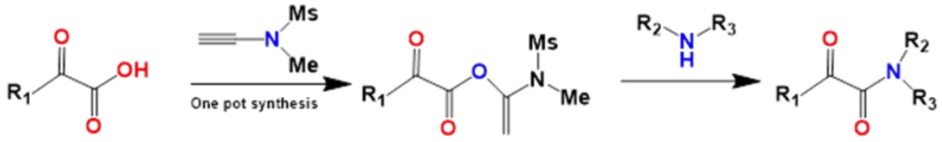
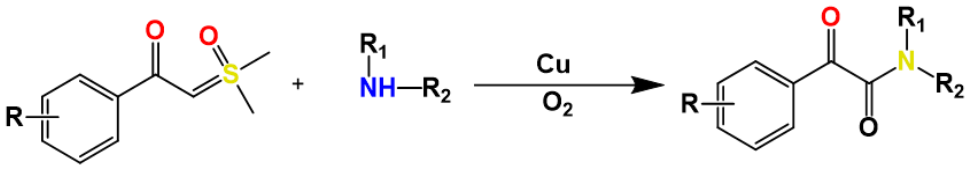
In 2022, Jang et. al., crafted 36 varied structural variants of α-ketoamides with a yield reaching 98%. They employed a single-step technique that combined α-keto acids and amines, using ynamides as coupling agents (**Scheme 1.8**) [141].



Scheme 1.8. One pot synthesis of α-ketoamides by using ynamides as coupling agents.

In 2023, Wang et. al., synthesized thirty-eight derivatives of α-ketoamides from sulfoxoniumylides and secondary amines by using copper catalyst [142]. This approach accommodated aryl, heteroaryl, and tert-butylsulfoxoniumylides, leading to a diverse range of α-ketoamides with favorable yields (**Scheme 1.9**).



Scheme 1.9. Synthesis of α-ketoamides from sulfoxoniumylides and secondary amines by using copper catalyst.

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Aβ aggregation kinetics. Notably, compound MD08 emerged as a particularly potent molecule in this context. Pharmacokinetic studies further elucidated the solubility and permeability characteristics of compound MD08. Additionally, at a concentration of 100 μM, MD08 exhibited the capacity to inhibit the heparin-induced tau protein aggregation. This inhibitory effect was magnified when the concentration was raised to 200 μM, indicating a dose-dependent inhibition of tau aggregation. Cytotoxicity assays conducted using MTT assay in SHSY5Y cell line didn't show any major toxicity. Further in vivo studies conducted on Aβ-injected models suggested that compound MD08 may enhance cognitive functions, especially when administered at a dosage of 10 mg/kg. An in silico ADME assessment was conducted on all the compounds, shedding light on the various drug-like properties of the synthesized molecules. Additionally, molecular docking and dynamic studies provided insights into the binding interactions and the stability of the ligand when in the presence of Aβ and tau peptides. Quantum chemical calculations pertaining to MD08 also elucidated its electronic and thermal properties. To conclude, this study accentuates the potential of MD08 as a noteworthy lead compound, meriting further exploration and development. Additionally, the findings strongly advocate for a comprehensive investigation into the heterocyclic derivatives of α-ketoamides as prospective therapeutic agents against AD.

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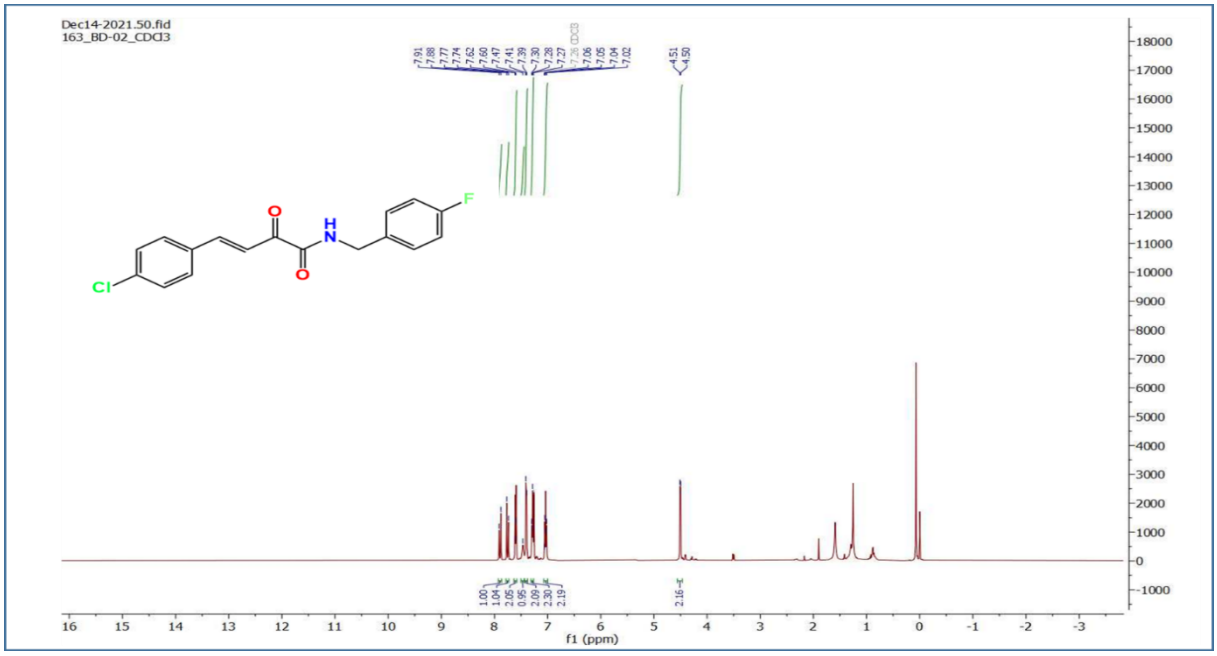
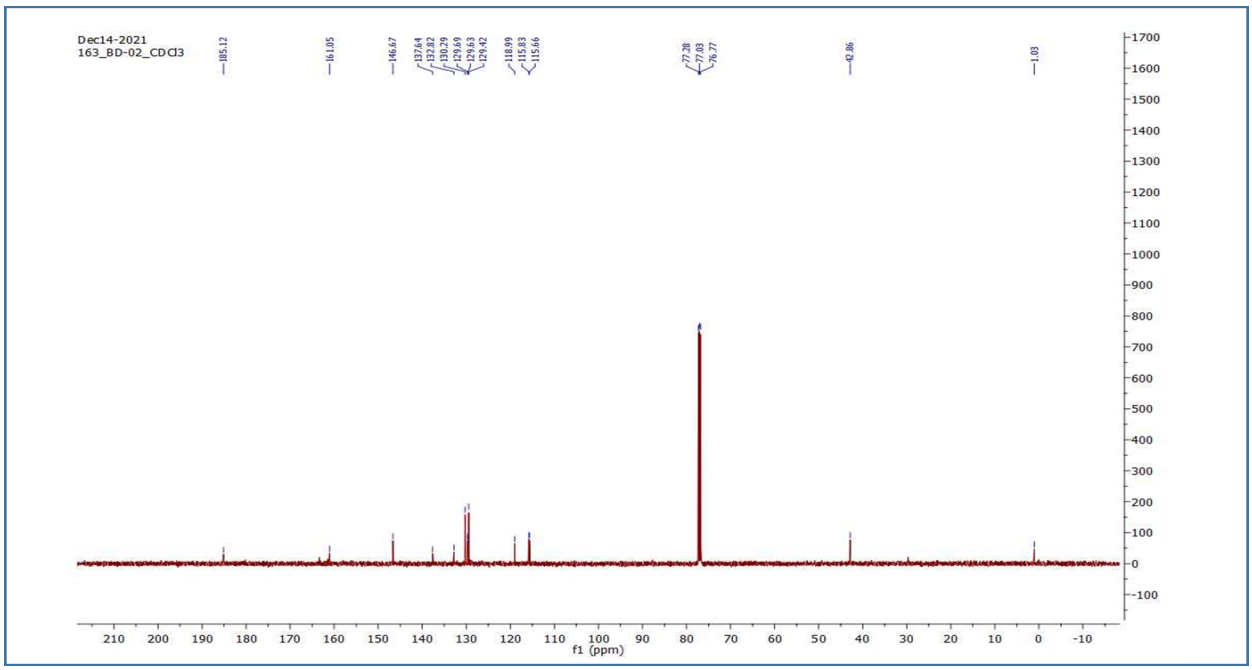
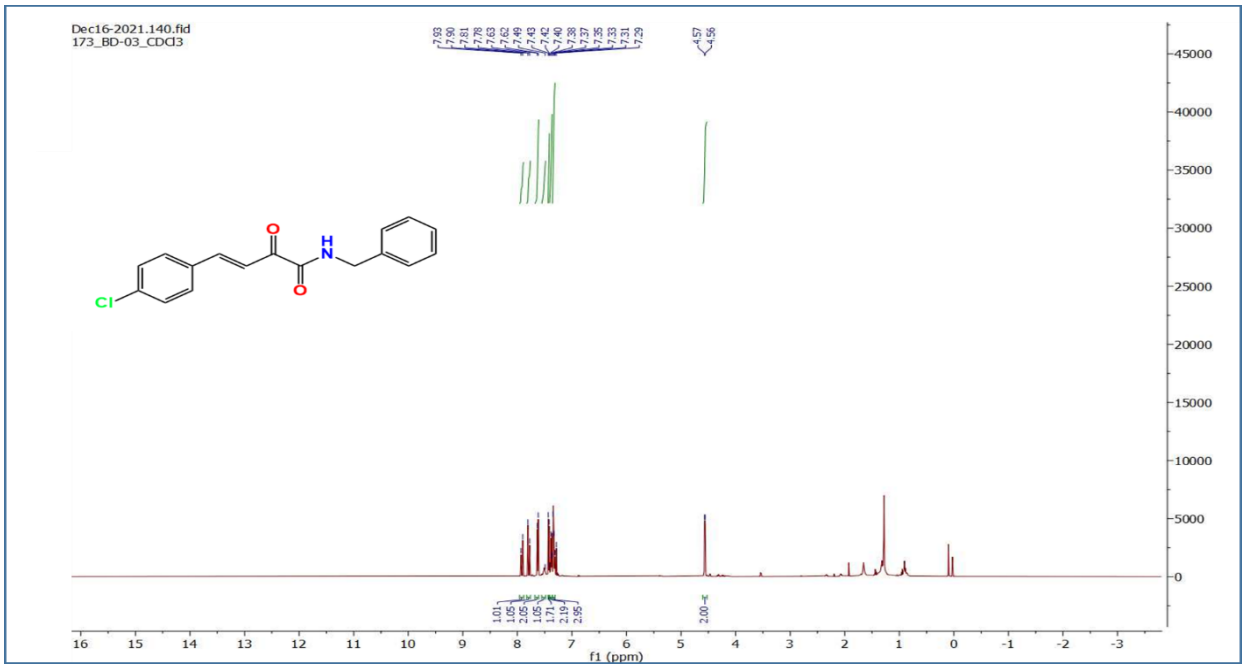
Annexure-I

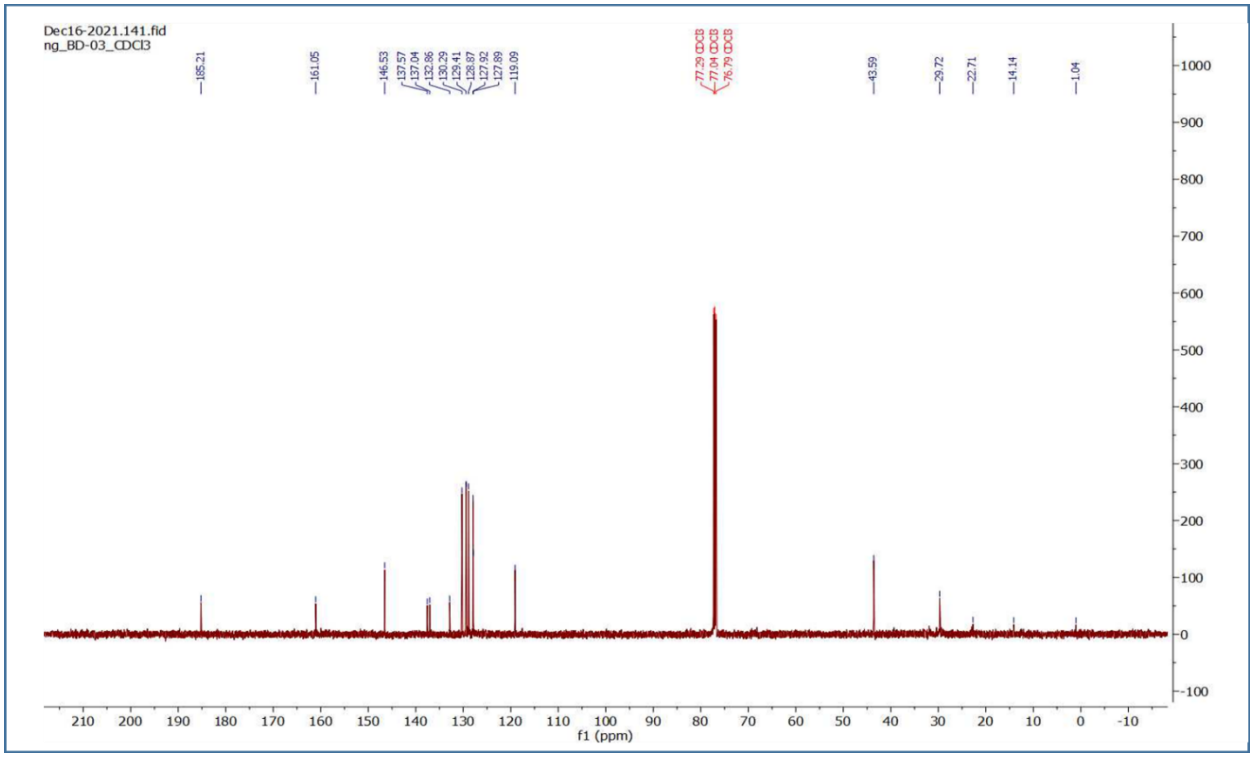
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD01



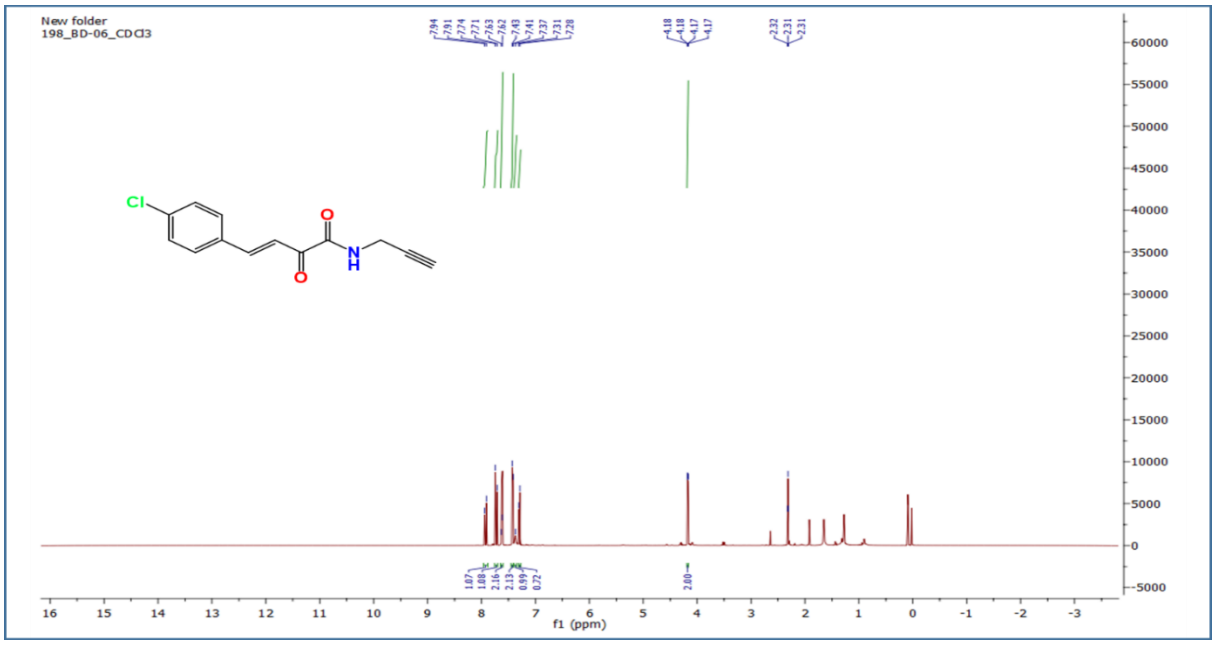


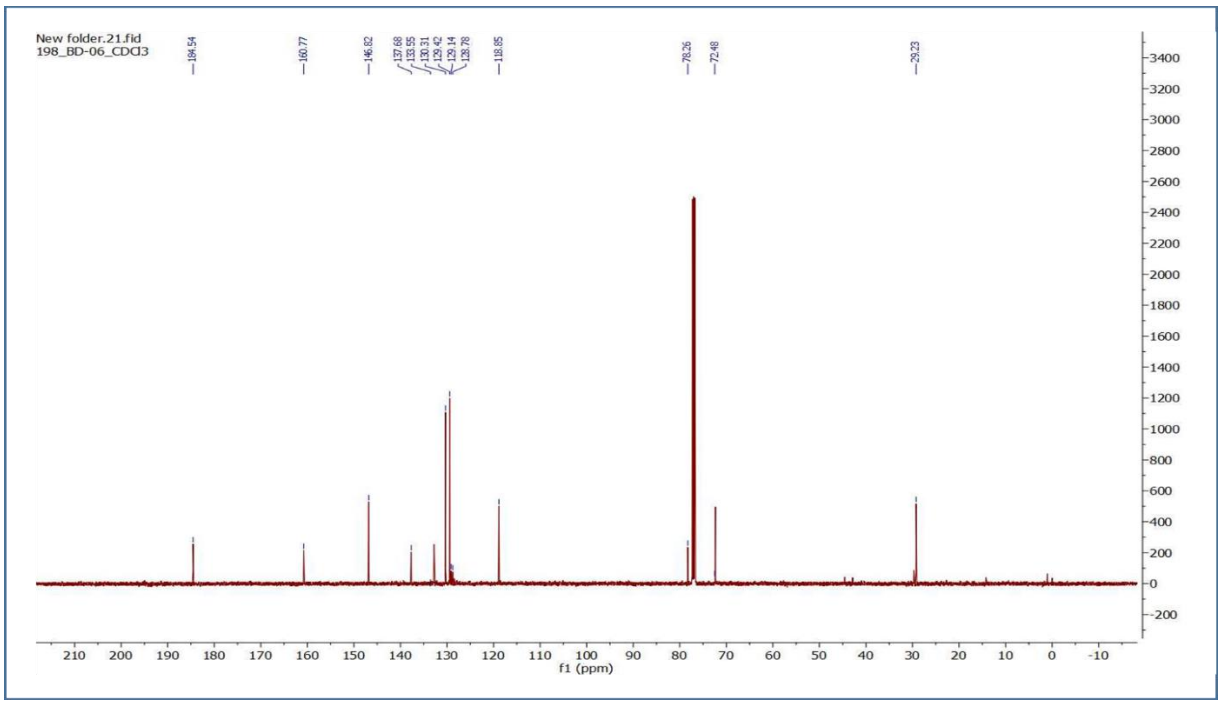
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD02





^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD03





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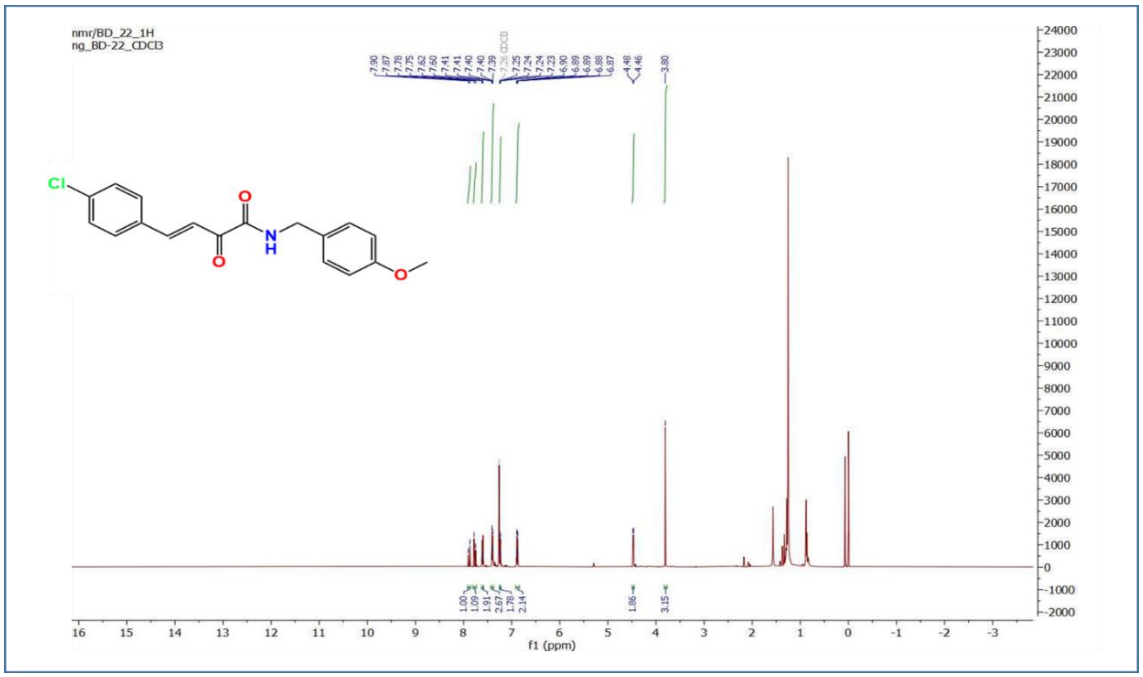

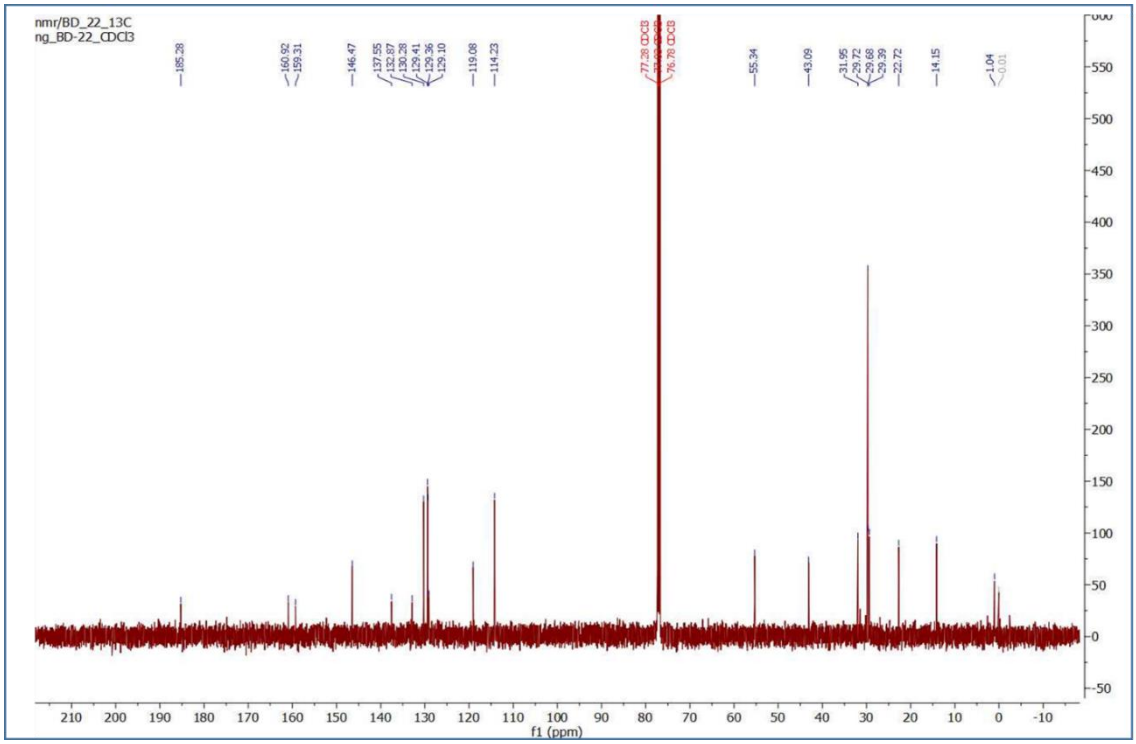

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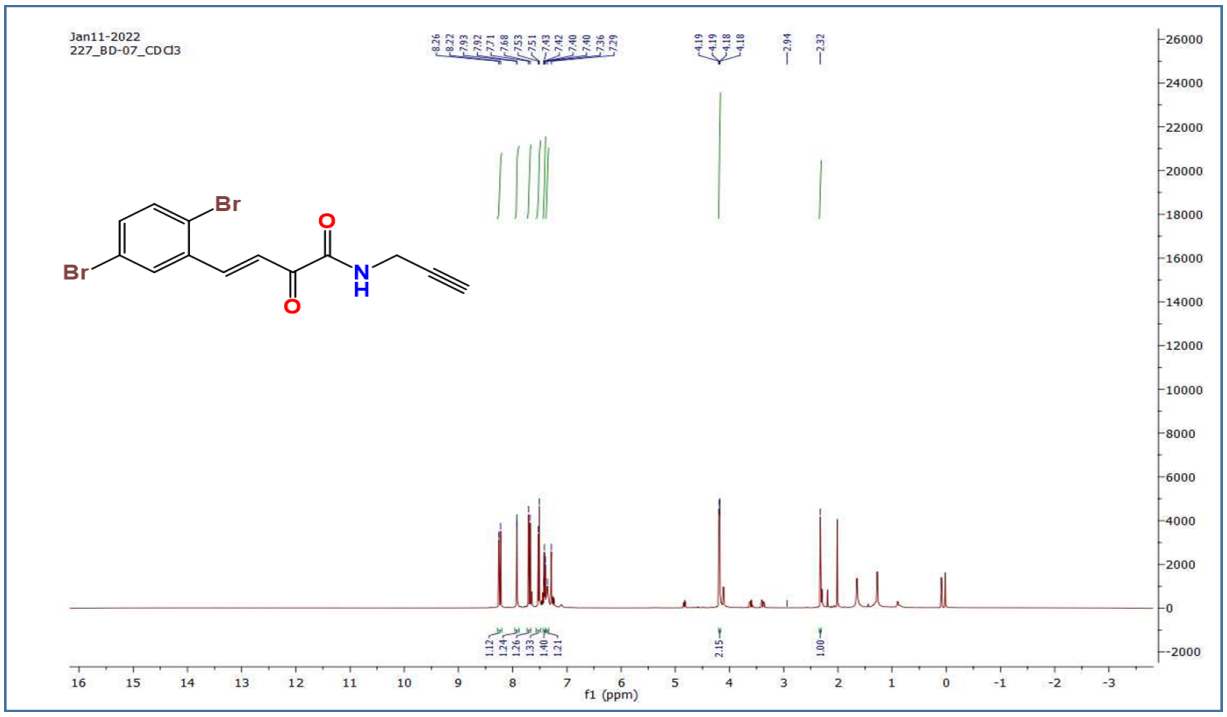

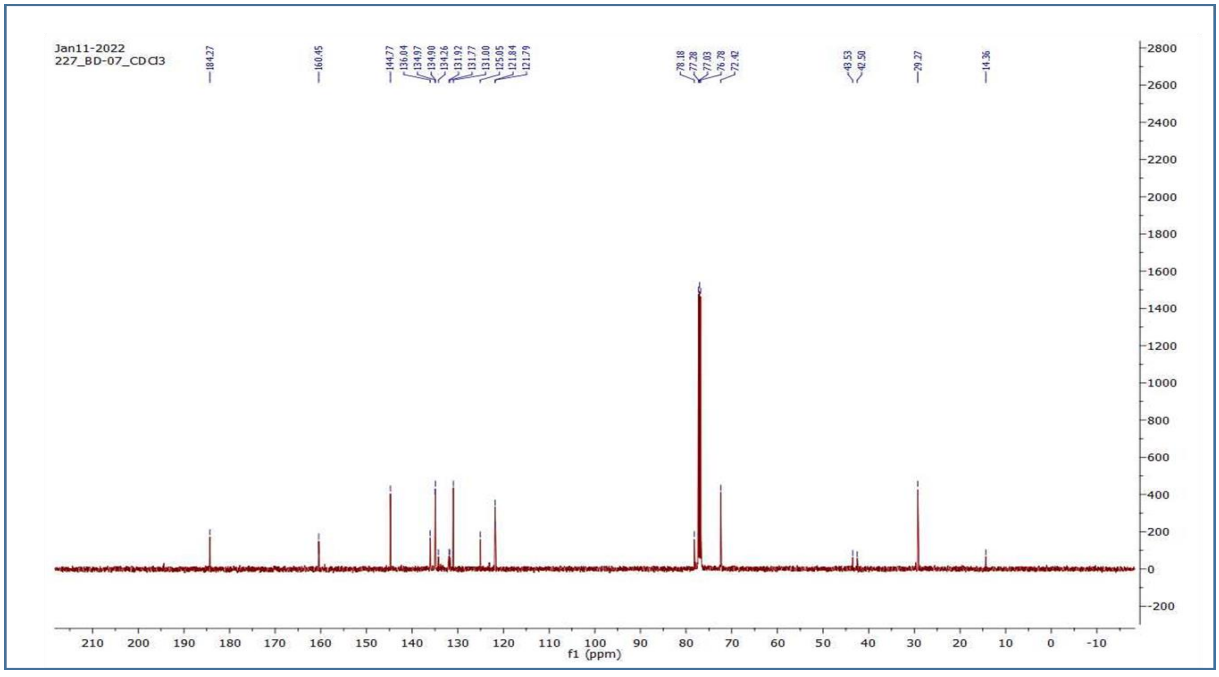

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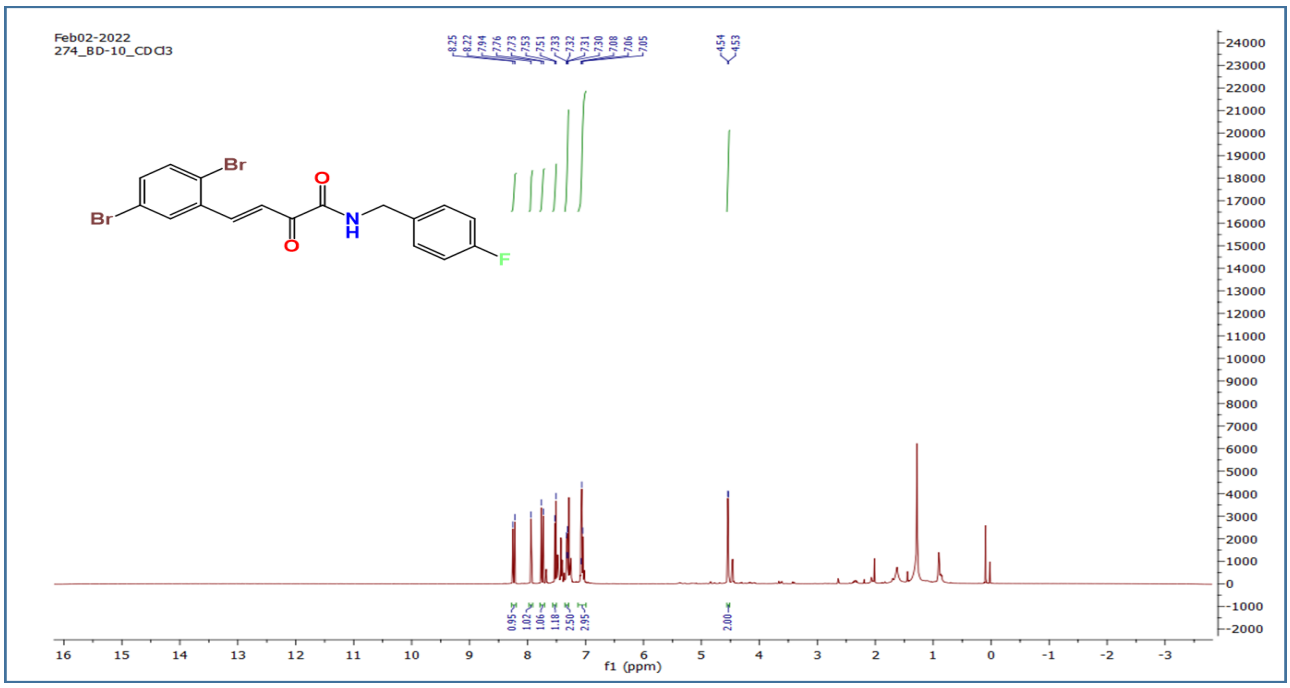
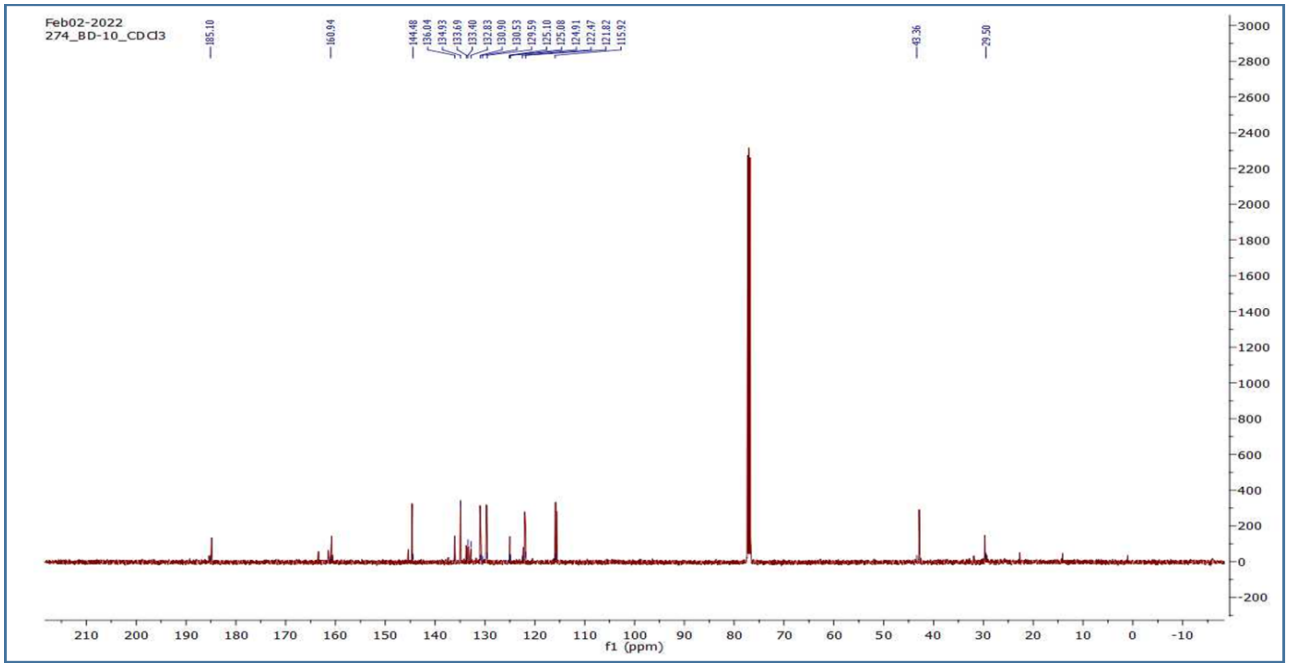
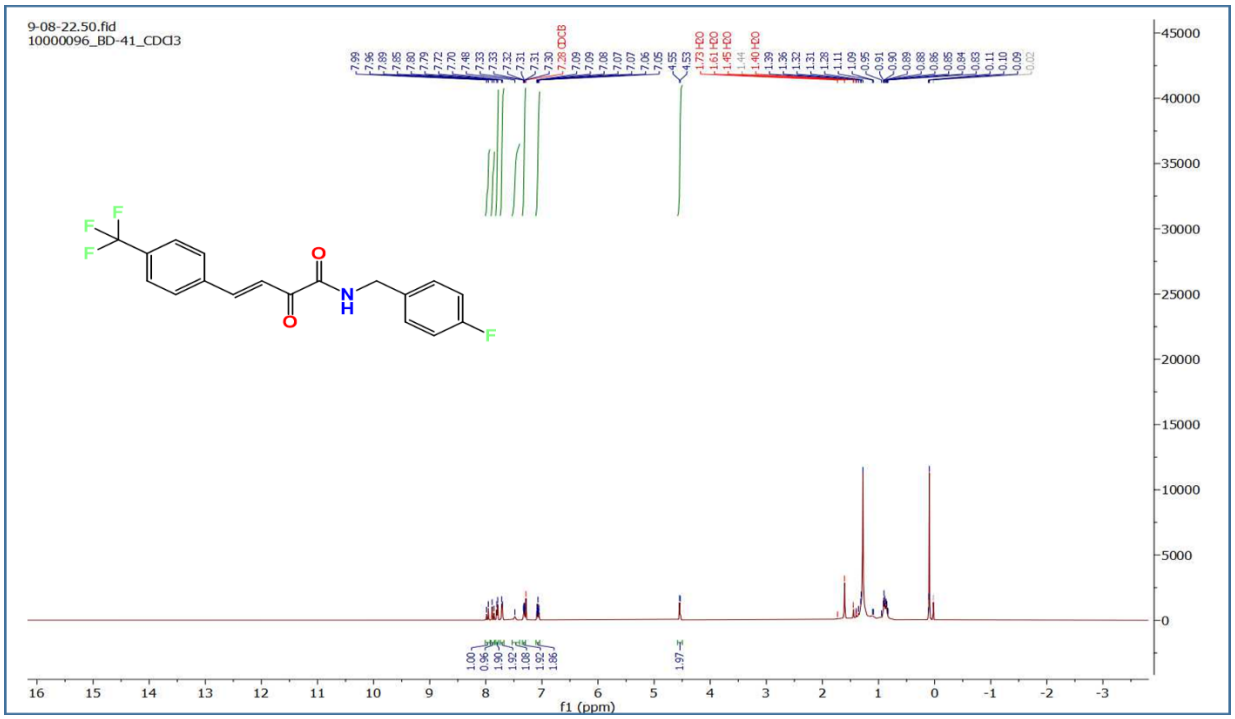
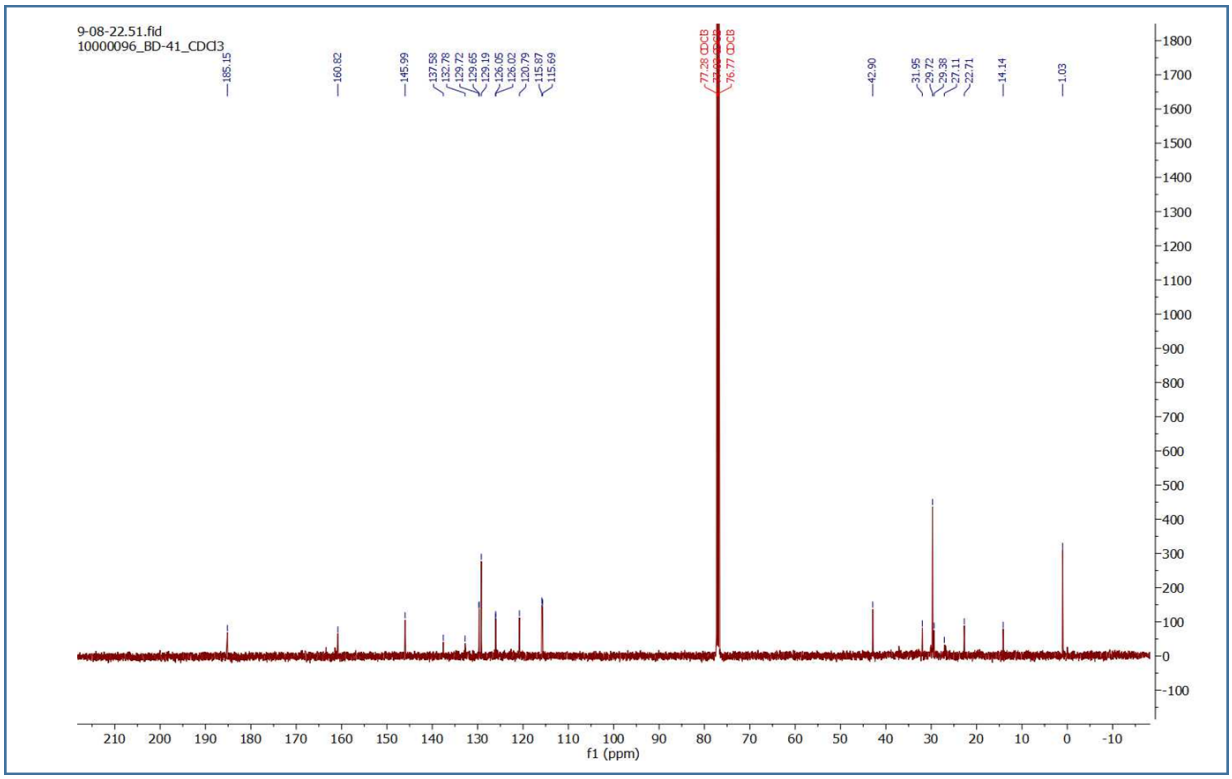


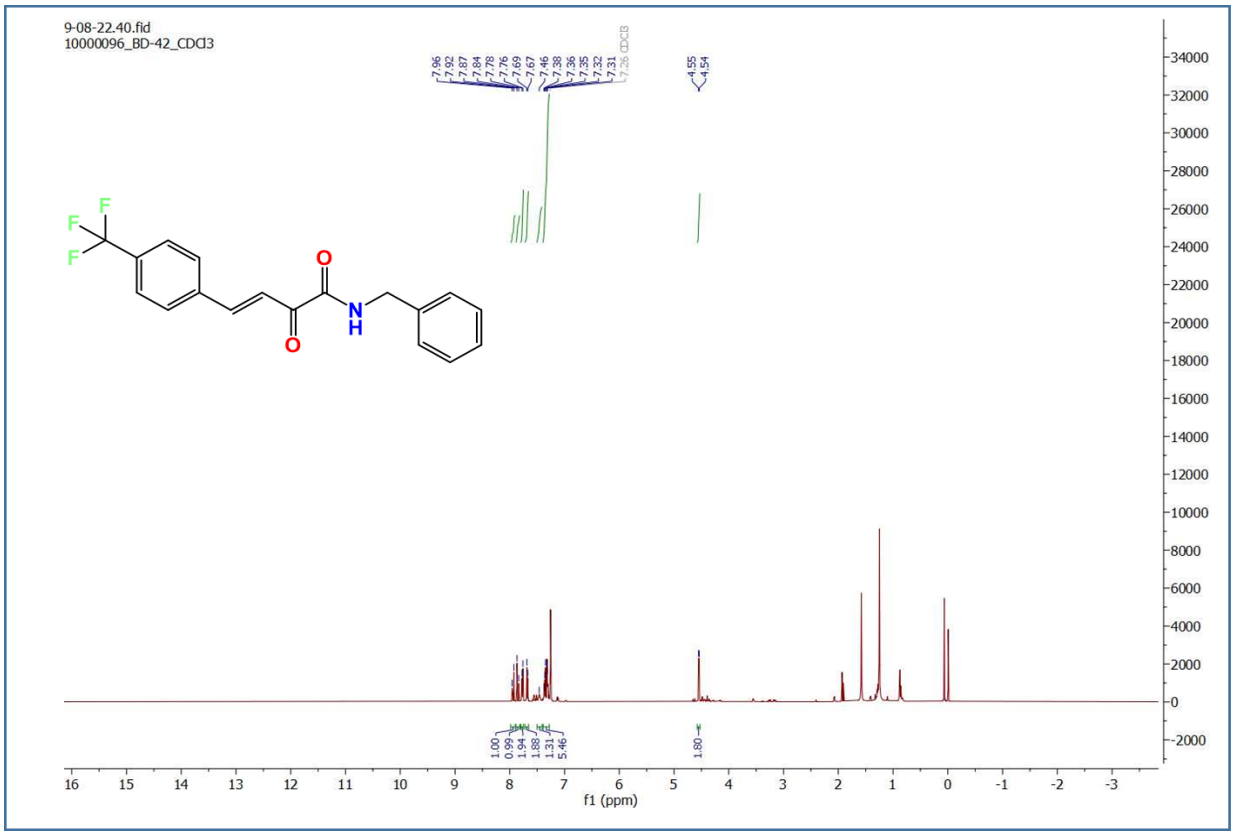


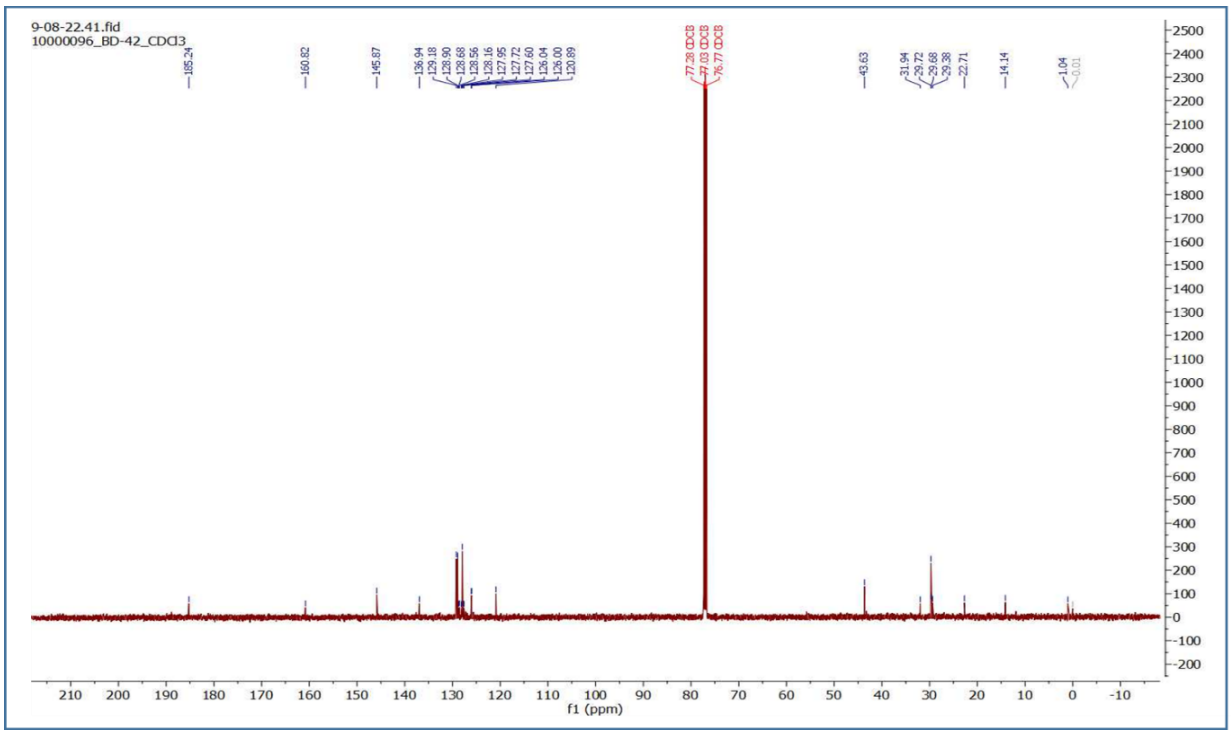
^{1}H, $^{13}C\{1H\}$ NMR spectra NMR of compound BD07



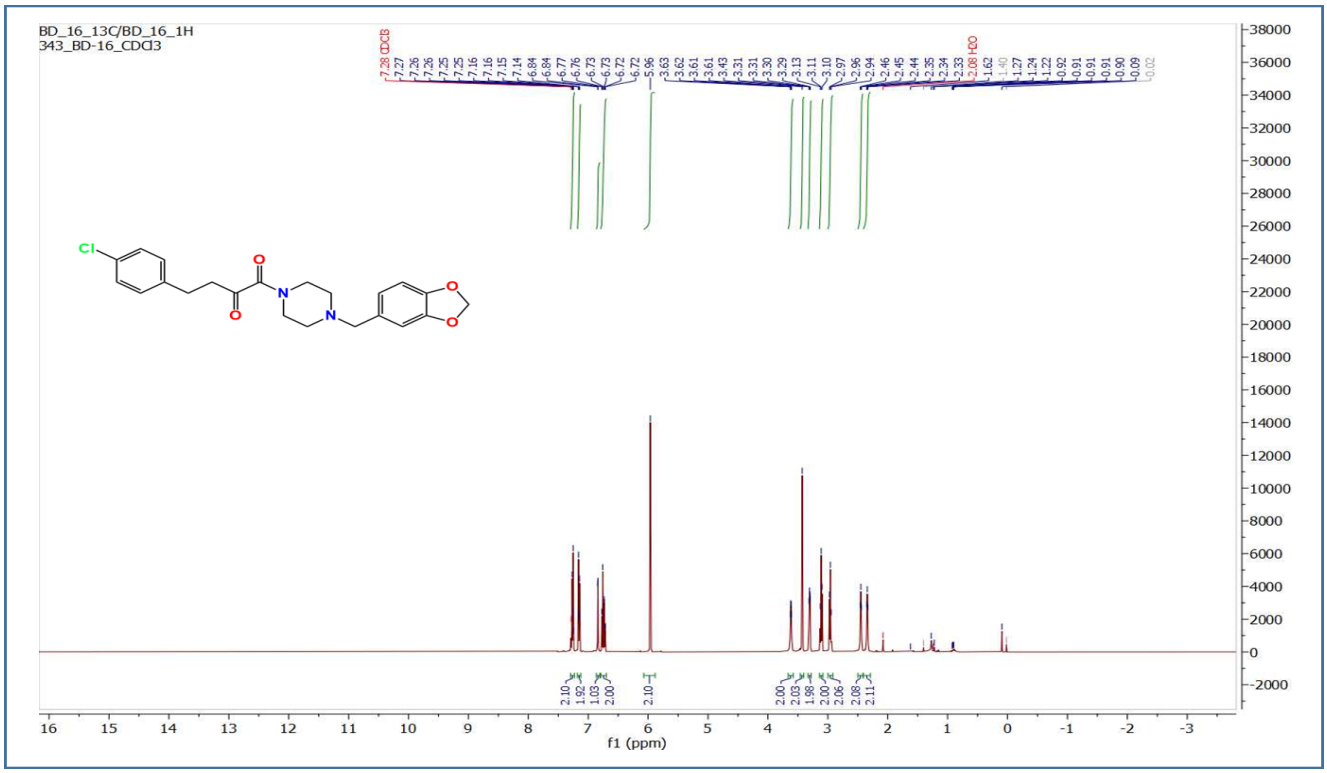


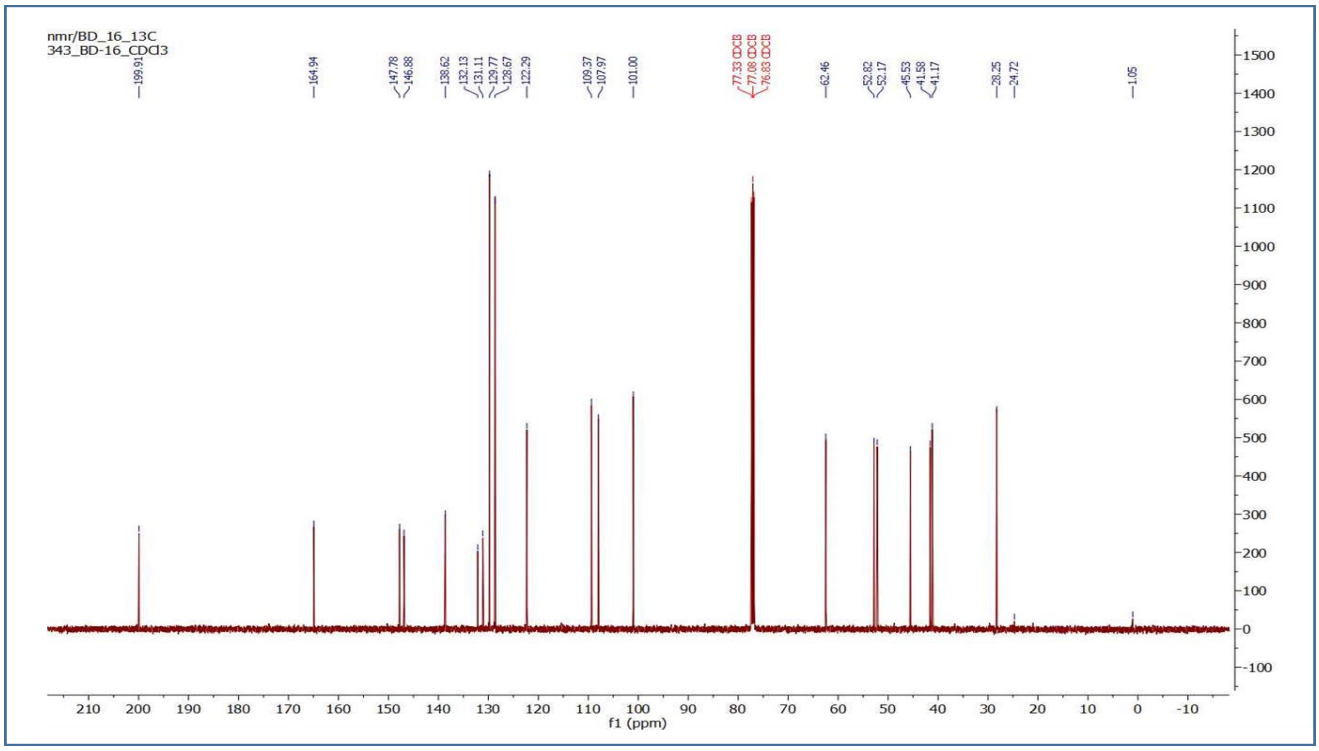
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD08



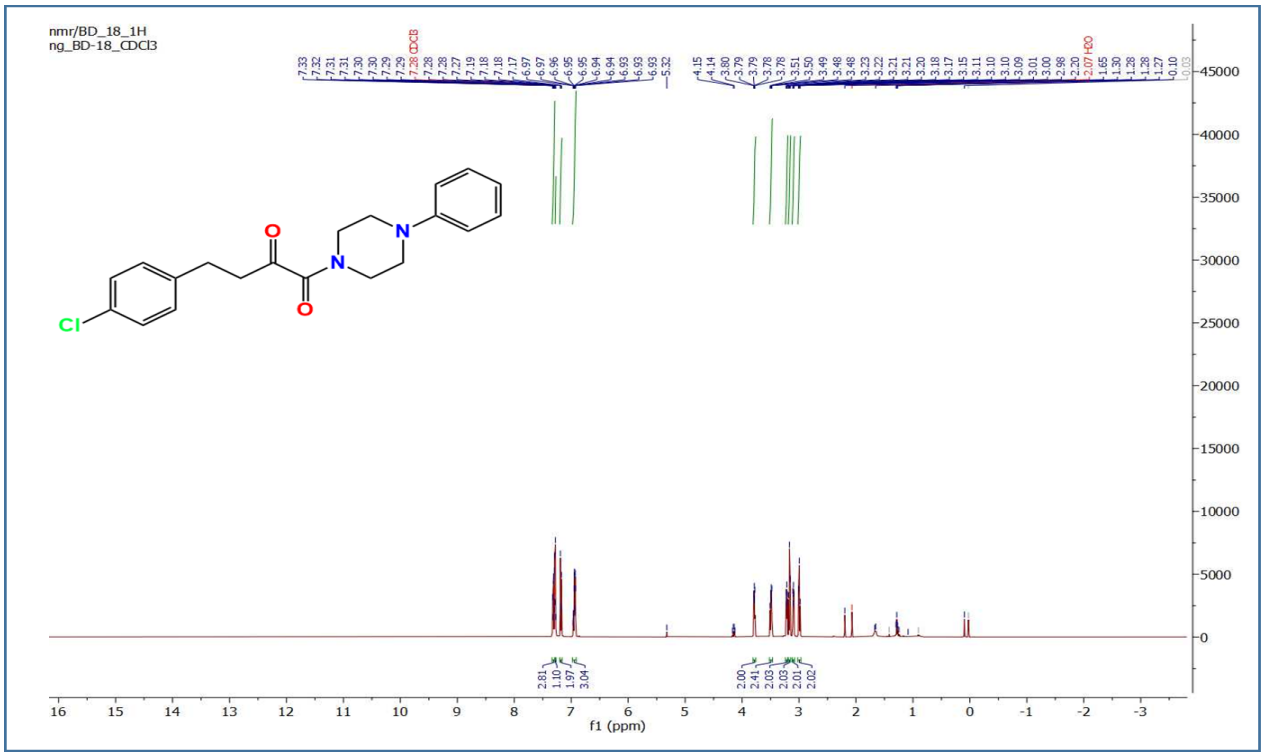


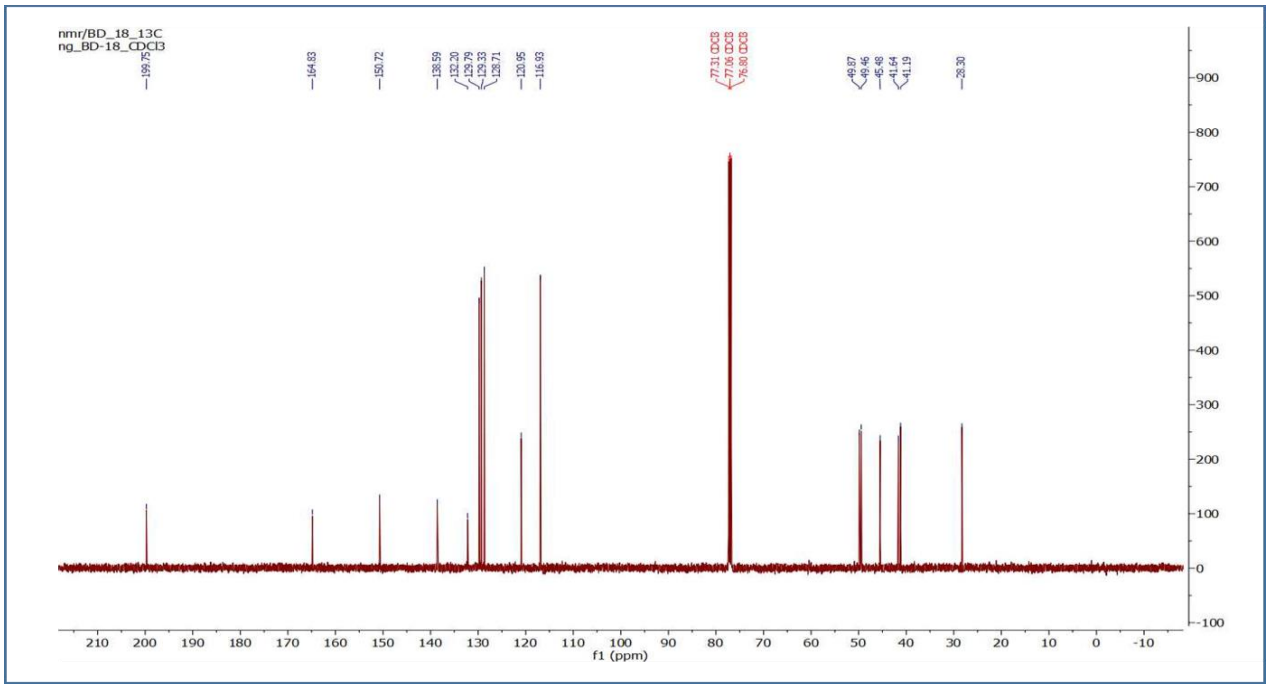
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD09



