111 (100). Anal calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.97; H, 4.11; N, 19.03.



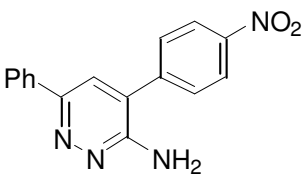
4d

3-Amino-6-methyl-4-pyridazinecarbonitrile (4d): Yellow powder from methanol/water; mp 141-3 °C. ^{1}H NMR (DMSO-d_6): δ = 2.44 (s, 3H, CH_3), 7.06 (s. 2H, NH_2), 7.70 (s, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 20.7 (q), 96.1 (s), 114.8 (s), 130.8 (d), 149.4 (s), 156.8 (s). IR: ν_{max}= 3382, 3312, 3153, 2234, 1645, 1535, 1140, 988, 957 cm^{-1}. MS: m/z (%) = 134 [M^+] (23), 111 (30), 97 (45), 69 (60), 57 (100). Anal calcd for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.58; H, 4.39; N, 41.87.



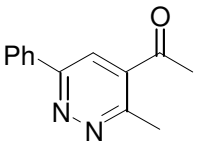
4e

6-Methyl-4-(phenylsulfonyl)-3-pyridazinamine (4e): Beige powder from methanol/water; mp 143-4 °C.^{1}H NMR (DMSO-d_6): δ = 2.53 (s, 3H, CH_3), 6.88 (s, 2H, NH_2), 7.66 (t, *J* = 8.0 Hz, 2H, Ar), 7.77 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H, Ar), 7.81 (s, 1H, Het), 8.08 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 2H, Ar). ^{13}C NMR (DMSO-d_6): δ = 20.5 (s), 122.3 (s), 126.4 (d), 127.8 (d), 129.7 (d), 134.7 (d), 138.6 (s), 151.4 (s), 153.2 (s). IR: ν_{max}= 3460, 3276, 3114, 1625, 1533, 1311, 1140, 1095, 765, 610 cm^{-1}. MS: m/z (%) = 249 [M^+] (11), 165 (18), 149 (24), 137 (31), 125 (59), 111 (100). Anal calcd for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86. Found: C, 52.93; H, 4.59; N, 16.73.



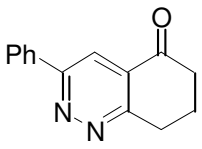
4f

4-(4-Nitrophenyl)-6-phenyl-3-pyridazinamine (4f): Yellow powder from methanol; mp 283-5 °C. ^{1}H NMR (DMSO-d_6): δ = 6.48 (s, 2H, NH_2, D_2O exch.), 7.38-7.50 (m, 3H, Ar), 7.82 (s, 1H, Het), 7.91 (dd, *J* = 8.4 Hz, 2H, Ar), 8.06 (d, *J* = 8.4 Hz, 2H, Ar), 8.36 (d, *J* = 8.4 Hz, 2H, Ar). ^{13}C NMR (DMSO-d_6): δ = 123.7 (s), 124.0 (d), 124.7 (d), 125.6 (d), 128.4 (d), 128.7 (d), 130.2 (d), 136.7 (s), 142.3 (s), 147.4 (s), 150.8 (s), 157.0 (s). IR: ν_{max}= 3483, 3282, 1634, 1592, 1514, 1347, 1182, 849, 699 cm^{-1}. MS: m/z (%) = 292 [M^+] (100), 245 (26), 195 (27), 162 (53). Anal calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.58; H, 4.02; N, 19.23.



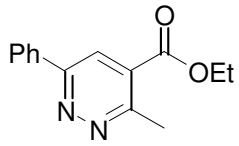
4g

1-(3-Methyl-6-phenyl-4-pyridazinyl)-1-ethanone (4g): Beige powder from diethyl ether/light petroleum ether; mp 88-9 °C. ^{1}H NMR ($CDCl_3$): δ = 2.65 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.45-7.51 (m, 3H, Ar), 7.87 (s, 1H, Het), 8.00-8.06 (m, 2H, Ar). ^{13}C NMR (DMSO-d_6): δ = 20.9 (q), 29.7(q), 122.3 (d), 126.9 (d), 129.0 (d), 130.2 (d), 135.1 (s), 135.6 (s), 154.6 (s), 157.9 (s), 201.2 (s). IR: ν_{max}= 1703, 1403, 1368, 1244, 1225, 782, 695 cm^{-1}. MS: m/z (%) = 212 [M$^+$] (100), 184 (15), 141 (65), 115 (57). Anal calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.70; H, 5.58; N, 13.07.



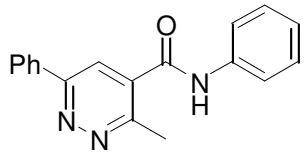
4h

3-Pheny1-5,6,7,8-tetrahydro-5-cinnolinone (4h):Yellow powder from $CHCl_3$; mp 102-3 °C. ^{1}H NMR (DMSO-d_6): δ = 2.15-2.22 (m, 2H, CH_2), 2.74-2.80 (m, 2H, CH_2), 3.29-3.35 (m, 2H, CH_2), 7.53-7.58 (m, 3H, Ar), 8.16-8.20 (m, 2H, Ar), 8.27 (s, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 20.7 (t), 28.8 (t), 38.0 (t), 118.7 (d), 126.8 (d), 128.5 (s), 129.1 (d), 130.1 (d), 135.6 (s), 158.6 (s), 160.9 (s), 197.5 (s). IR: ν_{max}= 1698, 1402, 784, 703 cm^{-1}. MS: m/z (%) = 224 [M$^+$] (46), 97 (100), 167 (24), 139 (38), 111(64). Anal calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.12; H, 5.54; N, 12.65.



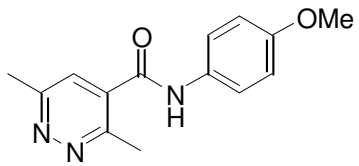
4i

Ethyl 3-methyl-6-phenyl-4-pyridazine carboxylate (4i): Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.44 (t, *J* = 7.2 Hz, 3H, CH_3), 3.02 (s, 3H, CH_3), 4.46 (q, *J* = 7.2 Hz, 2H, CH_2), 7.48-7.55 (m, 3H, Ar), 8.09-8.13 (m, 2H, Ar), 8.22 (s, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 14.7 (q), 22.4 (q), 62.8 (t), 124.3 (d), 127.4 (d), 129.3 (s), 129.6 (d), 130.7 (d), 136.1 (s), 157.5 (s), 158.9 (s), 165.7 (s). IR: ν_{max}= 1715, 1257, 1104, 1018, 774, 698 cm^{-1}. MS: m/z (%) = 242 [M$^+$] (100), 170 (27), 141 (62), 115 (65). Anal calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.58; H, 5.97; N, 11.36.



4j

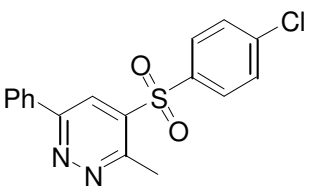
***N*4,6-Diphenyl-3-methyl-4-pyridazinecarboxamide (4j)**: White powder from ethyl acetate/ cyclohexane; mp 197-8 °C. ^{1}H NMR (DMSO-d_6): δ = 2.76 (s, 3H, CH_3), 7.16 (t, *J* = 7.8 Hz, 1H, Ar), 7.42 (t, *J* =8.0 Hz, 2H, Ar), 7.52-7.77 (m, 3H, Ar), 7.74 (d, *J* = 7.6 Hz, 2H, Ar), 8.23 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 2H, Ar), 8.35 (s, 1H, Het), 10.73 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 19.8 (q), 119.8 (d), 121.6 (d), 124.3 (d), 126.7 (d), 128.8 (d), 129.0 (d), 130.1 (d), 134.7 (s), 135.6 (s), 138.5 (s), 154.9 (s), 157.1 (s), 164.2 (s). IR: ν_{max}= 3254, 3193, 3137, 1682, 1600, 1553, 1324, 1264 cm^{-1}. MS: m/z (%) = 289 [M$^+$] (100), 260 (28), 141 (83), 115 (59). Anal calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.57; H, 5.34; N, 14.37.



4k

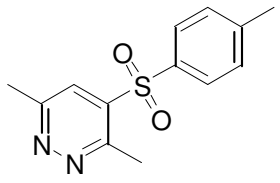
***N*(4-Methoxyphenyl)-3,6-dimethyl-4-pyridazinecarboxamide (4k):** White powder from methanol/water; mp 134-7 C°. ^{1}H NMR (DMSO-d_6): δ = 2.65 (s, 6H, 2CH_3), 3.74 (s, 3H, OCH_3), 6.94 (d, *J* = 9.2 Hz, 2H, Ar), 7.59-7.64 (m, 3H, Ar and Het), 10.51 (s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ = 19.6 (q), 21.2 (q), 55.2 (q), 113.9 (d), 121.3 (d), 124.1 (d), 131.5 (s), 134.2 (s), 153.7 (s), 155.9 (s), 158.1 (s), 163.9 (s). IR: ν_{max}= 3375, 3236, 3192, 1672, 1602, 1555, 1512, 1417, 1241, 1032, 818 cm^{-1}. MS: m/z (%) = 257 [M$^+$] (100), 214 (10), 135 (19). 122 (86). Anal calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.31; H, 5.67; N, 16.18.



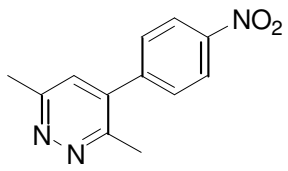
4l

4-[(4-Chlorophenyl)sulfonyl]-3-methyl-6-phenylpyridazine (4l): White powder from ethyl acetate/cyclohexane; mp 199-200 °C. ^{1}H NMR (DMSO-d_6): δ = 2.75 (s, 3H, CH_3), 7.59-7.63 (m, 3H, Ar), 7.77 (d, *J* = 8.4 Hz, 2H, Ar), 8.15 (d, *J* = 8.4 Hz, 2H, Ar), 8.23-8.25 (m, 2H, Ar), 8.61 (s, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 20.2 (q), 123.0 (d), 127.2 (d), 129.2 (d), 130.1 (d), 130.4 (d), 130.7 (d), 134,7 (s), 136.9 (s), 139.1 (s), 140.2 (s), 153.6 (s), 159.0 (s). IR: ν_{max}= 1398, 1330, 1159, 1091, 818, 760, 645 cm^{-1}. MS: m/z (%) = 344 [M$^+$] (50), 141 (100). Anal calcd for $C_{17}H_{13}N_2O_2SCl$: C, 59.21; H, 3.80; N, 8.12. Found: C, 59.02; H, 3.65; N, 7.97.



4m

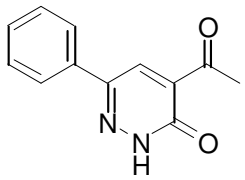
3,6-Dimethyl-4-[(4-methylphenyl)sulfonyl]pyridazine (4m): White powder from ethyl acetate/cyclohexane; mp 102-4 °C. ^{1}H NMR (DMSO-d_6): δ = 2.41 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 7.49 (d, *J* = 8.4 Hz, 2H, Ar), 7.86 (d, *J* = 8.4 Hz, 2H, Ar), 8.09 (s, 1H, Het). ^{13}C NMR (DMSO-d_6): δ = 20.0 (q), 21.1 (q), 21.4 (q), 125.4 (d), 128.2 (d), 130.4 (d), 135.2 (s), 138.9 (s), 145.8 (s), 152.5 (s), 160.6 (s). IR: ν_{max}= 1407, 1330, 1156, 822, 720, 662 cm^{-1}. MS: m/z (%) = 262 [M$^+$] (77), 139 (58), 125 (58), 111 (100). Anal calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.74; H, 5.56; N, 10.76.



4n

3,6-Dimethyl-4-(4-nitrophenyl)pyridazine (4n) Beige powder from methanol/water; mp 175-8 ° C. ^{1}H NMR (DMSO-d_6): δ = 2.55 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.51 (s, 1H, Het), 7.80 (d, *J* = 8.8 Hz, 2H, Ar), 8.35 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR (DMSO-d_6): δ = 20.4 (q), 21.2 (q), 123.7 (d), 126.5 (d), 130.3 (d), 137.3 (s), 143.2 (s), 147.5 (s), 154.5 (s), 158.1 (s). IR: ν_{max}= 1585, 1515, 1352, 1105, 853 cm^{-1}. MS: m/z (%) = 229 [M$^+$] (65), 111 (100). Anal calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.69; H, 4.76; N, 18.06.

