T.R
VAN YUZUNCU YIL UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
CHEMISTRY SCIENCE

SYNTHESIS OF THIENO-DIBENZOTHIOPHENE DERIVATIVES VIA CYCLIZATION REACTIONS

Ph.D. THESIS

PREPARED BY: Muheb A. S. ALGSO
SUPERVISOR : Prof. Dr. Arif KIVRAK

VAN-2018

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This study was supported by TUBİTAK (**115Z020**) and we would like to acknowledge networking contribution by the COST Action CM1407 "Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery".

VAN-2018

ACCEPTANCE AND APPROVAL PAGE

This thesis entitled "**SYNTHESIS OF THIENO-DIBENZOTHIOPHENE DERIVATIVES VIA CYCLIZATION REACTIONS**" presented by Muheb A. S. ALGSO under supervision of Prof. Dr. Arif KIVRAK in the department of Chemistry has been accepted as a Ph.D. thesis according to Legislations of Graduate Higher Education on 04/06/2018 with unanimity of votes of members of jury.

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This thesis has been approved by the committee of The Institute of Natural and Applied Sciences on 06/06/2018 with decision number 2018/28-5

Prof. Dr. Suat ŞENSOY
Director of Institute

KABUL VE ONAY SAYFASI

Kimya Anabilim Dalı'nda Prof. Dr. Arif KIVRAK danışmanlığında, Muhib A. S. ALGSO tarafından sunulan "**TİYENO-DİBENZOTİYOFEN TÜREVLERİNİN HALKALAŞMA TEPKİMELERİ İLE SENTEZİ**" isimli bu çalışma Lisansüstü Eğitim ve Öğretim Yönetmeliği'nin ilgili hükümleri gereğince 04/06/2018 tarihinde aşağıdaki jüri tarafından oy birliği ile başarılı bulunmuş ve doktora tezi olarak kabul edilmiştir.

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Prof. Dr. Nuri ŞENOĞLU
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THESIS STATEMENT

All information presented in the thesis obtained in the frame of ethical behavior and academic rules. In addition all kinds of information that does not belong to me have been cited appropriately in the thesis prepared by the thesis writing rules.

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ABSTRACT

SYNTHESIS OF THIENO-DIBENZOTHIOPHENE DERIVATIVES VIA CYCLIZATION REACTIONS

ALGSO, Muheb A.S.
Ph. D. Thesis, Department of Chemistry
Supervisor: Prof. Dr. Arif KIVRAK
June 2018, 195 Pages

Benzothiophene and derivatives have emerged as central candidates for pharmaceutical applications since they show remarkable analgesic, antiinflammatory, antibacterial antiparasitic, antitussive, hypoglycemic, antitumor and/or anticancer activities. They have also important compounds for material sciences. Many synthetic methods have been employed for the synthesis of this heterocyclic compounds and they have also been isolated from different kinds of plants and used to treat different diseases for many years. On the otherhand, there are a few studies for thieno-dibenzothiophenes which may have critical biological properties. In this study, we developed new methodologies for the synthesis of potentially biologically active thieno-dibenzothiophene derivatives containing fused heteroaromatics. A variety of organic reactions were used for the formation of desired products such as, Sonogashira Coupling Reactions, Electrophilic Cyclization Reactions and Suzuki-Miyaura Coupling reactions. Moreover, all synthesized intermediates and products were characterized by using spectroscopic methodologies.

Key words: Biological activities, Cyclization reactions, Dibenzothiophenes, Thieophenes.

ÖZET

TİYENO-DİBENZOTİYOFEN TÜREVLERİNİN HALKALAŞMA TEPKİMELERİ İLE SENTEZİ

ALGSO, Muheb A.S.
Doktora Tezi, Kimya Anabilim Dalı
Tez Danışmanı: Prof. Dr. Arif KIVRAK
Haziran 2018, 195 Sayfa

Benzotiyofen ve türevleri sahip oldukları analjezik, ateş düşürücü, antibakteriyel, antiparazitik, hipoglisemik, antitümör ve antikanser aktivitelerinden dolayı ilaç uygulamaları için çok büyük öneme sahip olmalarının yanında malzeme bilimi için de oldukça önemlidirler. Bu heterosiklik yapıların sentezi için farklı sentetik metotlar kullanılmakla birlikte bazıları doğal ürün olarak çeşitli bitkilerden de elde edilebilmektedirler. Ancak, bir benzotiyofen türevi olan ve potansiyel olarak biyolojik öneme sahip tiyeno-dibenzotiyofenler hakkında çok az çalışma mevcuttur ve bu türevlerin biyolojik özellikleri hakkında sadece bir kaç çalışma vardır. Bu çalışmada potansiyel biyolojik öneme sahip tiyeno[a]dibenzotiyofen türevlerinin sentezi için yeni ve uygulanabilir metotlar geliştirilmiştir. Farklı sentez yöntemleri hedeflenen moleküllerin eldesi için kullanılmıştır. Bunlardan bazıları Sonogashira Kenetlenme Tepkimesi, elektrofilik halkalaşma tepkimesi ve Suzuki-Miyaura kenetlenme tepkimesidir. Tepkimelerde elde edilen tüm ara ürün ve ürünlerin yapısal karakterizasyonları spektroskobik yöntemler ile kesin olarak belirlenmiştir.

Anahtar Kelimeler: Biyolojik, Dibenzotiyofenler aktiviteler, Halkalaşma tepkimeleri, Tiyofen.

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2018

Muheb A. S. ALGSO

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SYMBOLS AND ABBREVIATIONS

Some symbols and abbreviations used in this study are presented below, along with descriptions.

Symbolss	**Description**
br	broad (spectral)
^{o}C	degree celcius
δ	chemical shift in parts per million
d	doublet (spectral)
g	gram (s)
h	hour (s)
Hz	hertz
J	coupling constant
m	multiplet
mL	milliliter
mmole	millimole
Ph	phenyl
R	alkyl
Ar	aryl
ppm	parts per million (in NMR)
q	quartet (spectral)
r.t.	room temperature
s	singlet (spectral)
t	triplet (spectral)

Abbrevations	Description
DMF	*N*,*N*-Dimethylformamide
TLC	thin-layer chromatography
UV	ultravoilet
TMS	trimethylsilane
THF	tetra-hydrofuran
NMR	nuclear magnetic resonance
Et_3N	triethylamine
HRMS	high resolution mass spectrometry
IR	infrared

1. INTRODUCTION AND LITERATURE REWIEWS

1.1. Heterocyclic Compounds

Organic compounds and their reactions have been used for thousands of years while the science of organic chemistry is less than 200 years old. We live in an age of organic chemistry since there is an excellent relationship between the applications of organic chemistry and the standard of living. Organic chemistry is a wide field which intersects with biology, biochemistry, medicine, pharmacology, polymer technology, agriculture and petroleum engineering (Thomas et al., 1997).

Heterocyclic compounds are organic compounds which have at least one element other than carbon, such as oxygen, nitrogen or sulfur, within a ring skeleton. Heterocyclic compounds are not only found in natural products, such as aflatoxin B1, caffeine, reserpine and biotin (Aldrich et al., 1959) but also obtained synthetically. Heterocyclic compounds are generally classified according to the number of atoms on the ring. Many alkaloids, vitamins, antibiotics and synthetic medicines as well as dyestuffs are heterocyclic compounds. The seven of the top 10 best selling prescription drugs include heterocyclic moieties in their structures, which emphasizes the importance of heterocyclic compounds for human life (Reddy et al., 2004). Therefore, the synthesis of heterocyclic compounds has attracted great attention in organic community for a long time because of their biological activities, properties and applications (Campaigne, 1986).

The most major heterocycle compounds are those containing five or six membered rings and with heteroatoms as nitrogen (N), oxygen (O), or sulfur (S). The best known example and simple are pyridine, pyrrole, furan, and thiophene (Figure 1.1). The molecules of pyridine consist of a ring of six atoms, five carbon atoms and one nitrogen atom. Pyrrole, furan, and thiophene molecules each consist of five-membered rings contain four atoms of carbon and one atom of nitrogen, oxygen, or sulfur, respectively (Berquist et al., 1993).

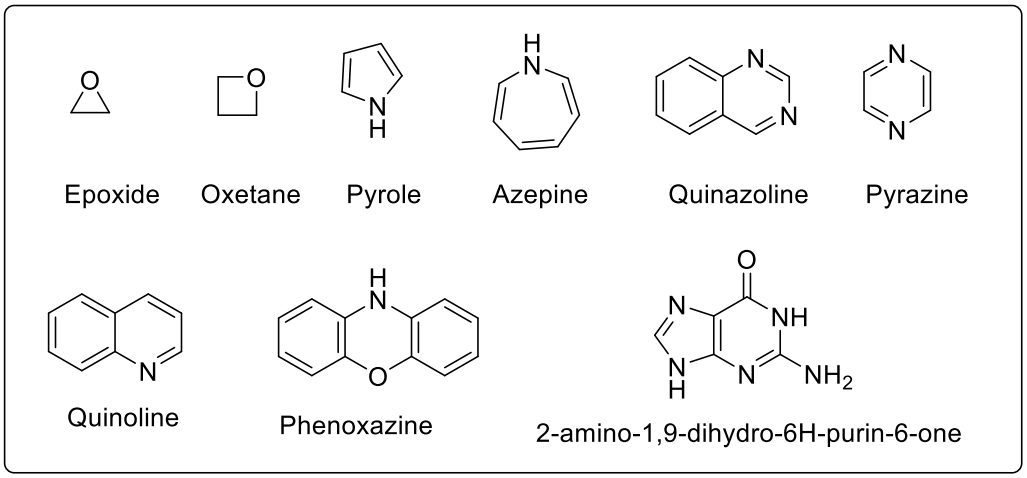


Figure 1.1. Some heterocyclic compounds.

Polyheterocyclic compounds are heterocyclic compounds consist of three cyclic unites or more fused together in one structure. Polyheterocyclic structures can be founded in many natural products. For example, alkaloids are the well known polyheterocyclic molecules due to their unique properties (Arora et al., 2007). Camptothecin (Efferth et al., 2007) is a quinoline alkaloid which inhibits the DNA enzyme topoisomerase, and Reserpine (Baumeister et al., 2003) is an indole alkaloid which has been used for the control of high blood pressure and the treatment of psychotic behavior. Other examples are Ajmaline (Siddiqui et al., 1931) and strychnine (Bonjoch et al., 2000), they are indole alkaloids used as antiarrhythmic agent and extremely toxic pesticide (Figure 1.2).

Purine derivatives are simple fused ring heterocycle compounds constitute an essential important and numerous family of natural products. Adenine and guanine are two of the integral bases that are essential components of DNA Structure. The structures of these compounds are shown in the Figure 1.3. Moreover, Xanthine and uric acid are member of purine families, and they are obtained from the metabolic oxidation of purines. Uric acid is normally excreted in the urine, an surplus serum accumulation of uric acid lead to an arthritic condition called gout (Rosemeyer et al., 2004).

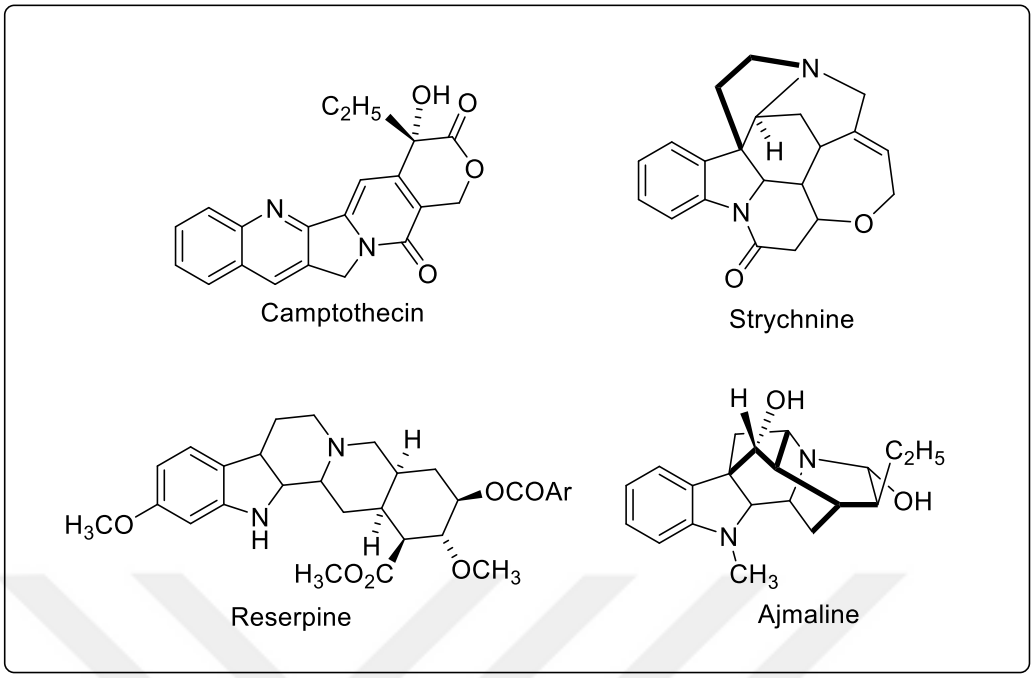


Figure 1.2. Some polyheterocyclic compounds.

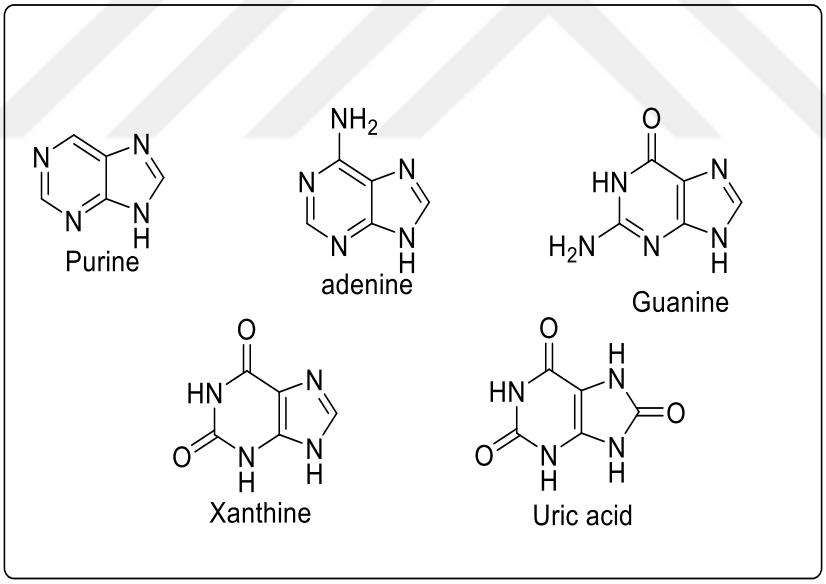


Figure 1.3. Purine derivatives.

Sulfur containing heterocyclic compounds are found in naturally, but less than their nitrogen and oxygen analogs (Cremlyn, 1996). Biotin and Thiamine are two members of the B-vitamin complex that is shown in Figure 1.4 (Winklera et al., 2005).

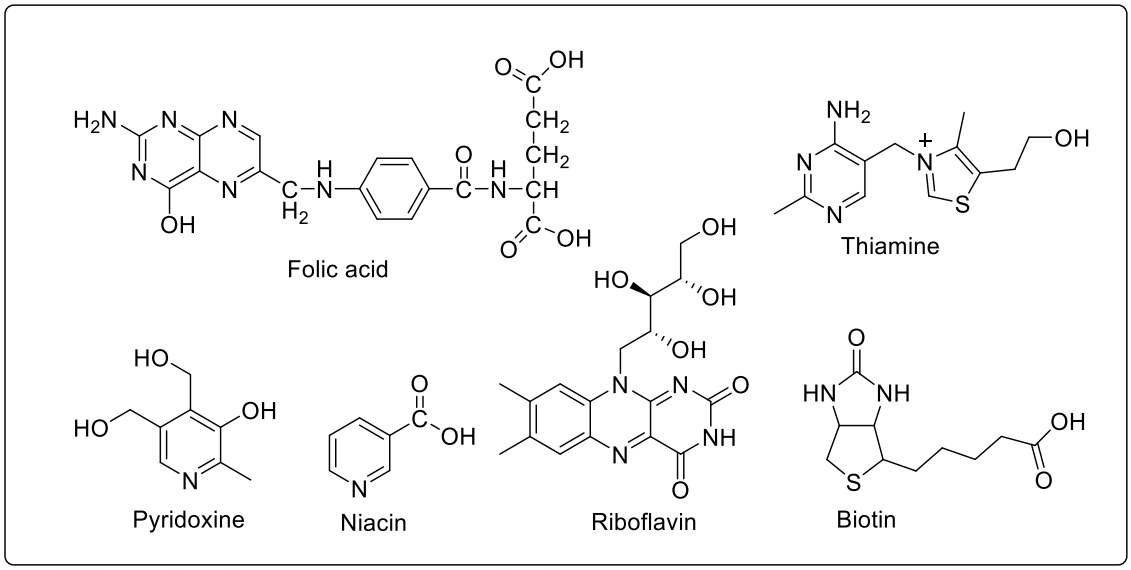


Figure 1.4. B-vitamin complex.

1.2. Thiophene, Benzothiophene, and Dibenzothiophene Compounds

1.2.1. Thiophenes

Thiophene and its derivatives are very important members of heterocyclic compounds because of critical properties. Thiophene is taken from the word theion, the Greek word for sulfur, and another Greek word phaino which means shinning. Thiophene structure can be found in a variety of natural products. Thiophene derivatives have been very well known for their therapeutic applications. Therefore, they have been used for the treatment of different diseases for hundred years.

Thiophene is five-membered ring with one sulfur atom (Figure 1.5). Thiophenes are very important classes of heterocyclic compounds that have possess interesting biological properties as well as interesting application as building blocks and reagents in organic synthesis. The stability of thiophene plays an important role in increasing and preparing different types for experimentation in the medical and pharmaceutical fields (Ward, 1944).

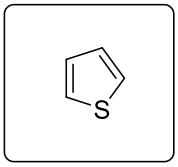


Figure 1.5. Thiophene structure.

Thiophene derivatives have been used as chemotherapeutic agent for the treatment of cancer (Raghav et al., 2001). Moreover, thiophene moiety carrying compounds exhibit various activities like for example 1-[1- (2, 5- dimethylthiophen- 3- yl) ethyl]- 1-hydroxyurea (Figure 1.6, compound 2) shows antiinflammatory activity, the maleate salt of 1-(2,5-dimethylthiophen- 3- yl)- 3-(5- methyl- 1 Himidazol- 4- yl) propan-1-one (Figure 1.6, compound 3) act as serotonin antagonists, and used in the treatment of Alzheimer's disease. The latter has also been employed in the formulation of inks for computer printers by the Xerox Group and as a raw material for herbicides/ pesticides. 2-butylthiophene (Figure 1.6, compound 4) has been employed as a raw material in the synthesis of anticancer agents and 2-octylthiophene (Figure 1.6, compound 5) has been employed in the synthesis of anti-atherosclerotic agents such as compound 6 (Figure 1.6, compound 1) (Jha et al., 2012).

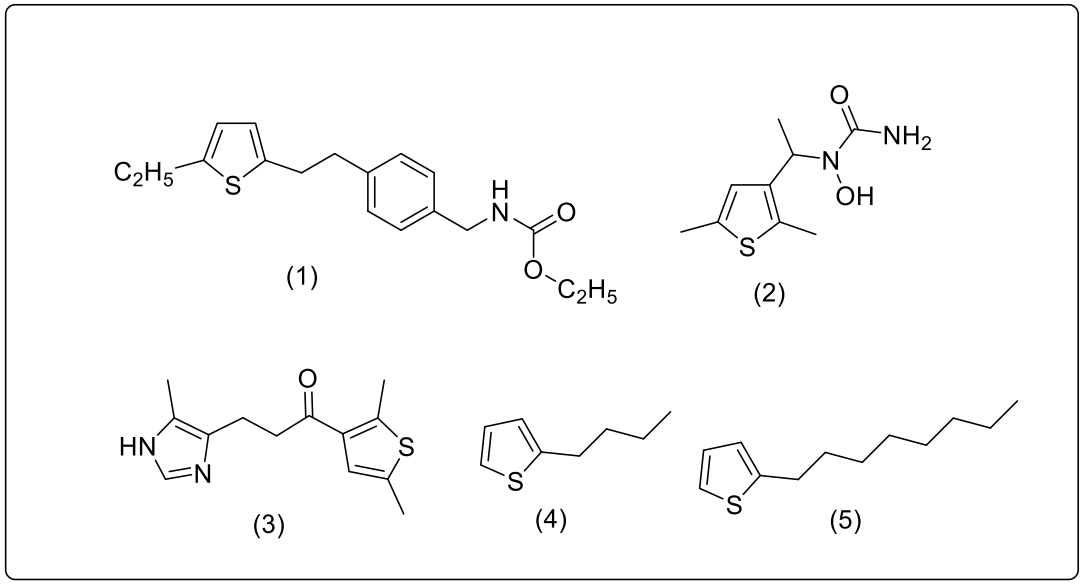


Figure 1.6. Some biologically active thiophene derivatives.

Thiophene derivatives are also very important for material sciences. They have been used in organic solar cells, OFETs, sensors, etc. Moreover, they have unique properties for optoelectronic applications such as electrochromic devices. In Figure 1.7, there are some examples of the thiophene using in material chemistry. Terthienyl as three thiophene units bounded together (thiophene trimer) found in the roots of marigolds and it provides nemicidal activities. In addition, UV irradiation of terthienyl can produces a general phototoxicity for many organisms. Thiophene derivatives have high conductivity, so they are good monomer for the preparation of corresponding polymers.

Polymers including of thiophene display interesting electromagnetic properties, and presentation of promise as organic metal such as conductors and photovoltaic materials. Recently, it was reported that tetracyanoquinodimethane and tetrathiofulvalene are the highest charge transfer properties (Smeets et al., 2003) as a polymer.

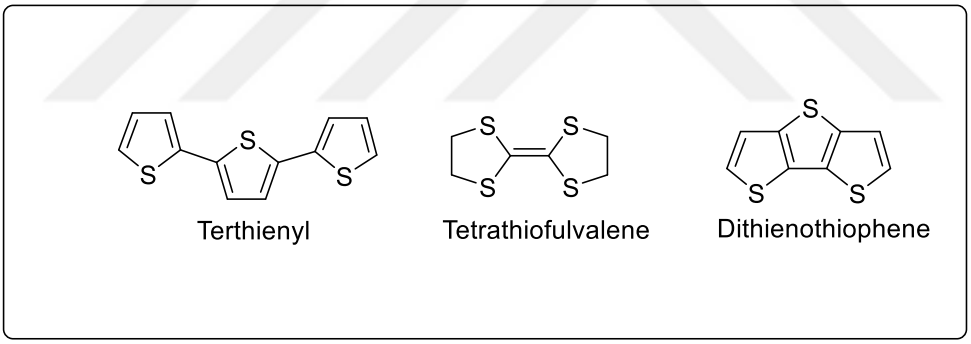


Figure 1.7. Some thiophene structures.

1.2.2. Benzothiophenes

Benzothiophene are to be an important role in the medicinal chemistry and material chemistry. They have been used as antibacterial, antifungal and antitubercular agents. Moreover, benzothiophene and it is derivatives have aromaticity makes are relatively stable and have wide range of applicability in the field of material chemistry (Cava et al., 1975).

Benzothiophene finds use in researches as a starting material for large synthesis, usually for the bioactive structures synthesis. It is found within the chemical structures of pharmaceutical drugs such as raloxifene 1 (Seeman et al., 2001), zileuton 2 (Lu et al., 2003), and sertaconazole 3 (Imming et al., 2006) (Figure 1.8), Especially, benzothiophene derivatives with substituted group as one of the substituents on the five membered rings have large medicinal value due to their promising pharmacological properties. Extensive research is now in course for other potential applications of this drug, namely for the treatment of Alzheimer's disease. In the same series a number of 3-(4-pyridinyl)amino benzothiophenes, which are selective serotonine re-uptake inhibitors, were prepared and may be useful in the treatment of central nervous system disorders, including obsessive compulsive disorders.

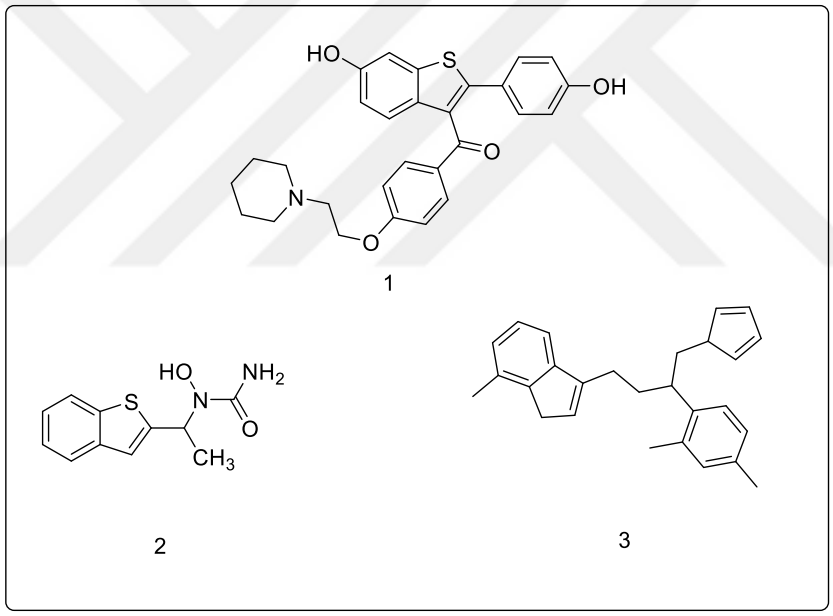


Figure 1.8. The structures of Raloxifene 1, Zileton 2, Sertaconazole 3.

Generally, benzothiophenes are prepared from intramolecular cyclization and from Claisen Rearrangement reactions (figure1.9). For example, benzothiophenes were regioselectively obtained from the intramolecular cyclization reaction of *o*-alkinylthioanisoles (figure 1.10). Recently, Mohanakrishnan *et al* was reported a novel method for the synthesis of benzothiophene and dibenzothiophene starting from thiophenes and 2,5-dimethoxy-THF by using zinc catalyst.

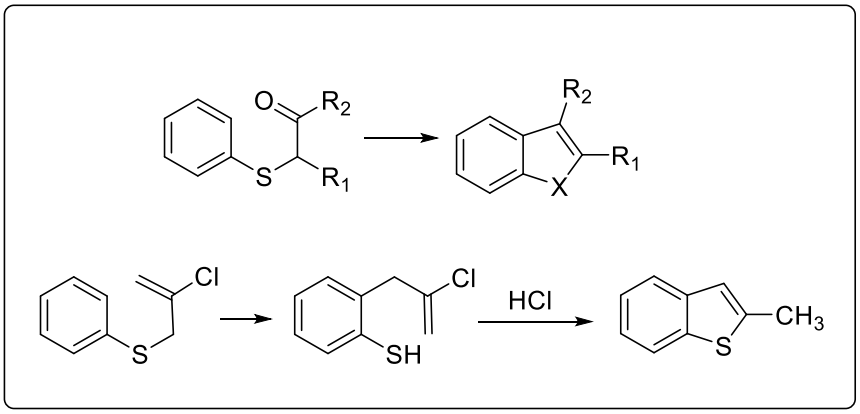


Figure 1.9. Synthesis of benzothiophenes via intramolecular cyclization reactions.

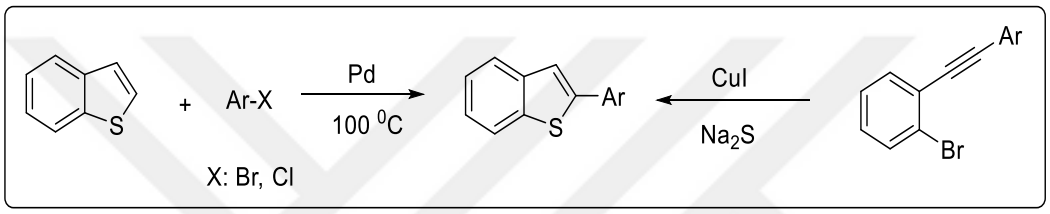


Figure 1.10. Synthesis of benzothiophenes via electophilic aromatic substitution reactions.

1.2.3. Dibenzothiophenes

Dibenzothiophenes, mostly isolated from nature as a side-product of petroleum, have been important role in material science. They were highly used in solar batteries, OLEDs, OFETs, and electrochromic materials. In addition, they have been used for biological applications (Figure 1.11). For example, dibenzothiophenes were easily oxidized to form the biologically important dibenzothiophene-sulfons by using various metal and organic catalysts. Last studies completed in recent years, dibenzothiophene containing molecules were found as novel inhibitors for some proteins found in DNA structure, and they have a potential for the treatment of cancer. Therefore, a facile and efficient synthetic approach to various derivatives of this valuable compound is in great demand. There are several reliable procedures for the synthesis of dibenzothiophenes, but most of them require the use of sulfur sources that have an unpleasant odor, such as P4S10, and the substrates used in the transformation are limited to a peculiar activated substrate that partakes in either an aromatic nucleophilic substitution (SNAr) or an

aromatic electrophilic substitution (SEAr) reaction (Figure 1.12) (Cullinane et al., 1936).

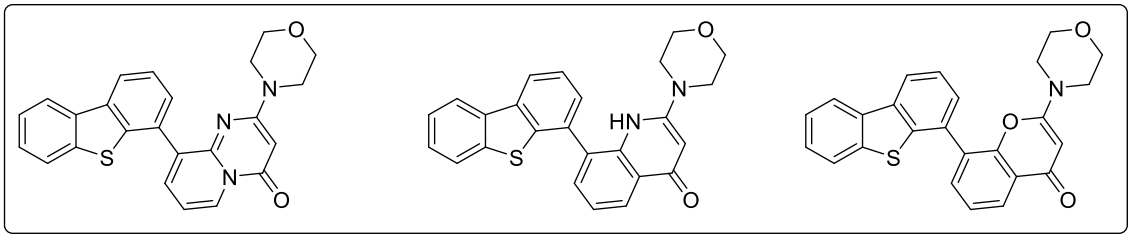


Figure 1.11. Biologically important dibenzothiophene derivatives.

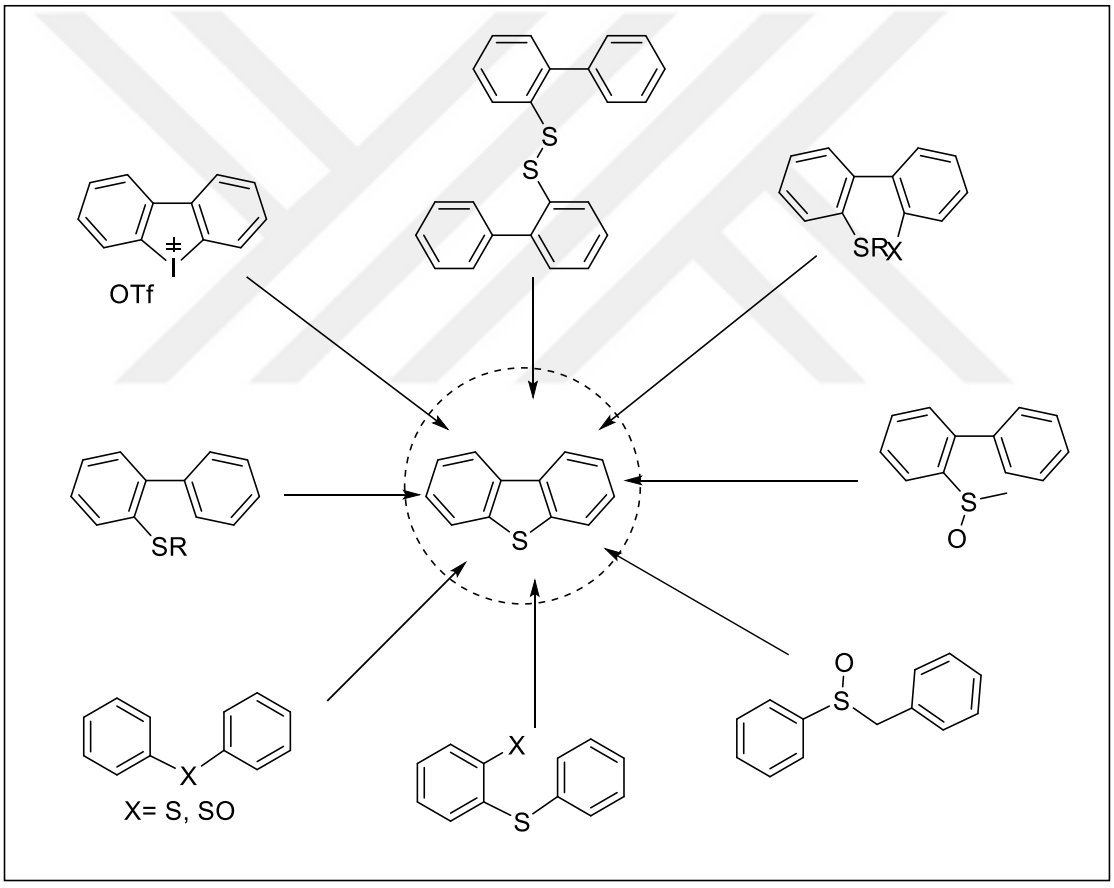


Figure 1.12**.** Various approaches to the preparation of dibenzothiophene.

1.3. Thieno-dibenzothiophenes

In literature, there are many synthetic methodologies for the preparation of benzothiophene and dibenzothiophene derivatives, but very limited synthetic route for the synthesis of thieno-dibenzothiophenes (Figure 1.13). Thieno-dibenzothiophenes are polyheteroaromatics with two sulfur atom on their structures. There are two possible isomers named thieno[2,3-a]dibenzothiophene and thieno[3,2-a]dibenzothiophene (Figure 1.13).

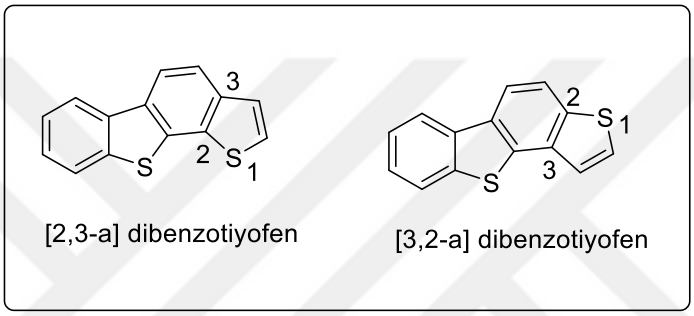


Figure 1.13. Some thieno-dibenzothiophene derivatives.

Firstly, Kudo et al (Kudo et al., 1984) used special alkene (structure A and B) as a starting compound. Thieno[2,3-a]dibenzothiophene (compound C) and thieno[3,2-a]dibenzothiophene (compound D) were obtained in 21% yields of compound C and 80% of compound D from the intramolecular cyclization reaction (Figure 1.14).

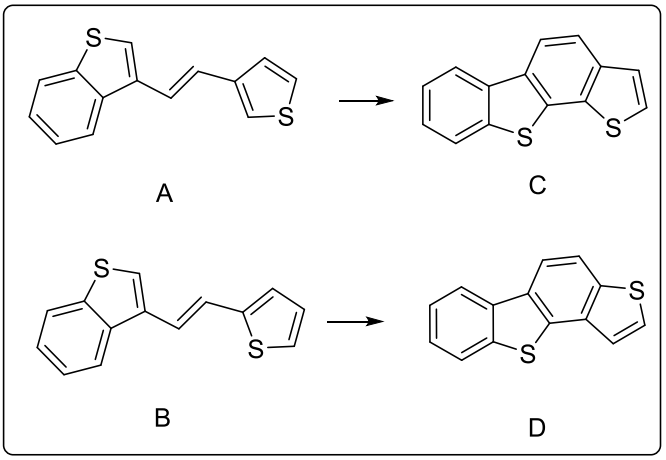


Figure 1. 14. Some reactions to prepare thieno[2,3-a]dibenzothiophene and thieno[3,2-a]dibenzothiophene.

The other method for the synthesis of thieno-dibenzothiophenes was found by Sankaar et all. (Sankar et al., 2017). They used 2-bromo-3- (phenylsulfonylmethyl) benzo[b]thiophene as a starting compound. Firstly, strong base activated the reaction to removing sulfonyl groups, then palladium catalyzed ring closing reaction gave the thieno-dibenzothiophene (F) at higher temperature. They obtained only one isomer in 62% yields. (Figure 1.15).

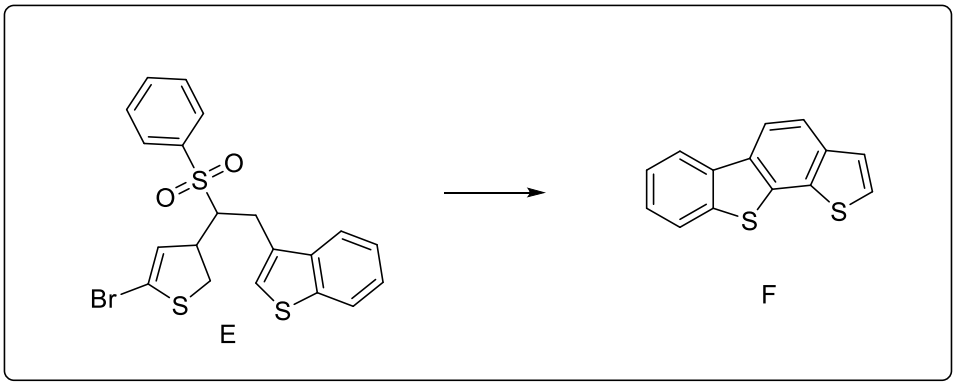


Figure 1.15. Reaction to preparation of thieno[2,3-a]dibenzothiopehen.

Yifan reported synthesis of heterotetracenes based on a platinum- and gold-catalyzed cyclization–alkynylation domino process using 3-ethynyl benzothiophenes (Yifan et al., 2017). They isolated thioeno[2,3-a]dibenzothiophenes and thieno[3,2-a]dibenzothiophene in 79% and 64% yields, respectively (Figure 1.16).

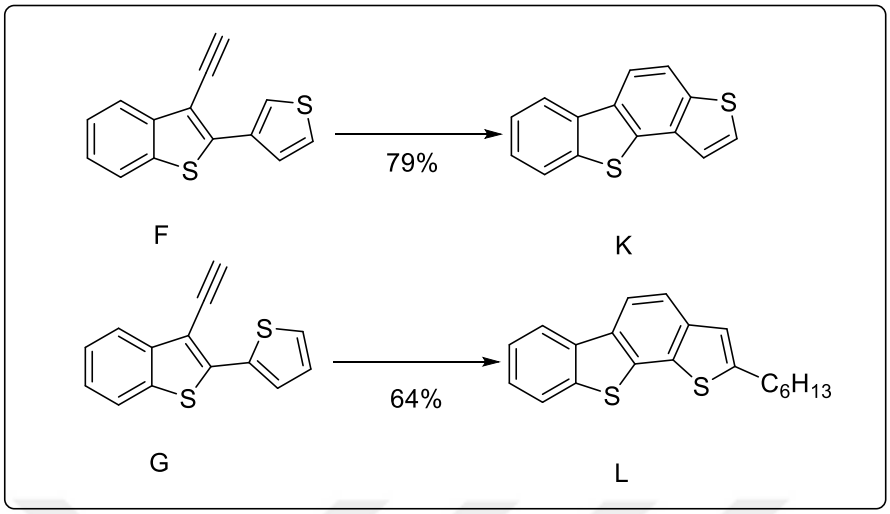


Figure 1.16. Some reactions to prepare thieno[2,3-a]dibenzothiophene and thieno[3,2-a]dibenzothiophene.

Dhayalan et al used annulation reaction between compound A and benzothiophene for the synthesis of thieno[b]dibenzothiopenes (Dhayalan et al., 2012). The reaction between benzothiophenes and compound A gave the two isomers mixtures (compounds B and C) with 54% yield in the presence of zinc catalyst (Figure 1.17).

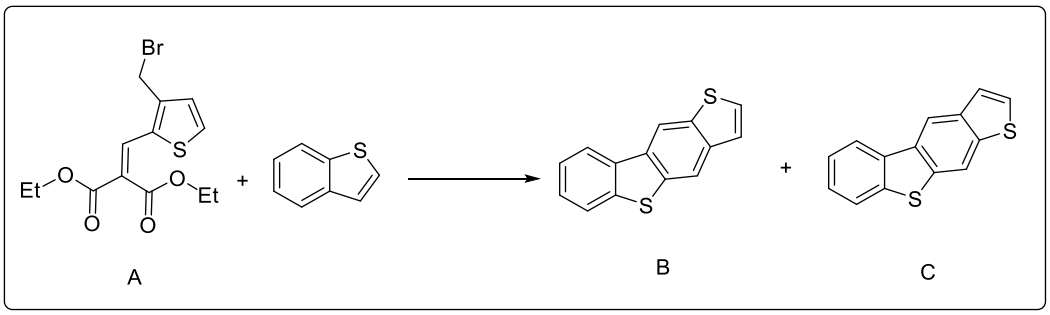


Figure 1.17. Annulation reaction to prepare of thieno[b]dibenzothiopenes.

1.4. Palladium Catalyzed Coupling Reactions

Palladium-catalyzed coupling reactions comprise a family of cross-coupling reactions that employ palladium complexes as catalysts. In 2010, the Nobel Prize in Chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their

work on palladium-catalyzed cross couplings in organic synthesis (Figure 1.18). On the other hand, there are a variety of coupling reaction have been used for the formation of organic compounds.

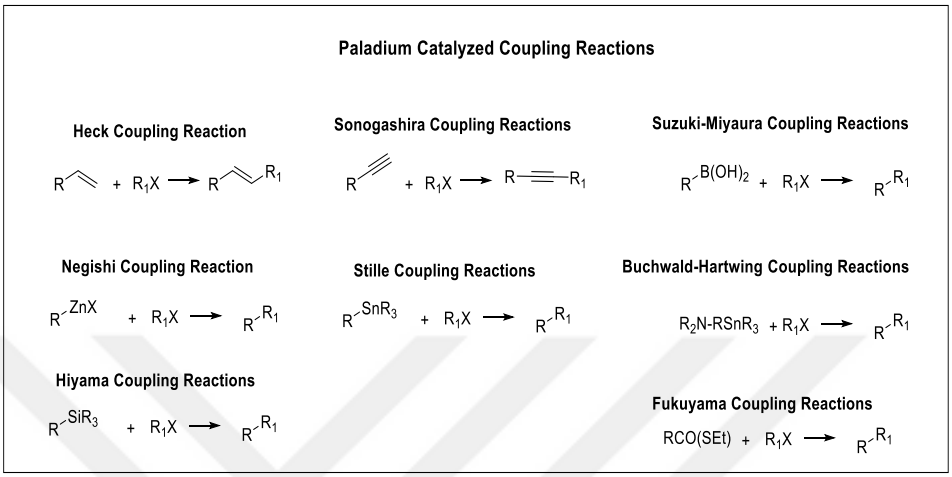


Figure 1.18. Palladium-catalyzed coupling reactions.

1.4.1. Sonogashira Coupling Reactions.

A modern and very important reaction in organic chemistry is the Sonogashira reaction discovered by Sonogashira in 1975. Sonogashira reaction is considered as a one to the family of palladium-catalyzed carbon–carbon coupling reactions, such as Heck reaction, Suzuki reaction, and Stille coupling reaction. The Sonogashira reaction is palladium-catalyzed cross-coupling of a vinyl or aryl halide with terminal alkyne by using copper (I) iodide as a co-catalyst (Figure 1.19), which converts the alkyne into a copper acetylide (*Sonogashira*, 2002). Sonogashira Coupling reactions need simple reaction conditions such as lower temperature, shorter reaction time. Moreover, Sonogashira Coupling reactions give the high yields and regioselectivity. The Sonogashira reactions are used in the synthesis of various organic compounds. For example, they are used for the synthesis of natural products, novel molecules for optoelectronic devices. We can see mechanism of Sonogashira coupling reaxtion at Figure 1.20.

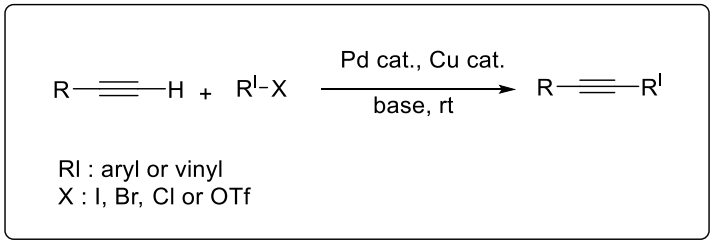


Figure 1.19. Sonogashira Coupling Reaction.

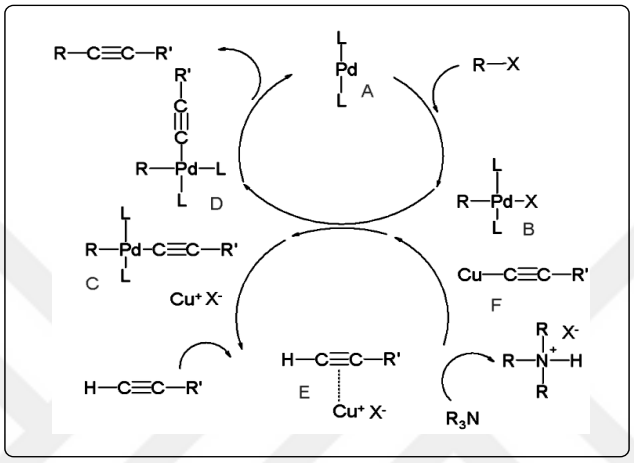


Figure 1.20. Mechanism of Sonogashira coupling reaction.

1.4.2. Heck reactions

The Heck reaction has been used in more than 100 different syntheses of natural products and biologically active compounds. The Heck reaction has also been used as an important carbon-carbon bond-forming step in the synthesis of other complex organic molecules such as steroids (Chang et al., 1990), strychnine (Rawal et al., 1994), and the diterpenoid scopadulcic acid B31. Palladium catalyzed Heck reactions need to alkene and halo-aryl compounds (Figure 1.21). They form the new C-C bonds which may be very important for the designing biologically active organic molecules. Moreover, alkene moieties have also critical roles for material science due to conductivity. Many researchers used Heck coupling reactions for the synthesis of new materials. The reaction mechanism (Figure 1.22) represented by the catalytic cycle for the Heck reaction involves a series of transformations around the palladium catalyst. The palladium(0) compound required in this cycle is generally prepared in situ from a palladium(II) precursor (Ozawa et al., 1992).

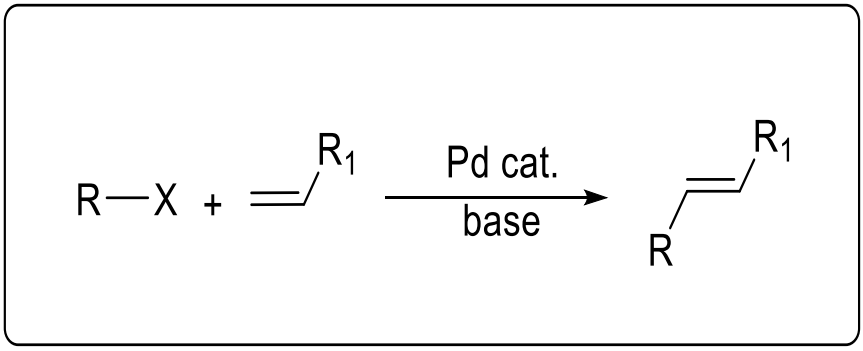


Figure 1.21. Examples of the use of the Heck reaction in natural product synthesis.

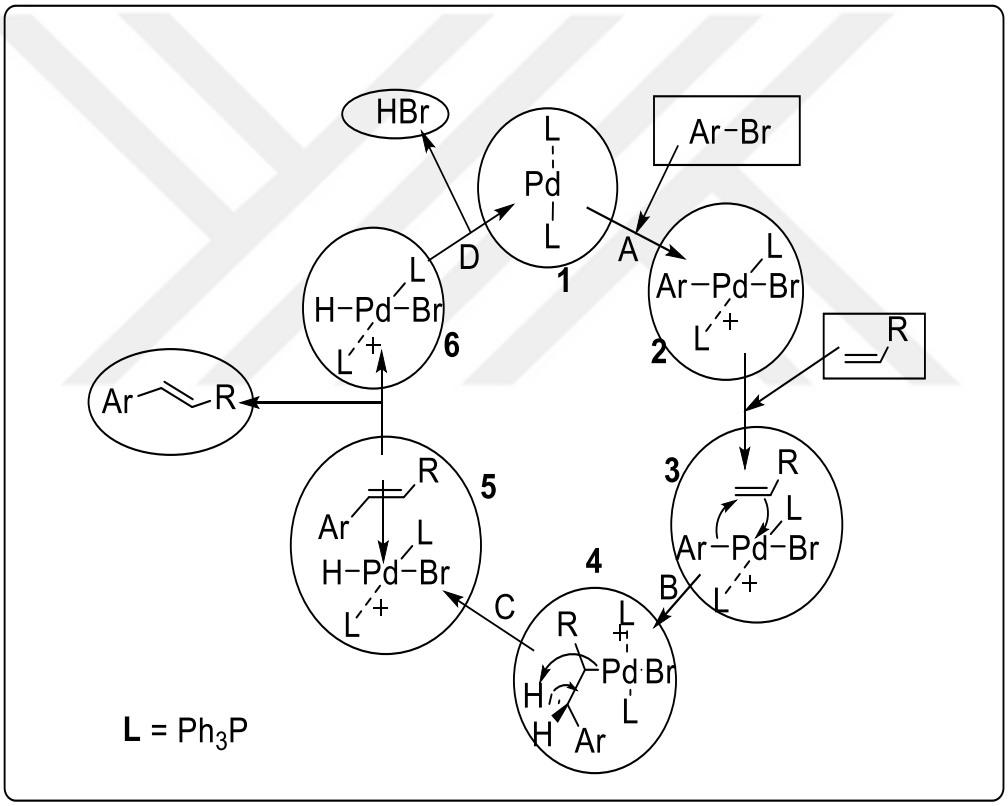


Figure 1.22. Heck reaction mechanism.

1.4.3. Negishi Coupling Reactions

The Negishi coupling is a widely employed transition metal catalyzed cross-coupling reaction. The reaction couples organic halides or triflates with organo zinc compounds, forming carbon-carbon bonds (C-C) in the reactions. A palladium (0)

species is generally utilized as the metal catalyst (Figure 1.23), though nickel is sometimes used (King et al., 1977). Generally, the leaving group X is chloride, bromide, or iodide, but triflate and acetyloxy groups are feasible as well. Chloride usually leads to slow reactions. They can be applied a variety of organic molecules including alkenyl, aryl, allyl, alkynyl. Triphenylphosphine.

The Negishi have also been frequently employed in natural product synthesis. Pumiliotoxin A is a toxic alkaloid found in the skin of frogs from the Dendrobatidae family that the frog uses for its defence. The total synthesis of pumiliotoxin A was performed by using Negishi coupling in one of the key step (Figure 1.24) (Hirashima et al., 1999).

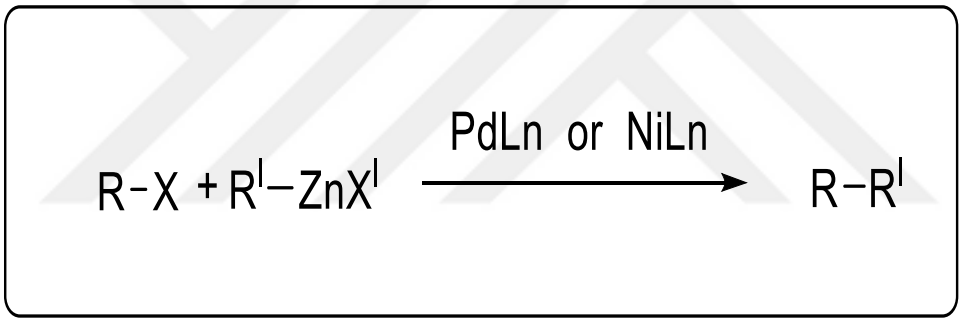


Figure 1.23. Negishi Coupling Reactions.

The reaction mechanism (Figure 1.25) is thought to proceed via a standard Pd catalyzed cross-coupling pathway, starting with a Pd(0) species, which is oxidized to Pd(II) in an oxidative addition step involving the organohalide species. This step proceeds with aryl, vinyl, alkynyl, and acyl halides, acetates, or triflates, with substrates following standard oxidative additionrelative rates (I>OTf>Br>>Cl) (Kurti et al., 2005).

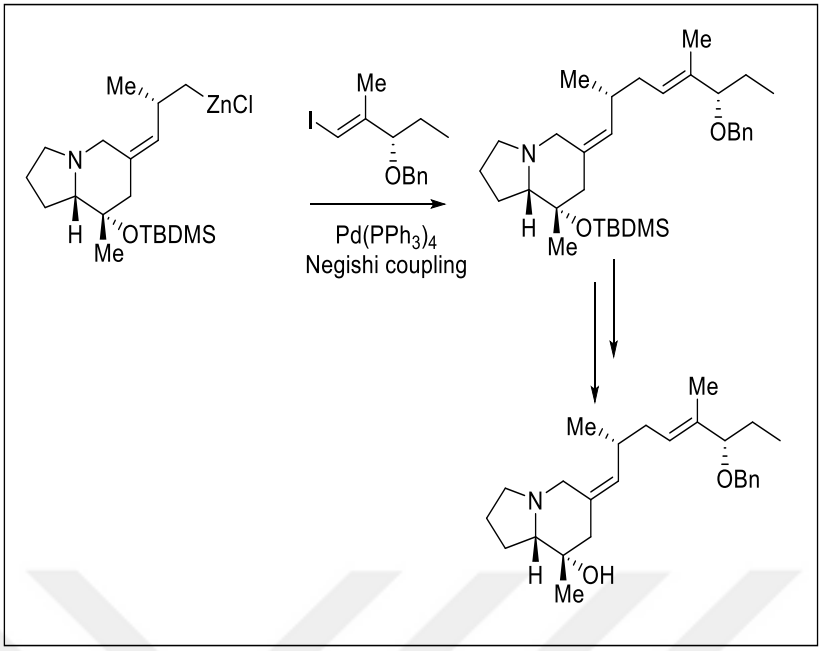


Figure 1.24. synthesis of Pumiliotoxin A.

1.4.4. Suzuki-Miyaura Coupling Reactions

The Suzuki reaction is an organic reaction, classified as a coupling reaction, where the coupling partners are boronic acids and an organo halide which catalyzed by a palladium(0) complex (Miyaura et al., 1979). The general scheme for the Suzuki reaction is shown below (Figure 1.26) where a carbon-carbon single bond is formed by coupling an organoboron species (R_1-BY_2) with a halide (R_2-X) in the presence of a palladium catalyst and a base.

1.5. Electrophilic Cyclization Reactions

Among known synthetic methodologies transition-metal-catalyzed annulations reactions are a direct way of synthesizing substituted heterocycles from acyclic precursors. However, the use of expensive transition metals and harsher reaction conditions, and intolerance to several functionalities limits the scope of these methodologies. In past decade there has been an impressive increase in the reports of heterocyclic synthesis, involving cyclization of an alkyne onto a tethered nucleophilic carbon or heteroatom with the help of an electrophile. Cyclization involving C, O, N, S and Se nucleophiles are well studied. The most commonly used electrophiles for these

cyclization reactions are I_2, ICl, $IPyBF_4$, Br_2, NBS, and PhSeBr. These cyclization reactions are effected by nucleophilicity, polarizability of the C-C triple bond, geometrical orientation of the functional groups, and the nature of the electrophile.

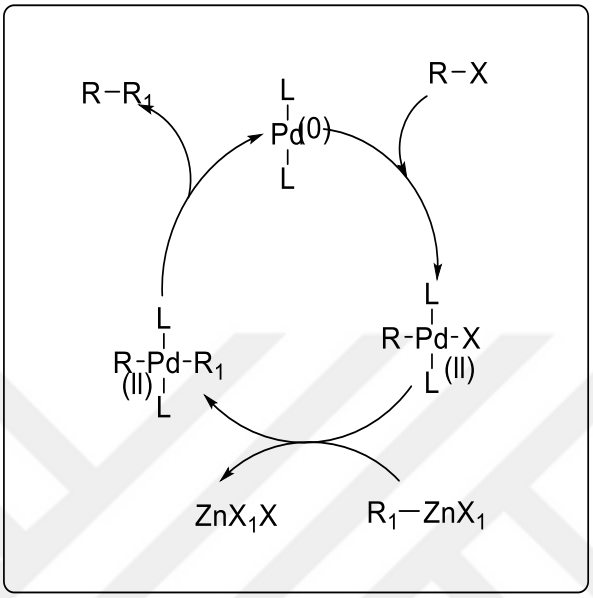


Figure 1.25. Negishi coupling reaction mechanism.

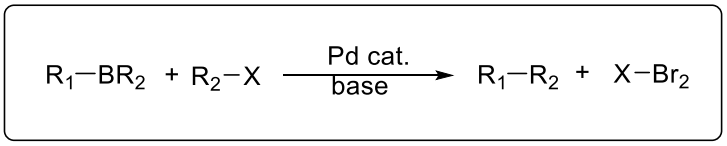


Figure 1.26. Suzuki-Miyaura Coupling Reactions.

In general, these electrophilic cyclization reactions are very efficient, afford clean reactions, proceed under very mild reaction conditions in short reaction times, and tolerate almost all important functional groups. Furthermore, the iodine-containing products can be further elaborated to a wide range of functionally-substituted derivatives using subsequent palladium-catalyzed processes. These reactions are generally believed to proceed by a stepwise mechanism involving electrophilic activation of the alkyne carbon-carbon triple bond, intramolecular nucleophilic attack on the cationic intermediate, and subsequent dealkylation (Figure 1.27).

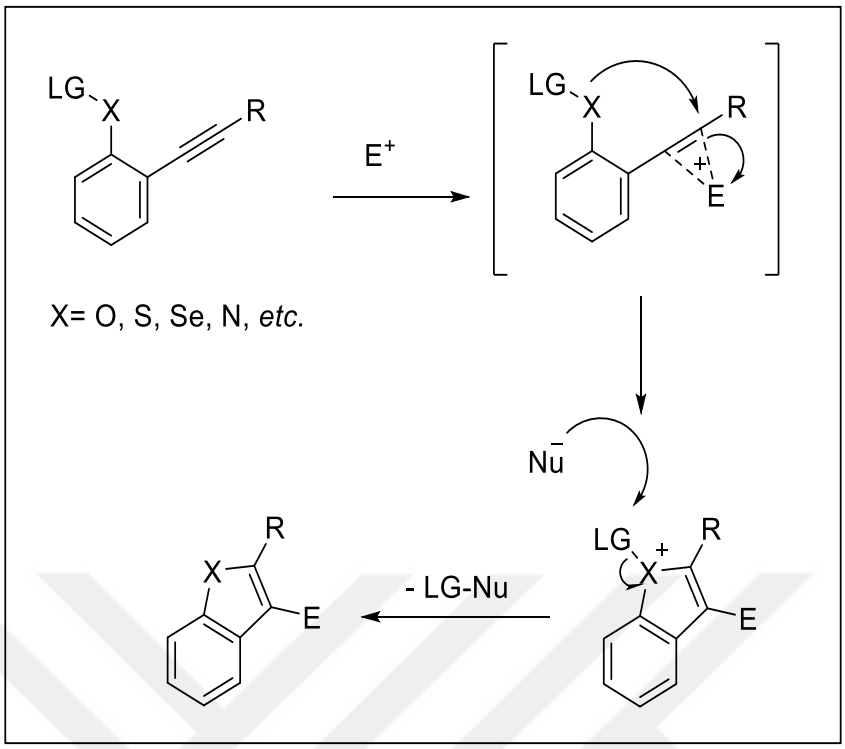


Figure 1.27. Electrophilic cyclization reaction mechanism.

A wide range of carbocycles and heterocycles have been prepared by the electrophilic cyclization of functionally-substituted alkynes (Larock, 2005) and by transition metal-catalyzed annulations (Skouta et al., 2007). Recently, we and others have reported that the electrophilic cyclization of alkynes using halogen, sulfur and selenium electrophiles can be a very powerful tool for the preparation of a wide variety of interesting carbocyclic and heterocyclic compounds (figure 1.28, and figure 1.29), including benzofurans (Arcadi et al., 1999, Yue et al., 2005, Yue et al., 2005), furans (Sniady et al., 2005, Yao et al., 2005, Liu et al., 2005), benzothiophenes (Larock et al., 2001, Yue et al., 2002, Hessian et al., 2003), thiophenes (Flynn et al., 2001), benzopyrans (Worlik et al., 2007), benzoselenophenes (Kesharwani et al., 2006, Bui et al., 2006), selenophenes (Alves et al., 2007), naphthols (Zhang et al., 2006), indoles (Yue et al., 2004, Barluenga et al., 2003), quinolines (Zhang et al., 2005), isoquinolines (Huang et al., 2002, Fisher et al., 2007), α-pyrones (Yao et alo., 2003), isocoumarins (Yao et al., 2003).

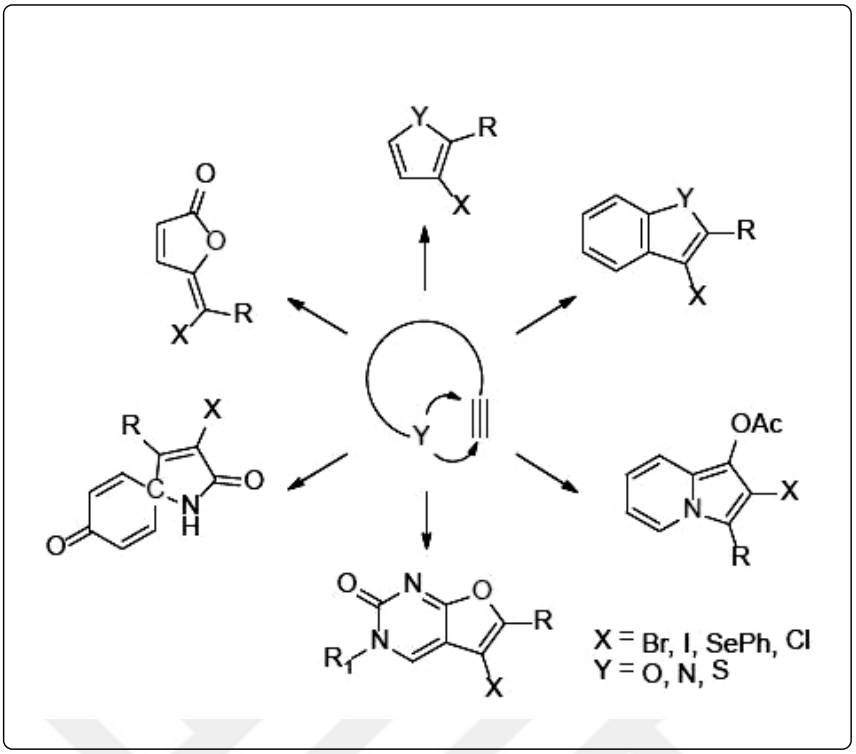


Figure 1.28. Examples of heterocycles formed via 5-endo- and 5-exo-dig cyclizations.

1,2,4-oxadiazoles (Kivrak et al., 2014, Zora et al., 2014), isochromenes (Barluenga et al., 2003, Yue et al., 2006), isoindolinones (Yao et al., 2005), naphthalenes (Barluenga et al., 2003), polycyclic aromatics (Yao et al., 2004, Yao et al., 2005), isoxazoles (Waldo et al., 2005, Waldo et al., 2007), dihydrobenzisoxazoles (Kivrak et al., 2010), chromones (Zhou et al., 2006, Likhar et al., 2008), bicyclic β-lactams (Ren et al., 1998), cyclic carbonates (Marshall et al., 1999), pyrazoles (Zora et al., 2011), pyrroles (Knight et al., 1998, Just et al., 2008), furanones (Crone et al., 2007, Just et al., 2008), *etc*.

Recently, it was reported that iodine mediated cascade cyclization (Figure 1.30) of thioanisole-substituted aryldiynes to form the iodo-substituted benzo[*b*]naphthothiophenes. These electrophilic cyclization reactions are exceptionally effective, afford clean responses reactions, proceed under very mild reaction conditions in brief reaction times, and endure almost all important functional groups (Ferrara et al., 2012), (Chen et al., 2014).

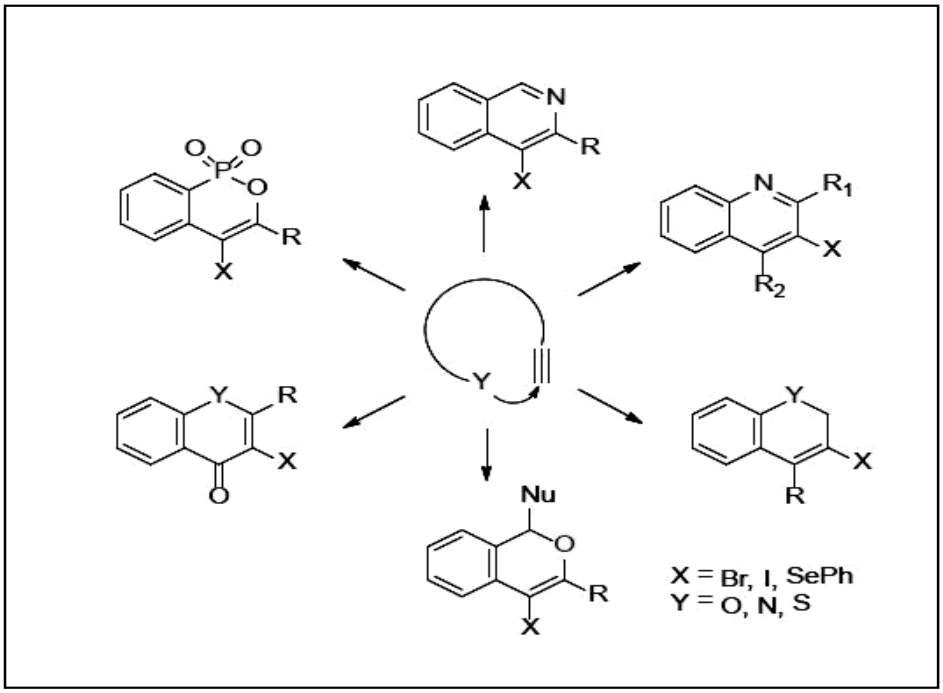


Figure 1.29. Examples of heterocycles formed via 6-endo-dig cyclizations.

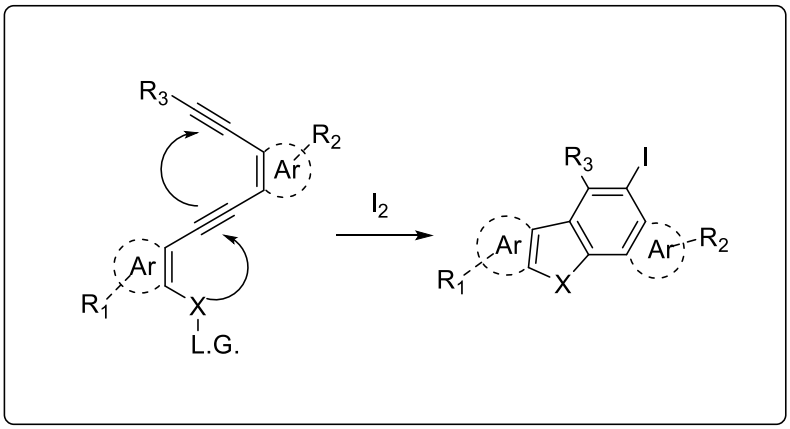


Figure 1.30. Cascade cyclization of methylthioaryl substituted aryldiynes with iodine.

1.6. The Aim of Study

In the present study, we investigated electrophilic cyclization of dialkynylic thiophenes compounds for the synthesis of thieno[a]dibenzothiophene isomers. Firstly, dialkynyl structures were synthesized as a starting molecules by using coupling

reactions. Then, iodide-catalyzed electrophilic cyclization reactions gave the our desired isomer in a moderate to high yields (Figure 1.31).

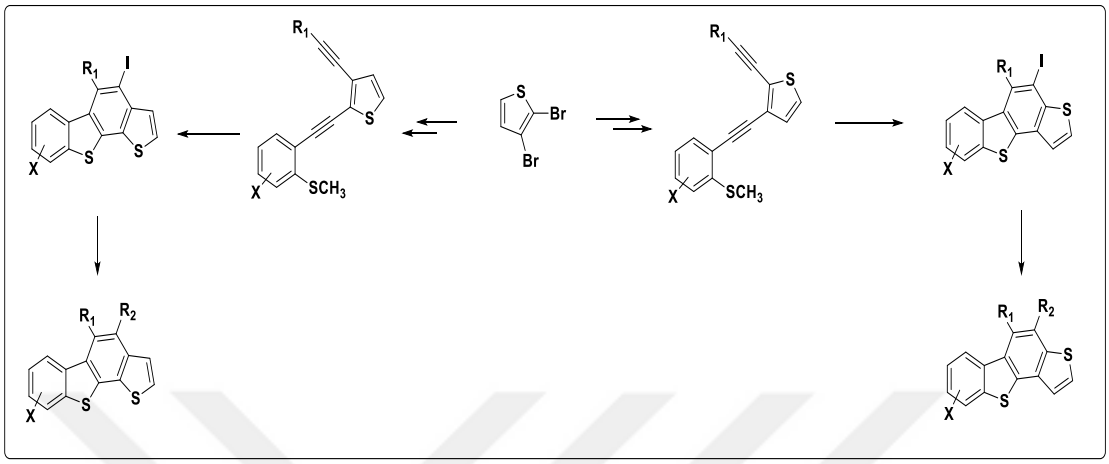


Figure 1.31. Synthesis of thieno-dibenzothiophene derivatives by using electrophilic cyclization reactions

2. METARIAL AND METHODS

2.1. Methods and apparatuses

The design, synthesis, and biological properties of novel thieno-dibenzothiophene derivatives were studied. The structures of the synthesized molecules were determined by ^{1}H and ^{13}C-NMR spectroscopy. ^{1}H and ^{13}C-NMR spectra were recorded on an Agilent NMR (400 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) were reported in hertz (Hz). In addition, spin multiplicities were presented by the following symbols: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). ^{13}C-NMR information was given in parentheses as C, CH, CH_2, and CH_3. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230-400 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel plates. The relative proportions of solvents in chromatography solvent mixtures referred to volume to volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in experiments were distilled for purity. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in an oven prior to use.

2.2. Synthesis of Compounds

2.2.1. Synthesis of thieno[2,3-a]dibenzothiophene derivatives

2.2.1.1. ((3-bromothiophen-2-yl)ethynyl)trimethylsilane (MH1):

To a solution of 2,3-dibromothiophene (0.52 mL, 4.6 mmol) in Et_3N (6 mL) were successively added CuI (54 mg, 0.28 mmol), $PdCl_2(PPh_3)_2$ (0.1 g, 0.15 mmol), and TMS−acetylene (0.76 mL, 5.5 mmol) at room temperature under argon. The mixture was stirred at 80 °C for 16 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel with hexane−EtOAc (400:1) to afford MH1

(65% yield) as an red oil (Figure 2. 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J_{AB}= 5.36 Hz, 1H), 6.94 (d, J_{AB}= 5.4 Hz, 1H), 0.30 (s, 9H) (Figure 2.2), ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1, 127.2, 116.9, 103.6, 95.9, 85.5, 0.05, IR (ATR) ν_{max} (cm^{-1}): 3107.5, 2980.5, 2890.2, 2359.7, 2342.4, 2148.2 (C≡C), 1249.1 (Si-CH_3), 837.6, 758.4, 707.4(Figure 2.3).

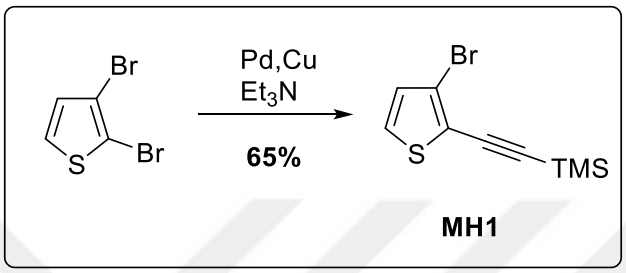


Figure 2.1. Synthesis of MH1 compound

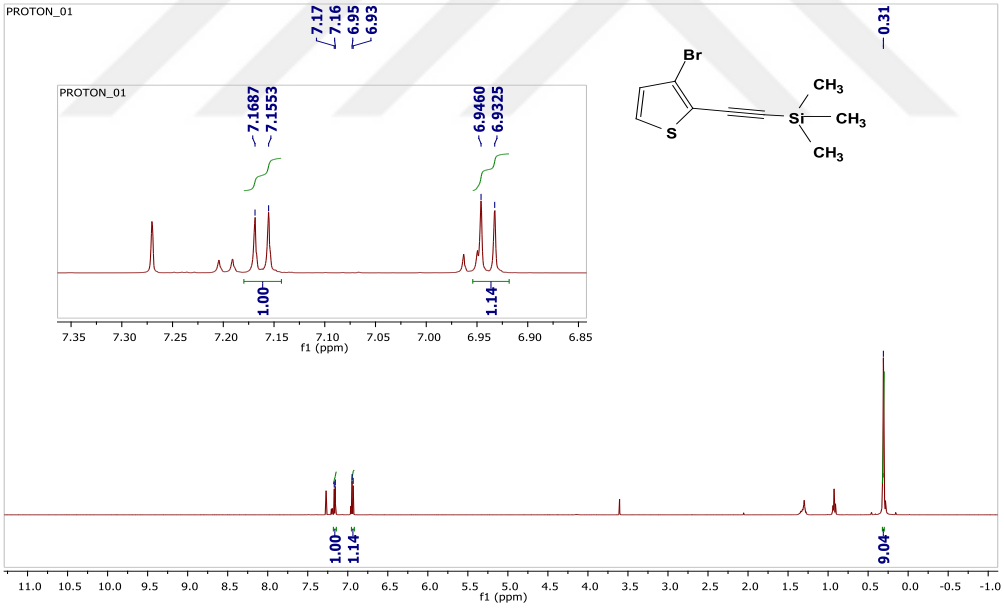


Figure 2.2. Representative ^{1}H NMR spectra of MH1.

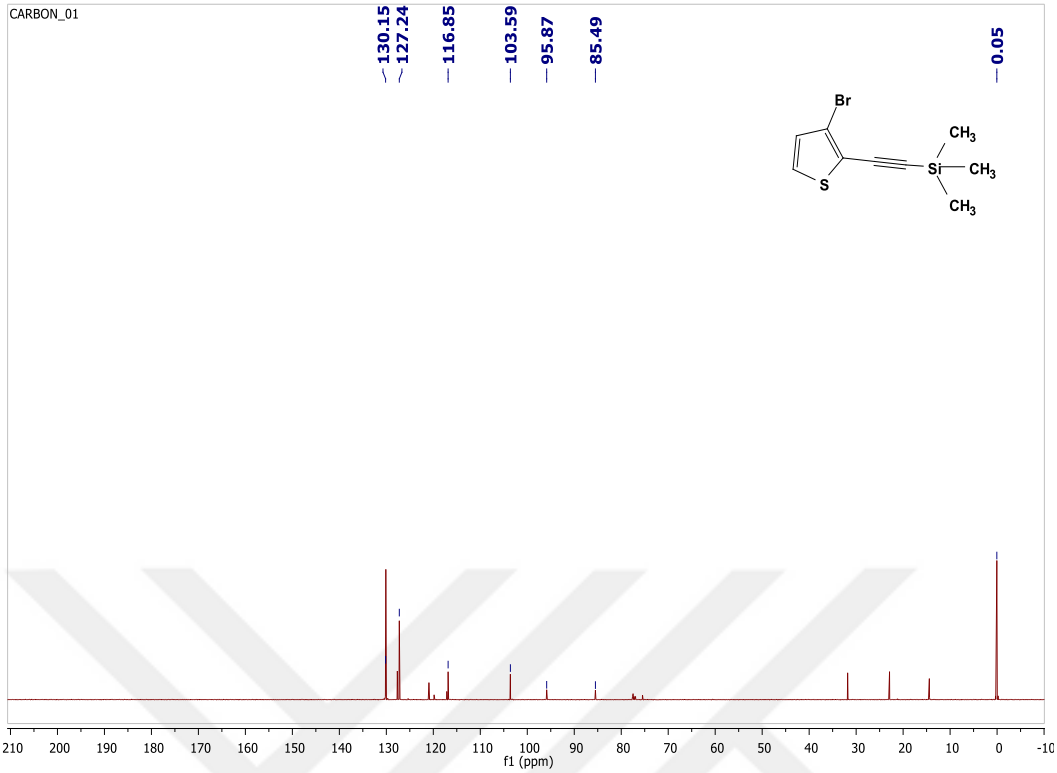


Figure 2.3. Representative ^{13}C NMR spectra of MH1.

2.2.1.2. Sonogashira palladium-catalyzed cross-coupling reaction between compound MH1 and terminals alkynes to Synthesis of trimethyl((3-(substituted ethynyl)thiophen-2-yl)ethynyl)silane derivatives:

General procedure: To a stirred suspension of MH1 (200 mg, 0.77 mmol), $PdCl_2(PhCN)_2$ (18.3 mg, 0.047 mmol), and CuI (9.0 mg, 0.047 mmol) in 1,4-dioxane (3 mL) were added diisopropylamine (1.9 mL, 3.84 mmol), terminal alkynes (0.92 mmol), and tri-tert-butylphosphine (18.7 mg, 0.092 mmol). After stirred at r.t. for 12 h, the reaction mixture was extracted with EtOAc, and the organic layer was dried through magnesium sulfate and then filtration, the filtrate was chromatographed on silica gel by hexane to afford the product.

Compound (MH2):

MH1 (200 mg, 0.77 mmol), $PdCl_2(PhCN)_2$ (18.3 mg, 0.047 mmol), and CuI (9.0 mg, 0.047 mmol), and ethynylbenzene (94.5 mg, 0.92 mmol) were employed to afford (80%) as a yellow oil of the indicated product(Figure 2.4). ^1H NMR (400 MHz, $CDCl_3$)

δ 7.59-7.64 (m, 2H), 7.39-7.43 (m, 3H), 7.18-7.21 (m,1H), 7.10-7.12 (m, 1H), 0.38 (s, 9H) Figure 2.4, ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.8, 129.4, 128.6, 128.55, 127.8, 126.3, 126.2, 123.3, 103.8, 96.9, 93.8, 84.1, 0.13 (Figure 2.6), IR (ATR) ν_{max} (cm^{-1}): 3101.2, 2970.3, 2896.8, 2360.1, 2208.5 (C≡C),2145.6 (C≡C), 1246.8 (Si-CH_3), 833.3, 753.6, 692.3.

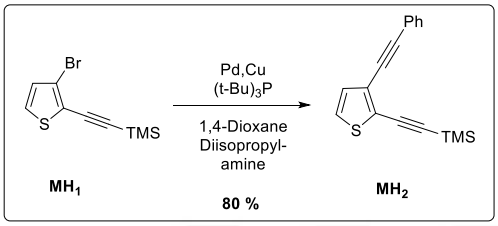


Figure 2.5. Synthesis of MH2 compound.

