## Electronic Supplementary Information

# Regioselective pyridazine synthesis from tetrazines and alkynyl sulfides

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## Contents

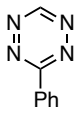


### General Information

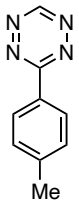
All reactions were performed with dry glassware under atmosphere of argon, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (Merck Chemicals, Silica Gel 60 F254, Cat. No. 1.05715). Column chromatography was conducted using silica-gel (Kanto Chemical Co., Inc., Silica Gel 60N, spherical neutral, particle size 40–50 μm, Cat. No. 37562-85 or particle size 63–210 μm, Cat. No. 37565-85). Preparative TLC (PTLC) was performed on silica gel (Wako Pure Chemical Industries Ltd., Wakogel B-5F, Cat. No. 230-00043). Melting points (Mp) were measured on an OptiMelt MPA100 (Stanford Research Systems), and are uncorrected. $^{1}$H NMR spectra were obtained with a Bruker AVANCE 400 spectrometer at 400 MHz. $^{13}$C NMR spectra were obtained with a Bruker AVANCE 400 spectrometer at 101 MHz. $^{19}$F NMR spectra were obtained with a Bruker AVANCE 400 spectrometer at 376 MHz. All NMR measurements were carried out at 25 ºC. $CDCl_3$ (Kanto Chemical Co. Inc., Cat. No. 07663-23) was used as a solvent for obtaining NMR spectra. Chemical shifts (δ) are given in parts per million (ppm) downfield from the solvent peak (δ 7.26 for $^{1}$H NMR in $CDCl_3$, δ 77.0 for $^{13}$C NMR in $CDCl_3$) as an internal reference with coupling constants (*J*) in hertz (Hz). The abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. High-resolution mass spectra (HRMS) were measured on a JEOL JMS-T100CS "AccuTOF CS" mass spectrometer (JEOL, Tokyo, Japan) under positive electrospray ionization ($ESI^{+}$) conditions or JMS-700 mass spectrometer (JEOL, Tokyo, Japan) under electron impact ionization (EI) conditions.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. 3-Phenyl-1,2,4,5-tetrazine (**4a**),[S1] 3-(*p*-tolyl)-1,2,4,5-tetrazine (**4b**),[S1] 3-(4-methoxyphenyl)-1,2,4,5-tetrazine (**4c**),[S1] 3-(4-fluorophenyl)-1,2,4,5-tetrazine (**4d**),[S1] 3-(4-chlorophenyl)-1,2,4,5-tetrazine (**4e**),[S1] 3-(4-bromophenyl)-1,2,4,5-tetrazine (**4f**),[S1] 3-benzyl-1,2,4,5-tetrazine (**4g**),[S1] methyl 3-(1,2,4,5-tetrazin-3-yl)propanoate (**4h**),[S2] *N*,4-dimethyl-*N*-(*p*-tolylethynyl)benzenesulfonamide (**10a**),[S3] diphenyl(*p*-tolylethynyl)phosphane (**10c**),[S4] (hept-1-yn-1-yloxy)benzene (**10d**),[S5] *N*-(hex-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide (**10e**),[S6] hex-1-yn-1-yldiphenylphosphane (**10g**),[S7] 1-chlorohex-1-yne (**10h**),[S8] 4-(ethylthio)but-3-yn-1-yl 4-methylbenzoate (**10k**),[S9] 1-(hex-1-yn-1-ylsulfonyl)-4-methylbenzene (**10t**),[S10] and 1-methyl-4-((*p*-tolylethynyl)sulfonyl)benzene (**10u**)[S10] were prepared according to the reported methods.

**Structures of Tetrazines 4 and Alkynes 10**




**4a**

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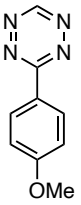


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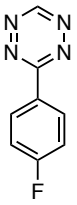


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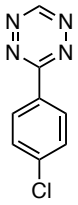


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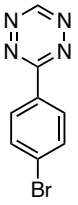


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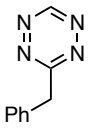


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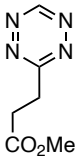


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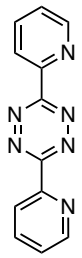

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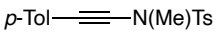


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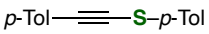


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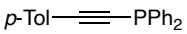


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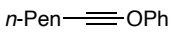


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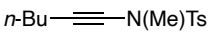


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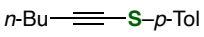


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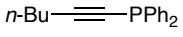


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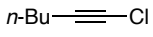


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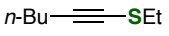


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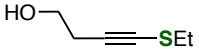


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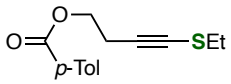


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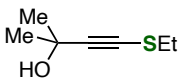


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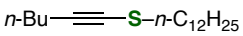


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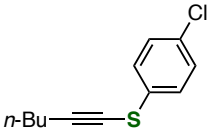


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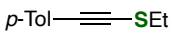


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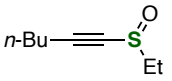


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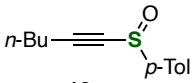


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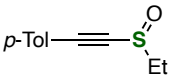


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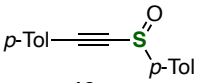
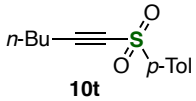
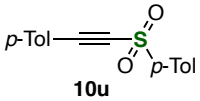



**10s**



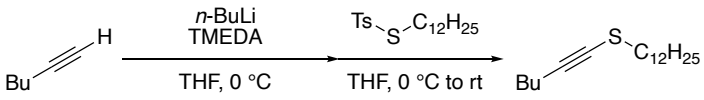

**10t**




**10u**

**Experimental Procedures**

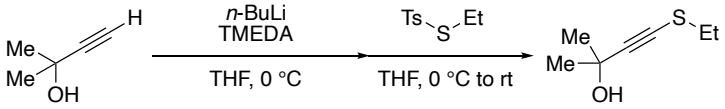
*A typical procedure for the preparation of alkynyl sulfides*[S14]




To a solution of 1-hexyne (342 μL, 3.00 mmol) dissolved in THF (15.0 mL) was added *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (444 μL, 3.00 mmol, 1.0 equiv) at 0 °C. After stirring for 30 min at the same temperature, to the mixture was slowly added *n*-BuLi (2.6 M in *n*-hexane, 1.1 mL, 3.0 mmol, 1.0 equiv) at 0 °C. After stirring for 20 min at the same temperature, to the mixture was slowly added *S*-dodecyl 4-methylbenzenesulfonothioate (1.07 g, 3.00 mmol, 1.0 equiv) dissolved in THF (6.0 mL) at 0 °C. After stirring for 20 min at the same temperature, the mixture was allowed to warm to room temperature. After stirring for 1 h at room temperature, the mixture was extracted with EtOAc (30 mL × 3). The combined organic extract was washed with brine (20 mL) and dried with $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 5/1) to give 1-(dodecylthio)-1-hexyne (**10m**) (341 mg, 2.11 mmol, 70%) as a yellow oil.

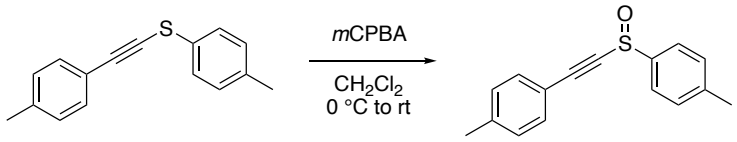
According to the procedure for preparing 1-(dodecylthio)-1-hexyne (**10m**), *p*-tolyl *p*-tolylethynyl sulfide (**10b**), hex-1-yn-1-yl *p*-tolyl sulfide (**10f**), ethyl hex-1-yn-1-yl sulfide (**10i**), 4-(ethylthio)but-3-yn-1-ol (**10j**), and 4-chlorophenyl hex-1-yn-1-yl sulfide (**10n**) were prepared from the corresponding alkyne and thiosulfonates. Sulfides **10b**, **10f**, **10i**, **10j**, and **10n** were identical in spectra data with those reported in the literature.

*Synthesis of alkynyl sulfides **10l***




To a solution of 2-methylbut-3-yn-2-ol (293 μL, 3.00 mmol) dissolved in THF (15.0 mL) was added *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (890 μL, 6.00 mmol, 2.0 equiv) at 0 °C. After stirring for 30 min at the same temperature, to the mixture was slowly added *n*-BuLi (2.6 M in *n*-hexane, 2.3 mL, 6.0 mmol, 2.0 equiv) at 0 °C. After stirring for 20 min at the same temperature, to the mixture was slowly added *S*-ethyl 4-methylbenzenesulfonothioate (648 mg, 3.00 mmol, 1.0 equiv) dissolved in THF (6.0 mL) at 0 °C. After stirring for 20 min at the same temperature, the mixture was allowed to warm to room temperature. After stirring for 1 h at room temperature, the mixture was extracted with EtOAc (30 mL × 3). The combined organic extract was washed with brine (20 mL) and dried with $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 5/1) to give 4-(ethylthio)-2-methylbut-3-yn-2-ol (**10l**) (341 mg, 2.11 mmol, 70%) as a yellow oil.

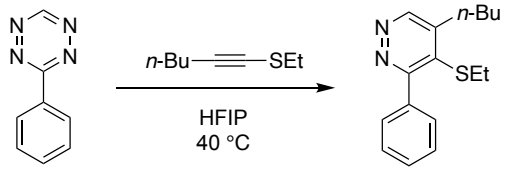
*A typical procedure for the preparation of alkynyl sulfoxides*[S15]




To a solution of *p*-tolyl *p*-tolylethynyl sulfide (119 mg, 0.500 mmol) in $CH_2Cl_2$ (2.5 mL) was slowly added *m*-chloroperbenzoic acid (*m*CPBA) (ca. 77%, 112 mg, ca. 0.5 mmol, ca. 1 equiv) at 0 °C. After stirring for 10 min at the same temperature, the mixture was allowed to warm to room temperature. After stirring for 2 h at room temperature, to the mixture was added an aqueous saturated solution of potassium carbonate (10 mL) and an aqueous saturated solution of sodium thiosulfate (10 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL × 3). The combined organic extract was washed with brine (20 mL) and dried with $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 2/1) to give 1-methyl-4-((*p*-tolylethynyl)sulfinyl)benzene (**10s**) (108 mg, 0.425 mmol, 85%) as a yellow solid.

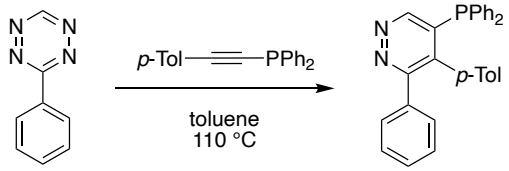
According to the procedure for preparing 1-methyl-4-((*p*-tolylethynyl)sulfinyl)benzene (**10s**), 1-(ethylsulfinyl)hex-1-yne (**10p**), 1-(hex-1-yn-1-ylsulfinyl)-4-methylbenzene (**10q**), and 1-((ethylsulfinyl)ethynyl)-4-methylbenzene (**10r**) were prepared from the corresponding alkynyl sulfides. Sulfoxides **10p**–**s** were identical in spectra data with those reported in the literature.

*A typical procedure for the synthesis of pyridazines in HFIP*



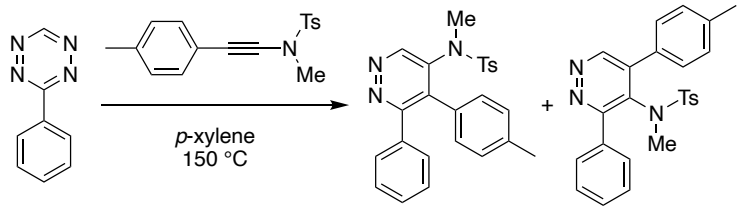

To a mixture of 3-phenyl-1,2,4,5-tetrazine (**4a**) (21.7 mg, 0.137 mmol, 1.00 equiv) and ethyl hex-1-yn-1-yl sulfide (**10i**) (29.6 mg, 0.208 mmol, 1.50 equiv) was added 1,1,1,3,3,3- hexafluoro-2-propanol (HFIP) (140 μL) in a 0.3 mL screw-top V-vial® with an open-top cap at room temperature. The mixture was heated at 40 °C (oil bath) with stirring for 72 h. After cooling to room temperature, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give 5-butyl-4-(ethylthio)-3-phenylpyridazine (**12i**) (30.4 mg, 0.112 mmol, 82%) as a yellow oil.

*A typical procedure for the synthesis of pyridazines in toluene*



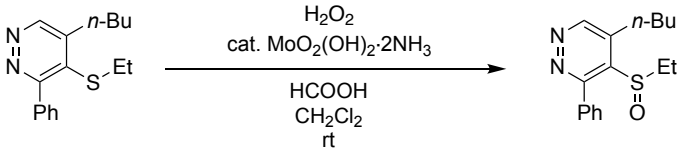

To a mixture of 3-phenyl-1,2,4,5-tetrazine (**4a**) (10.9 mg, 70.0 μmol, 1.00 equiv) and diphenyl(*p*-tolylethynyl)phosphane (**10c**) was added toluene (140 μL) in a 0.3 mL screw-top V-vial® with an open-top cap at room temperature. The mixture was heated at 110 °C (oil bath) with stirring for 24 h. After cooling to room temperature, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 5/1) to give 5-(diphenylphosphaneyl)-3-phenyl-4-(*p*-tolyl)pyridazine (**11c**) (15.5 mg, 36.0 μmol, 52%) as a yellow solid.

*Synthesis of pyridazines **11a** and **12a** in p-xylene*



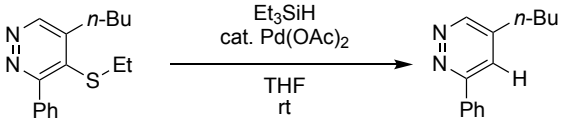

To a mixture of 3-phenyl-1,2,4,5-tetrazine (**4a**) (15.8 mg, 0.100 mmol, 1.00 equiv) and *N*,4-dimethyl-*N*-(*p*-tolylethynyl)benzenesulfonamide (**10a**) (44.9 mg, 0.150 mmol, 1.50 equiv) was added *p*-xylene (0.500 mL) in a 5 mL screw-top V-vial® with an open-top cap at room temperature. The mixture was heated at 150 °C (oil bath) with stirring for 43 h. After cooling to room temperature, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC ($CH_2Cl_2$/MeOH = 10/1) to give *N*,4-dimethyl-*N*-(6-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**11a**) and *N*,4-dimethyl-*N*-(3-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**12a**) (24.9 mg, 57.9 μmol, 58% (**11a**:**12a** = 16:84)) as a yellow solid.

*Synthesis of 5-butyl-4-(ethylsulfinyl)-3-phenylpyridazine (**12x**)*



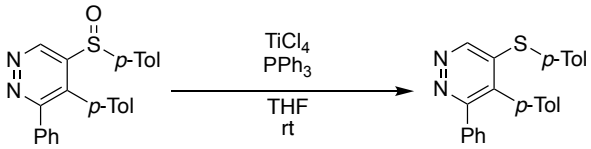

To a solution of 5-butyl-4-(ethylthio)-3-phenylpyridazine (**12i**) (21.8 mg, 80.0 μmol) in $CH_2Cl_2$ (0.70 mL) was added HCOOH (9.2 μL, 0.24 mmol, 3.0 equiv) at room temperature. After stirring at the same temperature, ammonium molybdate (2.9 mg, 16 μmol, 0.2 equiv) and 30% $H_2O_2$ (25 μL, 0.240 mmol, 3.0 equiv) were added to the reaction mixture. After stirring for 15 h at room temperature, the reaction was quenched with $H_2O$ (10 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL × 3). The combined organic extracted and washed with brine (10 mL) and $H_2O$ (10 mL). The mixture was dried with $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/2) to give 5-butyl-4-(ethylsulfinyl)-3-phenylpyridazine (**12x**) (10.6 mg, 37 μmol, 46%) as a red oil.

*Synthesis of 5-butyl-3-phenylpyridazine (**13**)*




To a solution of 5-butyl-4-(ethylthio)-3-phenylpyridazine (**12i**) (13.4 mg, 50.0 μmol) in THF (0.40 mL) was added $Pd(OAc)_2$ (0.8 mg, 1.5 μmol, 3 mol %) at room temperature. After stirring at the same temperature, $Et_3SiH$ (17 μL, 0.11 mmol, 2.1 equiv) was added to the reaction mixture at room temperature. After stirring for 65 h at the same temperature, the reaction was quenched with $H_2O$ (10 mL). The mixture was extracted with $CH_2Cl_2$ (20 mL × 3). The combined organic extract was washed with brine (10 mL) and dried with $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 2/1) to give 5-butyl-3-phenylpyridazine (**13**) (5.7 mg, 27 μmol, 55%) as a colorless solid.

*Synthesis of 3-phenyl-4-(p-tolyl)-5-(p-tolylthio)pyridazine (**11b**)*



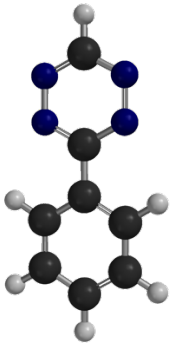

To a solution of 3-phenyl-4-(*p*-tolyl)-5-(*p*-tolylsulfinyl)pyridazine (**11aa**) (88.8 mg, 0.231 mmol) in THF (2.9 mL) was added $TiCl_4$ (38 μL, 0.35 mmol, 1.5 equiv) at room temperature. After stirring at the same temperature, $PPh_3$ (72.6 mg, 0.227 mmol, 1.2 equiv) in THF (1.7 mL) was added to the reaction mixture at room temperature. After stirring for 24 h at the same temperature, the reaction was quenched with aqueous saturated $NaHCO_3$(10 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic extract was washed with brine (10 mL) and dried with $Na_2SO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give 3-phenyl-4-(*p*-tolyl)-5-(*p*-tolylthio)pyridazine (**11b**) (25.5 mg, 69.2 μmol, 30%) as a yellow solid.

**Computational Methods**

Geometry optimizations and frequency calculations were performed at ωB97X-D/6-311+G(d,p) level of theory with Spartan 20 program (Wavefunction Inc. Irvine, CA) in the gas phase. Geometry optimizations from starting structures obtained in the gas phase and frequency calculations in the polar solvent (large dielectric, 37 for DMF) were conducted using C-PCM continuum model. Cartesian coordinates obtained by the DFT calculation with ωB97X-D/6-311+G(d,p) in the gas phase were shown as calculated geometries described below. All the stationary geometries were confirmed to be energy minima by achieving vibrational frequency analyses. Transition structures were also confirmed to be true transition states on the potential energy surfaces by achieving vibrational frequency analyses. Conformer searches of optimized structures were conducted with Spartan 20 program as calculations for "Equilibrium Conformer" and "Conformer Distribution".

Calculated Geometries

Optimized structure of **4a**



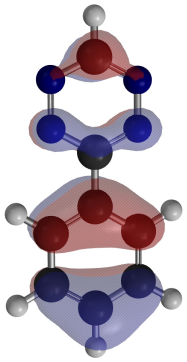
black: carbon, grey: hydrogen, blue: nitrogen

G = –527.223349 hartrees [ωB97X-D/6-311+G(d,p)]

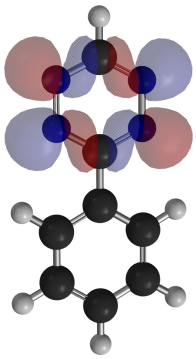
–527.236142 hartrees [ωB97X-D/6-311+G(d,p)] (polar solvent)

| | | | |
|---|---|---|---|
| H | 0.000101 | 0.000000 | 4.083212 |
| C | 0.000053 | 0.000000 | 2.998943 |
| C | -0.000130 | 0.000000 | 0.215045 |
| C | -1.203941 | 0.000000 | 2.303306 |
| C | 1.203973 | 0.000000 | 2.303160 |
| C | 1.207744 | 0.000000 | 0.916041 |
| C | -1.207906 | 0.000000 | 0.916188 |
| H | -2.143809 | 0.000000 | 2.843121 |
| H | 2.143872 | 0.000000 | 2.842914 |
| H | 2.140226 | 0.000000 | 0.365659 |
| H | -2.140693 | 0.000000 | 0.366379 |
| C | -0.000075 | 0.000000 | -1.262351 |
| N | -1.183020 | 0.000000 | -1.893842 |
| N | -1.182598 | 0.000000 | -3.200748 |
| N | 1.182986 | 0.000000 | -1.893626 |
| N | 1.182802 | 0.000000 | -3.200540 |
| C | 0.000157 | 0.000000 | -3.810085 |
| H | 0.000258 | 0.000000 | -4.892774 |

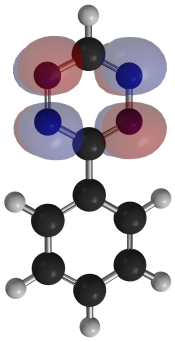
Representative molecular orbitals of **4a** [ωB97X-D/6-311+G(d,p)]



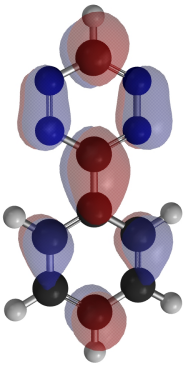
HOMO–1 –9.24 eV



HOMO –8.94 eV

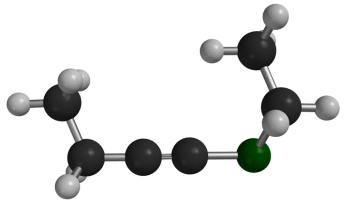


LUMO –1.21 eV



LUMO+1 –0.61 eV

Optimized structure of **10v**

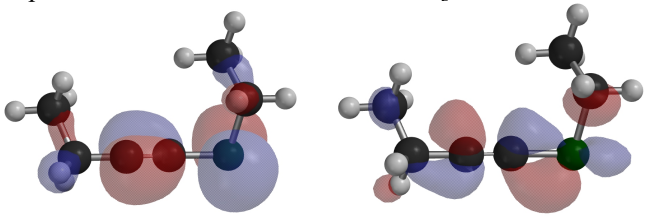


black: carbon, grey: hydrogen, green: sulfur

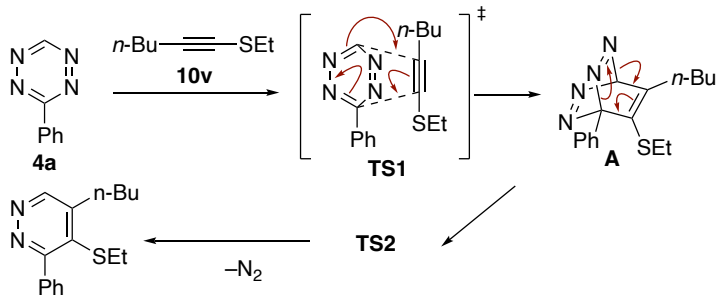
G = –632.666149 hartrees [ωB97X-D/6-311+G(d,p)]
–632.673007 hartrees [ωB97X-D/6-311+G(d,p)] (polar solvent)

| | | | |
|---|---|---|---|
| C | -1.192623 | 0.346700 | -0.807923 |
| C | -1.344459 | 0.140152 | 0.370531 |
| C | -0.990461 | 0.570580 | -2.237204 |
| H | -1.034811 | 1.643709 | -2.449962 |
| H | -1.825669 | 0.113116 | -2.777728 |
| S | -1.609357 | -0.159165 | 2.015944 |
| C | 0.057467 | 0.186894 | 2.691811 |
| H | 0.294680 | 1.230615 | 2.478838 |
| H | -0.075578 | 0.086367 | 3.771846 |
| C | 1.138273 | -0.749084 | 2.177536 |
| H | 2.102806 | -0.485961 | 2.621391 |
| H | 1.230568 | -0.672669 | 1.091651 |
| H | 0.913079 | -1.787582 | 2.429899 |
| C | 0.334297 | -0.007762 | -2.747629 |
| H | 0.441634 | 0.175493 | -3.819431 |
| H | 0.378759 | -1.085006 | -2.574505 |
| H | 1.181395 | 0.453602 | -2.235067 |

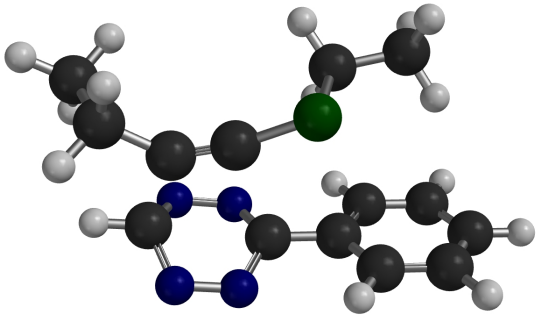
Representative molecular orbitals of **10v** [ωB97X-D/6-311+G(d,p)]



HOMO –7.93 eV LUMO –1.58 eV




Transition state structure **TS1**



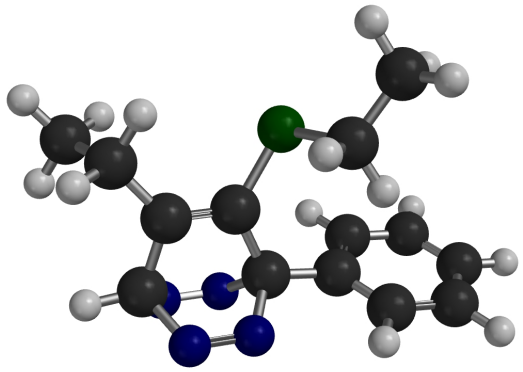
black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1159.839238 hartrees [ωB97X-D/6-311+G(d,p)]; Imaginary frequency: *i* 427 $cm^{-1}$

–1159.85921 hartrees [ωB97X-D/6-311+G(d,p)] (polar solvent); Imaginary frequency: *i* 440 $cm^{-1}$

| | | | |
|---|---|---|---|
| C | -2.402839 | 0.451505 | 0.102540 |
| C | -1.277870 | 0.888708 | -0.197483 |
| N | -0.459852 | -1.812111 | 0.839885 |
| N | -1.731389 | -1.990415 | 0.870732 |
| C | 0.031799 | -0.719230 | 1.473531 |
| C | -2.436269 | -0.964157 | 1.458864 |
| H | -3.506824 | -1.125414 | 1.505479 |
| N | -0.635607 | -0.204677 | 2.544396 |
| N | -1.902456 | -0.375450 | 2.585274 |
| C | 1.453219 | -0.377685 | 1.314086 |
| C | 4.141625 | 0.305857 | 1.009555 |
| C | 1.953372 | 0.792130 | 1.888936 |
| C | 2.310638 | -1.201351 | 0.579350 |
| C | 3.647296 | -0.860721 | 0.431855 |
| C | 3.291588 | 1.129912 | 1.737967 |
| H | 1.286907 | 1.425662 | 2.461901 |
| H | 1.920931 | -2.113747 | 0.143371 |
| H | 4.308512 | -1.510326 | -0.130974 |
| H | 3.670687 | 2.038988 | 2.191454 |
| H | 5.187424 | 0.568726 | 0.894888 |
| C | -3.824444 | 0.578682 | -0.335723 |
| H | -3.930537 | 1.521861 | -0.877057 |
| H | -4.472367 | 0.635821 | 0.544265 |
| S | 0.017036 | 1.735960 | -0.823107 |
| C | 0.677467 | 0.495748 | -2.013802 |
| H | -0.026896 | 0.433938 | -2.844758 |
| H | 0.699182 | -0.462336 | -1.494635 |
| C | -4.246866 | -0.589745 | -1.230389 |
| H | -3.646132 | -0.609227 | -2.142125 |
| H | -5.297133 | -0.484606 | -1.509847 |
| H | -4.118103 | -1.551537 | -0.729108 |
| C | 2.064670 | 0.916159 | -2.470373 |
| H | 2.758918 | 0.954453 | -1.626963 |
| H | 2.050118 | 1.892582 | -2.961386 |
| H | 2.444195 | 0.186045 | -3.190597 |

Optimized structure of intermediate **A**

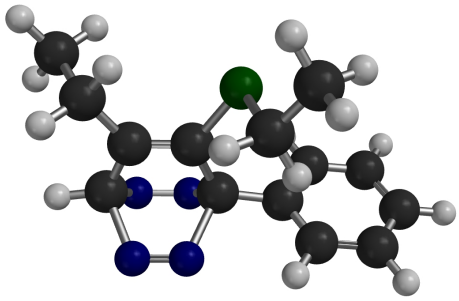


black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1159.917317 hartrees [ωB97X-D/6-311+G(d,p)]
–1159.931948 hartrees [ωB97X-D/6-311+G(d,p)] (polar solvent)

| | | | |
|---|---|---|---|
| C | 2.617919 | -0.694600 | -1.329973 |
| H | 3.674559 | -0.883675 | -1.479758 |
| N | 2.189997 | 0.512061 | -2.105988 |
| N | 0.986124 | 0.716179 | -2.058562 |
| C | 0.215939 | -0.278031 | -1.239312 |
| N | 1.801175 | -1.823127 | -1.912758 |
| N | 0.603779 | -1.622707 | -1.864543 |
| C | 2.169766 | -0.496604 | 0.079135 |
| C | 0.850173 | -0.276177 | 0.138560 |
| C | -1.265857 | -0.070166 | -1.356845 |
| C | -4.026686 | 0.284529 | -1.502182 |
| C | -1.793307 | 1.118561 | -1.853651 |
| C | -2.126832 | -1.084571 | -0.944326 |
| C | -3.501081 | -0.907716 | -1.015632 |
| C | -3.171028 | 1.294176 | -1.923270 |
| H | -1.124387 | 1.900866 | -2.189623 |
| H | -1.717750 | -2.014550 | -0.567254 |
| H | -4.162915 | -1.702571 | -0.691254 |
| H | -3.573795 | 2.222394 | -2.312646 |
| H | -5.100721 | 0.422316 | -1.558376 |
| S | -0.077631 | -0.128955 | 1.630058 |
| C | -0.591178 | 1.628585 | 1.557551 |
| H | 0.310868 | 2.242101 | 1.523211 |
| H | -1.160100 | 1.783803 | 0.640593 |
| C | -1.438368 | 1.958055 | 2.777675 |
| H | -0.885463 | 1.796094 | 3.706421 |
| H | -2.343739 | 1.346965 | 2.804269 |
| H | -1.740560 | 3.007499 | 2.743286 |
| C | 3.157426 | -0.617338 | 1.195123 |
| H | 2.725549 | -0.172728 | 2.094120 |
| H | 4.053839 | -0.041678 | 0.939610 |
| C | 3.539365 | -2.076481 | 1.466304 |
| H | 4.286400 | -2.137613 | 2.260850 |
| H | 3.956307 | -2.554394 | 0.575040 |
| H | 2.662211 | -2.650503 | 1.774148 |

Transition state structure **TS2**

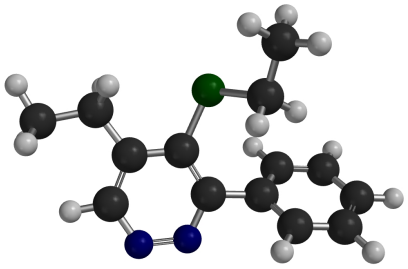


black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1159.913506 hartrees [ωB97X-D/6-311+G(d,p)]
Imaginary frequency: *i* 476 $cm^{-1}$

| | | | |
|---|---|---|---|
| C | 1.211524 | 2.587741 | -0.874015 |
| H | 1.339900 | 3.653467 | -1.019704 |
| N | 0.418044 | 1.992288 | -2.281861 |
| N | 0.315303 | 0.829481 | -2.264900 |
| C | 0.992559 | 0.108880 | -0.830886 |
| N | 2.440997 | 1.870990 | -0.943253 |
| N | 2.330656 | 0.626331 | -0.918884 |
| C | 0.337912 | 2.132697 | 0.204821 |
| C | 0.222388 | 0.787264 | 0.235706 |
| C | 0.947315 | -1.380942 | -0.965266 |
| C | 0.897629 | -4.166369 | -1.120572 |
| C | 0.082419 | -2.018378 | -1.850853 |
| C | 1.792597 | -2.146560 | -0.162752 |
| C | 1.764854 | -3.531475 | -0.236702 |
| C | 0.060335 | -3.407367 | -1.927824 |
| H | -0.562142 | -1.433001 | -2.494477 |
| H | 2.471726 | -1.649988 | 0.520872 |
| H | 2.422667 | -4.116820 | 0.395864 |
| H | -0.609317 | -3.894344 | -2.628208 |
| H | 0.879933 | -5.248727 | -1.182982 |
| S | -0.709616 | -0.110189 | 1.443701 |
| C | -2.225862 | -0.493671 | 0.486324 |
| H | -2.638638 | 0.447472 | 0.117429 |
| H | -1.946601 | -1.115185 | -0.365649 |
| C | -3.221031 | -1.218516 | 1.380943 |
| H | -3.503813 | -0.606594 | 2.241308 |
| H | -2.807700 | -2.160274 | 1.750111 |
| H | -4.127934 | -1.447176 | 0.815752 |
| C | -0.299078 | 3.137022 | 1.116183 |
| H | -1.115198 | 2.654464 | 1.657539 |
| H | -0.733973 | 3.937714 | 0.506995 |
| C | 0.704005 | 3.732536 | 2.110070 |
| H | 1.538027 | 4.216138 | 1.593420 |
| H | 1.115807 | 2.950842 | 2.752831 |
| H | 0.220736 | 4.479523 | 2.744006 |

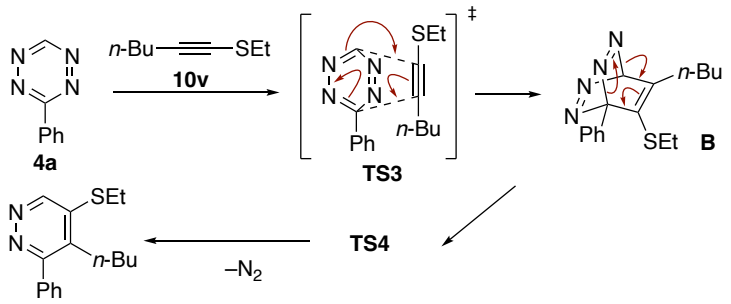
Optimized structure of **12ad**



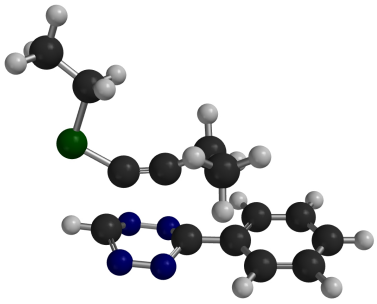
black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1050.502859 hartrees [ωB97X-D/6-311+G(d,p)]

| | | | |
|---|---|---|---|
| C | -0.149889 | 1.006665 | -0.782866 |
| C | 0.788525 | -0.013819 | -0.530375 |
| C | 2.097215 | 0.203692 | -0.964022 |
| C | 2.344672 | 1.449694 | -1.541757 |
| H | 3.335346 | 1.713376 | -1.892999 |
| N | 0.198653 | 2.182098 | -1.311826 |
| N | 1.441401 | 2.410498 | -1.679550 |
| C | -1.603556 | 0.888420 | -0.489063 |
| C | -4.331421 | 0.707157 | 0.062735 |
| C | -2.359128 | -0.157129 | -1.017710 |
| C | -2.228417 | 1.856429 | 0.294016 |
| C | -3.584895 | 1.761355 | 0.576423 |
| C | -3.717472 | -0.246056 | -0.742915 |
| H | -1.882774 | -0.904186 | -1.641865 |
| H | -1.643239 | 2.684404 | 0.677017 |
| H | -4.060708 | 2.514774 | 1.193967 |
| H | -4.298522 | -1.059876 | -1.161854 |
| H | -5.390890 | 0.633294 | 0.280938 |
| C | 3.185309 | -0.826985 | -0.789327 |
| H | 2.893623 | -1.731759 | -1.334004 |
| H | 3.197866 | -1.122350 | 0.264924 |
| C | 4.583369 | -0.404435 | -1.228007 |
| H | 5.287894 | -1.217272 | -1.041161 |
| H | 4.933817 | 0.470948 | -0.674792 |
| H | 4.624784 | -0.172379 | -2.295419 |
| S | 0.406249 | -1.547482 | 0.290013 |
| C | -0.579253 | -1.024078 | 1.746643 |
| H | -0.195949 | -0.058088 | 2.077895 |
| H | -1.621613 | -0.901311 | 1.455262 |
| C | -0.437686 | -2.075669 | 2.838008 |
| H | 0.597854 | -2.170866 | 3.171225 |
| H | -0.778725 | -3.055582 | 2.493864 |
| H | -1.052440 | -1.793483 | 3.696581 |




Transition state structure **TS3**



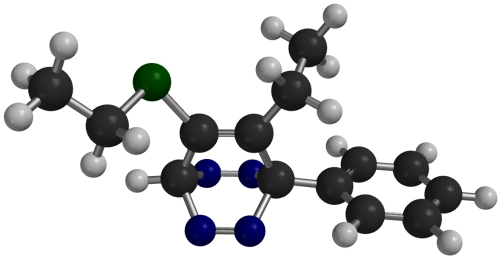
black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1159.835433 hartrees [ωB97X-D/6-311+G(d,p)]; Imaginary frequency: *i* 455 $cm^{-1}$