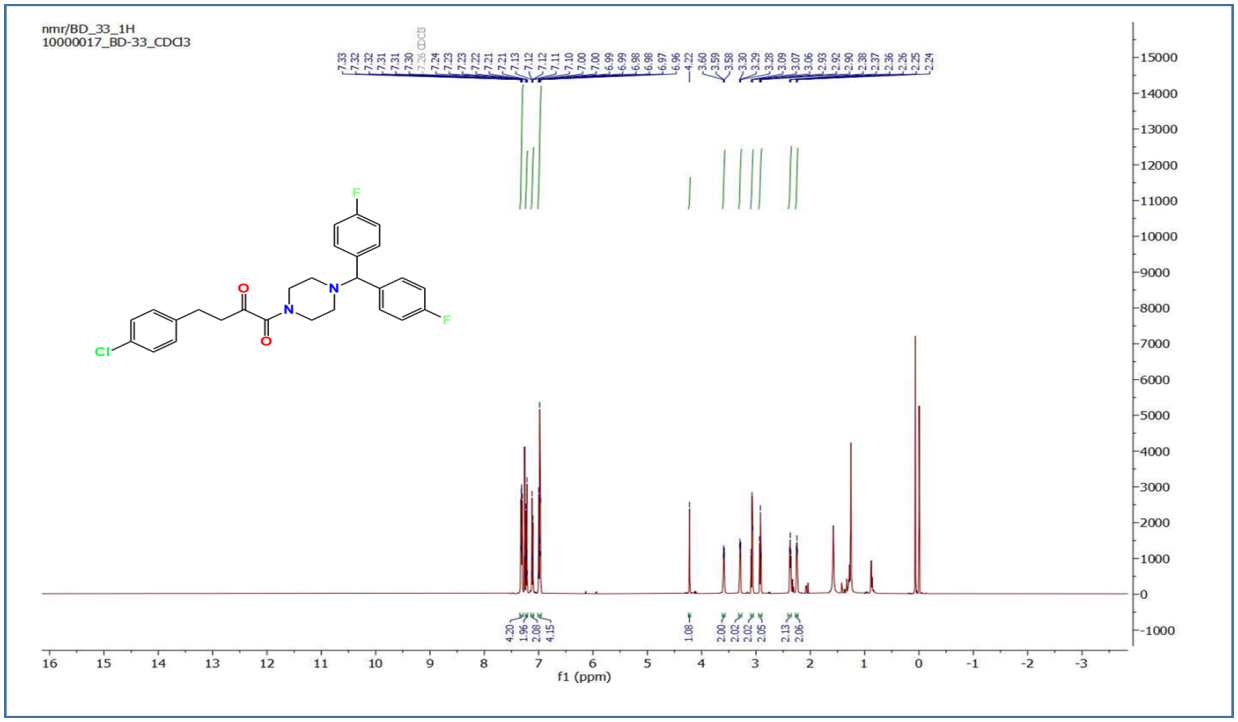


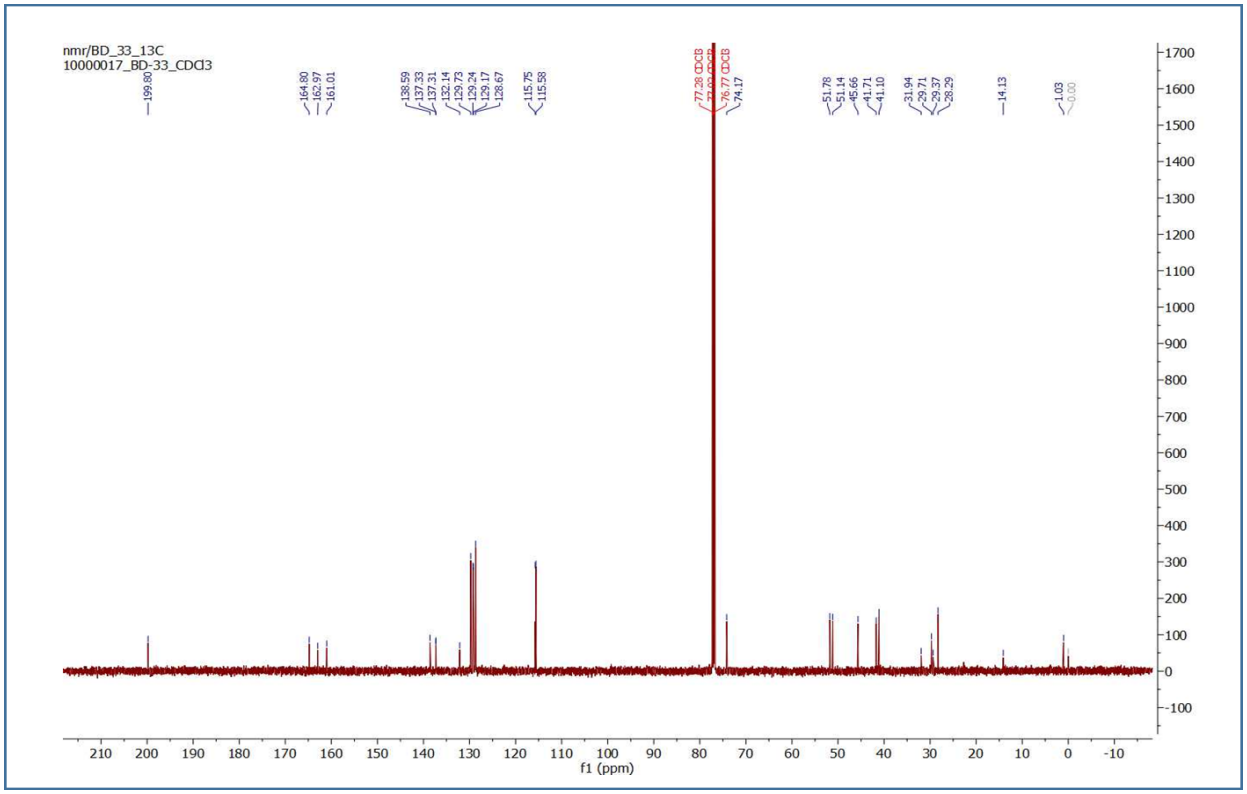
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD10



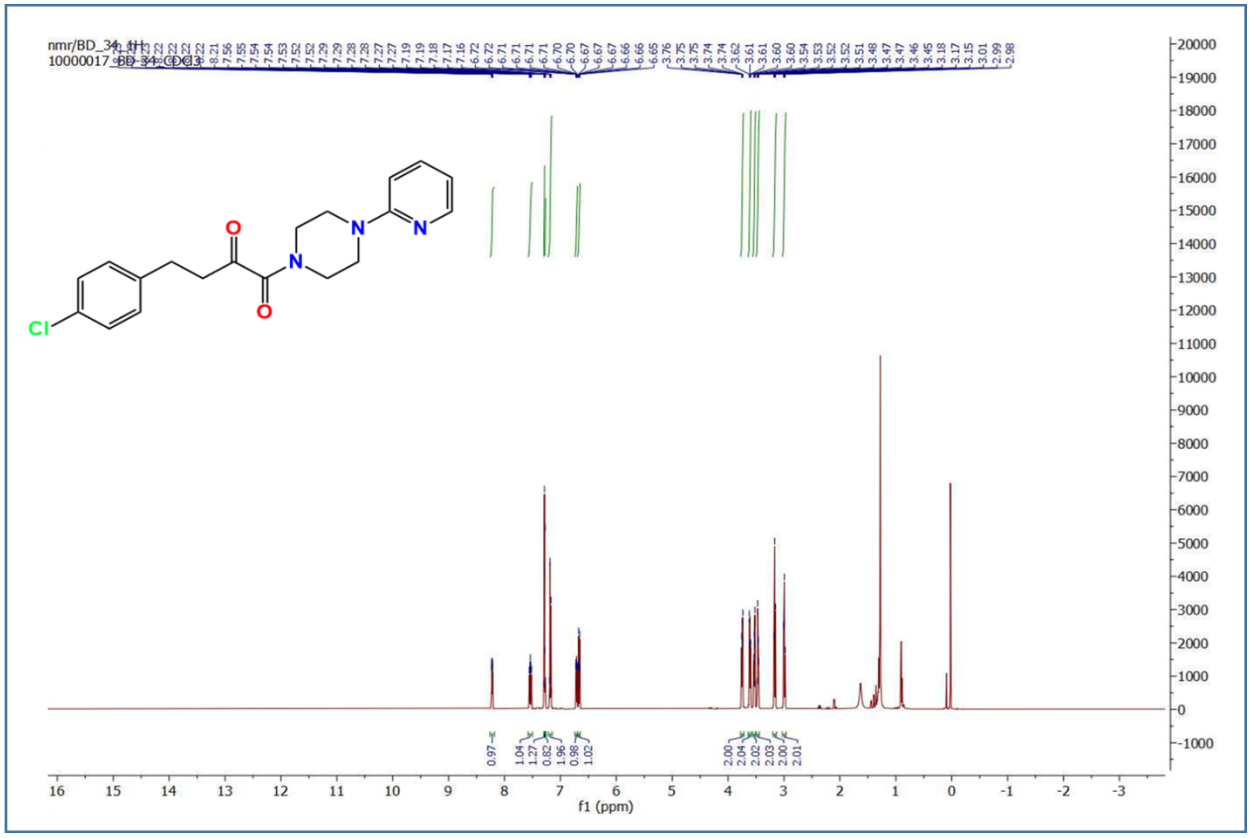


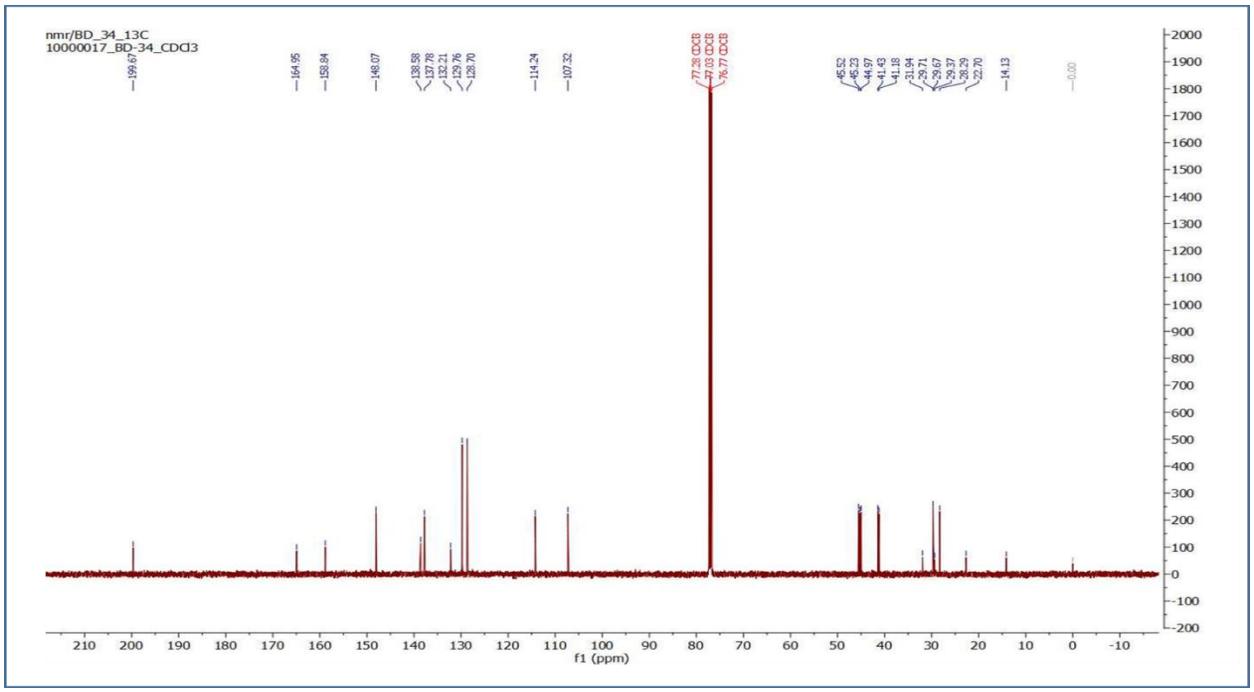
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD11



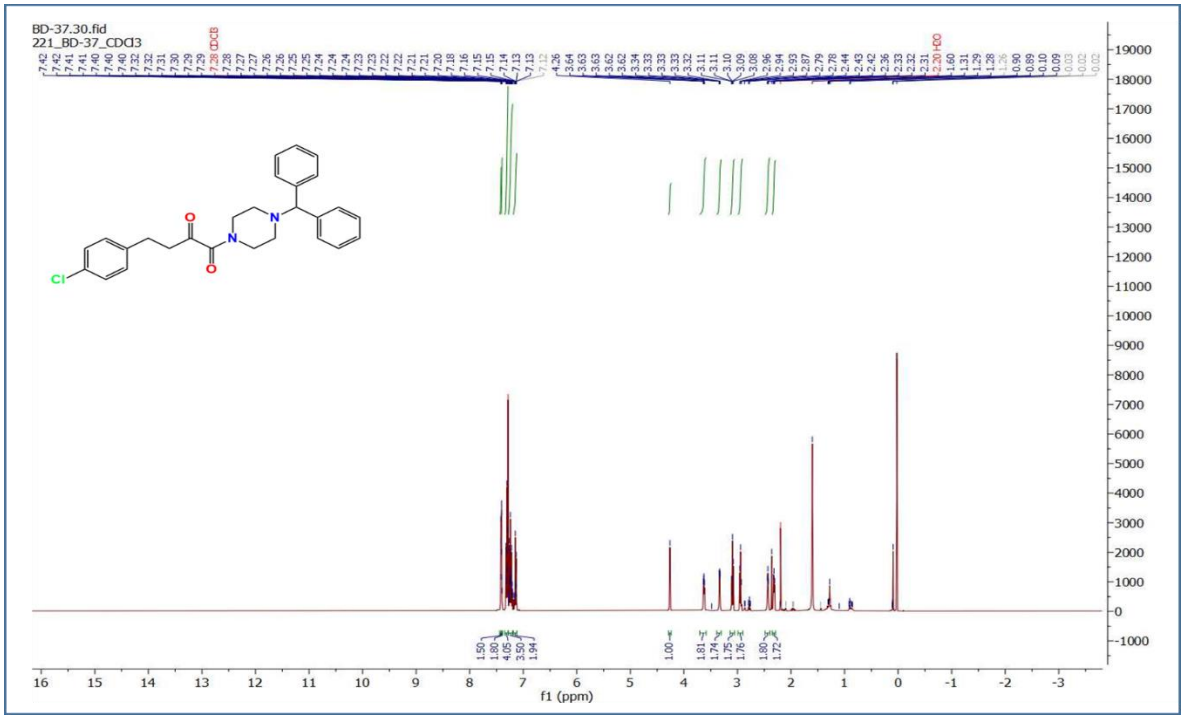


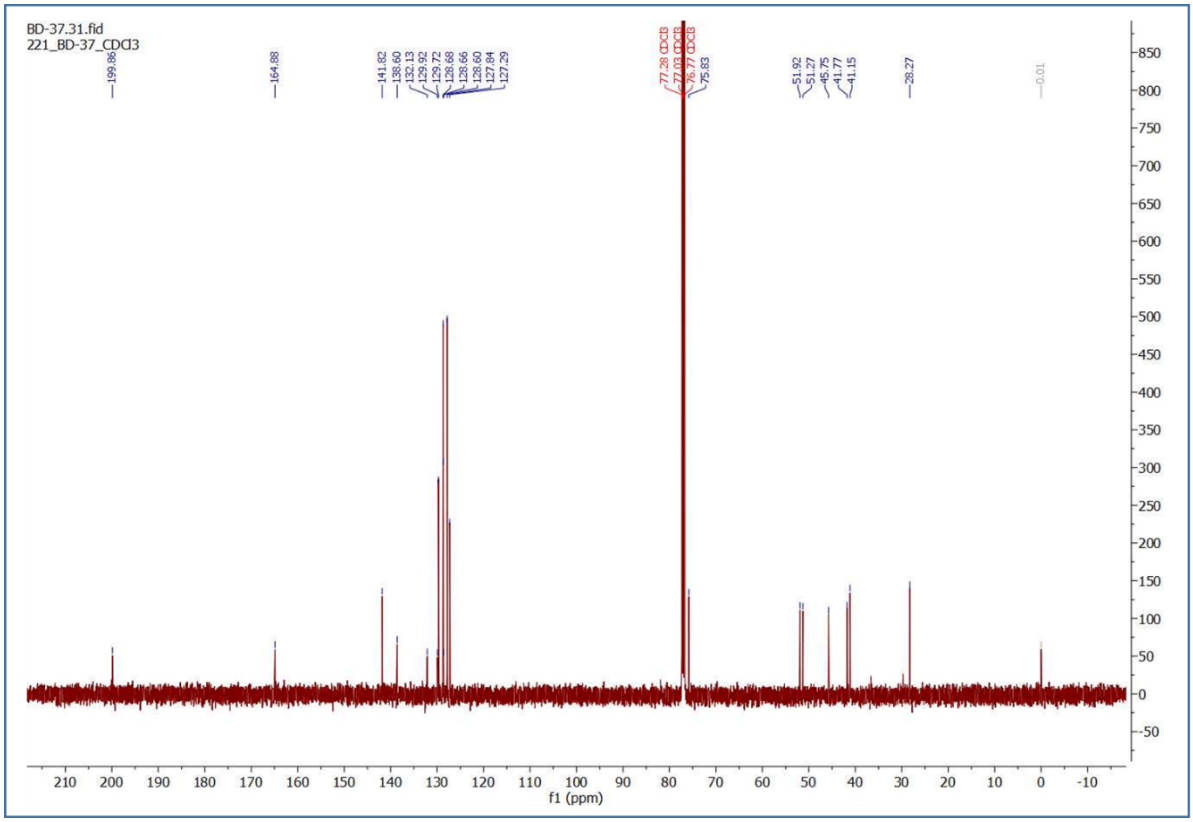
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD12



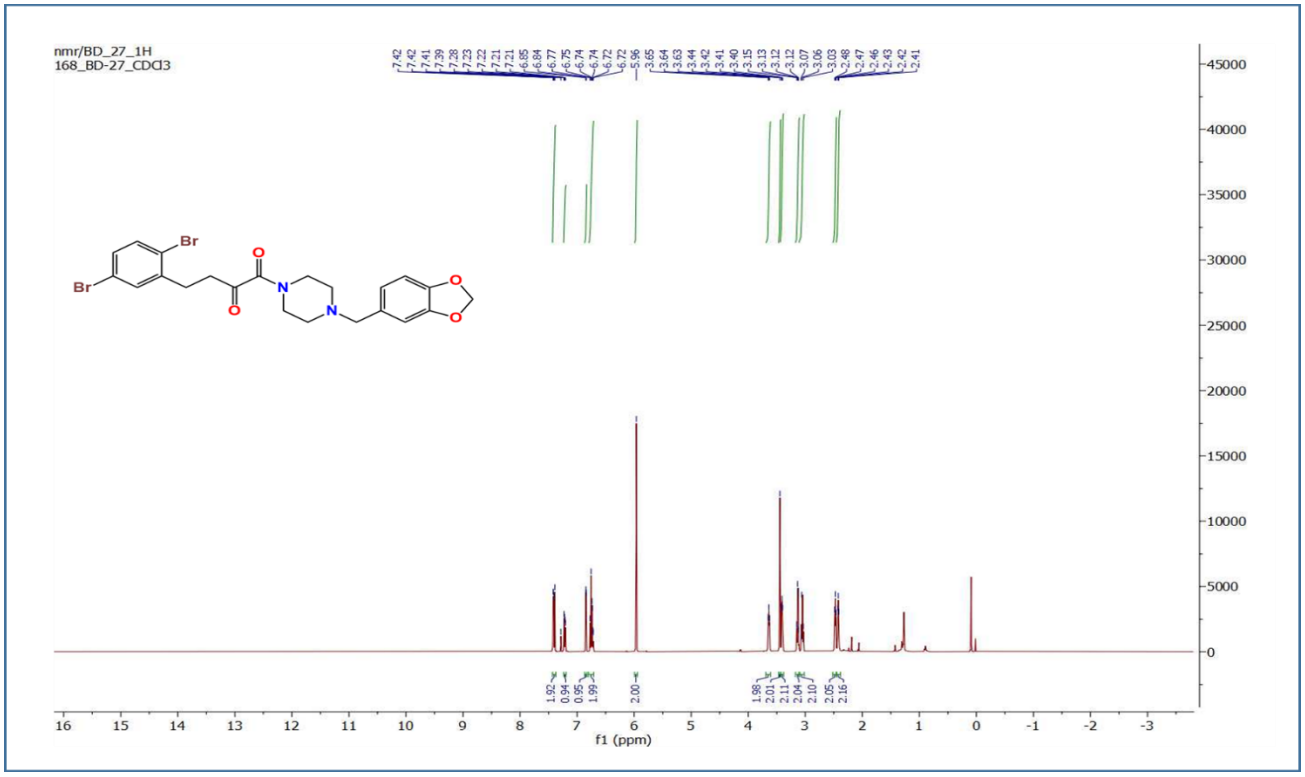


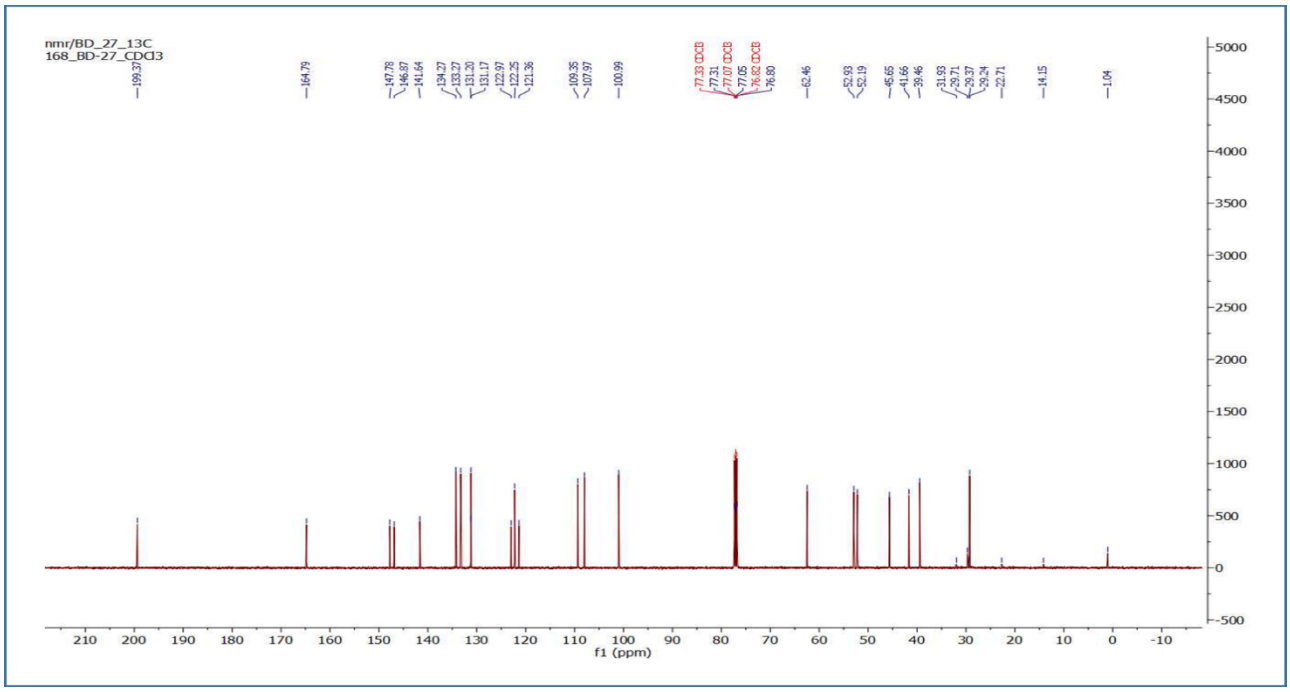
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD13



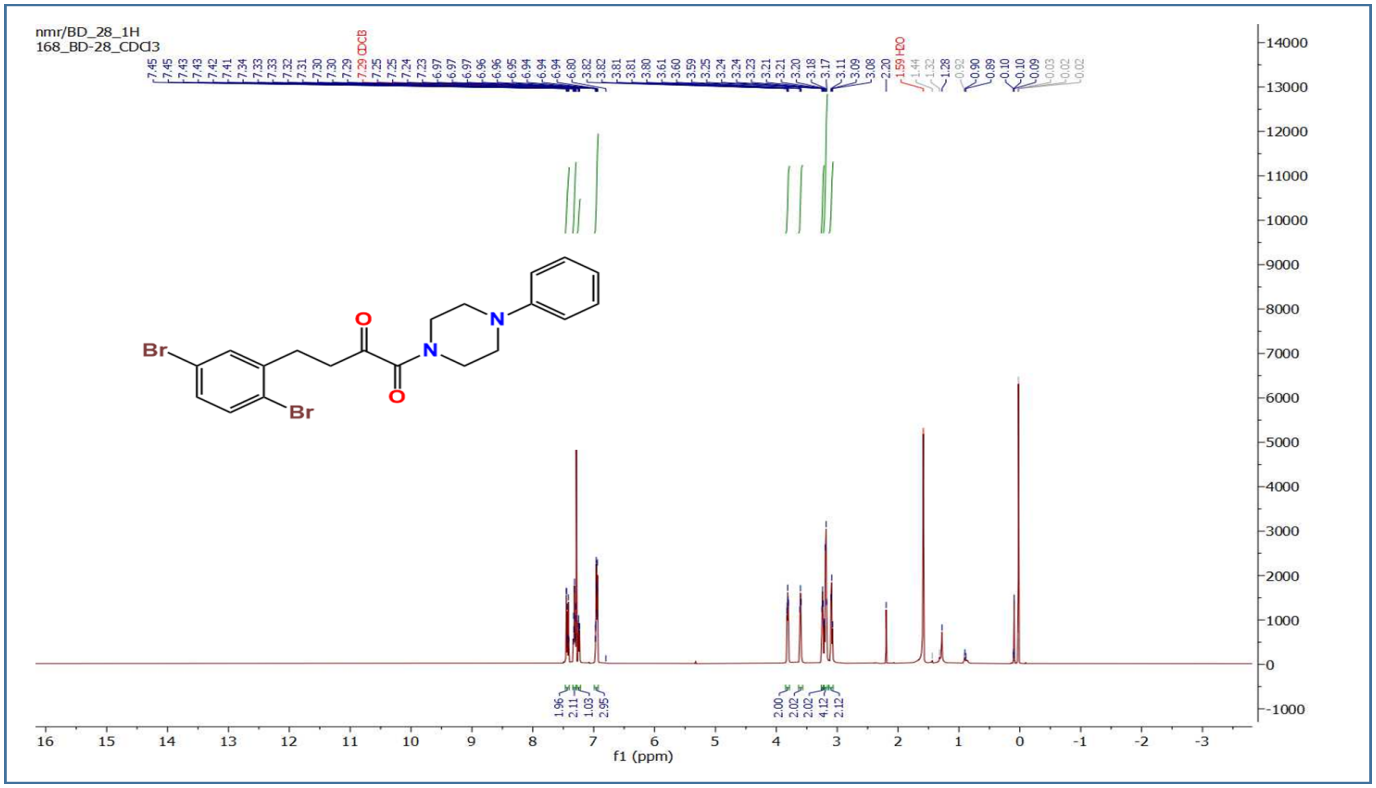


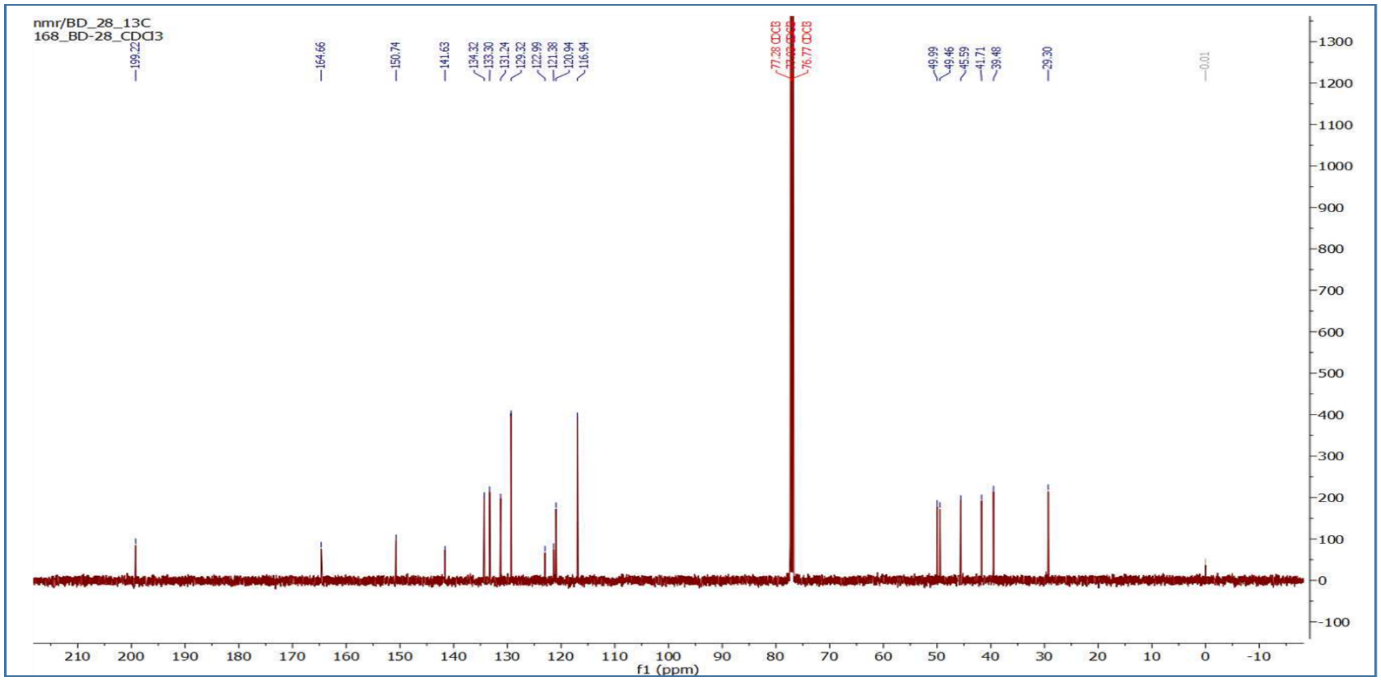
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD14



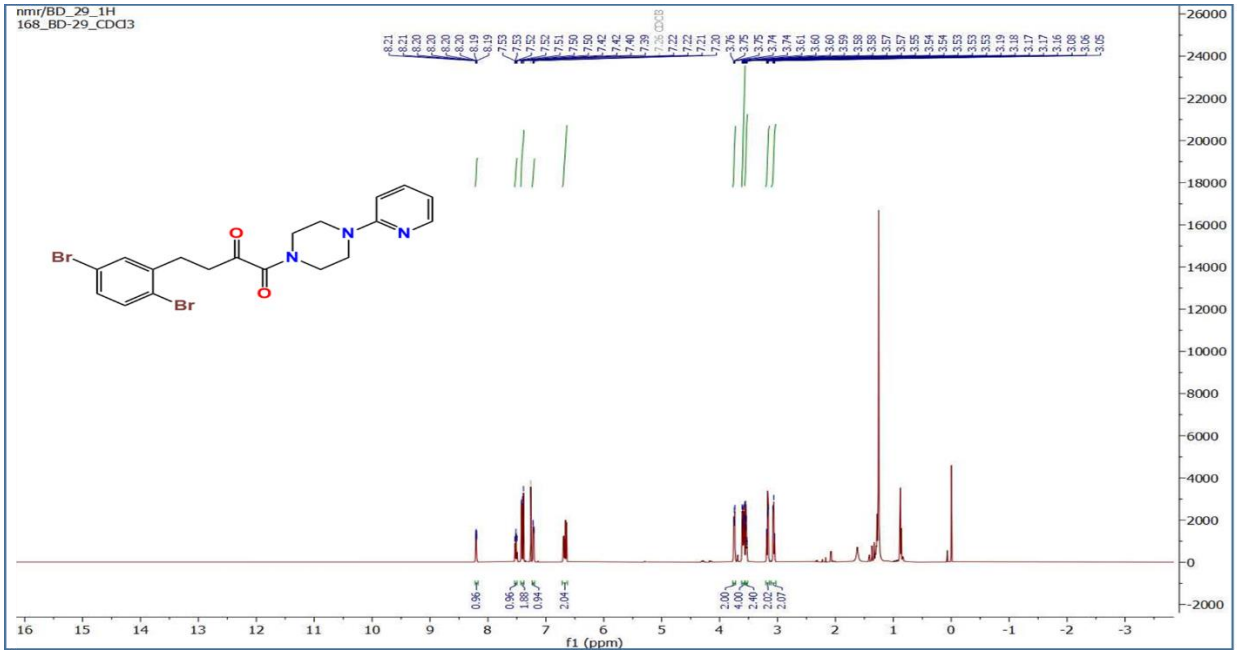


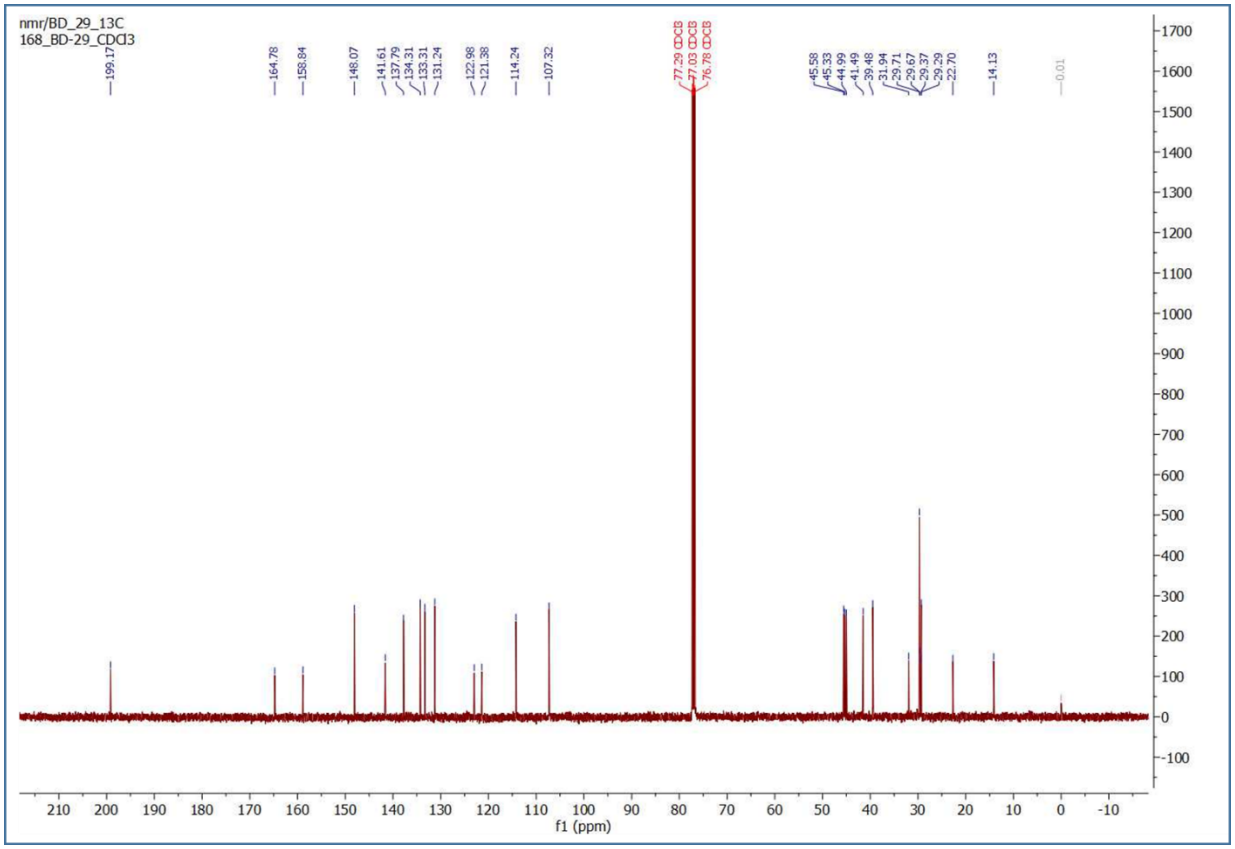
^{1}H, $^{13}C\{1H\}$ NMR spectra of compound BD15



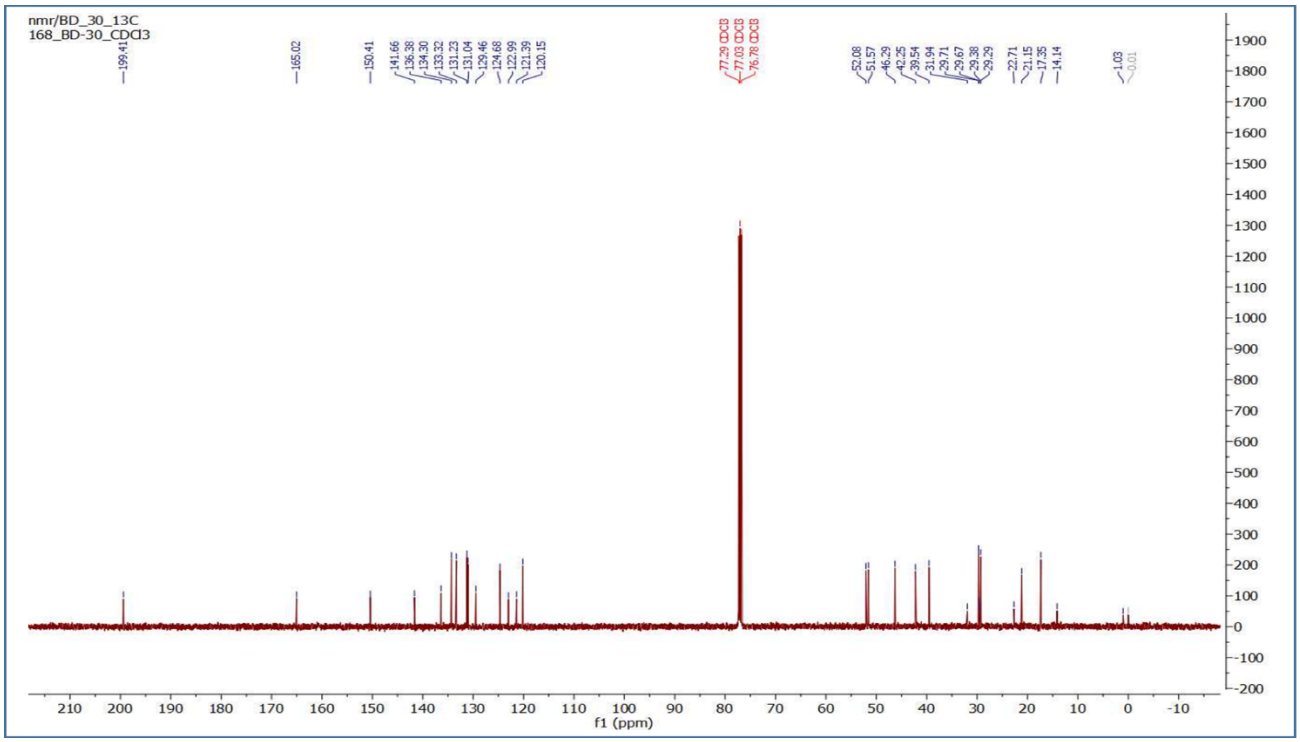


^{1}H, $^{13}C\{1H\}$ NMR spectra of BD16





^{1}H, $^{13}C\{1H\}$ NMR spectra of BD17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131.23
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129.46
124.68
122.99
121.39
120.15
77.29 CDCl3
77.03 CDCl3
76.78 CDCl3
52.08
51.57
46.29
42.25
39.54
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29.29
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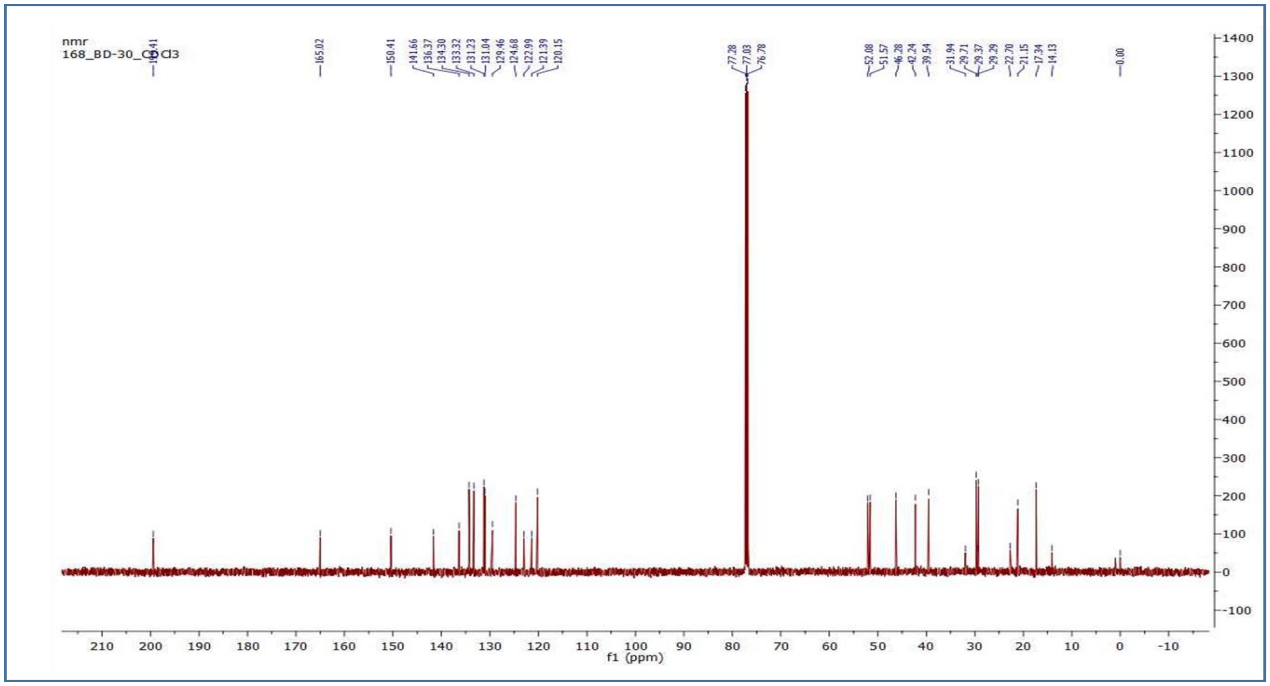
21.15
17.35
14.14
1.03
0.01
f1 (ppm)


nmr
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165.02
150.41
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136.37
134.30
133.32
131.23
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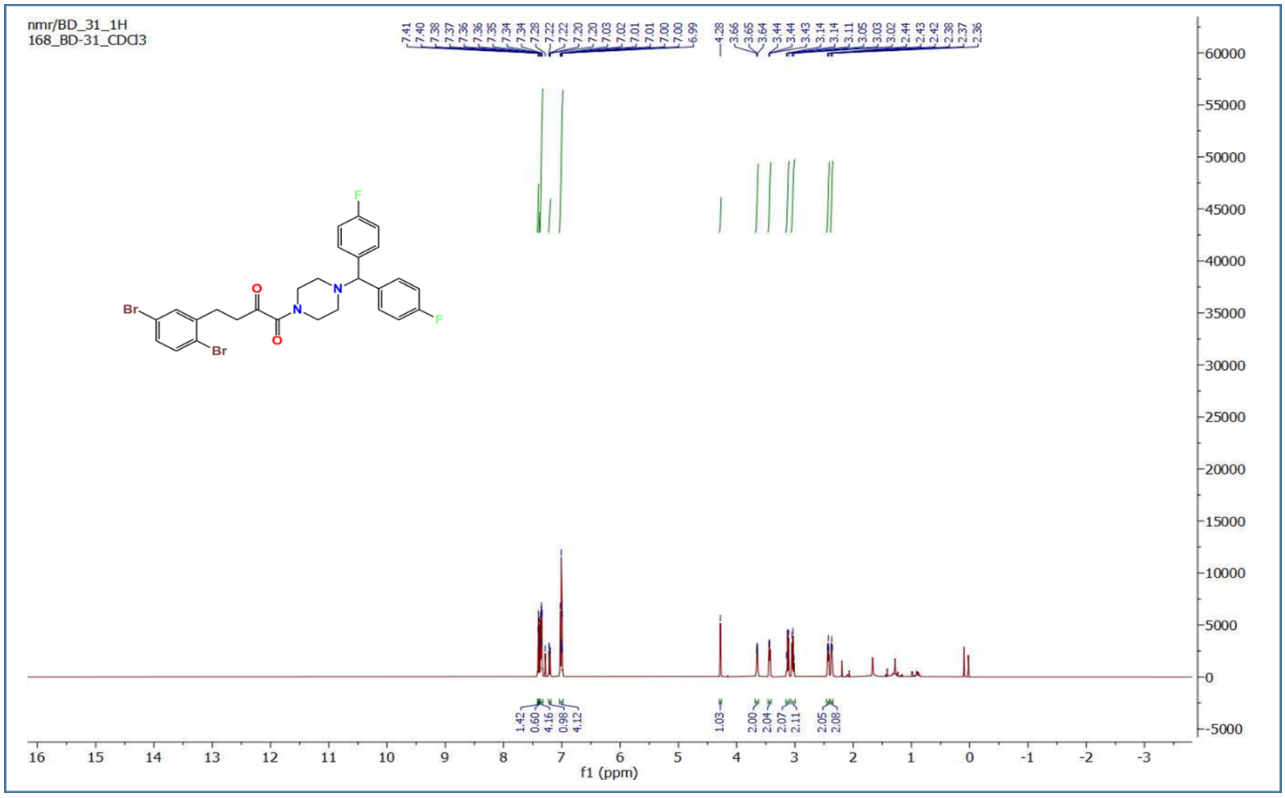
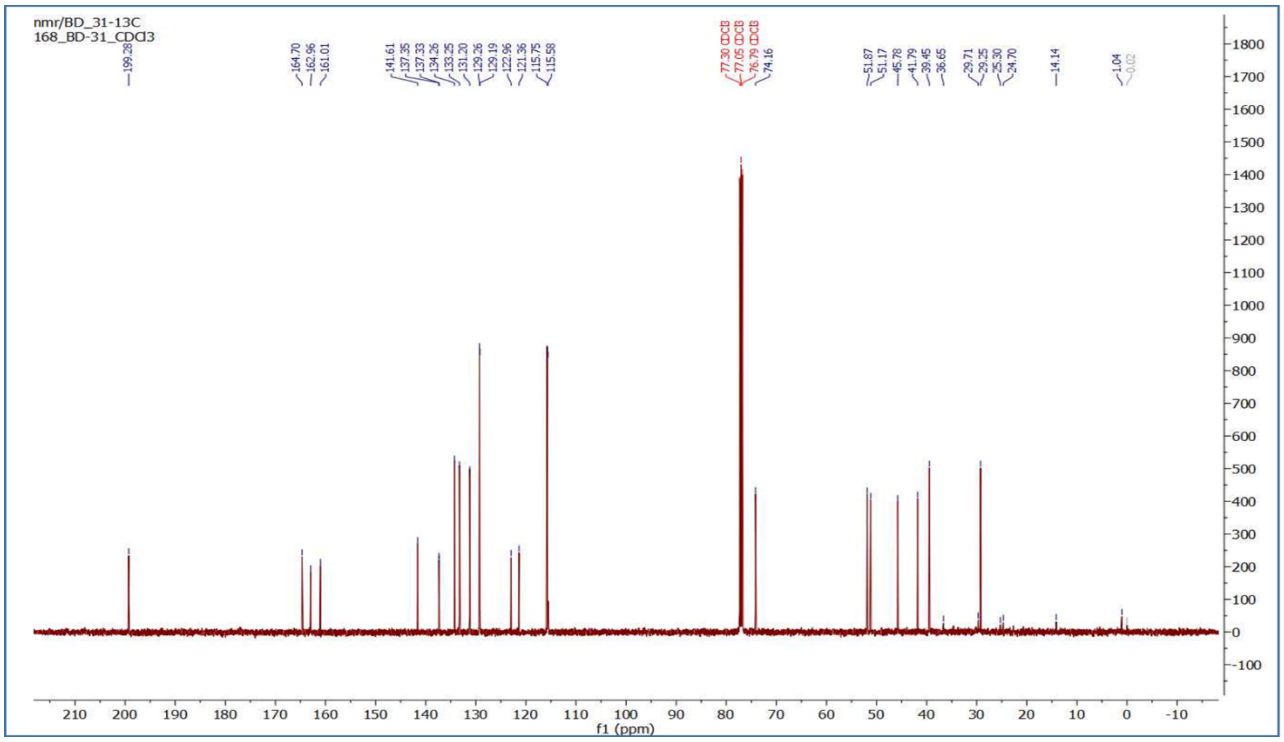
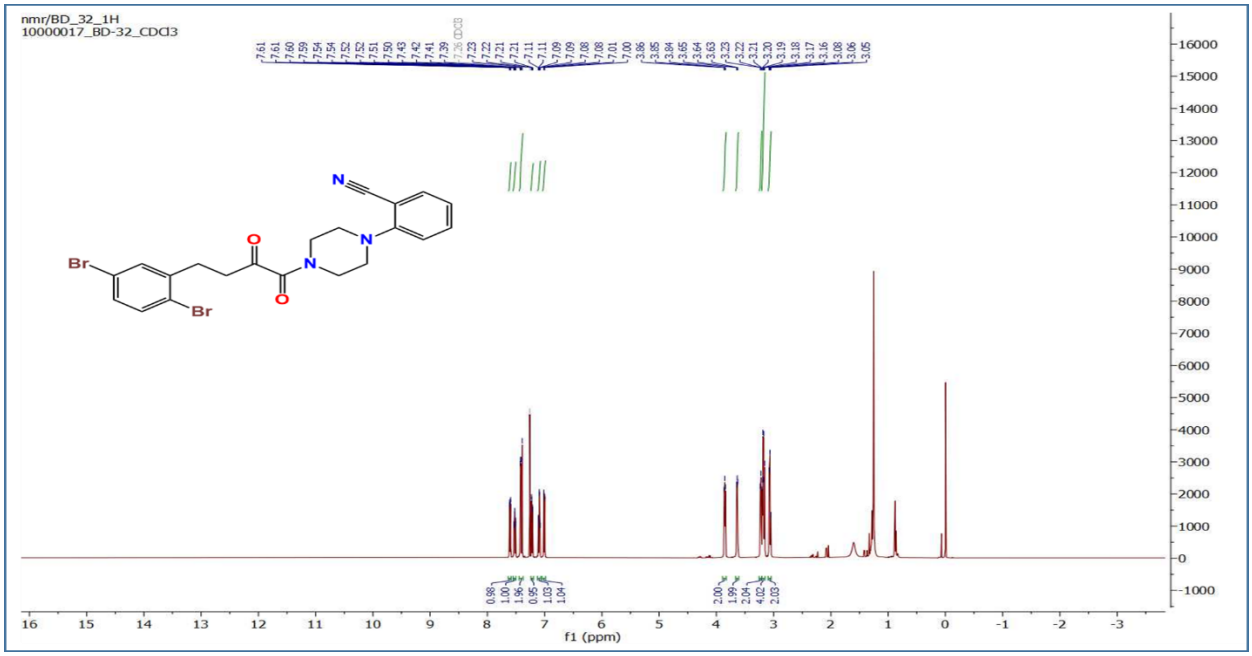
124.68
122.99
121.39
120.15
77.28
77.03
76.78
52.08
51.57
46.28
42.24
39.54
31.94
29.71
29.37
29.29
22.70
21.15
17.34
14.13
0.00
f1 (ppm)

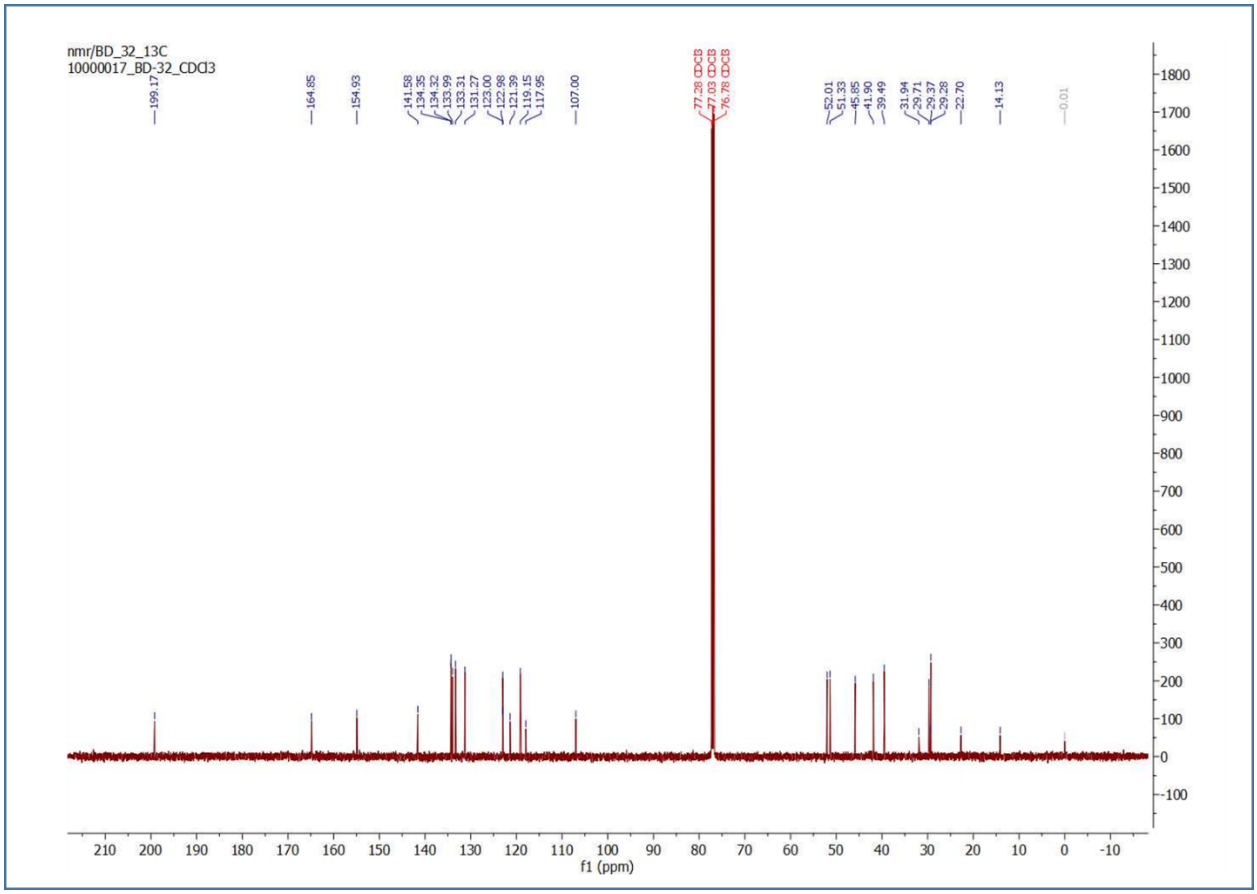
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD18



