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BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY

ONE-POT THREE-COMPONENT SYNTHESIS AND CHARACTERIZATION OF NITRO-INDENO-THIAZOLO-PYRIDINES IN PEG-400/AcOH

MASTER OF SCIENCE

ABDULKAREEM HANOON

ACADEMIC SUPERVISOR
Prof. Dr. Cevher ALTUĞ

BOLU, JULY 2023

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One-Pot Three-Component Synthesis and Characterization of Indeno-Thiazolo-Pyridines in PEG-400/AcOH, submitted by **Abdulkareem Afif Hanoon** and defended before the Examining Committe Members listed below in partial fulfillment of the requirements for the degree of **Master of Science** in **Department of Chemistry, Institute of Graduate Studies of Bolu Abant Izzet Baysal University in 26.07.2023** by

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ABSTRACT

ONE-POT THREE-COMPNENT SYNTHESIS AND CHARACTERIZATION OF NITRO-INDENO-THIAZOLO-PYRIDINES IN PEG-400/AcOH

MASTER THESIS
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BOLU, JULY 2023
(XVII + 58)

In this study, an efficient and eco-friendly method has been developed for the synthesis of a selected library of nitro-indeno-thiazolo-pyridine containing heterocyclic scaffold, via one-pot three-component reactions. In order to obtain desired products, 1,3-indandione, 2-nitro methylenethiazolidine and aromatic aldehyde derivatives were mixed in polyethylene glycol and acetic acid system under reflux temperature. The multi-component reaction (MCR) occurs first through Knoevenagel condensation followed by Michael addition. The products' yields range from moderate to good. All products were characterized by physical (m.p.) and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, and LC/MS) methods.

KEYWORDS: Heterocylic Compounds, Multi-Component Reactions (MCRs), 1,3-Indandione, Thiazolo[3,2-a]pyridines, 2-nitro methylenethiazolidine.

ÖZET

İNDENO-TİYAZOLO-PİRİDİNLERIN PEG-400/ACOH İÇERİSİNDE TEK KAPTA ÜÇ BİLEŞENLİ SENTEZİ VE KARAKTERİZASYONU

MASTER TEZİ
ABDULKAREEM HANOON
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: PROF. DR.CEVHER ALTUĞ
YARDIMCI TEZ DANIŞMANI DR.ÖĞRT.ÜYESI CEM GÖL)
BOLU, TEMMUZ - 2023
(XVII + 58)

Bu çalışmada, nitro-indeno-tiyazolo-piridin heterosiklik yapı birimi içeren yeni bir kütüphanenin tek kapta üç bileşenli reaksiyonla 1-4 saatte sentezlenmesi için verimli ve çevre dostu bir yöntem geliştirilmiştir. 1,3-İndandion, 2-nitrometilentiyazolidin ve aromatik aldehit türevleri polietilen glikol ve asetik asit sisteminde kaynama sıcaklığında karıştırılarak istenilen ürünler elde edildi. Çok bileşenli reaksiyon (MCR), önce Knoevenagel kondenzasyonu ve ardından Michael katılması yoluyla gerçekleşir. Ürünlerin verimleri orta ile iyi arasında değişmektedir. Tüm ürünler, fiziksel (m.p.) ve spektroskopik (IR, ^{1}H NMR, ^{13}C NMR ve LC/MS) yöntemlerle karakterize edildi.

ANAHTAR KELİMELER: Heterohalkalı bileşikler, Çok Bileşenli Reaksiyonlar (ÇBR), 1,3-İndandion, Tiyazolo [3,2-a] piridin, nitro metilentiyazolidin.

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LIST OF ABBREVIATIONS AND SYMBOLS

MCRs : Multi-component reactions

α : Alpha

AcOH : Acetic acid

PEG : Polyethylene glycol

Ar : Aryl or aromatic

1,4-DHP : 1,4-dihydropyridines

NLO : Nonlinear optical

NMP : N-Methyl-2-pyrrolidone

CDK2 : Cyclin-dependent kinase 2

ArOH : Phenol or aromatic alcohol

β : Beta

EtOH : Ethanol

^{13}C NMR : Carbon nuclear magnetic resonance

COOH : Carboxylic acid

$CDCl_3$-*d* : Deuterated chloroform

cm^{-1} : Reciprocal centimeter

CH_3ONa : Sodium methoxide

DMSO-d_6 : Deuterated dimethyl sulfoxide

Et_3N : Triethyl amine

EtOAc : Ethyl actetate

^{1}H NMR : Proton nuclear magnetic resonance

HIV : Human immunodeficiency viruses

H_2O_2 : Hydrogen peroxide

IR : Infrared

KBr : Potassium bromide

m.p. : Melting point

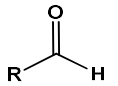
rt : Room temperature

TLC : Thin-layer chromatography

THF : Tetrahydrofuran

UV : Ultraviolet

FORMULAE



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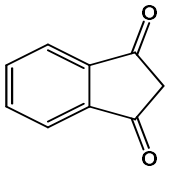

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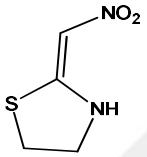

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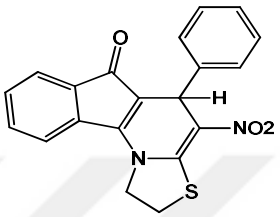

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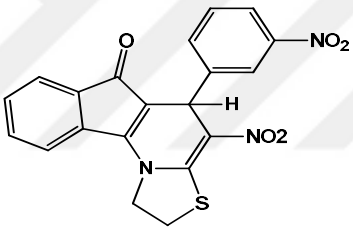

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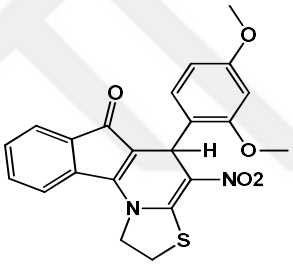

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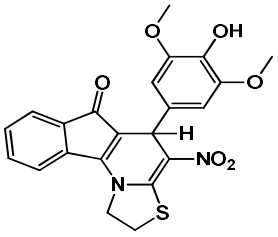

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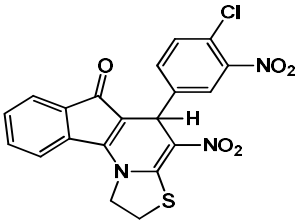

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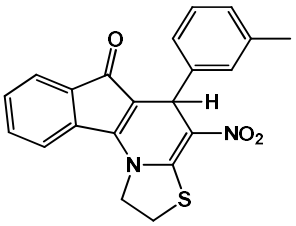

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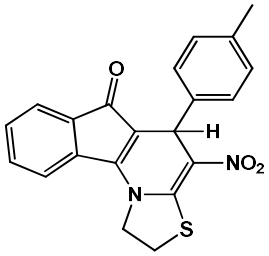

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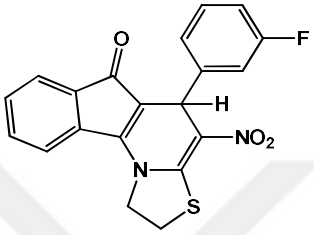

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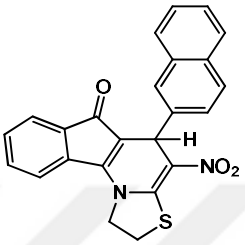

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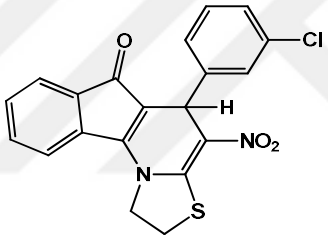

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To my big family

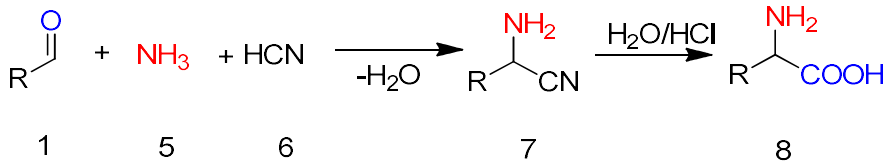
1. INTRODUCTION

1.1. Definition Of Multi-Component Reactions (MCRs)

Multi-Component Reactions (MCRs) are synthetic chemical reactions that involve the simultaneous combination of three or more reactants to form a single product molecule. Unlike traditional sequential reactions that require multiple steps, MCRs enable the efficient and rapid construction of complex molecules in a single step, They are typically employed to synthesize target molecules in a single step (as there is no need to identify intermediates and only one reaction vessel is required instead of costly equipment's),[1] saving time, and high-throughput production of tiny chemical compounds,[2] low cost, high yield (whole conversion), low energy, in addition to being environmentally friendly work steps (are acknowledged as green chemical processes).[3] Which makes it important as a result of its wide benefits as it has been used to generate diversity-oriented and biased combinatorial libraries, to synthesize extremely complex natural products, and to mass-produce therapeutic candidates,[4] as a result, MCRs has attracted a lot of attention recently in the medical and pharmaceutical fields,[5] such as antimicrobial, antibacterial, glucosidase inhibitor,[6] antidyslipidemic and antioxidant activities,[7] and antimalarial drug.[8] Since 1995, MCR research has naturally evolved into a rapidly developing subject area of chemical synthesis, many reviews and researchers that partly concentrate on various techniques for finding new MCRs garnering the attention of both academic and industrial fields.[9]

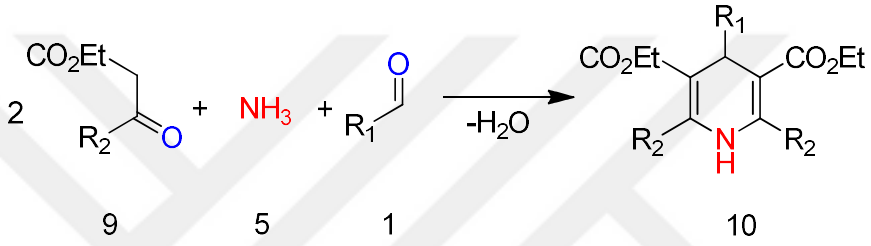
1.2. History Of Multi-Component Reactions (MCRs)

Over 150 years, in view of its importance and characteristics, the research was deepened by studies and research about MCRs. The first example of MCRs was proposed by Adolph Strecker in 1850,[10] which is known as Strecker reaction. He produced α-amino nitrile (7) in a single step by reacting an amine (ammonia) (5), hydrogen cyanide (6), in addition to an aldehyde (1), one of the best promising properties of this reaction is desired amino-acid (8) can be obtained by further hydrolysis of an α-amino nitrile (Scheme 1.1).



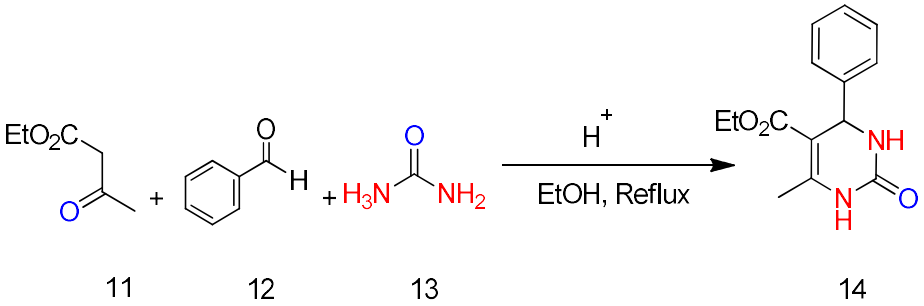
Scheme 1.1. The Strecker three-component process yields amino acids.

1,4-Dihydropyridines (also known as the 1,4-DHP compound) prepared by Arthur Rudolf Hantzsch via MCRs in 1882,[11] this reaction is made up of four components, substituted dihydropyridines obtained (10) from ammonia (5), aldehyde (1), in addition to two β-ketoesters equivalents (9) (Scheme 1.2).



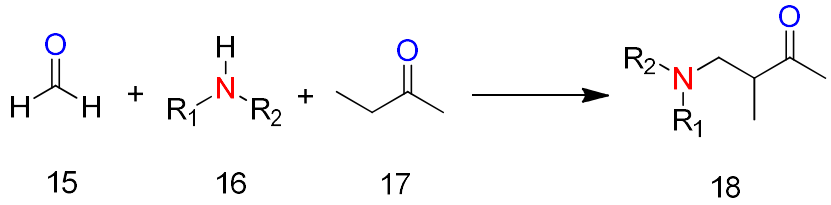
Scheme 1.2. Arthur Rudolf Hantzsch invented the synthesis of, 4-dihydropyridine.

In 1893, dihydropyrimidinones (14) was prepared by Italian chemist Pietro Biginelli.[12] To accomplish dihydropyridines', reaction of cyclo-condensation of ethyl β-ketoester (11), urea (13), and benzaldehyde (12), reacted in the presence of an acid as catalyst under reflux temperature. The product of Biginelli reaction has been commonly employed in the pharmaceutical industry such as calcium channel blockers and hypertension medicines (Scheme 1.3).[13]



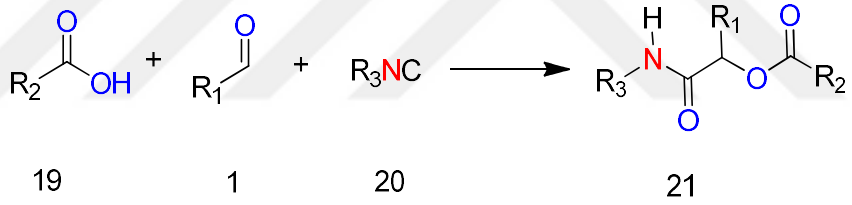
Scheme 1.3. Dihydropyrimidinone synthesis in one-pot by Biginelli reaction.

In 1912, Carl Mannich discovered the Mannich reaction.[14] It is a chemical process used to create α-aminocarbonyl (18) compounds by using formaldehyde (15), secondary amine (16), and ketones (17), via MCRs (Scheme 1.4).



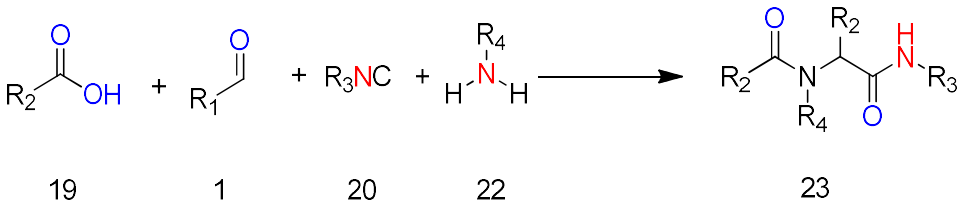
Scheme 1.4. Mannich base synthesis is based on α-amino-carbonyl synthesis.

Mario Passerini proposed the first isocyanide-based multi-component reactions (IMCRs) in 1921.[15] Which is known as the Passerini-three component reaction (P-3CR), and P-3CR provides for the one-step synthesis of α-acyloxy-carboxamides (21), by reacting carboxylic acid (19) as nucleophile, aldehyde or a ketone (1), and an isocyanide (20) (Scheme 1.5).



Scheme 1.5. Passerini's three-component synthesis of acyloxycarboxamides.

Continuing the evolution and history of MCRs, the Ugi-four component reaction (U-4CR) is an isonitrile-based MCR that offers a quick way to prepare α-acylamino amide derivatives (23),[16] obtained from the reaction of carboxylic acids (19), primary amines (22), aldehydes (1), and isocyanides (18). Furthermore, U-4CR has enhanced its efficiency in synthesizing a variety of organic compounds and macro-cyclic molecules, due to the extraordinary flexibility of the Ugi reaction when applied to various functional groups (Scheme 1.6). [17]



Scheme 1.6. Ugi reaction-based synthesis of α-acylamino amide.

Additionally, the integration of new MCR chemistries with recent concepts and advancements in virtual screening of chemical libraries needs a chemoinformatics strategy that is both integrated and comprehensive, MCRs have been demonstrated to be the most efficient method to a wide range of chemical synthetic issues, particularly the synthesis of natural-product-like compounds.[18]

1.3. Some Important Drug-Like Structure Synthesized by MCRs

Merck&Co developed a synthesis in which Ugi-type MCR is essential for the manufacture of its inhibitor Crixivan (Indinavir) (Figure 1.1), HIV protease inhibitors are recognized for their lengthy synthesis procedures, which make up at least 15 synthetic steps and make their manufacturing costly, as a result, the period will be shorter, easier, and more productive.[19]

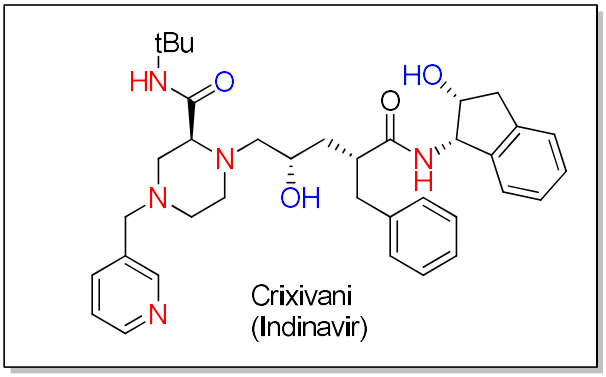


Figure 1.1. Crixivan, an anti-HIV drugs, incorporates Ugi-4CR.

Based on the Hantzsch synthesis, Nifedipin (Adalat^{R}) (Figure 1.2) prepared by the Bayer AG company, one of its most important applications is as a calcium channel blocker and treatment for cardiovascular disease. Bayer chemists

constructed a biased chemical library by changing the amine, aldehyde, and β-ketoacidester components, but only after Nifedipin had already been approved for use as a blood pressure lowering drug.[20]

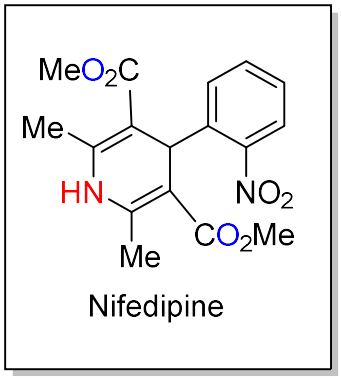


Figure 1.2. Nifedipine was synthesized by the Bayer AG Corporation in a single step.

Hoffmann-La Roche scientists in Basel created the first library of tiny drug-like compounds utilizing MCR chemistry in 1981, providing a library of Nocardicin A analogues (Figure 1.3).[21]

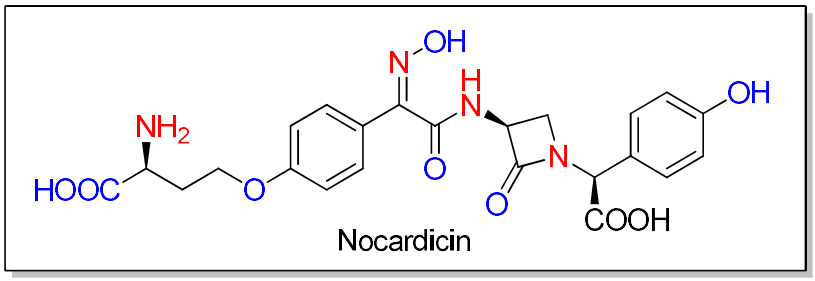


Figure 1.3. Nocardicin was synthesized by Hoffmann-La Roche scientists in Basel.

Ugi-3 component reactions are involving different isocyanides, aldehydes, and secondary amines can be used to synthesize the family of local anaesthetics, these compounds were created through traditional chemistry in the 1950s, resulting in multiple commercialized goods through various firms. With today's techniques, the entire class of these chemicals would be created via library synthesis in a single experiment and patented by a single company some of these compounds, Xylocain, Prilocaine, Tocainidin, and Aptocain (Figure 1.4).[22]

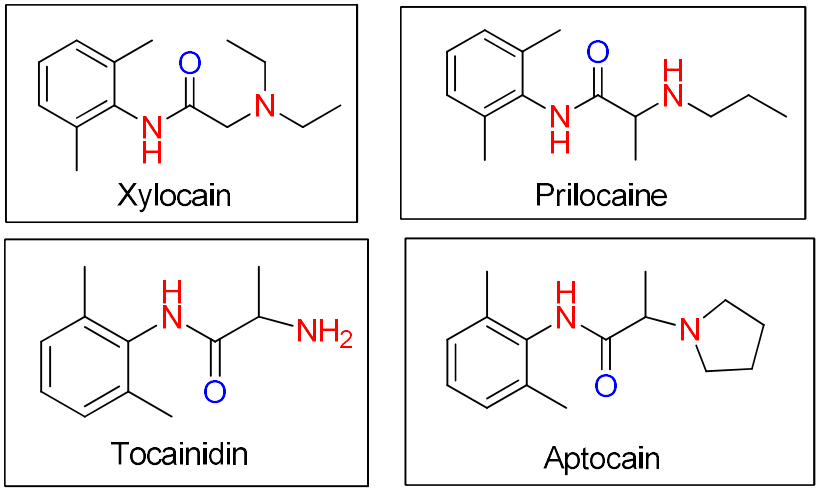


Figure 1.4. Potentially reachable via MCRs are offered products.

