ABANT IZZET BAYSAL UNIVERSITY

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

SYNTHESIS AND CHARACTERISATION OF THE NOVEL AZA(THIO) CROWN ETHERS CARRYING VARIOUS HETEROCYCLIC SCAFFOLDS

DOCTOR OF PHILOSOPHY

BESRA ÖZER

BOLU, MAY 2018

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APPROVAL OF THE THESIS

SYNTHESIS AND CHARACTERISATION OF THE NOVEL AZA(THIO) CROWN ETHERS CARRYING VARIOUS HETEROCYCLIC SCAFFOLDS submitted by **Besra ÖZER** in partial fulfillment of the requirements for the degree of **Doctor of Philosophy** in **Department of Chemistry, The Graduate School of Natural and Applied Sciences of ABANT İZZET BAYSAL UNIVERSITY in 24/05/2018** by

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Graduation date: ...../...../20....

Doc. Dr. Ömer ÖZYURT .....

Director of Graduate School of Natural and Applied Sciences

To My Family

DECLARATION

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Besra ÖZER

ABSTRACT

SYNTHESIS AND CHARACTERISATION OF THE NOVEL AZA(THIO) CROWN ETHERS CARRYING VARIOUS HETEROCYCLIC SCAFFOLDS

PHD THESIS
BESRA ÖZER
ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF.DR. YAŞAR DÜRÜST)

BOLU, MAY 2018

The coverage of this study is basically related to the synthesis various crown ethers containing nitrogen and sulfur atoms. Because many of these compounds are highly effective extractants for metal ions. Due to this feature, they found application in different areas. On the other hand, five membered heterocyclic compounds are one of the important part of 1,3-dipolar cycloaddition chemistry due to their importance in pharmaceutical chemistry, organic and bioorganic medicinal chemistry. In this regards, the biological effects and industrial uses of these macrocyclic compounds have encouraged us to synthesize macrocyclic compounds with 1,2,4-oxadiazoles and 1,2,3-triazoles which are not previously reported. The outcomes of this study were discussed in four parts;

In the first part of this work, we have focused on the synthesis of the benzotriazacrown ether and then it was reacted with the 3-*p*-phenylsubstituted- 5-chloromethyl-1,2,4-oxadiazoles. Moreover, dibenzodiazacrown carrying 1,2,4-oxadiazole moieties were obtained.

In the second part, novel benzodiazacrown ethers carrying chloro/azido methyl 1,2,4-oxadiazoles were synthesized with different stages. In addition, commercially obtained benzo-15-crown-5 was formylated according to the published literature procedure. Then, starting from this formylated crown, chloro/azido-methyl 1,2,4-oxadiazoles bearing benzocrown ethers were obtained in six different sections.

In the third section, 1,3-dipolar cycloadditions of the azamacrocycles carrying acetylenic side chain with 5-azidomethyl-1,2,4-oxadiazoles were accomplished in two protocols. First part contains the synthesis of the novel azamacrocycles carrying acetylenic side chain and then these dipolarophilic novel molecules have undergone cycloaddition with the different *p*-phenyl substituted 5-azidomethyl 1,2,4-oxadiazoles.

Finally, in addition to all parts in this thesis, a novel azathiacrown and dibenzocrown ethers carrying aldoxime and nitrile groups were obtained.

KEYWORDS: Azacrown Ether, 1,2,4-Oxadiazole, 1,2,3-Triazole, 1,3-Dipolar Cycloaddition, Ionophore

ÖZET

ÇEŞİTLİ HETEROHALKASAL YAPILAR TAŞIYAN YENİ AZA(TİYO) TAÇ ETERLERİN SENTEZİ VE KARAKTERİZASYONU

DOKTORA TEZİ
BESRA ÖZER
ABANT İZZET BAYSAL ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: PROF. DR. YAŞAR DÜRÜST)

BOLU, MAYIS - 2018

Bu çalışmanın içeriği esas olarak azot ve kükürt içeren çeşitli taç eterlerin sentezi ile ilgilidir. Çünkü bu bileşiklerin çoğunun metal iyonlarını bağlama kapasitesi oldukça yüksektir. Bu özelliklerinden dolayı farklı alanlarda yer bulurlar. Diğer taraftan, farmasötik kimya, organik, biyoorganik ve tıbbi kimyadaki öneminden dolayı beş üyeli heterohalkasal bileşikler 1,3–dipolar halkasal katılma tepkimelerinin önemli bir parçasıdır. Bu bakımdan biyolojik etkileri ve endüstriyel kullanımı bizi, daha önce yayınlanmamış olan 1,2,4-oksadiazol ve 1,2,3-triazol içeren makrohalkalı bileşikler sentezlemeye teşvik etti. Bu tezin sonuçları dört kısımda tartışıldı.

Bu çalışmanın ilk kısmında benzotriaza taç eterin sentezine odaklandık ve sonra bu taç eter 3-*p*-fenilsubstitue-5-klorometil-1,2,4-oksadiazoller ile tepkimeye sokuldu. Dahası, 1,2,4-oksadiazol kısımlı dibenzodiaza taç eterler elde edildi.

İkinci kısımda farklı aşamalarda yeni kloro/azido metil 1,2,4-oksadiazol taşıyan benzodiaza taç eterler sentezlendi. Buna ek olarak, satın alınan benzo-15-krovn-5 literatürdeki yayınlanmış prosedüre göre formillendi. Daha sonra formillenmiş bu taç eterden başlayarak, 6 farklı aşamada kloro/azido metil 1,2,4-oksadiazol taşıyan benzo taç eterler sentezlendi.

Üçüncü aşamada asetilenik kısımlı azamakro halkanın, 5-azidomethyl-1,2,4-oksadiazoller ile 1,3–dipolar halkasal katılması iki aşamada tamamlandı. İlk aşama, asetilenik kısım taşıyan yeni aza makrohalkalar içerir ve daha sonra bu dipolarofilik yeni moleküller *p*- fenilsubstitue 5-azidometil 1,2,4-oksadiazol ile halkasal katılmaya uğratıldı.

Son olarak bu tezin bütün aşamalarına ek olarak yeni bir aza/tiya taç eter ve aldoksim ve nitril grupları taşıyan dibenzo taç eterler elde edildi.

ANAHTAR KELİMELER: Azataç Eter, 1,2,4-Oksadiazol, 1,2,3-Triazol, 1,3-Dipolar Halkalı Katılma, İyonofor

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LIST OF ABBREVIATIONS AND SYMBOLS

IUPAC	**:** International Union of Pure and Applied Chemistry
PTC	**:** Phase Transfer Catalyst
TFA	**:** Trifluoroacetic Acid
HMTA	**:** Hexamethylenetetraamine
DMF	**:** *N*,*N*-Dimethylformamide
MO	**:** Molecular Orbital
FMO	**:** Frontier Molecular Orbital
1,3-DC	**:** 1,3-Dipolar cycloaddition
HOMO	**:** Highest Occupied Molecular Orbital
LUMO	**:** Lowest Unoccupied Molecular Orbital
R_f	**:** Retardation Factor
Hz	**:** Hertz
IR	**:** Infrared Spectroscopy
J	**:** Coupling Constants (NMR)
M.p.	**:** Melting Point
B.p.	**:** Boiling Point
$CDCl_3$	**:** Deuterated Chloroform
d	**:**Doublet (NMR)
dd	**:**Doublet of doublets (NMR)
m	**:** Multiplet (NMR)
HRMS	**:**High resolution mass spectrometry
IR	**:**Infrared spectroscopy
NMR	**:**Nuclear magnetic resonance
ppm	**:**Parts per million (NMR)
RT	**:**Room temperature
s	**:**Singlet (NMR)
t	**:**Triplet (NMR)

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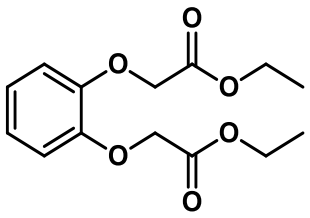
FORMULAE



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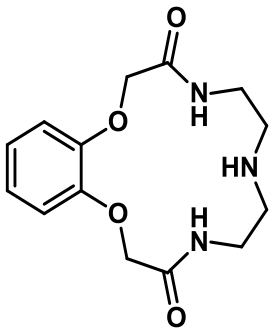

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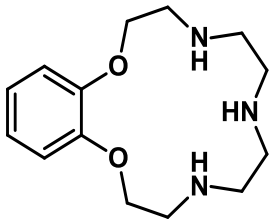

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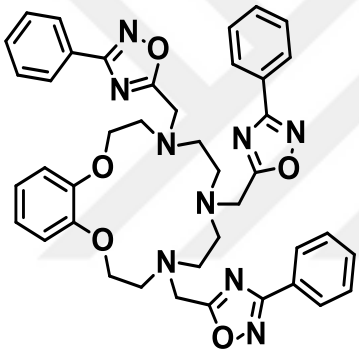

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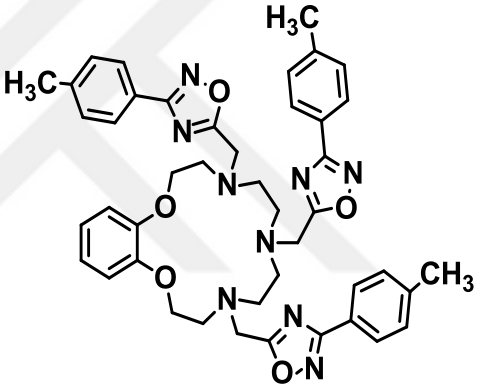

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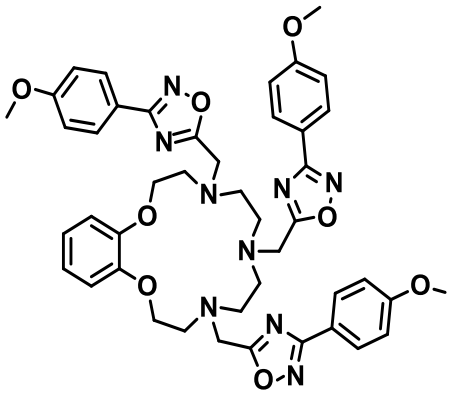

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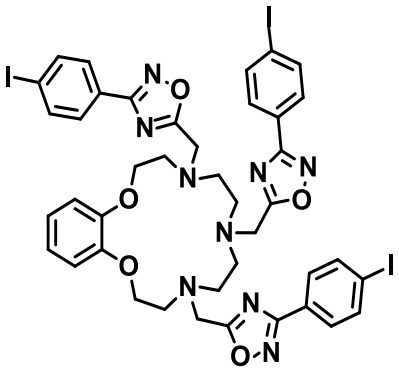

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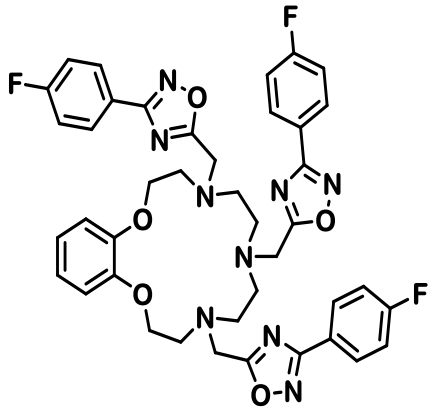

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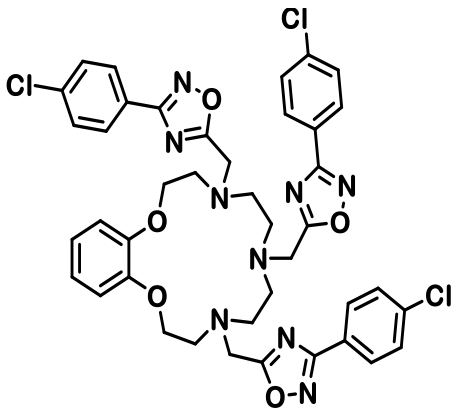

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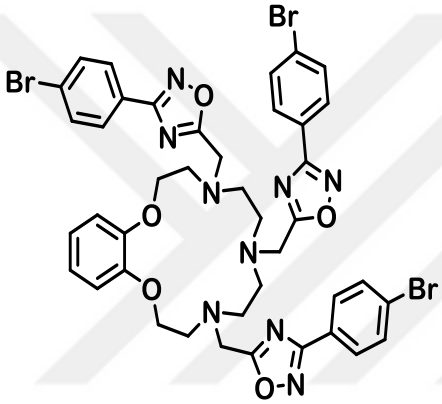

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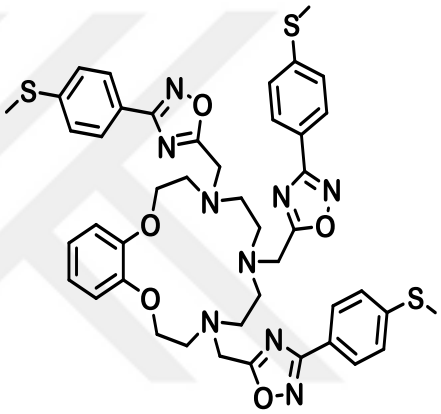

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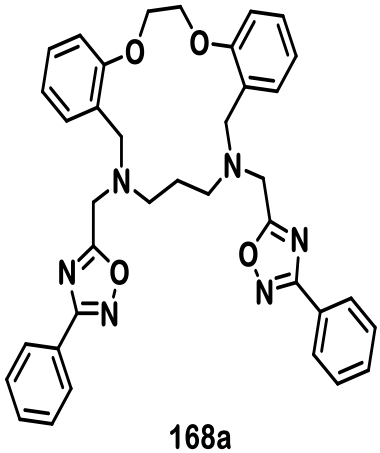

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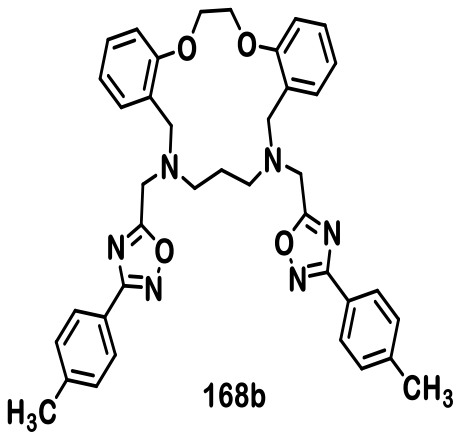

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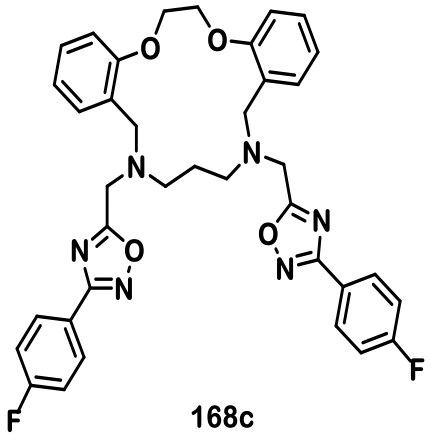

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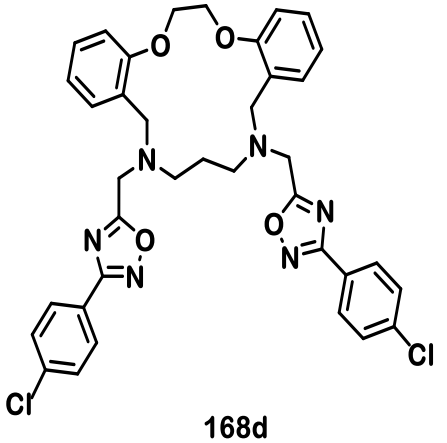

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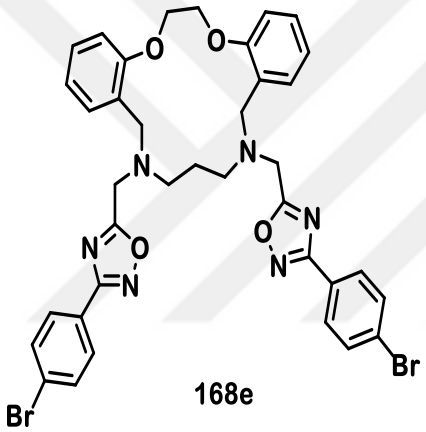

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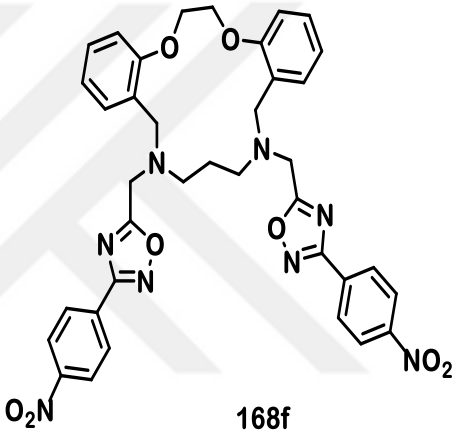

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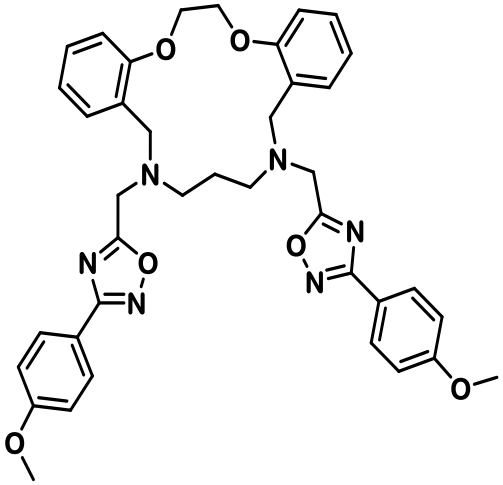

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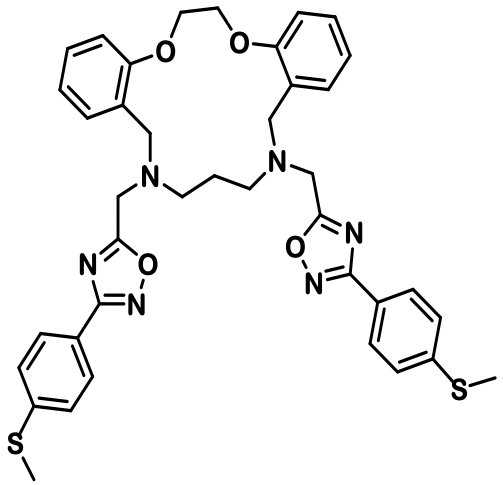

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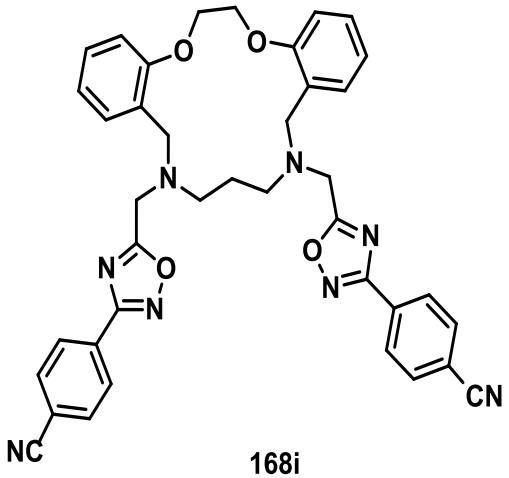

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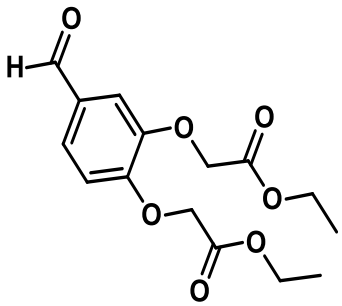

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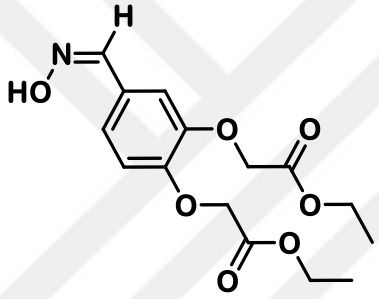

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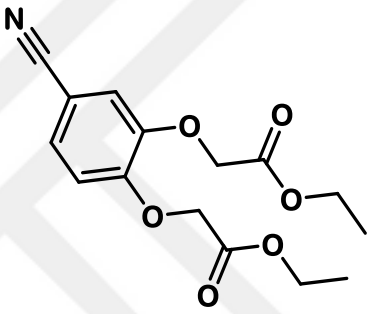

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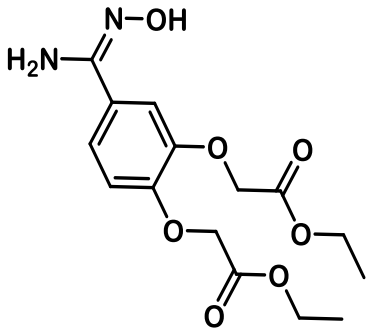

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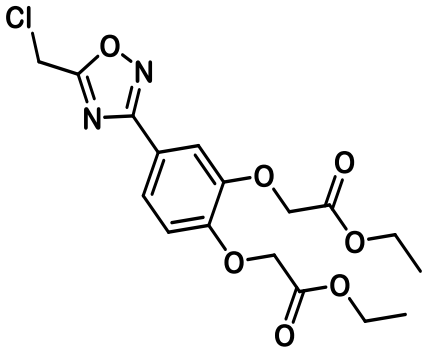

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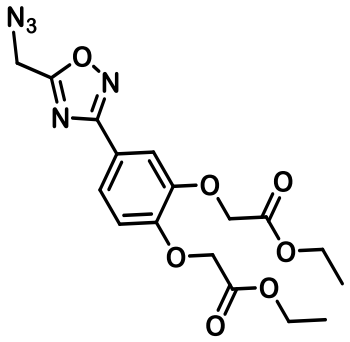

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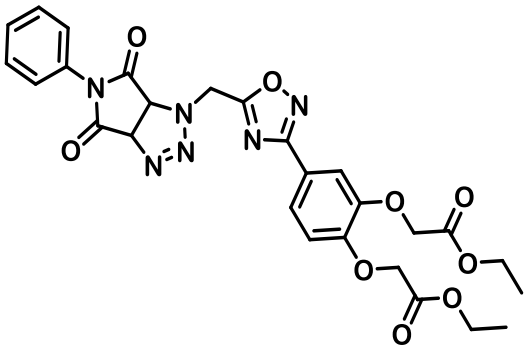

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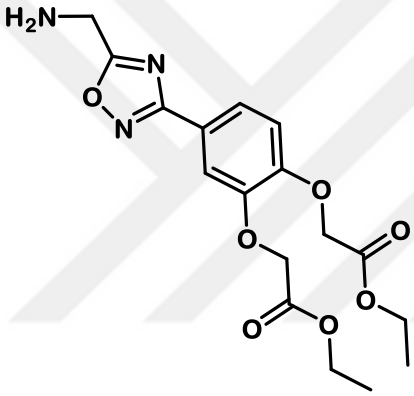

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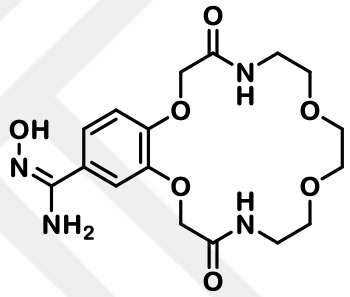

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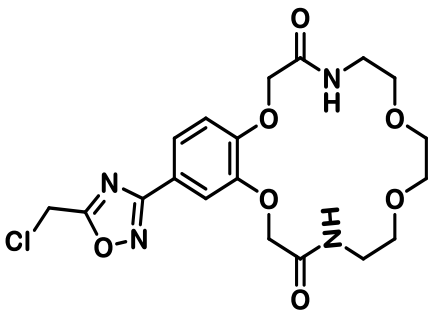

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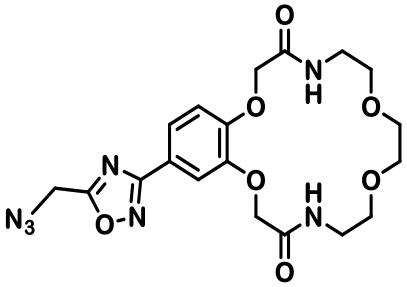

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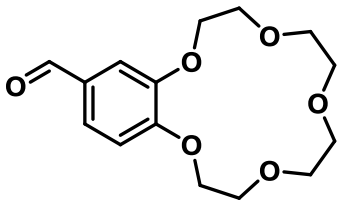

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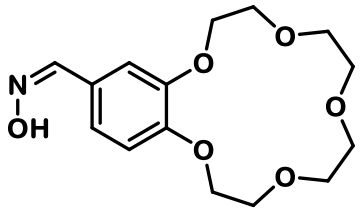

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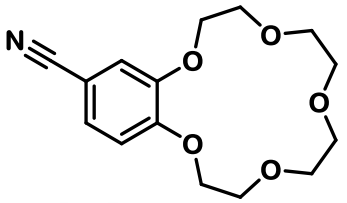

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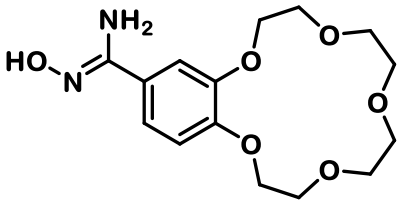

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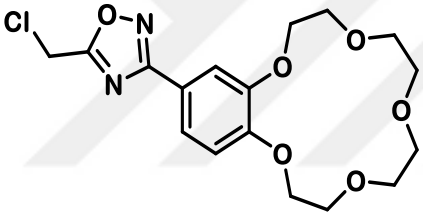

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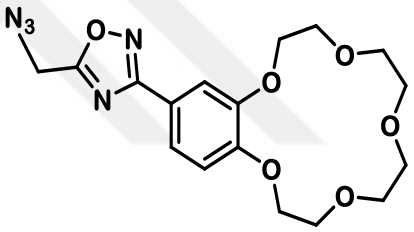

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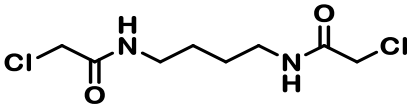

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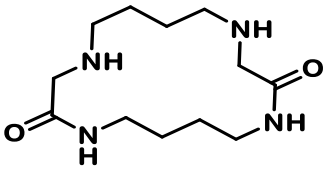

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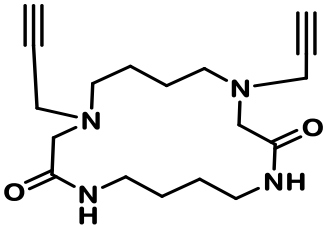

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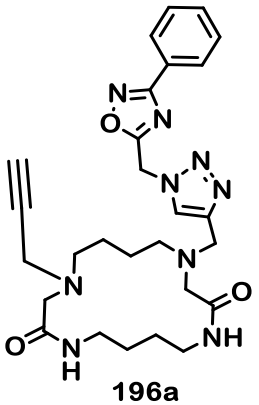

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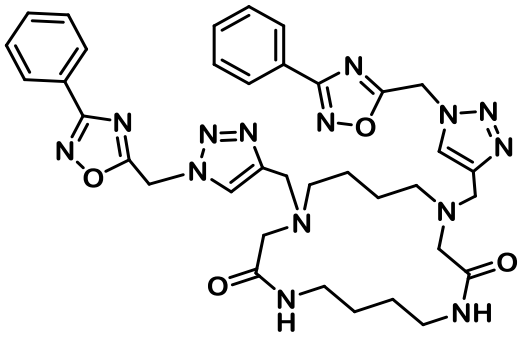

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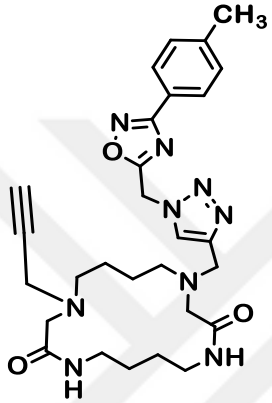

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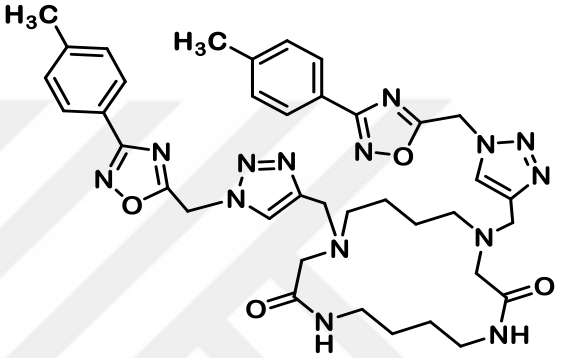

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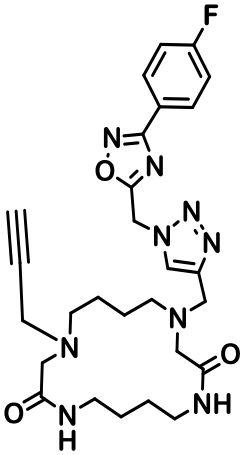

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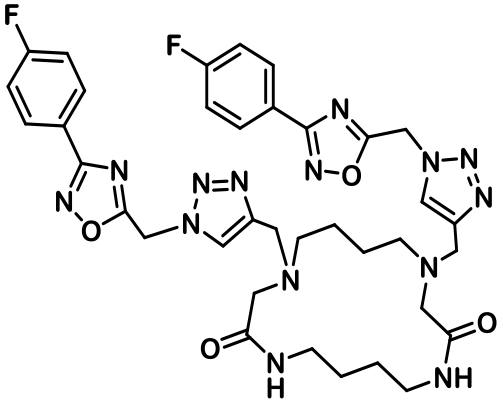

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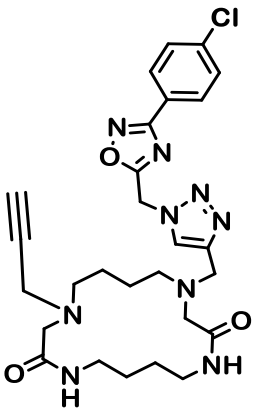

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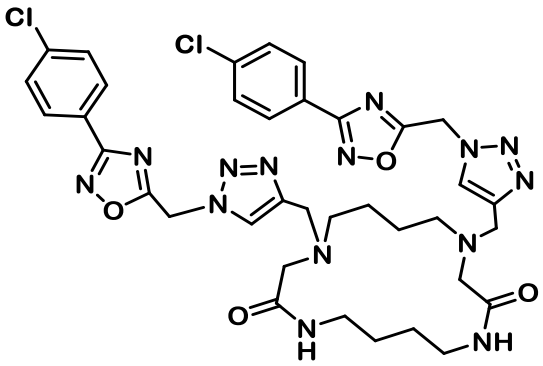

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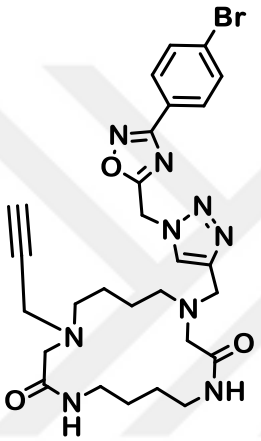

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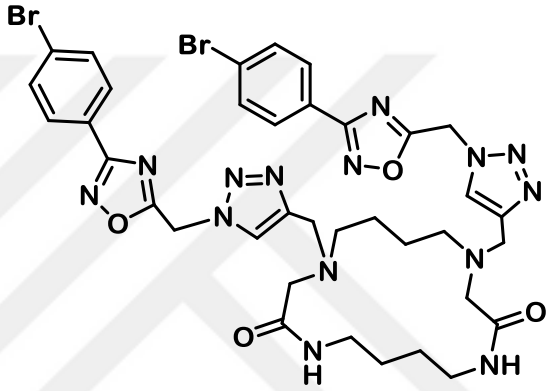

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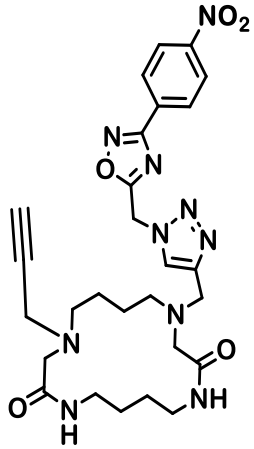

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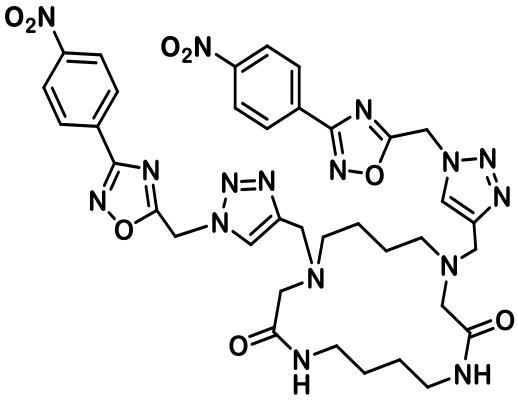

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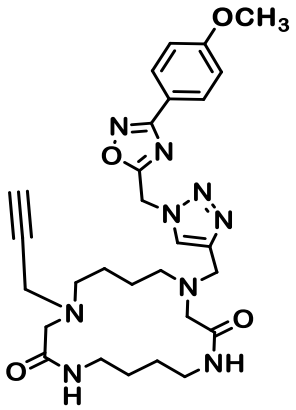

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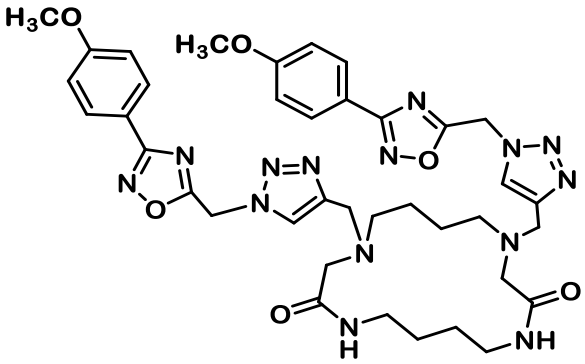

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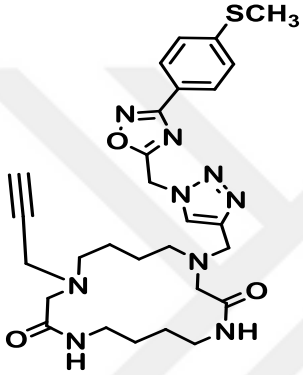

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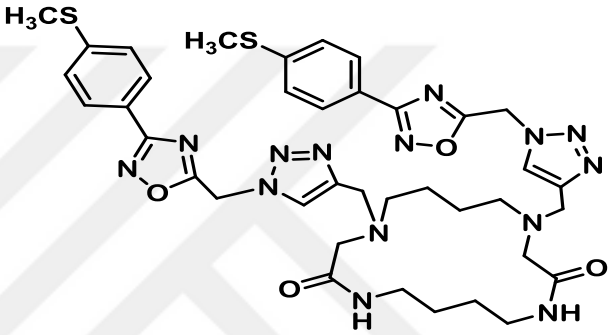

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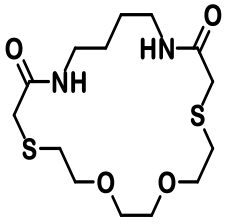

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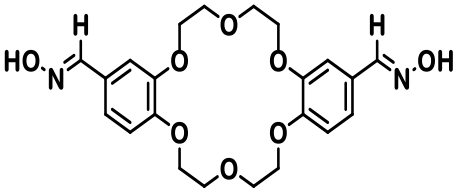

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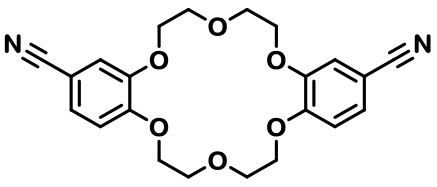

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1. INTRODUCTION

Macrocyclic compounds are one of the important parts of the supramolecular chemistry. Macrocyclic organic compounds contain a large ring with heteroatoms like O, N, S, P. The pioneers of this field; Cram, Lehn, and Pedersen, have been awarded with the Nobel Prize in Chemistry for the synthesis macrocyclic polyethers, that have high affinity with alkali, alkaline earth and transition metal cations. (Cram, 1974; Lehn, 1988; Pedersen, 1988).

Crown ethers which have been discovered by the Pedersen have a long history in macromolecular chemistry (Pedersen, 1967). In this thesis, we have focused on the crown ethers, since a developing interest has been directed on the crown ethers since 1967 (Kyba, et al., 1977; Collman, et al, 1998; Krishnakumar, et al., 2017; Zhang, et al., 2017). Crown ethers have found practical applications in many areas such as science and industry (Shing, et al., 2013; Sharghi and Beni, 2007; Elwahy and Abbas, 2008) due to their following characteristics:

i.They have excellent affinity towards the metal cations. (Herman, et al., 2003; Vaira, et al., 1999). This remarkable binding property has lead wide applications in cancer treatment (Ghosh and Wang, 2000), treatment of nuclear waste (Maciejewski, et al., 2009), removal of hazardous metals in contaminated water (Mane, et al., 2016), catalysis (Chen, et al., 1994).

ii. They have been found to exhibit anti-HIV (Bridger, et al., 1995), anti-protozoal (Wilson, et al. 2007; Reid, et al., 2008), antimicrobial (Abd El-Salam, et al., 2012), antibacterial (Tso and Fung, 1981; Tso et al.,1981), antifungal (Patil, et al., 2016) and also anticancer and DNA interaction activities (Kralj, et al., 2008).

iii. Some of these macrocycles can be used as phase transfer catalyst (PTC) (Gourdet, et al., 2010; Hausner, et al., 2005).

iv. Macrocyclic compounds have an important site to bind dye so they can remove dyestuff from waste water (Akceylan, et al., 2009; Yılmaz, et al,. 2007; Forgues and Ali, 2004).

v. Crown ethers can also be used as oxidizing agent in order to eradicate sulfur compounds from the diesel fuels by oxidizing sulfur compounds (Rakhmanov, et al., 2014).

Taking account of the historical background and characteristic features of macrocycles, namely azacrown ethers, reported in the literature and above-mentioned biological, environmental and industrial features of these class of organic compounds make them significant and profitable to carry out research. In this regard, we have focused on the azacrown ether synthesis in this thesis work.

1.1 CROWN ETHERS

Crown ethers are generally defined as cyclic oligomers of diethylene ether. A simple crown ether consists of repeating -CH_2CH_2O- units. Macrocyclic polyethers of the (-CH_2CH_2O-)*n* type, when *n* is equal or more than 4, are generally ascribed as crown ethers so that their systematic names are not much preferred (Gokel, 1991; Dietric and Lehn, 1993). Due to their structural appearance and ability to encircle cations, these macromolecules were called "crown" (Figure 1.1) (Pedersen, 1967). Actually, the crown ethers can be considered as " hard bases" owing to heteroatoms such as oxygen and nitrogen they possess, thus they prefer to bind to metal cations, that are " hard acids" (Pearson, 1963).

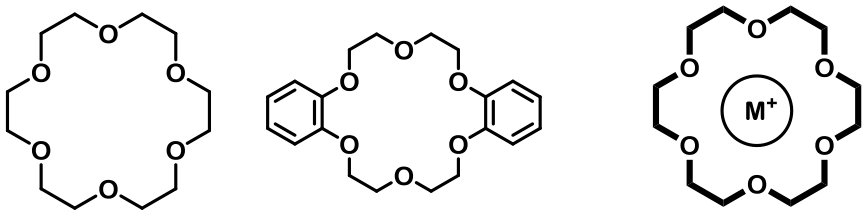


Figure 1. 1. Examples of commonly known crown ethers

In the literature, various crown ethers have been documented, due to their excellent properties and convenient applications (Forgues and Ali, 2004; Luboch et al., 2009; Steenland, et al 1997; Liang et al., 2006; Qin, et al., 2008; Athey and Kiefer, 2002). In particular, the binding nature of the crown ethers towards the transition and post transition metal cations comes out such as ionophore (Luboch, et

al., 2009; Ge, et al., 2012; Wysiecka,et al., 2003; Kim, et al., 2000; Bühlmann, et al., 1998) and chemosensor (Jeon, et al., 2009, Moczar et al., 2010) properties. In regards to highest affinity towards the metal cations, host-guest chemistry plays an important role in the literature (Huang, et al., 2005; Kimura, et al.,1982; Sarma, et al., 2010; Tsuchiya, et al., 2006).

1.1.1 Classes of Crown Ethers and Their Nomenclature

Pedersen has introduced an identifiable and uncomplicated nomenclature for the crown ethers. Since the systematic IUPAC nomenclature of these macrocycles can not be appropriate, Pedersen developed a nomenclature system for the crown ethers based on the following criteria (Pedersen, 1967);

(1) The quantity and the sort of hydrocarbon rings,

(2) The full number of atoms in the macrocycle,

(3) The word "crown" ,

(4) The number of heteroatoms (oxygen, nitrogen etc.) in the macrocycle.

If the oxygen atom is replaced with other heteroatoms such as N, these changes can be illustrated with a prefix of aza (Pedersen, 1967). Examples of several crown ethers used commonly and their names are shown below (Figure 1.2).

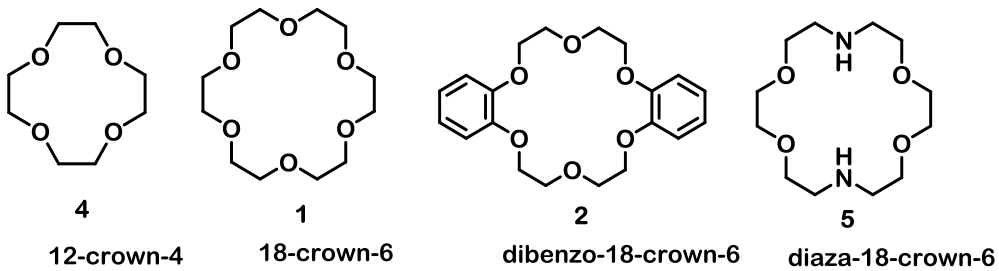


Figure 1. 2. Some crowns named according to Pedersen's method

Although there is an unpredictability on the location of heteroatoms, the Pedersen nomenclature is simple, so the ring size and number of heteroatoms can be

easily understood and these features have advantages for using the Pedersen nomenclature system.

The nomenclature system described by Pedersen (Pedersen, 1967) are referred to any medium sized macrocylic system. These systems having only oxygen atoms are attributed to coronands (Vögtle and Weber, 1974). In addition to coronands, different kinds of the associated compounds have been introduced. These are; lariat ethers, rotaxanes, cryptands, carcerands, calixarenes, cavitands, sepulchrates, podands, spherands (Dietrich, et al., 1993). While podands are acyclic counterpart in the macrocyclic system, the cryptands are bi or polycyclic counterparts containing any heteroatoms. Cryptates and coronates make complex with cryptands and coronands respectively (Gokel and Korzeniowski, 1982). Gokel and coworkers have demonstrated that the lariats which are monocyclic and have hanging arms with donor atoms. (Gokel, et al., 1980).

In 1974, Wong and his coworkers have reported bis-crown consisted of two macromolecules in its structure. Examples of the various type of macrocyclic compounds are illustrated in Figure 1.3.

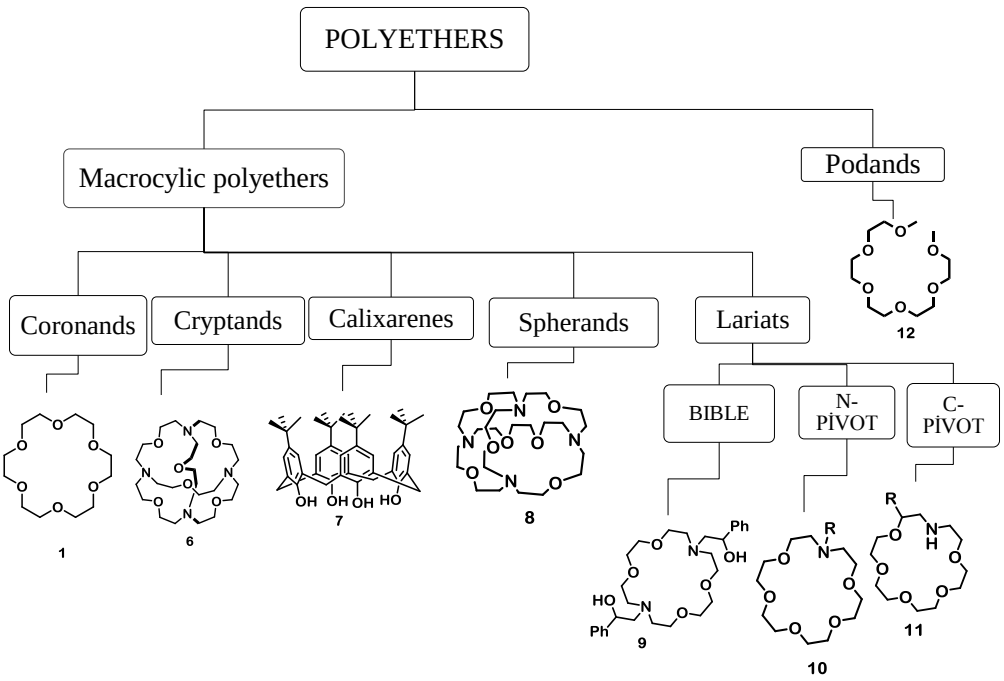


Figure 1. 3. Classifications of the polyethers and examples for each

1.1.2 Host-Guest Properties of Crown Ethers

Macrocyclic compounds possess a cavity depending on their size and atoms incorporated in the ring. This feature can lead to accomodate metal ions as host (Kimura, et al.,1982; Sarma, et al., 2010; Tsuchiya, et al., 2006). The factors affecting ligand-metal complexation and stability of the complexes have been summarized as depicted below (Pedersen, 1967).

- The cavity of the crown ethers and the relative sizes of the metal cation,
- The number of oxygen atom in the macrocycle,
- The planarity of the macrocycle ring,
- The symmetrical placement of the oxygen atoms,
- The basicity of the oxygen atoms,
- Steric hindrance in the polyether ring,
- The tendency of the ion to associate with the solvent,
- The electrical charge on the ring.

Several types of the complexes constructed by crown ethers have been reported in the literature (Kong, et al., 2003; Steenland, et al., 1997; Gasnier, et al., 2008; Cram, 1988; Pedersen, 1970). The type where the metal cation fits in the hole of crown ether and a 1:1 stochiometric ratio between metal and crown ether is maintained is called as “nesting” complex. But if the metal cation is even slightly large for the cavity of the crown ether a "perching" complex occurs. Sandwich and club-sandwich complexes form when metal cation is large to suit into the cavity (Figure 1.4) (Zhang, 1999).

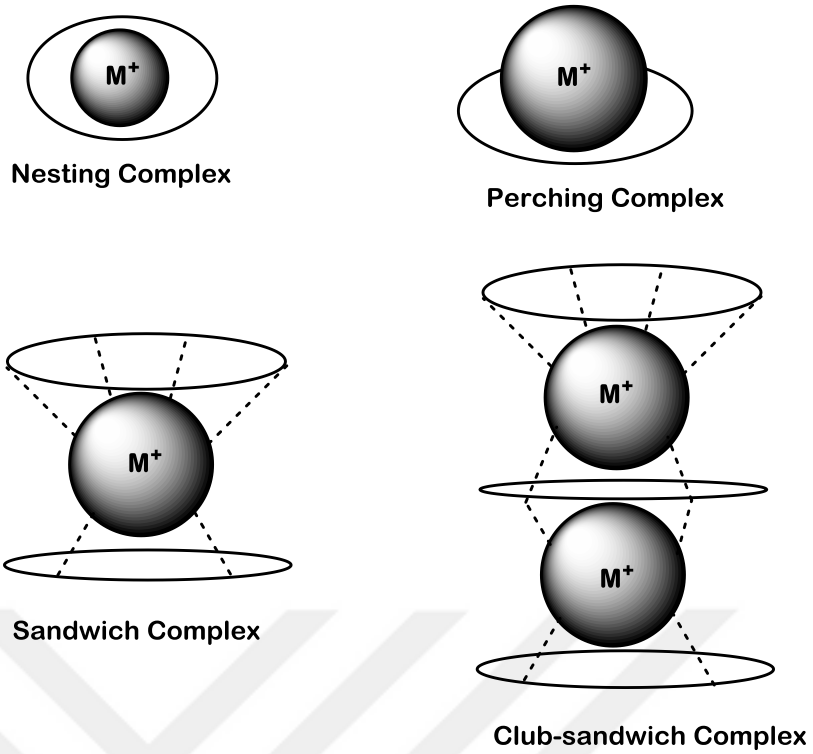


Figure 1. 4. Types of crown ether-metal complexes

The crown ethers form complexes not only with metal cations but also with ammonium ion, because of the similarity, in terms of charge and size, with K^+ (Pedersen, 1967). Organic molecules also behave as guest (Cram and Gokel, 1973; Gokel, et al., 2004; Kyba, et al., 1977). The benzenediazonium ion was complexed with the 21-crown-7 in solution (Figure 1.5) (Mageswaran, et al., 1979; Steenland, et al., 1997; Cram and Gokel, 1973; Kyba, et al., 1977; Gokel et al., 2004).

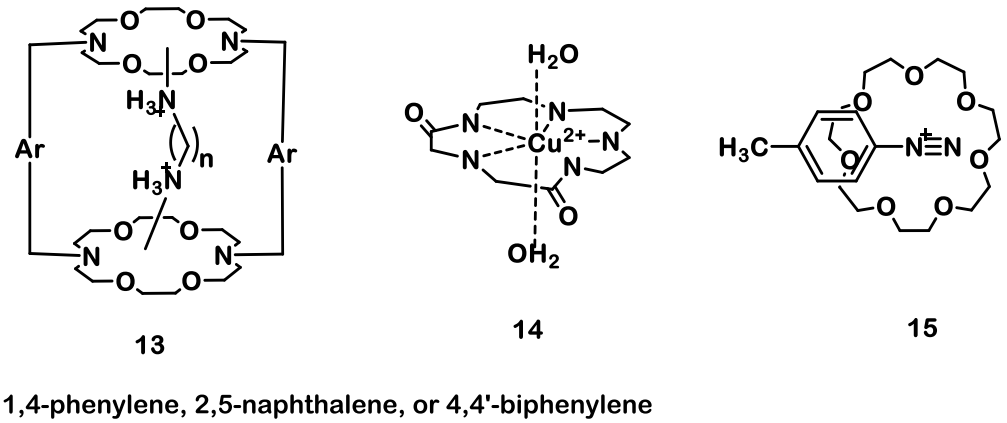


Figure 1. 5. Example for the sandwich and nesting type host-guest interaction

The host-guest relationship between macrocycle and a suitable molecule or an ion has been explained by taking account of electrostatic interaction, hydrogen bonding, π interactions, Van der Waals interaction (Kelly and Kim, 1994; Harger and Smith, 1986;Cram, 1988) or charge transfer interactions (Kyba, et al., 1977; Kumar et al., 1992) (Figure 1.6).

