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

SYNTHESIS OF NEW TRICYCLIC SPIRO-NAPHTHALENE-1,3,4-OXADIAZOLES VIA 1,3-DIPOLAR CYCLOADDITON REACTIONS

MASTER OF SCIENCE

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BOLU, JULY - 2023

APPROVAL OF THE THESIS

Synthesis of New Tricyclic Spiro-Naphthalene-1,3,4-Oxadiazoles via 1,3-Dipolar Cycloaddition Reactions submitted by **Yunus KESGUN** 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 28.07.2023** by

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ABSTRACT

SYNTHESIS OF NEW TRICYCLIC SPIRO-NAPHTHALENE-1,3,4-OXADIAZOLES VIA 1,3-DIPOLAR CYCLOADDITON REACTIONS
MSC THESIS
YUNUS KESGÜN
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INSTITUTE OF GRADUATE STUDIES
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BOLU, JULY 2023
(XV + 86)

This thesis presents a study on the synthesis of a new series of naphthoquinone derivatives via 1,3-dipolar cycloaddition reactions. Naphthoquinone skeletal structure is a synthetically important and adaptable class of chemical compounds, shows a wide range of biological and pharmacological activities. In this study, 2,3-disubstituted-1,4-naphthoquinones were reacted with various hydrazonyl chlorides in ethanol in the presence of triethylamine at boiling temperature to give twelve novel 2,3-bis(phenylthiol)-spiro[naphthalene-1,2'-[1,3,4]oxadiazole]-4-ones. The products precipitated in the reaction medium were purified by washing with cold ethanol. The yields obtained in the synthesis of the products were moderate to good. The synthesized compounds were characterized using various analytical techniques such as NMR spectroscopy, IR spectroscopy and mass spectrometry.

KEYWORDS: 1,3-Cycloaddition, 1,4-Naphtoquinone, 1,3,4-Oxadiazole, Spiro

ÖZET

1,3-DİPOLAR HALKA KATILMA REAKSİYONUYLA YENİ ÜÇ HALKALI SPİRO-NAFTALEN-1,3,4-OKSADİAZOLLERİN SENTEZİ
YÜKSEK LİSANS TEZİ
YUNUS KESGÜN
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: PROF. DR. CEVHER ALTUĞ)
BOLU, TEMMUZ 2023
(XV + 86)

Bu tez, 1,3-halka katılma reaksiyonları yoluyla yeni bir seri naftokinon türevlerinin sentezi üzerine bir çalışmayı sunmaktadır. Sentetik açıdan önemli ve uyarlanabilen bir kimyasal bileşik sınıfı olan naftakinon iskelet yapısı çok çeşitli biyolojik ve farmakolojik aktiviteler göstermektedir. Bu çalışmada, 2,3-disübstitüe-1,4-naftokinonlar, trietilamin varlığında etanol içerisinde çeşitli hidrazonil klorürler ile kaynama sıcaklığında reaksiyona sokularak on iki adet yeni 2,3-bis(feniltiyol)-spiro[naftalen-1,2'-[1,3,4]oksadiazol]-4-on türevleri elde edildi. Reaksiyon ortamında çöken ürünler soğuk etanol ile yıkanarak saflaştırıldı. Ürünlerin sentezinde elde edilen verimler, orta-iyi düzeydedir. Sentezlenen bileşikler, NMR spektroskopisi, IR spektroskopisi ve kütle spektrometrisi gibi çeşitli analitik teknikler kullanılarak karakterize edildi.

ANAHTAR KELİMELER: 1,3-Halka katılma, 1,4-naftakinon, 1,3,4-oksadiazol, spiro

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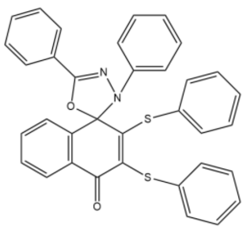
LIST OF ABBREVIATIONS AND SYMBOLS

Ar	: Aryl or aromatic
AcOH	: Acetic acid
Bu3P	: Tributylphosphine
CAN	: Ceric ammonium nitrate
CuI	: Copper(I) iodide
CrO_3	: Chromium trioxide
DCM	: Dichloromethane
DMC	: 2-Chloro-1,3-dimethylimidazolinium chloride
DMF	: Dimethylformamide
EDCl	: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	: Ethyl acetate
EtOH	: Ethanol
$FeCl_3$	: Iron(III) chloride
FMO	: Frontier molecular orbital
FTIR	: Fourier transform infrared spectroscopy
h	: Hour
HCl	: Hydrogen chloride
HMPA	: Hexamethylphosphoramide
HOMO	: Highest occupied molecular orbital
H_2O	: Water
H_2O_2	: Hydrogen peroxide
H_2SO_4	: Sulfuric acid
HRMS	: High-Resolution Mass spectrometry
Hz	: Hertz
I_2	: Iodine
J	: Coupling constant (NMR)
K_2CO_3	: Potassium carbonate
$K_2Cr_2O_7$	: Potassium dichromate
$KMnO_4$	: Potassium Permanganate
LUMO	: Lowest unoccupied molecular orbital
MeCN	: Acetonitrile

mg	: Milligram
mL	: Milliliter
mmol	: Millimolar
MnO_2	: Manganese dioxide
m.p	: Melting point
MW	: Microwave
NMR	: Nuclear magnetic resonance
$Na_2Cr_2O_7$	: Sodium dichromate
Ph	: Phenyl
Ph_3P	: Triphenylphosphine
$POCl_3$	: Phosphoryl chloride
Rf	: Retardation factor
Rt	: Room temperature
TEA	: Triethylamine
TEBA	: Benzyltriethylammonium
Tf_2O	: Triflic anhydride
THF	: Tetrahydrofuran
TLC	: Thin-layer chromatography
σ	: Sigma
Δ	: Heat

FORMULAE



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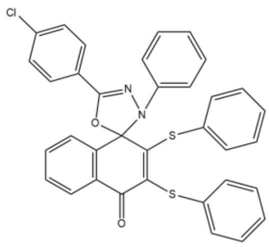

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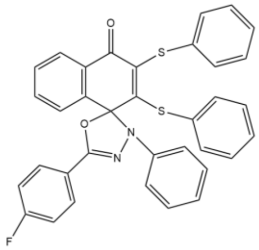

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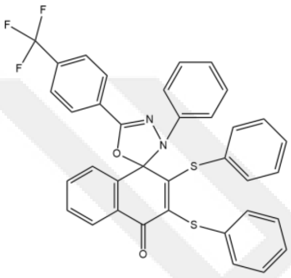

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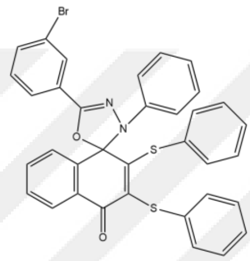

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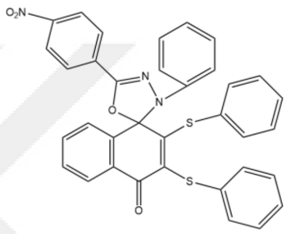

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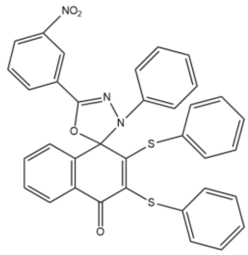

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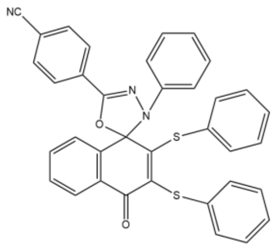

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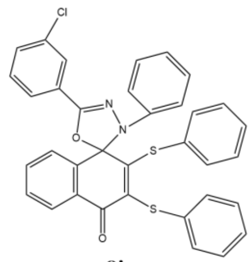

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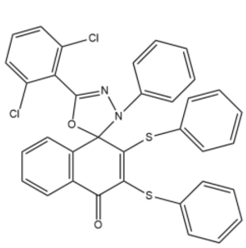

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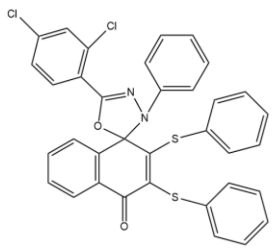

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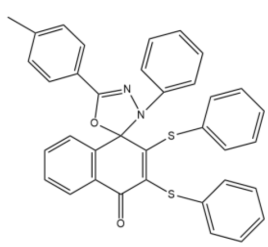

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1. INTRODUCTION

1.1 Heterocyclic Compounds

A significant family of organic chemicals known as heterocyclic compounds is crucial to many areas of organic chemistry. Heterocyclic compounds are circular substances whose ring structure includes atoms from at least two distinct elements, such as N, O and S. Due to their widespread presence in natural goods like nucleic acids, vitamins, alkaloids, and antibiotics, they play a crucial role in organic chemistry. Heteroatoms in heterocycles give substances special physical and chemical characteristics that are the basis for a variety of biological and therapeutic actions. Heterocyclic compounds critically contribute to the development of new drugs and emphasize their significance in the field of medicinal chemistry. Designing and synthesizing novel heterocyclic compounds with improved pharmacological properties is feasible. Pyridine, benzimidazole, pyrazole, furan, thiophene, quinones, isoxazole, and oxadiazole are a few examples of heterocyclic compounds with a diverse array of pharmacological properties. These properties can include anti-inflammatory, antifungal, antibacterial, anti-tuberculosis, analgesic, and antihypertensive activities. Among these heterocyclic compounds, quinones deserve special attention for their diverse pharmacological effects.

1.2 Quinones

Quinones, classified as organic compounds that exhibit a cyclic conjugated structure and contain a functional group with a two-carbon ketone. Quinones can be classified into several types based on the number and position of substituent groups attached to the ring structure. Benzoquinones, naphthoquinones, and anthraquinones are the most prevalent ones.[1] Based on their position on the benzene ring, there are three types of benzoquinones: ortho-, para-, and meta-benzoquinone. Meta-benzoquinone’s usability is limited by its instability and brief shelf life.[2]

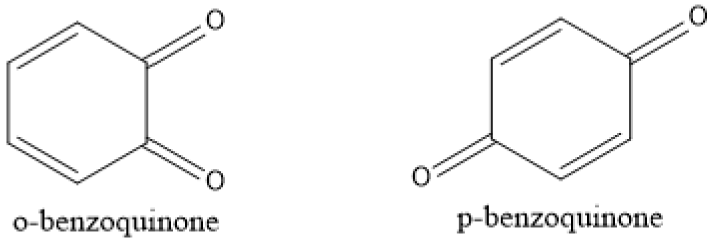
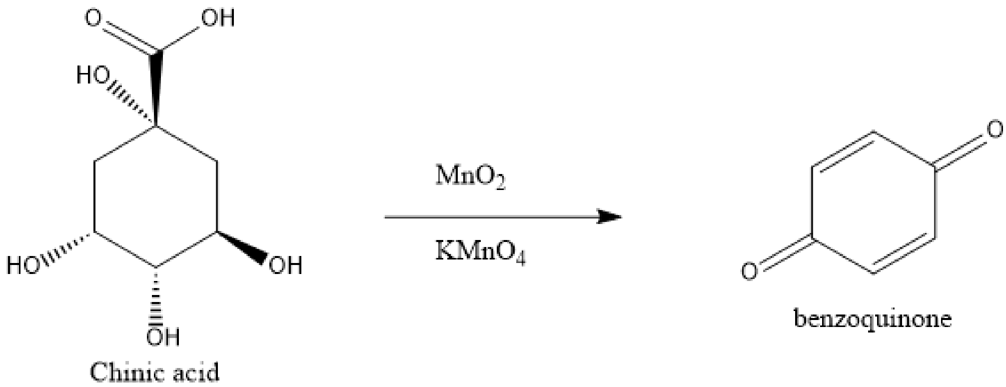


Figure 1.1: Molecular structures of both o-benzoquinone and p-benzoquinone are shown.

From the early 19th century, the first quinone, known as benzoquinone was synthesized by reacting chinic acid with manganese dioxide and sulfuric acid, an oxidation formation occurs.[3] Decarboxylation, dehydration, and oxidation occur during this reaction. The reaction is shown in Scheme 1.1 below.



Scheme 1.1: Preparation of benzoquinone from chinic acid

The structure of naphthoquinone consists of two fused benzene rings with two ketone groups attached at different positions. There are many naphthoquinones isomers that differ in the position of the carbonyl groups attached to the naphthalene ring. The most well-known are 1,2-naphthoquinone, 1,4-naphthoquinone, and 2,6-naphthoquinone. Anthraquinones consist of an anthracene ring with two ketone groups. Anthraquinones have several isomers. 1,2-, 1,4-, and 2,6-anthraquinones are most known.[4] The structures are as follows:

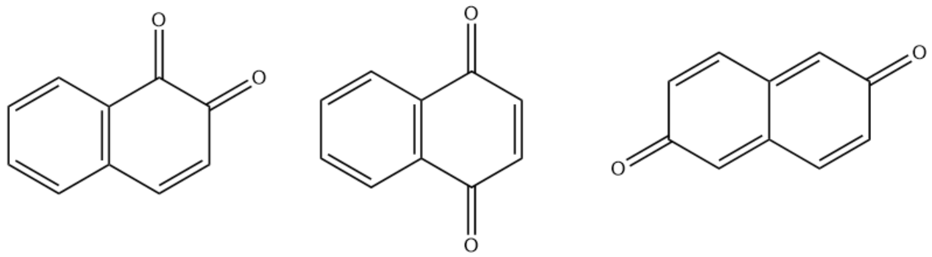


Figure 1.2: Isomers of naphthoquinones

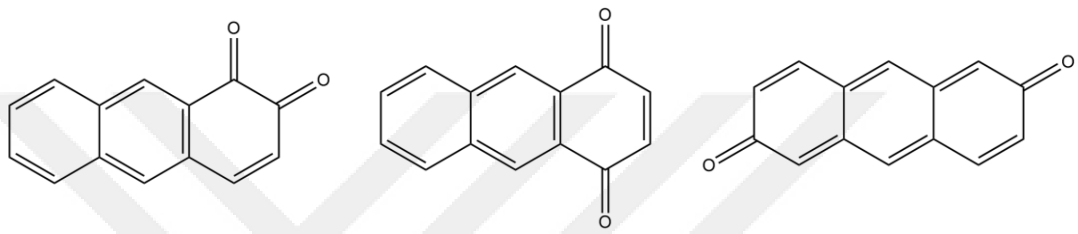
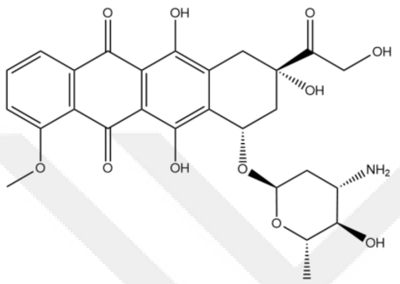


Figure 1.3: Isomers of anthraquinones

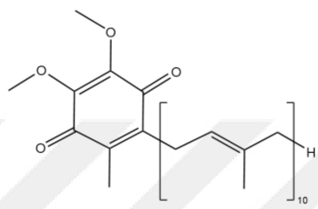
1.2.1 Biological Activities of Quinones

Quinone derivatives have diverse biological activities[5] such as anticancer[6], antiviral[7], antibacterial[8], anti-inflammatory[9], anti-artherosclerotic[10], analgesic[11], antioxidant[12], antimalarial[13], antitubercular[14], trypanocidal[15] as well as neuroprotective activities.[16]

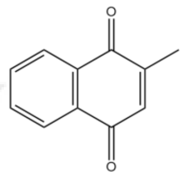
There are several drugs containing quinone structures that are used for various medical purposes. One example is Doxorubicin, which is used to treat cancer including breast cancer, and bladder cancer.[17] Another example is Coenzyme, Q10 also known as ubiquinone, which is involved in the electron transport chain in mitochondria and is also used as a dietary supplement and CoQ10 is leading to various health issues such as cardiovascular diseases, neurodegenerative disorders.[18] Another one is Menadione is a synthetic vitamin K compound that has a quinone structure. It is used as a nutritional supplement and is involved in blood clotting.[19] Lapachol which also exhibits anti-inflammatory, antineoplastic agent and antibacterial agent.[20] Atovaquone is used to treat and prevent malaria and other parasitic infections.[21] Mitomycin is a chemotherapy drug with antitumour properties derived from a species of soil fungus called Streptomyces caespitosus and has antibiotic structure.[22] Shikonin has documented anti-inflammatory and antimicrobial activities, making it an important drug in traditional medicine.[23] Mitoxantrone is a synthetic compound used as an anticancer drug in the treatment of various types of cancer, such as breast cancer and prostate cancer.[24]



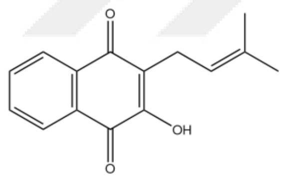
Doxorubicin



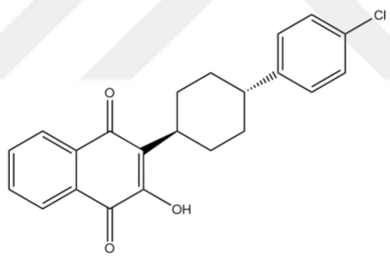
CoQ10



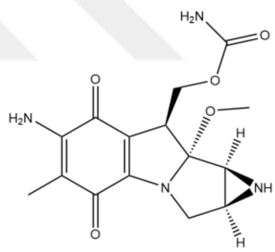
Menadione



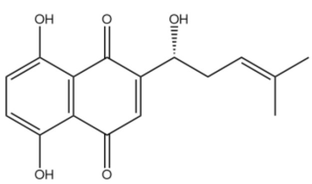
Lapachol



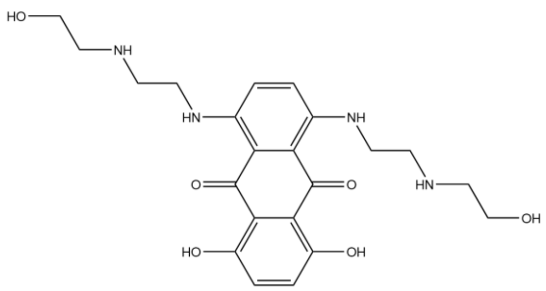
Atovaquone



Mitomycin C



Shikonin

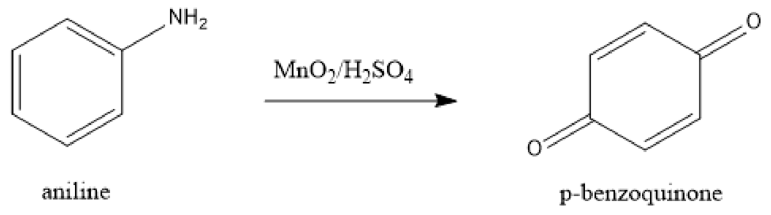


Mitoxantrone

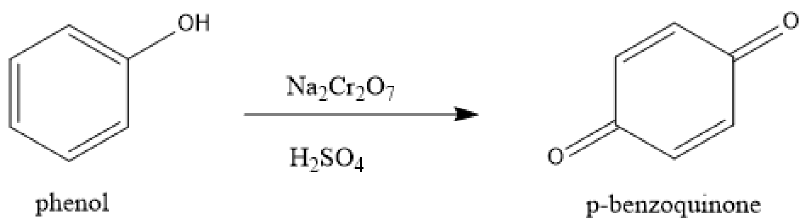
Figure 1.4: Some examples of drugs that contain quinone motif

1.2.2 Some Synthesis and Reactions of Quinone Derivatives

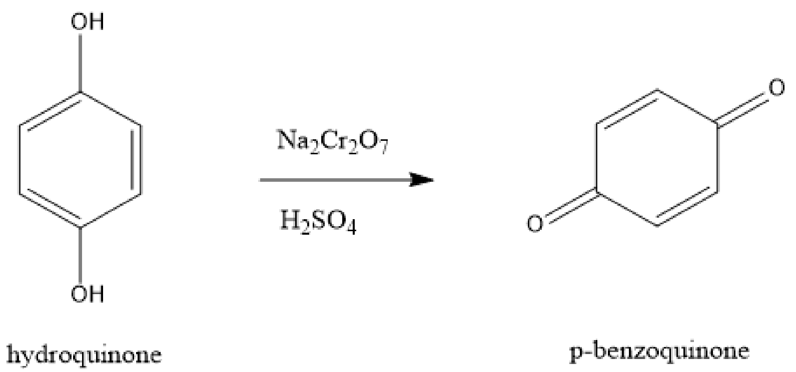
Oxidations reactions of some precursors such as anilines, phenols, or hydroquinone derivatives give quinone.[25-27]



Scheme 1.2: Acidified manganese dioxide reaction with aniline

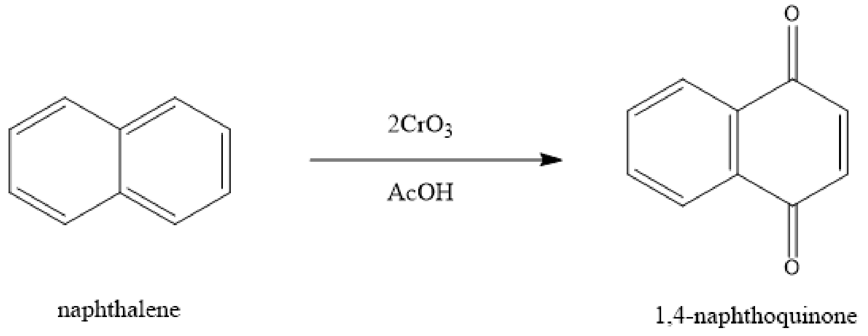


Scheme 1.3: Formation of benzoquinone from phenol



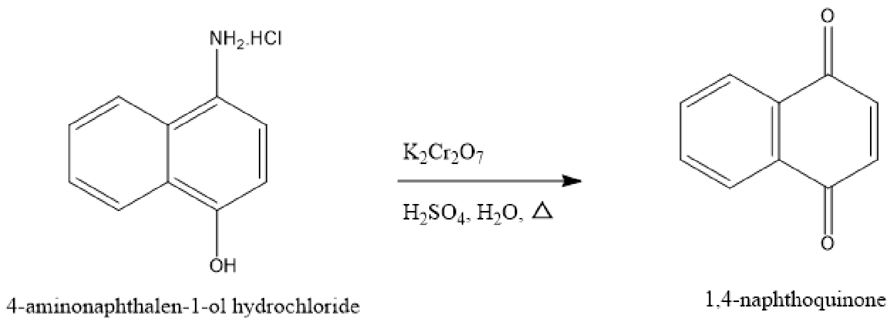
Scheme 1.4: Synthesis of p-benzoquinone from hydroquinone

A cost-saving method is to oxidise naphthalene using chromium trioxide in acetic acid.[28]



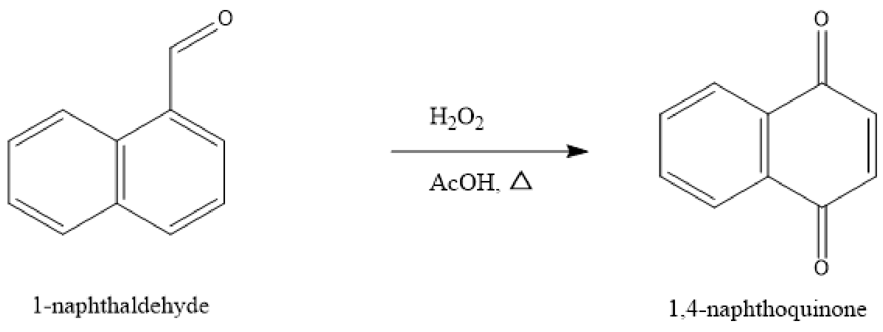
Scheme 1.5: Preparation of 1,4-naphthoquinone from naphthalene

Also, it has been reported that 1,4-naphthoquinone is obtained from 4-aminonaphthalen-1-ol hydrochloride by using potassium dichromate.[29]



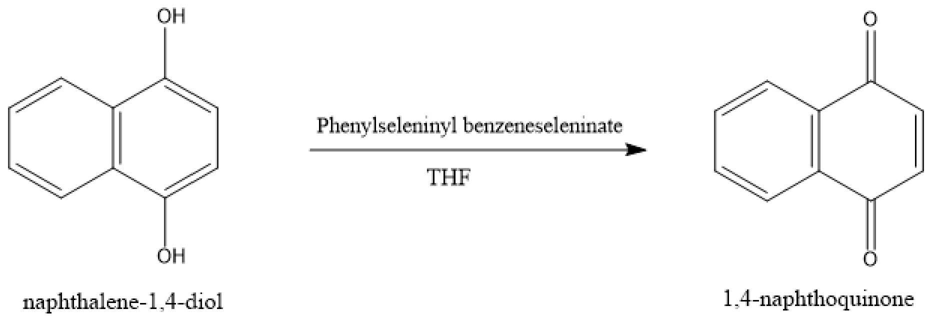
Scheme 1.6: Synthesis of 1,4-naphthoquinone

1,4-Naphthoquinone can be obtained by treating of 1,4-naphthaldehyde by using oxidizing agent such as H_2O_2 and AcOH. [30]



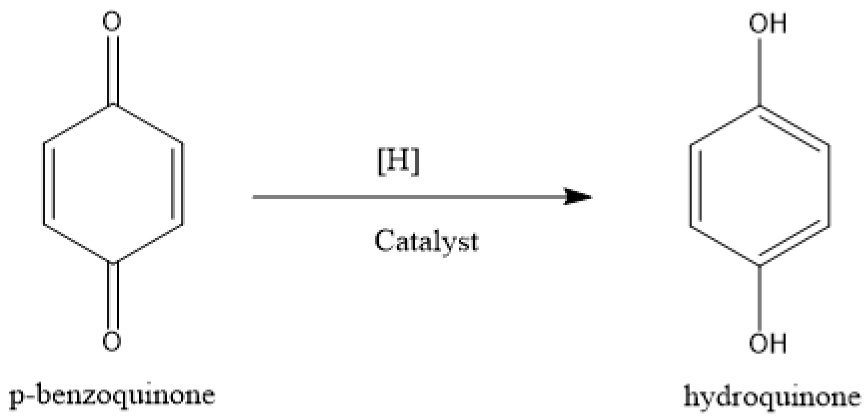
Scheme 1.7: Formation of 1,4-naphthoquinone

Another synthesis method for 1,4-naphthoquinone is obtained from naphthalene-1,4-diol with phenylseleninyl benzeneseleninate. [31]



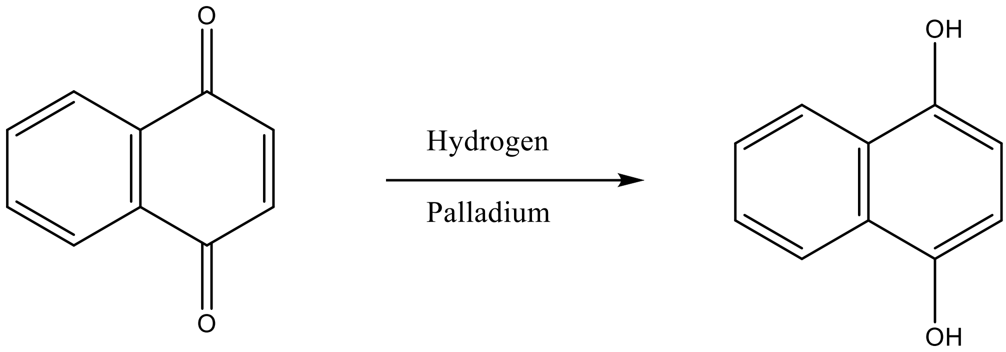
Scheme 1.8: Reaction with naphthalene-1,4-diol and phenylseleninyl benzeneseleninate

Quinones can undergo reduction through an assortment of methods, such as employing chemical reducing agents like sodium borohydride, lithium aluminum, and zinc. The process of hydrogenation can also be carried out electrochemically or with several reducing agents, such as metals in aqueous acid and catalytic hydrogenation. [32]



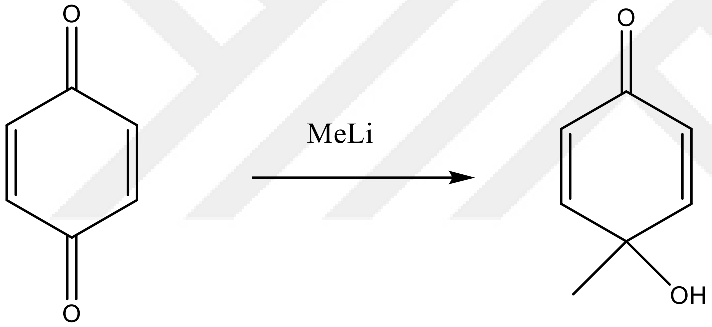
Scheme 1.9: Hydrogenation of p-benzoquinone

Naphthoquinone has the potential to undergo reduction through hydrogenation in the presence of palladium.[33]



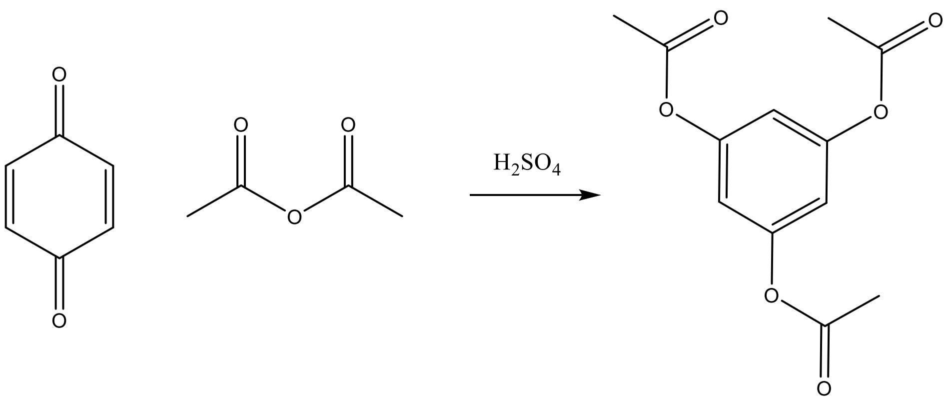
Scheme 1.10: Reduction of p-benzoquinone