1.4. Indan-1,3-dione Compounds

Indan-1,3-dione compounds are aromatic compounds with a molecular structure that is like that of the phthalic anhydride molecule, except for the oxygen atom, where the benzene atom is linked to a five membered ring as a diketone structure, and the acetophenone is a substitute in the alpha site of the phenyl ring, which has the general structure (Figure 1.5). Indan-1,3-dione is a flexible and increasingly crucial key component in chemical synthesis, Indan-1,3-dione has been intensively studied as a synthetic intermediary for the synthesis of a wide range of biologically active molecules, in medicine frequently used as anticoagulants to prevent blood clots and treat a wide range like deep vein thrombosis and pulmonary embolism, warfarin and phenindione are two examples of indandione compounds.[23] Furthermore, indane-1,3-dione is also an electron acceptor frequently employed in the manufacture of dyes for solar cell applications, photopolymerization initiators, and chromophores for NLO applications.[24]

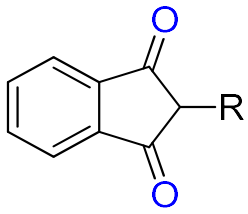
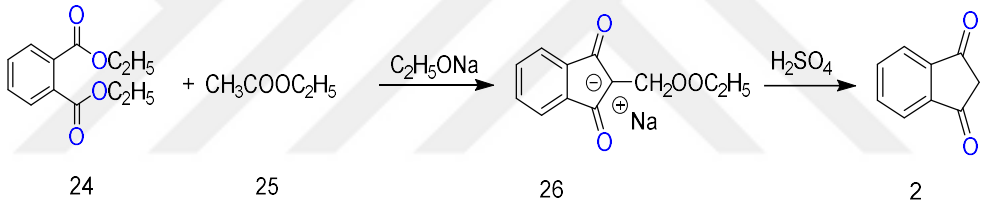


Figure 1.5. General structure of 1,3-Indandione.

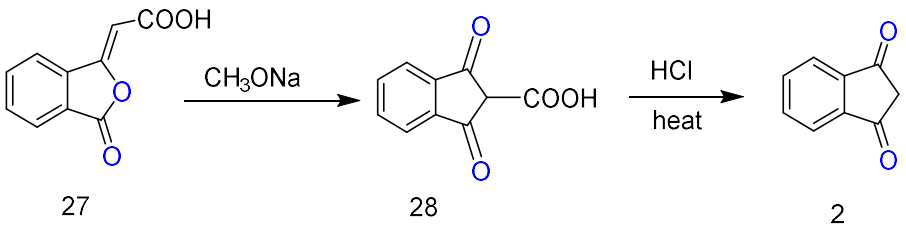
1.5. Synthetic Methods Of Indan-1,3-dione

Indane-1,3-dione can be synthesized following different synthetic procedures, the most straightforward one consists in the nucleophilic addition of alkyl acetate by Perkin reaction, by condensation diethyl phthalate (24) with ethyl acetate (25) in the presence of sodium ethoxide this intermediate (26) can be hydrolyzed and decarboxylated *in situ* under basic conditions (sulphuric acid) with heating to producing indane-1,3-dione (2) in the two steps (Scheme 1.7).[25] .



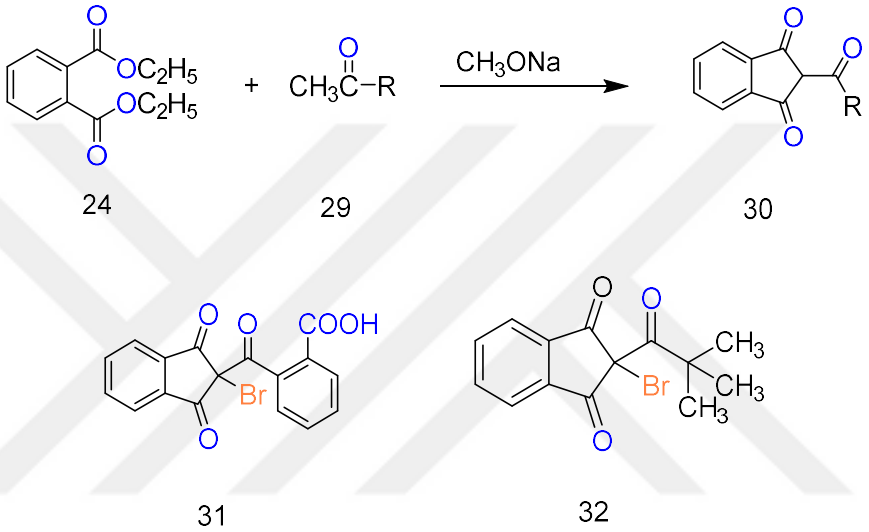
Scheme 1.7. Synthesis of indane-1,3-dione by Perkin reaction.

Phthalyl acetic acid (27) reacts with sodium methoxide (CH_3ONa) and the resulting product (28) is heated with hydrochloric acid to obtain Indane-1,3-dione (2) (Scheme 1.8).[26]



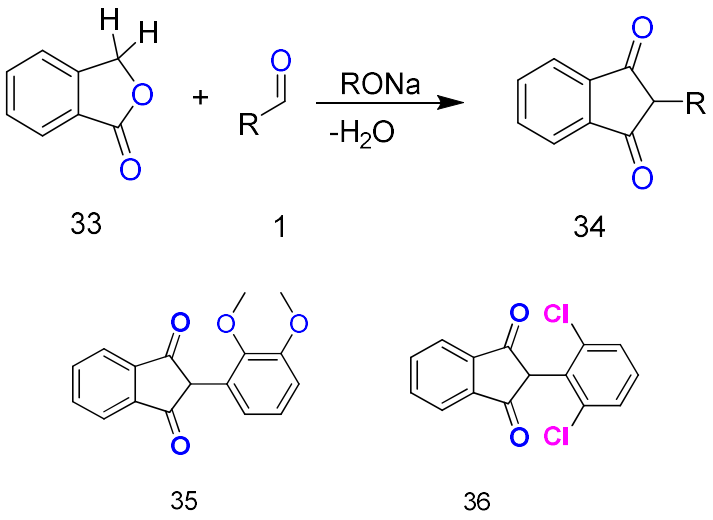
Scheme 1.8. Obtained 1,3-indanedione by Perkin reaction from phthalyl acetic acid.

Substituted indane-1,3-dione compounds (30) were synthesized by reacting diethyl phthalate (24) with ketones (29) containing an active methyl group and using sodium methoxide as a catalyst, among stabilizer compounds that undergo this reaction include (2-bromo-2-(2-carboxybezoyl)-1,3-indandione) (31) and pindone (32), and both compounds (31) and (32) exhibit anti-coagulant activity that varies depending to the degree of branching of the compensated acyl group(Scheme 1.9).[27]



Scheme 1.9. Synthesize of substituted 1,3-indanedione compounds by using sodium methoxide as a catalyst.

In addition, 2-aryl-1,3-indanione (33) was synthesized by reacting phthalide (32) with aromatic aldehyde (1) in the presence of a catalyst.[28] 2,(2,3-dimethoxy phenyl)-1,3-indandione (35) and 2,6-dichlorophenyl-1,3-indandione (36) were synthesized by this reaction (Scheme 1.10).



Scheme 1.10. Synthesized some of substituted 1,3-indanedione compounds from phthalide.

There are numerous additional derivatives of the chemical 1,3-indandione, such as (2,2-dihydroxyindan-1,3-dione) or ninhydrine (37), which is used to denote the amino acid with which a compound has a distinctive purple color (38),[29] as it is used in quantitative analysis (Figure 1.6).[30]

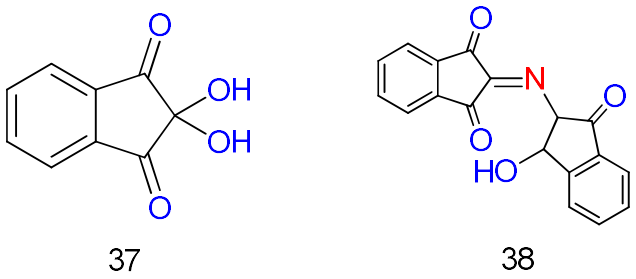
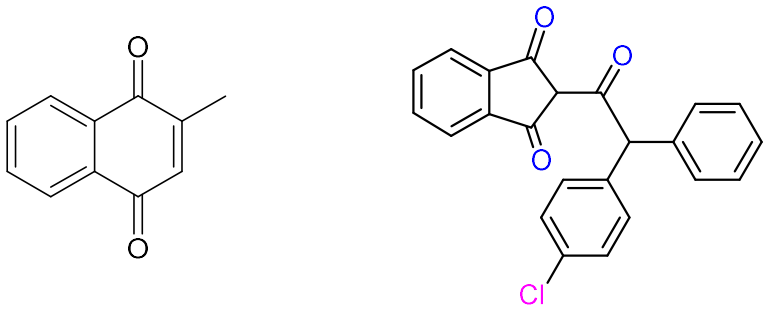


Figure 1.6. Some of substituted 1,3-indanedione compounds were synthesized.

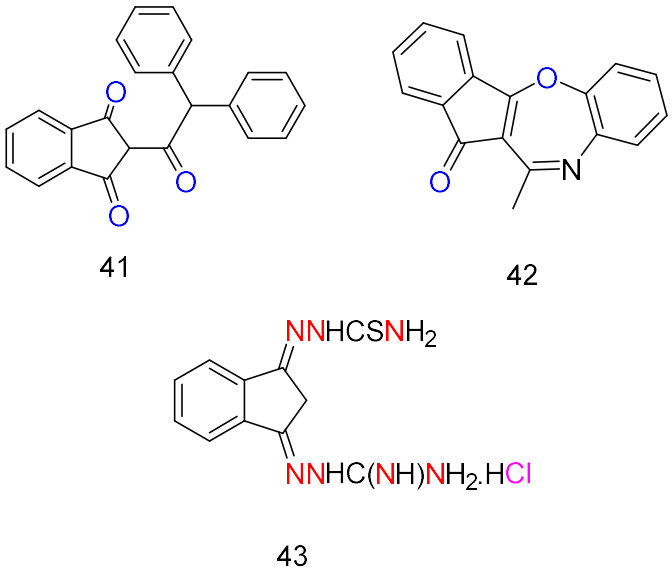
In general, indandione compounds, in addition to their effectiveness as anticoagulants, also have activity against the metabolism of vitamin K3 (39).[31] Chlorophacinone was discovered (40),[32][33] and its applications and uses, influences various types of rodents, used as exterminator for house and field mice and rats, due to its toxic effect on the tissue cells and chromosomes of those animals (Figure 1.7).[34]



39 40

Figure 1.7. S-(2,6-diphenyl-1,3,5,7-tetraoxo hydrindacene and Chlorophacinone.

Also, diphenadione (41),[35] (2-(b-diphenyl acetyl-1,3-indadione) or its sodium salt, which was used as a pesticide as a result of experiments conducted on a type of rice field mouse. Oxazepinone (42) resulted from condensation between 2-acetyl-1,3-indandione with o-hydroxy aniline, which was used as an anticoagulant compound.[36] As for compound (1,3-indandione dithio seimicarbazide) (43), it has tuberculostatic activity.[37] Also, some amino derivatives of indanedione compounds showed high effectiveness against the growth of a type of leukemia (cancer) cells and their lining cells, colon tumors and pulmonary vessels (Figure 1.8).[38]



41 42 43

Figure 1.8. Some of the substituted 1,3-indanedione compounds (diphenadione, Oxazepinone, (1,3-indandione dithio-semicarbazide).

1.6. Thiazolo[3,2-a]pyridines

A pyridine ring is fused to a thiazole ring to form the heterocyclic compounds known as thiazolopyridines, which are made up of thiazole rings attached to pyridine rings, the six-membered pyridine ring holds a nitrogen atom, while the five-membered thiazole ring has a sulfur and a nitrogen atom. Thiazolopyridines unique features and functions are a result of the unique structure that is created when these two rings combine, the following classes of thiazolopyridines can be identified (see Figure 1.9).[39]

Because of their wide variety of pharmacological activity and the potential for functionalization of synthetic derivatives at various molecular locations, thiazolopyridines, like purine bioisosteres, are a significant type of heterocyclic system that are being investigated extensively.[40]

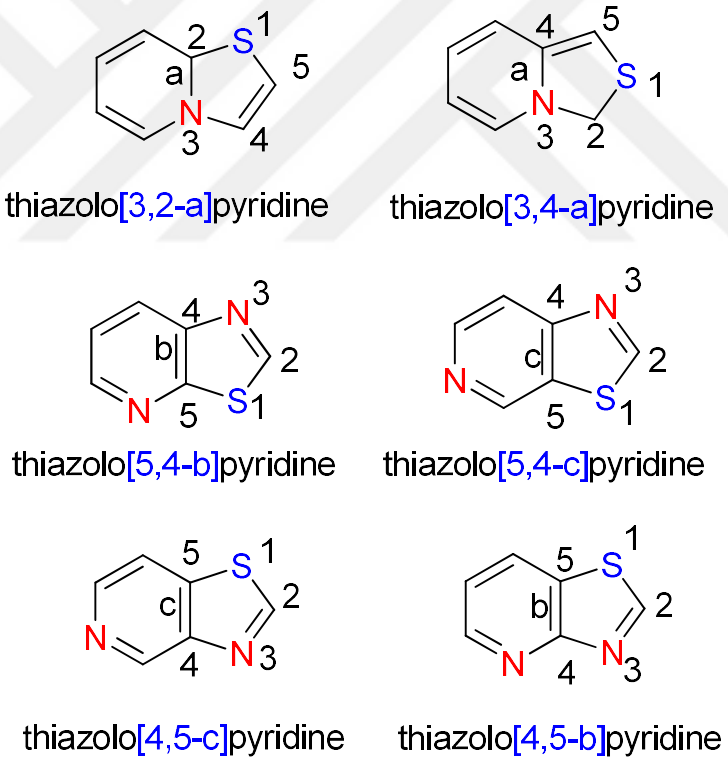
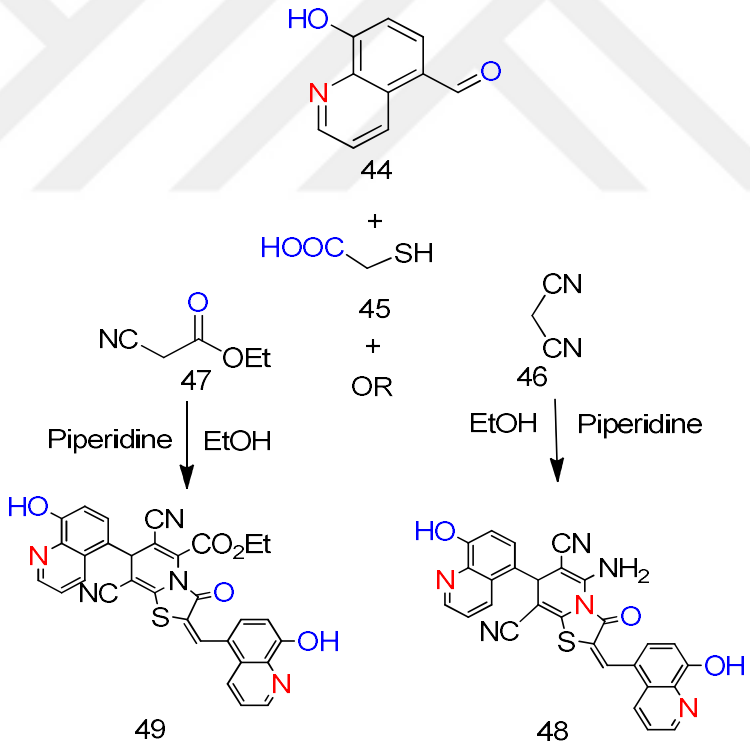


Figure 1.9. Six isomeric pyridine rings make up the category of thiazolopyridines.

Thiazolopyridines are among several compounds with physiological activity. Particularly, thiazolo[3,2-a]pyridine derivatives are utilized to treat lung cancer, leukemia, and melanoma because they have anticancer characteristics,[41] antimicrobial activity,[42] potential uterus stimulant,[43] potent CDK2-Cyclin A inhibitor,[44] also inhibiting beta-amyloid production.[45]

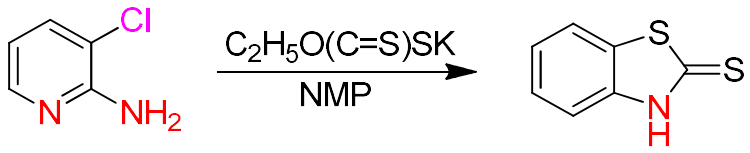
1.7. Some Reactions For Thiazolopyridine Synthesis

2-Mercaptoacetic acid (45), malononitrile (46) or ethyl cyanoacetate (47) they possess active methylene, and aromatic aldehyde (44) in the molar ratio of 1:2:2 in EtOH in the presence of piperidine were the major components in the synthesis of thiazolo[3,2-a] pyridine, these thiazolopyridine compounds (48) and (49) were effectively tested for antifungal activity against four different types of fungus (Scheme 1.11).[46]



Scheme 1.11. Marzoog S. Al-Thebeiti synthesized compounds of thiazolopyridine.

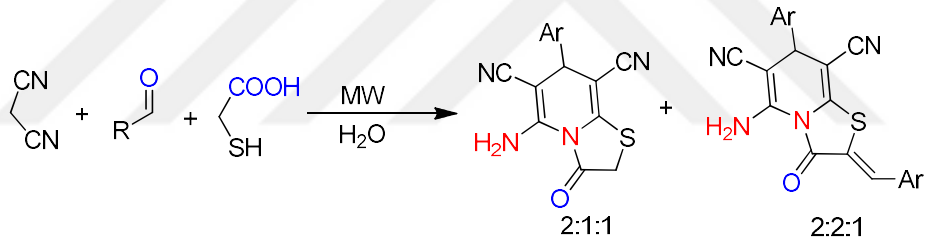
In 2009, thiazolo[4,5-b]pyridine-2(3H)-thione (51) obtained by reacting 2-amino-3-chloropyridine (50) with refluxing NMP and in presence potassium ethyl xanthate as catalyst (Scheme 1.12).[47]



50 51

Scheme 1.12. Thiazolo[4,5-b]pyridine-2(3H)-thione is produced by refluxing potassium ethyl xanthate in NMP.

And in the same year by green chemoselective synthesis, via MCRs malononitrile (46) reacting with 2-mercaptoacetic acid (45) and an aldehyde(1), in water via microwave-assisted, to afford thiazolo[3,2-a] pyridine derivatives (51) and (53) (Scheme 1.13).[48]



46 1 45 52 53

Scheme 1.13. Water-based thiazolo[3,2-a]pyridine synthesis using microwaves.

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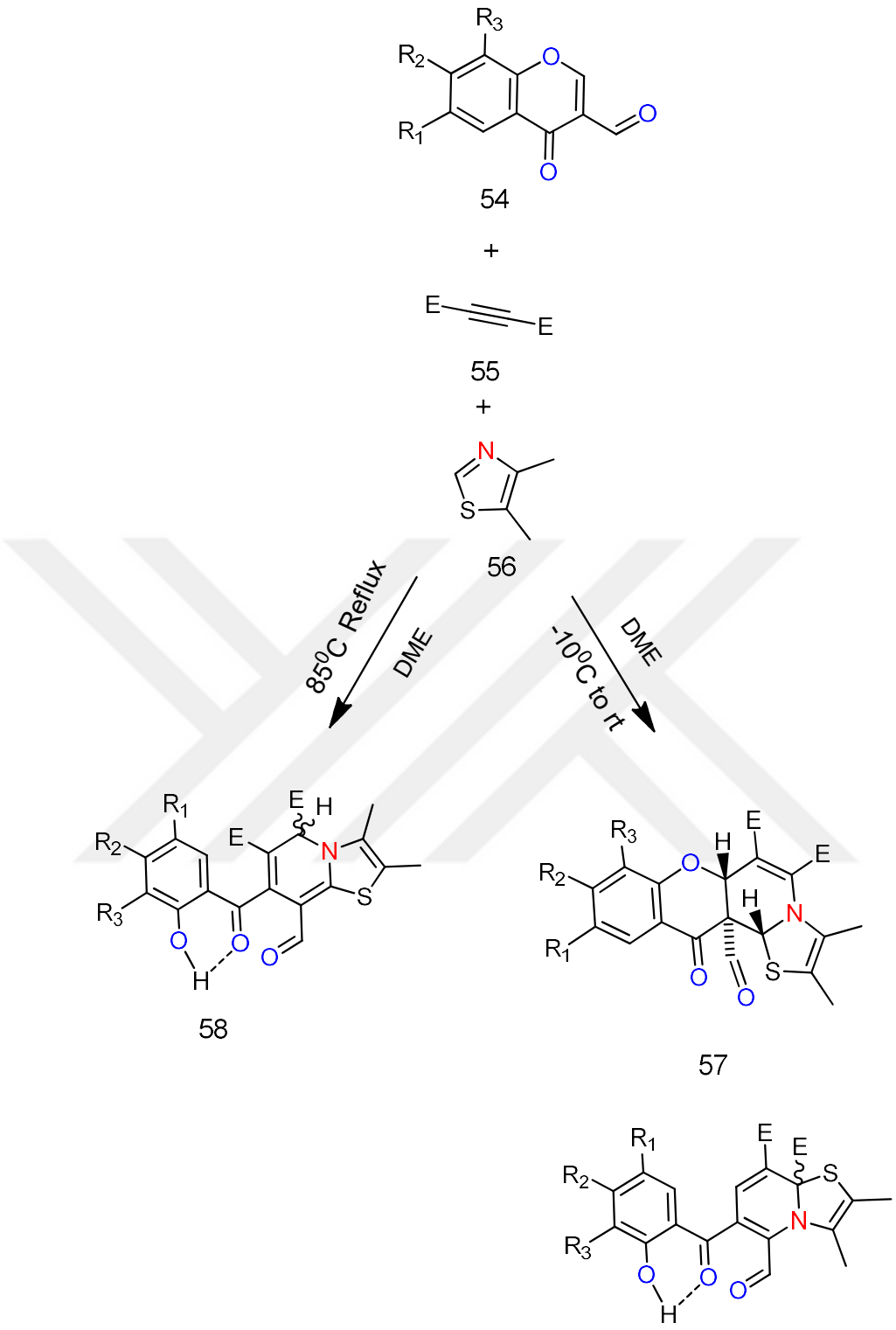
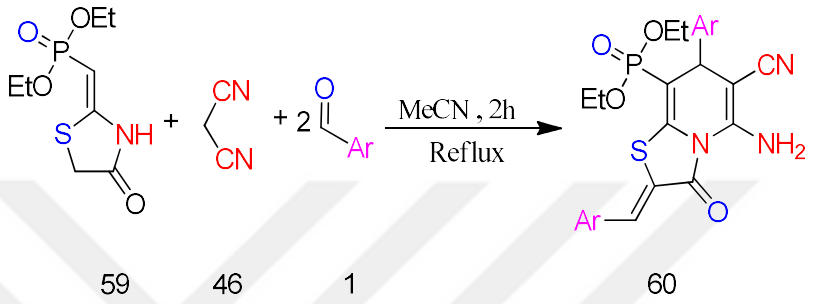
By using thiazole as reactant, and in presence 3-formylchromones (54) and acetylenedicarboxylates (55) and thiazole (56), thiazolopyridine derivatives (57)(58) are obtained at varied dimethoxyethane environments (Scheme 1.14).[49]



Scheme 1.14. Terzidis' synthesis of thiazolopyridine compounds.