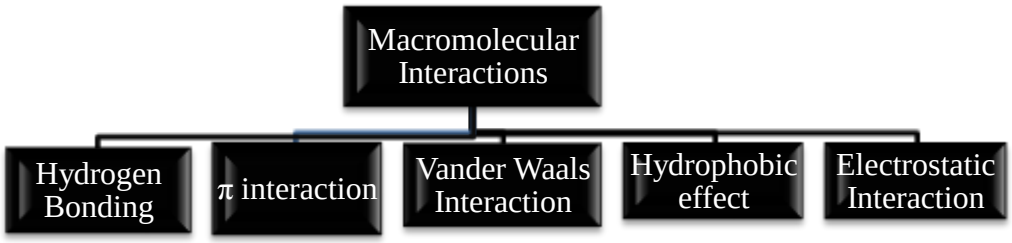
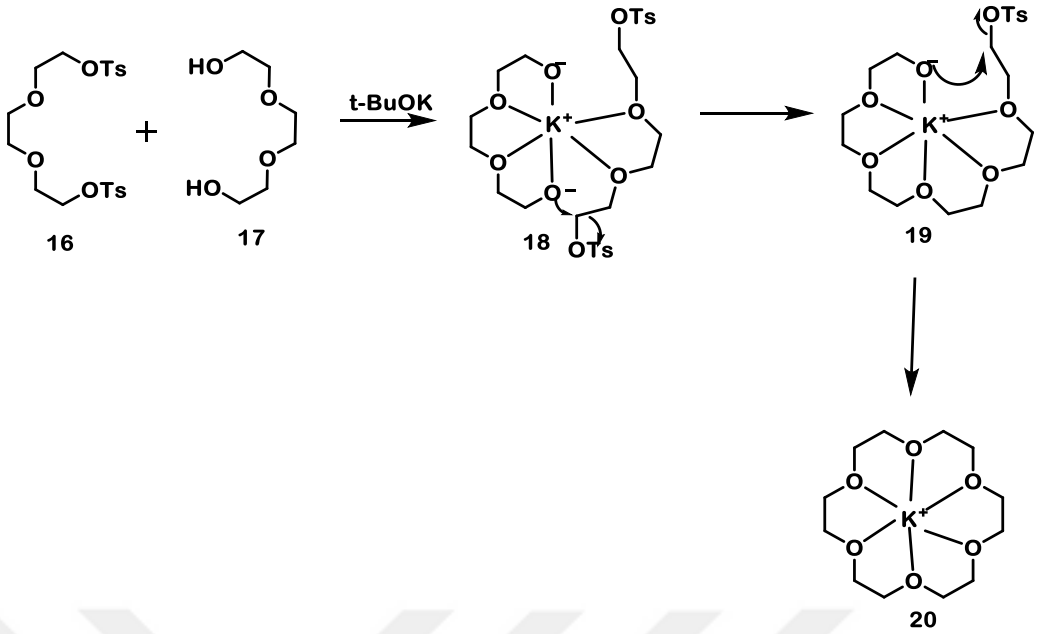


Figure 1. 6. Schematic illustration for macromolecular interactions

The complex formation of crown with alkali and alkaline earth metal cations was first announced by Pedersen (Pedersen, 1967) but an important concept about complexation was studied by Green who has proposed the "template effect". The study showed that the concentrations of the reactants did not affect the yield, despite changes in concentrations. But, however, upon replacement of *tert*-BuOK with Bu_4NOH, a significant increase in the yield was observed and thus metal cation exhibited some kind of template effect. The organization between open-chained ligand and cation involved an ion-dipole interaction. Template effect is exerted by K^+ cation and this promotes the intermolecular S_N2 reaction and the mechanism for templating is shown in Scheme 1.1 (Green, 1972).



Scheme 1.1. Mechanism for template effect

1.1.3 Applications of Crown Ethers

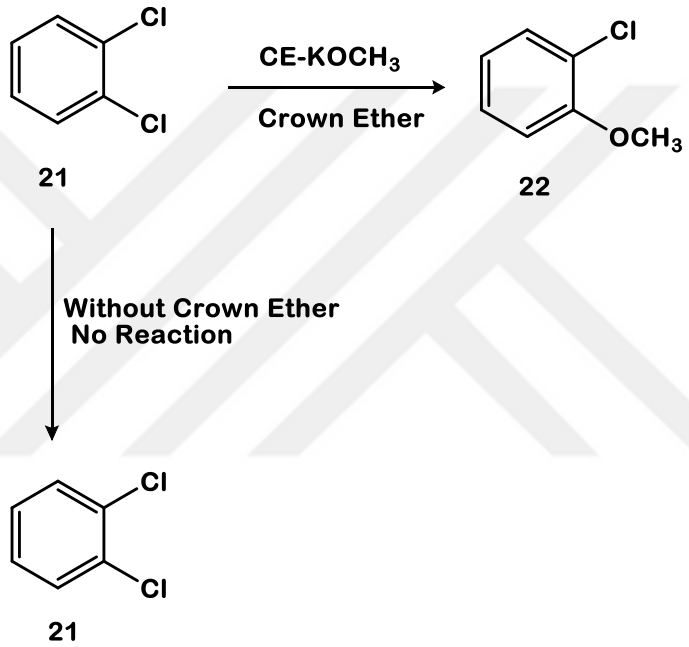
Crown ethers have attracted remarkable attention in various fields of science (Bühlmann, et al., 1998; Nezbedova, et al., 2001; Valeur and Leray, 2000; Quinn, et al., 2011; Mizukami, et al., 2002; Liu, et al., 2005). The selective binding properties of crown ethers with alkali and alkaline earth metal ions made them possible to be used as ionophores and ion-selective electrodes (Nakano, et al., 1990; Mashhadizadeh, et al., 2012; Kuhn and Erni, 1992; Gokel et al., 2004; Wygladacz and Malinowska, 2001).

Various methods are being used to clean the dye matter in waste water of some industries including textiles, leathers dyestuffs (Akceylan, et al., 2009; Yılmaz et al., 2007). But a better solution has been discovered to remove dyestuff by using sophisticated properties of macromolecules. Among them the crown ethers form highly efficient complexation with dyestuff because they have a suitable binding site (Yang, et al., 2014; Zarzeczańska, et al., 2016; Fedorova, et al., 2004).

Crown ethers are also being utilized as phase transfer catalysts (Hausner, et al., 2005;Cram and Sogah, 1981; Krakowiak, et al.,1989). Phase transfer catalyst (PTC) assists the transfer of reactant from one phase to another, so PTC have found

applications in some industrial processes. In order to decrease the disadvantages and to be more suitable in industry, PTC should be recovered. In this regard, Gourdet and his coworkers have studied the recovering properties of "light fluorous" crown ether (Gourdet, et al., 2010). Meanwhile in asymmetric synthesis, chiral crowns have also been reported as phase transfer catalysts (O'Donnell, 1993).

Besides the usage as phase transfer catalyst, crown ethers are also incorporated as anion activator causing a substitution reaction, otherwise it would be difficult to perform (Scheme 1.2) (Liotta and Harris, 1973).

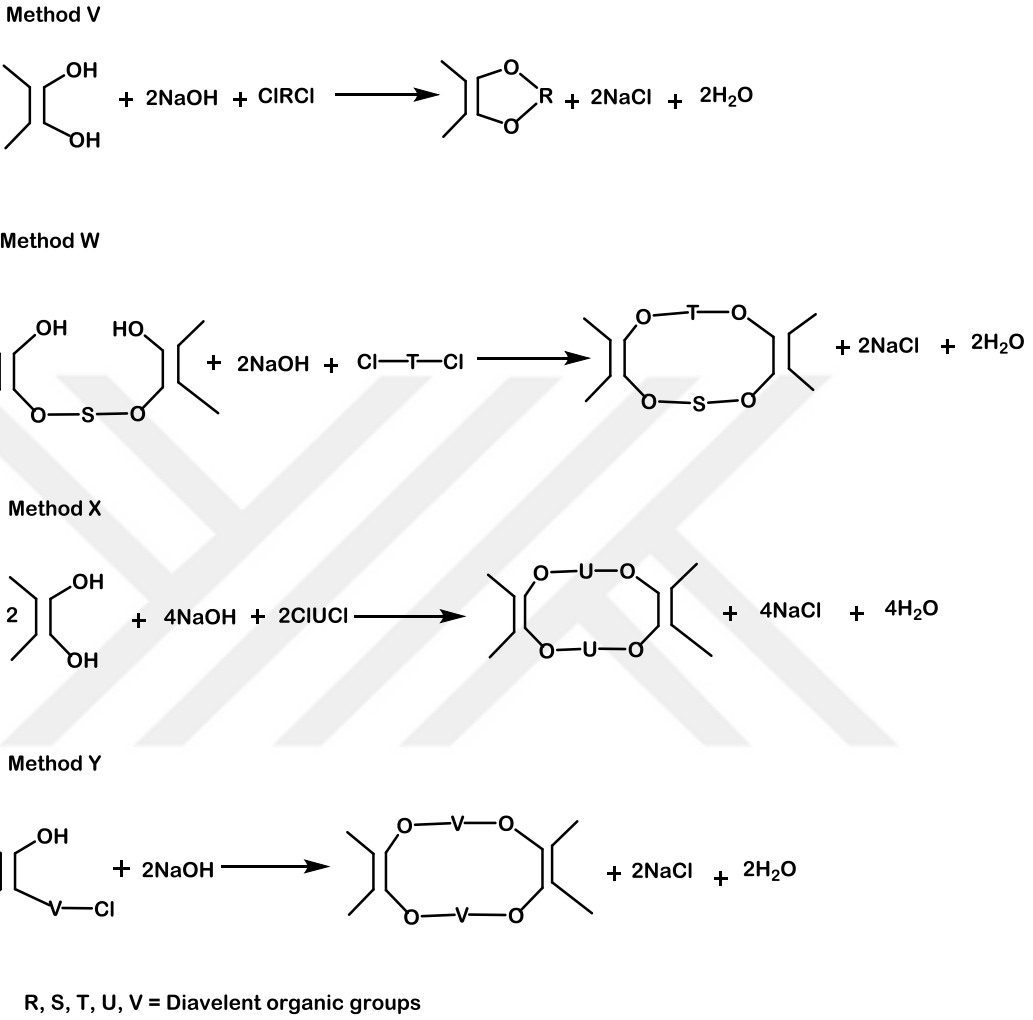


Scheme 1.2. Substitution reaction by means of crown ether

The macrocyclic ionophores have found potential applications in analytical chemistry, biochemical analysis and environmental protection due to their effective fluorescence spectral changes (Fages, et al., 1989; Bricks, et al.,2005; Shamsipure et al., 2008; Lin Ho, et al., 2009). More attention has been directed on fluorescence spectra rather than UV-visible spectra in the detection of the metal cations by using ion-selective ligands (Wysiecka, et al., 2011, Nunez et al., 2009). High selectivity, time response, resolution such advantages make them favourable (Valeur and Leray, 2000).

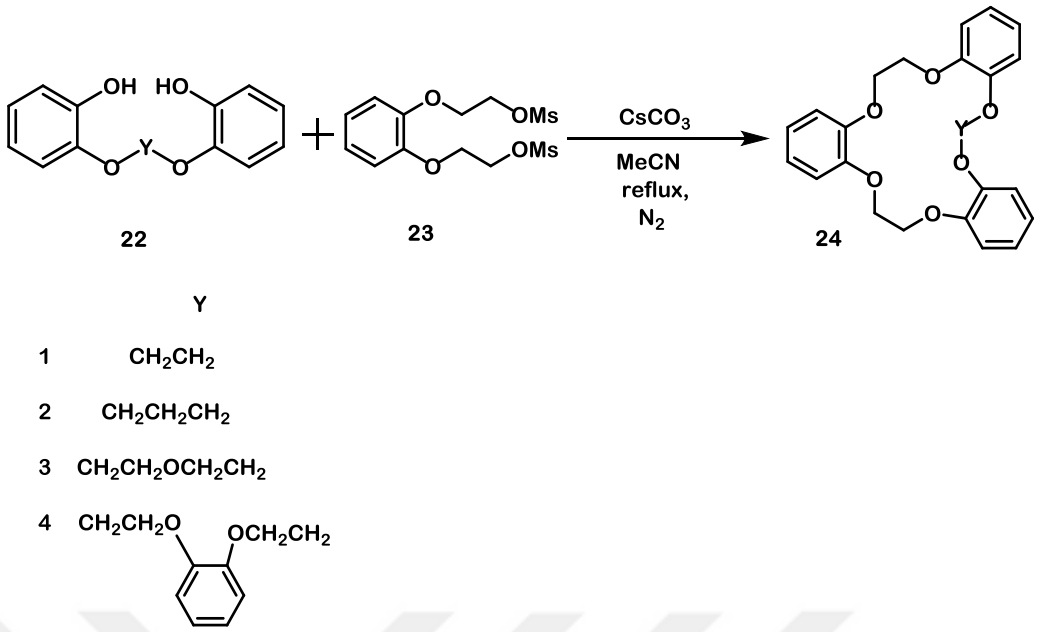
1.1.4 Synthesis of Crown Ethers

Pedersen recommended four different methods for the synthesis of the crown ethers as shown in Scheme 1.3.



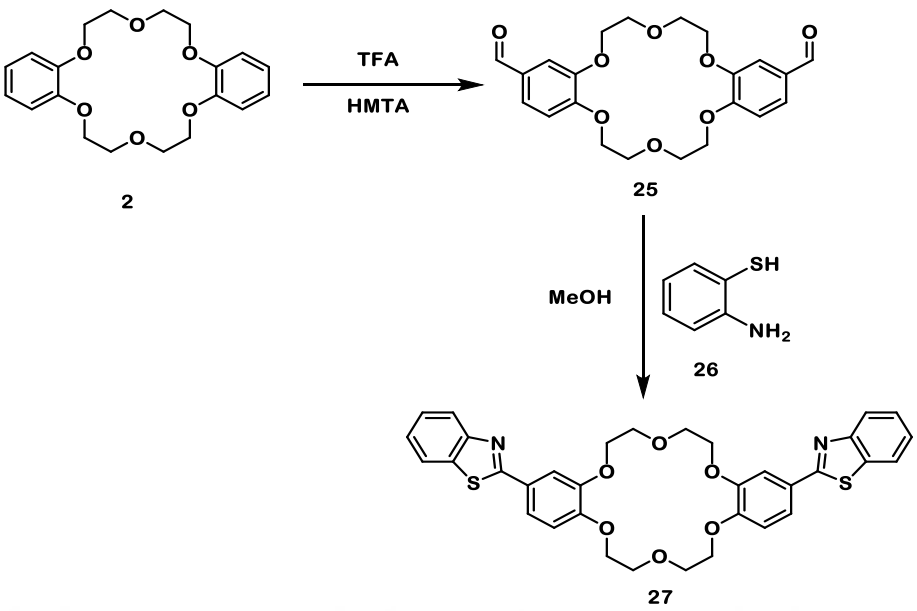
Scheme 1.3. Pedersen Methods for the preparation of crown ethers (Pedersen 1967)

Pedersen synthesized over sixty crown ethers by using the above methods. Method W is the most effective one, when compared with the other methods, leading to high yields. Dibenzo-18-crown-6 was obtained by using W type method by Pedersen (1967) and the researchers later followed this methodology to prepare various di, tri benzo crowns (Hanes, et al., 2006; Vaidya, 1996; Burk, et al., 2008). An example for the W type is shown in Scheme 1.4.



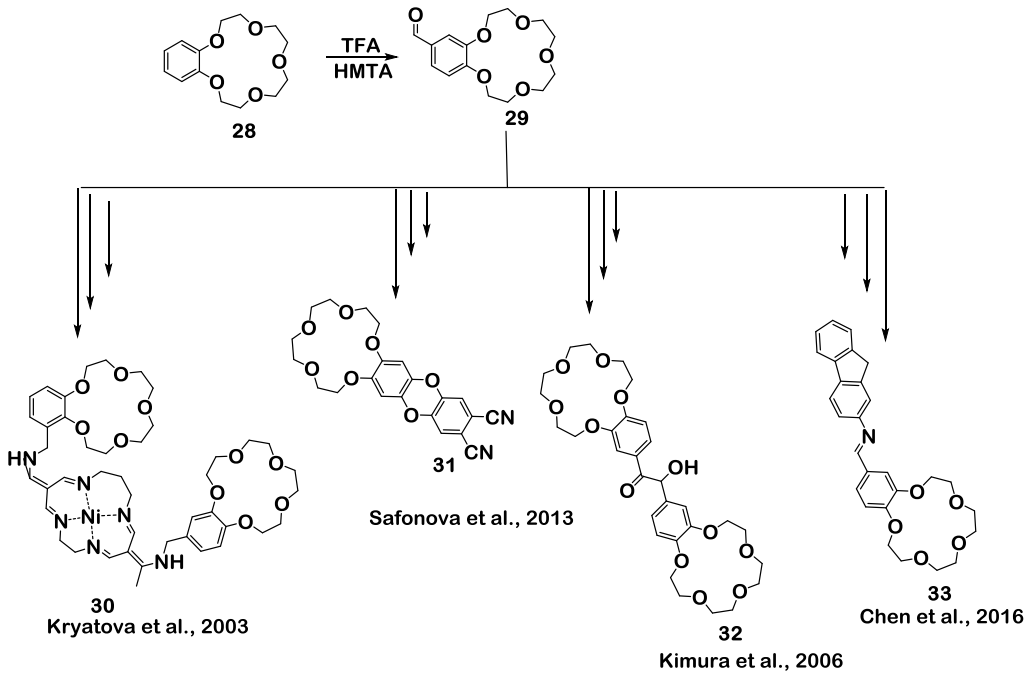
Scheme 1.4. Methodology for the synthesis of tri or tetrabenzo crowns

The formyl derivatives of benzocrowns are convenient intermediates for the synthesis of a variety of benzene bearing macrocyclic polyethers by using carbonyl function (Wada, et al., 1980; Kimura, et al., 2006; Chen, et al., 2016; Seyedi, et al., 2011; Kryatova, et al., 2003; Doğru, et al., 2015; Safonova, et al., 2013; Morgan et al., 2014; Volchkov, et al., 2016; Bourgeois, et al., 1999; Moghimi, 2002). An example of the synthesis of the benzo substituted crown was prepared (Jagadale et al. in 2015). Jagadale and his coworkers used TFA (trifloroacetic acetic) and HMTA (hexamethylenetetraamine) to obtain diformyl dibenzo-18-crown-6. The formylation is the first step to reach the desired compounds (Scheme 1.5) .



Scheme 1.5. A synthetic method for the synthesis of the dibenzothiazolyldi benzo-18-crown-6-ether starting from diformylatedbenzocrown

Various benzo-derivated crown ethers were reported in the literature (Patil, et al., 2016; Dhakal, et al., 2009; An, 1994; Deshmukh, et al., 2010; Bartsch and Eley 1996) some of which were derived from 3' formyl benzocrown **29 (**Scheme 1.6).



Scheme 1.6. Structures obtained from 3' formyl benzocrown 29

1.2 AZACROWN ETHERS

Azacrown ethers are the intriguing class of the compounds in the macrocyclic chemistry due to their strong capability to bind metal cations (Khoramdareh, et al., 2014; Xue, et al., 2002; Sakamoto, et al., 2011; You, et al., 1997). The binding properties of azacrowns can be regarded as intermediate between all-oxygen crowns and the all-nitrogen cyclams. Therefore azacrown ethers play a crucial role in coordination with cationic guests (Krakowiak, et al., 1989; Bordunov, et al., 1996; Ioannidis, et al., 2010). These guests should be organic and inorganic cations (Tsuchiya, et al., 2006; Wang and Lönnberg, 2006). Due to their unique host-guest property, aza-crowns have gained importance in different fields (Abbaspour, et al., 2011; Puyol, et al., 2007; Tsukube, 1986; Liu, et al., 1998; Hirano, et al., 2000; Shing, et al., 2013; Kaur, et al., 2012; Echegoyen, et al., 1994; Li, et al., 2012).

1.2.1 Nomenclature of Azacrowns

The azacrown ethers are named according to Pedersen. Below two examples are given (Pedersen, 1967) (Figure 1.7).

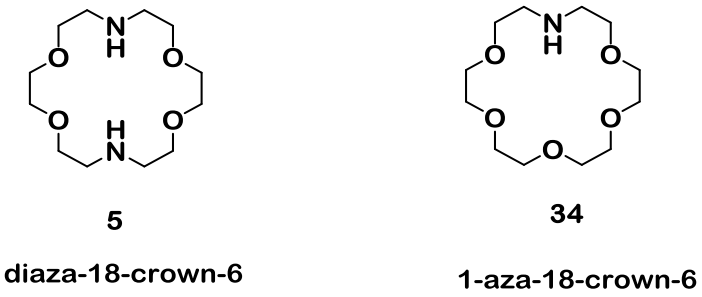
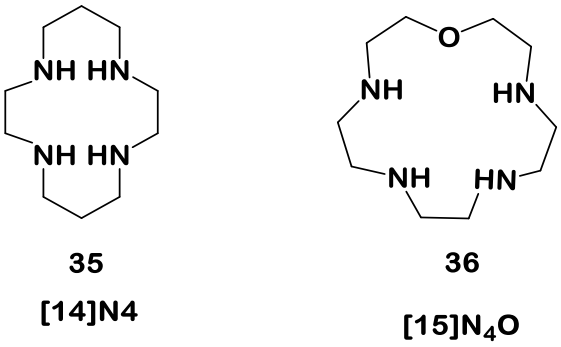


Figure 1. 7. Nomenclature of nitrogen macrocycles according to Pedersen

Busch and coworkers have recommended a different kind of nomenclature for crown ethers which contain nitrogen and/or oxygen atoms. In this structure, 36 is indicated as [15]aneN_4O (Figure 1.8). The explanation of this notation is that; the number in brackets shows the ring size and the word "ane" means the structure is a saturated compound, and at the end of the notation is of the number and kind of heteroatoms (Busch, et al., 1972). This cyclic tetraamine are often called cyclam.



35
[14]N4

36
[15]N_4O

Figure 1. 8. Nomenclature of nitrogen macrocycles according to Busch et. al

.

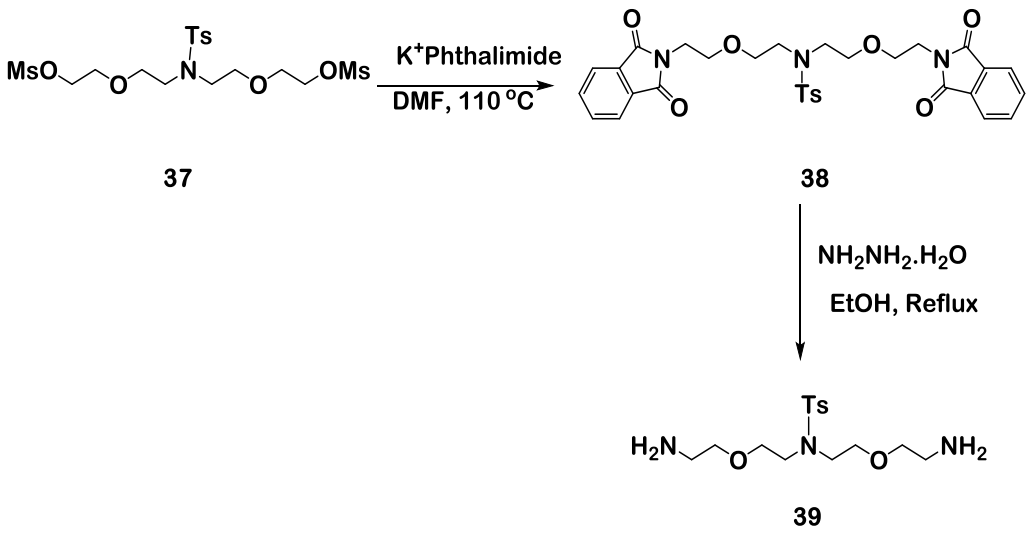
1.2.2 Synthesis of the Azacrown Macrocycles

Synthesis of the nitrogen-containing macrocycles has received interest due to binding properties with transition metal and other heavy metals, which have applied on various biological systems (Ranganathan, et al., 2002; Aguilar, et al., 2001; Long, 1999, Shing Wu, et al., 2013; Przybylski, et al., 2009). Aza crown synthesis has been based on high dilution technique, (Gokel, et al., 1982; Chavez and Sherry, 1989), template effect (Kulstat and Malmsten, 1979) and high-pressure approach (Jurczak and Pietraszkiewicz 1985; Richman and Atkins, 1974; Atkins, et al., 1988). Some of the synthetic procedures for macrocyclic polyamines as key precursors have been summarized below:

1.2.2.1 Synthetic Precursors of Azacrowns

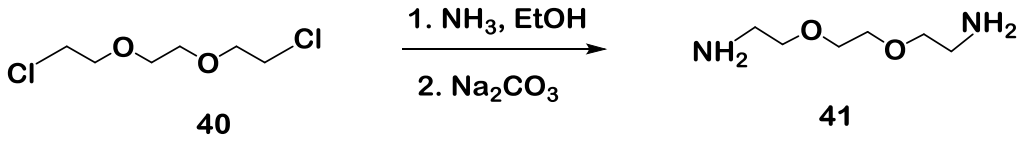
1.2.2.1.1 Preparation of Diamines

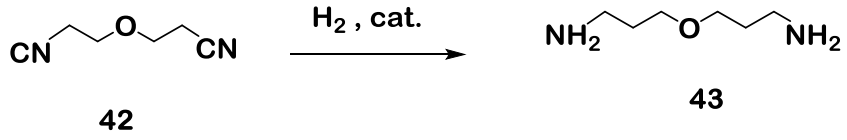
The preparation of the diamino aliphatic ether has been reported by the Krakowiak et al. by using a modified Gabriel synthesis (Krakowiak et al.,1992). Quici and coworkers have also used this method by reacting potassium phthalimide with dimesylated aliphatic ether **37**, followed by hydrolysis to obtain diamino aliphatic ether **39** (Scheme 1.7) (Quici et al., 1996).

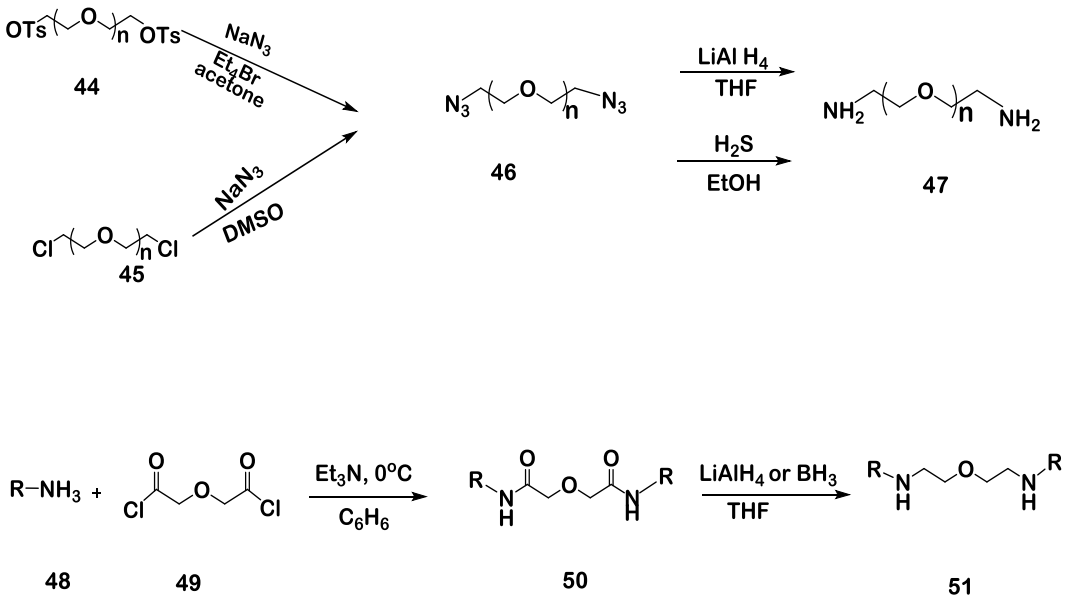


Scheme 1.7. Synthesis of diamino aliphatic ether by using Gabriel synthesis

In addition to Gabriel synthesis, various synthetic methods of aliphatic diaminoethers were reported and herein some of these diamine precursors of azacrowns are depicted in Scheme 1.8 (King and Krespan, 1974; Krakowiak, et al., 1989; Gatto, et al. 1986; Krakowiak, et al., 1988).

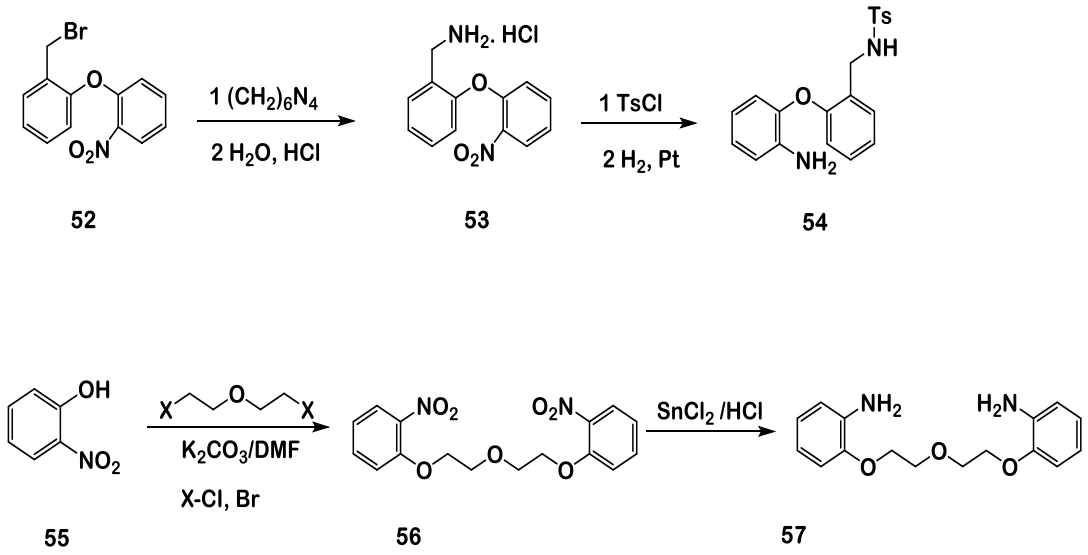






Scheme 1.8. Synthesis of diamino aliphatic ethers by using different methods

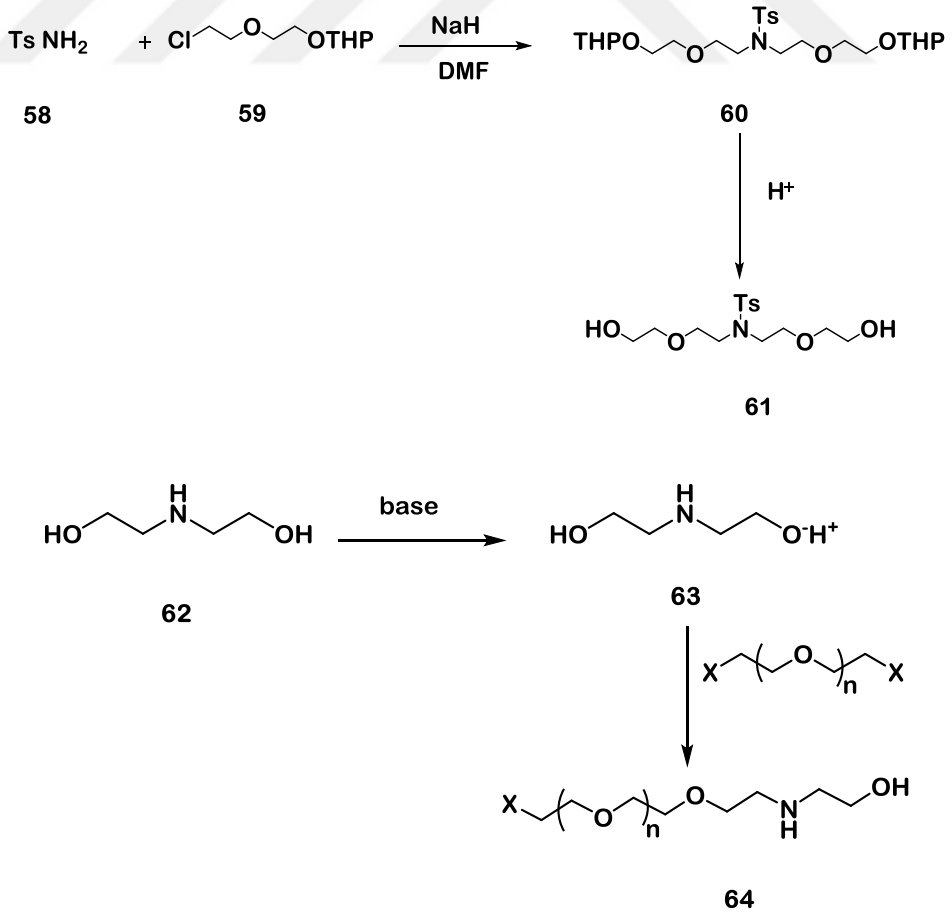
The aromatic diamines have been synthesized by reduction of nitro-containing aromatic compounds (Scheme 1.9) (Wu, 2000; Wysiecka, et al., 2007; Sharghi, et al., 2001; Lockhart, et al., 1977).

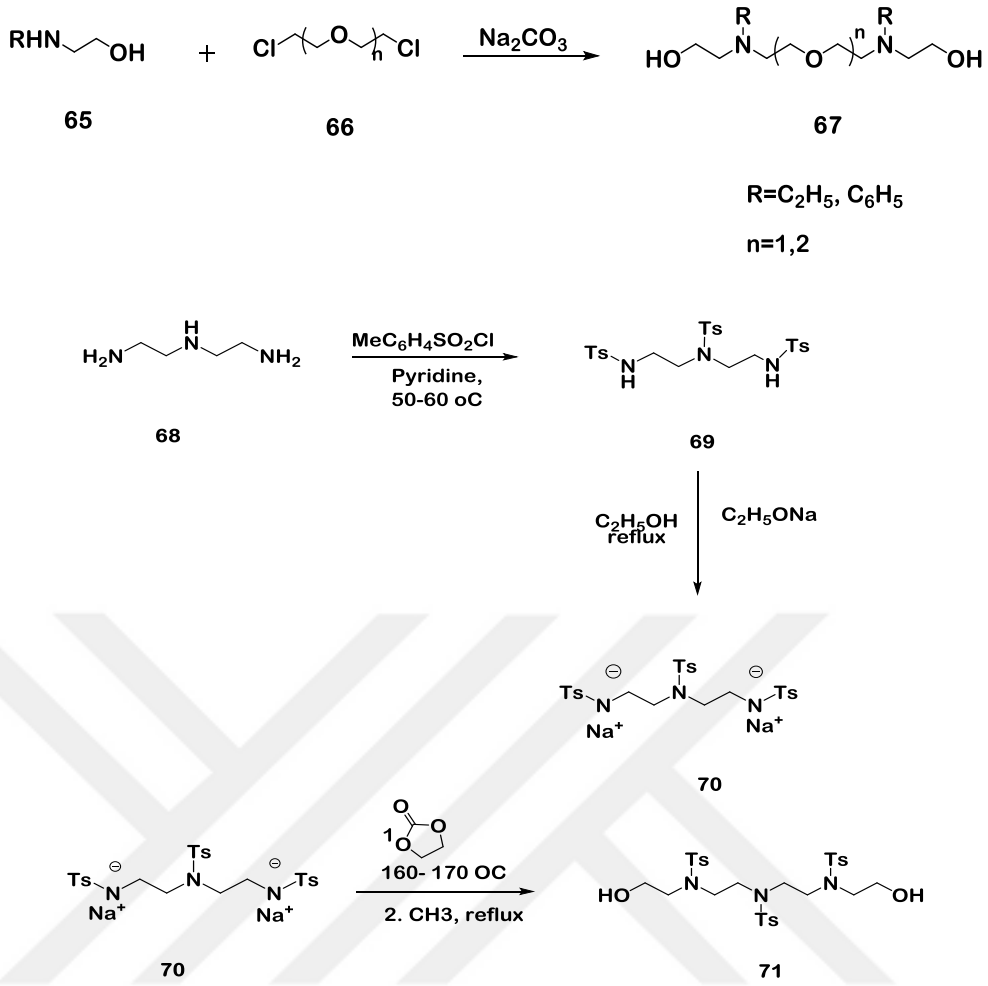


Scheme 1.9. Methods to prepare diamino ether by reduction of dinitro derivatives

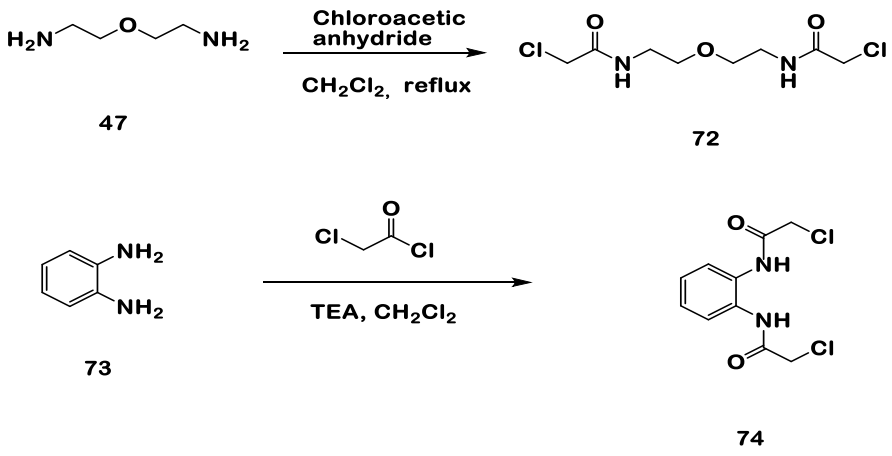
1.2.2.1.2 Preparation of Amino Diols and Amide-based Aliphatic ethers

An alternative way for the synthesis of nitrogen-containing crown ethers is to use amino, amino-diols and amide-based precursors. Amino or diamino diol precursors have been synthesized with or without protecting of amino group by tosyl chloride or THP (Scheme 1.10) (Anelli, et al., 1988; Huang, et al., 2009; Piatek, et al., 2001; Krakowiak and Bradshaw, 1992; Maeda, et al., 1983; Atkins et al., 1988; Romanski and Jaworski, 2017; Elwahy, 2003; Pastushok, et al., 1996). Protection or deprotection phases through final products actually exploit too many steps. Meanwhile tosyl group was found to affect the binding properties of crown ether towards the metal cations (Pratt and Sutherland, 1988). Also chloroacetyl chloride have been used to obtain amide-based precursors (Scheme 1.11) (Yang, et al., 1999; Krakowiak, et al., 1990, Sharma, et al., 2007; Song, et al., 2001; Krakowiak, et al., 2000; Rajakumar, et al., 2006). Here are some of the published methods regarding above-mentioned procedures (Schemes 1.10 and 1.11).





Scheme 1.10. Synthesis of the various amino diols



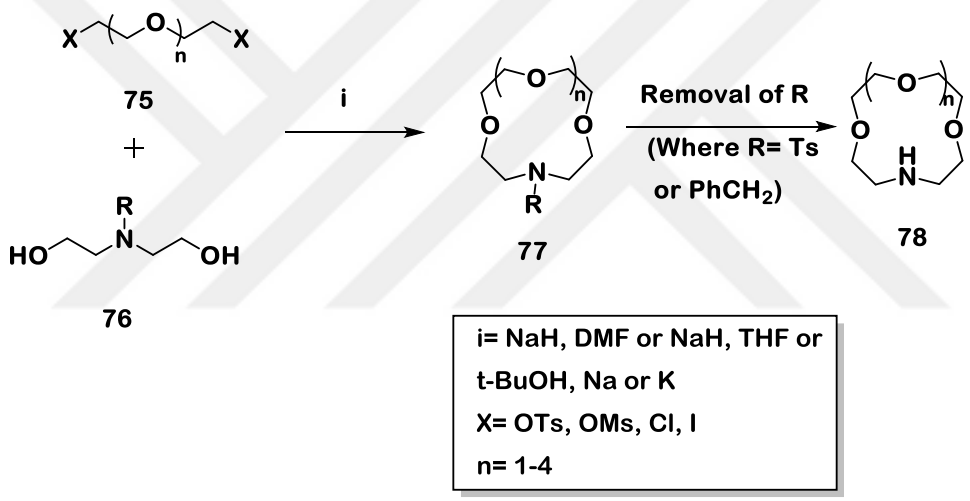
Scheme 1.7. Synthesis of amide-based precursors of crown ether

1.2.2.2 General Synthetic Methods Used To Prepare Azacrowns

Methods for the preparation of certain types of aza-macro heterocycles are illustrated below.

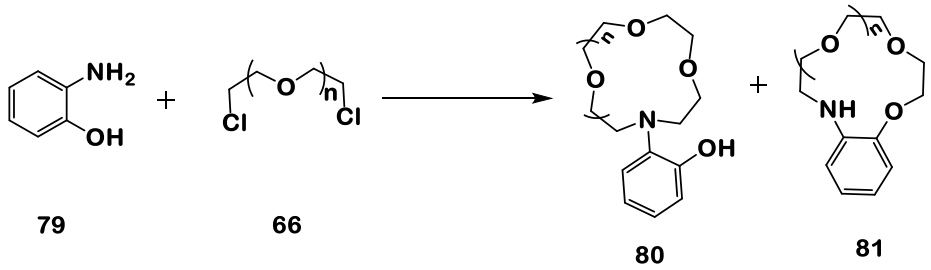
1.2.2.2.1 Mono/ Di/Polyaza- Crowns

The different types of monoazacrowns have been reported in the literature (Itoh and Shirakami, 2001). In order to synthesize this type of azacrowns, appropriate aliphatic and aromatic amines were reacted with the dihalide or ditosylated derivative of ethylene glycol (Johnson, et al., 1979; Schultz, et al., 1985; Amrani et al., 2007; Wu, et al., 2013). An example for the synthesis of the monoazacrown is shown below (Scheme 1.12) (White, et al., 1985)



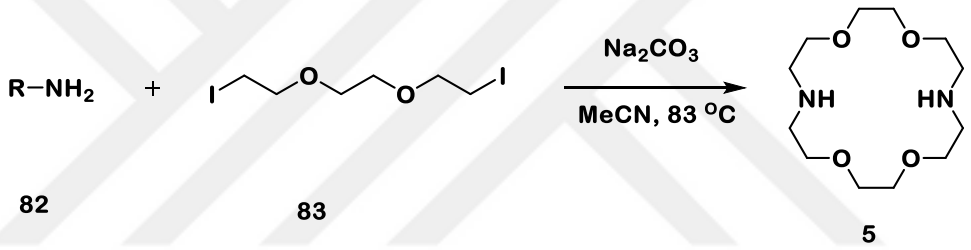
Scheme 1.8. A typical method for the synthesis of mono azacrown ether

The protection of the nitrogen with the tosyl group increases the acidity and also prevent the nitrogen to undergo additional reactions. For example, Lockhart and co-workers reacted 2-amino phenol **79** with the dihalides **66** without tosylation of nitrogen reaction yield two monoaza compounds (Scheme 1.13) (Lockhart, et al., 1977).



Scheme 1.9. A schematic synthesis of aza-crown without protection with by product

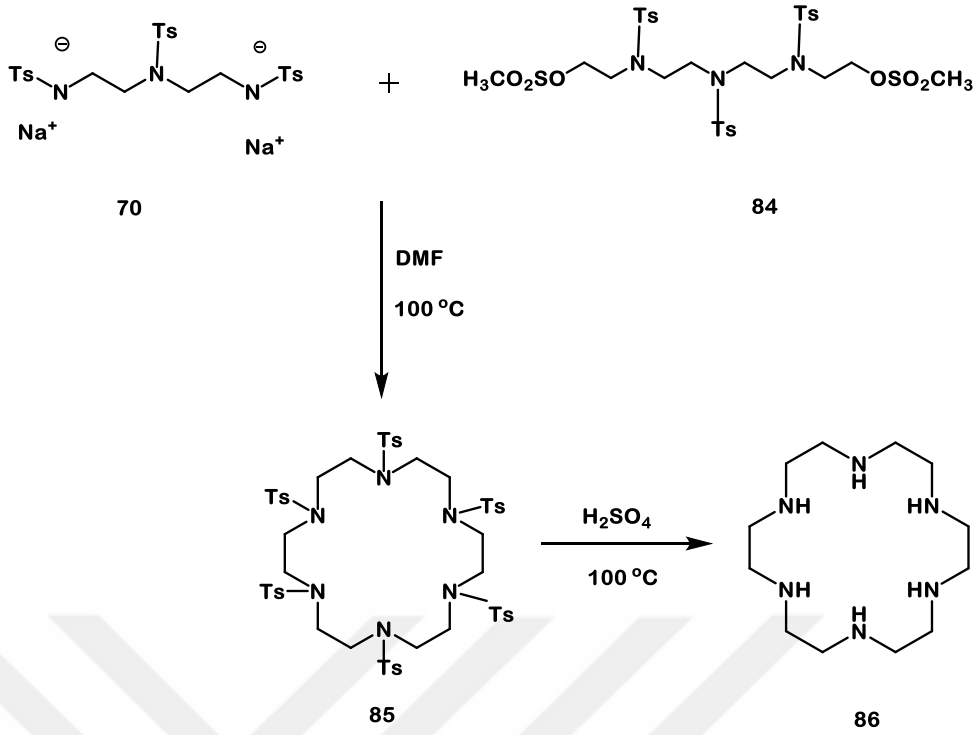
The diazacrown compounds are important for the synthesis of cryptand (Czech, et al., 1988) and for the sandwich type macromolecules (Fasseu, et al., 1998; Safonova, et al., 2013). Gatto and his coworkers synthesized diaza crown by one step cyclization (Scheme 1.14) (Gatto and Gokel,1984).



Scheme 1.10. Synthesis of the diazacrown by Gatto and coworkers

An alternative synthesis of diaza-crown was reported using alumina (Pietraszkiewicz, 1984). There are a number of synthetic routes of diazacrowns were also known (Zhang, et al., 1995; Börjesson and Welch, 1991; Lukyanenko, et al., 1988; Desreux, et al.,1977).

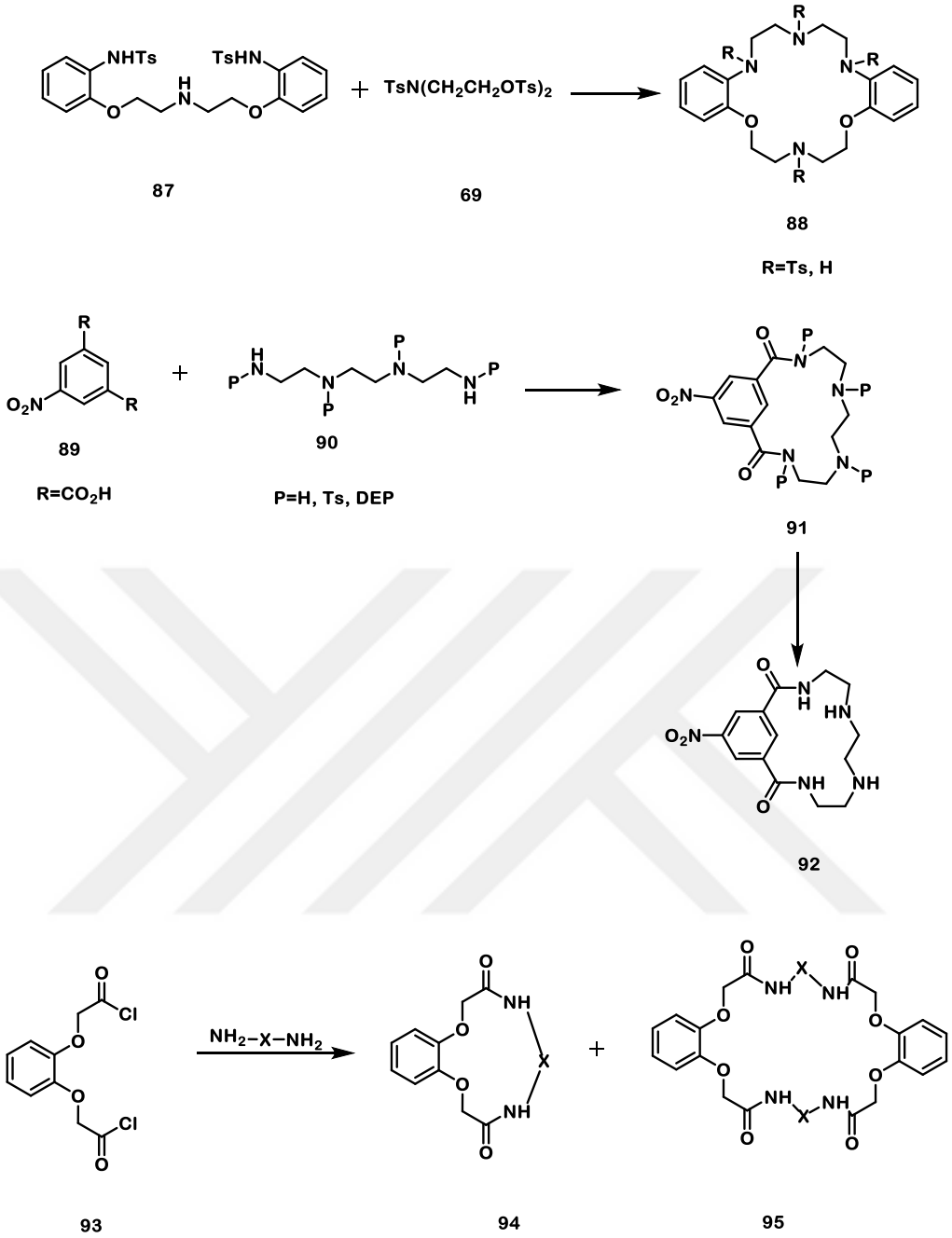
Atkins and co-workers obtained polyazacrowns by reacting the polyamine, which were tosylated with *p*-toluenesulfonyl chloride, with ditosylated oligoethylene glycol (Scheme 1.15) (Atkins, et al., 1988). In order to obtain unsubstituted polyaza crown, the compound **85** was protonated with conc. H_2SO_4. Polyazacrowns of different ring sizes bearing heteroatoms have been referred (Wei, et al., 1986; Huang, et al., 2009; Sun, et al., 1985; Grolik et al., 2012; Buschman and Mutihac, 2001; Sarma et al., 2010).



Scheme 1.11. Synthesis of polyazacrown **86** facilitated by tosyl chloride

1.2.2.2.2 Benzoaza-Crowns

Numerous synthetic methods for the azacrowns carrying benzo groups were reported (Scheme 1.16) (Hogberg and Cram, 1975; Kulikov et al., 2005; Gray, et al., 2007; Sharghi and Zare, 2006).

