

# Synthesis, Structural Characterization, DFT Calculations, Molecular Docking, and Molecular Dynamics Simulations of a Novel Ferrocene Derivative to Unravel its Potential Antitumor Activity

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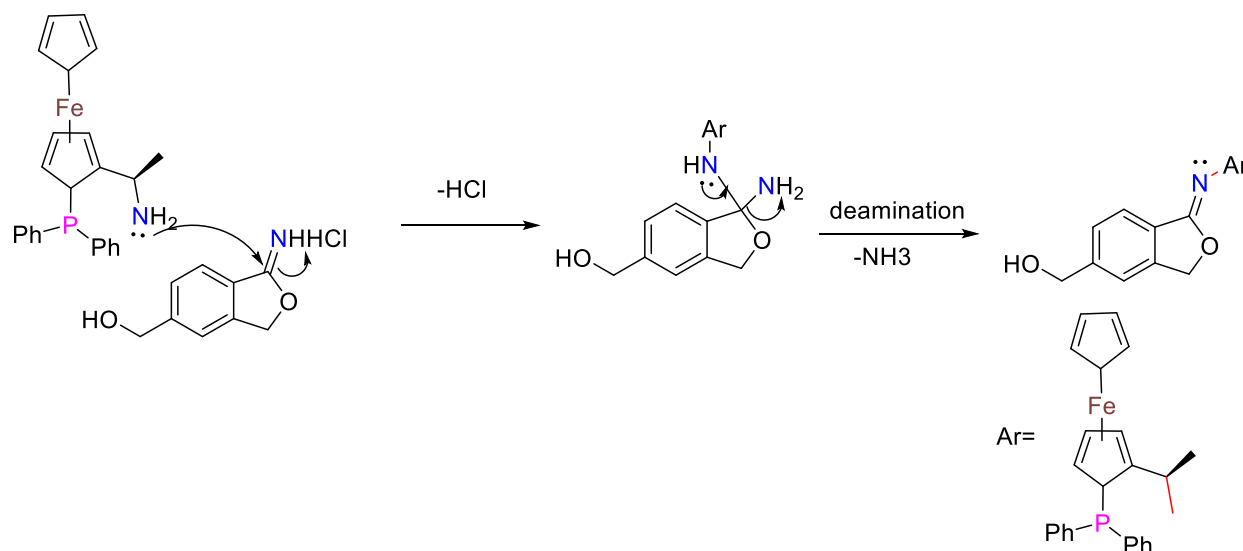
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## Supplementary Information

### SI 1. Proposed mechanism of the newly synthesized ferrocene derivative (10).



### SI 2. Molecular dynamics simulations.

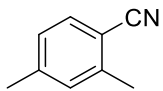
The MD simulations were carried out using the Desmond simulation package of Schrödinger LLC (Release, 2017). The NPT ensemble with the temperature of 300 K and a pressure of 1 bar was applied in all runs. The simulation length was 500 ns with a relaxation time of 1 ps for the ligands. The OPLS3 force field parameters were used in all simulations (Harder et al., 2016). The cutoff radius in Coulomb interactions was 9.0 Å. The orthorhombic periodic box boundaries were set 10 Å away from the protein atoms. The water molecules were explicitly described using the transferable intermolecular potential with the three points (TIP3P) model (Jorgensen, Chandrasekhar, Madura, Impey, & Klein, 1983; Neria, Fischer, & Karplus, 1996). Salt concentration was set to 0.15 M NaCl and was built using the System Builder utility of Desmond (Manual, 2009). The Martyna–Tuckerman–Klein chain coupling scheme with a coupling constant of 2.0 ps was used for the pressure control and the Nosé–Hoover chain coupling scheme for the temperature control (Martyna, Klein, & Tuckerman, 1992; Martyna, Tobias, & Klein, 1994). Nonbonded forces were calculated using a RESPA integrator where the short-range forces were updated every step and the long-range forces were updated every three steps. The trajectories were saved at 20 ns intervals for analysis. The behavior and interactions between the ligands and protein were analyzed using the Simulation Interaction Diagram tool implemented in the Desmond MD package. The

stability of MD simulations was monitored by looking at the RMSD of the ligand and protein atom positions in time.

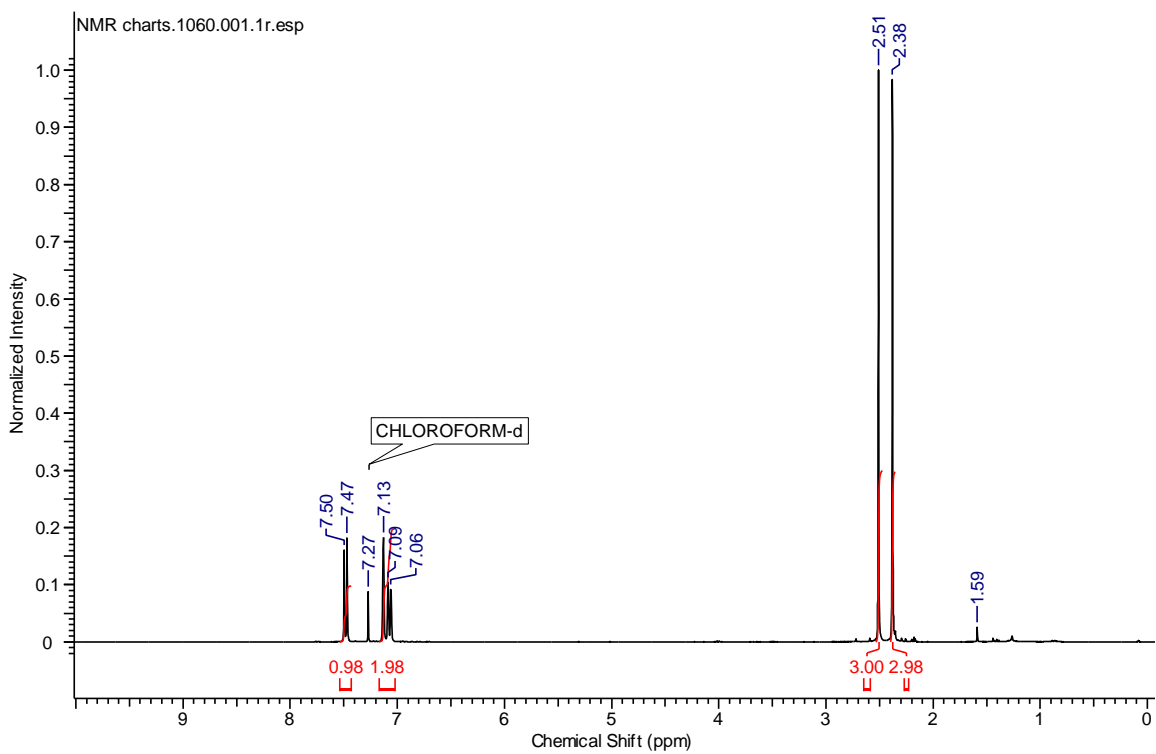
### **SI 3.** MD trajectory analysis and prime MM-GBSA calculations.

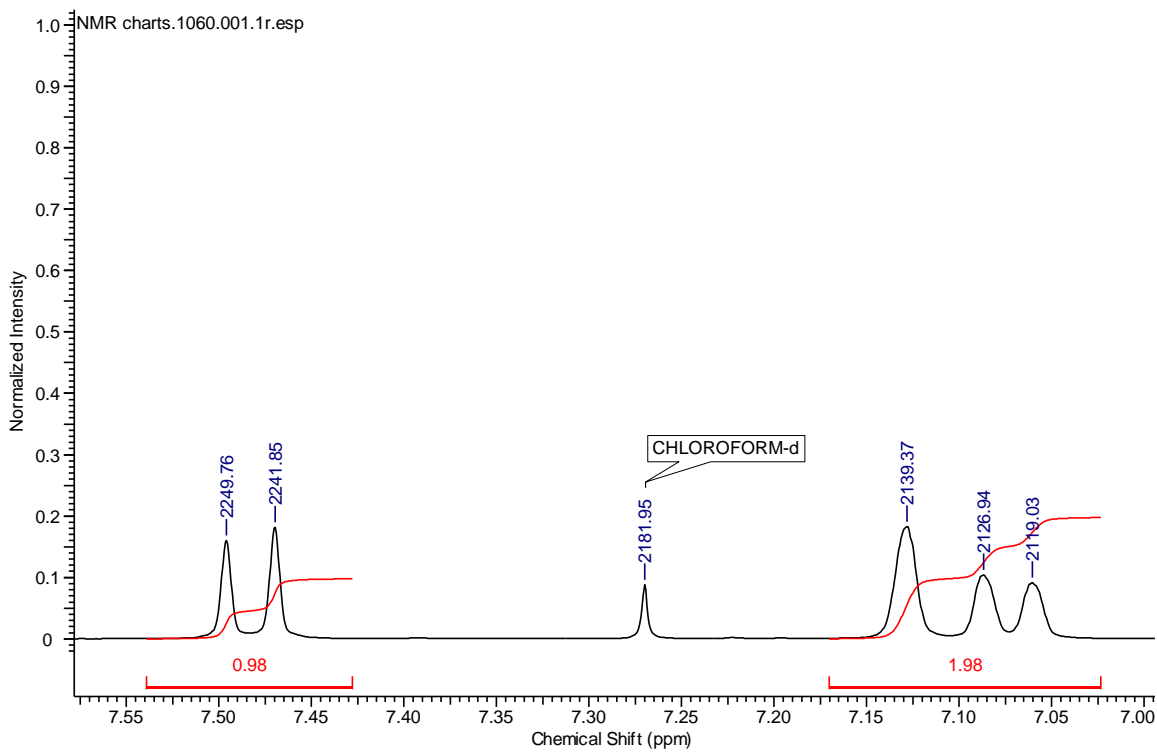
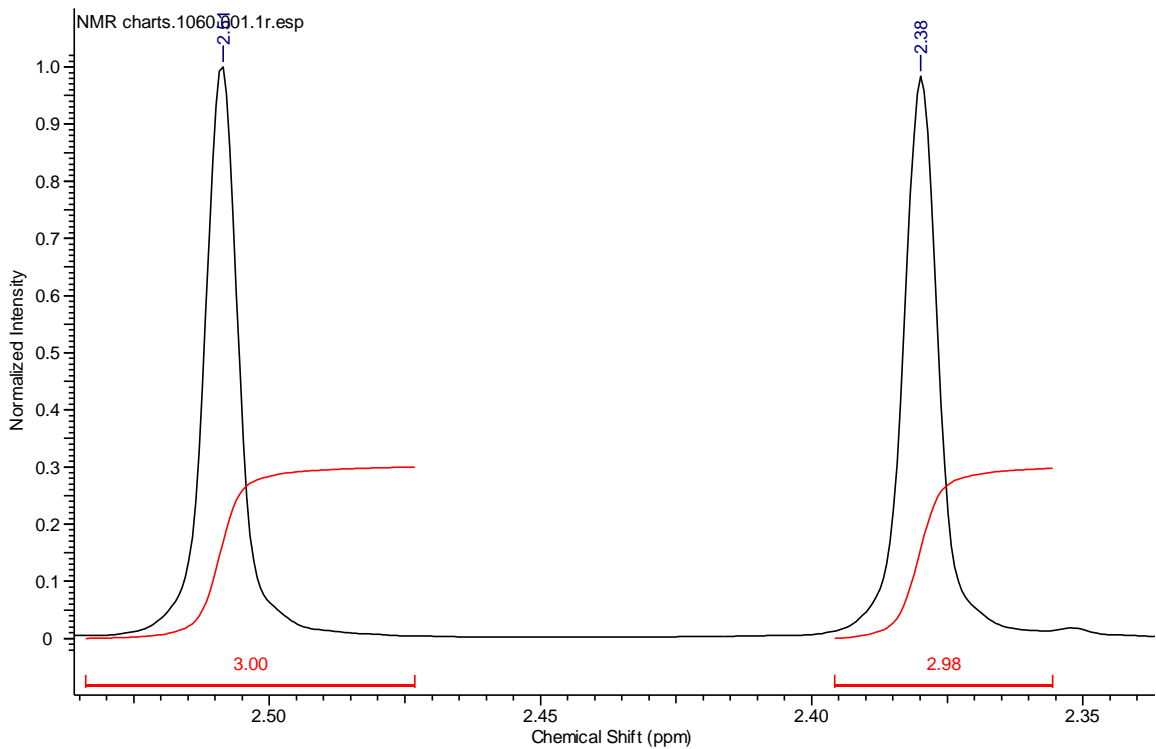
The simulation interactions diagram panel of Maestro software was used to monitor interactions contribution in the ligand-protein stability. The molecular mechanics generalized born/solvent accessibility (MM-GBSA) was performed to calculate the ligand binding free energies and ligand strain energies for docked compounds over the last 100 ns with `thermal_mmgsa.py` python script provided by Schrodinger which takes a Desmond trajectory file, splits it into individual snapshots, runs the MM-GBSA calculations on each frame, and outputs the average computed binding energy.