A variety of thiazolo[3,2-a]pyridin-8-yl-phosphonate derivatives (60) were synthesized via MCR by using diethyl (E)-((4-oxothiazolidin-2-ylidene)methyl)phospohonate (59), malononitrile (46), and two equivalents of different aromatic aldehydes (1). Regarding benefit, compared to control plants, tomato plants had at least two times as much biomass, branches, and leaf area (Scheme 1.15).[50]



Scheme 1.15. Synthesis of thiazolo[3,2-a]pyridin-8-yl-phosphonate derivatives using MCRs.

2. AIM AND SCOPE OF THE STUDY

Multi-component reactions (MCRs) are a crucial and effective technique in the field of producing small molecules, particularly heterocyclic compounds with therapeutic properties. New synthetic processes are needed to produce new sulfur and nitrogen-containing compounds with potential biological properties and applications in the pharmaceutical industry.

The main goal of this research is to synthesis number of indenone-fused thiazolo[3,2-a]pyridine derivatives in a single step by using one pot 3- multi-component reactions (MCRs) under mild conditions, with moderate yields, easy purification and saving time. All obtained compounds were verified using spectroscopic methods and might be promising candidates for future biological research.

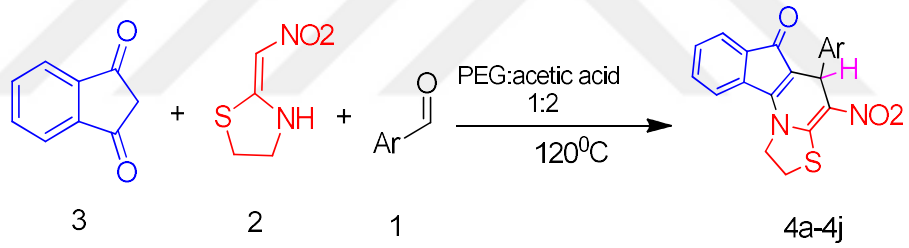
3. EXPERIMENTAL

3.1. Materials And Apparatus

Commercial reagents and chemicals used in both works were purchased from Sigma Aldrich. TLC were performed on Merck silica gel F-254 plates. Melting points (mp) were determined by using Mel-Temp® Digital Melting Point Apparatus (Cole-Parmer). FT-IR spectra were recorded on SHIMADZU FT-IR-8400S and on Perkin Elmer Spectrum FTIR-ATR spectrophotometer. NMR spectra were recorded on a Bruker Biospin 500 MHz NMR spectrometer in DMSO-d6 at room temperature. Coupling constants (J) are expressed in Hertz (Hz) and the chemical shifts are reported in parts per million (ppm). The splitting patterns are assigned as follows: s (singlet); d (doublet); m (multiplet); dd (doublets of doublet); td (triplets of doublet). LC/MS were carried out on a Bruker Daltonics micrOTOF-Q mass spectrometer (Bruker, Billerica, MA, USA) using electrospray ionization.

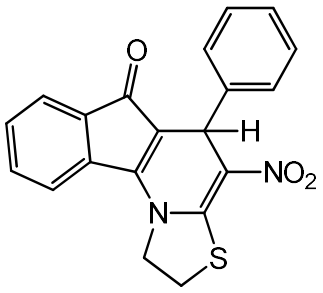
3.2. General Procedure For Synthesis Of Thiazolo[3,2-a]pyridine Derivatives

1,3-Indandione (1.0 eq.,1.0 mmol, 146 mg), 2-nitromethylene thiazolidine (2) (1.0 eq.,1.0 mmol, 146 mg), and aromatic aldehyde derivatives (1) (1.0 eq., 1.0 mmol) was suspended in 15 mL of solvent (1:2 mixture of polyethylene glycol 400 and acetic acid). After heating the reaction suspension to 120 ^{0}C, it gradually turns into a brown solution. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane, 1:1). The reaction mixture is cooled to room temperature after heating to the time required for each reaction **(Table 3.1)**, and the brown precipitate is filtered off. After that, it was washed with 96% ethanol followed by water to give the crude product and the crude product recrystallized from DMF:H_2O to afford the pure product which were further analyzed by IR, MASS, ^{1}H NMR, ^{13}C NMR, and LC/MS.



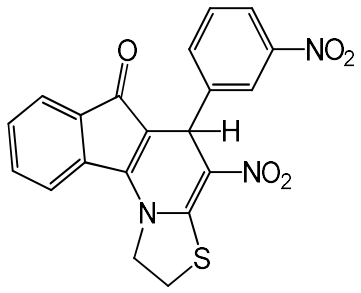
Scheme 3.1. Synthesis of Thiazolo[3,2-a]pyridine derivatives **4a-4j**.

3.2.1. 4-Nitro-5-phenyl-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one (4a)



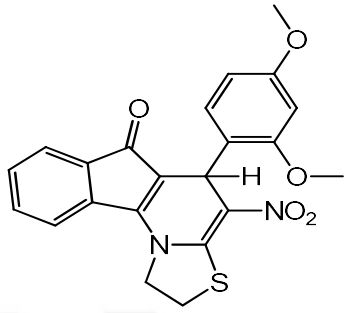
Dark Red solid, (75%); m.p. 277-278 ^{o}C, IR (KBr) (ν_{max} / cm^{-1}): 1698 (C=O), 1529 and 1368 (NO_2), 1210 (C-N), 752 (Ar). ^{1}H NMR (500 MHz, DMSO) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 7.32 (s, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.1 Hz, 1H), 5.10 (s, 1H), 4.95 (ddd, *J* = 9.8, 8.3, 5.5 Hz, 1H), 4.70 (dd, *J* = 18.7, 9.0 Hz, 1H), 3.58 (m, 2H). ^{13}C NMR (125 MHz, DMSO) δ 190.4, 159.4, 153.0, 143.2, 136.3, 133.2, 133.2, 130.9, 128.9, 128.7, 128.3, 128.2, 127.4, 125.6, 122.2, 114.3, 52.7, 38.1, 29.5. LC/MS m/z (ESI^{+}) for $C_{20}H_{14}N_2O_3S[M+H]^{+}$ 363.1 (MH^{+}, 100%), 102.2 (15%).

3.2.2. 4-Nitro-5-(3-nitrophenyl)-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one (4b)



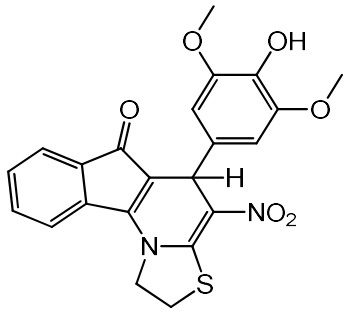
Dark Red solid, (94%); m.p. 277-278 ^{o}C, IR (KBr) (ν_{max} / cm^{-1}): 1683 (C=O), 1529 and 1368 (NO_2), 1211 (C-N), 756 (Ar). ^{1}H NMR (500 MHz, DMSO) δ 7.64 (d, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.15 (t, *J* = 7.4 Hz, 2H), 7.10 (m, 2H), 6.99 (d, *J* = 7.3 Hz, 1H), 5.04 (s, 1H), 4.99 – 4.91 (m, 1H), 4.68 (d, *J* = 9.4 Hz, 1H), 3.57 (t, *J* = 8.3 Hz, 2H). LC/MS m/z (ESI^{+}) for $C_{20}H_{13}N_3O_5S$ $[M+H]^{+}$ 408.1 (MH^{+}, 50%), 239.1 (10%), 102.3 (100%).

3.2.3. 5-(2,4-Dimethoxyphenyl)-4-nitro-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one (4c)



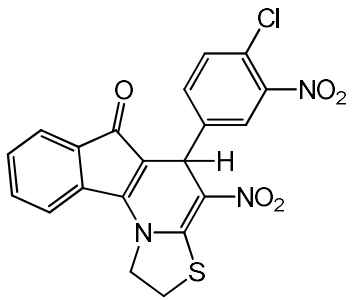
Dark Red solid, (70%); m.p. 270- 271 ºC, IR (KBr) (ν_{max} / cm^{-1}): 1678 (C=O), 1531 and 1368 (NO_2), 1207 (C-N), 752 (Ar). ^{1}H NMR (500 MHz, DMSO) δ 7.60 (d, *J* = 6.4 Hz, 1H), 7.42 (s, 1H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.28 (s, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.46 (s, 1H), 6.43 (d, *J* = 7.8 Hz, 1H), 5.18 (s, 1H), 4.91 (d, *J* = 6.3 Hz, 1H), 4.73 (d, *J* = 8.6 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.55 (s, 2H). ^{13}C NMR (125 MHz, DMSO) δ 190.2, 160.1, 159.1, 158.9, 153.1, 136.3, 133.4, 132.8, 131.4, 130.5, 125.3, 122.6, 122.0, 121.9, 113.8, 105.3, 99.2, 56.3, 55.5, 52.5, 34.0, 29.4. LC/MS m/z (ESI^+) for $C_{22}H_{18}N_2O_5S[M+H]^+$ 423.1 ($M+H^+$, 95%), 303.1 (50%), 285.0 (100%), 230.1 (7%), 153.3 (23%), 137.1 (7%), 102,3(23%).

3.2.4. 5-(4-Hydroxy-3,5-dimethoxyphenyl)-4-nitro-1,2 dihydroindeno[2,1-e]thiazolo[3,2 a]pyridin-6(5H)-one (4d)



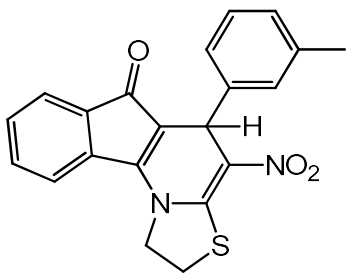
Dark Red solid, (70%); m.p. 270-271 ºC, IR (KBr) (ν_{max} / cm^{-1}): 3288 (OH) ,1685 (C=O), 1511 and 1368 (NO_2), 1200 (C-N), 1173 (C-O), 752 (Ar). ^{1}H NMR (500 MHz, DMSO) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.46 (td, *J* = 7.3, 1.7 Hz, 1H), 7.41 – 7.34 (m, 2H), 6.49 (s, 2H), 5.02 (s, 1H), 4.93 (m, 1H), 4.68 (dd, *J* = 18.8, 8.8 Hz, 1H), 3.71 (s, 6H), 3.56 (m, 2H). ^{13}C NMR (125 MHz, DMSO) δ 190.5, 159.0, 152.6, 148.3, 136.3, 135.5, 133.3, 133.2, 133.1, 130.8, 125.4, 122.5, 122.2, 114.3, 106.0, 56.6, 52.7, 37.8, 29.5. LC/MS m/z (ESI^+) for $C_{22}H_{18}N_2O_6S[M+H]^+$ 439.0 (MH^+, 100%), 285.0 (7%), 239.3 (13%), 102.2 (75%).

3.2.5. 5-(4-Chloro-3-nitrophenyl)-4-nitro-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one (4e)



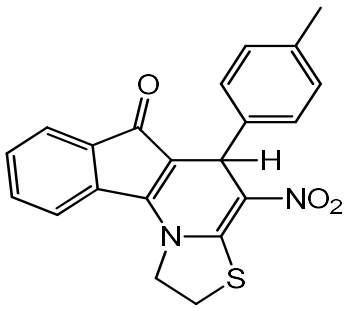
Light Red solid, (82%); m.p. 260-261 ºC, IR (KBr) (ν_{max} / cm^{-1}): 1730 (C=O), 1530 and 1384 (NO_2), 1206 (C-N), 1168 (C-O) . ^{1}H NMR (500 MHz, DMSO) δ 8.08 – 8.03 (m, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.69 (dd, *J* = 7.9, 5.2 Hz, 1H), 7.54 (s, 1H), 5.07 (s, 1H), 4.88 (dt, *J* = 10.0, 7.7 Hz, 1H), 4.75 (dt, *J* = 15.1, 7.5 Hz, 1H), 4.30 (ddd, *J* = 11.0, 8.5, 7.2 Hz, 1H), 3.87 (d, *J* = 1.3 Hz, 1H), 3.60 – 3.49 (m, 2H). ^{13}C NMR (125 MHz, DMSO) δ 197.5, 190.2, 162.3, 160.4, 153.5, 150.6, 148.1, 148.0, 144.1, 143.0, 135.7, 133.5, 133.3, 131.8, 131.6, 131.3, 125.5, 125.1, 123.9, 123.5, 122.9, 122.3, 117.3, 87.8, 63.3, 51.3, 38.0, 36.7, 29.5, 27.6. LC/MS m/z (ESI^+) for $C_{20}H_{12}ClN_3O_5S[M+H]^+$ 442.0 (100%), 405.9(5%), 102.2 (5%).

3.2.6. 4-Nitro-5-(m-tolyl)-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one (4f)



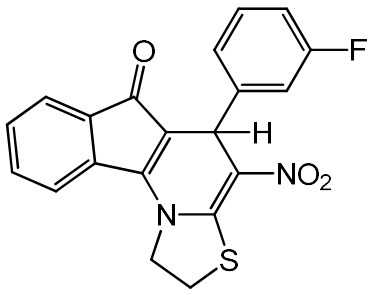
Dark Red solid, (75%); m.p. 277-278 ºC, IR (KBr) (ν_{max} / cm^{-1}): 2987 (CH3-streach), 1687 (C=O), 1525 and 1383 (NO_2), 1200 (C-N), ^{1}H NMR (500 MHz, DMSO) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 10.8, 4.2 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 6.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.07 (m, 2H), 7.00 (d, *J* = 7.3 Hz, 1H), 5.04 (s, 1H), 4.98 – 4.91 (m, 1H), 4.68 (dd, *J* = 18.6, 9.0 Hz, 1H), 3.61 – 3.54 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 190.3, 159.3, 152.9, 137.8, 136.2, 133.2, 133.1, 130.9, 128.7, 128.6, 128.1, 125.6, 125.4, 122.6, 122.2, 114.3, 52.6, 38.0, 29.4, 21.5. LC/MS m/z (ESI^+) for $C_{21}H_{16}N_2O_3S[M+H]^+$ 377.1 (MH^+,100%), 251.1(25%), 241.3 (15%), 102.2 (85%).

3.2.7. 4-Nitro-5-(p-tolyl)-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one (4g)



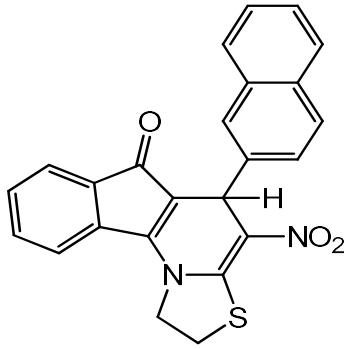
Dark Red solid, (80%); m.p. 267-268 ºC, IR (KBr) (ν_{max} / cm^{-1}): 1694 (C=O), 1520 and 1366 (NO_2), 1210 (C-N), 1167 (C-O).^{1}H NMR (500 MHz, DMSO) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.47 (td, *J* = 7.6, 1.2 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 6.2 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.05 (s, 1H), 4.95 (ddd, *J* = 10.1, 8.3, 5.5 Hz, 1H), 4.69 (dd, *J* = 18.8, 8.8 Hz, 1H), 3.58 – 3.54 (m, 2H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 190.4, 159.2, 152.9, 140.3, 136.6, 135.5, 135.3, 133.2, 133.1, 130.9, 129.2, 128.7, 128.1, 125.7, 122.6, 122.2, 114.4, 52.6, 37.7, 29.4, 21.8. LC/MS m/z (ESI$^+$) for $C_{21}H_{16}N_2O_3S[M+H]^+$ 377.0 (MH^+, 85%), 285.0 (15%), 241.1(15%), 102.3 (100%).

3.2.8. 5-(3-Fluorophenyl)-4-nitro-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one (4h)



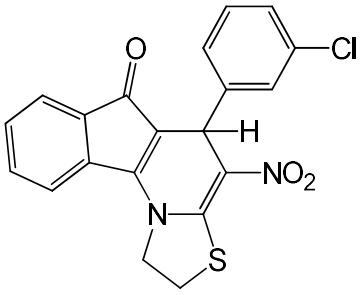
Dark Red solid, (82%); m.p. 279-280 ºC, IR (KBr) (ν_{max} / cm^{-1}): 2988 (ArC-H), 1689 (C=O), 1531 and 1368 (NO_2), 1203 (C-N), 1168 (C-O). ^{1}H NMR (500 MHz, DMSO) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.34 (dd, *J* = 9.2, 7.0 Hz, 2H), 7.20 – 7.14 (m, 2H), 7.03 (td, *J* = 8.6, 2.0 Hz, 1H), 5.13 (s, 1H), 4.99 – 4.90 (m, 1H), 4.71 (dd, *J* = 18.6, 8.9 Hz, 1H), 3.63 – 3.55 (m, 2H). ^{13}C NMR (125 MHz, DMSO) δ 190.2, 163.6, 159.7, 153.2, 146.0 (d, $^2J_{C-F}$ = 6.0 Hz), 136.2, 133.2, 131.0, 130.6 (d, $^4J_{C-F}$ = 8.2 Hz), 130.5, 125.1, 124.4, 122.2, 115.1, 115.1(d, $^1J_{C-F}$ = 21.7 Hz), 114.3(d, $^1J_{C-F}$ = 20.8 Hz), 113.6, 52.7, 38.0, 29.5. LC/MS m/z (ESI$^+$) for $C_{20}H_{13}FN_2O_3S[M+H]^+$ 381.0 (MH^+, 100%).

3.2.9. 5-(Naphthalen-2-yl)-4-nitro-1,2-dihydroindeno[2,1-e]thiazolo [3,2-a]pyridin-6(5H)-one (4i)



Dark Red solid, (72%); m.p. 283-284 ºC, IR (KBr) (ν_{max} / cm^{-1}): 1693 (C=O), 1539 and 1368 (NO_2), 1217 (C-N), 1167 (C-O. ^{1}H NMR (500 MHz, DMSO) δ 8.70 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.47 (dd, *J* = 13.6, 4.9 Hz, 1H), 7.42 (dd, *J* = 12.7, 5.0 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 6.00 (s, 1H), 5.07 – 4.96 (m, 2H), 4.78 (dd, *J* = 18.6, 8.7 Hz, 2H), 3.69 – 3.58 (m, 2H). LC/MS m/z (ESI+) for $C_{24}H_{16}N_2O_3S[M+H]^+$ 413.1 (MH+,100%), 358.9 (7%), 285.1 (45%).

3.3.10. 5-(3-Chlorophenyl)-4-nitro-1,2-dihydroindeno[2,1-e]thiazolo [3,2-a]pyridin-6(5H)-one (4j)



Red solid, (94%); m.p.287-288 ºC, IR (KBr) (ν_{max} / cm^{-1}): 1683 (C=O), 1586 (Ar), 1531 and 1368 (NO_2), 1203 (C-N), 1167 (C-O), 752 (Ar). ^{1}H NMR (500 MHz, DMSO) δ 7.98 (m, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.41 (d, *J* = 7.1 Hz, 1H), 7.37 (dd, *J* = 12.7, 6.1 Hz, 1H), 7.32 (d, *J* = 6.1 Hz, 1H), 7.29 – 7.25 (m, 1H), 5.14 (s, 1H), 4.99 – 4.90 (m, 1H), 4.76 – 4.68 (m, 1H), 3.58 (d, *J* = 9.0 Hz, 2H). LC/MS m/z (ESI^+) for $C_{20}H_{13}FN_2O_3S[M+H]^+$ 397.0 (MH^+, 90%), 239.1 (10%), 102.3 (100%).