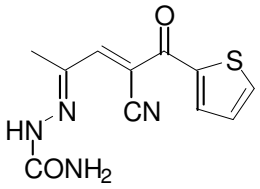
From the crude mixture of the reaction between **1a** and **2i** we also isolated pyridazinone **5a** in 11% yield.



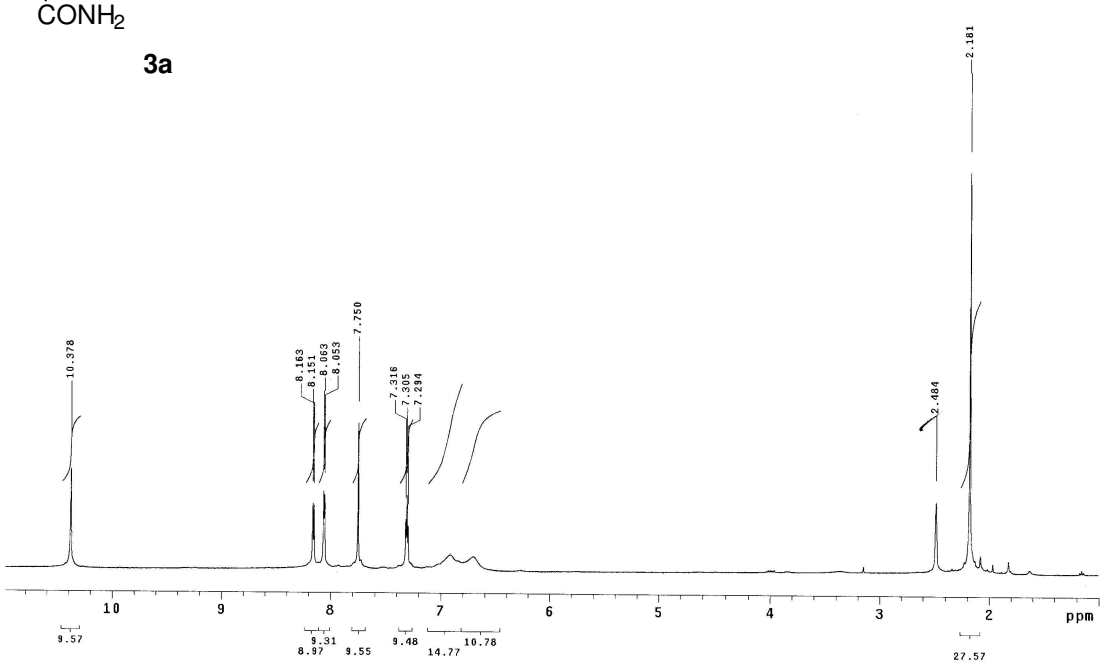
5a

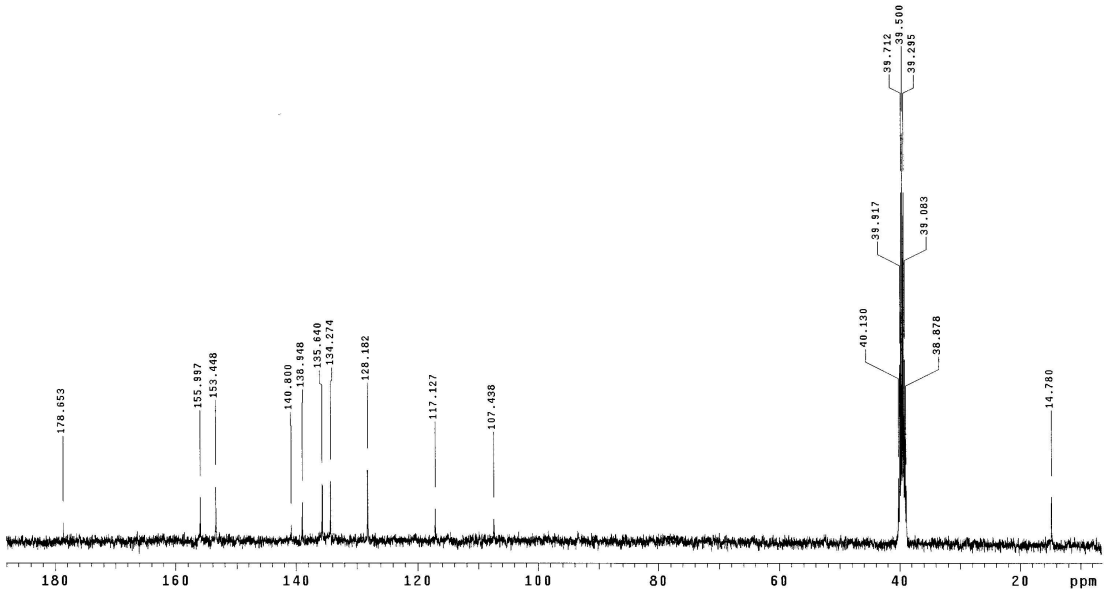
4-Acetyl-6-phenylpyridazin-3(2*H*)-one (5a):White powder from ethyl acetate/cyclohexane; mp 188-90 °C. ^{1}H NMR ($CDCl_3$): δ = 2.63 (s, 3H, CH_3), 7.45-7.53 (m, 3H, Ar), 7.88 (d, *J* = 8.4 Hz, 2H, Ar), 8.20 (s, 1H, Het), 13.79 (br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 30.5 (q), 125.7 (d), 129.0 (d), 129.4 (d), 130.2 (d), 134.2 (s), 136.1 (s), 134.1 (s), 158.7 (s), 197.1 (s). IR: ν_{max}= 3196, 3125, 1690, 1666, 1573, 1378, 1194, 889, 781, 765, 702 cm^{-1}. MS: m/z (%) = 214 [M^{+}] (100), 199 (18), 172 (29), 115 (56). Anal calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.34; H, 4.95; N, 12.96.

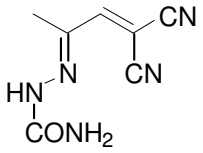
3. ^{1}H and ^{13}C NMR spectra of all products.



3a

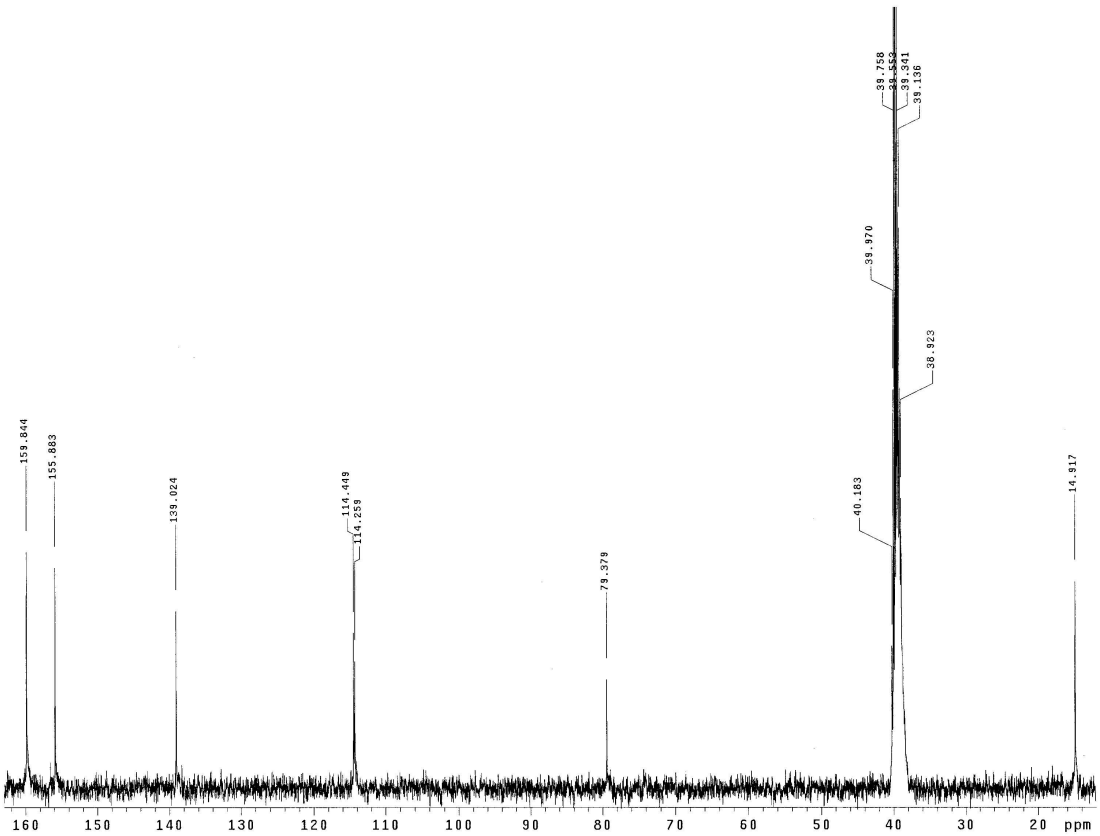


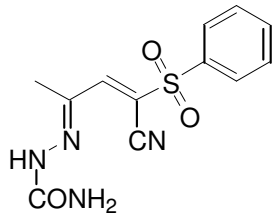



CN
N
CN
HN
CONH2

3b

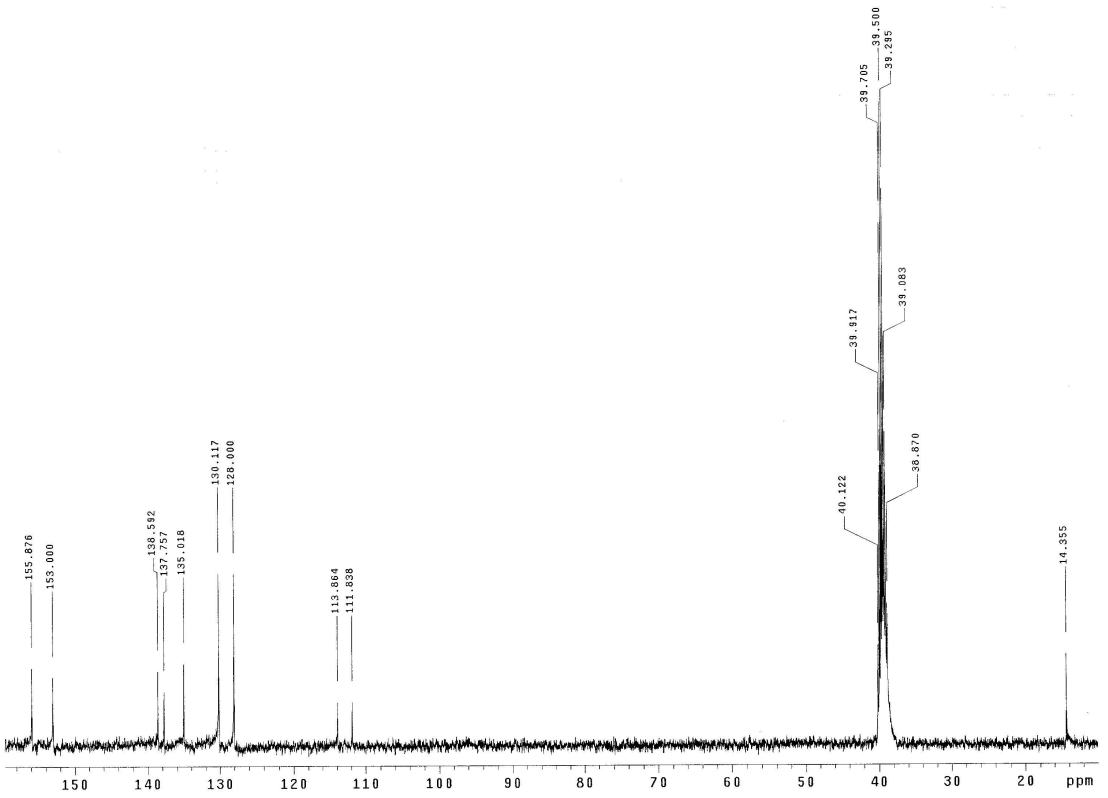
10.597
7.859
3.348
2.504
2.500
2.495
2.083
10
9
8
7
6
5
4
3
ppm
0.98
0.86
1.10
1.00
3.00

