T. C.
VAN YUZUNCU YIL UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY

SYNTHESIS OF NOVEL BENZOTHIOPHENE DERIVATIVES VIA CYCLIZATION REACTIONS

M.Sc. THESIS

PREPARED BY: Azad Khalaf HAMA
SUPERVISOR : Prof. Dr. Arif KIVRAK

VAN-2019

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ACCEPTANCE and APPROVAL PAGE

This thesis entitled "**SYNTHESIS OF NOVEL BENZOTHIOPHENE DERIVATIVES VIA CYCLIZATION REACTIONS**" presented by Azad Khalaf HAMA under supervision of Prof. Dr. Arif KIVRAK in the Department of Chemistry has been accepted as a M. Sc. thesis according to Legislations of Graduate Higher Education on 27/05/2019 with majority of votes members of jury.

Chair: Prof. Dr. Esvet AKBAŞ Signature:

Member: Prof. Dr. Arif KIVRAK Signature:

Member: Assist. Prof. Dr. Salih ÖZÇUBUKÇU Signature:

This thesis has been approved by the committee of The Institute of Natural and Applied Science on 30 / 05 / 2019 with decision number 2019/131-1

Signature

Prof. Dr. Sıtkı SENSOY

Director of Institute

KABUL ve ONAY SAYFASI

Kimya Anabilim Dalı'nda Prof. Dr. Arif KIVRAK danışmanlığında, Azad Khalaf HAMA tarafından sunulan **"YENİ BENZOTİYOFEN TÜREVLERİNİN HALKALAŞMA TEPKİMELERİ İLE SENTEZİ"** isimli bu çalışma Lisansüstü Eğitim ve Öğretim Yönetmeliği'nin ilgili hükümleri gereğince 27/05/2019 tarihin de aşağıdaki jüri tarafından oy birliği/oy çokluğu ile başarılı bulunmuş ve Yüksek Lisans tezi olarak kabul edilmiştir.

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Üye: Prof. Dr. Arif KIVRAK	İmza:
Üye: Dr. Öğr. Üyesi Salih ÖZÇUBUKÇU	İmza:

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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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Azad Khalaf HAMA

ABSTRACT

SYNTHESIS OF NOVEL BENZOTHIOPHENE DERIVATIVES VIA CYCLIZATION REACTIONS

HAMA, Azad Khalaf.
M.Sc. Thesis, Department of Chemistry
Supervisor: Prof. Dr. Arif KIVRAK
May 2019, 102 Pages

Benzothiophenes and their derivatives have been gained big importance as important candidates for pharmaceutical applications since they show remarkable analgesic, antibacterial, anti-inflammatory, antiparasitic, antifungal, hypoglycemic, antitumor and anticancer activities. They have also essential compounds for agrochemical and material sciences. Different kind of synthetic methods were employed for the synthesis of benzothiophene structures in literature. Moreover, they have been isolated from different kinds of plants and used to treat different type of diseases for many years. In the present study, a novel methodologies were investigated for the synthesis of anisole substituted benzothiophene derivatives. A variety of organic reactions were performed for the formation of desired benzothiophenes such as, Pd-catalyzed Sonogashira Coupling Reactions, Electrophilic Cyclization Reactions and Stille Coupling reactions. All synthesized compounds were characterized by using ^{1}H-NMR, ^{13}C-NMR, IR and HRMS.

Key words: Benzothiophenes, Cyclization reactions, Sonogashira coupling reactions.

ÖZET

YENİ BENZOTİYOFEN TÜREVLERİNİN HALKALAŞMA TEPKİMELERİ İLE SENTEZİ

HAMA, Azad Khalaf.
Yüksek Lisans Tezi, Kimya Anabilim Dalı
Tez Danışmanı: Prof. Dr. Arif KIVRAK
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Benzotiyofen 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. Yapısında benzotiyofen bulunduran moleküllerin sentezinde farklı sentetik metotlar kullanılmakla birlikte bazıları doğal ürün olarak çeşitli bitkilerden de elde edilebilmektedirler. Bu çalışmada biyolojik olarak aktivite gösterme potansiyeli olan benzotiyofen türevlerinin sentezi için yeni ve uygulanabilir metotlar geliştirilmiştir. Farklı sentez yöntemleri hedeflenen moleküllerin eldesi için kullanılmıştır. Bunlardan bazıları Pd-katalizörlü Sonogashira Kenetlenme Tepkimesi, Elektrofilik halkalaşma tepkimesi ve Suzuki-Miyaura kenetlenme tepkimesidir. Tepkimelerde elde edilen tüm ara ürün ve ürünlerin yapısal karakterizasyonları spektroskobik yöntemler (^{1}H-NMR, ^{13}C-NMR, IR ve Kütle) ile kesin olarak belirlenmiştir.

Anahtar kelimeler: Benezotiyofenler, Halkalaşma tepkimeleri, Sonogashira kenetlenme tepkimeleri.

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2019

Azad Khalaf Hama

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SYMBOLS AND ABBREVIATIONS

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

Symbols	Description
bs	Broad singlet
s	singlet (spectral)
d	doublet (spectral)
t	triplet (spectral)
q	quartet (spectral)
p	pentet (spectral)
m	multiplet (spectral)
δ	Chemical shift
ppm	parts per million (in NMR)
Hz	hertz
J	coupling constant
r.t	room temperature
hr	hour (s)
^{o}C	degree celcius
R	alkyl
Ar	aryl
mg	milligram
mL	milliliter
mmol	Millimole

Abbreviations	Description
$CDCl_3$	deuterochloroform
DCM	dichloromethane
DMF	N,N-dimethylformamide
Et_3N	triethylamine
EtOAc	ethyl acetate
MeOH	Methanol
NBS	N-bromosuccinicimide
THF	tetrahydrofuran
TMS	tetramethylsilane
TLC	thin-layer chromatography
HRMS	high resolution mass spectrometry
IR	Infrared
NMR	nuclear magnetic resonance
UV	Ultraviolet

1. INTRODUCTION AND LITERATURE REVIEWS

1.1. Heterocyclic Compounds

Heterocyclic compounds are the largest of the traditional divisions of organic chemistry and there are of huge importance biologically and industrially. For more than one century heterocyclic chemistry has been the largest area for research in organic chemistry. Heterocyclic compounds have been used in the development of biologically active compounds, also in the understanding of living processes and in improving the quality of life (Fadeyi et al., 2008).

Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon such as sulfur, oxygen and nitrogen as the common heteroatoms. The rings may be aromatic or non-aromatic according to the heteroatom(s) present in the ring structures. Heterocycles can be also classified as oxygen, nitrogen or sulfur based and, within each class, compounds are organized based on the size of the ring structure size determined by the total number of atoms. The type and size of ring structures together with the substituent groups of the core scaffold, impact strongly on the physicochemical properties. (Broughton and Watson, 2004; Gomtsyan, 2012).

The most common heterocyclices are those having five or six-membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S). The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan and thiophene. A molecule of pyridine contains a ring of six atoms-five carbon atoms and one nitrogen atom. Pyrrole, furan and thiophene molecules contains five-membered rings, composed of four atoms of carbon and one atom of nitrogen, oxygen and sulfur respectively (Figure 1.1) (Berquis et al., 1993). Heterocycles are important structural elements, which are present in natural products from all classes and also in many biologically active synthetic compounds. They often contribute significantly to their structural and physical properties as well as to their biological activity (Dua et al., 2011; Taylor et al., 2014).

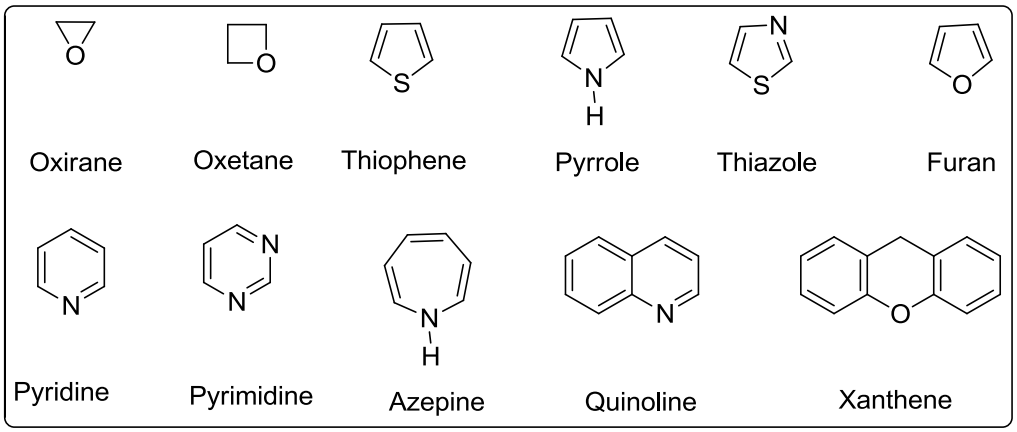


Figure 1.1. Some of heterocyclic compounds.

Oxygen heterocycles are mainly found in carbohydrates, polyketides, peptides and terpenoids. Nitrogen heterocycles are part of peptides and alkaloids. Both can of course also occur in the respective hybrid natural products. Sulfur-containing heterocycles are present in few polyketides and more widespread in peptidic natural products of both non-ribosomal and post-ribosomal modified origin (Fischbach and Walsh, 2006). Various compounds such as alkaloids antibiotic, essential amino acids, vitamin, hormone, hemoglobine, large number of dyes and synthetic drugs contain hetero cyclic ring systems (Mohammad and Mustapha, 2010).

Derivatives of the simple fused ring heterocycle purine constitute an especially important and abundant family of natural products. The amino compounds adenine and guanine are two of the complementary bases that are essential components of DNA, structures for these compounds are shown in the (Figure 1.2). Xanthine and uric acid are products of the metabolic oxidation of purines, uric acid is normally excreted in the urine an excess serum accumulation of uric acid may lead to an arthritic condition known as gout. Heterocyclic aromatic compounds are widely distributed pollutants in soil, air, sediments, surface water and groundwater, as well as in animal and plant tissues (Brack and Schirmer, 2003).

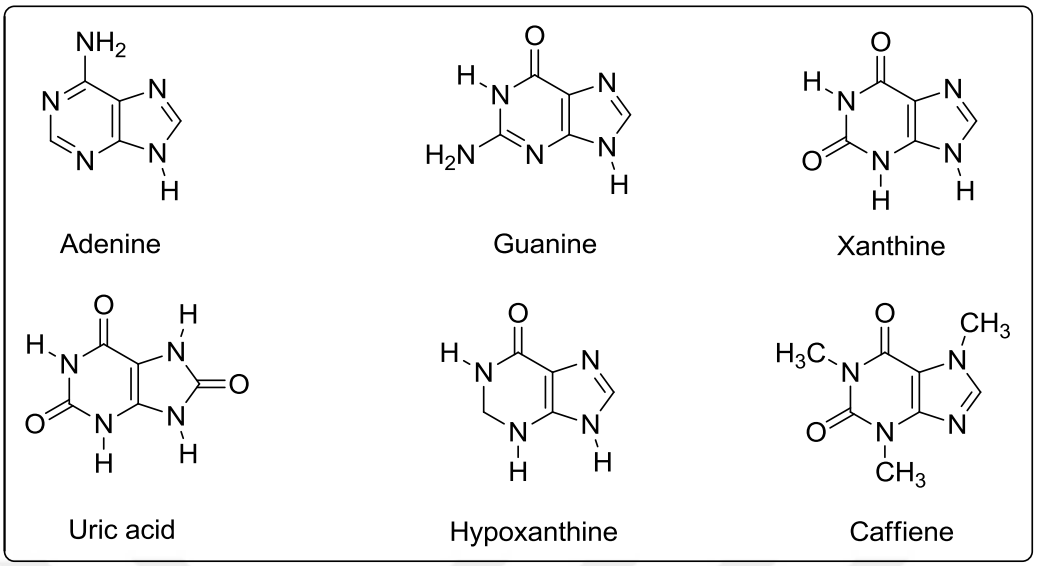


Figure 1.2. Purine derivatives.

Thiamine, pyridoxal, riboflavin and niacinamide are members of the vitamin-B complex is shown in (Figure 1.3) (Winklera et al., 2005). By increasing world's population and health troubles enlarge consequently need to find out new therapeutics for humanity, the design of drugs gives successful hopes in present and future technology since pharmacologically active heterocyclic compounds have vast role in regular clinical use (Patel and Mehta, 2010).

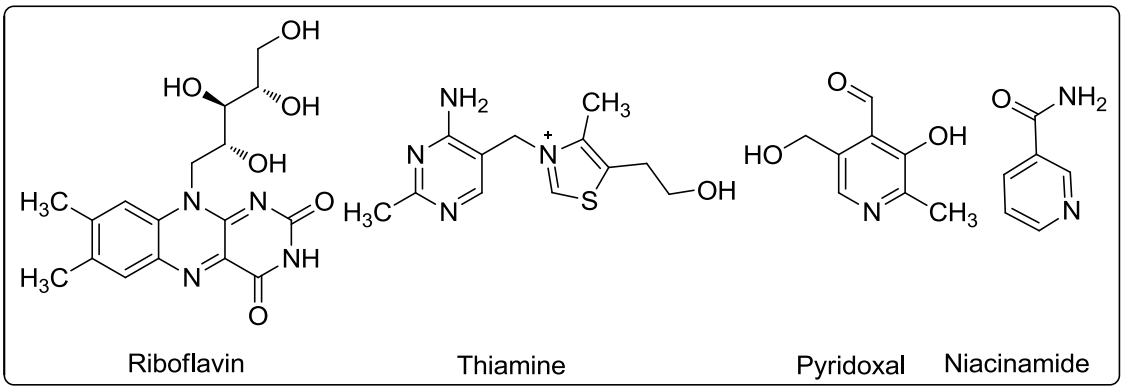


Figure 1.3. Some examples of vitamins.

Heteroaromatic compounds have very important roles in the discovery and development of new drug candidates due to their biological and pharmacological

properties (Brasholz et al., 2009; Kivrak, 2010). They have been used as anti-parasitic (Coa et al., 2015), anti-bacterial (Shakdofa et al., 2014), anti-cancer (Rahmouni et al., 2016), anti-fungal (Pathak et al., 2012), anti-inflammatory (Kazemizadeh et al., 2016) and antioxidant (Richardson et al., 2009) drugs for years. In addition, they are known as strong inhibitors of lipid peroxidation (Williams et al., 2004), potassium channel openers (Edwards and Weston, 1993), topoisomerase inhibitors (Pommier, 2006) and L1210 cell selectors (Grynyuk et al., 2016). Therefore heterocyclic chemistry is very important in the pharmaceutical industry for the synthesis of new drugs (Figure 1.4).

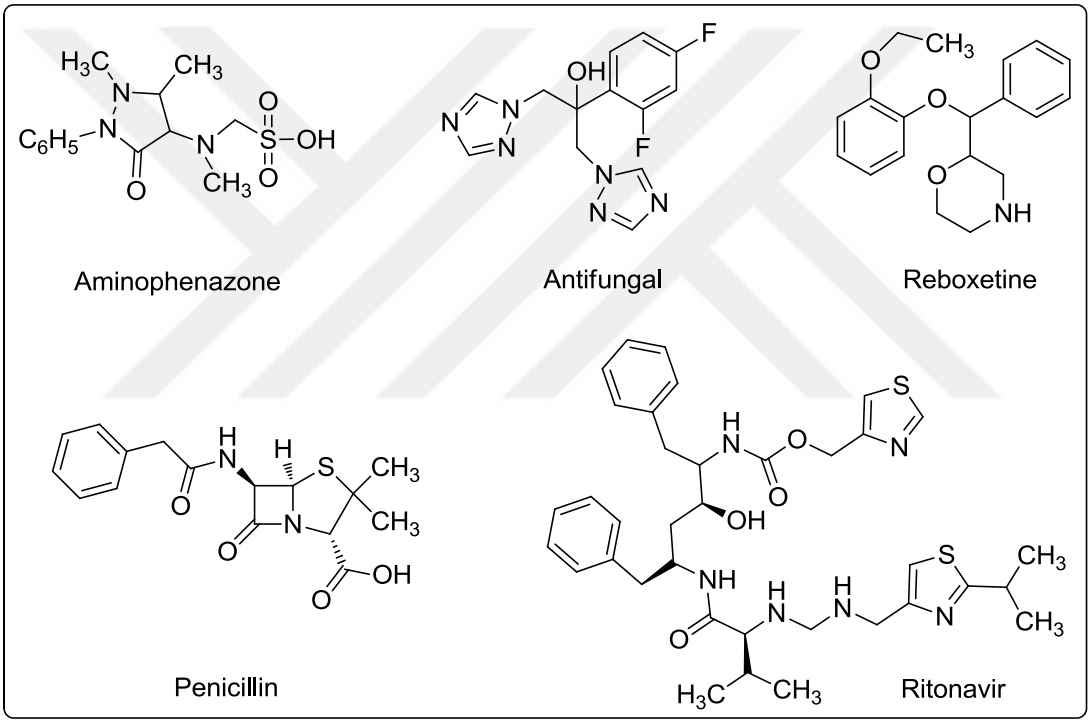


Figure 1.4. Pharmacologically active heterocyclic compounds.

1.2. Thiophene and Benzothiophene Compounds

1.2.1. Thiophenes

Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S (Figure

1.5). Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word theion, is the Greek word for sulfur, and another Greek word phaino which means shinning. The thiophene structure can be found in certain natural products and is incorporated in several pharmacologically active compounds (Mishra et al., 2011). The simple thiophenes are stable liquids which closely resemble the corresponding benzene compounds in boiling point and even in smell. They occur in coal tar distillates. The discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry.

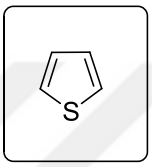


Figure 1.5. Thiophene structure.

Thiophenes are very essential classes of heterocyclic compounds which have possess exciting biological properties in addition to interesting utilization as construction blocks and reagents in organic synthesis. The thiophene stability plays a widely role in development and preparing different sorts for experimentation in the clinical/medical and pharmaceutical fields and plenty of drugs contain this heterocyclic core in the structure (Ward, 1994). Such as Spiriva, Xarelto, Plavix and Invokana are drugs in (Figure 1.6) (Sperry and Wrigh, 2005; Mohareb et al., 2014). In the other hand, thiophene derivatives have observed vast application in material science (Barbarella et al., 2005; Mishra, 2009), also in the field of pharmaceuticals such as antidepressants (Duloxetine), neuroleptics (Olanzapine), anthelmintics (Pyrantel), antidiabetics (Canagliflosin), antihistamines (Ketotifen), antiplatelets (Ticlopidine, Clopidogrel), antihypertensives (Eprosartan), antispasmodics (Tiemonium), analgesics (Sufentanil) and antimetabolics (Ralitrexed), these materials are contained thiophene structure (Sheridan, 2002), also includes anti-Alzheimer molecules (Yuan et al., 2013), anti-infectives and antiproliferative agents (Jun et al., 2014). Additionally, the thiophene ring has important application for many materials, for example liquid crystalline materials, light emitting, (Masui et al., 2004) and dyes for molecular photovoltaic (Koumura et al., 2006).

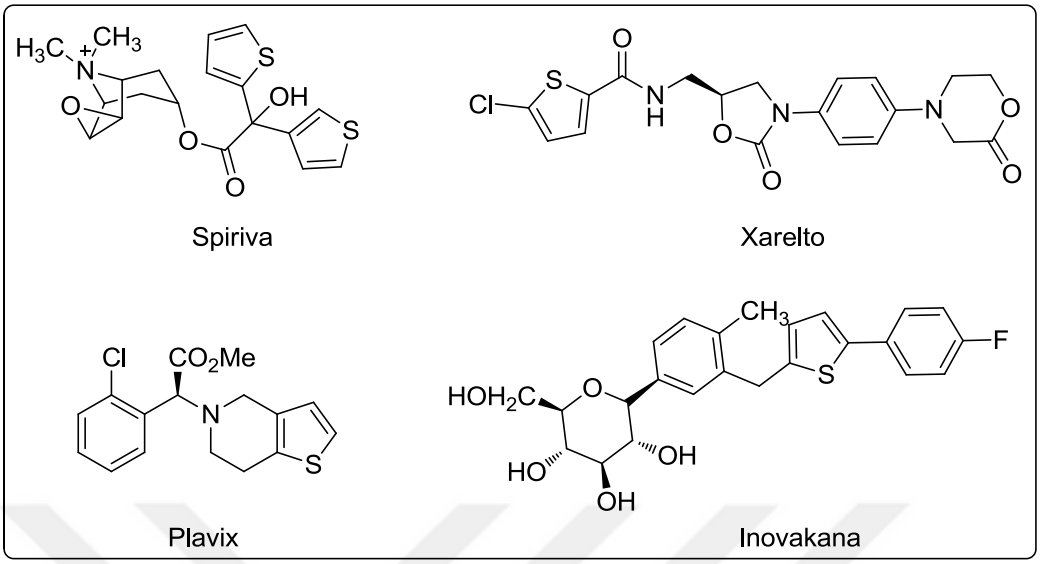


Figure 1.6. Some of drugs containing thiophene structure.

Thienothiophenes, consisting of two fused thiophene heterocycles have four isomers, namely, thieno[3,2-b]thiophene (a), thieno[2,3-b]thiophene (b), thieno[3,4-b]thiophene (c) and thieno[3,4-c]thiophene (d) (Figure 1.7) (Cinar and Ozturk, 2015), numerous fused thiophenes with various molecular structures have been designed as organic semiconductors in recent years (Kumaresan et al., 2014; Buyruk et al., 2016; Sevinis et al., 2016; Turkoglu, 2018).

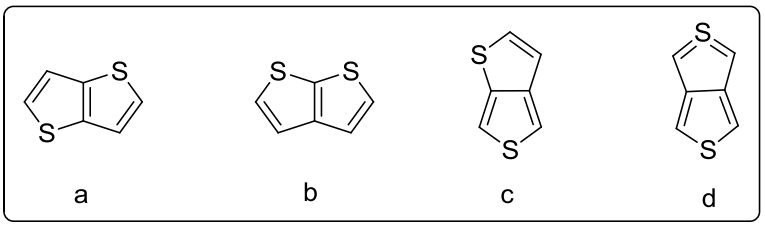


Figure 1.7. Thienothiophene isomers.

Synthetic methods involving sulfur-containing heterocycles have attracted significant attention. Thiophenes can undergo different reactions, such as pericyclic, electrophilic substitution and nucleophilic substitution reactions. However, the C-2 position of thiophene is the most reactive site, and numerous reactions have been reported such as

alkylation (Huang et al., 2005; Podder et al., 2007; Majer et al., 2009), arylation (Okazawa et al., 2002; Roger and Doucet, 2008; Hfaiedh et al., 2015), halogenation and homocoupling (Masui et al., 2004; Takahashi et al., 2006).

1.2.2. Benzothiophenes

The family of sulfur heterocycles includes highly stable aromatic compounds that display physicochemical properties with relevance in the design of new materials, especially those relating to molecular conductors and magnets (Cava et al., 1975; Shishoo and Jain, 1992). During the past few decades, interest has been rapidly growing in gaining insight into the properties and transformations of these heterocyclic systems owing to their potential applications. Among the sulfur heterocycles benzothiophene is a unique heterocyclic core that has been picturized as an important pharmacology of some bioactive molecules and therefore fascinated much interest (Bosin and Campaigne, 1977). Benzothiophene is a bicyclic (g) system in which benzene ring (f) is fused to the thiophene ring (e) at 4,5-positions. The positions of benzothiophene ring are numbered starting from heteroatom sulfure, as shown in (Figure 1.8).

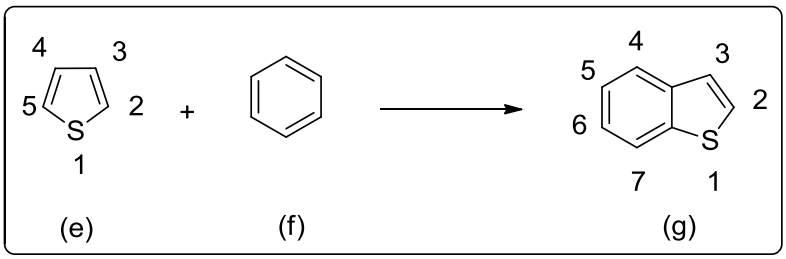


Figure 1.8. Numbering and tautomerism in benzothiophene.

Benzothiophene occurs naturally as a constituent of petroleum-related deposits such as lignite tar (Boberg et al., 1992), present in some natural products and its derivatives having diverse applications in medicinal chemistry and attracting great interest in industry as well as academia. They exhibit the wide range of biological/pharmacological activities such as anti-inflammatory, analgesics (Fakhr et al., 2009), anti-fungal (Jagtap and Agasimundin, 2015), antidepressant (Berrade et al.,

2011), estrogen receptor modulating (Qin et al., 2007), anti-mitotic (Romagnoli et al., 2007), enzyme inhibitors (Mourey et al., 2010), anticancer (Martorana et al., 2015; Sweidan etal., 2015), kinases inhibiting (Loidreau et al., 2015), anti-tubercular (Rao and Subramaniam, 2015), anticonvulsant (Zaher et al., 2010), anti-malarial (Banerjee et al., 2011; Rackham et al., 2013), anthelmintic (Naganagowda and Padmashali, 2010), antidiabetic, anti-hyperglycemic (Malamas et al., 2000), anti-angiogenic, bryoanthrathiophene (Kelly et al., 2000; Jeong et al., 2002) and pesticides (Kennedy and Summers, 1981). In additions, benzothiophene derivatives have been used as potential diagnostic agents in neurodegenerative disease for the treatment of Alzheimer's disease (Chang et al., 2006; Yang and Cui, 2014), inhibitors of human nicotinamide phosphoribosyltransferase (Chen et al., 2016), histamine antagonists (Santillan et al., 2010), Rho kinase inhibitors (Davis et al., 2010), inhibitors of fatty acid amide hydrolase (Johnson et al., 2009), antiallergy agents (Connor et al., 1992) and many other activities. Some of the benzothiophene derivatives including raloxifene, sertaconazole, benocyclidine, mobam and zileuton is shown in (Figure 1.9) (Jordan, 2003).

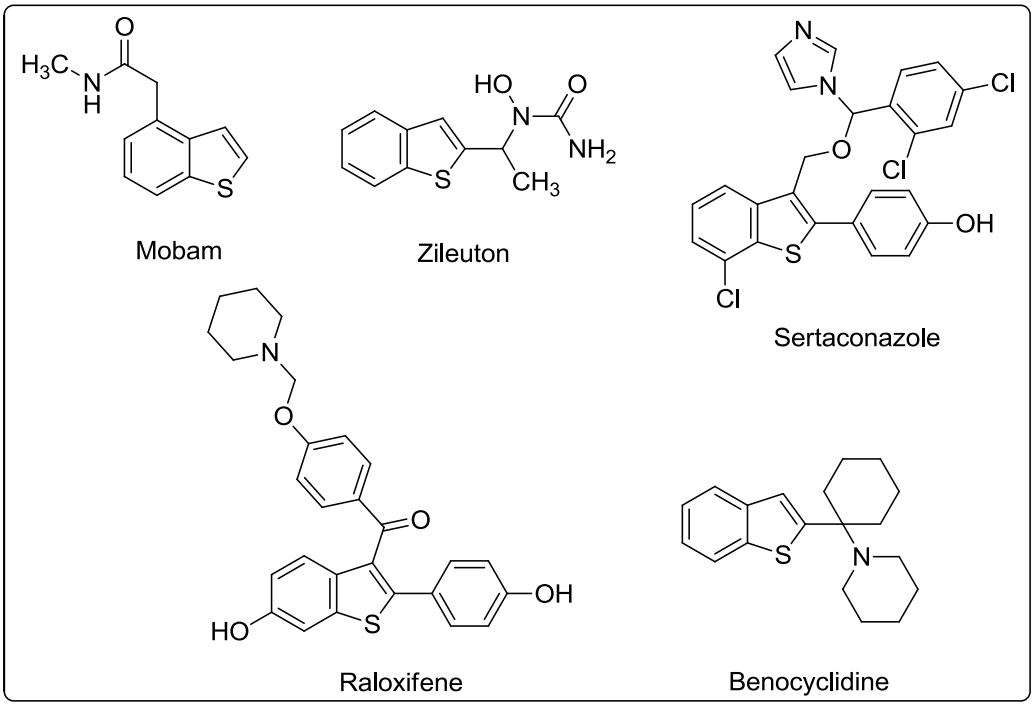


Figure 1.9. Drugs containing benzothiophene in thier ring sekelton.

The numbers of synthetic routes have been reported for the synthesis of benzothiophenes. Traditionally, an acid catalyzed domino cyclization/rearrangement reaction of a b-ketosulfide (a) to form 2-arylbenzothiophene (b) is widely accepted and used. Another strategy utilizes the Knoevenagel condensation of an S-benzyl ortho-acylthiophenol (d), generated in situ from an ortho-fluoroketone (e) and a benzyl thiol (f) (Kuhn et al., 2011). Willis and co-workers reported a pd-catalyzed approach, which uses an intramolecular C-S coupling reaction of an aryl halide with a thioketone (Willis et al., 2006). This methodology was originally developed for benzofuran formation from the oxygen analogues of thioketone (g), and the authors found that the same conditions were effective for sulfur compounds, giving fused benzothiophenes in moderate to good yields (c). More recently, a number of conceptually different approaches have been developed which disconnect different bonds of the benzothiophene ring (h). Catalytic approaches are of particular interests (Nakamura et al., 2004) (Figure 1.10).

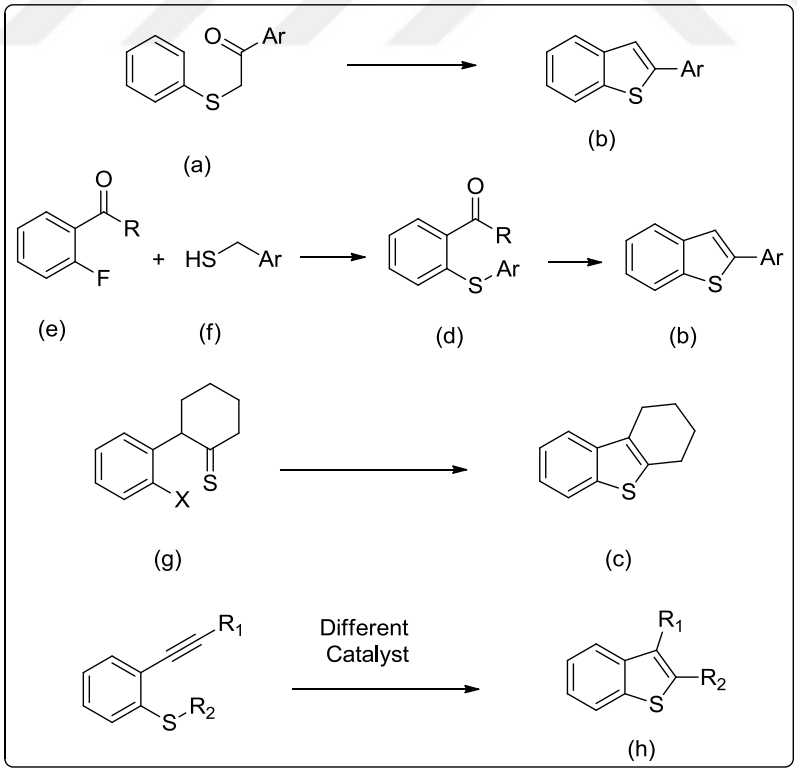


Figure1.10. Current approach for the synthesis benzothiophene derivatives.

Castle and co-workers are investigated 3-Chlorobenzo[b]thiophene-2-carboxyl chloride (j) was prepared from both cinnamic acid (i) and thionyl chloride by using pyridine as the catalyst in a medium chlorobenzene shows in (Figure 1.11) (Castle et al., 1987).

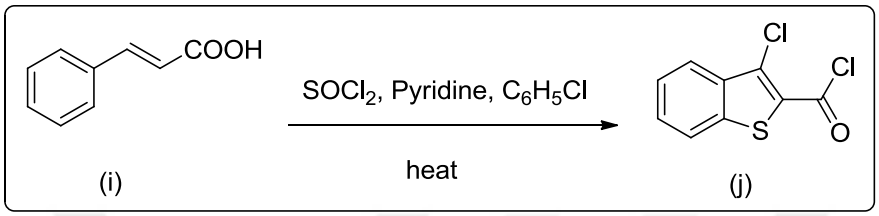


Figure 1.11. Synthesis of 3-Chlorobenzothiophene-2-carboxyl chloride.

1.3. Palladium Catalyzed Cross Coupling Reactions

The palladium-catalyzed cross-coupling application continues to serve as a remarkably powerful tool for the synthesis of new carbon-carbon and carbon-heteroatom bonds (Gildner and Colacot, 2015; Ruiz-Castillo and Buchwald, 2016), the significant improvements in catalyst design have propelled the technology forward in recent years. Central to these advancements has been the evolution of designer ligands which have allowed access to new catalyst systems that are capable of linking a broader range of coupling partners to carbon under milder reaction conditions or with lower catalyst loadings. Many of the more versatile ligands include monodentate and bidentate phosphine ligands (Hama et al., 2003; Hartwig, 2008; Fleckenstein and Plenio, 2010).

Palladium-catalyzed cross-coupling reactions are of strategic importance in the assembly of highly functionalized organic molecules (Nicolaou et al., 2005; Mandal et al., 2013). These reactions are typically performed under mild conditions, and are extensively used in the assembly of active pharmaceutical ingredients (Chemler et al., 2001; Pagliaro et al., 2012). Homogeneous palladium catalysis has gained enormous relevance in various coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Buchwald-Hartwig reactions (Figure 1.12). This type of catalysis provides high selectivities and yields (Garrett and Prasad, 2004; Welch et al., 2005).

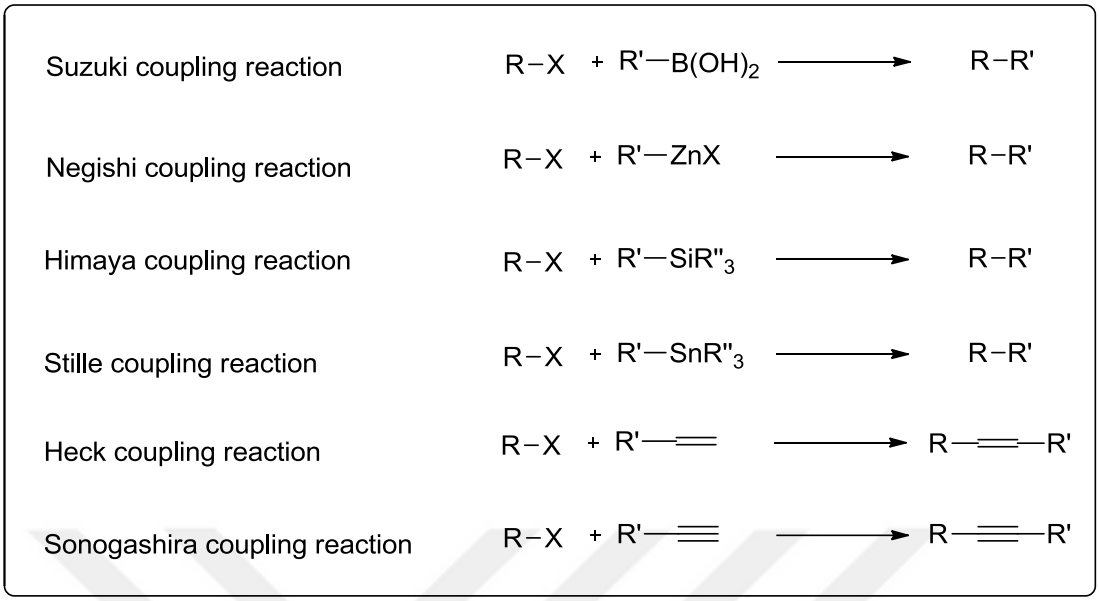


Figure 1.12. Palladium-catalyzed cross coupling reactions.

1.3.1. Stille Coupling reactions

The palladium catalyzed Stille reaction involves the coupling of an organotin compound with a variety of organic halide. This transformation has become a useful synthetic tool for carbon–carbon bond formation and can also be extended to numerous organic electrophiles that are shown in (Figure 1.13) (Stille, 1986). These reactions have been used in the syntheses of various biaryl compounds, which are important intermediates in the syntheses of natural products, functionalized polymers, and pharmaceuticals (Bringmann and Menche, 2001; Bringmann et al., 2004; Roberts et al., 2007).

The proposed mechanism for this coupling reaction is displayed in (Figure 1.14). and follows the general principles of other cross-coupling reactions catalyzed by transition metals (Espinet and Echavarren, 2004).

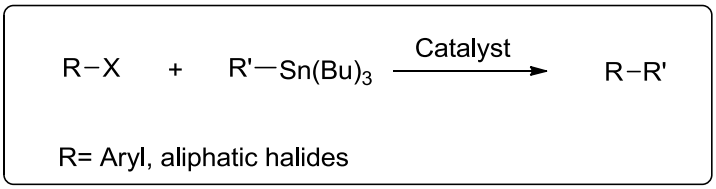


Figure 1.13. Stille coupling reaction.