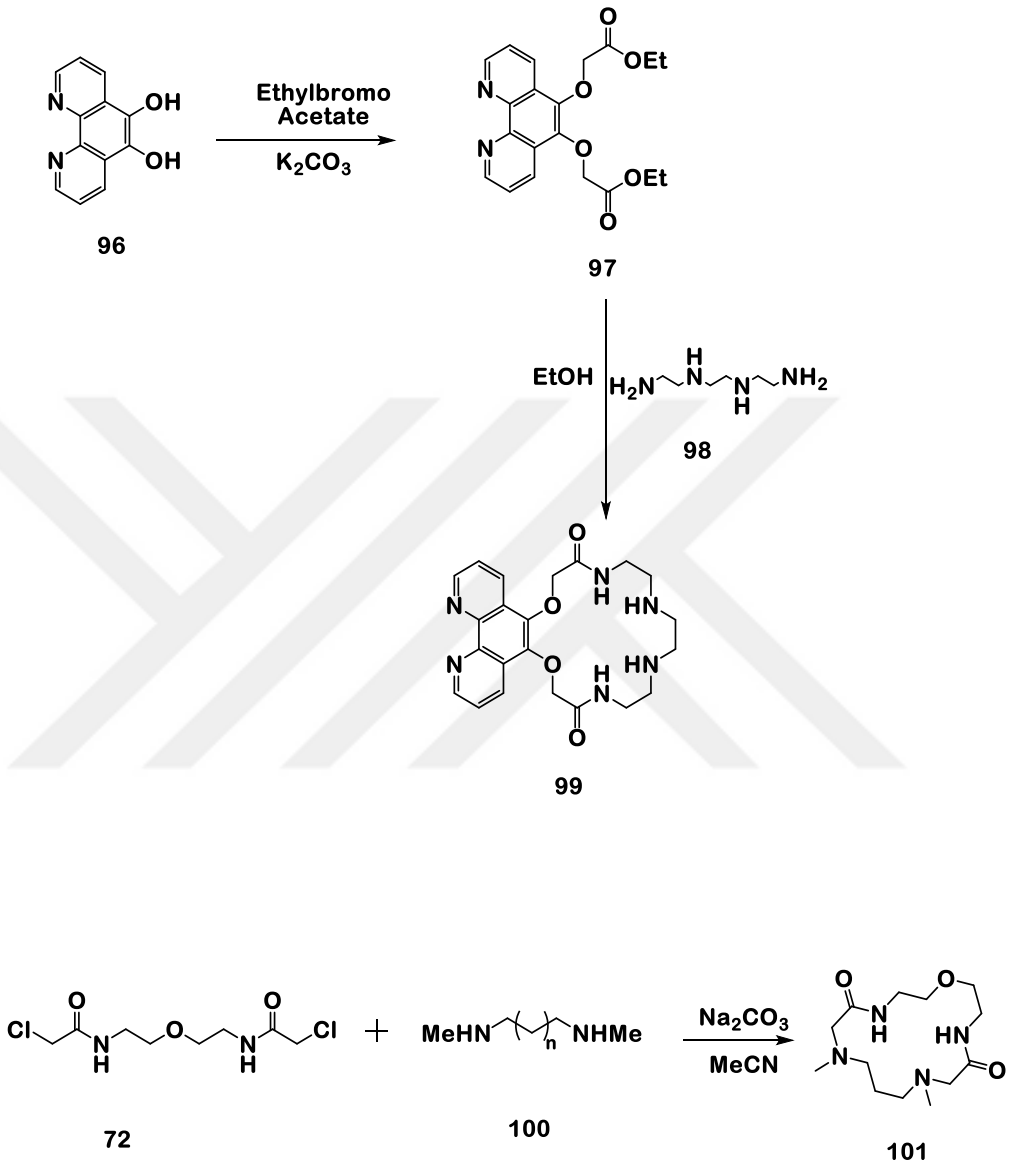


Scheme 1.12. Synthesis of dibenzo azacrowns

1.2.2.2.3 Amide-based Azacrowns

Macrocycles with amide groups have been synthesized by reacting primary amine derivatives with a diester precursor in an alcoholic solvent without a base (Sharghi, et al., 2007; Patra, et al., 2010; Jurczak, et al., 1991; Szumna, et al., 2002; Piatek, et al., 2004; Desreux, et al., 1993). But the addition of the diacid chloride to

the amine derivatives needed a base such as K_2CO_3 or Na_2CO_3 (Scheme 1.17) (Yang, et al., 1999; Patra et al., 2010).



Scheme 1.13. Synthetic routes for amide-based azacrowns

1.3 THIACROWN ETHERS

The replacement of one or more oxygen with the sulfur atom leads to new macrocycle named as thiacrown. Figure 1.9 illustrates some of the reported thiacrowns (Bradshaw, 1997; Pedersen 1971).

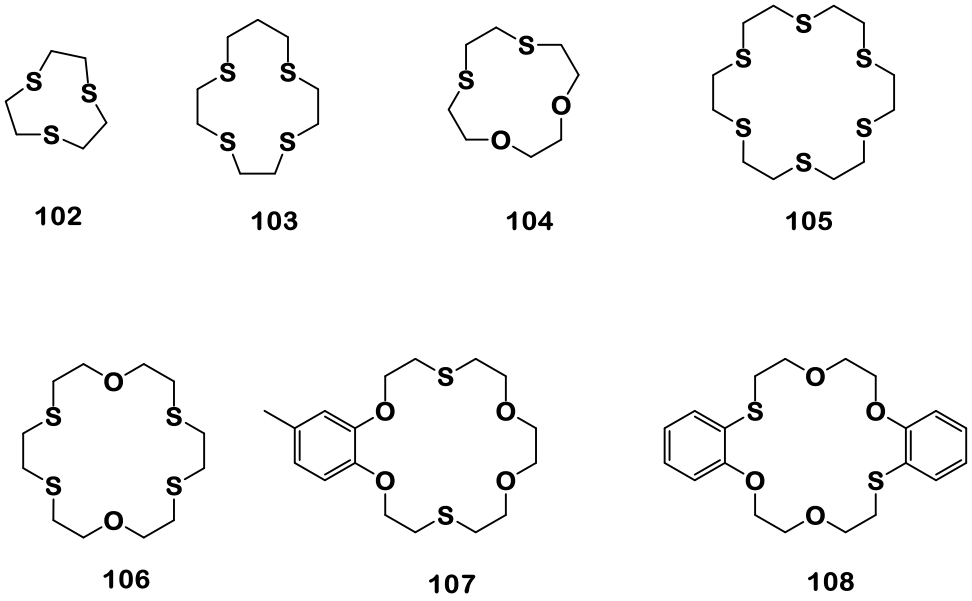


Figure 1. 9. Examples for some thiacrown ethers

According to Pedersen's work, the affinity towards the metal cations is affected by the atomic size and electronegativity when the oxygen is replaced by the sulfur atom. Oxygen is smaller than the sulfur atom, so the bond angle between C-O-C is greater than the the bond angle of the C-S-C. The C-O bond is more ionic than the C-S bond due to electronegativity. Due to these reasons sulfur has poor affinity towards the alkali metal cations but not for the soft metal cations (Pedersen, 1971; Rosen and Busch, 1969; Hartman and Cooper, 1986).

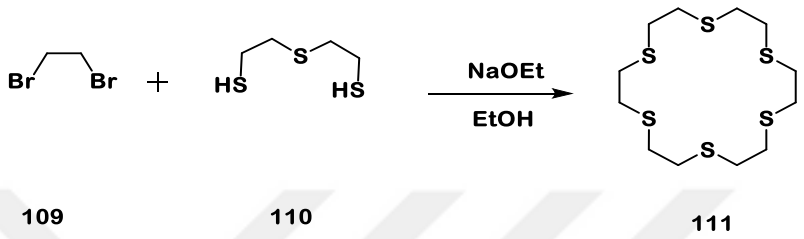
A variety of aza/oxacrown derivatives were reported as fluorescent chemosensors (McFarland and Finney, 2002; Lochman, et al., 2015; Nunez, et al., 2009; De Silva, et al., 2002; Xu, et al., 2001) whereas a small number of examples of thia-macrocycle were described as fluorescent metal cation sensors (Santis, et al., 1997; Lee, et al., 2001; Bronson, et al., 2001; Bricks, et al., 2005).

1.3.1 Synthetic Methods for Preparation of Thia Crowns

1.3.1.1 Synthesis of Sulfur containing Crown Ether

A few sulfur-containing cyclic compounds have been synthesized (Meadov and Reid, 1934; Dann, et al., 1961; Mortillaro et al., 1966,) before Pedersen has

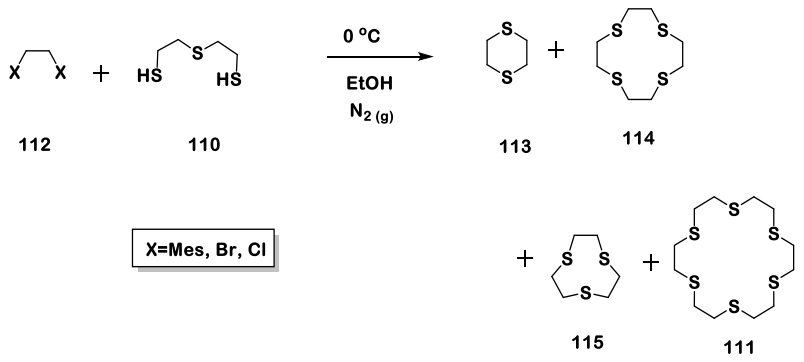
reported their affinity towards the metal cations (Pedersen, 1971). Then, a growing interest has been directed on the thia, oxa and aza macrocycles (Greene, 1972, Gerber, et al., 1977; Kimura, et al.,1982; Cram, 1988; Blake, et al., 2004; Volchkov, et al., 2016; Gürek and Bekaroğlu,1997; Ertem, et al., 2008). Meadov and Reid used different kind of dihalogenated ethane and dithiol derivatives in the presence of a base in EtOH to obtain sulfur containing macrocycles (Scheme 1.18) (Meadov and Reid,1934).



109 110 111

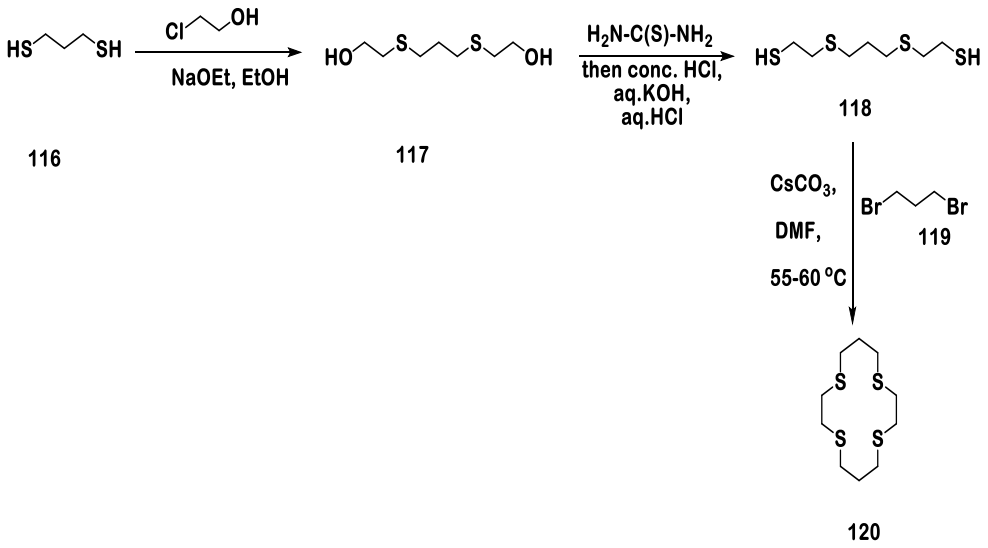
Scheme 1.14. Synthesis of the cyclic sulfur compounds

Gerber and his coworkers improved the yield of thiacrowns from 17% to 32% under inert atmosphere. The major product is **111,** but also the structures **113**, **114**, **115** as byproducts (Scheme 1.19) (Gerber, et al., 1977).



112 110 113 114 115 111

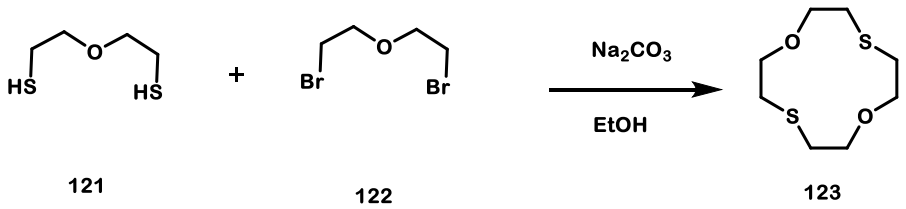
Scheme 1.15. Synthesis of the thiacrowns in highly diluted condition Buter and Kellog synthesized a type of cyclic sulfide in 7.5% yield yield by cesium carbonate (Scheme 1.20) (Buter and Kellog, 1993).



Scheme 1.16. Synthesis of the tetrathiacrown **120** by using $CsCO_3$ in DMF

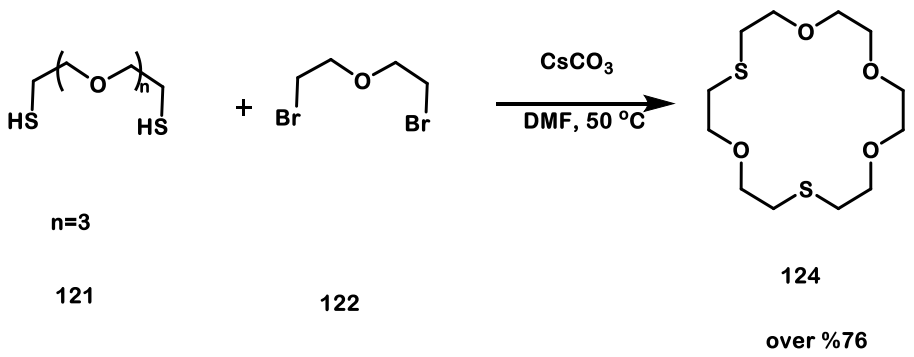
1.3.1.2 Oxygen and Sulfur containing Crown Synthesis

The thiacrown ethers were synthesized by reacting oligo-ethylene glycol dihalide with a dithiol (Scheme 1.21) (Dann, et al., 1961).



Scheme 1.17. The synthesis of thiacrown ether **123**

As their metal complexing capabilities are continuously drawing attention (Pedersen, 1971) the scientists those are interested in crown ethers tried to increase the yields of those molecules. In order to improve yields, they used highly diluted conditions (Bradshaw, et al., 1973, 1976, 1997; Bradshaw, 1997). In addition, Kellog et al., used Cs_2CO_3 in DMF (dimethylformamide) to increase the yield without using dilution conditions. They have been successful in the synthesis of thiacro**124** with higher yields (Scheme 1.22) (Stock and Kellogg, 1996).

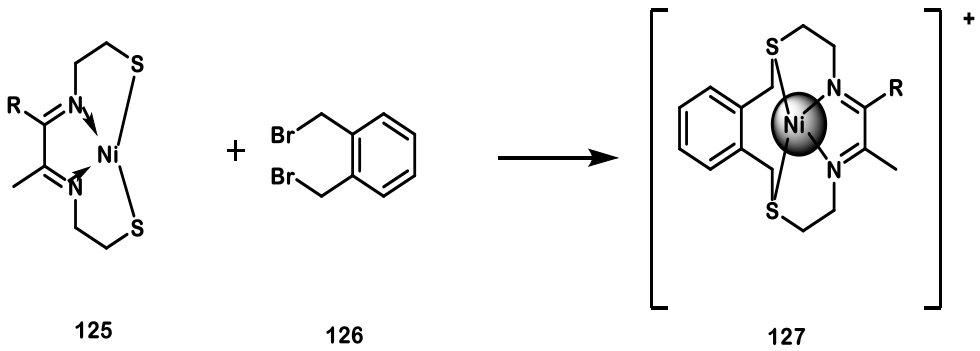


Scheme 1.18. Synthetic method of Stock and Kellog

One of the disadvantages of low-yielding synthesis of the thiacrowns is template effect. Although aza/oxa-crown ethers have strong template effects, low affinity of sulfur-containing crowns towards the alkali and alkaline earth metal cations induces also template effect giving rise to low yields (Bradshaw and Hui, 1974).

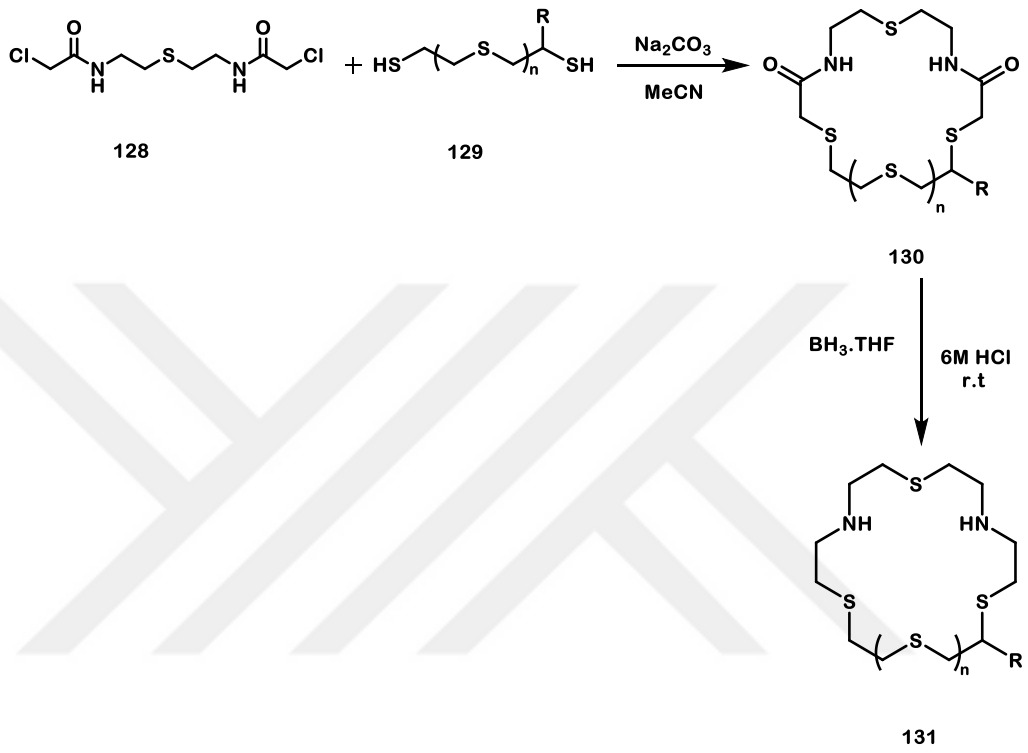
1.3.1.3 Synthesis of Nitrogen and Sulfur Containing Aliphatic and Aromatic Crown Ether

Various synthetic methods were reported for thia/aza crowns and their derivatives (Pedersen, 1971; Rostami, et al., 2012; Glenny, et al., 2006; Bradshaw and Izatt, 1997; Blake, et al., 2004; Caltagirone, et al., 2003; Van de Water, et al., 2000; Krylova, et al., 1999; Chartres, et al., 2006; Szczygelska-Tao, et al., 2004; Bricks, et al., 2005). For example, Busch and Thomson synthesized an example of sulfur and nitrogen containing macrocycle using metal template synthesis (Scheme 1.23) (Busch and Thomson, 1964).



Scheme 1.19. Template synthesis of thiaazacrown

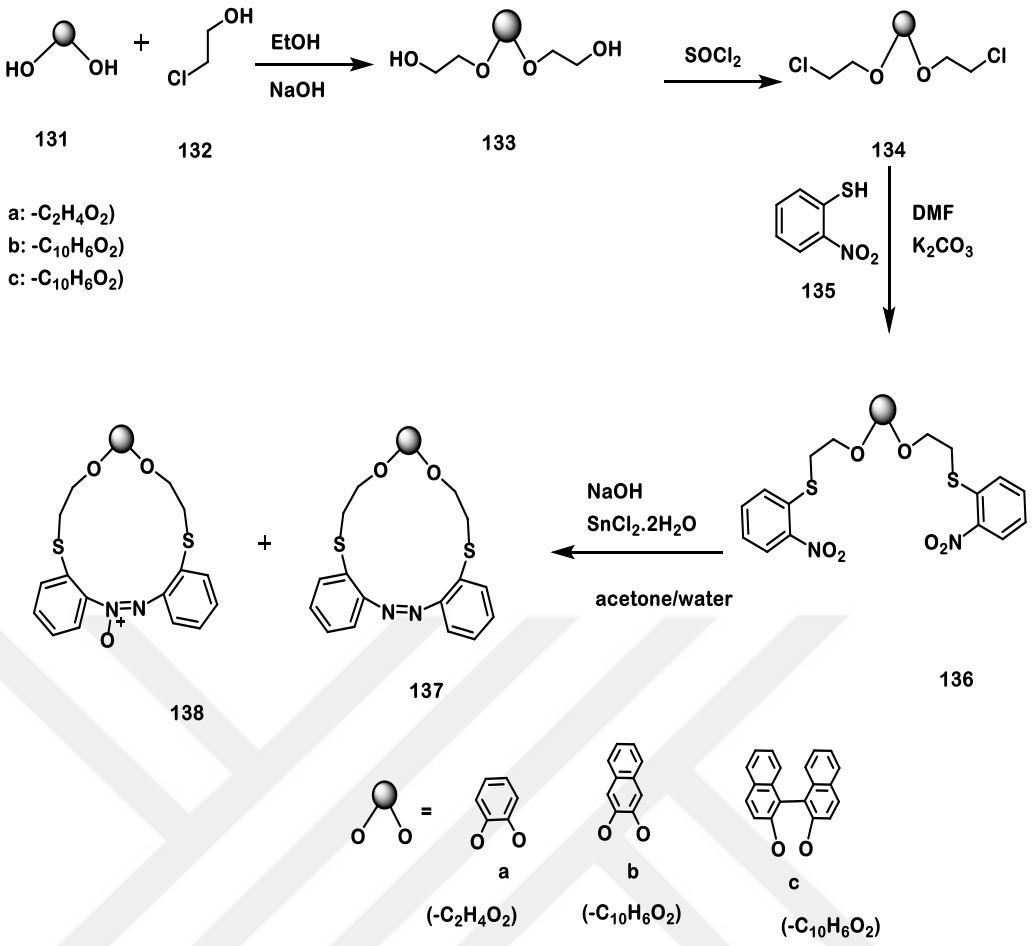
The crablike cyclization between bis-α-chloroamide and a diamine for the synthesis of azacrown ethers resulted in high yield (Yang, et al., 1999). In this regard, Bronson et al., reacted bis(chloroamide) with different ethanedithiol derivatives then BH_3.THF was used as reducing agent and final product **131** was obtained in high yield (Scheme 1.24) (Bronson, et al., 2001).



Scheme 1.20. A crab-like synthesis for azathiacrown

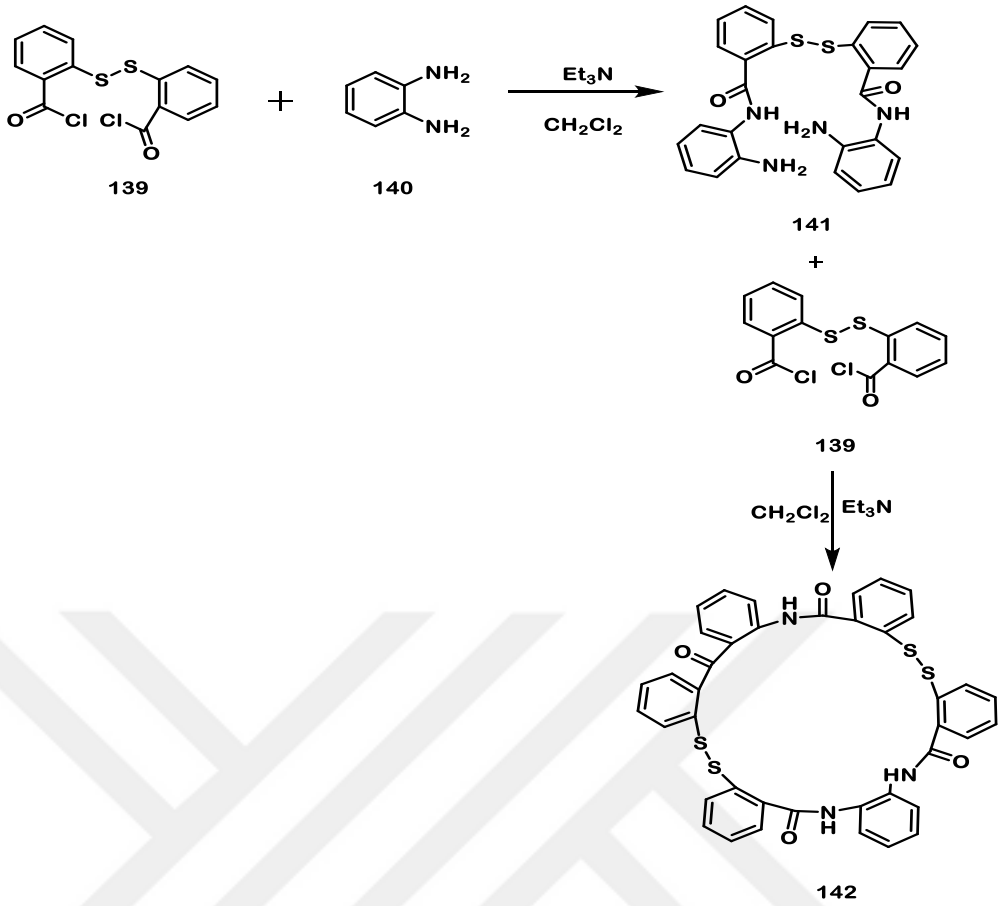
A number of aza, thiacrown compounds carrying aromatic groups were synthesized (Ertem et al., 2008; Szczygelska-Tao and Biernat, 1999; Szczygelska-Tao, et al., 2004; Caltagirone, et al., 2003; Blake et al., 2004; Wygladacz and Malinowska, 2001) along with the aliphatic crown ethers.

Kertmen and coworkers prepared azo and azoxythiacrowns by using catechol as starting material through a multi-step reaction sequence (Scheme 1.25) (Kertmen, et al., 2013).



Scheme 1.21. Multi-step reaction for the synthesis of thiazacrown

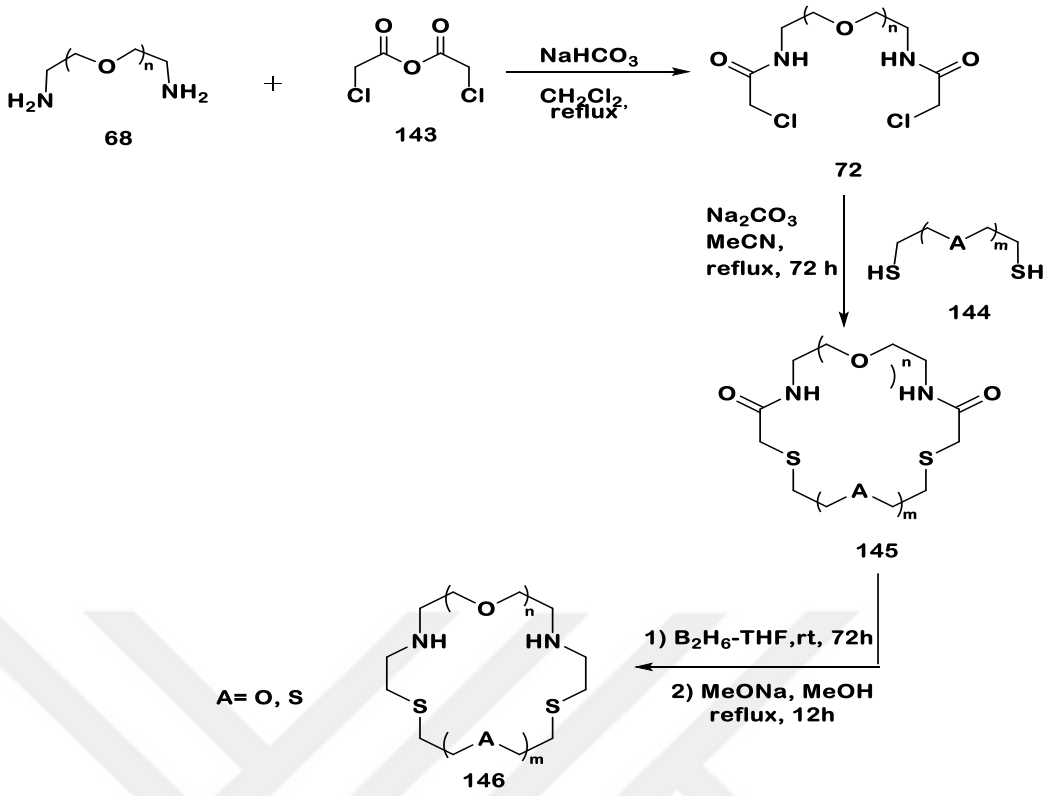
Ranganathan et al. reacted **139** with *o*-phenylenediamine and obtained thiaazacrown with hexabenzene ring (Scheme 1.26) (Ranganathan, et al., 2002).



Scheme 1.22. Synthetic routes for the synthesis of benzothiaza-crown

1.3.1.4 Synthesis of the Crown Compounds with Mixed Donor Atoms

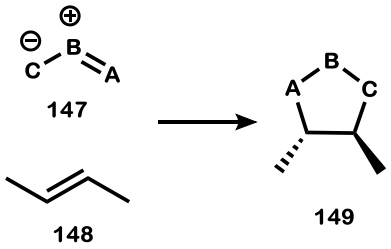
The synthesis of the crowns having mixed donor atoms (N,O,S) was reported by Bradshaw et al. by using diacylchloride, diamine and dithiols (Scheme 1.27) (Bradshaw, et al., 2000).



Scheme 1.23. Syntheses of diazadithiacrown ethers

1.4 1,3-DIPOLAR CYCLOADDITION CHEMISTRY

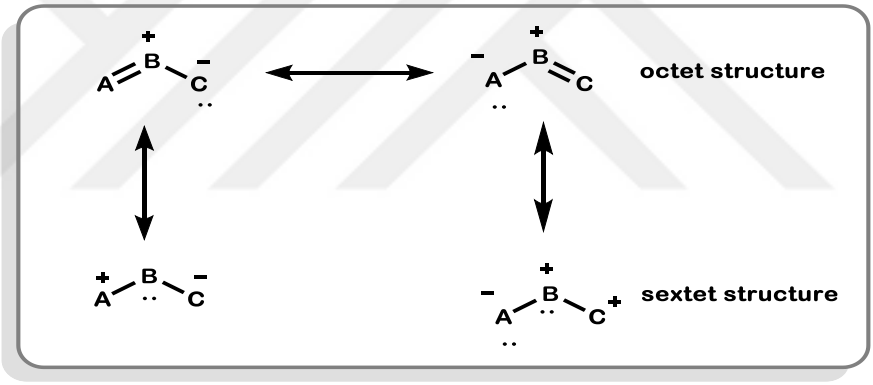
A general definition for the 1,3-dipolar cycloaddition is given as; a convenient method to create five-membered heterocycle in which a zwitterionic molecule (dipole) **147**, **150** reacted with a multiple bond system (dipolarophile) **148** (Scheme 1.28).



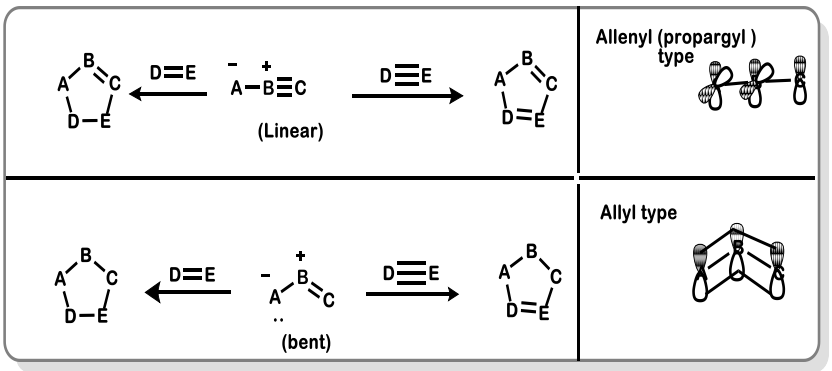
Scheme 1.24. An example of the 1,3-dipolar cycloaddition

1.4.1 Classification of Dipoles and Dipolarophiles

The concept of 1,3-dipolar cycloaddition was first defined by Huisgen. The 1,3-dipoles are classified as the allyl type, which structures are bent and allenyl (propargyl) type which are linear. In allyl anion type there are four electrons in three parellel p orbitals vertical to plane of the dipole. These electrons overlap to create reactive sites and the possible resonance structures are shown in scheme 1.29. In allyl type, negative charge is delocalized on the terminal atoms **A**, **C** while the central atom **B** bears the positive charge. In this regard, it would not be appropriate to attribute 1,3 dipoles as exactly electrophilic or nucleophilic; but instead one can say that 1,3-dipoles display both electrophilic and nucleophilic activity. If an extra π bond merger in the plane perpendicular allyl molecular orbital (MO), allenyl type 1,3-dipoles arise. The allyl, allenyl (propargyl) type and their reactions are shown below (Scheme 1.30) (Huisgen, 1961,1976).

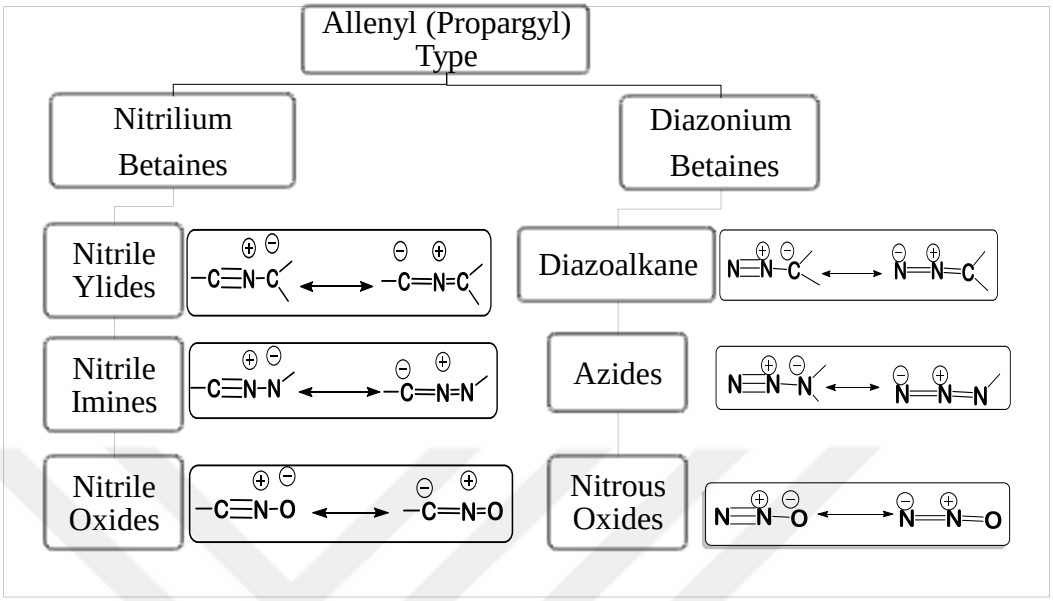


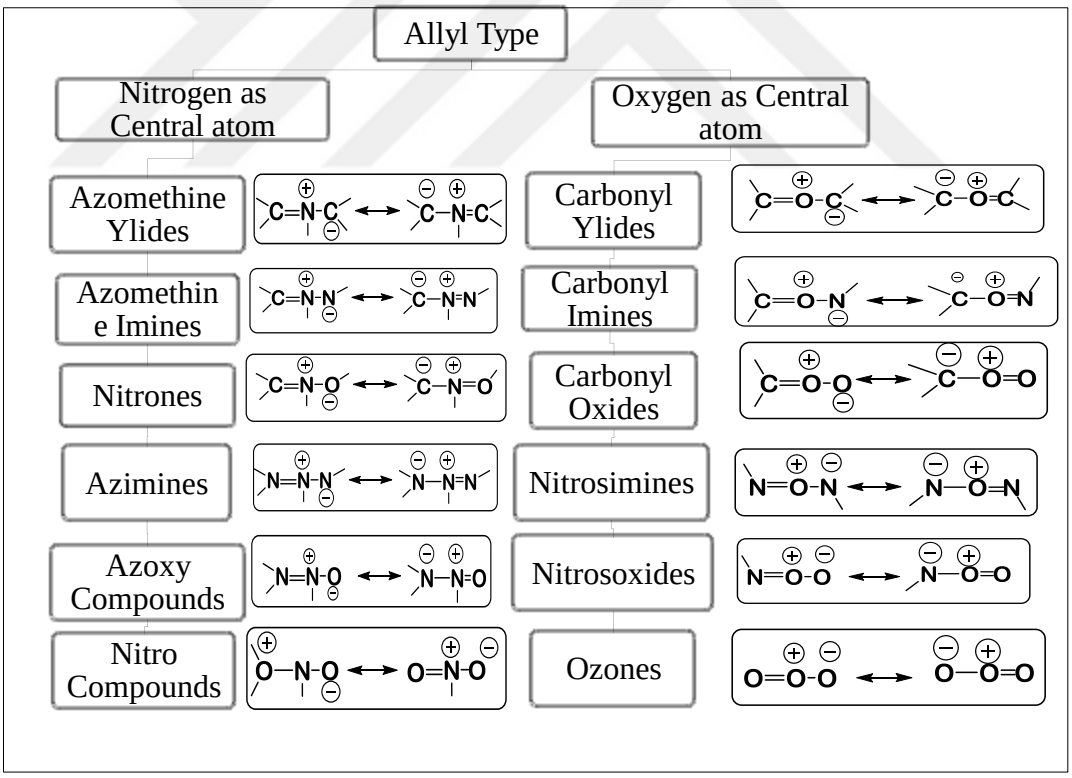
Scheme 1.25. Resonance structures of 1,3-dipole



Scheme 1.26. Types of 1,3-dipoles and their cycloadditions

A complete list which categorizes the 1,3-dipoles with their resonance structures by Huisgen is schematized (Scheme 1.31).





Scheme 1.27. Types of 1,3-dipoles with resonance structures

Dipolarophiles can be classified as electron poor, electron rich and conjugated structures which include 2π electrons and, react with 1,3-dipoles in suitable

conditions. The most commonly known dipolarophiles are α- β unsaturated aldehydes, alkynes, ketones, esters, vinylic ethers, allylic alcohols, and allylic halides (Houk, et al., 1973). Some of the dipolarophiles are exemplified below (Figure 1.10).

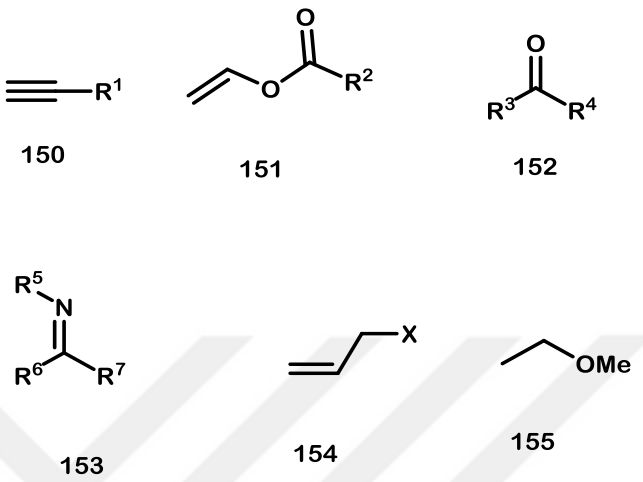
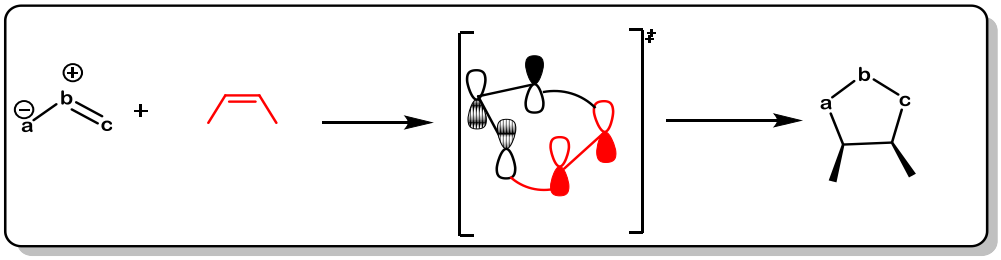


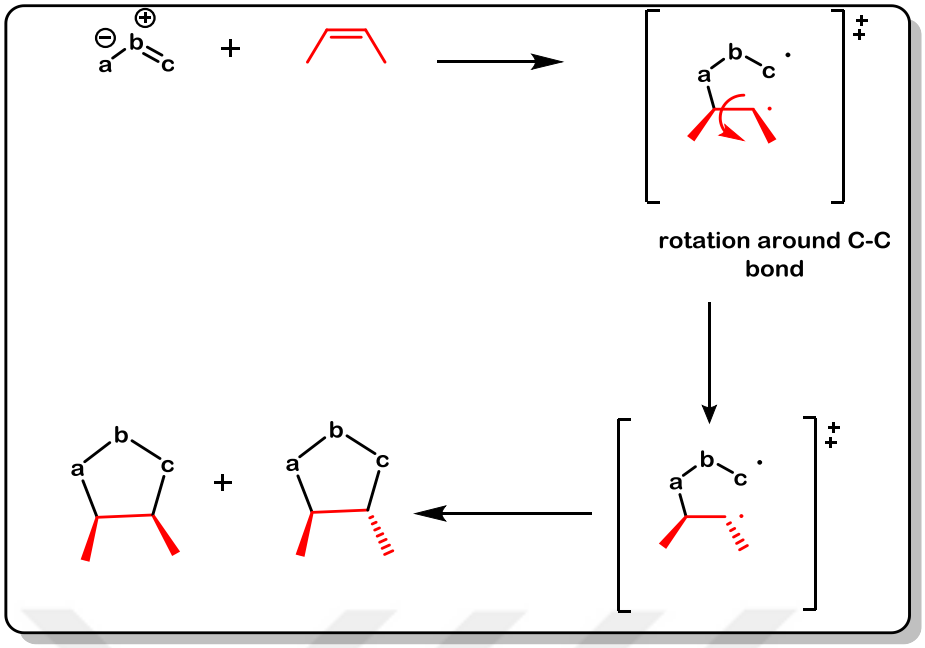
Figure 1.10. Examples for commonly known dipolarophiles

1.4.2 Mechanism of the 1,3-Dipolar Cycloadditions

Huisgen, in the mid 1960s, reported 1,3-dipolar cycloaddition reaction mechanism. According to Huisgen, the 4π electrons from the 1,3-dipoles and 2π electrons from the dipolarophiles create isochronously two new sigma bonds (Scheme 1.32) (Huisgen, 1963). On the other hand, Firestone made a clarification about the stepwise diradical pathway. In the stepwise reaction, diradicals occur and the C-C sigma bond of dipolarophile can rotate 180^{o} around itself, so that a mixture of *cis* and *trans* is obtained (Scheme 1.33) (Firestone, 1968).



Scheme 1.28. Concerted mechanism (Huisgen)



Scheme 1.29. Stepwise reaction mechanism (Firestone)

Frontier molecular orbital (FMO) approach is a convenient theory which describes the regioselectivity of the reaction of 1,3-dipolar cycloadditions and it relies on the character of the dipoles and dipolarophile. The FMO theory explains the interaction between $LUMO_{dipole}$ - $HOMO_{dipolarophile}$ and $HOMO_{dipole}$- $LUMO_{dipolarophile.}$ Sustman and coworkers classified the 1,3-dipolar cycloaddition in three types according to FMO theory. Furthermore, when an electron donating or withdrawing groups found on the dipole or dipolarophile, the FMO energies can change during 1,3-dipolar cycloaddition (Sustman and Trill, 1972). The type of FMO is shown in Figure 1.11.

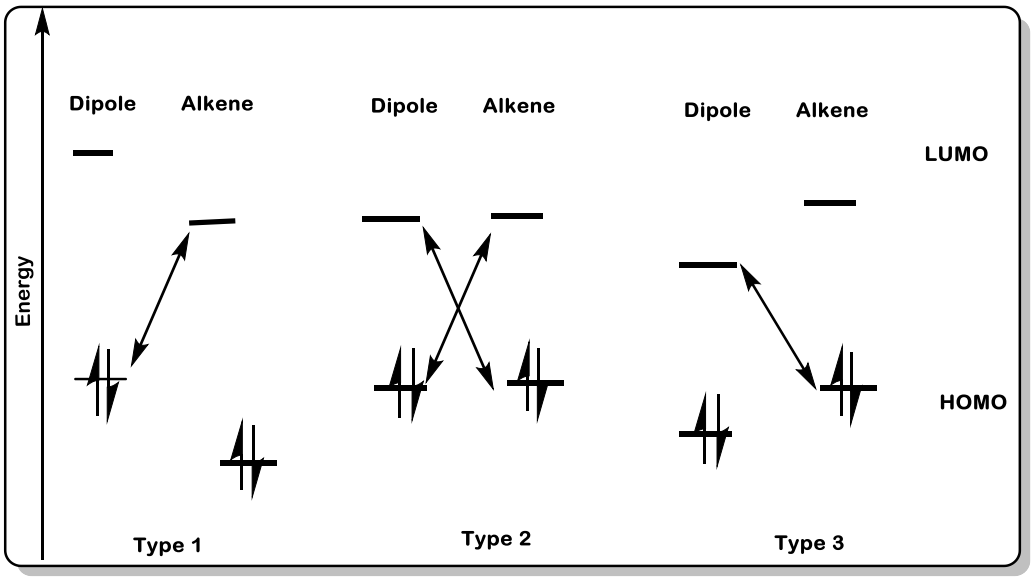
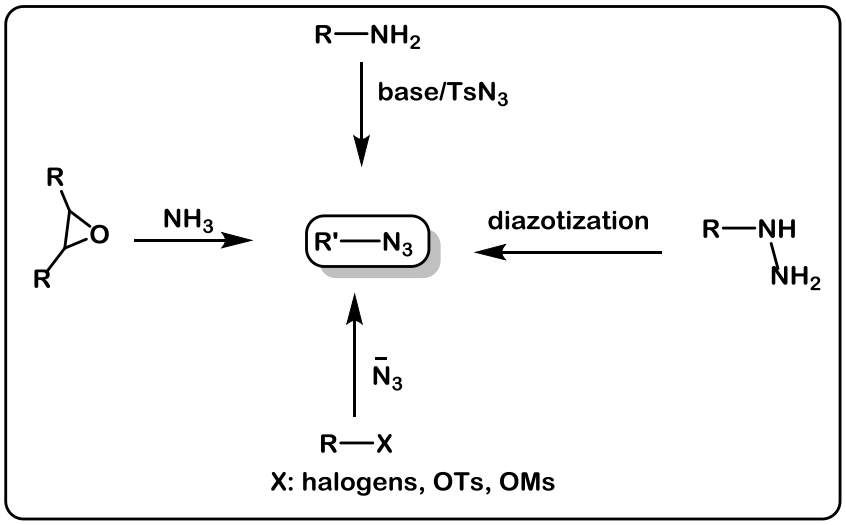


Figure 1.11. Energy diagram for the dipole-dipolarophile interactions

For the type 1; azomethine imine, carbonyl imine, and azomethine ylide, nitrile ylide, can be given as examples of HOMO-controlled dipoles or nucleophilic dipoles.
For the type 2; azide and a nitrile oxides are referred as ambiphilic dipole.
For the type 3; nitrous oxide and ozone are the given examples which are known as the electrophilic dipole.

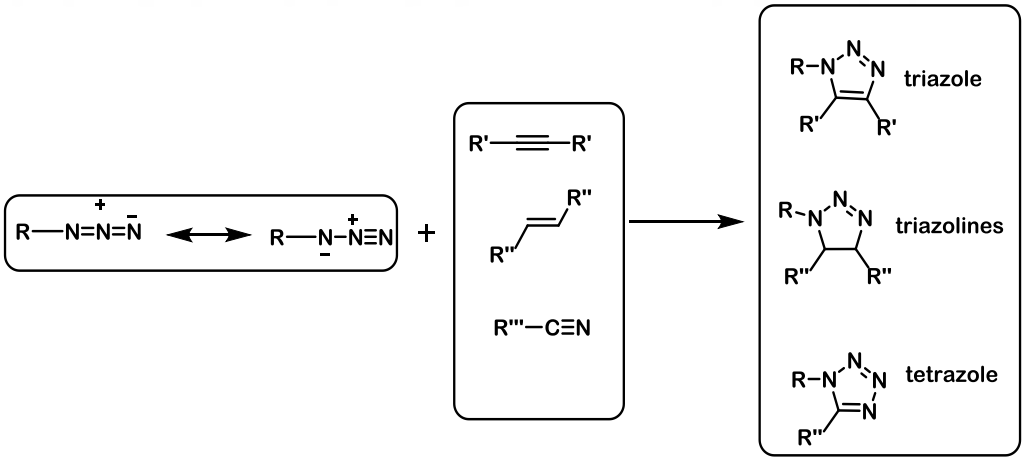
1.4.2.1 1,3-Dipolar Cycloaddition of Azides with Dipolarophiles

Organic azides can be prepared by different methods; these include ring opening reactions of epoxides and aziridines (Saito, et al., 1985), by diazo transfer (Tor et al., 2003), nucleophilic substitution (Dürüst et al., 2012, Lowe-Ma et al., 1990); from alcohols via the Mitsunobu reaction (Mitsunobu and Yamada,1967) and from the diazonium compounds (Scheme 1.34) (Butler, et al., 1998).



Scheme 1.30. Examples for organic azide synthesis

Azides, a type of 1,3-dipoles, can undergo [3+2] cycloaddition reaction with dipolarophiles such as alkenes, alkynes, carbonitriles to yield triazolines, triazoles as well as tetrazoles (Scheme 1.35) (Monasterio, et al., 2016; Chiba, 2012; Majumdar, et al., 2012; Chavan et al., 2017; Abbas et al., 2004; Joly, et al., 2009).



Scheme 1.31. 1,3-Dipolar cycloaddition of azide with unsaturated bonds

1.4.2.1.1 Biological activity of 1,2,3-triazoles

The 1,2,3-triazoles are one of the important classes of the nitrogen bearing heterocyclic compounds which are found in the molecular skeleton of some natural products (Asami et al., 2000). For this reason, the triazoles have been drawing

increasing attention in the pharmaceutical, organic, bioorganic and medicinal chemistry (Yang, et al., 2013; Zhang, et al., 2017; Ali, et al., 2017; Majumdar, et al., 2012; Chavan, et al., 2017; Babu, et al., 2015). The 1,2,3-triazole containing structures have been reported to possess some biological activities such as anti-tubercular (Ali, et al., 2017), antimicrobial and antibacterial (Kidwai, et al., 2001; Holla, et al.,1994) anti-HIV (Brik, et al., 2003), anti-fungal (Wu, et al., 2018) antitumor (Yamada, et al., 2018), antimicrobial (Khalil, 2010). Among these properties, the compound **156** acts as *M. tuberculosis DprE1 inhibitor (*Ali, et al., 2017),and the compound **157** acting as an HIV-*1 protease* inhibitor (Brik, et al., 2003). Two different triazole ring containing structures **158**, **159** can exhibit antiviral activity against the tobacco mosaic virus (Xia et al., 2006) and some antibiotic properties (Liang et al., 2005) (Figure 1.12).

