

Supplementary Material

Isoniazid linked to sulfonate esters via hydrazone functionality: Design, synthesis, and evaluation of antitubercular activity

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Department of Pharmaceutical Chemistry

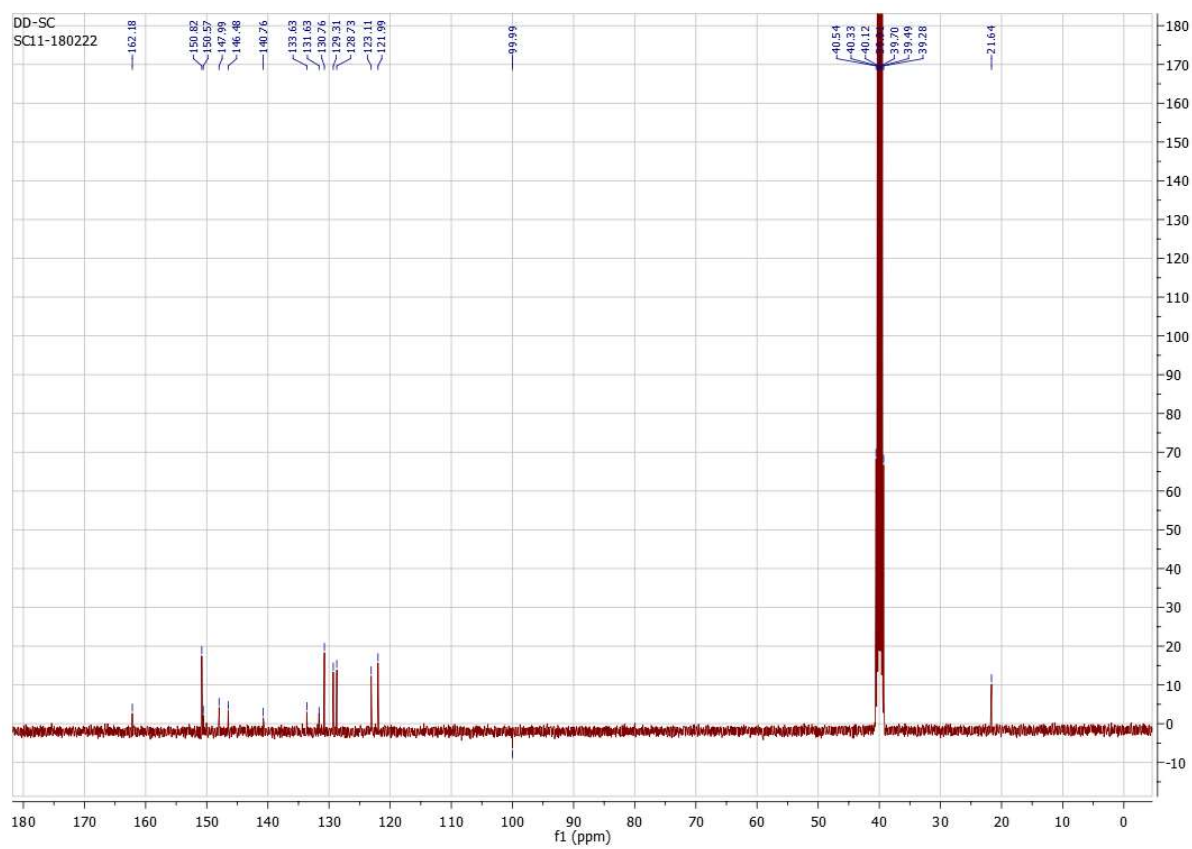
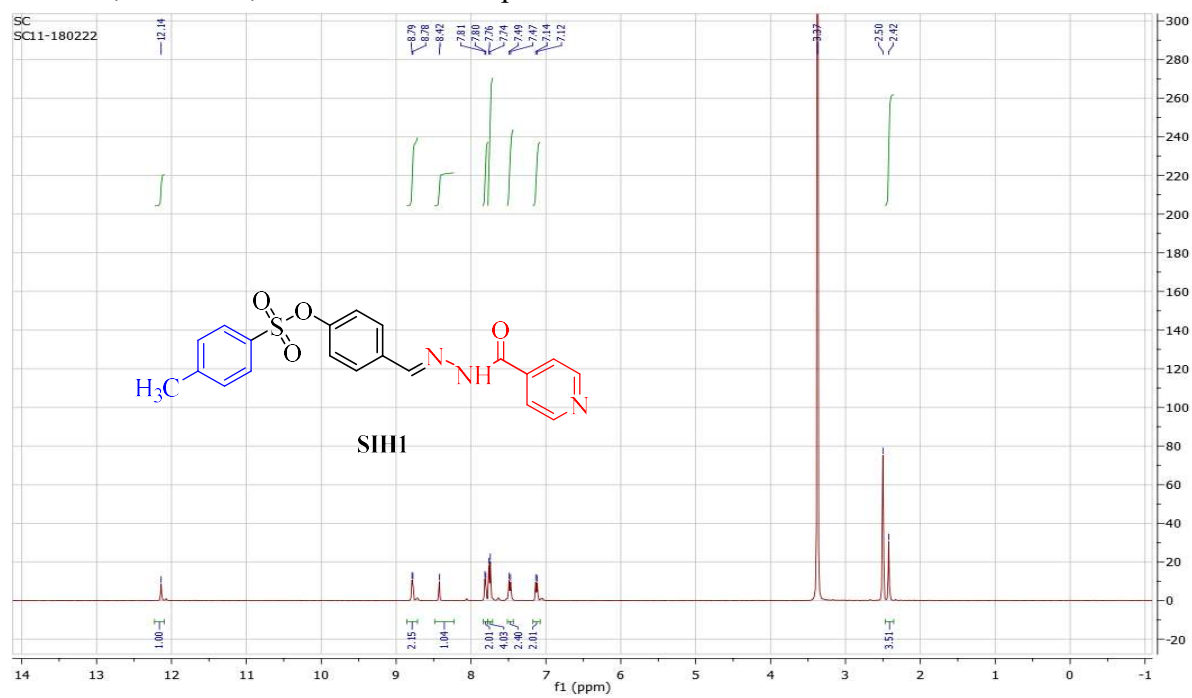
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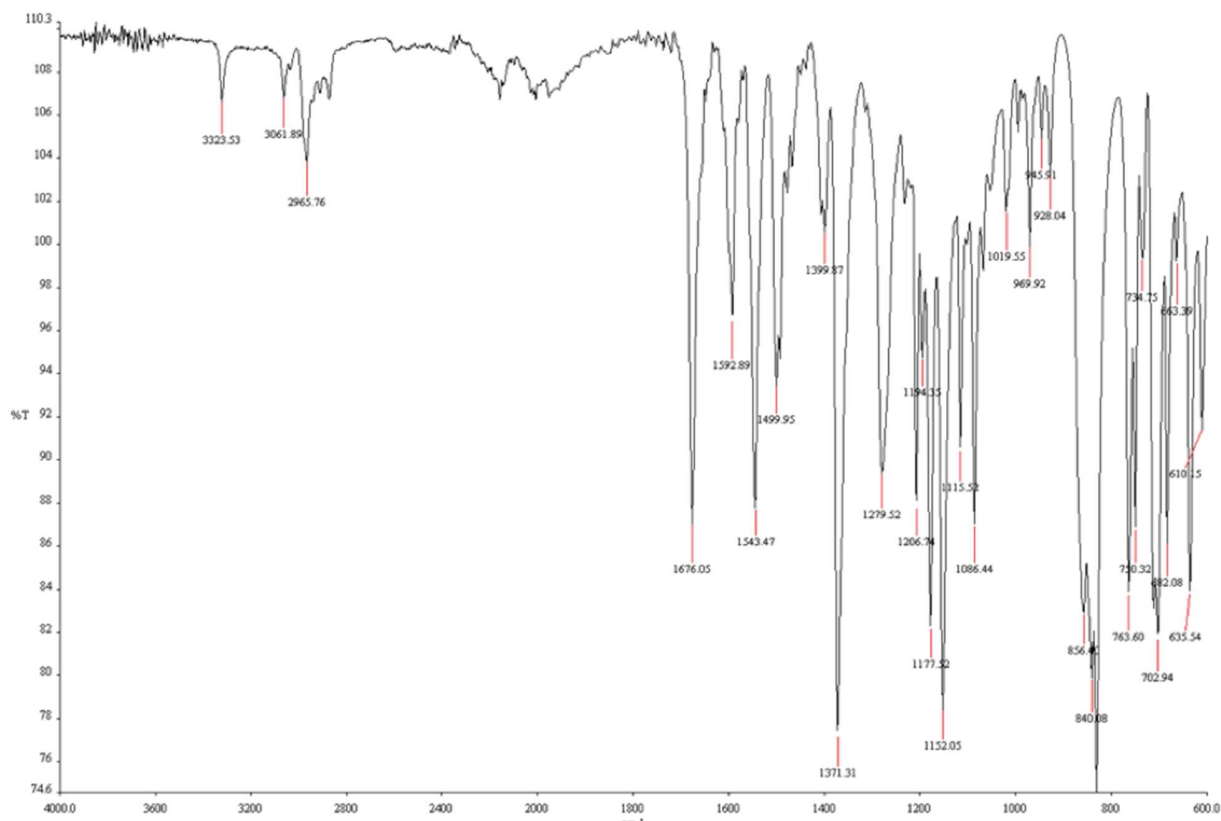
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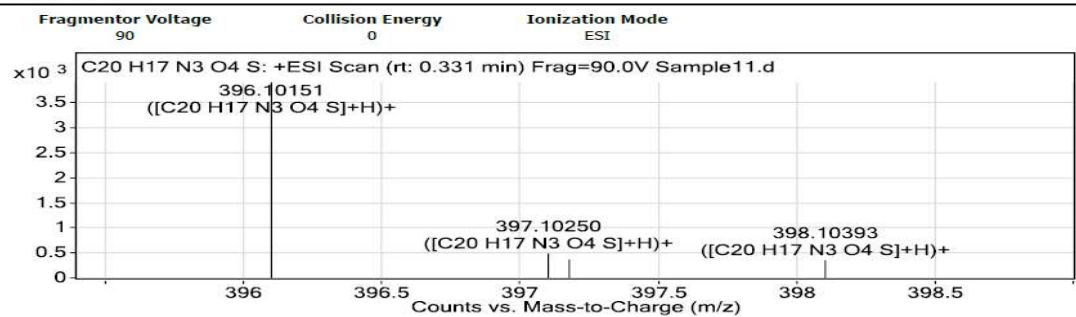
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^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH1**

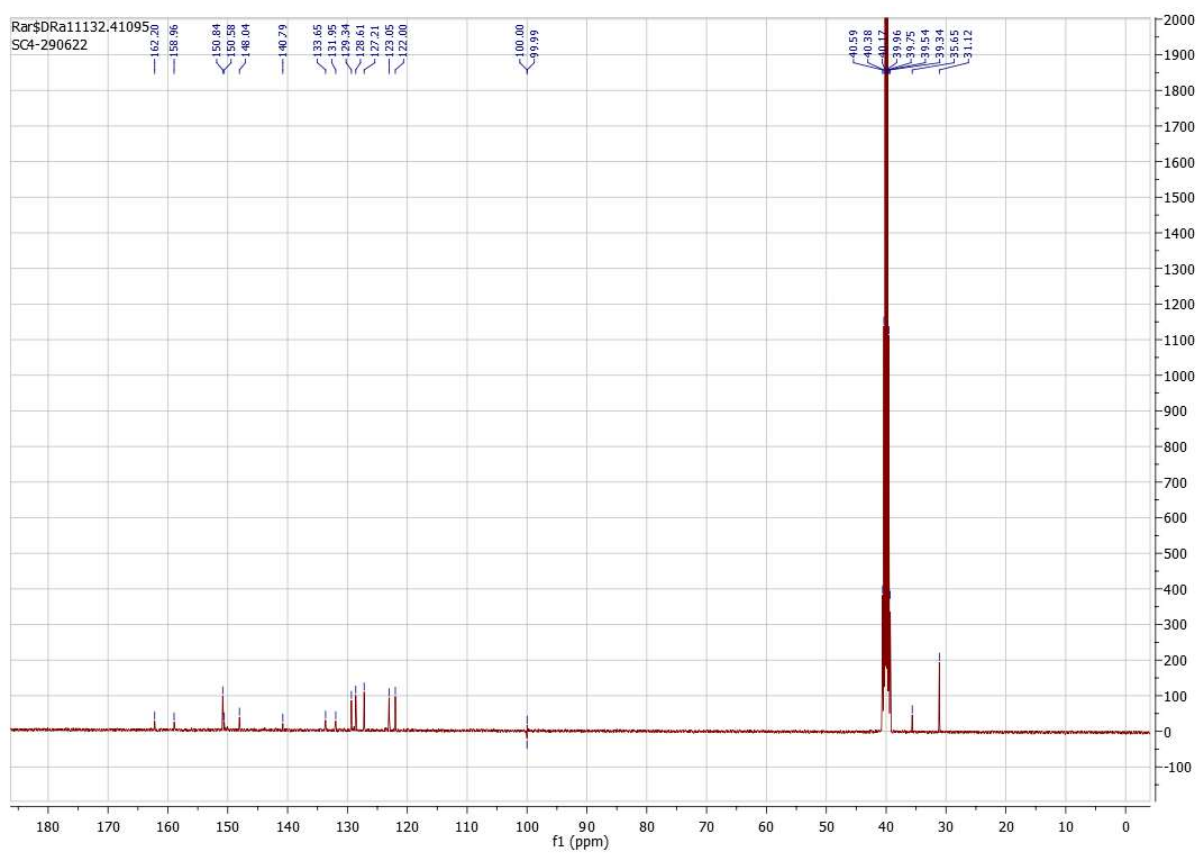
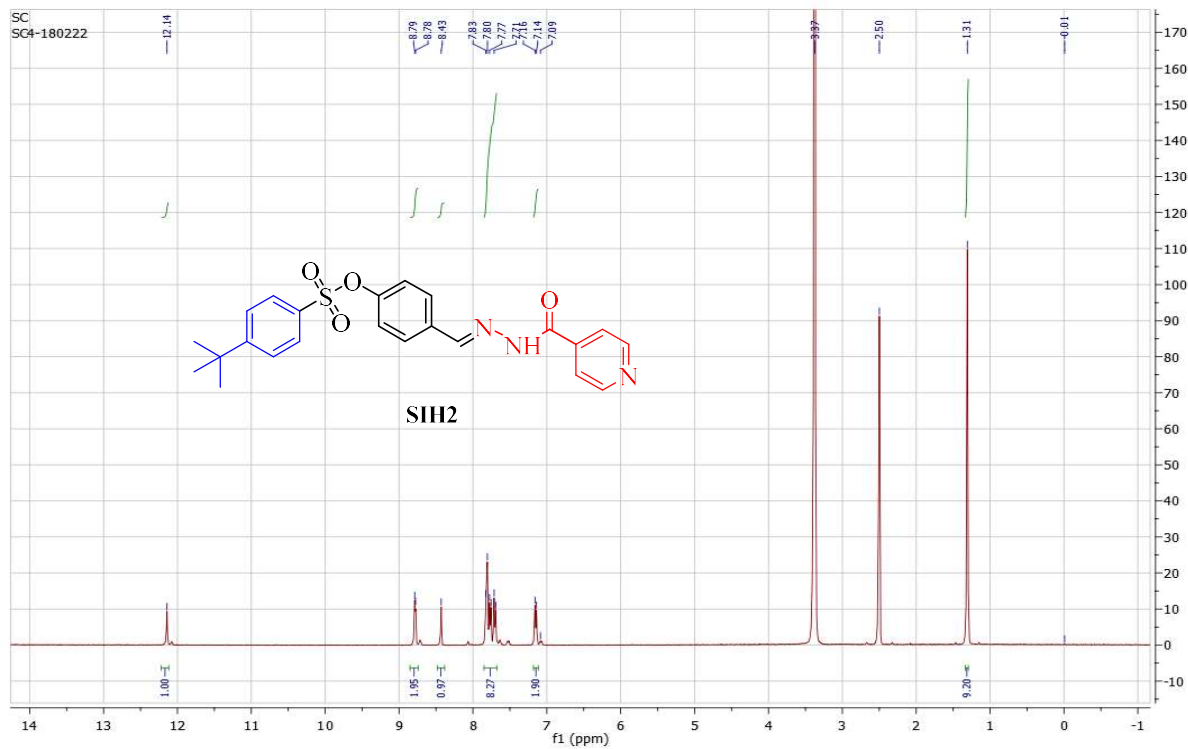