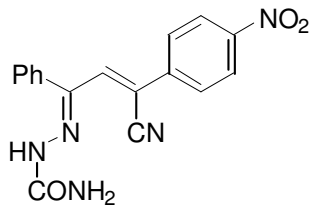

159.844
155.883
139.024
114.449
114.259
79.379
39.758
39.553
39.341
39.136
39.970
38.923
40.183
14.917
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
S
O
N
CN
HN
CONH2

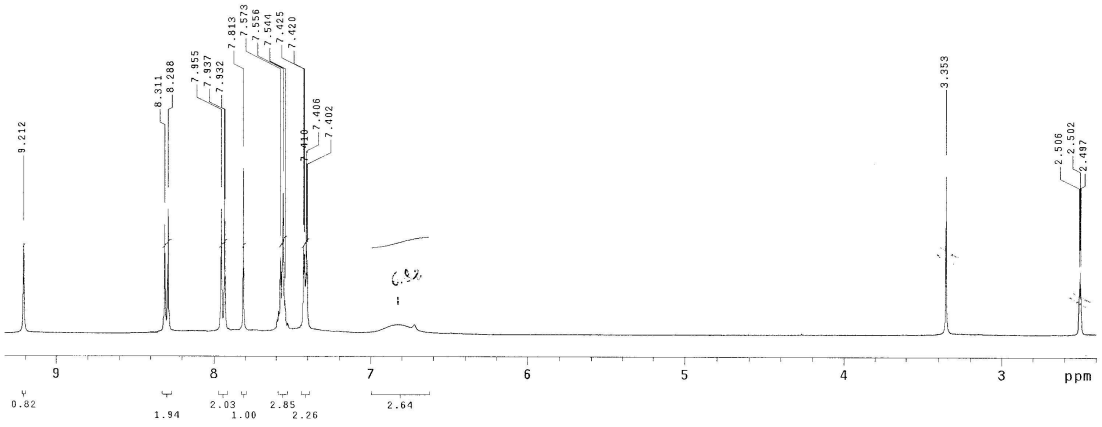
3c

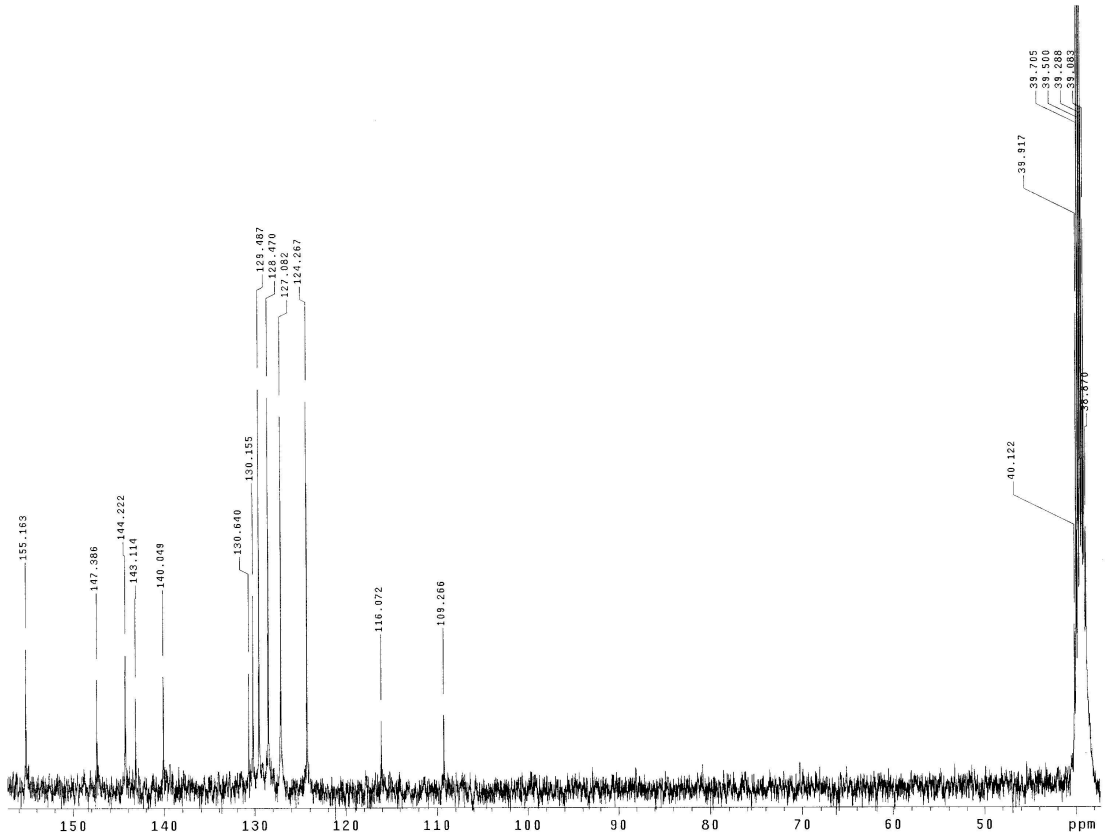
10.530
7.969
7.966
7.950
7.953
7.945
7.843
7.759
7.740
3.341
3.339
2.500
2.125
exch
exch
6.99
6.70
10
9
8
7
6
5
4
3
ppm
0.98
1.42
2.96 2.38
1.05
0.97
3.00

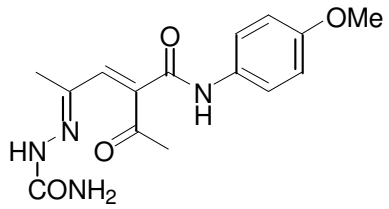

155.876
153.000
138.592
137.757
135.018
130.117
128.000
113.864
111.838
39.500
39.295
39.705
39.083
39.917
38.870
40.122
14.355
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


NO2
Ph
N
CN
HN
CONH2

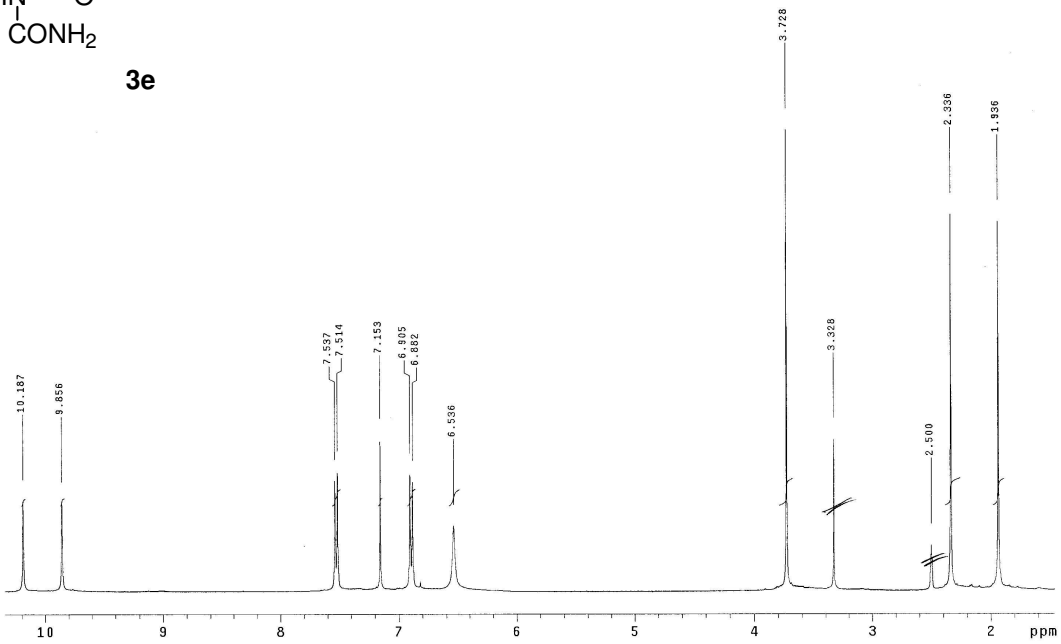
3d

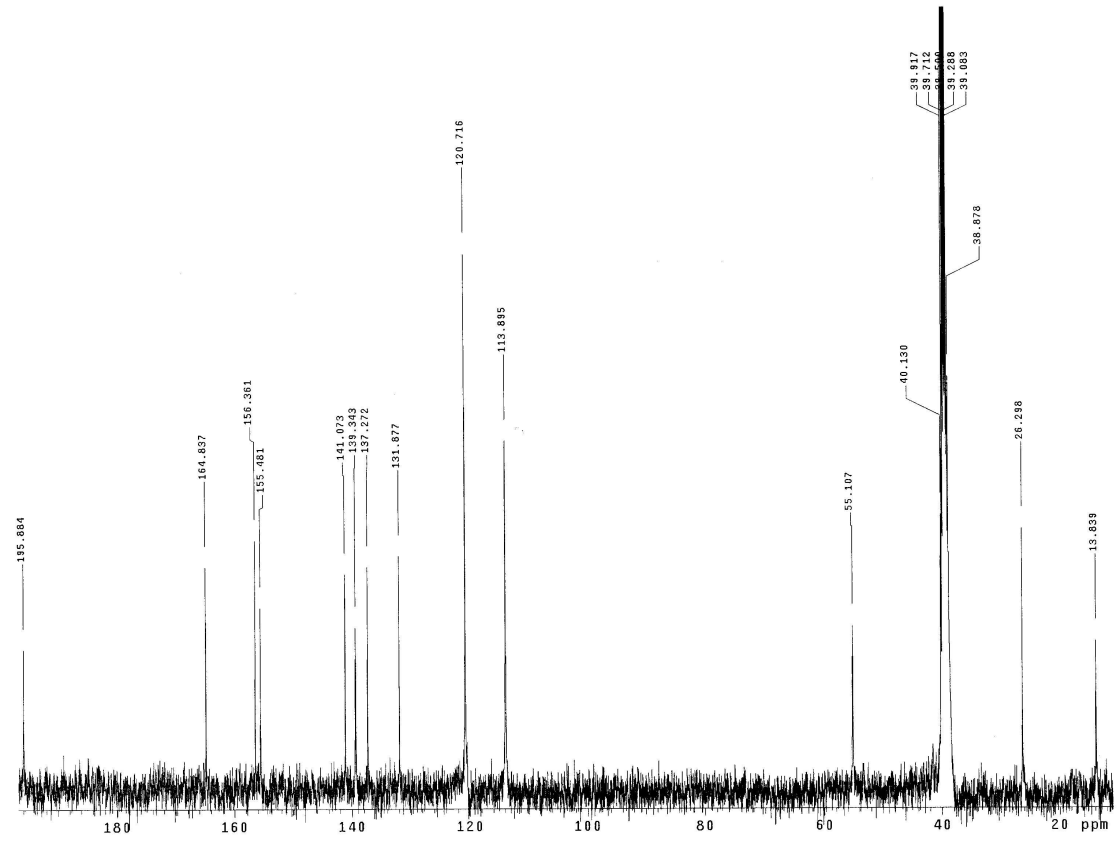

9.212
8.311
8.288
7.955
7.937
7.932
7.813
7.573
7.556
7.541
7.425
7.420
7.406
7.402
3.353
2.506
2.502
2.497
ppm

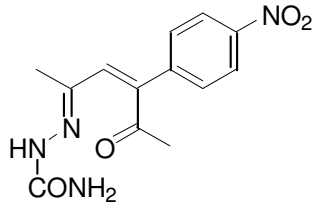

155.163
147.386
144.222
143.114
140.049
130.640
130.155
129.487
128.470
127.082
124.267
116.072
109.266
39.705
39.500
39.288
39.083
38.917
38.670
40.122
ppm


