

## 4-(Indol-3-yl) thiazole-2-amines and 4-indol-3-yl)thiazole acylamines as Novel antimicrobial agents. Synthesis, in silico and in vitro evaluation.

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**Table S1.** Antibacterial activity of methylindole derivatives. (MIC and MBC in mg/ml)

Compounds		<i>S.a.</i>	<i>B.c.</i>	<i>L.m.</i>	<i>E.c.</i>	<i>S.t.</i>	<i>En.cl.</i>
5g	MIC	>3.75	0.47	0.94	0.47	0.94	0.94
	MBC	>3.75	0.94	1.88	0.94	1.88	1.88
5h	MIC	>3.75	0.94	0.94	1.88	0.94	0.94
	MBC	>3.75	1.88	1.88	3.75	1.88	1.88
5i	MIC	>3.75	0.94	0.94	0.94	0.47	0.94
	MBC	>3.75	1.88	1.88	1.88	0.94	1.88
5j	MIC	>3.75	0.94	0.94	1.88	0.94	1.88
	MBC	>3.75	1.88	1.88	3.75	1.88	3.75
5k	MIC	>3.75	1.88	1.88	1.88	1.88	>3.75
	MBC	>3.75	3.75	3.75	3.75	3.75	>3.75
5p	MIC	>3.75	0.94	0.47	3.75	3.75	3.75
	MBC	>3.75	1.88	0.94	>3.75	>3.75	>3.75
5t	MIC	>3.75	>3.75	0.47	>3.75	>3.75	>3.75
	MBC	>3.75	>3.75	0.94	>3.75	>3.75	>3.75
5w	MIC	>3.75	0.94	1.88	1.88	>3.75	>3.75
	MBC	>3.75	1.88	3.75	3.75	>3.75	>3.75
6a	MIC	>3.75	>3.75	0.94	>3.75	>3.75	>3.75
	MBC	>3.75	>3.75	1.88	>3.75	>3.75	>3.75
6b	MIC	>3.75	>3.75	1.88	>3.75	>3.75	>3.75
	MBC	>3.75	>3.75	3.75	>3.75	>3.75	>3.75
6c	MIC	>3.75	>3.75	>3.75	>3.75	>3.75	>3.75
	MBC	>3.75	>3.75	>3.75	>3.75	>3.75	>3.75
6d	MIC	>3.75	1.88	0.94	>3.75	>3.75	>3.75
	MBC	>3.75	3.75	1.88	>3.75	>3.75	>3.75
6e	MIC	>3.75	>3.75	1.88	>3.75	>3.75	>3.75
	MBC	>3.75	>3.75	3.75	>3.75	>3.75	>3.75
6f	MIC	>3.75	>3.75	1.88	>3.75	>3.75	>3.75
	MBC	>3.75	>3.75	3.75	>3.75	>3.75	>3.75
Streptomycin	MIC	0.10±0.00	0.02±0.00	0.15±0.00	0.10±0.00	0.10±0.00	0.02±0.00
	MBC	0.20±0.01	0.05±0.00	0.30±0.01	0.20±0.00	0.20±0.01	0.05±0.00
Ampicillin	MIC	0.10±0.00	0.10±0.00	0.15±0.00	0.15±0.00	0.10±0.00	0.10±0.00
	MBC	0.15±0.00	0.15±0.00	0.30±0.02	0.20±0.01	0.20±0.00	0.15±0.01

**Table S2** Molecular docking free binding energies (kcal/mol) to antifungal targets of indole-based thiazole derivatives.

No	Est. binding energy(kcal/mol)		I-H	Residues involved in Hydrogen Bonds	Aromatic-positive ionizable	Hydrophobic interactions	Interactions with HEM601
	Dihydrofolate reductase	CYP51 <sub>Ca</sub>					

	(PDB: 4HOF)	(PDB: 5V5Z)	interactions				of CYP51 <sub>Ca</sub>
5a	-1.25	-8.35	1	Tyr64	-	Hem601, Ile131, Leu376, Met508	Hydrophobic
5c	-2.15	-7.96	1	Tyr118	-	Hem601, Tyr64, Tyr118, Ile131, Leu376, Met508	Hydrophobic
5d	-3.69	-11.62	1	Tyr132	Hem601	Hem601, Ile131, Tyr132, Phe288, Thr311, Leu376, Met508, Val509	Aromatic Fe binding Hydrophobic
5e	-3.45	-8.83	2	Tyr64, Tyr118	-	Hem601, Ile131, Leu300, Leu376, Met508	Hydrophobic
5f	-2.67	-8.05	1	Tyr132	-	Hem601, Tyr64, Ile131, Tyr132, His377, Met508	Hydrophobic
5i	-1.14	-8.13	1	Tyr118	-	Hem601, Tyr118, Ile131, Leu376, Met508	Hydrophobic
5l	-4.17	-11.13	2	Tyr132, Met508	Tyr188, Hem601	Hem601, Tyr118, Tyr122, Ile131, Tyr132, Phe233, Tyr305, Leu376, Met508, Val509	Aromatic Hydrophobic
5m	-3.67	-10.41	2	Tyr64, Tyr132	-	Hem601, Tyr118, Tyr132, Leu376, Met508, Val509	Hydrophobic
5n	-1.11	-9.46	2	Tyr118, Met508	Tyr132	Hem601, Ile131, Ile304, Leu376, Met508, Val509	Hydrophobic
5o	-2.03	-9.54	2	Tyr64, Tyr118	Tyr132	Hem601, Tyr118, Ile131, Leu376, Met508, Val509	Hydrophobic
5q	-1.18	-8.21	1	Tyr118	Tyr188	Hem601, Ile131, Tyr132, Leu376	Hydrophobic
5s	-3.97	-7.38	1	Tyr64	-	Hem601, Ile131, Tyr132, Met508	Hydrophobic
5u	-1.29	-8.21	1	Met508	Hem601	Hem601, Ile131, Tyr132, Leu376, Met508, Val509	Aromatic Hydrophobic
5v	-3.12	-9.75	1	Tyr64	Hem601	Hem601, Tyr118, Ile131, Tyr132, Leu376, Met508, Val509	Aromatic Hydrophobic
5x	-3.74	-12.55	1	Hem601	-	Hem601, Tyr118, Thr122, Phe126, Ile131, Tyr132, Phe288, Phe233, Thr311, Leu376, Phe380, Met508, Val509	Hydrogen bond Hydrophobic
Ketoconazole	-	-8.23	1	Tyr64	Hem601	Tyr118, Ile131, Tyr132, Hem601, Ile304, Leu300, Leu376, Met508	Aromatic, Hydrophobic

\*Number of hydrogen bonds.

**Table S3 .** Molecular docking free binding energies (kcal/mol) to antifungal targets of methylindole-based thiazole derivatives.

No	Est. binding energy(kcal/mol)	I-H*	Residues involved in	Aromatic-positive	Hydrophobic interactions	Interactions with
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	Dihydrofolate reductase (PDB: 4HOF)	CYP51 <sub>Ca</sub> (PDB: 5V5Z)		Hydrogen Bonds	ionizable interactions	HEM601 of CYP51 <sub>Ca</sub>	
5b	-3.26	-10.84	2	Tyr64, Tyr132	Tyr188	Hem601, Tyr118, Ile131, Tyr132, Leu376, Met508	Hydrophobic
5g	-3.14	-10.54	1	Hem601	-	Hem601, Phe126, Ile131, Tyr132, Phe233, Thr311, Leu376, Met508	Hydrogen bond, Hydrophobic
5h	-1.88	-8.15	-	-	-	Hem601, Phe126, Ile131, Leu376, Met508	Hydrophobic
5j	-3.16	-9.70	1	Tyr132	Hem601, Tyr188	Hem601, Tyr118, Ile131, Tyr132, Leu376, Met508	Aromatic, Hydrophobic
5k	-2.11	-9.41	1	Tyr64	-	Hem601, Tyr118, Ile131, Leu376, Met508	Hydrophobic
5p	-3.65	-8.76	1	Tyr132	Hem601	Hem601, Ile131, Tyr132, Thr311, Leu376, Met508	Aromatic, Hydrophobic
5r	-3.38	-11.15	-	-	Hem601	Hem601, Tyr118, Thr122, Ile131, Tyr132, Thr311, Leu376, Met508	Aromatic, Fe binding, Hydrophobic
5t	-3.47	-11.28	1	Hem601	Hem601	Hem601, Tyr118, Phe126, Ile131, Tyr132, Thr311, Leu376	Hydrogen bond, Aromatic, Fe binding, Hydrophobic
5w	-2.74	-7.82	-	-	-	Hem601, Tyr122, Phe126, Leu376, Met508	Hydrophobic
6b	-1.27	-8.73	1	Tyr64	-	Hem601, Tyr118, Ile131, Leu376, Met508	Hydrophobic
6c	-2.55	-11.02	1	Hem601	Tyr188, Hem601	Hem601, Tyr118, Tyr122, Ile131, Tyr132, Phe233, Leu376, Met508	Hydrogen bond, Aromatic, Hydrophobic
6d	-2.97	-9.72	2	Tyr64, Tyr132	Hem601	Hem601, Tyr118, Tyr132, Leu376, Met508	Aromatic, Hydrophobic
6g	-1.27	-10.88	1	Tyr118	Tyr132, Hem601	Hem601, Ile131, Tyr131, Phe126, Ile304, Leu376, Met508	Aromatic, Hydrophobic
Ketoconazole	-	-8.23	1	Tyr64	Hem601	Tyr118, Ile131, Tyr132, Hem601, Ile304, Leu300, Leu376, Met508	Aromatic, Hydrophobic

\*Number of hydrogen bonds.

**Table S4. Drug likeness predictions of tested compounds.**

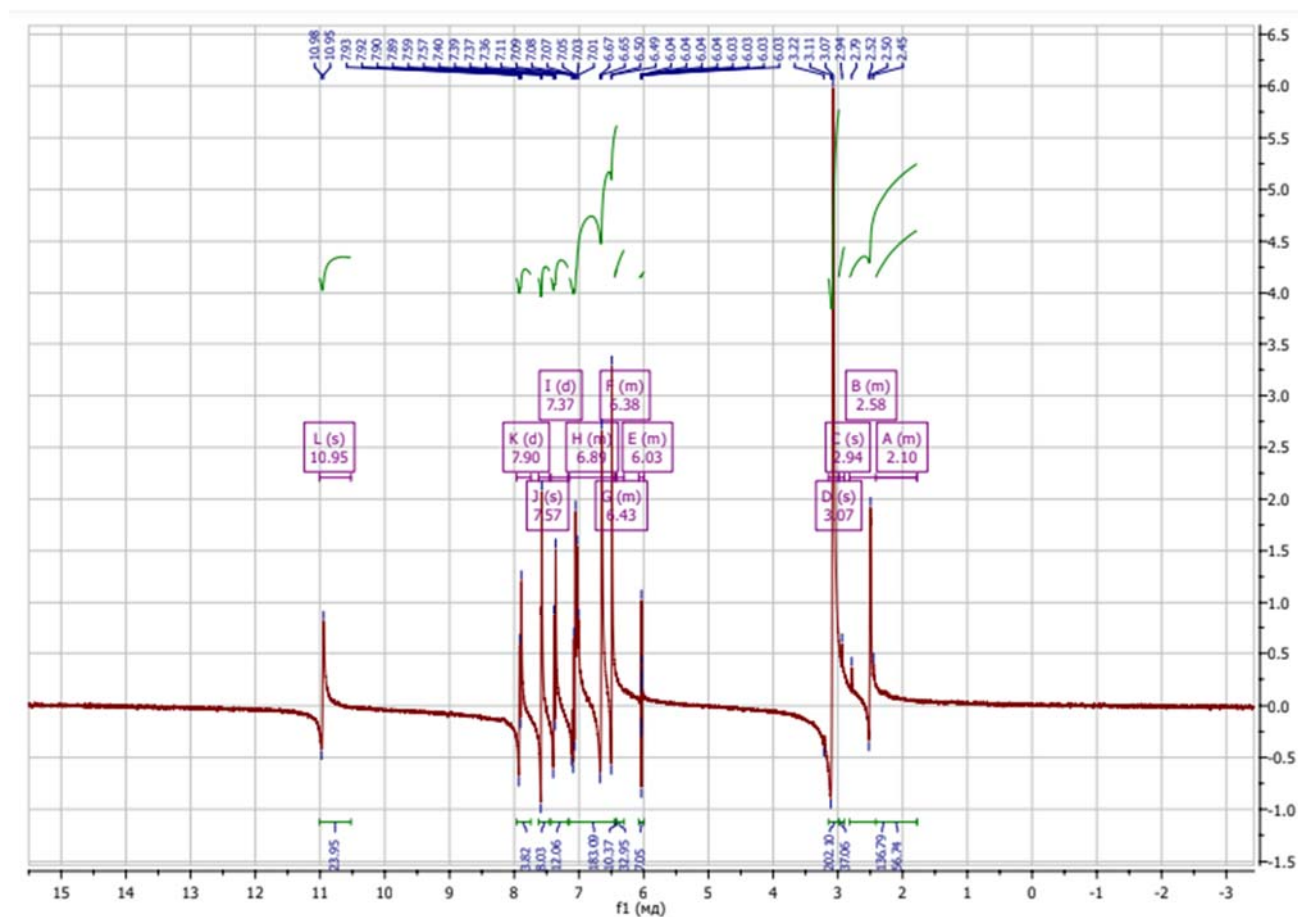
No	MW	Number of HBA <sup>a</sup>	Number of HBD <sup>b</sup>	Log $P_{o/w}$ (iLOGP) <sup>c</sup>	Log S <sup>d</sup>	TPSA <sup>e</sup>	BBB permeant <sup>f</sup>	Lipinski, Ghose, Veber, Egan, and Muegge violations	Bioavailability Score	Drug-likeness model score
5a	215.27	1	2	1.55	Moderately soluble	82.94	No	0	0.55	-1.71
5b	245.30	2	2	1.87	Moderately soluble	92.17	No	0	0.55	-1.16
5c	245.30	2	2	1.87	Moderately soluble	92.17	No	0	0.55	-1.16
5d	229.30	1	2	1.75	Moderately soluble	82.94	No	0	0.55	-1.57
5e	233.26	2	2	1.66	Moderately soluble	60.17	No	0	0.55	-1.38
5f	259.33	2	2	2.08	Moderately soluble	92.17	No	0	0.55	-0.57
5g	273.35	2	1	2.54	Moderately soluble	81.31	No	0	0.55	-0.90
5h	363.48	2	1	3.62	Poorly soluble	67.32	Yes	0	0.55	-0.29
5i	273.35	2	2	2.45	Moderately soluble	78.18	Yes	0	0.55	-0.51
5j	287.38	2	1	2.89	Moderately soluble	67.32	Yes	0	0.55	-0.83
5k	257.35	1	1	2.61	Moderately soluble	58.09	Yes	0	0.55	-1.42
5l	257.35	1	1	2.47	Moderately soluble	68.95	Yes	0	0.55	-1.22
5m	263.75	1	2	2.10	Moderately soluble	82.94	No	0	0.55	-0.74
5n	259.33	2	2	2.16	Moderately soluble	92.17	No	0	0.55	-0.96
5o	243.33	1	2	1.96	Moderately soluble	82.94	No	0	0.55	-1.01
5p	243.33	1	1	2.17	Moderately soluble	72.08	Yes	0	0.55	-1.48
5q	243.33	1	1	2.17	Moderately soluble	72.08	Yes	0	0.55	-1.47
5r	257.35	1	1	2.34	Moderately soluble	72.08	Yes	0	0.55	-1.42
5s	229.30	1	2	1.78	Moderately soluble	82.94	No	0	0.55	-0.88
5t	271.38	1	1	2.82	Moderately soluble	58.09	Yes	0	0.55	-1.34
5u	257.35	1	2	2.31	Moderately soluble	68.95	Yes	0	0.55	-0.96

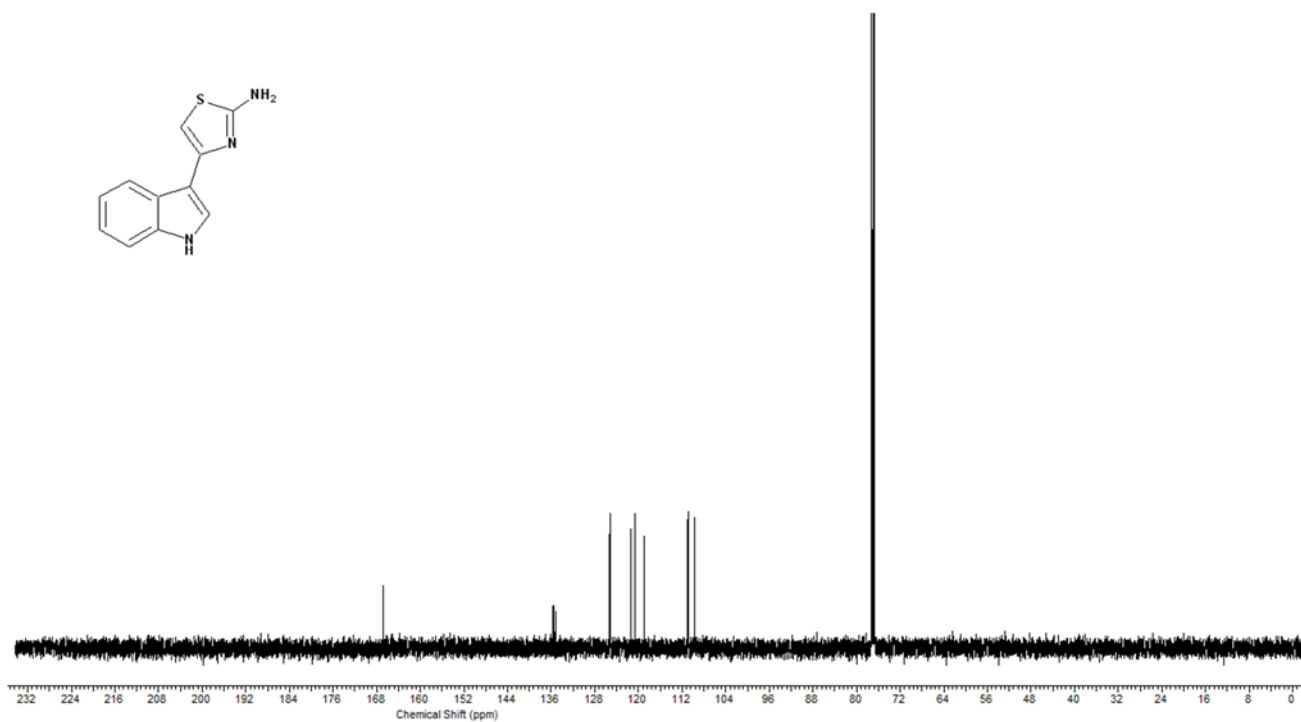
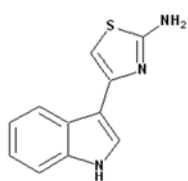
5v	259.33	2	2	2.15	Moderately soluble	78.18	Yes	0	0.55	-1.09
5w	243.33	1	1	2.17	Moderately soluble	72.08	Yes	0	0.55	-1.48
5x	270.35	2	2	2.15	Moderately soluble	81.31	No	0	0.55	-1.44

a) number of hydrogen bond acceptors; b) number of hydrogen bond donors; c) lipophilicity; d) Water solubility (SILICOS-IT [S=Soluble]); e) topological polar surface area ( $\text{\AA}^2$ ); f) Blood Brain Barrier permeant;

## $^1\text{H}$ -NMR AND $^{13}\text{C}$ -NMR OF COMPOUNDS

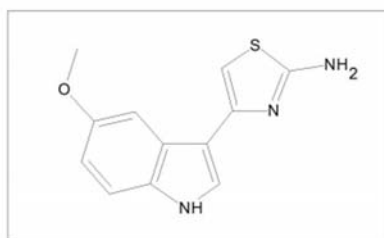
### Compound 5a





### Compound 5b

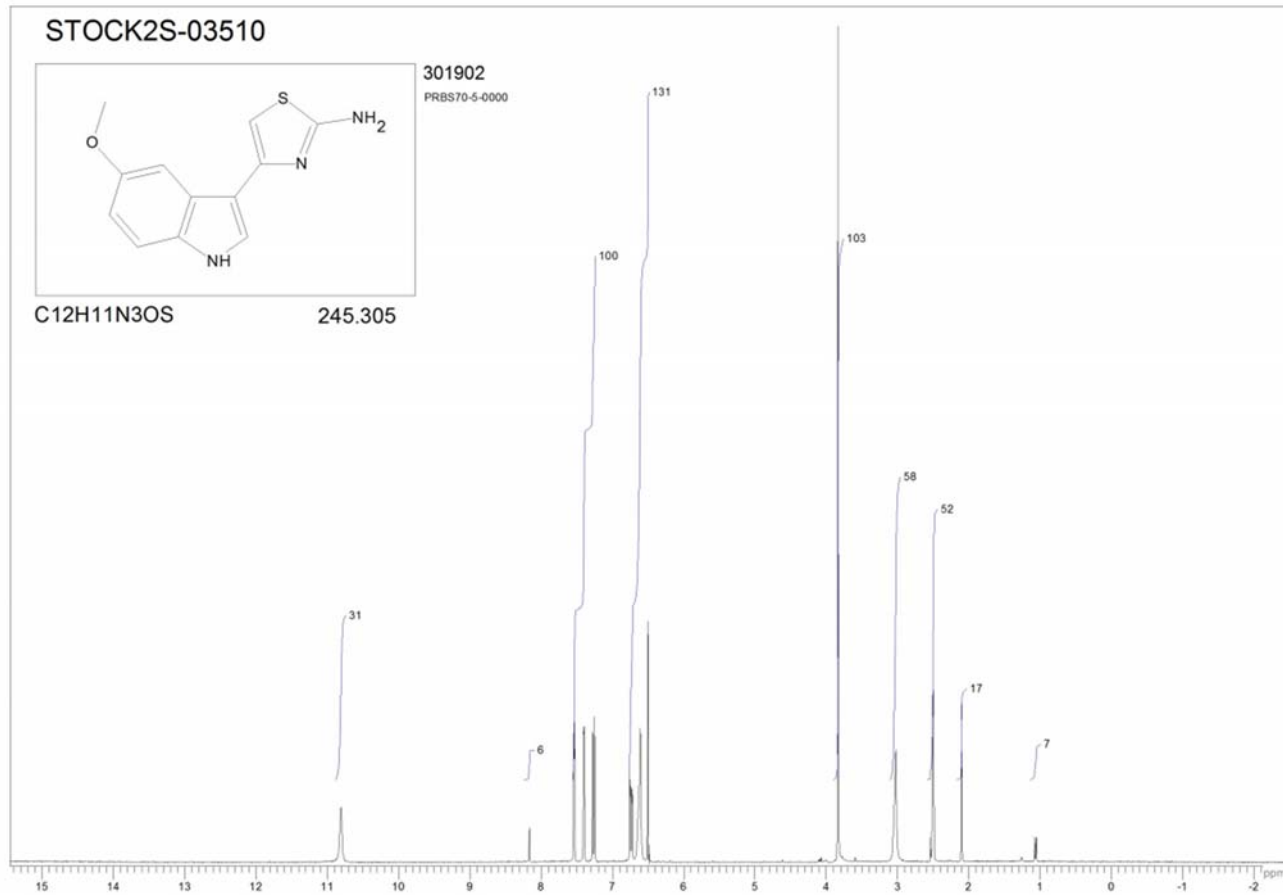
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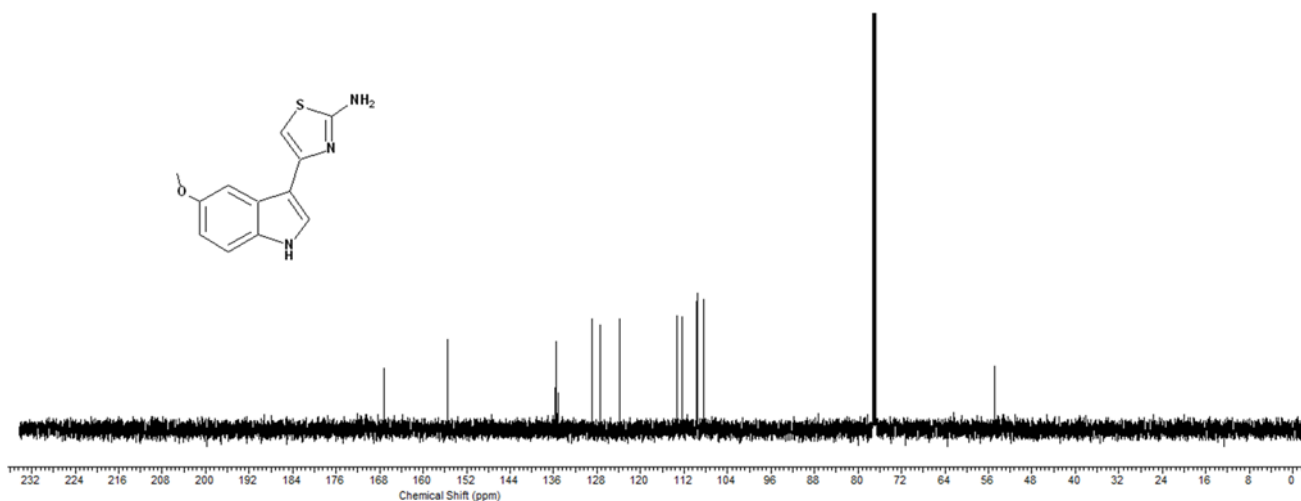