–1159.854682 hartrees [ωB97X-D/6-311+G(d,p)] (polar solvent); Imaginary frequency: *i* 429 $cm^{-1}$

| | | | |
|---|---|---|---|
| C | -1.849490 | -0.335972 | -0.261801 |
| C | -0.658901 | -0.017735 | -0.398538 |
| N | -0.223667 | -2.243789 | 1.404539 |
| N | -1.488224 | -2.409906 | 1.339325 |
| C | 0.221469 | -0.977877 | 1.670667 |
| C | -2.232402 | -1.265782 | 1.496382 |
| H | -3.305813 | -1.396551 | 1.428674 |
| N | -0.542618 | -0.163690 | 2.457493 |
| N | -1.809631 | -0.328534 | 2.405566 |
| C | 1.676656 | -0.740539 | 1.615169 |
| C | 4.422151 | -0.277720 | 1.451259 |
| C | 2.243892 | 0.358681 | 2.261740 |
| C | 2.495200 | -1.610161 | 0.890790 |
| C | 3.861233 | -1.377500 | 0.810128 |
| C | 3.610729 | 0.586289 | 2.179080 |
| H | 1.607164 | 1.020467 | 2.836007 |
| H | 2.051272 | -2.466879 | 0.397971 |
| H | 4.489932 | -2.057020 | 0.246024 |
| H | 4.044695 | 1.439364 | 2.688310 |
| H | 5.489467 | -0.097152 | 1.387919 |
| C | 0.519323 | 0.678417 | -0.923749 |
| H | 1.430803 | 0.104969 | -0.740712 |
| H | 0.395290 | 0.713545 | -2.013168 |
| S | -3.409356 | -0.345750 | -0.993466 |
| C | -2.999952 | 0.416644 | -2.603927 |
| H | -2.574952 | 1.403831 | -2.411000 |
| H | -2.243294 | -0.206682 | -3.084224 |
| C | -4.256735 | 0.514445 | -3.458048 |
| H | -4.009964 | 0.967283 | -4.421122 |
| H | -5.017565 | 1.136150 | -2.979765 |
| H | -4.687105 | -0.471497 | -3.650180 |
| C | 0.660272 | 2.096985 | -0.362447 |
| H | 1.558189 | 2.572649 | -0.763587 |
| H | 0.739558 | 2.075658 | 0.725329 |
| H | -0.207628 | 2.705360 | -0.626638 |

Optimized structure of **B**

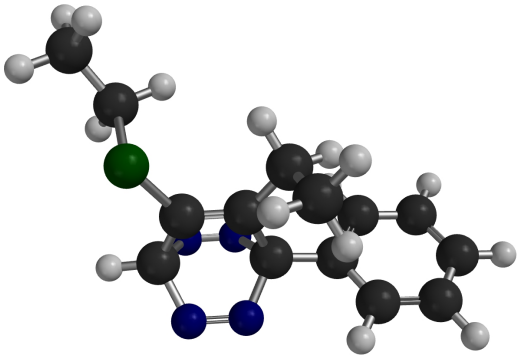


black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1159.917629 hartrees [ωB97X-D/6-311+G(d,p)]
–1159.931843 hartrees [ωB97X-D/6-311+G(d,p)] (polar solvent)

| | | | |
|---|---|---|---|
| C | 2.275112 | -0.072081 | -1.038841 |
| H | 3.356539 | -0.020597 | -1.056432 |
| N | 1.676077 | 1.074255 | -1.798980 |
| N | 0.461956 | 1.010177 | -1.888360 |
| C | -0.149913 | -0.215626 | -1.229491 |
| N | 1.805452 | -1.293399 | -1.783923 |
| N | 0.593273 | -1.365468 | -1.877461 |
| C | 1.623489 | -0.094729 | 0.304995 |
| C | 0.289889 | -0.171939 | 0.216665 |
| C | -1.622773 | -0.286115 | -1.508915 |
| C | -4.377756 | -0.401391 | -1.921370 |
| C | -2.383392 | 0.881290 | -1.501754 |
| C | -2.247041 | -1.510347 | -1.731307 |
| C | -3.620412 | -1.566054 | -1.935780 |
| C | -3.755591 | 0.823185 | -1.706027 |
| H | -1.895839 | 1.836727 | -1.345719 |
| H | -1.654192 | -2.416523 | -1.756520 |
| H | -4.098096 | -2.523414 | -2.110530 |
| H | -4.339103 | 1.736835 | -1.701109 |
| H | -5.448911 | -0.446451 | -2.082821 |
| S | 2.591481 | -0.096471 | 1.776436 |
| C | 3.334741 | 1.575003 | 1.654437 |
| H | 2.531874 | 2.310266 | 1.728249 |
| H | 3.803568 | 1.676651 | 0.673022 |
| C | 4.361032 | 1.766302 | 2.761801 |
| H | 5.169333 | 1.035612 | 2.682566 |
| H | 3.904508 | 1.666566 | 3.749614 |
| H | 4.797756 | 2.765351 | 2.692233 |
| C | -0.688190 | -0.261391 | 1.346743 |
| H | -0.240609 | 0.225170 | 2.217084 |
| H | -1.597123 | 0.288080 | 1.089614 |
| C | -1.045813 | -1.709267 | 1.700830 |
| H | -0.150988 | -2.267436 | 1.987097 |
| H | -1.512889 | -2.220082 | 0.856010 |
| H | -1.747449 | -1.732687 | 2.537945 |

Transition state structure **TS4**

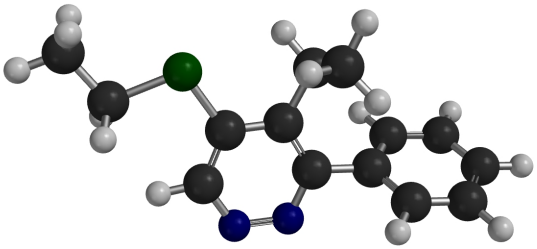


black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1159.91557 hartrees [ωB97X-D/6-311+G(d,p)]
Imaginary frequency: *i* 460 $cm^{-1}$

| | | | |
|---|---|---|---|
| C | 1.070811 | -0.009235 | -0.807119 |
| N | 0.336179 | -0.764819 | -2.196627 |
| N | 0.273360 | -1.928883 | -2.093235 |
| C | 0.897699 | -2.482140 | -0.622309 |
| N | 2.316442 | -0.727322 | -0.778040 |
| N | 2.234621 | -1.968826 | -0.689346 |
| C | 0.169254 | -0.437532 | 0.282700 |
| C | 0.087869 | -1.781863 | 0.376633 |
| S | -0.884854 | -2.683345 | 1.548787 |
| C | -2.429632 | -2.884051 | 0.577220 |
| H | -2.780219 | -1.889308 | 0.294609 |
| H | -2.198589 | -3.440797 | -0.333332 |
| C | -3.469721 | -3.615109 | 1.413850 |
| H | -3.707840 | -3.058946 | 2.324087 |
| H | -3.120609 | -4.609584 | 1.702287 |
| H | -4.391501 | -3.734283 | 0.839242 |
| C | -0.508965 | 0.553145 | 1.183250 |
| H | -1.436489 | 0.110033 | 1.553417 |
| H | -0.772225 | 1.449296 | 0.616719 |
| C | 0.380673 | 0.935798 | 2.372195 |
| H | 1.317617 | 1.385042 | 2.033091 |
| H | 0.619683 | 0.051570 | 2.968661 |
| H | -0.128781 | 1.657746 | 3.014639 |
| H | 0.863764 | -3.563141 | -0.646770 |
| C | 1.234297 | 1.447651 | -1.097399 |
| C | 1.493993 | 4.189494 | -1.537668 |
| C | 2.334577 | 2.138488 | -0.591973 |
| C | 0.268171 | 2.136193 | -1.829979 |
| C | 0.400351 | 3.501179 | -2.052198 |
| C | 2.459893 | 3.505324 | -0.807607 |
| H | 3.091997 | 1.599491 | -0.034883 |
| H | -0.581800 | 1.600627 | -2.237527 |
| H | -0.351197 | 4.026832 | -2.631047 |
| H | 3.315934 | 4.035984 | -0.405304 |
| H | 1.595240 | 5.255291 | -1.709021 |

Optimized structure of **11ad**



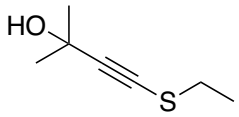
black: carbon, grey: hydrogen, blue: nitrogen, green: sulfur

G = –1050.504477 hartrees [ωB97X-D/6-311+G(d,p)]

| | | | |
|---|---|---|---|
| C | -0.514299 | 1.029153 | -0.607288 |
| C | 0.207076 | -0.094110 | -0.169012 |
| C | 1.588942 | 0.069589 | -0.081109 |
| C | 2.104909 | 1.319773 | -0.438141 |
| H | 3.165699 | 1.533225 | -0.407582 |
| N | 0.048417 | 2.200970 | -0.908246 |
| N | 1.355271 | 2.340367 | -0.824373 |
| C | -1.999525 | 1.008984 | -0.738659 |
| C | -4.779884 | 1.017547 | -0.976845 |
| C | -2.627115 | 0.215832 | -1.697516 |
| C | -2.774616 | 1.816665 | 0.090283 |
| C | -4.158931 | 1.817388 | -0.024936 |
| C | -4.010815 | 0.220919 | -1.817344 |
| H | -2.027748 | -0.395858 | -2.364023 |
| H | -2.285030 | 2.450640 | 0.820915 |
| H | -4.753337 | 2.448087 | 0.626550 |
| H | -4.488815 | -0.393407 | -2.572153 |
| H | -5.860173 | 1.020249 | -1.069039 |
| C | -0.478022 | -1.361669 | 0.274639 |
| H | 0.202100 | -2.208417 | 0.151206 |
| H | -1.342385 | -1.560318 | -0.359019 |
| C | -0.935709 | -1.269021 | 1.735421 |
| H | -0.092107 | -1.062529 | 2.398699 |
| H | -1.396577 | -2.207717 | 2.051235 |
| H | -1.672866 | -0.471319 | 1.856804 |
| S | 2.590631 | -1.272111 | 0.484726 |
| C | 4.284808 | -0.608884 | 0.393690 |
| H | 4.361472 | 0.270269 | 1.036483 |
| H | 4.500128 | -0.316315 | -0.635887 |
| C | 5.255981 | -1.688509 | 0.855675 |
| H | 5.197672 | -2.575859 | 0.221317 |
| H | 5.057241 | -1.988649 | 1.887026 |
| H | 6.277605 | -1.304966 | 0.806503 |

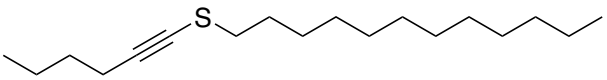
**Characterization Data of New Compounds**

4-(Ethylthio)-2-methylbut-3-yn-2-ol (**10l**)



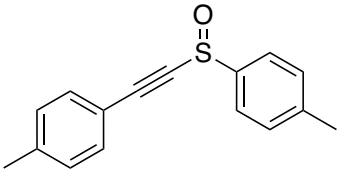
Yellow oil; TLC $R_f$ 0.26 (*n*-hexane/EtOAc = 5/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.38 (t, 3H, *J* = 7.3 Hz), 1.54 (s, 6H), 1.92–2.02 (br, 1H), 2.71 (q, 2H, *J* = 7.3 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 14.5, 29.5, 31.4, 66.0, 72.2, 98.6; IR (NaCl, $cm^{-1}$) 929, 1162, 1222, 2982, 3360; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_7H_{12}NaOS$ 167.0507; Found 167.0508.

Dodecyl hex-1-yn-1-yl sulfide (**10m**)



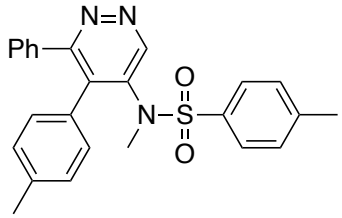
Colorless oil; TLC $R_f$ 0.50 (*n*-hexane only); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.84–0.95 (m, 6H), 1.20–1.58 (m, 22H), 1.66–1.78 (m, 2H), 2.30 (t, 2H, *J* = 6.8 Hz), 2.66 (t, 2H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 13.6, 14.1, 19.8, 21.9, 22.7, 28.3, 29.18, 29.24, 29.4, 29.5, 29.6, 29.66, 29.68, 30.9, 31.9, 35.5, 68.3, 94.2; IR (NaCl, $cm^{-1}$) 1465, 2855, 2926, 2956; HRMS (EI) *m/z*: $[M]^{\cdot+}$ Calcd for $C_{18}H_{34}S^{\cdot+}$ 282.2381; Found 282.2381.

1-Methyl-4-((*p*-tolylethynyl)sulfinyl)benzene (**10s**)



Yellow oil; TLC $R_f$ 0.40 (*n*-hexane/EtOAc = 2/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H), 2.44 (s, 3H), 7.13–7.18 (AA'BB', 2H), 7.34–7.42 (m, 4H), 7.73–7.80 (AA'BB', 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 21.5, 21.7, 85.6, 102.8, 116.7, 125.3, 129.3, 130.2, 132.2, 140.9, 141.3, 142.4; IR (NaCl, $cm^{-1}$) 813, 823, 1046, 1085, 2156; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}OS$ 255.0838; Found 255.0837.

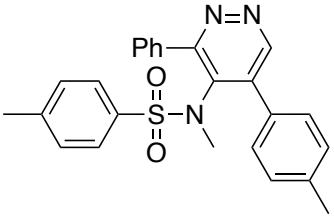
*N*,4-Dimethyl-*N*-(6-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**11a**)



**11a**

The ratio **11a**/**12a** was judged from $^1$H NMR analysis of the crude product. Minor isomer **11a** was obtained with *N*,4-dimethyl-*N*-(3-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**12a**). Yellow solid; Mp 296–298 °C; TLC $R_f$ 0.41 (*n*-hexane/EtOAc = 1/1); For **11a**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H), 2.49 (s, 3H), 2.82 (s, 3H), 6.93–7.02 (m, 4H), 7.05–7.09 (m, 2H), 7.18–7.45 (m, 5H), 7.61–7.64 (m, 2H), 8.88 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 21.3, 21.6, 38.1, 127.7, 127.9, 128.6, 129.3, 129.4, 129.5, 130.0, 130.1, 135.4, 136.5, 138.0, 138.6, 140.0, 144.5, 149.2, 162.2; IR (NaCl, $cm^{-1}$) 1087, 1157, 1345, 1512, 1561, 1671, 1685; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}N_3O_2S$ 430.1584; Found 430.1585.

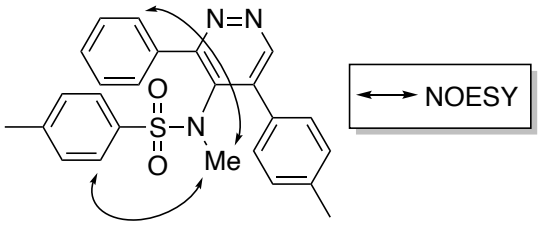
*N*,4-Dimethyl-*N*-(3-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**12a**)



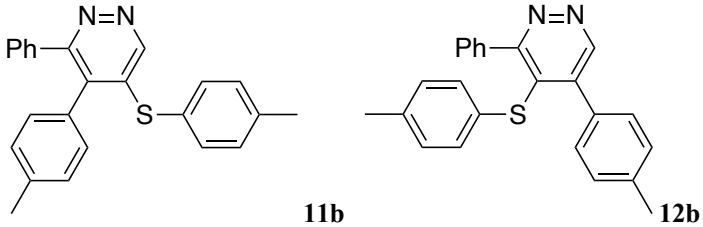
**12a**

An authentic sample of *N*,4-dimethyl-*N*-(3-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**12a**) was obtained by the purification with preparative TLC (dichloromethane/EtOAc = 10/1). Colorless solid; Mp 170–172 °C; TLC $R_f$ 0.30 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 2.42 (s, 3H), 2.83 (s, 3H), 6.92–7.03 (m, 4H), 7.20 (d, 2H, *J* = 8.0 Hz), 7.28–7.46 (m, 5H), 7.57–7.63 (m, 2H), 9.13 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 21.7, 21.8, 38.2, 127.3, 128.8, 129.0, 129.50 (two signals overlapped), 129.54, 129.9, 131.0, 136.3, 136.5, 137.9, 140.0, 140.8, 143.2, 153.1, 162.5; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{23}N_3NaO_2S$ 452.1409; Found 452.1404.

The regiochemistry of **12a** was determined by the NOESY experiments.



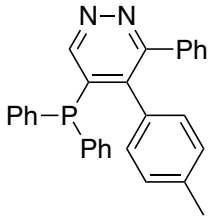

3-Phenyl-4-(*p*-tolyl)-5-(*p*-tolylthio)pyridazine (**11b**) and 3-phenyl-5-(*p*-tolyl)-4-(*p*-tolylthio)pyridazine (**12b**)



**11b** **12b**

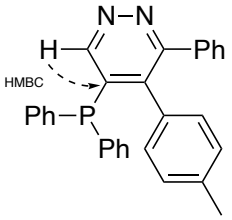
The ratio **11b**/**12b** was judged from $^1$H NMR analysis of the crude product. An inseparable mixture of **11b** and **12b** was obtained. Yellow solid; Mp 188–190 °C; TLC $R_f$ 0.61 (*n*-hexane/EtOAc = 1/1); For **12b**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.40 (s, 3H), 6.50–6.55 (AA'BB', 2H), 6.66–6.72 (AA'BB', 2H), 7.16–7.31 (m, 4H), 7.32–7.39 (m, 3H), 7.52–7.58 (m, 2H), 9.00 (s, 1H); For **11b**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 2.42 (s, 3H), 7.08–7.14 (AA'BB', 2H), 7.16–7.31 (m, 7H), 7.33–7.38 (m, 2H), 7.42–7.47 (AA'BB', 2H), 8.44 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 21.0, 21.3, 21.4, 127.8, 127.9, 128.4, 128.8, 129.0, 129.1, 129.2, 129.4, 130.0, 130.1, 131.1. 131.3, 131.6, 132.5, 134.7, 135.7, 136.7, 137.21, 137.24, 137.4, 139.1, 140.8, 142.6, 143.8, 146.5, 150.3, 157.9, 163.1; IR (NaCl, $cm^{-1}$) 816, 1208, 1490, 1510; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{21}N_2S$ 369.1420; Found 369.1421.

5-(Diphenylphosphaneyl)-3-phenyl-4-(*p*-tolyl)pyridazine (**11c**)

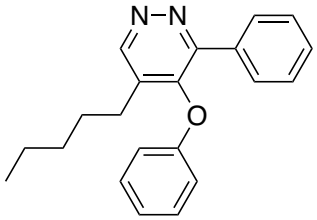


Yellow solid; Mp 165–167 °C; TLC $R_f$ 0.30 (*n*-hexane/EtOAc = 5/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H), 6.70–6.77 (AA'BB', 2H), 6.88–6.95 (AA'BB', 2H), 7.16–7.43 (m, 15H), 8.67 (d, 1H, $J$ = 1.2 Hz); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 21.3, 127.8, 128.4, 128.7, 128.9 (d, $J$ = 7.4 Hz), 129.6, 128.6 (d, $J$ = 2.9 Hz), 130.1, 132.3 (d, $J$ = 5.2 Hz), 134.1 (d, $J$ = 10.1 Hz), 134.2 (d, $J$ = 20.8 Hz), 137.0, 138.2, 139.1 (d, $J$ = 25.1 Hz), 143.9 (d, $J$ = 23.8 Hz), 152.4, 159.5 (d, $J$ = 1.1 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) δ –18.7 (t, $J$ = 7.9 Hz); IR (NaCl, cm$^{-1}$) 1338, 1435, 1487, 2923, 3053; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{29}H_{23}N_2NaP$ 453.1497; Found 453.1498.

The regiochemistry of **11c** was determined by the HMBC experiments.

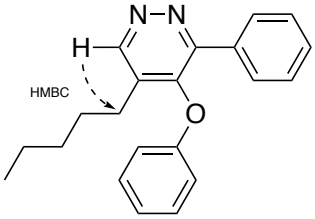


5-Pentyl-4-phenoxy-3-phenylpyridazine (**12d**)

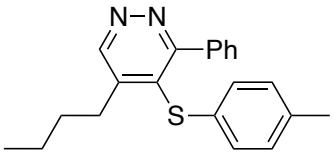


Colorless oil; TLC $R_f$ 0.38 (*n*-hexane/EtOAc = 3/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.81–0.89 (m, 3H), 1.21–1.32 (m, 4H), 1.54–1.67 (m, 2H), 2.56 (t, 2H, $J$ = 7.8 Hz), 6.62–6.70 (m, 2H), 6.92–6.99 (m, 1H), 7.13–7.21 (m, 2H), 7.30–7.40 (m, 3H), 7.78–7.88 (m, 2H), 9.07 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 22.2, 27.3, 28.4, 31.4, 115.4, 122.8, 128.2, 129.2, 129.4, 129.7, 134.0, 135.4, 150.6, 153.1, 156.4 (two signals overlapped); IR (NaCl, cm$^{-1}$) 1201, 1243, 1417, 1488, 2930; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{21}H_{22}N_2NaO$ 341.1630; Found 341.1628.

The regiochemistry of **12d** was determined by the HMBC experiments.

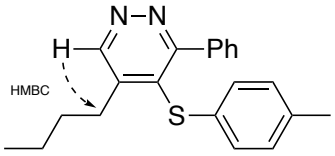


5-Butyl-3-phenyl-4-(*p*-tolylthio)pyridazine (**12f**)

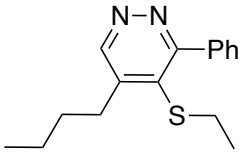


Yellow oil; TLC $R_f$ 0.52 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, 3H, *J* = 7.3 Hz), 1.34–1.46 (m, 2H), 1.56–1.67 (m, 2H), 2.23 (s, 3H), 2.82 (t, 2H, *J* = 7.9 Hz), 6.71 (d, 2H, *J* = 8.0 Hz), 6.87 (d, 2H, *J* = 8.0 Hz), 7.27–7.37 (m, 3H), 7.41–7.48 (m, 2H), 8.98 (s, 1H,); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 21.0, 22.6, 31.7, 31.8, 127.7, 128.6, 129.2, 129.7, 130.0, 130.7, 136.3, 137.0, 137.4, 145.2, 151.1, 163.6; IR (NaCl, $cm^{-1}$) 1265, 1491, 2930, 2959; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2NaS$ 357.1401; Found357.1401.

The regiochemistry of **12f** was determined by the HMBC experiments.

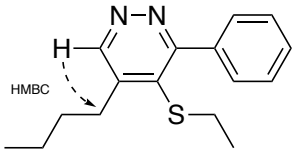


5-Butyl-4-(ethylthio)-3-phenylpyridazine (**12i**)

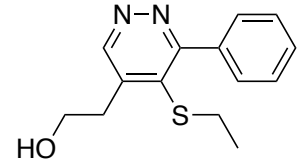


Yellow oil; TLC $R_f$ 0.39 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, 3H, *J* = 7.4 Hz), 0.99 (t, 3H, *J* = 7.3 Hz), 1.40–1.52 (m, 2H), 1.60–1.70 (m, 2H), 2.22 (q, 2H, *J* = 7.4 Hz), 2.90 (t, 2H, *J* = 7.9 Hz), 7.42–7.52 (m, 3H), 7.77–7.83 (m, 2H), 8.89 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 14.6, 22.5, 28.2, 31.7, 32.1, 128.3, 128.9, 129.0, 136.1, 137.9, 145.3, 150.4, 162.3; IR (NaCl, $cm^{-1}$) 1344, 1391, 1448, 2870, 2929, 2959; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaS$ 295.1245; Found 295.1239.

The regiochemistry of **12i** was determined by the HMBC experiments.

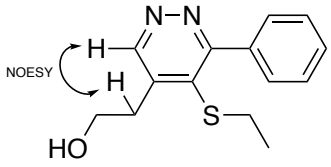


2-(5-(Ethylthio)-6-phenylpyridazin-4-yl)ethan-1-ol (**12j**)

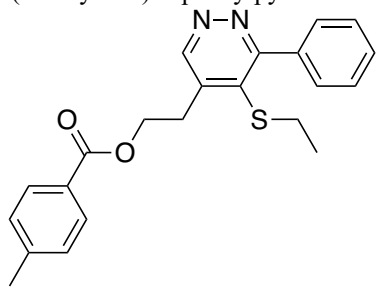


Yellow oil; TLC $R_f$ 0.48 (EtOAc only); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, 3H, *J* = 7.4 Hz), 2.22 (q, 2H, *J* = 7.4 Hz), 3.17 (t, 2H, *J* = 6.4 Hz), 3.94 (t, 2H, *J* = 6.4 Hz), 7.44–7.53 (m, 3H), 7.76–7.83 (m, 2H), 8.92 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 14.6, 28.4, 35.1, 61.5, 128.3, 129.0, 129.1, 137.2, 137.5, 142.4, 150.8, 162.3; IR (NaCl, $cm^{-1}$) 1025, 1053, 1391, 1447, 3307, 3325, 3335; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{16}N_2NaOS$ 283.0881; Found 283.0881.

The regiochemistry of **12j** was determined by the NOESY experiments.

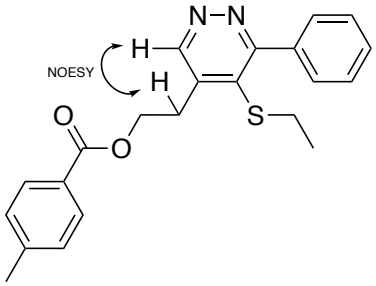



2-(5-Ethylthio)-6-phenylpyridazin-4-yl)ethyl 4-methylbenzoate (**12k**)

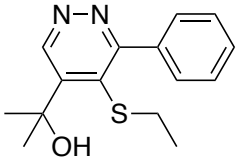



Yellow oil; TLC $R_f$ 0.48 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, 3H, *J* = 7.4 Hz), 2.24 (q, 2H, *J* = 7.4 Hz), 2.41 (s, 3H), 3.40 (t, 2H, *J* = 6.4 Hz), 4.62 (t, 2H, *J* = 6.4 Hz), 7.21–7.26 (AA'BB', 2H), 7.44–7.53 (m, 3H), 7.77–7.84 (AA'BB'C, 2H), 7.87–7.93 (AA'BB', 2H), 9.01 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 14.7, 21.7, 28.3, 31.4, 63.0, 126.8, 128.4, 128.9, 129.1, 129.2, 129.6, 137.0, 137.5, 141.0, 144.0, 150.7, 162.5, 166.3; IR (NaCl, $cm^{-1}$) 1109, 1177, 1273, 1716, 1720; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{22}N_2NaO_2S$ 401.1292; Found 401.1300.

The regiochemistry of **12k** was determined by the NOESY experiments.

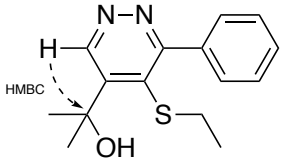



2-(5-Ethylthio)-6-phenylpyridazin-4-yl)propan-2-ol (**12l**)

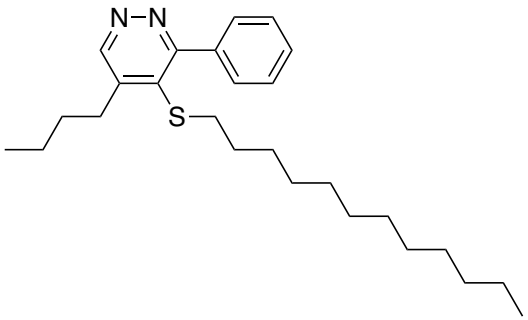



Yellow oil; TLC $R_f$ 0.34 (*n*-hexane/EtOAc = 1/2); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, 3H, *J* = 7.4 Hz), 1.79 (s, 6H), 2.24 (q, 2H, *J* = 7.4 Hz), 4.24–4.39 (br, 1H), 7.43–7.54 (m, 3H), 7.77–7.84 (m, 2H), 9.24 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 14.3, 29.1, 30.3, 72.8, 128.4, 129.1 (two signals overlapped), 134.1, 137.6, 147.0, 149.1, 163.4; IR (NaCl, $cm^{-1}$) 1189, 1343, 1358, 1376, 1447, 3308, 3320; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{18}N_2NaOS$ 297.1038; Found 297.1038.

The regiochemistry of **12l** was determined by the HMBC experiments.

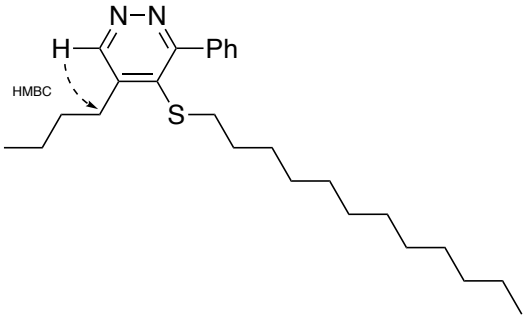



5-Butyl-4-(dodecylthio)-3-phenylpyridazine (**12m**)

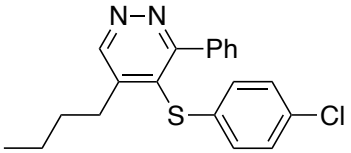



Yellow oil; TLC $R_f$ 0.40 (*n*-hexane/EtOAc = 2/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, 3H, $J$ = 7.0 Hz), 0.98 (t, 3H, $J$ = 7.4 Hz), 1.12–1.34 (m, 20H), 1.39–1.51 (m, 2H), 1.59–1.70 (m, 2H), 2.17 (t, 2H, $J$ = 7.4 Hz), 2.87 (t, 2H, $J$ = 7.8 Hz), 7.42–7.52 (m, 3H), 7.76–7.82 (m, 2H), 8.87 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.9, 14.1, 22.6, 22.7, 28.3, 28.9, 29.3, 29.35, 29.42, 29.5, 29.58, 29.61, 31.8, 31.9, 32.2, 34.1, 128.3, 128.7, 129.1, 136.7, 137.9, 145.2, 150.4, 162.4; IR (NaCl, cm$^{-1}$) 1464, 2855, 2925, 2956; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{40}N_2NaS$ 435.2810; Found 435.2810.

The regiochemistry of **12m** was determined by the HMBC experiments.

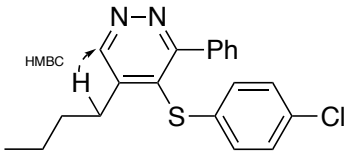



5-Butyl-4-((4-chlorophenyl)thio)-3-phenylpyridazine (**12n**)

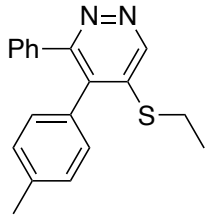



Colorless oil; TLC $R_f$ 0.45 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, 3H, $J$ = 7.4 Hz),1.35–1.47 (m, 2H), 1.59–1.70 (m, 2H), 2.86 (t, 2H, $J$ = 8.0 Hz), 6.66–6.76 (AA'BB', 2H), 6.98–7.05 (AA'BB', 2H), 7.27–7.46 (m, 5H), 9.02 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 22.6, 31.8, 32.0, 127.9, 128.8, 129.10, 129.13, 131.2, 132.7, 133.1, 135.6, 137.3, 145.3, 151.2, 163.4; IR (NaCl, cm$^{-1}$) 1012, 1090, 1475, 2929, 2958; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{19}ClN_2NaS$ 377.0855; Found 377.0854.

The regiochemistry of **12n** was determined by the HMBC experiments.

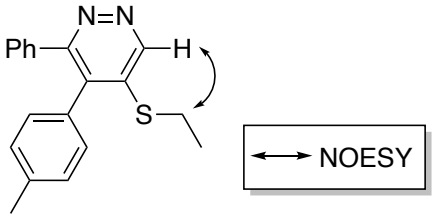



5-(Ethylthio)-3-phenyl-4-(*p*-tolyl)pyridazine (**11o**)

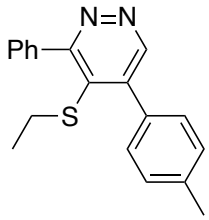



Colorless solid; Mp 134–136 °C; TLC $R_f$ 0.40 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.39 (t, 3H, $J$ = 7.4 Hz), 2.35 (s, 3H), 3.04 (q, 2H, $J$ = 7.4 Hz), 6.98–7.03 (AA'BB', 2H), 7.13–7.17 (AA'BB', 2H), 7.20–7.30 (m, 3H), 7.32–7.36 (AA'BB', 2H), 9.05 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.4, 21.4, 25.3, 127.8, 128.3, 129.3, 129.4, 130.0, 131.3, 135.9, 136.8, 138.6, 142.0, 145.4, 158.0; IR (NaCl, cm$^{-1}$) 1417, 1472, 1688, 1717, 1762, 1800, 1888, 1917; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2S$ 307.1263; Found 307.1264.

The regiochemistry of **11o** was determined by the NOESY experiments.

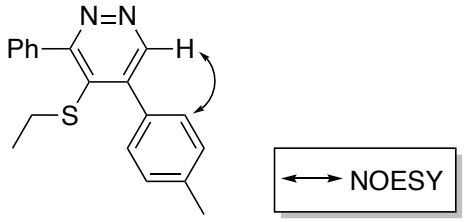



4-(Ethylthio)-3-phenyl-5-(*p*-tolyl)pyridazine (**12o**)

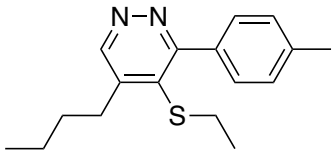



Yellow oil; TLC $R_f$ 0.55 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.80 (t, 3H, $J$ = 7.3 Hz), 2.08 (q, 2H, $J$ = 7.3 Hz), 2.45 (s, 3H), 7.31–7.36 (AA'BB', 2H), 7.45–7.56 (m, 5H), 7.77–7.82 (AA'BB', 2H), 8.92 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 14.3, 21.4, 28.3, 128.3, 128.8, 129.2, 129.4, 129.6, 132.9, 135.6, 137.6, 139.4, 142.1, 149.8, 162.7; IR (NaCl, cm$^{-1}$) 819, 995, 1055, 1264, 1304, 1727, 2926; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2S$ 307.1263; Found 307.1265.

The regiochemistry of **12o** was determined by the NOESY experiments.

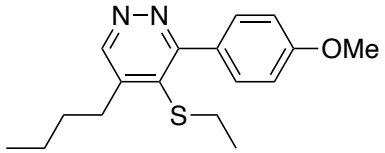



5-Butyl-4-(ethylthio)-3-(*p*-tolyl)pyridazine (**12p**)



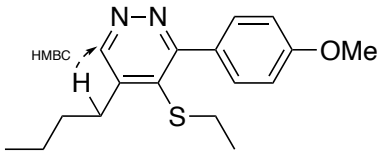

Yellow oil; TLC $R_f$ 0.45 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, 3H, $J$ = 7.4 Hz), 0.98 (t, 3H, $J$ = 7.3 Hz), 1.39–1.51 (m, 2H), 1.60–1.70 (m, 2H), 2.24 (q, 2H, $J$ = 7.4 Hz), 2.43 (s, 3H), 2.89 (t, 2H, $J$ = 7.8 Hz), 7.28 (d, 2H, $J$ = 8.6 Hz), 7.70 (d, 2H, $J$ = 8.1 Hz), 8.86 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 14.7, 21.4, 22.5, 28.2, 31.7, 32.1, 128.9, 129.0, 135.0, 136.0, 138.9, 145.3, 150.2, 162.3; IR (NaCl, cm$^{-1}$) 823, 1342, 1387, 1452, 2870, 2928, 2958; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{17}H_{22}N_2NaS$ 309.1401; Found 309.1399.

5-Butyl-4-(ethylthio)-3-(4-methoxyphenyl)pyridazine (**12q**)

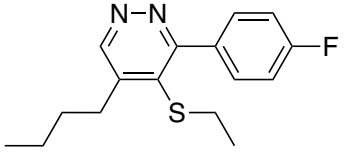



Yellow oil; TLC $R_f$ 0.20 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, 3H, $J$ = 7.4 Hz), 0.98 (t, 3H, $J$ = 7.3 Hz), 1.39─1.51 (m, 2H), 1.59–1.70 (m, 2H), 2.27 (q, 2H, $J$ = 7.4 Hz), 2.89 (t, 2H, $J$ = 7.8 Hz), 3.88 (s, 3H), 7.00 (d, 2H, $J$ = 8.7 Hz), 7.80 (d, 2H, $J$ = 8.8 Hz), 8.85 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 14.7, 22.6, 28.1, 31.7, 32.1, 55.3, 113.7, 130.2, 130.4, 135.9, 145.3, 150.1, 160.1 (two signals overlapped); IR (NaCl, cm$^{-1}$) 834, 1033, 1176, 1251, 1515, 1608, 2959; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{17}H_{22}N_2NaOS$ 325.1351; Found 325.1350.

The regiochemistry of **12q** was determined by the HMBC experiments.