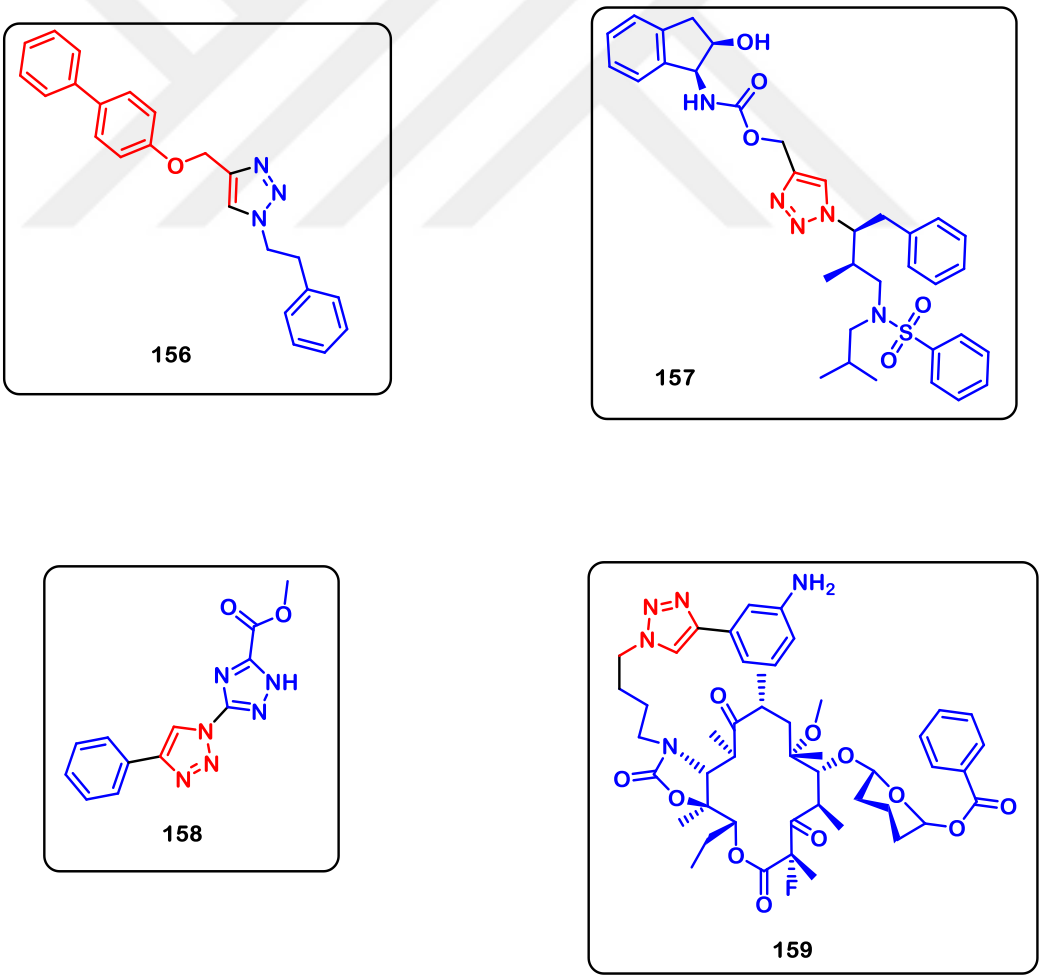


Figure 1.12. Some triazoles exhibiting biological activities

2. AIM AND SCOPE OF THE STUDY

During the past two decades, a growing interest has been focused on the chemistry of nitrogen and sulfur macrocycles. Because many of these compounds are highly effective extractants for metal ions (Mane, et al., 2016; Maciejewski, et al.,2009; Herman, et al., 2003; Wang, 2000; Vaira, et al., 1999) which can be used as precursors in the biosynthesis of certain types of alkaloids (Nezbedova, et al., 2001), fluorescent (Valeur and Leray, 2000), acting as anti-protozoal (Wilson et al., 2007; Reid et al., 2008), antimicrobial agent (Abd El-Salam, et al., 2012,) and especially acts as anti-HIV agents (Ranganatham, et al., 2002; Bridger, et al., 1995). Moreover, crown ethers have found applications in industry due to their metal sensing capability (Yang, et, al., 2014; Zarzeczańska, et al., 2016; Fedorova, et al., 2004). On the other hand, five-membered heterocyclic compounds are one of the important part of 1,3-dipolar cycloaddition chemistry. Due to their presence in the natural products, 1,2,3-triazole moiety have been taking growing interest in the pharmaceutical, organic, bioorganic and medicinal chemistry (Yang, et al., 2013; Zhang, et al., 2017; Ali, et al., 2017; Majumdar, et al., 2012; Chavan, et al., 2017; Babu, et al., 2015). Furthermore, 1,2,4-oxadiazole and 1,2,3-triazole-containing heterocyclic compounds have been found to exhibit various biological activities (Lamberth, 2007; Fink, et al., 1999). In this regard, the biological, medicinal importance and industrial usages of these macrocyclic and heterocyclic compounds have encouraged us to synthesize some novel N, O, S containing macrocycles with and without aromatic part (**164, 182, 184, 187, 188, 189, 193, 194, 199, 200, 201**), azacrown ethers with 1,2,4-oxadiazole moieties (**166(a-h), 168(a-i**)), azacrowns carrying 1,2,4 oxadiazole and 1,2,3-triazoles moieties **196,197(a-h)** and benzocrown ethers with chloro/azido-methyl 1,2,4-oxadiazoles (**185, 186, 190, 191**).

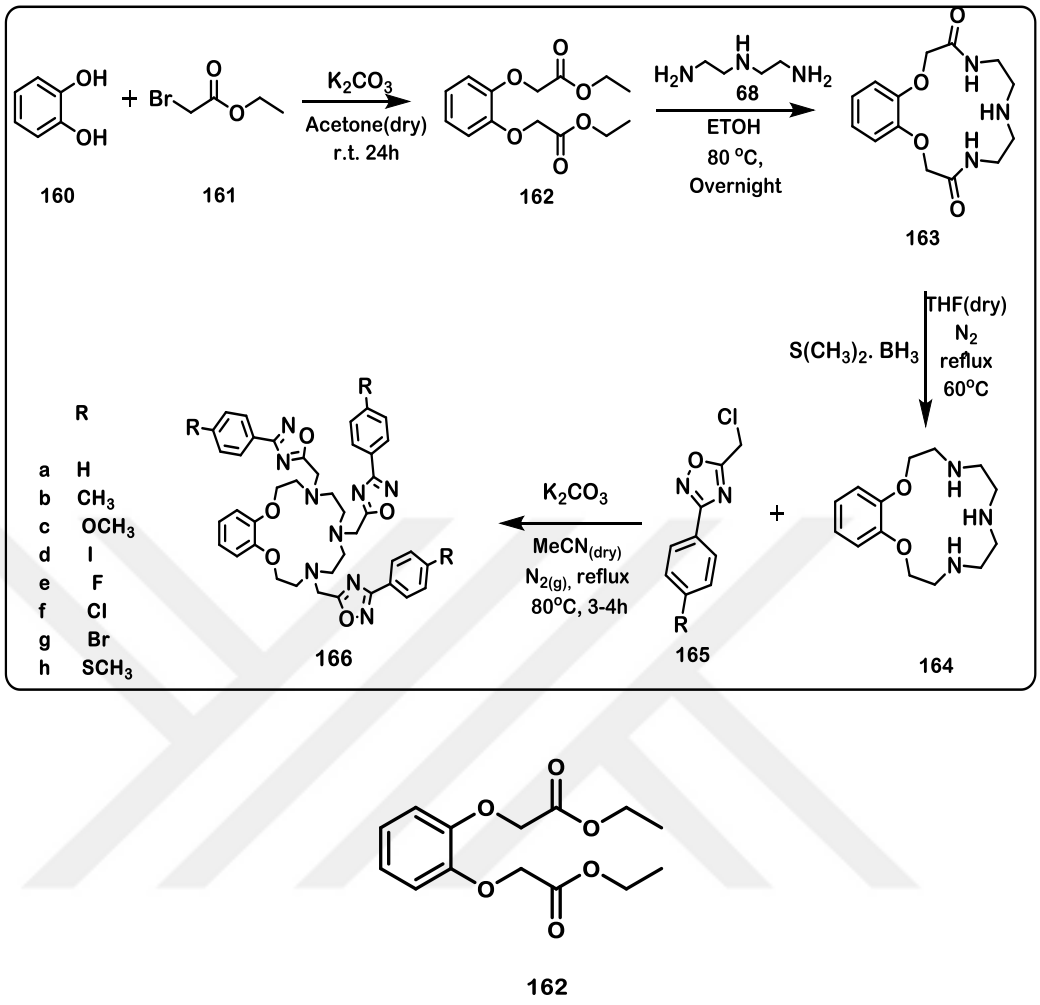
These novel azacrown ether structures carrying both 1,2,4-oxadiazole and 1,2,3-triazole scaffolds are expected to be potentially ionophores and bioactive molecules. All of the starting materials that led us to the target products, *p*-phenyl-substituted amidoximes, 5-chloromethyl 1,2,4-oxadiazoles, formylated benzocrowns and other intermediate reagents were obtained by us according to the previously

reported literature methods (Kumar, et al., 1992; Kimura, et al., 2006; Chen, et al., 2016; Safonova, et al., 2013; Jagadale, et al., 2015; Dürüst et al., 2012, 2015**)**. Since there are both electron-withdrawing and electron-releasing substituents in the *para* position of the phenyl ring on the starting compounds, effect of these groups on the structural properties would also be subject for us to evaluate further.

3. MATERIALS AND METHODS

Reagents were purchased from commercial sources and were used as received. Melting points were recorded in capillary tubes with a Meltemp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL and VARIAN spectrometers operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$. ^{1}H NMR chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hz, integration). Multiplicities are abbreviated as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). ^{13}C NMR chemical shifts are reported in parts per million from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm for carbon). IR spectra were recorded in KBr on Shimadzu spectrometer; $\tilde{\nu}$ in cm^{-1}. HRMS measurements were performed on Waters Synapt and Agilent Technologies 6224 spectrometers using the ionization modes specified. Routine TLC analyses were carried out on pre-coated silica gel plates with fluorescent indicator. Flash column chromatography was performed on silica gel (230-400 Mesh ASTM). A rotary TLC apparatus (Chromatotron) was utilized for further separation and purifications. Stain solutions of potassium permanganate and iodine were used for visualization of the TLC spots.

Experimental

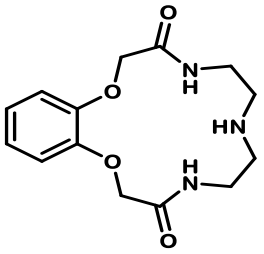


162

Synthesis of diethyl 2,2'-(1,2-phenylenebis(oxy))diacetate (162) (Kumar et al., 1992)

A suspension of K_2CO_3 (50 g, 0.36 mol) in dried acetone (400 ml) was added to the mixture of ethyl bromoacetate **161** (40.8 g, 0.24 mol) and catechol **160** (11 g, 0.1 mol). The resulting mixture was stirred at room temperature for 24 h. The mixture was filtered off and the precipitate was washed with acetone.Then combined solvent was evaporated. The remaining yellow oily crude product was purified by flash column chromatography with (EtOAc/*n*-hexane, 1:20) to give a yellow oil (20 g, 70%), R_f: 0.50 (EtOAC/*n*-hexane, 1:5). IR (KBr, *v*:cm^{-1}): 3066 (Ar., CH), 2982, 2935 (Aliph., CH), 1732 (C=O), 1593, 1504, 1458, 1442, 1377, 1273, 1188, 1068, 1030, 933, 960,752, 597, 428, 412. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.89 (m,

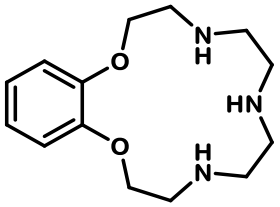
2H), 6.88 – 6.84 (m, 2H), 4.68 (s, 4H), 4.22 (q, *J* = 8.0 Hz, 4H), 1.25 (t, *J* = 8.0 Hz, 6H).



163

Synthesis of the 5,6,7,8,9,10-hexahydro-2H-benzo[b][1,4]dioxa [7,10,13] triaza cyclopentadecine-3,11(*4H,12H*)-dione (163) (Kumar et al., 1992)

Diethyl 2,2'-(1,2-phenylenebis(oxy))diacetate **162** (16.67 g, 0.059 mol) and ethylenetriamine **68** (6.100 g, 0.059 mol) were mixed in EtOH and the reaction mixture was refluxed. The solvent was evaporated under reduced pressure. Yellow solid was recrystallized with acetone/DCM mixture. Crystals were filtered off and product was obtained as white solid (7.89 g, 50%). R_f : 0.500 (MeOH), M.p: 235-236 ^oC IR (KBr, *v*:cm^{-1}): 3498, 3394, 3306 (NH), 3082, 3063 (Ar., CH), 2966, 2908, 2850 (Aliph., CH stretching), 1689, 1643 (C=O), 1593, 1527, 1504, 1473, 1442, 1330, 1288, 1257, 1219, 1130, 1049, 991, 922, 887, 848, 817, 783, 759, 678, 655, 586, 520, 482. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 2H), 6.96 (dd, *J* = 6.8, 3.3 Hz, 2H), 6.83 (dd, *J*= 5.3, 3.6 Hz, 2H), 4.46 (s, 4H), 3.46 (dd, *J* = 10.7, 5.1 Hz, 4H), 2.92 (t, *J* = 4.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.28, 146.18, 122.08, 112.35, 66.92, 47.49, 38.18. LC-MS (ES^+): *m/z* (M+H) : 294.



164

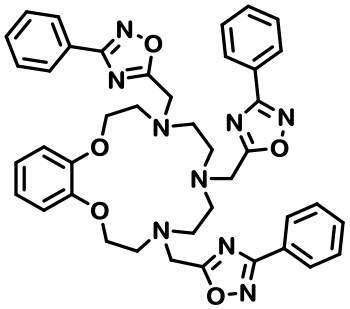
Synthesis of the 3,4,5,6,7,8,9,10,11,12-decahydro-2Hbenzo[b][1,4,7,10,13]dioxa triaza cyclopentadecine (164)

Crown **163** (5.637 g, 0.019 mol) was dissolved in THF (300 ml) then BH_3.DMS (15.33 ml) was added drop wise and mixture was refluxed, 60 ^oC, under N_2 atmosphere for 3h. After reaction was completed, THF was evaporated under the reduced pressure. When the temperature of the mixture reached to the room temperature, HCl (80 ml) was added and refluxed again at 80 ^oC for 2h. Then the reaction mixture was cooled to room temperature and NaOH solution was added to maintain pH at 13–14. Then it was extracted with CH_2Cl_2/H_2O. A white solid formed after evaporation of CH_2Cl_2 (3.300 g, 65%), R_f : 0.50 (MeOH), M.p: 90-91 ^oC. IR (KBr, *v*:cm^{-1}): 3296, 3221 (NH), 2918, 2885, 2812 (Aliph., CH stretching), 1595, 1508, 1458, 1398, 1377, 1327, 1257, 1222, 1126, 1041, 954, 902, 883, 842, 779, 736, 455, 430, 408. ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 1.6 Hz, 4H), 4.07 (t, *J* = 4.4 Hz, 4H), 2.98 (t, *J* =4.8 Hz, 4H), 2.85 – 2.79 (m, 4H), 2.73 – 2.65 (m, 4H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.72, 121.22, 113.10, 68.21, 49.49, 48.92, 47.79. LC-MS (ES^+): *m/z* (M+H) : 266. HRMS: *m/z* (ESI-TOF, [$M+H^+$]) calcd for $C_{14}H_{23}N_3O_2$: 266.1868; found: 266.1856.

General procedure for the preparation of (166a-h)

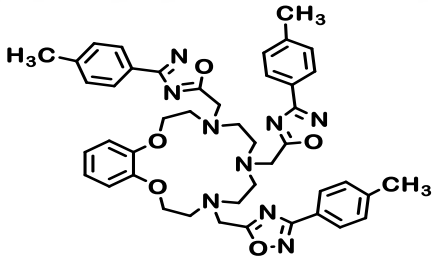
4,7,10-tris((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8,9,10,11,12-decahydro-2H-benzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166a)***

A mixture of benzodioxatriaza crown **164** (50 mg, 0.188 mmol), 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **165** (Dürüst et al., 2015) (110 mg, 0.565 mmol) and K_2CO_3 (78 mg, 0.567 mmol) was refluxed in MeCN under N_2 atmosphere for 2.5–3h. After completion of the reaction, as monitored by TLC (*n*-hexane/EtOAc, 2:1), the solvent was removed under reduced pressure. The crude product was then purified by column chromatography to give compound **166a.**



166a

Orange oil (60 mg, 43%). R_f : 0.76 (*n*-hexane/EtOAc, 2:1). IR (KBr, *v*:cm^{-1}): 3053 (Ar., CH), 2933, 2835 (Aliph., CH stretching), 1593, 1560 (C=N), 1504, 1446, 1356, 1265, 1255, 1219, 1124, 1041, 898, 694, 738. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (ddd, *J* = 7.4, 6.6, 1,6 Hz, 6H), 7.51 – 7.39 (m, 9H), 6.92 – 6.83 (m, 4H), 4.19 (s, *J* = 8.0 Hz, 6H), 4.13 (t, *J* = 4.4 Hz, 4H), 3.19 (t, *J* = 4.4 Hz, 4H), 3.11 (t, *J* = 6.7 Hz, 4H), 3.00 (t, *J* = 6.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.12, 168.28, 148.58, 131.32, 128.94, 127.58, 126.72, 121.19, 112.78, 67.39, 53.37, 52.90, 52.69, 50.00. LC-MS (ES^+): *m/z* (M+H) : 740. HRMS: m/z (ESI-TOF, [$M+H^+$]) calcd for $C_{41}H_{41}N_9O_5$: 740.3309; found: 740.3329.

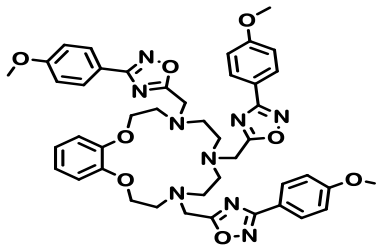


166b

4,7,10-Tris((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8,9,10,11,12-decahydro-2H-benzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166b)***

Yellow solid (90 mg, 41%), R_f : 0.78 (*n*-hexane/EtOAc, 2:1), M.p: 116-119 ^oC IR (KBr, *v*:cm^{-1}): 3034 (Ar., CH), 2922, 2864 (Aliph., CH stretching) 1616, 1591, 1560, 1504, 1481, 1452, 1411, 1346, 1253, 1219, 1180, 1122, 1041, 900, 829, 738, 414, 405. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (ddd, *J* =8.6, 5.0, 1.8 Hz, 6H), 7.27 – 7.21 (m, 6H), 6.90 – 6.85 (m, 4H), 4.18 (s, 6H), 4.12 (t, *J* = 4.4 Hz, 4H), 3.19 (t, *J* = 4.2 Hz, 4H), 3.11 (t, *J* = 6.3 Hz, 4H), 3.00 (d, *J* = 5.8 Hz, 4H), 2.38 (d, *J* = 8.5 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.91, 168.28, 148.58, 141.61, 129.63, 127.50, 123.89, 121.18, 112.78, 67.37, 53.33, 52.88, 52.67, 49.52, 21.68. LC-MS

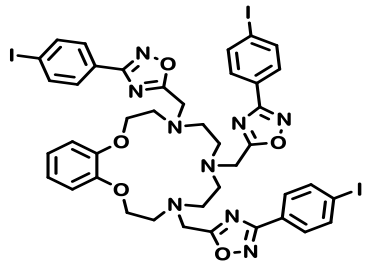
(ES$^+$): *m/z* (M+H) : 782. HRMS: m/z (ESI-TOF, [M+H$^+$]) calcd for $C_{44}H_{47}N_9O_5$: 782.3778; found: 782.3802.



166c

4,7,10-Tris((3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8, 9,10,11,12-decahydro-2Hbenzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166c)***

Yellow oil (150 mg, 48%). R_f : 0.30 (*n*-hexane/EtOAc, 2:1). IR (KBr, *v*:cm^{-1}): 3053 (Ar., CH), 2985, 2839 (Aliph., CH stretching), 1614, 1591, 1566, 1506, 1481, 1423, 1352, 1265, 1174, 1107, 1031, 896, 842, 738, 705, 439. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (ddd, *J* = 6.6, 6.5, 1.6 Hz, 6H), 6.96 – 6.91 (m, 6H), 6.90 – 6.85 (m, 4H), 4.16 (s, 4H), 4.14 – 4.08 (dt, *J* = 5.6, 1.7 Hz, 6H), 3.82 (d, *J* = 8.9 Hz, 9H), 3.20 – 3.16 (t, *J* = 4.6 Hz, 4H), 3.09 (t, *J* = 6.7 Hz, 4H), 2.97 (t, *J* = 6.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.84, 167.96, 161.97, 148.61, 129.18, 121.15, 119.20, 114.29, 112.78, 67.44, 60.48, 55.45, 53.36, 52.90, 49.54. LC-MS (ES$^+$): *m/z* (M+H) : 830. HRMS: *m/z* (ESI-TOF, [M+H$^+$]) calcd for $C_{44}H_{47}N_9O_8$: 830.3626; found: 830.3646.

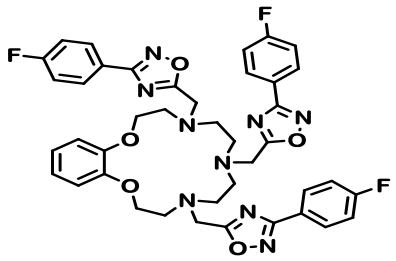


166d

4,7,10-Tris((3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8,9,10,11,12-decahydro-2H-benzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166d)***

White solid (67 mg, 48%). R_f : 0.60 (*n*-hexane/EtOAc, 2:1). IR (KBr, *v*:cm^{-1}): 306 (Ar., CH), 2955, 2924, 2854 (Aliph., CH stretching) 1651, 1589, 1458, 1402, 1342, 1265, 1118, 1049, 1006, 962. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 – 7.69 (m, 12H),

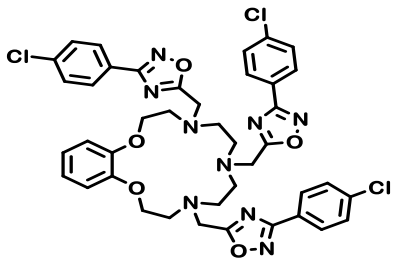
6.94 – 6.75 (m, 4H), 4.19 (s, 6H), 4.12 (t, *J* = 4.3 Hz, 4H), 3.19 (t, *J* = 4.4 Hz, 4H), 3.08 (s, 4H), 3.03 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.74, 148.47, 138.13, 129.04, 129.01, 126.13, 121.27, 112.77, 98.12, 53.50, 52.87, 49.93, 49.27, 48.66. LC-MS (ES^+): *m/z* (M+H) : 1118. HRMS: *m/z* (ESI-TOF, [M+H^+]) calcd for $C_{44}H_{38}N_9O_5$: 1118.0208; found:1118.0231.



166e

4,7,10-Tris((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8,9, 10,11,12-decahydro-2H-benzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166e)***

Yellow oil (55 mg, 51%). R_f : 0.87 (*n*-hexane/EtOAc, 2:1). M.p: 114-115^{o}C IR (KBr, *v*:cm^{-1}): 3053 (Ar., CH), 2985, 2928, 2852 (Aliph., CH stretching), 1608, 1575, 1483, 1417, 1348, 1338, 1265, 1226, 1157, 1124, 1043, 896, 846, 746, 704, 605. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.98 (m, 6H), 7.15 – 7.08 (m, 6H), 6.91 – 6.83 (m, 4H), 4.18 (s, 6H), 4.13 (t, *J* = 4.4 Hz, 4H), 3.19 (t, *J* = 4.3 Hz, 4H), 3.10 (t, *J* = 6.5 Hz, 4H), 2.99 (t, *J* = 6.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.19, 167.47, 165.90, 163.40, 148.51, 129.65, 122.93, 116.17, 112.69, 67.28, 53.42, 52.81, 52.62, 49.49. LC-MS (ES^+): *m/z* (M+H) : 794. HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{41}H_{39}F_3N_9O_5$: 794.3027; found: 794.3043.

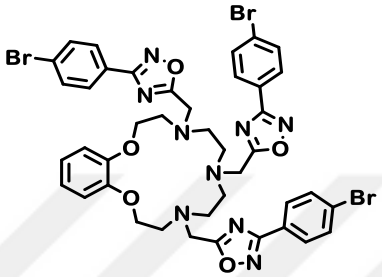


166f

4,7,10-Tris((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8, 9,10,11,12-decahydro-2H-benzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166f)***

White solid (96 mg, 80%). R_f : 0.90 (*n*-hexane/EtOAc, 2:1). M.p:118–119^{o}C. IR (KBr, *v*:cm^{-1}): 3053 (Ar., CH), 2983, 2928, 2841 (Aliph., CH stretching), 1602,

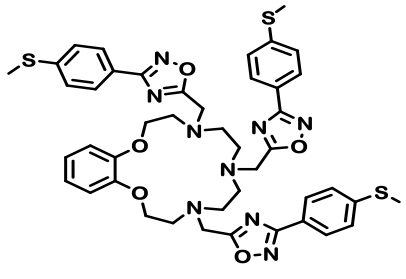
1589, 1558, 1504, 1473, 1410, 1346 1265, 1116, 1226, 1091, 1043, 1014, 896, 746, 704, 437. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.92 (m, 6H), 7.43 – 7.34 (m, 6H), 6.90 – 6.82 (m, 4H), 4.18 (s, 4H), 4.12 (t, *J* = 4.4 Hz, 6H), 3.19 (t, *J* = 4.5 Hz, 4H), 3.09 (t, *J* = 6.7 Hz, 4H), 2.97 (t, *J* = 6.5 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.53, 167.10, 148.53, 137.45, 129.25, 128.83, 125.18, 121.21, 112.74, 67.35, 53.49, 52.87, 50.07, 49.58. LC-MS (ES^+): *m/z* (M+H) : 844. HRMS: *m/z* (ESI-TOF, [M+H^+]) calcd for $C_{41}H_{39}Cl_3N_9O_5$:842.2140; found: 842.2164.



166g

4,7,10-Tris((3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8,9, 10,11,12-decahydro-2H-benzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166g)***

White solid (40 mg, 67%). R_f : 0.85 (*n*-hexane/EtOAc, 2:1). M.p: 113–114^{o}C. IR (KBr, *v*:cm^{-1}): 3063 (Ar., CH), 2924, 2850 (Aliph., CH stretching), 1599, 1560, 1504, 1469, 1406, 1344, 1253, 1217, 1122, 1068, 1041, 1010, 964, 904, 837, 740. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (ddd, *J* = 10.8, 5.5, 2.0 Hz, 6H), 7.60 – 7.52 (m, 6H), 6.92 – 6.83 (m, 4H), 4.18 (s, 6H), 4.12 (t, *J* = 4.3 Hz, 4H), 3.19 (t, *J* = 4.5 4H), 3.10 (s, 4H), 2.99 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.60, 148.49, 132.23, 132.20, 129.07, 125.91, 125.60, 121.25, 112.75, 67.28, 53.55, 53.49, 52.87, 49.55. LC-MS (ES^+): *m/z* (M+H) : 974. HRMS: *m/z* (ESI-TOF, [M+H^+]) calcd for $C_{41}H_{39}Br_3N_9O_5$:974.0625; found: 974.0644.

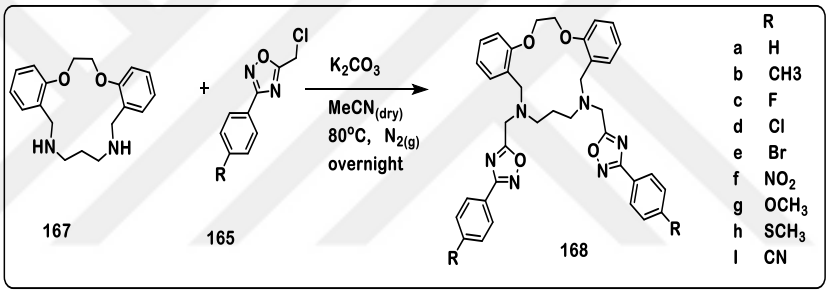


166h

4,7,10-Tris((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-3,4,5,6,7,8,9, 10,11,12-decahydro-2H-benzo[b][1,4,7,10,13]dioxatriazacyclopentadecine ***(166h)***

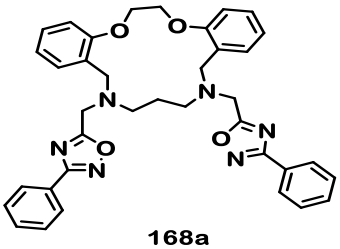
White solid (55mg, 38%). R_f: 0.85 (*n*-hexane/EtOAc, 2:1). M.p: 92-93^oC. IR (KBr, *v*:cm^{-1}): 3061 (Ar., CH), 2922, 2852 (Aliph., CH stretching), 1600, 1587, 1552, 1504, 1469, 1408, 1354, 1219, 1186, 1122, 1089, 1041, 1012, 962, 902, 831, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.89 (m, 6H), 7.28 – 7.23 (m, 6H), 6.91– 6.83 (m, 4H), 4.17 (s, 4H), 4.12 (t, *J* = 4.8 Hz, 6H), 3.18 (t, *J* = 4.4 Hz, 4H), 3.09 (t, *J* = 6.6 Hz, 4H), 2.98 (t, *J* = 6.5 Hz, 4H), 2.49 (s, 6H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.03, 167.93, 148.56, 143.03, 127.80, 125.79, 122.69, 121.13, 112.76, 67.37, 53.41, 52.86, 52.75, 49.84, 49.55, 15.24. LC-MS (ES^+): *m/z* (M+H) : 878. HRMS: *m/z* (ESI-TOF, [M+H^+]) calcd for $C_{44}H_{48}N_9O_5S_3$:979. 2941; found: 979.2962.

General procedure for the preparation of (168a-h)



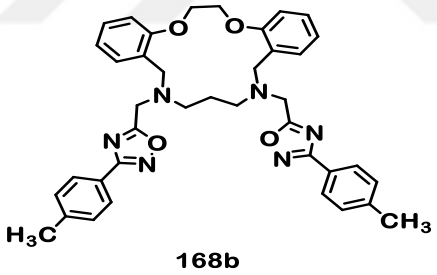
*6,10-Bis((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17,18-octahydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine **(168a)***

A mixture of 6,7,8,9,10,11,17,18-octahydro-*5H*-dibenzo[e,n] [1,4]dioxa [8,12]diaza cyclopentadecine **167** (80.3 mg, 0.257 mmol), 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (Dürüst et al., 2015) **165** (100 mg, 0.514 mmol) and K_2CO_3 (70 mg, 0.514 mmol) was refluxed in MeCN under $N_{2(g)}$ overnight. After completion of the reaction, as monitored by TLC (*n*-hexane/EtOAc, 2:1), the solvent was removed under reduced pressure. The crude product was then purified by column chromatography to give compound **168a**.



168a

White solid (150 mg, 92%). R_f : 0.88 (*n*-hexane/EtOAc, 1:1). M.p: 101–102^oC IR (KBr, *v*:cm^{-1}): 3063 (Ar., CH), 2931, 2831, 2576 (Aliph., CH), 1654, 1597, 1562, 1492, 1446, 1354, 1288, 1242, 1068, 1195, 1161, 1114, 1068, 1018, 1018, 941, 902, 756, 717, 694. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.2 Hz, 4H), 7.52 – 7.44 (m, 4H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.30–7.24 (m, 4H), 6.98–6.89 (ddd, *J* = 21.5, 10.7, 4.4 Hz, 4H), 4.36 (s, 4H), 3.96 (s, 4H), 3.86 (s, 4H), 2.79 (t, *J* = 6.8 Hz, 4H), 1.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.44, 168.20, 157.51, 132.62, 131.22, 128.92, 127.60, 126.91, 126.81, 125.79, 120.61, 111.25, 66.75, 52.86, 51.81, 46.2, 26.73. LC-MS (ES^+): *m/z* (M+H) : 629. HRMS: *m/z* (ESI-TOF, [$M+H^+$]) calcd for $C_{37}H_{37}N_6O_4$: 629. 2877; found: 629.2891.

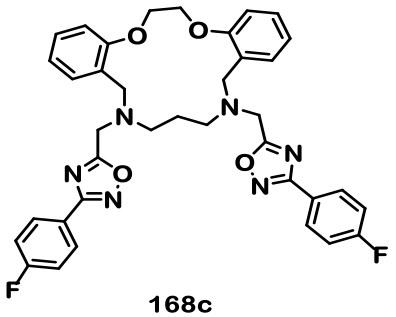


168b

6,10-Bis((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17,18-octahydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine ***(168b)***

White solid (150 mg, 95%). R_f : 0.87 (*n*-hexane/EtOAc, 1:1). M.p: 130-131 ^oC IR (KBr, *v*:cm^{-1}): 3036 (Ar., CH), 2928, 2866, 2831 (Aliph., CH), 1589, 1558, 1492, 1450, 1411, 1350, 1242, 1114, 1064, 1014 945, 898, 829, 736, 624, 509. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 4H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 6H), 6.94 (dt, *J* = 12.1, 6.8 Hz, 4H), 4.35 (s, 4H), 3.93 (s, 4H), 3.85 (s, 4H), 2.77 (t, *J* = 6.7 Hz, 4H), 2.40 (s, 6H), 1.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.28, 168.28, 157.50, 141.51, 132.61, 129.62, 129.02, 127.52, 125.88, 124.11, 120.60, 111.25, 66.75, 52.86, 51.85, 46.27, 25.47, 21.69. LC-MS (ES^+): *m/z* (M+H)

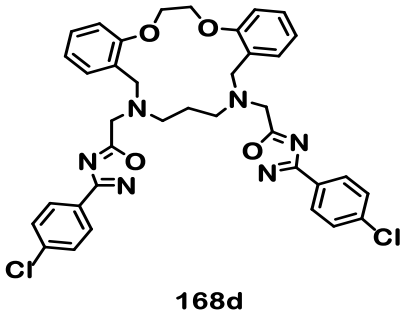
: 657. HRMS: *m/z* (ESI-TOF, [M+H$^+$]) calcd for $C_{39}H_{41}N_6O_4$: 657.3190; found: 657.3224.



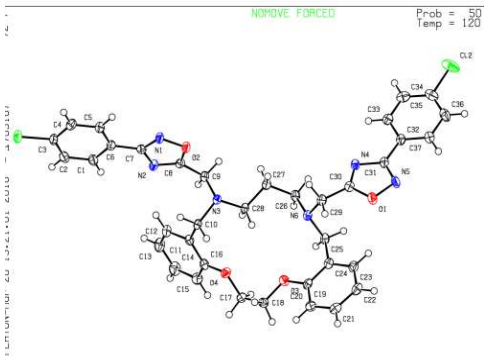
168c

6,10-Bis((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17,18-octahydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine ***(168c)***

White solid (140 mg, 89%). R_f : 0.65 (*n*-hexane/EtOAc, 1:1). M.p: 137-138 ^oC IR (KBr, *v*:cm^{-1}): 3066 (Ar., CH), 2928, 2835 (Aliph., CH), 1604, 1562, 1535 1481, 1450, 1415, 1350, 1288, 1234, 1157, 1114 1068, 1014 945, 844, 752, 605, 520. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 9.1, 5.9 Hz, 4H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.28 (td, *J* = 4.9, 1.7 Hz, 2H), 7.15 (t, *J* = 9.0 Hz, 4H), 6.98 – 6.89 (m, 4H), 4.36 (s, 4H), 3.93 (s, 4H), 3.85 (s, 4H), 2.77 (t, *J* = 7.5 Hz, 4H), 1.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.53, 167.50, 165.93, 163.23, 157.25, 132.58, 129.66, 125.80, 123.69, 120.60, 116.00, 111.25, 66.72, 52.95, 51.77, 46.21, 25.49. LC-MS (ES$^+$): *m/z* (M+H) : 665. HRMS: *m/z* (ESI-TOF, [M+H$^+$]) calcd for $C_{37}H_{35}F_2N_6O_4$: 665.2689; found: 665.2719.



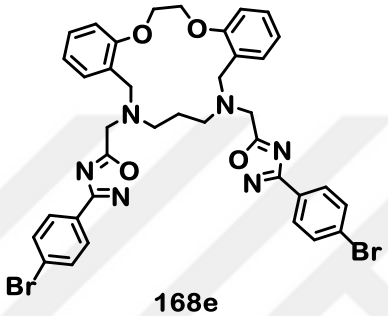
168d



6,10-Bis((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17,18-octahydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine ***(168d)***

White solid (130 mg, 76%). R_f : 0.85 (*n*-hexane/EtOAc, 1:1). M.p:112-113 ^oC IR (KBr, *v*:cm^{-1}): 3011 (Ar., CH), 2928, 2835 (Aliph., CH), 1600, 1558, 1492, 1450,

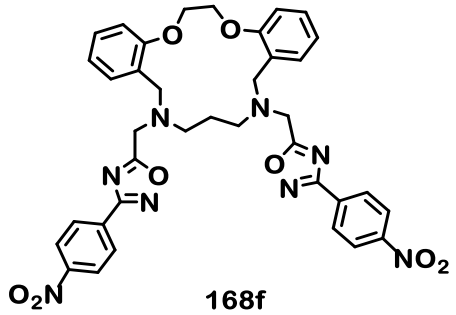
1408, 1384, 1346, 1242, 1114, 1091, 1049, 1014 941, 840, 748. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.2 Hz, 4H), 7.44 (d, *J* = 8.5 Hz, 4H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.6 2H), 6.97 – 6.87 (m, 4H), 4.35 (s, 4H), 3.93 (s, 4H), 3.85 (s, 4H), 2.77 (t, *J* = 6.6 Hz, 4H), 1.84 – 1.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.70, 167.41, 157.50, 137.34, 132.54, 129.24, 129.08, 128.90, 125.69, 125.42, 120.60, 111.24, 66.71, 53.01, 51.76, 46.25, 25.43. LC-MS (ES^+): *m/z* (M+H) : 697. HRMS: m/z (ESI-TOF, [$M+H^+$]). calcd for $C_{37}H_{35}Cl_2N_6O_4$: 697.2098; found: 697.2097.



168e

6,10-Bis((3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17,18-octahydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine ***(168e)***

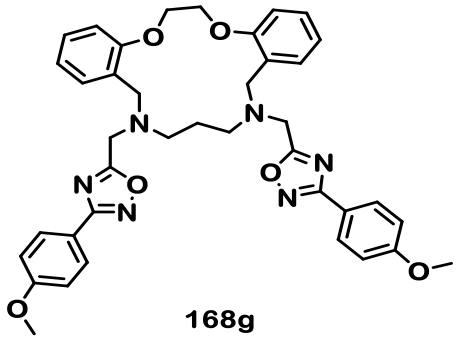
White solid (30 mg, 42%). R_f : 0.89 (*n*-hexane/EtOAc, 1:1). M.p: 170-171 ^{o}C IR (KBr, *v*:cm^{-1}): 3039 (Ar., CH), 2924, 2854 (Aliph., CH), 1620, 1597, 1562, 1492, 1450, 1404, 1384, 1342, 1238, 1114, 1068, 1010 833, 740, 694. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 4H), 7.59 (d, *J* = 8.4 Hz, 4H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.28 (td, *J* = 4.1, 1.1 Hz, 2H), 6.97- 6.89 (m, 4H), 4.35 (s, 4H), 3.91 (s, 4H), 3.84 (s, 4H), 2.75 (t, *J* = 6.8 Hz, 4H), 1.84-1.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.70, 167.50, 157.49, 132.56, 132.21, 129.13, 129.09, 125.87, 125.76, 125.69, 120.59, 111.24, 66.70, 53.02, 51.75, 46.27, 25.50. LC-M_S (ES^+): *m/z* (M+H) : 787. HRMS: *m/z* (ESI-TOF, [M+H]). calcd for $C_{37}H_{35}Br_2N_6O_4$: 785. 1087; found: 785.1064.



168f

6,10-Bis((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17,18-octa hydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine ***(168f)***

White solid (25 mg, 22%). R_f : 0.83 (*n*-hexane/EtOAc, 1:1). M.p: 151-153 ^oC (decomp.). IR (KBr, *v*:cm^{-1}): 3101 (Ar., CH), 2924, 2850 (Aliph., CH), 1600, 1562, 1527, 1492, 1450, 1415, 1342, 1292, 1242, 1107, 1064, 941, 852, 756, 732. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.8 Hz, 4H), 8.26 (d, *J* = 8.4 Hz, 4H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 6.98 – 6.90 (m, 4H), 4.35 (s, 4H), 3.96 (s, 4H), 3.86 (s, 4H), 2.80 (t, *J* = 6.3 Hz, 4H), 1.86 – 175 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.42, 166.70, 157.50, 149.48, 132.79, 132.54, 129.25, 128.54, 125.46, 124.11, 120.62, 111.23, 66.57, 52.78, 51.31, 46.33, 25.61. LC-MS (ES^+): *m/z* (M+H) : 719. HRMS: m/z (ESI-TOF, [$M+H^+$]) calcd for $C_{37}H_{35}N_8O_8$: 719.2579; found: 719.2605.

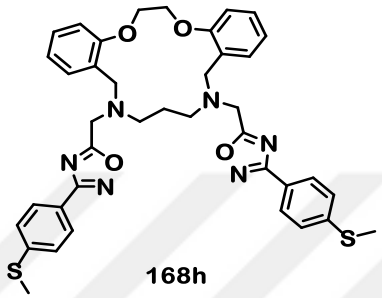


168g

6,10-Bis((3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17,18-octahydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine ***(168g)***

White solid (80 mg, 70%). R_f : 0.53 (*n*-hexane/EtOAc, 1:1). M.p: 146-148^oC IR (KBr, *v*:cm^{-1}): 3063 (Ar., CH), 2935, 2835 (Aliph., CH), 1612, 1597, 1562, 1481, 1450, 1423, 1350,1303, 1253, 1172, 1107, 1030, 941, 840, 752. ^1H NMR (400 MHz,

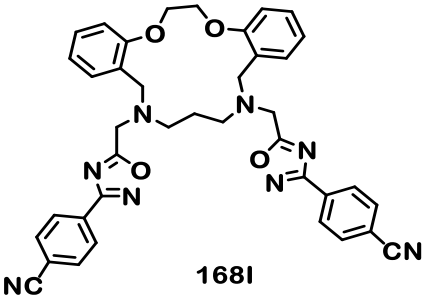
$CDCl_3$): δ 8.03 (d, *J* = 8.6 Hz, 4H), 7.36 (d, *J* = 7.0 Hz, 2H), 7.28 (td, *J* = 3.2, 1.5 Hz, 2H), 7.00 – 6.89 (m, 8H), 4.35 (s, 4H), 3.92 (s, 4H), 3.85 (s, 10H), 2.77 (t, *J* = 6.6 Hz, 4H), 1.85 – 1.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.23, 167.68, 161.59, 156.77, 132.64, 129.20, 129.03, 125.95, 120.33, 119.54, 114.22, 110.78, 66.72, 55.47, 52.90, 51.86, 46.27, 25.42. LC-MS (ES^+): *m/z* (M+H) : 689. HRMS: *m/z* (ESI-TOF, [M+H^+]) calcd for $C_{39}H_{41}N_6O_6$: 689.3088; found: 689.3119.



168h

6,10-Bis((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-6,7,8,9,10,11,17, 18-octahydro-5H-dibenzo[e,n][1,4,8,12]dioxadiazacyclopentadecine ***(168h)***

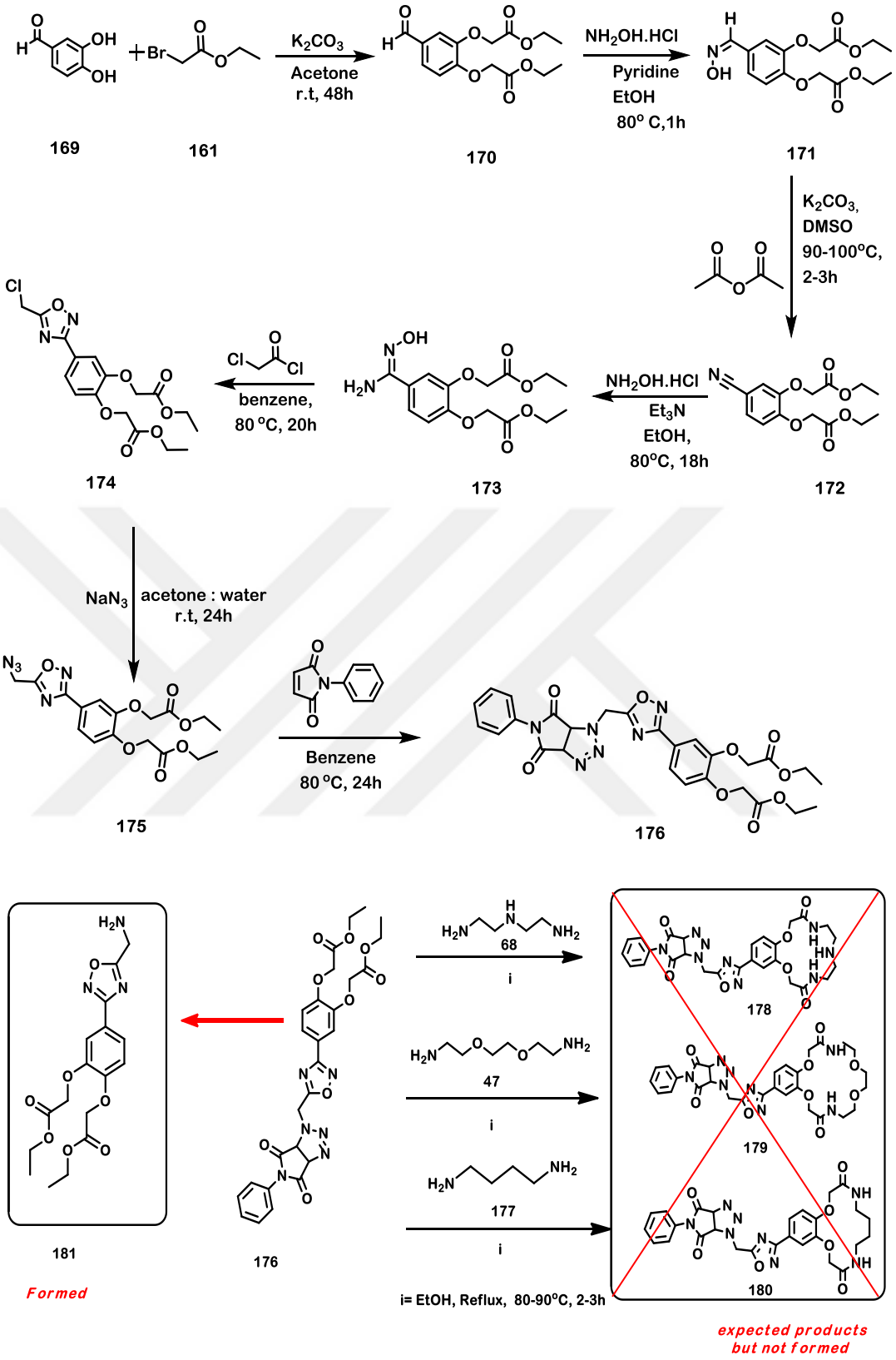
White solid (50 mg, 44%). R_f : 0.60 (*n*-hexane/EtOAc, 1:1). M.p: 163-164 ^oC IR (KBr, *v*:cm^{-1}): 3055 (Ar., CH), 2928, 2850 (Aliph., CH), 1600, 1589, 1546, 1492, 1446, 1408, 1350, 1265, 1242, 1184, 1118, 1087, 1053, 952, 898, 833. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.0 Hz, 4H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 6H), 6.98 – 6.87 (m, 4H), 4.35 (s, 4H), 3.93 (s, 4H), 3.85 (s, 4H), 2.77 (t, *J* = 6.0 Hz, 4H), 2.51 (s, 6H), 1.81 (t, *J* = 6.36 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.41, 167.70, 157.35, 142.78, 132.44, 128.99, 127.90, 125.94, 120.93, 117.73, 115.98, 111.08, 66.86, 52.78, 51.41, 31.82, 30.43, 22.85. LC-MS (ES^+): *m/z* (M+H) : 721. HRMS: *m/z* (ESI-TOF, [M+H^+]) calcd for $C_{39}H_{41}N_6O_6S_2$: 721.2631; found: 721.2635.

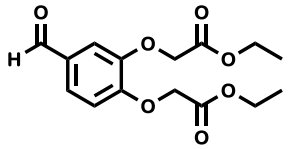


168I

4,4'-(((8,9,17,18-tetrahydro-5H-dibenzo[e,n][1,4]dioxa[8,12]diazacyclopenta decine-6,10(7H,11H)-diyl)bis(methylene))bis(1,2,4-oxadiazole-5,3-diyl))di benzonitrile ***(168i)***

White solid, (1.200 g, 68%), R_f : 0.38 (*n*-hexane/EtOAc, 2:1). M.p: 150-151 ^oC IR (KBr, *v*:cm^{-1}): 3055 (Ar., CH), 2928, 2854, (Aliph., CH), 2229 (C≡N), 1689, 1550, 1492, 1450, 1415, 1350, 1265, 1118, 1057, 1018, 937, 898, 852. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.3 Hz, 4H), 7.76 (dd, *J* = 7.5, 1.8 Hz, 4H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.30-7.25 (m, 2H), 6.97 – 6.89 (m, 4H), 4.35 (s, 4H), 3.95 (s, 4H), 3.85 (s, 4H), 2.78 (t, *J* = 6.5 Hz, 4H), 1.83 – 1.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.32, 166.61, 157.65, 132.64, 132.55, 131.11, 129.22, 127.91, 125.55, 120.93, 117.57, 114.72, 111.08, 66.62, 53.05, 46.18, 30.38, 29.89. LC-MS (ES^+): *m/z* (M+H) : 680.

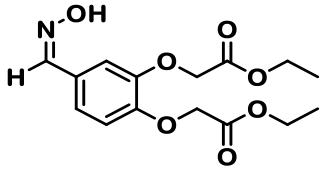

K2CO3
Acetone
r.t, 48h
NH2OH.HCl
Pyridine
EtOH
80° C,1h
K2CO3,
DMSO
90-100°C,
2-3h
NH2OH.HCl
Et3N
EtOH,
80°C, 18h
benzene,
80 °C, 20h
NaN3
acetone : water
r.t, 24h
Benzene
80 °C, 24h
i
i
i
i= EtOH, Reflux, 80-90°C, 2-3h
Formed
expected products
but not formed



170

Synthesis of diethyl 2,2'-((4-formyl-1,2-phenylene)bis(oxy))diacetate (170)

To the suspension of K_2CO_3 (87.60 g, 0.635 mol) in dried acetone was added to a mixture of ethylbromoacetate **161** (73 g, 0.44 mol) and 3,4-dihydroxybenzaldehyde **169** (24 g, 0.18 mol). The resulting mixture was stirred at room temperature for 48h. Then the mixture was filtered and the solvent was evaporated and yellow oily substance was purified with flash coloumn chromatography with DCM gave white solid (10 mg, 20%). R_f : 0.60 (*n*-hexane/EtOAc, 1:1). M.p: 62-63 ^oC. IR (KBr, *v*:cm^{-1}): 3115, 3047 (Ar., CH), 2978, 2939, (Aliph.CH), 1726 (Ester C=O), 1687 (Aldehyde C=O), 1587, 1514, 1444, 1431, 1307, 1273, 1265, 1232, 1213, 1174, 1139, 1055, 1028, 939, 887, 862, 819,794, 765. ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.45 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.77 (d, *J* = 13.5 Hz, 4H), 4.24 (q, *J* = 7.1Hz, 4H), 1.32 – 1.23 (m, 6H).^{13}C NMR (100 MHz, $CDCl_3$): δ 190.36, 168.57, 153.04, 148.26, 131.02, 126.74, 113.64, 113.10, 65.88, 60.77, 14.08. LC-M_S (ES^+): *m/z* (M+Na) : 333.