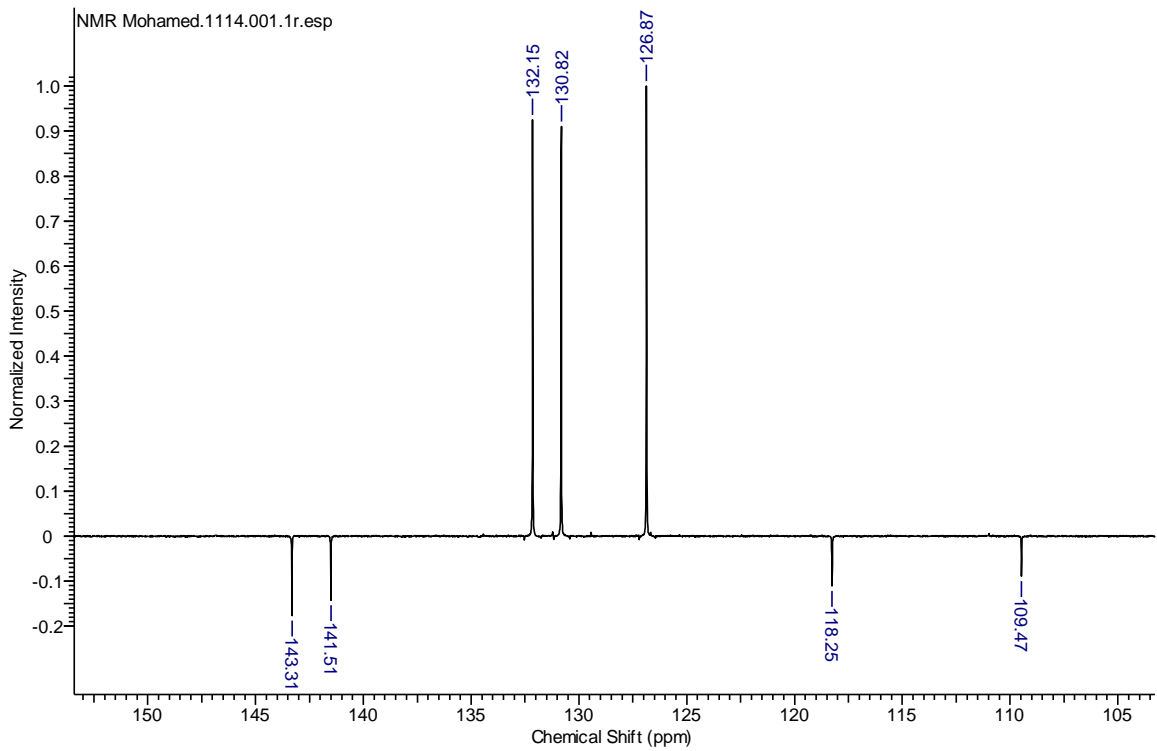
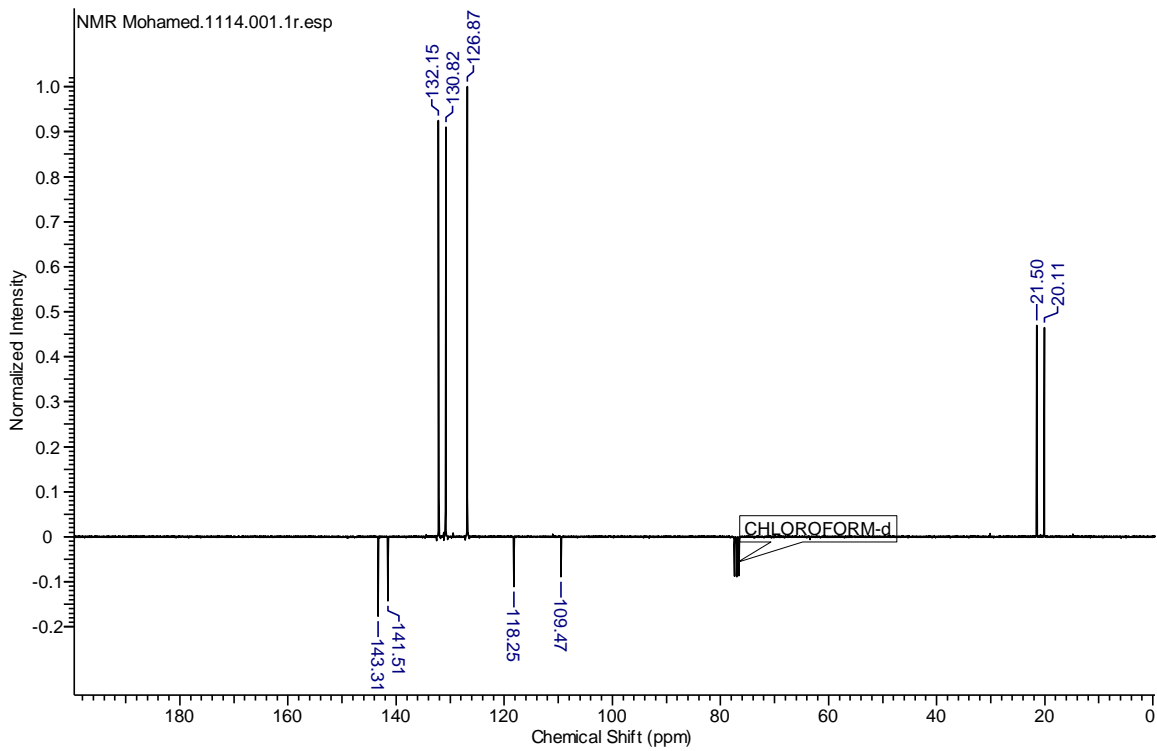
SI 4. Spectral data of compounds (IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HSQC, COSY,  $^{31}\text{P}$  NMR, Mass, and HRMS spectroscopy).

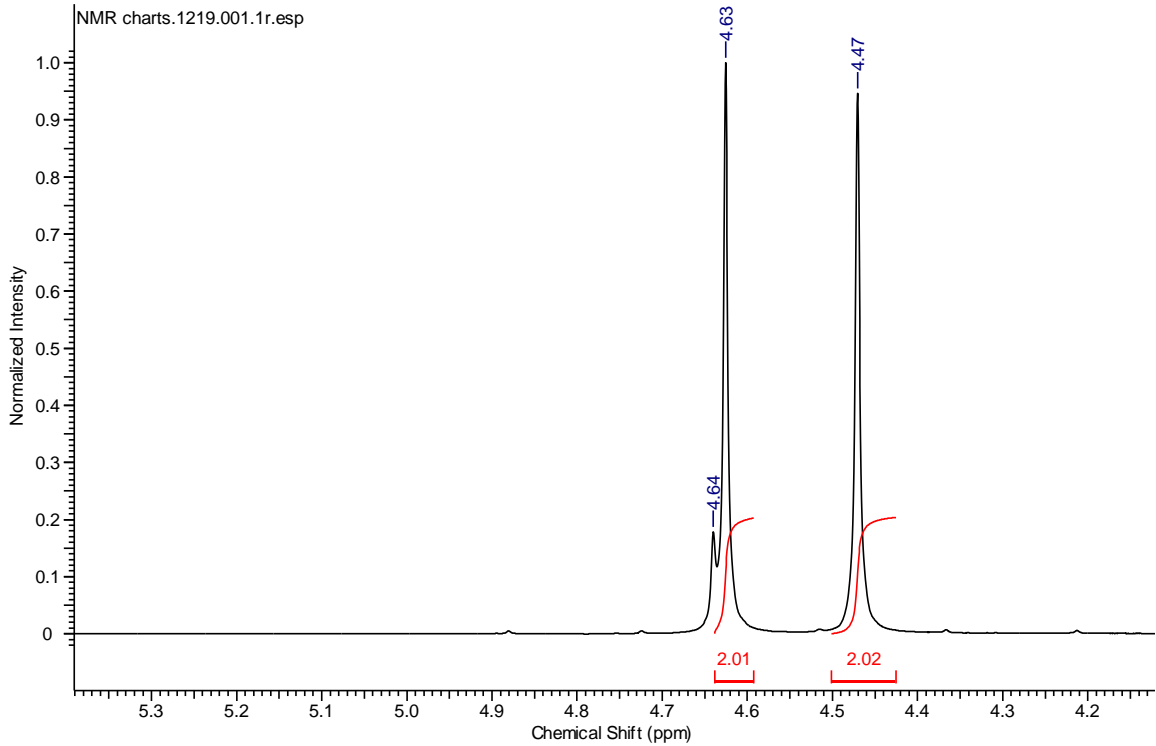
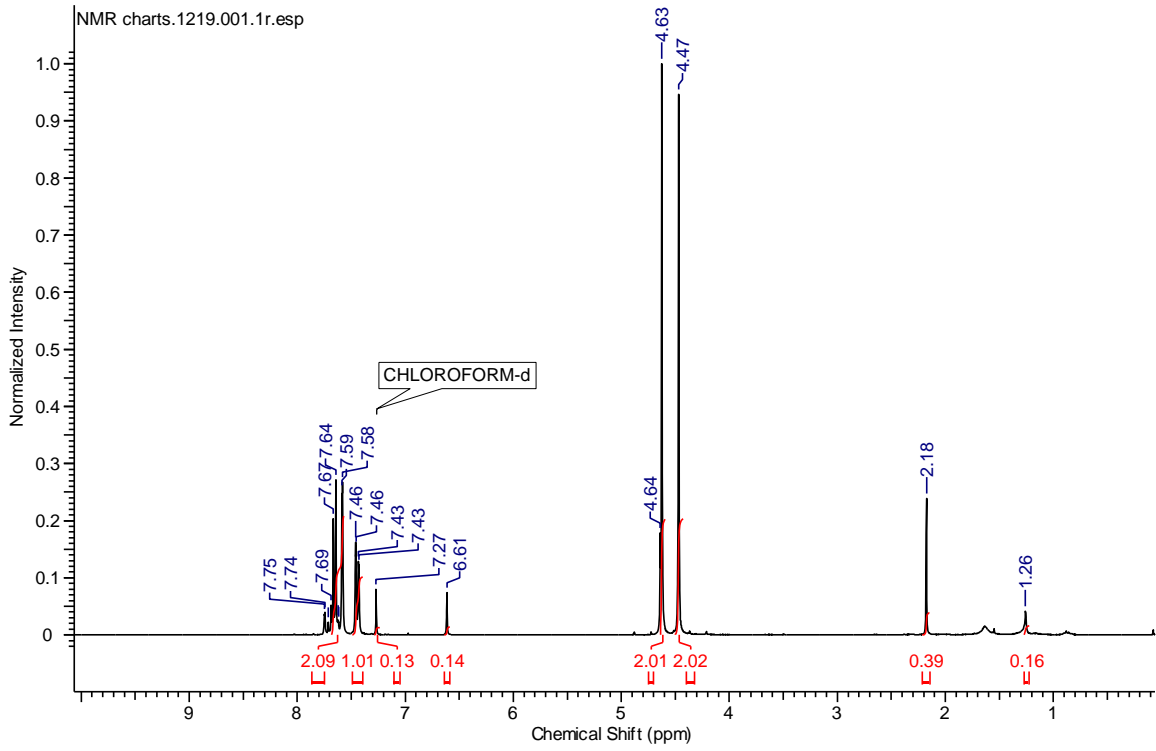
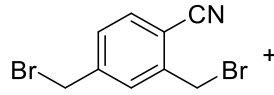