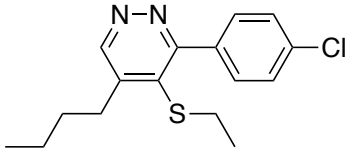



5-Butyl-4-(ethylthio)-3-(4-fluorophenyl)pyridazine (**12r**)



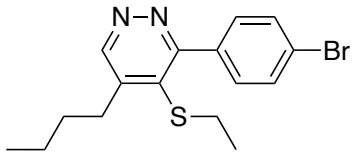

Yellow oil; TLC $R_f$ 0.50 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, 3H, $J$ = 7.4 Hz), 0.99 (t, 3H, $J$ = 7.3 Hz), 1.60–1.70 (m, 2H), 1.60–1.70 (m, 2H), 2.26 (q, 2H, $J$ = 7.4 Hz), 2.90 (t, 2H, $J$ = 7.8 Hz), 7.18 (t, 2H, $J$ = 8.6 Hz), 7.79–7.87 (m, 2H), 8.90 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 14.6, 22.5, 28.4, 31.7, 32.2, 115.4 (d, $J$ = 21.7 Hz), 131.0, 131.1 (d, $J$ = 8.3 Hz), 133.8 (d, $J$ = 3.4 Hz), 136.0, 145.6, 150.5, 163.1 (d, $J$ = 250 Hz); IR (NaCl, cm$^{-1}$) 840, 1225, 1512, 2930, 2960; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{19}FN_2NaS$ 313.1151; Found 313.1149.

5-Butyl-3-(4-chlorophenyl)-4-(ethylthio)pyridazine (**12s**)



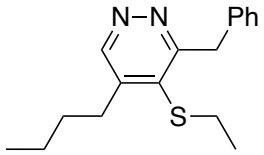
Yellow oil; TLC $R_f$ 0.40 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.90–1.04 (m, 6H) ,1.40–1.51 (m, 2H), 1.60–1.70 (m, 2H), 2.27 (q, 2H, *J* = 7.4 Hz), 2.90 (t, 2H, *J* = 7.8 Hz), 7.46 (d, 2H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 8.4 Hz), 8.90 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 14.6, 22.5, 28.5, 31.7, 32.1, 128.5, 130.5, 135.1, 136.0, 136.2, 145.7, 150.6, 161.4; IR (NaCl, cm$^{-1}$) 833, 1016, 1090, 1382, 1492, 2929, 2959; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{19}ClN_2NaS$ 329.0855; Found 329.0812.

3-(4-Bromophenyl)-5-butyl-4-(ethylthio)pyridazine (**12t**)



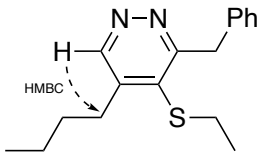
Yellow oil; TLC $R_f$ 0.43 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.90–1.13 (m, 6H), 1.40–1.51 (m, 2H), 1.60–1.70 (m, 2H), 2.27 (q, 2H, *J* = 7.6 Hz), 2.90 (t, 2H, *J* = 7.8 Hz), 7.59–7.65 (AA'BB', 2H), 7.69–7.76 (AA'BB', 2H), 8.90 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 14.6, 22.5, 28.5, 31.7, 32.1, 123.4, 130.7, 131.5, 136.0, 136.7, 145.7, 150.6, 161.4; IR (NaCl, cm$^{-1}$) 830, 1012, 1265, 2930, 2960; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{19}BrN_2Na$ 373.0354; Found 373.0350.

3-Benzyl-5-butyl-4-(ethylthio)pyridazine (**12u**)

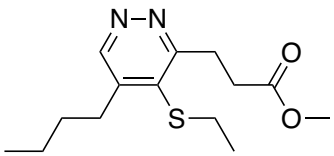


Brown oil; TLC $R_f$ 0.40 (*n*-hexane/EtOAc = 2/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, 3H, *J* = 7.3 Hz), 1.09 (t, 3H, *J* = 7.4 Hz), 1.34–1.47 (m, 2H), 1.55–1.68 (m, 2H), 2.51(q, 2H, *J* = 7.4 Hz), 2.86 (t, 2H, *J* = 7.9 Hz), 4.62 (s, 2H), 7.15–7.30 (m, 3H), 7.33 (d, 2H, *J* = 7.4 Hz), 8.91 (s, 1H),; $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.8, 14.9, 22.6, 30.5, 31.3, 32.1, 41.0, 126.4, 128.3, 129.1, 136.3, 138.7, 146.4, 150.9, 165.2; IR (NaCl, cm$^{-1}$) 1454, 1494, 2870, 2829, 2959; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaS$ 309.1401; Found 309.1401.

The regiochemistry of **12u** was determined by the HMBC experiments.



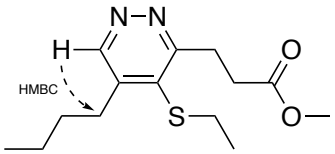
Methyl 3-(5-butyl-4-(ethylthio)pyridazin-3-yl)propanoate (**12v**)



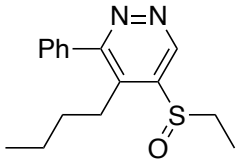
Orange oil; TLC $R_f$ 0.30 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, 3H, *J* = 7.4 Hz), 1.23 (t, 3H, *J* = 7.4 Hz), 1.35–1.45 (m, 2H), 1.55–1.67 (m, 2H), 2.81 (q, 2H, *J* = 7.4 Hz), 2.88 (t, 2H, *J* = 8.0 Hz), 3.00

(t, 2H, $J$ = 7.4 Hz), 3.53 (t, 2H, $J$ = 7.4 Hz), 3.67 (s, 3H), 8.88 (s, 1H),; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): δ 13.8, 15.0, 22.6, 29.4, 30.1, 31.5, 31.9, 32.3, 51.7, 135.9, 146.1, 150.9, 163.7, 173.6; IR (NaCl, $cm^{-1}$) 1169, 1195, 1733, 1739, 2930, 2958; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{22}N_2NaOS$ 305.1300; Found 305.1296.

The regiochemistry of **12v** was determined by the HMBC experiments.

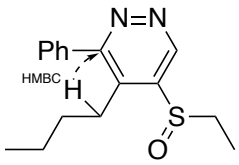



4-Butyl-5-(ethylsulfinyl)-3-phenylpyridazine (**11x**)

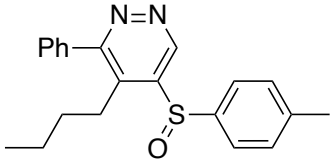



Colorless solid; Mp 95–97 °C; TLC $R_f$ 0.20 (*n*-hexane/EtOAc = 1/1); $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.74 (t, 3H, $J$ = 7.2 Hz), 1.10─1.50 (m, 7H), 2.52–2.84 (m, 2H), 2.86–3.15 (m, 2H), 7.50–7.64 (m, 5H), 9.56 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): δ 6.5, 13.3, 22.6, 28.1, 31.7, 49.4, 128.7, 129.0, 129.4, 136.2, 137.0, 143.2, 145.0, 161.9; IR (NaCl, $cm^{-1}$) 1009, 1026, 1047, 1057, 1397, 2932, 2959; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2OS$ 289.1369; Found 289.1370.

The regiochemistry of **11x** was determined by the HMBC experiments.

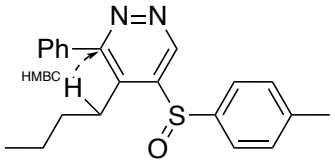



4-Butyl-3-phenyl-5-(p-tolylsulfinyl)pyridazine (**11y**)

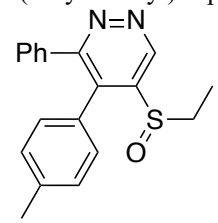



Red oil; TLC $R_f$ 0.41 (*n*-hexane/EtOAc = 1/1); $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.68 (t, 3H, $J$ = 7.2 Hz), 1.07–1.38 (m, 4H), 2.42 (s, 3H), 2.65–2.77 (m, 2H), 7.34 (d, 2H, $J$ = 8.0 Hz), 7.44–7.51 (m, 5H), 7.58 (d, 2H, $J$ = 8.0 Hz), 9.61 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): δ 13.3, 21.6, 22.7, 28.3, 31.1, 126.3, 128.6, 129.0, 129.3, 130.7, 136.2, 137.4, 139.6, 143.5, 144.7 (two signals overlapped), 162.2; IR (NaCl, $cm^{-1}$) 808, 1053, 1082, 1090, 1261; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2NaOS$ 373.1351; Found 373.1352.

The regiochemistry of **11y** was determined by the HMBC experiments.

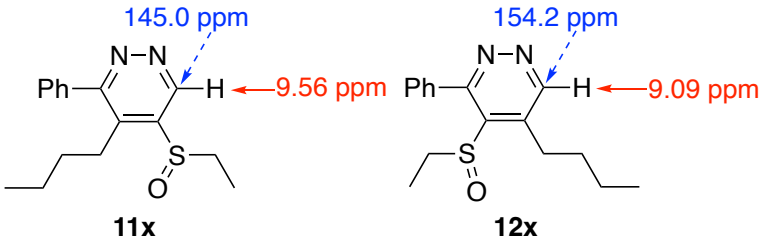


5-(Ethylsulfinyl)-3-phenyl-4-(*p*-tolyl)pyridazine (**11z**)



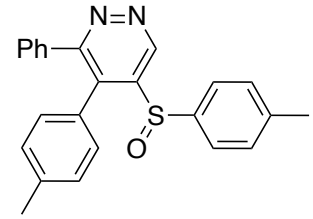
Brown oil; TLC $R_f$ 0.16 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 1.06 (t, 3H, *J* = 7.4 Hz), 2.23–2.35 (m, 1H), 2.37 (s, 3H), 2.54–2.66 (m, 1H), 6.75–7.14 (br, 2H), 7.14–7.24 (m, 2H), 7.25–7.30 (AA'BB'C, 2H), 7.30–7.33 (AA'BB'C, 1H), 7.35–7.40 (m, 2H), 9.68 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 5.6, 21.4, 45.8, 128.2, 128.9, 129.0, 130.0, 130.1, 135.7, 135.8, 139.9 (two signals overlapped), 143.2, 145.2, 159.0; IR (NaCl, $cm^{-1}$) 1029, 1062, 1109, 2933, 2978, 3058; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}N_2OS$ 323.1213; Found 323.1207.

According to the 1H and 13C NMR analyses of sulfinyl-substituted pyridazines **11x** and **12x**, the regiochemistry of **11z** was determined as a 5-sulfinylpyridazine. Significant low field shift of the proton next to the sulfinyl group clearly shows the regiochemistry.



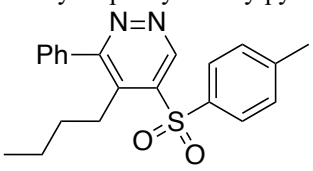

**11x** **12x**

3-Phenyl-4-(p-tolyl)-5-(p-tolylsulfinyl) pyridazine (**11aa**)



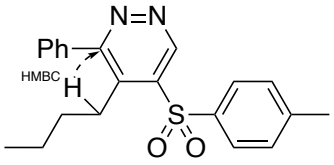
Colorless solid; Mp 140–142°C; TLC *R*$_f$ 0.55 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ2.29 (s, 3H), 2.39 (s, 3H), 6.92 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 7.18–7.35 (m, 9H), 9.87 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 21.40, 21.44, 125.8, 128.0, 128.9, 129.2, 129.5, 129.6, 129.9, 130.1, 135.6, 136.2, 139.1, 139.6, 142.7, 144.0, 145.9, 159.4; IR (NaCl, $cm^{-1}$) 1055, 1080, 1398, 1492, 1508, 1640; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{21}N_2OS$ 385.1369; Found 385.1365.

4-Butyl-3-phenyl-5-tosylpyridazine (**11ab**)

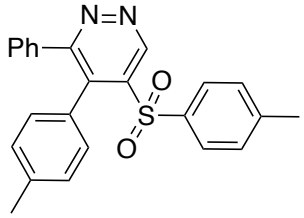


Yellow solid; Mp 147–150 °C; TLC *R*$_f$ 0.53 (*n*-hexane/EtOAc = 2/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.60 (t, 3H, *J* = 7.0 Hz), 0.95–1.16 (m, 4H), 2.47 (s, 3H), 2.95 (t, 2H, *J* = 8.0 Hz), 7.37–7.51 (m, 7H), 7.85 (d, 2H, *J* = 8.4 Hz), 9.53 (s, 1H) ; $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 13.2, 21.8, 22.9, 28.3, 31.5, 128.4, 128.6, 128.9, 129.3, 130.4, 136.0, 136.6, 139.4, 139.5, 146.0, 146.7, 164.8; IR (NaCl, $cm^{-1}$) 1100, 1153, 1324, 1348, 2959; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_2NaO_2S$ 389.1300; Found 389.1296.

The regiochemistry of **11ab** was determined by the HMBC experiments.

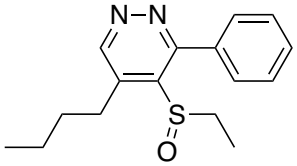



3-Phenyl-4-(*p*-tolyl)-5-tosylpyridazine (**11ac**)



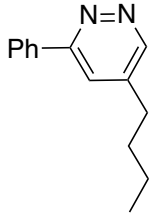

Colorless solid; Mp 148-150 °C; TLC $R_f$ 0.51 (*n*-hexane/EtOAc = 2/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H), 2.34 (s, 3H), 6.71 (d, 2H, *J* = 8.4 Hz), 6.94 (d, 2H, *J* = 8.0 Hz), 7.02 (d, 2H, *J* = 8.4 Hz), 7.10–7.28 (m, 7H), 9.93(s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 21.4, 21.6, 127.9, 128.2, 128.3, 128.4, 128.8, 129.3, 130.0, 130.2, 135.65, 135.73, 137.5, 139.0, 139.9, 145.0, 146.1, 162.5; IR (NaCl, cm$^{-1}$) 1083, 1110, 1155, 1306, 1322, 1342; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{20}N_2NaO_2S$ 423.1143; Found 423.1144.

5-Butyl-4-(ethylsulfinyl)-3-phenylpyridazine (**12x**)



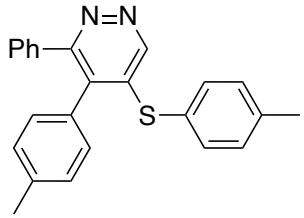

Red oil; TLC $R_f$ 0.25 (*n*-hexane/EtOAc = 1/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, 3H, *J* = 7.2 Hz), 1.18 (t, 3H, *J* = 7.4 Hz),1.43–1.88 (m, 4H), 2.72–2.85 (m, 1H), 2.90–3.13 (m, 2H), 3.42–3.53 (m, 1H), 7.45–7.60 (m, 5H), 9.09 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 7.8, 13.9, 22.9, 28.2, 33.7, 47.7, 128.6, 129.7, 129.8, 135.2, 140.0, 144.0, 154.2, 158.4; IR (NaCl, cm$^{-1}$) 1019, 1027, 1065, 1092, 1348, 1447, 1545, 2872, 2932, 2959; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2NaOS$ 311.1192; Found 311.1194.

5-Butyl-3-phenylpyridazine (**13**)




Colorless solid; Mp 61−63 °C;TLC $R_f$ 0.42 (*n*-hexane/EtOAc = 2/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.40 (t, 3H, *J* = 7.4 Hz), 1.38–1.50 (m, 2H), 1.64–1.77 (m, 2H), 2.72 (t, 2H, *J* = 7.8 Hz), 7.47–7.60 (m, 3H), 7.67 (d, 1H, *J* = 2.0 Hz), 8.04–8.15 (m, 2H), 9.03 (d, 1H, *J* = 2.0 Hz); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 14.1, 22.6, 32.3, 32.9, 123.8, 127.5, 129.3, 130.2, 137.0, 142.6, 151.6, 159.3; IR (NaCl, cm$^{-1}$) 1376, 1414, 1455, 1594, 2930, 2958; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{17}N_2$ 213.1386; Found 213.1386.

3-Phenyl-4-(p-tolyl)-5-(p-tolylthio)pyridazine (**11b**)



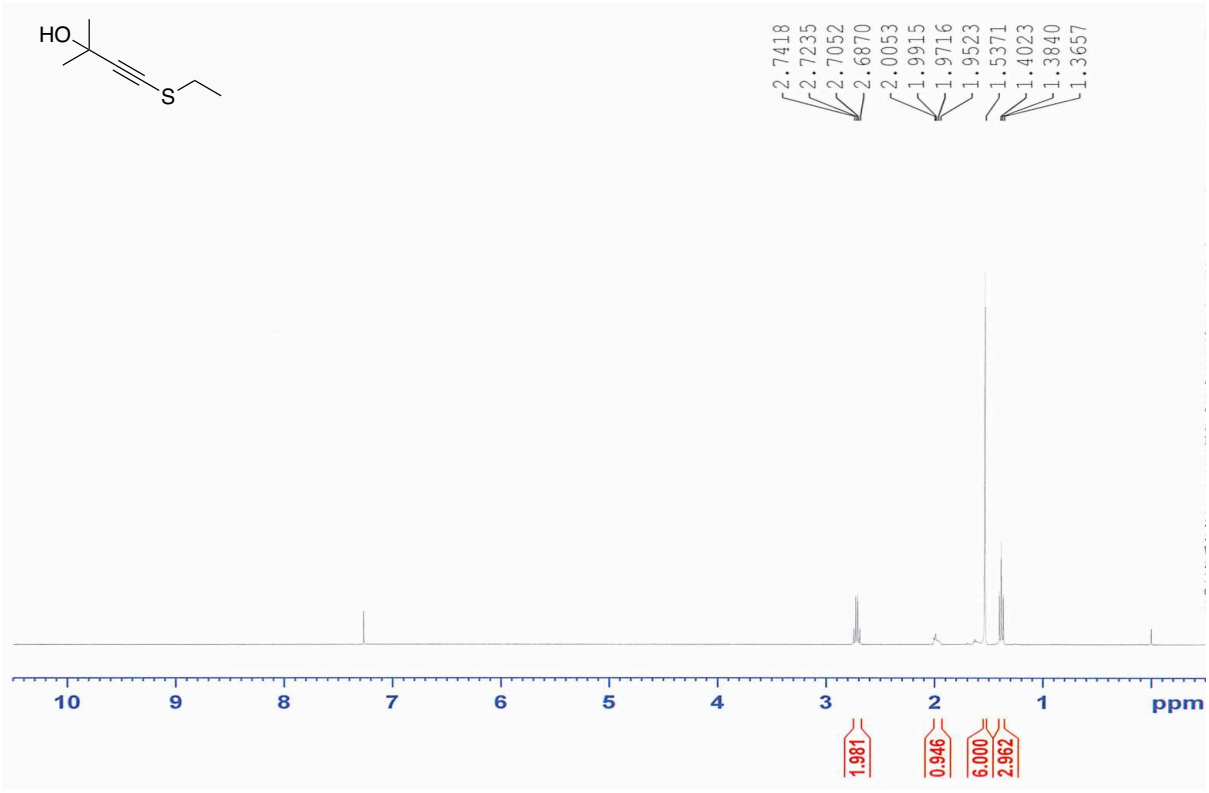

Yellow solid; Mp 188–190 °C; TLC $R_f$ 0.28 (*n*-hexane/EtOAc = 2/1); $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H), 2.41 (s, 3H), 7.07–7.13 (AA'BB', 2H), 7.15–7.31 (m, 7H), 7.32–7.39 (m, 2H), 7.40–7.47 (AA'BB', 2H), 8.45 (s, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz): δ 21.3, 21.4, 124.6, 127.9, 128.4, 129.4, 129.5, 130.1, 131.2, 131.4, 134.8, 135.7, 136.9, 138.8, 140.8, 143.8, 146.6, 158.0; IR (NaCl, cm$^{-1}$) 807, 816, 1208, 1490, 1508; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{21}N_2S$ 369.1420; Found 369.1421.

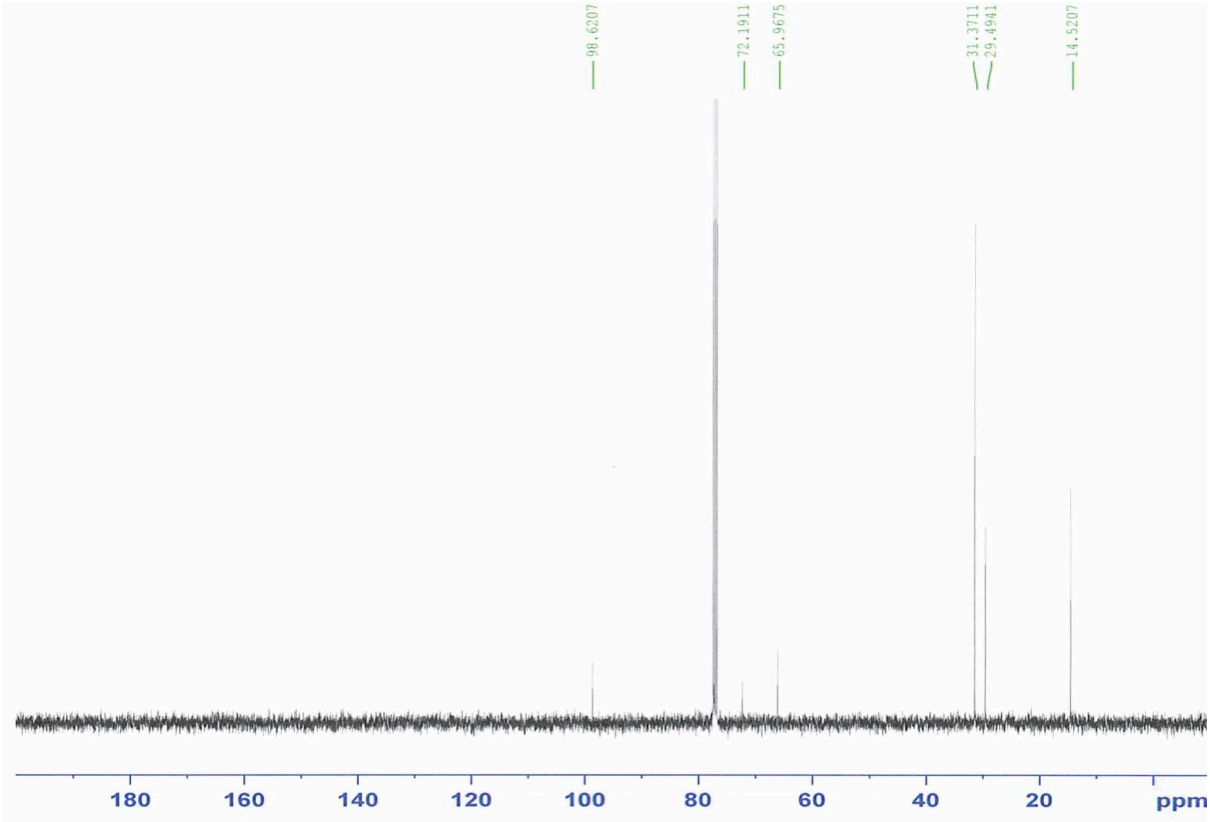
**References for the Electronic Supplementary Information**


S1 C. Yamamoto, M. Suzuki, S. Yoshida, *Bull. Chem. Soc. Jpn.* **2022**, *95*, 1741.
S2 Y. Xie, Y. Fang, Z. Huang, A. M. Tallon, C. W. am Ende, J. M. Fox, *Angew. Chem., Int. Ed.* **2020**, *59*, 16967.
S3 X. Zeng, Y. Tu, Z. Zhang, C. You, J. Wu, Z. Ye, J. Zhao, *J. Org. Chem*. **2019**, *84*, 4458.
S4 V. V. Afanasiev, I. P. Beletskaya, M. A. Kazankova, I. V. Efimova, M. U. Antipin, *Synthesis* **2003**, *18*, 2835.
S5 L. Hu, Q. Gui, X. Chen, Z. Tan, G. Zhu, *J. Org. Chem*. **2016**, *81*, 4861.
S6 N. Saito, K. Saito, M. Shiro, Y. Sato, *Org. lett*. **2011**, *13*, 2719.
S7 H. Hao, T. Bagnol, M. Pucheault, L. L. Shafer, *Org. Lett*. **2021**, *23*, 1974.
S8 X. Zhao, C. Fan, J. He, Y. Luo, *Org. Lett.* **2022**, *24*, 9169.
S9 A. Kobayashi, T. Matsuzawa, T. Hosoya, S. Yoshida, *RSC Adv.* **2023**, *13*, 839.
S10 N. Riddell, W. Tam, *J. Org. Chem.* **2006**, *71*, 1934.

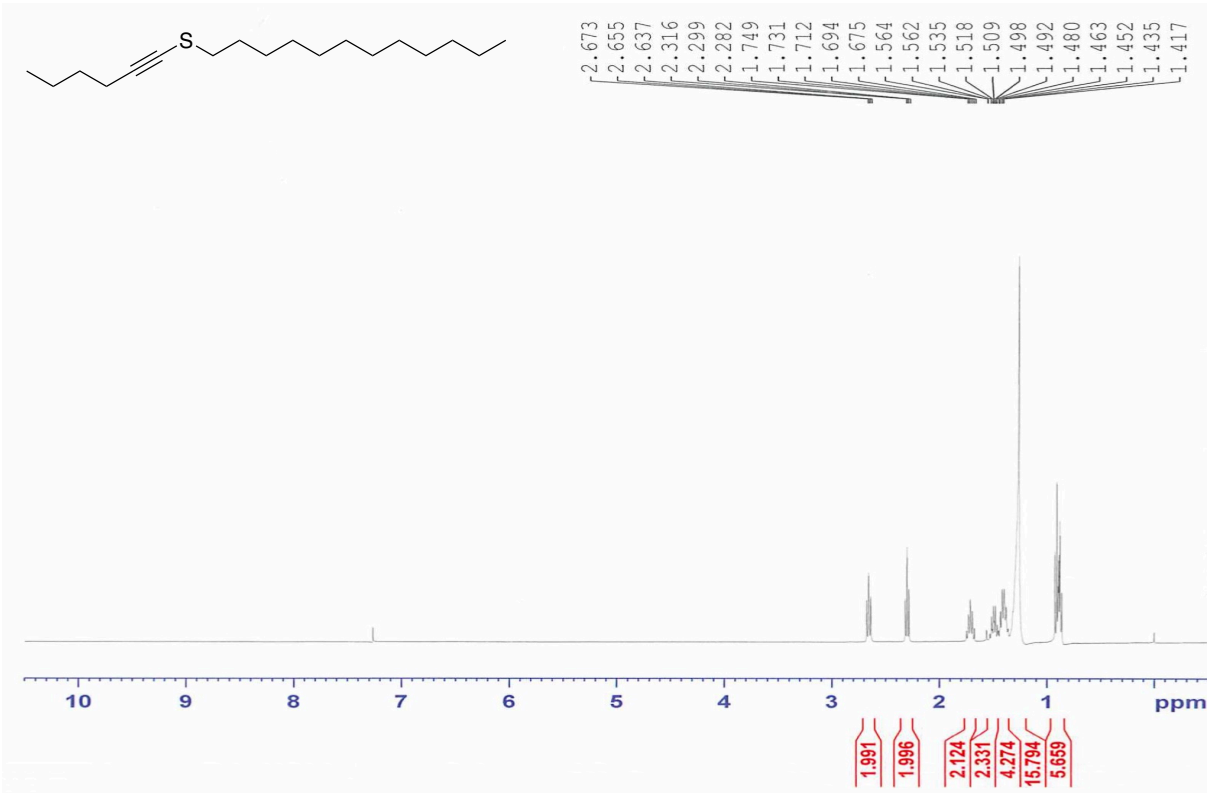
**H and $^{13}$C NMR Spectra of Compounds**

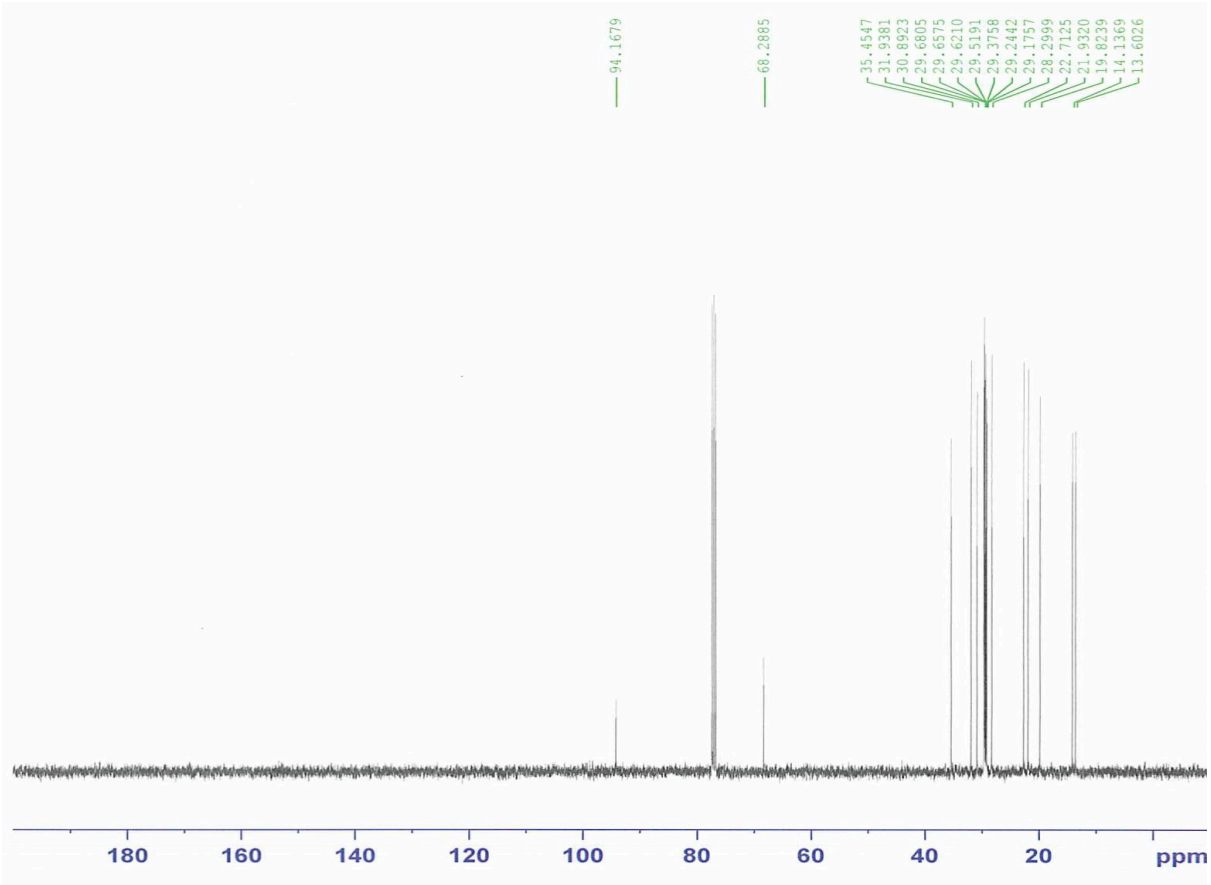
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 4-(ethylthio)-2-methylbut-3-yn-2-ol (**10l**) ($CDCl_3$)



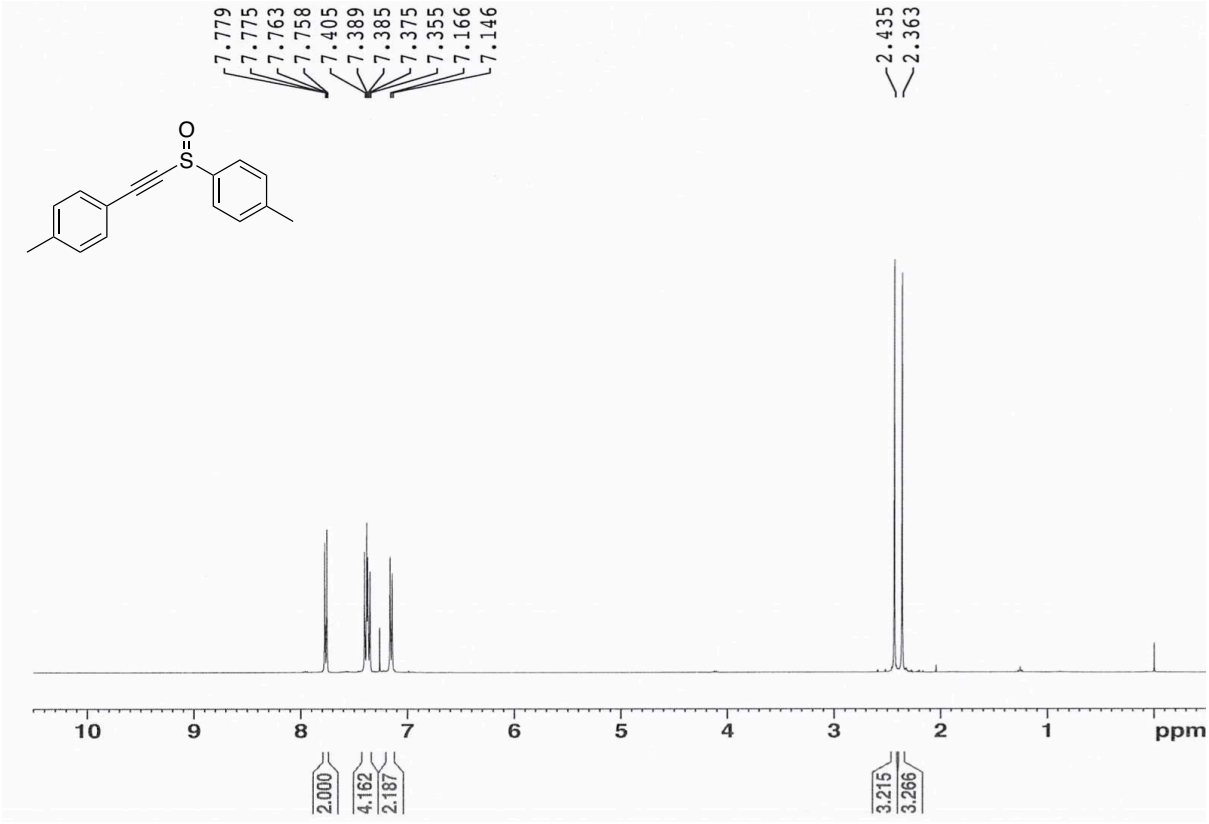



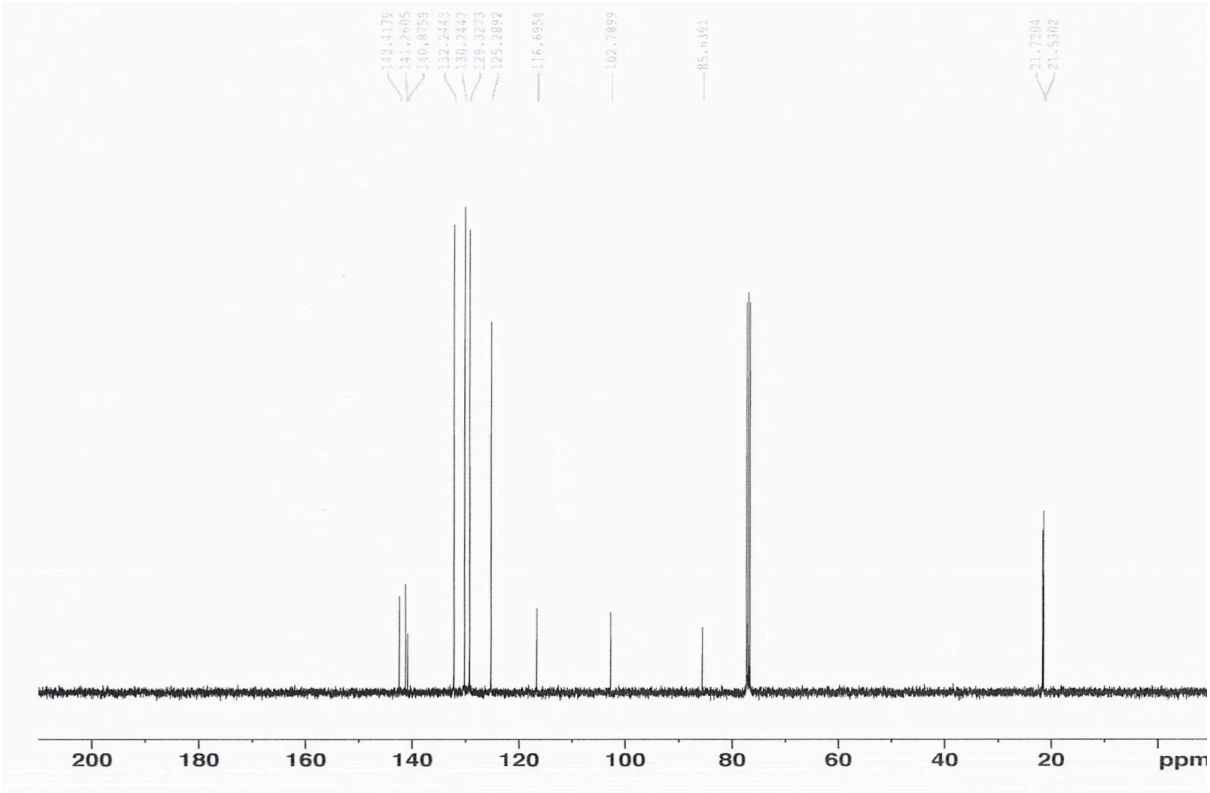
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of dodecyl hex-1-yn-1-yl sulfide (**10m**) ($CDCl_3$)



