T.R.
BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
Department of Chemistry

MULTICOMPONENT SYNTHESIS OF BENZOTHIAZOLE SULFONYL CONTAINING HETEROCYCLIC SCAFFOLDS

MASTER OF SCIENCE

FADEL T S ALMASSRI

ACADEMIC SUPERVISOR
Prof.Dr.Cevher ALTUĞ

BOLU, JUNE-2024

APPROVAL OF THE THESIS

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Fadel T S ALMASSRI

ABSTRACT

MULTICOMPONENT SYNTHESIS OF BENZOTHIAZOLE SULFONYL CONTAINING HETEROCYCLIC SCAFFOLDS
MASTER'S THESIS
FADEL T S ALMASSRI
BOLU ABANT IZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF.DR.CEVHER ALTUĞ)

BOLU, JUNE 2024
(xv + 86)

The synthesis of heterocyclic compounds plays a crucial role in pharmaceutical chemistry due to their diverse bioactivities. The ongoing quest for novel properties in an eco-friendly, efficient, and rapid manner is paramount. In this thesis, we achieved three- and four-component reactions using benzothiazole sulfonyl acetonitrile, aromatic aldehydes, and heterocyclic ketene aminals (HKA). Specifically, 2-nitro-methylenethiazoline was employed for the three-component reactions, while propane-1,3-diamine and 1,1-bis(methylthio)-2-nitroethylene were utilized for the four-component reactions. These methodologies yielded benzo[d]thiazol-2-ylsulfonyl thiazolo[3,2-a]pyridin-5-amines **51a-i** and benzothiazole sulfonyl pyrido[1,2-a]pyrimidines **54a-c**, respectively. Eleven novel fused heterocyclic compounds were synthesized, purified by simple method, and characterized using spectroscopic methods FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS, LCMS and physical properties melting point, and Rf values. The synthesized compounds demonstrated promising antibacterial, antimycobacterial, and antifungal activities, against Gram-positive and Gram-negative bacteria, the compounds exhibited MIC values ranging from 62.5 to 500 μg/mL, with 4 compounds showing notable activity at 62.5 μg/mL. For Mycobacterium tuberculosis H37Rv, the compounds displayed moderate activity (31.5 to 62.5 μg/mL), with 5 compounds being the most effective. Antifungal tests against Candida species revealed MIC values of 62.5 to 125 μg/mL, with 5 compounds showing significant activity. The observed activities of the synthesized compounds put them as promising subjects for continued biological investigation and potential development.

KEYWORDS: Pyrido[1,2-a]pyrimidine, Benzothiazole Sulfonyl Acetonitrile, Multi-Component Reactions, Thiazolo[3,2-a]pyridine.

ÖZET

BENZOTİYAZOL SÜLFONİL İÇEREN HETEROSİKLİK YAPILARIN ÇOK BİLEŞENLİ SENTEZİ
YÜKSEK LİSANS TEZİ
FADEL T S ALMASSRI
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI

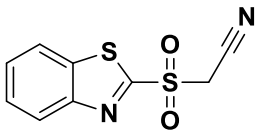
(TEZ DANIŞMANI: PROF.DR.CEVHER ALTUĞ)

BOLU, HAZİRAN - 2024
(xv + 86)

Heterosiklik bileşiklerin sentezi, biyolojik aktiviteleri nedeniyle farmasötik kimyada önemli bir rol oynamaktadır. Yeni şekilsel özelliklere sahip bu tip moleküllerin çevre dostu, verimli ve hızlı bir şekilde elde edilebilmesi oldukça önemlidir. Bu projede, benzotiyazol sülfonil asetonitril, aromatik aldehitler ve heterosiklik keten aminaller (HKA) kullanılarak üç ve dört bileşenli reaksiyonlar gerçekleştirilmiştir. Özellikle, üç bileşenli reaksiyonlar için 2-nitro-metilenetiyazolin, dört bileşenli reaksiyonlar için ise propan-1,3-diamin ve 1,1-bis(metiltiyo)-2-nitroetilen kullanılmıştır. Bu metodolojiler, sırasıyla benzo[d]tiazol-2-ilsülfonil tiyazolo[3,2-a]piridin-5-aminler (50a-i) ve benzotiyazol sülfonil pirido[1,2-a]pirimidinler (53a-c) elde edilmiştir. On bir yeni bitişik heterosiklik bileşik sentezlenmiş, etanol ile basit yeniden kristalleştirme ile saflaştırılmış ve spektroskopik yöntemler (IR, 1H NMR, 13C NMR, HRMS) ve fiziksel özellikler (erime noktası ve Rf değerleri) kullanılarak karakterize edilmiştir. Burada sentezlenen on bir bileşik, Gram-pozitif ve Gram-negatif bakterilere karşı umut verici antibakteriyel, antimikobakteriyel ve antifungal aktiviteler sergiledi. Bileşikler, 62,5 ila 500 µg/mL arasında değişen MIC değerleri sergiledi ve 4 bileşik 62,5 µg/mL'de kayda değer aktivite gösterdi. Mycobacterium tuberculosis H37Rv için bileşikler orta düzeyde aktivite (31,5 ila 62,5 µg/mL) sergilemiş olup, içlerinden 5 bileşik en etkili olanıdır. Candida türlerine karşı yapılan antifungal testler, 62,5 ila 125 µg/mL MİK değerleri ortaya çıktı ve 5 bileşik önemli aktivite gösterdi. Sentezlenen bileşiklerin gözlemlenen aktiviteleri, onları devam eden biyolojik araştırmalar ve potansiyel gelişim için umut verici bileşikler haline getirmektedir.

ANAHTAR KELİMELER: Pirido[1,2-a]pirimidin, Benzotiyazol Sülfonil Asetonitril, Çok Bileşenli Reaksiyonlar, Tiyazolo[3,2-a]piridin.

FORMULAE



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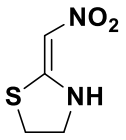

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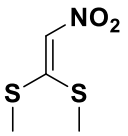

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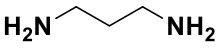

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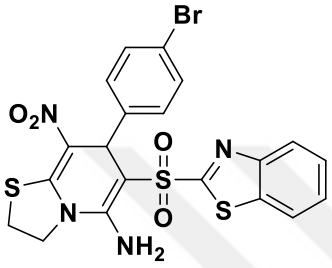

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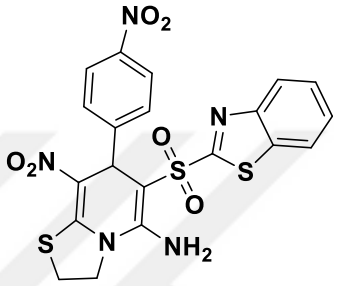

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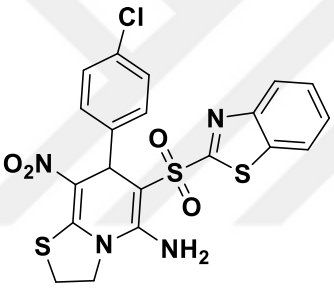

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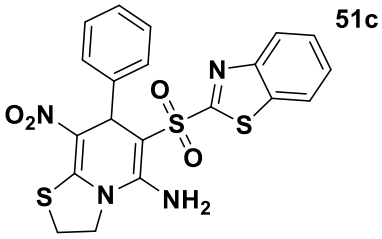

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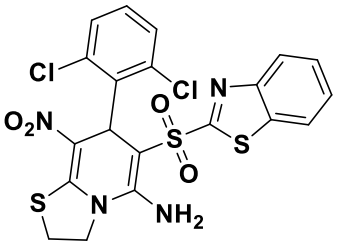

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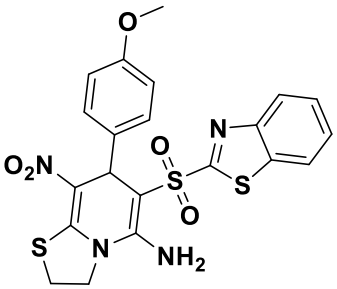

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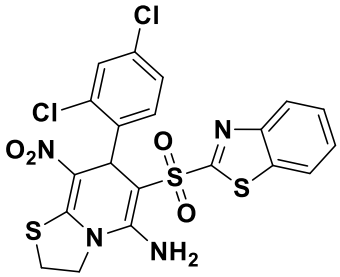

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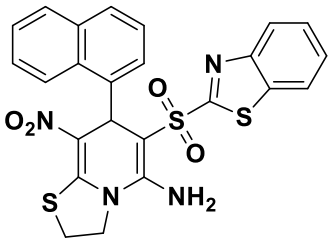

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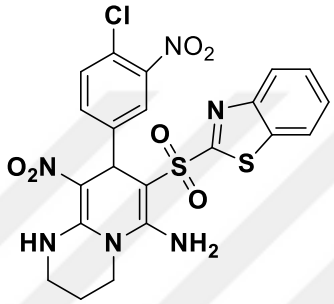

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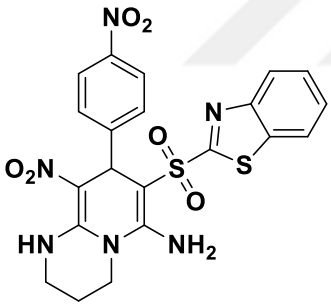

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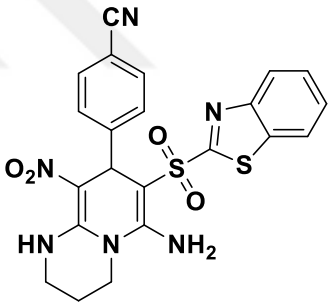

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LIST OF ABBREVIATIONS AND SYMBOLS

MCRs	**:** Multi-component reactions
DHP	**:** 1,4-Dihydropyridines
Ugi-4CR	**:** Ugi multi component reaction
P-3CR	**:** Passerini multi component reaction
CF_3SO_3H	**:** Trifluoromethanesulfonic acid
HKAs	**:** Heterocyclic ketene aminals
Ar	**:** Aromatic group
R	**:** Any group
HIV	**:** Human Immunodeficiency Virus
DMF	**:** Dimethyl form amide
DMSO	**:** Dimethyl sulfoxide
MeSO3H	**:** Methane sulfonic acid
r.t.	**:** Room temperature.
AcOH	**:** Acetic acid
H_2O_2	**:** Hydrogen peroxide
h	**:** hour
EtOH	**:** Ethyl Alcohol
Et_3N (TEA)	**:** Triethylamine
mL	**:** Milliliter
TLC	**:** Thin layer chromatography
^oC	**:** Celsius
m.p	**:** Melting point
m	**:** Multiplet (NMR)
t	**:** Triblet (NMR)
d	**:** doublet (NMR)
FTIR	**:** Fourier Transform Infrared Spectroscopy
Hz	**:** Hertz
CNS	**:** The central nervous system
NMR	**:** Nuclear magnetic resonanc
BTH	**:** Benzothaiol

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I would like in the first place to express my deepest gratitude to my supervisor Prof. Dr. CEVHER ALTUĞ for everything. Working under your supervision has been an enriching experience, and I am truly grateful for the opportunity to learn from your knowledge and expertise, your encouragement, and your advice while working on my research project. Your approachability, open-mindedness, and willingness to listen have fostered a collaborative atmosphere that has greatly contributed to my personal and professional growth throughout this research journey. Finally, I would like to thank my dear family, father, mother, aunt, brothers, and friends for their support during my education.

To my big family

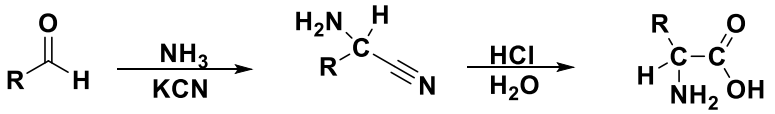
1. INTRODUCTION

1.1 Multicomponent reaction definition and history

With the speed of scientific evolution, the importance of novel molecules is required as a priority of humanity to find compounds with new properties and support human and scientific prosperity, so finding a way to keep pace with this development was necessary, especially the traditional organic synthesis with two component reaction with high cost, long process with possibility of low final yields wasn't enough.[1]

Multicomponent reactions (MCRs) in which three or more reagents in one pot with known and expected reaction mechanisms give a high atomic number complex and unique structure product, [2,3] its flexible transformation proved an efficient approach to discovering potential research of new bioactivity properties[4] in the medical and pharmaceutical fields,[5] such as antibacterial,[6] anticancer,[7] glucosidase inhibitory.[8]

The beginning of multicomponent reactions was in 1850 on Strecker reaction developed by Adolph Strecker as the first known documented multi-component reaction.[9] In a vessel, an aldehyde (1), ammonia (2), and potassium cyanide (3) react together to form α-aminonitrile (4). A hydrolysis process is employed to obtain the targeted amino acid (5). (Scheme 1.1)

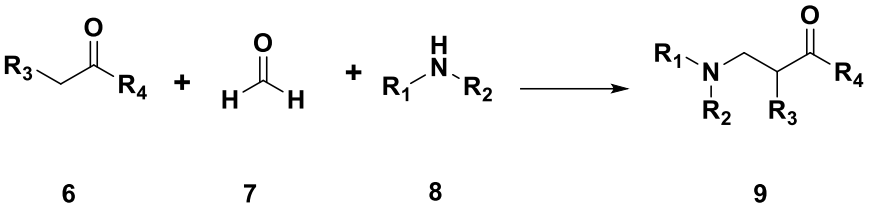


1 4 5

Scheme 1.1 Synthesis of amino-acid based on Stecker MCR method

Furthermore, the Mannich reaction by Carl Mannich involves the condensation of a compound that has active hydrogens with an amine and formaldehyde.[10] This reaction was first discovered in the early 20th century and MCR has since been recognized as a reaction for producing nitrogen-containing compounds,[11] involving the combination of three components: a ketone (6), formaldehyde (7), and an amine (8), to form a β-amino-ketone (9).[12] (Scheme 1.2)

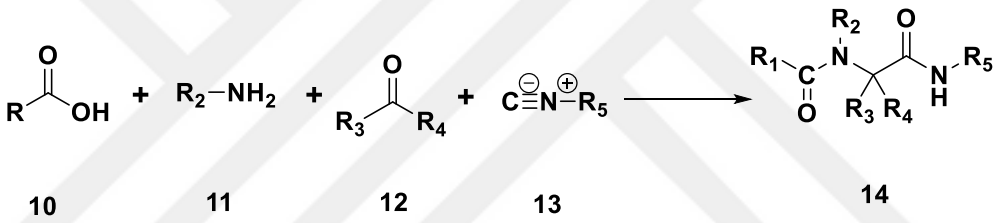
The wide applicability of the Mannich reaction in organic synthesis has made it a valuable tool in the chemical industry.[13]



6 7 8 9

Scheme 1.2 Form a β-amino-ketone by Mannich condensation reaction

In 1959, Ivar Karl Ugi introduced the most important four component condensation reaction, involving a carboxylic acid (10), an amine (11), ketone or aldehyde (12), and isocyanate (13) to form bis-amid (14),[14] (Scheme 1.3) Moving forward this multicomponent condensation the most known condensation types were discovered, such as carboxylic acids, hydrazoic acids, cyanates, and thio-cyanate.[15]

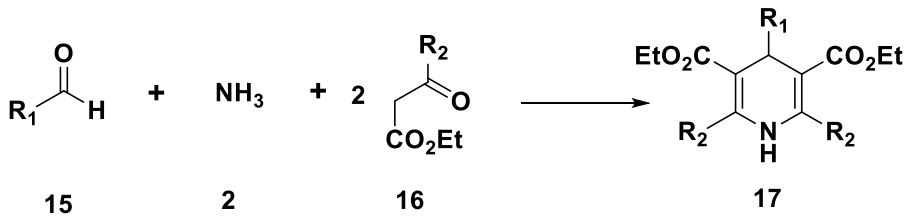


10 11 12 13 14

Scheme 1.3 Forming bis-amid by MCR

As a result of these MCRs performed, a multitude of compounds possessing diverse characteristics were produced, revealing unique bioactivities in a subset of these molecules, particularly the heterocyclic compounds. [16]

The first heterocyclic system based on multi-component reaction was discovered in 1882 by Arthur Rudolf Hantzsch, [17] the reactants to synthesize 1,4-dihydropyridines (DHP) (17) is ammonia (2), aldehyde (15), and 2 equivalent of β-ketoesters (16) (Scheme 1.4).

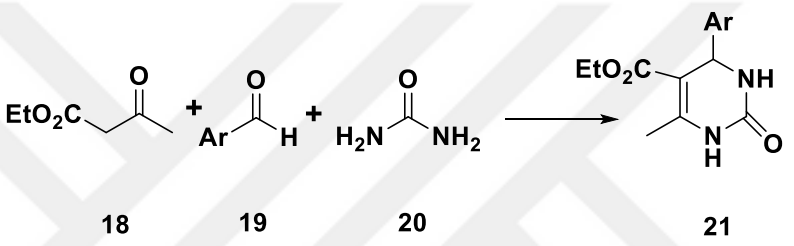


15 2 16 17

Scheme 1.4 Manufacturing of 1,4-dihydropyridines by A. R. Hantzsch

Producing (DHP) by using four component reaction opened a wide range of cyclization reactions. The DHP drugs has high effect on treatment of hypertension, and it's the most used drugs for this disease,[18] it has also a various therapeutic application.[19]

The synthesis of dihydropyrimidinones, also known as Biginelli compounds, has been a subject of significant interest due to their diverse pharmaceutical applications. Typically, dihydropyrimidinones (21) are obtained *via* the Biginelli reaction, which involves the condensation of β-dicarbonyl compounds (18), aldehydes (19), in the presence of urea (20) or thiourea using strongly acidic medium.[20] This reaction leads to producing 3,4-dihydropyrimidin-2-ones, which are important intermediates to obtain a diverse bioactive molecule.[21]



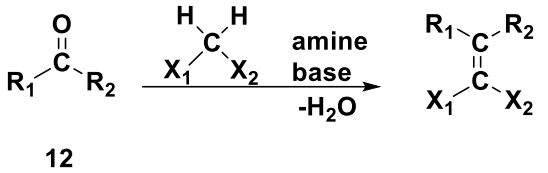
Scheme 1.5 Dihydropyrimidinones *via* the Biginelli reaction

The significance of dihydropyrimidinones lies in their broad pharmaceutical applications, including their potential as anti-cancer agents, anti-infective agents, and anti-neoplastic agents.[22, 23, 24] Additionally, the design of new derivatives and analogs of dihydropyrimidinones has been explored to enhance their pharmacological properties and biological activities.[25, 26]

The application of (MCRs) in the synthesis of particular compounds represents an essential purpose in organic chemistry. Furthermore, the application of multicomponent reactions in producing specific compounds, such as plant growth regulators, thiazole-3,2-a-pyridin-8-yl-phosphonates.[27]

In modern chemistry, the importance of MCRs and their strategies is a crucial chemistry science key in organic synthesis.[28] As an instance, the incorporation of Knoevenagel condensation as part of multi-component reaction strategies allows for the efficient preparation of a range of diverse compounds, such as the application of Knoevenagel condensation in producing chromene and imidazopyrimidine

derivatives,[29] and the multicomponent domino synthesis involving Knoevenagel condensation, cycloisomerization, and fragmentation,[30] these examples showing the pivotal role of this approach in advancements of organic chemistry for the construction of carbon-carbon bonds from activated methylene and aldehyde or ketone (12) (Scheme 1.6), and the production of structurally complex molecular structures.



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X_1, X_2 : CO_2R, CN, NO_2, etc.

Scheme 1.6 Knoevenagel condensation

Also, the Michael addition reaction is considered another strategy for forming carbon-carbon bonds, this reaction is a crucial process in multi-component reactions, facilitating the creation `of a highly versatile and efficient tool in materials chemistry, emphasizing the simplicity and effectiveness of the Michael addition reaction in yielding complex products. and adaptability of the Michael addition reaction in multi-component synthesis. [31]

Utilizing strategies in multi-component reactions is pivotal in designing and executing effective synthetic pathways. The use of these synthesis ways saves time and resources, as well as contributes to sustainability and environmentally friendly work. [32]

1.2 Important Drug-Like Molecules Synthesized by MCRs

The ability of MCRs to efficiently synthesize small molecules drug-like with huge structural variety has made them widely applicable in drug discovery and natural product synthesis. These examples the pivotal role of MCRs in the synthesis of important drug structures, such as a calcium channel blocker Nifedipine by Bayer company using a one-step multi-component reaction, [33] the anti-diabetic drug Saxagliptin based on the Strecker reaction, [34] using a Ugi-type MCR as a main synthetic process of bioavailable HIV protease inhibitor Crixivan (Indinavir),[35] the

thienopyridine antiplatelet agent, Clopidogrel,[36] has been synthesized through a three-component petasis (Petasis-3CRn) reaction, followed by an esterification reaction to obtain this significant drug[37]**(**Figure 1.1**),** highlighting their significance in pharmaceutical research and development.

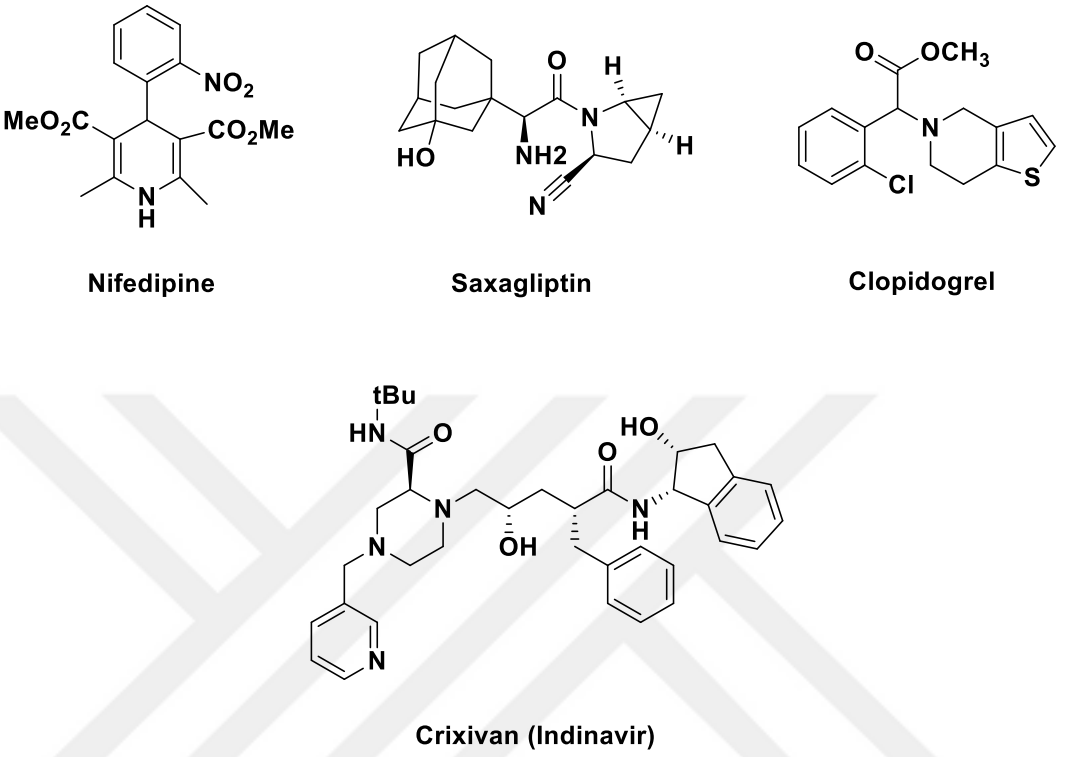


Figure 1.1 Important drugs based on MCR

1.3 Thiazolopyridines

Thiazolopyridine a heterocyclic molecule that has garnered significant attention due to its diverse biological activities and potential pharmaceutical applications.[38] In thiazolopyridine ring systems, two heterocyclic structures are fused together, giving rise to six reported systematic thiazolopyridine isomers in the literature.

Classification of thiazolopyridine is contingent upon the specific fusion pattern between the pyridine and thiazole, leading to following distinct classes, thiazolo[3,2-a]pyridine, thiazolo[3,4-a]pyridine, thiazolo[4,5-b]pyridine, thiazolo[4,5-c]pyridine, thiazolo[5,4-b]pyridine, and thiazolo[5,4-c]pyridine [39] (Figure 1.2).

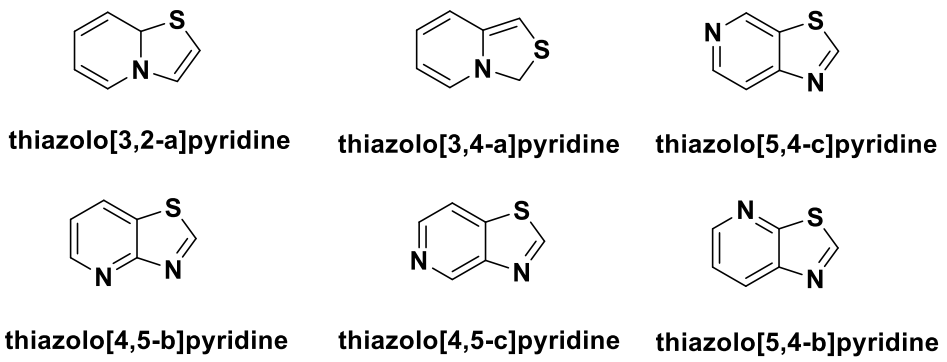


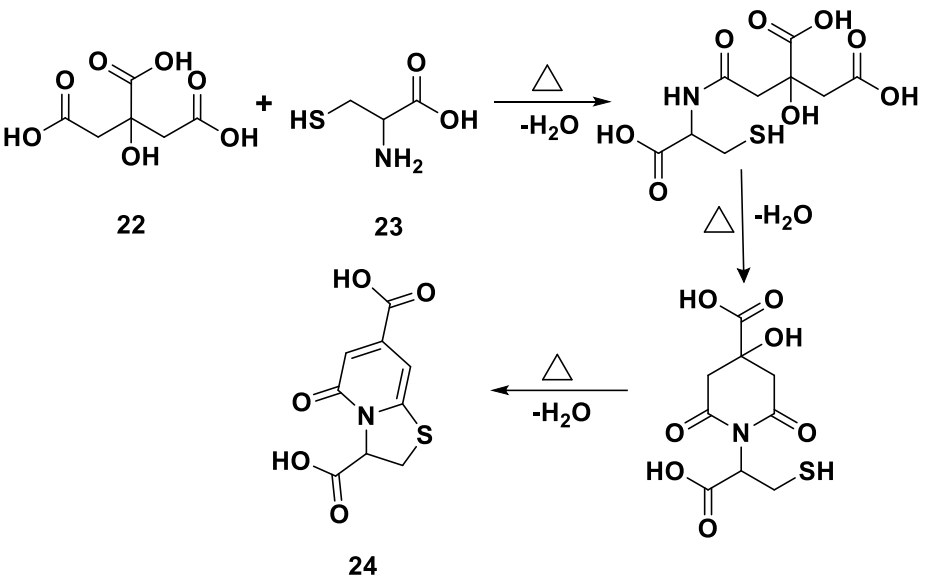
Figure 1.2 Classification of isomeric thiazolopyridines rings

Thiazolopyridine derivatives have been reported to exhibit a broad spectrum of biocompatible activity, such as anticancer,[40] antitubercular,[41] anti-inflammatory activities,[42, 43] and antimicrobial.[44]

Additionally, thiazolo[3,2-a]pyridines have shown impactful potential in the treatment of lung cancer,[45] leukemia,[46] and melanoma due to their notable anticancer properties.[47] These compounds also exhibit antimicrobial activity,[48] display potential as uterus stimulants,[49] and have the ability to inhibit β-amyloid production.[50]

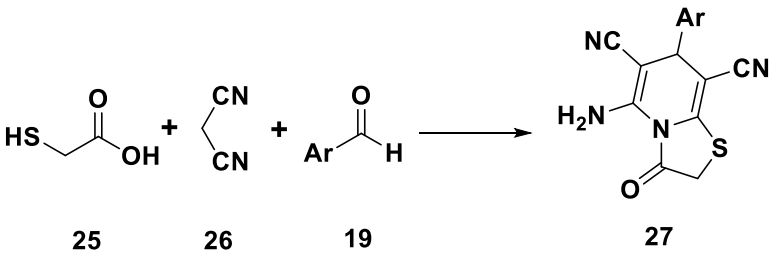
1.3.1 Some synthesis strategies of Thiazolopyridines

Synthesis of Thiazolo[3,2-a]pyridine (24) involves multi-dehydration reaction between citric acid (22) and cysteine (23), resulting in a new biocompatible heterocyclic compound.[51] (Scheme 1.7)



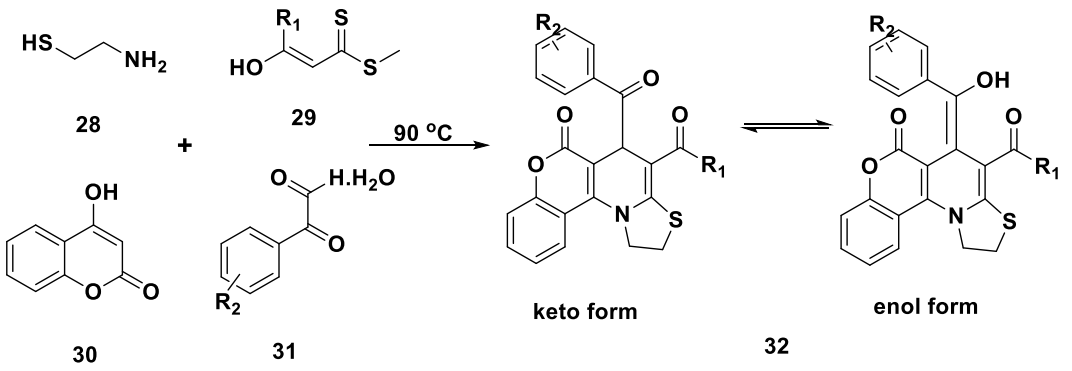
Scheme 1.7 Synthesis of thiazolopyridine *via* multi-dehydration reaction

Li et al. introduced a chemo-selective approach that prioritizes environmentally friendly approach for synthesizing thiazolo[3,2-a]pyridine (27) (Scheme 1.8) through three component of reactants involving 2-mercaptoacetic acid (25) malononitrile (26), and aldehyde (19) Subsequently, the evaluation of these derivatives for their antioxidant activity and cytotoxicity against carcinoma HCT-116 cells and mice lymphocytes has been discovered. Encouragingly, the results demonstrated significant anti-cancer properties, highlighting their potential as promising agents in cancer treatment.[52]



Scheme 1.8 Thiazolo[3,2-a]pyridine compounds through MCR

Employing a highly efficient multi-component reaction with a catalyst-free and solvent-free strategy was utilized to achieve the eco-friendly synthesis of thiazolo[3,2-a]pyridine hybrids (32) (Scheme 1.8), the combination of cysteamine (28), α-enolicdithioester (29), 1,3-diketones(30), and aryl glyoxal monohydrate (31) were considered as reagents of the reaction. This approach demonstrated excellent yield range, further emphasizing its green and sustainable nature.[53]



Scheme 1.9 Thiazolo[3,2-a]pyridines hybrids basing on four component reaction

1.4 Pyridopyrimidine

Pyridopyrimidines are heterocyclic compounds characterized by a fused 6,6-bicyclic structure comprising a pyridine ring fused to a pyrimidine. The position of the nitrogen atom in the pyridine moiety gives rise to six isomeric forms of pyridopyrimidines, as depicted in (Figure 1.3).[54] These scaffolds, serving as nitrogen bioisosters of quinoxaline, exhibit a vast scope of properties including anticancer properties, potential treatment of CNS disorders, and antiviral effects.[55] Their extensive use in medicinal chemistry is attributed to the availability of five substitution sites and the potential to access a variety of products, thereby covering a broad chemical area.

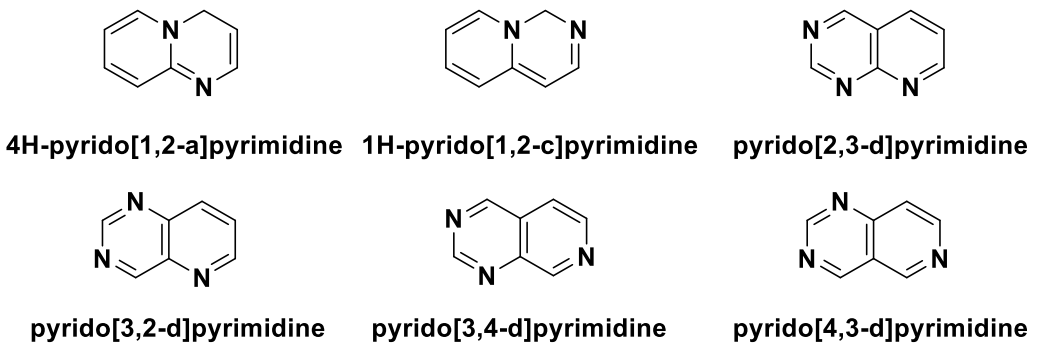


Figure 1.3 Classification of isomeric Pyridopyrimidines

The widespread utilization of these compounds in medicinal chemistry is attributed to the availability of five substitution sites and the potential to access a wide range of drugs and products, including the palbociclib Inhibitor of

Dihydrofolate Reductases, [56] antipsychotic and tranquilizer pirenperone, [57] anti-diarrheal (Figure 1.4). [58] This versatility allows for the coverage of a broad spectrum of therapeutic properties.