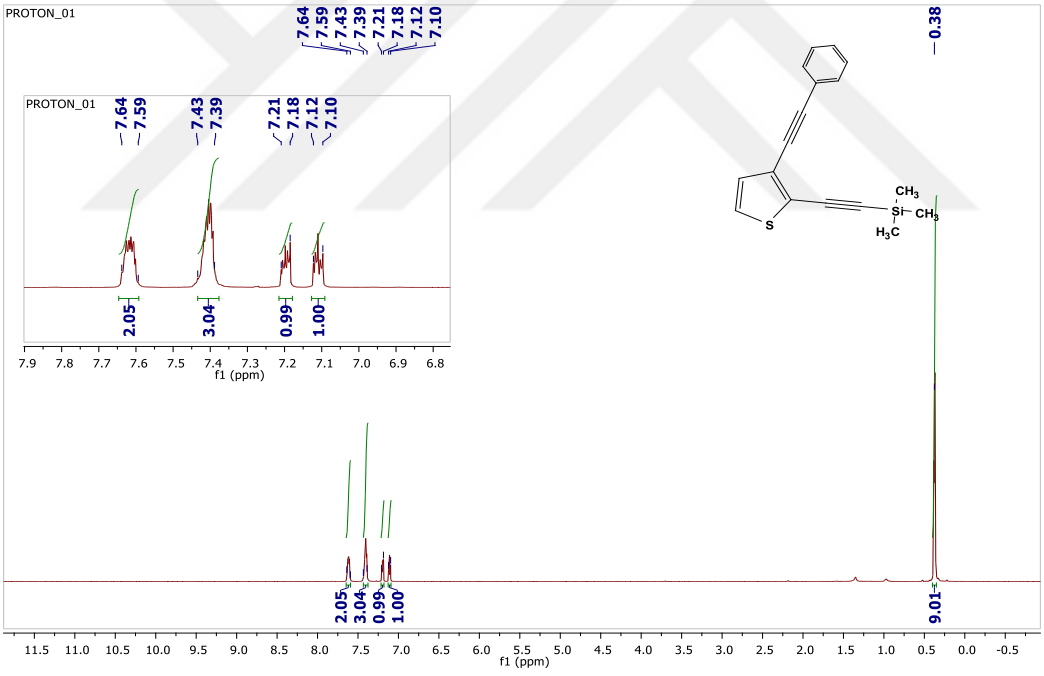


Figure 2.5. Representative ^{1}H NMR spectra of MH2.

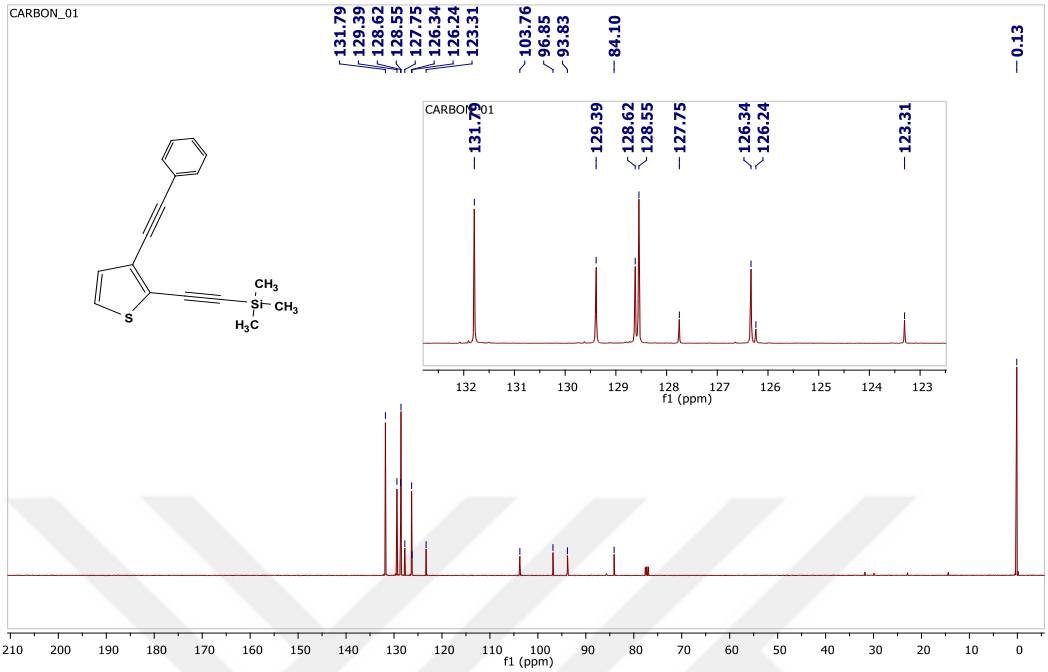


Figure 2.6. Representative ^{13}C NMR spectra of MH2.

Compound MH2BN:

MH1 (200 mg, 0.77 mmol), $PdCl_2(PhCN)_2$ (18.3 mg, 0.047 mmol), CuI (9.0 mg, 0.047 mmol), and 1-heptyne (89 mg, 0.92 mmol) were employed to afford (69%) as a yellow oil of the indicated product (Figure 2.7).

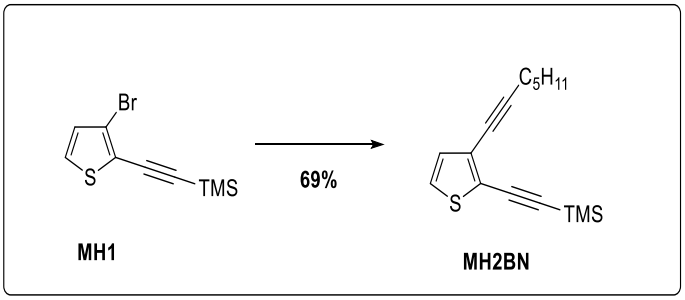


Figure 2.7. Synthesis of MH2BN compound.

^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J_{AB}= 4.0 Hz, 1H), 6.95 (d, J_{AB}= 4.0 Hz, 1H), 3.55 (s, 1H), 2.45 (t, 2H), 1.6 (p, 2H), 1.47 (p, 2H), 1.37 (h, 2H), 0.93 (t, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 128.9, 126.3, 123.9, 95.2, 84.7, 76.5, 74.8, 31.2, 28.5,

22.4, 19.8, 14.2, IR (ATR) ν_{max} (cm^{-1}): 3305.9, 2955.6, 2929.0, 2227.7, 2101.3, 1378.0, 726.6, 646.2, HRMS calcd for HRMS calcd for $C_{13}H_{14}S$, 202.0816, found 202.1863.

Compound (MH2C):

MH1 (200 mg, 0.77 mmol), $PdCl_2(PhCN)_2$ (18.3 mg, 0.047 mmol), CuI (9.0 mg, 0.047 mmol), and p-tolylacetylene (107 mg, 0.92 mmol) were employed to afford (97%) as an orange oil of the indicated product Figure 2.8. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0, 2H), 7.18 (t, 3H), 7.07 (d, *J* = 8.0 1H), 2.40 (s, 3H), 0.33 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 131.7, 129.4, 129.3, 128.0 Hz, 126.3, 125.9, 120.3, 103.6, 96.9, 94.1, 83.4, 21.8, 0.15, IR (ATR) ν_{max} (cm^{-1}): 3108.2, 2957.5, 2930.3, 2859.4, 2148.6 (C≡C),1249.3 (Si-CH_3), 839.5, 759.0, 708.3, HRMS calcd for $C_{18}H_{18}SSi$, 294.0898, found 294.0919.

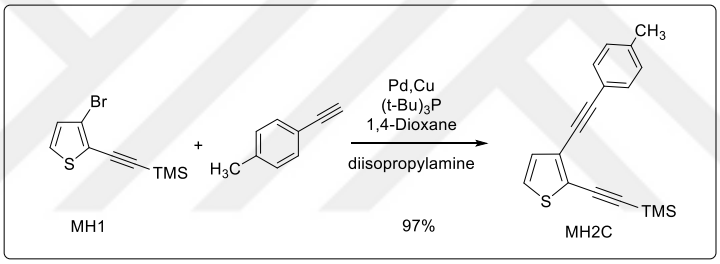


Figure 2.8**.** Synthesis of MH2C compound.

Compound (MH2D):

MH1 (500 mg, 1.93 mmol), $PdCl_2(PhCN)_2$ (45.9 mg, 0.12 mmol), CuI (22.7 mg, 0.12 mmol), 1,4-dioxane (3.8 mL), diisopropylamine (976.3 mg, 9.6 mmol), 2-ethynyl-1,4-dimethylbenzene (302.3 mg, 2.3 mmol), and tri-tert-butylphosphine (47 mg, 0.23 mmol) were employed to afford (68%) as a light yellow oil of the indicated product Figure 2.9. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.19 (d, *J* = 8.0, 1H), 7.16 (d, *J* = 8.0, 1H), 7.10-7.07 (m, 2H), 2.55 (s, 3H), 2.34 (s, 3H), 0.32 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.2, 132.6, 1329.6, 129.55, 129.5, 127.9, 126.4, 125.8, 122.8, 103.5, 96.9, 92.9, 87.5, 21.0, 20.8, 0.1, IR (ATR) ν_{max} (cm^{-1}): 2969.5, 2919.2, 2202.8, 2137.8, 1247.7, 836.9, 814.5, 757.2, HRMS calcd for $C_{19}H_{21}SSi$, 309.1055 $[M+H]^+$, found 309.1123 $[M+H]^+$.

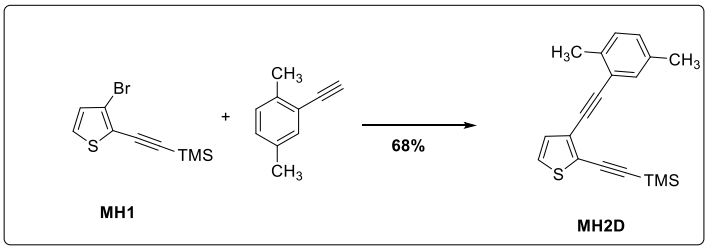


Figure 2.9. Synthesis of MH2D compound.

Compound (MH2E):

MH1 (500 mg, 1.93 mmol), $PdCl_2(PhCN)_2$ (45.92 mg, 0.119 mmol), CuI (22 mg, 0.119 mmol), 1,4-dioxane (3.8 mL), diisopropylamine (976.3 mg, 9.647 mmol), 1-ethynylnaphthalene (353.6 mg, 2.32 mmol), and tri-tert-butylphosphine (47 mg, 0.23 mmol) were employed to afford (67%) as a yellow oil of the indicated product (Figure 2.10).. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62-8.60 (m, 1H), 7.92-7.88 (m, 2H), 7.84-7.82 (m, 1H), 7.67-7.63 (m, 1H), 7.61-7.56 (m, 1H), 7.52-7.49 (m, 1H), 7.24 (d, J_{AB}= 4.0 Hz, 1H), 7.20 (d, J_{AB}= 4.0 Hz, 1H), 0.37 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 133.1, 130.7, 129.5, 129.0, 128.3, 127.5, 126.9, 126.5, 126.4, 126.3, 126.0, 125.3, 120.8, 103.8, 96.8, 91.7, 88.7, 0.08, IR (ATR) ν_{max} (cm^{-1}): 3118.9, 2980.3, 2139.6, 1399.2, 1250.9, 837.4, 772.3, 757.3, HRMS calcd for $C_{21}H_{18}SSi$, 330.0898, found 330.0912.

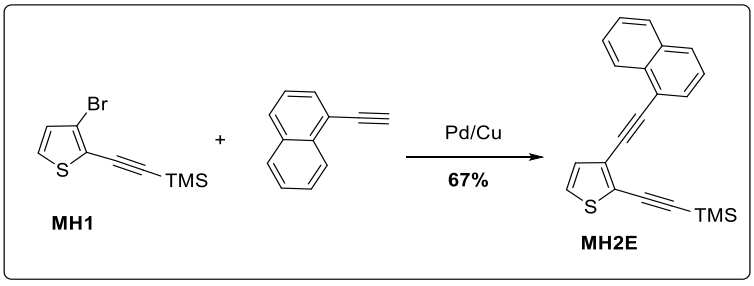


Figure 2.10. Synthesis of MH2E compound.

Compound(MH2F):

MH1 (286.3 mg, 1.1 mmol), $PdCl_2(PhCN)_2$ (26.18 mg, 0.068 mmol), CuI (13.0 mg, 0.068 mmol), 1,4-dioxane (3 mL), diisopropylamine (556.6 mg, 5.5 mmol), 1-ethynyl-4-methoxybenzene (175 mg, 1.32 mmol), and tri-tert-butylphosphine (26.81

mg, 0.132 mmol) were employed to afford (68%) as an orange oil of the indicated product(Figure 2.11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 12.0 Hz, 2H), 7.17 (d, J_{AB}= 4.0 Hz, 1H), 7.05 (d, J_{AB}= 4.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 3.84 (s, 3H), 0.30 (s, 9), ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 133.3, 129.4, 128.2, 126.3, 125.6, 115.4, 114.2, 103.5, 96.9, 93.9, 82.8, 55.5, 0.2, IR (ATR) ν_{max} (cm^{-1}): 3106.7, 2958.0, 2836.3, 2205.1, 2143.1, 1604.3, 1520.6, 1245.7, 828.5, HRMS calcd for $C_{18}H_{19}OSSi$, 311.0848 $[M+H]^+$, found 311.0940 $[M+H]^+$.

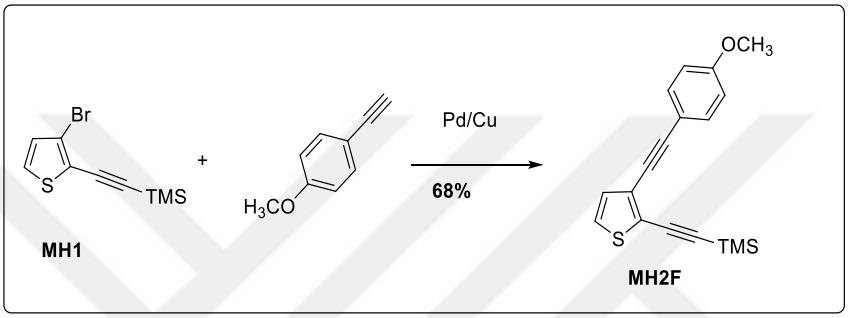


Figure 2.11. Synthesis of MH2F compound.

Compound(MH2G):

MH1 (500 mg, 1.93 mmol), $PdCl_2(PhCN)_2$ (45.9 mg, 0.119 mmol), CuI (22.7 mg, 0.12 mmol), 1,4-dioxane (3.8 mL), diisopropylamine (976.3 mg, 9.6 mmol), 2-ethynyl-6-methoxynaphthalene (423.4 mg, 2.32 mmol), and tri-tert-butylphosphine (47 mg, 0.23 mmol). Were employed to afford (57%) as a light yellow oil of the indicated product (Figure 2. 12**)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.72 (d, J = 12.0 Hz, 2H), 7.58 (d, J = 12.0 Hz, 1H), 7.20-7.10 (m, 4H), 3.94 (s, 3H), 0.36 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 134.4, 131.6, 129.6, 129.4, 129.1, 128.7, 128.0 Hz, 127.1, 126.3, 126.0, 119.7, 118.2, 106.0, 130.7, 96.9, 94.5, 83.8, 55.5, 0.2, IR (ATR) ν_{max} (cm^{-1}): 3676.0, 3102.0, 2971.6, 2937.8, 2900.5, 2360.1, 2139.5, 1625.3, 1597.9, 1480.4, 1246.5, 836.4, HRMS calcd for $C_{22}H_{21}OSSi$, 361.1004 $[M+H]^+$, found 361.1067 $[M+H]^+$.

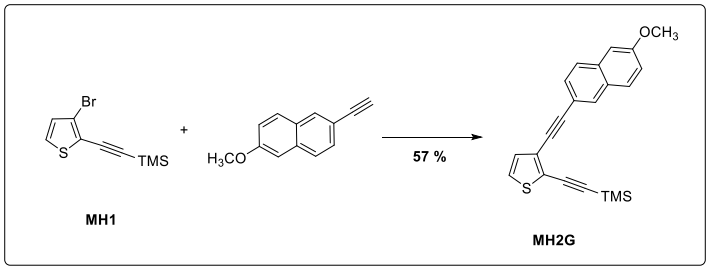


Figure 2.12. Synthesis of MH2G compound.

2.2.1.3. Synthesis of 2-ethynyl-3-(substitutedethynyl)thiophene derivatives:

General desilylation procedure to prepare the compounds MH3-MH3G: A solution of starting compound (2.4 mmol), methanol (24 mL), and THF (5 mL) was added K_2CO_3 (995 mg, 7.2 mmol). The mixture was stirred at room temperature for 60 min. The reaction mixture extracted with EtOAc. The organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography to give the product.

Compound MH3:

MH2 (672.8 mg, 2.4 mmol), methanol (24 mL), THF (5 mL), K_2CO_3 (995 mg, 7.2 mmol) were employed to afford 96% as yellow oil of the indicated product (Figure 2.13). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.59 (m, 2H), 7.35-7.39 (m, 3H), 7.22 (d, J_{AB}= 4.0 Hz, 1H), 7.10 (d, J_{AB}= 4.0 Hz, 1H), 3.65 (s, 1H) (Figure 2.14) ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 129.7, 128.8, 128.6, 128.1, 126.7, 125.0, 123.2, 93.7, 85.6, 83.6, 76.3 (Figure 2.15), IR (ATR) ν_{max} (cm^{-1}): 3286.6, 2988.1, 2359.7, 2341.5, 2204.4, 1485.7, 1442.3, 1254.0, 1069.7, 752.8, 727.6, 687.3.

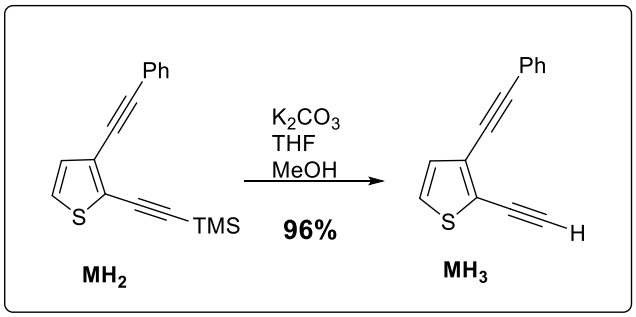


Figure 2.13. Synthesis of MH3 compound.

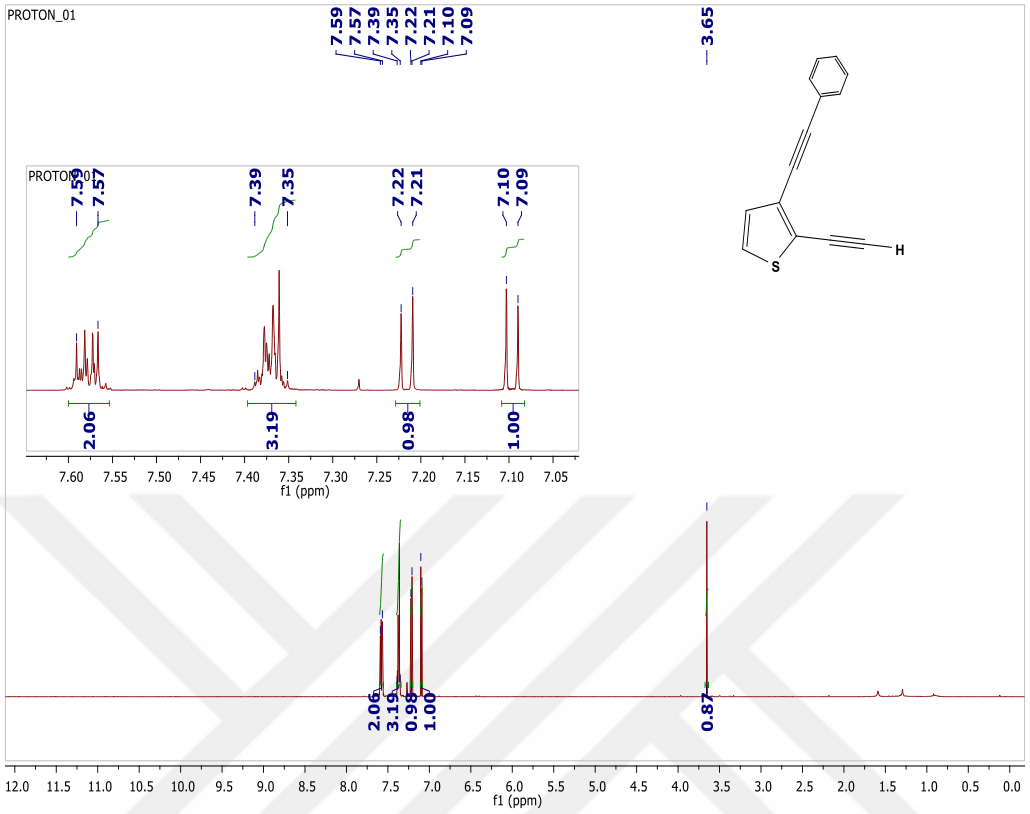


Figure 2.14. Representative ^{1}H NMR spectra of MH3.

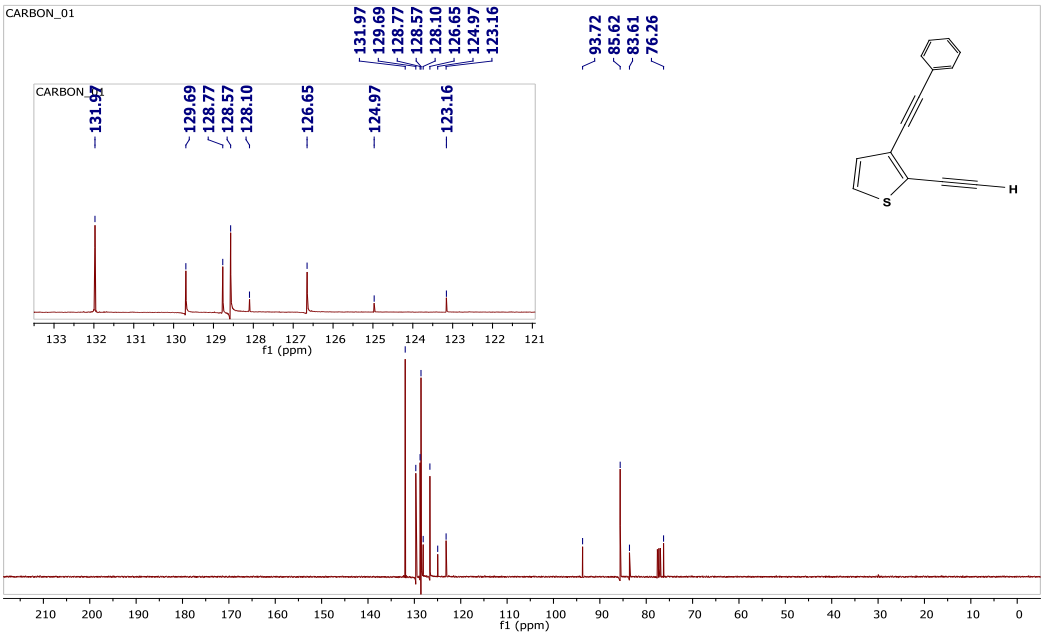


Figure 2.15. Representative ^{13}C NMR spectra of MH3.

Compound MH3BN:

MH2BN (511.6 mg, 1.86 mmol), methanol (24 mL), THF (5 mL), and K_2CO_3 (777.3 mg, 5.6 mmol) were employed to afford 91% yield as yellow oil of the indicated product (Figure 2.16). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J_{AB}= 4.0 Hz, 1H), 6.95 (d, J_{AB}= 4.0 Hz, 1H), 3.55 (s, 1H), 2.45 (t, J = 8.0 Hz, 2H), 1.64 (p, J = 4.0 Hz, 2H), 1.43-1.51 (m, 2H), 1.32-1.41 (m, 2H), 0.94 (t, J = 8.0 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 128.9, 126.3, 123.9, 95.2, 84.7, 76.5, 74.8, 31.2, 28.5, 22.4, 19.8, 14.2, IR (ATR) ν_{max} (cm^{-1}): 3305.9, 2955.6, 2929.0, 2227.7, 2101.3, 1378.0, 726.6, 646.2, HRMS calcd for $C_{13}H_{14}S$, 202.0816, found 202.1863.

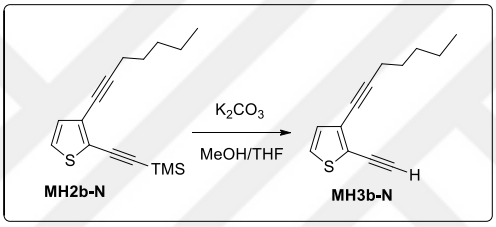


Figure 2.16. Synthesis of MH3BN compound.

Compound MH3C:

MH2C (706.5 mg, 2.4 mmol), methanol (24 mL), THF (5 mL), and K_2CO_3 (995 mg, 7.2 mmol) were employed to afford 96% yield as yellow oil of the indicated product (Figure 2.17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.48 (m, 2H), 7.21 (d, J_{AB}= 5.2 Hz, 1H), 7.16-7.19 (m, 2H), 7.07 (d, J_{AB}= 5.2 Hz, 1H), 3.64 (s, 1H), 2.39 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 131.9, 129.7, 129.3, 128.3, 126.6, 124.6, 120.0, 94.0 Hz, 85.5, 83.0, 76.3, 21.8, IR (ATR) ν_{max} (cm^{-1}): 3285.3 (≡C—H),3106.7, 2980.6, 2917.8, 2359.5, 2342.4, 2204.7 (C≡C),2099.5 (C≡C),1518.9, 1380.5, 813.8, 727.3, 644.9, HRMS calcd for $C_{15}H_{10}S$, 222.0503, found 222.0530.

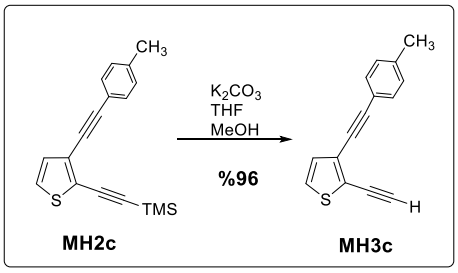


Figure 2.17. Synthesis of MH3C compound.

Compound MH3D:

MH2D (280 mg, 0.9 mmol), methanol (24 mL), THF (5 mL), and K_2CO_3 (378 mg, 2.73 mmol) were employed to afford 93% yield (Figure 2.18) as light yellow oil of the indicated product.

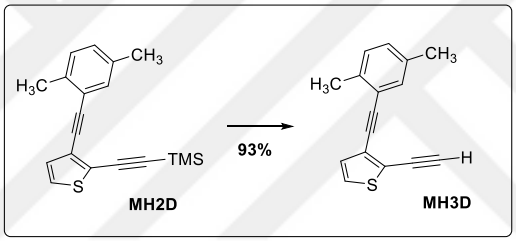


Figure 2.18. Synthesis of MH3D compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.22-7.23 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.09-7.12 (m, 2H), 3.66 (s, 1H), 2.55 (s, 3H), 2.36 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.2, 132.5, 129.7, 129.6, 129.57, 128.6, 126.6, 124.5, 122.6, 92.9, 87.1, 85.5, 76.5, 21.0, 20.6, IR (ATR) ν_{max} (cm^{-1}): 3269.3, 2980.5, 2917.6, 2205.3, 2102.8, 1456.5, 815.0, 729.9, 612.9, HRMS calcd for $C_{16}H_{13}S$, 237.0660 $[M+H]^+$, found 237.0776 $[M+H]^+$.

Compound MH3E:

MH2E (363.7 mg, 1.1 mmol), methanol (24 mL), THF (5 mL), and K_2CO_3 (456 mg, 3.30 mmol) were employed to afford 97% yield as yellow oil of the indicated product (Figure 2. 19).. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.62-7.66 (m, 1H), 7.56-7.59 (m, 1H), 7.47-7.51 (m, 1H), 7.19-7.25 (m, 2H), 3.78 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4

(include 2C), 130.7, 129.6, 129.3, 128.5, 128.3, 127.0, 126.8, 126.7, 126.6, 125.4, 125.0, 120.8, 92.0, 88.6, 85.8, 76.6, IR (ATR) ν_{max} (cm^{-1}): 3288.5, 2980.6, 2202.4, 2101.2, 1396.6, 797.4, 770.4, 726.7, HRMS calcd for $C_{18}H_{11}S$, 259.0503 $[M+H]^+$, found 259.0621 $[M+H]^+$.

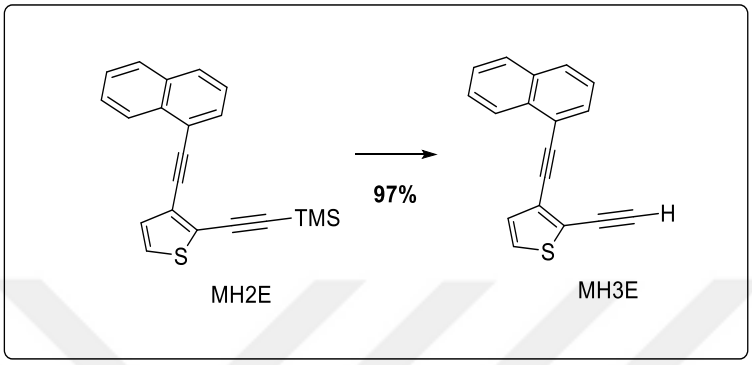


Figure 2.19. Synthesis of MH3E compound.

Compound MH3F:

MH2F (197 mg, 0.63 mmol), methanol (15 mL), THF (3 mL), and K_2CO_3 (263.2 mg, 1.90 mmol) were employed to afford 91% yield as light green solid of the indicated product (Figure 2.20). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J_{AB}= 8.0 Hz, 2H), 7.21 (d, J_{AB}= 4.0 Hz, 1H), 7.06 (d, J_{AB}= 4.0 Hz, 1H), 6.89 (d, J_{AB}= 8.0 Hz, 2H), 3.83 (s, 3H), 3.63 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 133.5, 129.7, 128.4, 126.6, 124.3, 115.2, 114.2, 93.8, 85.4, 82.4, 76.4, 55.5, IR (ATR) ν_{max} (cm^{-1}): 3243.6, 2922.0, 2203.1, 2094.6, 1621.2, 1247.8, 1026.8, 827.6, 719.4, 643.4, HRMS calcd for $C_{15}H_{11}OS$, 239.0452 $[M+H]^+$, found 239.0545 $[M+H]^+$.

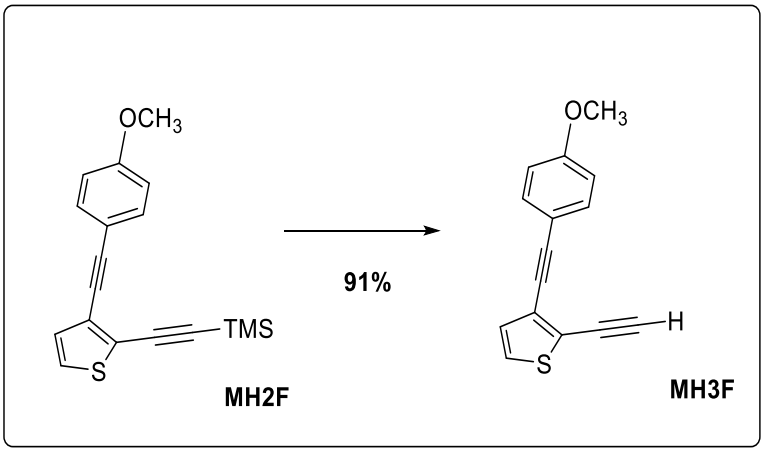


Figure 2.20. Synthesis of MH3F compound.

Compound MH3G:

MH2G (393 mg, 1.09 mmol), methanol (20 mL), THF (4 mL), and K_2CO_3 (451.9 mg, 3.27 mmol) were employed to afford 74% yield as light yellow solid of the indicated product (Figure 2.21**)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.72 (d, *J* = 12.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.17-7.24 (m, 2H), 7.12-7.14 (m, 2H), 3.94 (s, 3H), 3.71 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 134.5, 131.7, 129.7, 129.6, 129.2, 128.7, 128.3, 127.1, 126.6, 124.7, 119.7, 118.0 Hz, 106.1, 94.4, 85.6, 83.3, 76.4, 55.5, IR (ATR) ν_{max} (cm^{-1}): 3243.8, 2960.2, 2206.6, 2092.1, 1602.0, 1393.4, 1259.1, 1029.2, 844.9, 722.4, HRMS calcd for $C_{19}H_{12}OS$, 288.0609, found 288.0623

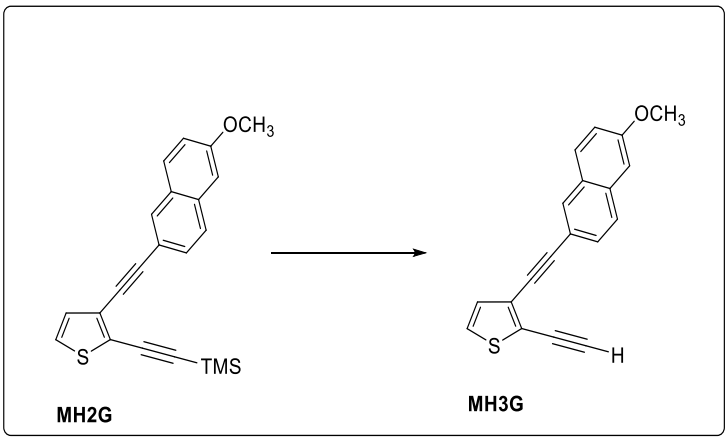


Figure 2.21**.** Synthesis of MH3G compound.

2.2.1.4. Sonogashira coupling reaction between 2-iodothioanisole and terminal alkynes

Starting compounds to preprae 2-((2-(methylthio)phenyl)ethynyl)-3-(substitutedethynyl)thiophene derivatives:

General procedure: solution of the terminal alkyne (0.648 mmol) in DMF (7.5 mL) were added 2-iodothioanisole (162 mg, 0.648 mmol), Triethylamine (3 mL), Pd(PPh3)2Cl2 (24.5 mg, 0.035 mmol), and the reaction mixture was stirred at room temperature under argon gas for 10 min. Then, CuI (6.66 mg, 0.035 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture extracted with with ethyl acetate- water. The organic extracts were dried over anhydrous MgSO4. After filtration and removal of solvent, the residue was purified by column chromatography to give the product.

Compound MH4:

MH3 (135 mg, 0.648 mmol), DMF (7.5 mL), 2-iodothioanisole (162 mg, 0.648 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (24.566 mg, 0.035 mmol), and CuI (6.66 mg, 0.035 mmol) were employed to afford 63% yield as yellow solid of the indicated (Figure 2.22).. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.11-7.15 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 4.0 Hz, 1H), 7.30-7.32 (m, 1H), 7.34-7.38 (m,3H), 7.52-7.54 (m, 1H), 7.61-7.63 (m, 2H) (Figure 2.23), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 84.3, 88.5, 93.8, 95.1, 121.1, 123.5, 124.3, 124.4, 126.2, 126.6, 126.8, 128.4, 128.5, 129.2, 129.9, 132.1, 132.4, 142.0 (Figure 2.24), IR (ATR) ν_{max} (cm^{-1}): 691.5, 719.2, 753.8, 1439.5, 2206.4 (C≡C), 2918.2, 2980.6, 3126.4, HRMS calcd for $C_{21}H_{15}S_2$, 331.0537 $[M+H]^+$, found 331.0617 $[M+H]^+$.

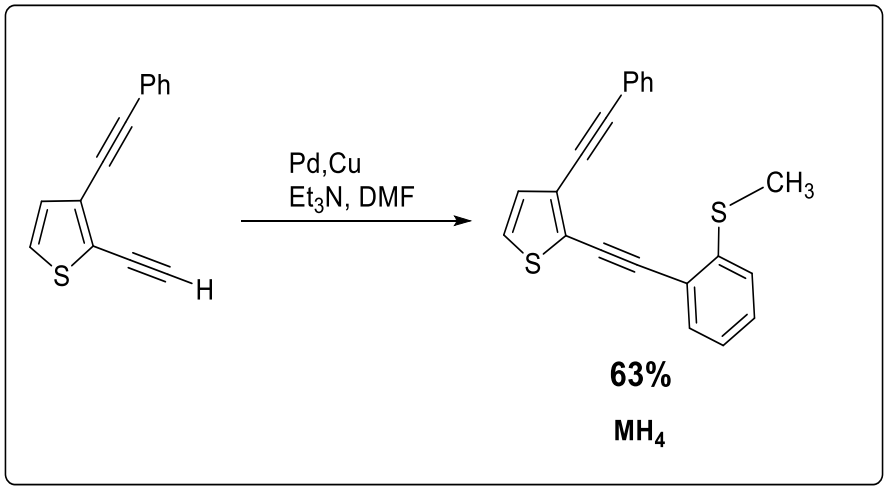


Figure 2.22. Synthesis of MH4 compound.

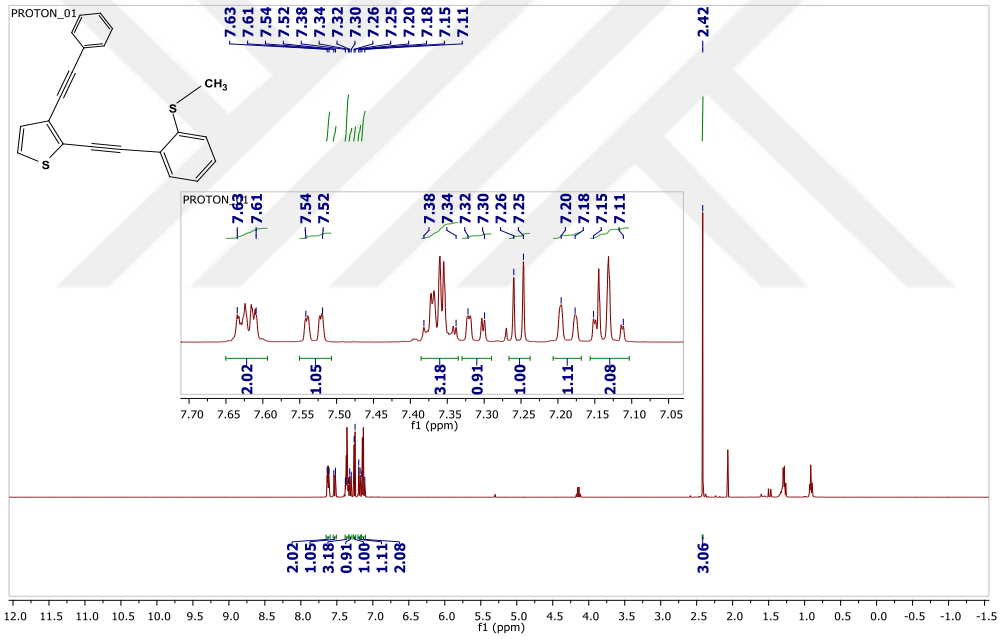


Figure 2.23. Representative ^{1}H NMR spectra of MH4.

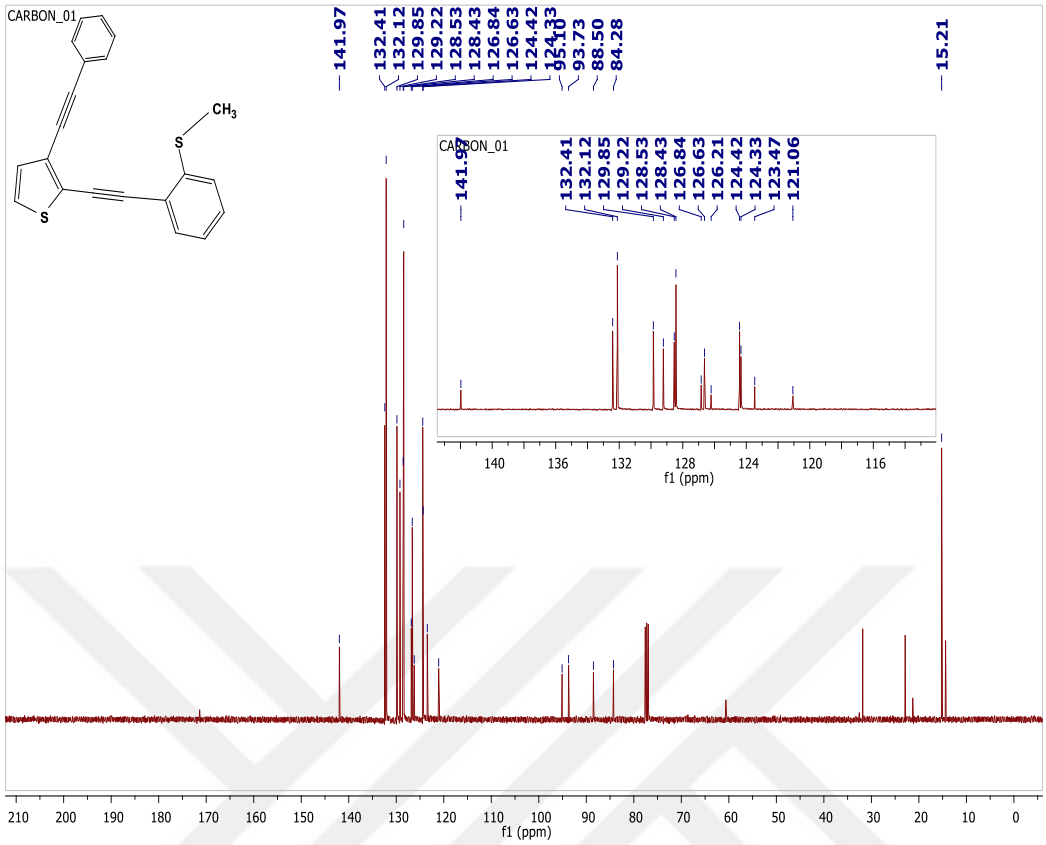


Figure 2.24. Representative ^{13}C NMR spectra of MH4.

Compound MH4B:

MH3B (364 mg, 1.8 mmol), DMF (7.5 mL), 2-iodothioanisole (450 mg, 1.799 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (68.2 mg, 0.097 mmol) and CuI (6.66 mg, 0.035 mmol) were employed to afford 73% yield as orange oil of the indicated product Figure 2.25. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 4.0 Hz, 1H), 7.18-7.20 (m, 2H), 7.12 (t, *J* = 4.0 Hz, 1H), 7.00 (d, *J* = 4.0 Hz, 1H), 2.52 (s, 3H), 2.49 (t, *J* = 4.0 Hz, 2H), 1.68 (p, *J* = 4.0, 2H), 1.44-1.52 (m, 2H), 1.33-1.40 (m, 2H), 0.91 (t, *J* = 4.0 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 132.4, 129.9, 129.1, 127.7, 126.3, 125.1, 124.5, 124.4, 121.3, 95.2, 94.2, 88.5, 75.2, 31.3, 28.6, 22.4, 19.9, 15.4, 14.1, IR (ATR) ν_{max} (cm^{-1}): 2954.2, 2921.7, 2225.6, 1464.1, 1432.4, 747.0, 723.0, HRMS calcd for $C_{20}H_{21}S_2$, 325.1006 $[M+H]^+$, found 325.1095 $[M+H]^+$.

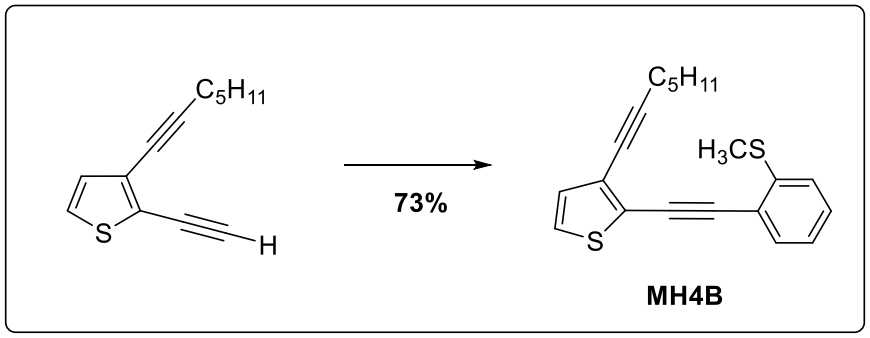


Figure 2.25. Synthesis of MH4B compound.

Compound MH4C:

MH3C (135 mg, 0.648 mmol), DMF (7.5 mL), 2-iodothioanisole (162 mg, 0.648 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (24.5 mg, 0.035 mmol), and CuI (6.66 mg, 0.035 mmol) were employed to afford 58% yield as light yellow solid of the indicated product (Figure 2.26). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.55 (m, 3H), 7.30-7.35 (m, 1H), 7.25 (d, 8.0 Hz, 1H), 7.16-7.21 (m, 3H), 7.09-7.14 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 138.7, 132.4, 132.0, 131.9, 129.8, 129.3, 129.2, 127.1, 126.6, 125.9, 124.4, 121.2, 120.4, 95.0, 94.0 Hz, 88.6, 83.7, 21.7, 15.2, IR (ATR) ν_{max} (cm^{-1}): 3101.7, 2980.7, 2917.1, 2189.1 (C≡C),1435.3, 952.7, 743.6. HRMS calcd for $C_{22}H_{17}S_2$, 345.4924 $[M+H]^+$, found 345.0773 $[M+H]^+$.

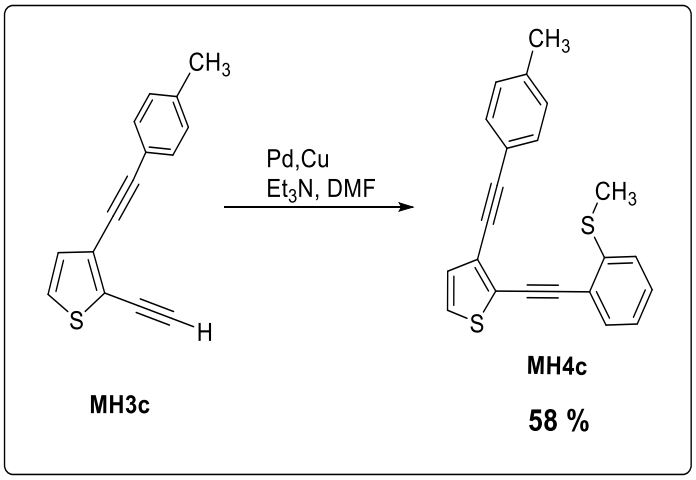


Figure 2.26. Synthesis of MH4C compound.

Compound MH4D:

MH3D (165.4 mg, 0.699 mmol), DMF (7.5 mL), 2-iodothioanisole (175.1 mg, 0.70 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (26.4 mg, 0.0376 mmol), and CuI (6.66 mg, 0.035 mmol) were employed to afford 97% yield as yellow oil of the indicated product (Figure 2.27). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.30-7.35 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.04-7.14 (m, 4H), 2.52 (s, 3H), 2.44(s, 3H), 2.33(s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 137.5, 135.0, 132.8, 132.5, 129.8, 129.6, 129.5, 129.49, 129.2, 128.0 Hz, 127.2, 126.6, 124.4, 123.0, 121.2, 94.9, 93.0, 88.6, 87.7, 21.0, 20.6, 15.2, IR (ATR) ν_{max} (cm^{-1}): 2953.3, 2920.3, 2852, 2193, 1463.3, 807.9, 722.3, HRMS calcd for $C_{23}H_{19}S_2$, 359.0850 $[M+H]^+$, found 359.0944 $[M+H]^+$.

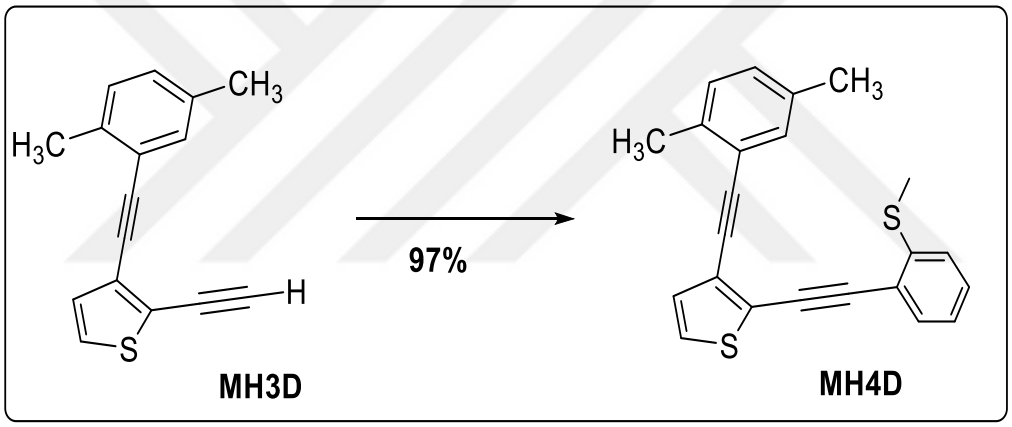


Figure 2.27. Synthesis of MH4D compound.

Compound MH4E:

MH3E (219 mg, 0.849 mmol), DMF (7.5 mL), 2-iodothioanisole (212.5 mg, 0.849 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (32.1 mg, 0.045 mmol), and CuI (8.7 mg, 0.045 mmol) were employed to afford 99% yield as yellow oil of the indicated product (Figure 2. 28). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 8.0 Hz, 1H), 7.85-7.88 (m, 3H), 7.56-7.59 (m, 1H), 7.46-7.53 (m, 2H), 7.38-7.42 (m, 1H), 7.32-7.36 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 4.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.12-7.16 (m, 1H), 2.36 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 133.4, 133.3, 132.7, 130.8, 129.8, 129.3, 129.1, 128.3, 127.1, 127.0, 126.8, 126.76, 126.6, 126.3, 125.4, 124.4, 124.35, 121.1, 121.0, 95.24, 91.99, 89.15, 88.57, 15.13, IR (ATR) ν_{max}

(cm^{-1}): 3056.2, 2980.4, 2920.9, 2194.2, 1434.9, 1400.1, 800.5, 753, 732.3, HRMS calcd for $C_{25}H_{17}S_2$, 381.0693 $[M+H]^+$, found 381.0776 $[M+H]^+$.

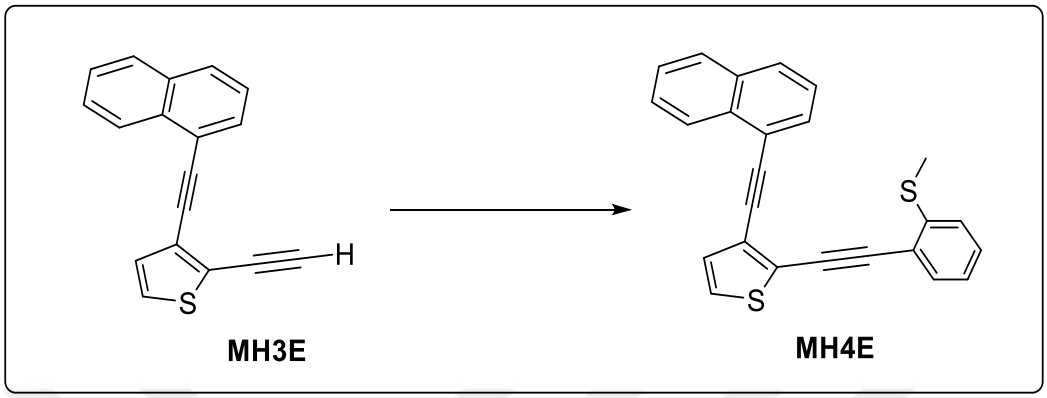


Figure 2.28. Synthesis of MH4E compound.

Compound MH4F:

To a solution of MH3F (123 mg, 0.519 mmol), DMF (7.5 mL), 2-iodothioanisole (129 mg, 0.518 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (19.6 mg, 0.028 mmol), and CuI (5.3 mg, 0.028 mmol) were employed to afford 79% yield as orange solid of the indicated product (Figure 2. 29) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.57 (m, 3H), 7.29-7.33 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.11-7.15 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 2.43 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 141.9, 133.5, 132.4, 129.8, 129.1, 127.2, 126.5, 125.5, 124.43, 124.42, 121.2, 115.5, 114.1, 94.9, 93.8, 88.6, 83.0, 55.5, 15.2, IR (ATR) ν_{max} (cm^{-1}): 2958.4, 2920.3, 2191.4, 1603.6, 1520.3, 1245.9, 1028.7, 829.9, 748.2, 725.4, HRMS calcd for $C_{22}H_{16}OS_2$, 360.0643, found 360.0661

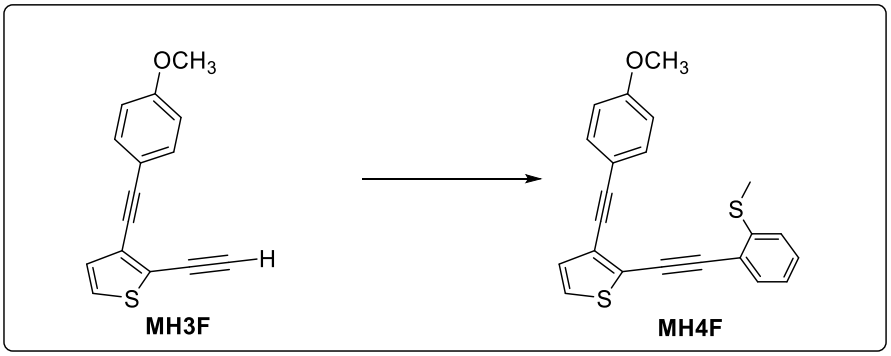


Figure 2.29. Synthesis of MH4F compound.

Compound MH4G:

MH3G (242 mg, 0.839 mmol), DMF (7.5 mL), 2-iodothioanisole (209.8 mg, 0.838 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (31.8 mg, 0.045 mmol), and CuI (8.62 mg, 0.045) were employed to afford as 76% yield light yellow solid of the indicated product (Figure 2.30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 4.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.11-7.19 (m, 5H), 3.92 (s, 3H), 2.39 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 142.0, 134.4, 132.5, 132.0, 129.9, 129.6, 129.4, 129.2, 128.7, 127.1, 126.9, 126.6, 126.0, 124.5, 124.4, 121.2, 119.6, 118.4, 106.1, 95.1, 94.5, 88.7, 84.1, 55.6, 15.2, IR (ATR) ν_{max} (cm^{-1}): 311.1, 2980.5, 2925.1, 2191.6, 2042.6, 1398.3, 1211.9, 1025.9, 855.5, 725.9, HRMS calcd for $C_{26}H_{19}OS_2$, 411.0799 $[M+H]^+$, found 411.0888 $[M+H]^+$.

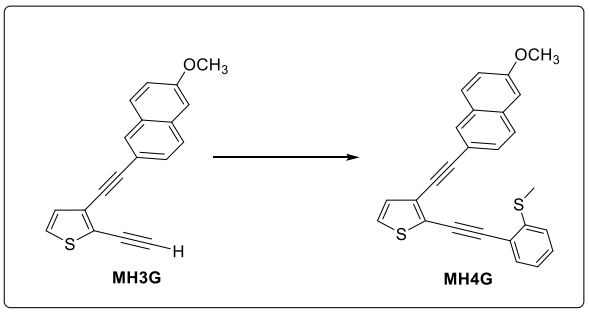


Figure 2.30. Synthesis of MH4G compound.

2.2.1.5. Iodine-mediated intramolecular electrophilic aromatic cyclization of the compounds MH4 derivatives:

General procedure: To a solution of the starting compound (one of the MH4 derivative) (200 mg, 0.6 mmol) in CH_2Cl_2 (8 mL) iodine was added (458.1 mg, 1.8 mmol), and the mixture was stirred at room temperature for 60 min. The saturated aqueous solution of $Na_2S_2O_3$ was added subsequently into the reaction mixture and extracted by DCM. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography to afford the product.

Compound MH7 and MH17:

MH4 (200 mg, 0.6 mmol), CH_2Cl_2 (8 mL), I_2 (458.1 mg, 1.8 mmol) were employed to afford MH7 (31% yield as yellow solid) and MH17 (59% yield as white crystal) of the indicated products(Figure 2.31).

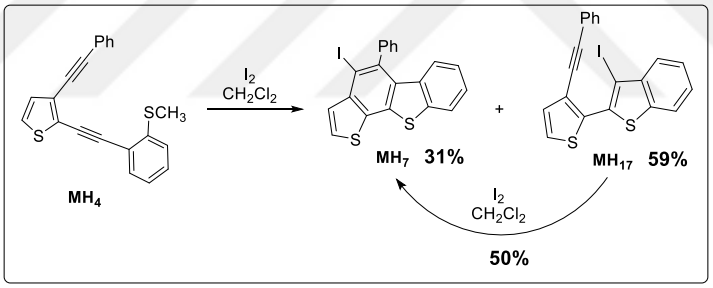


Figure 2.31. Synthesis of MH7 and MH17 compounds.

MH7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.46 (m, 2H), 7.51-7.65 (m, 5H), 7.62 (d, J_{AB}= 4.0 Hz, 1H), 7.78 (d, J_{AB}= 4.0 Hz, 1H), 7.84-7.86 (m, 1H), 8.42-8.45 (m, 1H) (Figure 2.32**)**, ^{13}C NMR (100 MHz, $CDCl_3$) δ 93.8, 122.8, 124.2, 124.8, 125.2, 126.8, 128.9, 129.0, 129.1, 129.9, 130.3, 131.6, 134.8, 138.3, 138.6, 140.4, 141.5, 143.5 (Figure 2.33**)**, IR (ATR) ν_{max} (cm^{-1}): 691.8, 719.1, 828.7, 1306.1, 2918.6, 2980.6, 3127.1, HRMS calcd for $C_{20}H_{11}IS_2$, 441.9347, found 441.9329.

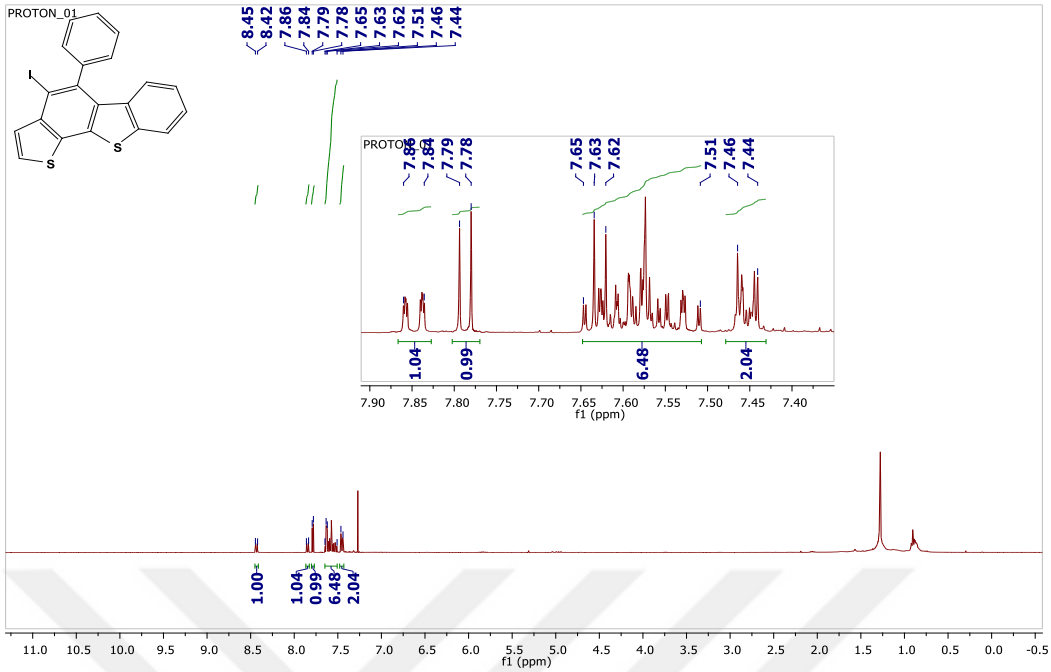


Figure 2.32. Representative ^{1}H NMR spectra of MH7.

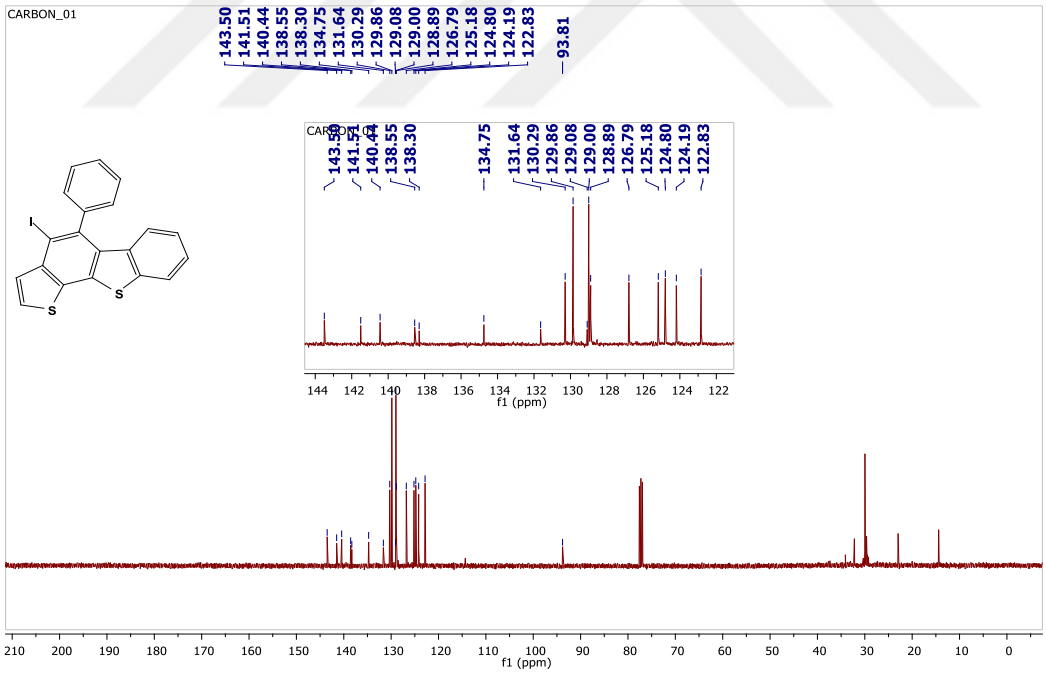


Figure 2.33. Representative ^{13}C NMR spectra of MH7.

MH17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 4.0 Hz, 1H), 7.28-7.32 (m, 3H), 7.39-7.49 (m, 5H), 7.79-7.81 (m, 1H), 7.84-7.87 (m, 1H) (Figure 2.34**)**, ^{13}C NMR

(100 MHz, $CDCl_3$) δ 83.4, 85.0, 94.1, 122.3, 123.2, 123.3, 125.7, 126.2, 126.8, 126.9, 128.5, 128.7, 131.1, 131.7, 134.7, 137.4, 139.6, 141.8 (Figure 2.6), IR (ATR) ν_{max} (cm^{-1}): 688.5, 719, 750.1, 1246.6, 2202.6 (C≡C), 2852.7, 2922.4, 2980.4, 3103.6, HRMS calcd for $C_{20}H_{11}IS_2$, 441.9347, found 441.9359.

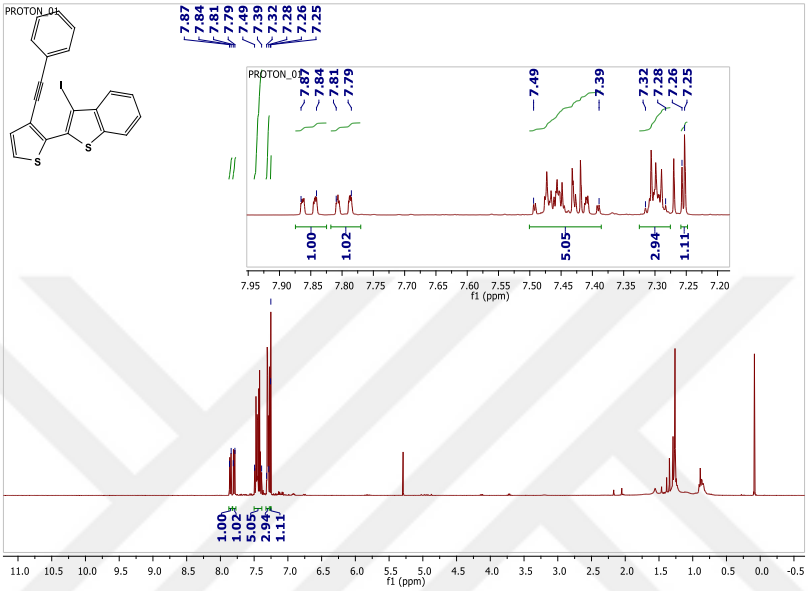


Figure 2.34. Representative ^1H NMR spectra of MH17.

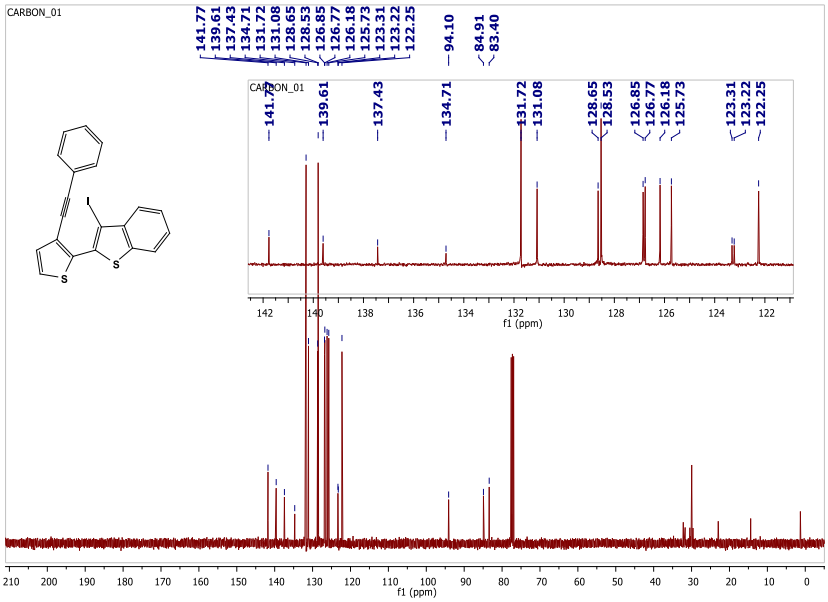


Figure 2.35. Representative ^{13}C NMR spectra of MH17.

MH7 from MH17:

To a solution of compound MH17 (100 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) in the presence of I_2 (229 mg, 0.9 mmol) was stirred at room temperature for 60 min. The saturated aqueous solution of $Na_2S_2O_3$ was added subsequently into the reaction mixture and extracted by EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography to afford MH7 (50% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.46 (m, 2H), 7.51-7.65 (m, 5H), 7.62 (d, J_{AB}= 4.0 Hz, 1H), 7.78 (d, J_{AB}= 4.0 Hz, 1H), 7.84-7.86 (m, 1H), 8.42-8.45 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 93.8, 122.8, 124.2, 124.8, 125.2, 126.8, 128.9, 129.0, 129.1, 129.9, 130.3, 131.6, 134.8, 138.3, 138.6, 140.4, 141.5, 143.5, IR (ATR) ν_{max} (cm^{-1}): 691.8, 719.1, 828.7, 1306.1, 2918.6, 2980.6, 3127.1, HRMS calcd for $C_{20}H_{11}IS_2$, 441.9347, found 441.9329.

Compound MH17B:

MH4B (383 mg, 1.182 mmol), CH_2Cl_2 (15 mL), I_2 (893 mg, 3.54 mmol) were employed to afford 97% yield as light yellow solid of the indicated product (Figure 2.36). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.45-7.50 (m, 2H), 7.40-7.44 (m, 1H), 7.04 (d, J = 4.0 Hz, 1H), 2.74-2.82 (m, 2H), 7.57-1.66 (m, 2H), 1.28-1.35 (m, 4H), 0.87 (t, J = 4.0 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 141.5, 139.9, 133.9, 132.1, 128.6, 127.0, 126.8, 126.1, 125.6, 122.2, 109.5, 88.5, 84.2, 50.2, 30.7, 27.9, 22.7, 14.2, IR (ATR) ν_{max} (cm^{-1}): 2951.1, 2922.5, 2853.1, 1452.8, 1246.3, 830.6, 749.6, 723.4, 660.4, HRMS calcd for $C_{19}H_{17}IS_2$, 435.9816, found 435.9884.

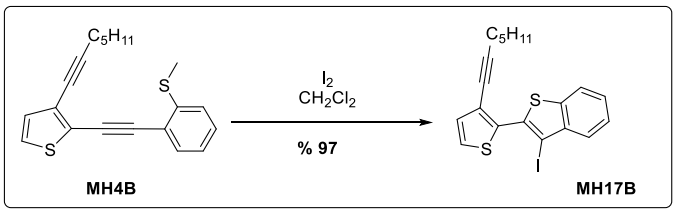


Figure 2.36. Synthesis of MH17B compound.

Compounds MH7C and MH17C: MH4C (350 mg, 1.017 mmol), CH_2Cl_2 (25 mL), and I_2 (768 mg, 3.051 mmol) were employed to afford MH7C (as a white solid,

64% yield) and MH17C (as a Brown solid, 31%) of the indicated products (Figure 2.37). MH7C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.64-7.60 (m, 2H), 7.54-7.50 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.52 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.6, 140.4, 138.7, 138.5, 138.4, 134.8, 131.5, 130.3, 129.7, 129.6, 129.0, 126.7, 125.1, 124.7, 124.2, 122.8, 94.0 Hz, 21.8, IR (ATR) ν_{max} (cm^{-1}): 2980.6, 2918.5, 1335.8, 1101.9, 818.8, 739.4, 709.4, 645.8, HRMS calcd for $C_{21}H_{13}IS_2$, 455.9503, found 455.95151

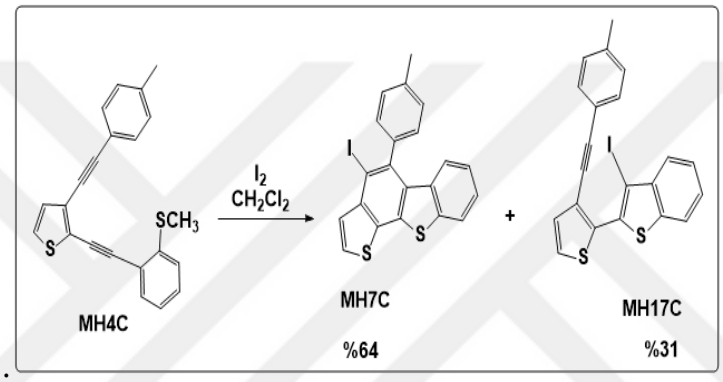


Figure 2.37. Synthesis of MH7C and MH17C compounds.

MH17C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.85 (m, 2H), 7.53-7.45 (m, 4H), 7.23-7.20 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 144.6, 141.8, 139.9, 138.9, 131.6, 129.34, 129.31, 128.2, 128.2, 127.3, 126.9, 126.2, 125.8, 122.4, 101.7, 91.2, 84.5, 21.7, IR (ATR) ν_{max} (cm^{-1}): 2954.7, 2920.3, 1435.2, 814.2, 755.7, 729.2, 700, HRMS calcd for C21H13IS2, 455.9503, found 455.9527.

MH7C from MH17C:

To a solution of compound MH17C (100 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) in the presence of I_2 (219.2 mg, 0.87 mmol) was stirred at room temperature for 60 min. The saturated aqueous solution of $Na_2S_2O_3$ was added subsequently into the reaction mixture and extracted by EtOAc. The combined organic extracts were dried over anhydrous MgSO4. After filtration and removal of solvent, the residue was purified by

column chromatography to afford MH7C (61% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.64-7.60 (m, 2H), 7.54-7.50 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.52 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.6, 140.4, 138.7, 138.5, 138.4, 134.8, 131.5, 130.3, 129.7, 129.6, 129.0, 126.7, 125.1, 124.7, 124.2, 122.8, 94.0 Hz, 21.8, IR (ATR) ν_{max} (cm^{-1}): 2980.6, 2918.5, 1335.8, 1101.9, 818.8, 739.4, 709.4, 645.8, HRMS calcd for $C_{21}H_{13}IS_2$, 455.9503, found 455.95151.

Compound MH7D:

MH4D (169 mg, 0.47 mmol), CH_2Cl_2 (10 mL), and I_2 (356 mg, 1.41 mmol) were employed to afford MH7D as a white solid Figure 2.38. (59 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.61-7.66 (m, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.30-7.35(m, 2H), 7.09 (s, 1H), 2.46 (s, 3H), 2.08 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 141.4, 140.5, 138.4, 138.2, 136.0, 134.8, 133.3, 131.4, 130.6, 130.2, 130.0, 129.9, 129.0, 126.7, 125.1, 124.7, 124.1, 122.9, 94.3, 21.4, 19.2, IR (ATR) ν_{max} (cm^{-1}): 2953.5, 2916.5, 2853.1, 1444.5, 1094.2, 733.1, 750, 698.5, HRMS calcd for C22H15IS2, 469.9660, found 469.9685

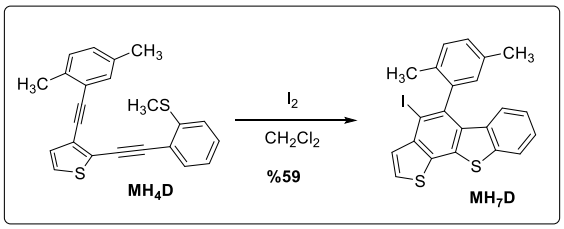


Figure 2.38**.** Synthesis of MH7D compound.

Compound MH7E: MH4E (154.5 mg, 0.40 mmol), CH_2Cl_2 (10 mL), and I_2 (306 mg, 1.218 mmol) were employed to afford MH7E as a white solid Figure 2.39. (70 % yield). ^{1}H NMR (400 MHz, D-DMSO) δ 8.20(d, *J* = 8.0 Hz, 1H), 7.99-8.11 (m, 3H), 7.67-7.77 (m, 2H), 7.45-7.54 (m, 2H), 7.28 (t, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.85 (t, *J* = 8.0 Hz, 1H), 5.95 (d, *J* = 4.0 Hz, 1H), ^{13}C NMR (100 MHz, D-DMSO) δ 141.9, 141.2, 138.31, 138.29, 135.3, 133.9, 133.5, 131.5, 131.47, 130.4, 129.4, 129.0, 128.7, 128.0 Hz, 127.3, 127.0, 126.9, 126.7, 125.1, 125.0, 124.4, 123.8, 96.6, 60.2, IR

(ATR) ν_{max} (cm^{-1}): 3049.9, 29922.5, 2852.7, 1357.5, 775.5, 741.8, 730.1, HRMS calcd for $C_{24}H_{13}IS_2$, 491.9503, found 491.9519

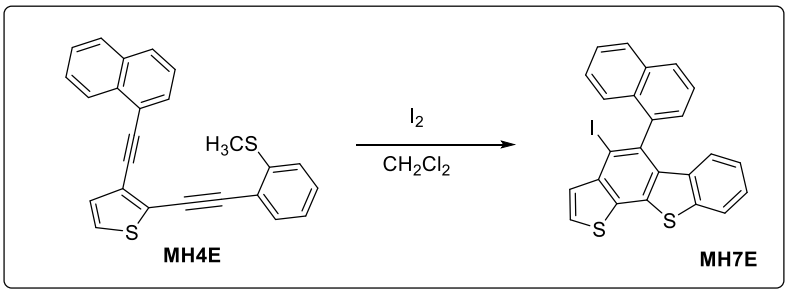


Figure 2.39. Synthesis of MH7E compound.

Compound MH7F:

MH4F (290 mg, 0.80 mmol), CH_2Cl_2 (10 mL), and I_2 (608 mg, 2.4 mmol) were employed to afford MH7F as a light brown solid Figure 2.40 (99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55-7.61 (m, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.36-7.38 (d, J_{AB}= 8.0 Hz, 2H), 7.09-7.11 (d, J_{AB}= 8.0 Hz, 2H), 3.94 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 141.5, 140.4, 138.6, 138.1, 135.9, 134.7, 131.4, 131.1, 130.2, 128.9, 126.6, 125.1, 124.6, 124.1, 122.7, 114.2, 94.5, 55.5, IR (ATR) ν_{max} (cm^{-1}): 2960.9, 2917.4, 1606.5, 1511.8, 1238.3, 1024.7, 834.6, 744.8, 712.3, HRMS calcd for $C_{21}H_{13}IOS_2$, 471.9452, found 471.9455.

Compound MH7G:

MH4G (223 mg, 0.543 mmol), CH_2Cl_2 (15 mL), and I_2 (410 mg, 1.63 mmol) were employed to afford MH7G as a light yellow solid (64% yield) (Figure 2.41). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.79-7.84 (m, 3H), 7.60-7.63 (m, 2H), 7.48-7.53 (m, 2H), 7.23-7.28 (m, 2H), 3.99 (s, 3H), ^{13}C NMR

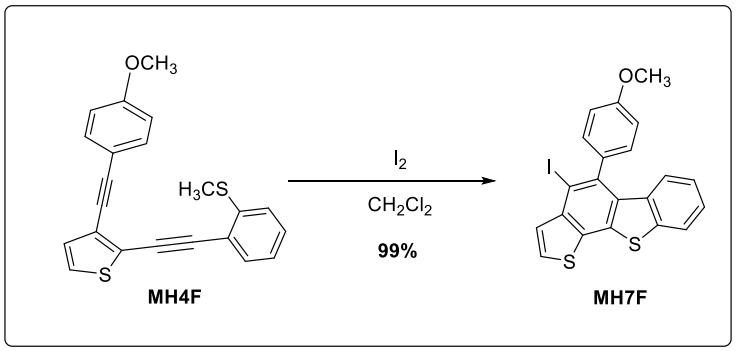


Figure 2.40**.** Synthesis of MH7F compound.

(100 MHz, $CDCl_3$) δ 158.6, 141.6, 140.5, 138.74, 138.71, 138.5, 134.8, 134.7, 131.6, 130.3, 130.2, 129.1, 129.05, 128.9, 128.2, 127.5, 126.8, 125.2, 124.8, 124.2, 122.9, 119.5, 106.2, 94.2, 55.7, IR (ATR) ν_{max} (cm^{-1}): 2916.3, 2848.3, 1296, 1267.6, 1210, 1028.3, 862.3, 745.3, HRMS calcd for $C_{25}H_{15}IOS_2$, 521.9609, found 521.9631.

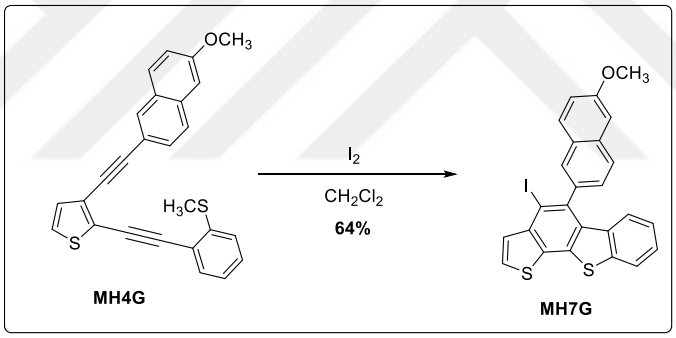


Figure 2.41. Synthesis of MH7G compound.