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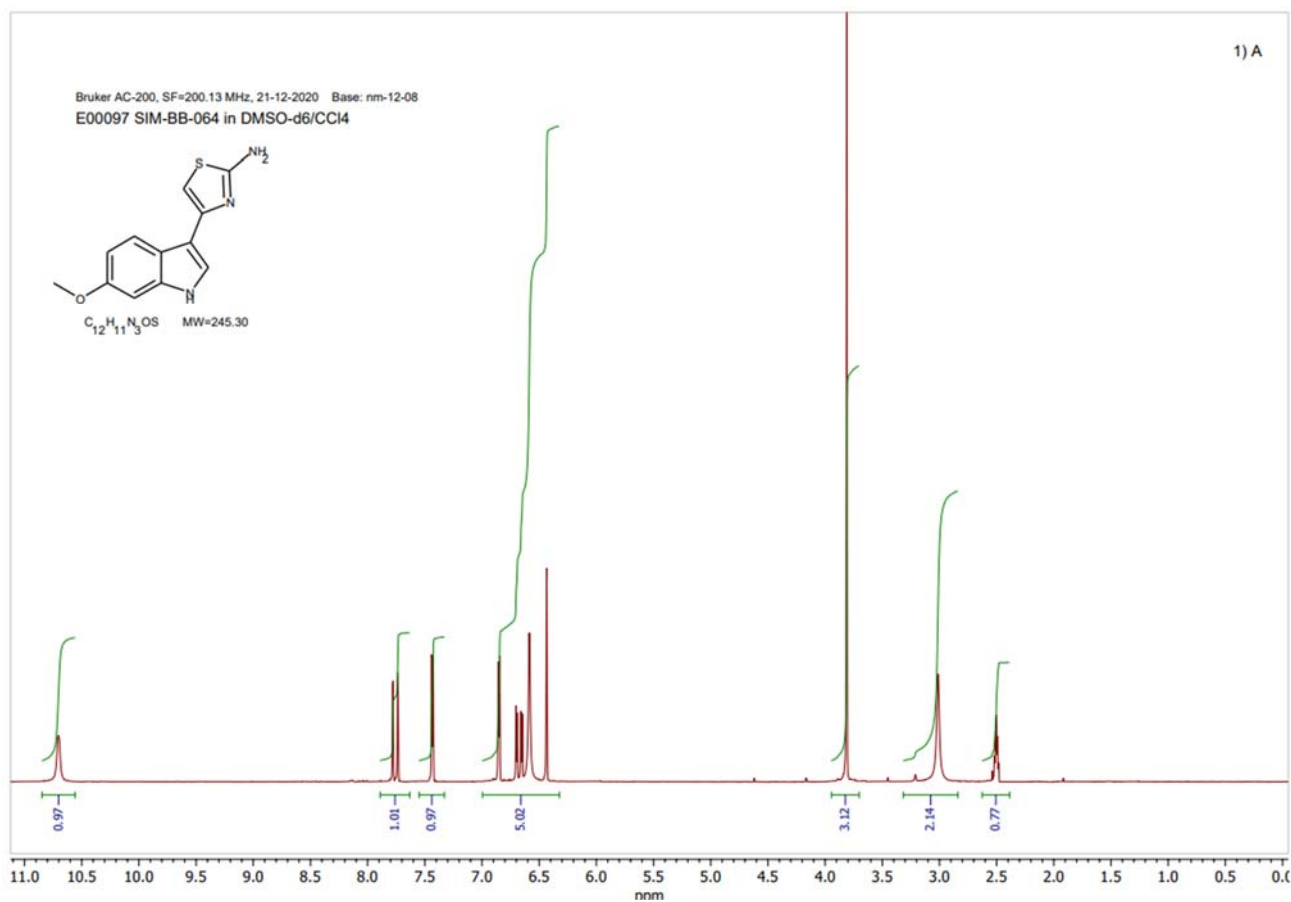
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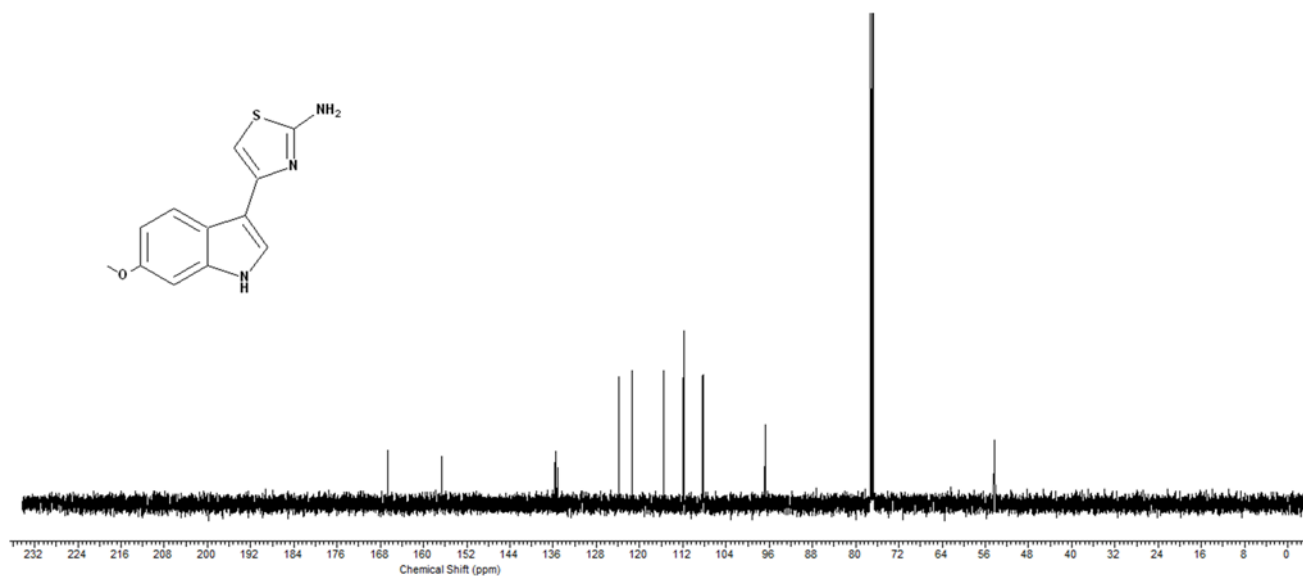
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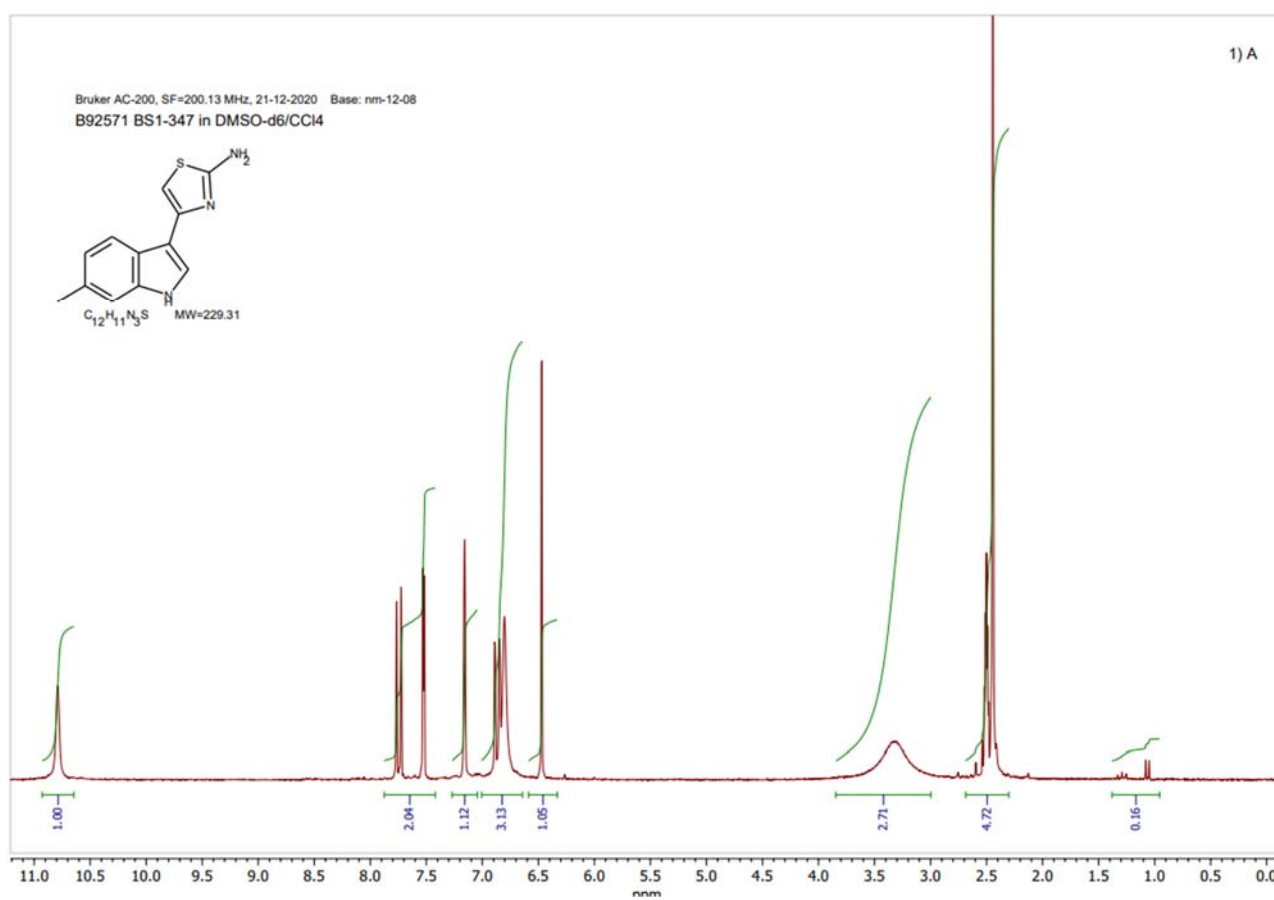


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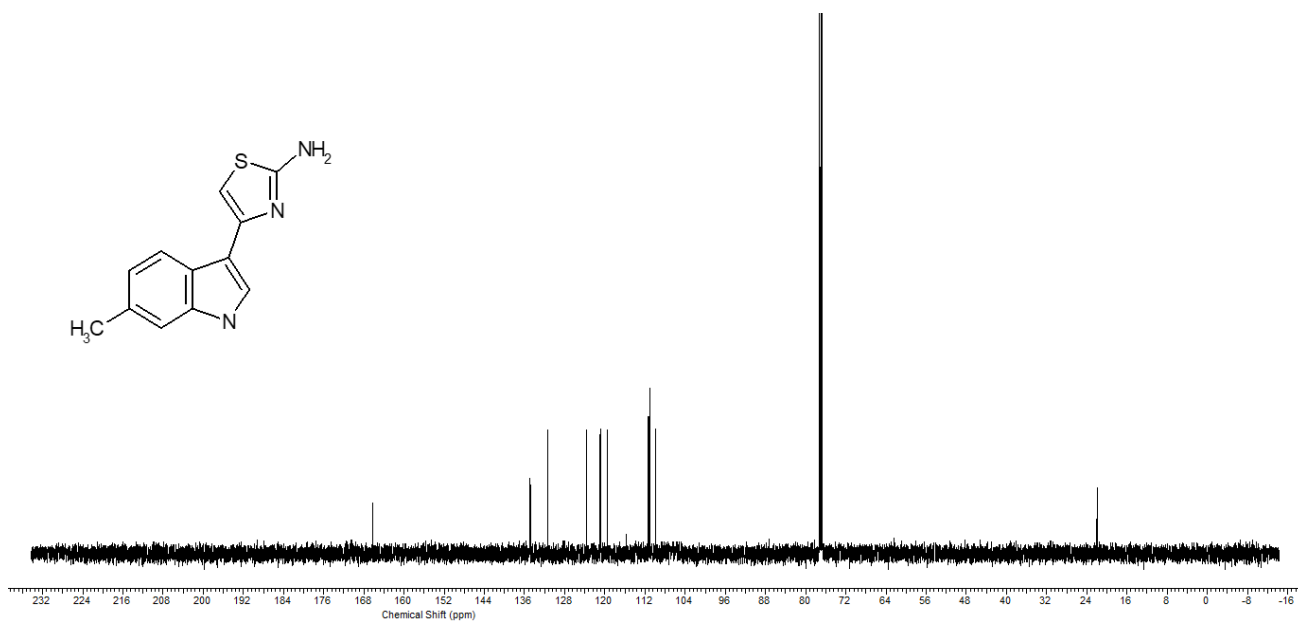
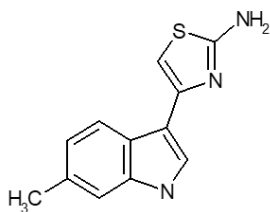




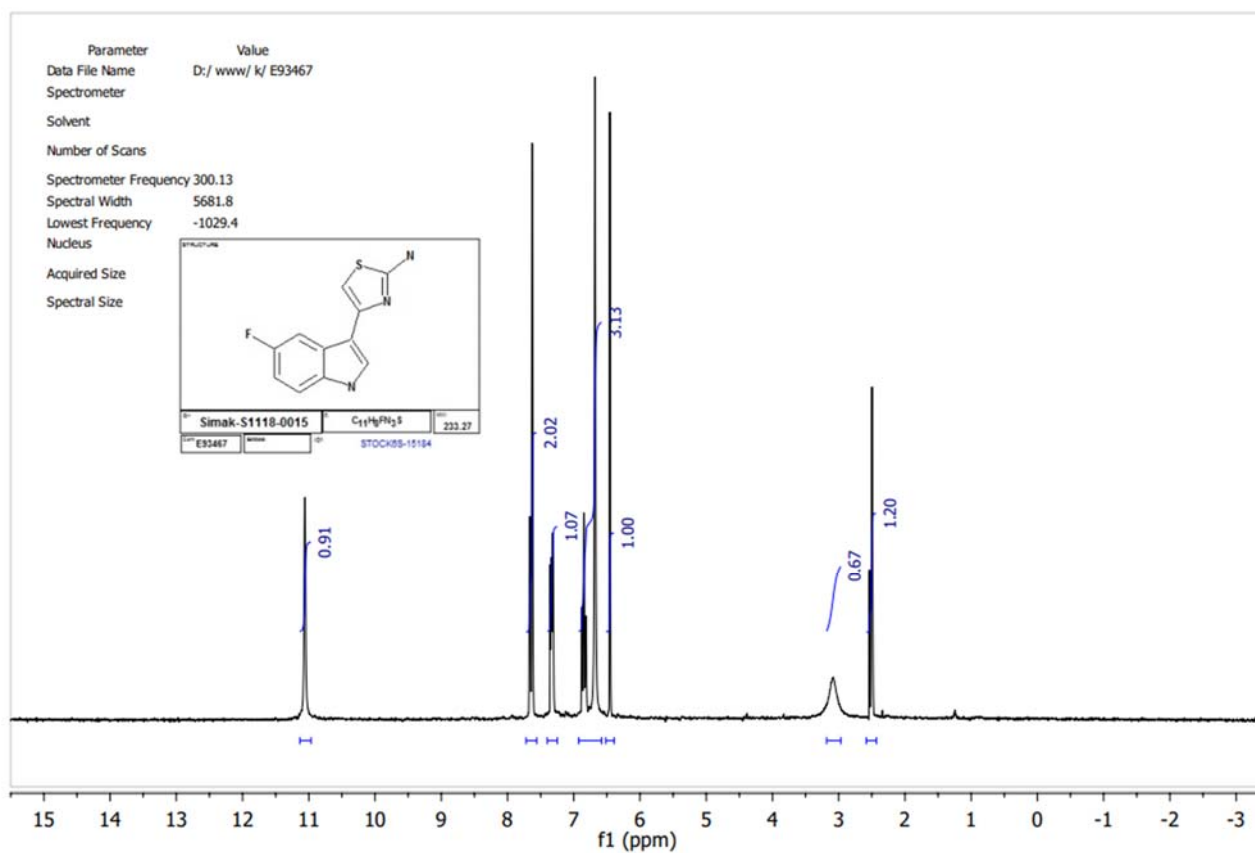
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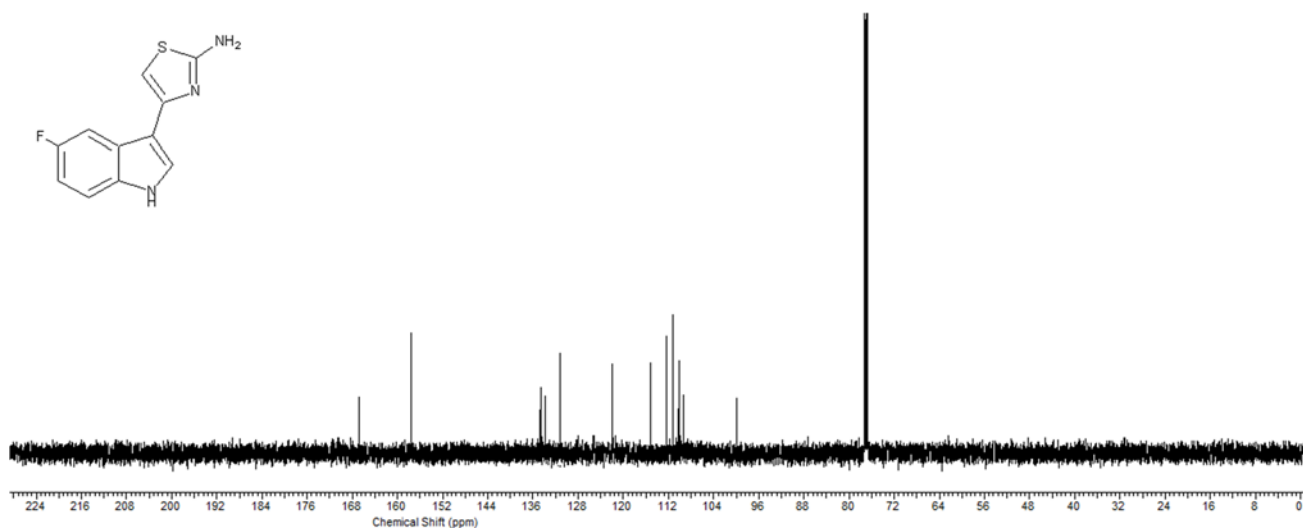