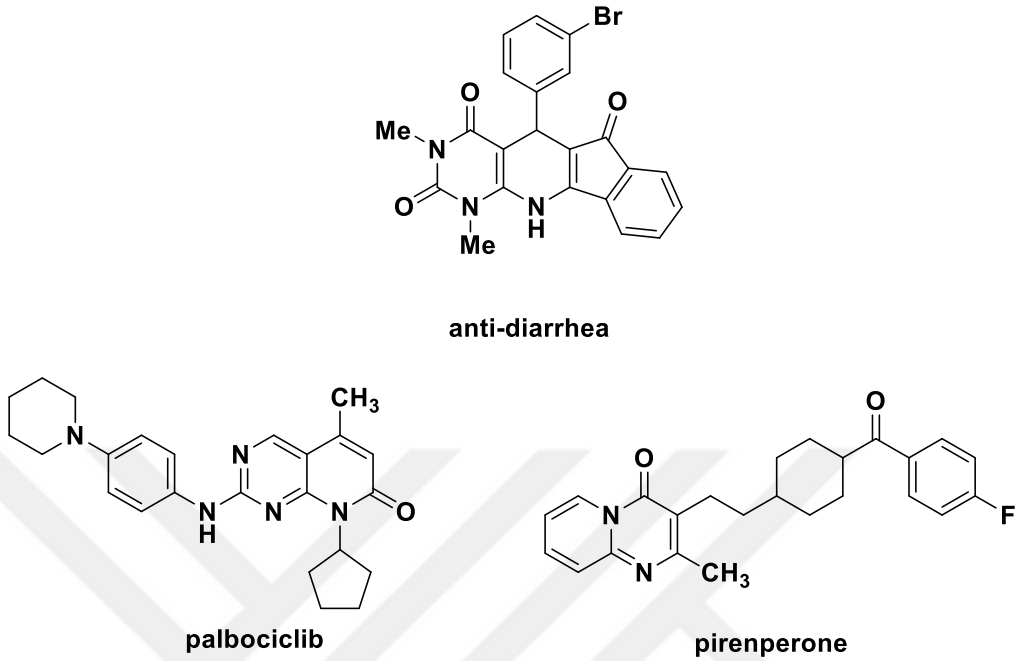
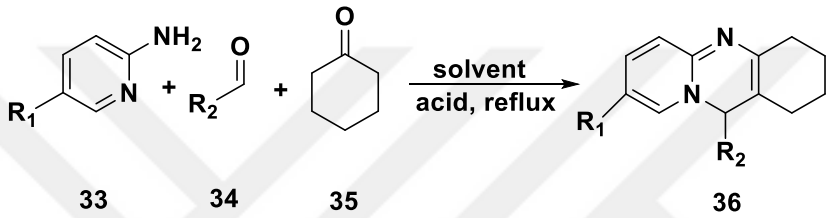


Figure 1.4 Some examples of bioactive pyridopyrimidines

Pyrido[1,2-a]pyrimidine has been the subject of wide researches, with studies reporting its diverse pharmacological activities and potential applications in medicinal chemistry. Pyrido[1,2-a]pyrimidine compounds have been investigated for their inhibitory properties, exhibiting antioxidant activity.[59] additionally, the bioactivity of pyrido[1,2-a]pyrimidine molecules has been attributed to their ubiquity and importance as a scaffold in natural and pharmacologic products.[60] Furthermore, the synthesis and functionalization of 4H-pyrido[1,2-a]pyrimidin-4-one, the significant biological activity of this compounds has been explored, highlighting its potential for various applications.[61]

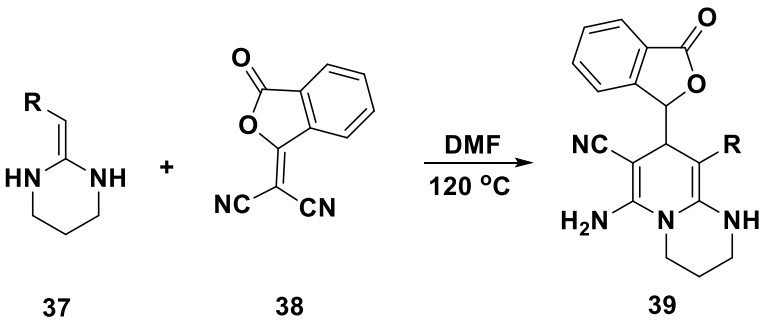
1.4.1 Some synthesis strategies of Pyrido[1,2-a]pyrimidine

The condensation of synthesis of pyrido[1,2-a]pyrimidines through 2-aminopyridines with various nucleophiles has gained significant attention. Multicomponent reactions have stood out as a remarkably efficient and effective approach for the production of pyridopyrimidines, yielding desirable products. In one such method, a three-component reaction was employed, involving the condensation of equimolar amounts of 2-aminopyridines (33), aldehyde or ketone (34), and cyclohexanone (35), with CF_3SO_3H catalyst at 110°C. The result of reaction was formation of a derivatives of pyrido[1,2-a]pyrimidines (36) (Scheme 1.10).[62]



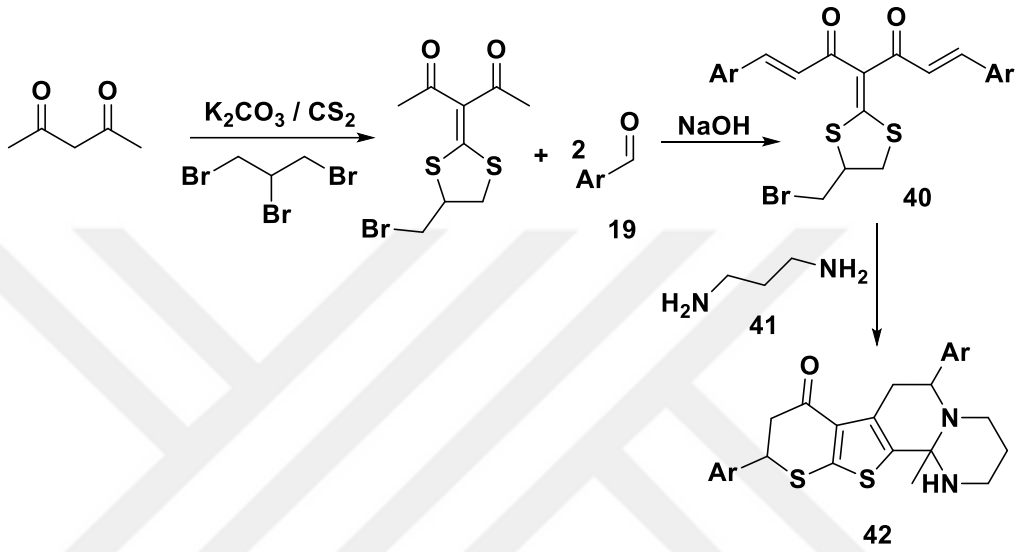
Scheme 1.10 Pyrido[1,2-a]pyrimidines through MCR

A highly efficient approach has been established for synthesizing a unique class of polyfunctionalized 1,4-dihydropyridine-fused 1,3-diazaheterocycles. This method involves a mixture of heterocyclic ketene aminals (HKAs) (37), 2-[3-oxoisobenzofuran-1(3H)ylidene]-malononitrile. (38) The outcome of this reaction is the formation of derivatives of pyrido[1,2-a]pyrimidine, presenting a novel structural motif with diverse functional groups yielded pyrido[2,3-d]pyrimidine compounds (39) in favorable yields, as illustrated in (Scheme 1.11).[63]



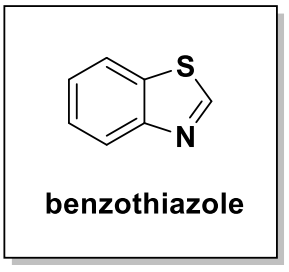
Scheme 1.11 A recent production of pyrido[2,3-d]pyrimidine

A catalysis-free, domino multi-step reaction of dialkenoylketene S,S-acetals (40) in combination with 1,3-propane-diamine (41) has been employed for the synthesis of thiopyranothienopyrido[1,2-a]pyrimidinones (42) using a tetracyclic system. Surprisingly, this reaction yielded an unexpected tetracyclic molecule, as depicted in (Scheme 1.12). It is anticipated that this domino reaction will exhibit remarkable potency, given the importance of diamines and similar bi-nucleophiles as versatile reagents in numerous synthetic transformations.



Scheme 1.12 Synthesis a pyrido[1,2-a]pyrimidinones *via* multi-step reaction tetracyclic system

1.5 Benzothiazole

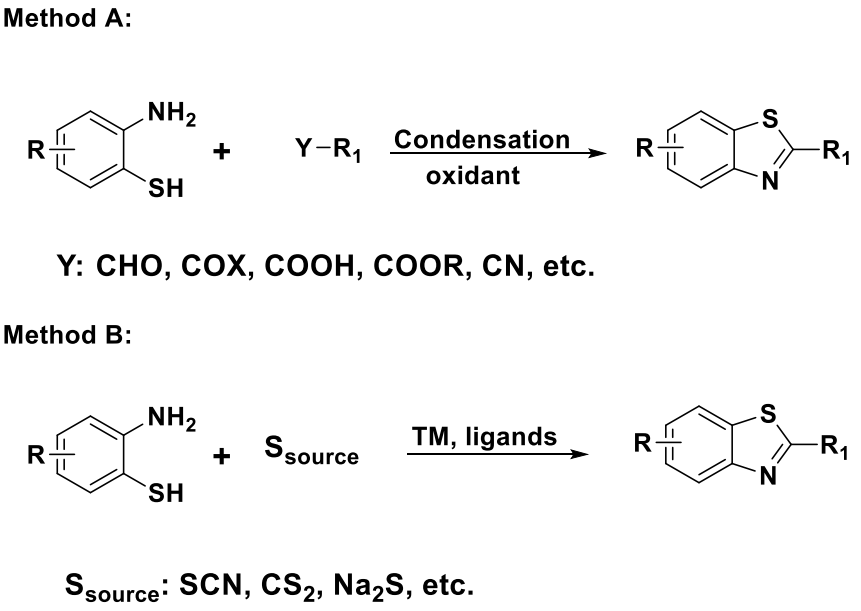


Benzothiazole stands as an exemplary category within the sulfur-containing heterocycles, characterized by the fusion of a thiazole ring and a benzene ring. This structural arrangement defines the fundamental framework of benzothiazole compounds, and it has emerged as a subject of considerable stemming from its broad range of biocompatibility activities.[64, 65] It serves as a precursor in the generation of pharmaceuticals with antitubercular, antimalarial, antidiabetic,[66] anticonvulsant,[67] anti-inflammatory,[68] and antitumor activities.[69] Additionally, benzothiazole and its derivatives have been employed as enzyme inhibitors,[70] plant growth regulators,[71] fluorescence materials,[72] and

organic optoelectronic materials. [73] Furthermore, benzothiazoles represent a significant category of chemical intermediates for a broad selection of nature-derived compounds and drugs due to their unique pharmaceutical and biocompatible activities.[74]Production of benzothiazoles holds significant significance for their extensive applications, and the development of streamlined approaches is crucial for their functionality.[75]

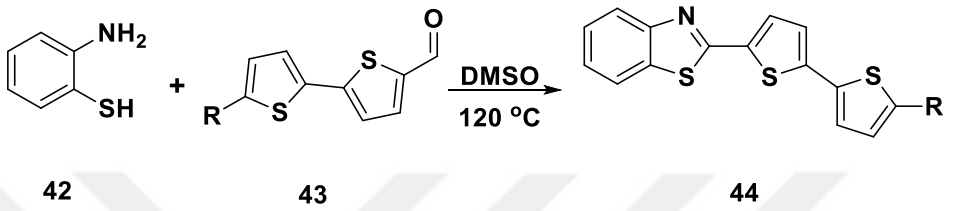
1.5.1 Some synthesis of benzothiazole

Benzothiazoles can be synthesized through various methods, 2-aminobenzenethiol reacts with carbonyl or cyano compounds through a condensation reaction which is the pinnacle frequently employed approach (Method A).[76, 77] Additionally, researchers have discovered alternative routes for benzothiazole synthesis, including reaction containing an ortho-halogenated aniline can work with carbon disulfide, isothiocyanates and piperidine, aldehydes and sulfur, or carbon disulfide and thiol. (Method B). [78],[79] (Scheme 1.13) These diverse synthetic pathways offer flexibility and options for accessing benzothiazole derivatives.



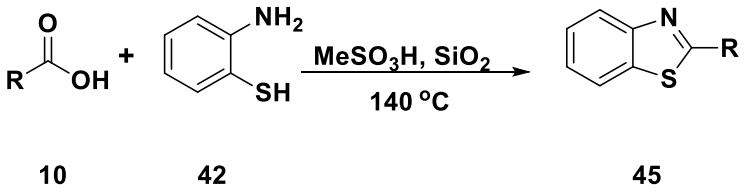
Scheme 1.13 Synthesis of benzothiazole *via* condensation reaction

Batista et al., [80] highlighted the synthesis of 2-bisthiophene benzothiazole compounds (44) through 2-aminobenzenethiol (42), 5-aldehyde bisthiophene compounds (43) and condensation reaction. This reaction was conducted under reflux conditions for 1 hour through the use of dimethyl sulfoxide (DMSO), as illustrated in (Scheme 1.14). The synthesized products were further characterized for their fluorescence properties, along with an excellent yield and significant Stokes' shifts. These compounds exhibit high fluorescence intensity, making them promising candidates for applications as fluorescent markers.



Scheme 1.14 Benzothiazole compounds *via* condensation

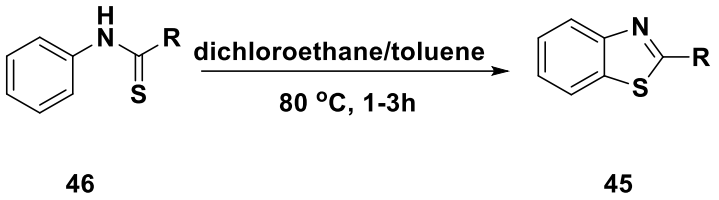
In their research, Sharghi et al. [81] investigated a highly efficient method for synthesizing a range of substituted benzothiazole compounds (45). This method involved reaction of 2-aminobenzenethiol (42) and various carboxylic acids (10), as depicted in (Scheme 1.15). Notably, the researchers developed a novel heterogeneous mixture comprising methane sulfonic acid and silica gel, which served as a rapid and effective intermediate for the reaction between aryl carboxylic acids and 2-aminothiophenol. This innovative approach facilitates the synthesis of benzothiazoles with enhanced efficiency and convenience.



Scheme 1.15 Benzothiazole production *via* condensation of 2-aminobenzothiol with carboxylic acid

The cyclization method with highly capable of synthesizing 2-substituted benzothiazoles, this method involved the radical cyclization of thioformanilides (46) which promoted by chloranil under irradiation carried out in a solvent system of 1,2-dichloroethane and toluene at 80 °C, as depicted in (Scheme 1.16) with

straightforward protocol, the resulting benzothiazole could be conveniently separable from the mixture. Rey research provide a convenient and reliable approach for obtaining 2-substituted benzothiazole compounds.



46 45

Scheme 1.16 Cyclization method for synthesizing benzothiazoles

In addition to their industrial applications, benzothiazoles are also utilized in the synthesis of important and clinically used drugs. These drugs incorporate the benzothiazole ring structure and have demonstrated significant therapeutic value, such as the Immunosuppressive Agent and antiviral agent Frentizole,[82] Thioflavin-T which is work as Amyloid Imaging Agent, [83] the antiparkinsonian agent Pramipexole,[84] and Ethoxzolamide as a Diuretic agent[85] (Figure 1.5).

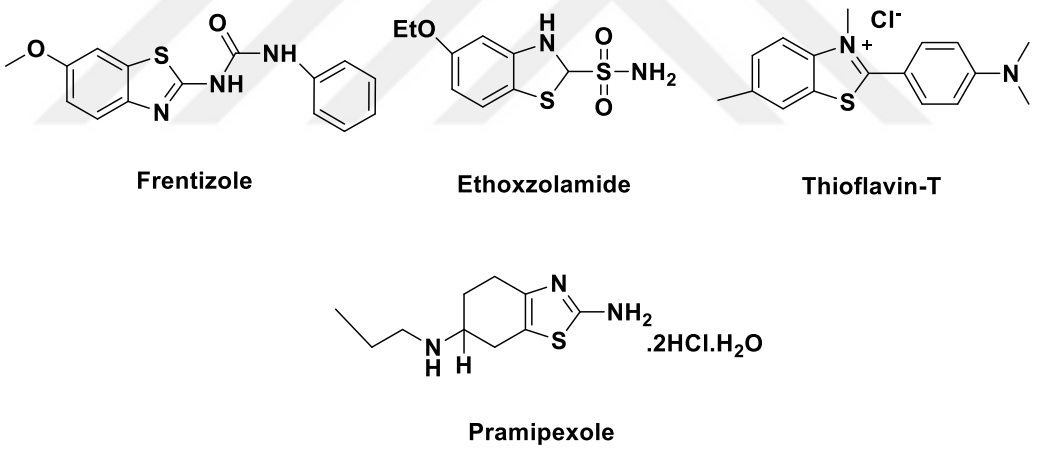


Figure 1.5 Some successful benzothiazole based clinically available drugs

Benzothiazoles are widely used and globally synthesized industrial chemicals, with applications including vulcanization accelerators in rubber production, antimicrobial, anti-algal agents, herbicides and fungicides, and antifreeze for automobiles.[86] Benzothiazole is a versatile compound with diverse biological, pharmaceutical, and industrial applications. Its significance in pharmaceuticals, optoelectronic materials, and various industrial processes underscores the need for continued research into its synthesis, properties, and potential environmental and health impacts.

2. AIM AND SCOPE OF THE STUDY

The unique importance of sulfonyl benzothiazole derivatives led us to search more about it and find novel molecules with a new bioactivity property, by using multi-component reactions (MCRs) that have effective techniques in the field of producing small molecules, particularly heterocyclic compounds with therapeutic properties in order to discover novel sulfur and nitrogen-containing compounds with promising biological properties and potential applications in the pharmaceutical industry, there is a growing demand for the development of innovative synthetic processes.

The exploration of new methodologies is essential to expand the repertoire of available compounds and facilitate advancements in drug discovery and development. And with all the knowledge we have, we succeeded in combining the benzothiazole group with thiazolopyridine, and pyridopyrimidine together with some derivatives by using three and four multi-component reactions (MCRs) under mild conditions, giving as a result moderate yields, saving time. The compounds obtained in this study were thoroughly validated through rigorous spectroscopic analysis, reinforcing their authenticity and reliability.

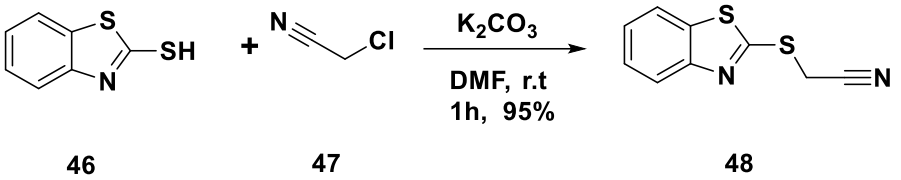
3. RESULTS AND DISCUSSUION

The considerable importance of benzothiazole derivatives in various fields, particularly in bioactivity, has motivated us to synthesize our target compounds using multicomponent reactions (MCRs) that incorporate diverse groups like amino, pyridine, sulfone, and nitro. Since multi-component reactions has gained widespread recognition pertaining to synthetic organic compounds on account to their numerous advantages, including energy and time efficiency, eco-friendly, and simplicity, with high applicability in drug production and manufacturing processes.[87,88]

Extensive research has been conducted on nitro-containing compounds, revealing their intriguing chemical properties and their potential as versatile building blocks for synthesizing diverse functionalized compounds. Of particular interest are nitroalkenes containing heteroatoms, which serve as excellent electrophiles capable of undergoing conjugate addition reactions with nucleophiles and radicals. This reactivity enables the forming of complex molecular structures to provide valuable opportunities for the synthesis an extensive variety of compounds with diverse functionalities. Additionally, 2-methylene substituted-thiazolidine and substituted-pyrimidine compounds are considered essential starting materials for cyclization reactions, for their properties containing electrophilic and nucleophilic centers.[89]

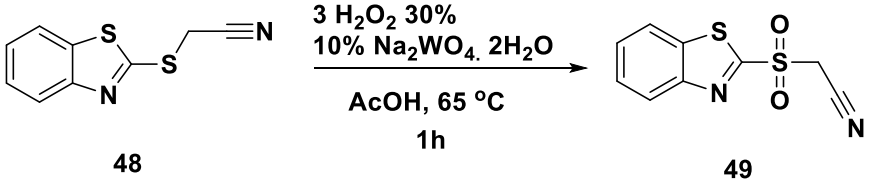
In accordance with existing scientific knowledge, we aimed to synthesize (benzothiazol-2-ylsulfonyl)-8-nitro-7-aromatic-thiazolo [3,2-a] pyridin-5-amine **51a-i** and (benzothiazol-2-ylsulfonyl)-8-nitro-7-aromatic-pyrido[1,2-a]pyrimidin-6-amine derivatives **54a-c** *via* one-pot three and four component reactions using a mild conditions, respectively.

Firstly, preparation of the methyl nitrile group, formation of thioether, namely 2-(benzothiazol-2-ylthio) acetonitrile **48** starting of 2-mercaptobenzothiazole **46** and Chloroacetonitrile **47**, using the solvent DMF and potassium carbonate as a base (Scheme 3.1). The development of the reaction was monitored using thin layer chromatography (TLC), 1 hour was enough for conversion of all reactants into product **47** with an excellent yield.[90]



Scheme 3.1 Synthesis of thioether **48**

FT-IR analysis of compound **48** revealed a characteristic nitrile peak at approximately 2245 cm^{-1}. The second step was sulfonation of sulfur in compound **48** to get 2-(benzo[d]thiazol-2-ylsulfonyl) acetonitrile **49**. The multicomponent reaction trials of compound **48** did not proceed as desired. We have tried different solvents such as ethanol, methanol and TEA, piperidine as bases, at 80 ^oC. It might be the reason of first formation of Knoevenagel intermediate didn't observe under these conditions due to the relatively low acidity of the methylene protons, the used bases couldn't achieve to deprotonate of those protons. However, the sulfonation of sulfur results compound **49** effectively addressed this limitation by increasing the methylene protons acidity through electron withdrawing property of the sulfone and nitrile groups. Additionally, the oxidation reaction yielded satisfactory results with high yields, utilizing hydrogen peroxide and acetic acid as a solvent and 10% sodium tungstate dihydrate as the catalyst.[91]



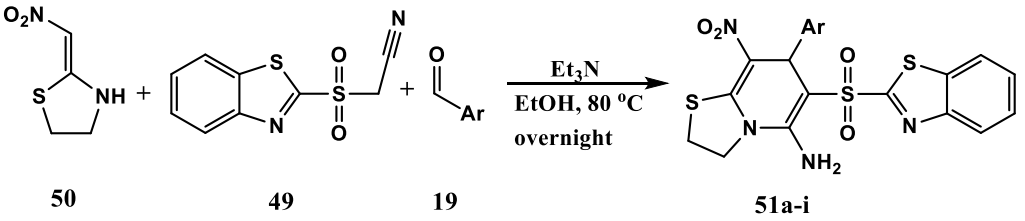
Scheme 3.2 Oxidation of thioethers to sulfone

FT-IR analysis was used to characterize Compound **49**. This is a widely accepted analytical technique that provides information about the functional groups and structural features of a molecule.

The FT-IR spectrum of Compound **49** exhibited characteristic tops. Peaks at approximately 1345 cm-1 and 1146 cm-1 are indicative of SO2 functional groups. A peak around 2269 cm-1 corresponds to a nitrile (C≡N) group. These specific peak positions and assignments provide strong evidence for the presence of these functional groups in Compound **49**.

The synthesis of the target molecules **51a-i** under mild reaction conditions facilitated an effortless and straightforward work-up process, eliminating the need for chromatography techniques. Notably, this efficient synthetic approach yielded good product yields, further highlighting its practicality and effectiveness.

The spectroscopic and physical properties of all compounds were determined by FT-IR, ^{1}H NMR, ^{13}C NMR, LC-MS, HR-MS and Mp. Following the previous application conditions studied in 2020,[92] using water as a solvent gave a reduced yield compared to our optimized condition. However, the dryness of ethanol is essential in getting a good yield because whenever the reaction was set in wet ethanol, the reaction did not occur as smoothly as the dry one while also taking longer to get to the final products and having lower yields. This is returned to the effect that the water has a possible negative impact on the Knoevenagel condensation, even trace amounts of water can decrease yields of the products.[93] Also the presence of water can affect the catalytic activity of organic strong bases.[94] The three multicomponent reaction getting the targeted **51a-i** compounds was a reaction of 2-(benzo[d]thiazol-2-ylsulfonyl)acetonitrile **49**, with 2-nitromethylene thiazolidine **50** and aromatic aldehydes **19** were performed in dry ethanol at reflux temperature in the presence catalytic amount of TEA and monitored by TLC. The reaction was stirred overnight for all conversion of the starting materials into the products.



50 **49** **19** **51a-i**

Scheme 3.3 Synthesis of thiazolopyridine derivatives

Compound	Ar	Yield %	Mp °C
51a	4-Br-C_6H_4	70	208-209
51b	4-NO_2-C_6H_4	69	228-229
51c	4-Cl-C_6H_4	59	214-215
51d	C_6H_5	62	216-217
51f	2,6-DiCl-C_6H_3	53	217-218

51g	4-MeO-C_6H_4	66	213-214
51h	2,4-DiCl-C_6H_3	82	224-225
51i	1-Naphthyl	74	220-221

Table 3.1 Substituents and yields of compounds **51a-i**

The spectroscopic data was done by FT-IR, ^{13}C-NMR, ^{1}H-NMR, LC-MS and HR-MS and it provides strong evidence and complete support for the accurate identification and characterization of these compounds. 6-(Benzo[d]thiazol-2-ylsulfonyl)-8-nitro-7-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine **51d** was used as a model for discussion of the measurement and with checking all measured data we can confirm that all data were identical to the desired compound.

Starting with the analysis FT-IR spectrum found 2 peaks around 3340 and 3200 cm^{-1} giving good evidence that C-NH_2 comes from Michael addition reaction between NH and nitrile group, peak 1670 cm^{-1} related CH=CH comes from the benzene ring, 1593 and 1422 cm_{-1} related to C-NO_2, and 1322 and 1131 cm^{-1} give strong evidence for symmetrical and unsymmetrical sulfonyl stretchings. (Figure 3.1)

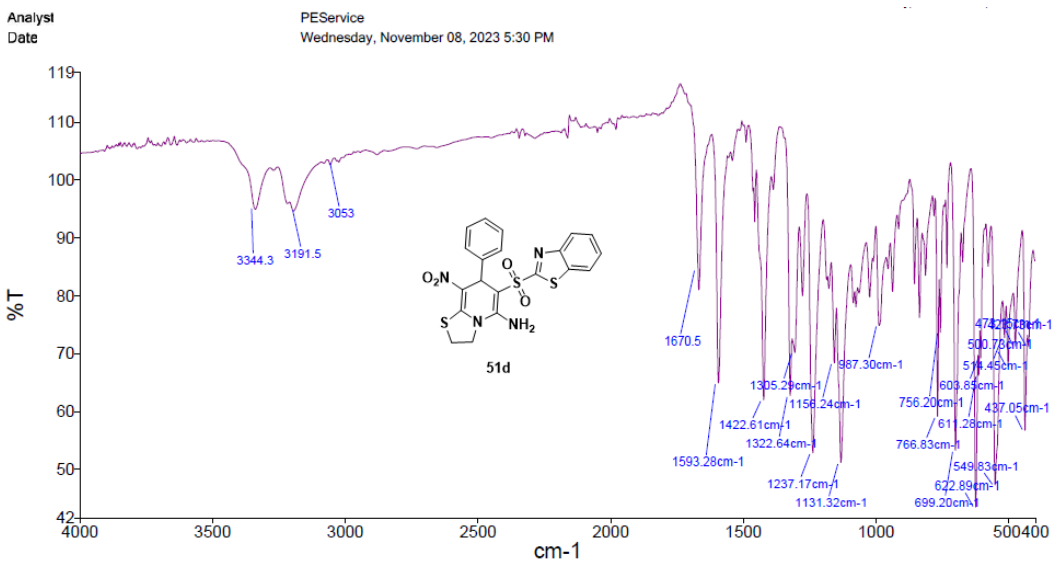


Figure 3.1 FT-IR spectrum for the model compound **51d**

And for ^{1}H NMR identification process of the structures based on the hydrogen's atoms on the molecule, from the data of NH_2 protons indicated as a singlet at around

7.1 ppm and at 7.1-7.3 ppm as range, and CH proton of pyridine ring appeared as a singlet peak at 5.31 ppm and at range 5.23-6.12 ppm, and for aliphatic two protons of S-CH_2 peaks has appeared at 4.35 for **51d** and around 4.6-4.31 ppm at range for the rest products and for aliphatic N-CH_2 protons at 3.42 and 4.31-3.4 ppm as range. The molecule **51d** has a total of 16 hydrogen atoms and the ^{1}H NMR spectrum matches up with this reported number (Figure 3.2).

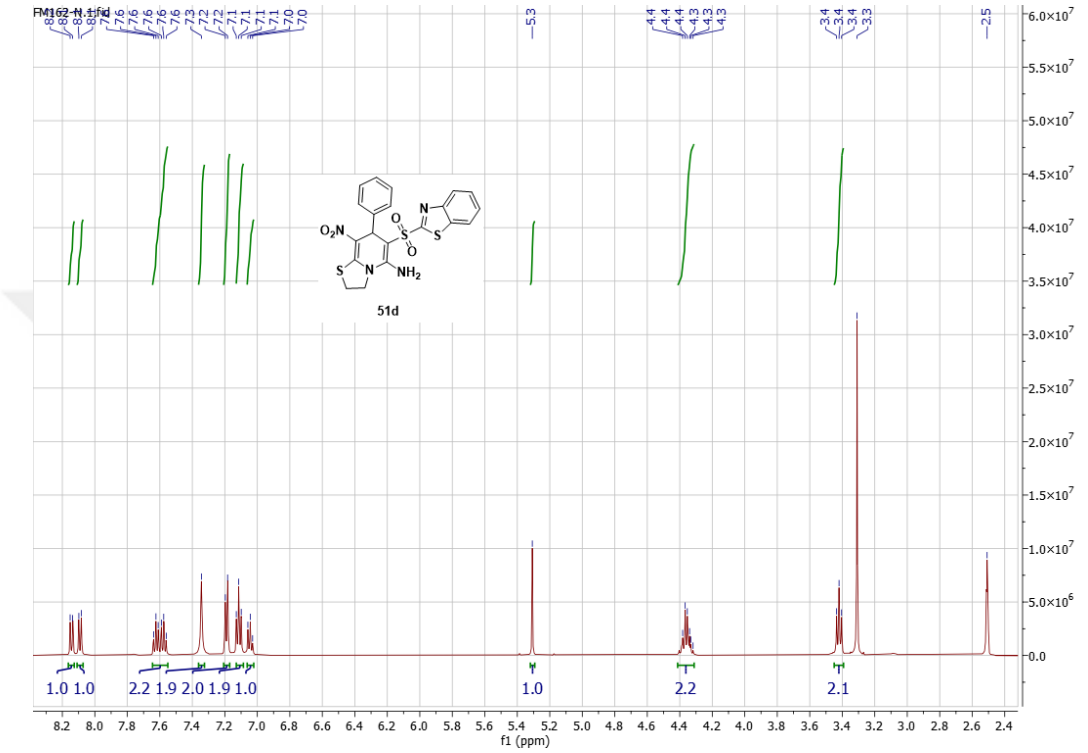


Figure 3.2 ^{1}H NMR spectrum for the model compound **51d**

For ^{13}C-NMR spectrum for compounds **51a-i** the pyridine CH peak was found around 28.0-28.6 ppm, carbon C-NO_2 indicated around 121.0-123.4 ppm, the carbon of pyridine C-NH_2 was found around 152.0-152.5 ppm, and the carbon in benzothiazole S-C-N indicated around 169.7-170.4 ppm (Figure 3.3).

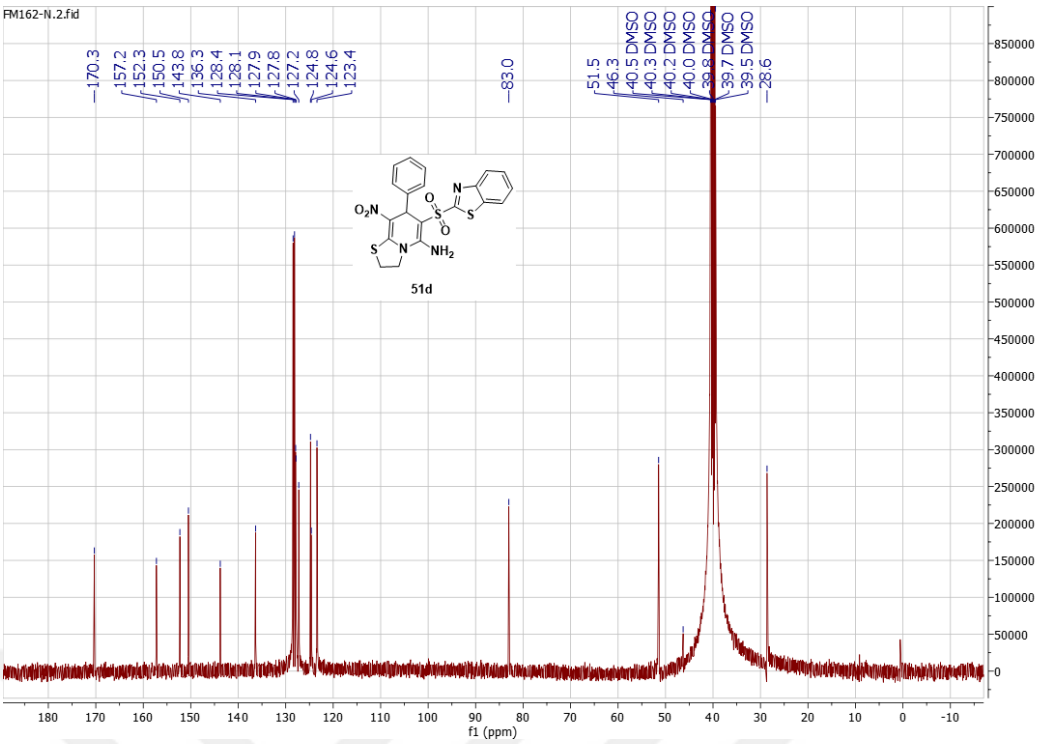


Figure 3.3 ^{13}C NMR spectrum of the model compound **51d**

LC/MS give good evidence to provide the targeted products by their masses, **51d** has $C_{20}H_{16}N_4O_4S_3$ as chemical formula and 472 m/z (TOF ES^-) and spectrum showed the base-line corresponding with a deaminated compound as 456.4 (M^+-NH_2, 100%), and sodium ionate with 46% (495.6, M^++Na^+), the exact mass for targeted mass structure with 8% (472.5, M^+), and denitrated target structure with 4% (425.4, M^+-NO_2) (Figure 3.4). HR-MS found M^+, 472.0339, $C_{20}H_{15}ClN_4O_4S_3$ M^+ requires 472.0333.

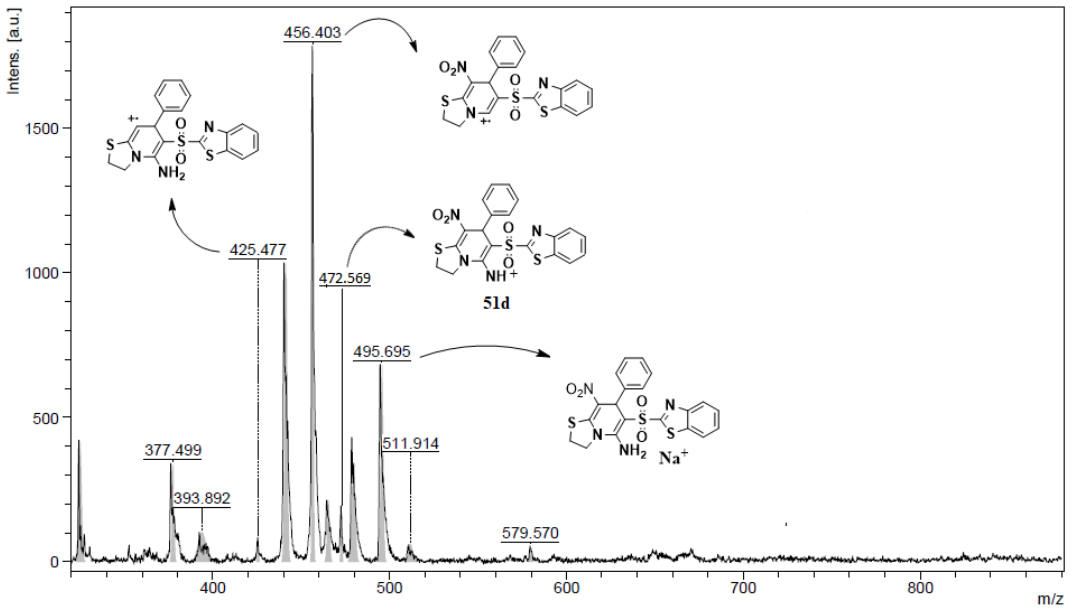
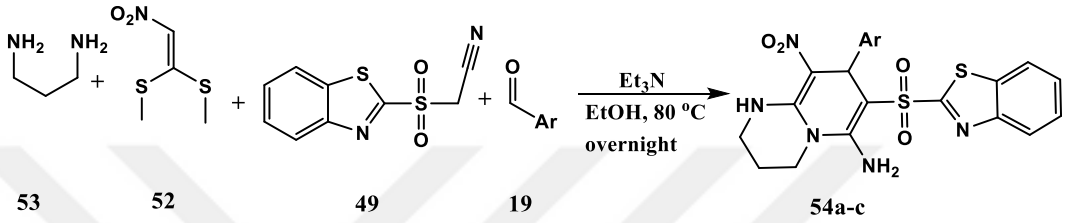


Figure 3.4 LC/MS spectrum of the model compound **51d**

The four multicomponent reaction targeted **54a, 54b,** and **54c** compounds. (Table 3.2) In order to obtain the **54a-c** reaction of (2-nitroethene-1,1-diyl)bis(methylsulfane) **52** with propane-1,3-diamine **53** were mixed for 5h then 2-(benzo[d]thiazol-2 -ylsulfonyl)acetonitrile **49**, and aromatic aldehydes **19** added to the reaction mixture in the presence of 0.5 equivalent of TEA in dry ethanol at reflux temperature and the formation of reaction was confirmed by TLC. Adding the four components together at the same time increases the reaction time and produces undesired intermediates. The reaction was stirred overnight for all conversion of the starting materials into the products. (Scheme 3.5)



53 52 49 19 54a-c

Scheme 3.5 Synthesis of pyridopyrimidine derivatives **54a-c**

Compound	Ar	Yield %	Mp °C
54a	4-NO_2-C_6H_4	64	220-221
54b	3-NO_2-4-Cl-C_6H_3	55	215-216
54c	4-CN-C_6H_4	54	216-217

Table 3.2 Substituents and yields of compounds **54a, 54b** and **54c**

The spectroscopic data obtained by FT-IR, ^{13}C-NMR, ^{1}H-NMR, LC-MS and HR-MS provide strong evidence for accurately identifying and characterizing **54a-c** compounds. The **54a** model was used as a basis for the discussion of the measurements. In FT-IR, three medium peaks were found around 3387, 3340, and 3320 cm^{-1}, related to NH_2 and NH, and two peaks around 1530, and 1420 cm^{-1} were related to the carbon nitro group, and for the 1313 and 1136 cm^{-1}, considered to be strong evidence for symmetry and asymmetry SO_2. (Figure 3.5)

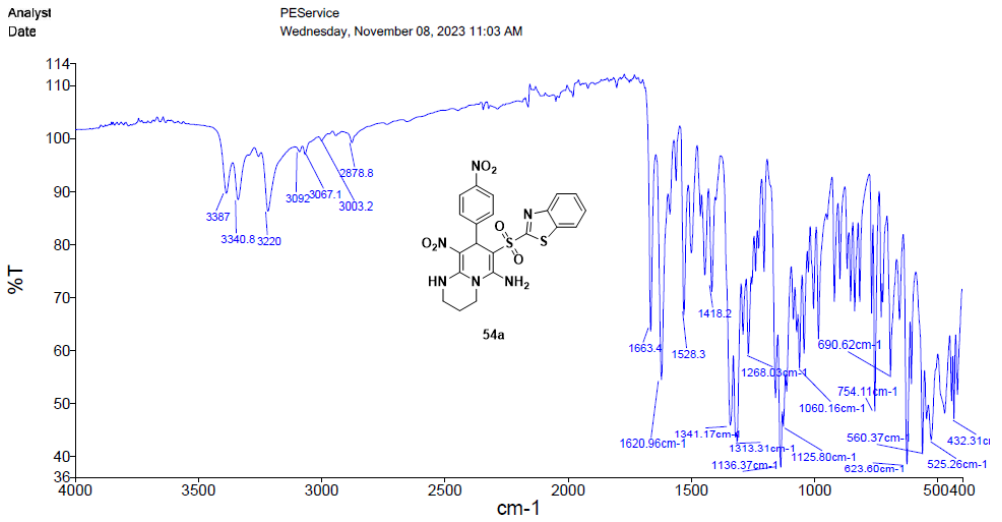


Figure 3.5 FT-IR spectrum for the model compound **54a**

For ^{1}H NMR identifying the structures depending on the hydrogen atoms on the molecule, from the data of NH proton in pyrimidine was found as a singlet at around 11.2 ppm and the range 11.22-11.25 ppm, and NH_2 protons indicated as a singlet at around 7.4 ppm, while the range of signal was around 7.43-7.33 ppm, and the CH proton signal from the pyridine ring was observed as a singlet peak at 5.36 ppm and for the other products, the corresponding protons signals fell within the range of 5.42-5.36 ppm. For the aliphatic region, six protons were observed for $3CH_2$. Two protons appeared as a multiplet at 3.91-3.79 ppm and around 3.9-3.7 ppm at the range, and two from CH_2, appeared at 3.58 ppm, with 3.61-3.56 ppm as range and CH_2 observed at 2.16-1.86 ppm, and at range 2.14-1.83 ppm. The **54a** molecule has a total of 18 hydrogen atoms and the ^{1}H NMR spectral data aligns with this number (Figure 3.6).