2.2.1.6. Sonogashira coupling reaction between the 4-iodo-5-substituted thieno[2,3-a]dibenzothiophene compounds and terminal alkynes:

General procedure: To a solution of MH7G or MH7D (0.0765 mmol) in DMF (3.0 mL) were added terminal alkyne (0.082 mmol), Triethylamine (1 mL), $Pd(PPh_3)_2Cl_2$ (2.687 mg, 0.0038 mmol), and the reaction mixture was stirred at room temperature under argon gas for 10 min. Then, CuI (0.728 mg, 0.0038 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture extracted with with CH_2Cl_2. The organic extracts were dried over anhydrous

$MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography to give the product.

Compound MH42A:

MH7G (40 mg, 0.0765 mmol), DMF (3.0 mL), ethynylbenzene (8.3 mg, 0.082 mmol), Triethylamine (1 mL), $Pd(PPh_3)_2Cl_2$ (2.7 mg, 0.0038 mmol), and CuI (0.72 mg, 0.004 mmol) were employed to afford 92% yield as white solid of the indicated product (Figure 2.42**)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H), 7.92-7.96 (m, 2H), 7.84-7.88 (m, 3H), 7.60-7.66 (m, 2H), 7.49-7.53 (t, *J* = 4.0 Hz, 1H), 7.22-7.29 (m, 7H), 4.00 (s, 3H) (Figure 2.44), ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 140.9, 139.9, 138.3, 136.3, 135.3, 134.7, 134.5, 132.7, 131.6 (include 2C), 130.1, 129.3, 129.2, 129.0, 128.7, 128.5, 126.9, 126.6, 125.4, 125.1, 124.9, 124.2, 123.5, 122.9, 119.3, 115.9, 106.1, 96.9, 88.0 ,55.6 (Figure 2.45), IR (ATR) ν_{max} (cm^{-1}): 2954.4, 2923.3, 2853.9, 1723.5, 1266.5, 1212.1, 1034.1, 848.8, 743.6, HRMS calcd for $C_{33}H_{20}OS_2$, 496.0956, found 496.0955.

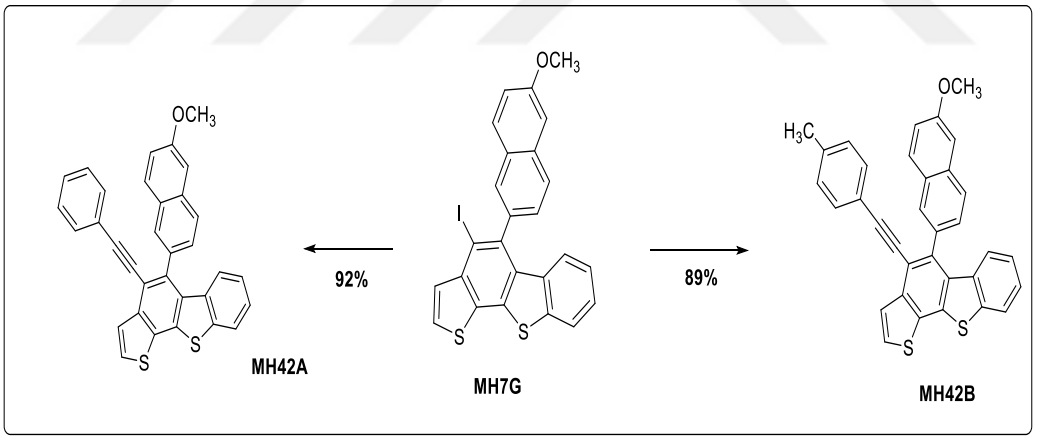


Figure 2.42. Synthesis of MH42A and MH42B compounds.

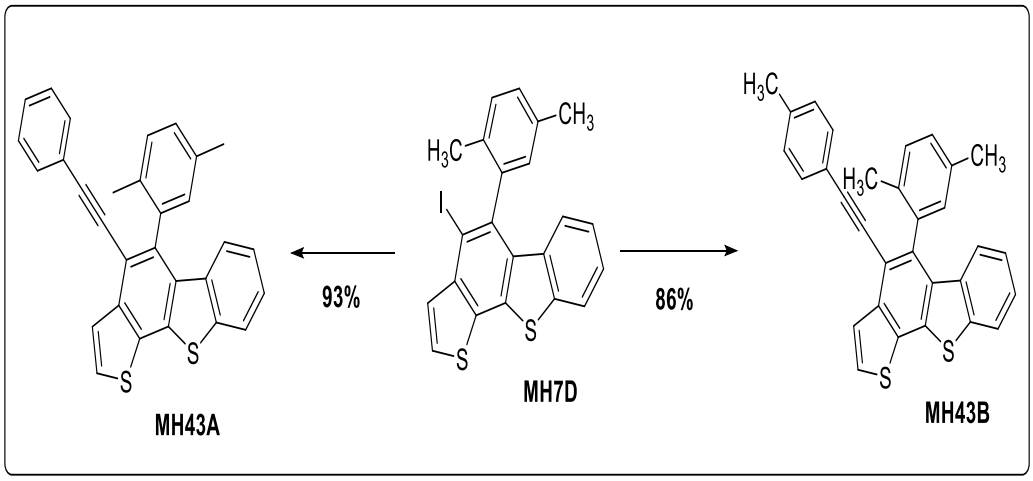


Figure 2.43. Synthesis of MH43A and MH43B compounds.

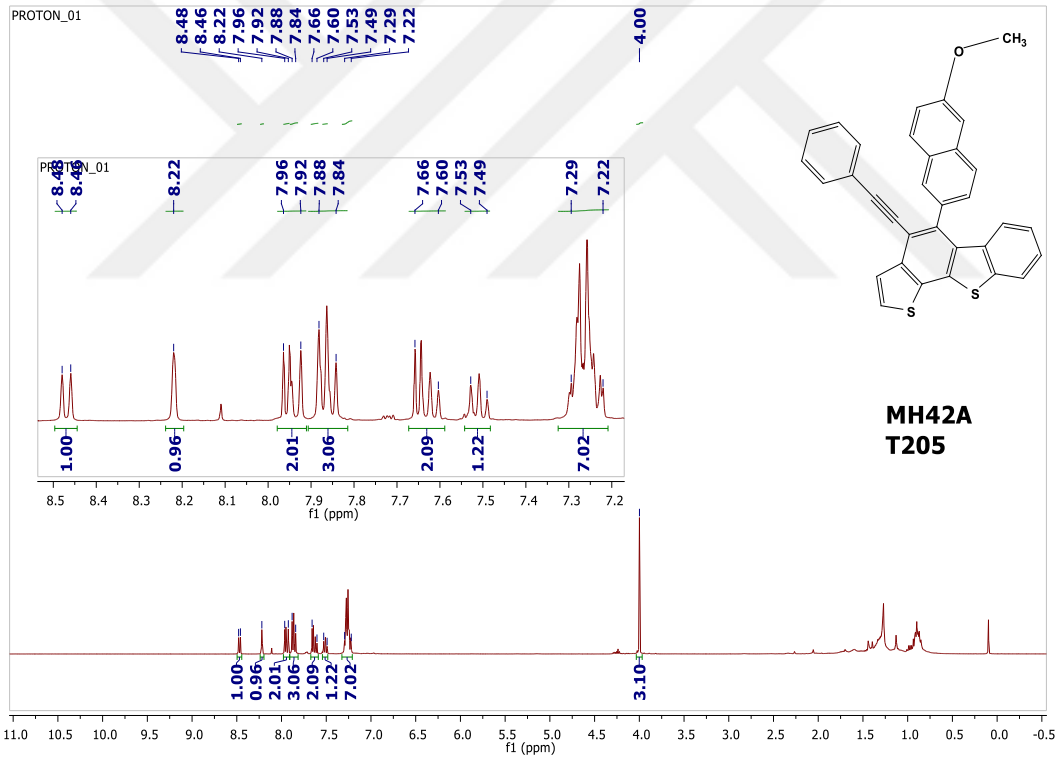


Figure 2.44. Representative ^{1}H NMR spectra of MH42A.

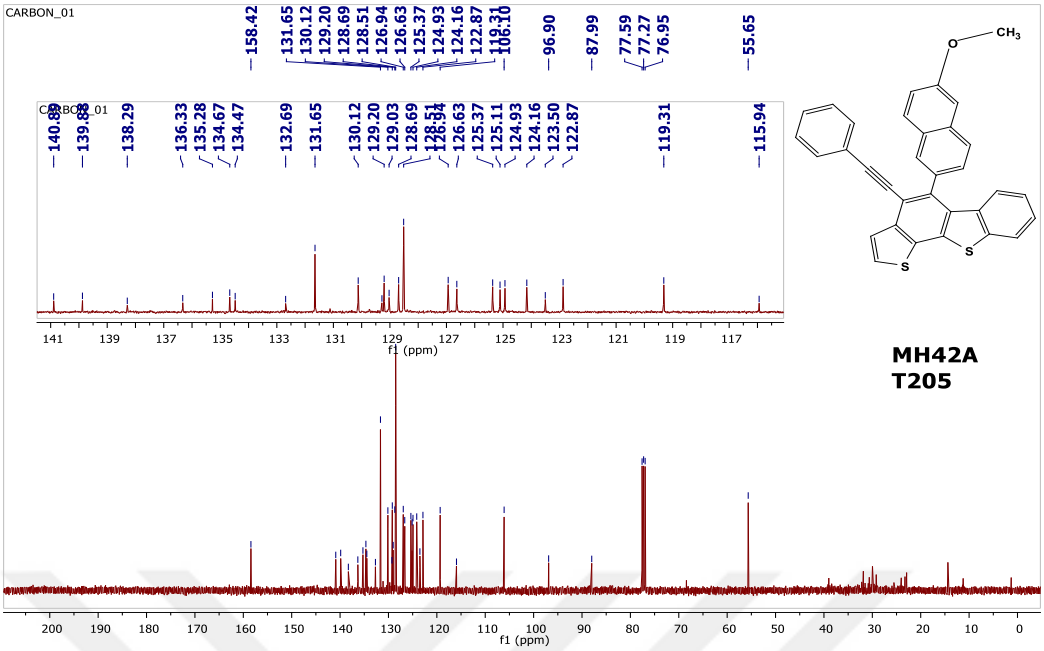


Figure 2.45. Representative ^{13}C NMR spectra of MH42A.

Compound MH42B:

MH7G (40 mg, 0.0765 mmol), DMF (3.0 mL), 1-ethynyl-4-methylbenzene (9.53 mg, 0.082 mmol), Triethylamine (1 mL), $Pd(PPh_3)_2Cl_2$ (2.687 mg, 0.0038 mmol), and CuI (0.728 mg, 0.0038 mmol) were employed to afford 89% yield as yellow solid of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 8.22 (s, 1H), 7.84-7.95 (m, 5H), 7.60-7.65 (m, 2H), 7.50 (t, J = 8.0 Hz, 1H), 7.22-7.28 (m, 2H), 7.16-7.18 (d, J_{AB}= 8.0 Hz, 2H), 7.04-7.06 (d, J_{AB}= 8.0 Hz, 2H), 4.00 (s, 3H), 2.31 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 140.8, 139.8, 138.7, 138.3, 136.1, 135.3, 134.6, 134.5, 132.7, 131.5, 130.1, 129.3, 129.2, 129.1, 129.0, 128.7, 126.9, 126.6, 125.3, 125.1, 125.0, 124.1, 122.9, 120.4, 119.3, 116.2, 106.1, 97.2, 87.4, 55.6, 21.7, IR (ATR) ν_{max} (cm^{-1}): 2957, 2924.1, 1628.7, 1603.5, 1213, 1030, 856.5, 814.1, 752.5, 726.1, HRMS calcd for $C_{34}H_{22}OS_2$, 510.1112, found 510.1111.

Compound MH43A:

MH7D (40 mg, 0.085 mmol), DMF (3.0 mL), ethynylbenzene (9.3 mg, 0.091 mmol), Triethylamine (1.0 mL), $Pd(PPh_3)_2Cl_2$ (2.98 mg, 0.0042 mmol), and CuI (0.809 mg, 0.0042 mmol) were employed to afford 93% yield as a yellow solid of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.94 (d, J

= 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.61-7.67 (m, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.25-7.34 (m, 7H), 2.43 (s, 3H), 2.17 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.3, 138.6, 138.3, 136.7, 135.4, 135.3, 134.0 Hz, 132.6, 131.7, 130.6, 130.3, 129.7, 129.5, 128.9, 128.5, 126.6, 125.3, 125.1, 124.7, 124.1, 123.6, 123.0, 116.4, 96.8, 87.5, 21.3, 19.4, IR (ATR) ν_{max} (cm^{-1}): 2956.4, 2921.6, 2853.3, 2206.4, 1719.2, 1442.6, 1265.6, 1099.5, 751, HRMS calcd for $C_{30}H_{20}S_2$, 444.1006, found 444.1006.

Compound MH43B:

MH7D (40.0 mg, 0.085 mmol), DMF (3.0 mL), 1-ethynyl-4-methylbenzene (10.58 mg, 0.091 mmol), Triethylamine (1.0 mL), $Pd(PPh_3)_2Cl_2$ (2.98 mg, 0.0042 mmol), and CuI (0.809 mg, 0.0042 mmol) were employed to afford 86% yield as a yellow solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 4.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.60-7.66 (m, 2H), 7.50 (t, *J* = 4.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.23-7.26 (m, 2H), 7.09-7.15 (m, 4H), 2.41 (s, 3H), 2.34 (s, 3H), 2.15 (s, 3H),, ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.3, 138.7, 138.69, 138.3, 136.5, 135.4, 135.36, 134.0 Hz, 131.6, 130.6, 130.3, 129.7, 129.4, 129.3, 128.8, 126.5, 125.2, 125.1, 124.8, 124.1, 123.0, 120.5, 116.7, 97.1, 86.9, 21.8, 21.3, 19.4, IR (ATR) ν_{max} (cm^{-1}): 2956.9, 2922.4, 2854, 1722.7, 1461.7, 1265.9, 1116, 1100.8, 730.1, HRMS calcd for $C_{31}H_{22}S_2$, 458.1163, found 458.1164.

2.2.1.7. Stille coupling reaction between the iodo substituted compound (MH7F) and 2-(tributylstannyl)thiophene or 2-(tributylstannyl)furan:

General procedure: To a mixture of the compound MH7F (50 mg, 0.1 mmol), 2-(tributylstannyl)thiophene or 2-(tributylstannyl)furan (0.127 mmol) and toluene (10 ml) was added $Pd(PPh_3)_4$ (6.1 mg, 0.0052) under argon gas, the mixture was reflux overnight at 110 ^oC. The reaction mixture extracted with with CH_2Cl_2. The organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography to give the product.

Compound MH44A:

MH7F (50 mg, 0.1 mmol), 2-(tributylstannyl)thiophene (47 mg, 0.127 mmol), toluene (10 ml), and $Pd(PPh_3)_4$ (6.1 mg, 0.0052) were employed to afford 93% yield as a yellow solid of the indicated product (Figure 2.46). (Note: this compound has splitting for NMR data), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 8.0 Hz, 1H), 7.88-7.95 (m, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.52-7.57 (m, 3H), 7.32-7.34 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 6.91-7.02 (m, 3H), 3.86 (s, 3H) (Figure 2.47)., ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 140.6, 140.3, 139.4, 139.0, 135.4, 133.4, 133.0, 131.4, 130.0, 129.1, 127.5, 126.7, 126.6, 126.4, 125.1, 125.0, 124.5, 124.0 Hz, 122.8, 122.1, 113.9, 155.4 (Figure 2.48)., IR (ATR) ν_{max} (cm^{-1}): 2980.6, 2925.2, 1513.4, 1243, 1174.8, 1028.6, 831.7, 694.6, HRMS calcd for $C_{25}H_{16}OS_3$, 428.0363, found 428.0366

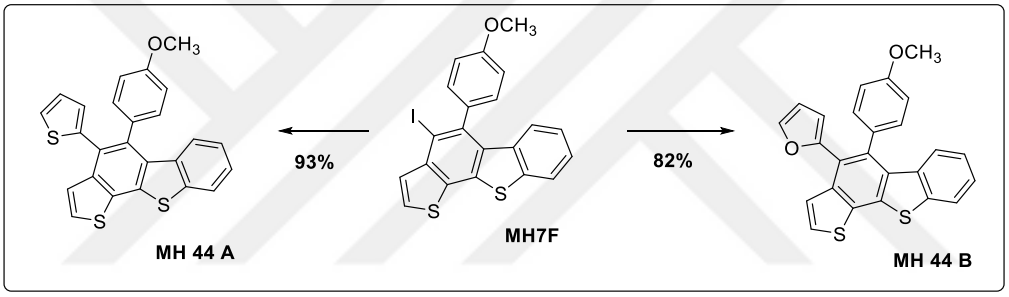


Figure 2.46**.** Synthesis of MH44A and MH44B compounds.

Compound MH44B:

MH7F (50 mg, 0.1 mmol), 2-(tri-n-butylstannyl)furan (45 mg, 0.127 mmol), toluene (10 ml), and $Pd(PPh_3)_4$ (6.1 mg, 0.0052) were employed to afford 82% yield as a yellow solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.80-7.82 (d, J_{AB}= 8.0 Hz, 1H), 7.61-7.65 (m, 1H), 7.58-7.60 (d, J_{AB}= 8.0 Hz, 1H), 7.48-7.54 (m, 2H), 7.33-7.35 (d, J_{AB}= 8.0 Hz, 2H), 6.98-7.01 (d, J_{AB}= 8.0 Hz, 2H), 6.38-6.39 (m, 1H), 6.04 (d, J = 4.0 Hz, 1H), 3.90 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.0, 142.2, 140.7, 139.6, 137.5, 135.4, 133.6, 132.7, 132.4, 131.0, 128.9, 126.4, 125.1, 125.0, 124.7, 124.1, 124.0 Hz, 122.8, 114.2, 111.8, 111.3, 55.8, IR (ATR) ν_{max} (cm^{-1}): 2951.6, 2923.5, 1514.3, 1246.1, 1171.8, 837.9, 720.9, HRMS calcd for $C_{25}H_{17}O_2S_2$, 413.0592 $[M+H]^+$, found 413.0670 $[M+H]^+$.

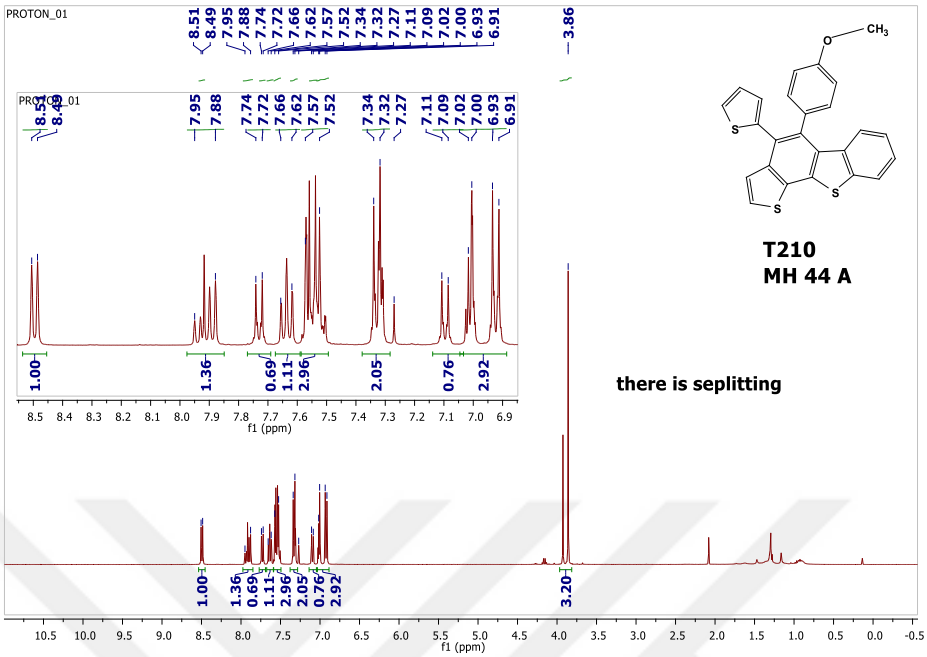


Figure 2.47. Representative ^{1}H NMR spectra of MH44A.

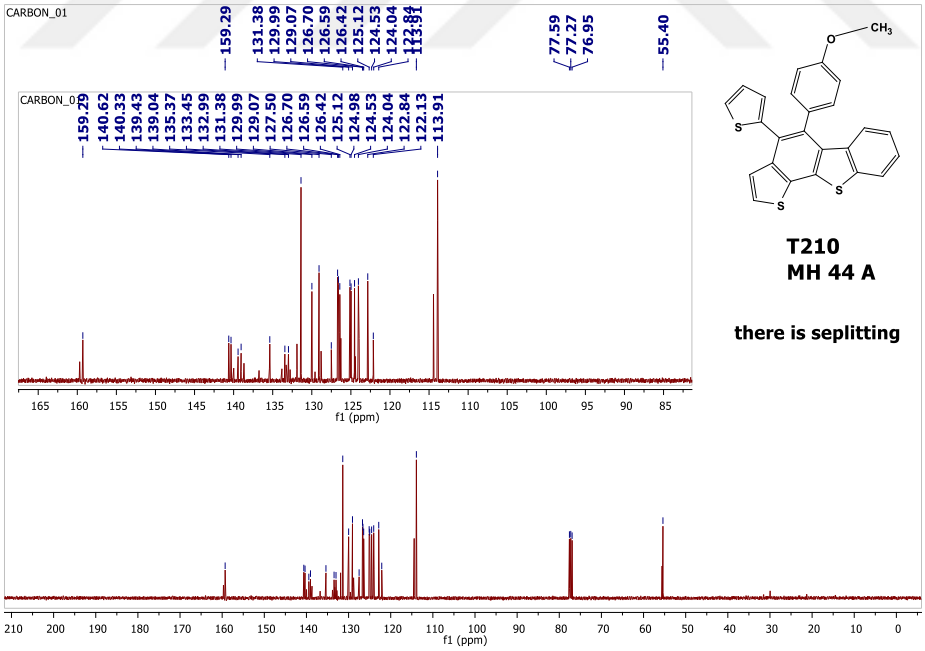


Figure 2.48. Representative ^{13}C NMR spectra of MH44A.

2.2.2. Synthesis of thieno[3,2-a]dibenzothiophene derivatives

2.2.2.1. Sonogashira coupling reaction to preparation of the trimethyl ((2(methylthio) phenyl) ethynyl)silane (MH6)

To a stirred mixture of the 2-iodothioanisole (2.48 mmol, 620 mg), THF (8 mL), ethynyltrimethylsilane (2.97 mmol, 303 mg), triethylamine (12.4 mmol, 1252 mg), $PdCl_2(PPh_3)_2$ (0.06 mmol, 42.1 mg) under argon gas was added CuI (0.06 mmol,11.4 mg), The resulting mixture was stirred at room temperature for 12 h. Water (30 mL) was added to the reaction mixture. The resulting solution was extracted with DCM (3×30 mL). The organic layer was dried over anhydrous MgSO4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel using hexanes as mobile phase. This compound was obtained as a light yellow oil in an 95% yield (Figure 2.49). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4-7.42 (m, 1H), 7.24-7.28 (m, 1H), 7.02-7.12 (m, 2H), 0.28 (s, 9H), 2.46 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 132.7, 129.1, 124.1, 123.9, 121.1, 102.3, 101.4, 15.0, 0.13, IR (ATR) ν_{max} (cm^{-1}): 3059.4, 2980.5, 2920.7, 2890.6, 2154.7 (C≡C),1435.5, 1248.3 (Si-CH_3), 838, 747.6, 685.2 (S-C).

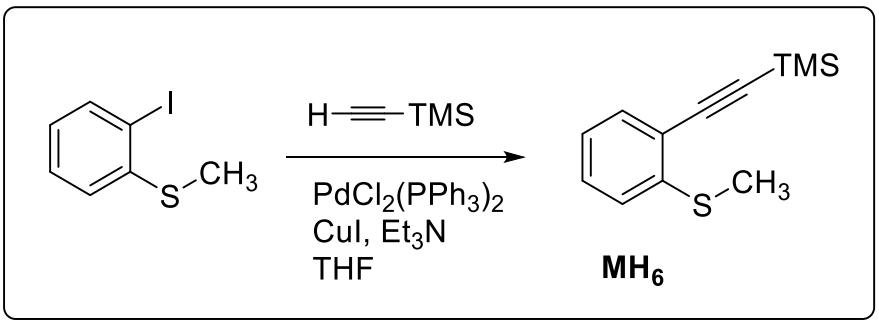


Figure 2.49. Synthesis of MH6 compound.

Desilylation Reaction to prepare (MH9)

A solution of compound MH6 (2 g, 9.09 mmol), methanol (60 mL), and THF (20 mL) was added K_2CO_3 (3.72 g, 27 mmol). The mixture was stirred at room temperature for 60 min. The reaction mixture extracted with EtOAc. The organic extracts were dried over anhydrous MgSO4. After filtration and removal of solvent, the

residue was purified by column chromatography to give the product. This compound was obtained as yellow oil in an 91% yield (Figure 2.50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.42 (m,1H), 7.23-7.28 (m, 1H), 7.09-7.11 (m, 1H), 7.0-7.05 (m,1H), 3.47 (s, 1H), 2.42 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 133.1, 129.3, 124.2, 124.1, 120.1, 83.7, 81.0, 60.3, IR (ATR) ν_{max} (cm^{-1}): 3058.3, 2982, 3281.3 (≡C—H), 2920.2, 2101.8 (C≡C), 1432.7, 747.9, 614.6 (S-C), HRMS calcd for C_9H_9S, 149.0347 $[M+H]^+$, found 149.0248 $[M+H]^+$.

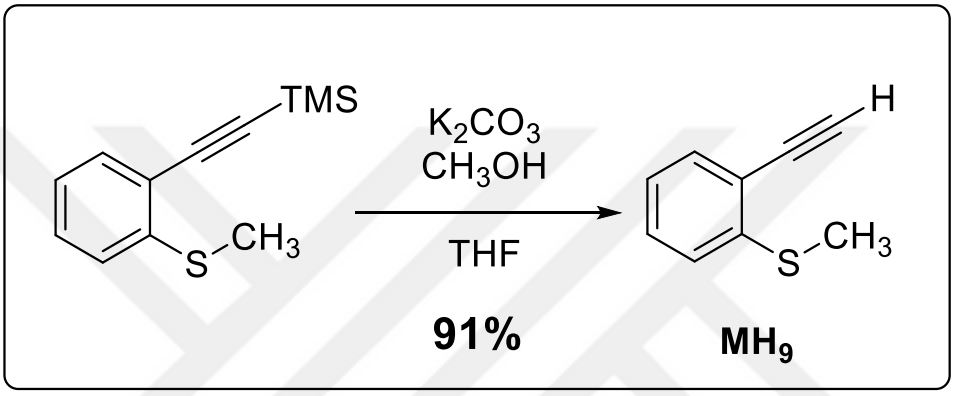


Figure 2.50. Synthesis of MH9 compound.

2.2.2.2. Sonogashira coupling reaction to preparation of trimethyl((3-((2-(methylthio)phenyl)ethynyl)thiophen-2-yl)ethynyl)silane (MH13)

To a stirred suspension of MH1 (619 mg, 2.39 mmol), $PdCl_2(PhCN)_2$ (56.7 mg, 0.14 mmol), and CuI (28.1 mg, 0.14 mmol) in 1,4-dioxane (5 mL) were added diisopropylamine (1205 mg, 11.9 mmol), MH9 (384 mg, 2.6 mmol), and tri-tert-butylphosphine (45.9 mg, 0.286 mmol). After being stirred at rt for 12 h, the reaction mixture was diluted with EtOAc and filtered through a short pad of silica gel (Figure 2.51) The filtrate was concentrated in vacuum, and the residue was chromatographed on silica gel (hexane) to afford MH13 (50%) as a brown oil (Figure 2.51). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29 (s, 9H), 2.52 (s, 3H), 7.09-7.10 (d, J_{AB}= 4.0 Hz, 1H), 7.11-7.14 (m, 1H), 7.17-7.18 (d, J_{AB}= 4.0 Hz, 1H), 7.19-7.21 (m, 1H), 7.30-7.34 (m, 1H), 7.49-7.51 (m, 1H) (Figure 2.52),, ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2, 15.4, 90.3, 91.0, 96.7, 103.9, 121.5, 124.4, 124.5, 126.2, 126.3, 127.5, 129.1, 129.8, 132.9, 141.7 (Figure

2.53), IR (ATR) ν_{max} (cm^{-1}): 644.46, 748.18, 838.24, 1248.31 (Si-CH_3), 1462.81, 2142.9 (C≡C), 2342.6, 2359.8, 2890.5 ,2919.8, 2980.5, 3105.5, HRMS calcd for $C_{18}H_{19}S_2Si$, 327.0619 $[M+H]^+$, found 327.0703 $[M+H]^+$.

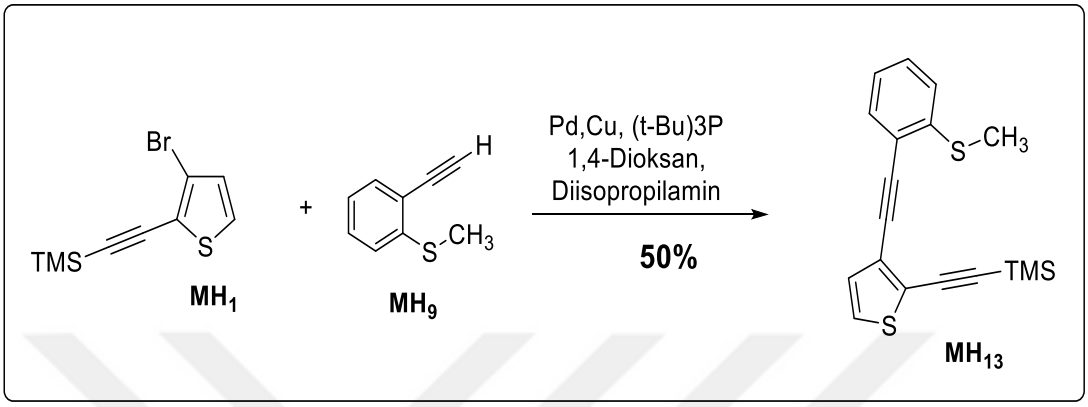


Figure 2.51. Synthesis of MH13 compound.

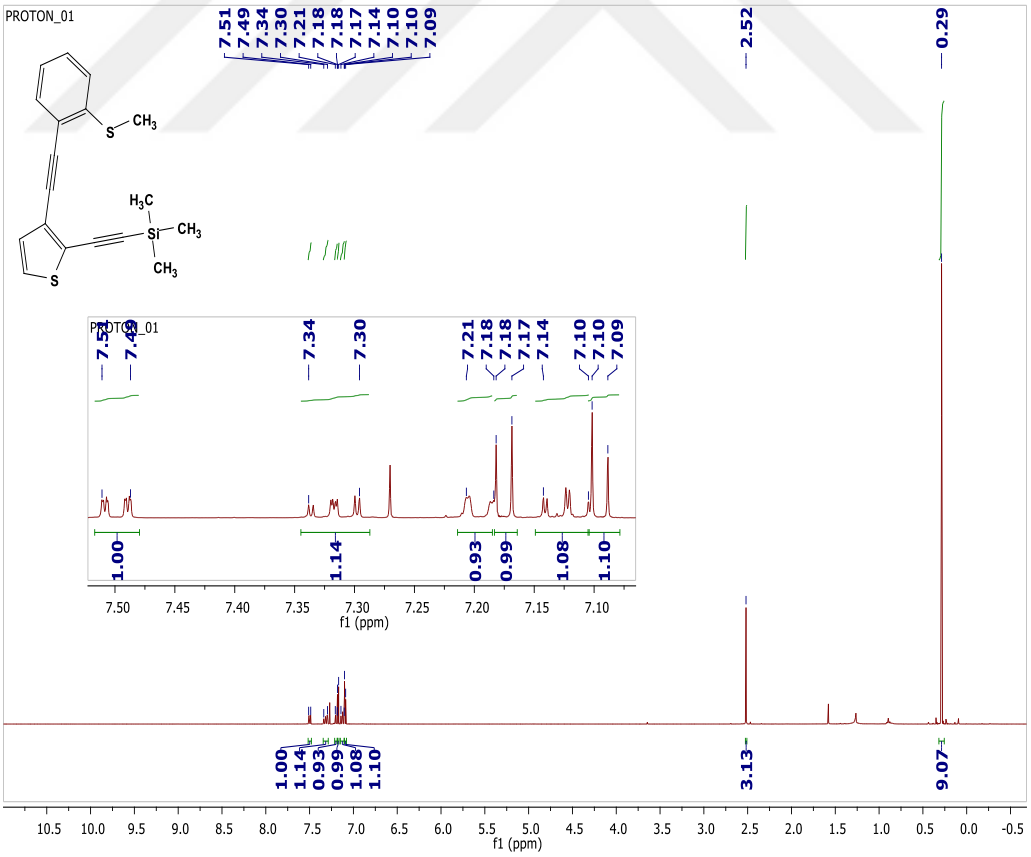


Figure 2.52. Representative ^1H NMR spectra of MH13.

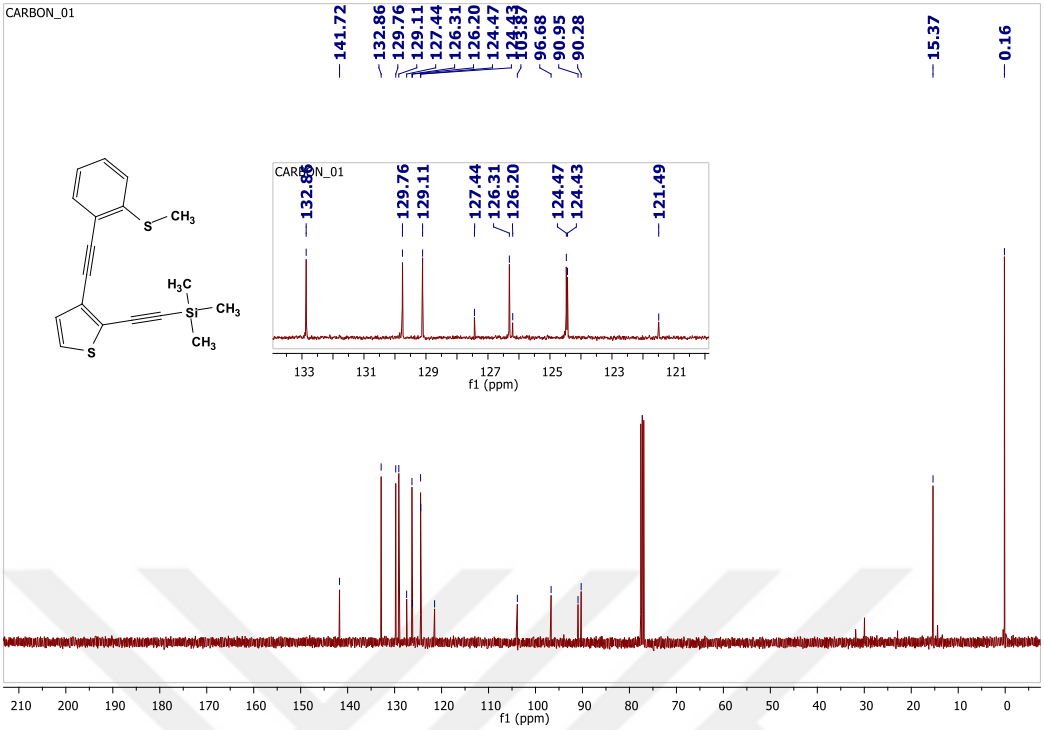


Figure 2.53. Representative ^{13}C NMR spectra of MH13.

2.2.2.3. Desilylation Reaction to prepare 2-ethynyl-3-((2-(methylthio) phenyl) ethynyl)thiophene (MH15)

To a solution of compound MH13 (563 mg, 1.72 mmol), methanol (25 mL), and THF (7 mL) was added K_2CO_3 (715 mg, 5.1 mmol). The mixture was stirred at room temperature for 120 min. The reaction mixture extracted with EtOAc. The organic extracts were dried over anhydrous MgSO4. After filtration and removal of solvent, the residue was purified by column chromatography to give the product. This compound was obtained as brown oil in an 98% yield (Figure 2.54). ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.65 (s, 1H), 7.11-7.15 (m, 1H), 7.12-7.13 (d, J_{AB}= 4.0 Hz, 1H), 7.18-7.20 (m, 1H), 7.12-7.22 d, J_{AB}= 4.0 Hz, 1H), 7.30-7.34 (m, 1H), 7.51-7.53 (m, 1H) (Figure 2.55), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 76.3, 85.8, 89.8, 91.0, 121.2, 124.4, 124.5, 124.9, 126.6, 127.9, 129.2, 129.8, 132.9, 141.8 (Figure 2.56**)**, IR (ATR) ν_{max} (cm^{-1}): 645.1, 729.5, 747, 1430.5, 1462.2, 2098.9 (C≡C), 2199.9 (C≡C), 2917.4, 3104.1, 3280.6 (≡C—H), HRMS calcd for $C_{15}H_{11}S_2$, 255.0224 $[M+H]^+$, found 255.0300 $[M+H]^+$.

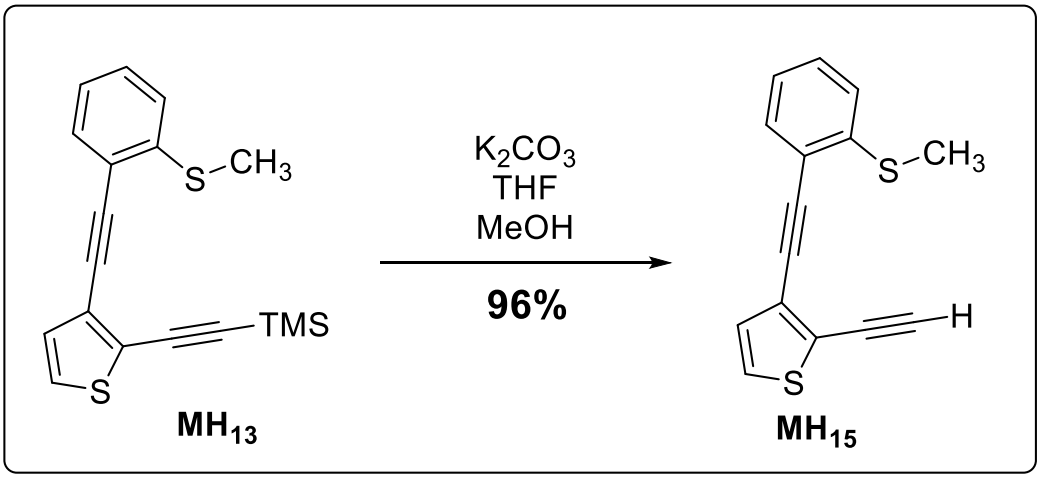


Figure 2.54. Synthesis of MH15 compound.

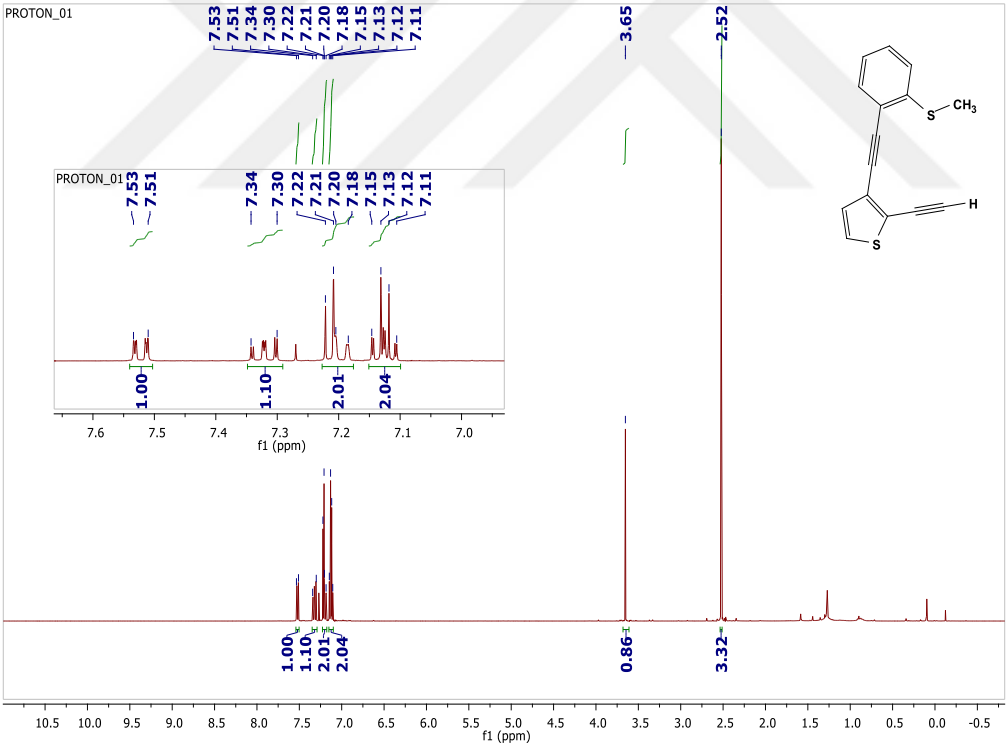


Figure 2.55. Representative ^{1}H NMR spectra of MH15.

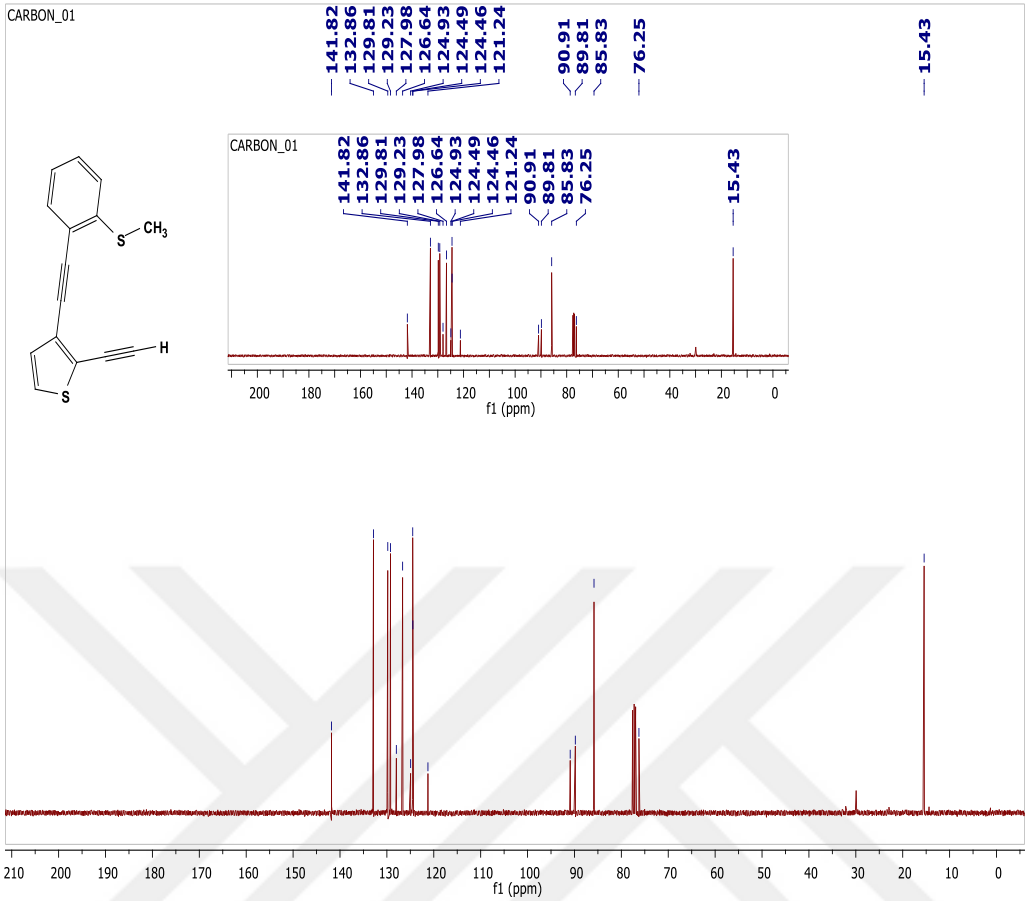


Figure 2.56. Representative ^{13}C NMR spectra of MH15.

2.2.2.4. Sonogashira coupling reaction to preparation of 3-((2-(methylthio)phenyl) ethynyl)-2-(substitutedethynyl)thiophene derivatives

General procedure for the reaction between MH15 and arylbromid compounds: To a stirred suspension of arylbromid (0.78 mmol), $PdCl_2(PhCN)_2$ (17 mg, 0.044 mmol), and CuI (8.5 mg, 0.044 mmol) in 1,4-dioxane (2 mL) were added diisopropylamine (363.9 mg, 3.59 mmol), MH15 (0.78 mmol), and tri-tert-butylphosphine (14.0 mg, 0.087 mmol). After being stirred at rt for 12 h, the reaction mixture was diluted with EtOAc and filtered through a short pad of silica gel. The filtrate was concentrated in vacuum, and the residue was chromatographed on silica gel (hexane) to afford the product.

General procedure for the reaction between MH15 and aryl iodide compounds: Solution of MH15 (0.7 mmol) in THF (7.5 mL) were added aryliodid compounds (0.7 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (24.566 mg, 0.035 mmol), and the reaction mixture was stirred at room temperature under argon gas for 10 min. Then, CuI (6.66 mg, 0.035 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture extracted with with CH_2Cl_2. The organic extracts were dried over anhydrous MgSO4. After filtration and removal of solvent, the residue was purified by column chromatography to give the product.

Compound MH19:

2-Bromothiophene (128.3 mg, 0.78 mmol), $PdCl_2(PhCN)_2$ (17.1 mg, 0.044 mmol), CuI (8.5 mg, 0.044 mmol, 1,4-dioxane (2 mL), diisopropylamine (363.9 mg, 3.59 mmol), MH15 (200 mg, 0.78 mmol), and tri-tert-butylphosphine (14 mg, 0.087 mmol) were employed to afford 91 % as a yellow solid of the indicated product (Figure 2.57).^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.03-7.05 (m, 1H), 7.10-7.15 (m, 2H), 7.17-7.19 (m, 1H), 7.24 (d, J = 4.0 Hz, 1H), 7.29-7.36 (m, 3H), 7.51-7.54 (m, 1H) (Figure 2.58), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 86.0, 90.4, 90.9, 91.3, 121.4, 123.2, 124.3, 124.4, 126.1, 126.7, 126.9, 127.4, 128.2, 129.1, 129.8, 132.7, 132.9, 142.1 (Figure 2.59**)**, IR (ATR) ν_{max} (cm^{-1}): 640.9, 702.7, 839.1, 983.2, 1433.6, 1462.9, 2147.6 (C≡C), 2193.1 (C≡C), 2858.3, 2920, 2956.3, 3105.6, HRMS calcd for $C_{19}H_{12}S_3$, 336.0101, found 336.0101.

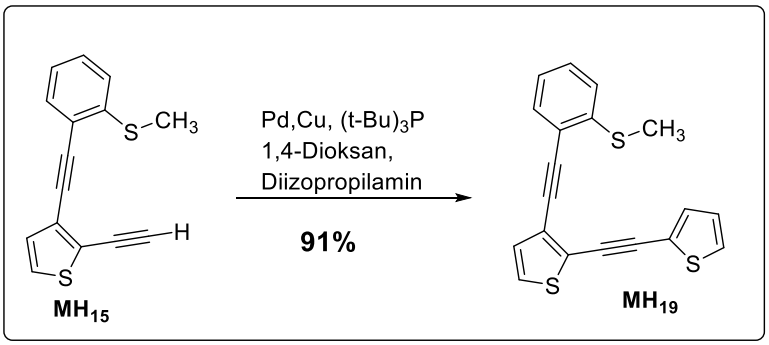


Figure 2.57. Synthesis of MH19 compound.

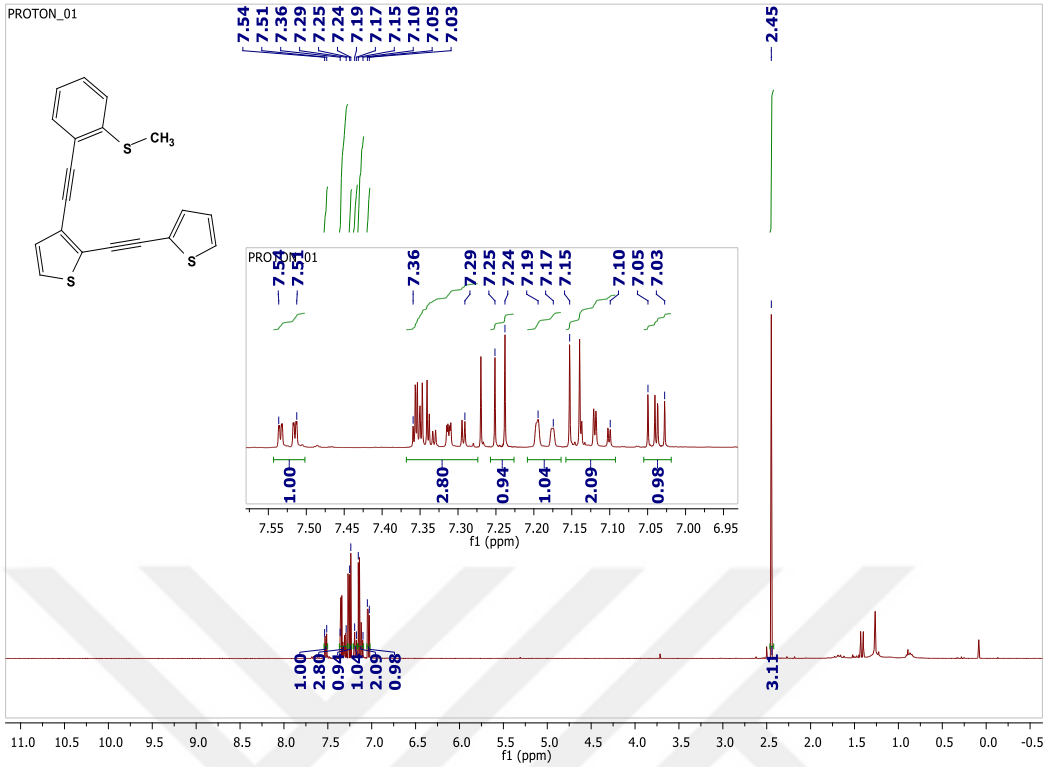


Figure 2.58. Representative ^{1}H NMR spectra of MH19.

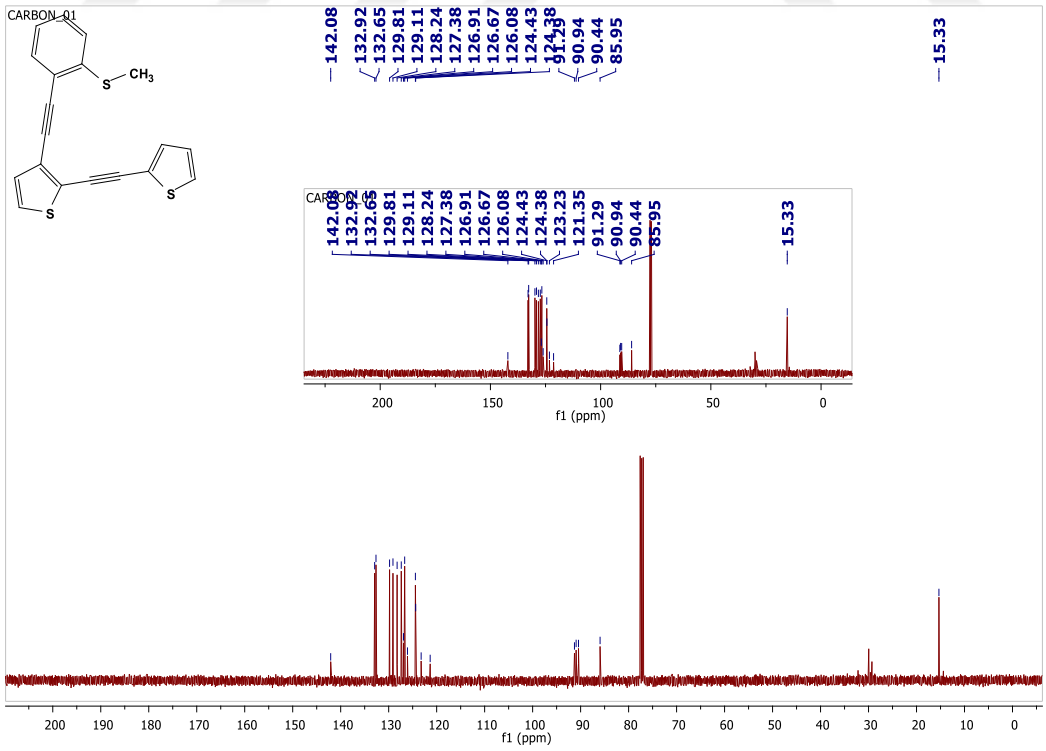


Figure 2.59. Representative ^{13}C NMR spectra of MH19.

Compound MH19B:

Bromobenzene (104.4 mg, 0.28 mmol), $PdCl_2(PhCN)_2$ (14.4 mg, 0.037 mmol), CuI (7.1 mg, 0.037 mmol), 1,4-dioxane (2 mL), diisopropylamine (307.4 mg, 3.03 mmol), MH15 (169 mg, 0.66 mmol), and tri-tert-butylphosphine (11.72 mg, 0.073 mmol) were employed to afford 69% as a brown solid of the indicated product (Figure 2.60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.11-7.15 (m, 1H), 7.16-7-17 (d, J_{AB}= 4.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.23-7.24 (d, J_{AB}= 4.0 Hz, 1H), 7.30-7.34 (m, 1H), 7.35-7.39 (m, 3H), 7.53-7.55 (m, 1H), 7.60-7.63 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 82.4, 90.5, 91.1, 97.8, 121.4, 123.2, 124.3, 124.4, 126.3, 126.5, 126.8, 128.5, 128.8, 129.1, 129.8, 132.0, 132.6, 142.0, IR (ATR) ν_{max} (cm^{-1}): 637.4, 718.9, 753.4, 1421.9, 2206.9 (C≡C), 2339.3, 2359.8, 2918.1, 2980.5, 3050.5, HRMS calcd for $C_{21}H_{15}S_2$, 331.0537 $[M+H]^+$, found 331.0616 $[M+H]^+$.

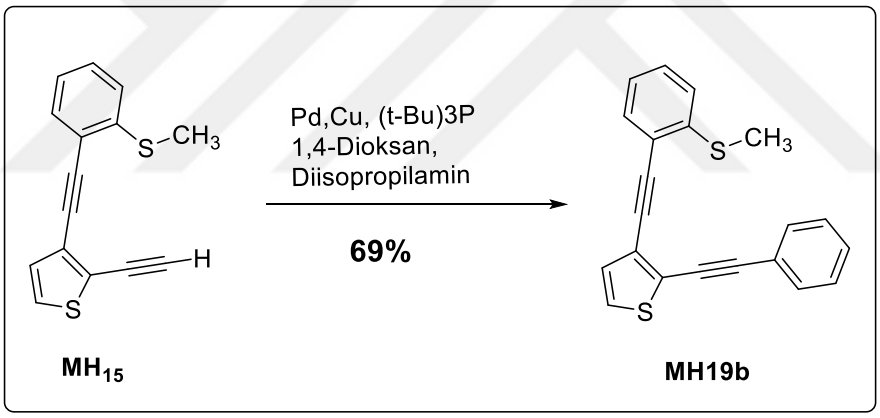


Figure 2.60. Synthesis of MH19B compound.

Compound MH19C:

3-Bromothiophene (128.3 mg, 0.78 mmol), $PdCl_2(PhCN)_2$ (17.1 mg, 0.044 mmol), CuI (8.5 mg, 0.044 mmol), 1,4-dioxane (2 mL), diisopropylamine (363.9 mg, 3.59 mmol), MH15 (200 mg, 0.78 mmol), and tri-tert-butylphosphine (14 mg, 0.087 mmol) were employed to afford 87% as a brown solid of the indicated product (Figure 2.61). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.61 (m, 1H), 7.50-7.52 (m, 1H), 7.29-7.33 (m, 2H), 7.25-7.27 (m, 1H), 7.21-7.23 (d, J_{AB}= 8.0 Hz, 1H), 7.18-7.20 (m, 1H), 7.13-7.15 (d, J_{AB}= 8.0 Hz, 1H), 7.10-7.14 (m, 1H), 2.43 (s, 3H), ^{13}C NMR (100 MHz,

$CDCl_3$) δ 142.0, 132.7, 130.2, 129.83, 129.80, 129.6, 129.1, 126.8, 126.5, 126.2, 125.5, 124.5, 124.4, 121.5, 93.0, 91.0, 90.6, 81.8, 15.3, IR (ATR) ν_{max} (cm^{-1}): 3056.6, 2980.5, 2920.6, 2359.7, 2342.6 , 2200 (C≡C),1380.5, 1157, 691.5, HRMS calcd for $C_{19}H_{13}S_3$, 336.0101 $[M+H]^+$, found 337.0176 $[M+H]^+$.

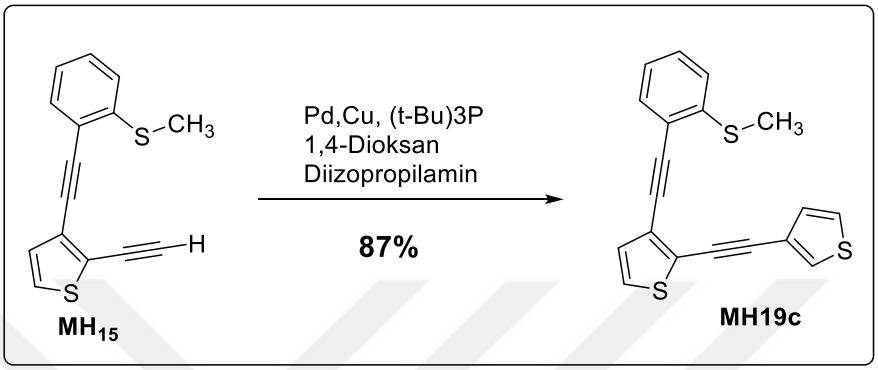


Figure 2.61. Synthesis of MH19C compound.

Compound MH19D:

4-bromoaniline (169 mg, 0.983 mmol), $PdCl_2(PhCN)_2$ (21.3 mg, 0.055 mmol), CuI (10.6 mg, 0.055 mmol), 1,4-dioxane (4 mL), diisopropylamine (454.2 mg, 4.48 mmol), MH15 (250 mg, 0.98 mmol), and tri-tert-butylphosphine (17.3 mg, 0.108 mmol) were employed to afford 41% as a green oil of the indicated product (Figure 2.62.). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.32-7.28 (m, 1H), 7.18-7.16 (m, 2H), 7.13-7.09 (m, 2H), 6.62 (d, J = 12.0 Hz, 2H), 3.90 (b, 2H), 2.43

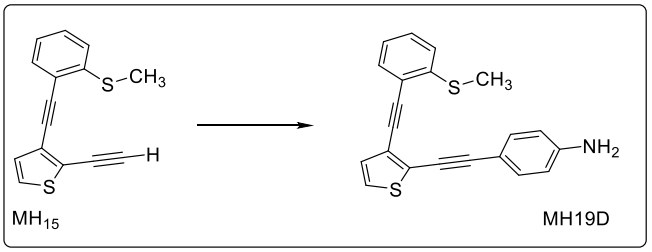


Figure 2.62. Synthesis of MH19D compound.

(s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 141.9, 133.4, 132.5, 129.7, 128.9, 127.4, 125.7, 125.5, 124.4, 124.3, 121.5, 114.8, 112.3, 98.9, 90.8, 90.7, 80.3, 15.2, IR (ATR)

ν_{max} (cm^{-1}): 3371, 2955.9, 2922.3, 2853.5, 2182.4, 1602.7, 1461.6, 1260.7, 10.69.6, 747.4, 727.1, HRMS calcd for $C_{21}H_{16}NS_2$, 345.0646 $[M+H]^+$, found 346.0722 $[M+H]^+$.

Compound MH19E:

N,*N*-Dimethyl-4-bromoaniline (196.6 mg, 0.983 mmol), $PdCl_2(PhCN)_2$ (21.3 mg, 0.055 mmol), CuI (10.6 mg, 0.055 mmol), 1,4-dioxane (4 mL), diisopropylamine (454 mg, 4.48 mmol), MH15 (250 mg, 0.98 mmol), and tri-tert-butylphosphine (17.3 mg, 0.108 mmol) were employed to afford 11% as a red oil of the indicated product (Figure 2.63). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 1H), 7.48 (d, *J* = 12.0 Hz, 2H), 7.33-7.28 (m, 1H), 7.20-7.10 (m, 4H), 6.66 (d, *J* = 8.0 Hz, 2H), 3.00 (s, 6H), 2.45 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 141.9, 133.2, 132.6, 130.5, 129.6, 128.9, 127.8, 125.4, 125.2, 124.4, 121.7, 111.8, 109.8, 99.5, 91.0, 90.6, 80.4, 40.4, 15.4, IR (ATR) ν_{max} (cm^{-1}): 2970.53, 2920.52, 2185.56, 1603.81, 1526.88, 1359.63, 948.65, 750.03, HRMS calcd for $C_{23}H_{20}NS_2$, 374.0959 $[M+H]^+$, found 374.1036 $[M+H]^+$.

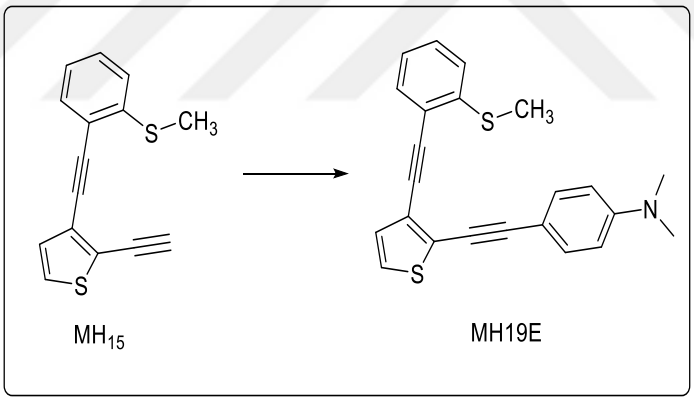


Figure 2.63. Synthesis of MH19E compound.

Compound MH19F:

2-Bromopyridine (155.3 mg, 0.983 mmol), $PdCl_2(PhCN)_2$ (21.3 mg, 0.055 mmol), CuI (10.6 mg, 0.055 mmol), 1,4-dioxane (4 mL), diisopropylamine (454 mg, 4.48 mmol), MH15 (250 mg, 0.98 mmol), and tri-tert-butylphosphine (17.3 mg, 0.108 mmol) were employed to afford 70 % as a yellow solid of the indicated product (Figure 2.64). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.0 Hz, 1H), 7.67-7.63 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.54-7.52 (m, 1H), 7.31-7.26 (m, 2H), 7.24-7.20 (m, 1H), 7.17-7.08

(m, 3H), 2.43 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 143.3, 142.0, 136.2, 132.6, 129.9, 129.1, 127.8, 127.7, 127.5, 125.1, 124.4, 124.2, 123.0, 121.1, 96.6, 91.4, 90.2, 82.1, 15.2, IR (ATR) ν_{max} (cm^{-1}): 2980.5, 2919., 2198.6, 1579.2, 1462.7, 1431.3, 1264.9, 952.8, 749.1, 730.3, HRMS calcd for $C_{20}H_{14}NS_2$, 331.0489 $[M+H]^+$, found 332.0567 $[M+H]^+$.

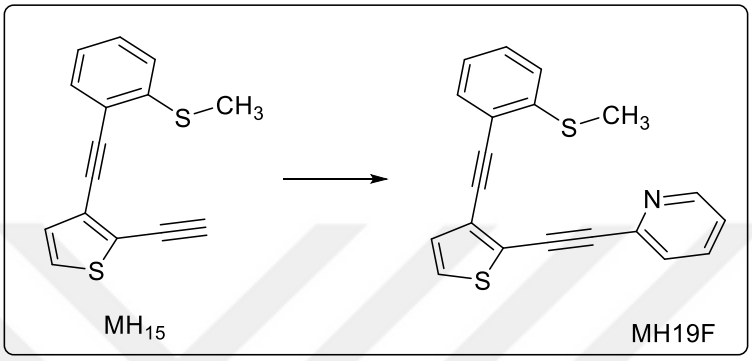


Figure 2.64. Synthesis of MH19F compound.

Compound MH19G:

3-Bromopyridine (155.3 mg, 0.983 mmol), $PdCl_2(PhCN)_2$ (21.3 mg, 0.055 mmol), CuI (10.6 mg, 0.055 mmol), 1,4-dioxane (4 mL), diisopropylamine (454.2 mg, 4.48 mmol), MH15 (250 mg, 0.98 mmol), and tri-tert-butylphosphine (17.3 mg, 0.108 mmol) were employed to afford 78 % as a yellow solid of the indicated product (Figure 2.65).. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 4.0 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 7.85-7.83 (m, 1H), 7.50-7.48 (m, 1H), 7.31-7.24 (m, 3H), 7.15-7.07 (m, 3H), 2.40 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 148.7, 141.9, 138.8, 132.5, 129.9, 129.2, 127.5, 127.1, 125.3, 124.3, 124.0 Hz, 123.2, 120.9, 120.4, 94.0 Hz, 91.3, 90.1, 85.7, 15.1, IR (ATR) ν_{max} (cm^{-1}): 3103.5, 3088.1, 3033.7, 2918., 2208.8, 1556.9, 1428.8, 951, 748.5, 726.3, 718.9, 700.8, HRMS calcd for $C_{20}H_{14}NS_2$, 332.0489 $[M+H]^+$, found 332.0569 $[M+H]^+$.

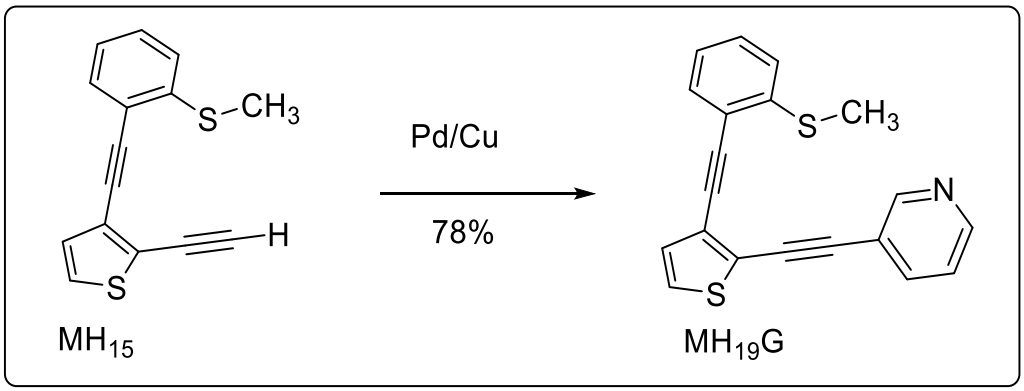


Figure 2.65. Synthesis of MH19G compound.

Compound MH46A:

MH15 (178 mg, 0.7 mmol), THF (7.5 mL), 4-iodothioanisole (175 mg, 0.7 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (24.5 mg, 0.035 mmol), and CuI (6.66 mg, 0.035 mmol) were employed to afford 62% yield as yellow oil of the indicated product (Figure 2.66). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.58 (m, 3H), 7.29-7.33 (m, 1H), 7.11-7.21 (m, 4H), 6.90 (d, J = 16.0 Hz, 2H), 3.83 (s, 3H), 2.43 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 141.9, 133.5, 132.5, 129.7, 129.0, 126.9, 126.1, 125.8, 124.4, 124.3, 121.4, 115.2, 114.1, 98.0 Hz, 90.8, 90.6, 81.1, 55.5, 15.2, IR (ATR) ν_{max} (cm^{-1}): 3104.4, 2918.3, 2834.9, 2194.8, 1602.9, 1519.2, 1504.3, 1288.3, 1246.1, 1171.7, 829.5, 747.8, HRMS calcd for $C_{22}H_{17}OS_2$, 361.0643 $[M+H]^+$, found 361.0729 $[M+H]^+$.

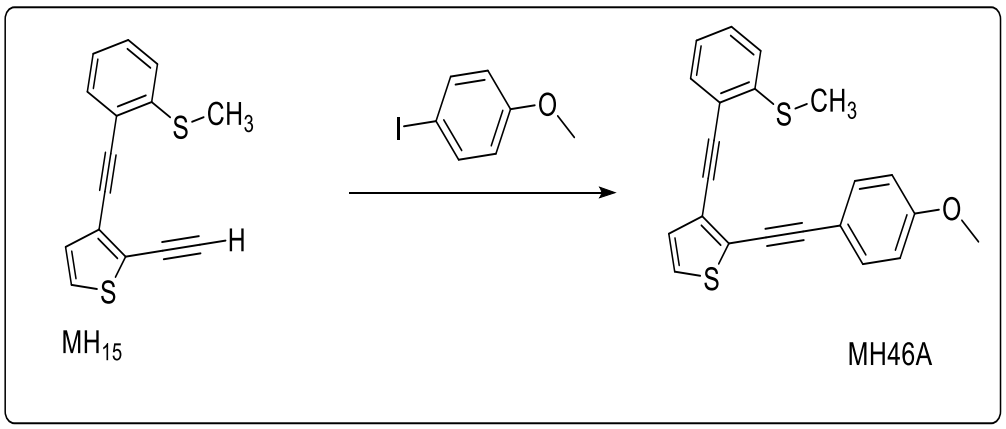


Figure 2.66. Synthesis of MH46A compound.

Compound MH46B:

MH15 (250 mg, 0.98 mmol), THF (7.5 mL), 1-iodonaphthalene (249.7 mg, 0.98 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (34.4 mg, 0.049 mmol), and CuI (9.3 mg, 0.049 mmol) were employed to afford 83% yield as yellow oil of the indicated product (Figure 2.67). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 8.0 Hz, 1H), 7.84-7.88 (m, 3H), 7.58-7.60 (m, 1H), 7.47-7.53 (m, 2H), 7.38-7.40 (d, 1H), 7.32-7.37 (m, 1H), 7.28-7.29 (d, J_{AB}= 4.0 Hz, 1H), 7.23-7.24 (d, J_{AB}= 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.12-7.16 (m, 1H), 2.37 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 133.3, 133.2, 132.9, 130.8, 130.0, 129.3, 129.2, 128.4, 127.2, 126.9, 126.8, 126.7, 126.65, 126.5, 125.4, 124.4, 124.3, 121.3, 120.8, 96.2, 91.2, 90.7, 87.2, 15.2, IR (ATR) ν_{max} (cm^{-1}): 3054.7, 2918.0, 2191.7, 1582.2, 1431, 1069.2, 798.2, 771.4, 748.3, 725.3, 642.2, HRMS calcd for $C_{25}H_{17}S_2$, 381.0693 $[M+H]^+$, found 381.0777 $[M+H]^+$.

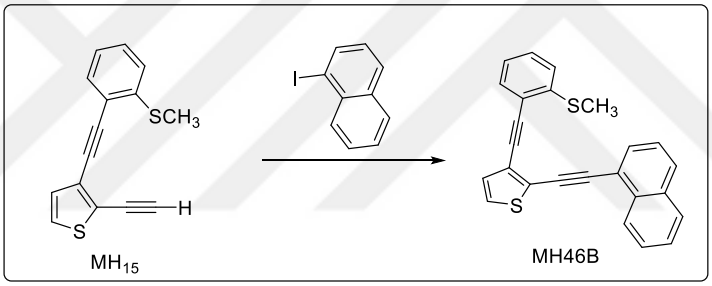


Figure 2.67. Synthesis of MH46B compound.

Compound MH46C:

MH15 (250 mg, 0.98 mmol), THF (7.5 mL), methyl-4-iodobenzoate (257.5 mg, 0.98 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (34.4 mg, 0.049 mmol), and CuI (9.3 mg, 0.049 mmol) were employed to afford 81% yield as light yellow solid of the indicated product (Figure 2.68). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-8.05 (d, J_{AB}= 12.0 Hz, 2H), 7.64-7.67 (d, J_{AB}= 12.0 Hz, 2H), 7.51-7.54 (d, J = 12.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.26-7.28 (d, J_{AB}= 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.16-7.17 (d, J_{AB}= 4.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 3.93 (s, 3H), 2.44 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 142.0, 132.6, 131.8, 130.0, 129.8, 129.6, 129.2, 127.9, 127.5, 127.1, 125.7, 124.4, 124.3, 121.2, 96.9, 91.4, 90.3, 85.4, 52.4, 52.5, 15.2, IR (ATR) ν_{max}

(cm^{-1}): 2980.5, 2918.3, 2191.3, 1707.4, 1192.3, 1278.1, 1105.7, 956, 748.9, 720.2, HRMS calcd for $C_{23}H_{17}OS_2$, 389.0592 $[M+H]^+$, found 389.0663 $[M+H]^+$.

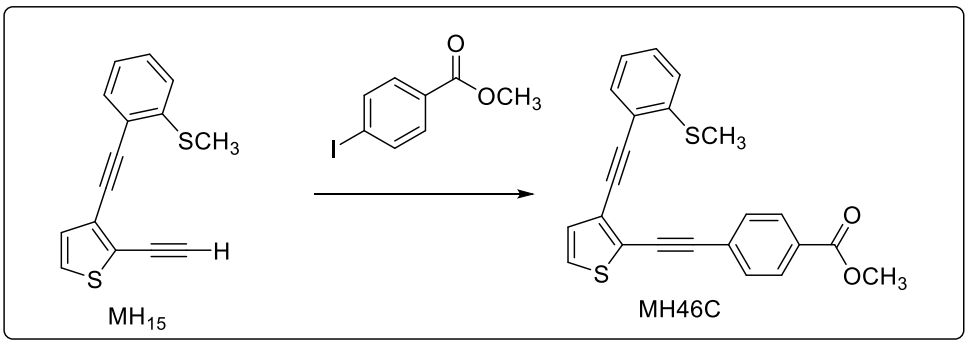


Figure 2.68. Synthesis of MH46C compound.

Compound MH46D:

MH15 (250 mg, 0.98 mmol), THF (7.5 mL), 5-iodothiophene-2-carbaldehyde (218.1 mg, 0.98 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (34.4 mg, 0.049 mmol), and CuI (9.3 mg, 0.049 mmol) were employed to afford 78 % yield as yellow solid of the indicated product (Figure 2.69). ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.52-7.55 (m, 1H), 7.30-7.32 (m, 2H), 7.26 (d, J = 4.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.11-7.17 (m, 2H), 6.83 (d, J = 4.0 Hz, 1H), 2.5 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 152.9, 142.1, 141.9, 132.8, 130.1, 129.4, 128.8, 128.4, 124.5, 124.4, 123.7, 121.5, 121.0, 118.0 Hz, 92.2, 89.8, 89.5, 86.3, 15.3, IR (ATR) ν_{max} (cm^{-1}): 3094.2, 2980.5, 2209.7, 2193.8, 1664.7, 1382.7, 1273.6, 1030.1, 956.1, 740.7, HRMS calcd for $C_{20}H_{13}O_2S_2$, 349.0279 $[M+H]^+$, found 349.0371 $[M+H]^+$.

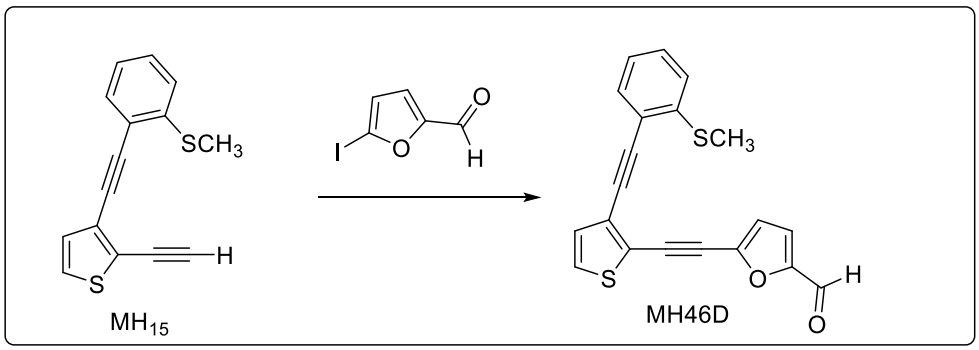


Figure 2.69. Synthesis of MH46D compound.

Compound MH46E:

MH15 (250 mg, 0.98 mmol), THF (7.5 mL), 4-iodoaniline (215.2 mg, 0.98 mmol), Triethylamine (3 mL), $Pd(PPh_3)_2Cl_2$ (34.4 mg, 0.049 mmol), and CuI (9.3 mg, 0.049 mmol) were employed to afford 83% yield as orange-red oil of the indicated product (Figure 2.70). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.51 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.26-7.30 (m, 1H), 7.14-7.17 (m, 2H), 7.08-7.12 (m, 2H), 6.63 (d, *J* = 8.0 Hz, 2H), 3.19 (b, 2H), 2.41 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 141.9, 133.4, 132.5, 129.7, 128.9, 127.4, 125.7, 125.4, 124.4 (include 2C), 121.6, 114.8, 112.4, 98.9, 90.8, 90.7, 80.3, 15.3, IR (ATR) ν_{max} (cm^{-1}): 3472.1, 3377.4, 2918.9, 2182.3, 1617, 1602.7, 1521.3, 1292.3, 826.9, 748.4, HRMS calcd for $C_{21}H_{16}NS_2$, 346.0646 $[M+H]^+$, found 346.0721 $[M+H]^+$.

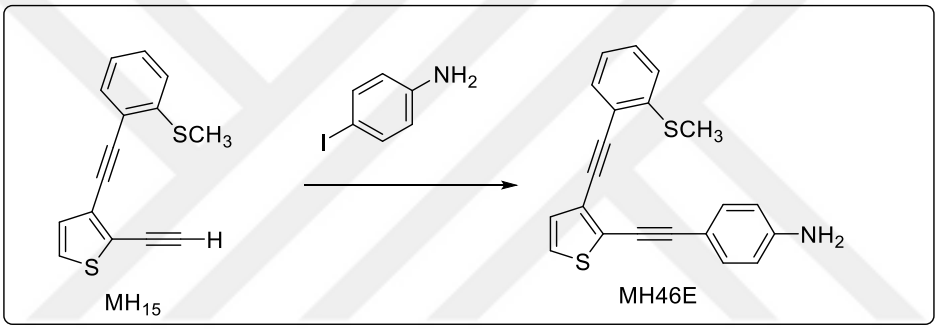


Figure 2.70. Synthesis of MH46E compound.

2.2.2.5. Iodine-mediated intramolecular electrophilic aromatic cyclization to preparation of 4-iodo-5-substituted-thieno[3,2-a]dibenzothiophene derivatives:

General procedure: To a solution of reactant compound (0.32 mmol) in CH_2Cl_2 (8 mL) in the presence of I_2 (247 mg, 0.98 mmol) was stirred at room temperature for 30 min. The saturated aqueous solution of $Na_2S_2O_3$ was added subsequently into the reaction mixture and extracted by EtOAc. The combined organic extracts were dried over anhydrous MgSO4. After filtration and removal of solvent, the residue was purified by column chromatography to afford the product.