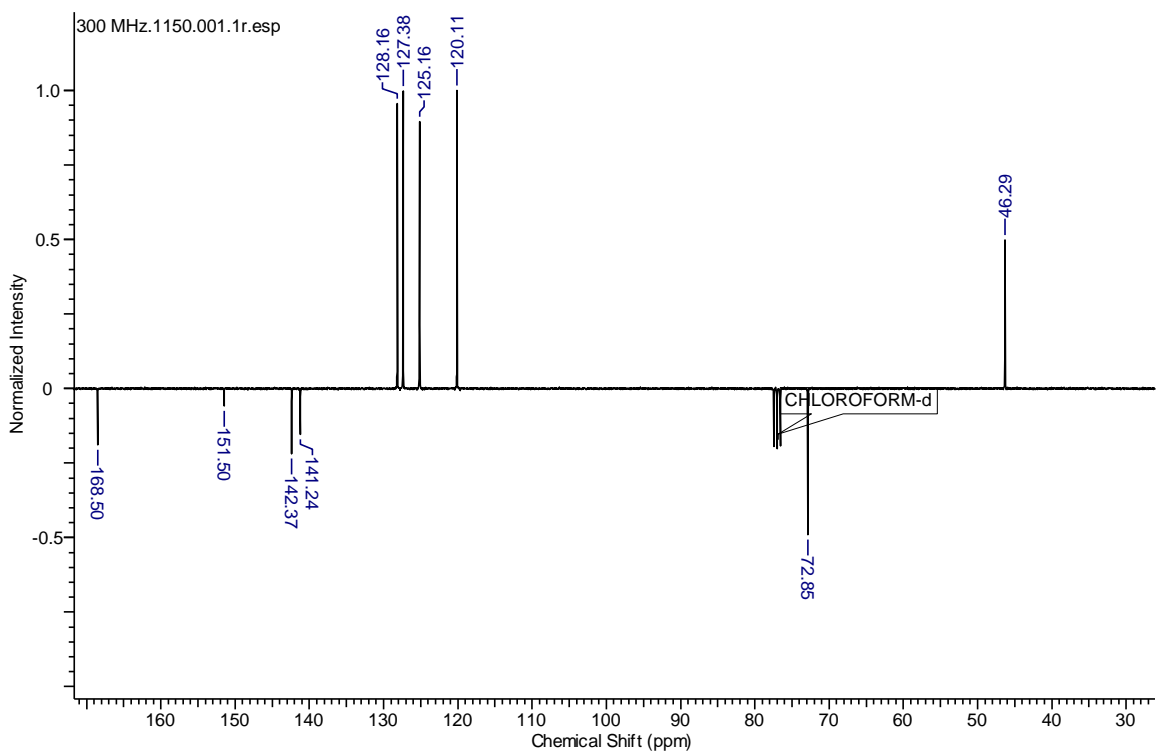
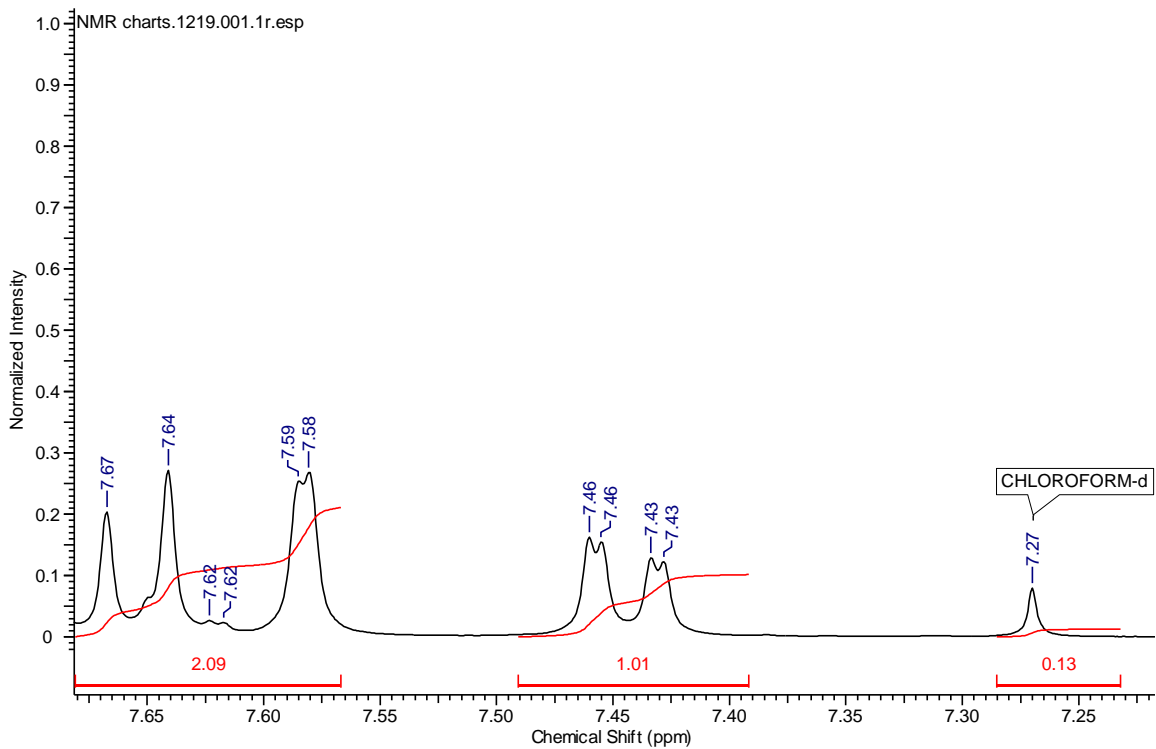
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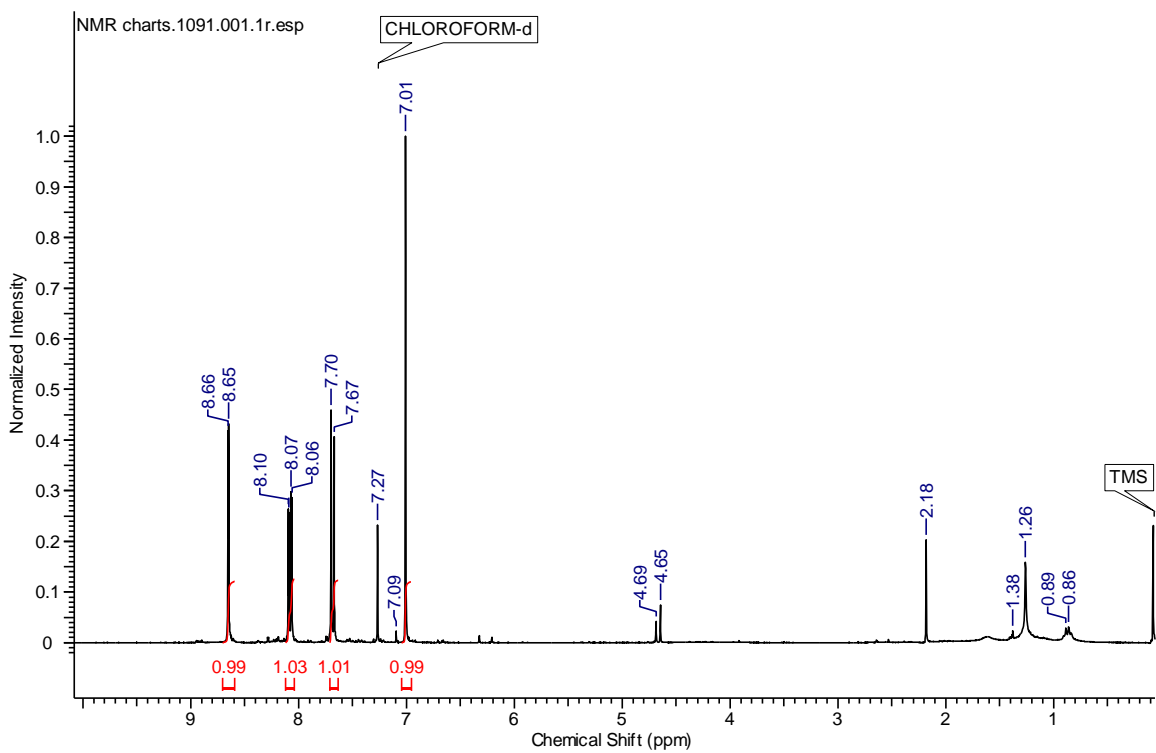
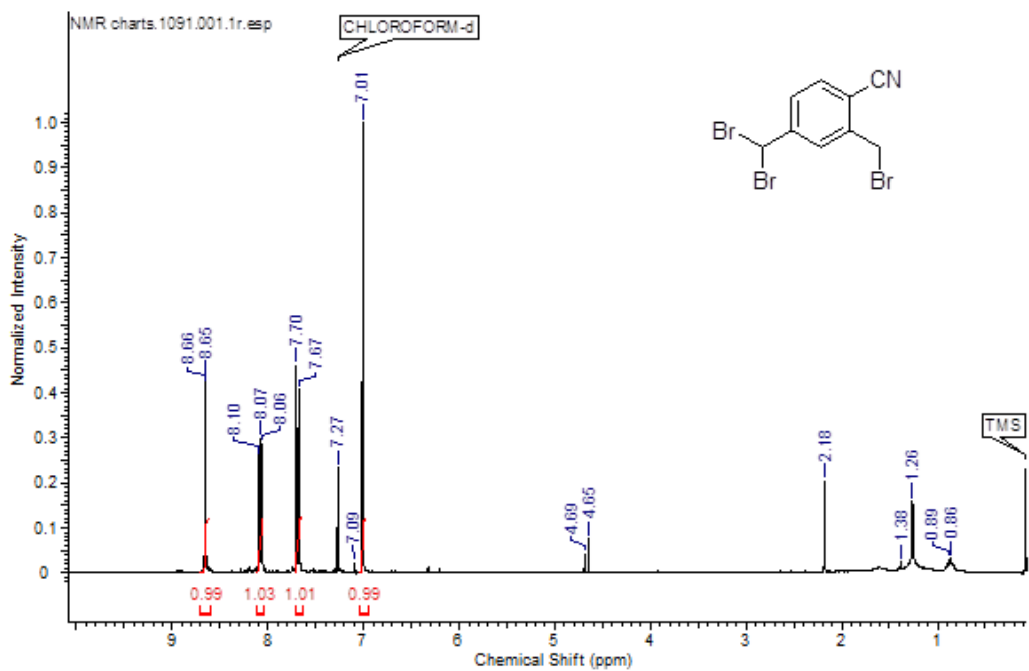


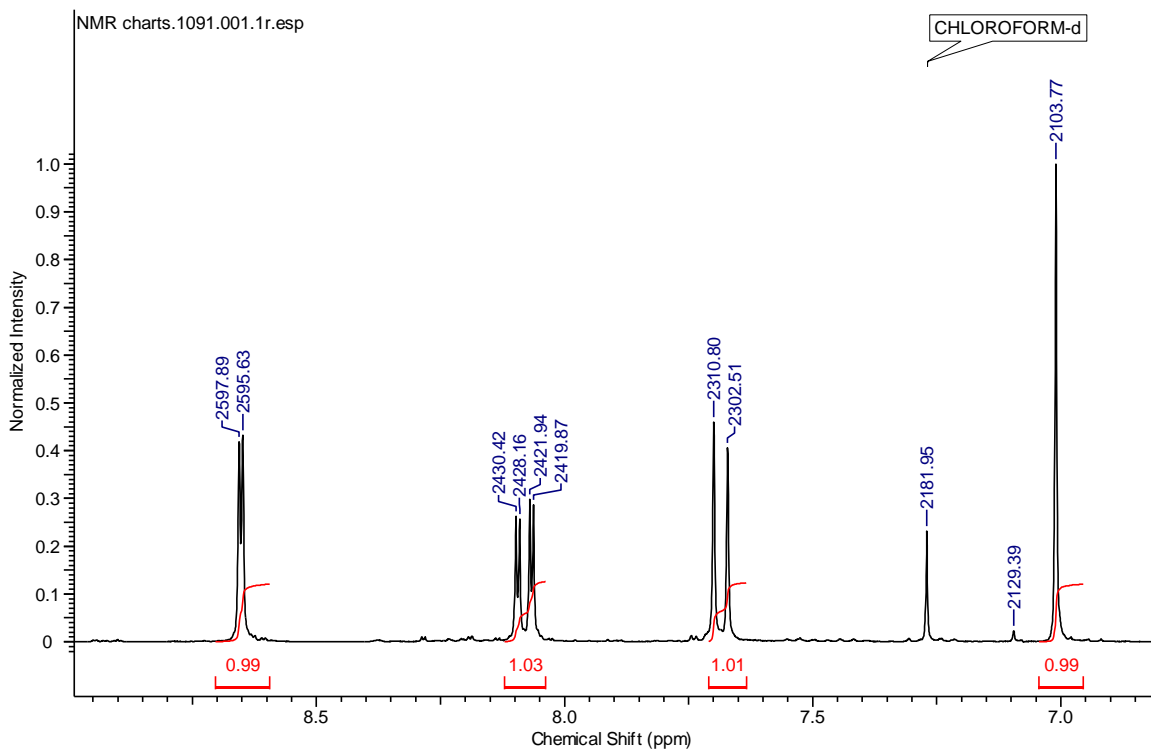
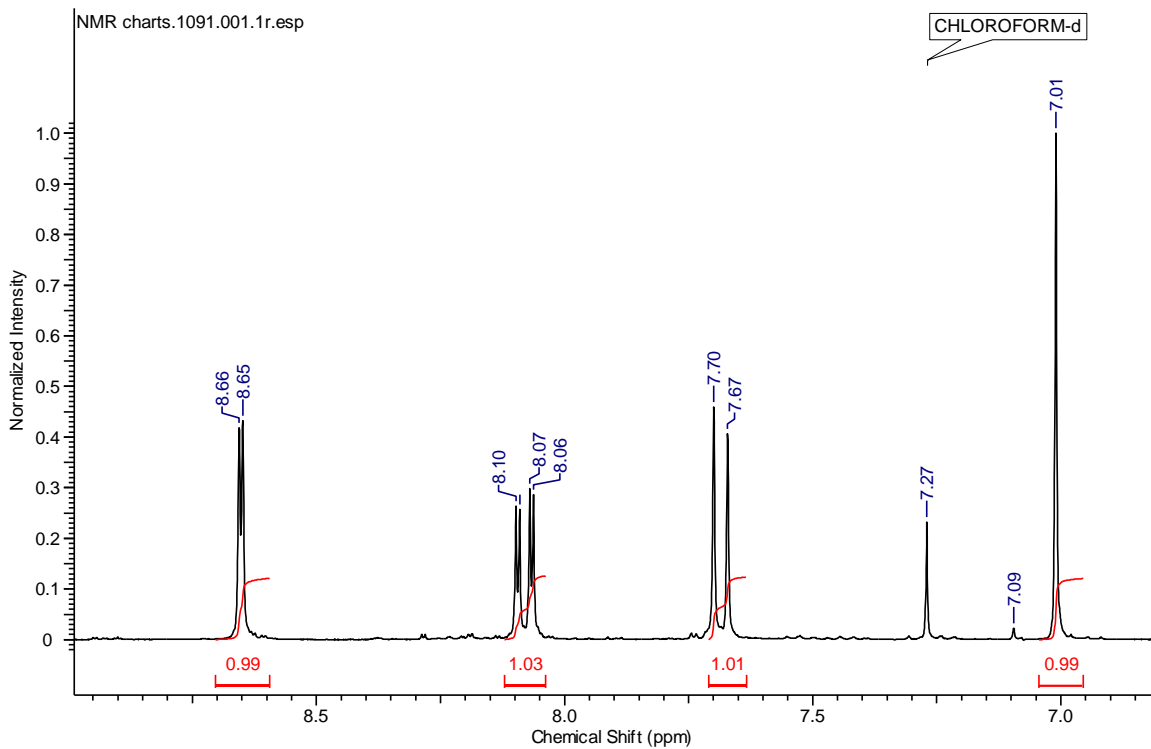


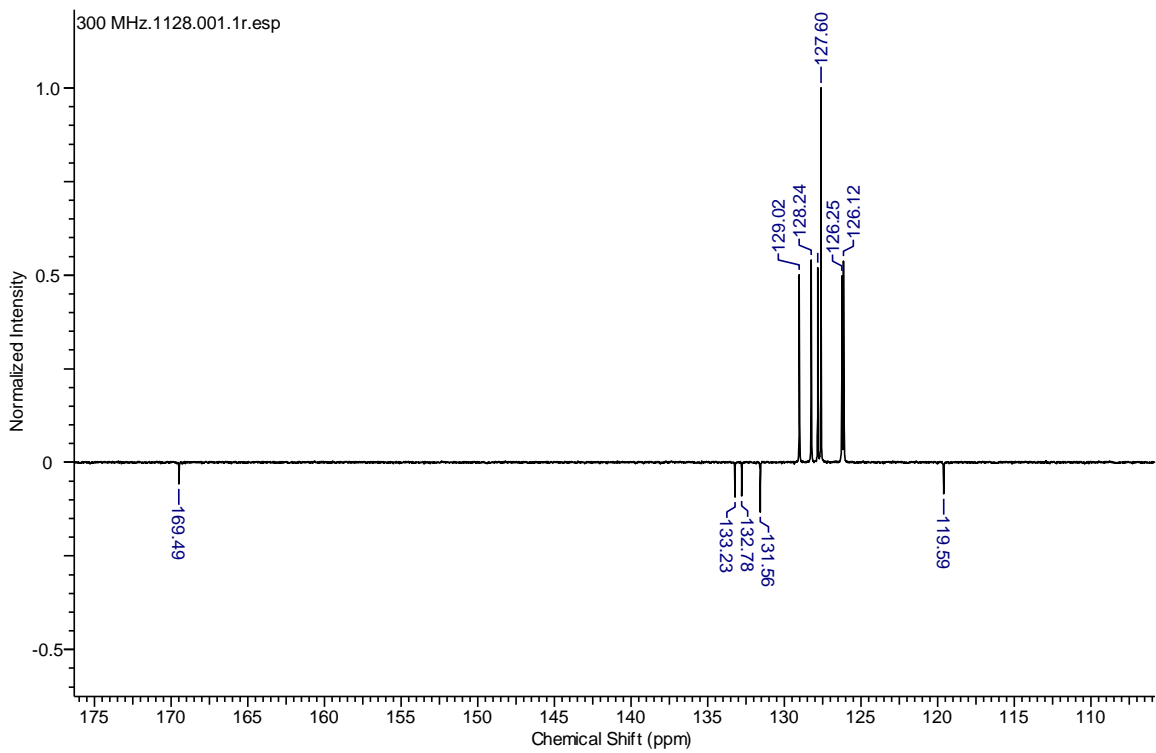
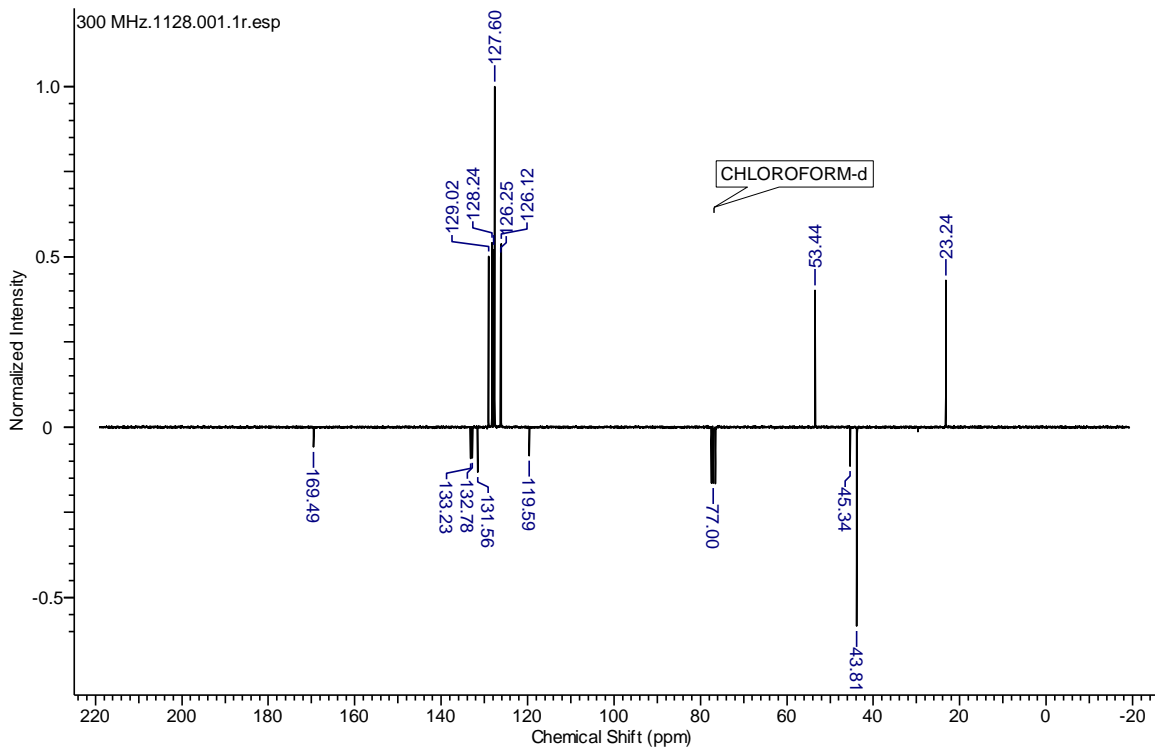