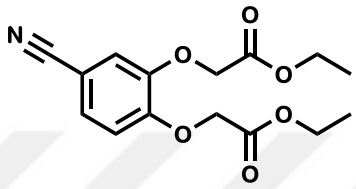


171

Synthesis of the (*Z*)-diethyl 2,2'-((4-((hydroxyimino)methyl)-1,2-phenylene) bis(oxy)) diacetate (171)

Diethyl 2,2'-((4-formyl-1,2-phenylene)bis(oxy))diacetate **170** (10 g, 0.0322 mol), hydroxylaminehydrochloride (3.58 g, 0.052 mol) and pyridine (150 ml), were mixed in EtOH (250 ml) and the reaction mixture was refluxed at 80^oC for 2h. The reaction mixture was then evaporated under reduced pressure, extracted with EtOAC/H_2O to give a white solid (5.92g, 59%). R_f: 0.71 (*n*-hexane/EtOAc, 1:1).

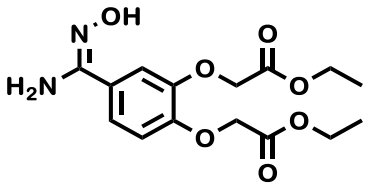
M.p: 88-89 ^{o}C. IR(KBr, *v*:cm^{-1}): 3448, (N-OH), 3080 (Ar. C-H), 2983, 2935, 2874, 2781 (Aliph.C-H), 1753 (C=O), 1604 (C=N), 1583, 1514, 1442, 1379, 1278, 1205, 1170, 1145, 1064, 1026, 958, 860, 810, 758, 705, 439. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 7.06 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.72 (d, *J* = 1.6 Hz, 4H), 4.29 – 4.21 (qd, *J* = 7.1, 0.7 Hz, 4H), 1.27 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.37, 149.57, 149.50, 148.26, 126.41, 122.64, 114.88, 112.04, 66.09, 61.19, 14.06. LC-MS (ES^{+}): *m/z* (M+Na) : 348.



172

Synthesis of the diethyl 2,2'-((4-cyano-1,2-phenylene)bis(oxy))diacetate (172)

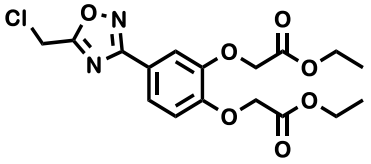
(*Z*)-Diethyl2,2'-((4-((hydroxyimino)methyl)-1,2-phenylene)bis(oxy))diacetate **171** (9.8 g , 0.0301 mol) and K_2CO_3 (8.73 g, 0.063 mol) were stirred in DMSO (25 ml) for 1h then acetic anhydride (6.46 g, 0.063 mol) was added and refluxed for 2h. Then, the reaction mixture was cooled to the room temperature. the mixture was poured into the ice and stirred until a precipitate occurs. The precipitate was filtered off and dried to give a white solid, (8.60 g, 93%). R_f : 0.87 (*n*-hexane/EtOAc, 1:1). M.p: 70-71 ^{o}C. IR (KBr, *v*:cm^{-1}): 3061 (Ar. C-H), 2985, 2916, 2848, 2611 (Aliph.C-H), 2227 (C≡N), 1753, 1602, 1585, 1512, 1442, 1379,1267, 1062, 1028, 856, 812, 734. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.08 (d, *J* = 1.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.72 (d, *J* = 15.7 Hz, 4H), 4.30 – 4.20 (m, 4H), 1.29 (q, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.04, 151.75, 147.88, 127.47, 118.34, 114.45, 66.51, 66.01, 61.48, 47.55, 14.10. LC-MS (ES^{+}): *m/z* (M+Na) : 331.



173

Synthesis of the (*Z*)-diethyl2,2'-((4-(*N'*-hydroxycarbamimidoyl)-1,2-phenylene) bis(oxy))diacetate (173)

Diethyl 2,2'-((4-cyano-1,2-phenylene)bis(oxy))diacetate **172** (101mg, 0.329 mmol), hydroxylaminehydrochloride (36.36 mg, 0.5264 mmol)**,** and Et_3N (79.9 mg, 0.7896 mmol), were dissolved in EtOH (50 ml), then it was refluxed under $N_{2(g)}$, for 18h. The solvent was evaporated and extracted with CH_2Cl_2/H_2O. The crude product was purified with flash coloumn chromatography with (EtOAC/*n*-hexane, 3:1). White solid, (55 mg, 50%). R_f: 0.32 (*n*-hexane/EtOAc, 1:3). M.p: 111-112 ^oC. IR (KBr, *v*:cm^{-1}): 3491, 3387 (NH), 3348(OH), 3086 (Ar., C-H), 2985 (Aliph.C-H), 1751 (C=O), 1651 (C=N),1608, 1523, 1435, 1381, 1334, 1284,1230, 1203, 1165, 1122, 1064, 1018, 929. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 1.7 Hz, 1H), 7.35 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.01 (d, *J* = 143.6 Hz, 2H), 4.74 (s, 4H), 4.23 (q, *J* = 7.2 Hz, 4H), 1.82 (s, 1H), 1.26 (td, 7.1, 1.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.88, 149.47, 147.51, 126.25, 124.86, 120.04, 115.01, 113.05, 66.28, 61.75, 14.20. LC-MS (ES^+): *m/z* (M+H) : 341.

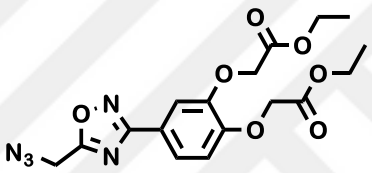


174

Synthesis of diethyl2,2'-((4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-1,2-phenyle ne)bis (oxy))diacetate (174)

(*Z*)-Diethyl2,2'-((4-(*N*'-hydroxycarbamimidoyl)-1,2-phenylene)bis(oxy))dia cetate **(173)** (50 mg, 0.147 mmol) was dissolved in benzene (50 ml) by heating, then chloroacetyl chloride (26.56 mg, 0.236 mmol) in benzene (2.5 ml) was added

dropwise and reaction mixture was refluxed for 20h. Benzene was evaporated and then the remaining crude mixture was extracted with EtOAc/H_2O and purified with flash column chromatography with (EtOAc/*n*-hexane 1:4) to give a white solid (40 mg, 68%), R_f : 0.70 (*n*-EtOAc/*n*-hexane, 1:4). M.p: 83-84 ^oC. IR (KBr, *v*:cm^{-1}): 3090 (Ar., C-H), 2989,2916 (Aliph.C-H), 1759, 1747 (C=O), 1597, 1577, 1539, 1496, 1485, 1442, 1404,1369, 1319, 1280, 1226, 1203, 1145, 1060, 1022, 1010, 925, 875, 810, 756, 732, 705, 659, 597. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.75 (s, 4H), 4.70 (s, 2H), 4.29 – 4.21 (m, 4H), 1.27 (ddd, *J* = 7.2, 5.9, 4.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.28, 168.48, 150.59, 148.04, 122.23, 120.19, 114.62, 113.59, 66.57, 65.99, 61.53, 33.41, 14.78. LC-MS (ES^+): *m/z* (M+Na) : 421**.**

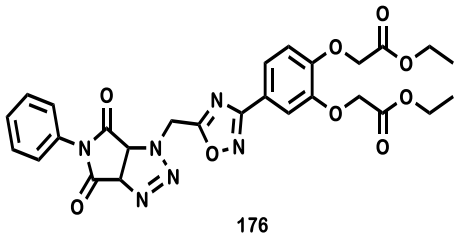


175

Synthesis of diethyl2,2'-((4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene)bis(oxy))diacetate (175)

To a stirred solution of diethyl 2,2'-((4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene)bis(oxy))diacetate **174** (400 mg, 1.003 mmol) in a 20 mL water/acetone mixture (1:4) was added NaN_3 (71.73 mg, 1.003 mmol). The resulting suspension was stirred at room temperature for 2d. Dichloromethane (DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with DCM and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude azide was purified by flash column chromatography. White solid, (240 mg, 93%). R_f : 0.45 (EtOAc/MeOH, 5:1). M.p: 56-57 ^oC. IR (KBr, *v*:cm^{-1}): 3055, (Ar., C-H), 2985, (Aliph.C-H), 2110 (N=N=N), 1757, 1735 (C=O), 1610, 1579, 1438, 1379, 1298, 1265, 1207, 1193, 1147, 1064, 740, 704. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (ddd, *J* = 8.3, 6.4, 1.9 Hz, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.76 (s, 4H), 4.58 (s, 2H), 4.25 (qd, *J* = 7.1, 2.5 Hz, 4H), 1.31 – 1.24 (m, 6H). ^{13}C NMR (100

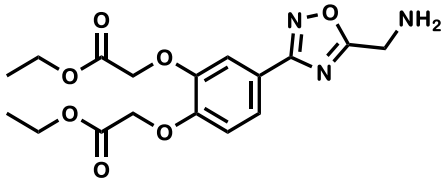
MHz, $CDCl_3$): δ 173.80, 169.07, 150.26, 148.29, 122.60, 120.03, 115.60, 113.64, 66.57, 61.85, 45.29, 33.59, 14.48. LC-MS (ES^+): *m/z* (M+Na) : 428.



176

Synthesis of diethyl 2,2'-((4-(5-((4,6-dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo [3,4-d][1,2,3]triazol-1(3aH)-yl)methyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene)bis (oxy))diacetate (176)

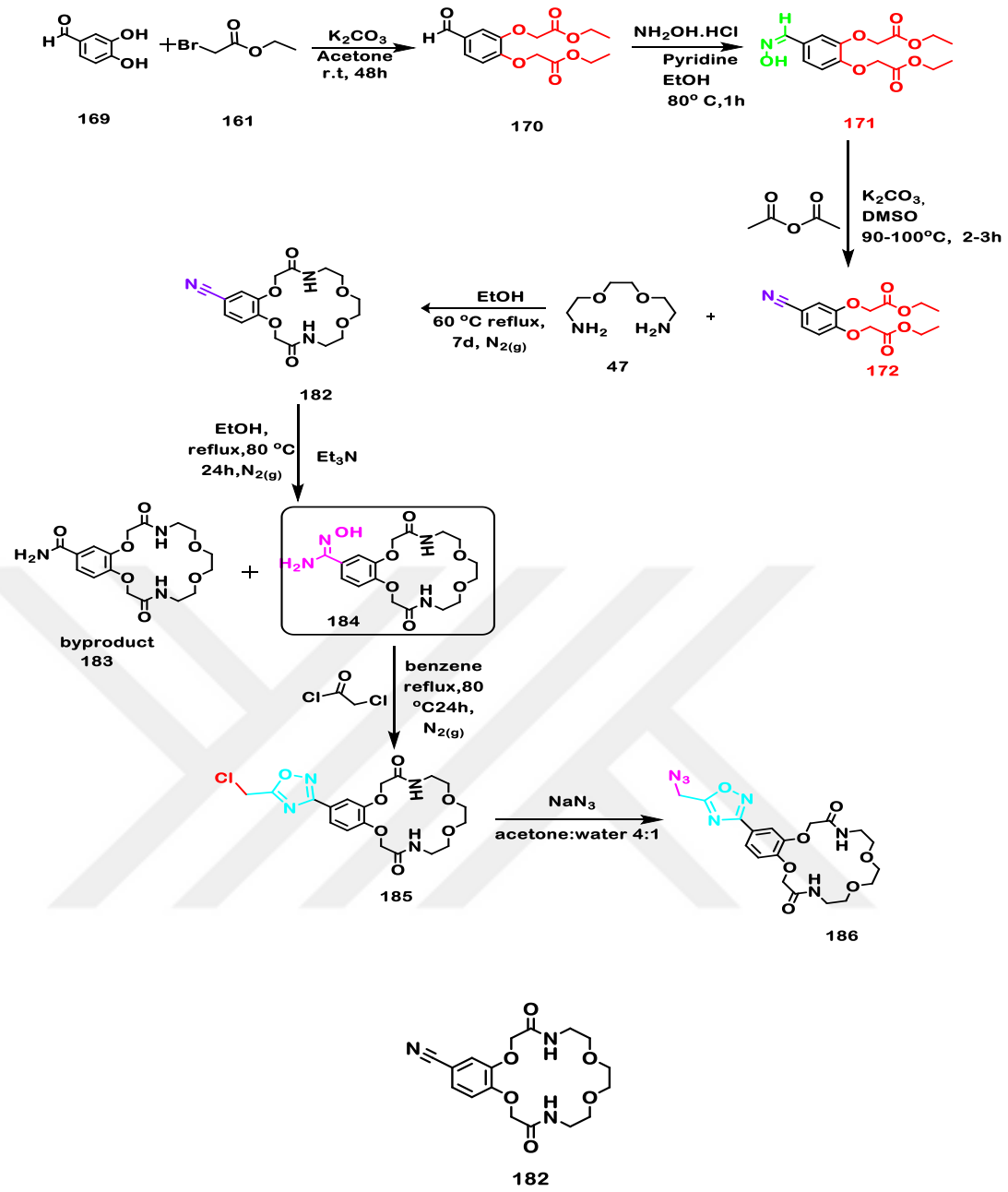
Diethyl 2,2'-((4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene) bis (oxy))diacetate **175** (928 mg, 2.29 mmol) and *N*-phenylmaleimide (436 mg, 2.52 mmol) were mixed in benzene (30 ml) and refluxed for 24h. After reaction was completed, benzene was evaporated under the reduced pressure and then purified by the flash coloumn chromatography (EtOAc/*n*-hexane, 1:2). White solid (160 mg 61%). R_f : 0.50 (EtOAc/*n*-hexane, 1:1). M.p: 77-78 ^oC. IR (KBr, *v*:cm^{-1}): 3055 (Ar. C-H), 2987 (Aliph.C-H), 1755 (C=O), 1730 (Ester C=O), 1481, 1421, 1379, 1265, 1193, 1064, 1028, 896, 746, 705. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.48 (t, *J* = 2.9 Hz, 1H), 7.42 – 7.36 (m, 3H), 7.23 – 7.17 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.87 (d, *J* = 10.8 Hz, 1H), 5.54 (d, *J* = 14.6 Hz, 1H), 5.28 (s, 2H), 4.77 – 4.70 (m, 4H), 4.24 (q, *J* = 7.2 Hz, 4H), 1.27 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.90, 170.75, 168.85, 168.63, 168.48, 167.88, 150.06, 147.80, 128.98, 126.47, 126.23, 122.39, 119.75, 114.43, 113.74, 83.31, 66.56, 61.45, 57.01, 44.41, 14.38. LC-MS (ES^+): *m/z* (M+Na) : 601.



181

Synthesis of diethyl 2,2'-((4-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene)bis(oxy))diacetate (181)

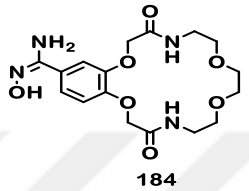
Diethyl 2,2'-((4-(5-((4,6-dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-d][1,2,3]triazol-1(3aH)-yl)methyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene)bis(oxy))diacetate **(176)** (383 mg, 0.662 mmol**)** was dissolved by heating in EtOH then 2,2'-(ethane-1,2-diylbis(oxy))bis(ethan-1-amine**) 47** (98 mg, 0.662 mmol) was added dropwise refluxed at 80-90 ^{o}C for 3h. EtOH was evaporated and the crude product was purified by flash coloumn chromatography (EtOAc/MeOH, 8:1) to give a yellow solid (150 mg, 60%). R_f : 0.40 (EtOAc/MeOH, 5:1). IR (KBr, *v*:cm^{-1}): 3389, 3327 (N-H), 3057 (Ar., C-H), 2983, 2933 (Aliph.C-H), 1735 (C=O), 1610, 1572, 1535, 1492, 1438, 1369, 1267, 1193, 1145, 1116, 1064, 1028, 858, 734. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.74 (s, 4H), 4.23 (qd, *J* = 7.1, 1.9 Hz, 4H), 4.10 (s, 2H), 1.90 (s, 2H), 1.25 (ddd, *J* = 15.6, 9.6, 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.98, 168.77, 167.69, 150.32, 147.96, 122.09, 120.72, 114.59, 113.53, 65.78, 61.58, 38.24, 14.21. LC-M_S (ES^+): *m/z* (M+H) 380.



Synthesis of 3,14-dioxo-2,3,4,5,6,8,9,11,12,13,14,15dodecahydrobenzo[b][1,4, 10, 13, 7,16]tetraoxadiazacyclooctadecine-18-carbonitrile (182)

Diethyl 2,2'-((4-cyano-1,2-phenylene)bis(oxy))diacetate **172** (7 g, 0.023 mol**)** was dissolved by heating in EtOH then 2,2'-(ethane-1,2-diylbis(oxy))bis(ethan-1-amine**)** **47** (6 g, 0.034 mol) was added dropwise and stirred at room temperature for 24h. EtOH was evaporated and the crude product was purified by flash column chromatography (EtOAc/MeOH, 5:1) to give a white solid **182** (3.100 g, 39%). R_f:

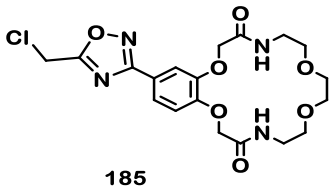
0.44 (EtOAc/MeOH, 5:1). M.p: 222-223 ^{o}C (decomposed). IR (KBr, *v*:cm^{-1}): 3404, 3340 (NH), 3070 (Ar. C-H), 2929, 2881, 2856 (Aliph.C-H), 2224 (C≡N), 1662 (N-C=O), 1600, 1554, 1516, 1442, 1421, 1348, 1332, 1273, 1238, 1147, 1112, 1039, 962, 871, 817. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 6.97 (t, *J* = 6.7 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 4.58 (d, *J* = 15.5 Hz, 4H), 3.62 – 3.49 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.77, 150.35, 146.86, 127.70, 115.87, 113.01, 105.78, 70.31, 70.28, 69.80, 67.71, 38.80. LC-MS (ES^{+}): *m/z* (M+Na) : 386.



184

Synthesis of the (*E*)-*N*'-hydroxy-3,14-dioxo2,3,4,5,6,8,9,11,12,13,14,1dodecahydrobenzob[b][1,4,10,13,7,16]tetraoxadiazacyclooctadecine-18-carboximidamide (184)

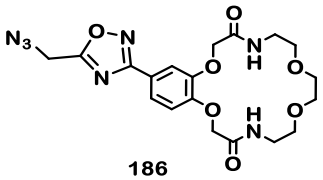
3,14-Dioxo-2,3,4,5,6,8,9,11,12,13,14,15dodecahydrobenzo[b][1,4,10,13,7, 16]tetraoxadiazacyclooctadecine-18-carbonitrile **182** (3.22 g, 8.9 mmol), hydroxyl amine hydrochloride (1.323 g, 17.7 mmol)**,** and Et_3N (1.348 g, 12.45 mmol) were disolved in EtOH (50 ml), then the mixture was refluxed under N_2 atmosphere, for 24h. EtOH was evaporated and extracted with CH_2Cl_2/H_2O. The crude product was purified with flash column chromatography (EtOAc/MeOH 5:1) to give **184** as a white solid, (2.786 g, 79%). R_f : 0.250 (EtOAc/MeOH 5:1). M.p: 226-228 ^{o}C (decomposed). IR (KBr, *v*:cm^{-1}): 3471, 3377 (NH), 3230 (OH), 3057 (Ar. C-H), 2895, 2875 (Aliph.C-H), 1662, 1647 (N-C=O), 1577, 1541, 1523, 1464, 1440, 1383, 1350, 1267, 1211, 1130, 1101, 1041, 964, 950, 815, 792, 696, 665, 605. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.64 (s, 1H), 7.86 (s, 1H), 7.77 (q, *J* = 5.4 Hz, 2H), 7.50 (td, *J* = 8.5, 1.9 Hz, 2H), 7.21 (s, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 4.52 (d, *J* = 2.9 Hz, 4H), 3.46 (t, 8H), 2.49 – 2.41 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.10, 166.96, 148.80, 145.90, 127.56, 121.50, 113.00, 112.60, 69.34, 68.84, 67.60, 67.56. LC-M_S (ES^{+}): *m/z* (M+H) : 397.



185

Synthesis of 18-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-5,6,8,9,11,12,13,15octa hydrobenzo[b][1,4,10,13,7,16]tetraoxadiazacyclooctadecine-3,14(2H,4H)-dione (185)

(*E*)-*N*'-hydroxy-3,14-dioxo-3,4,5,6,8,9,12,13,14,15-decahydro-2H,11H-benzo[b][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-18-carboximidamide **184** (1.552 g, 3.918 mmol) was dissolved in benzene (500 ml) then chloroacetylchloride (0.295 g, 2.612 mmol) in benzene (50 ml) was added dropwise and reaction mixture was refluxed for 24h. Benzene was evaporated and then the crude mixture was extracted with EtOAC/H_2O and purified with flash column chromatography (EtOAC/MeOH, 5:1) to give **185** as a white solid, (100 mg, 10%). R_f : 0.45 (EtOAc/MeOH, 5:1). M.p: 173-174 ^oC. IR (KBr, *v*:cm^{-1}): 3340 (NH), 3012 (Ar. C-H), 2928, 2862 (Aliph.C-H), 1670 (N-C=O), 1600, 1543, 1473, 1427, 1346, 1257, 1138, 1114, 1041. 891, 871, 821, 732. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.08 (s, 2H),6.98 (d, J = 8.5 Hz, 1H), 4.72 (s, 2H), 4.64 (d, *J* = 11.0 Hz, 4H), 3.59 (d, *J* = 7.1 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.34, 167.98, 167.23, 149.20, 146.88, 122.15, 120.37, 112.97, 111.99, 70.19, 69.70, 67.69, 67.54, 38.74. LC-M (ES^+): *m/z* (M+Na) : 477.

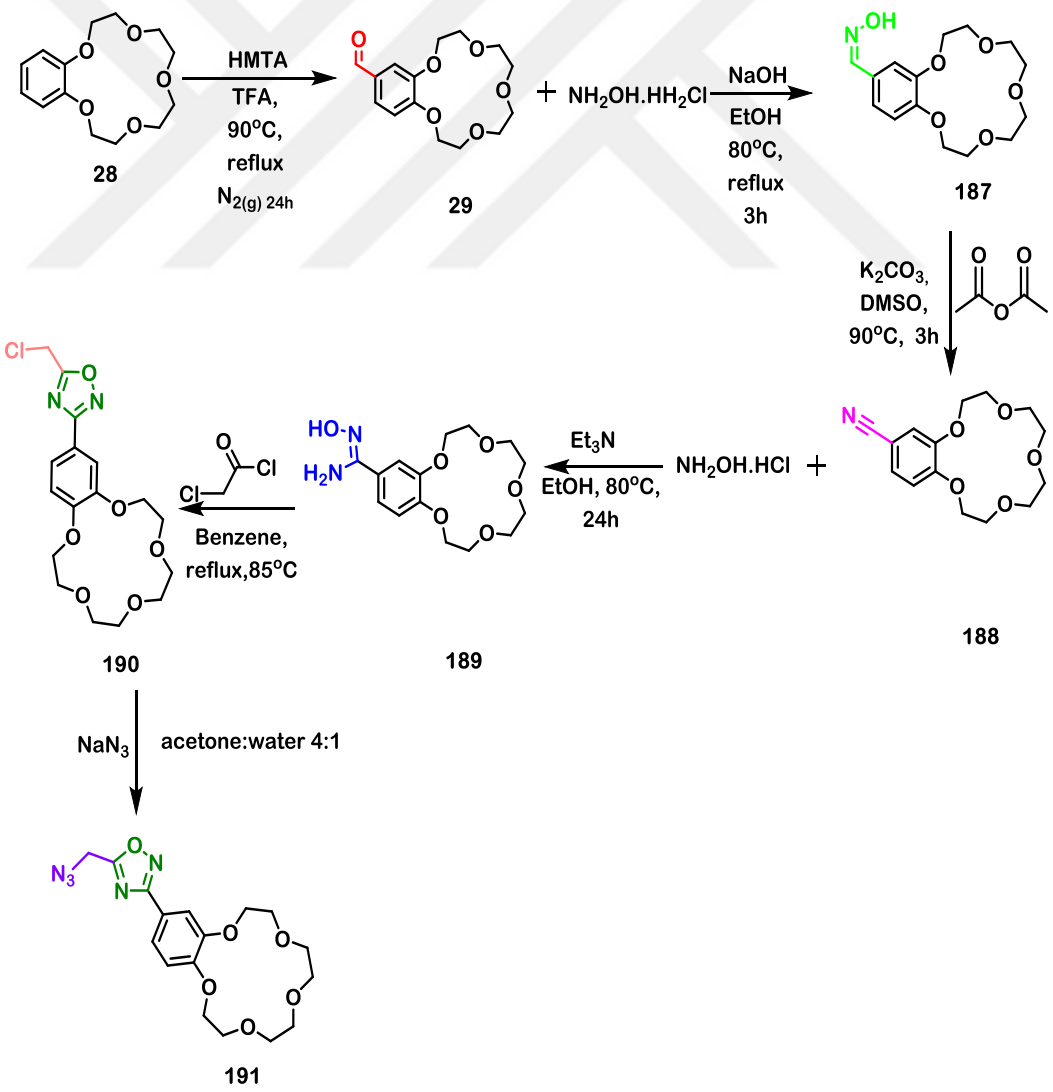


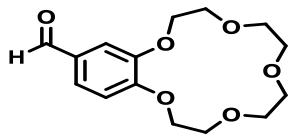
186

Synthesis of 18-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-5,6,8,9,12,13-hexahydro-2 H,11H-benzo[b][1,4,10,13]tetraoxa[7,16]diazacyclooctadecine-3,14(4H,15H)-dio ne (186)

A stirred suspension of 18-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-5,6,8,9, 11,12,13,15octahydrobenzo[b][1,4,10,13,7,16]tetraoxadiazacyclooctadecine-3,14(2 H,4H)-dione **185** (0.255 g, 0.561 mmol) in 10 mL water/acetone mixture (1:4) was added NaN_3 (0.04 g, 0.617 mmol). The resulting suspension was stirred at room

temperature for 6d. Dichloromethane (DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with DCM and the combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, and the crude azide was purified by flash column chromatography to give a white solid (240 mg, 93%). R_f: 0.45 (EtOAc/MeOH, 5:1). M.p: 186-187 ^oC. IR (KBr, *v*:cm^{-1}): 3417 (NH), 3055 (Ar., C-H), 2939, 2862, 2685 (Aliph.C-H), 2102 (N=N=N) 1674 (N-C=O), 1608, 1531, 1481, 1438, 1342, 1265, 1207, 1141, 1114, 887. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (ddd, *J* = 8.0, 5.9, 1.8 Hz, 1H), 7.63 (dd, *J* = 3.8, 2.1 Hz, 1H), 7.07 (t, *J* = 11.3 Hz, 2H), 6.99 (dd, *J* = 8.7, 2.3, 1H), 4.72 (s, 2H), 4.69 – 4.56 (m, 4H), 3.62 – 3.56 (m, 12H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 173.68, 167.79, 167.18, 149.25, 146.92, 122.10, 120.40, 113.02, 112.06, 69.88, 67.59, 45.06, 38.75, 33.24. LC-MS (ES^+): *m/z* (M+Na) : 485.

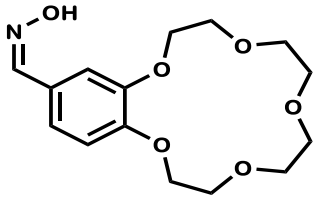




29

Synthesis of 2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13] pentaoxacyclopentadecine-15-carbaldehyde (29) (Kimura et al., 2006, Chen et al., 2016, Safonova et al., 2013)

A mixture of benzo-15-crown-5 **(28)** (3.554 g, 0.013 mol) and TFA (9.87 mL) was stirred under N_2 atmosphere for 1h then HMTA (2.622 g, 0.019 mol) was added and the reaction mixture was refluxed at 80 ^{o}C with stirring for 17h. Then the reaction mixture was cooled to room temperature and HCl (15 mL) was added. The mixture was further refluxed at 95 ^{o}C for 1.5h. After completed, the mixture was cooled to room temperature and water is added into the mixture than extracted with benzene, benzene was removed under vacuum, product **29** was obtained as a yellow solid (2 g, 77 %). R_f : 0.29 (MeOH). M.p: 82-83^{o}C. IR (KBr, *v*:cm^{-1}): 3080 (Ar., C-H), 2949, 2929, 2870, 2821, 2729 (Aliph.C-H), 1689 (aldehyde C=O), 1599, 1587, 1512, 1440, 1404, 1398, 1271, 1244, 1139, 1118, 1087, 1051,.1043, 977, 925, 891, 864. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.43 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.37 (d, *J* = 1.9 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 4.21 – 4.16 (m, 4H), 3.94 – 3.88 (m, 4H), 3.78 – 3.74 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.86, 154.57, 149.37, 130.18, 126.90, 111.89, 111.18, 71.19, 70.32, 69.05, 68.74. LC-MS (ES^{+}): *m/z* (M+Na) : 319.

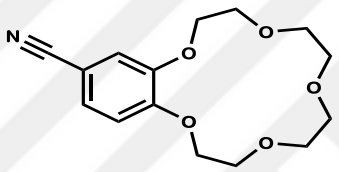


187

Synthesis of (*Z*)-2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecine-15-carbaldehyde oxime (187)

2,3,5,6,8,9,11,12-Octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecine-15-carbaldehyde **29** (2.665 g, 8.99 mmol) was dissolved in EtOH and sequently a

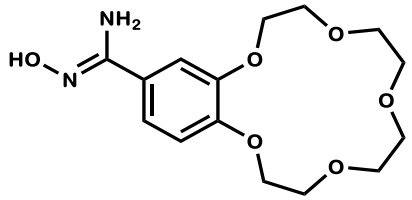
solution of hydroxylaminehydrochloride (5.88 g, 84.5 mmol) and NaOH (2.66 g, 66.6 mmol) in water was added. The reaction mixture was refluxed at 80^{o}C for 3h. After reaction completed, EtOH was evaporated under reduced pressure. Then it was extracted with CH_2Cl_2/H_2O and a white solid **187** was obtained (1.940 g, 69%). R_f : 0.711 (*n*-EtOAc/MeOH 5:1). M.p: 61-62 ^{o}C. IR (KBr, *v*:cm^{-1}): 3238 (N-OH), 3080 (Ar., C-H), 2929, 2872 (Aliph. C-H), 1600 (C=N), 1581, 1518, 1456, 1435, 1359, 1340, 1273, 1232, 1138, 1051, 910, 862, 844, 802, 729, 644, 621. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 6.98 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 4.15 (dd, *J* = 8.9, 5.1 Hz, 4H), 3.91 (dd, *J* = 8.8, 4.7 Hz, 4H), 3.76 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.79, 149.92, 149.25, 125.29, 121.83, 113.04, 110.56, 71.05, 70.25, 69.53, 68.54. LC-MS (ES^{+}): *m/z* (M+H) : 312.



188

Synthesis of 2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecine-15-carbo nitrile (188)

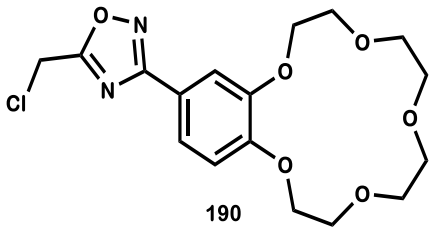
(*Z*)-2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecine-15-carbaldehydeoxime **187** (2.100 g, 6.75 mmol) and K_2CO_3 (2.049 g, 14.84 mmol) were stirred in DMSO (8 ml) for 1h, then acetic anhydride (1.515 g, 14.84 mmol) was added and the reaction mixture was refluxed for 2h. Then the reaction mixture was maintained to cool to the room temperature and the mixture was poured into the ice and stirred until a precipitate occurs. The precipitate was filtered off and dried to give a white solid (1.760 g, 89%). R_f: 0.711 (*n*-EtOAc/MeOH, 5:1). M.p: 105-106 ^{o}C. IR (KBr, *v*:cm^{-1}): 3128, 3063 (Ar., C-H), 2939, 2877, 2823 (Aliph.C-H), 2225 (C≡N), 1599, 1518, 1452, 1421, 1334, 1274, 1240, 1139, 1093, 1047, 981, 939, 875, 788, 696, 619. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 8.6, 1.6 HZ, 1H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.17– 4.11 (m, 4H), 3.94 – 3.87 (m, 4H), 3.77 – 3.72 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.05, 149.04, 126.72, 119.16, 116.38, 112.93, 103.98, 71.13, 70.32, 69.16, 68.65. LC-MS (ES^{+}): *m/z* (M+Na) : 316.



189

Synthesis of (*Z*)-N'-hydroxy-2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13] pe ntaoxacyclopentadeci ne-15-carboximidamide (189)

2,3,5,6,8,9,11,12-Octahydrobenzo[b][1,4,7,10,13]pentaoxacyclopentadecine-15-carbonitrile **188** (1.669 g, 5.69 mmol), hydroxylamine hydrochloride (0.790 g, 11.38 mmol) and Et_3N (0.862 g, 8.535 mmol) were dissolved in EtOH (50 ml), then the mixture was refluxed under N_2 atmosphere, for 24h. EtOH was evaporated and extracted with CH_2Cl_2/H_2O. The crude product was purified with flash column chromatography (EtOAc/MeOH 5:1) to give a white solid (500 mg, 27%). R_f: 0.32 (EtOAc/MeOH 5:1). M.p: 196-197 ^oC. IR (KBr, *v*:cm^{-1}): 3425 (NH), 3255 (N-OH), 3128, 3063 (Ar., C-H), 2951, 2928, 2739, 2677 (Aliph.C-H), 1654 (C=N), 1604, 1519, 1465, 1435,1381,1261, 1219,1122,1095, 1037, 968, 945, 806, 783. ^1H NMR (400 MHz, $CDCl_3$): δ 9.44 (s, 1H), 7.16 (dd, *J* = 15.3, 10.0, 2H), 6.91 (dd, *J* = 16.0, 8.2 Hz, 1H), 5.72 (s, 2H), 4.01 (d, *J* = 3.1 Hz, 4H), 3.69 (s, 4H), 3.05 – 2.88 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.22, 149.55, 148.25, 126.58, 118.90, 113.48, 111.43, 70.55, 69.93, 69.05, 68.69. LC-M (ES^+): *m/z* (M+H) : 327.

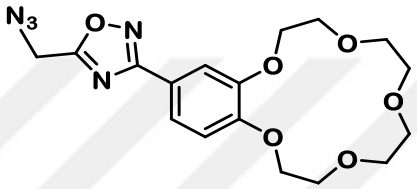


190

Synthesis of 5-(chloromethyl)-3-(2,3,5,6,8,9,11,12-octahydrobenzo[b] [1,4,7,10, 13]pentaoxacyclopenta decin-15-yl)-1,2,4-oxadiazole (190)

(*Z*)-*N*'-hydroxy-2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7,10,13]pentaoxa cyclopentadecine-15-carboximidamide (140 mg, 0.43 mmol) was dissolved in benzene (100 ml) then chloroacetyl chloride (32.3 mg, 0.29 mmol) in benzene (5ml),

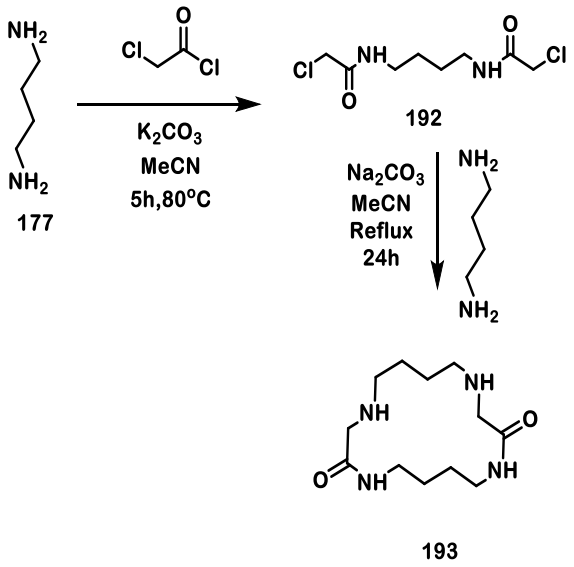
was added dropwise and the reaction mixture was refluxed for 24 h. Benzene was evaporated. It was extracted with EtOAC/H_2O and purified with flash column chromatography with (EtOAC/MeOH, 5:1) to give a white solid (15 mg, 17%). R_f: 0.47 (EtOAc/MeOH, 5:1). M.p: 157-158 ^oC. IR (KBr, *v*:cm^{-1}): 3028 (Ar., C-H), 2924, 2874, 2592, 2457 (Aliph.C-H), 1600, 1577, 1481, 1446, 1361, 1346, 1265, 1130, 1107, 1045, 941, 848, 732, 578. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.52 (d, *J* = 2.2 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.71 (s, 2H), 4.21 – 4.15 (m, 4H), 3.91 (dd, *J* = 8.9, 3.8 Hz, 4H), 3.75 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.19, 168.78, 151.82, 149.07, 121.37, 121.33, 118.76, 112.95, 111.95, 71.09, 70.32, 69.37, 68.90, 33.34. LC-MS (ES^+): *m/z* (M+Na) : 407.



191

Synthesis of 5-(azidomethyl)-3-(2,3,5,6,8,9,11,12octahydrobenzo[b] 1,4,7,10, 13]pentaoxacyclopentade cin-15-yl)-1,2,4-oxadiazole (191)

To a stirred solution of 5-(chloromethyl)-3-(2,3,5,6,8,9,11,12-octahydroben zo[b][1,4,7,10,13] pentaoxacyclopentadecin-15-yl)-1,2,4-oxadiazole **190** (25 mg, 0.065 mmol) in a 10 mL water/acetone mixture (1:4) was added NaN_3 (4.65 mg, 0.071 mmol). The resulting suspension was stirred at room temperature for 3d. Dichloromethane (DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with DCM and the combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, and the crude azide was purified by flash column chromatography to give a white solid (20 mg, 80%). R_f: 0.30 (EtOAc/MeOH, 5:1). M.p: 123-124 ^oC. IR (KBr, *v*:cm^{-1}): 3055 (Ar., C-H), 2924, 2874 (Aliph.C-H), 2110 (N=N=N) , 1600, 1577, 1485, 1446, 1265, 1130,1049, 941, 848, 783, 744. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (ddd, *J* = 8.4, 6.6, 1.9 Hz, 1H), 7.55 (dd, *J* = 4.4, 1.9 Hz, 1H), 6.92 (dd, *J* = 8.4, 1.7 Hz, 1H), 4.59 (s, 2H), 4.22 – 4.16 (m, 4H), 3.92 (dd, *J* = 8.0, 3.7 Hz, 4H), 3.76 (s, 8H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 173.94, 167.06, 149.25, 146.92, 122.10, 120.40, 113.02, 112.09, 112.06, 67.28, 45.06, 38.75, 33.24. LC-MS (ES^+): *m/z* (M+Na) : 414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NH2
177
Cl
Cl
O
K2CO3
MeCN
5h,80°C
Cl
NH
NH
Cl
O
O
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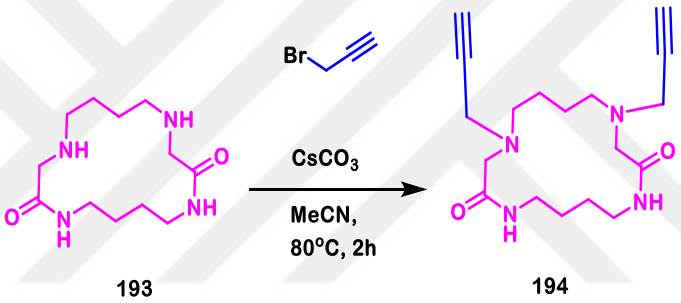
MeCN
Reflux
24h
NH2
NH2
NH
NH
O
NH
O
NH
193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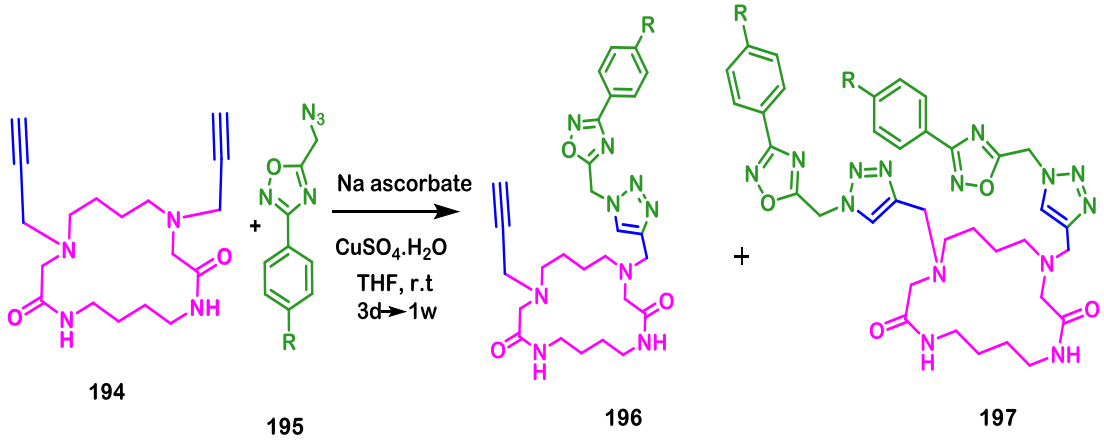
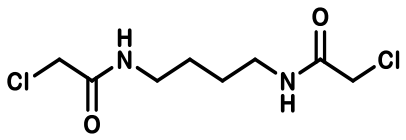
CsCO3
MeCN,
80°C, 2h
NH
NH
O
N
H
O
NH
193
N
N
O
NH
194

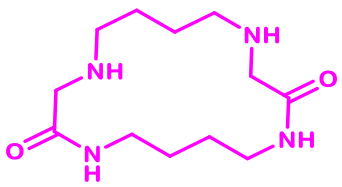

N3
O
N
N
+
R
Na ascorbate
CuSO4.H2O
THF, r.t
3d→1w
194
195
R
R
196
R
R
197



192

Synthesis of *N,N'*-(butane-1,4-diyl)bis(2-chloroacetamide) (192)

In a 500 ml three-necked round-bottomed flask, equipped with a magnetic stirrer, cooling bath, internal thermometer and dropping funnel, 1,4-diaminobutane (10.0 g, 0.113 mol) was dissolved in methylene chloride (100 ml). To the above stirred solution was added distilled water (80 ml) and potassium carbonate (31.6 g, 0.222 mol). The resultant mixture was ice-cooled and chloroacetyl chloride (24.5 ml, 0.222 mol) was then added over a period of 60–90 min, while the temperature is maintained below 10°C. The reaction mixture was then allowed to warm to room temperature and the precipitate was filtered to provide the crude product as a white solid. It was taken into 150 ml of water, stirred further vigorously for 2h and refiltered. The precipitate was then dried overnight in a vacuum oven at 60°C to yield the desired compound as a white solid (19.84 g, 74 %). M.p. 132–133 °C. IR (KBr, *v*:cm^{-1}): 3321 (NH), 2939, 2928, 1643 (C=O), 1610, 1550, 1504, 1454. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 2H, NHCO), 3.99 (s, 4H), 3.04 (d, *J* = 2.2 Hz, 4H), 1.37 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.96 (C=O), 42.61, 39.32, 26.69. LC-MS (ES^{+}): *m/z* (M+H) : 264.

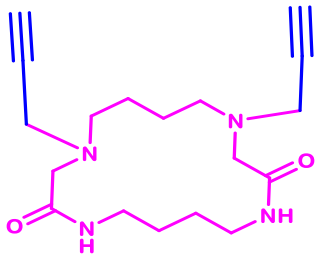


193

Synthesis of 1,4,9,12-tetraazacyclohexadecane-2,11-dione (193)

N,N'-(Butane-1,4-diyl)bis(2-chloroacetamide) (5 g, 0.02 mol), 1, 4-butanediamine (1.83 g, 0. 021 mol) were mixed in acetonitrile (100 mL) under nitrogen gas, then Na_2CO_3 (48.51 g, 0.46 mol) is added portionwise with mechanical stirring. The reaction mixture was further stirred at 80 ^{o}C for 24 h. When the reaction was completed as monitored by TLC, the mixture was filtered off. The solvent was evaporated under the reduced pressure. The crude product was purified by column chromatography on silica gel using DCM/MeOH (3:1) to give **193** as a white solid

(1.161 g 21 %). M.p: 141–142 °C. R_f: 0.25 (DCM/MeOH, 5:2). IR (KBr, *v*:cm^{-1}): 3356 (NH), 3321 (NH), 3267 (NH), 2943, 2874, 1643 (C=O), 1539, 1442, 1242, 1153, 848. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 2H, NHCO), 3.37– 3.28 (m, 4H), 3.23 (s, 4H), 2.60 (t, *J* = 6.5 Hz, 4H), 1.63–1.48 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.94 (C=O), 52.89 ($NHCH_2C$=O), 50.12, 37.77, 27.75, 27.52. LC-MS (ES^+): *m/z* (M+H) : 257.



194

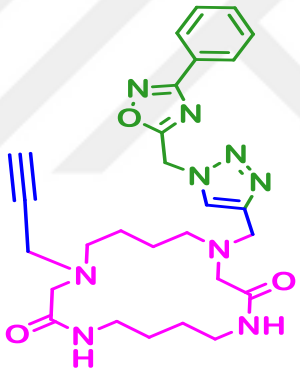
Synthesis of 1,12-di(prop-2-yn-1-yl)-1,4,9,12tetraazacyclohexadecane-2,11-dione (194)

1,4,9,12-Tetraazacyclohexadecane-2,11-dione **193** (519 mg, 2.025 mmol) was dissolved in acetonitrile (30 mL) and cesium carbonate (2.836 g, 8.71 mmol) was added followed by propargyl bromide (0.721 mL, 8.096 mmol). Molecular sieves (4Å) were added to the reaction mixture and was stirred under refluxed for 2.5 h. After the reaction was completed (monitored by TLC), it was filtered off the precipitate and washed with acetonitrile. Solvent was evaporated under the reduced pressure. Crude product was then purified by flash column chromatography (EtOAc/MeOH, 5:1) to give **194** as a white solid (362 mg, 54%). Mp 164-165°C. IR (KBr, *v*: cm^{-1}): 3344 (NH), 3308 (C≡C-H), 3273 (NH), 3232 (NH), 2939, 2868, 2818, 2096 (C≡C), 1647 (C=O), 1529, 1464, 1334, 1280, 1124. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (br s, 2H), 3.35 (s, 4H), 3.29 (s, 4H), 3.10 (s, 4H), 2.53 (s, 4H), 2.20 (s, 2H), 1.53 (s, 4H), 1.44 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.82 (C=O), 78.16, 73.40, 58.42, 54.90, 44.71, 37.96, 27.85, 26.06. LC-MS (ES^+): *m/z* (M+H) : 333.

General procedure for the preparation of the compounds 196a-h and 197a-h

Synthesis of 4-((1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione ***(196a)*** *and 4,9-bis((1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl)methyl)-1,4 ,9,12-tetraazacyclohexadecane-2,11-dione* ***(197a)***

To a stirred solution of 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole **195a** (55 mg, 0.274 mmol) and azacrown-alkyne **194** (50 mg, 0.150 mmol) in tetrahydrofuran (25 mL) was added aqueous copper sulfate (13.7 mg, 0.055 mmol). Sodium ascorbate (27.1 mg, 0.137 mmol) was then added portionwise in 10 min. The reaction mixture was stirred for 3d to 2 weeks at room temperature. Solvent was evaporated and the crude material was purified by flash column chromatography (EtOAc/MeOH, 6:1) to give (**196a)** and **(197a)**.

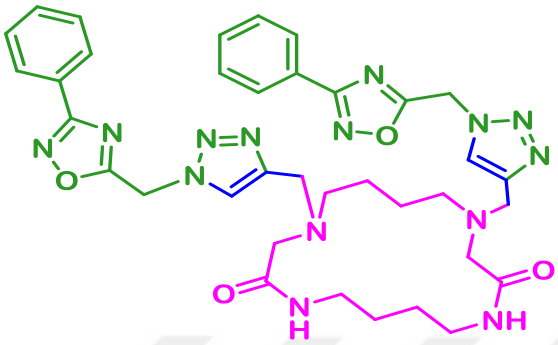


196a

4-((1-((3-Phenyl-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl)methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione ***(196a)***.

Yellow oil (30 mg, 38%). R_f: 0.489 (EtOAc/MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3344 (NH), 3302 (C≡C-H), 3136, 3070, 2935, 2862, 2380 (C≡C) 1638 (C=O), 1600, 1527, 1446, 1350, 1276, 1114. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.6 Hz, 2H), 7.78 (s, 1H), 7.56 – 7.40 (m, 4H), 7.31 – 7.26 (m, 1H), 5.91 (s, 2H, NHC=O), 5.27 (s, 1H, CH_2N-triazole), 3.82 (s, 2H, CH_2-C≡C), 3.35 (s, 1H), 3.26 (d, *J* = 14.8 Hz, 4H), 3.34 (d, *J* = 1.6 Hz, 1H), 3.26 (d, *J* = 14.8 Hz, 2H), 3.09 (d, *J* = 5.6 Hz, 2H), 2.62 – 2.46 (dt, *J* = 24.4, 6.8, 6.4 Hz, 2H), 2.19 (br s, 1H), 1.57-1.35 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.32 (C=O), 171.14 (C=O), 171.09 (C=N), 168.95

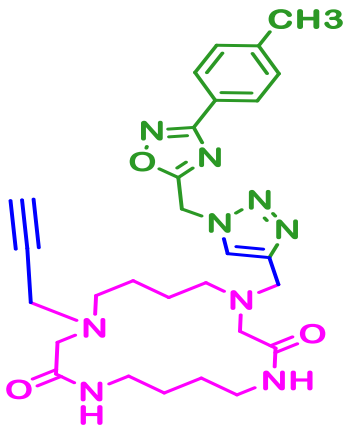
(C=N), 145.36, 131.85, 129.09, 128.92, 127.60, 125.82, 123.54, 78.19, 73.39, 58.45, 58.36, 58.31, 55.73, 54.98, 50.55, 45.33, 44.76, 38.12, 38.03, 27.60, 26.14, 25.93. HRMS: m/z (ESI-TOF, [M+H$^+$]) calcd for $C_{27}H_{35}N_9O_3$: 534.2941; found: 534.2920.



