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Review article

Pyrrolopyrimidines: An update on recent advancements in their medicinal attributes

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ABSTRACT

Fused heterocycles are reported to demonstrate variety of biological activities such as anticancer, antibacterial, antifungal and anti-inflammatory, and are thus exhaustively utilized in the field of medicinal chemistry. Pyrrolopyrimidines is one of the major classes of fused heterocycles which are extensively reported throughout the literature. Several reports suggest that pyrrolopyrimidine as fused scaffold possess more diverse and potent pharmacological profile than individual pyrrole and pyrimidine nucleus. Different pathological targets require different structural attributes reflected via varied substitutions, thus in recent years, researchers have employed various synthetic strategies to achieve desired substitutions on the pyrrolopyrimidine nucleus. In this review, authors highlight the recent advancement in this area, special focus was laid on the pharmacological profile and structure-activity relationship studies (SAR) of various synthesized pyrrolopyrimidine derivatives.

1. Introduction

Fused pyrimidines are one of the interesting class of heterocycles, which have been extensively explored by medicinal chemists due to their vast pharmacological profile [1]. One of the reasons for such interesting pharmacological potential could be the presence of fused pyrimidines in several physiological molecules. Several fused pyrimidine molecules such as purines, xanthines, pteridines, alloxazines, quinazolines, pyrrolopyrimidines, pyridopyrimidines, triazolo pyrimidines, pyrimidoazepines, furopyrimidines and thiazolopyrimidines are well-established as antibacterial, anticancer, antifungal, and anti-inflammatory agents [1]. Some of these derivatives containing fused pyrimidine nucleus are shown in Fig. 1. Among various fused pyrimidines, pyrrolopyrimidines have gained attention of many researchers as a useful scaffold with varied biological activities such as anticancer, antibacterial, anti-inflammaotory and antiviral agents. The initial work on pyrrolopyrimidines began with the discovery of purine derivatives e.g. 6-mercaptopurine as antitumor agent. Initial studies were followed by exhaustive research focussed on pharmacological spectrum of purines and its analogues, in particular deaza analogues, pyrrolo [2,3-*d*]pyrimidines and pyrrolo[3,2-*d*]pyrimidines [2]. Additionally in the mid-nineteenth century, a few natural product based nucleoside antibiotics, tubercidin, toyocamycin, and sanguivomycin were also isolated and identified. Interestingly enough all of these natural product based anti-biotics consisted of pyrrolo[2-3-*d*]pyrimidine nucleus [2]. Later with the disclosure of different biological activities, especially antitumor potential of substituted 4-aminopyrrolo-[3,2-d]- pyrimidines, researchers shifted their focus towards the second isomer. Some of the FDA approved anti-cancer drugs also contain pyrrolopyrimidine nucleus including Pemetrexed used as antifolate [3], Ruxolitinib, Tofacitinib [4], Baricitinib [5] and Ribociclib [6] used as tyrosine kinase inhibitors, as shown in Fig. 2. Currently, some pyrrolopyrimidine derivatives are in clinical trials against various pathological targets. AZD5363, reported as potent Akt inhibitor, is currently in phase I of clinical trial, in combination with docetaxel and prednisolone for the treatment of metastatic castration resistant prostate cancer (mCRPC). The phase I clinical trial data suggests that in phase II, dose of 320 mg of AZD5363 two times a day and in combination with docetaxel and prednisolone (full dose) is recommended for continuous 4 days [7]. Additionally, due significant preclinical results of AZD5363 in combination with enzalutamide (ENZ) against castrate-resistant prostate cancer in ENZ-resistant cell line, this combination has been put forward for clinical evaluation [8]. TAK-285, a tyrosine

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Review article

Role of sulphur-heterocycles in medicinal chemistry: An update

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ABSTRACT

From many decades, *S*-heterocycles have maintained their status as an important part and core of FDA approved drugs and medicinally active compounds. With exhaustive exploration of nitrogen heterocycles in medicinal chemistry, researchers have shifted their interest towards other heterocycles, especially, *S*-heterocycles. Thus several attempts have been made to synthesize a variety of new sulphur containing compounds with high medicinal value and low toxicity profile, in comparison to previous *N*-heterocycles. Till today, *S*-heterocycle containing compounds have been largely reported as anticancer, antidiabetic, antimicrobial, antihypertension, antiviral, antinflammatory etc. In this review, the authors have tried to provide a critical analysis of synthesis and medicinal attributes of sulphur containing heterocycles such as thiirane, thiophene, thiazole, thiopyran, thiazolidine etc reported within last five years to emphasize the significance and usefulness of these *S*-heterocycles in the drug discovery process.

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Review

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Future Medicinal Chemistry

An update on chemical classes targeting ERK1/2 for the management of cancer

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Cancer, still in the limelight due to its dreadful nature, shows overexpression of multiple signaling macromolecules leading to failure of many chemotherapeutic agents and acquired resistance to chemotherapy. These factors highlight the significance of shifting toward targeted therapy in cancer research. Recently, ERKs (ERK1 and 2) have been established as a promising target for the management of various types of solid tumors, due to their aberrant involvement in cell growth and progression. Several ERKs inhibitors have reached clinical trials for the management of cancer and their derivatives are being continuously reported with noteworthy anticancer effect. This review highlights the recent reports on various chemical classes involved in the development of ERKs inhibitors along with their *in vitro* and *in vivo* activity and structure–activity relationship profile.

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Keywords: cancer • ERK1/ERK2 • ERK inhibitors • heterocycles

From many decades, cancer remains a terrible disease and a challenge for the researchers due to its poor prognosis [1–3]. Although a number of chemotherapeutic agents are available in the market for the treatment of cancer, they fail to cure the disease for various reasons [4,5]. One of the main reasons for their failure is the occurrence of drug resistance. Resistance can occur due to alterations in the genes during the treatment, overexpression of the molecular targets and cross linking of the various signaling pathways [6]. Thus, the need of the hour is to focus on the targeted therapy rather than chemotherapy. Continuously, researchers are putting their efforts into identifying new targeted therapies with great efficacy and less toxicity in comparison to chemotherapy [7,8]. The use of various modern techniques like high-throughput screening (HTS), bioinformatics, genomics and molecular biology helps in the identification of new therapeutic targets with higher degree of relevance in the treatment of cancer [9,10]. Various studies have identified many potential targets and ERKs [11], ERK1 and ERK2 are one of the promising targets among them, which seek the attention of many researchers. ERK1 and ERK2 belong to the mitogen-activated family, thus also known as mitogen-activated protein kinases (MAPKs) [12]. Both ERK1 and ERK2 contain 85% of the same amino acid sequence. These are categorized as RAS–RAF–MEK–ERK signaling cascade due to their active participation in the cell functions like cell growth, cell differentiation and proliferation [13–15]. The proto-oncogenic drivers like mutation leads to dysregulation and increased kinases activity [16]. Due to this increased phosphorylation, ERKs have been involved in various types of cancers like breast, lung, prostate and ovarian cancer [17]. During normal physiological conditions, MAPKs activated by Ras/Raf proteins such as A-Raf, B-Raf or C-Raf and various other growth factors, bind to the surface of the receptors [18]. The activated MAPKs further phosphorylates other downstream isoforms of ERK, especially ERK1 and ERK2, the key kinase effector of the pathway, which further leads to the activation of many transcription factors (Figure 1) [19]. In cancer, there is an abnormal activation of the ERK pathway caused by the overactivation of growth factor receptors and mutations in RAS and BRAF proteins [20]. Approximately 33 and 8% of the human cancers are found to have overexpressed RAS and BRAF proteins, respectively [21]. Thus, researchers get encouraged by these findings and are involved in the development of small-based molecules targeting ERK signaling cascade for the management of cancer. Till date, several ERK inhibitors have been reported; based on their mechanism, ERK inhibitors have been categorized

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Identifying novel putative ERK1/2 inhibitors via hybrid scaffold hopping –FBDD approach

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Communicated by Ramaswamy H. Sarma

ABSTRACT

ERK inhibitors are continuously explored by the researchers due to their clinical significance in resistant tumor cell lines. Though many ERK1/2 inhibitors are reported, there is still need to identify novel hits to increase the number of molecules in clinical trials. Therefore, an urgent need is to examine the existing chemical space for ERK inhibitory potential with an aim to develop novel scaffolds which can act as potent ERKs inhibitors. In this study, Ulixertinib, a known ERK2 inhibitor was selected to perform scaffold hopping to discover new scaffolds with similar binding mode followed by molecular docking analysis of the hits with highest similarity score to determine, both the binding mode and affinity in the catalytic domain of ERK2. The top hit was then subjected to FBDD to identify side chains which could enhance the binding affinity in the catalytic domain of ERK2. Again, docking analysis was performed to validate and determine their binding affinity. Further the top hit identified after docking analysis was subjected to molecular dynamic simulations. Overall, 3 hits (ligand **6**, **8** and **10**) were found to possess optimum pharmacodynamic and pharmacokinetic profile, *in-silico*, to be claimed as putative ERK2 inhibitors. This study disclosed new lead molecules with putative ERK2 inhibitory potential which may be further validated *via* biological evaluation.

ARTICLE HISTORY
Received 14 October 2020
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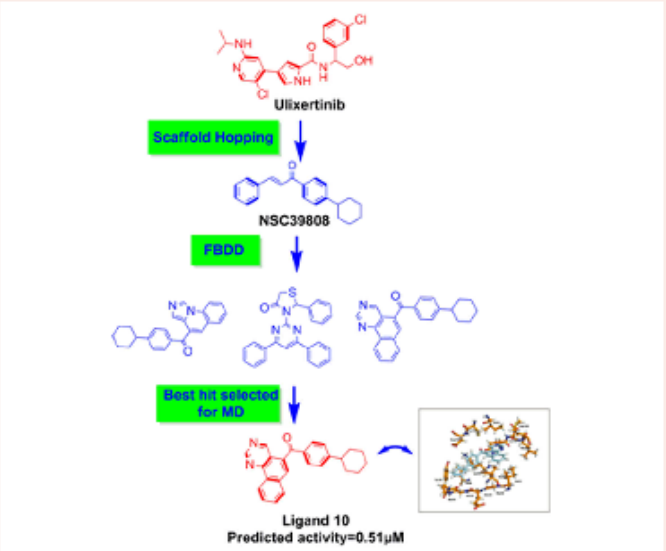
KEYWORDS
ERK2 inhibitors; in-silico; Scaffold hopping; FBDD; molecular docking



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SAR AND QSAR IN ENVIRONMENTAL RESEARCH
https://doi.org/10.1080/1062936X.2021.1973094

Structure based designing of thiazolidinone-pyrimidine derivatives as ERK2 inhibitors: Synthesis and in vitro evaluation

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[a]Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga, India; [b]Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda, India; [c]Integrative Physiology and Pharmacology, Institute of Biomedicine, Faculty of Medicine, University of Turku, Turku, Finland; [d]Department of Chemistry, Maharishi Markandeshwar (Deemed to Be University), Ambala, India; [e]CSIR-North East Institute of Science and Technology, Jorhat, India

ABSTRACT

Breast cancer has been associated with an overexpression of various molecular targets; accordingly, various target-specific chemotherapeutic agents have been developed. Inhibition of ERK2, a member of MAPK pathway, is an important target involved in the treatment of both oestrogen receptor-positive and triple-negative breast cancer. Thus, in continuation of our previous work on the ERK2 target, we here report novel inhibitors of this kinase. Out of three lead molecules reported in our previous study, we selected the thiazolidinone-pyrimidine scaffold for further development of small molecule inhibitors of ERK2. Analogues of the lead molecule were docked in the target kinase, followed by molecular dynamic simulations and MM-GBSA calculations. Analogues maintaining key interactions with amino acid residues in the ATP-binding domain of ERK2 were selected and duly synthesized. In vitro biochemical evaluation of these molecules against ERK2 kinase disclosed that two molecules possess significant kinase inhibitory potential with IC_{50} values ≤ 0.5 μM.