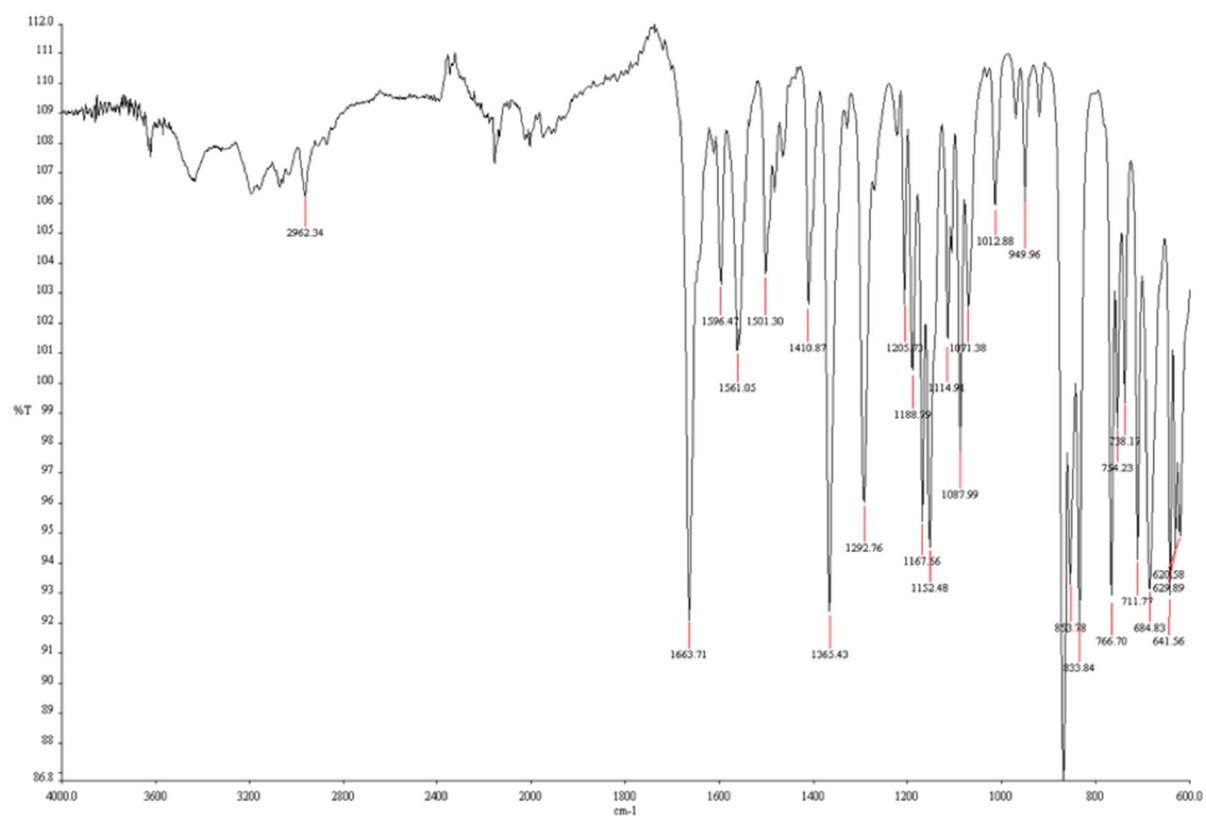


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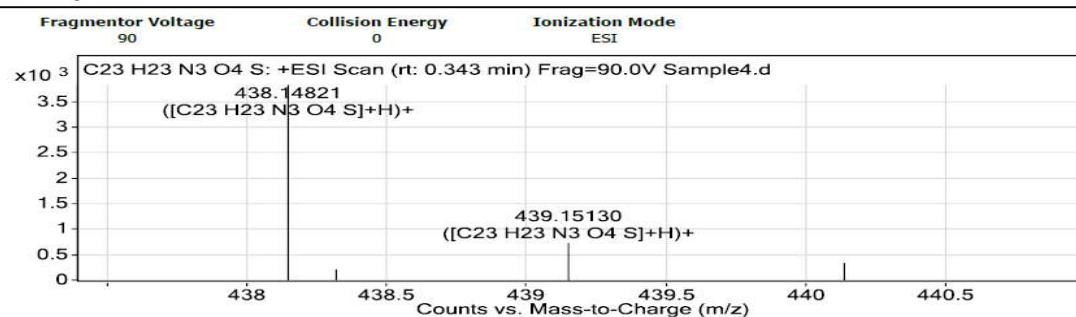


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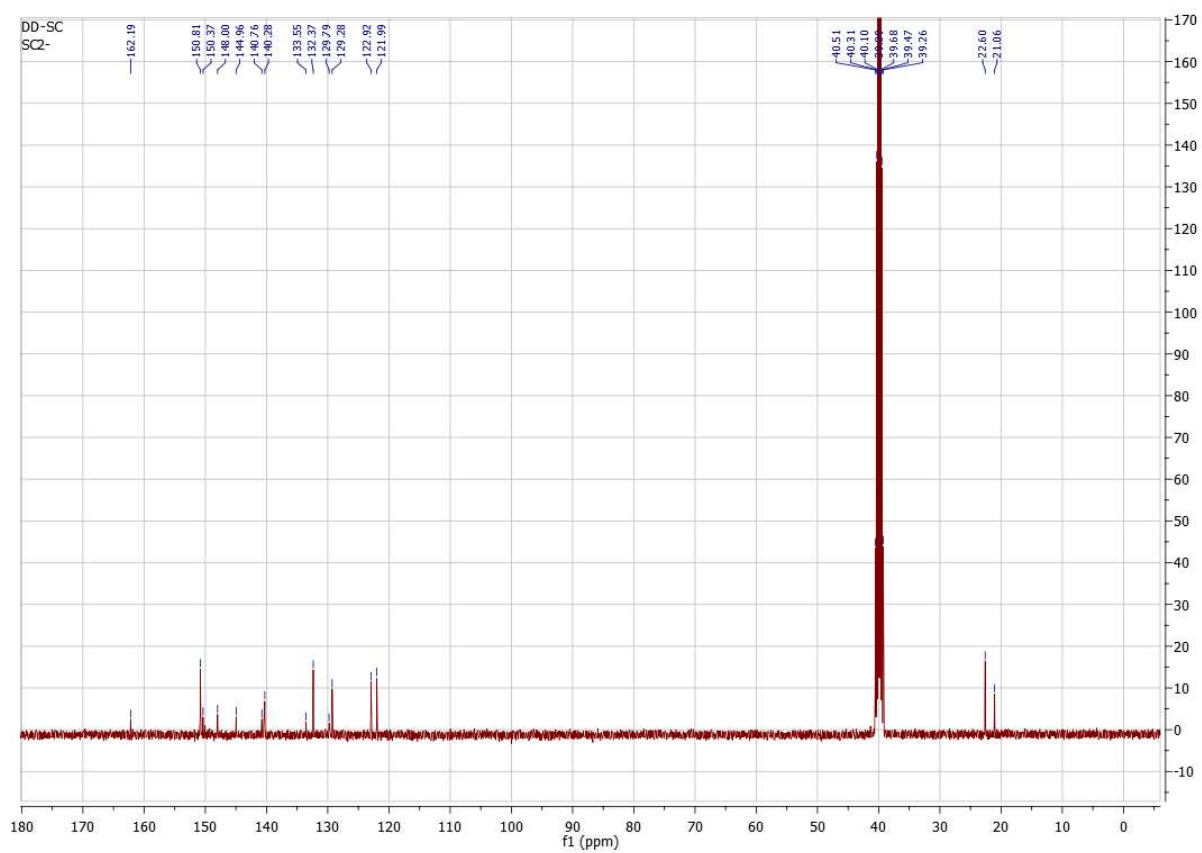
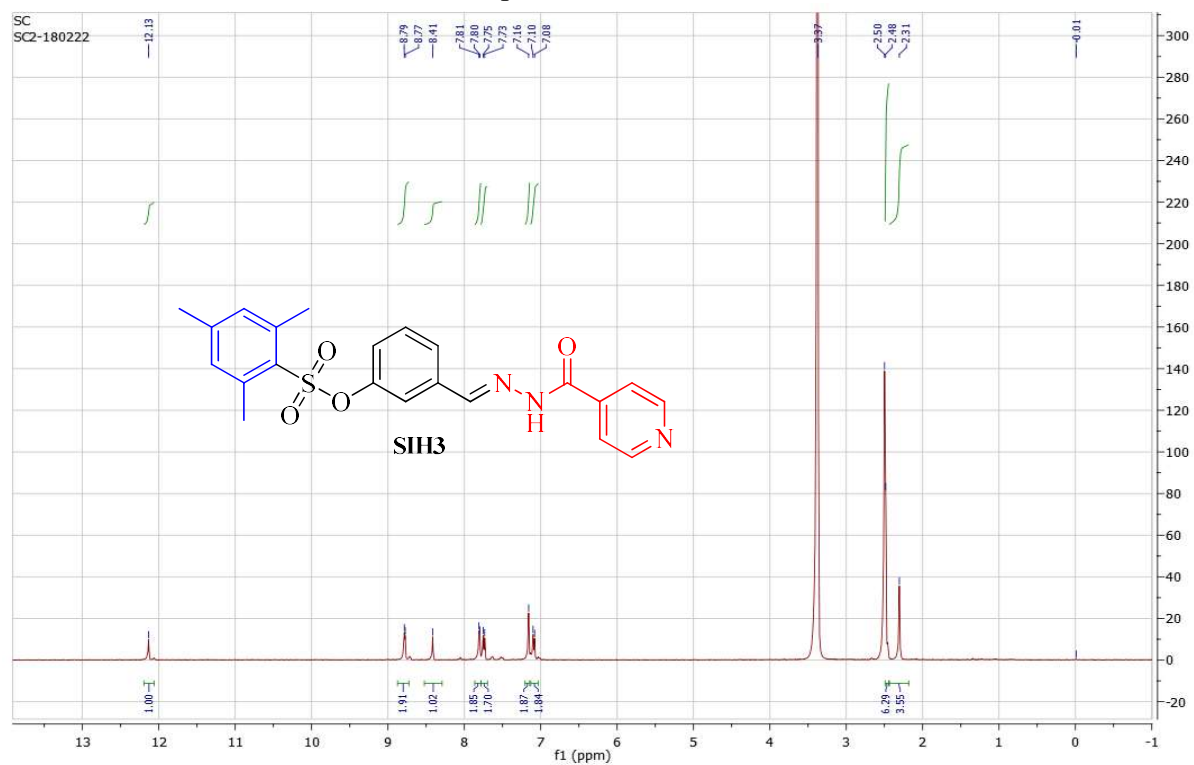


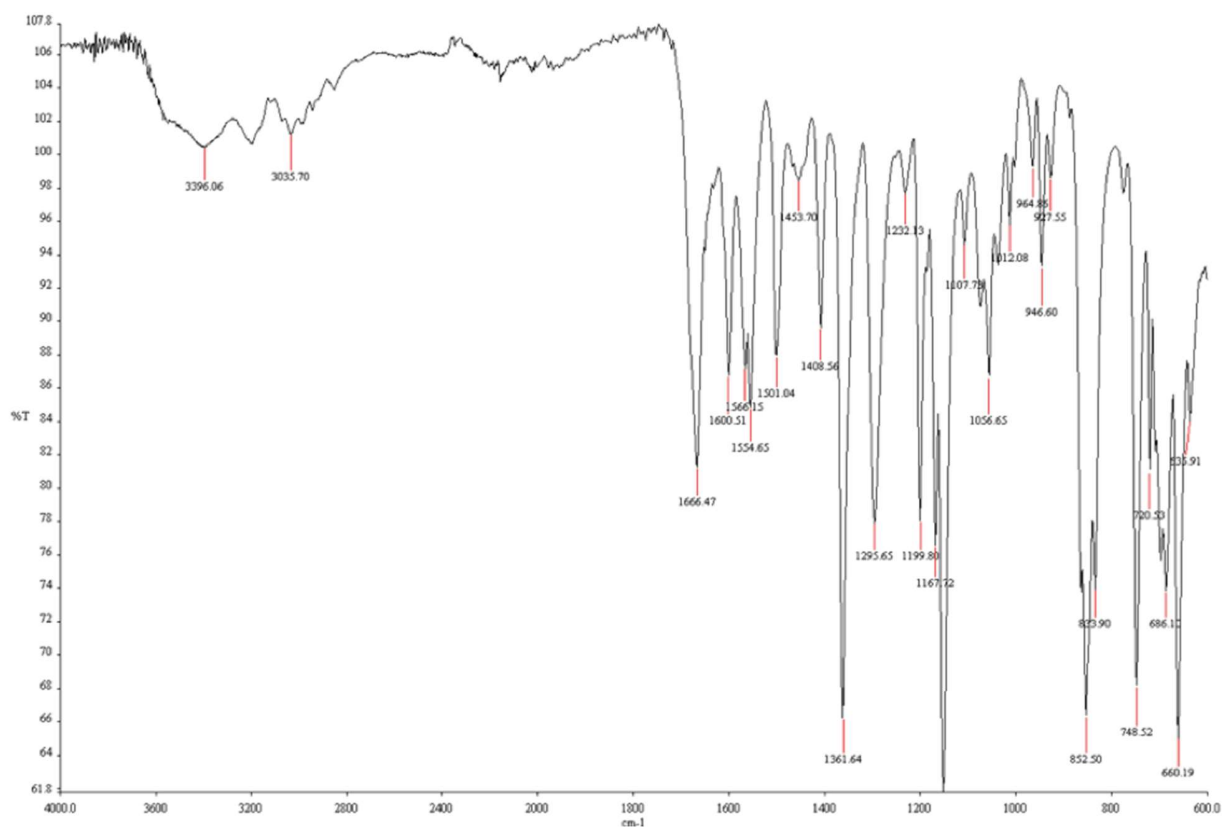


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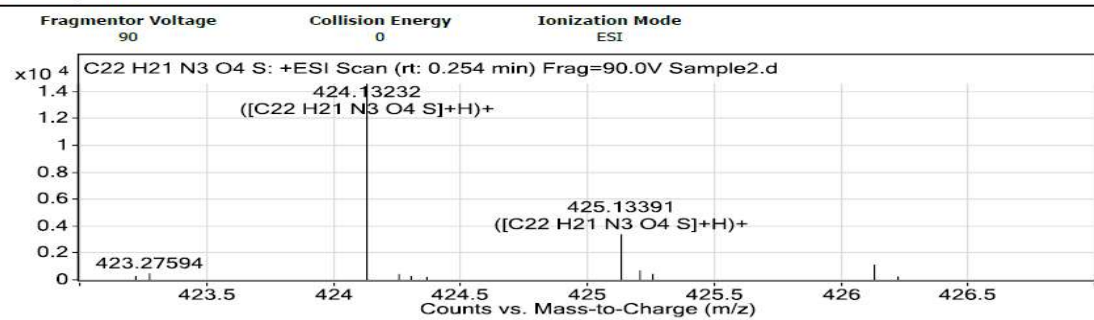


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH3**

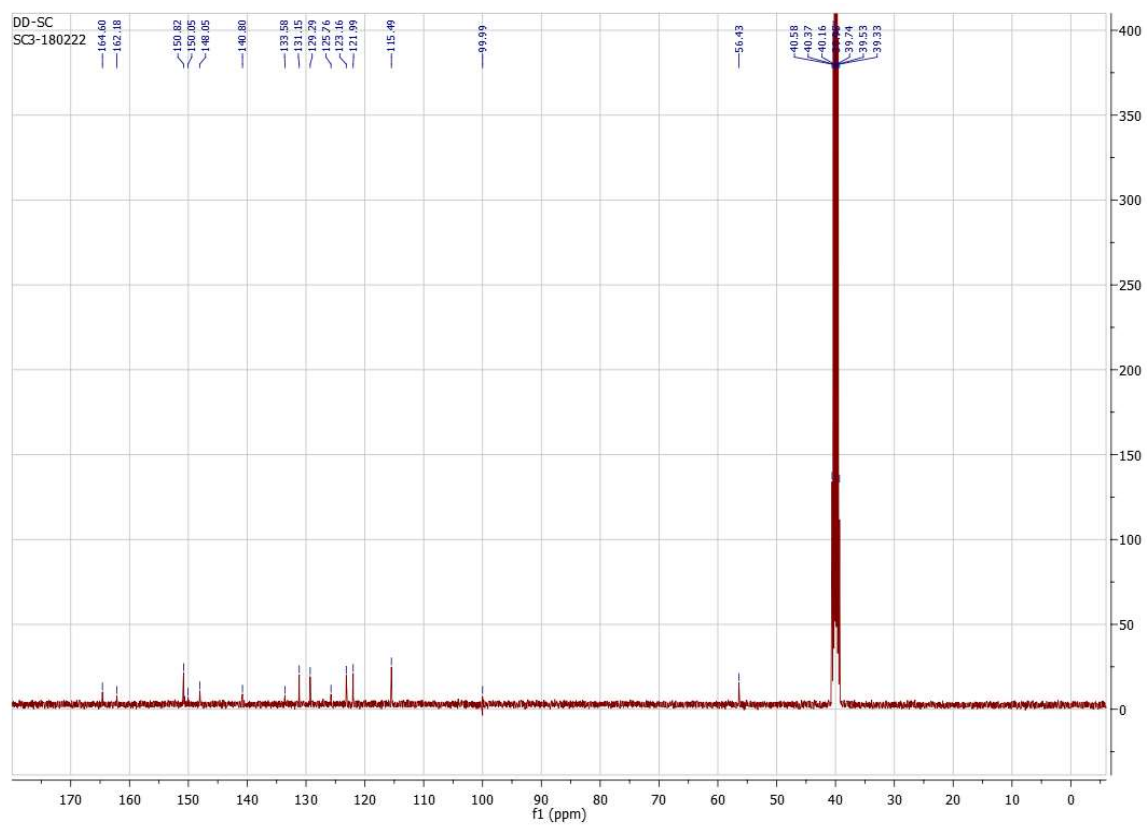
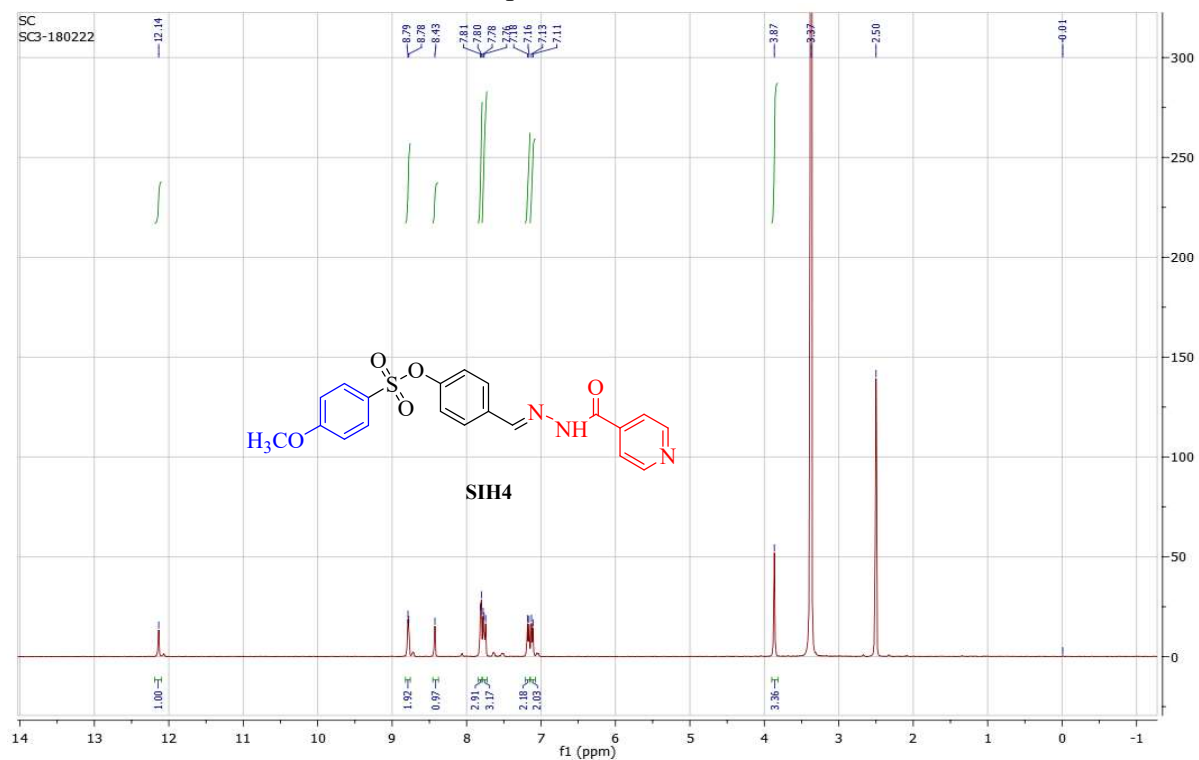