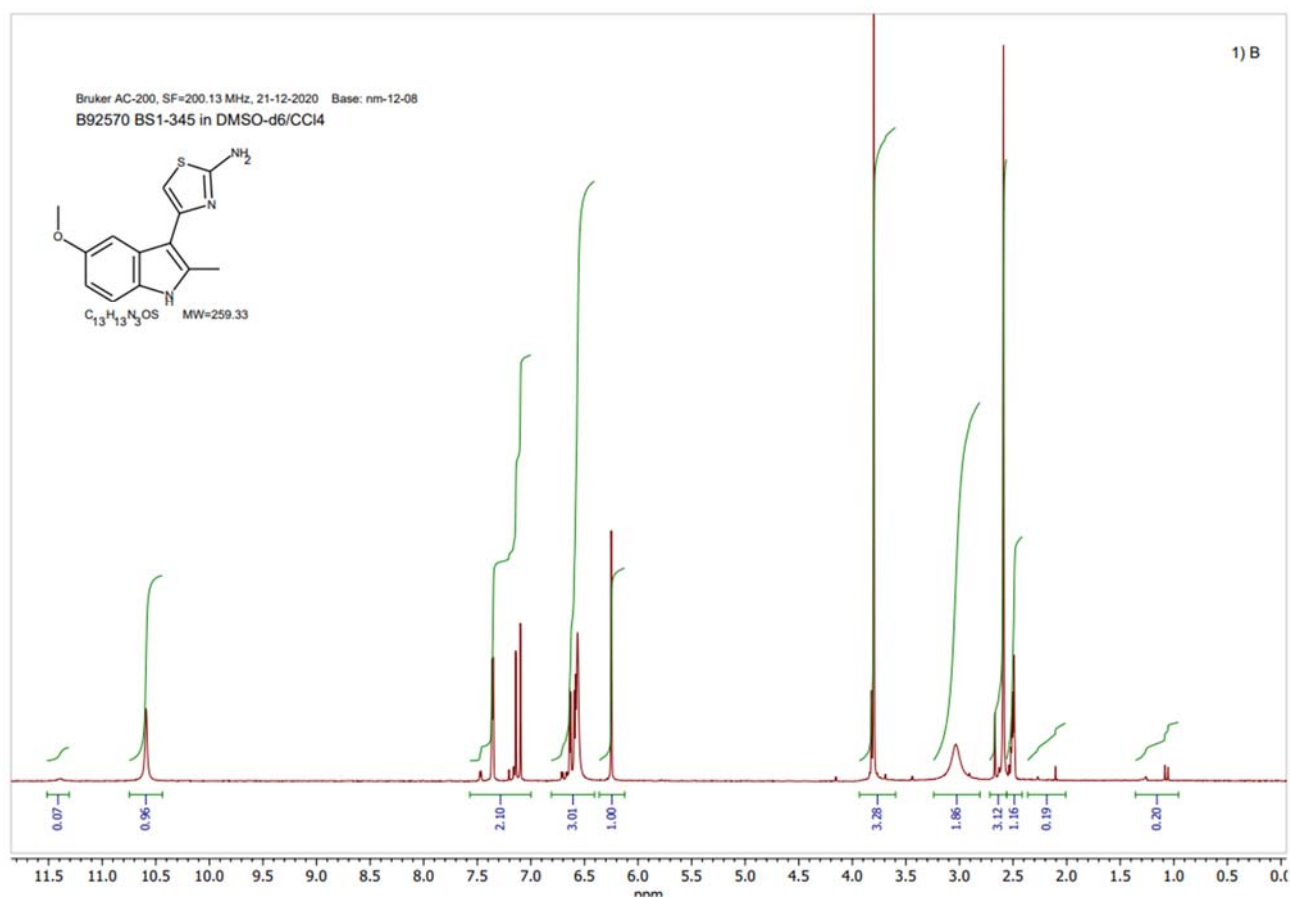


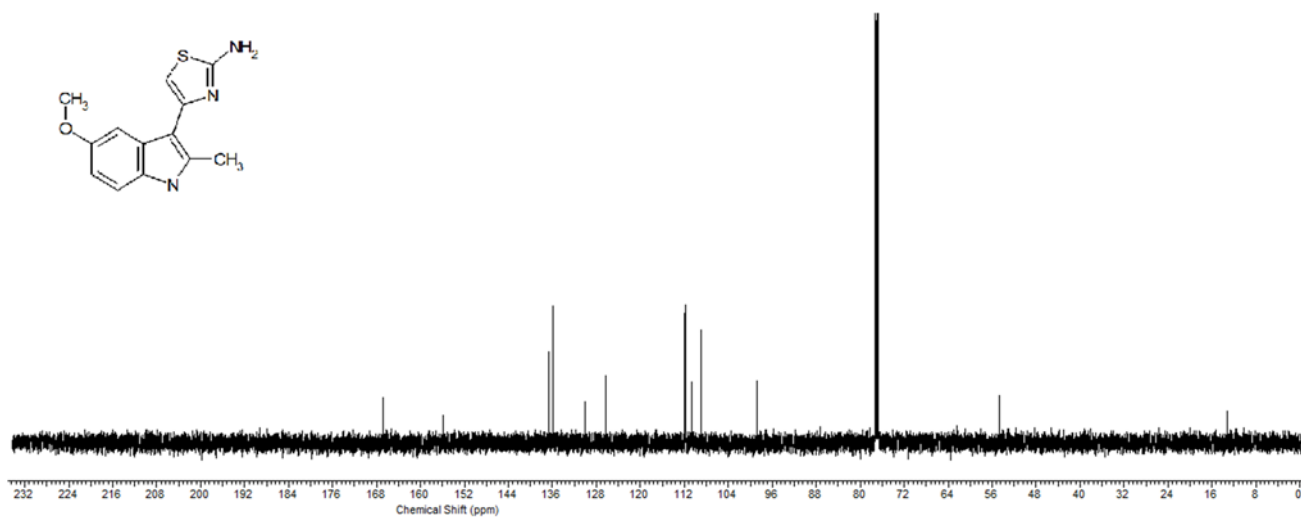
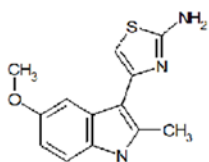
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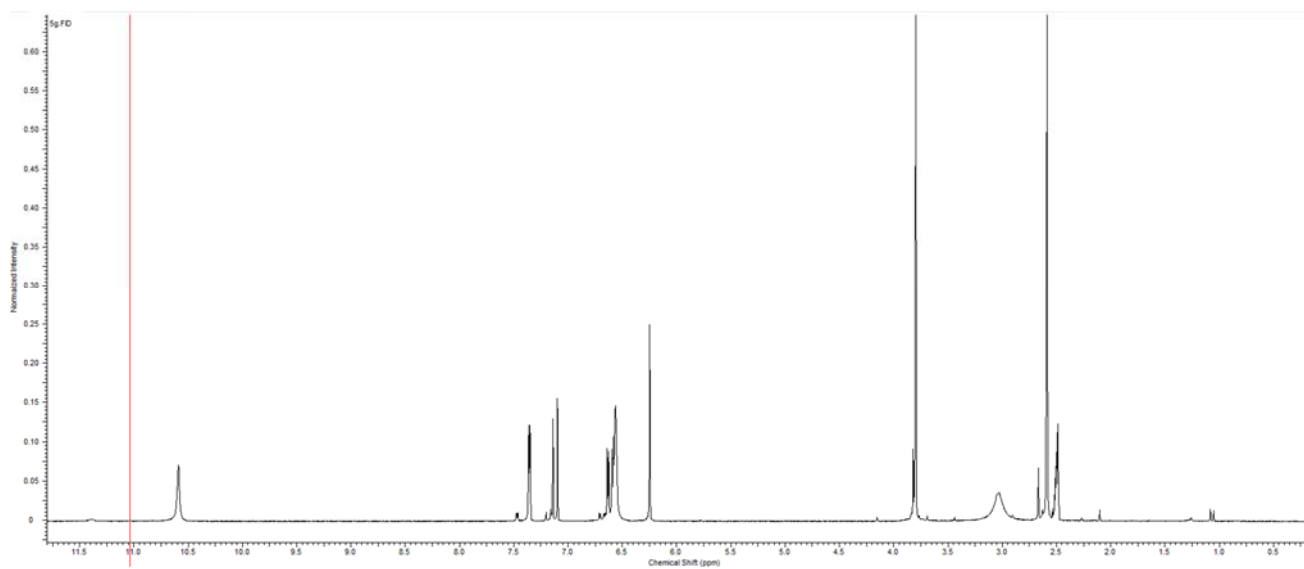


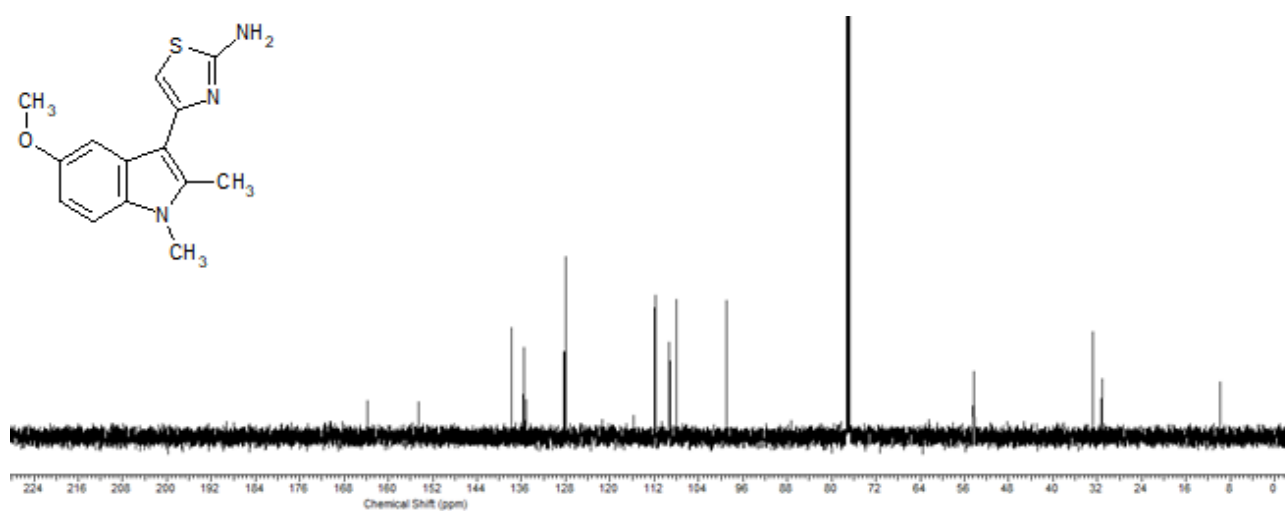
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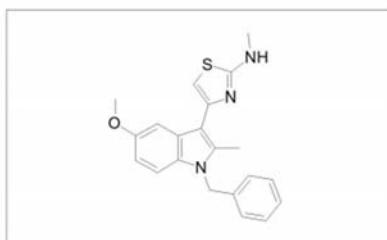
**Compound 5g**





Compound 5h

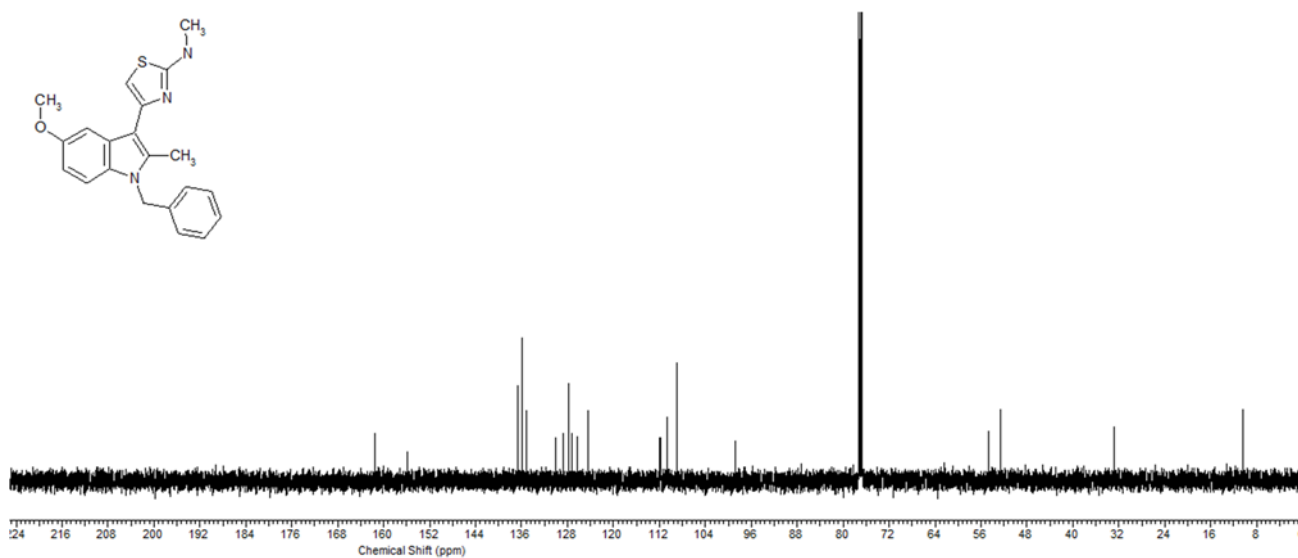
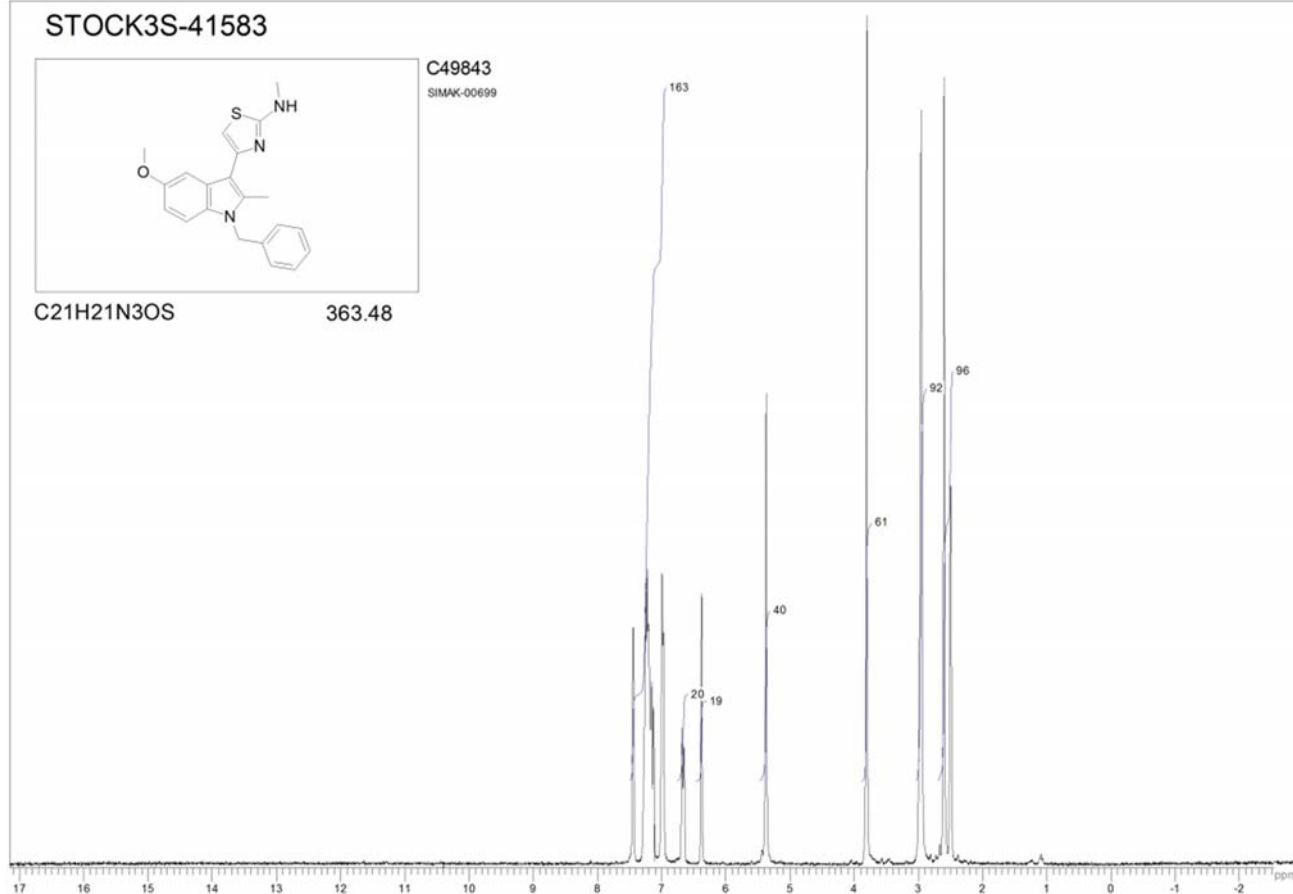
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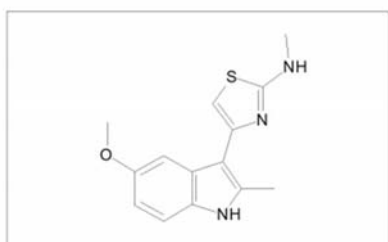
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C49843  
SIMAK-00699



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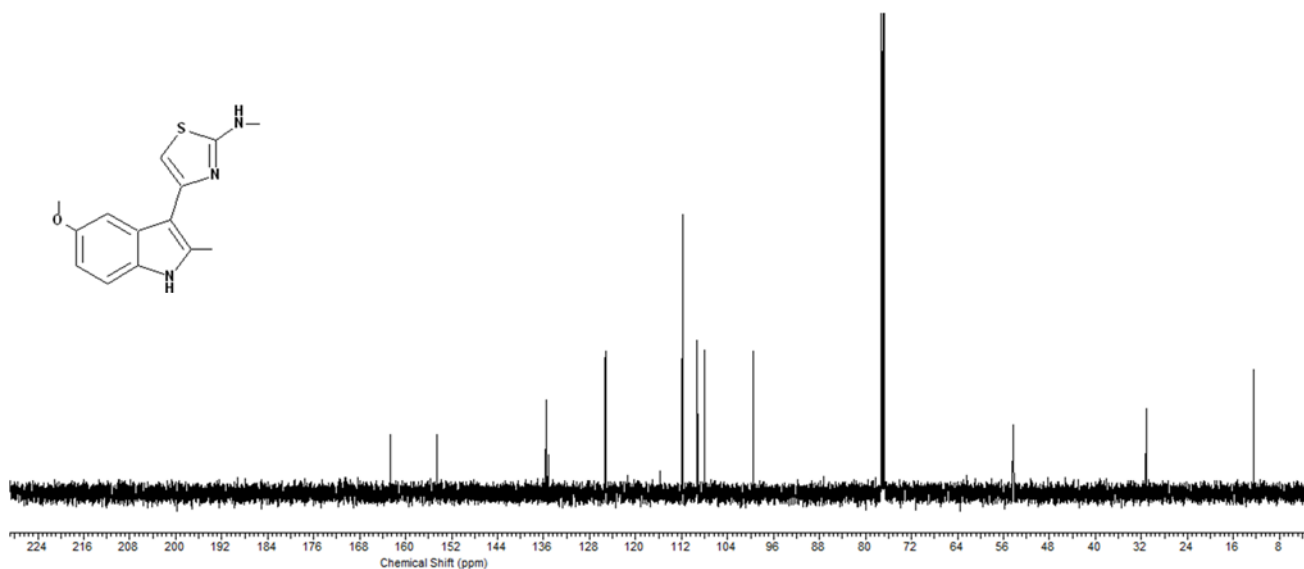
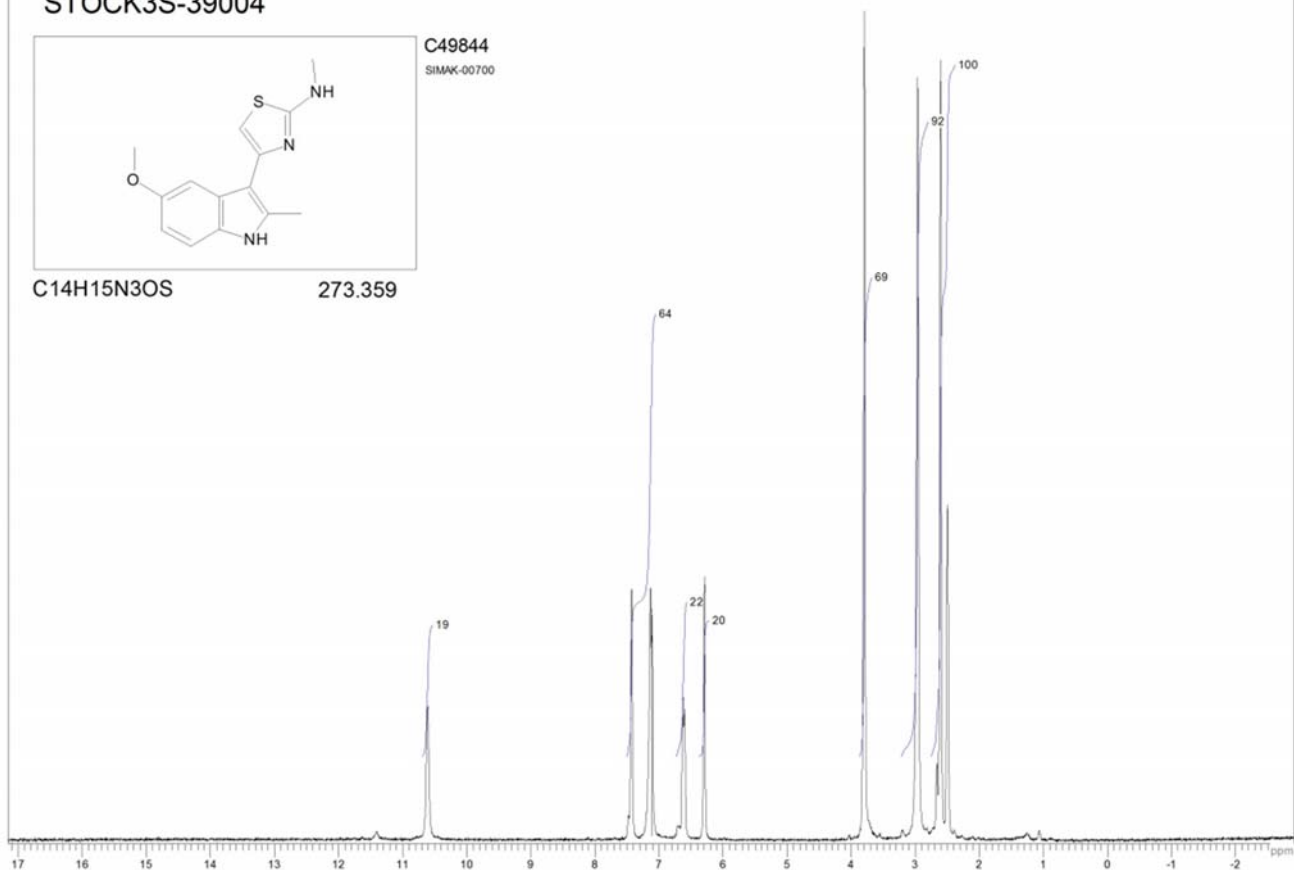
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C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>OS