ARTICLE HISTORY
Received 10 July 2021
Accepted 23 August 2021

KEYWORDS
Thiazolidinone-pyrimidine; molecular dynamic simulations; ERK2; enzymatic assay

Introduction

Breast cancer forms the second leading cause of death around the globe and has an adverse impact on women's health [1]. On the basis of overexpression of molecular targets, breast cancer is classified into many types such as ER/PR+ (overexpression of oestrogen and progesterone receptors; 70% of all breast cancers) and HER2+ (human epidermal growth factor receptor 2; 20% of breast cancers) [2]. A critical subtype of breast cancer is triple-negative breast cancer (TNBC), which is the most aggressive form of breast cancer and considered as most lethal because of the absence of molecular targets such as HER2, ER and PR [2]. As TNBC lacks overexpression of ER, PR and HER2, it is resistant towards hormonal and targeted therapies. However, pathways like mitogen-activated protein kinase (MAPK) have been reported to be

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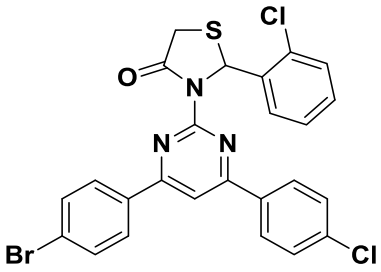
Appendix

Compound 8b:



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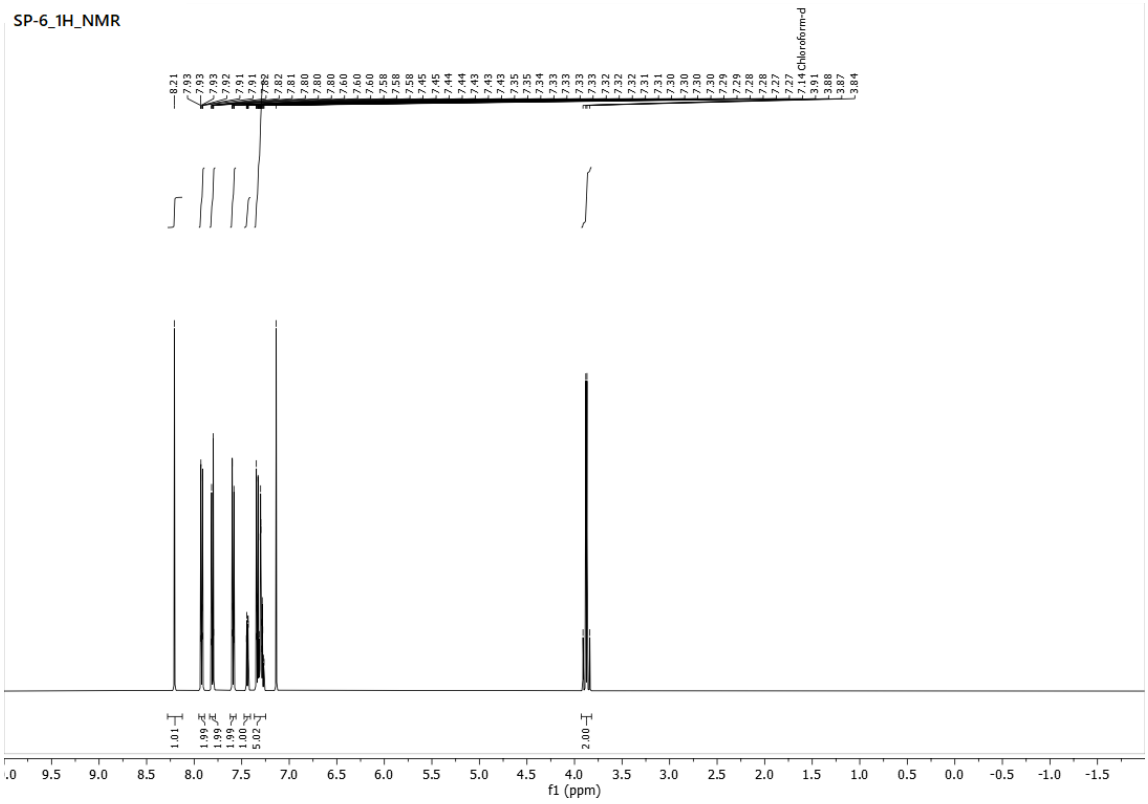
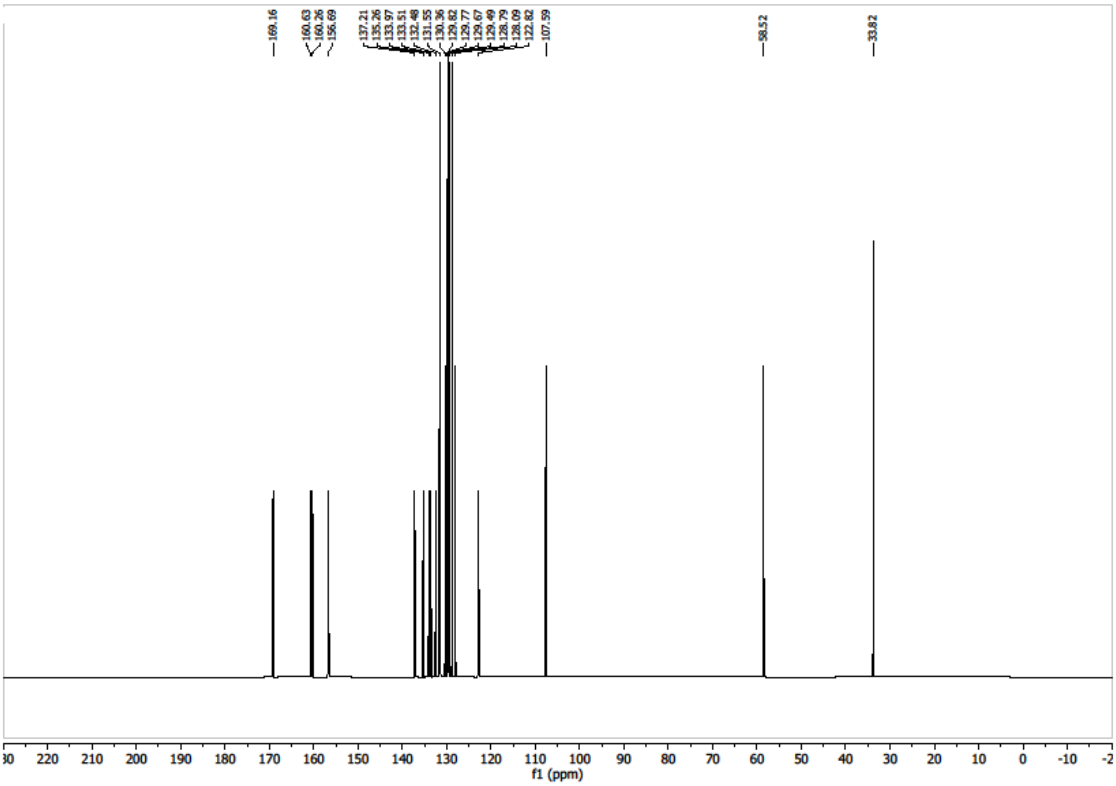
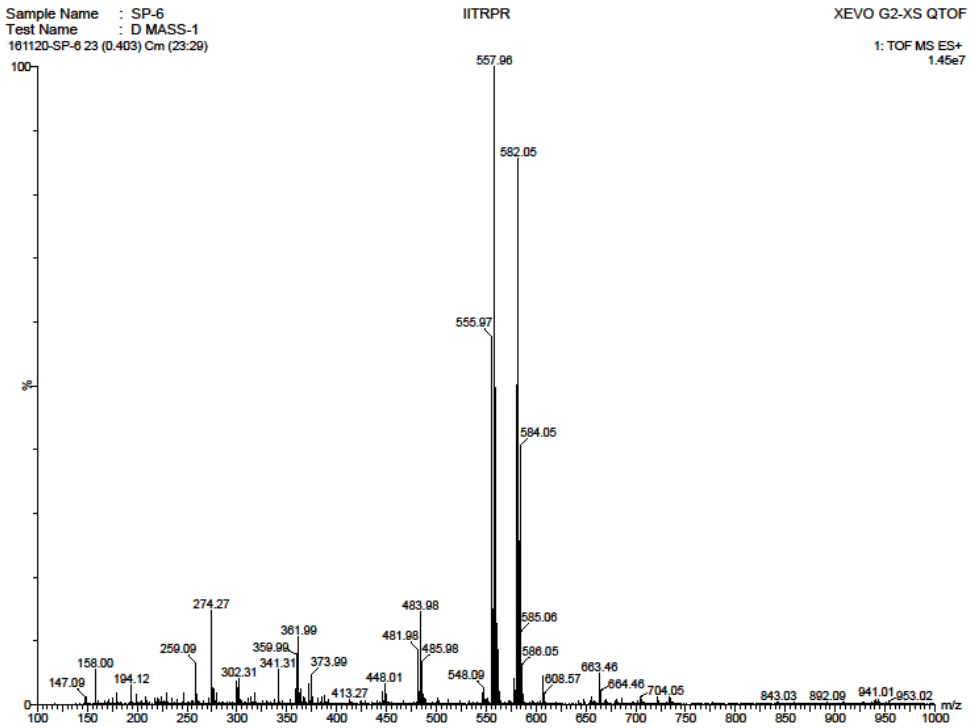


^{13}C NMR:


169.16
160.63
160.26
156.69
137.21
135.26
133.97
133.51
132.48
131.55
130.36
129.82
129.77
129.67
129.49
128.79
128.09
122.82
107.59
58.52
33.82
f1 (ppm)

MASS: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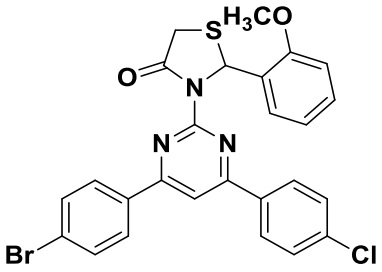
Test Name : D MASS-1
161120-SP-6 23 (0.403) Cm (23:29)
IITRPR
XEVO G2-XS QTOF
1: TOF MS ES+
1.45e7
100
%
0
557.96
582.05
555.97
584.05
585.06
586.05
483.98
481.98
485.98
274.27
361.99
359.99
341.31
373.99
259.09
158.00
147.09
194.12
302.31
448.01
413.27
548.09
608.57
663.46
664.46
704.05
843.03
892.09
941.01
953.02
m/z
100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000

Compound 8c:



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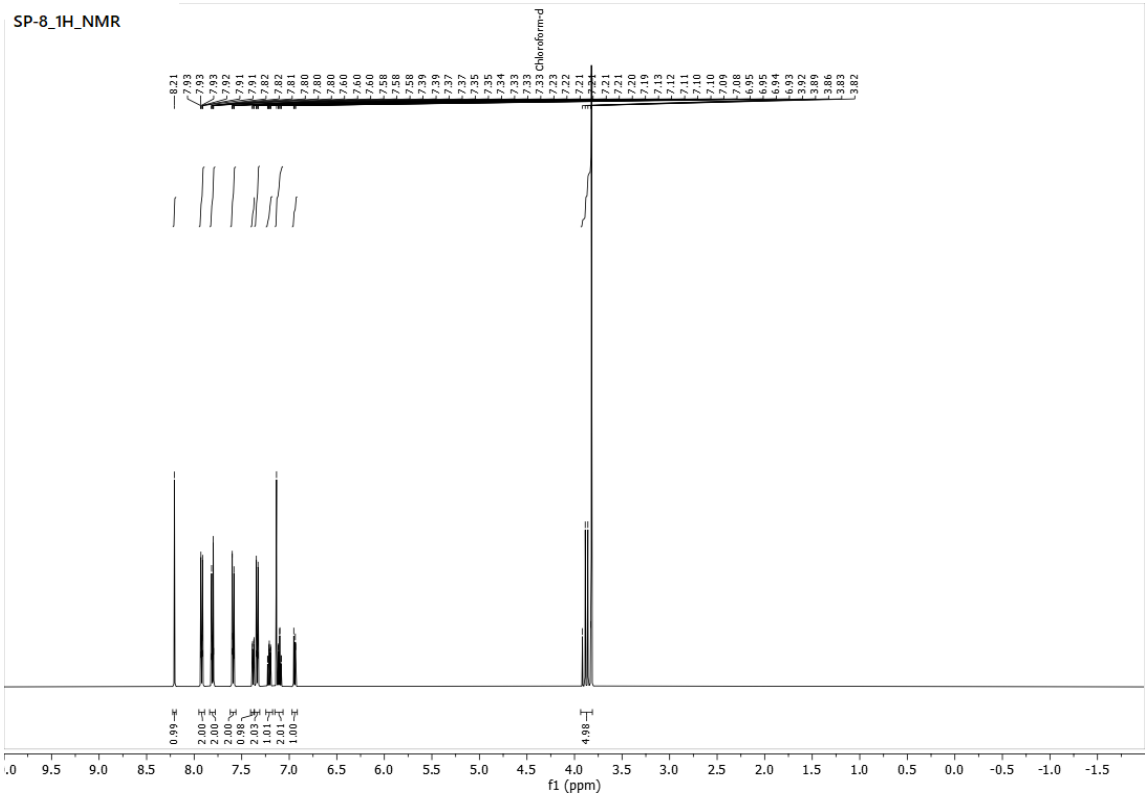

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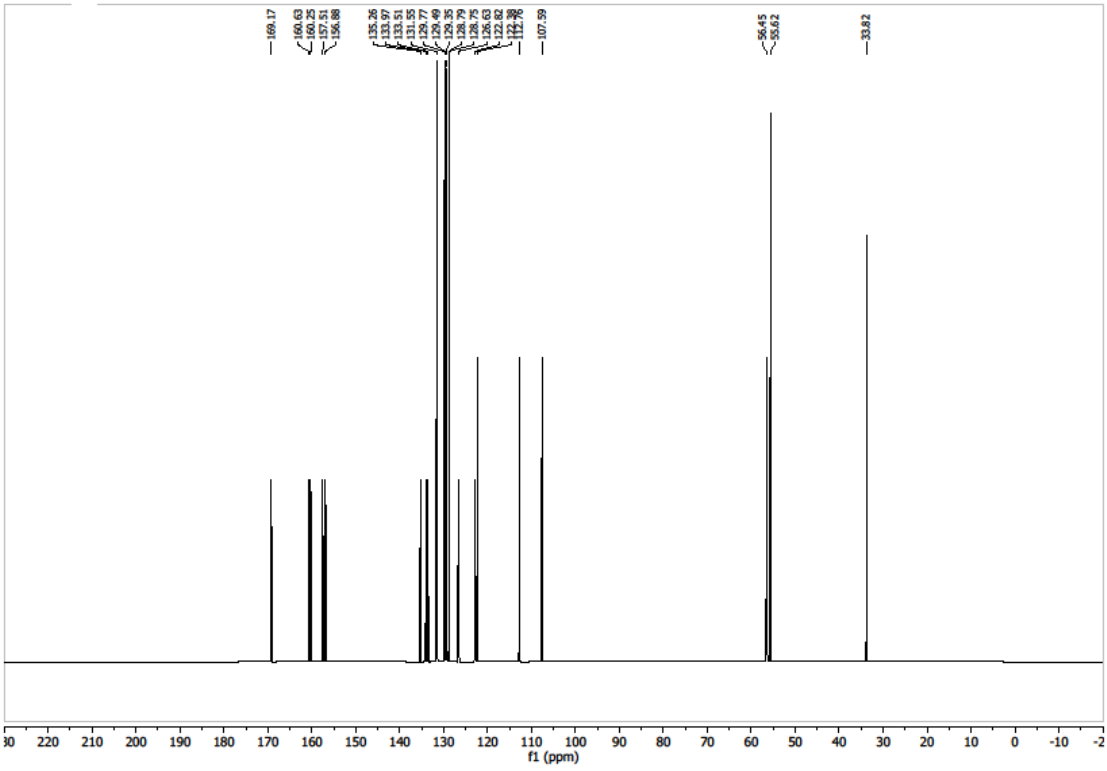
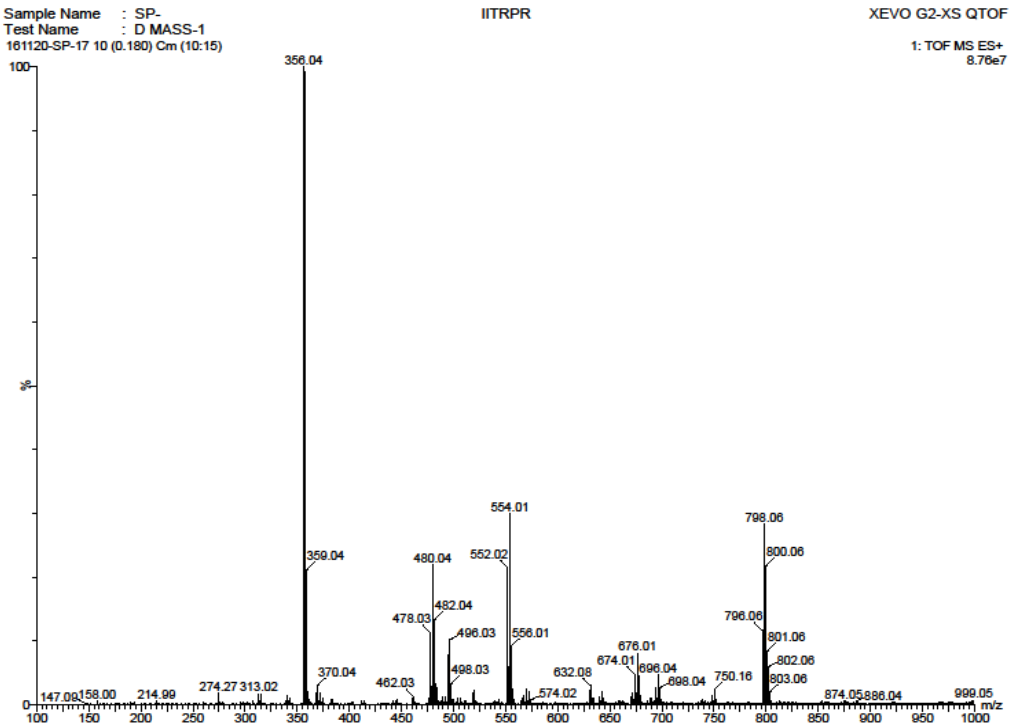
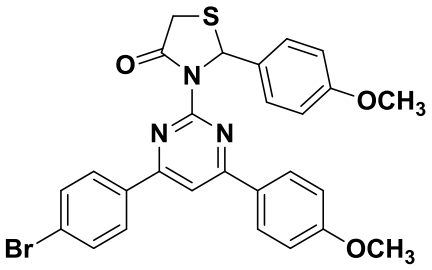

169.17
160.63
160.25
157.51
156.88
135.26
133.97
133.51
131.55
129.77
129.49
129.35
128.79
128.75
126.63
122.62
112.78
107.59
56.45
55.62
33.82
f1 (ppm)

MASS:


Sample Name : SP-
Test Name : D MASS-1
161120-SP-17 10 (0.180) Cm (10:15)
IITRPR
XEVO G2-XS QTOF
1: TOF MS ES+
8.76e7
%
m/z
356.04
359.04
480.04
552.02
554.01
798.06
800.06
796.06
801.06
802.06
803.06
482.04
478.03
496.03
556.01
676.01
674.01
696.04
698.04
750.16
632.08
574.02
498.03
462.03
370.04
147.09
158.00
214.99
274.27
313.02
874.05
886.04
999.05

Compound 8j:



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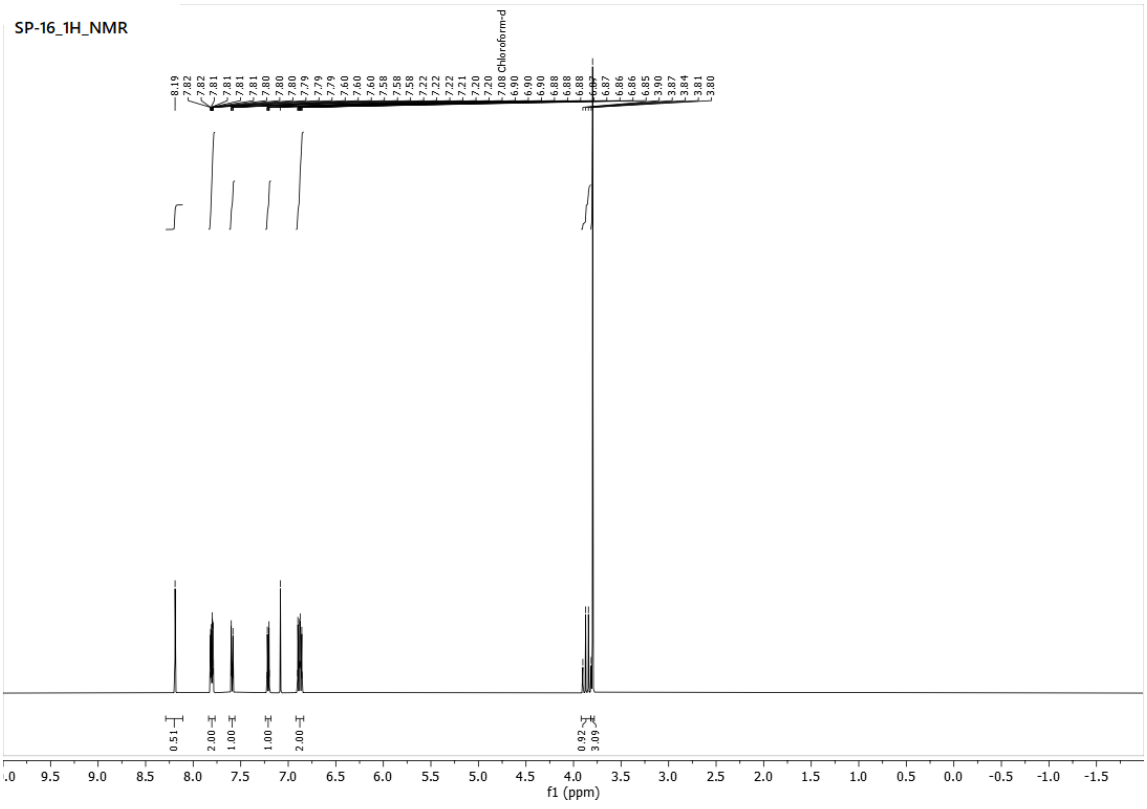