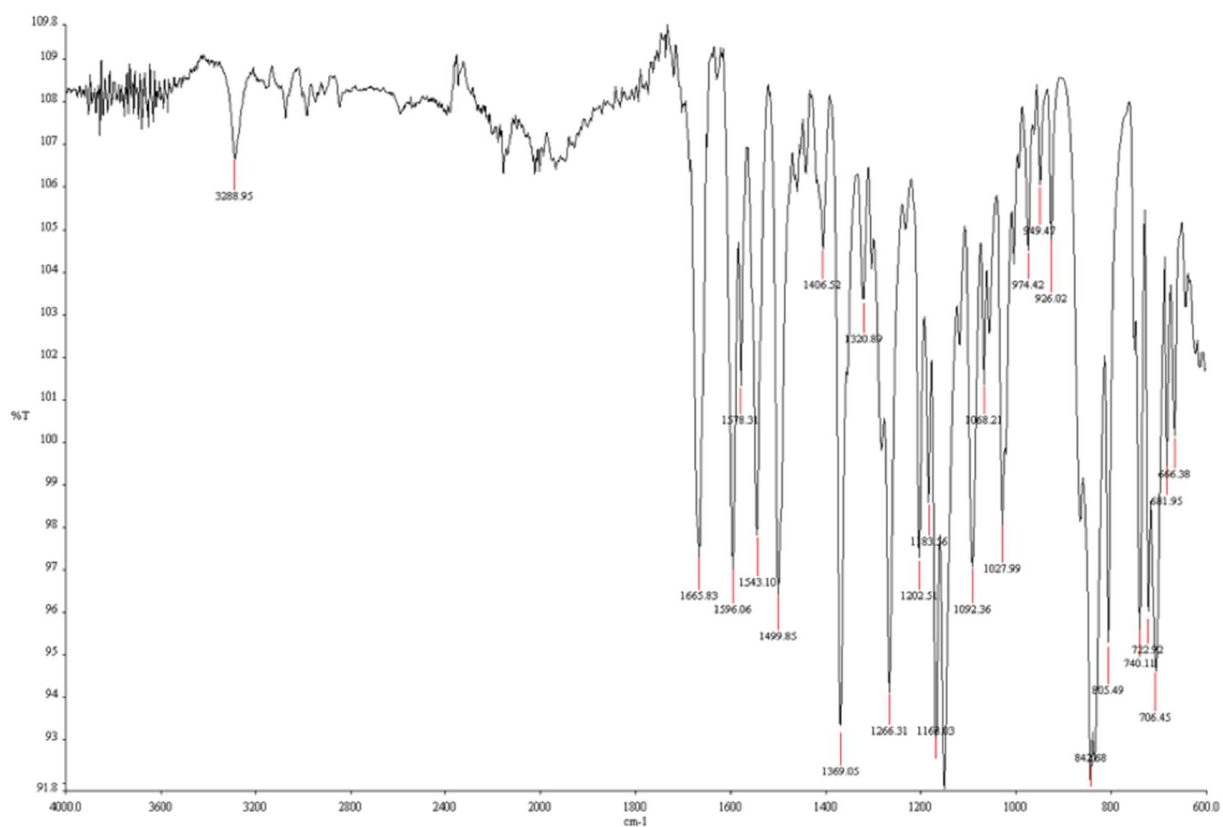


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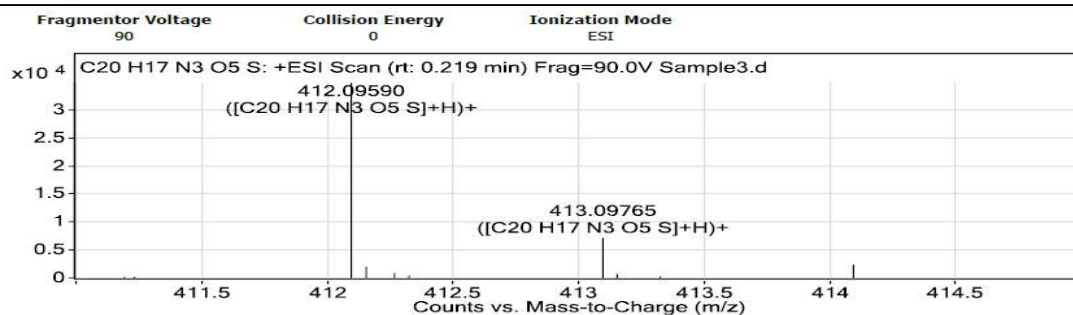


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH4**

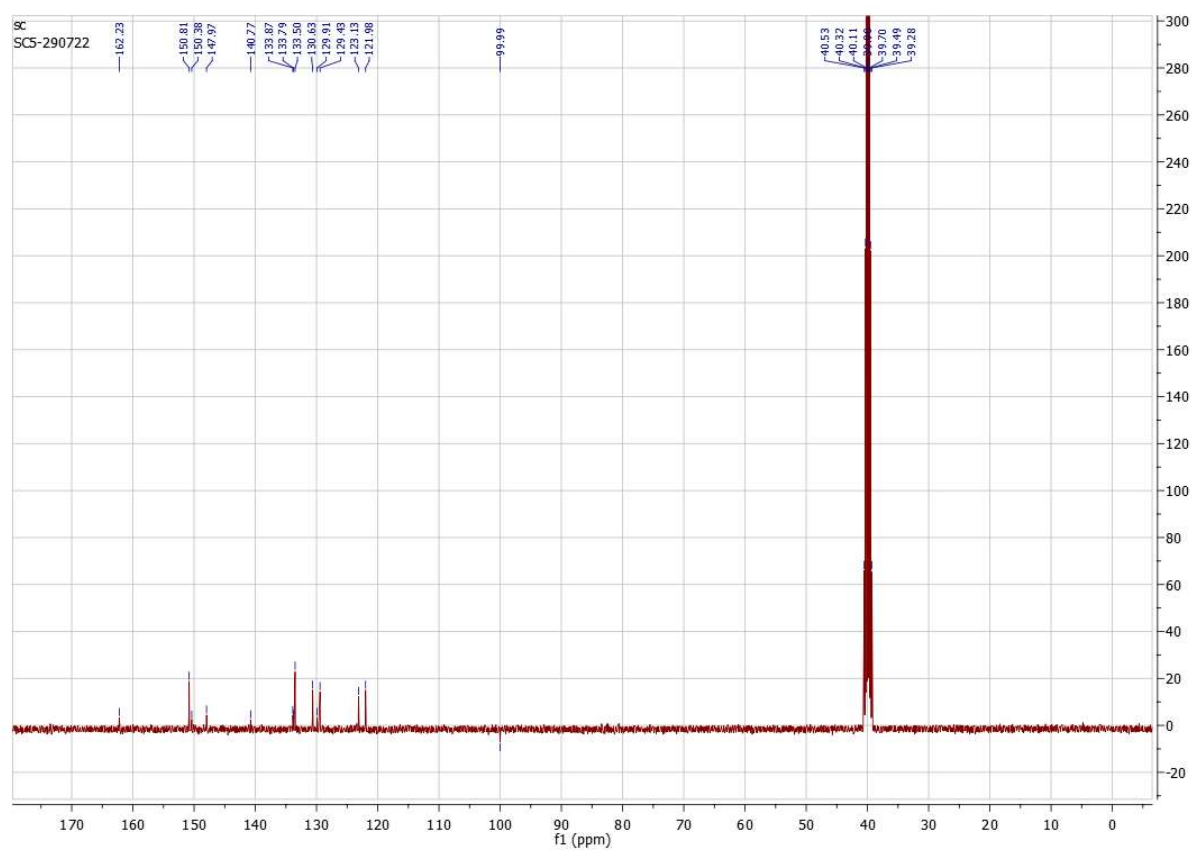
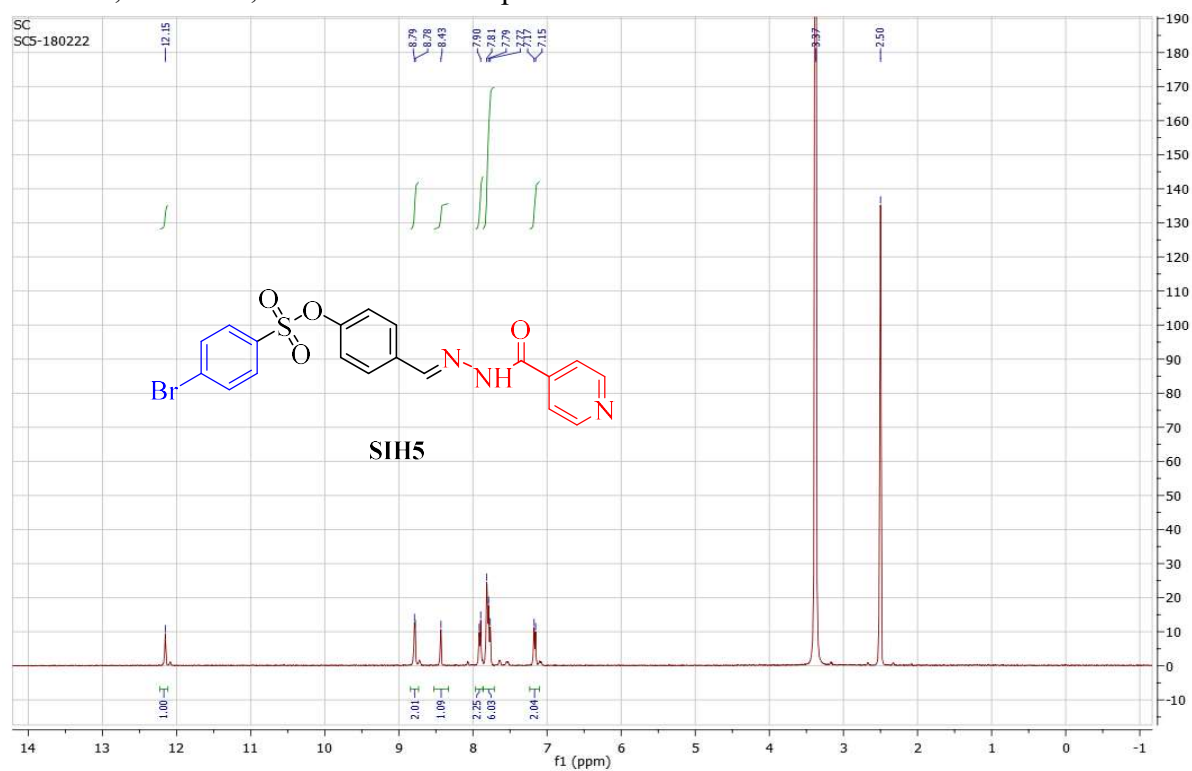


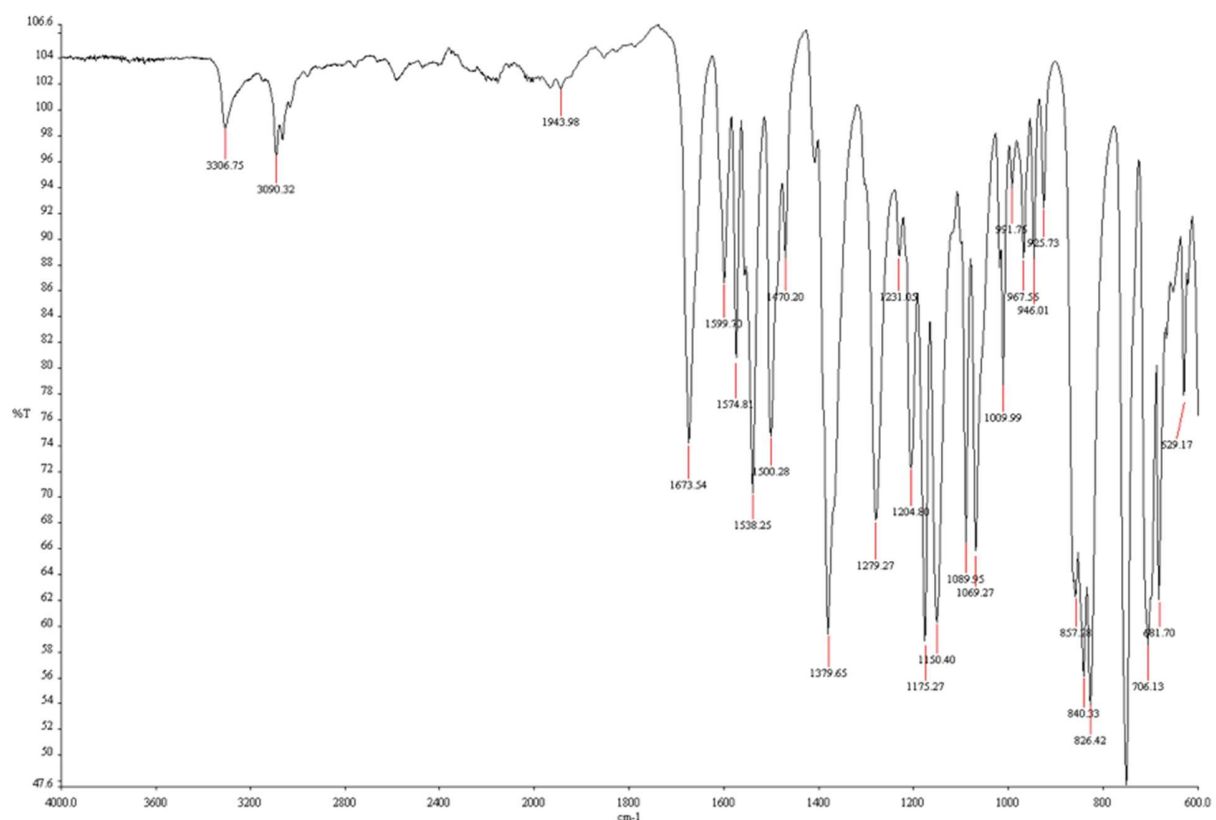


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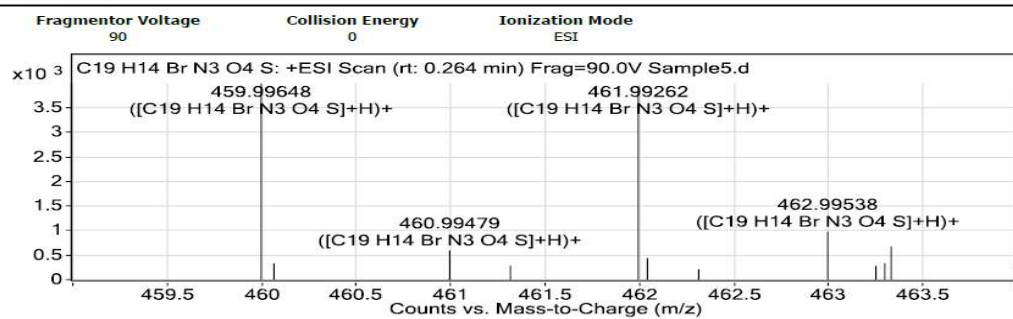