4. RESULTS AND DISCUSSION

4.1. The Results And Discussion Of Synthesis (4a-4j)

The requisite aldehydes, indane-1,3-dione and 2-nitromethylenethiazolidine were refluxed in a mixture of acetic acid and polyethylene glycol-400 (PEG), to obtain nitro-indeno-thiazolo-pyridines derivatives via one pot 3-component reactions. The compounds **(4a-4j)** were obtained at given time in **Table 4.1**. The progress of the reactions was monitored by TLC in a solvent mixture (1:1 ethyl acetate-hexane) as mobile phase. After being thoroughly washed by ethanol and water samples dried and analytically pure forms were obtained after recrystallization from DMF/H_2O. The reaction is carried out in a single reaction vessel under the prescribed reaction conditions, allowing for the presence of all three components, and does not require the use of costly catalysts or harsh reagents. The key advantage of this approach is the formation of cyclic compounds through the Michael reaction and the construction of complex molecular scaffolds in a single step, leading to the rapid generation of diverse compound libraries.

Meanwhile,,[51] Nasir et al. devised a one-pot 4-component synthesis of indanone-fused thiazolo[3,2-a]pyridines in the presence of a base and solvent selection plays a critical role in controlling the reaction outcome and diastereoselectivity. However, comparing the literature, our method is characterized by the fact that a larger number of aldehyde derivatives were reacted *via* a one-pot 3-component reaction, and the products were obtained in less time.[52]

The IR, ^{1}H, ^{13}C NMR, and LC/MS categorically confirmed the structures of the final products. The IR spectra of compounds **4a-4j** exhibited C=O stretching vibration from 1678-1730 cm^{-1}. Additionally, stretching vibrations of NO_2 has two peaks, first one between 1366-1384 cm^{-1}, second peaks at 1511-1531 cm^{-1}, and C-N were observed at 1210- 1167 cm^{-1}. The LC/MS of compounds **(4a-4j)** revealed molecular ion peaks at appropriate m/z values, confirming the hypothesized structures. ^{1}H NMR spectrum of **4a-4j** showed three multiples for two CH_2 groups in H**b**, H**c** atoms, in H**c** atom has one multiples (δ 3.59-3.41 ppm, 2H), and H**b** position is showing two different signals (δ 4.73-4.65 ppm, 1H) and (δ 4.97-4.86 ppm, 1H) due to diastereoselectivity of H**a** and H**b**, as for methine proton in H**a** position there is one singlet (δ 5.04-6.00 ppm, H**a**) **(Figure 4.1)**, and aromatic region of the spectrum (δ 7.19 - 7.55 ppm, 9H) suits with the expected number of aromatic moieties. ^{13}C NMR spectra for **4a-4j** indicated to (29.4-34.0 ppm, CH), (34.0-38.1 ppm, CH_2S), (51.3-52.7 ppm, CH_2N), (113.2-117.3 ppm, CNO_2), (122.2-143.2 ppm, C=C–CO) and 11 signals between (122.5-135.3 ppm) for the aromatic moieties, (152.6-153.6 ppm, Ar), (159.0-160.4 ppm, NCN) and carbonyl peaks arised at around 190.2-190.5 ppm.

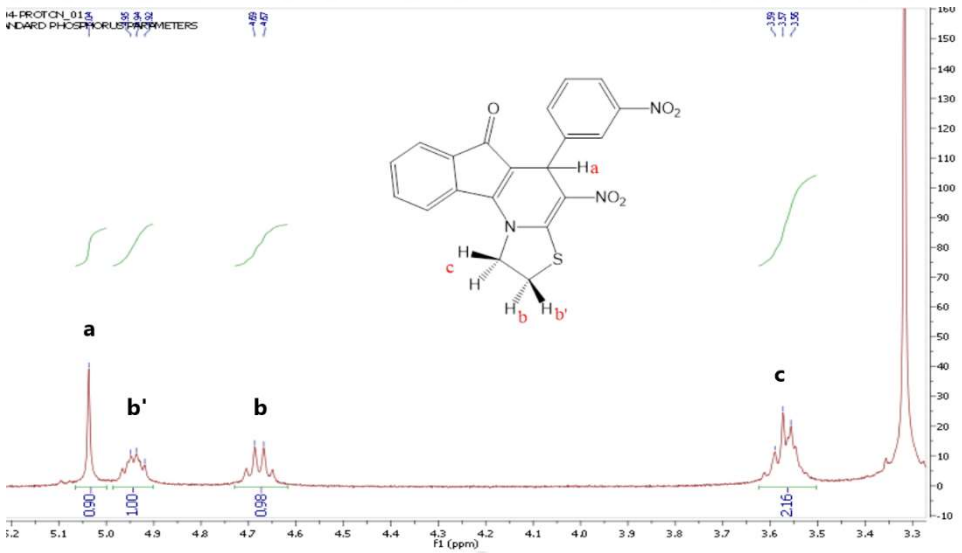
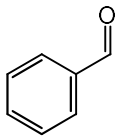
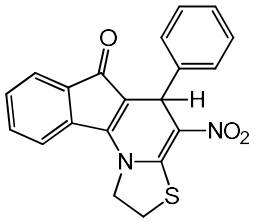
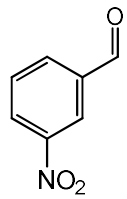
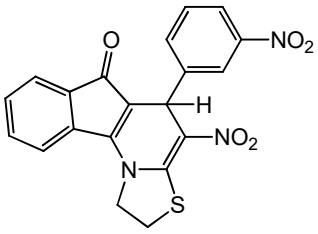
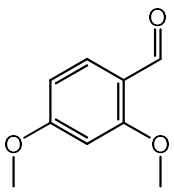
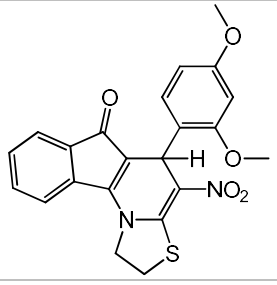
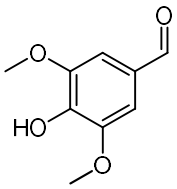
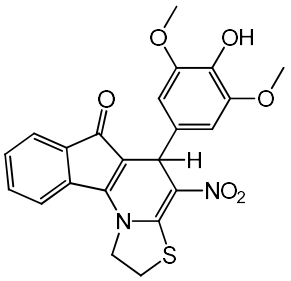
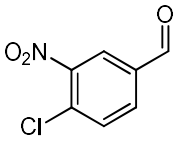
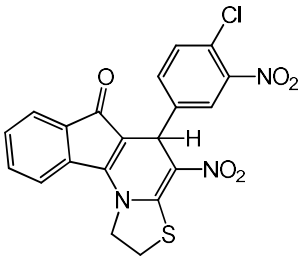
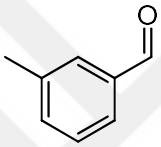
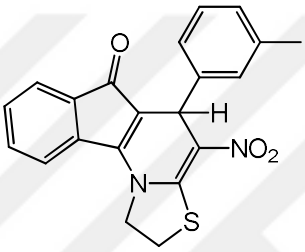
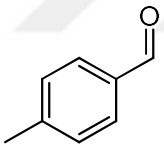
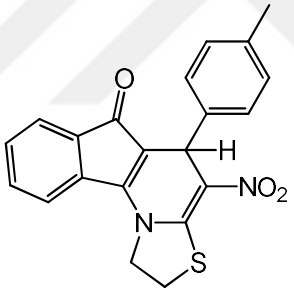
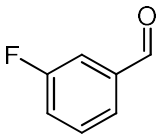
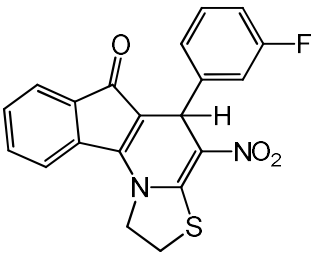
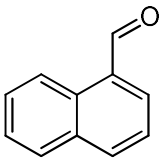
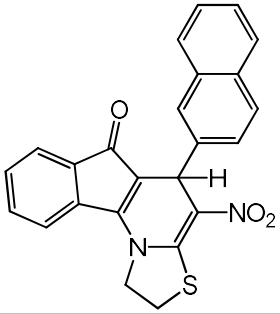


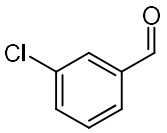
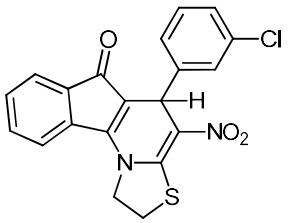
Figure 4.1. Explain ^{1}H NMR to the (a,b,c) signals to **4b.**

Acetic acid (pKa= 4.76) is a commonly used solvent in organic reactions due to its ability to dissolve a wide range of organic compounds, and also act as a catalyst or participate in certain reaction steps. On the other hand, PEG is a viscous liquid that can serve as a reaction medium or co-solvent, it can help to improve the solubility of reactants and stabilize reaction intermediates, and what distinguishes both acetic acid and polyethylene glycol are non-toxicity, as a green and effective. The combination of acetic acid and polyethylene glycol can be employed as a reaction medium to optimize various reaction parameters, for example, the ratio of acetic acid to polyethylene glycol can be adjusted to achieve the desired solvent properties, viscosity, or pH conditions. This flexibility allows for the customization of the reaction system to suit specific MCRs, leading to improved reaction outcomes, given that, 1:1 was not suitable for the carrying out of the reaction in our study, the ratio of 2:1 (CH_3COOH: PEG) was appropriate, in addition, the reaction was conducted at room temperature but there was no reaction.

Table 4.1. Synthesis of **4a-4j**

En	4	ArCHO	Product	Yield (%)	Time (h)	Mp (^{0}C)
1	**4a**			75	1h	277-278
2	**4b**			75	3h	277-278
3	**4c**			70	3h	270-271

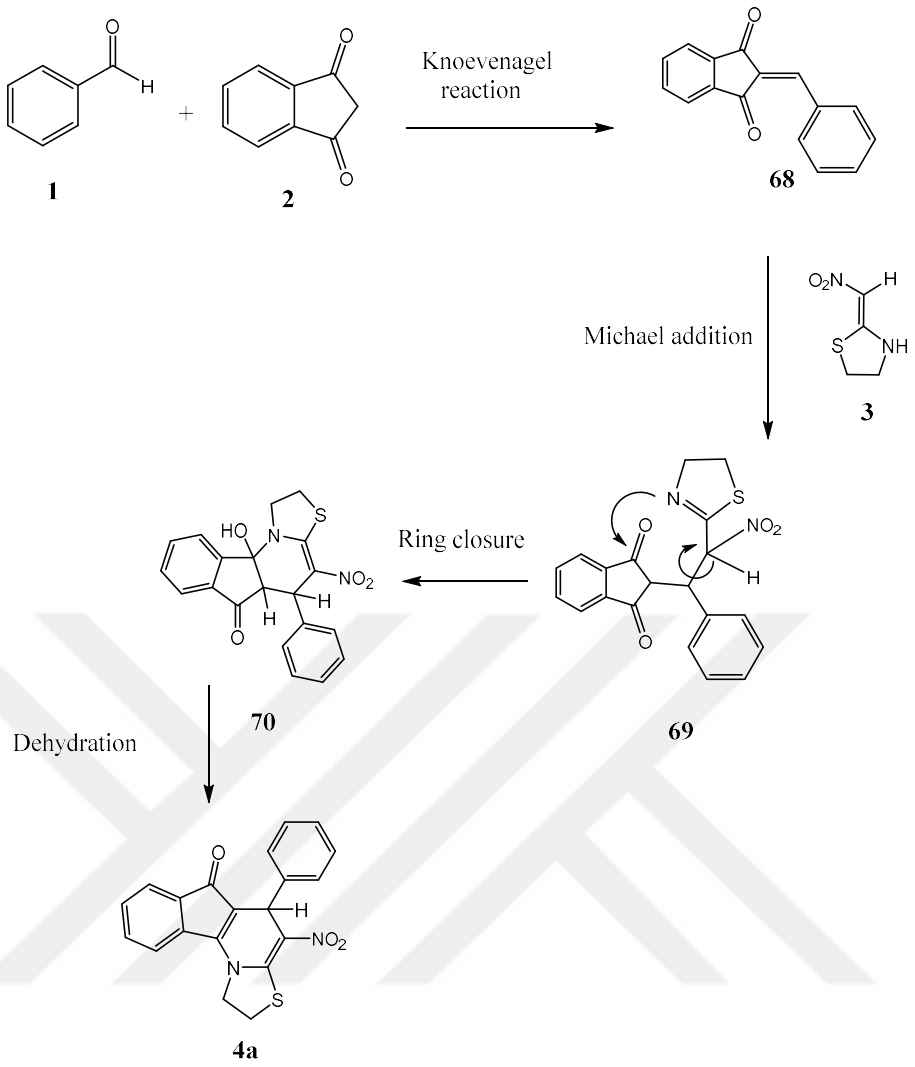
4	**4d**			70	3h	270-271
5	**4e**			82	4h	260-261
6	**4f**			75	3h	277-278
7	**4g**			80	3h	267-268
8	**4h**			82	4h	279-280
9	**4i**			72	4h	283-284

10	**4j**			94	4h	287-288

For the compound 5-(3-fluorophenyl)-4-nitro-1,2-dihydroindeno[2,1-e]thiazolo[3,2-a]pyridin-6(5H)-one appears fluorine-carbon coupling in four positions **(Scheme 4.1)**, giving doublet peaks, C_1 and C_2 are the neighboring two carbons for C-F appear in 115.1 (d, $^4J_{C-F}$ = 21.7 Hz), 114.3 (d, $^3J_{C-F}$ = 20.8 Hz), respectively, also for C_3 show up 130.6 (d, $^2J_{C-F}$ = 8.2 Hz) and for C_4 in 145, (d, J_{C-F} = 6.0 Hz).

4.2. Proposed Mechanism of the Synthesis of the Target Molecule

The first step of mechanism involves Knoevenagel reaction, by react 1,3-indandione with aldehyde, this step 1,3-indandione undergoes enolization, one of the keto groups in forms an enolate ion by abstracting a proton from the alpha carbon. The resulting enolate anion (resonance-stabilized) is indicated, the enolate anion acts as a nucleophile and attacks the aldehyde to give intermediate **(68)**. Then second step that followed Michael addition by attack 2-nitromethylenethiazolidine act as Michael donor on **(68)** represents Michael acceptor, by attack hydrogen of double bond of 2-nitromethylene to **(68)** and formed **(69)**, then the nitrogen in thiazolidine ring attack one of the two carbonyl which is consider electrophile, this step represent N-cyclization, this step is followed by the process of forming a new ring. This proton transfer generates a more stable tautomeric form of the intermediate. In end of the mechanism **(71)** undergoes by dehydrogenation and remove water from keto-enol tautomeric equilibrium to produce **(72)** represent the final structure (Figure 4.2).



Scheme 4.1. Mechanistic explanation for the formation.

5. CONCLUSIONS AND RECOMMENDATION

In the present study, a series of nitro-indeno-thiazolo-pyridines derivatives were synthesized based on 1,3-indandione, 2-nitromethylenethiazolidine and aromatic aldehyde derivatives through one pot 3- component reaction. Acetic acid and polyethylene glycol-400 were utilized as reaction medium, and their impact on the reaction process was studied. Our products achieved by moderate to good yields (70-94 %).

6. REFERENCES

[1] Mironov MA. Design of multi-component reactions: from libraries of compounds to libraries of reactions. QSAR & Combinatorial Science. 2006 Jun;25(5-6):423-31, DOI:10.1002/qsar.200540190 .

[2] Weber L. Multi-component reactions and evolutionary chemistry. Drug Discovery Today. 2002 Jan 15;7:143-7. DOI:10.1016/S1359-6446(02)00010-7

[3] Choudhury LH, Parvin T. Recent advances in the chemistry of imine-based multicomponent reactions (MCRs). Tetrahedron. 2011 Oct 10;67(43):8213. DOI:10.1016/j.tet.2011.07.020

[4] Shang S, Tan DS. Advancing chemistry and biology through diversity-oriented synthesis of natural product-like libraries. Current Opinion In Chemical Biology. 2005 Jun 1;9(3):248-58. DOI:10.1016/j.cbpa.2005.03.006

[5] Kalinski C, Umkehrer M, Weber L, Kolb J, Burdack C, Ross G. On the industrial applications of MCRs: Molecular diversity in drug discovery and generic drug synthesis. Molecular diversity. 2010 Aug;14(3):513-22. DOI:10.1007/s11030-010-9225-x

[6] Karami M, Hasaninejad A, Mahdavi H, Iraji A, Mojtabavi S, Faramarzi MA, Mahdavi M. One-pot multi-component synthesis of novel chromeno [4, 3-b] pyrrol-3-yl derivatives as alpha-glucosidase inhibitors. Molecular Diversity. 2021 Oct 25:1-3. DOI:10.1007/s11030-021-10337-w

[7] Kumar A, Maurya RA, Sharma S, Kumar M, Bhatia G. Synthesis and biological evaluation of N-aryl-1,4-dihydropyridines as novel antidyslipidemic and antioxidant agents. European Journal of Medicinal Chemistry.2010Feb1;45(2):501-9. DOI:10.1016/j.ejmech.2009.10.036

[8] Musonda CC, Taylor D, Lehman J, Gut J, Rosenthal PJ, Chibale K. Application of multi-component reactions to antimalarial drug discovery. Part 1: Parallel synthesis and antiplasmodial activity of new 4-aminoquinoline Ugi adducts. Bioorganic & Medicinal Chemistry Letters. 2004 Aug 2;14(15):3901-5. DOI:10.1016/j.bmcl.2004.05.063

[9] Bienaymé, H., Hulme, C., Oddon, G. and Schmitt, P. (2000), Maximizing Synthetic Efficiency: Multi-Component Transformations Lead the Way. Chem.Eur. J,6:3321-3329. DOI:10.1002/1521-3765(20000915)6:18<3321::AIDCHEM3321>3.0.CO;2-A

[10] Kouznetsov VV, Galvis CE. Strecker reaction and α-amino nitriles: Recent advances in their chemistry, synthesis, and biological properties. Tetrahedron. 2018 Feb 22;74(8):773-810. DOI:10.1016/j.tet.2018.01.005

[11] Hosseinnejad T, Omrani-Pachin M, Heravi MM. Joint Computational and Experimental Investigations on the Synthesis and Properties of Hantzsch-type Compounds: An Overview. Current Organic Chemistry. 2019 Jun1 ; 23(13):1421-38. DOI:10.2174/1385272823666190808110837

[12] Qu H, Li X, Mo F, Lin X. Efficient synthesis of dihydropyrimidinones via a three-component Biginelli-type reaction of urea, alkylaldehyde and arylaldehyde. Beilstein Journal of Organic Chemistry. 2013 Dec 11;9(1):2846-51. DOI:10.3762/bjoc.9.320

[13] Farghaly AM, Rizk OH, Darwish I, Hamza M, Altowyan MS, Barakat A, Teleb M. Design, Synthesis, Pharmacodynamic and In Silico Pharmacokinetic Evaluation of Some Novel Biginelli-Derived Pyrimidines and Fused Pyrimidines as Calcium Channel Blockers. Molecules. 2022 Mar 30;27(7):2240. DOI:10.3390/molecules27072240

[14] Gao Q, Zhu Q, Zheng J, Yuan S, Wang Y, Zhao R, Liu Y, Gui X, Wang C, Volodine A, Jin P. Positively charged membranes for dye/salt separation based on a crossover combination of Mannich reaction and prebiotic chemistry.

Journal of Hazardous Materials. 2022 Oct 15;440:129744. DOI:10.1016/j.jhazmat.2022.129744

[15] Quazi S, Rashid MT, Malik JA, Gavas S. The Discovery of Noval Antimicrobial Agents through the Application of Isocyanide-Based Novel Multicomponent Reactions. Antibiotics. 2023 May 4;12(5):849. DOI:10.3390/antibiotics12050849

[16] Anugu N, Thunga S, Poshala S, Kokatla HP. N-Oxide-Induced Ugi Reaction: A Rapid Access to Quinoline-C2-amino Amides via Deoxygenative C (sp2)–H Functionalization. The Journal of Organic Chemistry. 2022 Jul 18;87(15):10435-40. DOI:10.1021/acs.joc.2c00904

[17] Domling A, Wang W, Wang K. Chemistry and biology of multicomponent reactions. Chemical Reviews. 2012 Jun 13;112(6):3083-135. DOI:10.1021/cr100233r

[18] Orru Michiel RVA de G. Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds. Synthesis (Stuttg) 2003;1471–1499. DOI:10.1055/s-2003-40507

[19] Akritopoulou-Zanze I. Isocyanide-based multicomponent reactions in drug discovery. Current opinion in chemical biology. 2008 Jun 1;12(3):324-31. DOI:10.1016/j.cbpa.2008.02.004

[20] Brinkerhoff RC, Santa-Helena E, do Amaral PC, Cabrera DD, Ongaratto RF, de Oliveira PM, D'Oca CD, Gonçalves CA, Nery LE, D'Oca MG. Evaluation of the antioxidant activities of fatty polyhydroquinolines synthesized by Hantzsch multicomponent reactions. RSC Advances. 2019 ; 9(43):24688-98. DOI:10.1039/C9RA04758A

[21] Isenring HP, Hofheinz W. A simple two-step synthesis of diphenylmethyl esters of 2-oxo-1-azetidineacetic acids. Synthesis. 1981;1981(05):385-7. DOI:10.1055/s-1981-29461

[22] Hulme C, Gore V. Multi-component Reactions: Emerging Chemistry in Drug Discovery From Xylocain to Crixivan. Current Medicinal Chemistry. 2003 Jan 1;10(1):51-80. DOI:10.2174/0929867033368600

[23] Chetkina LA, Belsky VK. X-Ray structure investigation of 1,3- indandione and 1,3-dicyanomethyleneindan derivatives: A Review. Crystallography Reports. 2008 Jul;53:579-607. DOI:10.1134/S1063774508040081

[24] Winzenberg KN, Kemppinen P, Scholes FH, Collis GE, Shu Y, Singh TB, Bilic A, Forsyth CM, Watkins SE. Indan-1,3-dione electron-acceptor small molecules for solution-processable solar cells: a structure property correlation. Chemical Communications. 2013;49(56):6307-9. DOI:10.1039/C3CC42293C

[25] Patel A, Giles D, Basavarajaswamy G, Sreedhar C, Patel A. Synthesis, pharmacological evaluation and molecular docking studies of indanone derivatives. Medicinal Chemistry Research. 2012 Dec;21:4403-11. DOI:10.1007/s00044-012-9973-5

[26] I.F. Finer, "Organic Chemistry", II, 5th ed, (1975).