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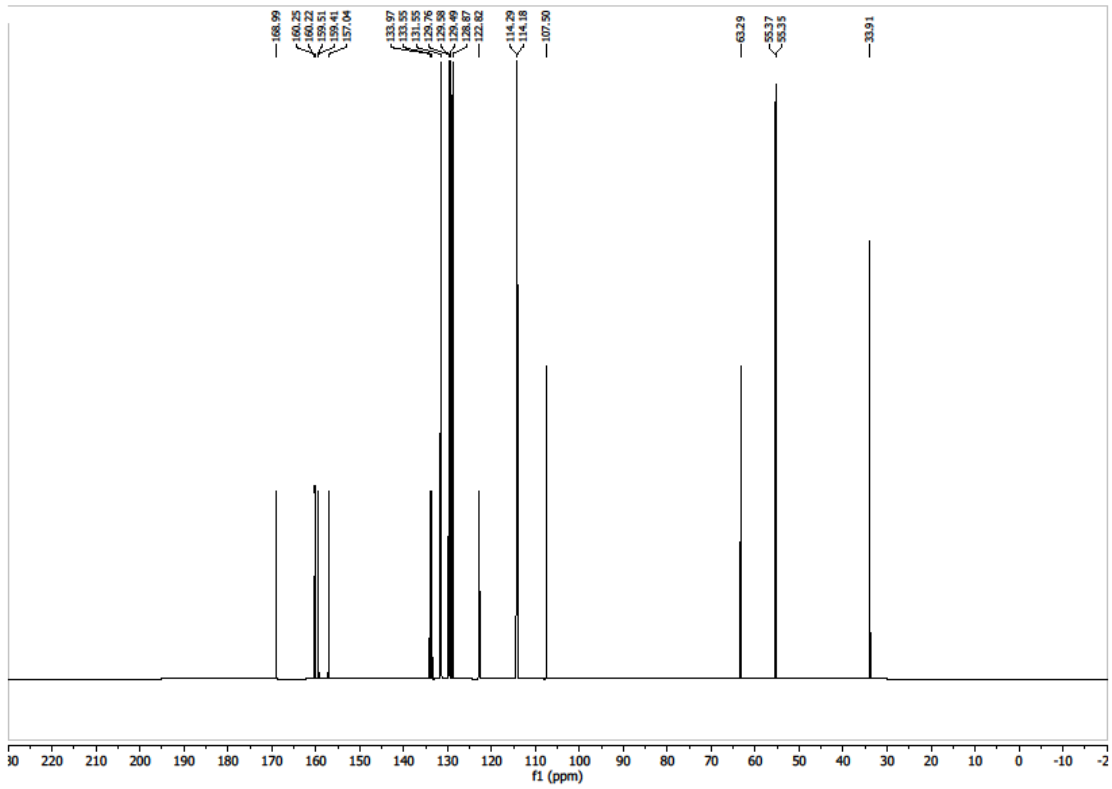
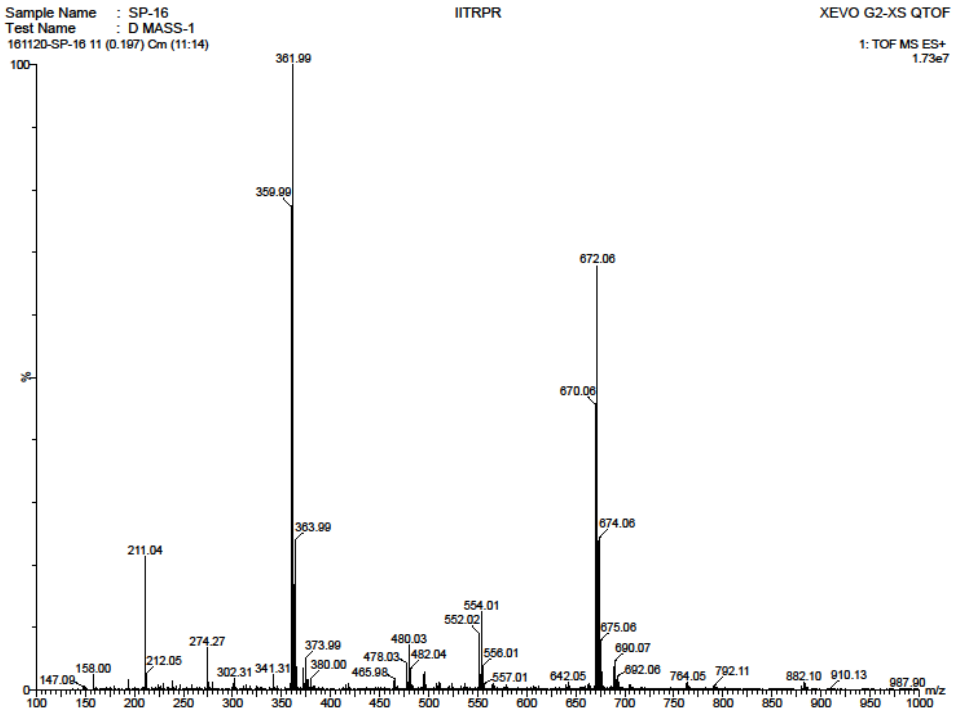
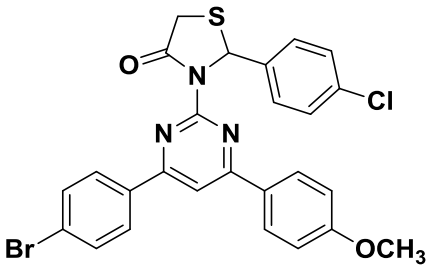

168.99
160.25
160.22
159.51
159.41
157.04
133.97
133.55
131.55
129.76
129.38
128.49
128.87
122.82
114.29
114.18
107.50
63.29
55.37
55.35
33.91
f1 (ppm)

MASS:


Sample Name : SP-16
Test Name : D MASS-1
161120-SP-16 11 (0.197) Cm (11:14)
IITRPR
XEVO G2-XS QTOF
1: TOF MS ES+
1.73e7
%
m/z
361.99
359.99
672.06
670.06
674.06
363.99
211.04
554.01
552.02
675.06
690.07
692.06
480.03
482.04
478.03
556.01
557.01
373.99
380.00
465.98
274.27
212.05
158.00
147.09
302.31
341.31
642.05
764.05
792.11
882.10
910.13
987.90

Compound 8k:



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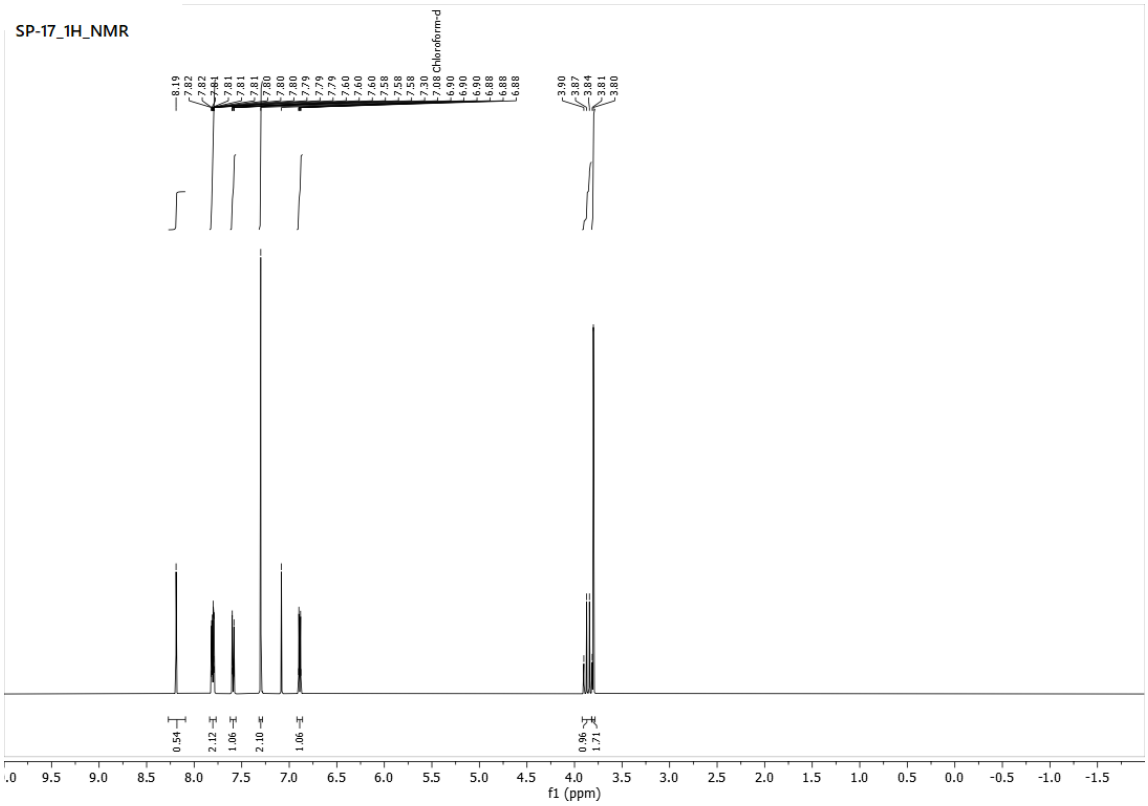