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH5**

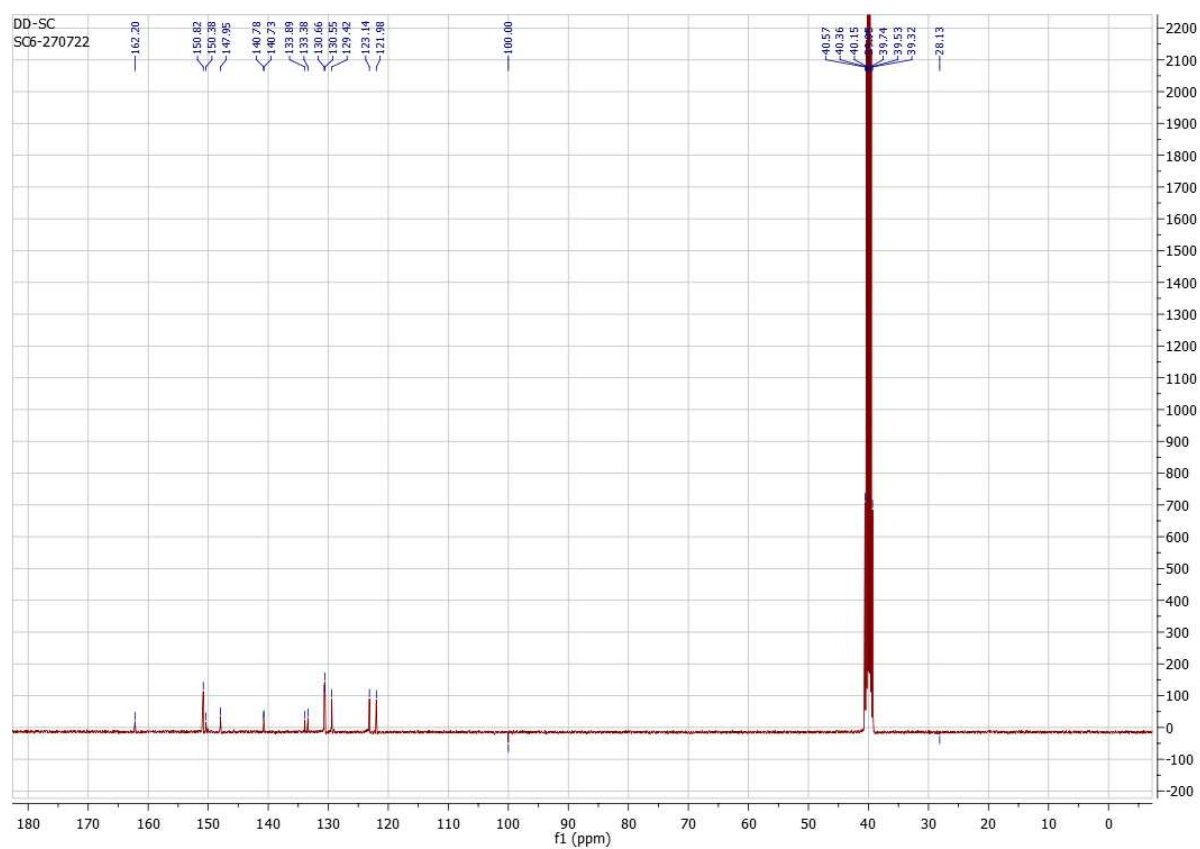
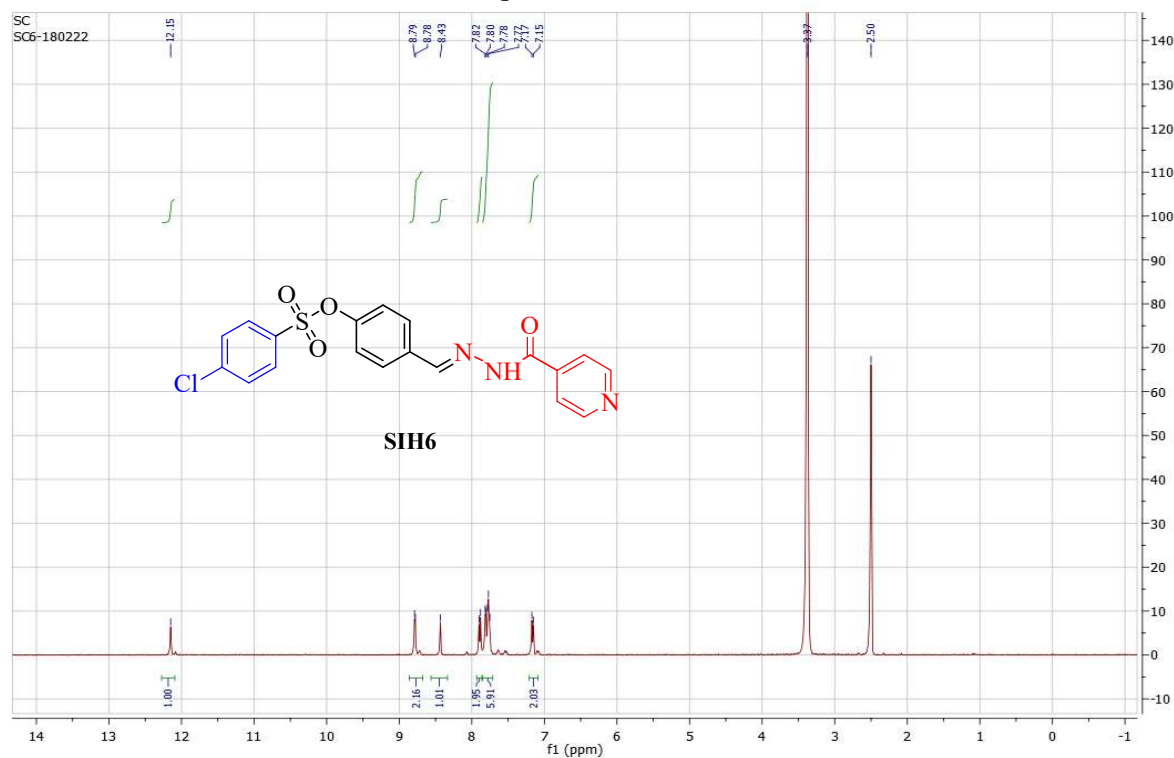


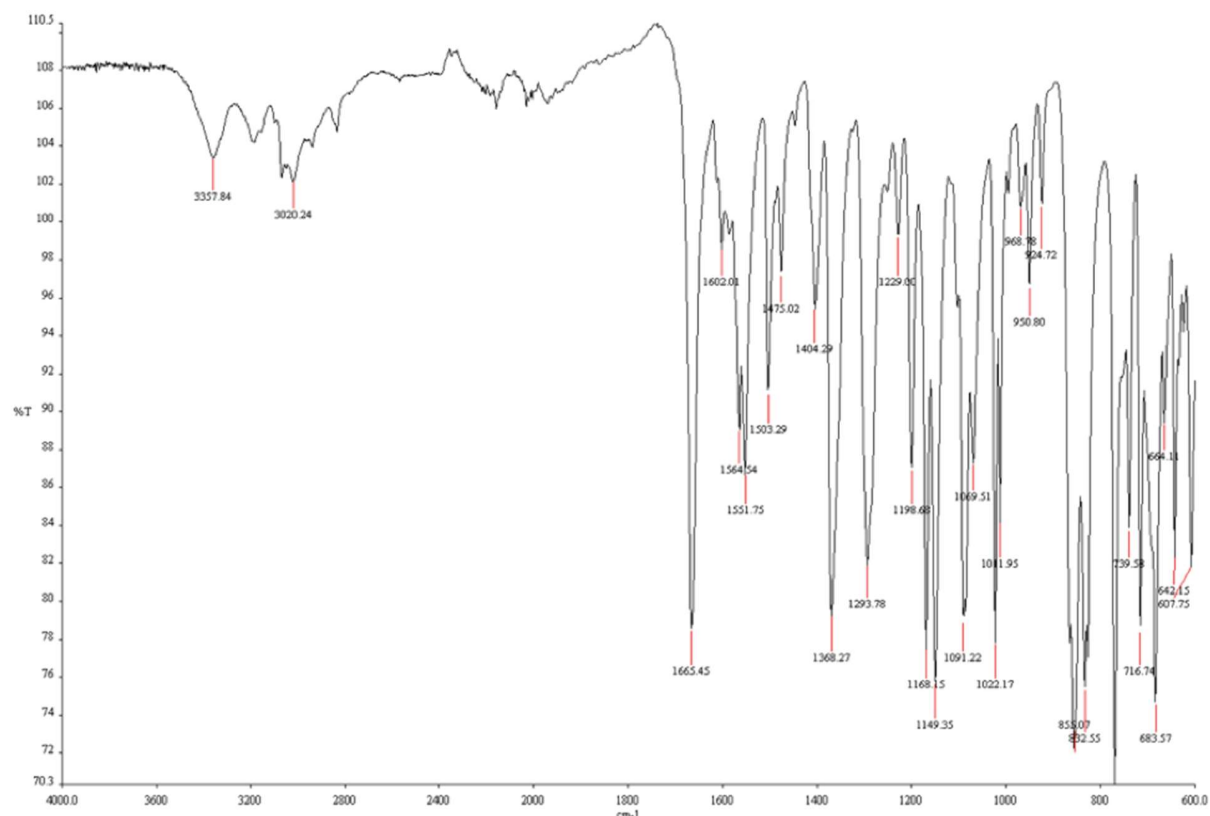


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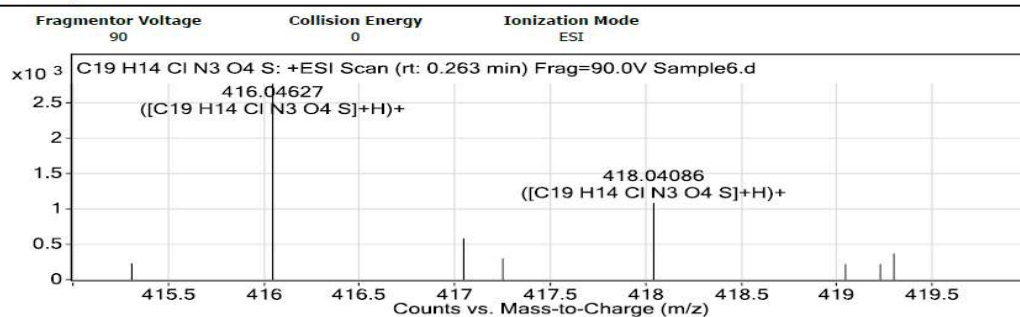


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH6**

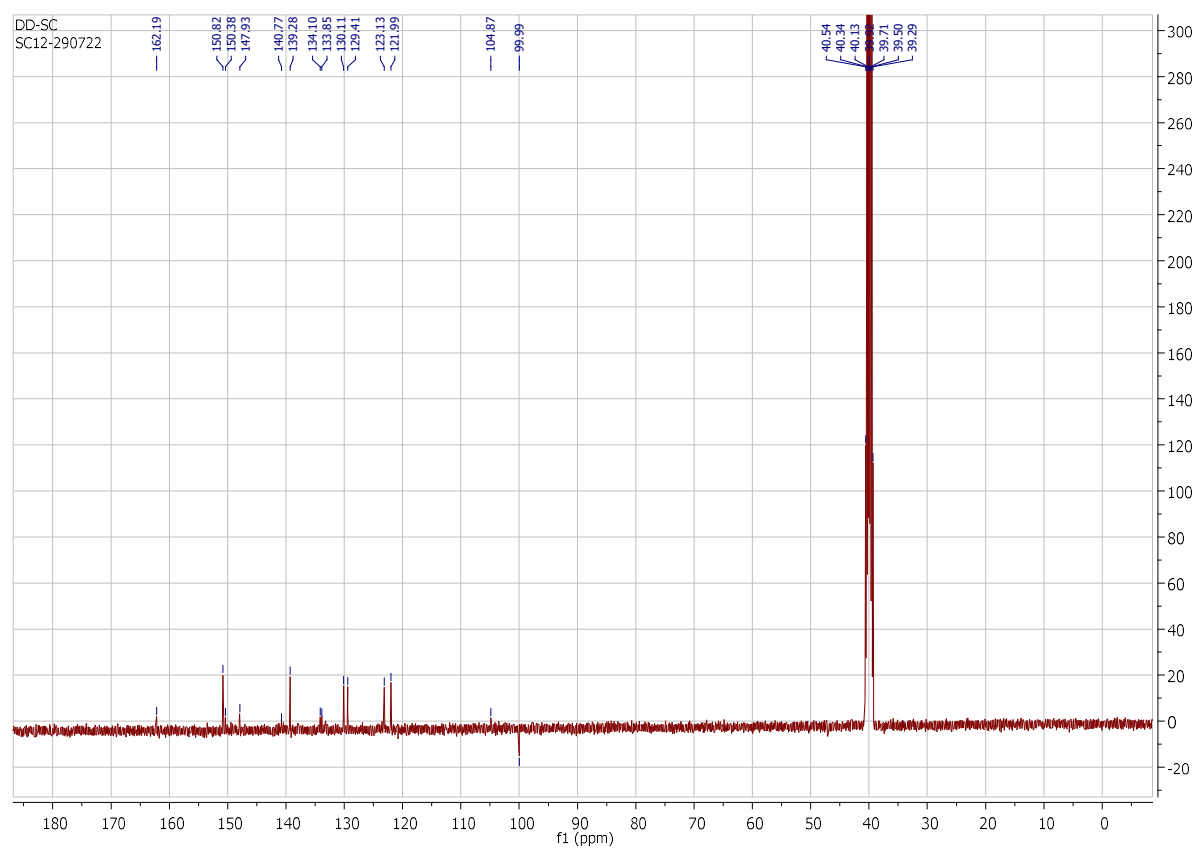
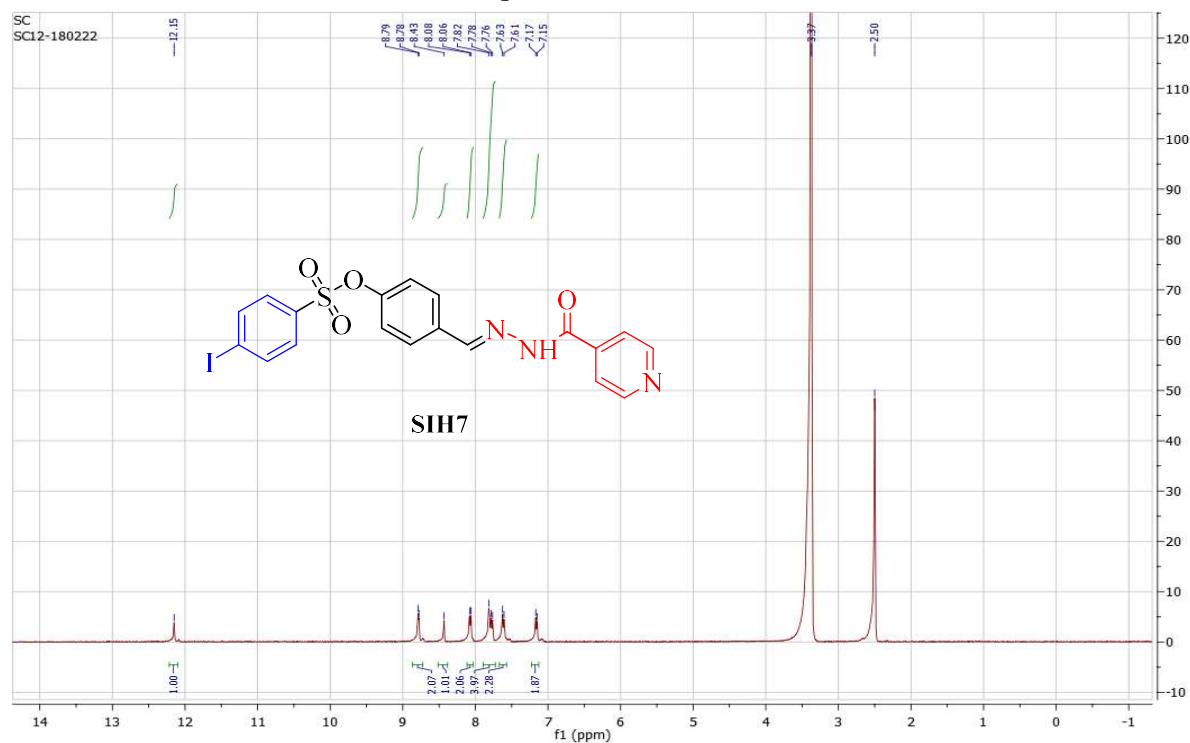