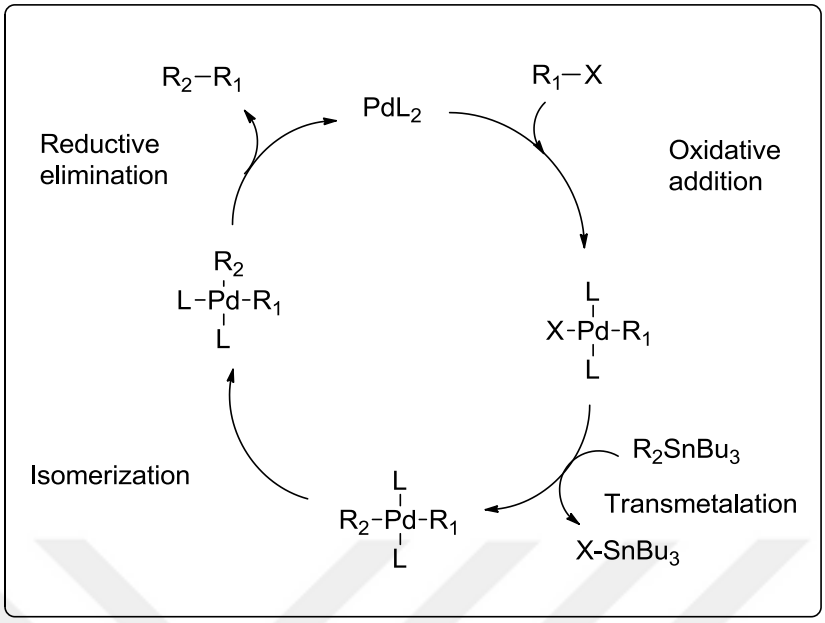


Figure 1.14. Proposed mechanism of Stille coupling reaction.

1.3.2. Sonogashira Coupling Reactions

One of the most important methods for the preparation of aryl-alkynes and conjugated enynes is the palladium-catalyzed coupling of terminal alkynes with aryl or vinyl halides which was described for the first time by Sonogashira (Sonogashira et al., 1975). Usually, the Sonogashira coupling is carried out in the presence of catalytic amounts of a palladium(II) complex as well as copper(I) iodide in an amine as solvent (Figure 1.15).

The Sonogashira coupling reaction is frequently utilized as a key step in natural product synthesis (Brandsma et al., 1998). Recent applications of this reaction include the synthesis of oligomeric, polymeric, and dendritic acetylene compounds, which are potentially useful in optical and electronic applications (Maier, 1995; Grissom et al., 1996). Sonogashira coupling reactions need simple reaction conditions such as lower temperature and shorter reaction time. Moreover, Sonogashira coupling reactions give the high yields and regioselectivity. General reaction mechanism of Sonogashira coupling reactions are shown in (Figure 1.16).

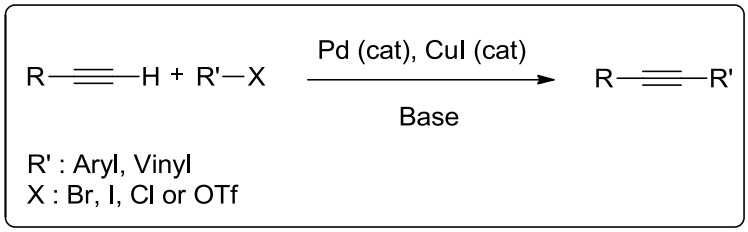


Figure 1.15. Sonogashira coupling reaction.

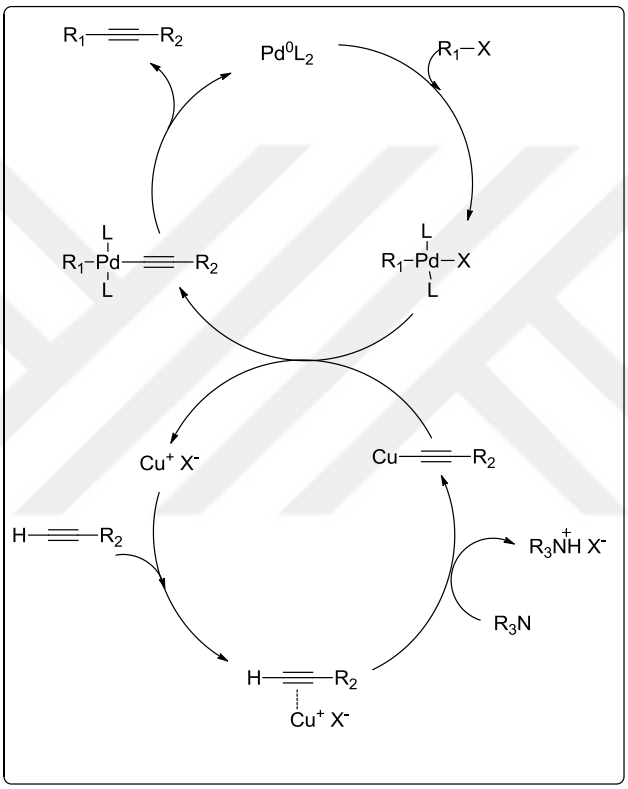


Figure 1.16. Mechanism of Sonogashira coupling reaction.

1.4. Electrophilic Cyclization Reactions

Alkynes are versatile building blocks in organic synthesis, a wide range of carbocycles and heterocycles have been prepared by the electrophilic cyclization of functionally substituted alkynes and by transition metal-catalyzed annulations. 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, 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 1.17).

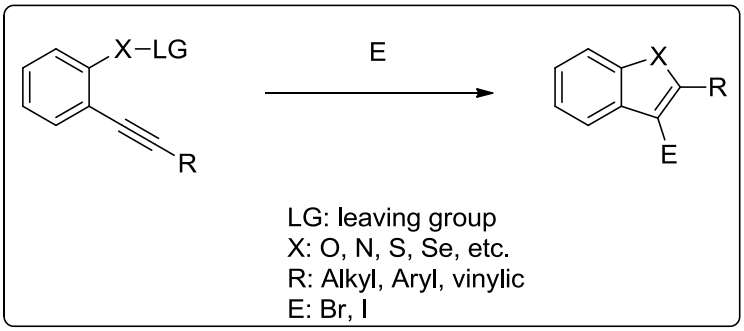


Figure 1.17. Electrophilic cyclization reaction.

Recently, it was reported the electrophilic cyclization reaction of alkynes by using halogen, sulfur and selenium electrophiles can be a very powerful tool for the preparation of a variety of interesting carbocyclic and heterocyclic compounds, including benzofurans (Yao et al., 2005) furans (Sniady et al., 2005; Arimitsu et al., 2008), benzothiophenes (Yue and Larock, 2002; Hessian and Flynn, 2003), thiophenes, benzopyrans (Worlikar et al.,2007), benzoselenophenes (Bui and Flynn, 2006), selenophenes (Alves et al., 2007), naphthols (Zhang et al., 2006), indoles (Barluenga et al., 2003; Amjad and Knight , 2004), quinolines (Zhang et al., 2005), isoquinolines (Fischer et al., 2007; Huang et al., 2002), α-pyrones, isocoumarins (Yao and Larock, 2003), isochromenes (Barluenga et al., 2003; Yue et al., 2006), isoindolinones (Yao and Larock, 2005), naphthalenes (Barluenga et al., 2003) and polycyclic aromatics (Yao et al., 2005), isoxazoles (Waldo and Larock, 2007), chromones (Zhou et al., 2006; Likhar et al., 2008), bicyclic lactams (Ren et al., 1998), cyclic carbonates (Marshall and Yanik, 1999), pyrroles (Knight et al., 1998), furopyridines (Arcadi et al., 2002), spiro[4.5]trienones (Tang et al., 2008), coumestrol and coumestans (Yao et al., 2005), furanones (Crone and Kirsch, 2007), benzothiazine-1,1-dioxides (Barange et al., 2007) etc. Heterocyclic rings can be formed through endo or exo cyclization modes, depending on the chain length, the substitution pattern on the chain, and the electrophile employed (Figure 1.18).

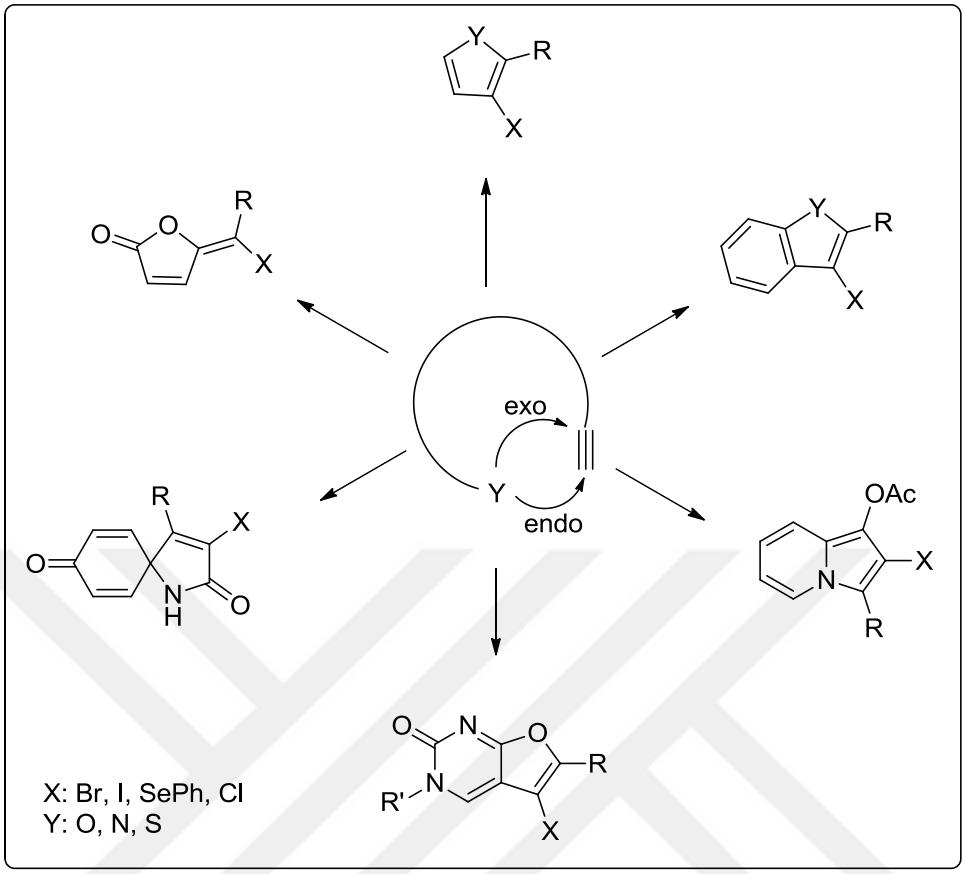


Figure 1.18. Heterocycles formed via electrophilic cyclization reactions.

Electrophilic cyclization reactions are generally very efficient, provide clean reactions, proceed under very mild reaction conditions, and tolerate nearly all critical functional groups. Additionally, the iodine-obtaining products can be further elaborated to a broad range of functionally substituted derivatives utilizing subsequent palladium-catalyzed processes. These reactions are typically believed to continue by a stepwise mechanism including activation electrophiles on the alkyne carbon-carbon bonds, intramolecular nucleophilic attack on the cationic intermediates, and subsequent dealkylation (Figure 1.19)

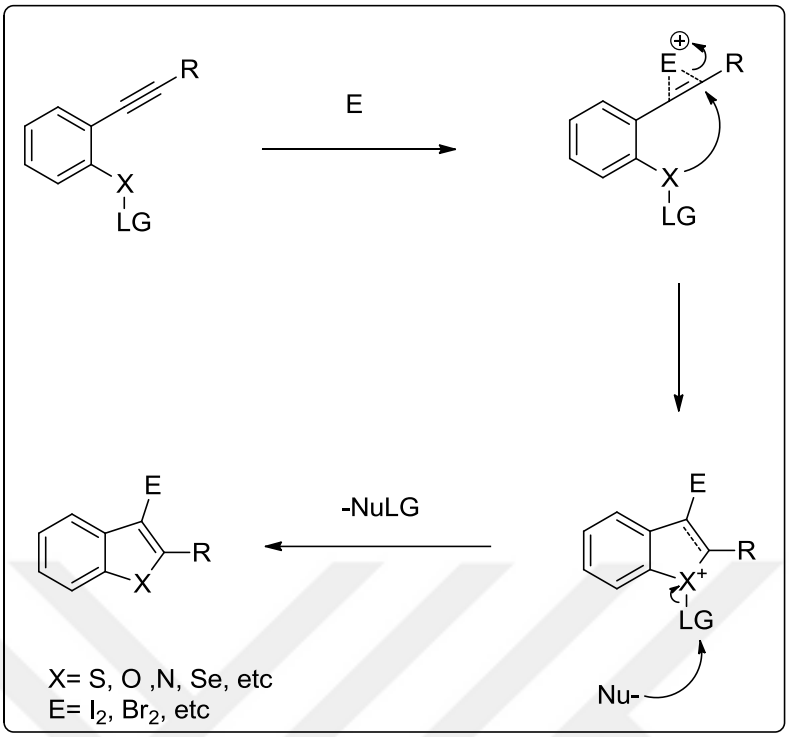


Figure 1.19. General mechanism electrophilic cyclization reaction.

1.5. The Aim of Study

The purpose of this thesis was to developed new methodologies for the synthesis of novel benzothiophene derivatives containing anisole-thiophene moities. In the first part of study, necessary alkynyl structure was synthesized starting from anisole by using palladium catalyzed coupling reactions. Then, we investigated electrophilic cyclization reactions for the formation of 3-iodo-benzothiophene derivatives. Finally, Pd-catalyzed Sonogashira cross coupling reactions and Stille coupling reactions were used for the synthesis of novel benzothiophene derivatives (Figure 1.20).

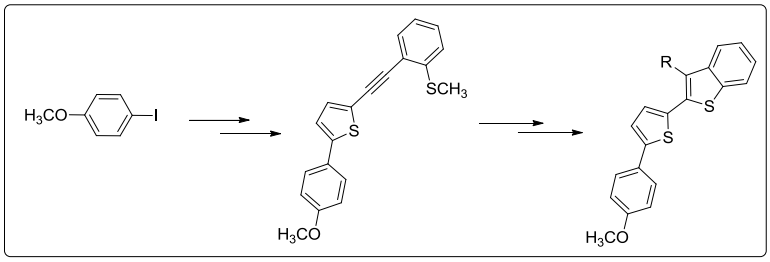


Figure 1.20. Synthesis of benzothiophene derivatives.

2. MATERIALS AND METHODS

2.1. Methods and Apparatuses

Characterization of the molecules was carried out by infrared, mass, and nuclear magnetic resonance spectra ^{1}H and ^{13}C-NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent NMR (400 MHz) Spectrometer using $CDCl_3$ as solvent. Spectra were processed with MestReNova software. In addition, using tetramethysilane (TMS) as an internal reference and the chemical shift values (δ) are given in parts per million (ppm). The ^{1}H NMR data are reported different spin multiplicity were showed by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet) m (multiplet), brs (broad singlet), coupling constants (*J*), were reported in hertz (Hz) and number of protons. The ^{13}C NMR data are reported types of carbon that includes: C, CH, CH_2, and CH_3. All reactions were monitored by thin layer chromatography (TLC) coated with (0.25 mm) silica gel plates, and visualization was achieved using UV light flash chromatography was performed by using silica gel (Merck 230−400 mesh), using the mobile phase indicated. Separation and Purification of compounds were checked by TLC after that by column chromatography. All of the organic solvents were dried over appropriate drying agents and distilled prior to use. Unless otherwise noted, organic extracts were dried with $MgSO_4$.

2.2. Synthesis of Compounds

2.2.1. Synthesis of benzothiophene derivatives

2.2.1.1. Synthesis of 2-(4-methoxyphenyl)thiophene (AD1)

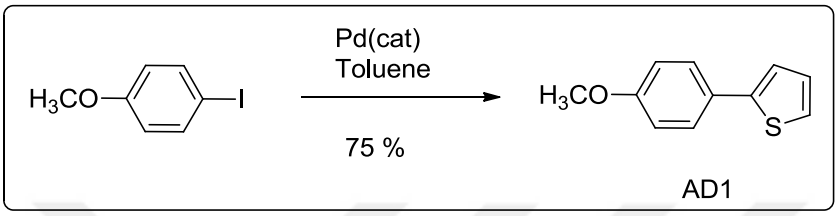


Figure 2.1. Synthesis of compound AD1.

To a solution of the 4-iodoanisole (23.4 mg, 0.1 mmol) and 2-(tributylstannyl)thiophene (0.2 mmol) in toluene were added $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol) under argon athmosphere at room temperature. Then, reaction mixture was stirred at 110 ^oC for 3 hours. After reaction was over, the resulting mixture was extracted with DCM (3x20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) as the eluent to afford the 2-(4-methoxyphenyl)thiophene AD1 (75% yield) as a white solid (Figure 2.1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 2H), 7.22-7.25 (m, 2H), 7.08 (q, J = 3.84 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H, Ar-OCH_3) (Figure 2.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 144.4, 128.0, 127.3, 127.2, 123.8, 122.1, 114.3, 55.3 (Figure 2.3); IR (KBr, thin film) ν_{max} (cm^{-1}): 3098.9, 3074.2, 3003.5, 2961.1, 2913.4, 2835.1, 1974.4, 1883.9, 1800.2, 1734.3, 1604.7, 1570.4, 1498.5, 1454.4, 1244.3, 1030.4, 697.0, HRMS calcd for $C_{11}H_{10}OS$, 190.0452 $[M+H]^+$, found 190.0503 $[M+H]^+$.

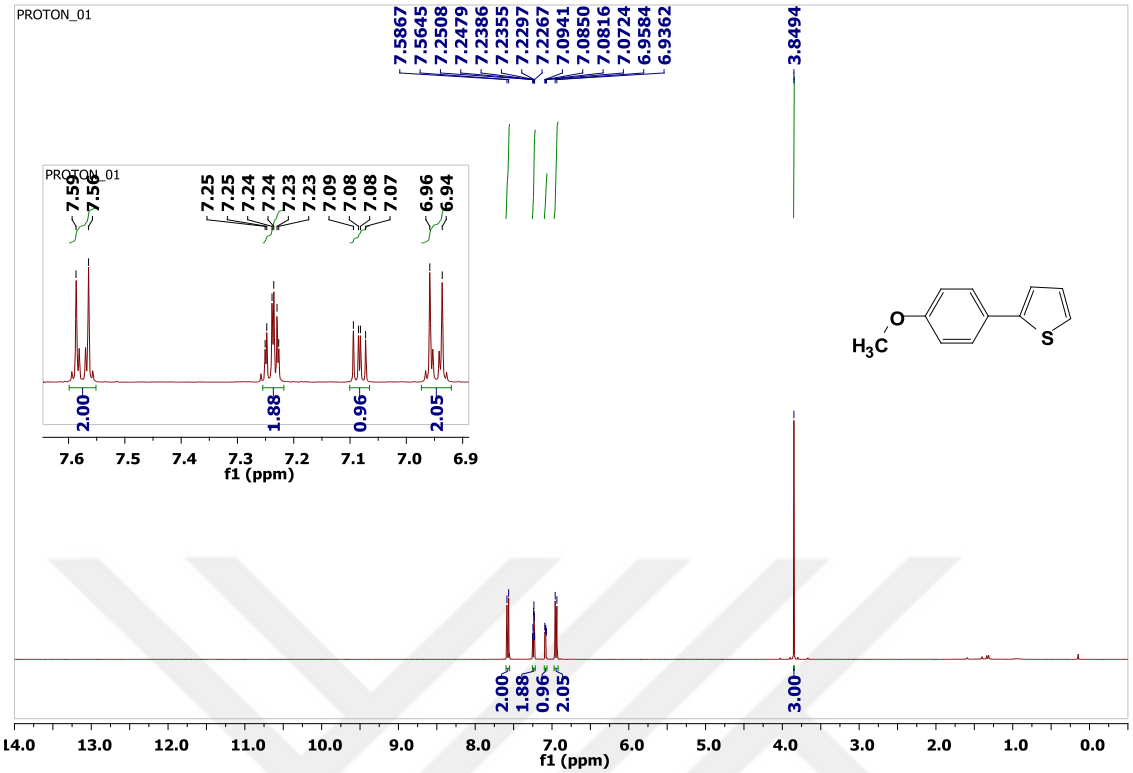


Figure 2.2. ^{1}H NMR spectra of AD1.

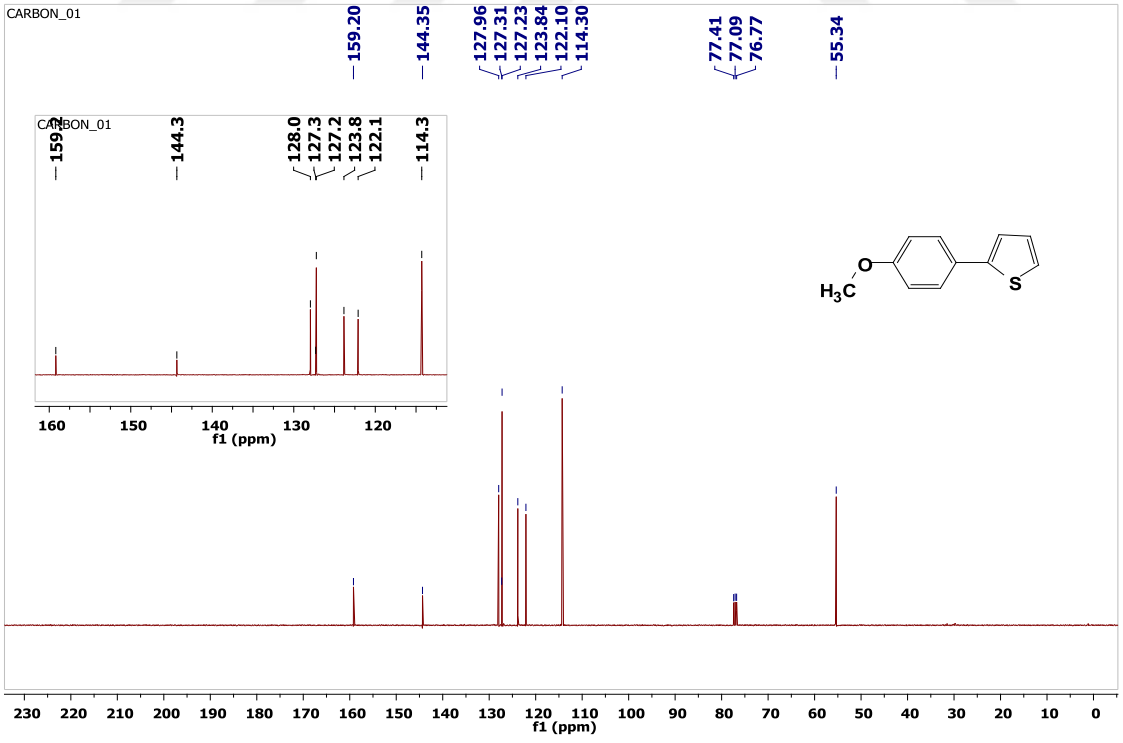


Figure 2.3. ^{13}C NMR spectra of AD1.

2.2.1.2. Synthesis of trimethyl((2-(methylthio)phenyl)ethynyl)silane (AD2)

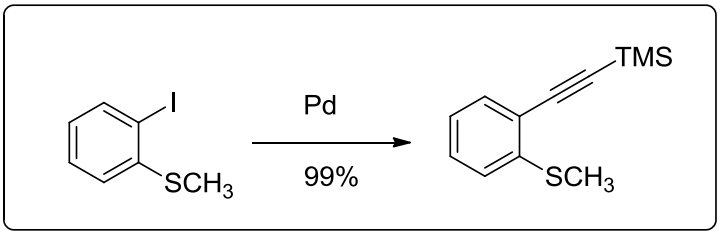


Figure 2.4. Synthesis of compound AD2.

To a stirred solution of 2-iodothioanisole (620.3 mg, 2.48 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol) in THF (10 mL) and triethylamine (10 mL) under argon were added trimethylsilylacetylene (304.8 mg, 3.1 mmol) and CuI (11.4 mg, 0.06 mmol). The mixture was stirred at room temperature for 3 hours. After reaction was over, the resulting solution was diluted with satd.brine and extracted with EtOAc (3x20 mL). The combine organic phase was dried with anhydrous $MgSO_4$. After filtration and evaporated to removal solvent, the residue purified by using flash column chromatography on silica gel using Hexane/Ethyl acetate (50:1) as the eluent to afford the desired product AD2 (99 % yield) as a pale yellow oil (Figure 2.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.64 Hz, 1H), 7.27 (td, *J* = 7.68 and 1.36 Hz, 1H), 7.12 (d, *J* = 7.92 Hz, 1H), 7.05 (t, *J* = 7.56 Hz, 1H), 2.46 (s, 3H, Ar-SCH_3), 0.31 (s, 9H of TMS) (Figure 2.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 132.6, 129.0, 124.0, 123.8, 121.1, 102.2, 101.3, 14.9, 0.0 (Figure 2.6); IR (KBr, thin film) ν_{max} (cm^{-1}): 3059.5, 2980.6, 2920.7, 2890.6, 2154.7 (C≡C), 1435.6, 1248.3 (Si-CH_3), 838.1, 747.6, 685.2 (S-C), HRMS calcd for $C_{12}H_{16}SiS$, 220.0742 $[M+H]^+$, found 220.0742 $[M+H]^+$.

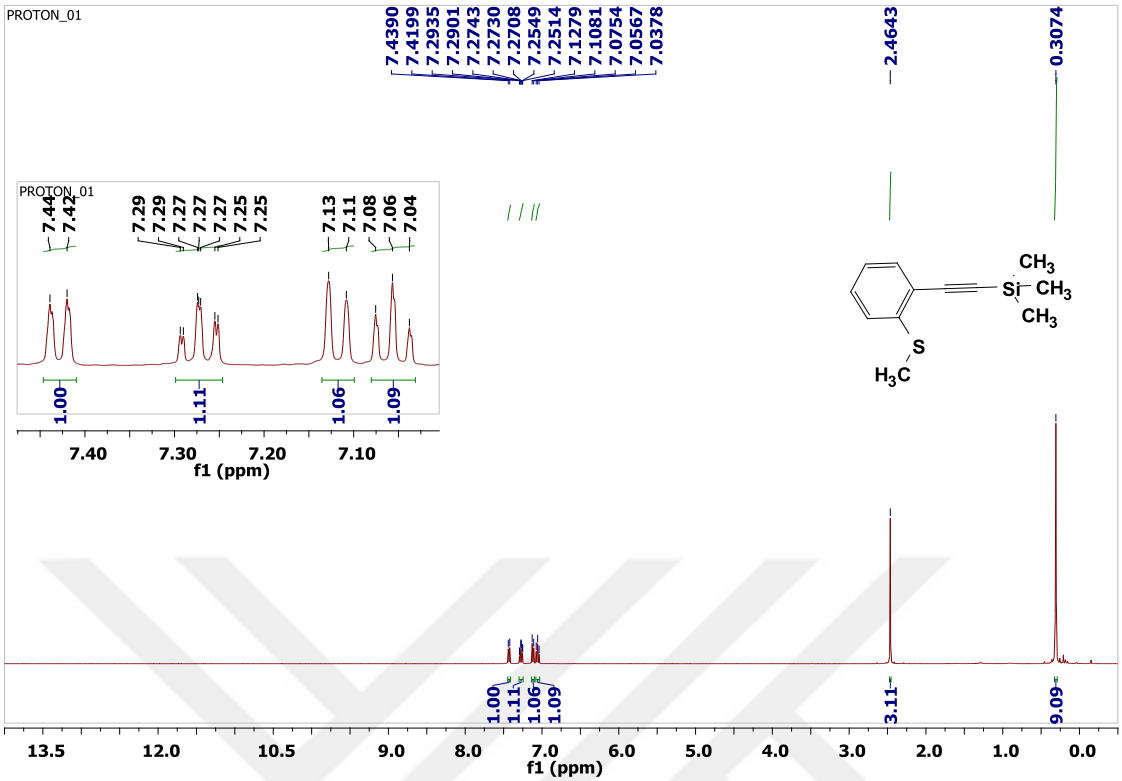


Figure 2.5. ^{1}H NMR spectra of AD2.

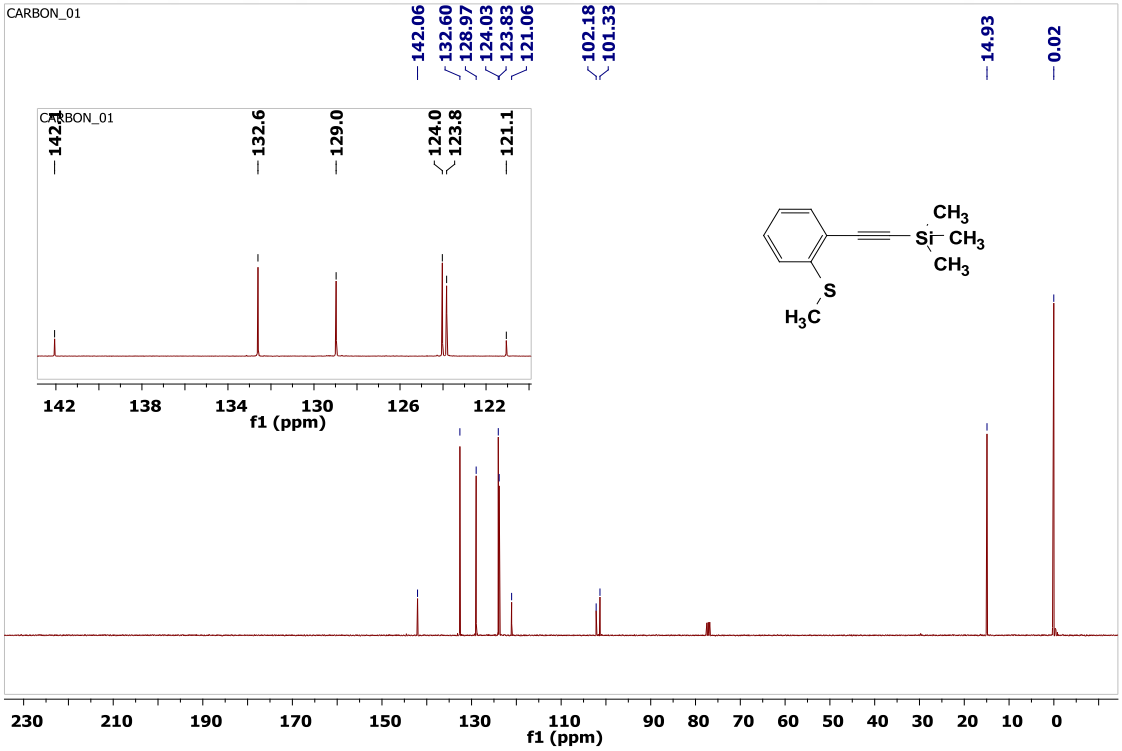


Figure 2.6. ^{13}C NMR spectra of AD2.

2.2.1.3. Synthesis of 2-bromo-5-(4-methoxyphenyl)thiophene (AD3)

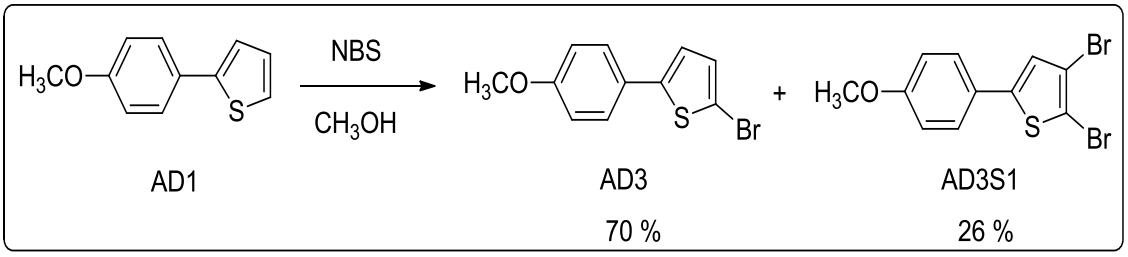


Figure 2.7. Synthesis of AD3 and AD3S1.

To a solution of AD1 (298 mg, 1.56 mmol) and NBS (278.0 mg, 1.56 mmol) in chloroform (20 mL) was stirred at 0 ^{o}C for 4 hours. After reaction was over, the resulting solution was diluted with satd.brine, and extracted with chloroform (3x20 mL). The combine organic phase was dried with anhydrous $MgSO_4$. After filtration and evaporated to removal solvent, the residue purified by using flash column chromatography on silica gel using Hexane/Ethyl acetate (50:1) as the eluent to afford two different compounds AD3 as a white solid (70 % yield) and AD3S1 as a white solid (26 % yield) (Figure 2.7.).

AD3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.84 Hz, 2H), 7.01 (d, *J* = 3.84 Hz, 1H), 6.93 (d, *J* = 3.84 Hz, 1H), 6.91 (d, *J* = 8.84 Hz, 2H), 3.83 (s, 3H, Ar-OCH_3) (Figure 2.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.8, 130.8, 126.9, 126.5, 122.2, 114.4, 110.2, 55.4 (Figure 2.9); IR (KBr, thin film) ν_{max} (cm^{-1}): 3095.3, 3057.9, 3013.6, 2953.66, 2915.6, 2837.04, 1971.9, 1882.6, 1745.1, 1606.3, 1537.4, 1502.4, 1467.1, 1434.8, 1285.0, 1178.1, 1112.5, 1030.7, HRMS calcd for $C_{11}H_9OSBr$, 269.9537 $[M+H]^+$, found 269.9587 $[M+H]^+$.

AD3S1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 2.24 and 2.04 Hz, 2H), 7.01 (d, *J* = 2.28 Hz, 1H), 6.95 (dd, *J* = 2.2 and 2.04 Hz, 2H), 3.85 (s, 3H, Ar-OCH_3) (Figure 2.10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 134.0, 133.5, 130.2, 124.4, 114.1, 110.8, 106.1, 55.4, (Figure 2.11); IR (KBr, thin film) ν_{max} (cm^{-1}): 3086.3, 3005.0, 2959.5, 2927.0, 2833.1, 1918.9, 1847.8, 1641.3, 1608.0, 1537.4, 1573.5, 1495.9, 1452.6,

1248.7, 1175.6, 1110.3, 1032.4, 980.7, HRMS calcd for $C_{11}H_8OSBr_2$, 347.8642 $[M+H]^+$, found 347.8652 $[M+H]^+$.

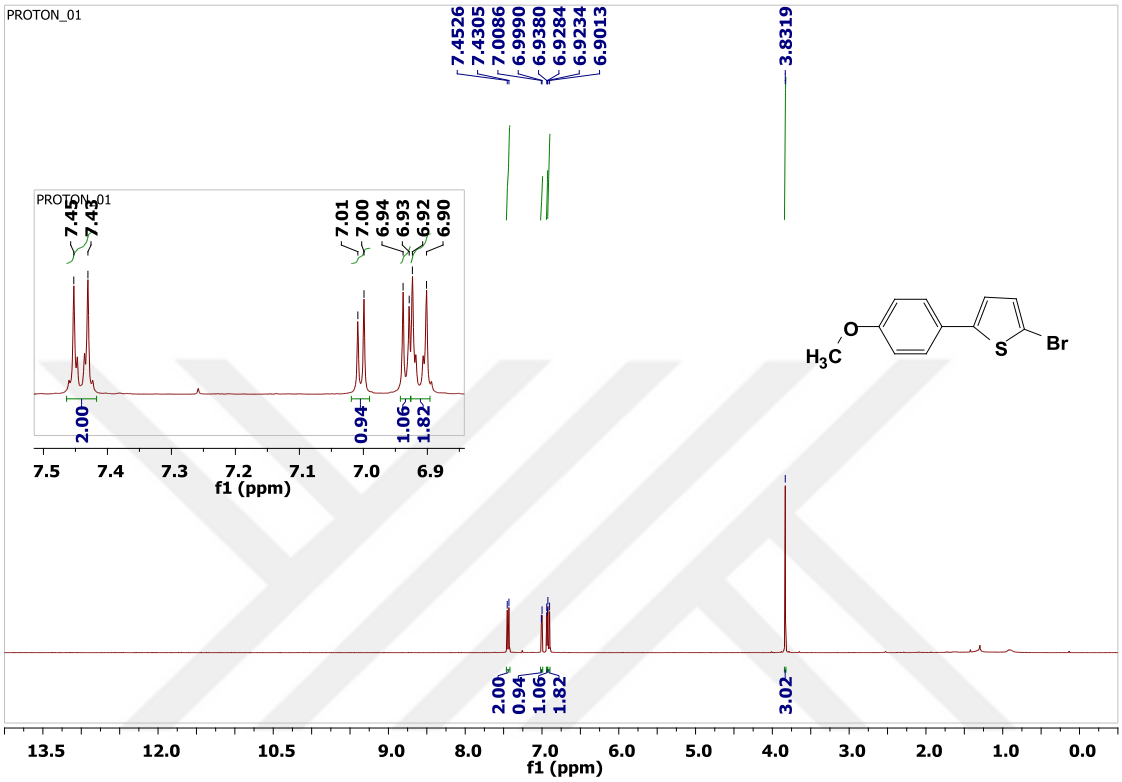


Figure 2.8. ^{1}H NMR spectra of AD3.