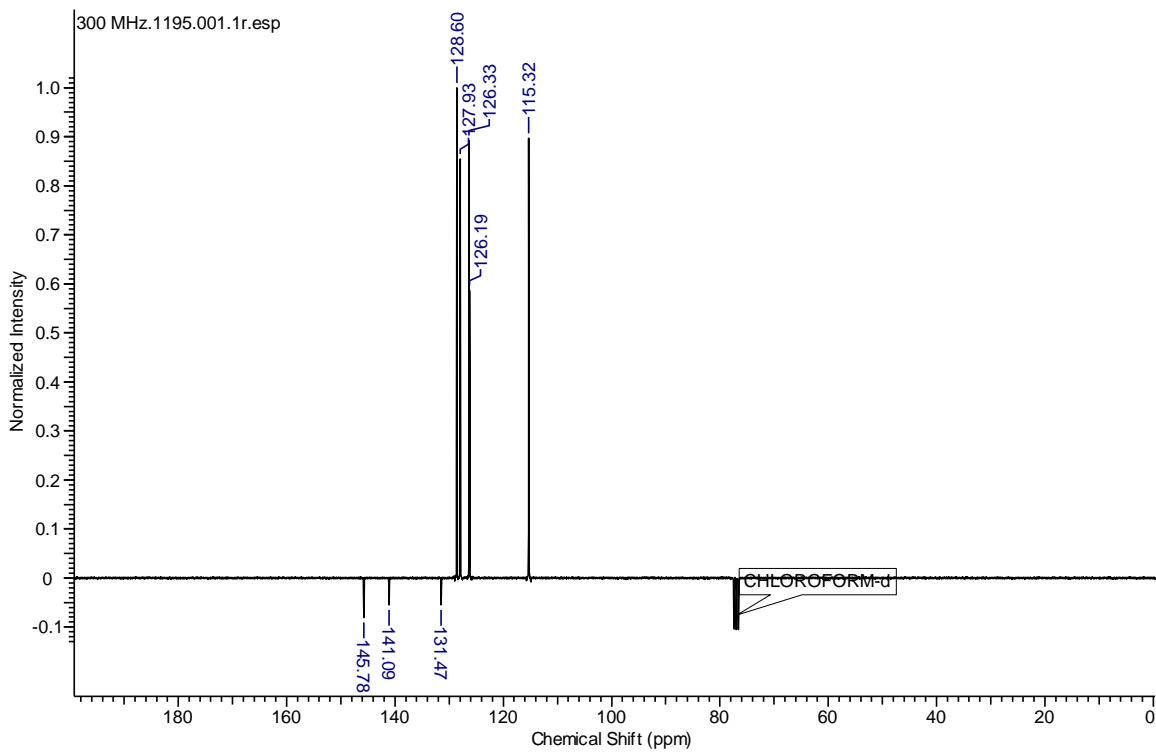
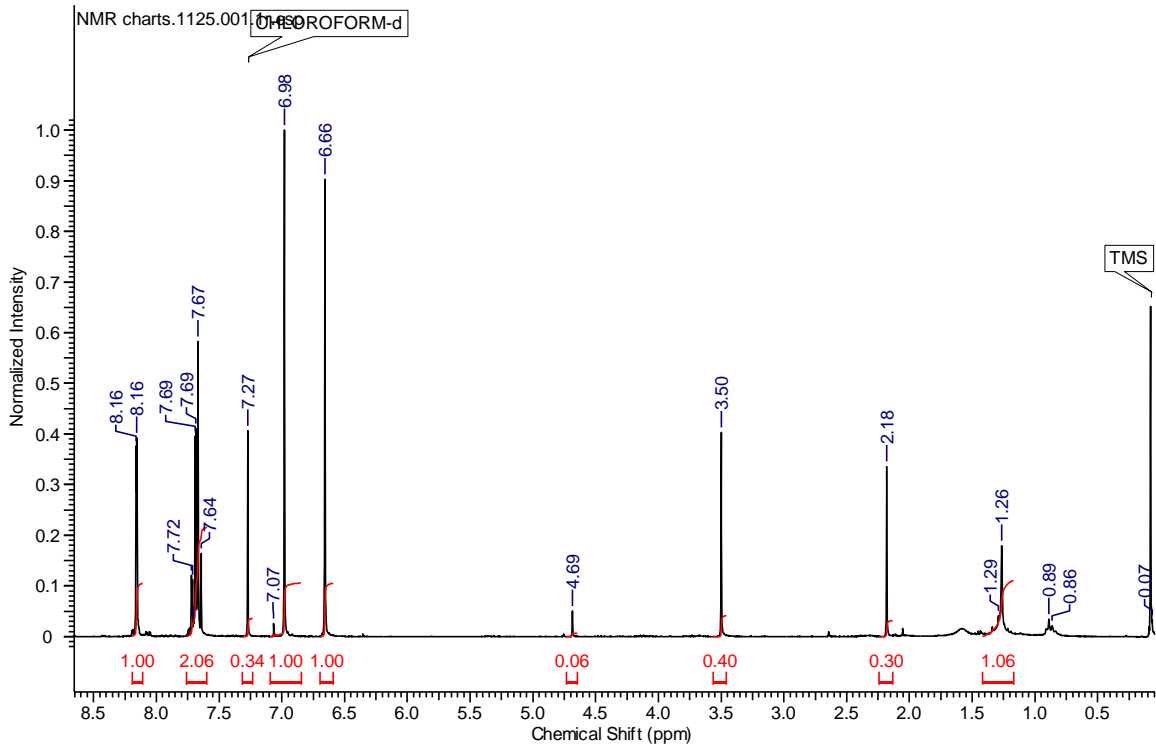
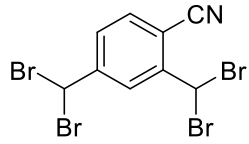


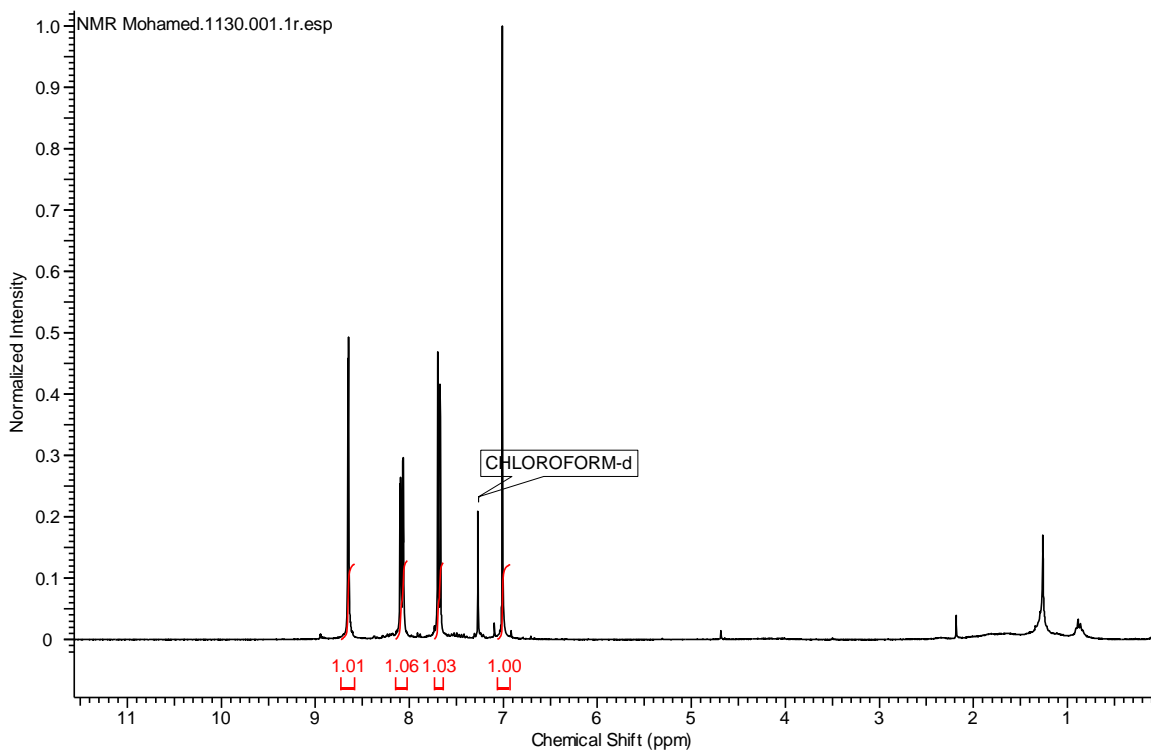
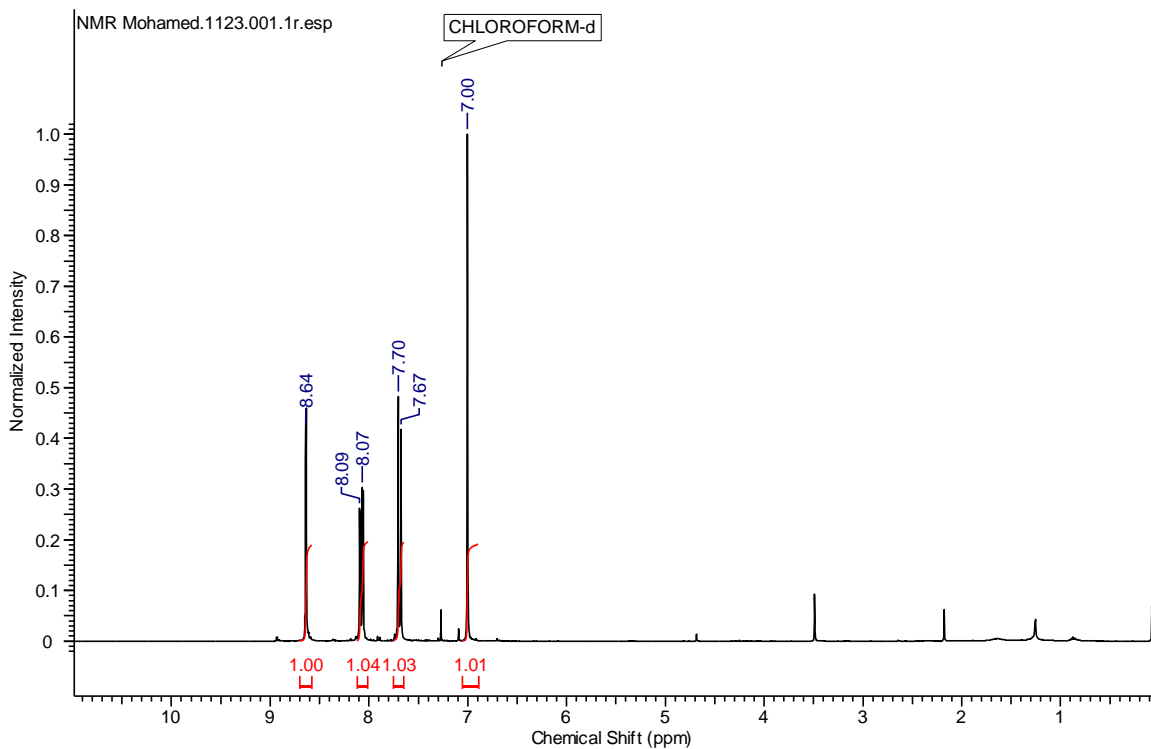
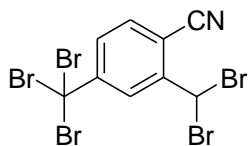