OMe
O
N
H
N
HN
O
CONH2

3e

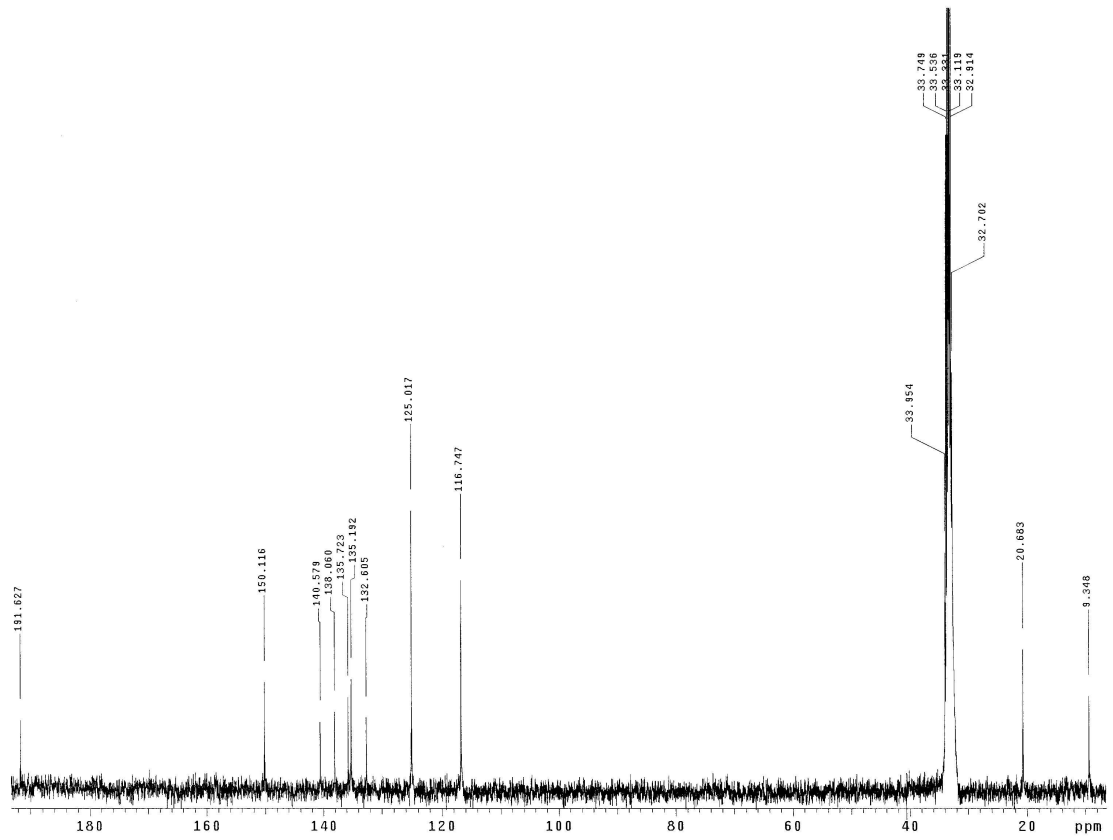

10.187
9.856
7.537
7.514
7.153
6.905
6.882
6.536
3.728
3.328
2.500
2.336
1.936
10
9
8
7
6
5
4
3
2
ppm

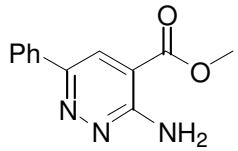

195.884
164.837
156.361
155.481
141.073
139.343
137.272
131.677
120.716
113.895
55.107
40.130
39.917
39.712
39.500
39.288
39.083
38.878
26.298
13.839
180
160
140
120
100
80
60
40
20
ppm


NO2
N
HN
O
CONH2

3f

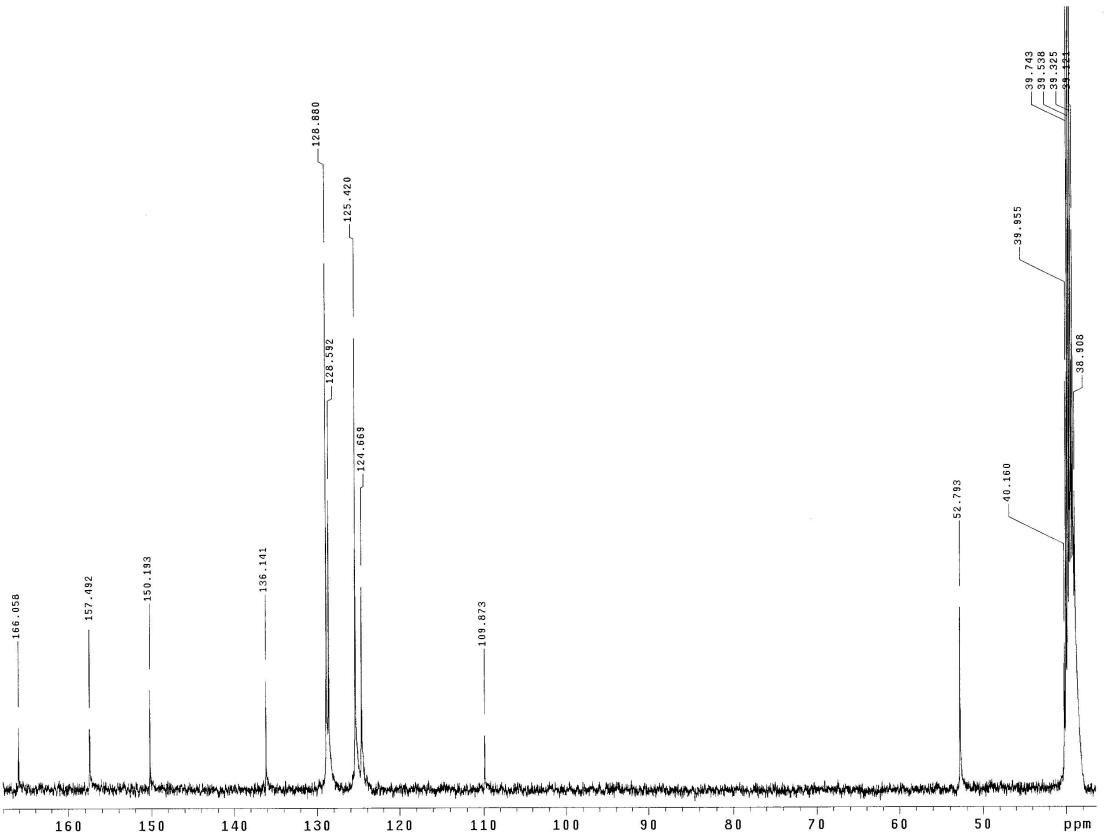
9.702
8.234
8.228
8.216
8.212
7.424
7.418
7.407
7.402
6.24
3.382
2.505
2.500
2.495
2.390
1.432
ppm
0.99
1.87
2.82
3.27
3.00
2.95

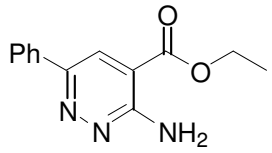

191.627
150.116
140.579
138.060
135.723
135.192
132.605
125.017
116.747
33.954
33.749
33.536
33.331
33.119
32.914
32.702
20.683
9.348
ppm


Ph
O
O
N
N
NH2

4a

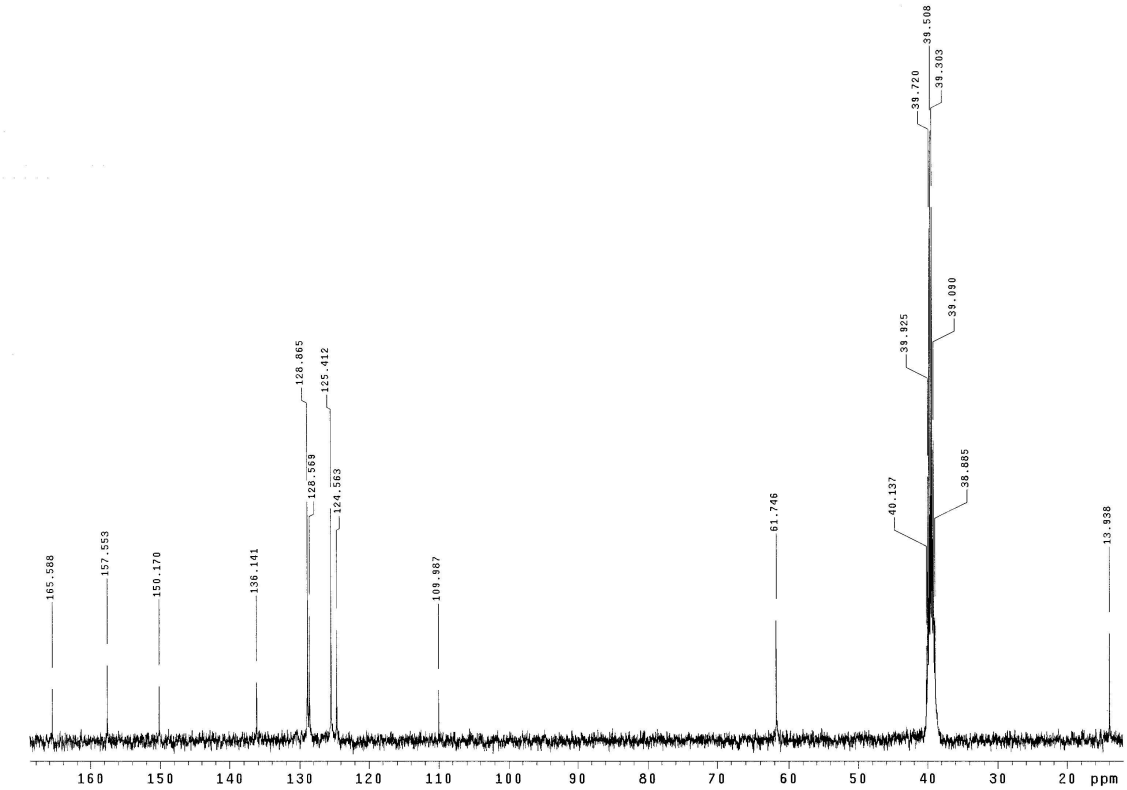
8.174
8.015
7.994
7.515
7.513
7.495
7.492
7.476
7.444
7.438
7.423
7.417
7.408
7.405
3.813
3.341
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.02
2.15
2.43
3.02
3.00

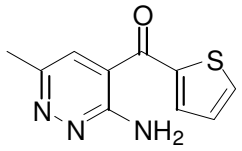

166.058
157.492
150.183
136.141
128.880
128.592
125.420
124.669
109.873
52.793
40.160
39.955
39.743
39.538
39.325
38.908
160
150
140
130
120
110
100
90
80
70
60
50
ppm


Ph
O
O
N
N
NH2

4b

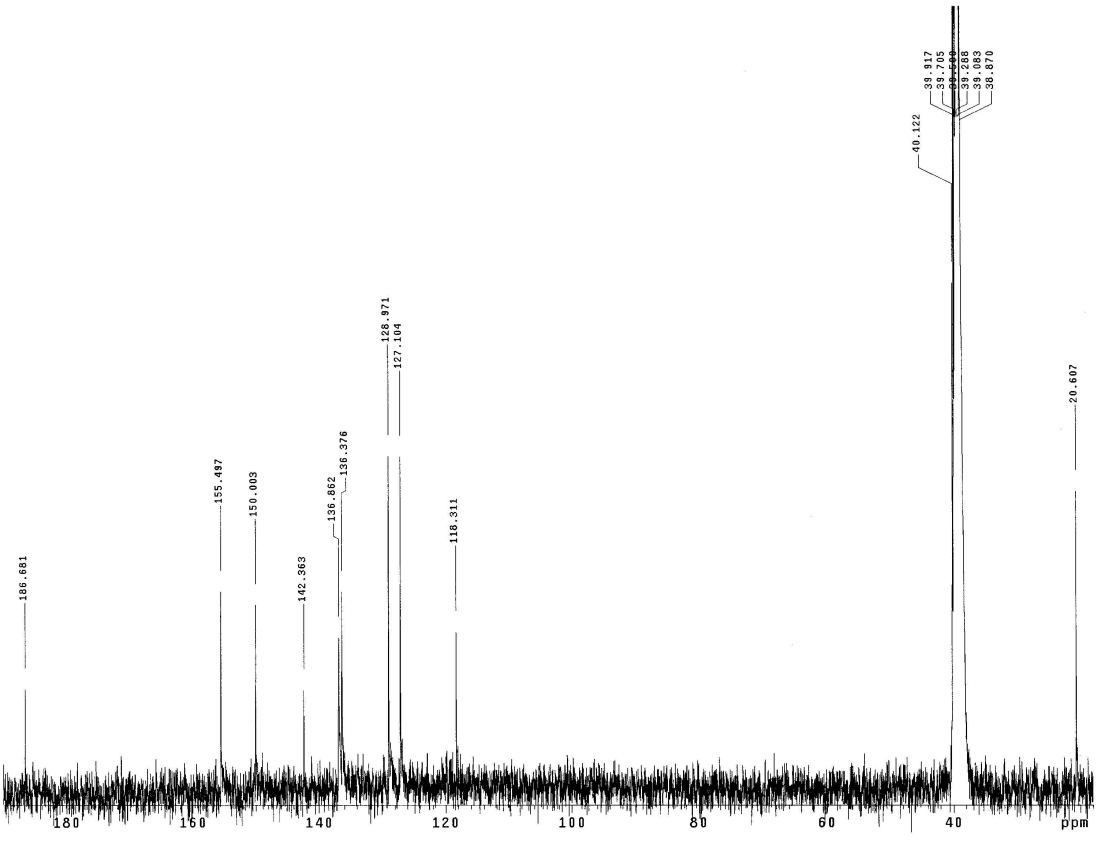
8.162
8.012
8.009
7.991
7.518
7.501
7.481
7.444
7.427
7.420
7.408
7.405
4.404
4.386
4.369
4.351
3.338
2.505
2.500
2.496
1.378
1.360
1.342
8
7
6
5
4
3
2
ppm
0.95
1.92
2.13
2.77
2.07
3.00