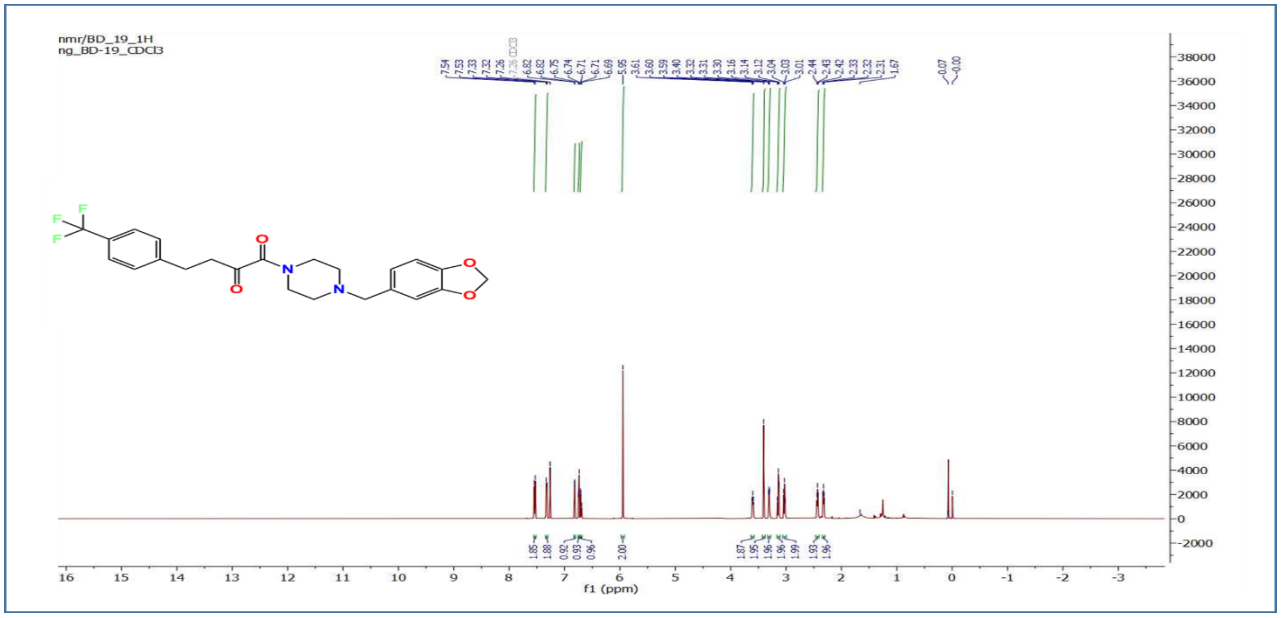


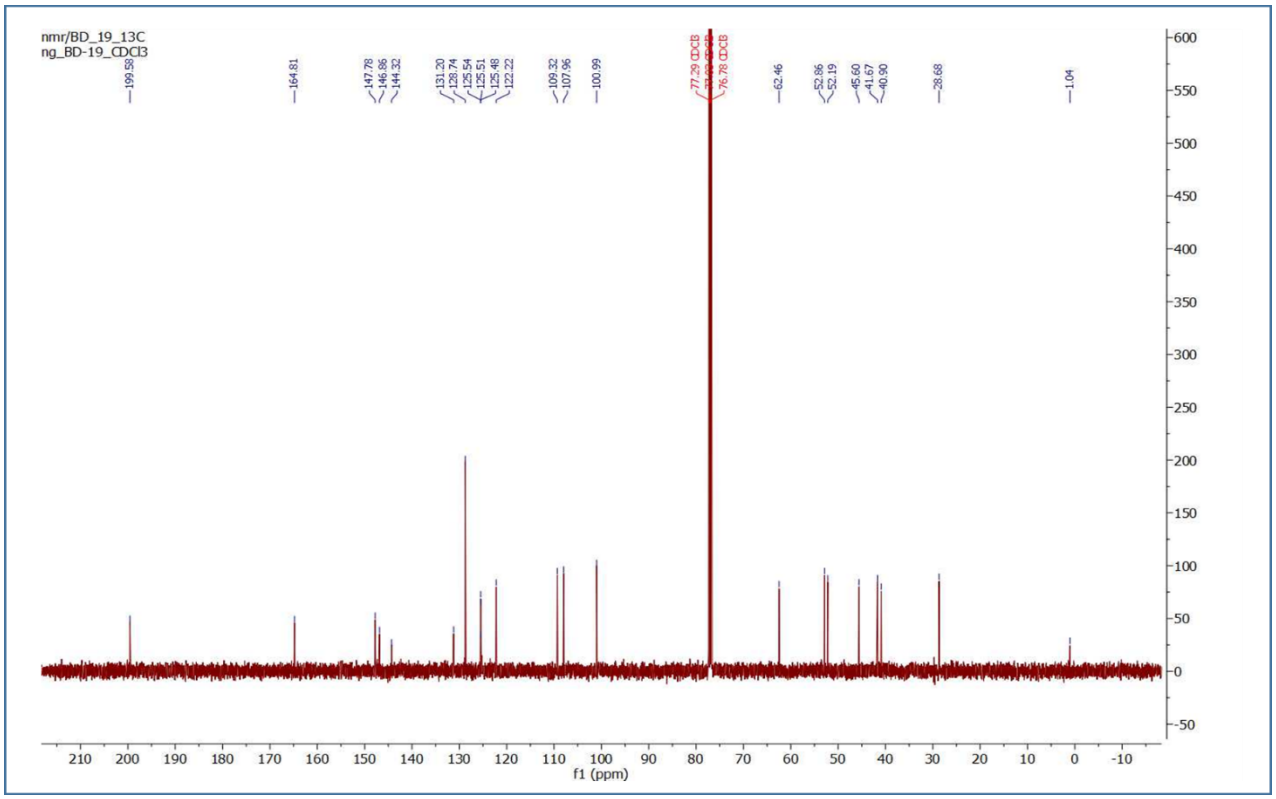
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD19



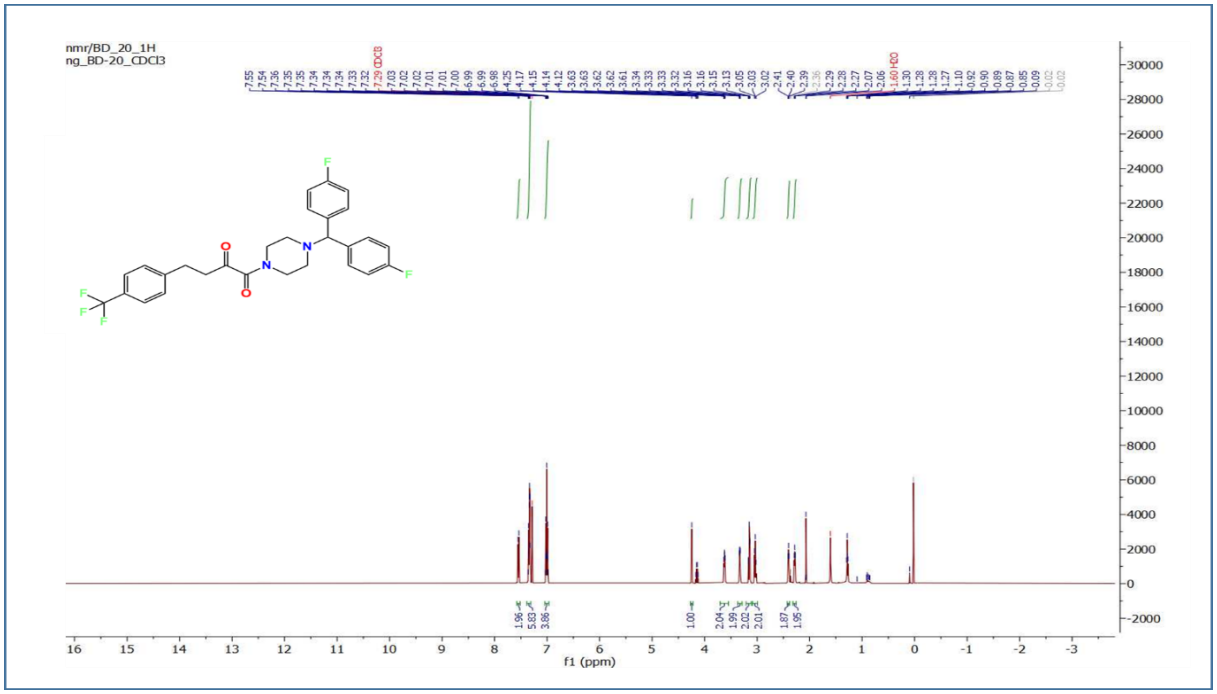


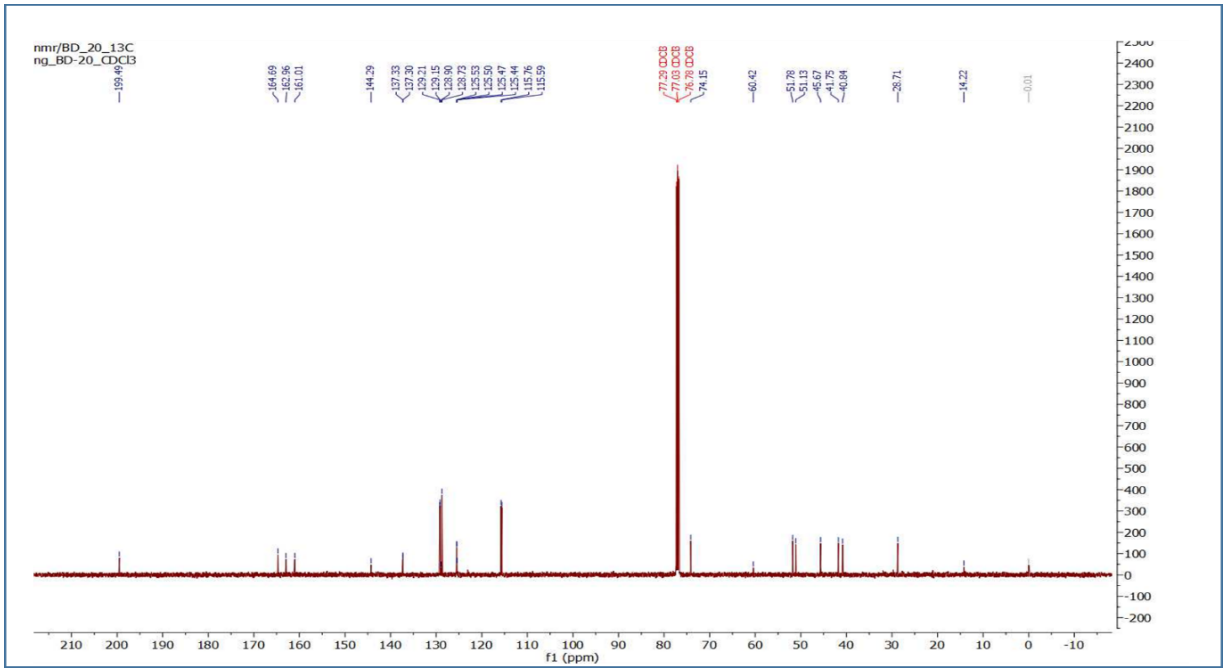
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD20



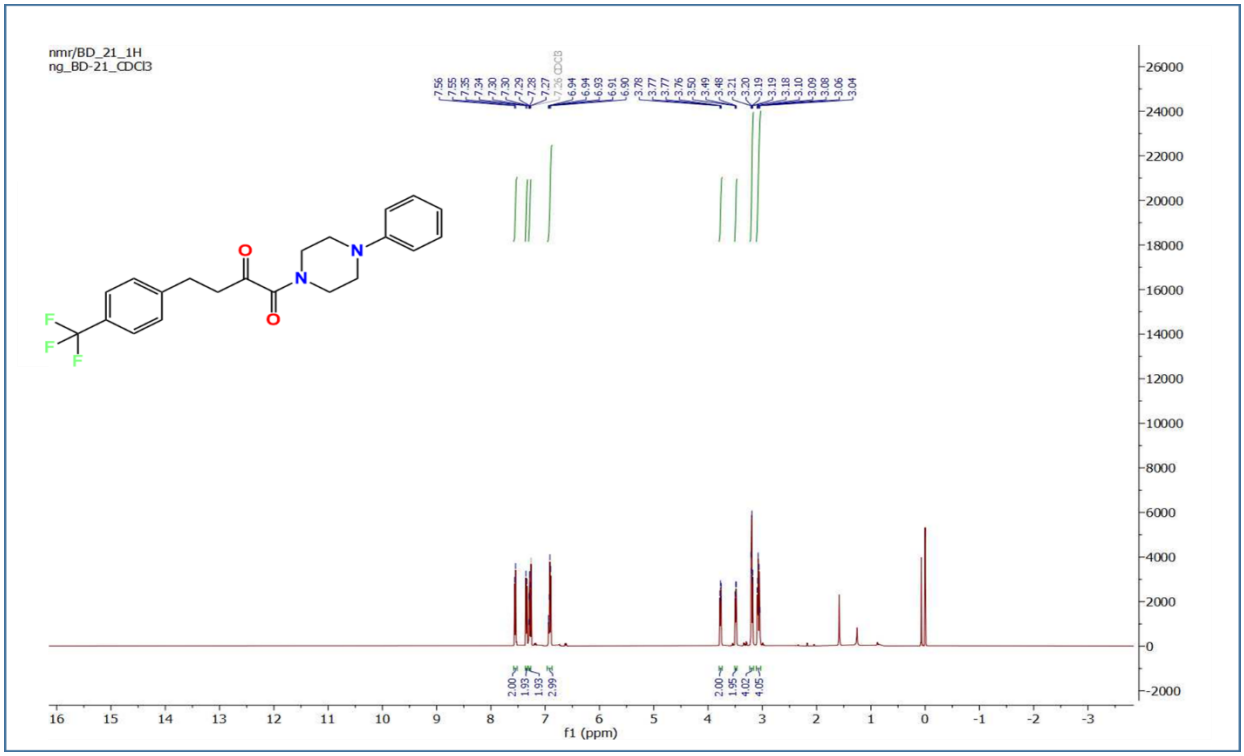


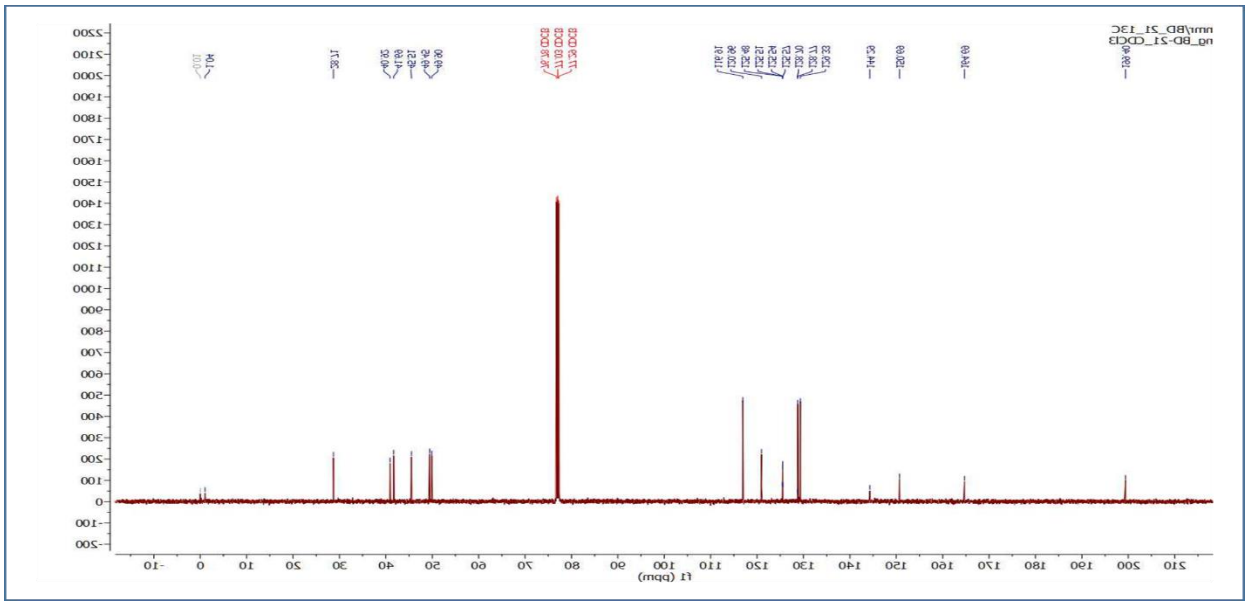
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD21



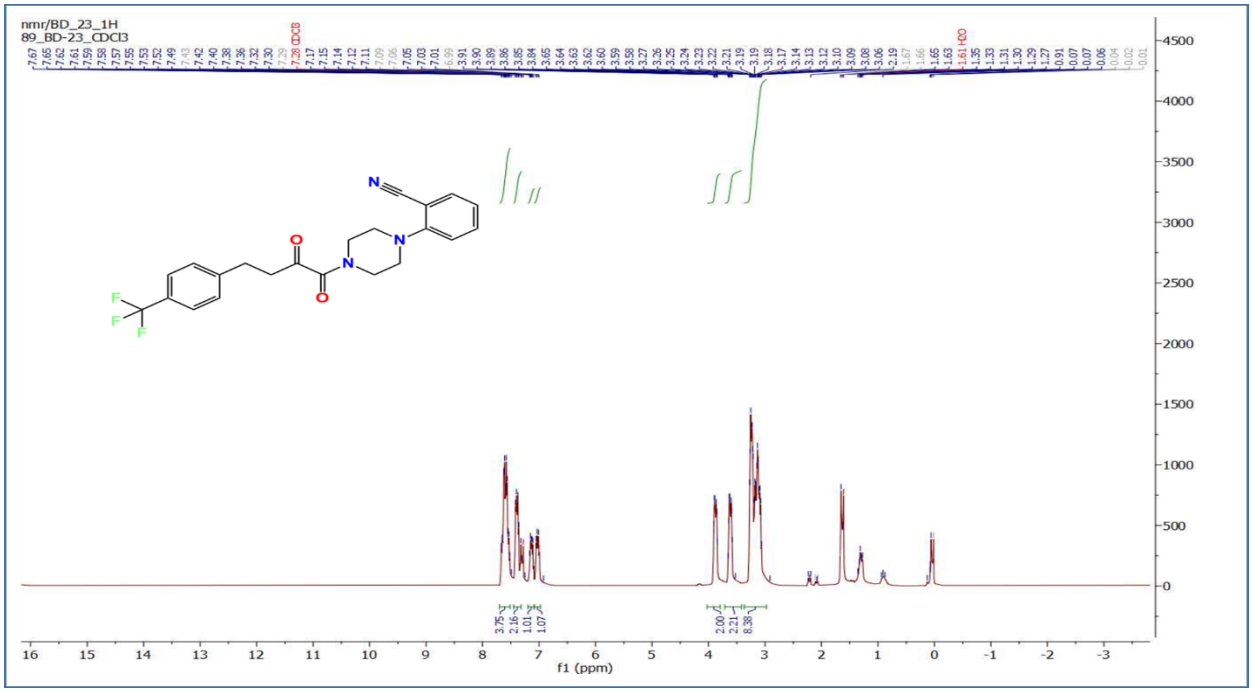


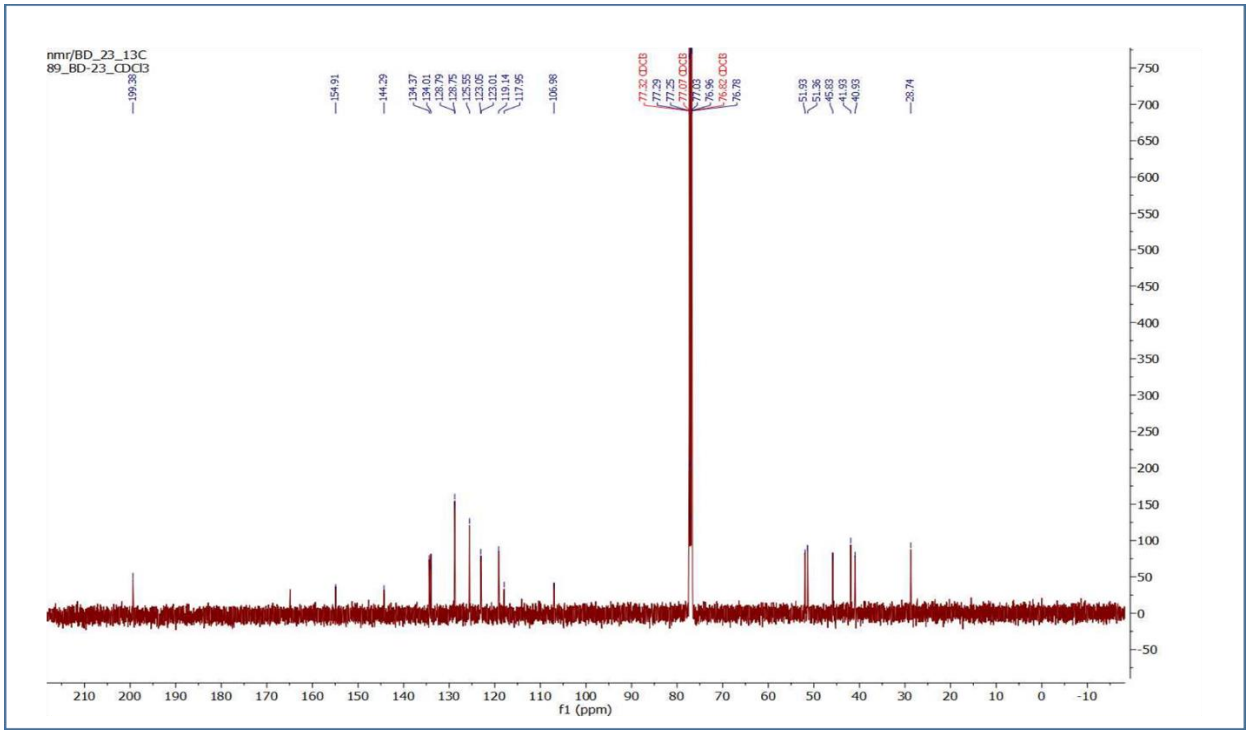
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD22



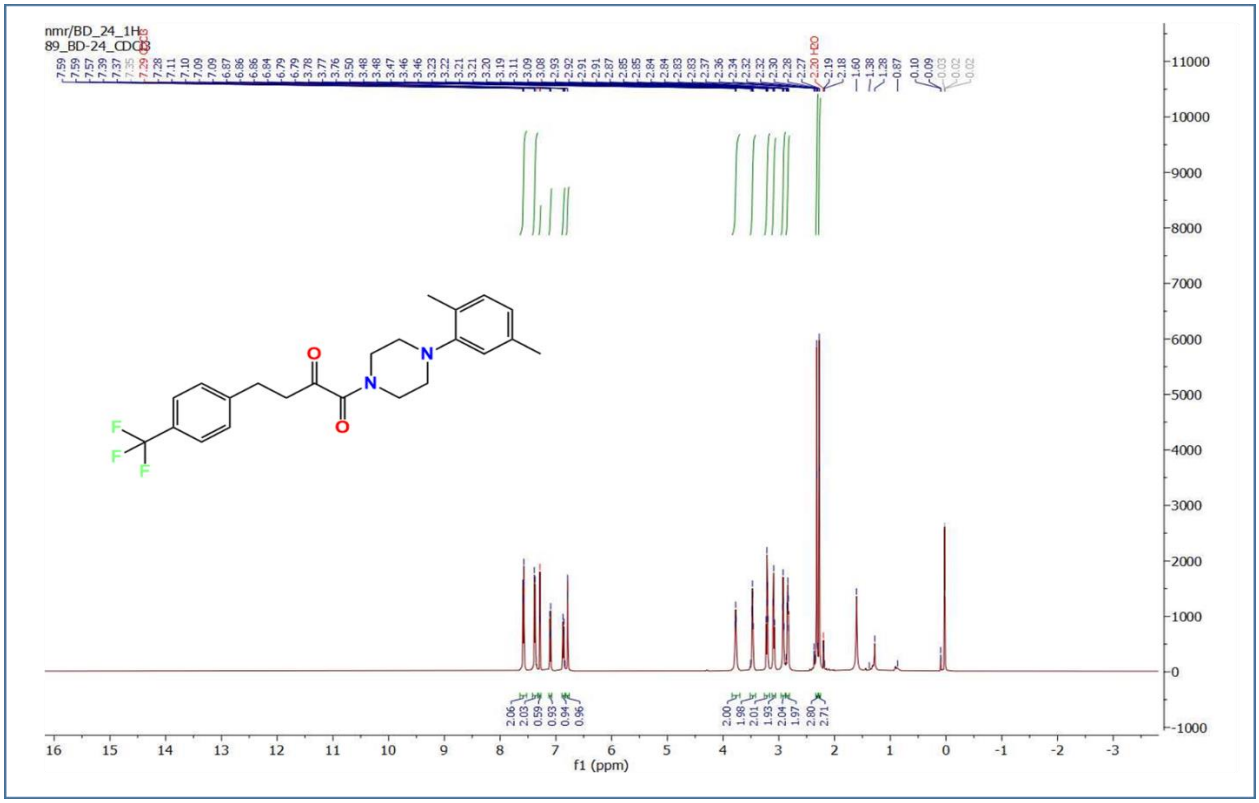


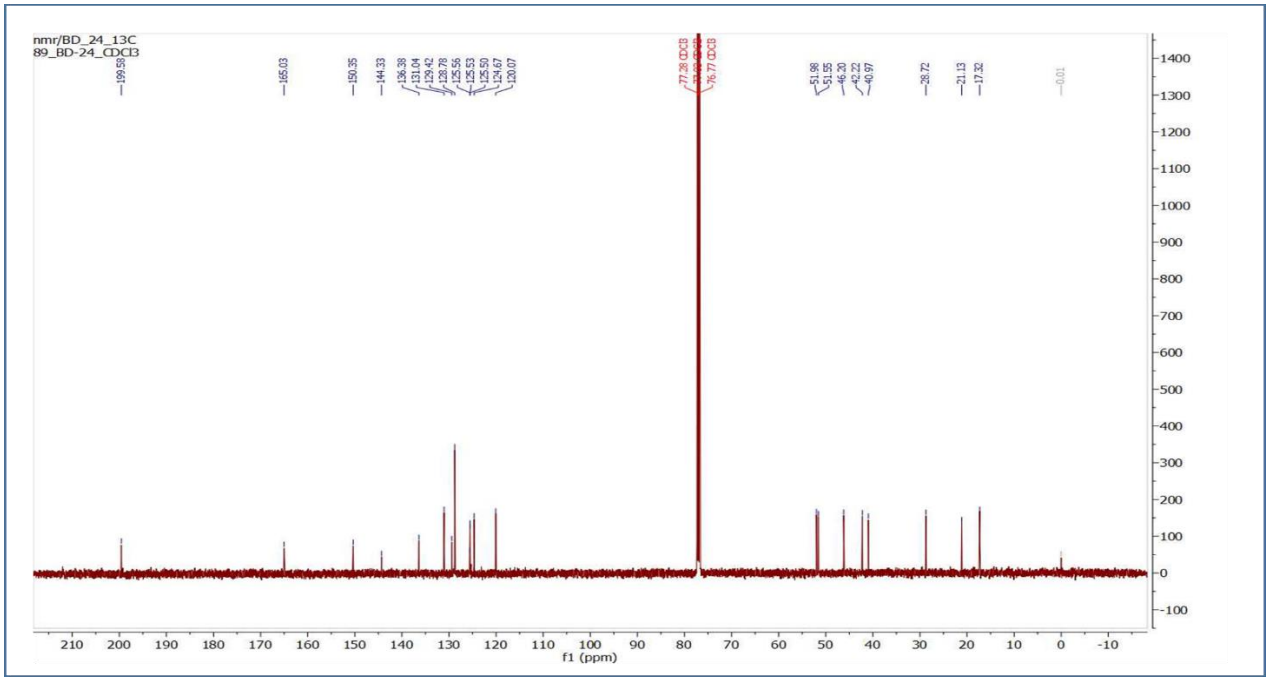
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD23



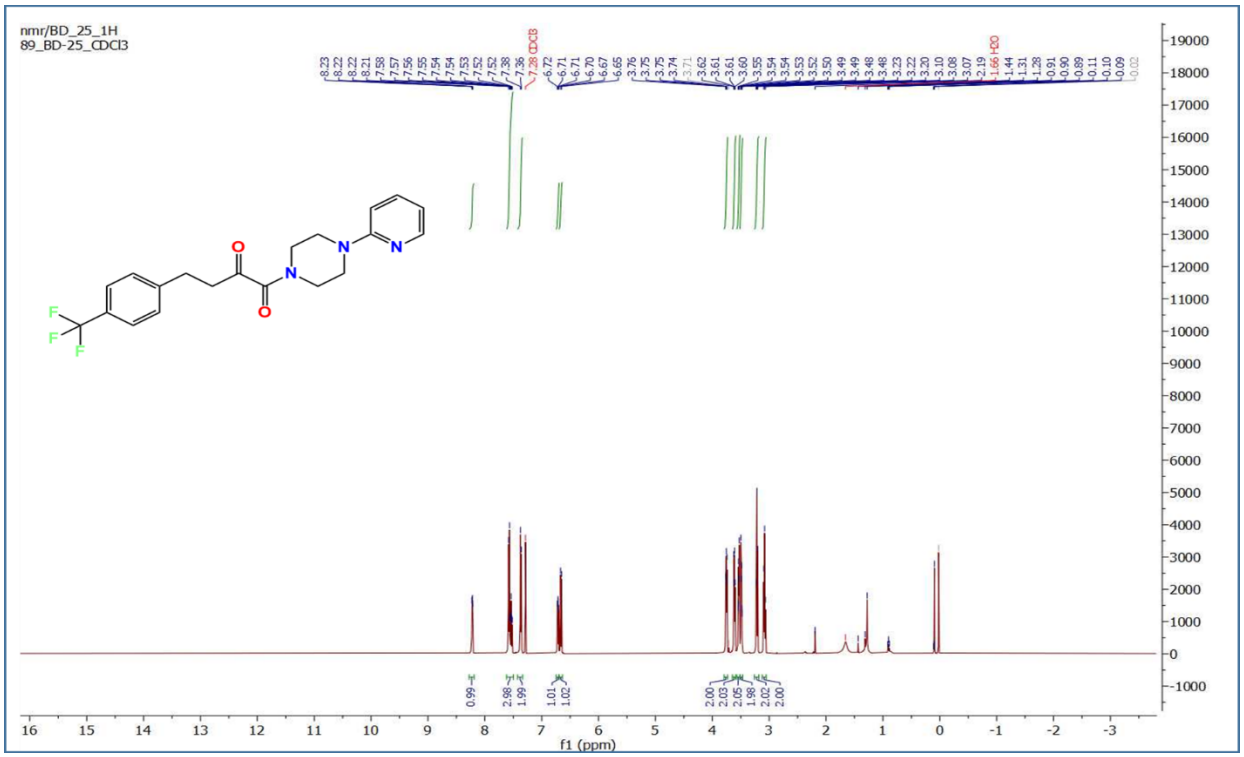


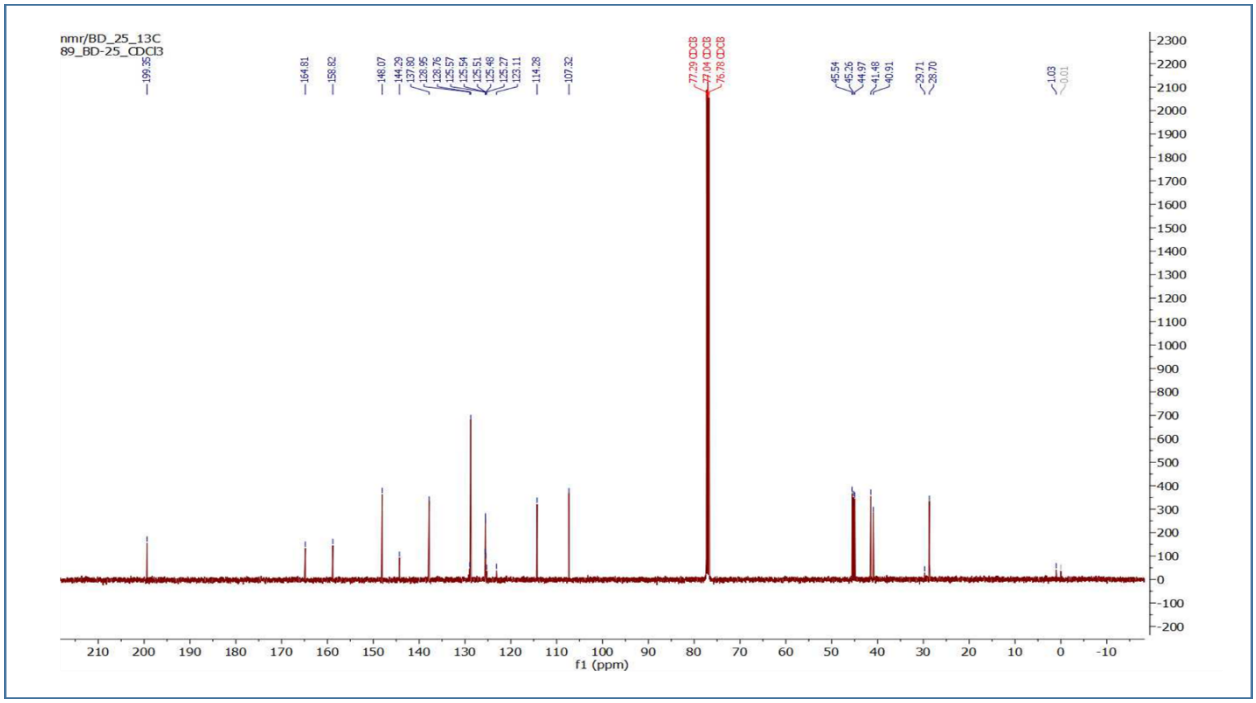
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD24



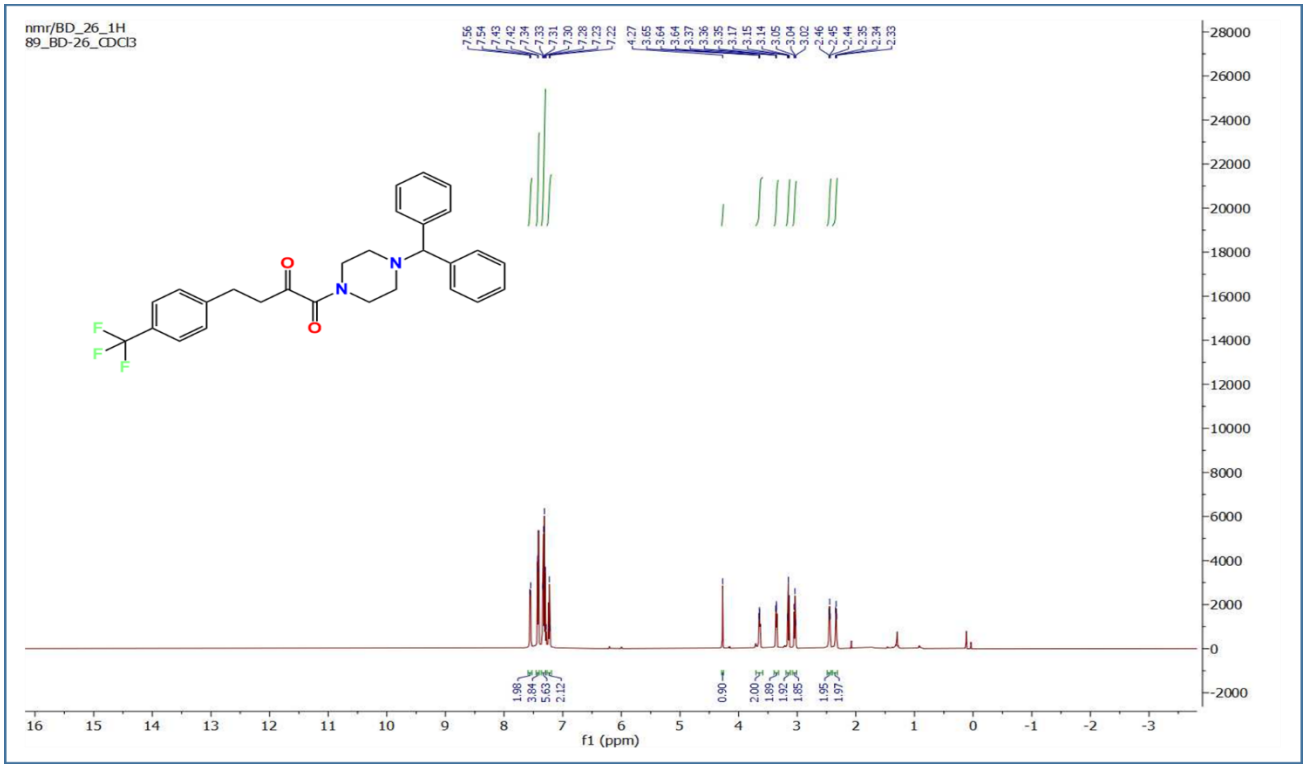


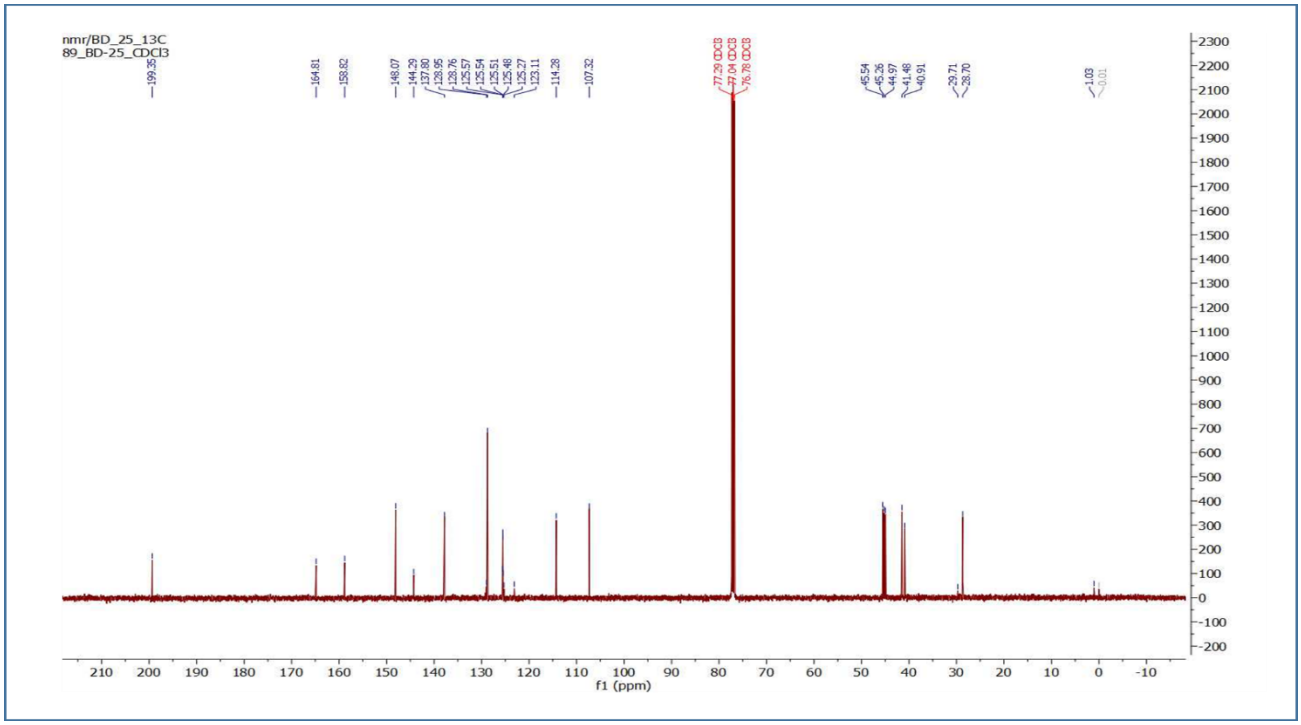
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD25



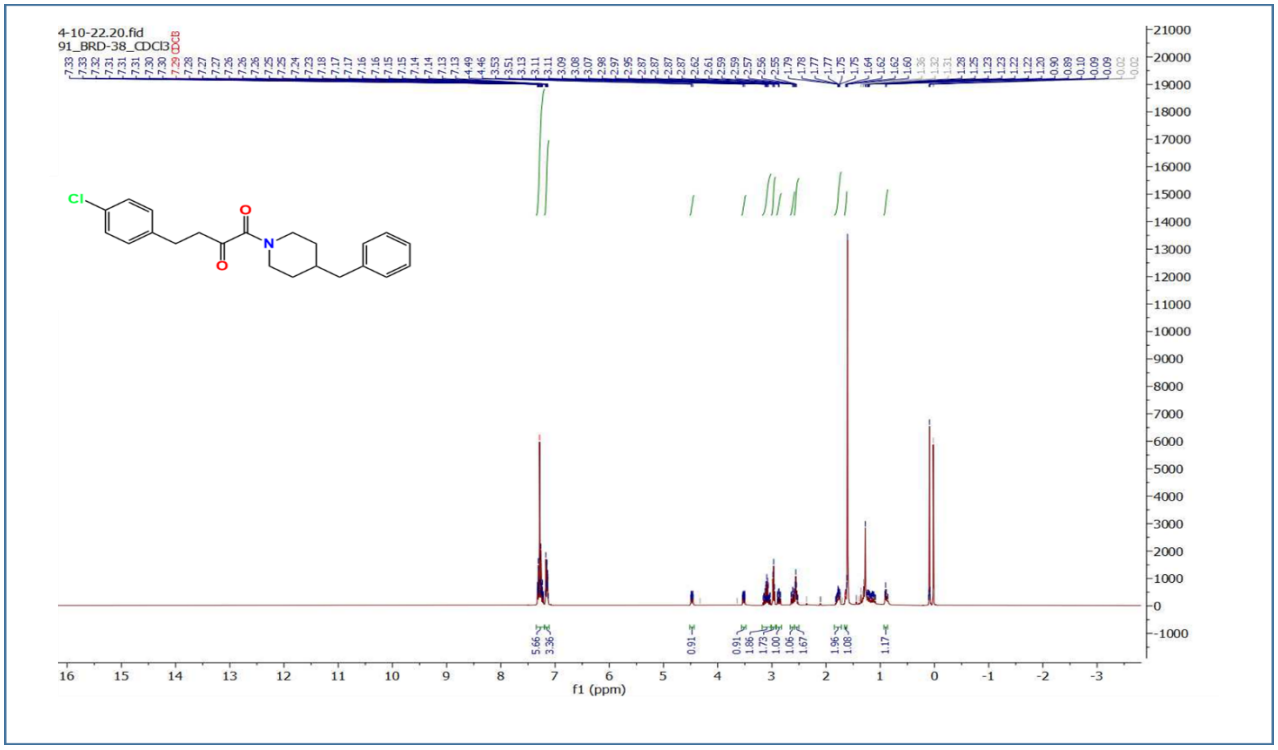


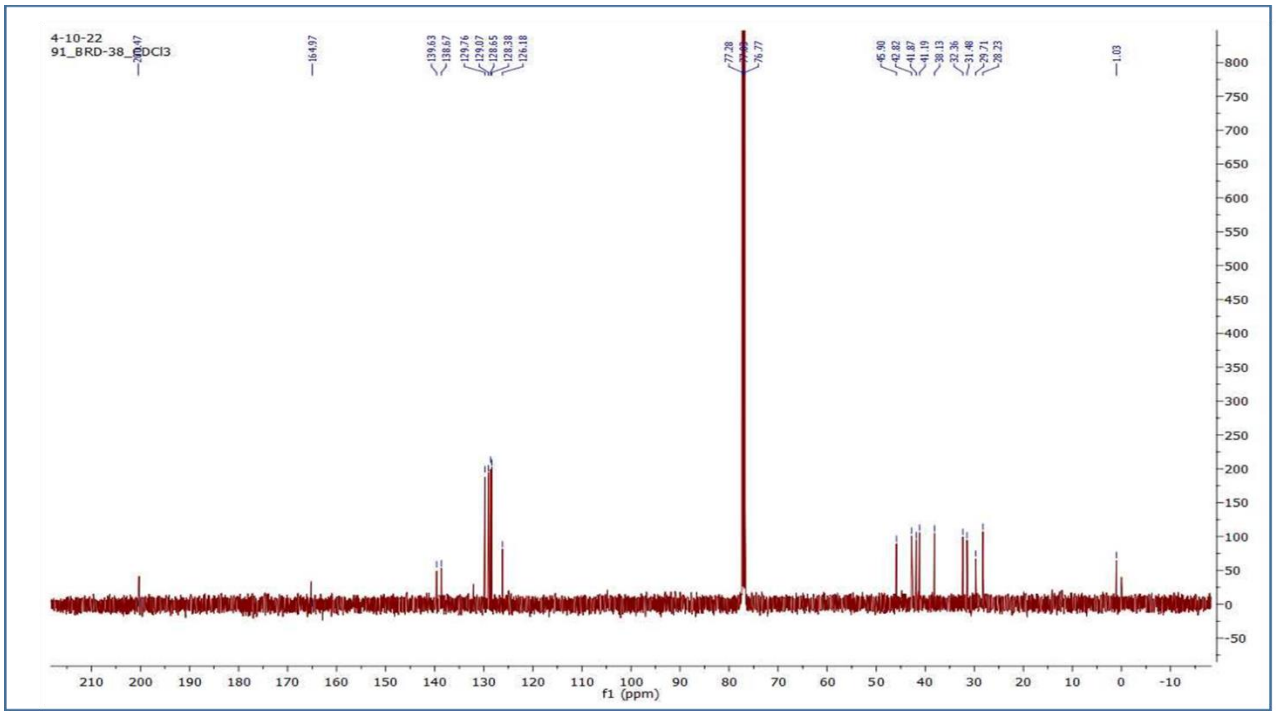
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD26



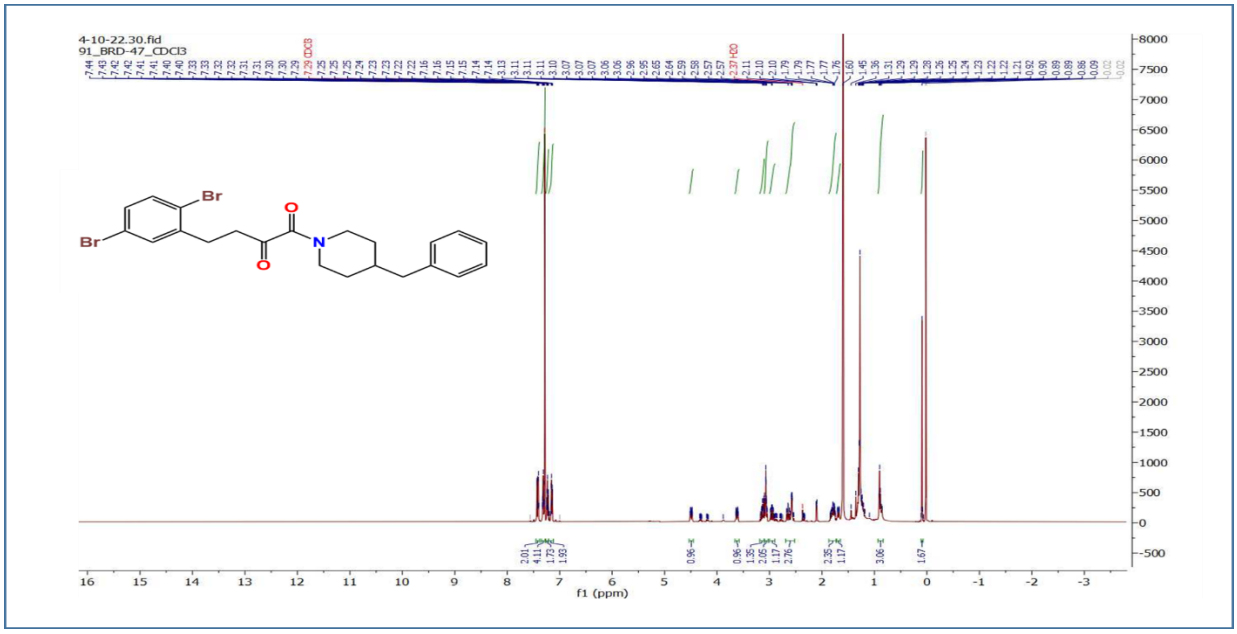


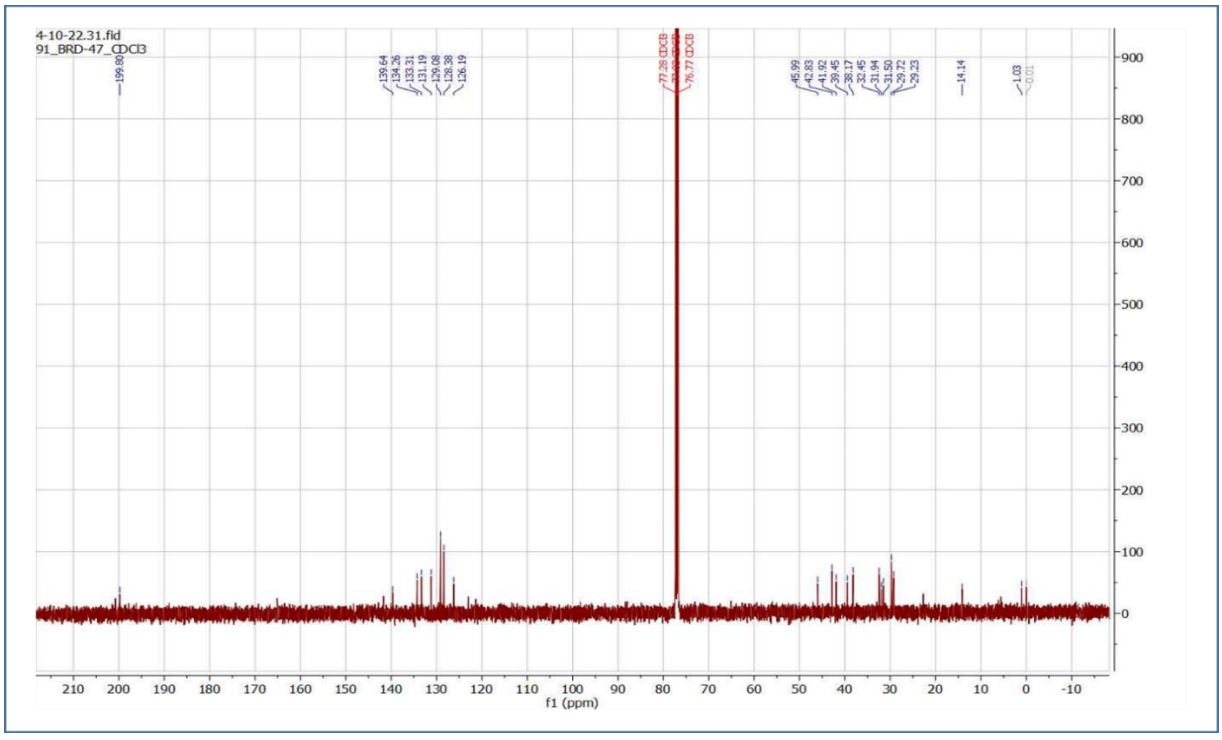
^{1}H, $^{13}C\{1H\}$ NMR spectra of BD27



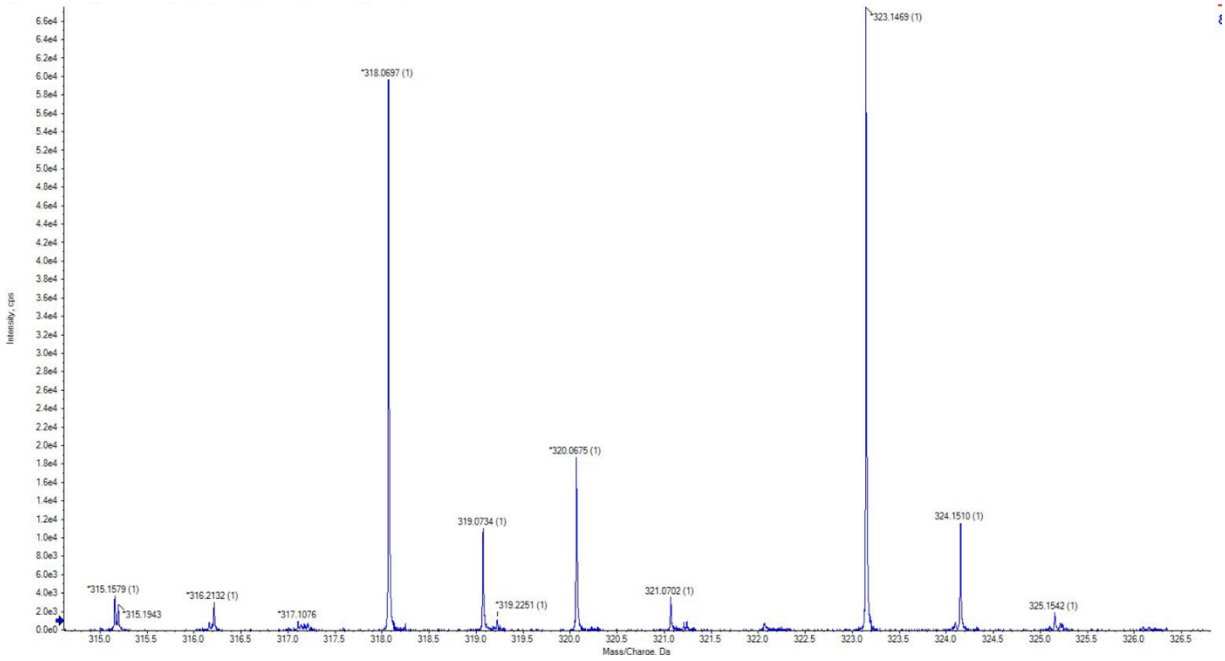


^{1}H, $^{13}C\{1H\}$ NMR spectra of BD28

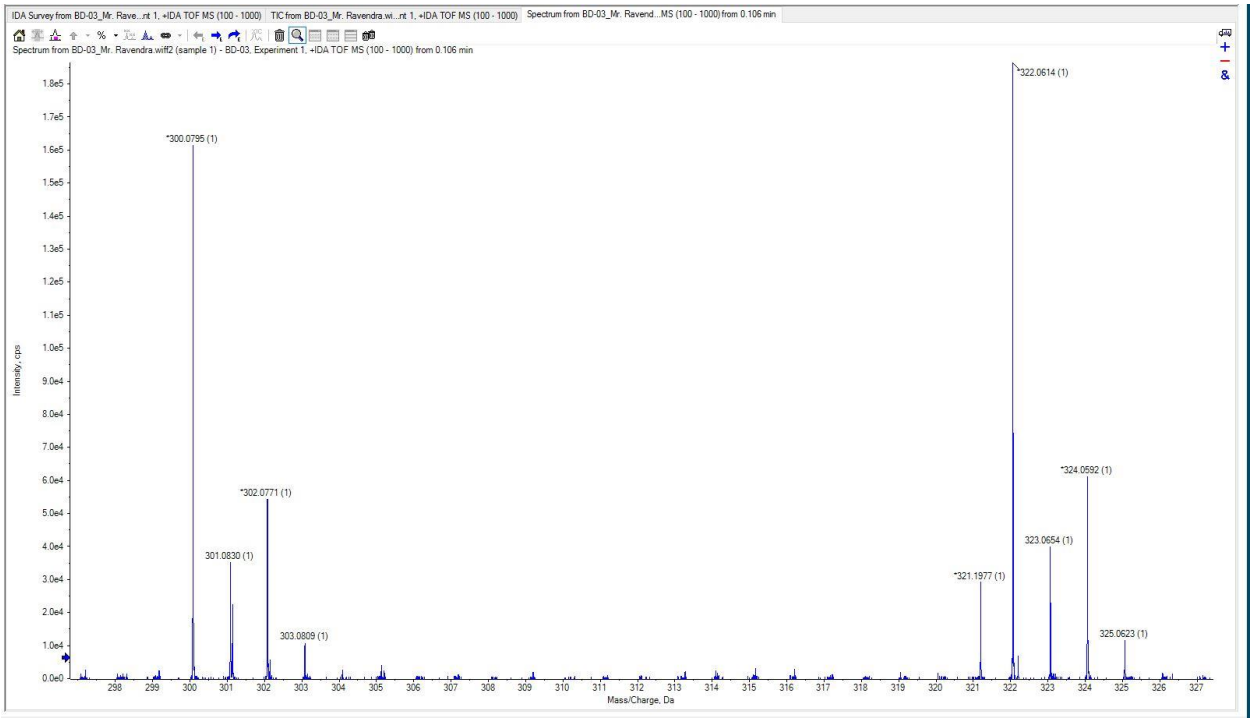




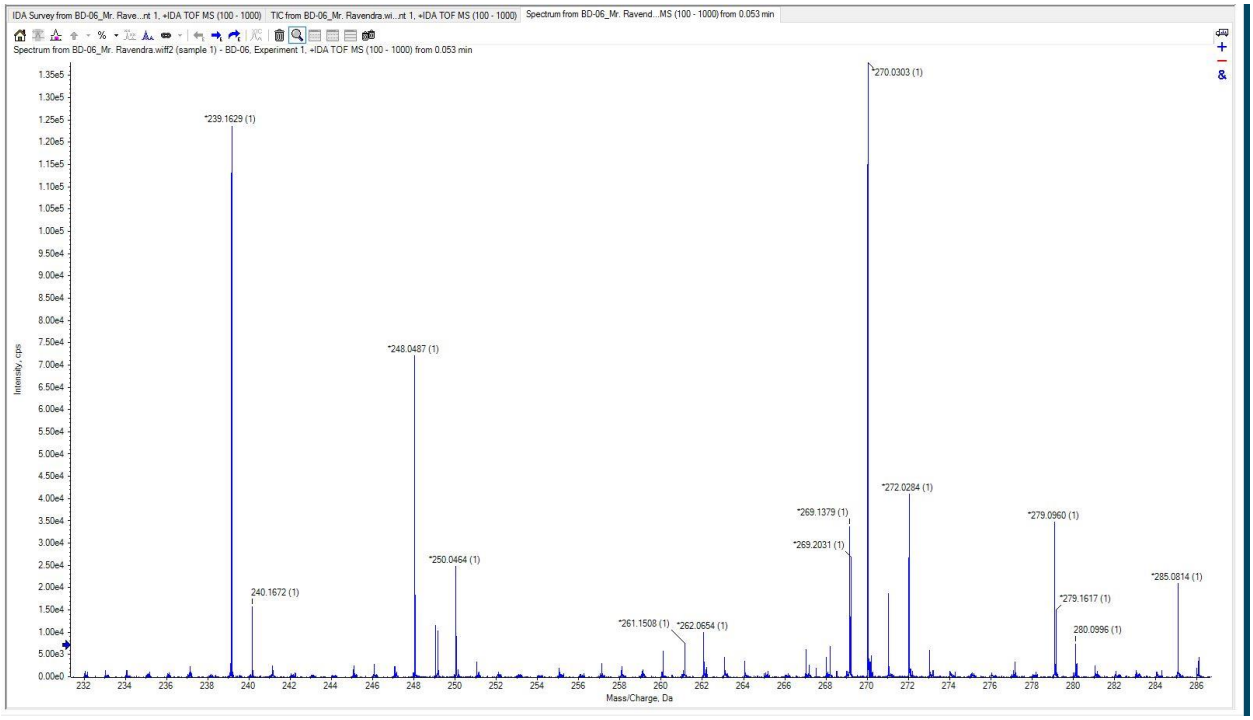
HRMS of Compound BD01



HRMS of Compound BD02



HRMS of Compound BD03



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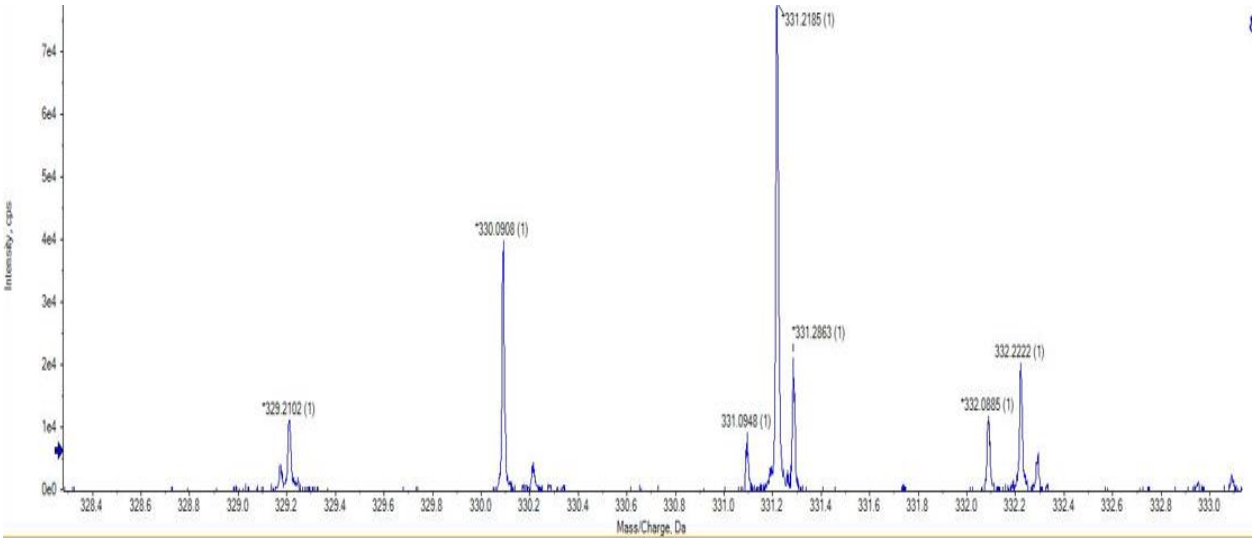