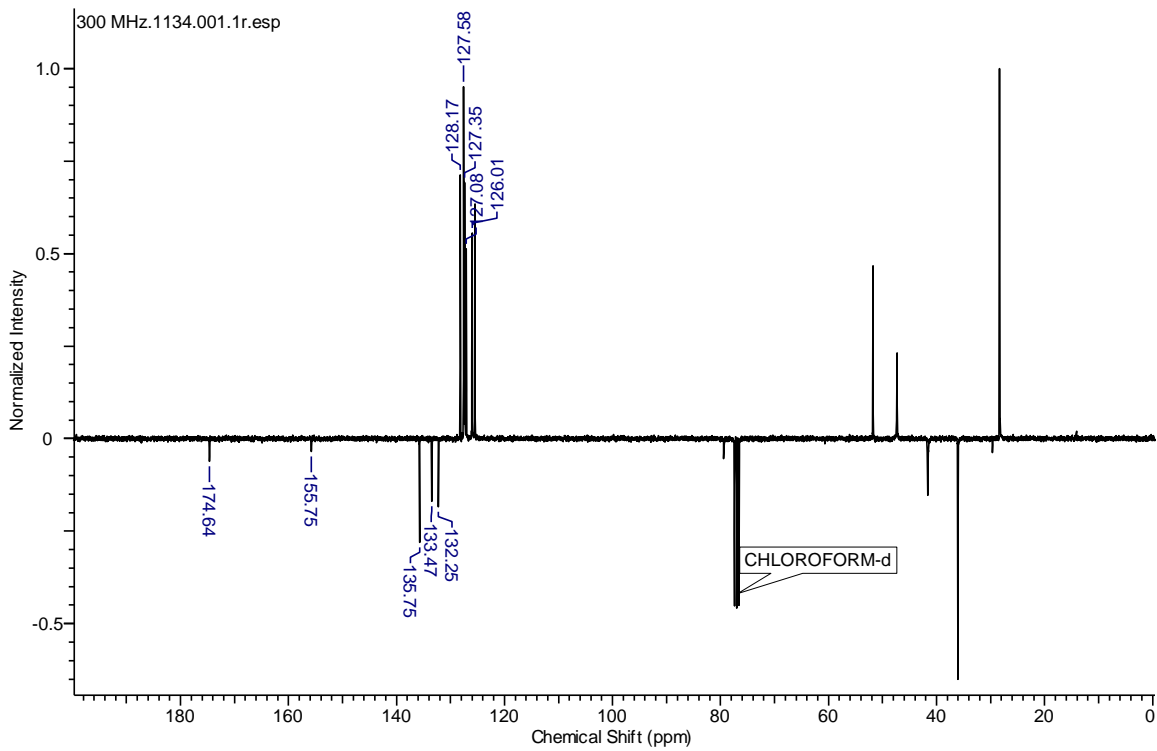
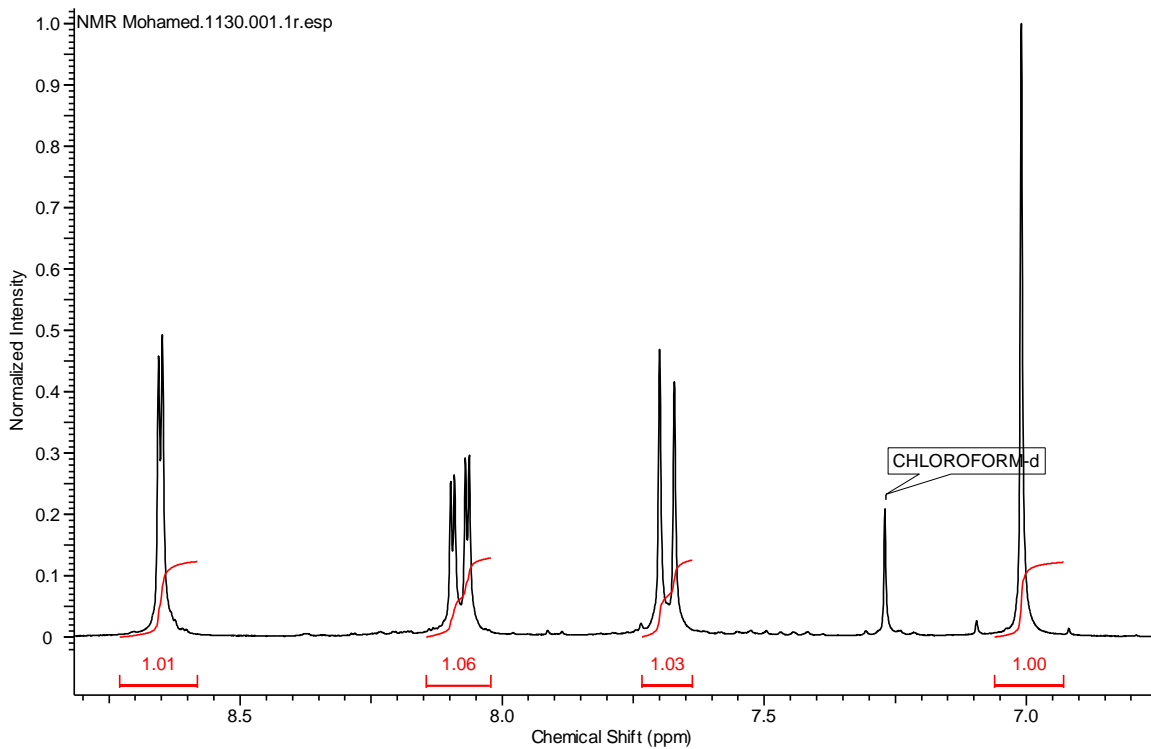


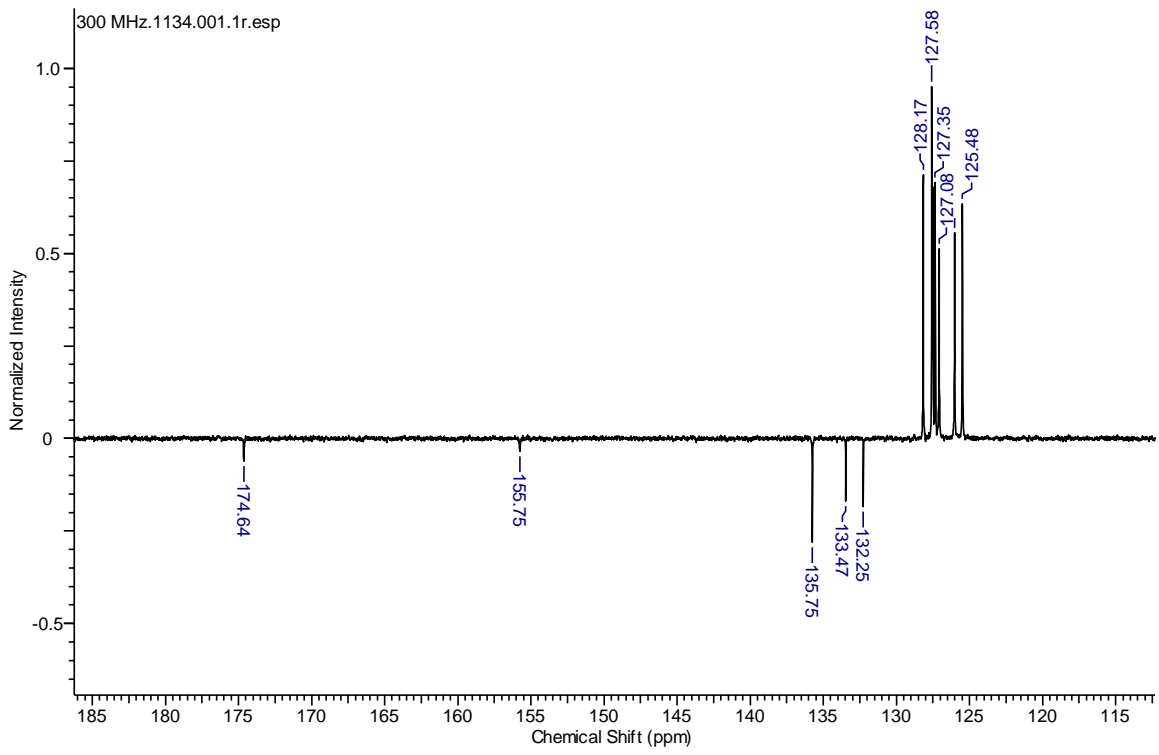


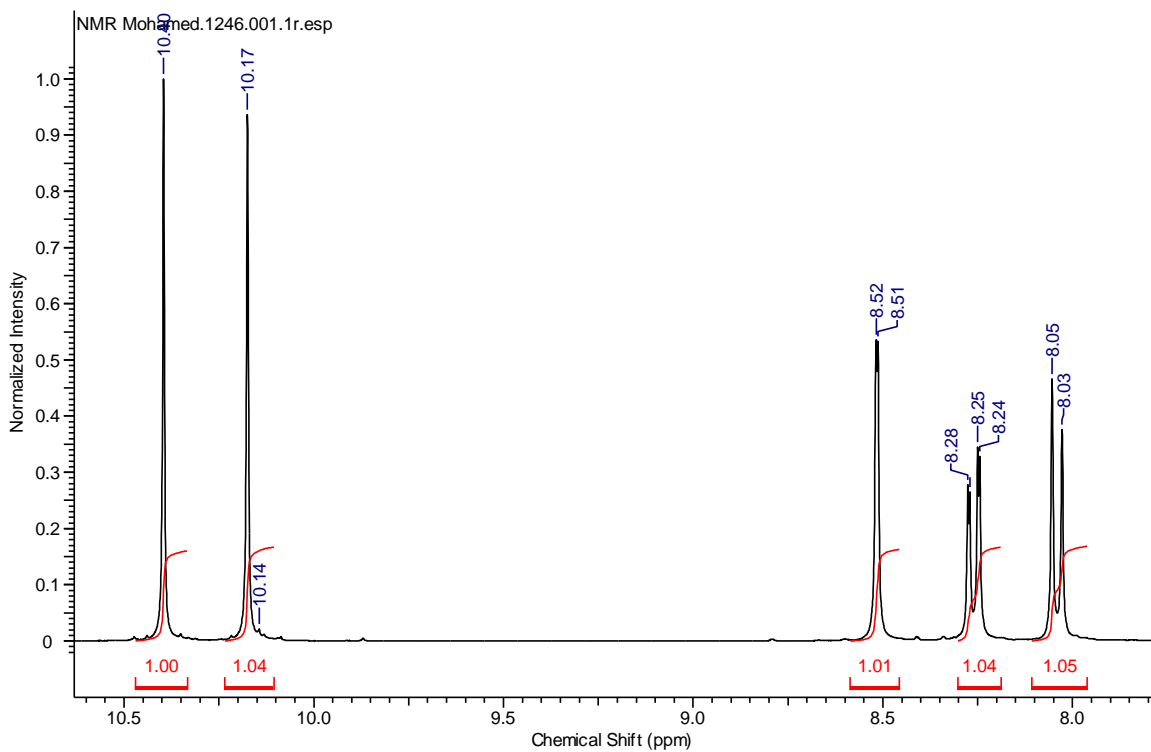
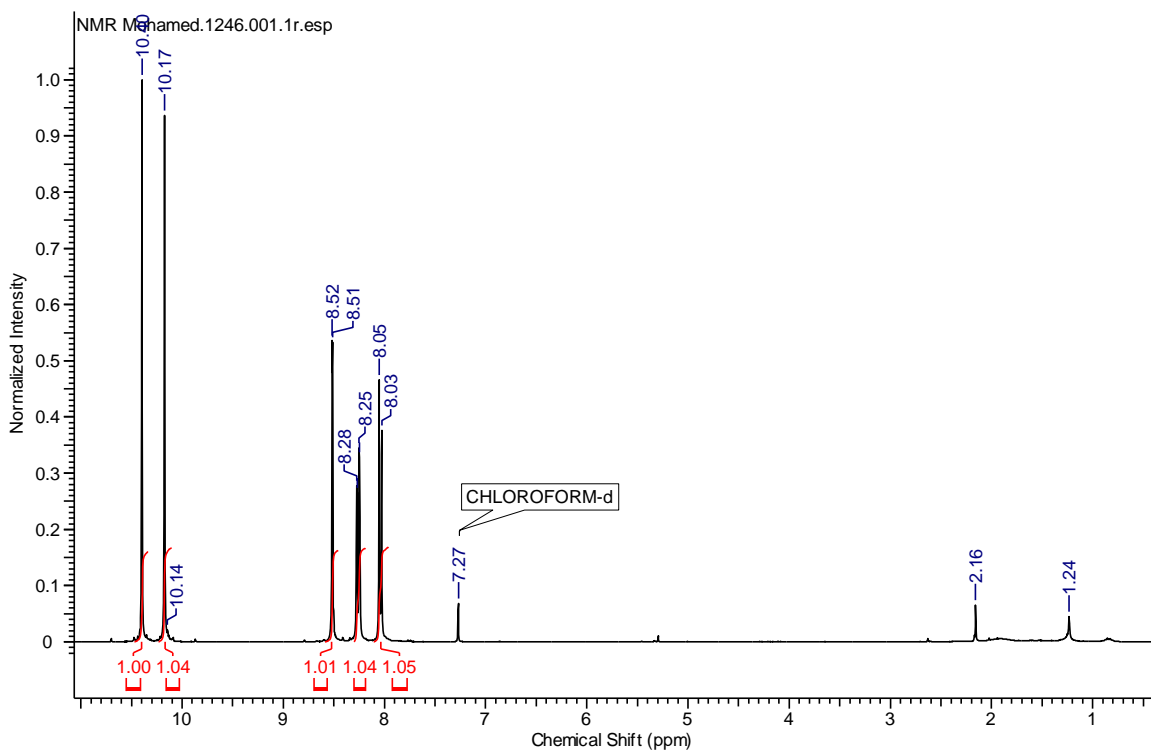
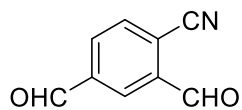