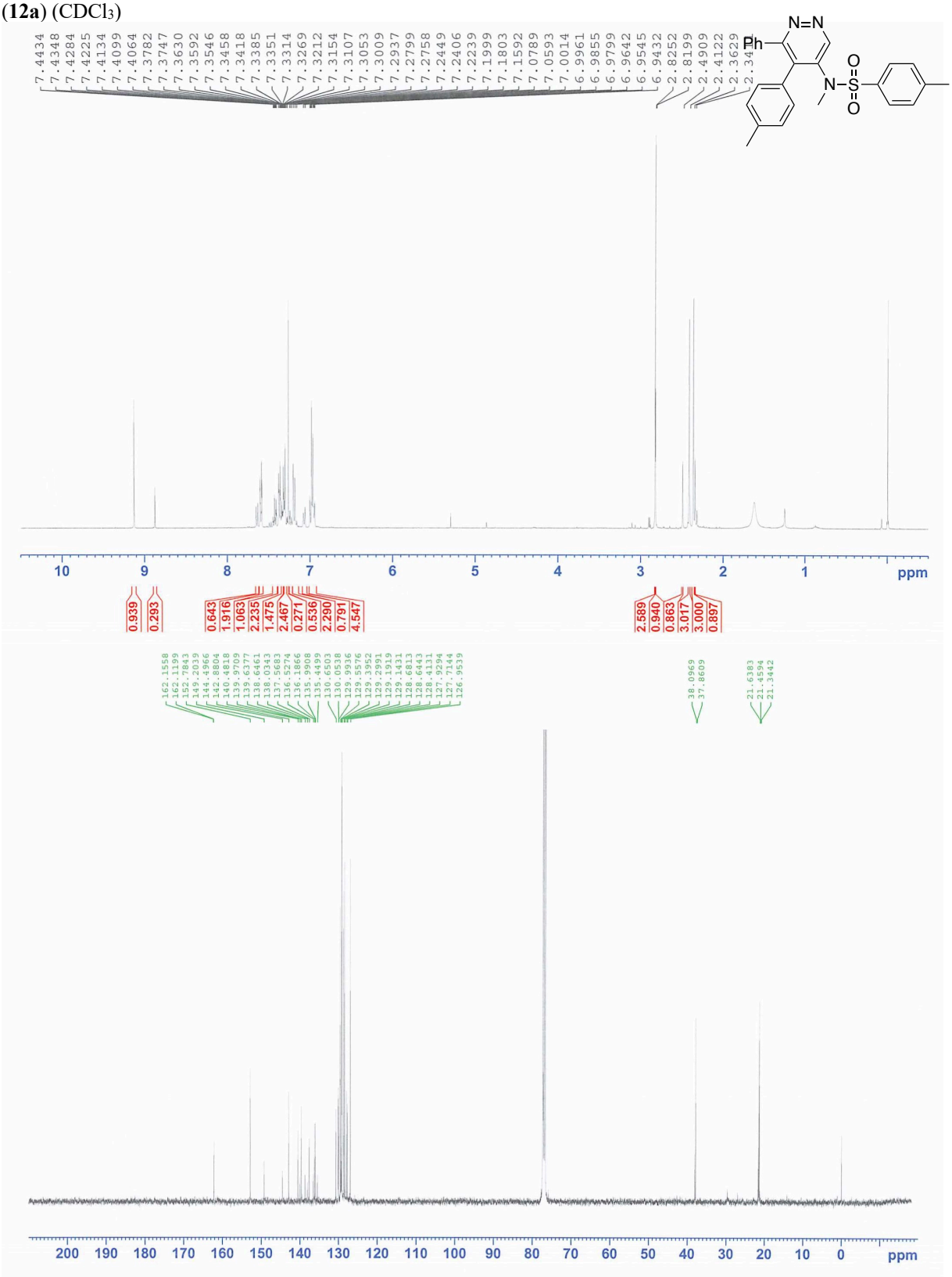



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 1-methyl-4-((*p*-tolylethynyl)sulfinyl)benzene (**10s**) ($CDCl_3$)

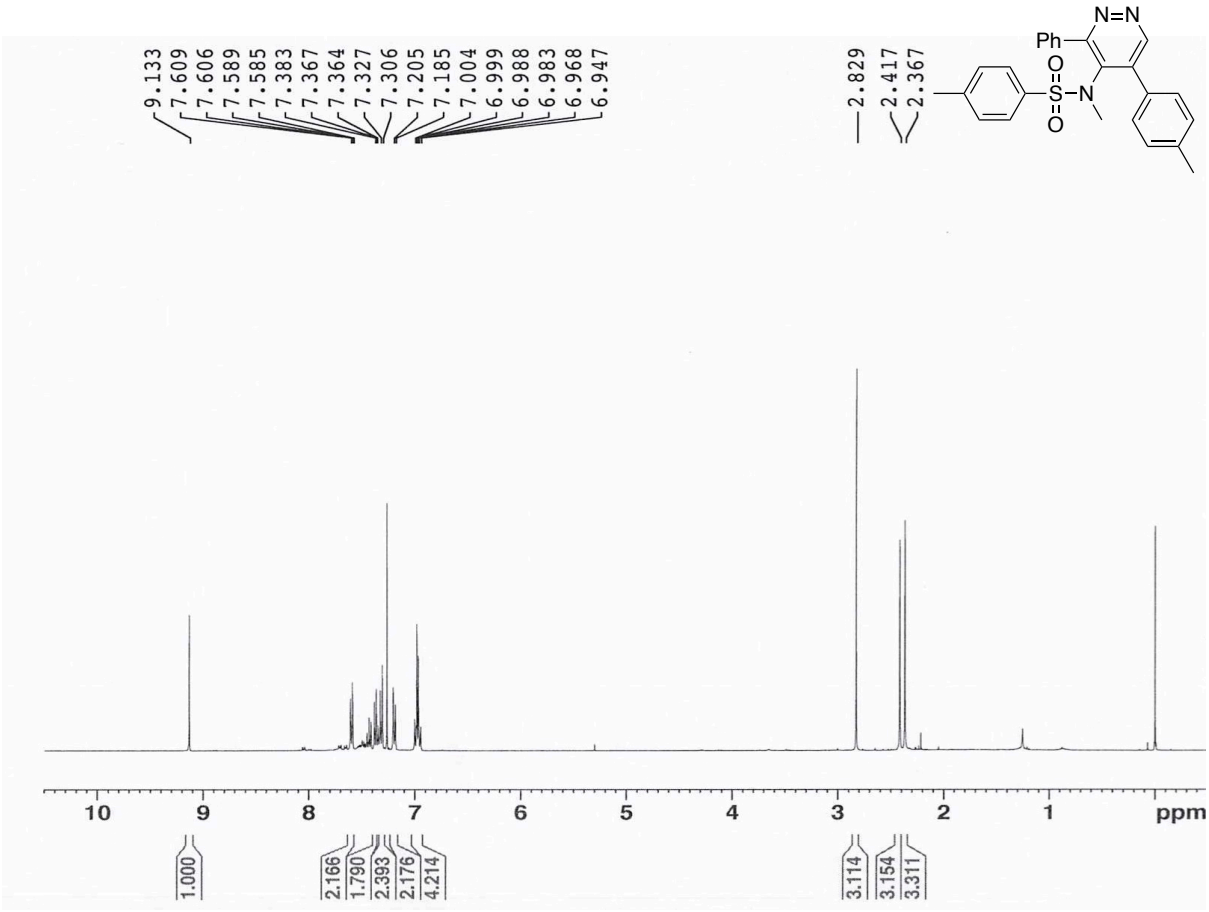


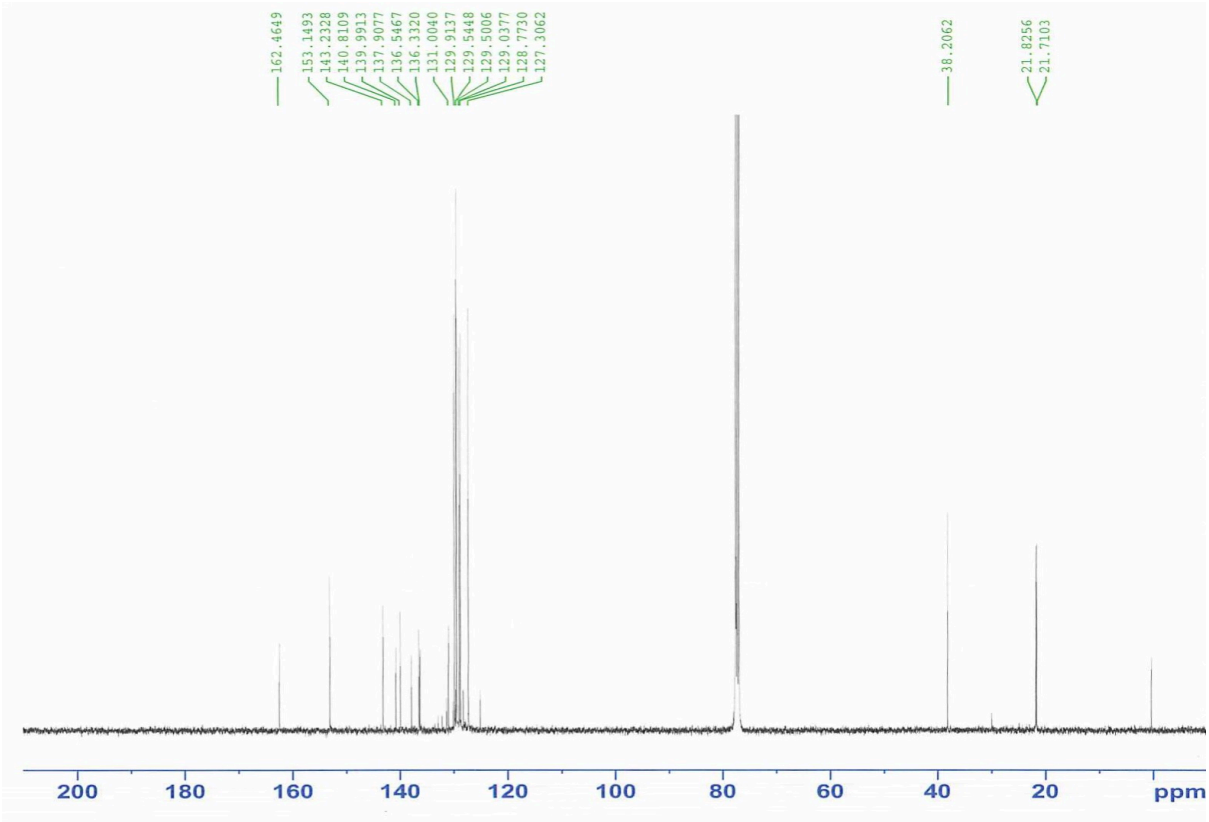



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of *N*,4-dimethyl-*N*-(6-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**11a**) with *N*,4-dimethyl-*N*-(3-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**12a**) ($CDCl_3$)

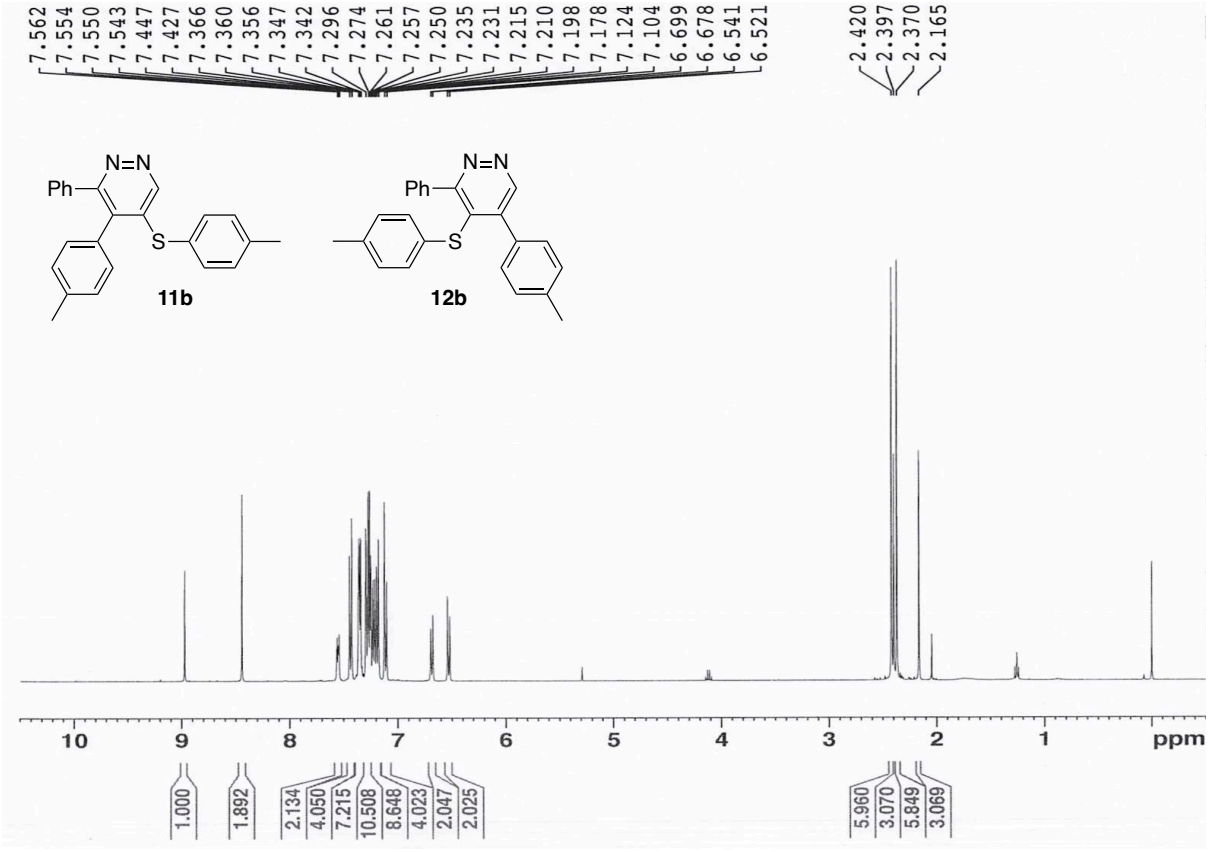


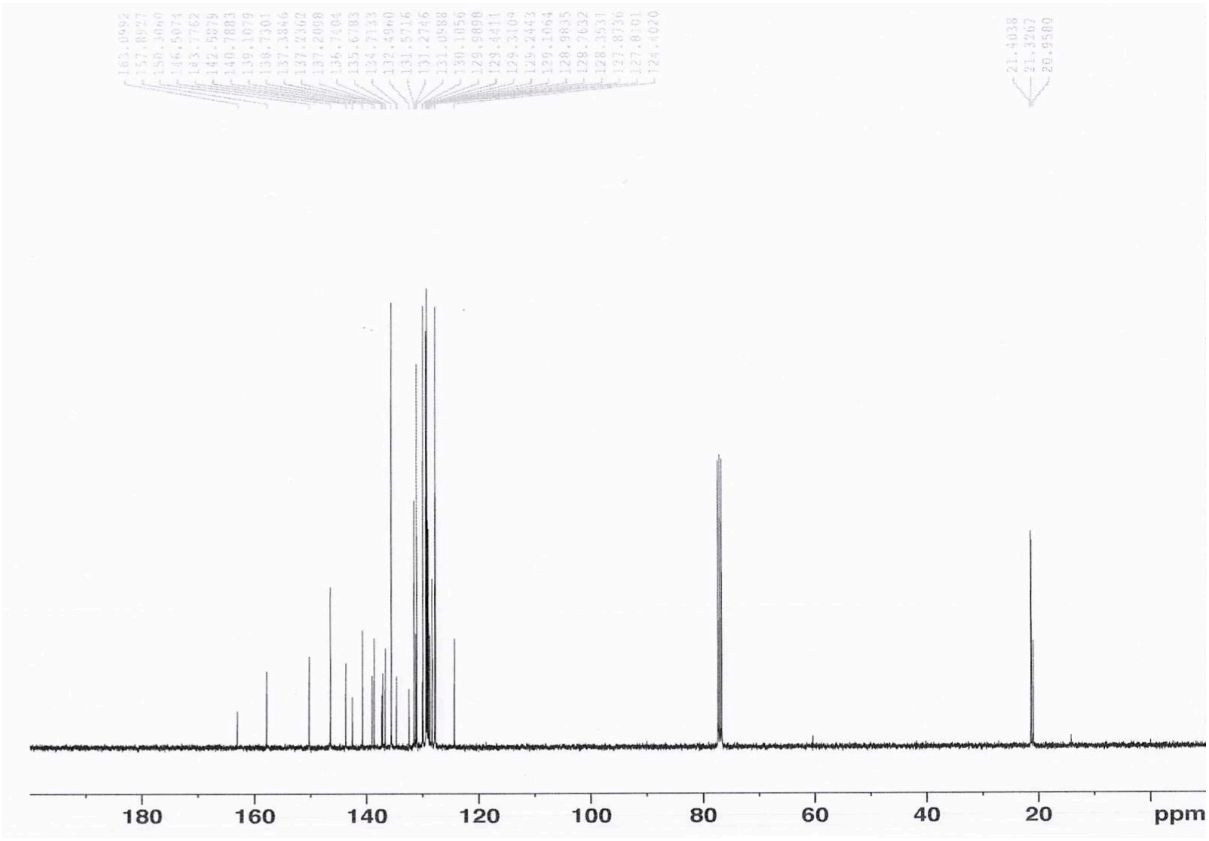
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of *N*,4-dimethyl-*N*-(3-phenyl-5-(*p*-tolyl)pyridazin-4-yl)benzenesulfonamide (**12a**) ($CDCl_3$)



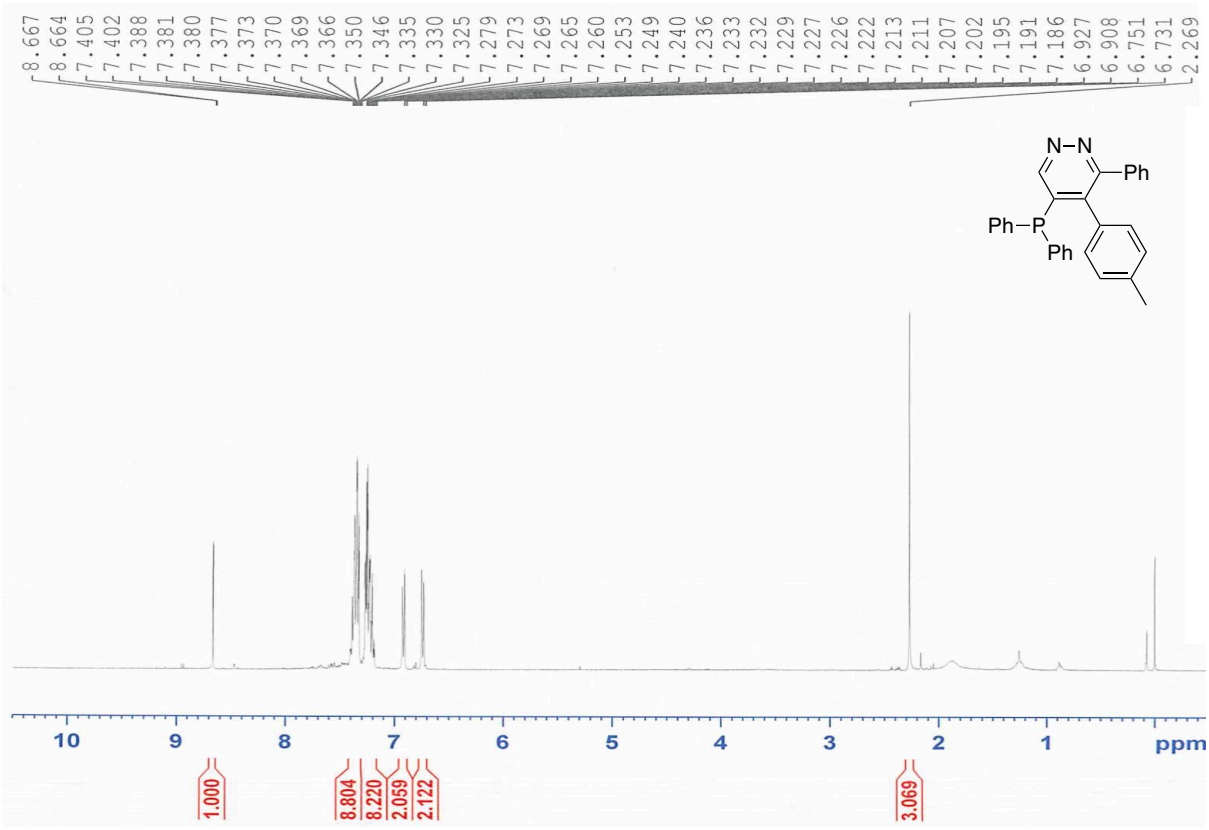



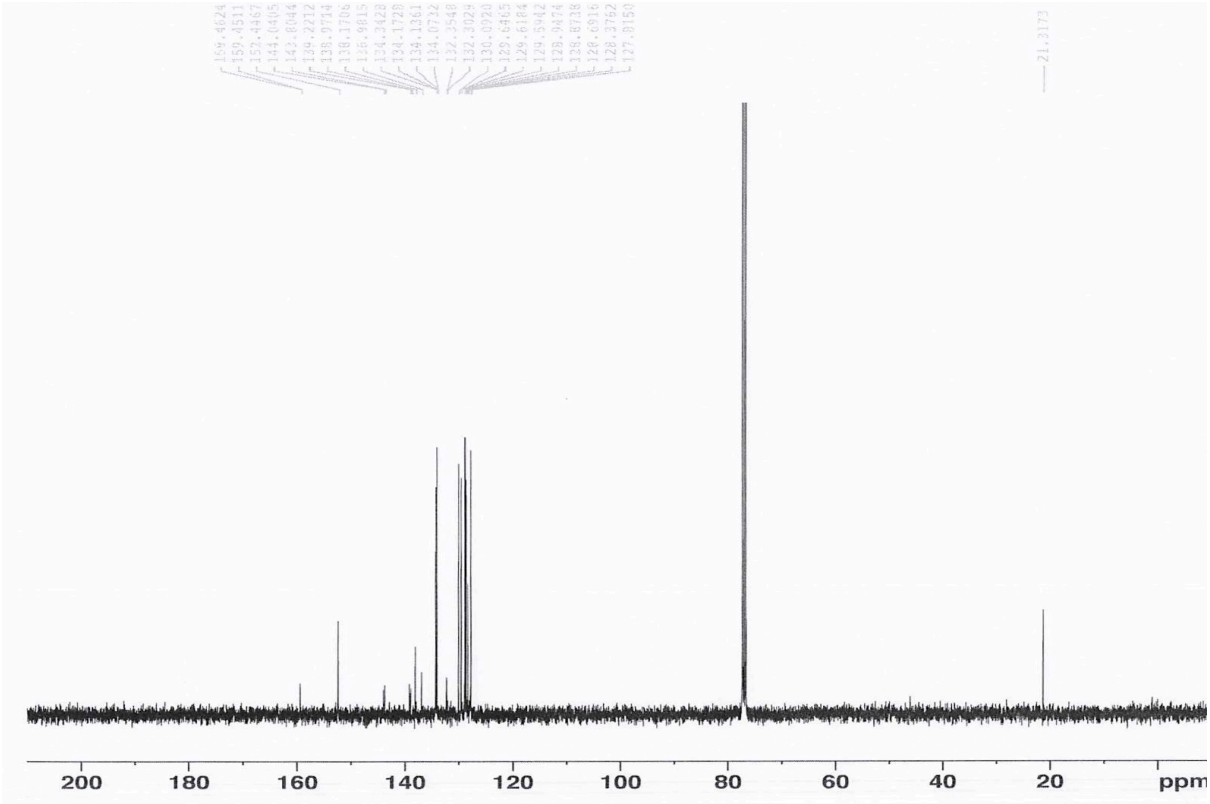
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 3-phenyl-4-(*p*-tolyl)-5-(*p*-tolylthio)pyridazine (**11b**) and 3-phenyl-5-(*p*-tolyl)-4-(*p*-tolylthio)pyridazine (**12b**) ($CDCl_3$)



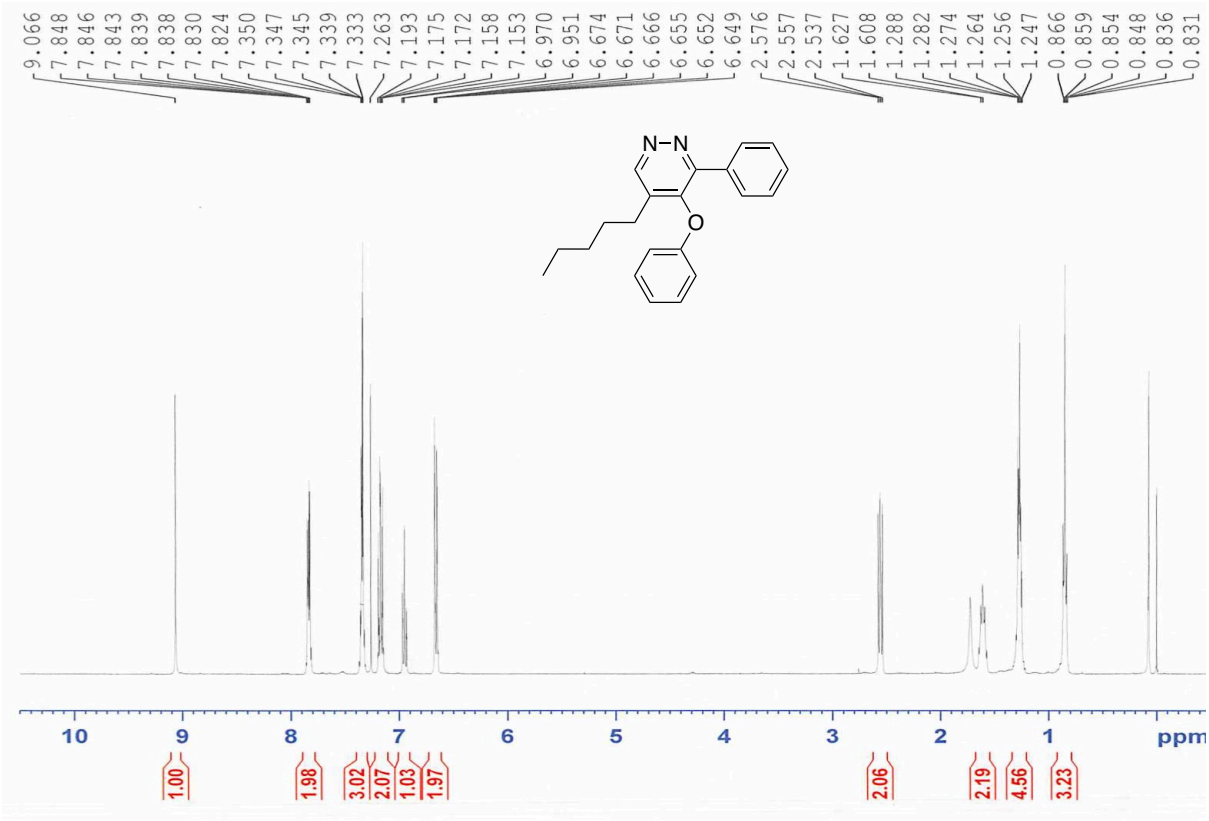



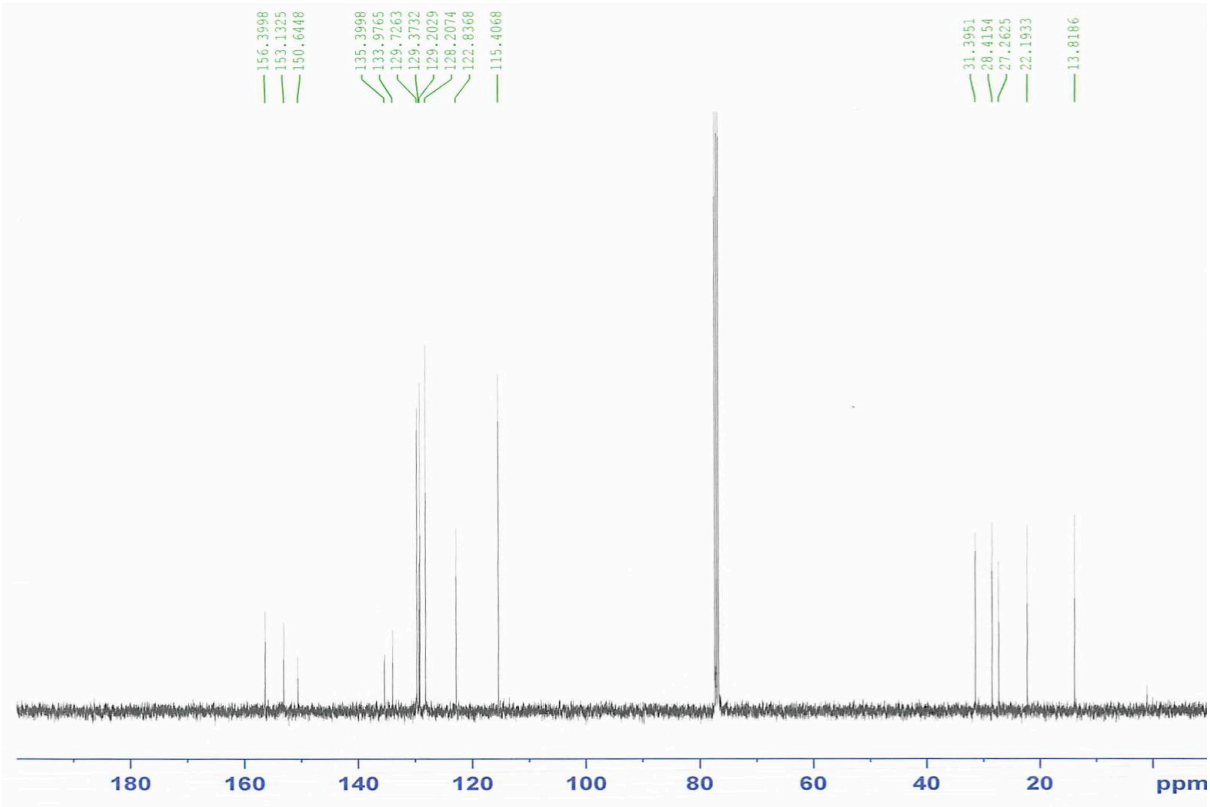
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-(diphenylphosphaneyl)-3-phenyl-4-(*p*-tolyl)pyridazine (**11c**) ($CDCl_3$)



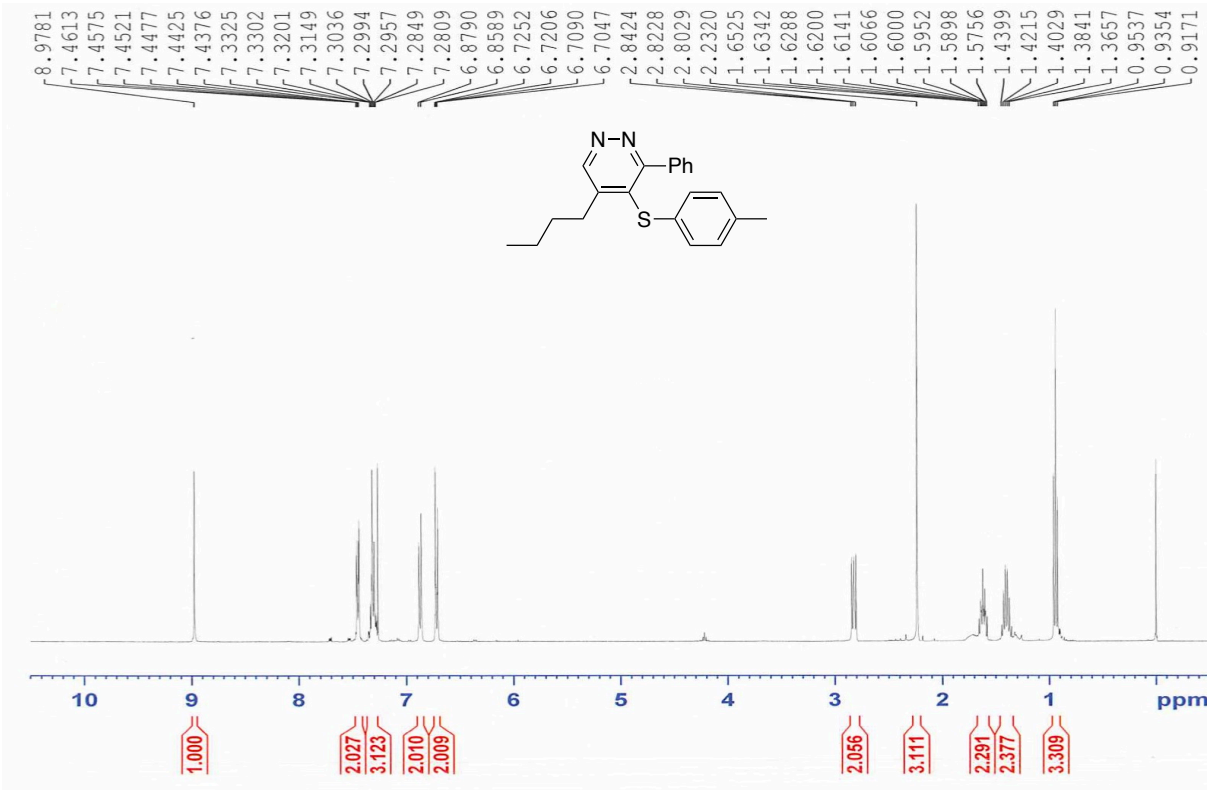



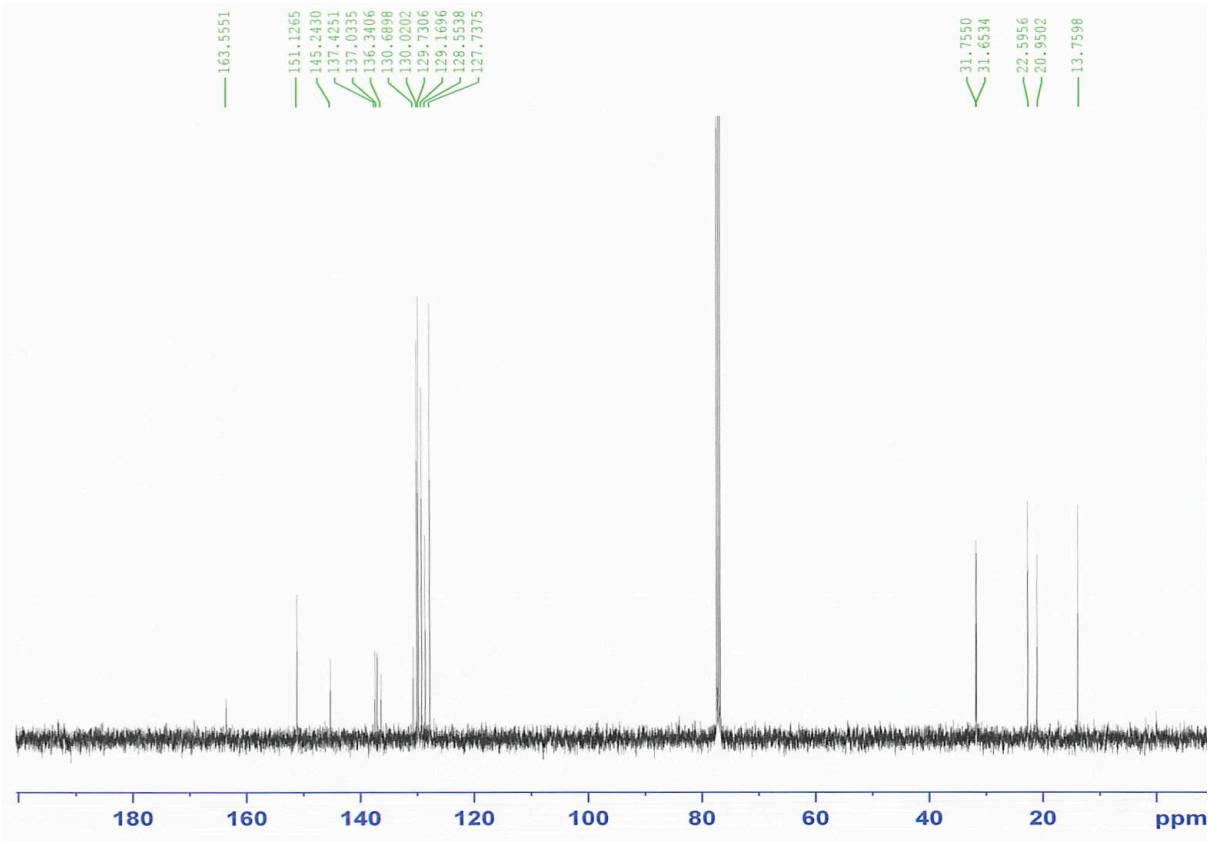
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-pentyl-4-phenoxy-3-phenylpyridazine (**12d**) ($CDCl_3$)