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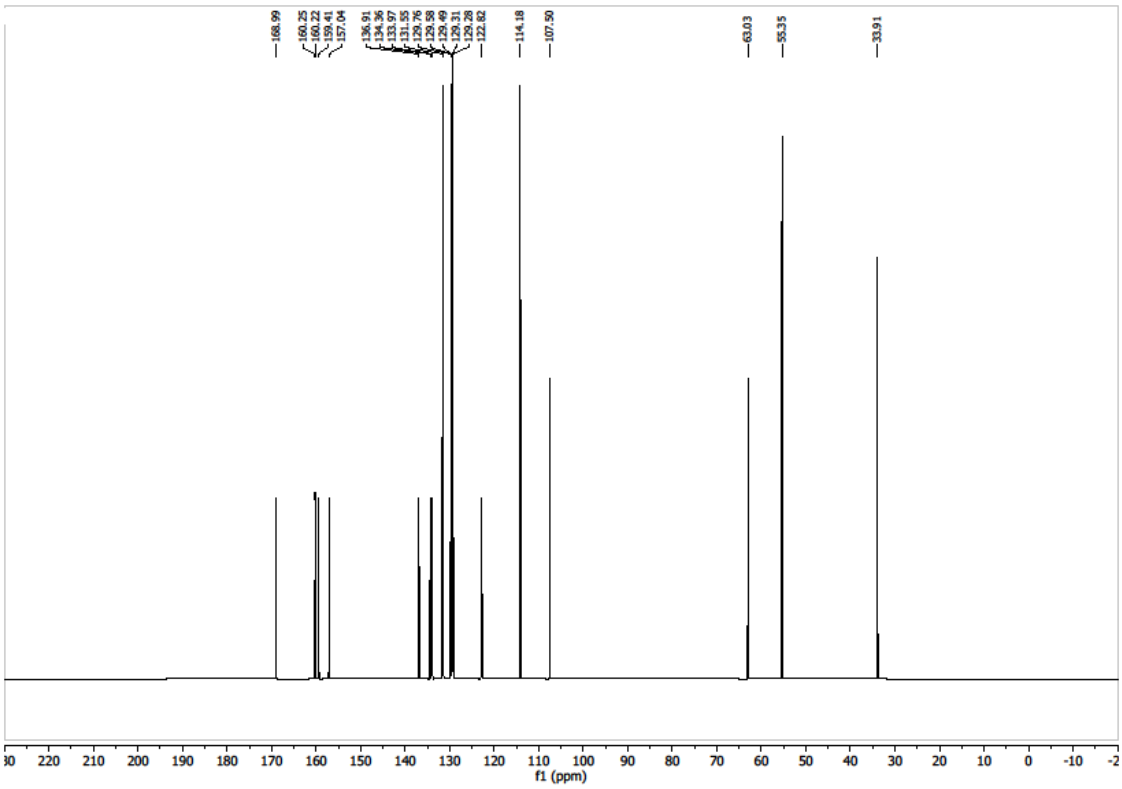
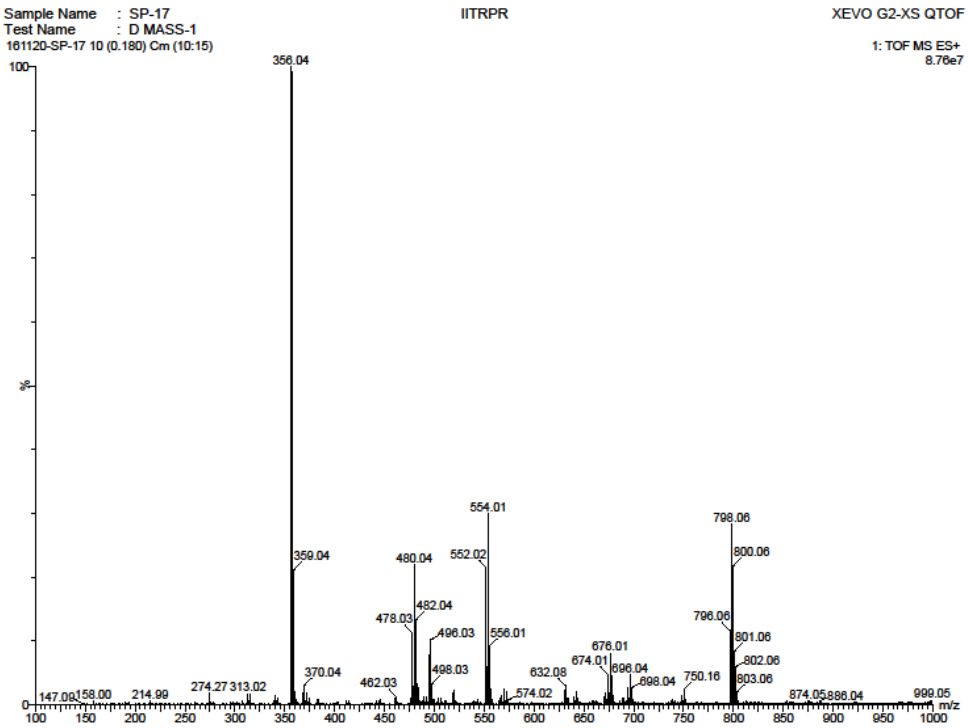
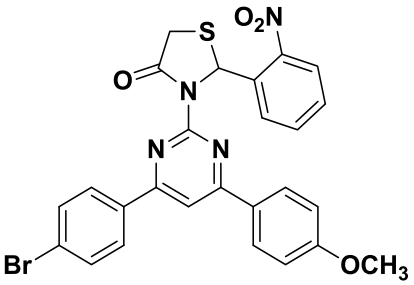

168.99
160.25
160.22
159.41
157.04
136.91
134.36
133.97
131.55
129.76
129.58
129.49
129.31
129.28
122.62
114.18
107.50
63.03
55.35
33.91
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

MASS:


Sample Name : SP-17
Test Name : D MASS-1
161120-SP-17 10 (0.180) Cm (10:15)
IITRPR
XEVO G2-XS QTOF
1: TOF MS ES+
8.76e7
100
%
0
356.04
359.04
554.01
552.02
480.04
482.04
478.03
496.03
556.01
498.03
370.04
462.03
632.08
574.02
676.01
674.01
696.04
698.04
750.16
798.06
800.06
796.06
801.06
802.06
803.06
147.08
158.00
214.99
274.27
313.02
874.05
886.04
999.05
m/z
100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000

Compound 8l:



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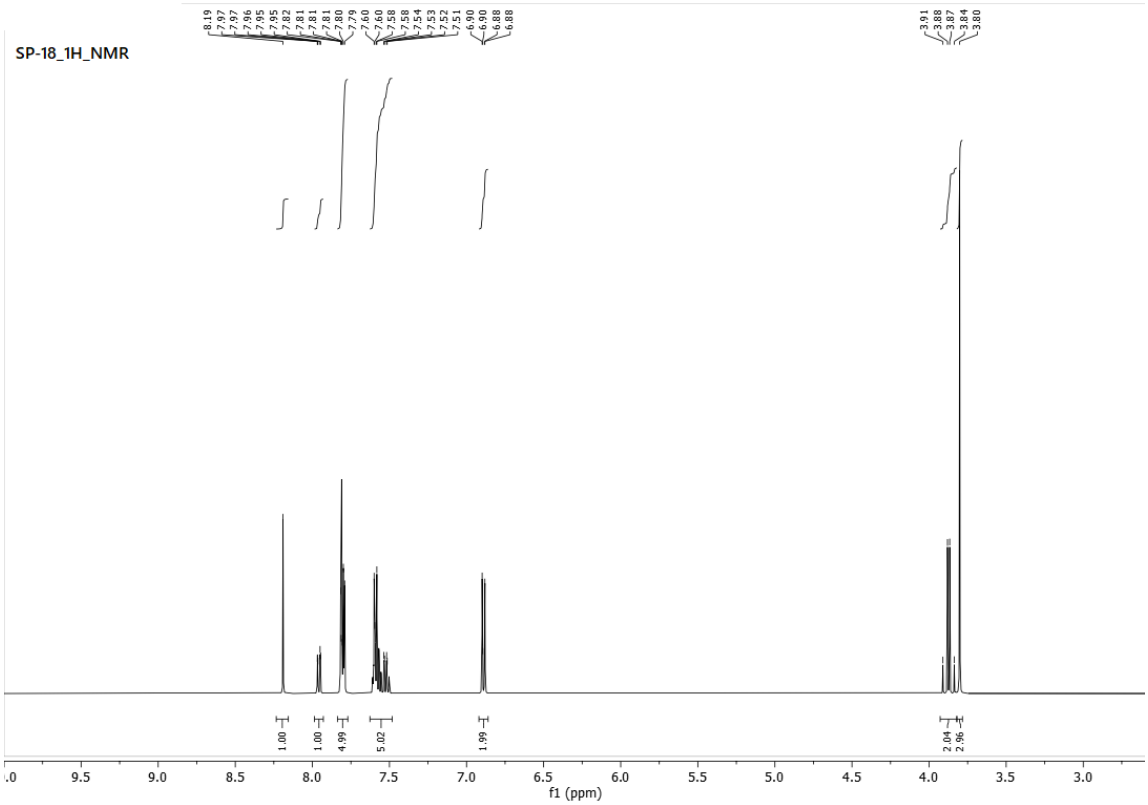

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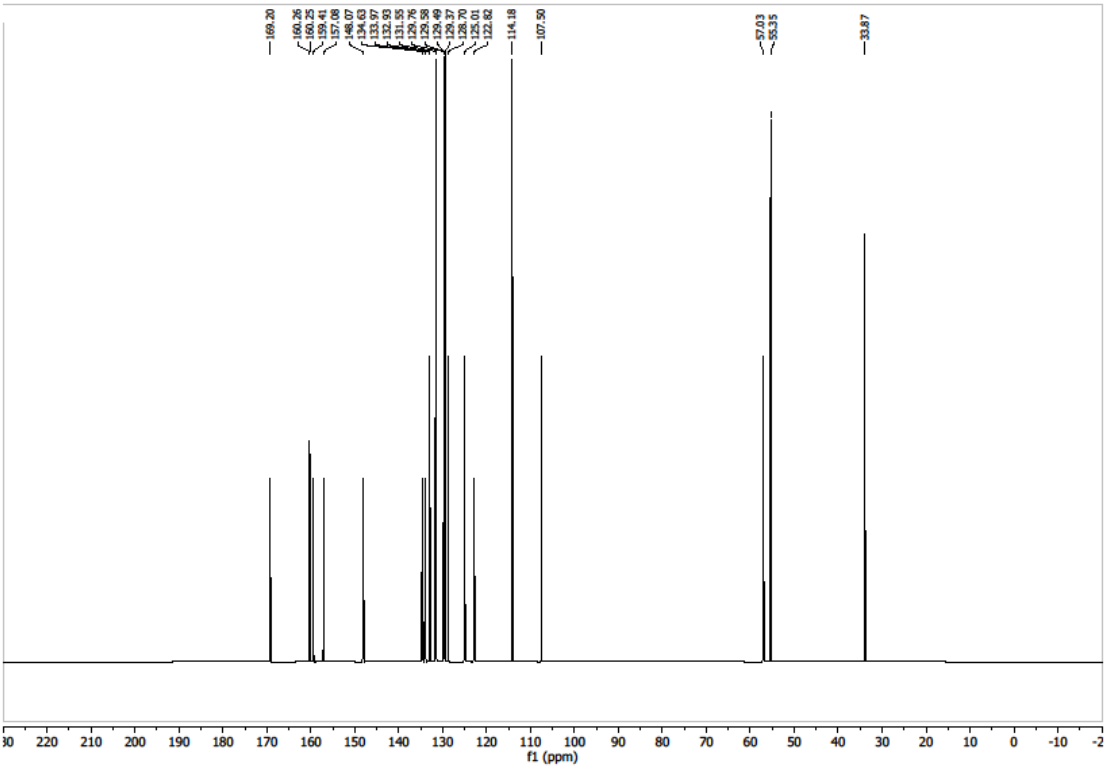
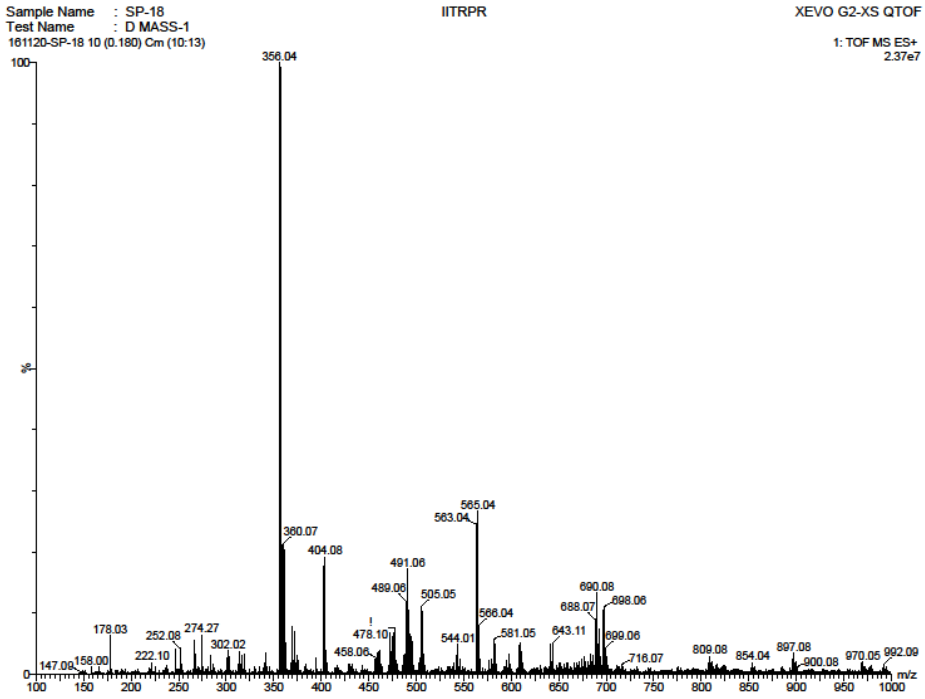