2.2.2.5.1. 4-iodo-5-(thiophen-2-yl)-dibenzo[b,d]thiopheno[2,1-b]thiophene (MH20):

MH19 (110 mg, 0.32 mmol), CH_2Cl_2 (8 mL), and I_2 (247 mg, 0.98 mmol) were employed to afford 60 % yield as yellow solid of the indicated product (Figure 2.71). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44-8.52 (m, 2H), 7.81-7.86 (m, 2H), 7.47-7.60 (m, 3H), 7.24-7.28 (m, 2H) (Figure 2.72), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 143.3, 140.3, 139.7, 135.7, 133.3, 131.0, 129.5, 129.4, 129.1, 127.4, 127.3, 126.6, 125.0, 124.2, 123.1, 122.9, 93.2 (Figure 2.72), IR (ATR) v_{max} (cm^{-1}): 3091.1, 2980.5, 2922.3, 2359.7, 2342.5, 1395.5, 692.4, HRMS calcd for $C_{18}H_9IS_3$, 447.8911, found 447.8926.

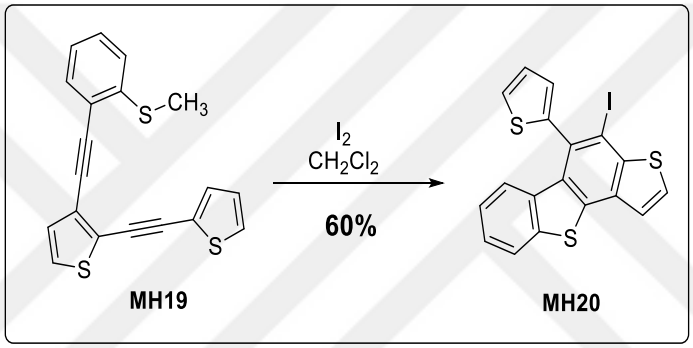


Figure 2.71. Synthesis of MH20 compound.

2.2.2.5.2. 3-iodo-2-(2-(phenylethynyl)thiophen-3-yl)benzo[b]thiophene (MH20b):

MH19b (180 mg, 0.544 mmol), CH_2Cl_2 (8.5 mL), and I_2 (411 mg, 1.63 mmol) were employed to afford 70 % yield as yellow crystals of the indicated product (Figure 2.74). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.88 (m, 2H), 7.45-7.51 (m, 3H), 7.40-7.44 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.30-7.33 (m, 3H) (Figure 2.75), ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 139.5, 138.0 Hz, 136.7, 131.6, 129.7, 128.9, 128.5, 126.4, 126.3, 125.9, 125.6, 123.1, 122.9, 122.3, 97.8, 82.6, 81.6 (Figure 2.76), IR (ATR) v_{max} (cm^{-1}): 3053.3, 2980.4, 2921.9, 2852., 2360.4, 2193 (C≡C),1430.3, 752.5, 689.7, HRMS calcd for $C_{20}H_{11}IS_2$, 441.9347, found 441.9368.

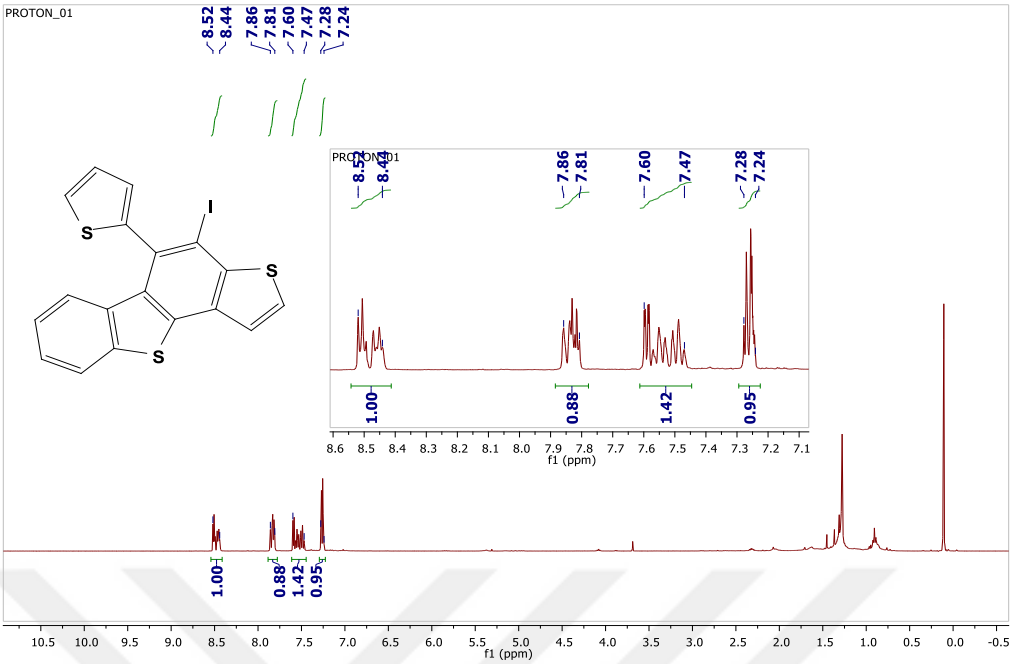


Figure 2.72. Representative ^{1}H NMR spectra of MH20.

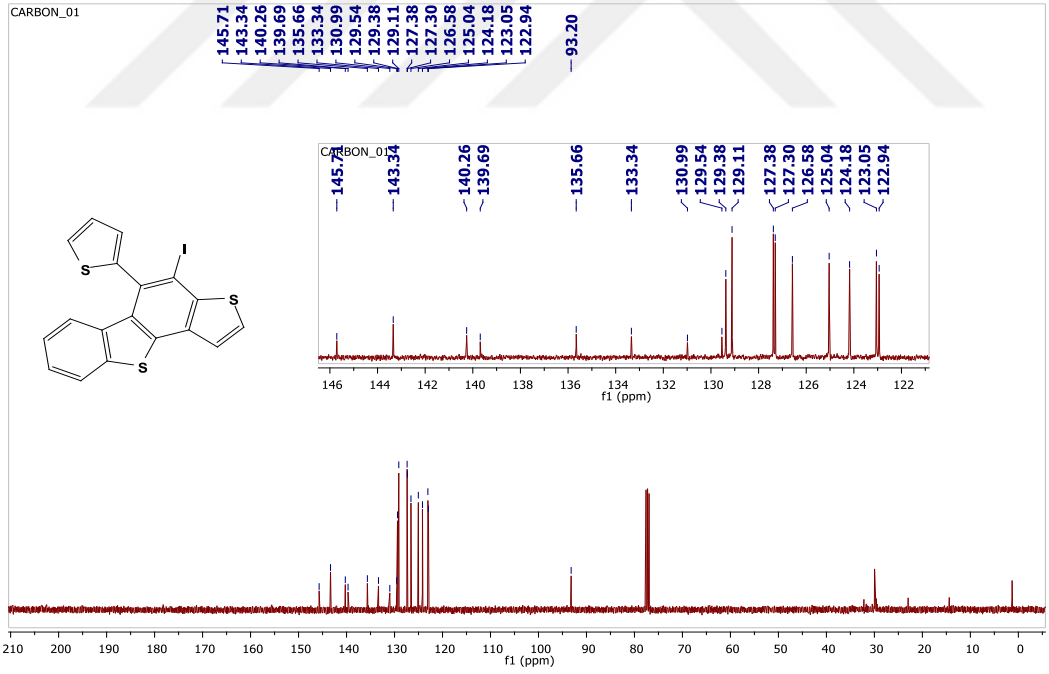


Figure 2.73. Representative ^{13}C NMR spectra of MH20.

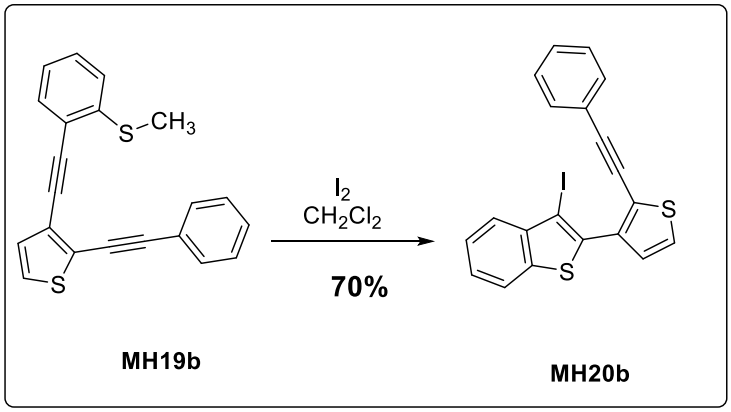


Figure 2.74. Synthesis of MH20B compound.

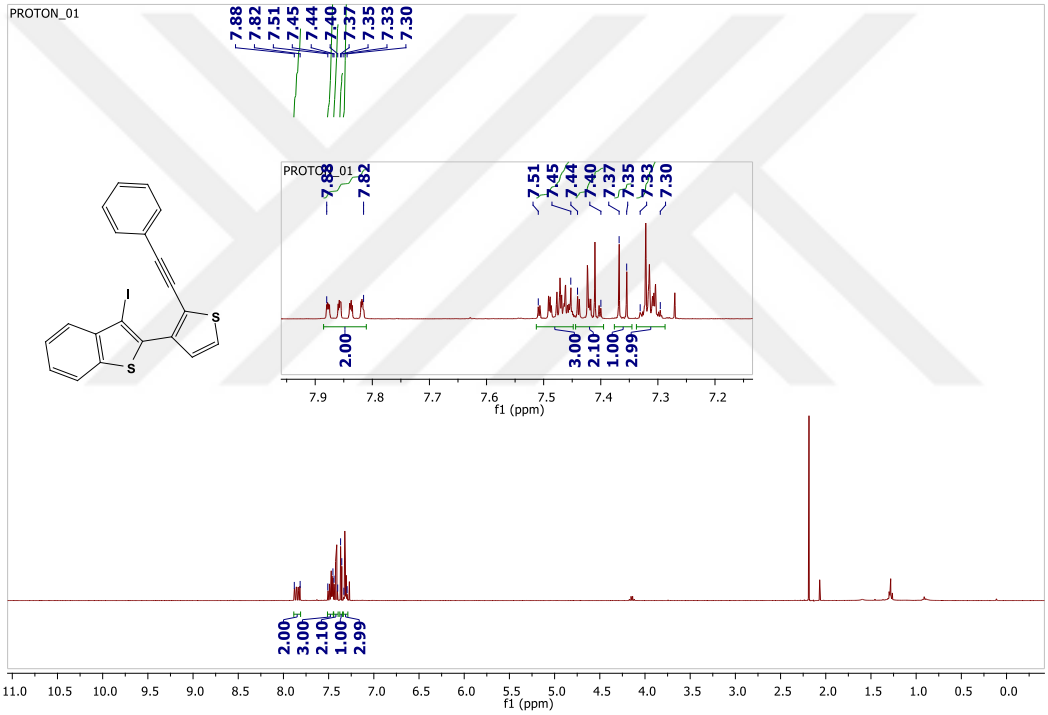


Figure 2.75. Representative ^{1}H NMR spectra of MH20B.

Compound MH20C:

MH19C (150 mg, 0.44 mmol), CH_2Cl_2 (8.0 mL), and I_2 (343.6 mg, 1.36 mmol) were employed to afford the products as mixture cannot be separated by column chromatography with different solvents (Figure 2.77).

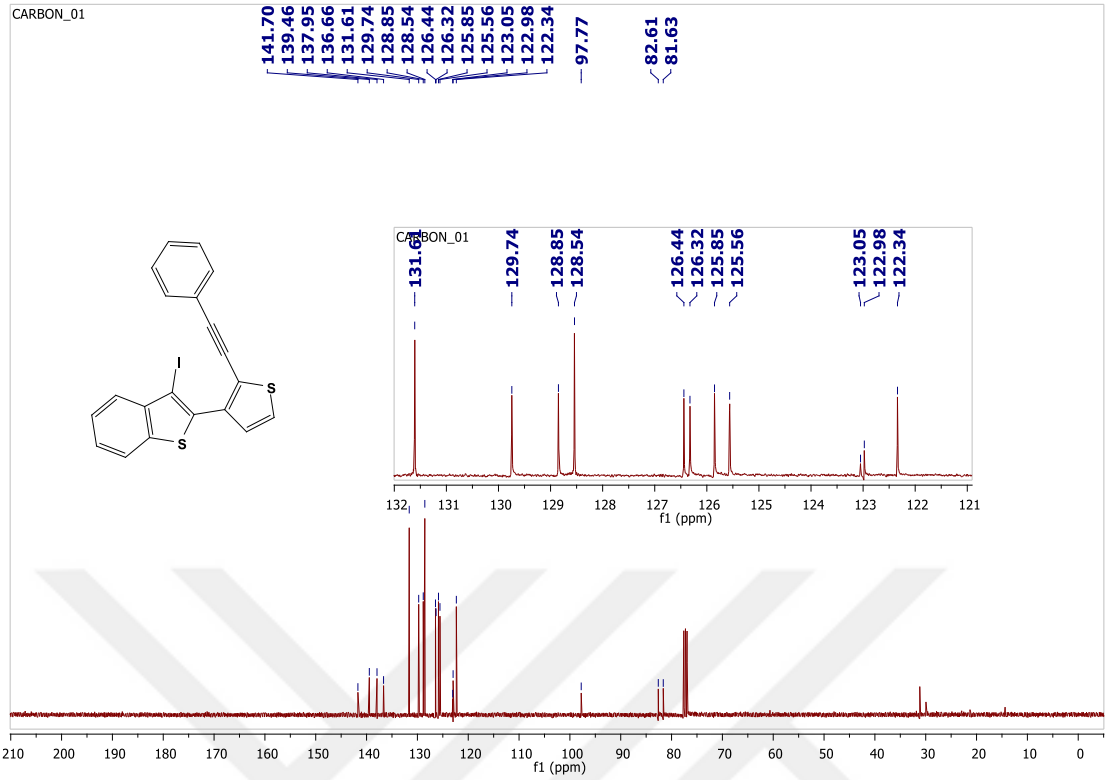


Figure 2.76. Representative ^{13}C NMR spectra of MH20B.

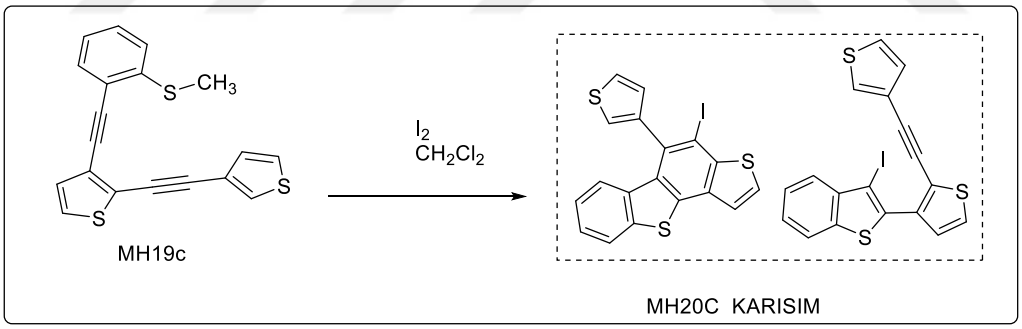


Figure 2.77. Synthesis of MH20C as mixture compounds.

Compound MH20F:

MH19F (185 mg, 0.558 mmol), CH_2Cl_2 (8.5 mL), and I_2 (422.3 mg, 1.67 mmol) were employed to afford 66 % yield as light yellow crystals of the indicated product (Figure 2.78).

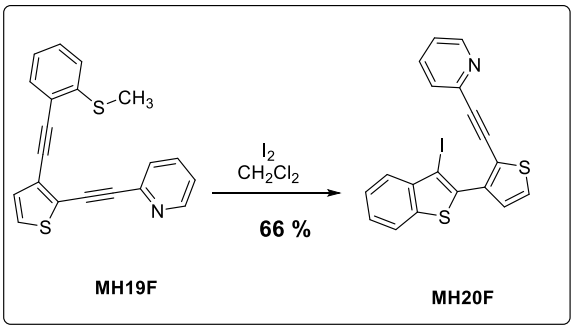


Figure 2.78. Synthesis of MH20F compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 8.0 Hz, 1H), 7.81-7.86 (m, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.39-7.43 (m, 4H), 7.18-7.22 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 143.2, 141.7, 139.5, 139.1, 136.3, 136.3, 129.8, 127.6, 127.5, 126.5, 125.9, 125.6, 123.2, 122.4, 121.9, 96.5, 82.5, 81.9, IR (ATR) ν_{max} (cm^{-1}):3059.2, 2957.2, 2923.5, 2209, 1579, 1484.4, 1430.5, 1409.9, 846.1, 745.2, 722.3, HRMS calcd for $C_{19}H_{11}INS_2$, 443.9299 $[M+H]^+$, found 443.9294 $[M+H]^+$.

Compound MH20G:

MH19G (200 mg, 0.6 mmol), CH_2Cl_2 (8.5 mL), and I_2 (458.18 mg, 1.81 mmol) were employed to afford 76 % yield as yellow crystals of the indicated product (Figure 2.79). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 7.81-7.86 (m, 2H), 7.72 (d, 2H), 7.40-7.50 (m, 4H), 7.21-7.24 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 148.9, 141.6, 139.3, 138.8, 138.4, 136.2, 129.8, 127.1, 126.5, 126.0, 125.7, 123.2, 122.3, 122.0, 120.2, 94.2, 85.9, 81.9, IR (ATR) ν_{max} (cm^{-1}): 3052.2, 3027.4, 2923.6, 2200.3, 1401, 1247.9, 1019.8, 910.7, 739.6, 697.9, HRMS calcd for $C_{19}H_{11}INS_2$, 443.9299 $[M+H]^+$, found 443.9377 $[M+H]^+$.

Compound MH48A:

MH46A (126.2 mg, 0.35 mmol), CH_2Cl_2 (8.5 mL), and I_2 (264 mg, 1.05 mmol) were employed to afford 75% yield as white solid of the indicated product (Figure 2.80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43-8.48 (m, 2H), 7.83 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.51-7.55 (m, 1H), 7.44-7.49 (m, 1H), 7.38-7.40 (d, J_{AB}= 8.0 Hz, 2H), 7.09-7.11 (d, J_{AB}= 8.0 Hz, 2H), 3.94 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 145.7, 140.3, 138.5, 137.6, 135.8, 135.4, 132.6, 131.1, 129.4, 128.3, 126.3, 124.9,

124.1, 122.9, 122.8, 114.2, 91.3, 55.5, IR (ATR) ν_{max} (cm^{-1}): 2922.5, 2852.8, 1507.5, 1240.6, 1174, 835.5, 758.6, 707.5, HRMS calcd for $C_{21}H_{13}IOS_2$, 471.9452, found 471.9461

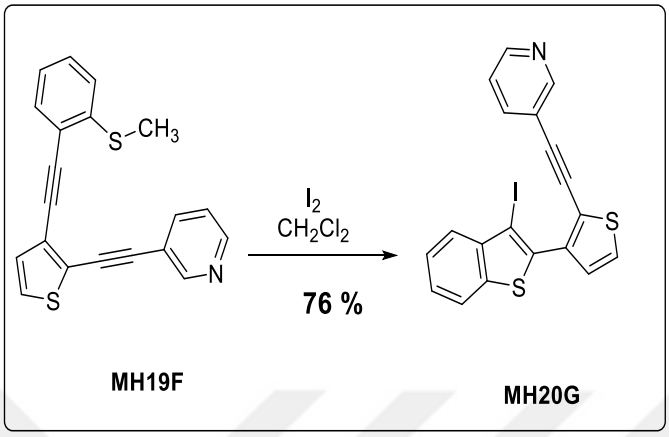


Figure 2.79. Synthesis of MH20G compound.

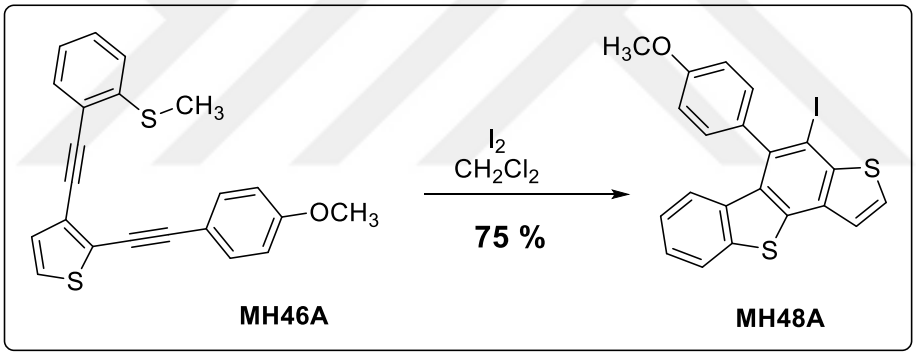


Figure 2.80. Synthesis of MH48A compounds

Compound MH48B:

MH46B (276.2 mg, 0.725 mmol), CH_2Cl_2 (8.5 mL), and I_2 (548 mg, 2.177 mmol) were employed to afford the products as a mixture cannot be separated by column chromatography with different solvents (Figure 2.81).

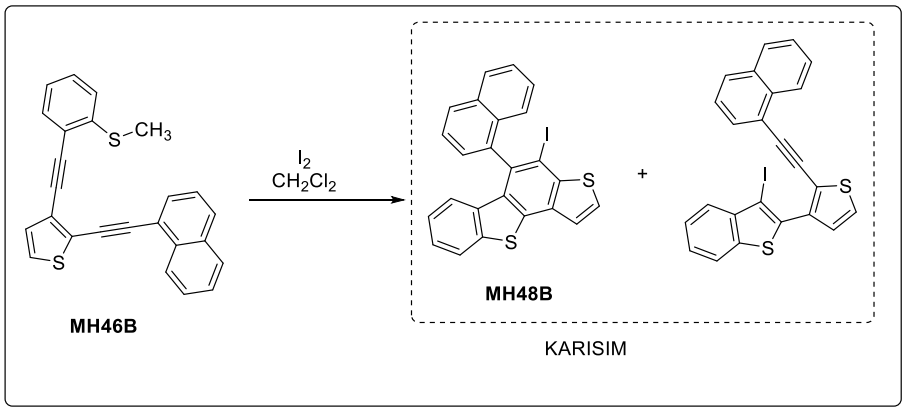


Figure 2.81. Synthesis of MH48B compound as mixture compounds.

Compound MH47:

MH13 (130 mg, 0.398 mmol) in CH_2Cl_2 (8.5 mL), and I_2 (301 mg, 1.196 mmol) were employed to afford the products as a mixture cannot be separated by column chromatography with different solvents (Figure 2.82).

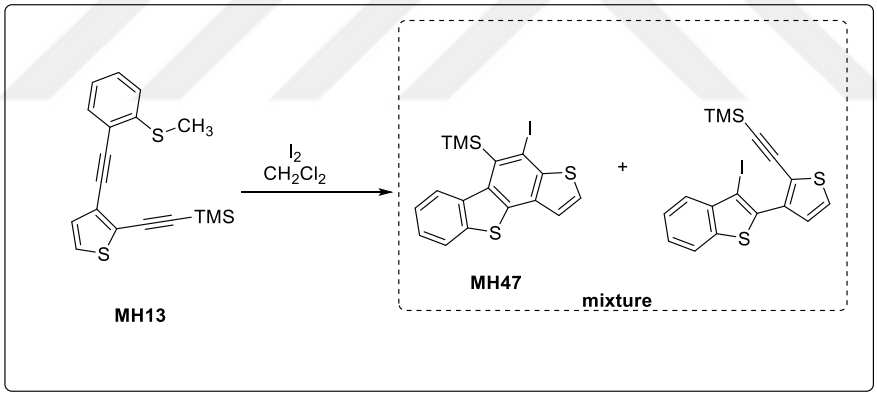


Figure 2.82**.** Synthesis of MH47 compound as mixture compounds.

2.2.2.5.3. Sonogashira coupling reaction to prepare 4-(p-tolylethynyl)-5-(thiophen-2-yl)-thieno[3,2-a]dibenzothiophene (MH21):

To a stirred mixture of the MH20 (0.16 mmol, 72 mg), DMF (3.5 mL), 1-ethynyl-4-methylbenzene (0.17 mmol, 19.9 mg), triethylamine (1.0 mL), $PdCl_2(PPh_3)_2$ (0.008 mmol, 5.6 mg) under argon gas was added CuI (0.008 mmol,1.52 mg), The resulting mixture was stirred at room temperature for 12 h. Water (30 mL) was added to

the reaction mixture. The resulting solution was extracted with DCM (3×30 mL). The organic layer was dried over anhydrous MgSO4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel using hexanes as mobile phase. This compound was obtained as a yellow solid in an (94.2%) yield (Figure 2.83). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 8.0 Hz, 1H), 8.26-8.27 (d, J_{AB}= 4.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.80-7.81 (d, J_{AB}= 4.0 Hz, 1H), 7.48-7.63 (m, 4H), 7.43 (d, J = 8.0 Hz, 2H), 7.27-7.29 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 2.84 (s, 3H) (Figure 2.84)., ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 140.6, 139.5, 139.2, 139.1, 136.1, 133.7, 131.8, 129.6, 129.4, 129.2, 129.1, 128.2, 127.2, 127.0, 126.4, 125.0, 124.1, 123.0, 122.1, 120.2, 116.1, 99.0, 86.5, 21.9 (Figure 2.85)., IR (ATR) ν_{max} (cm^{-1}): 3050, 2980.5, 2919.5, 2360.2, 2203.5 (C≡C),812.2, 685.3, 650.9, HRMS calcd for $C_{27}H_{16}S_3$, 436.0414, found 436.0416.

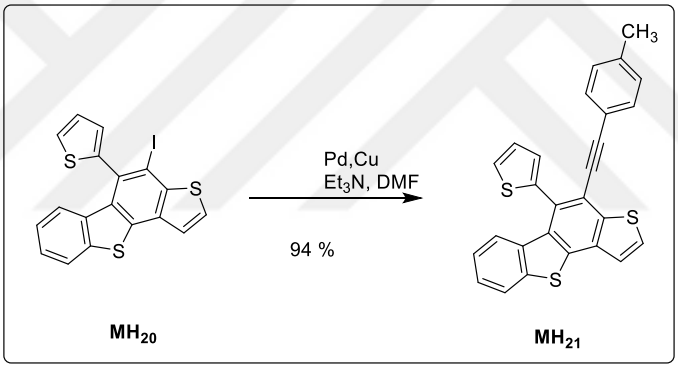


Figure 2.83. Synthesis of MH21 compound compound.

2.2.2.6. Stille coupling reaction to prepare MH49 compound:

To a miture of the compound MH48A (100 mg, 0.21 mmol), 2-(tri-n-butylstannyl)furan (90.7 mg, 0.25 mmol) and toluene (10 ml) was added $Pd(PPh_3)_4$ (12.24 mg, 0.001) under argon gas, the mixture was reflux overnight at 100 ^{o}C. The reaction mixture extracted with with CH_2Cl_2. The organic extracts were dried over anhydrous MgSO4. After filtration and removal of solvent, the residue was purified by column chromatography to give the product (Figure 2.86). This compound was obtained as a yellow solid in an 86.44% yield (Figure 2.86) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 8.0 Hz, 1H), 8.30-8.31 (d, J_{AB}= 4.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.77-7.78

(d, J_{AB}= 4.0 Hz, 1H), 7.54-7.58 (m, 1H), 7.50-7.51 (m, 1H), 7.45-7.49 (m, 1H), 7.35-7.39 (d, J_{AB}= 16.0 Hz, 1H), 7.02-7.06 (d, J_{AB}= 16.0 Hz, 1H), 6.39-6.40 (m, 1H), 6.04-6.05 (m, 1H), 3.92 (s, 3H) (Figure 2.87)., ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 151.6, 142.0, 140.7, 140.5, 137.8, 136.3, 134.6, 132.6, 131.2, 131.0, 129.0, 128.8, 126.1, 124.8, 124.1, 123.0, 122.96, 121.3, 114.5, 111.7, 111.5, 55.5 (Figure 2.88), IR (ATR) ν_{max} (cm^{-1}): 2952.2, 2923.2, 2831.8, 1508.9, 1237.9, 1173.1, 1025.5, 841.5, 727.6, 720.3, HRMS calcd for $C_{25}H_{16}O_2S_2$, 412.0592, found 412.0589.

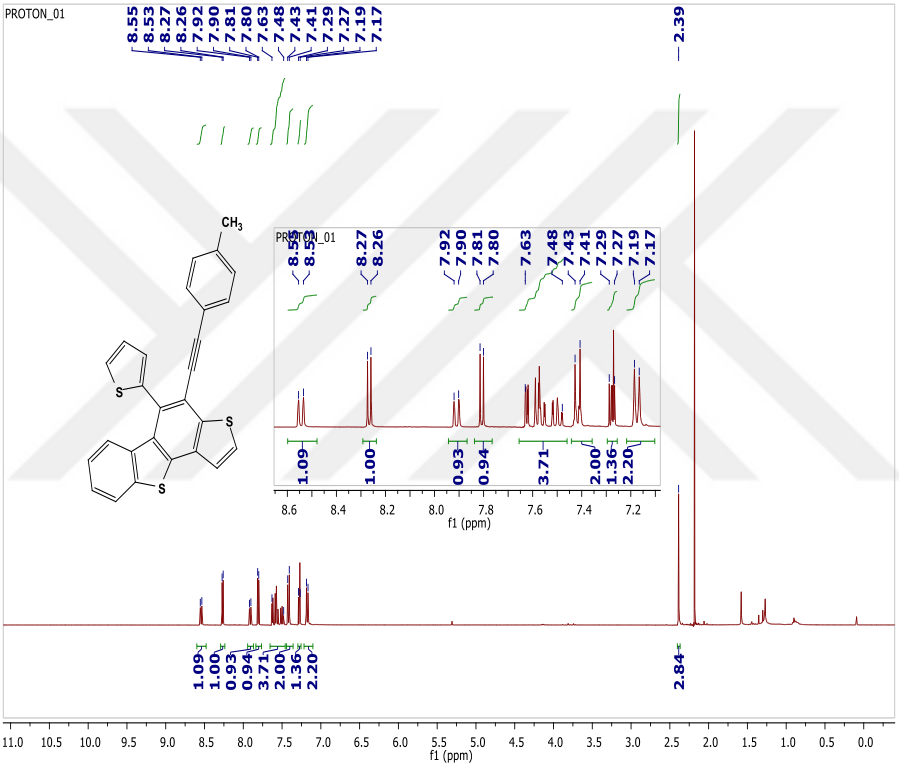


Figure 2.84. Representative ^{1}H NMR spectra of MH21.

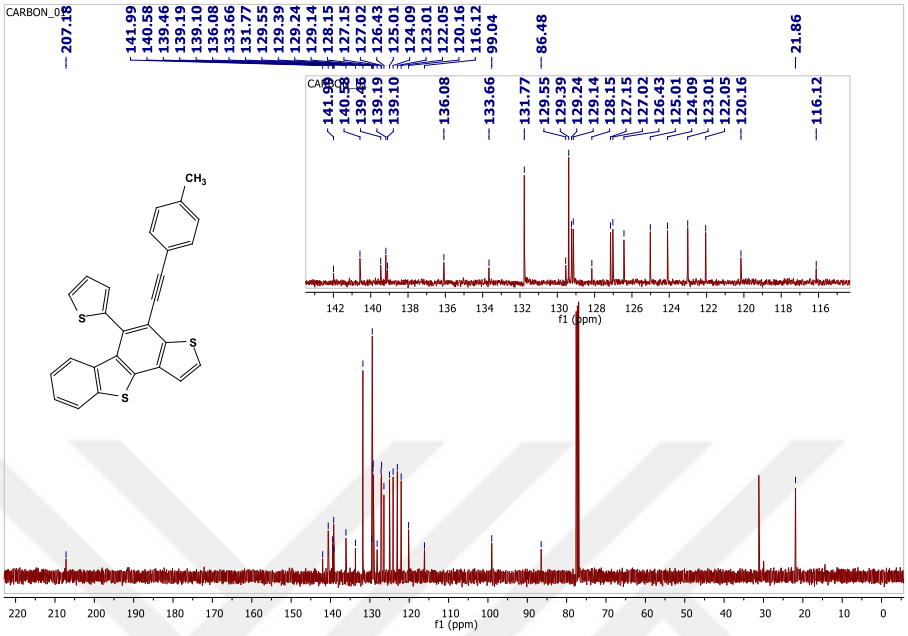


Figure 2.85. Representative ^{13}C NMR spectra of MH21.

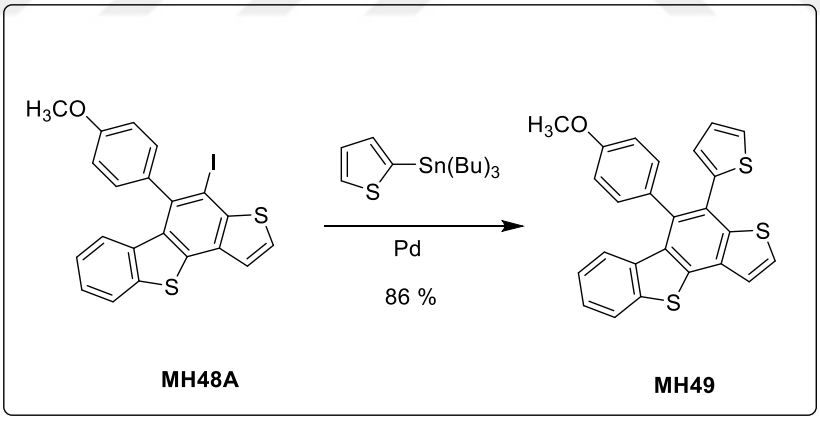


Figure 2.86. Synthesis of MH49 compound.

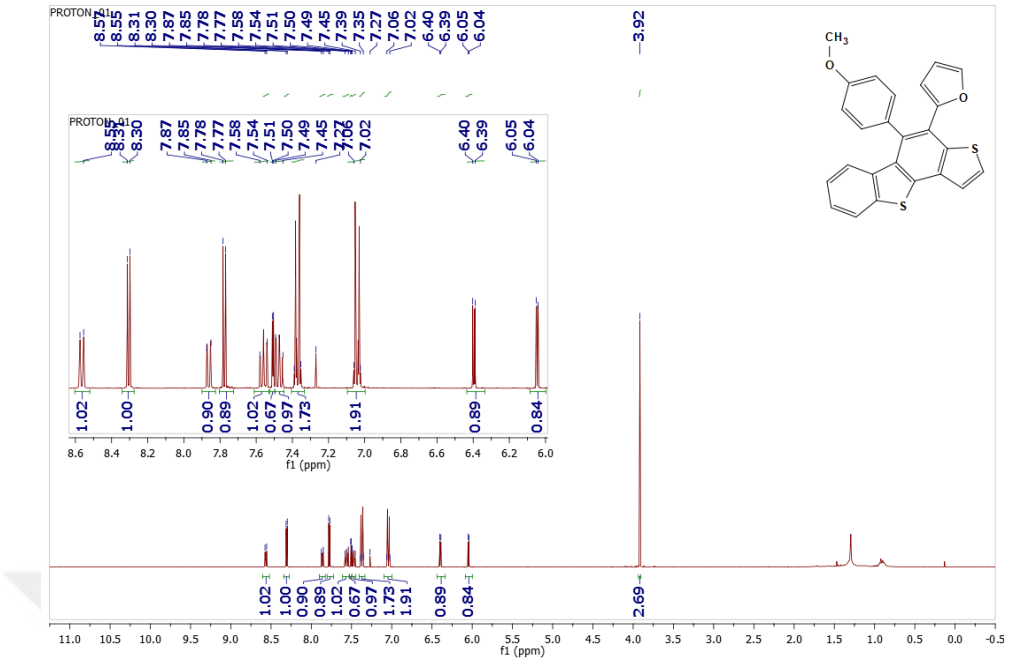


Figure 2.87. Representative ^{1}H NMR spectra of MH49.

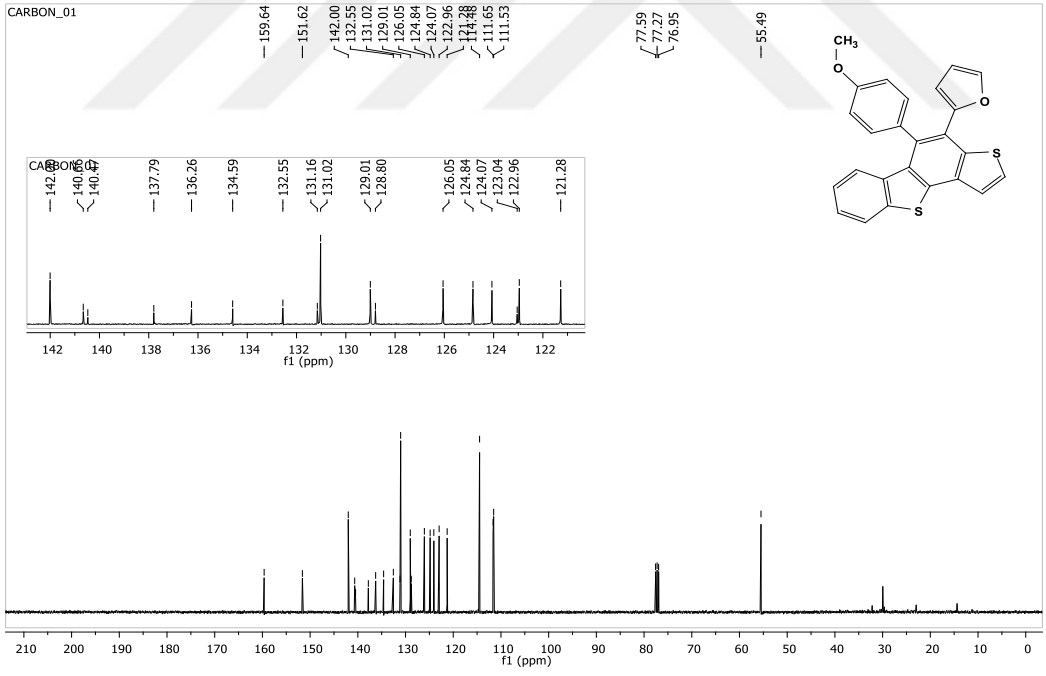


Figure 2.88. Representative ^{13}C NMR spectra of MH49.

3. RESULTS AND DISCUSSION

3.1. Synthesis of thieno[2,3-a]dibenzothiophene derivatives

3.1.1. Synthesis of ((3-bromothiophen-2-yl)ethynyl)trimethylsilane compound (MH1)

Compound MH1 was prepared by using literature procedure (Avelina et al., 2008). When 2,3-dibromothiophene was allowed to react with trimethylsilylacetylene in the presence of PdCl2(PPh3)2 as the catalyst, CuI as co-catalyst, and Et3N as a base, compound MH1 was isolated in 65% yield (Figure 3.1). These types Sonogashira coupling reaction have high selectivity for the synthesis of 2-alkynyl substituted thioephenes as a major product (Figure 3.1).

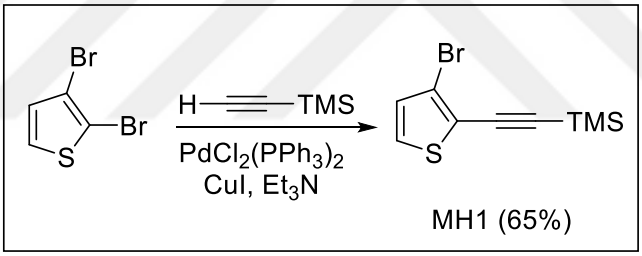


Figure 3.1. Synthesis of the compound MH1.

3.1.2. Synthesis of trimethyl ((3-(substituted ethynyl) thiophen-2-yl) ethynyl) silane compounds (MH2-2G)

After isolation of MH1, MH2 was synthesized by using second Sonogashira coupling reaction. Firstly, we used a same reaction condition as METHOD A (Figure 3.2) that was applied of preparation MH1 compound. The reaction between compound MH1 and phenylacetylene in the presence of Pd catalyst and CuI at 80 ^{o}C for 16 h., the desired compound MH2 was obtained in 20% yield. The low yield was not good as starting compound that must run to additional steps until final product, then we tried different procedure to increase the yield percentage of the product

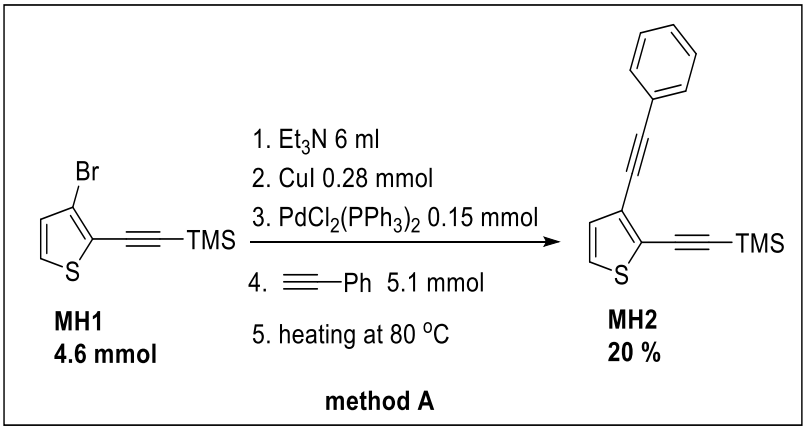


Figure 3.2: Synthesis MH2 compound via METHOD A.

METHOD B: Secondly, we tried to different procedure which was reported by Kimio (Kimio et al., 2011) (Figure 3.3). MH1, diisopropylamine, phenylacetylene, and $P(t\text{-}Bu)_3$ was stirred in THF under inert athmosphere. After 10 min., CuI and $PdCl_2(PhCN)_2$ were added, and the mixture was refluxed for overnight for the formation of MH2. After isolation, we did not increase the yields (26% yield) of desired product MH2 by using METHOD B

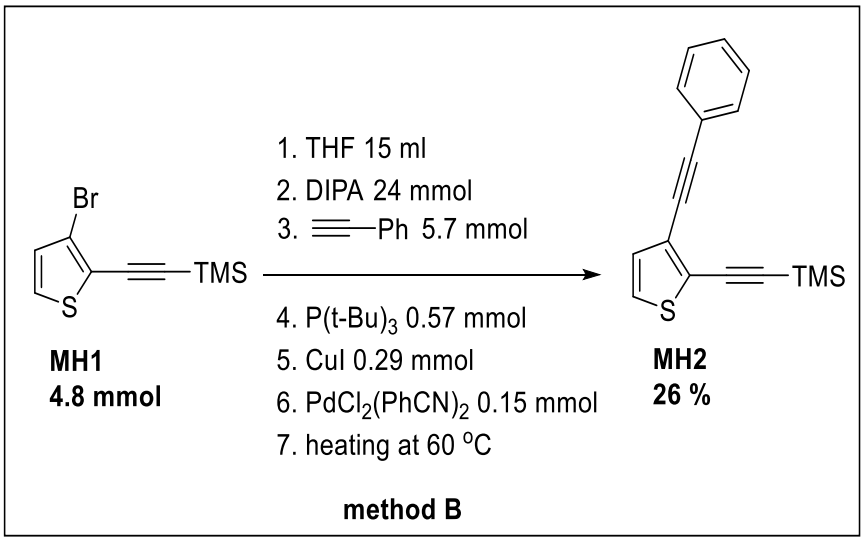


Figure 3.3. Method B for the synthesis of MH2.

METHOD C: was also modified Sonogashira coupling reaction for the synthesis of MH2 (Saori et al., 2012) (Figure 3.4). According to modified procedure, a mixture of MH1, $PdCl_2(PhCN)_2$, and CuI were stirred in 1,4-dioxane. Then, diisopropylamine, phenylacetylene, and *tert*-butylphosphine were added, stirred at room temperature for 6 h. After purification by column chromatography, desired compound MH2 was obtained in 80% yield. It is important to increase the yield of dialkynyl intermediates which have critical intermediates for the synthesis of thienodibenzothiophene isomers. As seen Table 1, a variety of dialkynylic compounds were synthesized by using METHOD C. The yields changed from 57% to 97% (Table 3.1). The highest yield was obtained from the coupling reaction between MH1 and p-tolylacetylene. Moreover, napthyl substituted MH2E and MH2G were isolated in 69% and 57% yields, respectively.

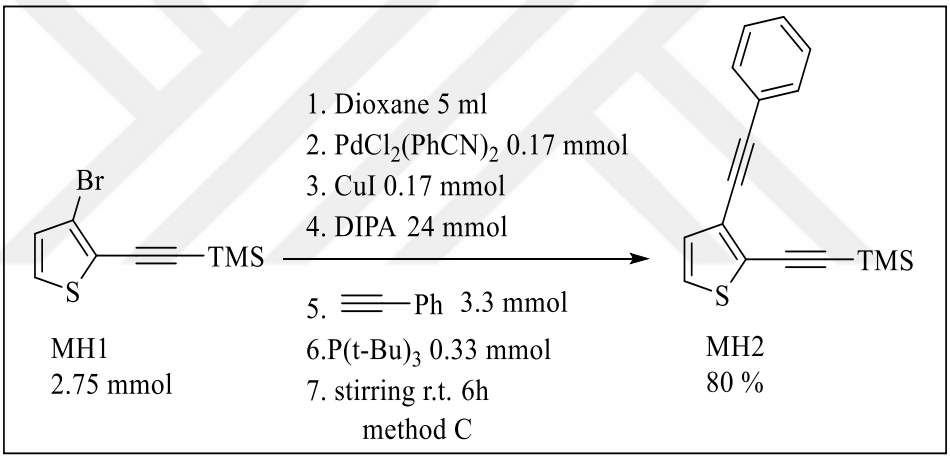
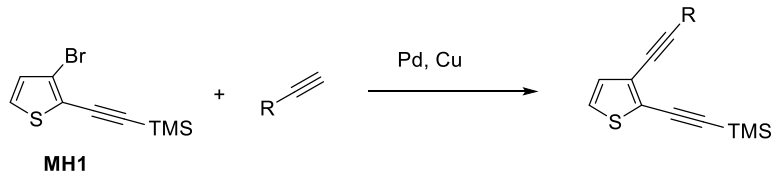
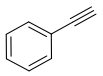
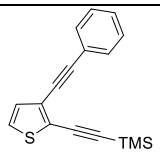
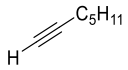
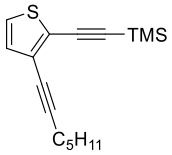
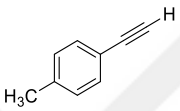
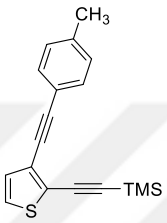
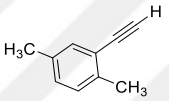
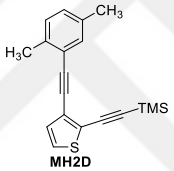
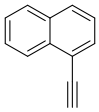
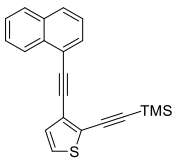
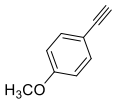
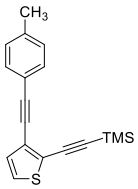
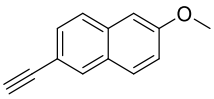
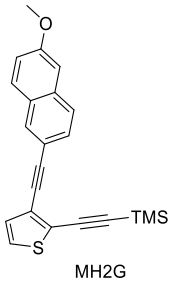


Figure 3.4. Method C for synthesis MH2 compound.

Table 3.1. Synthesis of MH2-2G derivatives by using method C

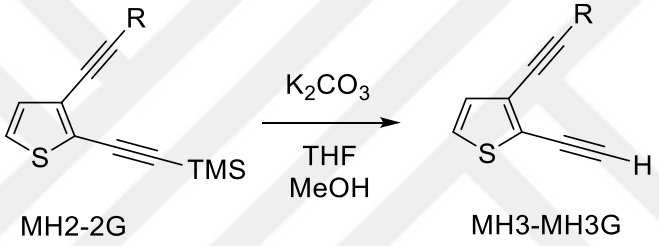


entry	alkyne	product	Yield %
1		 **MH2**	80
2		 **MH2b-N**	69
3		 **MH2C**	97
4		 **MH2D**	68
5		 **MH2E**	69
6		 **MH2F**	68
7		 MH2G	57

3.1.3. Synthesis of 2-ethynyl-3-(substitutedethynyl)thiophene derivatives

We used TMS as a prodecting groups for the formation of dialkynlic thiophenes. Then, terminal alkyne moities required for the Sonogashira coupling reaction with 2-iodothioanisole. Therefore, we used desilation reaction to remove the TMS our structure. When MH2 and K_2CO_3 was stirred in MeOH-THF mixture at room temperature, corresponding terminal alkyne was formed. All MH2-MH2G derivatives underwent to desilation reaction for the formation of corresponding terminal alkynes (Table 3.2).

Table 3.2. Desilylation reactions for the formation of 2-ethynyl-3-(substituted-ethynyl) thiophene MH3 derivatives



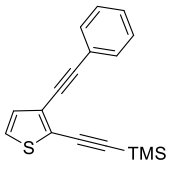
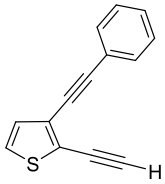
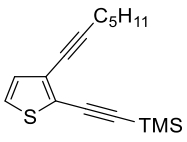
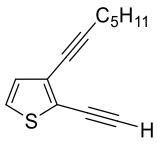
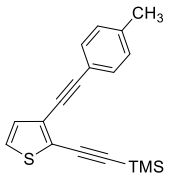
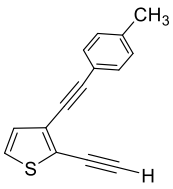
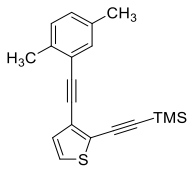
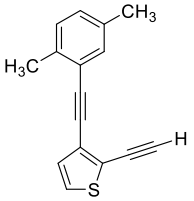
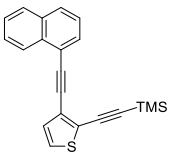
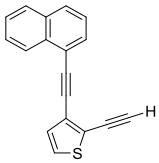
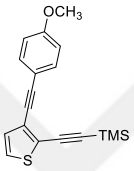
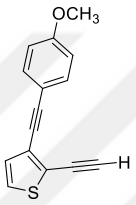
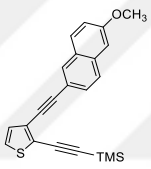
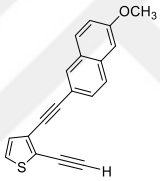
entry	reactant	product	Yield%
1	 MH2	 MH3	96
2	 MH2b-N	 MH3B	91
3	 MH2C	 MH3c	96

Table 3.2. continued

4	 MH2D	 MH3D	93
5	 MH2E	 MH3E	97
6	 MH2F	 MH3F	91
7	 MH2G	 MH3G	74

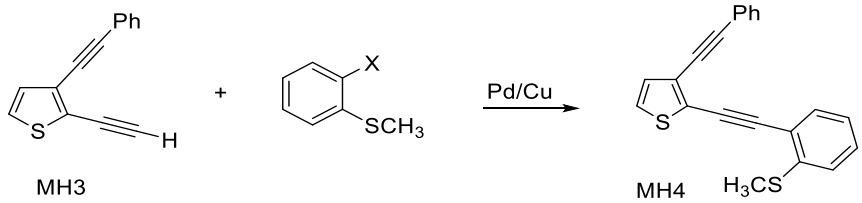
3.1.4. Synthesis of 2-((2-(methylthio)phenyl)ethynyl)-3 (substitutedethynyl) thiophene derivatives (MH4-4G)

The Sonogashira coupling reaction between terminal alkynes (MH3-3G) and 2-halo thioanisole was tested to finding best yields of desired starting compound (Table 3.5). We used different Pd catalysts, solvents, bases, reactants for modified Sonogashira coupling reaction.

Initilally, the reaction between MH3 and 2-bromothioanisole in the presence of $PdCl_2(PPh_3)_2$ as a catalyst and CuI in THF under inert gases for 12 h., we did not obtain any products (Entry 1, Table 3.3). Then, we tried to use different reaction conditions (entry 2, Table 3.3). When MH3 was allowed to react with 2-bromothioanisole with $PdCl_2(PhCN)_2$, (t-Bu)$_3$P, and CuI in 1,4-dioxane and DIPA at room temperature. desired

compound MH4 was formed in 43 % yiels. If the same procedure (Entry 2) was repeated with 2-iodothioanisole, the yield increased to 51% yields (Entry 4, Table 3.5). When DMF was used as a solvent, the highest yield was obtained from the reaction between MH2 and 2-iodothioanisole in the presence of $PdCl_2(PPh_3)_2$ catalyst

Table 3.3. Optimization conditions for Sonogashira coupling reaction between MH3 and 2-halo thioanisole



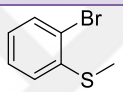
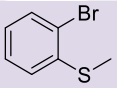
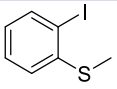
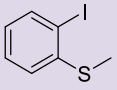
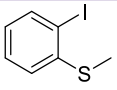
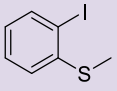
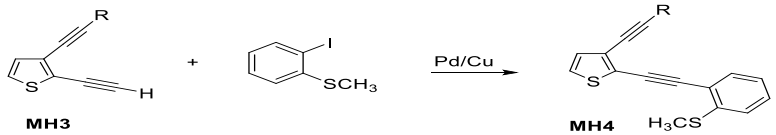
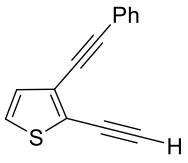
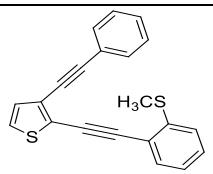
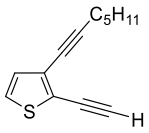
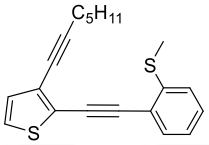
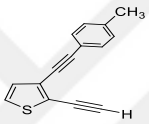
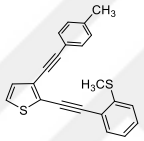
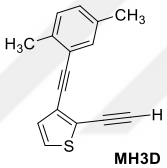
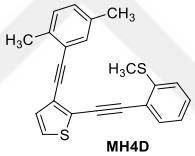
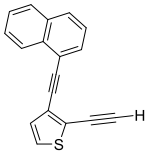
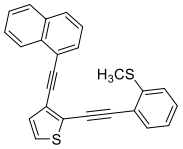
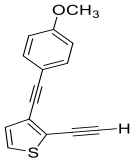
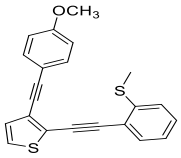
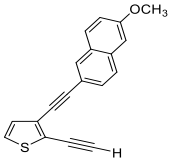
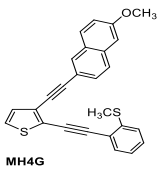
entry	MH3	2-halo thioanisole	solvent	base	Pd	CuI	another component	pro. % (MH4)
1	3.0 mmol		THF 10 ml	Et_3N 15 ml	$PdCl_2(PPh_3)_2$ 0.08 mmol	0.08 mmol	------	0.0
2	3.3 mmol	 2.7 mmol	1,4-dioxane 5 ml	DIPA 13.7 mmol	$PdCl_2(PhCN)_2$ 0.17 mmol	0.17 mmol	$(t\text{-Bu})_3P$	43
3	2.9 mmol	 3.1 mmol	THF 8 ml	Et_3N 12.4 mmol	$PdCl_2(PPh_3)_2$ 0.06 mmol	0.06 mmol	------	40
4	3.3 mmol	 2.75 mmol	1,4-dioxane 5 ml	DIPA 13.7 mmol	$PdCl_2(PhCN)_2$ 0.17 mmol	0.17 mmol	$(t\text{-Bu})_3P$	51
5	0.65 Mmol	 0.65 mmol	DMF 7.5 ml	Et_3N 3 ml	$PdCl_2(PPh_3)_2$ 0.035 mmol	0.035 mmol	------	35
6	0.65 mmol	 0.65	DMF 7.5 ml	Et_3N 3 ml	$PdCl_2(PPh_3)_2$ 0.035 mmol	0.035 mmol	------	63

Table 3.4. Synthesis of MH4-4G derivatives by the reaction between terminal alkynes (MH3-3G) and 2-iodo thioanisole

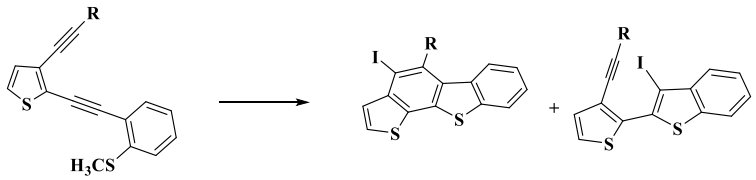


entry	Starting compound	product	Yield%
1	 MH3	 MH4	63
2	 MH3B	 MH4B	73
3	 MH3c	 MH4c	58
4	 MH3D	 MH4D	97
5	 MH3E	 MH4E	99
6	 MH3F	 MH4F	79
7	 MH3G	 MH4G	76

3.1.5. Synthesis of 4-iodo-5-substituted-thieno[2,3-a]dibenzothiophene

Iodine-mediated intramolecular electrophilic aromatic cyclization reaction (Cascade cyclization reaction) was applied on the MH4-4G compounds for the synthesis of 4-iodo-5-substituted thieno[2,3-a]dibenzothiophene derivatives (Table 3.5).

Table 3.5. Iodine-mediated intramolecular electrophilic aromatic cyclization reactions



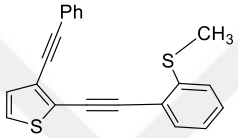
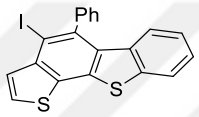
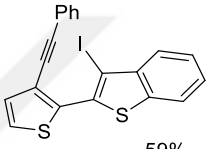
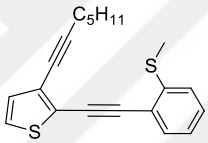
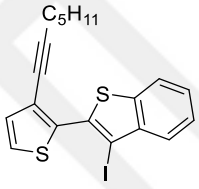
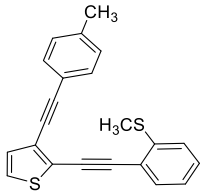
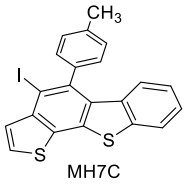
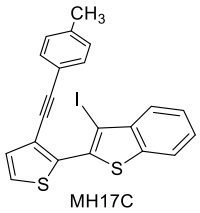
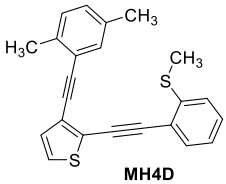
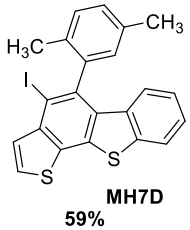
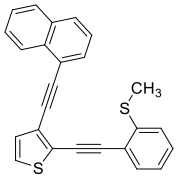
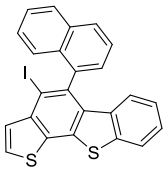
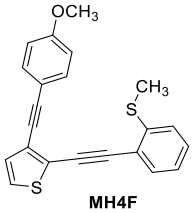
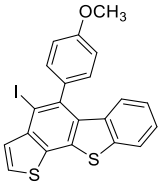
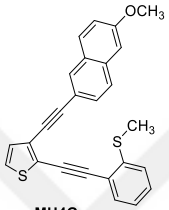
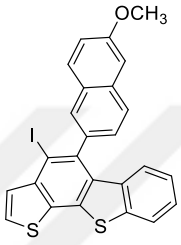
entry	Starting compound	Product(s)
1	 MH4	 MH7 31% +  MH17 59%
2	 MH4B	 MH17B 97%
3	 MH4c	 MH7C 64% ve  MH17C 31%
4	 **MH4D**	 **MH7D** **59%**

Table 3.5. continued

5	 MH4E	 MH7E 70%
6	 MH4F	 MH7F 99%
7	 MH4G	 MH_7G 64%

When Compound MH4 was allowed to eletrophilic cyclization reaction with molecular iodine, 4-iodo-5-phenylthieno[2,3-a]dibenzothiophene MH7 was formed as desired product (31% yield). Moreover, compound MH17 was also isolated with 59% yield.

A variety of aromatic compounds (MH4) were tested for cascade electrophilic cyclization reaction. When pentyl-substituted starting compound MH4B was undergone to electrophilic cyclization, the only MH17B was formed in 97% yield. Compound MH4C also treated with iodine, desired product MH7C and undesired compound MH17C were obtained in 64% and 31% yields, respectively.

The yield of the desired compound MH7C was more than the yield of desired compound MH7. This result displayed that Electron Donating groups may be help to increase the yields. As a result, the more rich electronically alkyne on the MH4 could be undergo cascade cyclization by iodine for the formation of iodo-substituted thieno[2,3-a]dibenzothiophene. When methoxy-substituted MHF was used for electrophilic cyclization reactions, 99% yield of MH7F was isolated. If polyaromatics like naftyl groups were applied for cyclization reaction, only desired products were formed as MH7E and MH7G (Table 3.5, entry 5 and 7).

The mechanism for formation of the benzothiophene product (compound 2) as undesired compound is iodocyclization mechanism can be explaining in Figure 3.5.

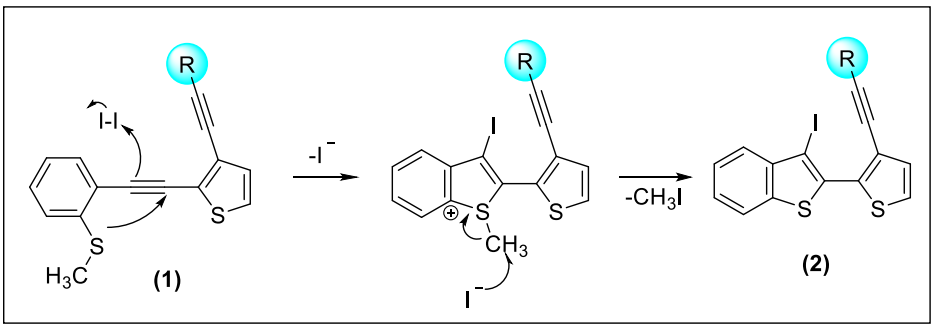


Figure 3.5. Mechanism reaction for benzothiophenes synthesis.

And the first possible mechanism for formation of the desired product as thieno[2,3-a]dibenzothiophene (3) can be shown in figure 3.6. firstly by formation of benzothiophene compound (2) by iodocyclization reaction, and then benzothiophene continous to unter additional iodocyclization step to give the product (3).

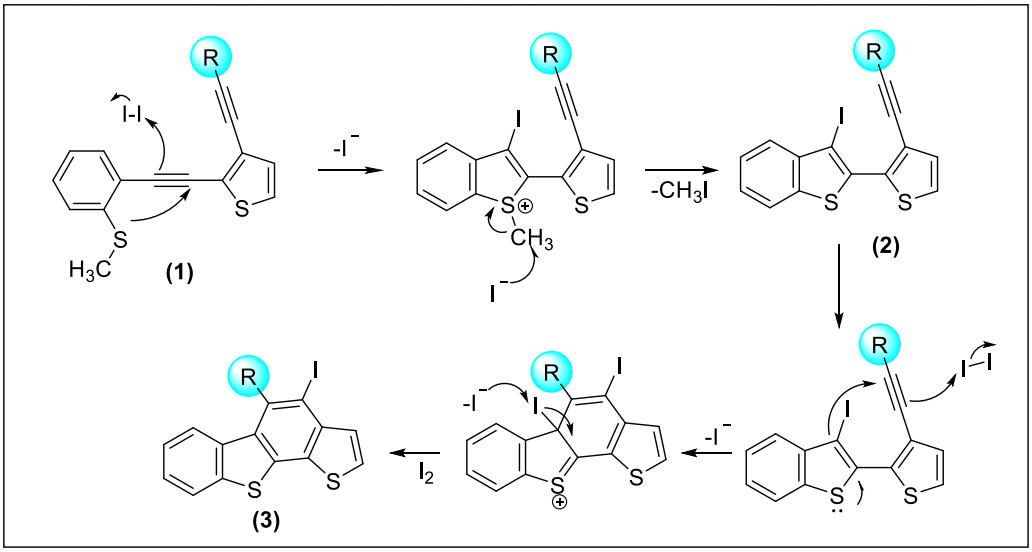


Figure 3.6. Iodo cyclization mechanism reaction to formation of thieno[2,3-a]dibenzothiophenes.

The second possible mechanism for formation of the desired product as thieno[2,3-a]dibenzothiophene is cascade iodo cyclization mechanism (shown in Figure

3.7). this mechanism is multiple steps mechanism give directly our thieno[2,3-a]dibenzothiophene derivatives.

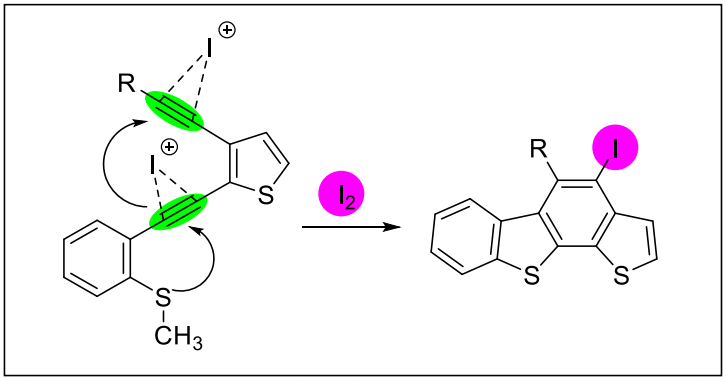


Figure 3.7. Cascade iodo cyclization mechanism for formation of thieno[2,3-a]dibenzothiophene derivatives.

After cascade cyclization reactions, we proposed that if MH17, MH17B, and MH17C were again treated with molecular iodine (Figure 3.8), they could be produce the MH7. Therefore, three examples were chosen for second electrophilic cyclization reaction in the presence of molecular iodine. When MH17 was allowed to cyclization reaction by using different equivalent of iodine such as 1 equiv., 3 equiv and excess, we obtained the desired compound in 35% yield. Interestingly, pentyl susbtituted MH17B did not give the electrophilic cyclization. Compound MH17C reacted with iodine, 60% yields of product was formed.

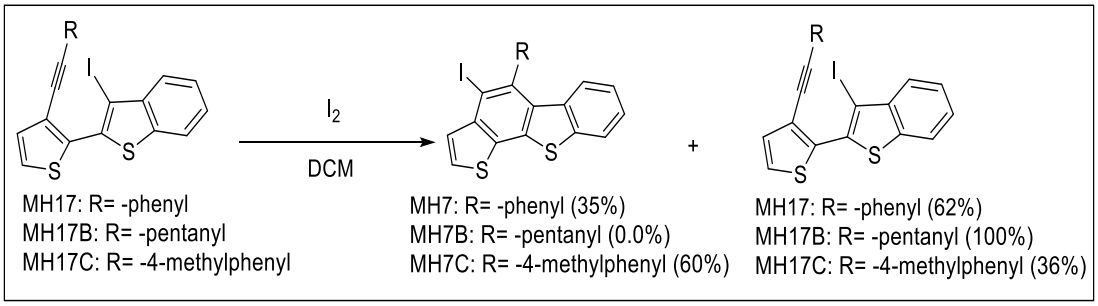


Figure 3.8. Synthesis of MH7 from the MH17.

3.1.6. Synthesis of 4,5-disubstituted-thieno[2,3-a]dibenzothiophene compounds

Aryl halide compounds are very important in organic chemistry due to they can be use as starting materials for the formation of natural products. Moreover, we need to increase the number of compounds for the testing biological properties or optoelectronic applications. Therefore, Halogenes have very critical roles for library studies. We tested two essential coupling reactions including Sonogashira Cross coupling reactions and Stille Coupling reactions for the synthesis of 4,5-disubstituted thieno[2,3-a]dibenzothiophene (Figure 3.9).

Pd catalyzed Sonogashira coupling reaction used for the synthesis of MH42A , MH42B, MH43A and MH43B from the MH7D and MH7G as a starting compounds. When compounds MH7G and MH7D were allowed to react with phenylacetylene in the presence of $Pd(PPh_3)_2Cl_2$ at room temperature, MH43A a MH42A was obtained in 92% and 93% yields, respectively. If the same reaction was performed with p-tolylacetylene, MH42B and MH43B formed with 89% and 86% yields. Our results showed that iodo-thieno[2,3-a]dibenzothiophenes could be elaborated more derivatives by using Sonogashira coupling reactions.

Stille coupling reactions are also important in organic chemistry. When MH7F was reacted with 2-(tributylstannyl)thiophene in the presence of $Pd(PPh_3)_4$ as catalyst in toluene under reflux for overnight, MH44A and MH44B were synthesized (92% and 81%). Stille coupling reaction formed the new carbon-carbon bonds between heteroaromatic compounds (thiophene and furan) and iodo-thieno[2,3-a]dibenzothiophenes with a high yields (Figure 3.10). As a results, we could be synthesized many thieno[2,3-a]dibenzothiophenes derivatives by using Stille coupling reactions.

3.2. Synthesis of thieno[3,2-a]dibenzothiophene derivatives

3.2.1. Synthesis of 2-ethynyl-3-((2-(methylthio)phenyl)ethynyl) thiophene (MH15)

Thieno[3,2-a]dibenzothiophene derivatives were synthesized by using different methodologies. Firstly, compound MH6 was synthesized from the reaction between 2-

iodothioanisole and ethynyltrimethylsilane via Pd-catalyzed Sonogashira coupling reaction (95% yield, Figure 3.11). Then, protecting group was removed to form the terminal alkyne MH9 (91%). Compound MH9 have very critical roles for the synthesis of thieno[3,2-a]dibenzothiophene isomers. In the lights of our knowledge, when MH9 was allowed to react with MH1 in the presence of Pd catalyst, MH13 was obtained in 50% yields. MH13 was undergone to desilylation reaction, desired terminal alkyne MH15 formed in 96% yield.

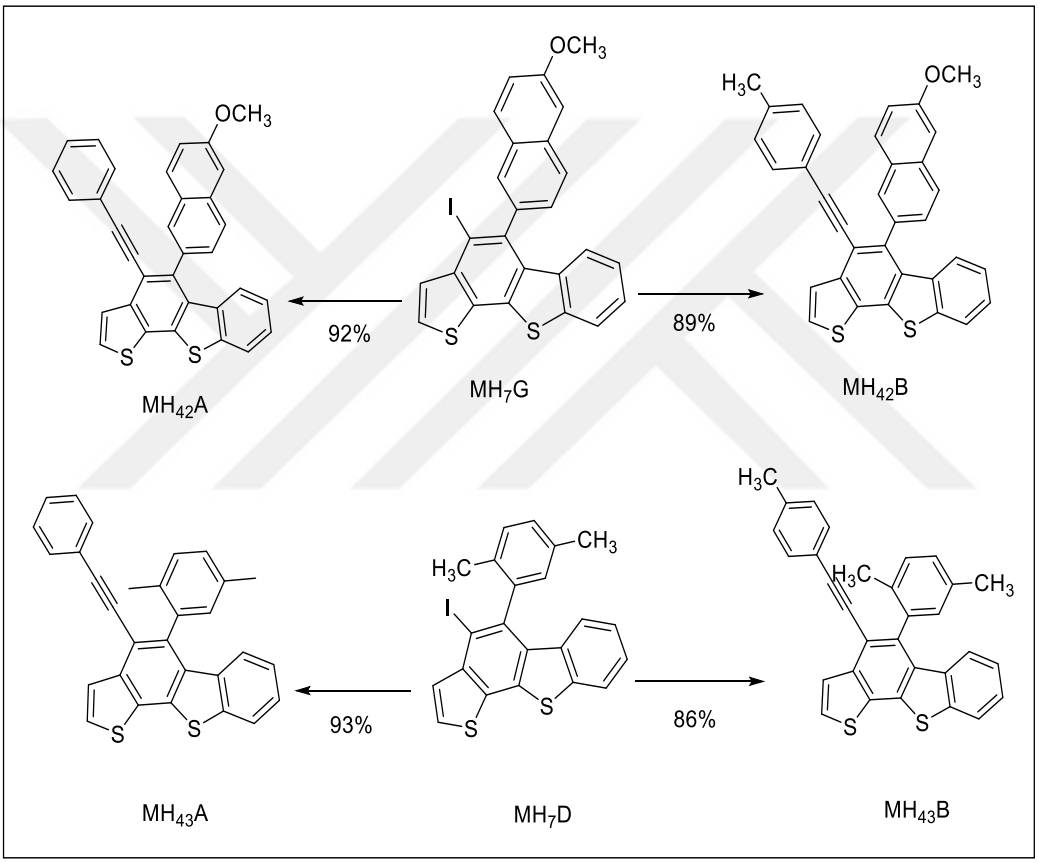


Figure 3.9. Sonogashira coupling reactions between the 4-iodo-5-substituted thieno[2,3-a]dibenzothiophenes and terminal alkynes.

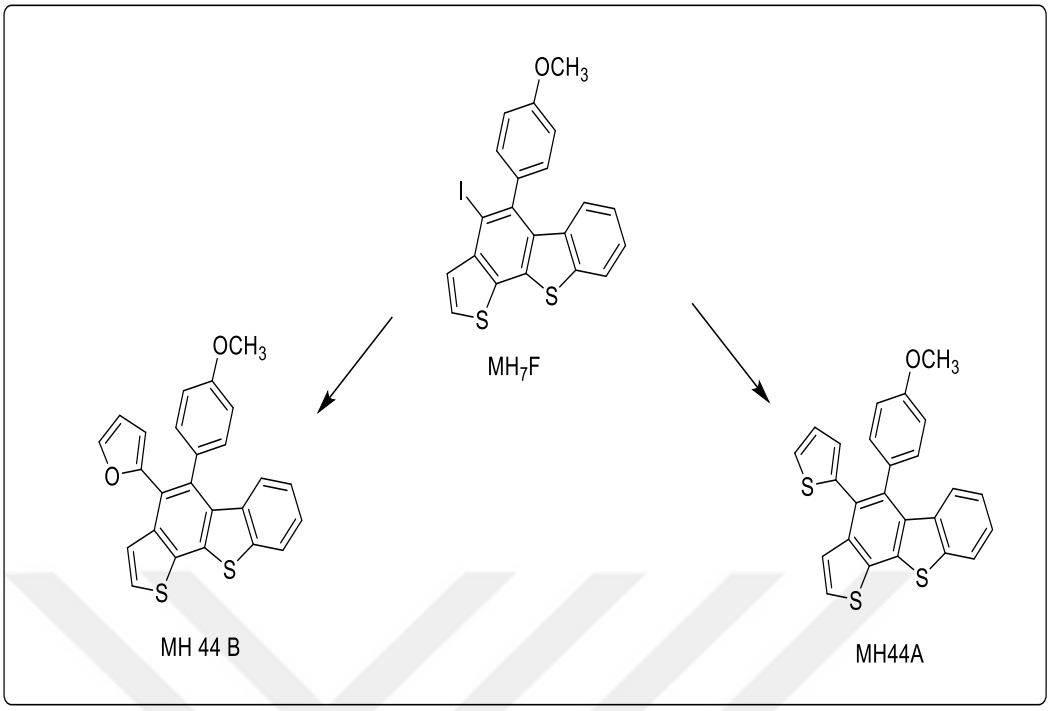


Figure 3.10. Synthesis of MH44A and MH44B compounds via Stille coupling reactions

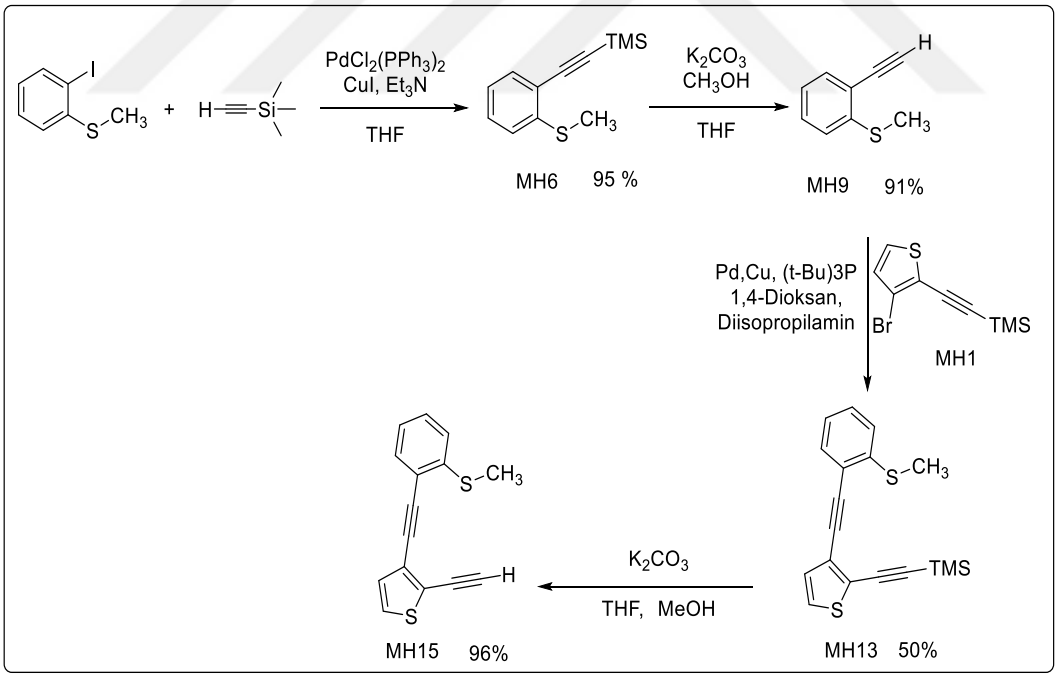


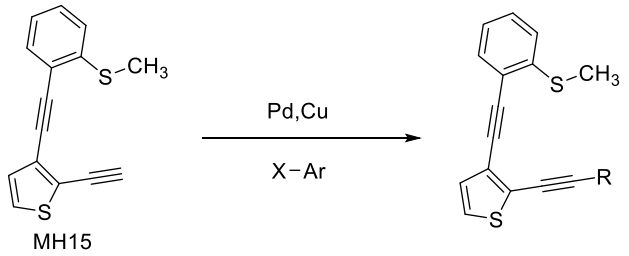
Figure 3.11. Synthesis of 2-ethynyl-3-((2-(methylthio)phenyl)ethynyl)thiophene (MH15).

3.2.2. Synthesis of 3-((2-(methylthio)phenyl)ethynyl)-2-(substitutedethynyl) thiophene derivatives

As seen Table 3.6, compound MH15 could be very important precursors for the synthesis of a variety of dialkynilic thiophenes via Sonogashira coupling reaction. In our study, we used aryl, heteroaryl and polyaryl halides for coupling reactions to give the corresponding compounds as MH19.