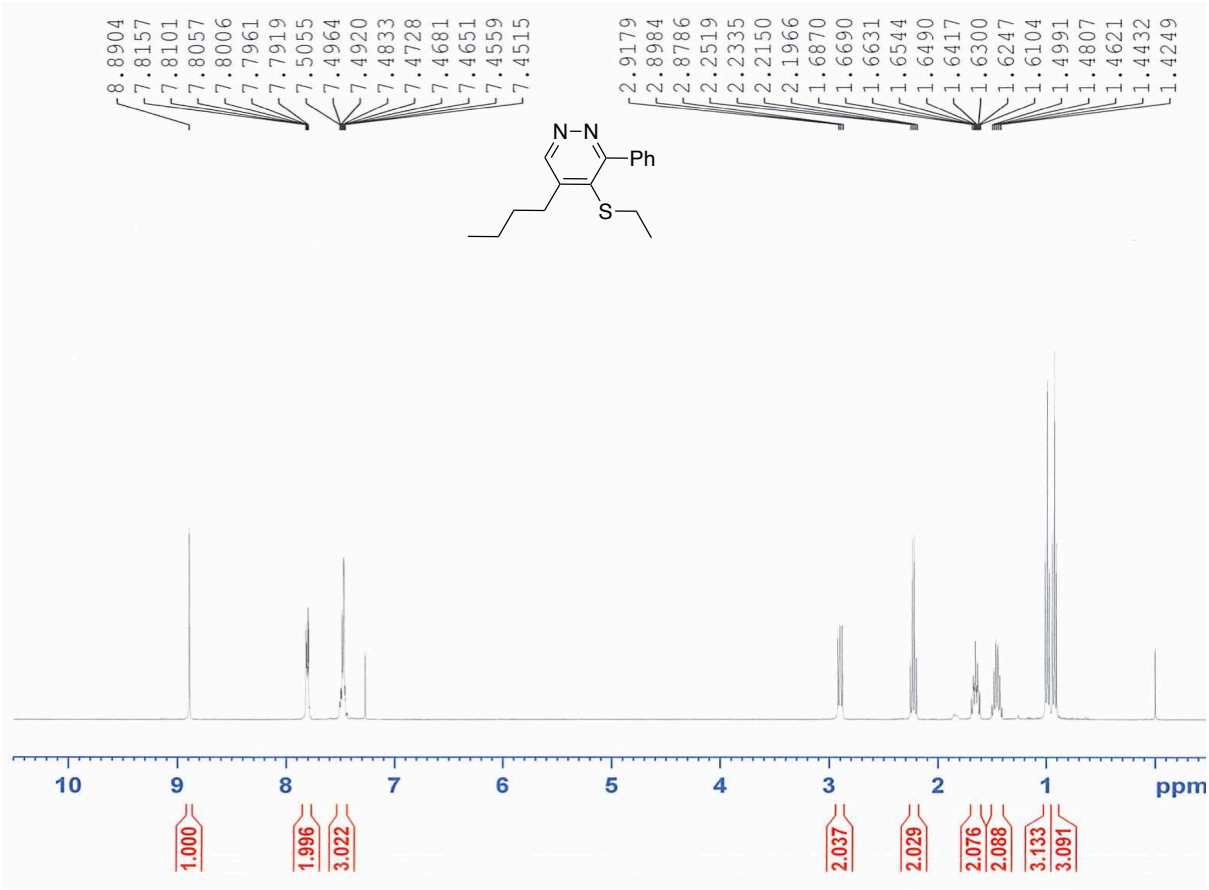



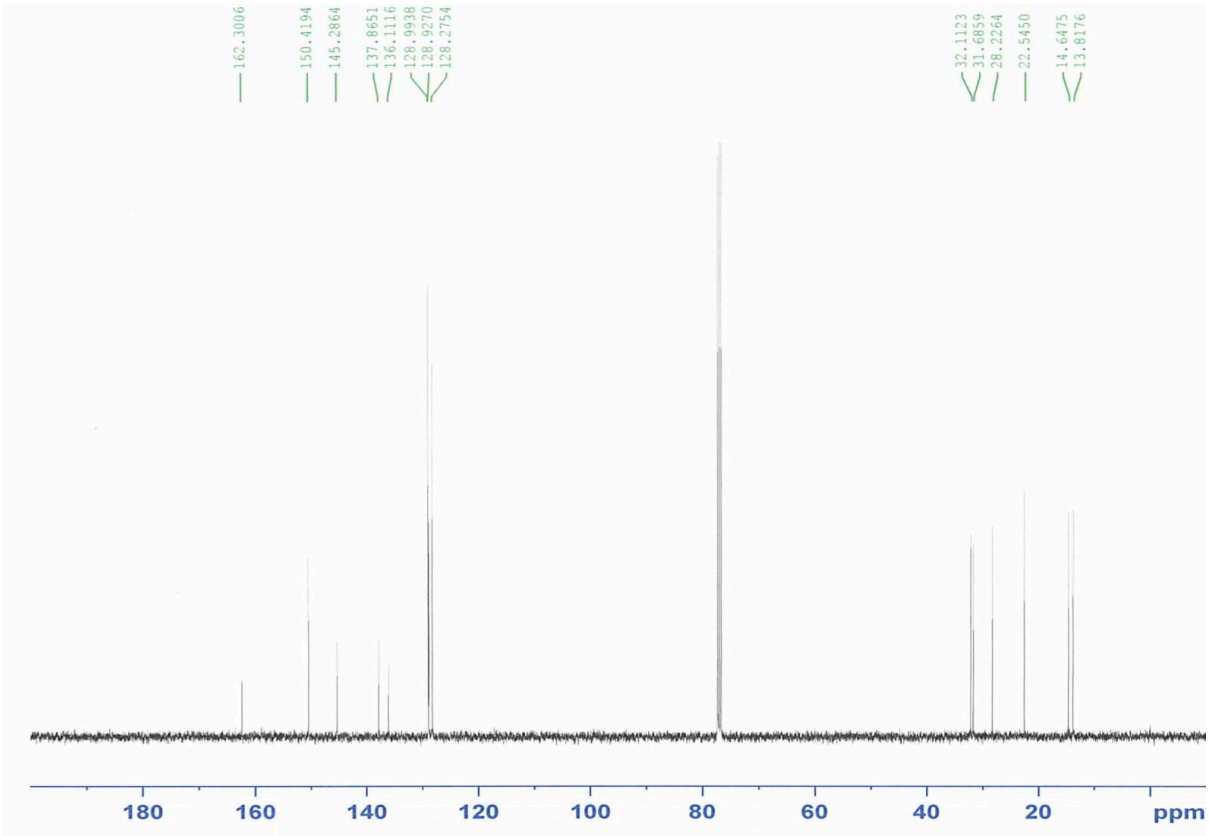
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-3-phenyl-4-(*p*-tolylthio)pyridazine (**12f**) ($CDCl_3$)



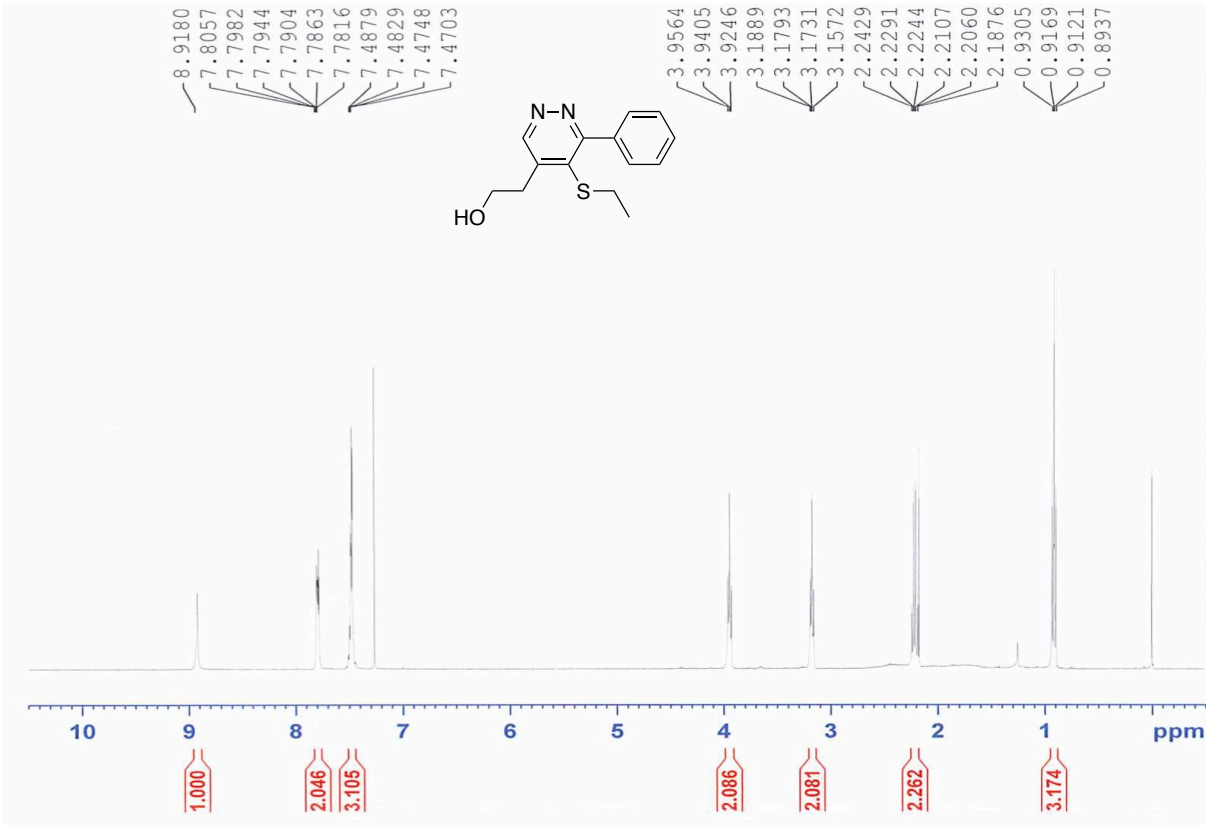



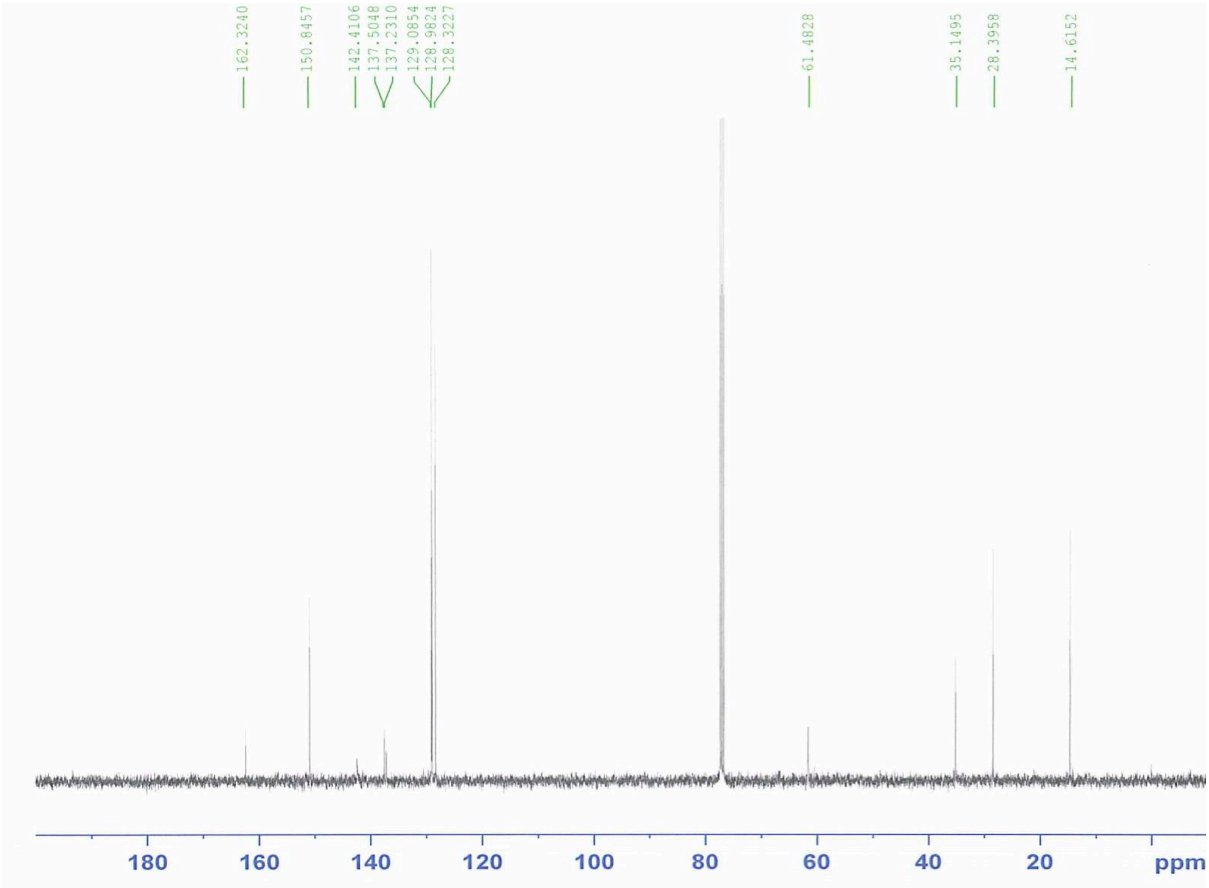
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-4-(ethylthio)-3-phenylpyridazine (**12i**) ($CDCl_3$)



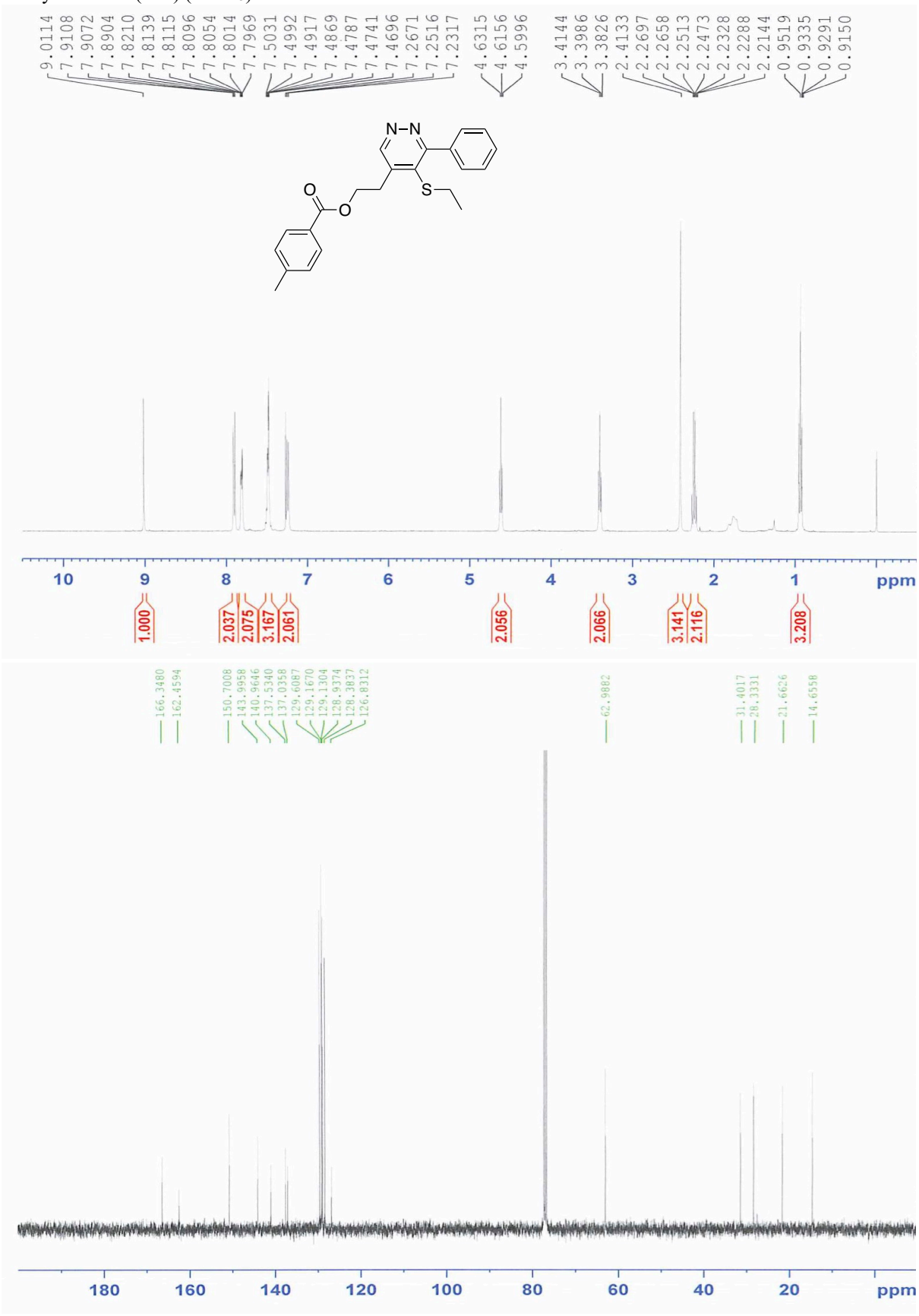



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 2-(5-(ethylthio)-6-phenylpyridazin-4-yl)ethan-1-ol (**12j**) ($CDCl_3$)

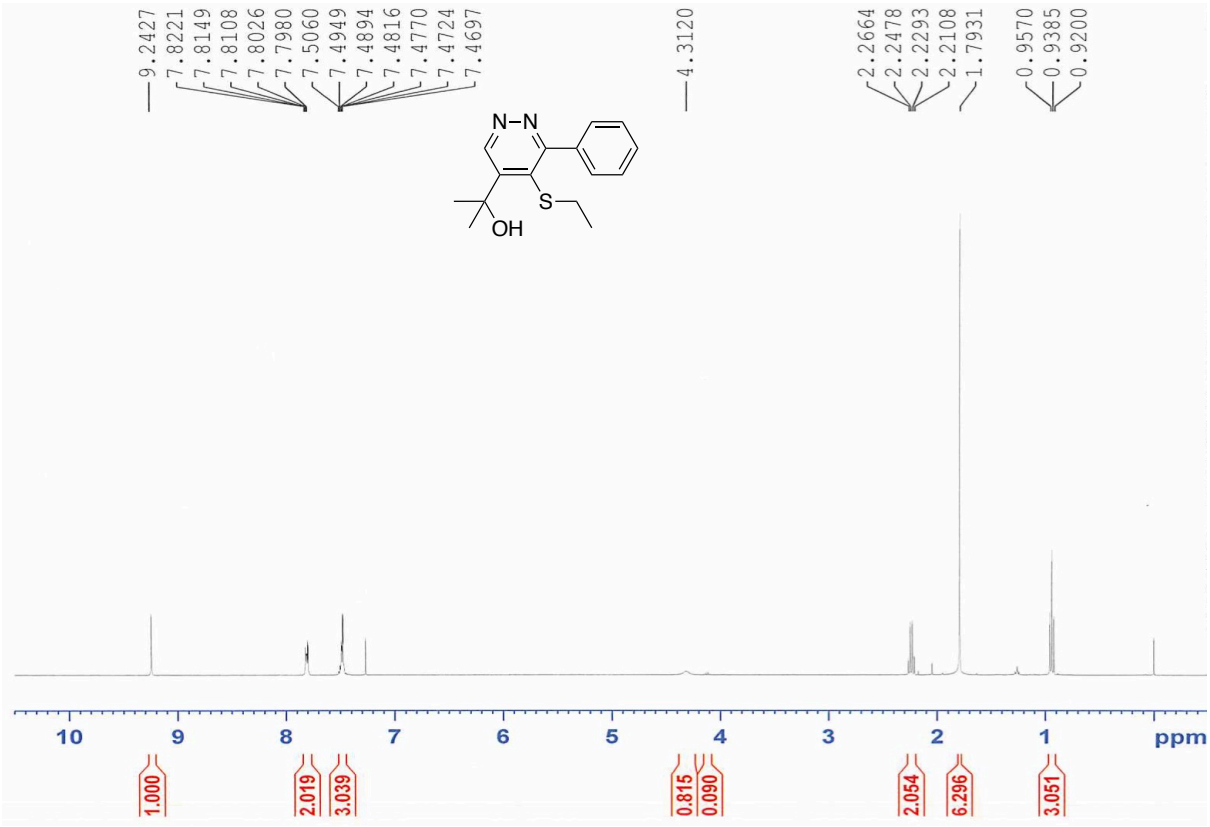


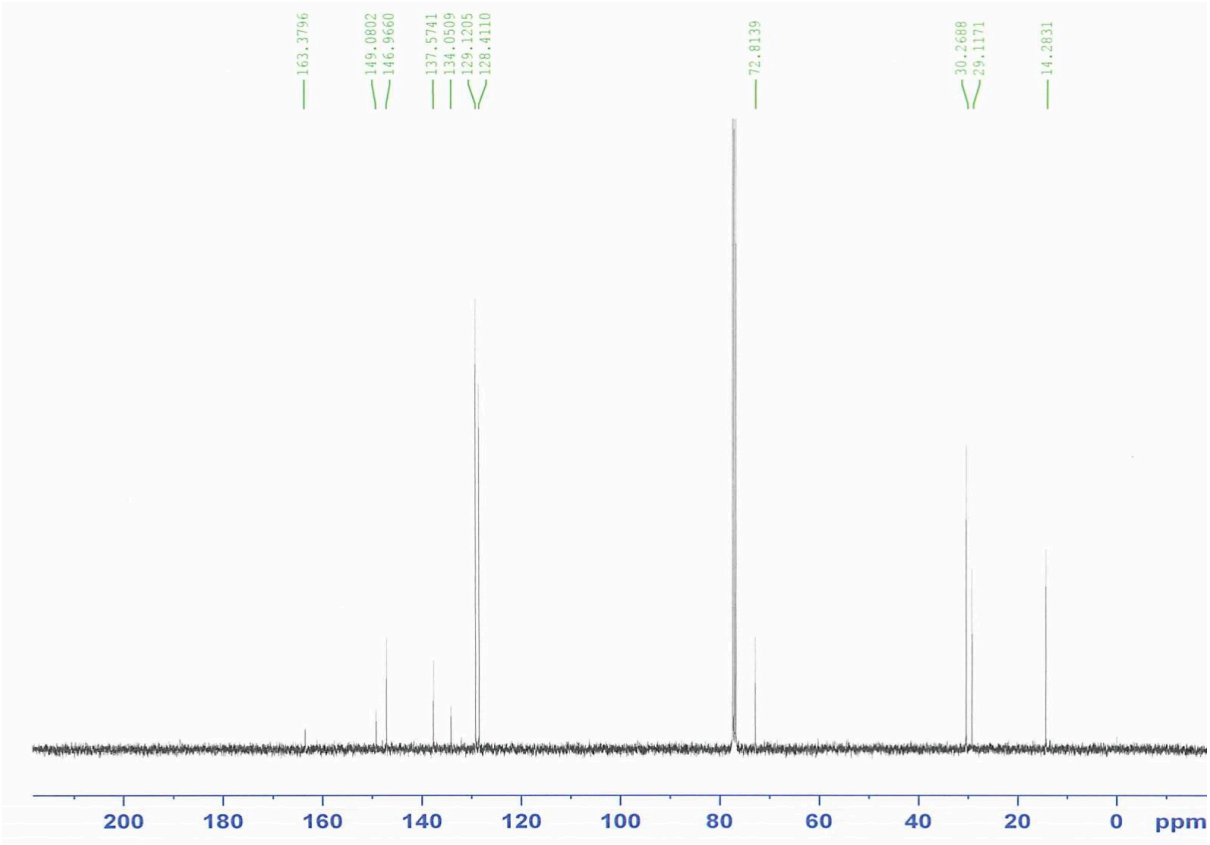



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 2-(5-ethylthio)-6-phenylpyridazin-4-yl)ethyl 4-methylbenzoate (**12k**) ($CDCl_3$)

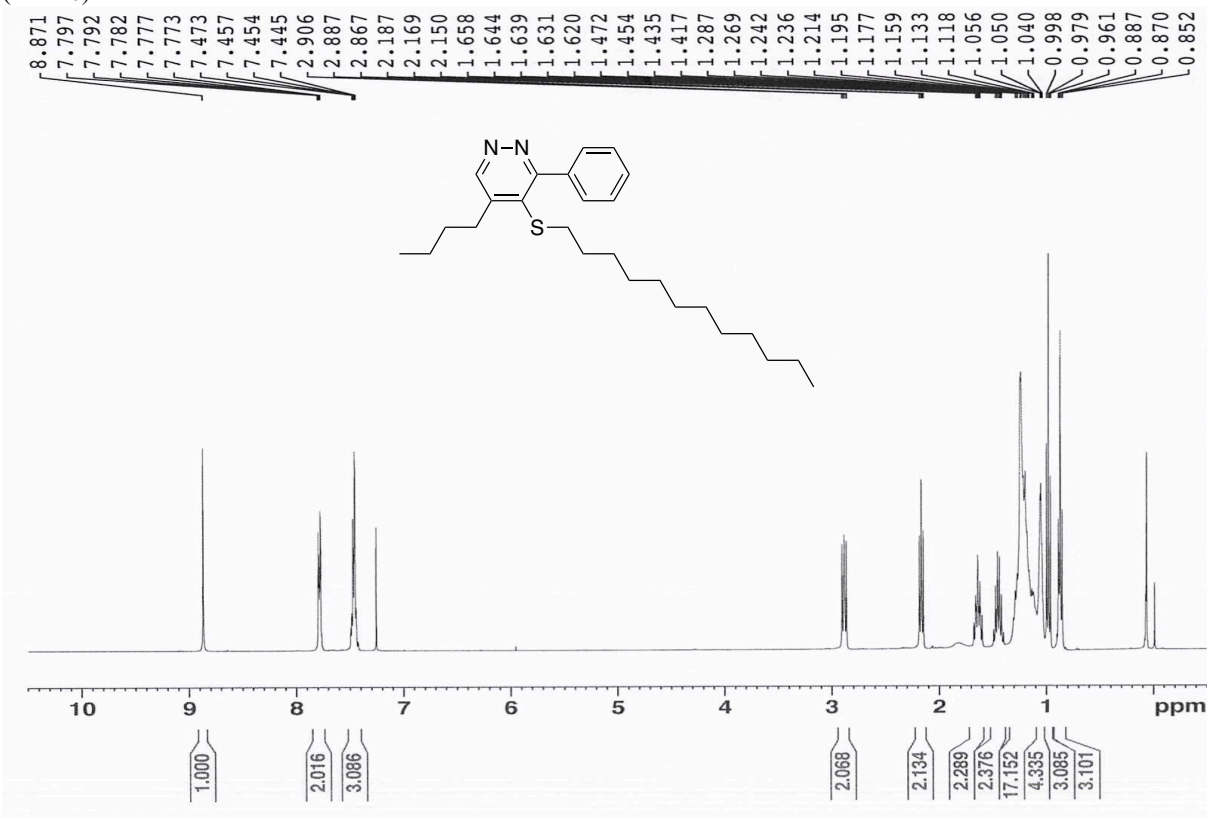


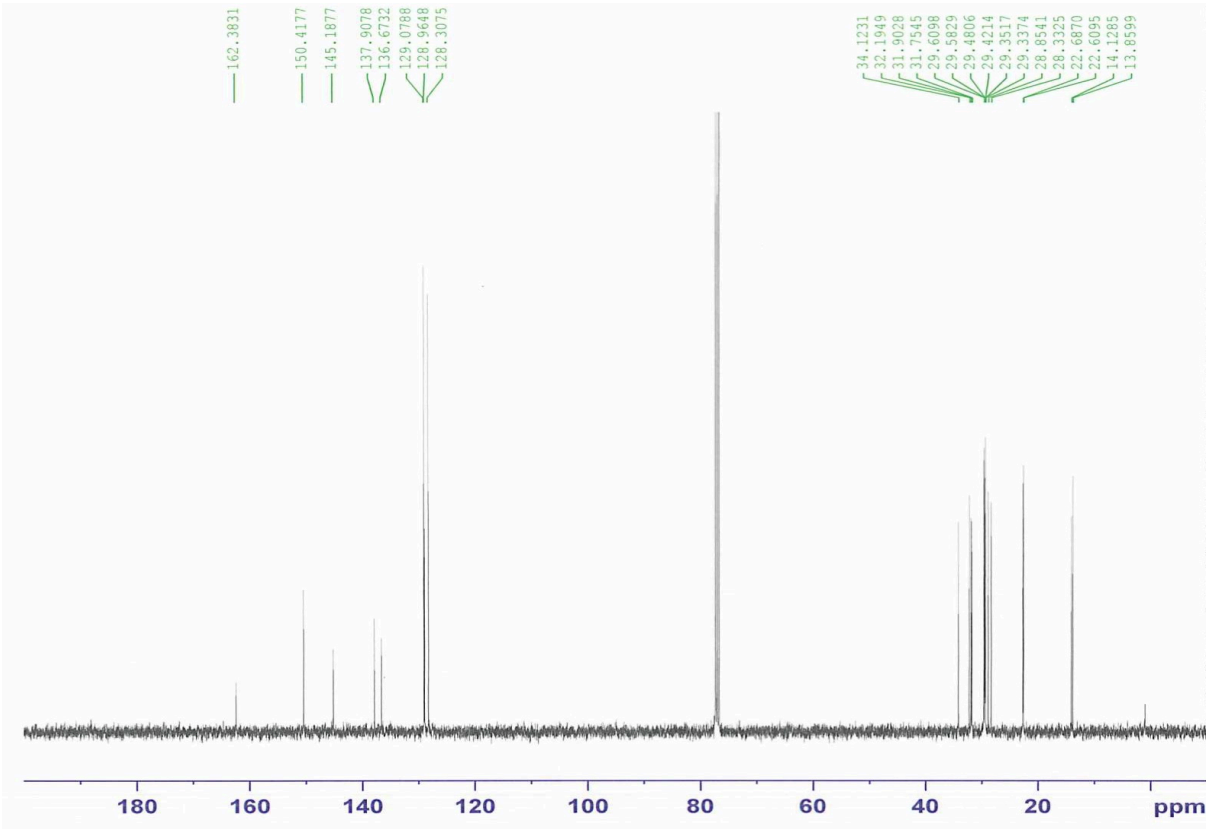
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 2-(5-ethylthio)-6-phenylpyridazin-4-yl)propan-2-ol (**12l**) ($CDCl_3$)



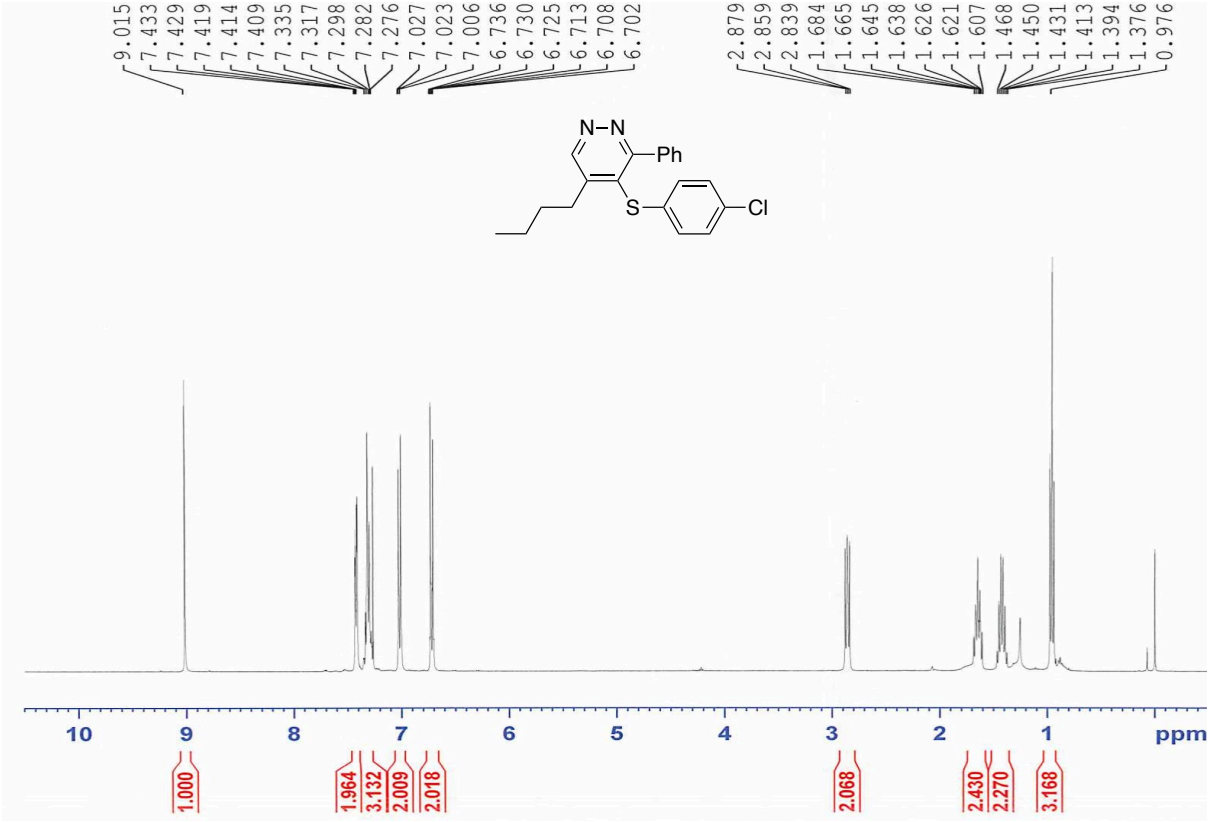



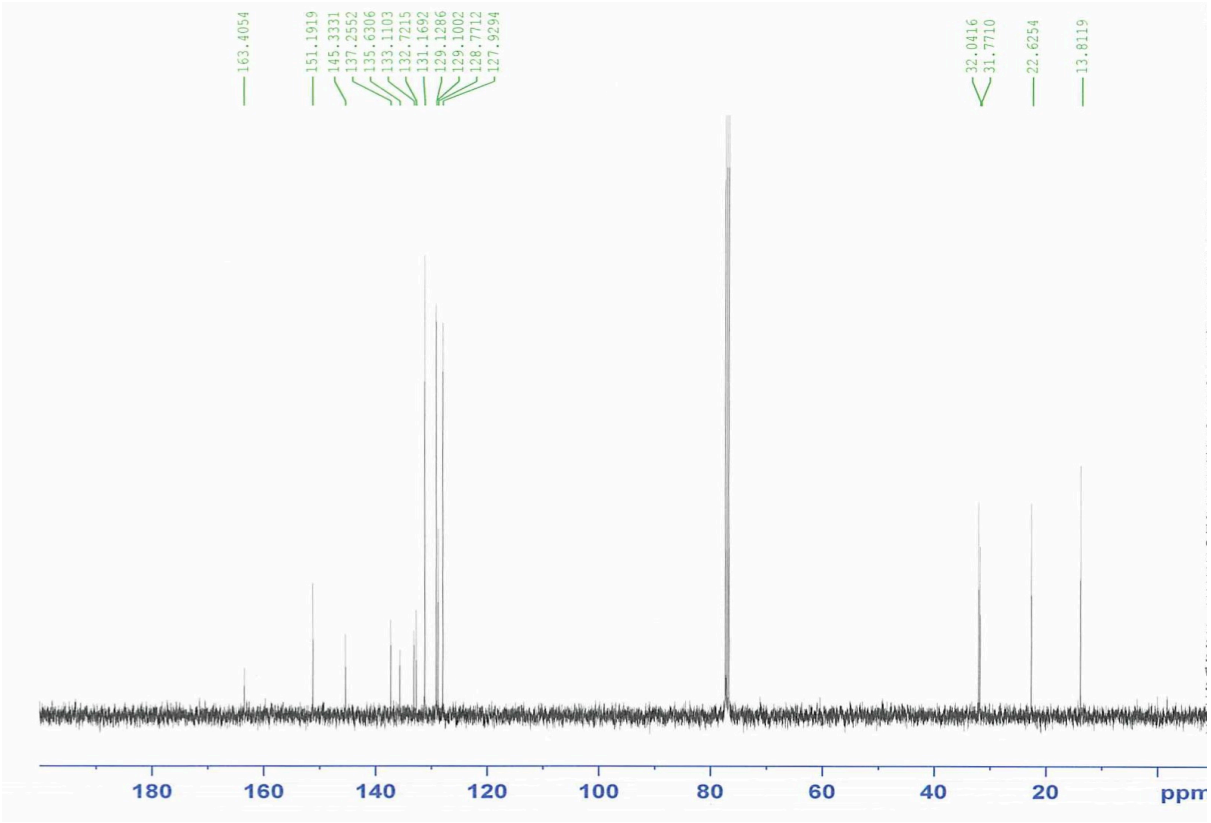
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-4-(dodecylthio)-3-phenylpyridazine (**12m**) ($CDCl_3$)