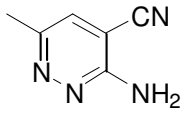

165.588
157.553
150.170
138.141
128.865
128.569
125.412
124.563
109.987
61.746
40.137
39.925
39.720
39.508
39.303
39.090
38.885
13.938
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
S
N
N
NH2

4c

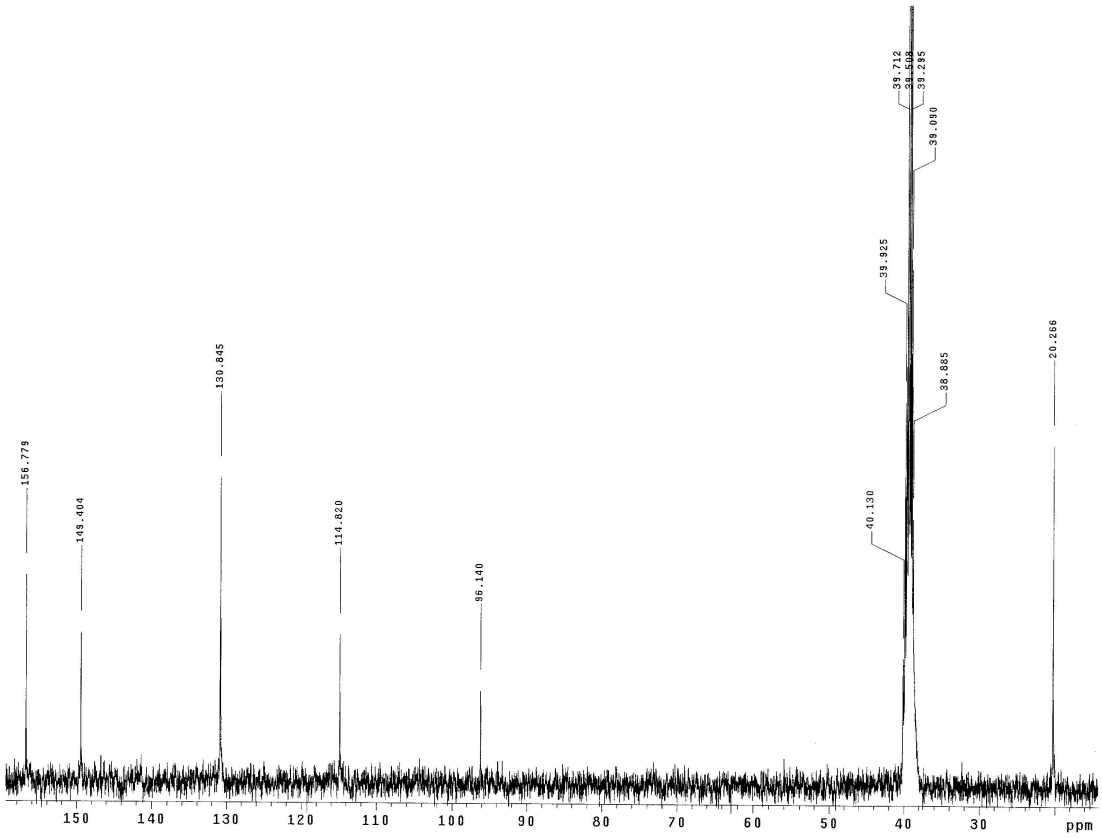
8.197
8.186
7.781
7.772
7.495
7.309
7.288
7.288
6.648
3.340
2.499
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
0.89
1.03
1.00
1.06
1.90
4.99

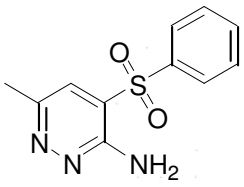

186.681
155.497
150.003
142.363
136.862
136.376
128.971
127.104
118.311
40.122
39.917
39.705
39.496
39.288
39.083
38.870
20.607
180
160
140
120
100
80
60
40
ppm


CN
N
N
NH2

4d

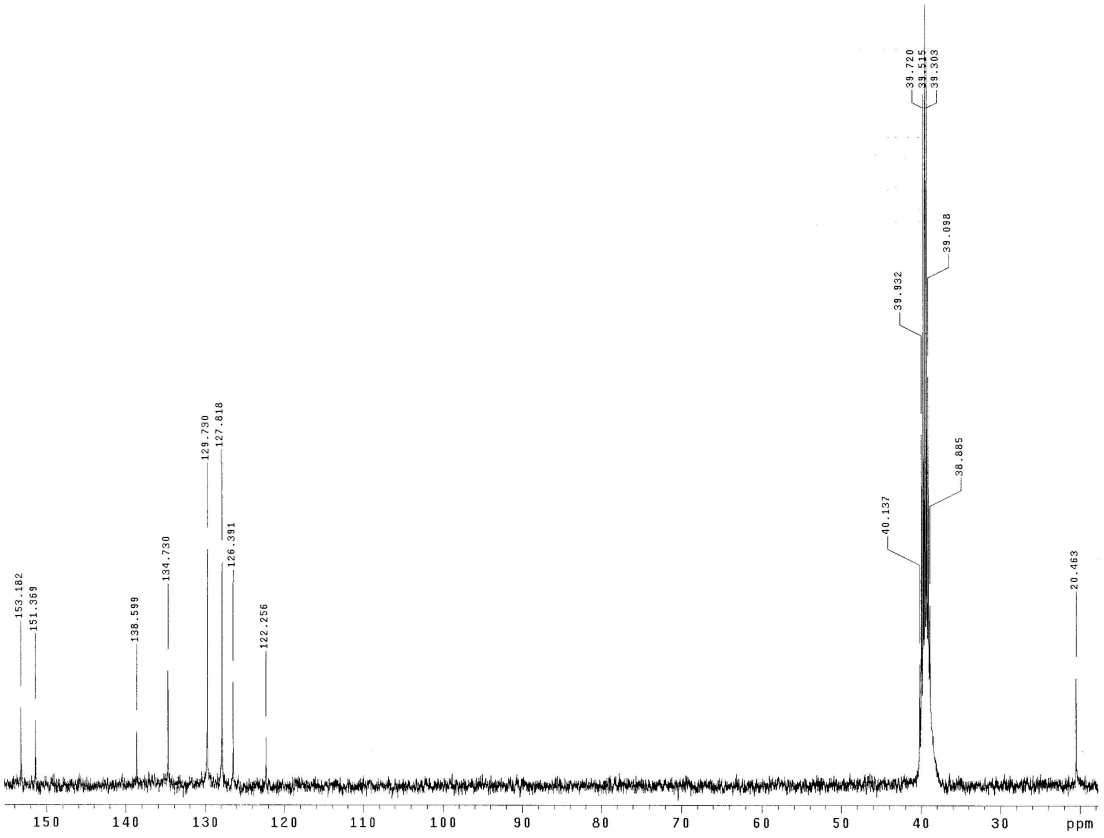
2.439
3.367
7.696
7.063
exch.
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
0.74
1.99
3.00

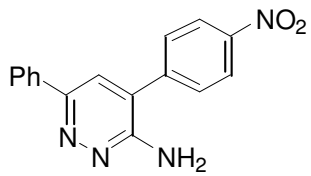

39.712
39.508
39.295
39.090
38.925
38.885
20.266
40.130
156.779
149.404
130.845
114.820
86.140
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm



4e

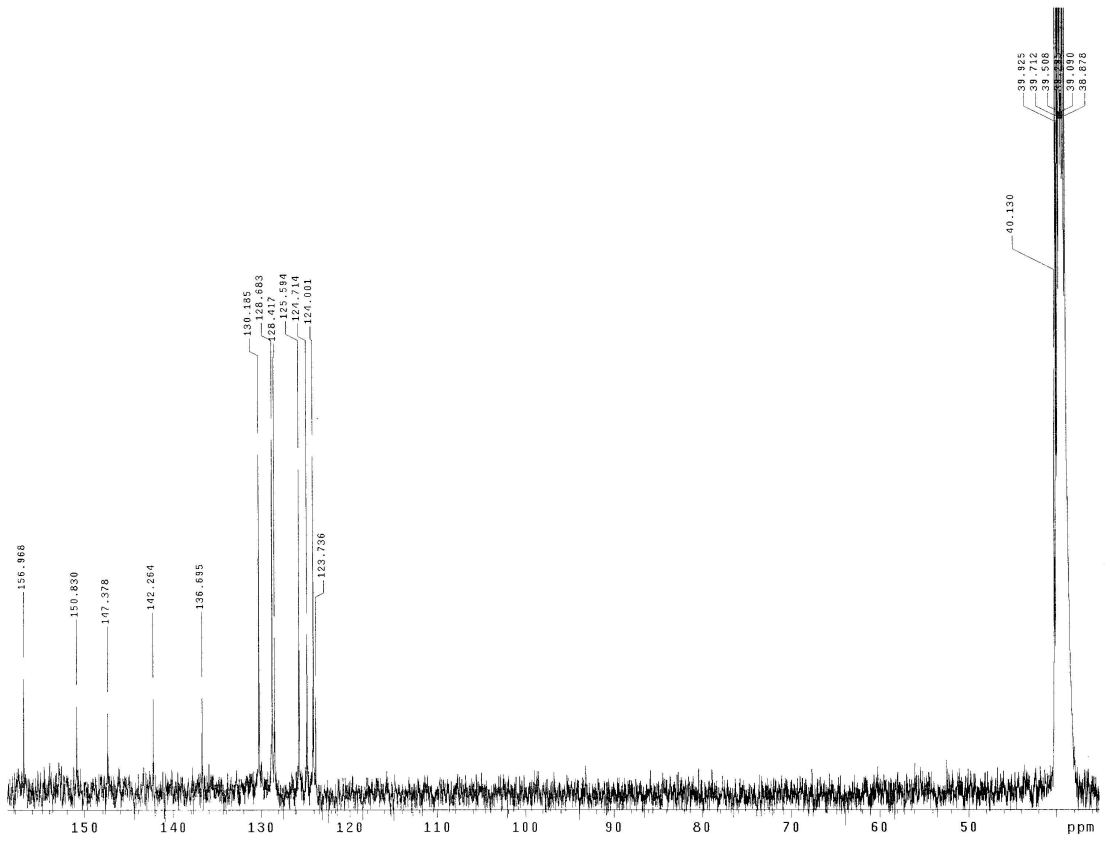
8.096
8.078
8.075
7.815
7.795
7.793
7.775
7.758
7.755
7.679
7.660
8.099
7.640
6.881
exch
3.352
2.533
2.500
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
1.78
2.04
2.00
1.58
2.72

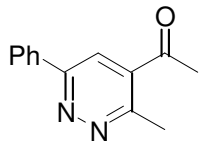

39.720
39.515
39.303
39.098
39.932
38.885
40.137
153.182
151.369
138.599
134.730
129.730
127.818
126.391
122.256
20.463
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