[27] R.L. Horton &. K.C.Murdock, J.Org.Chem.,25, 938- J.Org.Chem.,25, 938-941. (1960). DOI:10.1021/jo01076a017

[28] Lombardino JG, Wiseman EH. Antinflammatory 2-aryl-1, 3- indandiones. Journal of Medicinal Chemistry. 1968 Mar;11(2):342-7. DOI:10.1021/jm00308a035

[29] McCaldin DJ. The chemistry of ninhydrin. Chemical Reviews. 1960 Feb 1;60(1):39-51. DOI:10.1021/cr60203a004

[30] Becker HD, Russell GA. Preparation of β-Keto Sulfones by Condensation of Aromatic Esters with Dimethyl Sulfone1, 2. The Journal of Organic Chemistry. 1963 Jul;28(7):1896-8. DOI:10.1021/jo01042a503

[31] Green J. Antagonists of vitamin K. Vitamins & Hormones. 1967 Jan 1;24:619-32. DOI:10.1016/S0083-6729(08)60226-5

[32] Dolmella A, Gatto S, Girardi E, Bandoli G. X-ray structures of the anticoagulants coumatetralyl and chlorophacinone. Theoretical calculations and SAR investigations on thirteen anticoagulant rodenticides. Journal of Molecular Structure. 1999 Dec 7;513(1-3):177-99. DOI:10.1016/S0022-2860(99)00119-2

[33] Moriceau MA, Lefebvre S, Fourel I, Benoit E, Rattner BA, Lattard V. Accidental chlorophacinone exposure of lactating ewes: clinical follow-up and human health dietary implications. Food and Chemical Toxicology. 2020 Sep 1;143:111518. DOI:10.1016/j.fct.2020.111518

[34] Pelz HJ, Prescott CV. Resistance to anticoagulant rodenticides. Rodent Pests and their Control'.(Ed. AP Buckle, RH Smith) pp. 2015 Apr 24:195-201. DOI:10.1079/9781845938178.0187

[35] WE. Braselton JR. RD. Neiger, Rh-Poppenge, J.Vet.Diagn Invenst, 4(4), 441-6, (1992).

[36] Amer FA, Afsah ES, Etman H. Condensation of 2-Acetyl-1, 3-indandione with Amines and Diazonium Salts. Zeitschrift für Naturforschung B. 1979 Jun 1;34(6):867-70. DOI:10.1515/znb-1979-0621

[37] Ritschel WA, Orth H. Testing of tablets with prolonged action. Enzyme activity during the modified half-change method. Journal of Pharmaceutical Sciences. 1967 Jun 1;56(6):773-5. DOI:10.1002/jps.2600560630

[38] Prasher P, Sharma M. Medicinal chemistry of indane and its analogues: A mini review. ChemistrySelect. 2021 Mar 19;6(11):2658-77. DOI:10.1002/slct.202100177

[39] Othman IM, Gad-Elkareem MA, Radwan HA, Badraoui R, Aouadi K, Snoussi M, Kadri A. Synthesis, structure-activity relationship and in silico studies of novel pyrazolothiazole and thiazolopyridine derivatives as prospective antimicrobial and anticancer agents. ChemistrySelect. 2021 Aug 20;6(31):7860-72. DOI:10.1002/slct.202101622

[40] Kaminskyy D, Kryshchyshyn A, Lesyk R. 5-Ene-4-thiazolidinones–An efficient tool in medicinal chemistry. European Journal of Medicinal chemistry. 2017 Nov 10;140:542-94. DOI:10.1016/j.ejmech.2017.09.031

[41] Al-Omary FA, Hassan GS, El-Messery SM, El-Subbagh HI. Substituted thiazoles V. Synthesis and antitumor activity of novel thiazolo [2, 3-b] quinazoline and pyrido [4, 3-d] thiazolo [3, 2-a] pyrimidine analogues. European Journal of Medicinal Chemistry. 2012 Jan 1;47:65-72. DOI:10.1016/j.ejmech.2011.10.023

[42] Kamat V, Santosh R, Poojary B, Nayak SP, Kumar BK, Sankaranarayanan M, Faheem, Khanapure S, Barretto DA, Vootla SK. Pyridine-and thiazole-based hydrazides with promising anti-inflammatory and antimicrobial activities along with their in-silico studies. ACS Omega. 2020 Sep 25;5(39):25228-39. DOI:10.1021/acsomega.0c03386

[43] Halim SA, Khalil AK. TD-DFT calculations, NBO analysis and electronic absorption spectra of some thiazolo [3, 2-a] pyridine derivatives. Journal of Molecular Structure. 2017 Nov 5;1147:651-67. DOI:10.1016/j.molstruc.2017.06.098

[44] Boominathan M, Nagaraj M, Maheshwaran C, Muthusubramanian S, Bhuvanesh N. One-Pot Green Synthesis of Thiazolo [3, 2-a] pyridine Derivatives via Tandem Cyclization in Aqueous Media. Journal of Heterocyclic Chemistry. 2014 Jan;51(1):244-8. DOI:10.1002/jhet.1650

[45] Vadivelan S, Sinha BN, Irudayam SJ, Jagarlapudi SA. Virtual screening studies to design potent CDK2-cyclin A inhibitors. Journal of Chemical Information and Modeling. 2007 Jul 23;47(4):1526-35. DOI:10.1021/ci7000742

[46] Marzoog S. Al-Thebeiti; "Synthesis of some new thiazolo[3,2-a]pyridines and related heterocyclic systems". Il Farmaco, 2000, 55, 109–118. DOI:10.1016/S0014-827X(99)00130-5

[47] Rao AU, Palani A, Chen X, Huang Y, Aslanian RG, West Jr RE, Williams SM, Wu RL, Hwa J, Sondey C, Lachowicz J. Synthesis and structure–activity relationships of 2-(1, 4′-bipiperidin-1′-yl) thiazolopyridine as H3 receptor antagonists. Bioorganic & medicinal chemistry letters. 2009 Nov 1;19(21):6176-80. DOI:10.1016/j.bmcl.2009.09.006

[48] Shi F, Li C, Xia M, Miao K, Zhao Y, Tu S, Zheng W, Zhang G, Ma N. Green chemoselective synthesis of thiazolo [3, 2-a] pyridine derivatives and evaluation of their antioxidant and cytotoxic activities. Bioorganic & medicinal chemistry letters. 2009 Oct 1;19(19):5565-8. DOI:10.1016/j.bmcl.2009.08.046

[49]Terzidis MA, Stephanidou-Stephanatou J, Tsoleridis CA, Terzis A, Raptopoulou CP, Psycharis V. Expeditious one-pot synthesis of highly substituted thiazolo [3,2-a] pyridines involving chromones. Tetrahedron. 2010 Jan 23;66(4):947-54. DOI:10.1016/j.tet.2009.11.096

[50] Altuğ C, Yakubu Saleh L, Caner E, Güneş H, Sameeullah M. Multicomponent synthesis of novel thiazolo[3,2-a]pyridin-8-yl-phosphonates as a model of plant growth regulator. Phosphorus, Sulfur, and Silicon and the Related Elements. 2019 Feb 1;194(1-2):111-9. DOI:10.1080/10426507.2018.1513515

[51] Nasir S, Hosseini FS, Bayat M. Solvent-controlled dehydration and diastereoselective formation of indanone-fused Thiazolo [3, 2-a] pyridines via a one-pot four-component reaction. Tetrahedron. 2018 Aug 16;74(33):4409-17. DOI:10.1016/j.tet.2018.07.005