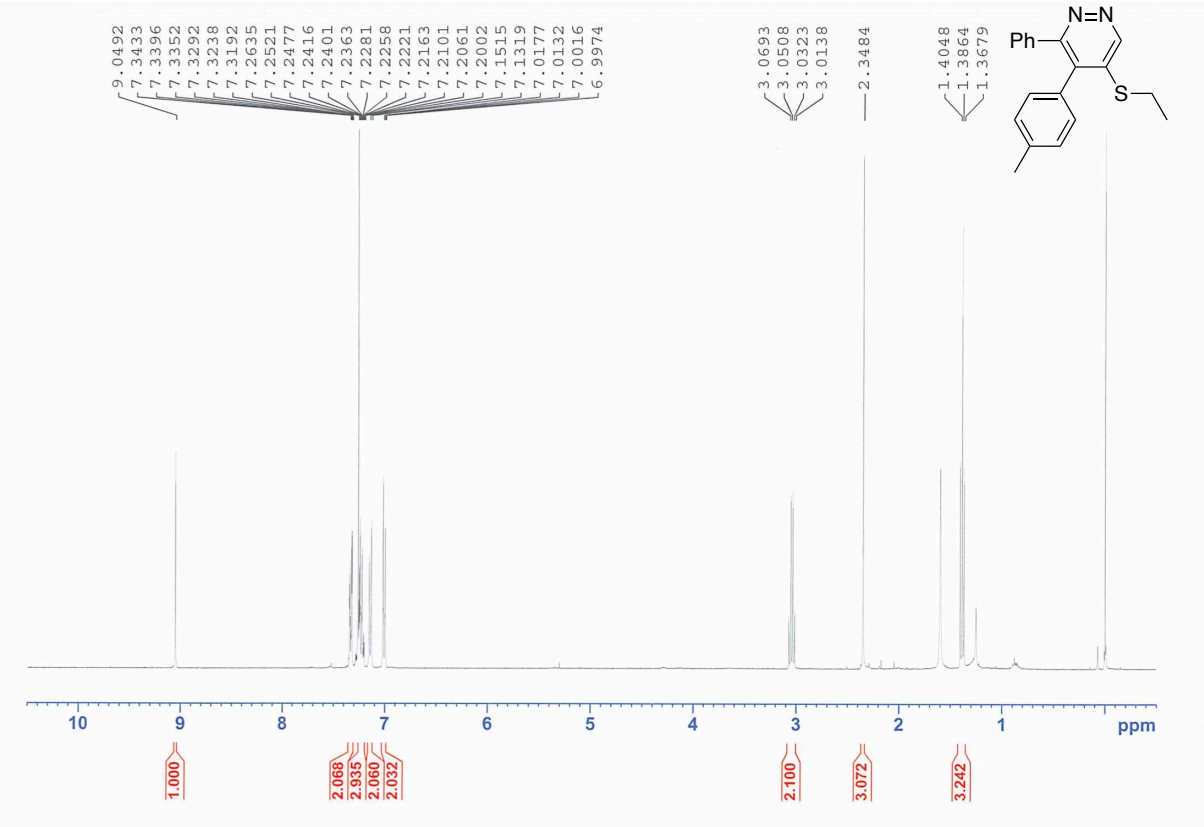



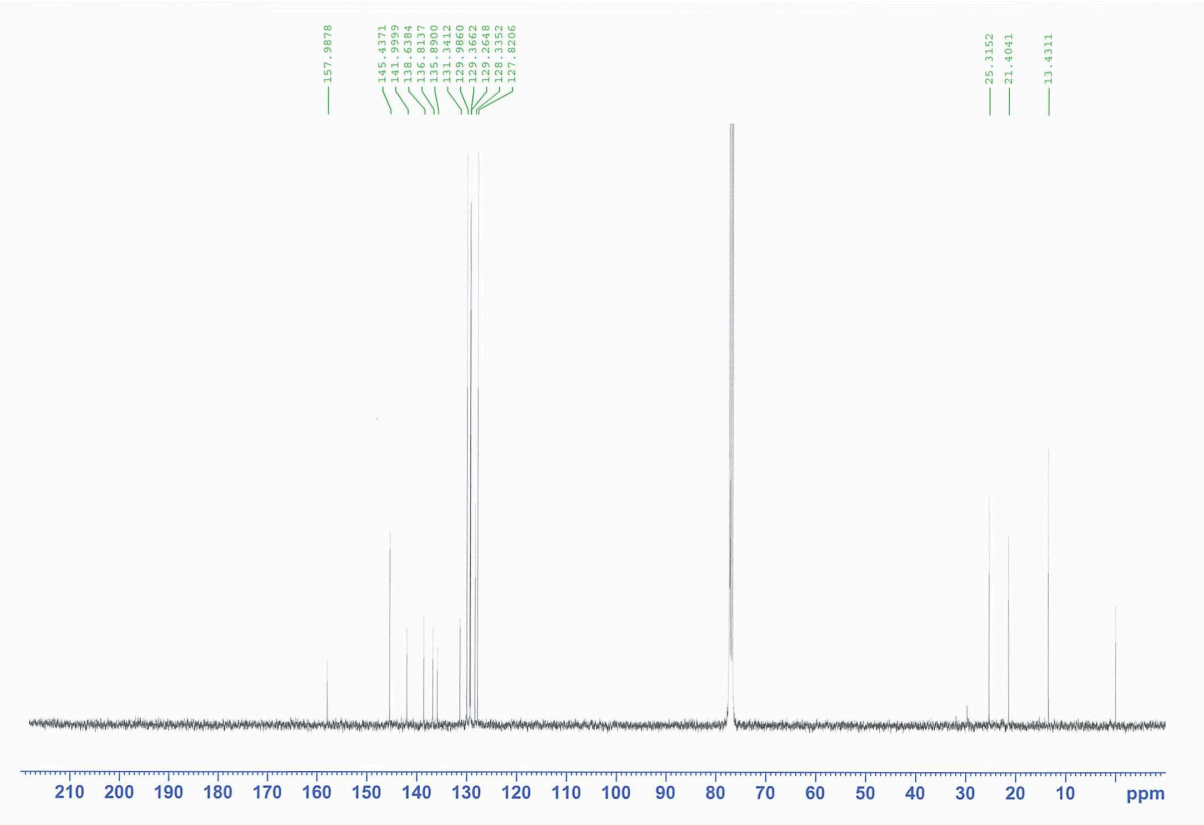
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-4-((4-chlorophenyl)thio)-3-phenylpyridazine (**12n**) ($CDCl_3$)



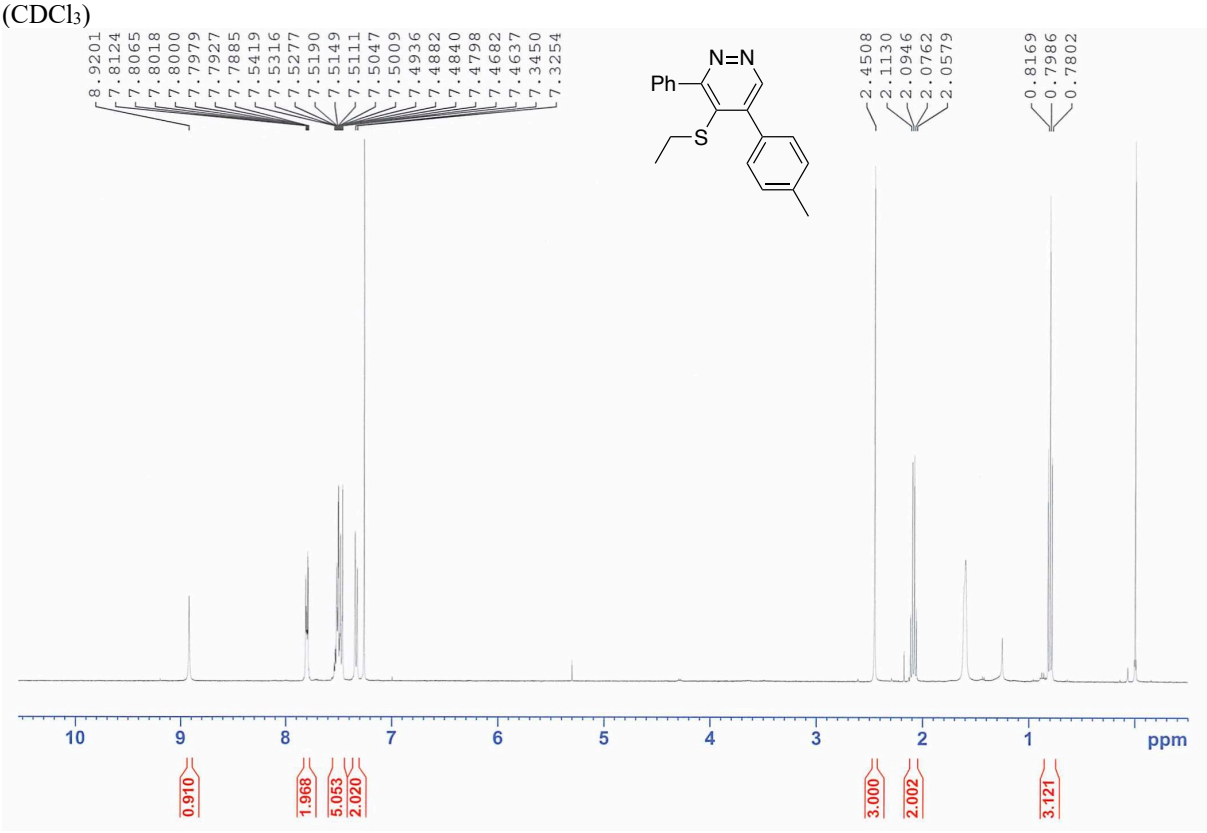



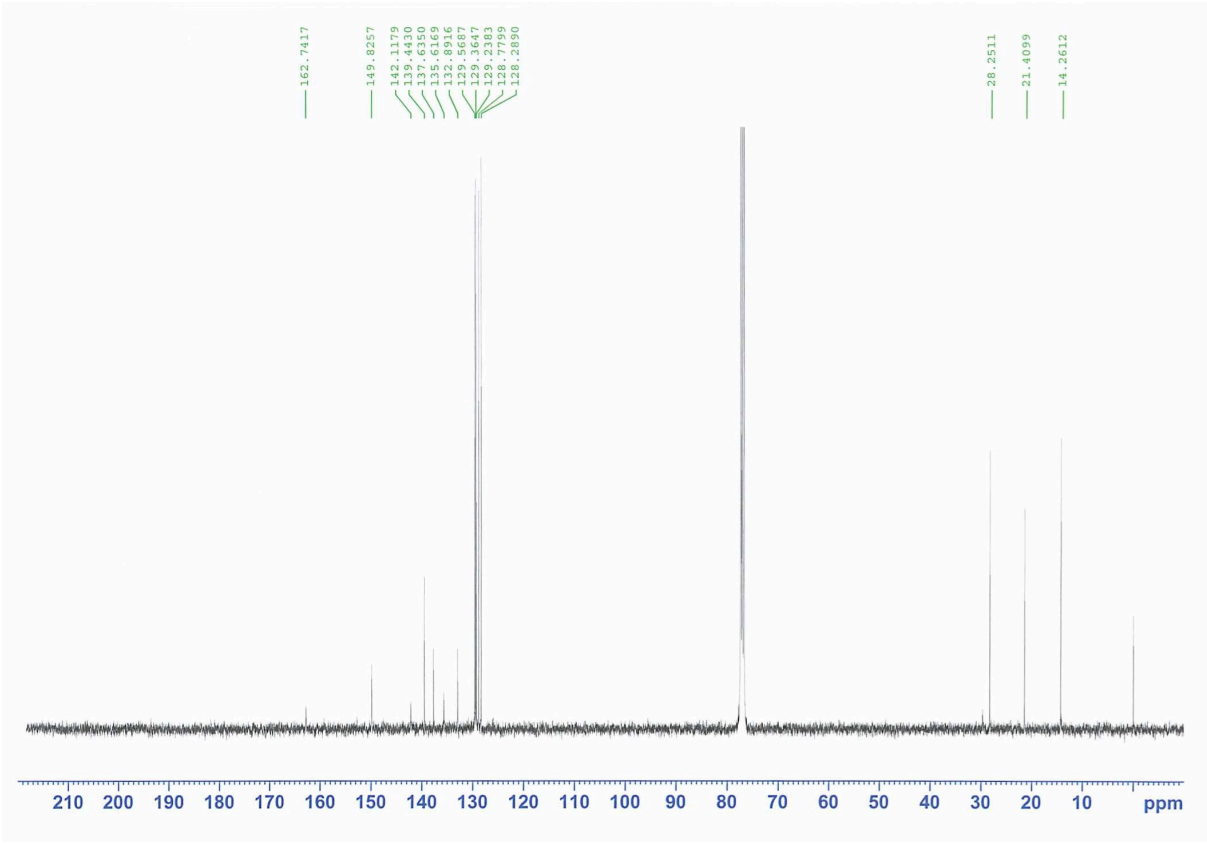
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-(ethylthio)-3-phenyl-4-(*p*-tolyl)pyridazine (**11o**) ($CDCl_3$)



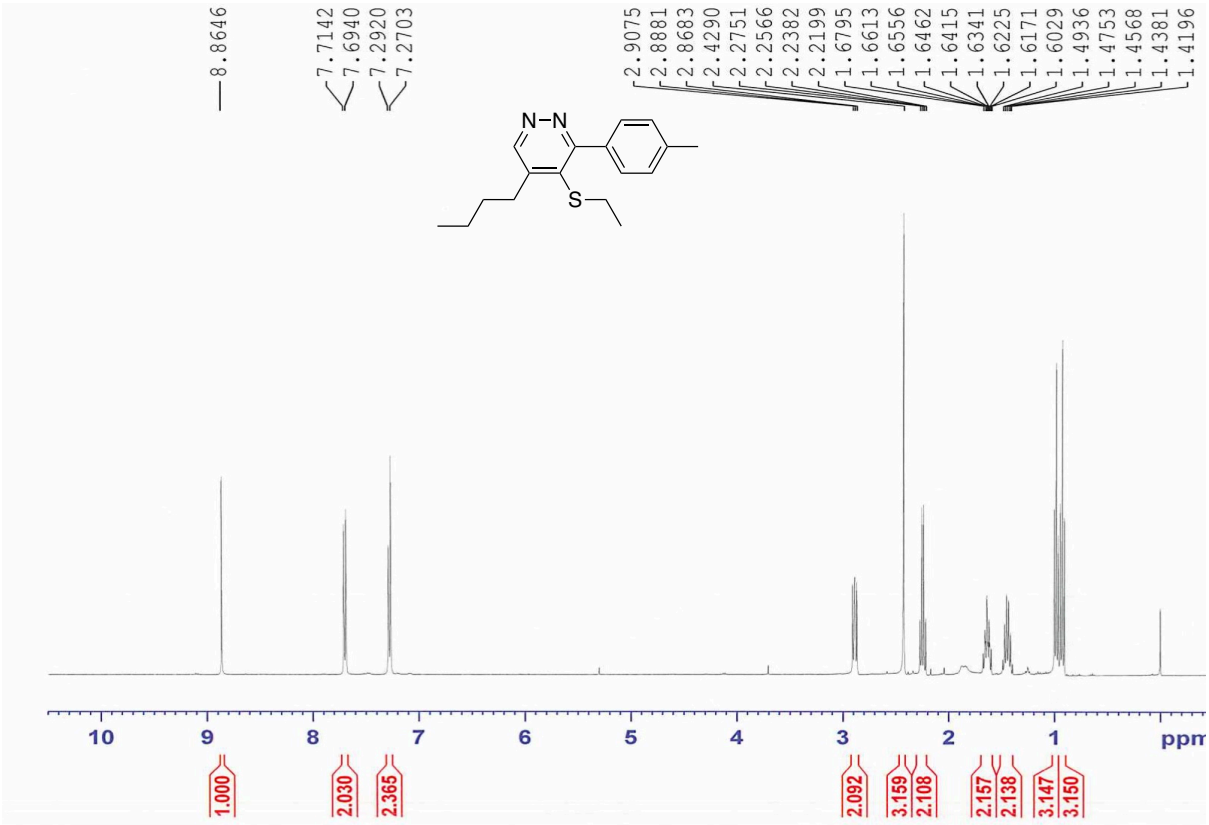



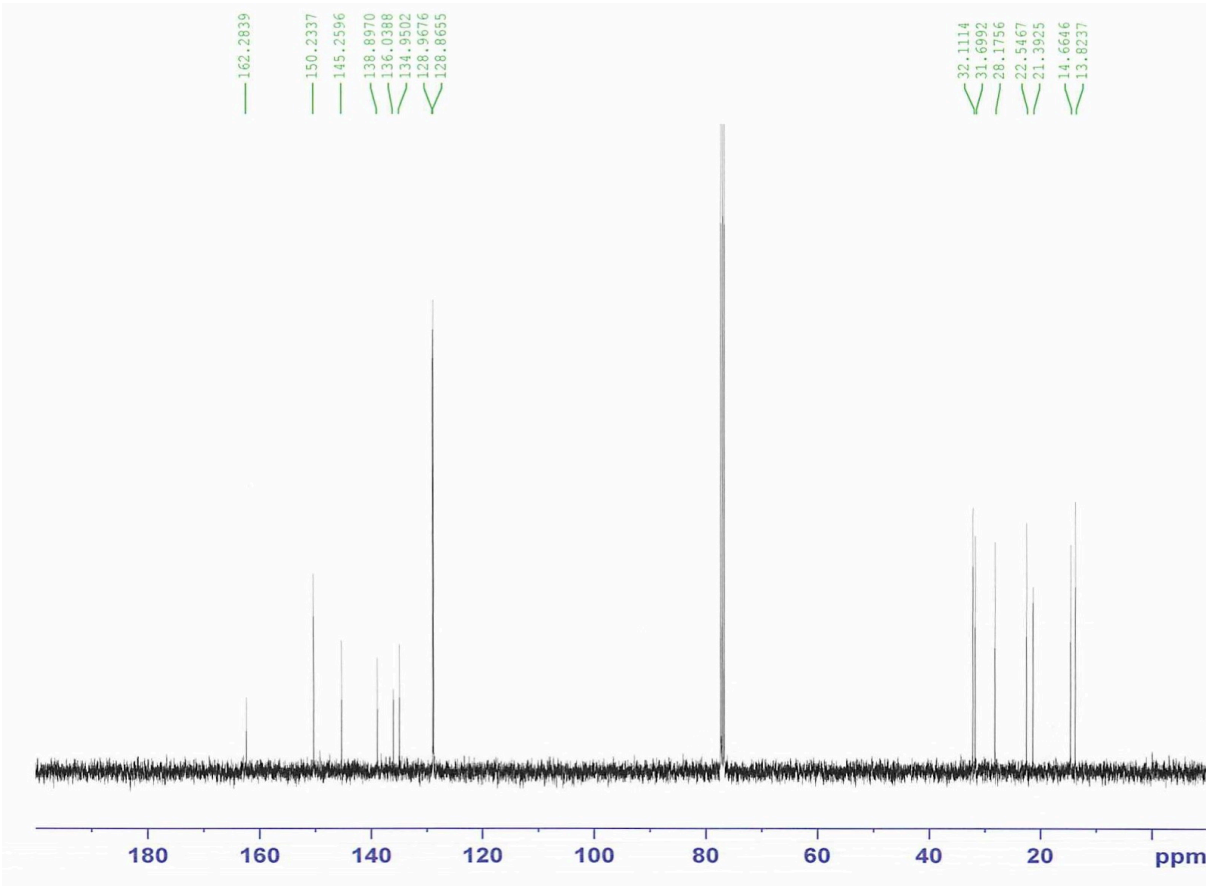
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 4-(ethylthio)-3-phenyl-5-(*p*-tolyl)pyridazine (**12o**) ($CDCl_3$)



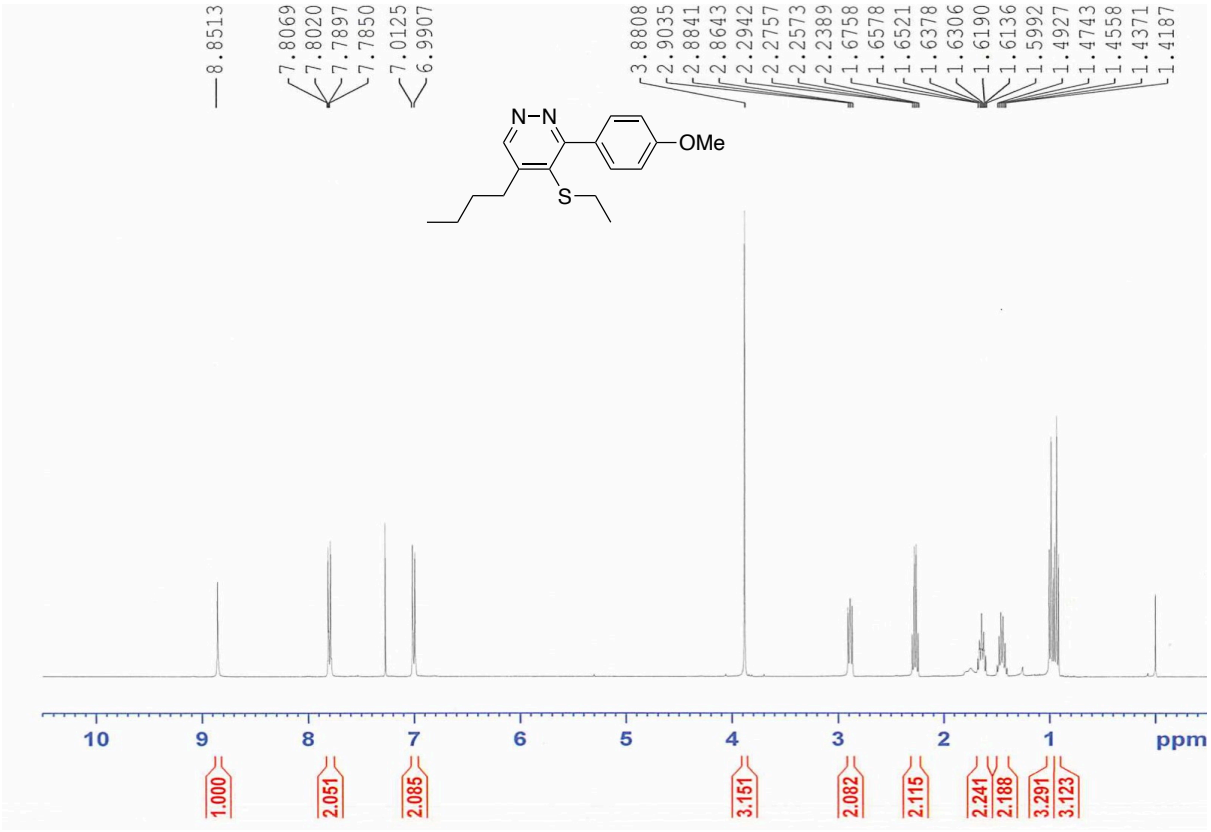



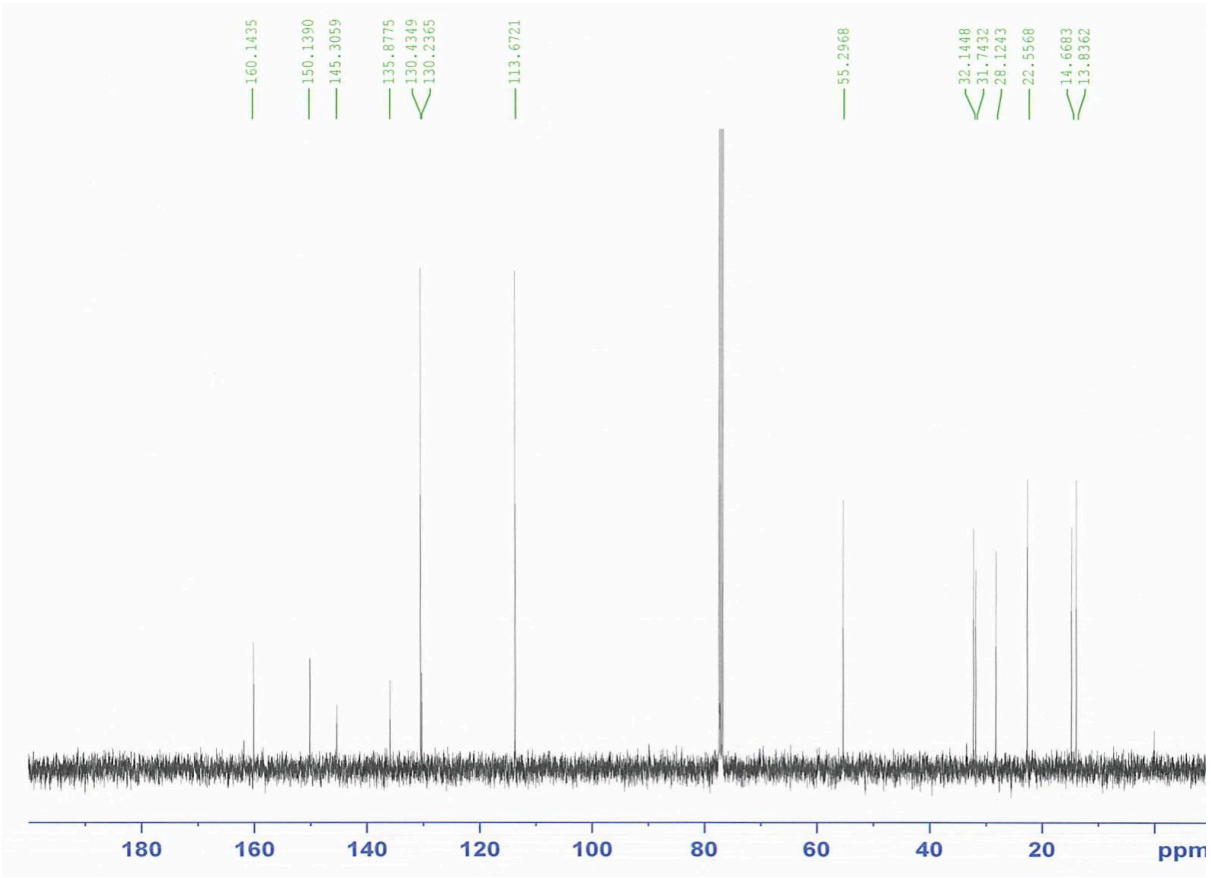
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-4-(ethylthio)-3-(*p*-tolyl)pyridazine (**12p**) ($CDCl_3$)



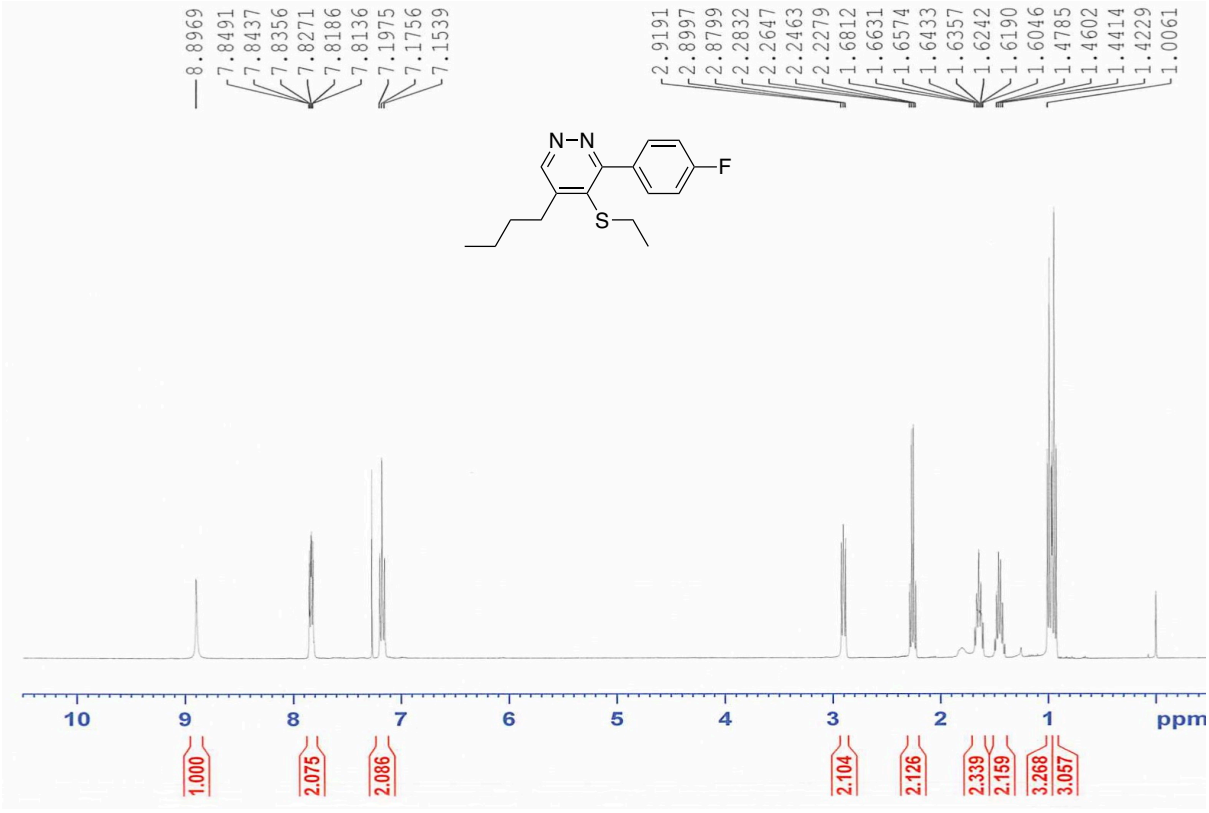



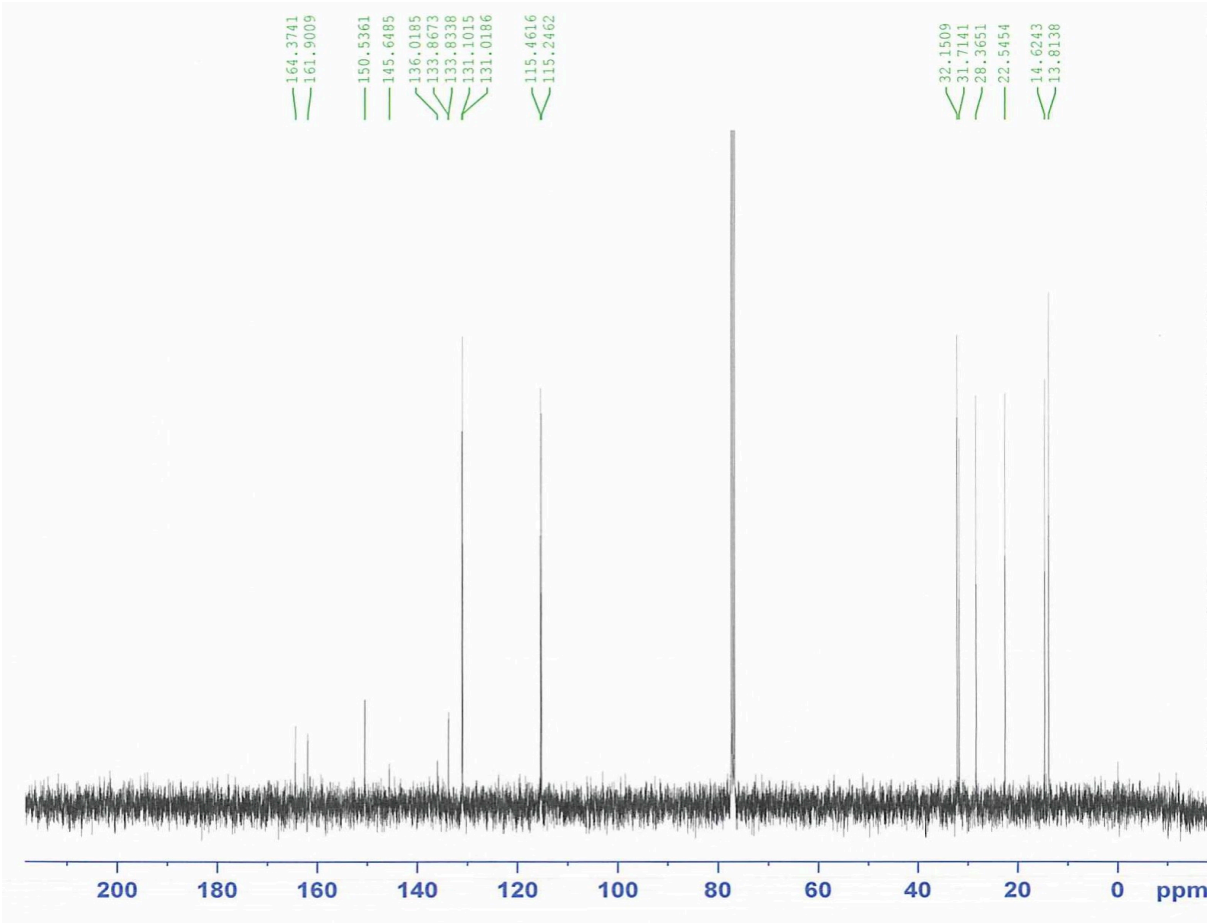
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-4-(ethylthio)-3-(4-methoxyphenyl)pyridazine (**12q**) ($CDCl_3$)



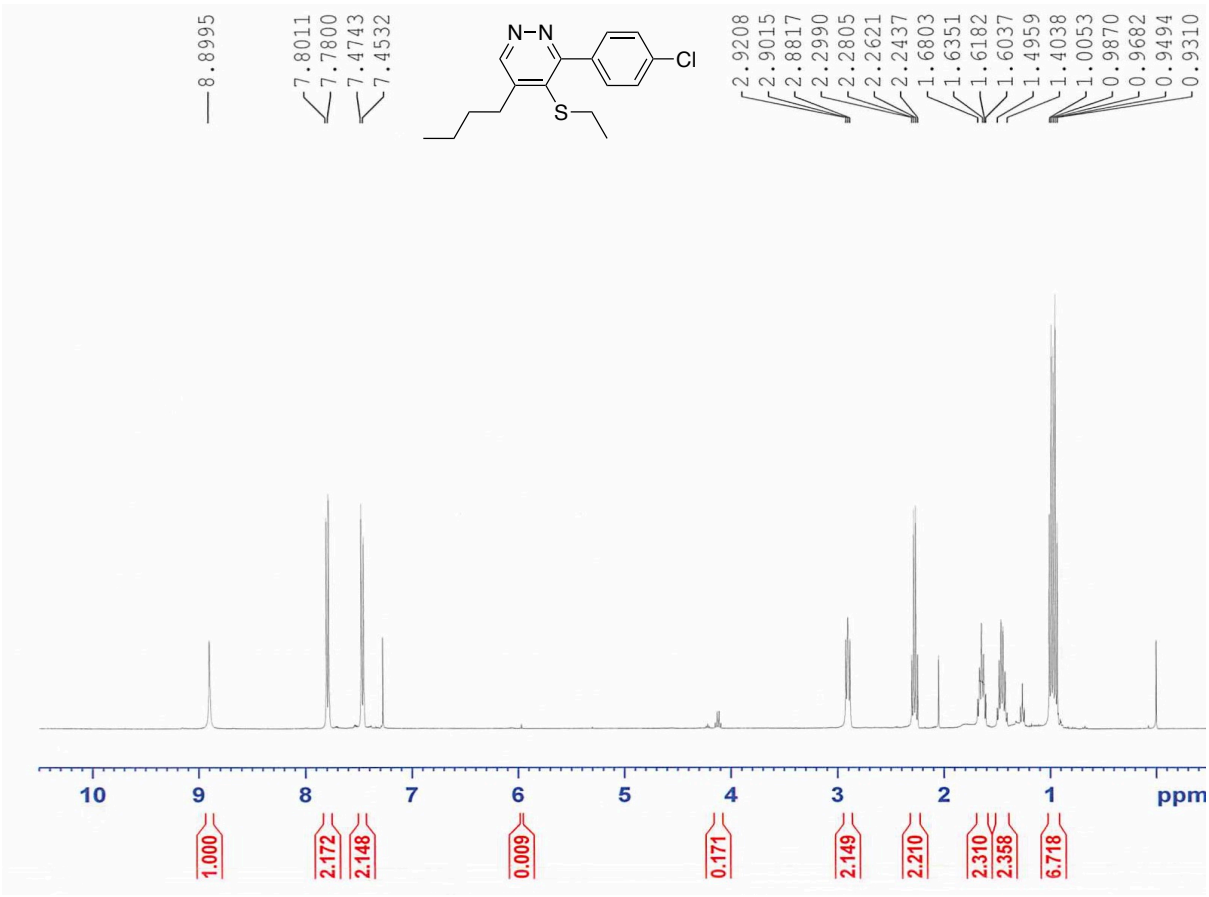



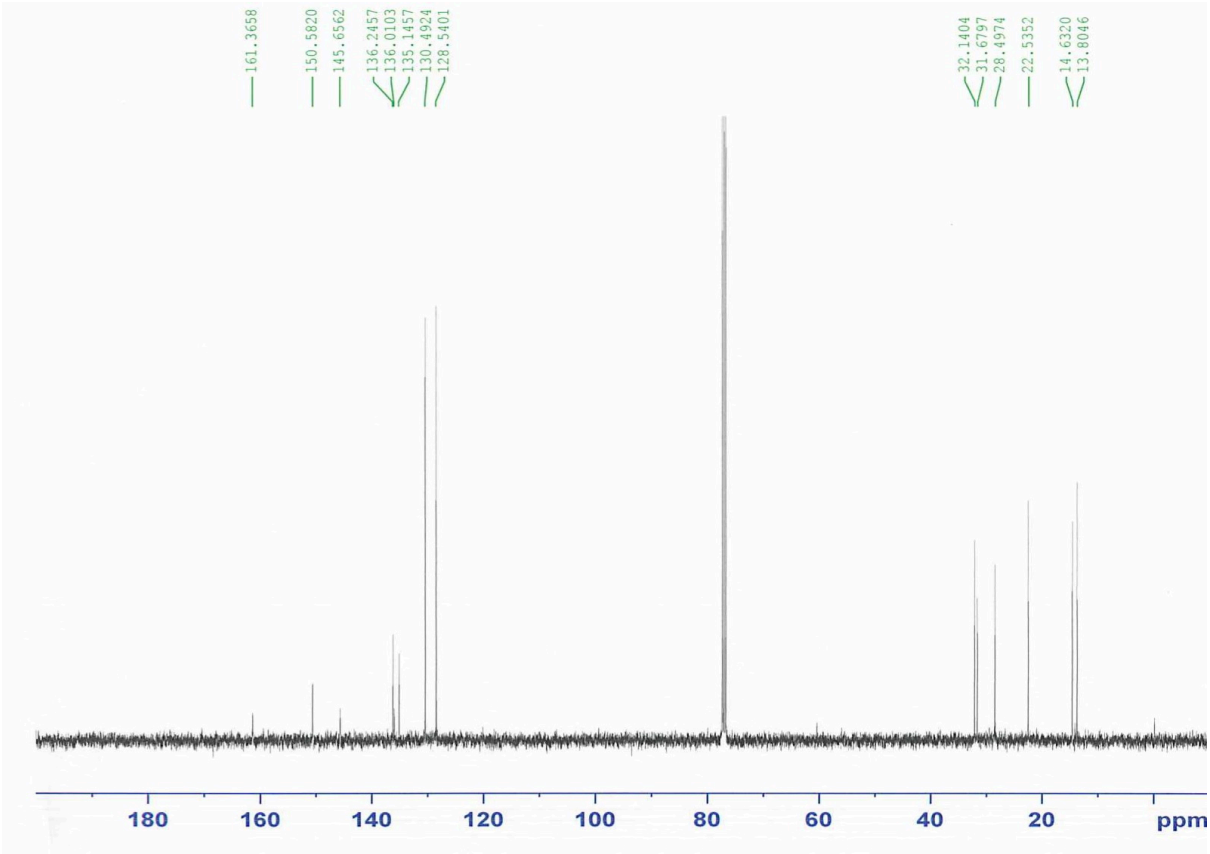
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-4-(ethylthio)-3-(4-fluorophenyl)pyridazine (**12r**) ($CDCl_3$)