Our optimized procedure was applied for the synthesis of MH19 derivatives for arylbromides. When MH15 was reacted with arylbromide in the presence of $PdCl_2(PhCN)_2$ tri-tert-butylphosphine and CuI in 1,4-dioxaneidiisopropylamine MH15 (0.78 mmol), MH19- MH19B, MH19C, MH19D, Mh19E, MH19F and MH19G were obtained between moderate to high yields (Table 3.6). When iodoaryl was applied for the formation of desired dialkynilic compounds, we performed standard Sonogashira coupling procedures, $PdCl_2(PPh_3)_2$ and CuI were used as a catalyst, and Et_3N was used as base. We synthesized different dialkynilic compounds (MH46A-D) by using this procedure.

Table 3.6. Sonogashira coupling reaction to preparation of 3-((2-(methylthio) phenyl) ethynnyl)-2-(substitutedethynyl)thiophene derivatives.



MH15

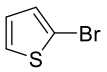
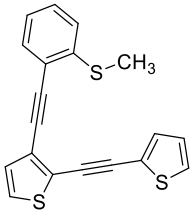
entry	arylhalide	product	Yield%
1		 MH19	91

Table 3.6. continued

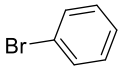
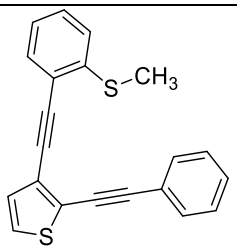
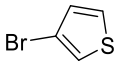
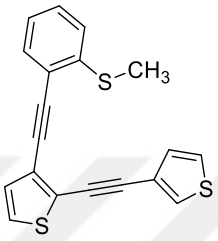
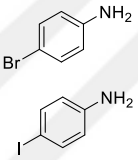
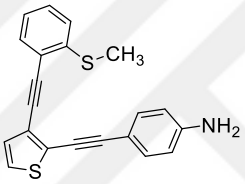
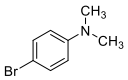
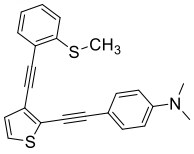
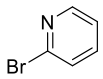
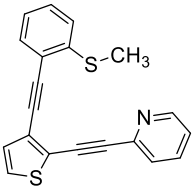
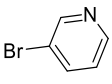
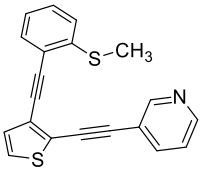
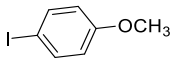
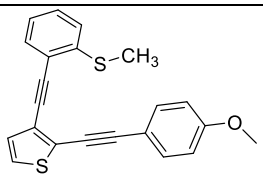
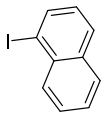
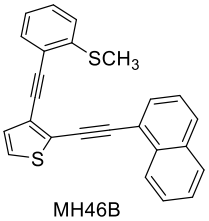
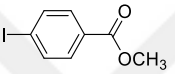
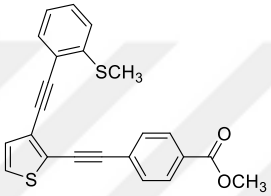
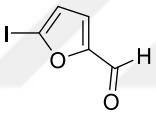
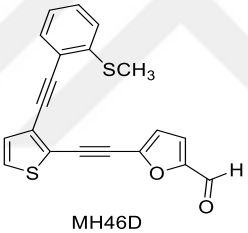
2		 MH19B	69
3		 MH19C	87
4		 MH19D / MH46E	MH19D= 41 MH46E= 83
5		 MH19E	10
6		 MH19F	70
7		 MH19G	78

Table 3.6. continued

8		 MH46A	62
9		 MH46B	83
10		 MH46C	81
11		 MH46D	78

3.2.3. 4-Iodo-5-substituted-thieno[3,2-a]dibenzothiophene derivatives

After preparation of necessary starting compounds, we investigated electrophilic cyclization reactions for the formation of 4-iodo-5-substituted-thieno[3,2-a]dibenzothiophene derivatives. Similarly, molecular iodine was used for cascade intramolecular electrophilic cyclization reaction in DCM at room temperature.

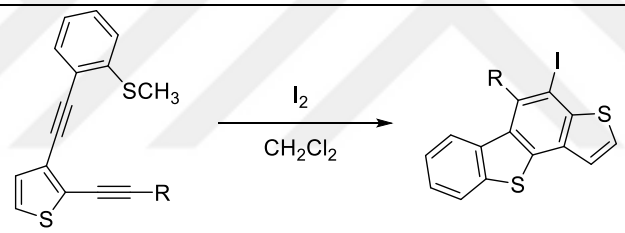
When MH19 was allowed to cyclization reaction, desired product was isolated in 60% yields of MH20 compound (entry 1, table 3.7). We also synthesized our designed molecules as a methoxy-substitued MH48A. On the other hand, MH19B,

MH19F and MH19G did not gave the cascade electrophilic cyclization (Table 3.6, Entries 2,6 and 7). We observed only corresponding benzothiophenes.

If MH19C treated with molecular iodine (entry 3, table 3.7), we observed only one spot on the TLC. After NMR analysis, we investigated that there were two compounds. One is our desired compounds, and second is benzothiophenes obtained from first electrophilic cyclization reaction. We also similar mixtures when MH46B and MH13 was used a starting compounds. We did not achieved separation these compounds from each other.

Interestingly, amine-substituted alkynilic compounds decomposed after addition of molecular iodine in DCM. Therefore, we did not found any product from these cyclization rections. All results are shown in Table 7.

Table 3.7. Iodine-mediated intramolecular electrophilic aromatic cyclization to preparation of 4-iodo-5-substituted-thieno[3,2-a]dibenzothiophene derivatives



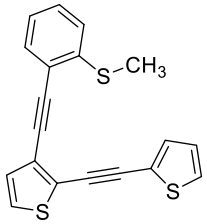
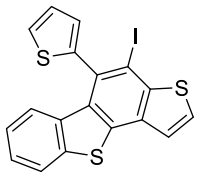
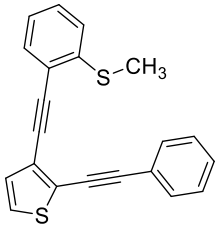
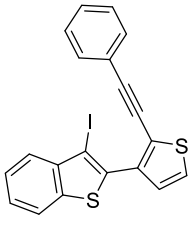
entry	reactant	Product with Yield%
1	 MH19	 MH20 60%
2	 MH19B	 MH20B 70%

Table 3.7. continued

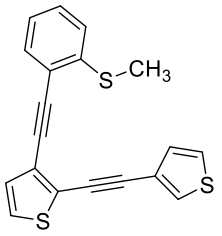
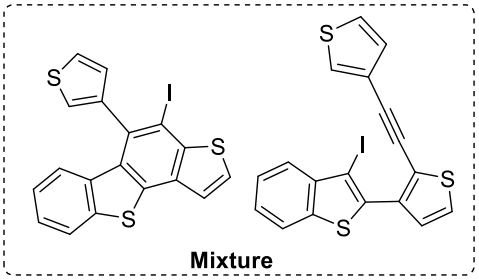
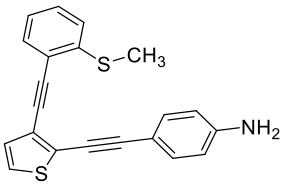
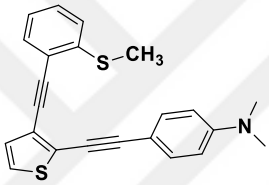
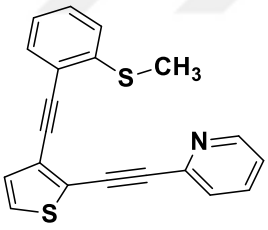
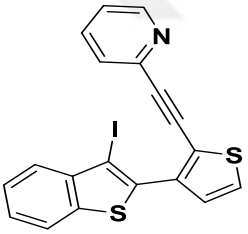
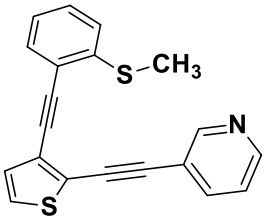
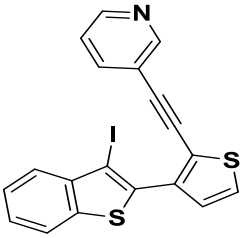
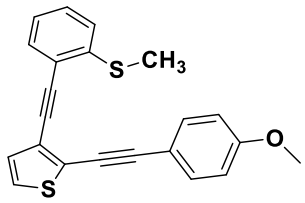
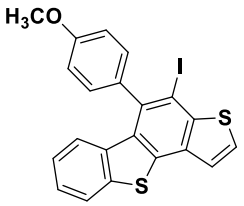
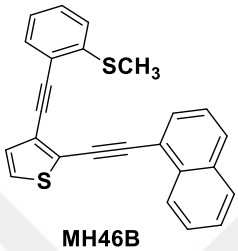
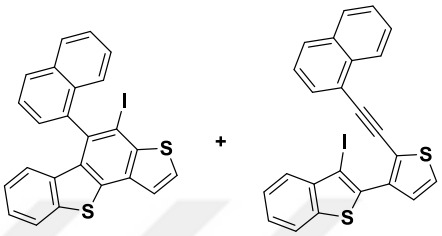
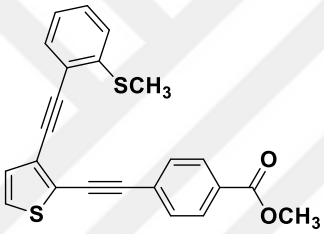
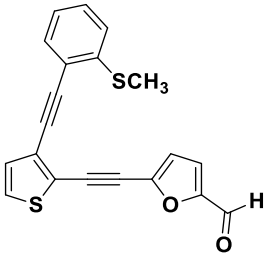
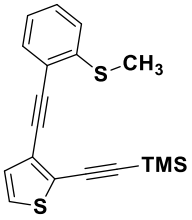
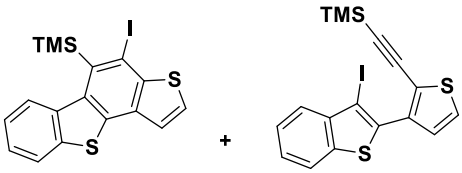
3	 MH19C	 Mixture
4	 MH19D / MH46E	under decomposition during iodine treating
5	 MH19E	under decomposition during iodine treating
6	 MH19F	 MH20F 66 %
7	 MH19G	 MH20G 76 %

Table 3.7. continued

8	 MH46A	 MH48A 75 %
9	 MH46B	 Mixture
10	 MH46C	under decomposition during iodine treating
11	 MH46D	under decomposition during iodine treating
12	 MH13	 Mixture MH47

The mechanism for formation of the benzothiophene product (compound 2) as undesired compound is iodocyclization mechanism can be explaining in figure 3.12.

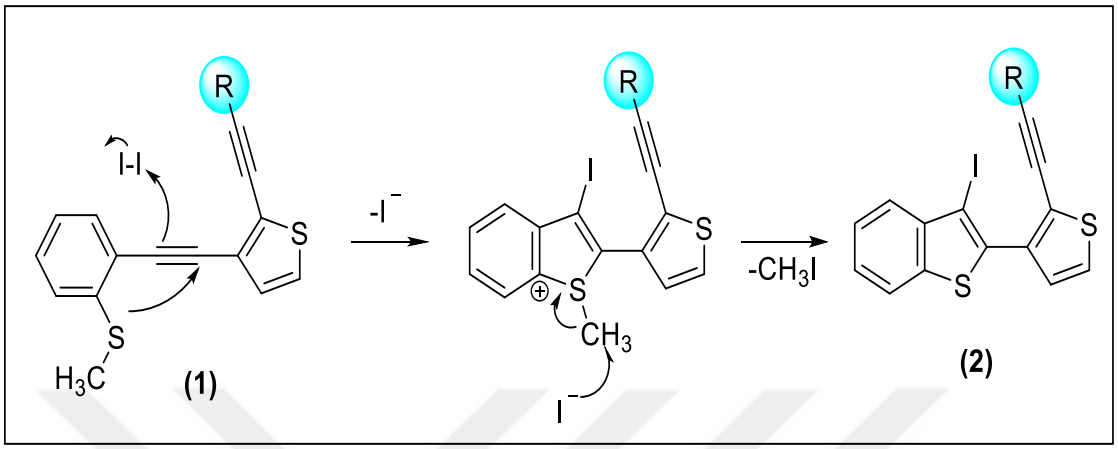


Figure 3.12. Mechanism reaction for benzothiophenes synthesis.

And the first possible mechanism for formation of the desired product as thieno[3,2-a]dibenzothiophene (3) can be shown in figure 3.13. firstly by formation of benzothiophene compound (2) by iodocyclization reaction, and then benzothiophene continous to unter additional iodocyclization step to give the product (3).

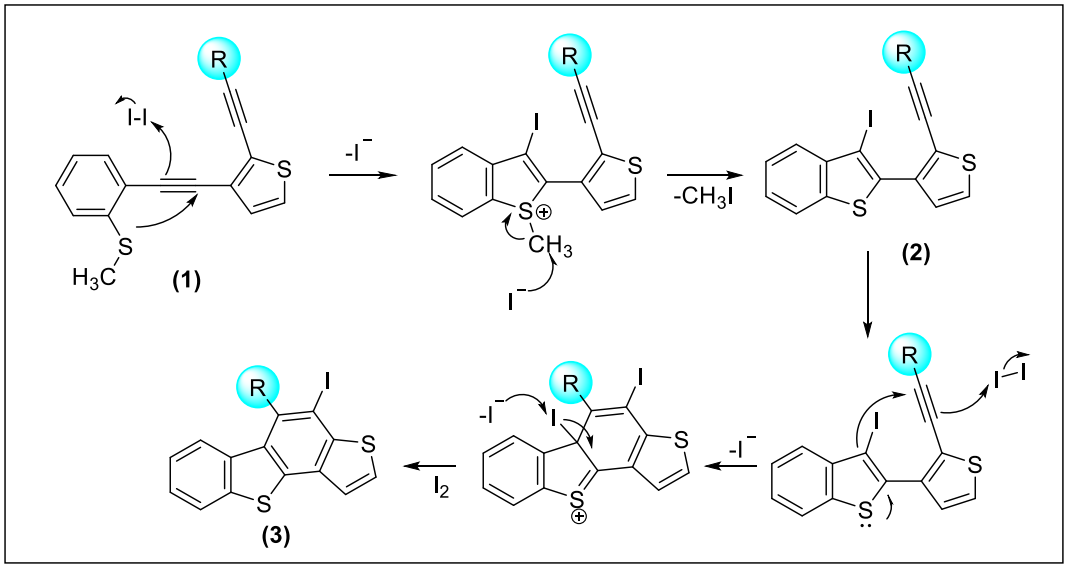


Figure 3.13. Iodo cyclization mechanism reaction to formation of thieno[3,2-a]dibenzothiophenes.

The second possible mechanism for formation of the desired product as thieno[3,2-a]dibenzothiophene is cascade iodo cyclization mechanism (shown in Figure 3.14). this mechanism is multiple steps mechanism give directly our thieno[3,2-a]dibenzothiophene derivatives.

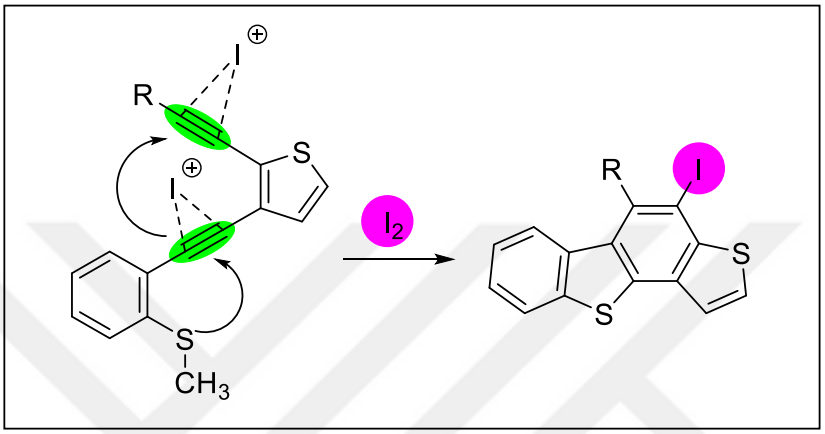


Figure 3.14. Cascade iodo cyclization mechanism for formation of thieno[3,2-a]dibenzothiophene derivatives.

3.2.4. Synthesis of 4-(p-tolylethynyl)-5-(thiophen-2-yl)-thieno[3,2-a] dibenzothiophene (MH21)

As shown in Figure 3.21, compound MH20 was allowed to react with 1-ethynyl-4-methylbenzene via Pd-Catalyzed Sonogashira coupling reaction, we synthesized MH21 with 94% yield. We improved that our thienodibenzotihophenes could be used for the formation of new compounds.

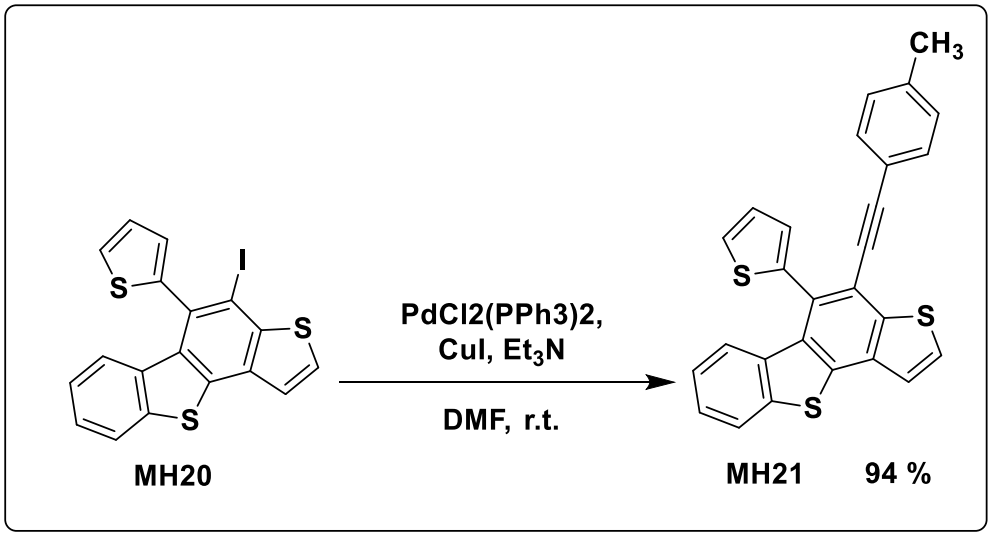


Figure 3.15. Sonogashira coupling reaction to prepare 4-(p-tolylethynyl)-5-(thiophen-2-yl)-thieno[3,2-a]dibenzothiophene (MH21).

3.2.4.1. Synthesis of 4-(2-thiophenyl)-5-(thiophen-2-yl)-thieno[3,2-a] dibenzothiophene (MH49):

Stille coupling reactions was also tested for the synthesis of MH49. When MH48A was allowed to react with 2-(tri-n-butylstannyl)furan in the presence of $Pd(PPh_3)_4$ in Toluene under reflux, expected product was obtained in 86% yield. (Figure 3.16)

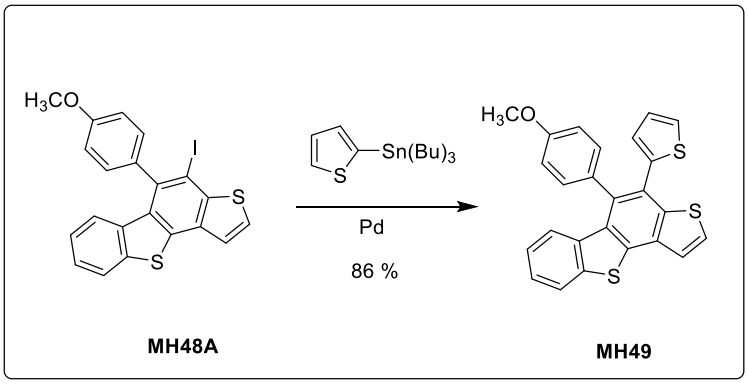


Figure 3.16. Stille coupling reaction to prepare MH49 compound.

4. CONCLUSION

In the present study, we developed a novel methods for the synthesis of thieno[2,3-a]thiophene and thieno[3,2-a]thiophene derivatives by using electrophilic cyclization reactions. In the first part of study, we prepared dialkynilic-thiophene derivatives as a starting compounds by using Pd-catalyzed Sonogashira cross coupling reactions. After isolation of dialkynilic-thiophenes, electrophilic cyclization reaction was used for the synthesis of thieno[2,3-a]thiophene and thieno[2,3-a]thiophene in the presence of molecular iodine. Thieno[2,3-a]thiophene were obtained in moderate to high yields from the cascade electrophilic cyclization reactions. During this cyclization, we also isolated benzothiohenes derivatives as a side-product. Interestingly, we obtained only two derivatives of thieno[3,2-a]thiophene after iodine-catalyzed cyclization reaction.

In the last part of the study, Sonogashira coupling reactions and Stille coupling reactions were tested for the increasing of thieno[2,3-a]thiophene and thieno[3,2-a]thiophene derivatives.

In conclusion, synthesis of thieno[2,3-a]thiophene and thieno[2,3-a]thiophene via electrophilic cyclization reactions were performed successfully. İodo-substituted thieno-dibenzothieophenes could be new starting compound for the synthesis of biologically important structures by using metal catalyst coupling reactions.

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APPENDIX A: NMR DATA

NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer

^{1}H and ^{13}C NMR spectra of products are given below.

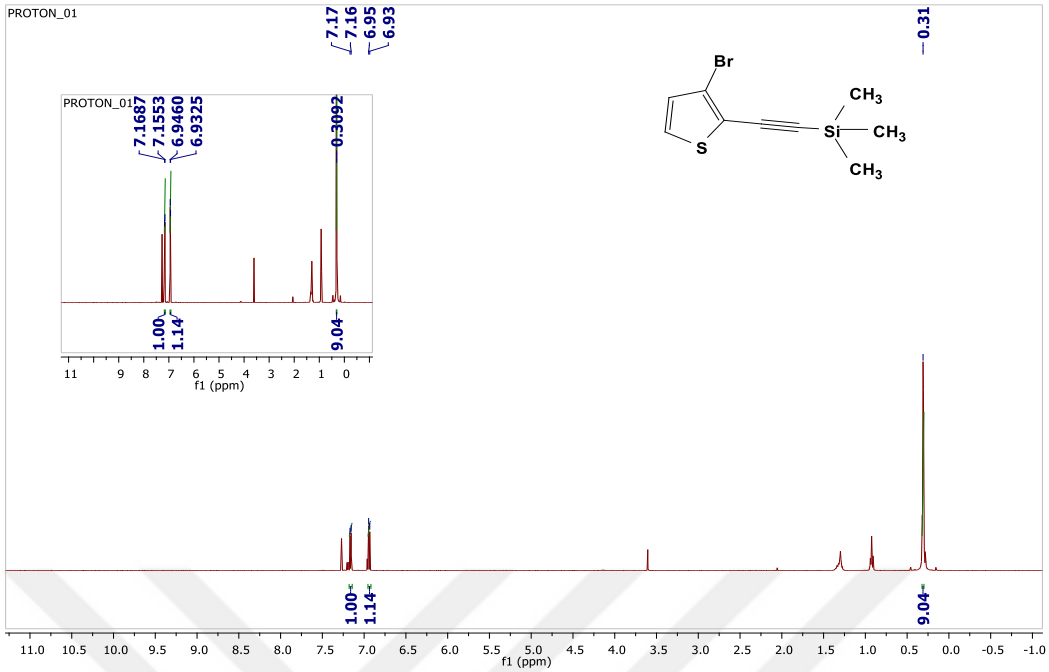

Figure M1. ^{1}H NMR spectra of MH1.

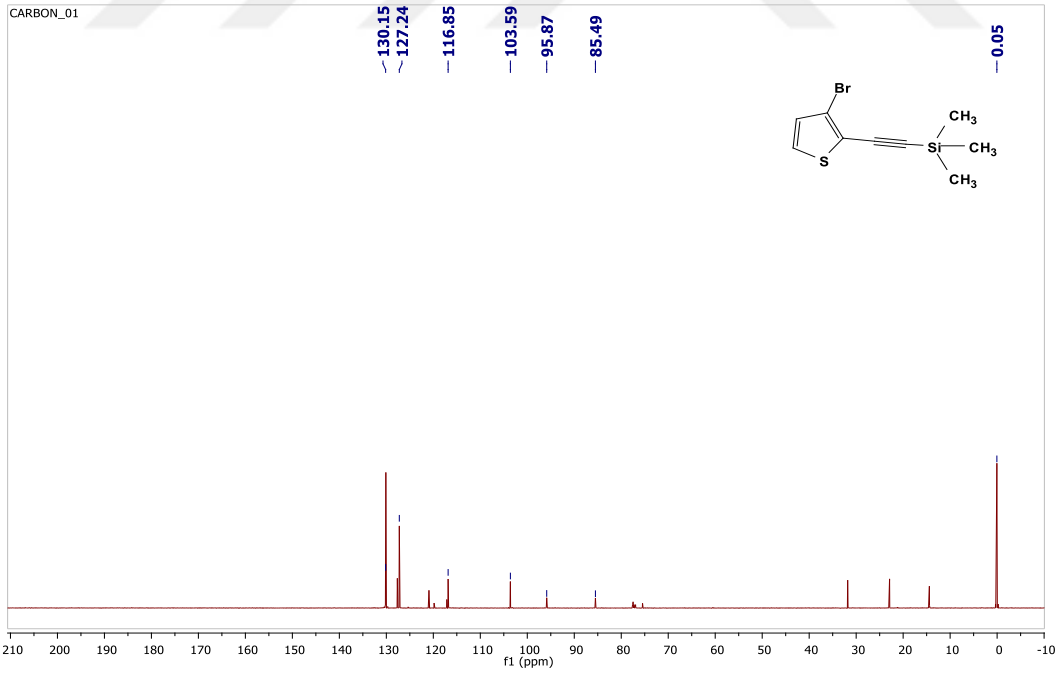

Figure M2. ^{13}C NMR spectra of MH1.

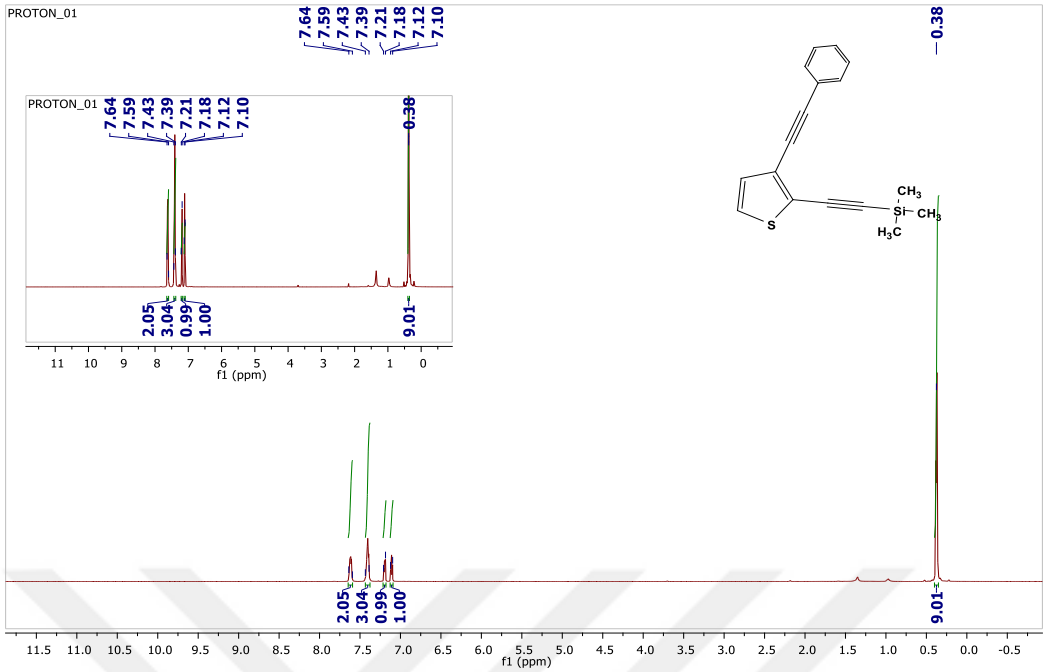

Figure M3. ^{1}H NMR spectra of MH2.

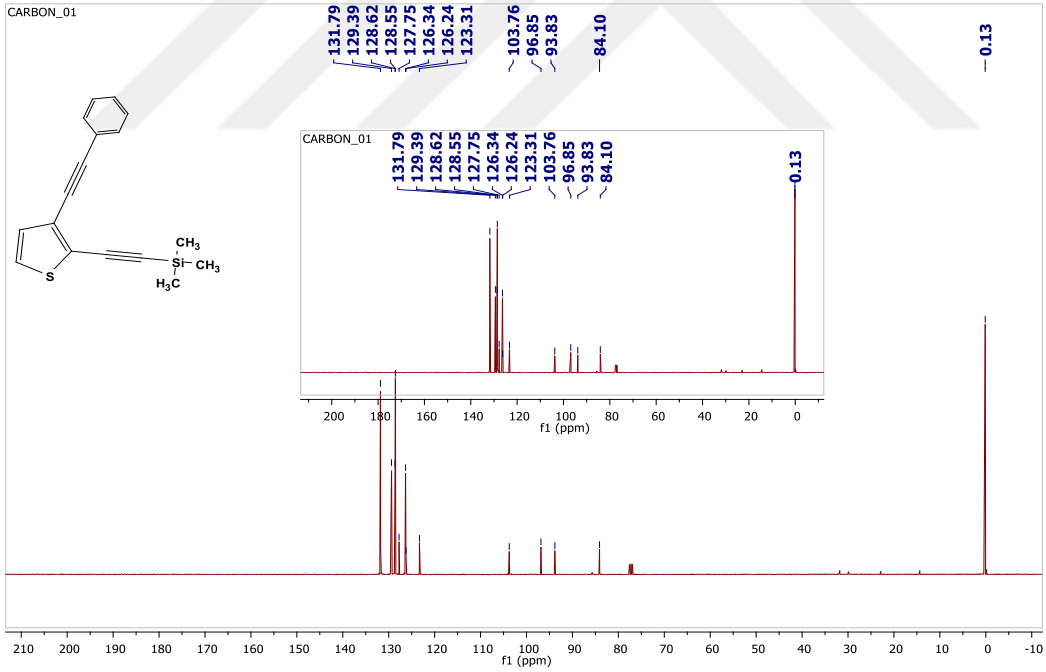

Figure M4. ^{13}C NMR spectra of MH2.

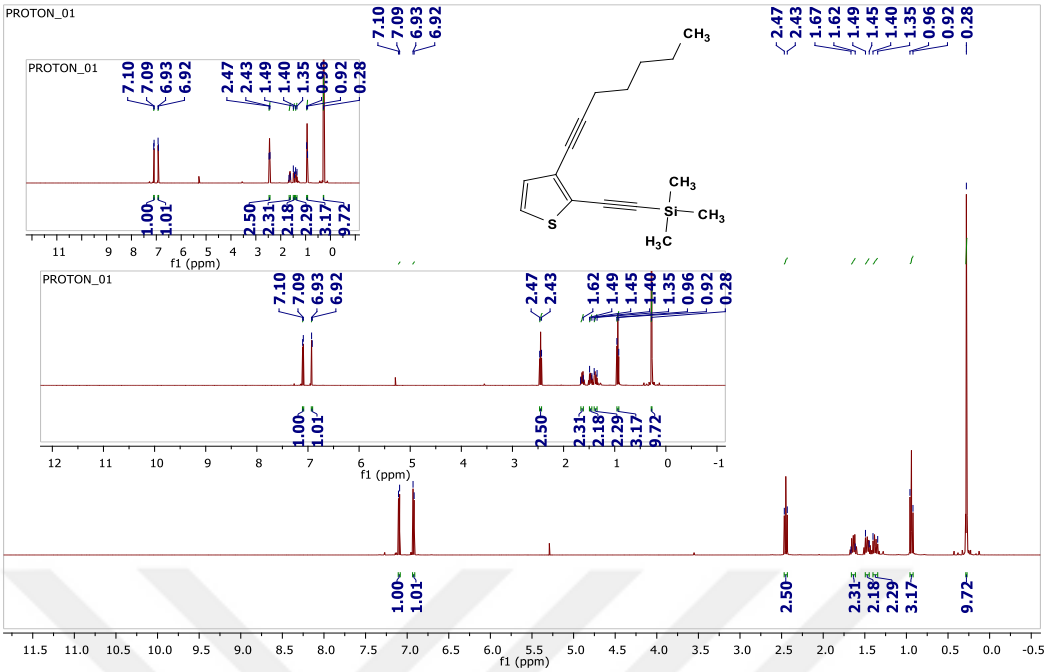

Figure M5. ^{1}H NMR spectra of MH2BN.

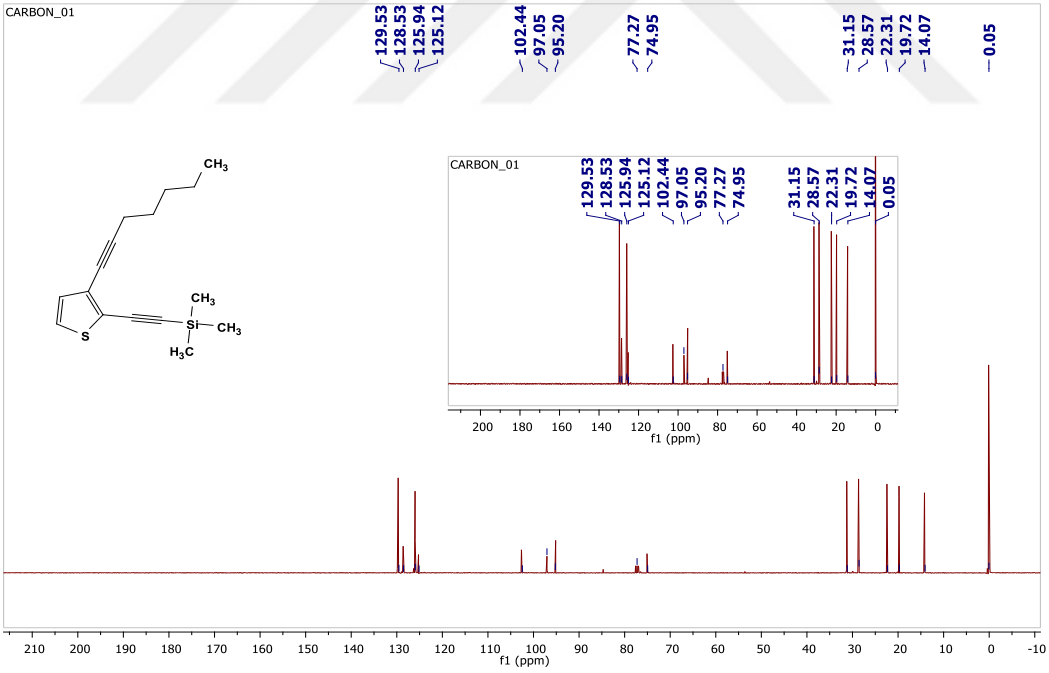

Figure M6. ^{13}C NMR spectra of MH2BN.

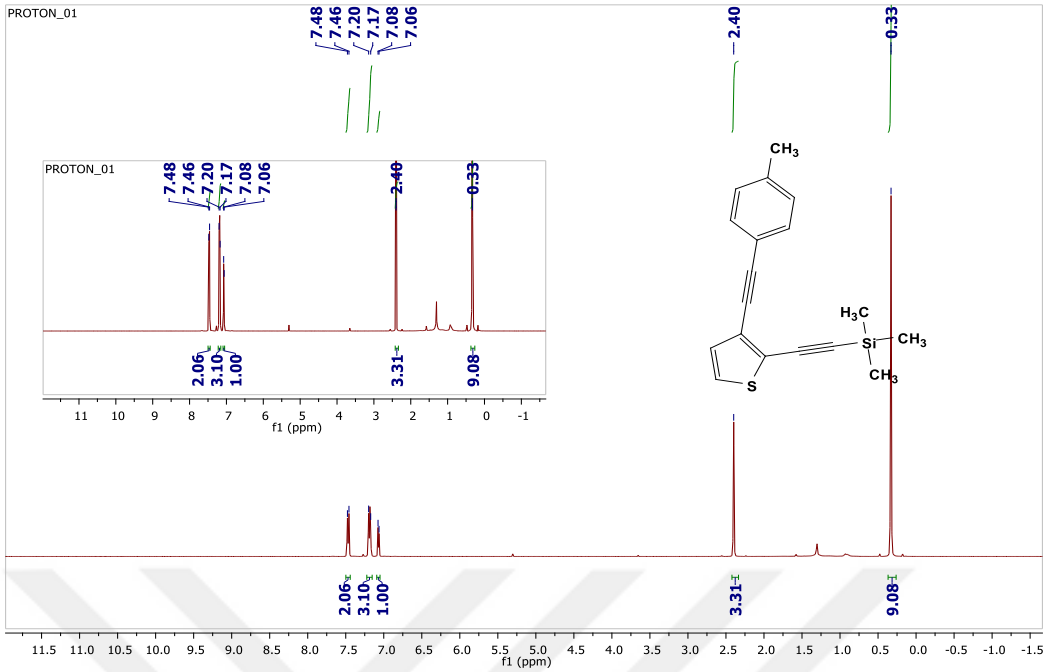

Figure M7. ^{1}H NMR spectra of MH2C.

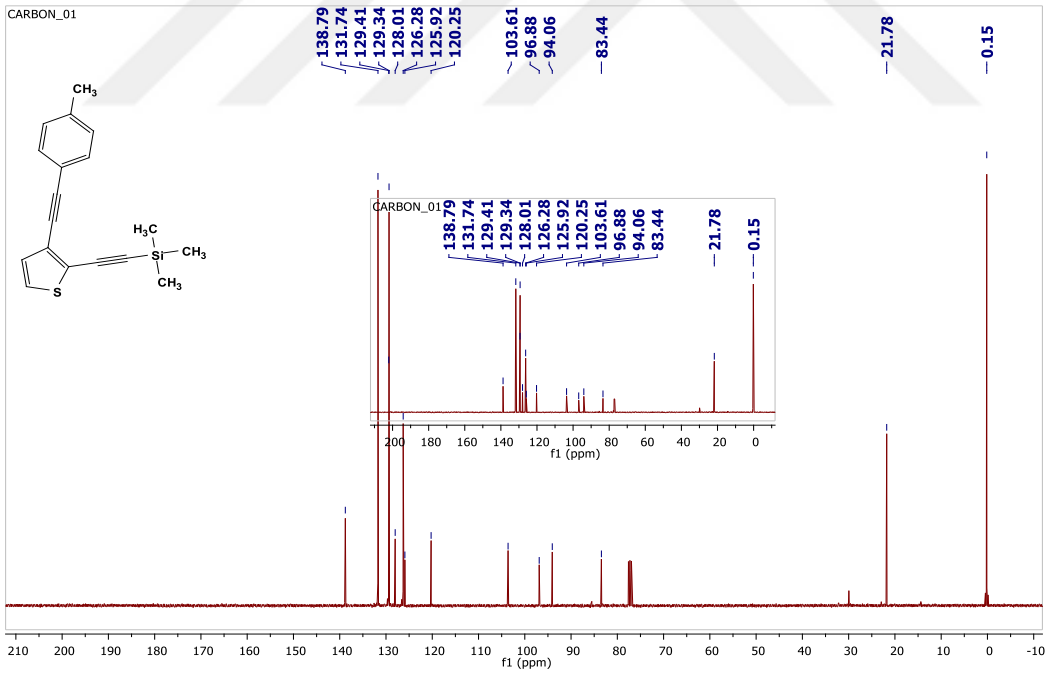

Figure M8. ^{13}C NMR spectra of MH2C.

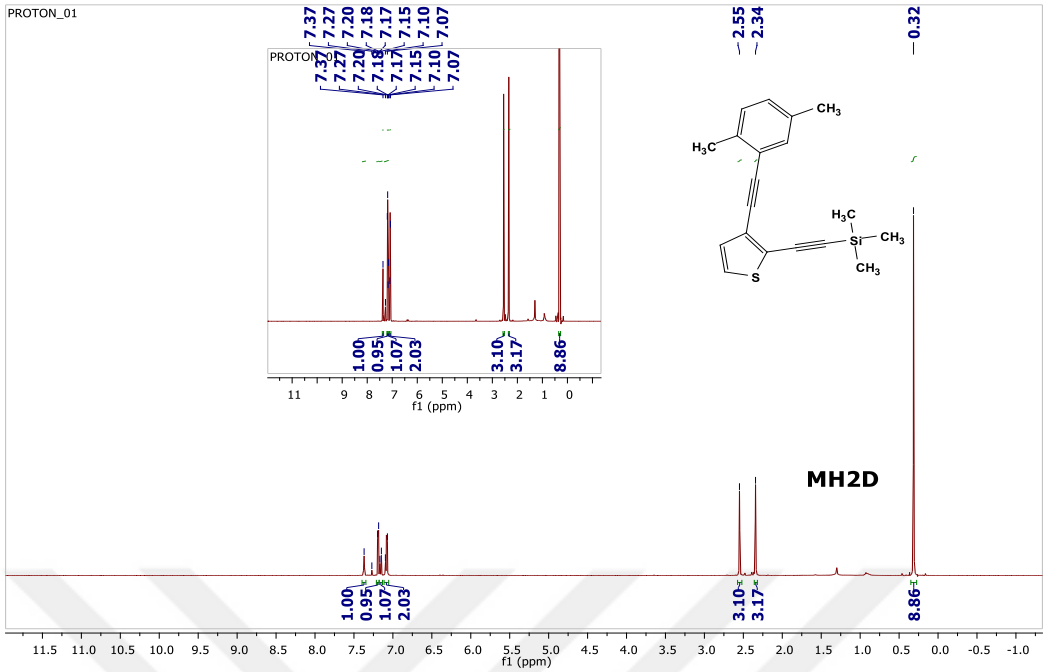

Figure M9. ^{1}H NMR spectra of MH2D.

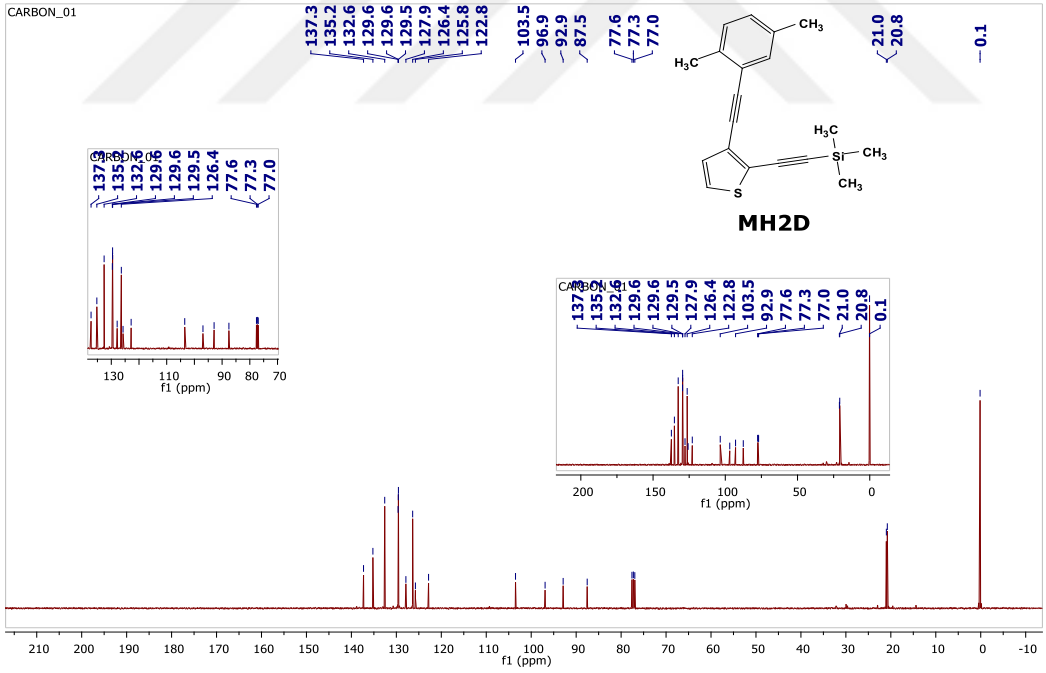

Figure M10. ^{13}C NMR spectra of MH2D.

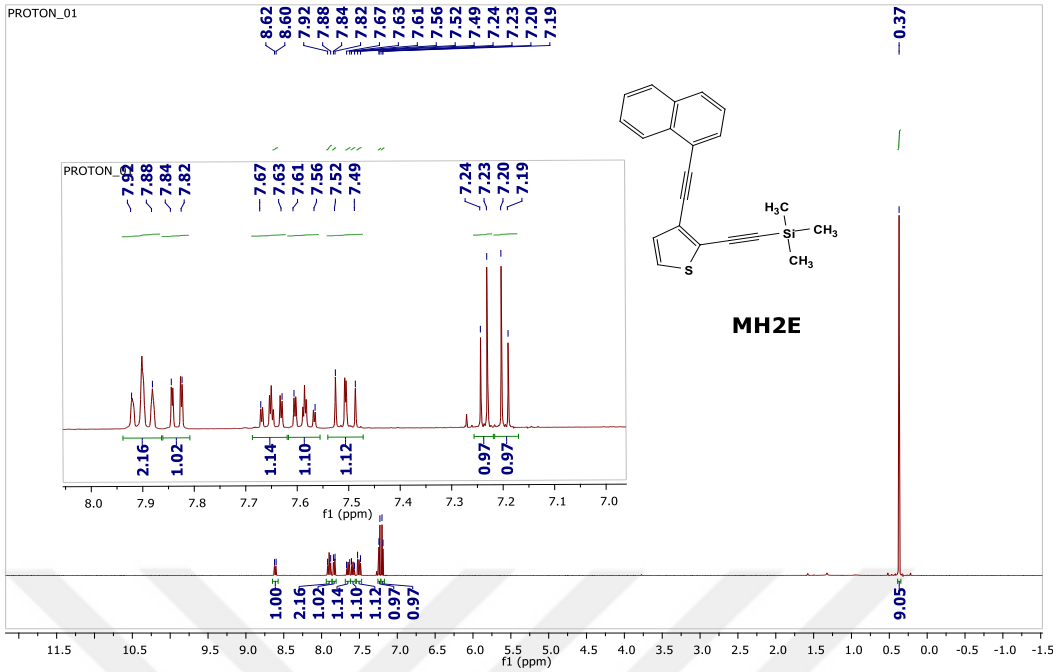

Figure M11. . ^{1}H NMR spectra of MH2E.

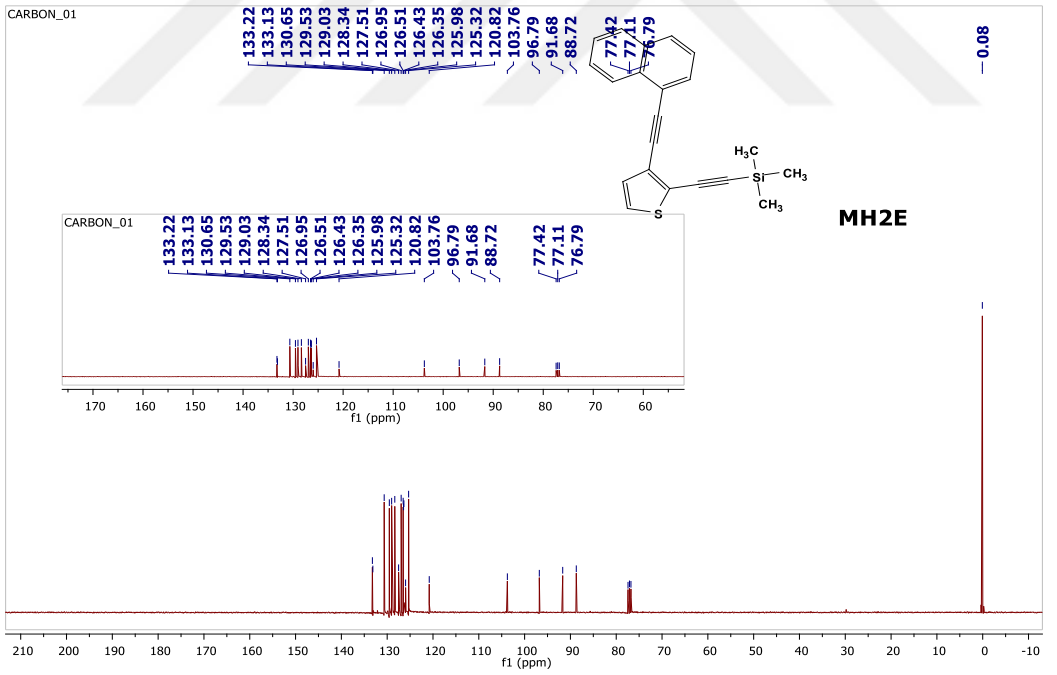

Figure M12. ^{13}C NMR spectra of MH2E.

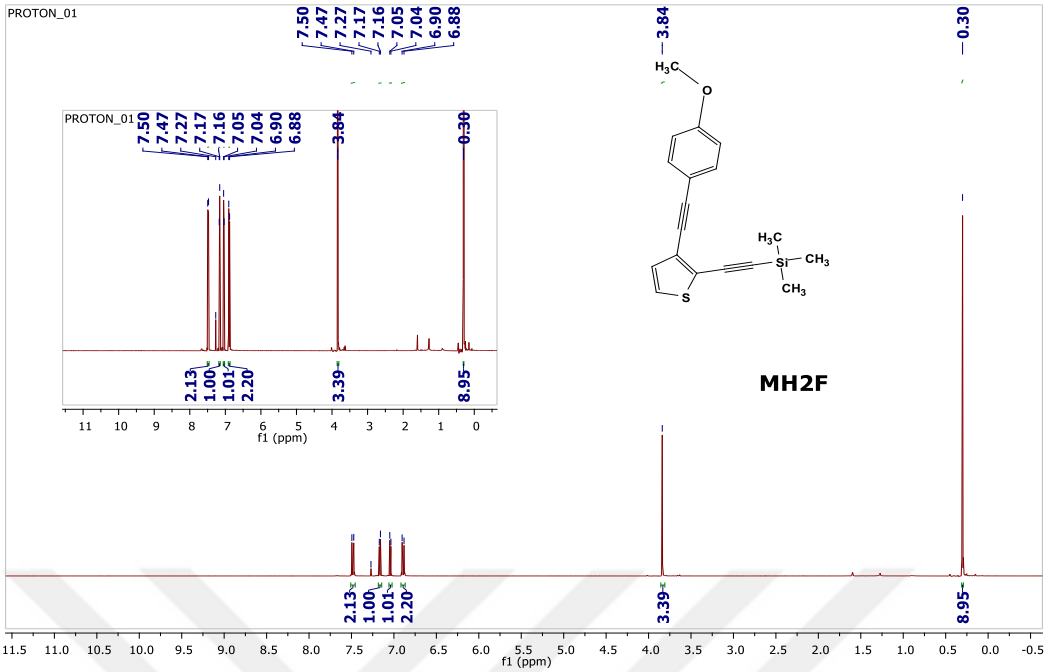

Figure M13. ^{1}H NMR spectra of MH2F.

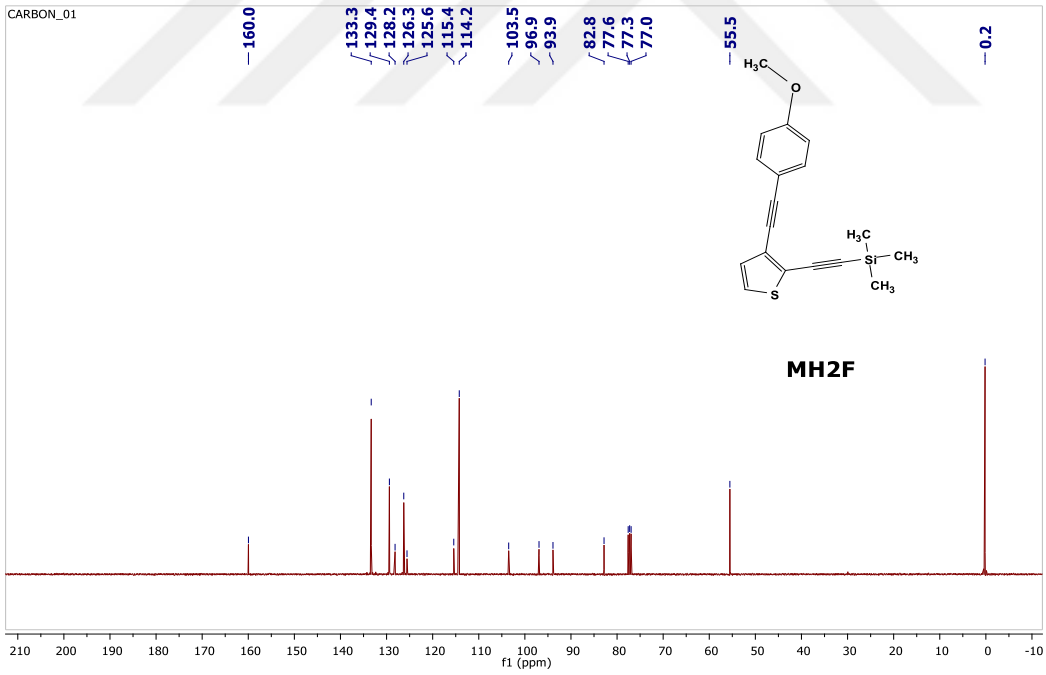

Figure M14. ^{13}C NMR spectra of MH2F.

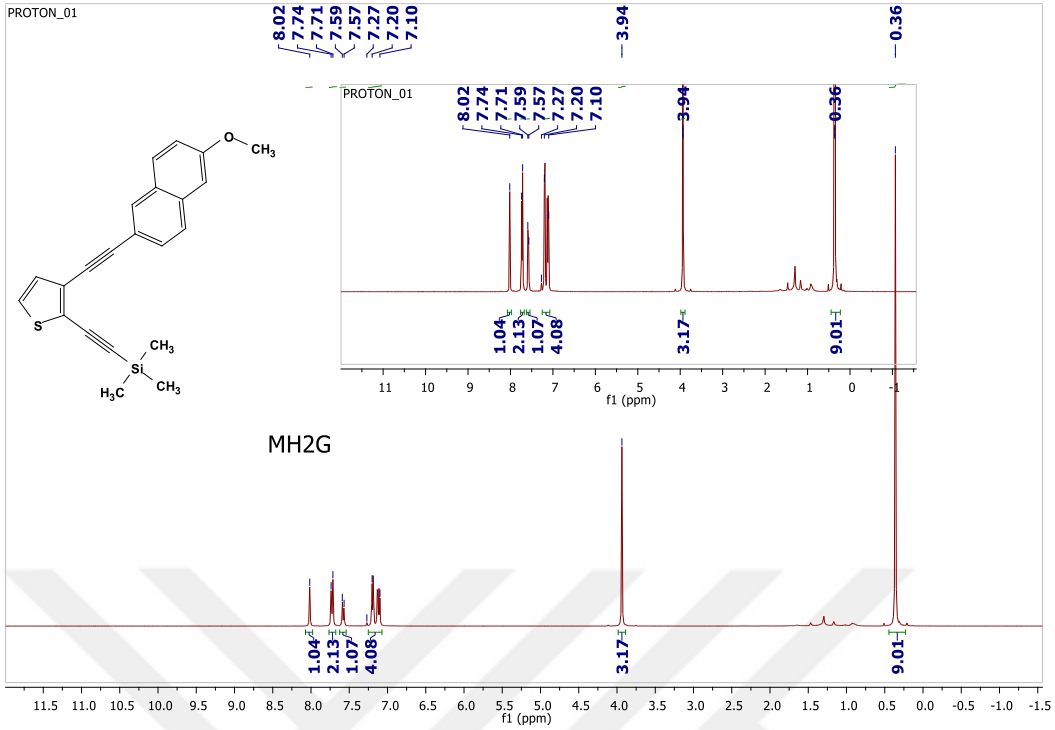

Figure M15. ^{1}H NMR spectra of MH2G.

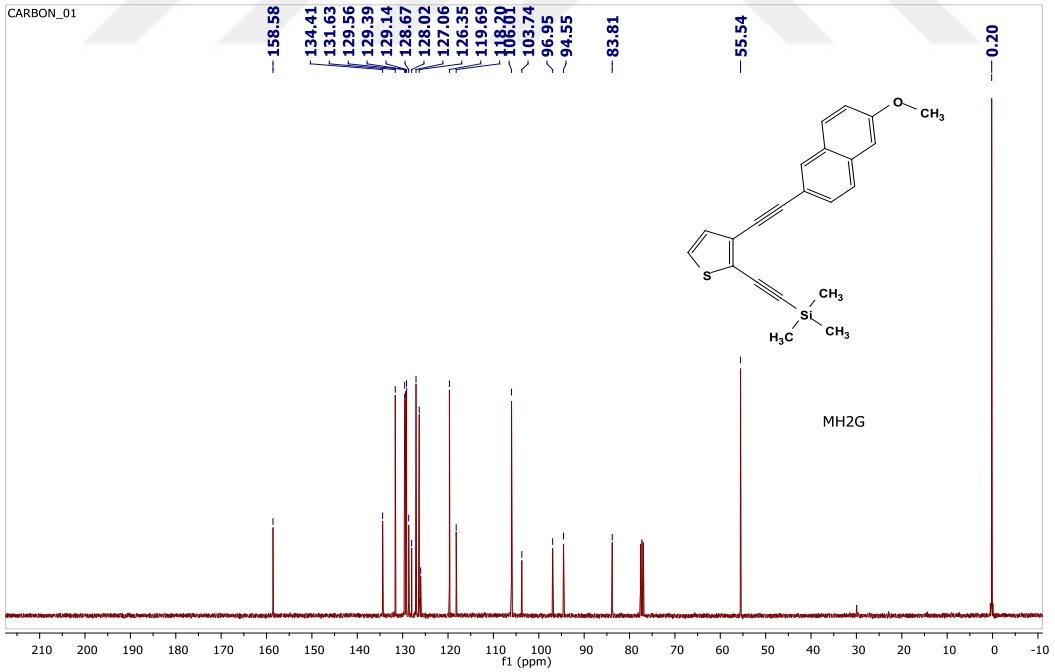

Figure M16. ^{13}C NMR spectra of MH2G.

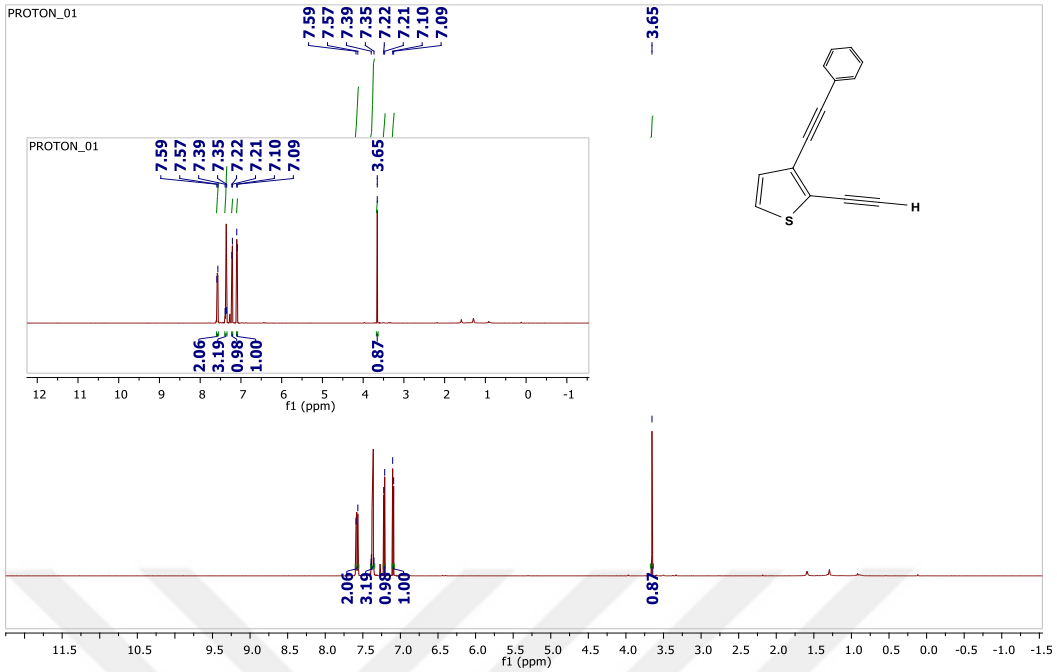

Figure M17. ^{1}H NMR spectra of MH3.

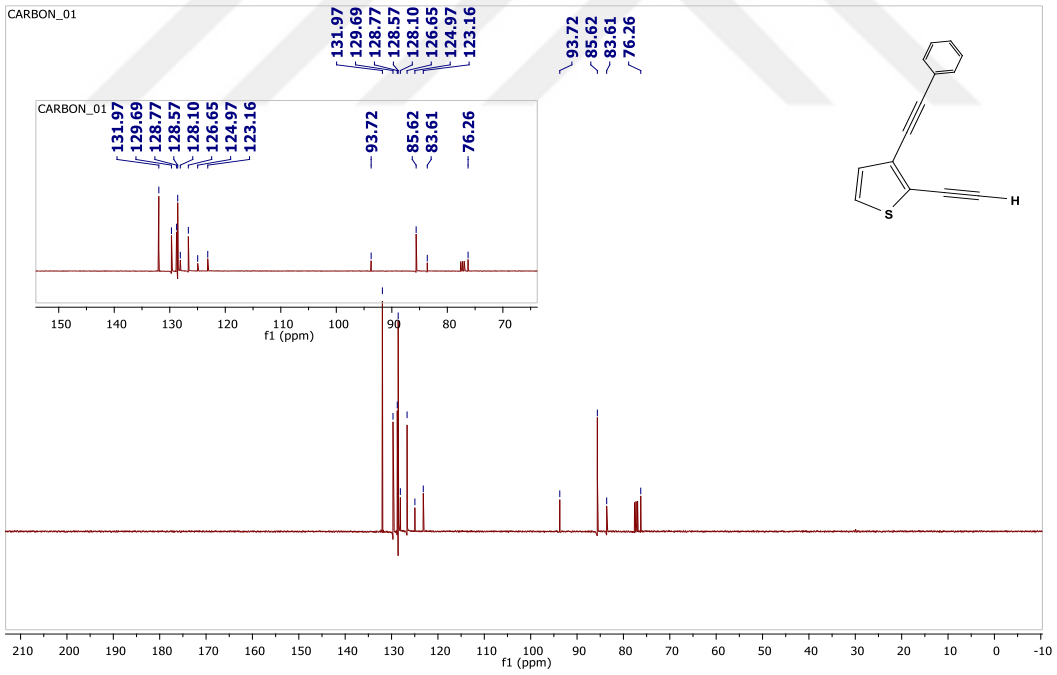

Figure M18. ^{13}C NMR spectra of MH3.

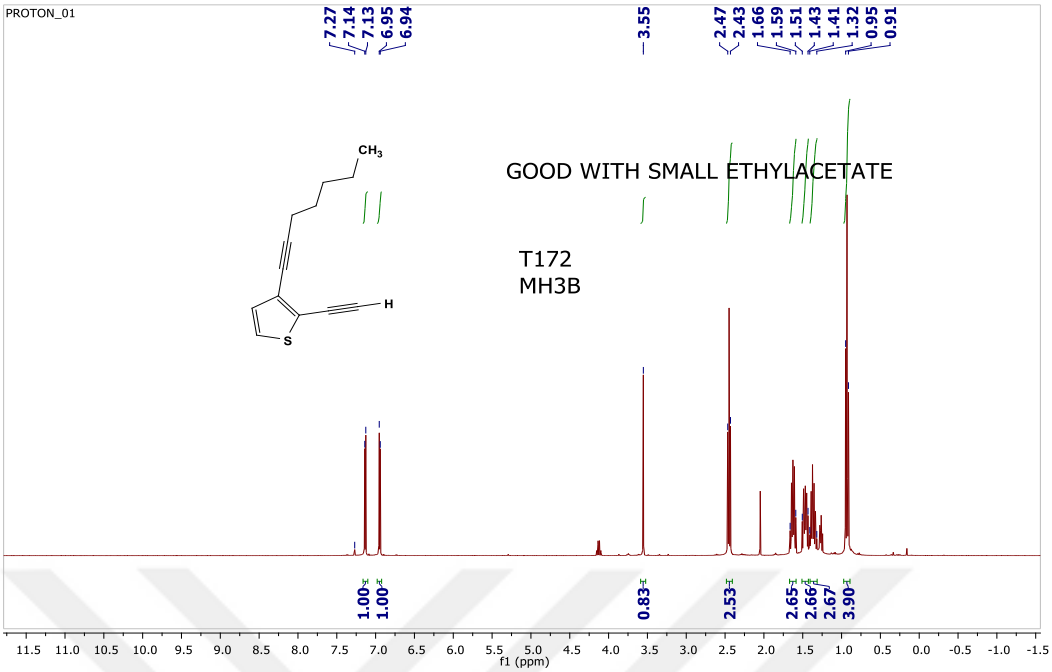

Figure M19. ^{1}H NMR spectra of MH3BN.

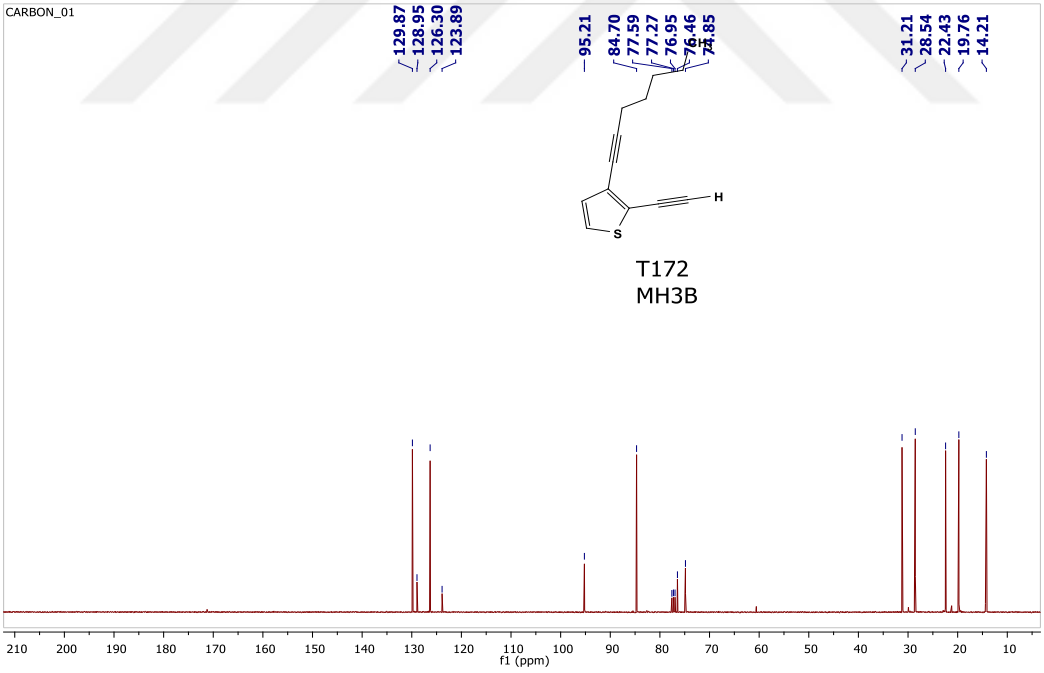

Figure M20. ^{13}C NMR spectra of MH3BN.

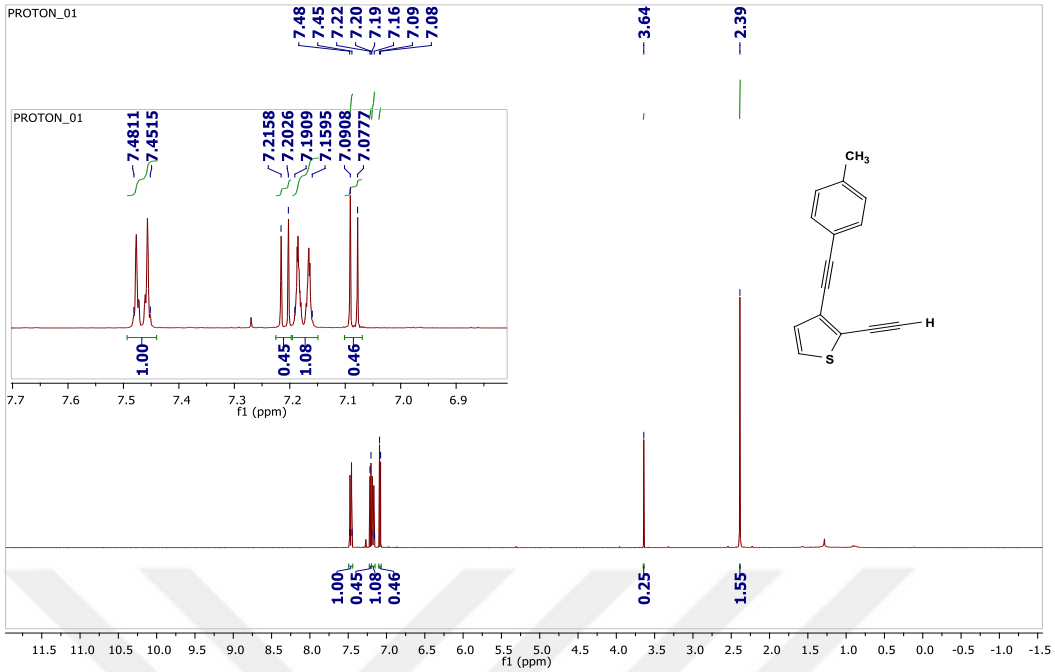

Figure M21. ^{1}H NMR spectra of MH3C.

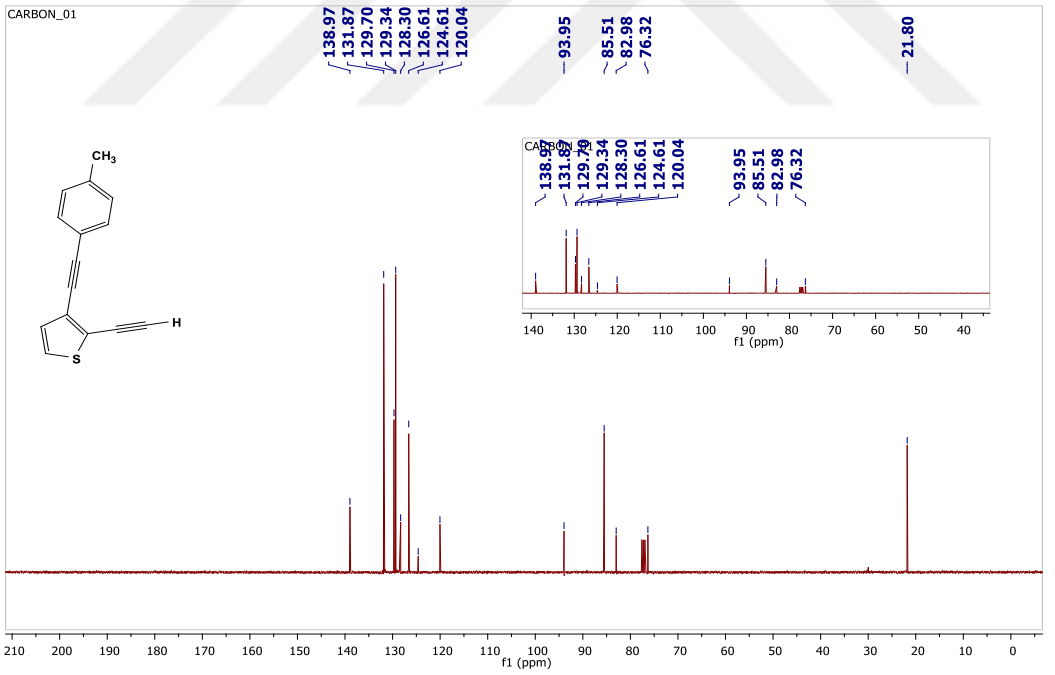

Figure M22. ^{13}C NMR spectra of MH3C.

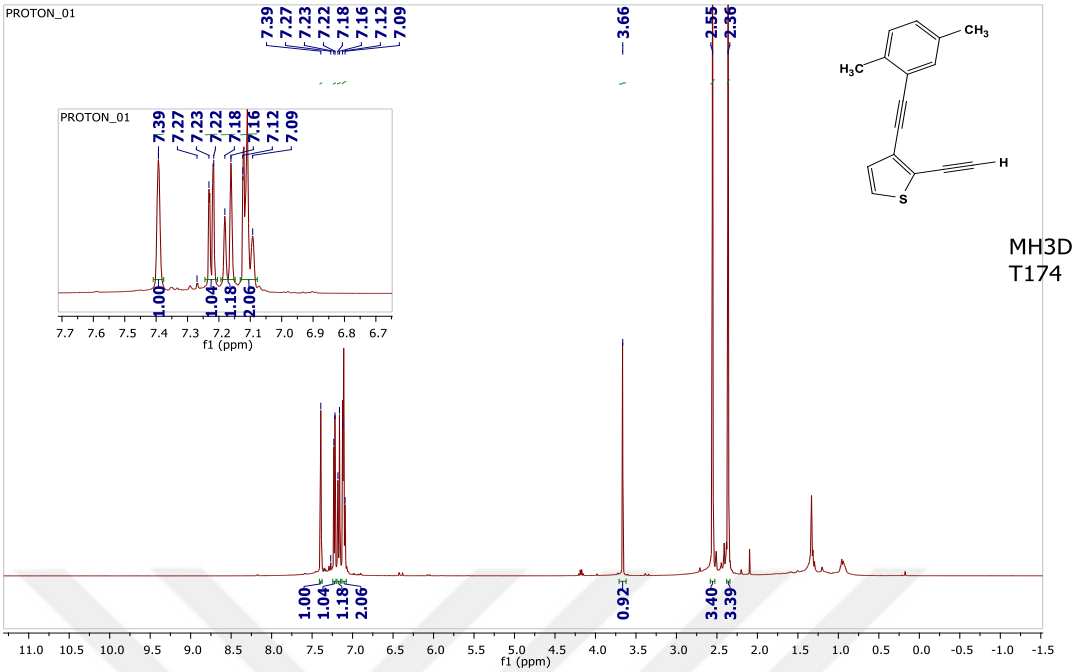

Figure M23. ^{1}H NMR spectra of MH3D.

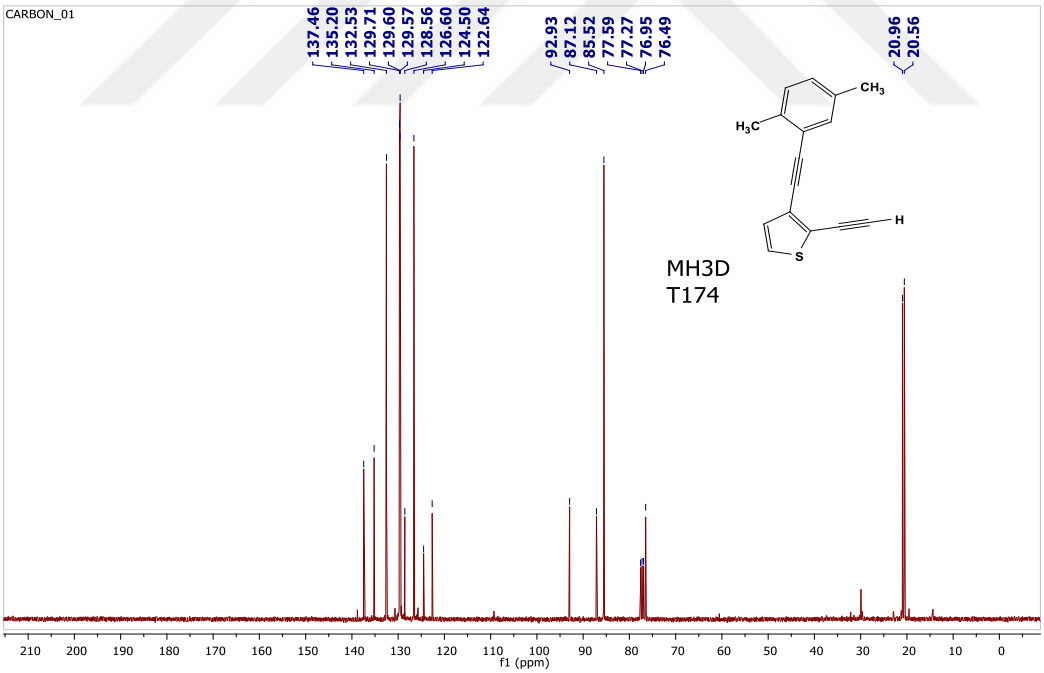

Figure M24. ^{13}C NMR spectra of MH3D.

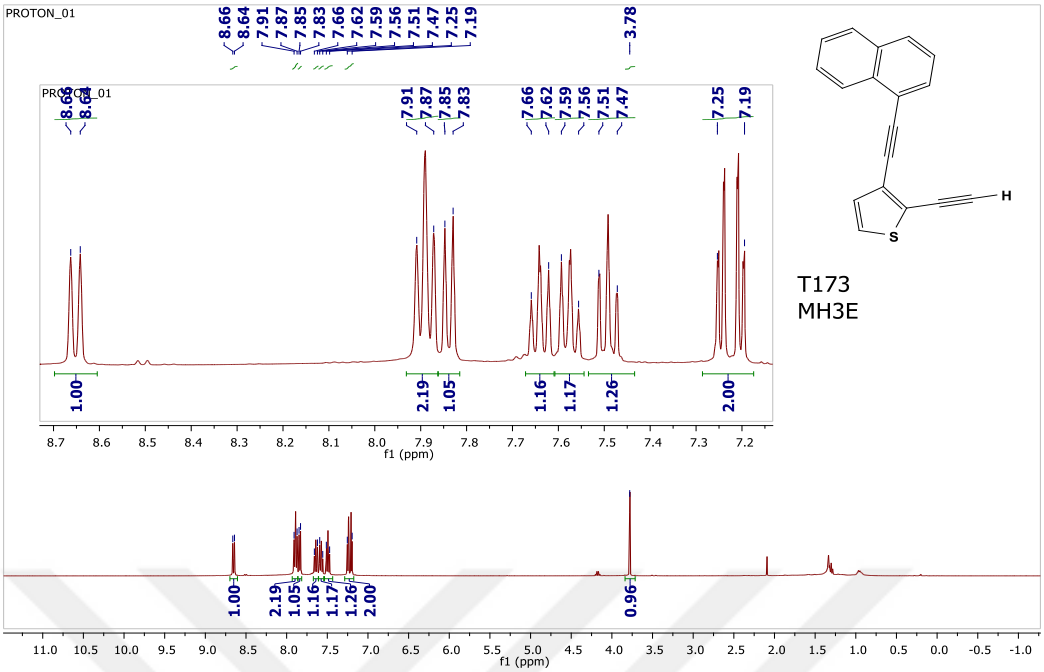

Figure M25. ^{1}H NMR spectra of MH3E.