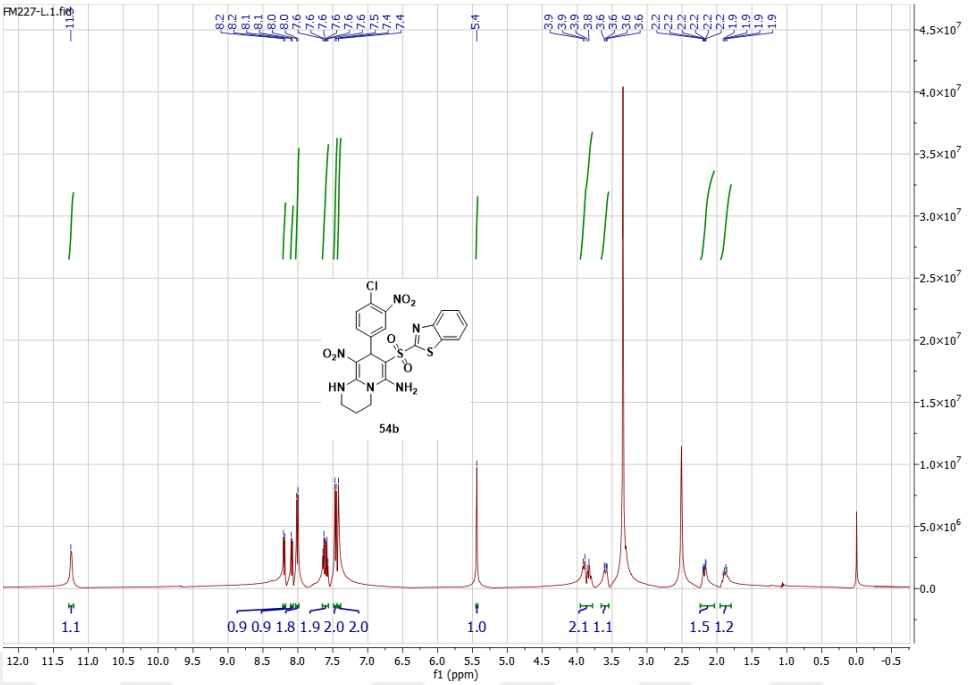


Figure 3.6 ^{1}H NMR spectrum for the model compound **54a**

^{13}C-NMR spectrum counts on the number of carbons in the structure for compounds **54a-c** the pyridine CH peak was found around 20.09-20.19 ppm, carbon C-NO_2 of the pyridine ring indicated around 109.1-108.8 ppm, the carbon of pyridine C-NH_2 was found around 150.4-147.5 ppm, and the carbon in benzothiazole S-C-N indicated around 169.8-169.6 ppm (Figure 3.7).

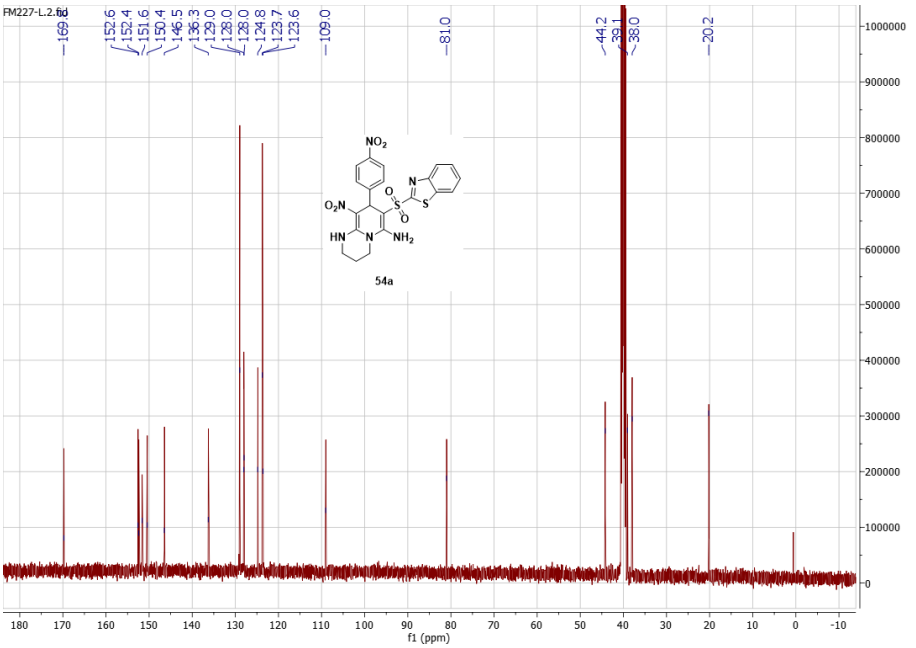


Figure 3.7 ^{13}C-NMR spectrum for the model compound **54a**

The LC/MS data provides strong support for the targeted products. The mass measurement indicated a molecular formula of $C_{21}H_{18}N_6O_6S_2$, with a parent ion m/z of 515.1 (TOF ES-). The spectrum also showed evidence of several key fragment ions a deaminated compound at 456.4 m/z (100%, M+-NH_2), the protonated molecular ion at 515.1 m/z (37% M+H), the sodium ionate at 438.2 m/z (29% abundance), and a denitrated species at 468.7 m/z (15% abundance) (Figure 3.8). HR/MS found M^+, 514.0728, $C_{21}H_{18}N_6O_6S_2$ [M^+] requires 514.0729.

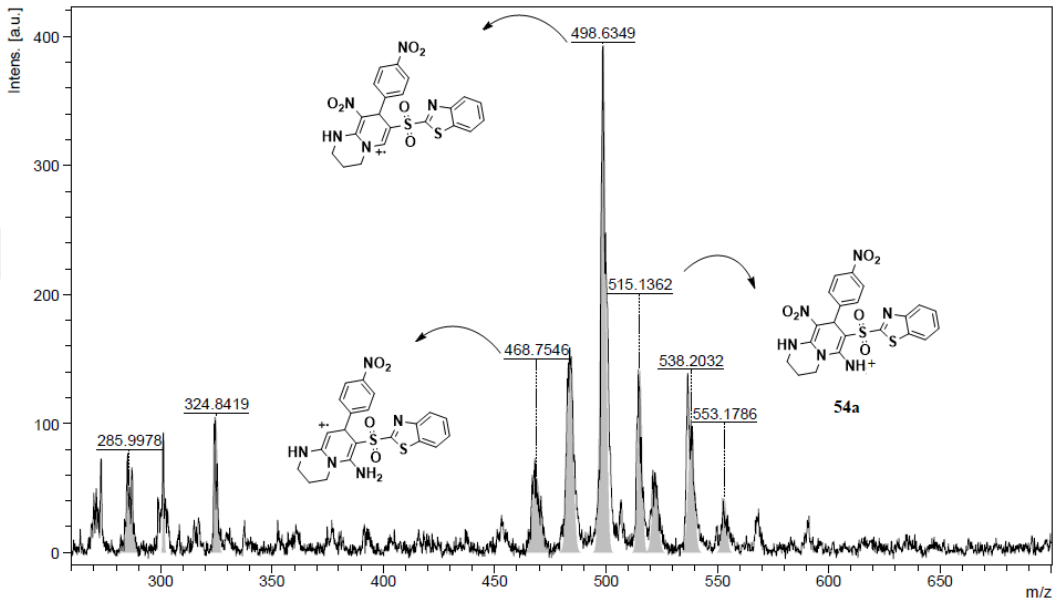
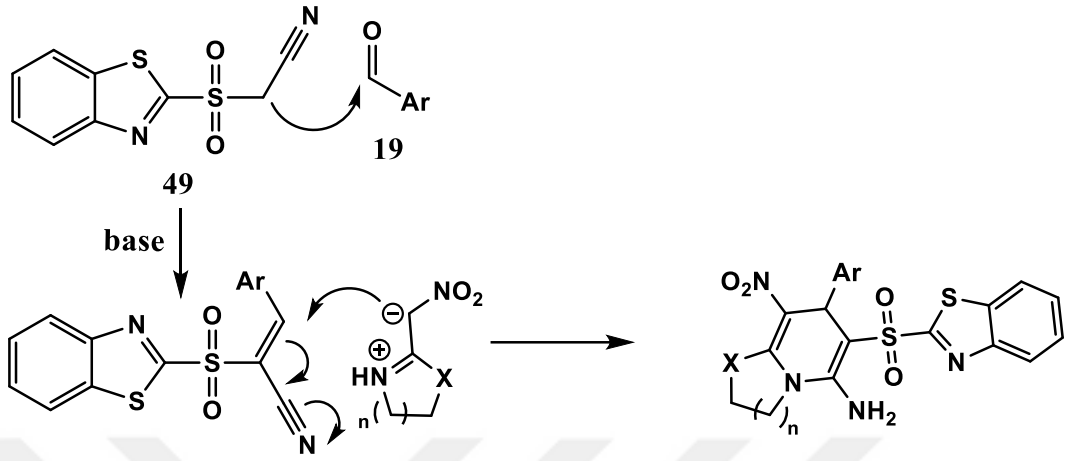


Figure 3.8 LC/MS spectrum of the model compound **54a**

The mechanism of both multi-component reactions begins with the Knoevenagel condensation of active nitro-methylene derivatives, benzothiazole sulfonyl acetonitrile, with aldehydes in the presence of a catalytic amount of triethylamine (TEA) as a base catalyst. TEA deprotonates the active methylene group of benzothiazole sulfonyl acetonitrile, generating a nucleophilic enolate ion. The enolate ion then attacks the carbonyl carbon of the aldehyde, forming a carbon-carbon double bond and resulting in a condensation product. In the subsequent step, the β-nitroenamine undergoes a Michael addition, possibly resonance form of HKAs attacks to Knoevenagel intermediate. This addition forms a new carbon-carbon bond, creating an intermediate that undergoes an intramolecular cyclization. The cyclization likely occurs *via* a nucleophilic attack within the intermediate, leading

to the formation of the pyridine ring. The overall process yields the desired molecules **51a-i** and **54a-c** as the final products, each containing the newly formed pyridine ring structure. (Scheme 3.3)



Scheme 3.3 The proposed mechanism of target molecules based on Knoevenagel condensation and Michael addition cyclization reaction

3.1 Biological activity of compounds 51a-i and 54a-c

An investigation of the biological functionality of this new series synthesized benzothiazole sulfonyl containing heterocyclic molecules **51a-i** and **54a-c** for their antibacterial, antimycobacterial, and antifungal activities revealed promising moderate activities. However, the biological target and the mode of action of these molecules are currently unknown.

3.1.1 Antibacterial activity

Samples	*Staphylococcus aureus* (ATCC 25925)	*Escherichia coli* (ATCC 25923)	*Acinetobacter baumannii* (ATCC 02026)	*Bacillus subtilis* (ATCC 6633)	*Aeromonas hydrophila* (ATCC 95080)	*M. tuberculosis* H37RV
51a	500	250	125	250	62,50	62,50
51b	500	250	125	125	125	62,50
51c	250	125	125	125	125	31,25
51d	500	125	62,50	250	62,50	31,25
51f	250	250	62,50	125	62,50	62,50
51g	500	250	125	250	125	31,25
51h	250	250	125	250	125	62,50
51i	500	125	125	125	62,50	62,50
54a	500	250	125	250	125	62,50
54b	250	125	62,50	125	62,50	31,25
54c	500	250	62,50	250	62,50	31,25
Ampicillin	31,25	15,62	125	0,9	31,25	---
Isoniazid	---	---	---	---	---	0,12
Rifampicin	---	---	---	---	---	0,97

Table 3.3 The MIC values (***μ***g/mL) of the tested molecules against the Gram (+) and Gram (-) bacteria and ***M. tuberculosis*** H37Rv strain

Thus the molecules **51a-i** and **54a-c** were screened against standard bacterial strains as gram positives bacteria such as Staphylococcus aureus (ATCC 25925) and Bacillus subtilis (ATCC 6633), and gram negative bacteria such as ***Escherichia coli*** (ATCC 25923), *Acinetobacter baumanii* (ATCC 02026), and *Aeromonas hydrophile* (ATCC 95080) which were obtained from Refik Saydam Hıfzısıhha Institute, Ankara, Turkey and the ampicillin was used as control drug. The tested molecules inhibited the growth of bacteria at minimum inhibitory concentrations MIC values in the range of 62.5–500 ***μ***g/ml. The control,

ampicillin, showed activity against the indicated ***bacteria*** with a range of 0.9 -125 ***μ***g/mL. of MIC values. The obtained results of the ampicillin drug and the antibacterial activities of tested molecules are given in (Table 3.3)

Thus the molecules **51d, 51f, 54b** and **54c** showed the better activities than the others when tested against *Acinetobacter baumannii* and *Aeromonas hydrophila* bacterial strains in the MIC values of 62.5 (***μ***g/mL) and also **51a** and **51i** showed the same activities against *Aeromonas hydrophila.*

3.1.2 Anti-tuberculosis activity

The newly prepared compounds **51a-i** and **54a-c** were also tested against ***M. tuberculosis*** H37Rv strain and rifampicin and isoniazid (INH) (Sigma I3377) were used as standard reference drugs measured by means of MIC values (μg/ml). The screened molecules (Table 3.3) showed moderate activity, in the range of 31.5–62.5 μg/ml when compared to isoniazid and rifampicin as known control drugs. However, the molecule showed better activity against ***M. tuberculosis*** H37Rv when compared to anti-bacterial activity. The compounds **51d, 51c, 51g, 54b,** and **54c** revealed the highest activities with the MIC values 31,25 μg/ml. Whereas the compound **51a, 51b, 51f, 51h, 51i, and 54a** showed the activity in the value of 62.5 μg/ml.

3.1.3 Antifungal activity

Antifungal activity of benzothiazole sulfonyl containing heterocyclic compounds **51a-i** and **54a-c** were screened against *Candida albicans* ATCC 14053, *Candida tropicalis* ATCC 1369, *Candida glabrata* ATCC 1512, and the fluconazole was used as control drug. The tested molecules inhibited the growth of fungus at MIC values in the range of 62.5–125 ***μ***g/ml. The control, fluconazole, showed activity against the indicated ***fungus*** with a range of 3.9 -31.25 ***μ***g/mL of MIC values. The obtained results of the fluconazole drug and the antifungal activities of tested molecules are given in (Table 3.4).

samples	*Candida albicans* ATCC 14053	*Candida tropicalis* ATCC 1369	*Candida glabrata* ATCC 15126
51a	62,50	125	62,50
51b	125	62,50	62,50
51c	62,50	125	62,50
51d	62,50	62,50	125
51f	125	62,50	125
51g	125	125	125
51h	125	125	125
51i	62,50	62,50	62,50
54a	125	62,50	62,50
54b	62,50	62,50	62,50
54c	125	125	125
Fluconazole	31,25	15,62	3,90

Table 3.4 Antifungal activity and the MIC values (μg/mL) of the tested molecules against the *Candida albicans*, *Candida tropicalis*, and *Candida glabrata*

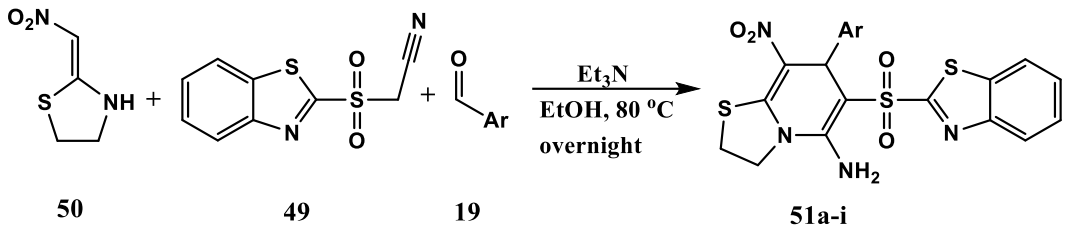
Thus, the molecules **51a, 51c, 51d, 51i** and **54b** showed the better activities then the others when tested against *Candida albicans* ATCC 14053 with the MIC values 62.5 µg/ml and **51b, 51d, 51f, 51i, 54a, and 54b** revealed moderate activities against *Candida tropicalis* ATCC 1369 with the MIC values 62.5 µg/ml. In addition, **51a, 51b, 51c, 51i, 54a** and **54b** observed moderate activities when screened against *Candida glabrata* ATCC 15126 with the MIC values 62.5 µg/ml.

4. EXPERIMENTAL

4.1 Materials And Apparatus

The commercial chemicals and reagents used were purchased from Sigma Aldrich. TLC has been performed on Merck silica gel F-254 plates. Melting points (Mp) were determined in an open glass capillary with an uncorrected MELTEMP apparatus, and solution of permanganate was used for the visualization of the TLC spots. The Perkin Elmer Spectrum FTIR-ATR spectrophotometer was used to record the FT-IR spectra. The NMR spectra for **51a-i** and **54a-c** were measured at room temperature using a Bruker Biospin 500 MHz NMR spectrometer in DMSO-d6. The coupling constants (J) are reported in Hertz (Hz), and the chemical shifts are expressed in parts per million (ppm). The splitting patterns are assigned as follows: singlet (s), doublet (d), multiplet (m), doublets of doublet (dd), and triplets of doublet (td). The LCMS measurements were obtained from MALDI-TOF Bruker Microflex LT. The HRMS measurements were obtained from Agilent 6545 QTOF LC/MS, Finnigan VG Platform or Finnigan MAT 95S, JASCO 2000.

4.2 Benzothiazole sulfonyl thiazolo[3,2-a]pyridine derivatives 51a-i



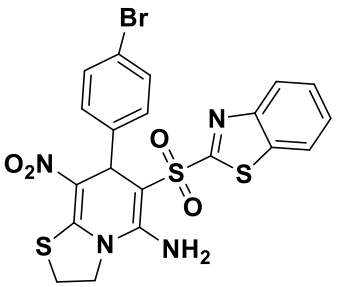
Scheme 4.2.1. Preparation of Thiazolo[3,2-a]pyridine derivatives **51a-i**

4.2.1 Procedure For The Formation Of benzothiazole sulfonyl thiazolo[3,2-a]pyridine derivatives 51a-i

The synthesis method was applied for a reaction of 2-(benzo[d]thiazol-2-ylsulfonyl)acetonitrile **49** (1.0 mmol, 238.28 mg), 2-nitromethylenethiazoline **50** (1.0 mmol, 1.0 eq., 146 mg), and aromatic aldehyde **19** (1.0 mmol, 1.0 eq.,) were mixed in dry Ethanol EtOH (8mL) in a round-bottomed flask and the mixture was heated with stirring until all reactants dissolved. Then triethylamine TEA (0.5 eq., 0.5 mmol) was added dropwise to the reaction mixture while refluxing for overnight. The product collected by filtrating the solid and washing with a minimal amount of cold ethanol and dried under vacuum pressure, to send for analysis.

4.2.2. Analysis Data for all Thiazolo[3,2-a]pyridine derivatives.

4.2.2.1 6-(Benzo[d]thiazol-2-ylsulfonyl)-7-(4-bromophenyl)-8-nitro-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51a)

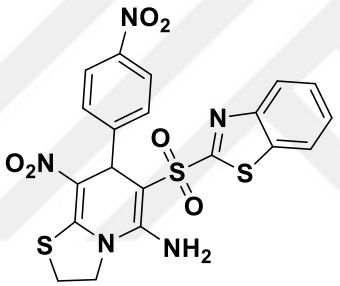


51a

Yellow powder, (70%); M.P. 208-209 ˚C, Rf: 0.4, V̇max (ATR, cm^{-1}) 3440-3349 (NH, NH_2), 1631 (C=C), 1593, 1444 1327 (asym. SO_2), 1225, 1151 (sym. SO_2). ^1H

NMR (500 MHz, DMSO) δ 8.17 (1H, d, J = 7.8, BTH CH), 8.09 (1H, d, J = 8.1, BTH CH), 7.67 – 7.54 (2H, m, 2CH), 7.41 (2H, s, NH_2), 7.26 (2H d, J = 8.3, BTH 2CH), 7.13 (2H, d, J = 8.4, 2CH), 5.25 (1H s, CH), 4.35 (2H, t, J = 7.5, CH2), 3.42 (2H t, J = 7.6, CH_2). ^{13}C NMR (125 MHz, DMSO) δ 170.1 (BTH, C), 157.6 (BTH, C), 152.3 (C), 150.4 (C), 143.0 (BTH, C), 135.3 (BTH, C), 131.25 (2CH), 130.5 (CH), 128 (BTH, CH), 127.9 (BTH, CH), 124.8 (BTH, CH), 123.4 (C), 120.5 (C), 82.4 (C), 51.4 (CH), 45.3 (CH_2), 28.5 (CH). $C_{20}H_{15}BrN_4O_4S_3$ m/z (TOF ES^-) 504.2 (M^+-NO_2, 8%) 535.6 (M^+-NH_2, 100%), 551.6 (M^+, 67%), 573.3 (M + Na^+, 19%). HR/MS found M^+, 549.9440, $C_{20}H_{15}BrN_4O_4S_3$ [M^+] requires 549.9438.

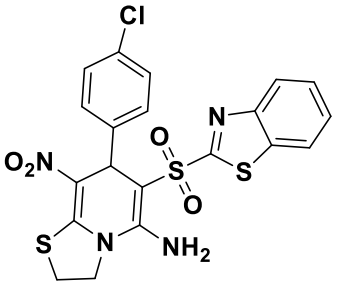
4.2.2.2 6-(Benzo[d]thiazol-2-ylsulfonyl)-8-nitro-7-(4-nitrophenyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51b)



51b

Yellow powder, (69%); M.P. 228-229 ˚C, Rf: 0.2, V̇max (ATR, cm^{-1}) 3454-3340 (NH, NH_2), 1626, 1587, 1514, 1409, 1327 (asym. SO_2), 1244, 1225, 1151 (sym. SO_2). ^1H NMR (500 MHz, DMSO) δ 8.14 (1H, d, J = 7.7, BTH, CH), 8.04 (1H, d, J = 7.8, BTH, CH), 7.92 (2H, d, J = 8.6, BTH, 2CH), 7.62 – 7.54 (2H, m, 2CH), 7.49 (2H, s, NH_2), 7.45 (2H, d, J = 8.7, 2CH), 5.39 (1H, s, CH), 4.42 – 4.34 (2H, m, CH_2), 3.45 (2H, t, CH_2). ^{13}C NMR (125 MHz, DMSO) δ 169.9 (BTH, C), 158.2 (BTH, C), 152.2 (BTH, C), 150.7 (C), 150.54 (C), 146.6 (C), 136.2 (BTH, C), 129.7 (CH), 128.0 (BTH, CH), 124.7 (BTH, CH), 123.6 (2CH), 123.5 (BTH, CH), 123.3 (BTH, CH), 81.8 (C), 57.0 (CH), 51.6 (CH), 46.2 (CH_2), 28.6 (CH_2). $C_{20}H_{15}N_5O_6S_3$ m/z (TOF ES^-) 517.1 (M^+,100%), 501.7 (M^+-NH_2, 77%), 540 (M + Na^+, 11%). HR/MS found M^+, 517.0189, $C_{20}H_{15}N_5O_6S_3$ [M^+] requires 517.0184.

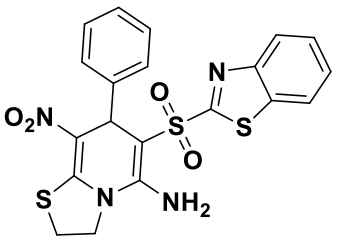
4.2.2.3 6-(Benzo[d]thiazol-2-ylsulfonyl)-7-(4-chlorophenyl)-8-nitro-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51c)



51c

Yellow powder, (59%); Mp 214-215 ˚C, Rf: 0.3 Vmax (ATR, cm-1) 3451-3351 (NH, NH2), 1631 (C=C), 1588, 1404, (asym. SO_2), 1223, 1151 (sym. SO_2). ^{1}H NMR (500 MHz, DMSO) δ 8.17 (1H, d, J = 8.1, BTH, CH), 8.08 (1H d, J = 9.1, BTH, CH), 7.67 – 7.55 (2H, m, BTH, 2CH), 7.38 (2H, s, NH_2), 7.19 (2H, d, J = 8.8, 2CH), 7.13 (2H, d, J = 8.8, 2CH), 5.28 (1H, s, CH), 4.36 (2H, t, J = 8.1, CH_2), 3.42 (2H, t, J = 8.0, CH_2). ^{13}C NMR (125 MHz, DMSO) δ 170.1 (BTH, C), 157.5 (BTH, C), 152.3 (BTH, C), 150.5 (C), 142.0 (C), 136.3 (C), 131.9 (BTH, C), 130.1 (2CH), 128.3 (2CH), 128.0 (CH), 127.9 (CH), 124.8 (CH), 124.1 (CH), 123.4 (C), 82.5 (C), 51.5 (C), 46.3 (CH_2), 39.7 (CH_2), 28.6 (CH). $C_{20}H_{15}ClN_4O_4S_3$ m/z (TOF ES^-) 490.36 (M^+-NH_2, 100%), 506.7 (M^+, 50%), 530 (M + Na^+, 19%). HR/MS found M^+, 505.9939, $C_{20}H_{15}ClN_4O_4S_3$ [M^+] requires 505.9944.

4.2.2.4 6-(Benzo[d]thiazol-2-ylsulfonyl)-8-nitro-7-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51d)

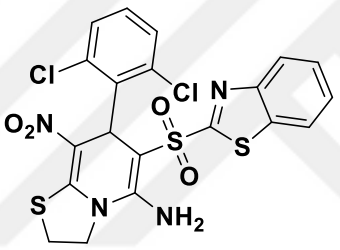


51d

Light yellow powder, (62%); Mp 216-217˚C, Rf: 0.3 Vmax (ATR, cm^{-1}) 3344-3191 (NH, NH_2), 1670 (C=C), 1593, 1422, 1322 (asym. SO_2), 1237, 1131 (sym. SO_2). ^{1}H NMR (500 MHz, DMSO) δ 8.15 (1H, d, BTH, CH), 8.09 (1H, d, BTH CH), 7.60

(2H, dddd, J = 23.9, 8.3, 7.1, 1.3, BTH, 2CH), 7.34 (2H, s, NH_2), 7.19 (2H, d, 2CH), 7.11 (2H, t, J = 7.6, 2CH), 7.06 (1H, t, CH), 5.31 (1H, s, CH), 4.42 – 4.31 (2H, m, CH_2), 3.42 (2H, t, J = 7.6 CH_2). ^{13}C NMR (125 MHz, DMSO) δ 170.3 (BTH, C), 157.2 (BTH, C), 152.3 (C), 150.5 (C), 143.8 (C), 136.4 (BTH, C), 128.4 (2CH), 128.1 (2CH), 127.9 (BTH, CH), 127.2 (BTH, CH), 124.8 (BTH, CH), 124.5 (BTH, CH), 123.4 (C), 83.0 (C), 51.5 (CH_2), 46.3 (CH_2), 28.5 (CH). $C_{20}H_{16}N_4O_4S_3$ m/z (TOF ES^-) 425.4 (M^+-NO_2, 4%) 456.4 (M^+-NH_2, 100%), 472.5 (M^+, 8%), 495.6 (M + Na^+, 46%). HR/MS found M^+, 472.0339, C20H15ClN4O4S3 [M^+] requires 472.0333.

4.2.2.5 6-(Benzo[d]thiazol-2-ylsulfonyl)-7-(2,6-dichlorophenyl)-8-nitro-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51f)

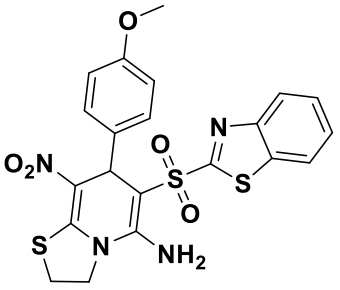


51f

Orange powder, (53%); Mp 217-218 ˚C, Rf: 0.4 Vmax (ATR, cm-1) 3468-3355 (NH, NH2), 1615(C=C), 1588, 1409, 1316 (asym. SO_2), 1224, 1120 (sym. SO_2). ^{1}H NMR (500 MHz, DMSO) δ 8.16 (1H, d, J = 9.4, BTH, CH), 8.09 (1H, d, J = 9.4, BTH CH), 7.66 – 7.57 (2H, m, BTH, 2CH), 7.50 (2H, s, NH_2), 7.35 (1H s, CH), 7.06 (1H s, CH), 6.12 (1H, s, CH), 4.60 – 4.52 (2H, m, 2CH), 4.31 – 4.23 (2H, m, 2CH). ^{13}C NMR (125 MHz, DMSO) δ 169.7 (BTH, C), 159.2 (BTH, C), 152.3 (C), 151.4 (C), 138.3 (C), 136.4 (CH), 135.4 (C), 130.0 (C), 129.3 (CH), 129.1 (2CH), 127.9 (BTH, CH), 127.8 (BTH, CH), 124.8 (BTH, CH), 123.4 (BTH, C), 121.0 (C), 79.6 (C), 51.3 (CH_2), 37.4 (CH_2), 28.0 (CH). $C_{20}H14Cl_2N_4O_4S_3$ m/z (TOF ES-) 541.0 (M+ H, 100%), 525.6 (M+-NH2, 35%), 563.6 (M + Na+, 50%). HR/MS found M^+, 539.9550 , $C_{20}H14Cl_2N_4O_4S_3$ [M^+] requires 539.9554.

.

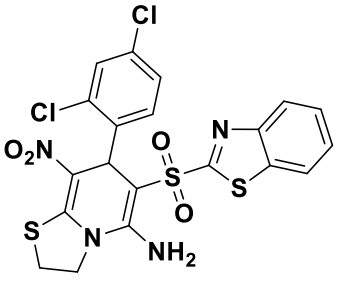
4.2.2.6 6-(Benzo[d]thiazol-2-ylsulfonyl)-7-(4-methoxyphenyl)-8-nitro-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51g)



51g

Orange powder, (66%); Mp 213-214 ˚C, Rf: 0.3, V̇max (ATR, cm^{-1}) 3472-3333 (NH, NH_2), 3060,2989,2832 (C-H), 1616 (C=C), 1582, 1411, 1302 (asym. SO_2), 1228, 1116 (sym. SO_2). ^1H NMR (500 MHz, DMSO) δ 8.14 (1H, d, J = 8.3, BTH, CH), 8.08 (1H, d, J = 9.1, BTH, CH), 7.69 – 7.53 (2H, m, BTH, 2CH), 7.32 (2H, s, NH_2), 7.06 (2H, d, J = 9.0, 2CH), 6.60 (2H, d, J = 9.0, CH), 5.23 (1H, s, CH), 4.35 (2H, ddd, J = 14.8, 6.9, 3.0, CH_2), 3.56 (3H, s, methyl, CH_3), 3.41 (2H, t, J = 7.9, CH_2). ^{13}C NMR (125 MHz, DMSO) δ 170.4 (C), 158.5 (BTH, C), 156.8 (BTH, C), 152.3 (C), 150.4 (C), 136.4 (BTH, C), 135.7 (C), 129.3 ($2CH_2$), 127.8 (BTH, CH), 127.8 (BTH, CH), 124.8 (BTH, CH), 124.7 (BTH, CH), 123.3 (C), 113.7 (2CH), 83.3 (C), 55.3 (methyl, CH_3), 51.4 (CH_2), 39.3 (CH_2), 28.6 (CH). $C_{21}H_{18}N_4O_5S_3$ m/z (TOF ES^-) 471.0 (M^+-OCH_3, 39%) 486.0 (M^+-NH_2, 67%), 502.0 (M^+, 100%), 523.7 (M + Na^+ -2H, 43%). HR/MS found M^+, 502.0437, $C_{21}H_{18}N_4O_5S_3$ [M^+] requires 502.0439.

4.2.2.7 6-(Benzo[d]thiazol-2-ylsulfonyl)-7-(2,4-dichlorophenyl)-8-nitro-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51h)

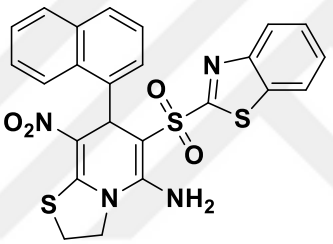


51h

Yellow powder, (82%); Mp 224-225 ˚C, Rf: 0.4, V̇max (ATR, cm^{-1}) 3461-3337 (NH, NH_2), 1619 (C=C), 1582, 1446, 1300 (asym. SO_2), 1227, 1120 (sym. SO_2). ^1H

NMR (500 MHz, DMSO) δ 8.17 (1H, d, BTZ Ar CH), 8.07 (1H, d, J = 9.4, BTH, CH), 7.66 – 7.55 (2H, m, BTH, 2CH), 7.46 (2H, s, NH_2), 7.33 (2H, d, J = 9.3, 2CH), 7.15 (1H, s, CH), 5.58 (1H, s, CH), 4.39 (2H ddt, J = 45.3, 11.4, 8.3, CH_2), 3.42 (2H, t, CH_2). ^{13}C NMR (125 MHz, DMSO) δ 169.9 (BTH, C), 158.3 (BTH, C), 152.2 (C), 150.7 (C), 139.2 (C), 136.3 (BTH, C), 134.2 (C), 134.2 (CH), 132.6 (CH), 129.0 (CH), 128.0 (CH), 127.9 (BTH, CH), 127.3 (BTH, CH), 124.7 (BTH, 2CH), 123.4 (C), 122.5 (C), 81.4 (C), 51.49 (CH_2), 38.8 (CH_2), 28.3 (CH). $C_{20}H_{14}Cl_2N_4O_4S_3$, 439.9 m/z (TOF ES^-), 324.1 (M^+-NH_2-sulfonyl benzothaizol, 100%), 510 (M^+- Cl^- + 3H, 19%) 564.6 (M ^{37}Cl + Na^+, 31%). HR/MS found M^+, 539.9559, $C_{20}H_{14}Cl_2N_4O_4S_3$ [M^+] requires 539.9554.