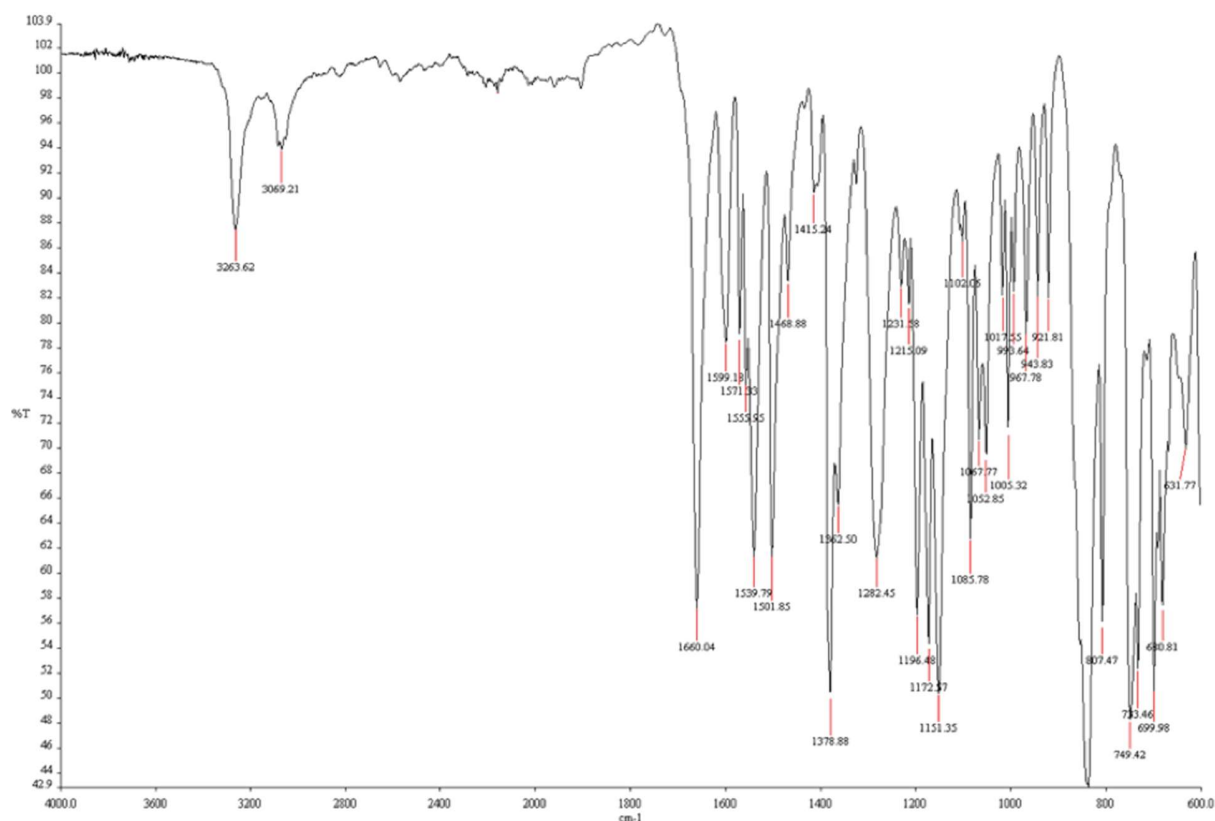


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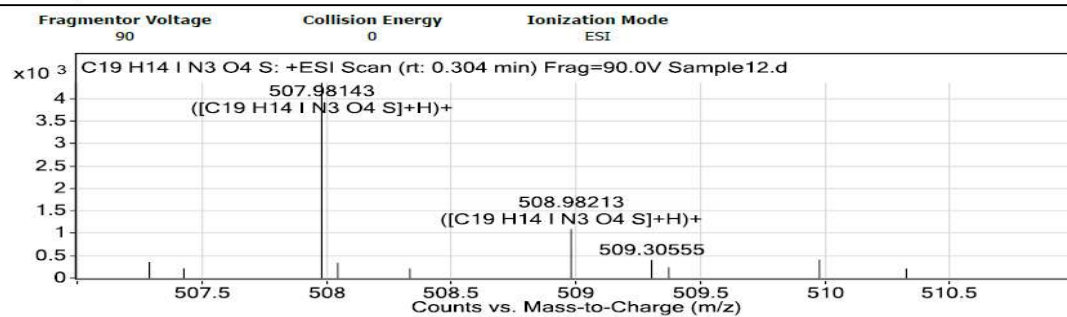


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH7**

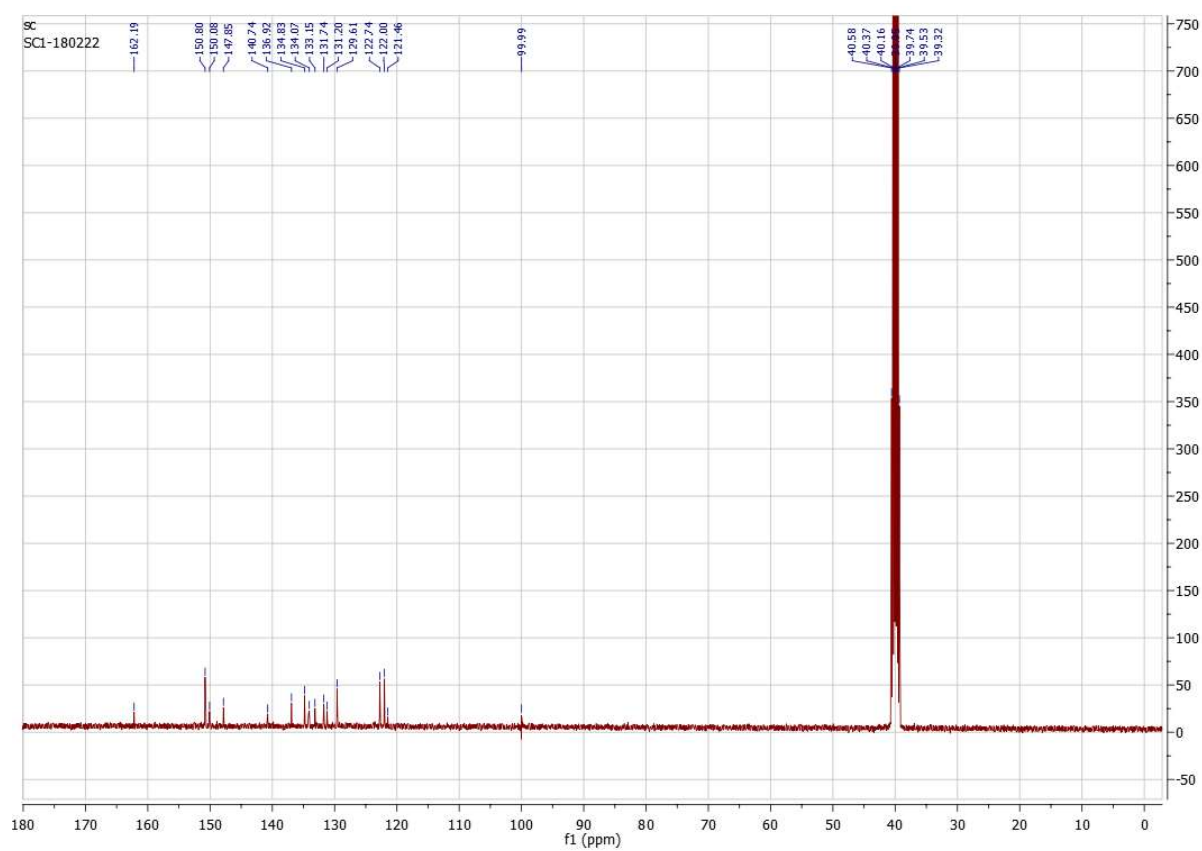
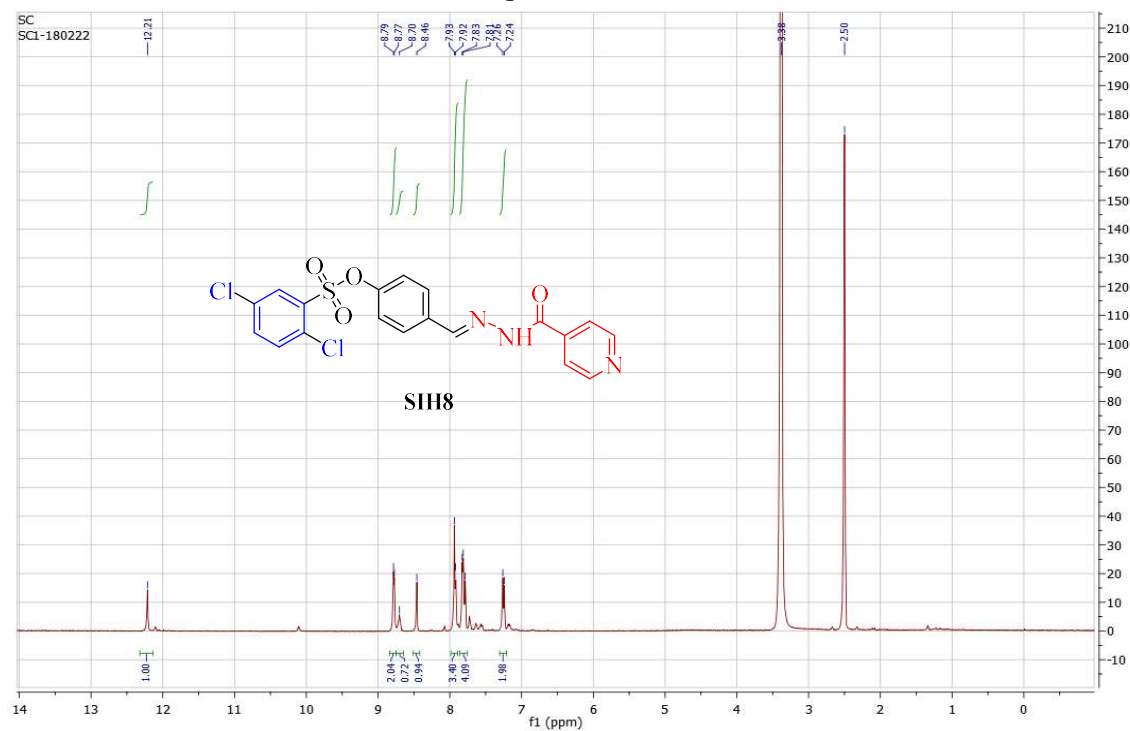


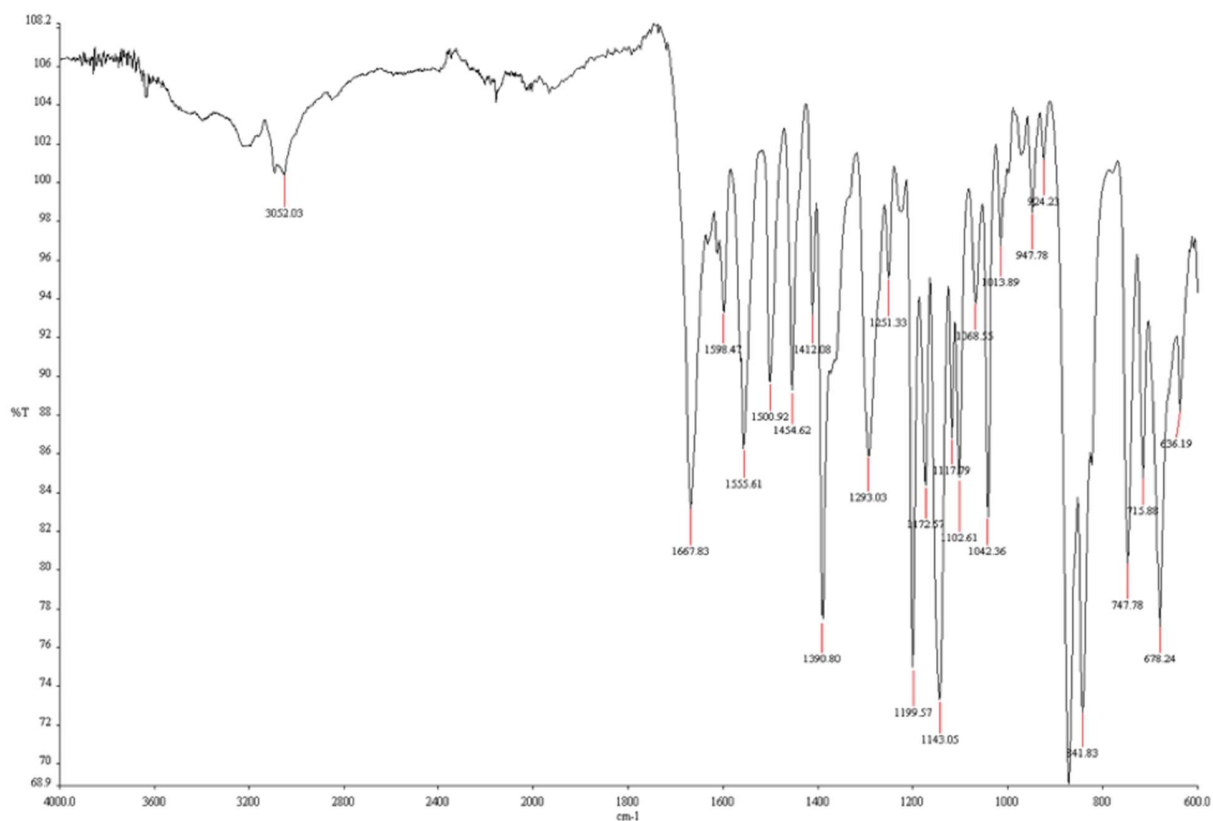


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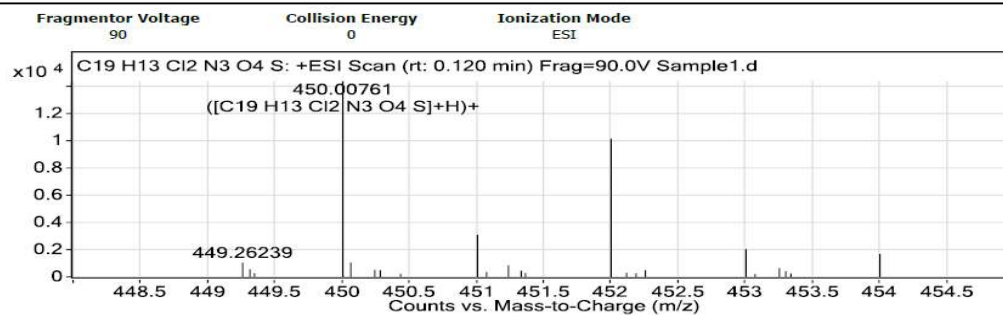


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH8**

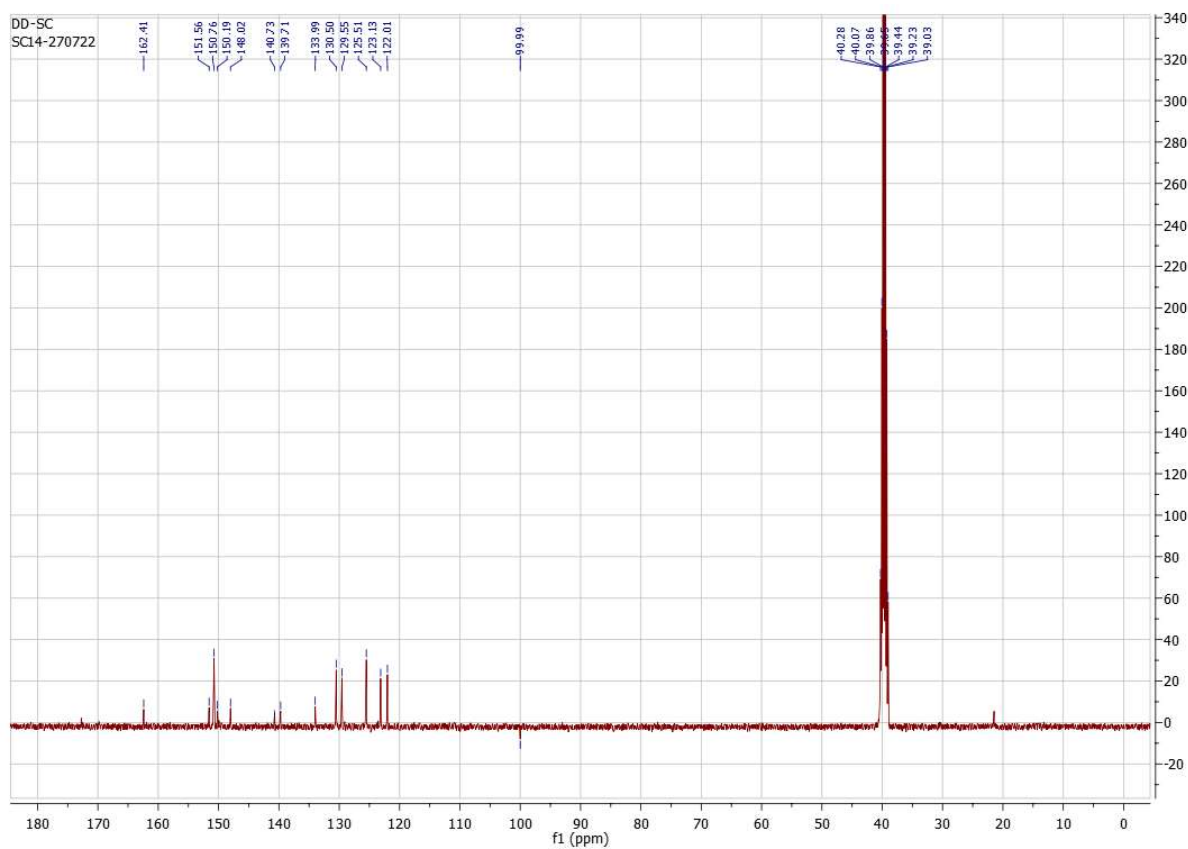
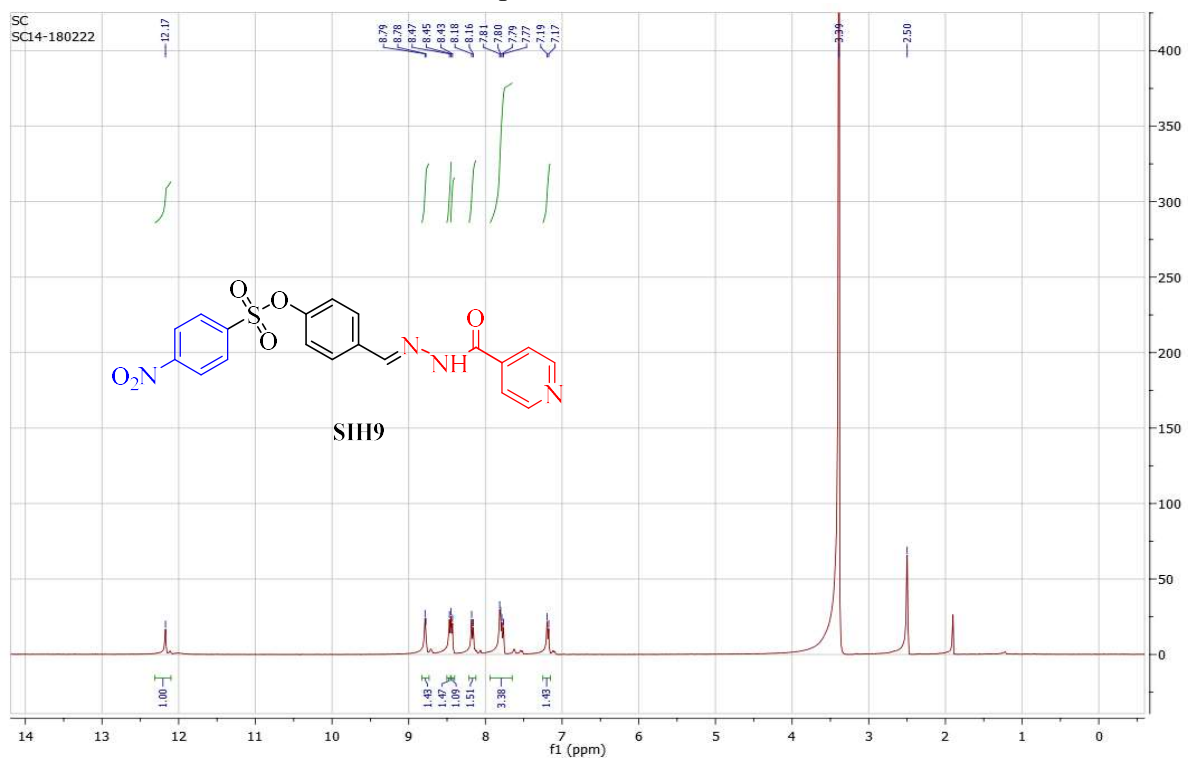