7. APPENDICES

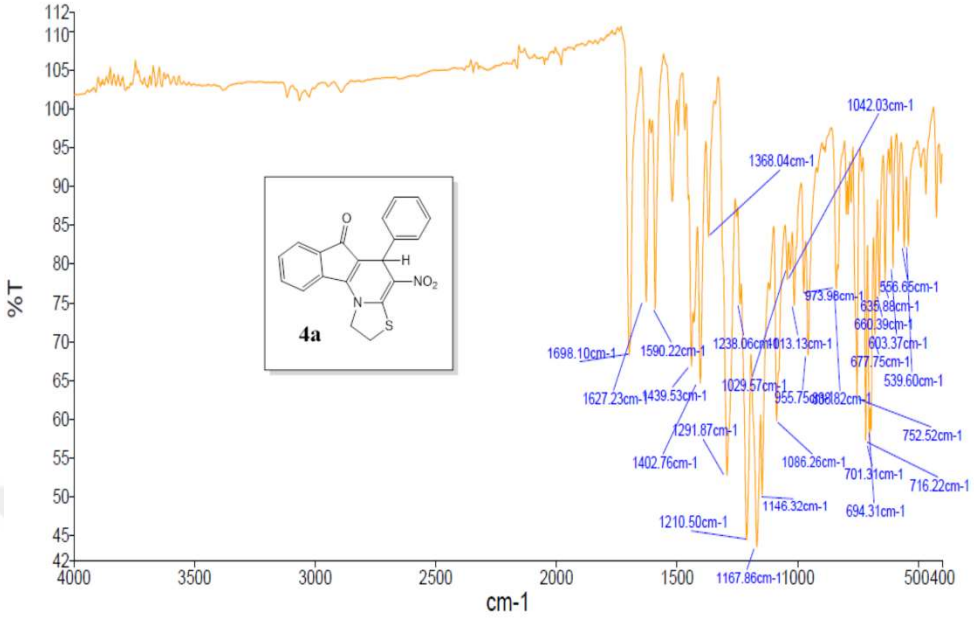


Figure 7.1. IR spectrum of compound **4a**

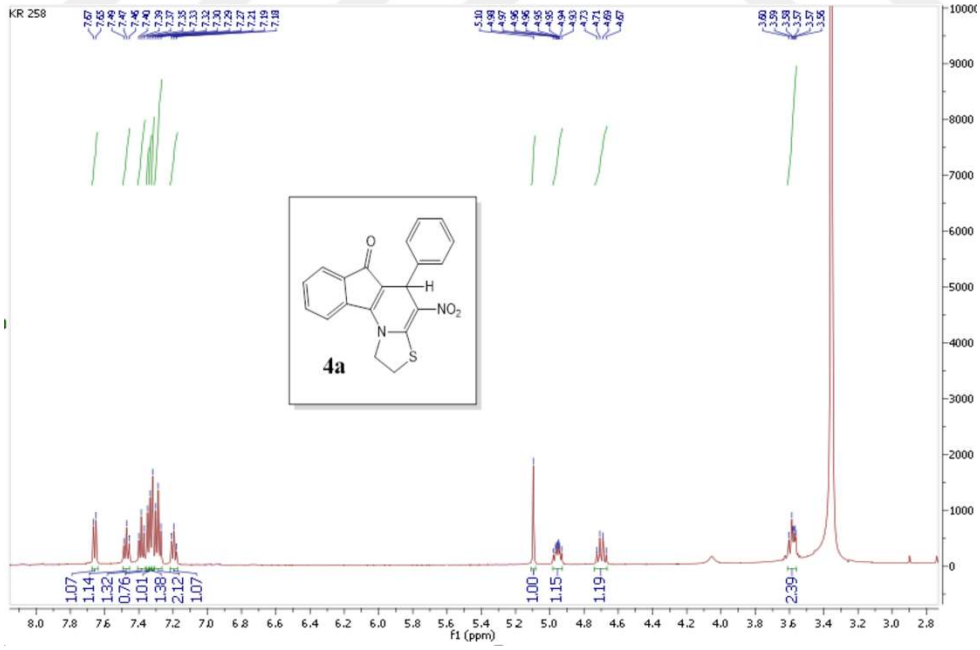


Figure 7.2. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4a**

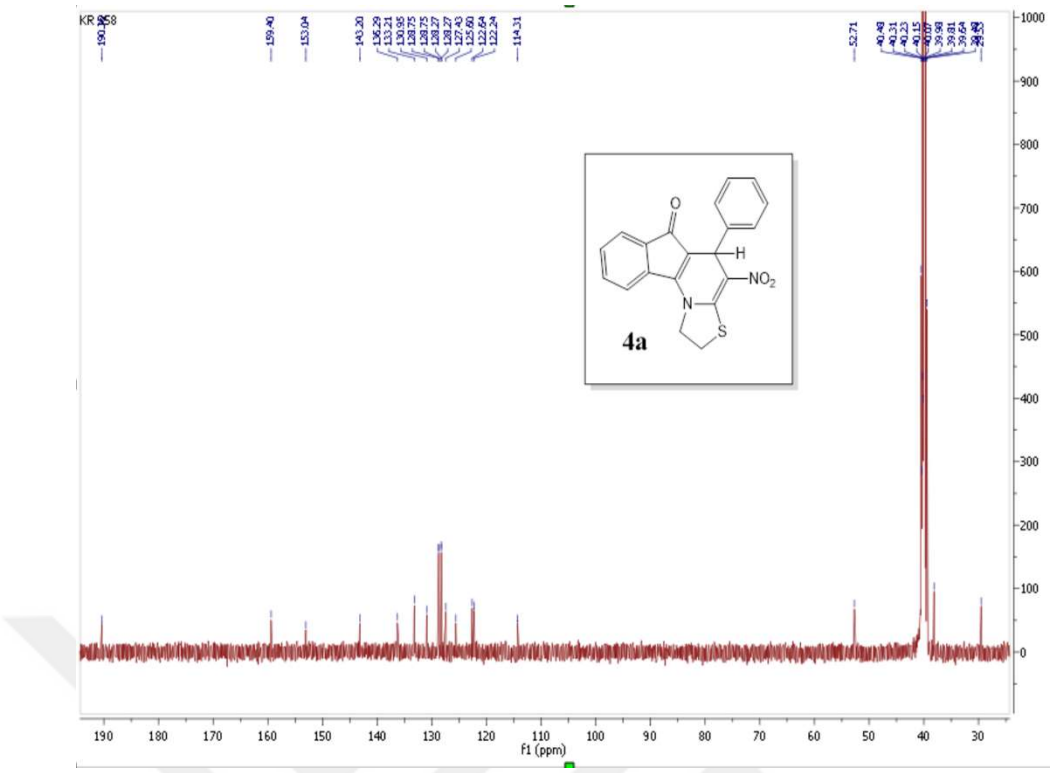


Figure 7.3. ^{13}C NMR (125 MHz, DMSO) spectrum of compound **4a**

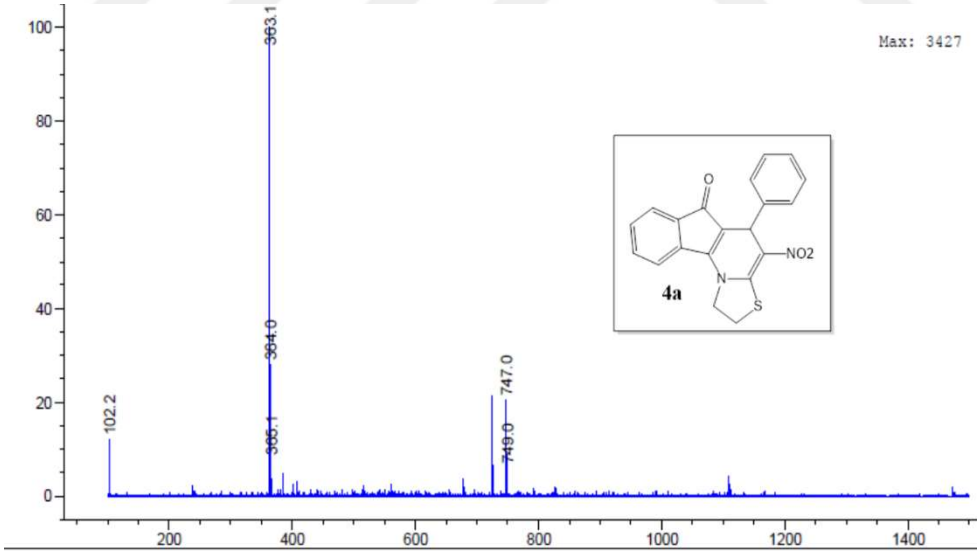


Figure 7.4. LC/MS spectrum of compound **4a**

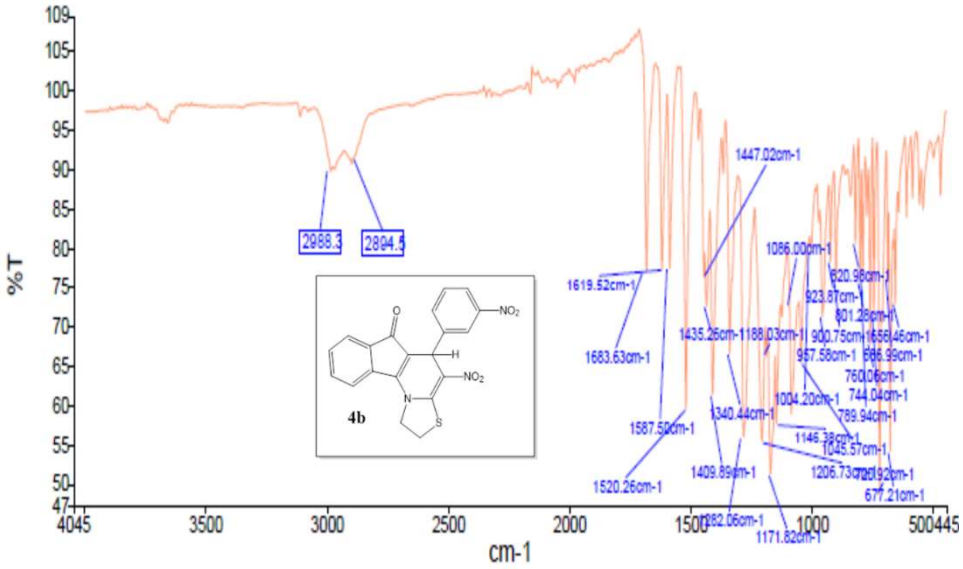


Figure 7.5. IR spectrum of compound **4b**

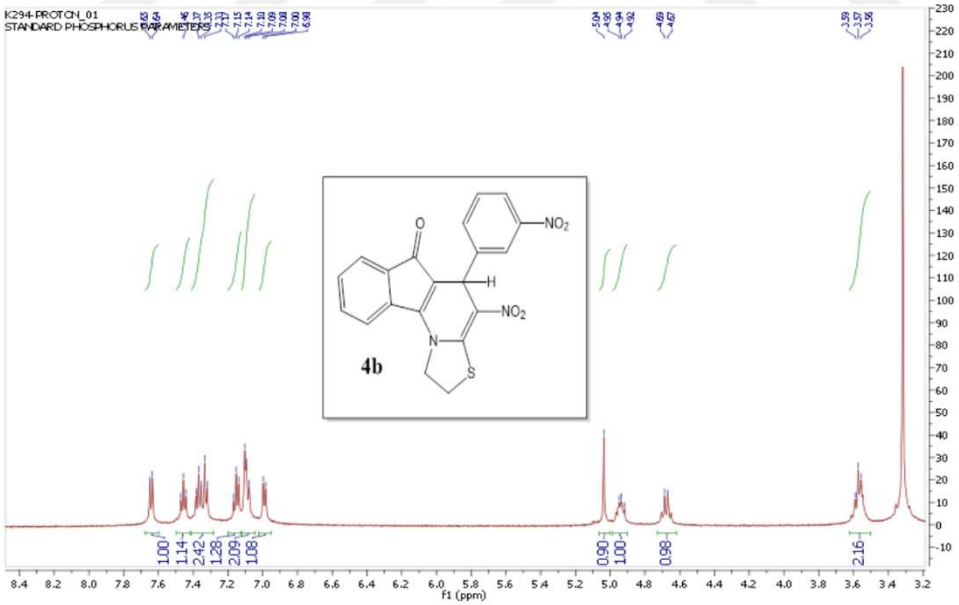


Figure 7.6. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4b**

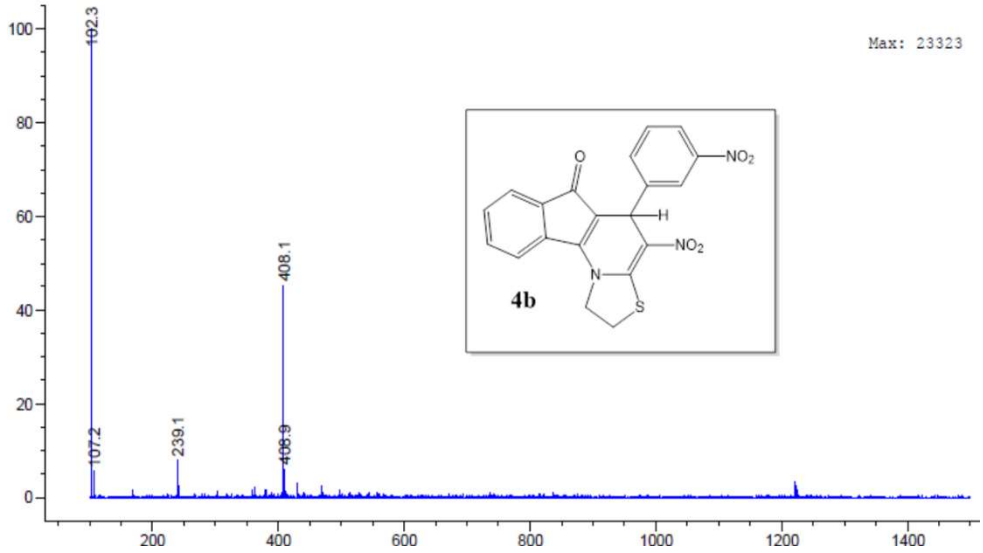


Figure 7.7. LC/MS spectrum of compound **4b**

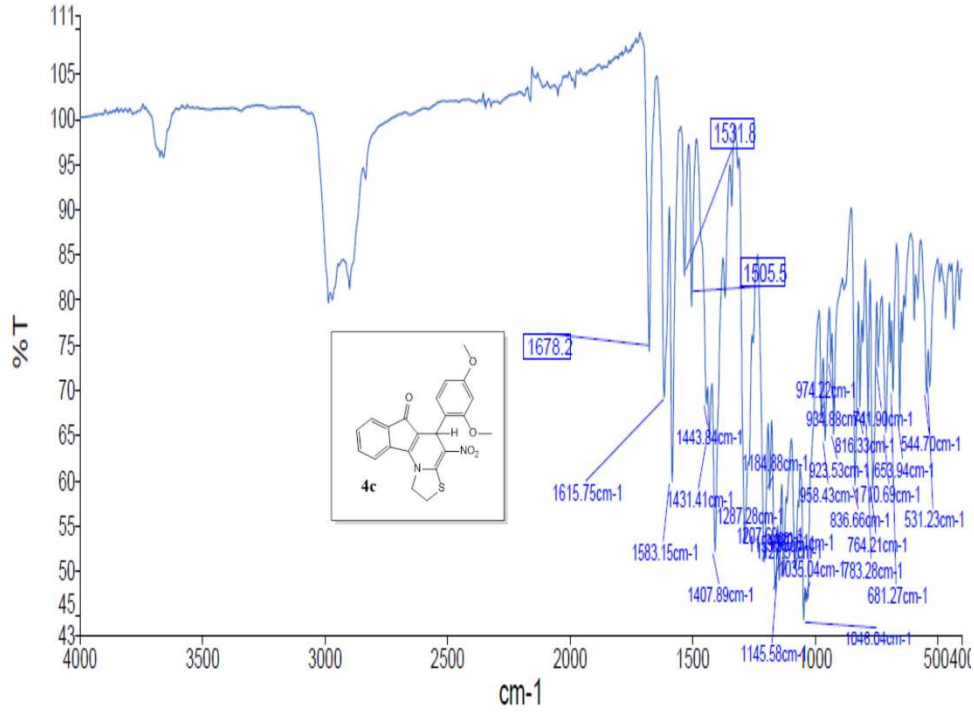


Figure 7.8. IR spectrum of compound **4c**

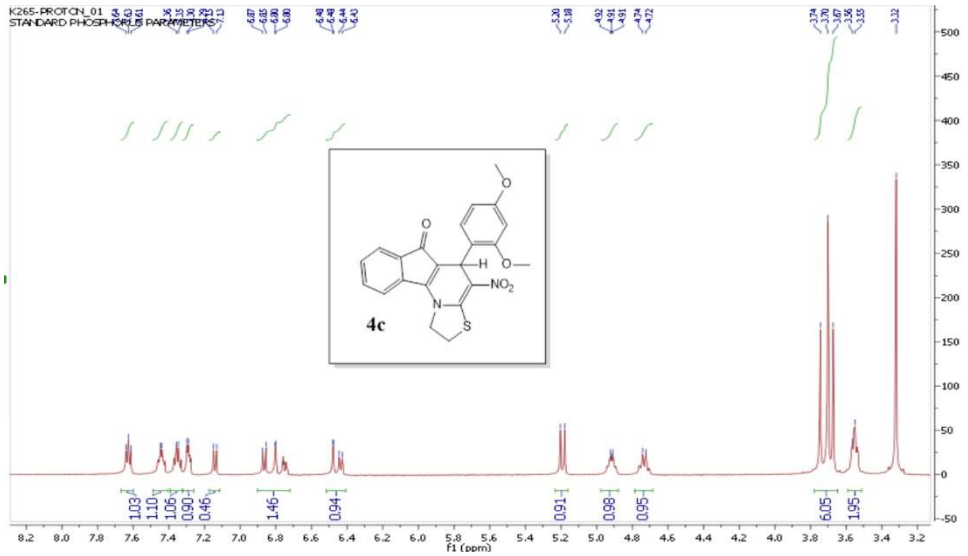


Figure 7.9. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4c**

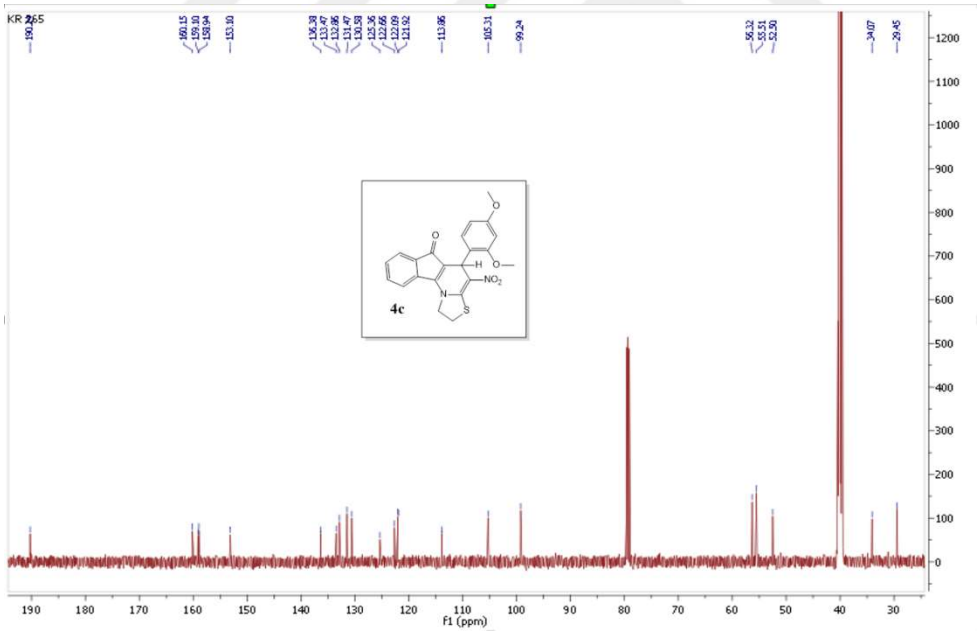


Figure 7.10. ^{13}C NMR (125 MHz, DMSO) spectrum of compound **4c**

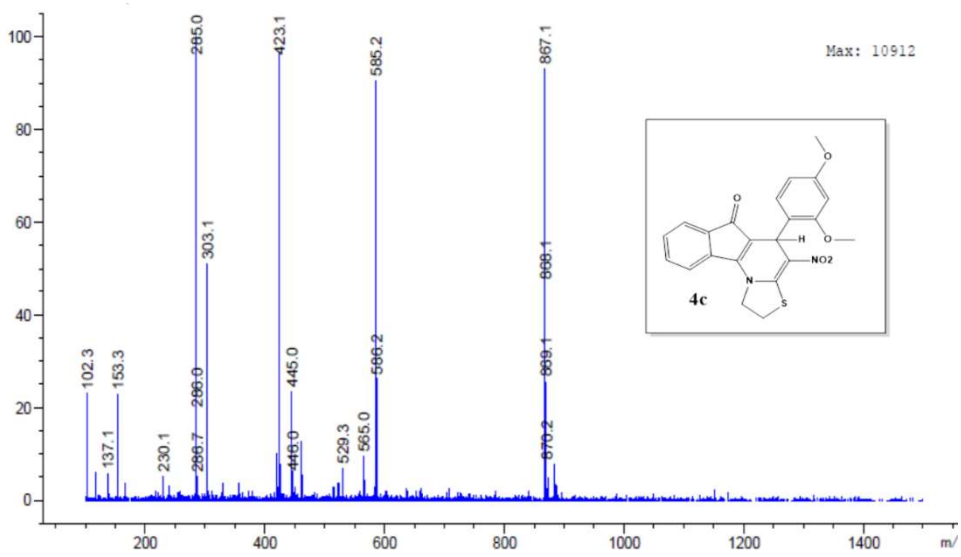


Figure 7.11. LC/MS spectrum of compound **4c**

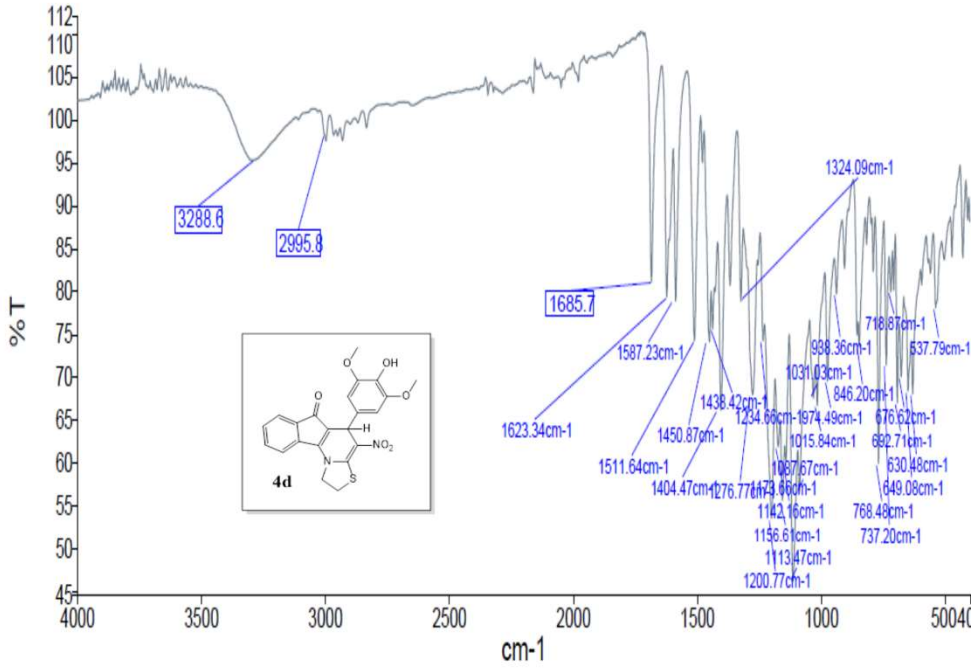


Figure 7.12. IR spectrum of compound **4d**

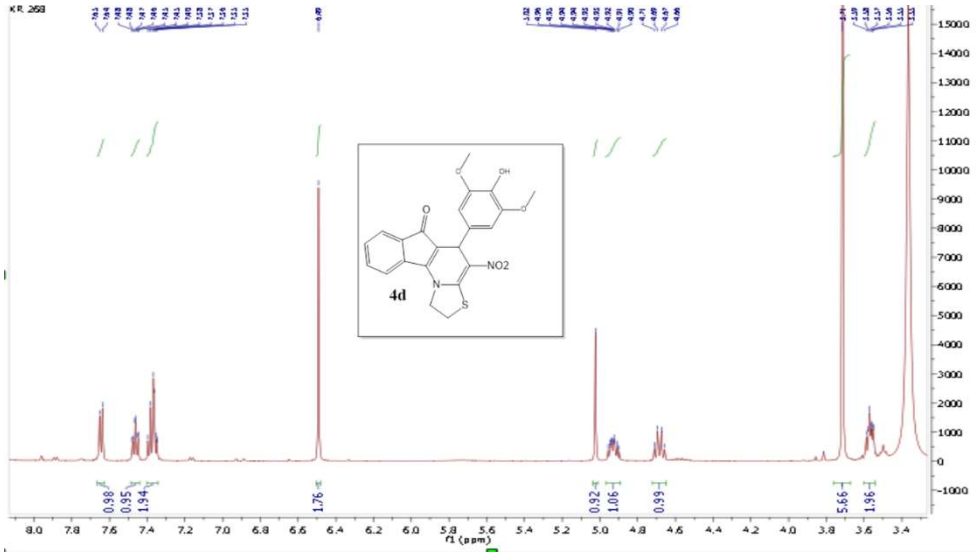