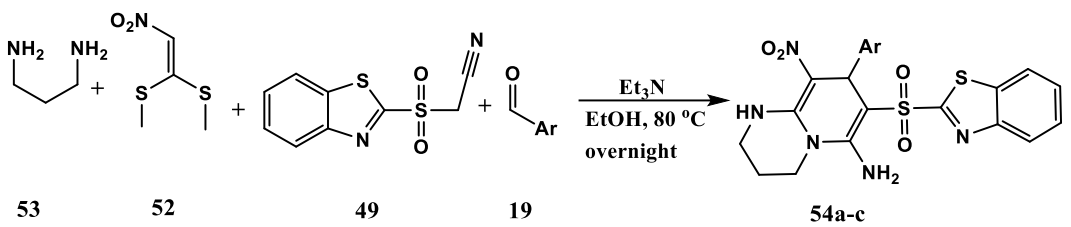
4.2.2.8 6-(Benzo[d]thiazol-2-ylsulfonyl)-7-(naphthalen-1-yl)-8-nitro-2,3-dihydro-7H-thiazolo[3,2-a]pyridin-5-amine (51i)



51i

Yellow powder, (74%); M.P. 220-221 ˚C, Rf: 0.4, V̇max (ATR, cm^{-1}) 3458-3337 (NH, NH_2), 1620 (C=C), 1587, 1409, 1311 (asym. SO_2), 1229, 1156 (sym. SO_2). ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (1H s,BTH CH), 8.31 – 8.23 (2H m, 2xBTH CH), 8.07 (1H d, *J* = 9.9, BTH CH), 7.94 (1H s, CH), 7.82 (1H d, *J* = 10.3, CH), 7.70 (2H s, NH_2), 7.65 – 7.55 (2H s, 2CH), 7.34 (1H s, CH), 6.90 (1H d, *J* = 8.9, CH), 6.29 (1H s, CH), 4.74 (1H s, CH), 4.68 – 4.58 (1H m, CH), 4.30 – 4.20 (1H m,), 3.30 – 3.05 (1H m, CH). ^{13}C NMR (125 MHz, DMSO) δ 170.0 (BTH, C), 157.0 (BTH, C), 152.2 (C), 150.3 (C), 141.9 (C), 136.2 (2CH), 133.2 (C), 131.2 (CH), 128.3 (CH), 127.8 (CH), 127.8 (CH), 127.2 (CH), 126.1 (C), 125.8 (2CH), 125.0 (CH), 124.7 (CH), 123.2 (C), 122.2 (C), 84.8 (C), 51.56 (CH_2), 35.0 (CH_2), 28.5 (CH). $C_{24}H_{18}N_4O_4S_3$ m/z (TOF ES^-) 505.9 (M^+-NH_2, 57%), 522.1 (M^+, 100%), 545.2 (M + Na^+, 36%). HRMS found M^+, 522.0487, C24H18N4O4S3 [M^+] requires 522.0490.

4.3 Synthesis of Benzothiazole Sulfonyl Pyrido[1,2-a]Pyrimidine Derivatives.



53 52 49 19 54a-c

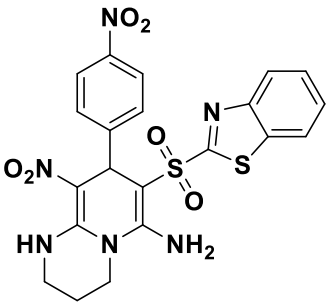
Scheme 4.3.1 Formation of Pyrido[1,2-a]Pyrimidine derivatives **54a, 54b** and **54c**

4.3.1 Procedure for the Formation of Benzothiazole Sulfonyl Pyrido[1,2-a]Pyrimidine Derivatives 54a, 54b and 54c

2-Nitroethene-1,1-diyl-bis(methylsulfane) **52** (1.0 mmol, 165.23 mg) refluxed with propane-1,3-diamine **53** (1.1 eq., 1.1 mmol, 81.54 mg) in ethanol. To this mixture 2-(benzo[d]thiazol-2-ylsulfonyl) acetonitrile **49** (1.0 eq., 1.0 mmol, 238.28 mg) and an aromatic aldehyde **19** (1.0 eq., 1.0 mmol) were added in dry ethanol in the presence of triethylamine (0.5 eq., 0.5 mmol, 50 mg) and the reaction left to reflux for overnight. The progress of the reaction was monitored by TLC. The product collected by filtrating the solid and washing it with a minimal amount of cold ethanol and dried under vacuum pressure to send for analysis.

4.3.2. Pyrido[1,2-a]pyrimidin-6-amine derivatives

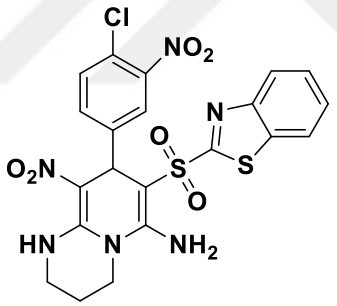
4.3.2.1 7-(Benzo[d]thiazol-2-ylsulfonyl)-9-nitro-8-(4-nitrophenyl)-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrimidin-6-amine (54a)



54a

Lemon yellow powder, (64%); Mp 220-221 ˚C, V̄max (ATR, cm^{-1}) 3443-3347 (NH, NH_2), 3074, 3063, 2989, 2875 (aliphatic CH), 1340 (asym. SO_2), 1123 (sym. SO_2). ^1H NMR (500 MHz, DMSO) δ 11.24 (1H s, NH), 8.20 (1H d, BTH, CH), 8.09 (1H d, BTH, CH), 8.01 (2H d, 2CH), 7.66 – 7.56 (2H m, BTH, 2CH), 7.46 (2H d, 2CH), 7.42 (2H s, NH_2), 5.44 (1H s, CH), 3.90 (2H d, J = 12.7, CH_2), 3.83 (2H td, J = 11.9, 4.5, CH_2), 3.59 (2H d, J = 9.1, CH_2). ^{13}C NMR (125 MHz, DMSO) δ 169.7 (BTH, C), 152.5 (BTH, C), 152.3 (C), 151.5 (C), 150.4 (C), 146.5 (C), 136.3 (BTH, C), 129 (2CH), 128 (BTH, CH), 124 (BTH, CH), 123.7 (2CH), 123.5 (BTH, 2CH), 109.0 (C), 81 (C), 44.2 (CH_2), 39 (CH_2), 37.9 (CH_2), 20.2 (CH). $C_{21}H_{18}N_6O_6S_2$ m/z (TOF ES^-) 468.7 (M^+-NO_2, 15%) 498.6 (M^+-NH_2, 100%), 515.1 (M^+H, 37%), 438.2 (M + Na^+, 29%). HR/MS found M^+, 514.0728, $C_{21}H_{18}N_6O_6S_2$ [M^+] requires 514.0729.

4.3.2.2 7-(Benzo[d]thiazol-2-ylsulfonyl)-8-(4-chloro-3-nitrophenyl)-9-nitro-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrimidin-6-amine (54b).

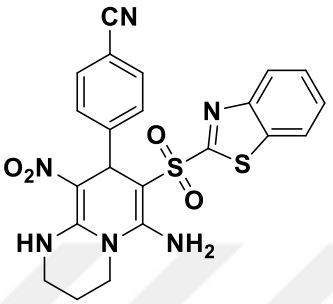


54b

Beige powder, (55%); Mp 215-216 ˚C, V̄max (ATR, cm^{-1}) 3387-3340 (NH, NH_2), 3220 (NH),1528 (NO_2) 1341 (asym. SO_2), 1136 (sym. SO_2). ^1H NMR (500 MHz, DMSO) δ 11.26 (1H s, NH), 8.20 (1H d, J = 8.4, BTH, CH), 8.08 (1H d, J = 8.8, BTH, CH), 7.74 (1H s, CH), 7.67 – 7.56 (2H m, BTH, 2CH), 7.52 (2H s, NH_2), 7.44 (2H s, CH), 5.38 (1H s, CH), 3.85 (2H d, J = 25.8, CH_2), 3.60 (2H s, CH_2), 2.00 (2H d, J = 143.5, CH_2). ^{13}C NMR (125 MHz, DMSO) δ 169.6 (BTH, C), 152.6 (BTH, C), 152.4 (C), 150.3 (C), 147.5 (C), 145.0 (C), 136.2 (CH), 133.2 (BTH, C), 131.7 (CH), 128.1 (CH), 128.0 (C), 124.8 (BTH, CH), 124.4 (BTH, CH), 123.6 (BTH, CH), 123.5 (BTH, CH), 110.0 (C), 80.5 (C), 44.4 (CH_2), 39.07 (CH_2), 37.51 (CH_2), 20.09 (CH). $C_{21}H_{17}ClN_6O_6S_2$ m/z (TOF ES^-) 531.8 (M^+-NH_2, 100%), 548.6 (M^+,

86%), 572.1 (M+ Na^+,32%). HR/MS found M^+, 548.0330, $C_{21}H_{17}ClN_6O_6S_2$ [M^+] requires 548.0339.

4.3.2.3 4-(6-Amino-7-(benzo[d]thiazol-2-ylsulfonyl)-9-nitro-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrimidin-8-yl)benzonitrile (54c).



54c

Light lemon-yellow powder, (54%); Mp 216-217 ˚C, V̄max (ATR, cm^{-1}) 3440-3347 (NH, NH_2), 2232 (CN), 1609, 1348 (asym. SO_2), 11125 (sym. SO_2). ^{1}H NMR (500 MHz, DMSO) δ 11.23 (1H s, NH), 8.20 (1H d, *J* = 9.0 Hz, BTH, CH), 8.09 (1H d, *J* = 9.0,BTH, CH), 7.65 (2H m, BTH, 2CH), 7.60 (2H d, 2CH), 7.38 (2H *J* = 8.7 d, 2CH), 7.34 (2H s,NH_2), 5.41 (1H s, CH), (2H 4.06 – 3.79 m, CH_2), 3.60 (2H d, *J* = 17.7,CH_2), 2.01 (2H d, *J* = 146.1,CH_2). ^{13}C NMR (125 MHz, DMSO) δ 169.8 (BTH, C), 152.5 (BTH, C), 152.4 (C), 150.4 (C), 149.5 (C), 136.3 (BTH, C), 132.5 (2CH), 128.7 (2CH), 128.0 (BTH, CH), 128 (BTH, CH), 124.8 (BTH, CH,), 123.6 (BTH, CH), 119.3 (C), 109.6 (C), 109.1 (C), 81.0 (C), 44.1 (CH2), 39.0 (CH_2), 38.1 (CH_2), 20.2 (CH). $C_{22}H_{18}N_6O_4S_2$ m/z (TOF ES^-) 493.4 (M^+, 67%) 477.4 (M^+-NH_2, 100%). HR/MS found M+, 494.0837, $C_{22}H_{18}N_6O_4S_2$ [M+] requires 494.0830.

5. CONCLUSIONS

The objective of this study is to discover new and active scaffolds by combining highly active functional groups, such as benzothiazole, sulfonyl group, nitro-containing compounds, thiazolidine, pyrimidine, and pyridine rings. Finding a facile pathway to obtain a large molecule containing this complex combination that has high expected biological effects is considered essential in the pharmaceutical field.

In this particular investigation, we have successfully synthesized derivatives of benzothiazole sulfonyl thiazolo[3,2-a]pyridine, as well as pyrido[1,2-a]pyrimidine, obtained by a reaction of benzothiazole sulfonyl acetonitrile, 2-nitromethylene thiazolidine, (2-nitroethene-1,1-diyl)bis(methylsulfane), propane-1,3-diamine and various aromatic aldehyde derivatives.

Multi-component reactions played the main role in this work due to their ability to accept the various functional groups easily and these MCRs developed built upon Knoevenagel condensation and Michael addition reaction in both three and four-component reactions.

By using mild conditions, the dryness of solvent plays a key role in increasing yield, and TEA as a base. The products were confirmed through determination measurements, including, the purity of the compounds that had been checked using TLC, and found as one spot, while each compound has a distinct Retention factor and distinct melting point, then measuring FT-IR giving an initial overview of the authenticity of the compounds, ^{1}H-NMR, analysis confirming the number of hydrogens associated in the molecule structure while ^{13}C-NMR enables more detailed structural characterization of the carbons in the molecule, LC-MS, and HR-MS were used to verify the molar masses of each sample. The products obtained moderate to high yields with just washing from cold ethanol.

The eleven compounds demonstrated promising to moderate antibacterial, anti-tuberculosis, and antifungal activities. Against Gram-positive and Gram-negative bacteria, the compounds exhibited MIC values ranging from 62.5 to 500 μg/mL, with **51d**, **51f**, **54b**, and **54c** showing notable activity at 62.5 μg/mL. For Mycobacterium tuberculosis H37Rv, the compounds displayed moderate activity (31.5 to 62.5 μg/mL), with **51d**, **51c**, **51g**, **54b**, and **54c** being the most effective. Antifungal tests against Candida species revealed MIC values of 62.5 to 125 μg/mL,

with **51a**, **51c**, **51d**, **51i**, and **54b** showing significant activity. However, these molecules' biological targets and modes of action are currently unknown. These results suggest compounds are promising candidates to enhance properties and pharmaceutical validity they can be subject to further researches.

6. APPENDICES

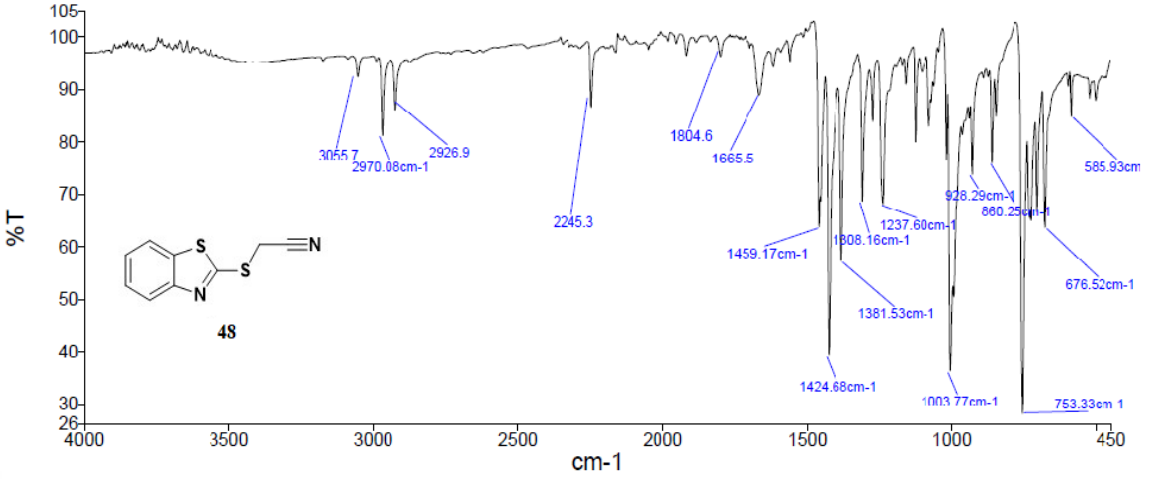


Figure 6.1 FT-IR data for the **48** compound

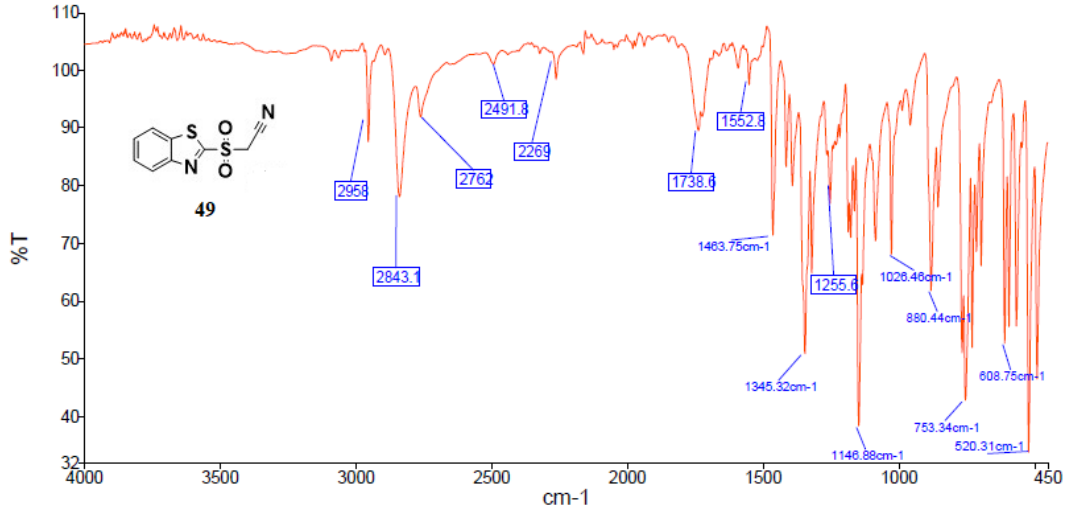


Figure 6.2 FT-IR data for the **49** compound

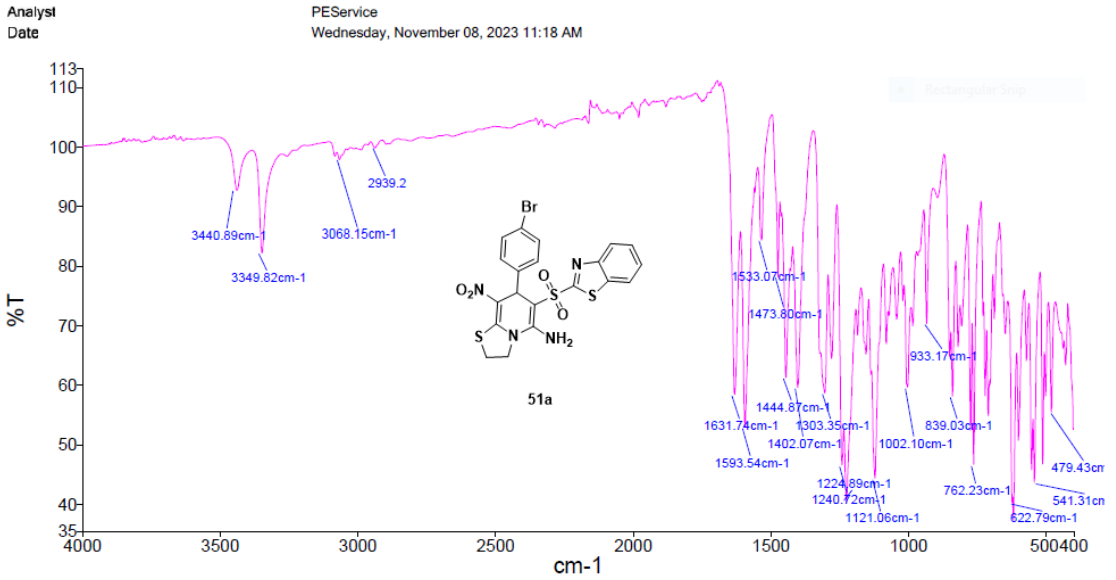


Figure 6.3 FT-IR data for the **51a** compound

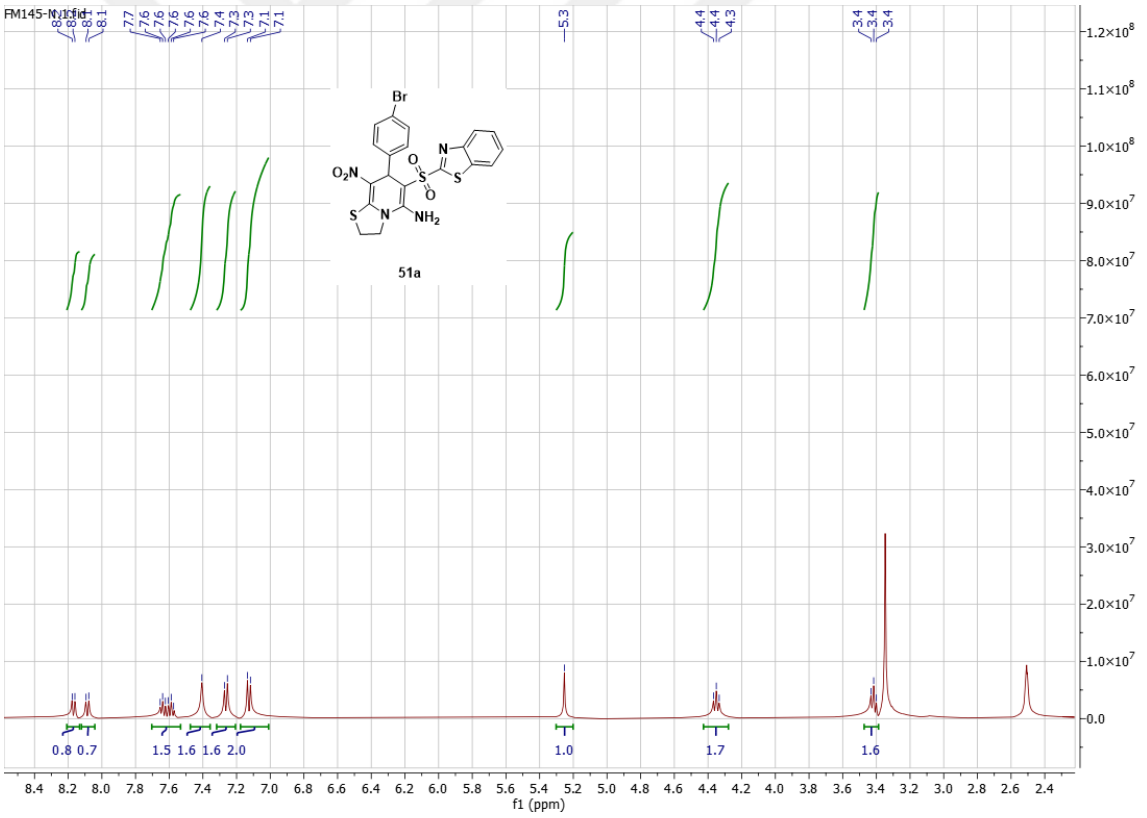


Figure 6.4 ^{1}H NMR data for the **51a** compound

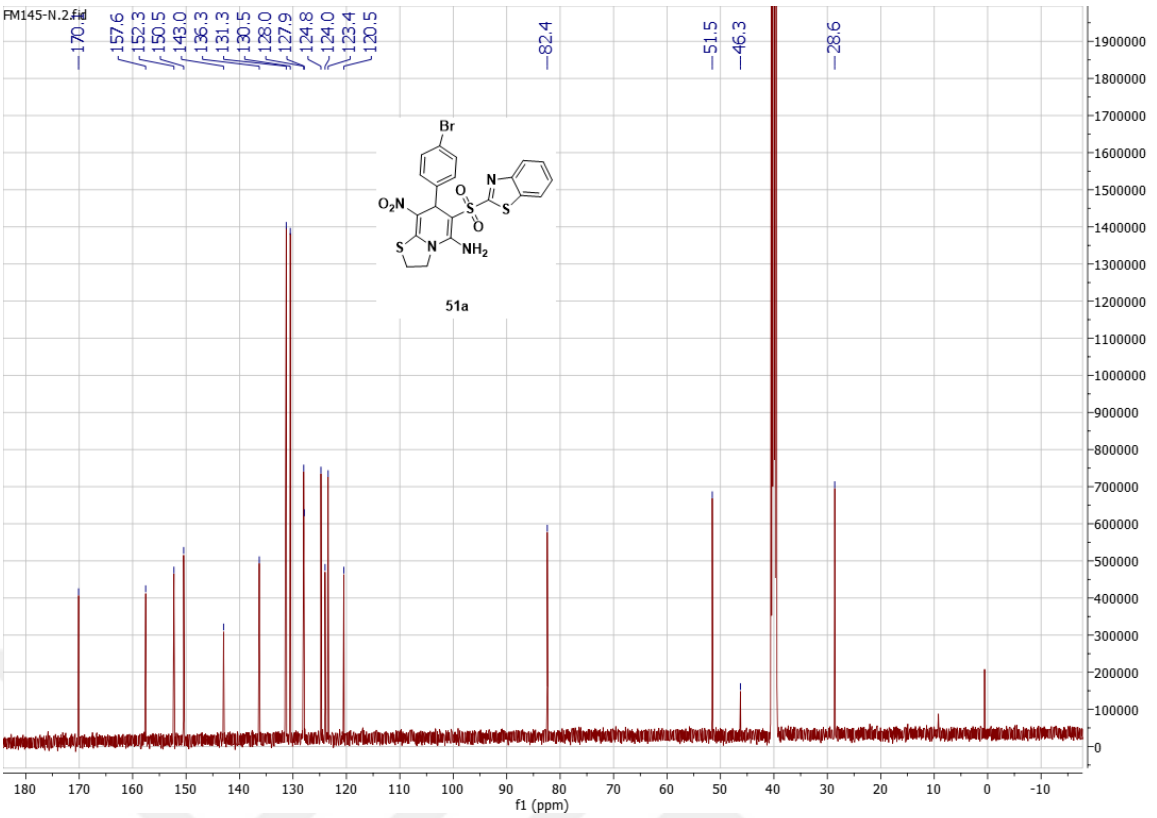


Figure 6.5 ^{13}C NMR data for the **51a** compound

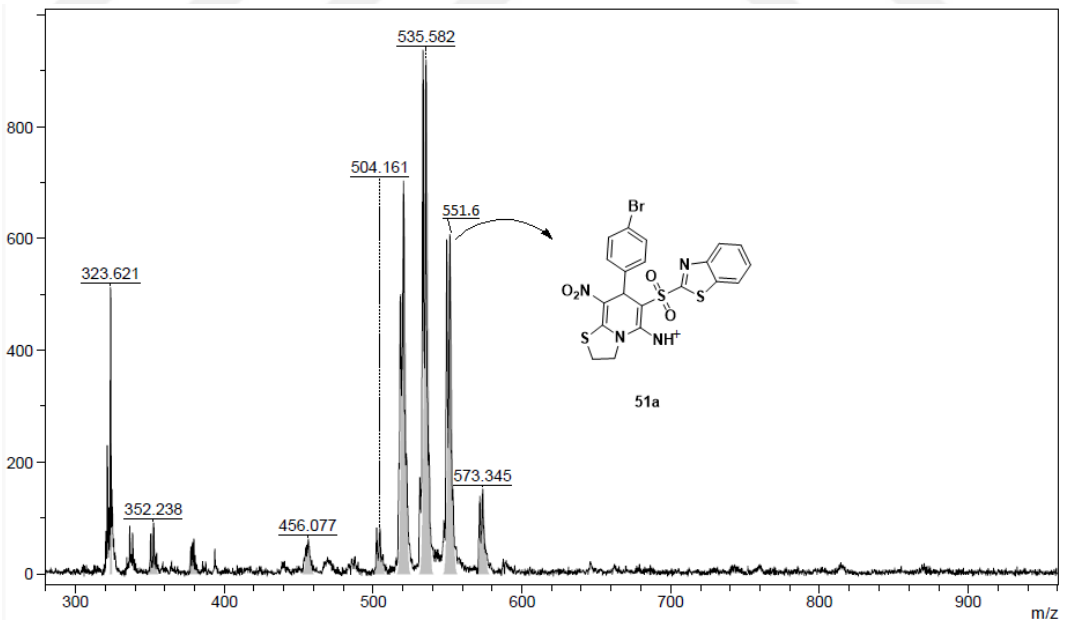


Figure 6.6 LC/MS data for the **51a** compound

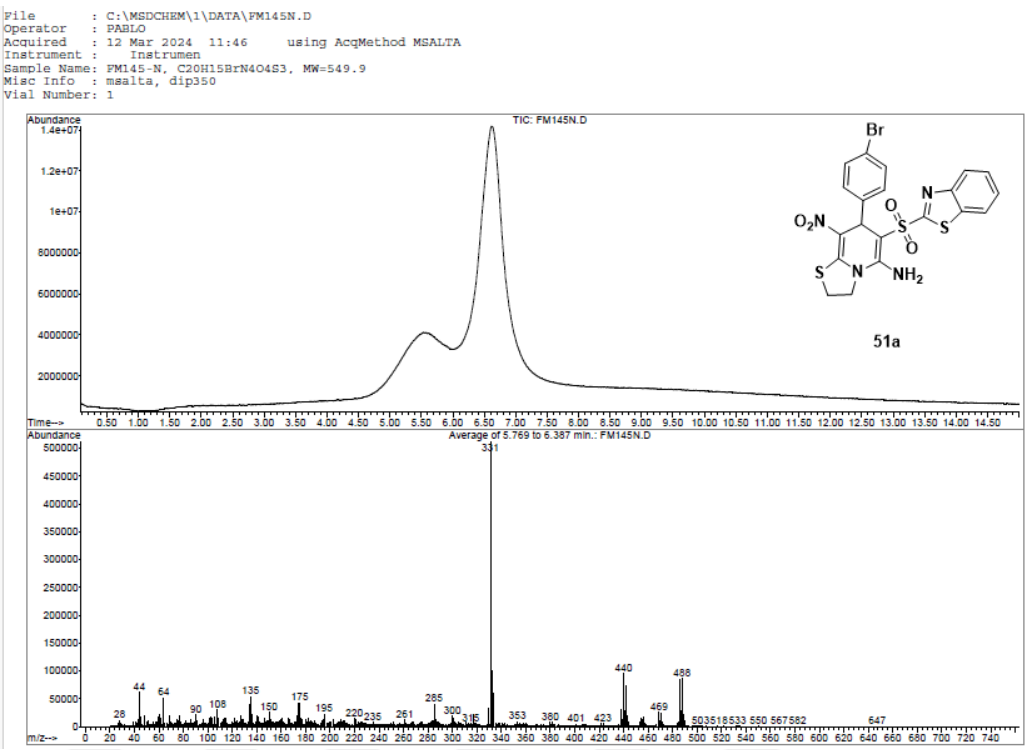
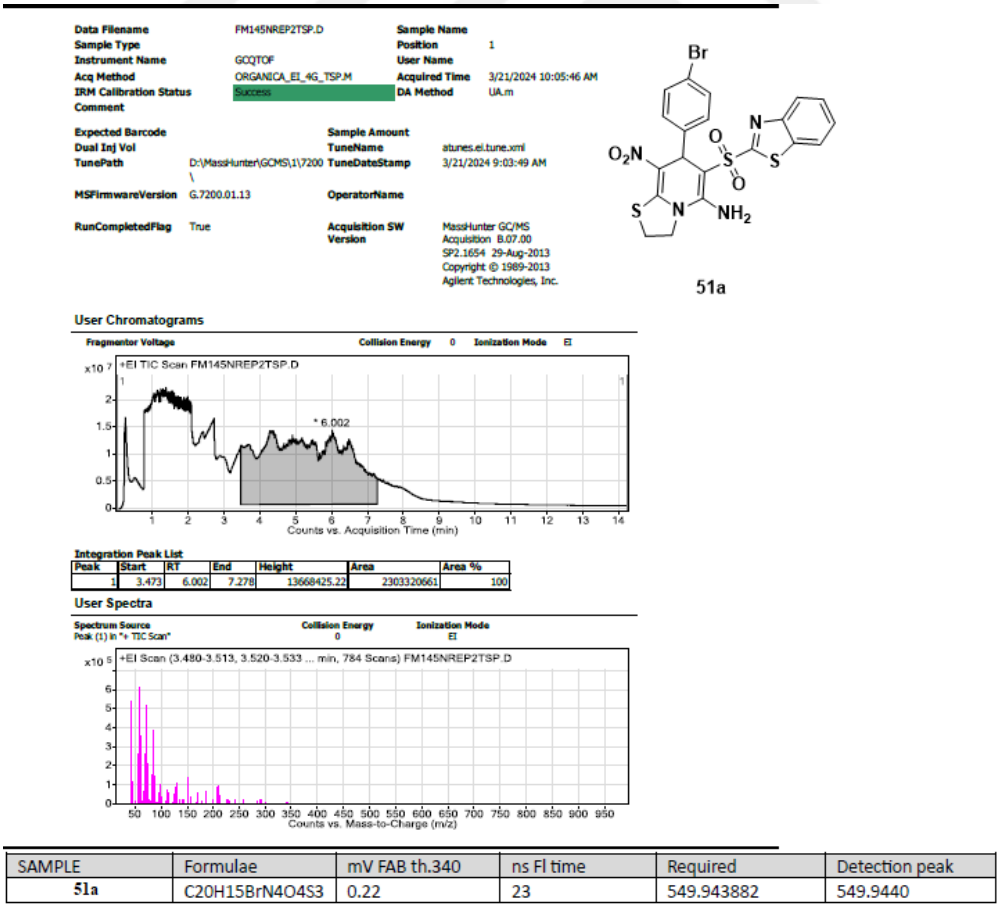


Figure 6.7 HR/MS data for the **51a** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
51a	C20H15BrN4O4S3	0.22	23	549.943882	549.9440