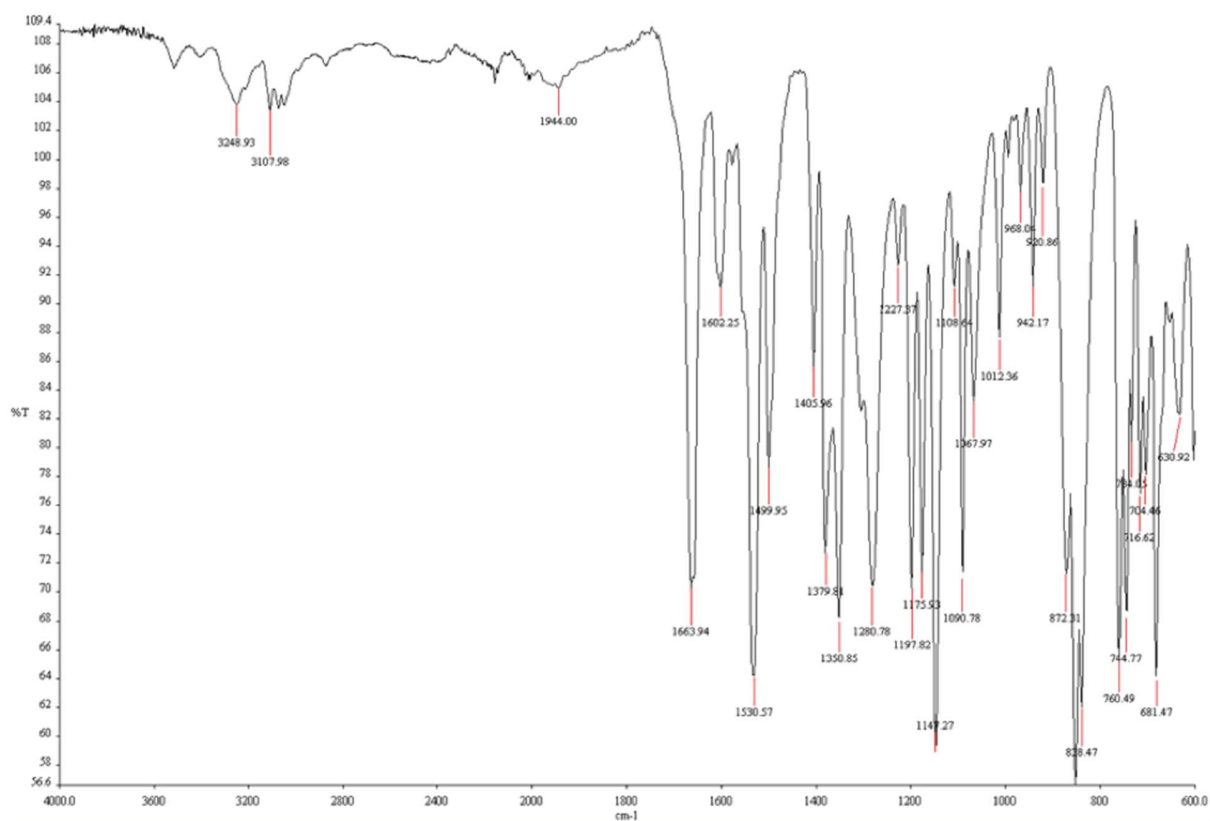


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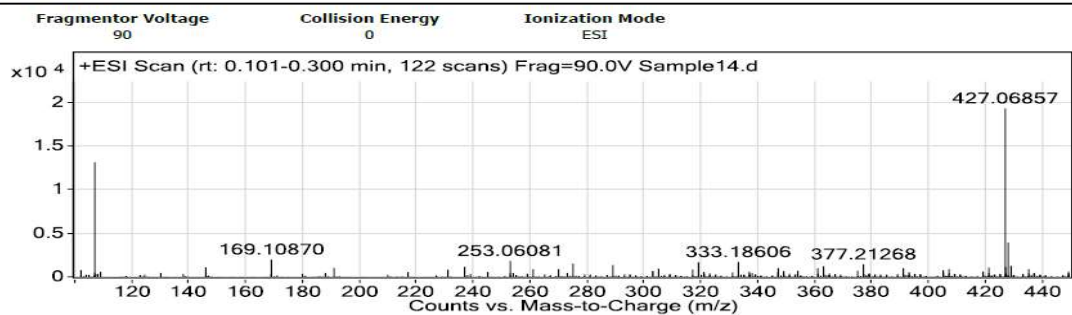


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH9**





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Chemical structure of SIH10 is shown above the spectrum:

O=[N+]([O-])c1ccc(cc1)S(=O)(=O)Oc2ccc(cc2)/C=N/NC(=O)c3ccncc3

SIH10

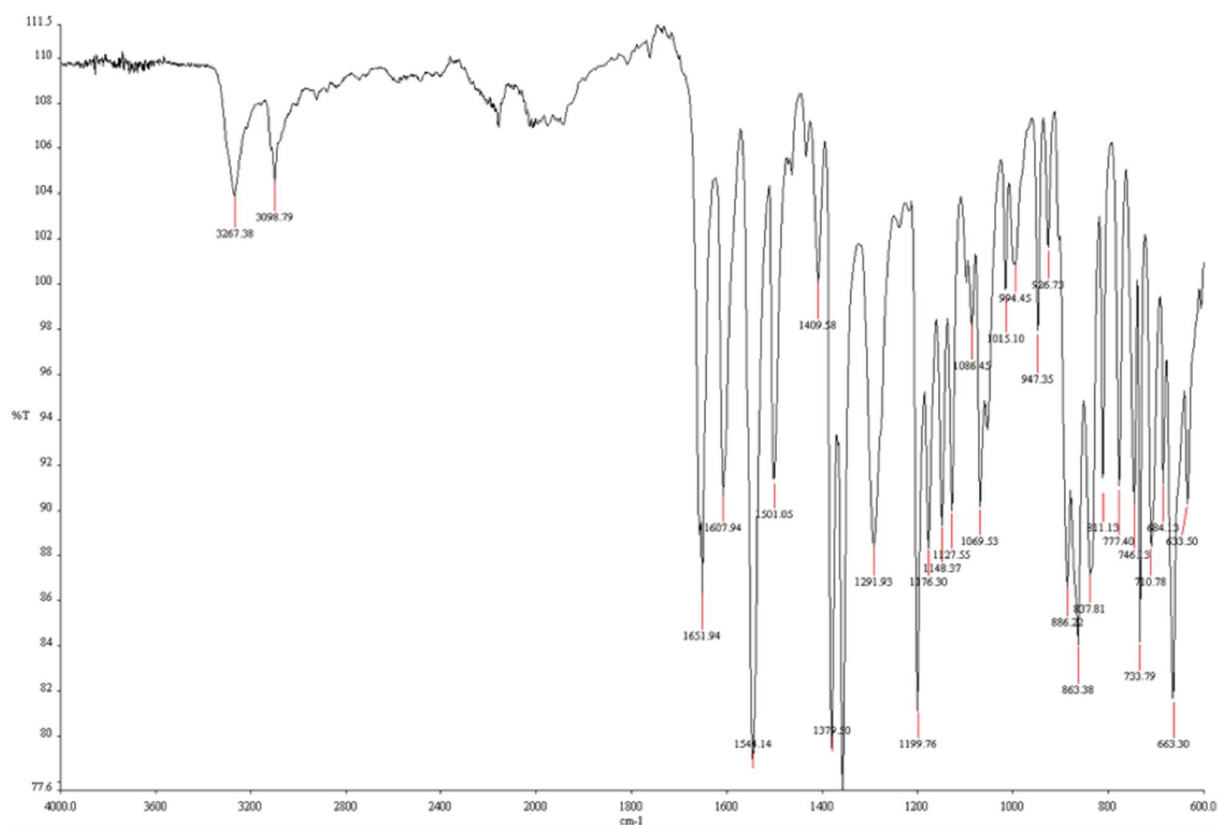
Chemical shift (ppm) values labeled on the spectrum:

- 12.17
- 8.79, 8.78, 8.67, 8.65, 8.50, 8.43, 8.30, 8.28, 7.99, 7.97, 7.95, 7.93, 7.91, 7.80, 7.79, 7.76, 7.73, 7.71
- 3.39
- 2.50

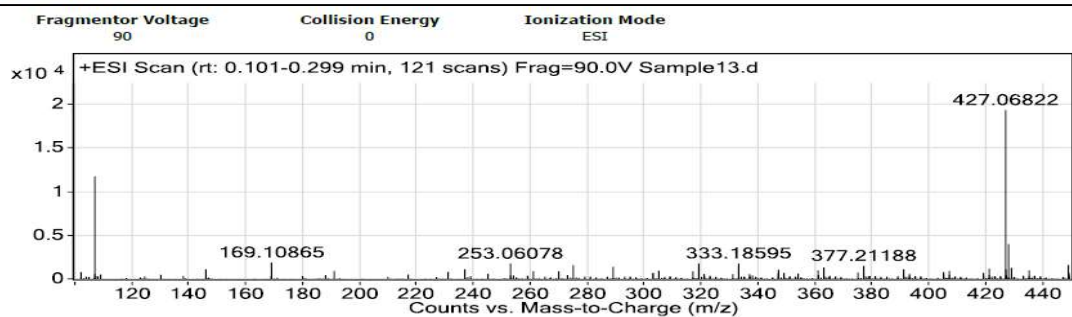
Integration values labeled below the spectrum:

- 1.00
- 1.60
- 0.87
- 0.80
- 0.78
- 1.03
- 3.48
- 1.70
- 1.00
- 1.70

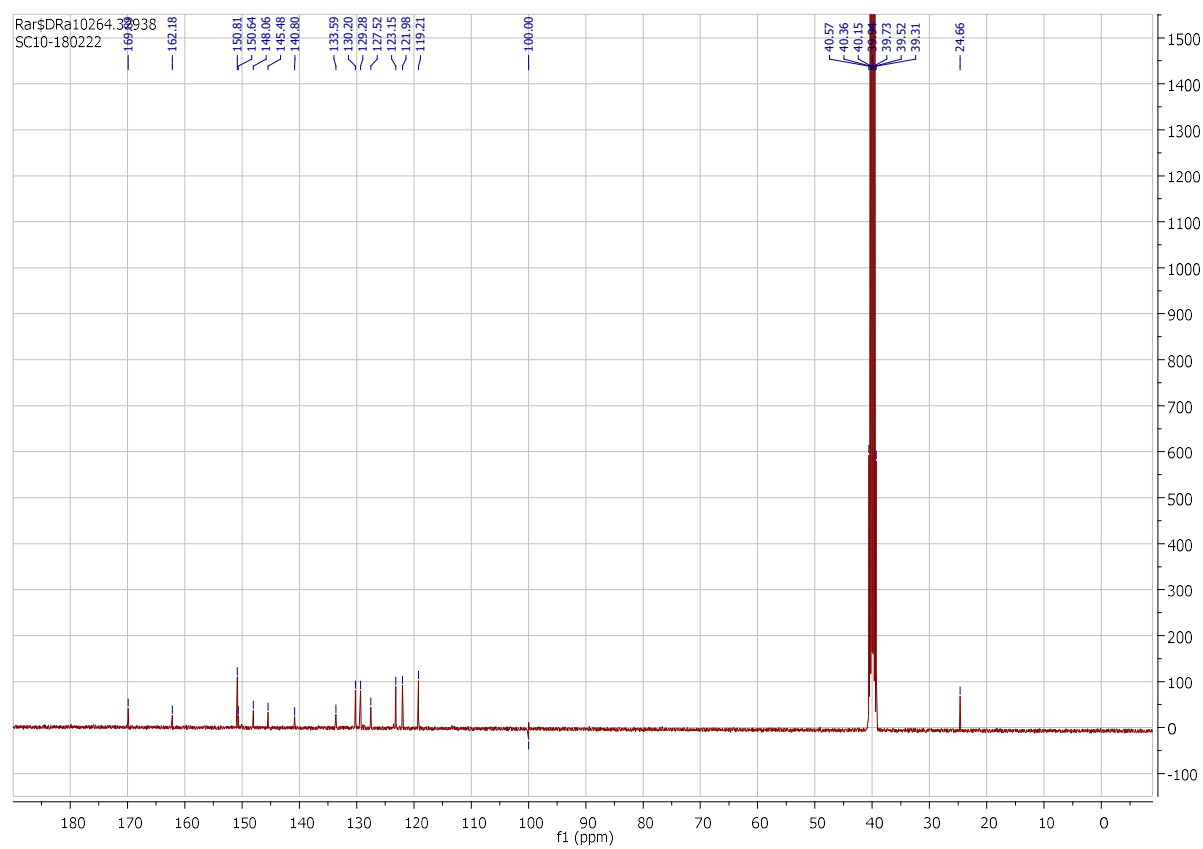
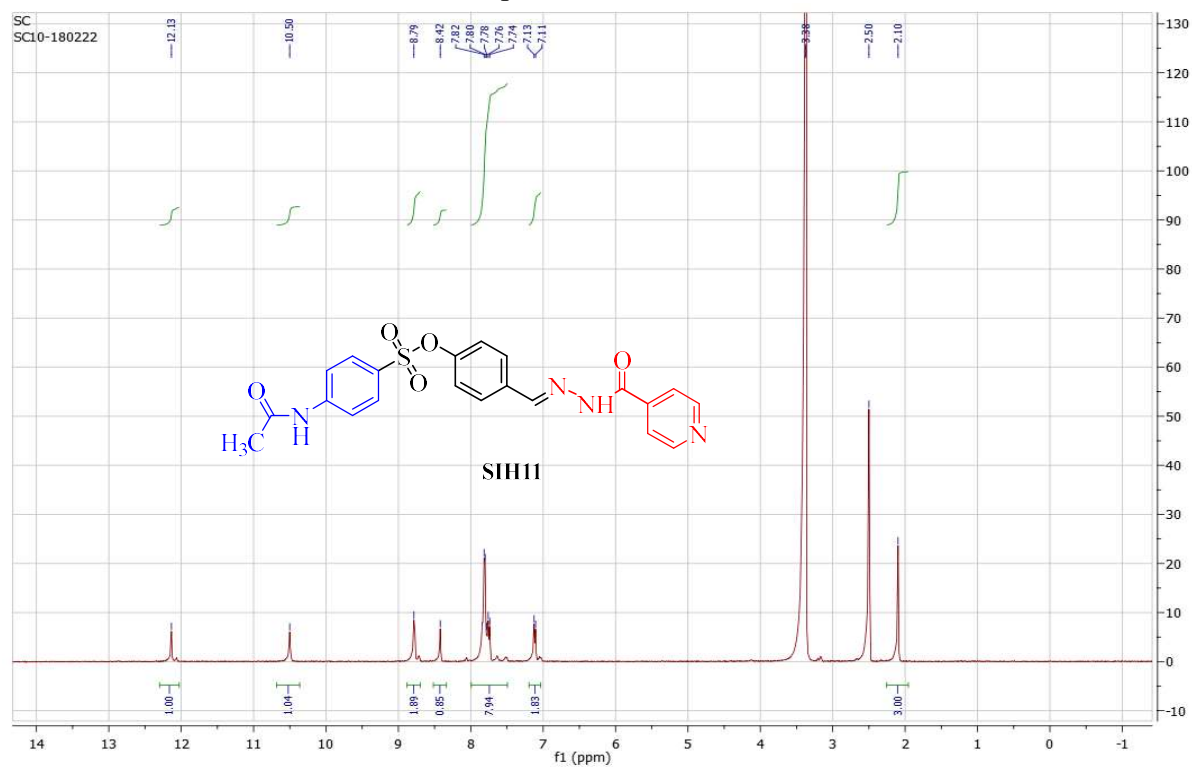