197a

4,9-Bis((1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl)methyl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione ***(197a)***

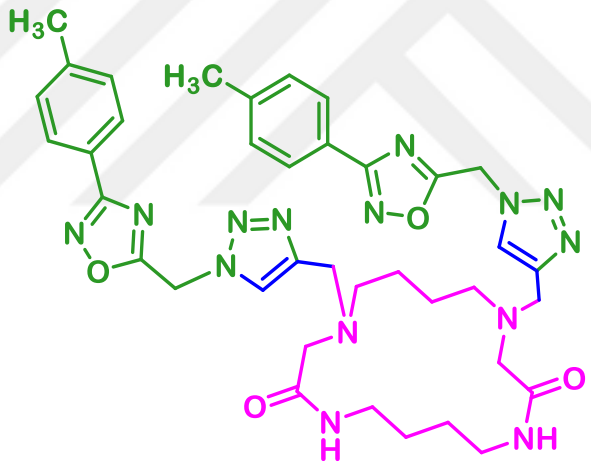
Yellow oil (100 mg, 73%). R_f: 0.378 (EtOAc/MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3348 (NH), 3136, 3055, 2939, 2862, 2831, 1662 (C=O), 1600, 1527, 1446, 1350, 1269, 1114. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.93 (m, 4H), 7.82 (s, 2H), 7.52–7.37 (m, 8H), 5.89 (s, 4H), 3.76 (s, 4H), 3.19 (s, 4H), 3.05 (s, 4H), 2.49 (s, 4H), 1.49 (d, *J* = 6.7 Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.47 (C=O), 171.37 (C=N), 168.86 (C=N), 145.52, 131.83, 129.41, 129.07, 128.88, 127.54, 125.80, 123.71, 58.50, 55.79, 50.52, 45.32, 38.12, 27.32, 26.03. HRMS: m/z (ESI-TOF, [M+H$^+$]) calcd for $C_{36}H_{42}N_{14}O_4$: 735.3592; found: 735.3581.



196b

4-(Prop-2-yn-1-yl)-9-((1-((3-(p-tolyl)-1,2,4-oxadiazol-5yl)methyl)-1H-1,2,3-triazol-5-yl)methyl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione ***(196b)***

White solid (30 mg, 44%). R_f: 0.480 (EtOAc/ MeOH, 5:1). Mp 146-147°C. IR (KBr, *v*: cm^{-1}): 3348 (NH), 3302 (C≡C-H), 3140, 3051, 2935, 2862, 1662 (C=O), 1597, 1531, 1450, 1269, 1230. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.86 (m, 2H), 7.77 (s, 1H), 7.25 (dd, *J* = 4.4, 3.5 Hz, 4H), 5.89 (d, *J* = 1.0 Hz, 2H), 3.81 (s, 2H), 3.33 (d, *J* = 9.4 Hz, 2H), 3.31–3.20 (m, 4H), 3.09 (d, *J* = 6.0 Hz, 4H), 2.54 (dd, *J* = 13.2, 6.8 Hz, 2H), 2.49 (t, *J* = 6.4 Hz, 2H), 2.38 (s, 3H), 2.18 (d, *J* = 1.4 Hz, 1H), 1.53 (s, 4H), 1.47 (dd, *J* = 18.9, 8.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.97 (C=O), 168.86, 142.19, 129.67, 127.42, 122.91, 77.98 (C≡C), 73.31 (C≡C), 61.75, 58.31, 55.55, 54.80, 50.52, 45.27, 44.58, 38.00, 27.48, 25.70, 21.58. LC-MS (ES^+): m/z (M+H) : 548. HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{28}H_{37}N_9O_3$: 548.3089; found: 548.3099.

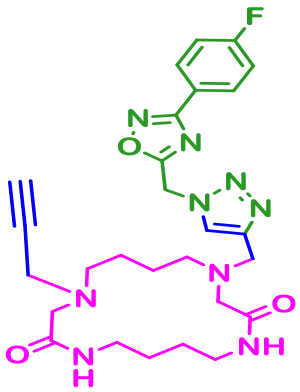


197b

4,9-Bis((1-((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl)methyl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione ***(197b)***

Yellow oil (50 mg, 53%). R_f: 0.375 (EtOAc /MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3348 (NH), 3136, 2939, 2862, 1658 (C=O), 1597, 1531, 1481, 1454, 1411, 1346, 1273, 1226. ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.6 Hz, 4H), 7.80 (s, 2H), 7.50 (t, *J* = 5.2 Hz, 2H), 7.26–7.24 (m, 4H), 5.88 (s, 4H), 3.78 (s, 4H), 3.23 (s, 4H), 3.07 (s, 4H), 2.51 (s, 4H), 2.37 (s, 6H), 1.52 (d, *J* = 10.7 Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.03 (C=O), 168.83, 142.16, 130.85, 127.40, 122.92, 58.44, 55.40, 50.55, 45.27, 38.09, 27.24, 25.83, 21.55. LC-MS (ES^+): m/z (M+H) : 763.

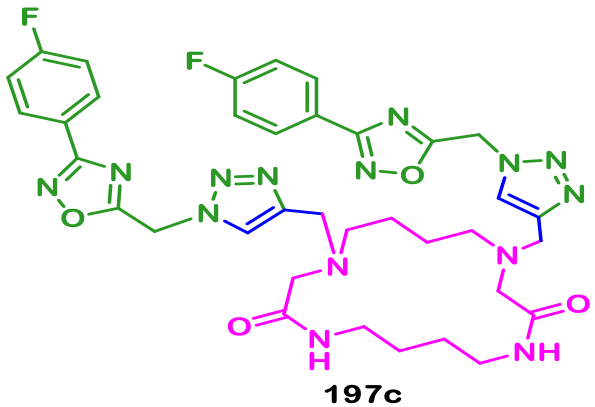
HRMS: m/z (ESI-TOF, [M+H$^+$]) calcd for C_{38} H_{46} $N_{14}O_4$: 763.3905; found: 763.3916.



196c

4-((1-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraaza cyclohexadecane-2,11-dione ***(196c)***

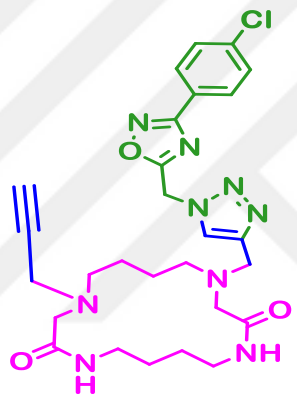
Yellow oil. (35 mg, 43%). R_f: 0.405 (EtOAc/MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3348, (NH), 3302, 3140, 2858, 1662 (C=O), 1585, 1531, 1481, 1450, 1419, 1342, 1226. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–7.98 (dd, *J* = 8.0, 5.6 Hz, 2H), 7.77 (s, 1H), 7.46 (br s, 1H), 7.26 (d, *J* = 6.4 Hz, 1H), 7.18–7.11 (t, *J* = 8.0 Hz, 2H), 5.91 (s, 2H), 3.80 (s, 2H), 3.35 (s, 2H), 3.25 (d, *J* = 9.2 Hz, 4H), 3.09 (s, 4H), 2.63–2.44 (dt, *J* = 16.0, 12.0, 5.6 Hz, 4H), 2.19 (s, 1H), 1.61–1.38 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.46 (C=O), 171.13, 168.13, 164.91 (d, *J* = 251.3 Hz, C-F), 145.40, 129.90, 129.81, 123.54, 122.09, 122.06, 116.47, 116.25, 78.21 (C≡C), 73.39 (C≡C), 58. 47, 58.32, 55.73, 55.06, 45.29, 44.84, 38.12, 38.04, 27.61, 27.58, 26.12, 25.96. HRMS: m/z (ESI-TOF, [M+H$^+$]) calcd for $C_{27}H_{35}FN_9O_3$: 552.2847; found: 552.2827.



197c

4,9-Bis((1-((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H1,2,3-triazol-5-yl) methyl)-1,4,9,12-tetraazacyclohexadecane 2,11-dione ***(197c)***

White solid (70 mg, 61%). R_f: 0.262 (EtOAc/ MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3348 (NH), 3140, 3055, 2939, 2862, 2831, 1666 (C=O), 1597, 1566,1527, 1469, 1408, 1342, 1265. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04–7.95 (m, 4H), 7.82 (d, *J* = 14.6 Hz, 2H), 7.53–7.44 (m, 2H), 7.12 (t, *J* = 8.2 Hz, 4H), 5.90 (s, 4H), 3.76 (d, *J* = 15.2 Hz, 4H), 3.21 (s, 4H), 3.04 (d, *J* = 15.1 Hz, 4H), 2.51 (s, 4H), 1.52 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.53 (C=O), 171.36, 168.08, 164.87 (d, *J* = 251.3 Hz, C-F), 145.58, 129.86, 129.77, 123.62, 122.07, 122.03, 116.44, 116.22, 60.49, 58.51, 55.87, 50.54, 45.28, 38.13, 27.35, 26.07. HRMS: m/z (ESI-TOF, $[M+H^+]$) calcd for $C_{36}H_{41}F_2N_{14}O_4$: 771.3401; found: 771. 3391.

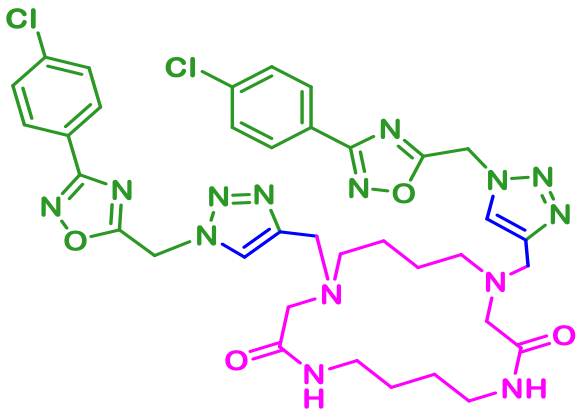


196d

4-((1-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraaza cyclohexadecane-2,11-dione ***(196d)***

Yellow oil (30 mg, 30%). R_f: 0.420 (EtOAc/ MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3348 (NH), 3302, 3136, 3055, 2935, 2862, 1662 (C=O), 1597, 1527, 1465, 1408, 1384, 1342, 1265. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.93 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.76 (s, 1H), 7.47–7.41 (dd, *J* = 8.4, 1.2 Hz, 3H), 7.29–7.26 (m, 1H), 5.91 (s, 2H), 3.81 (s, 2H), 3.40–3.01 (m, 5H), 2.60–2.48 (dt, *J* = 20.8, 12.0, 5.6 Hz, 4H), 2.21–2.16 (m, 2H), 1.90–1.65 (br s, 4H), 1.60–1.15 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.63 (C=O), 171.39, 168.13, 145.62, 138.04, 129.42, 128.88, 124.30, 123.60, 78.23 (C≡C), 73.37 (C≡C), 58.49, 58.42, 55.73, 55.11, 54.93, 50.46, 45.28, 44.88, 44.73, 38.13, 38.04, 37.98, 29.78, 27.85, 27.63, 27.58, 26.13, 26.09, 25.99.

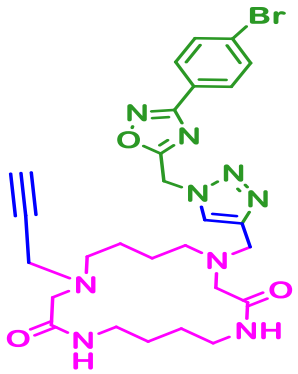
HRMS: m/z (ESI-TOF, [M+H$^+$]) calcd for $C_{27}H_{35}ClN_9O_3$: 568.2551; found: 568.2539.



197d

4,9-Bis((1-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-1,4,9,12-tetraazacyclohexadecane-2,11 -dione ***(197d)***

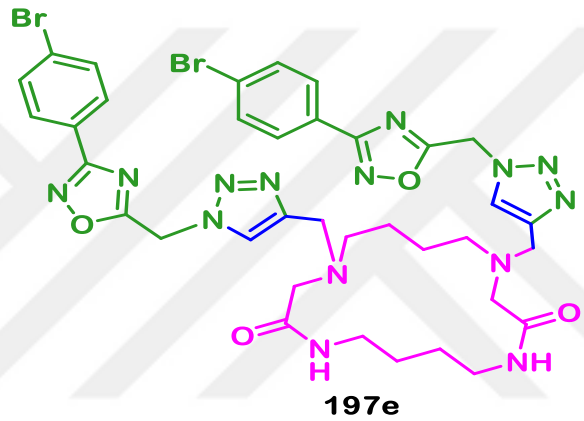
Yellow oil (60 mg, 42%). R_f: 0.320 (EtOAc/MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3348 (NH), 3136, 2928, 2854, 1658 (C=O), 1597, 1570,1527, 1465, 1408, 1342, 1265. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.89 (m, 4H), 7.80 (s, 2H), 7.51–7.45 (br t, *J* = 5.6 Hz, 2H), 7.44–7.38 (dd, *J* = 8.8, 2.4 Hz, 4H), 5.89 (s, 4H), 3.77 (s, 4H), 3.21 (br s, 4H), 3.05 (br s, 4H), 2.50 (br s, 4H), 1.21 (br s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.63 (C=O), 171.39, 168.13, 145.62, 138.04, 129.42, 128.88, 124.30, 123.60, 58.52, 55.89, 50.56, 45.28, 38.15, 31.99, 30.36, 29.77, 29.73, 29.69, 29.58, 29.43, 29.23, 27.35, 26.08. HRMS: m/z (ESI-TOF, [M+H$^+$]) calcd for $C_{36}H_{41}Cl_2N_{14}O_4$: 803.2812; found: 803.2804.



196e

4-((1-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraaza cyclohexadecane-2,11-dione ***(196e)***

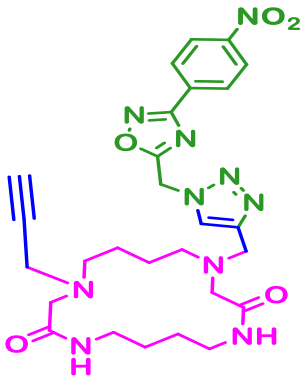
Yellow oil (35 mg, 38%). R_f: 0.410 (EtOAc/ MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3425, 3360 (NH), 3302, 3055, 2935, 2866, 1666 (C=O), 1597, 1527, 1469, 1423, 1404, 1342, 1265. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.87 (d, *J* = 8.4 Hz, 2H), 7.76 (br s, 1H), 7.62–7.58 (d, *J* = 8.4 Hz, 2H), 7.45 (br s, 1H), 7.28–7.22 (m, 1H), 5.91 (s, 2H), 3.82 (s, 2H), 3.57 (s, 1H), 3.36 (s, 1H), 3.27 (d, *J* = 16.0 Hz, 4H), 3.09 (s, 4H), 2.61–2.48 (dt, *J* = 22.8, 16.4, 6.4 Hz, 4H), 1.70 (br s, 6H), 1.60–1.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.46, 171.12, 167.99, 132.42, 132.23, 129.09, 126.52, 124.77, 123.47, 78.04 (C≡C), 74.10 (C≡C), 58.49, 58.34, 55.29, 50.48, 45.29, 44.88, 38.13, 38.04, 27.64, 27.58, 26.11, 25.98. HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{27}H_{35}BrN_9O_3$: 612.2046; found: 612.2026.



197e

4,9-Bis((1-((3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-1,4,9,12-tetraazacyclohexadecane 2,11-dione ***(197e)***

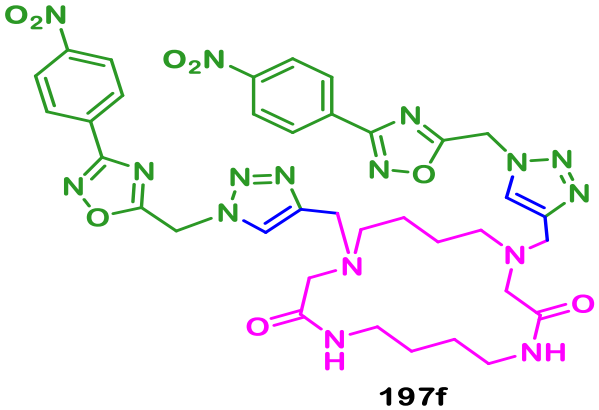
Yellow oil (95 mg, 71%). R_f: 0.273 (EtOAc/MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3348 (NH), 3140, 3055, 2939, 2862, 2831, 1666 (C=O), 1597, 1566, 1527, 1469, 1408, 1342, 1265. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.85 (m, 4H), 7.79 (s, 2H), 7.59 (dd, *J* = 11.1, 3.4 Hz, 4H), 7.49 (t, *J* = 5.3 Hz, 2H), 5.91 (s, 4H), 3.80 (s, 4H), 3.24 (s, 4H), 3.08 (s, 4H), 2.53 (s, 4H), 1.53 (d, *J* = 9.6 Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.59 (C=O), 171.32, 168.26, 132.41, 129.06, 126.52, 124.75, 123.52, 58.54, 55.89, 50.62, 45.28, 38.17, 27.36, 26.08. HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{36}H_{41}Br_2N_{14}O_4$: 891.1802; found: 891.1828.



196f

4-((1-((3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraazacyclo hexadecane-2,11-dione ***(196f)***

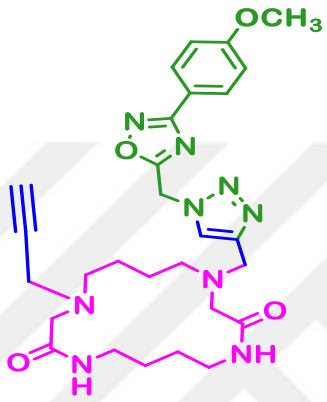
Yellow oil (45 mg, 35%). R_f: 0.522 (EtOAc/MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3448 (NH), 3302, 3140, 3101, 2939, 2862, 1662 (C=O), 1612, 1531, 1450, 1415, 1342, 1292. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.9 Hz, 2H), 8.20 (dd, *J* = 7.3, 6.7 Hz, 2H), 7.79 (s, 1H), 7.41 (t, *J* = 5.2 Hz, 1H), 7.29–7.25 (m, 1H), 5.96 (s, 2H), 3.81 (s, 2H), 3.35 (d, *J* = 1.7 Hz, 2H), 3.32–3.20 (m, 4H), 3.06 (d, *J* = 12.5 Hz, 4H), 2.53 (dt, *J* = 13.1, 5.9 Hz, 4H), 2.19 (s, 1H), 1.53 (s, 4H), 1.52–1.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.37 (C=O), 171.22, 171.15, 170.92, 167.41, 149.78, 145.51, 131.68, 128.67, 124.31, 123.64, 78.25 (C≡C), 73.38 (C≡C), 58.51, 58.29, 50.29, 45.24, 45.00, 38.13, 38.04, 27.64, 27.49, 26.07. HRMS: m/z (ESI-TOF, [M+H]) calcd for $C_{27}H_{35}N_{10}O_5$: 579.2792; found: 579.2771.



197f

4,9-Bis((1-((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-1,4,9,12-tetraazacyclohexadecane-2, 11-dione ***(197f)***.

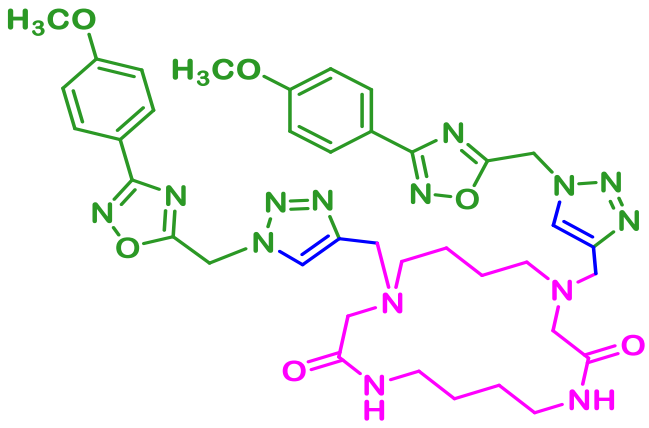
Yellow solid (75 mg, 41%). R_f: 0.370 (EtOAc/ MeOH, 5:1). Mp 133–134°C. IR (KBr, *v*: cm^{-1}): 3348 (NH), 3136, 2928, 2854, 1658 (C=O), 1597, 1570,1527, 1465, 1408, 1342, 1265. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.0 Hz, 4H), 8.18 (d, *J* = 8.4 Hz, 4H), 7.82 (s, 2H), 7.48 (t, *J* = 5.2 Hz, 2H), 5.96 (s, 4H), 3.81 (s, 4H), 3.21 (br s, 4H), 3.06 (s, 4H), 2.53 (s, 4H), 1.53 (br s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.36 (C=O), 171.38, 167.39, 149.76, 145.62, 131.65, 128.65, 124.30, 123.65, 58.48, 55.98, 50.54, 45.25, 38.16, 27.37, 26.09. HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{36}H_{41}N_{16}O_8$: 825.3293 ; found: 825.3261.



196g

4-((1-((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetraaza cyclohexadecane-2,11-dione ***(196g).***

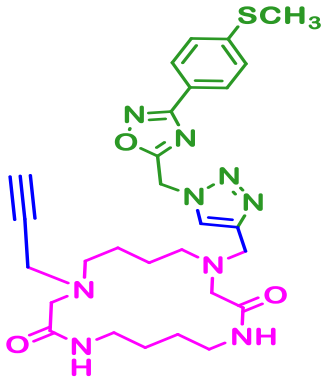
White solid (30 mg, 36%). R_f: 0.300 (EtOAc/MeOH, 5:1). Mp 124–125 °C. IR (KBr, *v*: cm^{-1}): 3441, 3348 (NH), 3302, 3136, 3059, 2939, 2839, 1662 (C=O), 1573, 1531, 1481, 1423, 1346, 1257. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.92 (m, 2H), 7.76 (s, 1H), 7.48 (t, *J* = 5.3 Hz, 1H), 7.25 (t, *J* = 4.3 Hz, 1H), 6.96–6.93 (m, 2H), 5.88 (s, 2H), 3.82 (t, *J* = 3.3 Hz, 3H), 3.80 (s, 2H), 3.34 (d, *J* = 1.2 Hz, 2H), 3.26 (d, *J* = 14.7 Hz, 4H), 3.08 (d, *J* = 3.1 Hz, 4H), 2.52 (dt, *J* = 13.0, 6.0 Hz, 4H), 2.18 (d, *J* = 0.9 Hz, 1H), 1.53 (s, 4H), 1.50–1.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.01 (C=O), 171.19, 168.62, 162.39, 145.37, 129.26, 123.51, 118.19, 114.47, 78.19 (C≡C), 72.87 (C≡C), 58.47, 55.76, 54.96, 53.55, 50.54, 45.32, 44.72, 38.10, 38.01, 27.63, 26.18, 25.93. HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{28}H_{37}N_9O_4$: 564.3047; found: 564.3041.



197g

4,9-Bis((1-((3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione ***(197g)****.*

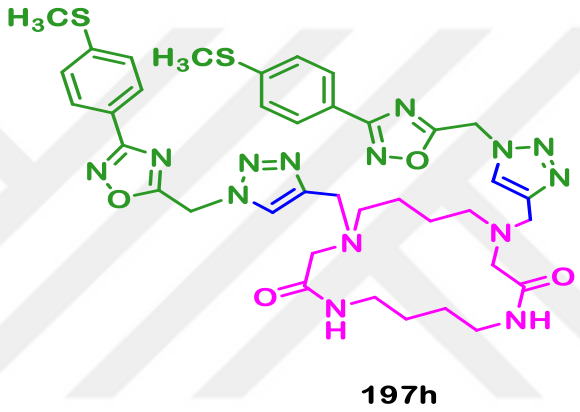
White solid (54 mg, 46%). R_f: 0.180 (EtOAc/ MeOH, 5:1). Mp 191–192 °C. IR (KBr, *v*: cm^{-1}): 3332 (NH), 3124, 2935, 2839, 1658 (C=O), 1612, 1597, 1573,1527, 1481, 1346, 1303. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.2 Hz, 4H), 7.79 (s, 2H), 7.46 (dd, *J* = 12.7, 7.3 Hz, 2H), 6.91 (t, *J* = 7.5 Hz, 4H), 5.86 (s, 4H), 3.81 (d, *J* = 0.8 Hz, 6H), 3.78–3.74 (m, 4H), 3.21 (s, 4H), 3.05 (s, 4H), 2.49 (s, 4H), 1.50 (d, *J* = 11.0 Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.10 (C=O), 171.33, 168.57, 162.35, 145.57, 129.22, 123.59, 118.18, 114.44, 58.56, 55.78, 55.50, 50.55, 45.31, 38.11, 27.37, 26.07. HRMS: m/z (ESI-TOF, $[M+H^+]$) calcd for $C_{38}H_{46}N_{14}O_6$: 795.3803; found: 795.3804.



196h

4-((1-((3-(4-(Methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl) methyl)-9-(prop-2-yn-1-yl)-1,4,9,12-tetra azacyclohexadecane-2,11-dione ***(196h).***

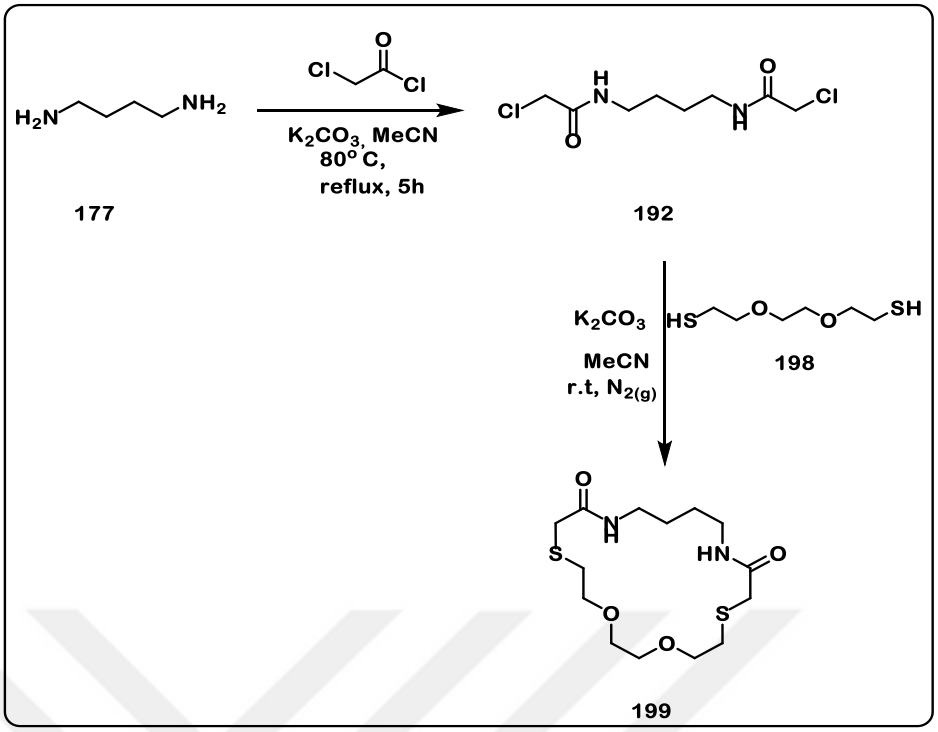
Yellow oil (40 mg, 38%). R_f: 0.522 (EtOAc/MeOH, 5:1). IR (KBr, *v*: cm^{-1}): 3448 (NH), 3302 (C≡CH), 3136, 3055, 2931, 2858, 1662 (C=O), 1597, 1527, 1469, 1408, 1346, 1269. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.76 (s, 1H), 7.47 (t, *J* = 5.3 Hz, 1H), 7.27 (t, *J* = 6.1 Hz, 3H), 5.90 (s, 2H), 3.81 (s, 2H), 3.35 (t, *J* = 3.9 Hz, 2H), 3.26 (d, *J* = 15.1 Hz, 4H), 3.09 (d, *J* = 3.7 Hz, 4H), 2.59–2.53 (m, 3H), 2.52–2.46 (m, 4H), 2.19 (dd, *J* = 2.2, 1.5 Hz, 1H), 1.54 (s, 4H), 1.52–1.42 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.29 (C=O), 171.38, 168.56, 145.61, 143.90, 127.78, 125.79, 123.61, 121.92, 78.22 (C≡C), 73.37 (C≡C), 58.48, 55.74, 55.02, 50.53, 45.32, 44.78, 38.11, 38.03, 27.61, 26.16, 25.96, 15.04 (SCH_3). HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{28}H_{37}N_9O_3S$:580.2818; found: 580.2803.

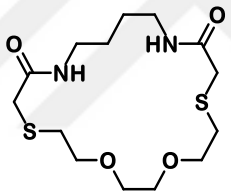


197h

4,9-Bis((1-((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-5-yl)methyl)-1,4,9,12-tetraazacyclohexadecane-2,11-dione ***(197h)***

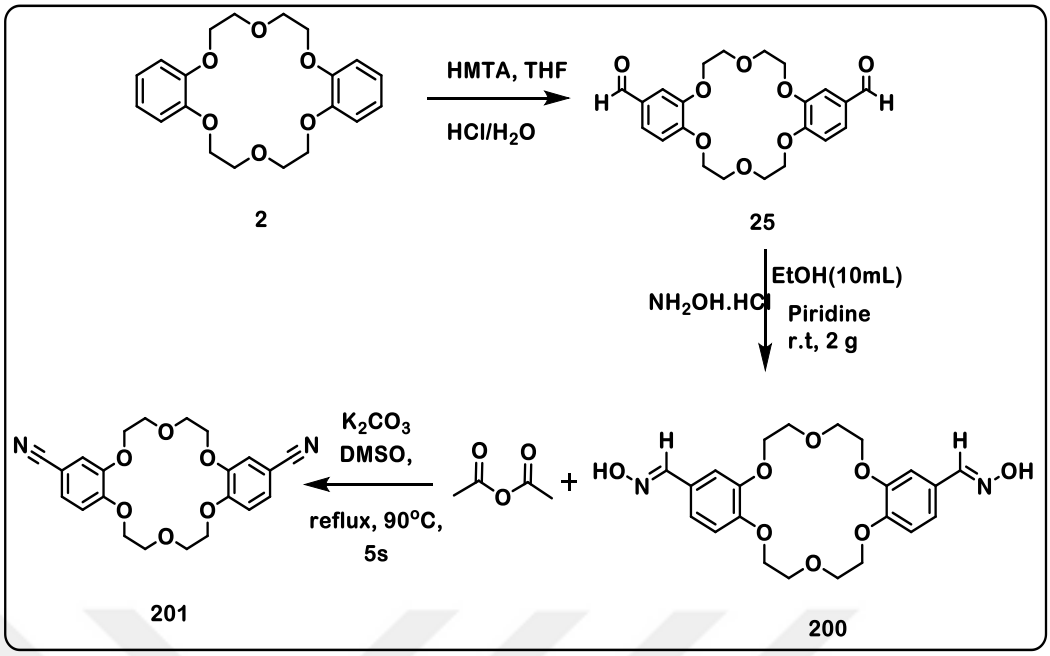
White solid (60 mg, 41%). R_f: 0.370 (EtOAc/MeOH, 5:1). Mp 184-185 °C. IR (KBr, *v*: cm^{-1}): 3441 (NH), 3147, 2924, 2854, 1647 (C=O), 1593, 1527, 1465, 1465, 1408, 1384, 1346. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 4H), 7.80 (s, 2H), 7.48 (t, *J* = 5.5 Hz, 2H), 7.27–7.24 (m, 4H), 5.88 (s, 4H), 3.76 (s, 4H), 3.21 (s, 4H), 3.05 (s, 4H), 2.49 (dd, *J* = 11.4, 3.4 Hz, 10H), 1.50 (d, *J* = 10.8 Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.29 (C=O), 171.38, 168.56, 145.61, 143.90, 127.78, 125.79, 123.61, 121.92, 58.56, 55.82, 50.56, 45.31, 38.13, 27.35, 26.07, 15.01 (SCH_3). HRMS: m/z (ESI-TOF, [M+H^+]) calcd for $C_{38}H_{46}N_{14}O_4S_2$: 827.3346; found: 827.3316.

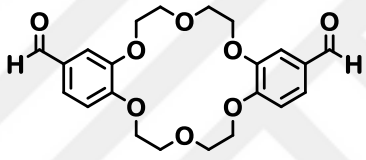




Synthesis of the 1,4-dioxa-7,18-dithia-10,15-diazacycloicosane-9,16-dione (199)

N,*N*′-(Butane-1,4-diyl)bis(2-chloroacetamide) **192** (2.268 g, 9.41 mol)**,** 2,2'-(ethane-1,2-diyl bis (oxy))diethanethiol **198** (1.714 g, 9.41 mol) and K_2CO_3 (5.198 g, 37.63 mol) were mixed in MeCN and stirred at room temperature for 2d. When reaction completed, MeCN was evaporated under the reduced pressure. the crude product was purified by column chromatography (EtOAC/MeOH, 5:1) to give a white solid (2.100 g, 64%). R_f : 0.311 (EtOAc/MeOH, 5:1). M.p: 115–116 ^oC. IR (KBr, *v*:cm^{-1}): 3294 (NH), 3074, 2924, 2866, 2746, 1651 (C=O), 1546, 1438, 1419, 1307, 1242, 1099, 1041, 979, 883, 732, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 2H), 3.70 (t, *J* = 5.4 Hz, 4H), 3.61 (d, *J* = 0.8 Hz, 4H), 3.31 (dd, *J* = 6.3, 3.2 Hz, 4H), 3.26 (s, 4H), 2.74 (t, *J* = 5.4 Hz, 4H), 1.59 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.89, 70.87, 70.10, 39.24, 36.56, 32.43, 26.84. LC-MS (ES^+): *m/z* (M+Na) : 373.

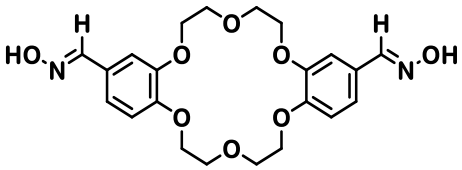




25

Synthesis of the 6,7,9,10,17,18,20,21-octahydrodibenzo[b,k][1,4,7,10,13, 16]hexa oxacyclo octadecine-2,14-dicarbaldehyde (25) (Jagadale et al., 2015)

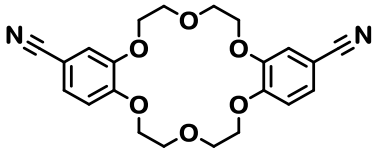
A mixture of dibenzo-18 –crown-6 **2** (1 mol, 3.60 g) and TFA (18mL) was stirred under $N_{2(g)}$ for 1h then HMTA (2.5 mol, 3.50 g) was added and the reaction mixture was refluxed at 80 ^{o}C with stirring for 17h. Then the reaction mixture was cooled to room tempereature and additional TFA (36.5 ml) was added to the mixture and refluxed again at 95 ^{o}C for 1.5h. After completion of reaction the mixture it was cooled to room temperature and water was added to the mixture. A precipitate occurred and it was filtered off then heated with acetone it was filtered once again and orange product was yielded (900 mg, 22 %). R_f : 0.29 (MeOH). M.p: 194–195 ^{o}C (decomp.). IR (KBr, v:cm^{-1}): 3190, 3070 (Ar. C-H) 2928, 2835, (Aliph.C-H), 1685 (C=O), 1589, 1438, 1338, 1138, 1053. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 2H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.48 (t, *J* = 3.3 Hz, 1H), 7.33 (d, *J* = 1.8 Hz, 2H), 7.13 (s, 1H), 7.11 (s, 1H), 4.21 – 4.04 (m, 8H), 3.82 (s, 8H). ^{13}C NMR (100 MHz, , DMSO-d_6): δ 191.95 (C=O), 153.81, 148.75, 126.63, 112.19, 110.28, 69.13, 68.52, 68.07. LC-MS (ES^{+}): *m/z* (M+Na): 439.



200

Synthesis of the (1*E*,1'*E*)-14-((E)-(hydroxyimino)methyl)-6,7,9, 10,17,18, 20,21-octahydrodibenzo[b,k][1,4,7,10,13,16]hexaoxacyclooctadecine-2-carbaldehydeoxime (200)

6,7,9,10,17,18,20,21-octahydrodibenzo[b,k][1,4,7,10,13,16]hexaoxacyclo octadecine-2,14-dicarbaldehyde **25** (1.93 mmol, 0.805 g) was dissolved in pyridine (5ml) and EtOH (50 ml) mixture. Then hydroxylamine hydrochloride (6.19 mmol, 0.429 g) was added which was dissolved in water (2 ml) and the reaction mixture was stirred for 2d. It was extracted with (DCM/H_2O) then the crude product was recrystallized with EtOH to give a light orange solid (600 mg, 70%). R_f : 0.22 (MeOH). M.p: 149–150^{o}C (decomposed). IR (KBr, v:cm^{-1}) 3417, 3282 (O-H), 3086 (Ar.C-H) 2928, 2889 (Aliph.C-H), 1604 (C=N), 1519, 1435, 1330. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 2H), 7.98 (s, 2H), 7.13 (d, *J* = 1.5 Hz, 1H), 7.04 (t, *J* = 3.1 Hz, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.93 (d, *J* = 6.3 Hz, 1H), 6.89 (d, *J* = 6.6 Hz, 1H), 4.04 (s, 8H), 3.80 (s, 8H).^{13}C NMR (100 MHz, DMSO-d_6): δ 149.37, 148.49, 126.19, 120.75, 112.54, 109.39, 69.51, 67.75. LC-MS (ES$^+$): *m/z* (M+H): 447.



201

Synthesis of the 6,7,9,10,17,18,20,21-octahydrodibenzo[b,k][1,4,7,10, 13,16]hexa oxacyclooctadecine-2,14-dicarbonitrile (201)

(*1Z,1'Z*)-14-((*Z*)-(hydroxyimino)methyl)-6,7,9,10,17,18,20,21octahydrodi benzo[b,k][1,4,7,10,13,16] hexaoxacyclooctadecine-2-carbaldehyde oxime **(200)** (1.345 mmol, 600 mg), acetic anhydride (0.532ml) and K_2CO_3 (5.65 mmol, 779 mg) mixed in DMSO at room temperature and stirred about for 30 min. Then it was refluxed at 100^{o}C for 7h than heating was stopped and the mixture was stirred

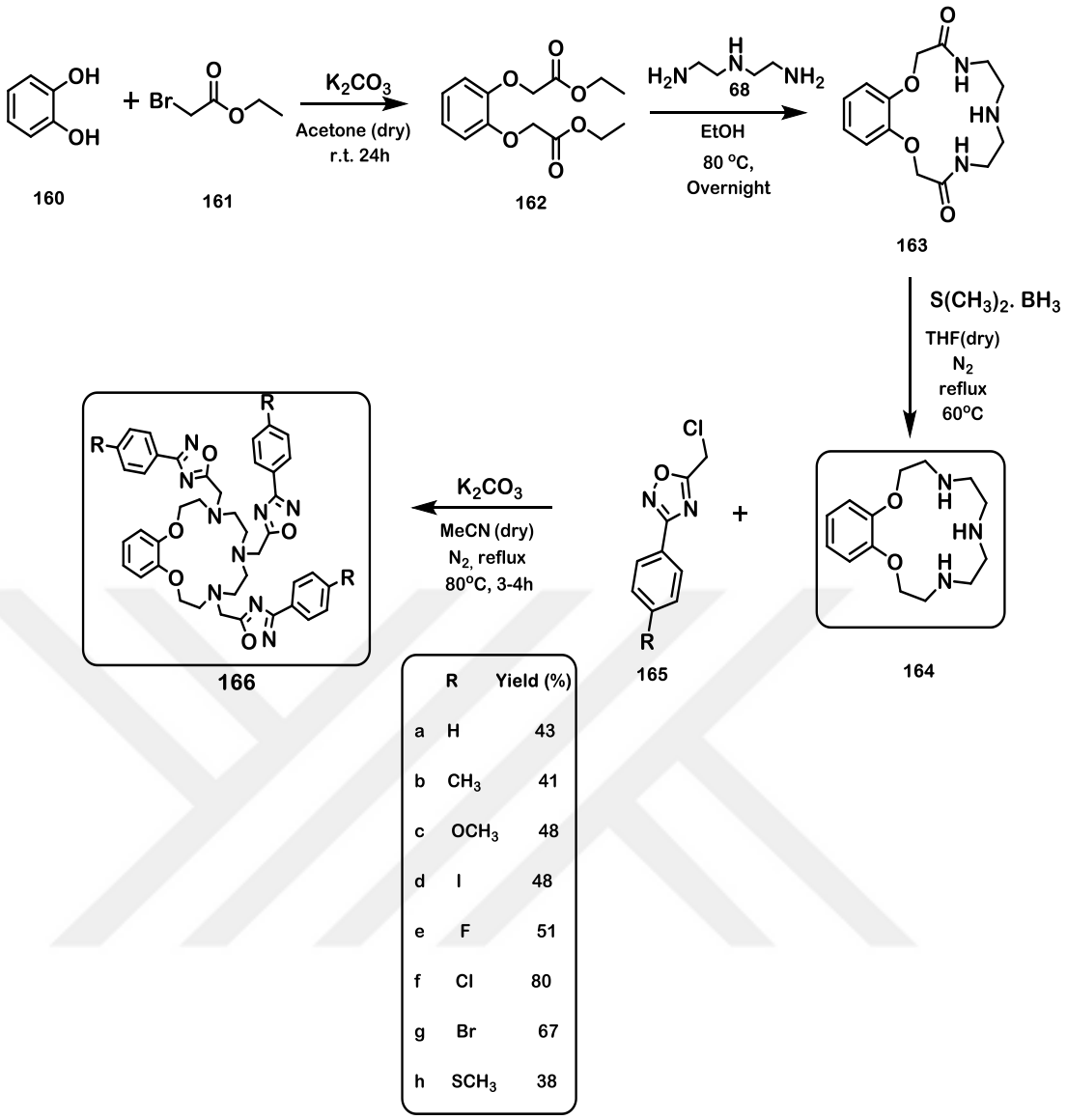
overnight at room temperature. After reaction was completed, the mixture was poured into the cold water than precipitate formed was extracted with (DCM/H_2O) to give a yellow solid. Recrystallized with acetone to give a yellow solid (321 mg, 57 %). R_f :0.13 (MeOH). M.p: 189–190 ^oC (decomposed). IR (KBr, v:cm^{-1}): 3082 (Ar. C-H) 2935, 2872, 2852 (Aliph.C-H), 2222 (C≡N), 1446, 1329, 1249, 1138, 1060, 976, 952, 864, 783, 617. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69-6.89(m, 6H), 438-3.83(m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.35 (C-O), 148.52 (C-O), 126.63 (C=C), 119.33 (C≡N), 114.90, 112.04 103.93(-C=C),69.33 (-CH_2-). LC-MS (ES^+): *m/z* (M+Na): 433.

4. RESULTS AND DISCUSSION

4.1 Synthesis of Crown Ethers and Azacrowns bearing 1,2,4-Oxadiazole Moieties

Taking into account of the literature knowledge that we have already referred the coverage of this part of our work is basically related to synthesis of benzo-di/triazacrown ethers with *p*-phenylsubstituted-1,2,4-oxadiazoles **(166a-h)**, **(168a-i)** and a novel synthetic route for the benzotriazacrown ether **164**.

The azacrown **163** has been obtained by using a procedure which has been reported previously by Kumar and his coworkers in 1992. In order to achieve our goal we have focused on the reduction of macrocycle **163** by using dimethylsulfide-borane complex. To our best knowledge, there have not been any reported synthetic route on the reduction of azacrown **163** by using DMS.BH_3. Thus, the product **164** is a new compound. In the second step, the reduced compound **164** was reacted with *p*-phenylsubstituted-5-(chloromethyl)-3-phenyl-1,2,4-oxadiazoles **(165a-h)** (Dürüst, et al., 2012, 2015) carrying both electron-releasing and electron-withdrawing groups (Scheme 4.36).



	R	Yield (%)
a	H	43
b	CH_3	41
c	OCH_3	48
d	I	48
e	F	51
f	Cl	80
g	Br	67
h	SCH_3	38

Scheme 4.32. Synthesis of the benzotriazacrowns with 1,2,4-oxadiazole group (**166a-h**)

The structures of the newly synthesized **164** and **166(a-h)** have been successfully characterised on the basis of IR, ^{1}H-NMR, ^{13}C-NMR, LC-MS spectra and HRMS measurements.

Primary indication of the product **164** is the dissappearance of the carbonyl groups in the IR spectra.The appearance of the two new methylenic protons and carbons regarding three oxadiazolylmethyl groups at around 2.98 ppm as triplet in the ^{1}H NMR and ^{13}C NMR spectra, respectively. Upon the examination of the ^{1}H NMR spectrum of compound **163**, methylene and two NH protons which are closer to the carbonyl have appeared respectively at 4.46 and 7.79 ppm as singlets, After

reduction, these protons shift to 4.07 and 2.50 ppm respectively, due to lack of carbonyl groups as we can see in Figure 4.13.The LC-MS and HRMS spectra also confirmed the expected product.

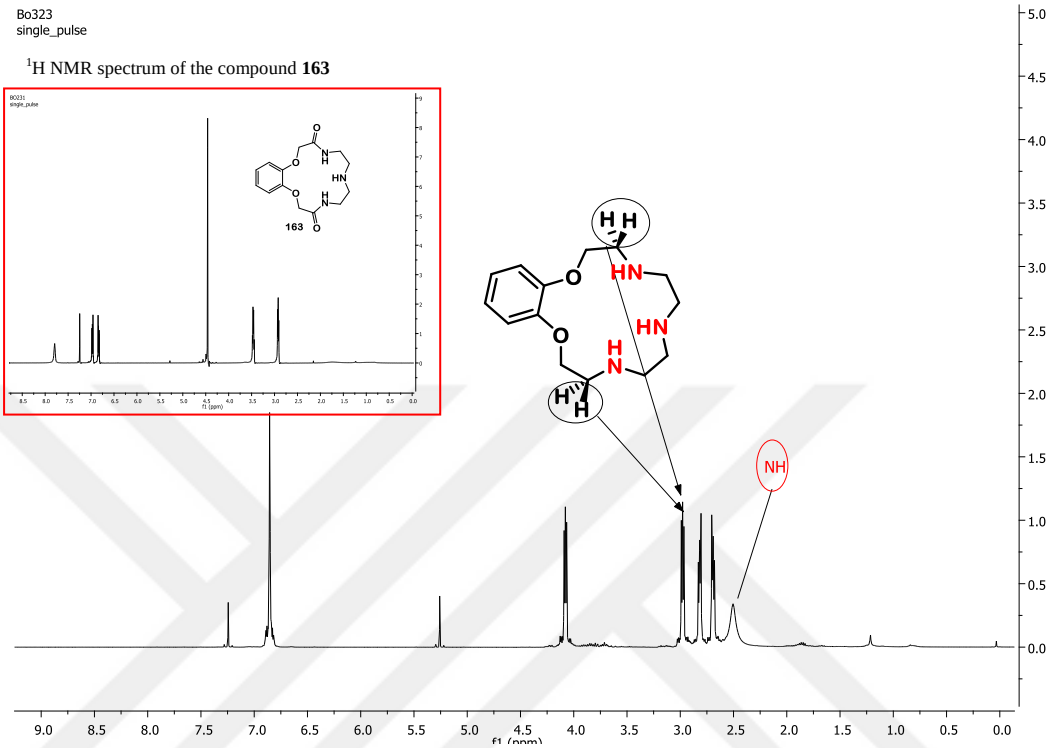


Figure 4.13. ^{1}H NMR spectrum of compound **164**

N-Substitution of benzodioxatriaza crown **164** by 5-chloromethyl-1,2,4-oxadiazoles **165(a-h)** gave *N,N',N''*-trisubstituted products **166(a-h).** The first confirmative data for the new products were the disappearance of NH absorptions in the IR spectra. Secondly, in the proton NMR spectra of these products, along with aromatic protons arising from both oxadiazole and benzodioxatriaza crown, signals at around 8.04-6.87 ppm were evidences. ^{13}C NMR signals of methylene carbons have appeared at around 52 ppm. All these findings have been supported by the LC–MS spectra at which base peak was observed at *m/z* 740 for the compound **166a**, as a representative example (Figure 4.14 and 4.15). These are supported by the HRMS measurements.