Figure 6.8 HR/MS report for the **51a** compound

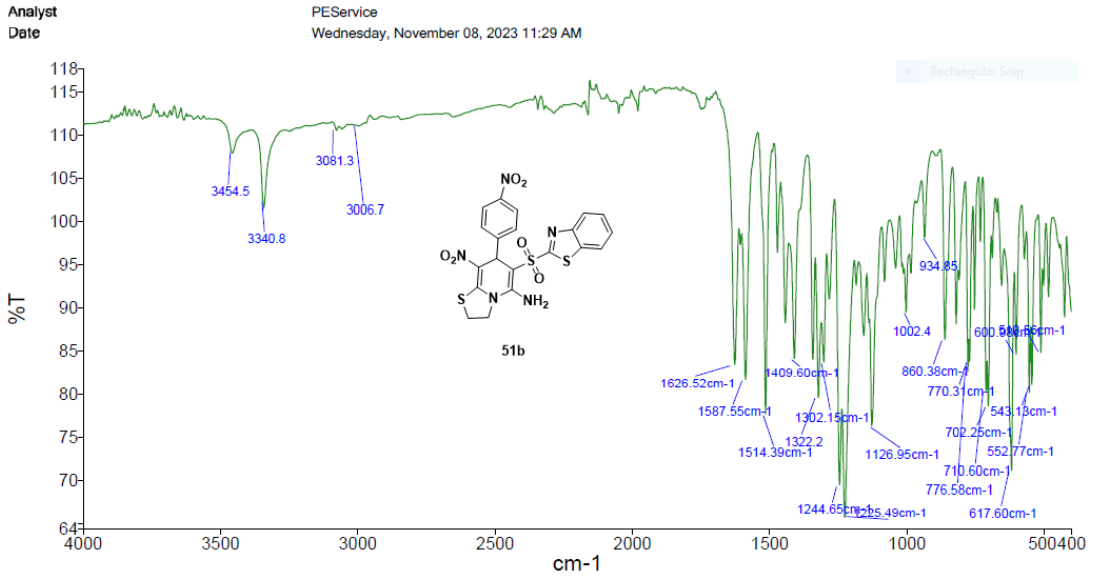


Figure 6.9 FT-IR data for the **51b** compound

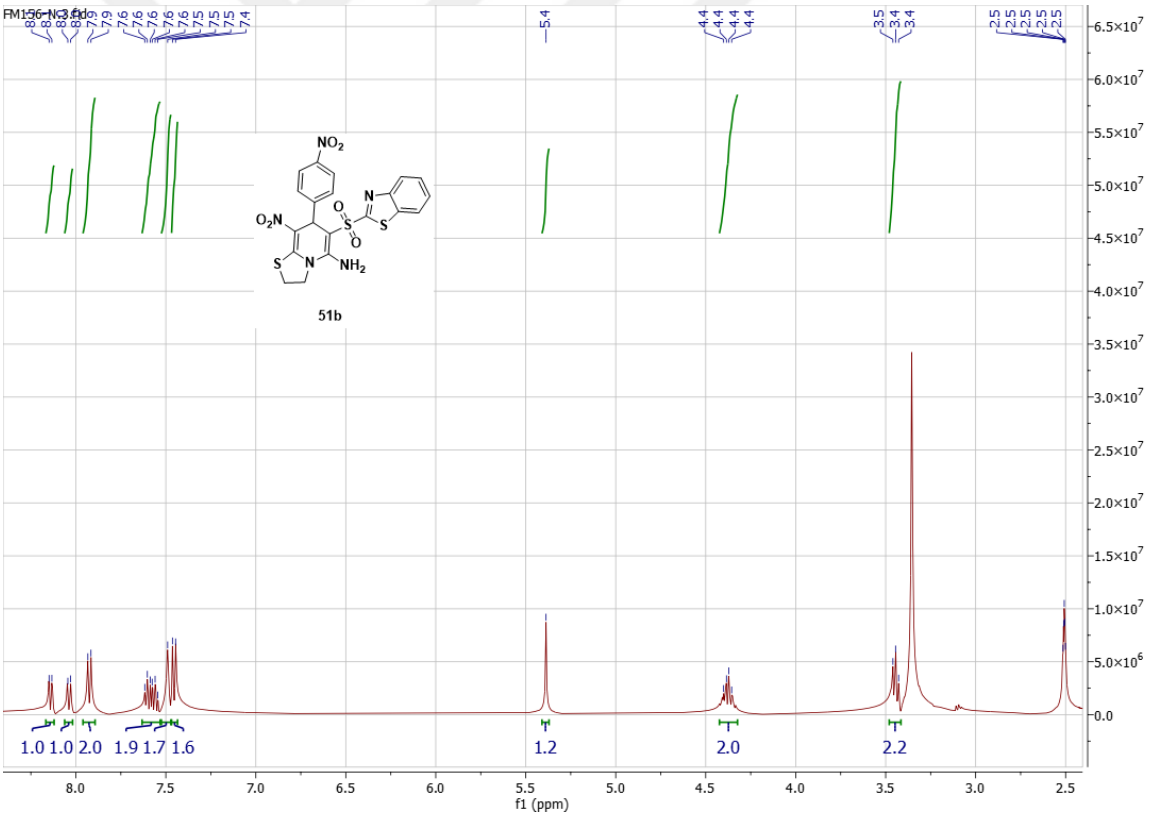


Figure 6.10 ^{1}H NMR data for the **51b** compound

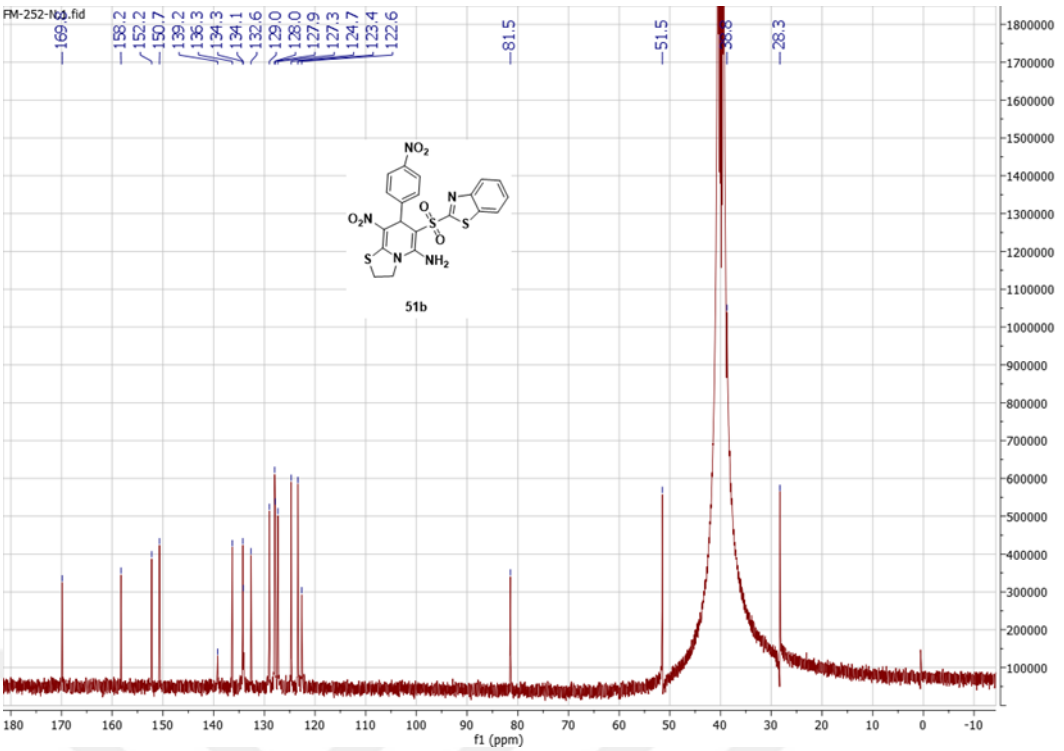


Figure 6.11 ^{13}C NMR data for the **51b** compound

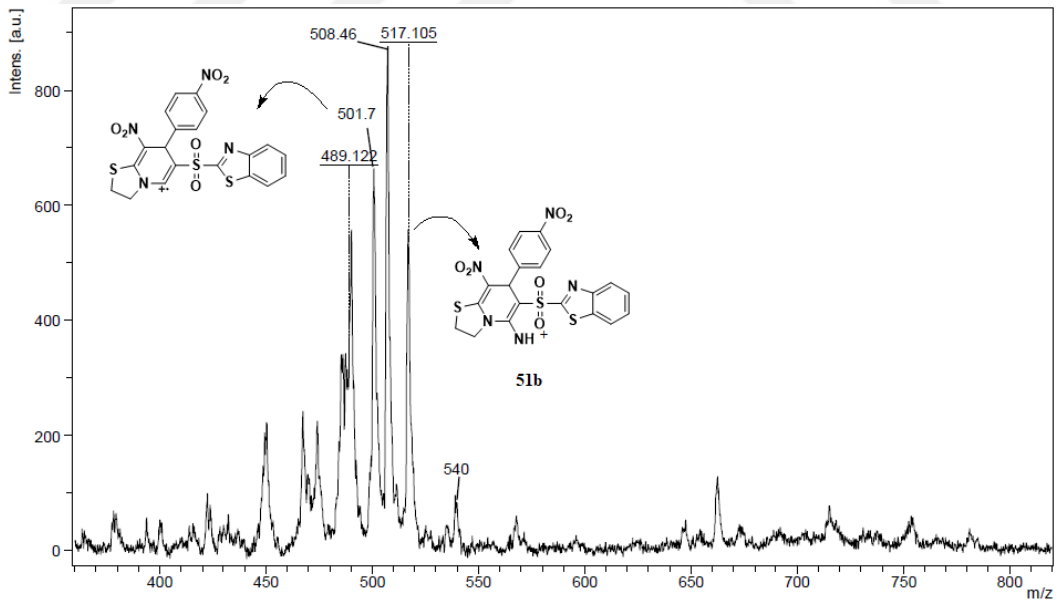


Figure 6.12 LC/MS data for the **51b** compound

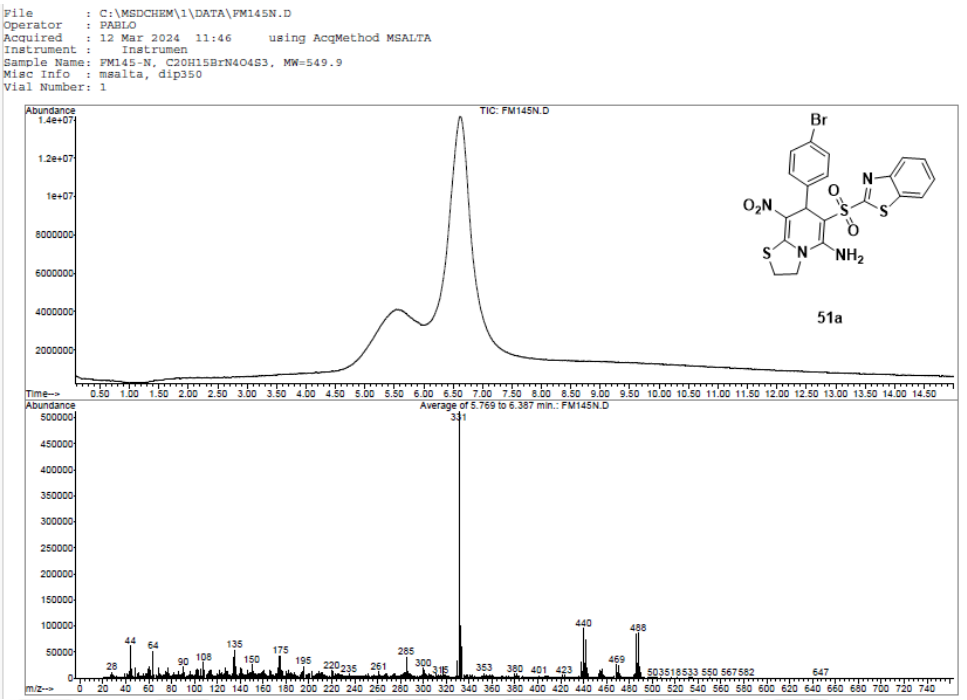
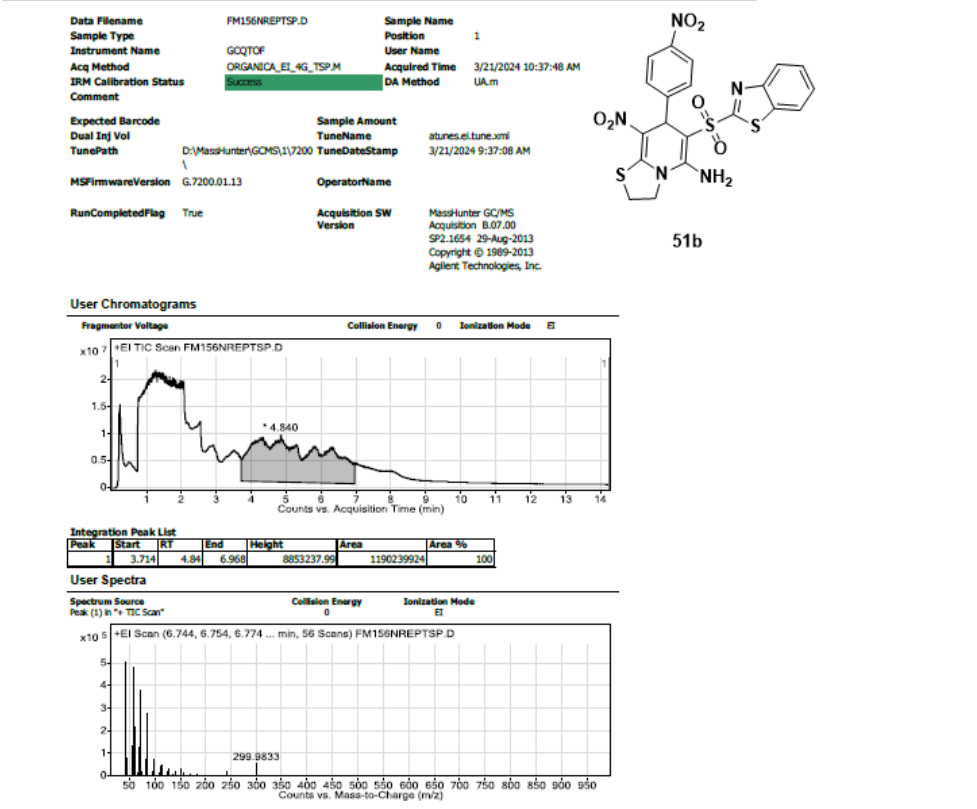


Figure 6.13 HR/MS data for the **51b** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
51b	C20H15N5O6S3	0.20	13	517.018451	517.0189

Figure 6.14 HR/MS report for the **51b** compound

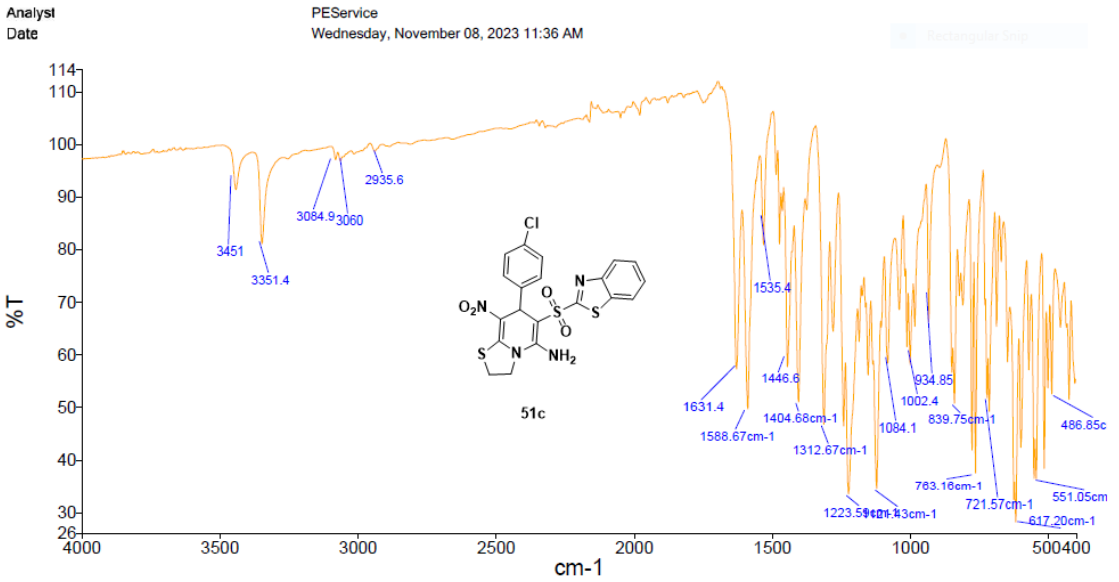


Figure 6.15 FT-IR data for the **51c** compound

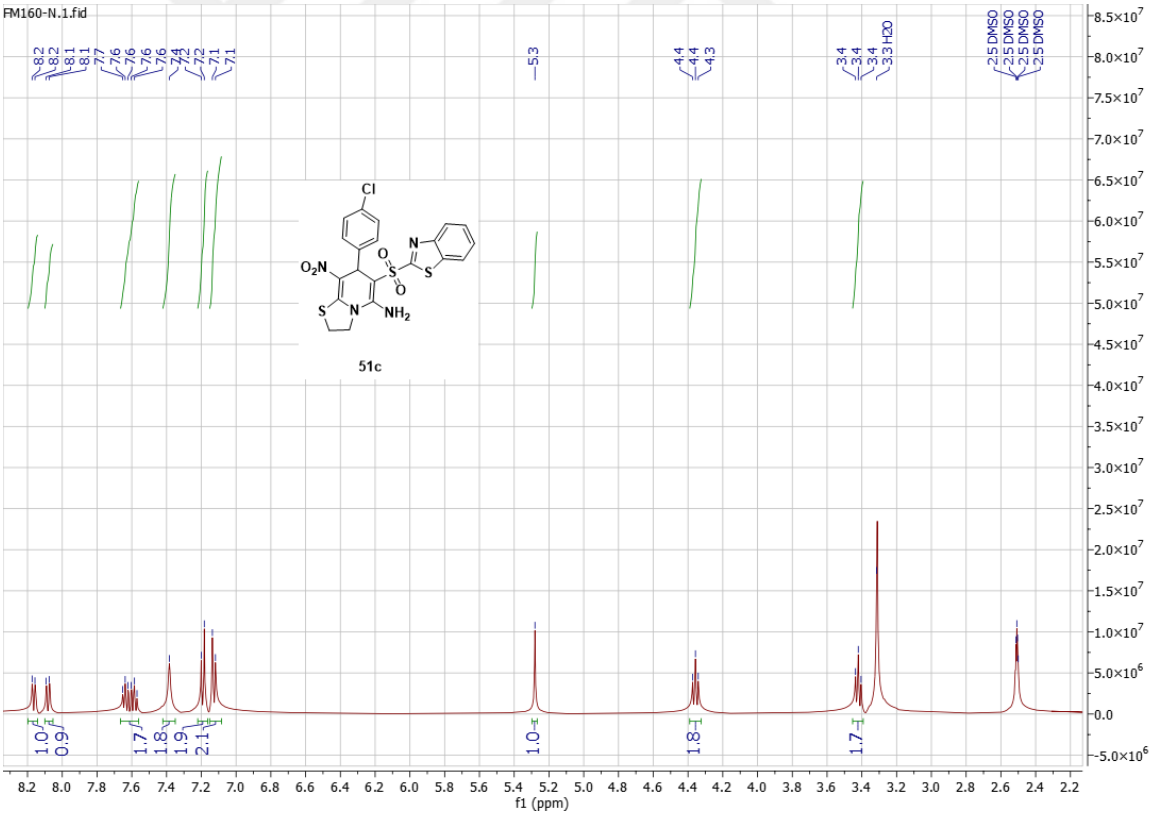


Figure 6.16 ^{1}H NMR data for the **51c** compound

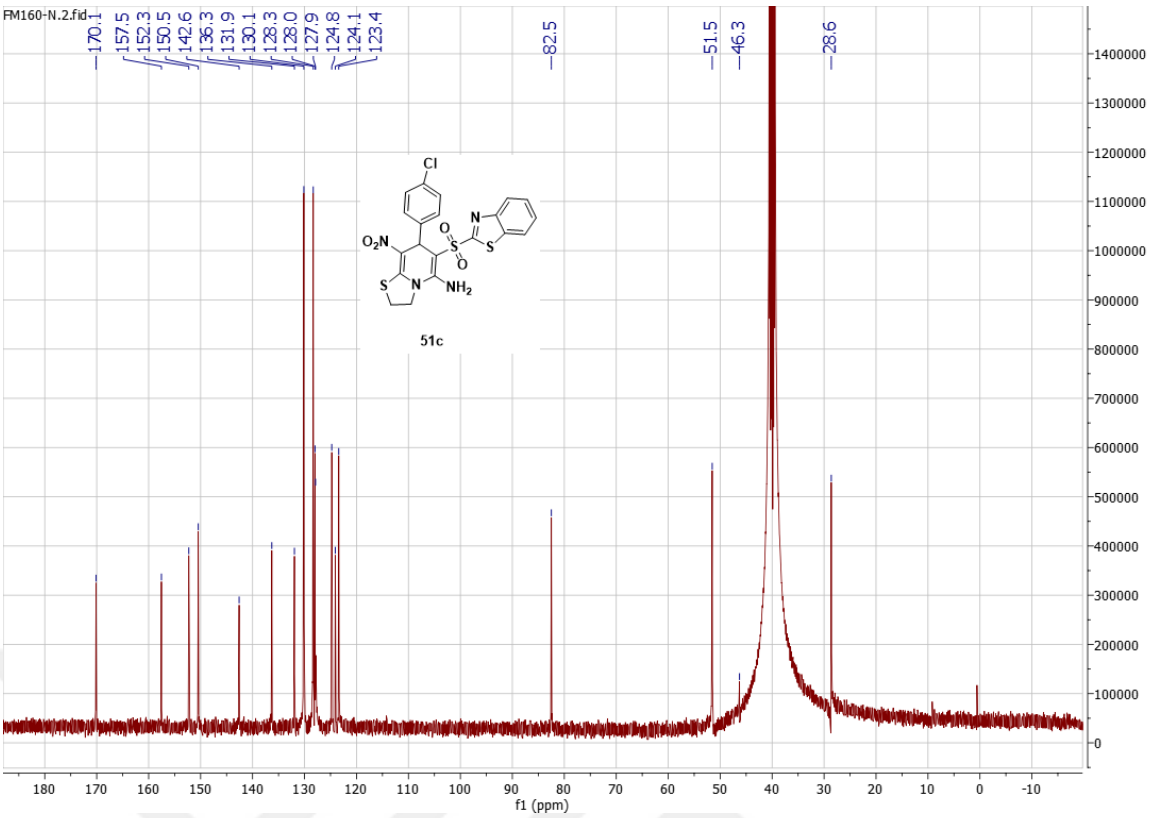


Figure 6.17 ^{13}C NMR data for the **51c** compound

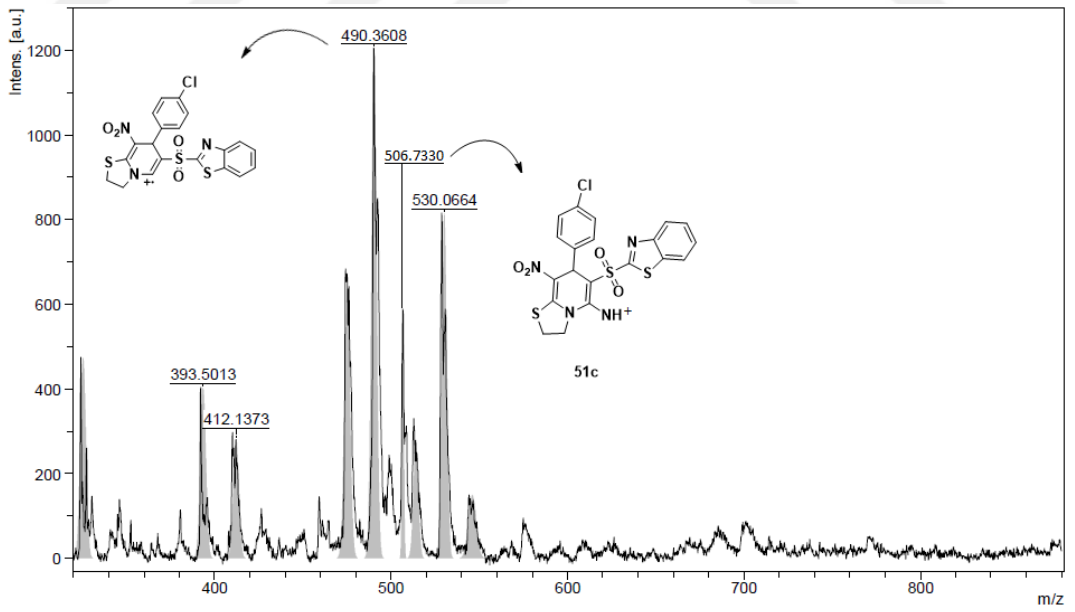


Figure 6.18 LC/MS data for the **51c** compound

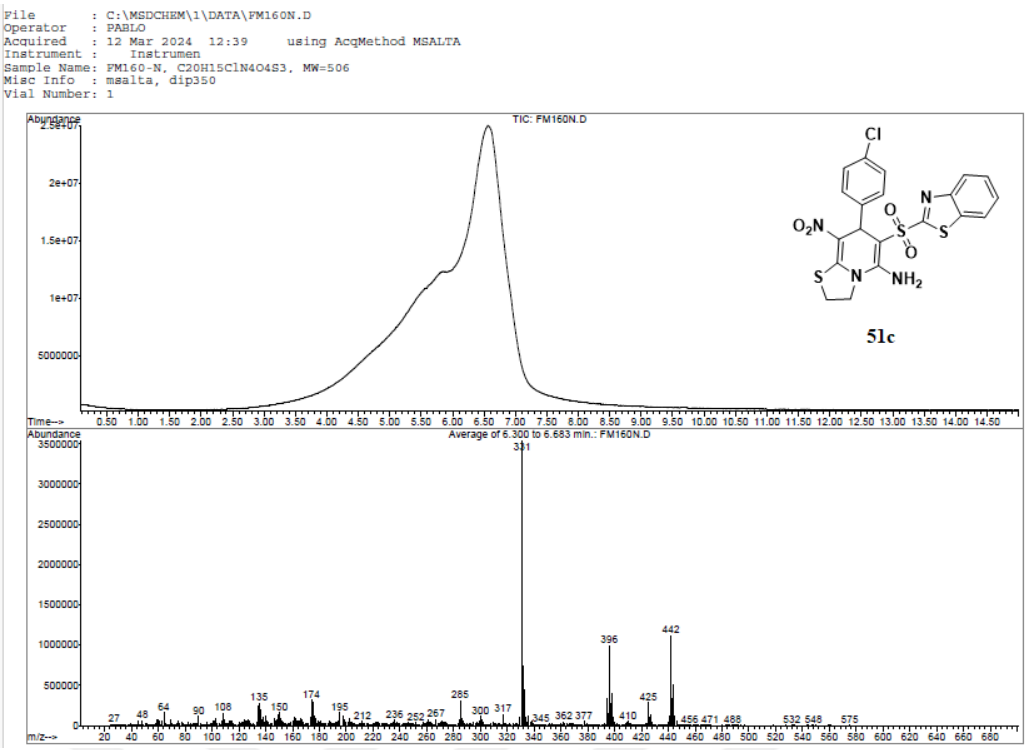
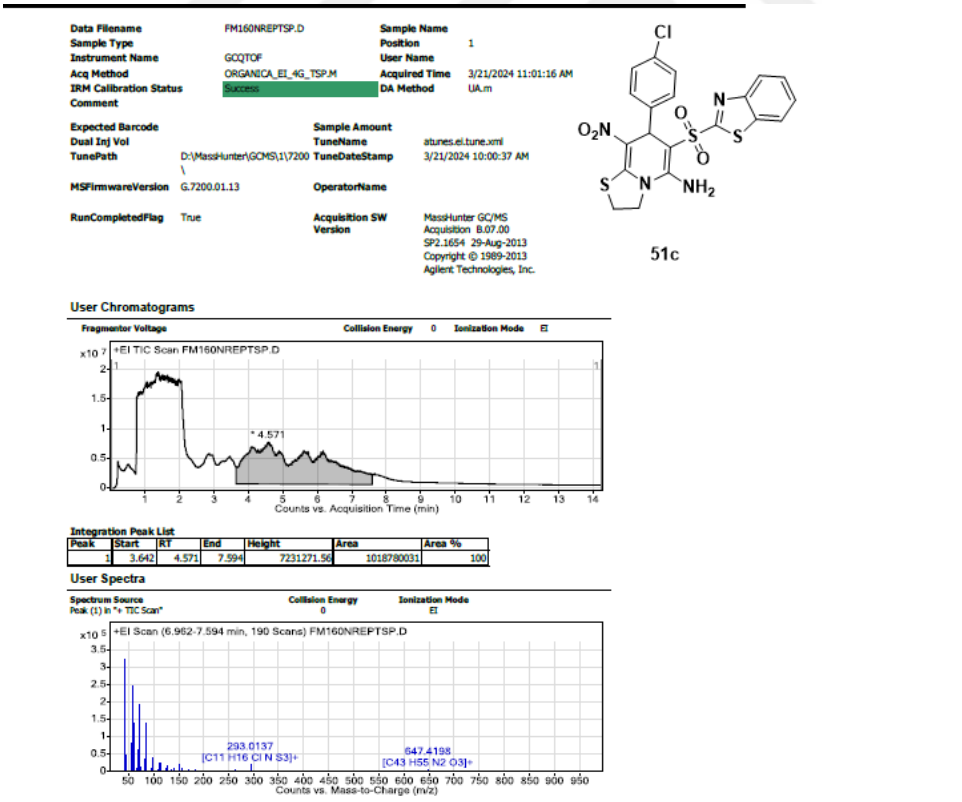


Figure 6.19 HR/MS data for the **51c** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
51c	C20H15ClN4O4S3	0.20	43	505.994400	505.9939

Figure 6.20 HR/MS report for the **51c** compound

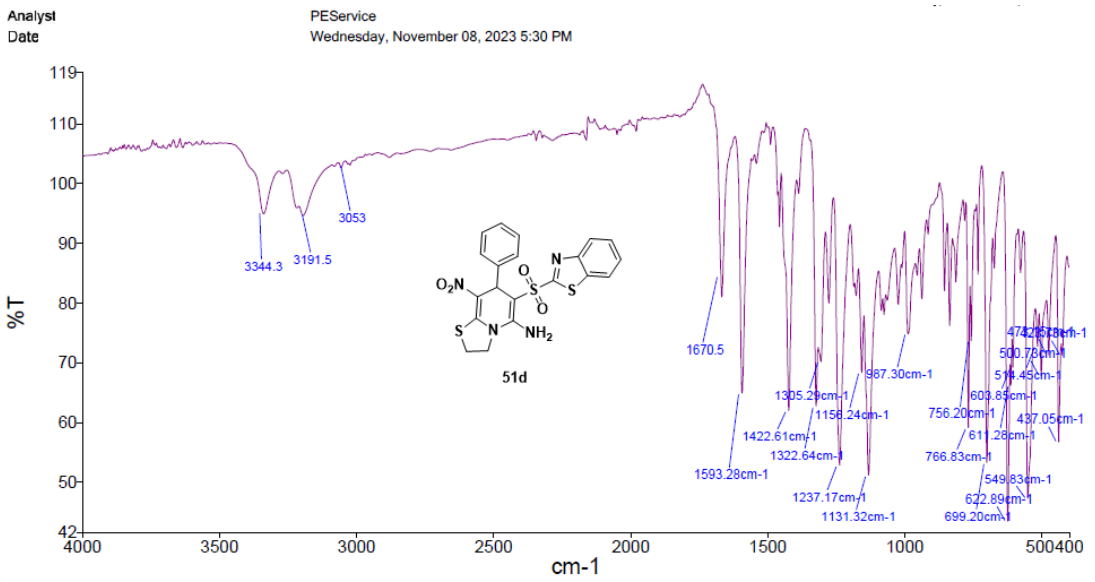


Figure 6.21 FT-IR data for the **51d** compound

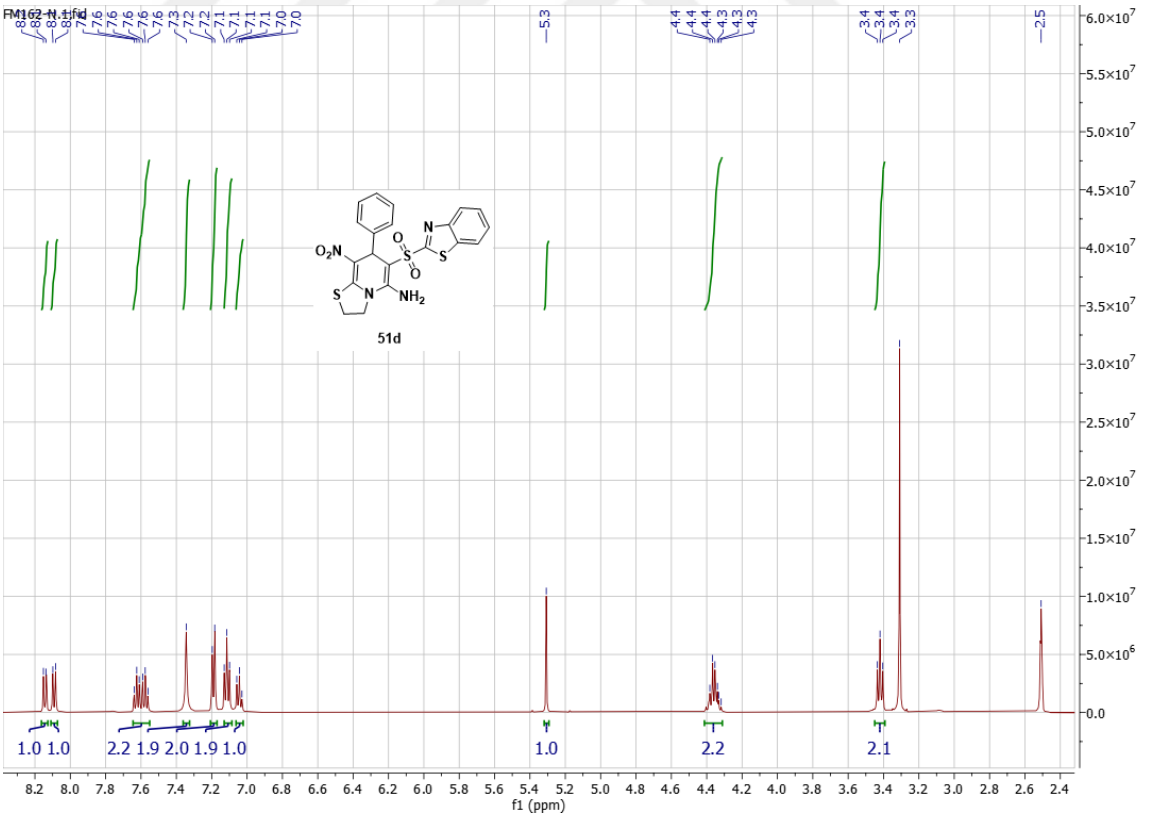


Figure 6.22 ^{1}H NMR data for the **51d** compound

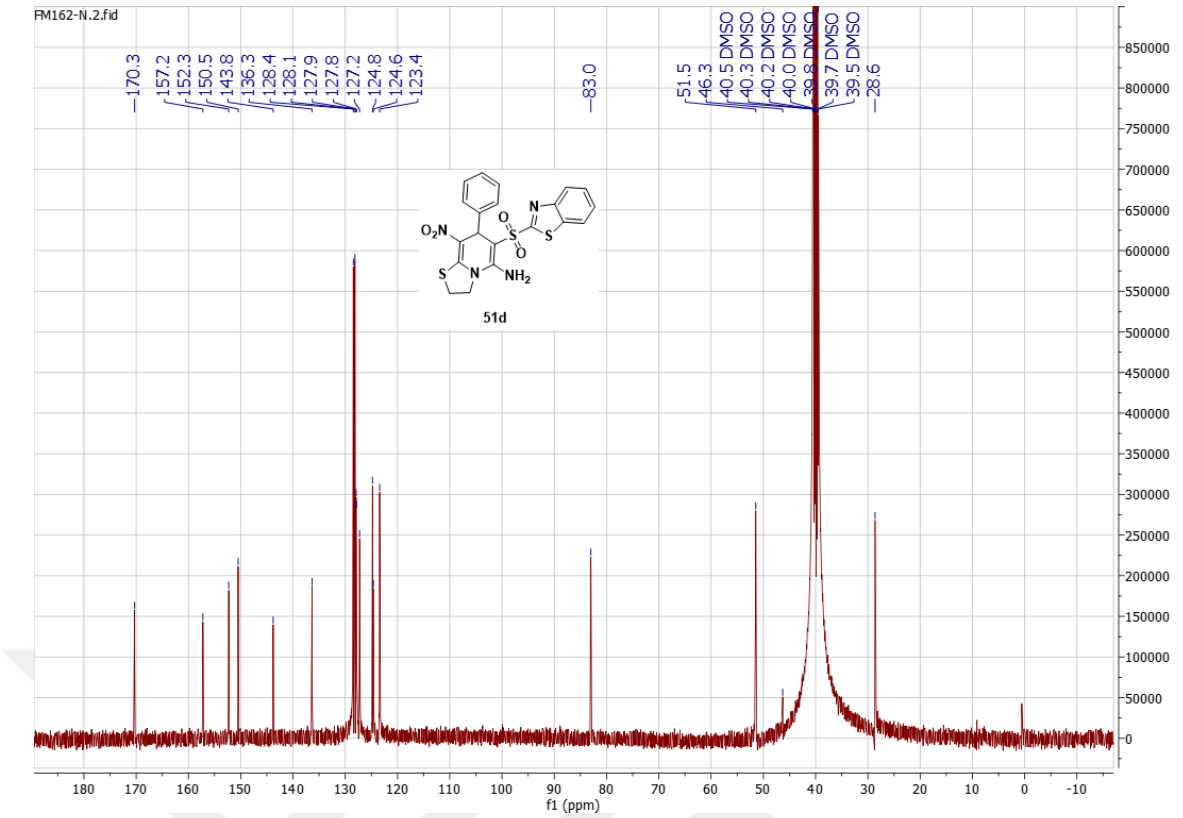


Figure 6.23 ^{13}C NMR data for the **51d** compound

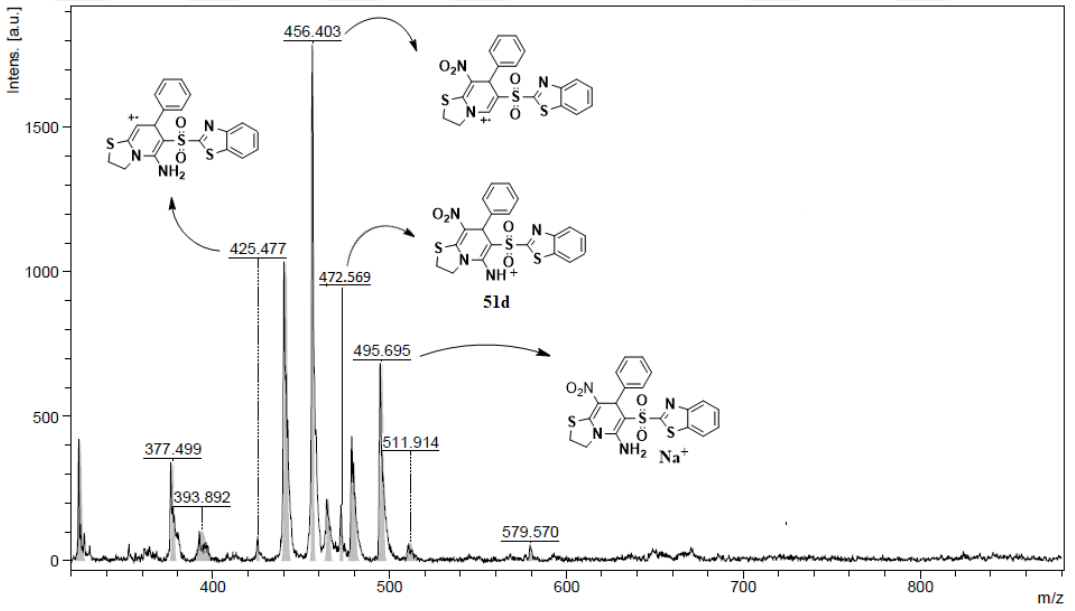


Figure 6.24 LC/MS data for the **51d** compound

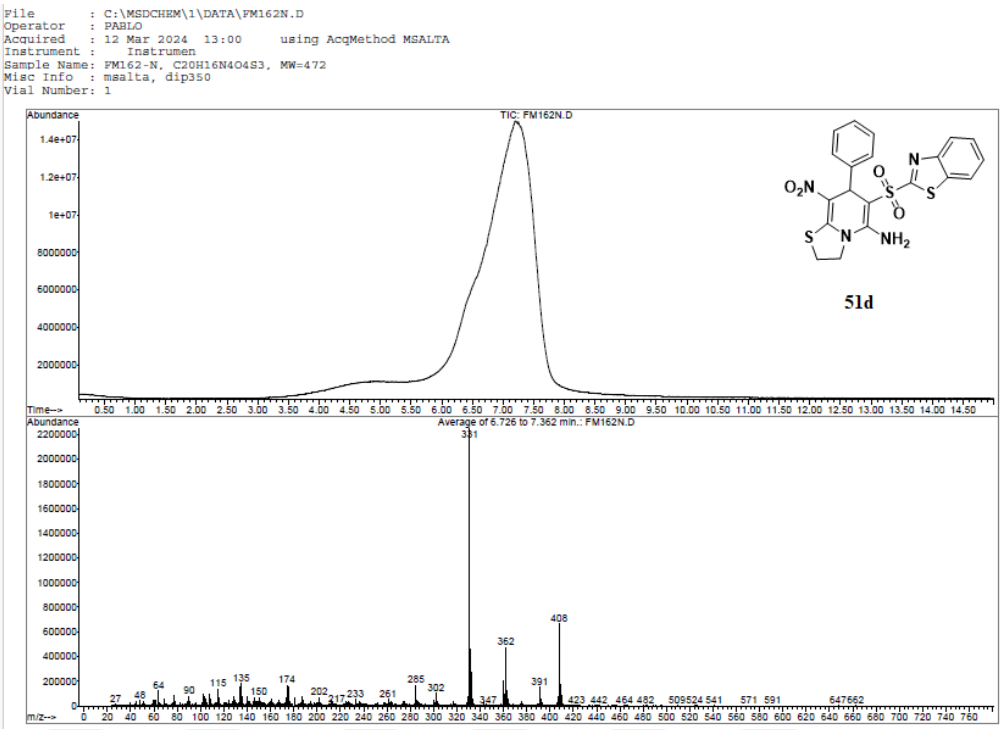
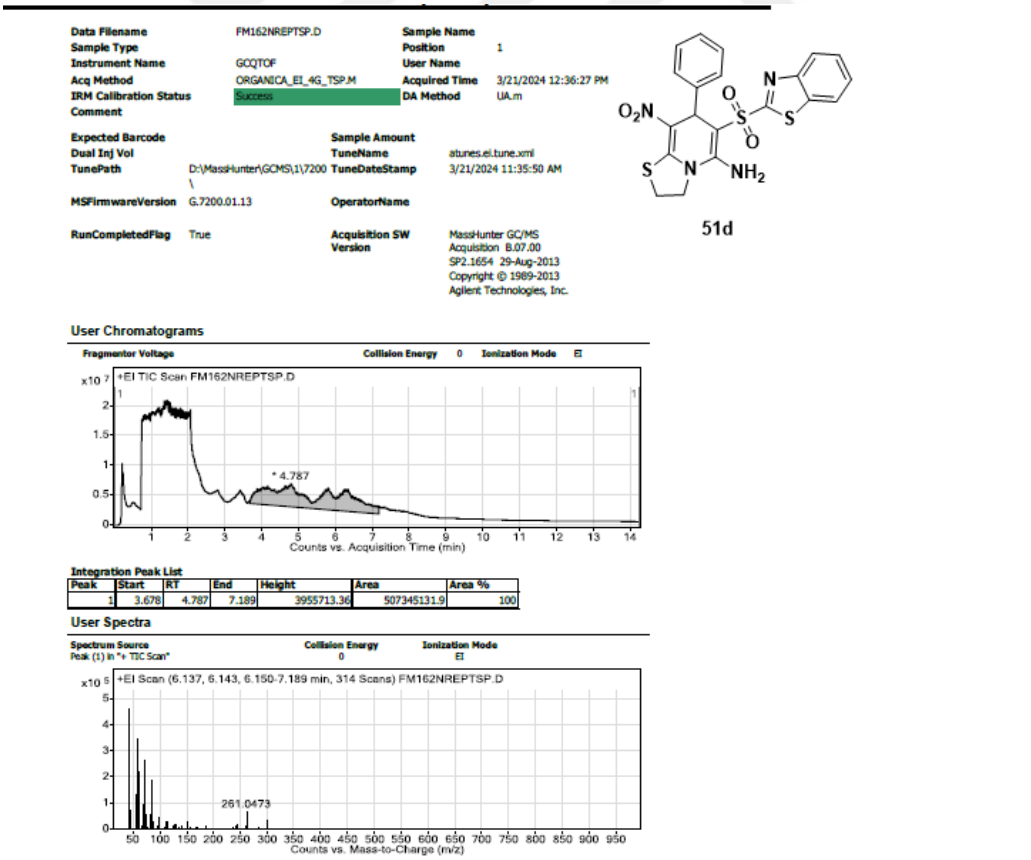