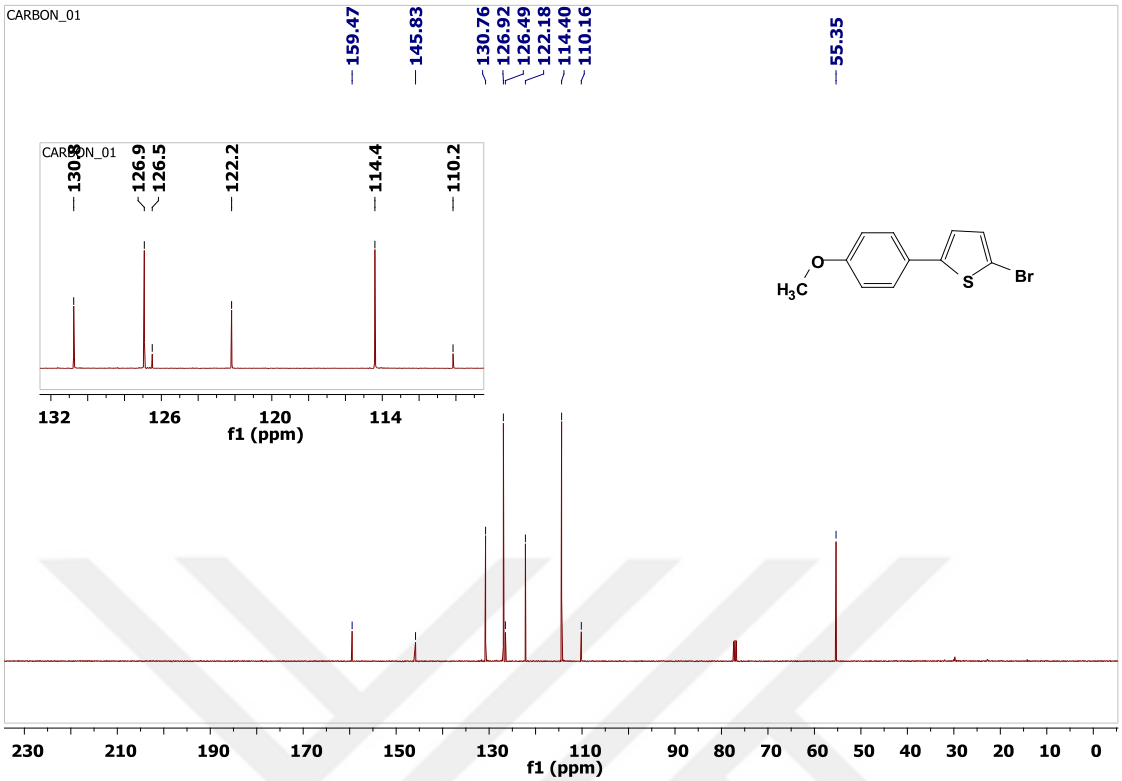


Figure 2.9. ^{13}C NMR spectra of AD3.

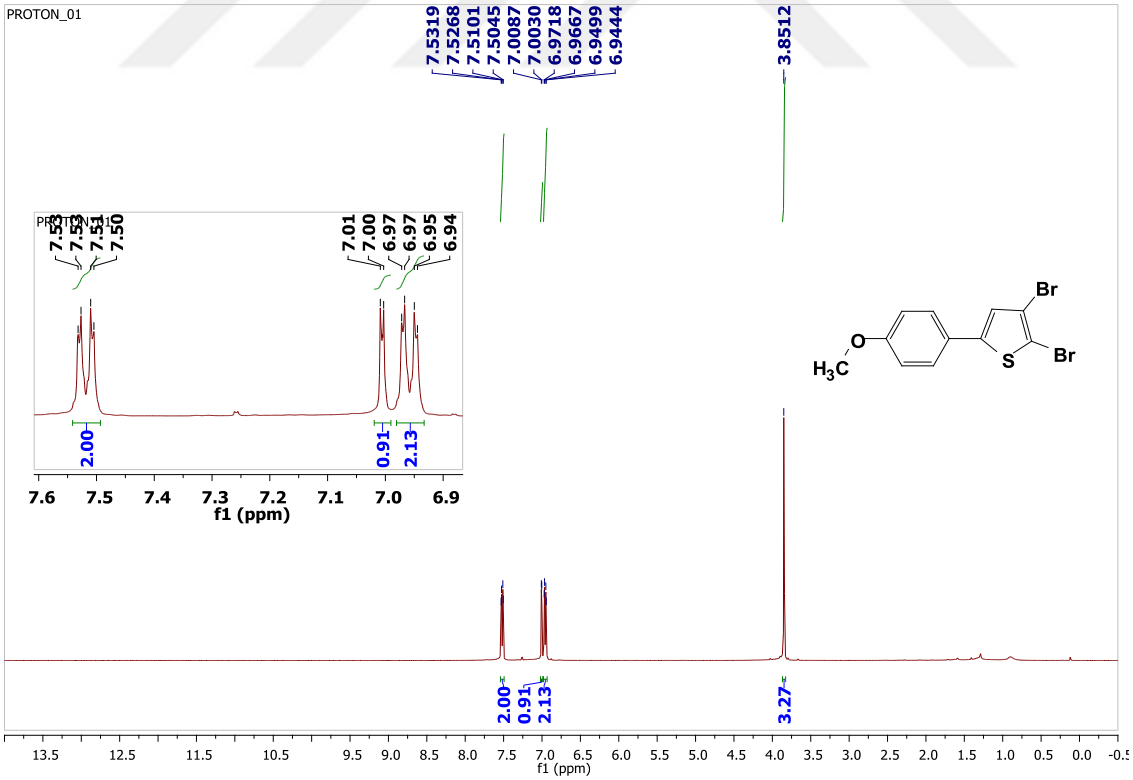


Figure 2.10. ^{1}H NMR spectra of AD3S1.

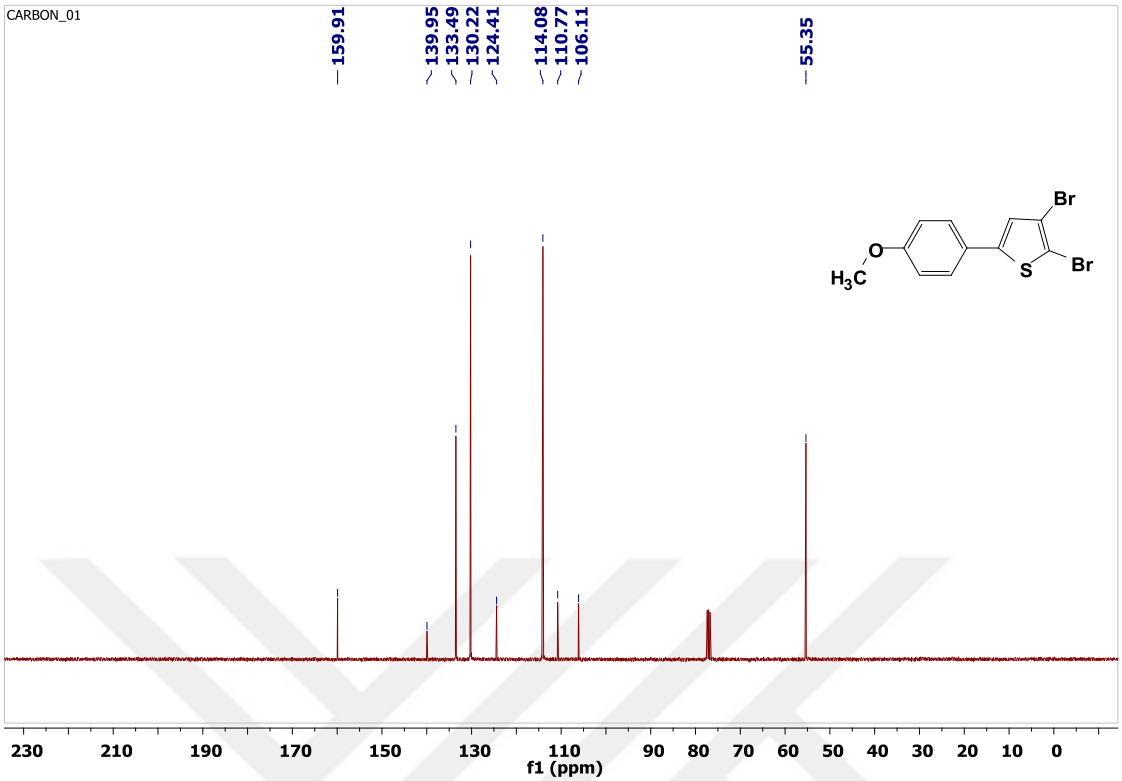


Figure 2.11. ^{13}C NMR spectra of AD3S1.

2.2.1.4. Desilylation Reaction to Synthesis of (2-ethynylphenyl)(methyl)sulfane (AD4)

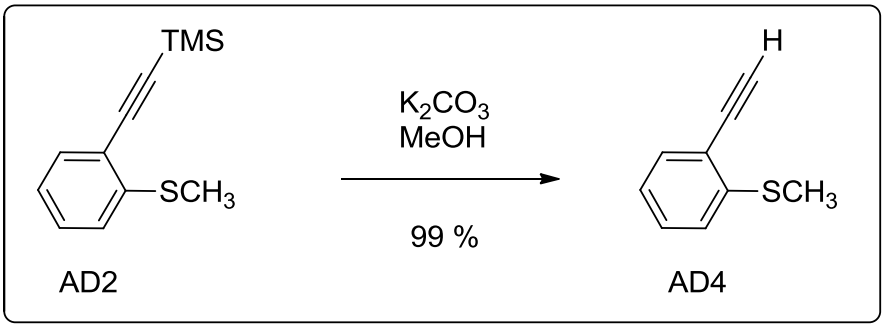


Figure 2.12. Synthesis of compound AD4.

To a solution of AD2 (749 mg, 3.4 mmol) in methanol (30 mL) was added K_2CO_3 (967 mg, 7 mmol). The mixture was stirred at room temperature for 30 min. After reaction was over, the resulting solution was diluted with satd.brine, and extracted with EtOAc (3x20 mL). The combine organic phase was dried with anhydrous $MgSO_4$.

After filtration and evaporated to removal solvent, the residue purified by using flash column chromatography on silica gel using Hexane/Ethyl acetate (9:1) as the eluent to afford the desired product AD4 (99 % yield) as a yellow oil (Figure 2.12). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.64 Hz, 1H), 7.30 (t, *J* = 7.84 Hz, 1H), 7.15 (d, *J* = 8.04 Hz, 1H), 7.08 (t, *J* = 7.52 Hz, 1H), 3.49 (s, 1H), 2.47 (s, 3H, Ar-SCH_3) (Figure 2.13); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 133.1, 129.3, 124.3, 124.2, 120.2, 83.6, 81.1, 15.1 (Figure 2.14); IR (KBr, thin film) ν_{max} (cm^{-1}): 3058.3, 2982.1, 3281.3 (≡C—H), 2920.3, 2101.9 (C≡C), 1432.7, 747.9, 614.6 (S-C), HRMS calcd for C_9H_8S, 148.0347 $[M+H]^+$, found 149.0248 $[M+H]^+$.

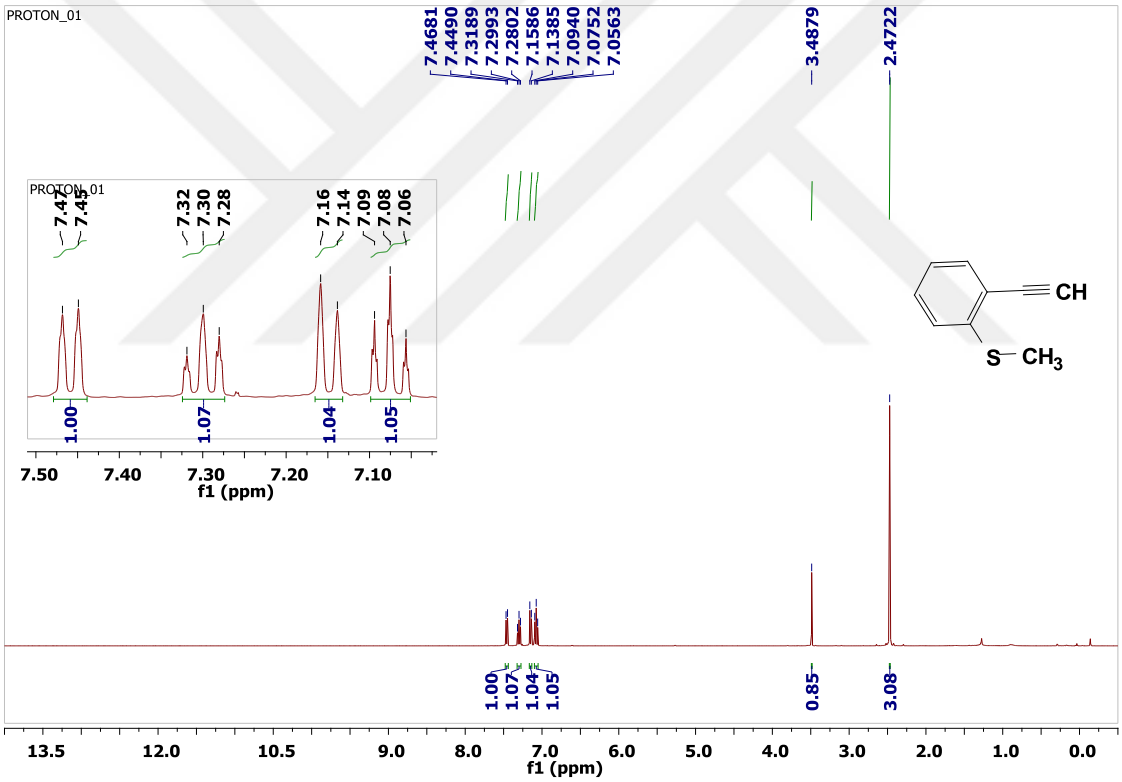


Figure 2.13. ^{1}H NMR spectra of AD4.

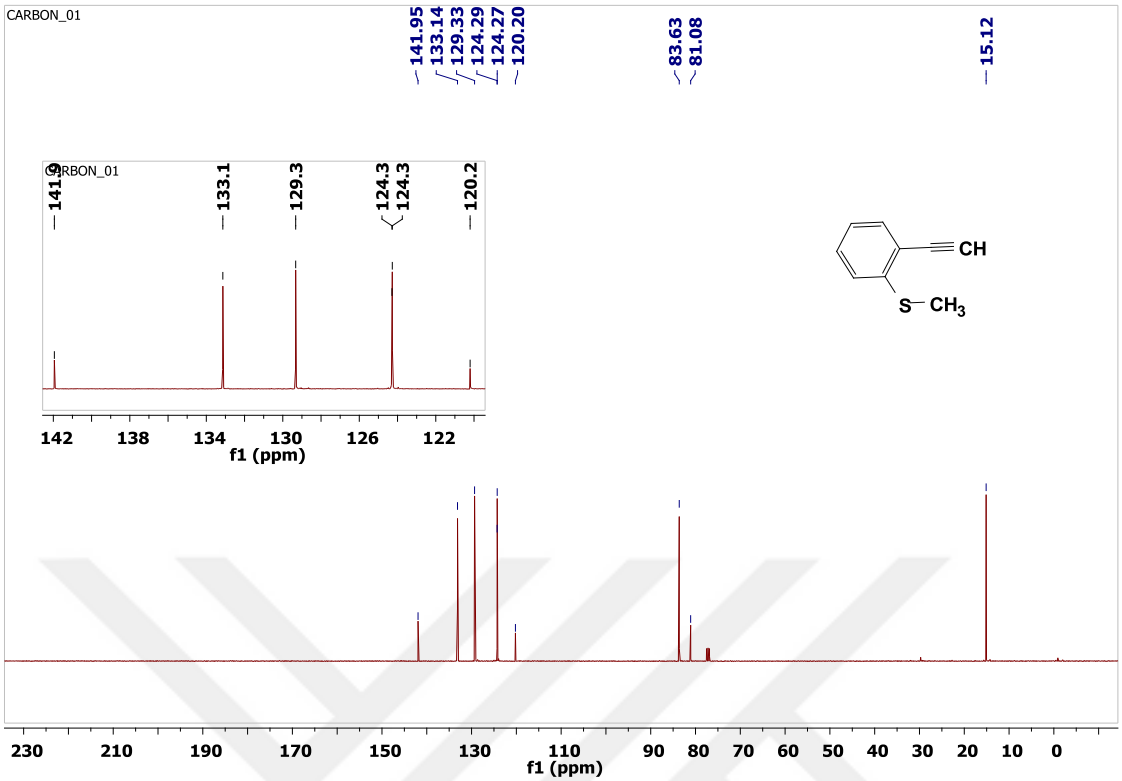


Figure 2.14. ^{13}C NMR spectra of AD4.

2.2.1.5. Sonogashira Coupling Reaction between compound (AD3) and terminal alkyne compound (AD4) to Synthesis of 2-(4-methoxyphenyl)-5-((2-(methylthio)phenyl)ethynyl)thiophene (AD5)

To a solution of AD3 (118 mg, 0.44 mmol), AD4 (81.5 mg, 0.55 mmol) in THF (8 mL), triethylamine (6 mL) and $PdCl_2(PPh_3)_2$ (0.03 mmol) were added CuI (3.8 mg, 0.02 mmol) under argon athmosphere. Then reaction mixture was stirred at 70 ^oC for 9 hours. After reaction was over, the resulting solution was diluted with satd.brine, and extracted with EtOAc (3x20 mL). The combine organic phase was dried with anhydrous $MgSO_4$. After filtration and evaporated to removal solvent, the residue purified by using flash column chromatography on silica gel using Hexane/Ethyl acetate (100:1) as the eluent to afford AD5 (78 % yield) as a yellow solid (Figure 2.15). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 7.68 Hz, 1H), 7.29 (td, *J* = 7.4 and 3.8 Hz, 2H), 7.19 (d, *J* = 7.64 Hz, 1H), 7.14-7.11 (m, 2H), 6.92 (d, *J* = 8.84 Hz, 2H), 3.83 (s, 3H), 2.52 (s, 3H) (Figure 2.16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 146.3, 141.6,

133.2, 132.0, 128.9, 127.2, 126.6, 124.3, 124.2, 122.1, 121.2, 121.1, 114.4, 91.1, 89.5, 55.4, 15.1 (Figure 2.17); IR (KBr, thin film) ν_{max} (cm^{-1}): 3079.6, 3002.2, 2962.1, 2920.9, 2853.4, 2198.8, 2360.1, 1943.3, 1877.3, 1729.6, 1605.0, 1571.3, 1536.3, 1507.0, 1451.0, 1433.5, 1251.0, 1178.8, 1111.1, 1068.1, 1044.7, 1023.7, HRMS calcd for $C_{20}H_{16}OS_2$, 336.0643 $[M+H]^+$, found 336.0678 $[M+H]^+$.

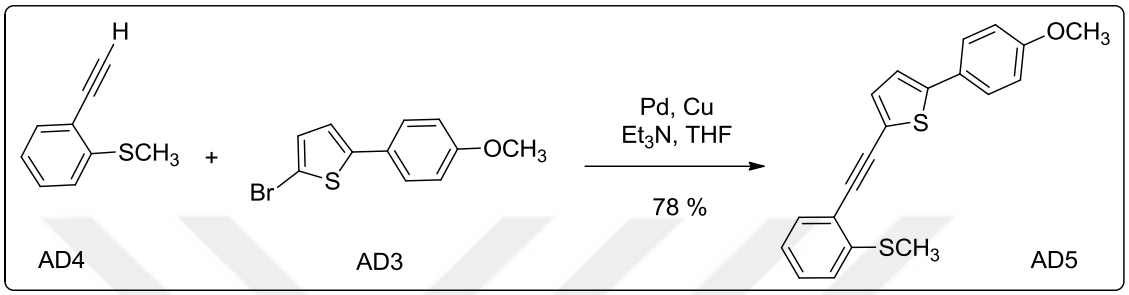


Figure 2.15. Synthesis of compound AD5.

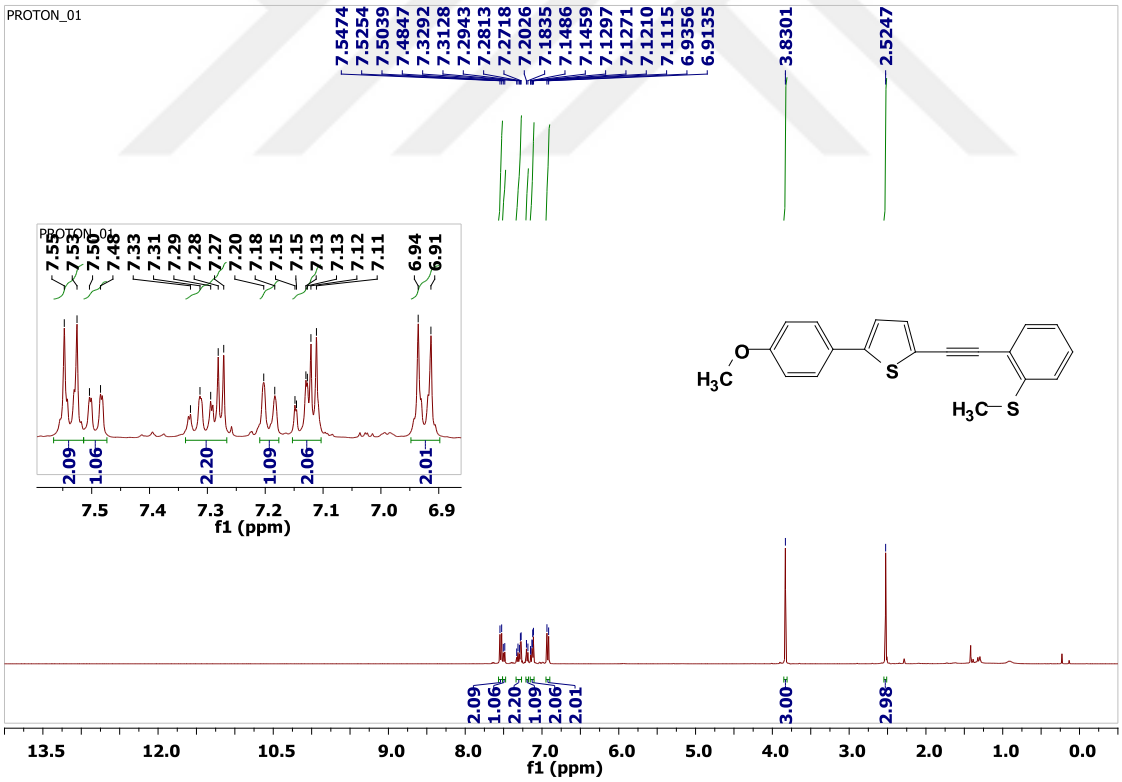


Figure 2.16. ^{1}H NMR spectra of AD5.

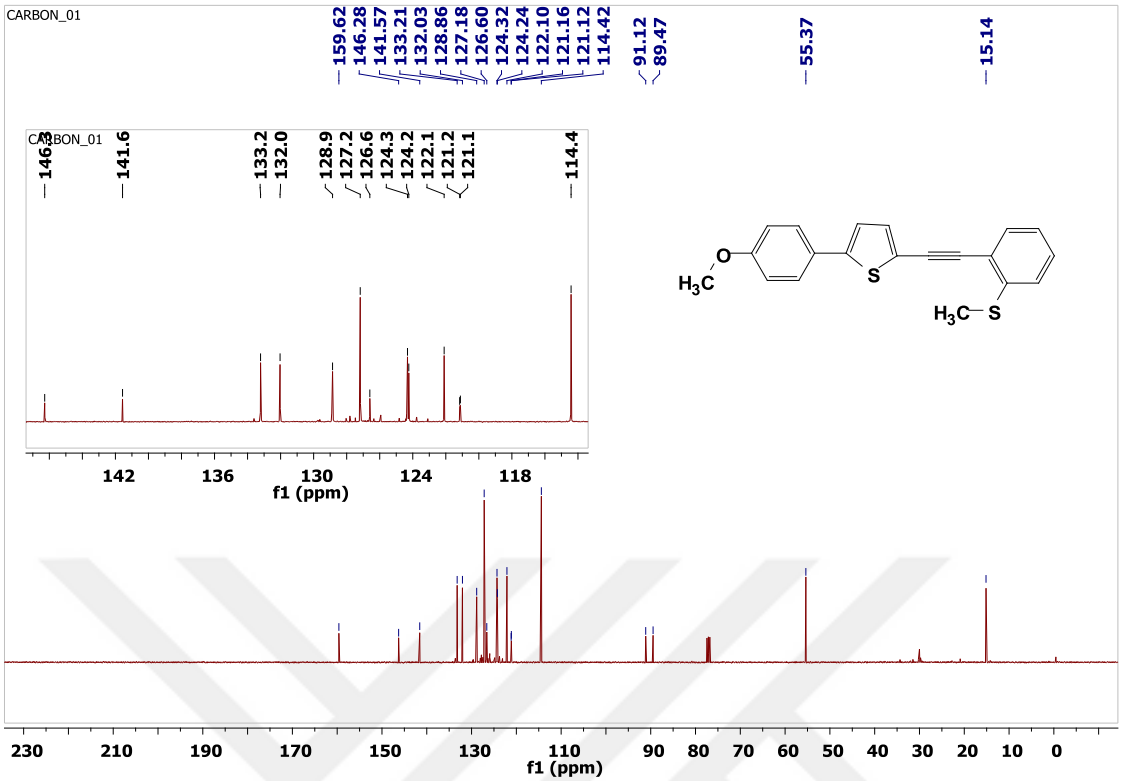


Figure 2.17. ^{13}C NMR spectra of AD5.

2.2.1.6. Electrophilic Cyclization Reaction to Synthesis of 3-iodo-2-(5-(4-methoxyphenyl)thiophen-2-yl)benzo[b]thiophene (AD6)

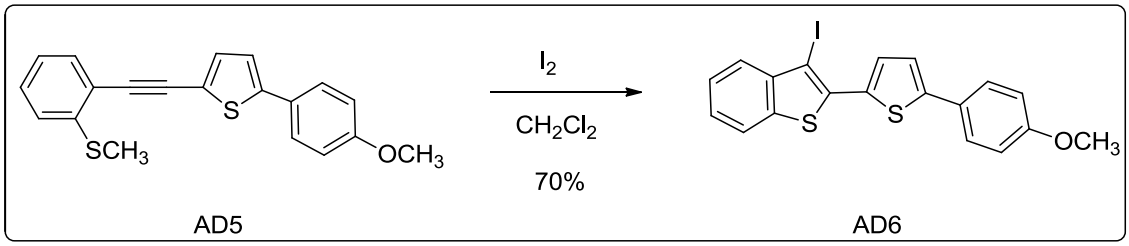


Figure 2.18. Synthesis of compound AD6.

To a solution of compound AD5 (336.5 mg, 1 mmol) in dichloromethane (15 mL) was added iodine (761.4 mg, 3 mmol). The mixture stirred at room temperature for 30 min. When reaction was over, the saturated aqueous solutions of $Na_2S_2O_3$ were added subsequently into the reaction mixture and extracted with DCM. The crude

products were dried with $MgSO_4$. After filtration and evaporated to removal solvent, the residue purified by using flash column chromatography on silica gel using Hexane/Ethyl acetate (50:1) as the eluent to afford the desired product AD6 (70% yield) as a yellow solid (Figure 2.18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.80 (m, 1H), 7.72-7.74 (m, 1H), 7.59 (d, *J* = 6.68 Hz, 2H), 7.56 (d, *J* = 3.88 Hz, 1H), 7.44 (td, *J* = 1.96 and 1.12 Hz, 1H), 7.36 (td, *J* = 0.8 and 1.24 Hz, 1H), 7.24 (d, *J* = 3.84 Hz, 1H), 6.94 (d, *J* = 8.88 Hz, 2H), 3.85 (s, 3H) (Figure 2.19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 146.1, 142.4, 137.7, 136.0, 133.8, 129.5, 127.2, 126.6, 126.1, 125.7, 125.6, 122.3, 121.8, 114.4, 78.4, 55.4 (Figure 2.20); IR (KBr, thin film) ν_{max} (cm^{-1}): 3057.3, 3015.3, 2959.0, 2930.6, 2833.7, 1934.5, 1900.1, 1880.1, 1780.1, 1539.6. 1510.9, 1487.8, 1456.7, 1251.7, 1244.2, 1177.5, 1113.8, 1078.7, HRMS calcd for $C_{19}H_{13}OS_2I$, 447.9452 $[M+H]^+$, found 447.9453 $[M+H]^+$.

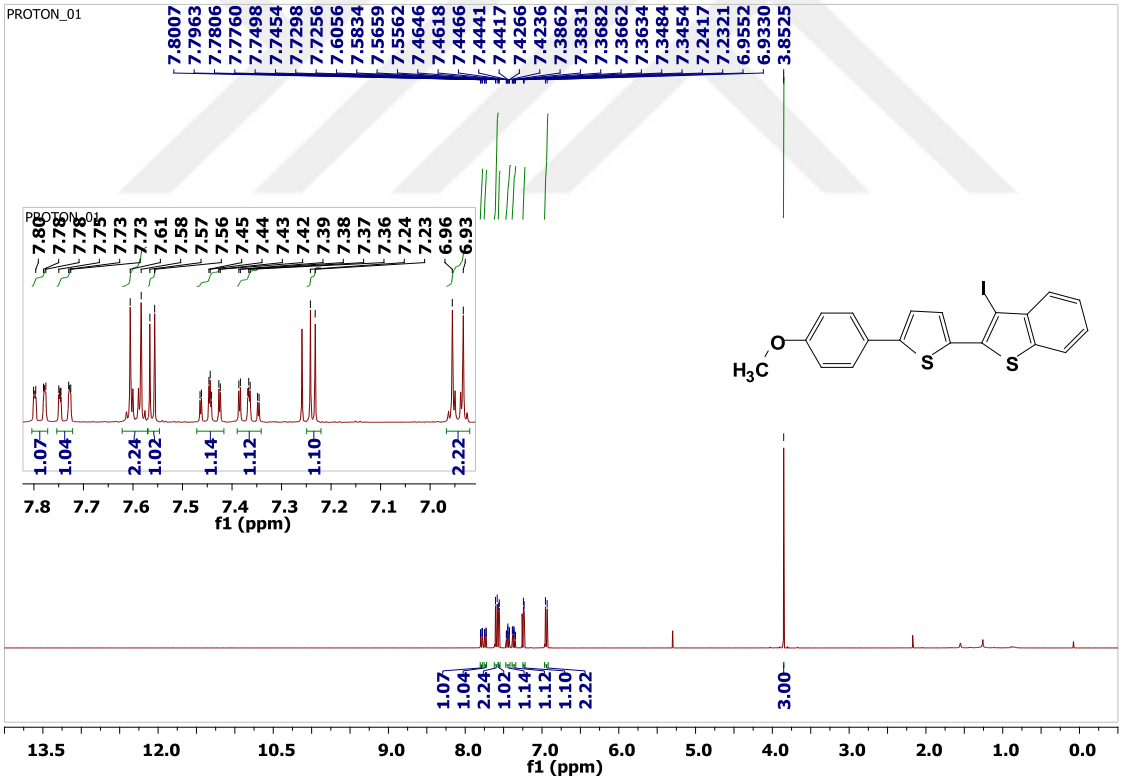


Figure 2.19. ^{1}H NMR spectra of AD6.

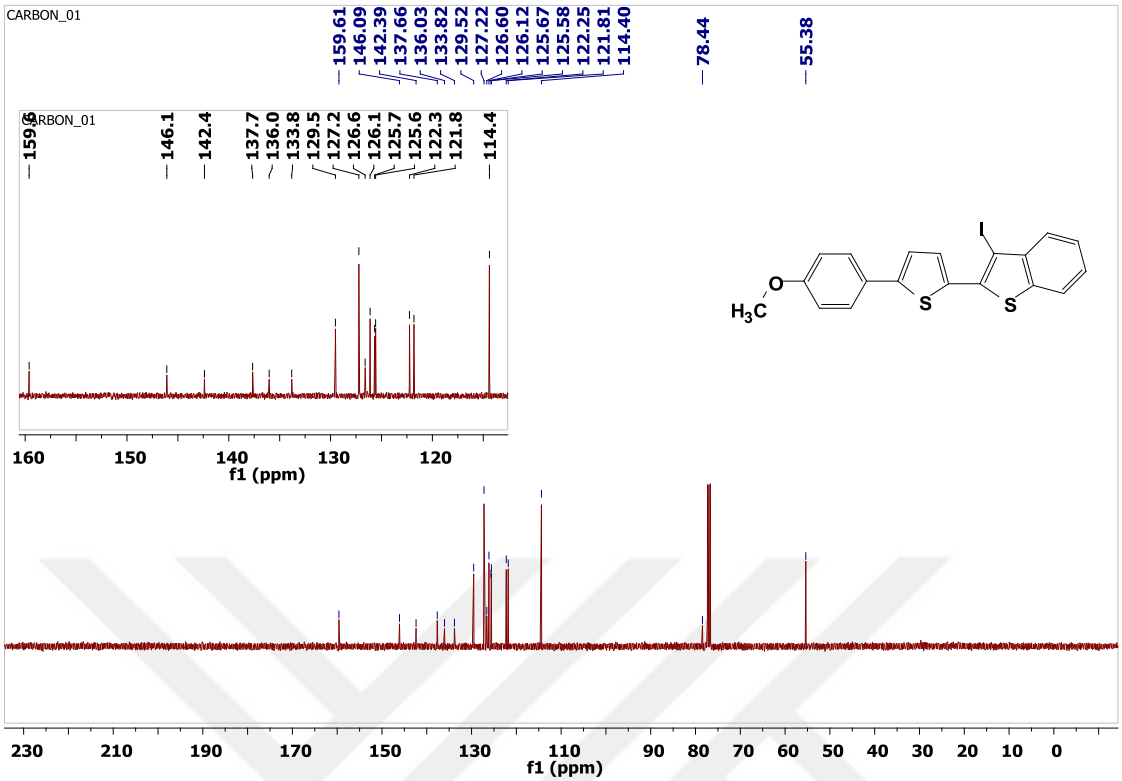


Figure 2.20. ^{13}C NMR spectra of AD6.

2.2.1.7. Stille coupling reaction between the iodo substituted compound (AD6) and 2-(tributylstannyl)thiophene or 2-(tributylstannyl)furan:

General procedure:

To a solution of AD6 (0.5 mmol) and aryl stannane (2-(tributylstannyl)thiophene or (tributylstannyl)furan) (0.6 mmol) in toluene (10 mL) were added $Pd(PPh_3)_4$ (0.03 mmol) under argon, the reaction mixture stirred at 110 ^oC for overnight. After reaction was over, the resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) as the eluent to afford the AD8 or AD10.

Compound AD8:

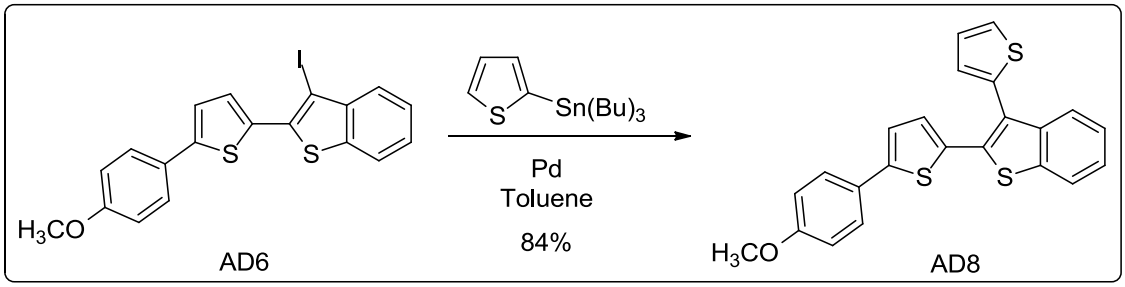


Figure 2.21. Synthesis of AD8 compound.

AD6 (100 mg, 0.5mmol), 2-(tri-n-butylstannyl)thiophene (99.95 mg, 0.6 mmol) in toluene (10 mL) and $Pd(PPh_3)_4$ (15.5 mg, 0.03 mmol) to give (84% yield) as a brown solid of AD8 (Figure 2.21). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, *J* = 3.24 Hz, 1H), 7.55-7.57 (m, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.36 (q, *J* = 3.08 Hz, 2H), 7.24 (q, *J* = 3.52 Hz, 1H), 7.19 (dd, *J* = 3.48 and 1.16 Hz, 1H), 7.15 (d, *J* = 3.84 Hz, 1H), 7.07 (d, *J* = 4.24 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H) (Figure 2.22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 145.8, 141.7, 137.4, 135.9, 134.9, 134.1, 129.2, 128.3, 127.7, 127.5, 127.1, 126.8, 125.0, 124.9, 123.2, 122.1, 121.8, 114.3, 55.4 (Figure 2.23); IR (KBr, thin film) ν_{max} (cm^{-1}): 3065.3, 2991.3, 2923.1, 2851.4, 2835.1, 1951.2, 1916.5, 1892.0, 1800.6, 1755.3, 1648.0, 1604.2, 1564.7, 1508.3, 1451.6, 1247.4, 1177.3, 1113.3, 1030.2, HRMS calcd for $C_{23}H_{16}OS_3$, 404.0363 $[M+H]^+$, found 404.0376 $[M+H]^+$.

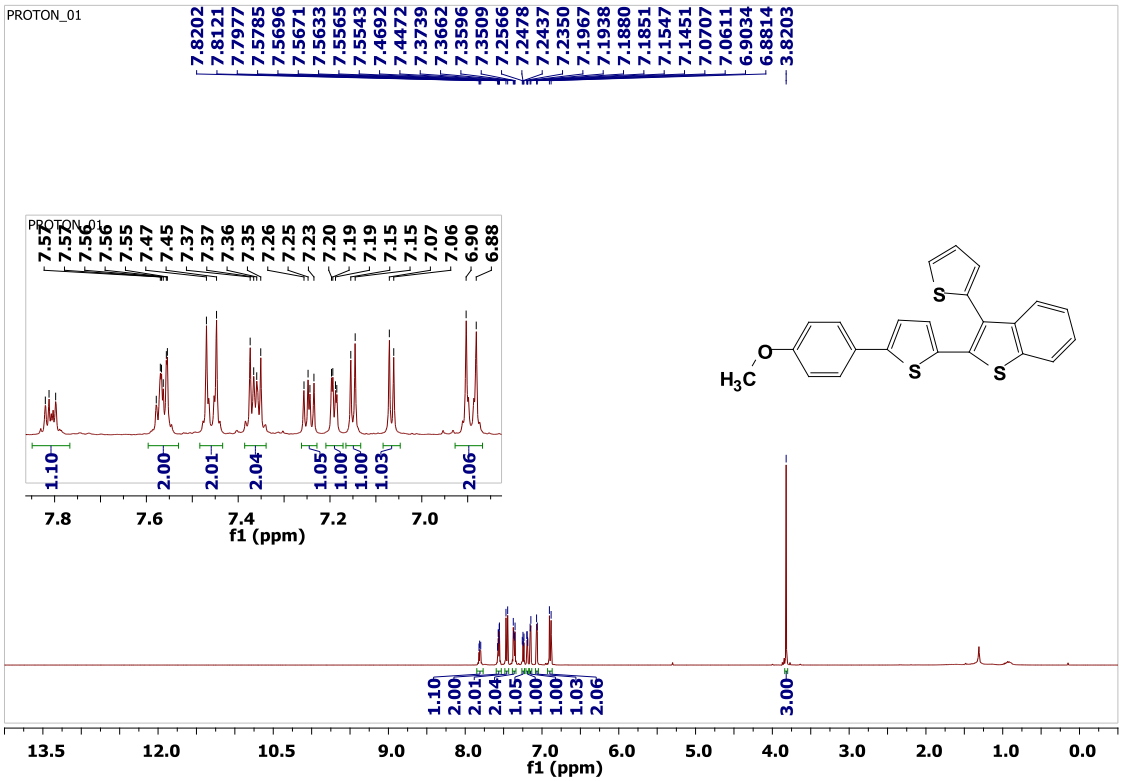


Figure 2.22. ^{1}H NMR spectra of AD8.