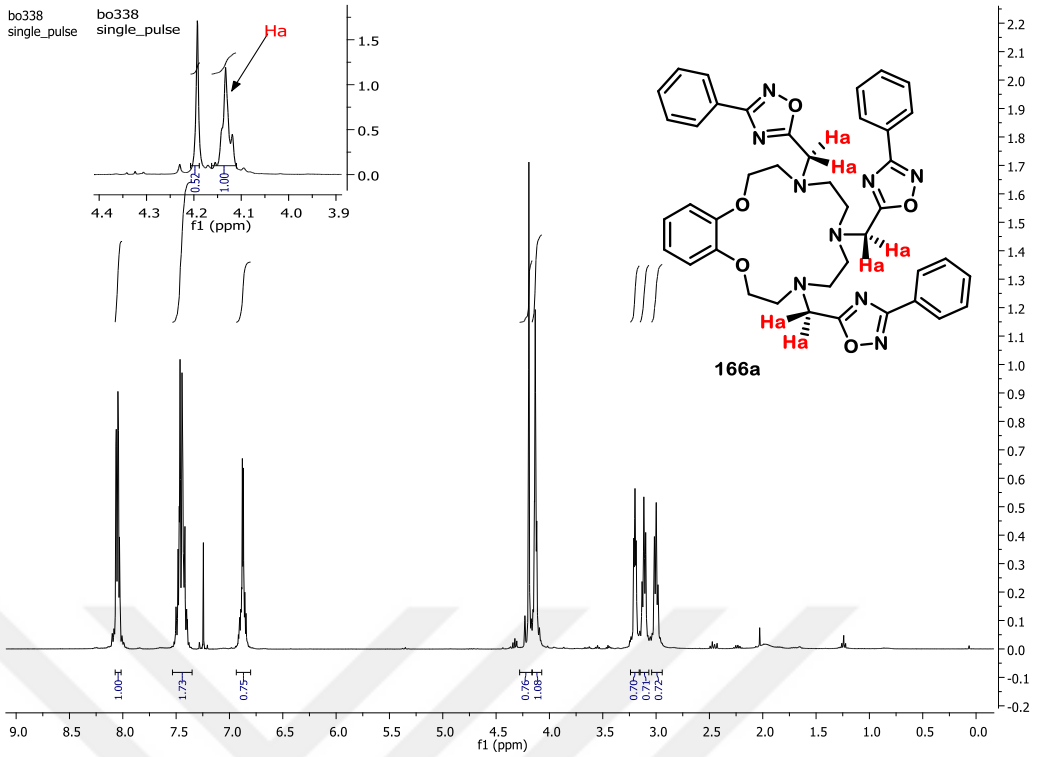


Figure 4.13. ^{1}H NMR spectrum of compound **166a**

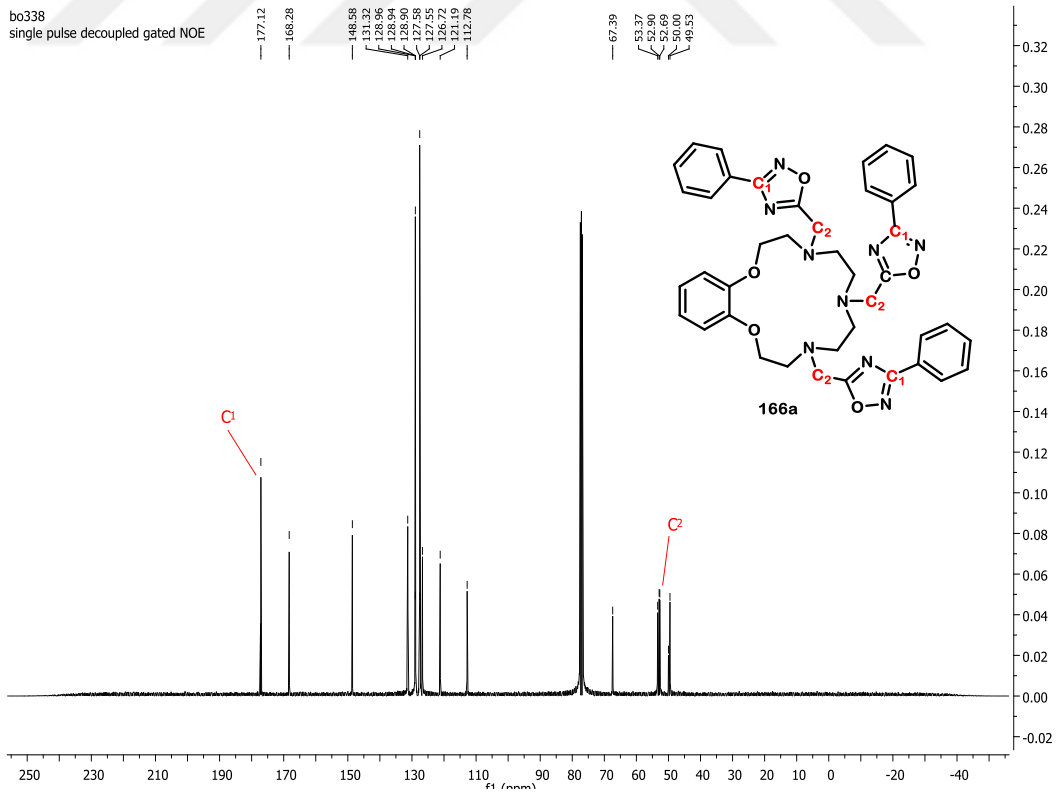
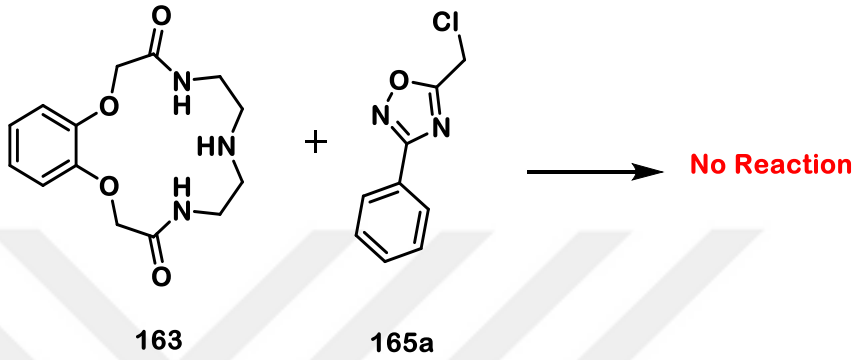


Figure 4.14. ^{13}C NMR spectrum of compound **166a**

In addition, the crown ether **163** was reacted with 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazoles **165a** (Scheme 4.37). The reaction of these two reagents did not end up with any anticipated product. Due to this failed attempt, the reactants were further tried to react in different conditions but no reaction occurred at all (Table 4.1). This may be attributed to a strong intramolecular hydrogen bonding interaction within macrocyclic ether **163** diminishing the availability of nitrogen lone pair.



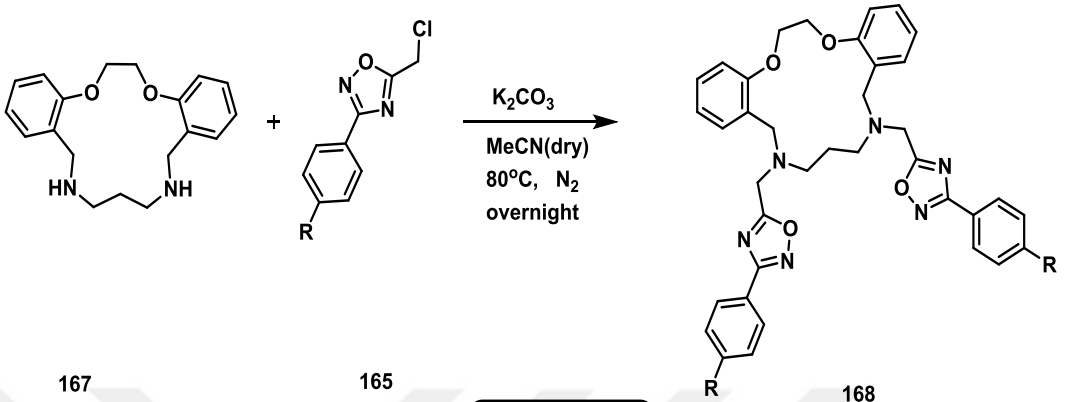
Scheme 4.33. Reaction of azacrown **163** with 1,2,4-oxadiazole **165a**

Table 4.1. Different tried conditions for reaction of the compounds **163, 165a**

Type	Base	Solvent	Temperature (^{o}C)	Product
1	K_2CO_3	MeCN	80	No Reaction
2	K_2CO_3	MeCN	R.T	NoReaction
3	K_2CO_3	MeCN/H_2O	120	No Reaction
4	K_2CO_3	DMF	100	No Reaction
5	Et_3N	MeCN	80	No Reaction
6	NaOH	MeCN	80	No Reaction
7	NaH	THF	65	No Reaction

The second part of this work utilizes dibenzodioxadiazacrown **167** which has been subject to numerous works as a key starting material (Hogberg and Cram, 1975; Kulikov et al., 2005; Gray, et al., 2007; Sharghi and Zare, 2006). In this regard, 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **165a** was reacted with benzodioxadiaza

crown **163** under reflux in acetonitrile. Then, *N*,*N*-disubstitution of benzodioxa diazacrown with the 5-chloromethyl-1,2,4-oxadiazoles **165(a-i)** were performed and eight novel products were obtained through this reaction (Scheme 4.38).



	R	Yield(%)
a	H	92
b	CH3	95
c	F	89
d	Cl	84
e	Br	42
f	NO_2	22
g	OCH_3	70
h	SCH_3	44
i	CN	68

Scheme 4.34. Synthesis of the *p*-substituted 6,10-bis((3-phenyl-1,2,4-oxadia methyl)-6,7,8,9,10,11,17,18-octahydro-*5H*-dibenzozol-5-yl [e,n][1,4]dioxa[8, 12]diazacyclo pentadecine **168(a-i)**

All these products were identified by their physical and spectral characteristics. Thus, in the ^{1}H NMR spectrum of the compound **168f** (Figure 4.16) sixteen protons can be observed at around 8.3–6.9 ppm and two methyl protons of the dibenzodixoadiaza appeared at around 3.97 ppm as singlet. The other singlets arising from methylenic protons; the one from 1,2,4-oxadiazoles and another one which are closer to nitrogens originated from the crown ether resonated at around 3.95–3.86 ppm. In the ^{13}C NMR spectrum, seventeen relevant different carbons are present (Figure 4.16) and the LC–MS spectrum showed molecular ion as base peak at m/z 719 (Figure 4.19). The physical and spectral characteristics have also been

supported by HRMS measurements for **168(a-i)**. In addition, recrystallization of compound **168d** from $CHCl_3$ gave single fine crystals and structure of this compound was elucidated by single crystal X–Ray diffraction (Figure 4.18).

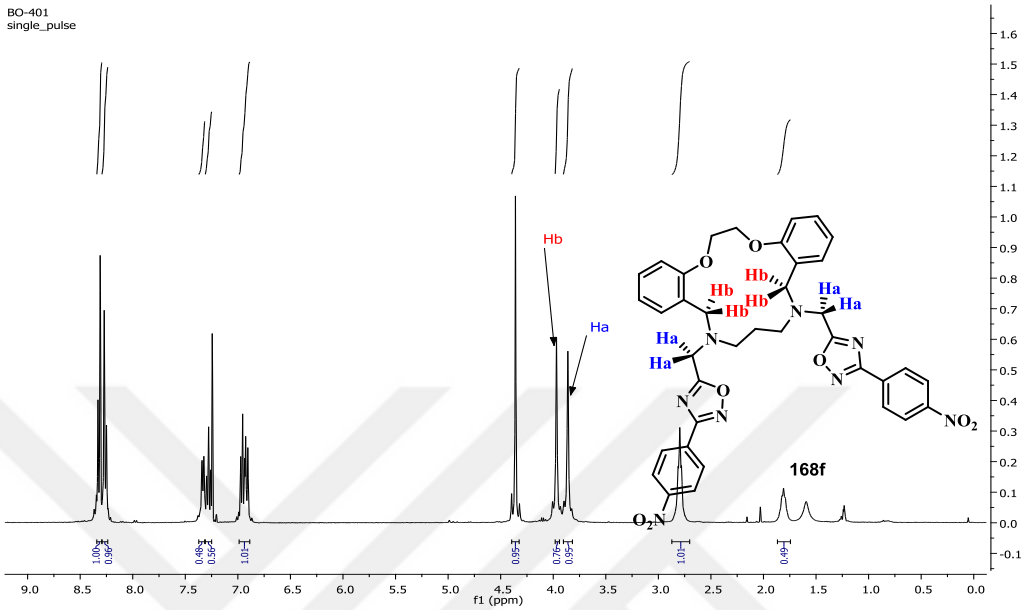


Figure 4.15. ^{1}H NMR spectrum of compound **168f**

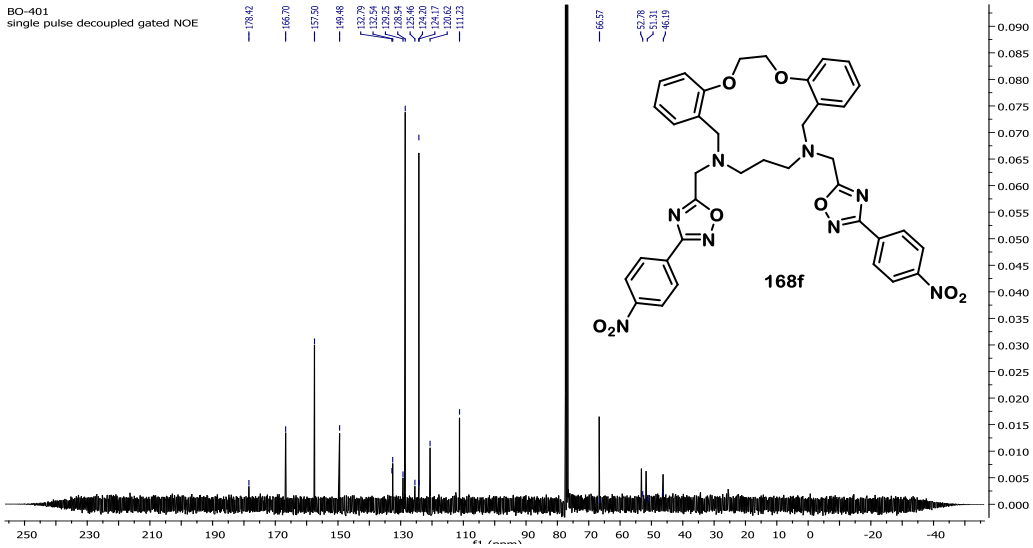


Figure 4.16. ^{13}C NMR spectrum of compound **168f**

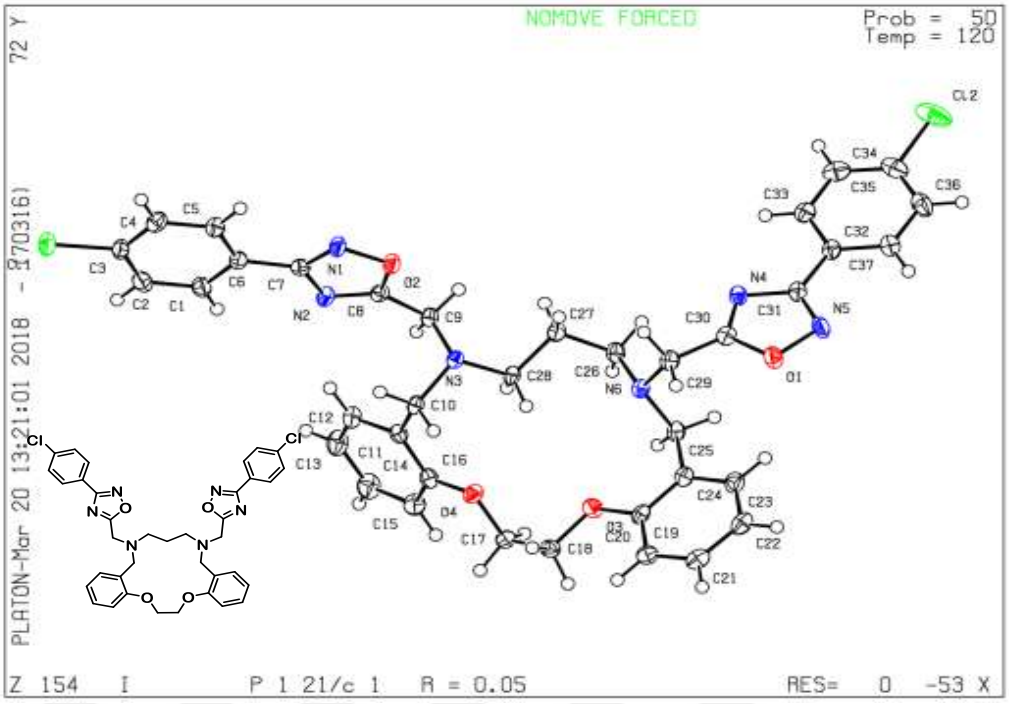


Figure 4.17. X-ray ORTEP view of compound **168d**

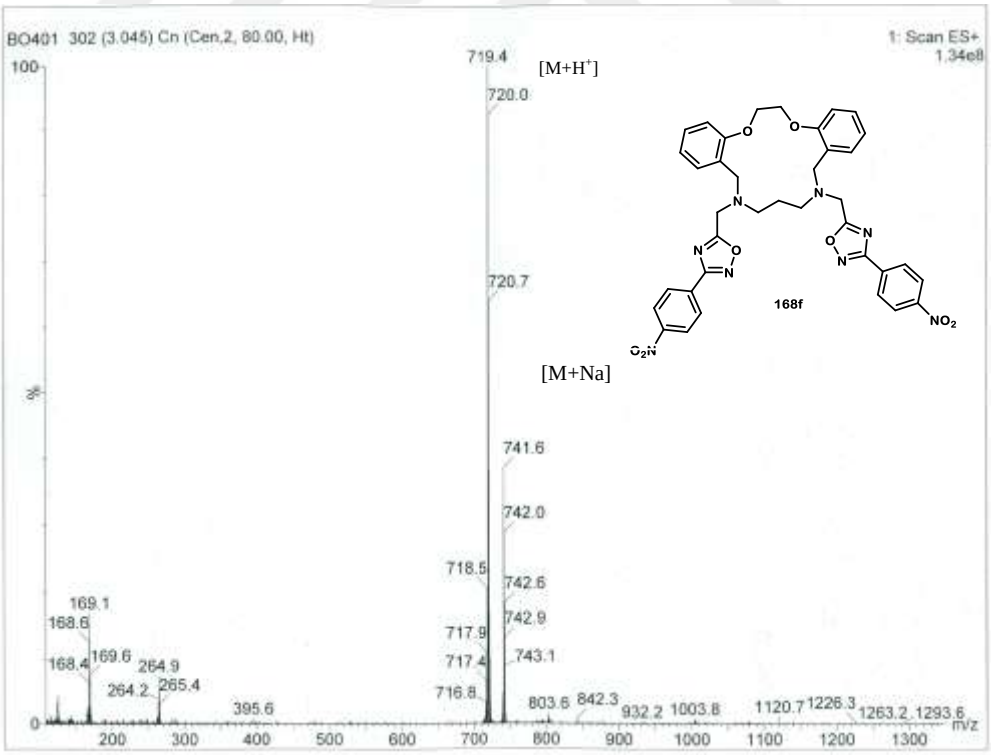
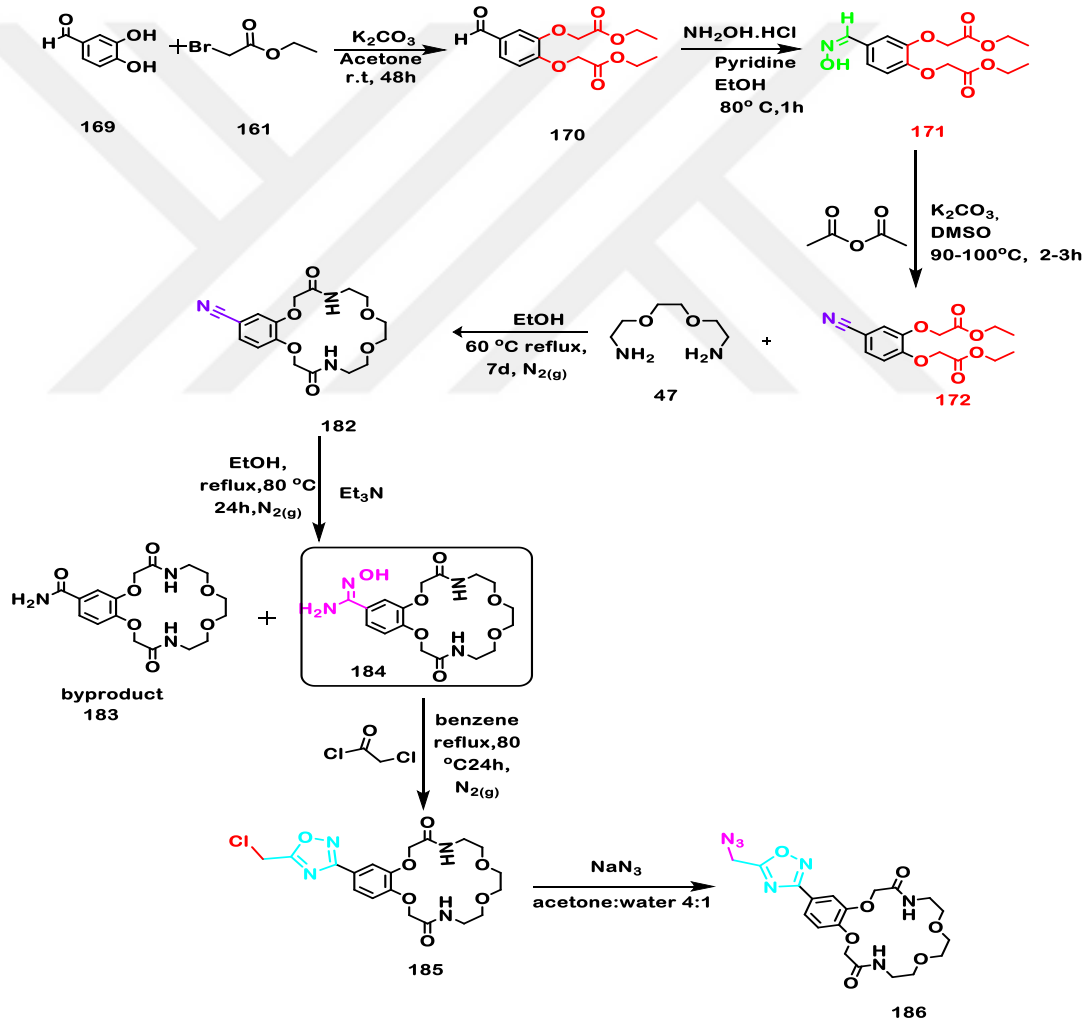


Figure 4.18. LC-MS Spectrum of compound **168f**

4.2 Synthesis of the Benzocrown Ethers Bearing Chloro/Azido methyl 1,2,4-oxadiazole

In this part, azacrown ethers with 1,2,4-oxadiazole moieties **185, 186** were synthesized in different seven stages. In order to synthesize target products **185**, **186,** 3,4-dihydroxybenzaldehyde **169** was subjected to undergo reaction with ethylbromoacetate to yield **170**. Then it was converted into the aldoxime **171** by using hydroxylamine hydrochloride and pyridine. After having been synthesized the compound **172**, it was treated with the 1,8-diamino-3,6-dioxaoctane **47**. The products **185** and **186** were obtained by using the compound **184** (Scheme 4.39).



Scheme 4.35. Synthesis of the benzodiazacrown ethers carrying chloromethyl 1,2,4-oxadiazole and azidomethyl 1,2,4-oxadiazoles **185** and **186**

The IR spectrum of **170** showed the carbonyl stretching vibrations arising from the ester at 1761, 1726 cm^{-1} and aldehyde at 1687 cm^{-1} (Figure 4.20). When the ^{1}H NMR was run in $CDCl_3$ the methylene protons which are adjacent to carbonyl groups appeared at 4.77–4.74 ppm as singlet and other methylene protons resonated at 4.24 ppm as quartet. In addition, the methyl protons at the range 1.32–1.23 ppm were also confirmative (Figure 4.21).

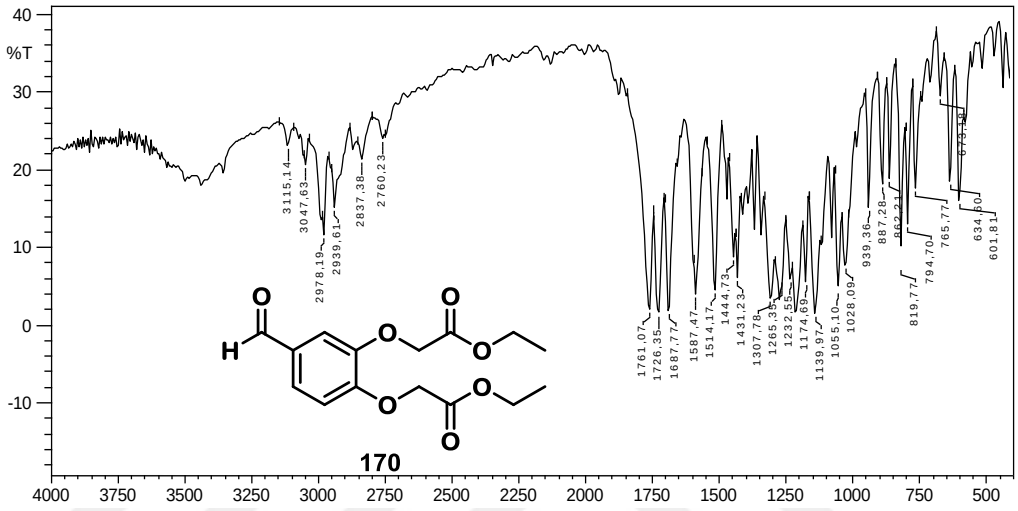


Figure 4.19. IR spectrum of compound **170**

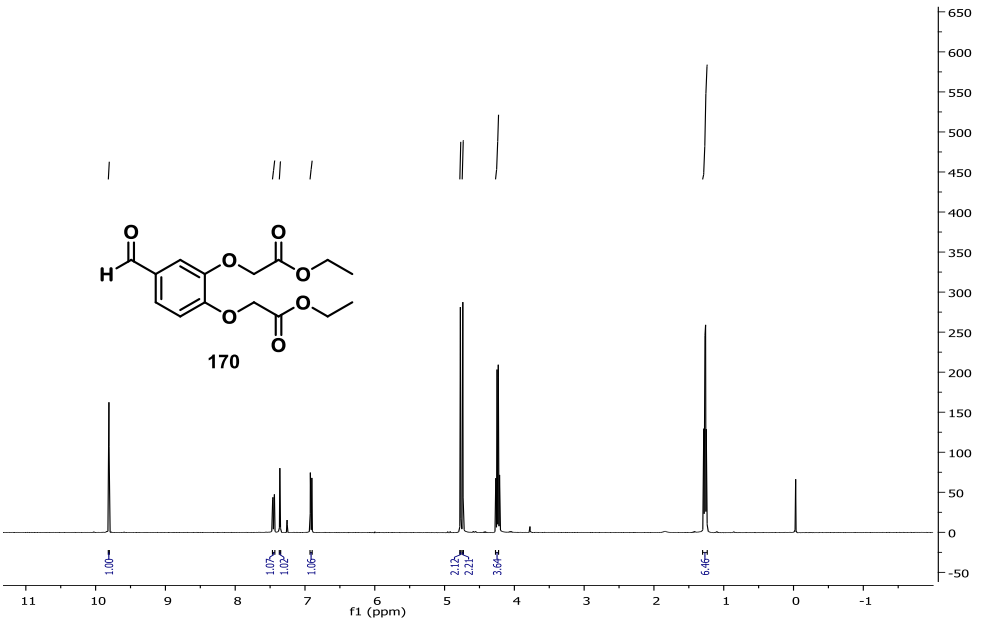


Figure 4.20. ^{1}H NMR spectrum of compound **170**

The IR characteristics of **171** is the appearance of the N-OH as a broad band at 3448 cm^{-1} and C=N stretching vibration at 1604 cm^{-1} (Figure 4.22). The molecular ion as base peak in the LC-MS spectrum was also in accord with the molecular weight (Figure 4.23).

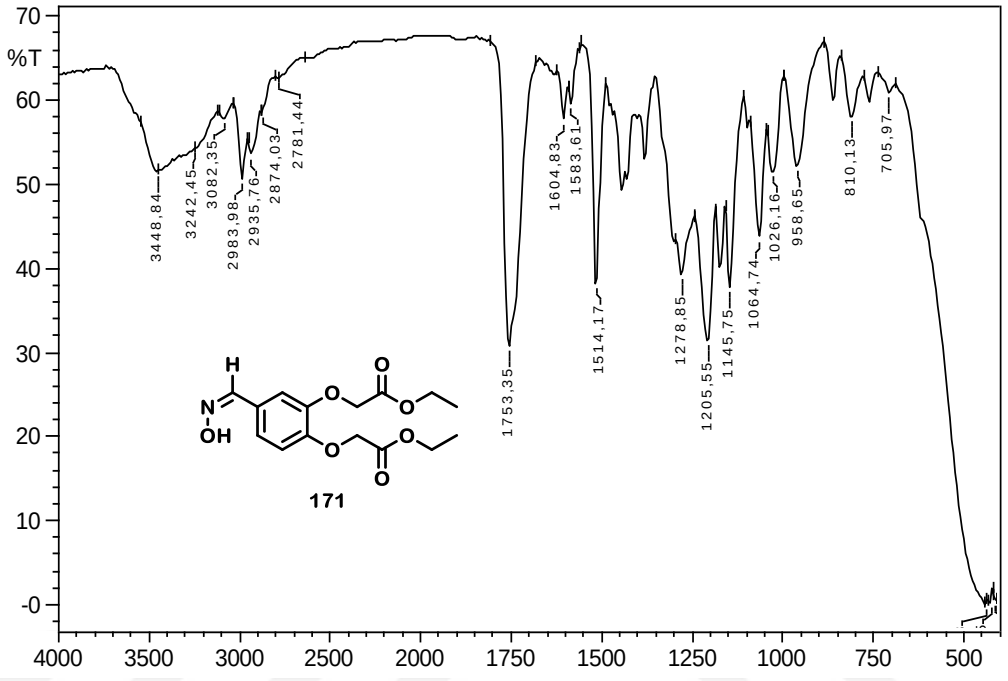


Figure 4.21. IR spectrum of compound **171**

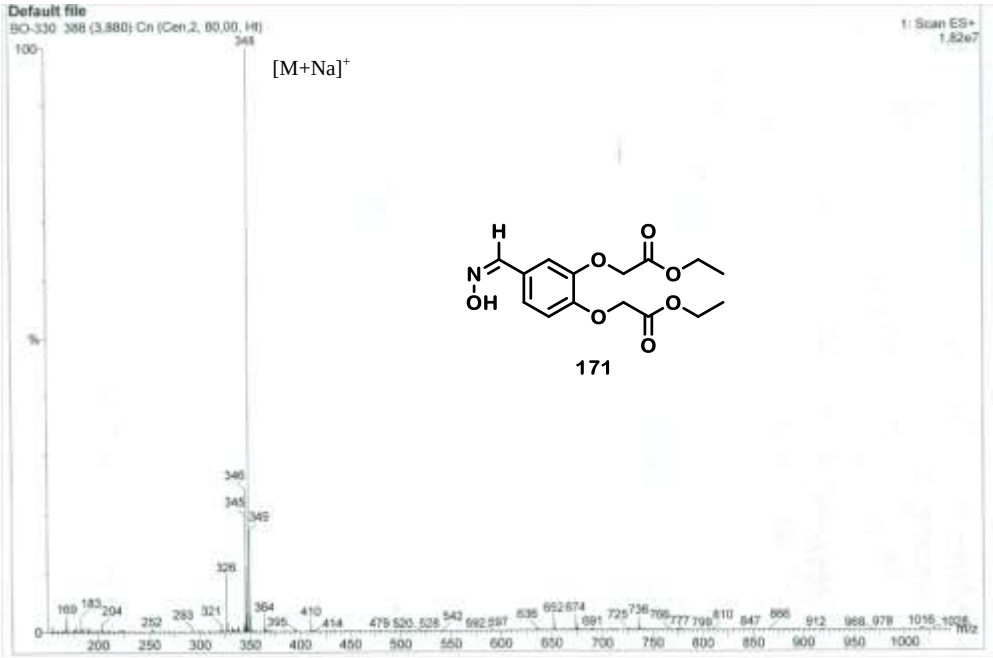


Figure 4.22. LC-MS Spectrum of compound **171**

As for the nitrile **172**, the C≡N absorption was diagnosed at 2227 cm^{-1} in the IR spectrum (Figure 4.24). ^{1}H NMR spectrum also exhibited the relevant signals corresponding to the structure (Figure 4.25) .

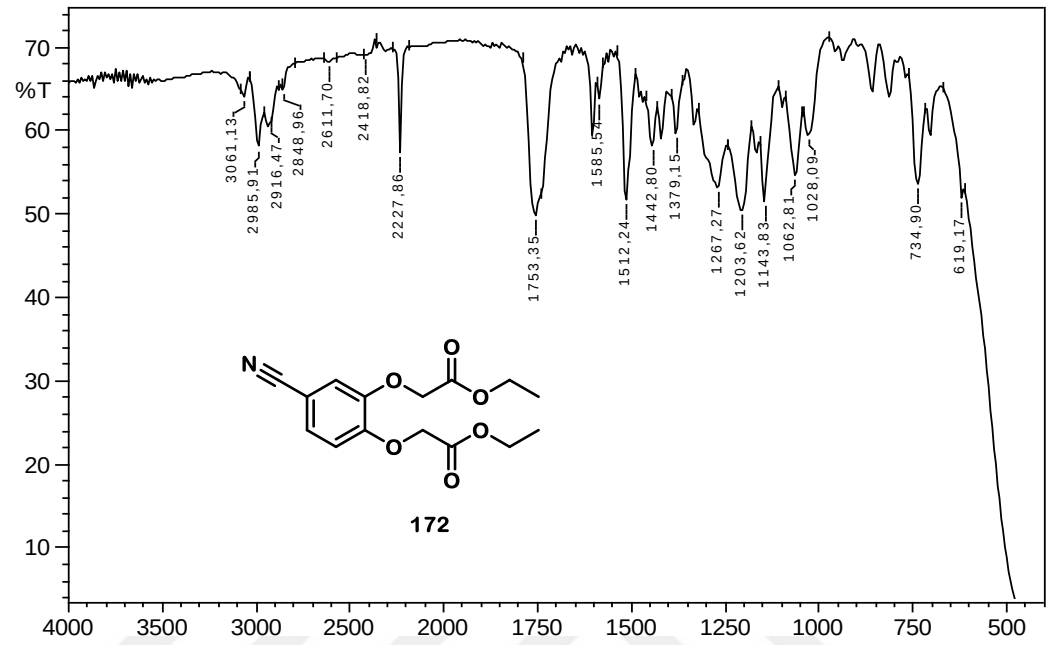


Figure 4.23. IR spectrum of compound **172**

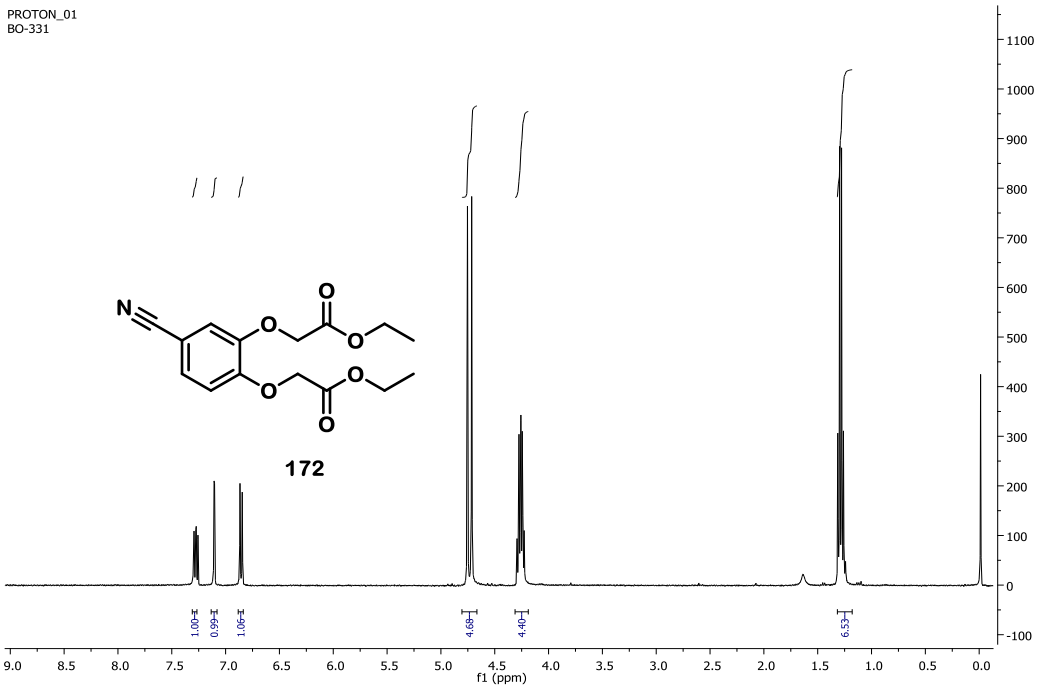


Figure 4.24. ^{1}H NMR spectrum of compound **172**

For compound **182**, first indication for the structural elucidation is the NH absorbtions at 3404 and 3340 cm^{-1} in the IR spectrum which were proved in the ^{1}H NMR spectrum at 6.98 ppm. In addition, methylene protons which are adjacent to carbonyl, there are twelve protons at around 3.57–3.55 ppm (Figure 4.26). The ^{13}C-NMR and LC-MS spectra supported the structure.

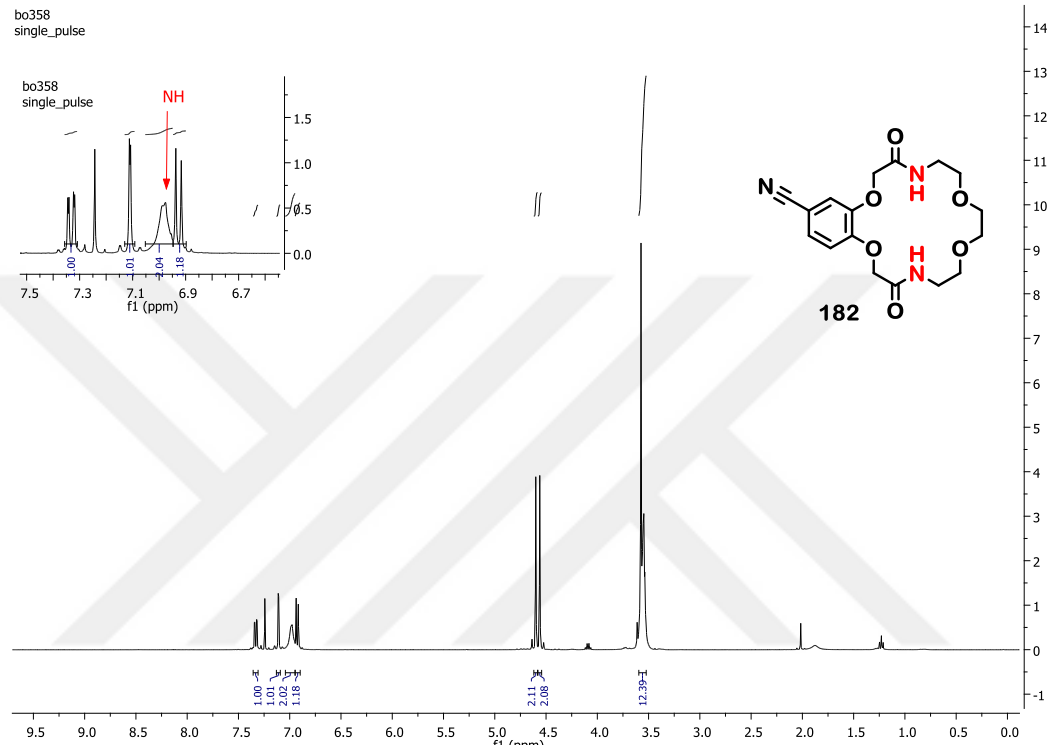


Figure 4.25. ^{1}H NMR spectrum of compound 182

In the direction of our purpose we synthesized the product **184** and byproduct **183** which was possibly generated by a Beckman rearrangement pathway. Then diazacrown ether with chloromethyl-1,2,4-oxadiazole group **185** was obtained through **184**. NMR data are in accord with the structures. In this regard, upon examination of the ^{1}H NMR spectrum, the protons of NH_2 and OH which are originated from the compound **184** disappeared and CH_2 protons that are originated chlorometyl-1,2,4-oxadiazole observed at 4.72 ppm as singlet (Figure 4.27). These structural evidences are also supported by $[M+Na]^+$ at 477 *m/z* in LC–MS spectra (Figure 4.28).

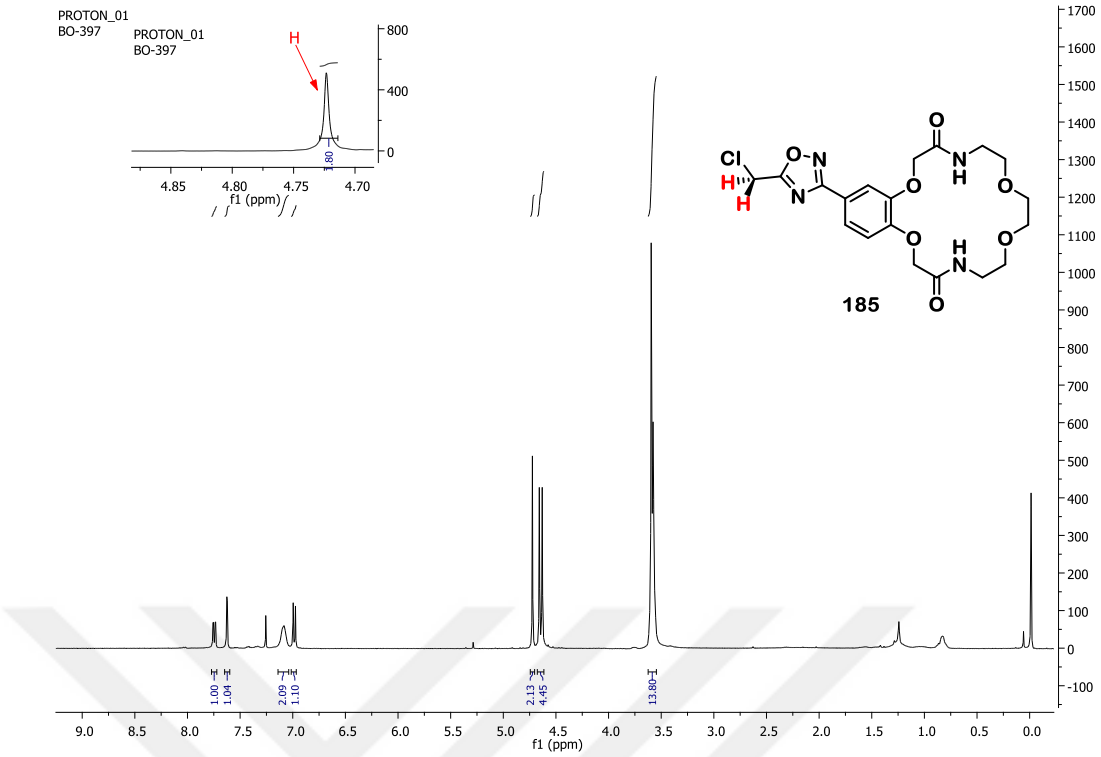


Figure 4.26. ^{1}H NMR spectrum of compound **185**

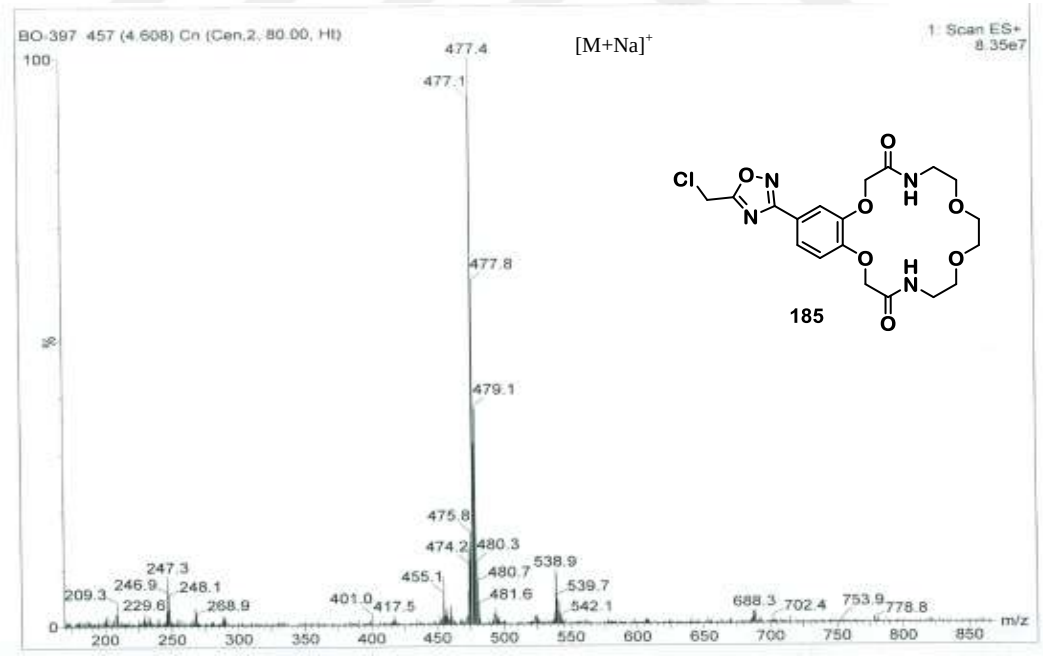


Figure 4.27. LC-M S Spectrum of compound **185**

The final product for this part is the azide **186**. Benzodiazacrown ether with 5-chloromethyl-1,2,4-oxadiazole **185** were reacted with sodium azide at room temperature in acetone/water mixture to afford benzodiazacrown ether with 5-

azidomethyl-1,2,4-oxadiazole **186**. The structural confirmation of the compound **186** is first provided by the IR spectrum at which N=N=N absorption can be seen at 2102 cm^{-1} (Figure 4.29). The molecular ion peak was also in accord with the structure (Figure 4.30).

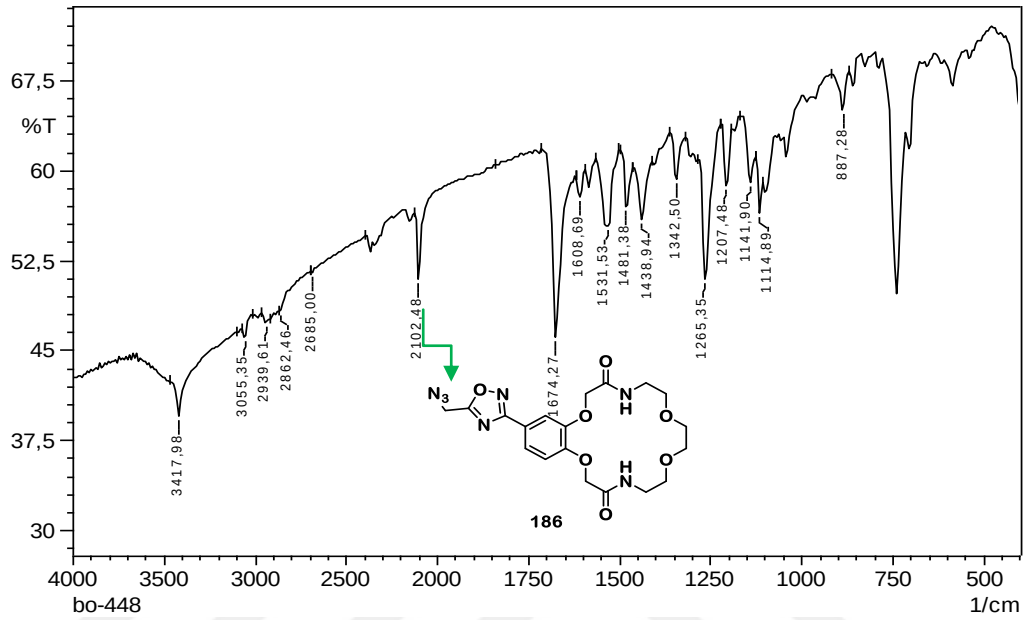


Figure 4. 28. IR spectrum of compound **186**

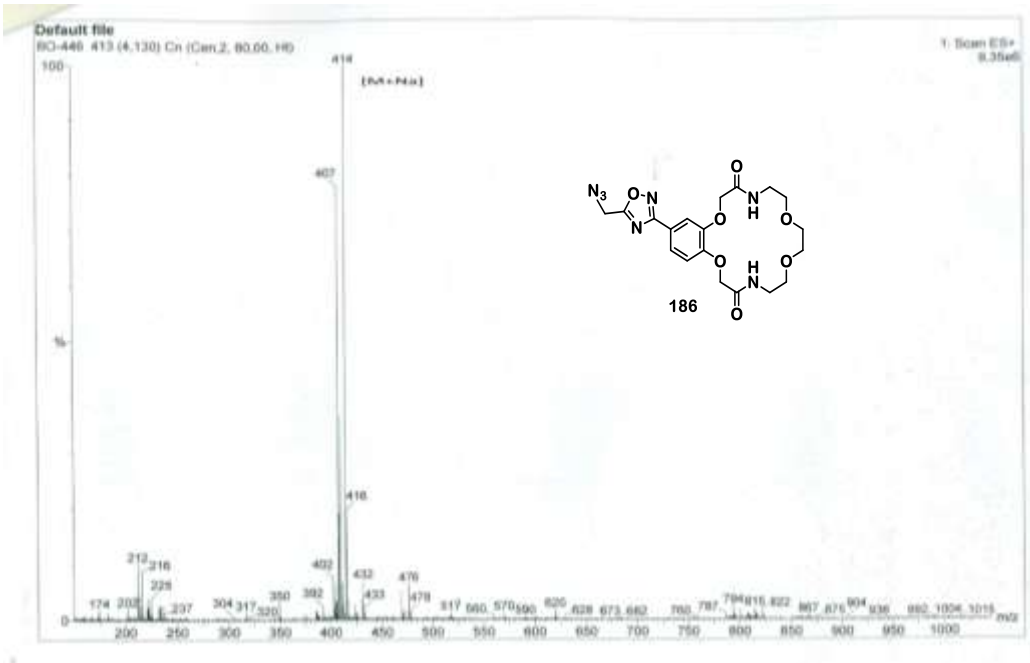
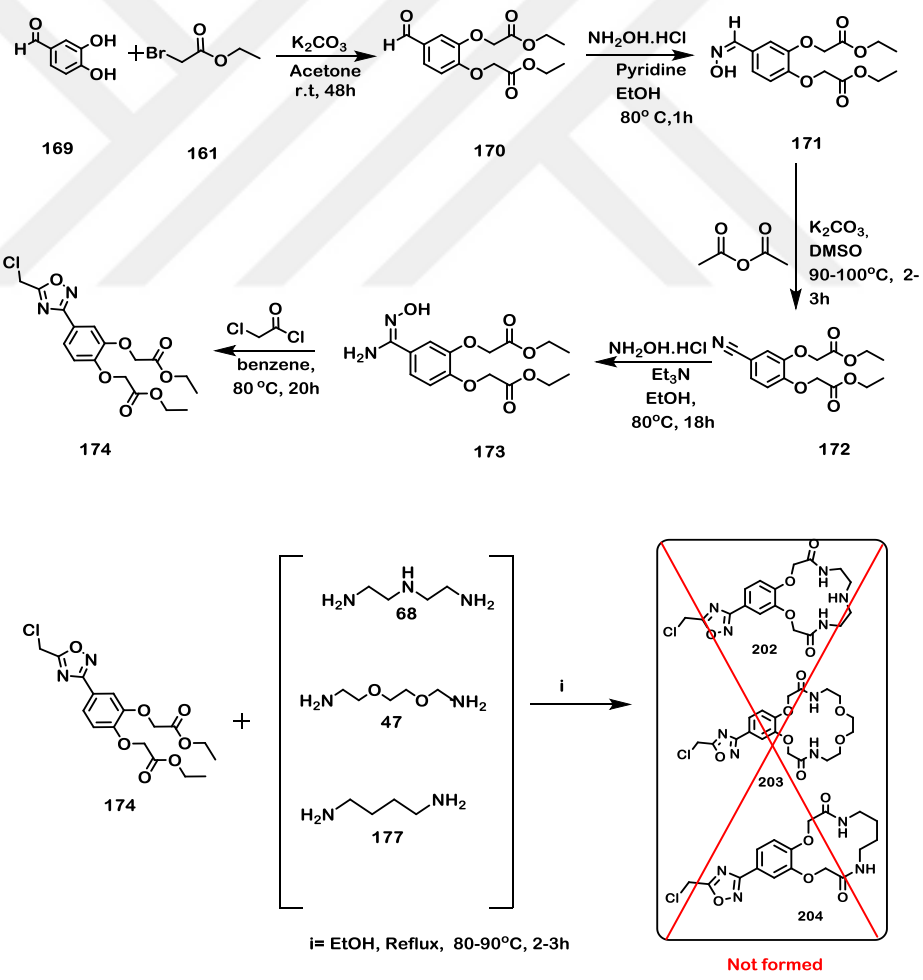


Figure 4.29. LC-MS Spectrum of compound **186**

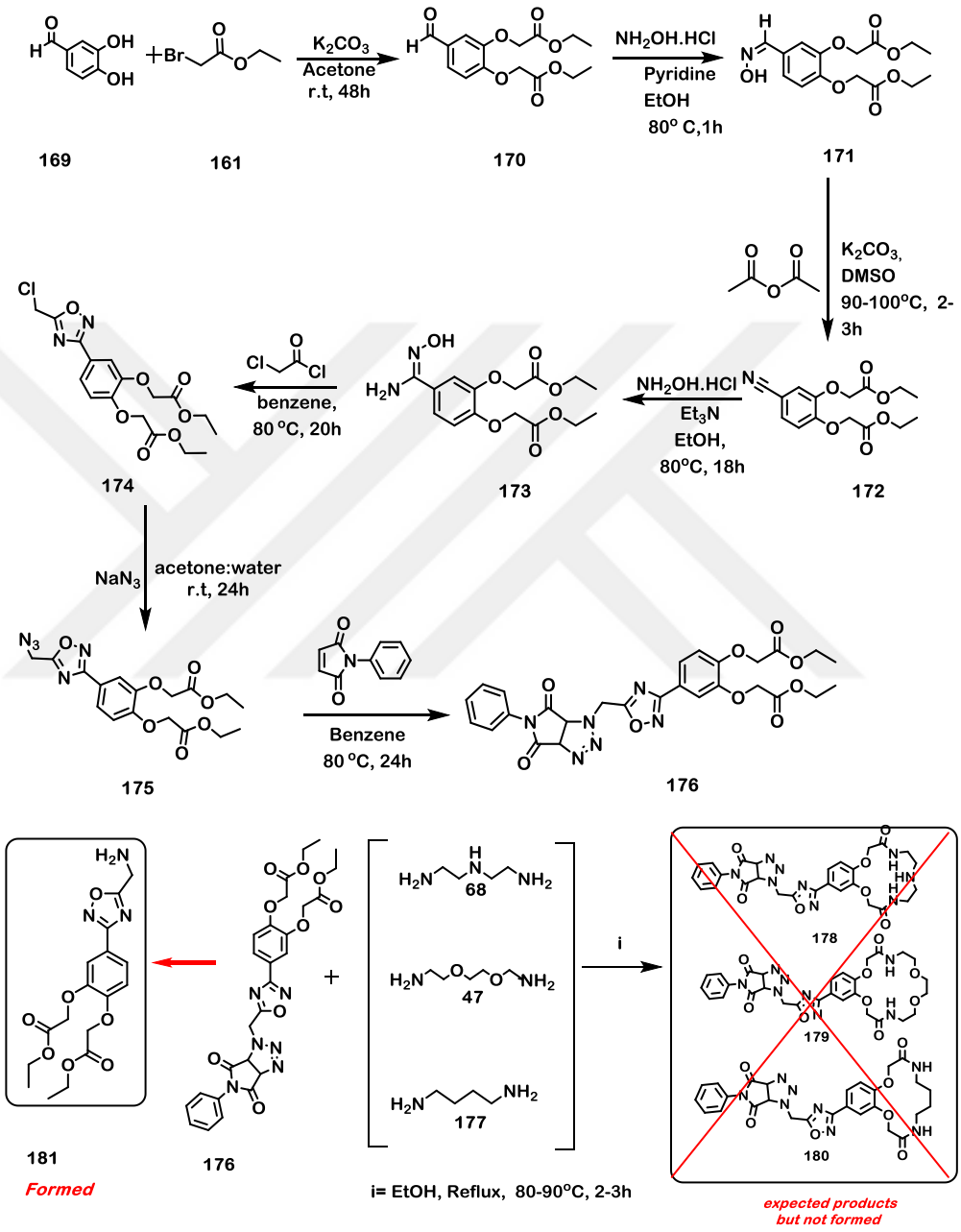
All these new synthesized compounds **170, 171, 172, 173, 174, 175, 176, 181, 182, 184, 185, 186** have been successfully characterised on the basis of IR, ^{1}H-NMR, ^{13}C-NMR, LC-MS spectra.