In general, when a Grignard reagent reacts with benzoquinone, the carbonyl groups are reduced to hydroxyl groups (-OH) via a nucleophilic addition reaction. [34]



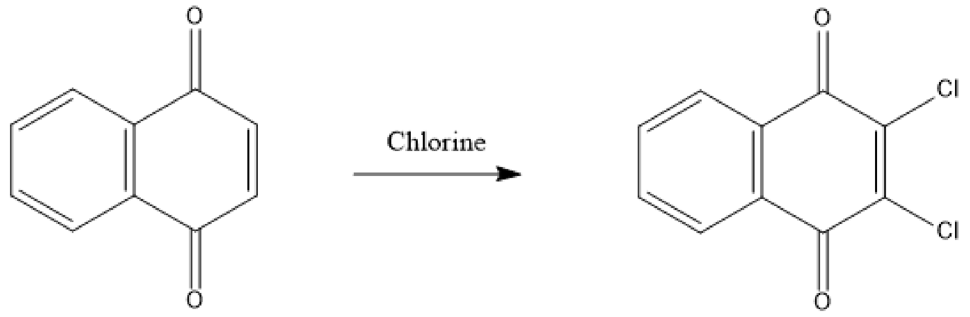
Scheme 1.11: Grignard reaction of para-benzoquinone

One of another reaction of quinone is the Thiele reaction, when para-benzoquinone reacts with acetic anhydride and sulfuric acid, it forms benzene-1,2,4-triyl triacetate. [35]



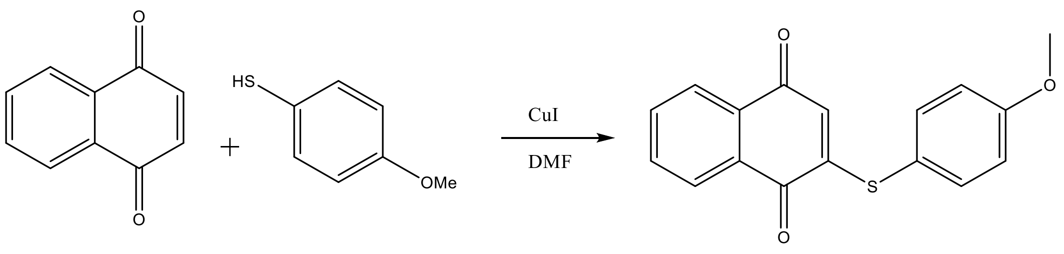
Scheme 1.12: Thiele-Winter reaction of para-benzoquinone

Halogenation of 1,4-naphthoquinone involves a substitution process where one or more hydrogen atoms within the naphthoquinone molecule are substituted with halogen atoms. Typically, the reaction occurs in the presence of a halogenating agent, including bromine or chlorine. [36]



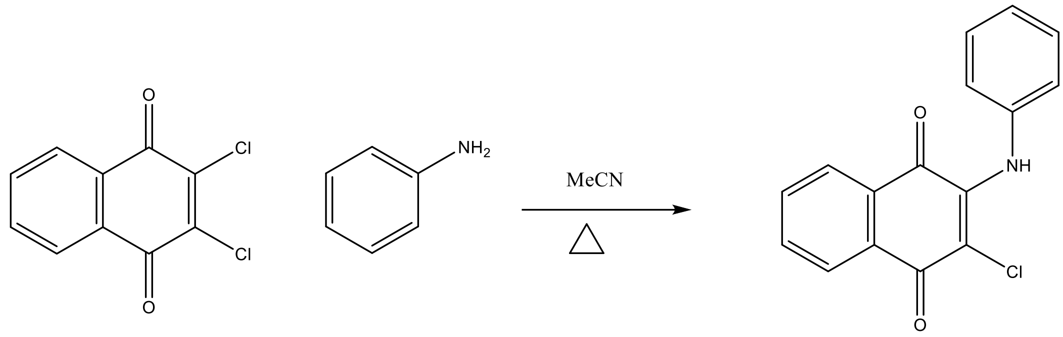
Scheme 1.13: Halogenation of 1,4-naphthoquinone

1,4-Naphthoquinone can undergo addition reactions with various nucleophiles, including alcohols, amines, and thiols. Cuprous iodide (CuI) was employed as a catalyst for the formation of 2-thioaryl variations of 1,4-naphthoquinone using 1,4-naphthoquinone and 4-methoxythiophenol as reactants.[37]



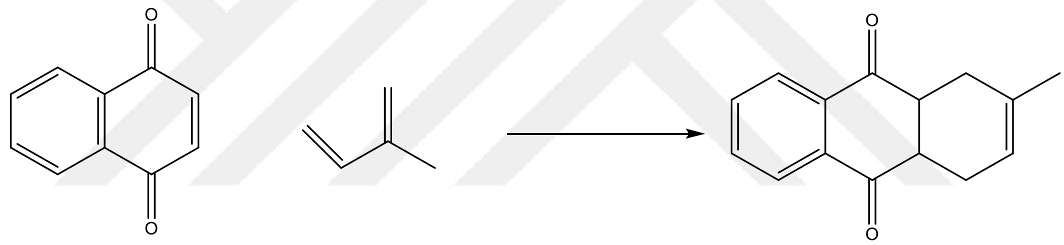
Scheme 1.14: 1,4-Naphthoquinone reaction with 4-methoxythiophenol

When Halogen-substituted naphthoquinones react with diverse nucleophiles such as amines, thiols, and alcohols, nucleophilic substitution reactions can occur. 2,3-Dichloro-1,4-naphthoquinone was reacted with aniline in acetonitrile with the assistance of refluxing for the production of phenylaminonaphthoquinone. [38]



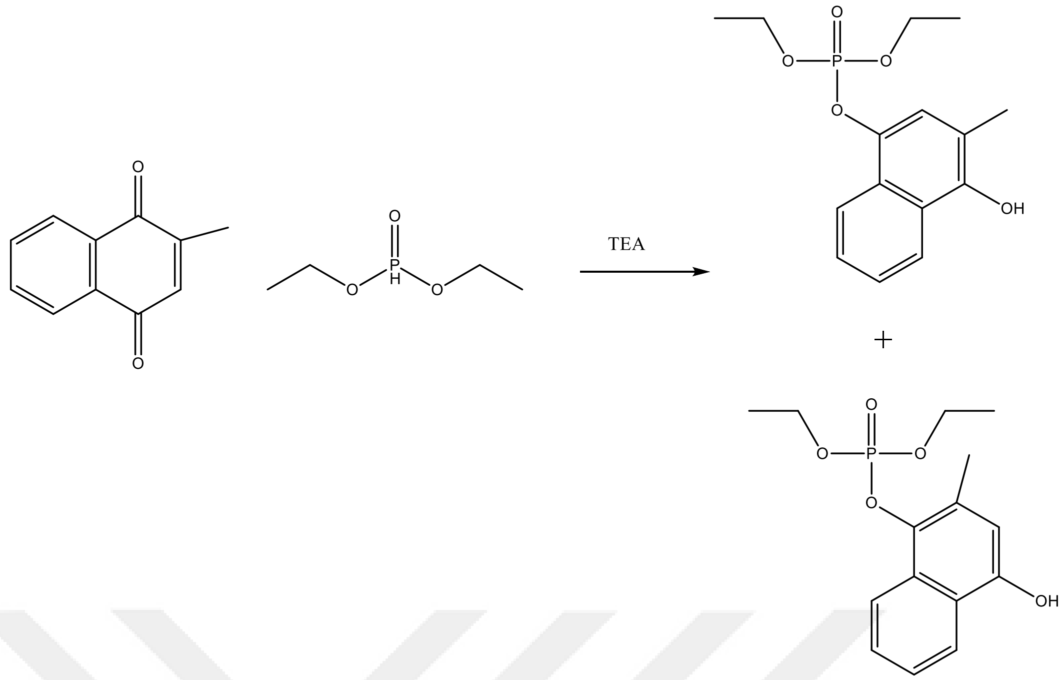
Scheme 1.15: The interaction between 2,3-Dichloro-1,4-naphthoquinone and aniline

The Diels-Alder reaction of 1,4-naphthoquinones involves the cycloaddition of a diene and a dienophile, resulting in the formation of a cyclic compound. In this chemical process, the 1,4-naphthoquinone acts as a dienophile and reacts with a diene, such as isoprene, to form a fused-ring system.[39]



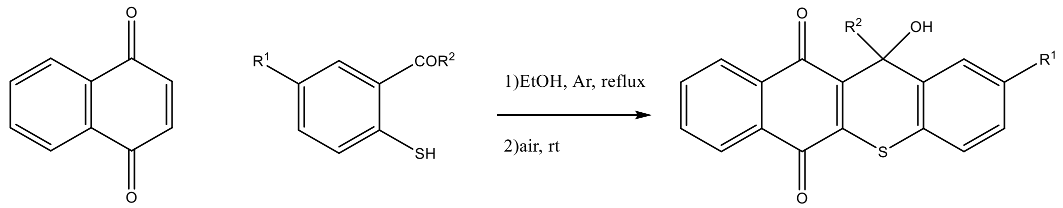
Scheme 1.16: The Diels-Alder reaction of 1,4-naphthoquinone

A mixture of 1- and 4-(dialkyl phosphates) is produced when 2-methyl-1,4-naphthaquinone is generated through a reaction with dialkyl phosphites in the presence of triethylamine.[40]



Scheme 1.17: Reaction of 2-methyl-1,4-naphthaquinone and dialkyl phosphites

The formation of 12H-benzo[b]thioxanthene quinones is achieved through a reaction involving 1,4-naphthoquinone and 2-acylbenzenethiols. This reaction proceeds sequentially through conjugate addition, aldol reaction, and atmospheric oxidation steps.[41]



Scheme 1.18: Synthesis of 12H-benzo[b]thioxanthene quinones

1.3 Oxadiazoles

Oxadiazoles, a type of organic compound, possess a ring structure comprising five members. These compounds have various chemical characteristics due to their unusual configurations. It is particularly significant because oxadiazole can occur in four different configurations: 1,2,3, 1,2,4, 1,2,5, and 1,3,4-oxadiazole. The nitrogen and oxygen atoms are specifically positioned within the five-membered ring according to the numbering scheme employed for these isomers. It is interesting to note that the common formula across all these isomers is $C_2H_2ON_2$. Oxadiazoles, a type of organic compound, possess a ring structure comprising five members. Each of these forms follows a general formula of $C_2H_2ON_2$.

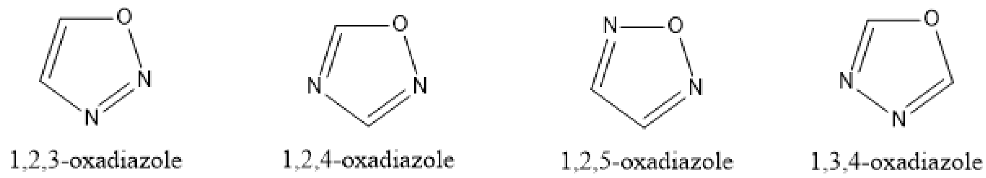
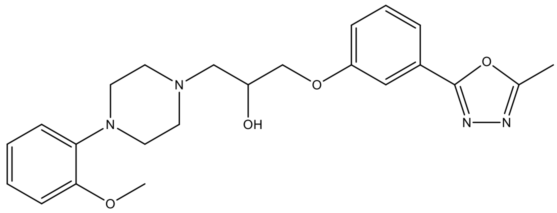


Figure 1.5: Different isomeric variations of oxadiazole

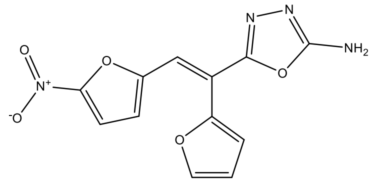
1.3.1 Some Important Drugs of 1,3,4-Oxadiazole Moieties

1,3,4-Oxadiazole moieties show diverse biological activities which leads to significant focus in drug discovery.[43] Among them, although not exclusively, are antifungal[44], analgesic[45], anti-inflammatory[46], antibacterial[47], antitumor[48], anticancer[49], antimicrobial[50], antihypertensive[51], anticonvulsant[52], anti-diabetic[53], antioxidant[54], and neuroprotective effects.[55] Several pharmaceutical compounds incorporate the ring structure of 1,3,4-oxadiazole.

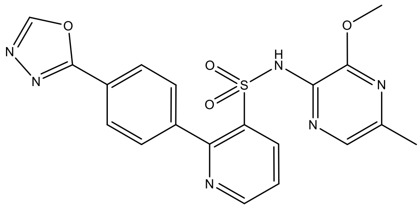
Nesapidil is a pharmaceutical compound with various applications in the medical field. It is primarily recognized as a vasodilator which is used in anti-arrhythmic and antihypertensive therapies. [56] Furamizole, a member of the nitrofuran group, exhibits antibacterial properties. [57] Zibotentan is a drug that contains an oxadiazole nucleus and has been investigated for its potential anticancer properties. [58] Raltegravir is a type of antiretroviral medication classified as an integrase strand transfer inhibitor (INSTI), which is used in the treatment of HIV infection. [59].



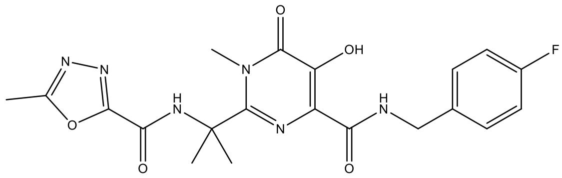
Nesapidil (antihypertensive)



Furamizole (antibacterial)



Zibotentan (anti-cancer)

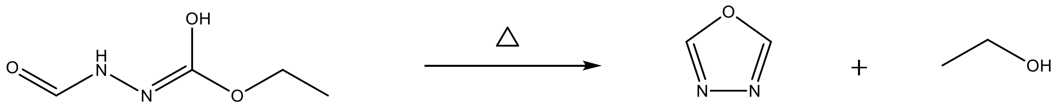


Raltegravir (anti-retroviral)

Figure 1.6: Some drugs containing 1,3,4-oxadiazole

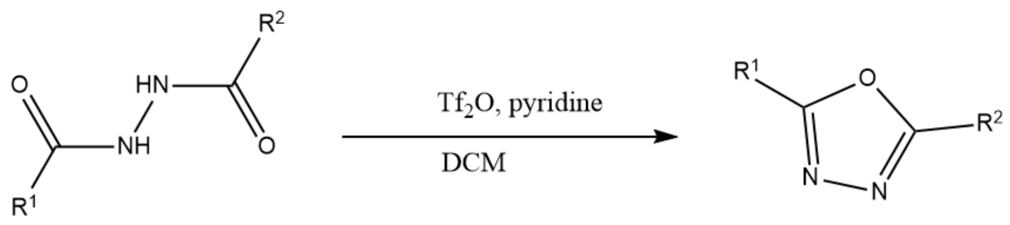
1.3.2 Synthesis of Some 1,3,4-Oxadiazoles

In 1965, Ainsworth provided the initial description of the synthesis of unsubstituted 1,3,4-oxadiazole. The process involved the application of thermolysis at atmospheric pressure to convert formylhydrazone ethylformate into the desired compound. [60]



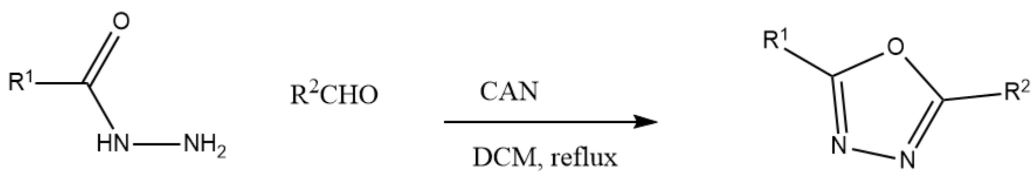
Scheme 1.19: Thermal decomposition as a method for synthesizing 1,3,4-oxadiazole

Liras et al. devised a method to achieve the efficient cyclization of diacylhydrazines under milder conditions by employing triflic anhydride (Tf_2O). The formation of 1,3,4-oxadiazole was accomplished by utilizing the diacylhydrazines dissolved in dichloromethane and subjecting them to the influence of triflic anhydride in the presence of pyridine.[61]



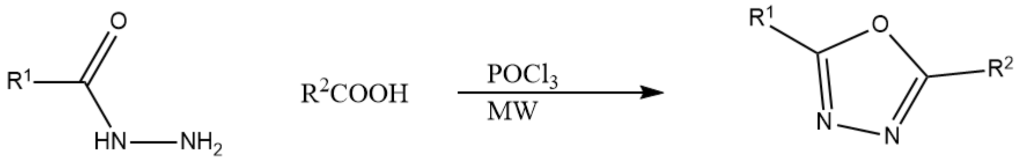
Scheme 1.20: The production of 2,5-disubstituted-1,3,4-oxadiazole

Moderate to good yields of the 1,3,4-oxadiazole derivatives with 2,5-substitutions were obtained when acyl hydrazides and aromatic aldehydes were stirred in dry dichloromethane under reflux conditions, utilizing CAN as the catalyst.[62]



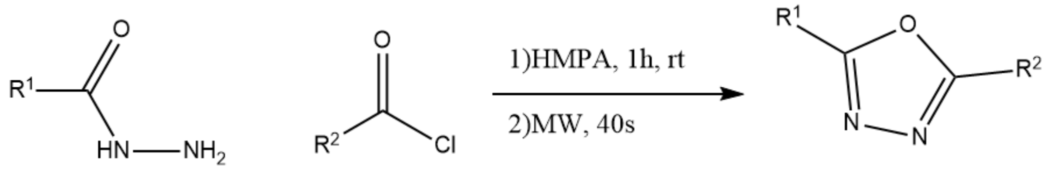
Scheme 1.21: The production of 2,5-disubstituted 1,3,4-oxadiazoles utilizing one-pot method

Various methods have been employed to synthesize 1,3,4-oxadiazoles, including their preparation using microwave irradiation. To obtain 1,3,4-oxadiazoles with substitutions at positions 2 and 5, hydrazides were subjected to reactions with a variety of carboxylic acids, employing phosphorous oxychloride as a facilitating reagent.[63]



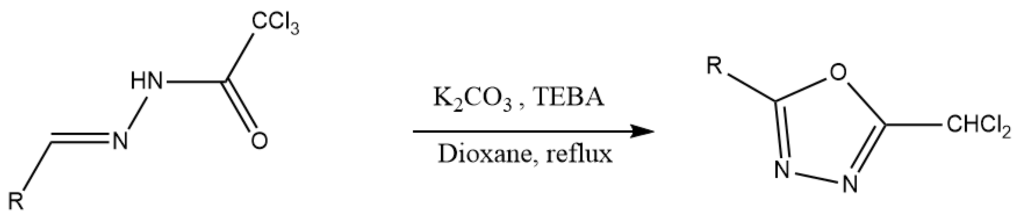
Scheme 1.22: The production of 2,5-disubstituted 1,3,4-oxadiazoles employing microwave irradiation

A rapid and efficient one-pot method has been described for synthesizing a wide range of 1,3,4-oxadiazoles with substitutions at positions 2 and 5. The described method involves the interaction between monoarylhydrazides and acyl chlorides in Hexamethylphosphoramide (HMPA) solvent, utilizing microwave heating. This approach offers several advantages, such as impressive product yields, rapid reaction kinetics, and a straightforward procedure. Notably, this technique obviates the requirement for additional acid catalysts or dehydrating agents. The elimination of these supplementary components streamlines the process and contributes to the overall efficiency of the methodology.[64]



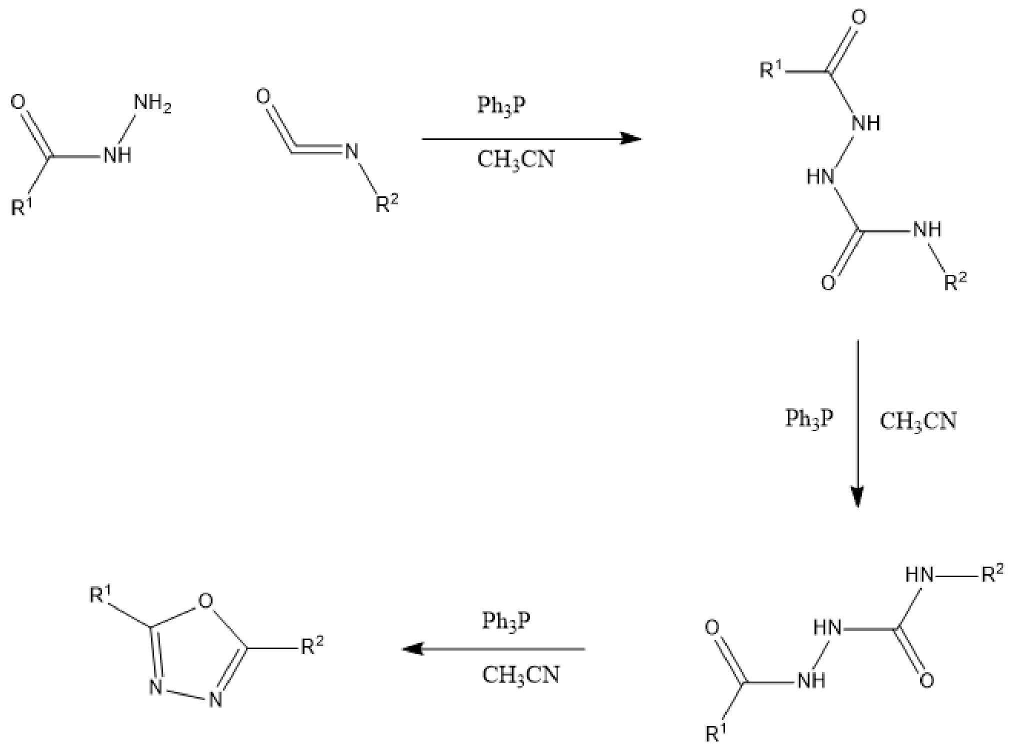
Scheme 1.23: The reaction with monoarylhydrazides and acid chlorides

1,3,4-Oxadiazole derivations were synthesized by Kaim et al. using a non-acidic approach. The method involved the treatment of various aldehyde hydrazones, carrying out the reaction using a phase transfer approach with potassium carbonate, leading to the production of 1,3,4-oxadiazole compounds.[65]



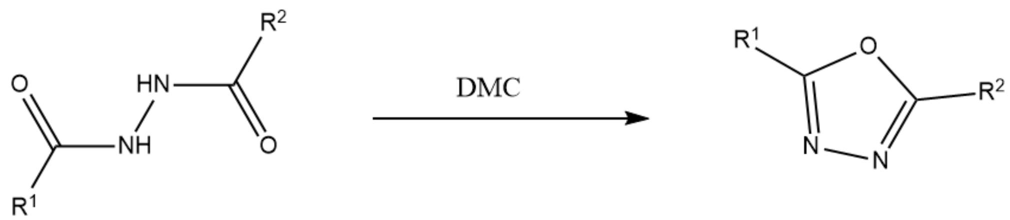
Scheme 1.24: Production of 1,3,4-oxadiazole via aldehyde hydrazone reaction

Kosmrlj et al. carried out a study which is about the reaction between certain diazenes and triphenylphosphine or tributylphosphine in solution under ambient conditions to synthesize 1,3,4-oxadiazoles. The synthesis process involved several steps. Firstly, the formation of semicarbazides with 1,4-disubstituted was reacted with isocyanates and acyl groups in an acetonitrile solvent. The resulting starting material was then put through a reaction with a solution of triethylamine, and either tributylphosphine (Bu_3P) or triphenylphosphine (Ph_3P). This reaction yielded diazenes, which were subsequently subjected to cyclization using phosphanes, resulting in the production of 1,3,4-oxadiazole compounds.[66]



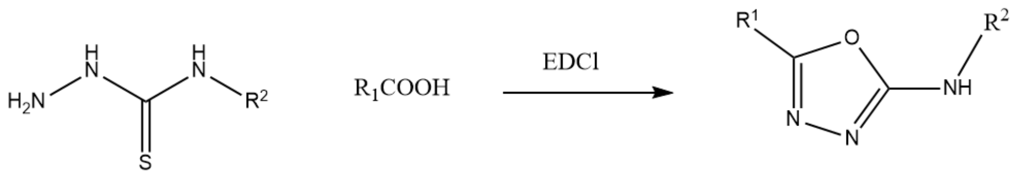
Scheme 1.25: Manufacture of 1,3,4-oxadiazole with the employment of Ph_3P

Isobe and Ishikawa introduced a strikingly efficient approach for the synthesis of 1,3,4-oxadiazoles in 1999. To create 1,3,4-oxadiazole derivatives, the researchers utilized (DMC) 2-chloro-1,3-dimethylimidazolinium chloride as a highly effective dehydrating chemical. By combining TEA and dichloromethane, they were able to achieve impressive yields of up to 100% in specific instances. Moreover, this technique proved successful in directly reacting acylhydrazine with carboxylic acids which give desired oxadiazole derivatives. [67]



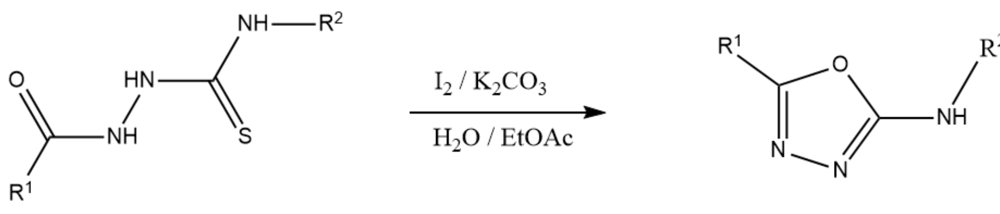
Scheme 1.26: DMC-assisted preparation of 1,3,4-oxadiazole

Chekler and colleagues have introduced a simple single-step method for synthesizing substituted 2-amino-1,3,4-oxadiazoles using dichloromethane (DCM) or dimethylformamide (DMF) as solvents. This method represents a significant advancement compared to previously reported synthesis methods. By combining carboxylic acids with thiosemicarbazides, the desired oxadiazoles were obtained with moderate to good yields. Notably, the resulting products generally precipitated from the reaction mixture. To explore the applicability of this reaction, the researchers conducted experiments using various aromatic, aliphatic, and heteroaromatic carboxylic acids along with different substituted thiosemicarbazides, aiming to investigate the scope and limitations of the reaction. [68]



Scheme 1.27: The process for producing 1,3,4-oxadiazoles

In 2012, Guin and colleagues introduced an inventive and efficient technique for crafting 2-amino-1,3,4-oxadiazoles utilizing starting compounds of thiosemicarbazide. This approach harnessed environmentally friendly iodine as the reagent and potassium carbonate salt, all within a two-phase medium encompassing ethyl acetate and water. One remarkable aspect of this approach is its remarkable adaptability to various functional groups, rendering it highly versatile for potential industrial implementations. Furthermore, the yields obtained through this approach were notably substantial, further elevating its attractiveness for real-world application.[69]



Scheme 1.28: Synthesis of 1,3,4-oxadiazole using iodine

1.4 1,3-Dipolar Cycloaddition

The 1,3-Dipolar cycloaddition process holds significant importance within the realm of organic chemistry. This reaction leads to the formation of a five-membered ring by merging a 1,3-dipole and a dipolarophile through the establishment of fresh sigma (σ) bonds.[70] These reactions have gained substantial utility in the domain of organic synthesis, finding practical applications across diverse fields like pharmaceuticals, materials chemistry, and the synthesis of natural compounds. The notion of 1,3-dipolar cycloaddition was initially introduced by Rolf Huisgen in 1960.[71] This reaction transpires between a 1,3-dipole, a dipolar compound with electron delocalization over three atoms, and an unsaturated system.

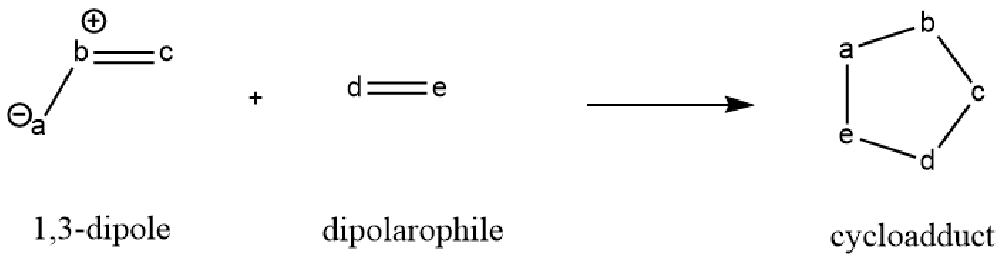


Figure 1.7: General representation of 1,3-dipolar cycloaddition

The mechanism of 1,3-dipolar cycloaddition involves a concerted, pericyclic shift in which two π-electrons from the dipolarophile and four electrons from the dipolar compound participate. This reaction exhibits stereo conservation, meaning it preserves the stereochemistry of the starting materials. It can be categorized as a [4π + 2π] cycloaddition, related to the Diels-Alder reaction.[72]

1.4.1 1,3-Dipole and Dipolarphile

An organic entity known as a ylide, commonly referred to as a 1,3-dipole, exhibits the distribution of both positive and negative charges across a trio of atoms. These dipoles typically incorporate atoms such as nitrogen, carbon, oxygen, or sulfur. They can be classified as either allyl-type or propargyl/allenyl-type inner salts. In both cases, the 1,3-dipoles involve the sharing of four electrons within the

π-system across three atoms, resulting in the formation of a five-membered ring when interacting with a dipolarophile. The dipolarophile itself may contain a double or triple bond. Examples of 1,3-dipoles include azides, nitrile oxides, nitrones, and diazo compounds. And alkenes, alkynes, carbonyls, imines, and various other compounds with multiple bonds are examples of dipolarophiles, which typically have 2π electrons in their moiety.[73]

Dipolarophiles refer to molecules containing double bonds that undergo cycloaddition reactions with 1,3-dipoles. They can be classified into three primary categories: conjugated dipolarophiles, electron-deficient dipolarophiles, and electron-rich dipolarophiles.