Figure 6.25 HR/MS data for the **51d** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
FM 162-N	C20H16N4O4S3	0.30	33	472.033372	472.0339

Figure 6.26 HR/MS report for the **51d** compound

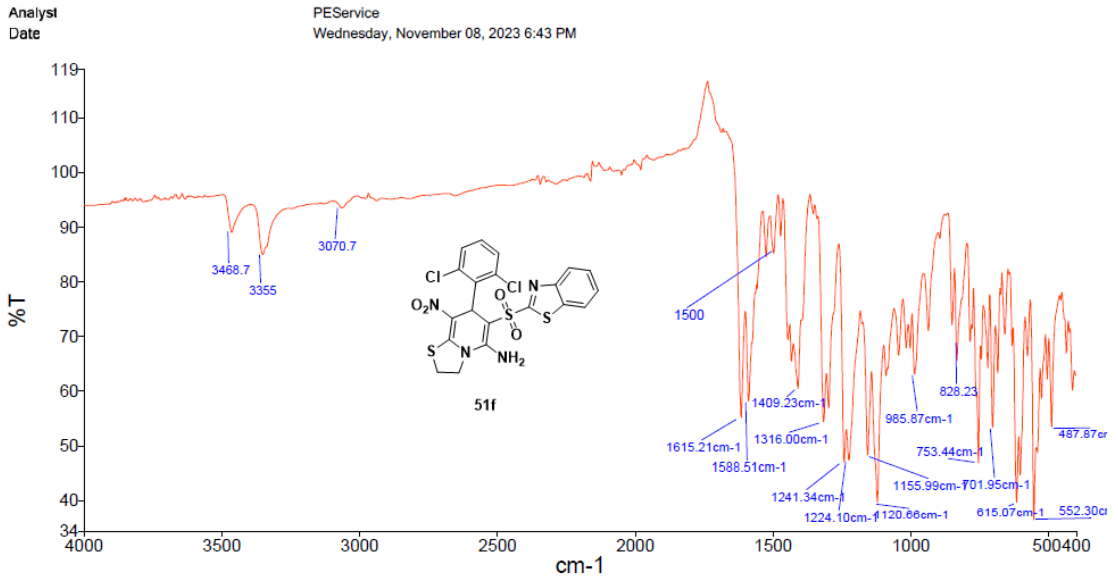


Figure 6.27 FT-IR data for the **51f** compound

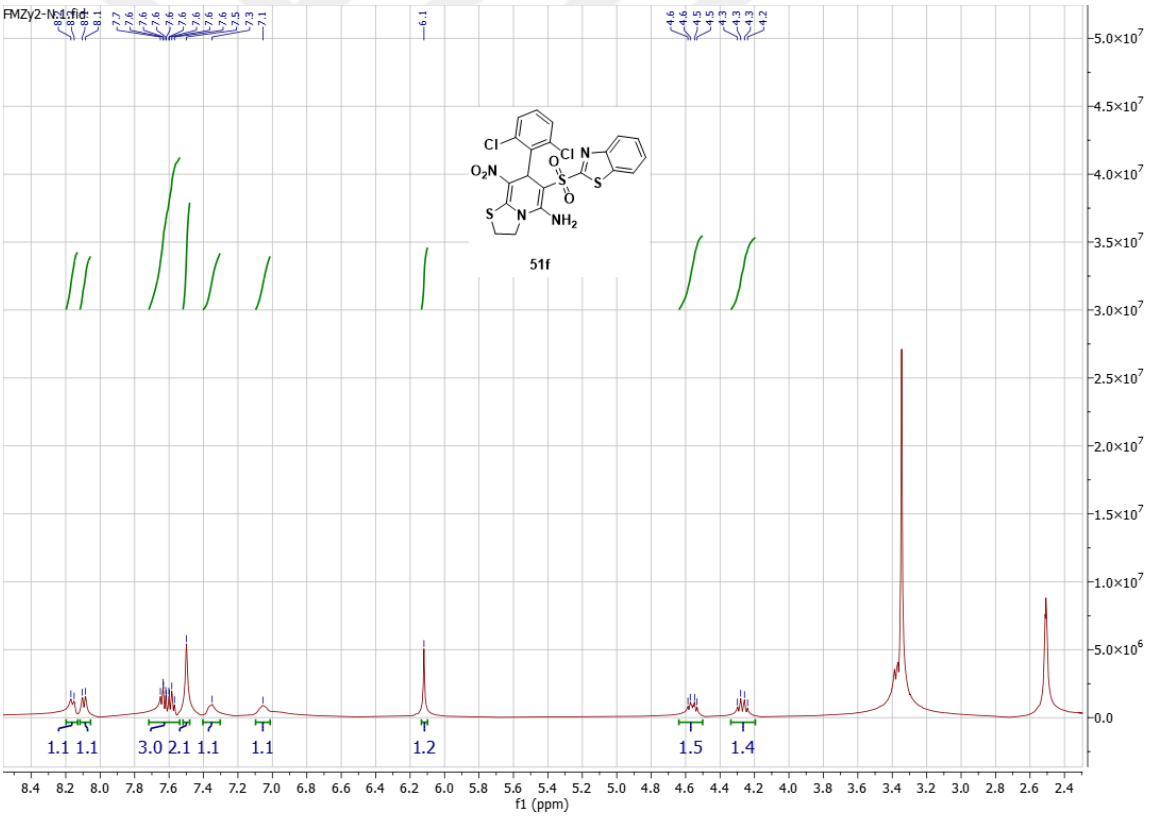


Figure 6.28 ^{1}H NMR data for the **51f** compound

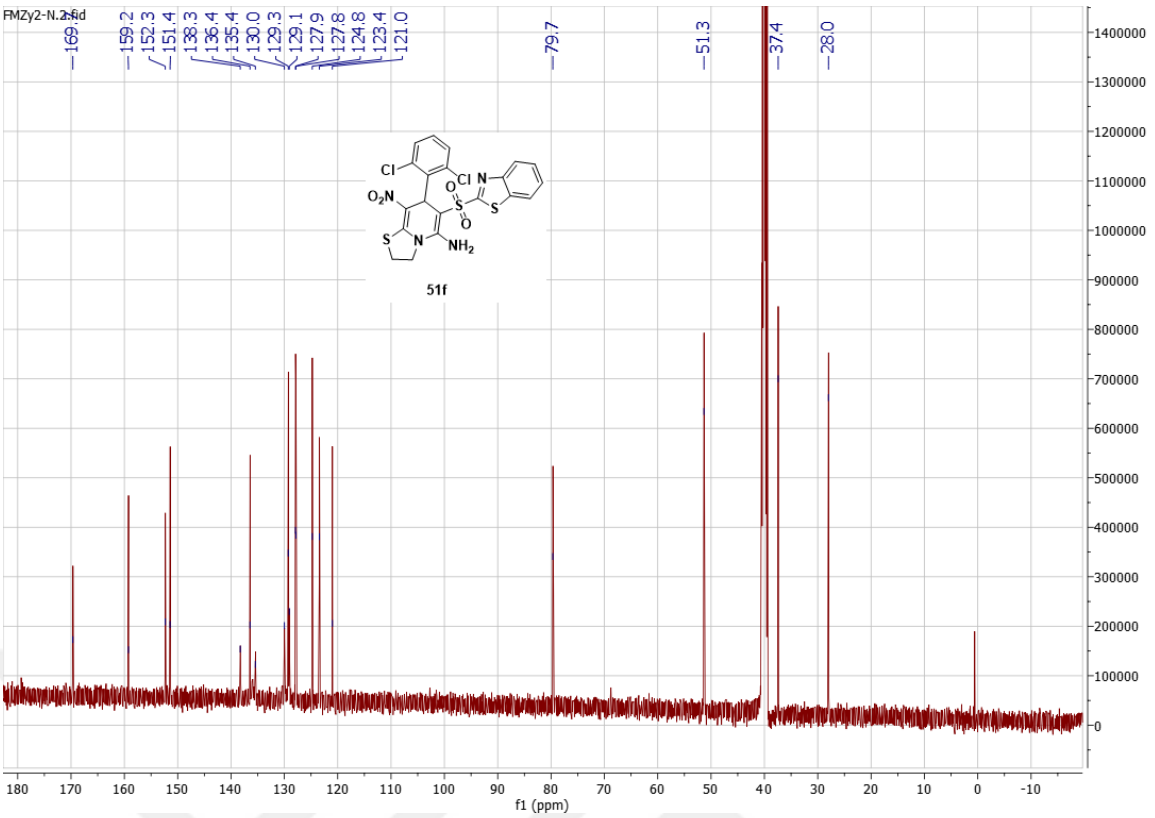


Figure 6.29 ^{13}C NMR data for the **51f** compound

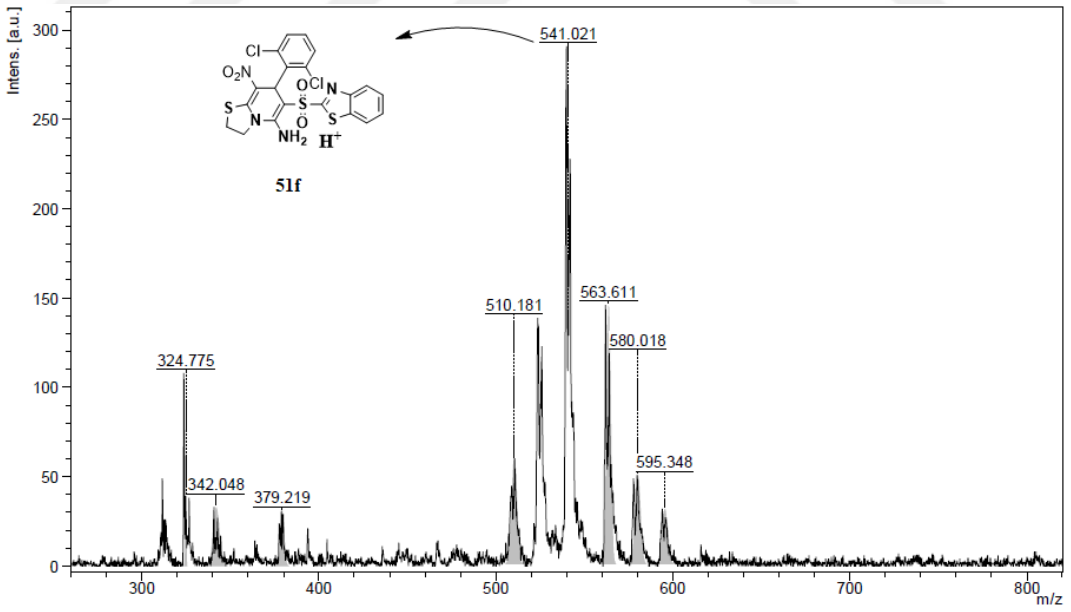
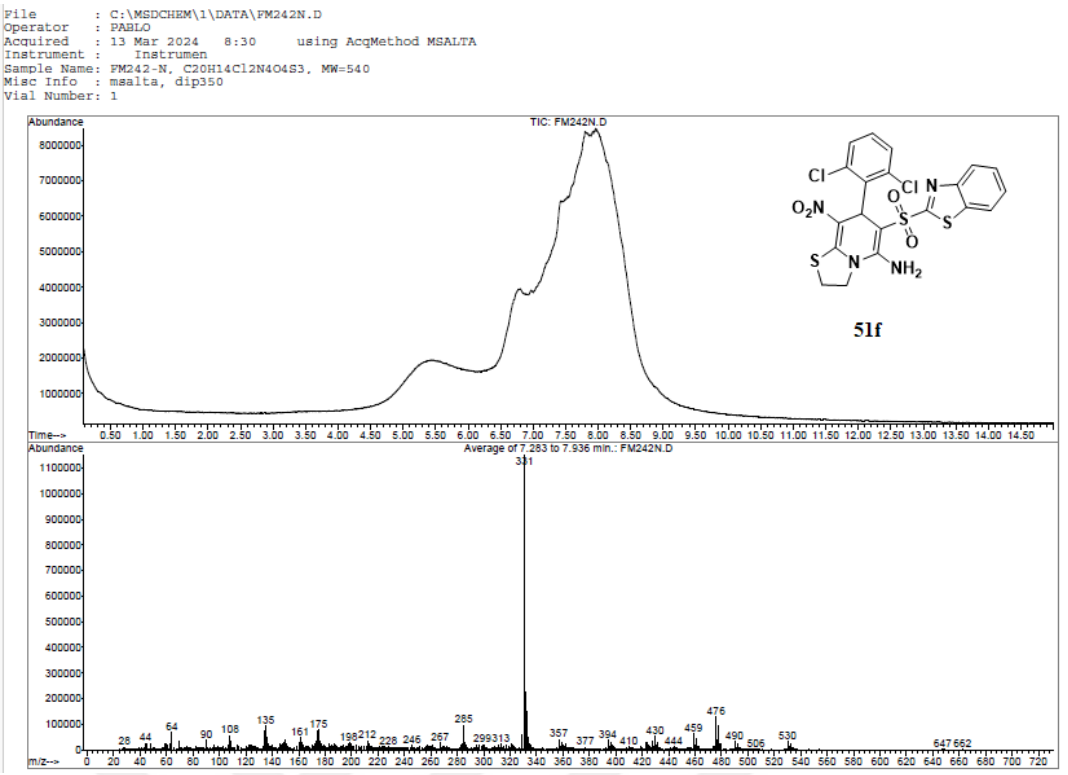
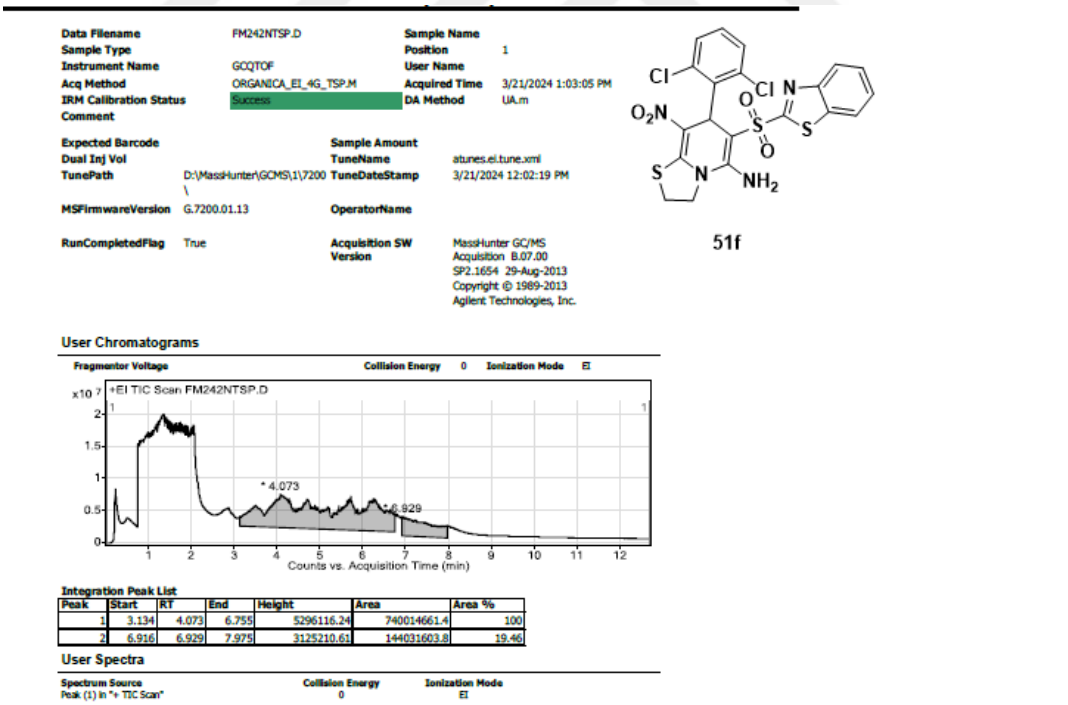


Figure 6.30 LC/MS data for the **51f** compound



51f

Figure 6.31 HR/MS data for the **51f** compound



51f

SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
51f	C20H14Cl2N4O4S3	0.10	13	539.955428	539.9550

Figure 6.32 HR/MS report for the **51f** compound

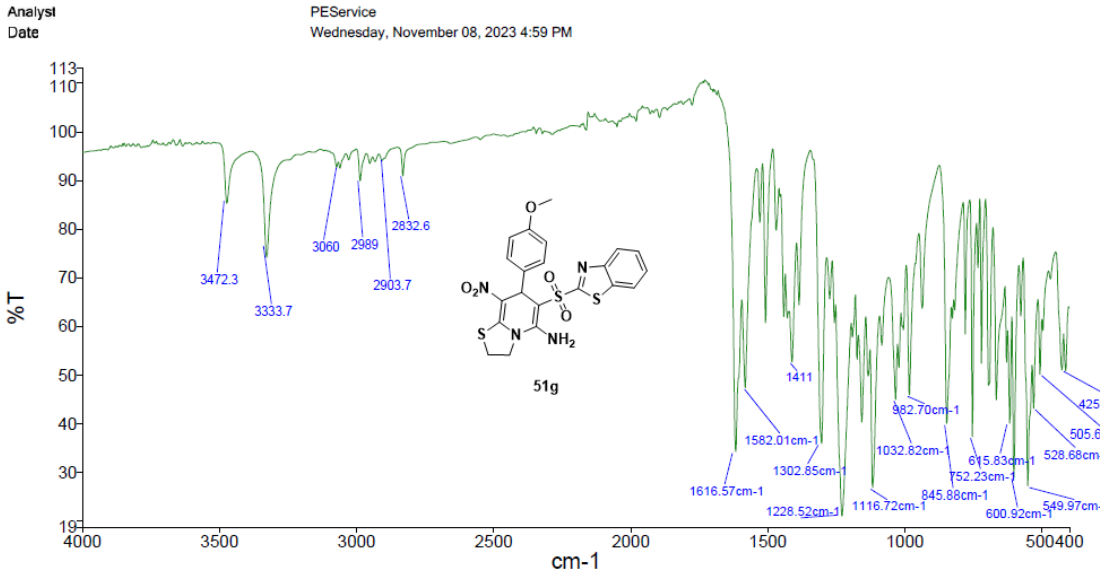


Figure 6.33 FT-IR data for the **51g** compound

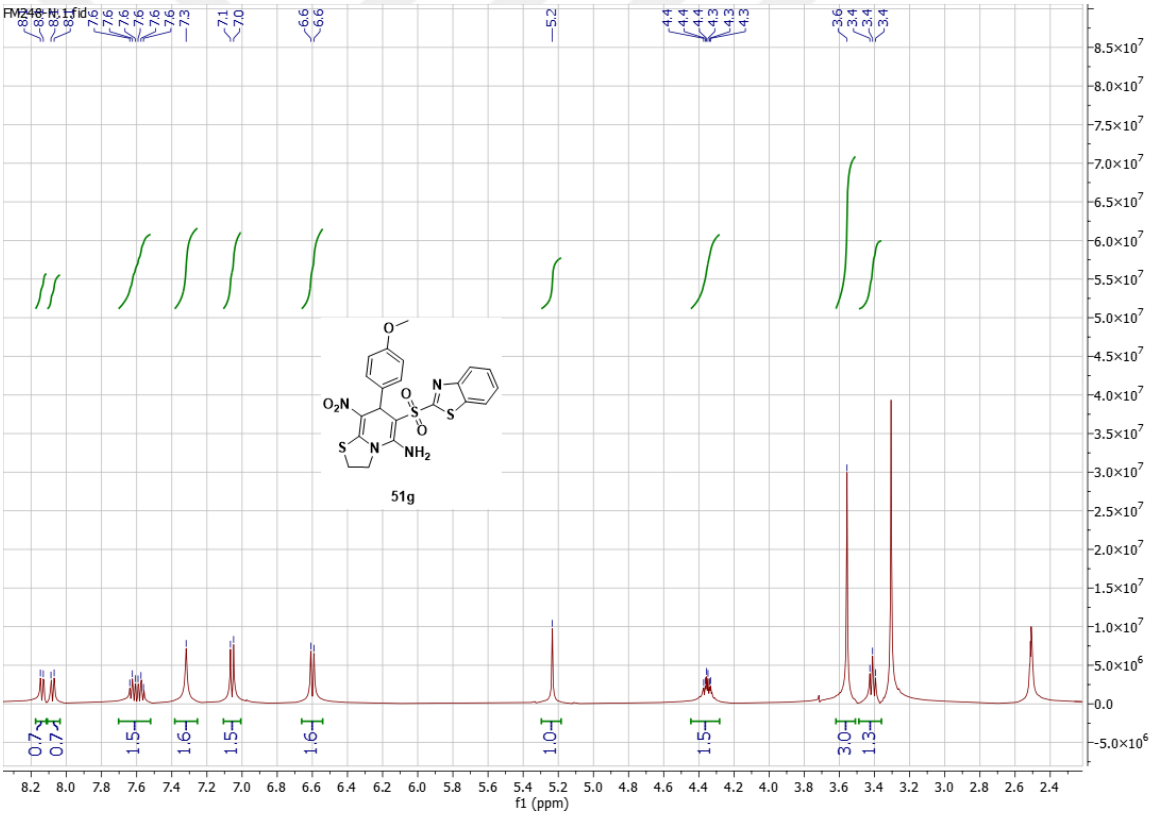


Figure 6.34 ^{1}H NMR data for the **51g** compound

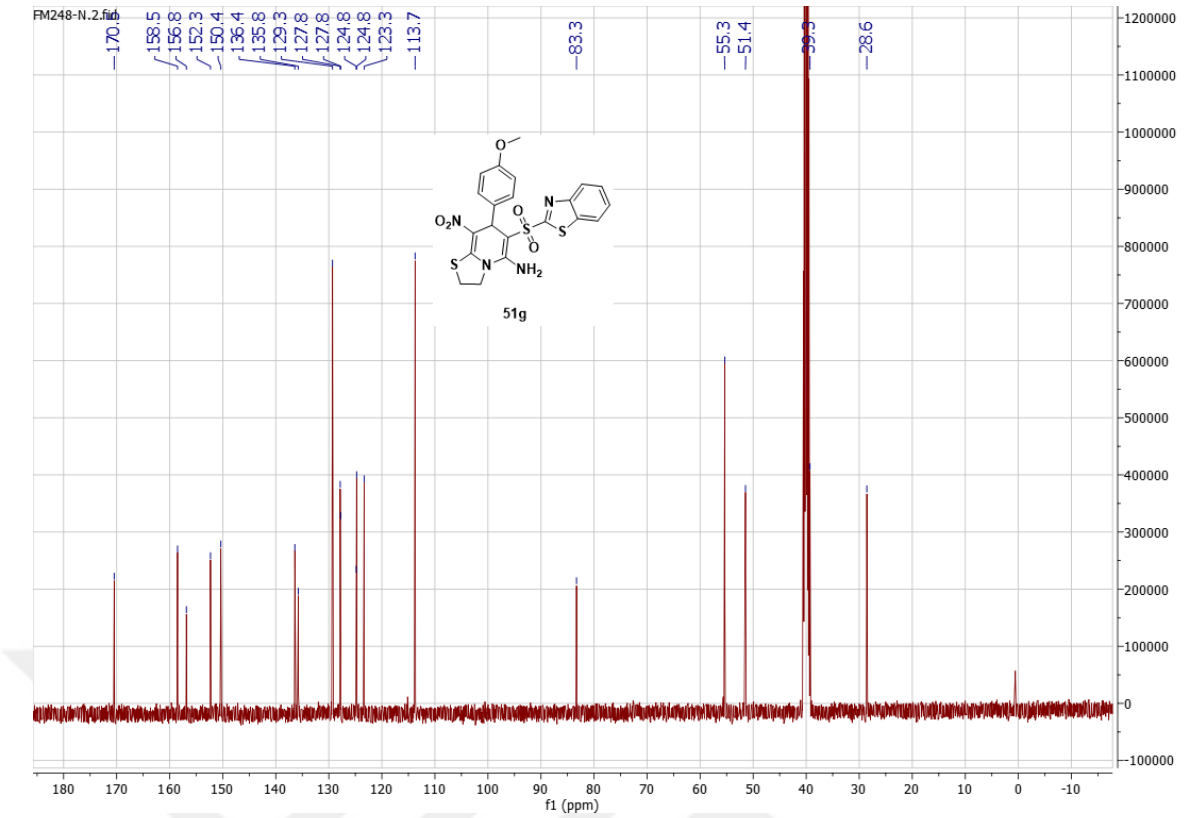


Figure 6.35 ^{13}C NMR data for the **51g** compound

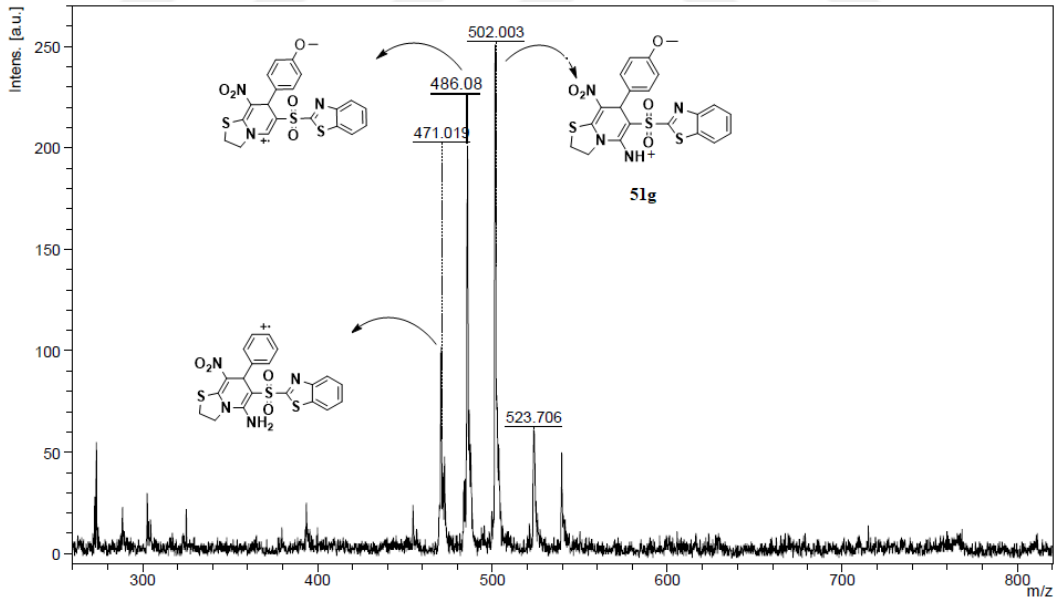
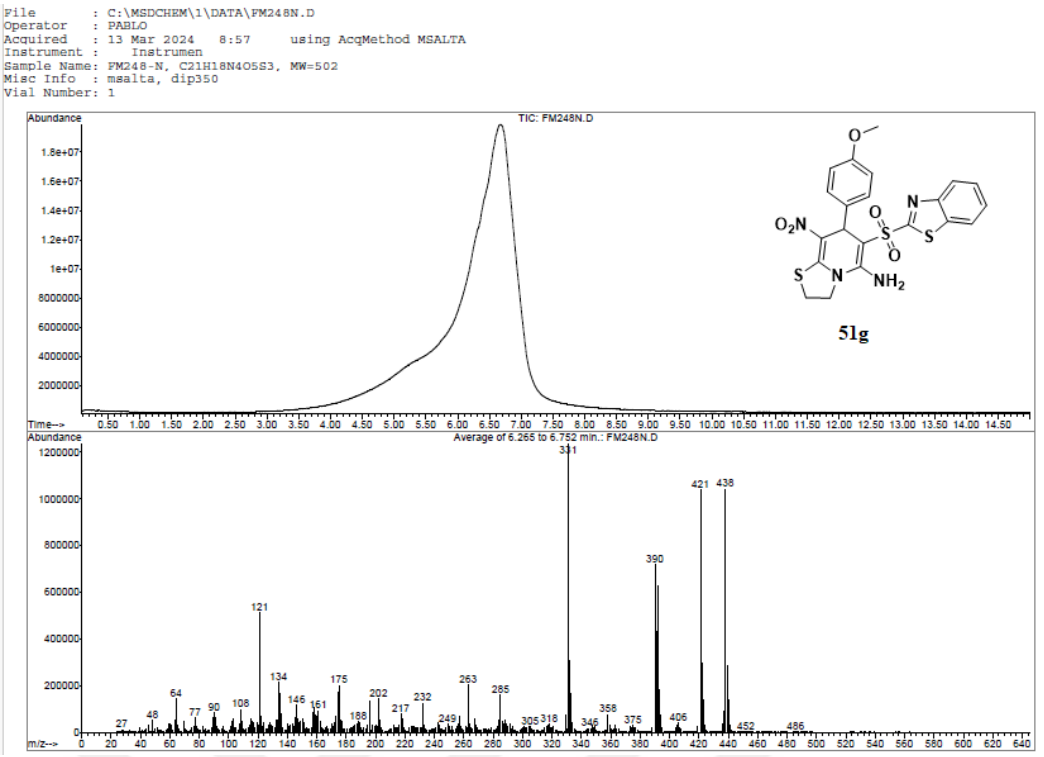
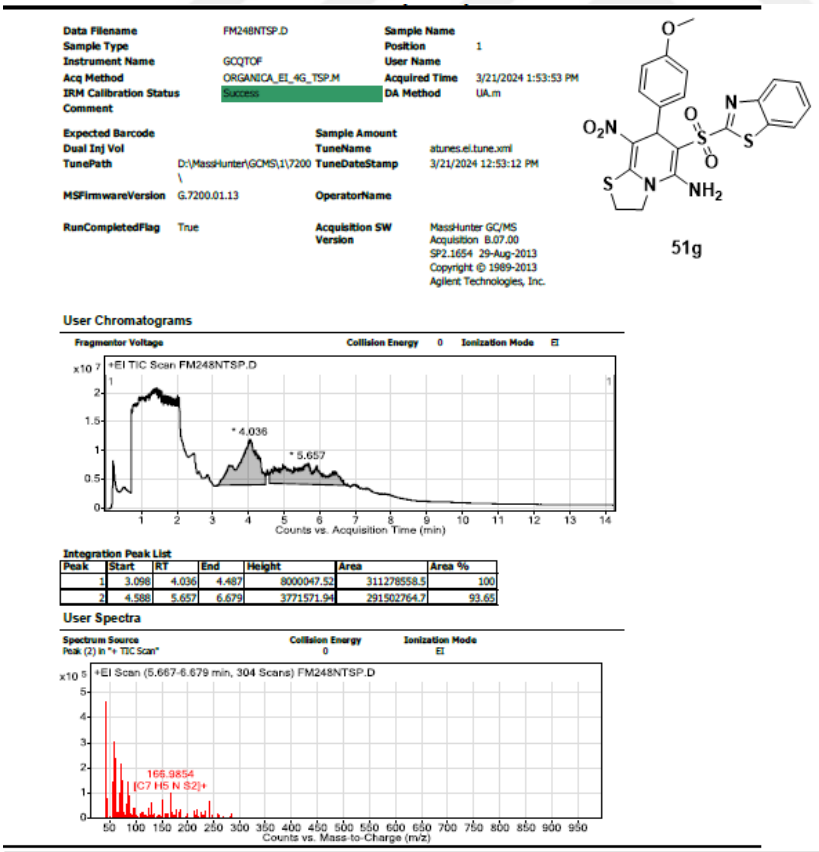


Figure 6.36 LC/MS data for the **51g** compound



51g

Figure 6.37 HR/MS data for the **51g** compound



51g

SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
51g	C21H18N4O5S3	0.10	13	502.043937	502.0437