Figure 7.13. [1]H NMR (500 MHz, DMSO) spectrum of compound **4d**

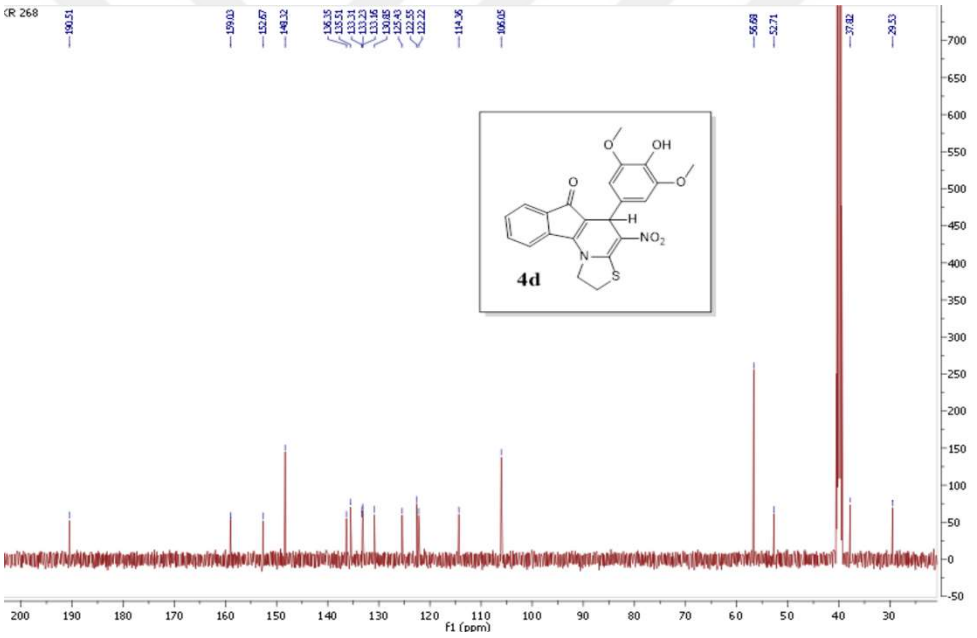


Figure 7.14. [13]C NMR (125 MHz, DMSO) spectrum of compound **4d**

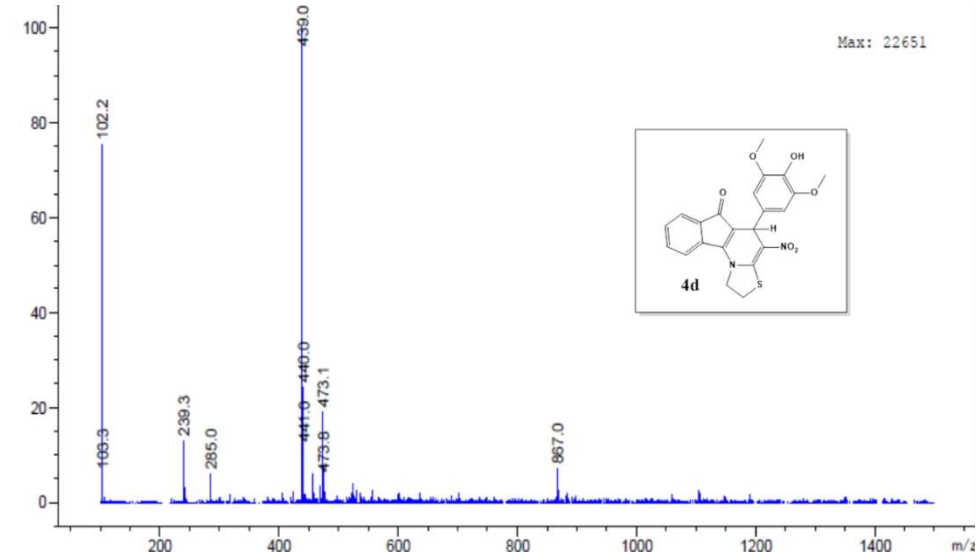


Figure 7.15. LC/MS spectrum of compound **4d**

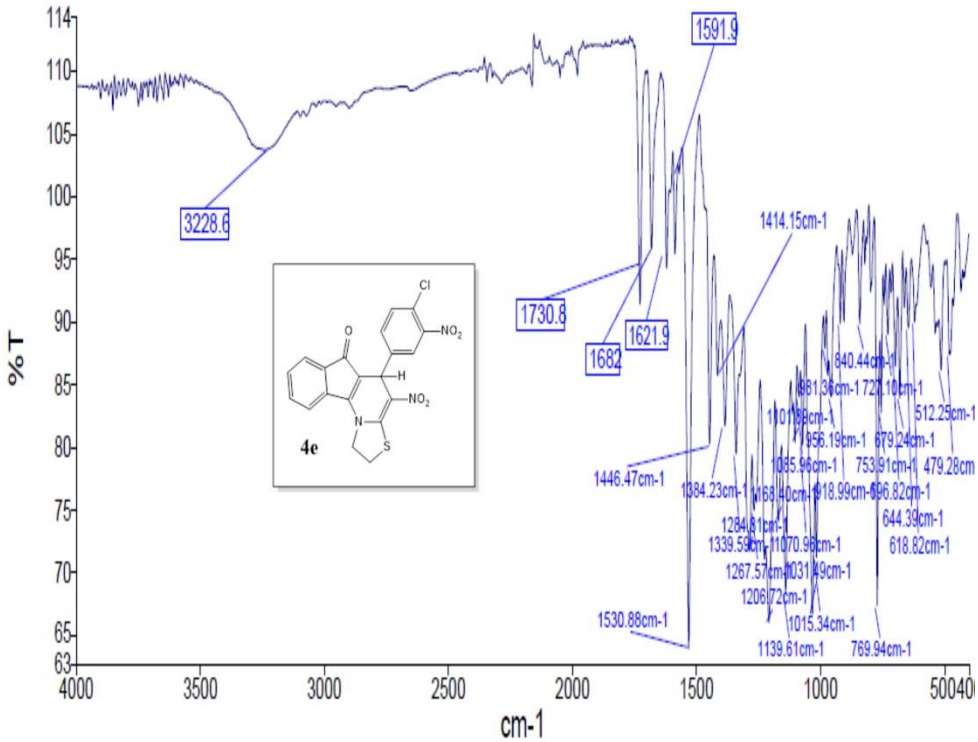


Figure 7.16. IR spectrum of compound **4e**

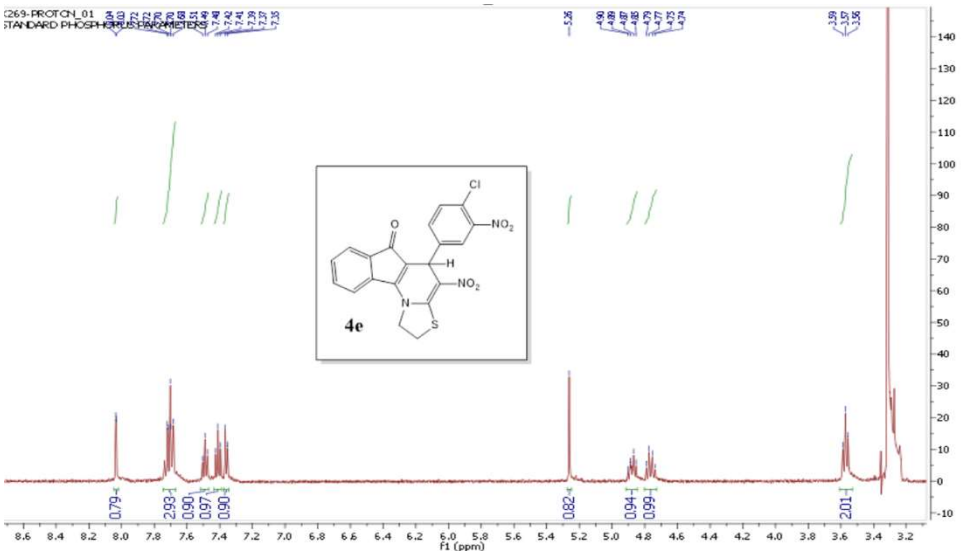


Figure 7.17. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4e**

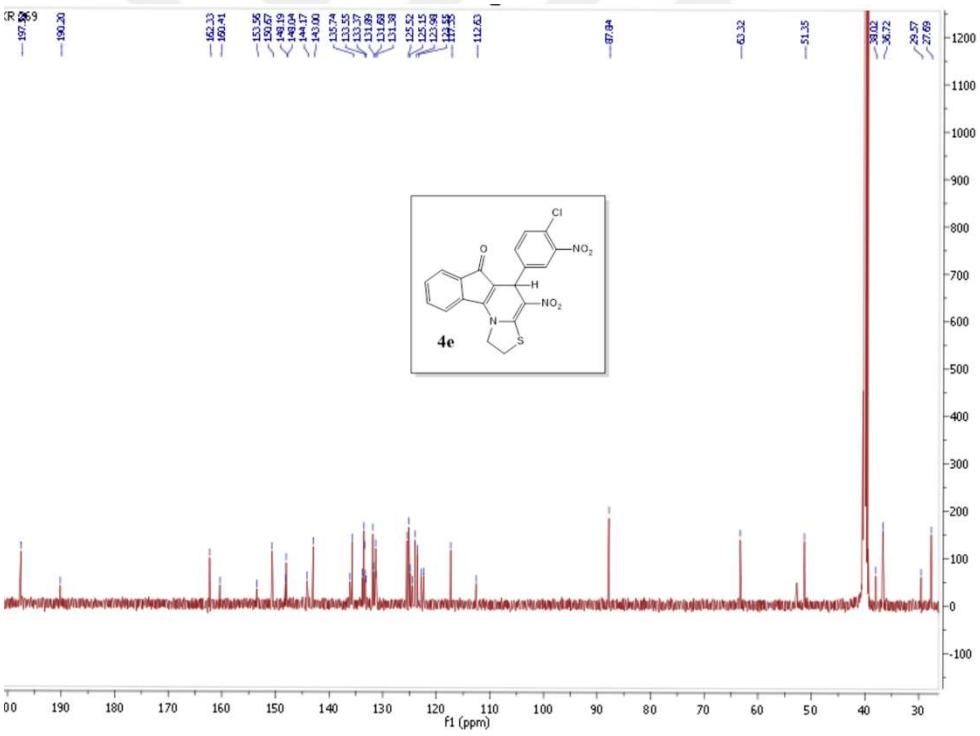


Figure 7.18. ^{13}C NMR (125 MHz, DMSO) spectrum of compound **4e**

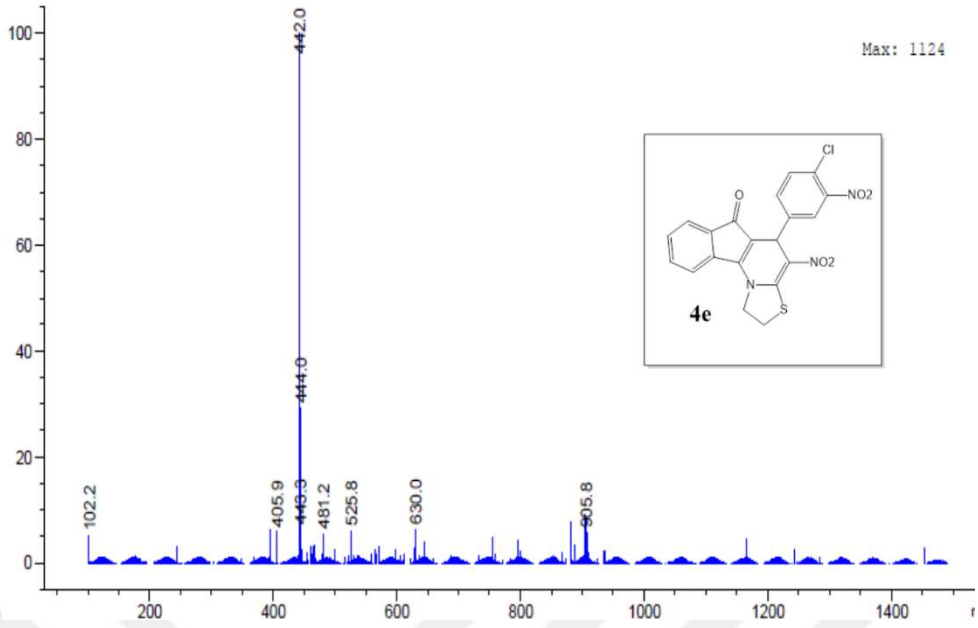


Figure 7.19. LC/MS spectrum of compound **4e**

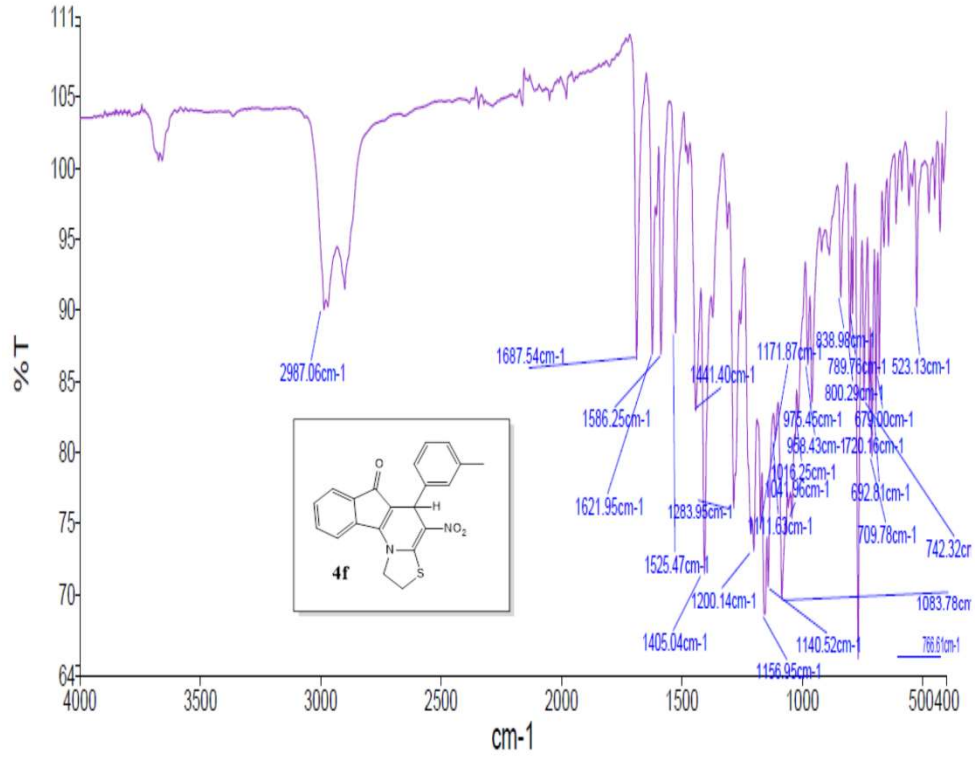


Figure 7.20. IR spectrum of compound **4f**

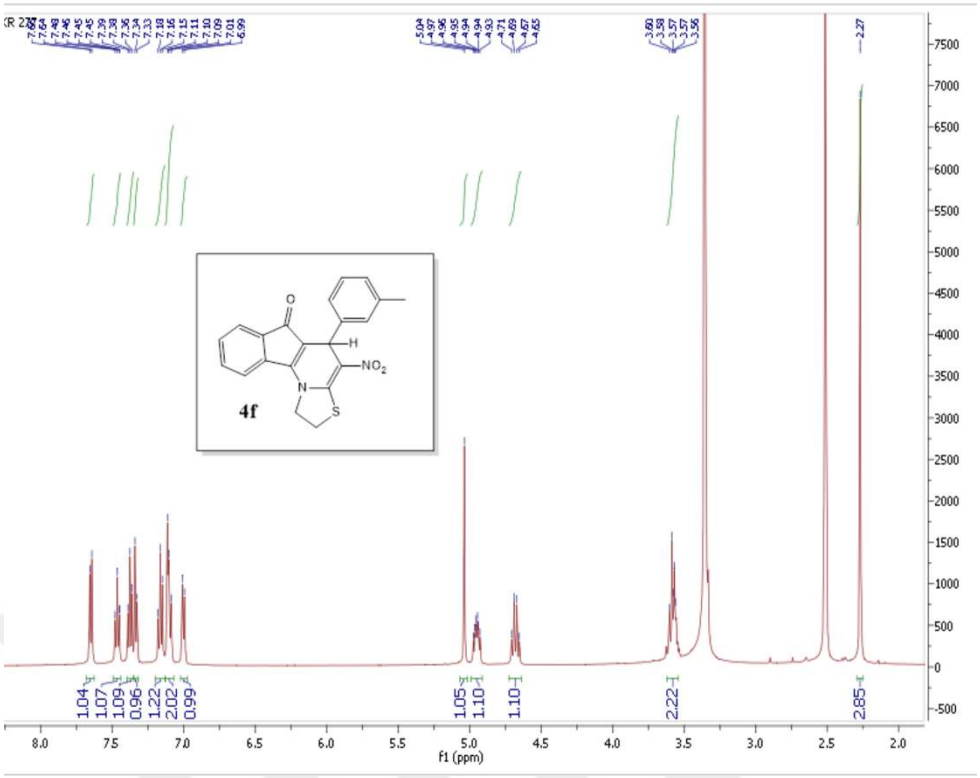


Figure 7.21. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4f**

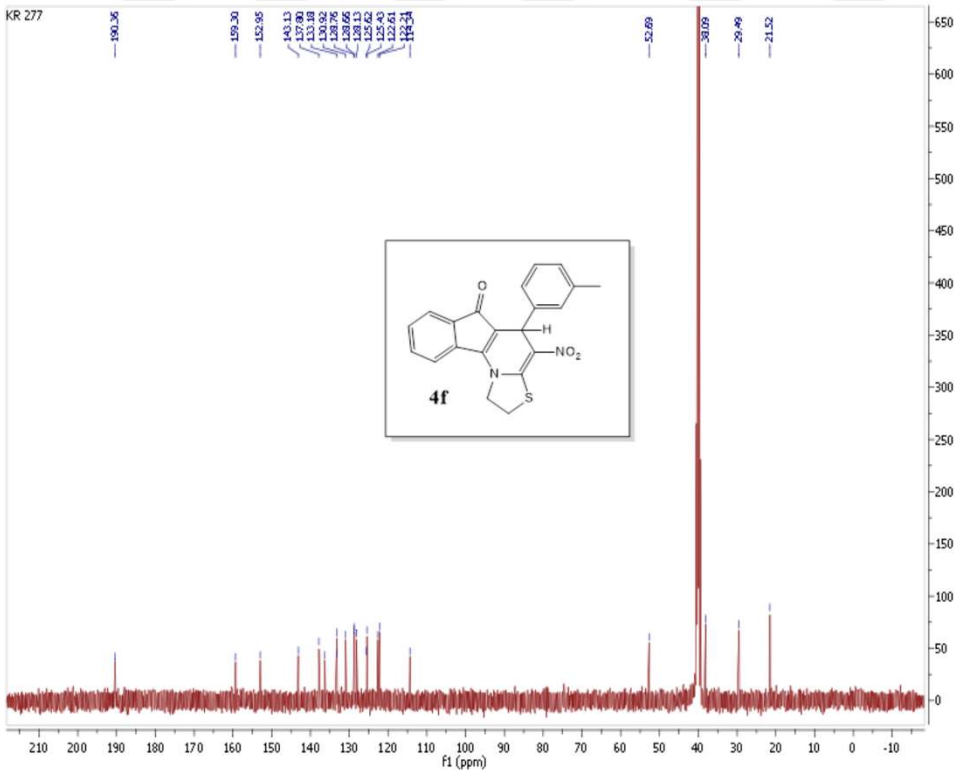


Figure 7.22. ^{13}C NMR (125 MHz, DMSO) spectrum of compound **4f**

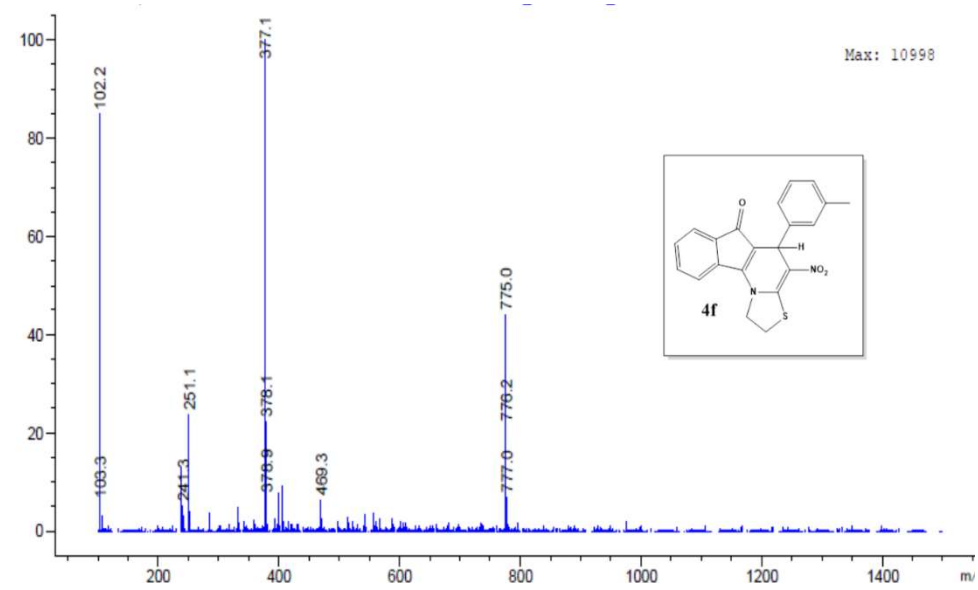


Figure 7.23. LC/MS spectrum of compound **4f**

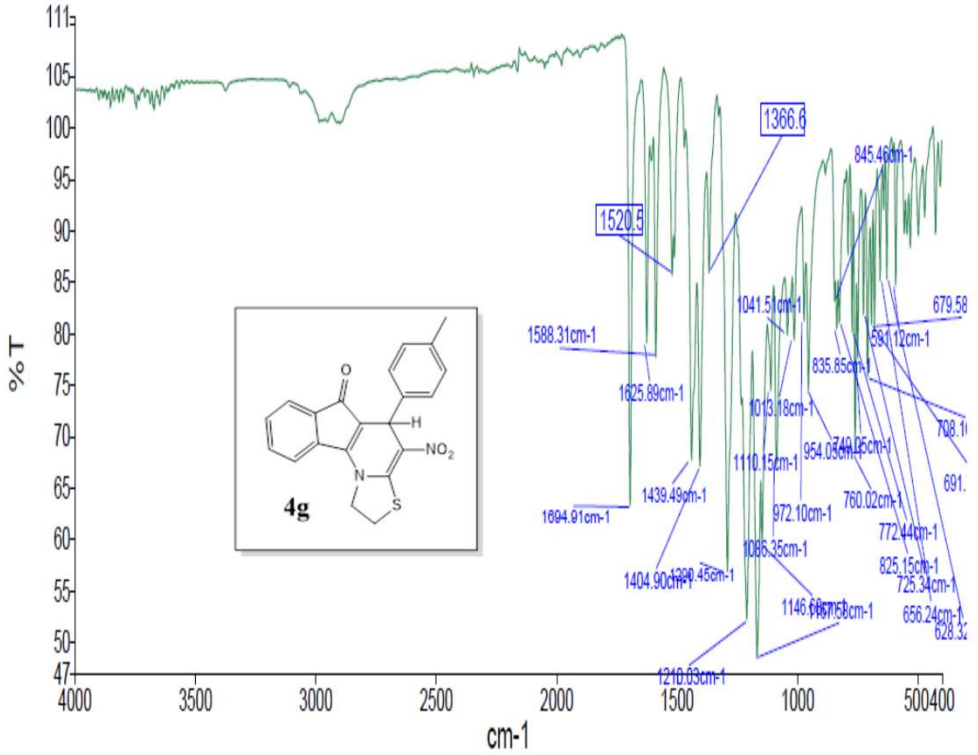


Figure 7.24. IR spectrum of compound **4g**

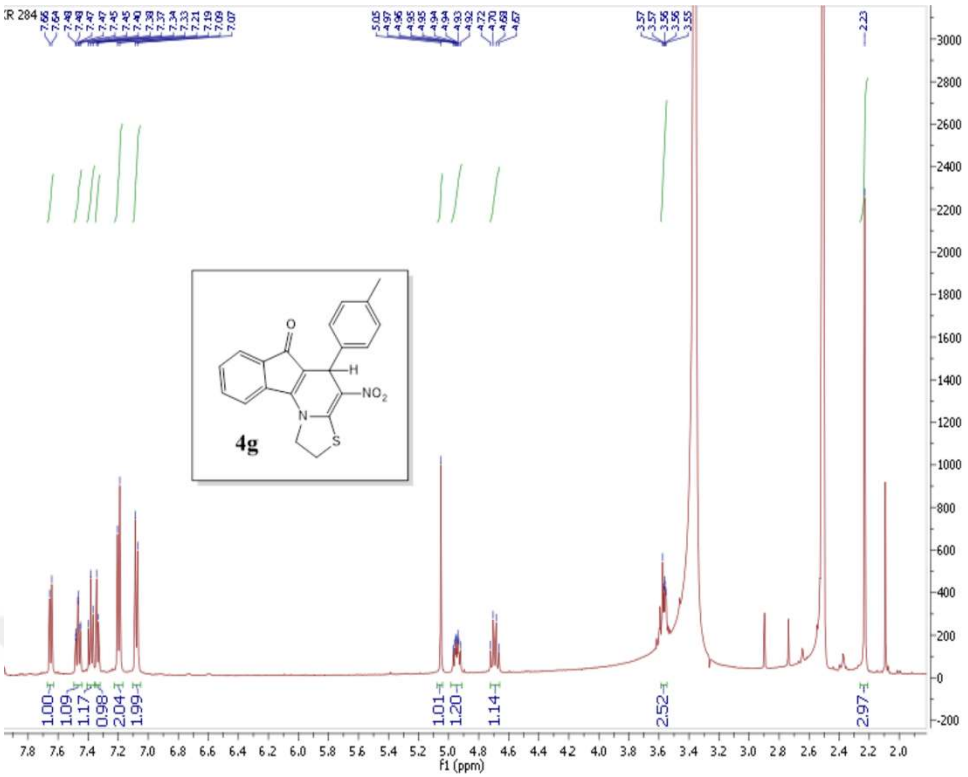