1.4.2 Frontier Molecular Orbital (FMO) Theory of 1,3-Dipolar Cycloaddition

The comprehension of 1,3-Dipolar cycloaddition can be enhanced by employing the principles of Frontier Molecular Orbital (FMO) theory. FMO theory, a conceptual framework in organic chemistry, centers around the interactions and energies of HOMO (the highest occupied molecular orbital) and LUMO (the lowest unoccupied molecular orbital) of the reacting species. FMO theory provides insights into the coordinated interactions associated with 1,3-dipolar cycloaddition. According to Sustmann's classification based on FMO theory, there are three categories of cycloaddition processes. The primary grouping encompasses the interaction between the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile, which is also recognized as LUMO-dipolarophile interactions. These distinct reactions, labeled as 1,3-DC reactions with normal electron order (NED), hold significant importance in categorizing a wide array of 1,3-DC reactions. The second categorization involves the dominant interaction between the LUMO of the dipole and the HOMO of the dipolarophile, termed electronic inverse ordering (IED) in 1,3-DC reactions. The third grouping is characterized by the equivalent energies of the HOMO and LUMO of the dipole-dipolarophile pairing. In such instances, interactions involving LUMO-dipolarophile-HOMO-dipole and LUMO-dipole HOMO-dipolarophile dynamically shape the reactivity and chemical nature of the process, enabling the coexistence of NED and IED mechanisms.[74]

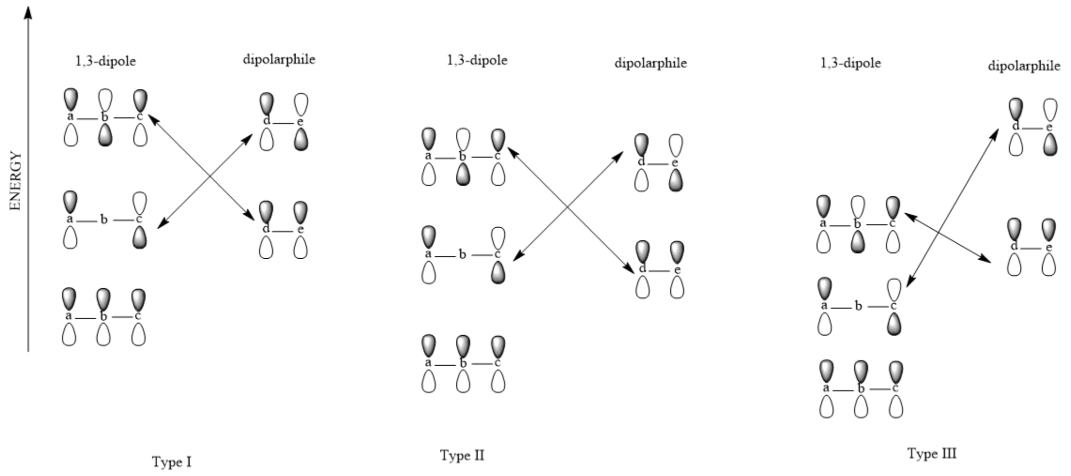


Figure 1.8: 1,3-dipolar cycloaddition through molecular orbital interactions

1.5 Hydrazonyl Chlorides

Hydrazonyl chlorides exhibit unique structural characteristics and belong to a significant compound class. These compounds are defined by the incorporation of a hydrazone functional group (-NHN=) linked to a chlorine atom. The chlorine atom within hydrazonyl chlorides imparts electrophilic reactivity, rendering these substances valuable intermediates in the realm of organic synthesis.[75]

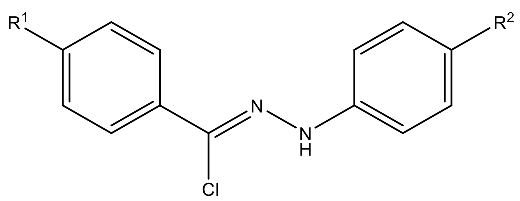
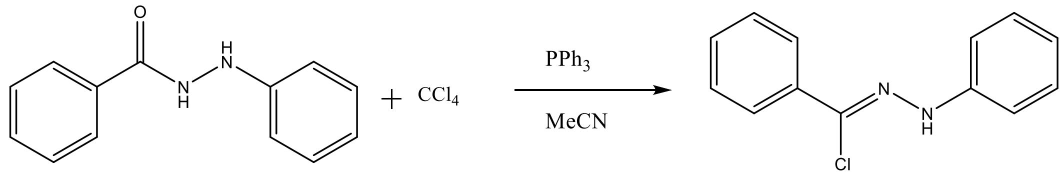


Figure 1.9: General representation of hydrazonyl chloride

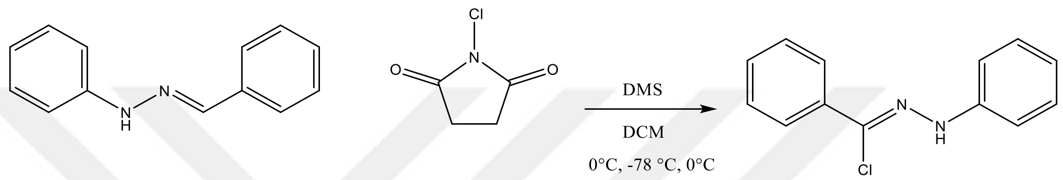
1.5.1 Preparation of Hydrazonyl Chlorides

Hydrazonyl chloride can be prepared by using benzoyl phenylhydrazine, carbon tetrachloride (CCl_4), and triphenylphosphine (PPh_3) in acetonitrile at room temperature. [76]



Scheme 1.29: Formation of hydrazonyl chloride using benzoyl phenylhydrazine

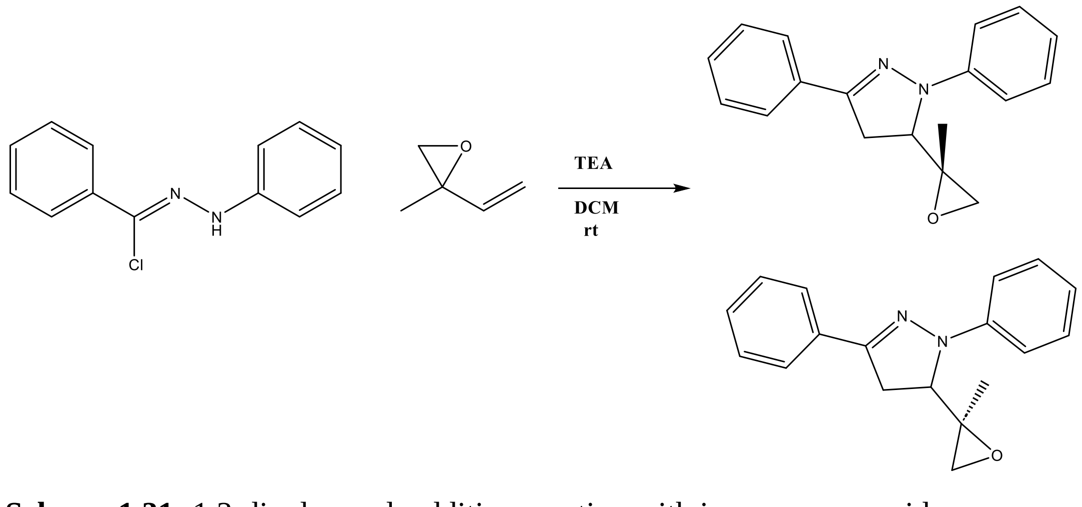
The reaction with diphenylhydrazone, N-chlorosuccinimide, and dimethyl sulfide (DMS) under -40°C resulted in the synthesis of hydrazonyl chlorides.[77]



Scheme 1.30: Reaction with diphenylhydrazone and N-chlorosuccinimide

1.5.2 Cycloaddition Reaction of Hydrazonyl Chlorides

Hydrazonyl chlorides can undergo cycloaddition reactions, such as the 1,3-dipolar cycloaddition with isoprene monoxide in dry dichloromethane to give regioselective 5-(2-methyloxiranyl)-4,5-dihydropyrazole products. This reaction takes place in the presence of Et_3N and under a nitrogen atmosphere.[78]



Scheme 1.31: 1,3-dipolar cycloaddition reaction with isoprene monoxide

2. AIM AND SCOPE OF THE STUDY

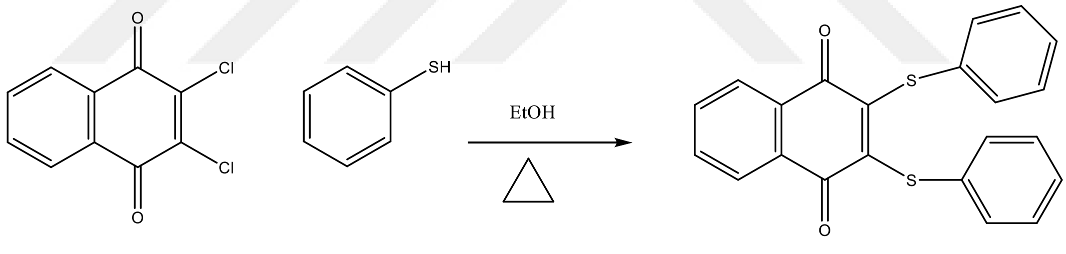
This thesis involves the design and synthesis of a new naphthoquinone derivative containing a functional group that can undergo 1,3-dipolar cycloaddition reactions. And also the research aims to generate a library of novel compounds and evaluate their potential as prospective candidates for future biological research.

First, 2,3-dichloronaphthoquinone was reacted with thiophenol in EtOH to obtain 2,3-diphenylthio-1,4-naphthoquinone and then it was reacted with various aryl N-hydrazonyl chlorides in the presence of TEA to obtain desired 5'-aryl-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-ones. The final products were characterized using FTIR, HRMS, ^{13}C NMR, and ^{1}H NMR spectroscopy, and their melting points and RF values were also determined.

3. MATERIALS AND APPARATUS

Commercially available reagents and solvents from Merck and Sigma-Aldrich were procured and utilized for the experiments. Fourier Transform Infrared (FT-IR) spectra were carried out using a Perkin Elmer Spectrum Two FTIR-ATR spectrophotometer. Varian INOVA NMR Spectrometer was used for C (125 MHz) and H NMR (500 MHz) in DMSO-d6. Chemical shifts were expressed in parts per million (ppm), while coupling constants (J) were reported in Hertz (Hz). Heidolph MR Hei-Standart was used as a magnetic stirrer with heating. The Rotary Evaporator used was of the Heidolph model. MELTEMP apparatus was used as the Melting Point Determination Device. Agilent ZQ instrument (HRMS) was utilized as the Mass Spectrometer. For reaction monitoring, thin layer chromatography (Merck 5735) was conducted containing a fluorescent indicator.

3.1 The preparation of 2-3-bis(phenylthio)naphthalene-1,4dione

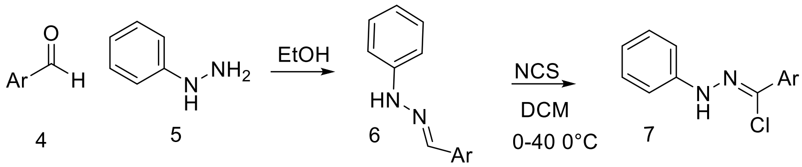


1 **2** **3**

Thiophenol **2** (20 mmol, 2203 mg) was added dropwise to the stirring solution of 2,3-dichloro-1,4-naphtoquinone **1** (10 mmol, 2270 mg) in 50 mL absolute EtOH at reflux temperature for 1 hour. After filtration, the product was recrystallized with EtOAc/Hex.[79]

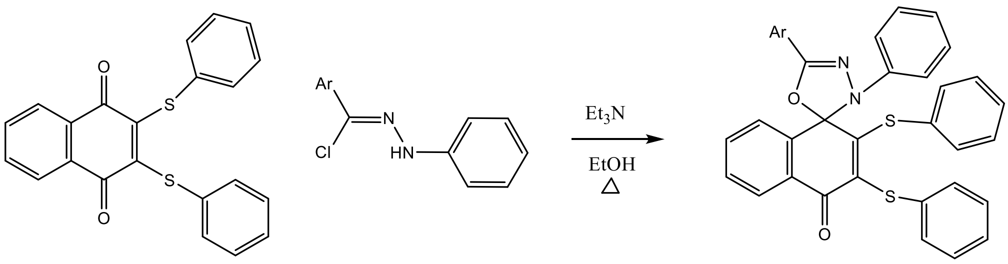
Orange needles (3,55 g 95%). Rf : (EtOAc:Hex-1:5) = 0.4, mp= 151-152^{o}C(literature=150^{o}C), νmax (KBr, cm-^{1}) 1665.95cm^{-1} (C=O). ^{1}H NMR (500 MHz, DMSO): δ 7.90 (m, 2H), 7.82 (m, 2H), 7.41 (m, 4H), 7.30 (m, 6H). ^{13}C NMR (125 MHz, DMSO), 178.2(C=O), 147.8, 134.1, 133.9, 132.6, 130.0, 129.2, 127.3, 126.6. HRMS required for $C_{22}H_{14}O_2S_2$ $[M+H]^+$ 374,0435 and 374.0437 found.

3.2 Hydrazonyl Chloride General Preparation



The aldehyde **4** and phenylhydrazine hydrochloride **5** were combined in a suitable flask. The reaction mixture was stirred at room temperature. The progress of the reaction was periodically monitored using TLC. The reaction mixture was concentrated. After that, 1.5 equivalent of NCS was dissolved in DCM. Then the mixture was stirred 5 minutes at 0 °C. 2 equivalent of Me_2S in DCM (1 mmol/mL) was added dropwise to the reaction mixture. The temperature of the reaction was lowered to -40°C. 1 equivalent of phenyl derivative **6** in DCM (1 mmol/3 mL) was added dropwise to the above reaction system. After an hour, the reaction temperature was increased to 0°C. The solvent was evaporated and extracted with dichloromethane 3 times after the reaction was completed, confirmed by checking TLC analysis. The desired compound was purified column chromatography or recrystallized with DCM/petroleum ether.[80]

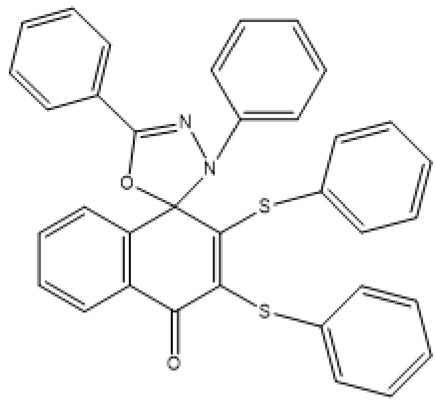
3.3 General Procedure for the synthesis of 5'-aryl-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



3 **7** **8**

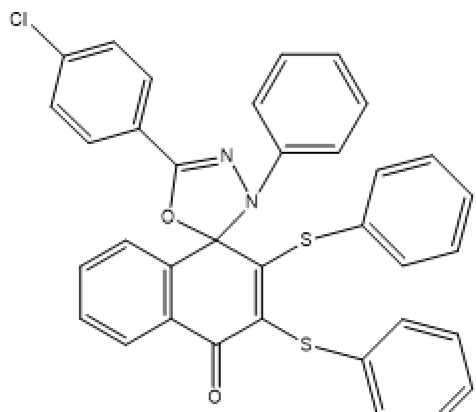
A suspension of 2,3-bis(phenylthio)naphthalene-1,4-dione (0.5 mmol, 187 mg) **3** and hydrazonyl chloride (0.6 mmol, 1.2 equiv) **7** and triethylamine (TEA) (1.5 equiv.) in ethanol (10 mL) was heated under reflux temperature. After 30 minutes the product was waited to cool to room temperature then, filtrated and washed with ethanol.

3.3.1 3',5'-Diphenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



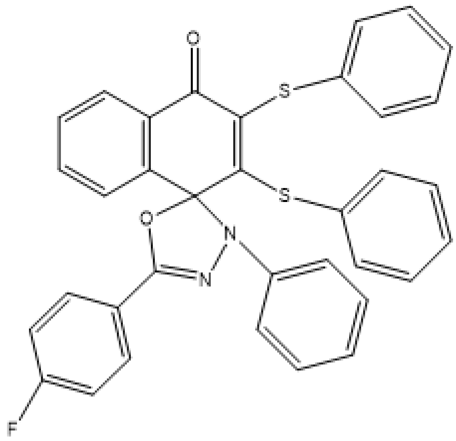
Brown solid, (235 mg, 83 %). Rf : (EtOAc:Hex-1:5) = 0.52, mp= 152-153^{o}C, νmax (KBr, cm-^{1}) 1664 cm-1 (C=O), 1594 cm-1 (C=N). ^{1}H NMR (500 MHz, DMSO) δ 7.95 (dd, J = 7.8, 1.4 Hz, 1H), 7.81 (d, J = 1.5 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.79 – 7.74 (m, 1H), 7.71 – 7.64 (m, 2H), 7.53 – 7.44 (m, 3H), 7.32 – 7.19 (m, 10H), 7.14 (d, J = 1.6 Hz, 1H), 7.13 – 7.12 (m, 1H), 6.96 – 6.87 (m, 3H). ^{13}C NMR (125 MHz, DMSO) δ 177.0 (C=O), 153.5, 151.5, 143.3, 140.8, 138.9, 135.1, 133.9, 133.9, 131.3, 131.0, 130.0, 129.9, 129.6, 129.4, 129.2, 129.0, 127.8, 127.4, 127.4, 127.2, 125.9, 124.2, 120.9, 113.8, 95.3. HRMS required for $C_{35}H_{24}N_2O_2S_2$ [M-$C_{12}H_{10}S_2$]$^{+}$ 350.1055 and found 350.1039.

3.3.2 5'-(4-Chlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



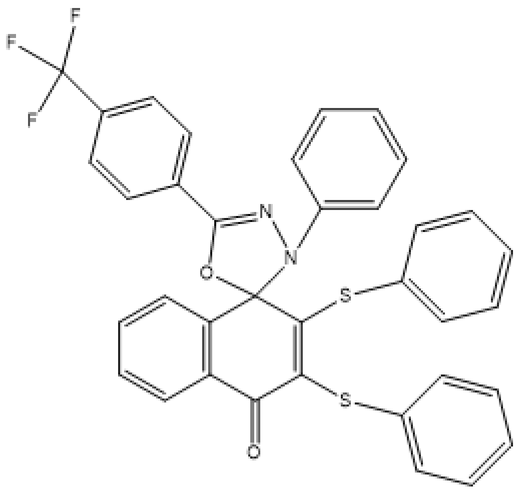
Orange solid, (256 mg , 85 %). Rf : (EtOAc:Hex-1:5) = 0.56, mp= 166-167^{o}C, νmax (KBr, cm-^{1}) 1652.29 cm^{-1} (C=O), 1593.46 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO) δ 7.95 (d, J = 7.8 Hz, 1H), 7.78 (dd, J = 11.3, 7.8 Hz, 3H), 7.68 (dd, J = 13.0, 7.3 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.32 – 7.20 (m, 10H), 7.14 (d, J = 7.7 Hz, 2H), 6.93 – 6.89 (m,3H). ^{13}C NMR (125 MHz, DMSO) δ 176.9 (C=O), 153.2, 150.7, 143.3, 140.6, 138.7, 135.6, 135.1, 133.8, 133.7, 131.3, 130.0, 129.9, 129.6, 129.6, 129.4, 129.2, 129.2, 127.8, 127.6, 127.5, 127.4, 127.2, 123.0, 121.1, 113.8, 95.6. HRMS required for $C_{35}H_{23}ClN_2O_2S_2$ [M-C_6H_5S]$^+$ 492.0699 and found 492.0714.

3.3.3 5'-(4-Fluorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



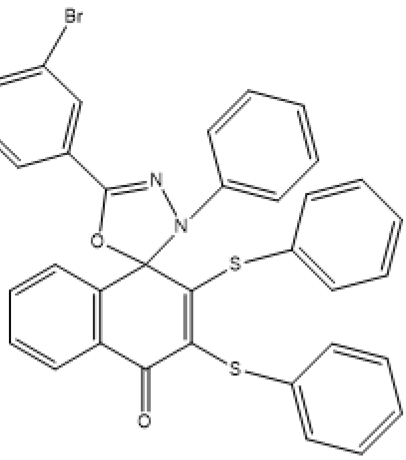
Brown solid, (232 mg, 79 %). Rf : (EtOAc:Hex-1:5) = 0.54, mp= 157-158^{o}C, νmax (KBr, cm-^{1}) 1651 cm^{-1} (C=O), 1591.51 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO): δ 7.95 (d, J = 7.8 Hz, 1H), 7.86-7.83 (m, J = 8.5Hz, 2H), 7.77 (t, J = 7.6 Hz, 1H), 7.70-7.65 (m, J = 7.4 Hz, 2H), 7.36 – 7.19 (m, 13H), 7.14 (d, 1H), 6.93-6.88 (m, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO) δ 176.9 (C=O), 164.5, 162.5, 153.4, 150.8, 143.3, 140.8, 138.8, 135.1, 133.9, 131.3, 129.9, 129.6, 129.4, 129.2, 128.5(d, J = 9.0 Hz) , 128.4, 127.8, 127.5, 127.4 (d, J = 12.7 Hz), 127.2, 120.9(d, J = 14.9 Hz), , 120.8, 116.3, 116.2, 113.8, 95.4. HRMS required for $C_{35}H_{23}FN_2O_2S_2$ [M-H]$^+$ 586,1185 and found 586.1178.

3.3.4 3'-Phenyl-2,3-bis(phenylthio)-5'-(4-(trifluoromethyl)phenyl)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



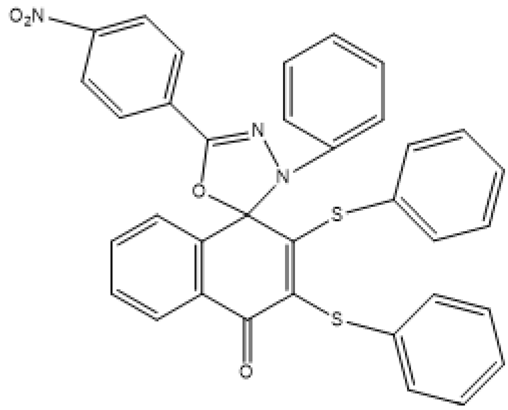
Red solid, (252 mg, 79%). Rf : (EtOAc:Hex-1:5) = 0.57, mp= 145-146°C, νmax (KBr, cm-¹) 1669.6 cm^{-1} (C=O), 1597.46 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO): δ 7.97 (t, J = 8.4 Hz, 3H), 7.83 (d, J = 8.3 Hz, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.31 – 7.19 (m, 10H), 7.14 (d, J = 7.4 Hz, 2H), 6.96 – 6.91 (m, 3H). ^{13}C NMR (125 MHz, DMSO) δ 176.9 (C=O), 152.9, 150.3, 143.5, 140.4, 138.6, 135.2, 133.8, 133.6, 131.4, 130.6, 130.3, 130.1, 129.9, 129.9 (d, J = 5.7 Hz), 129.7, 129.6, 129.5, 129.2, 128.0, 127.8, 127.5 (d, J = 12.8 Hz), 127.4, 127.3, 127.1, 126.5, 126.0(d, J = 4.2 Hz), 126.0, 124.9, 122.7, 121.3, 114.0, 95.9. HRMS required for $C_{36}H_{23}F_3N_2O_2S_2$ $[M-H]^+$ 636,1153 and found 636.1122.

3.3.5 5'-(3-Bromophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



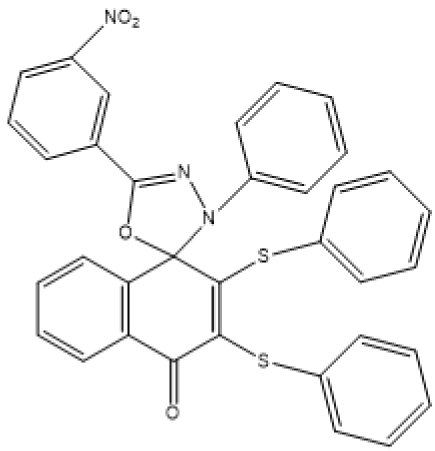
Brown solid, (278 mg , 86%). Rf : (EtOAc:Hex-1:5) = 0.58 , mp= 170-171°C, νmax (KBr, cm-¹) 1664.39 cm^{-1} (C=O), 1591.90 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO): δ 7.96 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 7.7 Hz, 2H), 7.71 – 7.66 (m, 3H), 7.43 (t, J = 8.0 Hz, 1H), 7.31 – 7.22 (m, 10H), 7.14 (d, J = 7.7 Hz, 2H), 6.94 – 6.88 (m, 3H). ^{13}C NMR (125 MHz, DMSO) δ 176.9 (C=O), 152.7, 150.1, 143.8, 140.6, 138.7, 135.1, 133.8, 133.7, 133.6, 131.3, 131.2, 130.0, 129.9, 129.5, 129.5, 129.4, 129.2, 128.1, 127.8, 127.4, 127.4, 127.2, 126.3, 124.8, 122.1, 121.2, 114.0, 95.8. HRMS required for $C_{35}H_{23}BrN_2O_2S_2$ $[M-C_{12}H_{10}S_2]^+$ 428.016 and found 428.0158.

3.3.6 5'-(4-Nitrophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



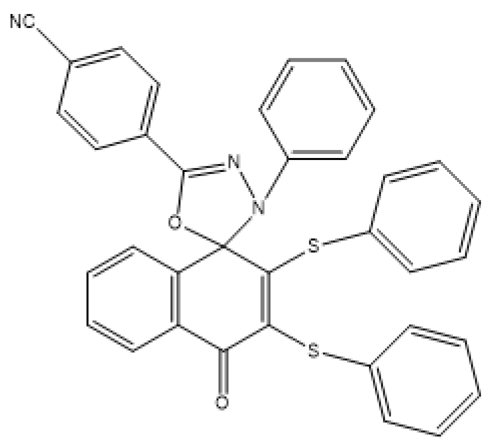
Red solid, (227 mg, 74%). Rf : (EtOAc:Hex-1:5) = 0.32, mp= 194-195ºC , vmax (KBr, cm-¹) 1666.85 cm^{-1} (C=O), 1593.33 cm-1 (C=N). ^{1}H NMR (500 MHz, DMSO): δ 8.30 – 8.27 (m, 2H), 8.02 – 7.96 (m, 3H), 7.80 – 7.77 (m, 1H), 7.73 – 7.67 (m, 2H), 7.32 – 7.19 (m, 10H), 7.16 – 7.13 (m, 2H), 6.97 – 6.94 (m, 3H). 13C NMR (125 MHz, DMSO) δ 176.8 (C=O), 152.6, 149.9, 149.7, 148.2, 143.5, 140.1, 138.4, 135.2, 135.1, 133.7, 133.3, 131.4, 129.9, 129.9, 129.7, 129.6, 129.5, 129.3, 129.2, 127.5, 126.8, 124.3, 121.6, 114.0, 96.1. HRMS required for $C_{35}H_{23}N_3O_4S_2$ $[M-C_6H_5S]^+$ 504.1018 and found 504.1013.

3.3.7 5'-(3-Nitrophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



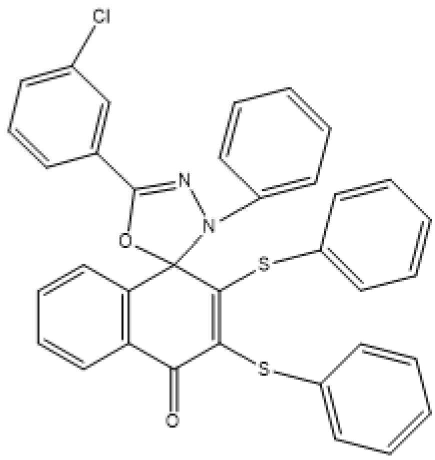
Brown solid, (215 mg, 70 %). Rf : (EtOAc:Hex-1:5) = 0.28, mp= 179-180ºC, νmax (KBr, cm-¹) 1664.62 cm^{-1} (C=O), 1532.53 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO): δ 8.37 – 8.37 (m, 1H), 8.31 (ddd, J = 8.3, 2.4, 1.0 Hz, 1H), 8.17 (dt, J = 7.8, 1.3 Hz, 1H), 7.98 (dd, J = 7.7, 1.4 Hz, 1H), 7.80 – 7.72 (m, 3H), 7.68 (ddd, J = 8.5, 7.1, 1.4 Hz, 1H), 7.29 (dddd, J = 8.3, 6.2, 4.0, 1.4 Hz, 6H), 7.25 – 7.21 (m, 3H), 7.18 – 7.15 (m, 3H), 6.97 – 6.92 (m, 1H). ^{13}C NMR (125 MHz, DMSO) δ 176.8(C=O), 152.4, 149.8, 148.0, 143.9, 140.4, 138.6, 135.1, 133.8, 133.4, 131.6, 131.4, 130.8, 129.9, 129.8, 129.6, 129.5, 129.2, 129.2, 127.7, 127.4, 125.6, 125.2, 121.4, 120.0, 114.1, 96.2. HRMS required for $C_{35}H_{23}N_3O_4S_2$ $[M-C_{12}H_7S]^+$ 430.0862 and found 430.0873.