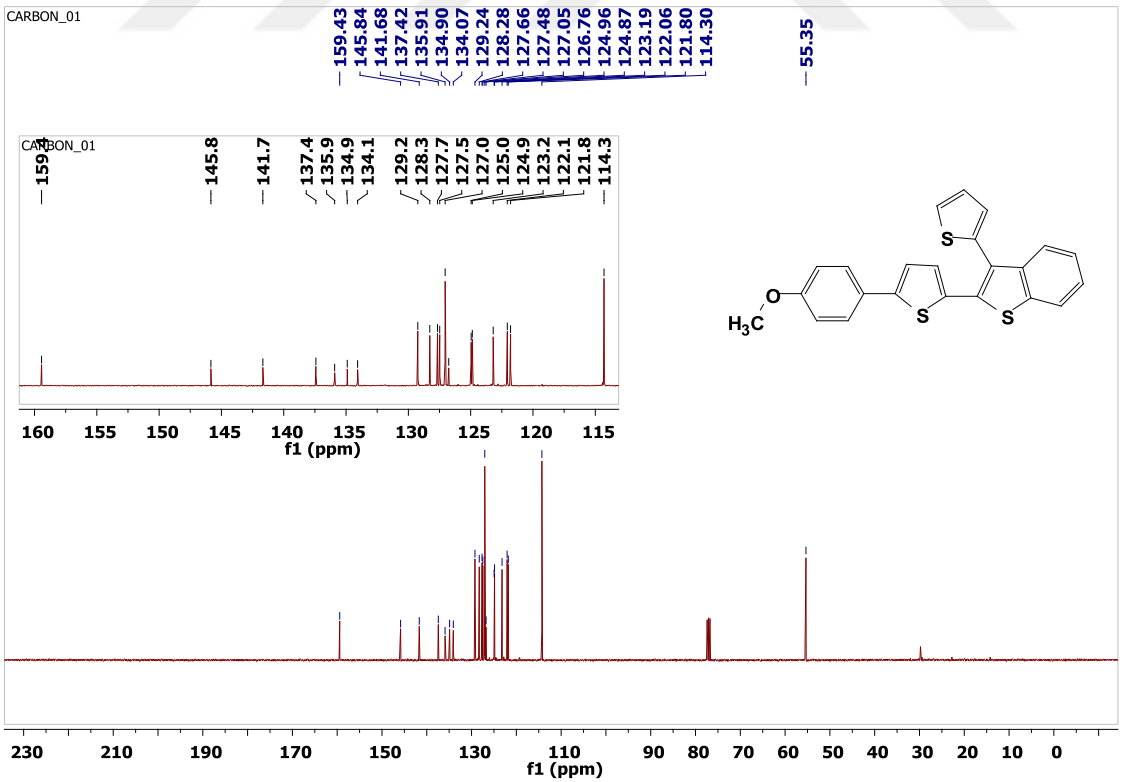


Figure 2.23. ^{13}C NMR spectra of AD8.

Compound AD10:

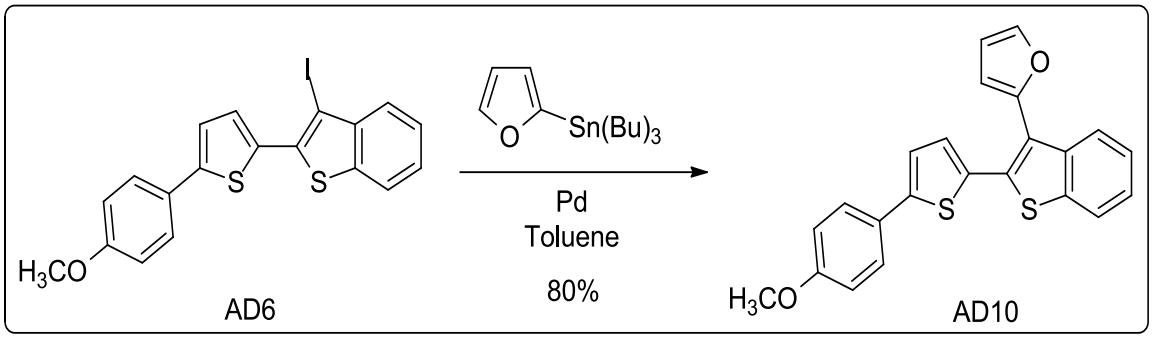


Figure 2.24. Synthesis of AD10.

AD6 (100 mg, 0.5mmol), 2-(tri-n-butylstannyl)furan (95.65 mg, 0.6 mmol) in toluene (10 mL), and $Pd(PPh_3)_4$ (15.5 mg, 0.03 mmol) to give AD10 (80 % yield) as a brown solid (Figure 2.24). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.85 (m, 2H), 7.67 (bs, 1H), 7.53 (d, *J* = 8.76 Hz, 2H), 7.39-7.42 (m, 2H), 7.19 (dd, *J* = 3.84 and 3.84 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 1.16 Hz, 2H), 3.86 (s, 3H) (Figure 2.25); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 147.4, 146.0, 142.7, 140.3, 138.0, 136.1, 133.9, 128.6, 127.1, 126.8, 125.0, 124.9, 123.3, 122.33, 122.3, 122.0, 114.4, 111,4, 111.0, 55.4 (Figure 2.26); IR (KBr, thin film) ν_{max} (cm^{-1}): 3125.5, 3058.6, 3017.0, 2957.3, 2920.8, 2850.6, 1871.81, 1805.7, 1602.7, 1571.4, 1518.8, 1478.7, 1440.7, 1288.4, 1251.0, 1155.1, 1111.5, 1021.6, 826.1, 734.1, 673.8, HRMS calcd for $C_{23}H_{16}O_2S_2$, 388.0592 $[M+H]^+$, found 388.0591 $[M+H]^+$.

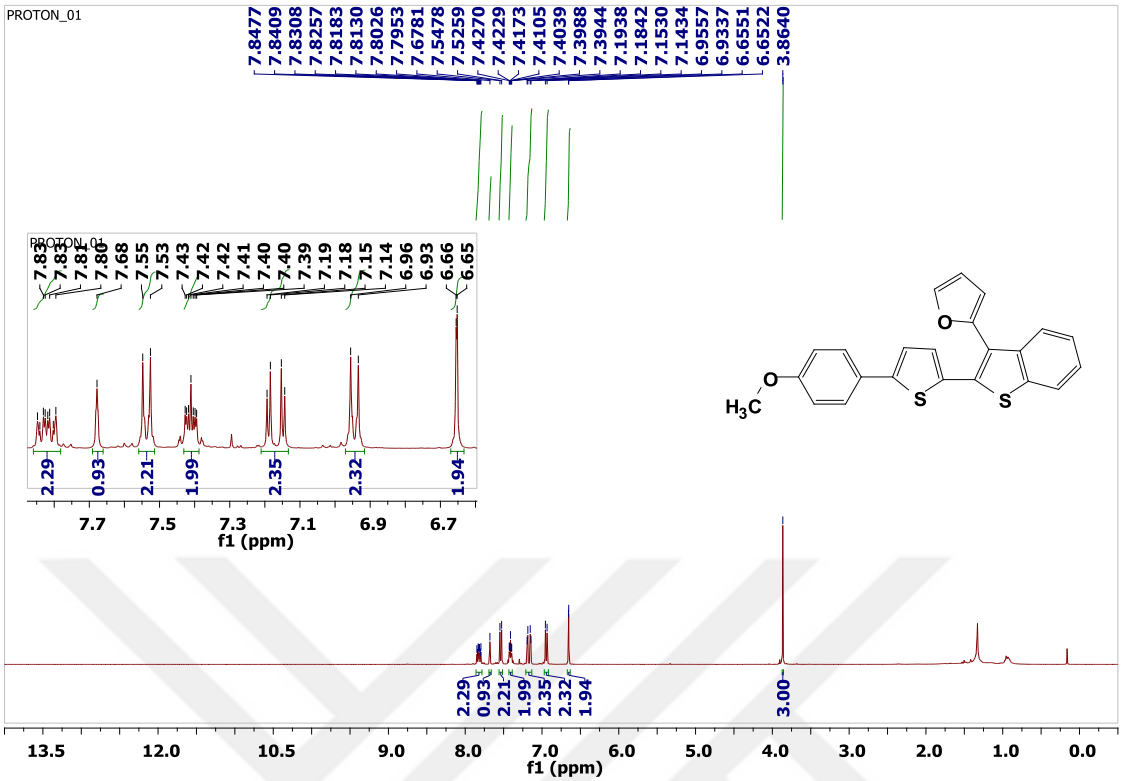


Figure 2.25. ^{1}H NMR spectra of AD10.

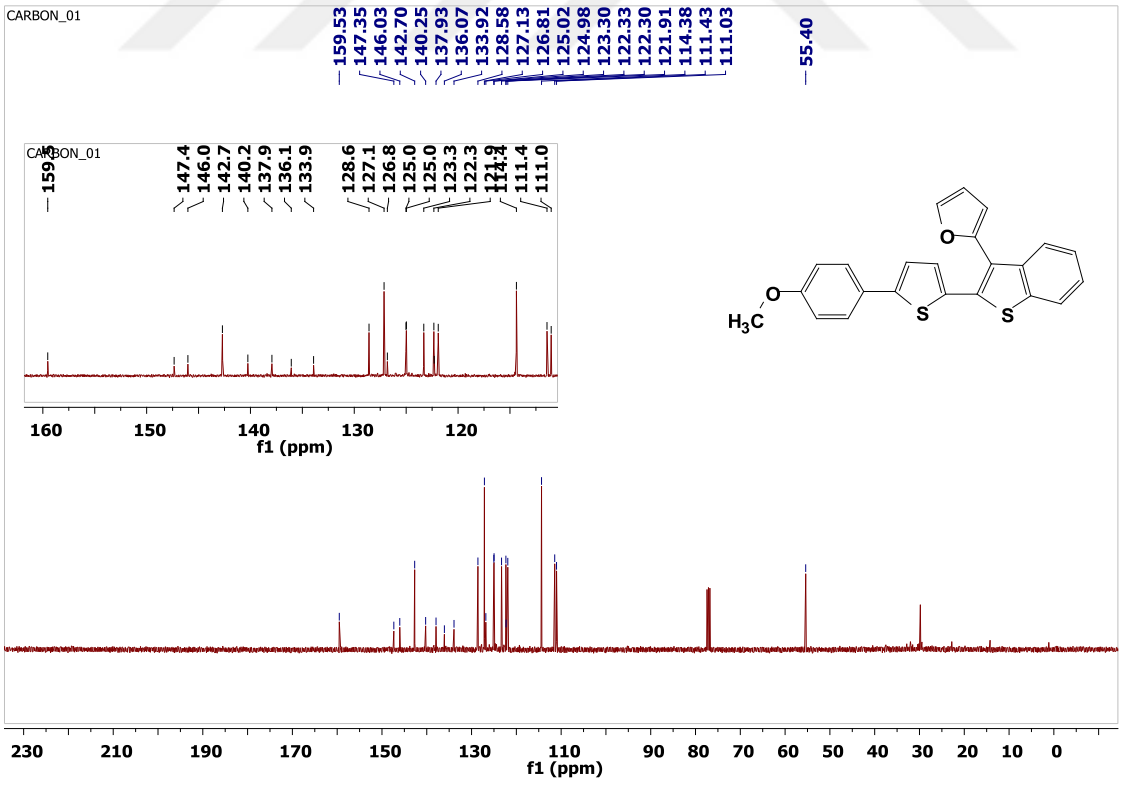


Figure 2.26. ^{13}C NMR spectra of AD10.

2.2.1.8. Sonogashira coupling reaction between the iodo compound (AD6) and terminal alkynes:

General procedure:

To a stirred solution of AD6 (0.7 mmol), $PdCl_2(PPh_3)_2$ (0.035 mmol) in DMF (7 mL) and triethylamine (3 mL) were added terminal alkyne (0.75 mmol) and CuI (2.13 mmol) under argon atmosphere. The resulting solution stirred at room temperature for overnight. After reaction was over, the resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, the residue was purified by column chromatography on silica gel using Hexane/EtOAc (100:1) as the eluent to afford the desired products (AD9, AD11, AD12, AD14, AD15, AD16, AD17 and AD19). (Figure 2.27).

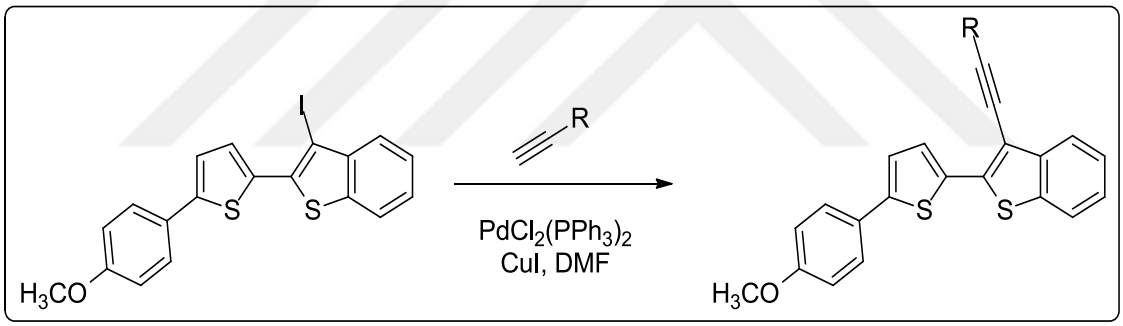


Figure 2.27. Synthesis of derivatives via Sonogashira coupling reaction.

Compound AD9:

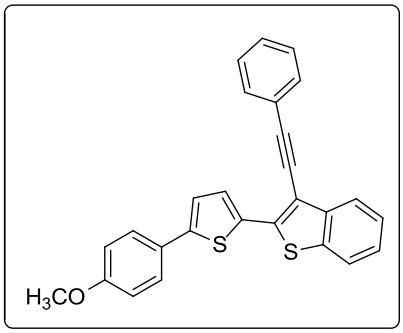


Figure 2.28. Synthesis of AD9.

The AD6 (100 mg, 0.7 mmol) in DMF (7mL), triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.9 mg, 0.035 mmol), phenylacetylene (24.5 mg, 0.75 mmol), and CuI (2.1 mg, 0.035 mmol) to give AD9 (94% yield) as a yellow solid (Figure 2.28). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.88 Hz, 1H), 7.76 (t, *J* = 7.72 Hz, 3H), 7.59 (q, *J* = 3.92 Hz, 3H), 7.47 (d, *J* = 7.48 Hz, 4H), 7.40 (t, *J* = 7.48 Hz, 1H), 7.23 (d, *J* = 3.84 Hz, 1H), 6.96 (d, *J* = 8.64 Hz, 2H), 3.87 (s, 3H) (Figure 2.29); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 145.6, 140.7, 140.2, 136.7, 134.6, 131.6, 128.6, 128.5, 128.1, 127.2, 126.9, 125.4, 125.1, 123.5, 123.1, 122.3, 121.9, 114.5, 112.3, 98.0, 84.4, 55.4 (Figure 2.30); IR (KBr, thin film) ν_{max} (cm^{-1}): 3062.4, 3005.5, 2957.4, 2922.3, 2853.4, 1761.6, 1945.4, 1604.7, 1571.6, 1538.7, 1479.2, 1455.6, 1438.9, 1251.1, 1181.3, 1066.9, 1029.9, 930.7, HRMS calcd for $C_{27}H_{18}OS_2$, 422.0799 $[M+H]^+$, found 422.0809 $[M+H]^+$.

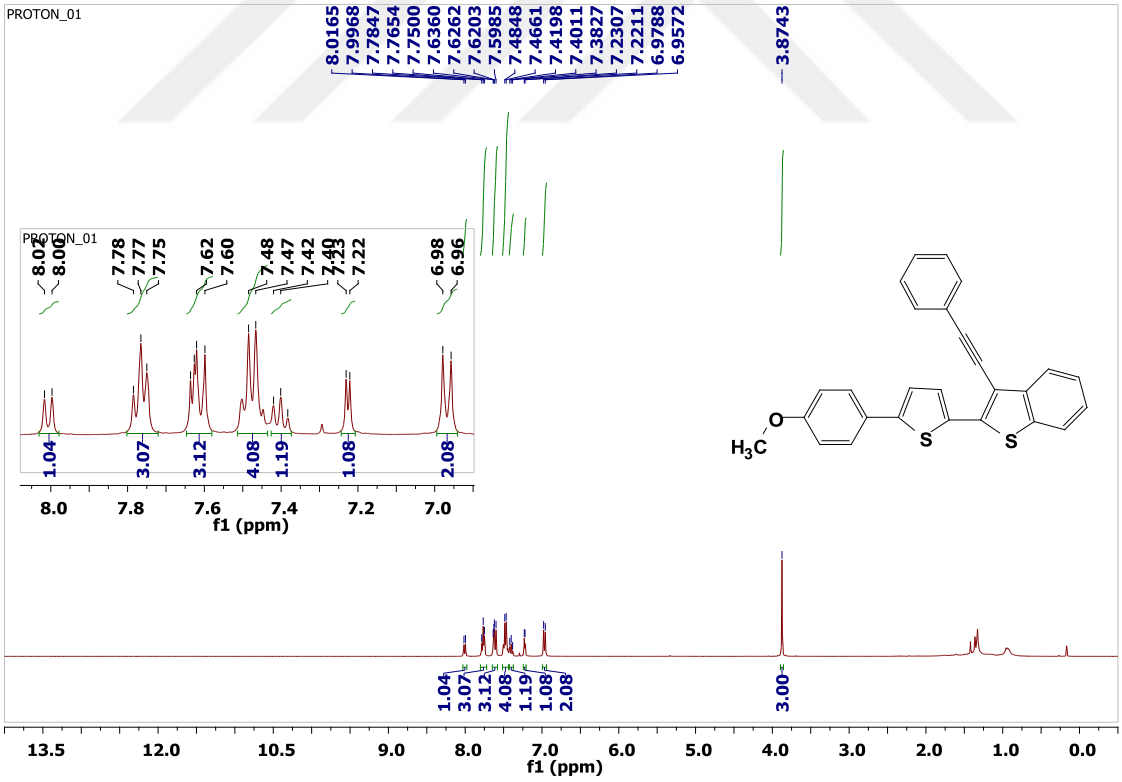


Figure 2.29. ^{1}H NMR spectra of AD9.

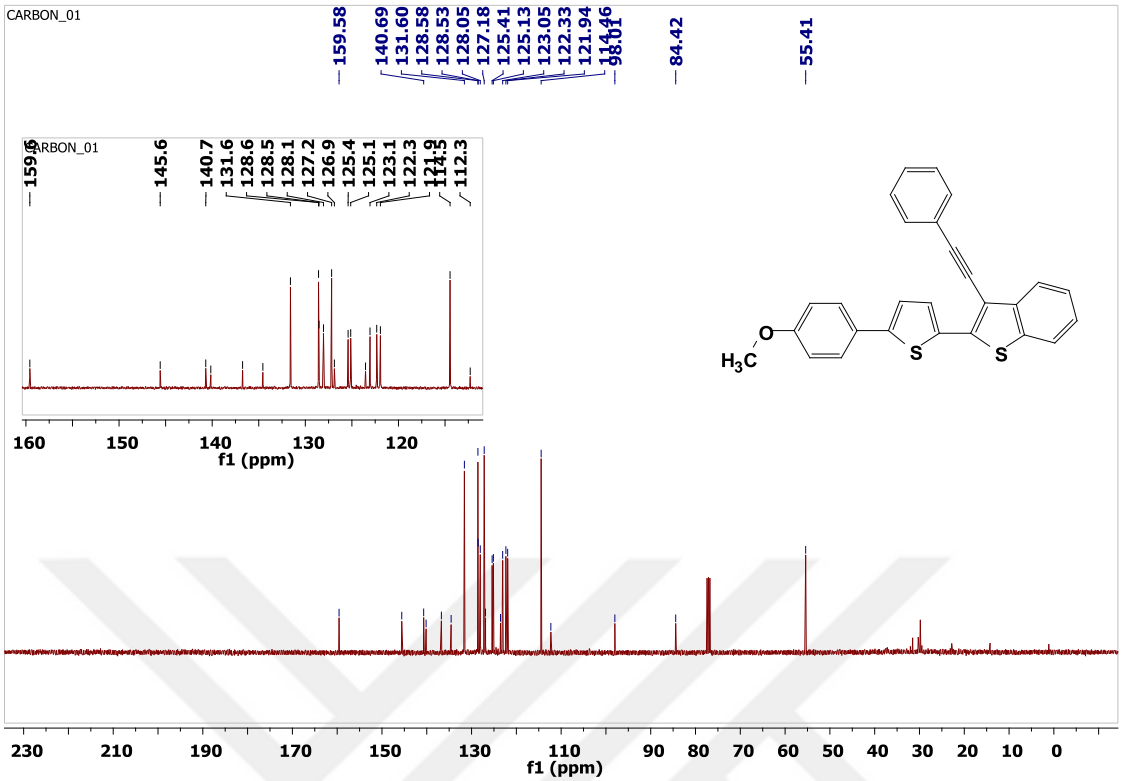


Figure 2.30. ^{13}C NMR spectra of AD9.

Compound AD11:

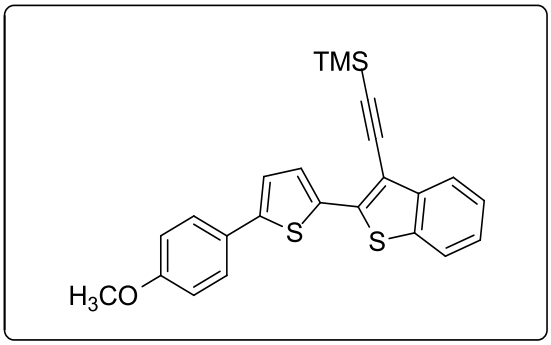


Figure 2.31. Synthesis of AD11.

The AD6 (100 mg, 0.7 mmol) in DMF (7 mL) and triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.85 mg, 0.035 mmol), ethynyltrimethysilane (23.5 mg, 0.75 mmol), and CuI (2.13 mg, 0.035 mmol) to give AD11 (73 % yield) as a brown solid (Figure 2.31). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.76 Hz, 1H), 7.72 (d, *J* = 7.88 Hz, 1H),

7.56-7.60 (m, 3H), 7.42 (td, *J* = 7.88 and 0.92 Hz, 1H), 7.33 (td, *J* = 7.24 and 1.28 Hz, 1H), 7.19 (d, *J* = 3.88 Hz, 1H), 6.94 (d, *J* = 8.84 Hz, 2H), 3.85(s, 3H), 0.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.5, 141.1, 140.8, 136.5, 134.5, 128.0, 127.2, 127.1, 126.8, 125.3, 125.0, 123.0, 122.2, 121.8, 114.4, 104.2, 99.3, 55.4, 0.05; IR (KBr, thin film) ν_{max} (cm^{-1}): 3058.7, 2954.4, 2923.6, 2851.7, 2149.7, 1605.7, 1542.6, 1488.4, 1448.7, 1439.2, 1243.9, 1179.3, 1113.9, 1032.8, 841.8, 798.5, 659.0, 599.0, HRMS calcd for $C_{24}H_{22}OS_2Si$, 419.0975 $[M+H]^+$, found 419.0954 $[M+H]^+$.

Compound AD12:

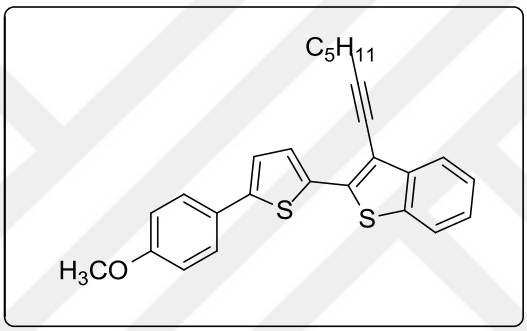


Figure 2.32. Synthesis of compound AD12.

The AD6 (100 mg, 0.7 mmol) in DMF (7 mL) and triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.85 mg, 0.035 mmol), 1-heptyne (18.49 mg, 0.75 mmol), and CuI (2.13 mg, 0.035 mmol) to give AD12 (90 % yield) as a yellow solid (Figure 2.32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.92 Hz, 1H), 7.77 (d, *J* = 7.88 Hz, 1H), 7.60-7.64 (m, 3H), 7.46 (t, *J* = 7.32 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 3.84 Hz, 1H), 7.00 (d, *J* = 8.76 Hz, 2H), 3.90 (s, 3H), 2.72 (t, *J* = 7.08 Hz, 2H), 1.85 (pen, *J* = 7.24 Hz, 2H), 1.64 (pen, *J* = 6.88 Hz, 2H), 1.48 (sxet, *J* = 7.32 Hz, 2H), 1.01 (t, *J* = 7.32 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 144.9, 141.2, 138.8, 136.7, 134.8, 127.5, 127.2, 127.0, 125.2, 124.9, 123.1, 122.2, 121.9, 114.4, 113.3, 99.9, 75.2, 55.4, 31.4, 28.4, 22.4, 20.2, 14.1; IR (KBr, thin film) ν_{max} (cm^{-1}): 3058.4, 3002.3, 2952.7, 2926.4, 2853.8, 2216.4, 2360.1, 1606.2, 1570.2, 1514.8, 1493.1, 1449.3, 1287.3, 1255.9, 1177.7, 1111.9, 1034.0, 830.7, 794.4, 754.4, 637.2, 577.6, HRMS calcd for $C_{26}H_{24}OS_2$, 416.1269 $[M+H]^+$, found 416.1288 $[M+H]^+$.

Compound AD14:

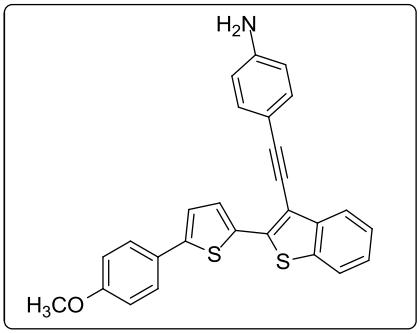


Figure 2.33. Synthesis of compound AD14.

The compound AD6 (100 mg, 0.7 mmol) in DMF (7 mL) and triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.85 mg, 0.035 mmol), 4-ethynylaniline (28 mg, 0.75 mmol), and CuI (2.13 mg, 0.035 mmol) to give AD14 (69 % yield) as a brown solid (Figure 2.33). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.92 Hz, 1H), 7.73 (d, *J* = 7.88 Hz, 1H), 7.58 (t, *J* = 3.76 Hz, 3H), 7.51 (d, *J* = 8.44 Hz, 2H), 7.40-7.44 (m, 1H), 7.33-7.36 (m, 1H), 7.20 (d, *J* = 3.88 Hz, 1H), 6.93 (d, *J* = 8.36 Hz, 2H), 6.71 (d, *J* = 8.36 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 146.9, 145.1, 140.7, 138.7, 136.7, 134.8, 133.0, 127.6, 127.1, 127.0, 125.3, 124.9, 123.1, 122.2, 121.8, 114.9, 114.4, 113.0, 112.8, 99.0, 82.3, 55.4; IR (KBr, thin film) ν_{max} (cm^{-1}): 3453.4, 3357.9 (-NH_2), 3060.6, 2922.4, 2852.2, 2190.5, 1618.6, 1605.6, 1507.4, 1486.3, 1441.0, 1287.6, 1250.6, 1177.1, 1030.5, 823.7, 793.0, 630.5, HRMS calcd for $C_{27}H_{19}NOS_2$+Na, 460.0823 $[M+Na]^+$, found 460.0800 $[M+Na]^+$.

Compound AD15:

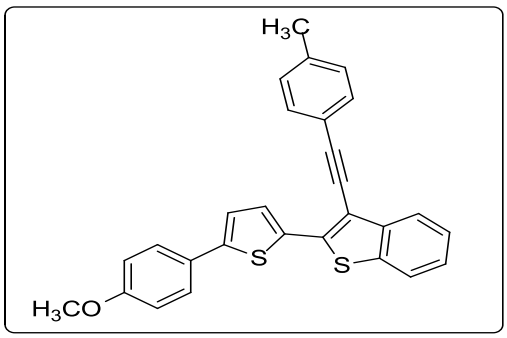


Figure 2.34. Synthesis of AD15.

The AD6 (100 mg, 0.7 mmol) in DMF (7 mL) and triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.85 mg, 0.035 mmol), 4-ethynyltoluene (27.8 mg, 0.75 mmol), and CuI (2.13 mg, 0.035 mmol) to give (77 % yield) as a yellow solid of compound AD15 (Figure 2.34). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.88 Hz, 1H), 7.74 (d, *J* = 7.88 Hz, 1H), 7.56-7.60 (m, 5H), 7.43 (t, *J* = 7.08 Hz, 1H), 7.35 (t, *J* = 8.04 Hz, 1H), 7.17-7.25 (m, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.4, 140.7, 139.7, 138.7, 136.7, 134.6, 131.4, 129.3, 127.9, 127.1, 126.9, 125.3, 125.0, 123.0, 122.3, 121.9, 120.4, 114.4, 112.5, 98.2, 83.7, 55.4, 29.7; IR (KBr, thin film) ν_{max} (cm^{-1}): 3063.0, 2920.6, 2851.0, 1729.5, 1604.7, 1571.2, 1483.0, 1446.21, 1288.3, 1252.0, 1180.0, 1031.4, 794.5, 755.7, 634.6, HRMS calcd for $C_{28}H_{20}OS_2$+Na, 459.0870 $[M+Na]^+$, found 459.0847 $[M+Na]^+$.

Compound AD16:

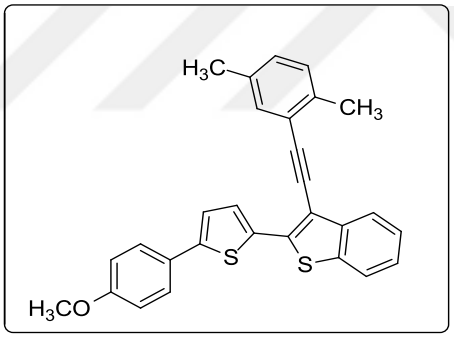


Figure 2.35. Synthesis of AD16.

The compound AD6 (100 mg, 0.7 mmol) in DMF (7 mL) and triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.85 mg, 0.035 mmol), 2-ethynyl-1,4-dimethylbenzene (31 mg, 0.75 mmol), and CuI (2.13 mg, 0.035 mmol) to afford compound AD16 (78 % yield) as an orenge solid (Figure 2.35). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.84 Hz, 1H), 7.74 (d, *J* = 7.88 Hz, 1H), 7.55-7.59 (m, 4H), 7.34-7.46 (m, 2H), 7.19 (t, *J* = 3.88 Hz, 2H), 7.11 (d, *J* = 7.76 Hz, 1H), 6.93 (d, *J* = 8.84 Hz, 2H), 3.85 (s, 3H), 2.64 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 145.4, 140.8, 139.5, 136.9, 136.7, 135.2, 134.5, 132.5, 129.6, 129.5, 127.9, 127.1, 126.9, 125.3, 125.1, 123.0, 122.9, 122.2, 121.9, 114.4, 112.7, 97.3, 87.6, 55.4, 20.9, 20.7; IR (KBr, thin film) ν_{max} (cm^{-1}):

2919.9, 2852.4, 2049.1, 1606.9, 1540.9, 1499.8, 1447.9, 1287.9, 1246.6, 1177.1, 1029.9, 822.1, 741.9, 722.6, 637.5, 581.1, HRMS calcd for $C_{29}H_{22}OS_2$+Na, 473.1028 $[M+Na]^+$, found 473.1004 $[M+Na]^+$.

Compond AD17:

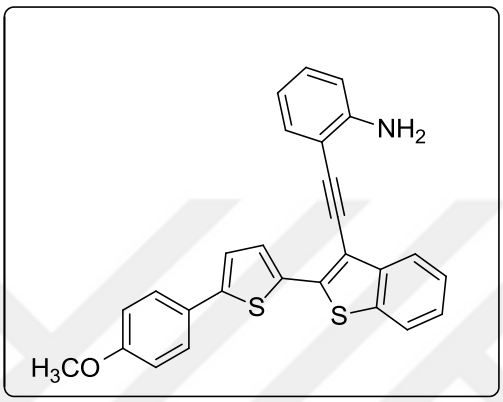


Figure 2.36. Synthesis of AD17.

The AD6 (100 mg, 0.7 mmol) in DMF (7 mL), triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.85 mg, 0.035 mmol), 2-ethynylaniline (28 mg, 0.75 mmol) and CuI (2.13 mg, 0.035 mmol) to give AD17 (98 % yield) as a brown solid (Figure 2.36). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.72 Hz, 1H), 7.73 (d, *J* = 7.88 Hz, 1H), 7.53-7.56 (m, 4H), 7.40 (tt, *J* = 8.04 and 6.92 Hz, 2H), 7.16-7.23 (m, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.78 (q, *J* = 7.52 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 148.0, 145.4, 140.6, 139.4, 136.7, 134.3, 132.4, 130.1, 127.9, 127.1, 126.7, 125.4, 125.1, 122.9, 122.3, 121.9, 118.1, 114.5, 114.4, 112.4, 108.1, 94.9, 89.1, 55.4; IR (KBr, thin film) ν_{max} (cm^{-1}): 3475.1, 3375.7 (-NH_2), 3059.4, 2927.9, 2177.5, 2361.2, 1733.9, 1923.8, 1607.0, 1518.2, 1484.7, 1450.4, 1244.9, 1177.2, 1111.6, 1024.5, 901.8, 826.5, 743.1, 635.9, 586.5, HRMS calcd for $C_{27}H_{19}NOS_2$+Na, 460.0823 $[M+Na]^+$, found 460.0800 $[M+Na]^+$.

Compond AD19:

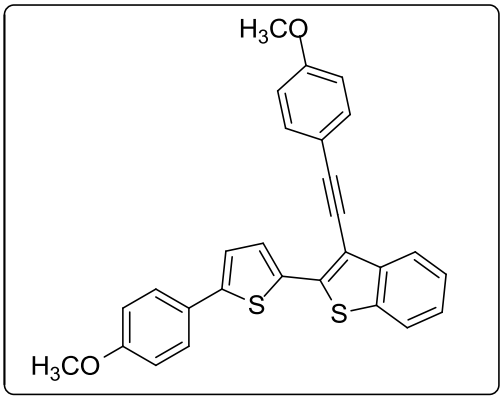


Figure 2.37. Synthesis of AD19.

The AD6 (100 mg, 0.7 mmol), in DMF (7 mL), triethylamine (3 mL), $PdCl_2(PPh_3)_2$ (7.85 mg, 0.035 mmol), 1-ethynyl-4-methoxybenzene (31.66 mg, 0.75 mmol), and CuI (2.13 mg, 0.035 mmol) to give product AD19 (92 % yield) as a yellow solid (Figure 2.37). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.84 Hz, 1H), 7.74 (d, *J* = 7.88 Hz, 1H), 7.56-7.64 (m, 5H), 7.43 (t, *J* = 7.12 Hz, 1H), 7.35 (t, *J* = 8.04 Hz, 1H), 7.20 (d, *J* = 3.88 Hz, 1H), 6.94 (t, *J* = 8.92 Hz, 4H), 3.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.5, 145.3, 140.7, 136.7, 134.7, 133.0, 130.9, 128.8, 127.8, 127.1, 126.9, 125.3, 125.0, 123.0, 122.3, 121.9, 115.5, 114.4, 114.2, 98.1, 83.0, 55.4; IR (KBr, thin film) ν_{max} (cm^{-1}): 3073.0, 2999.7, 2959.5, 2930.1, 2361.2, 2199.9, 1603.3, 1596.2, 1506.0, 1451.78, 1433.7, 1288.9, 1247.2, 1177.0, 1027.0, 823.9, 757.6, 668.1, HRMS calcd for $C_{28}H_{20}O_2S_2$+Na, 475.0820 $[M+Na]^+$, found 475.0796 $[M+Na]^+$.