Figure 6.38 HR/MS report for the **51g** compound

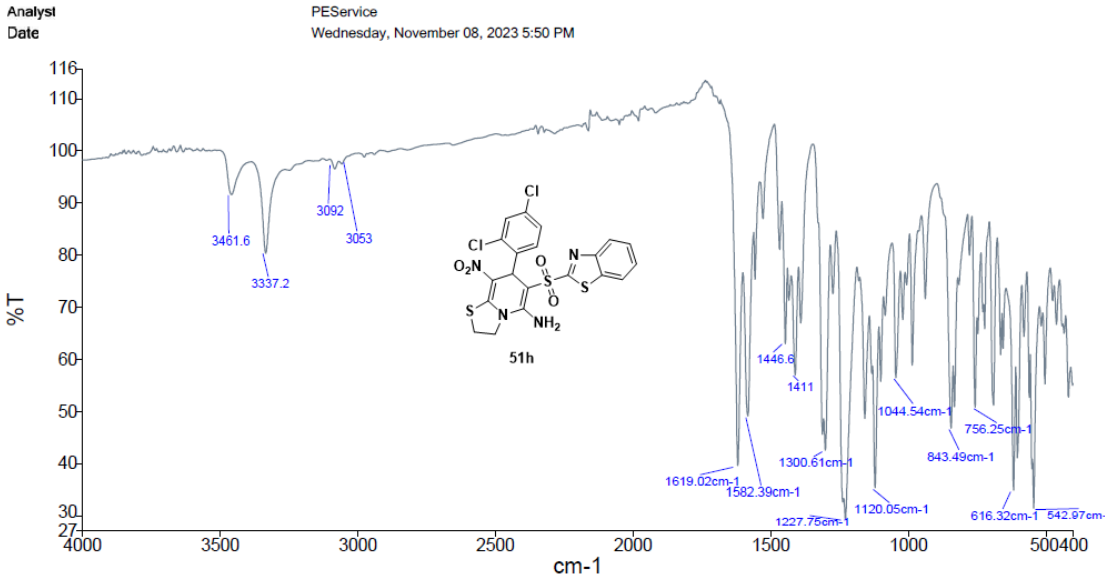


Figure 6.39 FT-IR data for the **51h** compound

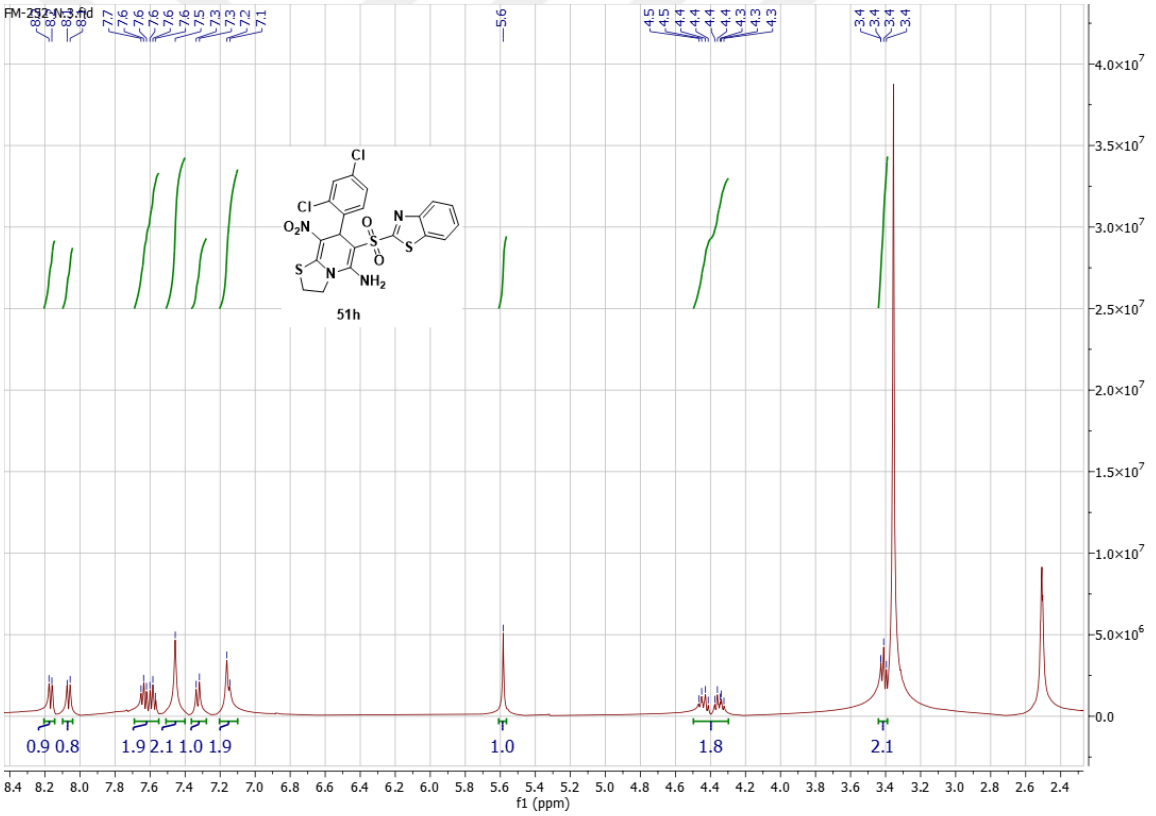


Figure 6.40 ^{1}H NMR data for the **51h** compound

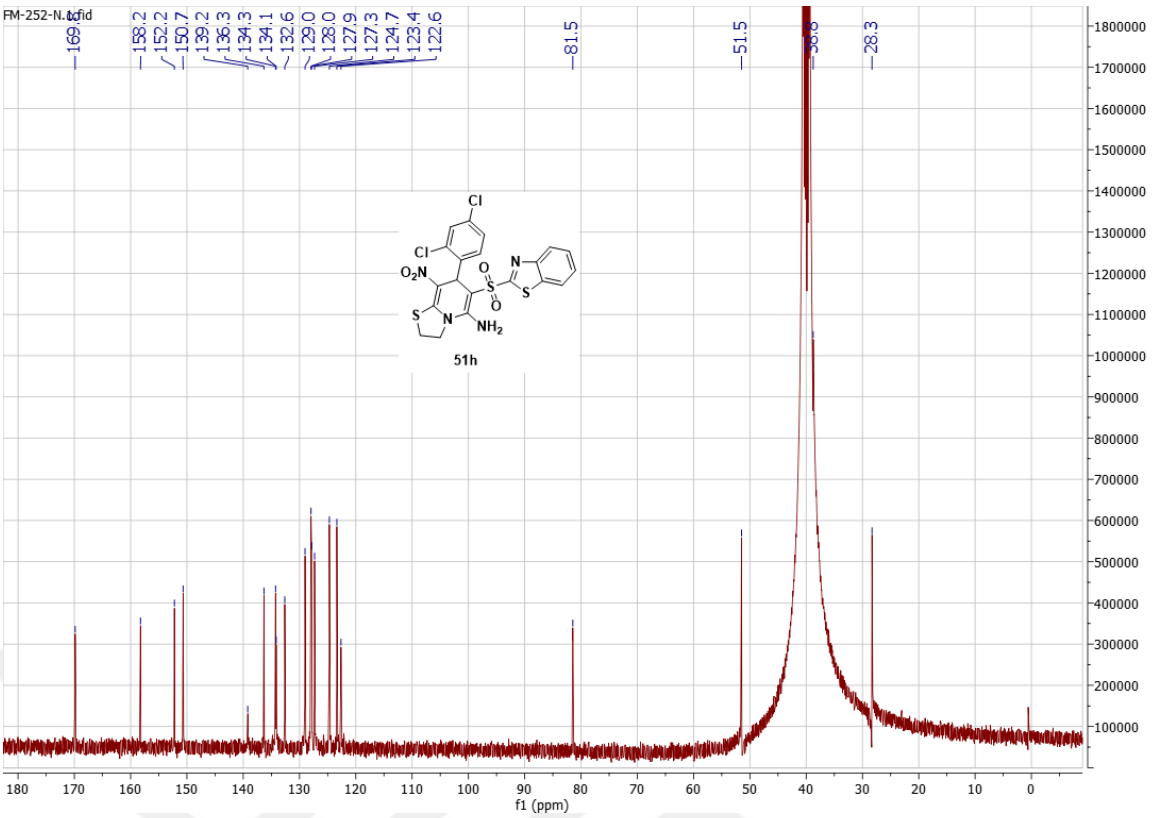


Figure 6.41 ^{13}C NMR data for the **51h** compound

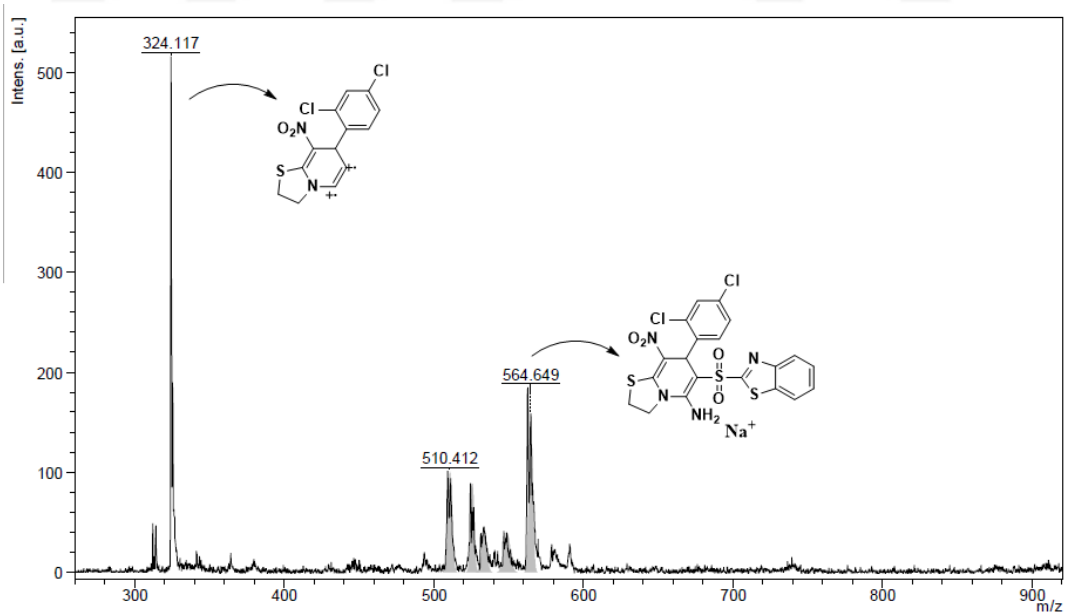


Figure 6.42 LC/MS data for the **51h** compound

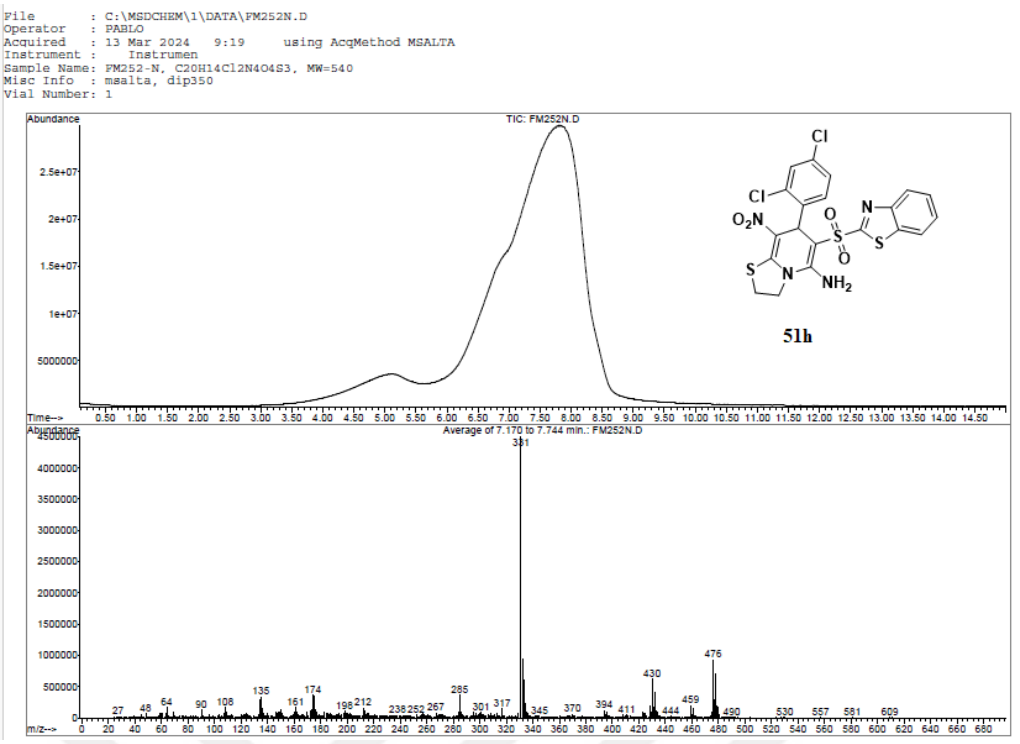
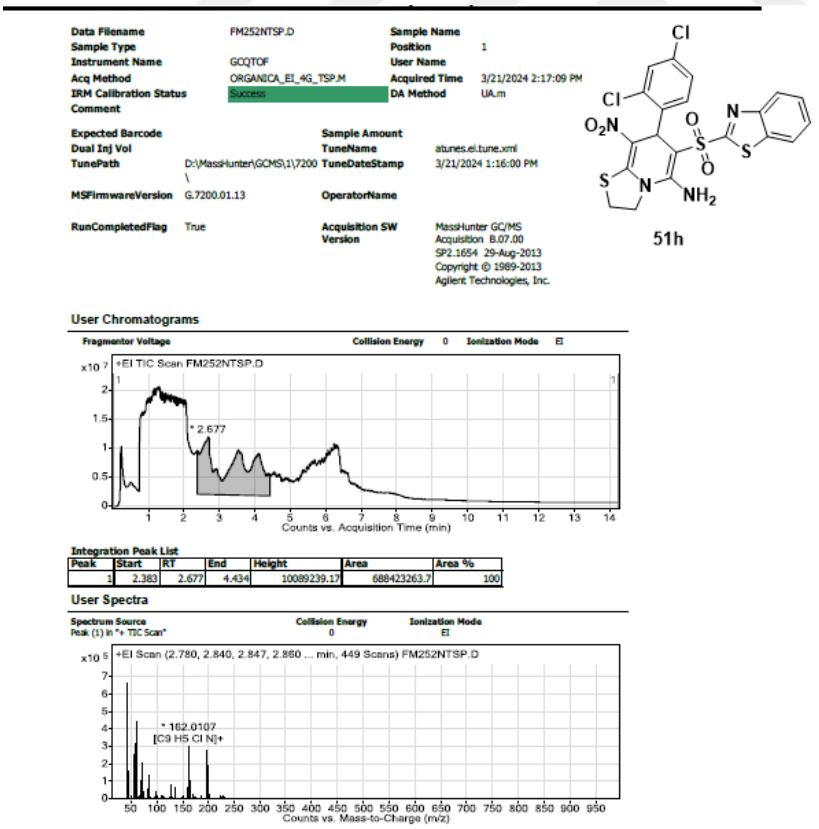


Figure 6.43HR/MS data for the **51h** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
51h	C20H14Cl2N4O4S3	0.10	13	539.955428	539.9559

Figure 6.44HR/MS report for the **51h** compound

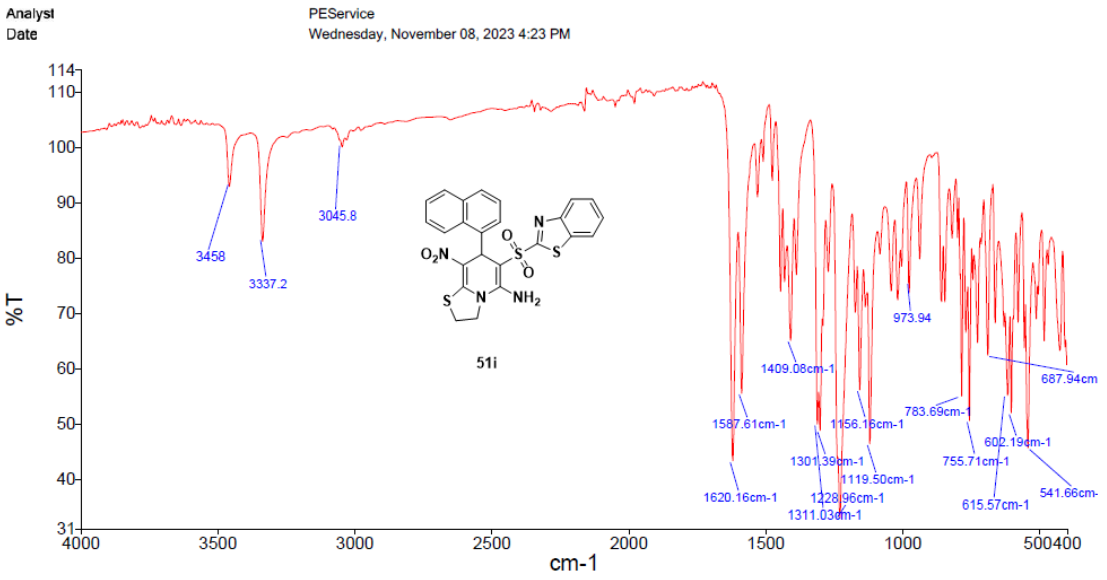


Figure 6.45 FT-IR data for the **51i** compound

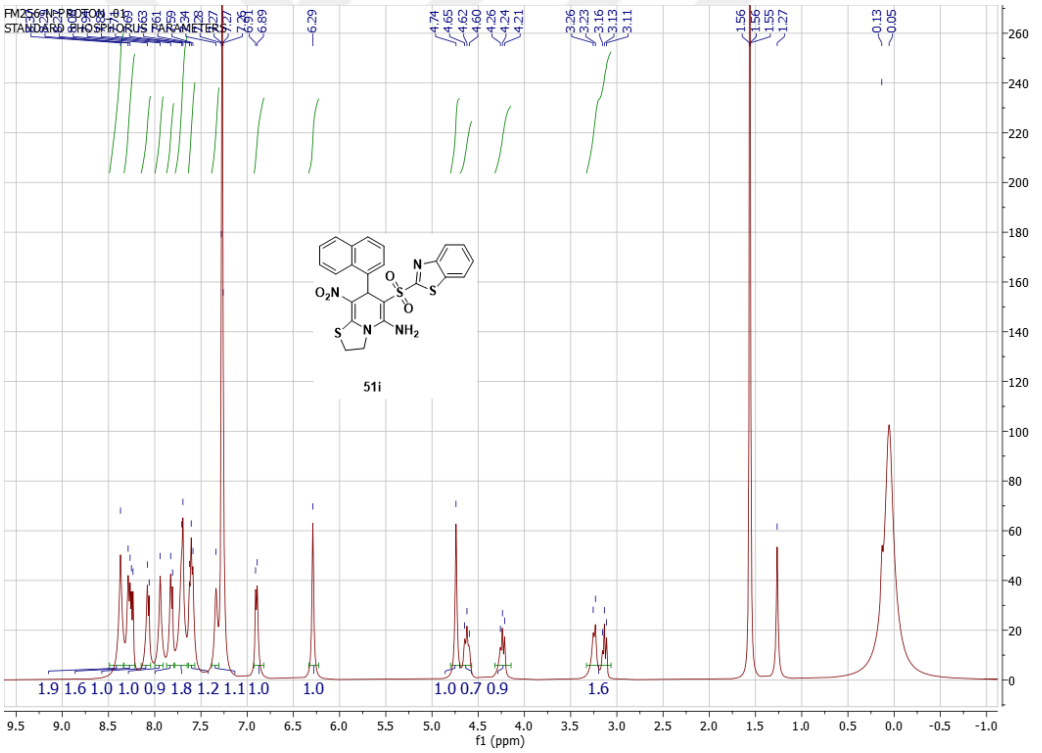


Figure 6.46 ^{1}H NMR data for the **51i** compound

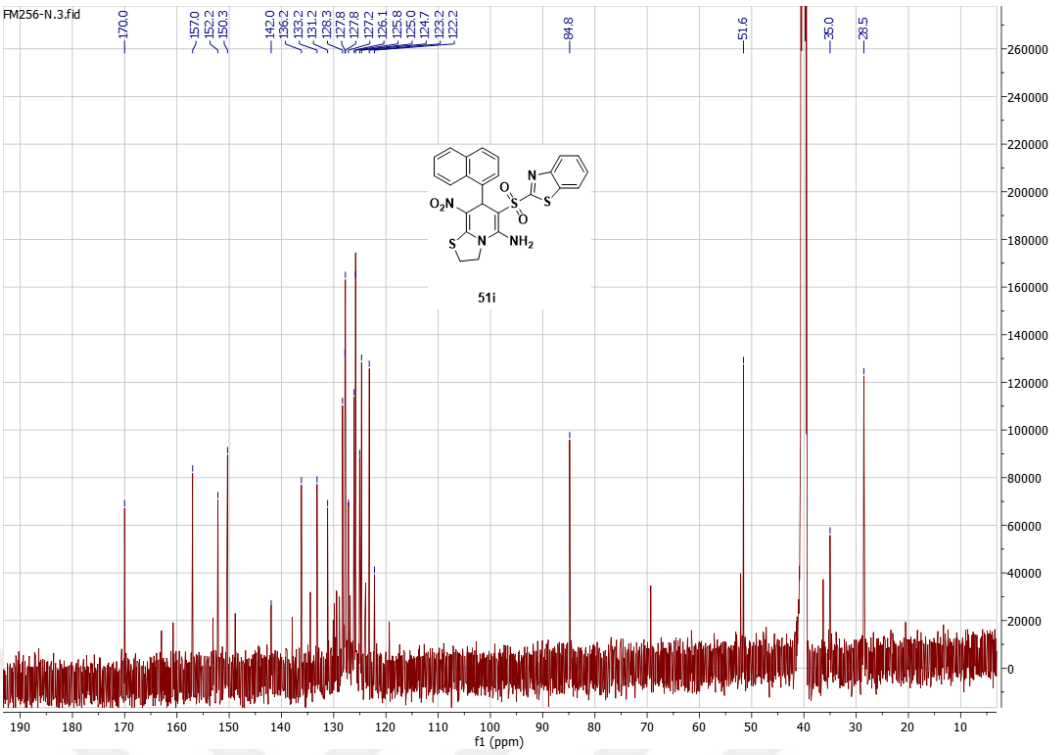


Figure 6.47 ^{13}C NMR data for the **51i** compound

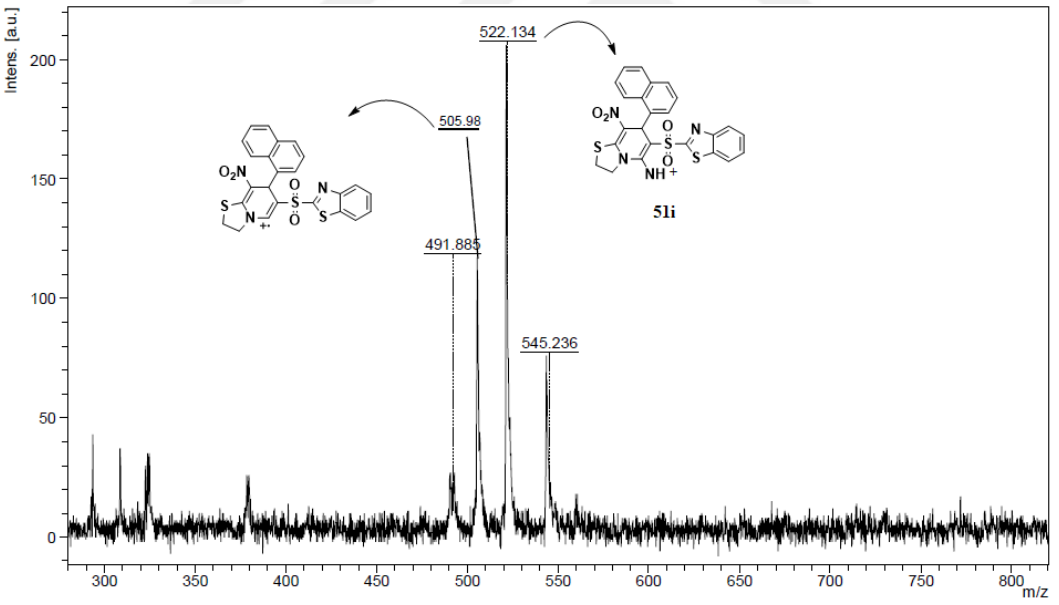
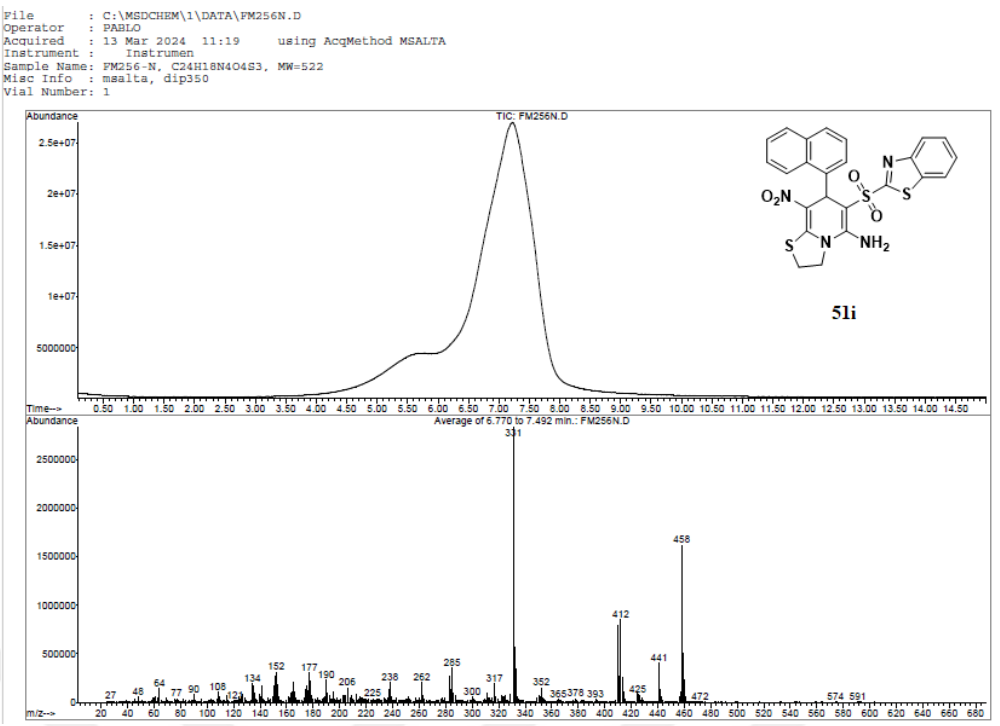
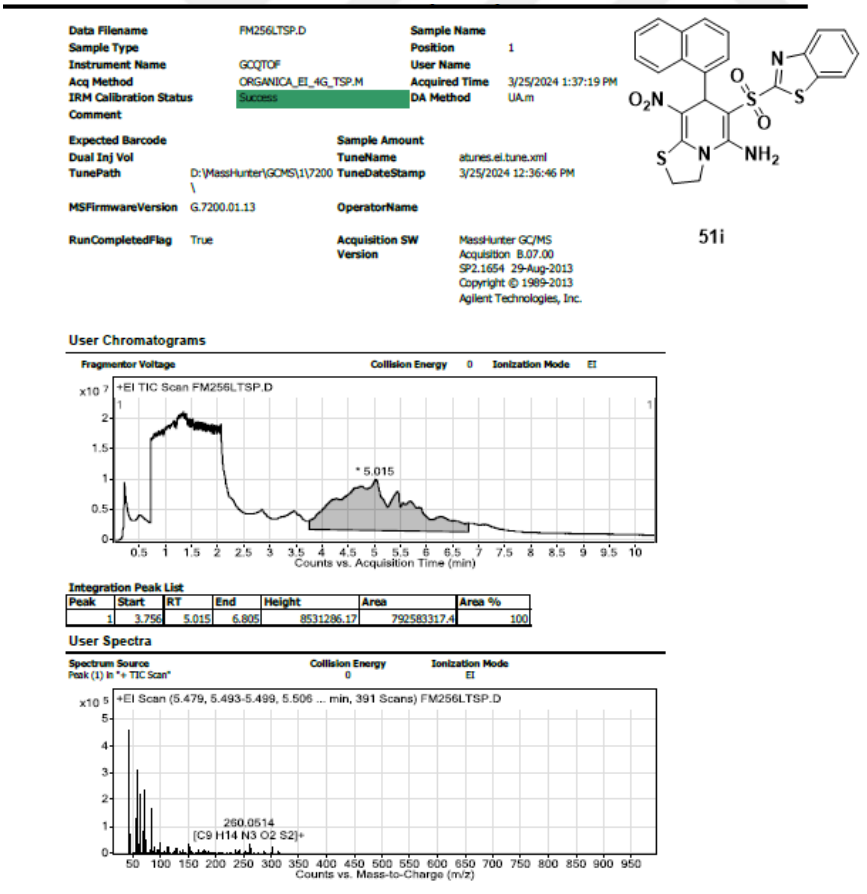


Figure 6.48 LC/MS data for the **51i** compound



51i

Figure 6.49 HR/MS data for the **51i** compound



51i

SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
51i	C24H18N4O4S3	0.08	12	522.049022	522.0487