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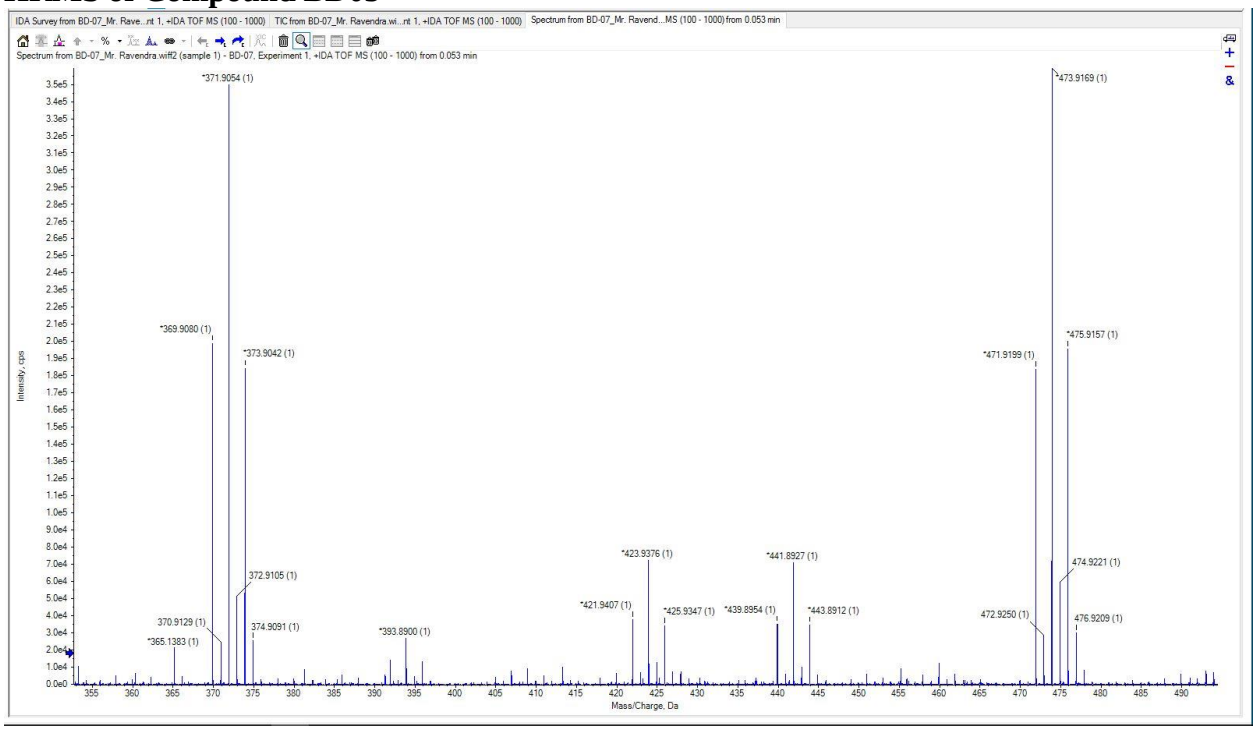

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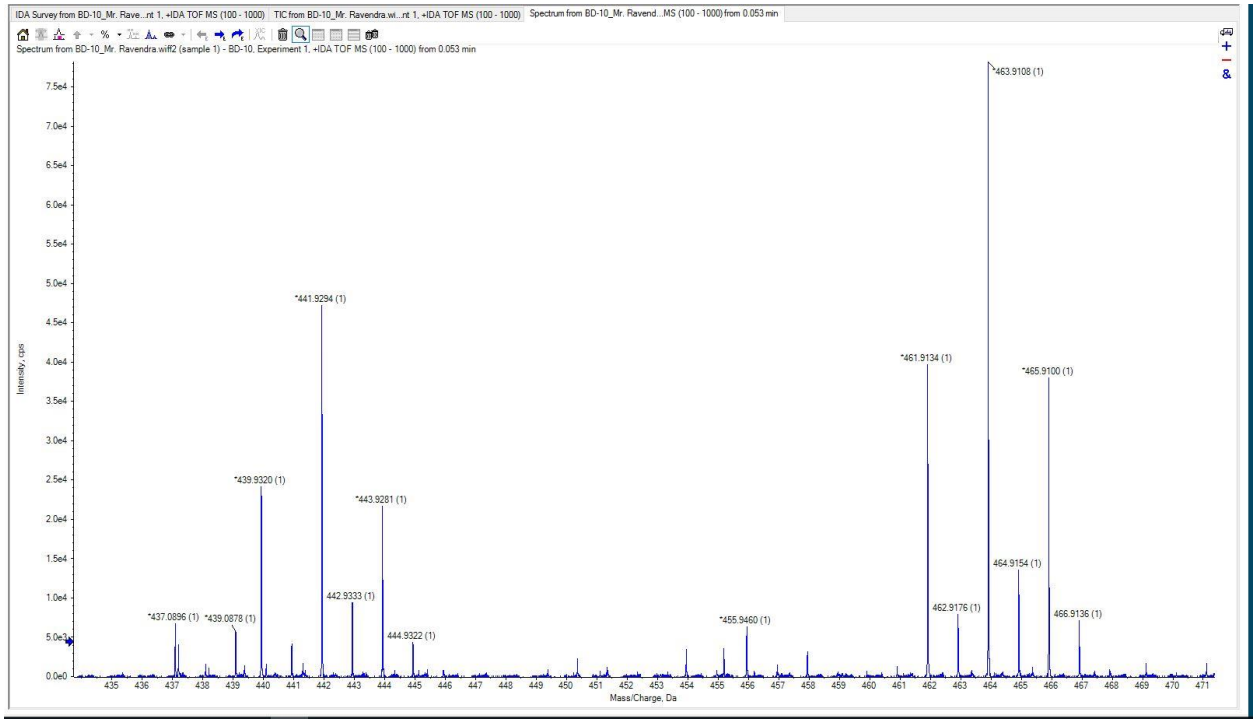

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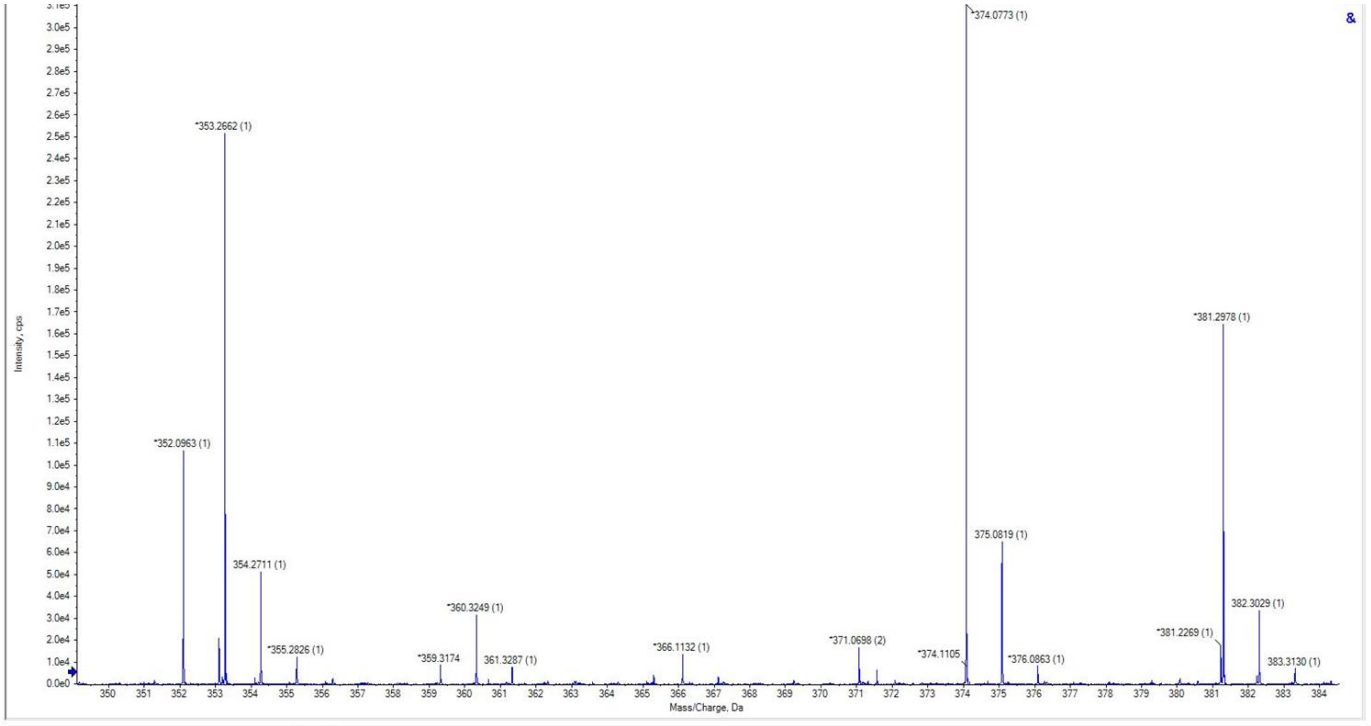

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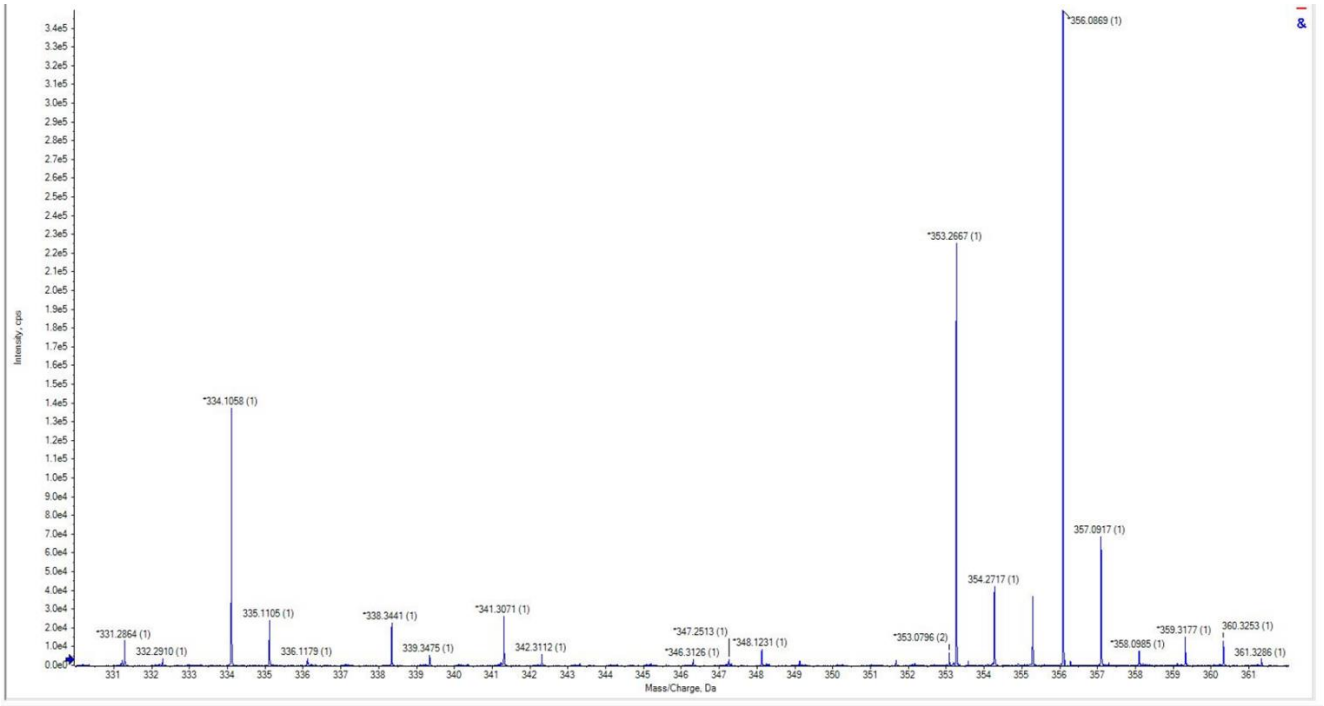
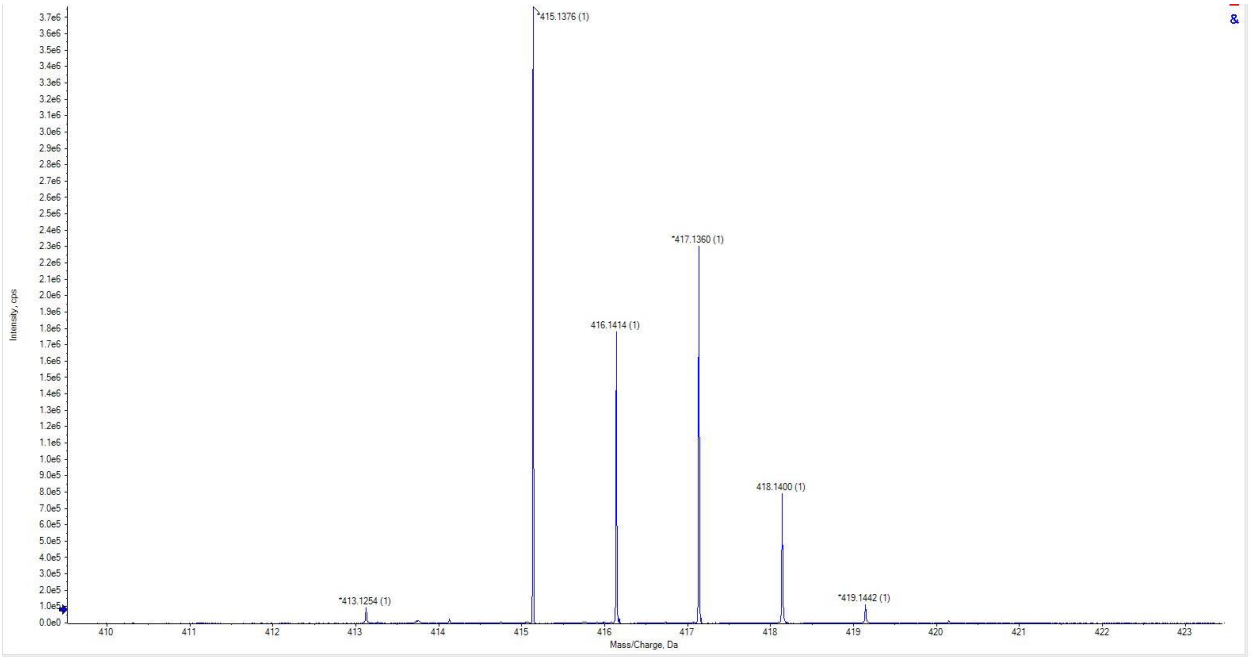


HRMS of Compound BD09



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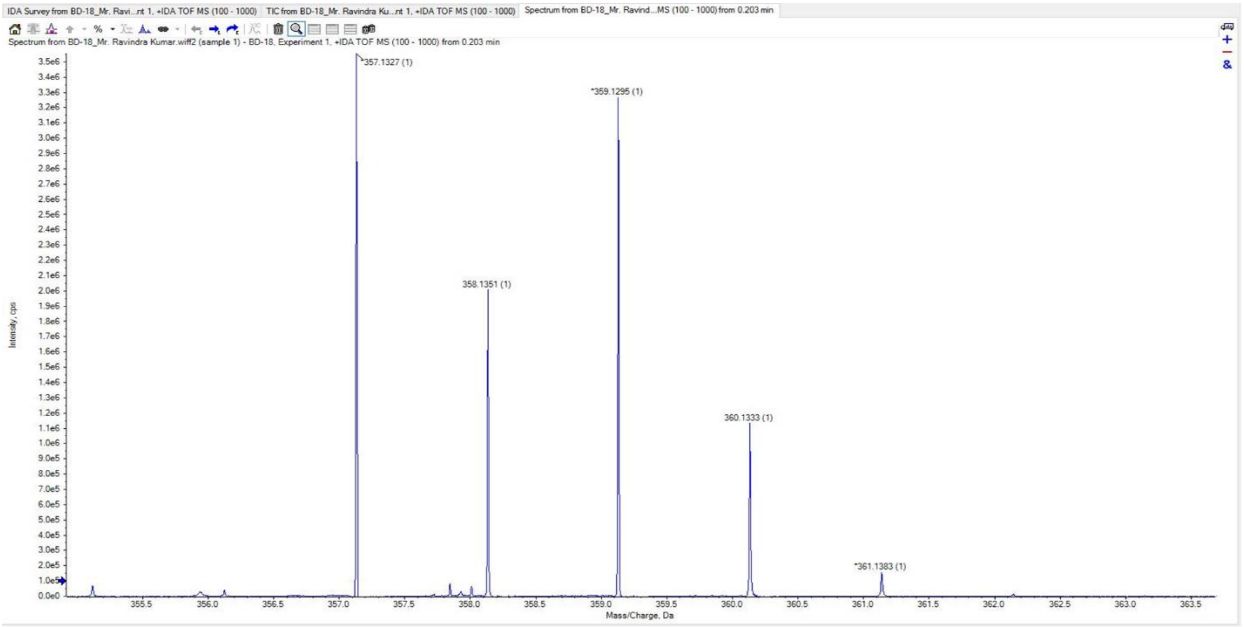
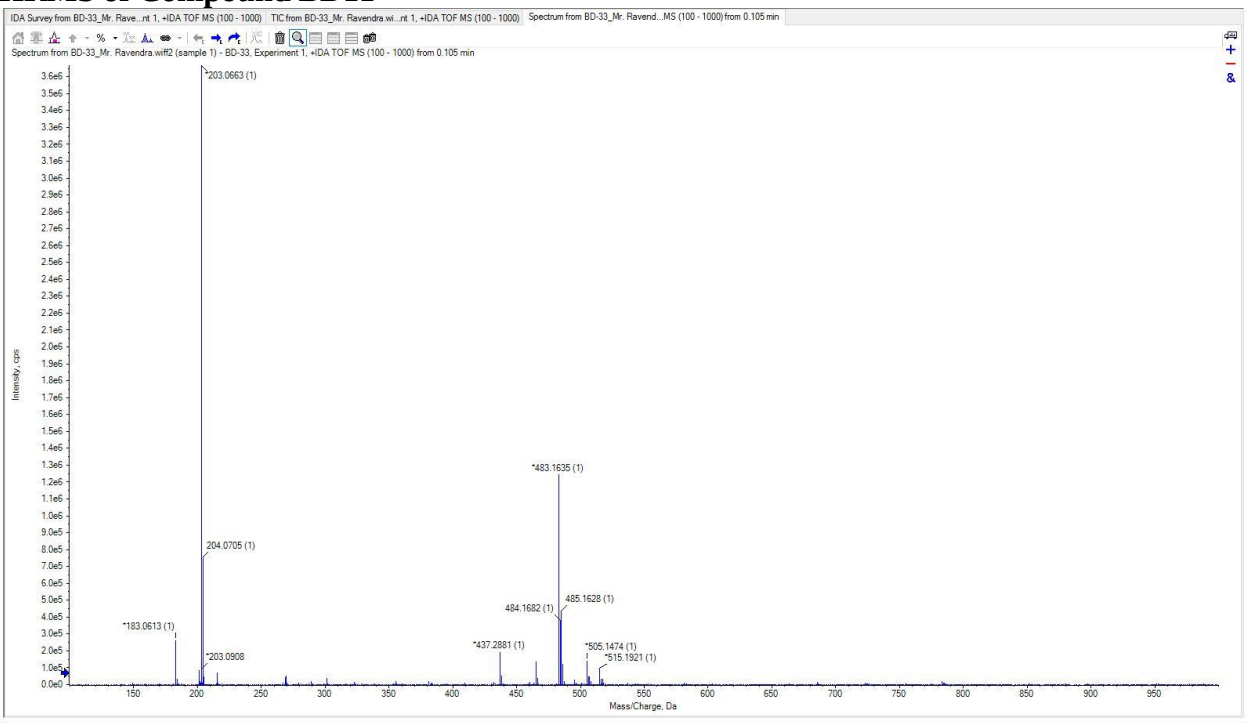


HRMS of Compound BD11



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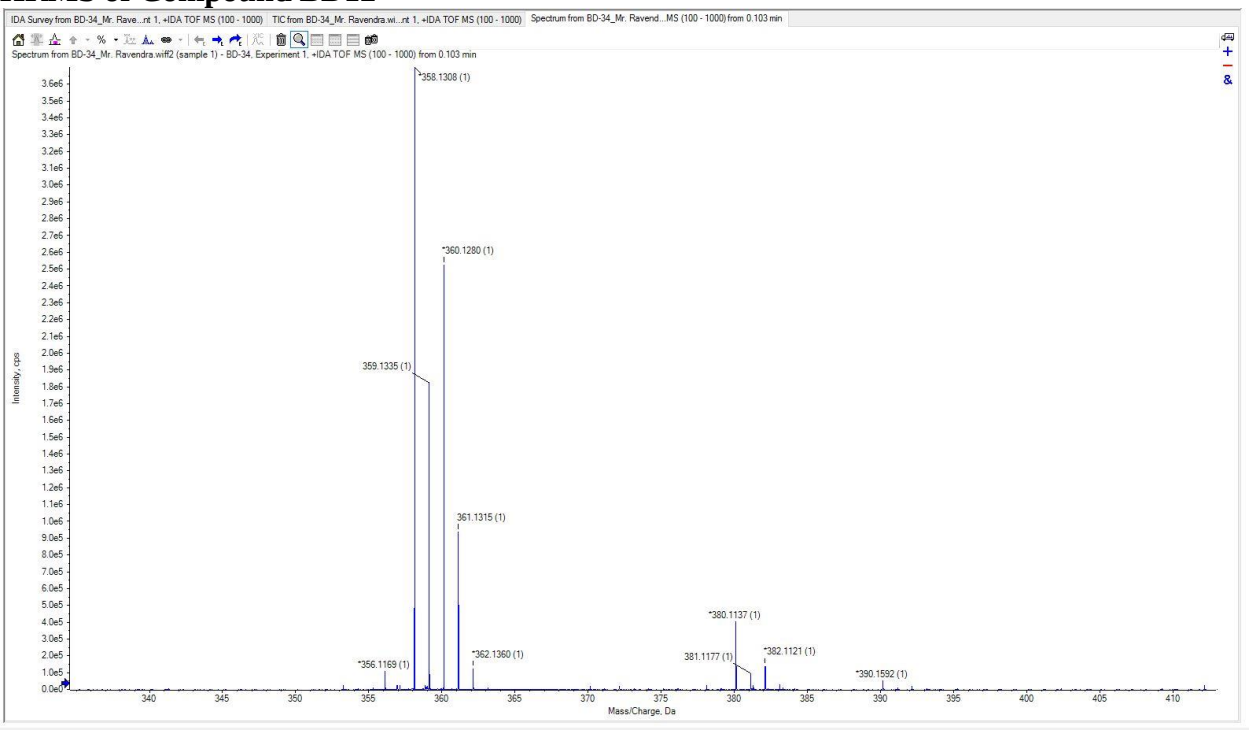

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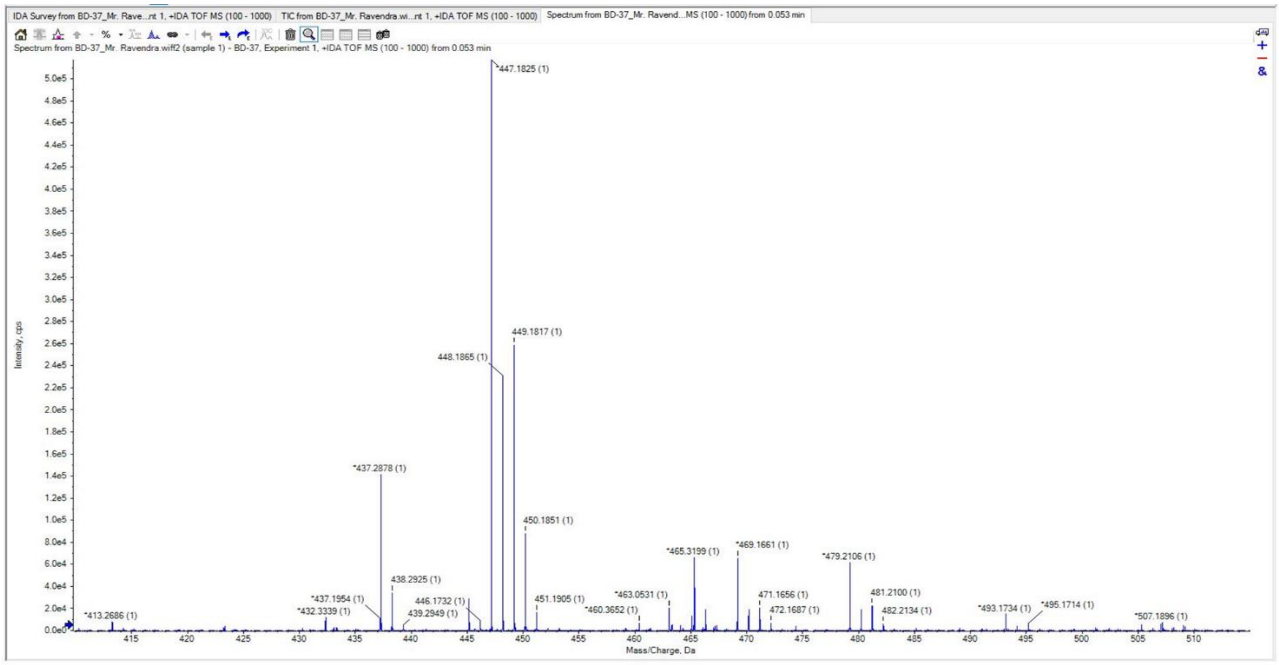
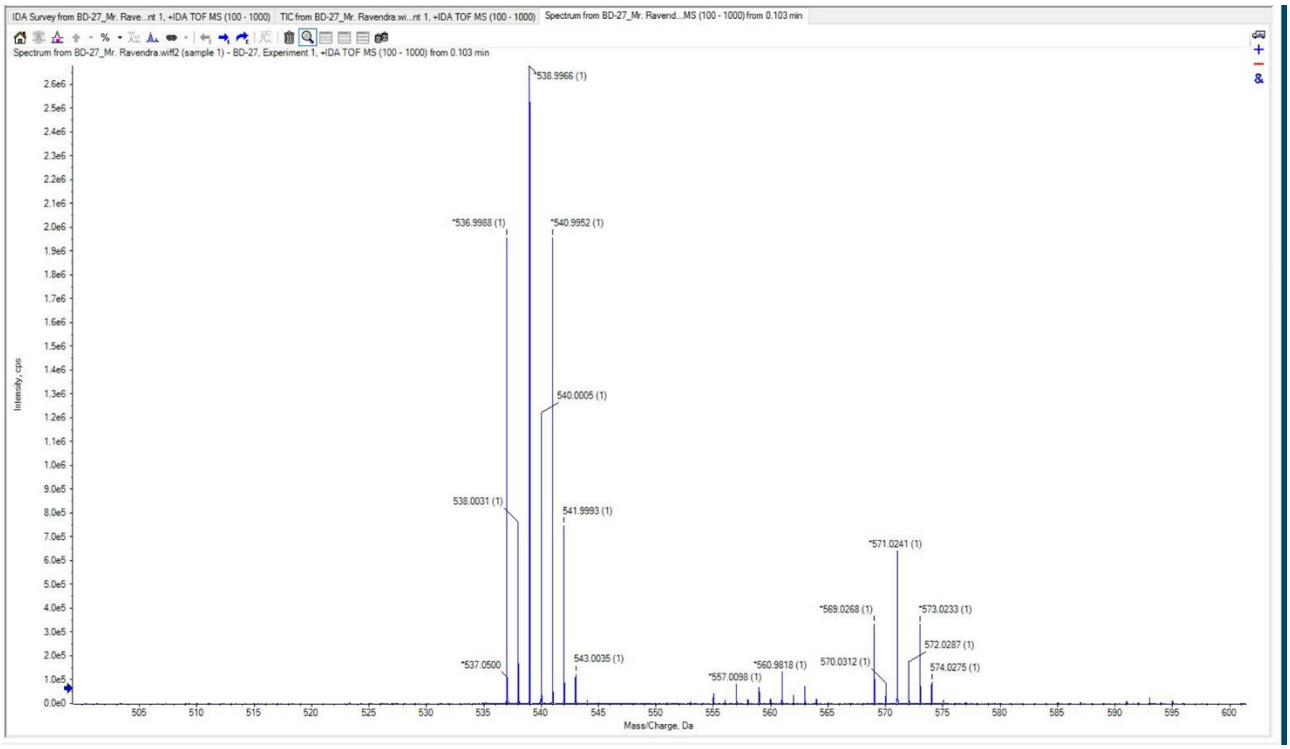
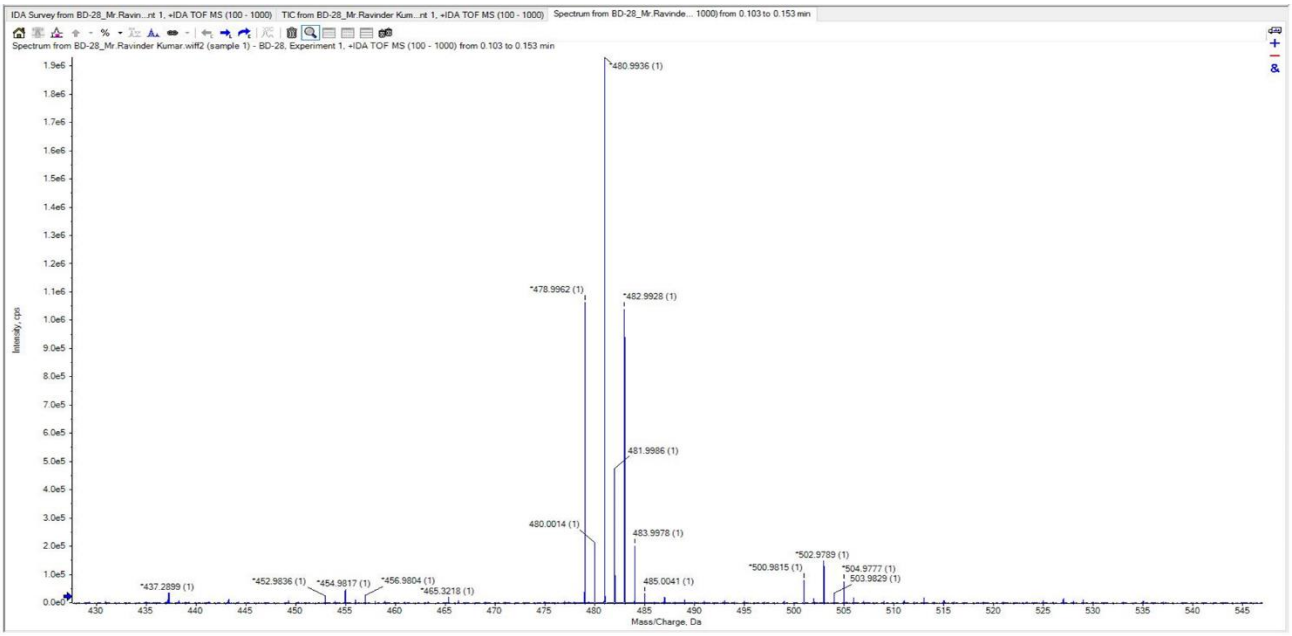


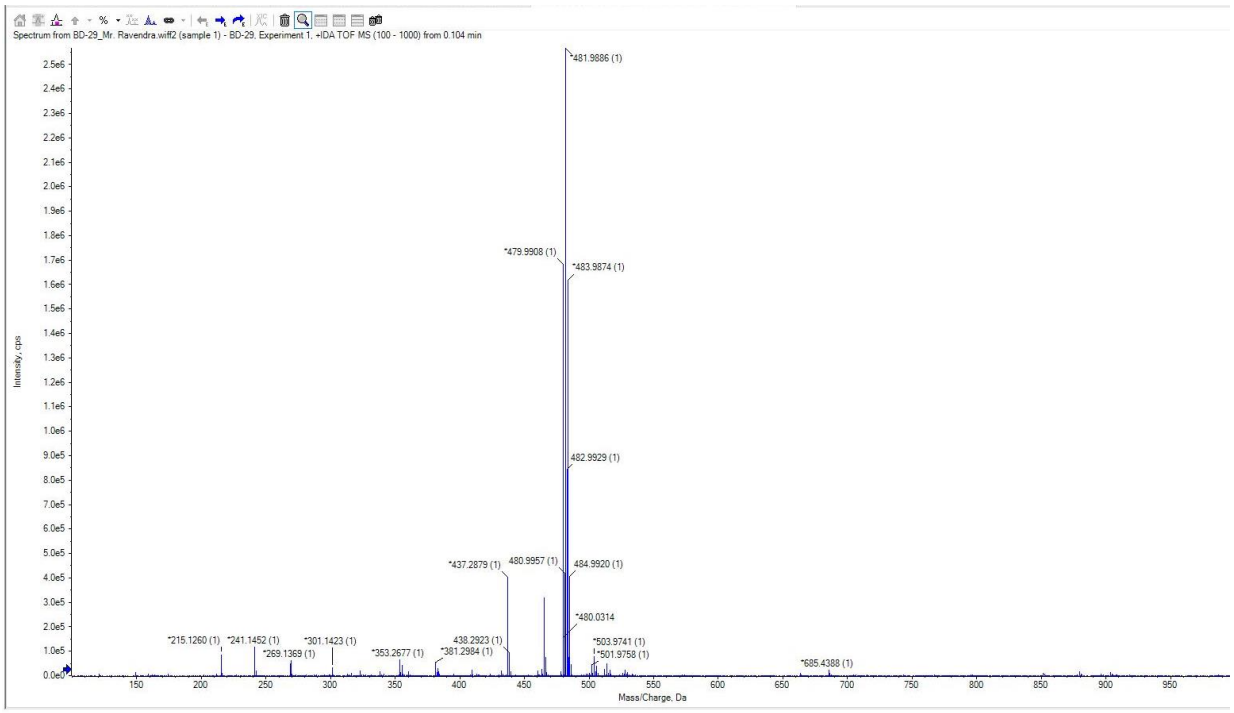
HRMS of Compound BD14



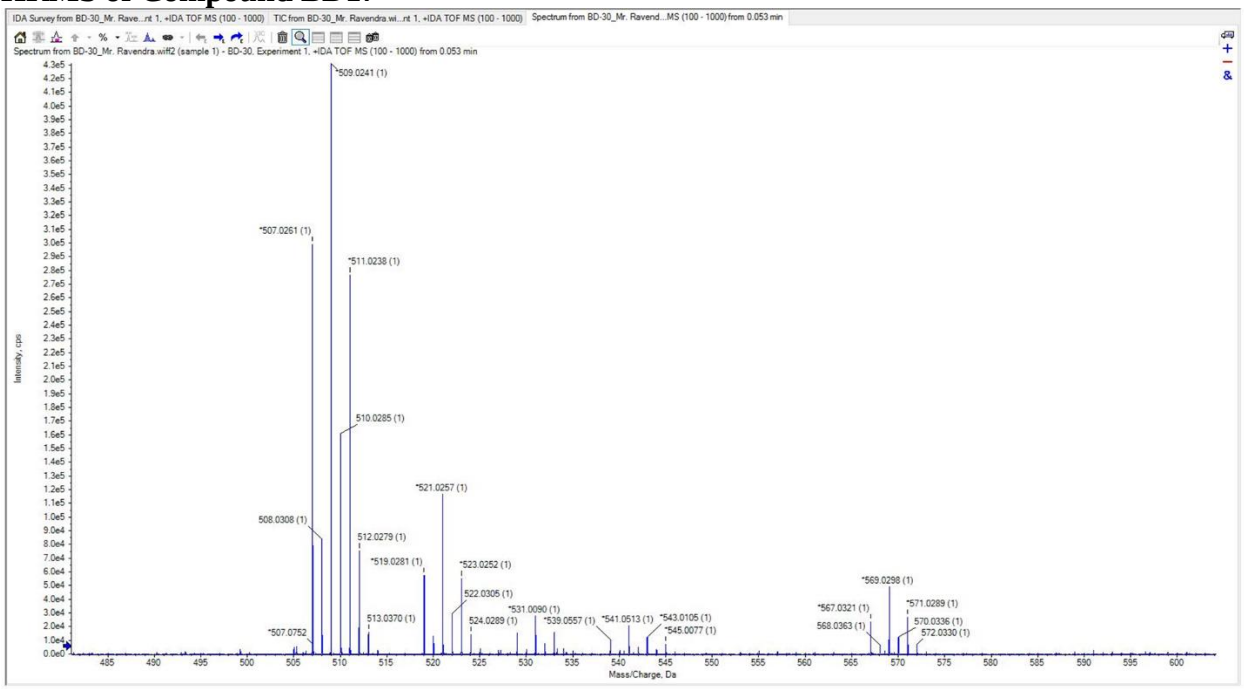
HRMS of Compound BD15



HRMS of Compound BD16



HRMS of Compound BD17



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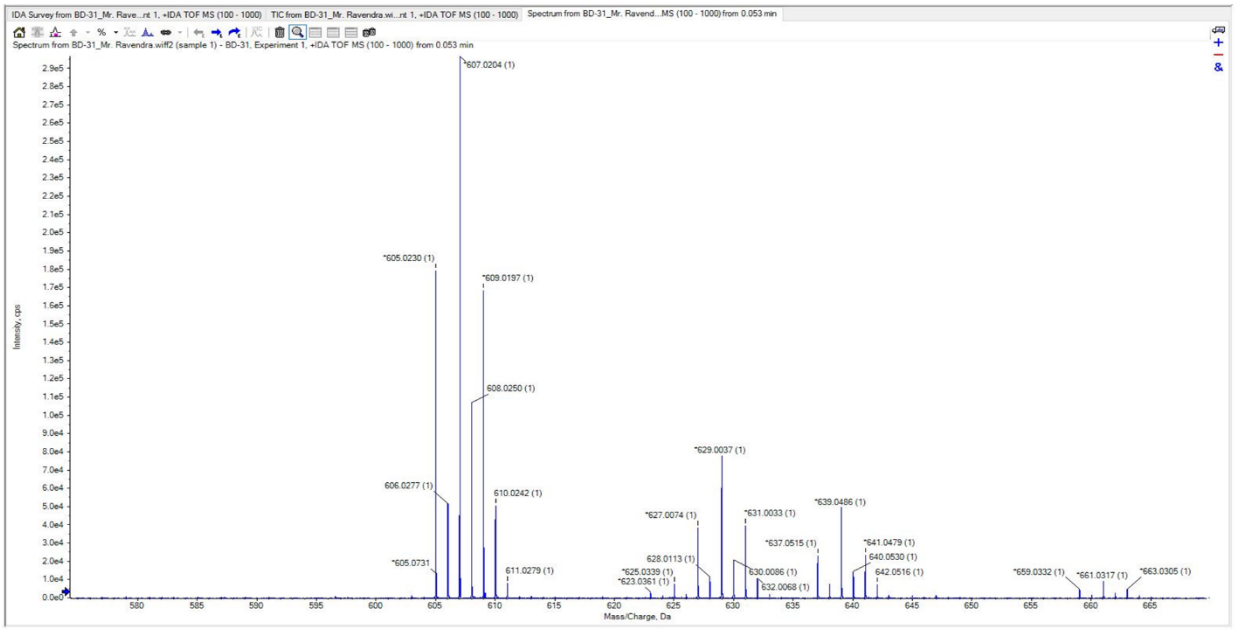
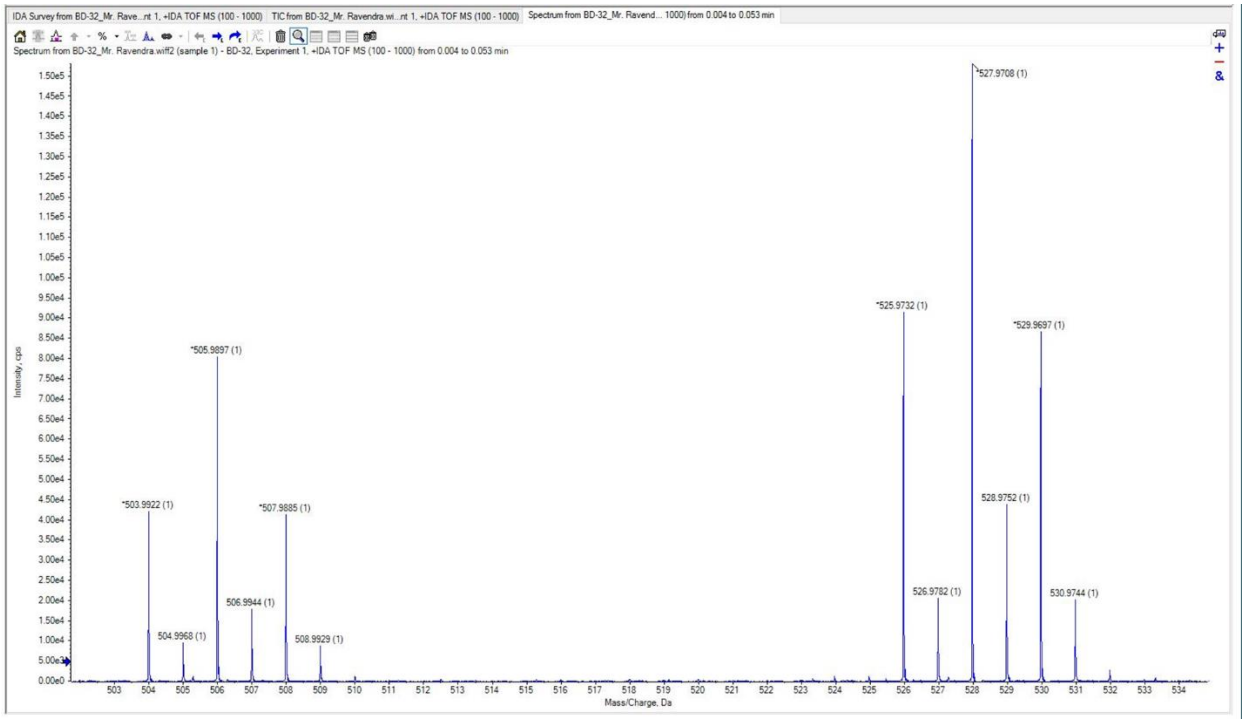
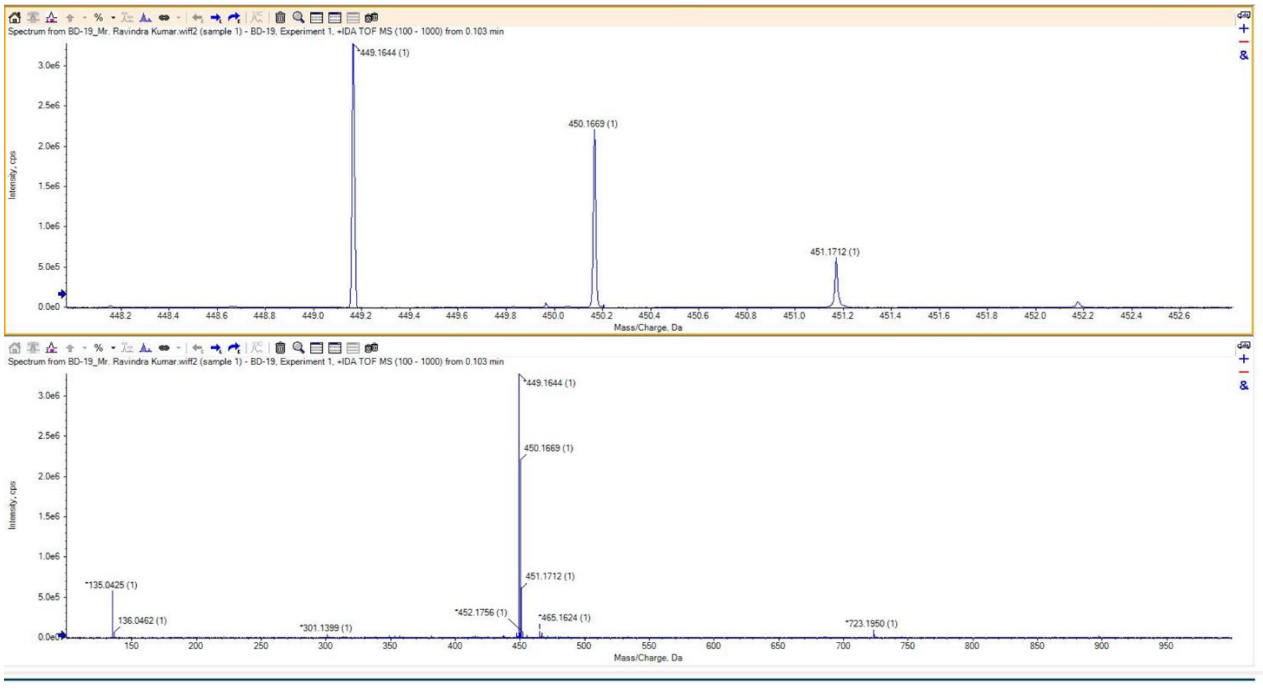


HRMS of Compound BD19



HRMS of Compound BD20



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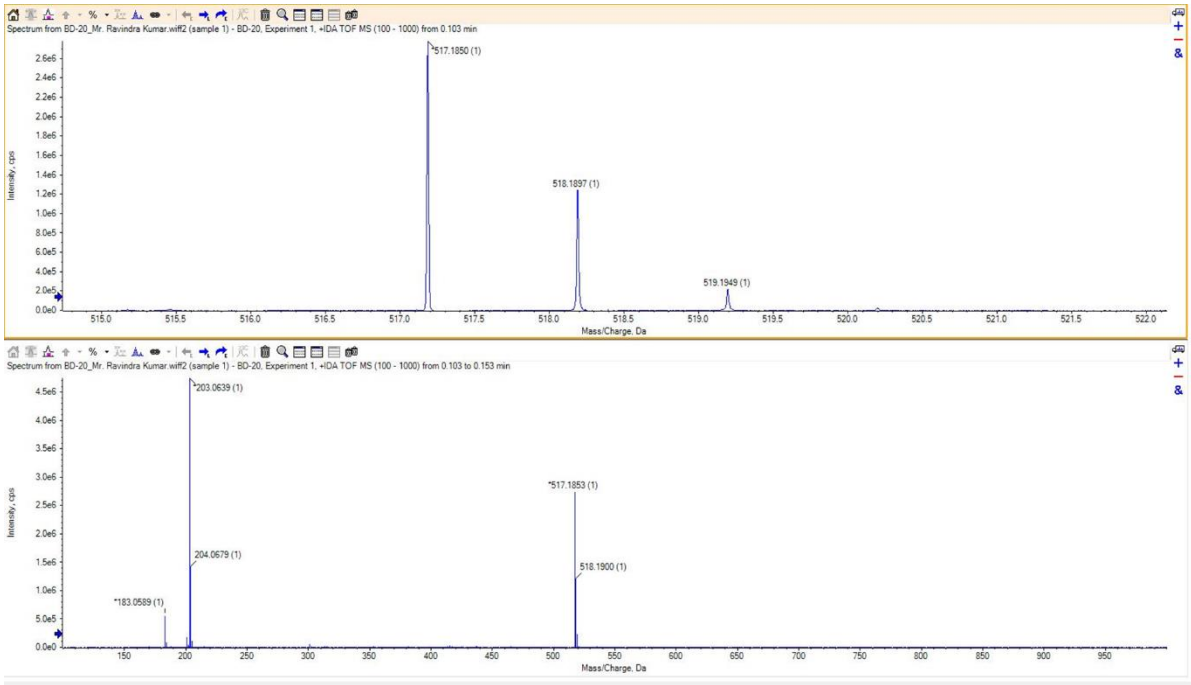
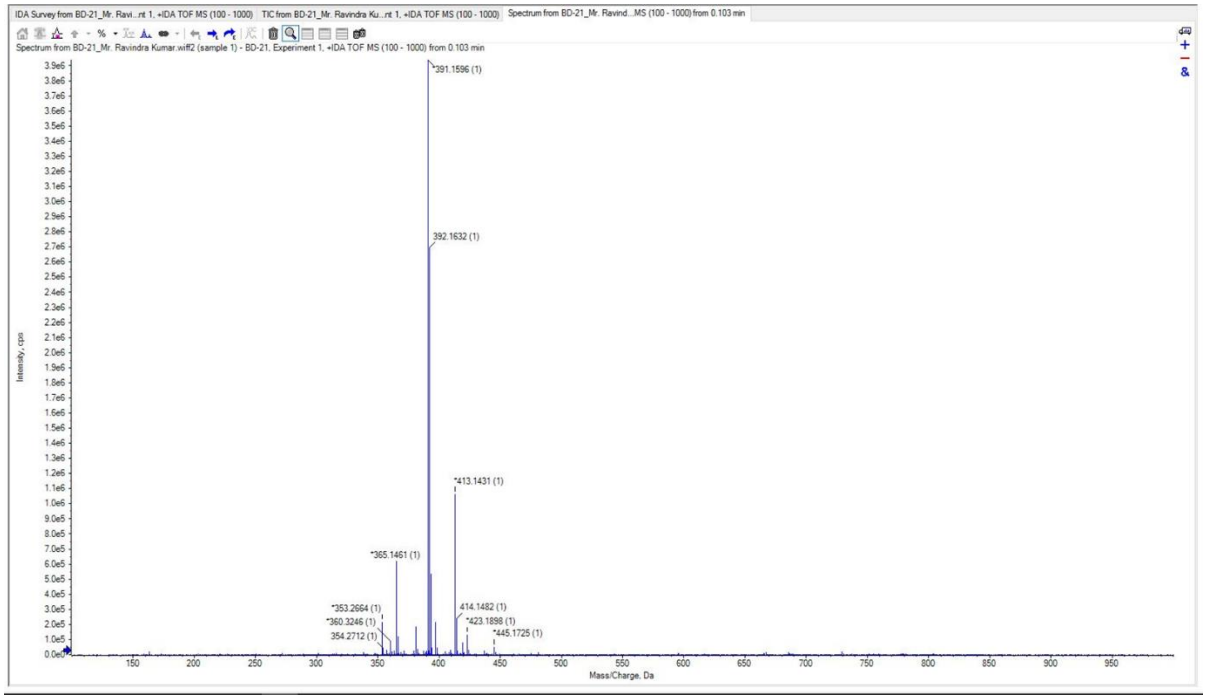
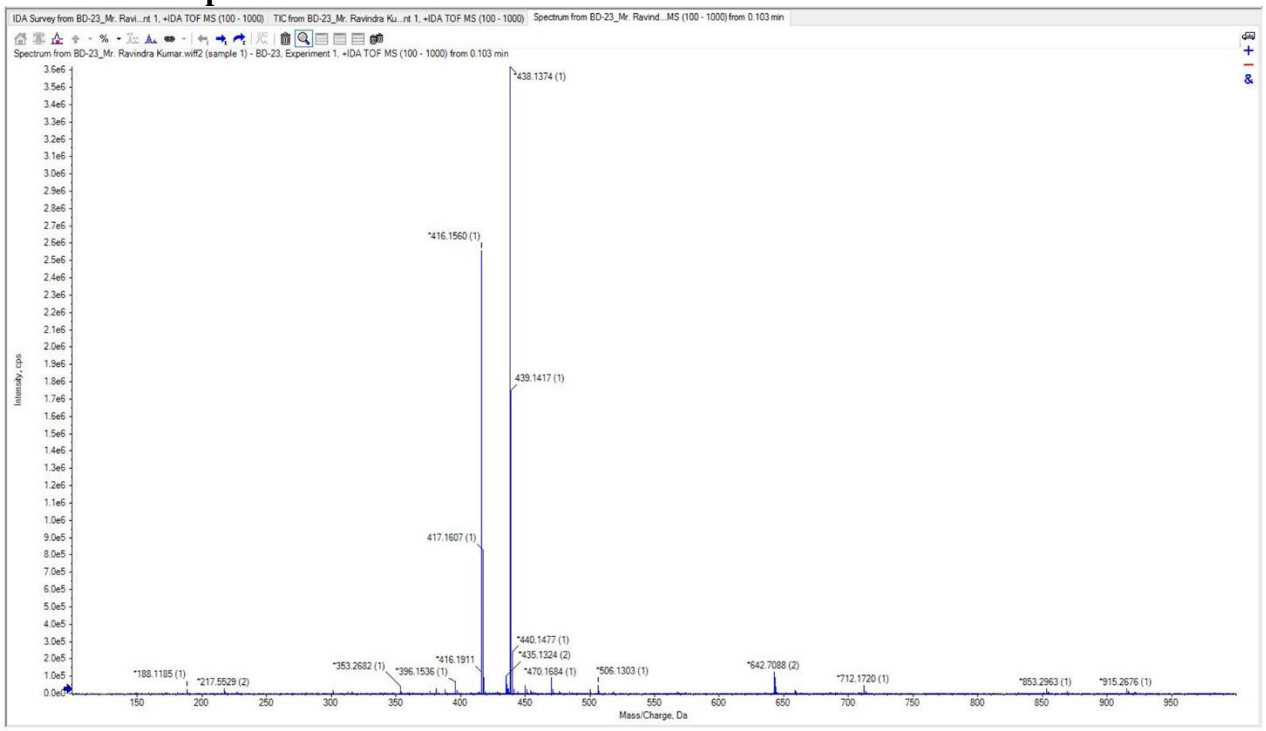