169.20
160.26
160.25
159.41
157.08
146.07
134.63
133.97
132.93
131.55
129.76
129.58
129.49
129.37
128.70
125.01
122.82
114.18
107.50
57.03
55.35
33.87
f1 (ppm)

MASS: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XEVO G2-XS QTOF
1: TOF MS ES+
2.37e7
%
m/z
356.04
360.07
404.08
491.06
489.06
505.05
565.04
563.04
566.04
544.01
581.05
643.11
688.07
690.08
698.06
699.06
716.07
809.08
854.04
897.08
900.08
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274.27
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222.10
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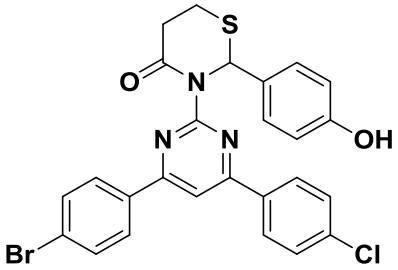
147.09
458.06
478.10

Compound 10d:



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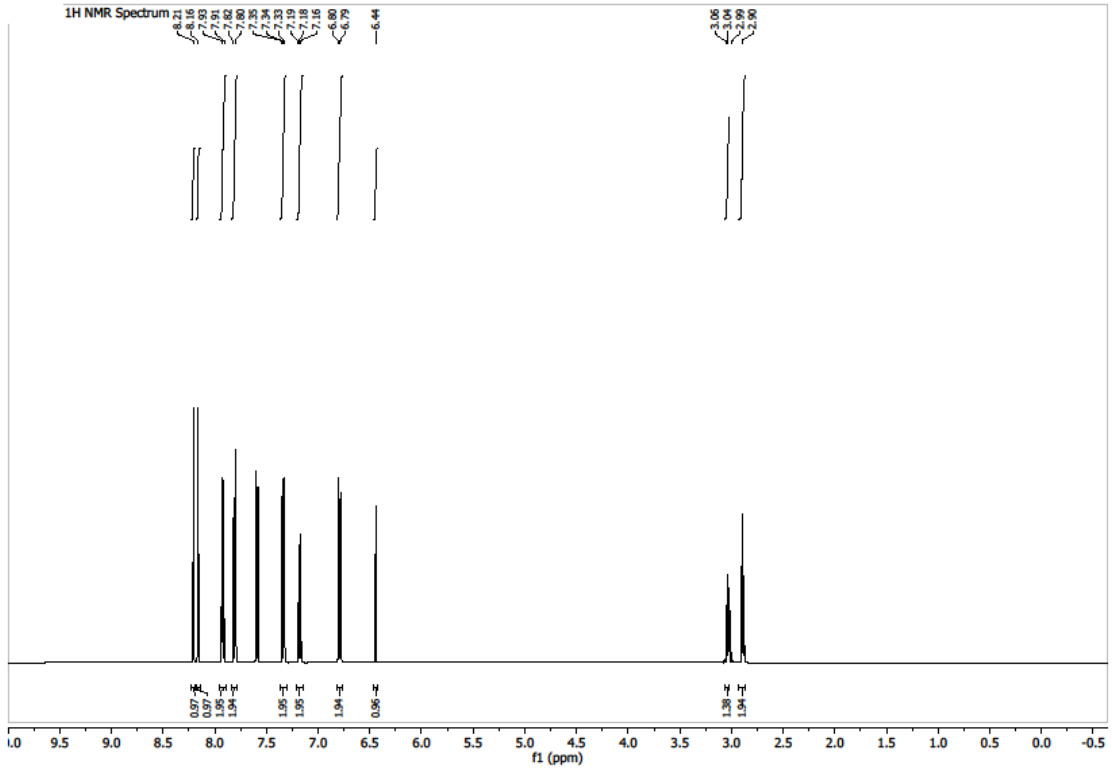

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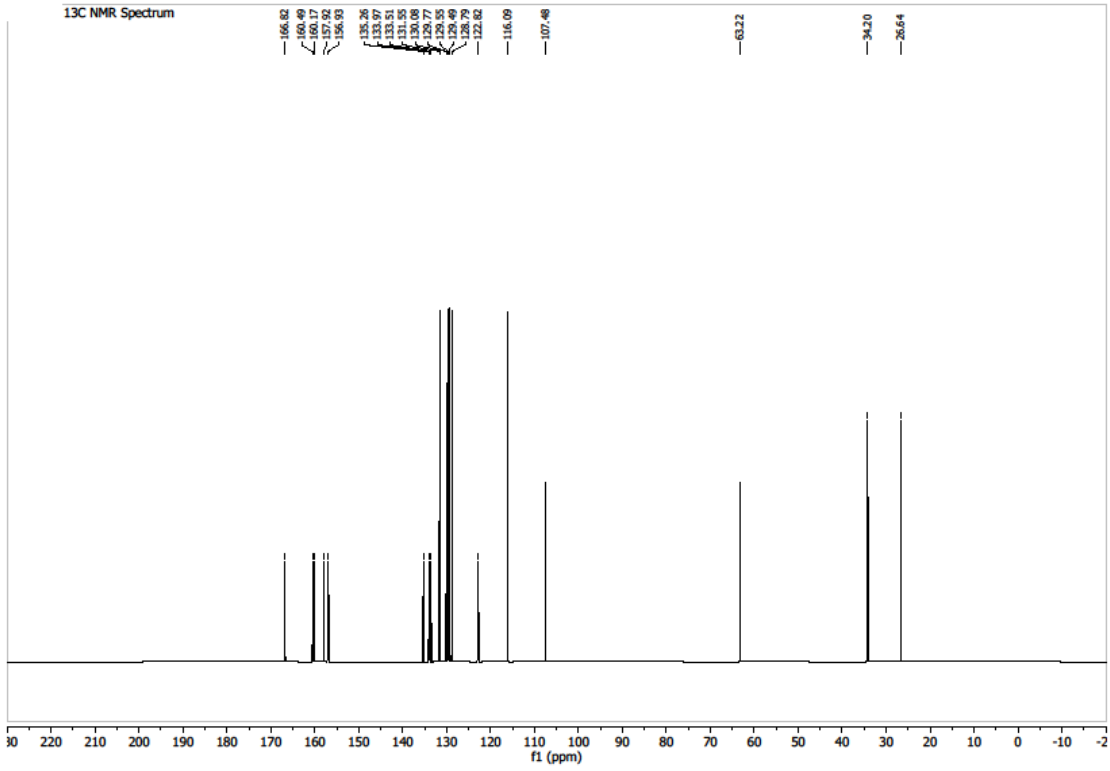
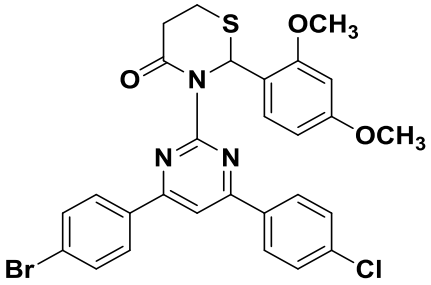
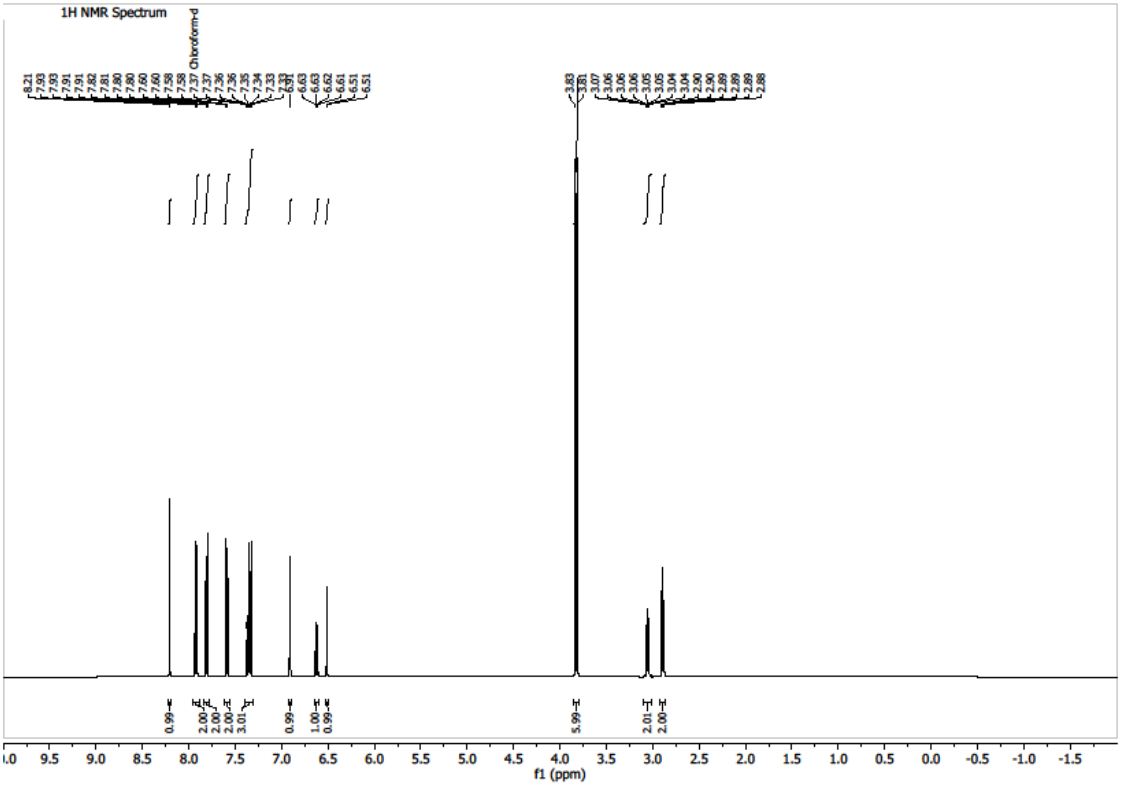

13C NMR Spectrum
166.82
160.49
160.17
157.92
156.93
135.26
133.97
133.51
131.55
130.08
129.77
129.55
129.49
128.79
122.82
116.09
107.48
63.22
34.20
26.64
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