Figure 6.50 HR/MS report for the **51i** compound

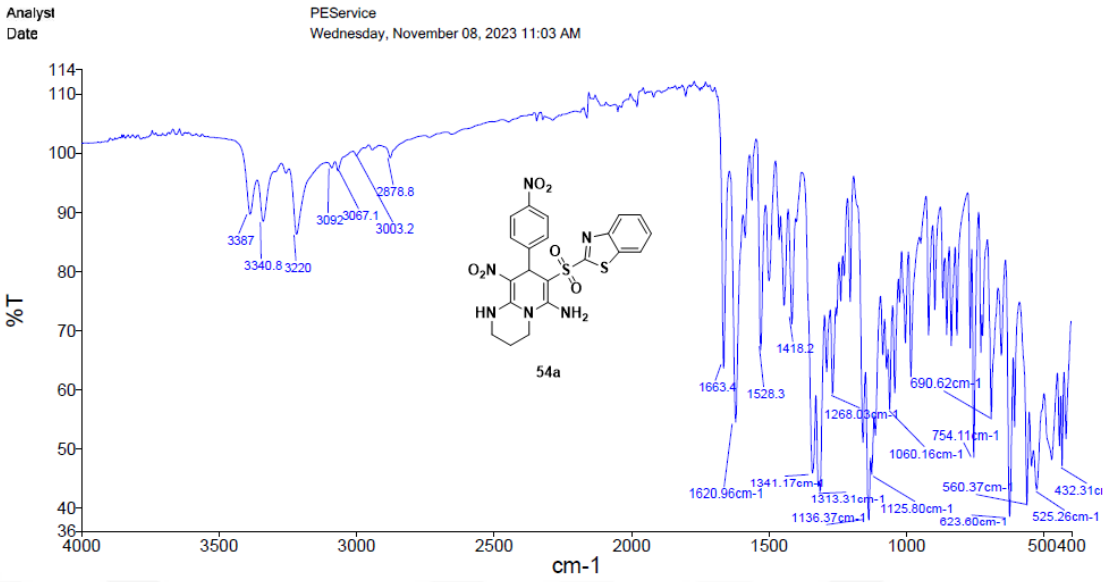


Figure 6.51 FT-IR data for the **54a** compound

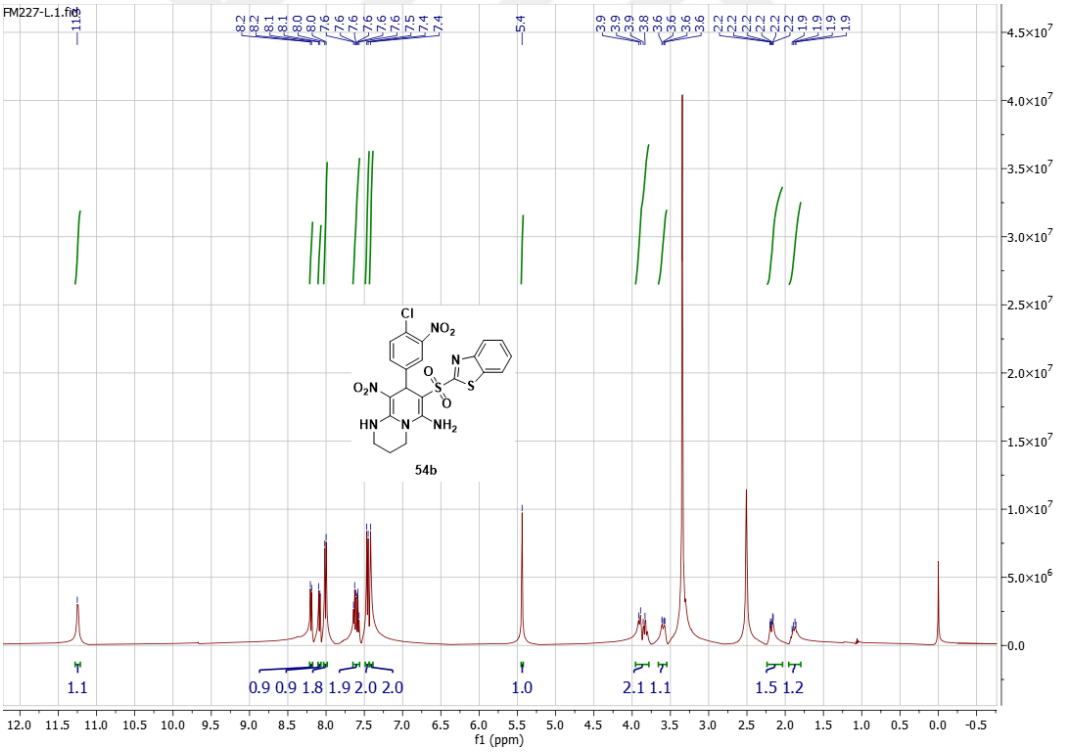


Figure 6.52 ^{1}H NMR data for the **54a** compound

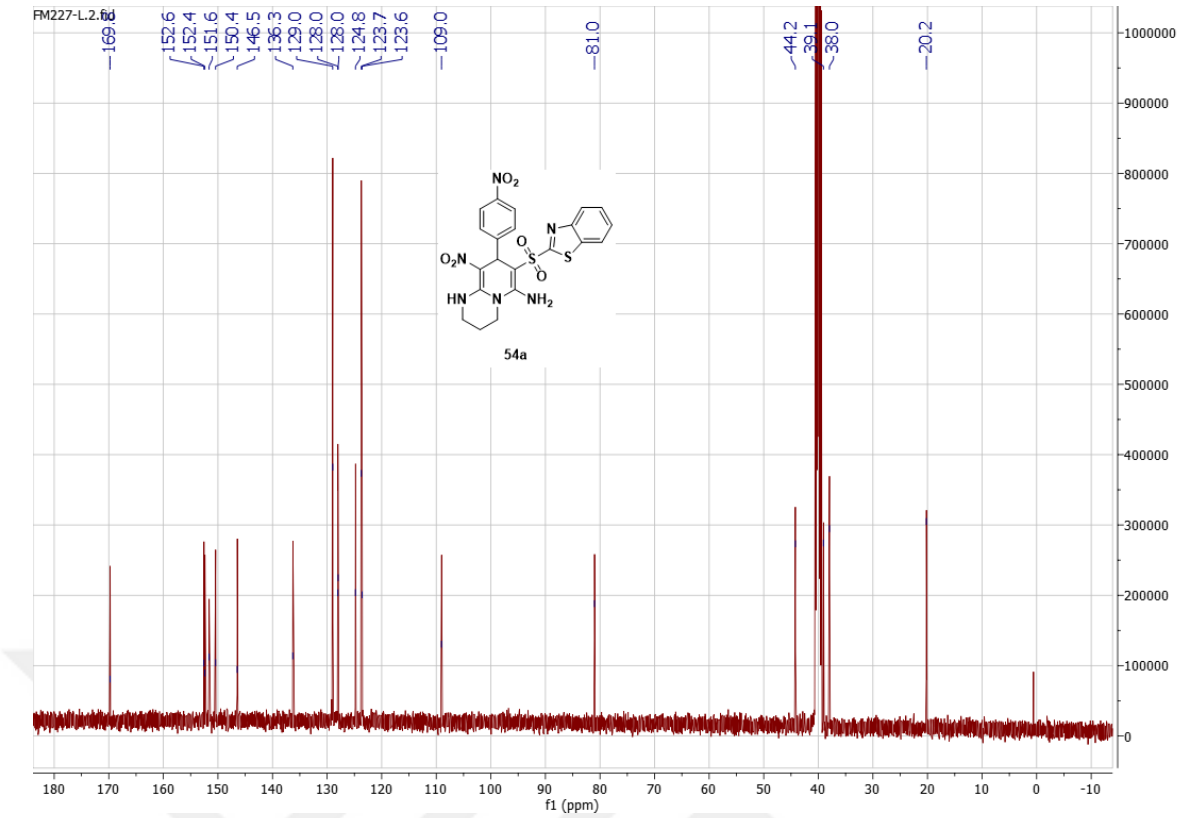


Figure 6.53 ^{13}C NMR data for the **54a** compound

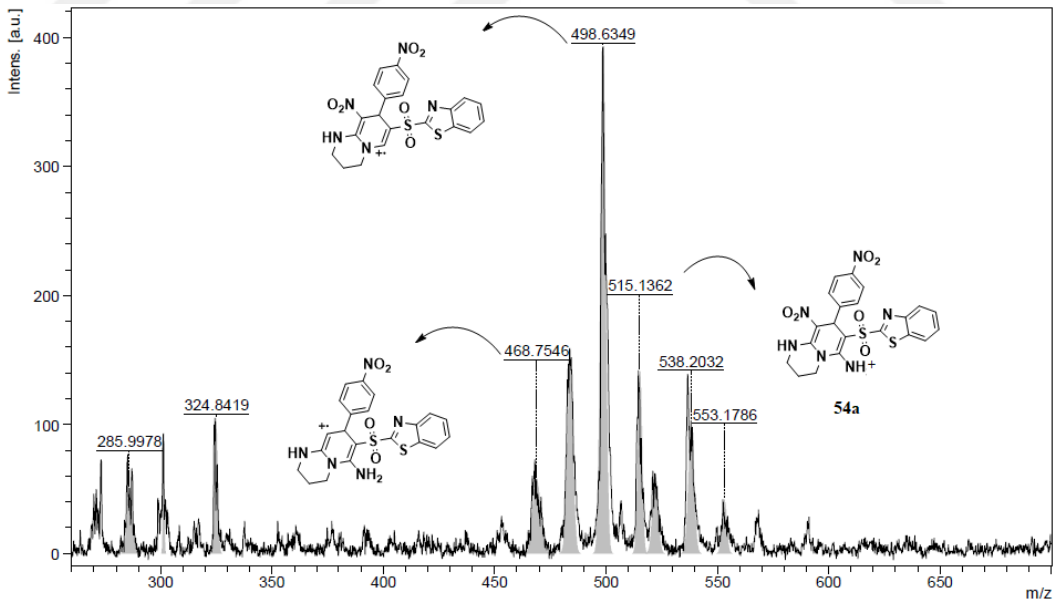


Figure 6.54 LC/MS data for the **54a** compound

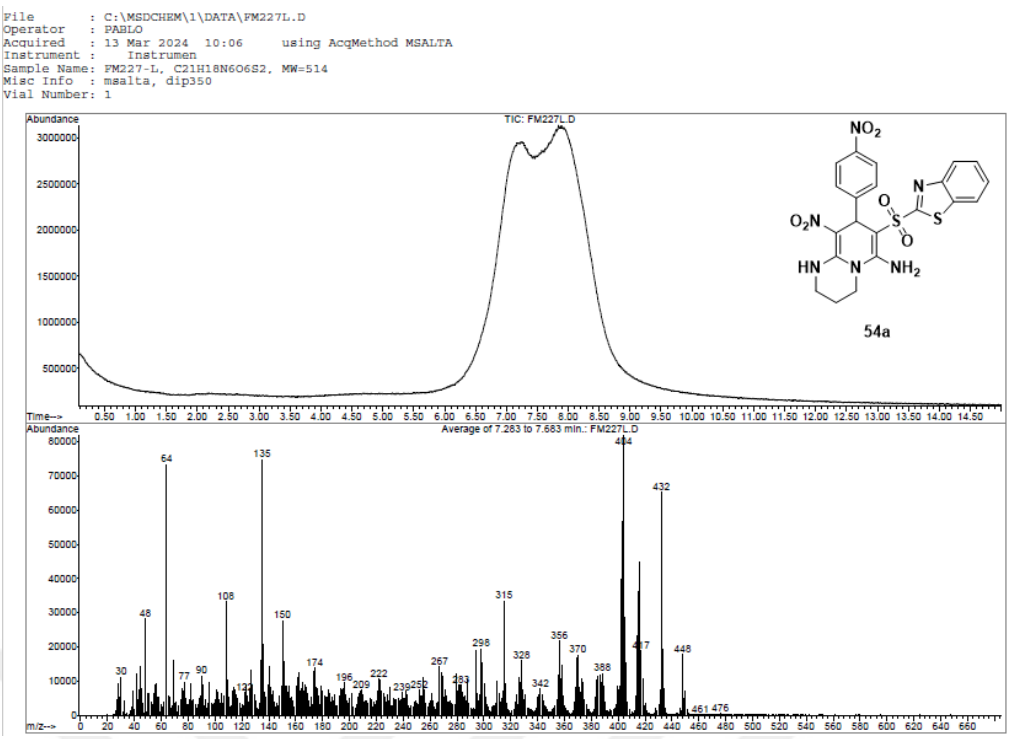
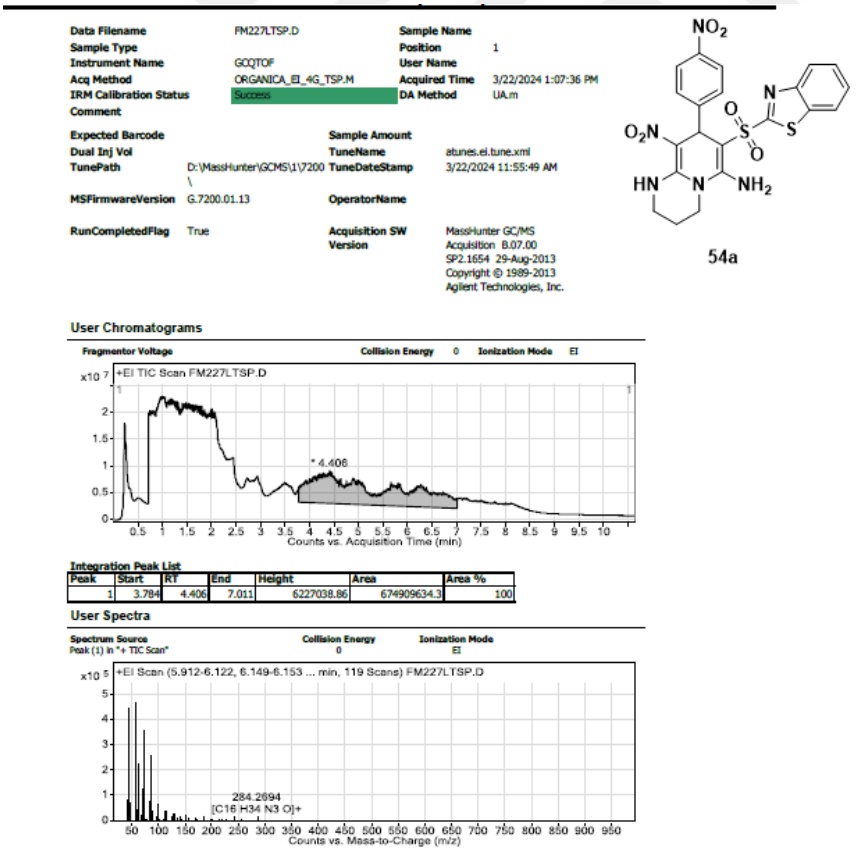


Figure 6.55 HR/MS data for the **54a** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
54a	C21H18N6O6S2	0.21	21	514.072928	514.0728

Figure 6.56 HR/MS report for the **54a** compound

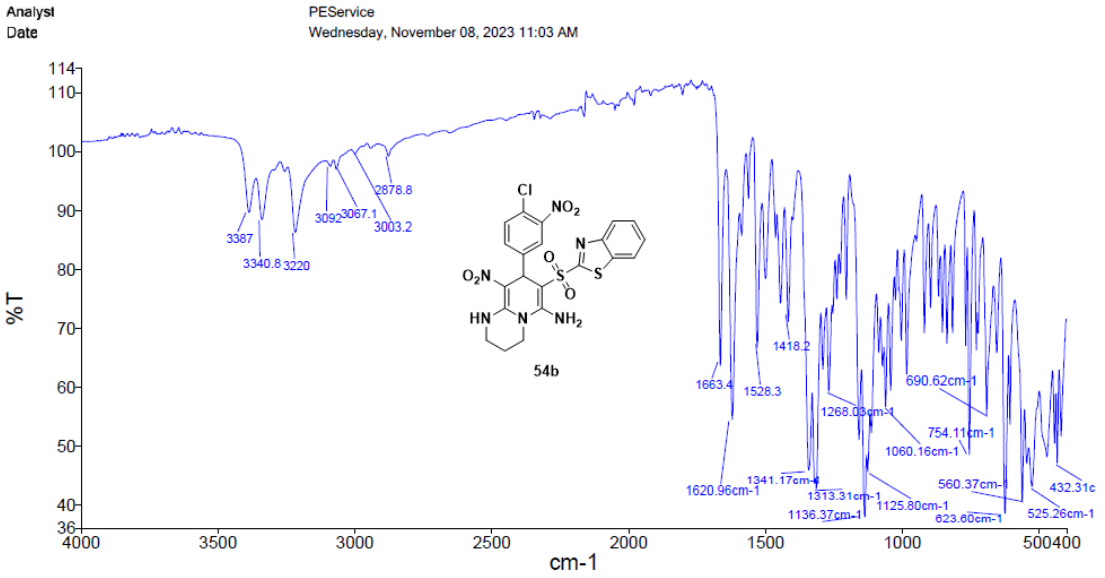


Figure 6.57 FT-IR data for the **54b** compound

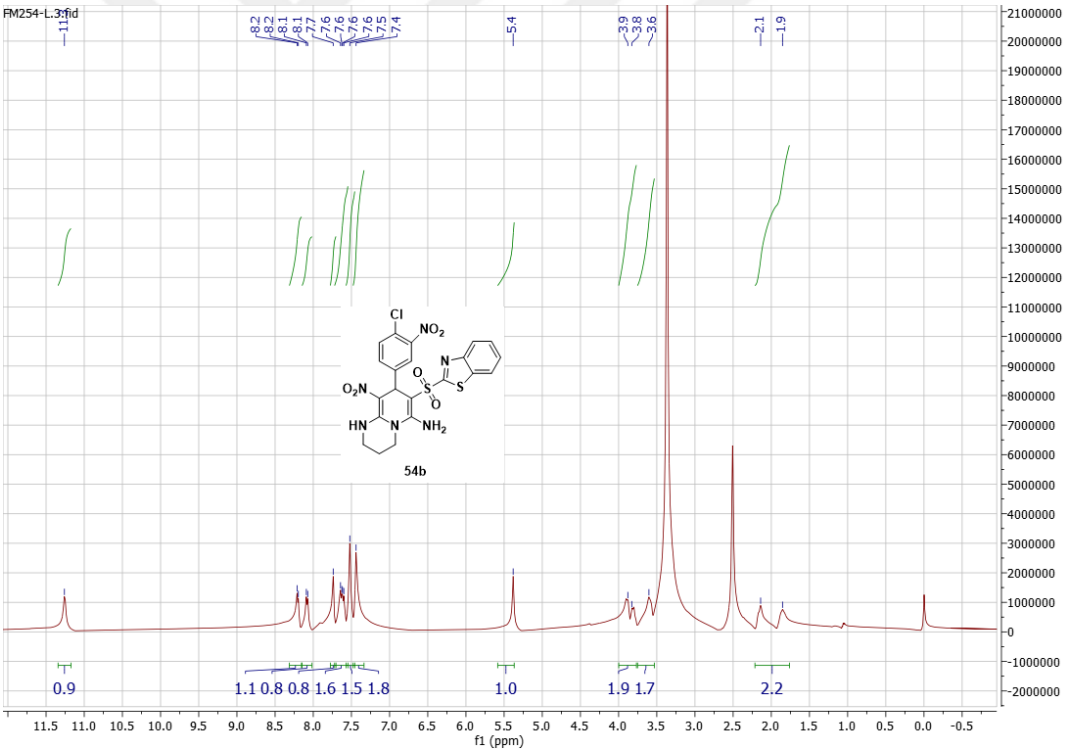


Figure 6.58 ^{1}H NMR data for the **54b** compound

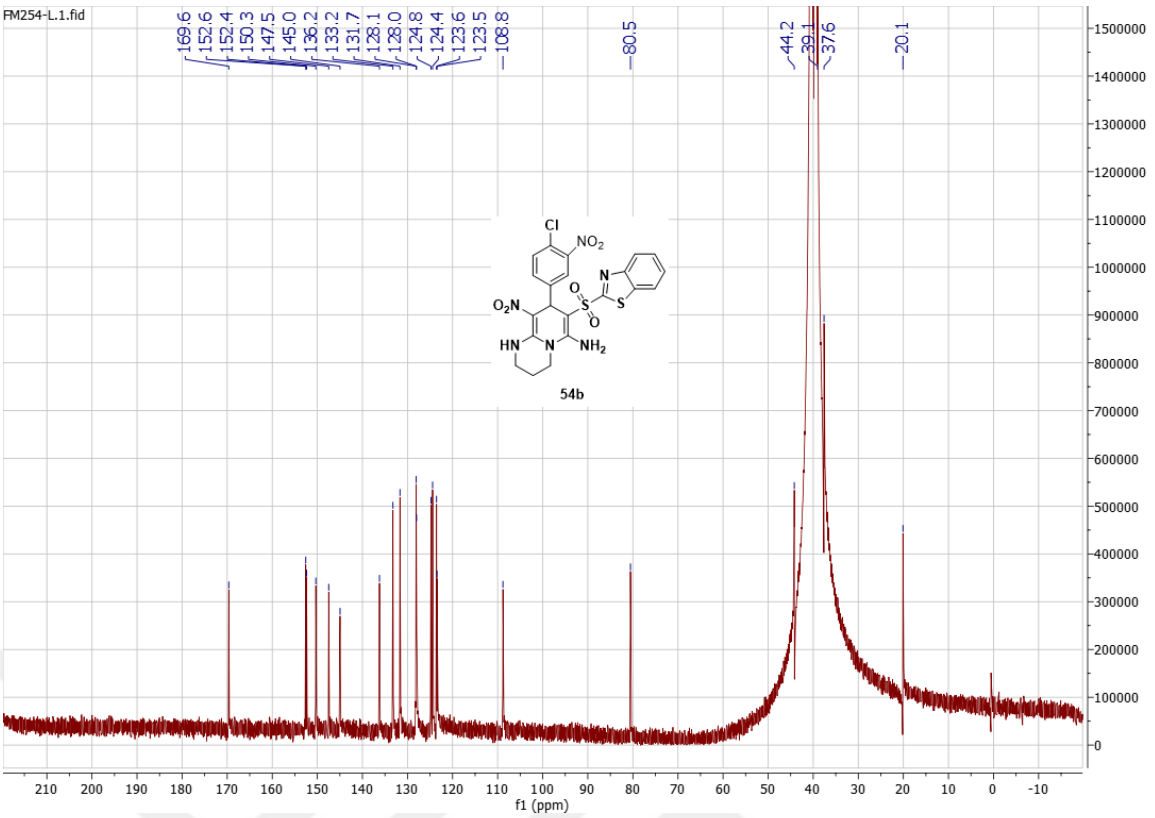


Figure 6.59 ^{13}C NMR data for the **54b** compound

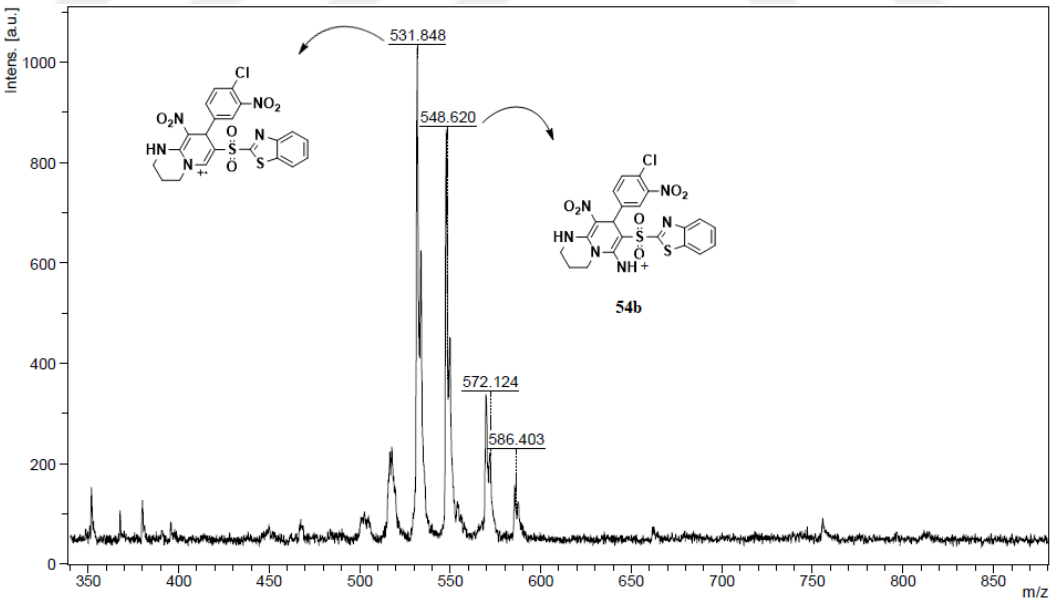


Figure 6.60 LC/MS data for the **54b** compound

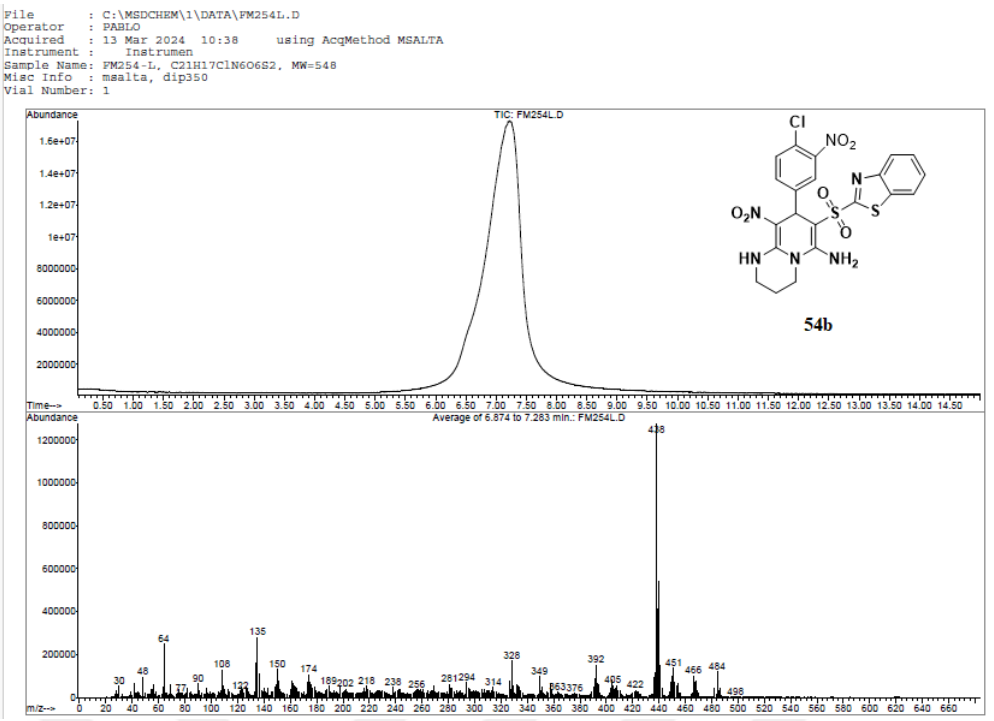
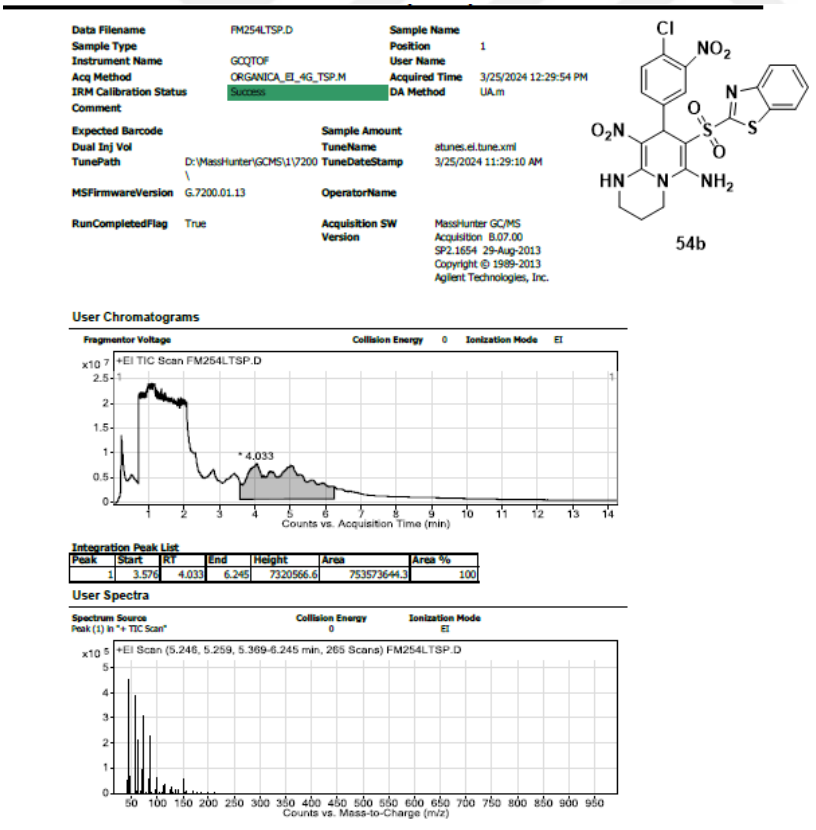


Figure 6.61 HR/MS data for the **54b** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
54b	C21H17ClN6O6S2	0.11	27	548.033956	548.0330

Figure 6.62 HR/MS report for the **54b** compound

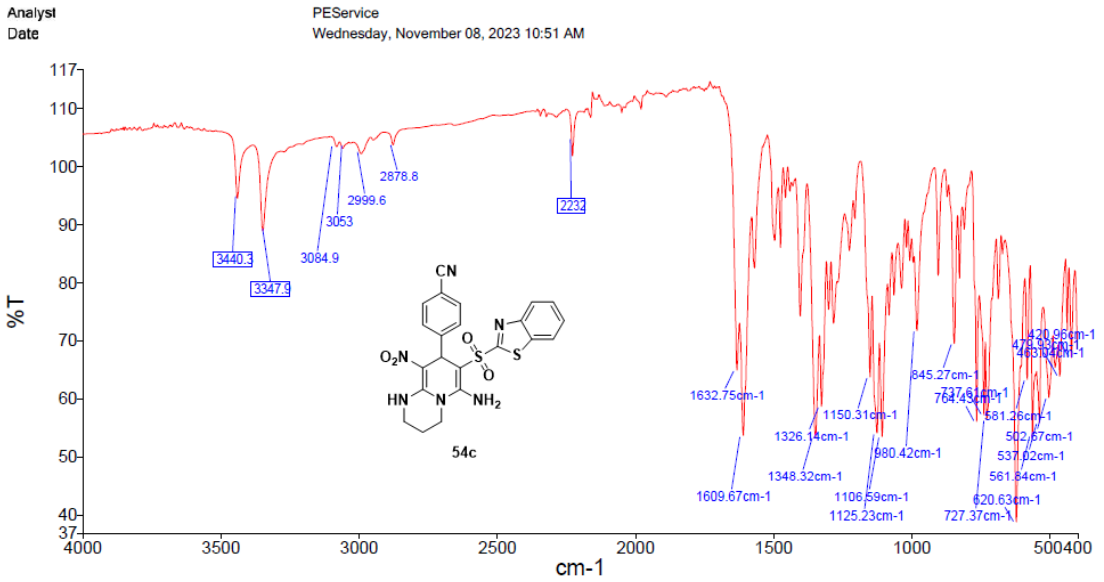


Figure 6.63 FT-IR data for the **54c** compound

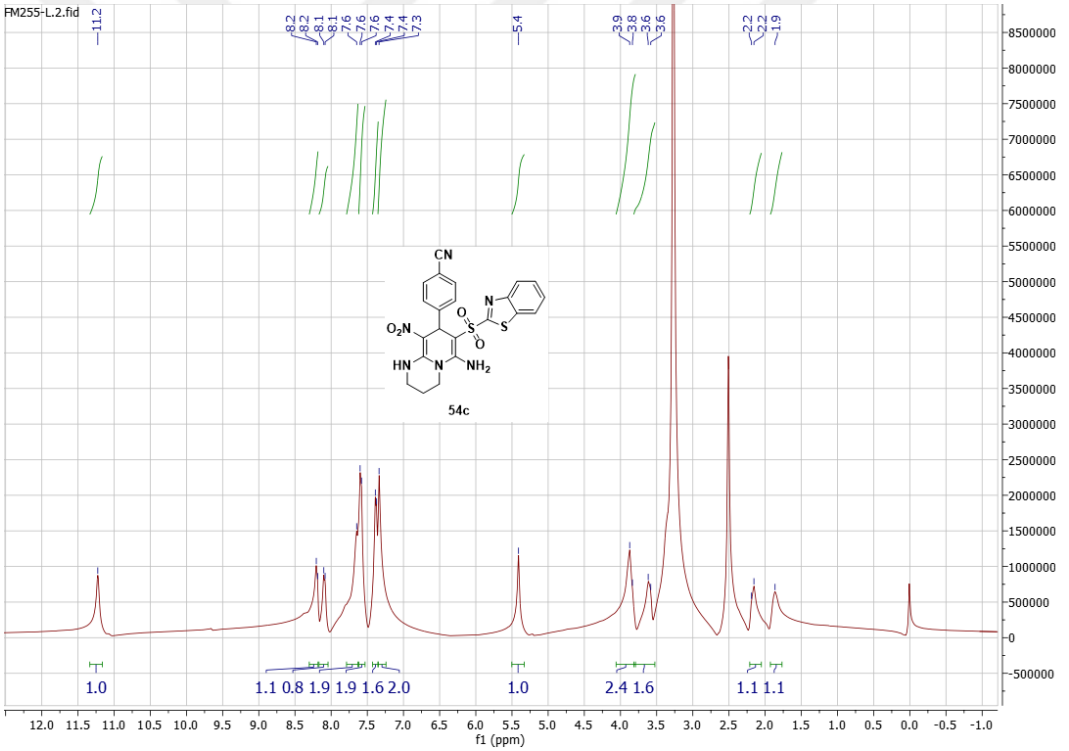


Figure 6.64 ^{1}H NMR data for the **54c** compound

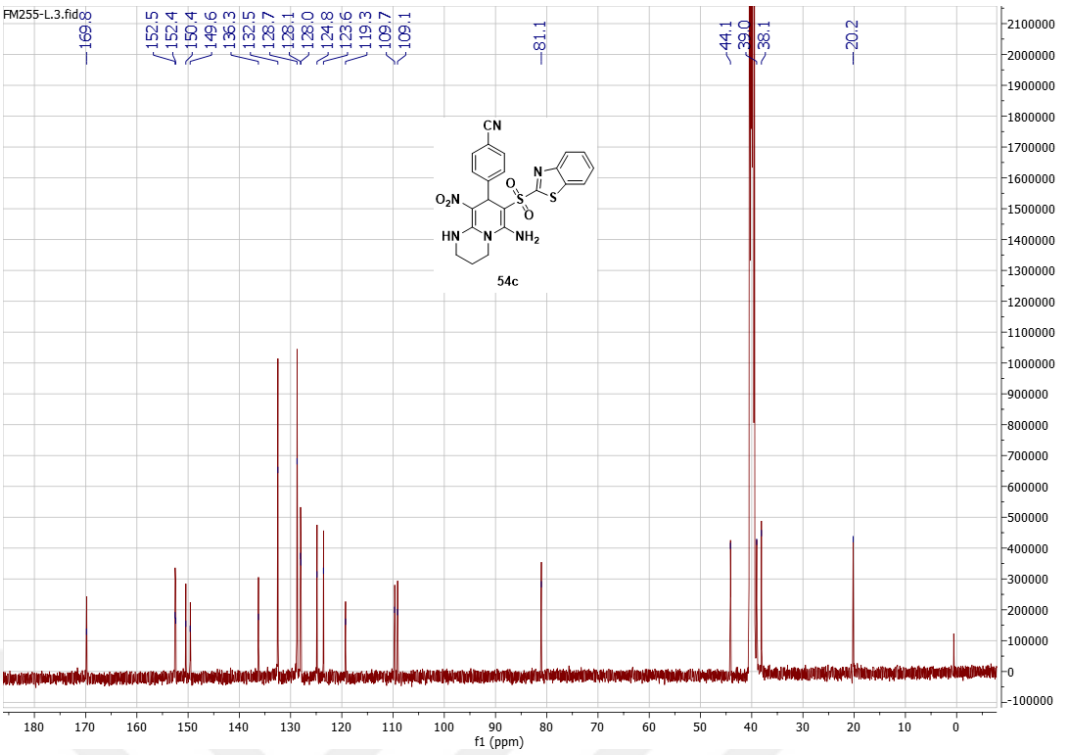


Figure 6.65 ^{13}C NMR data for the **54c** compound

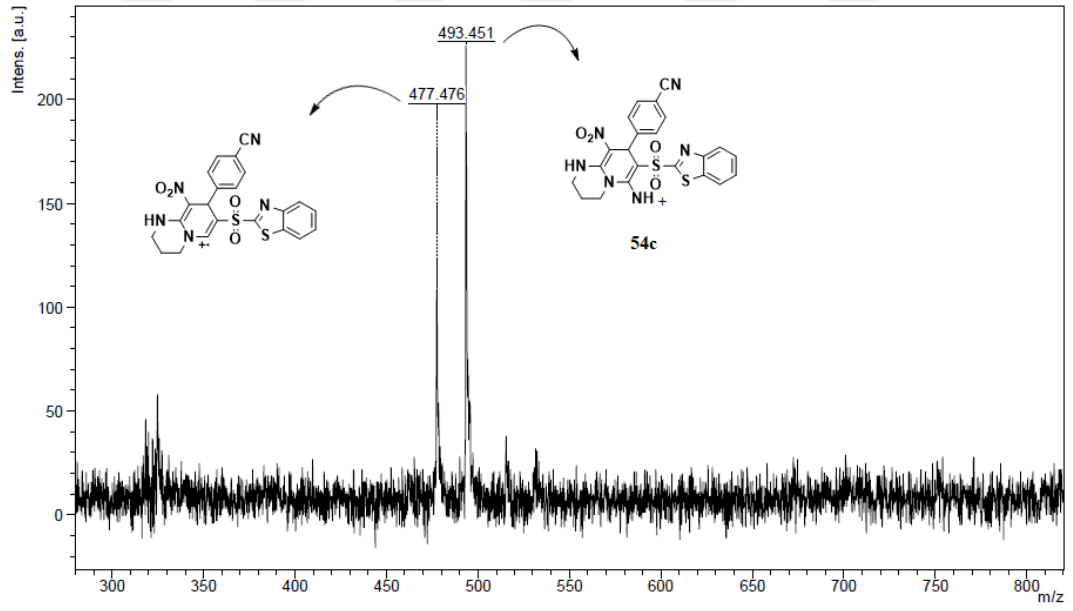


Figure 6.66 LC/MS data for the **54c** compound

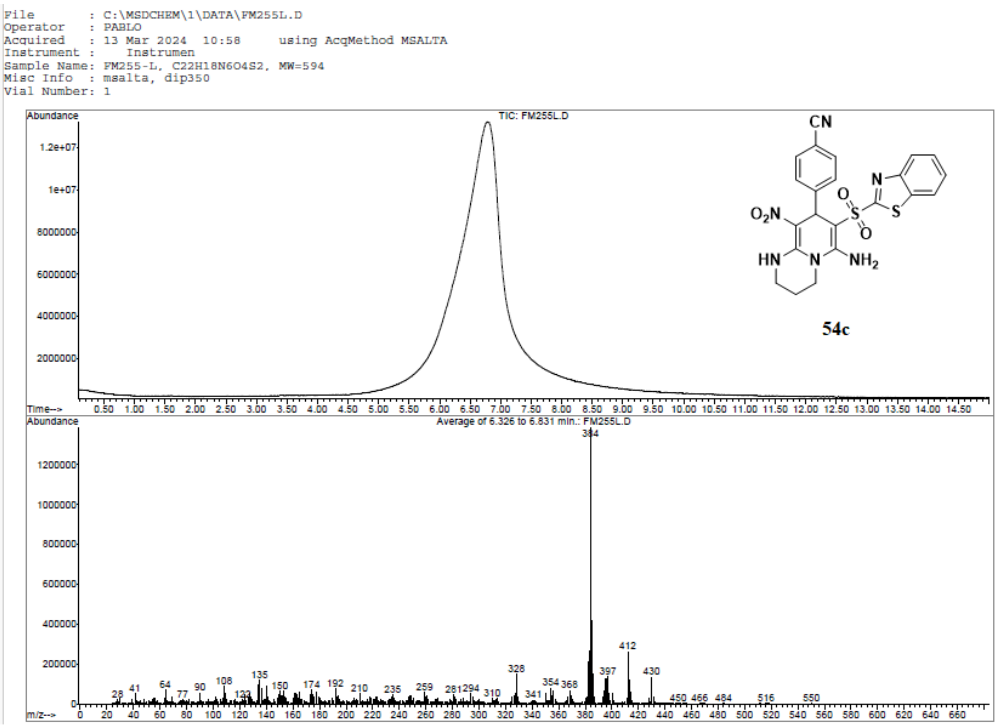
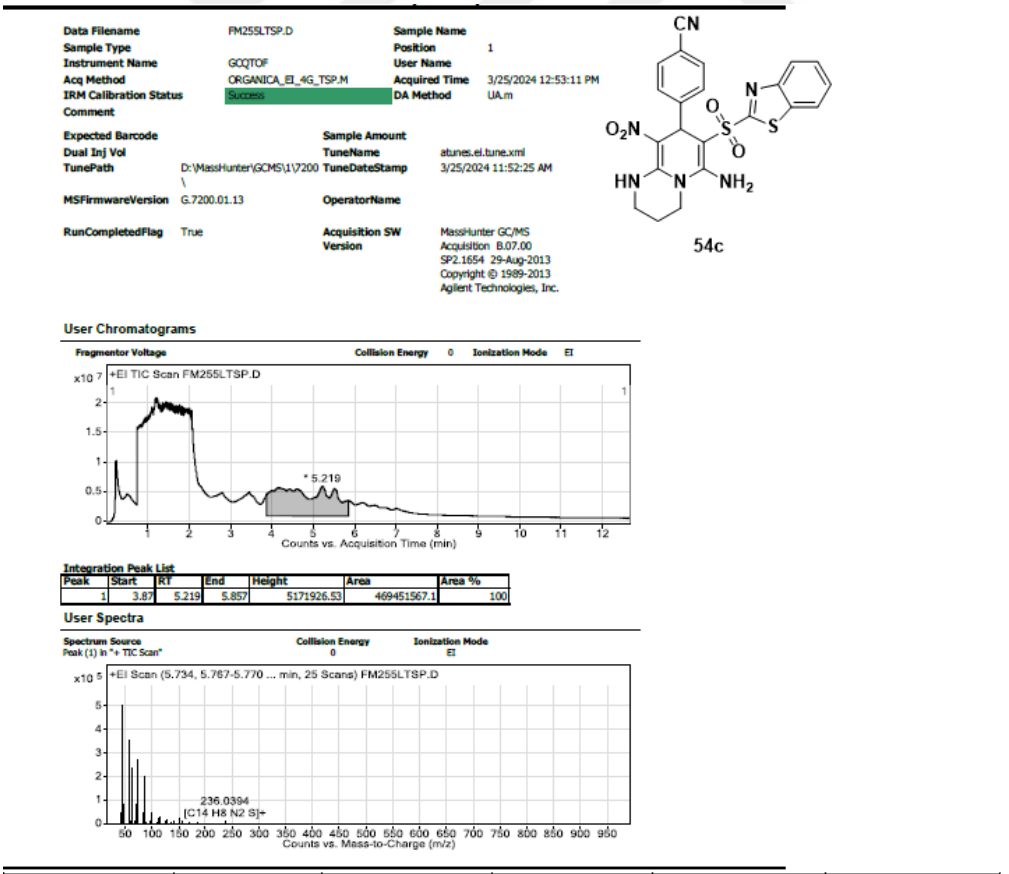


Figure 6.67 HR/MS data for the **54c** compound



SAMPLE	Formulae	mV FAB th.340	ns FI time	Required	Detection peak
54c	C22H18N6O4S2	0.51	17	494.083098	494.0837

Figure 6.68 HR/MS report for the **54c** compound

7. REFERENCE

All source citations in this thesis follow the American Psychological Association (APA) 7th edition guidelines.

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