3.3.8 4-(4-Oxo-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-5'-yl)benzonitrile



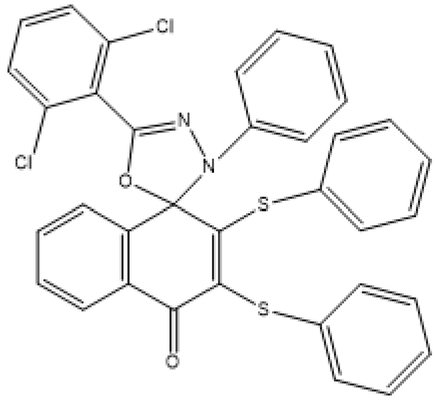
Orange solid, (211 mg, 88 %). Rf : (EtOAc:Hex-1:5) = 0.2, mp= 189-190ºC, νmax (KBr, cm-¹) 1651.70 cm^{-1} (C=O), 1590.68 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO): δ7.96 (d, J = 8.1 Hz, 1H), 7.79 – 7.76 (m, 1H), 7.71 – 7.66 (m, 2H), 7.30 – 7.21 (m, 12H), 7.14 (dd, J = 7.1, 1.7 Hz, 3H), 6.96 – 6.92 (m, 3H). ^{13}C NMR (125 MHz, DMSO): δ 176.8 (C=O), 152.7, 150.1, 143.5, 140.2, 138.5, 135.1, 133.7, 133.4, 132.9, 131.4, 129.9, 129.7, 129.7, 129.5, 129.4, 129.2, 129.2, 128.2, 127.5, 127.5, 127.2, 126.3, 121.5, 118.3 (CN), 114.0, 112.7, 96.0. HRMS required for $C_{36}H_{23}N_3O_2S_2$ $[M-C_{12}H_{10}S_2]^+$ 375.1008 and found 375.1009.

3.3.9 5'-(3-Chlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



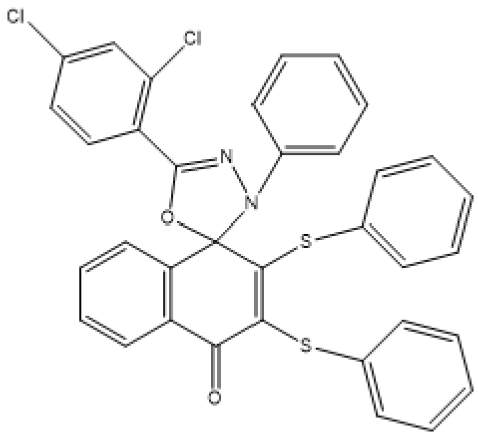
Brown solid, (256 mg, 85%). Rf : (EtOAc:Hex-1:5) = 0.57, mp= 165-166°C, νmax (KBr, cm^{-1}) 1664.5 cm^{-1} (C=O), 1592.63 cm^{-1} (C=N). ^1H NMR (500 MHz, DMSO) δ 7.96(dd, J = 7.8, 1.4 Hz, 1H), 7.79 – 7.66 (m, 6H), 7.56 (dt, J = 8.1, 1.5 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.31 – 7.20 (m, 10H), 7.14 (d, J = 3.5 Hz, 2H), 6.94 – 6.90 (m, 2H). ^{13}C NMR (125 MHz, DMSO): δ 176.8 (C=O), 152.0, 147.0, 143.7, 140.5, 137.7, 135.6, 134.7, 134.5, 133.8, 131.5, 131.4, 130.1, 129.5, 129.5, 129.3, 129.2, 129.0, 128.3, 127.4, 127.3, 127.1, 123.1, 120.9, 113.5, 96.0. HRMS required for $C_{35}H_{23}ClN_2O_2S_2$ $[M-C_{12}H_{10}S_2]^+$ 384.0666 and found 384.0657.

3.3.10 5'-(2,6-Dichlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



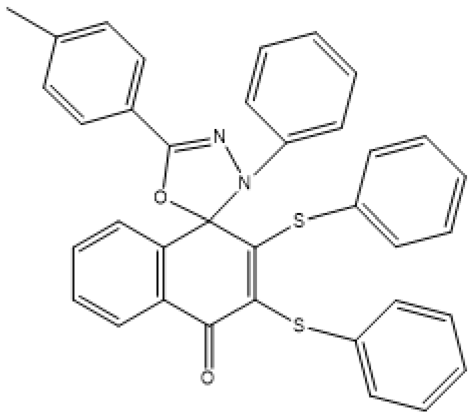
Orange solid, (248 mg, 78 %). Rf : (EtOAc:Hex-1:5) = 0.36, mp= 173-174ºC, vmax (KBr, cm-¹) 1661.79 cm^{-1} (C=O), 1598.76 cm^{-1} (C=N), ^{1}H NMR (500 MHz, DMSO) δ 7.92 (d, J = 7.9 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.69 – 7.66 (m, 1H), 7.64 – 7.58 (m, 3H), 7.34 – 7.21 (m, 11H), 7.11 (d, J = 7.3 Hz, 2H), 6.92 – 6.89 (m, 2H). 13C NMR (125 MHz, DMSO): δ 176.8(C=O), 152.0, 147.0, 143.7, 140.5, 137.7, 135.6, 134.7, 134.5, 133.8, 131.5, 131.4, 130.1, 129.5, 129.5, 129.3, 129.2, 129.0, 128.3, 127.4, 127.3, 127.1, 123.1, 120.9, 113.5, 96.0. HRMS required for $C_{35}H_{22}Cl_2N_2O_2S_2$ $[M+H]^+$ 636.0500 and found 636.0515.

3.3.11 5'-(2,4-Dichlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



Brown solid, (271 mg, 85 %). Rf : (EtOAc:Hex-1:5) = 0.36, mp= 155-156ºC, vmax (KBr, cm-¹) 1658.56 cm^{-1} (C=O), 1588 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO) δ 7.95 (d, J = 7.8 Hz, 1H), 7.82 – 7.66 (m, 5H), 7.49 (dt, J = 8.6, 1.8 Hz, 1H), 7.31 – 7.20 (m, 10H), 7.14 (dt, J = 6.9, 1.5 Hz, 2H), 6.94 – 6.91 (m, 3H). 13C NMR (125 MHz, DMSO): δ 176.8 (C=O), 152.0, 147.0, 143.7, 140.5, 137.7, 135.6, 134.7, 134.5, 133.8, 131.5, 131.4, 130.1, 129.5, 129.5, 129.3, 129.0, 128.9, 128.3, 127.4, 127.3, 127.1, 123.1, 120.9, 113.5, 96.0. HRMS required for $C_{35}H_{22}Cl_2N_2O_2S_2$ $[M-C_{12}H_{10}S_2]^+$ 418.0276 and found 418.0275.

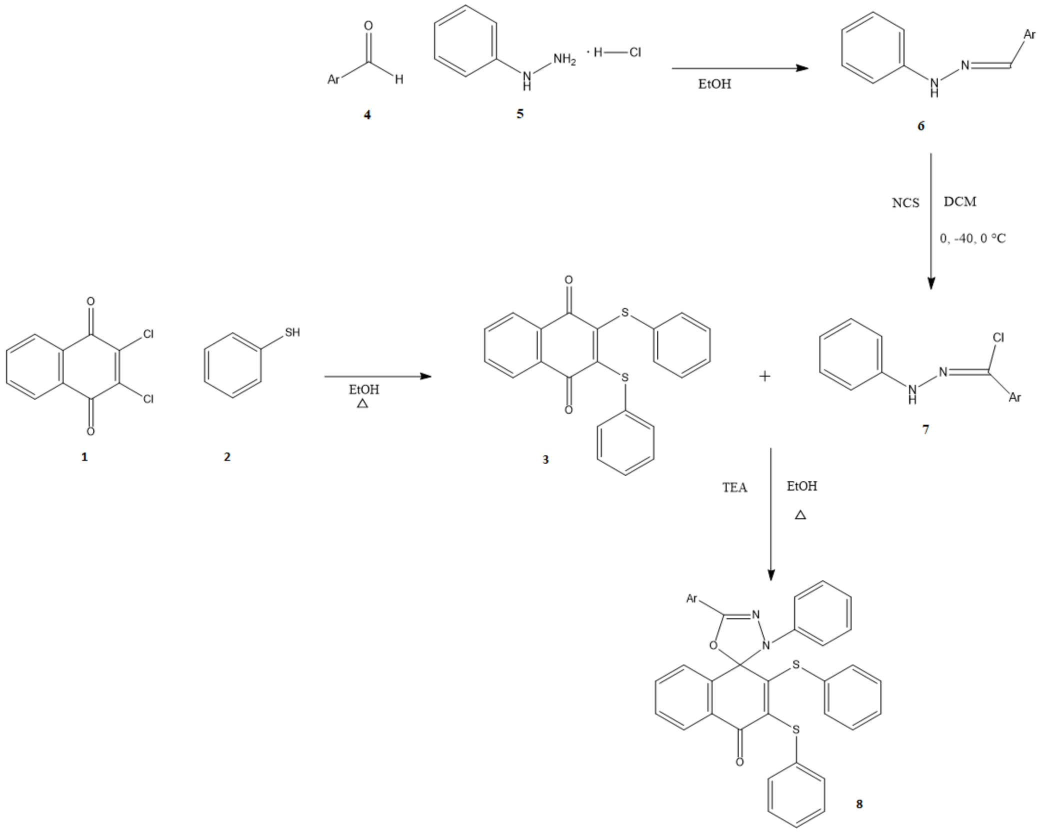
3.3.12 3'-Phenyl-2,3-bis(phenylthio)-5'-(p-tolyl)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one



Brown solid, (233 mg , 80 %). Rf : (EtOAc:Hex-1:5) = 0.57, mp= 163-164^{o}C, vmax (KBr, cm-^{1}) 1655.78 cm^{-1} (C=O), 1590.86 cm^{-1} (C=N). ^{1}H NMR (500 MHz, DMSO) δ 7.94 (d, J = 26.0 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.70 – 7.64 (m, 4H), .29 – 7.26 (m, 10H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, DMSO): δ 176.9(C=O), 153.7, 151.6, 143.2, 141.0, 140.8, 138.9, 134.0, 133.9, 131.3, 130.0, 129.9, 129.8, 129.8, 129.5, 129.3, 129.1, 129.1, 127.3, 126.0, 125.9, 121.4, 120.7, 120.7, 113.7, 95.1, 21.1. HRMS required for $C_{36}H_{26}N_2O_2S_2$ [M-$C_{12}H_{10}S_2$]$^{+}$ 364.1212 and found 364.1202.

4. RESULTS AND DISCUSSION

Firstly, 2,3-dichloronaphthoquinone **1** was reacted with thiophenol **2** in ethanol at reflux temperature. The formation of the product was confirmed by TLC and followed the recrystallization with EtOAc/Hex to give 2,3-disubstituted-1,4-naphthoquinone **3**. Then the product **3** was reacted with various hydrazonyl chlorides **7** in the presence of triethylamine in EtOH at reflux temperature with moderate to good yields. The structures of derivatives **8a-l** were analyzed through spectroscopic methods including IR, ^{1}H NMR, ^{13}C NMR, HRMS, and also physical properties including melting points, and Rf values as well. The reaction conditions were optimized in terms of temperature, base, solvent, and equivalence of the reactants. When the reaction was performed in acetonitrile the product was observed with lower yields compared to ethanol as a solvent. Additionally, the best yields were achieved when the equivalence of hydrazonyl chlorides was 1.2 equivalent and NaOH, pyridine, and NaOEt gave lower yields compared to Et_3N. The solubility of the starting compound **3** was low in EtOH at room temperature. So, the solution was heated up to 60 °C then the hydrazonyl chloride and the base were added subsequently. The progress of the reaction was monitored by TLC and the observable precipitate formed when the reaction mixture was left to room temperature. The formed precipitate was filtered and washed with ethanol to obtain pure product.

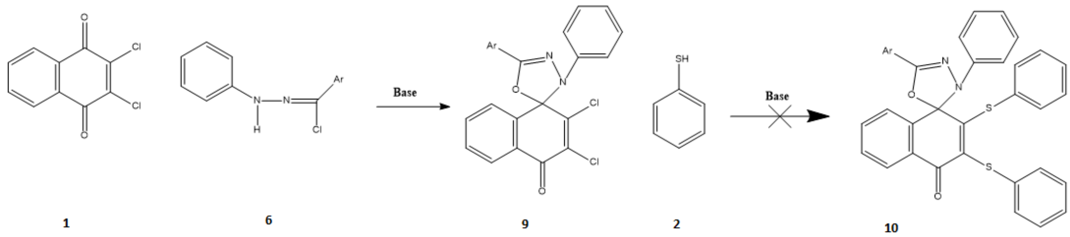


Scheme 4.1: General reaction scheme for 8a-l

Compound	Ar	Yield %	Melting Point °C
8a	Ph	83	152-153
8b	4-ClC_6H_4	85	166-167
8c	4-FC_6H_4	79	157-158
8d	4-$CF_3C_6H_4$	79	145-146
8e	3-BrC_6H_4	86	170-171
8f	4-$NO_2C_6H_3$	74	194-195
8g	3-$NO_2C_6H_3$	70	179-180
8h	4-CNC_6H_4	88	189-190
8i	3-ClC_6H_4	85	165-166
8j	2,6-DiClC_6H_3	78	173-174
8k	2,4-DiClC_6H_3	85	155-156
8l	4-$CH_3C_6H_4$	80	163-164

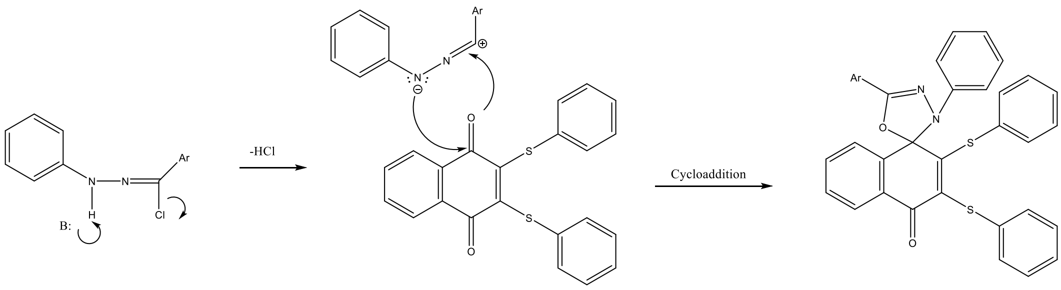
Table 4.1: Reaction yields and melting points of 8a-l

Moreover, 2,3-dichloronaphthoquinone **1** was reacted with the aryl hydrazonyl chloride **6** as described in the literature.[81] Then that product **9** was tried to react with thiophenol **2** in the presence of base, but no new product was observed. Scheme 4.2 is shown below. The reason might be attributed to the lower electrophilic character of double on 2,3-dichloro substituted part due to the formed spiro cycle next to it.



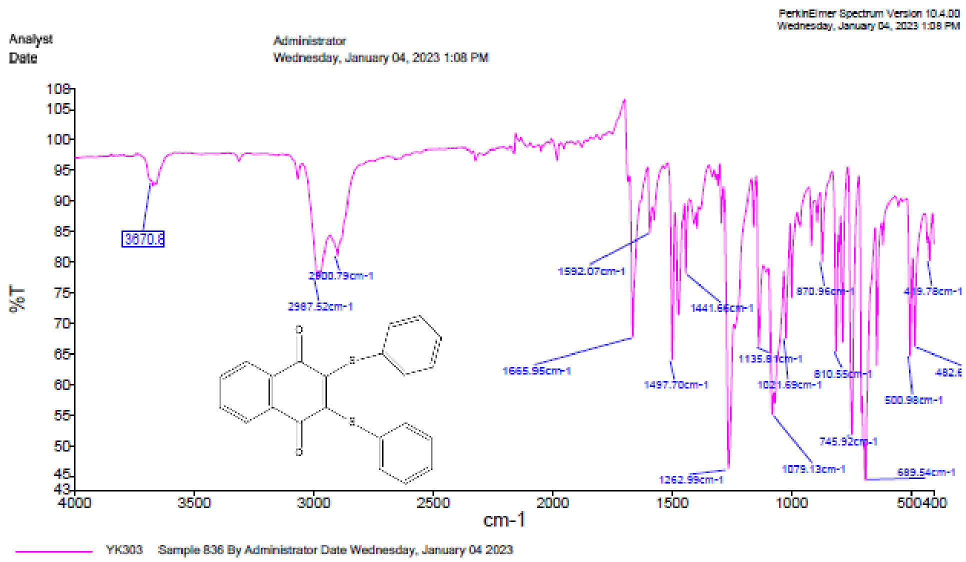
Scheme 4.2: Reaction with 5'-aryl-2,3-dichloro-3'-phenyl-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one and thiophenol

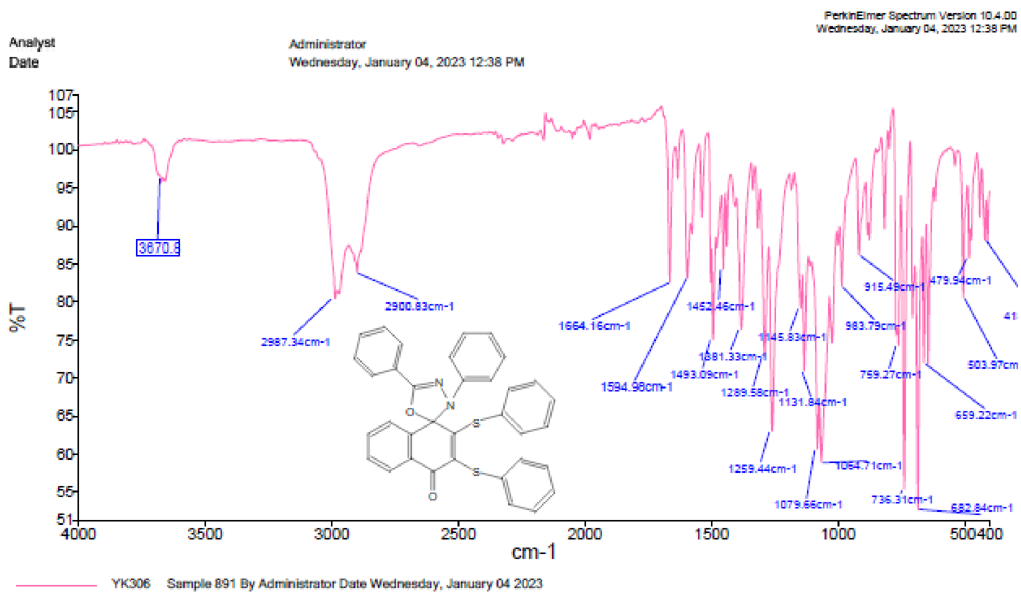
Scheme 4.3 presents proposed a mechanism for the synthesis of the new compounds **8a-l**. Initially, a base is utilized to deprotonate the hydrazonyl chloride, leading to the formation of a nitrile imine. Subsequently, a cycloaddition reaction takes place between the nitrilimine and one of the carbonyl groups on the napthoquinone. Despite attempts to employ two or three equivalents of hydrazonyl chlorides, a double-sided cycloaddition product could not be obtained, possibly due to the electron demand on the napthoquinone. Following the initial cycloaddition, the electron demand might be insufficient for a second cyclization with the nitrilimine.



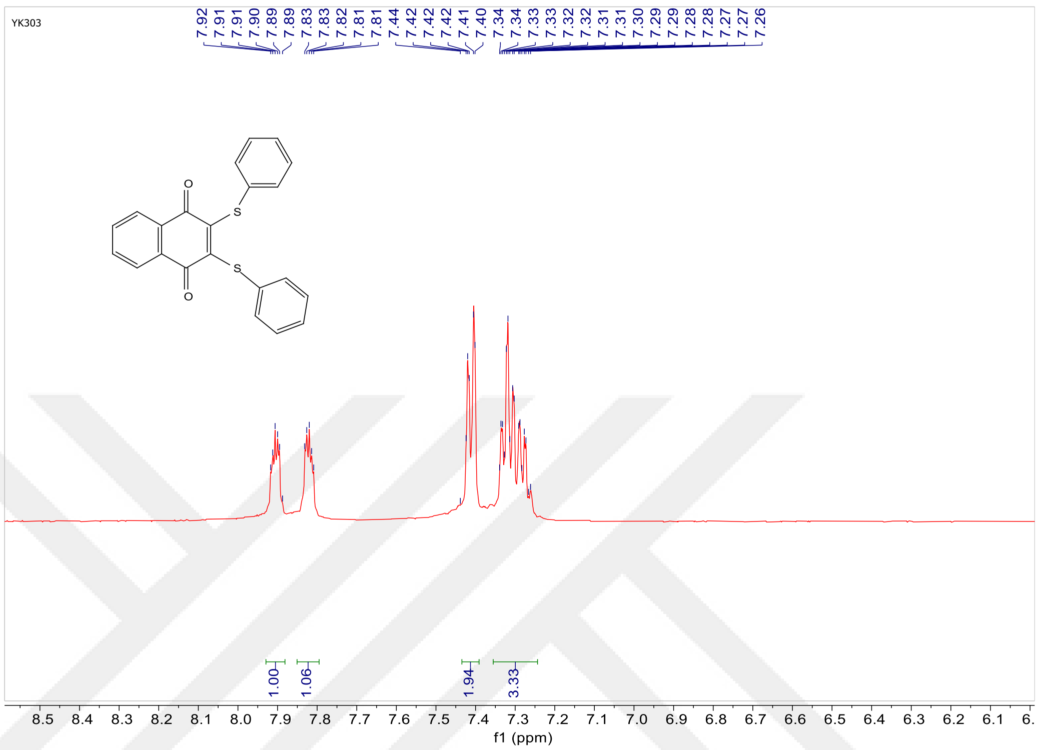
Scheme 4.3: Proposed reaction mechanism

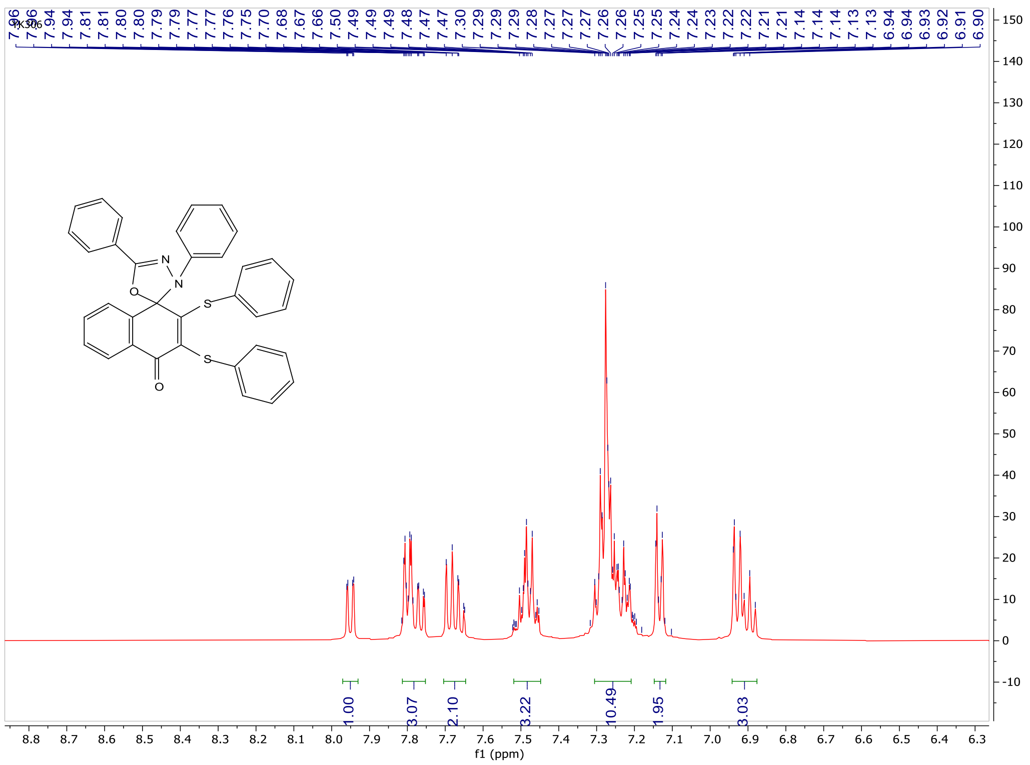
Significant stretching frequencies for the C=O group of quinone were observed in the IR spectra at approximately 1590 cm^{-1} and 1660 cm^{-1} for 2,3-bis(phenylthio)naphthalene-1,4-dione **3** and derivatives of **8a-l**.



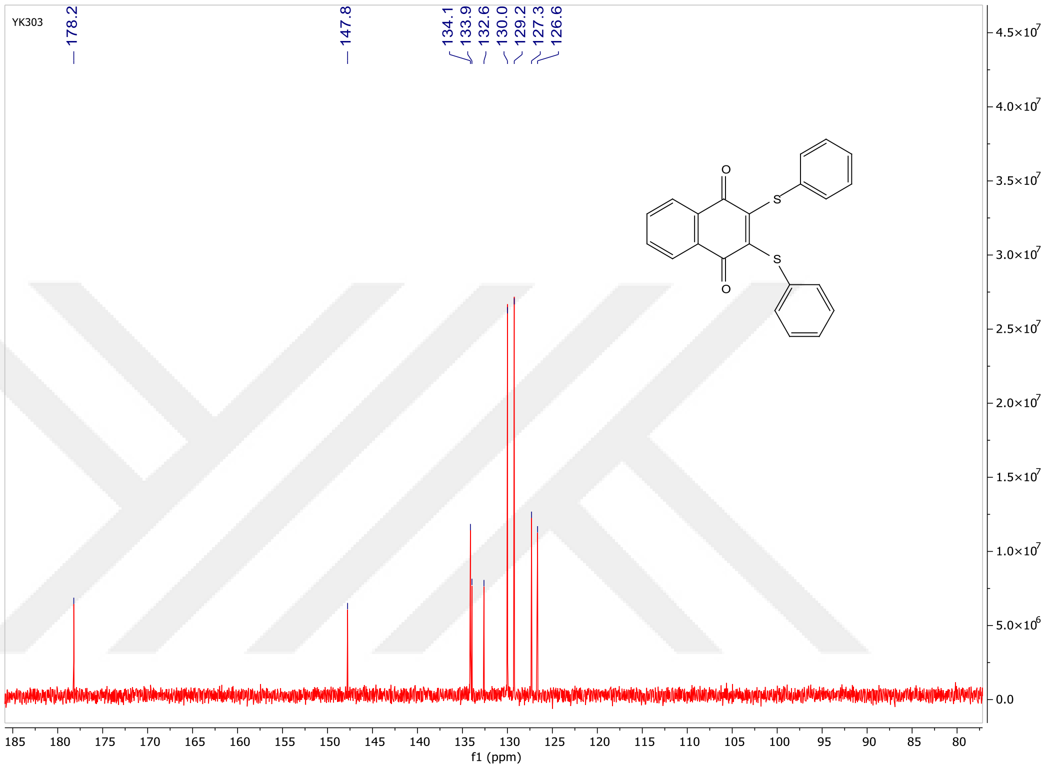


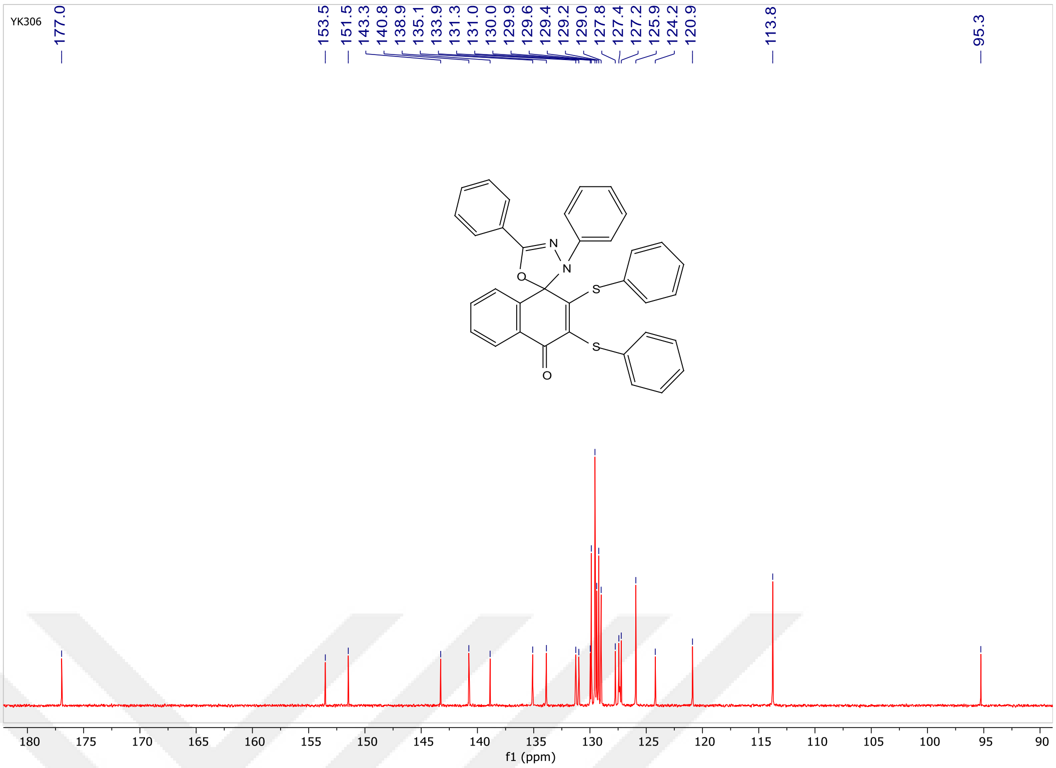
Signals corresponding to N-phenyl protons were identified in compounds **8a-l** within the chemical shift around 6.90 ppm and for S-phenyl protons were identified around 7.29 ppm for **3 and 8a-l**.