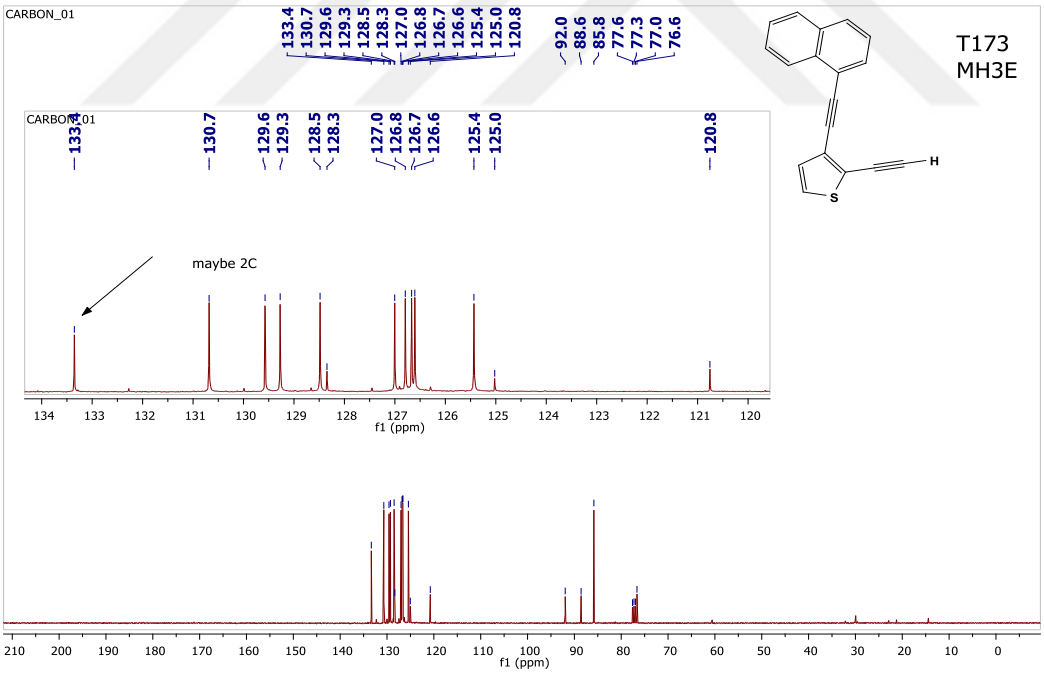

Figure M26. ^{13}C NMR spectra of MH3E.

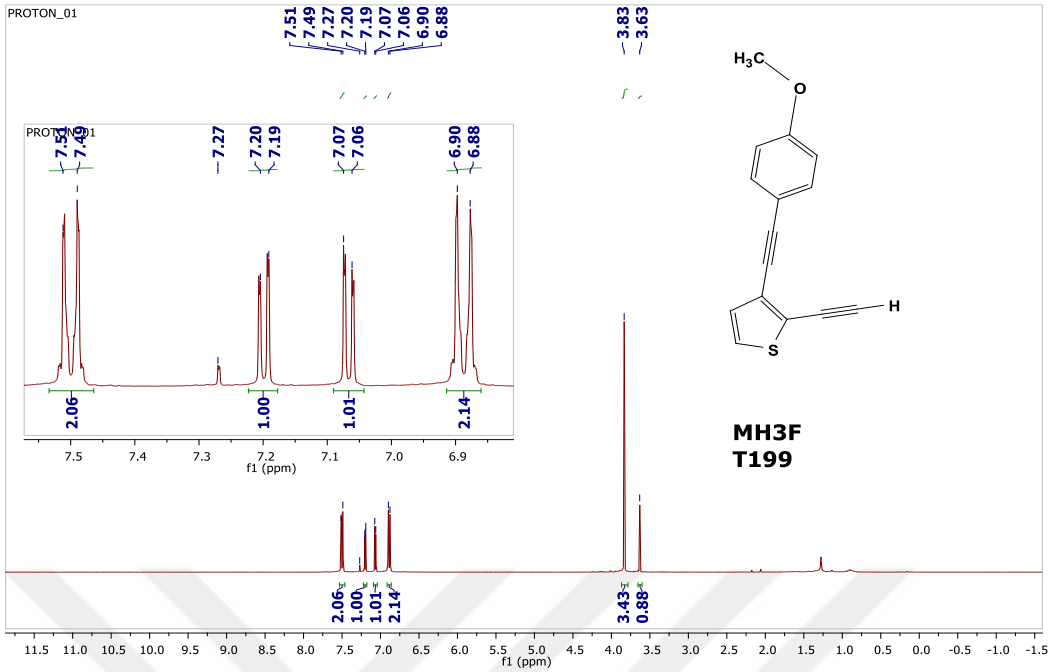

Figure M27. ^{1}H NMR spectra of MH3F.

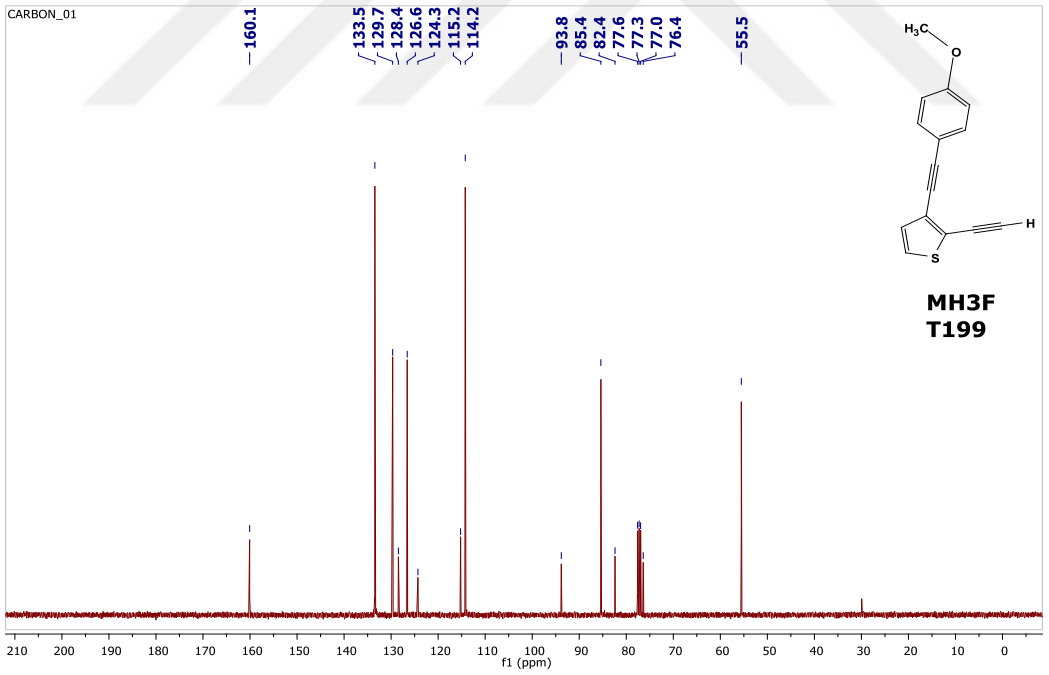

Figure M28. ^{13}C NMR spectra of MH3F.

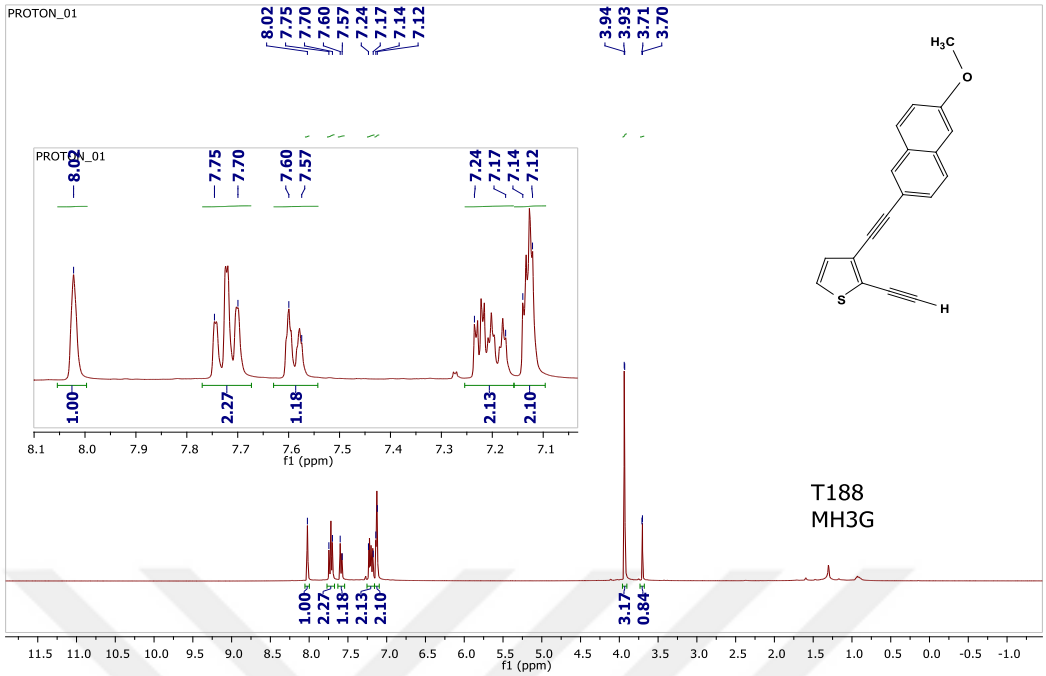

Figure M29. ^{1}H NMR spectra of MH3G.

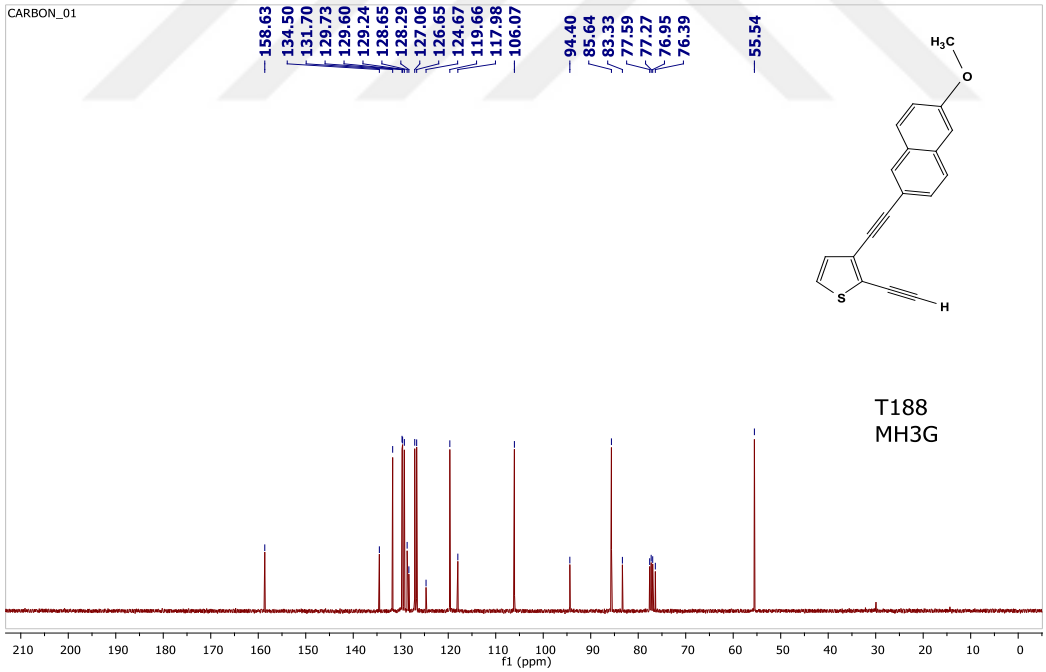

Figure M30. ^{13}C NMR spectra of MH3G.

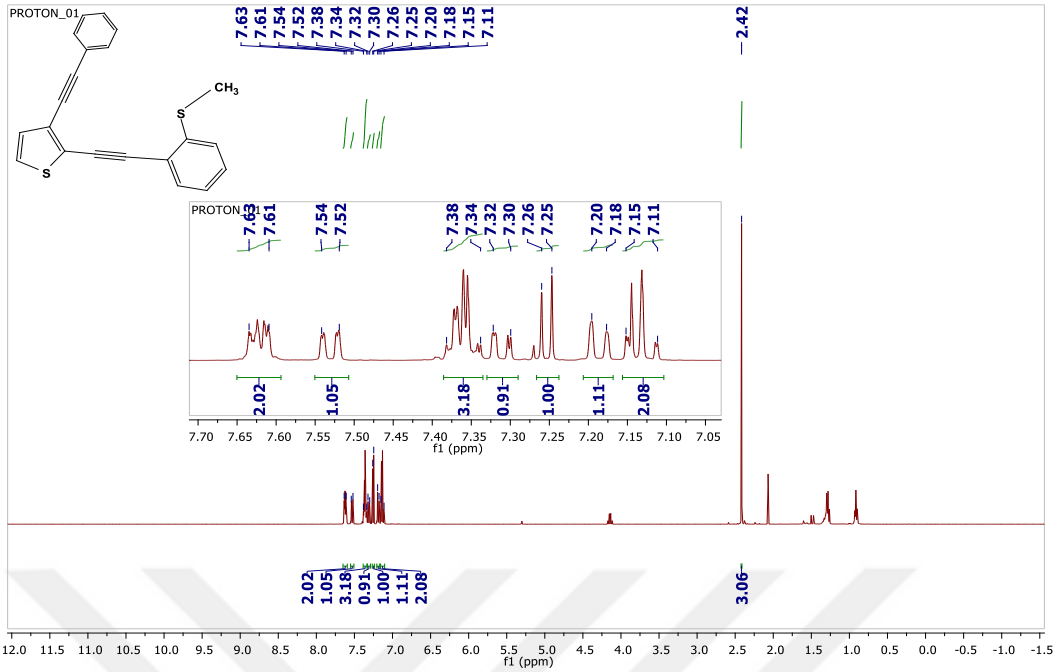

Figure M31. ^{1}H NMR spectra of MH4.

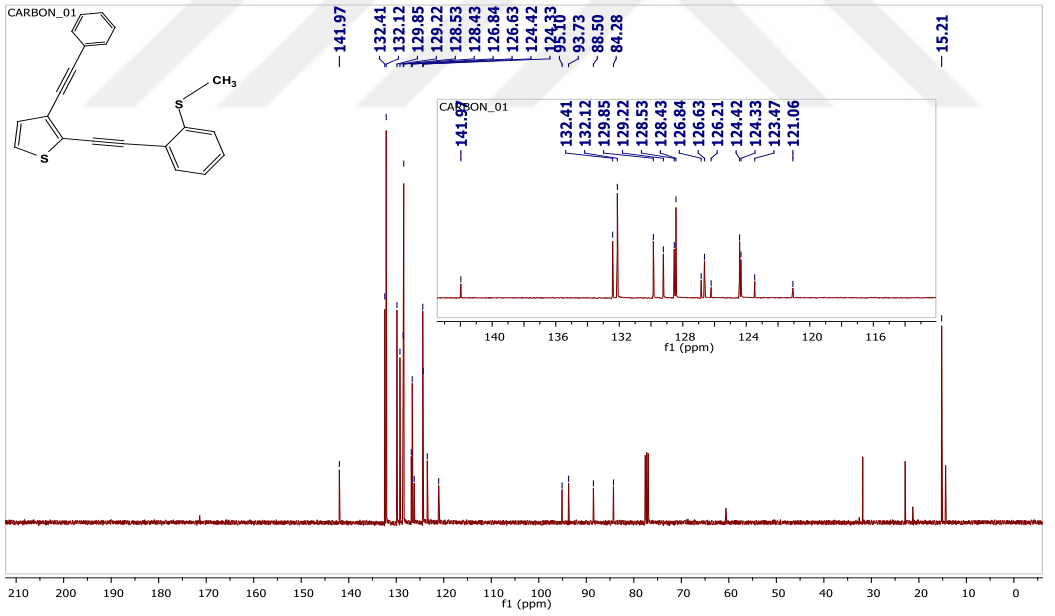

Figure M32. ^{13}C NMR spectra of MH4.

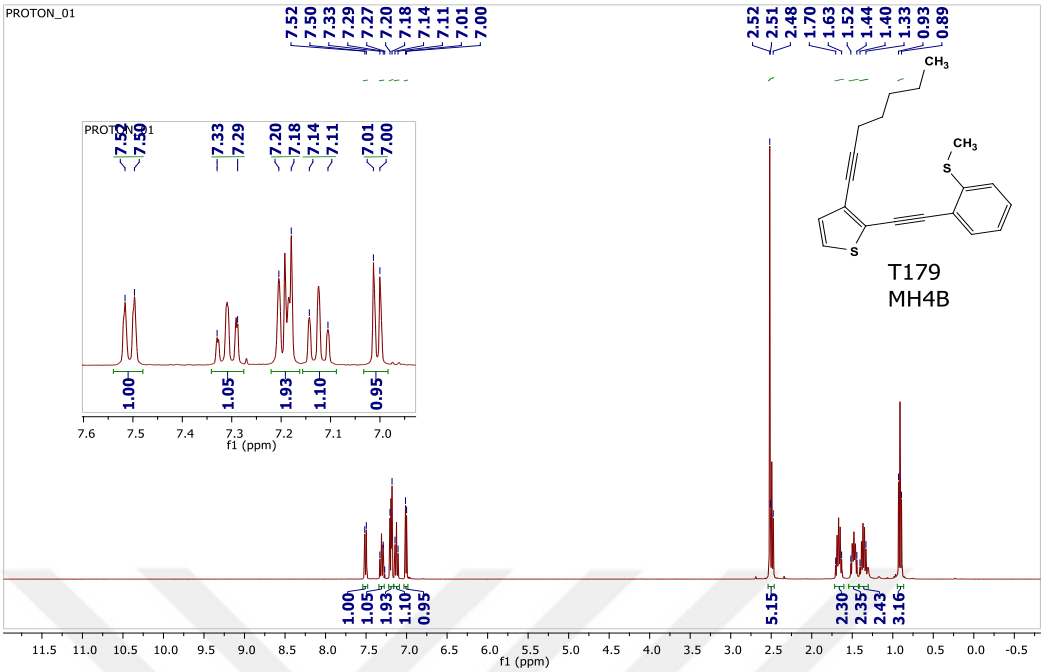

Figure M33. ^{1}H NMR spectra of MH4B.

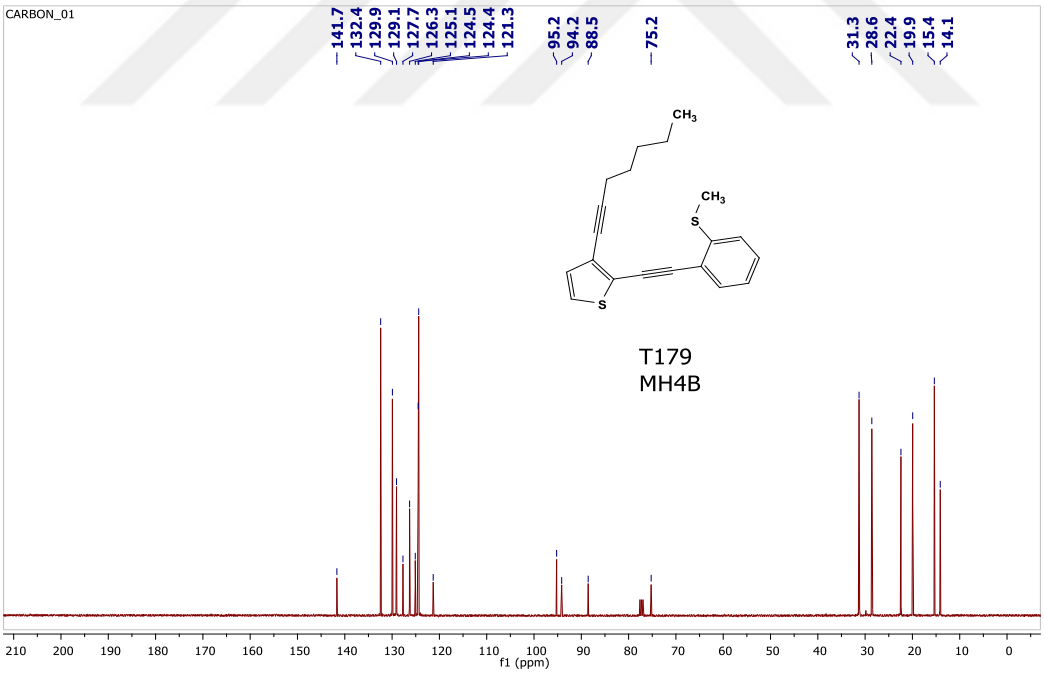

Figure M34. ^{13}C NMR spectra of MH4B.

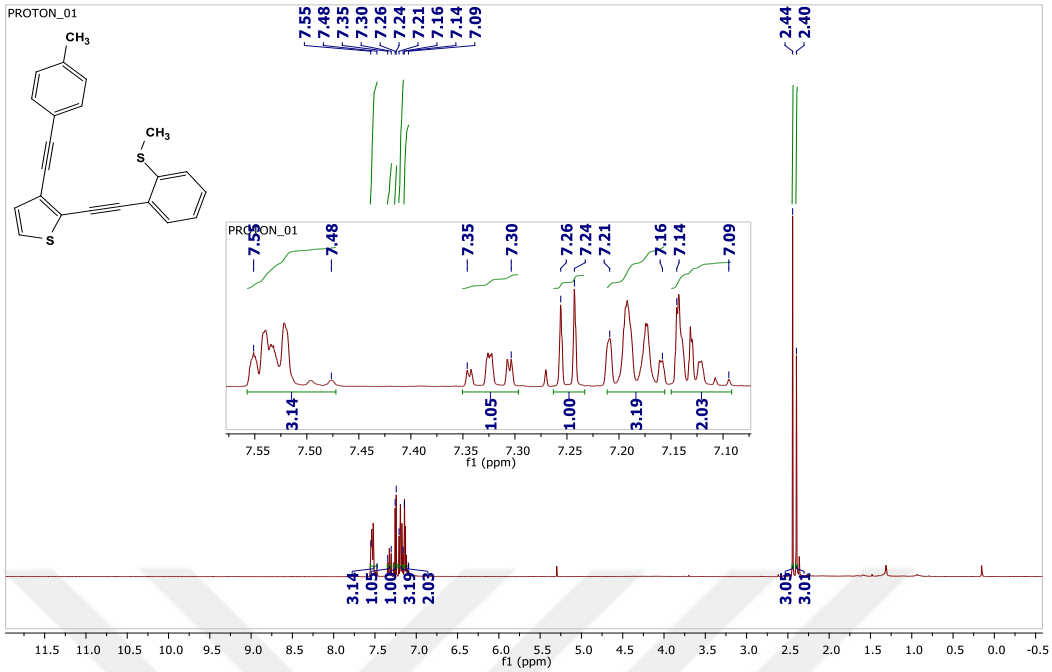

Figure M35. ^{1}H NMR spectra of MH4C.

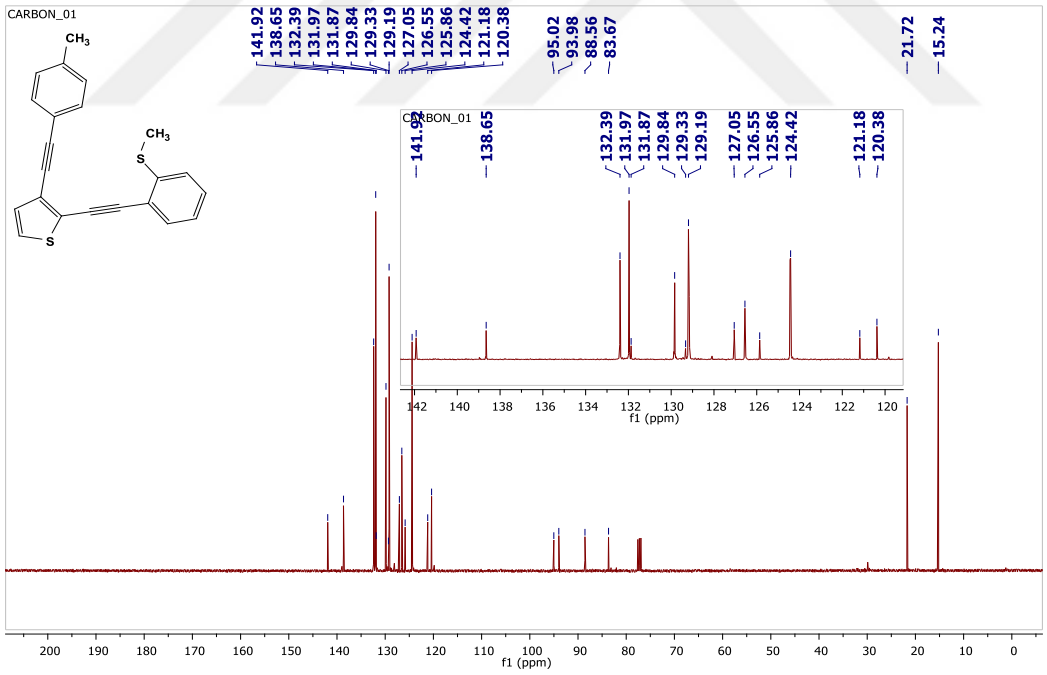

Figure M36. ^{13}C NMR spectra of MH4C.

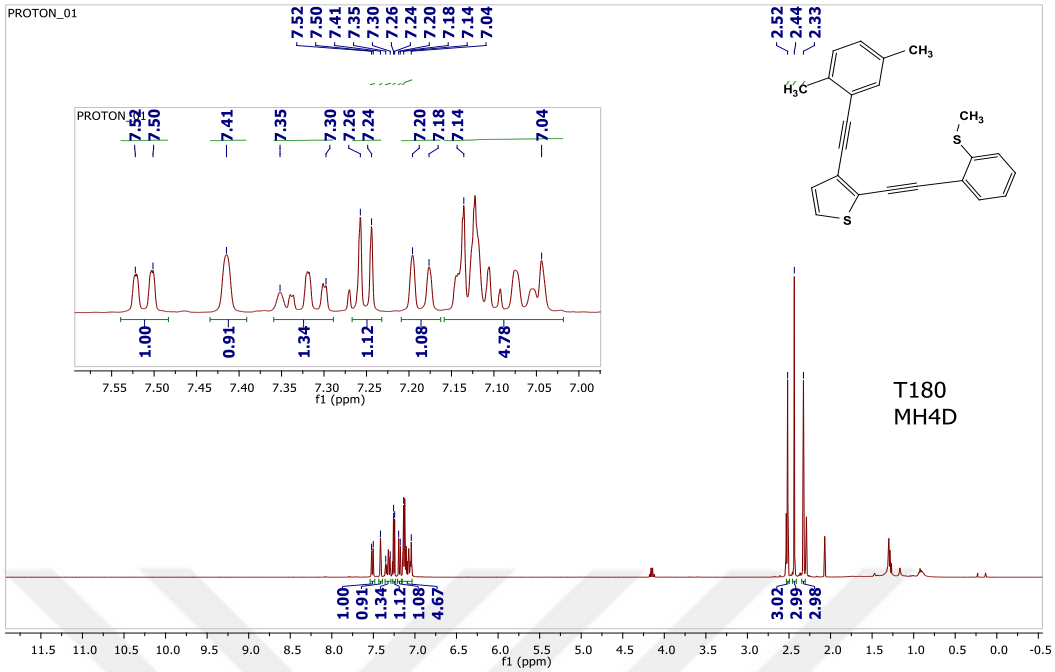

Figure M37. ^{1}H NMR spectra of MH4D.

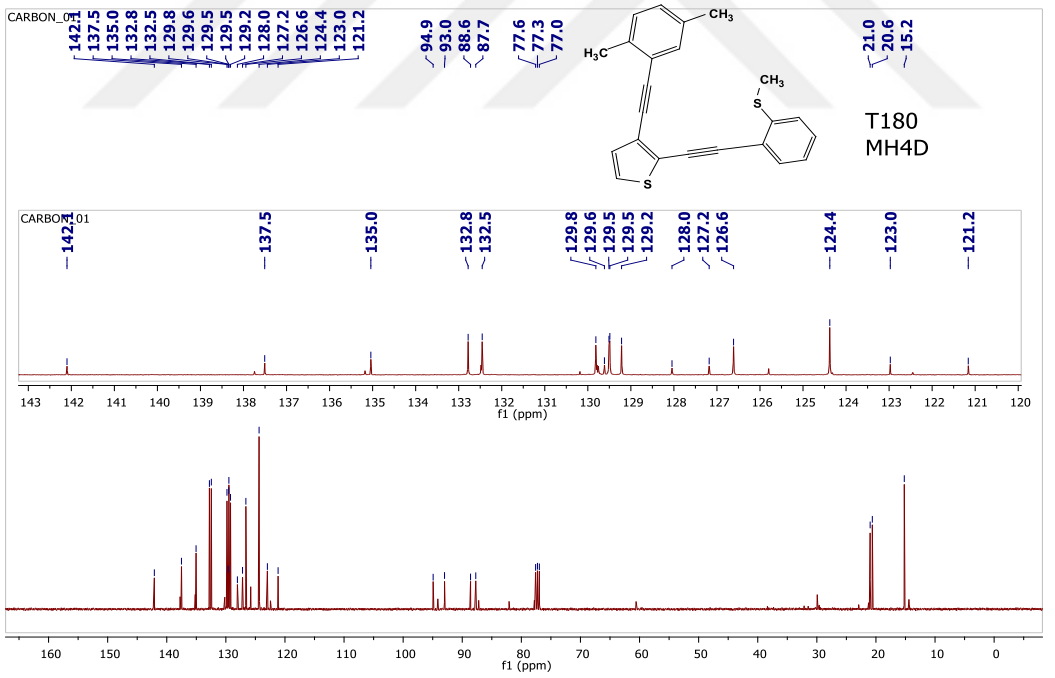

Figure M38. ^{13}C NMR spectra of MH4D.

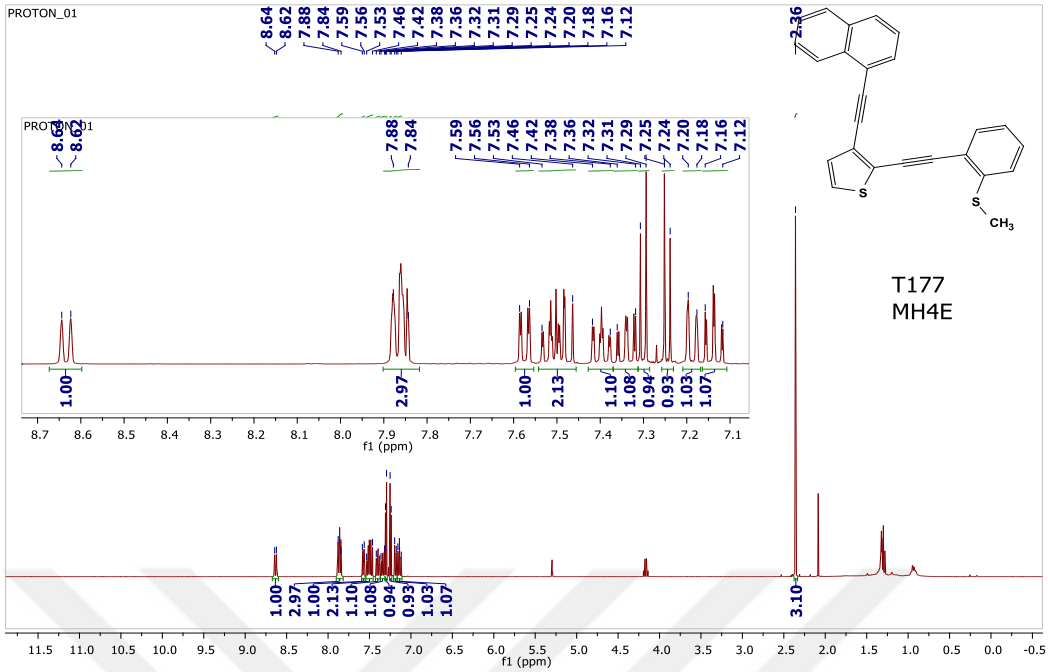

Figure M39. ^{1}H NMR spectra of MH4E.

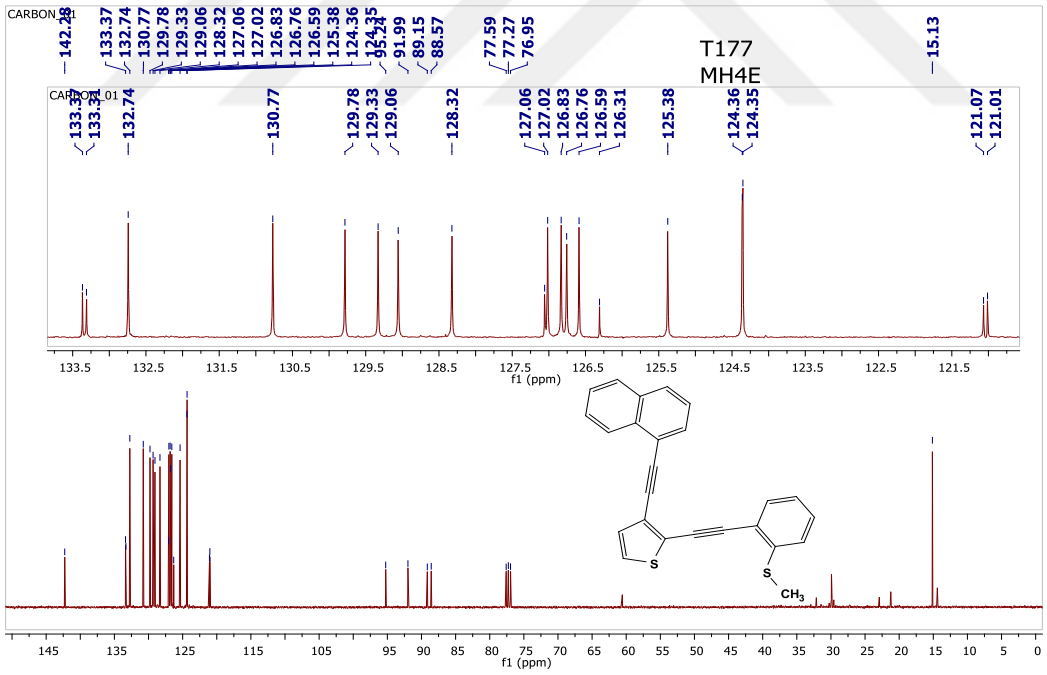

Figure M40. ^{13}C NMR spectra of MH4E.

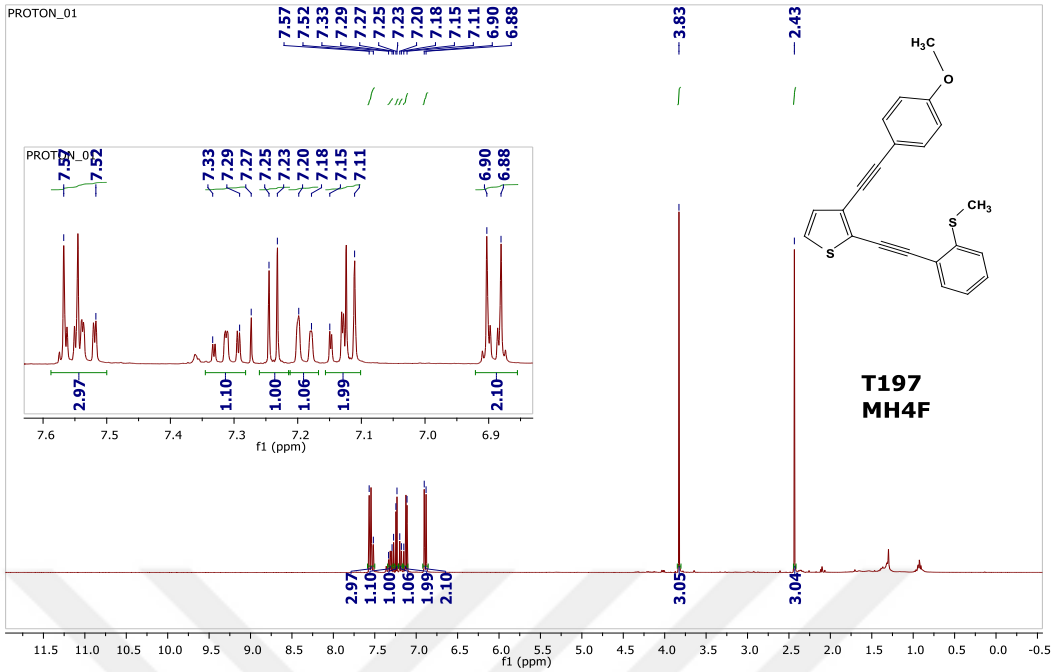

Figure M41. ^{1}H NMR spectra of MH4F.

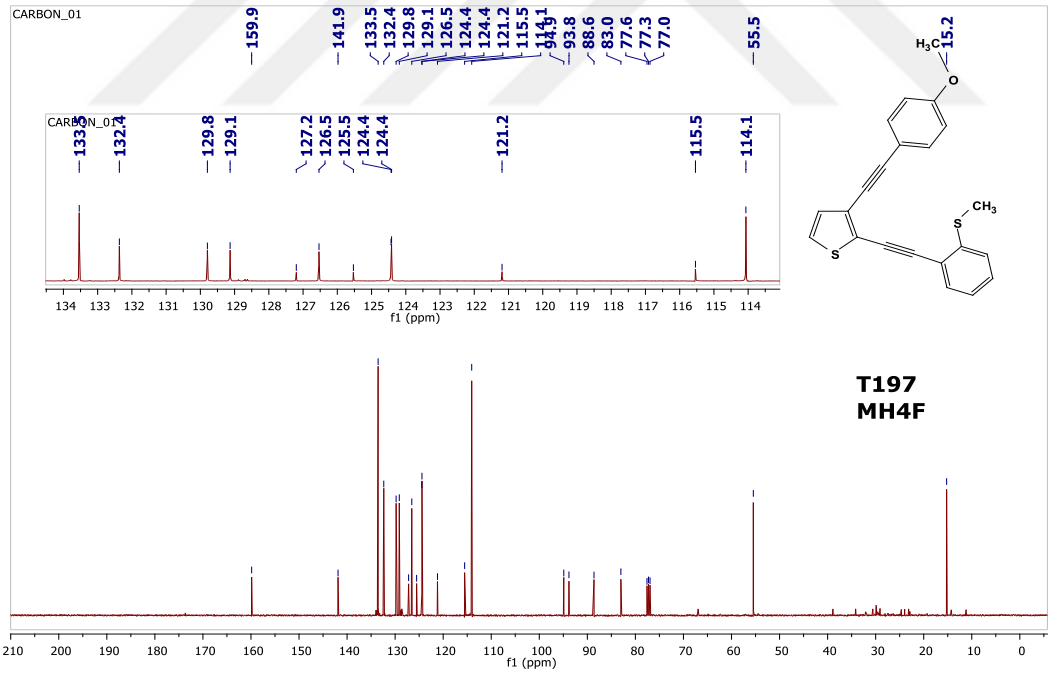

Figure M42. ^{13}C NMR spectra of MH4F.

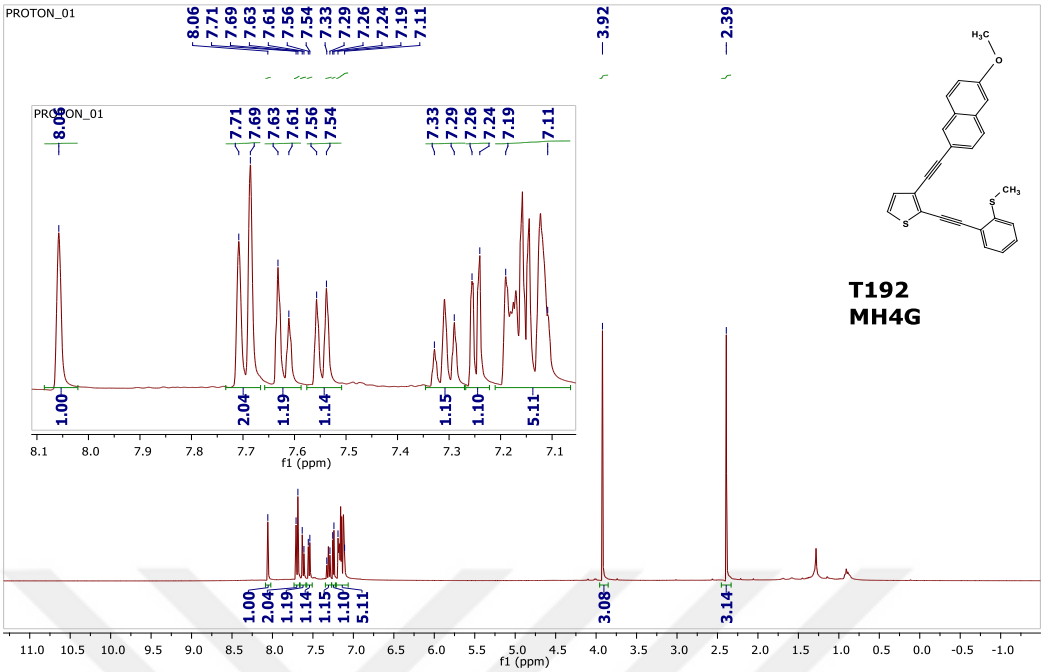

Figure M43. ^{1}H NMR spectra of MH4G.

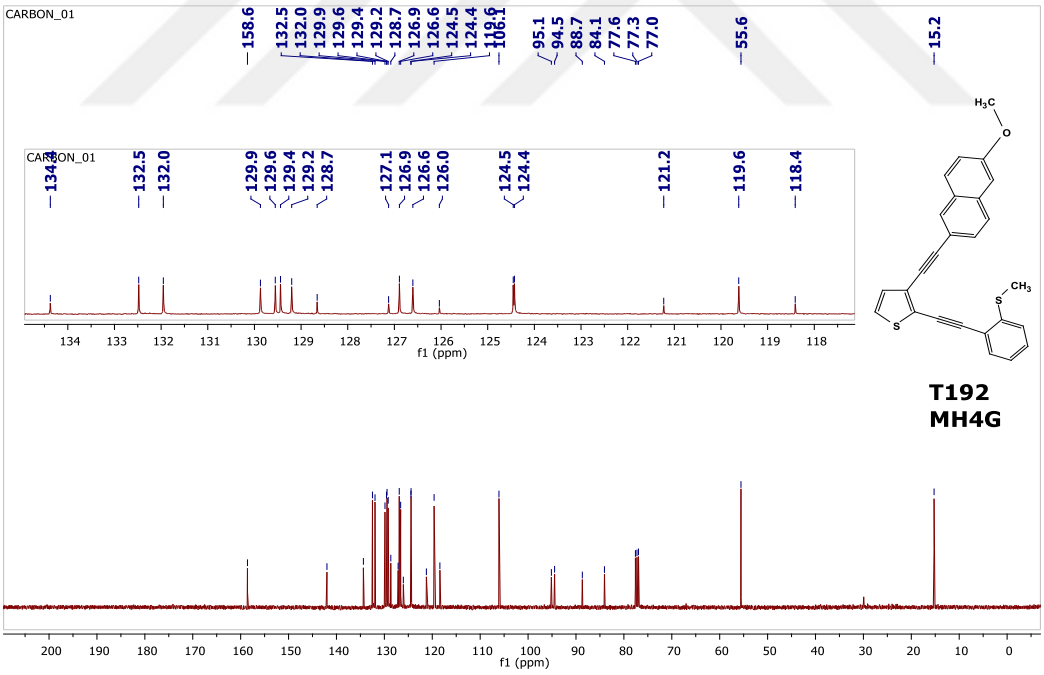

Figure M44. ^{13}C NMR spectra of MH4G.

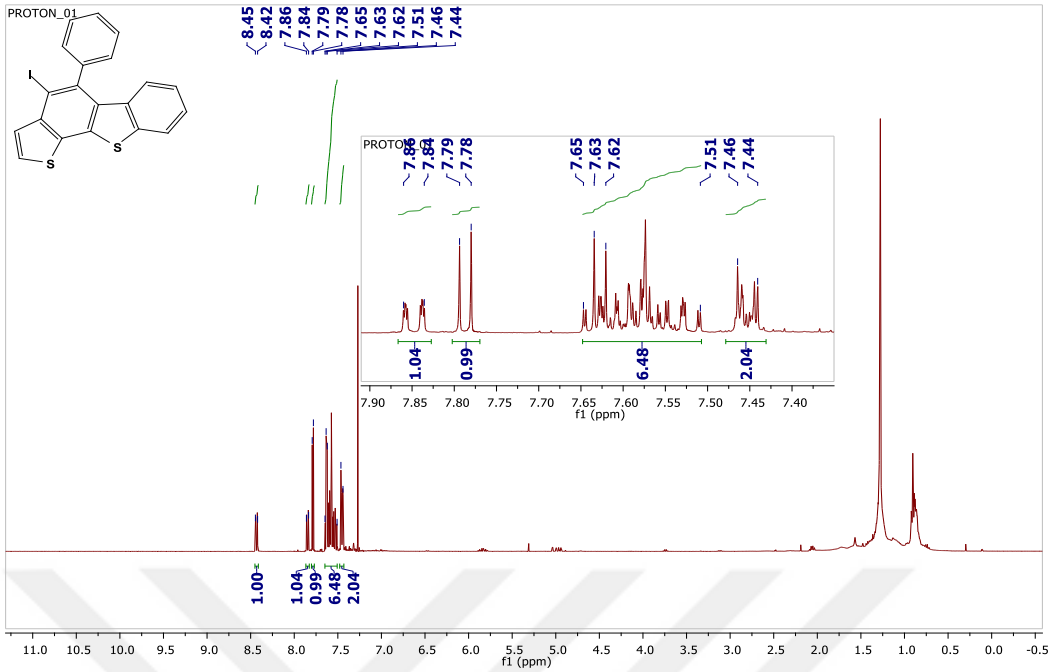

Figure M45. ^{1}H NMR spectra of MH7.

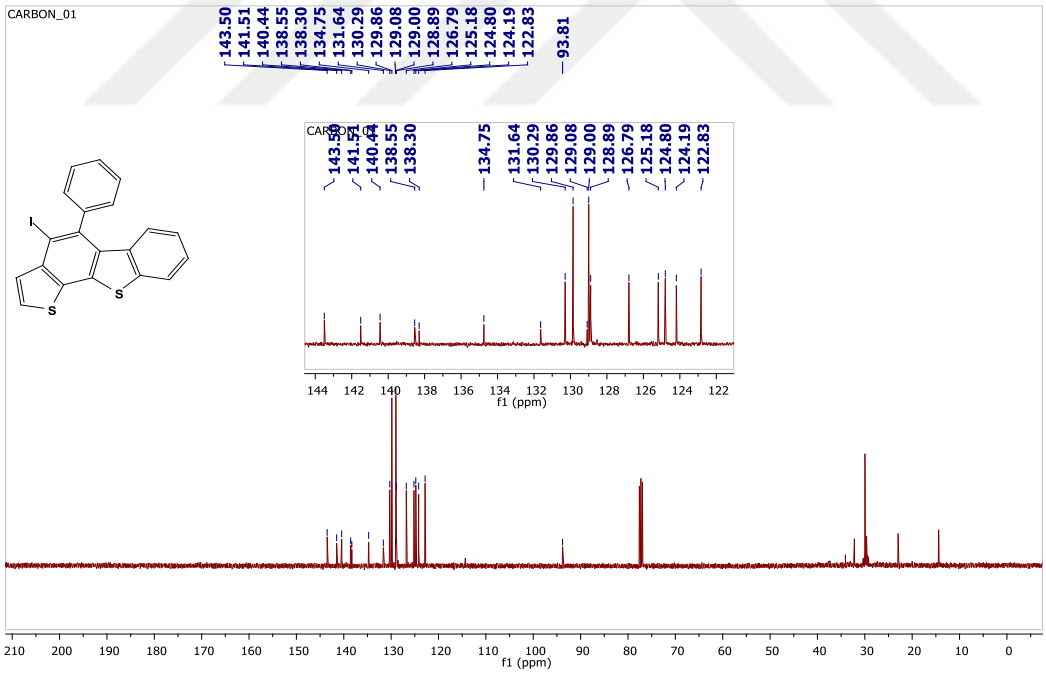

Figure M46. ^{13}C NMR spectra of MH7.

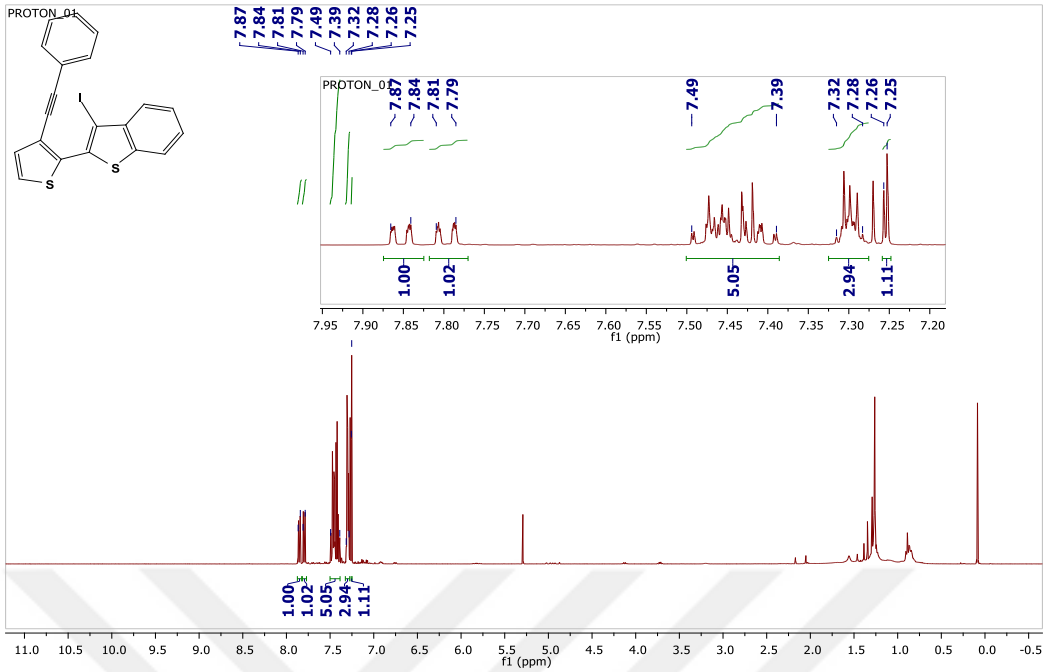

Figure M47. ^{1}H NMR spectra of MH17.

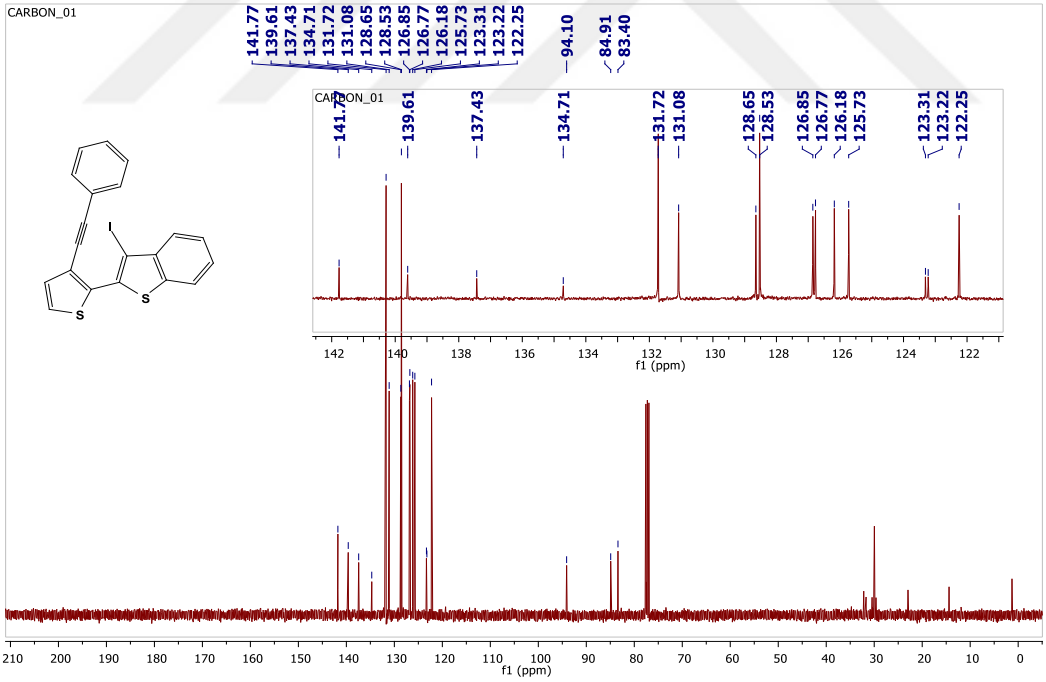

Figure M48. ^{13}C NMR spectra of MH17.

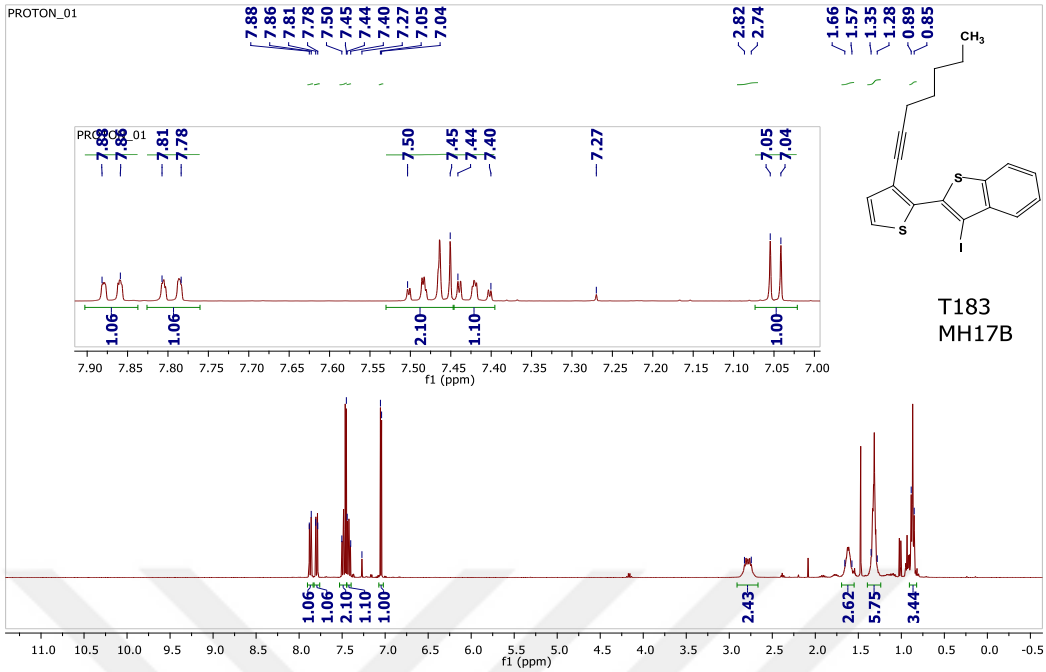

Figure M49. ^{1}H NMR spectra of MH17B.

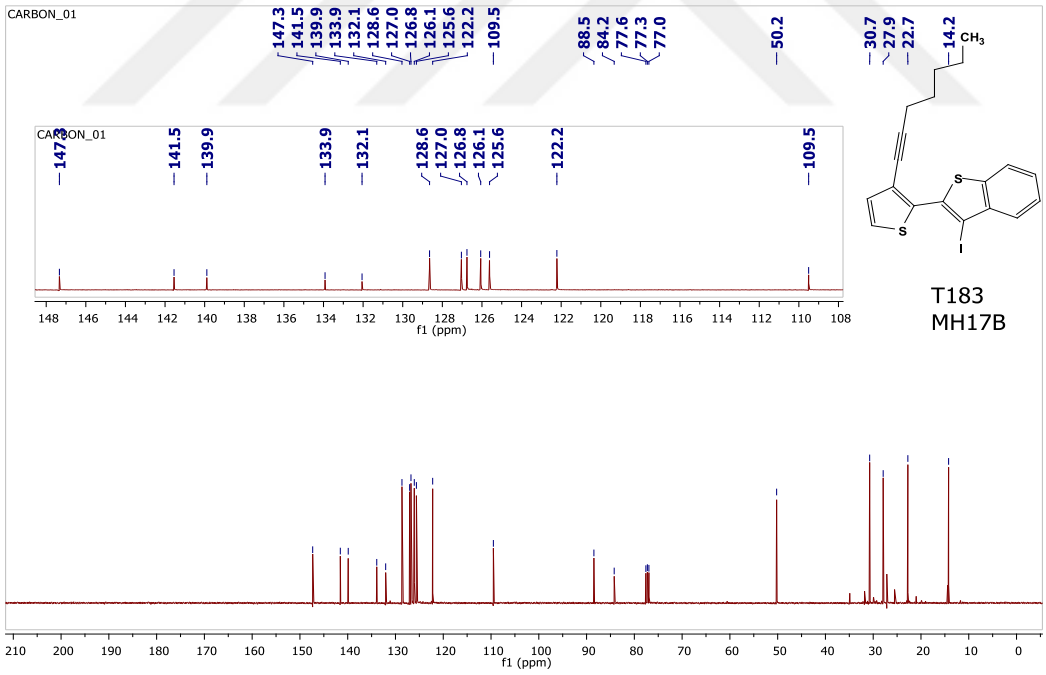

Figure M50. ^{13}C NMR spectra of MH17B.

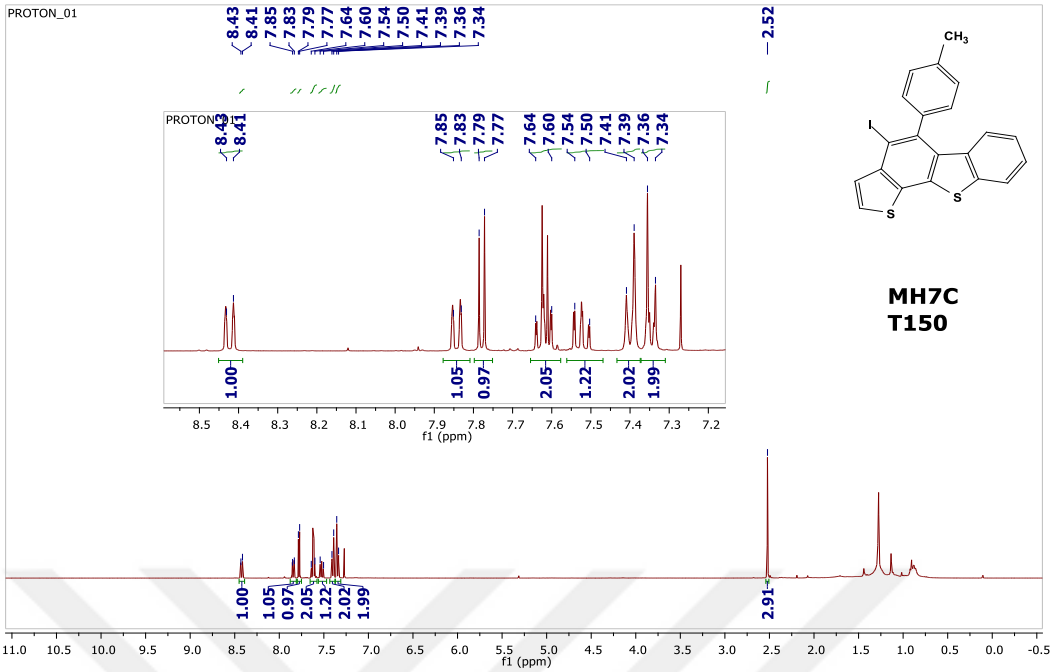

Figure M51. ^{1}H NMR spectra of MH7C.

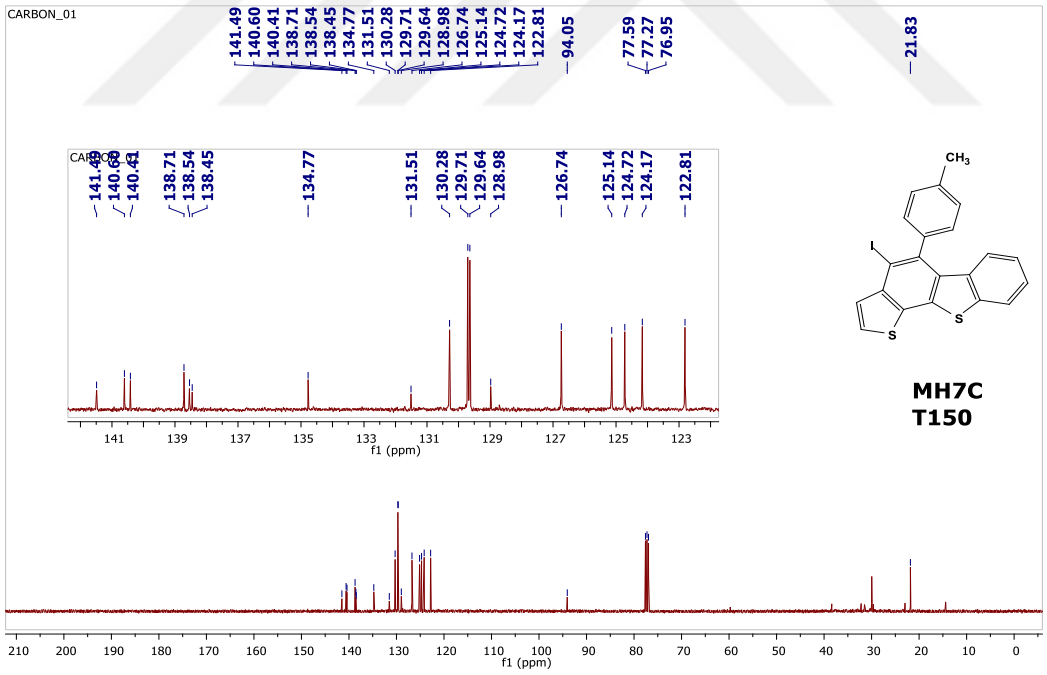

Figure M52. ^{13}C NMR spectra of MH7C.

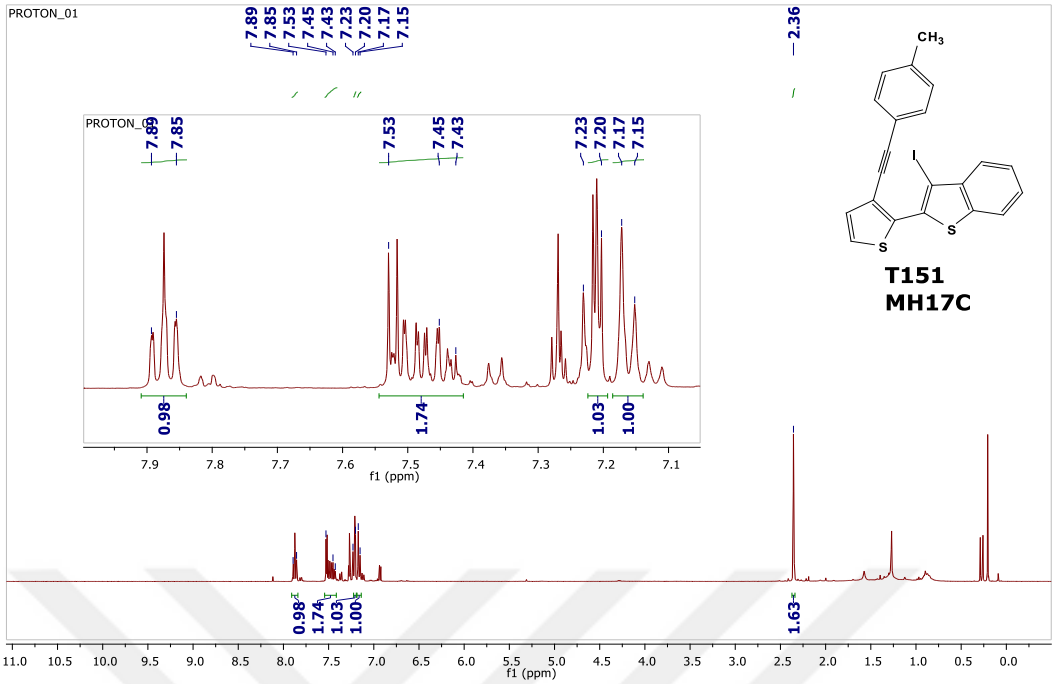

Figure M53. ^{1}H NMR spectra of MH17C.

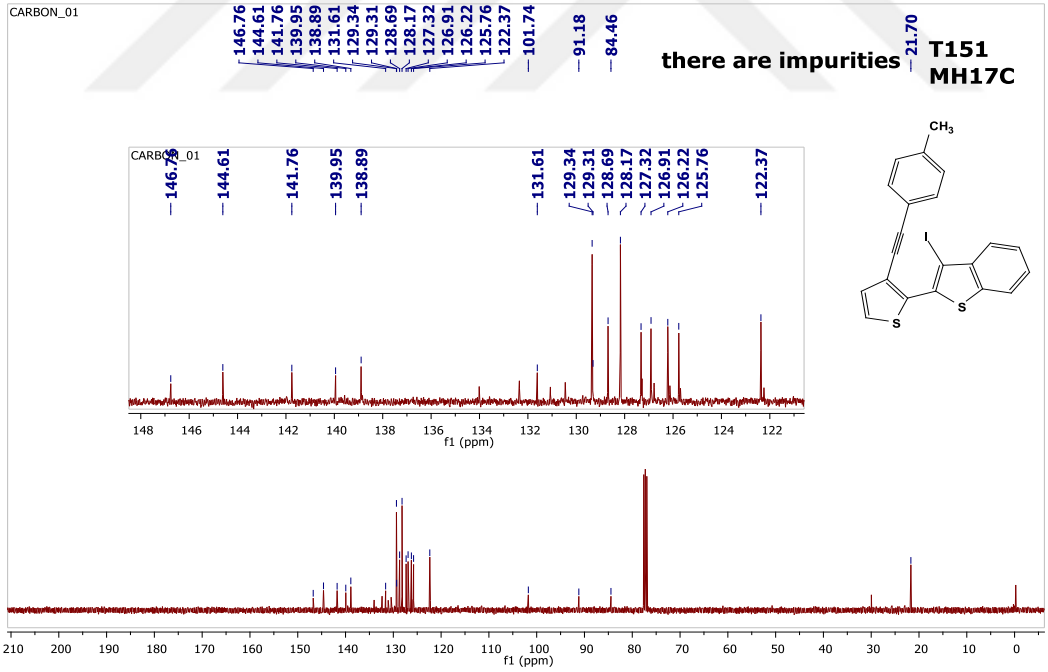

Figure M54. ^{13}C NMR spectra of MH17C.

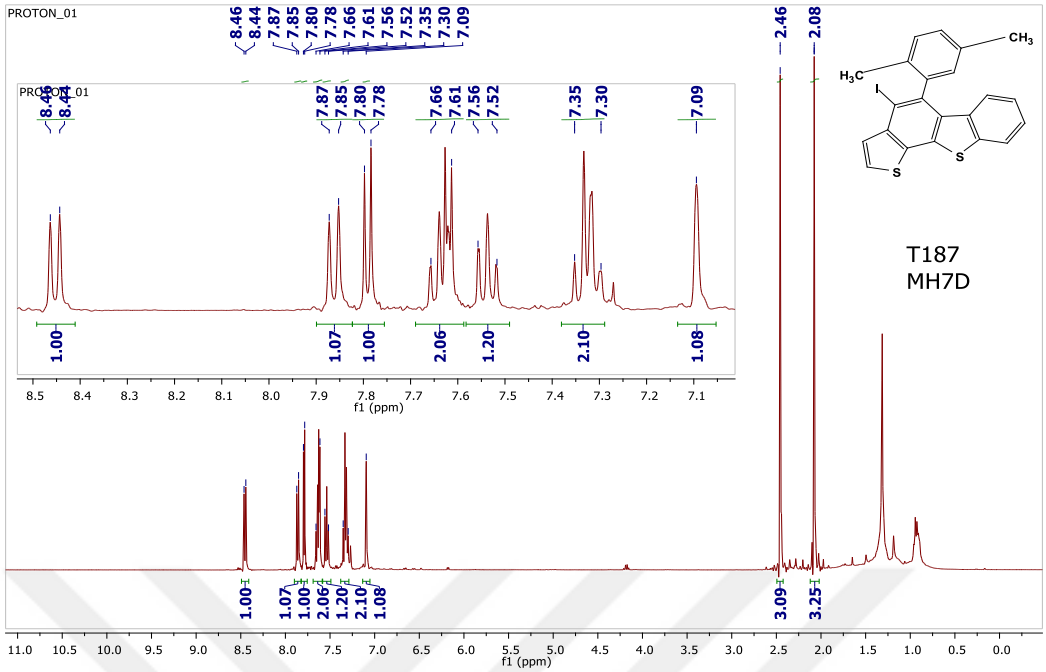

Figure M55. ^{1}H NMR spectra of MH7D.

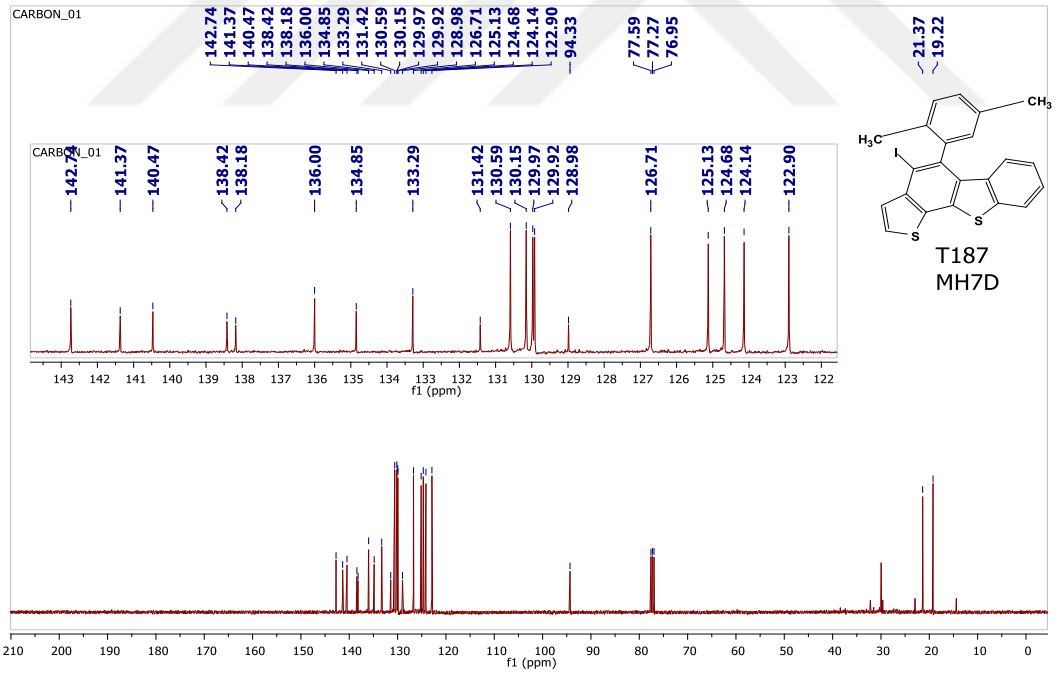

Figure M56. ^{13}C NMR spectra of MH7D.

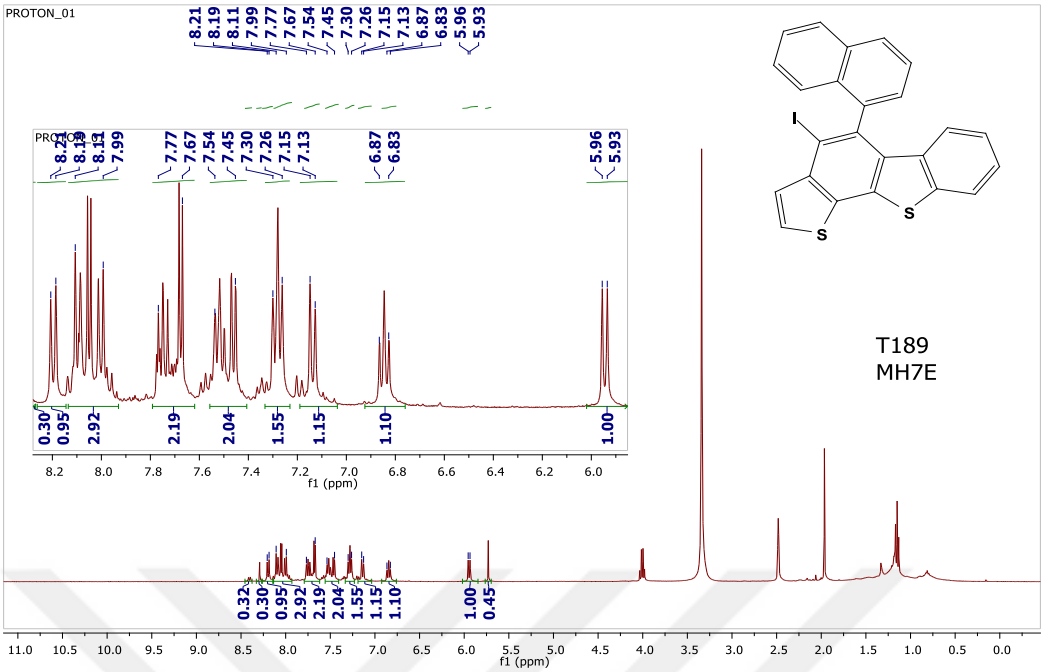

Figure M57. ^{1}H NMR spectra of MH7E.

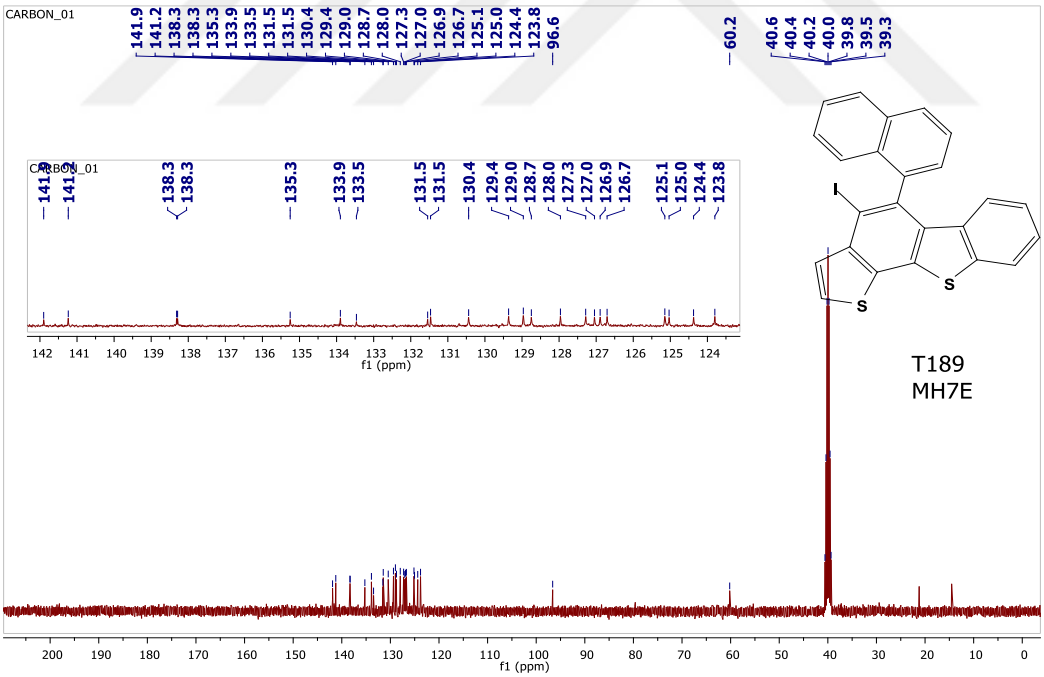

Figure M58. ^{13}C NMR spectra of MH7E.

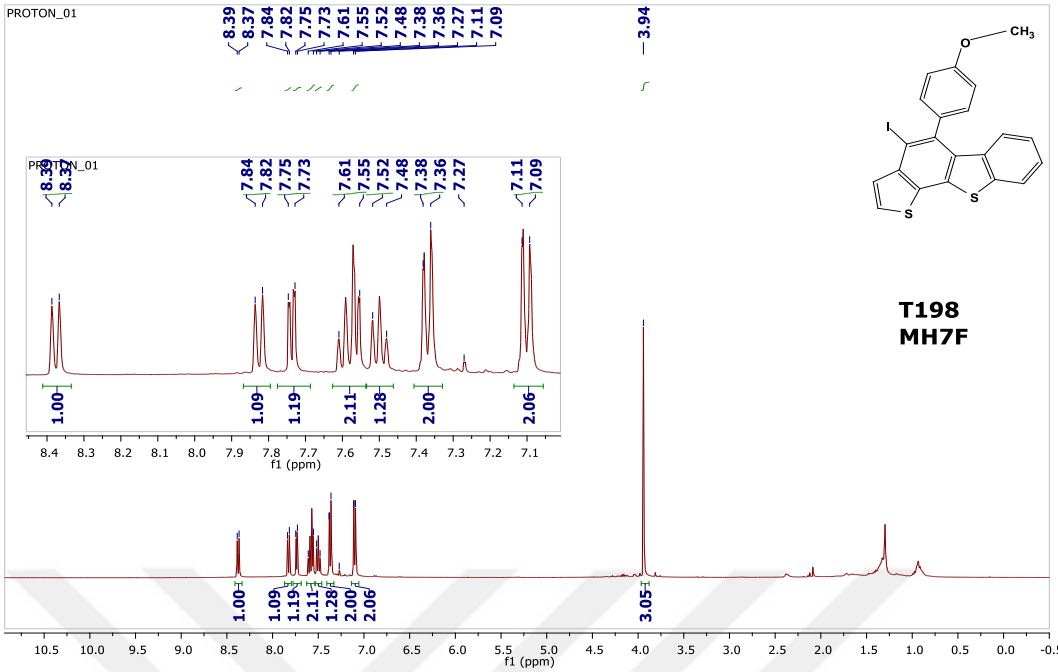

Figure M59. ^{1}H NMR spectra of MH7F.

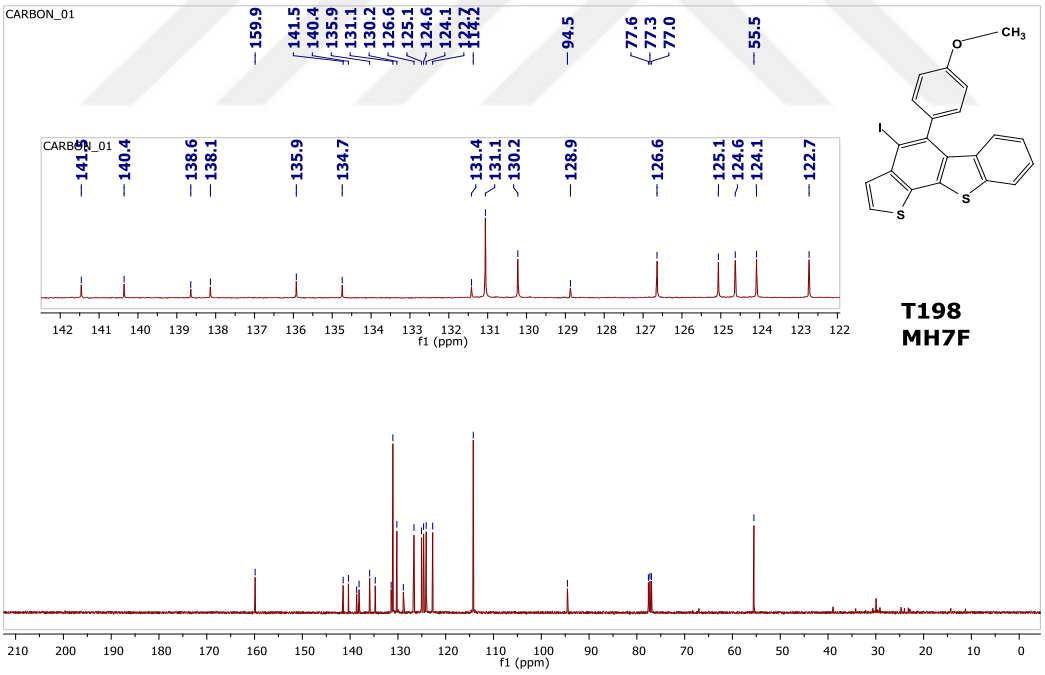

Figure M60. ^{13}C NMR spectra of MH7F.