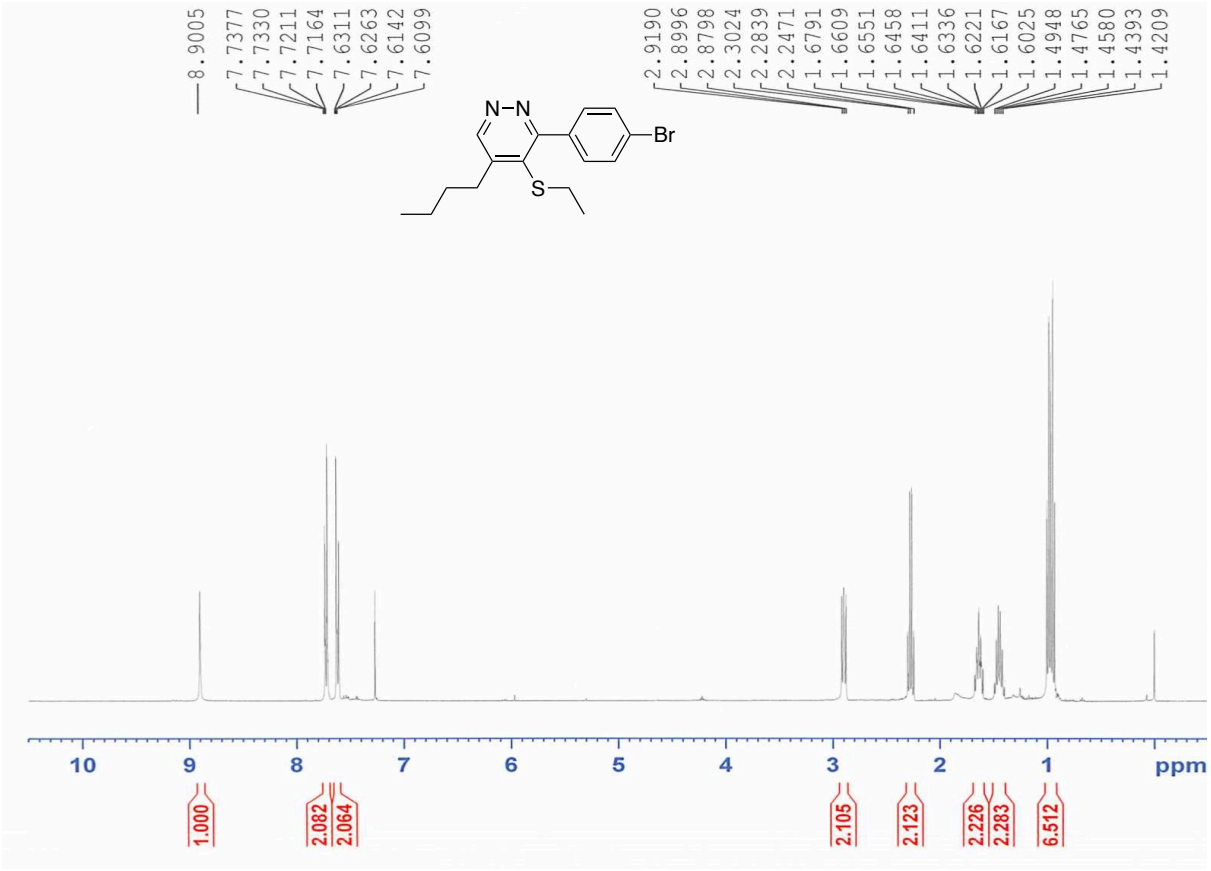



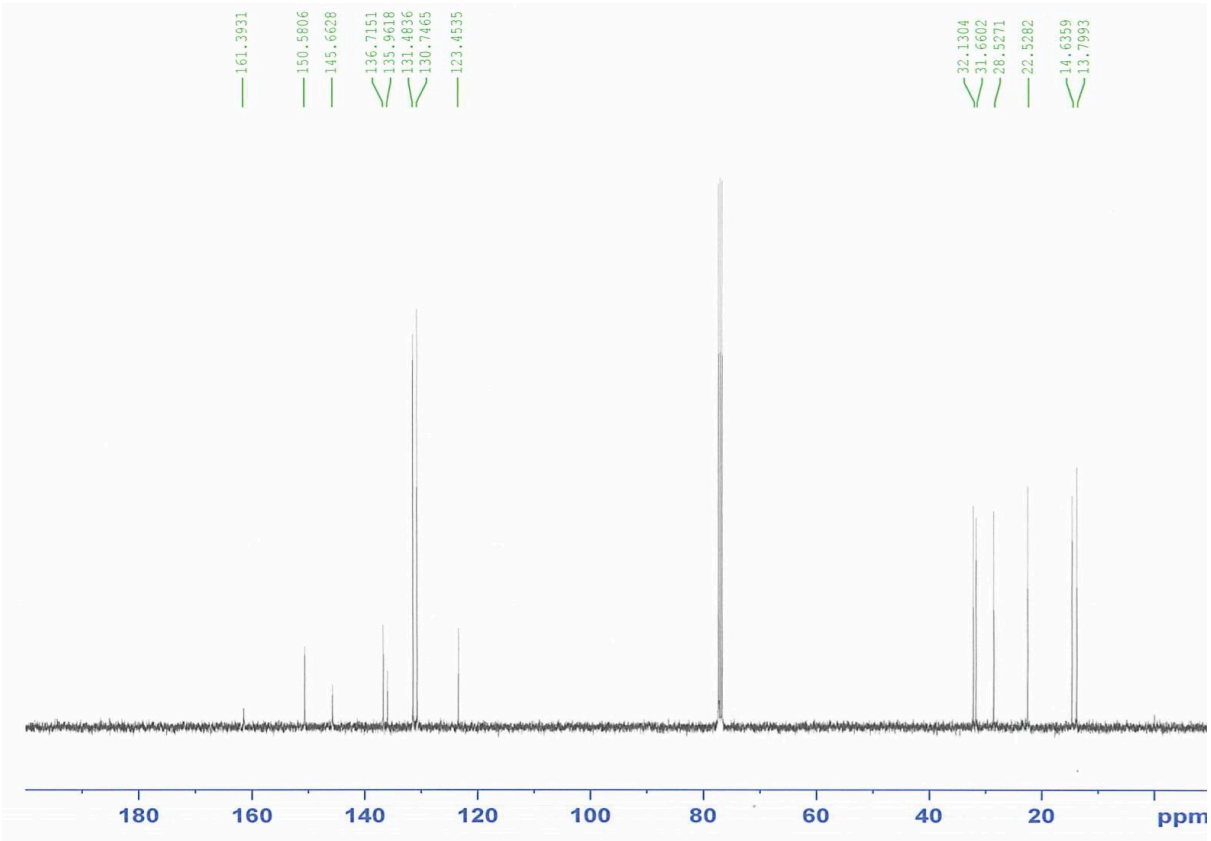
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-3-(4-chlorophenyl)-4-(ethylthio)pyridazine (**12s**) ($CDCl_3$)



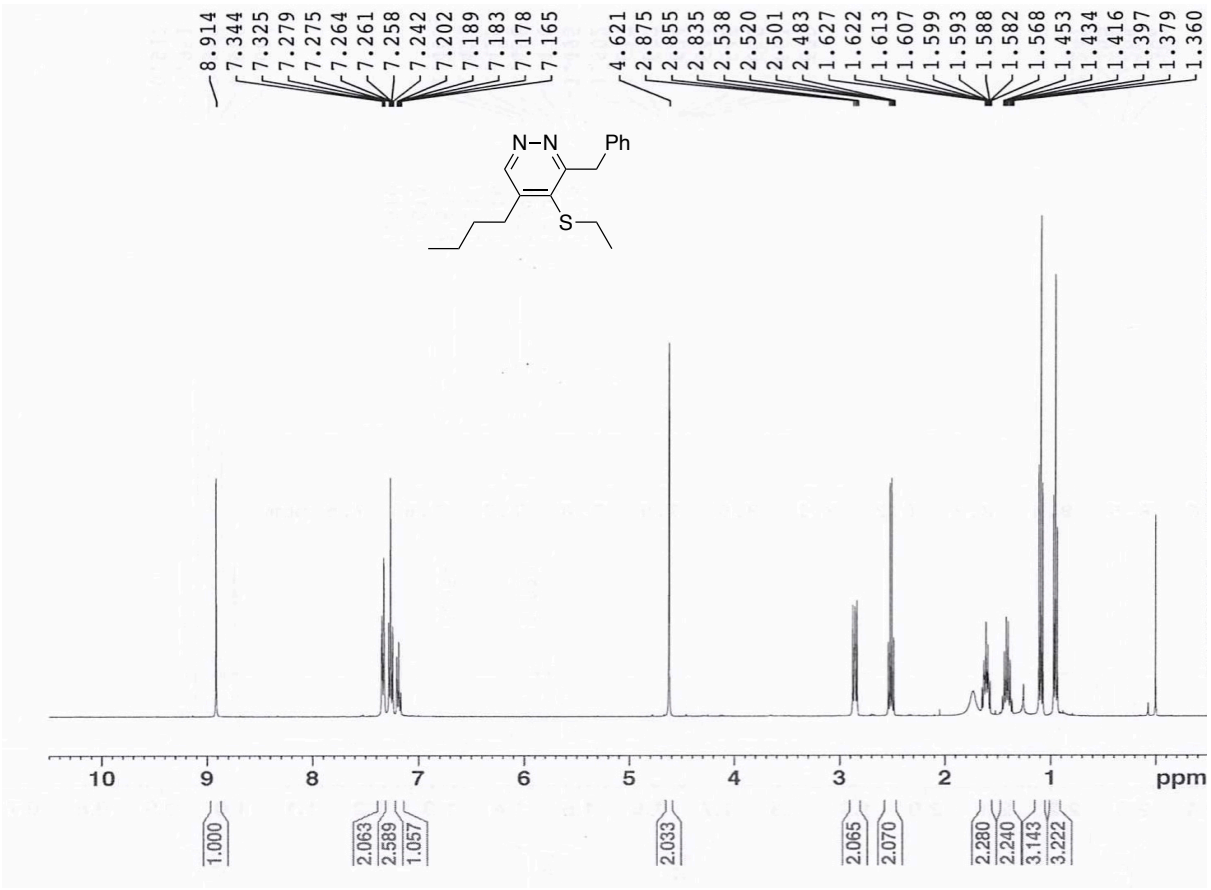



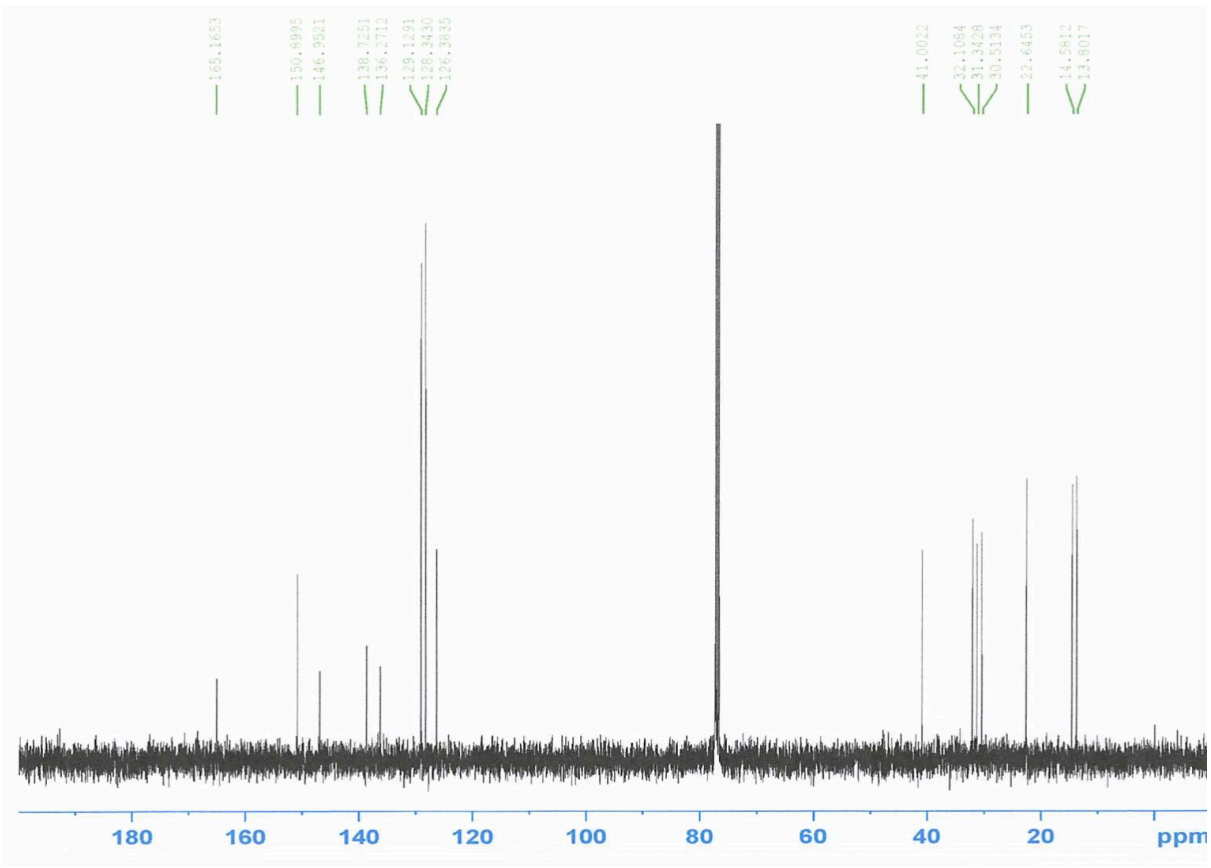
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 3-(4-bromophenyl)-5-butyl-4-(ethylthio)pyridazine (**12t**) ($CDCl_3$)



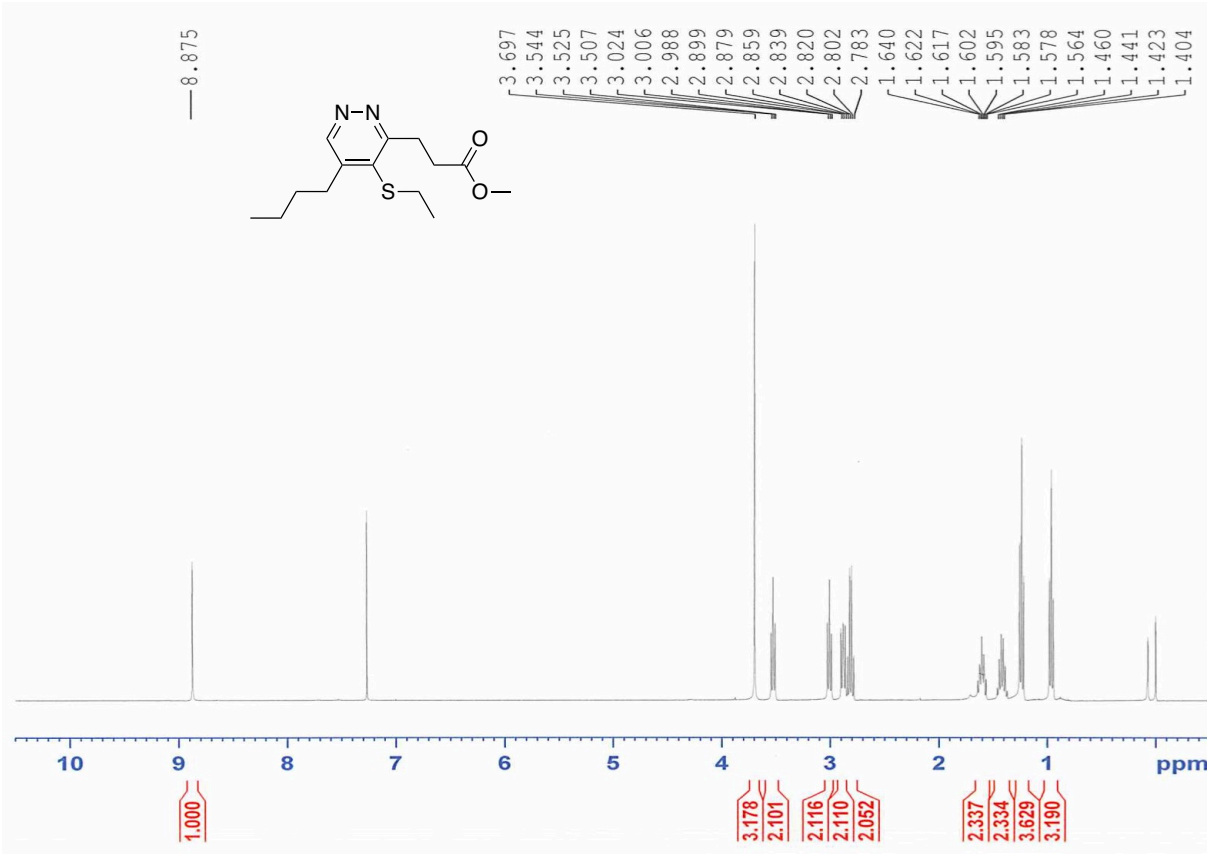



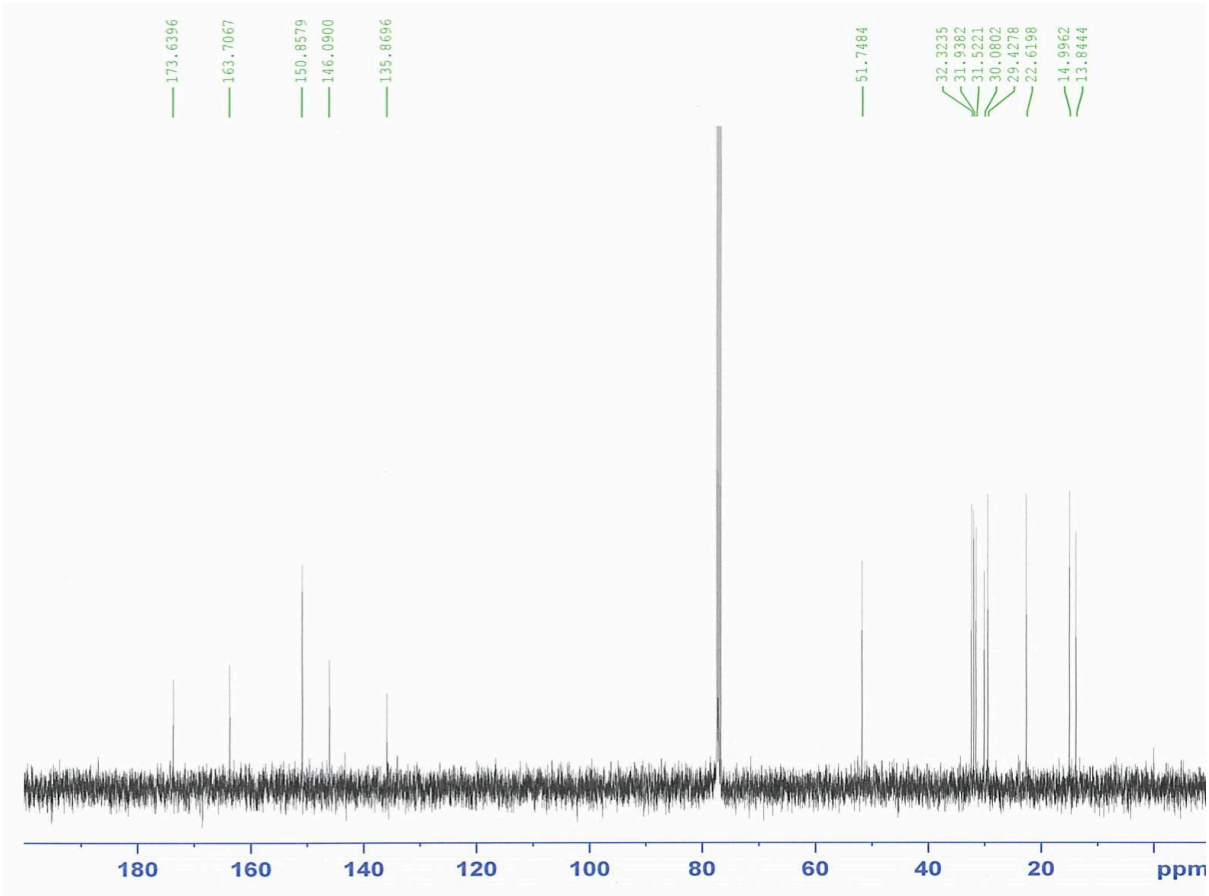
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 3-benzyl-5-butyl-4-(ethylthio)pyridazine (**12u**) ($CDCl_3$)



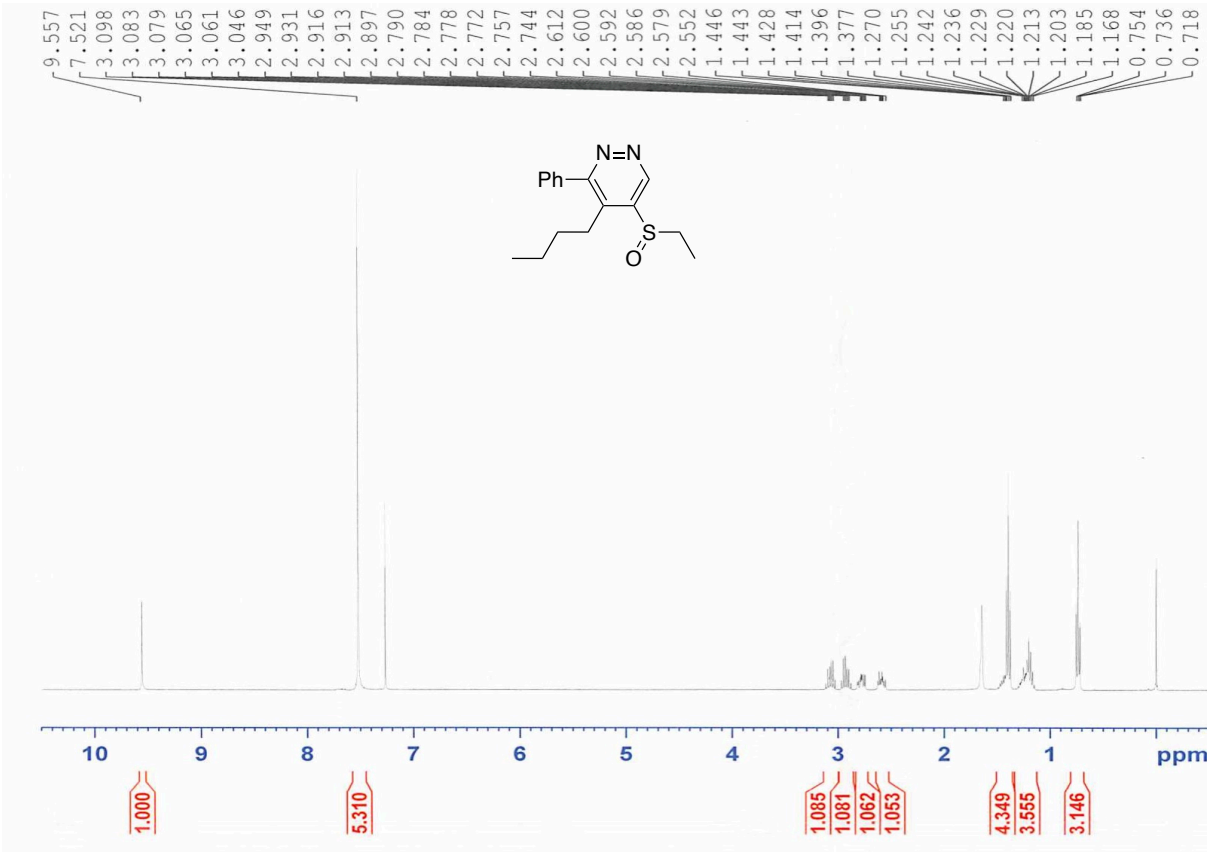



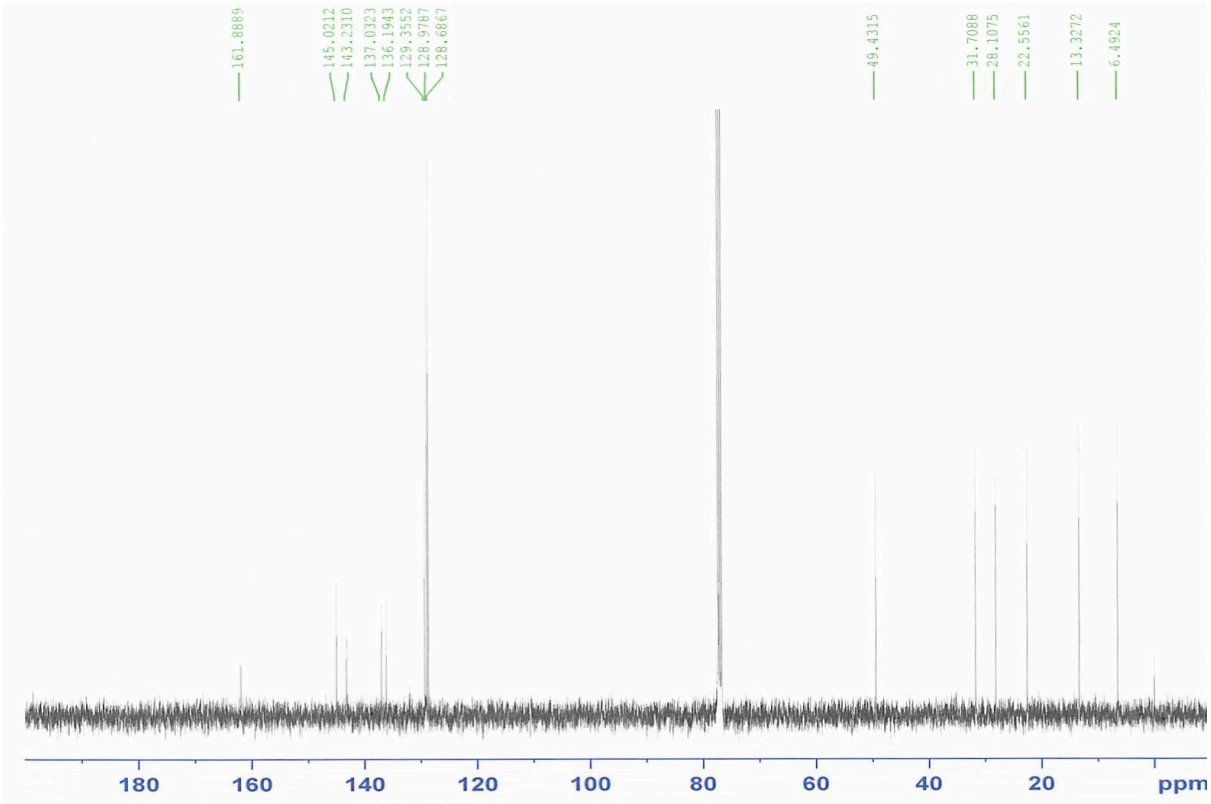
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of methyl 3-(5-butyl-4-(ethylthio)pyridazin-3-yl)propanoate (**12v**) ($CDCl_3$)



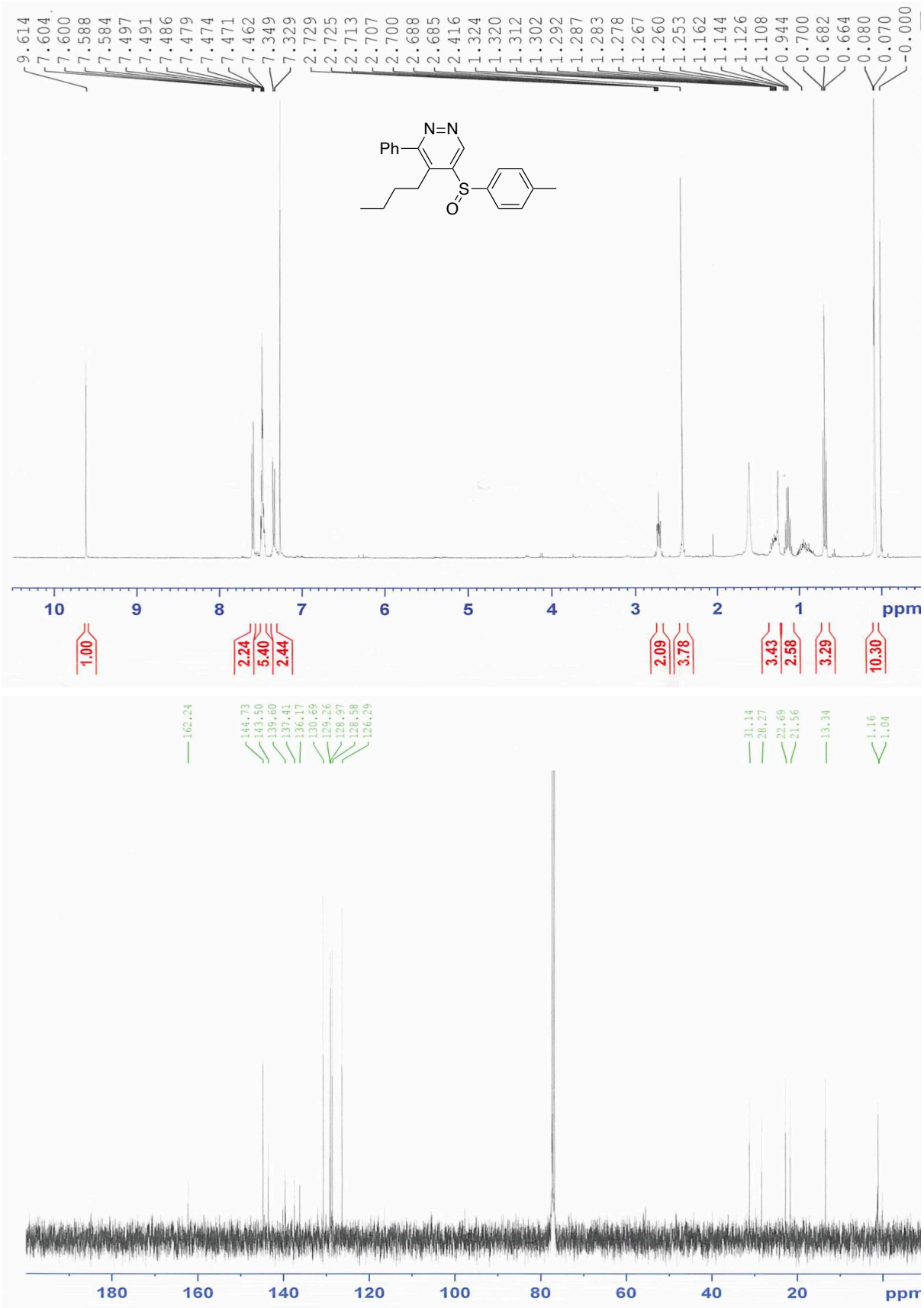



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 4-butyl-5-(ethylsulfinyl)-3-phenylpyridazine (**11x**) ($CDCl_3$)

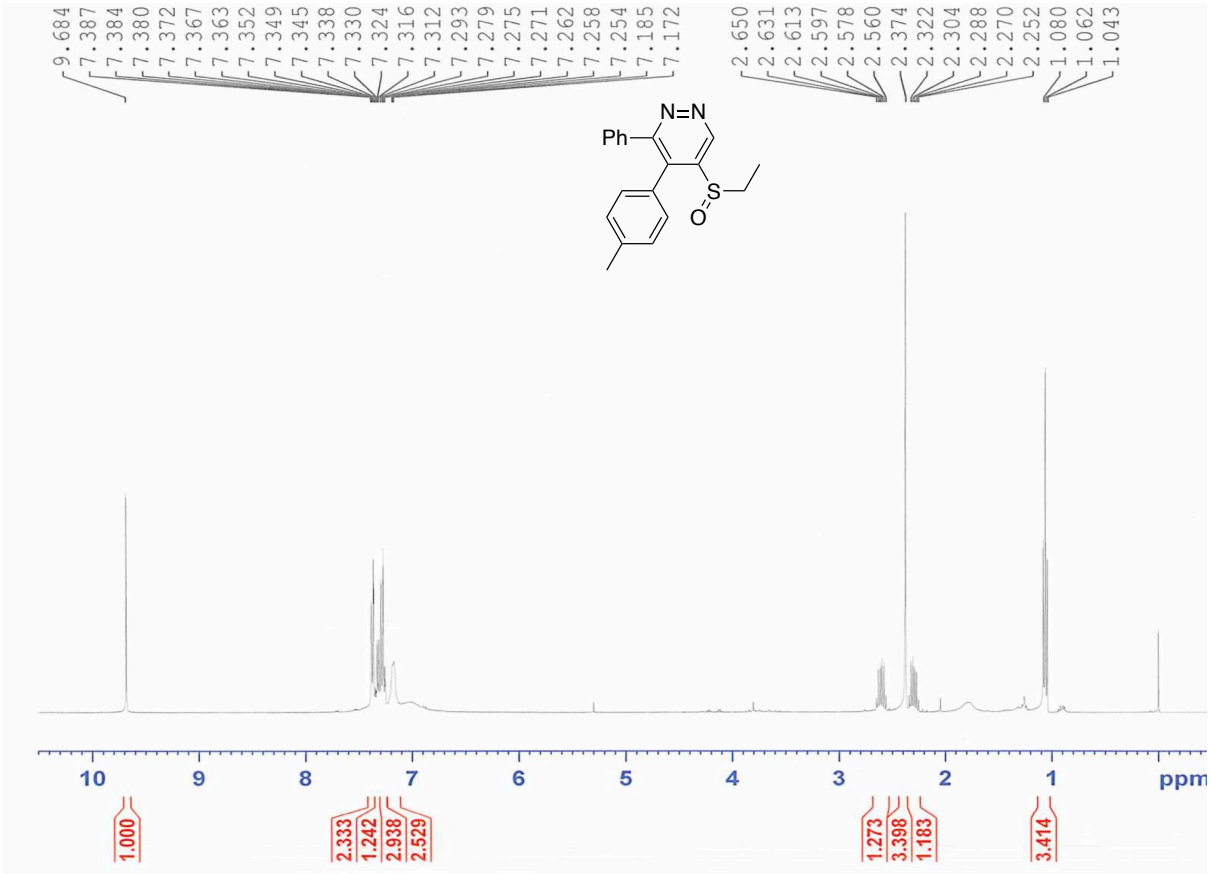


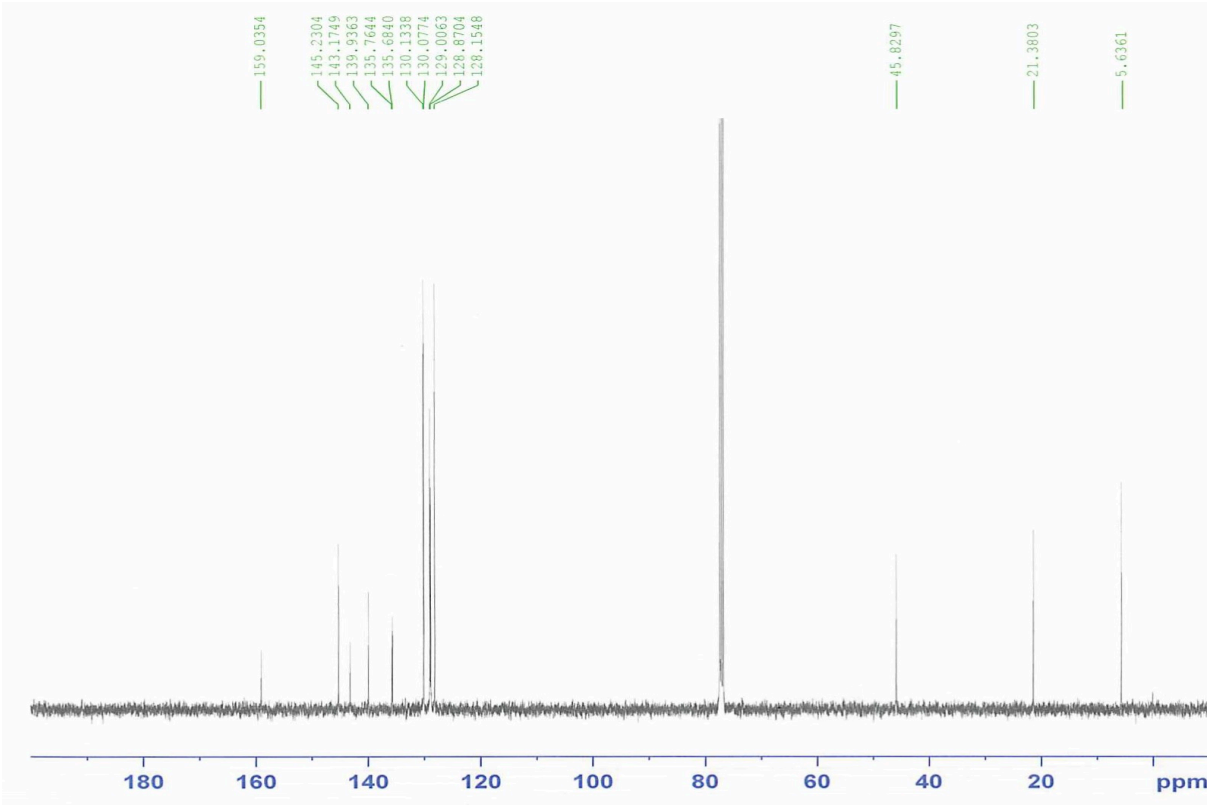



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 4-butyl-3-phenyl-5-(p-tolylsulfinyl)pyridazine (**11y**) ($CDCl_3$)