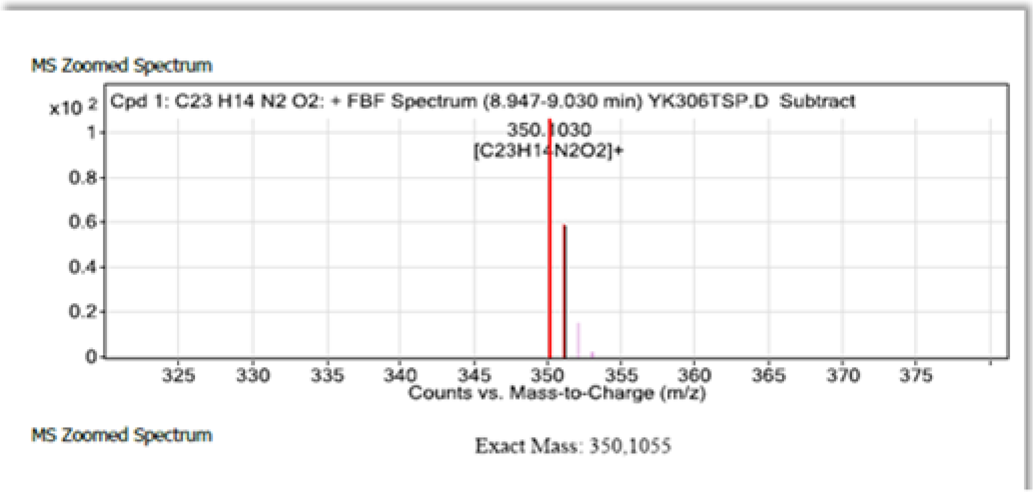


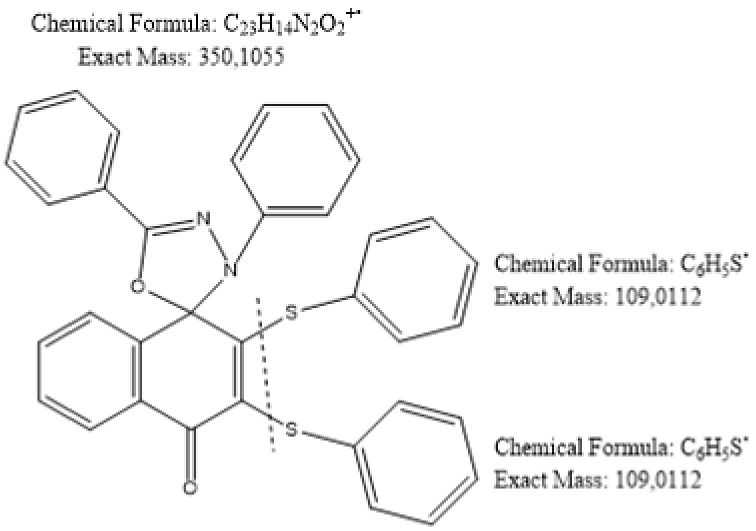
In addition, ^{13}C NMR analysis revealed the presence of carbonyl signals around 176.8-178.2 ppm for **3** and **8a-l** respectively, and quaternary carbon signals around 95.1-96.2 ppm for **8a-l**. Also, a signal around 152.0-153.7 ppm was observed for the O**C**N in the oxadiazole for **8a-l**.




YK306
177.0
153.5
151.5
143.3
140.8
138.9
135.1
133.9
131.3
131.0
130.0
129.9
129.6
129.4
129.2
129.0
127.8
127.4
127.2
125.9
124.2
120.9
113.8
95.3
O
N
N
S
S
O
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
f1 (ppm)

The HRMS data conclusively demonstrates that the molecule underwent fragmentation from the S-phenyl moiety.





Cpd.	HRMS		Cpd.	HRMS	
8	Calculated	Found	**8**	Calculated	Found
8a	350.1055	350.1039	**8g**	430.0862	430.0873
8b	492.0699	492.0714	**8h**	375.1008	375.1009
8c	586,1185	586.1178	**8i**	384.0666	384.0657
8d	636,1153	636.1122	**8j**	636.0500	636.0515
8e	428.0160	428.0158	**8k**	418.0276	418.0275
8f	504.1018	504.1013	**8l**	364.1212	364.1202

Table 4.2: HRMS data of compounds 8a-l

5. CONCLUSIONS AND RECOMMENDATIONS

To summarize, we have successfully synthesized 5'-aryl-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro [naphthalene-1,2'- [1,3,4]oxadiazol]-4-one derivatives. First, 2,3-dichloronaphthoquinone was reacted with thiophenol and the product was reacted with hydrazonyl chlorides that prepared from aldehyde. The structural spectra characterization of the compounds was determined using IR, ^{1}H NMR, ^{13}C NMR, and HRMS measurements for all the compounds. The obtained compounds have potential biological activity against acute myeloid leukemia cancer cell lines. The biological studies are still under investigation for these novel compounds.

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7. APPENDICES

2,3-Bis(phenylthio)naphthalene-1,4-dione

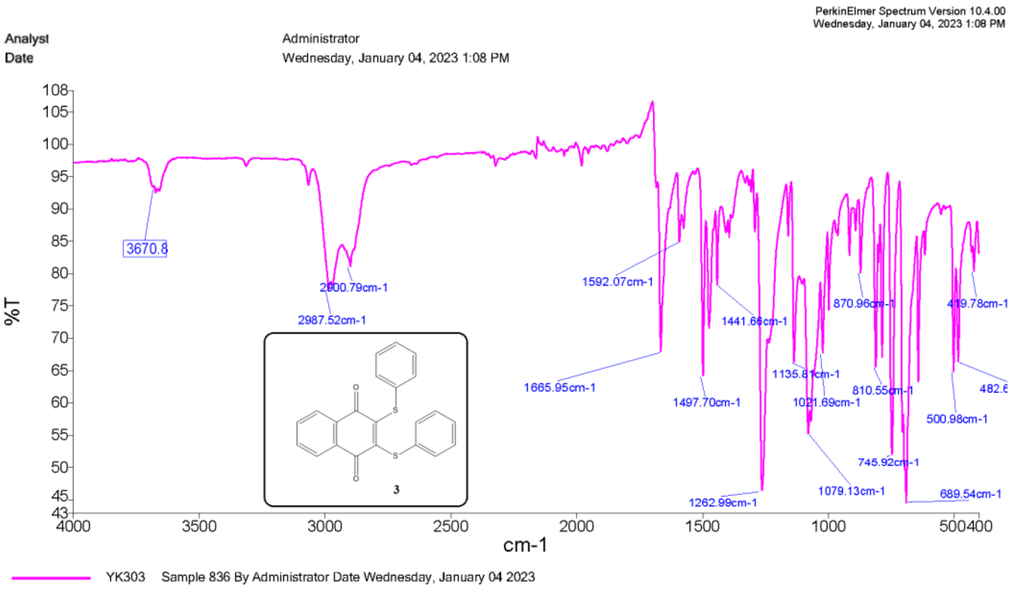


Figure 7.1. IR spectrum of compound **3**

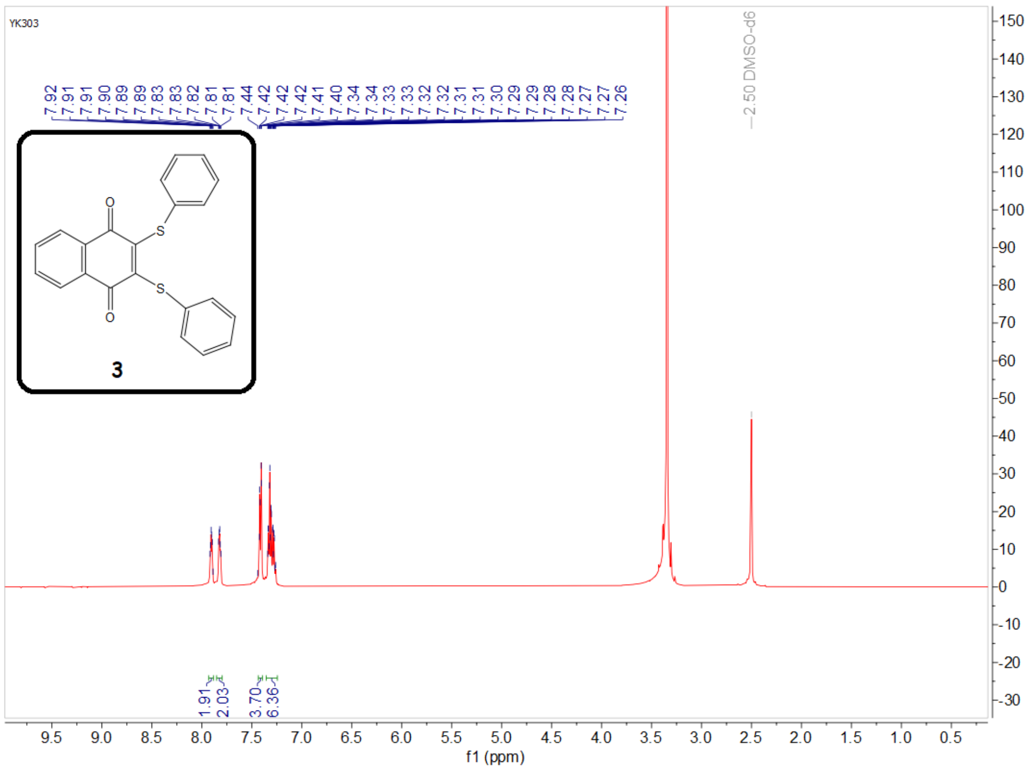


Figure 7.2. ^{1}H NMR spectrum of compound **3**

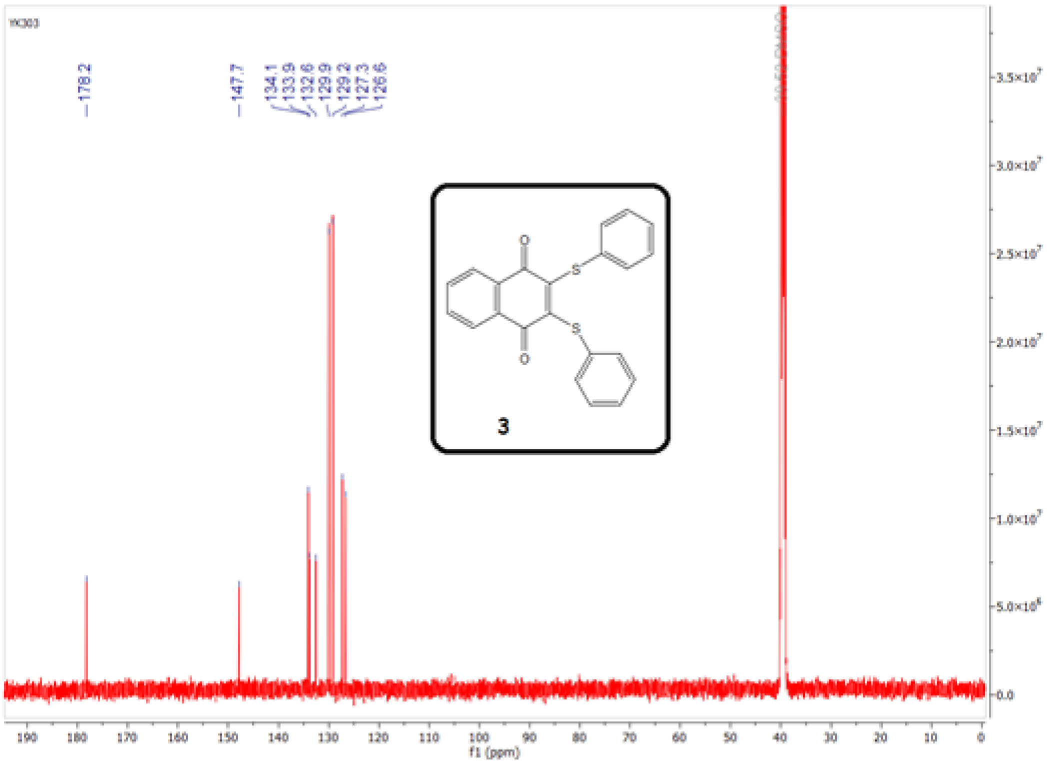


Figure 7.3. ^{13}C NMR spectrum of compound **3**

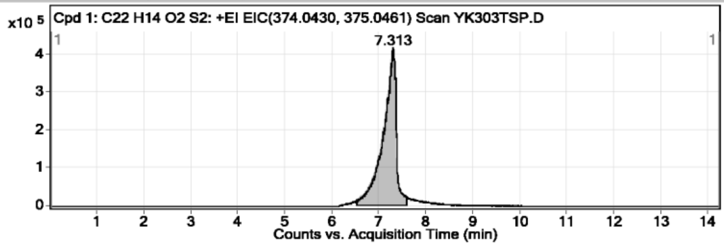
Target Compound Screening Report

Data File	YK303TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	5/23/2023 9:27:18 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

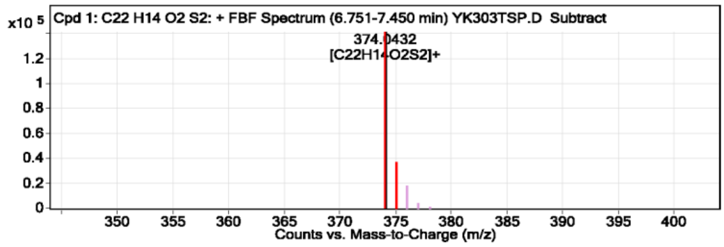
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C22 H14 O2 S2	374.0435	374.0437	65.99	0.43	374.0432	7.313	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C22 H14 O2 S2	374.0435	374.0437	65.99	0.43	374.0432	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.4. HRMS spectrum of compound **3**

3',5'-Diphenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

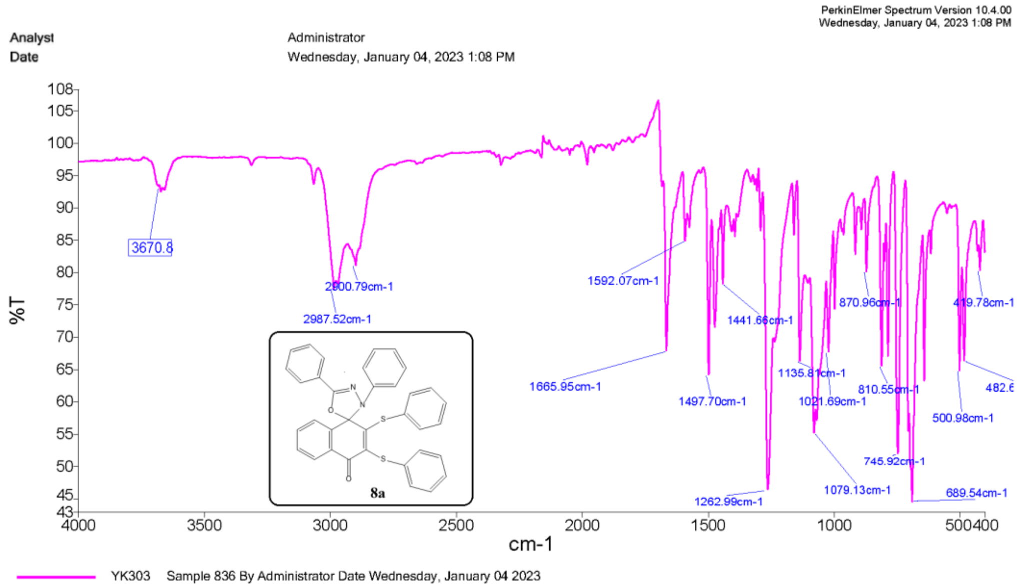


Figure 7.5. IR spectrum of compound **8a**

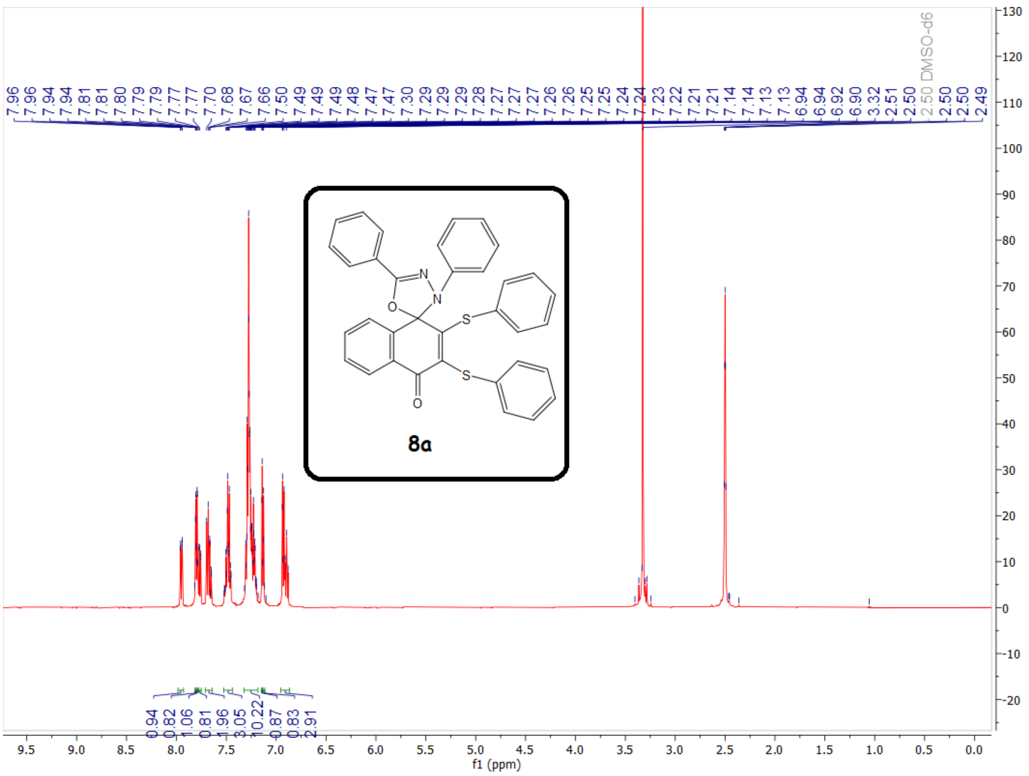


Figure 7.6. ^{1}H NMR spectrum of compound **8a**

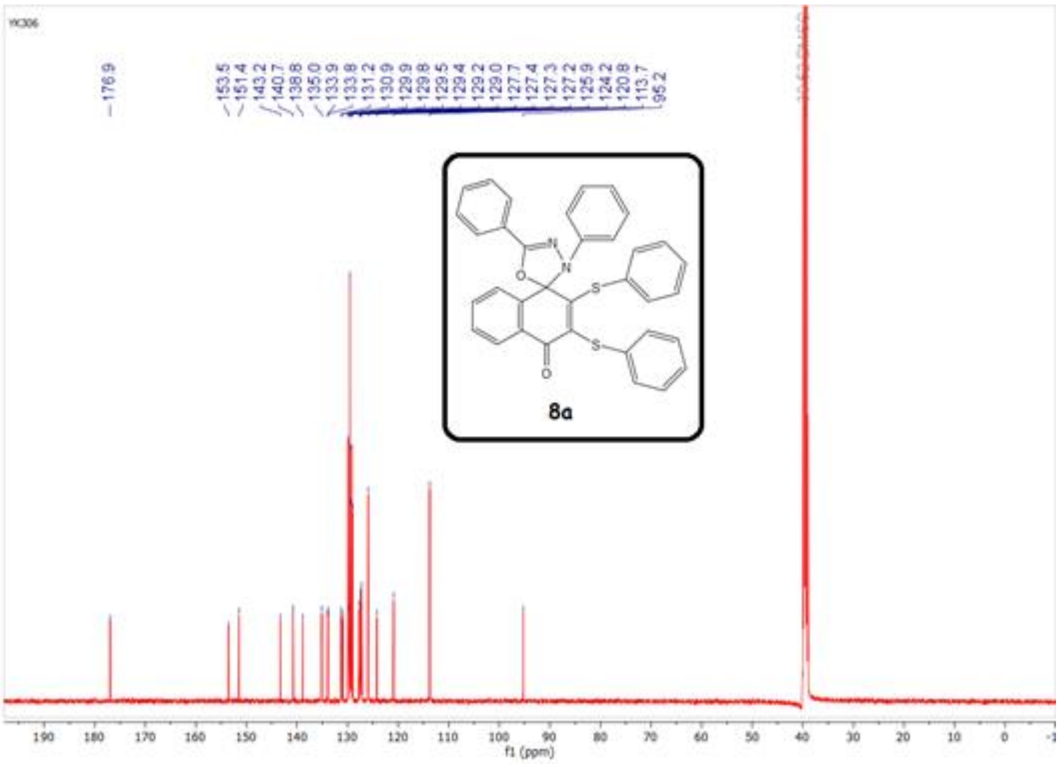


Figure 7.7. ^{13}C NMR spectrum of compound **8a**

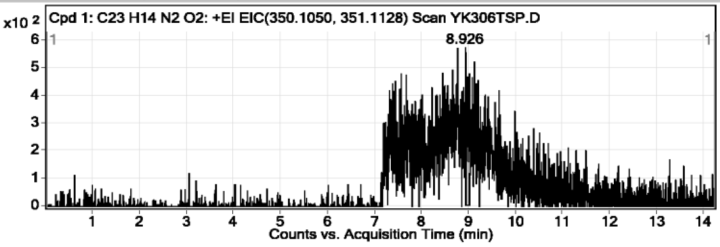
Target Compound Screening Report

Data File	YK306TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	5/23/2023 10:26:35 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

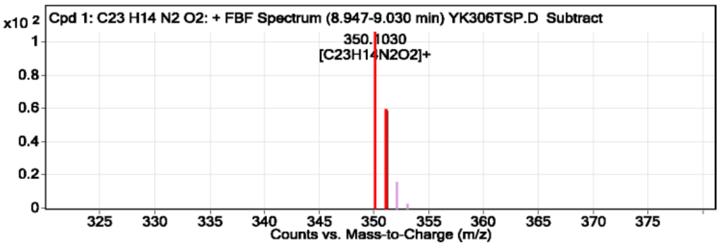
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C23 H14 N2 O2	350.1055	350.1039	43.58	-4.76	351.1116	8.96	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C23 H14 N2 O2	350.1055	350.1039	43.58	-4.76	351.1116	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.8. HRMS spectrum of compound **8a**

5'-(4-Chlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

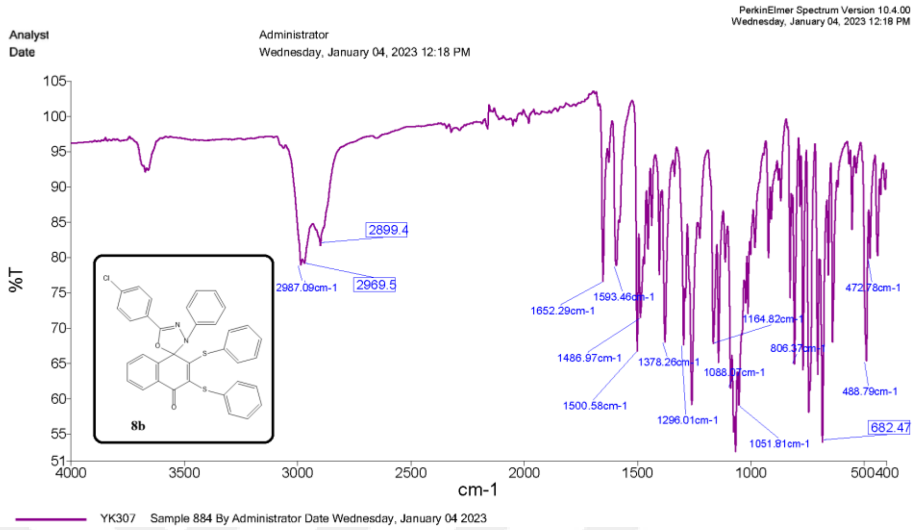


Figure 7.9. IR spectrum of compound **8b**

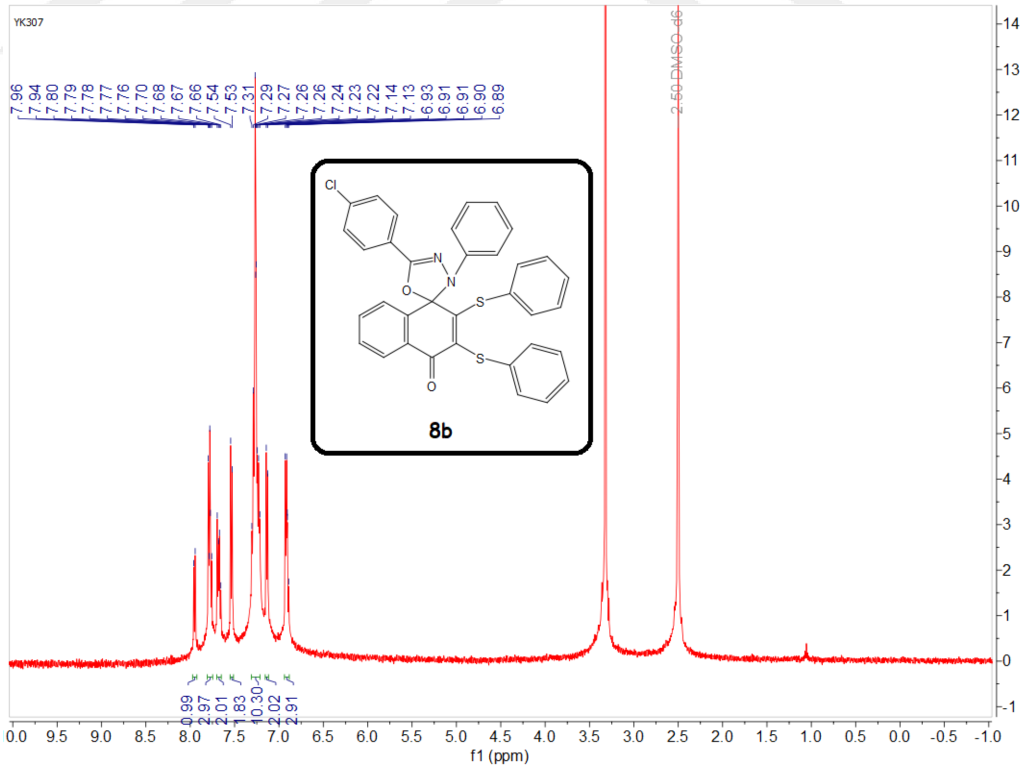


Figure 7.10. ^{1}H NMR spectrum of compound **8b**

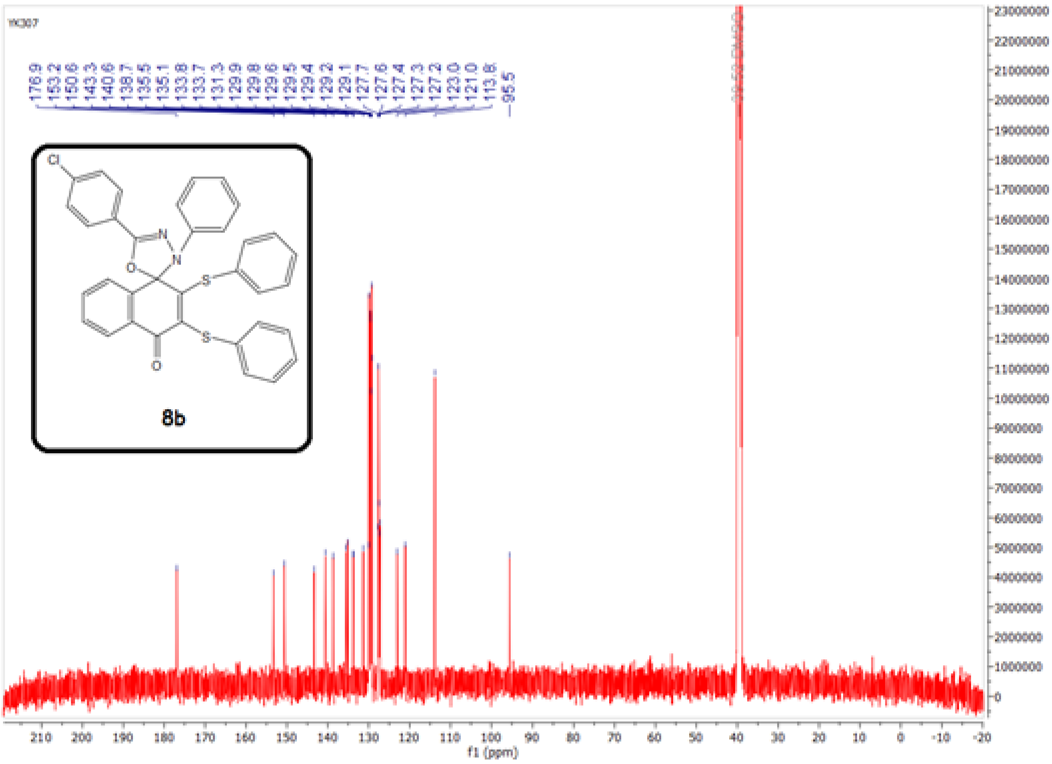


Figure 7.11. ^{13}C NMR spectrum of compound **8b**

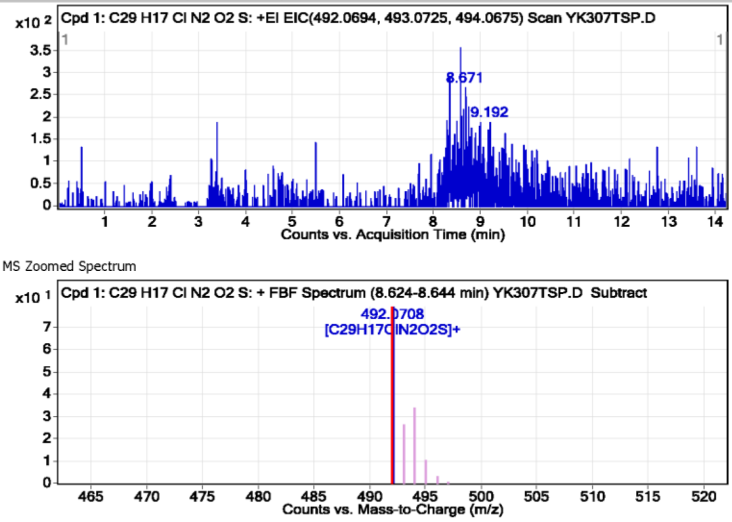
Target Compound Screening Report

Data File	YK307TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 9:20:29 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C29 H17 Cl N2 O2 S	492.0699	492.0714	43.41	2.94	492.0708	8.624	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	Obs. m/z	Find Cpds Algorith
C29 H17 Cl N2 O2 S	492.0699	492.0714	43.41	2.94	492.0708	Find By Formula