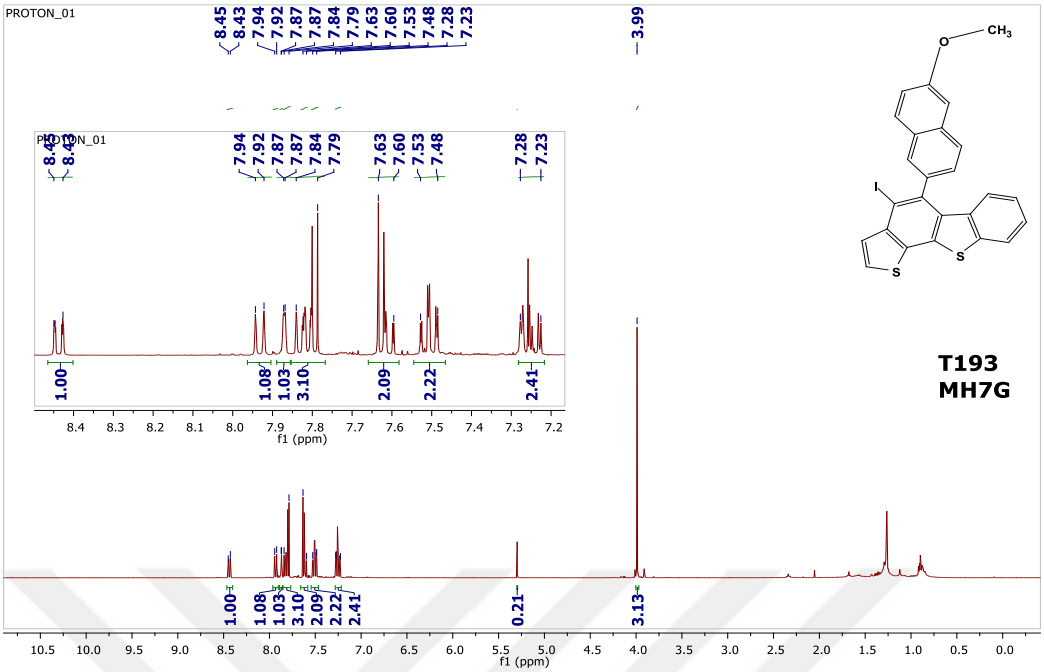

Figure M61. ^{1}H NMR spectra of MH7G.

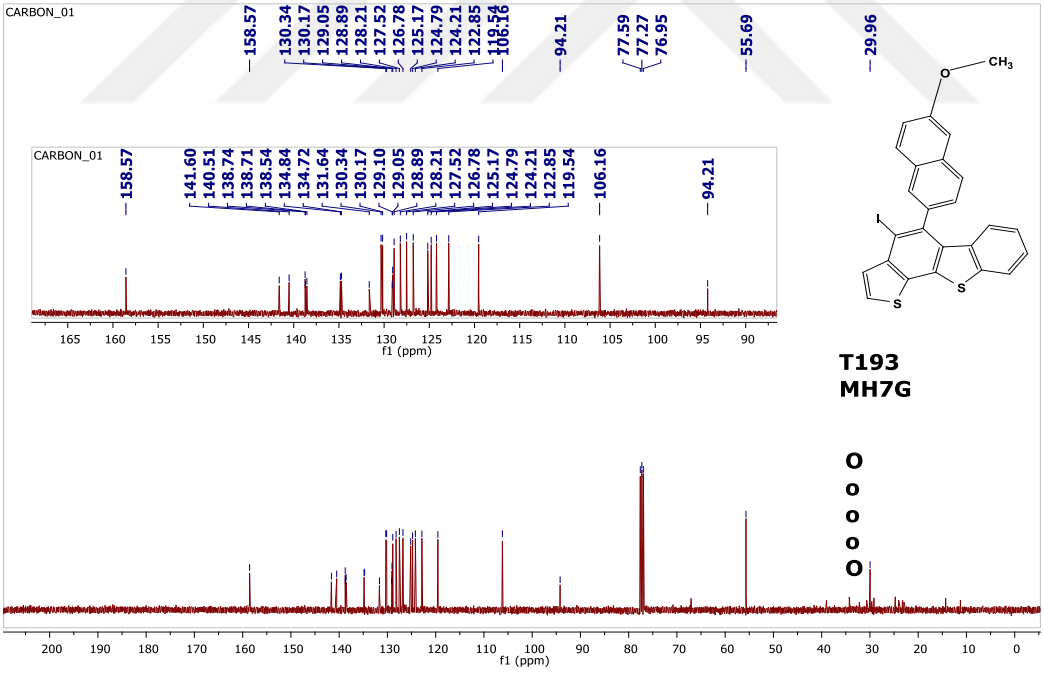

Figure M62. ^{13}C NMR spectra of MH7G.

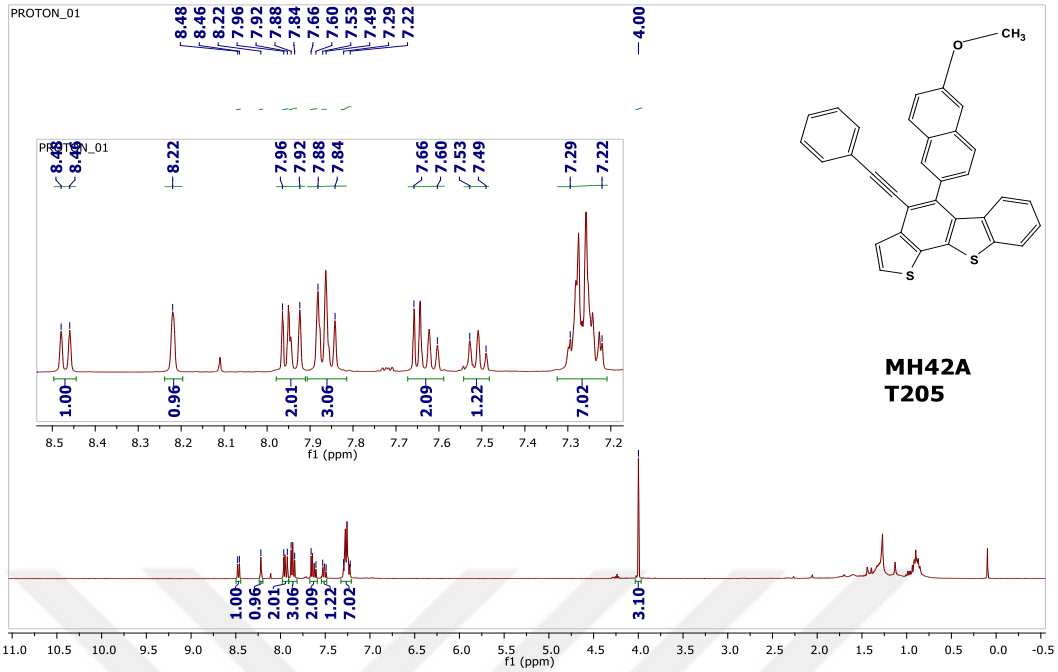

Figure M63. ^{1}H NMR spectra of MH42A.

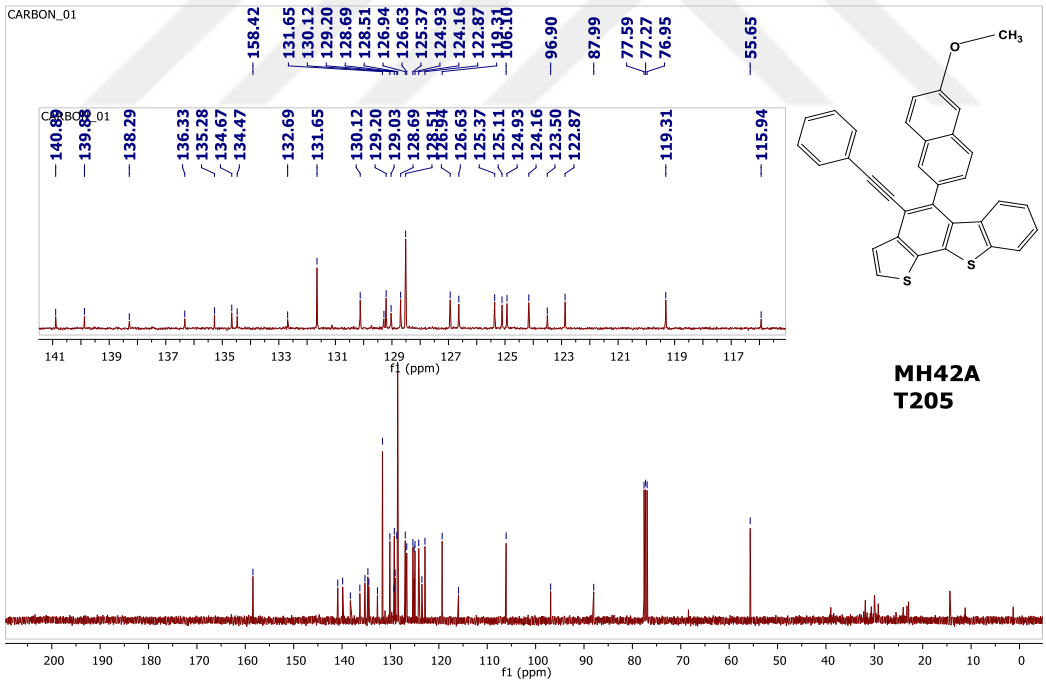

Figure M64. ^{13}C NMR spectra of MH42A.

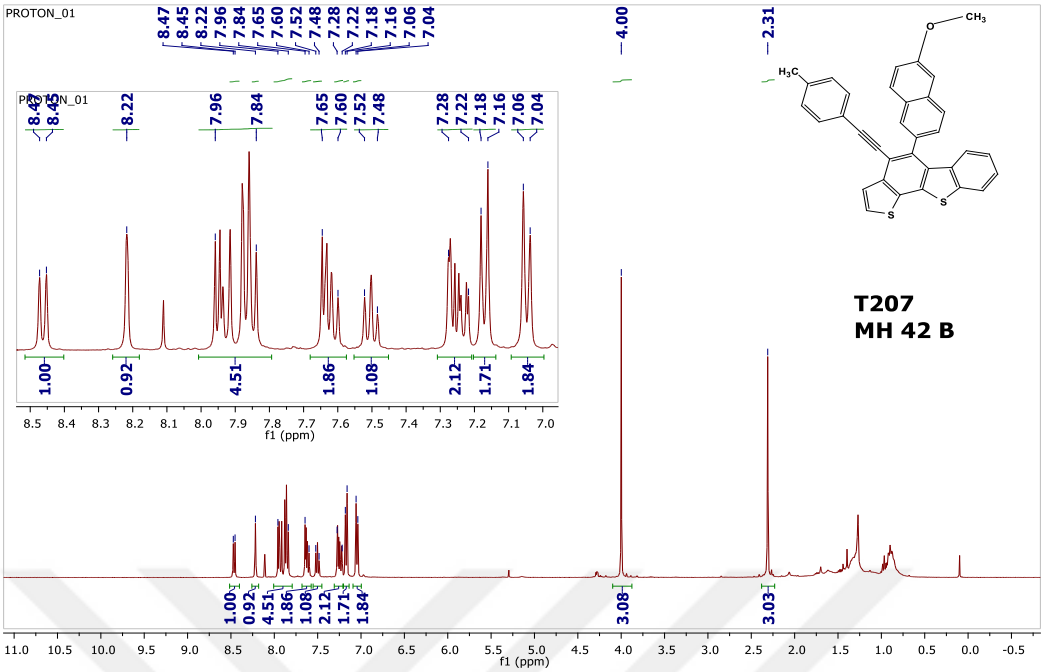

Figure M65. ^{1}H NMR spectra of MH42B.

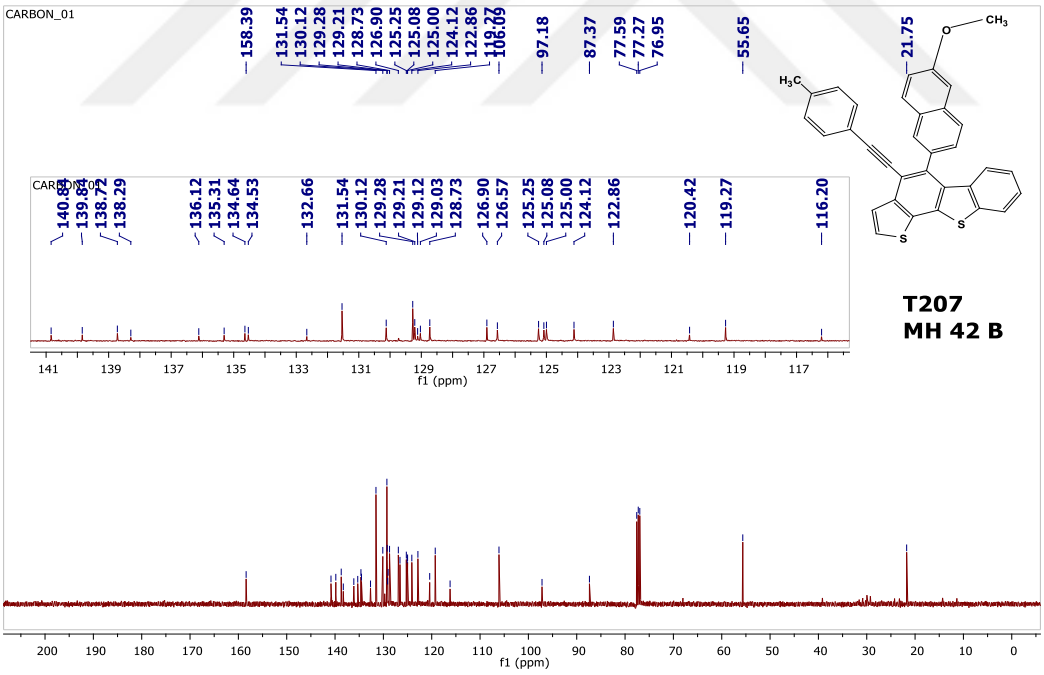

Figure M66. ^{13}C NMR spectra of MH42B.

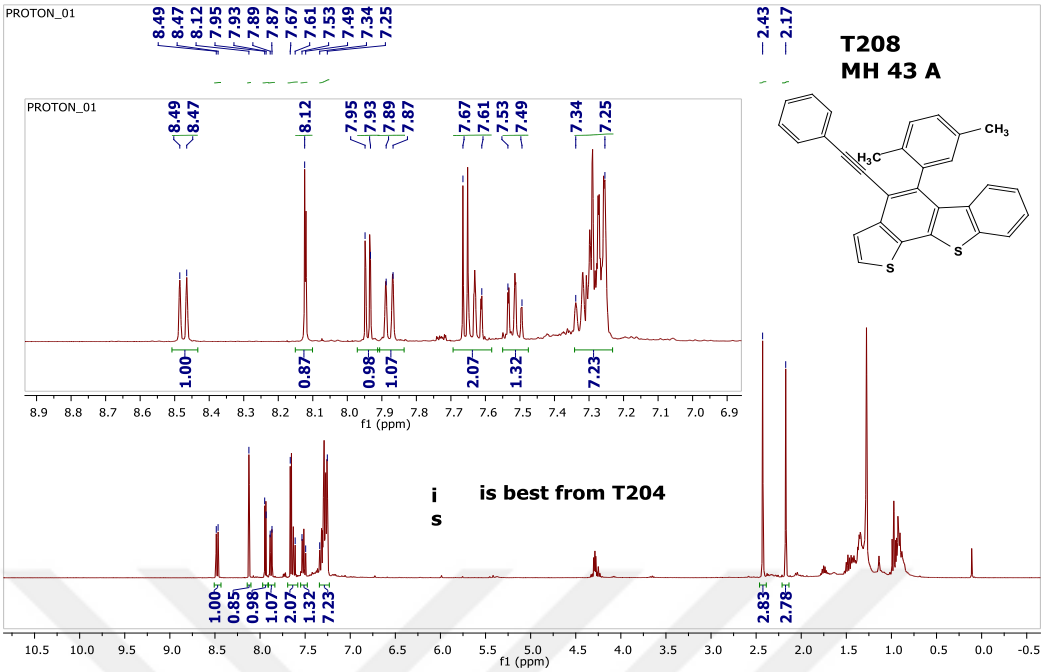

Figure M67. ^{1}H NMR spectra of MH43A.

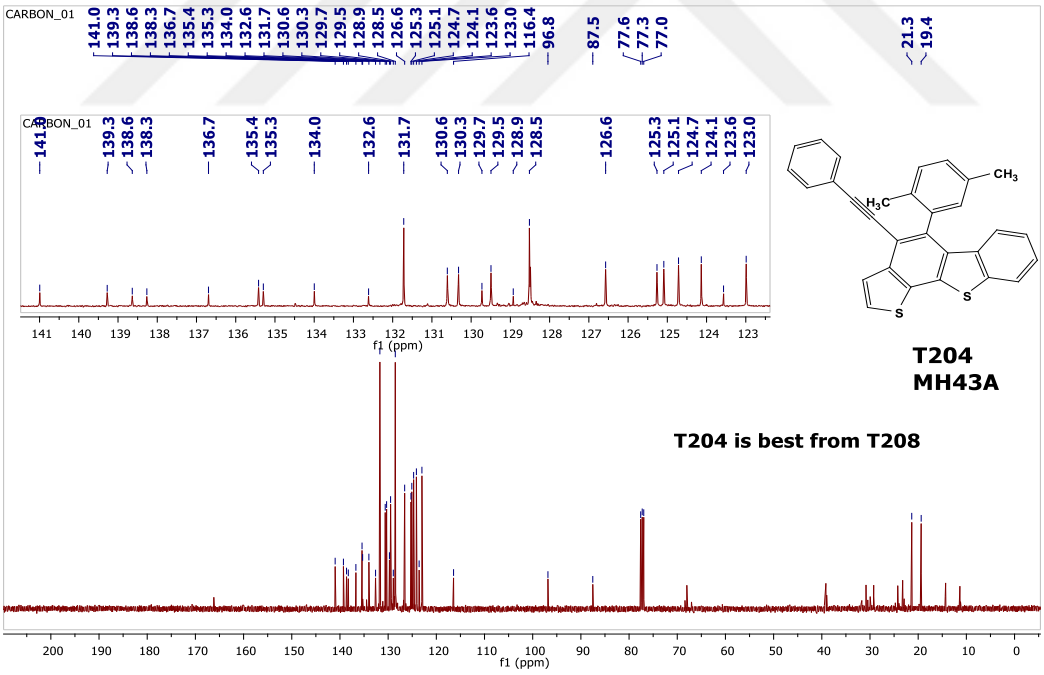

Figure M68. ^{13}C NMR spectra of MH43A.

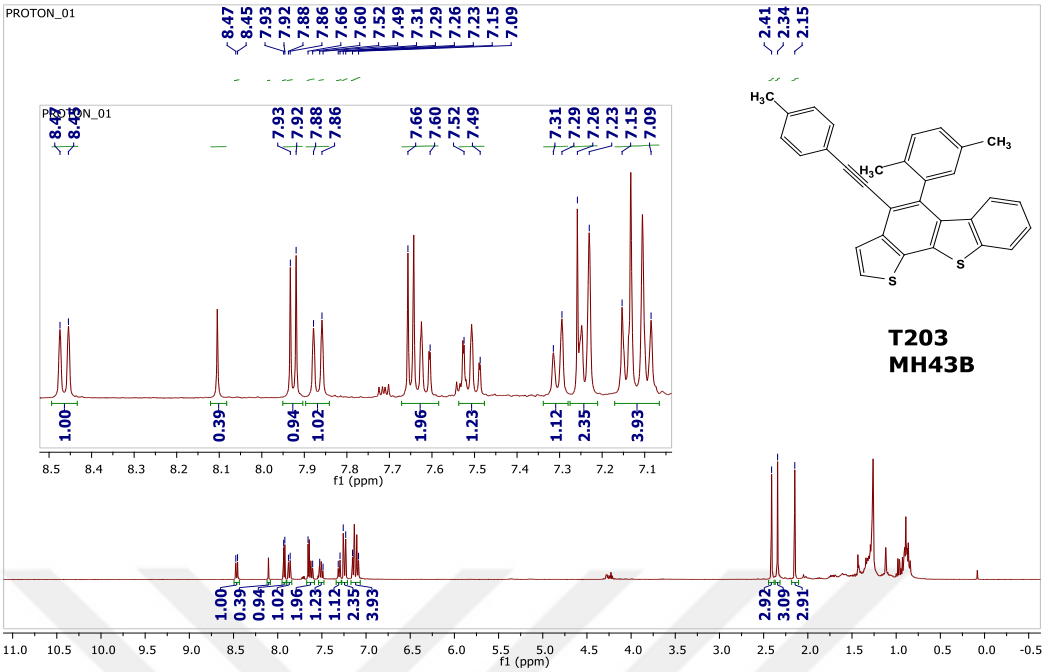

Figure M69. ^{1}H NMR spectra of MH43B.

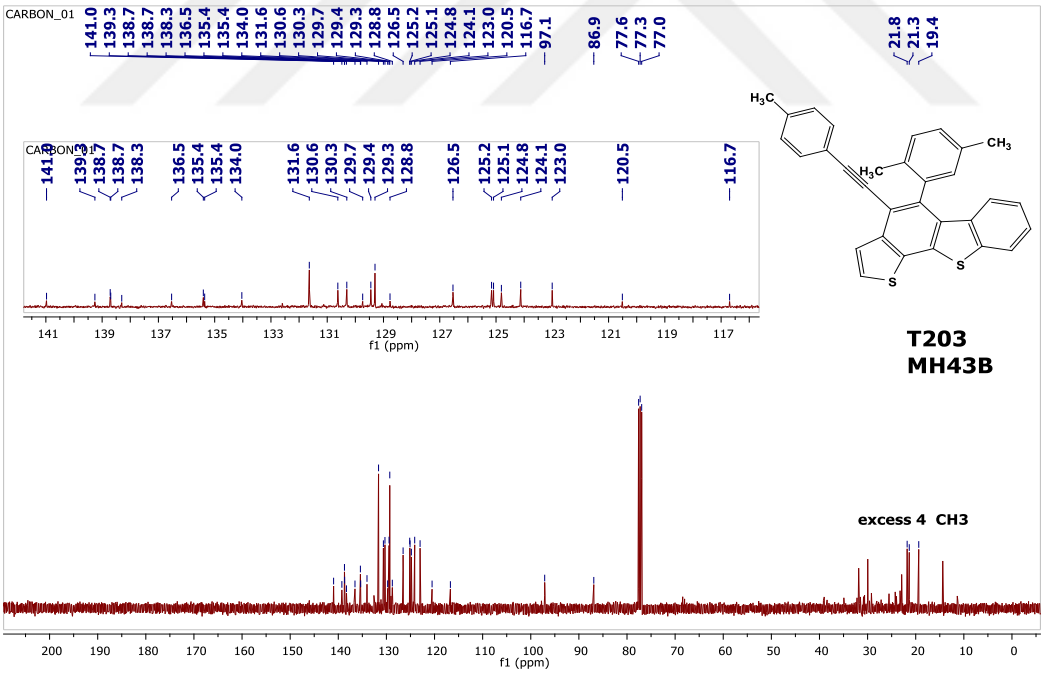

Figure M70. ^{13}C NMR spectra of MH43B.

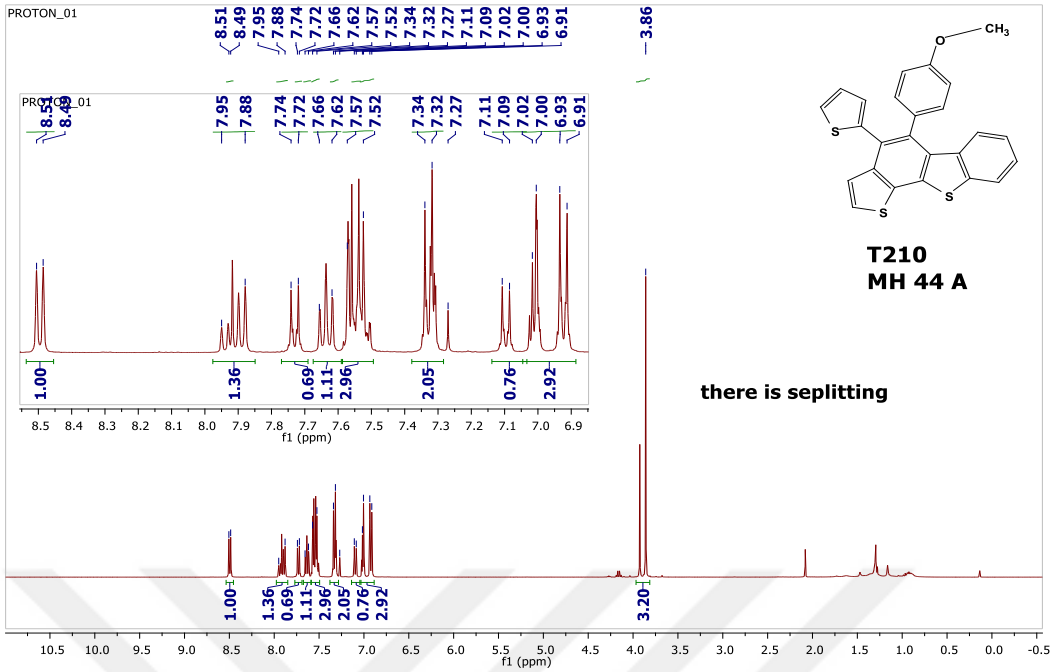

Figure M71. ^{1}H NMR spectra of MH44A.

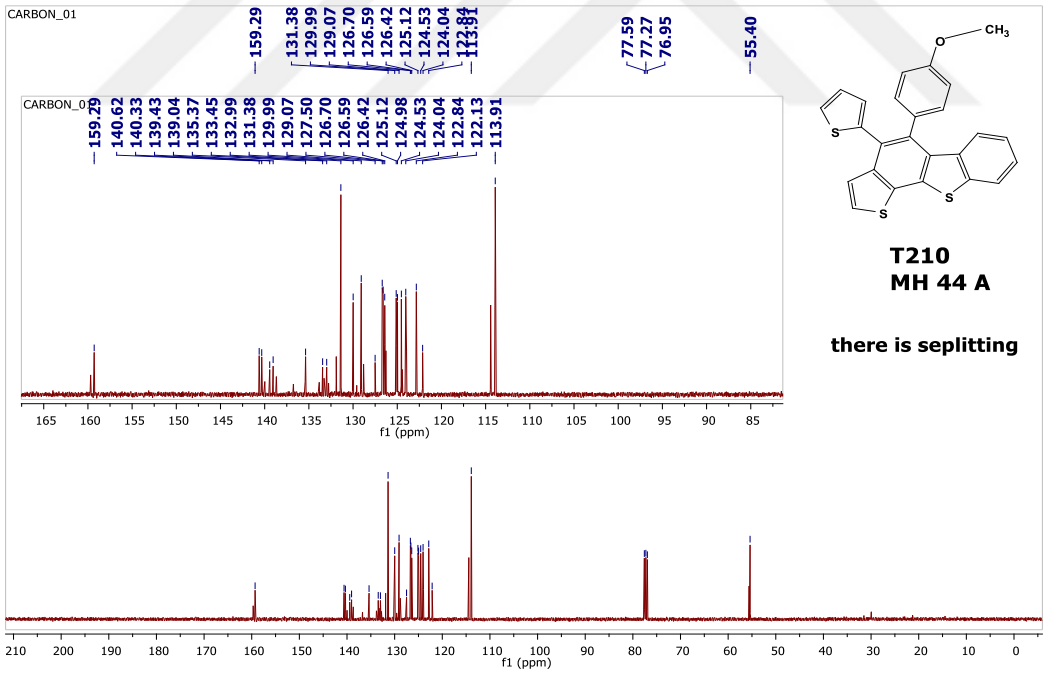

Figure M72. ^{13}C NMR spectra of MH44A.

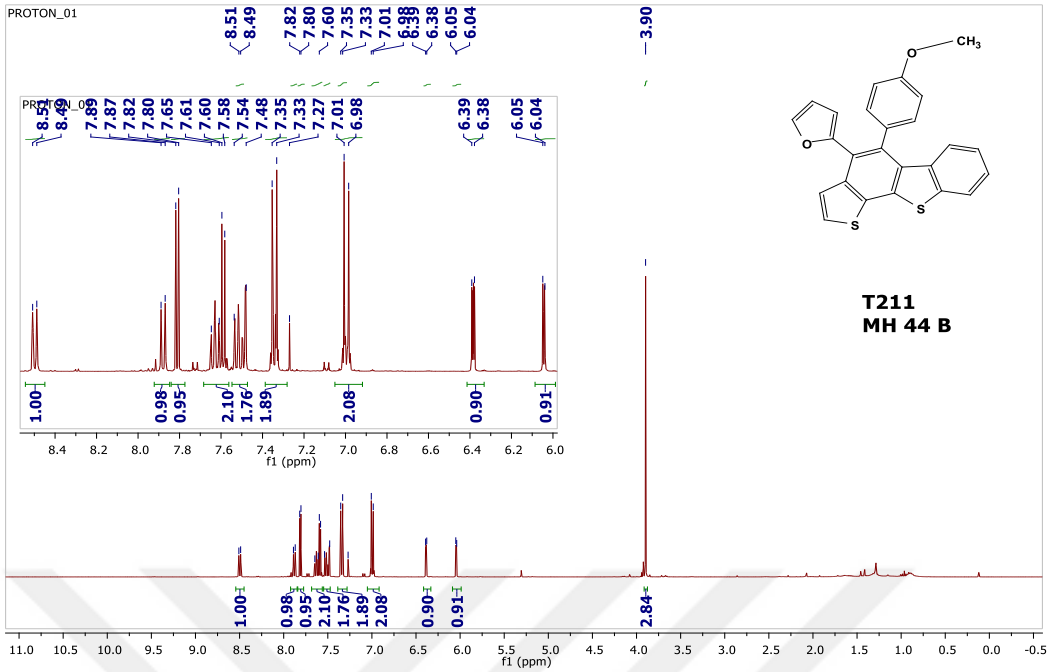

Figure M73. ^{1}H NMR spectra of MH44B.

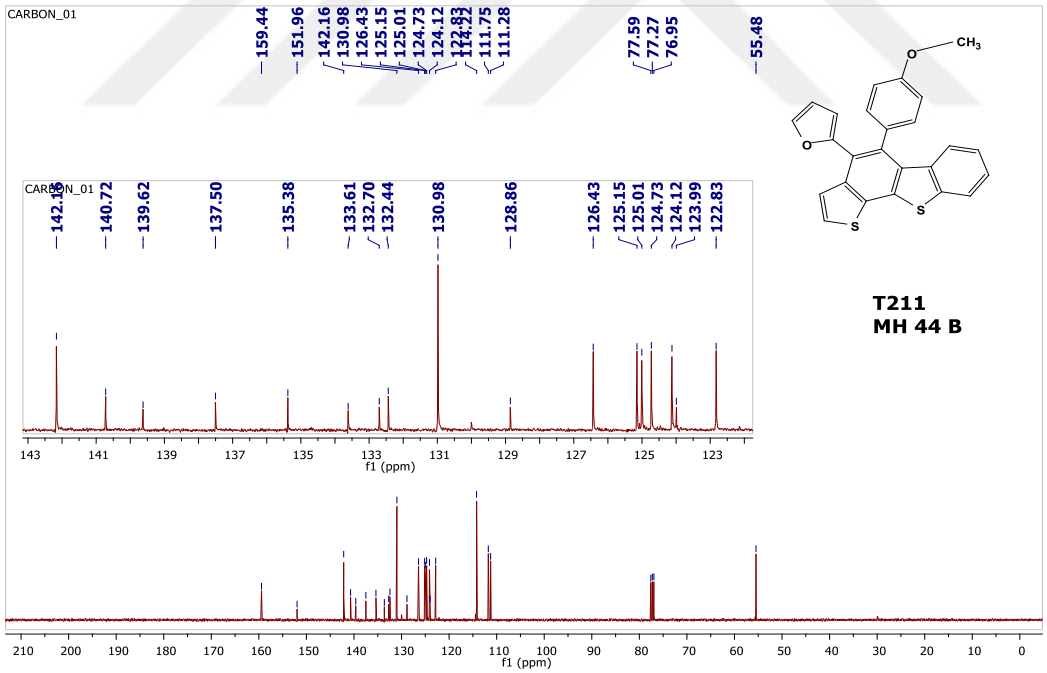

Figure M74. ^{13}C NMR spectra of MH44B.

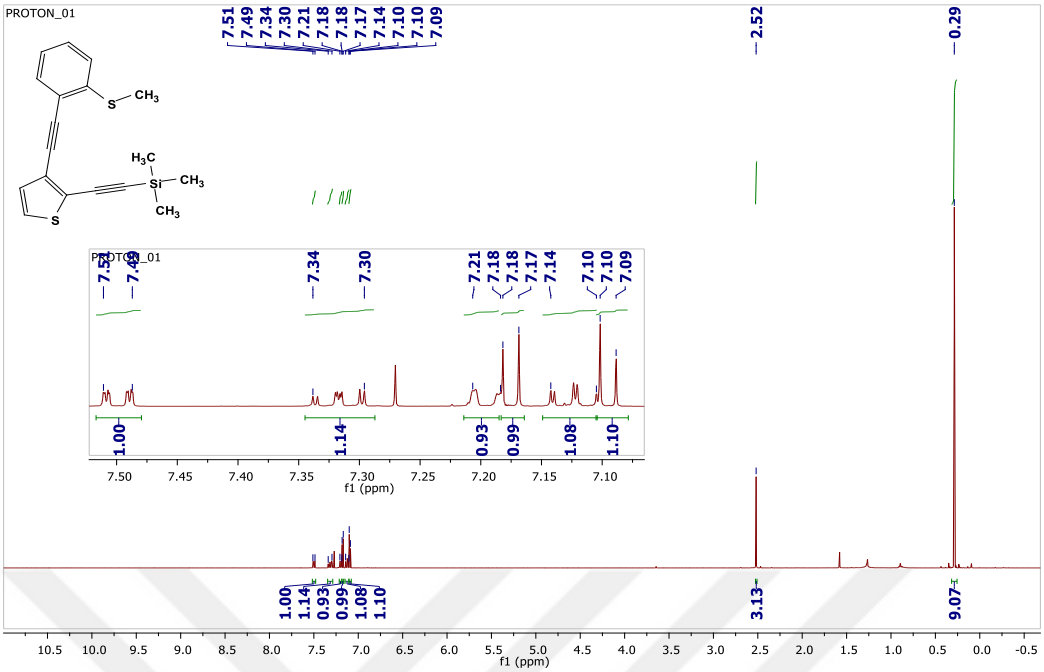

Figure M75. ^{1}H NMR spectra of MH13.

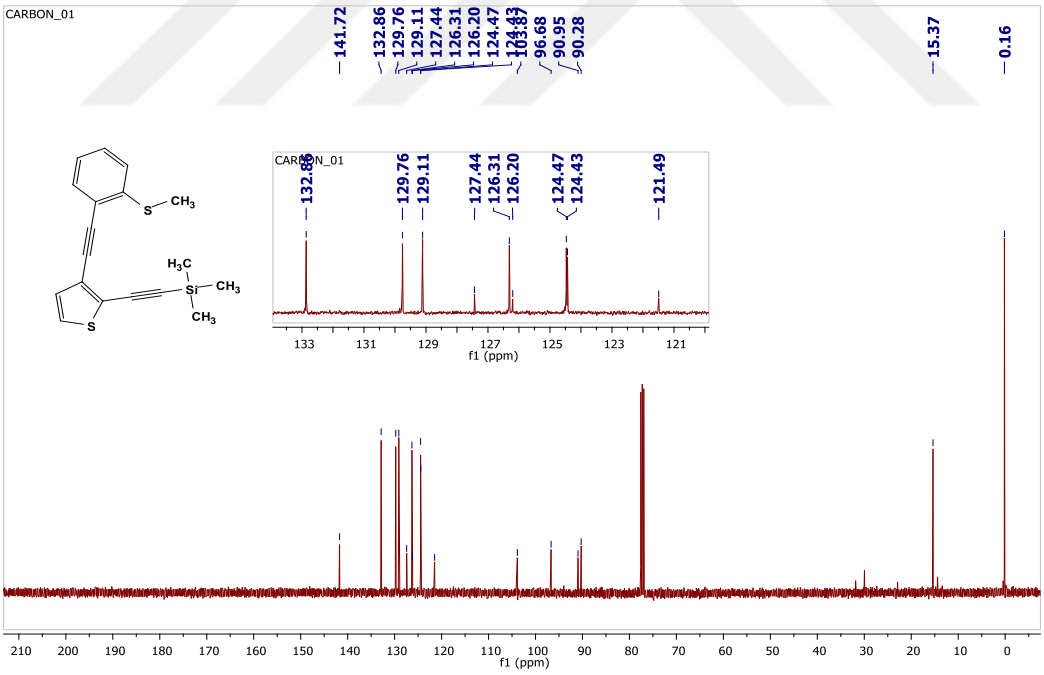

Figure M76. ^{13}C NMR spectra of MH13.

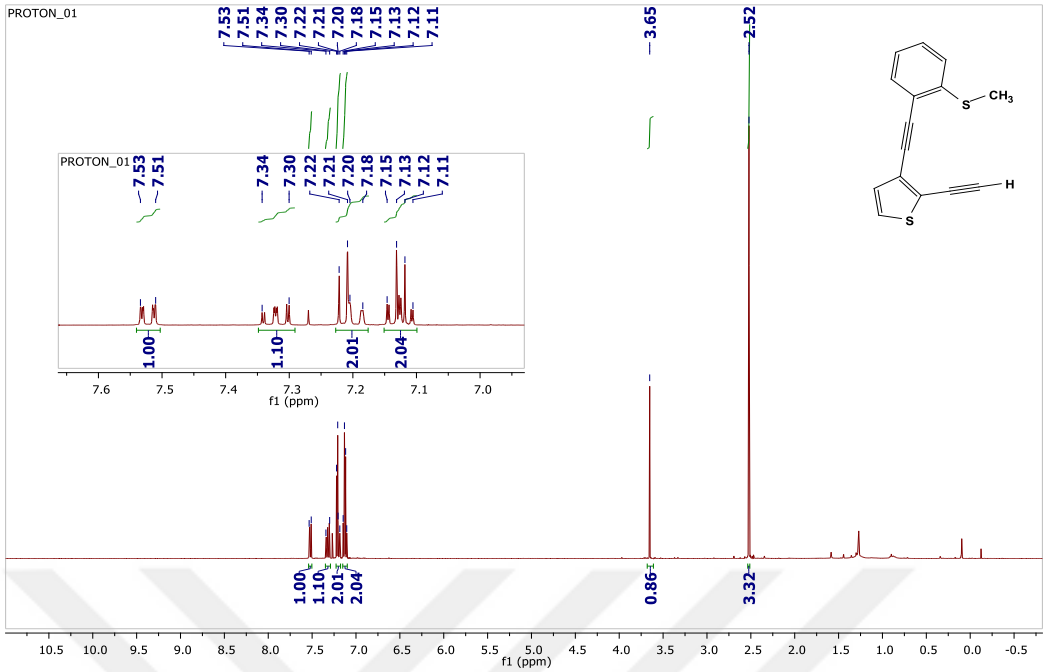

Figure M77. ^{1}H NMR spectra of MH15.

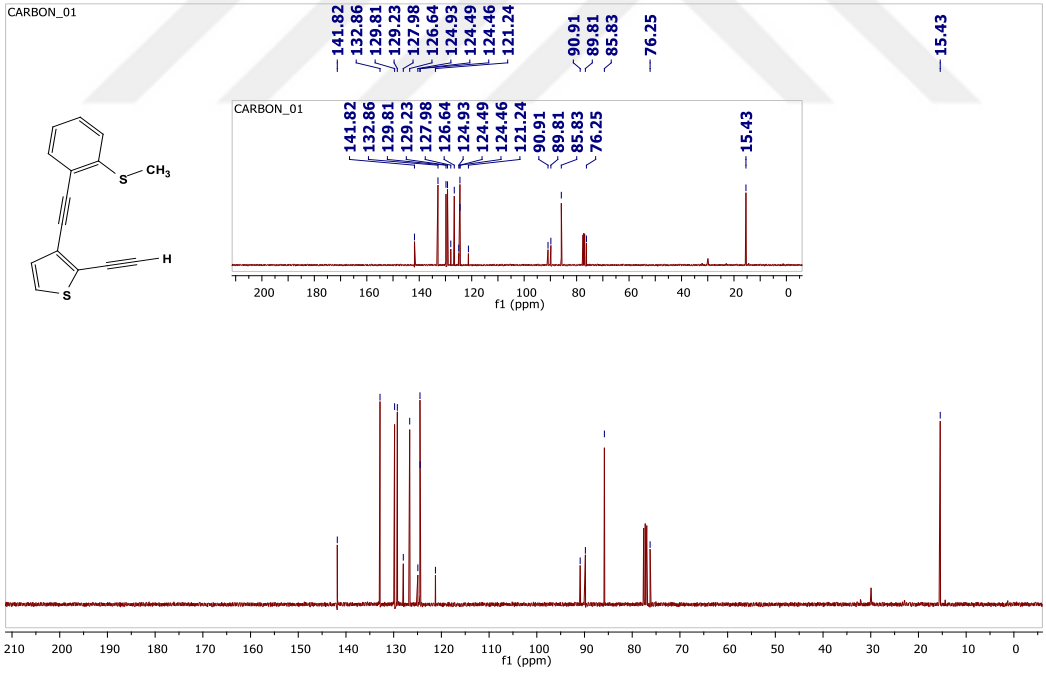

Figure M78. ^{13}C NMR spectra of MH15.

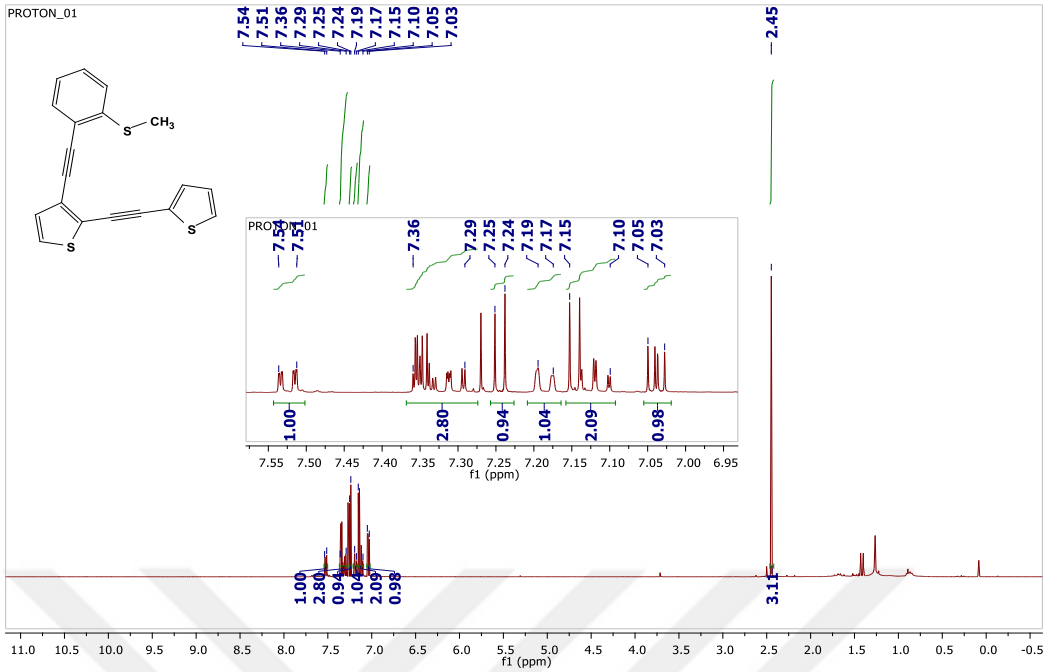

Figure M79. ^{1}H NMR spectra of MH19.

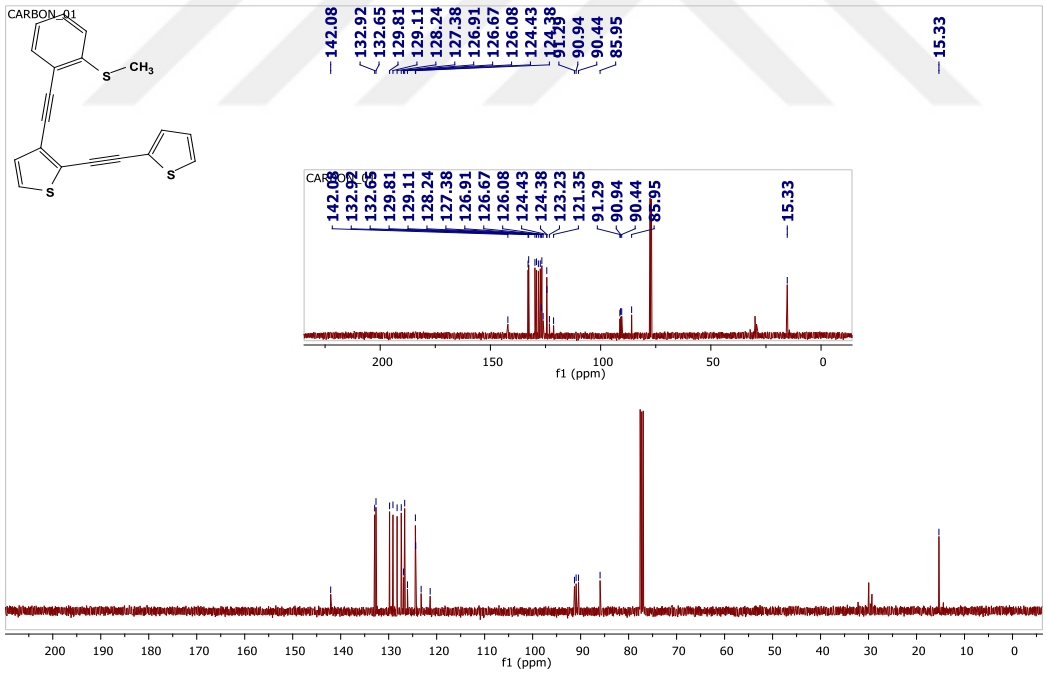

Figure M80. ^{13}C NMR spectra of MH19.

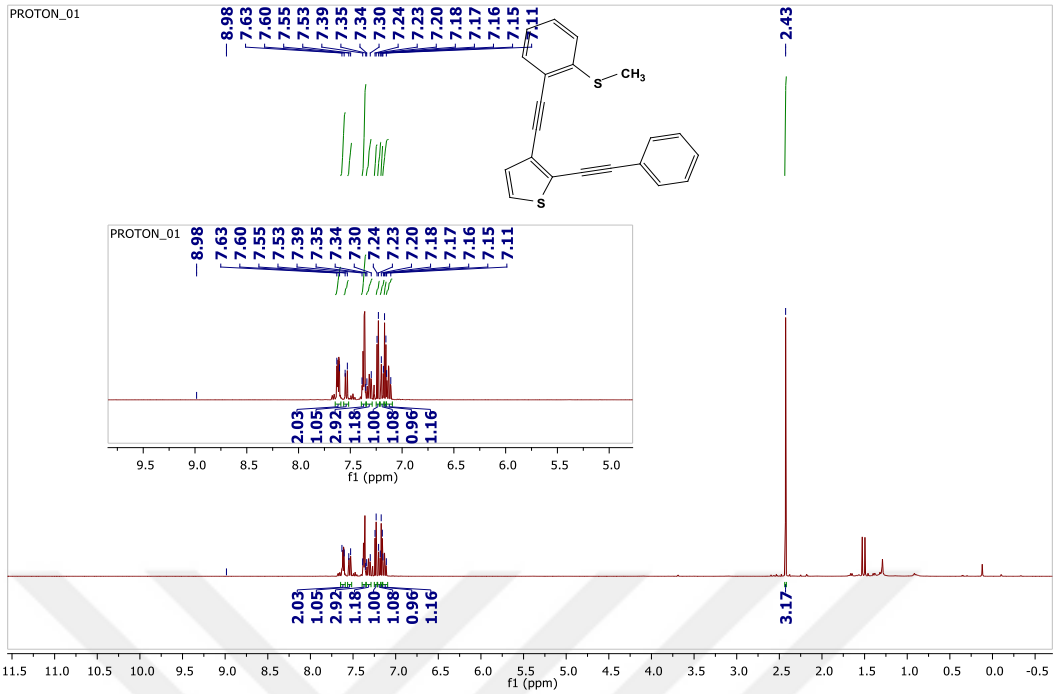

Figure M81. ^{1}H NMR spectra of MH19B.

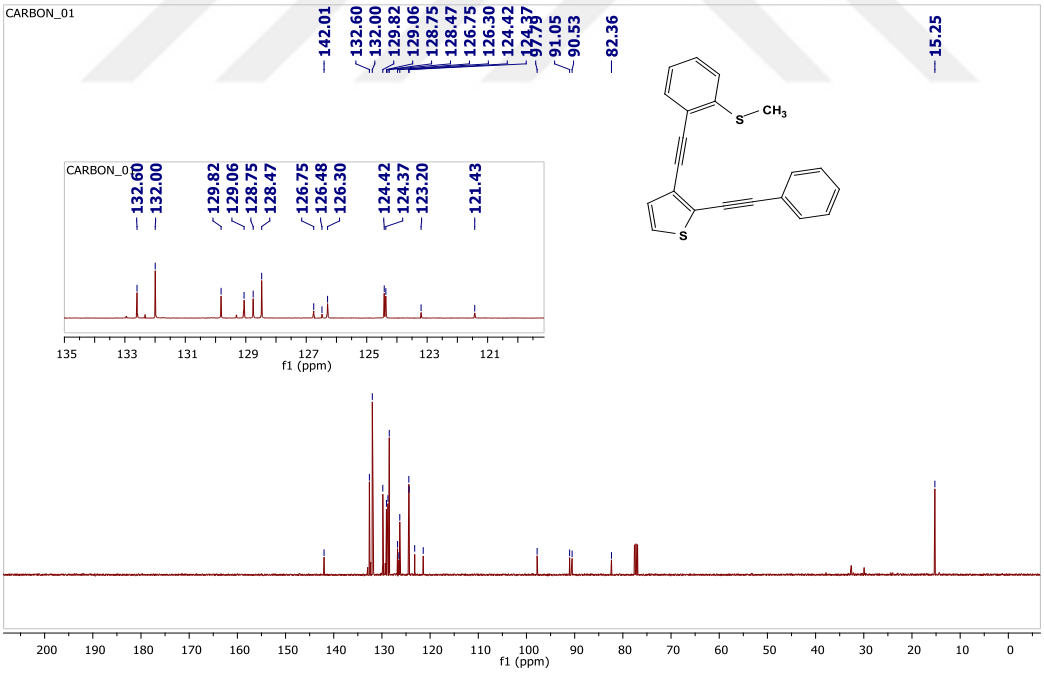

Figure M82. ^{13}C NMR spectra of MH19B.

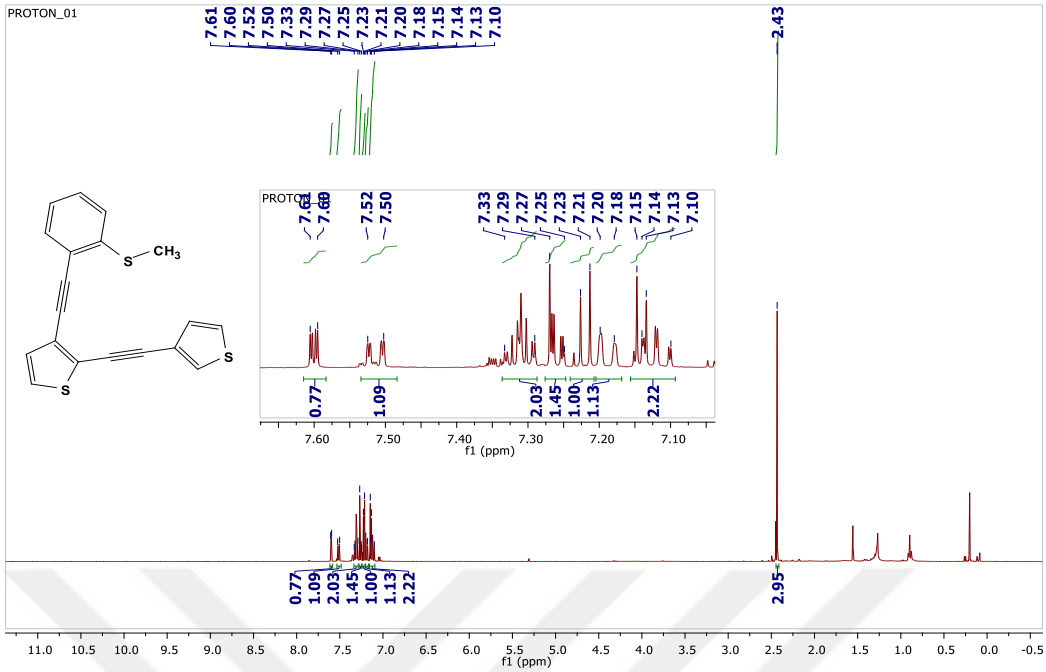

Figure M83. ^{1}H NMR spectra of MH19C.

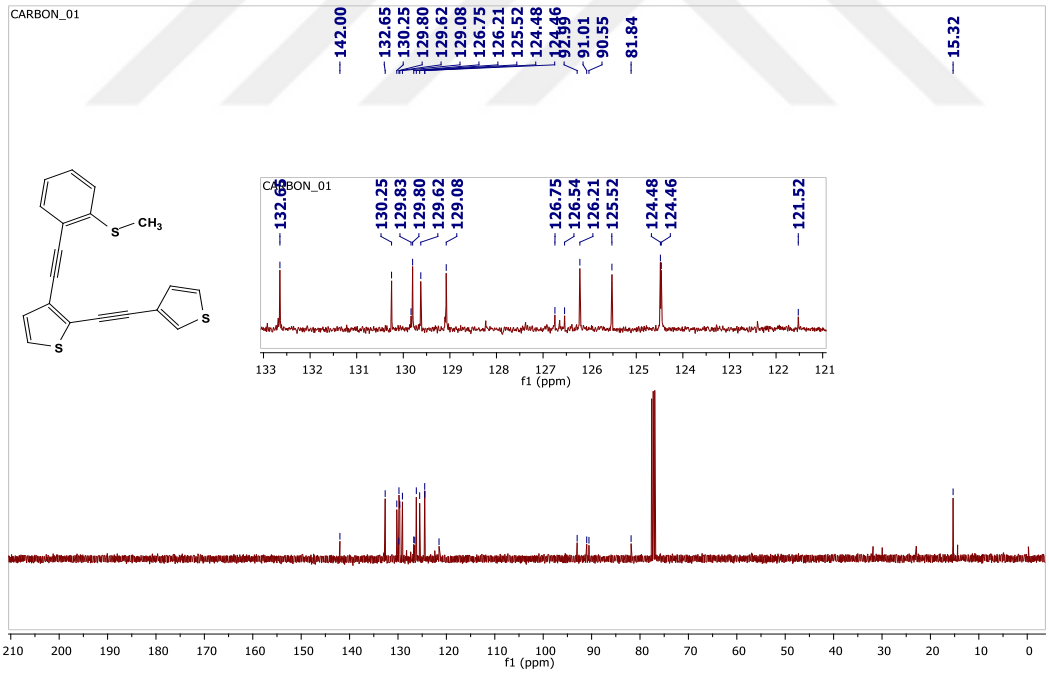

Figure M84. ^{13}C NMR spectra of MH19C.

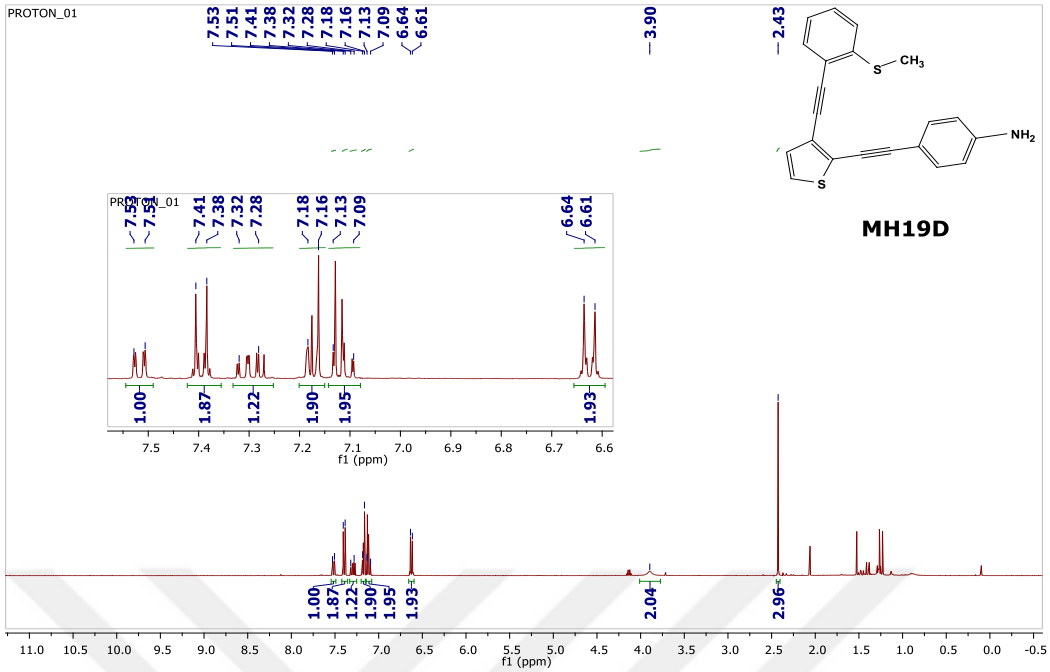

Figure M85. ^{1}H NMR spectra of MH19D.

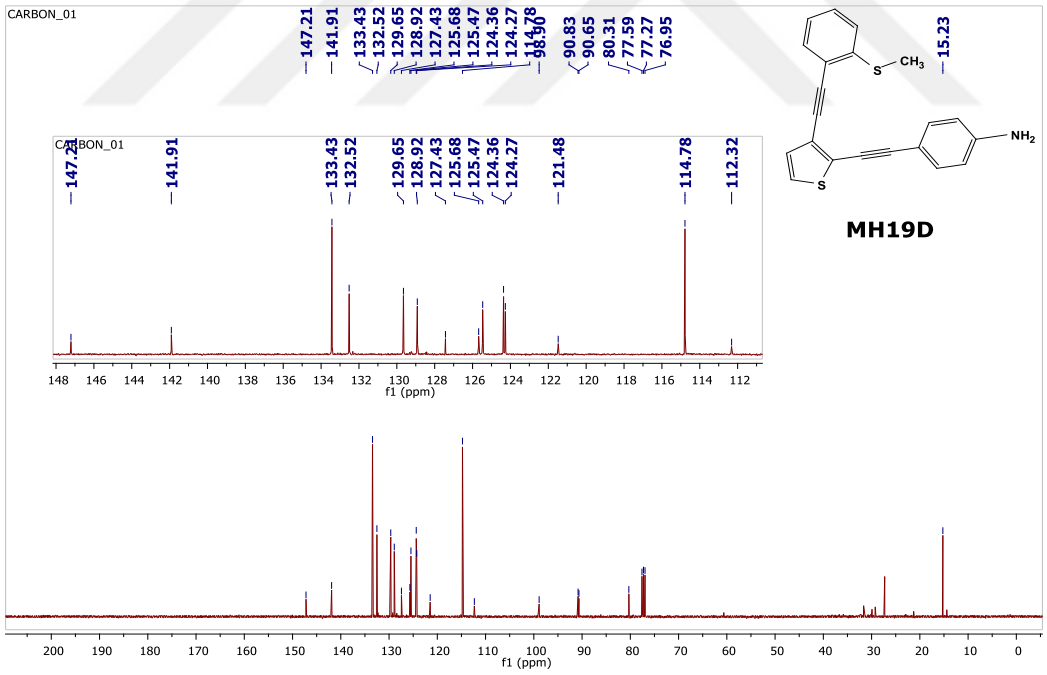

Figure M86. ^{13}C NMR spectra of MH19D.

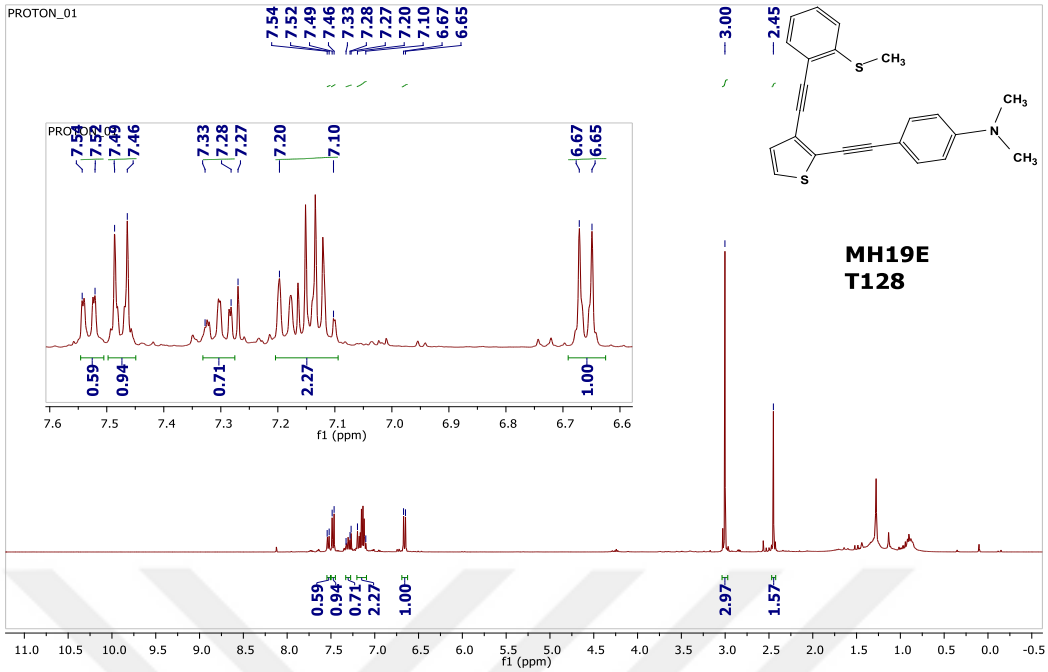

Figure M87. ^{1}H NMR spectra of MH19E.

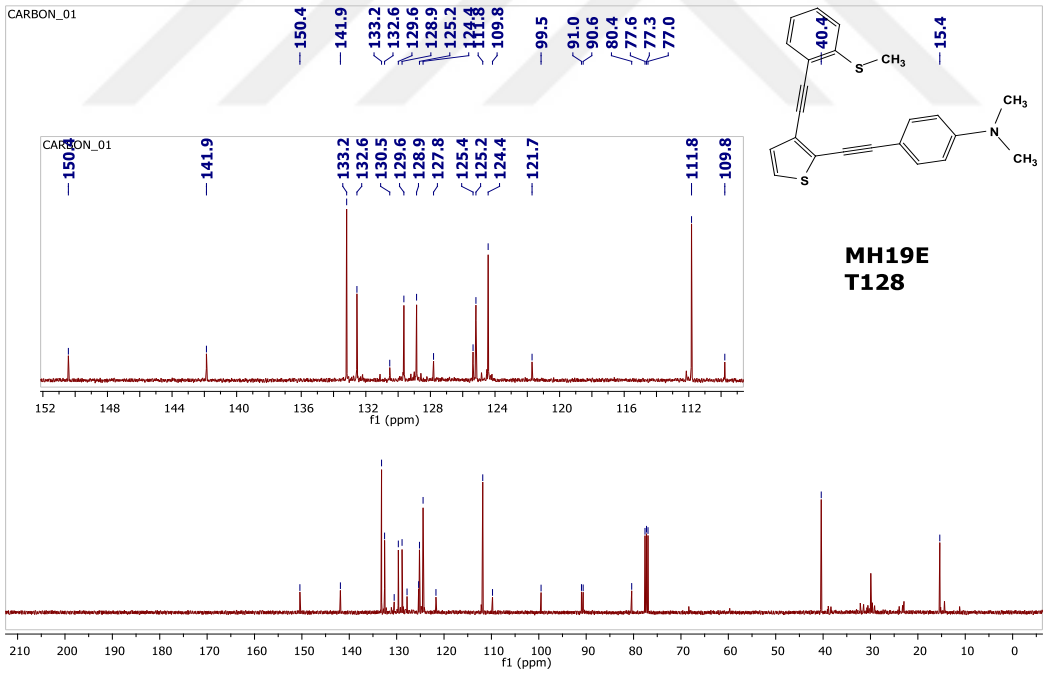

Figure M88. ^{13}C NMR spectra of MH19E.

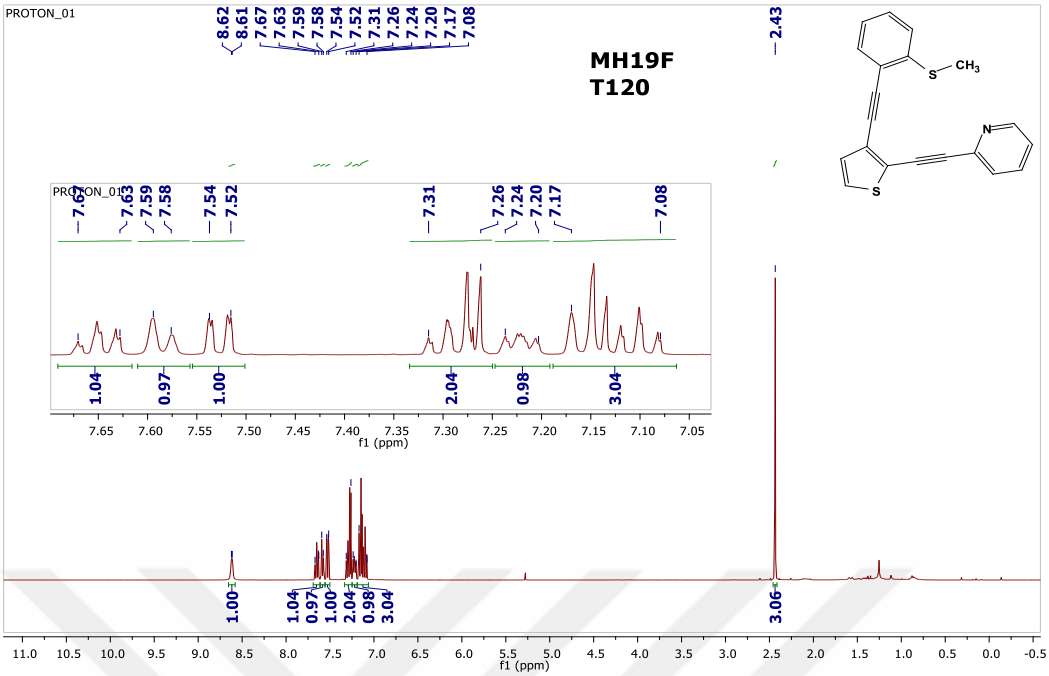

Figure M89. ^{1}H NMR spectra of MH19F.

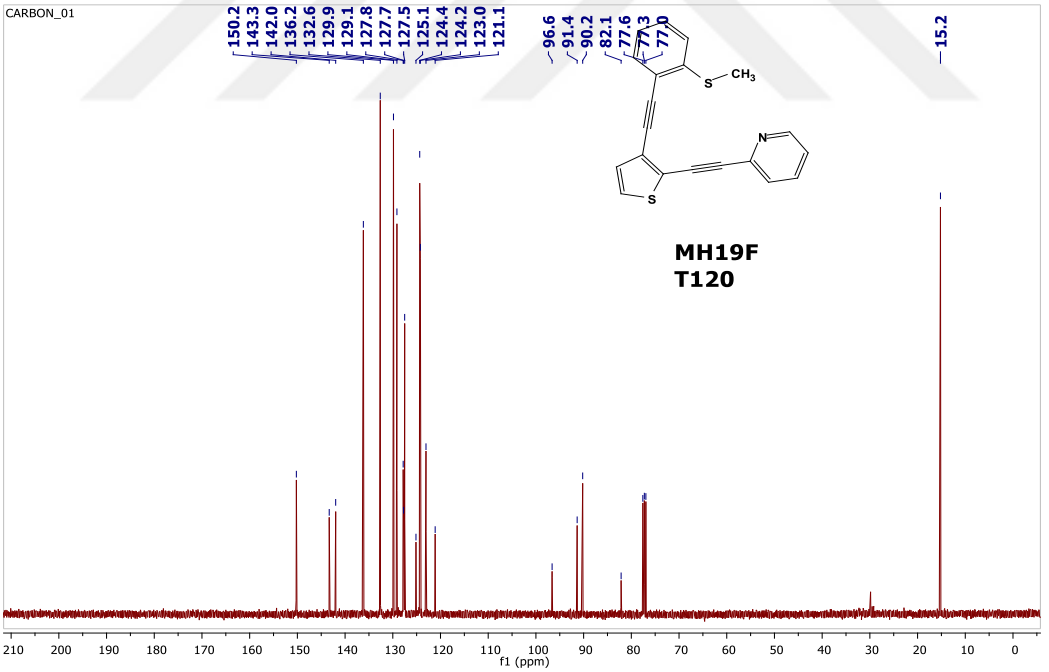

Figure M90. ^{13}C NMR spectra of MH19F.

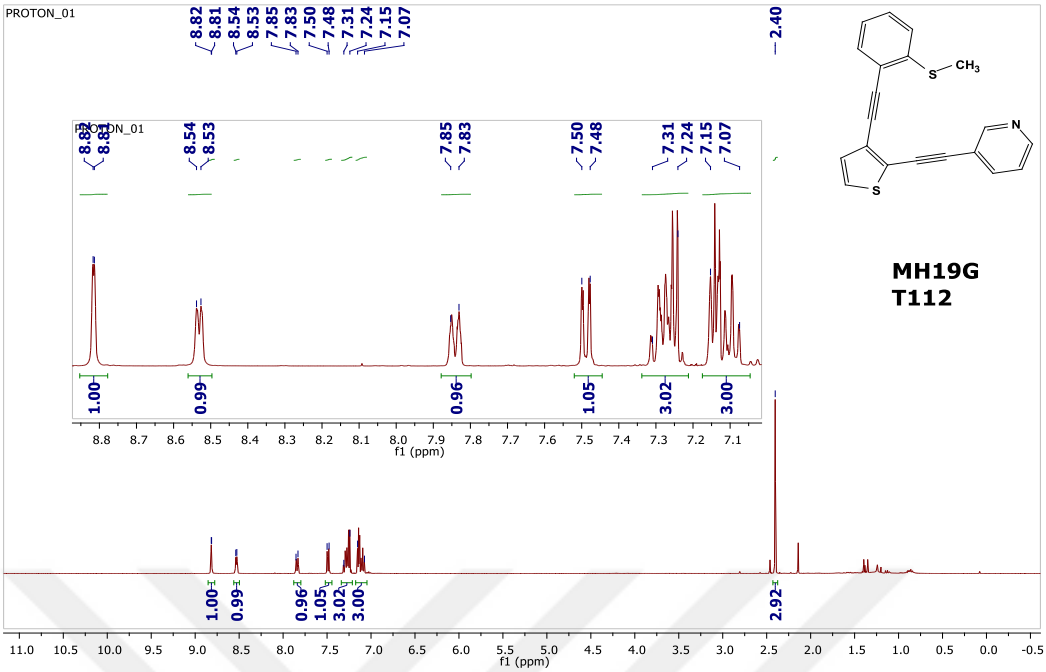

Figure M91. ^{1}H NMR spectra of MH19G.

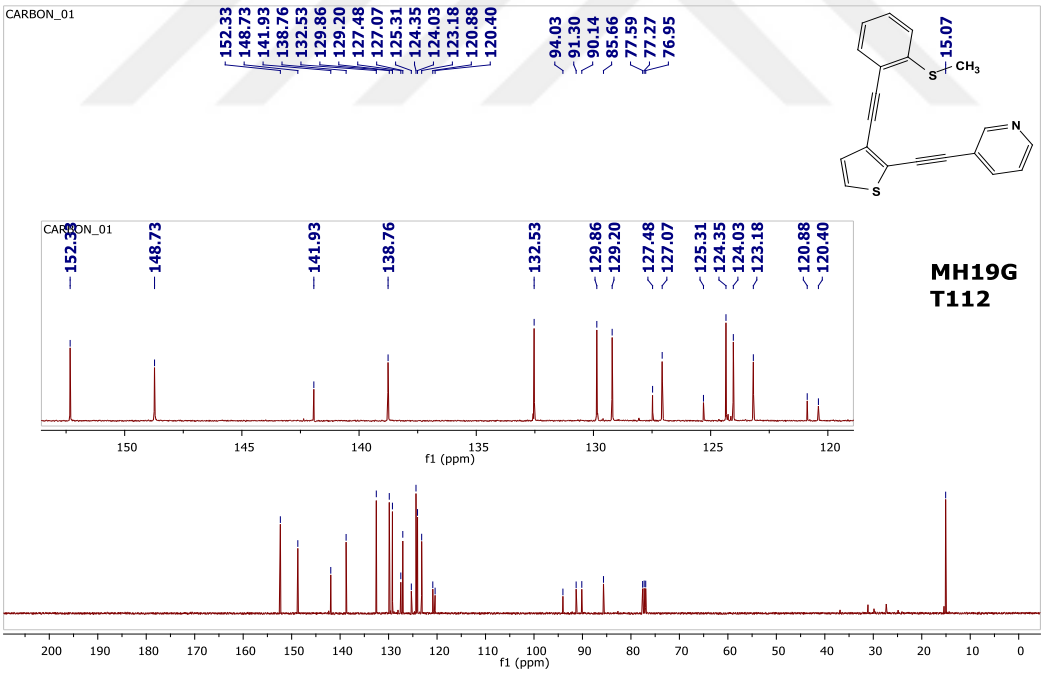

Figure M92. ^{13}C NMR spectra of MH19G.

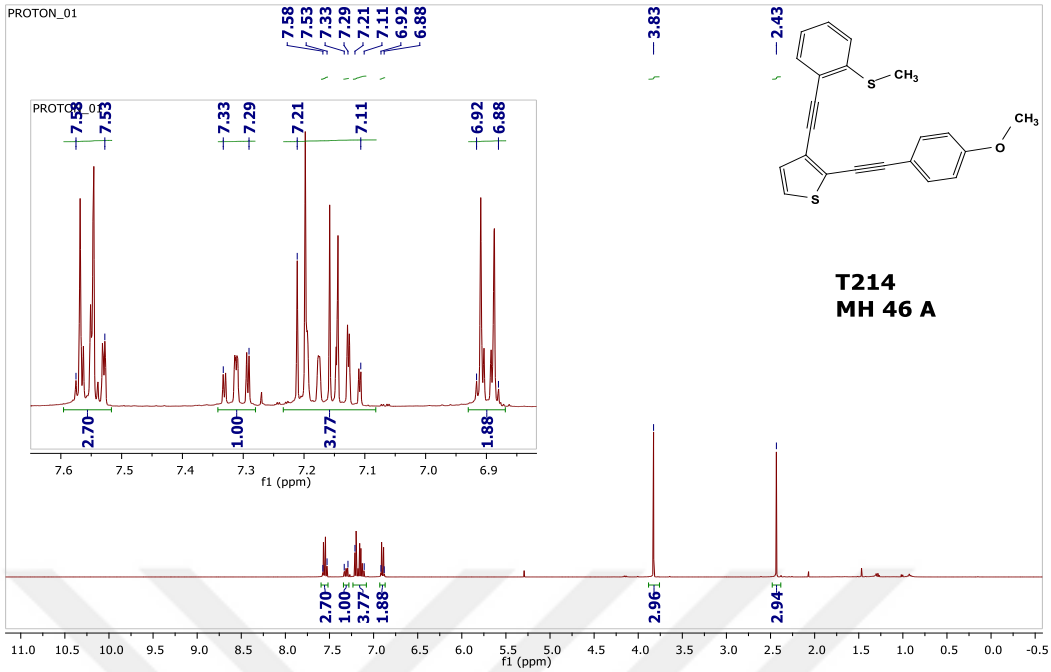

Figure M93. ^{1}H NMR spectra of MH46A.

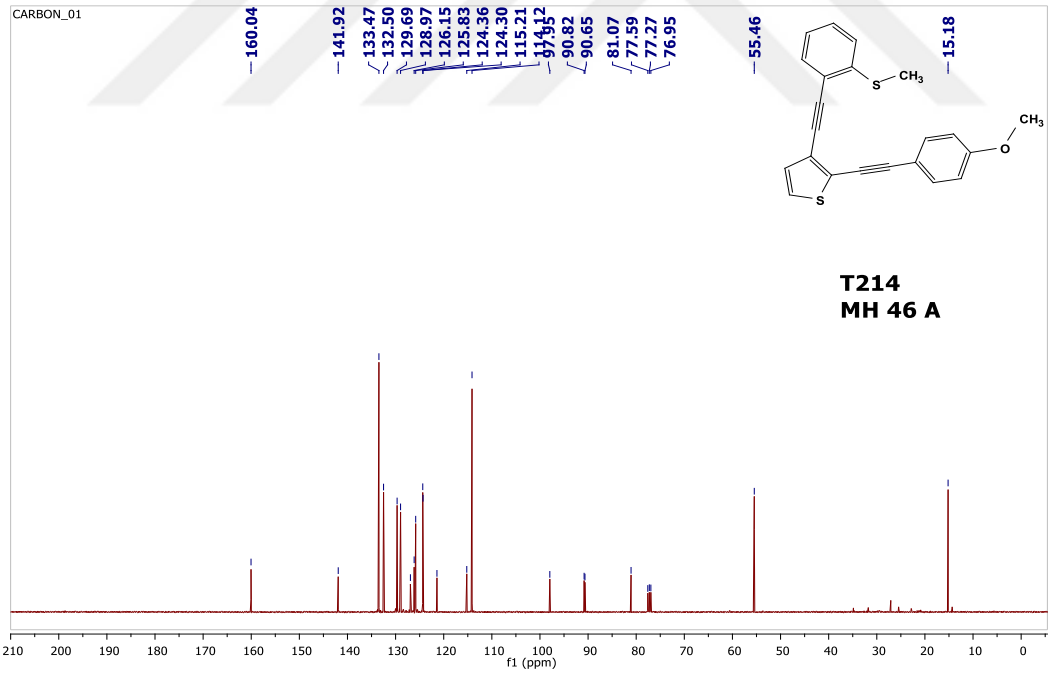

Figure M94. ^{13}C NMR spectra of MH46A.