3. RESULTS AND DISCUSSION

3.1. Synthesis of benzothiophene derivatives

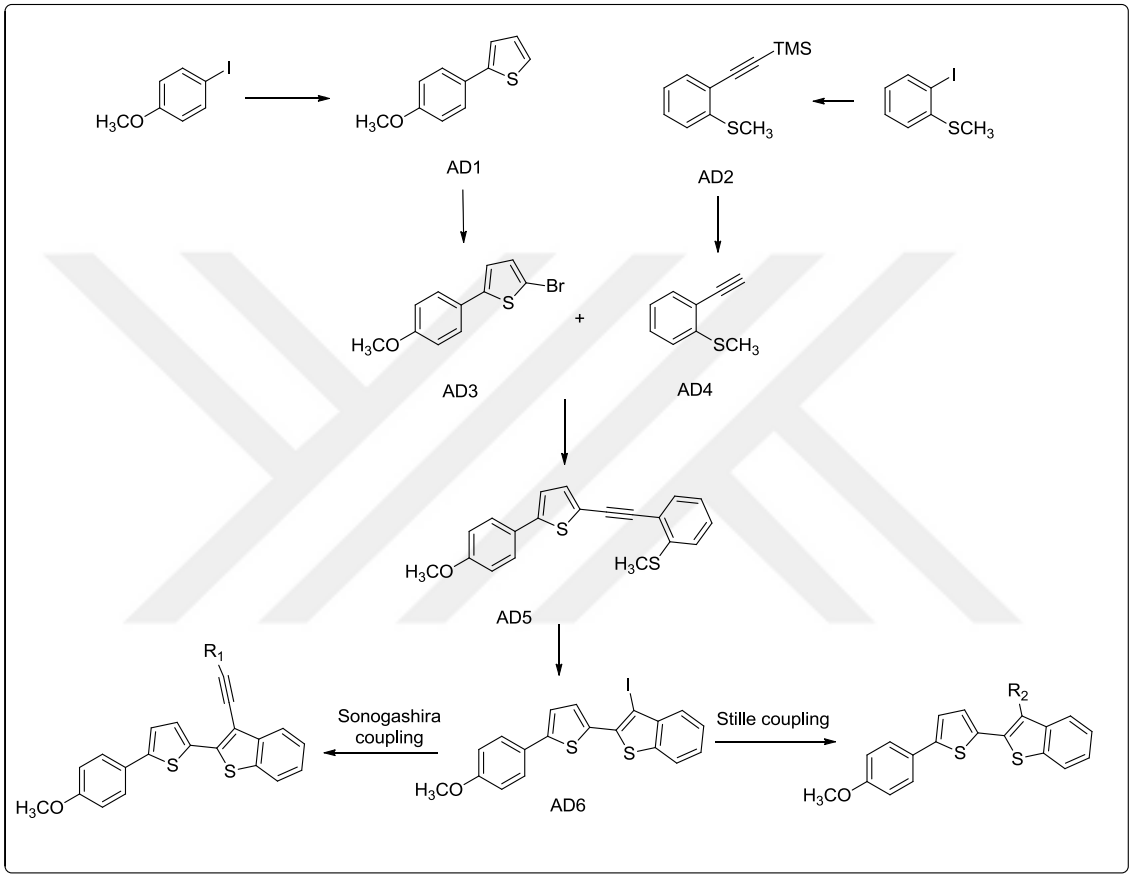


Figure 3.1. General synthetic pathway for the synthesis of benzothiophene.

3.1.1. Synthesis of 2-(4-methoxyphenyl)thiophene compound (AD1)

Aryl halide compounds are very important in organic chemistry because they can be used as starting materials for the formation of more complex natural products. Moreover, they are used for the increase the number of compounds before the testing biological properties or optoelectronic applications. Therefore, halogens have very critical roles for library studies. In the present study, Stille Coupling reactions and Sonogashira Cross coupling reactions were used for the synthesis of necessary starting

compounds and their derivatives. In addition, Electrophilic cyclization reaction was employed for the formation of 3-iodo substituted benzothiophene derivatives

In our study, Pd catalyzed Stille coupling reactions was firstly performed for the synthesis of AD1 as a starting compound. When 4-iodoanisole was allowed to react with 2-(tributylstannyl)thiophene in the presence of $Pd(PPh_3)_4$ as catalyst in toluene under argon at 110 ˚C for 3 hours, AD1 compound was obtained in 75 % yield as a white solid (Figure 3.2). The proposed reaction mechanism for the formation of desired compound AD1 are shown in (Figure 3.3).

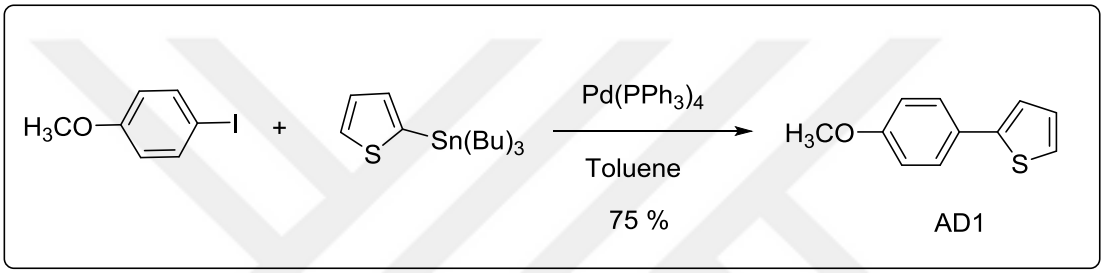


Figure 3.2. Synthesis of AD1.

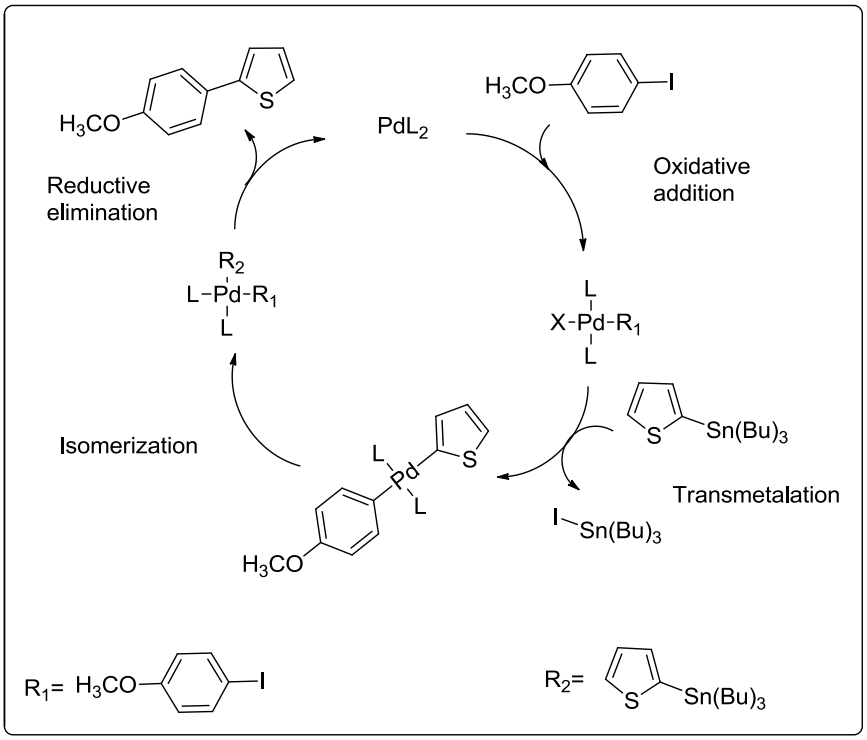


Figure 3.3. Proposed reaction mechanism for Stille coupling reaction.

3.1.2. Synthesis of 2-bromo-5-(4-methoxyphenyl)thiophene (AD3)

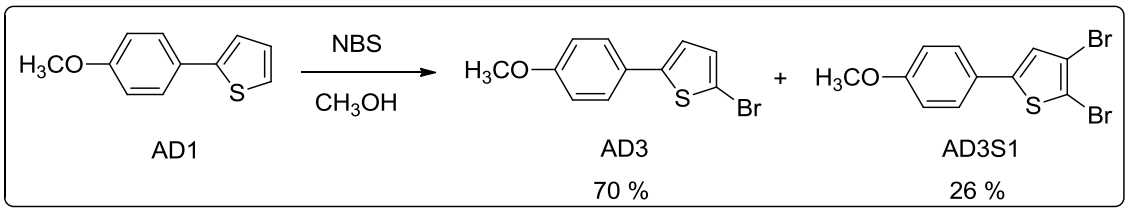


Figure 3.4. Synthesis of 2-bromo-5-(4-methoxyphenyl)thiophene (AD3).

In our methodology, we need to bromo substituted thiophenes before Sonogashira coupling reactions, so we synthesized AD3 by using bromination reactions. When AD1 was undergone to halogenation by *N*-bromosuccinimide (NBS) in chloroform for 3 hours at 0 ^{o}C, AD3 was obtained in 70% yield as a major product. Moreover, di-bromo substituted AD3S1 was formed in 26% yield as a minor product (Figure 3.4).

3.1.3. Synthesis of trimethyl((2-(methylthio)phenyl)ethynyl)silane (AD2)

Sonogashira coupling reactions are very useful to give the alkynylic intermediates. In literature, there are many different Sonogashira coupling reactions were applied for the preparation of complex organic structures. In our study, we prepared (2-ethynylphenyl)(methyl)sulfane AD4 by starting from 2-iodothioanisole by using Sonogashira coupling reaction (Avelina et al., 2008). If 2-iodothioanisole was reacted with trimethylsilylacetylene in the presence of $PdCl_2(PPh_3)_2$ as the catalyst, CuI as co-catalyst, and Et_3N as a base, compound AD2 was formed in 99% yield (Figure 3.5). After preparation of compound AD2, we used desilylation reaction to remove of the TMS protecting group. When compound AD2 was allowed to react with K_2CO_3 in methanol at room temperature for 2 hours, we obtained desired terminal alkyne AD4 in an excellent 99 % yield (Figure 3.6).

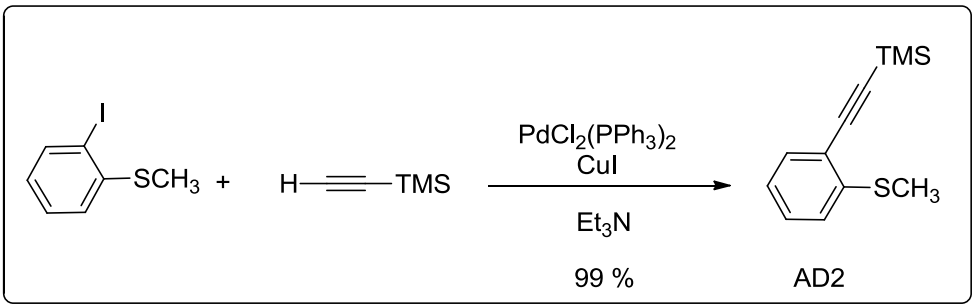


Figure 3.5. Synthesis of AD2.

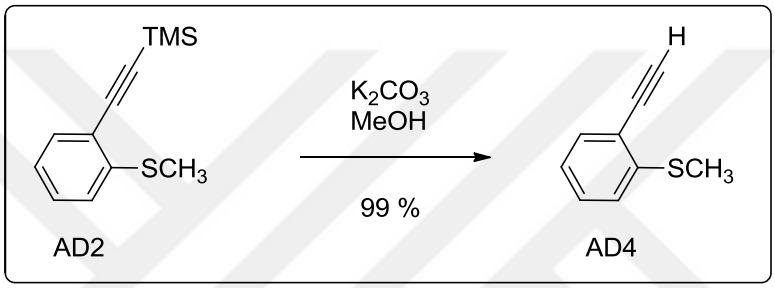


Figure 3.6. Desilylation reaction for the synthesis of compound AD4.

3.1.4. Synthesis of 2-(4-methoxyphenyl)-5-((2-(methylthio) phenyl) ethynyl) thiophene (AD5)

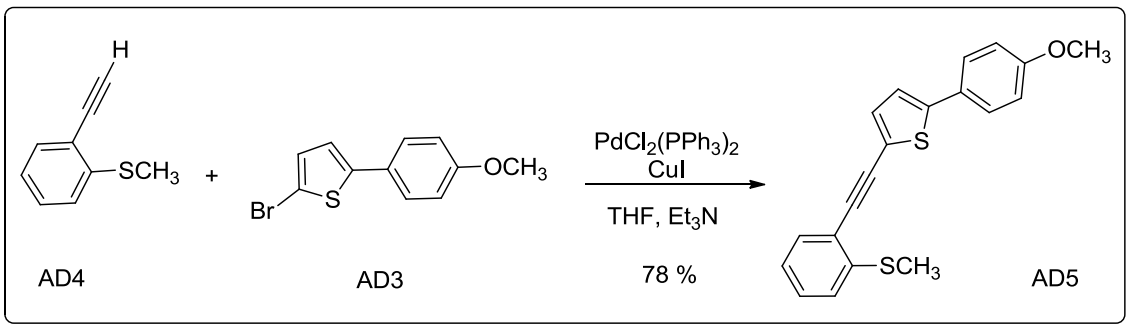


Figure 3.7. Synthesis of compound AD5 via Sonogashira coupling reaction.

After characterization of the desired starting compounds (AD3 and AD4) reaction, we synthesized our alkynylic intermediates AD5 by using Sonogashira coupling reaction. When AD3 was undergone to coupling reaction with AD4 in the

presence of Pd-catalyst, we obtained AD5 in 78% yield. The coupling reaction was carried out $PdCl_2(PPh_3)_2$ catalyst, CuI as co-catalyst, Et_3N as a base at 70 ^oC for 16 hours under inert athmosphere (Figure 3.7). As shown in (Figure 3.8), the possible reaction mechanism was proposed for the formation of desired compound AD5.

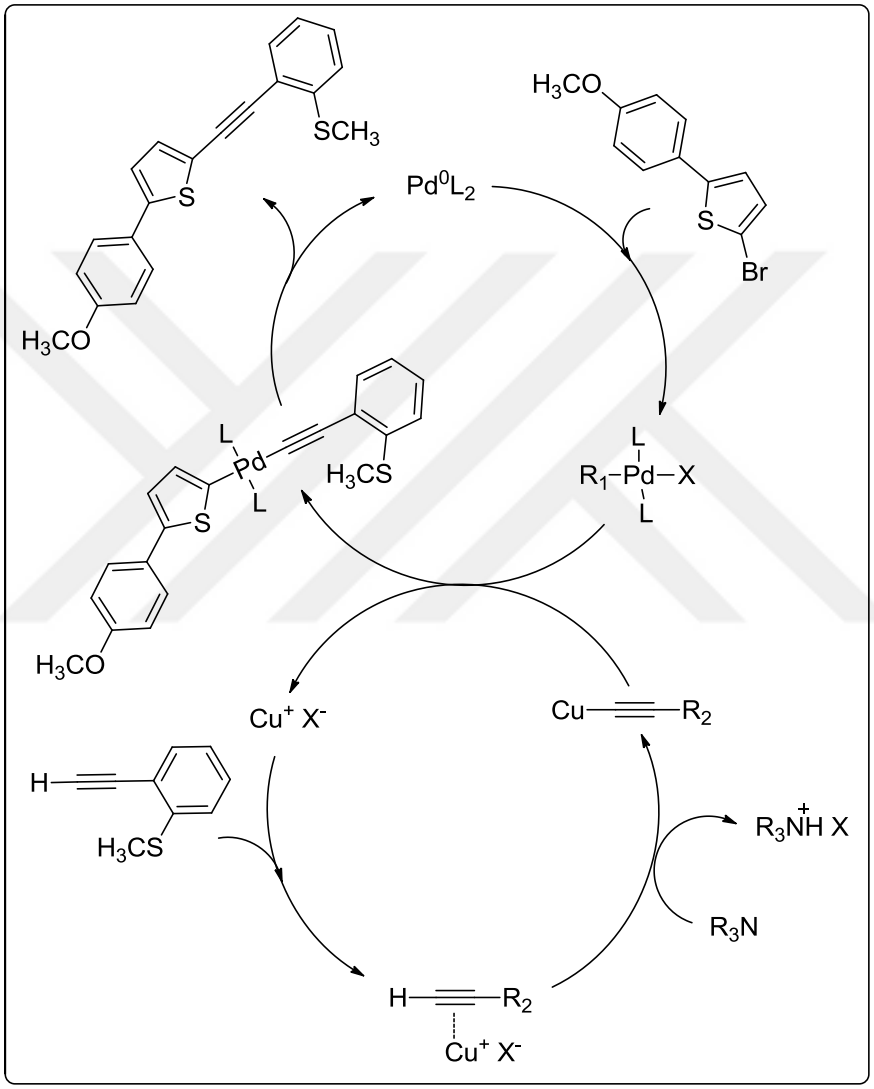


Figure 3.8. Proposed reaction mechanism for Sonogashira coupling reaction to AD5.

3.1.5. Synthesis of 3-iodo-2-(5-(4-methoxyphenyl)thiophen-2-yl)benzo[b]thiophene (AD6)

Last decades, electrophilic cyclization reactions have been gained big importance for the synthesis of new heteroaromatic molecules. A variety of heterocyclic compounds including indoles, benzothiophenes, furans, quinones, pyroles etc. have been synthesized by using electrophilic cyclization reactions. These type cyclization reactions are very useful for design of novel heteroaromatics. Recently, Kıvrak et al. investigated novel synthetic methologies for the formation of pyrazoles, benzothiophenes. In our study, we tried to synthesize novel thiophene-substituted benzothiophenes by starting from anisole. For the formation of 3-iodobenzothiophene derivative AD6, we used standard electrophilic cyclization procedures in the presence of molecular iodide. When AD5 was reacted with molecular iodide in dichloromethane at room temperature for 30 minutes, we obtained regioselectively desired product AD6. The isolated yield was to be 70% yield (Figure 3.9).

The possible reaction mechanism for the formation of benzothiophene AD6 was displayed in (Figure 3.10).

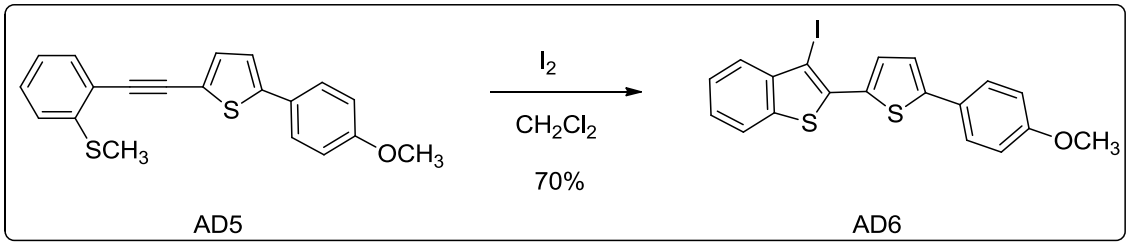


Figure 3.9. Electrophilic cyclization reaction for the formation of AD6.

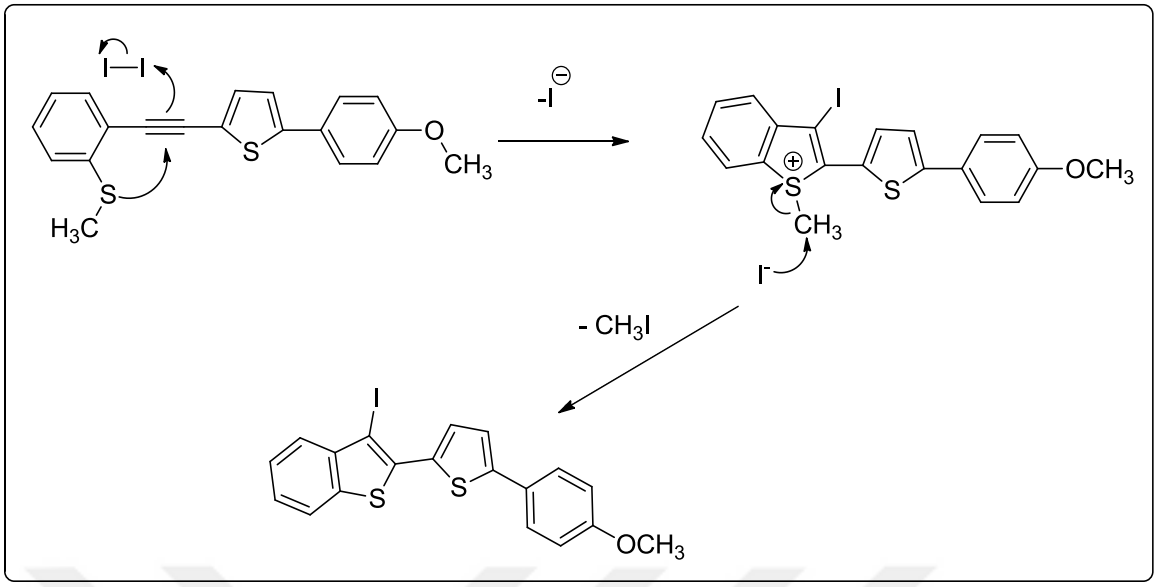


Figure 3.10. Possible reaction mechanism for electrophilic cyclization reaction.

3.1.6. Stille Coupling reactions

In the second part of our studies, we were tried to synthesis 3-hetero substituted benzothiophenes by using Pd catalyzed Stille coupling reactions. Firstly, AD6 was reacted with 2-(tributylstannyl)thiophene in the presence of $Pd(PPh_3)_4$ as catalyst in Toluene at 110^{o}C for overnight, desired product AD8 was formed in 84% yield (Figure 3.11). In addition, same reaction conditions were applied for the synthesis of AD10 in 80% yield of desired compound was isolated as a single product (Figure 3.12).

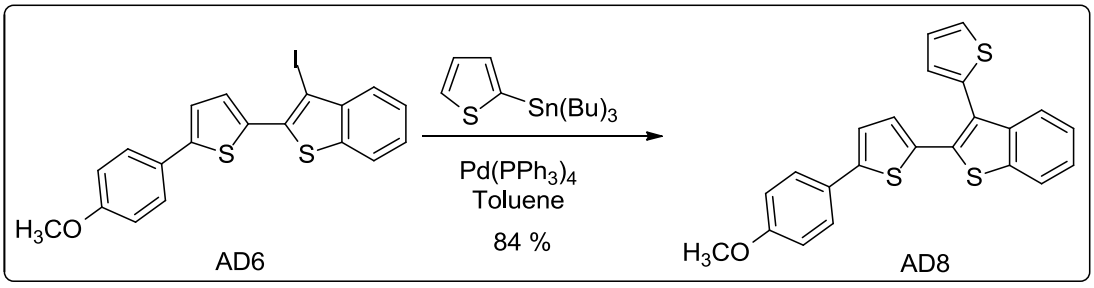


Figure 3.11. Synthesis of compound AD8 via Stille coupling reactions.

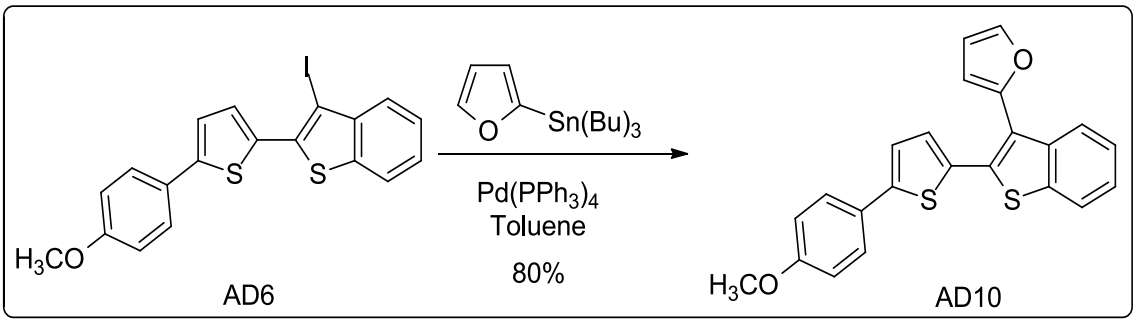
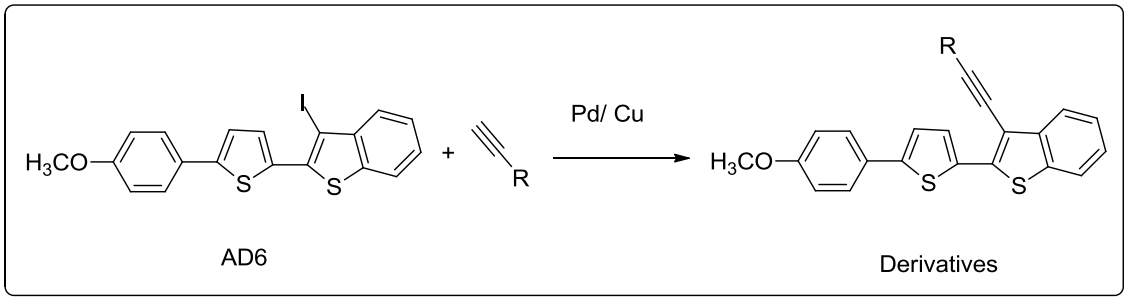


Figure 3.12. Synthesis of compound AD10 via Stille coupling reactions.

3.1.7. Synthesis of 2-(5-(4-methoxyphenyl)thiophen-2-yl)-3-(substituted-ethynyl)benzo[b]thiophene

After isolation and characterization of AD6, the coupling properties were tested by using Sonogashira reaction in the presence of Pd-catalyst. As seen in Table (3.1), a variety of 3-alkynylic-benzothiophene derivatives (AD9, AD11, AD12, AD14, AD15, AD16, AD17 and AD19) were synthesized from coupling reactions. When AD6 was allowed to react with phenylacetylene in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in DMF/Et_3N at room temperature, AD9 was obtained in 94% yield. When the effect of alkyl chains were tested by using TMS and heptyl, the 73% yield of AD11 and 90% yield of AD12 was found, respectively. If the same reaction condition was applied for the synthesis of AD14, the isolated yield was found as 69% yields. Notably, AD15 was obtained in moderate yield (77%). Interestingly, the reaction between AD6 and 2-iodoaniline gave the highest yield as 98% yields. It was also tested for coupling reactions for poly-substituted compounds, we isolated in 80% yields of expected product AD16. When our standard reaction conditions were used for the formation of compound AD19, we obtained in 92% yields. As a result, Sonogashira cross coupling reactions were found to be general for a wide range of our halo-aromatic compounds and tolerated the presence of aromatic, poly-aromatic and heteroaromatic moieties with electron-withdrawing and electron-donating substituents.

Table 3.1: Synthesis of benzothiophene derivatives via Sonogashira coupling reactions.



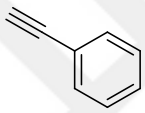
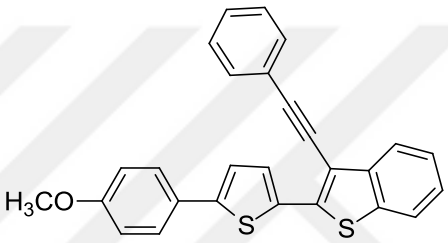
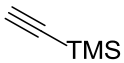
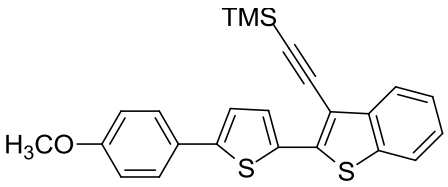
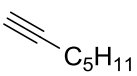
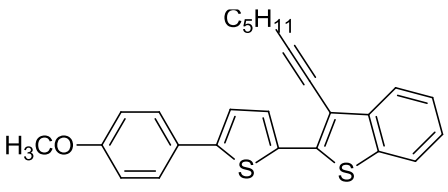
No	Alkyne	Product	Yield %
1		 AD9	94
2		 AD11	73
3		 AD12	90

Table 3.1. Synthesis of benzothiophene derivatives via Sonogashira coupling reactions (continued)

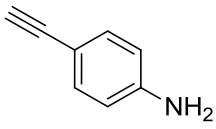
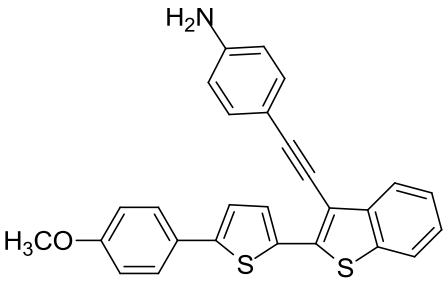
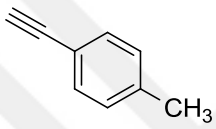
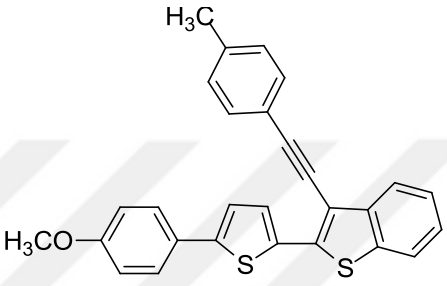
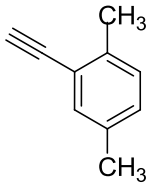
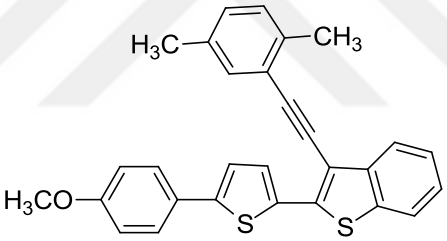
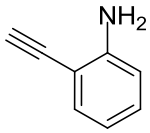
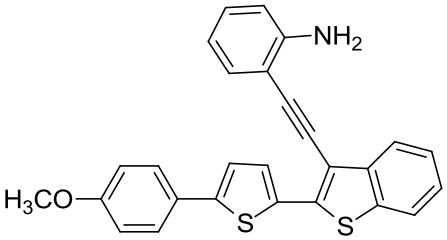
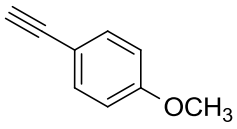
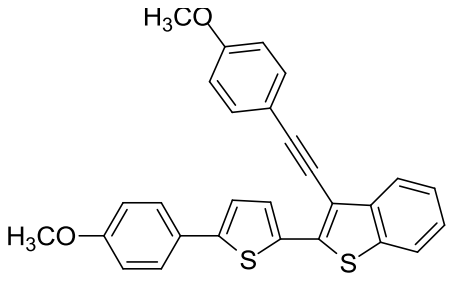
4		 AD14	69
5		 AD15	77
6		 AD16	80
7		 AD17	98

Table 3.1. Synthesis of benzothiophene derivatives via Sonogashira coupling reactions (continued)

8		 AD19	92

4. CONCLUSION

S-Containing heterocyclic compounds are important class of compounds in pharmaceutical and agrochemical industries. Especially, thiophenes, benzothiophene and their derivatives have various advantages for biological applications. In recent year, fused heterocyclic compounds have been successfully synthesized by using a variety of synthetic path ways. Moreover, the importance role of sulfur containing heterocycles prompted scientist to find the novel benzothiophene derivatives.

In the present study, we developed a novel method for the synthesis of anisole substituted benzothiophene derivatives by using electrophilic cyclization reactions and coupling reactions. In the first part of study, we prepared novel alkynylic-thiophene starting from anisole by using Pd-catalyzed Sonogashira and Stille cross coupling reactions. After isolation and characterization of alkynylic-thiophene AD5, electrophilic cyclization reaction was carried out for the formation of 3-iodo substituted AD6.

In the last part of our study, Sonogashira coupling reactions and Stille coupling reactions were performed for the synthesis of benzothiophene derivarives. Then, it was tested for coupling reactions with a variety of ethynyl and heteroaryl derivatives. As a result, it was found that AD6 might be useful precursor for the synthesis of potentially active novel organic molecules via coupling reactions in future studies. Moreover we characterized all intermediates and final product by using spectroscopic methods including IR, ^{1}H NMR, ^{13}C NMR, Mass and chemical analysis, and we proposed reaction mechanism.

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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.

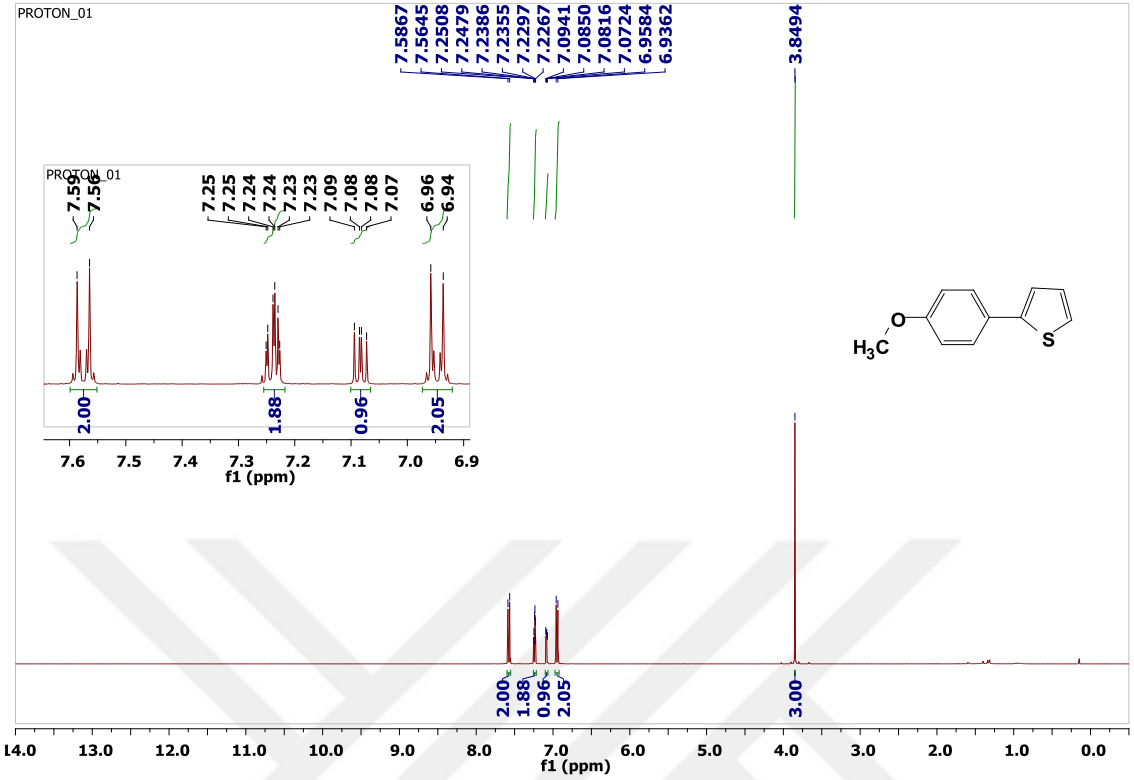


Figure A 1. ^{1}H NMR spectra of AD1.

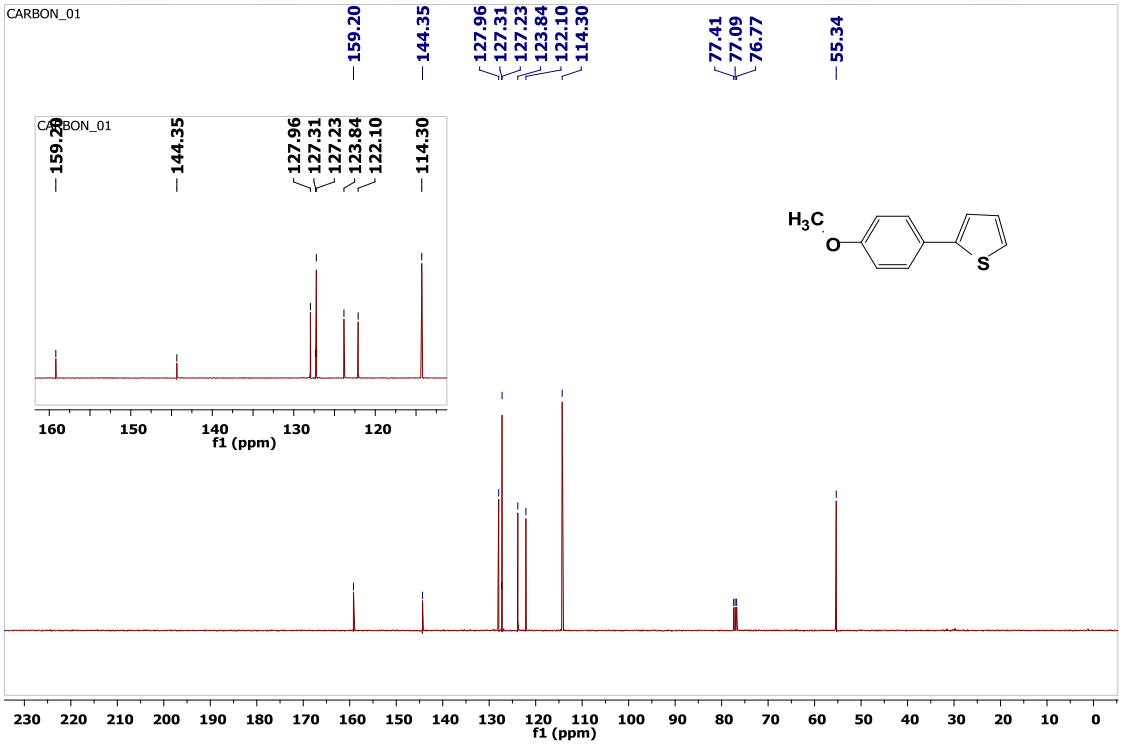


Figure A 2. ^{13}C NMR spectra of AD1.