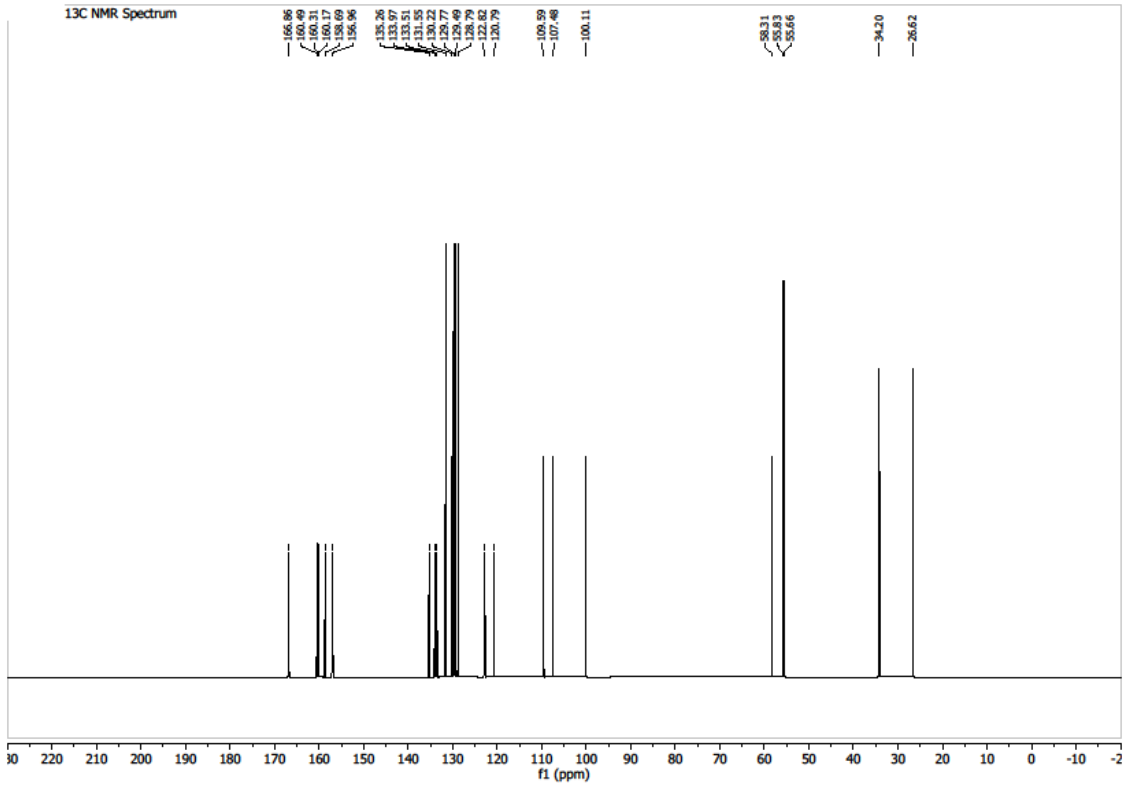
Compound 10f:



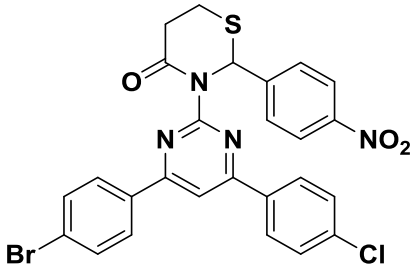
^{1}H NMR:



^{13}C NMR:


13C NMR Spectrum
166.86
160.69
160.31
160.17
158.69
156.96
135.26
133.97
133.51
131.55
130.22
129.77
129.49
128.79
122.82
120.79
109.59
107.48
100.11
58.31
56.93
55.66
34.20
26.62
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 10g:



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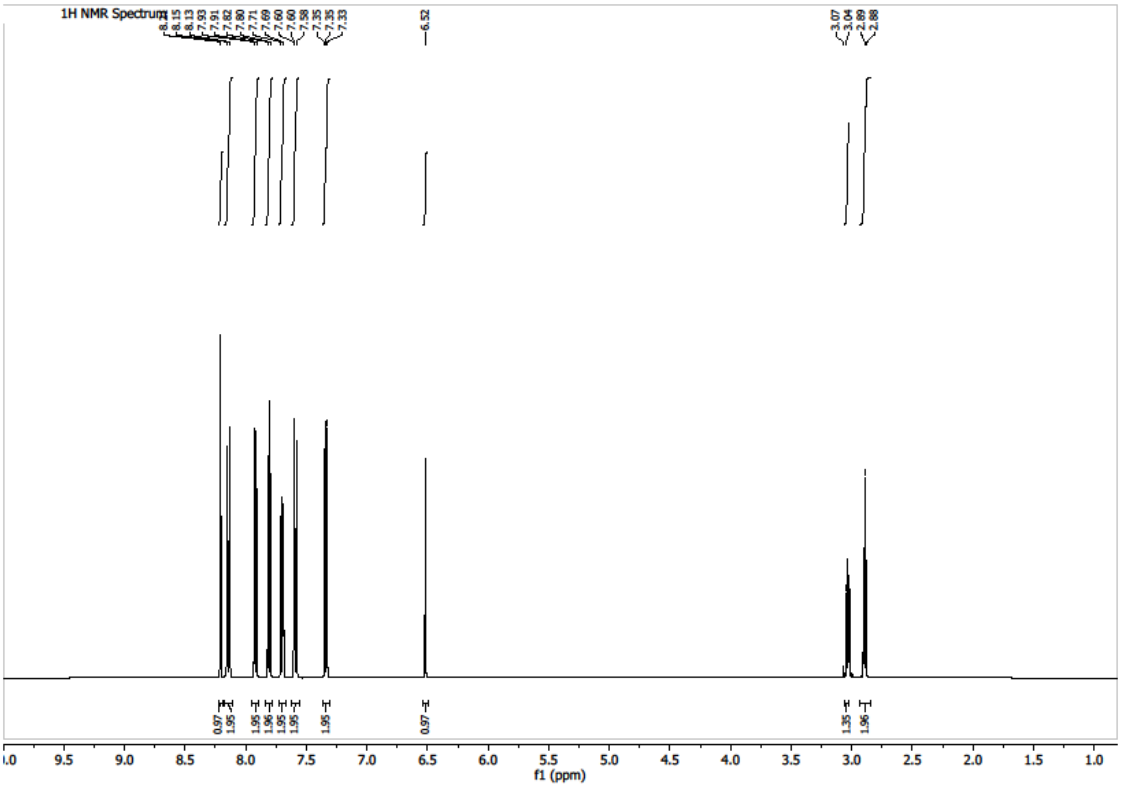
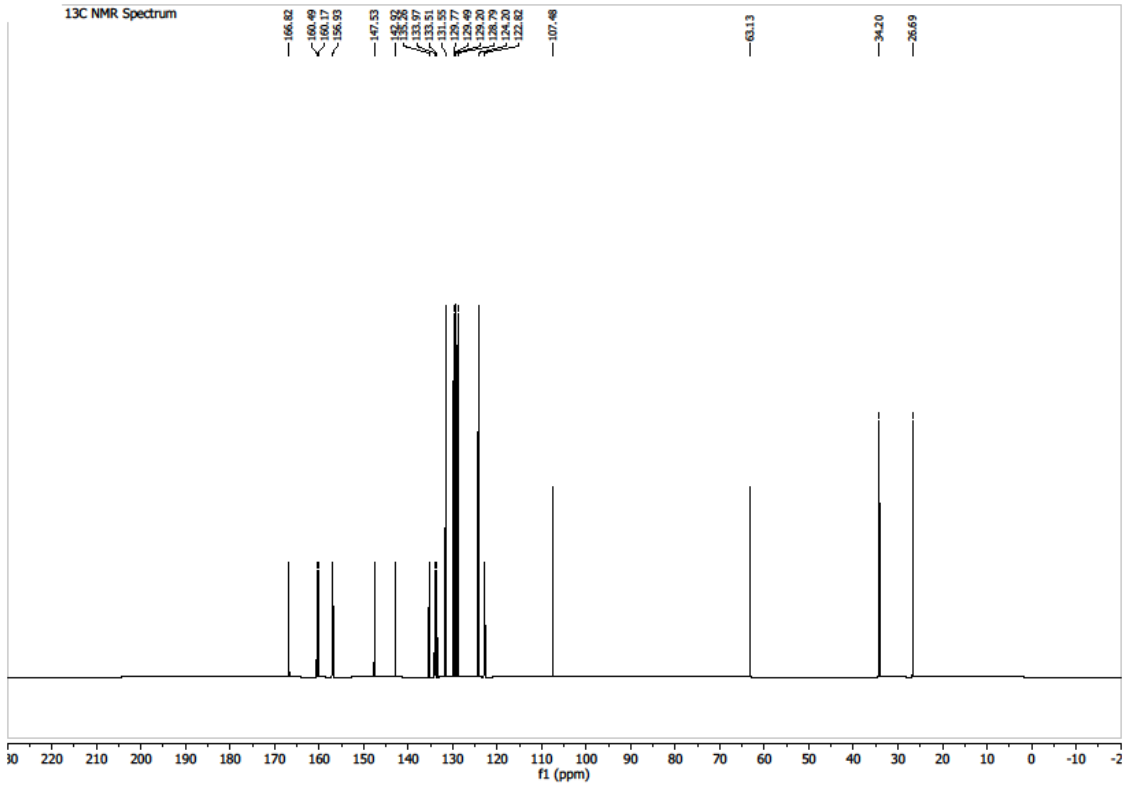
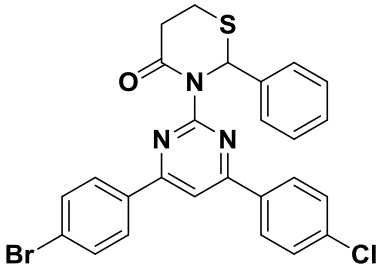


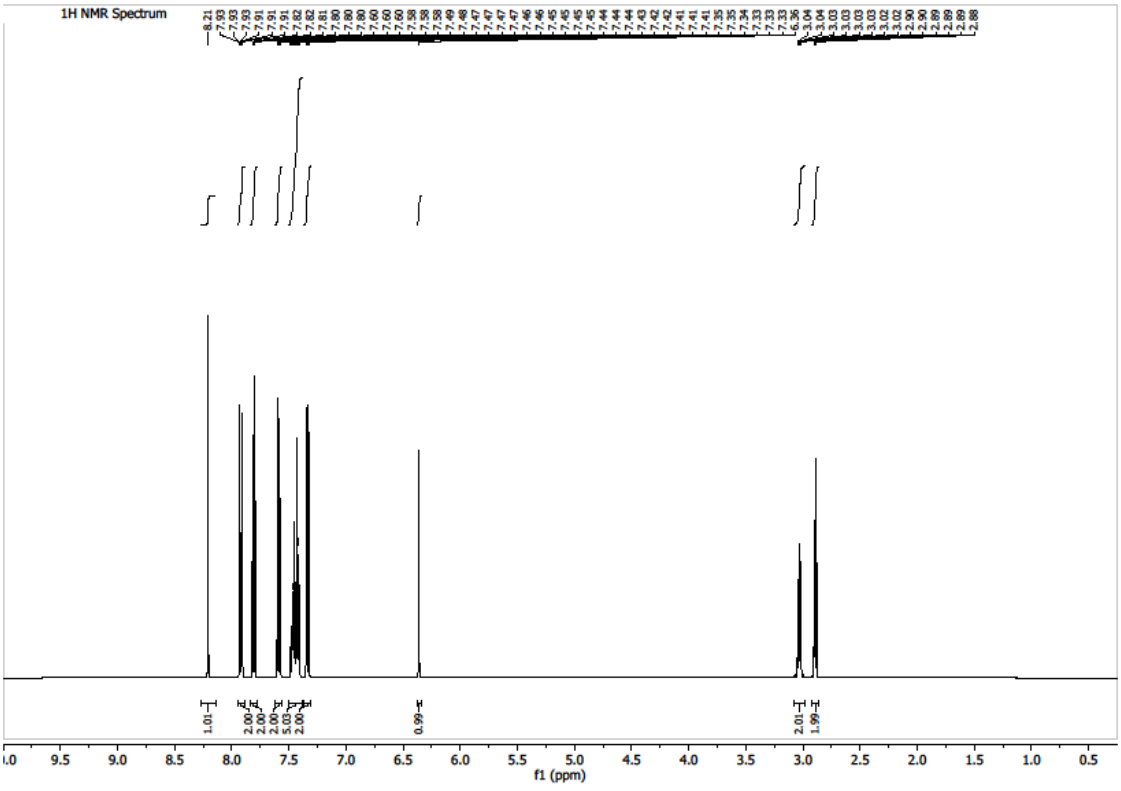
^{13}C NMR:


13C NMR Spectrum
166.82
160.49
160.17
156.93
147.53
107.48
63.13
34.20
26.69
f1 (ppm)

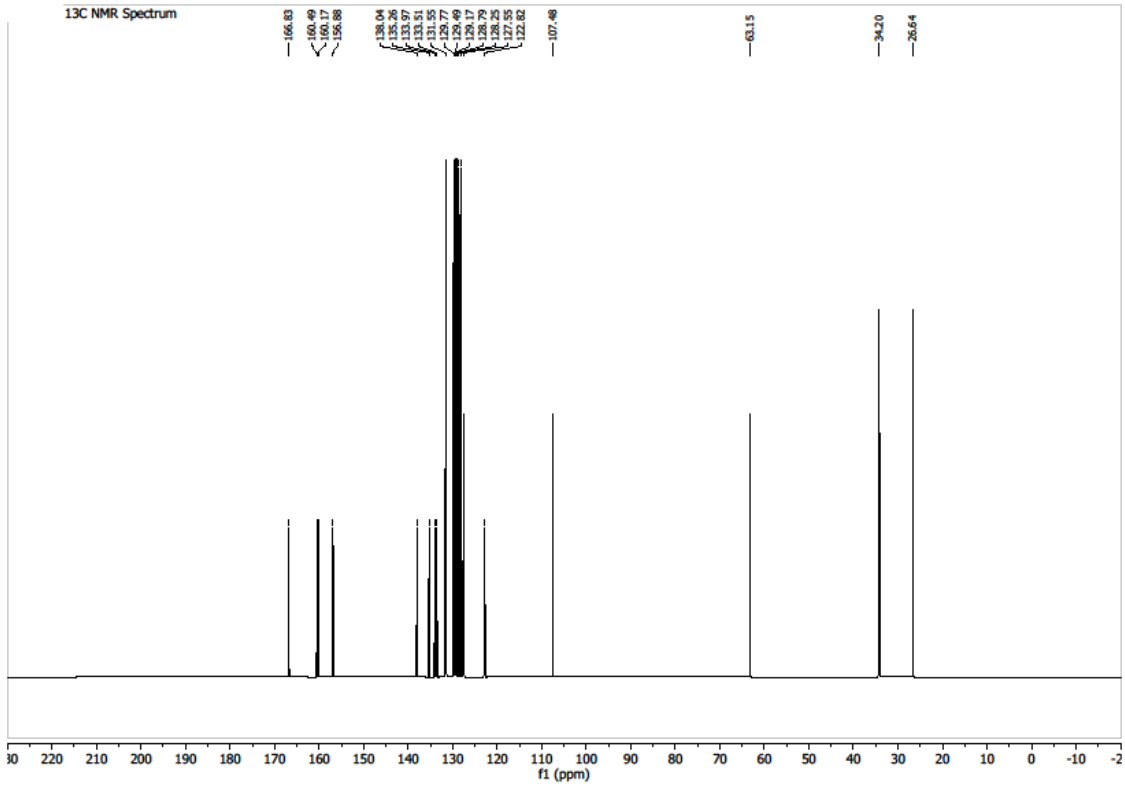
Compound 10h:



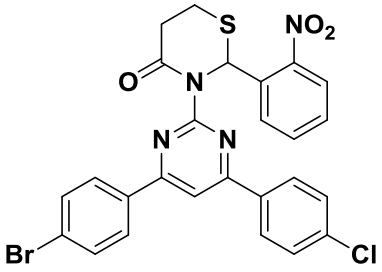
^{1}H NMR:



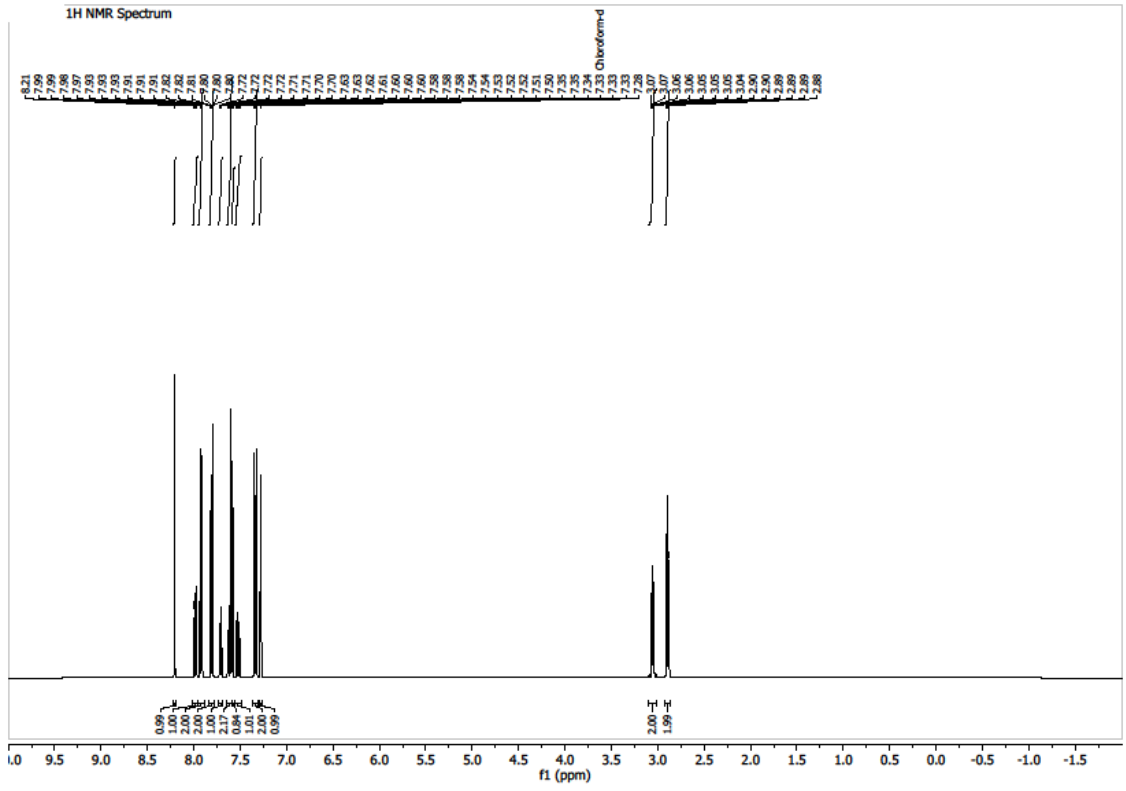
^{13}C NMR:


13C NMR Spectrum
166.83
160.49
160.17
156.88
138.04
135.26
133.97
133.51
131.55
129.77
129.49
128.77
128.79
128.25
127.55
122.82
107.48
63.15
34.20
26.64
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

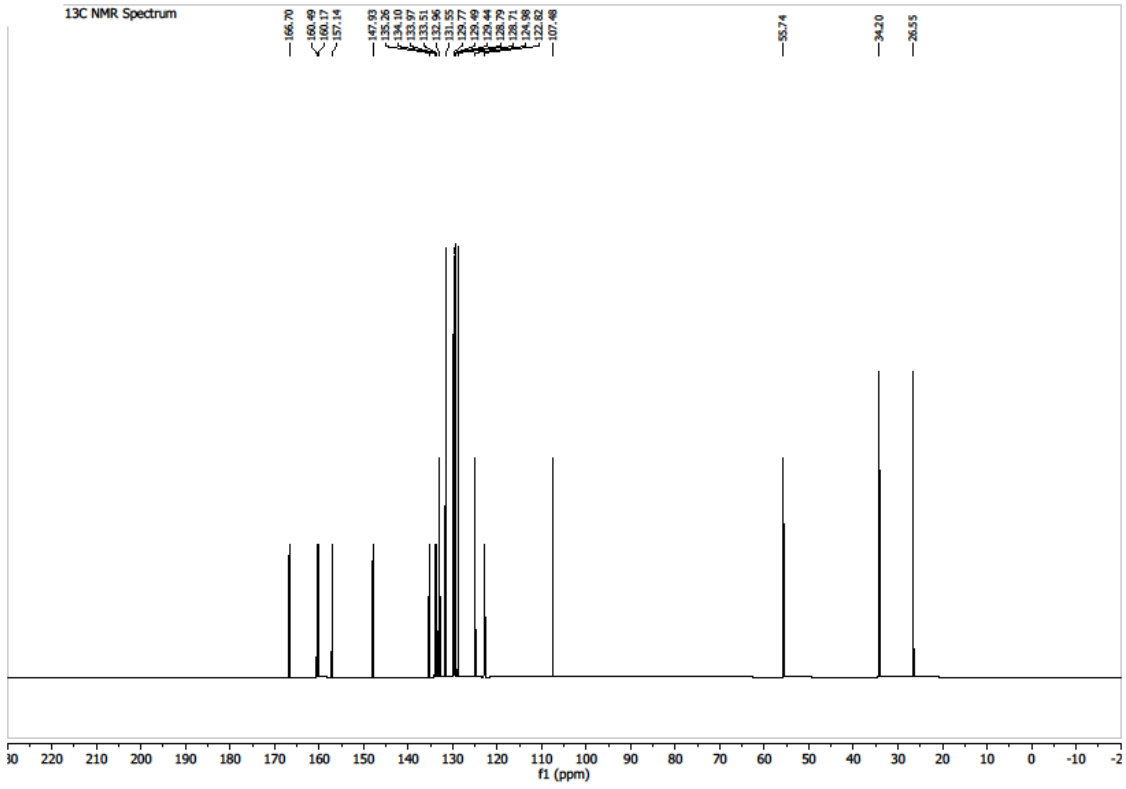
Compound 10i:



^{1}H NMR:



^{13}C NMR:


13C NMR Spectrum
166.70
160.49
160.17
157.14
147.93
135.36
134.10
133.97
133.51
132.96
131.55
129.77
129.49
129.44
128.79
128.71
125.86
125.82
107.48
55.74
34.20
26.55
f1 (ppm)