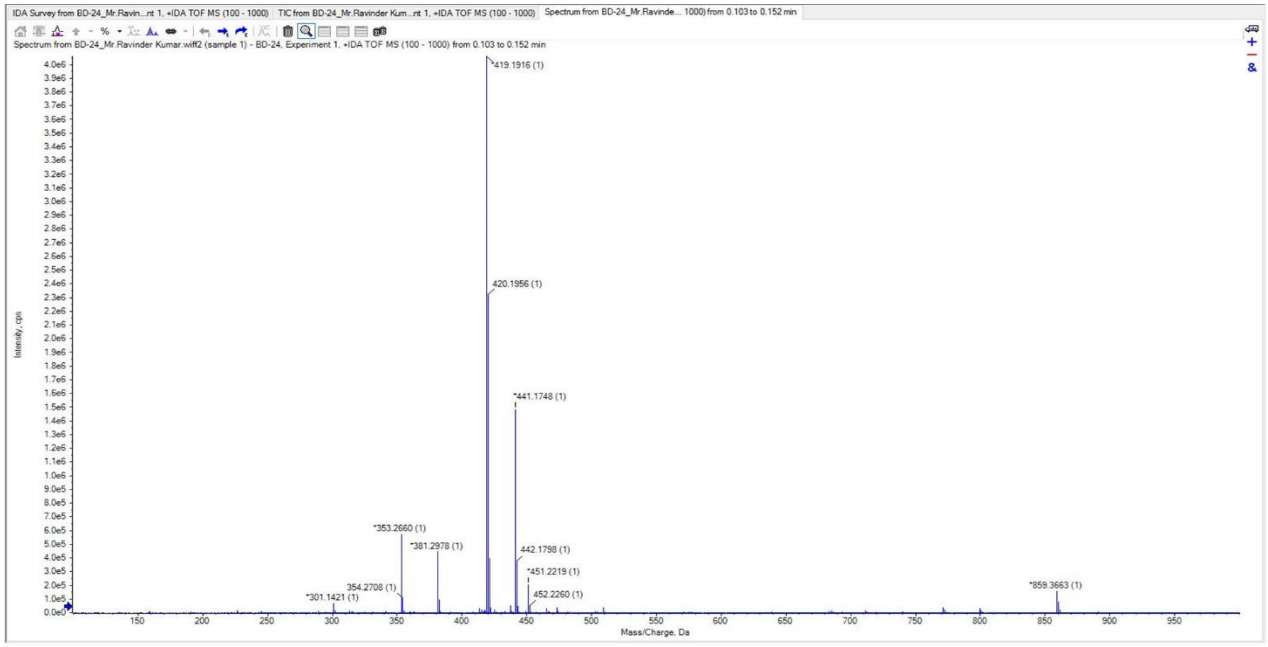
HRMS of Compound BD22



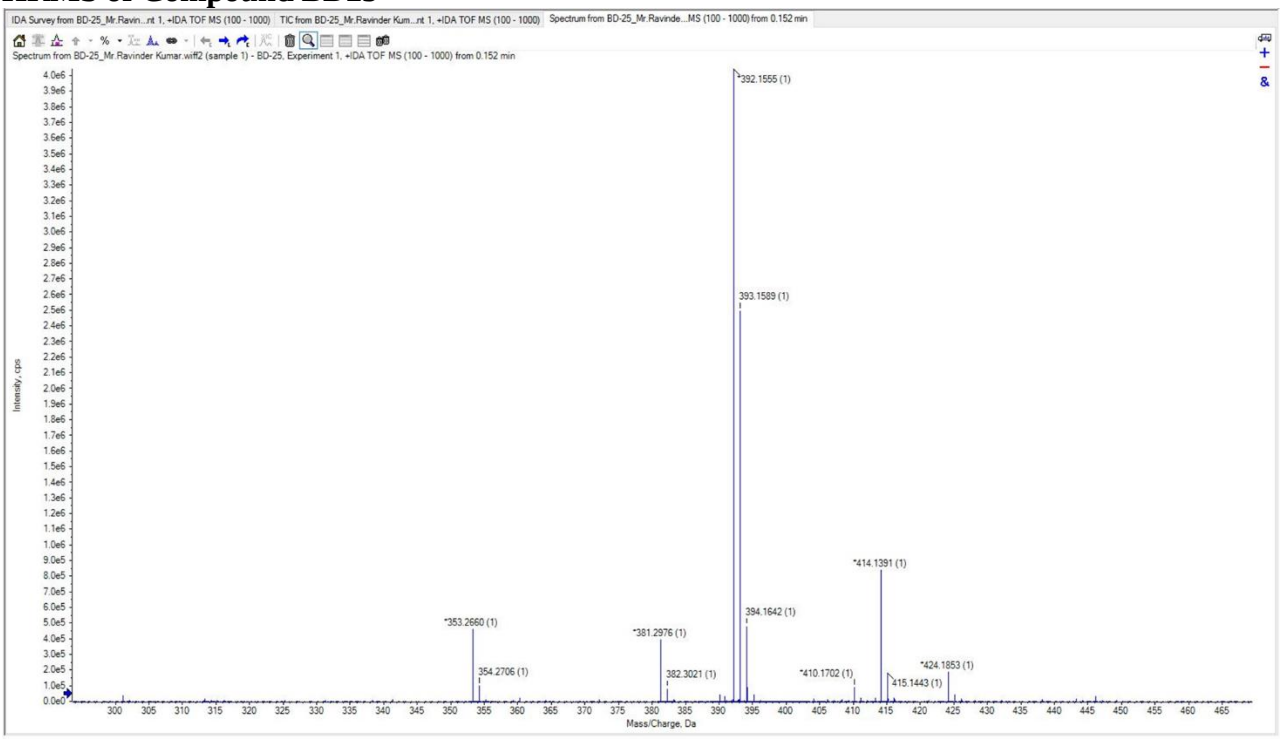
HRMS of Compound BD23



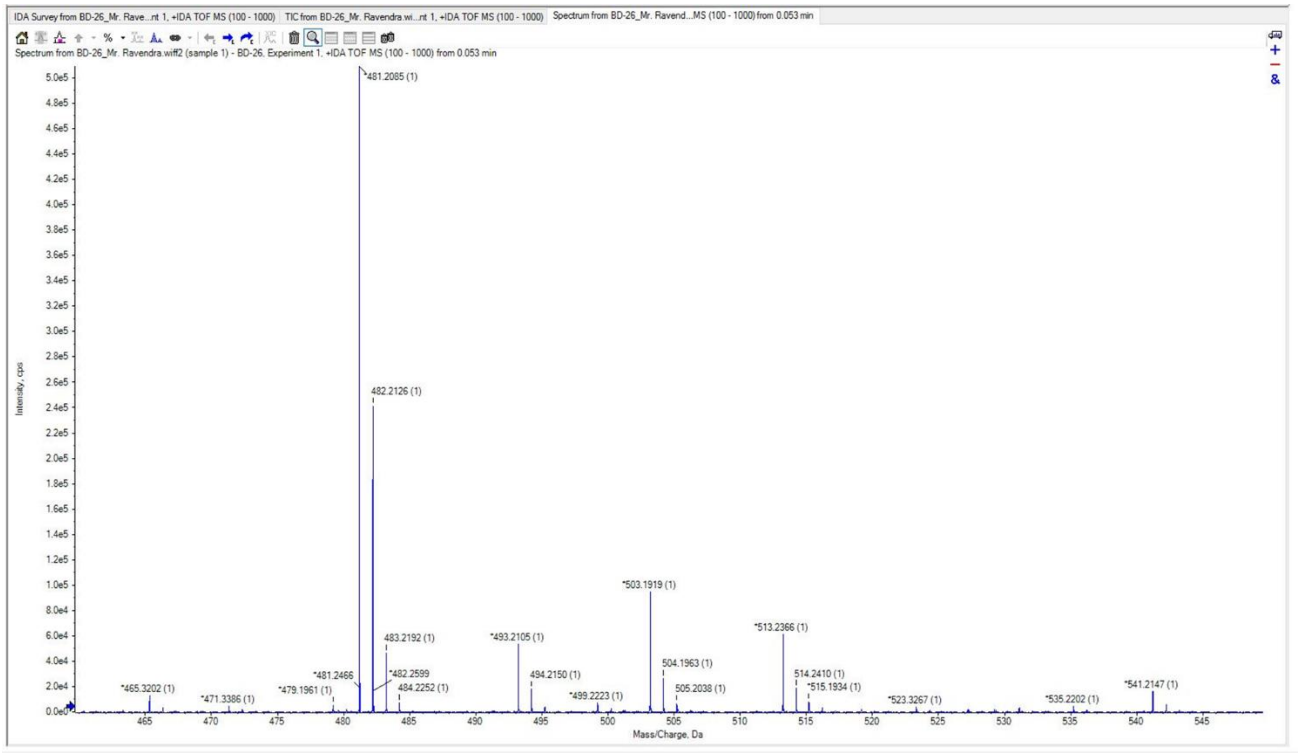
HRMS of Compound BD24



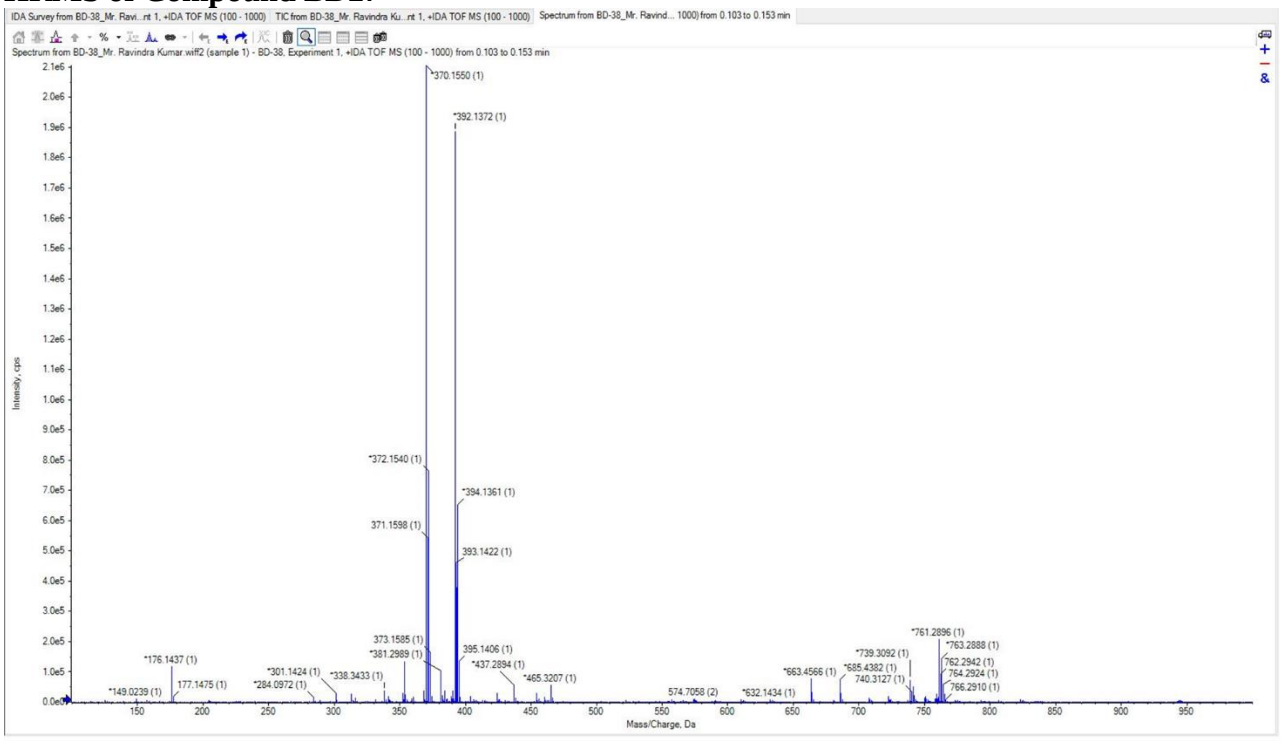
HRMS of Compound BD25



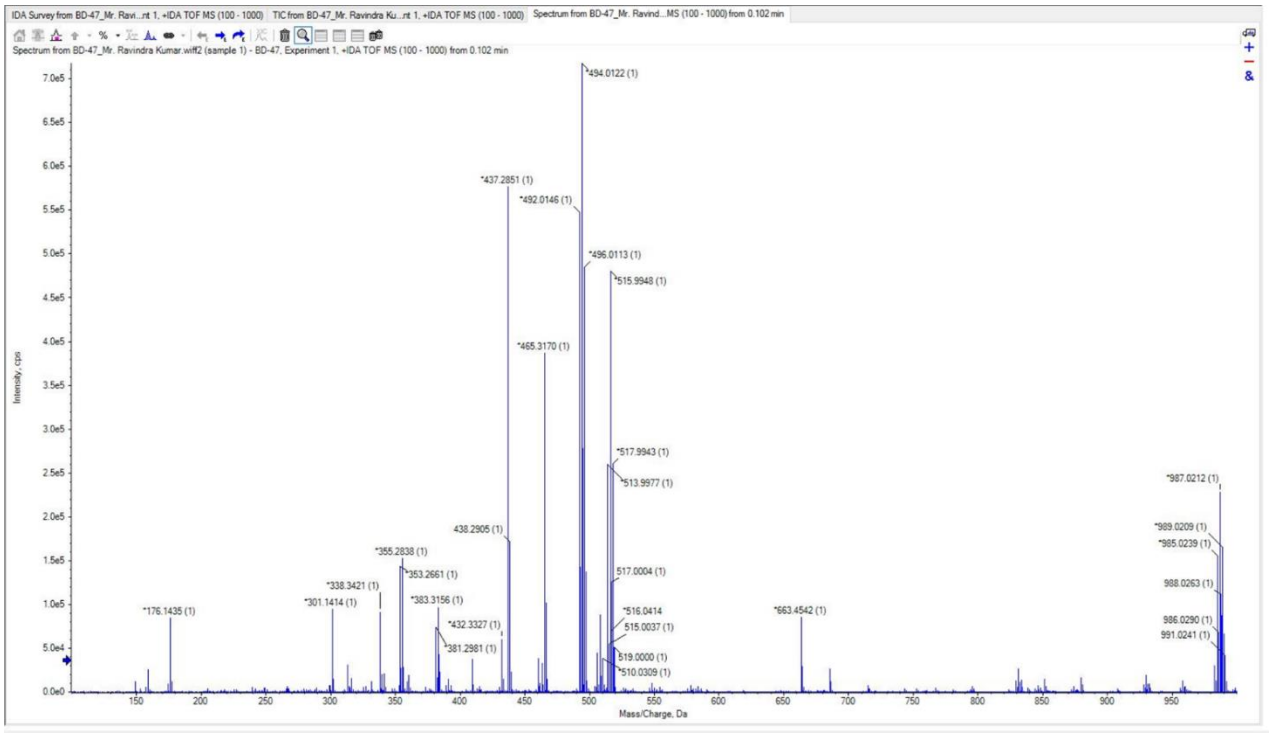
HRMS of Compound BD26



HRMS of Compound BD27



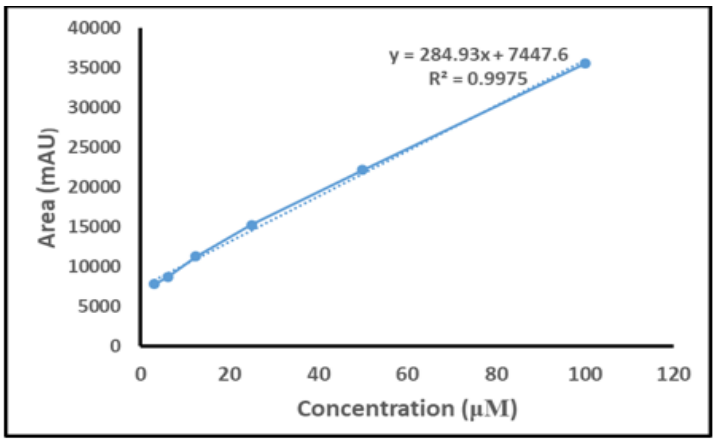
HRMS of Compound BD28



HPLC Data

Calibration curve and HPLC chromatogram obtained from HPLC analysis for compound BD23

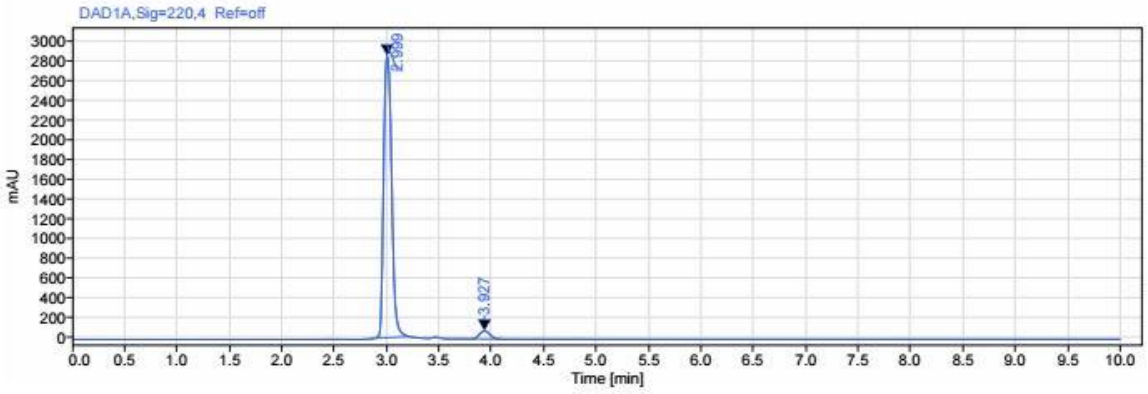
The calibration curve for hit compound BD23 was obtained by RP-HPLC by using the instrument Agilent 1260 infinity II and the solvent system used acetonitrile and water ratio 90:10. Column specification: Poroshell 123, EC C18 4µm, 4.6*150mm.



Single Injection Report

Agilent

Data file:	BD23_6.2520221205 061805.dx		
Sequence Name:	BD23_23_2320221205 060924	**Project Name:**	HPLC
Sample name:	BD23_6.25	**Operator:**	SYSTEM (SYSTEM)
Instrument:	HPLC	**Injection date:**	2022-12-05 06:19:01+05:30
Inj. volume:	20.000	**Location:**	
Acq. method:	BD-23.amx	**Type:**	Calibration
Processing method:	bhanu2.pmx	**Sample amount:**	0.00
Manually modified:	Manual Integration		

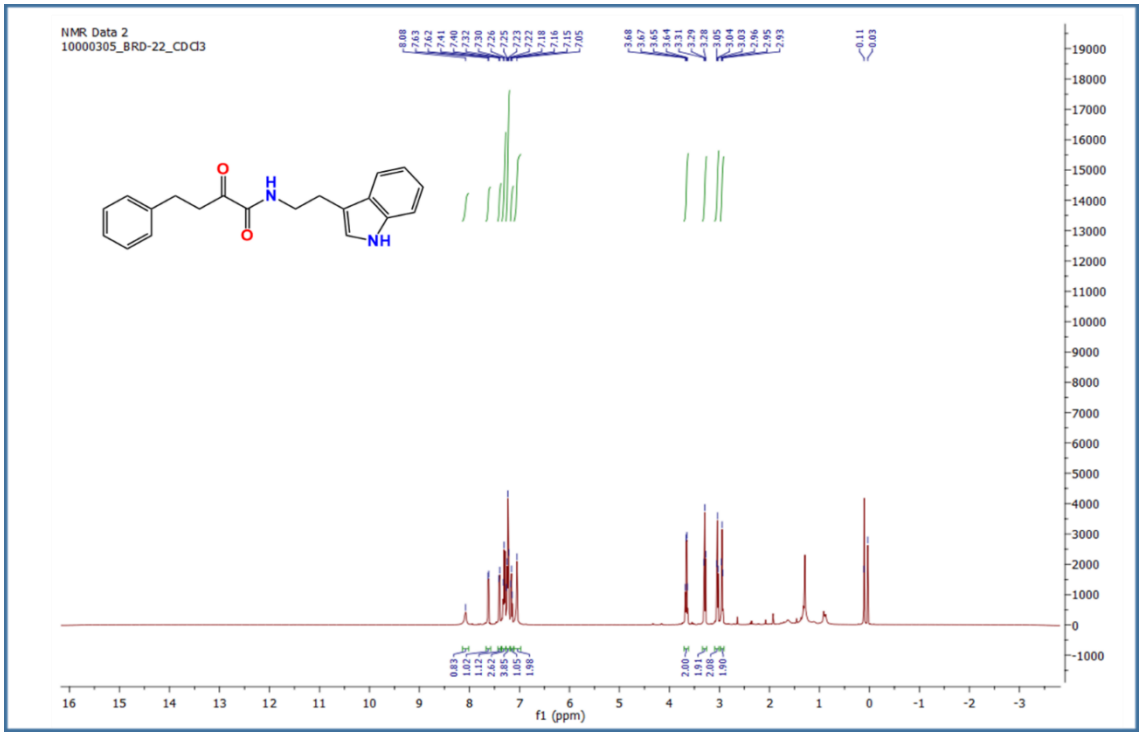


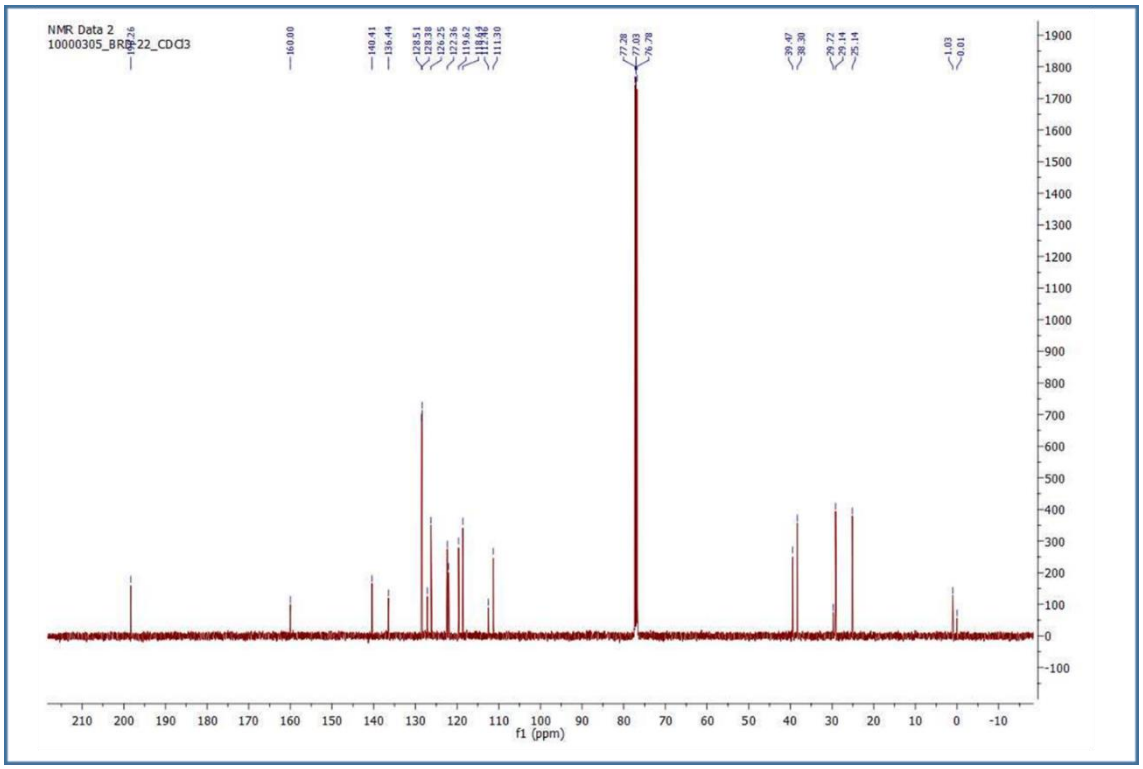
Signal: DAD1A,Sig=220,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
2.999	MM m	0.35	15224.63	2855.00	96.46	
3.927	MM m	0.28	557.96	79.57	3.54	
		Sum	**15782.59**			

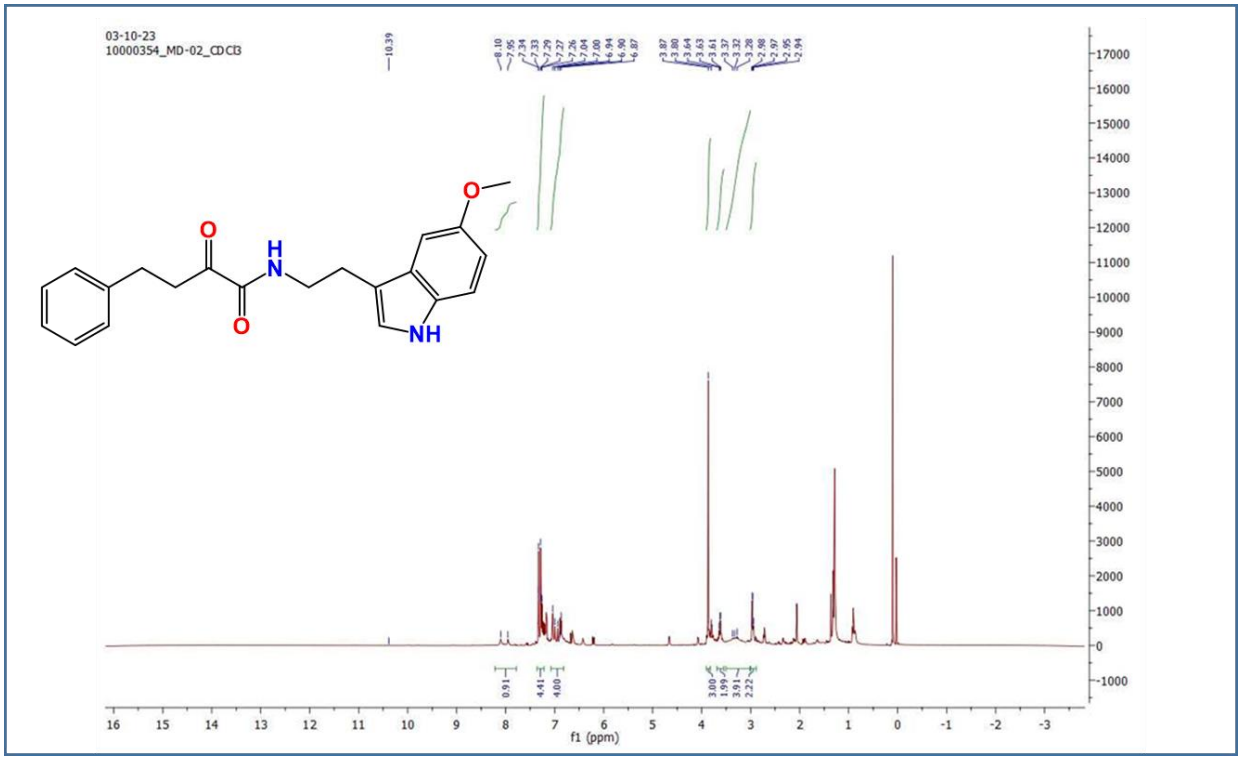
Annexure-II

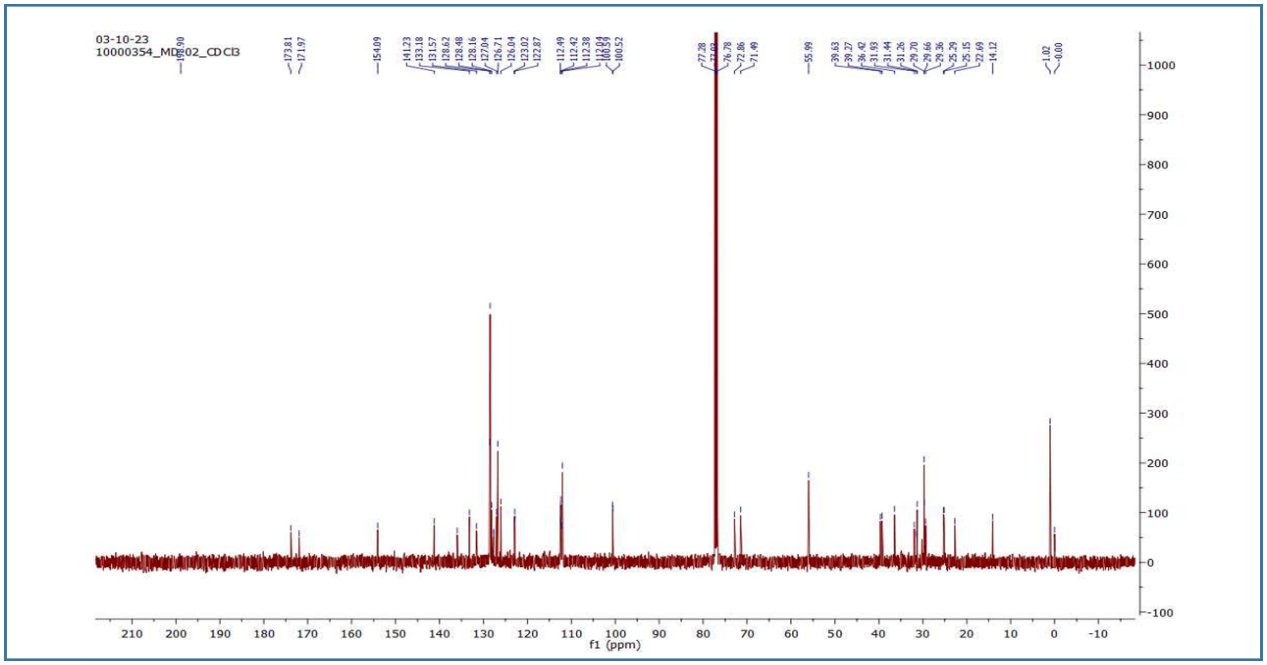
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD01



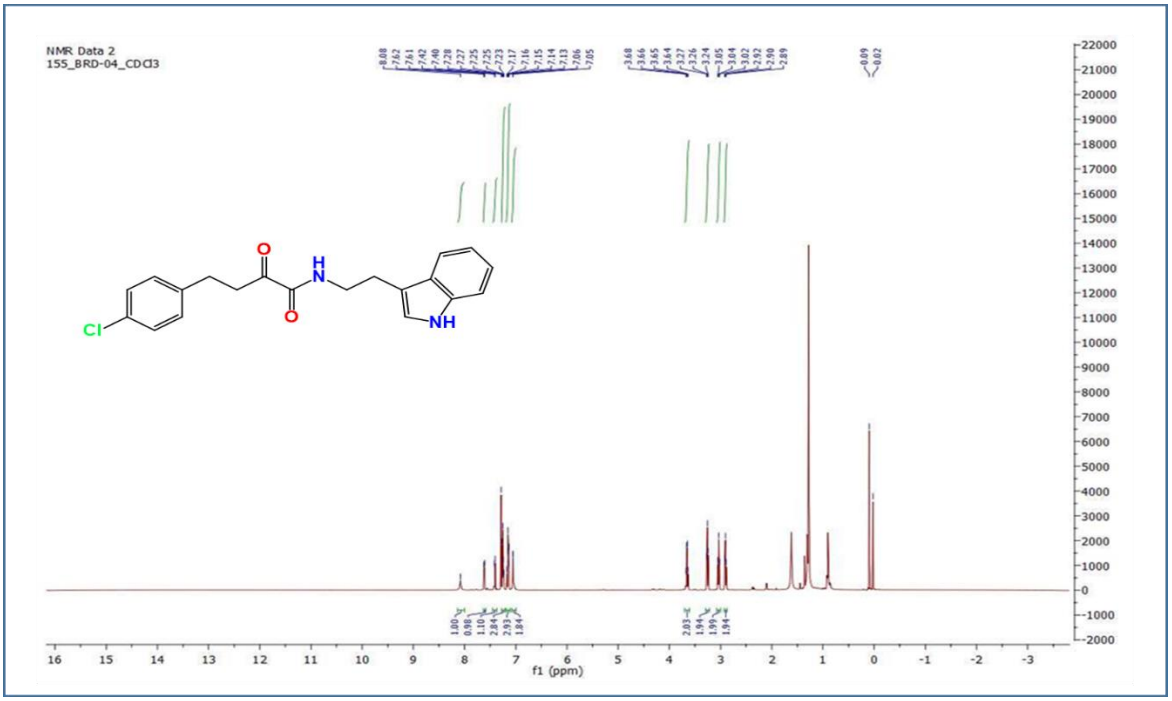


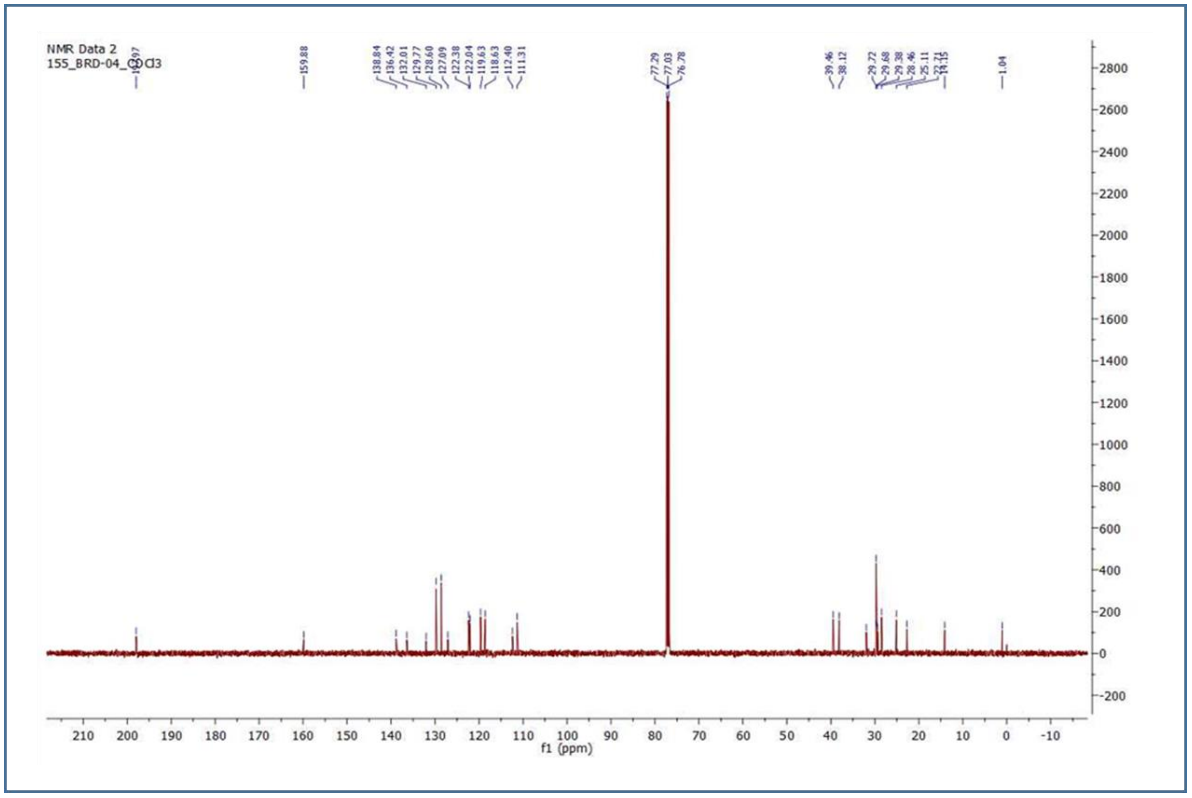
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD02



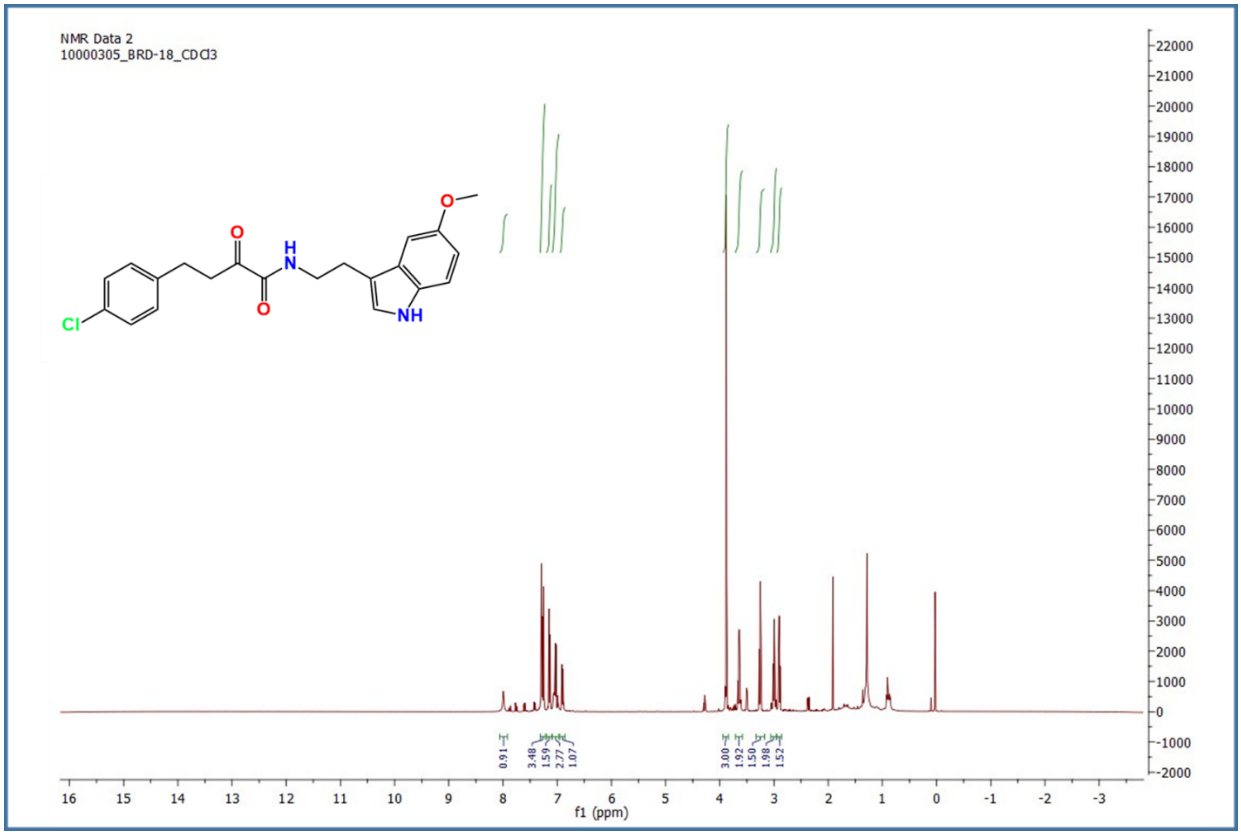


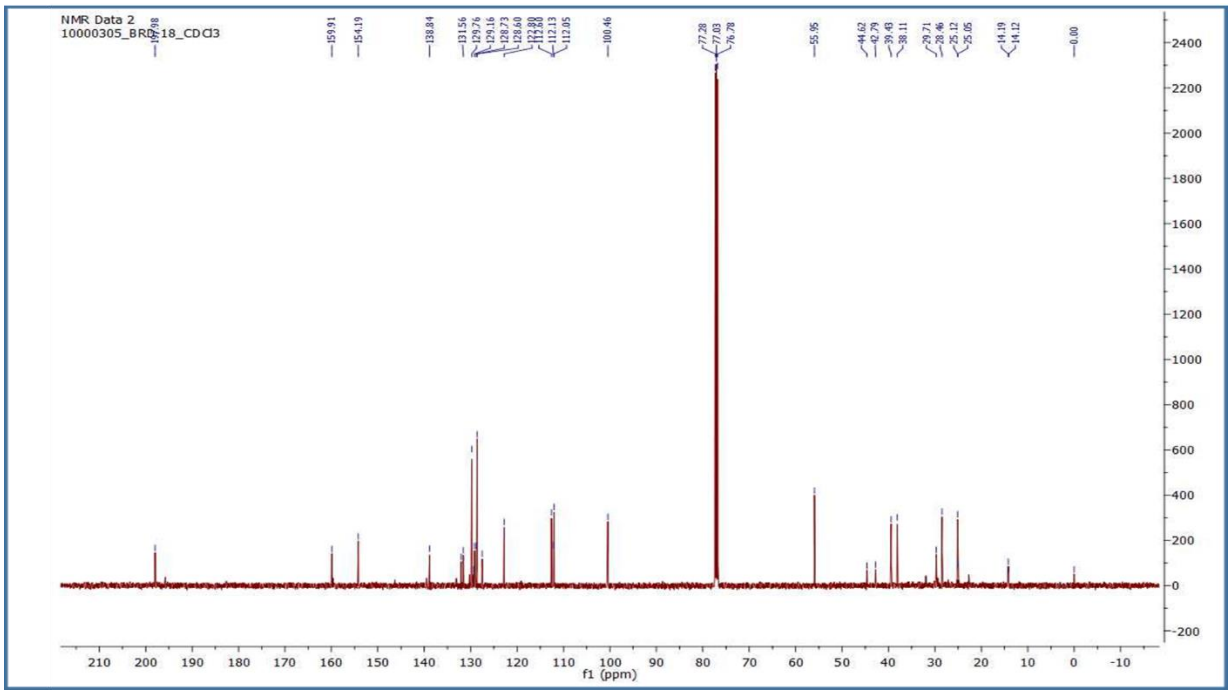
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD03



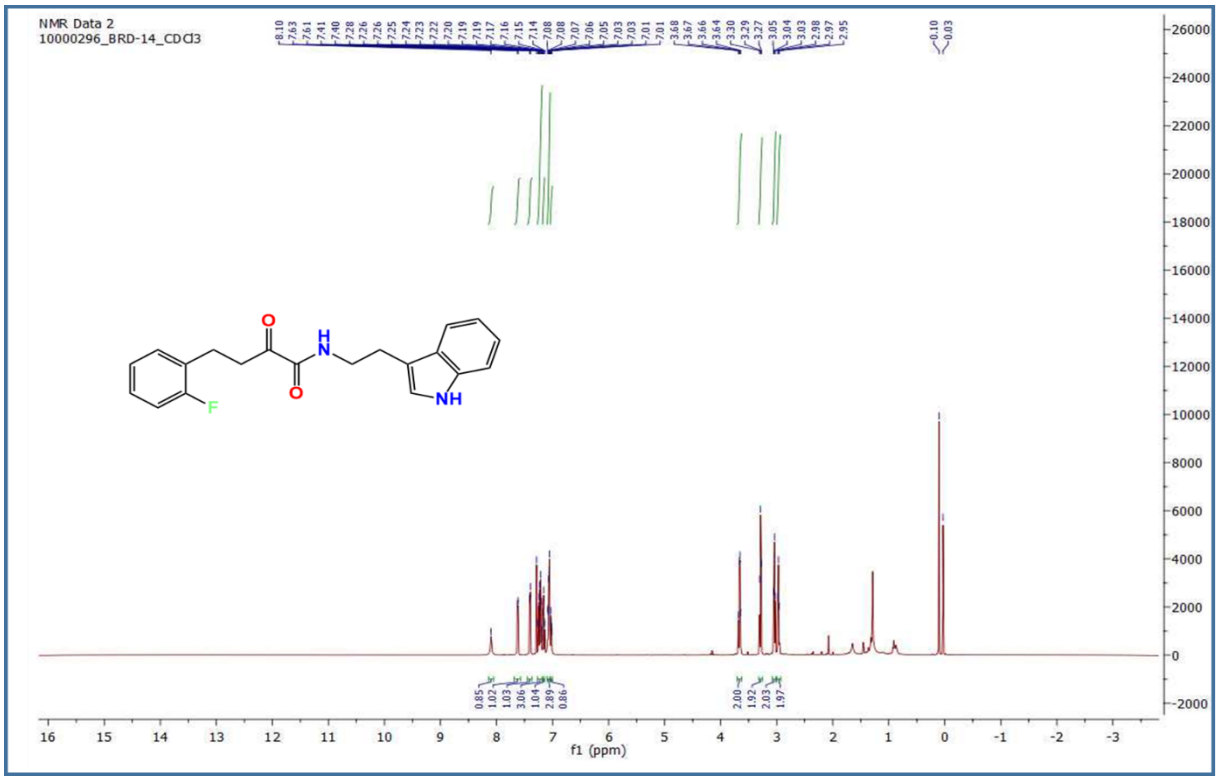


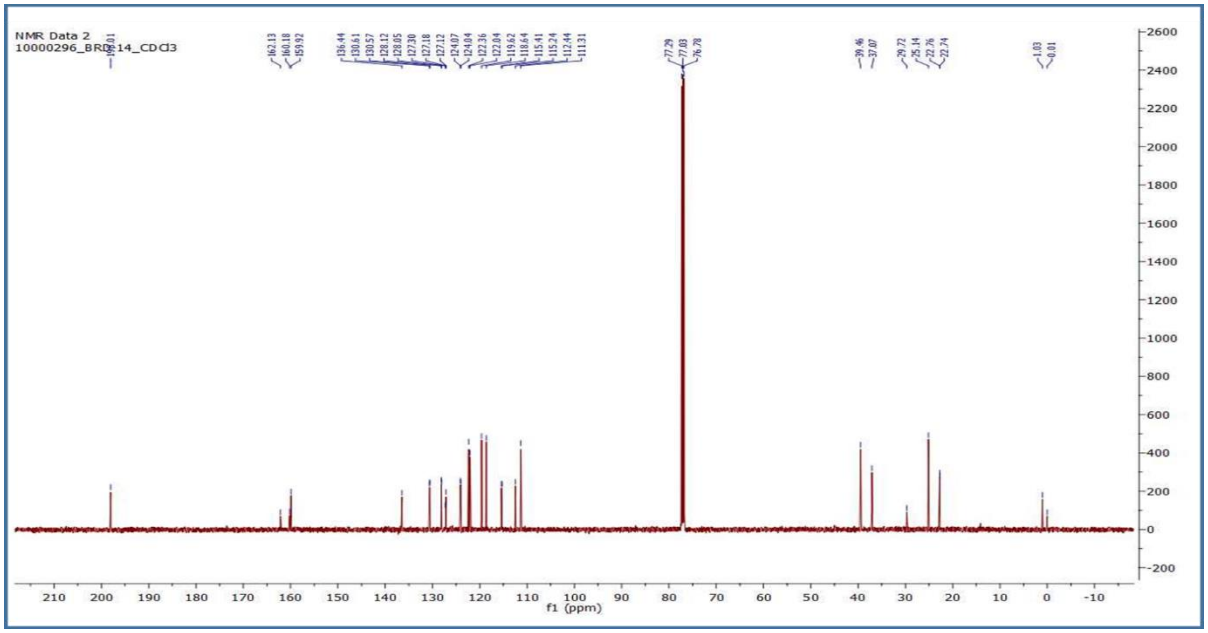
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD-04



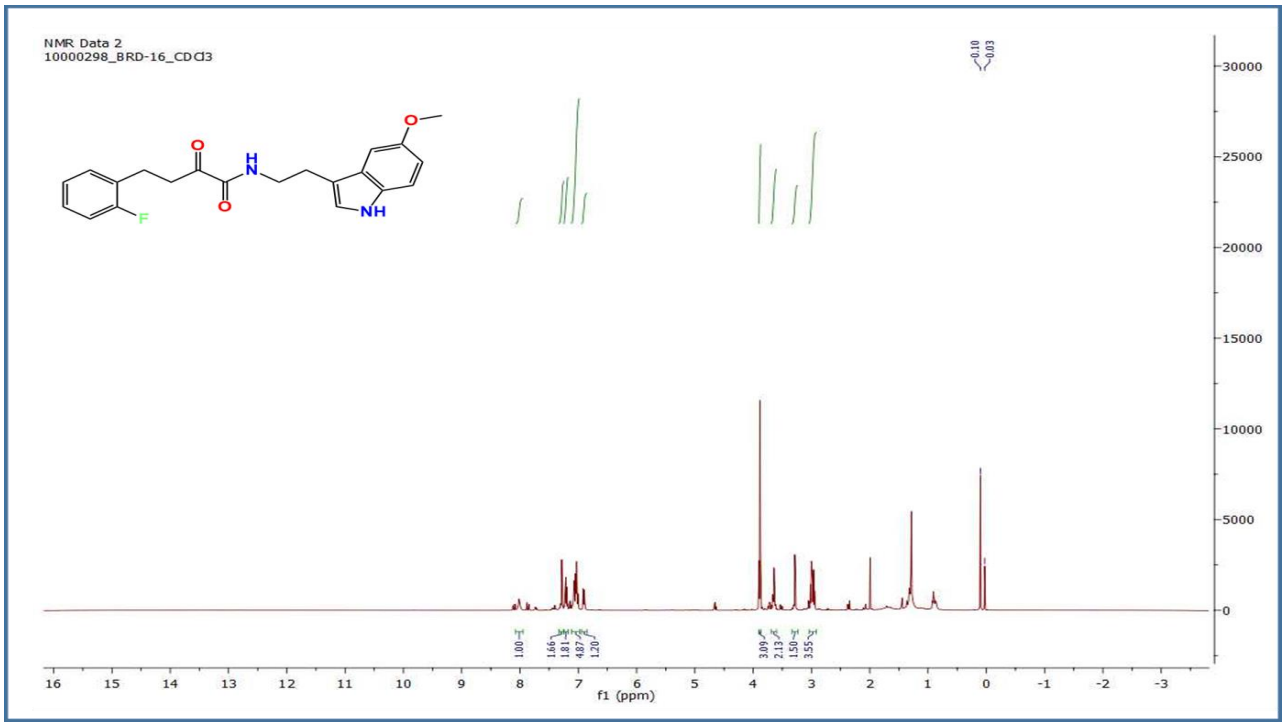


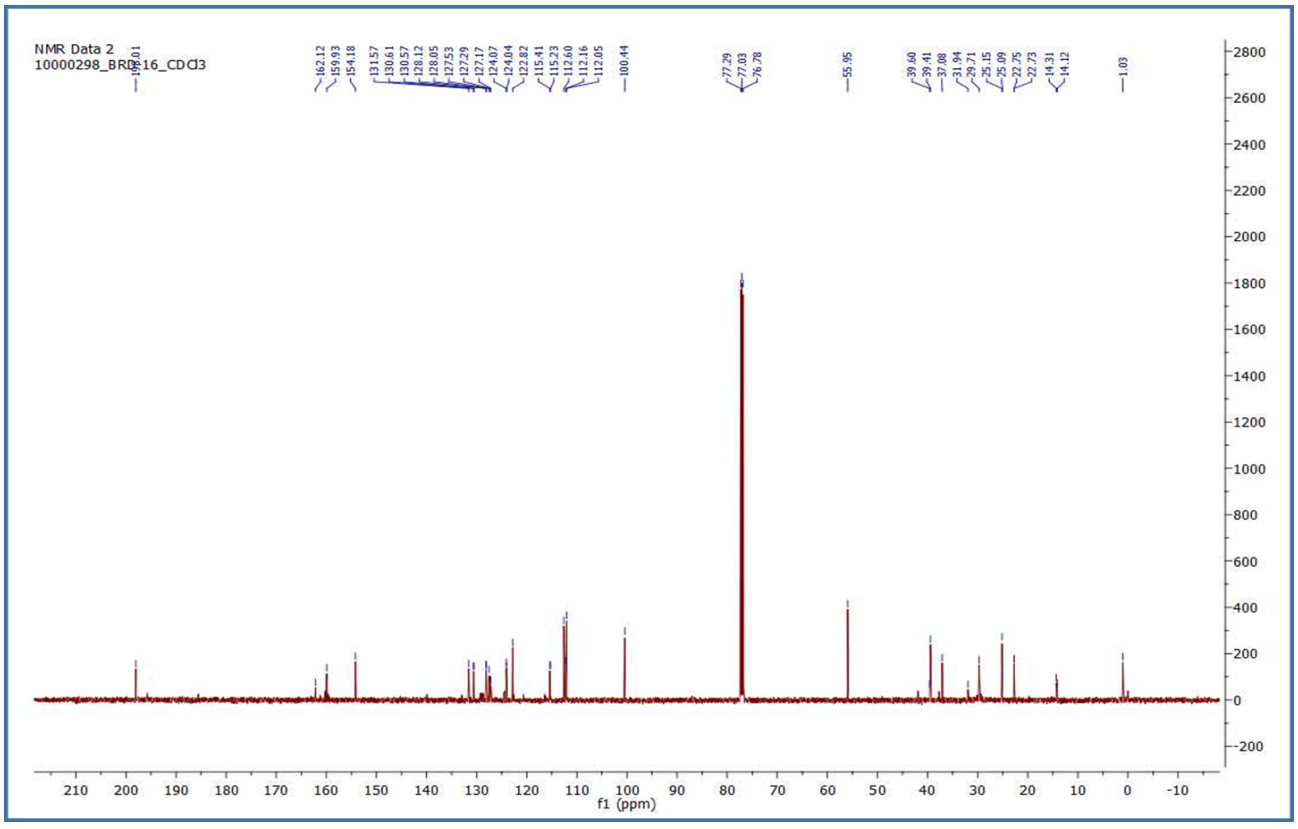
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD05



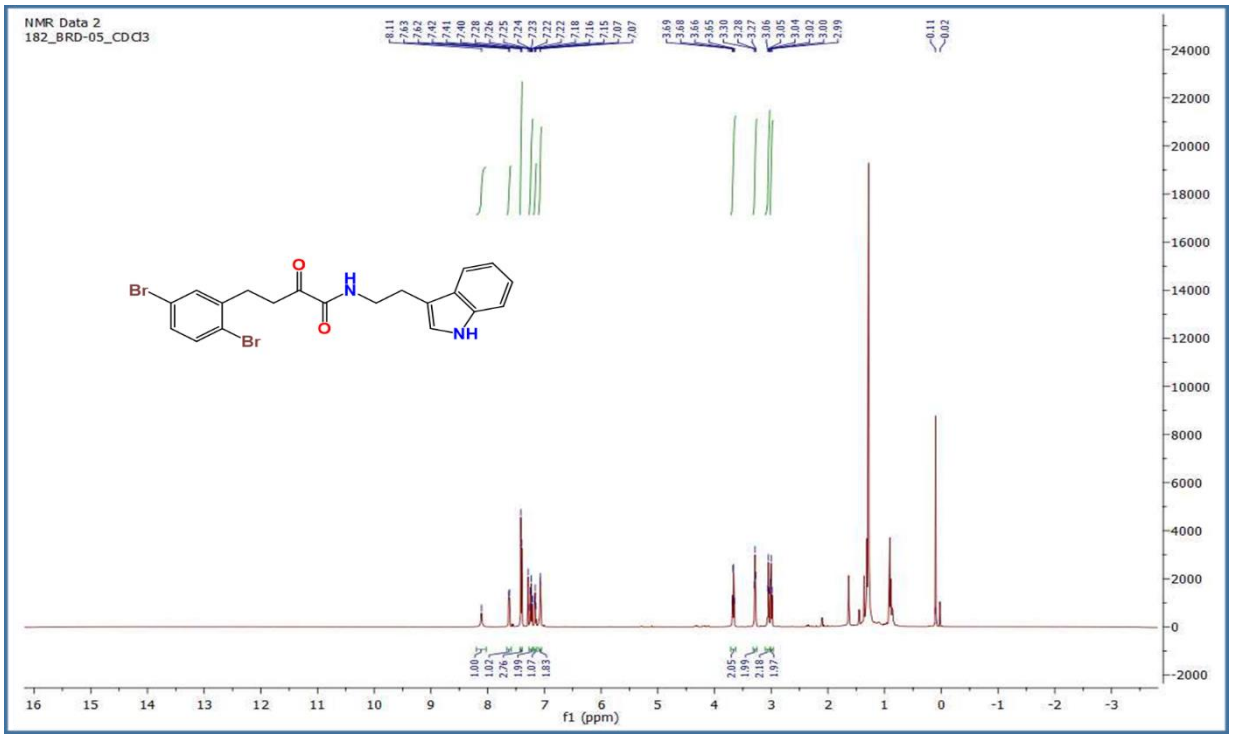


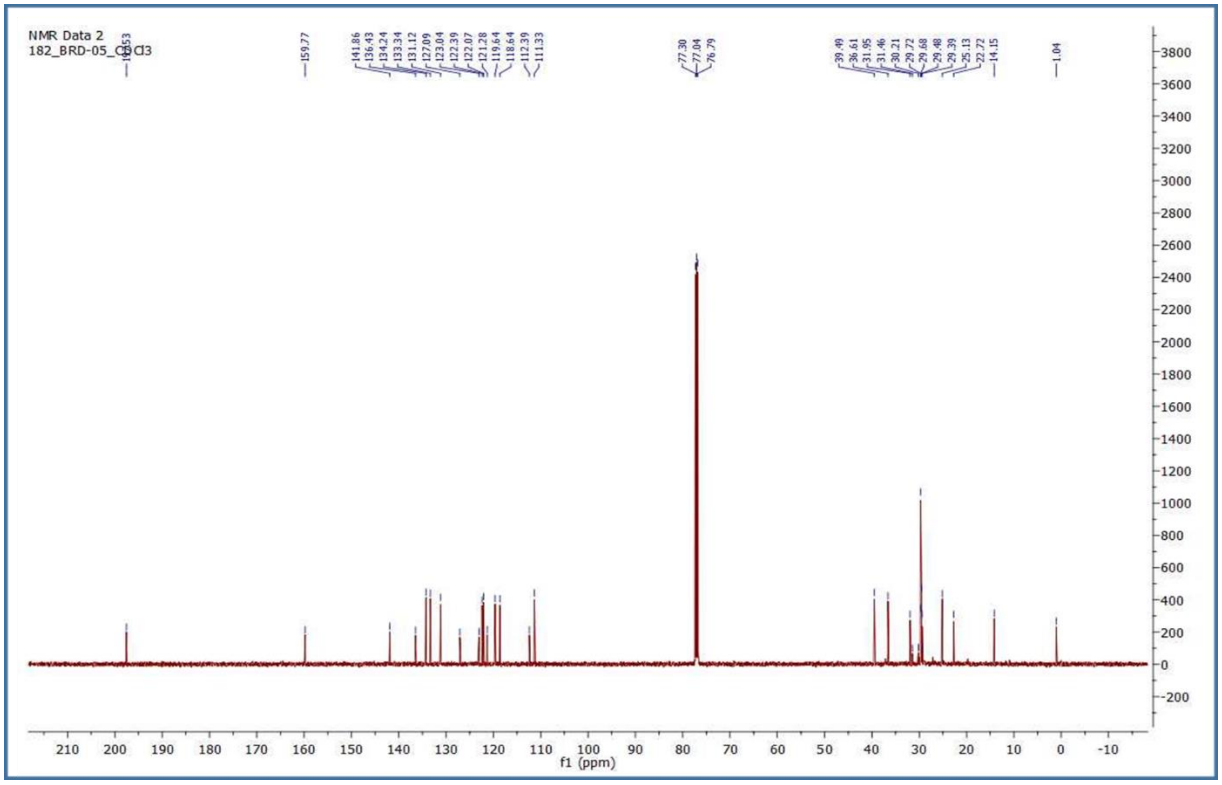
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD06



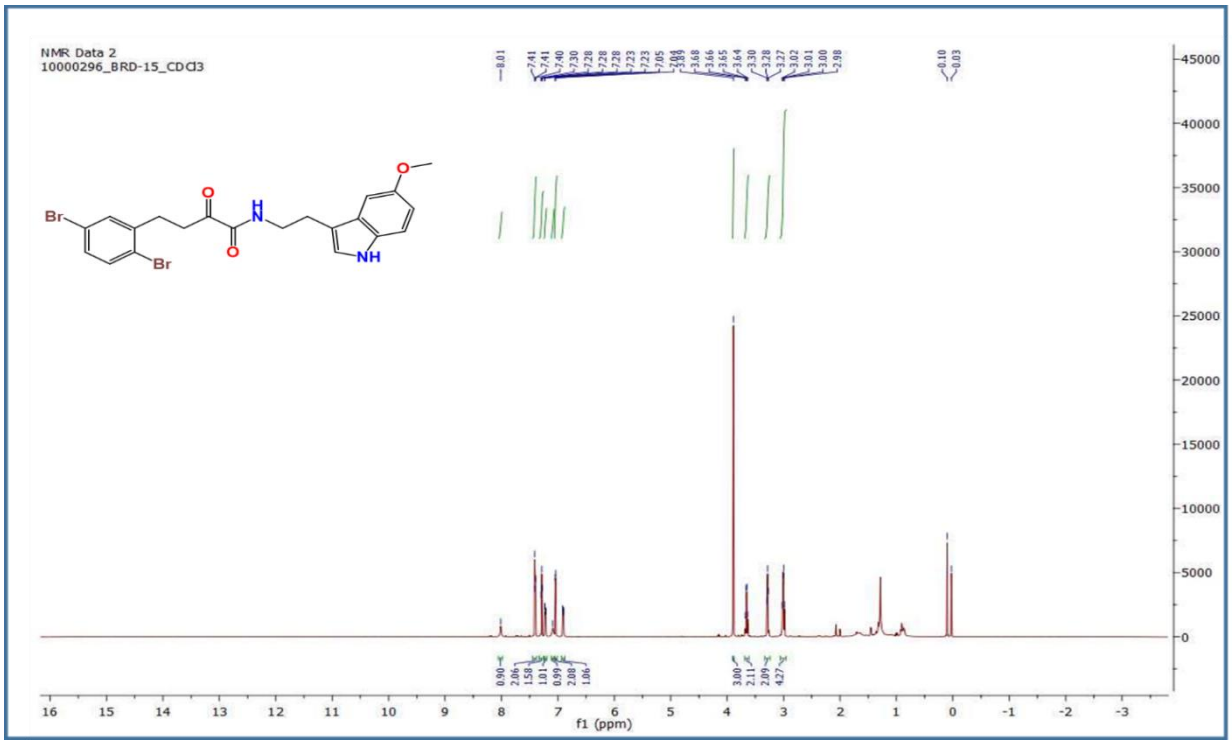


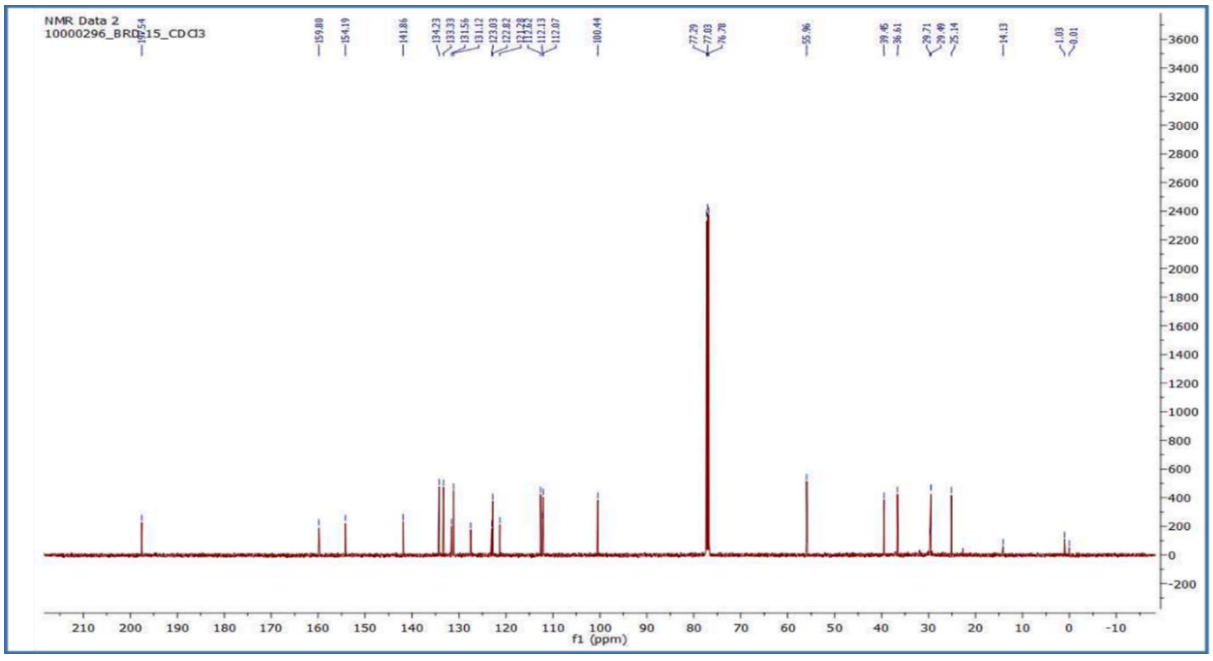
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD07