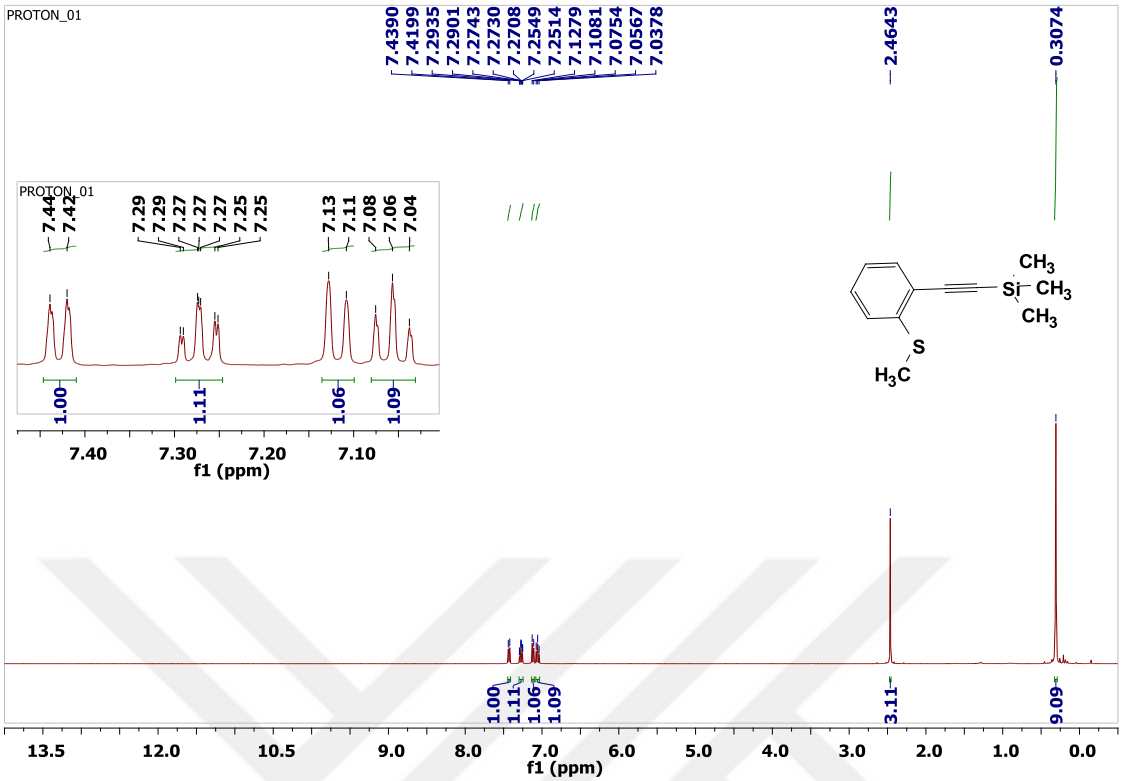


Figure A 3. ^{1}H NMR spectra of AD2.

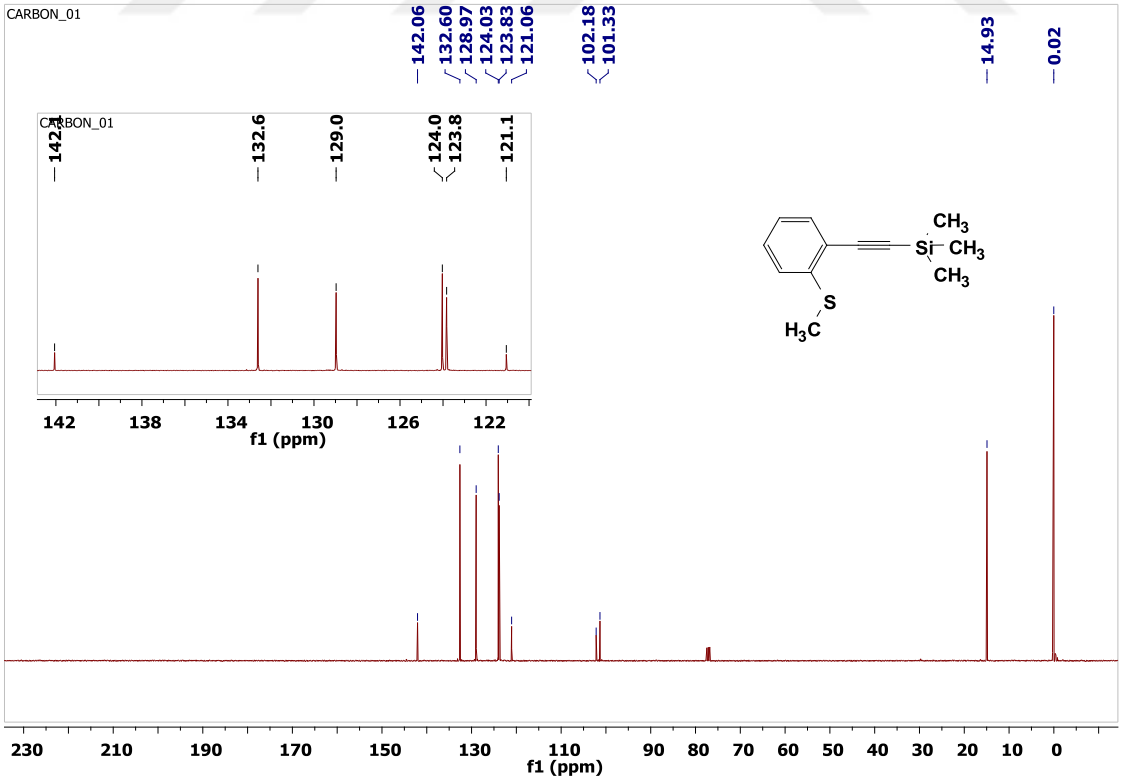


Figure A 4. ^{13}C NMR spectra of AD2.

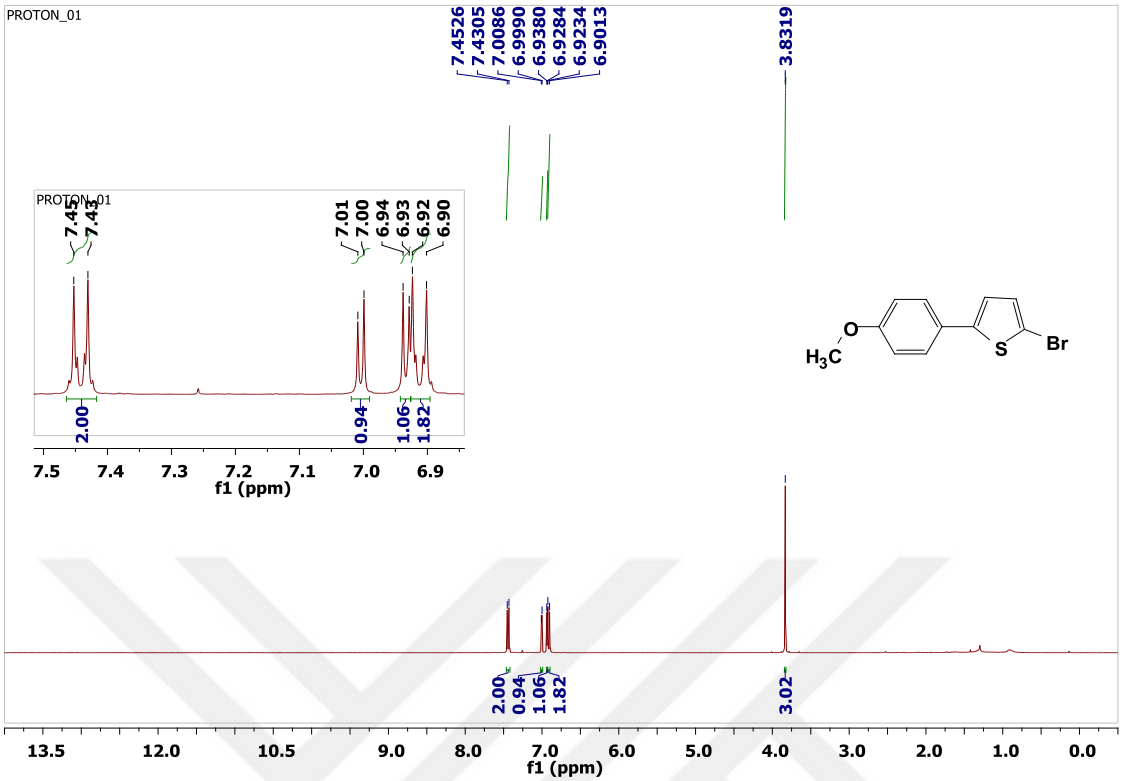


Figure A 5. ^{1}H NMR spectra of AD3.

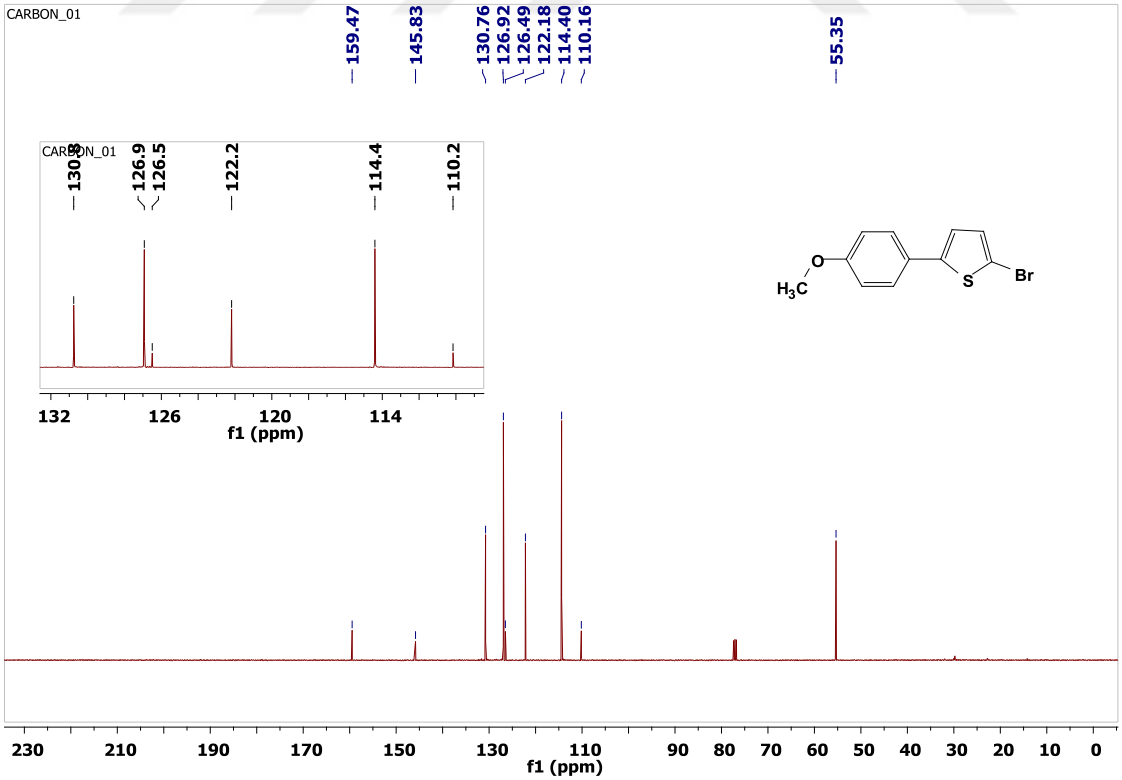


Figure A 6. ^{13}C NMR spectra of AD3.

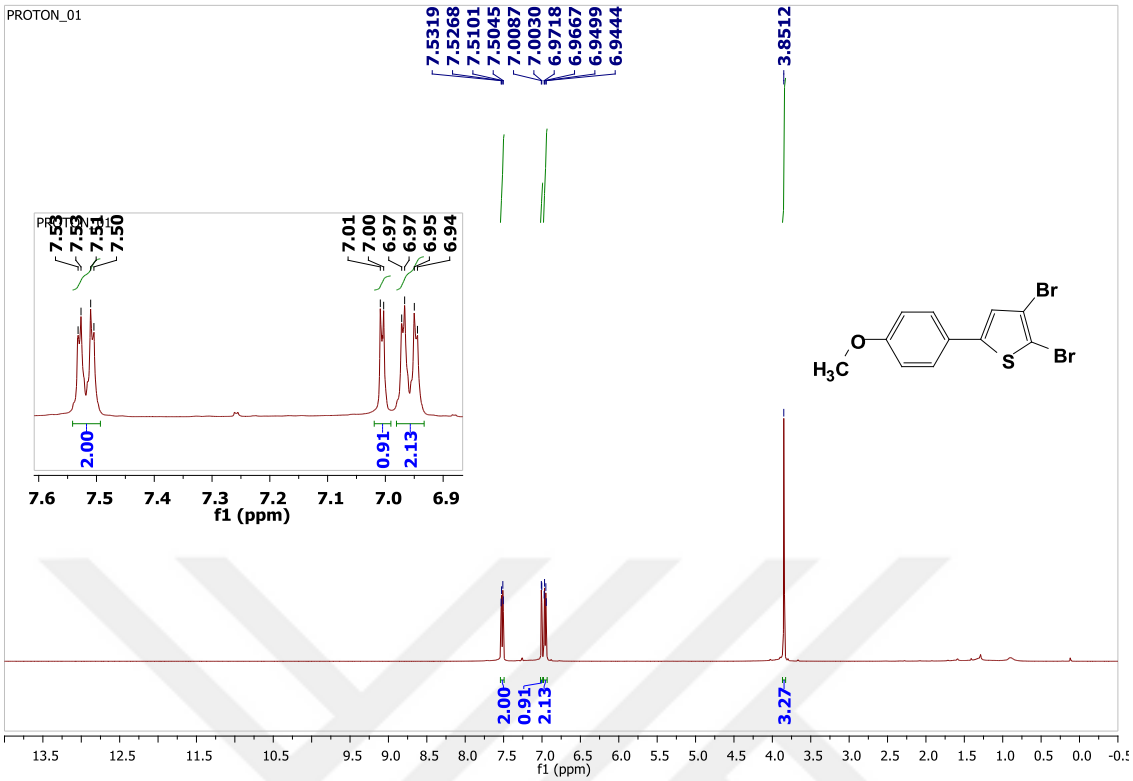


Figure A 7. ^{1}H NMR spectra of AD3S1.

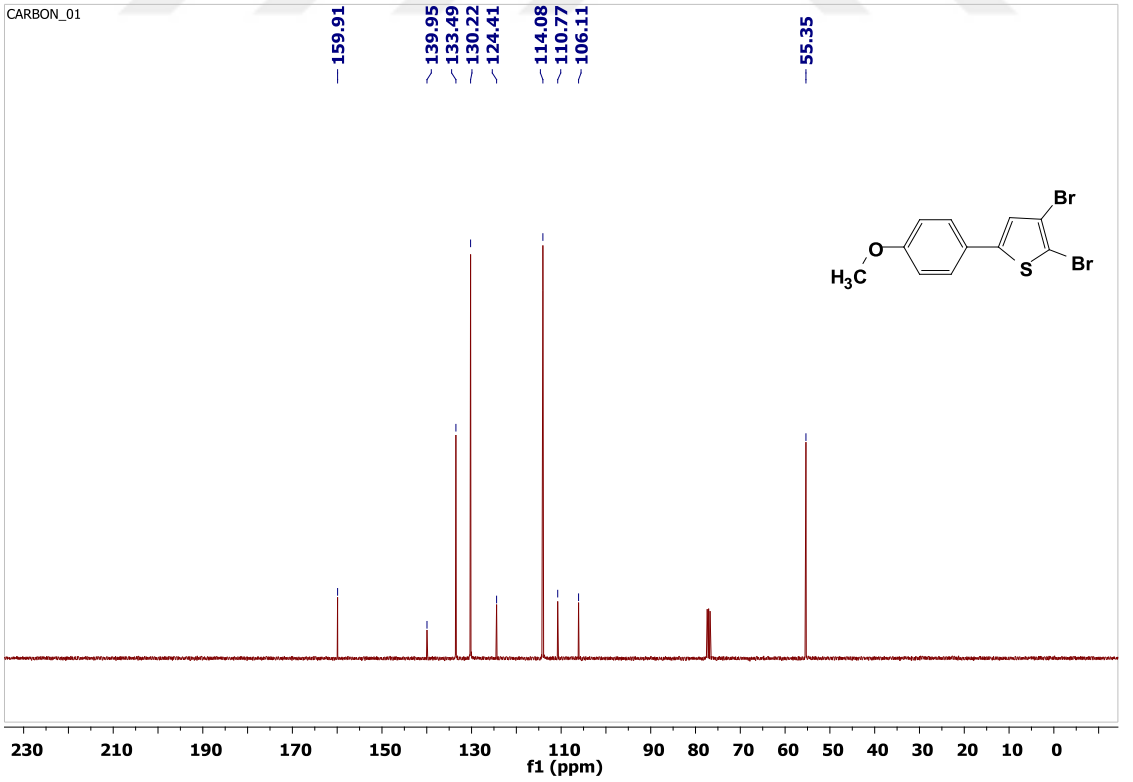


Figure A 8. ^{13}C NMR spectra of AD3S1.

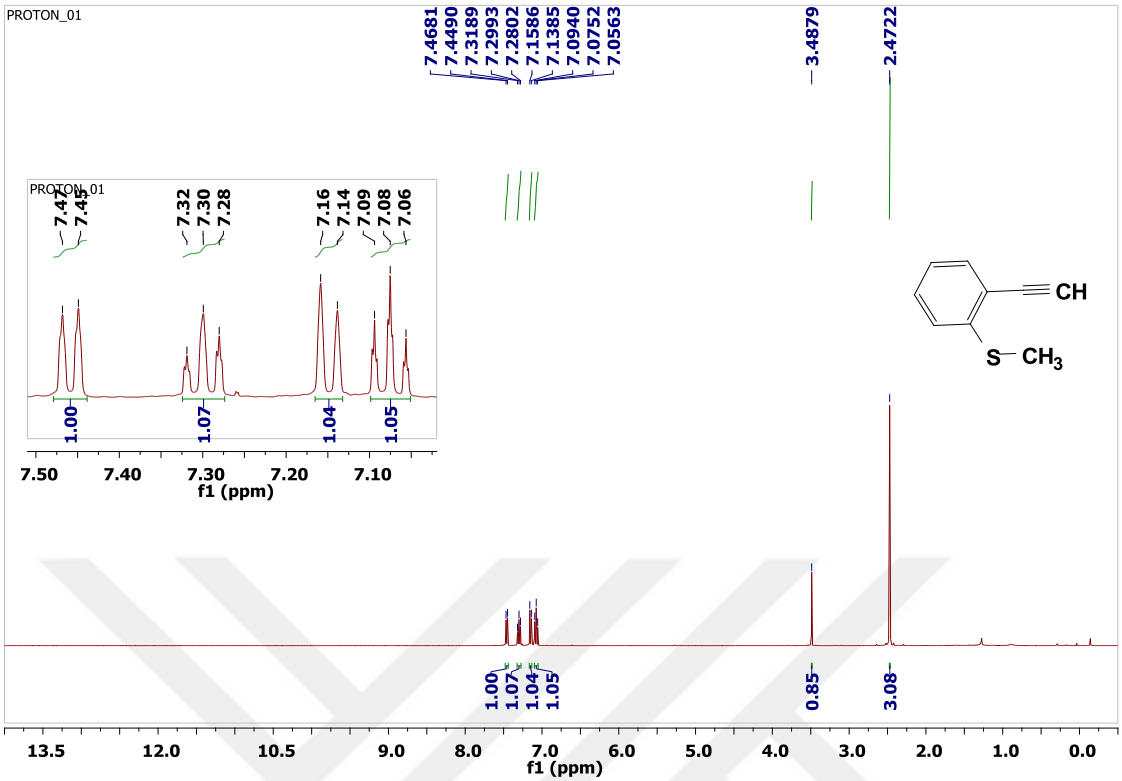


Figure A 9. ^{1}H NMR spectra of AD4.

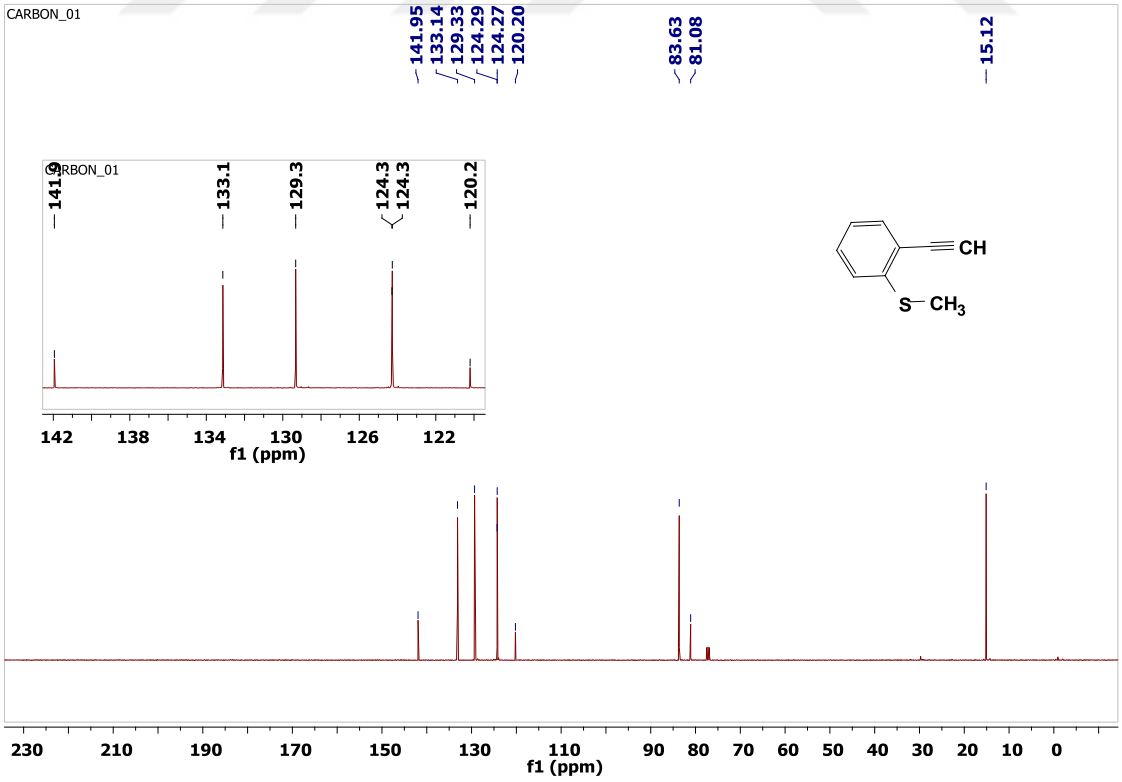


Figure A 10. ^{13}C NMR spectra of AD4.

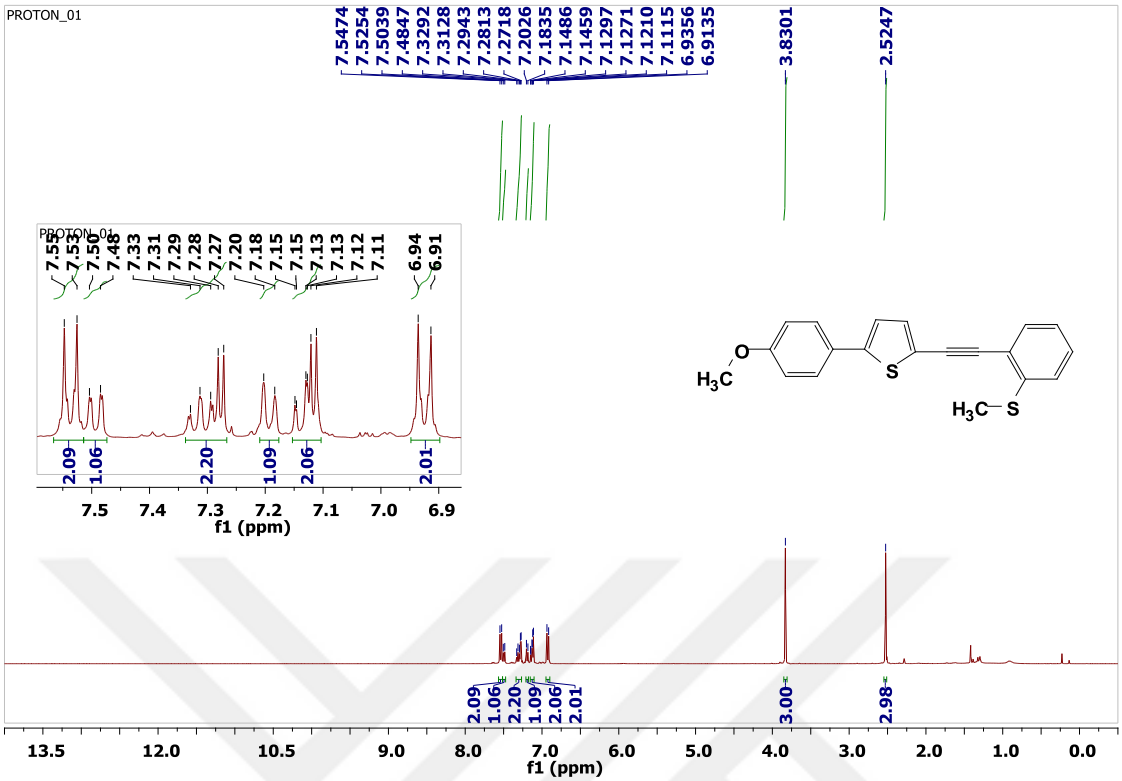


Figure A 11. ^{1}H NMR spectra of AD5.

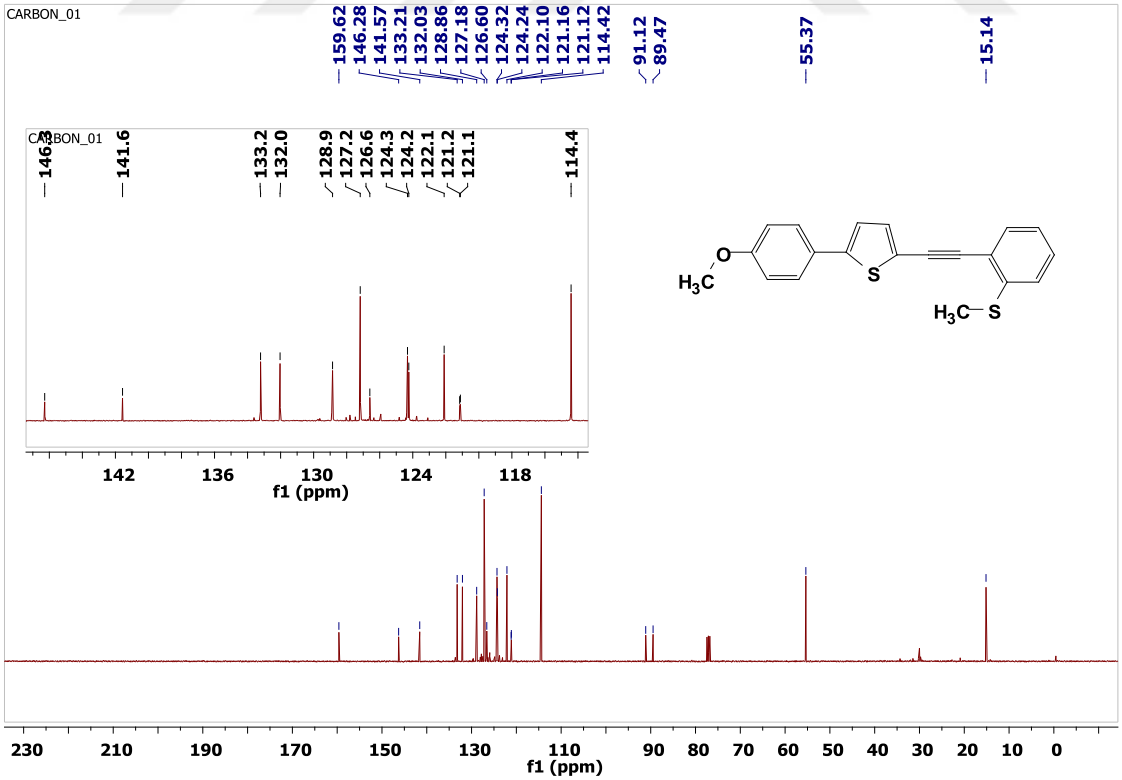


Figure A 12. ^{13}C NMR spectra of AD5.

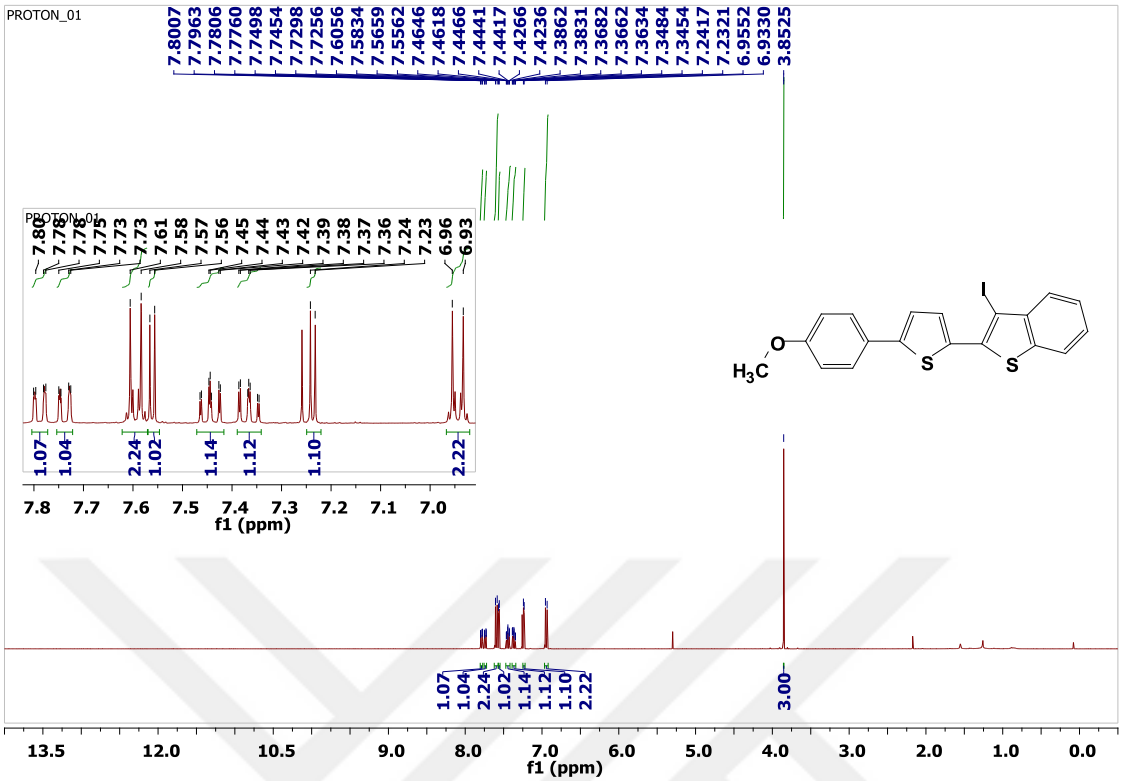


Figure A 13. ^{1}H NMR spectra of AD6.

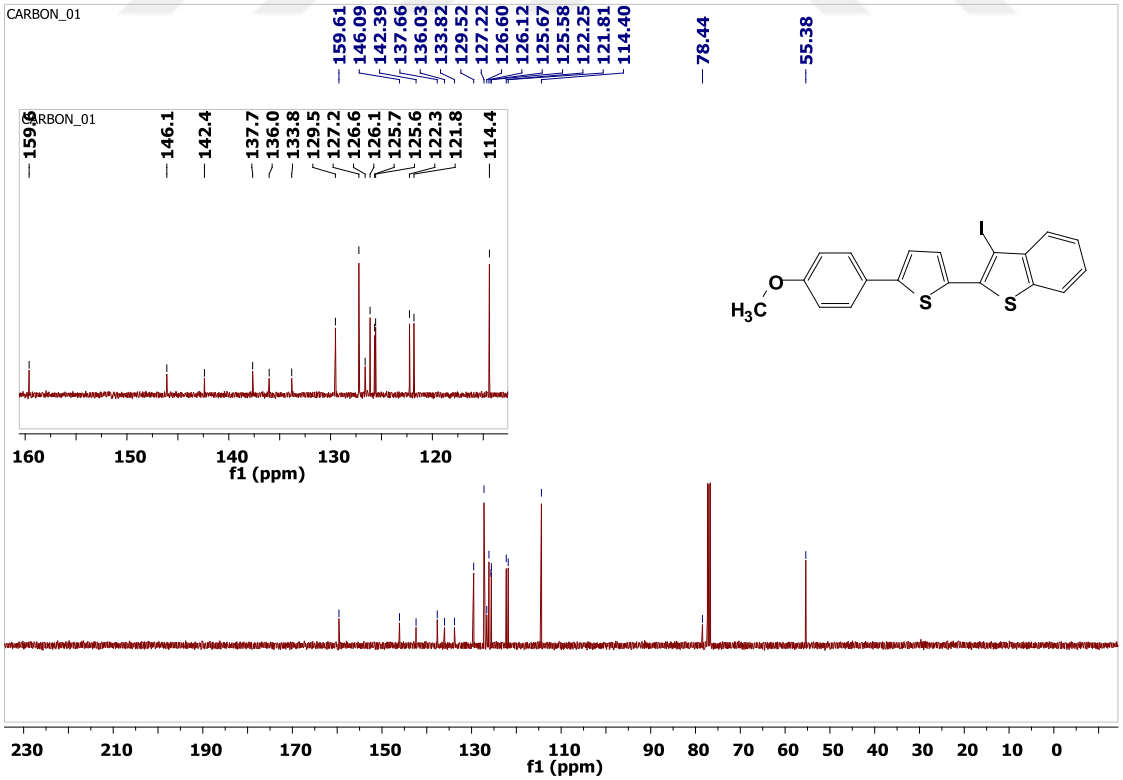


Figure A 14. ^{13}C NMR spectra of AD6.

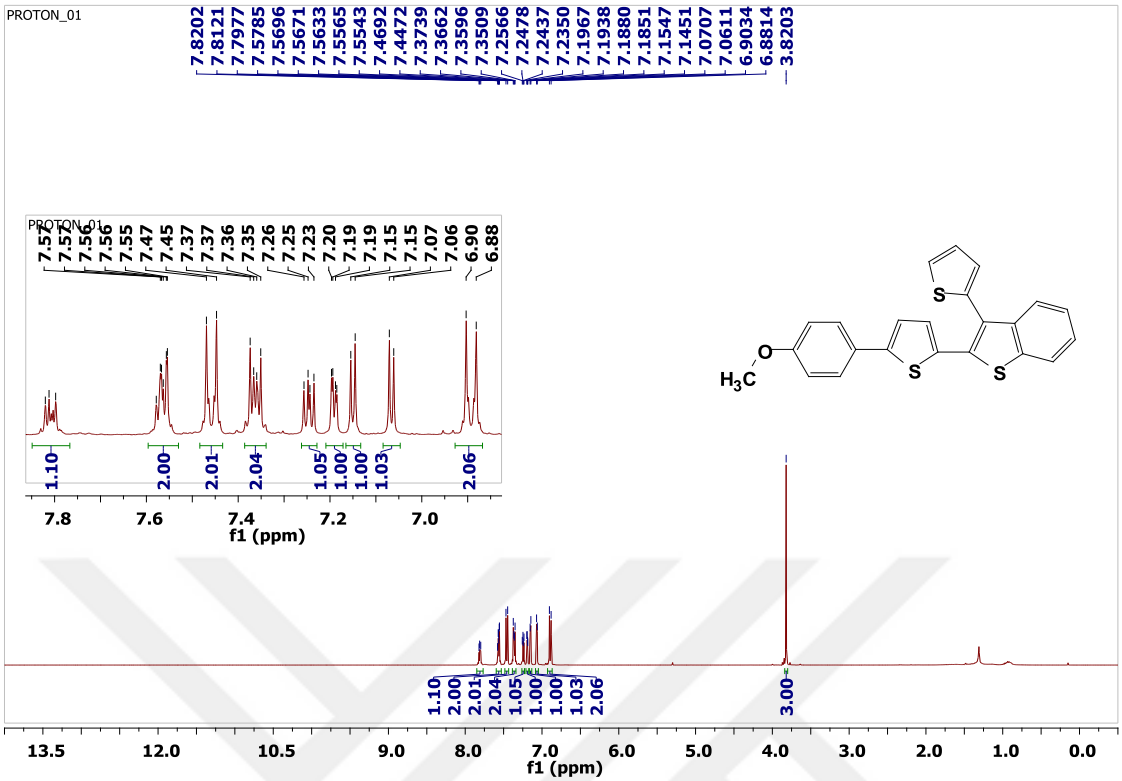


Figure A 15. ^{1}H NMR spectra of AD8.

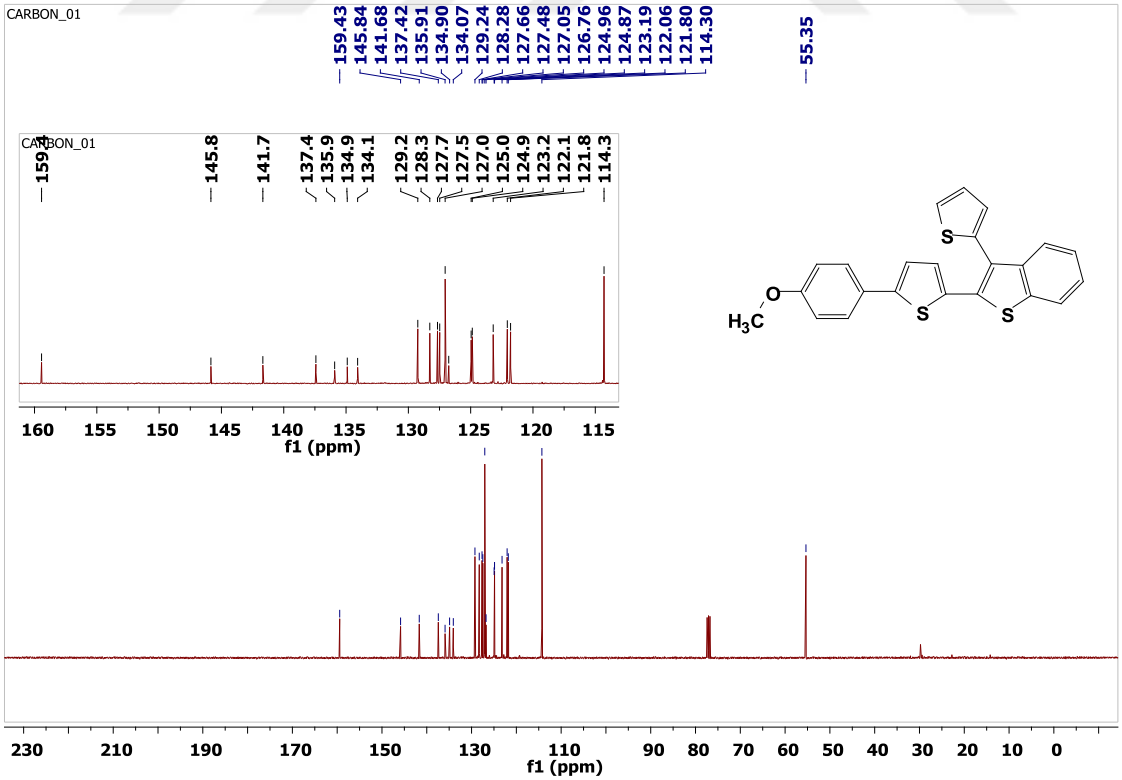


Figure A 16. ^{13}C NMR spectra of AD8.