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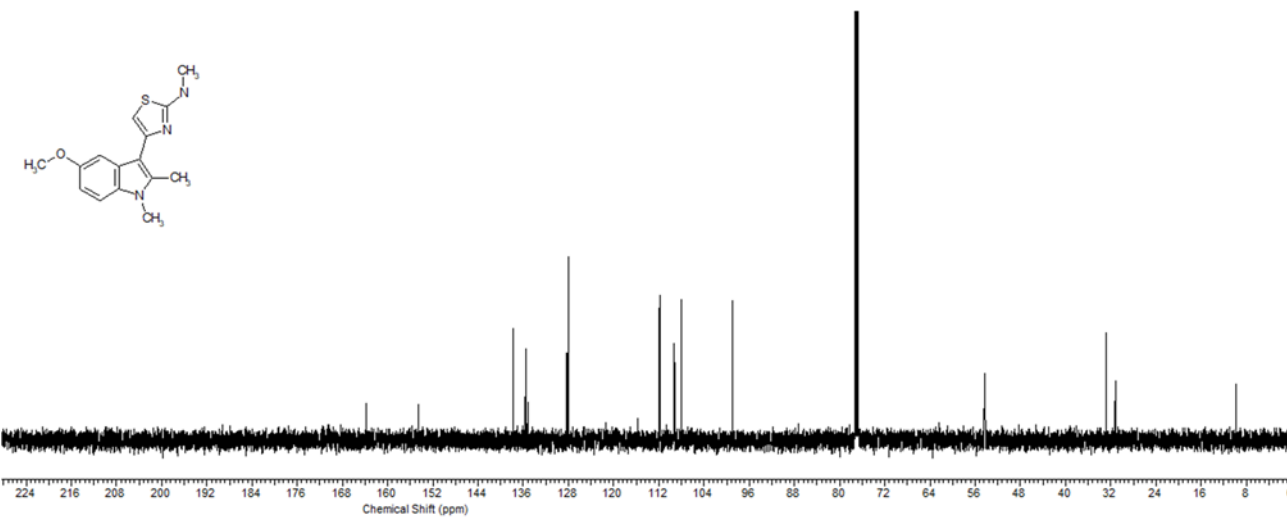
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Compound 5j

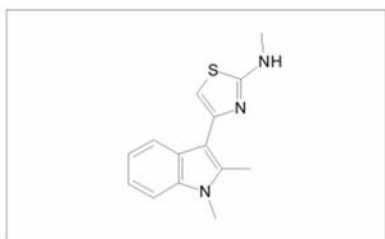
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### Compound 5k

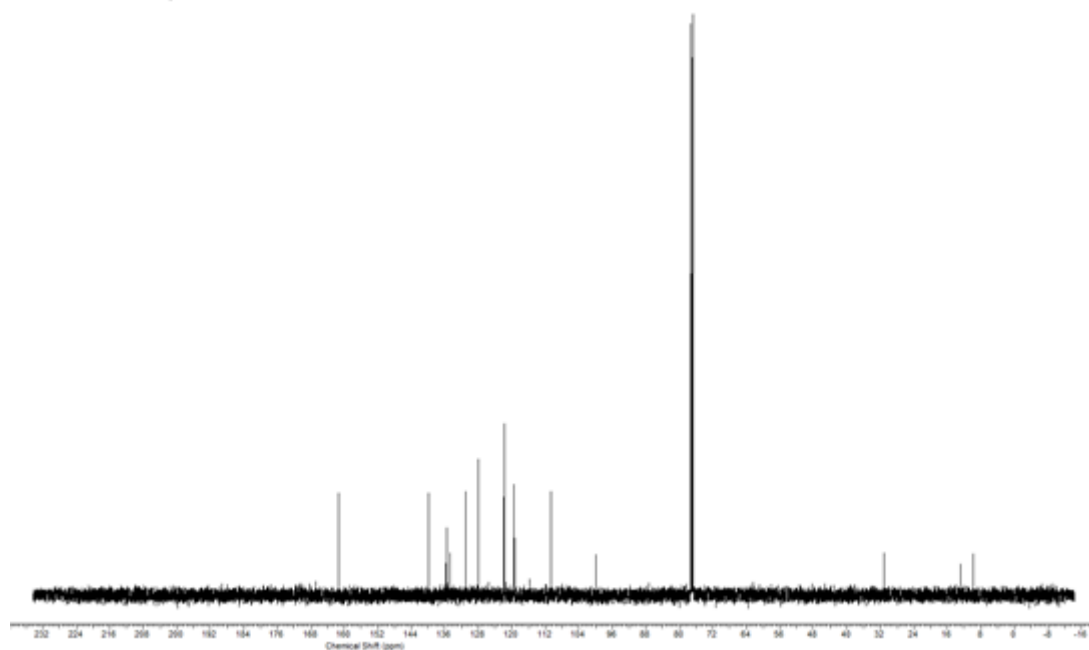
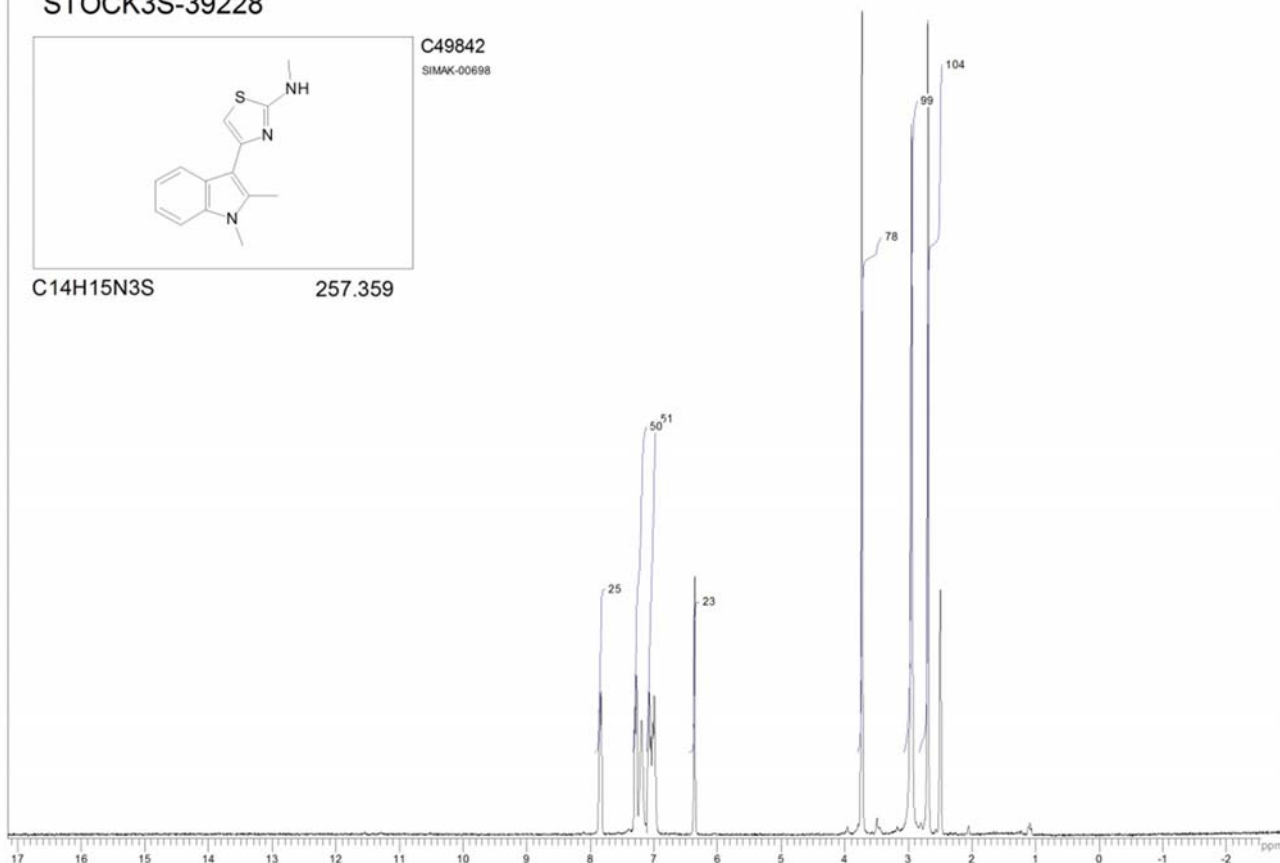
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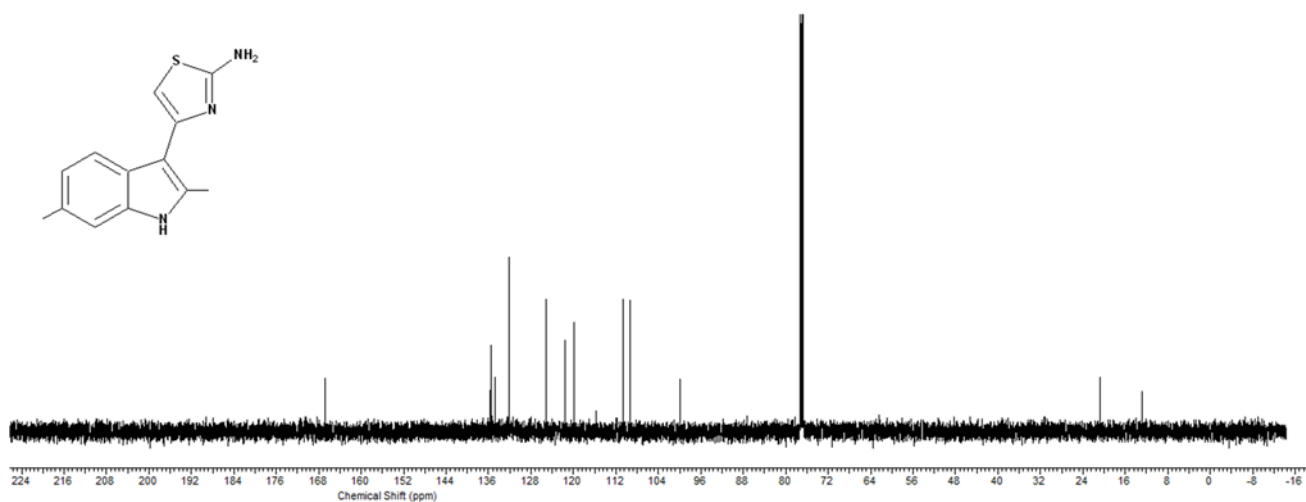
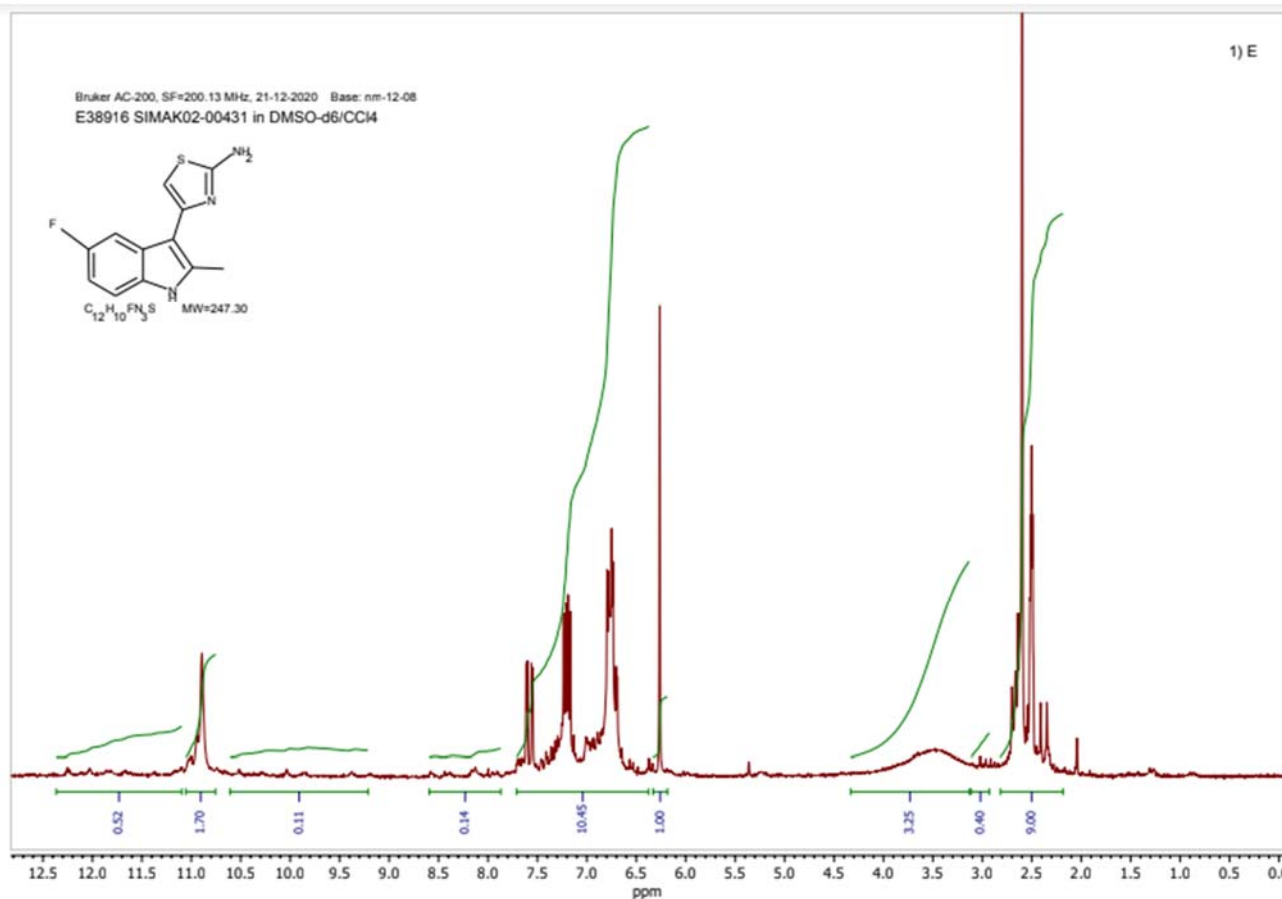
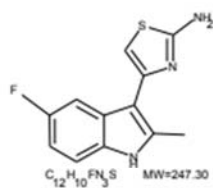


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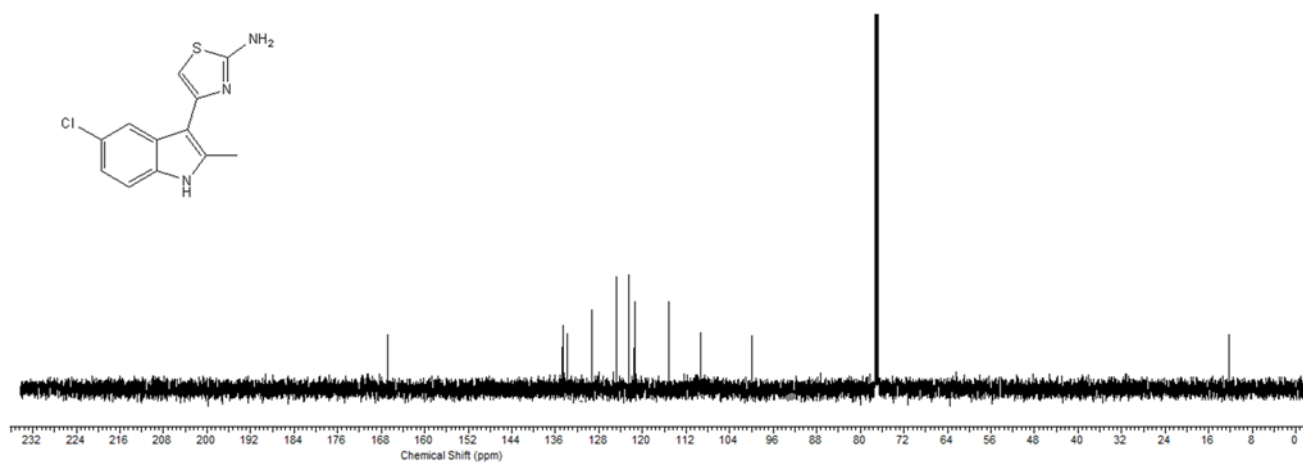
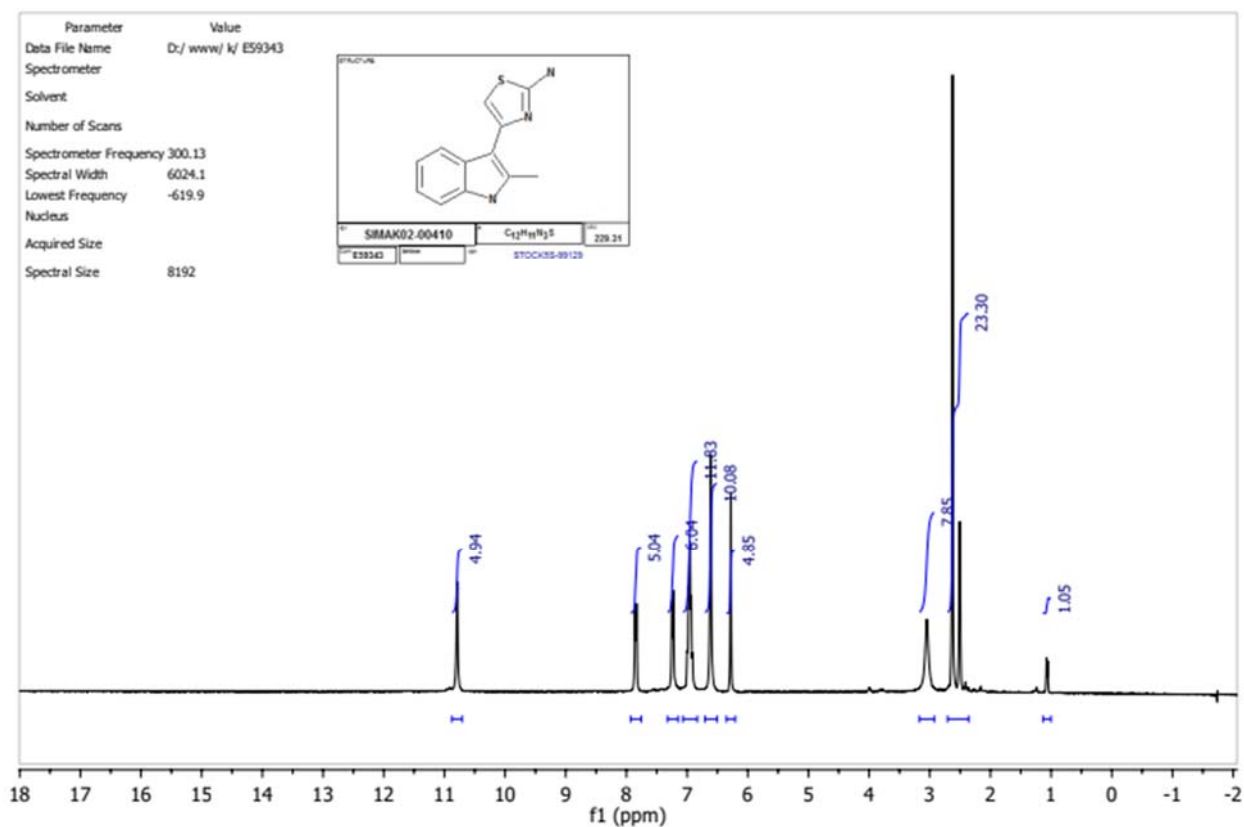