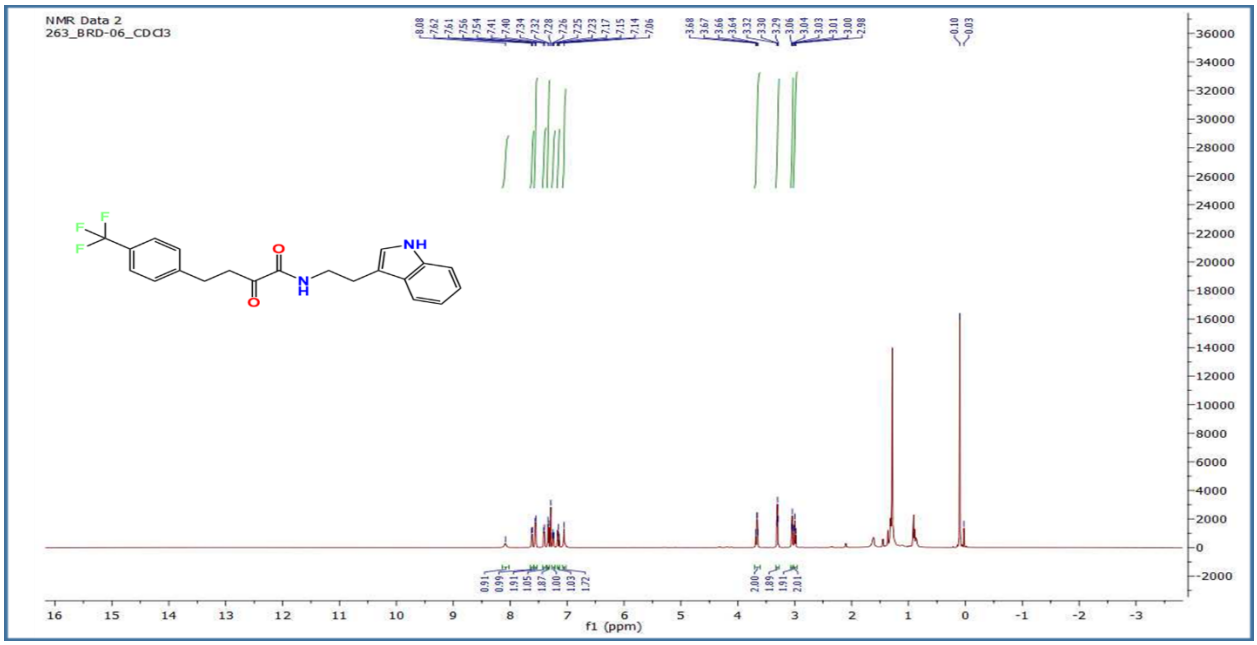


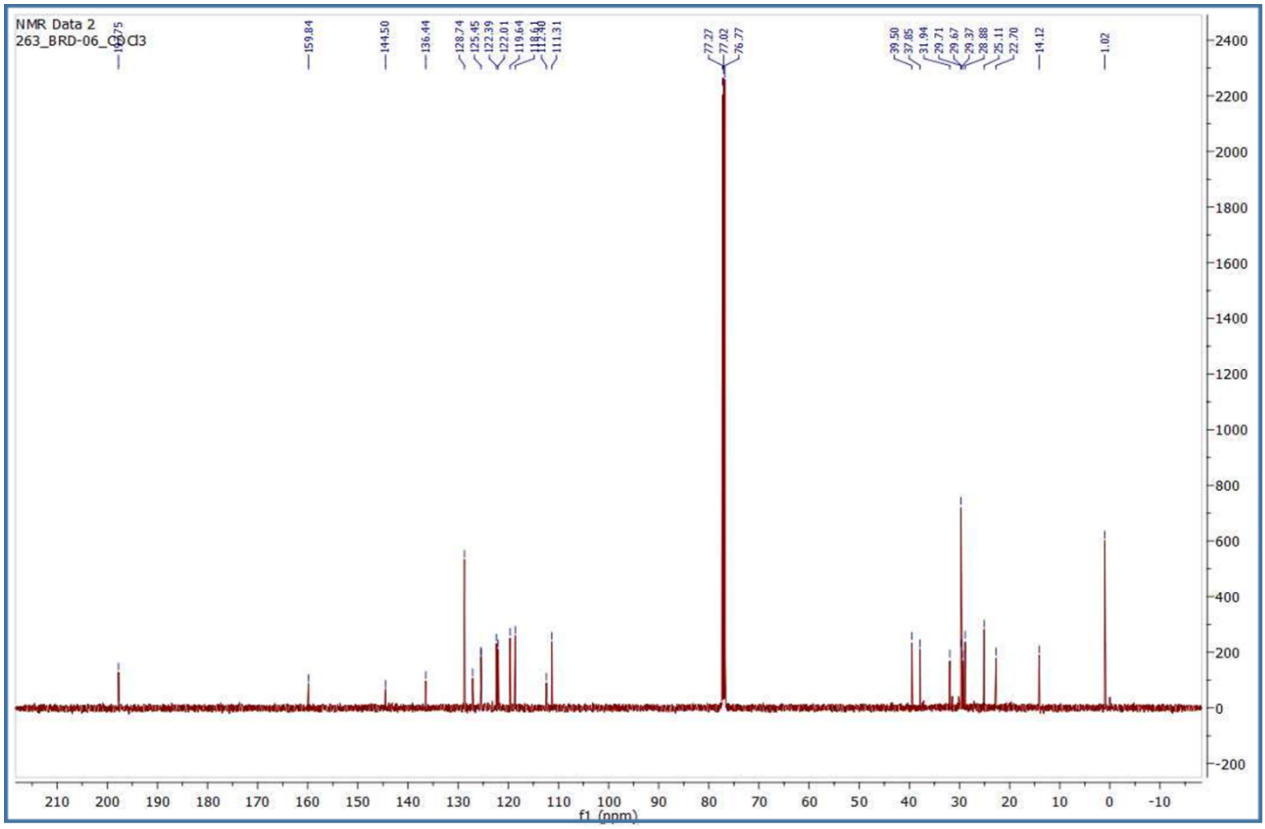
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD08



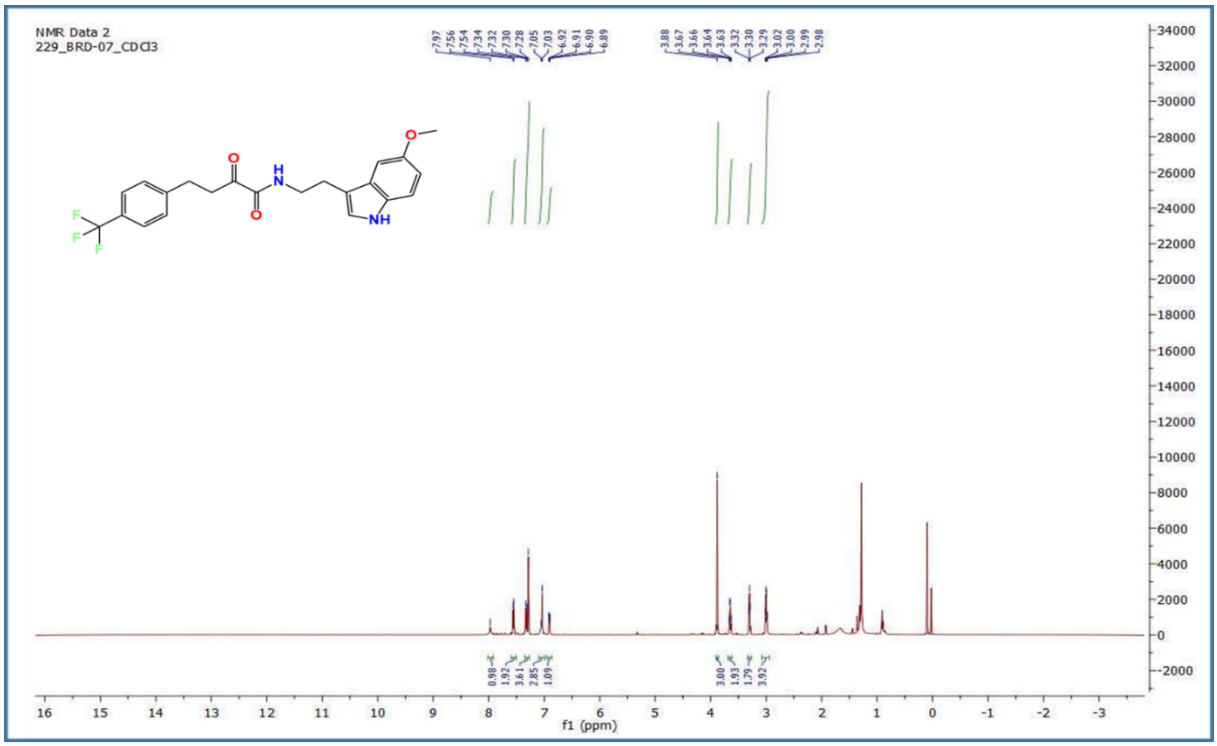


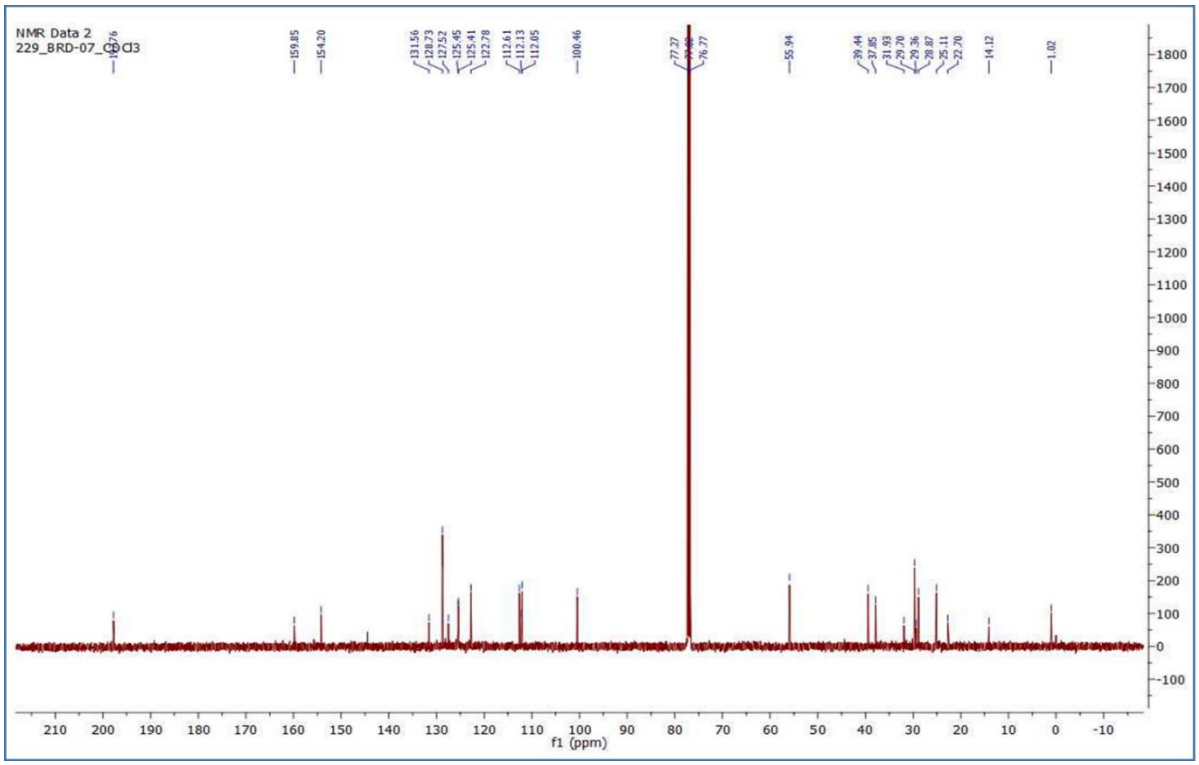
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD09



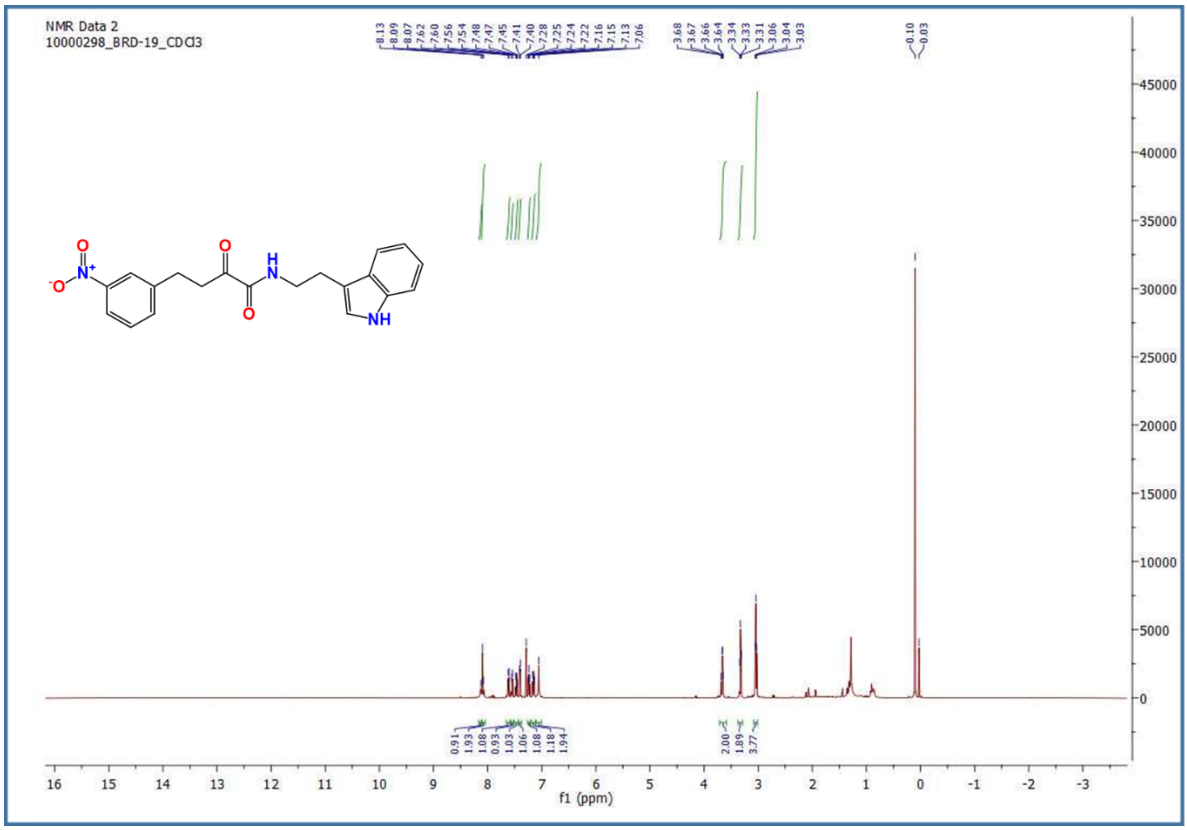


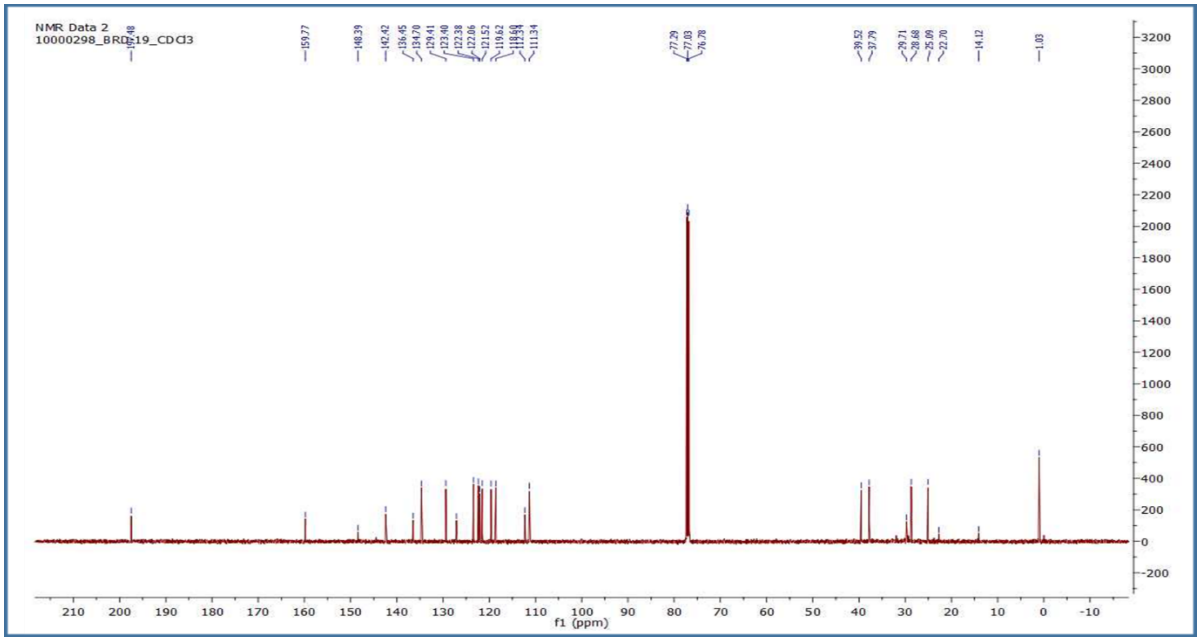
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD10



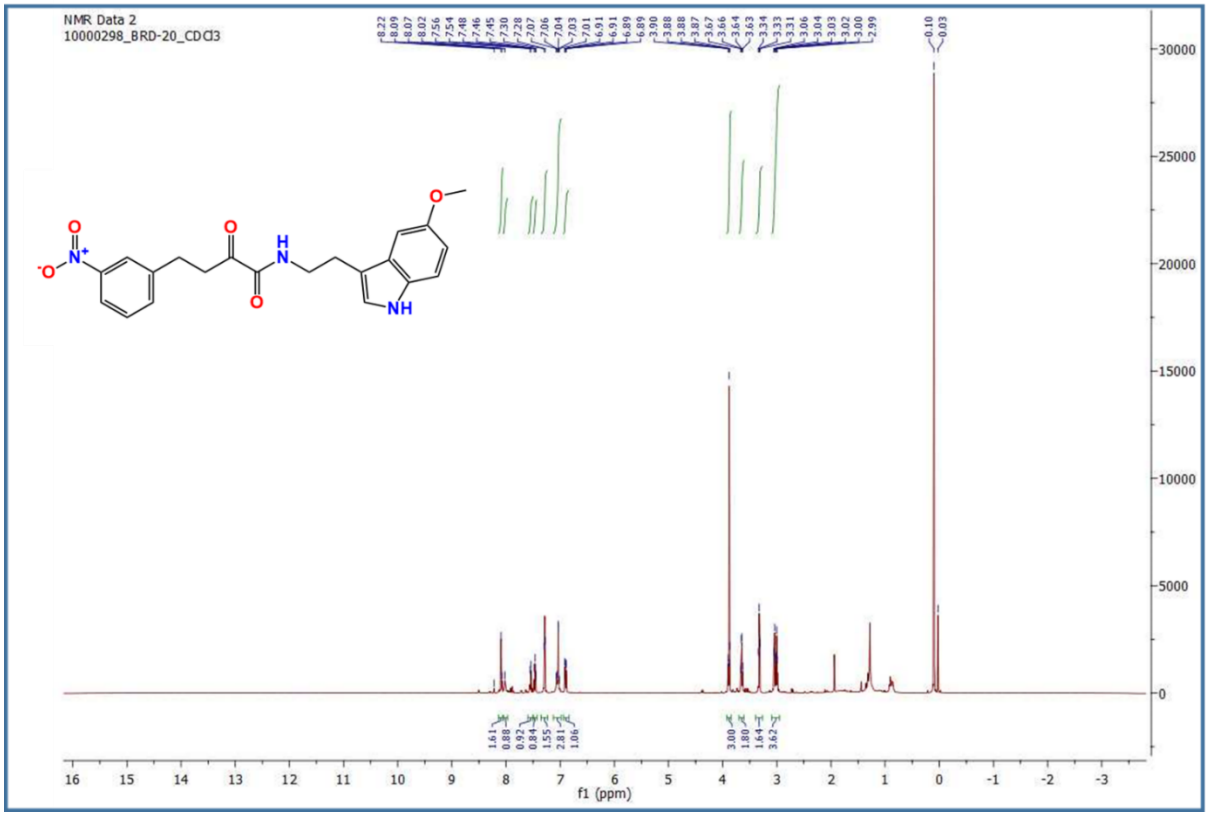


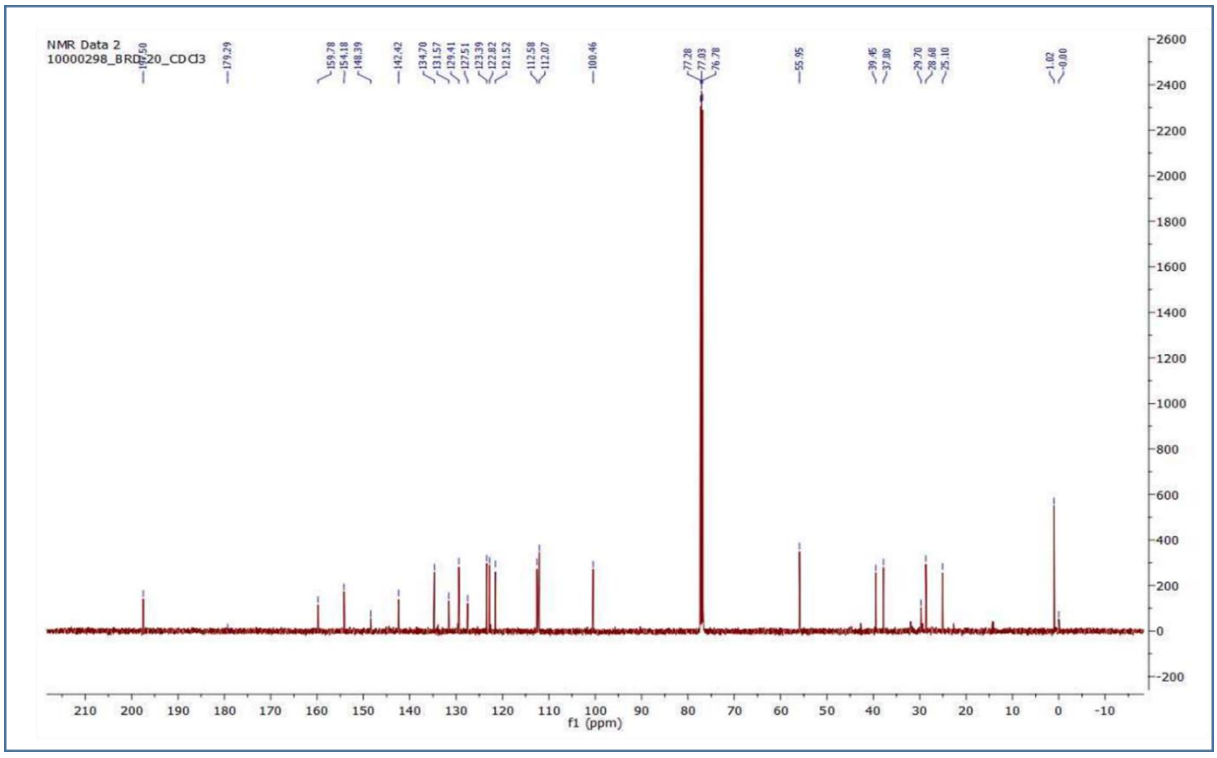
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD11



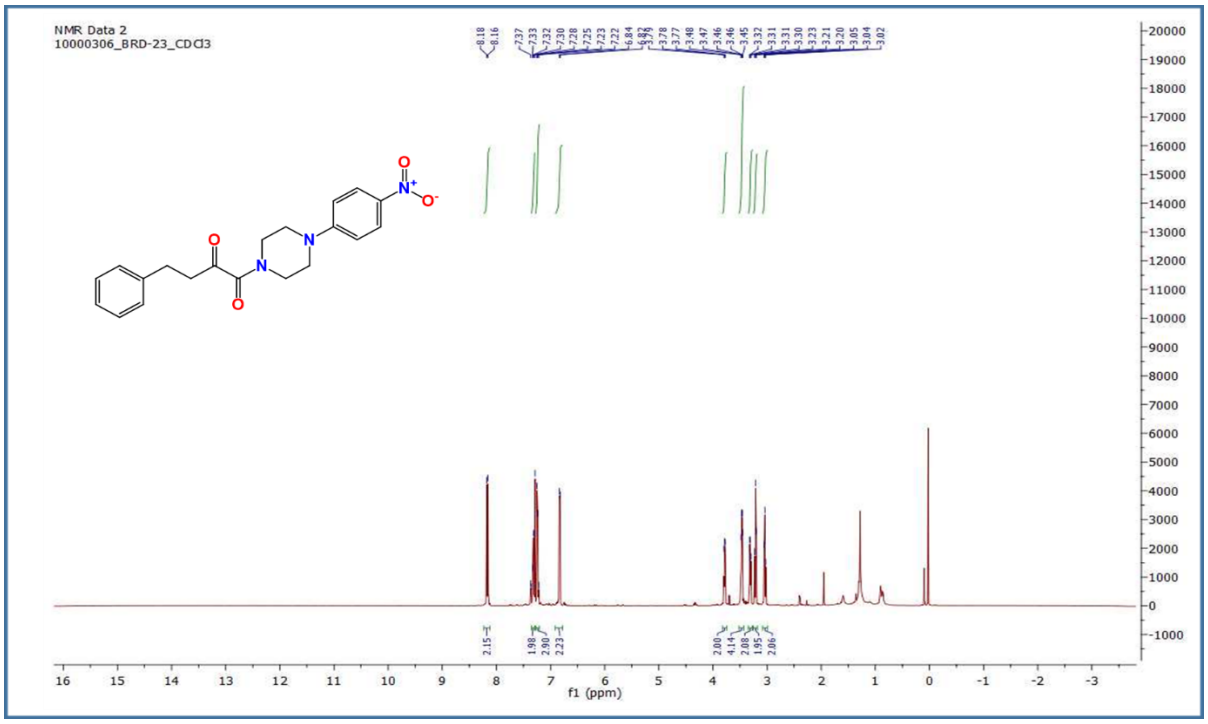


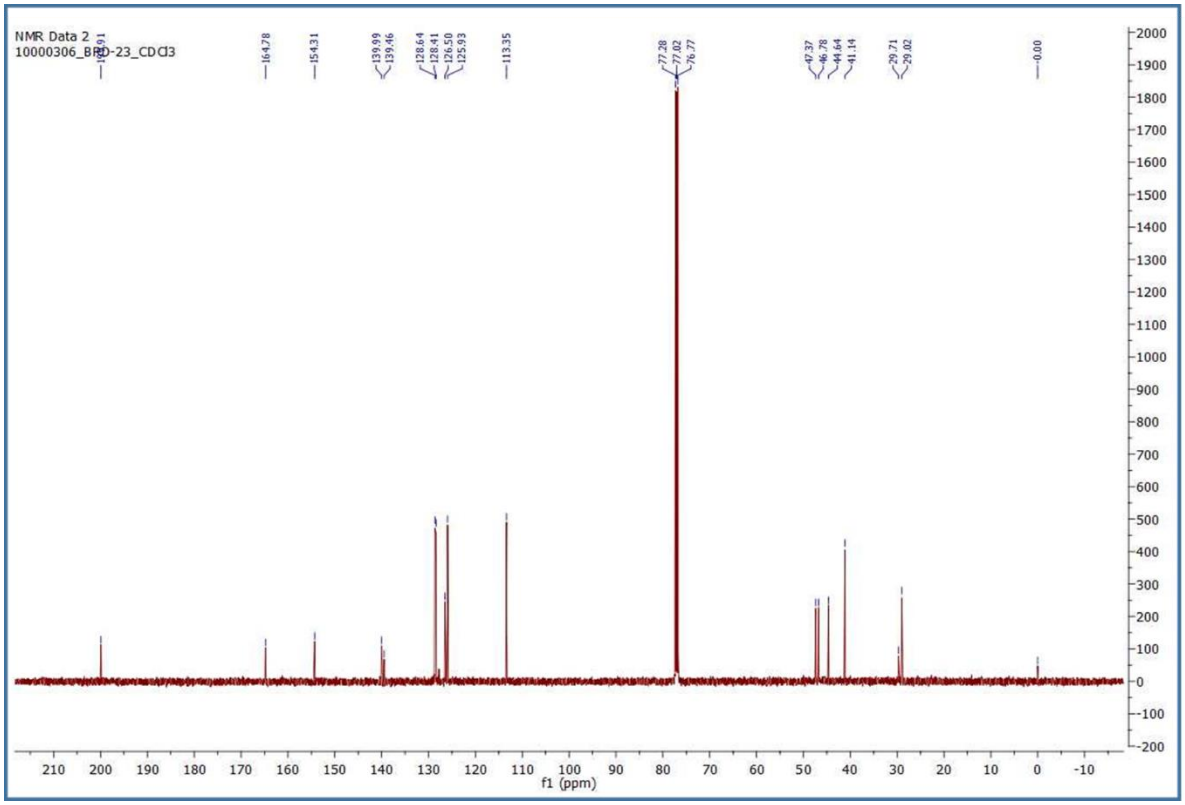
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD12



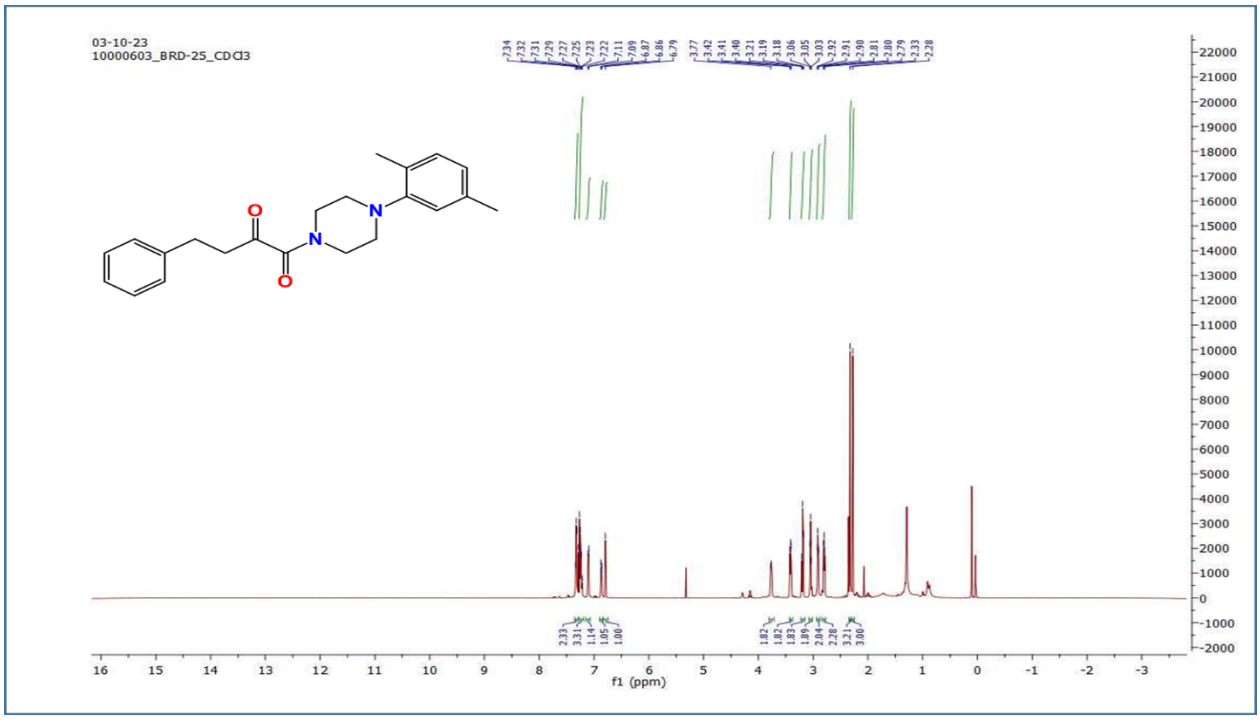


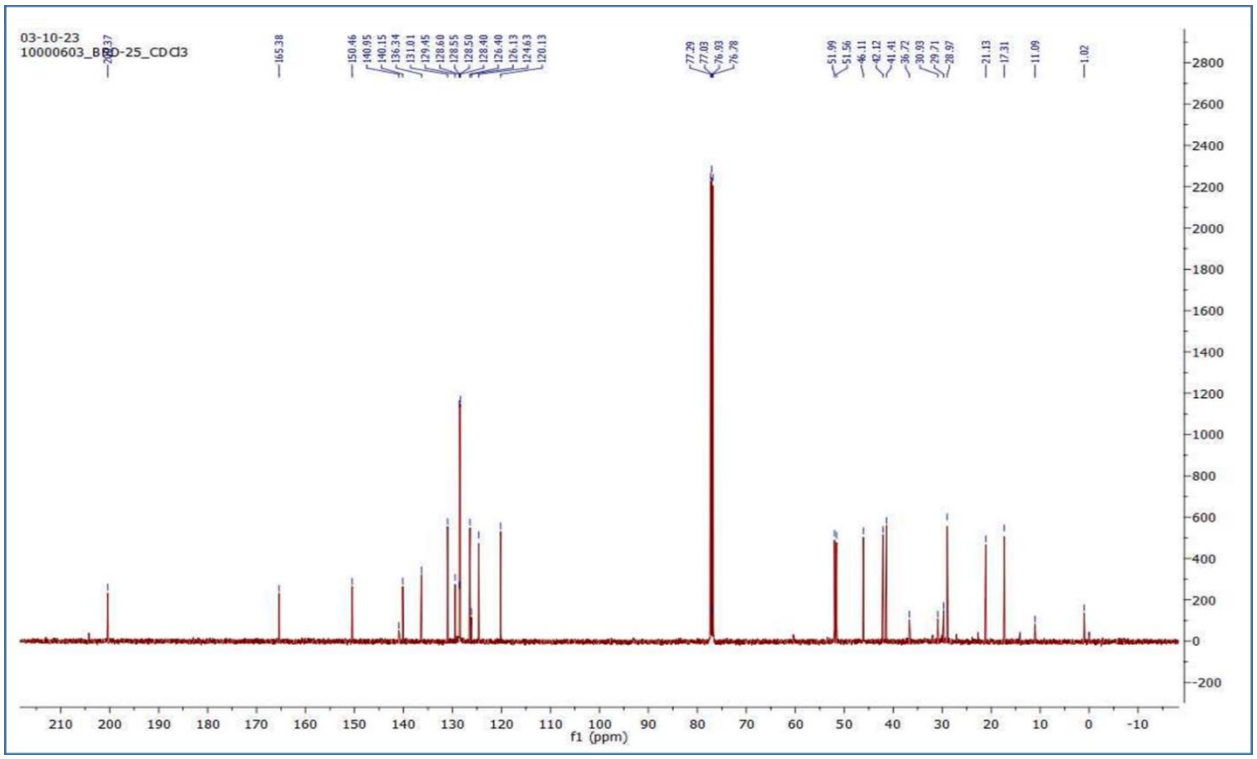
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD13



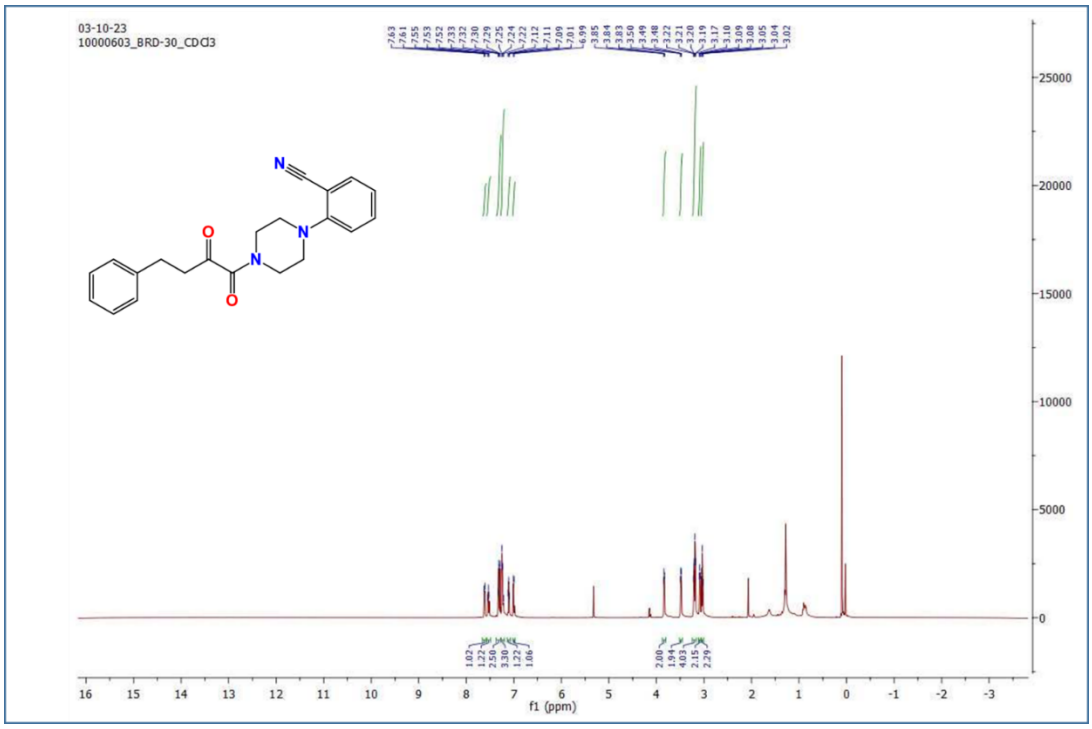


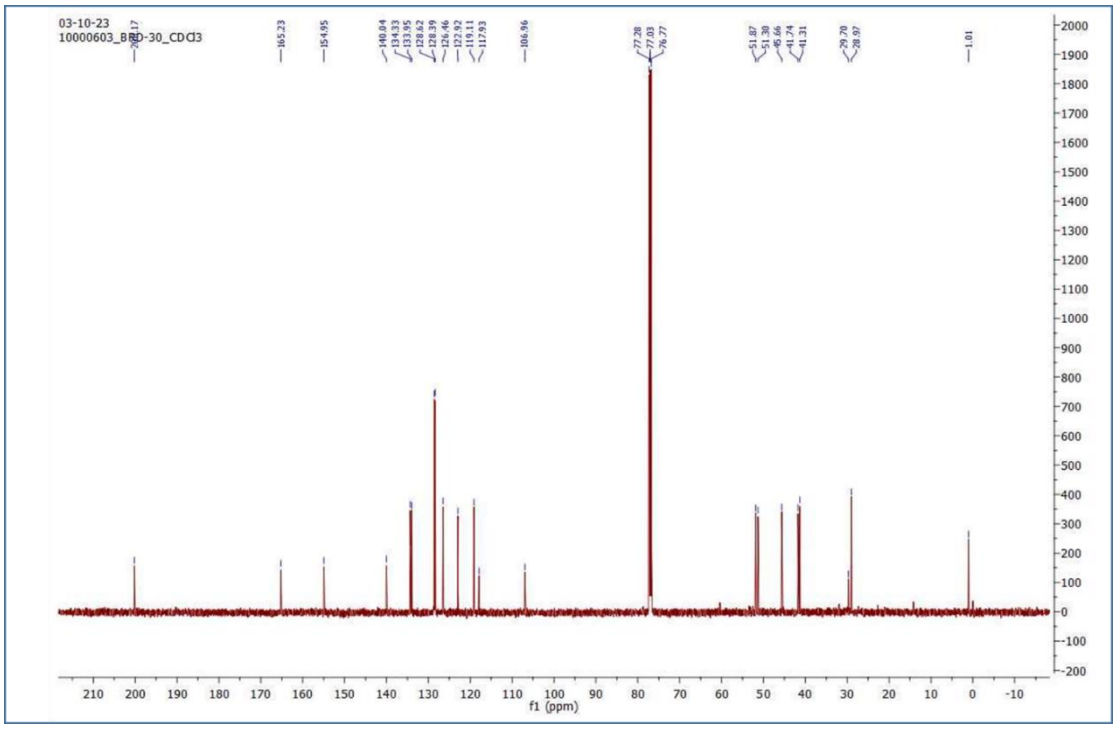
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD14



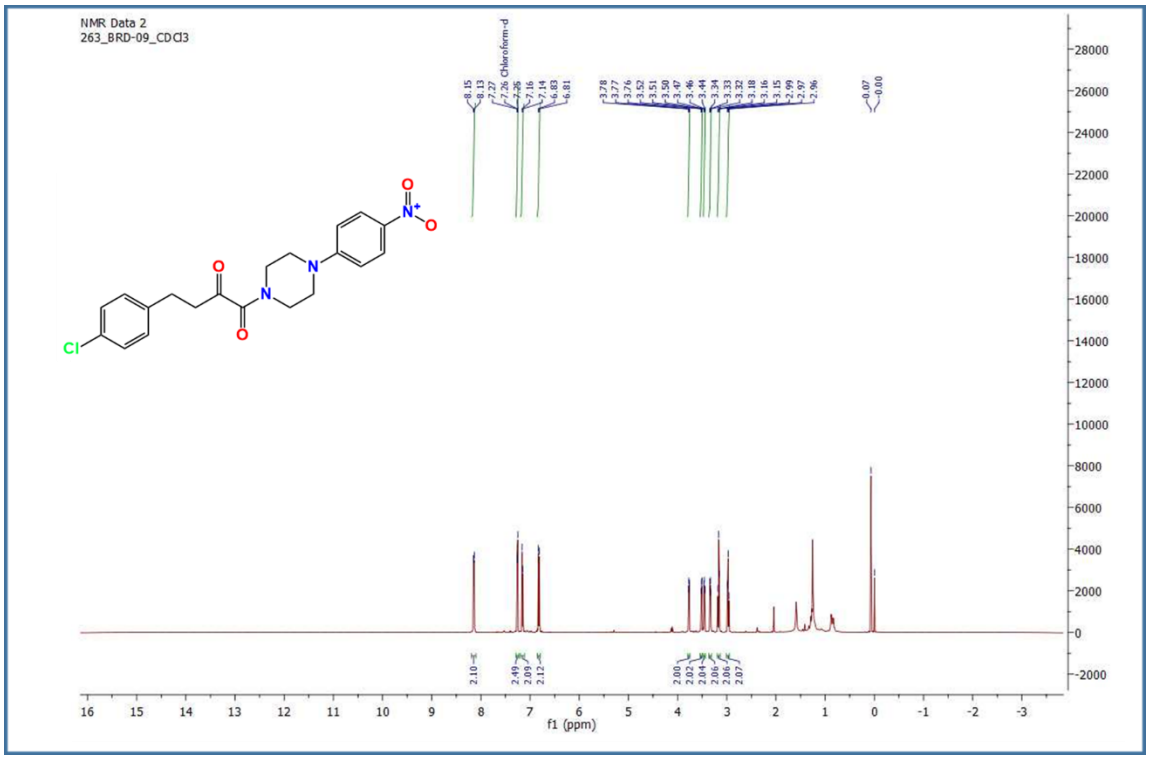


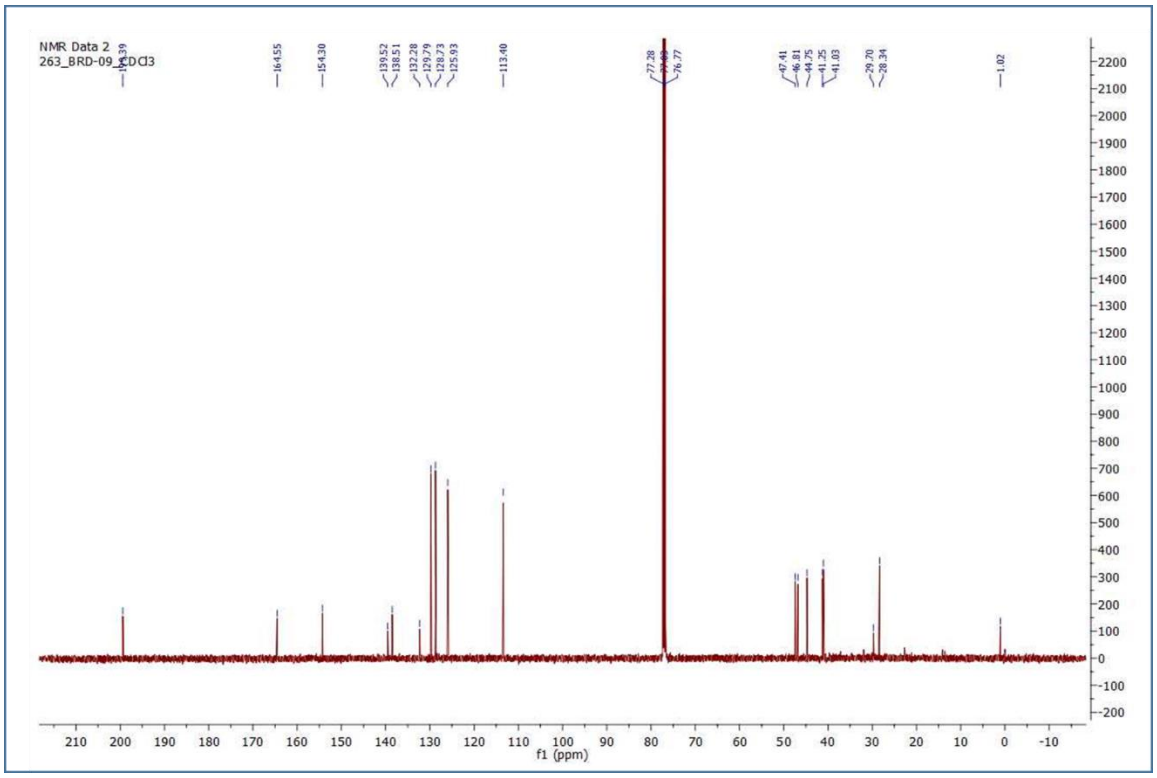
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD15



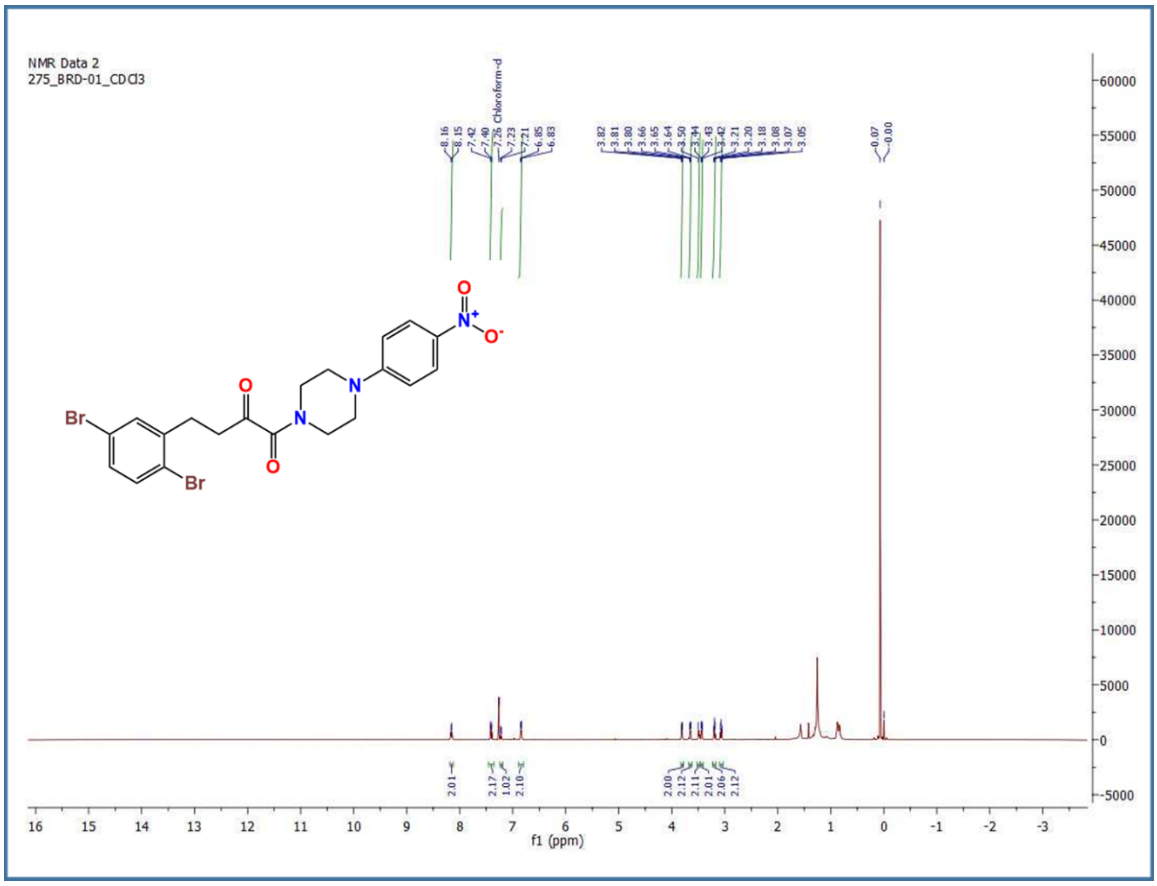


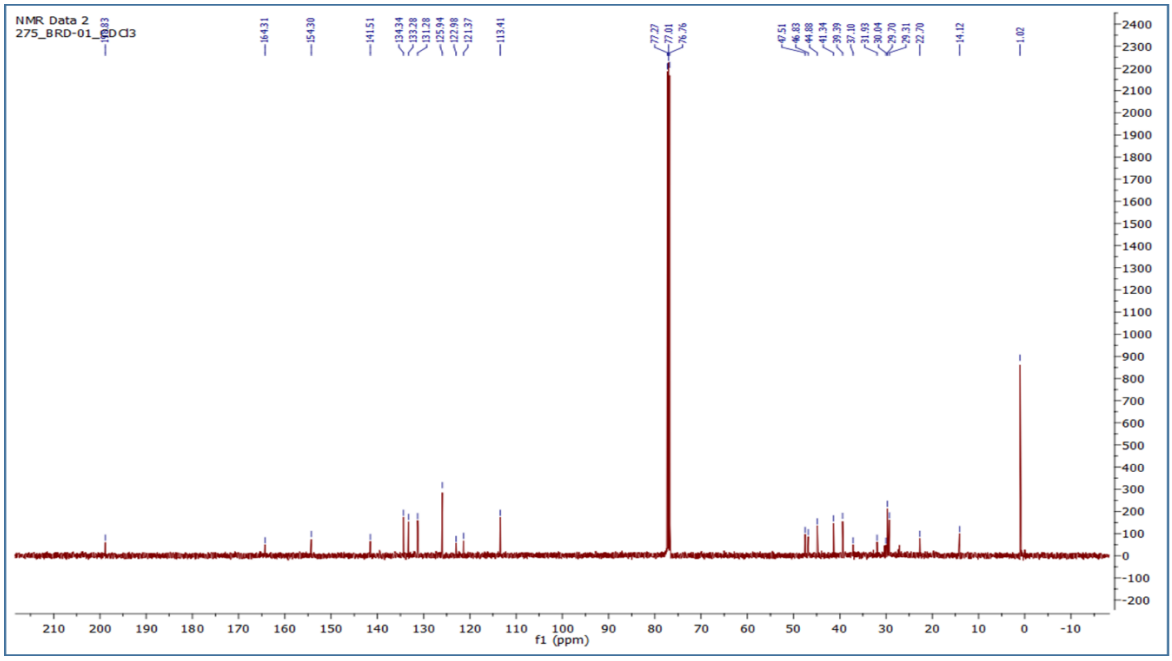
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD16



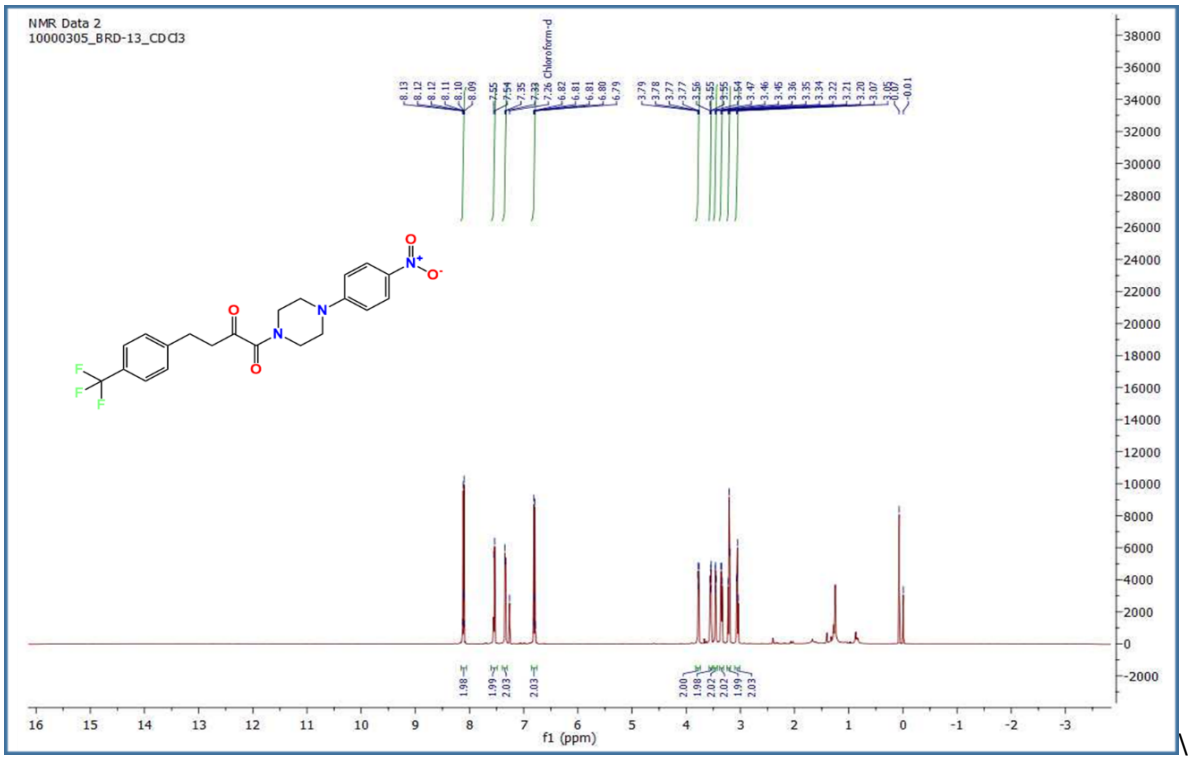


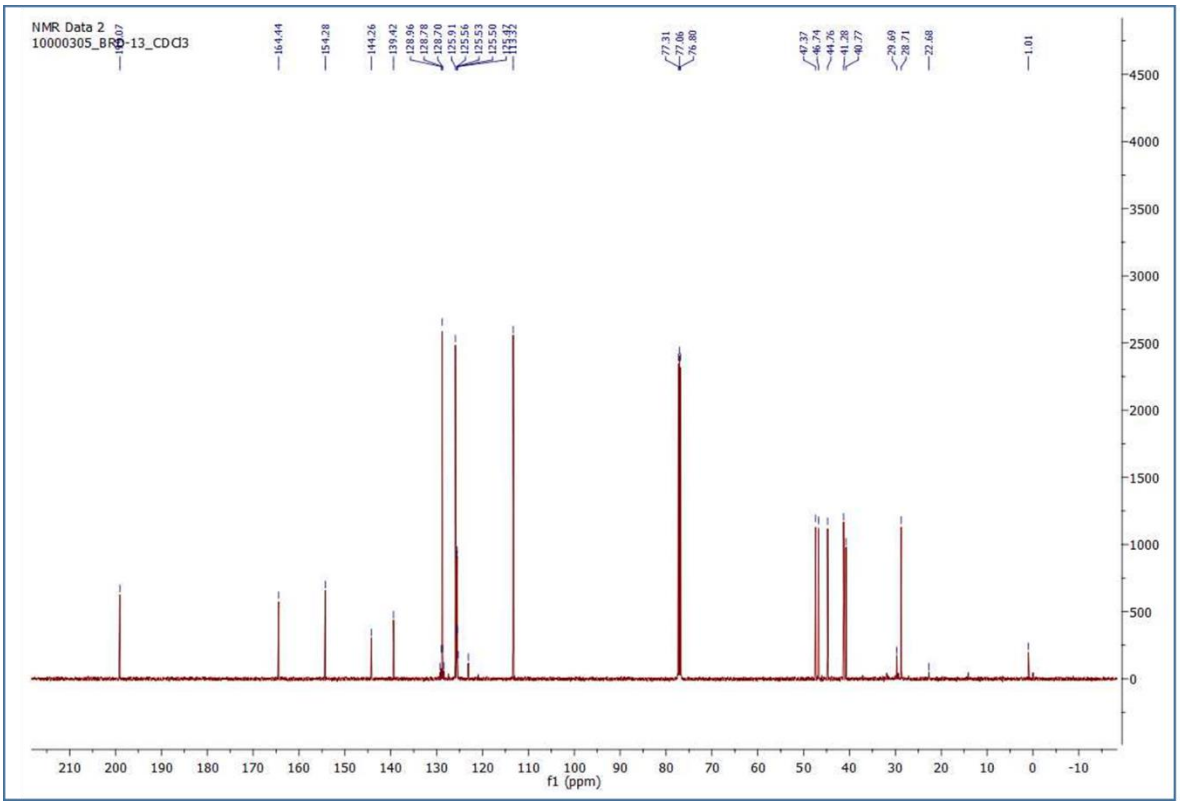
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD17