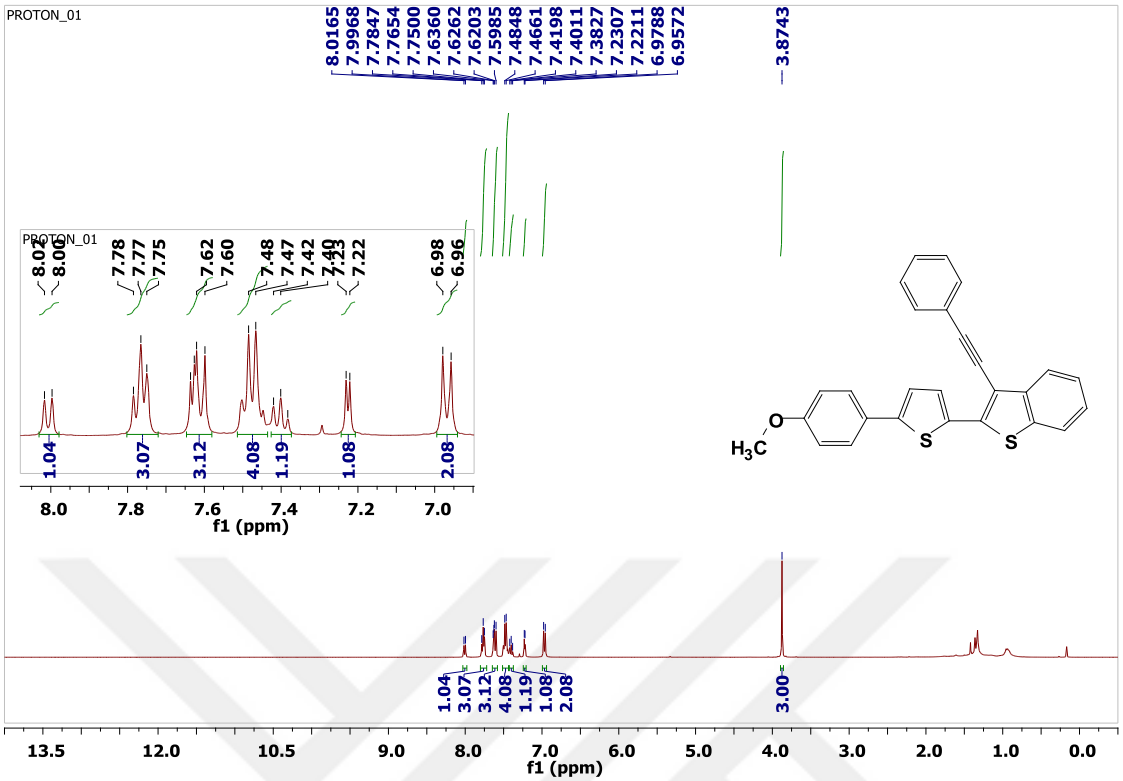


Figure A 17. ^{1}H NMR spectra of AD9.

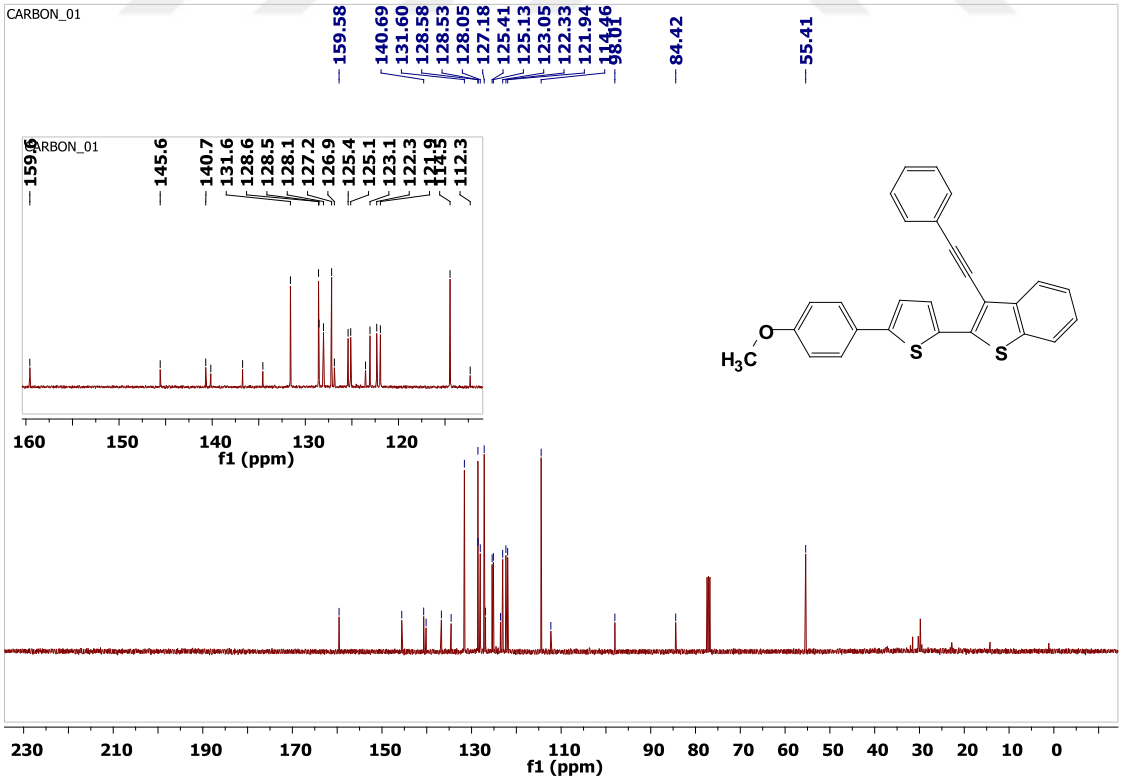


Figure A 18. ^{13}C NMR spectra of AD9.

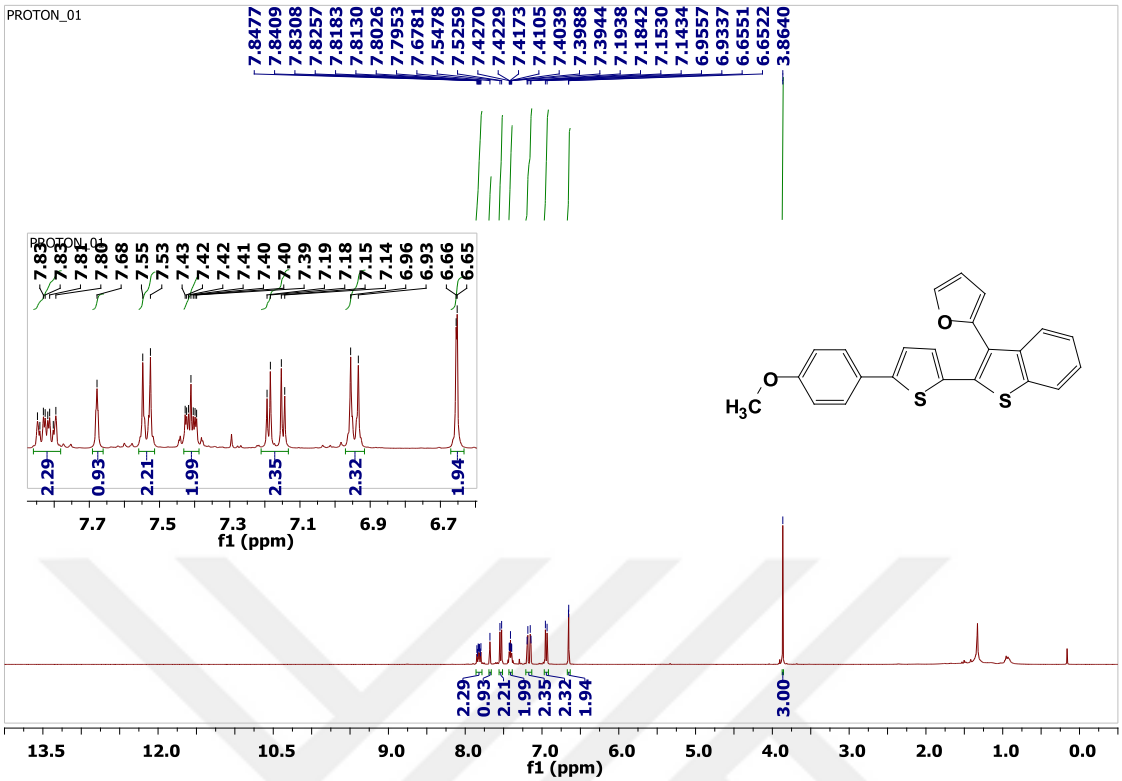


Figure A 19. ^{1}H NMR spectra of AD10.

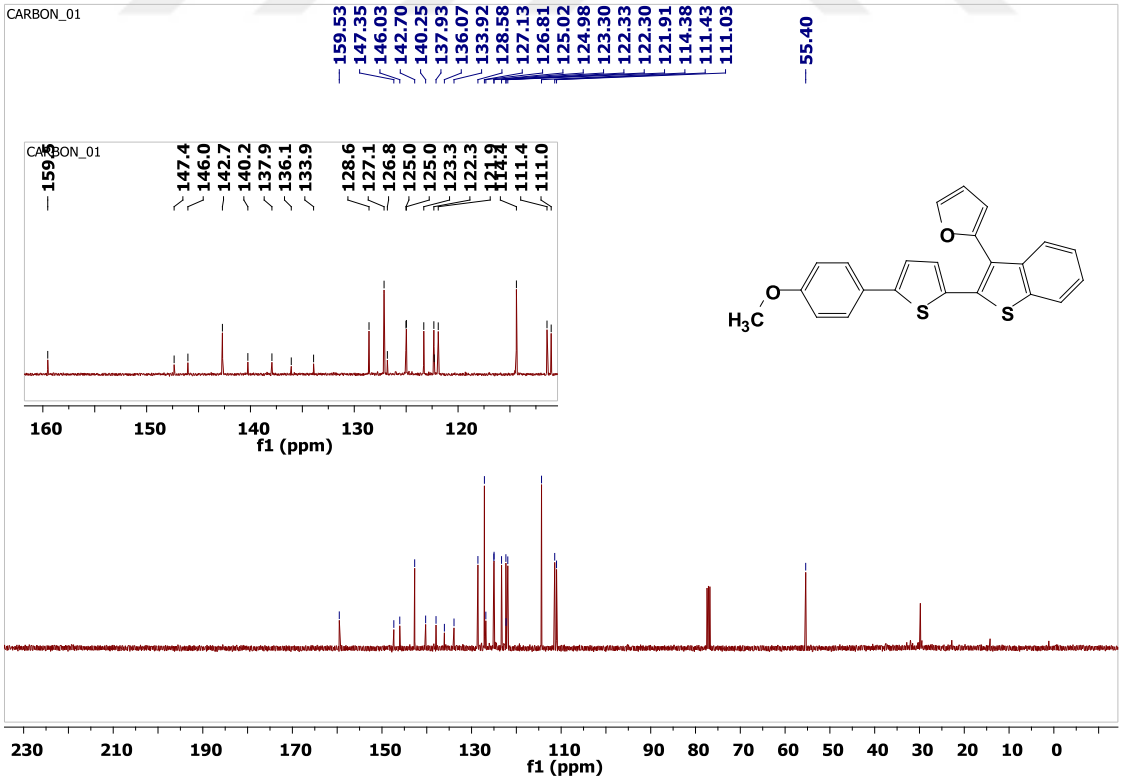


Figure A 20. ^{13}C NMR spectra of AD10.

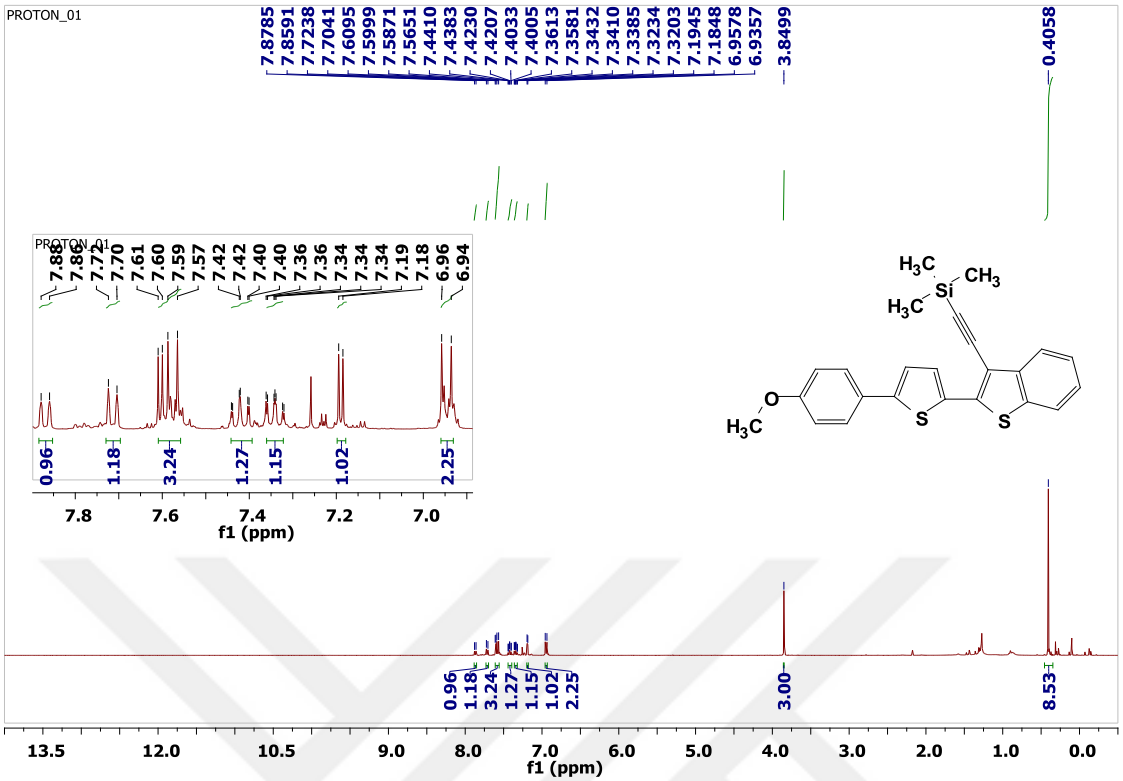


Figure A 21. ^{1}H NMR spectra of AD11.

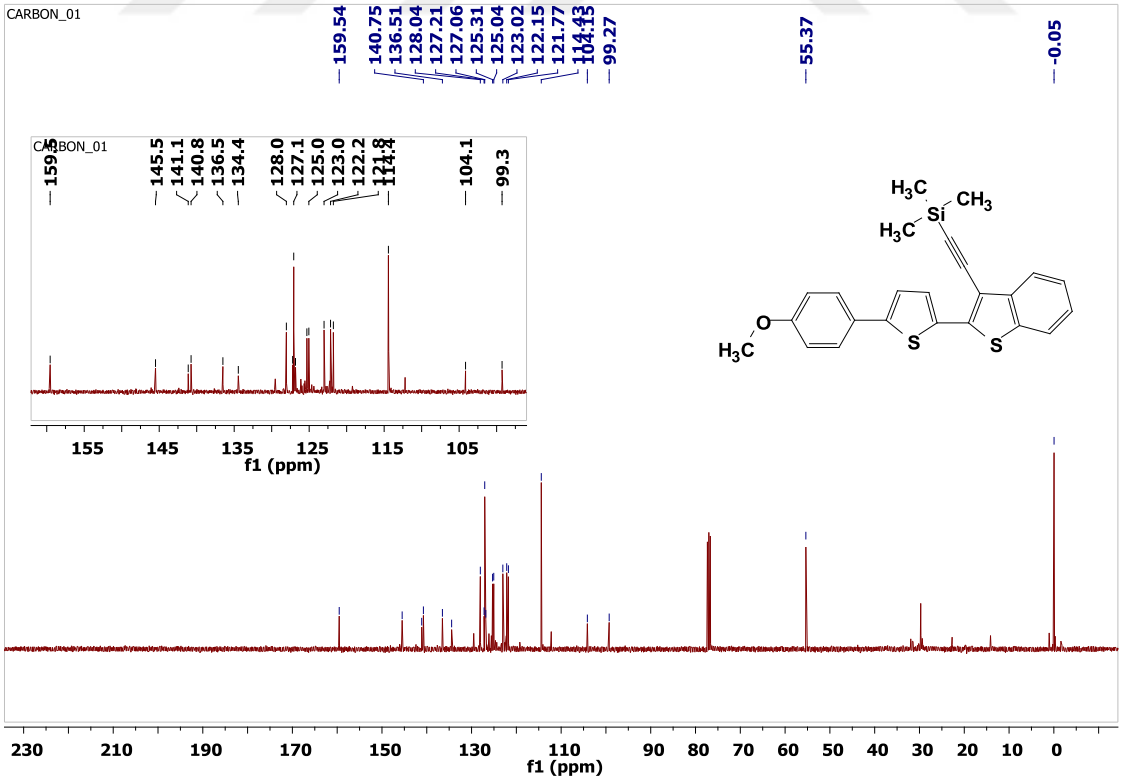


Figure A 22. ^{13}C NMR spectra of AD11.

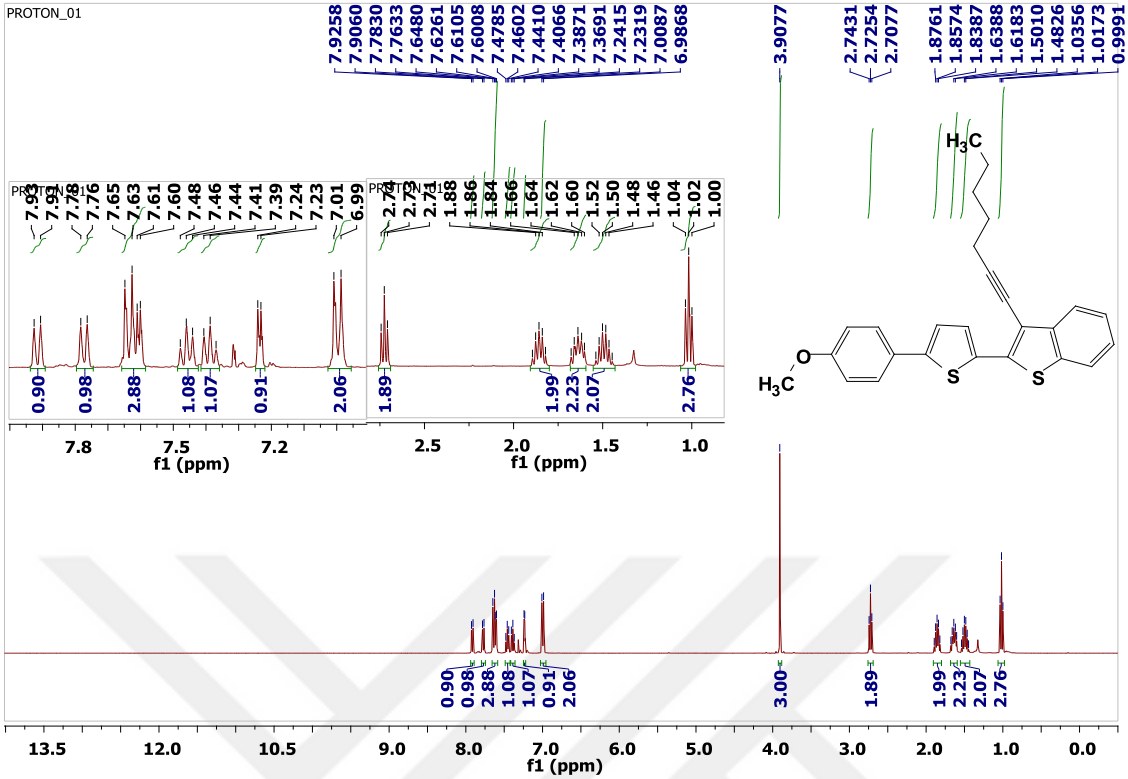


Figure A 23. ^{1}H NMR spectra of AD12.

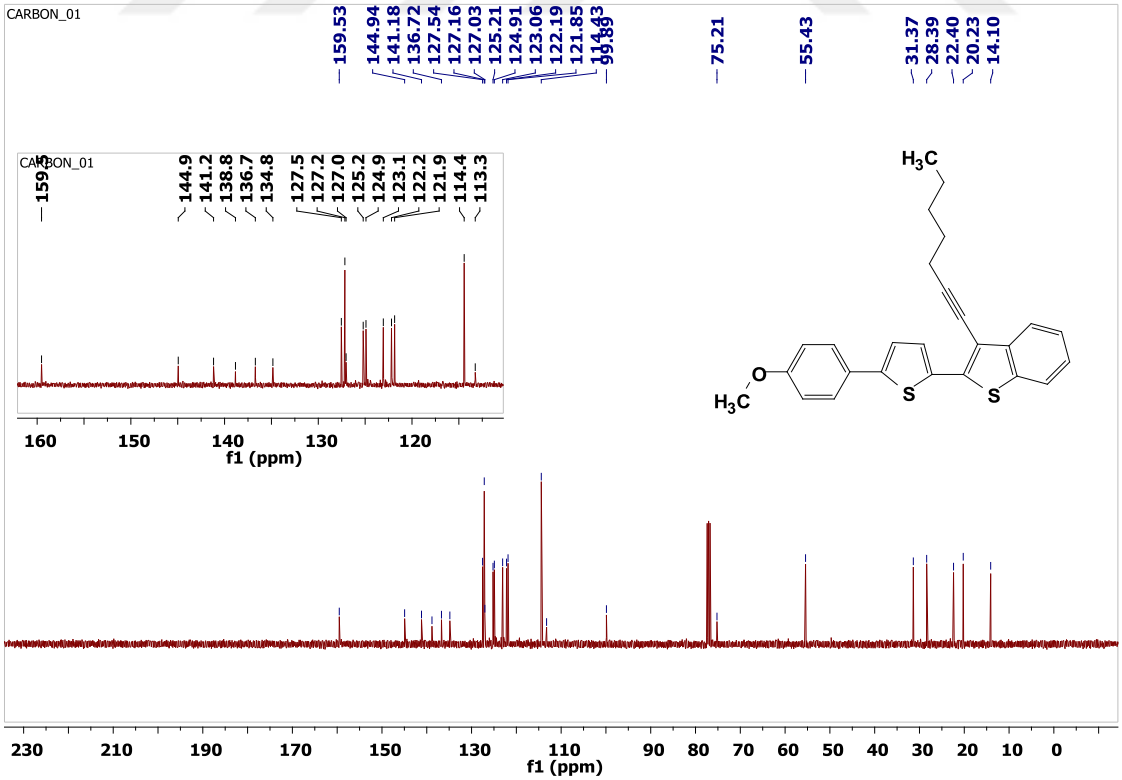


Figure A 24. ^{13}C NMR spectra of AD12.

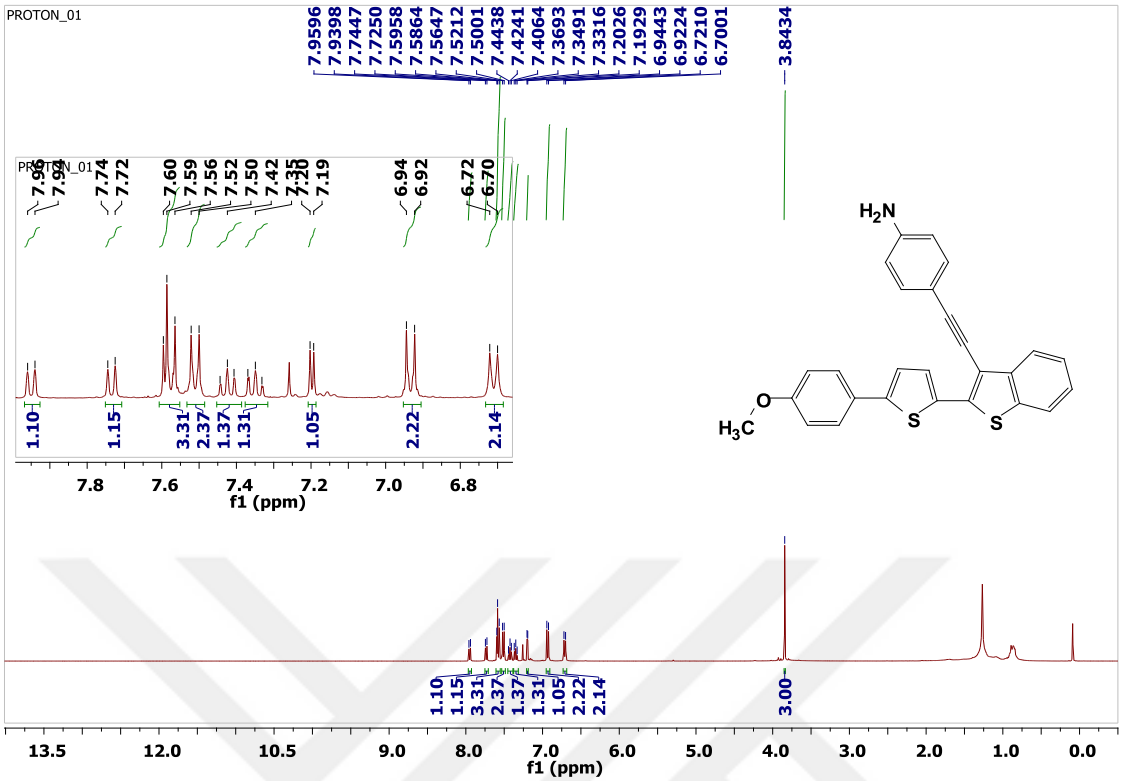


Figure A 25. ^{1}H NMR spectra of AD14.

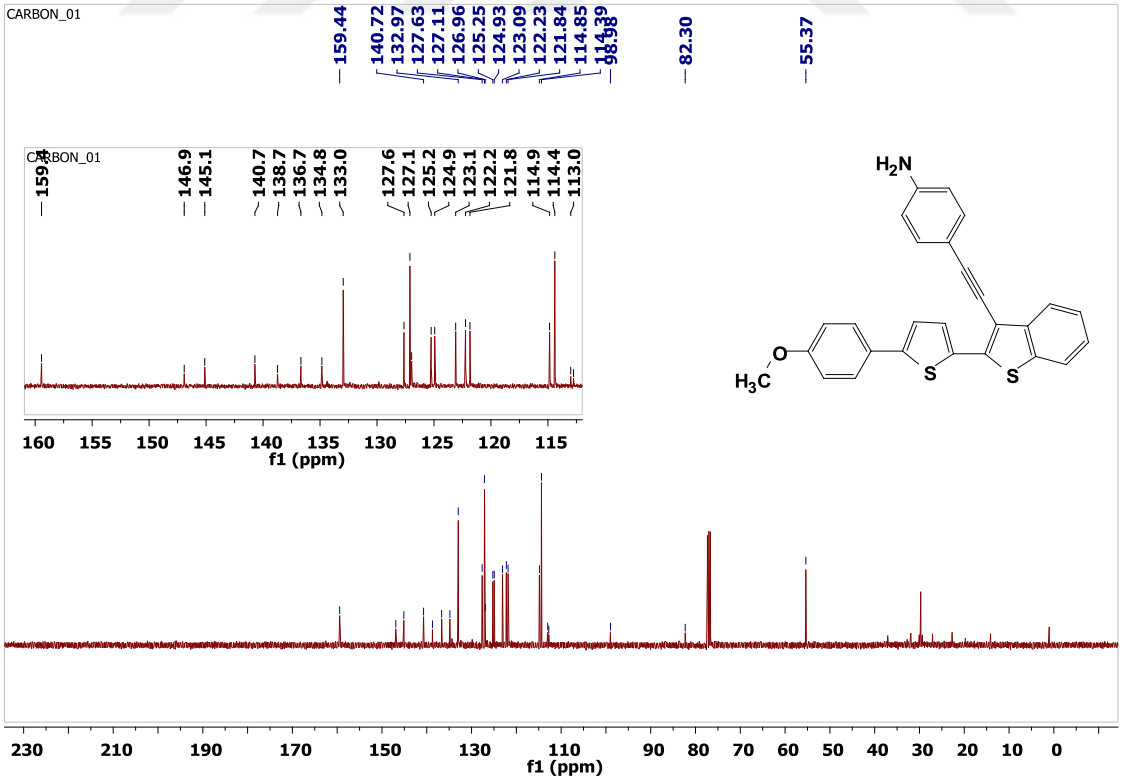


Figure A 26. ^{13}C NMR spectra of AD14.

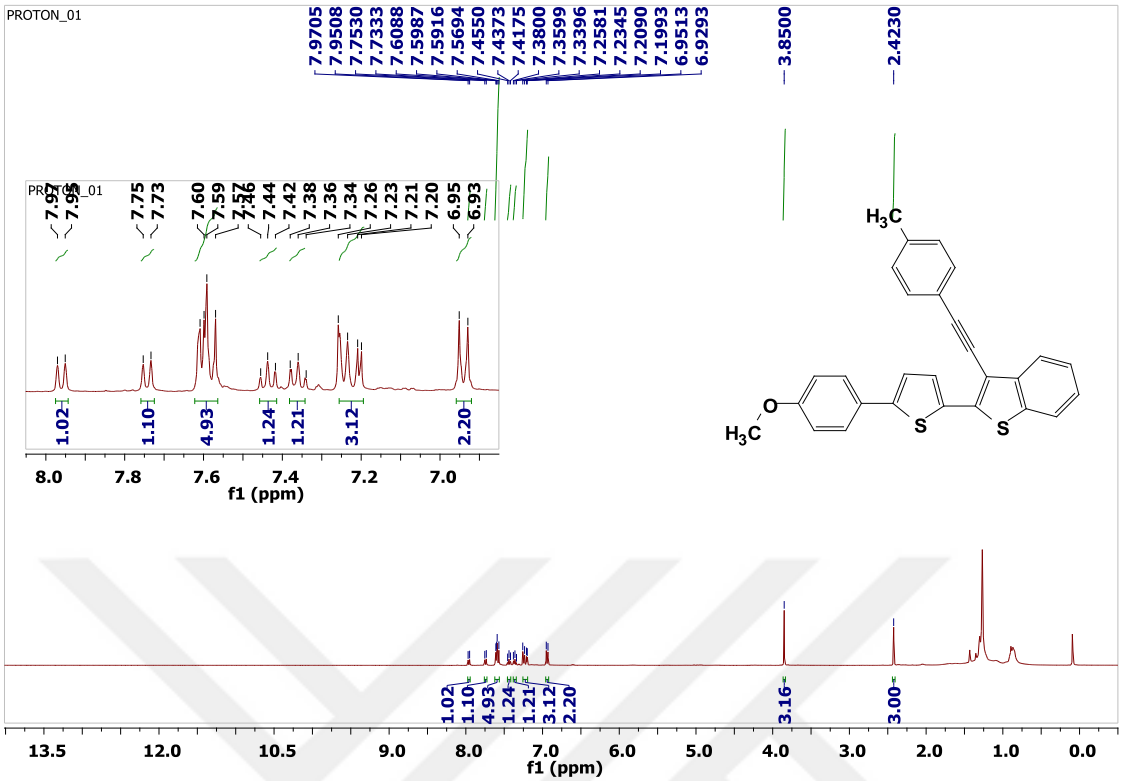


Figure A 27. ^{1}H NMR spectra of AD15.

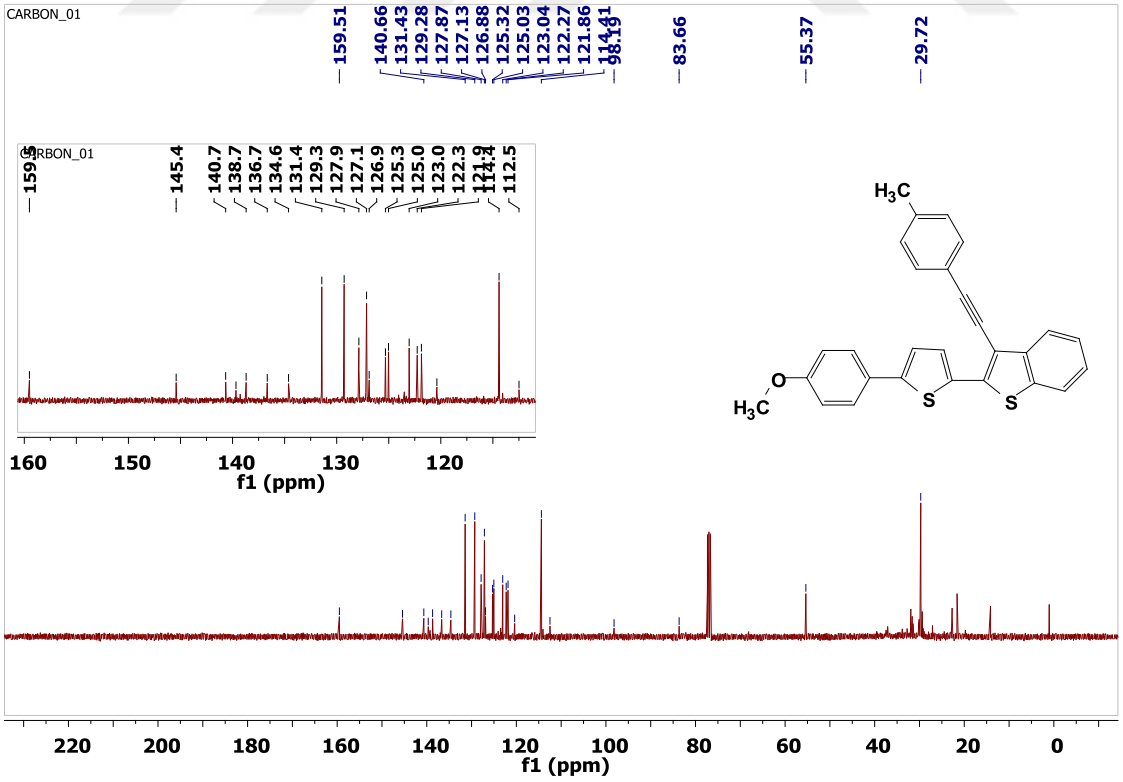


Figure A 28. ^{13}C NMR spectra of AD15.

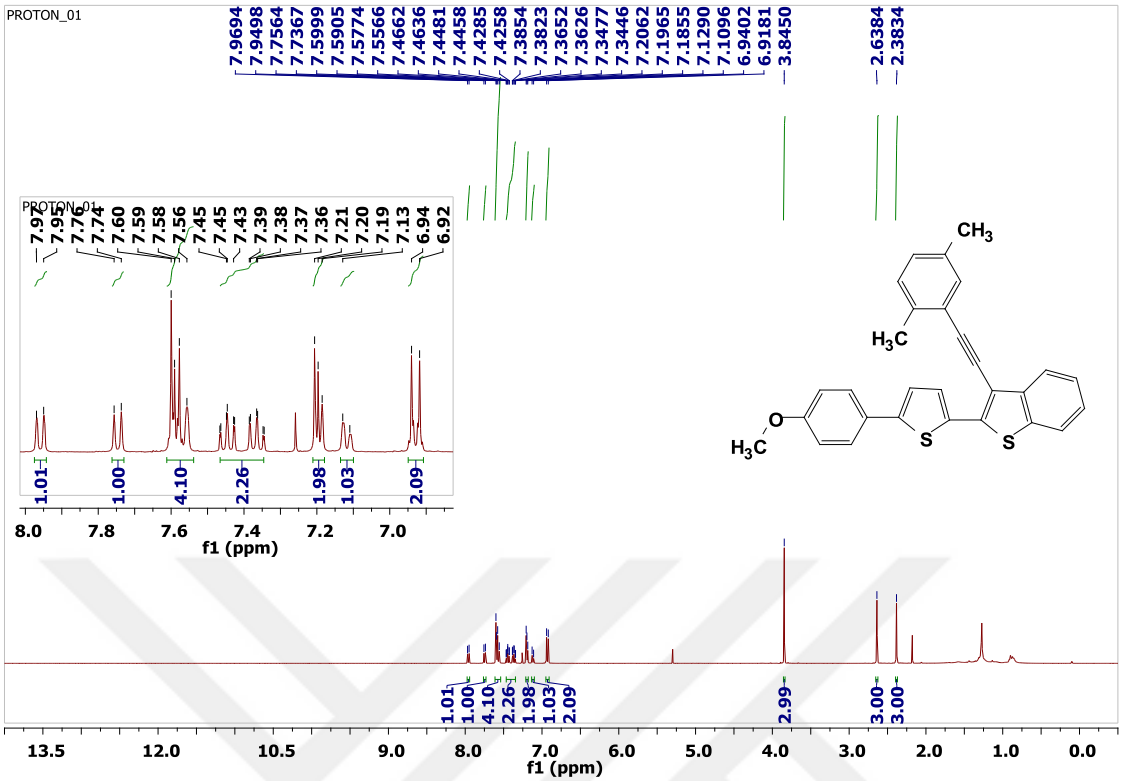


Figure A 29. ^{1}H NMR spectra of AD16.