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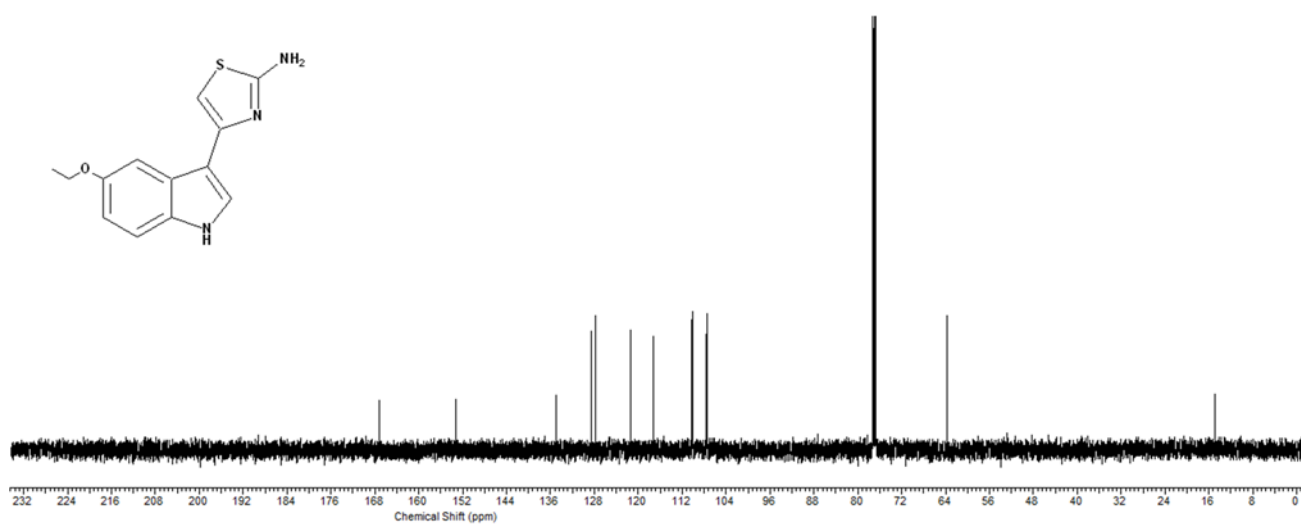
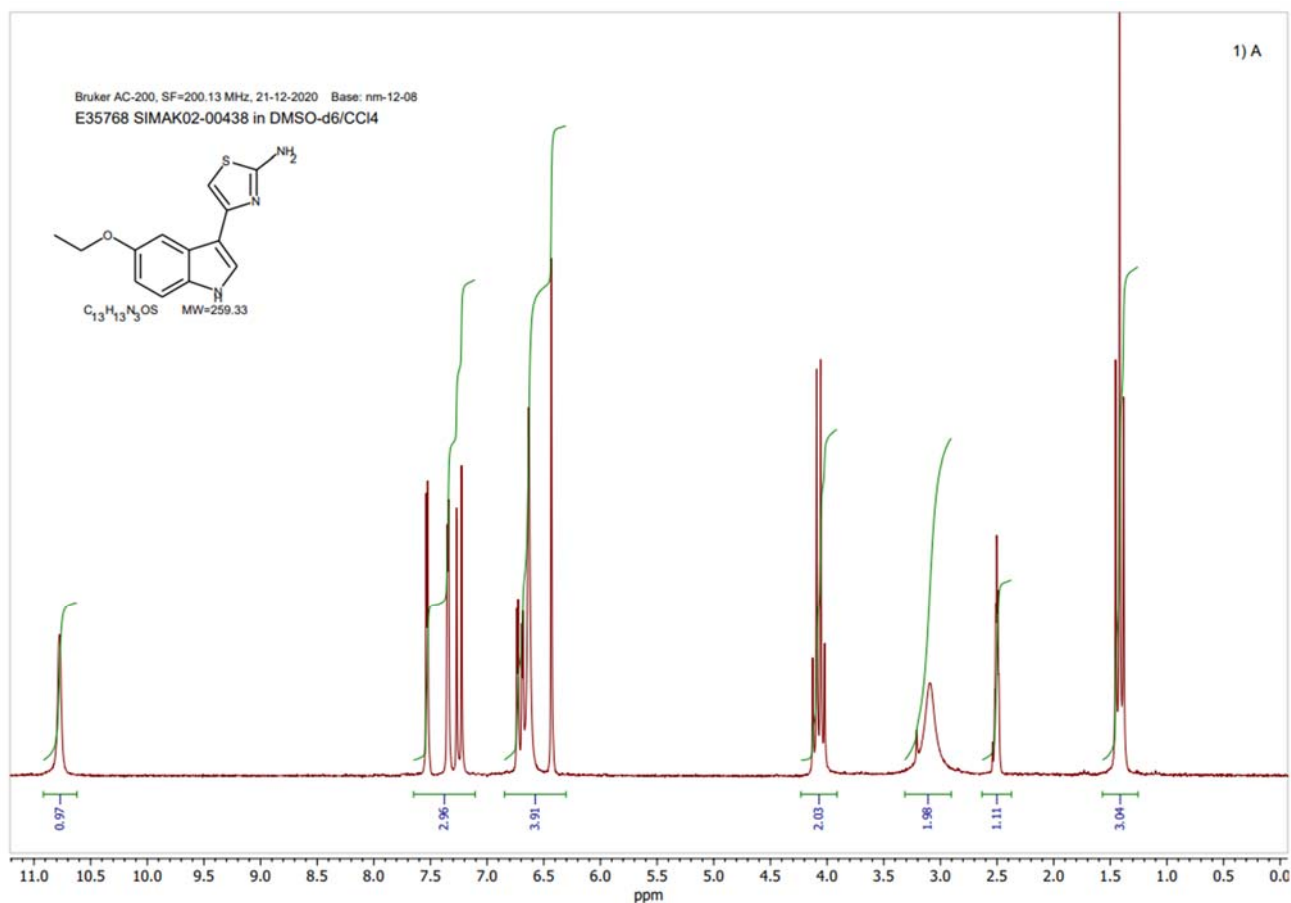
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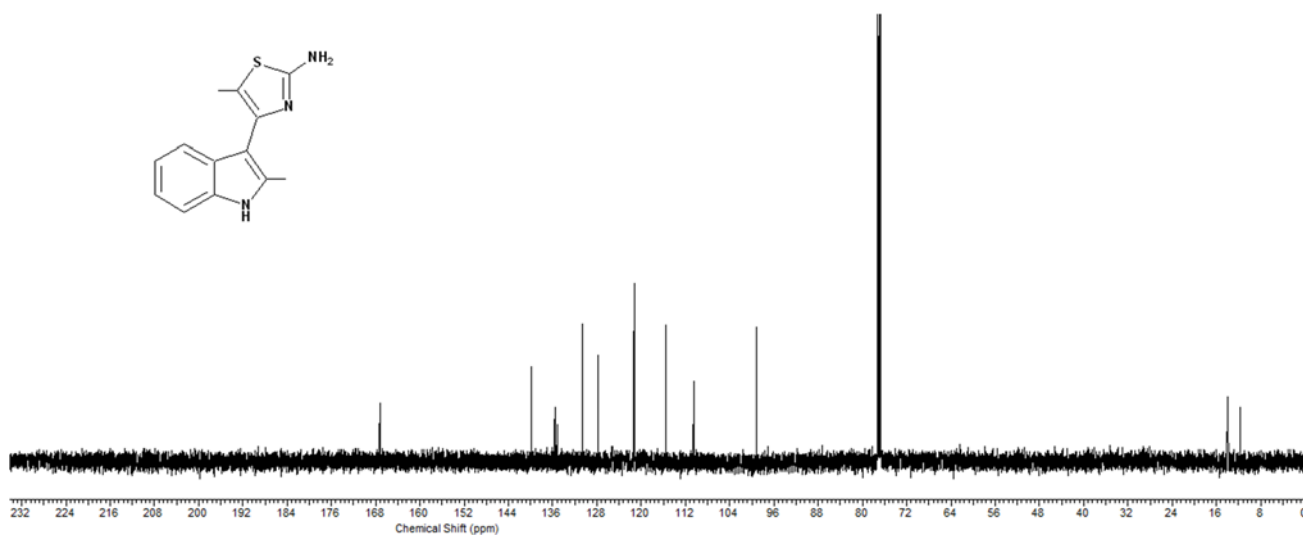
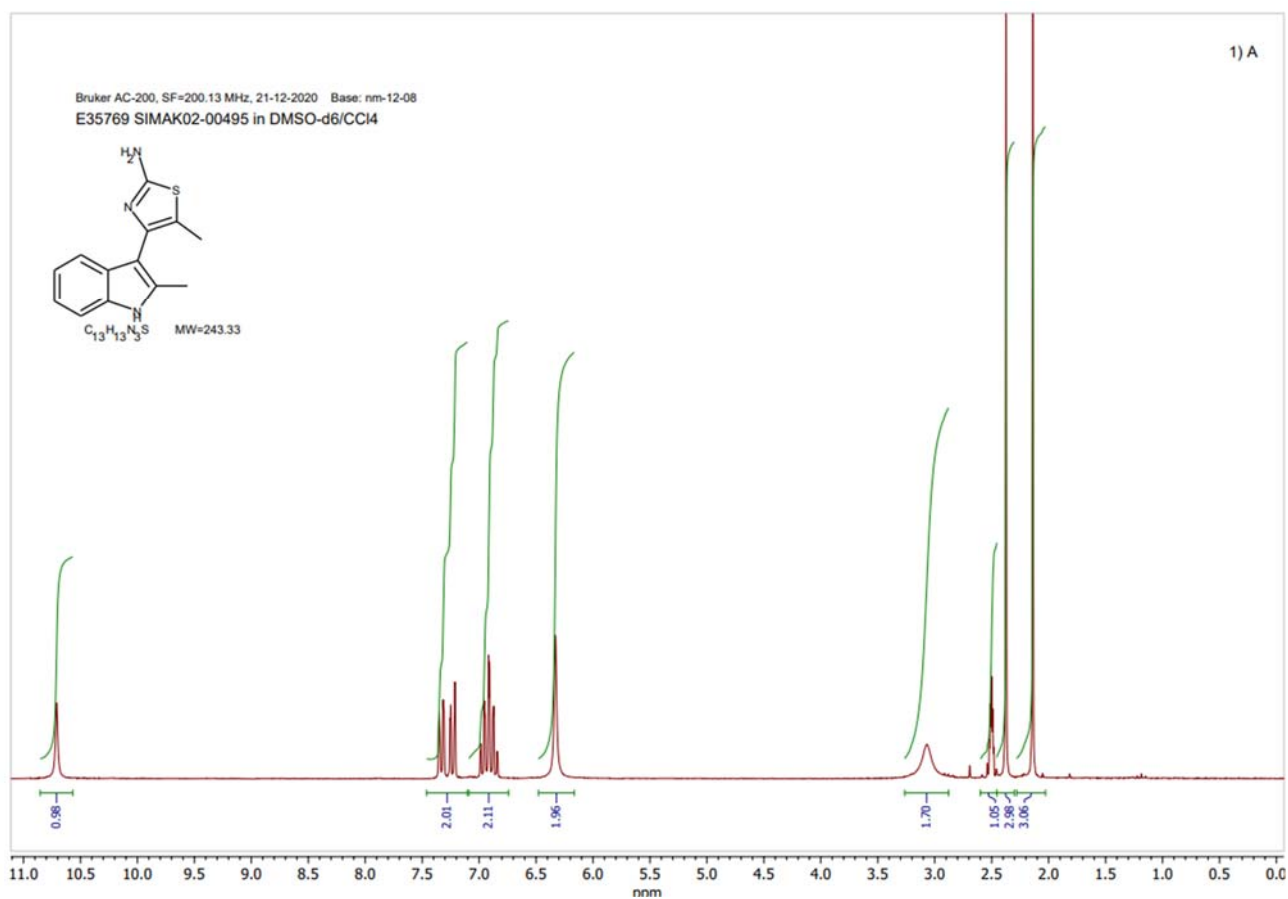
Compound 5m



Compound 5n



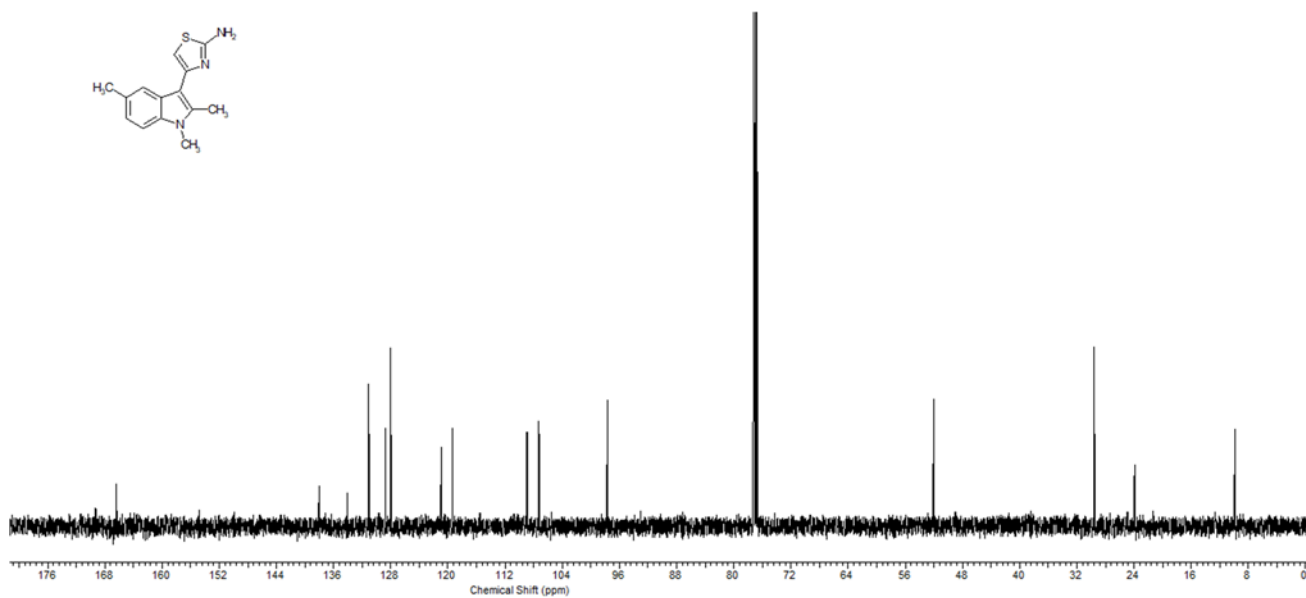
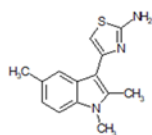
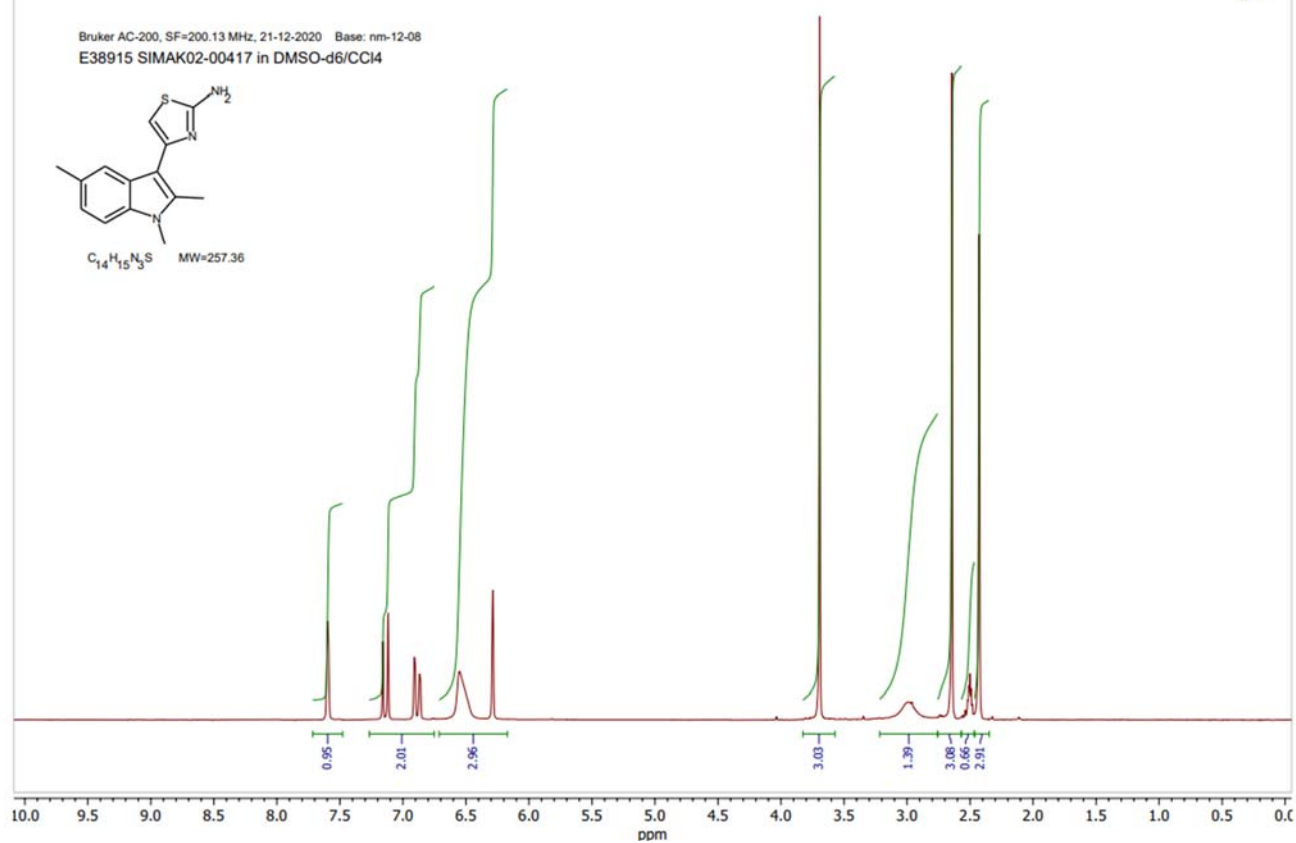
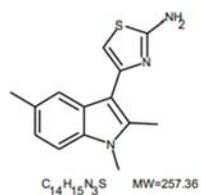
Compound 5o



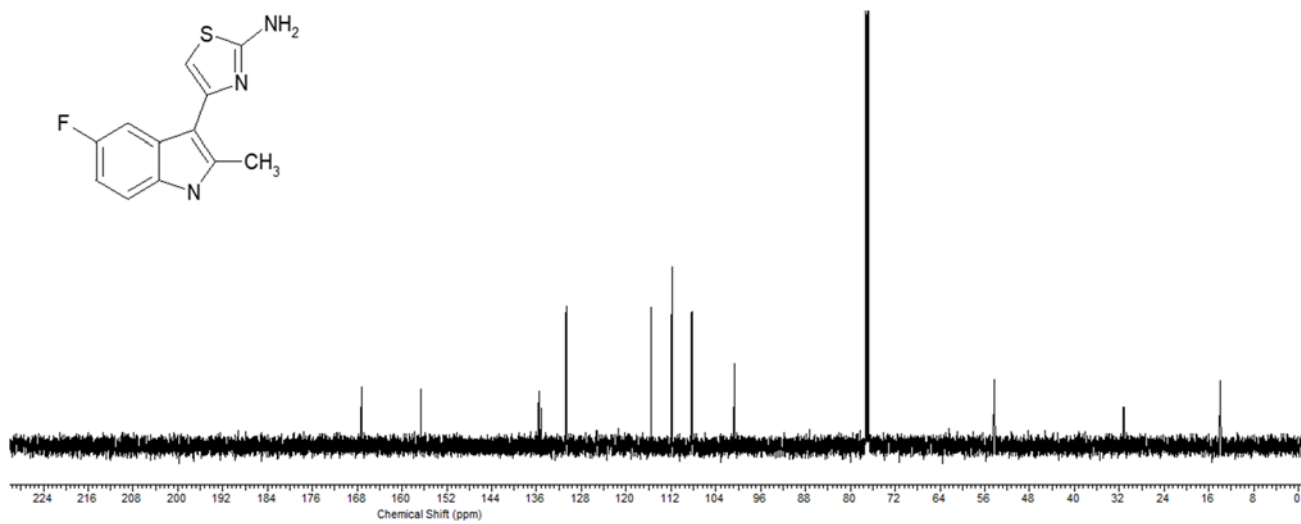
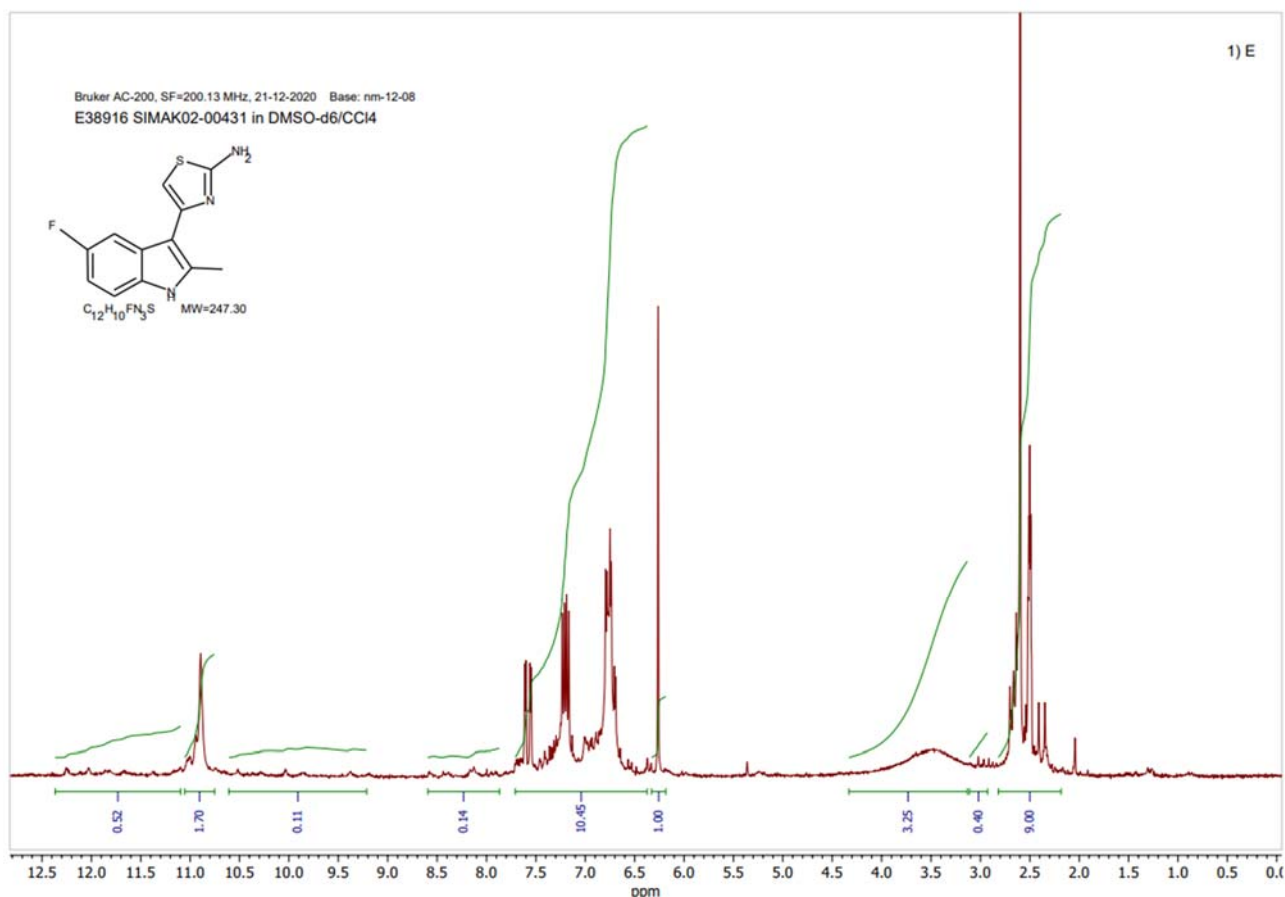
Compound 5p

1) A

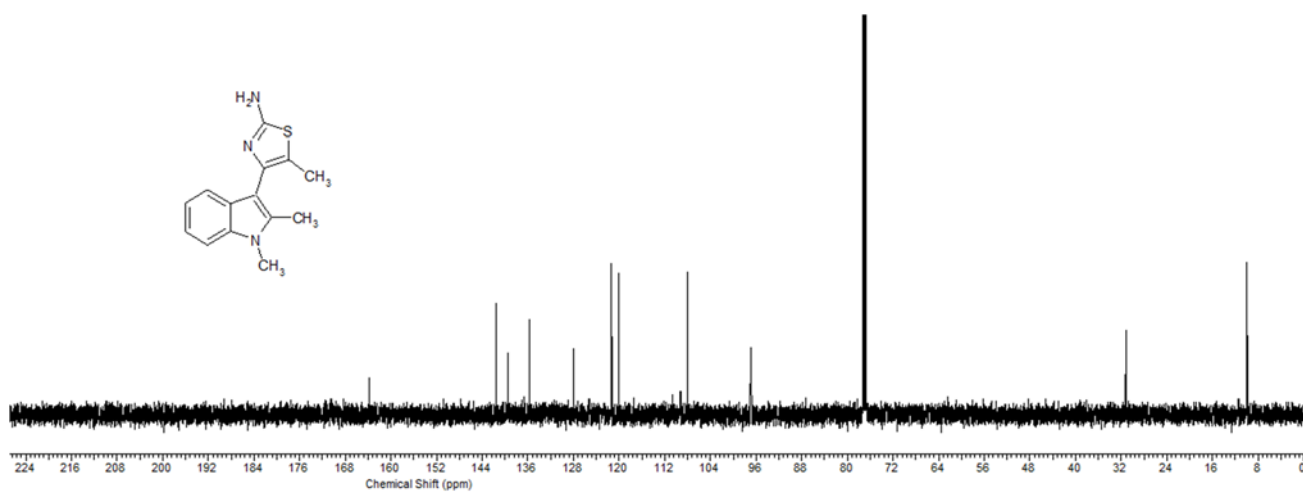
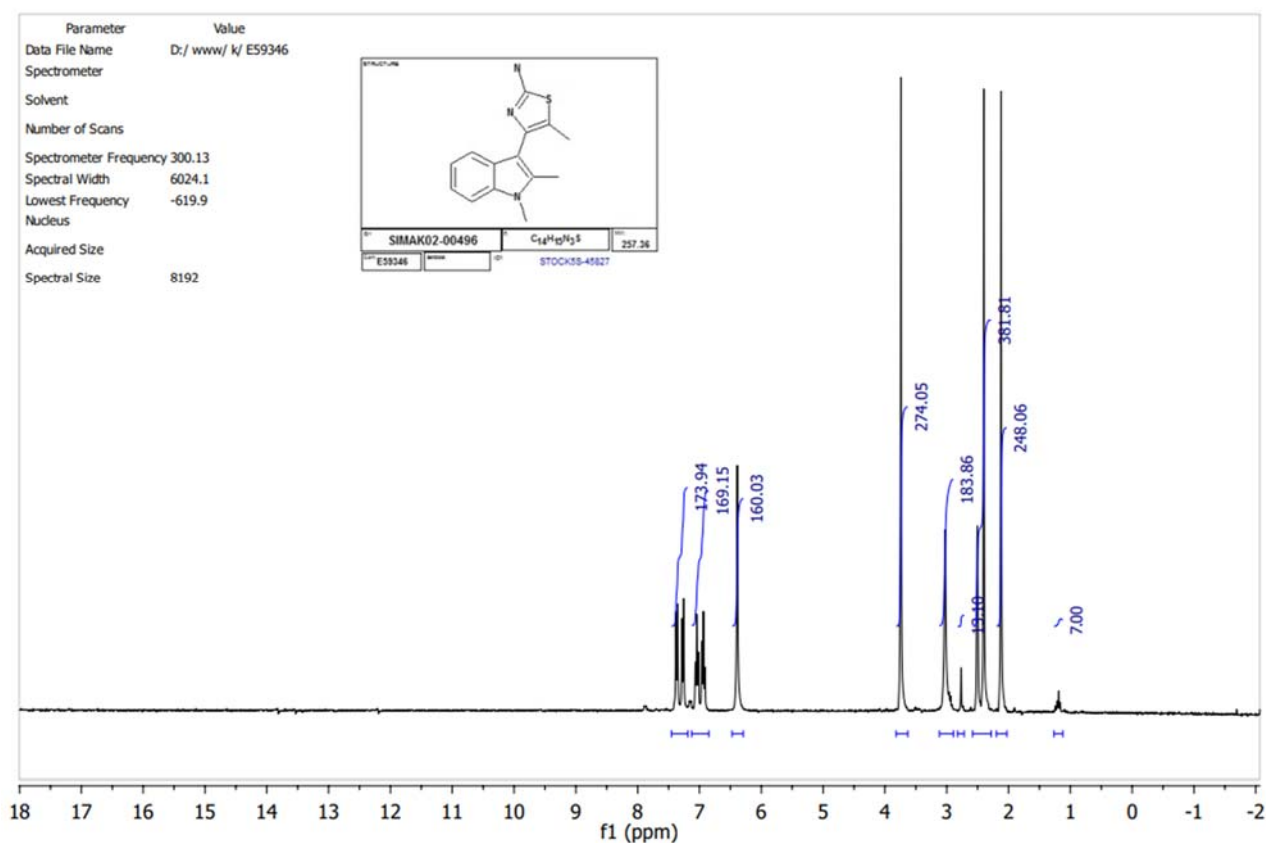
Bruker AC-200, SF=200.13 MHz, 21-12-2020 Base: nm-12-08  
E38915 SIMAK02-00417 in DMSO-d6/CCl4