Ph
N
N
NO2
NH2

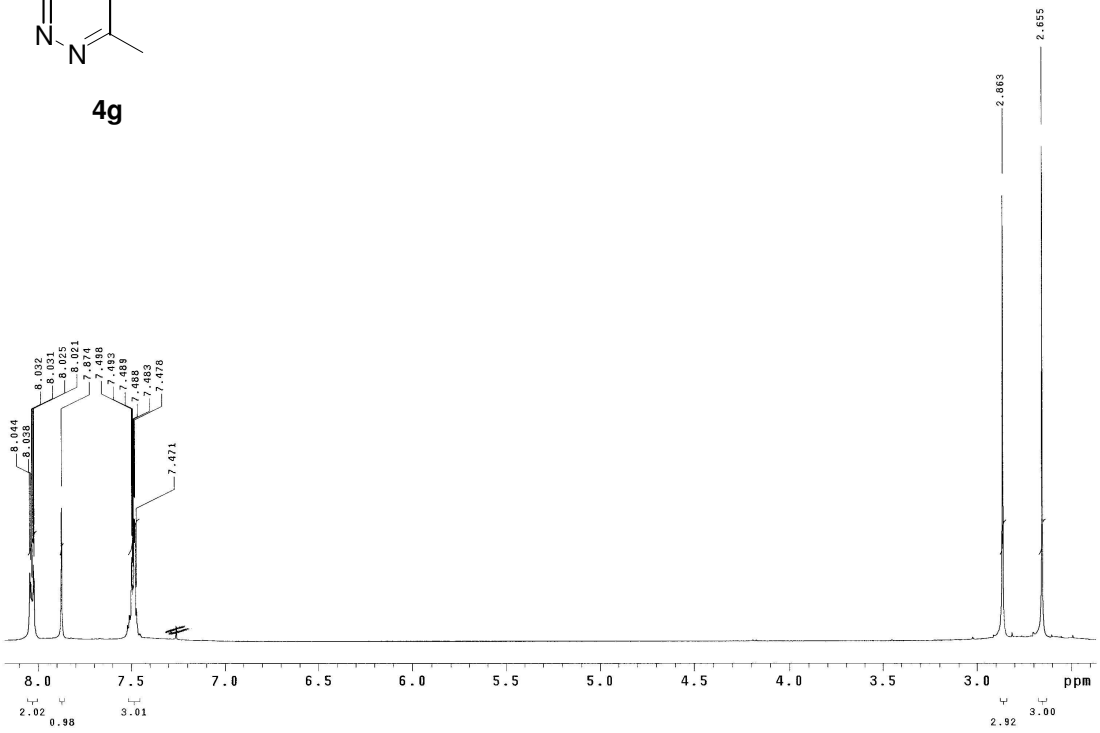
4f

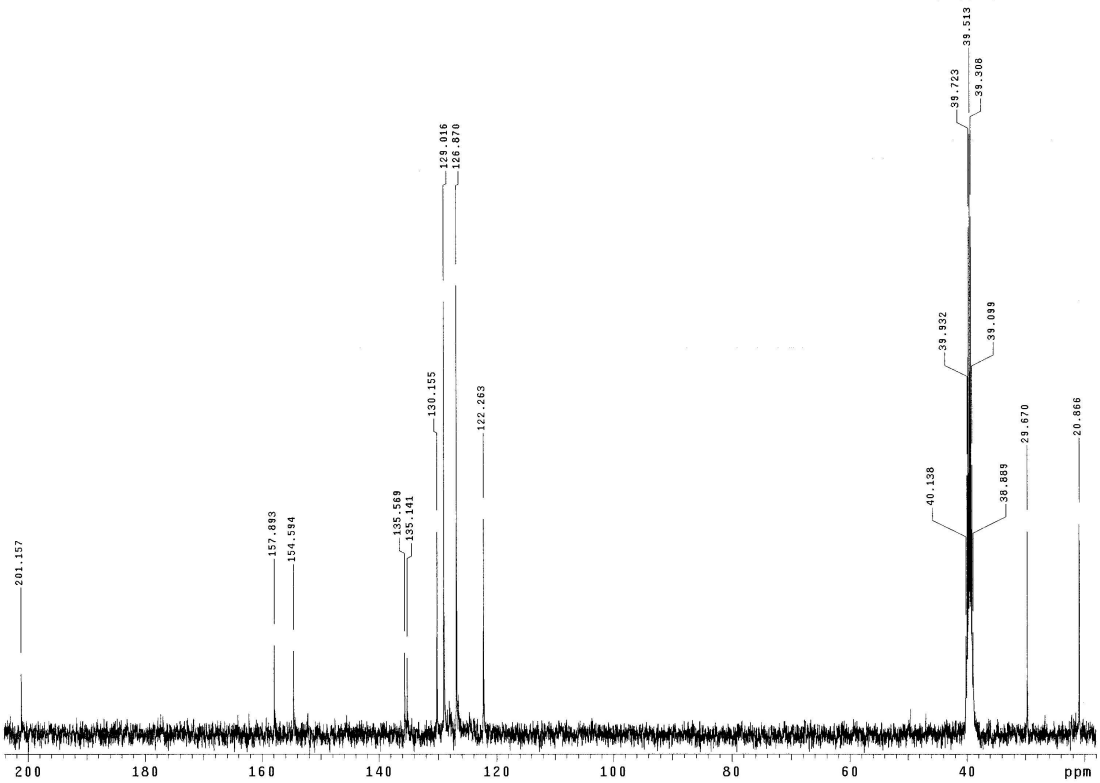
8.375
8.354
8.333
8.075
8.054
7.926
7.908
7.905
7.904
7.825
7.498
7.481
7.461
7.427
7.410
7.39
6.479
3.344
3.343
2.504
2.500
2.495
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
1.80
1.90
2.01
1.00
1.97
1.11
1.81

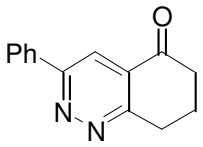

156.968
150.830
147.378
142.264
136.695
130.185
128.683
128.417
125.594
124.714
124.001
123.736
40.130
39.925
39.722
39.518
39.090
38.878
150
140
130
120
110
100
90
80
70
60
50
ppm


Ph
O
N
N

4g

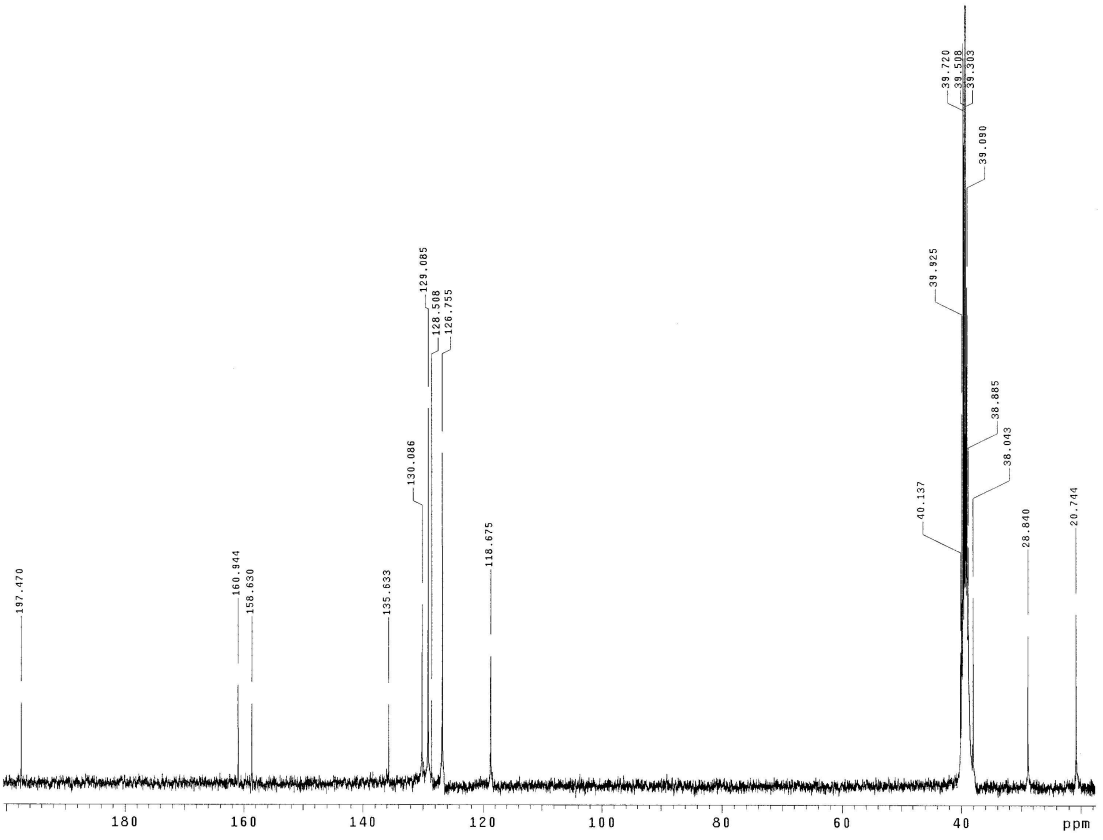

8.044
8.038
8.032
8.031
8.025
8.021
7.874
7.498
7.493
7.488
7.483
7.478
7.471
2.863
2.655
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
2.02
0.98
3.01
2.92
3.00

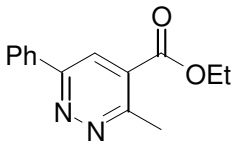

201.157
157.893
154.584
135.569
135.141
130.155
129.016
126.870
122.263
40.138
39.932
39.723
39.513
39.308
39.099
38.889
29.670
20.866
200
180
160
140
120
100
80
60
40
ppm