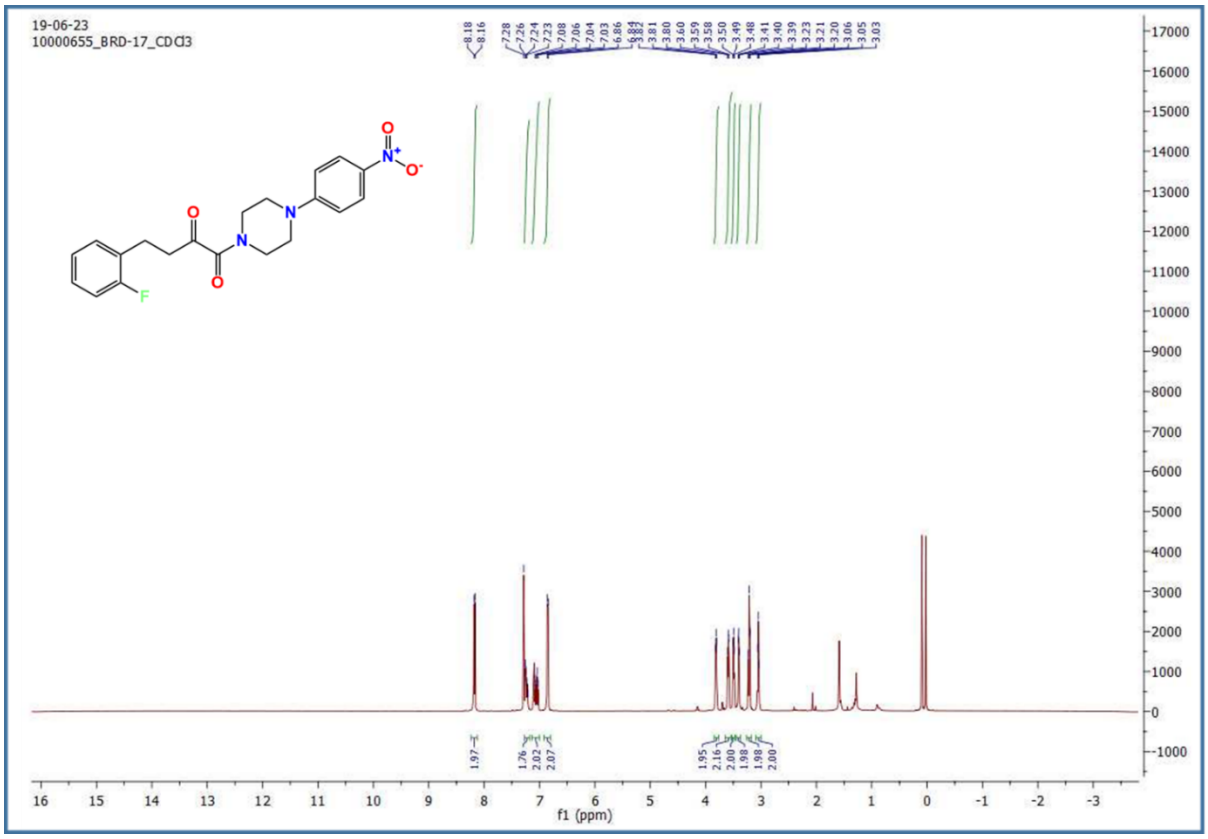


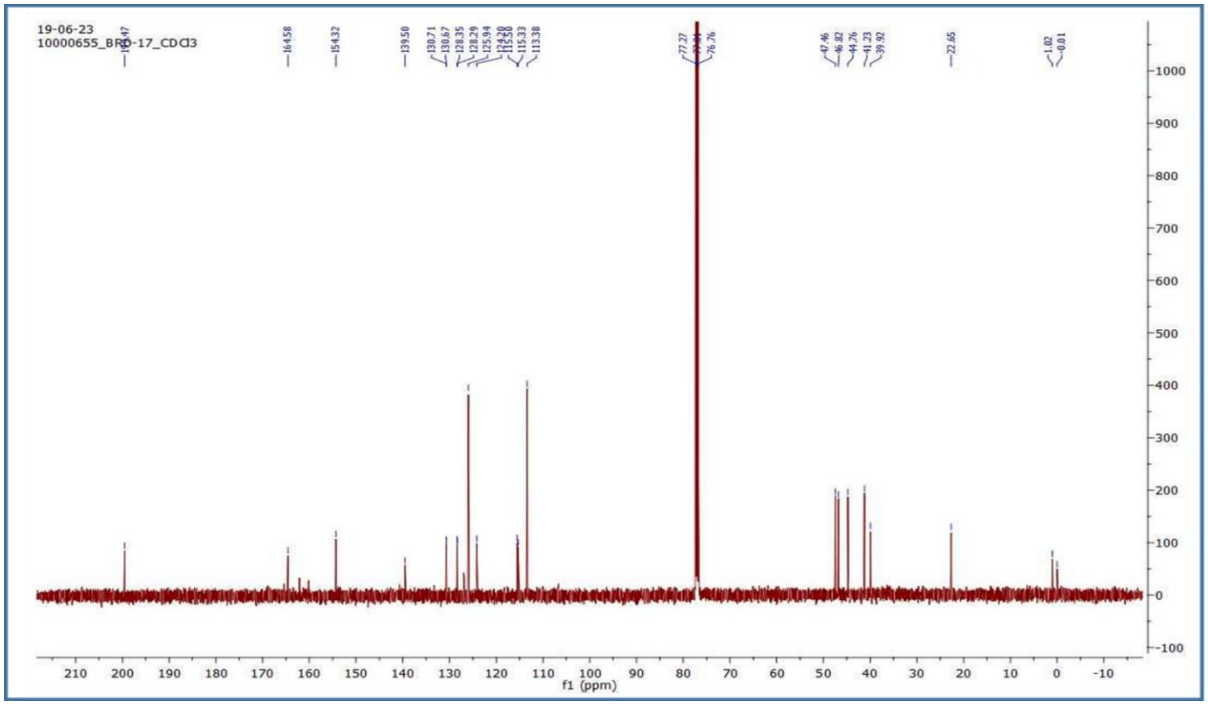
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD18



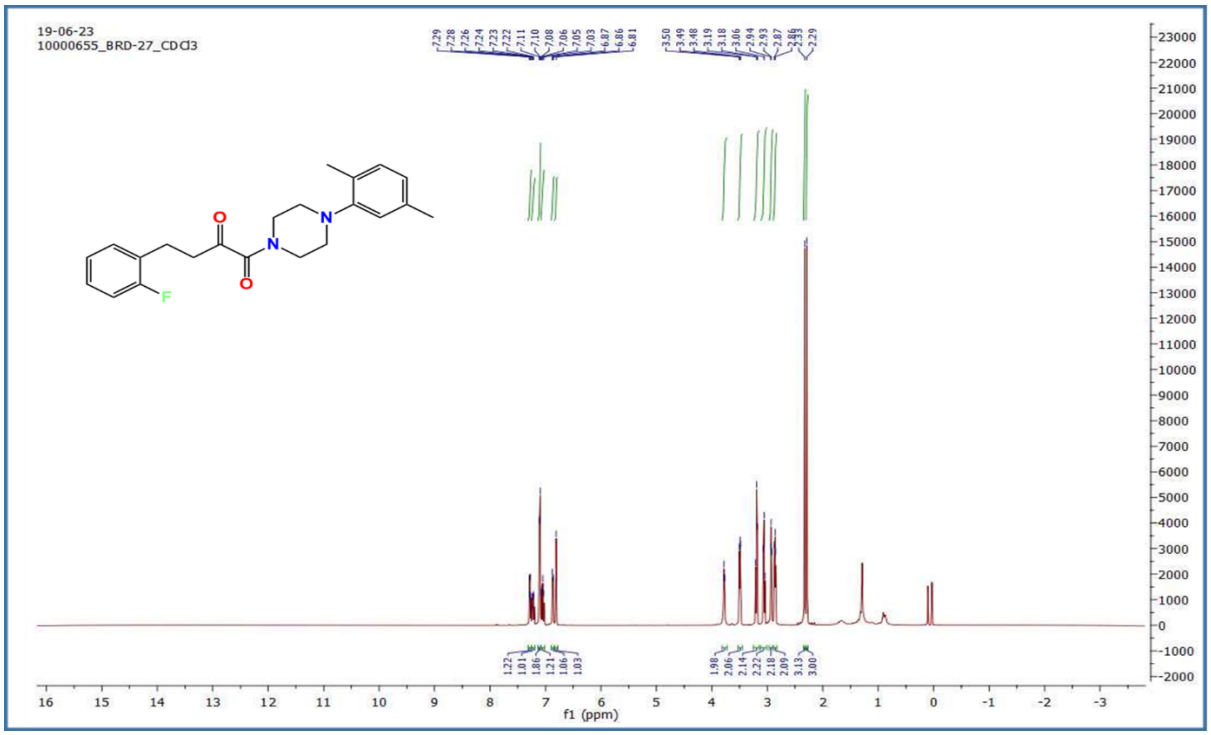


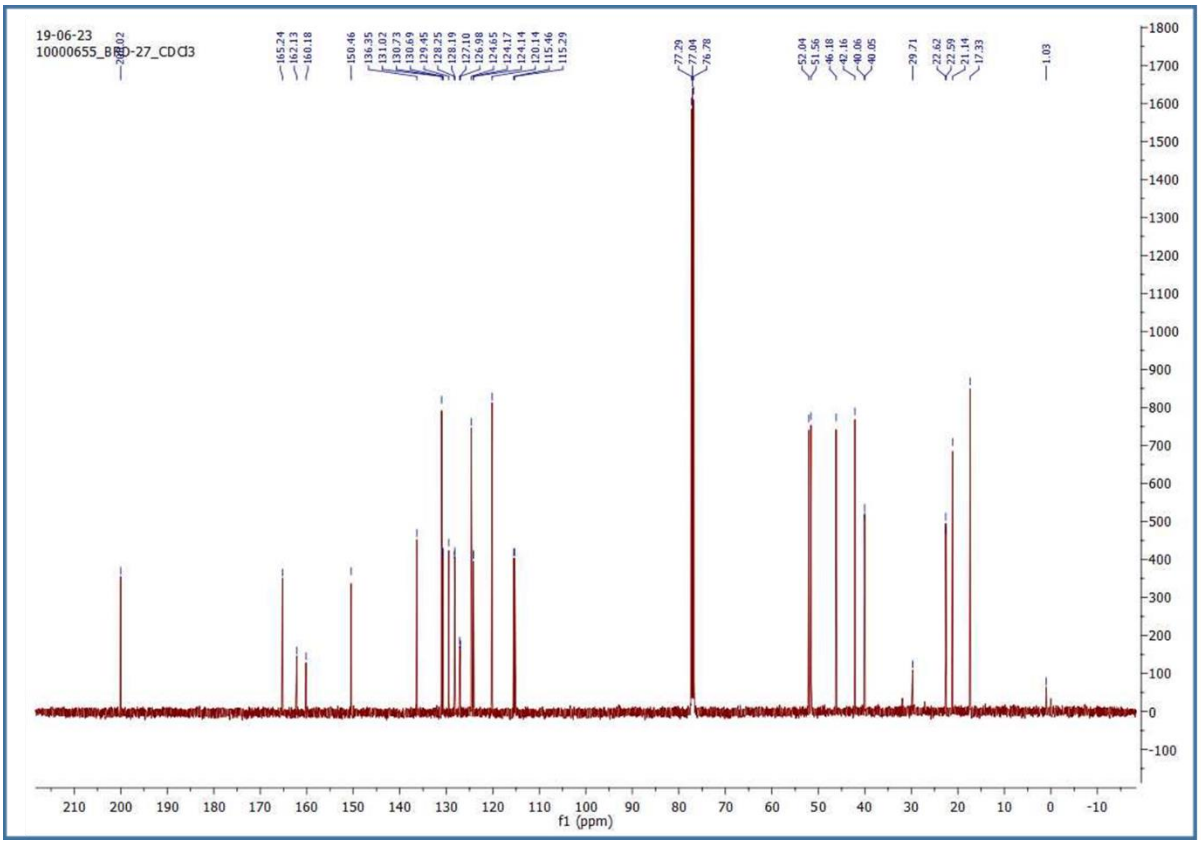
^{1}H, $^{13}C\{1H\}$ NMR spectra of Compound MD19



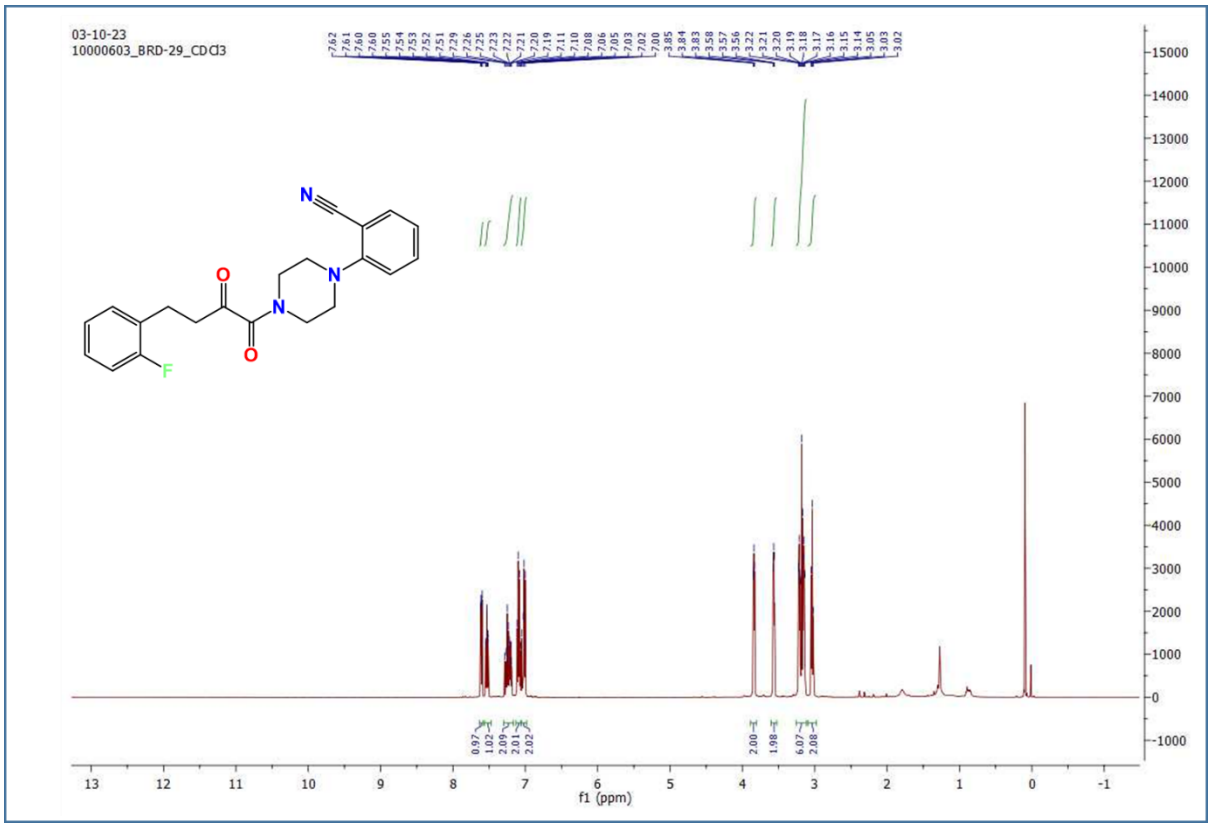


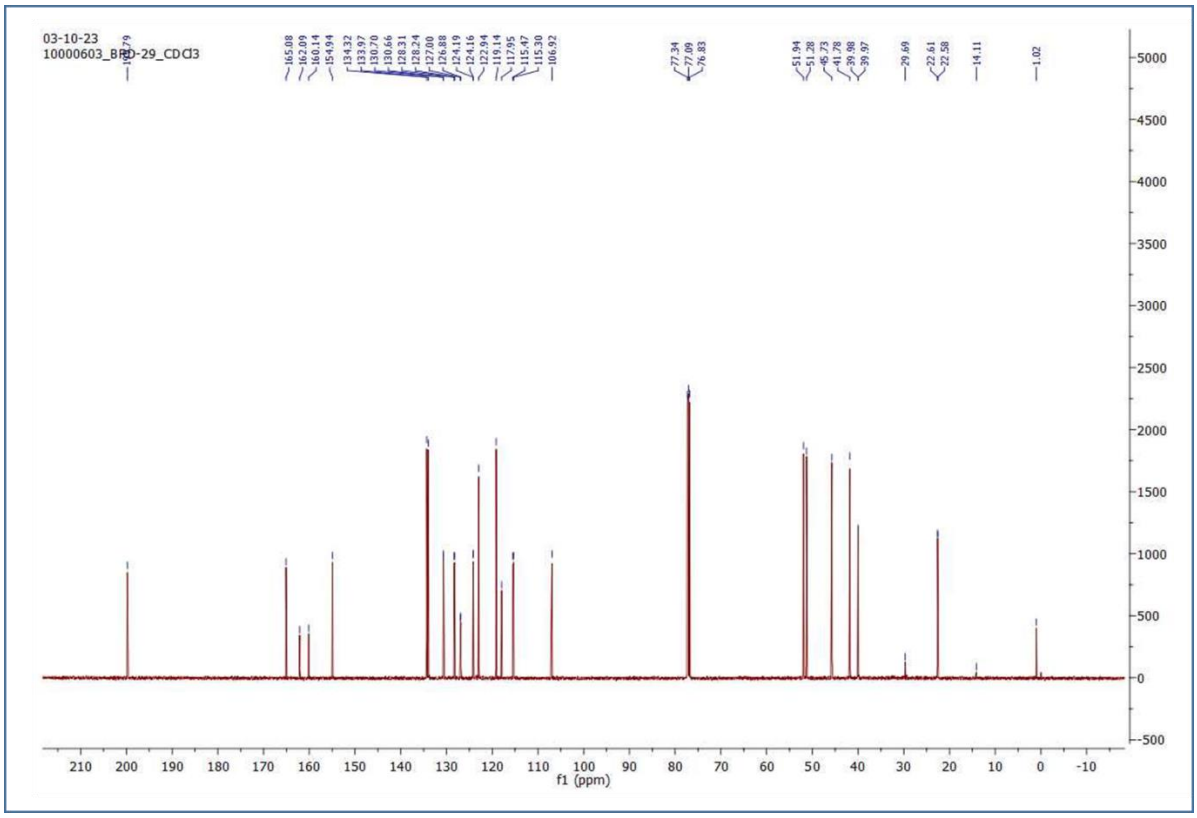
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD20



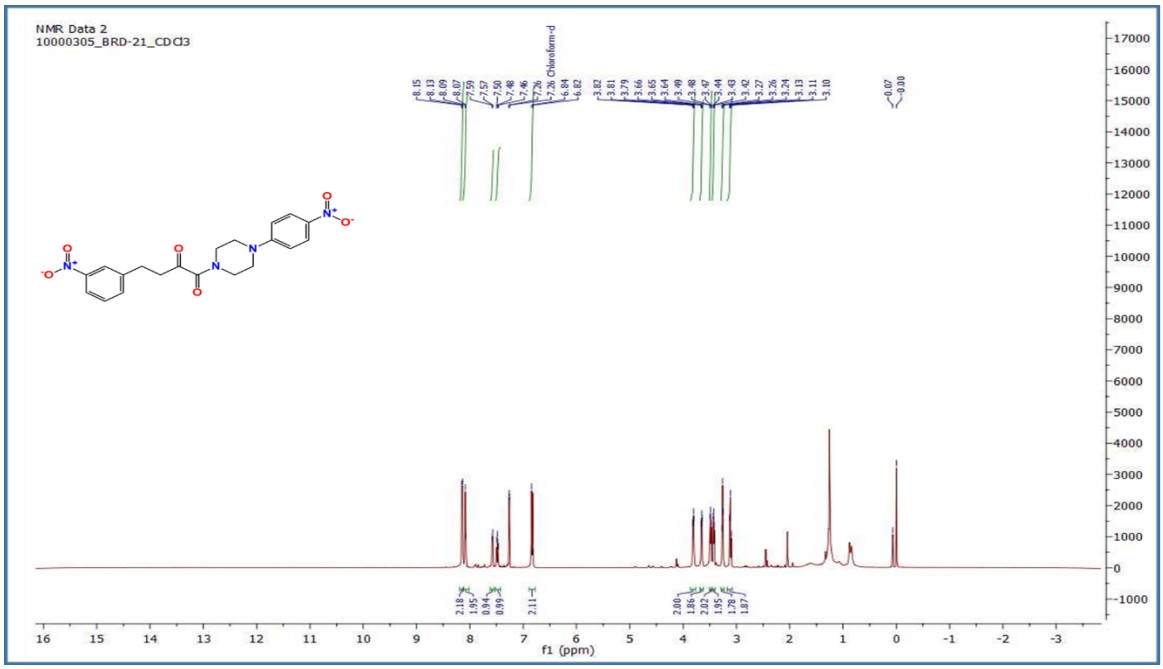


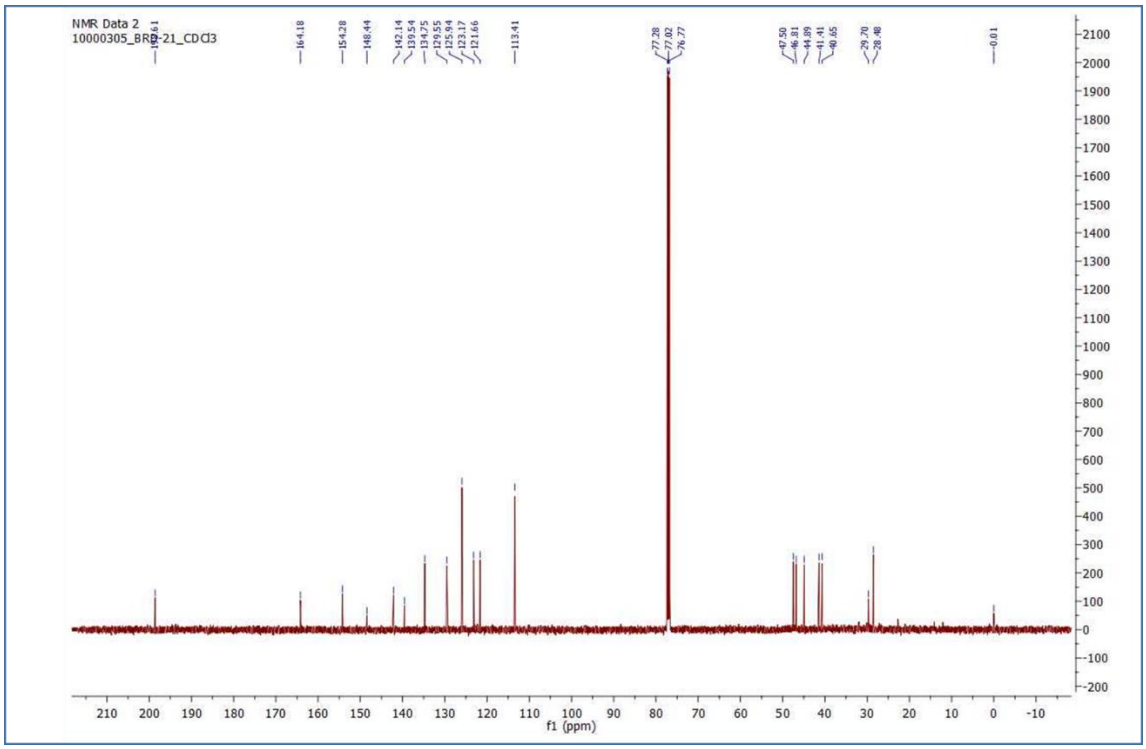
^{1}H, $^{13}C\{1H\}$ NMR Spectra of compound MD21



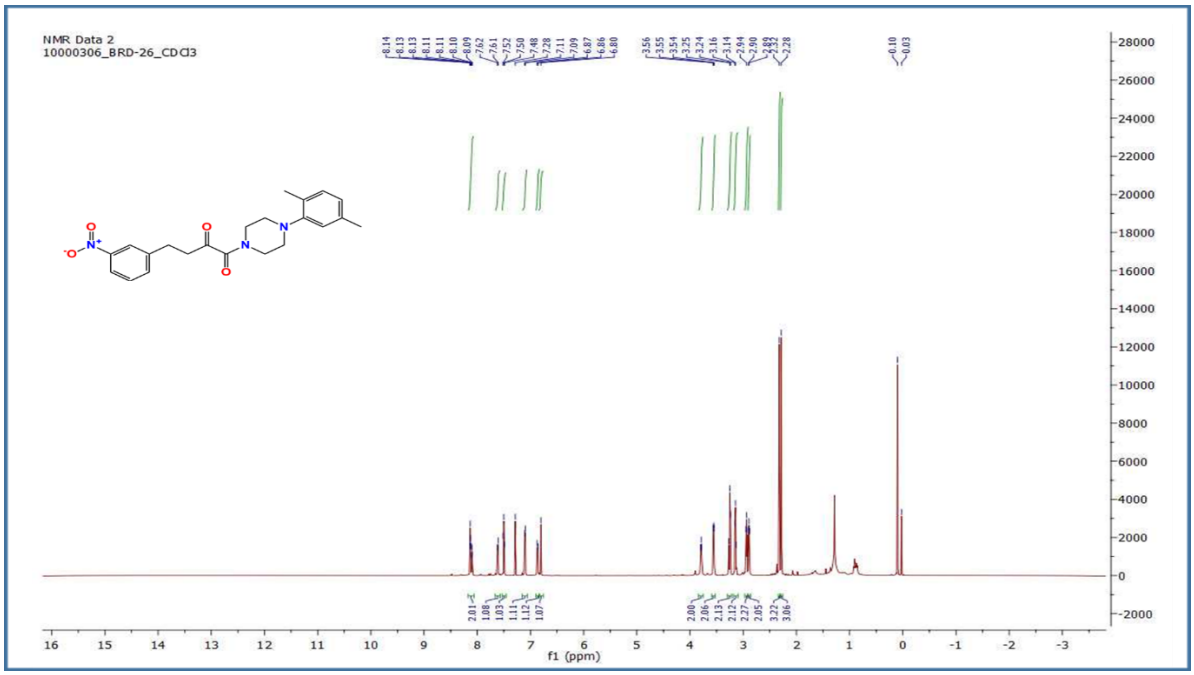


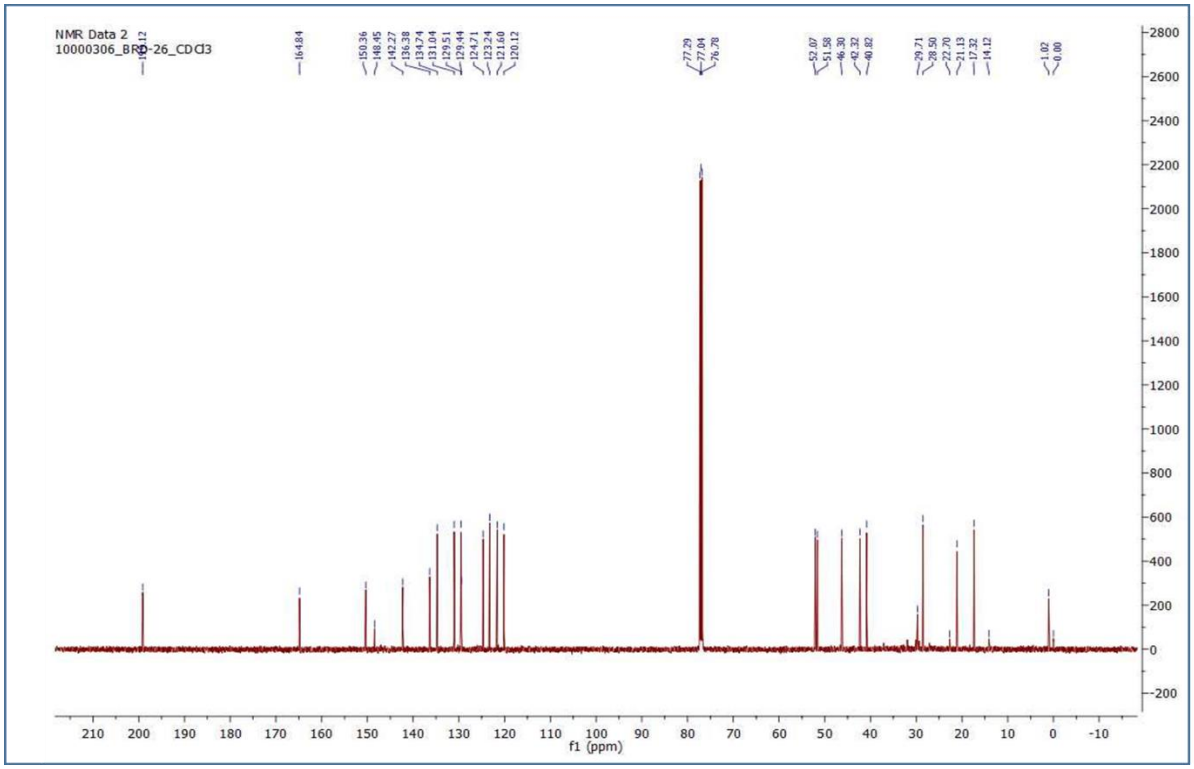
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD22



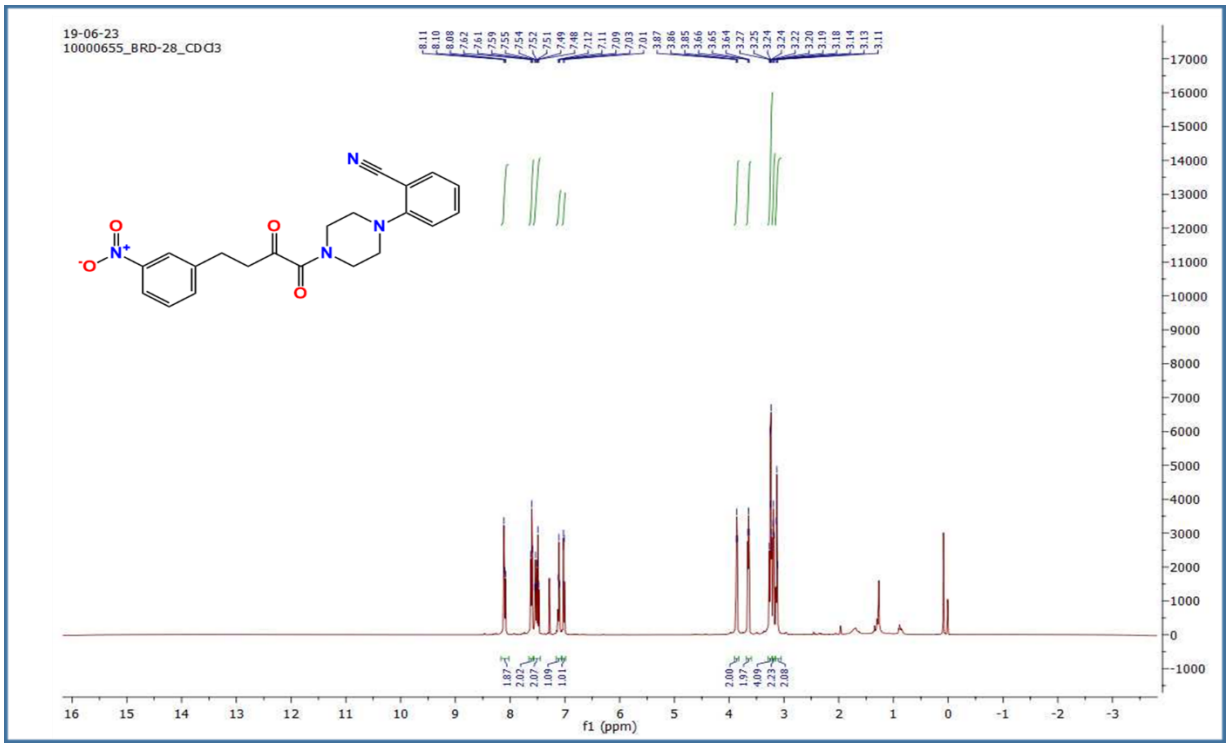


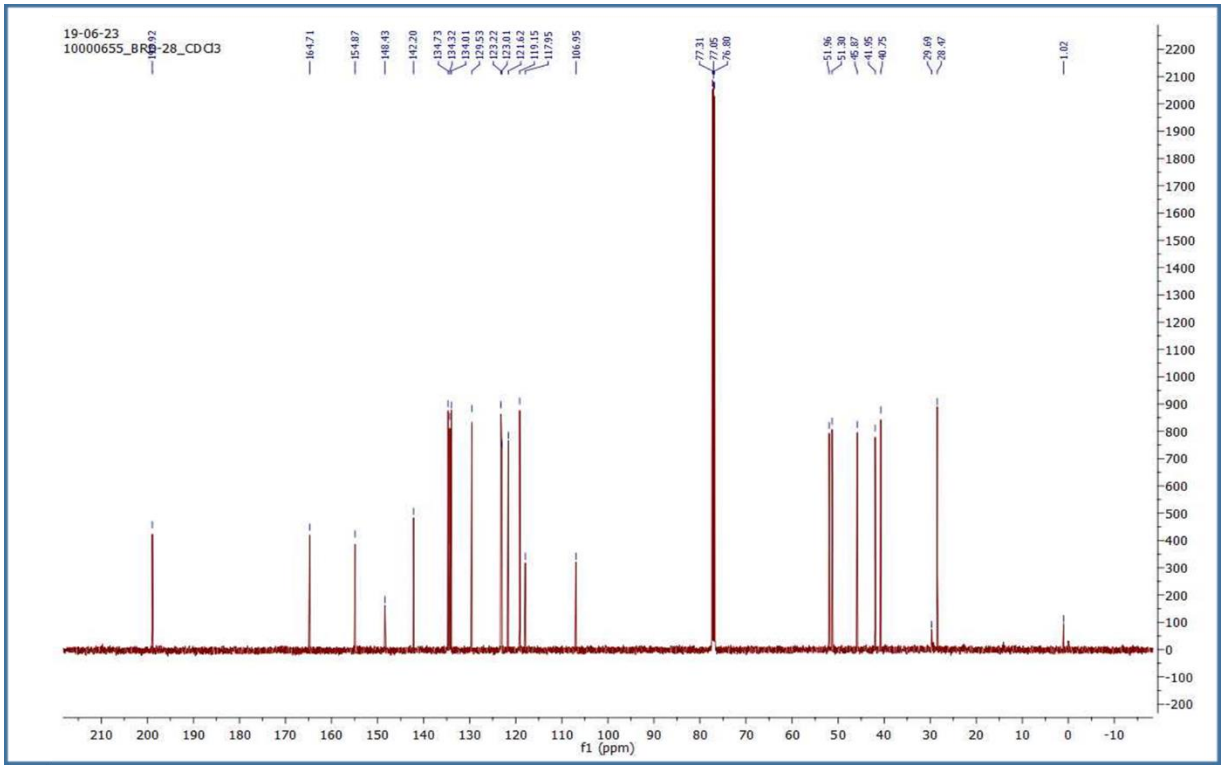
^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD23





^{1}H, $^{13}C\{1H\}$ NMR Spectra of Compound MD24





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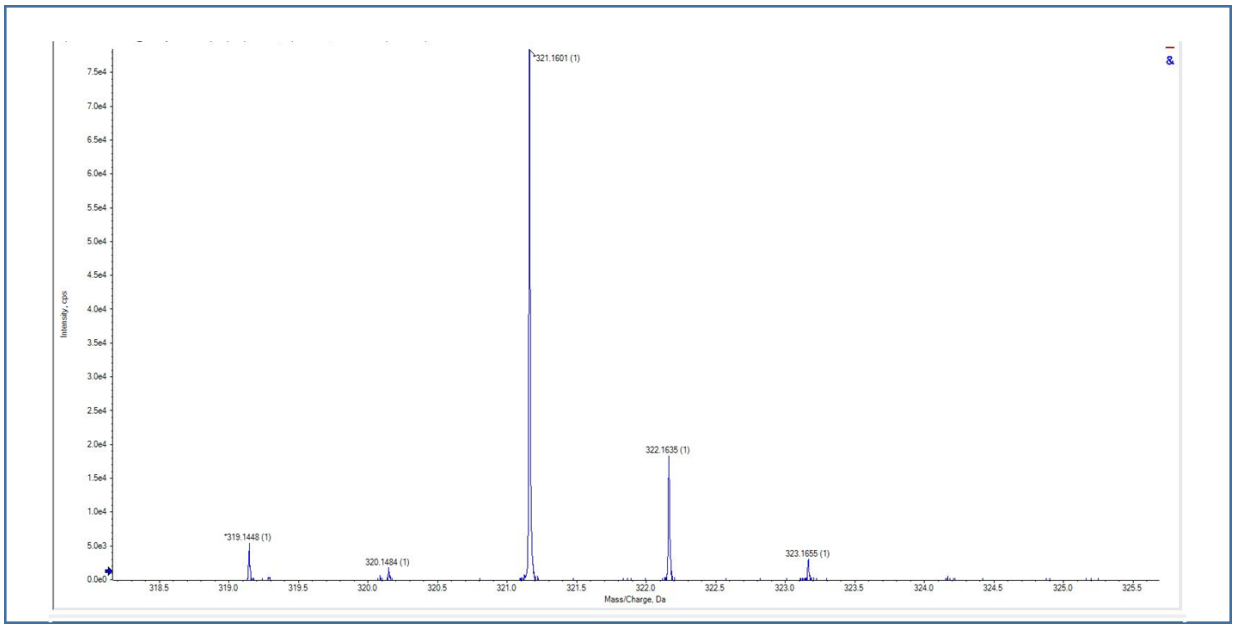
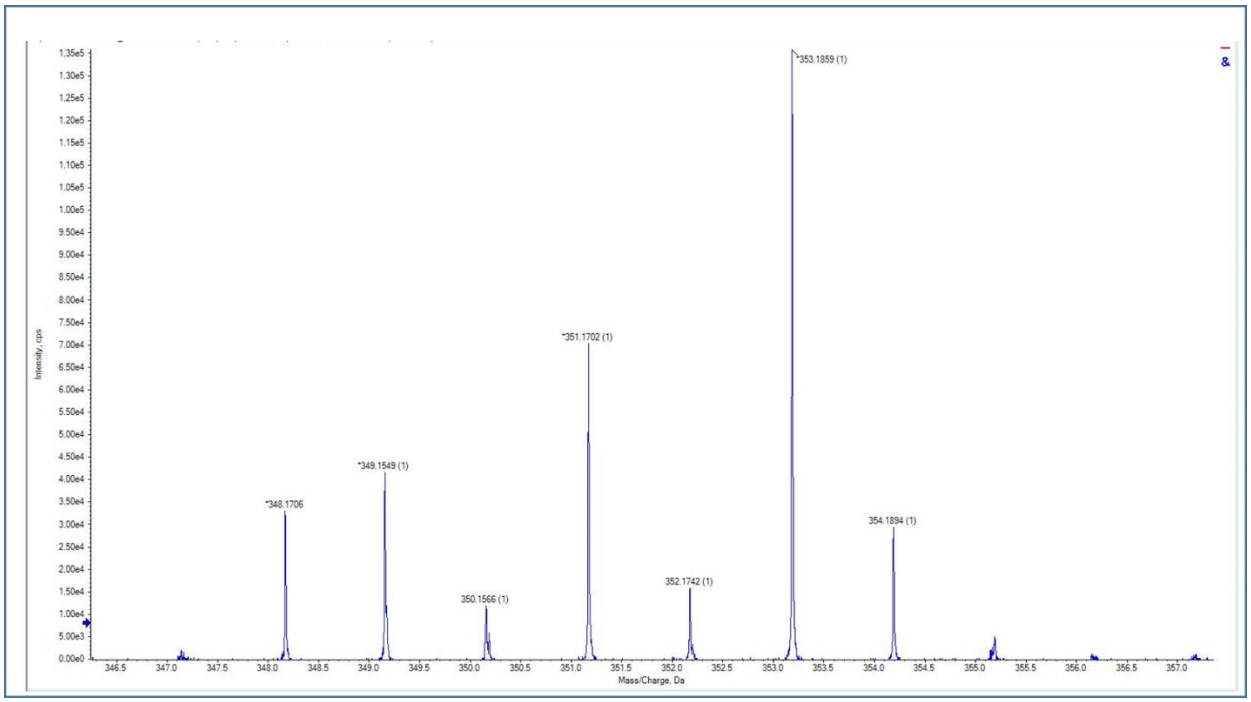


HRMS of MD02



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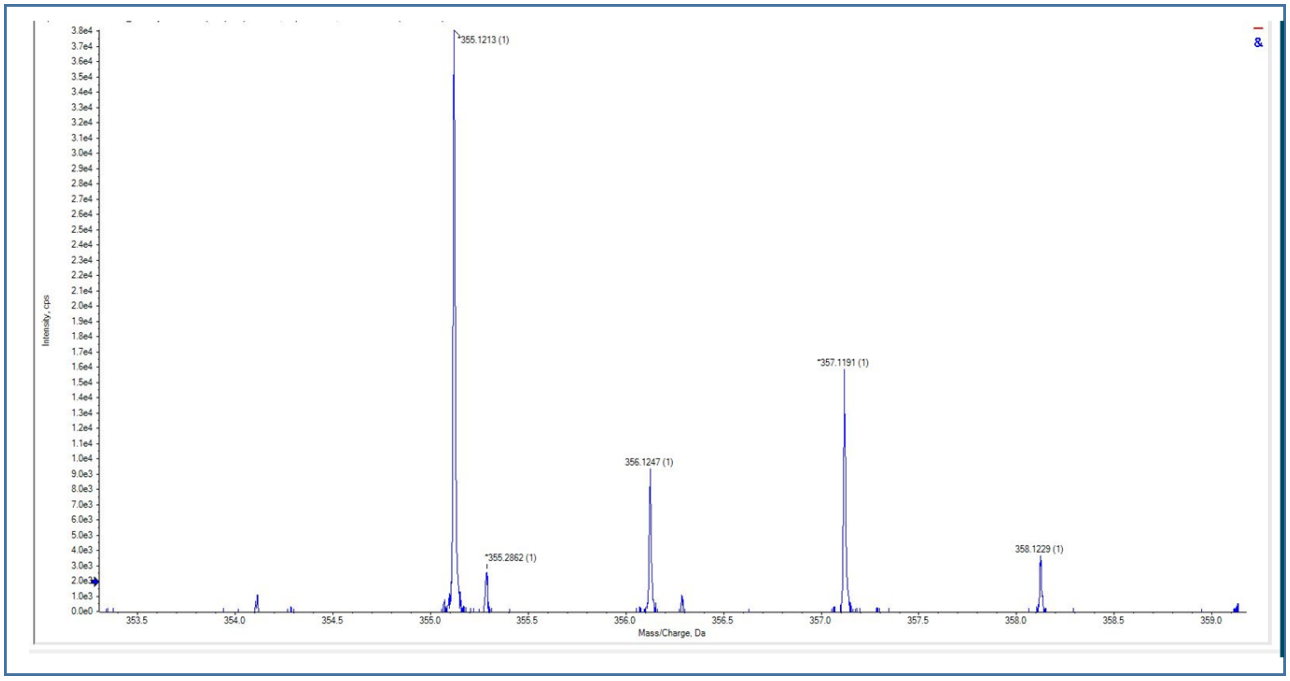

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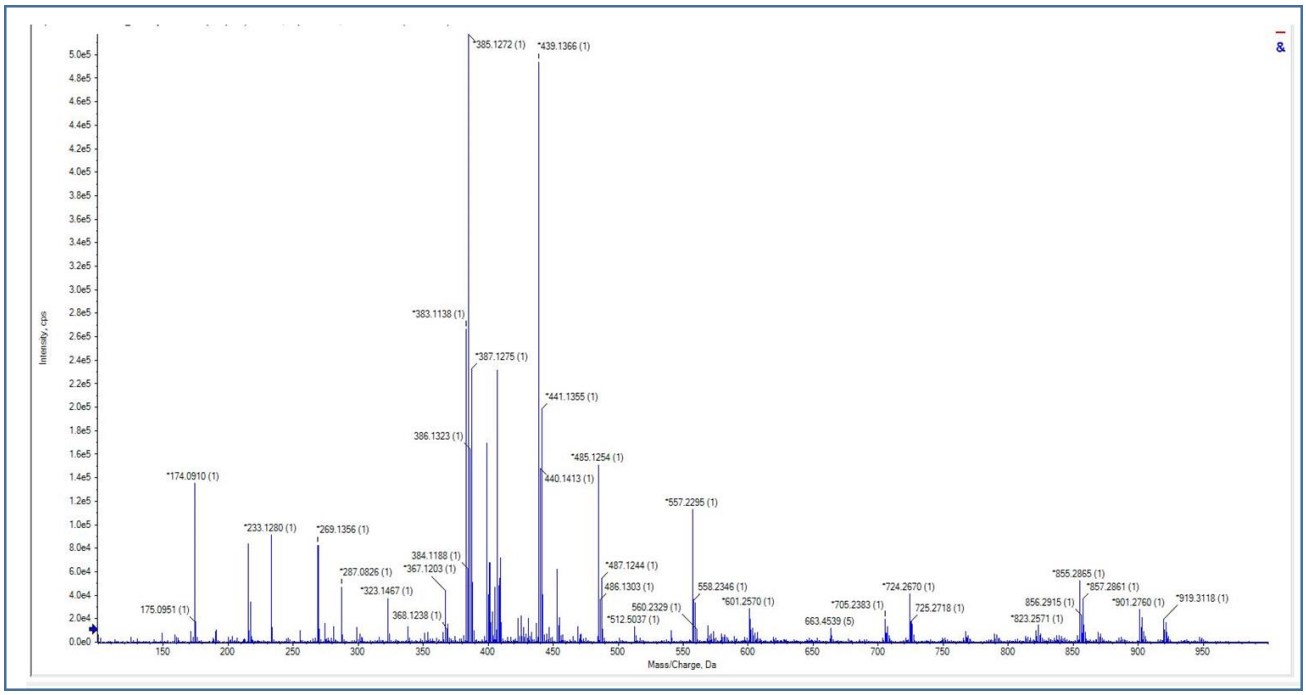
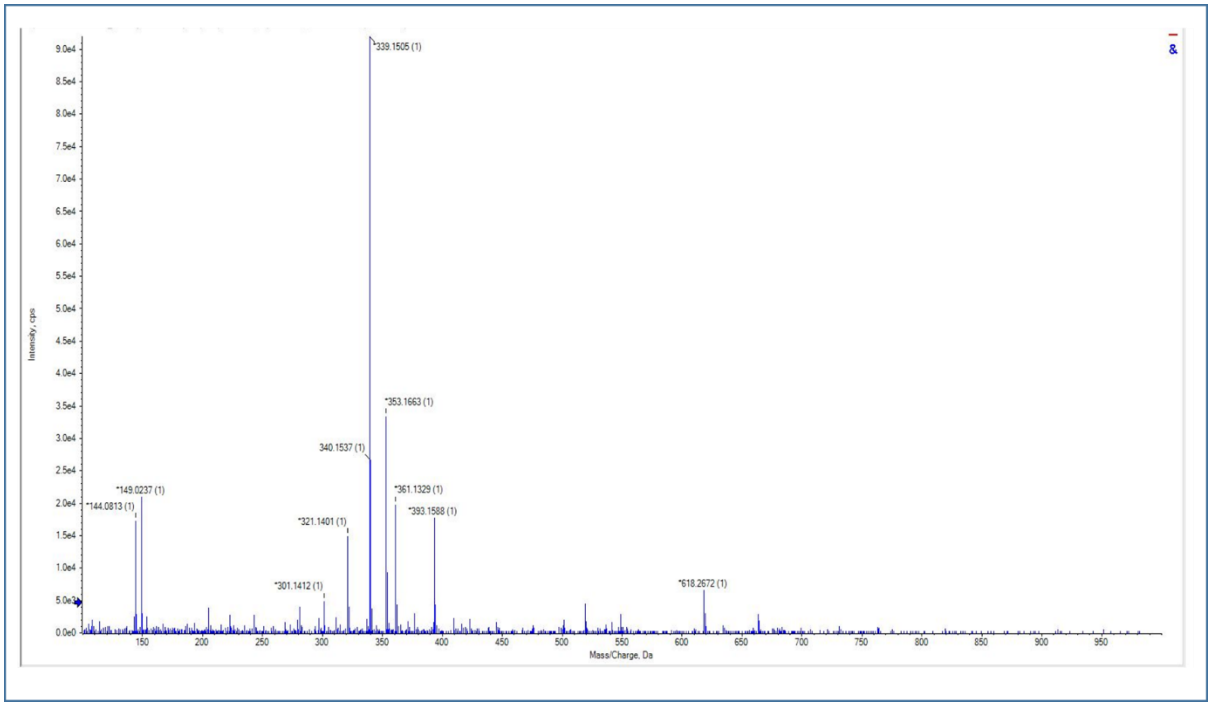


HRMS of MD05



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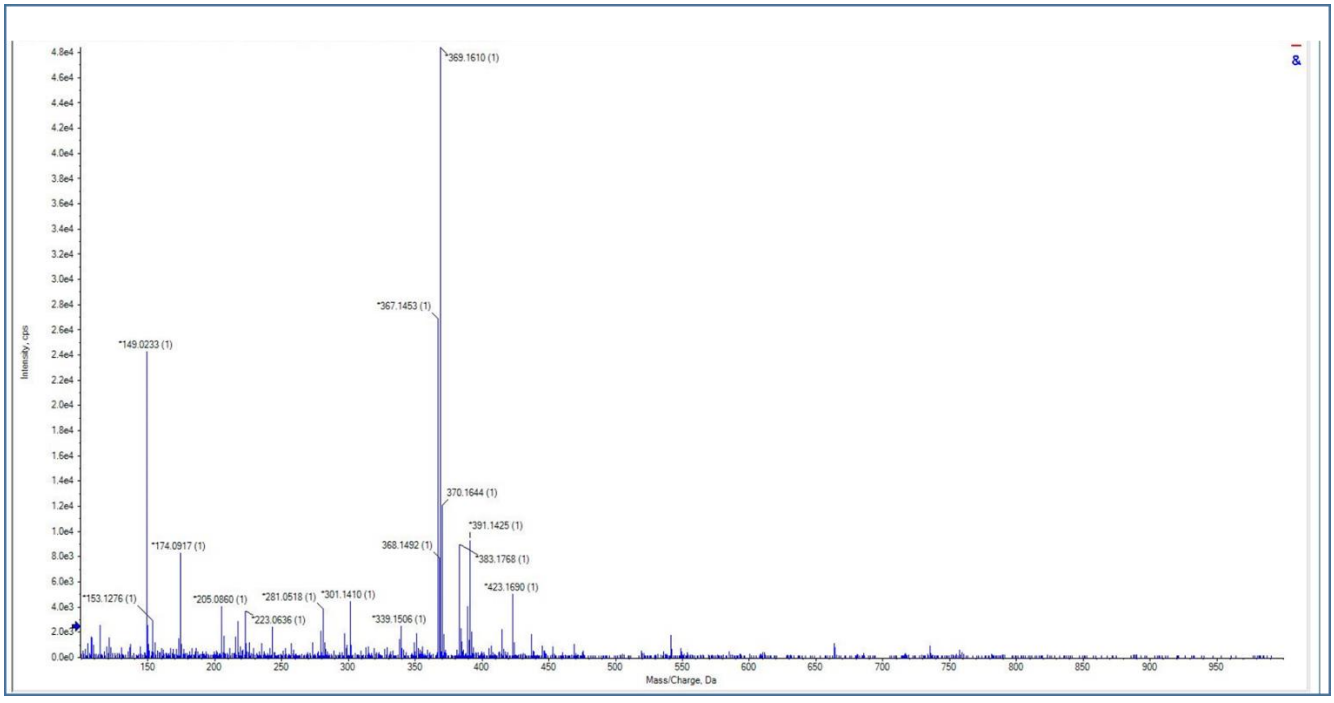
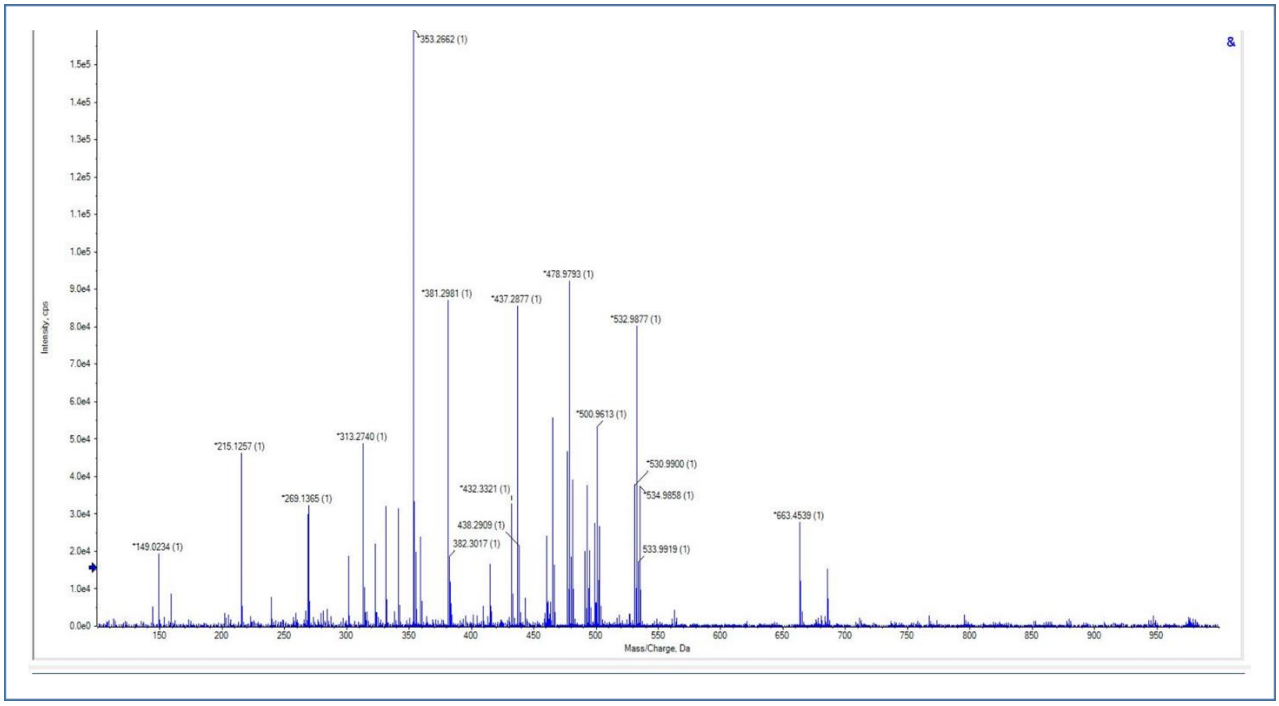
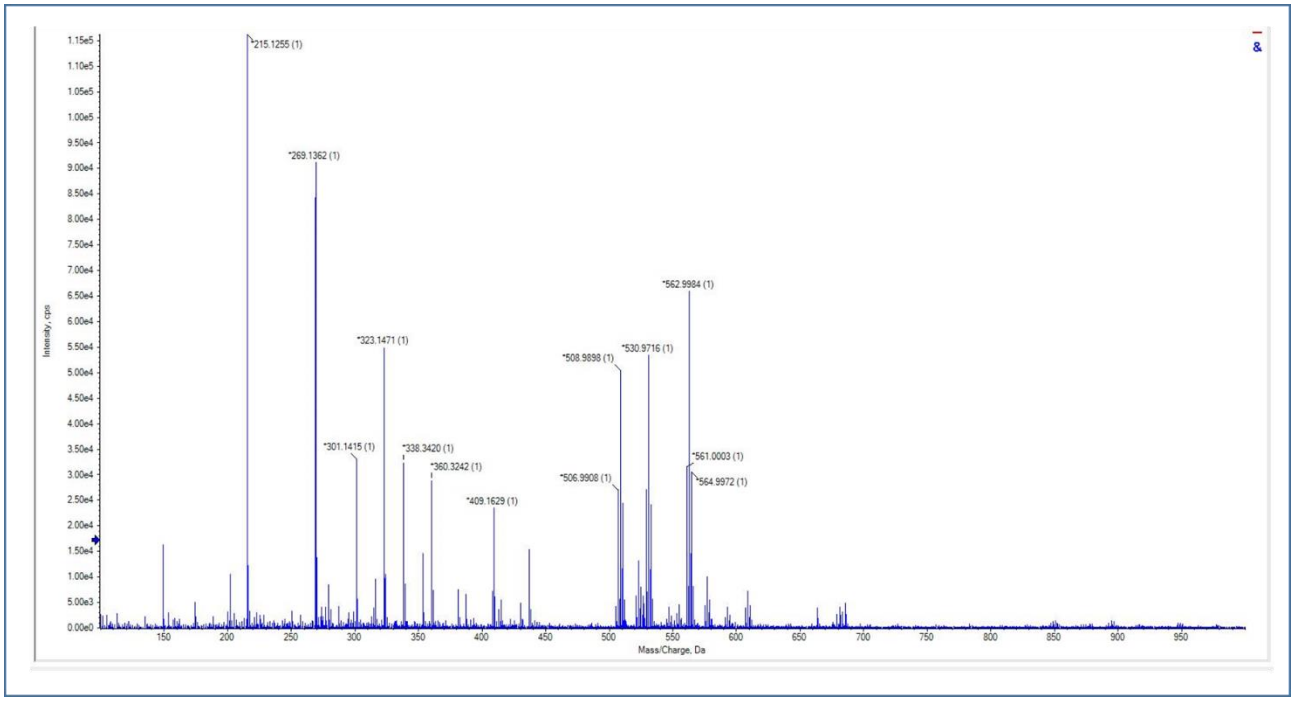