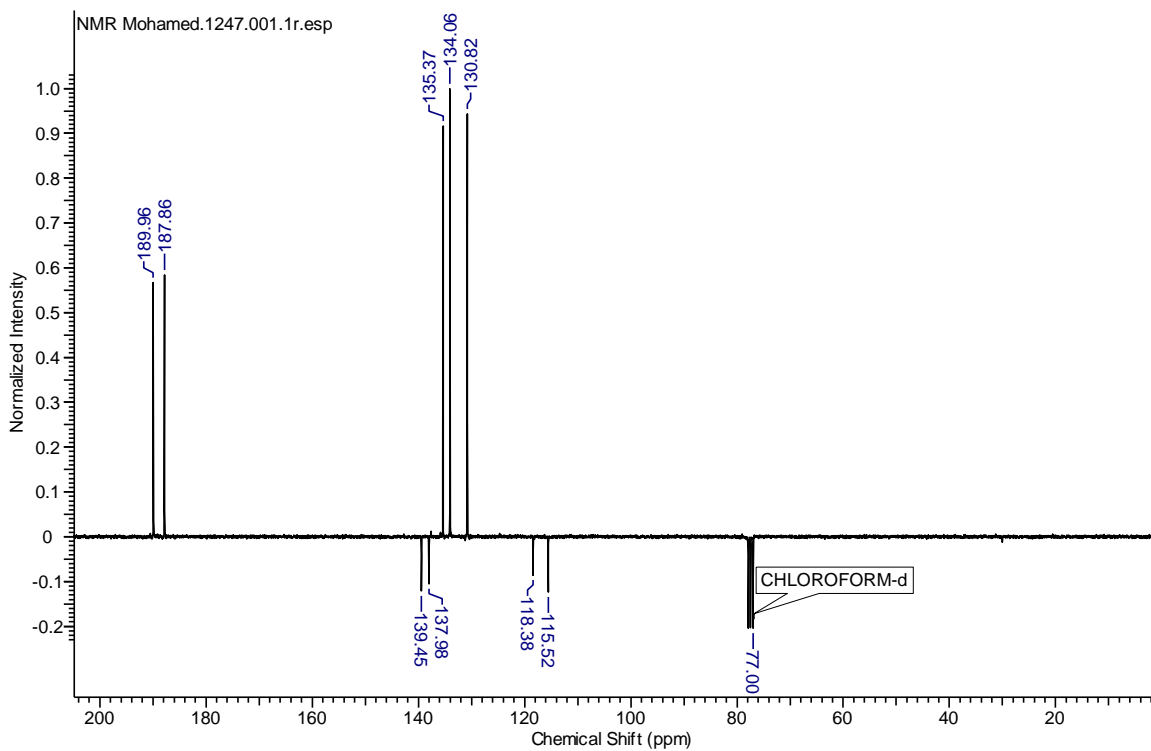
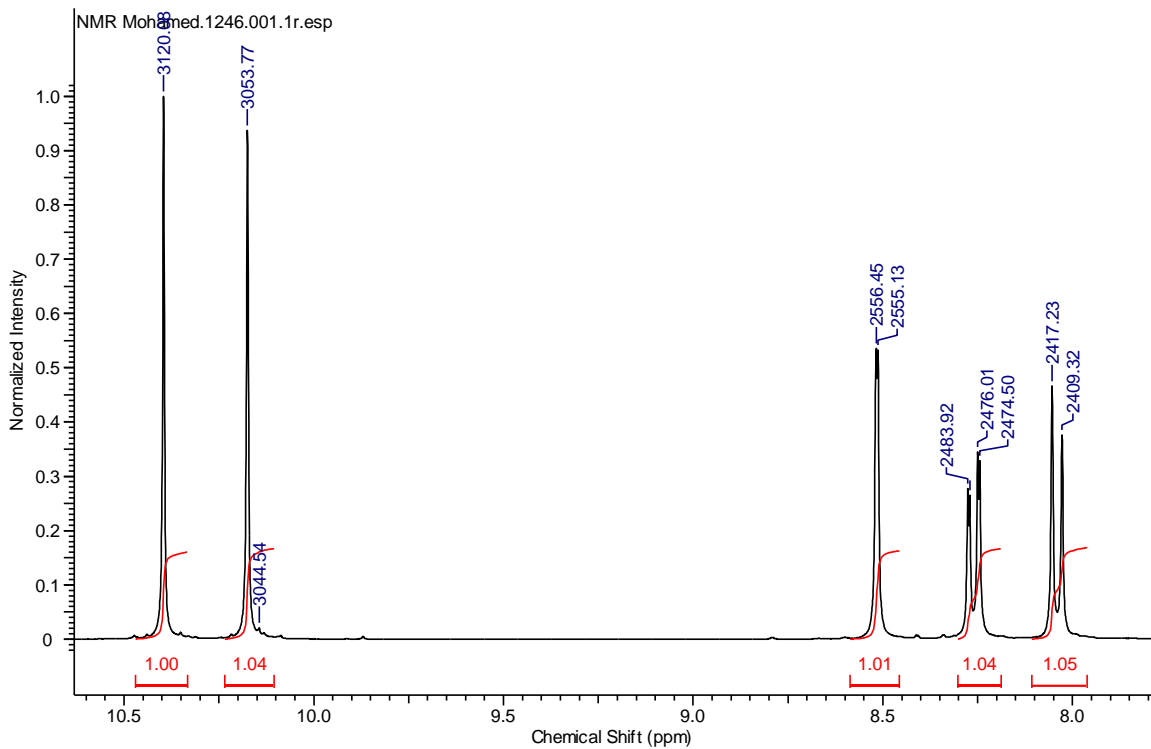


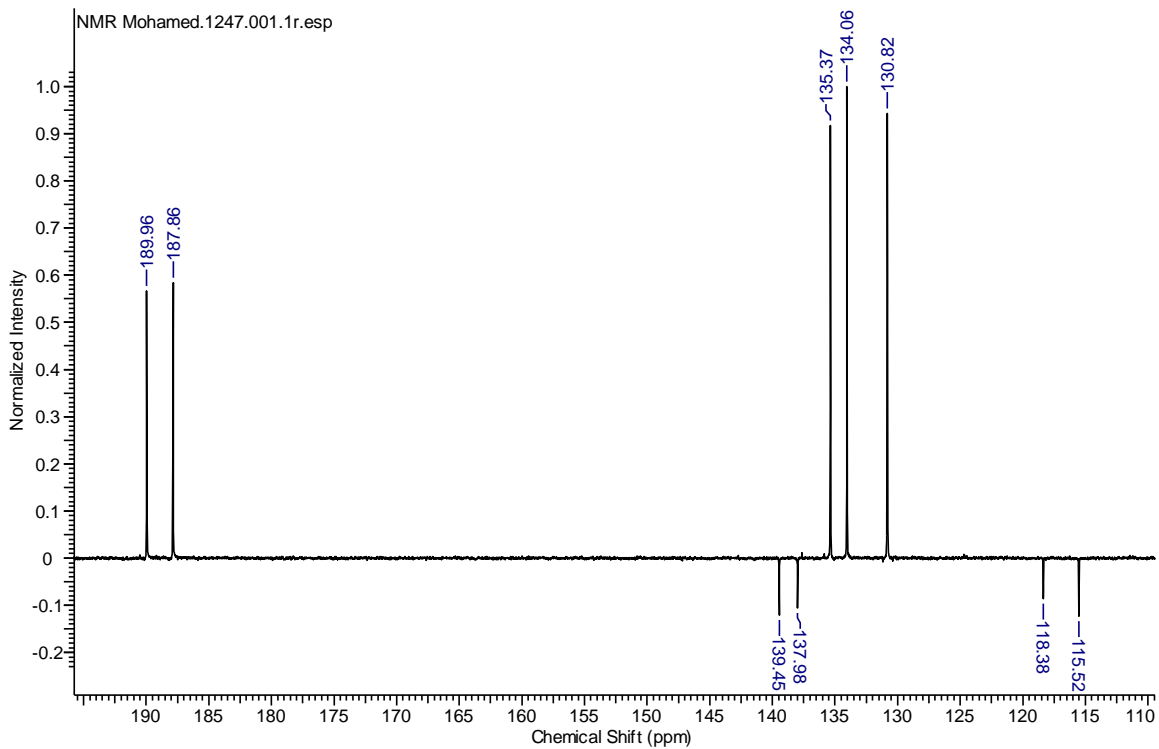


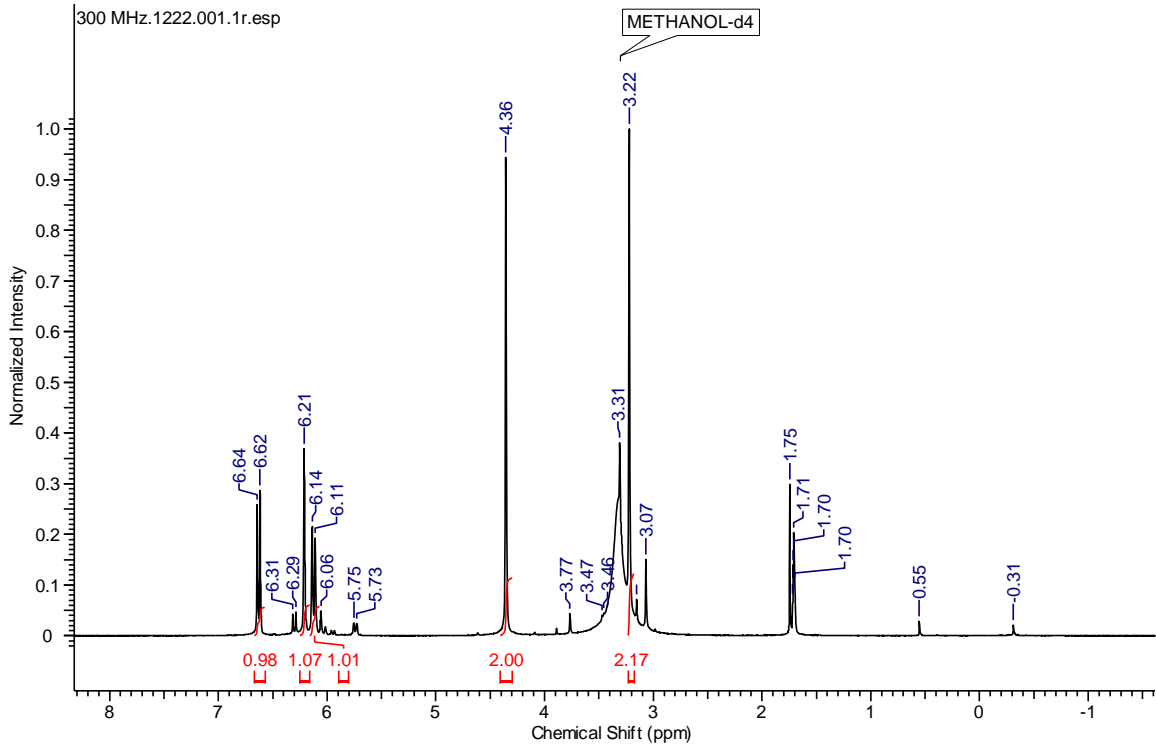
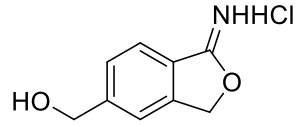


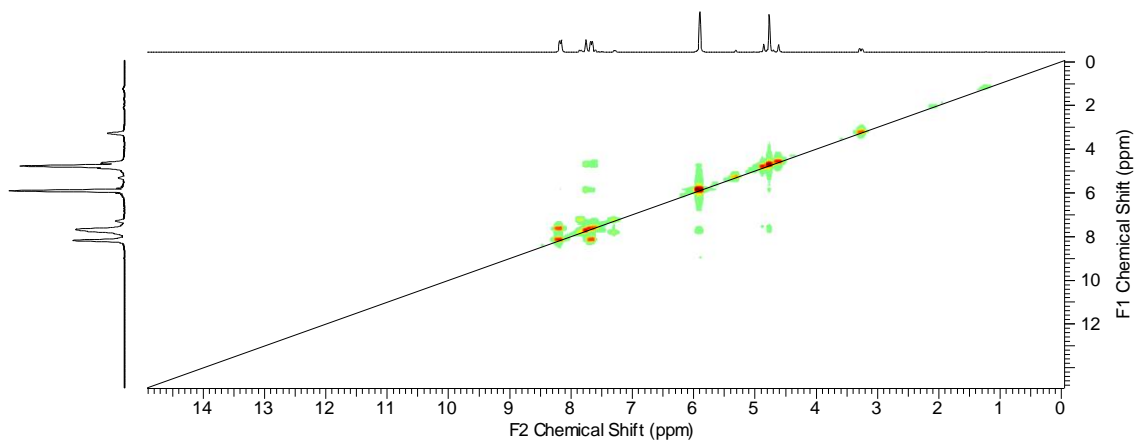
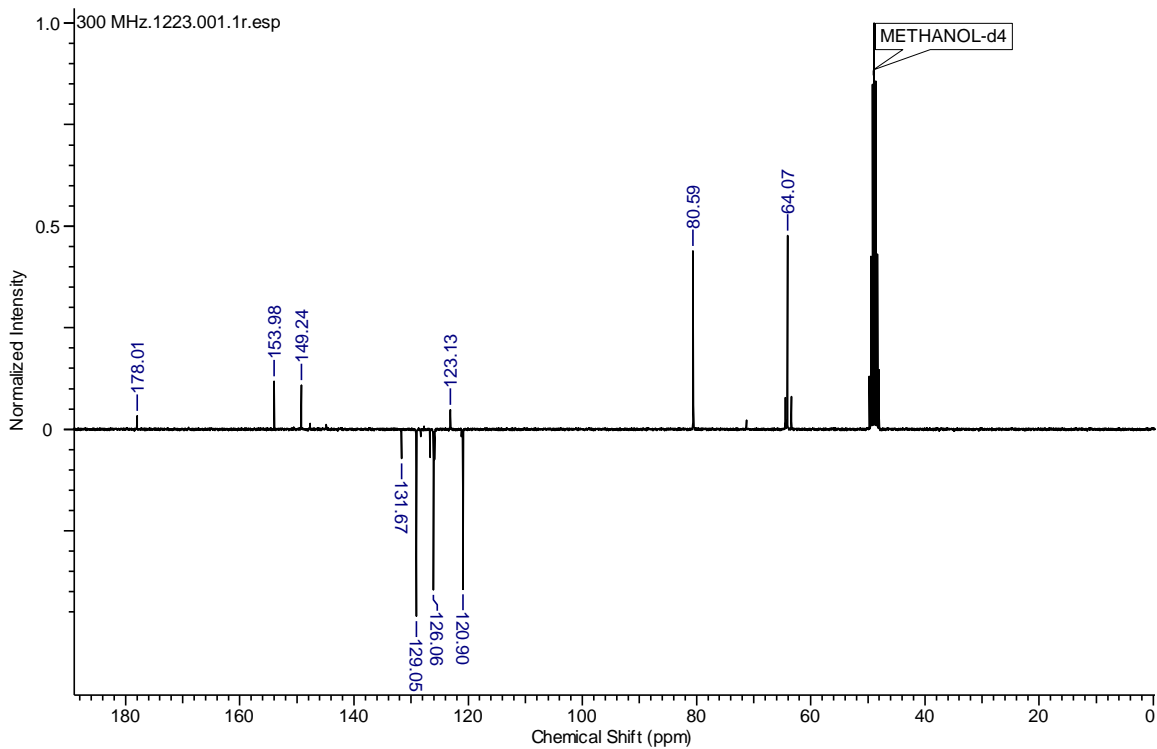