Ph
N
N
O

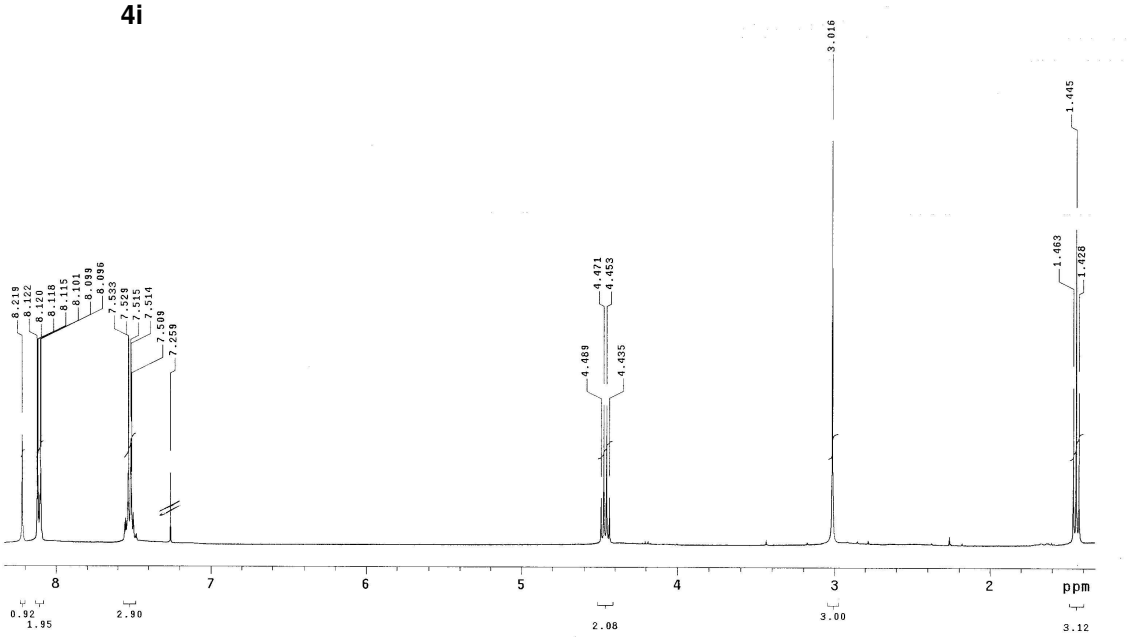
4h

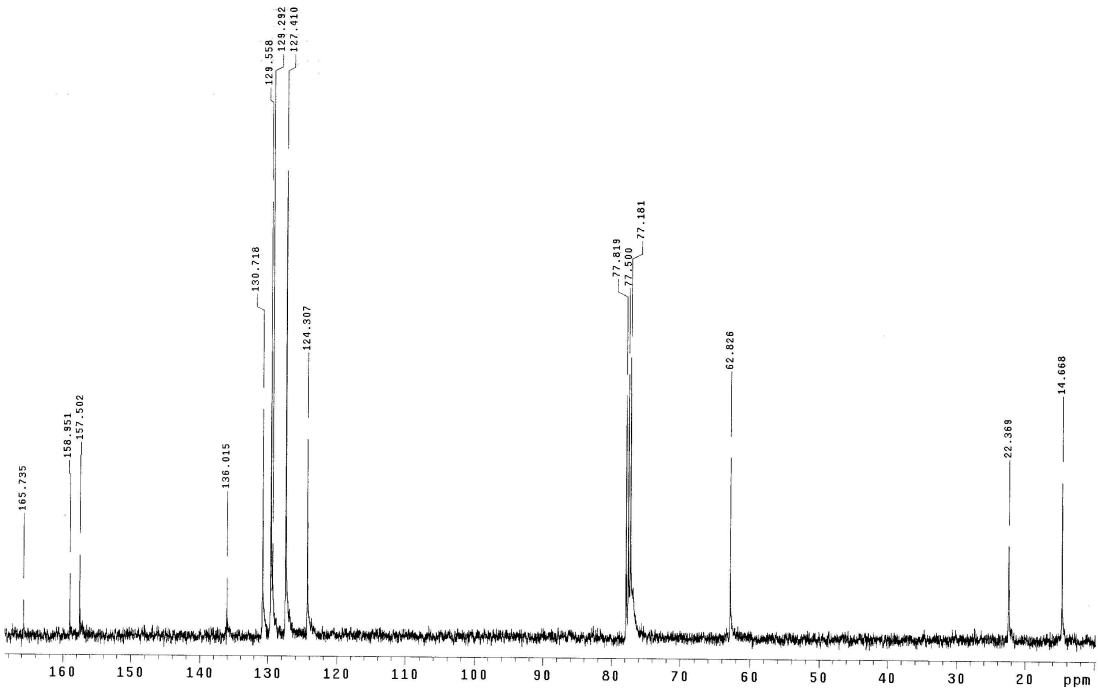
8.268
8.196
8.191
8.186
8.182
8.180
8.176
8.172
7.575
7.574
7.570
7.562
7.560
7.556
7.552
7.544
3.351
3.335
3.319
3.304
2.790
2.775
2.757
2.505
2.500
2.496
2.210
2.195
2.179
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
1.00
2.15
2.98
2.82
2.29
2.34

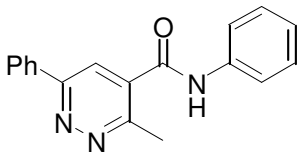

197.470
160.944
158.630
135.633
130.086
129.085
128.568
126.755
118.675
39.720
39.508
39.303
39.090
38.885
38.043
28.840
20.744
180
160
140
120
100
80
60
40
ppm


O
Ph
OEt
N
N

4i

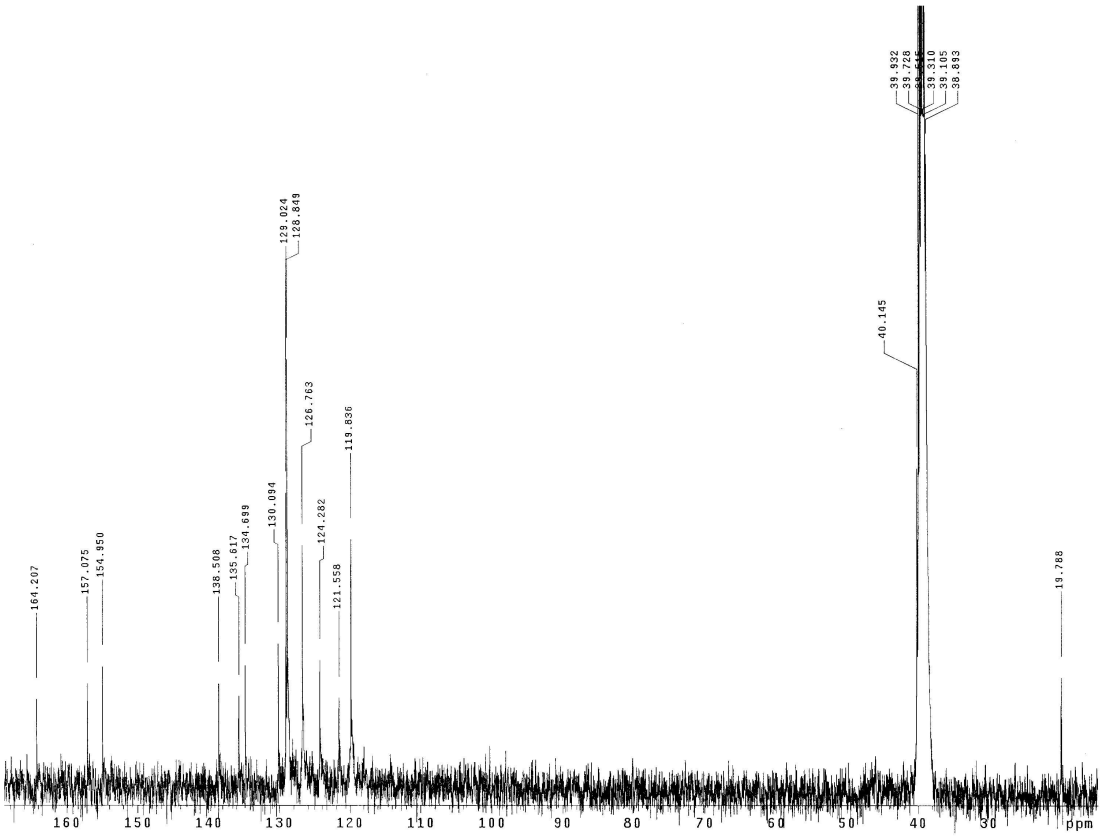

8.219
8.122
8.120
8.118
8.115
8.101
8.099
8.096
7.533
7.528
7.515
7.514
7.509
7.259
4.471
4.453
4.439
4.435
3.016
1.463
1.445
1.428
8
7
6
5
4
3
2
ppm
0.92
1.95
2.90
2.08
3.00
3.12

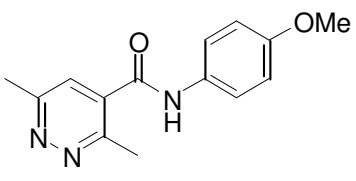

165.735
158.951
157.502
136.015
130.718
129.558
129.292
127.410
124.307
77.819
77.500
77.181
62.826
22.369
14.668
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Ph
O
N
H
N
N

4j

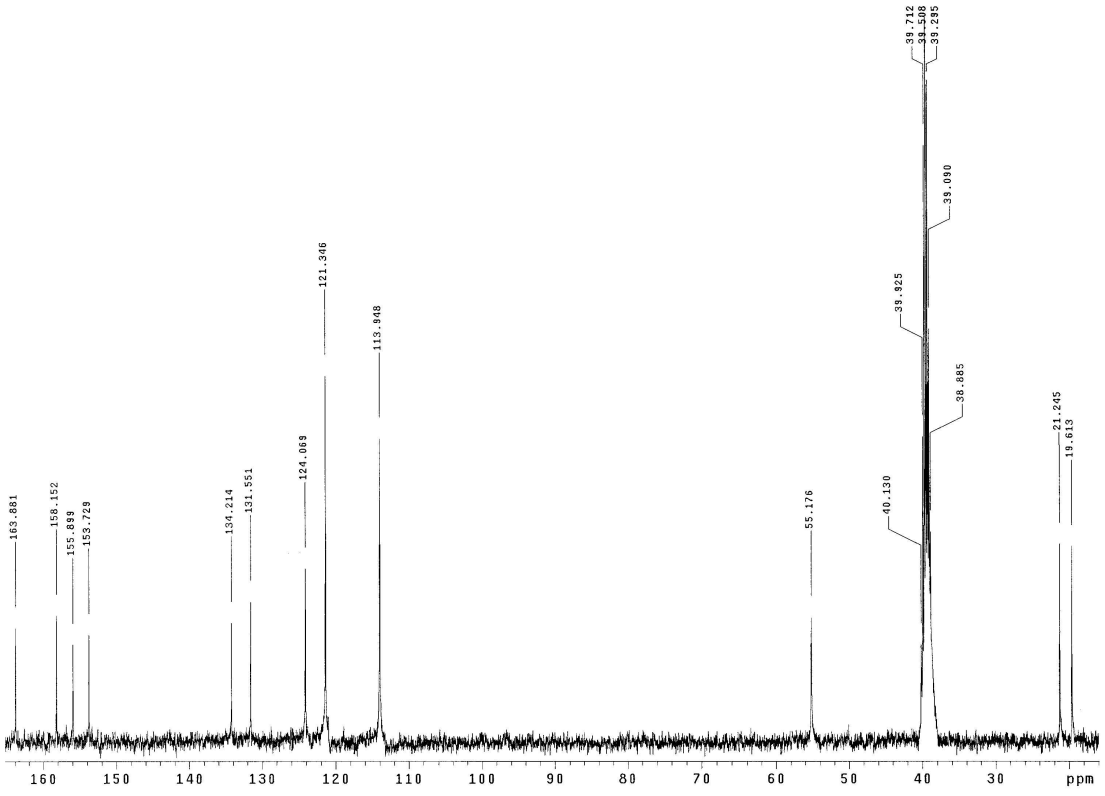
10.731
8.346
8.239
8.235
8.220
8.216
7.750
7.731
7.608
7.603
7.588
7.587
7.569
7.556
7.549
7.419
7.399
7.379
7.180
7.162
7.143
3.338
2.757
10
9
8
7
6
5
4
3
ppm
0.86
2.14
1.07
3.51
2.14
2.29
1.11
3.00

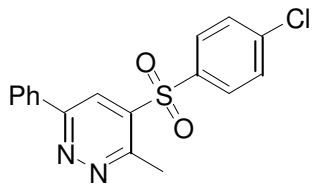

164.207
157.075
154.950
138.508
135.617
134.699
130.094
129.024
128.849
126.763
124.282
121.558
119.836
40.145
39.932
39.728
39.524
39.320
39.116
38.893
19.788
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


OMe
O
N
H
N
N

4k

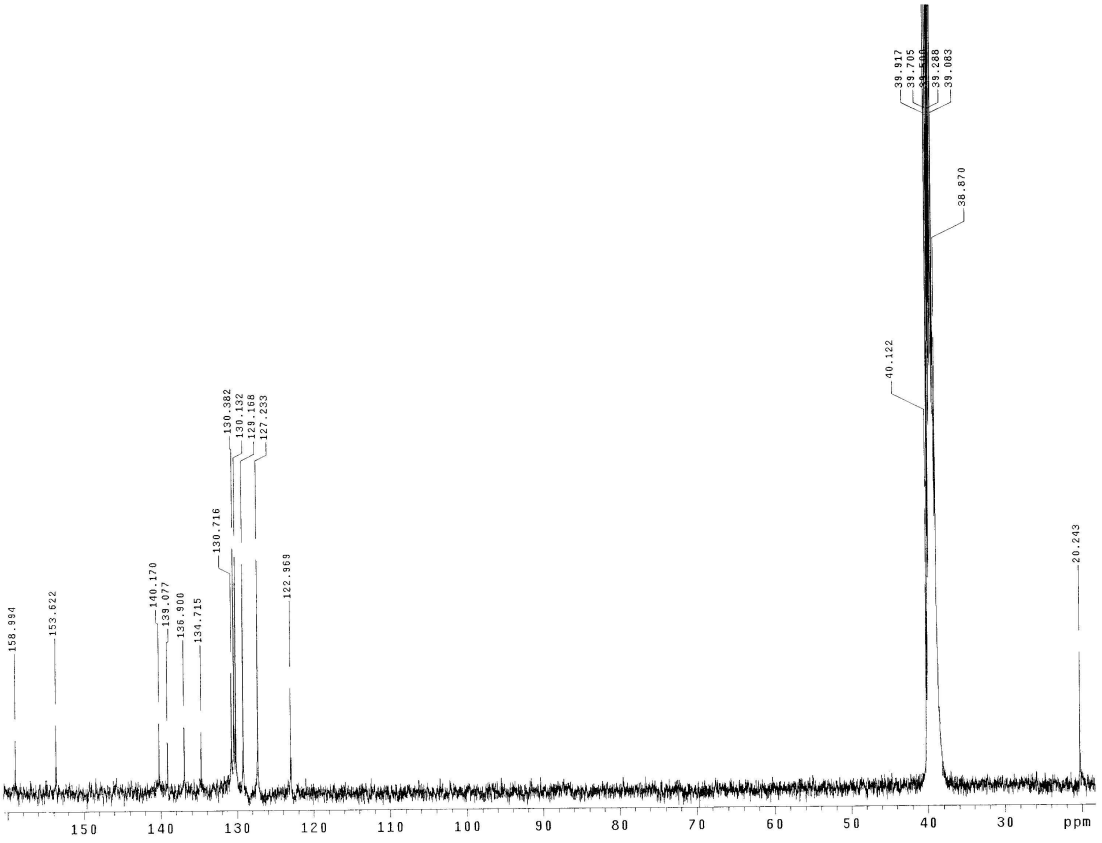
10.508
esch
7.639
7.625
7.602
6.958
6.935
3.345
3.345
2.642
2.500
10
9
8
7
6
5
4
3
ppm
0.94
2.84
1.95
3.00
5.84