HRMS of MD07



HRMS of MD08



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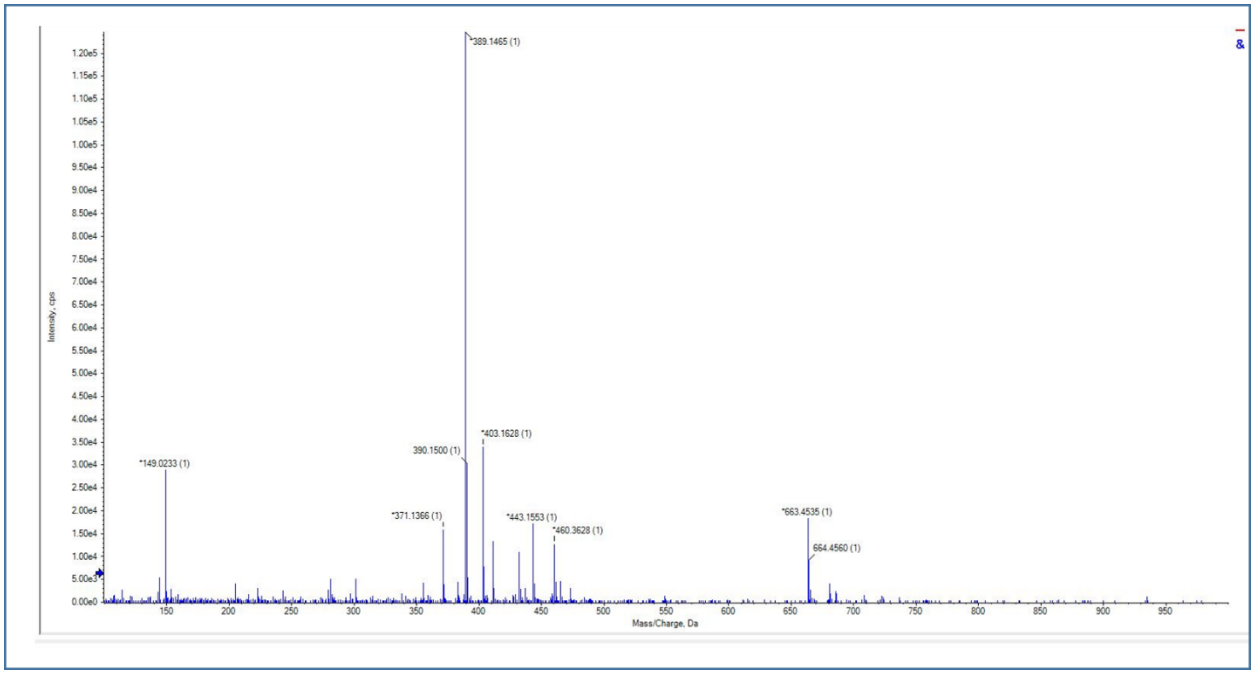

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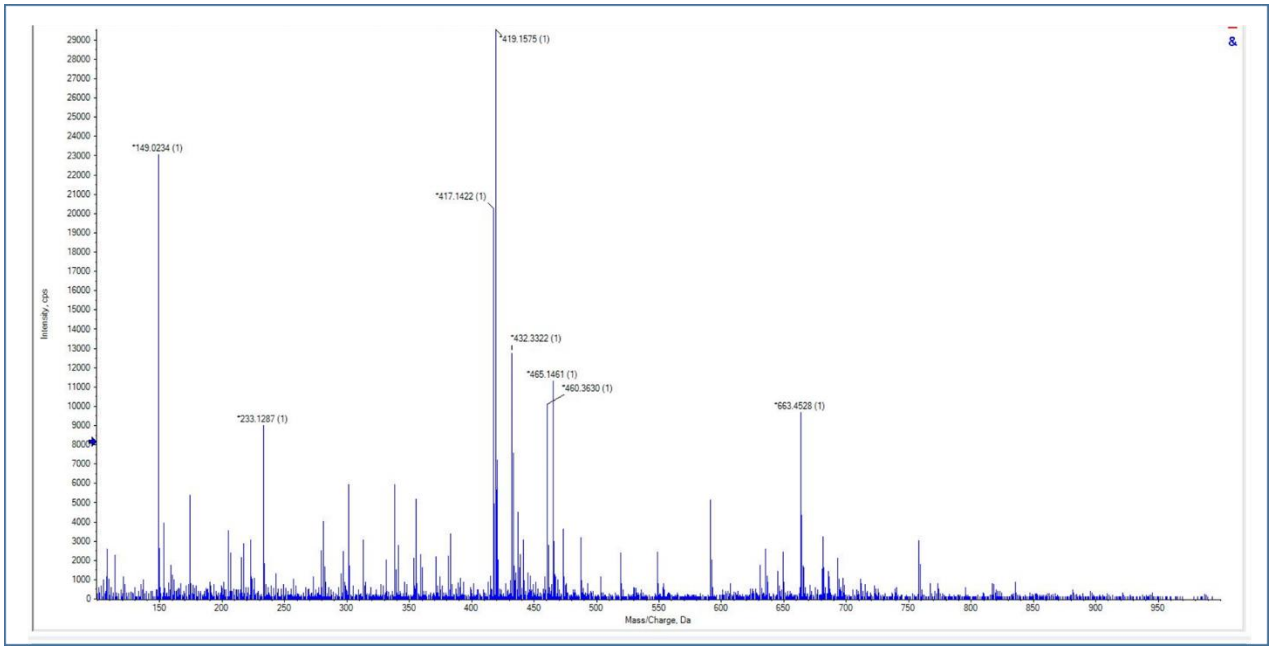
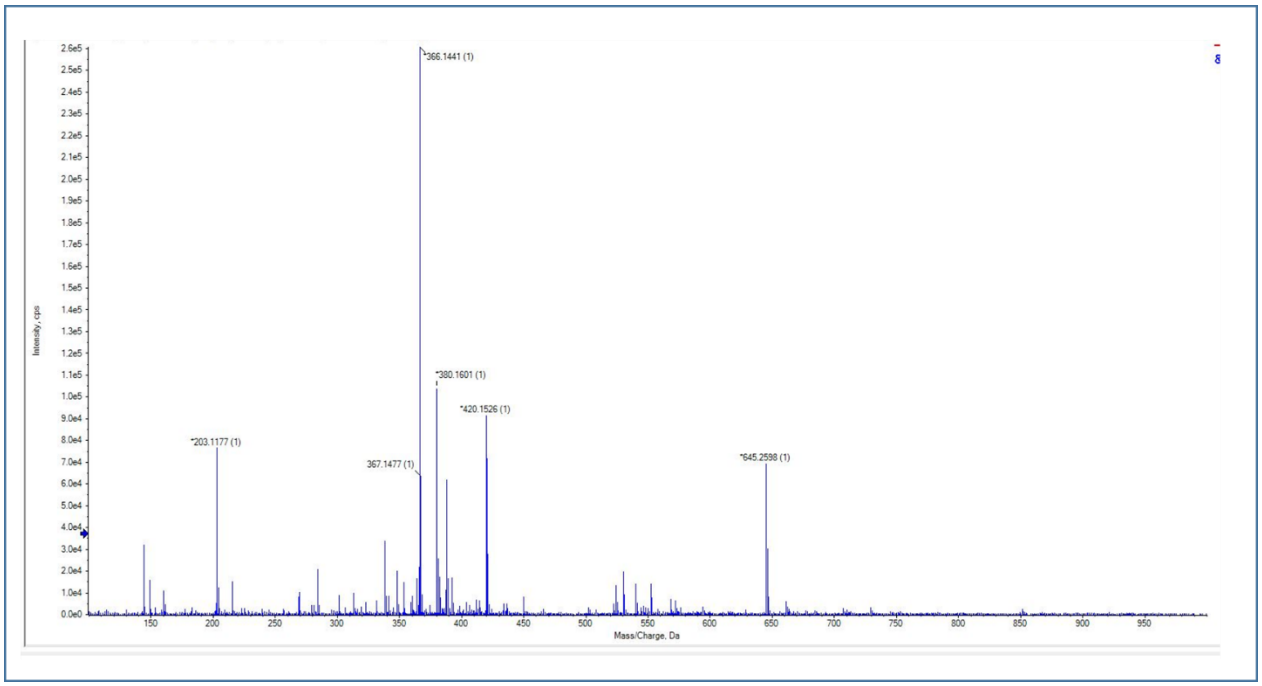


HRMS of MD11



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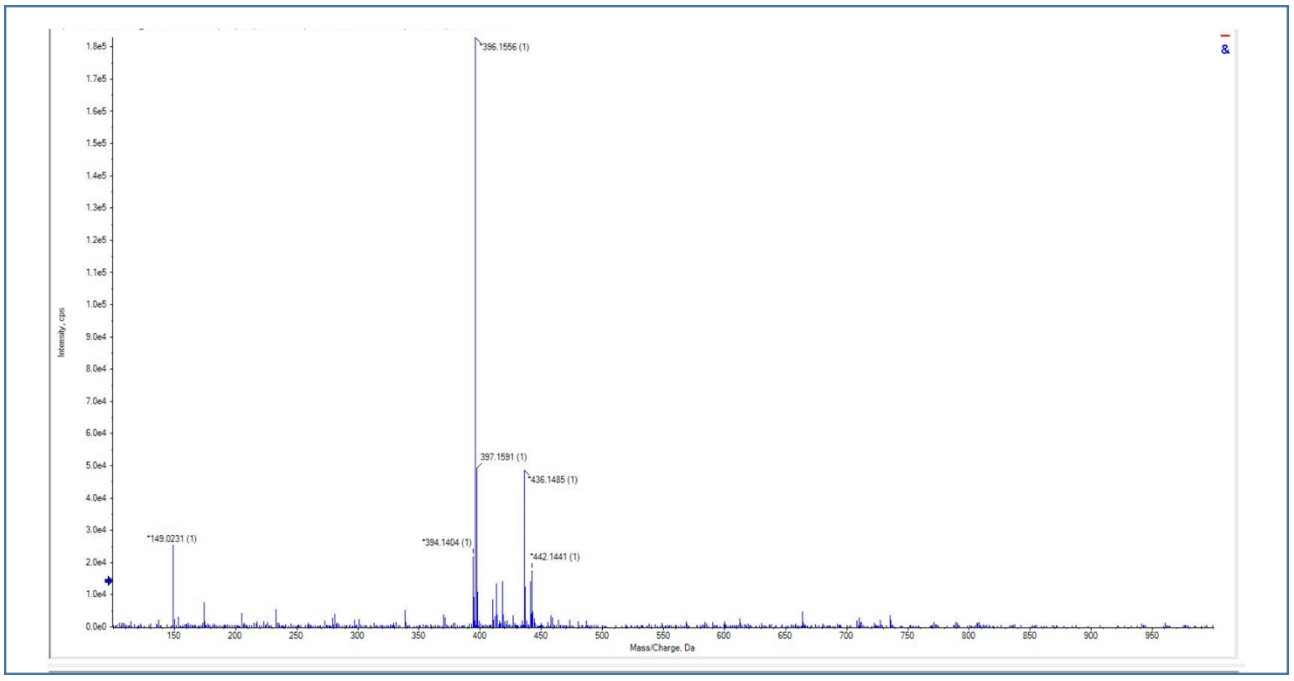

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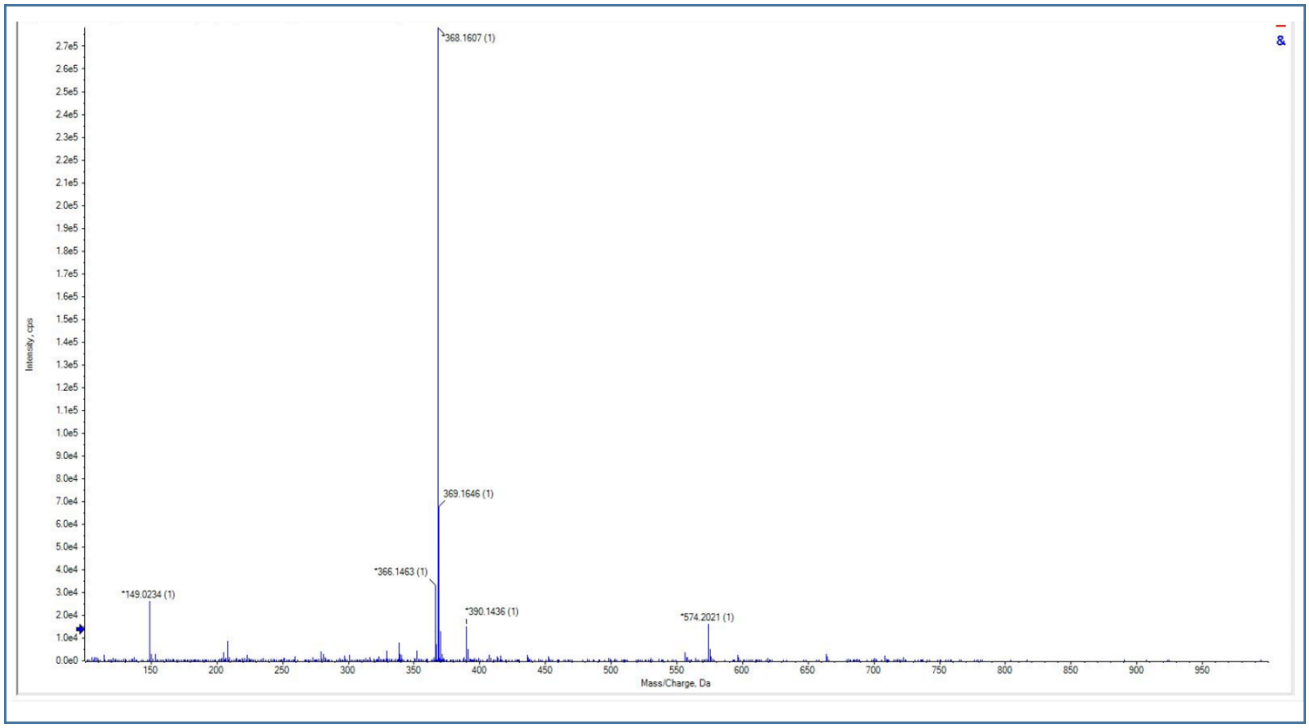

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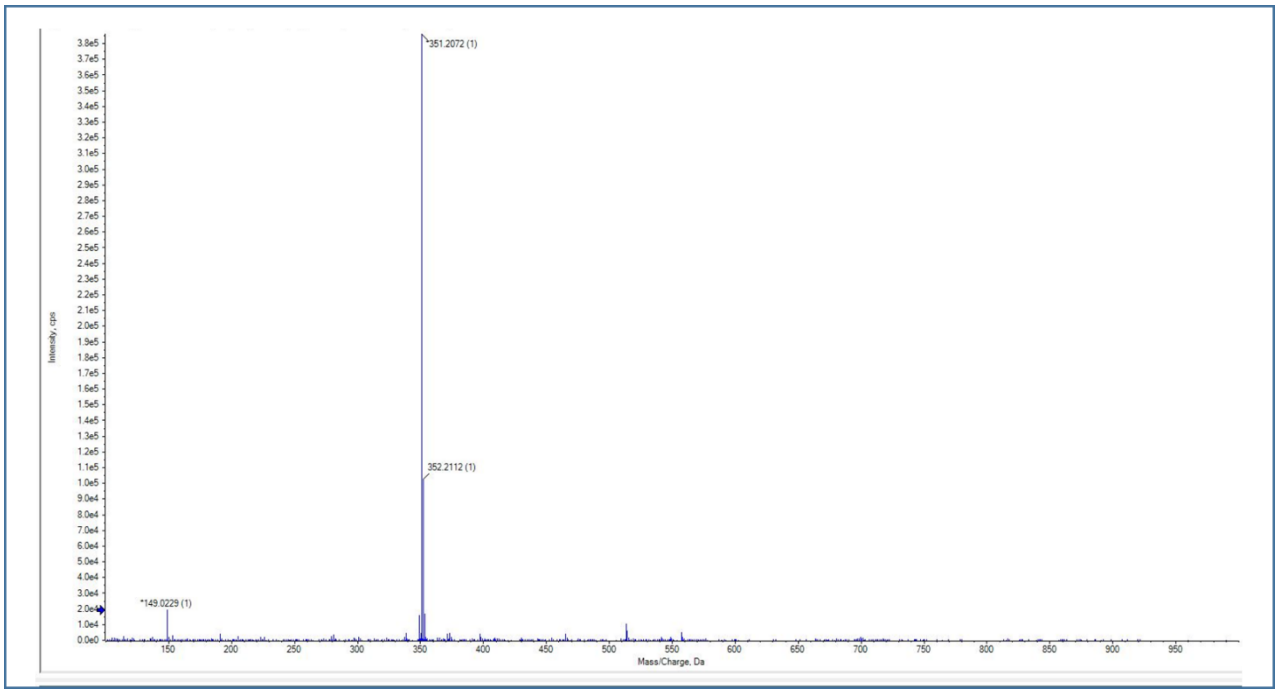

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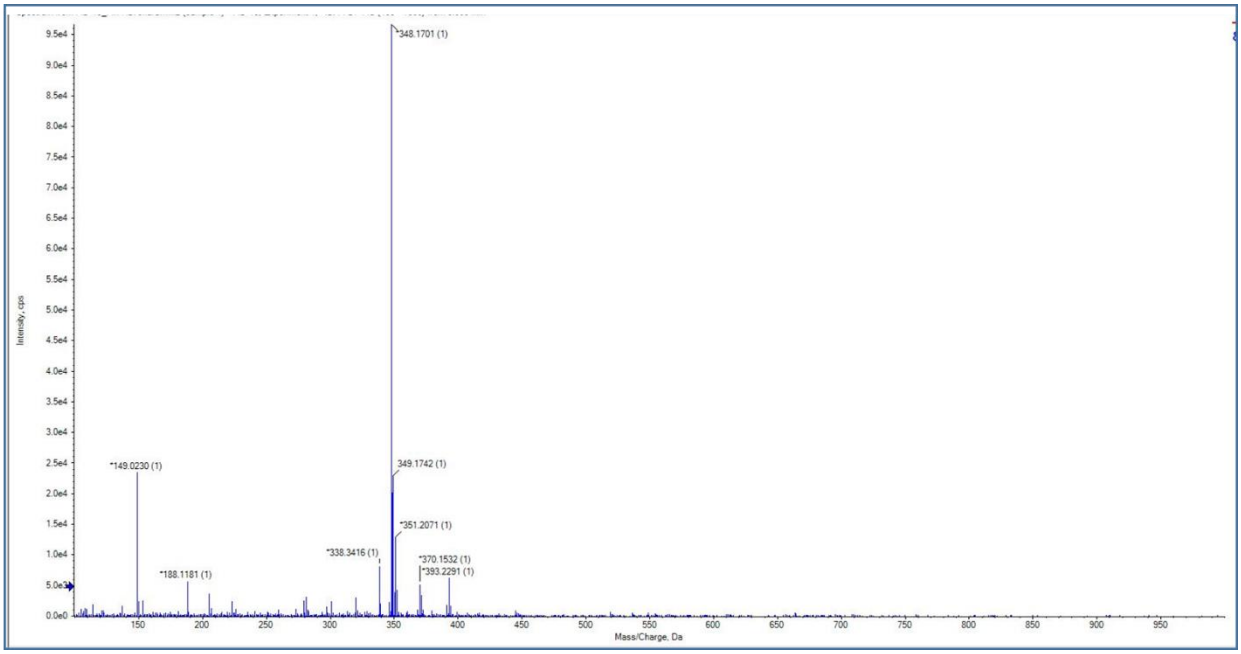

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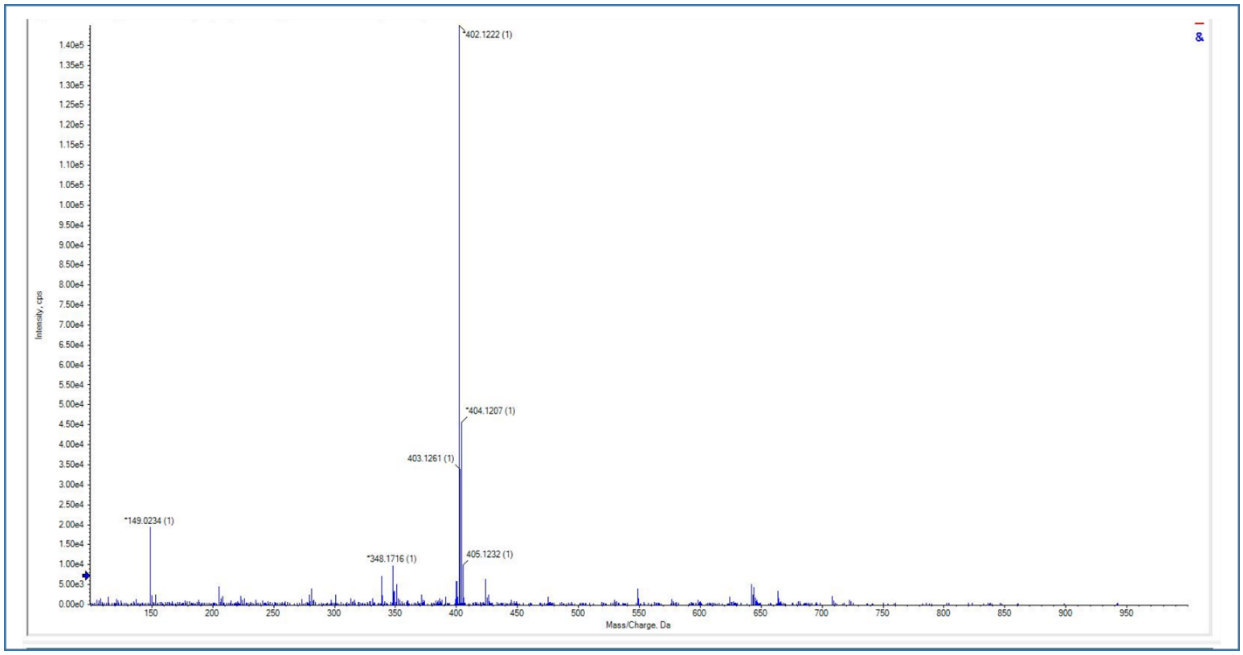

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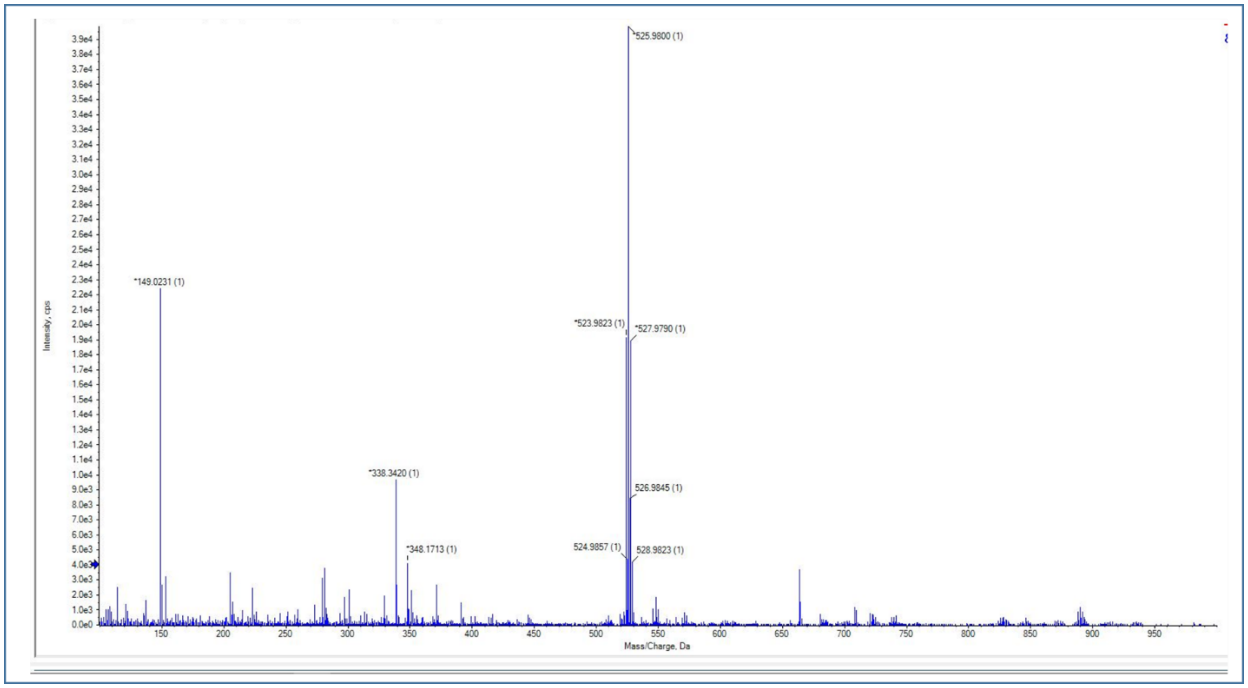

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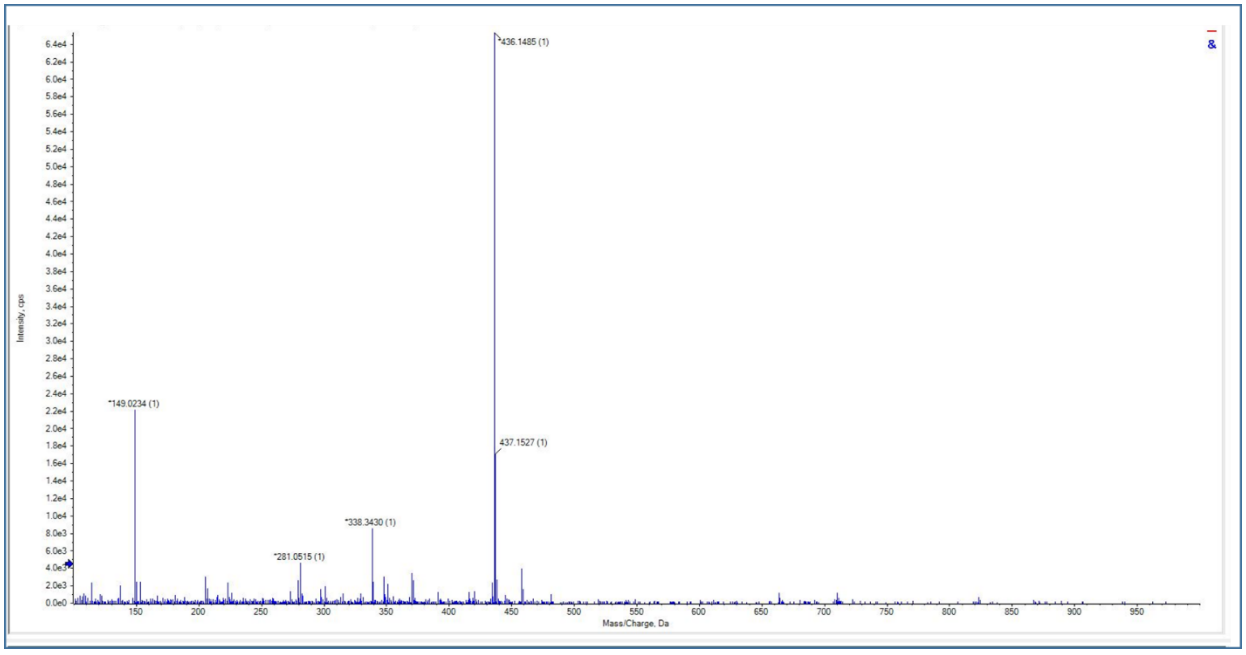
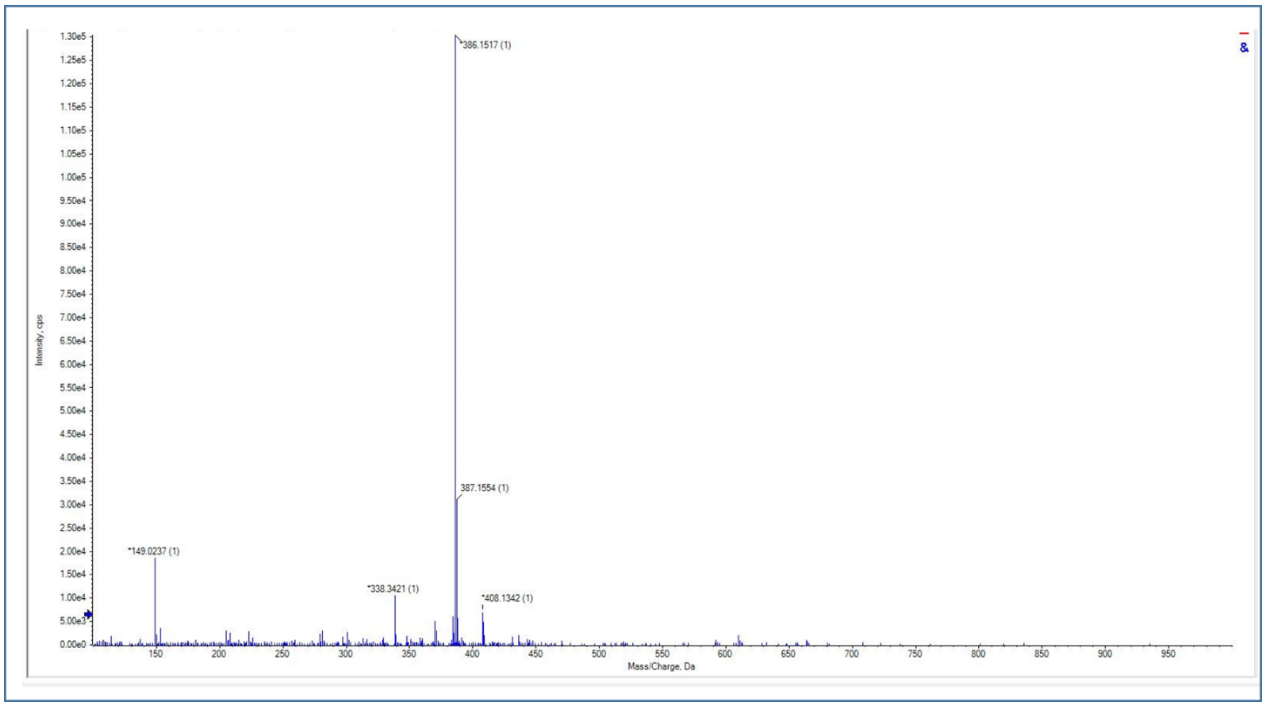
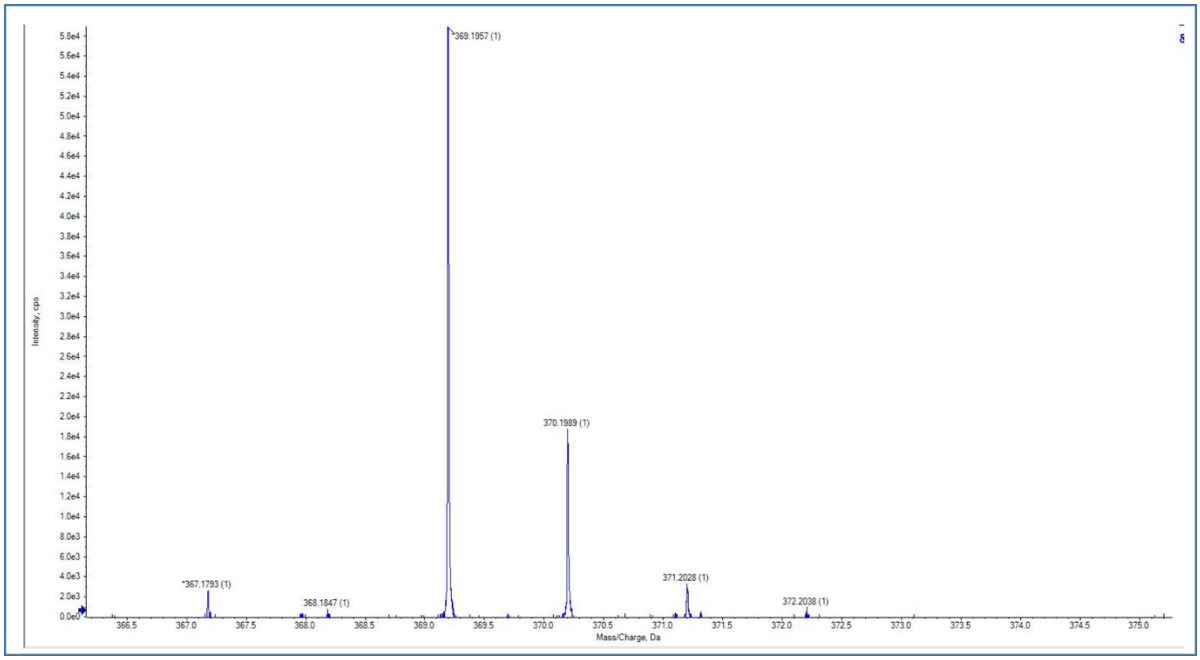


HRMS of MD19



HRMS of MD20



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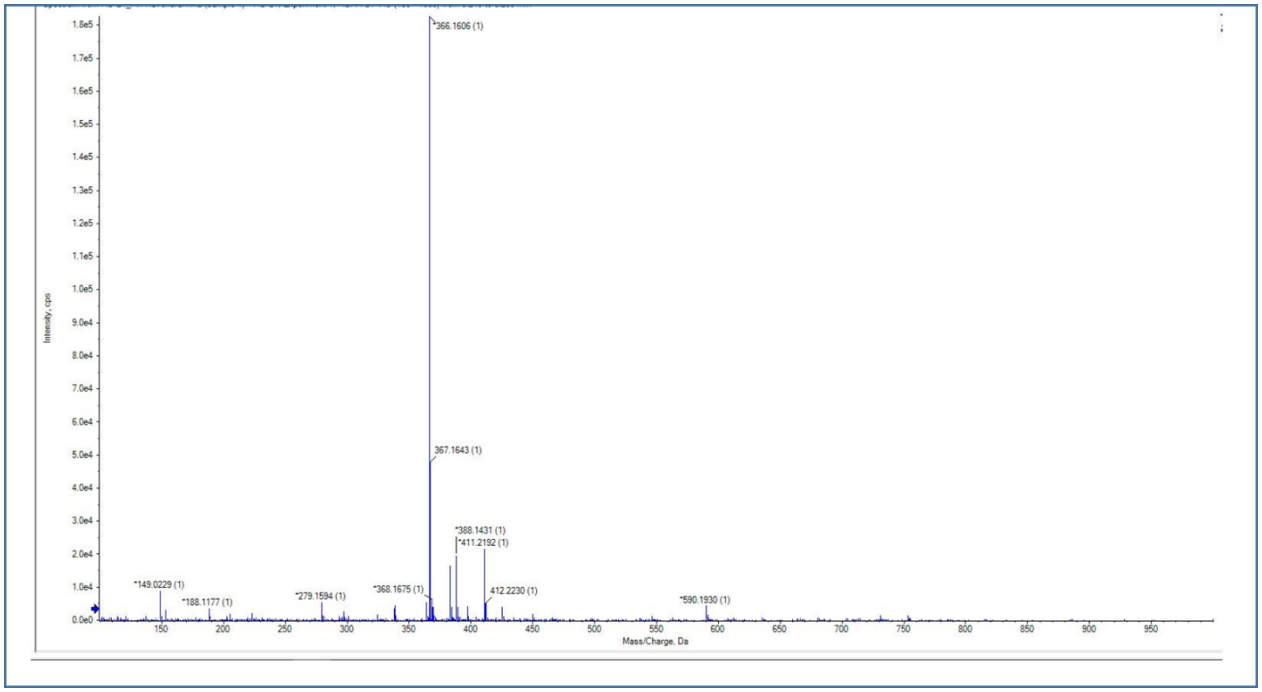

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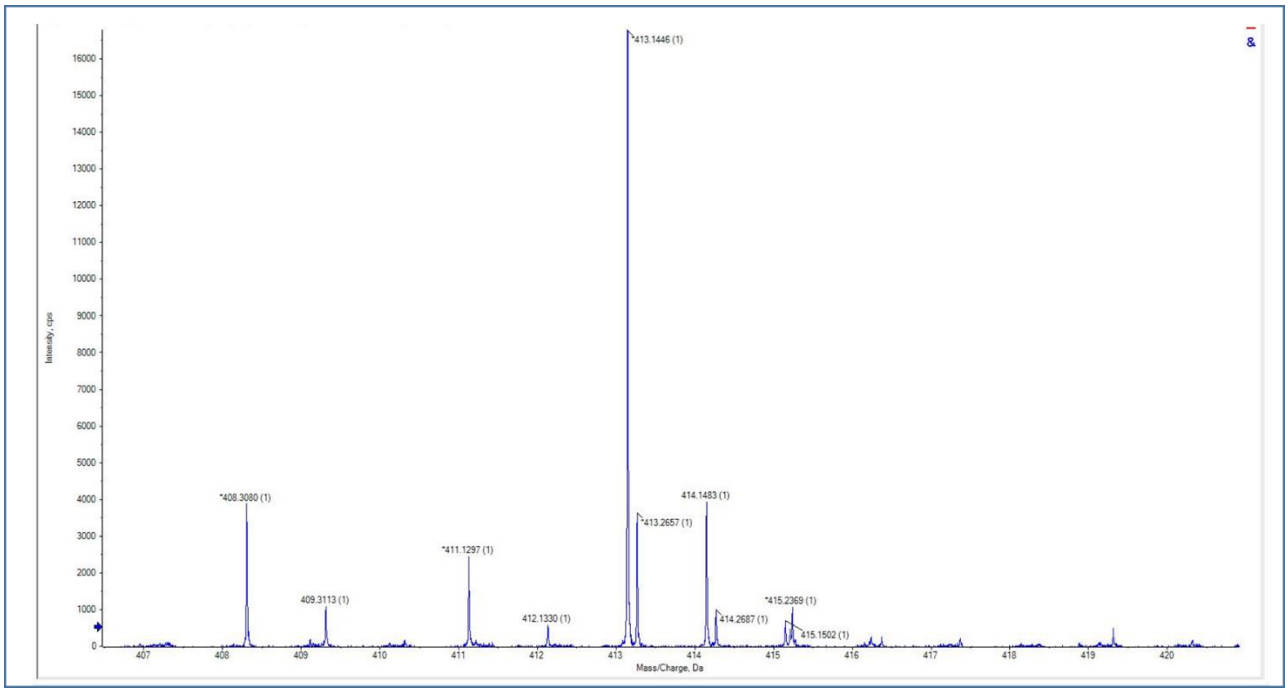

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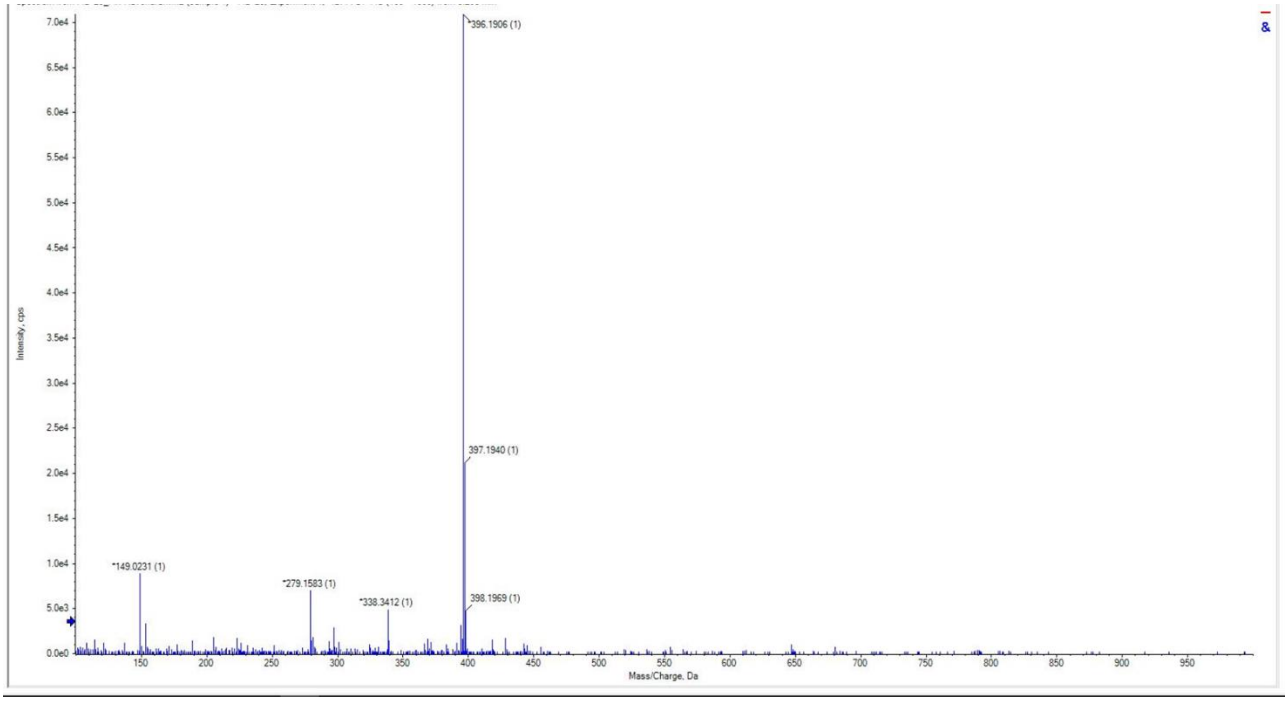

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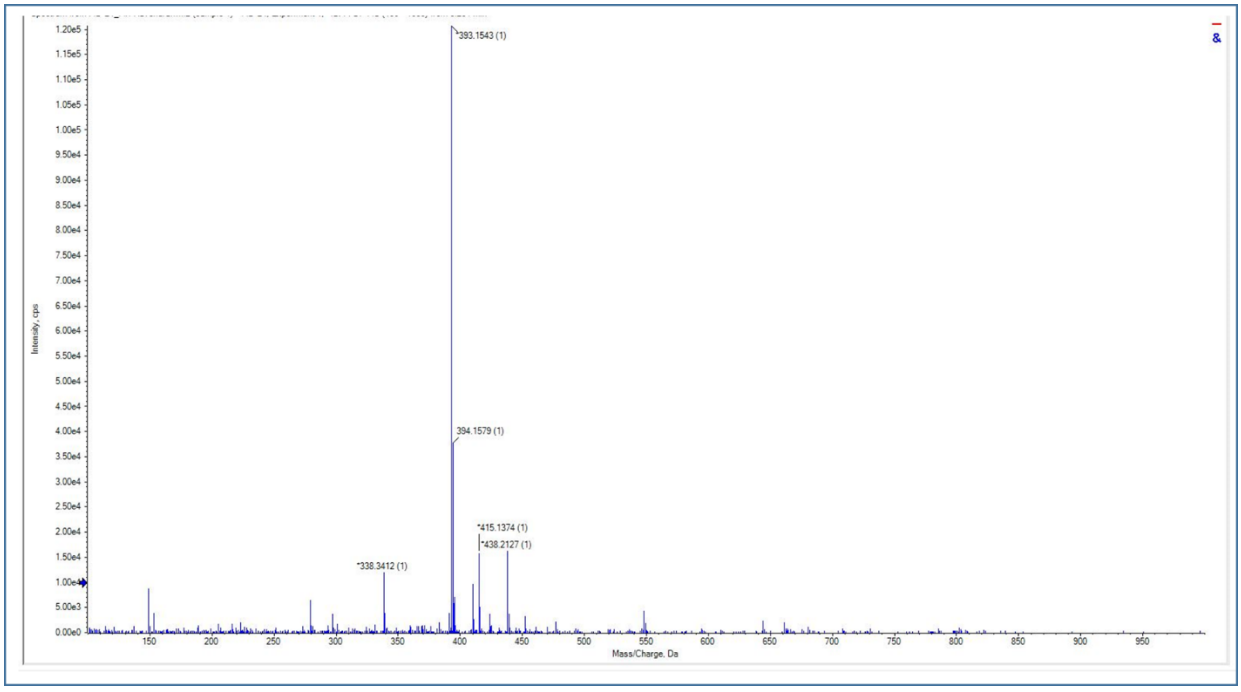
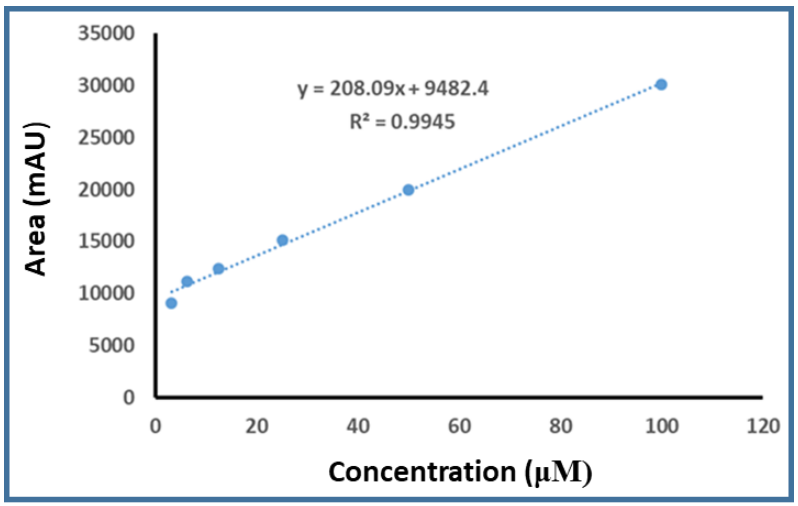


Calibration curve and HPLC chromatogram obtained from HPLC analysis for compound MD08

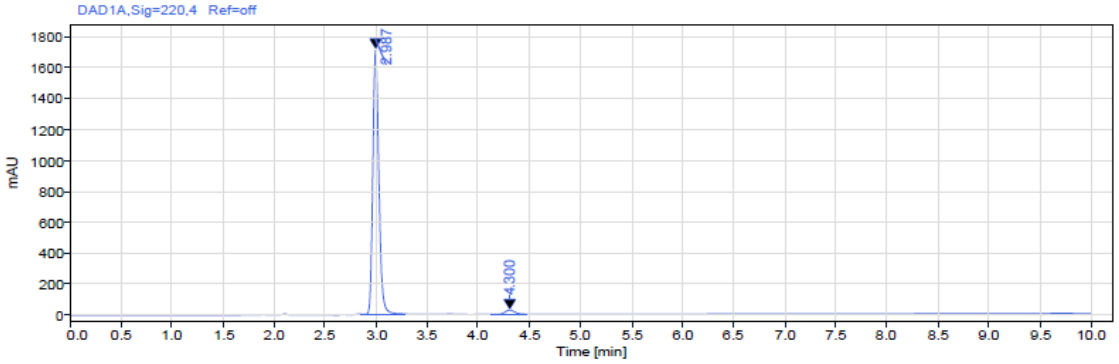
The calibration curve for hit compound MD08 was obtained by RP-HPLC by using the instrument Agilent 1260 infinity II and the solvent system used acetonitrile and water ratio 90:10. Column specification: Poroshell 123, EC C18 4µm, 4.6*150mm.



Single Injection Report

Agilent

Data file:	MD08		
Sequence Name:	MD08_11-07_2320221209	**Project Name:**	HPLC
Sample name:	MD08	**Operator:**	SYSTEM (SYSTEM)
Instrument:	HPLC	**Injection date:**	2022-12-09 03:49:32-08:00
Inj. volume:	20.000	**Location:**	
Acq. method:	ketoamide.amx	**Type:**	Calibration
Processing method:	bhanu2.pmx	**Sample amount:**	0.00
Manually modified:	Manual Integration		



Signal: DAD1A,Sig=220,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%
2.987	MM m	0.44	6975.62	1714.50	97.56
4.300	MM m	0.35	174.43	26.87	2.44
		Sum	**7150.04**		

Annexure-III

List of Publications

From Thesis

1. **Das B**, Baidya AT, Devi B, Rom T, Paul AK, Thakur B, Darreh-Shori T, Kumar R. *Synthesis, single crystal X-ray, DFT, spectroscopic, molecular docking studies and in vitro biological evaluation of compound N-benzyl-4-(4-chlorophenyl)-2-oxobutanamide*. Journal of Molecular Structure. 2023 Mar 15; 1276:134782.

2. **Das B**, Mathew AT, Baidya AT, Devi B, Salmon RR, Kumar R. *Artificial intelligence assisted identification of potential tau aggregation inhibitors: ligand-and structure-based virtual screening, in silico ADME, and molecular dynamics study*. Molecular Diversity. 2023 Apr 6:1-9.

3. **Das B**, Baidya AT, Thakur B, Darreh-Shori T, Kumar R. *Design, Synthesis, and Biological evaluation of novel protein aggregation modulators as potential therapeutic against Alzheimer's disease*. (*Manuscript under preparation*).

4. **Das B**, Baidya ATK, Mathew AT, Yadav AK, Kumar R. *Structural modification aimed for improving solubility of lead compounds in early phase drug discovery*. Bioorg Med Chem. 2022; 56:116614.

Other than thesis

1. Mathew AT, Baidya ATK, **Das B**, Devi B, Kumar R. *N-glycosylation induced changes in tau protein dynamics reveal its role in tau misfolding and aggregation: A microsecond long molecular dynamics study*. Proteins. 2023;91(2):147-60.
2. Devi B, Vasishta SS, **Das B**, Baidya ATK, Rampa RS, Mahapatra MK, et al. *Integrated use of ligand and structure-based virtual screening, molecular dynamics, free energy calculation and ADME prediction for the identification of potential PTP1B inhibitors*. Molecular diversity. 2023.
3. Baidya ATK, **Das B**, Devi B, Långström B, Ågren H, Darreh-Shori T, et al. *Mechanistic Insight into the Inhibition of Choline Acetyltransferase by Proton Pump Inhibitors*. ACS Chem Neurosci. 2023;14(4):749-65.
4. Nag S, Baidya ATK, Mandal A, Mathew AT, **Das B**, Devi B, et al. *Deep learning tools for advancing drug discovery and development*. 3 Biotech. 2022;12(5):110.
5. Akhilesh, Baidya ATK, Uniyal A, **Das B**, Kumar R, Tiwari V. *Structure-based virtual screening and molecular dynamics simulation for the identification of sphingosine*

kinase-2 inhibitors as potential analgesics. J Biomol Struct Dyn. 2022;40(23):12472-90.

Book chapter

1. *Polyphenol: Development of Polyphenol-Inspired Derivatives Targeting Pathological Factors of AD* in Natural Product-based Synthetic Drug Molecules in Alzheimer's Disease: Therapeutic & Theranostic agents. Springer Verlag, Singapore; 2023.

Patent application

1. Piperazine, Piperidine, and Indole-Substituted 1,2-Dicarbonyl Compounds as amyloid aggregation modulators: synthesis and application thereof. Indian Patent application submitted. August 2023.

Conference presentation

1. "*Synthesis, Single crystal structure, and Amyloid Beta Aggregation Inhibition Activity of Novel α-Ketoamide Derivative*" **International Society for Molecular and Cellular Mechanisms (ISMND)** NextGen 2023 International Virtual Conference. August 23-24. 2023.
2. "*Exploring Potential Tau Aggregation Inhibitors: AI Assisted Ligand and Structure Based Virtual Screening, In Silico ADME, and Molecular Dynamics Analysis*" **AI-SPARK Conference**, NIPER Mohali, October 9-11, 2023

Journal of Molecular Structure 1276 (2023) 134782

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journal homepage: www.elsevier.com/locate/molstr

Synthesis, single crystal X-ray, DFT, spectroscopic, molecular docking studies and *in vitro* biological evaluation of compound N-benzyl-4-(4-chlorophenyl)-2-oxobutanamide

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[b] Department of Chemistry, National Institute of Technology Kurukshetra, Kurukshetra 136119, Haryana, India
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ABSTRACT

Several α-ketoamides from natural as well as synthetic sources have been shown to possess multitude of biological activities due to their versatile nature and presence of multiple reactive centres giving them both electrophilic and nucleophilic characters. This makes them a key scaffold in chemistry and chemical biology. In this paper, we have reported the synthesis of ***N*-benzyl-4-(4-chlorophenyl)-2-oxobutanamide (1)** from β,γ-unsaturated α-hydroxythioester. Single crystal X-ray diffraction study was performed to determine the three-dimensional (3D) structure of the compound 1**.** Further, the 3D structure was optimised through DFT calculations using B3LYP/6-311G(d,p) basis set, followed by FTIR and NMR spectra calculation. The wavelength of maximum absorbance (λ) and the band gap energy of compound **1** were derived for methanol using the TD-DFT/6-311G(d,p) approach and compared to experimental results. The different intermolecular and intramolecular interactions such as H-O, H-Cl, H-C, H-N, and other possible interactions in the crystal structure were explored using Hirsfeld surfaces analysis and fingerprint plots. Additionally, Coulomb energy, dispersion energy, total energy, and total energy annotated were calculated by energy framework calculations demonstrating that electrostatic and repulsion forces are relevant to the topology of the overall interaction energies in the crystal. Finally, from the DFT optimized structure, the molecular electrostatic potential (MEP) map and Mulliken charges were generated and the natural bond (NBO) analysis was performed in order to investigate the interaction between various orbital and lone pairs occurring within the compounds. Based on the geometric and spectroscopic parameters, the experimental and theoretical results were indistinguishable. Additionally, *in vitro* amyloid beta 1-42 ($A\beta_{42}$) aggregation assay revealed that the compound 1 modulated the aggregation profile of $A\beta_{42}$ and the MTT cellular cytotoxicity assay showed that the compound is not toxic to cells. Further, molecular docking study resulted in the determination of interaction of compound **1** with the $A\beta_{42}$ fibrils. In summary, the present work can be helpful for the design, and synthesis of novel α-ketoamides as potential modulators of amyloid beta aggregation.

1. Introduction

α-Ketoamide is a privileged motif as well as the key intermediate in medicinal, synthetic chemistry, and chemical biology. It contains reactive ambident electrophile and nucleophile moiety, displaying two possible nucleophilic reaction sites together with two electrophilic centers, whose reactivity can be augmented through the selection of specific activation modes [1]. Many natural products contain α-ketoamide in their main scaffold owing the potential therapeutic efficacy motivating researchers to design α-ketoamide derivatives to develop compounds tailored to interact with different biological targets for providing therapeutics for the clinical management of a number of pathological conditions [2,3]. In another word, 1,2-dicarbonyl compounds are important life-related structures that are abundantly found in nat-

Abbreviations: AD, Alzheimer's disease; PLAAT, Phospholipase and acetyltransferase; Aβ, Amyloid beta; APP, Aβ precursor protein; TMS, Tetramethylsilane; HS, Hirshfeld Surface; MEP, Molecular electrostatic potential; FMOs, Frontier molecular orbitals; MPA, Mulliken population analysis; NBO, Natural bond orbital.

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E-mail address: rajnish.phe@iitbhu.ac.in (R. Kumar).

https://doi.org/10.1016/j.molstruc.2022.134782
0022-2860/

Molecular Diversity
https://doi.org/10.1007/s11030-023-10645-3

ORIGINAL ARTICLE

Artificial intelligence assisted identification of potential tau aggregation inhibitors: ligand- and structure-based virtual screening, in silico ADME, and molecular dynamics study

Bhanuranjan Das[1] · Alen T. Mathew[1] · Anurag T. K. Baidya[1] · Bharti Devi[1] · Rahul Rampa Salmon[1] · Rajnish Kumar[1]

Received: 29 October 2022 / Accepted: 29 March 2023

Abstract
Alzheimer's disease (AD) is a severe, growing, multifactorial disorder affecting millions of people worldwide characterized by cognitive decline and neurodegeneration. The accumulation of tau protein into paired helical filaments is one of the major pathological hallmarks of AD and has gained the interest of researchers as a potential drug target to treat AD. Lately, Artificial Intelligence (AI) has revolutionized the drug discovery process by speeding it up and reducing the overall cost. As a part of our continuous effort to identify potential tau aggregation inhibitors, and leveraging the power of AI, in this study, we used a fully automated AI-assisted ligand-based virtual screening tool, PyRMD to screen a library of 12 million compounds from the ZINC database to identify potential tau aggregation inhibitors. The preliminary hits from virtual screening were filtered for similar compounds and pan-assay interference compounds (the compounds containing reactive functional groups which can interfere with the assays) using RDKit. Further, the selected compounds were prioritized based on their molecular docking score with the binding pocket of tau where the binding pockets were identified using replica exchange molecular dynamics simulation. Thirty-three compounds showing good docking scores for all the tau clusters were selected and were further subjected to in silico pharmacokinetic prediction. Finally, top 10 compounds were selected for molecular dynamics simulation and MMPBSA binding free energy calculations resulting in the identification of UNK_175, UNK_1027, UNK_1172, UNK_1173, UNK_1237, UNK_1518, and UNK_2181 as potential tau aggregation inhibitors.

Keywords Alzheimer's disease · Tau aggregation inhibitors · Artificial intelligence · PyRMD · Molecular dynamics · Replica exchange molecular dynamics · MMPBSA

Introduction

Alzheimer's disease (AD) is a multifactorial disorder that affects millions of people worldwide and is characterized by severe cognitive impairment, neurodegeneration, and other behavioural changes [1, 2]. According to the World Alzheimer's report 2019, 80% of the population is concerned about developing AD, and there is a general perception that this disease is incurable. Due to its multifactorial nature, our understanding of the pathogenesis of AD is limited and remains elusive. Several hypotheses have been proposed regarding AD, including the cholinergic hypothesis, amyloid-β (Aβ) and tau hypothesis, oxidative stress hypothesis, and metal chelation hypothesis, which facilitate drug discovery and development. Protein misprocessing is a hallmark of AD, involving the accumulation of Aβ peptides and abnormal tau protein as amyloid senile plaques and neurofibrillary tangles, respectively, in the brain [3–5]. These histopathological hallmarks play a crucial role in the pathological progression of AD, and different molecular mechanisms and biological processes are responsible for their occurrence.

Recent literature provides a comprehensive summary of the discovery and development of preclinical drug candidates and drugs under clinical trials for AD [6, 7]. However, the therapeutic management of AD is currently limited to symptomatic treatment using cholinesterase inhibitors such as Donepezil, Memantine, Galantamine, and Rivastigmine [8]. Although Aducanumab, a disease-modifying agent,

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