MS Zoomed Spectrum

Figure 7.12. HRMS spectrum of compound **8b**

5'-(4-Fluorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

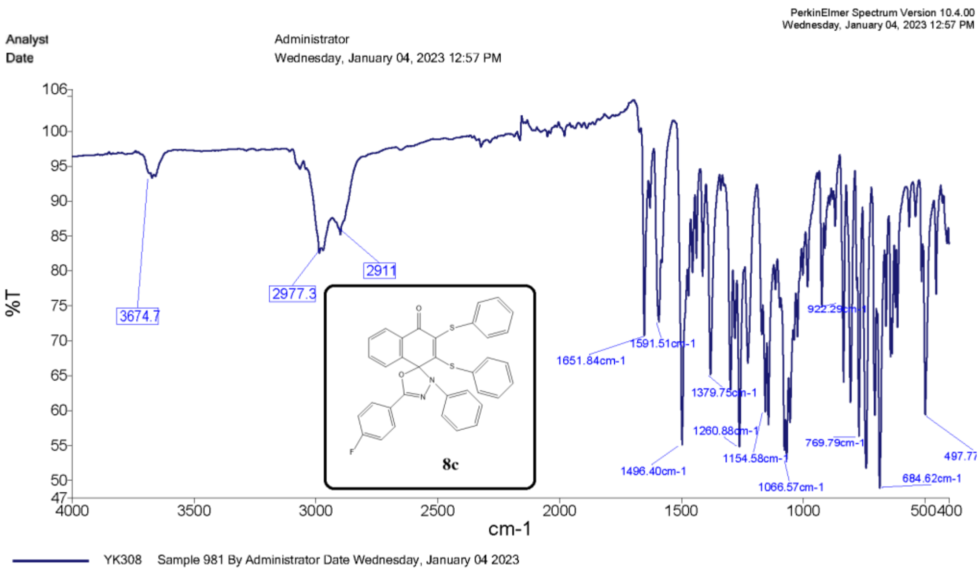


Figure 7.13. IR spectrum of compound **8c**

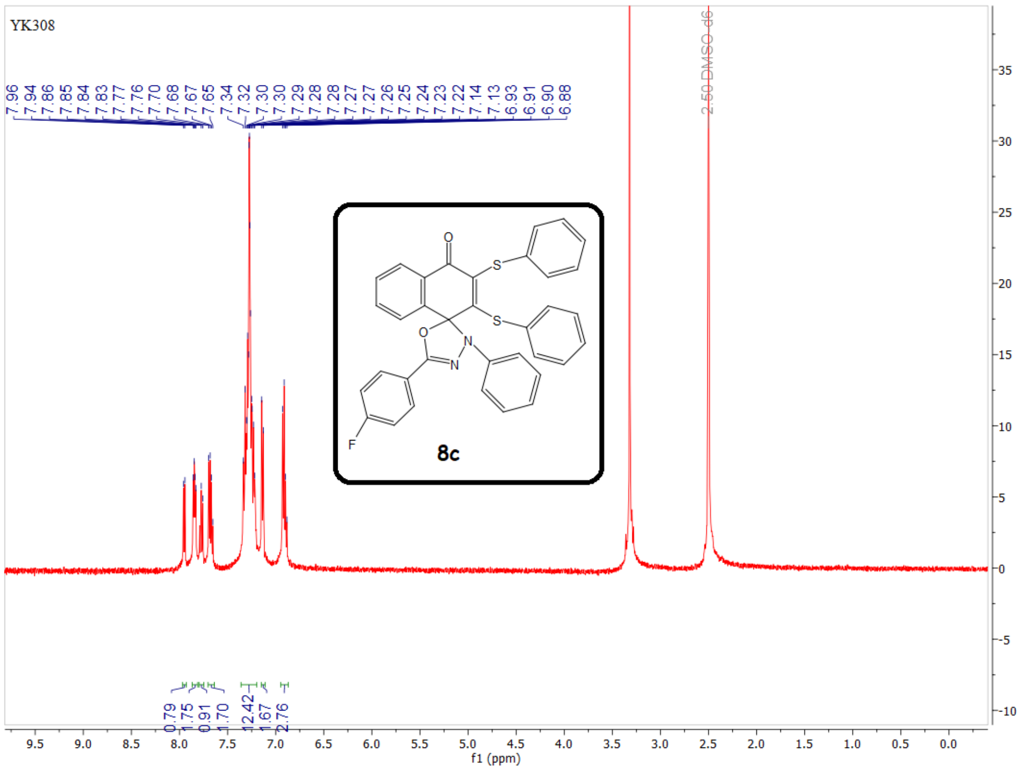


Figure 7.14. ^{1}H NMR spectrum of compound **8c**

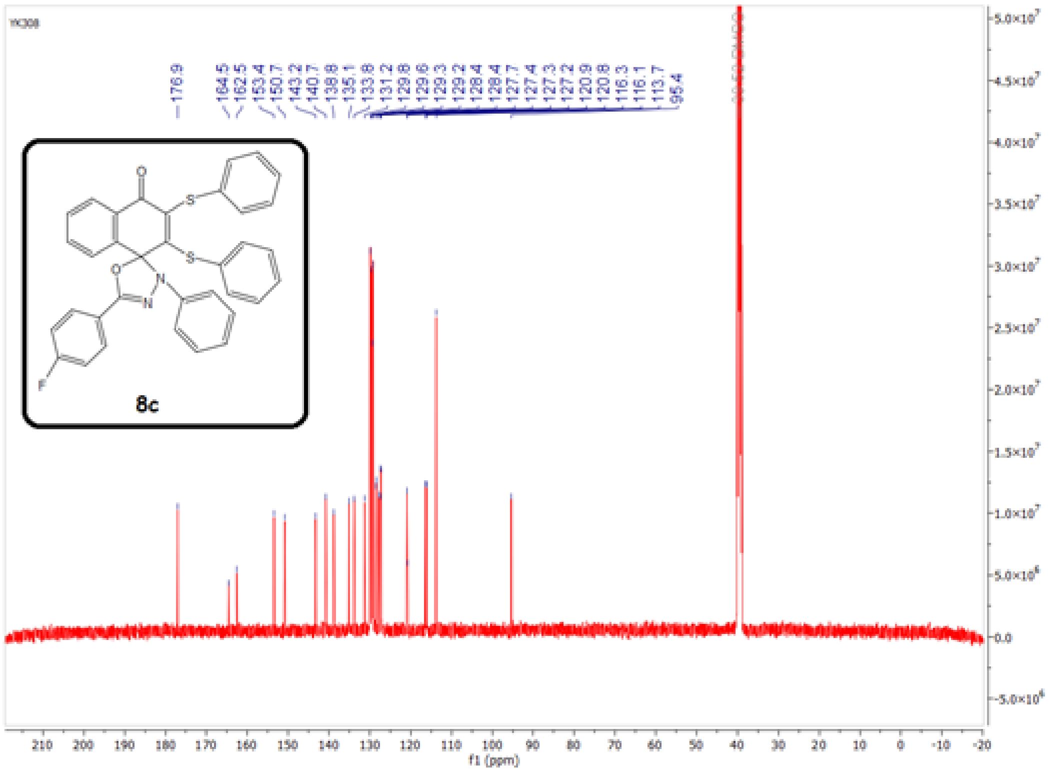


Figure 7.15. ^{13}C NMR spectrum of compound **8c**

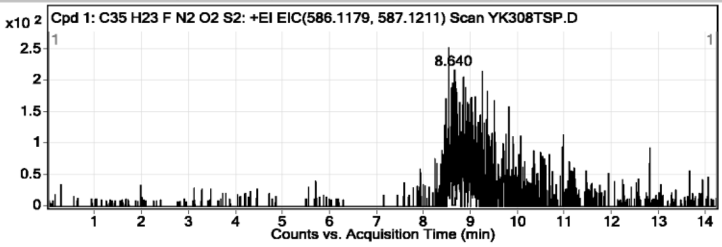
Target Compound Screening Report

Data File	YK308TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 9:56:35 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

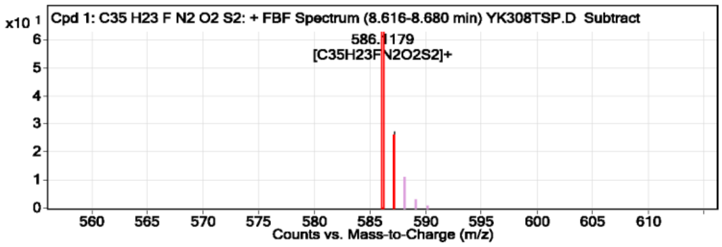
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C35 H23 F N2 O2 S2	586.1185	586.1178	58.32	-1.13	586.1179	8.64	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	Obs. m/z	Find Cpds Algorith
C35 H23 F N2 O2 S2	586.1185	586.1178	58.32	-1.13	586.1179	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.16. HRMS spectrum of compound **8c**

3'-Phenyl-2,3-bis(phenylthio)-5'-(4-(trifluoromethyl)phenyl)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

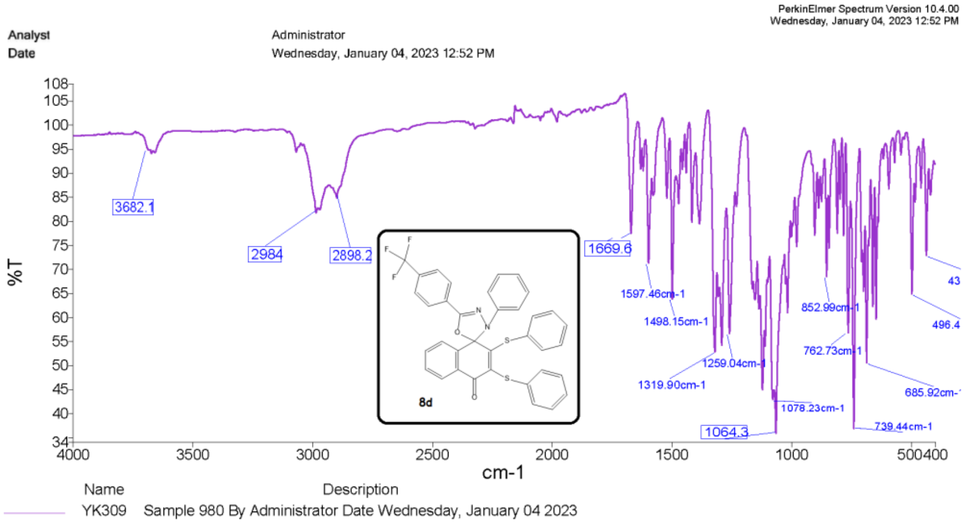


Figure 7.17. IR spectrum of compound **8d**

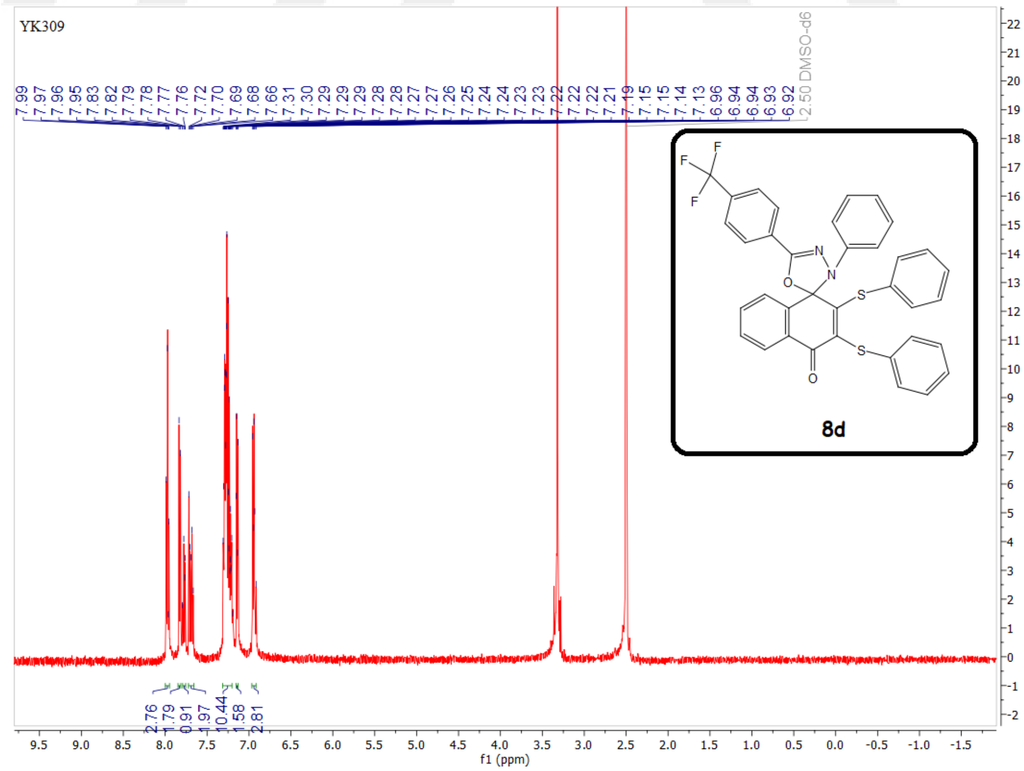


Figure 7.18. ^{1}H NMR spectrum of compound **8d**

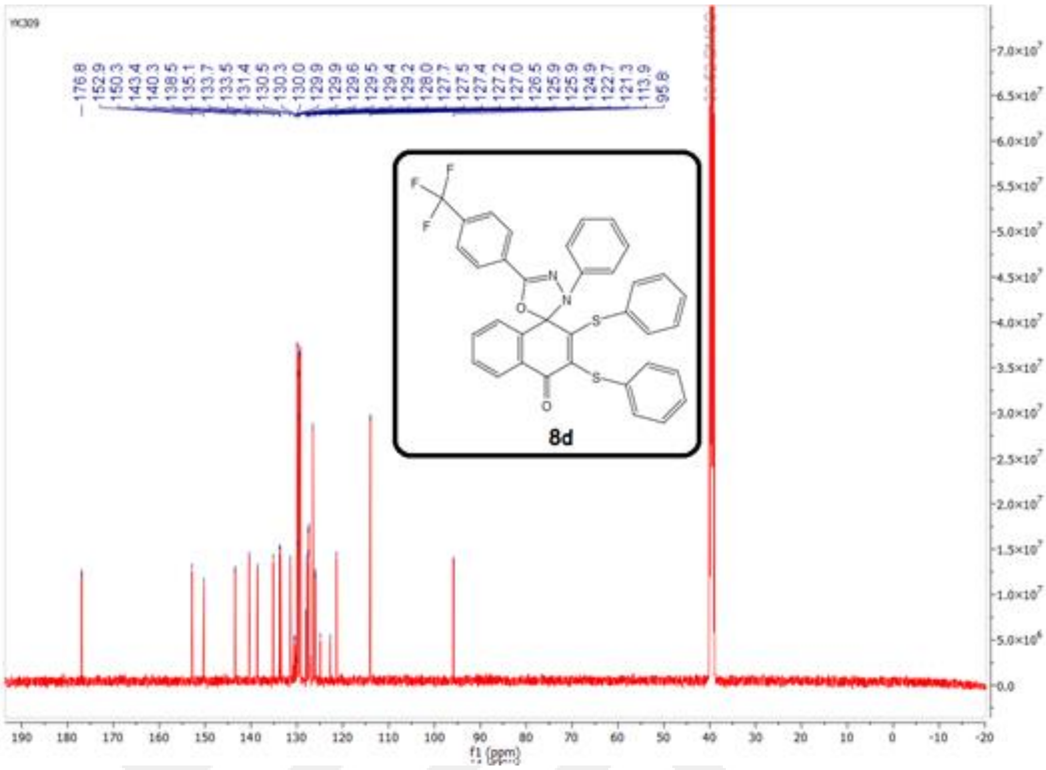


Figure 7.19. ^{13}C NMR spectrum of compound **8d**

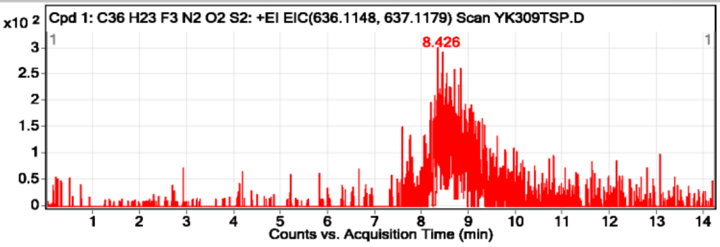
Target Compound Screening Report

Data File	YK309TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 10:20:58 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

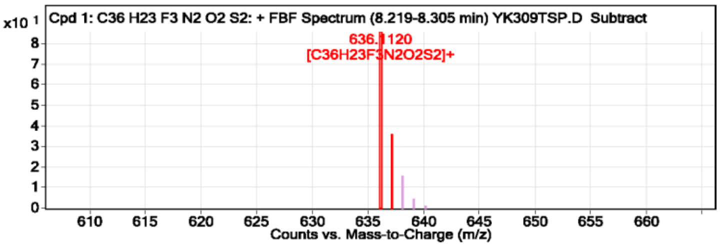
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C36 H23 F3 N2 O2 S2	636.1153	636.1122	48.7	-4.92	636.112	8.265	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C36 H23 F3 N2 O2 S2	636.1153	636.1122	48.7	-4.92	636.112	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.20. HRMS spectrum of compound **8d**

5'-(3-Bromophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

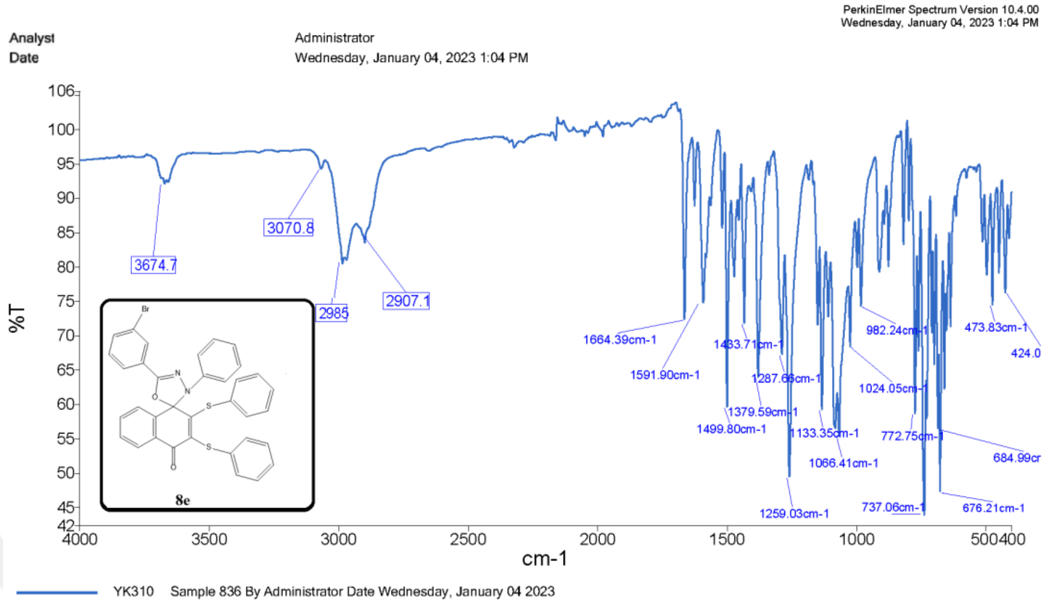


Figure 7.21. IR spectrum of compound **8e**

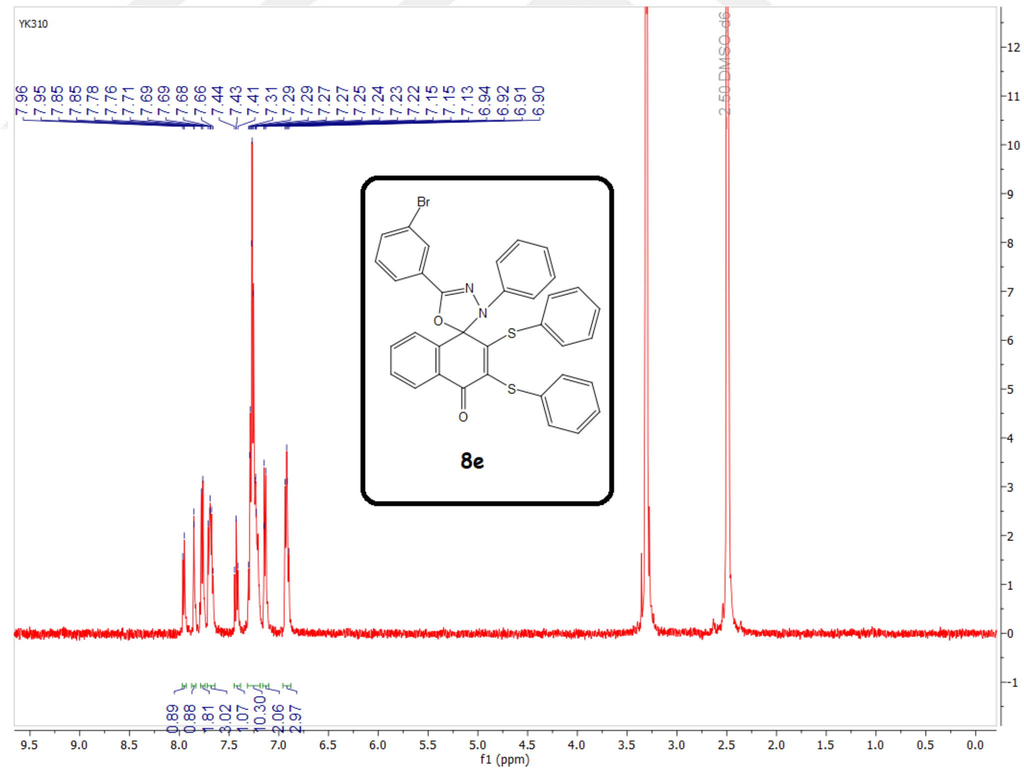


Figure 7.22. ^{1}H NMR spectrum of compound **8e**

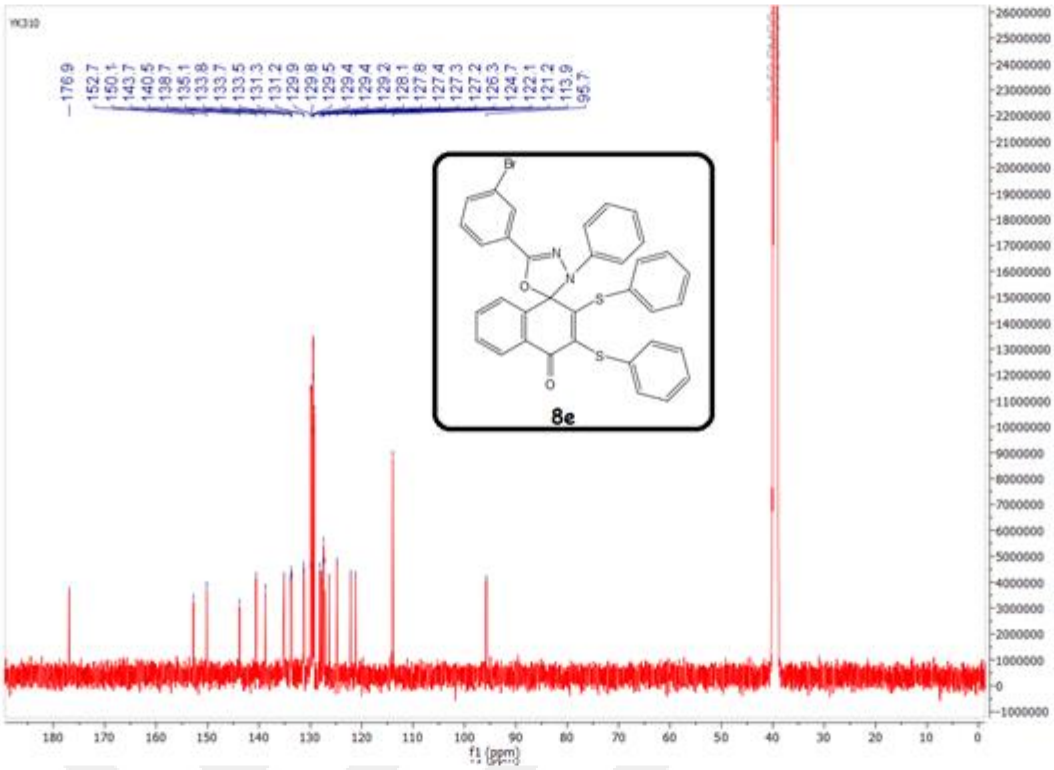


Figure 7.23. ^{13}C NMR spectrum of compound **8e**

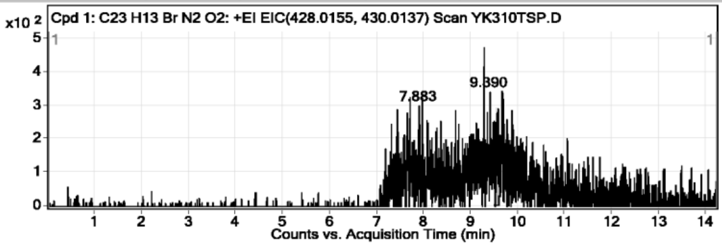
Target Compound Screening Report

Data File	YK310TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 10:51:26 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

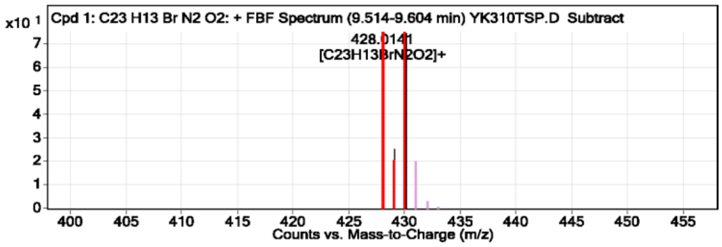
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C23 H13 Br N2 O2	428.016	428.0158	65.29	-0.51	428.0141	9.56	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C23 H13 Br N2 O2	428.016	428.0158	65.29	-0.51	428.0141	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