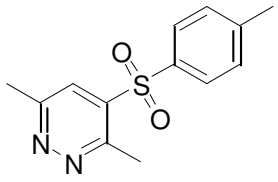

163.881
158.152
155.899
153.729
134.214
131.551
124.069
121.346
113.948
55.176
39.712
39.508
39.295
39.090
38.925
38.885
40.130
21.245
19.613
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


Cl
O
S
O
Ph
N
N

4l

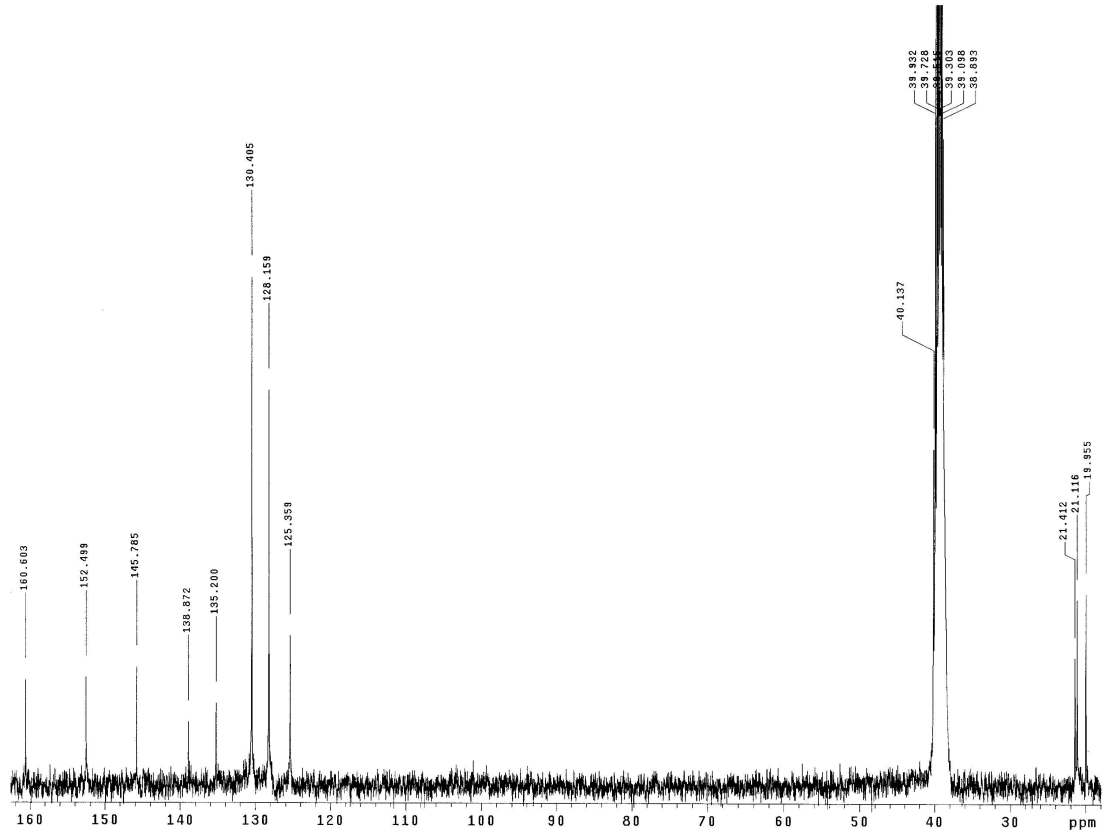
8.607
8.246
8.240
8.267
8.260
8.139
7.781
7.760
7.671
7.607
7.604
3.355
2.753
2.500
8
7
6
5
4
3
ppm
0.98
2.14
2.22
2.06
3.16
3.00

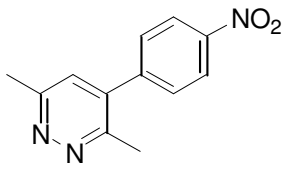

158.984
153.622
140.170
139.077
136.900
134.715
130.716
130.382
130.132
128.168
127.233
122.969
39.917
39.705
39.288
39.083
38.870
40.122
20.243
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm



4m

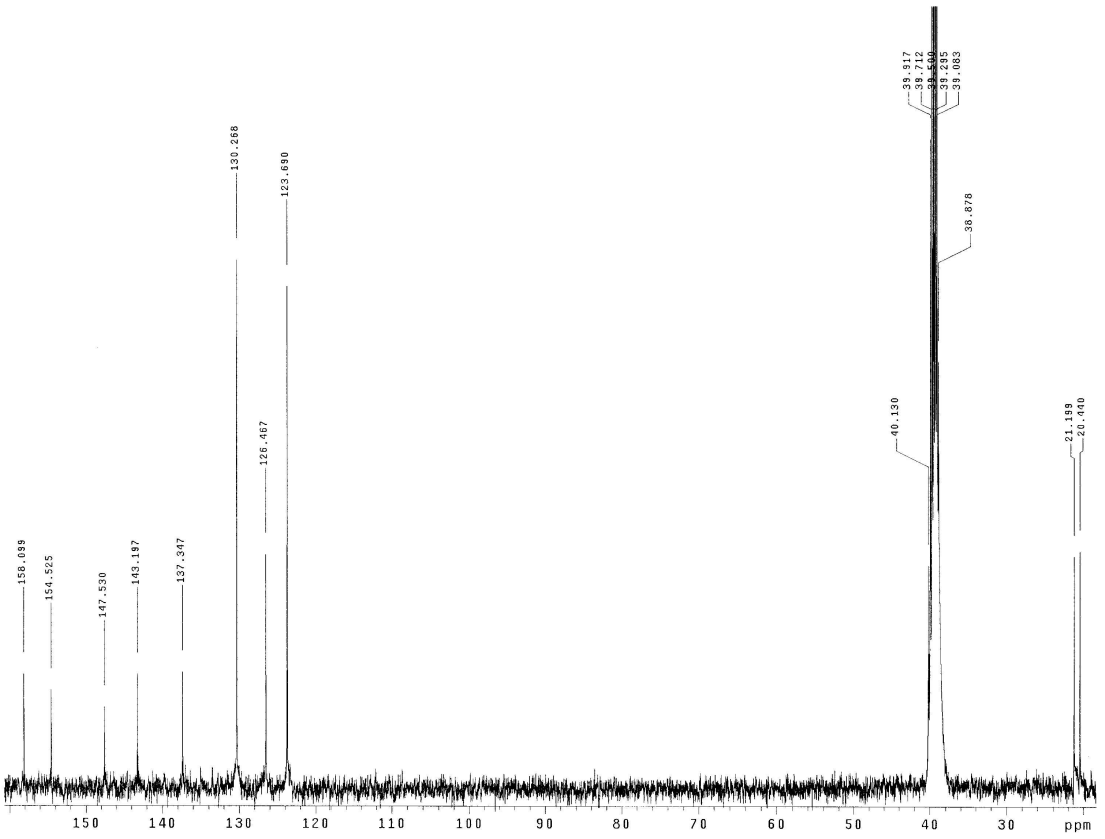
8.098
7.877
7.856
7.506
7.485
3.382
3.381
3.380
3.379
3.378
3.377
3.376
3.375
3.374
3.363
2.743
2.643
2.505
2.500
2.486
2.409
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
0.86
1.98
2.03
2.90
2.88
3.00

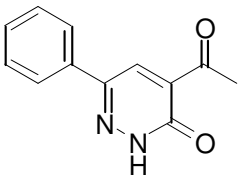

160.603
152.499
145.785
138.872
135.200
130.405
128.159
125.359
40.137
39.932
39.728
39.523
39.318
39.113
38.908
38.693
21.412
21.116
19.955
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


NO2
N
N

4n

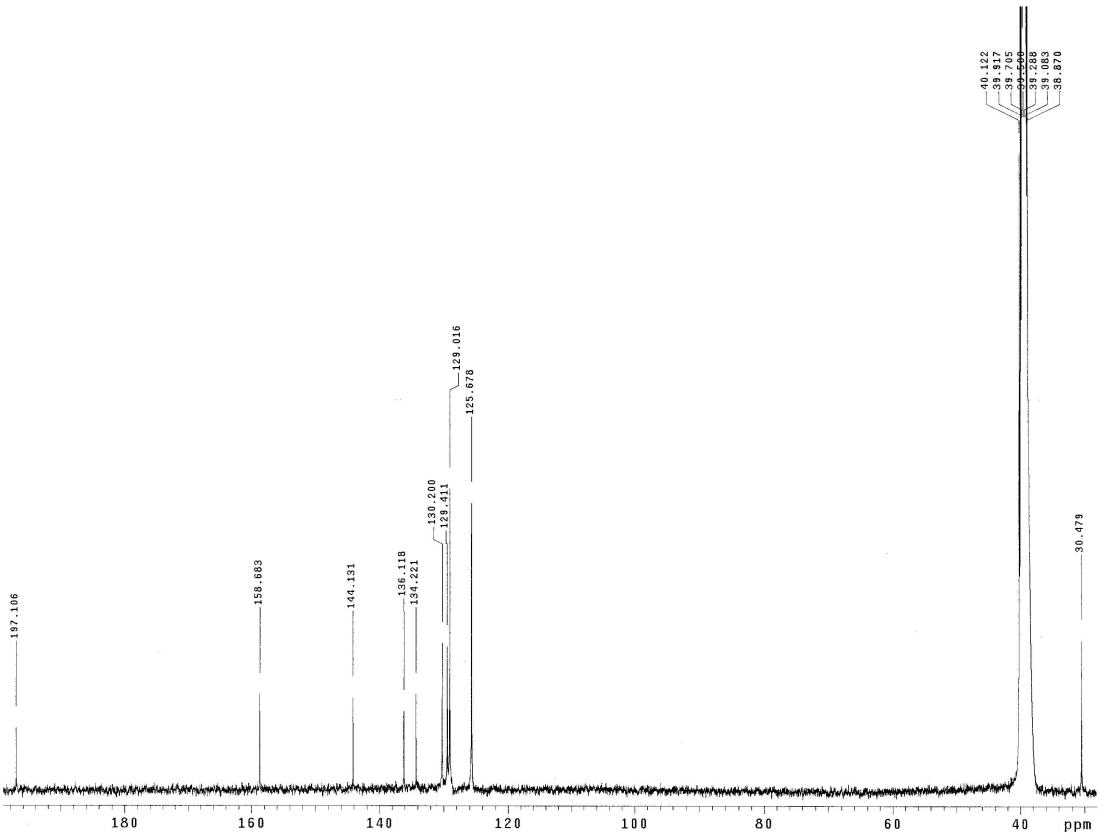
8.366
8.362
8.344
7.815
7.793
7.506
3.356
2.640
2.552
2.505
2.500
2.495
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
1.90
2.00
1.00
3.15
3.00


158.089
154.525
147.530
143.187
137.347
130.268
126.467
123.690
40.130
38.878
21.199
20.440
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm



5a

13.703
8.198
7.893
7.883
7.873
7.869
7.525
7.519
7.514
7.503
7.484
7.477
7.473
7.467
7.461
3.332
3.309
2.628
2.509
2.505
2.500
2.485
2.492
ppm
0.63
0.95
1.98
3.04
3.00


197.106
158.683
144.131
136.118
134.221
130.200
129.411
129.016
125.678
40.122
39.917
39.705
39.288
39.083
38.870
30.479
ppm

4. References and notes

[1] (a) Sommer, S. *Tetrahedron Lett.* **1977**, *18*, 117–120.

(b) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671–672.

(c) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 873–874.

[2] South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *J. Org. Chem.* **1996**, *61*, 8921–8934.