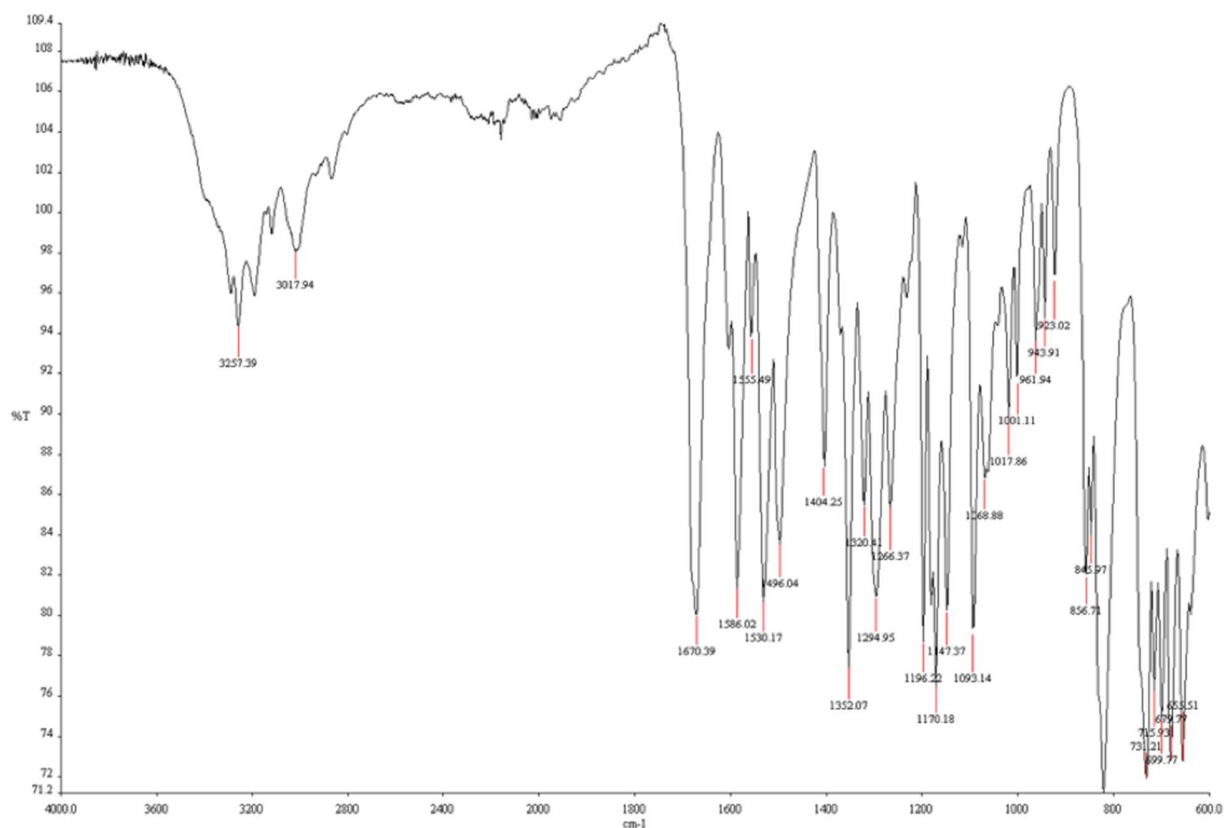


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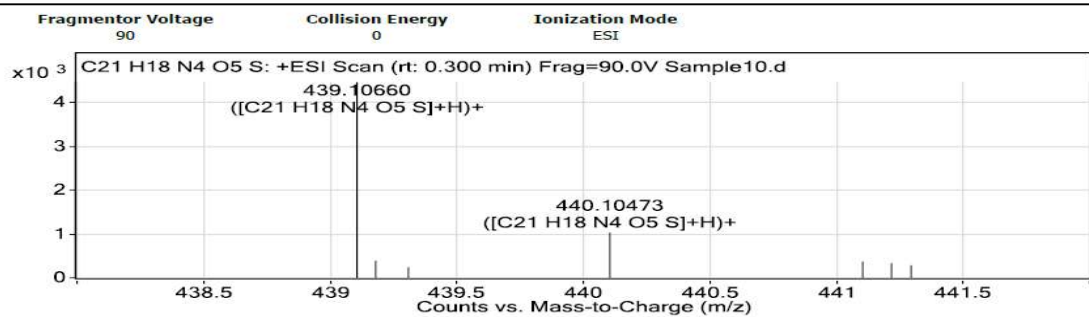


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH11**

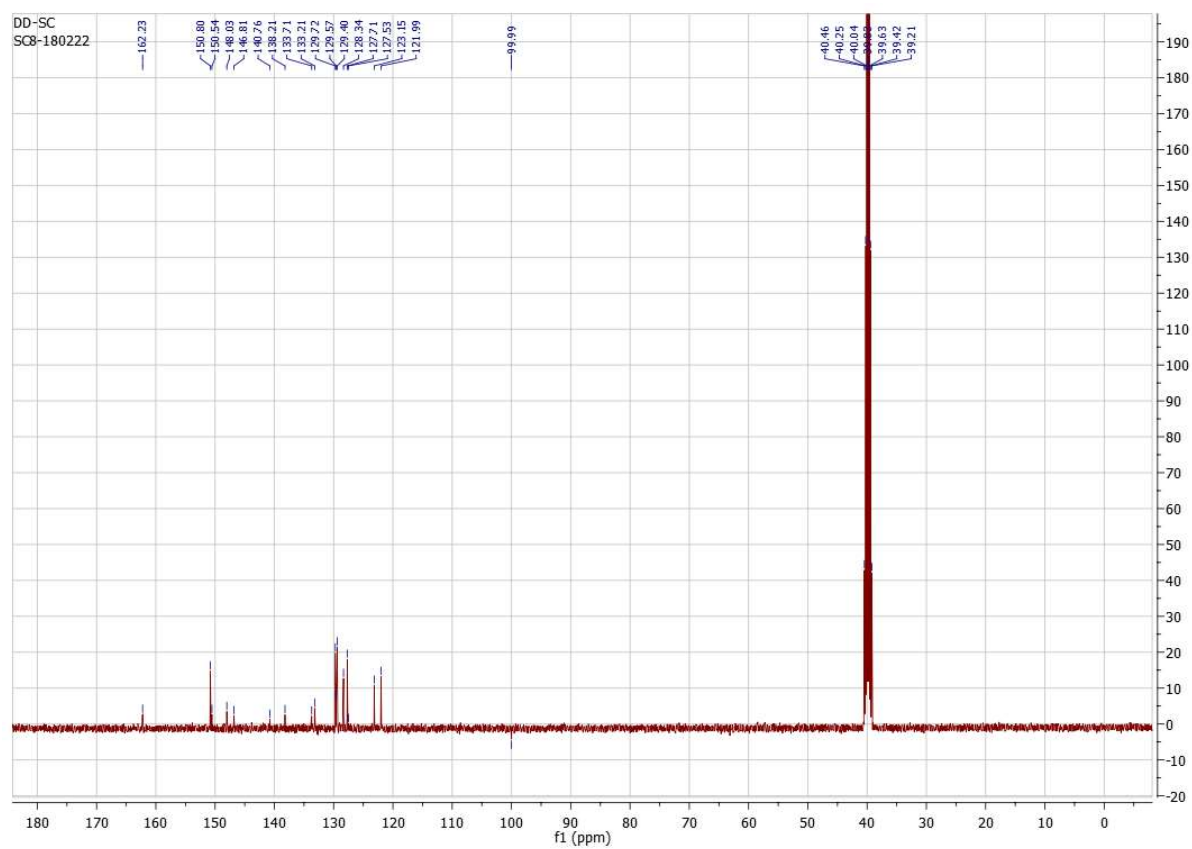
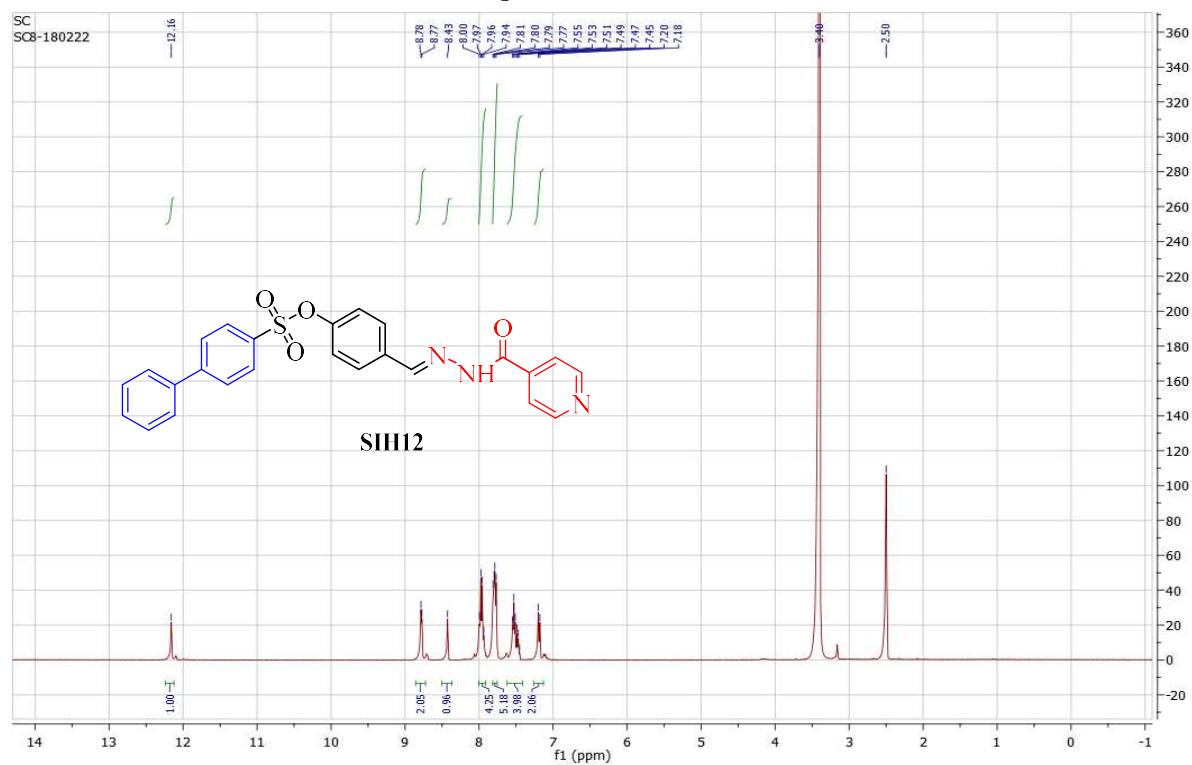


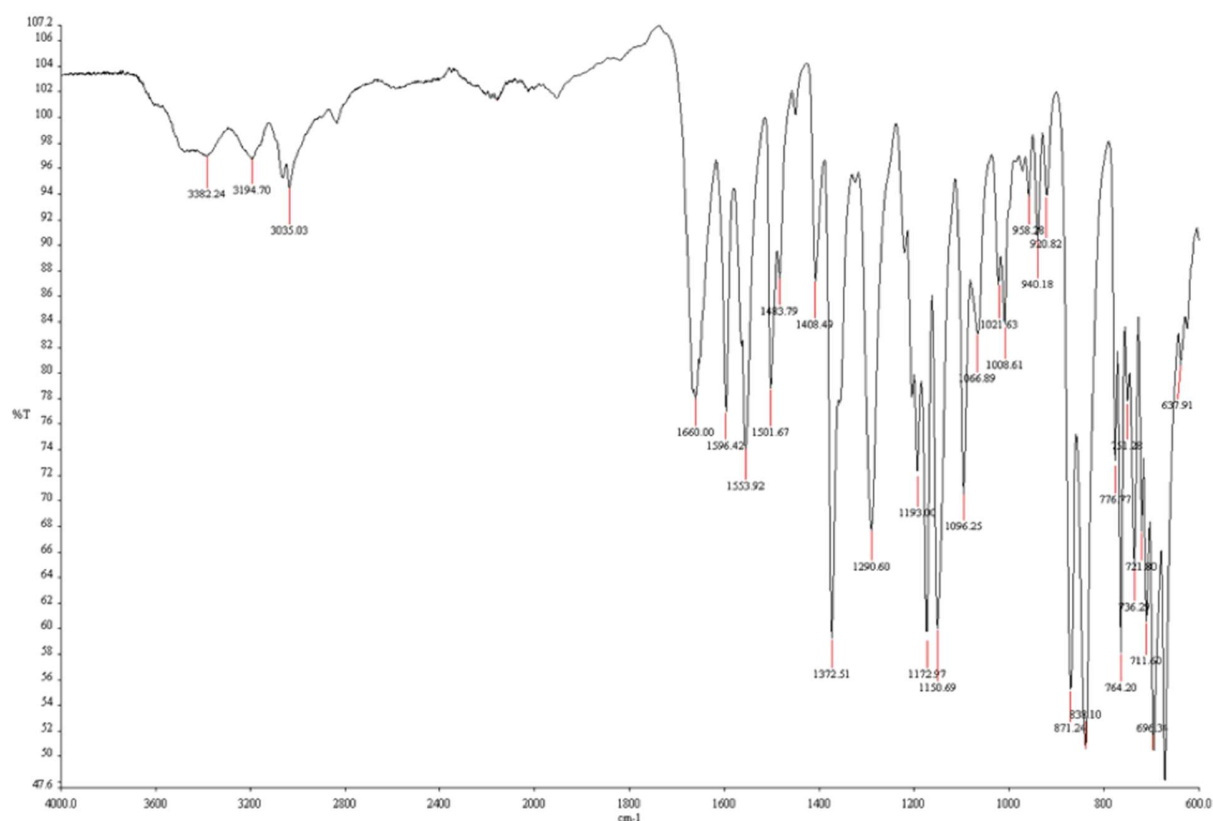


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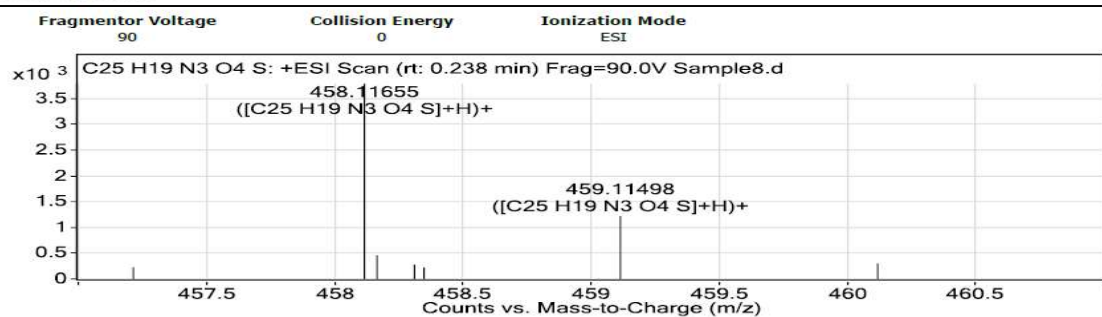


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH12**

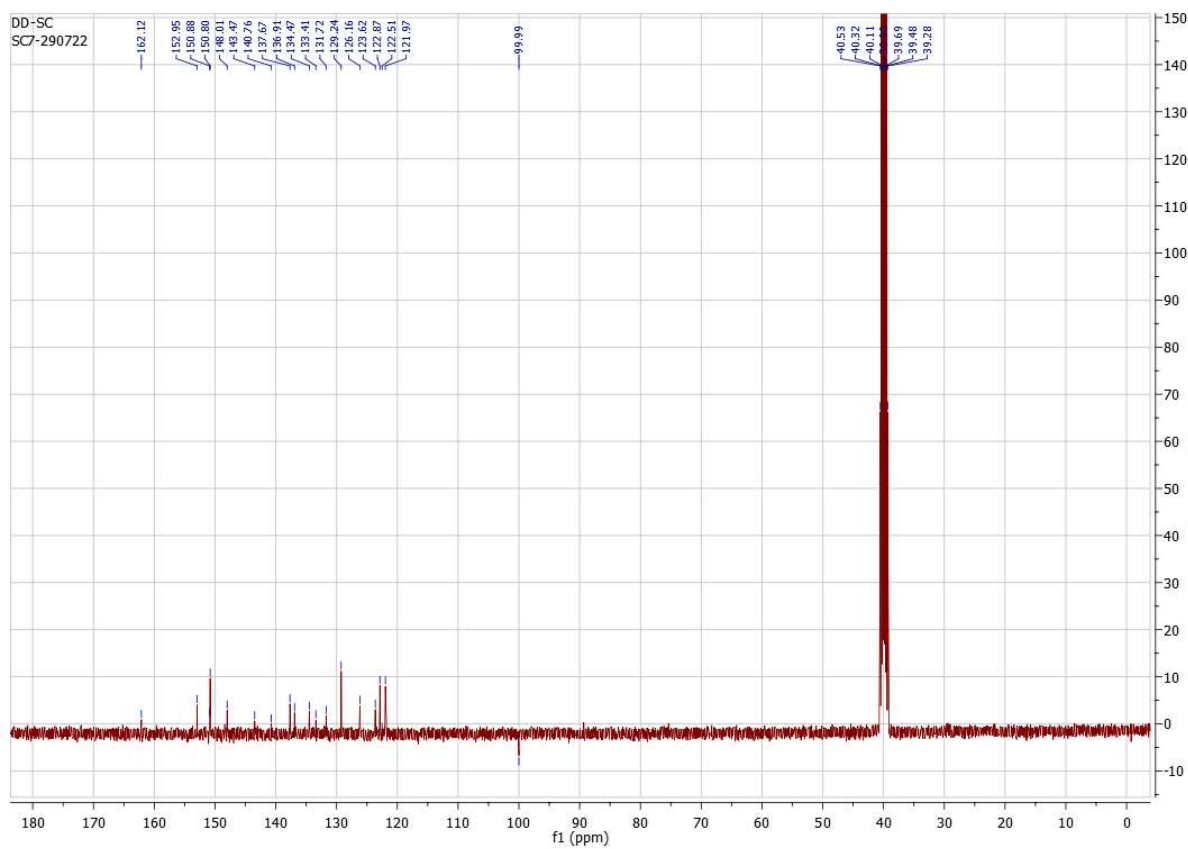
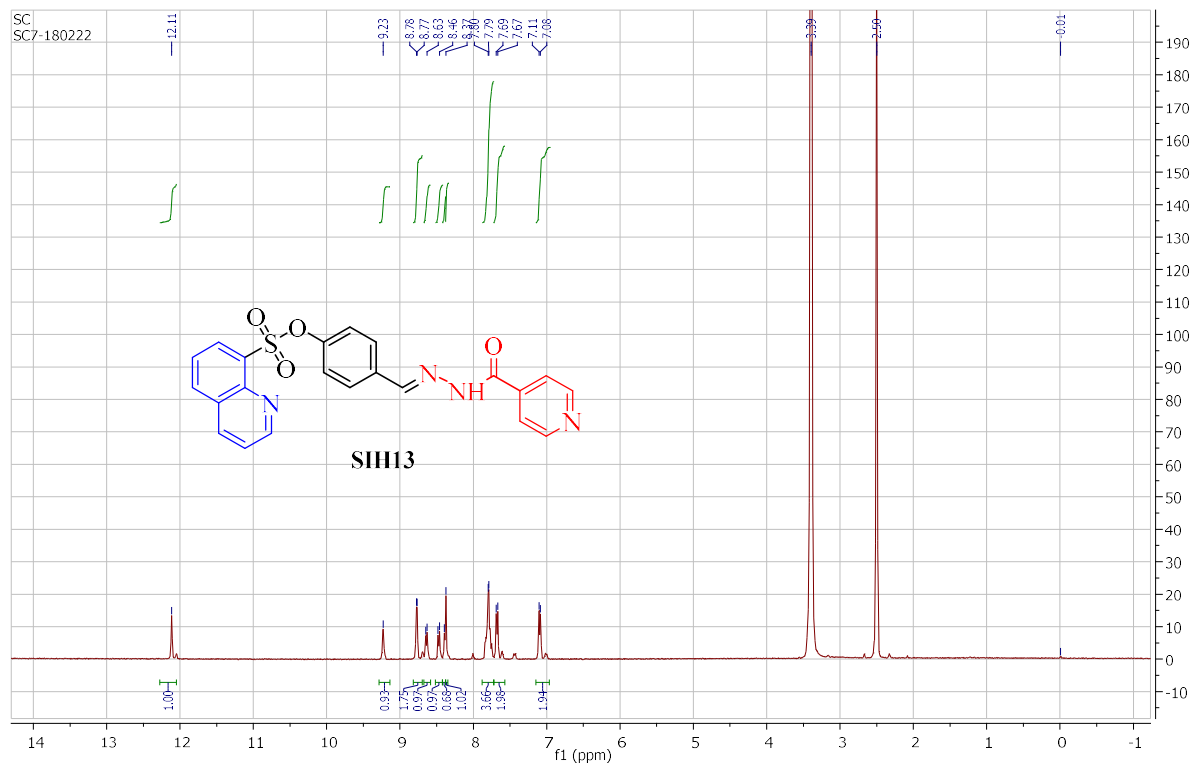