Figure 7.24. HRMS spectrum of compound **8e**

5'-(4-Nitrophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

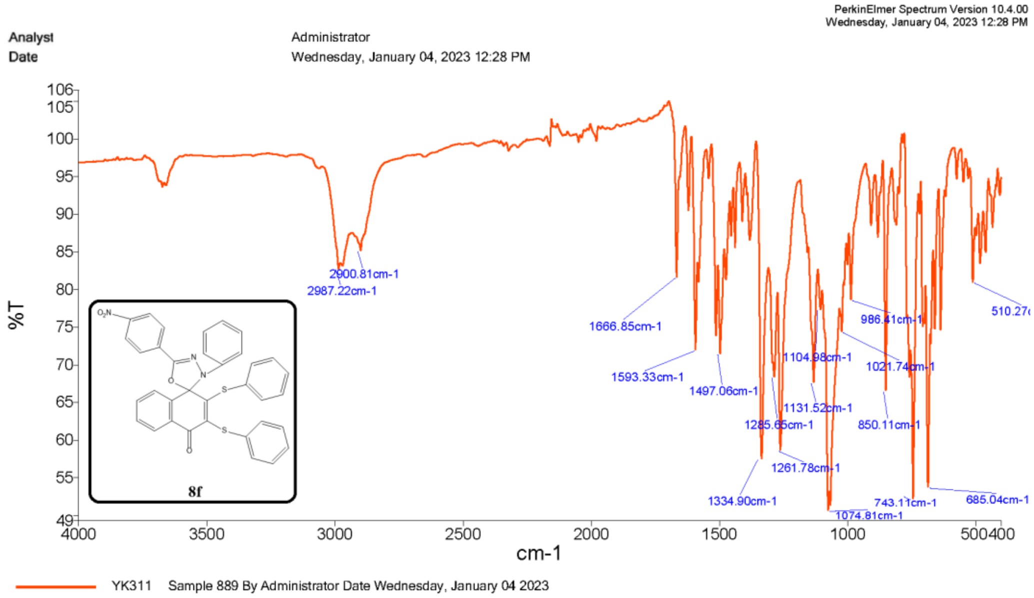


Figure 7.25. IR spectrum of compound **8f**

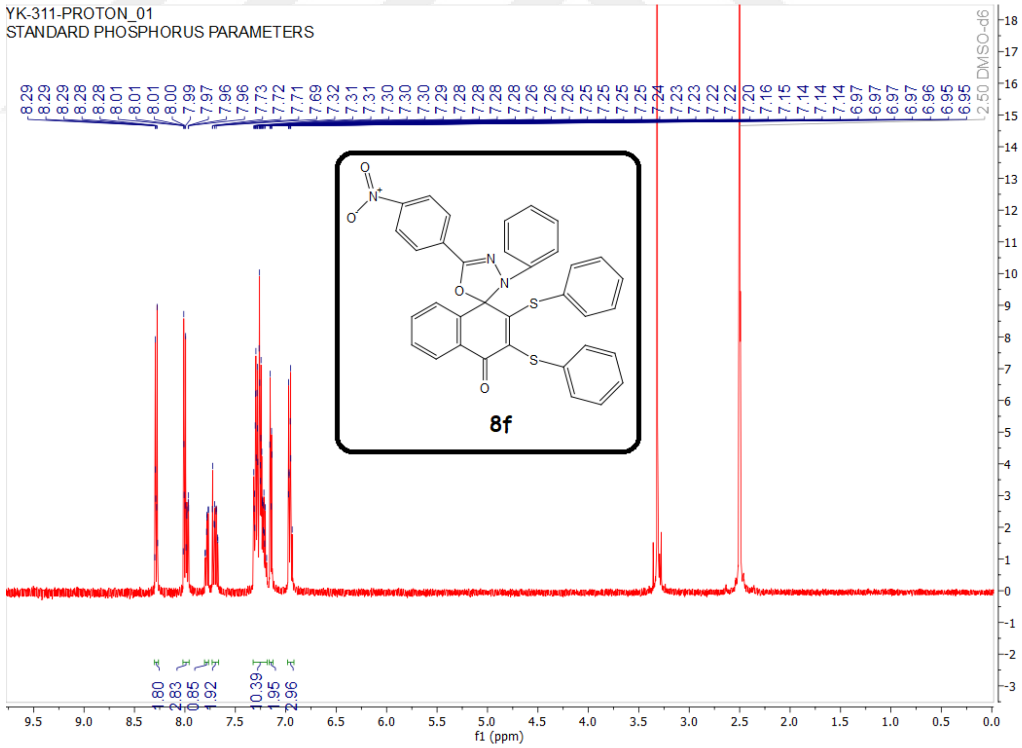


Figure 7.26. ^{1}H NMR spectrum of compound **8f**

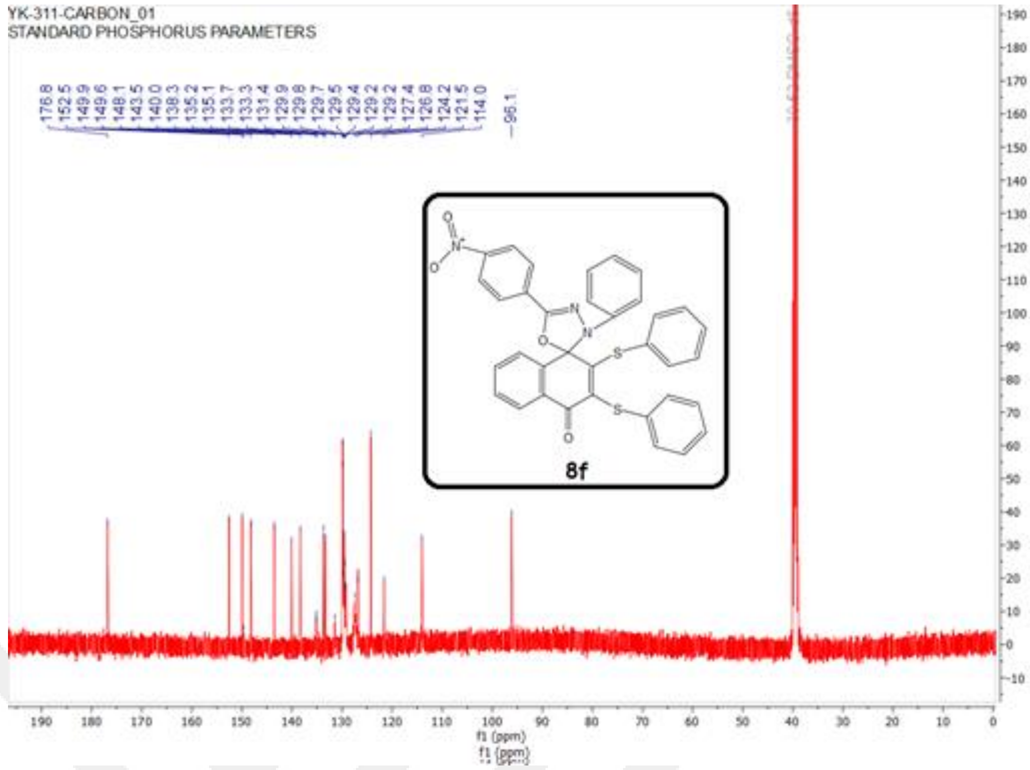


Figure 7.27. ^{13}C NMR spectrum of compound **8f**

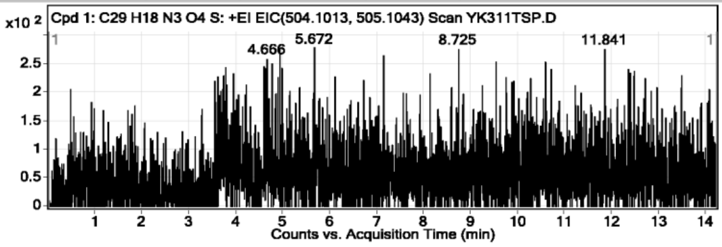
Target Compound Screening Report

Data File	YK311TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 12:30:26 PM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

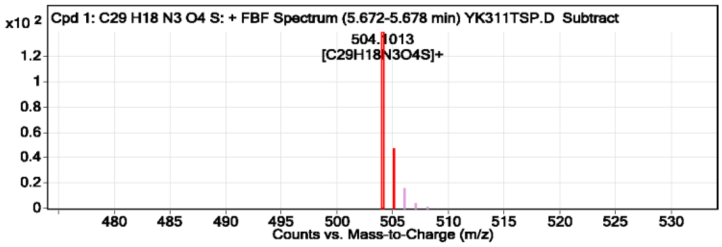
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C29 H18 N3 O4 S	504.1018	504.1013	65.38	-1.03	504.1013	5.672	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	Obs. m/z	Find Cpds Algorith
C29 H18 N3 O4 S	504.1018	504.1013	65.38	-1.03	504.1013	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.28. HRMS spectrum of compound **8f**

5'-(3-Nitrophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

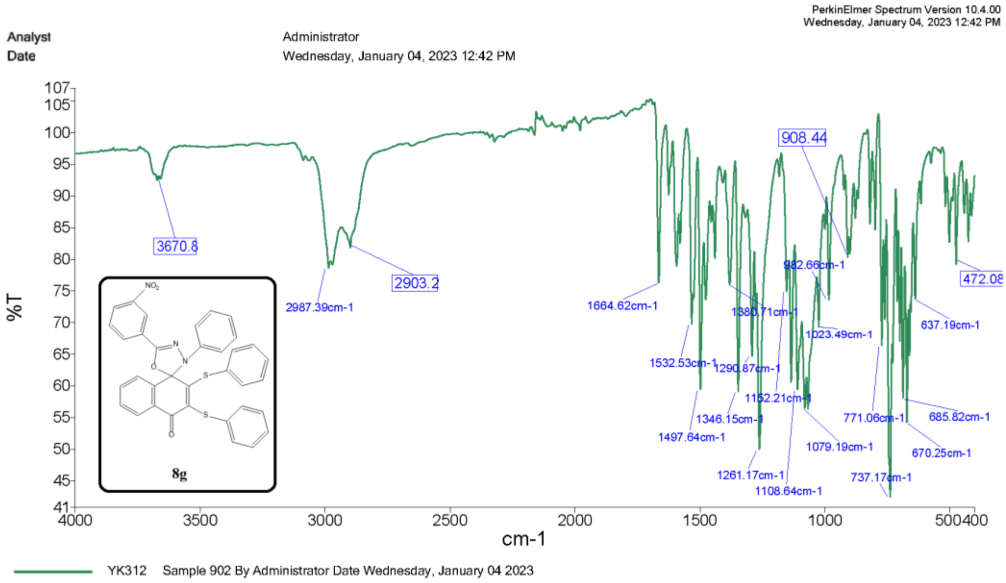


Figure 7.29. IR spectrum of compound **8g**

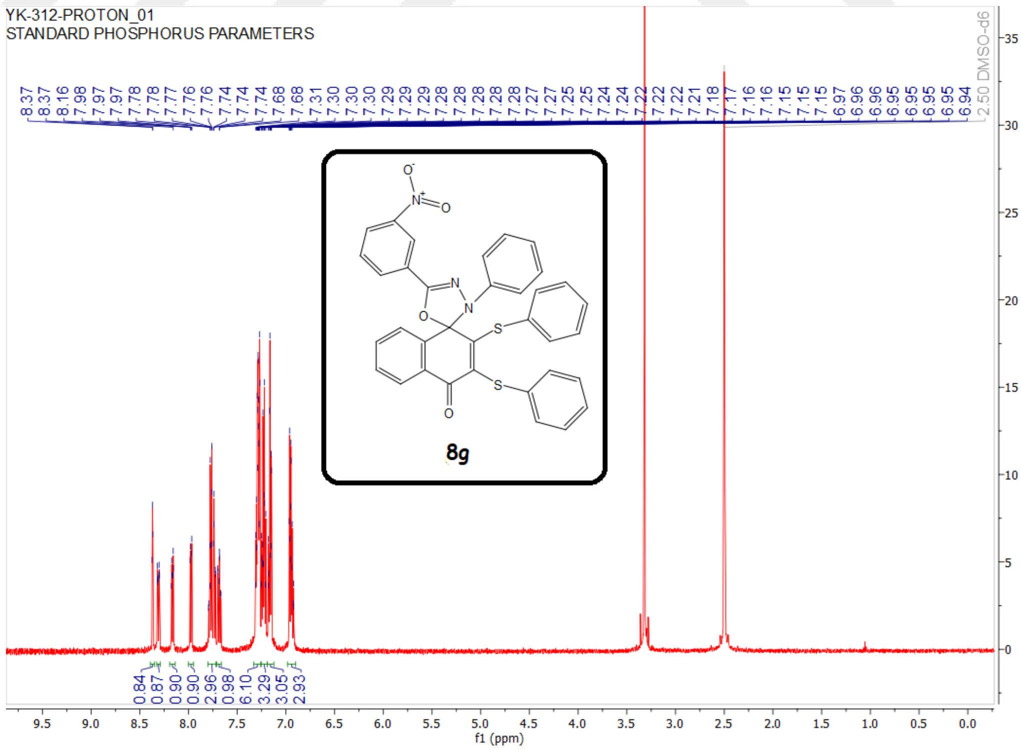


Figure 7.30. ^{1}H NMR spectrum of compound **8g**

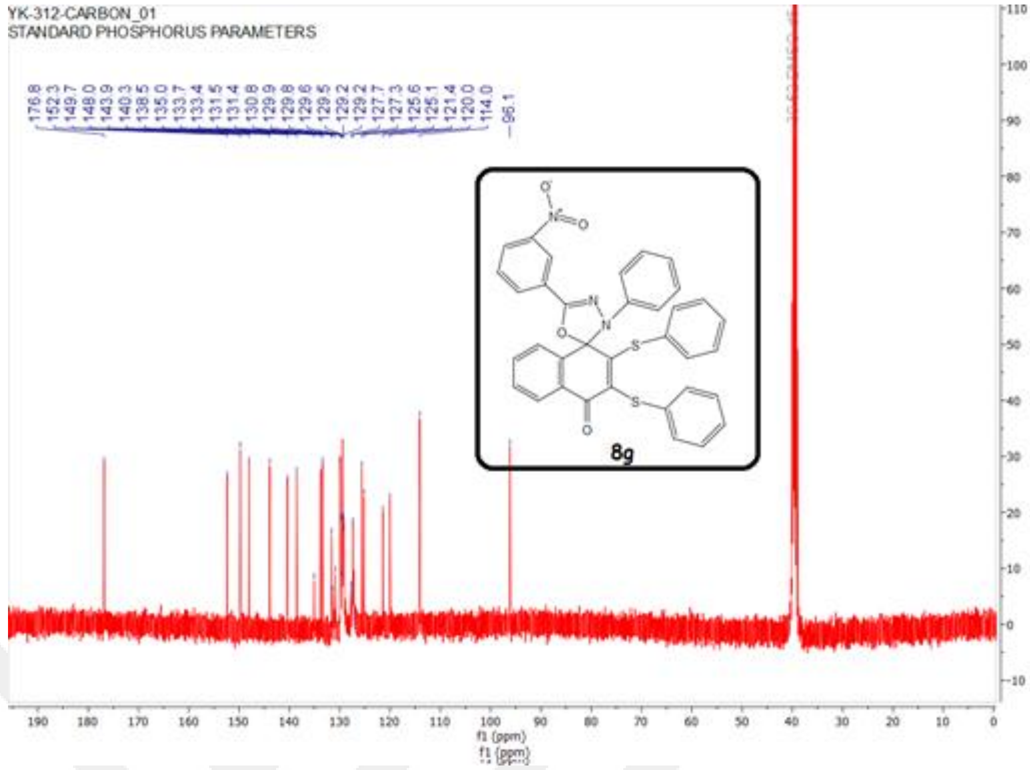


Figure 7.31. ^{13}C NMR spectrum of compound **8g**

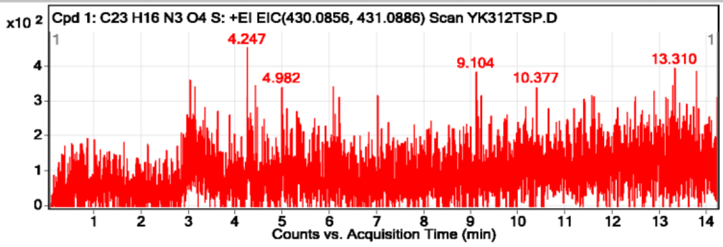
Target Compound Screening Report

Data File	YK312TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 1:05:28 PM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

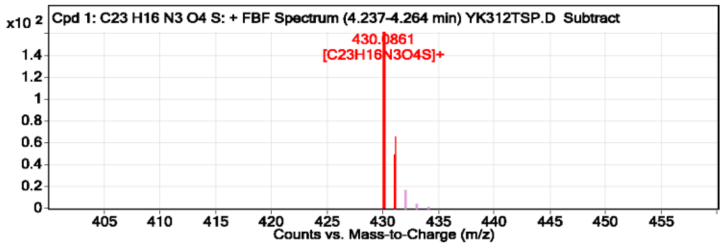
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C23 H16 N3 O4 S	430.0862	430.0873	55.89	2.66	430.0861	4.247	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C23 H16 N3 O4 S	430.0862	430.0873	55.89	2.66	430.0861	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

Figure 7.32. HRMS spectrum of compound **8g**

4-(4-Oxo-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-5'-yl)benzonitrile

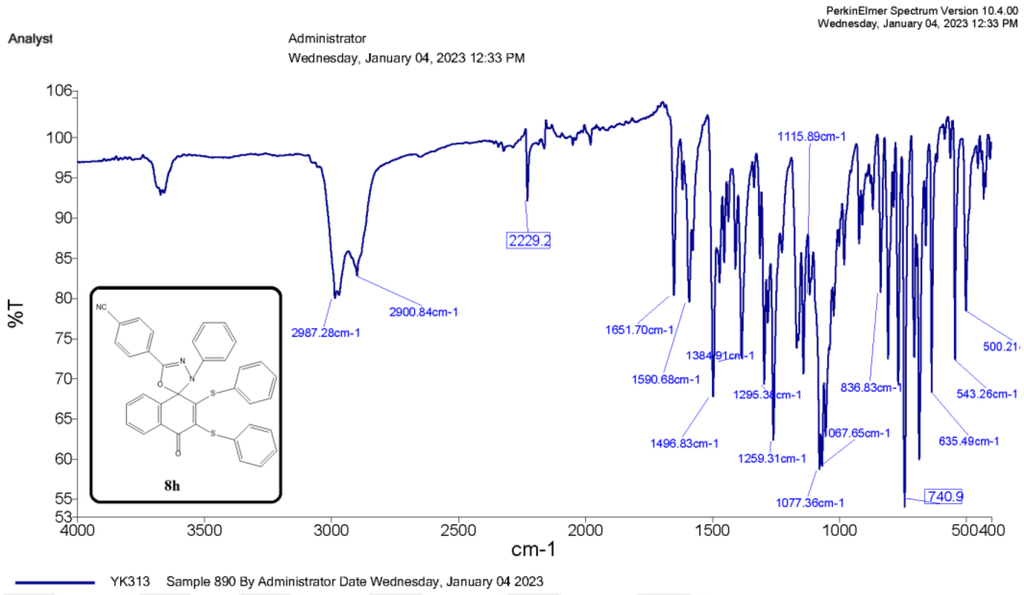


Figure 7.33. IR spectrum of compound **8h**

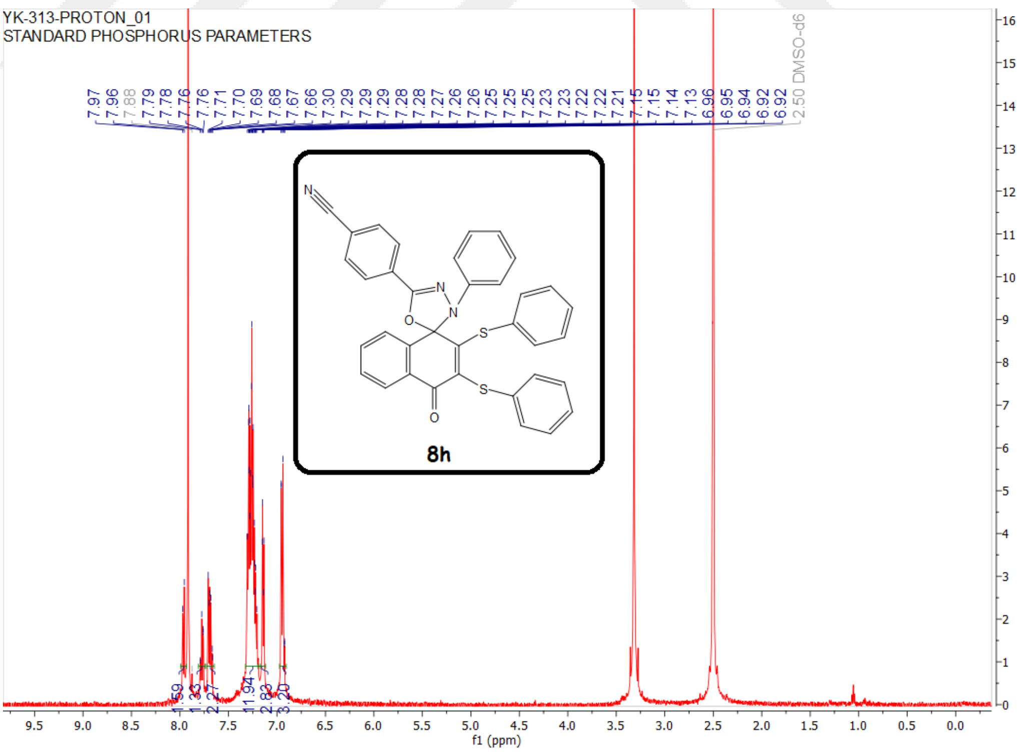


Figure 7.34. ^{1}H NMR spectrum of compound **8h**

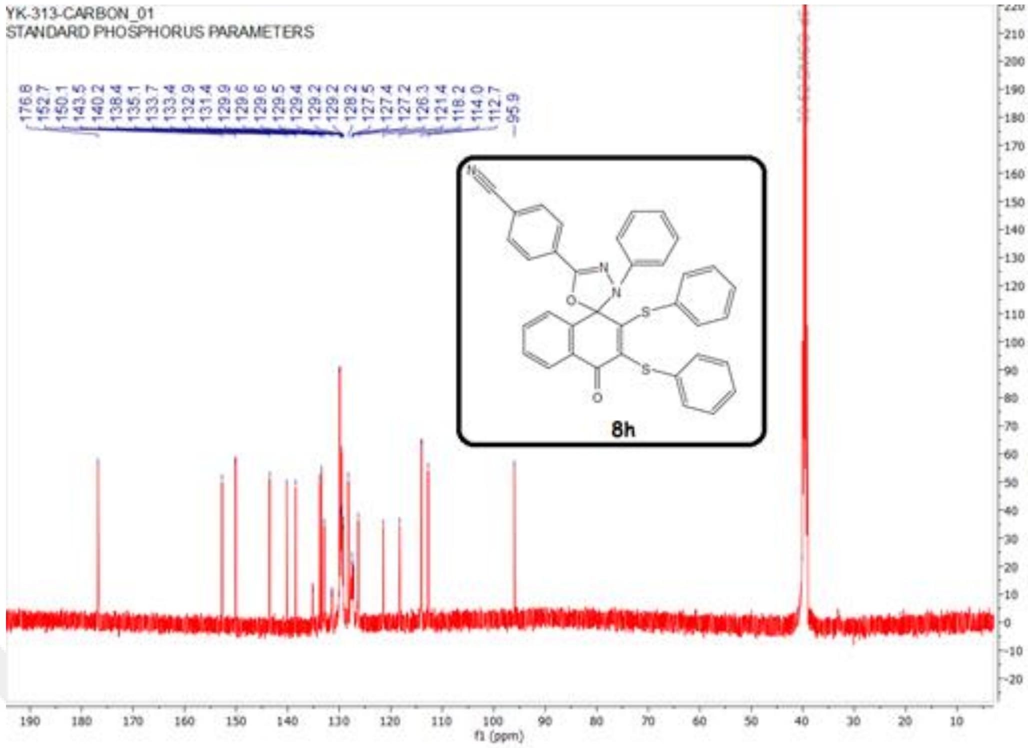


Figure 7.35. ^{13}C NMR spectrum of compound **8h**

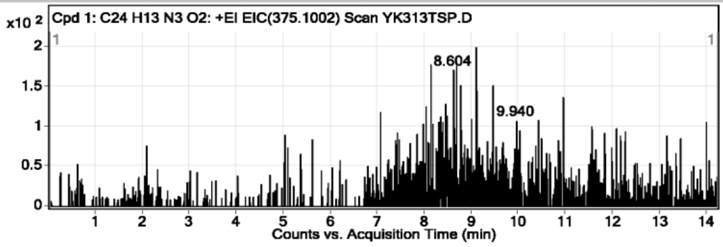
Target Compound Screening Report

Data File	YK313TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 1:46:07 PM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

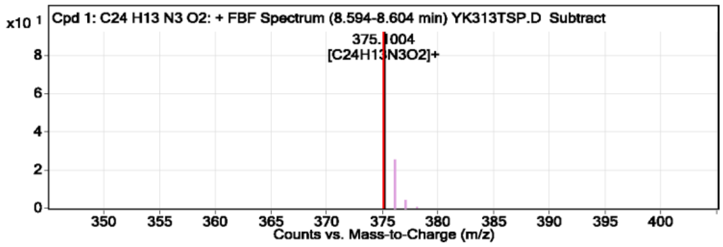
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C24 H13 N3 O2	375.1008	375.1009	47.54	0.44	375.1004	8.604	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C24 H13 N3 O2	375.1008	375.1009	47.54	0.44	375.1004	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.36. HRMS spectrum of compound **8h**

5'-(3-Chlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

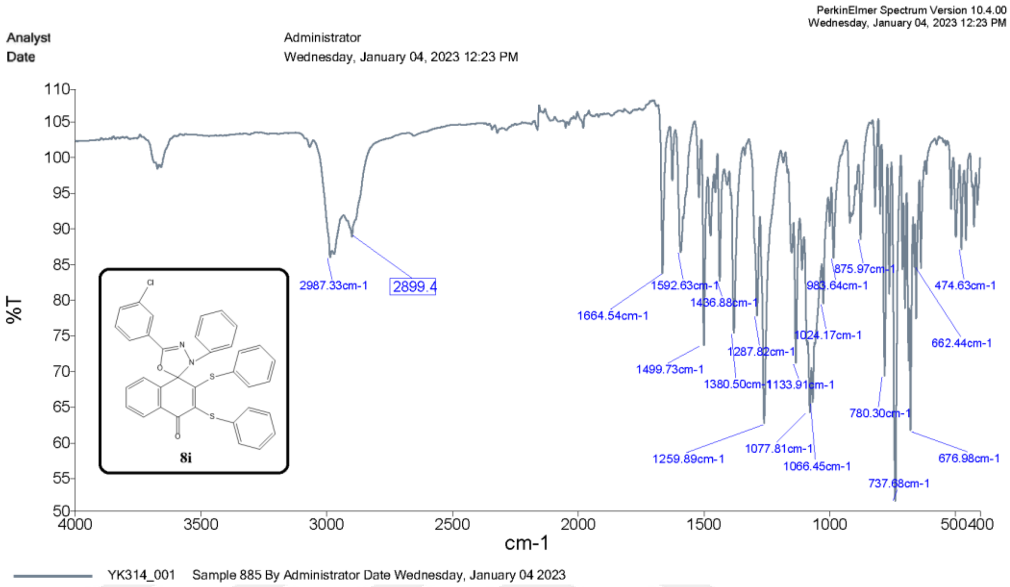


Figure 7.37. IR spectrum of compound **8i**

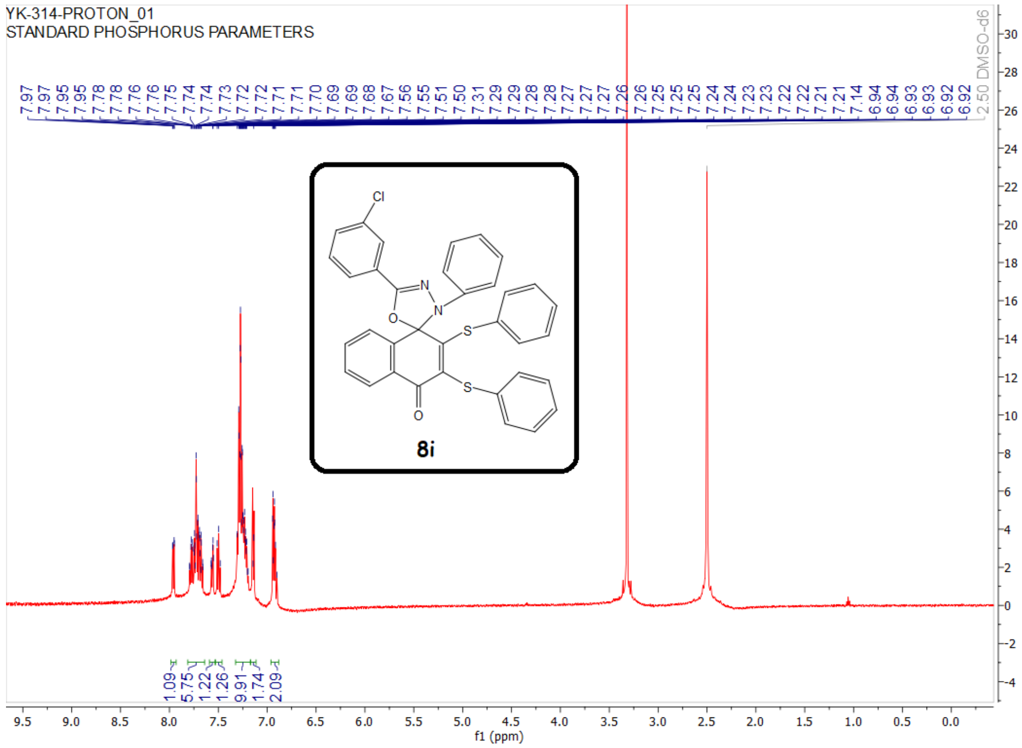


Figure 7.38. ^{1}H NMR spectrum of compound **8i**

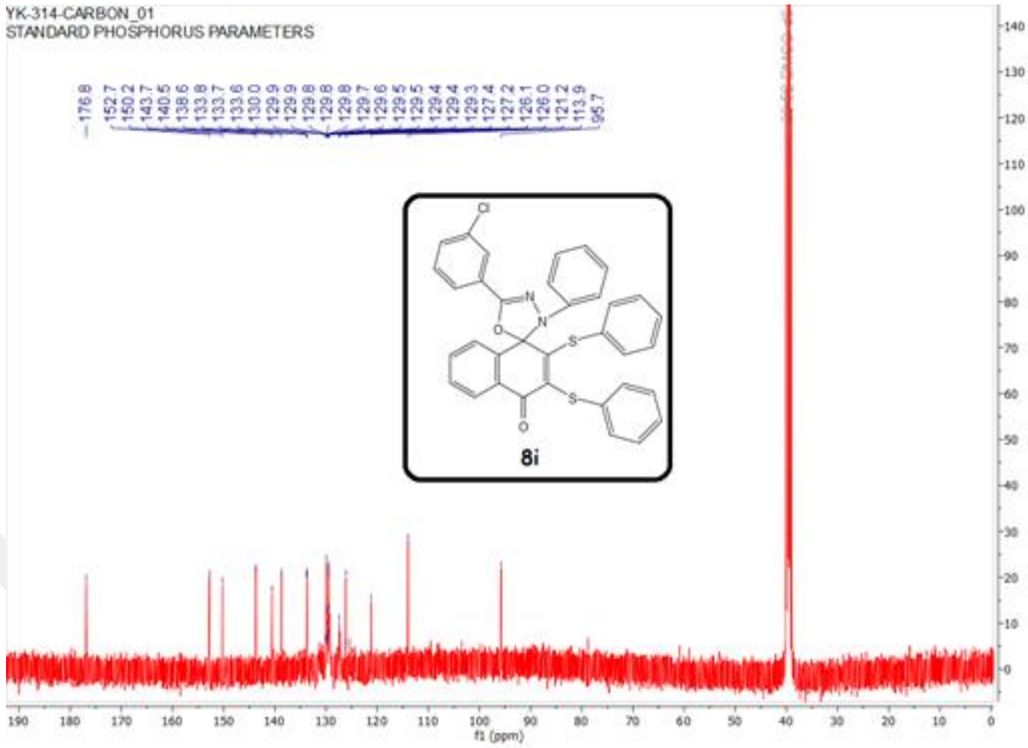


Figure 7.39. ^{13}C NMR spectrum of compound **8i**

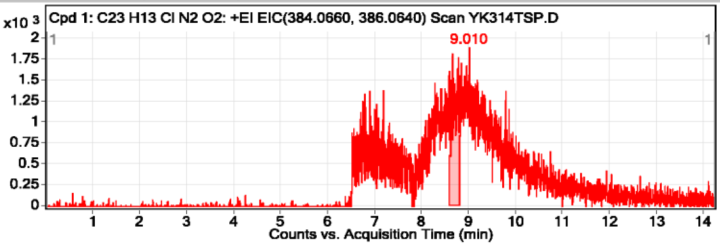
Target Compound Screening Report

Data File	YK314TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/8/2023 2:19:59 PM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