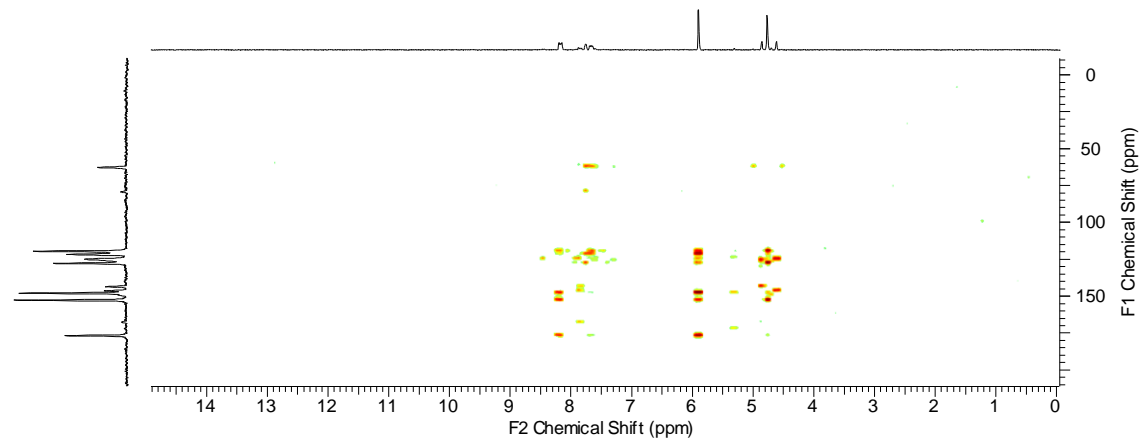
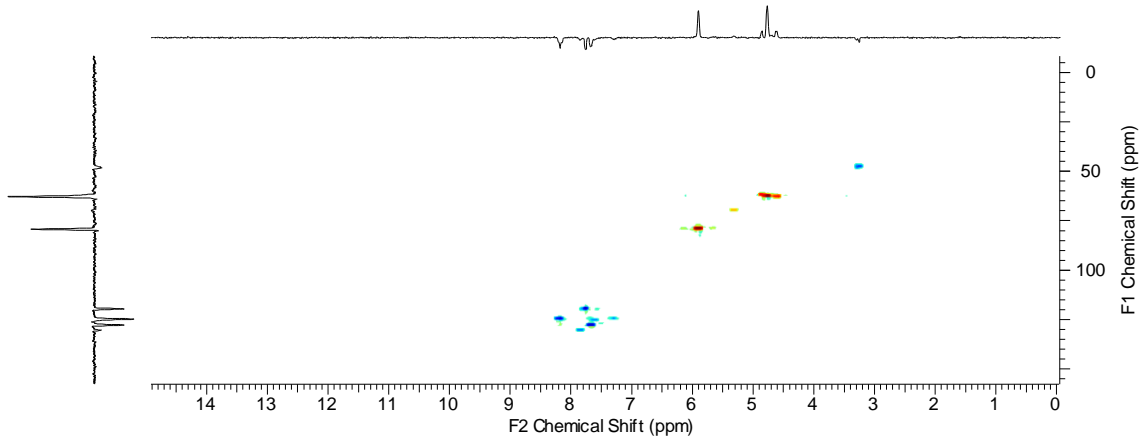


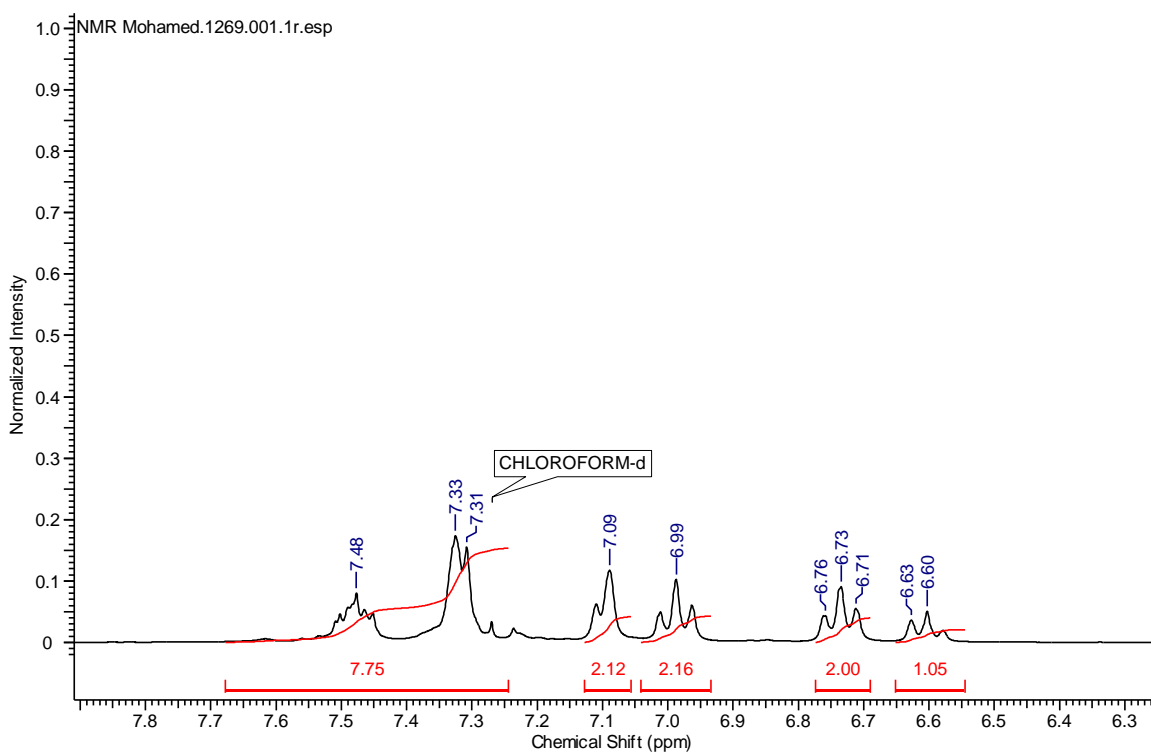
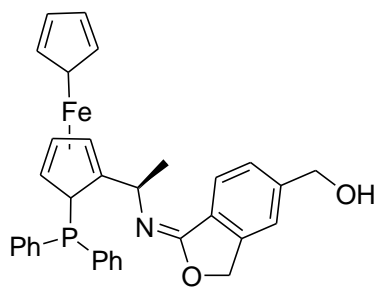


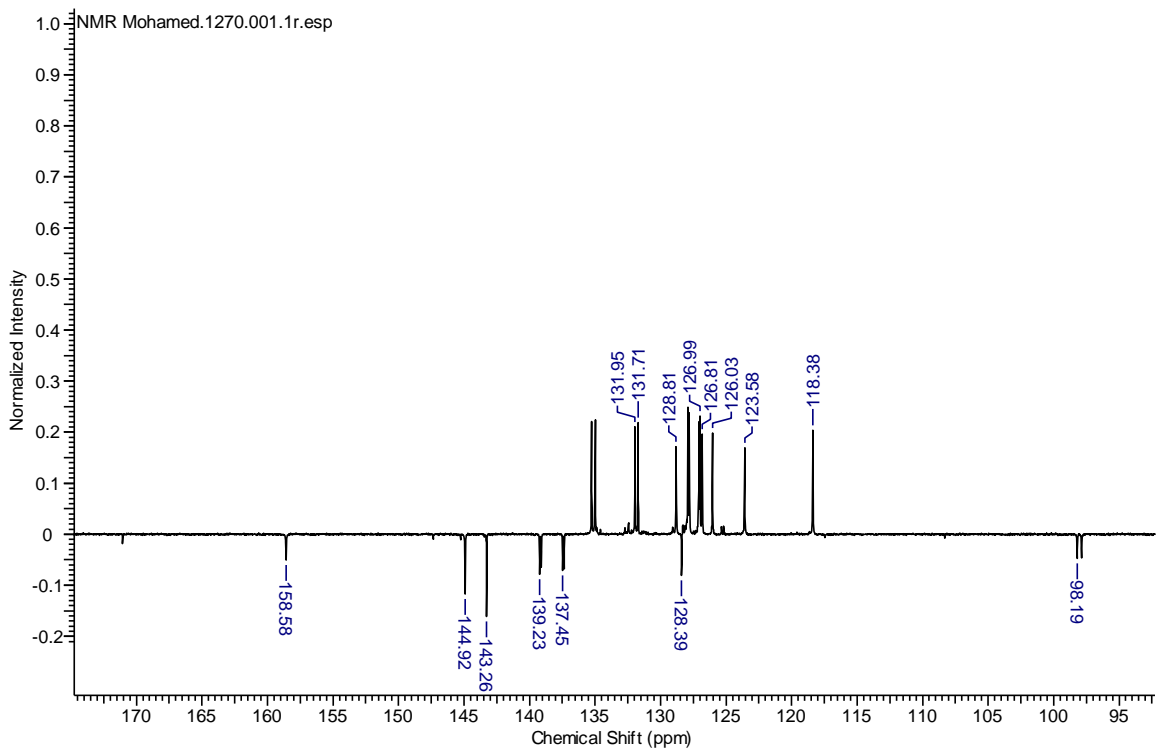
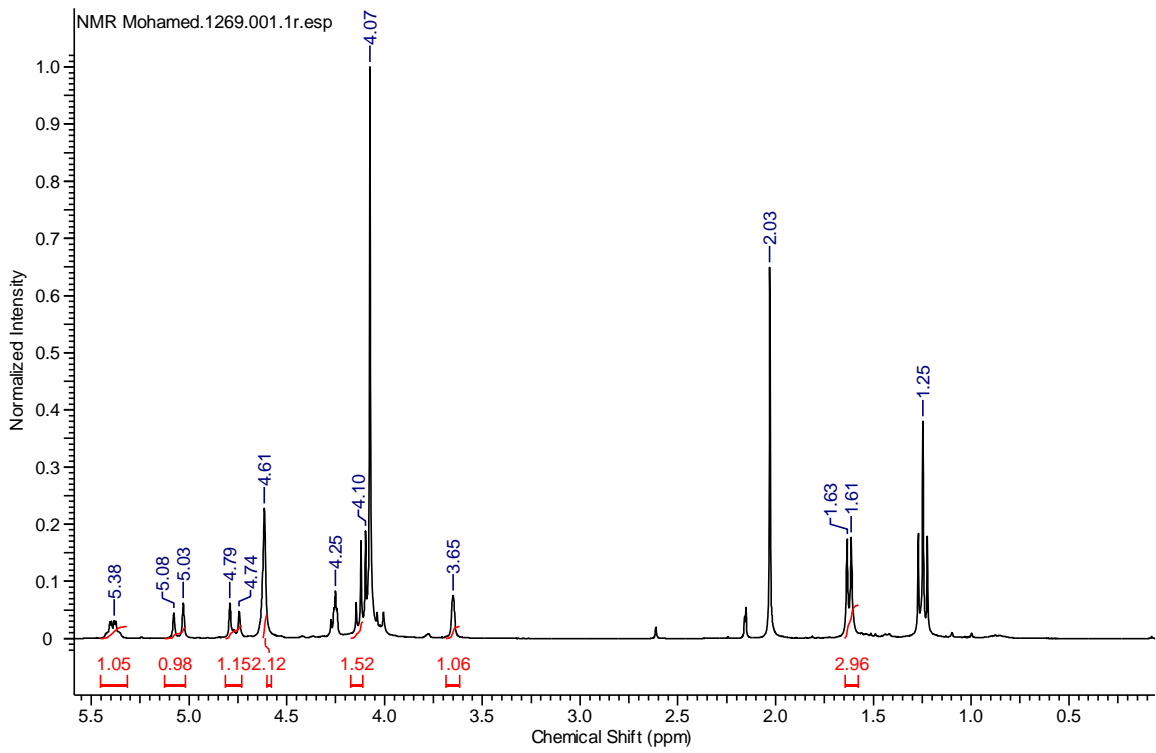