Figure 7.25. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4g**

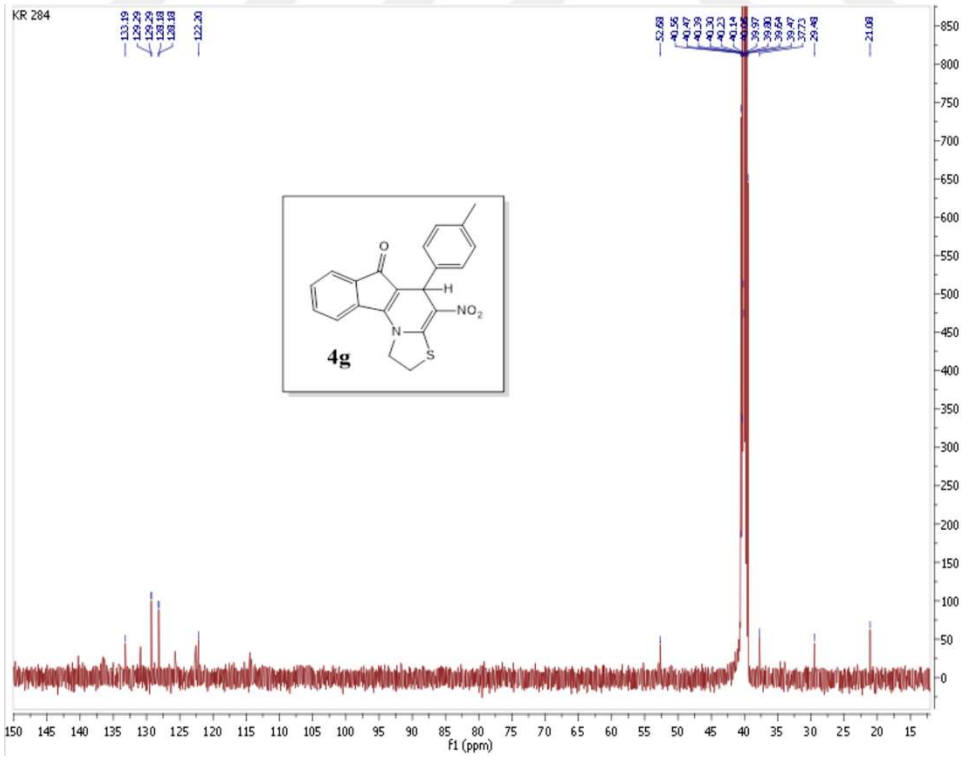


Figure 7.26. ^{13}C NMR (125 MHz, DMSO) spectrum of compound **4g**

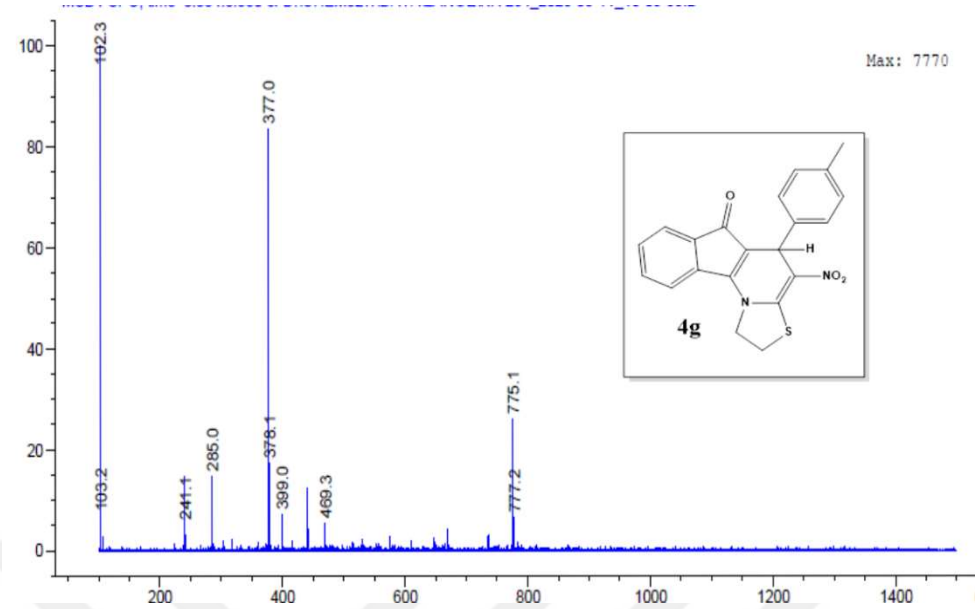


Figure 7.27. LC/MS spectrum of compound **4g**

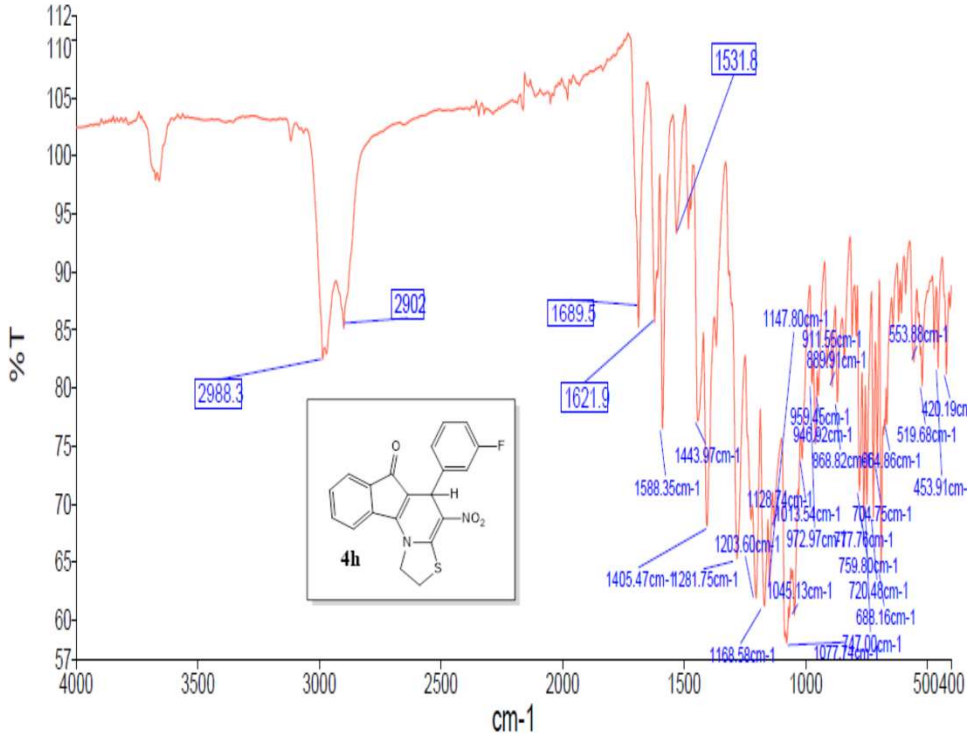


Figure 7.28. IR spectrum of compound **4h**

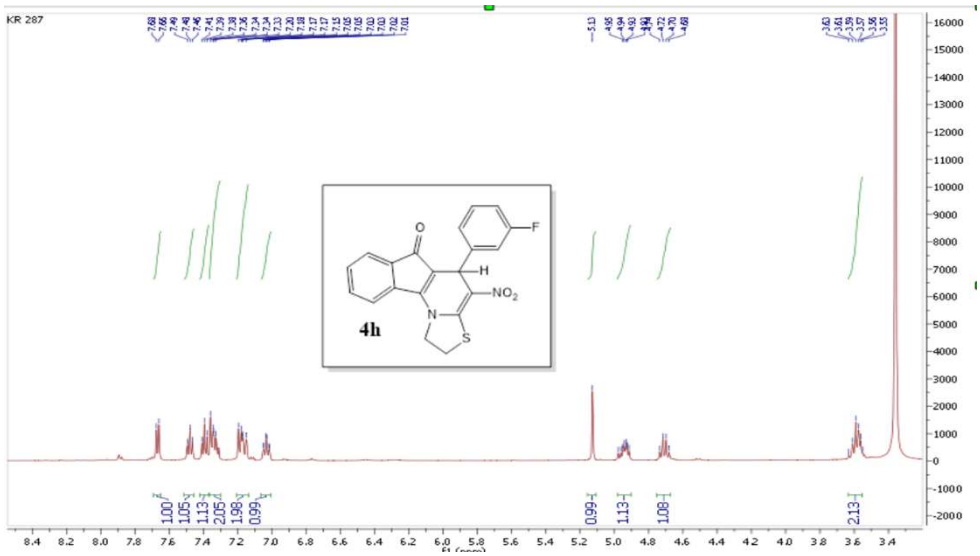


Figure 7.29. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4h**

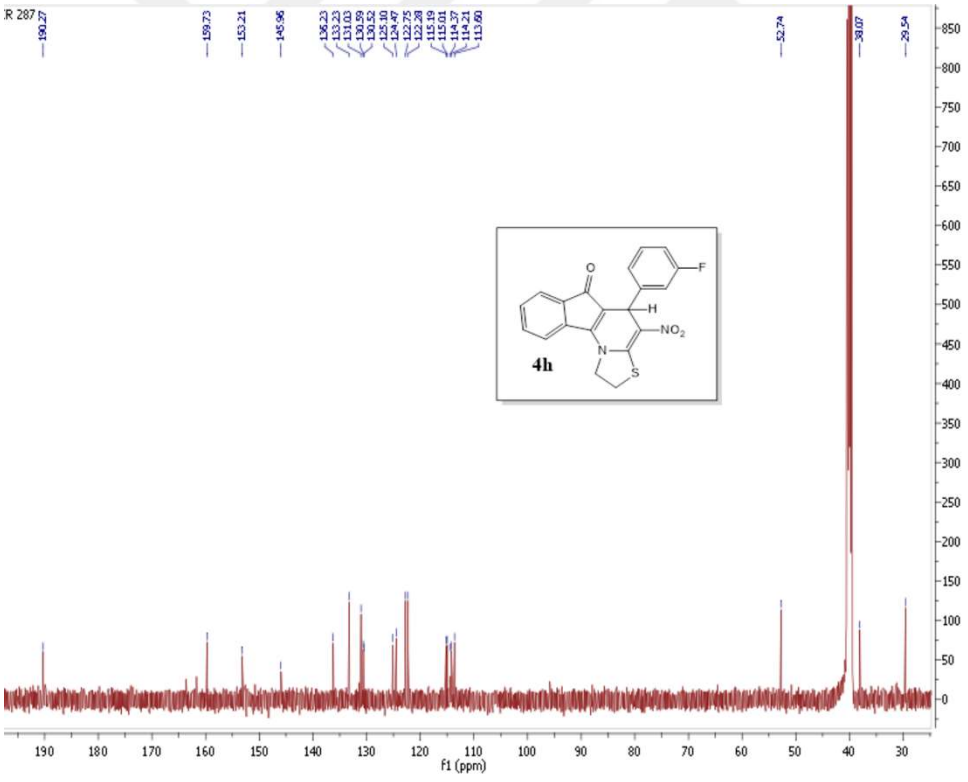


Figure 7.30. ^{13}C NMR (125 MHz, DMSO) spectrum of compound **4h**

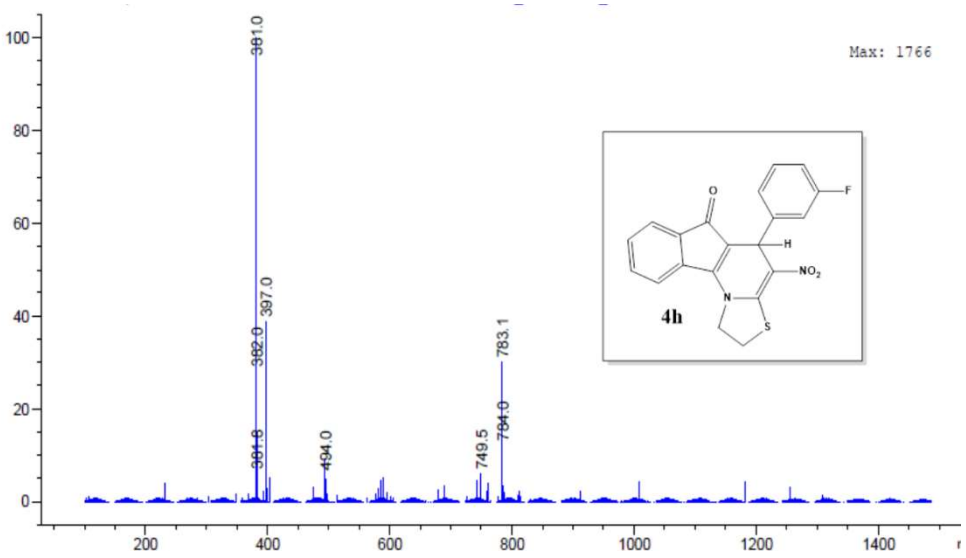


Figure 7.31. LC/MS spectrum of compound **4h**

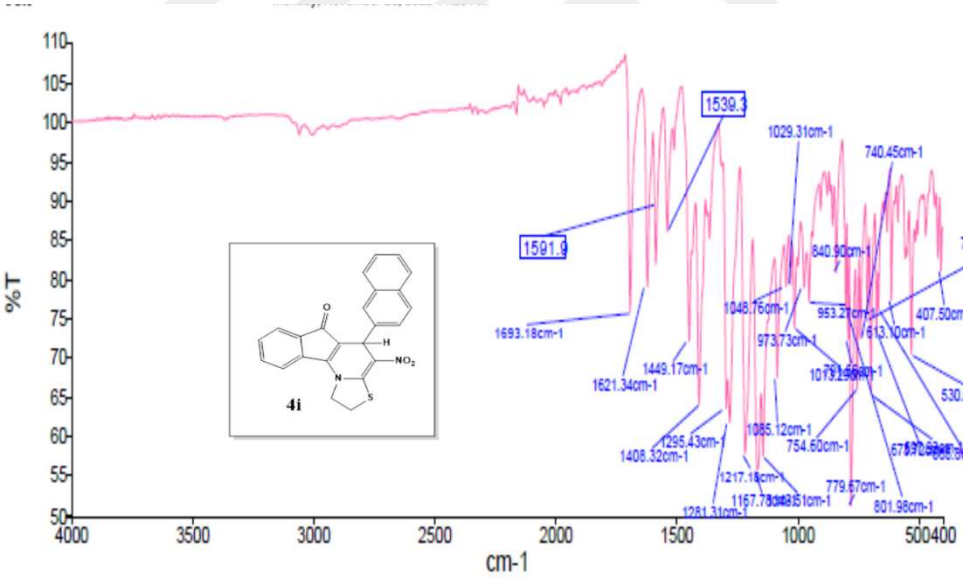


Figure 7.32. IR spectrum of compound **4i**

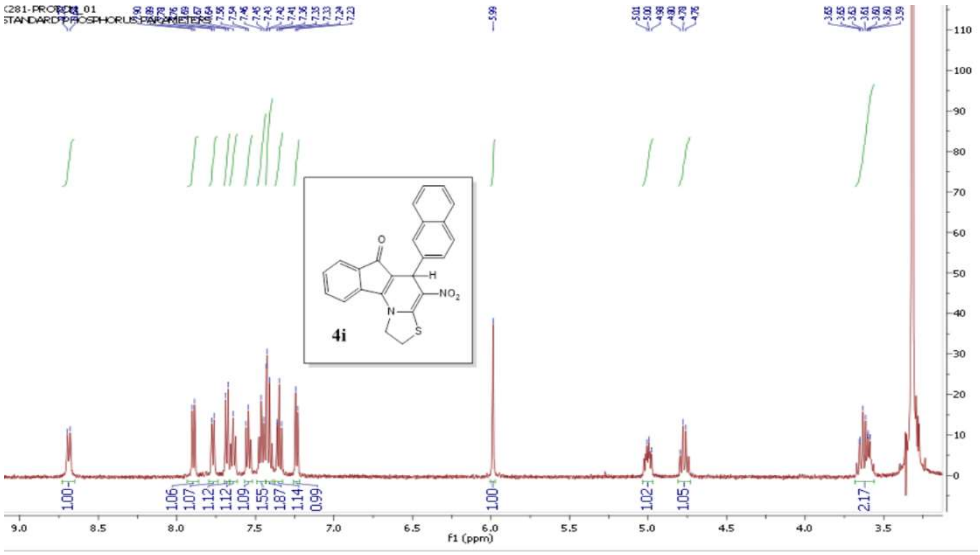


Figure 7.33. ^{1}H NMR (500 MHz, DMSO) spectrum of compound **4i**

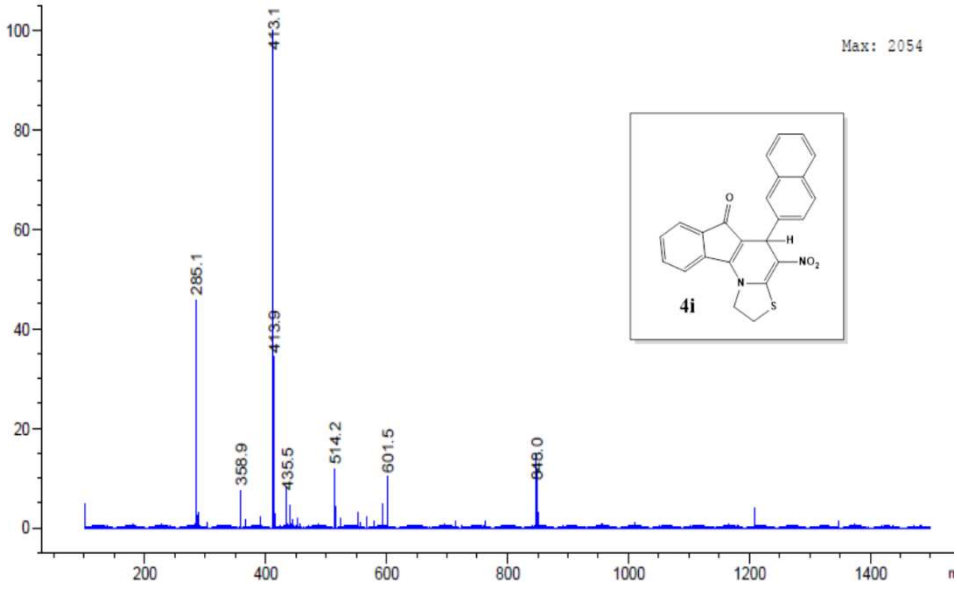


Figure 7.34. LC/MS spectrum of compound **4i**

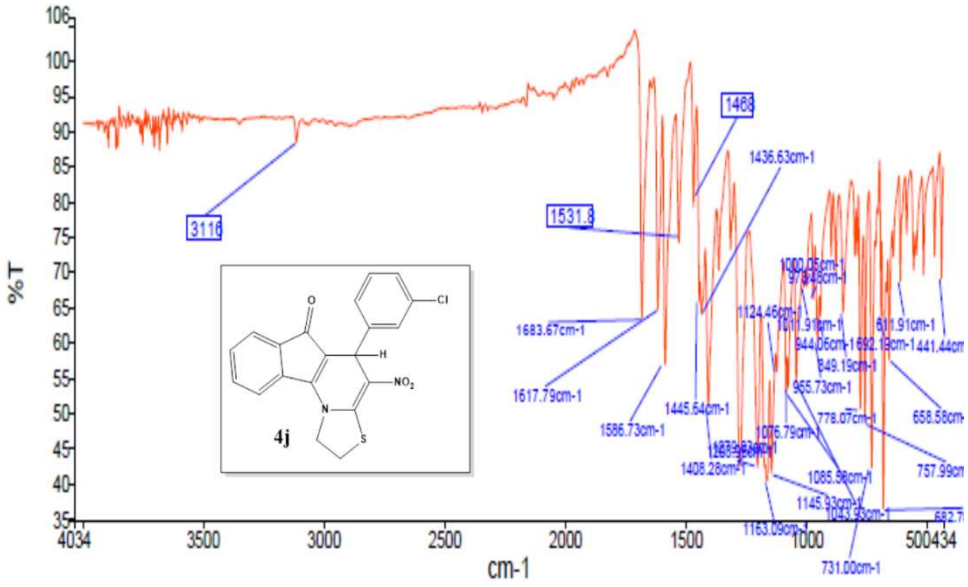


Figure 7.35. IR spectrum of compound **4j**

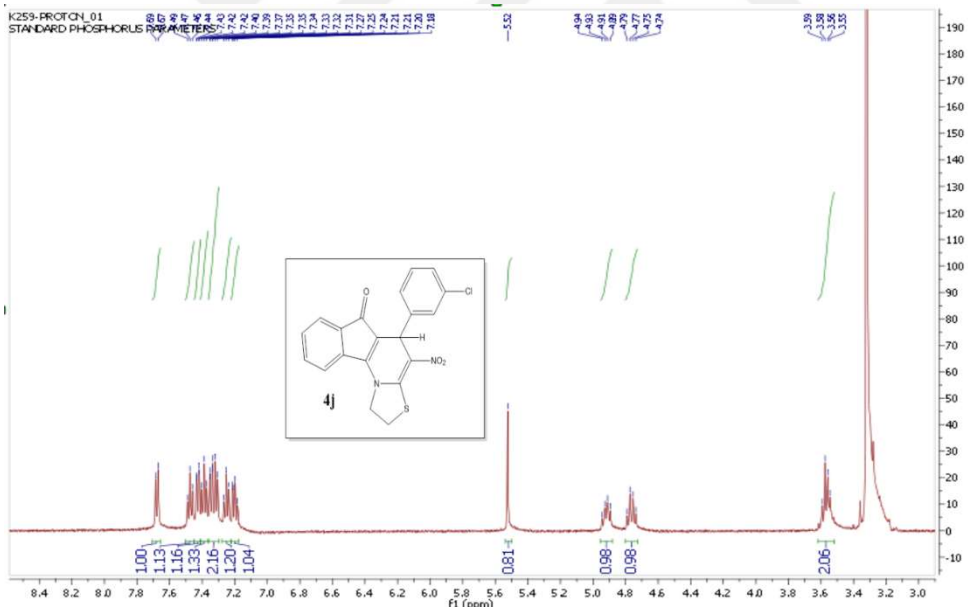


Figure 7.36. 1H NMR (500 MHz, DMSO) spectrum of compound **4j**

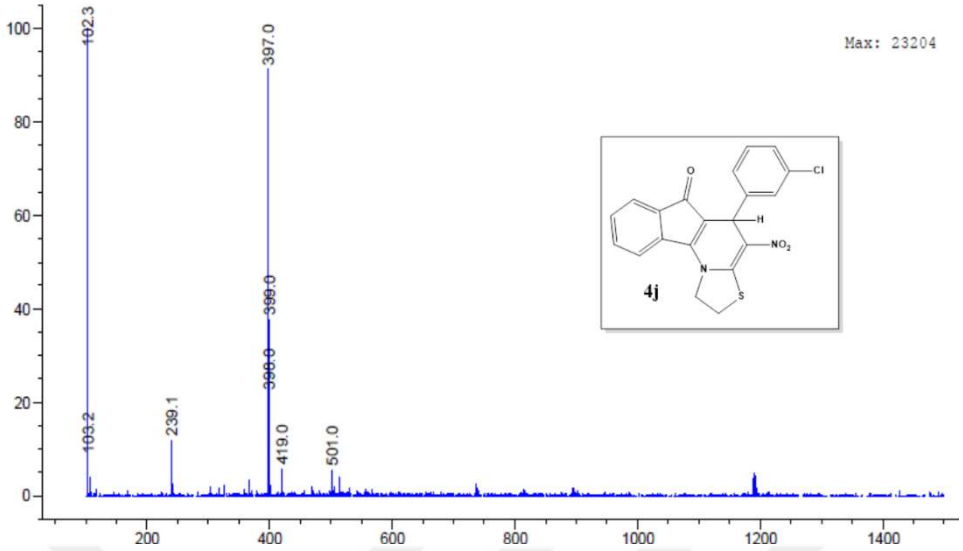


Figure 7.37. LC/MS spectrum of compound **4j**