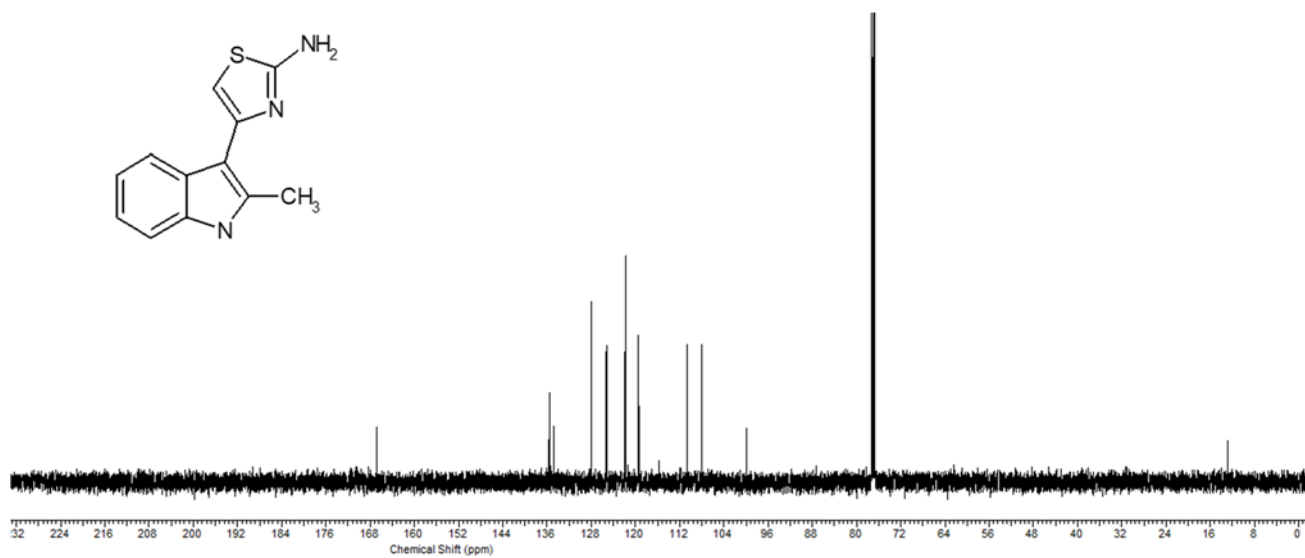
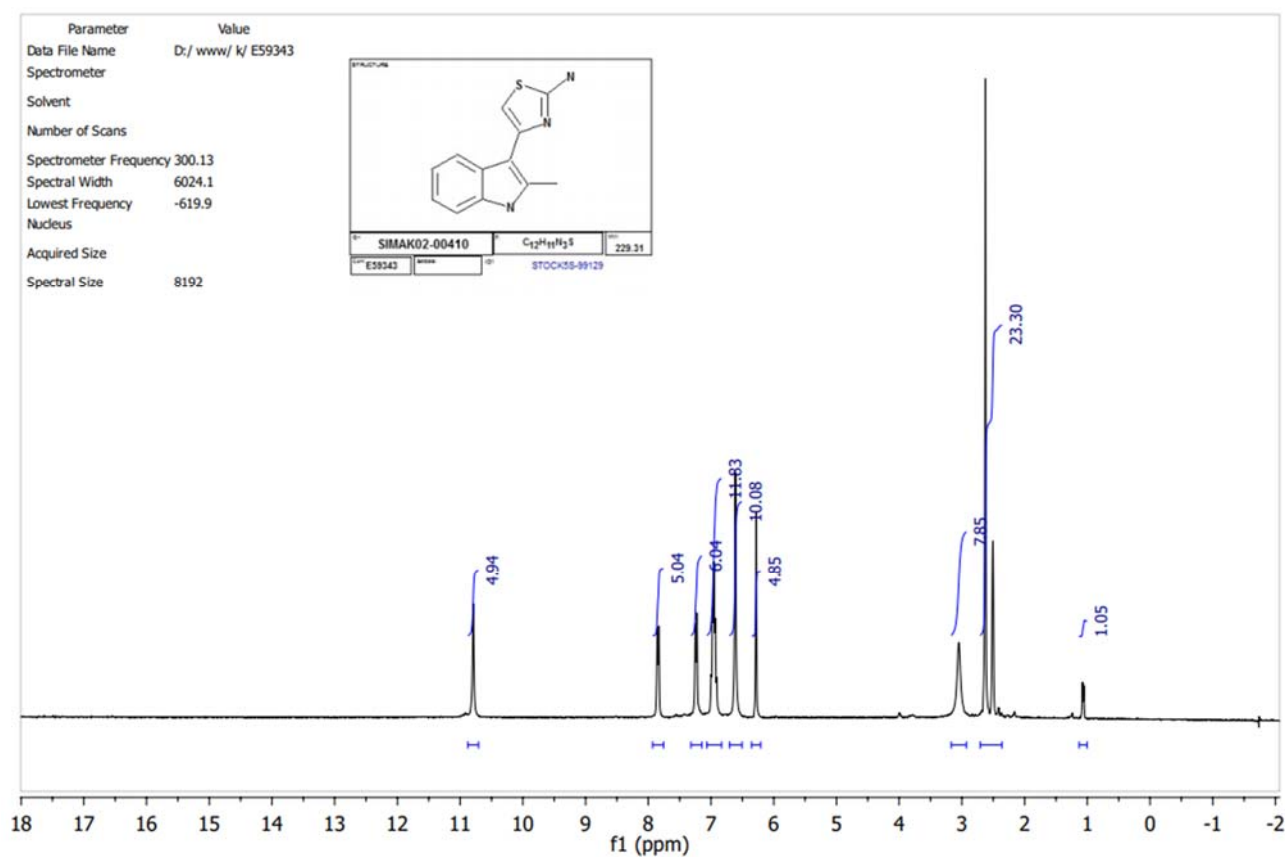
Compound 5q



Compound 5r

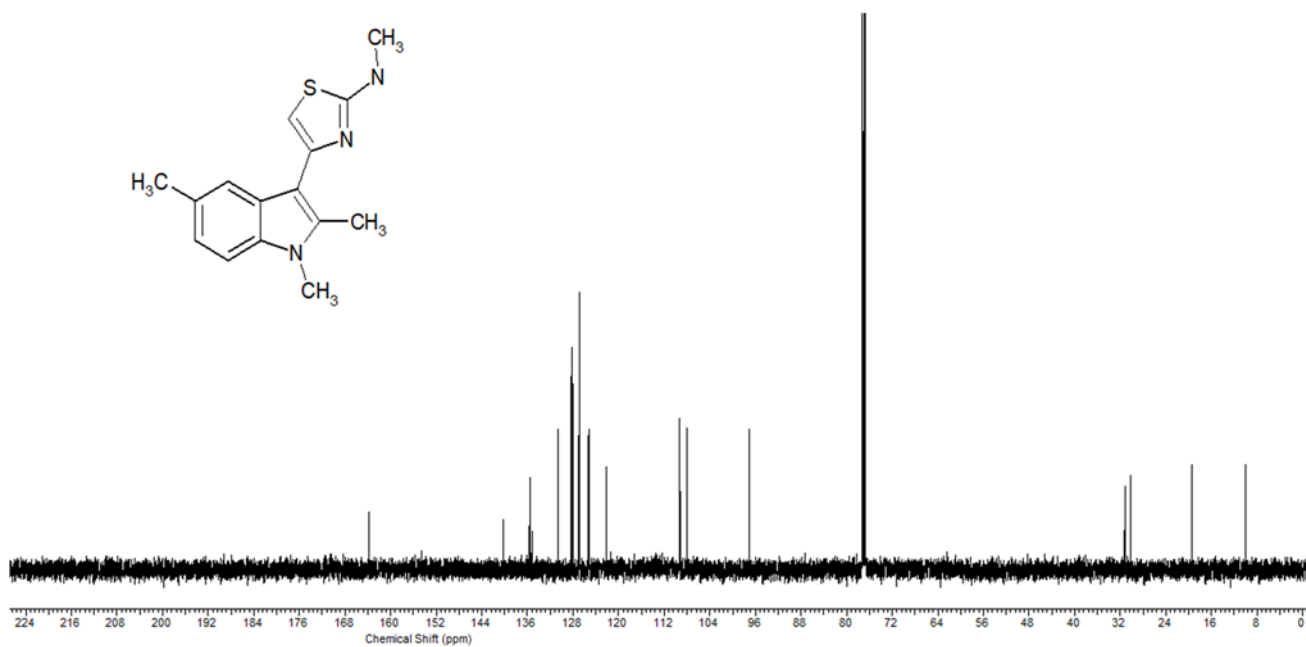
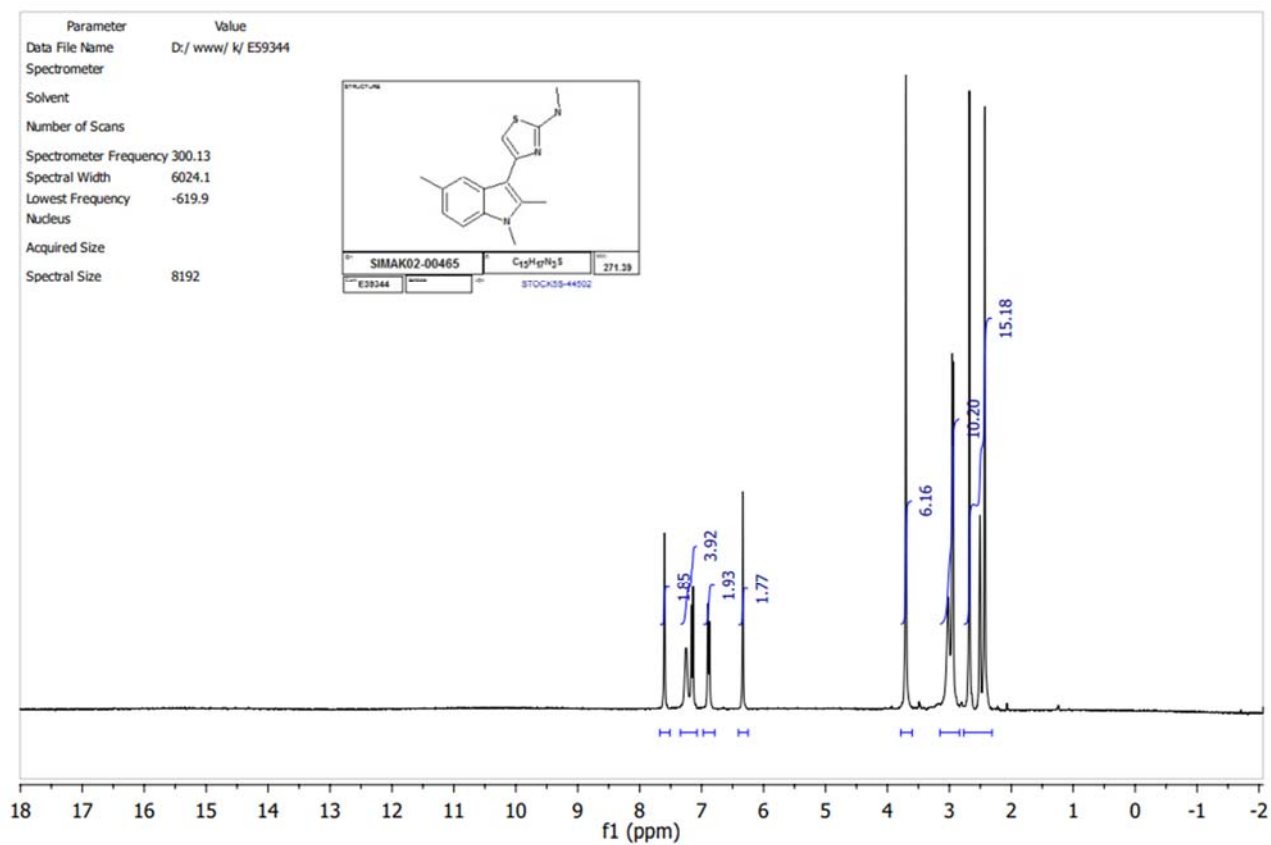


Compound 5s

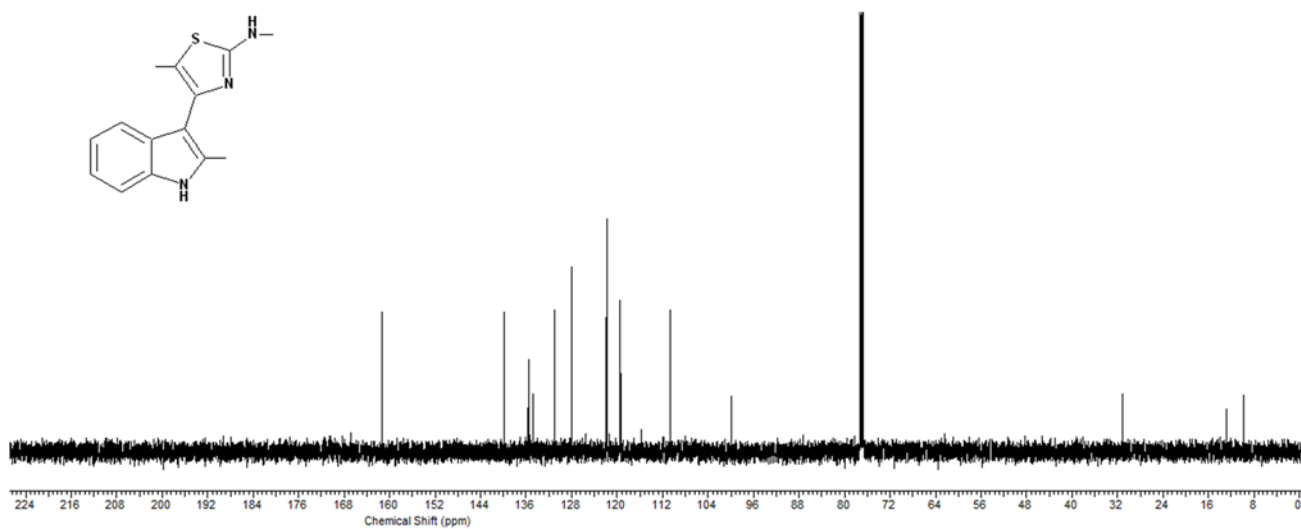
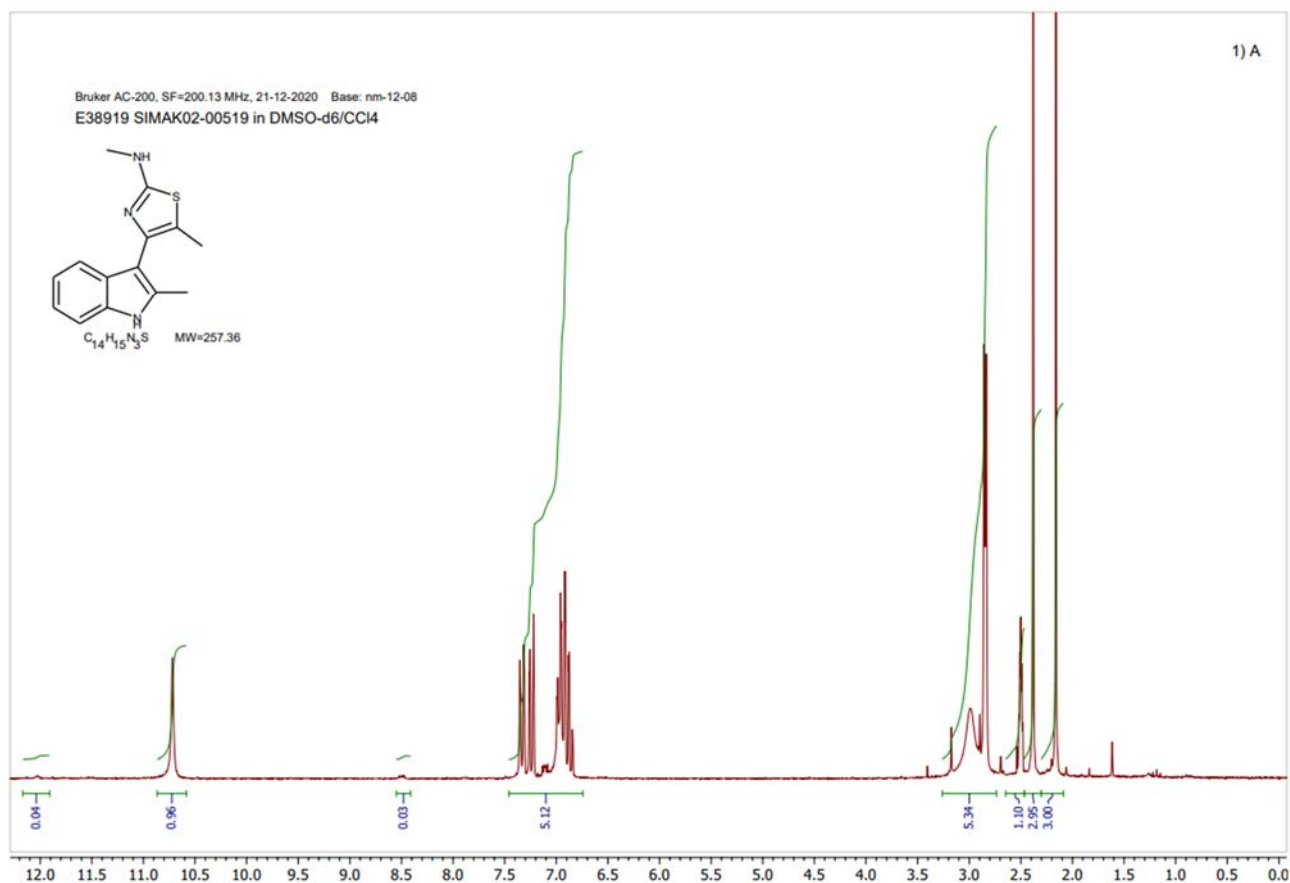