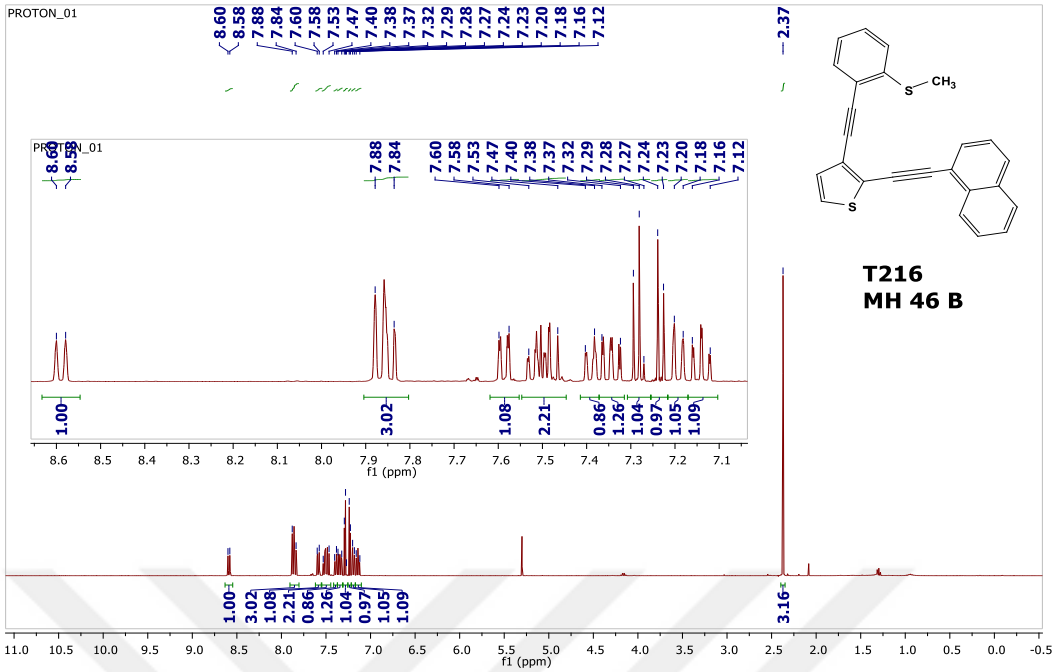

Figure M95. ^{1}H NMR spectra of MH46B.

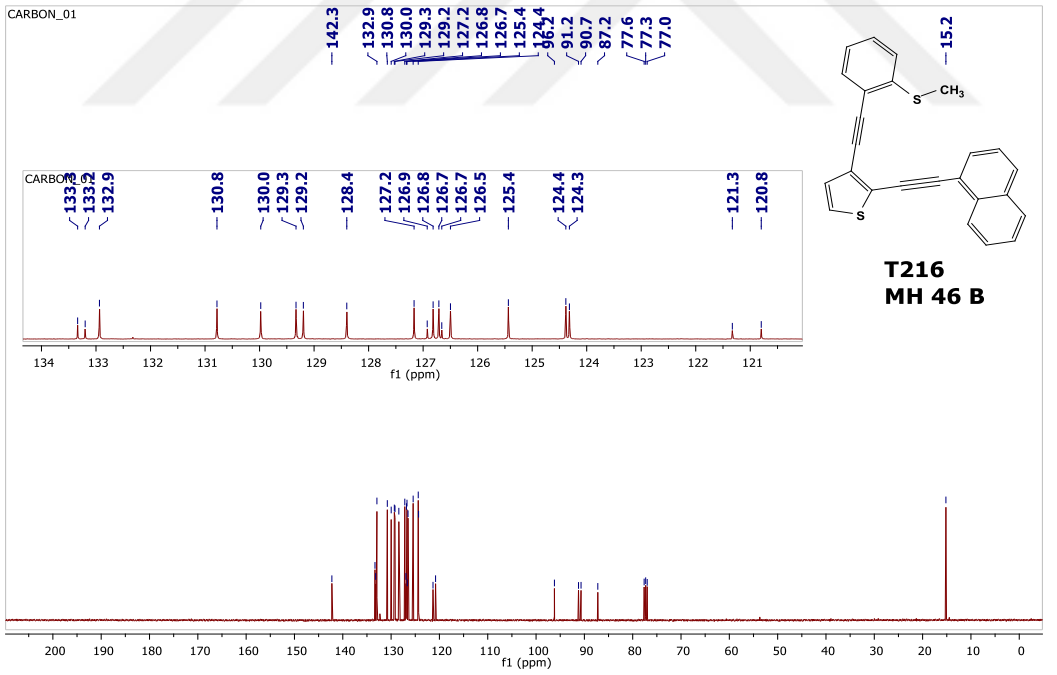

Figure M96. ^{13}C NMR spectra of MH46B.

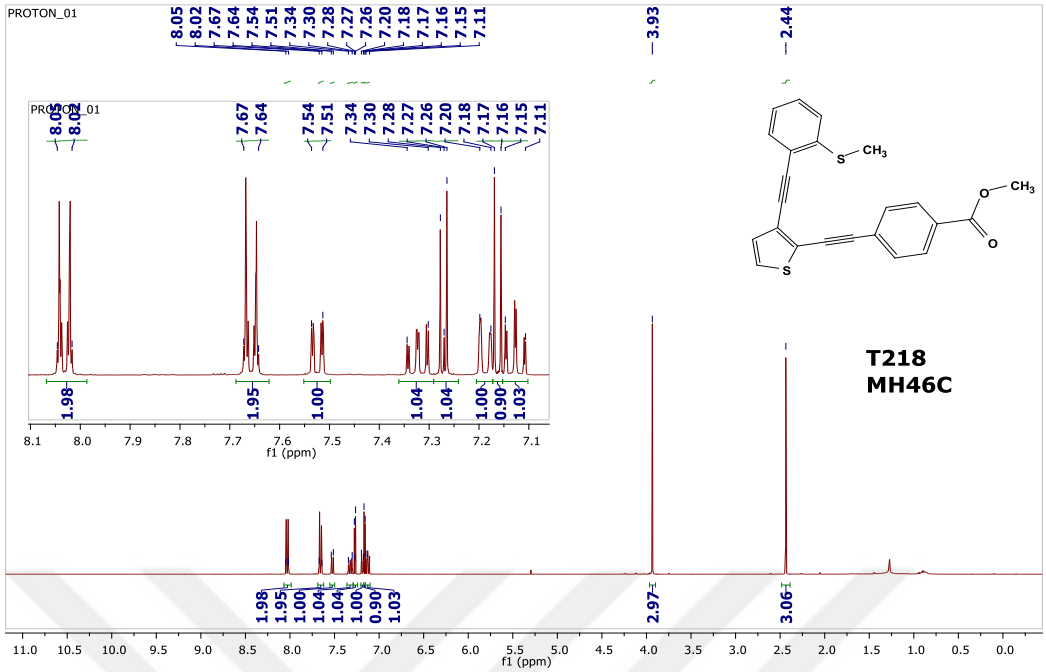

Figure M97. ^{1}H NMR spectra of MH46C.

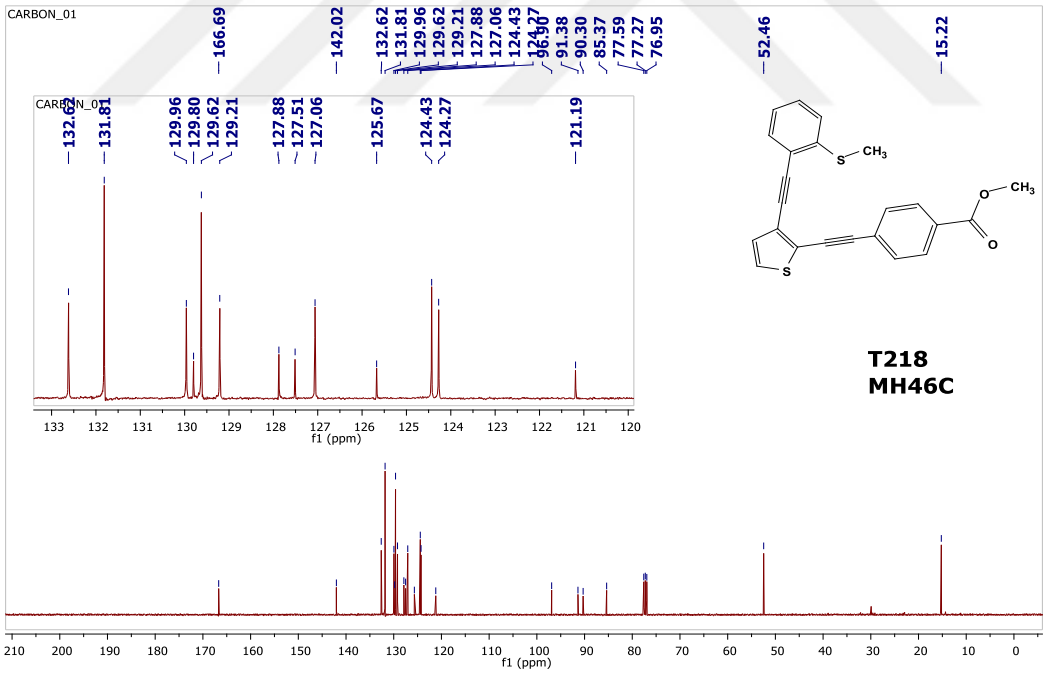

Figure M98. ^{13}C NMR spectra of MH46C.

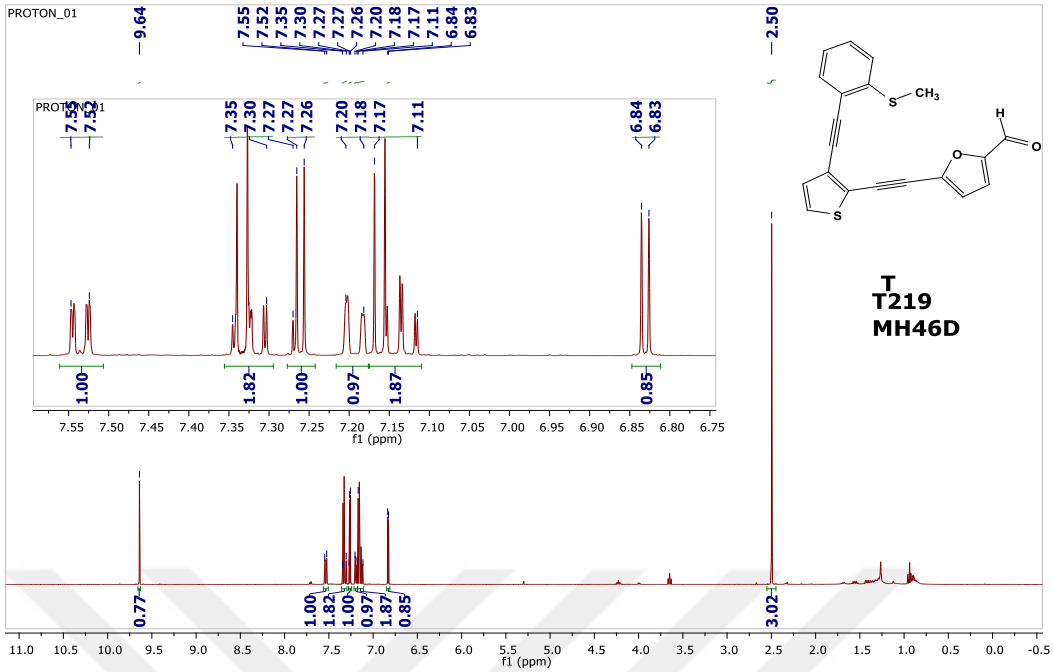

Figure M99. ^{1}H NMR spectra of MH46D.

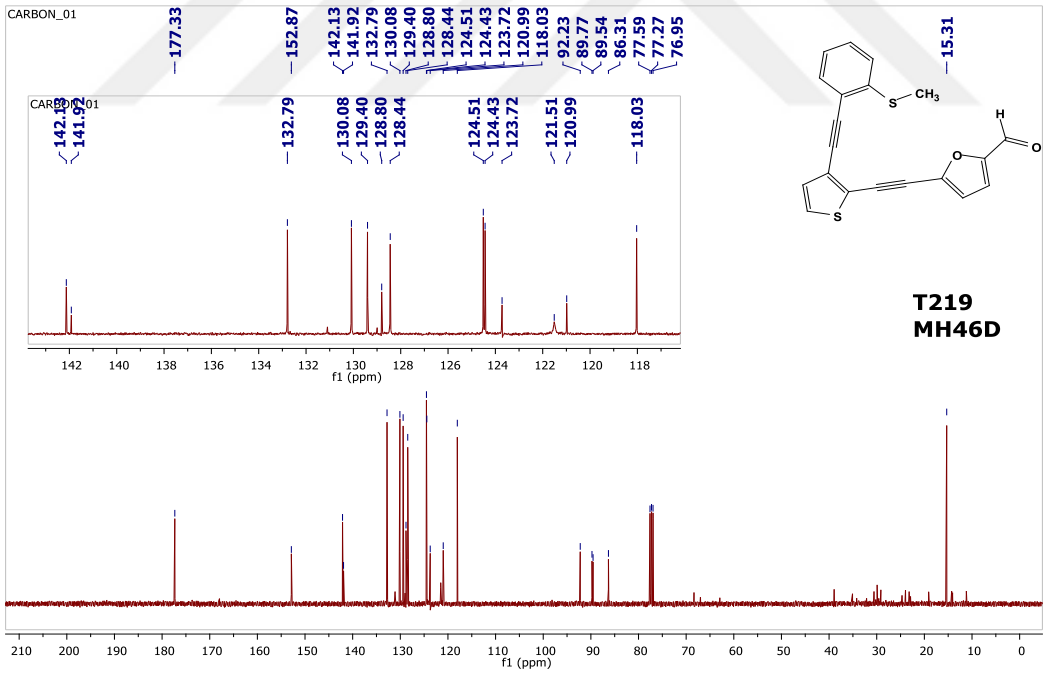

Figure M100. ^{13}C NMR spectra of MH46D.

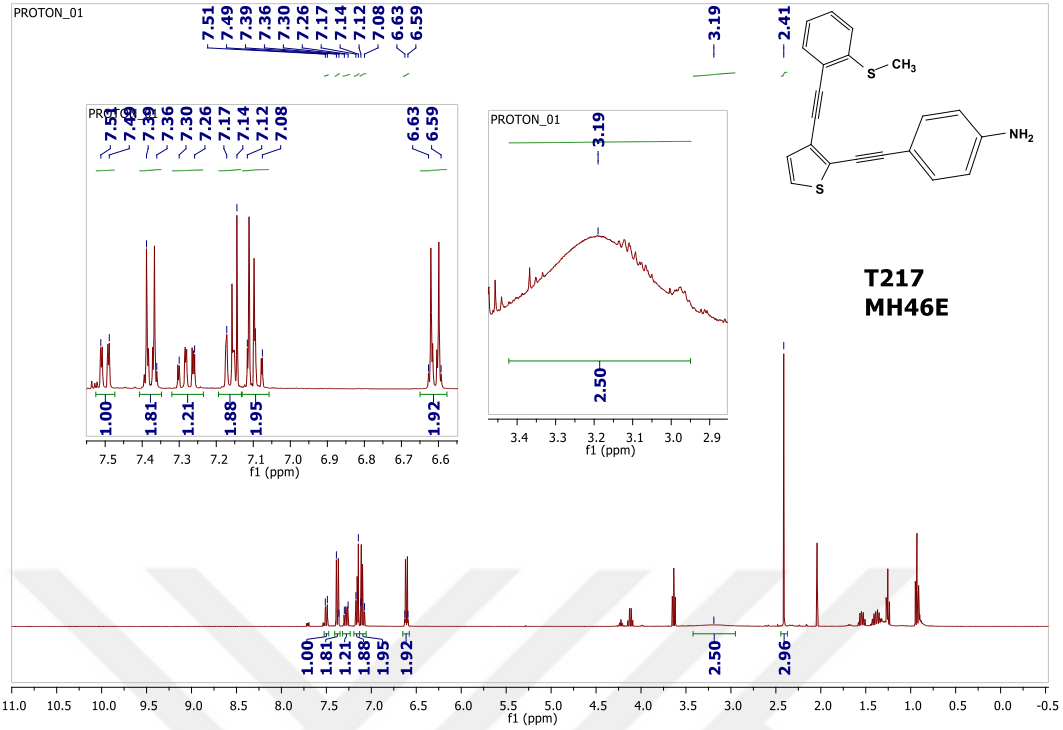

Figure M101. ^{1}H NMR spectra of MH46E.

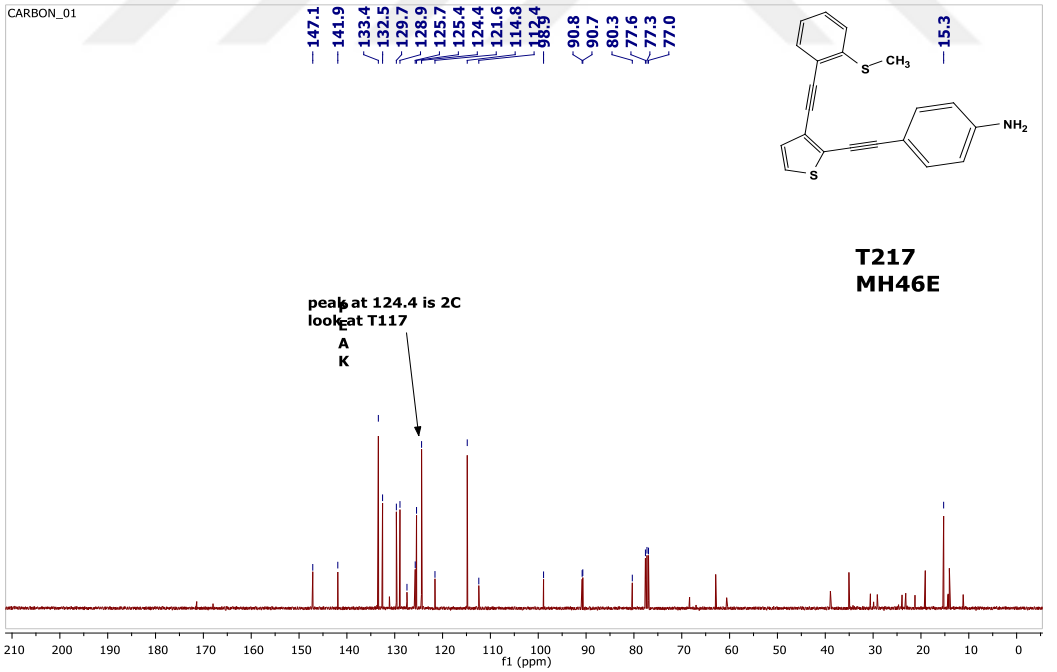

Figure M102. ^{13}C NMR spectra of MH46E.

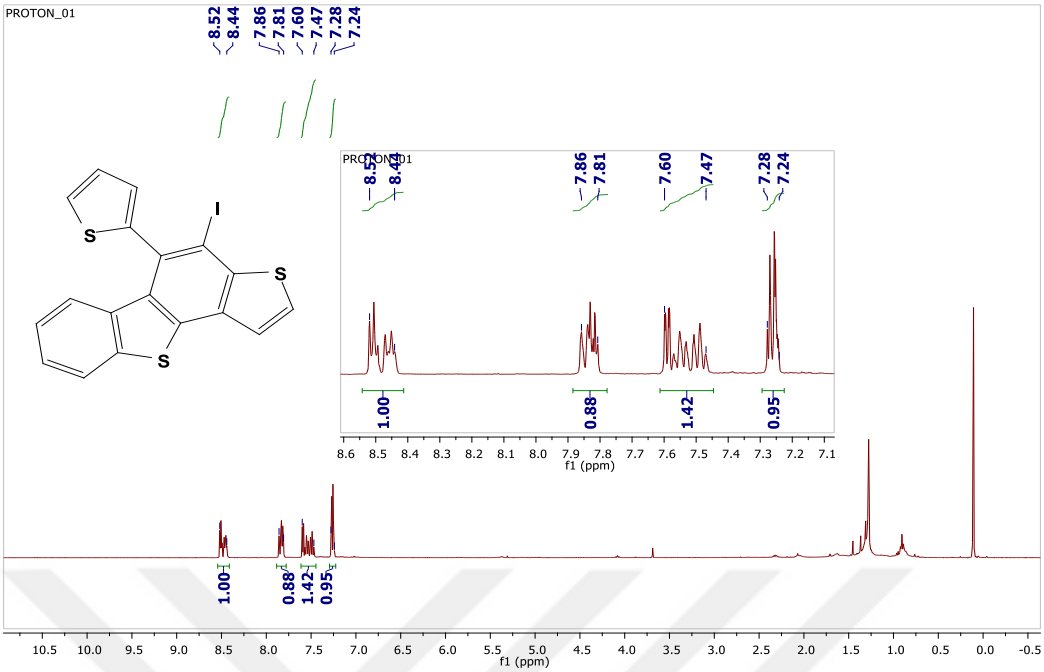

Figure M103. ^{1}H NMR spectra of MH20.

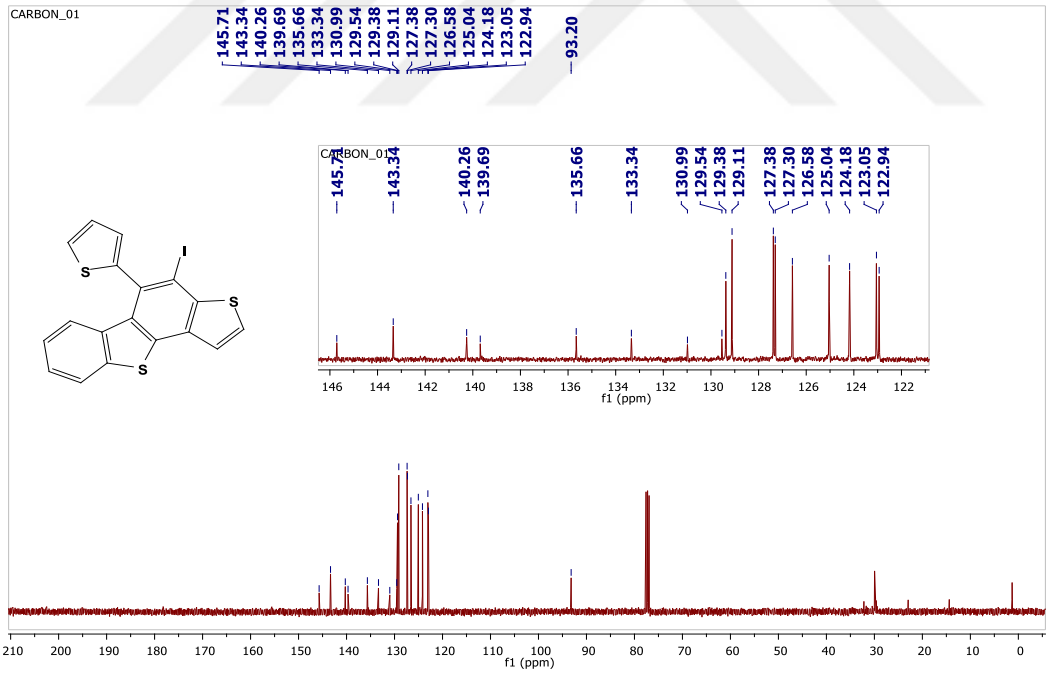

Figure M104. ^{13}C NMR spectra of MH20.

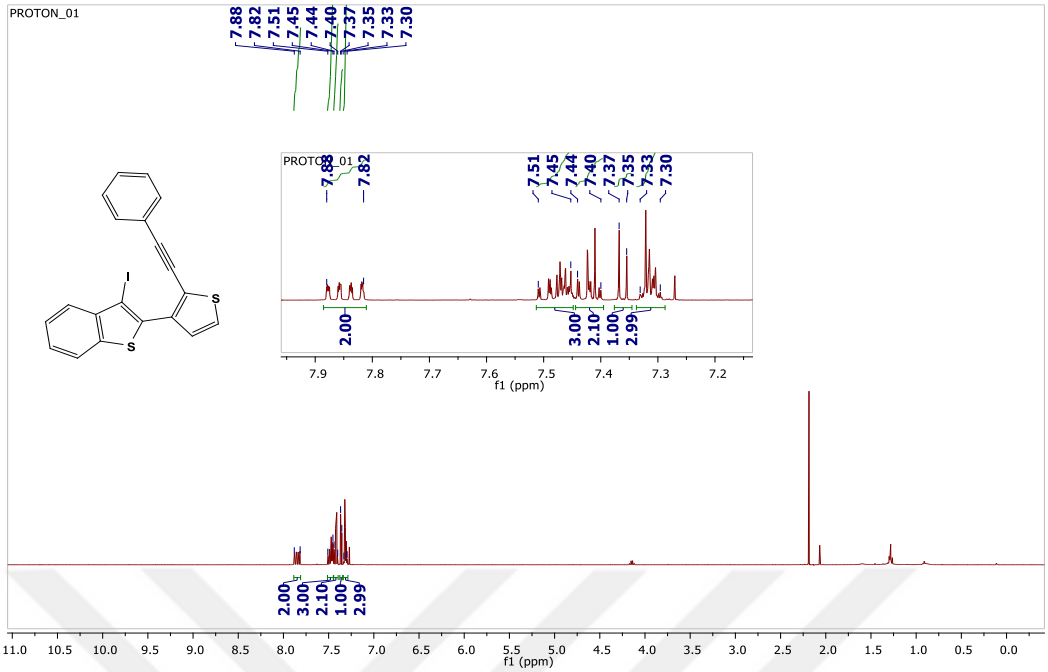

Figure M105. ^{1}H NMR spectra of MH20B.

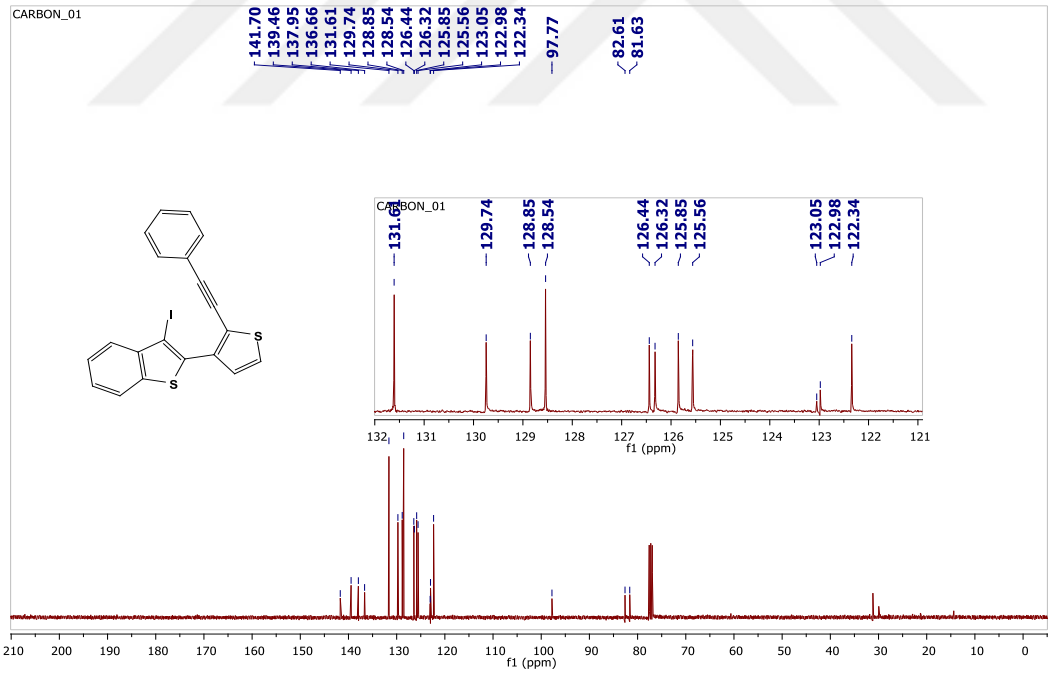

Figure M106. ^{13}C NMR spectra of MH20B.

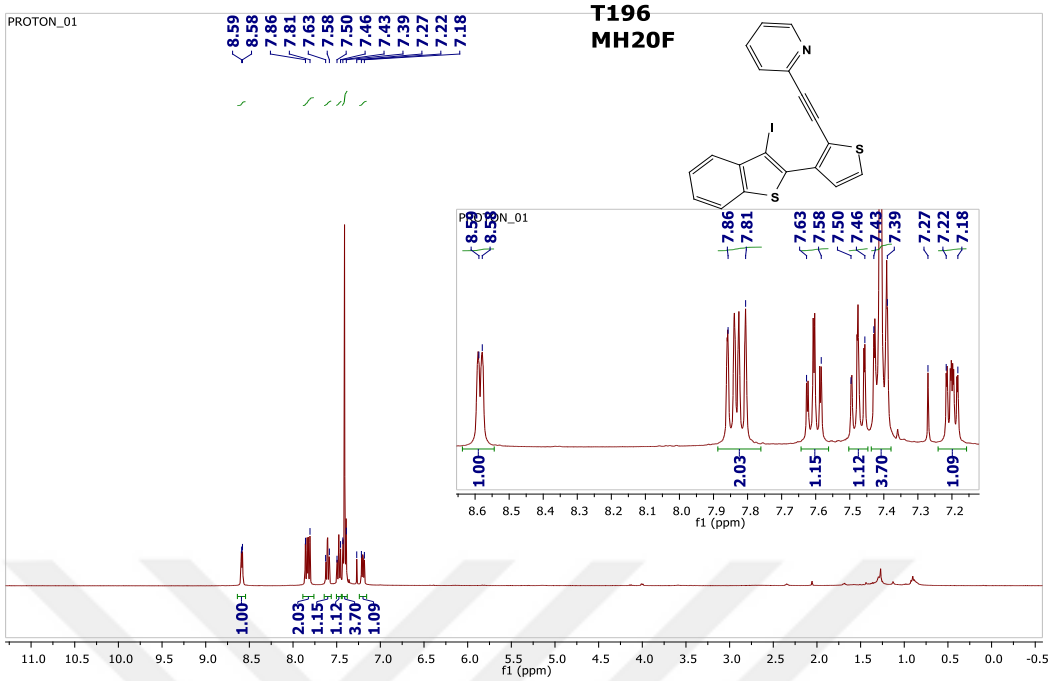

Figure M107. ^{1}H NMR spectra of MH20F.

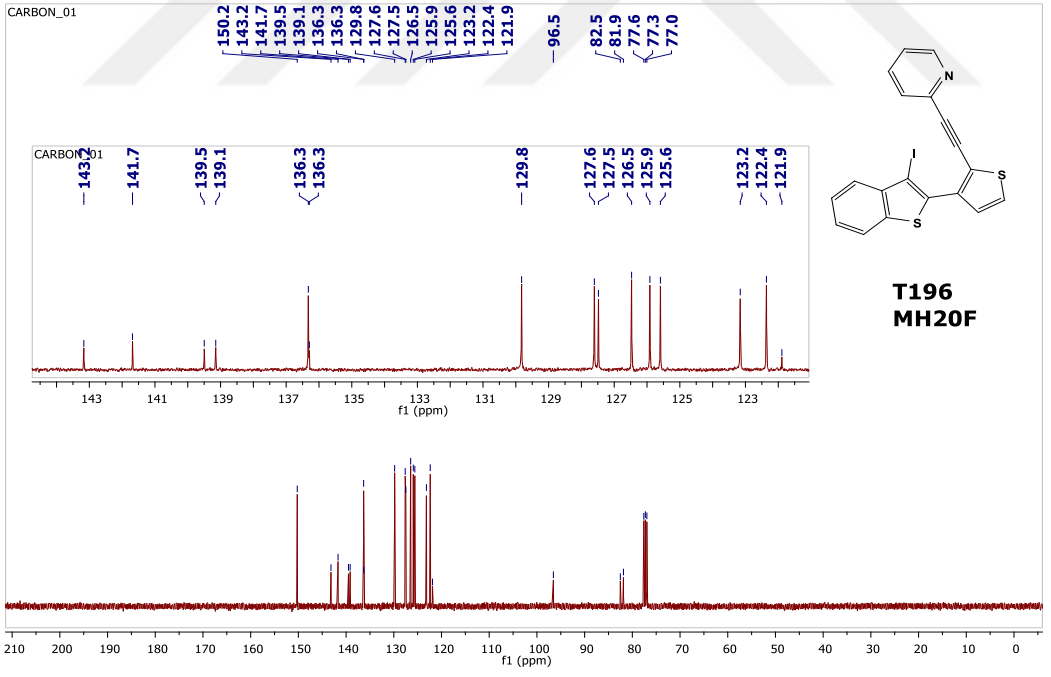

Figure M108. ^{13}C NMR spectra of MH20F.

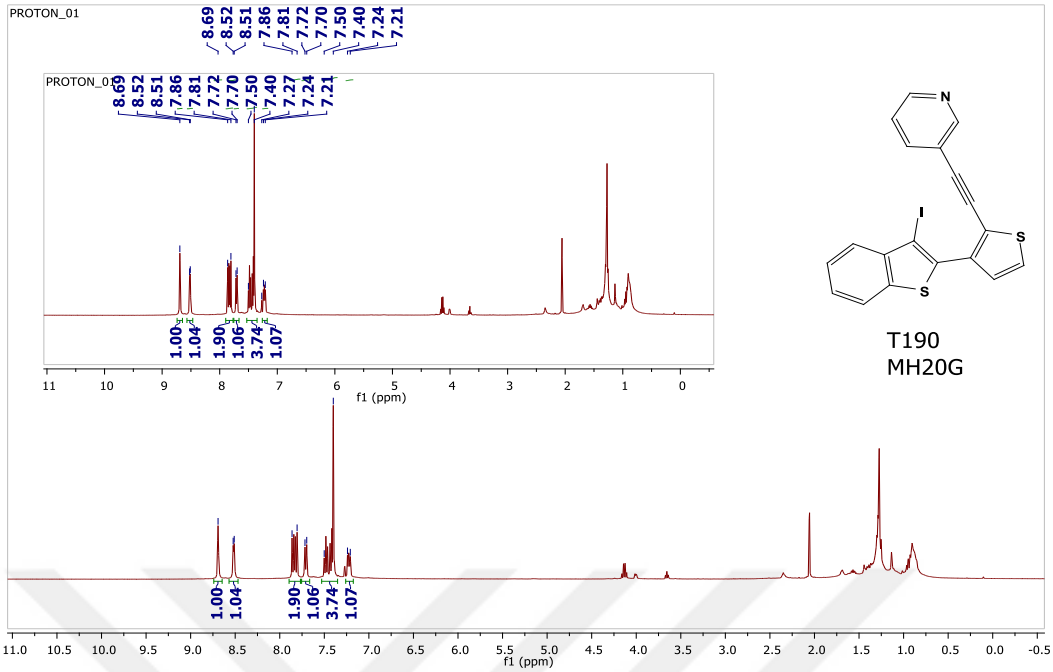

Figure M109. ^{1}H NMR spectra of MH20G.

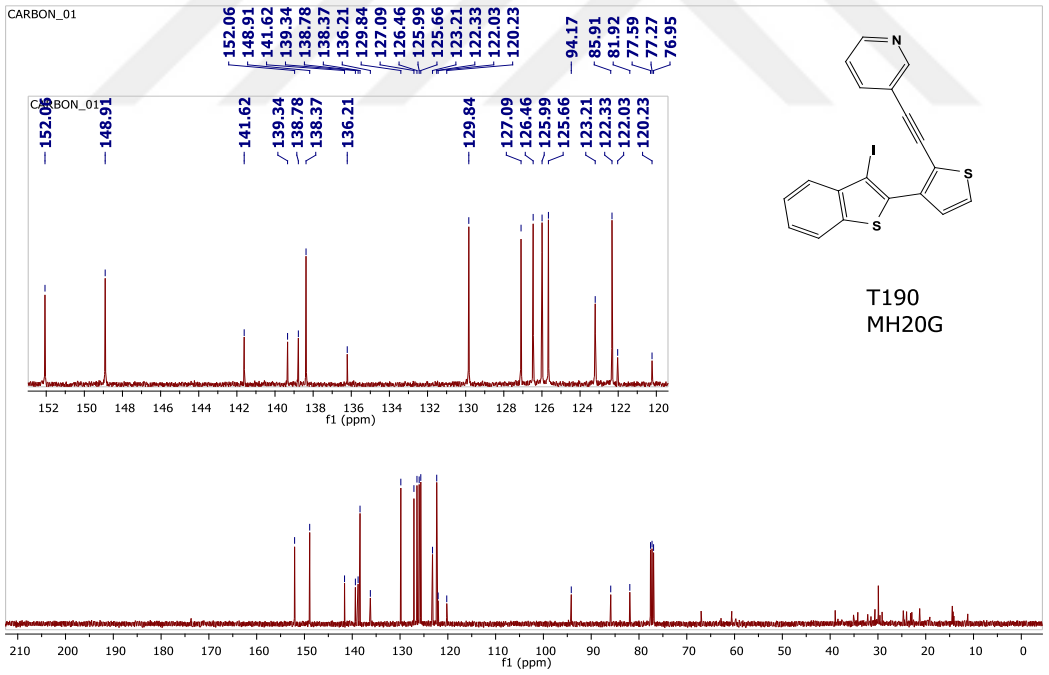

Figure M110. ^{13}C NMR spectra of MH20G.

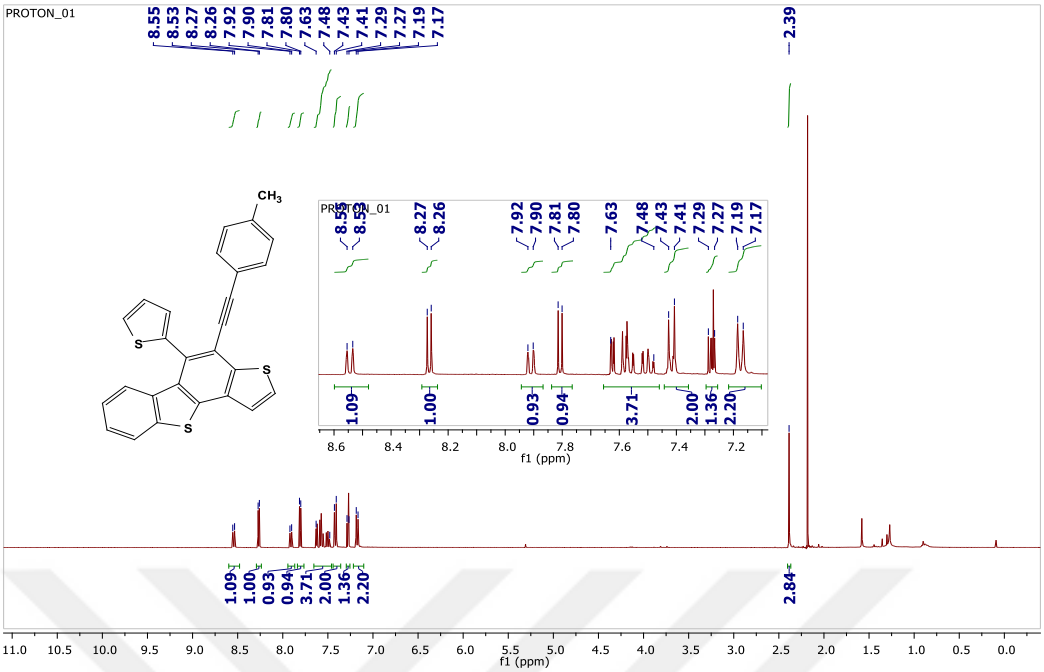

Figure M111. ^{1}H NMR spectra of MH21.

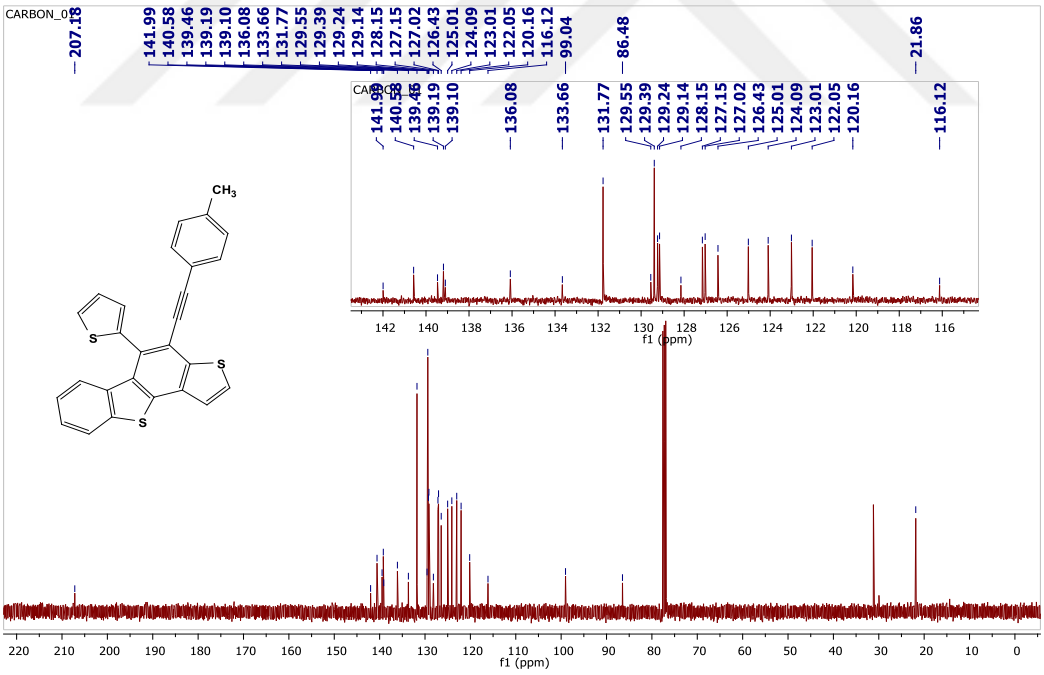

Figure M112. ^{13}C NMR spectra of MH21.

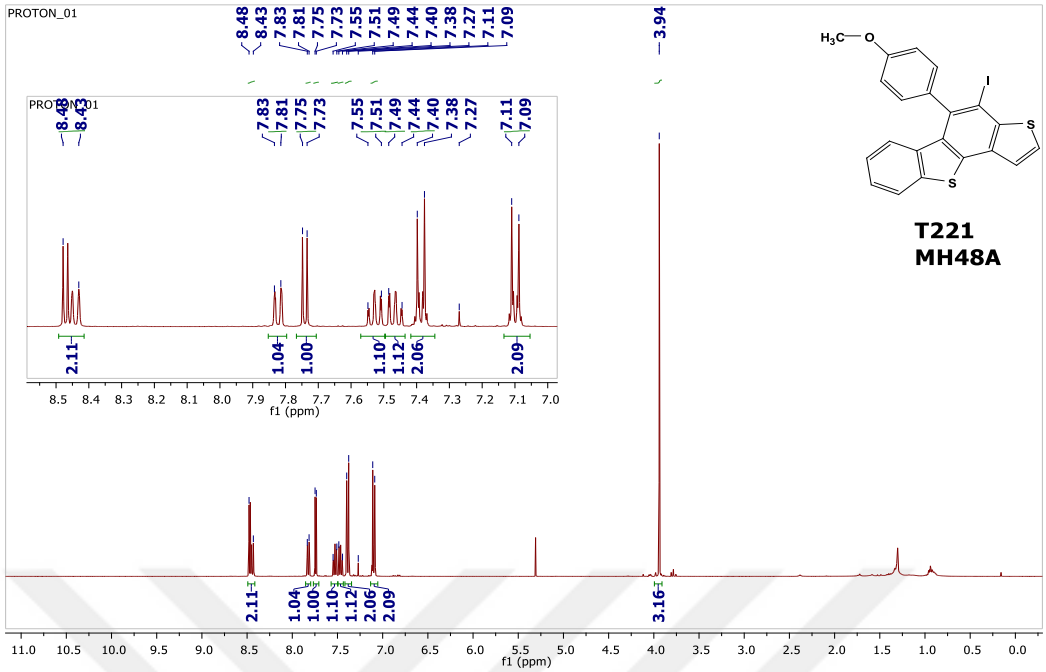

Figure M113. ^{1}H NMR spectra of MH48A.

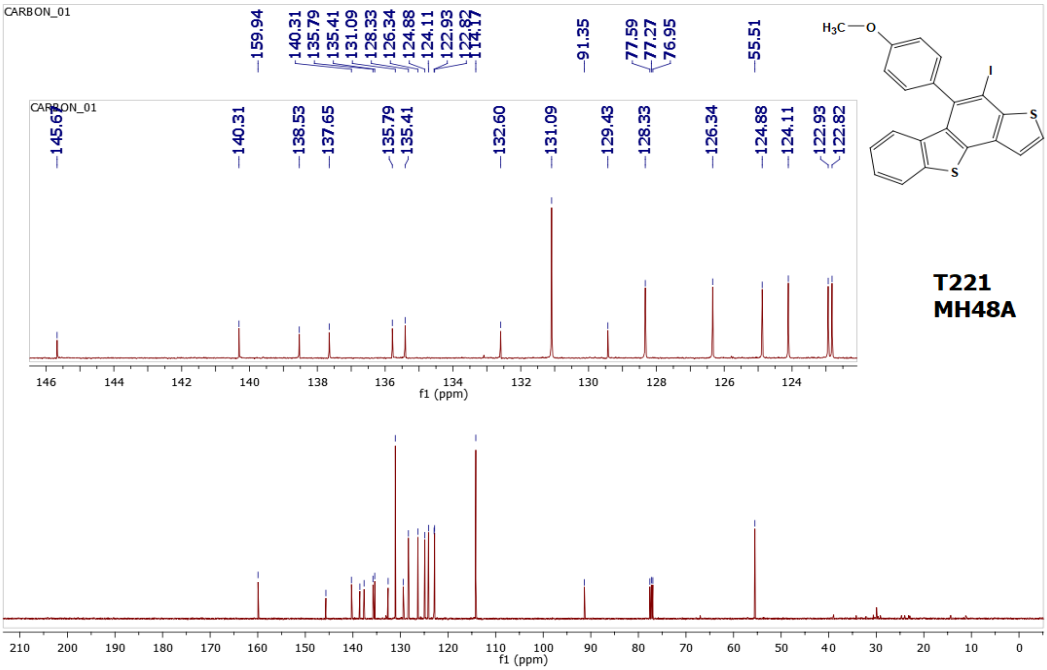

Figure M114. ^{13}C NMR spectra of MH48A.

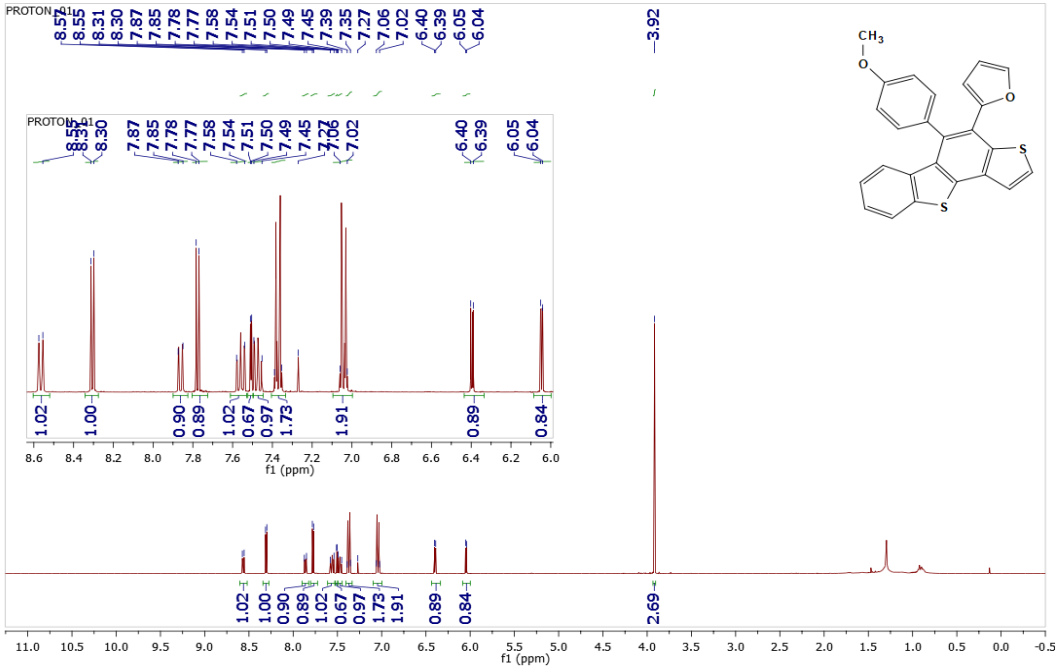

Figure M115. ^{1}H NMR spectra of MH49.

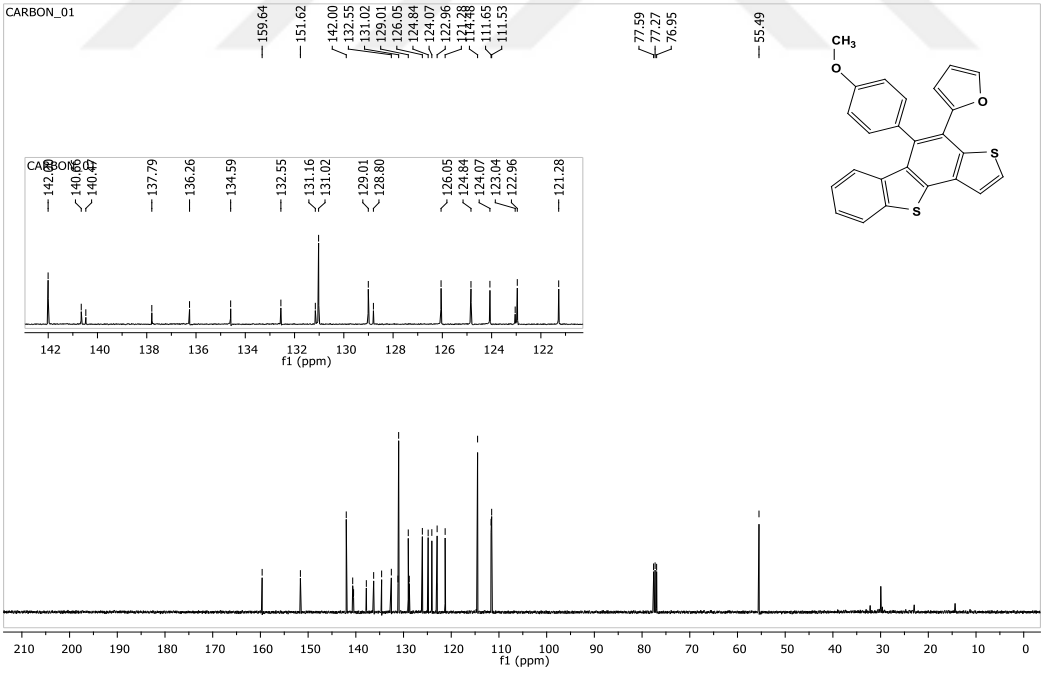

Figure M116. ^{13}C NMR spectra of MH49.

APPENDIX B: EXTENDED TURKISH SUMMARY

(GENIŞLETILMIŞ TÜRKÇE ÖZET)

TİYENO-DİBENZOTİYOFEN TÜREVLERİNİN HALKALAŞMA TEPKİMELERİ İLE SENTEZİ

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Tez Danışmanı: Prof. Dr. Arif KIVRAK

1. GİRİŞ

Yeni ilaçların keşfi için özellikle ilaç potansiyeline sahip organik maddelerin sentezi ve izolasyonu çok önemlidir. Ayrıca sentezlenen maddelerin çok farklı sübstitüentlere sahip olması veya farklı sübstitüentler ile türevlendirilmesi de kritik öneme sahiptir. İlaç araştırmalarında ana yapıya farklı gruplar bağlanarak ya yapının biyolojik özelliği artırılmakta ya da tamamen yeni bir özelliğe sahip bir yapı elde edilmektedir. Dünya üzerinde kullanılan ilaçların yapılarına bakıldığında çoğunlukla yapısında hetero atom bulunan organik maddeler olduğu görülmektedir. Bir malzemenin ilaç olabilmesi için gerekli aşamalardan başarı ile geçmesi gerekmektedir. Bu aşamaların birincisi organik malzemelerin tasarımı, sentezi, saflaştırılması ve karakterizasyonudur. Tasarım aşamasında ilaç potansiyeli olabilmesi için Lipinskii Kuralına (belli sayıda heteroatom, çözünürlük, moleküler ağırlığının 500 g/mol den az olması vb.) uyması gereklidir. İkinci aşamada ise hedeflenen organik bileşiğin yüksek verimler ve uygulanabilir yöntemler ile sentezlenmesi gerekmektedir. İlaç uygulamaları için elde edilen bileşiğin oldukça saf halde olması doğru sonuçların elde edilmesi için büyük önem arz etmektedir. Elde edilen maddenin yapısal karakterizasyonu hem sentetik olarak elde edilen hem de doğadan izole edilen türevleri için çok önemlidir. Ayrıca yapıların farklı sübstitüentlere sahip olması veya türevlendirilebilir olması ilaç araştırmaları için kritiktir. Özellikle ABD gibi gelişmiş ülkelerde üniversiteler arası işbirliği yapılarak ilaç potansiyeline sahip yapılar

türevlendirilmekte ve belirli merkezlere gönderilerek bu yapıların etkileri araştırılmaktadır. Bu araştırmalar sonucunda belli hastalıkların tedavisinde kullanılmak üzere ilaçlar keşfedilmektedir.

İlaç olarak kullanılan doğal bileşiklerin doğadan izole edilmesi, izole edilen bileşiklerin yapılarının tam olarak belirlenmesi, hangi hastalıkların tedavisinde kullanılacaklarının bulunması ve bu maddelerin sentetik olarakta elde edilip edilmeyeceğinin bulunması çok önemlidir. Günümüzde doğada bulunan organik yapılardan bazılarını ilaç olarak kullanmaktayız. Ancak doğada bulunan ve keşfedilmeyi bekleyen ne kadar madde olduğu büyük bir soru işaretidir. Keşfedilmiş yapıların sentetik olarak elde edilmesi kadar henüz doğada olup olmadığını bilmediğimiz yeni hetero- veya karbo- organik maddelerin elde edilmesi de çok önemlidir.

Bu çalışmada geliştirdiğimiz yeni yöntemler ile yeni tiyeno-dibenzotiyofen türevlerini sentezledik.Tiyeno-dibenzotiyofenler ilaç olma potansiyeline sahip ve Lipinskii kuralına uyan heterosiklik yapılardır. Tiyeno-dibenzotiyofenler gibi biyolojik önemi henüz bilinmeyen ve hastalıklara karşı çok yeni ve farklı davranımlar gösterebilecek türevlerin sentezlenmesi ilaç araştırmaları için çok önemlidir. Tiyeno-dibenzotiyofenler için yapılan literatür araştırmamıza göre nerdeyse yok denecek kadar az sentez yöntemi vardır ve bu yöntemler oldukça fazla dezavantaja sahiptir (zor tepkime koşulları, sınırlı sayıda türevlendirilebilmesi, düşük verim, yüksek sıcaklık vb.). Bu çalışmada geliştirdiğimiz yeni yöntemler ile 2 ana yapıya sahip Tiyeno-dibenzotiyofenler rejio-seçiçi olarak sentezlenmiştir.

2. MATERYAL, YÖNTEM VE BULGULAR

2.1. Tiyeno[2,3-a]dibenzotiyofen sentezleme yöntemi ve elde edilen bulunan bulgular

Bu çalışma kapsamında tiyeno[2,3-a]dibenzotiyofenlerin sentezi için aşağıdaki sentez basamakları kullanılmıştır. Bu yöntemler kullanılarak yukarıda detayları verilen deneyler ile gerçekleştirilmiş ve hedeflenen ürünler sentezlenmiştir. Elde edilen tüm ara ürün ve ürünler izole edilerek yapısal karakterizasyonları spektroskobik yöntemler kullanılarak yapılmıştır. Önerilen yöntemlerde kullanılan deneysel yöntemlerin bazıları literatür de olan metotlardır. Bunlar için ilk olarak literatürdeki yöntemler aynen kullanılmıştır. Ayrıca yöntemlerin bazıları modifiye edilerek bizim yapılarımıza uygun hale getirilerek deneysel çalışmalar yapılmıştır.

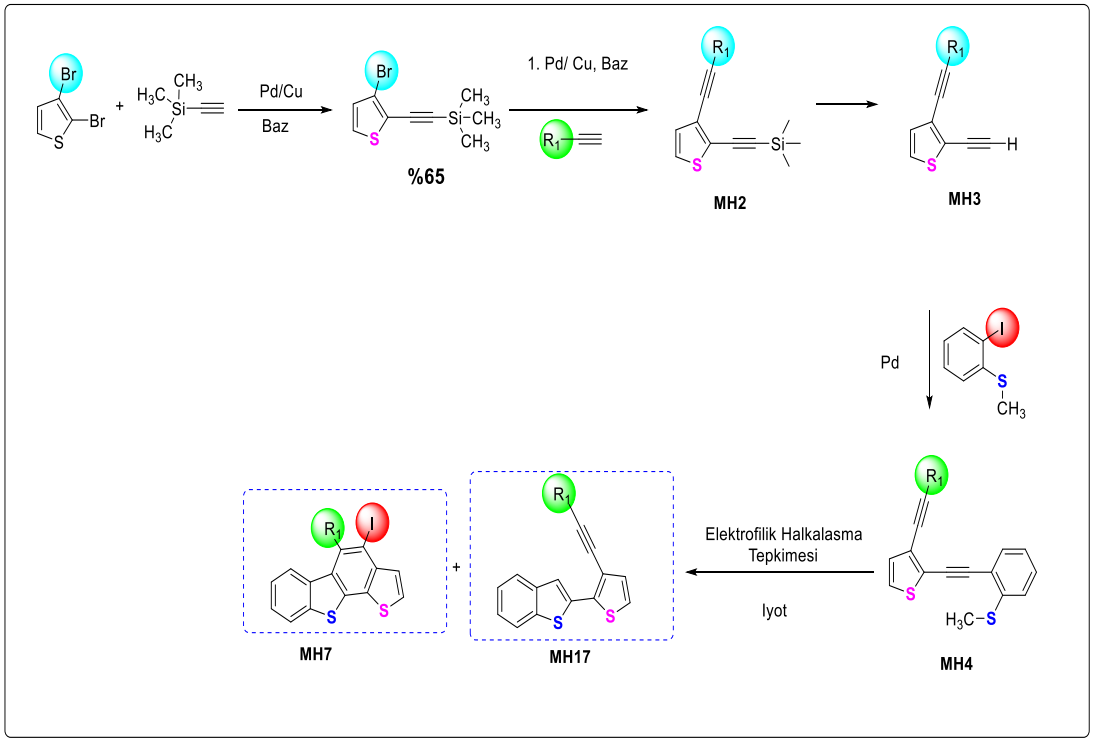
Deneysel çalışmalarda 2,3-dibromotiyofen başlangıç maddesi olarak kullanılmıştır. Bilindiği gibi tiyofen 2 ve 5 konumundan kolaylıkla türevlendirilebilen bir moleküldür. Literatüre bakıldığında bu bileşik ile gerçekleştirilen palatyum katalizörlü Sonogashira Kenetlenme tepkimelerinde ana rün olarak 2 konumunda alkin bağlanmaktadır. Eğer fazla miktarda alkin tepkimelerde kullanılırsa dialkinil tiyofenlerde elde edilebilmektedir. 2,3-Dibromotiyofenin bu şekilde Sonogashira kenetlenme tepkimesinde büyük seçiçiliğe sahip olması bizim iki izomerimizide sentezlememiz için çok kritik bir role sahiptir. 2,3-Dibromotiyofen ilk olarak paladyum katalizörlüğünde asetiltrimetil silan ile kenetlenme tepkimesine sokularak 2 konumundan yapıya alkin bağlanmıştır(Şekil 2.1**).** Daha sonra gerekli izomerin sentezlenmesi için tiyofenin 3 konumundan alkin türevlerinin bağlanması gerçekleştirilmiştir. Bu kenetlenme tepkimeleri için farklı aromatik alifatik ve poliaromatik alkin türevleri reaktant olarak kullanılmıştır. Bu ikinci Sonogashira kenetlenmesi ile 7 farklı türev yüksek verimler ile izole edilmiştir. Bunlardan fenil asetilen ile gerçekleşen tepkimeden %80 gibi iyi bir verim ile MH2 yapısı elde

edildiken, en yüksek verimi p-tolilasetilen ile gerçekleştirilen ürün vermiştir (%97 MH2C). Bu tepkimelerde ilginç olan yapısında metoksi grubu bulan türevin en düşük verim (%55, MH2F) elde edilmiş olmasıdır.

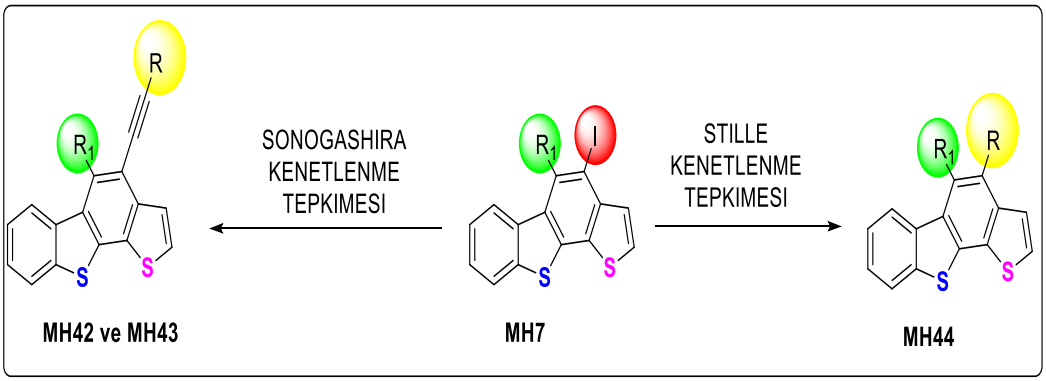
MH2 türevleri izole edildikten ve yapısl karakterizasyonları tamamlandıktan sonra hedeflenen ürün için yapıdaki TMS koruyucu grubunun uzaklaştırılmasıdır. Bunun için zayıf bazik ortamda ve oda sıcaklığında istenilen birincil alkinler (MH3) elde edilmiştir. Bu tepkimede genel olarak verimler %90 üstündedir, sadece MH3G yapısı %74 verim ile izole edilmiştir. Bizim için en kritik role sahip olan başlangıç maddesinin (MH4) sentezi için elde edilen MH3 türevleri ile 2-iyodotiyoanisol kenetlenme tepkimesine sokulmuştur. Bu paladyum katalizörlü kenetlenme tepkimesi ile yüksek verimler ile MH4 türevleri (%58-%99) izole edilmiştir. Fenil substitüe türev %62 gibi bir verim ile sentezlenirken, ek yüksek verimi 2-naftilasetilen substitüe türev vermiştir (%99).

Çalışmanın ana konusu elektrofilik halkalaşma tepkimesi ile tiyenodibenzotiyofen türevlerinin sentezidir. Bu türevlerin sentezi için moleküler iyot ortamında elektrofilik halkalaşma tepkimeleri gerçekleştirilmiştir. Bunun için ilk olarak MH4 ile halkalaşma tepkimesi gerçekleştirilmiştir. Bu tepkime sonuçunda iki farklı ürün izole edilmiştir. Bunlardan birincisi %31 gibi bir verim ile hedeflenen ürün MH7 dir. Bu ürün ile birlikte mono halkalaşma ürünü olan MH17 de (%50) tepkime sonunda ortamda kalmıştır. MH17 için ayrıca bir teori geliştirilmiştir. Buna göre tekrar iyot ortamında halkalaşma tepkimesi sokulduğunda istenin ürünü verebilmesidir. Bunun için MH17 nin başlangıç maddesi olduğu elektrofilik halkalaşma tepkimesi gerçekleştirildiğinde bu sefer %50 gibi bir verim ile hedeflenen molekülün oluştuğu bulunmuştur. Aynı tepkime alkil substitüte türev (MH7B) için uygulandığında %97 gibi çok yüksek bir verim ile sadece MH17B elde edilebilmiştir. MH4C ile gerçekleştirilen halkalaşma tepkimesinden ise MH7C (%64) ve MH17C (%31) izole edilmiştir (Tablo 3.4). Ayrıca elektrofilik halkalaşma tepkimesi kullanılarak MH7D, MH7E, MH7F ve MH7G oldukça yüksek verimler ile sentezlenmişler. Sentezlenen tüm ürünlerin yapısal karakterizasyonları spektroskobik yöntemler kullanılarak belirlenmiştir.

Tiyeno[2,3-a]dibenzotiyofen türevlerin kenetlenme Tepkimeleri ile türevledirilebilir olmaları özellikle biyolojik araştırmalar için çok büyük öneme sahiptir. Geliştirdiğimiz yeni yöntemler ile yapısında iyot bulunan tiyenobenzotiyofen türevleri sentezlenmiştir. Proje kapsamında bu yapıların kenetlenme tepkimeleri ile türevlendirilebilir olduklarını gösterdik. Bunun için ilk olarak paladyum katalizörlü kenetlenme tepkimesi olan Sonogashira kenetlenme tepkimesini seçtik. Örnek olarak MH7G ve MH7D ürünleri bu tepkimeler için seçilmiştir. Buna göre fenil asetieln ile kenetlenme tepkimeleri sonuçunda MH42A ve MH43A oldukça yüksek verimler ile sentezlenmiştir (sırasıyla %92 ve %93) (Şekil 2.2).



Şekil 2.1. Tiyeno[2,3-a]dibenzotiyofen türevlerin sentezi.



Şekil 2.2. Sonogashira kenetlenme tepkimesi kullanılarak tiyenodibenzotiyofen türevlendirilmesi.

Ayrıca tolilasetilen kullanılarak yapılan Sonogashira tepkimesi sonucunda %89 MH42B ve %86 MH43B elde edilmiştir. Bu dört türevde bize göstermektedir ki Sonogashira kenetlenme tepkimesi kullanılarak tiyenodibenzotiyofen türevleri istenildiği kadar türevlendirilebilmektedir.

2.2. Tiyeno[3,2-a]dibenzotiyofen sentezleme yöntemi ve elde edilen bulgular

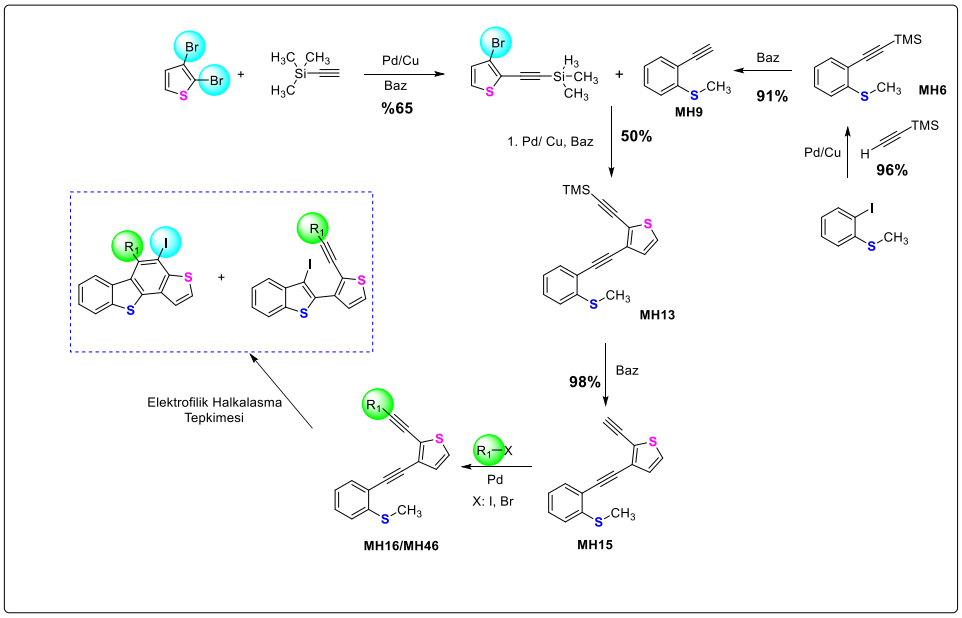
Tiyeno[3,2-a]dibenzotiyofenlerin sentezi için aşağıda verilen tepkimeler kullanılmıştır. Burada ilk olarak 2,3-dibromotiyofenden ile TMS-asetilen tepkimeye sokularak palatyum katalizörlüğünde %65 gibi bir verim ile 2- alkinil-tiyofen sentezlenmektedir. Hedeflenen izomerin elde edilebilmesi için 3 konumundan tiyoanisolün yapıya bağlanması gerekmektedir. Bu başlangıç maddesi ise 2-iyodotiyoanisolden başlanarak sentezlenmiştir. Burasa ilk olarak 2-iyodotiyoanisol ve TMS-asetilen palatyum katalizörlü Sonıogashira kenetlenme tepkimesine sokulmakta ve MH6 izole edildikten sonta bazik ortamda TMS uzaklaştırılarak oldukça yüksek bir verim ile MH9 (%91) asetil tiyoanisol sentezlenmektedir. 2-alkinil-tiyofen ve 2-etiniltiyoanisol tekrar kenetlenme tepkimesi sokularak %50 verim ile 2,3-dialkiniltiyofen MH13 sentezlenmektedir. Tiyofenin 3 konumundan Sonogashira kenetlenmesi 2 konumuna göre oldukça zordur. Ancak bizim sistemimizde verim oldukça iyi bulunmuştur. Daha sonra yapıdan TMS uzaklaştırılarak bileşiğimiz

türevlendirilebilir hale getirilmiştir. Burada yapısında brom veya iyot bulunduran aromatikler kullanılarak yapıya aril grupları bağlanmıştır. Bu tepkimeler için ilk olarak 2-bromo tiyofen ile kentlenme tepkimesi gerçekleştiirlmiş, %99 gibi oldukça yüksek verim ile MH19 izole edilmiştir. Daha sonra bromobenzen ile tepkime yapılmış ve %70 verim bulunmuştur. Bu tepkimelerde hem brom hemde iyot substitüe reaktantlar kullanılabilmektedir. En ilginç sonuç p-bromoanilin ve p-iyodoanilin ile gerçekleştirilen tepkimede görülmüştür. p-Bromoanilin ile gerçekleştirilen kenetlenme tepkimesinden %41 gibi düşük bir verim ile MH19D elde edildi iken bu tepkime p-iyodoanilin ile gerçekleştirildiğinde verim %83 e çıkmıştır. Bu tepkime için piriridn ve naftalen içeren gruplarda yapıya bağlanarak halkalaşma tepkimesi için gerekli başlangıç maddesi MH16/MH46 türevleri sentezlenmiştir.

Böylece elektrofilik halkalaşma tepkimesinde kullanılacak olan başlangıç maddelerimiz sentezlenmiştir. Elektrofilik halkalaşma için ilk olarak fenil substitüe türev test edilmiştir. Ancak standart tepkime koşulumuzda sadece tek halkalaşma tepkimesi gerçekleşerek indol yapısında madde kalmıştır. Diğer taraftan 2-tiyofenil türev halkalaşma tepkimesine sokulduğunda %60 gibi bir verim ile hedeflenen ürün MH20 sentezlenmiştir. Fenil ve tiyofen yapıları karşılaştırıldığında tiyofen daha elektron verme özelliğine sahip bir bileşiktir. Buna göre elektron veren yapılar hedeflenen ürünümüzü daha yüksek verimler ile verebilme potansiyeline sahiptirler. Sentezlenen 3-tiyenil substitüe başlangıç maddesi MH16C elektrofilik halkalaşma tepkimesine sokulduğunda hem ürün hemde mono haalkalaşma ürünü oluşmuştur (Şekil 2.3) (NMR sonucuna göre) ancak bu karışım ne yazık ki birbirinden ayrılamamıştır. Bunun için ileri seviye ayırma yöntemlerine ihtiyaç vardır. Benzer bir durum naftalen içeren bileşik içinde geçerlidir. Ürün ile mono halkalaşma ürünü karışım halindedir. İlginç bir şekilde yapısında pridin bulunduran başlangıç maddeleri elektrofilik halkalaşmaya sokuldukla iside mono halkalaşma ürününü vermektedirler (MH20F ve MH20G).

3. TARTIŞMA VE SONUÇ

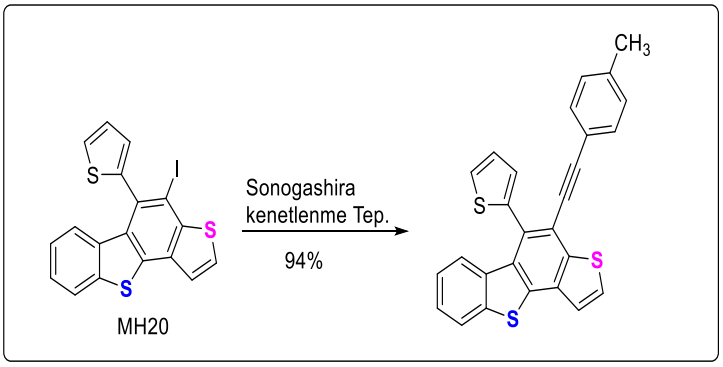
Bizim teorimize göre elektron veren grup içeren bileşiklerin daha iyi sonuç vermesi beklenmektedir. Yapısında metoksi gubu bulunduran MH46A ile gerçekleştirilen halkalaşma tepkimesinden %75 verim ile tek madde olarak hedeflenen ürün sentezlenmiştir. Ne yazikki yapısında amin ve N,N-dimetil amin bulunduran gruplar tepkimede bozulmuş ve hiç bir ürün oluşumu gözlenmemiştir. Buna benzer bozulma durumu MH46C ve MH46F yapılarında da gözlemlenmiştir. Bunun nedeni için araştırmalar devam etmektedir.



Şekil 2.3. Tiyeno[3,2-a]dibenzotiyofenlerin iyot ortamında elektrofiilik halkalaşma tepkimesi ile sentezi.

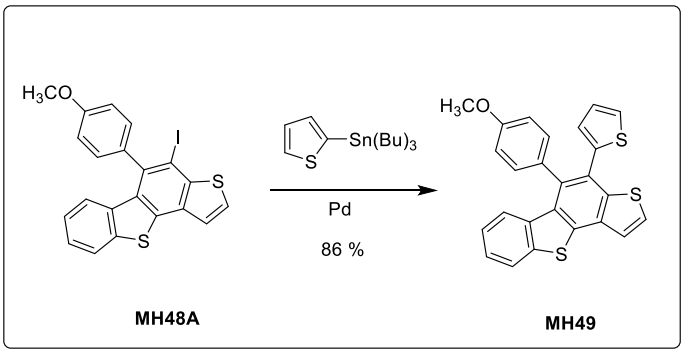
Proje kapsamında yapısında iyot bulunduran tiyeno[3,2-a]dibenzotiyofenlerin kenetlenme tepkimeleri ile türevlendirilmeside hedeflenmektedir. Bunun için ilk olarak yaptığımız Sonogashira kenetlenme tepkimesinde oldukça yüksek bir verim (%94)(Şekil 2.4) ile tepkime gerçekleşmiştir. Bu sayede elektrofilik halkalaşma tepkimesinden elde edilen ürünlerin kenetlenme tepkimelerinde kullanılabilirliği

kanıtlanmıştır. Özellikle biyolojik araştırmalar için yapıların farklı türevlerinin sentezlenmesi çok önemlidir.



Şekil 2.4. Tiyeno[3,2-a]dibenzotiyofenlerin Sonogashira Kenetlenme Tepkimesi ile türevlendirilmesi.

Sentezlenen tiyeno[3,2-a]dibenzotiyofenlerin ayrıca Stille kentlenme tepkimesi ile türevledirilebilri olduğuda test edilmiştir. Bilindiği gibi Stille kenetlenme tepkimesi ile yeni karbon karbon bağı oluşarak iki aromatik veya heteroaromatik bileşik birleştirilmektedir. Bu kenetlenme tepkimesi için örnek olarak MH48A seçilmiştir. Paladyum katalizörlüğünde ve toluen çözücüsü içerisinde gerçekleştirildiğinde %86 gibi yüksek bir verim ile ürün elde edilmiştir. Buna göre tiyenobenzotiyofenler Stille kentlenme tepkimesi ile istenildiği kadar türevlendirilebilirler(Şekil 2.5)



Şekil 2.5. Stille Kenetlenme tepkimesi ile tiyeno[3,2-a]dibenzotiyofenler türevlendirilmesi.

Sentez için sonuç olarak, projemizin amacı yeni geliştirdiğimiz yöntemler ile tiyeno[2,3-a]dibenzotiyofen ve tiyeno[3,2-a]dibenzotiyofenlerin sentezlenmesidir. Proje kapsamında tüm ara ürünler sentezlenmiş ve yapısal karakterizasyonları yapılmıştır. Hedeflenen ürünümüz tiyeno[2,3-a]dibenzotiyofen ve türevleri oldukça iyi verimler ile sentezlenmiştir. Bu tepkimlerden bazılarında mono halkalaşma ürünü oluşmuş olmasına rağmen bu yapılar ikinci bir elektrofilik halkalaşma tepkimesine sokularak istenilen ürün izole edilmiştir. Ayrıca sentezlenen tiyeno[2,3-a]dibenzotiyofenlerin yapısında iyot bulunmasından dolayı kenetlenme tepkimeleri türevlendirilebilir oldukları kanıtlanmıştır. Projede ayrıca tiyeno[2,3-a]dibenzotiyofenler için yeni bir yöntem geliştirilerek rejiyo seçiçi olarak hedeflenen ürün eldesi için çalışmalar devam etmektedir.

Projemizde yer alan ikinci izomerimiz tiyeno[3,2-a]dibenzotiyofenler içinde ara ürünler sentezlenmiş ve yapısal karakterizasyonları tamamlanmıştır. elektrofilik halkalaşma tepkimesi kullanılarak yapısında iyot bulunan tiyeno[3,2-a]dibenzotiyofenler elde edilmesinde rağmen, çoğunlukla mono halkalaşma ürünleri izole edilebilmiştir. Son basamakta yine kenetlenme tepkimeleri ile türevlendiriebilir oldukları kanıtlanmıştır. Türevlendirme için istenildiği kadar yeni molekül elde edilebilecektir.

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❖ Research Published

- ✓ "*Characterization Study of Synthetic Iron Oxide nanoparticles at Different Temperature*" by Saad Fadhil Ramadhan and Muheb Amjad Saadaldein and Revink Ali Ramadhan, *International Journal of Current Engineering and Technology*. ISSN 2277 – 4106. Accepted 25 November 2013, Available online 01 December 2013, Vol.3, No.5 (December 2013).
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❖ Work Experience

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❖ Scientific Conferences

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