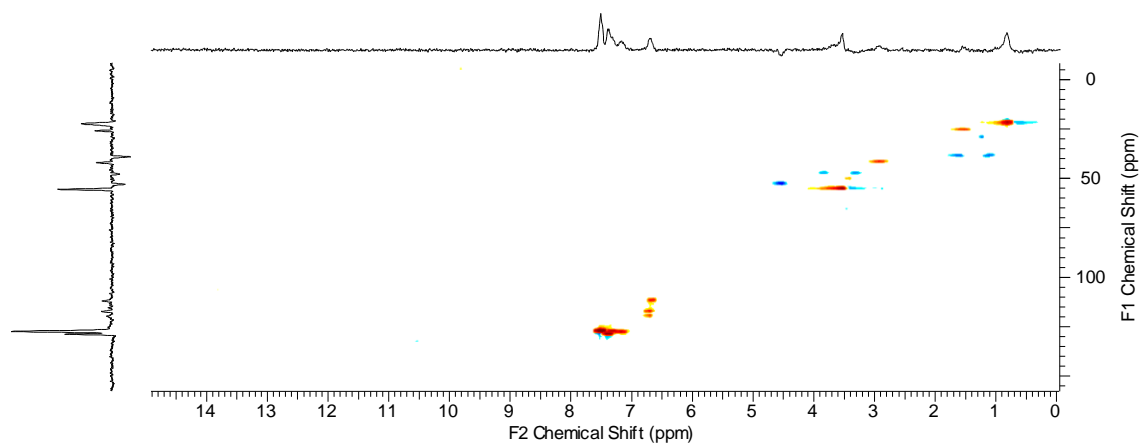
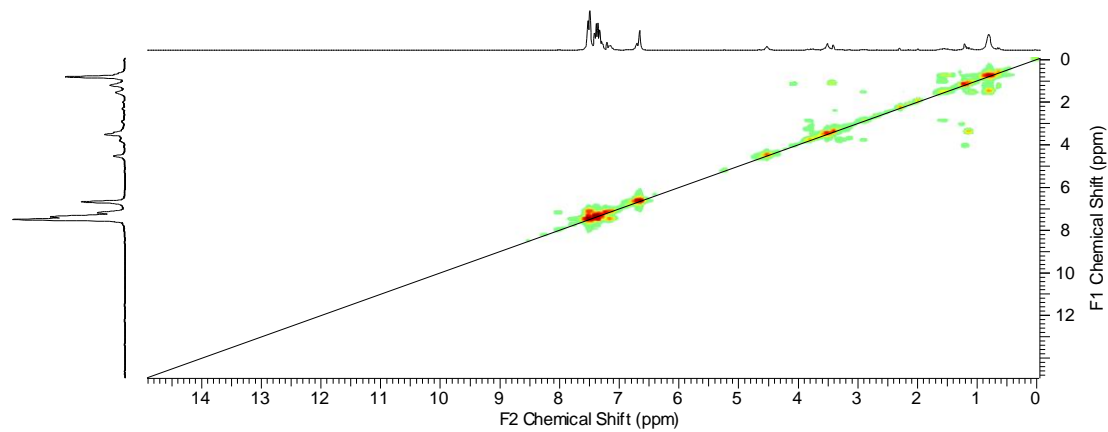
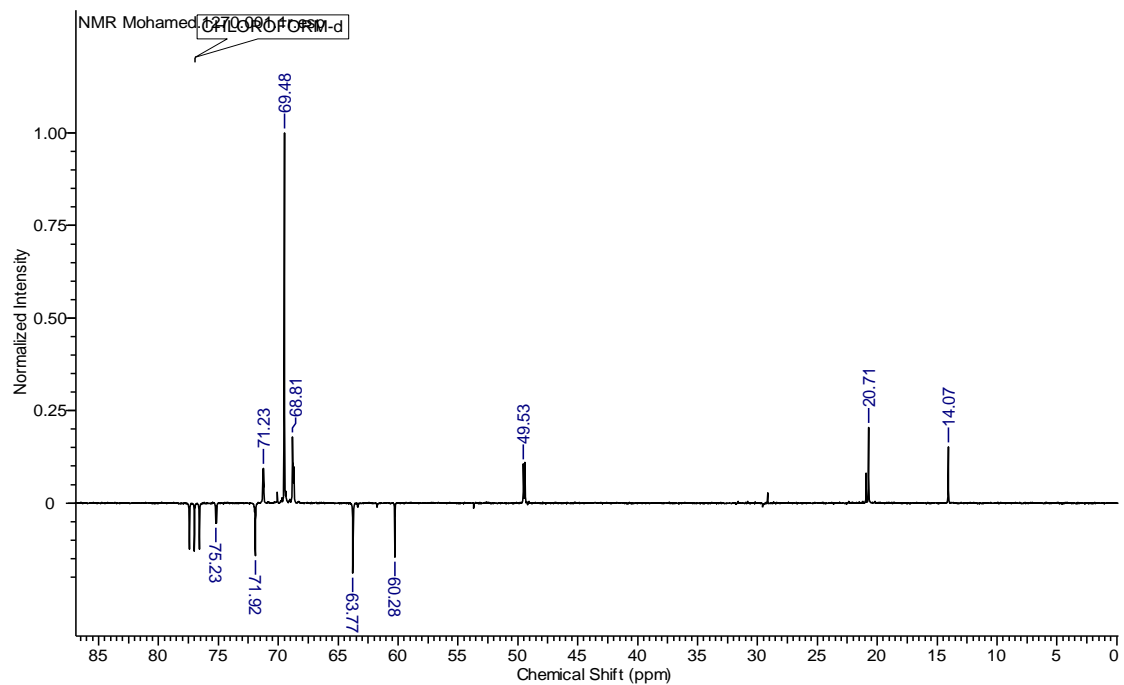






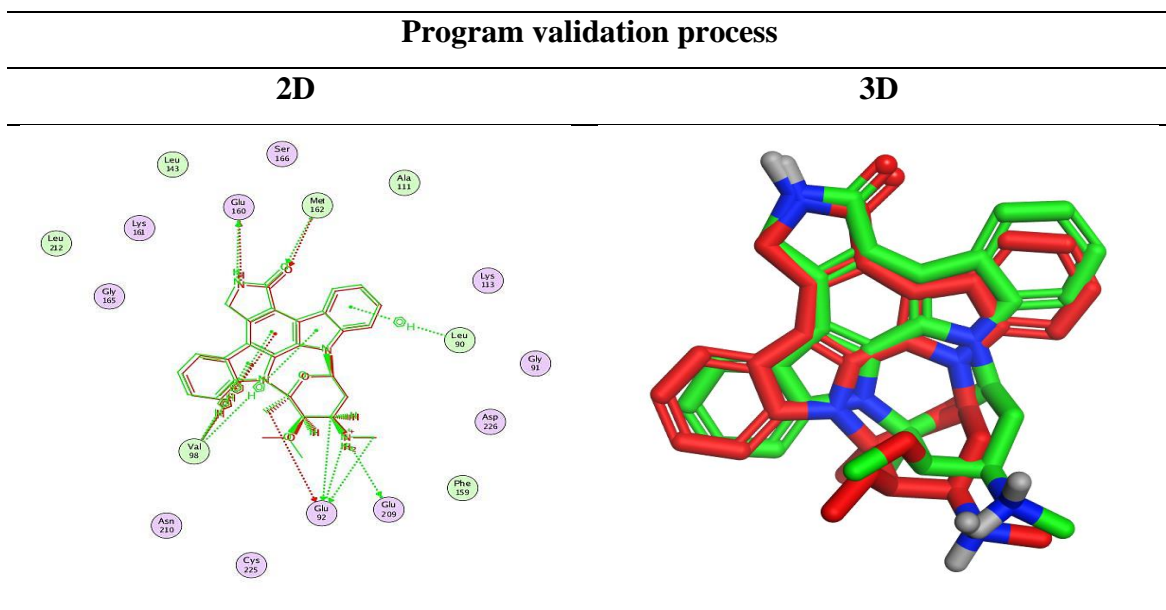








**Figure SI 1.** The 2D and 3D snapshots for the validation process of the MOE program describe the superimposition of both the native co-crystallized (green) and redocked (red) poses of staurosporine.



**Table SI 1.** Coordinates of the optimized ferrocene complex (compound 10) at B3LYP/6-311+G\* level of theory.

C	0.96592100	1.49319500	1.70566000
C	-0.45225300	1.53727300	1.76362800
C	1.41744600	2.28058900	0.58511100
C	-0.89650500	2.34190700	0.67786700
C	0.23390300	2.81261100	-0.05483900
C	1.21872500	-0.69817500	-1.15185000
C	0.28617500	-0.00902700	-1.98109600
C	0.49350800	-1.34395800	-0.10799400
C	-1.01785400	-0.23250000	-1.45241200
C	-0.89262900	-1.05503800	-0.29255300
Fe	0.16533600	0.70892200	-0.02842500
P	3.15948400	2.88660400	0.34101800
C	4.06560300	1.78904000	-0.85846000
C	3.56890900	1.67639100	-2.16703100
C	5.33462000	1.25687000	-0.58019600
C	4.30033100	1.00905500	-3.14703000
H	2.62120500	2.14662300	-2.41744400
C	6.06286700	0.58852700	-1.56592700
H	5.77260000	1.36322900	0.40517700
C	5.54544000	0.45306900	-2.85252500
H	3.89167800	0.94256000	-4.15094300
H	7.03966500	0.17853000	-1.32263000
H	6.11351400	-0.06500200	-3.62032400

C	3.91490700	2.38515400	1.97334300
C	4.14743500	1.06469300	2.38987900
C	4.26495000	3.41981600	2.84963300
C	4.70126900	0.79142900	3.63837900
H	3.89680800	0.24237800	1.72841600
C	4.81681700	3.15196000	4.10404000
H	4.10132400	4.44842600	2.54254200
C	5.03707200	1.83592800	4.50174700
H	4.87075900	-0.23865000	3.93948900
H	5.07734100	3.97307000	4.76567500
H	5.46881200	1.62241200	5.47527400
C	0.08020600	3.78993100	-1.21095900
C	-0.54755300	4.43897000	-4.16598900
C	-0.36910700	4.38640500	-5.58265000
C	-1.23997000	4.95592400	-6.47085300
C	-2.40180400	5.64893000	-5.98967400
C	-2.55975500	5.74461000	-4.58570000
C	-1.68367800	5.17469200	-3.67985600
C	0.52779700	3.74073000	-3.53877200
C	0.90493000	3.62795500	-5.83864700
H	-1.06662400	4.88515800	-7.54363000
H	-3.41369300	6.30115500	-4.20011800
H	-1.86563000	5.30382200	-2.62022400
H	0.75374700	2.71724500	-6.43350100
C	-3.37044000	6.27664500	-6.92665100

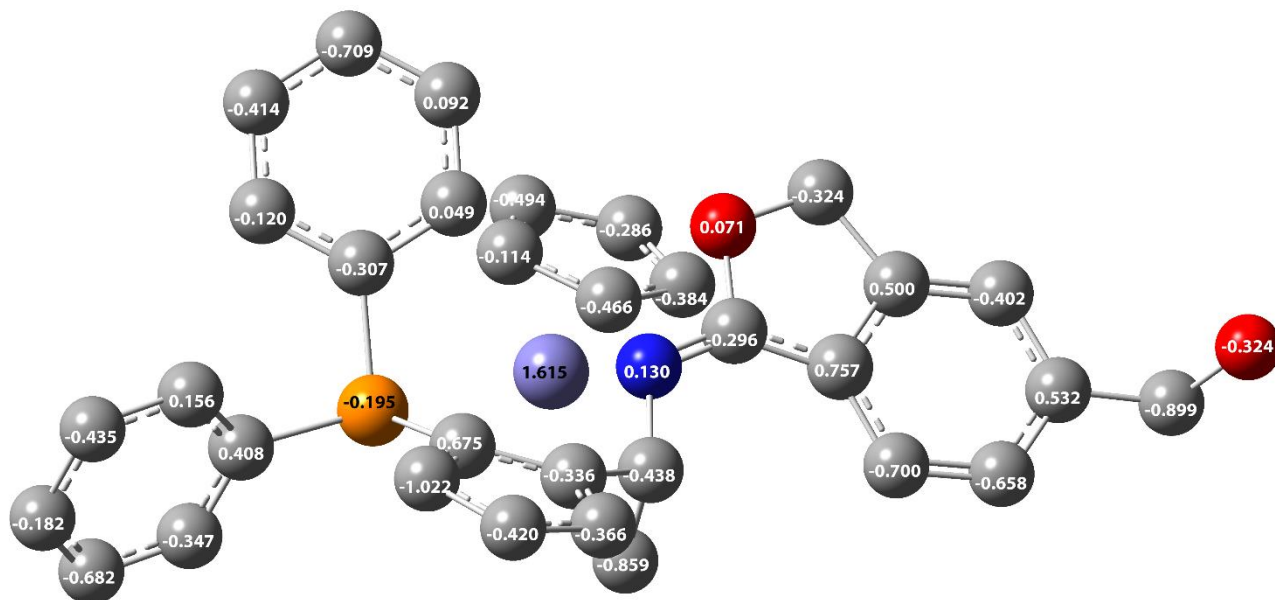
H	-3.98357400	7.01978200	-6.39922200
H	-2.87283000	6.78536000	-7.76096100
O	-4.27317300	5.33118400	-7.58889600
H	-4.36976200	4.58501100	-6.98200500
O	1.39084500	3.25189200	-4.54548800
N	0.90643300	3.42361200	-2.33612800
H	1.67268700	4.23282600	-6.33947500
H	-0.98889900	3.75275000	-1.47011600
C	0.38087700	5.22591100	-0.71586500
H	1.43108100	5.31429800	-0.43011800
H	0.18514800	5.94471100	-1.51496100
H	-0.24094600	5.48874600	0.14825300
H	2.29147800	-0.69060500	-1.27292400
H	1.59976600	0.96082400	2.39687400
H	-1.07675700	1.02135200	2.48084500
H	-1.92615700	2.54752900	0.41581200
H	0.53047300	0.63203300	-2.81486000
H	-1.93607400	0.18653800	-1.83950900
H	-1.70096400	-1.37739400	0.34963100
H	0.91903400	-1.92659000	0.69765500

**Table SI 2.** Atomic charges on atoms (excluding hydrogen atoms) of ferrocene derivative (**10**) calculated at the B3LYP/6-311+G\* level of theory.

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**Hirshfeld charges**

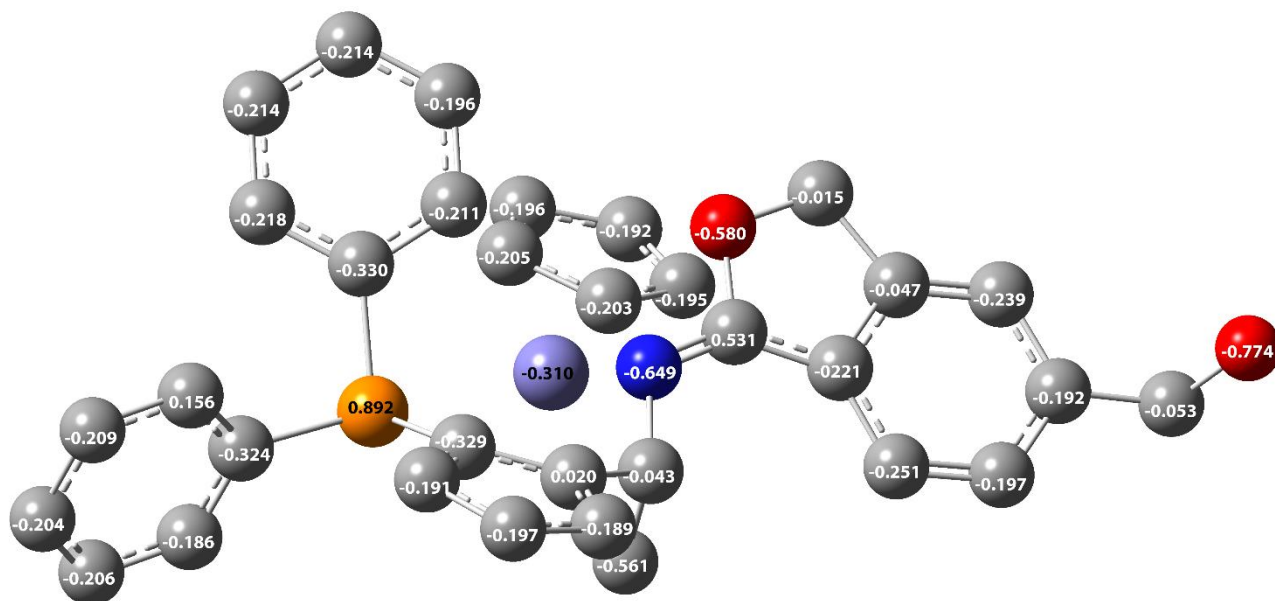
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**NBO charges**

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