Compound 5t



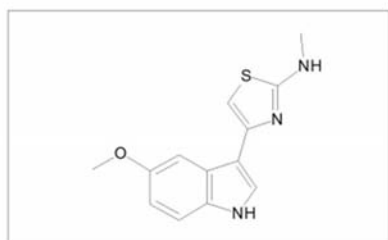


Compound 5u



Compound 5V

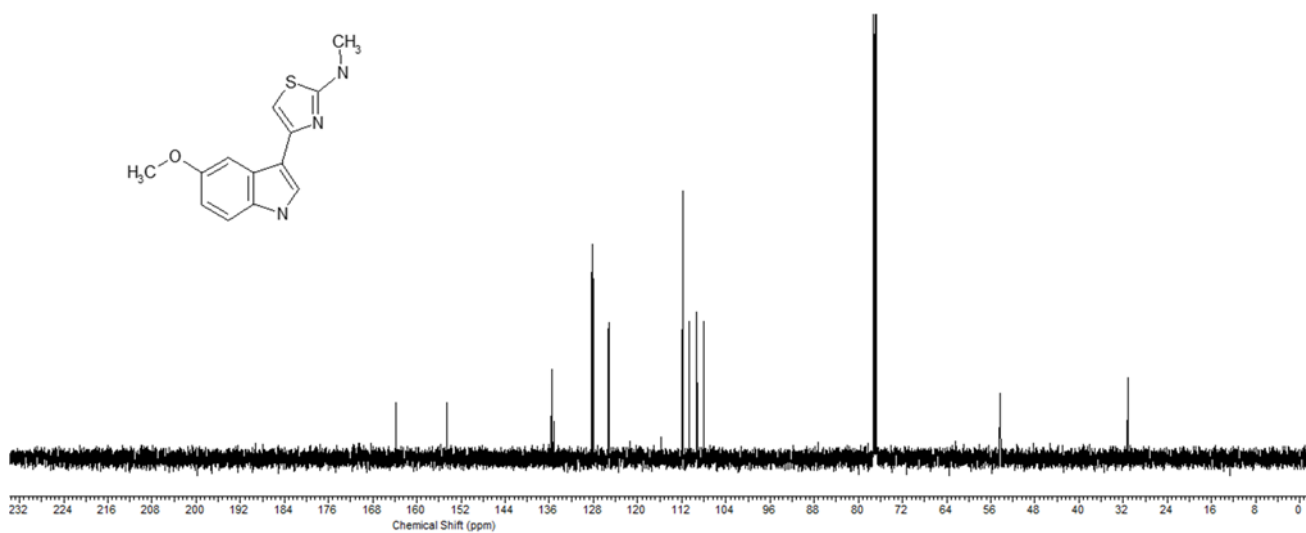
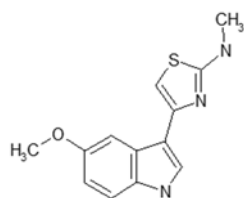
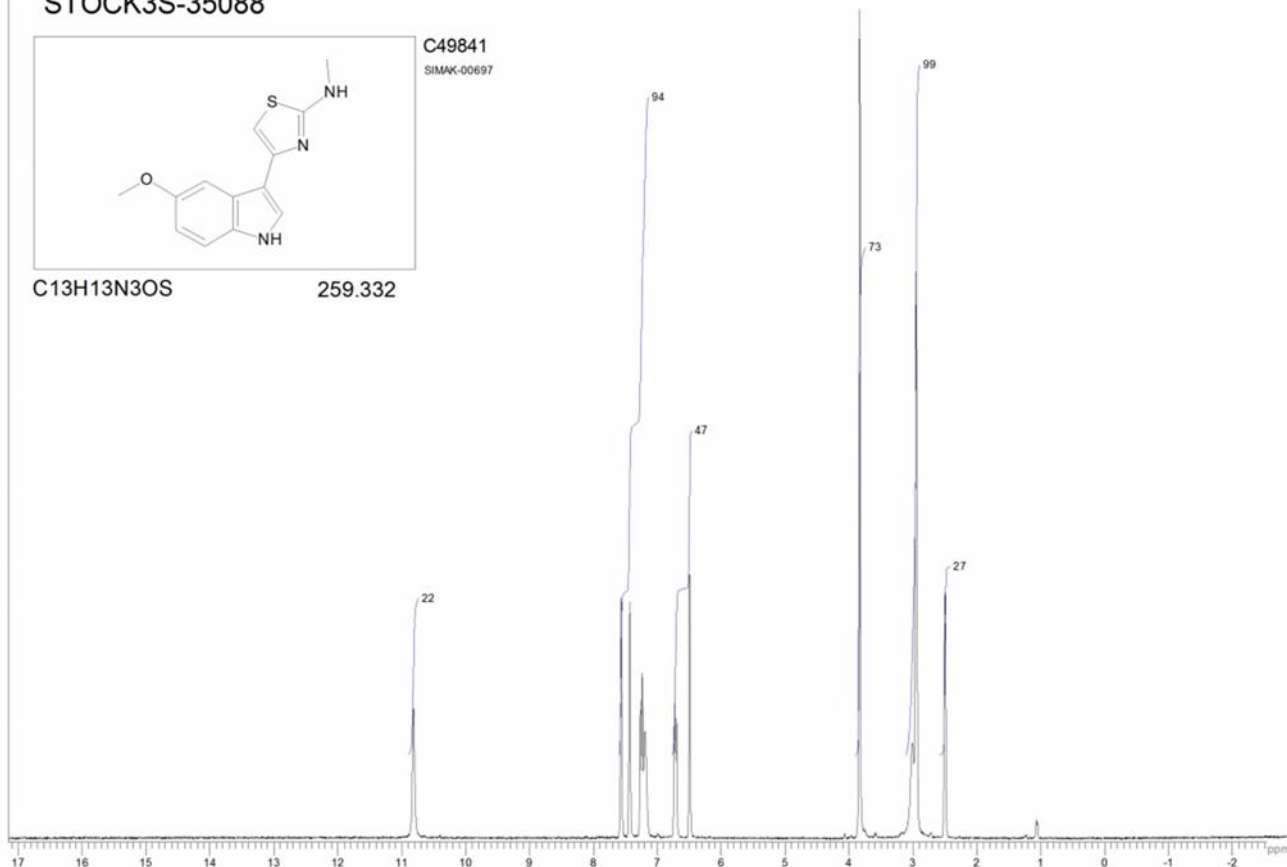
STOCK3S-35088



C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>OS

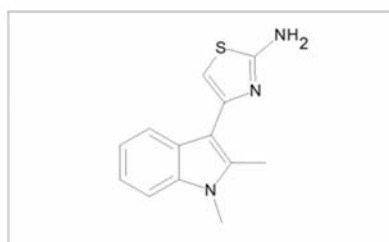
259.332

C49841  
SIMAK-00697



Compound 5W

STOCK4S-31337

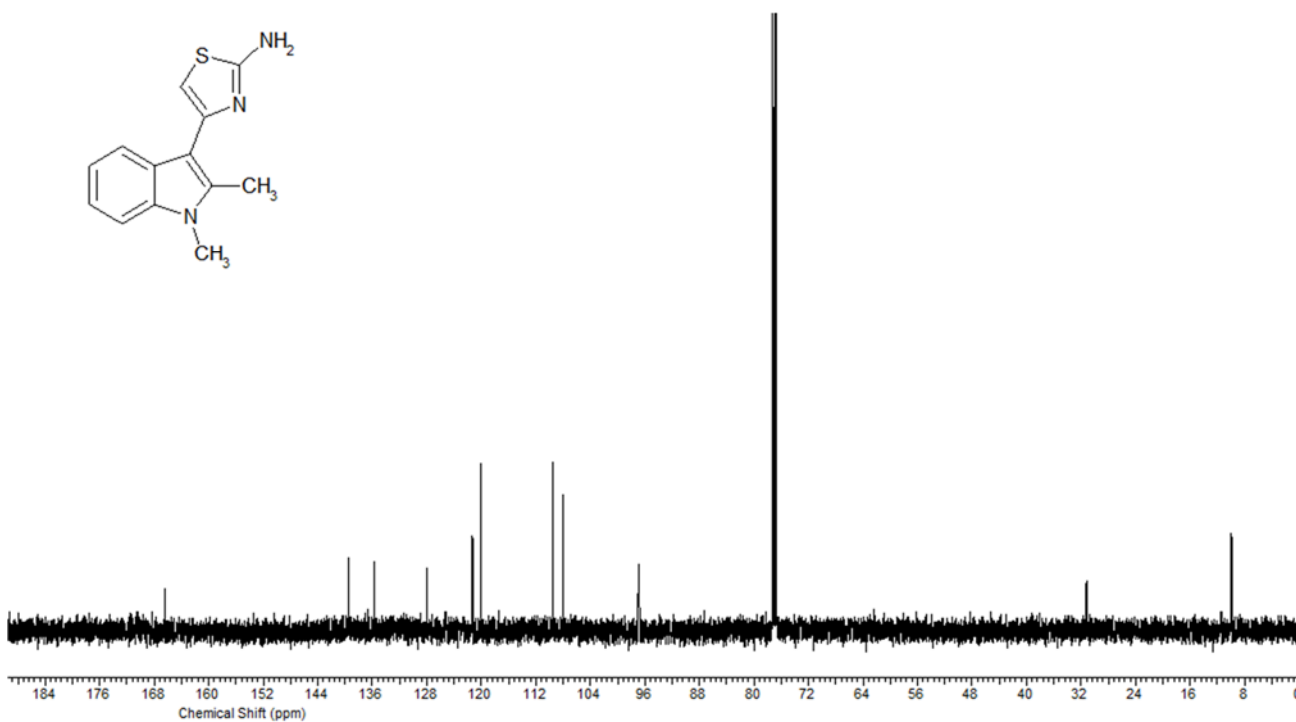
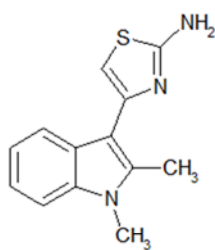
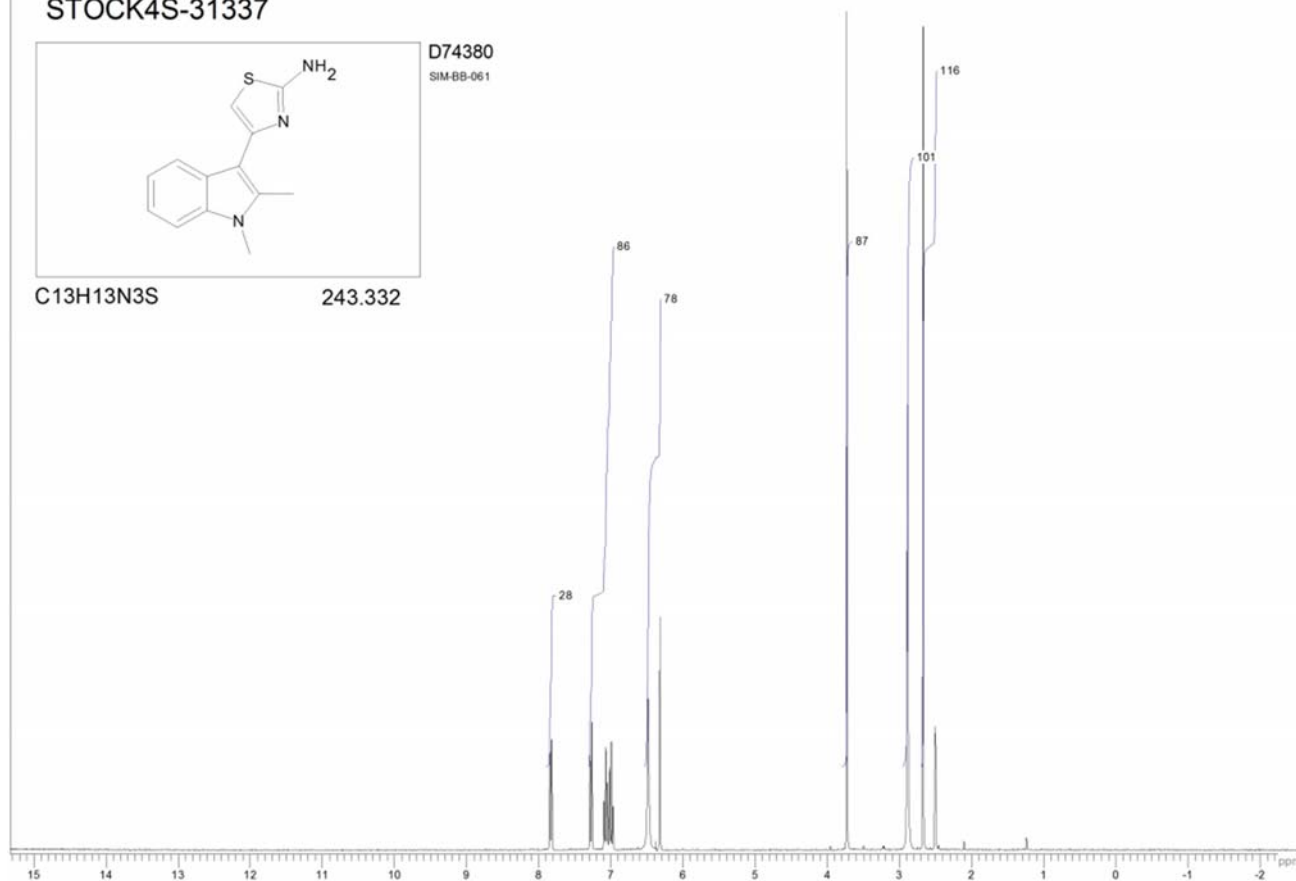


C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>S

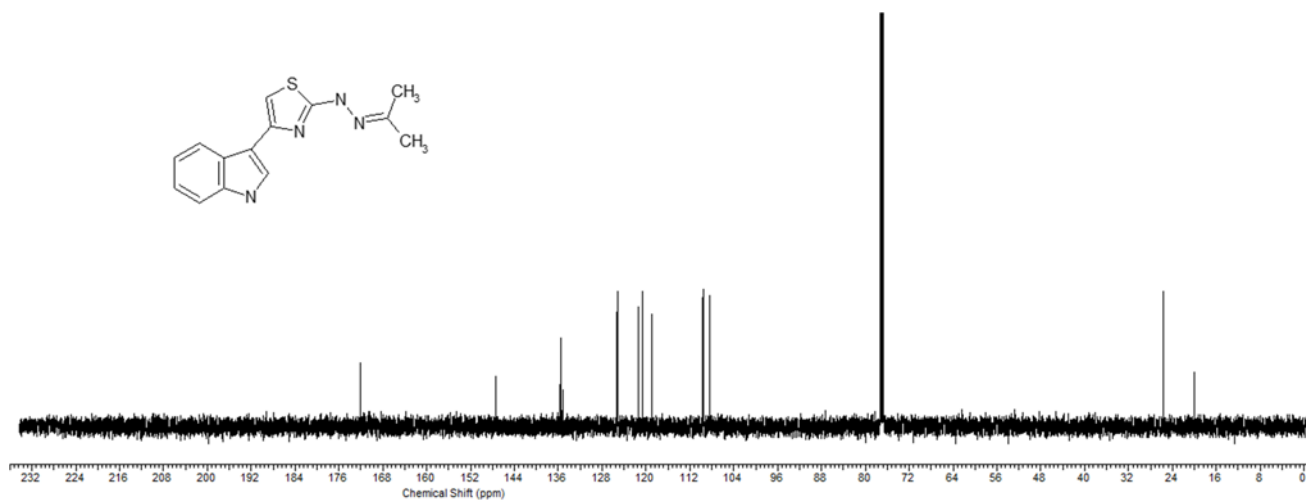
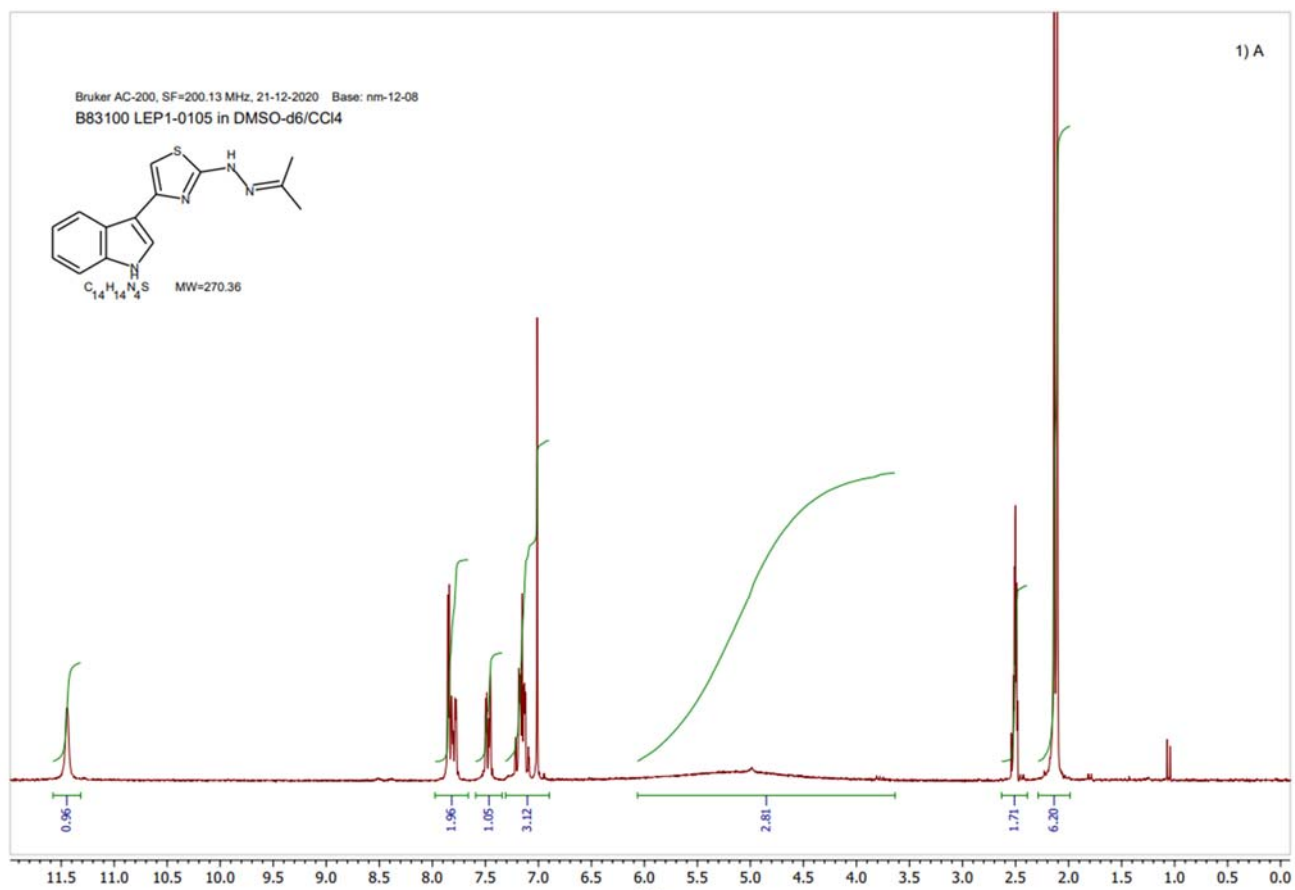
243.332

D74380

SIM-BB-061

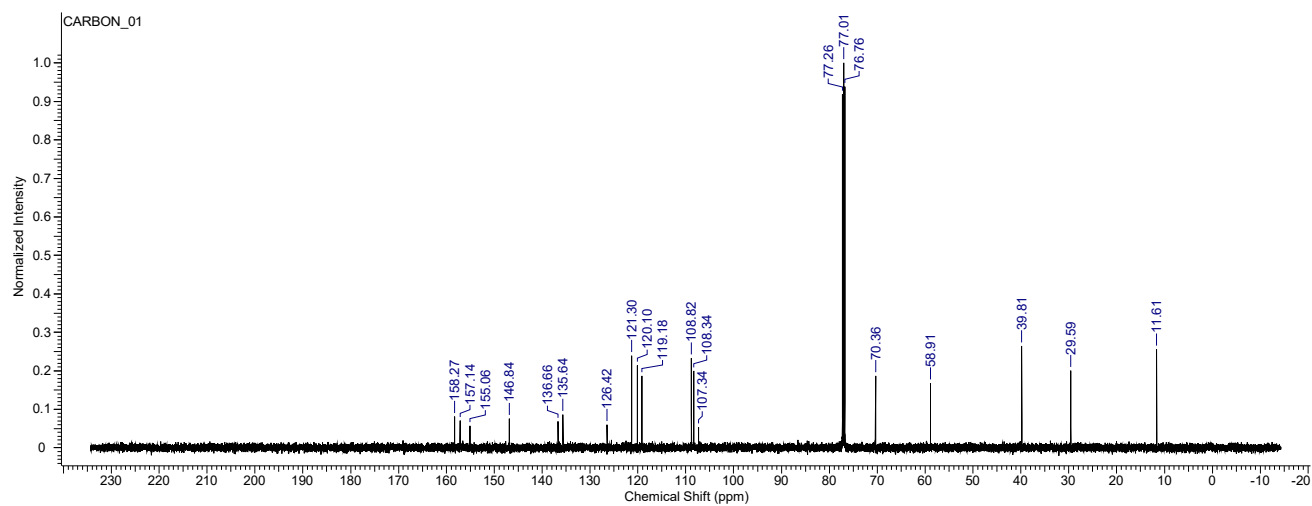
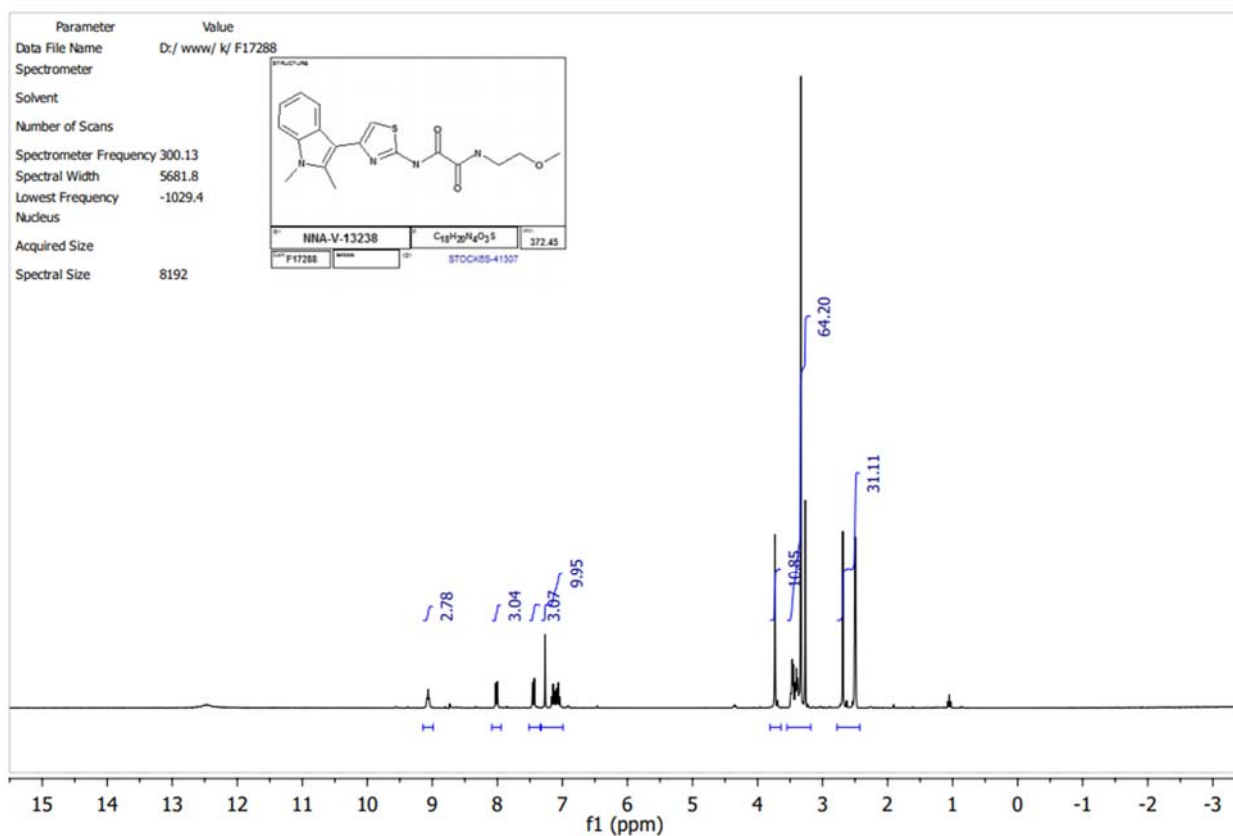