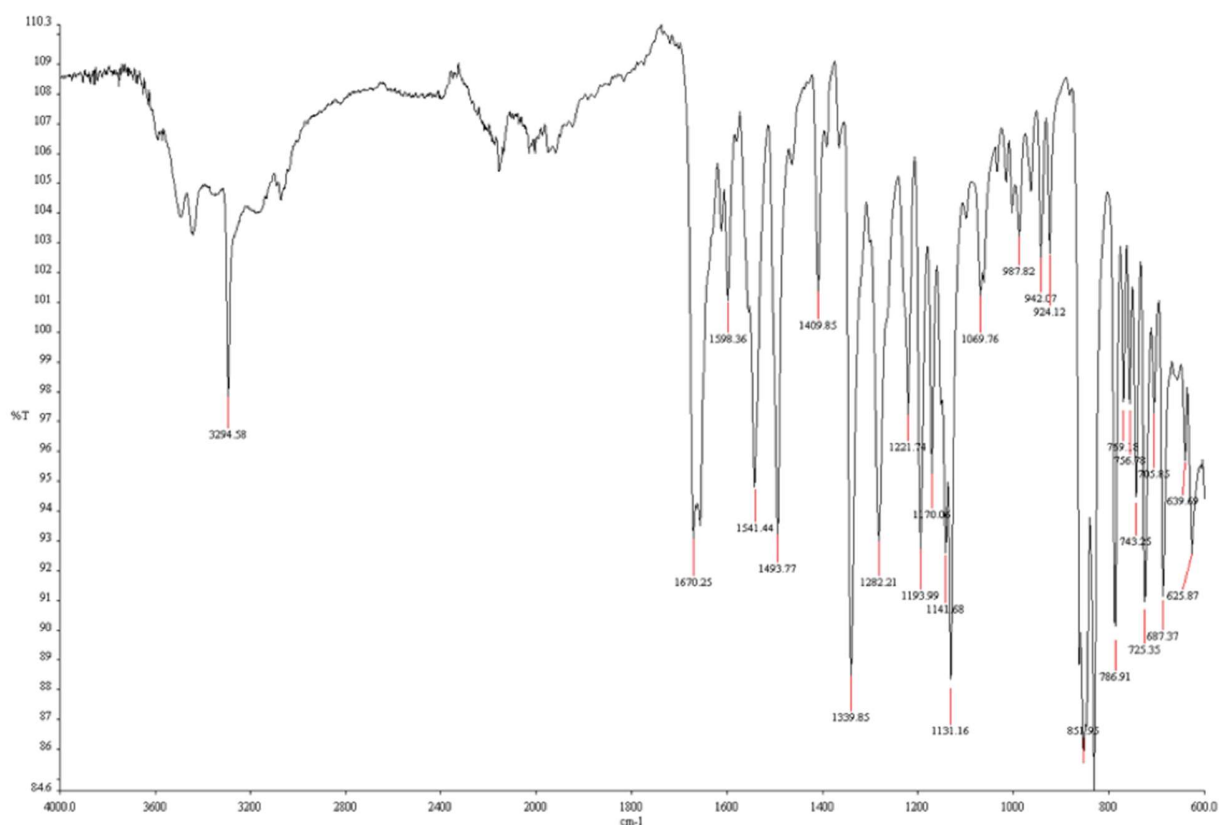


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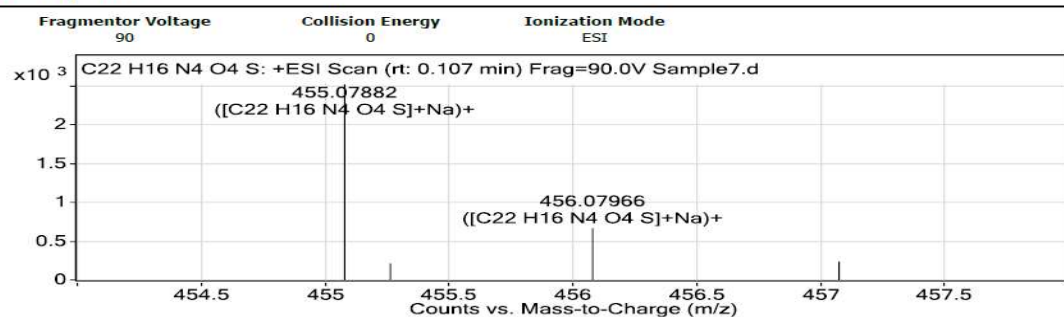


^1H NMR, ^{13}C NMR, HRMS and FTIR spectra of **SIH13**





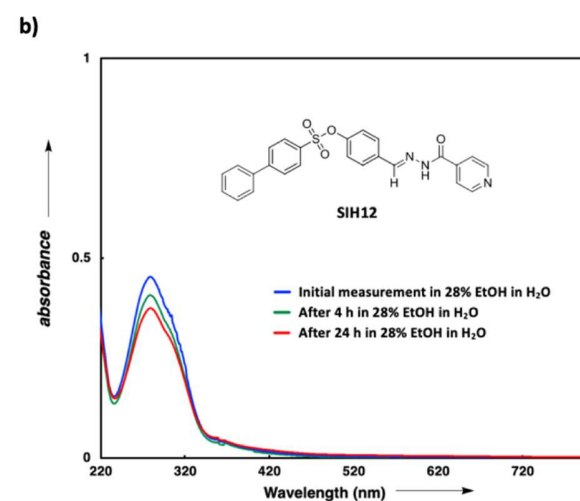
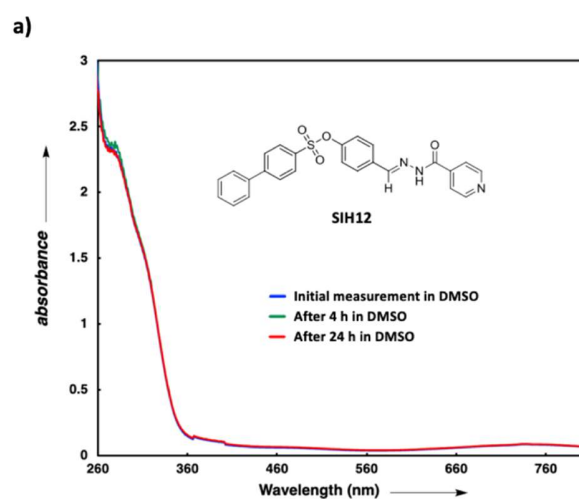
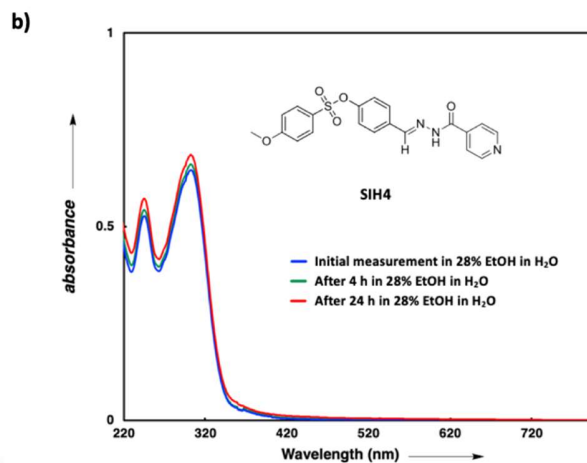
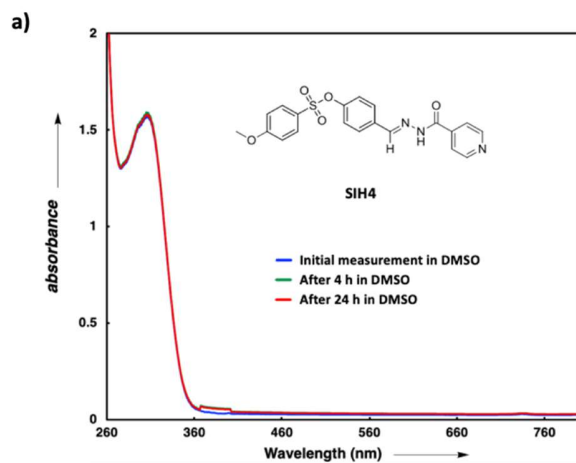
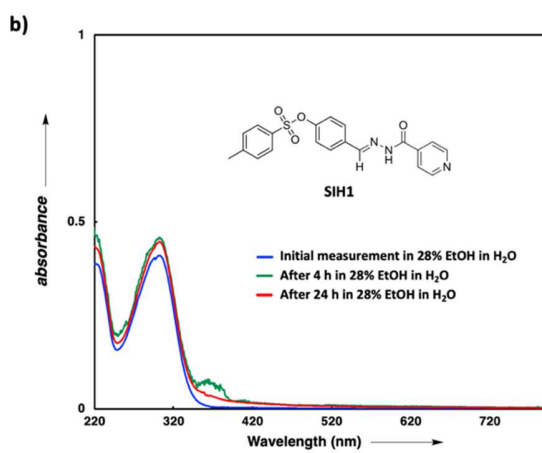
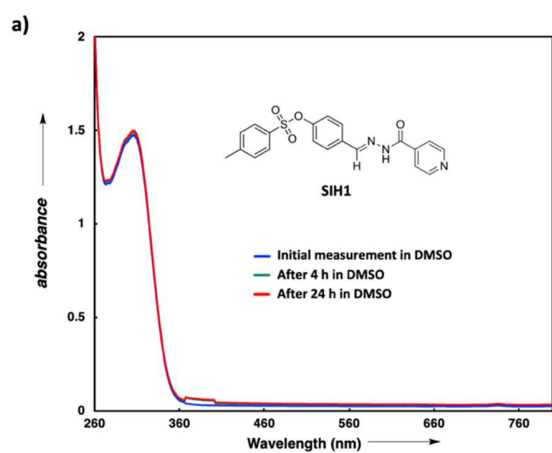
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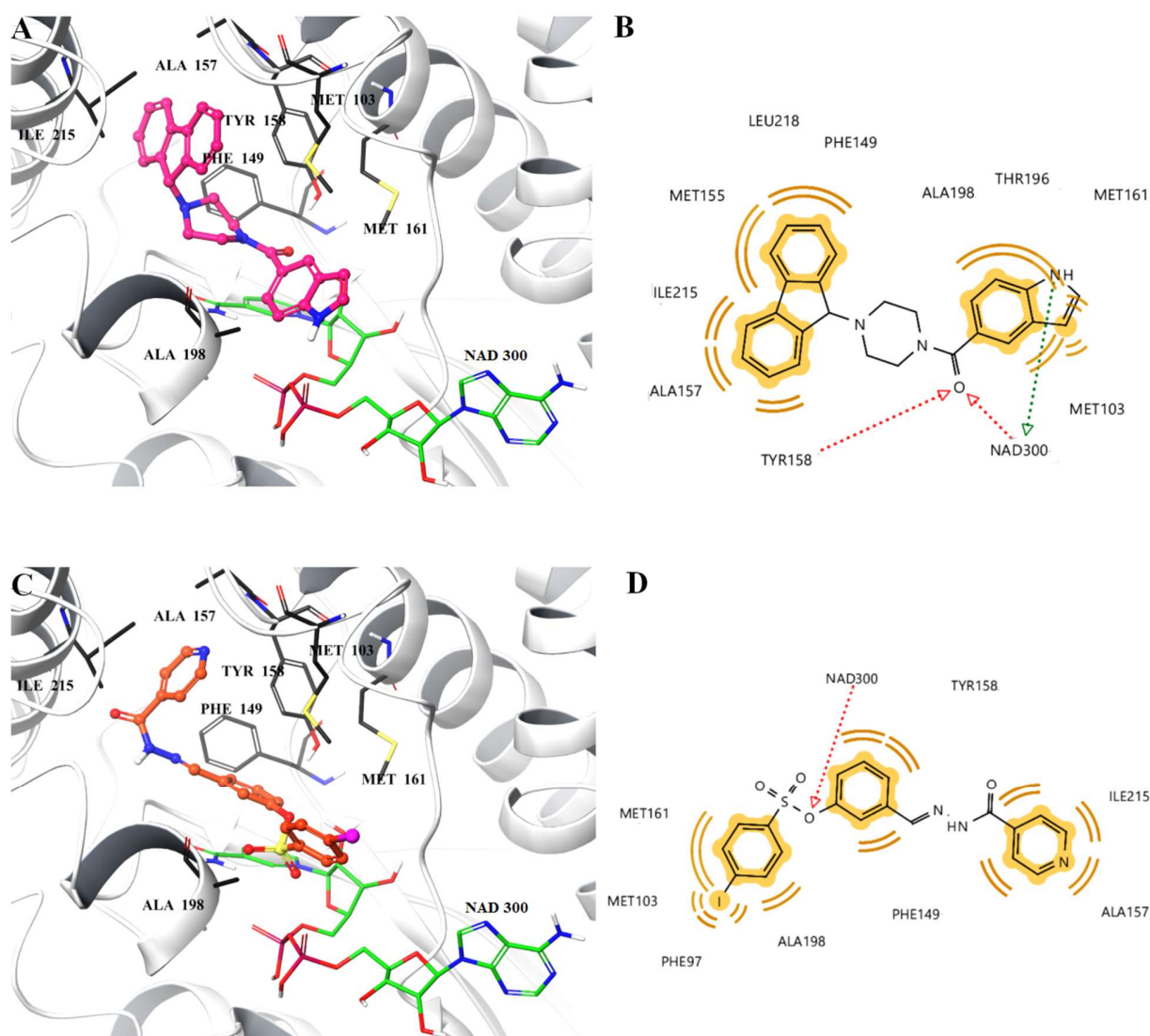
InhA optimised sequence:

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TTGCTAAGACGGTGTGCGCATTGCTGAGCGATTGGCTGCCGGCGACACGGGTGA
TATTATCTATGCGGATGGTGGCGCGCATACCCAGCTGTTG

Stability studies in water and DMSO



Molecular docking studies



3D view of GEQ (A) and the most plausible binding mode of **SIH7** (C) in the active pocket of InhA (PDB ID:1P44). Ligands are shown as colored balls and sticks, protein backbone as white cartoons, and amino acid residues participating in the binding of both ligands as gray sticks. 2D depictions of enzyme-ligand interactions are provided for GEQ (B) and **SIH7** (D): Hydrogen bond acceptors-red arrows, hydrogen bond donor-green arrow, and hydrophobic interactions-yellow spheres.

Initially, we examined the binding mode of GEQ, the co-crystallized ligand of 1P44. This inhibitor binds to the InhA enzyme through hydrogen bonds with NAD⁺ and Tyr158, like most of the direct inhibitors of InhA reported in the literature. Furthermore, two terminal aromatic rings were responsible for forming hydrophobic contacts within the lipophilic pockets of the active site. Subsequently, we analyzed the docking pose of **SIH7** in the same binding pocket. **SIH7** demonstrated a similar orientation with GEQ and formed hydrogen bond with the cofactor NAD through the sulfonate moiety. Additionally, aromatic rings mediated hydrophobic interactions

within the same lipophilic pockets occupied by the co-crystallized ligand. However, hydrogen bond with Tyr158 as one of the key interactions of direct InhA inhibitors lacks for **SIH7**. Consequently, although **SIH7** occupies the native ligand-binding pocket with many common interactions, the lacking hydrogen bond with Tyr158 can explain the moderate InhA inhibitory activity of **SIH7**.