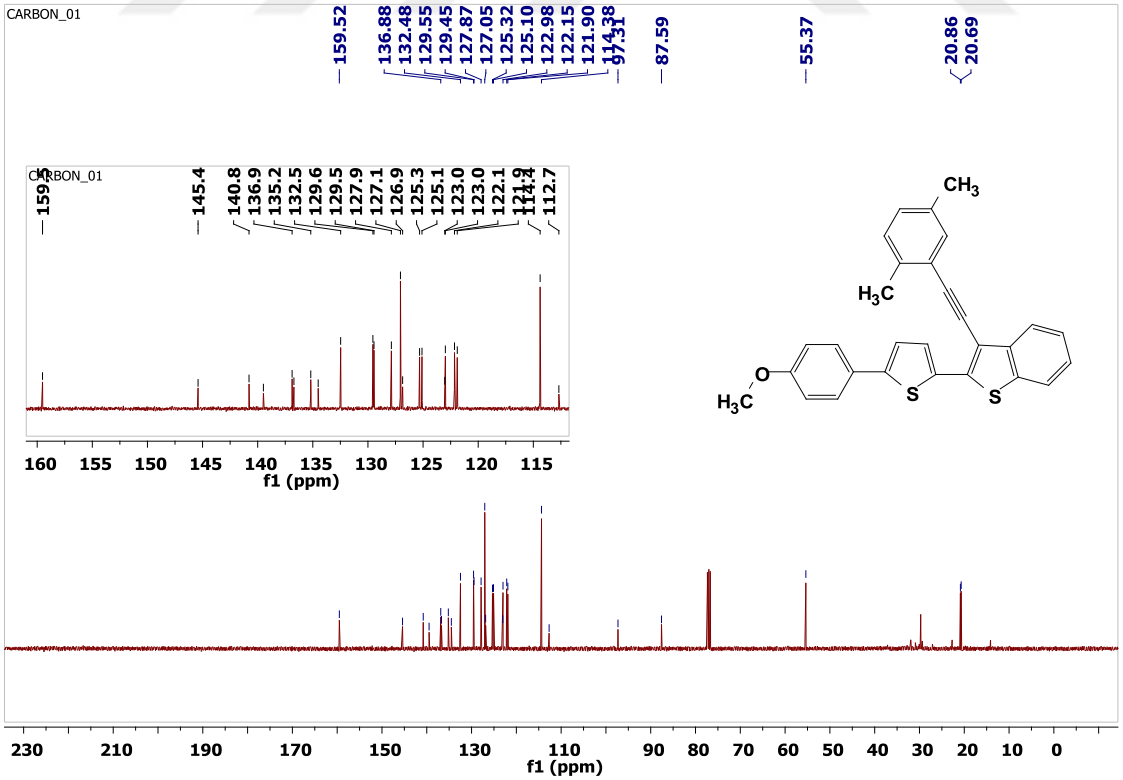


Figure A 30. ^{13}C NMR spectra of AD16.

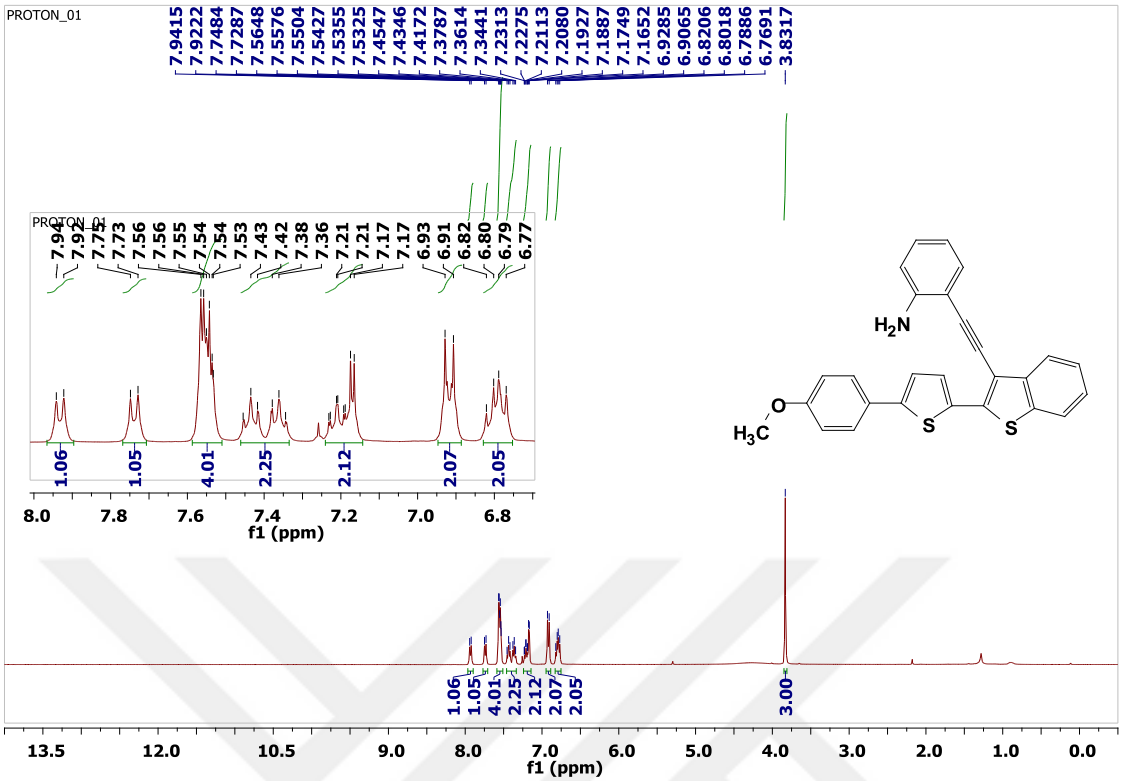


Figure A 31. ^{1}H NMR spectra of AD17.

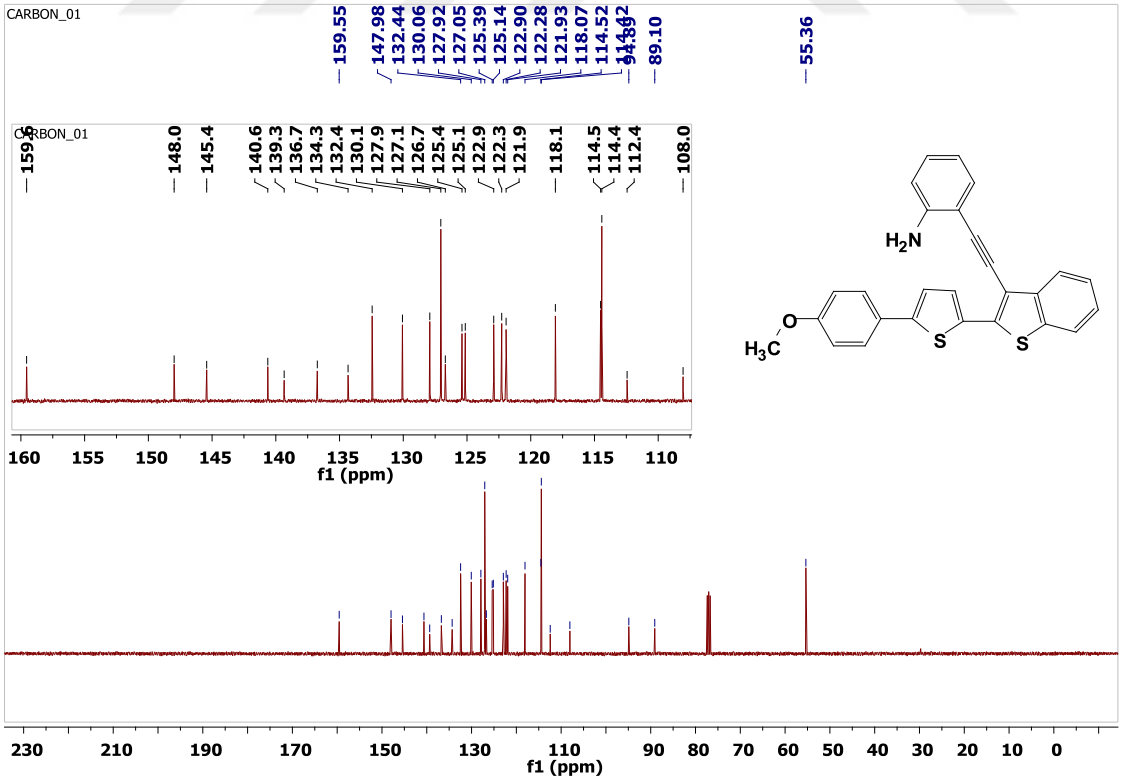


Figure A 32. ^{13}C NMR spectra of AD17.

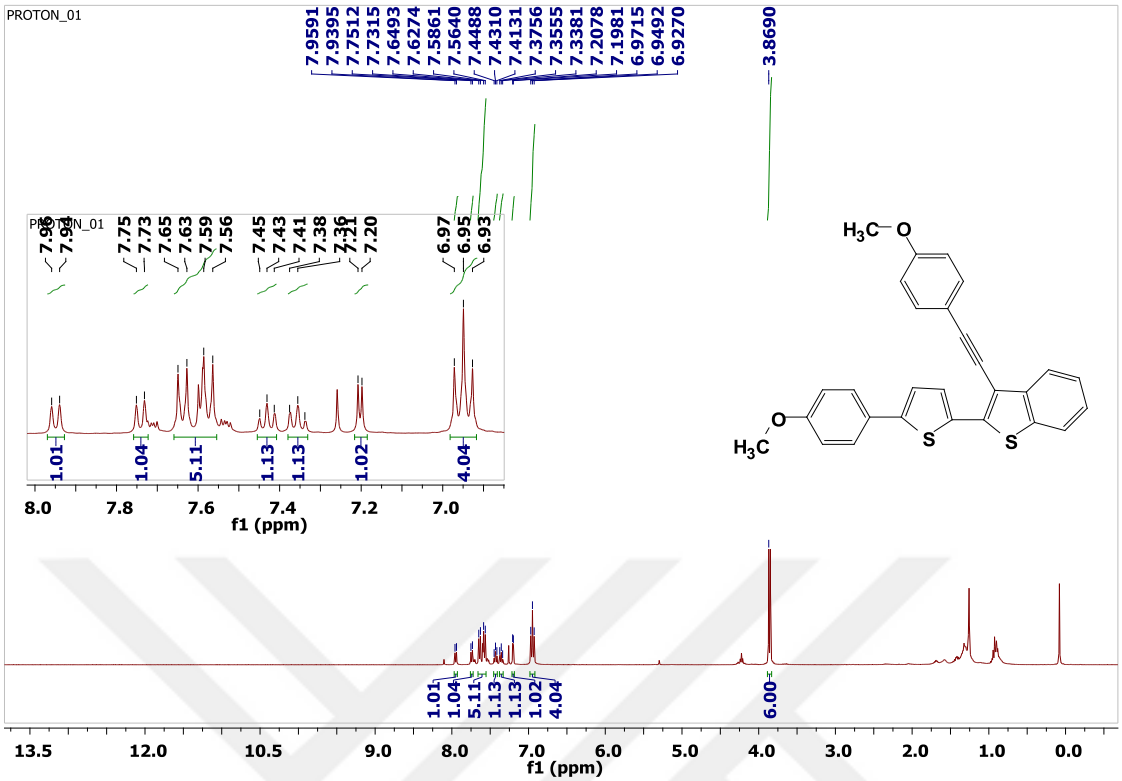


Figure A 33. ^{1}H NMR spectra of AD19.

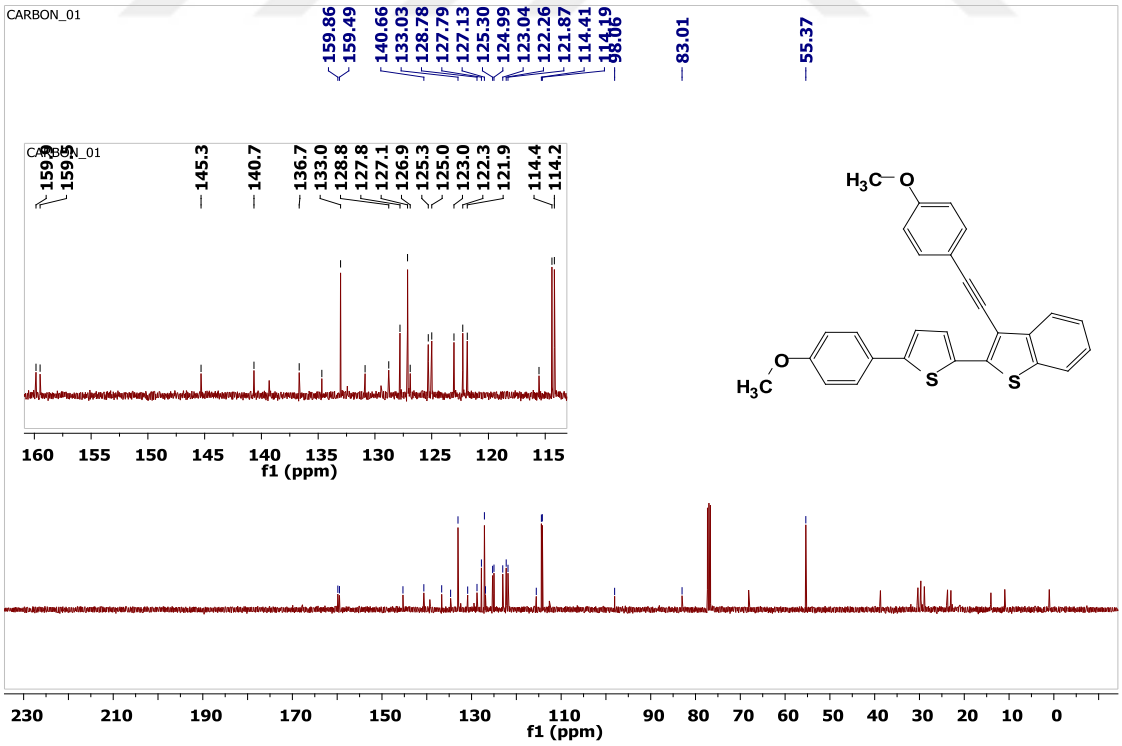


Figure A 34. ^{13}C NMR spectra of AD19.

APPENDIX B: EXTENDED TURKISH SUMMARY (GENİŞLETİLMİŞ TÜRKÇE ÖZET)

YENİ BENZOTİYOFEN TÜREVLERİNİN HALKALAŞMA TEPKİMELERİ İLE SENTEZİ

HAMA, Azad Khalaf.
Yüksek Lisans Tezi, Kimya Anabilim Dalı
Tez Danışmanı: Prof. Dr. Arif KIVRAK

1. GİRİŞ

Günümüzde artan hastalıkların tedavisi için ilaç potansiyeline sahip yeni organik maddelerin sentezi ve izolasyonu çok önemlidir. Sentezlenen organik moleküller farklı sübstitüentlere sahip olması ve/veya farklı sübstitüentler ile türevlendirilmesi de oldukça kritik öneme sahip olabilmektedirler. İlaç araştırmalarında temel ana yapıya farklı gruplar bağlanarak ya temel yapının biyolojik özelliği artırılmakta ya da tamamen yeni bir özelliğe sahip yeni bir organik molekül elde edilmektedir. Günümüzde kullanılan ilaçların organik yapılarına bakıldığında çoğunlukla yapısında hetero atom bulunan organik maddeler olduğu görülmektedir. Bir organik veya biojenerik malzemenin ilaç olabilmesi için belli kurallar çerçevesinde 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 sentezlenen organik bileşiğin oldukça saf halde olması doğru sonuçların elde edilmesi için büyük önem arz etmektedir. Ayrıca yapıların farklı sübstitüentlere sahip olması

veya türevlendirilebilir olması ilaç araştırmaları için kritiktir. Son on yıllar da özellikle gelişmiş ülkelerin üniversiteleri arasında yapılan işbirliği ile ilaç potansiyeline sahip yeni organik yapılar sentezlenerek türevlendirilmekte ve belirli merkezlere gönderilerek bu yapıların ilaç olarak kullanıla bilirlikleri araştırılmaktadır. Bu araştırmalar sonucunda belli hastalıkların tedavisinde kullanılmak üzere ilaçlar keşfedilmektedir.

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.

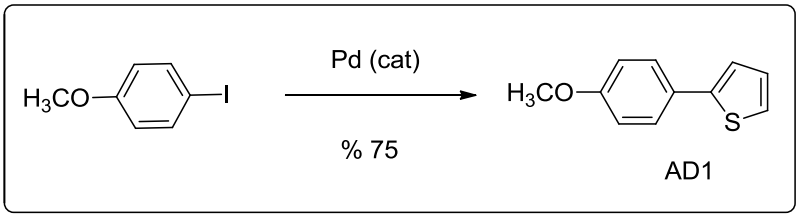
Yeni yöntemler ile yeni benzotiyofen türevlerini geliştirdiğimiz yöntem ile sentezledik. Ilaç olma potansiyeline sahip olan Benzotiyofenler Lipinskii kuralına uyan heterosiklik yapılardır. Benzotiyofen türevleri biyolojik önemi henüz bilinmeyen ve hastalıklara karşı çok yeni ve farklı davranımlar gösterebilecek türevlerin sentezlenmesi ilaç araştırmaları için çok önemlidir. Benzotiyofenler 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 benzotiyofenler rejio-seçiçi olarak sentezlenmiştir.

2. BULGULAR VE TARTIŞMA/SONUÇ

2.1. Benzotiyofen için bulunan bulgular

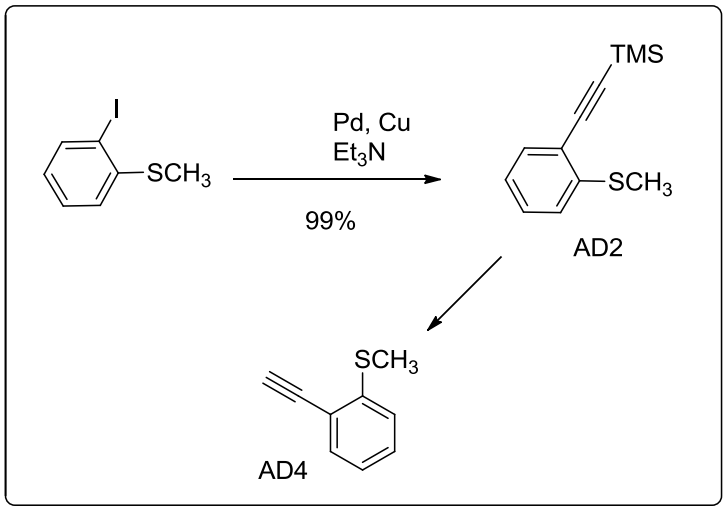
Bu çalışma kapsamında benzotiyofenlerin sentezi için aşağıdaki sentez basamakları kullanılmıştır. Bu yöntemler kullanılarak detayları verilen deneyler ile gerçekleştirilmiş ve hedeflenen ürünler sentezlenmiştir. Elde edilen tüm ara ürün ve ürünler izole edilerek yapısal karakterizasyonları spektroskobik 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.

Bu çalışmada 4-iyodo anisol başlangıç maddesi olarak kullanılmıştır. (tribütilstanil)tiyofen ile Stille kenetlenme tepkimesi kullanılarak % 75 gibi bir verim ile AD1 sentezlenmiştir (Şekil 2.1).



Şekil 2.1 AD1' in sentezlenmesinin Şeması

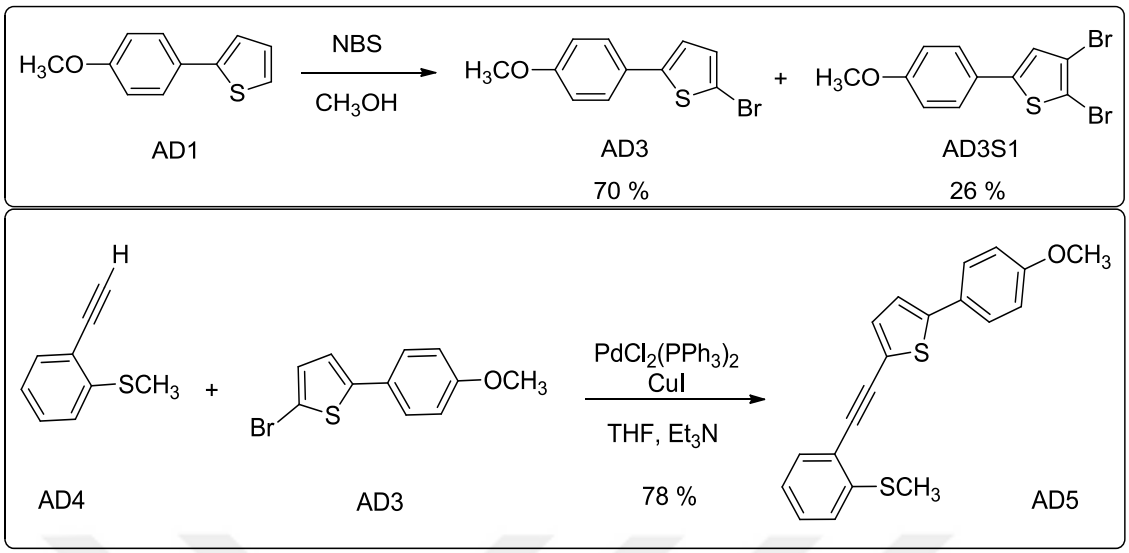
2-iyodotiyoanisol ile trimetilsililasetilen ile Sonogaşhira kenetlenme tepkimesi kullanılarak AD2 molekülü % 99 gibi yüksek bir verim ile hedeflenen molekül sentezlenmiştir (Şekil 2.2).



Şekil 2.2 AD2 ve AD4 yapılarının sentezi

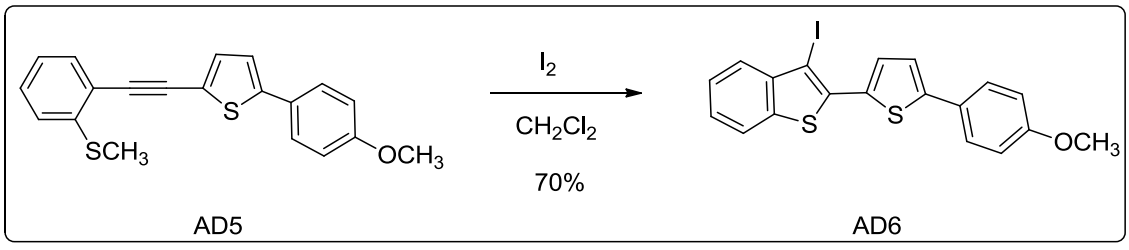
Daha sonra AD2 türevi izole edilip ve yapısal karakterizasyonu tamamlandıktan sonra hedeflenen ürün için yapıdaki TMS koruyucu grubunun uzaklaştırılması gerekmektedir. Bunun için zayıf bazik ortamda ve oda sıcaklığında istenilen birincil alkinler (AD4) elde edilmiştir. Bu tepkimede yaklaşık olarak %99 gibi yüksek verim ile istenilen ürün elde edilmiştir.

Diğer taraftan AD1 molekülü N-Bromo süksinamide ile bromlama reaksiyonu sonucunda sonraki basamakta kullanılmak üzere AD4 molekülü ve ikili katılma ürünü olan AD3S1 bileşiğide sentezlenmiştir. AD4 molekülü ile Pd tuzu katalizör yardımıyla sonogashira kenetlenme tepkimesi sonucu hedeflenen (Şekil 2.3) AD5 ürünü sentezlenmiş ve yapısal karakterizasyonu yapılmıştır.

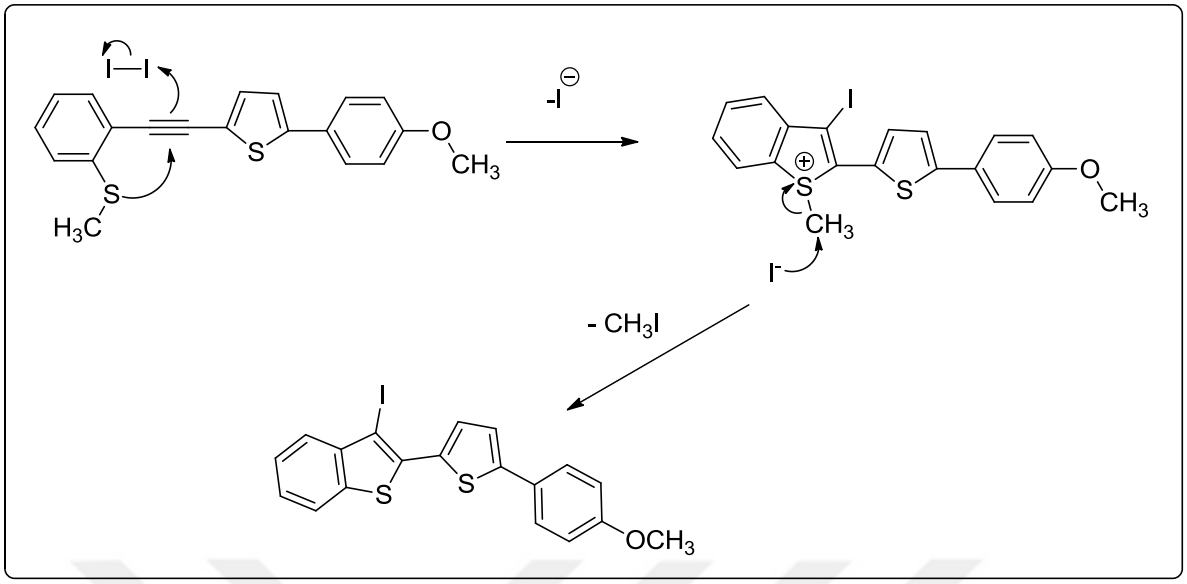


Şekil 2.3 AD3 ve AD5 yapılarının sentezi.

Çalışmanın ana konusu elektrofilik halkalaşma tepkimesi ile benzotiyofen türevlerinin sentezidir. Bu türevlerin sentezi için moleküler iyot ortamında elektrofilik halkalaşma tepkimeleri gerçekleştirilmiştir. Bunun için ilk olarak AD5 ile elektrofilik halkalaşma tepkimesi sonucunda AD6 yı Şekil 2.4 görüldüğü üzere sentezlenmiştir. Reaksiyonun gerçekleştiği yönüyle önerilen mekanizma Şekil 2.5 görülmektedir.

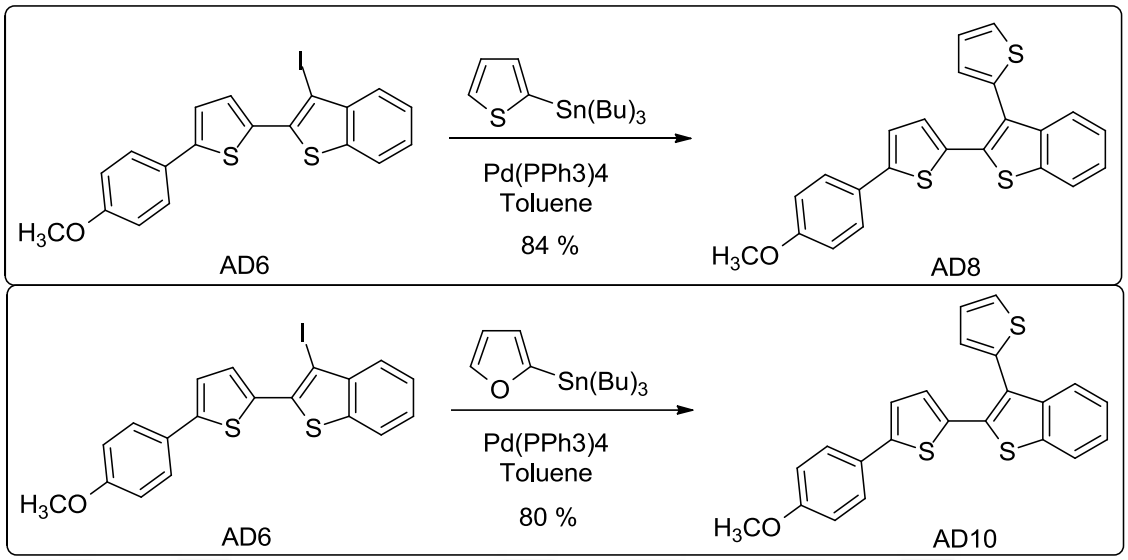


Şekil 2.4 3-İyodo- benzotiyofen sentezi.



Şekil 2.5 Elekrofilik halkalaşma tepkimesi için önerilen tepkime mekanizması.

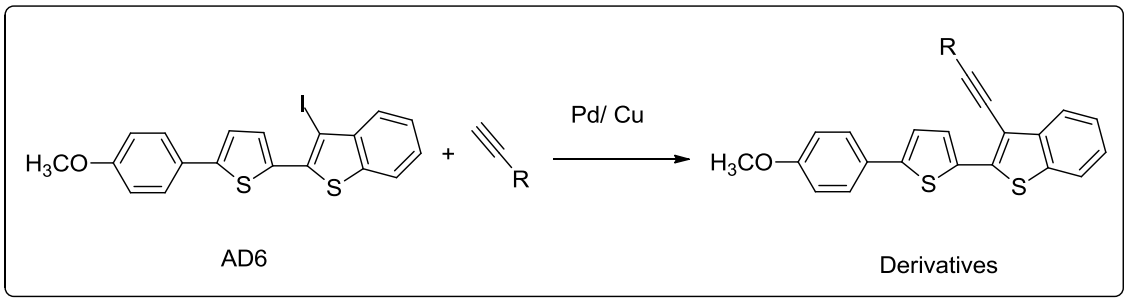
Benzotiyofen türevleri kenetlenme Tepkimeleri ile türevledirilebilir olmaları özellikle biyolojik araştırmalar için çok büyük öneme sahiptir. Geliştirdiğimiz yeni yöntemler ile yapısında iyot bulunan benzotiyofen türevleri sentezlenmiştir. Bunun için ilk olarak paladyum katalizörlü kenetlenme tepkime türlerinden olan Still kenetlenme tepkimesini seçtik. Örnek olarak AD8 ve AD10 ürünleri bu tepkimeler için seçilmiştir. Buna göre 2- tribütiltinfuran ve 2- tribütiltintiyofen ile kenetlenme tepkimeleri sonuçunda AD8 ve AD10 yüksek verimler ile sentezlenmiştir (sırasıyla %84 ve %80). Şekil 2.6 da ise reaksiyonun gerçekleştiği basamağının organik moleküllerin şekilleri görülmektedir.

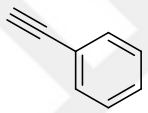
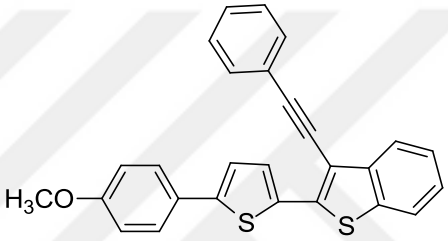
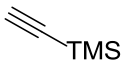
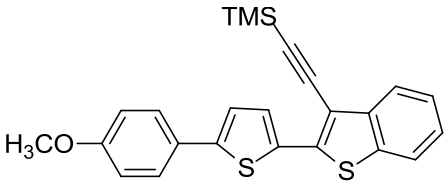
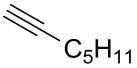
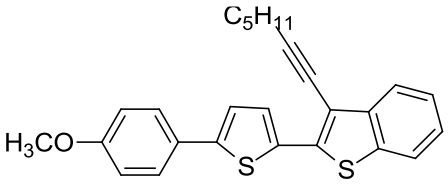


Şekil 2.6 Still kenetlenme tepkimesi ile AD8 ve AD10 yapılarının sentezi.

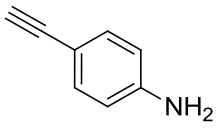
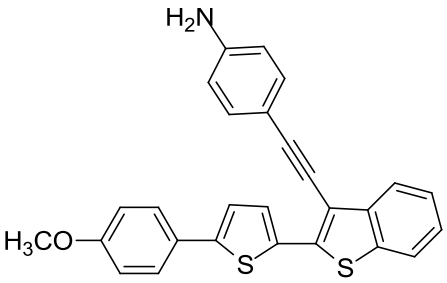
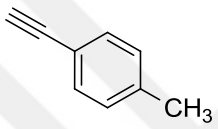
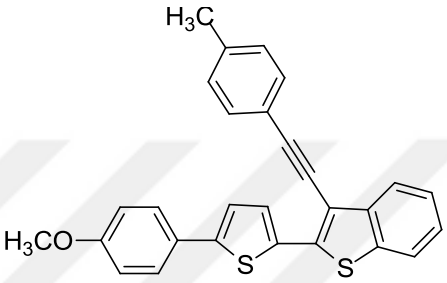
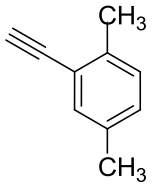
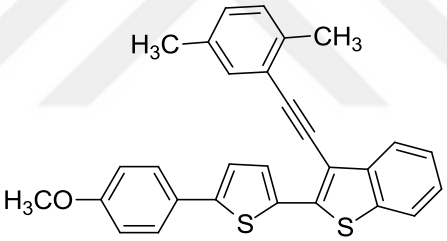
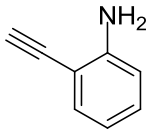
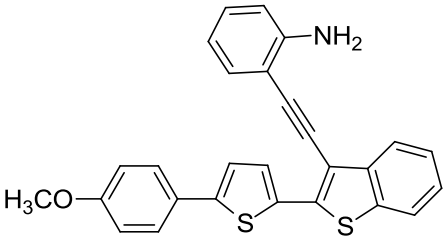
Bir paladyum katalizörlü kenetlenme tepkimesinin diğer türlerinden biri olan Sonogashira kenetlenmesi ile de sentezlediğimiz benzotiyofen bileşiği yapısında bulunan halojenür sayesinde türevlendirilmiştir ve elde edilen türevlerin karakterizasyon yapılış olup ürünlerin kodları ve verimleri sırasıyla AD9 %94, AD11 % 73, AD12 %90, AD14 %69, AD15 %77, AD16 %80, AD17 %98 ve AD19 %92 gibi iyi verimler ile yeni benzotiyofen türevleri sentezlenmiştir.

Tablo 2.1. Benzotiyofenlerin Sonogashira kenetlenme tepkimesi ile türevlendirilmesi.

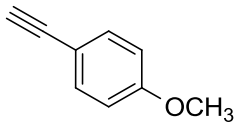
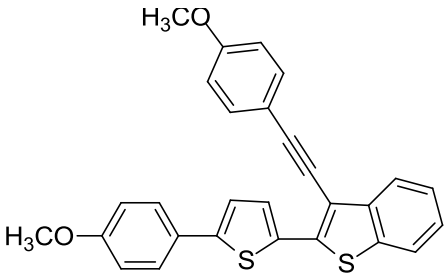


No	Alkin	Ürün	Verim, %
1		 AD9	94
2		 AD11	73
3		 AD12	90

Tablo 2.1. devamı.

4		 AD14	69
5		 AD15	77
6		 AD16	80
7		 AD17	98

Tablo 2.2. devamı.

8		 AD19	92

2.2 Sonuç

Yapısında kükürt gibi bir heteroatom bulunduran organic moleküller hem ilaç kimyası hem de malzeme kimyası için oldukça önemlidir. Özellikle tiyofen ve benzotiyofenler sahip oldukları biyolojik özelliklerinden dolayı yoğun olarak kullanılmaktadırlar. Bu önemli heteroaromatik yapıların sentezi ve özelliklerinin bulunması üzerine son yıllarda oldukça yoğun çalışmalar yapılmaktadır. Bu yapıların sentezi için yeni ve etkili sentez yöntemleri geliştirilmeye çalışılmaktadır.

Bu çalışmada, yeni benzotiyofen türevlerinin sentezi için etkili ve uygulanabilir metodlar geliştirilmiştir. Buna göre kenetlenme tepkimeleri, elektrofilik halkalaşma tepkimeleri kullanılarak hedeflenen benzotiyofenler elde edilmiştir. Çalışmanın ilk bölümünde 3 knumunda iyot bulunan AD6 yapısı rejiyoseçiçi olarak sentezlenmiştir. Daha sonar özellikle biyolojik uygulamalar için önemli olan türevlendirilebilme kabiliyeti test edilmiştir. AD6 yapısı hem Stille kenetlenme tepkimesine hem de Sonogashira Kenetlenme tepkimesine sokularak 3 konumuna farklı substitüentler bağlanması başarı ile gerçekleştirilmiştir. Bu sonuçlara göre sentezlediğimiz AD6 yapısı farklı türevlerin sentezi için oldukça önemli bir başlangıç maddesidir. Çalışmada sentezlenen tüm ara ürünlerin ve ürünlerin yapısal karakterizasyonu spektroskobik yöntemler kullanılarak gerçekleştirilmiştir.

CURRICULUM VITAE

- Personal Information

Name: Azad Khalaf HAMA.

Date of birth: 1/7/1990

Nationality: Iraq

Telephone: +964 7705446056

Language: Kurdish - English - Turkish

Email: azad.khalaf@yahoo.com

- Education

He was student at the University of Sulaimani \ College of Education –Kalar, during the years **(2008-2012)**, and was awarded Bachelor's degree in Chemistry **(B.Sc)** with the srandard **Good**. And average grade for the four academic years is **(75.406)** from the top ten and stood the **(2nd)** for the first trial.

Started M.Sc. of Science degree at Yüzüncü Yil University in Van –Turkey, during the years **(2017-2019).**

UNIVERSITY OF VAN YUZUNCU YIL
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Statute: M. Sc. X Ph.D. □

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Prof. Dr. AGFKIVRAK

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