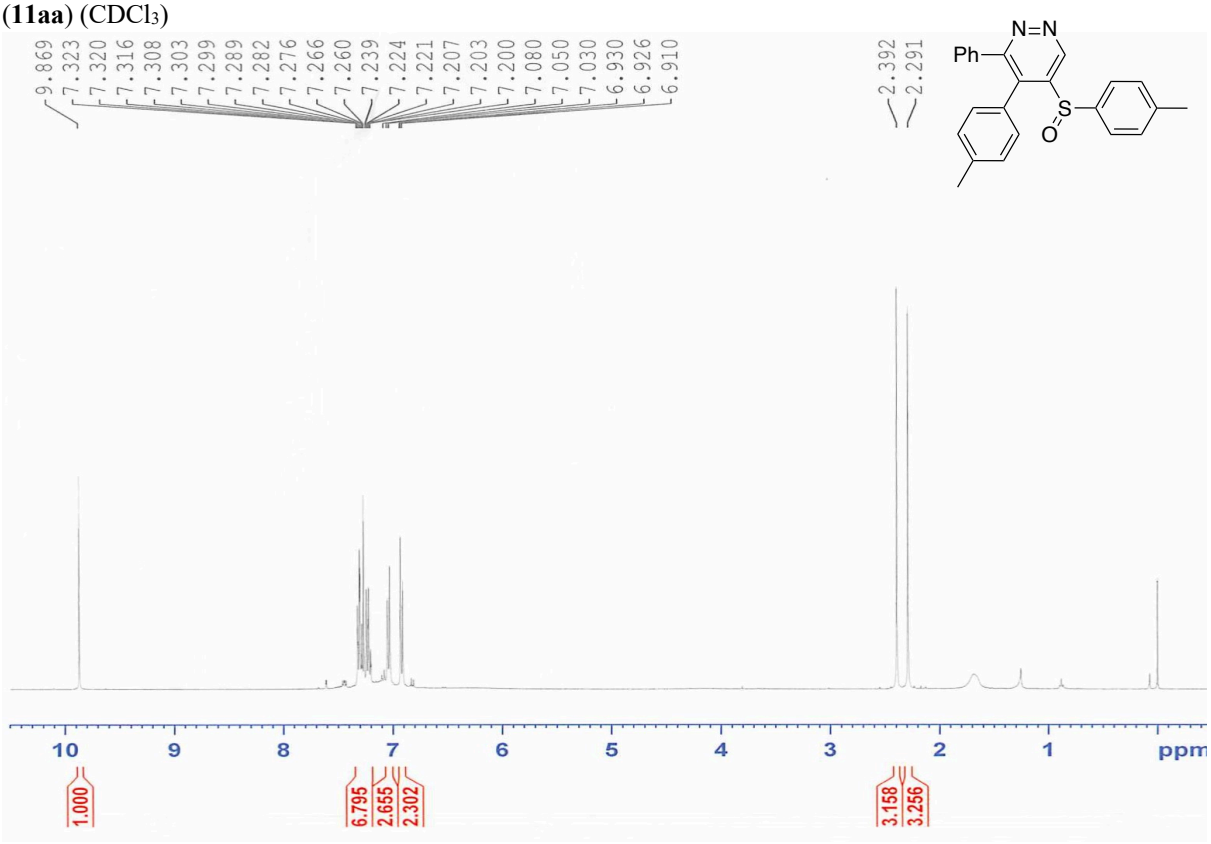


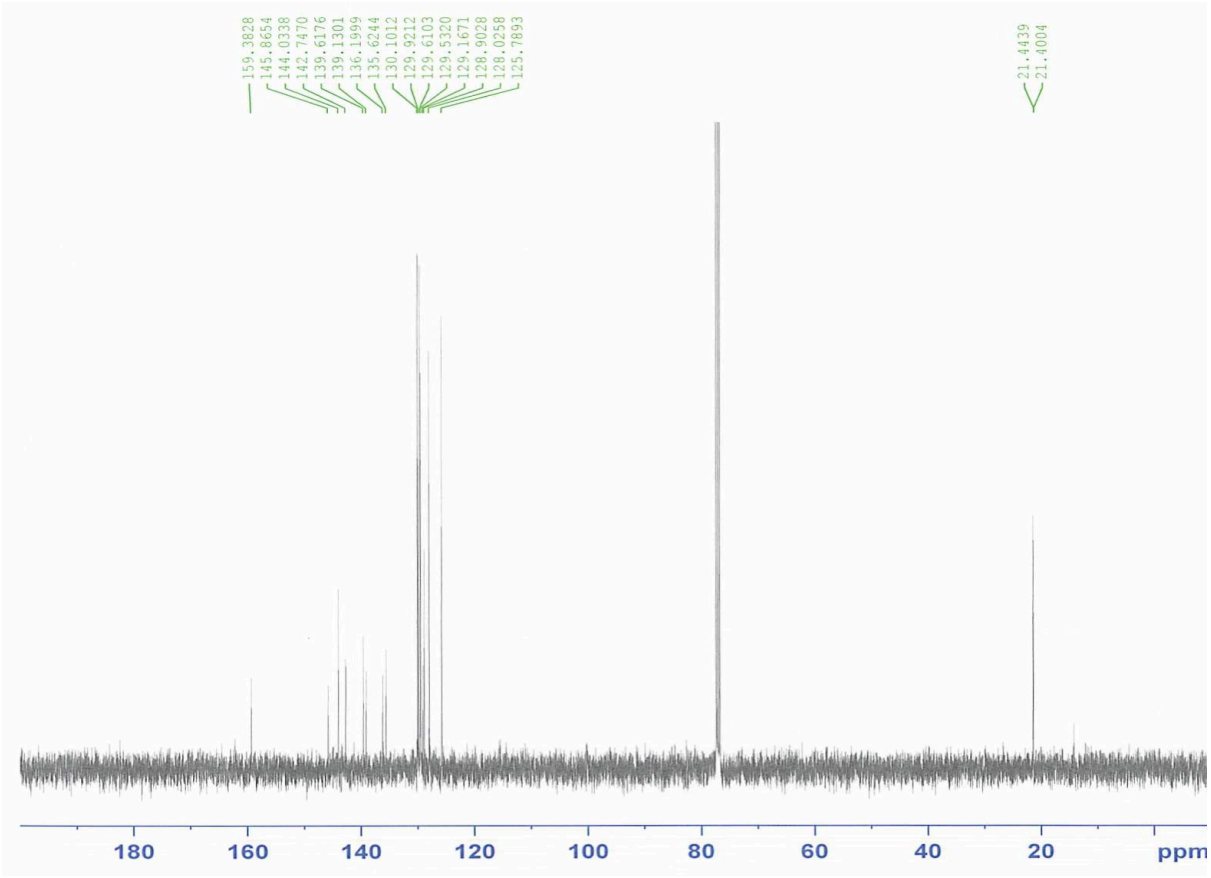
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-(ethylsulfinyl)-3-phenyl-4-(*p*-tolyl)pyridazine (**11z**) ($CDCl_3$)



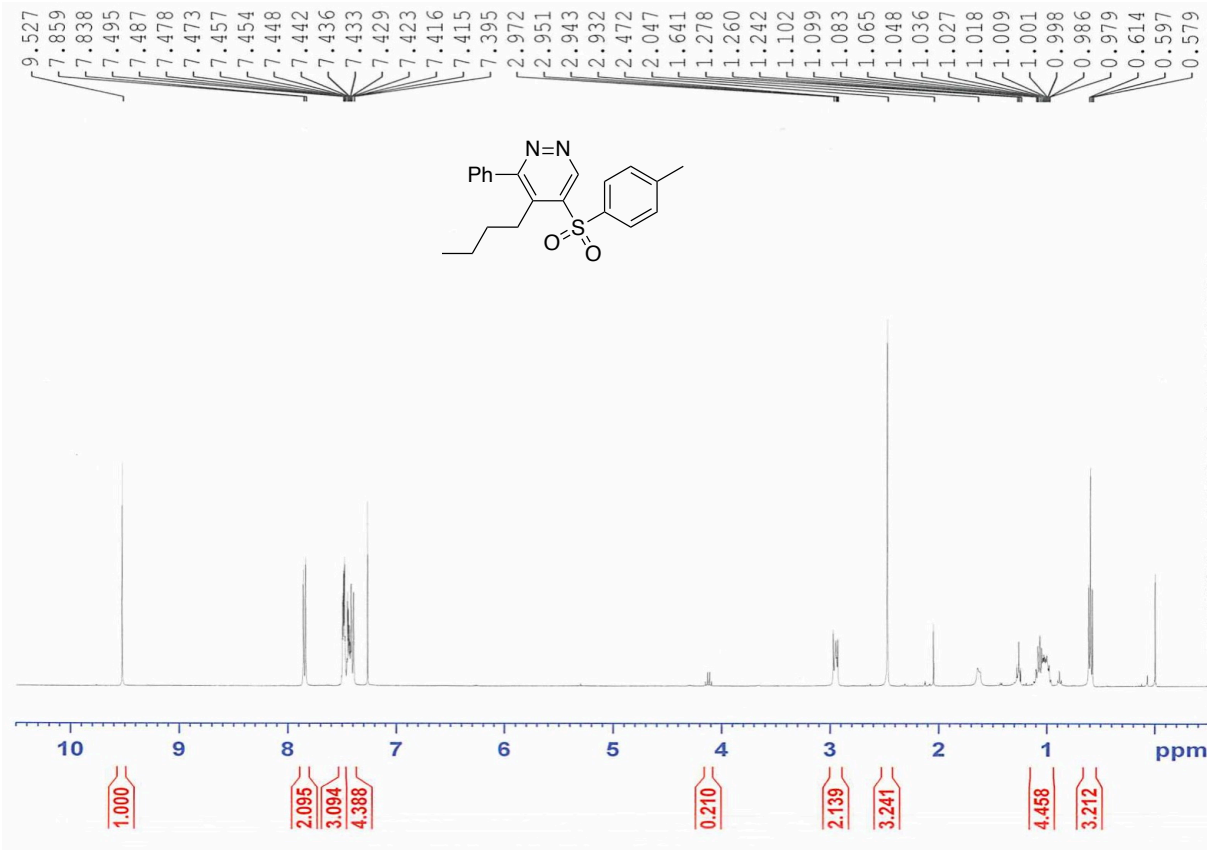



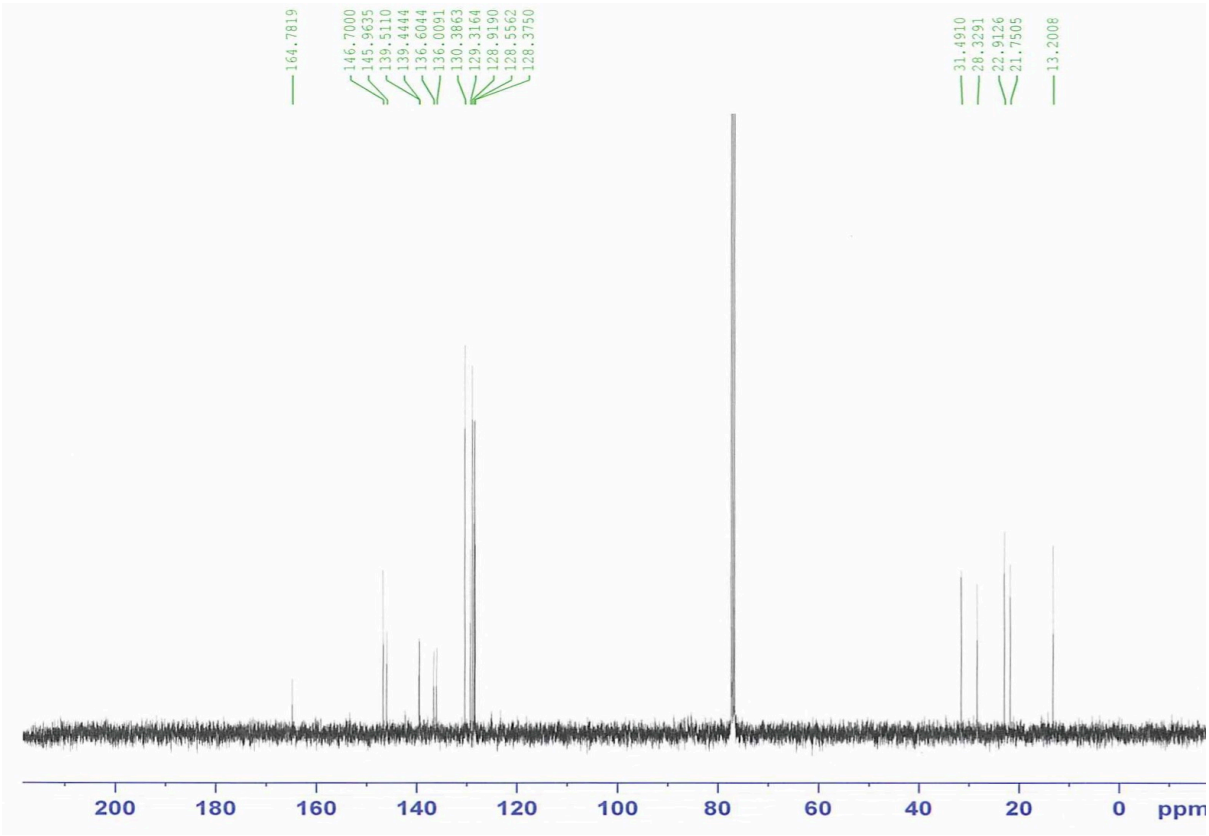
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 3-Phenyl-4-(p-tolyl)-5-(*p*-tolylsulfinyl) pyridazine (**11aa**) ($CDCl_3$)



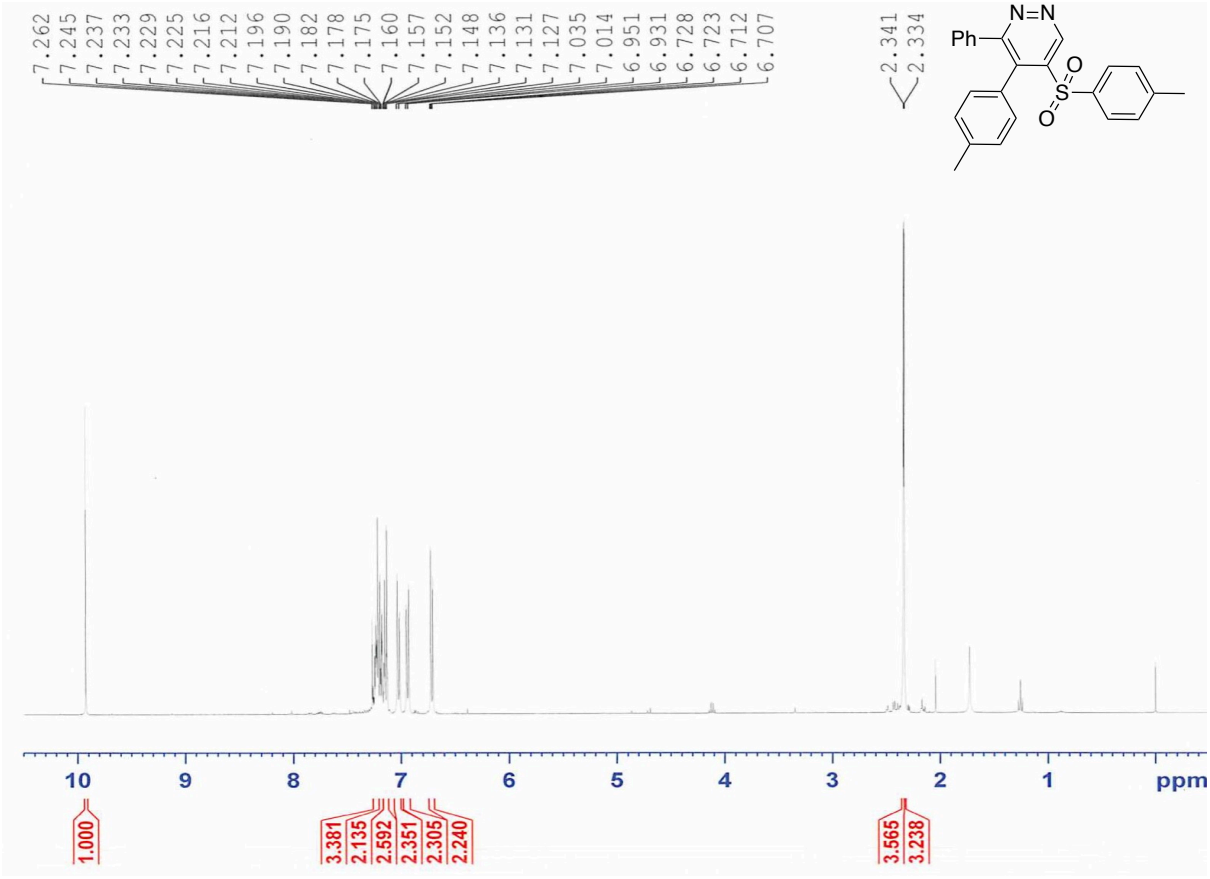



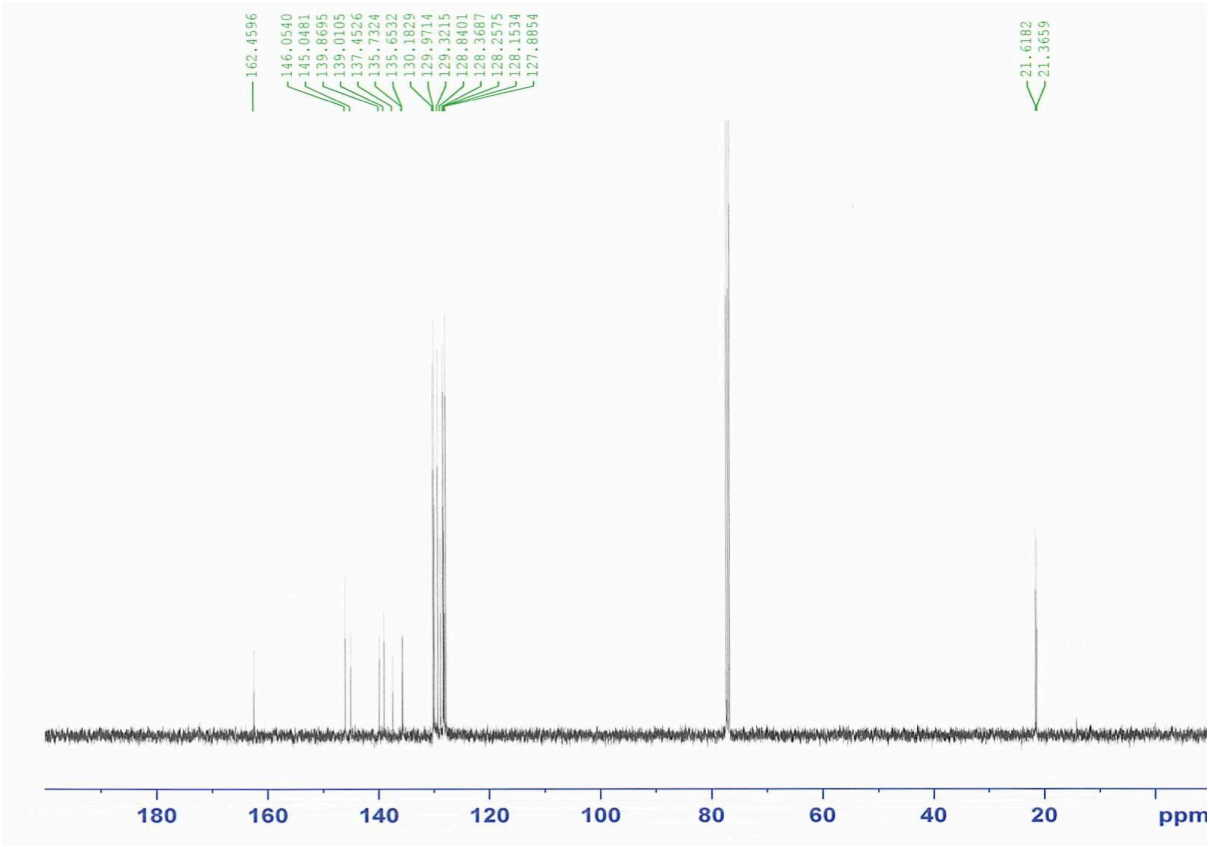
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 4-butyl-3-phenyl-5-tosylpyridazine (**11ab**) ($CDCl_3$)



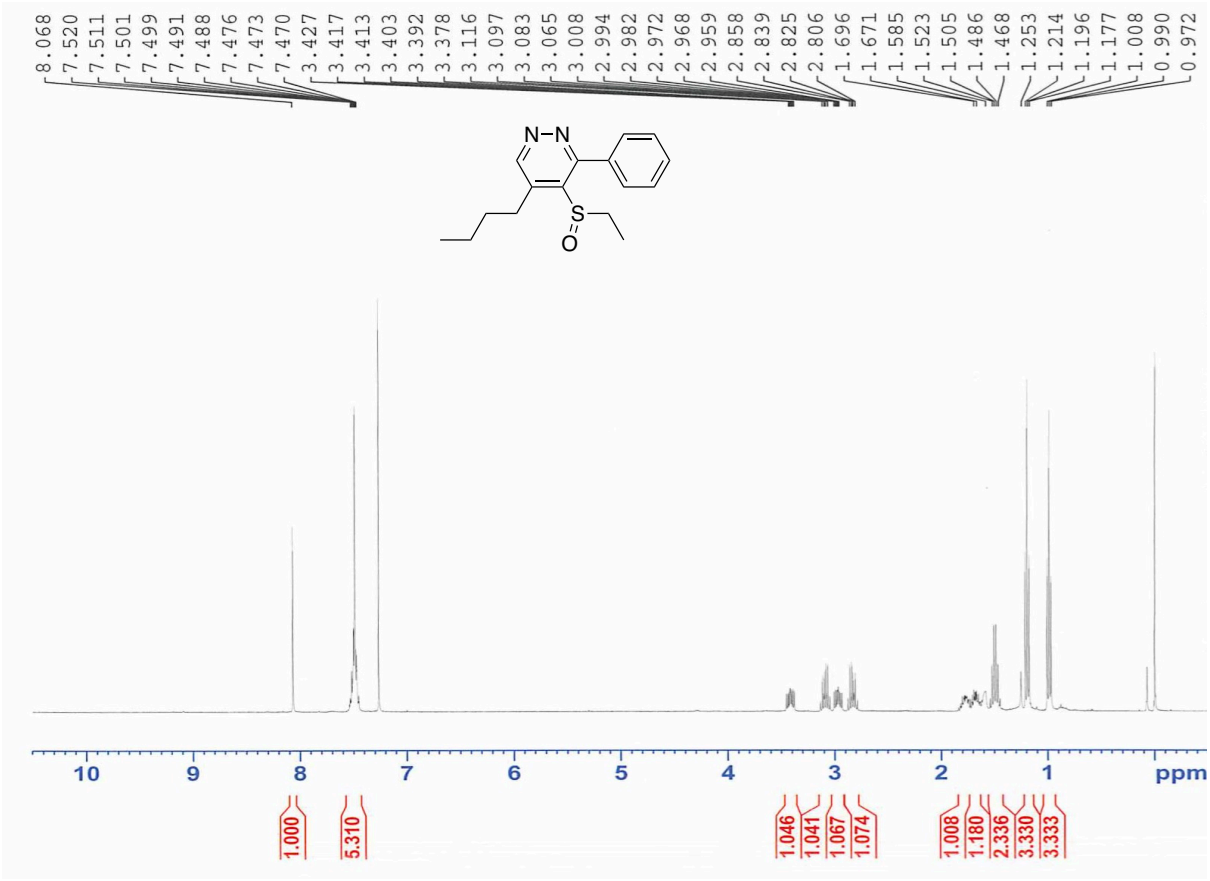



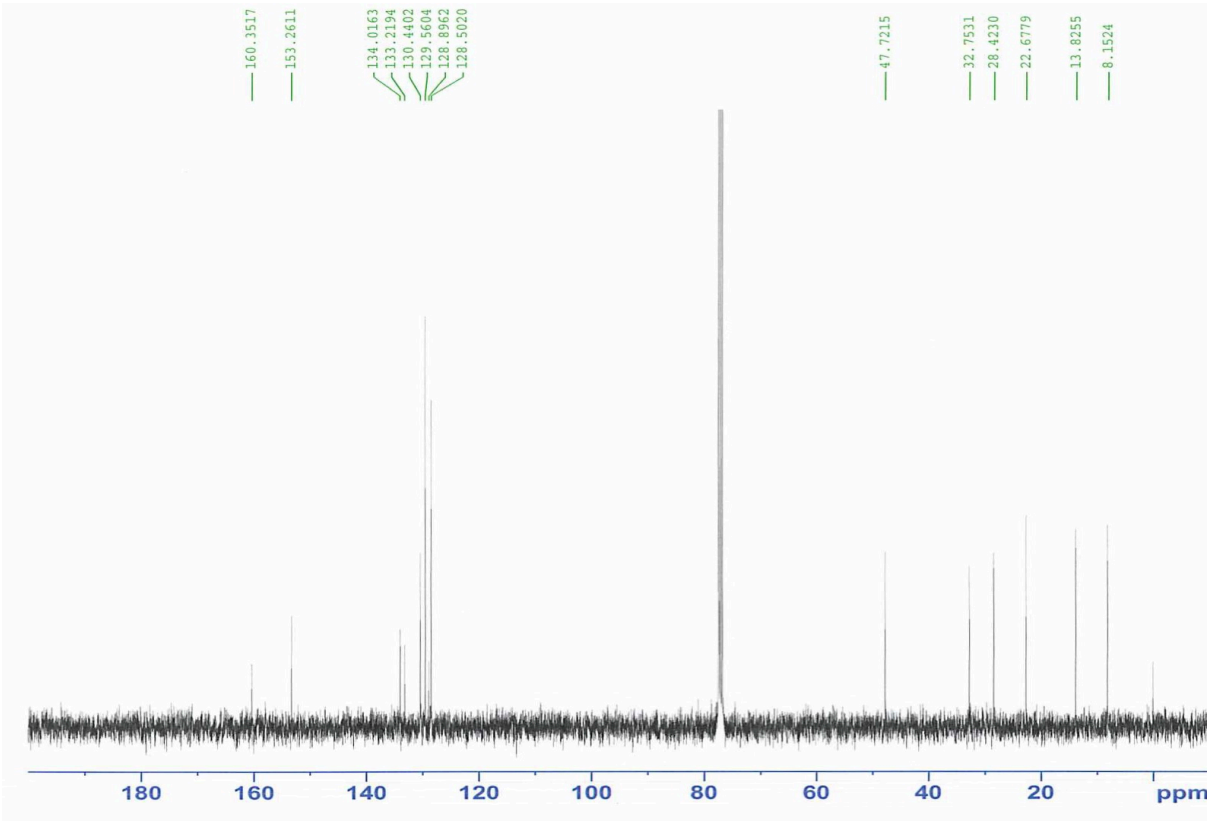
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 3-phenyl-4-(*p*-tolyl)-5-tosylpyridazine (**11ac**) ($CDCl_3$)



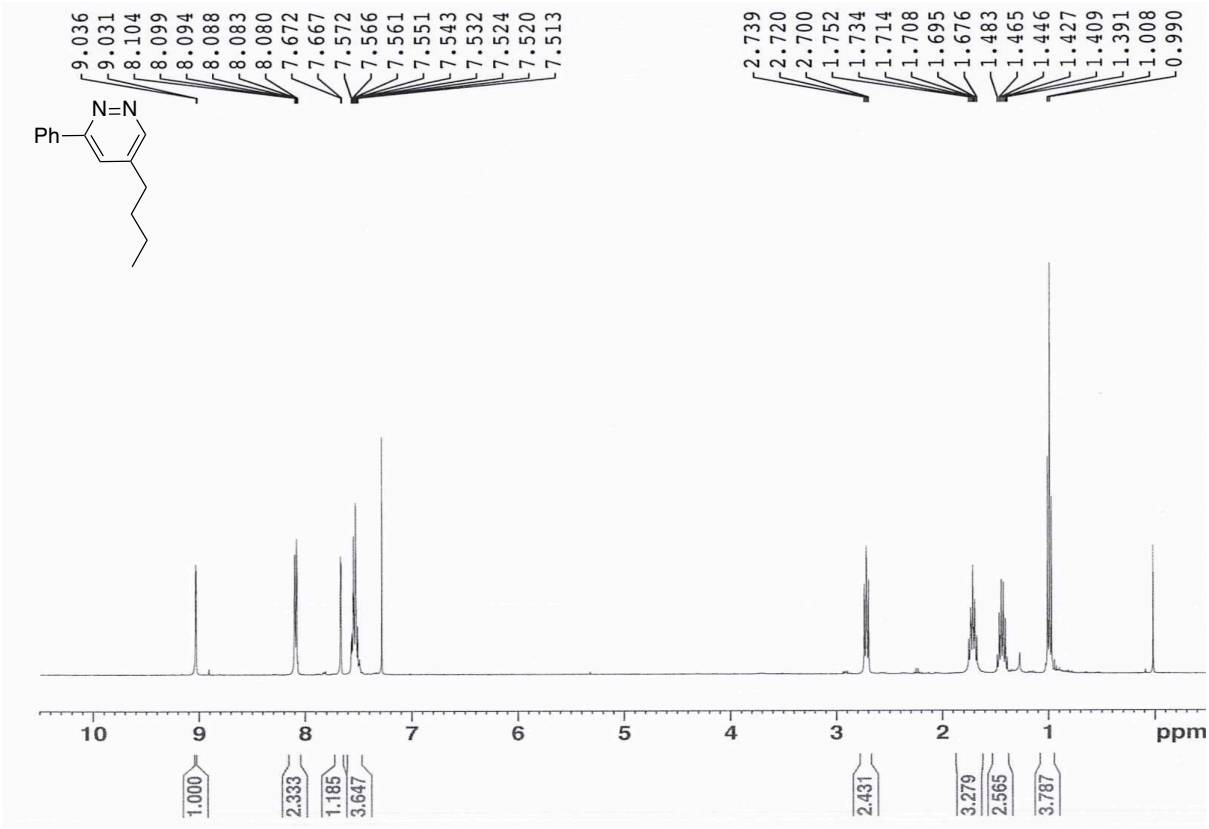



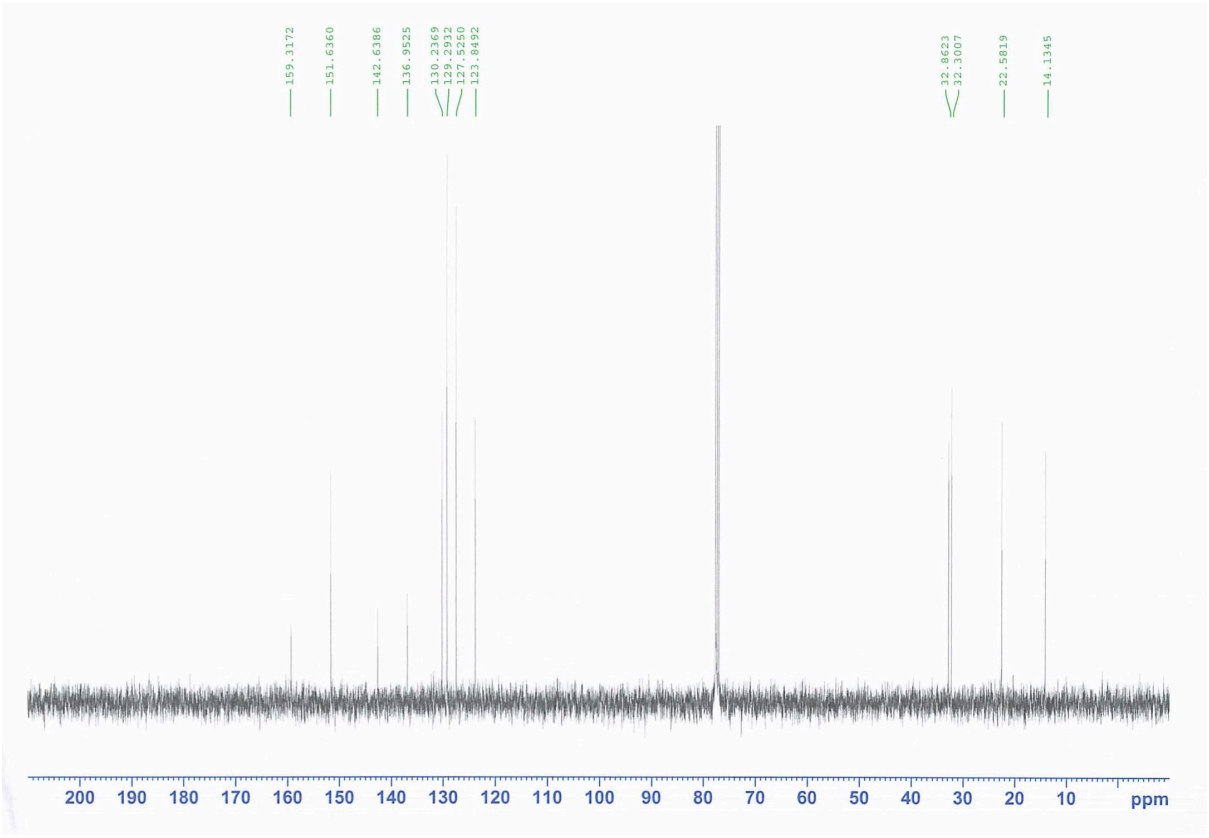
$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-4-(ethylsulfinyl)-3-phenylpyridazine (**12x**) ($CDCl_3$)



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 5-butyl-3-phenylpyridazine (**13**) ($CDCl_3$)



$^{1}$H NMR (400 MHz) and $^{13}$C NMR (101 MHz) spectra of 3-phenyl-4-(p-tolyl)-5-(p-tolylthio)pyridazine (**11b**) ($CDCl_3$)