Compound 5X



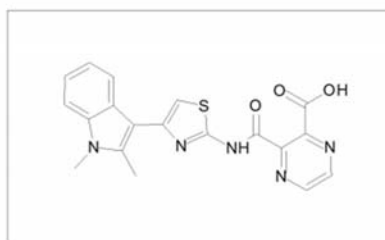
Compound 6a





Compound 6c

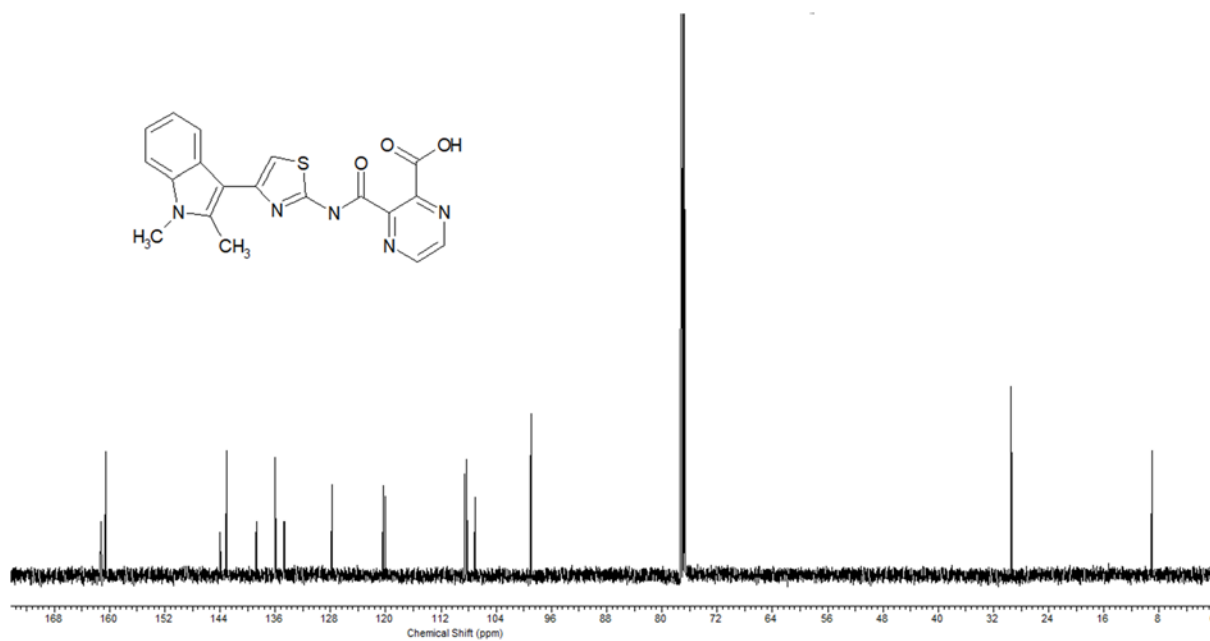
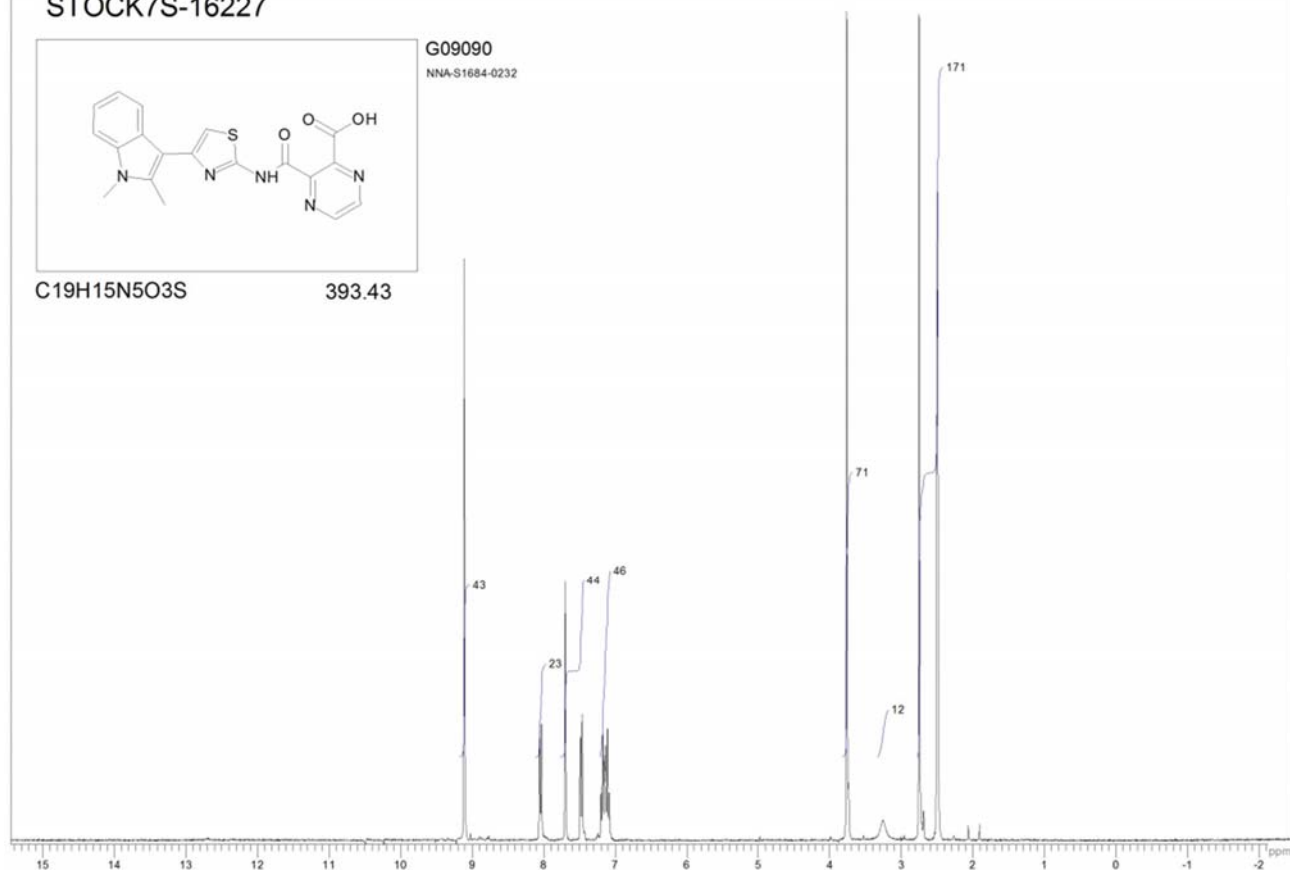
STOCK7S-16227



G09090  
NNA-S1684-0232

C19H15N5O3S

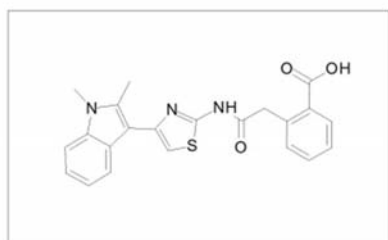
393.43



Compound 6d



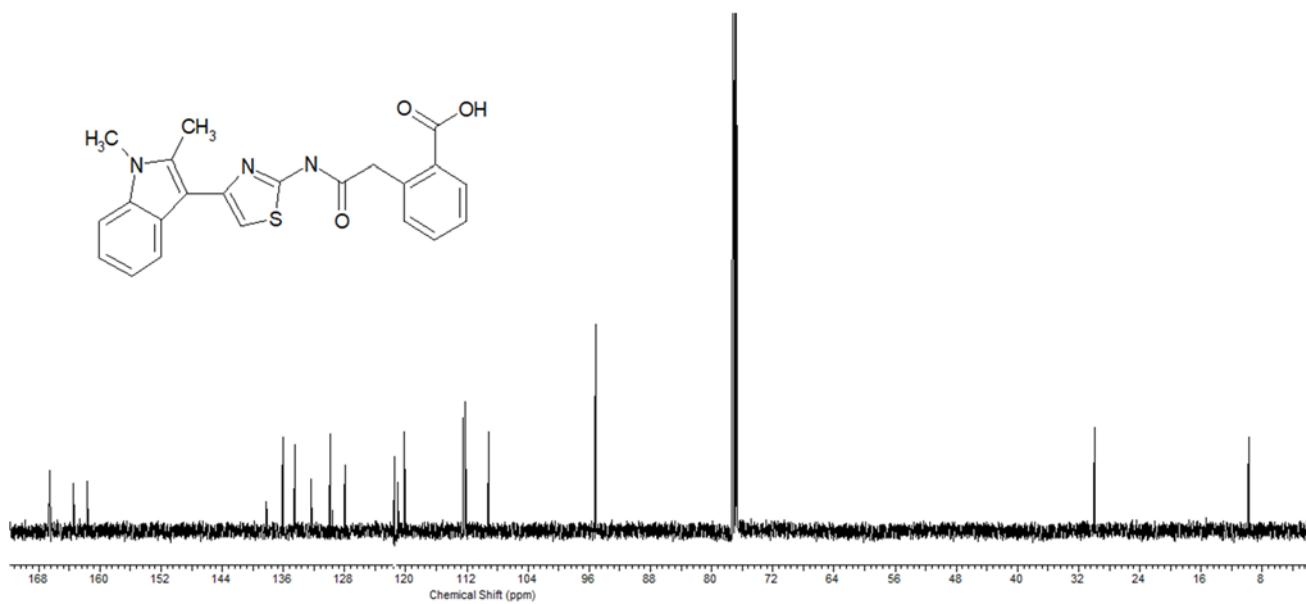
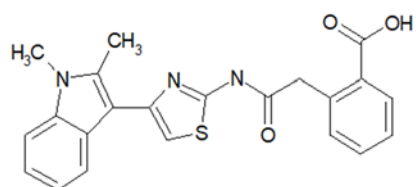
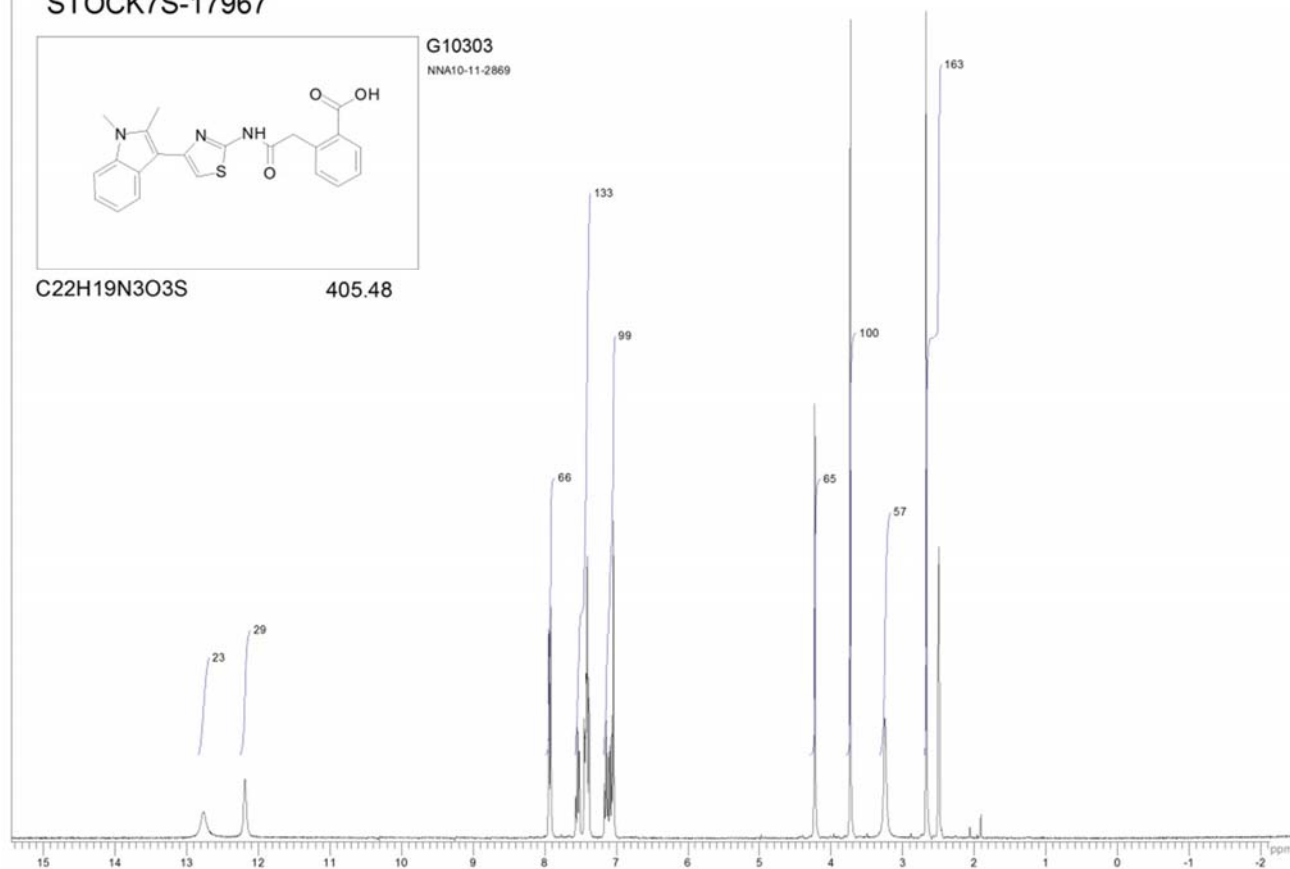
STOCK7S-17967



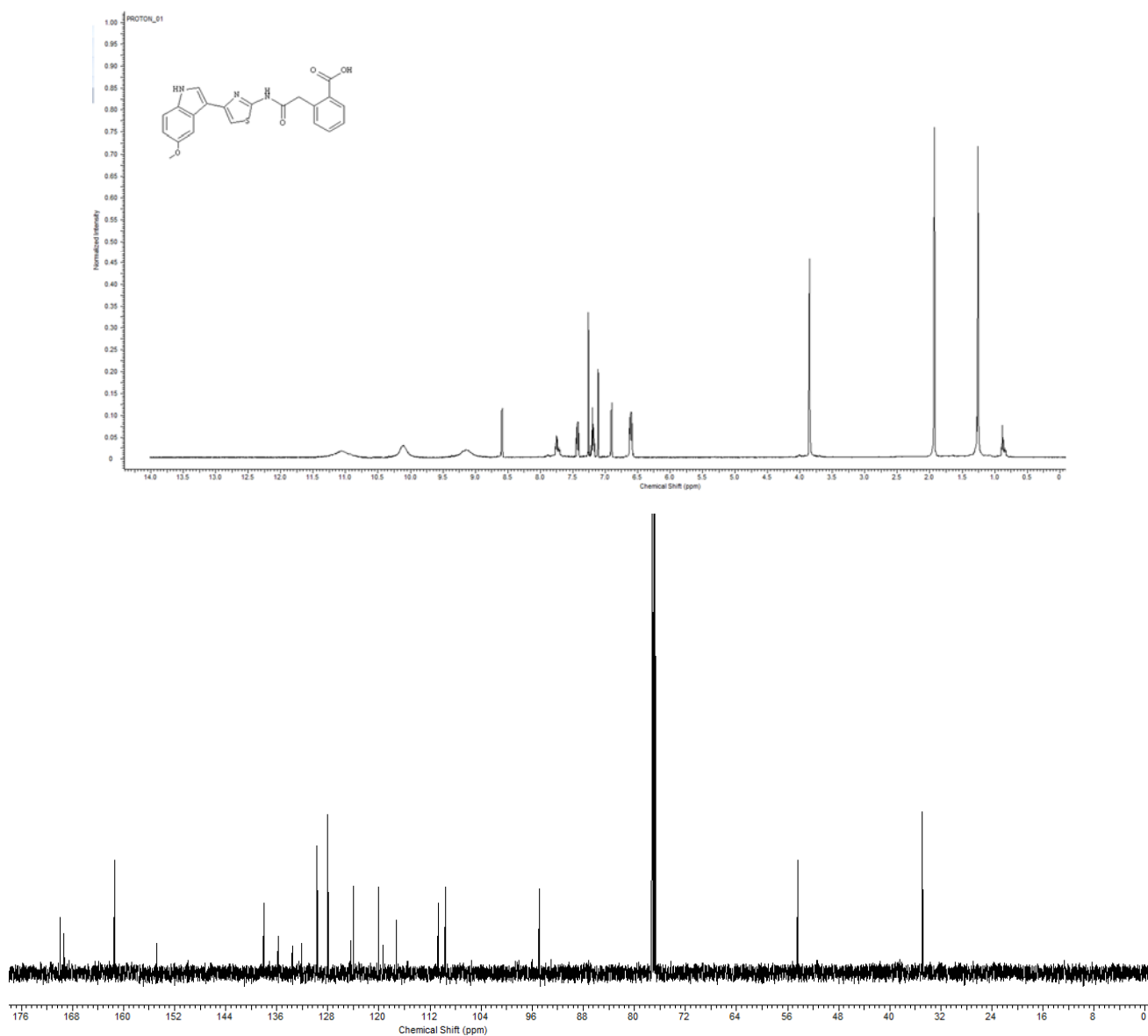
G10303  
NNA10-11-2869

C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S

405.48

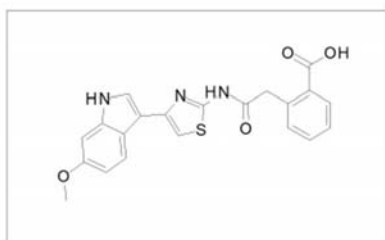


Compound 6e



Compound 6f

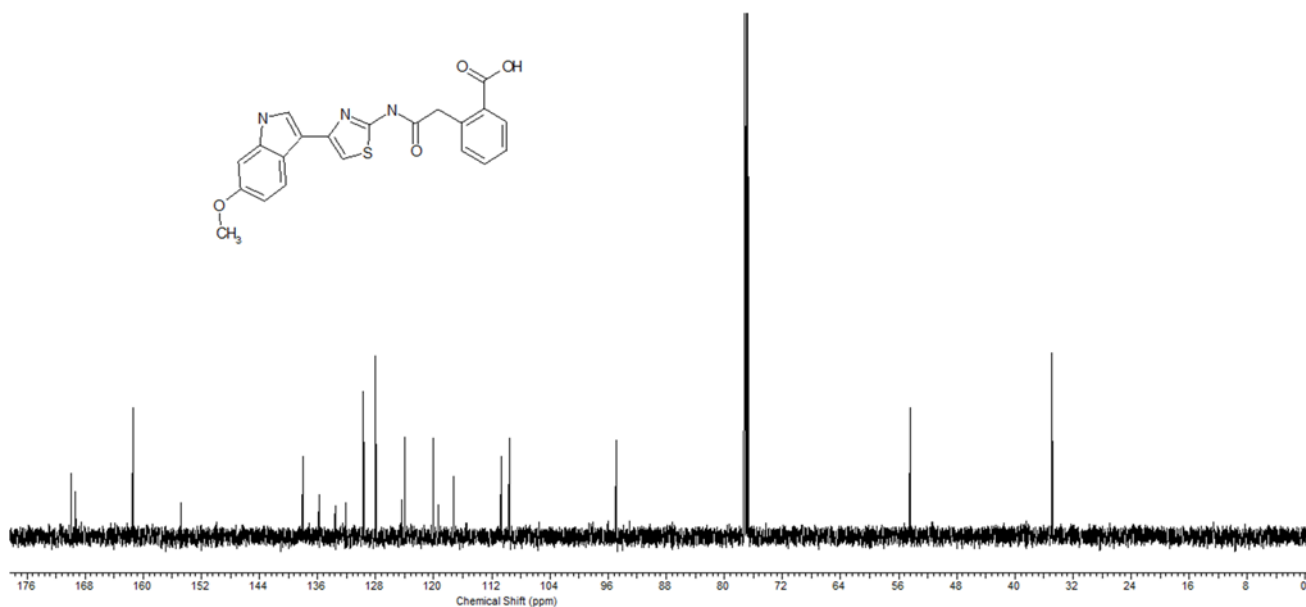
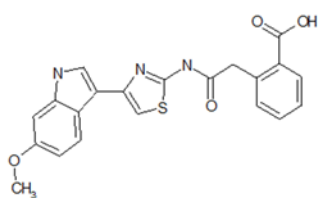
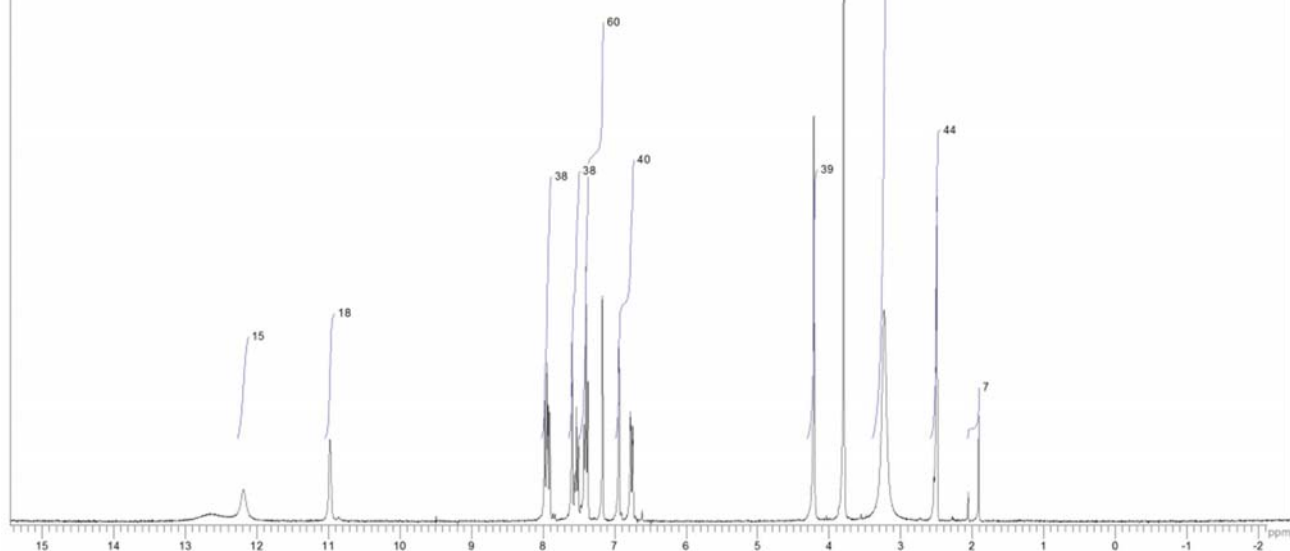
STOCK7S-24499



G19010  
NNA10-11-2898

C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S

407.45



5g OXI H 28480  
5l 23917 oxi H

5m 46779 oxi H  
6E 24276 OXI C