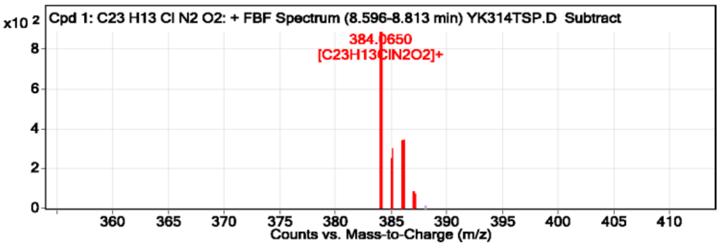
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C23 H13 Cl N2 O2	384.0666	384.0657	86.05	-2.15	384.065	8.663	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C23 H13 Cl N2 O2	384.0666	384.0657	86.05	-2.15	384.065	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.40. HRMS spectrum of compound **8i**

5'-(2,6-Dichlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

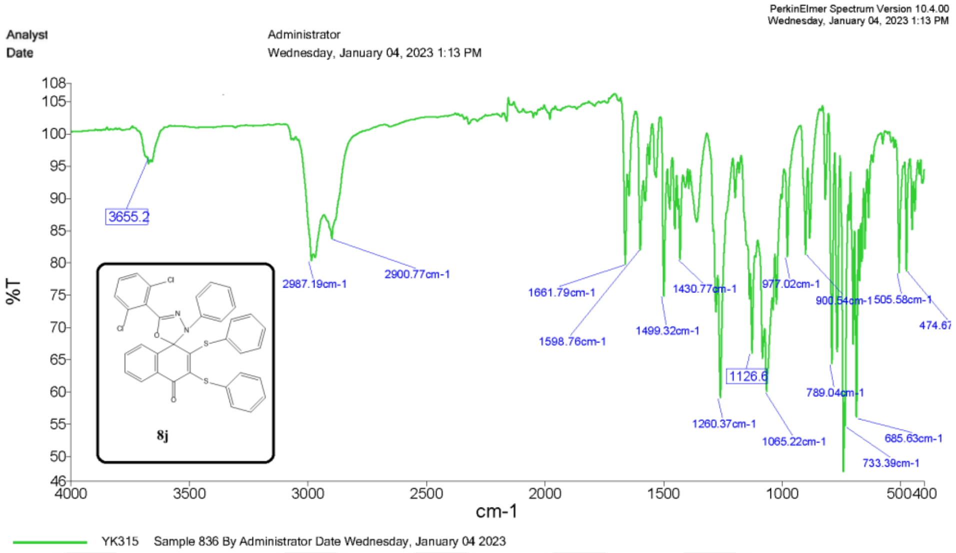


Figure 7.41. IR spectrum of compound **8j**

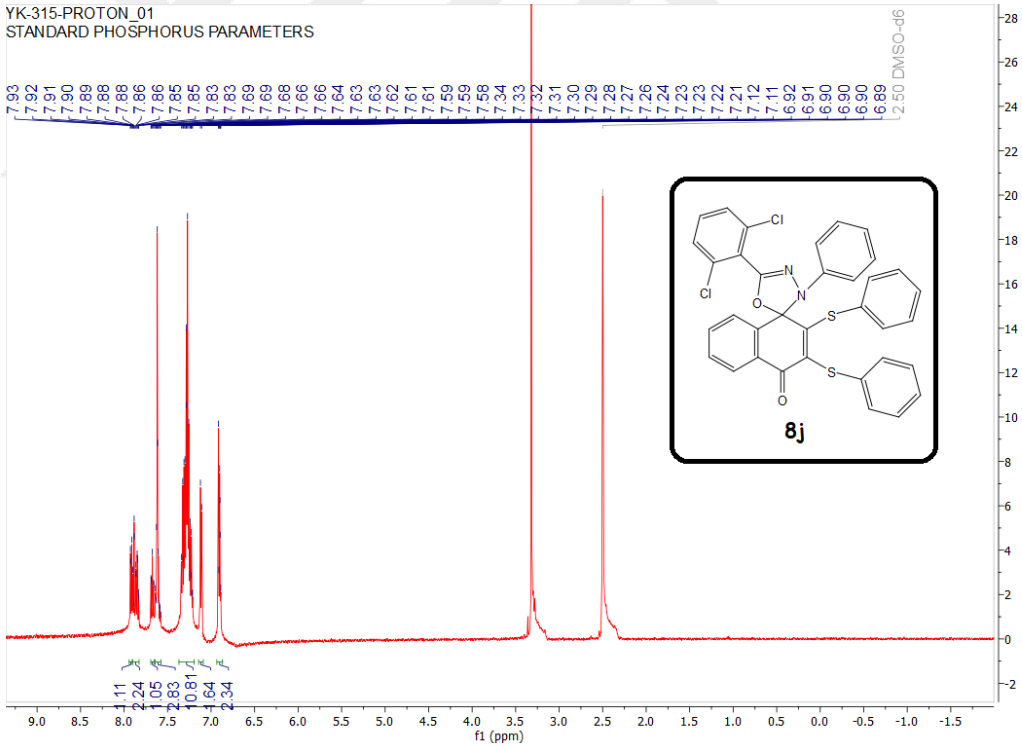


Figure 7.42. ^{1}H NMR spectrum of compound **8j**

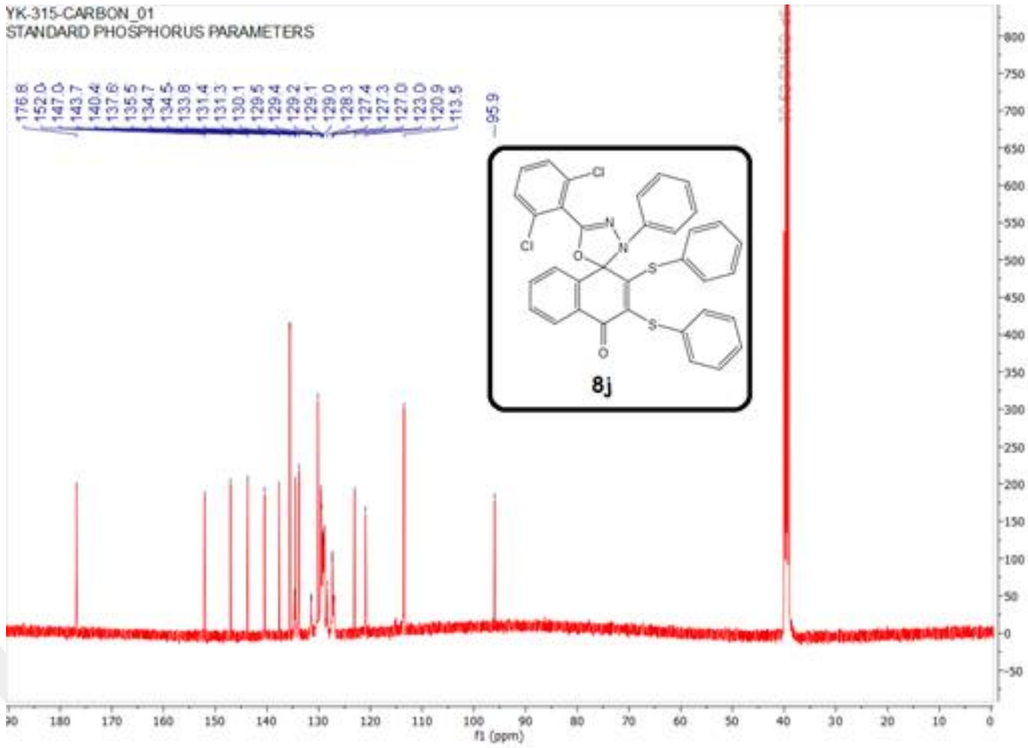


Figure 7.43. ^{13}C NMR spectrum of compound **8j**

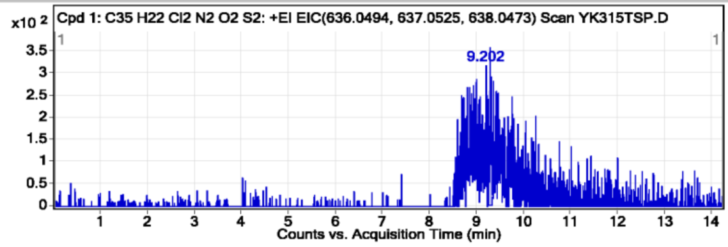
Target Compound Screening Report

Data File	YK315TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/9/2023 8:44:17 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

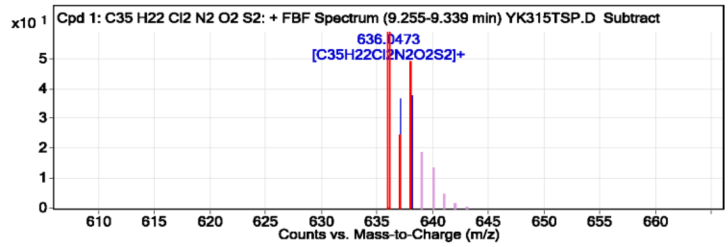
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C35 H22 Cl2 N2 O2 S2	636.05	636.0515	57.83	2.38	636.0473	9.292	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C35 H22 Cl2 N2 O2 S2	636.05	636.0515	57.83	2.38	636.0473	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.44. HRMS spectrum of compound **8j**

5'-(2,4-Dichlorophenyl)-3'-phenyl-2,3-bis(phenylthio)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

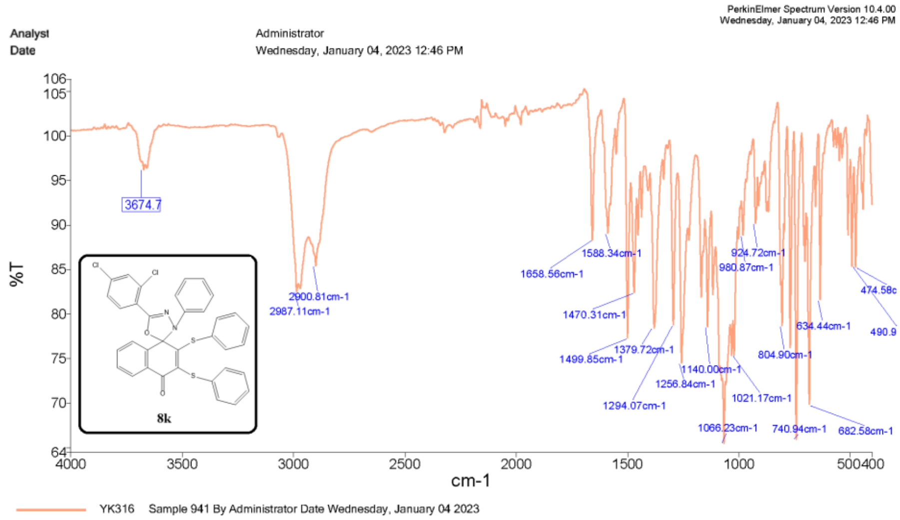


Figure 7.45. IR spectrum of compound **8k**

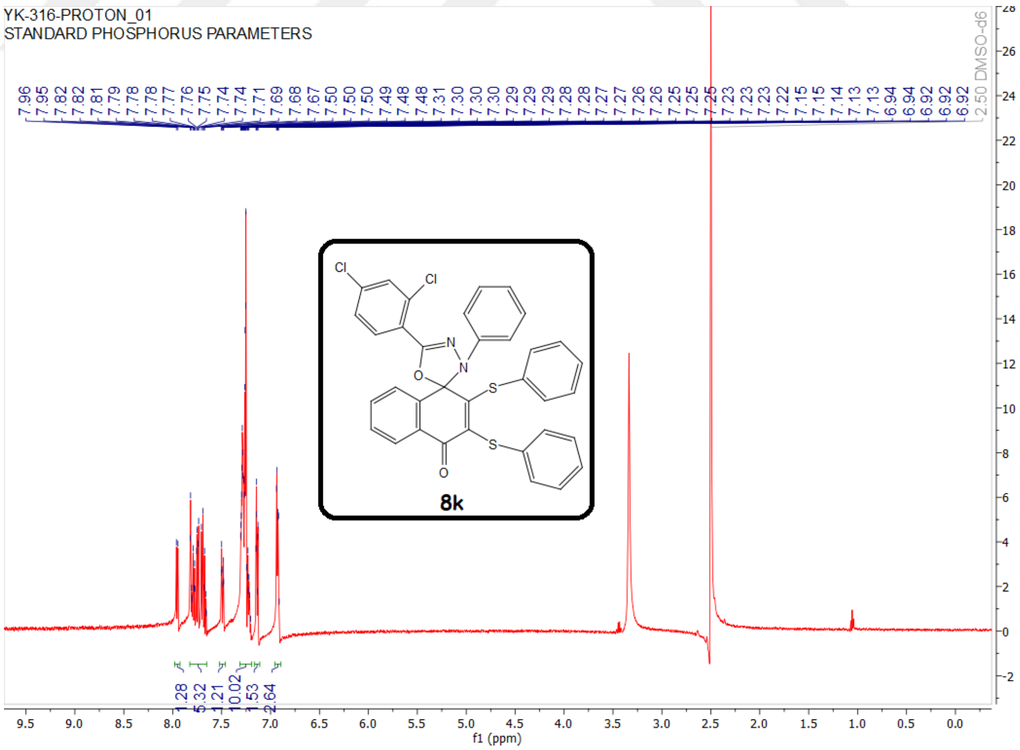


Figure 7.46. ^{1}H NMR spectrum of compound **8k**

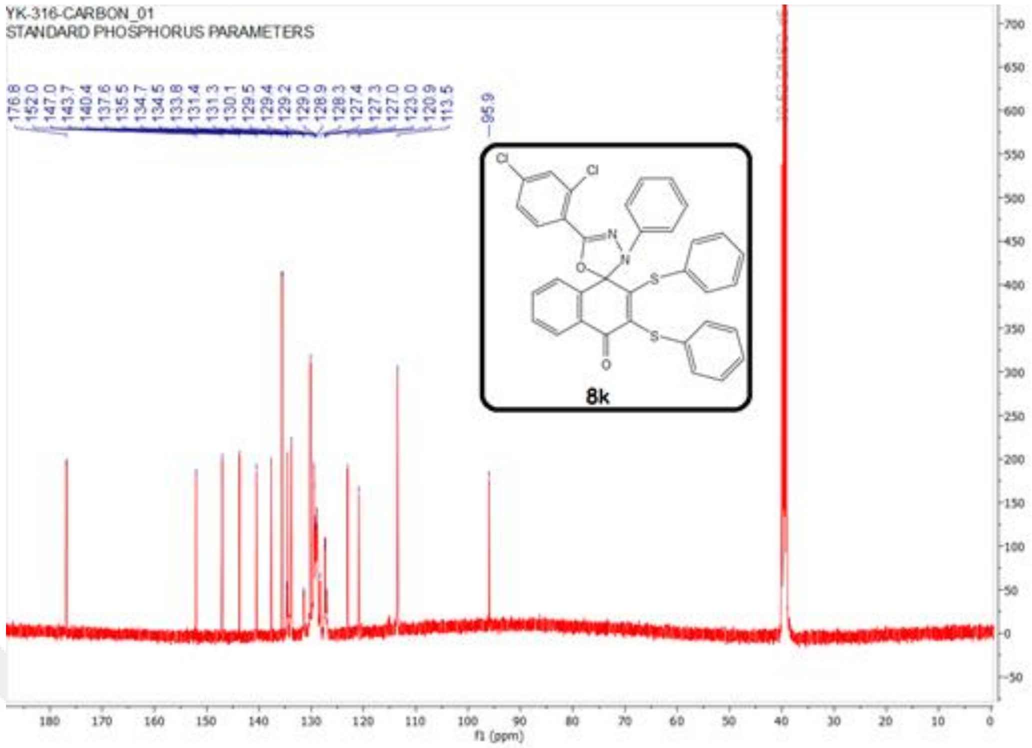


Figure 7.47. ^{13}C NMR spectrum of compound **8k**

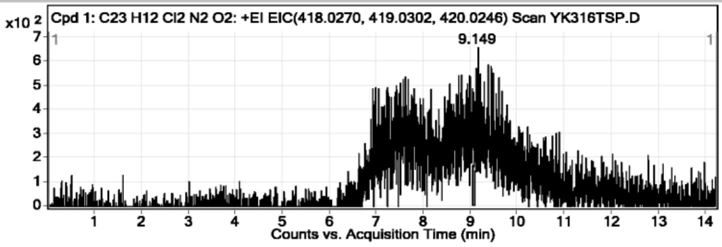
Target Compound Screening Report

Data File	YK316TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/9/2023 9:18:48 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

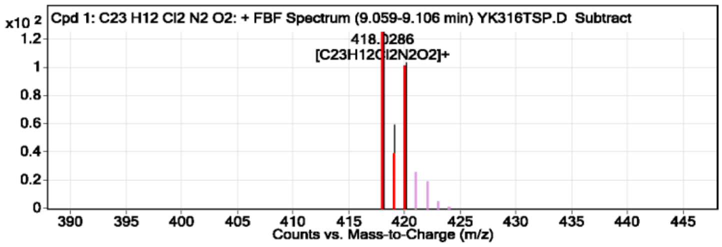
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C23 H12 Cl2 N2 O2	418.0276	418.0275	67.43	-0.15	418.0286	9.102	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C23 H12 Cl2 N2 O2	418.0276	418.0275	67.43	-0.15	418.0286	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

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Figure 7.48. HRMS spectrum of compound **8k**

3'-Phenyl-2,3-bis(phenylthio)-5'-(p-tolyl)-3'H,4H-spiro[naphthalene-1,2'-[1,3,4]oxadiazol]-4-one

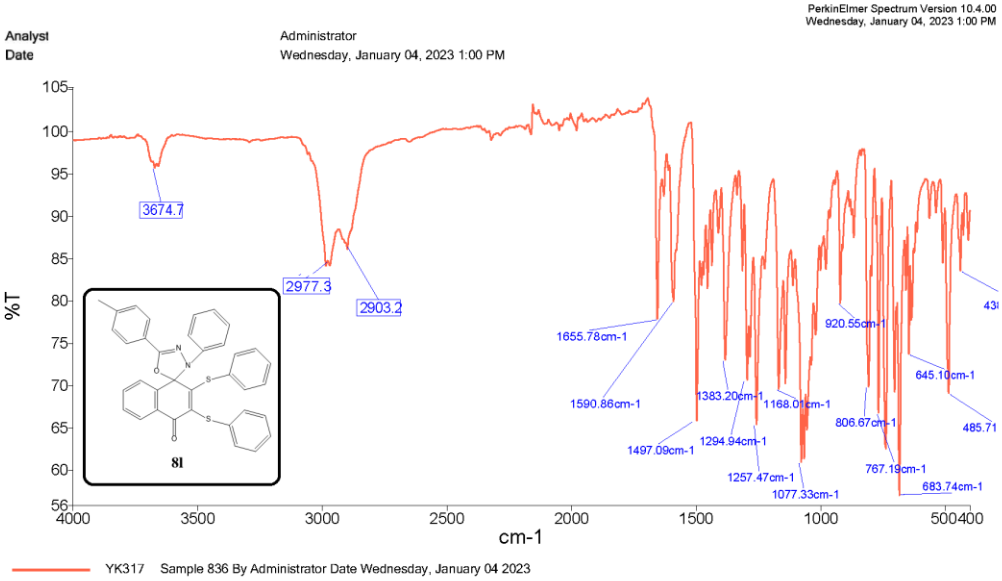


Figure 7.49. IR spectrum of compound **8l**

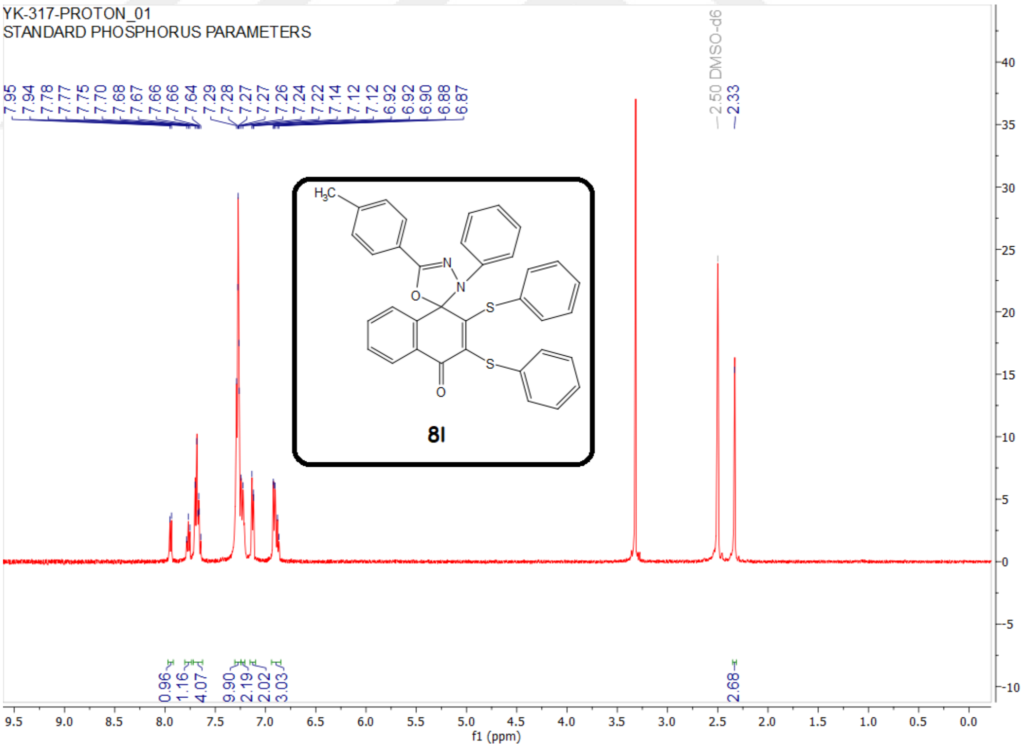


Figure 7.50. ^{1}H NMR spectrum of compound **8l**

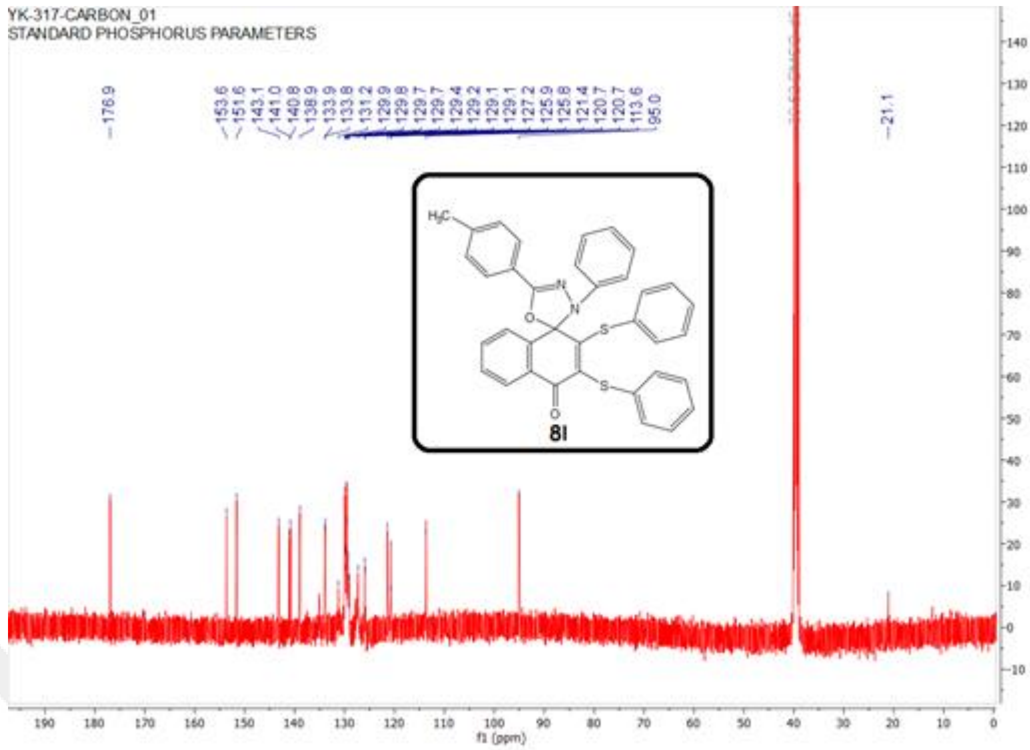


Figure 7.51. ^{13}C NMR spectrum of compound **8l**

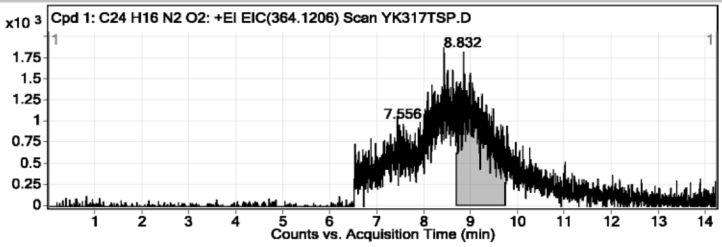
Target Compound Screening Report

Data File	YK317TSP.D	**Sample Name**	
Position	1	**Instrument Name**	GCQTOF
Operator Name		**Acq Method**	ORGANICA_EI_4G_TSP.M
Acquired Time	6/9/2023 10:11:39 AM	**IRM Calibration Status**	Success
DA Method	UA.m	**Comment**	

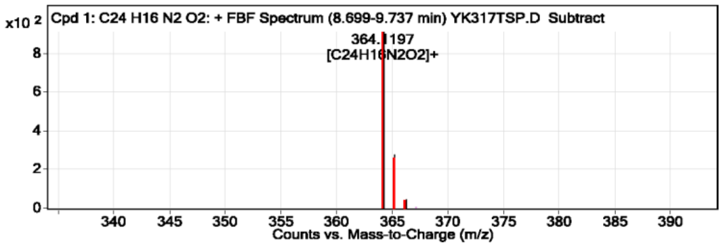
Compound Table

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass Error (ppm)	Obs. m/z	Ret.T	Find Comp. Algorith
C24 H16 N2 O2	364.1212	364.1202	94.15	-2.7	364.1197	8.832	Find By Formula

Tgt Formula	Tgt Mass	Obs. Mass	Tgt Score	Mass error (ppm)	*Obs. m/z*	Find Cpds Algorith
C24 H16 N2 O2	364.1212	364.1202	94.15	-2.7	364.1197	Find By Formula



MS Zoomed Spectrum



MS Zoomed Spectrum

Figure 7.52. HRMS spectrum of compound **8l**