During the attempts of synthesizing the target products **186** and **185**, we have tried some synthetic routes (Schemes 4.39, 4.40) which resulted in an unexpected amine **181** (Scheme 4.41). We experienced some difficulties to obtain the macrocycles using various diamines (Scheme 4.40). At the beginning of this part, the product **174** was synthesized by using 3,4-dihydroxybenzaldehyde, its structure was verified by the physical and spectral characteristics. Then, we intended to obtain the benzo-di/tri aza crown ether with 1,2,4-oxadiazole moiety **202**, **203**, **204**, but these three reactions failed anyway (Scheme 4.40).



Scheme 4.36. Synthesis of the 2,2'-((4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene)bis(oxy))diacetate **174** and treatment with different types of amines **68, 47, 177**

These unsuccessful trials have forced us to think about what if we would treat 5-(azidomethyl)-1,2,4-oxadiazole **175** with the dipolarophile *N*-phenylmaleimide and thus we could manage to obtain the crown ether by the treatment of amines **68**, **47**, **177** with the ester **176** (Scheme 4.41).



Scheme 4.37. Treatment of diethyl 2,2'-((4-(5-(chloromethyl)-1,2,4-oxadiaz ol-3-yl)-1,2-phenylene)bis(oxy))diacetate **174** with different types of amines

The expected product **176** was elucidated by the IR, (^{1}H, ^{13}C) NMR, LC-MS spectra, and physical characteristics. Checking the ^{1}H NMR spectrum we can see the two methylene protons of the 1,2,4-oxadiazole at around 5.28 ppm as singlet, in addition, the aromatic protons originated from the *N*-phenylmaleimide appeared at around 7.40–7.21 ppm. The 1,2,4-triazole ring protons of cycloadduct can be seen at around 5.86 and 5.54 ppm. (Figure 4.31). In the ^{13}C NMR spectra, the corresponding carbon signals are present.

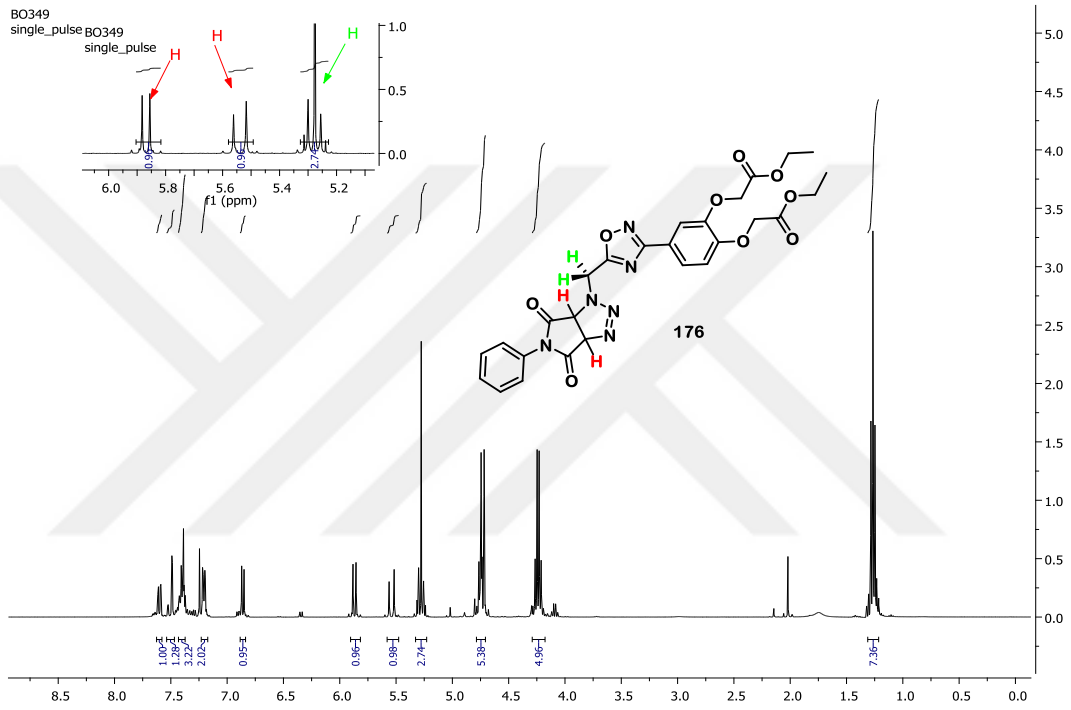


Figure 4.30. ^{1}H NMR spectrum of compound **176**

The attempted and forced reactions of the different amines **68, 47, 177** with the diester **176**, did not result in any final products **178, 179, 180**, but instead, the only product was 2,2'-((4-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-1,2-phenylene) bis(oxy))diacetate **181** which was elucidated by IR, NMR, LC-MS data**.** ^{1}H NMR spectrum reveals that disappearance of the aromatic proton of the *N*-phenylmaleimide and protons in the 1,2,3-triazole ring and especially appearance of the protons of NH_2 are the strong evidences. Those are supported by the thirteen different carbons via ^{13}C NMR spectrum. LC-MS spectrum shows the molecular ion as base peak at *m/z* 380 (Figure 4.32- 4.34).

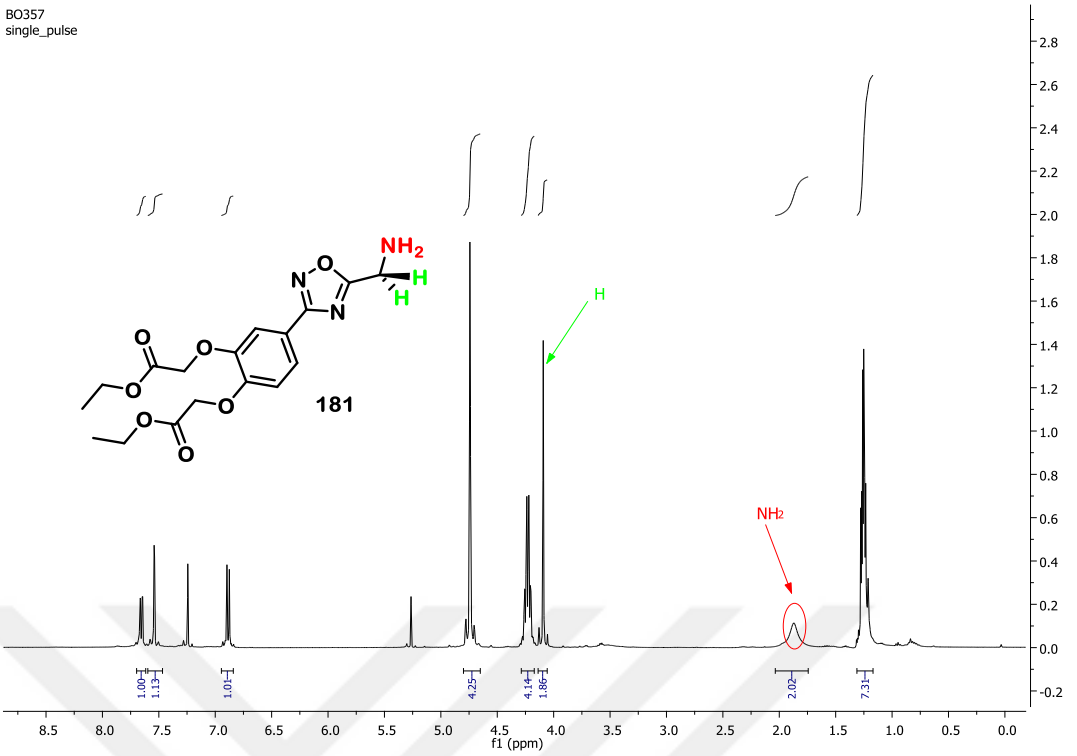


Figure 4.31. ^{1}H NMR spectrum of compound **181**

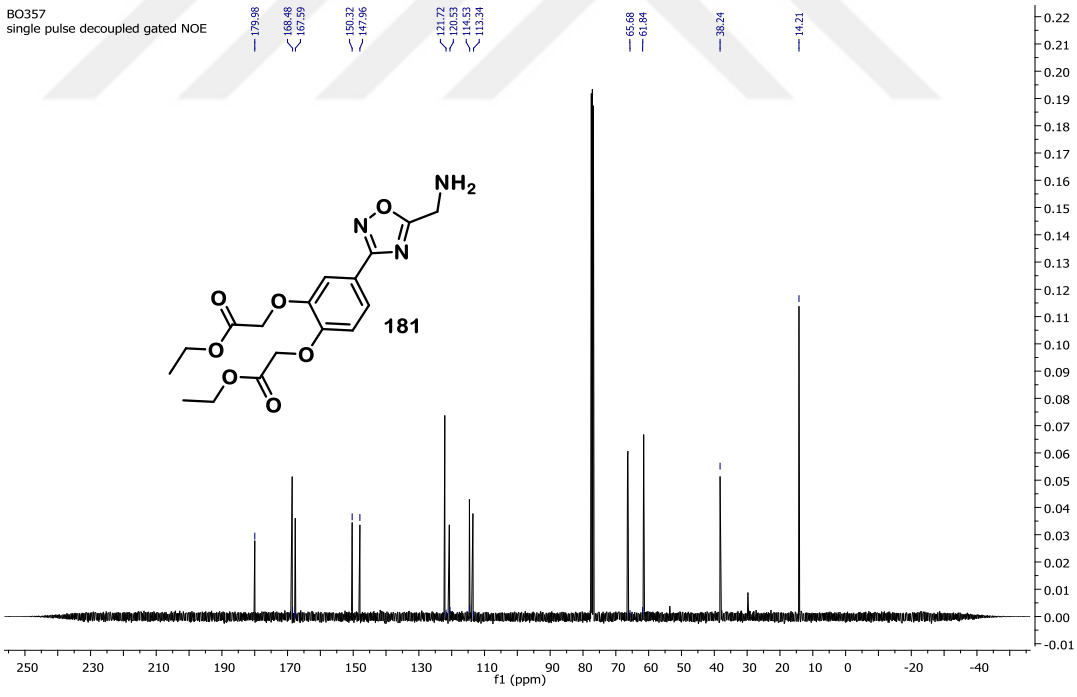


Figure 4.32. ^{13}C NMR spectrum of compound **181**

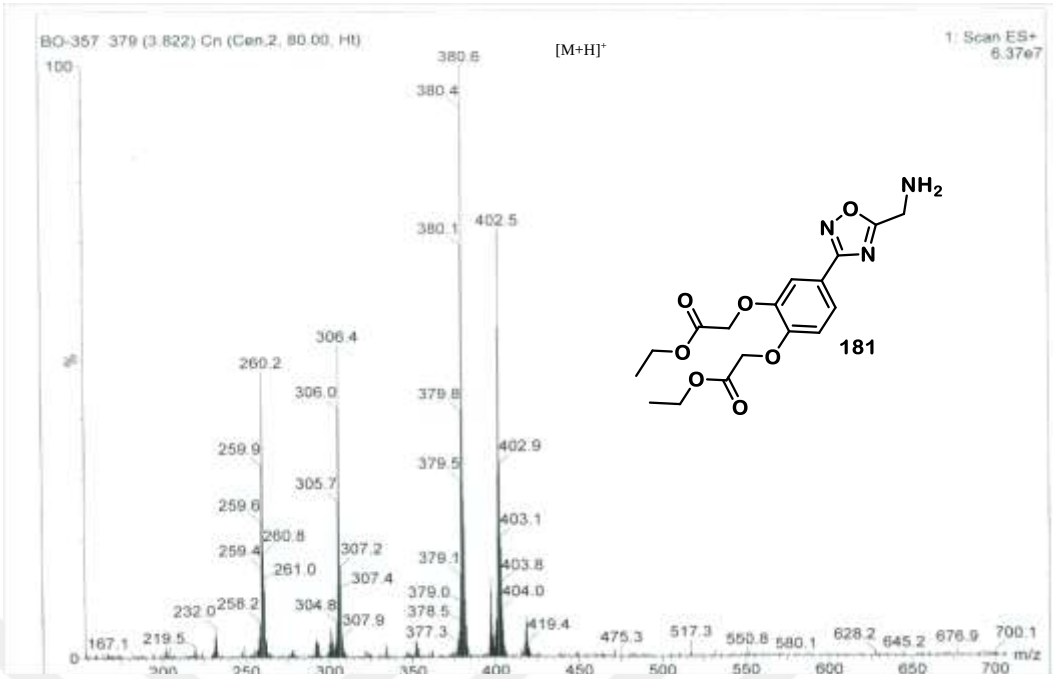
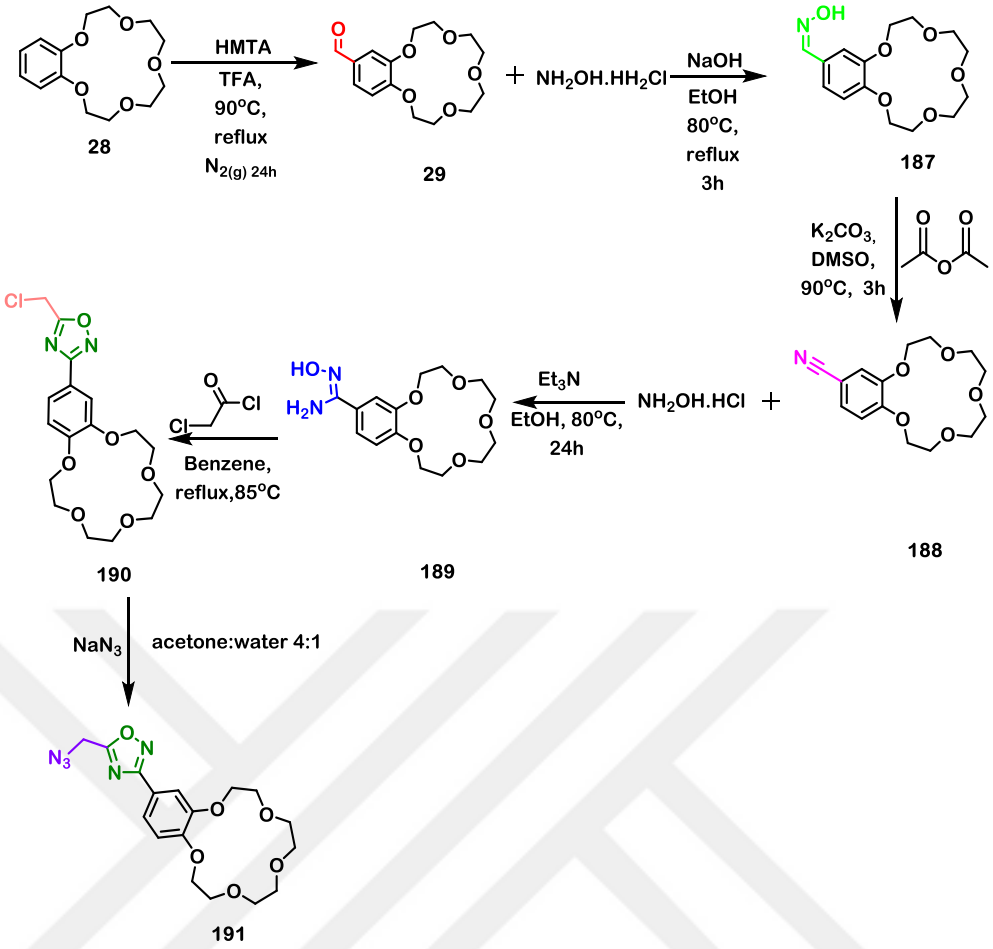


Figure 4.33. LC-MS spectrum of the compound **181**

This unexpected product **181** forced us to think about how to synthesize the aza-crown ethers with 1,2,4-oxadiazole moieties **185, 186** and finally we could manage, as we discussed above (Scheme 4.41) .

Inspired by the products depicted in Scheme 4.39 we have made substantial efforts to synthesize 5-(azidomethyl)-3-(2,3,5,6,8,9,11,12-octahydrobenzo[b][1,4,7, 10,13]pentaoxacyclopentadecin-15-yl)-1,2,4-oxadiazole **191** starting from benzo-15-crown-5 **28**. Initially, we formylated benzo-15-crown-5 **28** to yield aldehyde **29** according to the literature procedure (Kimura et al., 2006, Chen et al., 2016, Safonova et al., 2013). Then successive five steps led us to target azide **191** (Scheme 4.42).



Scheme 4.38. 5-(Azidomethyl)-3-(2,3,5,6,8,9,11,12-octahydrobenzo [b][1,4, 7,10,13 pentaoxacyclopentadecin-15-yl)-1,2,4-oxadiazole **191** by using benzo-15-crown-5 **28**

Upon examination of IR spectrum of **187** (Figure 4.35), we can clearly see the dissappearance of the carbonyl absorption and an emerging broad OH absorption band at around 3269 cm^{-1} regarding aldoxime. In the ^{13}C NMR spectrum (Figure 4.36) the disappearance of the carbonyl carbon signal confirmed the IR spectrum. These evidences are verified by LC-MS and ^{1}H NMR spectra.

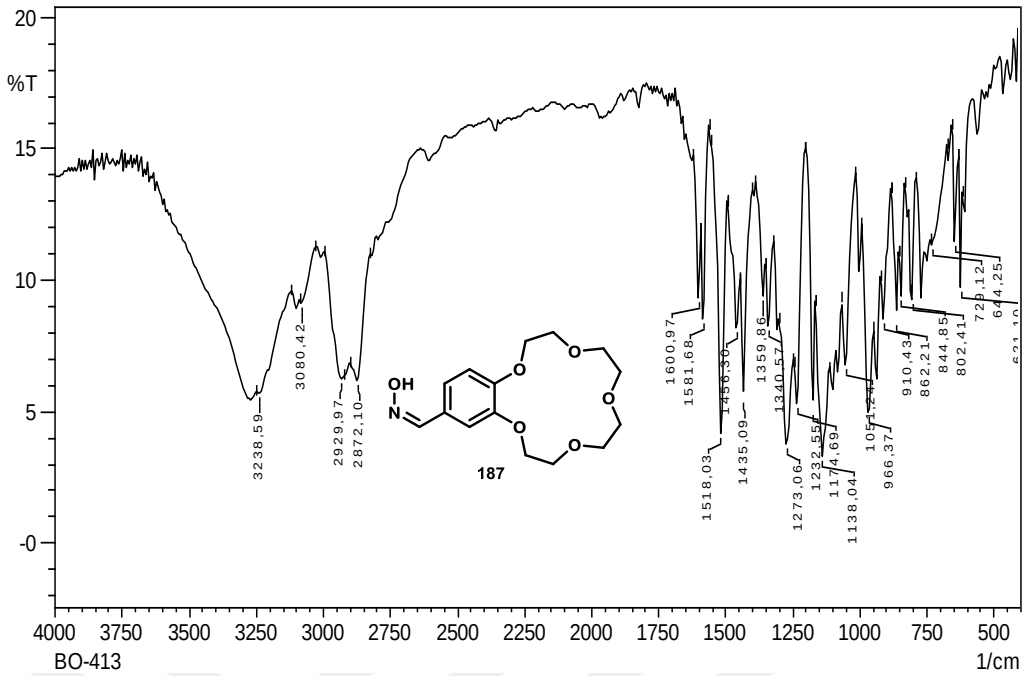


Figure 4.34. IR spectrum of compound **187**

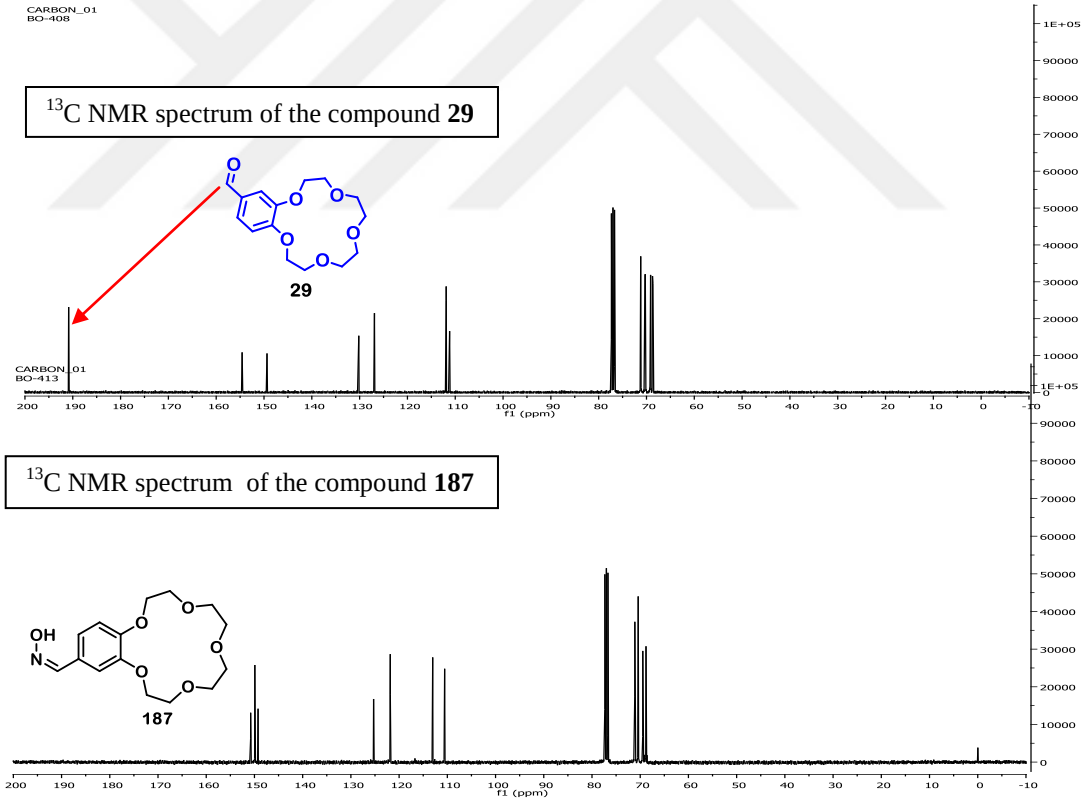


Figure 4.35. ^{13}C NMR spectra of compounds **29** and **187**

In the third step of these synthetic routes, the compound **188** was prepared by using acetic anhydride and K_2CO_3 in DMSO. The product was elucidated by physical and spectral characteristics. IR spectrum of **188** showed strong nitrile

absorption at 2225 cm^{-1} (Figure 4.37). The structure was confirmed by LC–MS; $[M+Na]^+$ at 316 *m/z* in (Figure 4.38) and ^1H, ^{13}C NMR spectra.

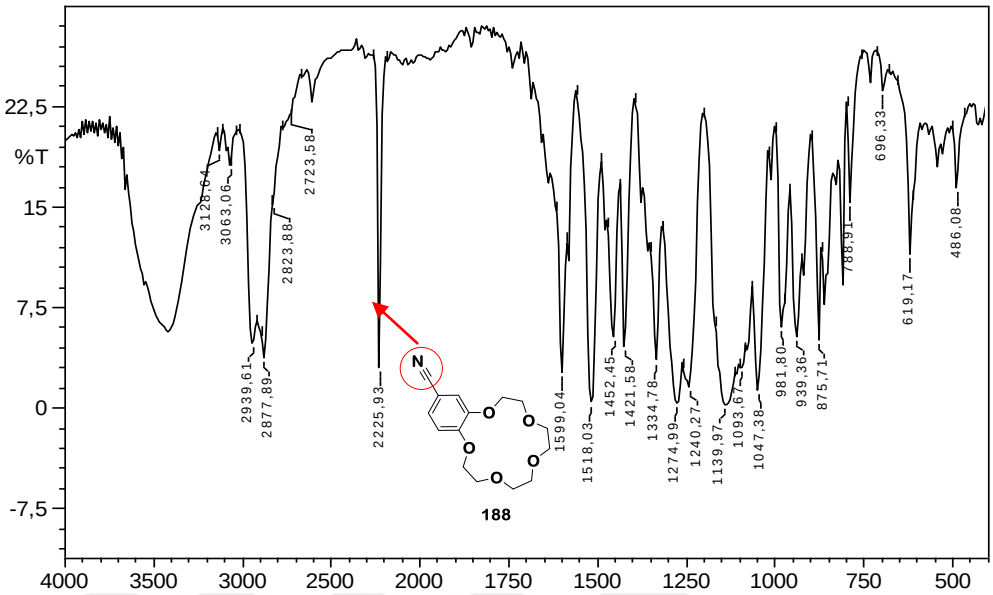


Figure 4.36. IR spectrum of compound **188**

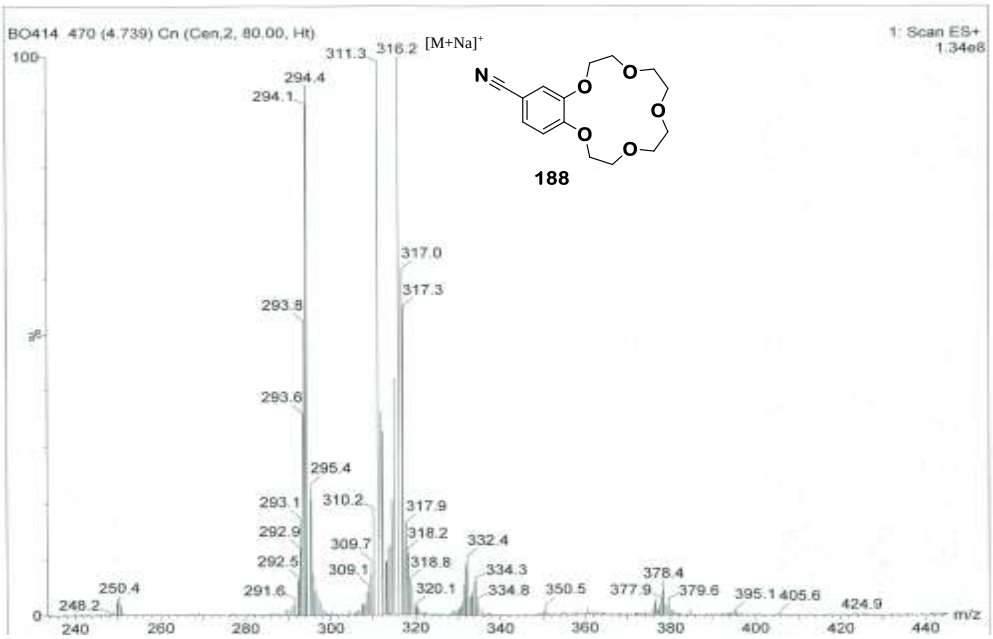


Figure 4.37. LC-MS Spectrum of compound **188**

In order to synthesize benzo-15-crown-5 carrying 5-(chloromethyl)-1,2,4-oxadiazole group **190**, the amidoxime **189** was first obtained via nitrile **188** (Scheme 4.42) and it was identified by using the spectral and physical data. In ^1H NMR

spectrum, the protons of the NH_2 and OH, which are originated from the amidoxime **189** disappeared and CH_2 protons originated from chloromethyl 1,2,4-oxadiazole **190** were observed at 4.71 ppm as singlet (Figure 4.39). $[M+H]^+$ at 407 *m/z* in LC-MS spectra coincided with structure (Figure 4.40).

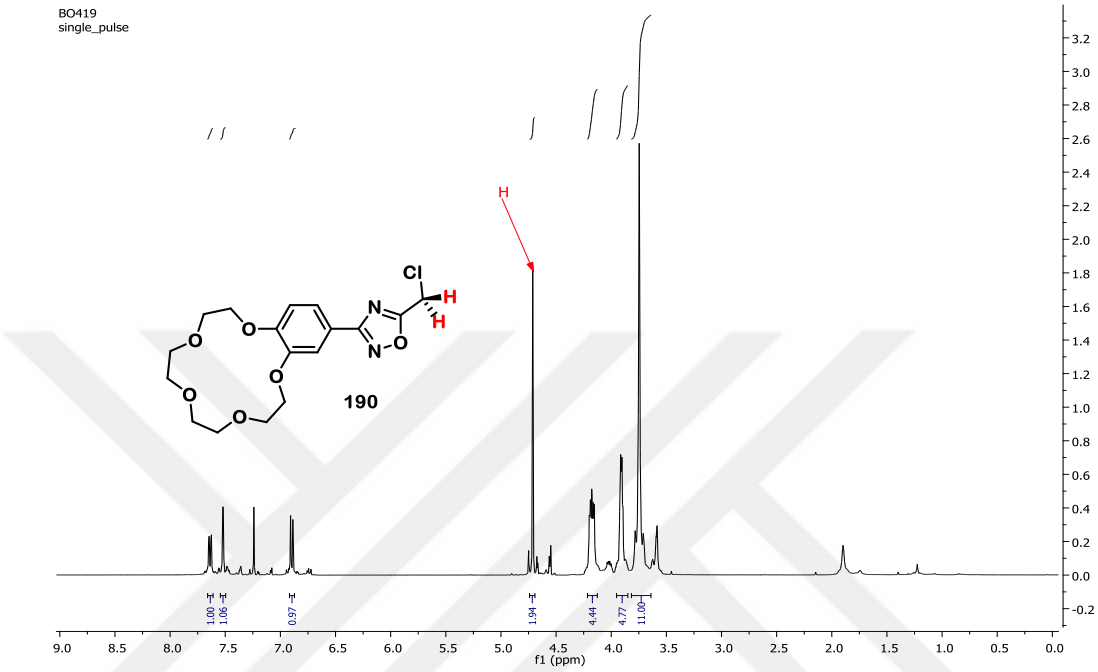


Figure 4.38. ^{1}H NMR spectrum of compound **190**

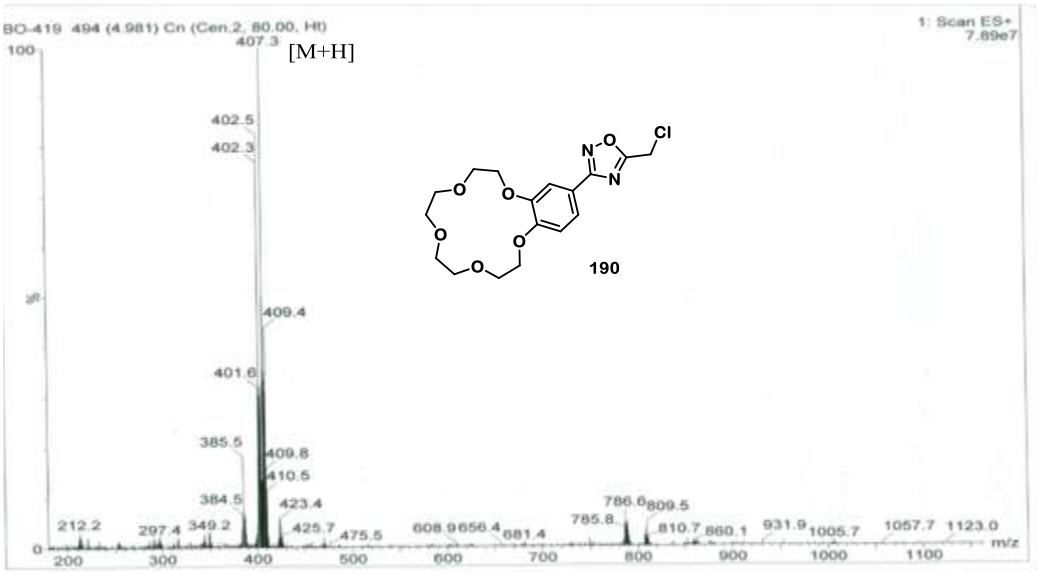


Figure 4.39. LC-MS Spectrum of compound **190**

The final step for this part is the identification of the benzocrown ether with 5-(azidomethyl)-1,2,4-oxadiazole **191**. When we compared the IR spectra of **190** and **191** (Figure 4.41), the only difference between them was azide group streching vibration which appeared at 2111 cm^{-1} in IR spectrum (Figure 4.41).

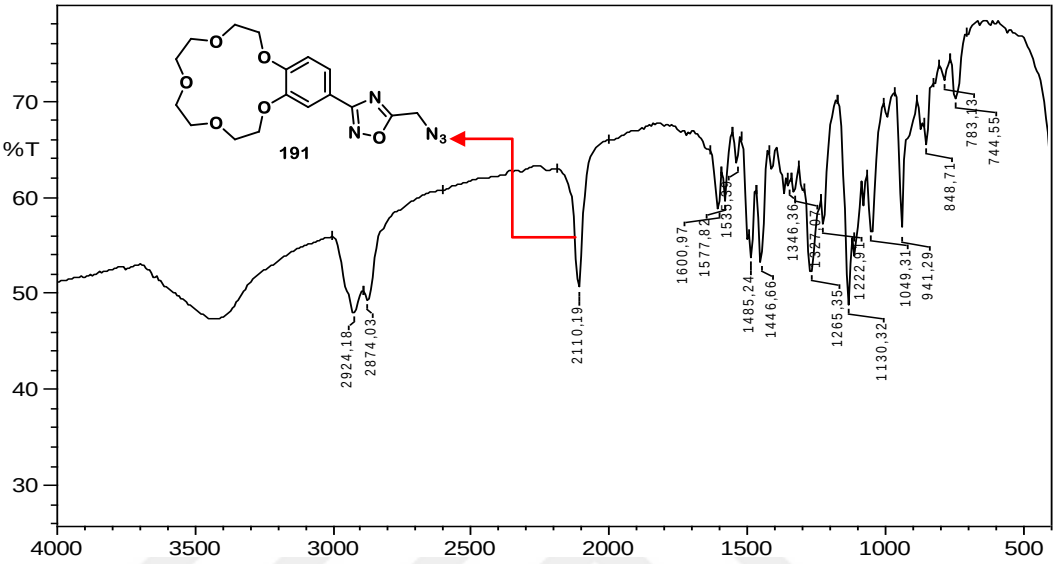


Figure 4.40. IR spectrum of compound **191**

LC-MS data also supported the structure of the compound **191** (Figure 4.42). along with the relevant ^{1}H and ^{13}C NMR resonances.

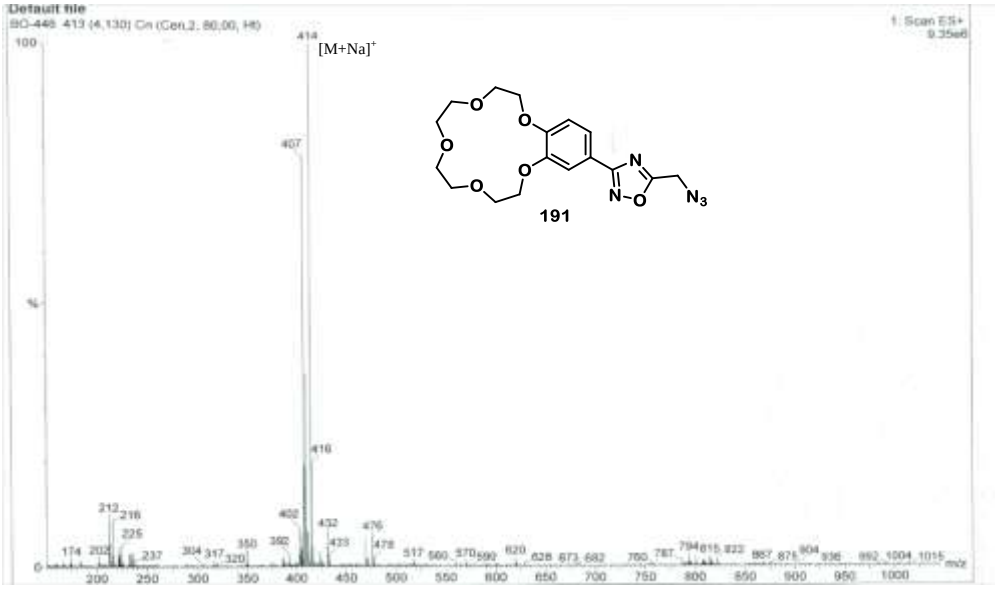
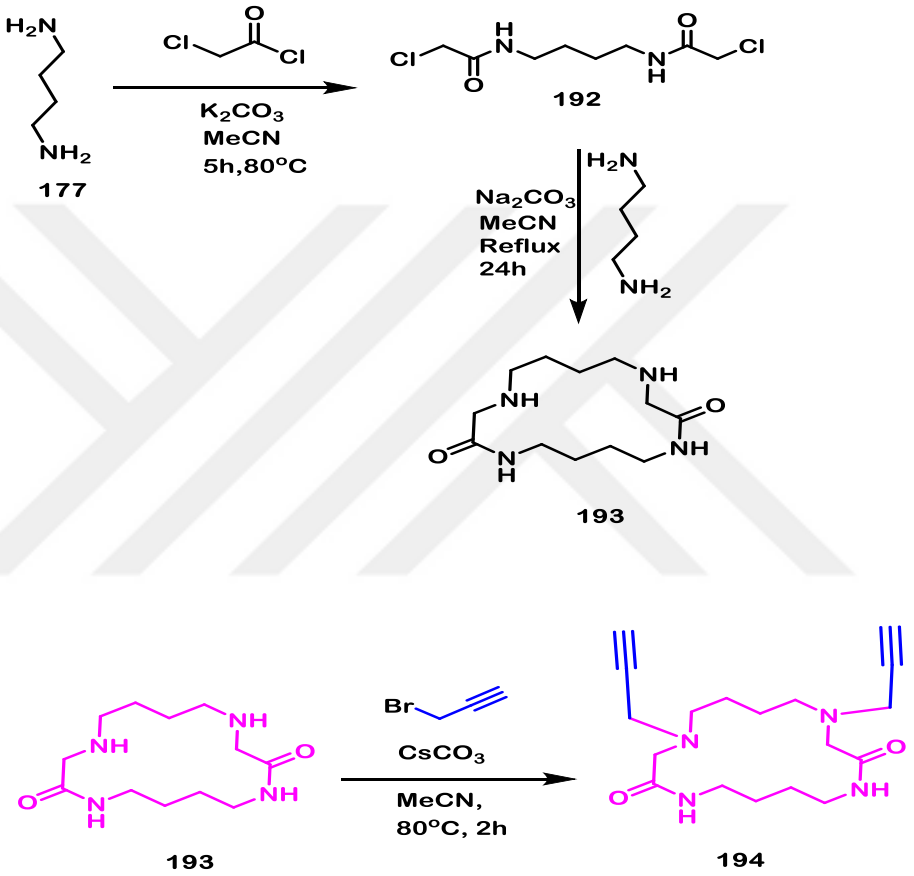


Figure 4.41. LC-MS spectrum of compound **191**

4.3 1,3-Dipolar Cycloadditions of Azamacrocycles carrying Acetylenic Side Chain with Azidomethyl 1,2,4-Oxadiazoles

In this part, we report a practical synthetic sequence for the synthesis of novel cycloadducts **196, 197 (a-h)** (Scheme 4.44). In accordance with our goal, first protocol is a two-step sequence of synthesis of **193** (Scheme 4.43).



Scheme 4.39. Synthesis of the tetraazamacrocycle **193** and azamacrocycle carrying acetylenic group **194**

Upon examination of ^{1}H NMR spectrum of **193**, NH protons and methylenic protons which are closer to the carbonyl appeared at around 7.40, 3.23 ppm as singlet, respectively. The other NH protons which are originated from 1,4-diamino butane **177** and four methylene groups appeared at around 1.63–1.48 ppm as multiplet. In addition, totally eight remaining methylene protons can be seen at 3.37–3.28 ppm as multiplet and 2.60 ppm as triplet. In the ^{13}C NMR spectrum, the

carbonyl carbons at 171 ppm and totally six different related carbons can be seen (Figure 4.43). LC-MS data also supported the structure.

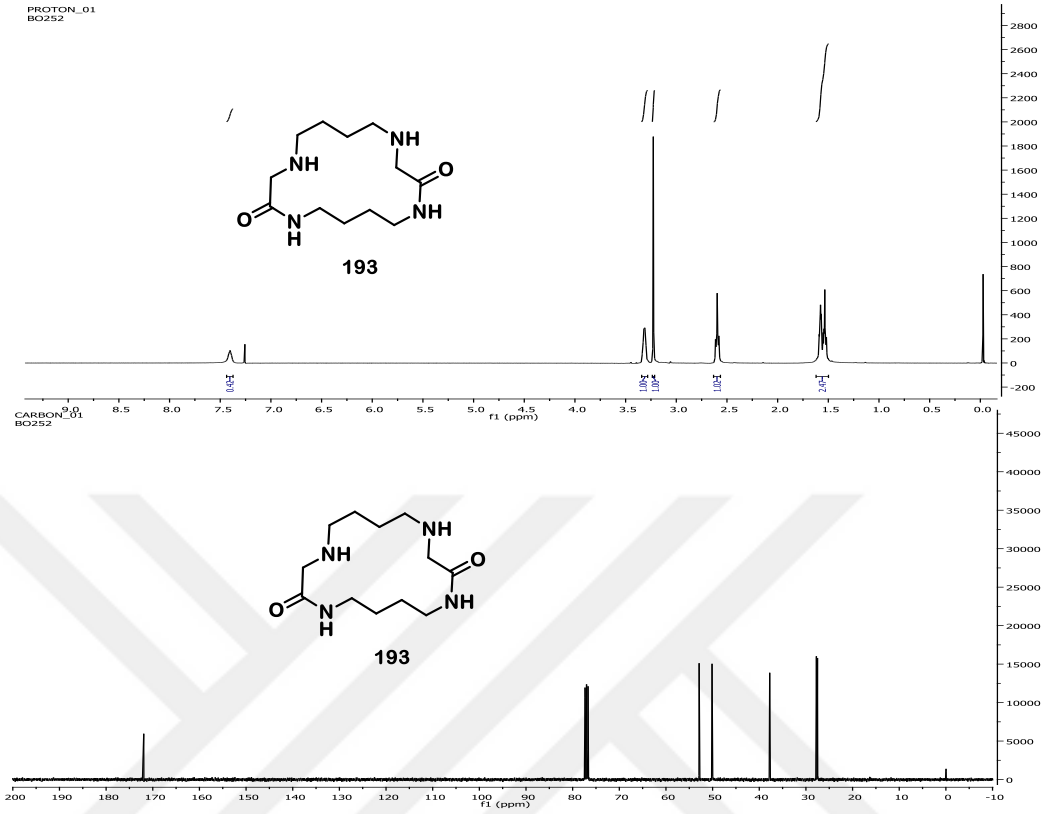


Figure 4.42. ^{13}C and ^{1}H NMR spectrum of the compound **193**

The second step is the synthesis of the dipolarophile **194** by using propargyl bromide as shown in Scheme 4.43. Indicative characteristics in the IR spectra are (C≡C–H), N-H and carbonyl absorptions. Those were supported by the ^{1}H NMR at which two methylenic protons seen at around 3.36 ppm and two acetylenic protons at 2.20 ppm, and carbonyl carbons at around 170 ppm. These structural evidences were also confirmed by $[M+H]^+$ at 333 *m/z* in LC–MS spectra. The (^{1}H, ^{13}C) NMR spectra of the compound **194** are shown below as a representative example (Figure 4.44 and 4.45).

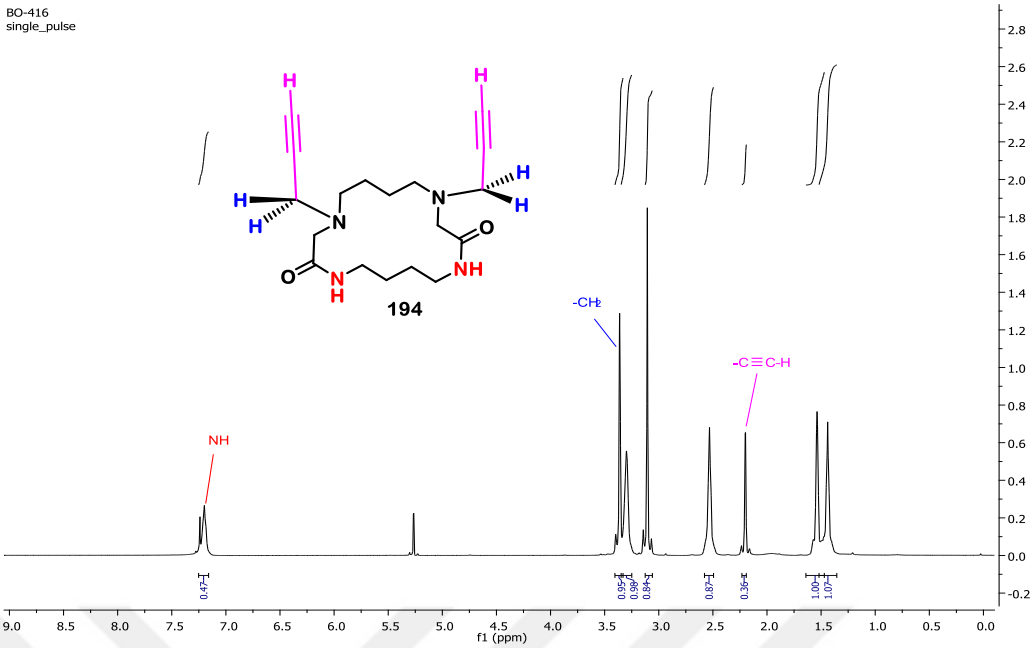


Figure 4.43. ^{1}H NMR of the compound **194**

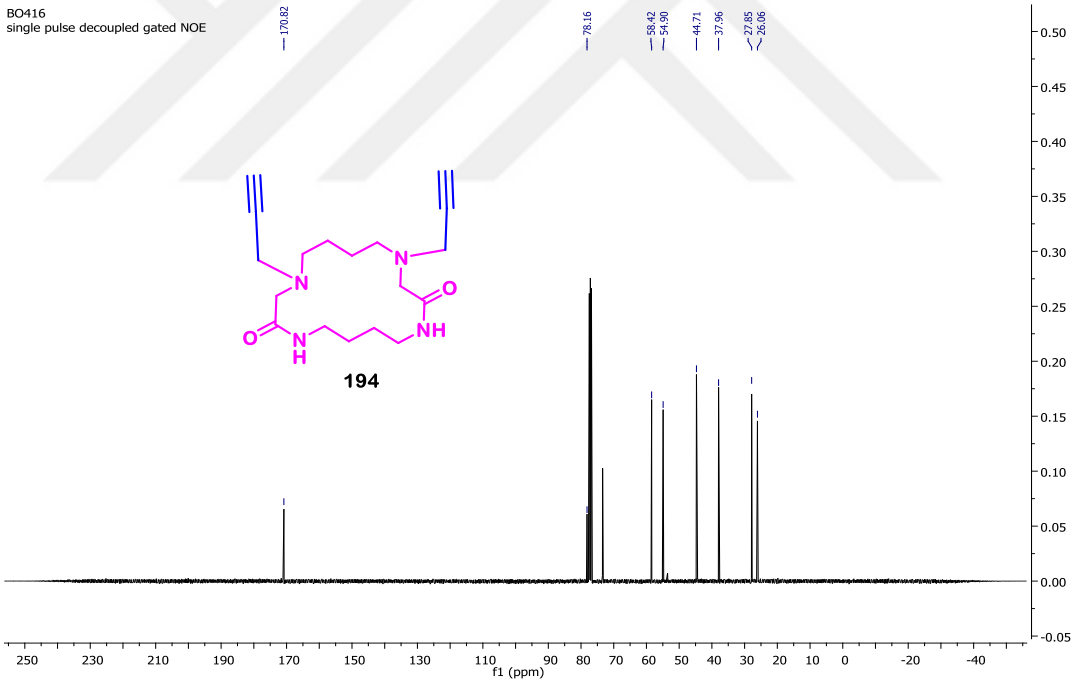
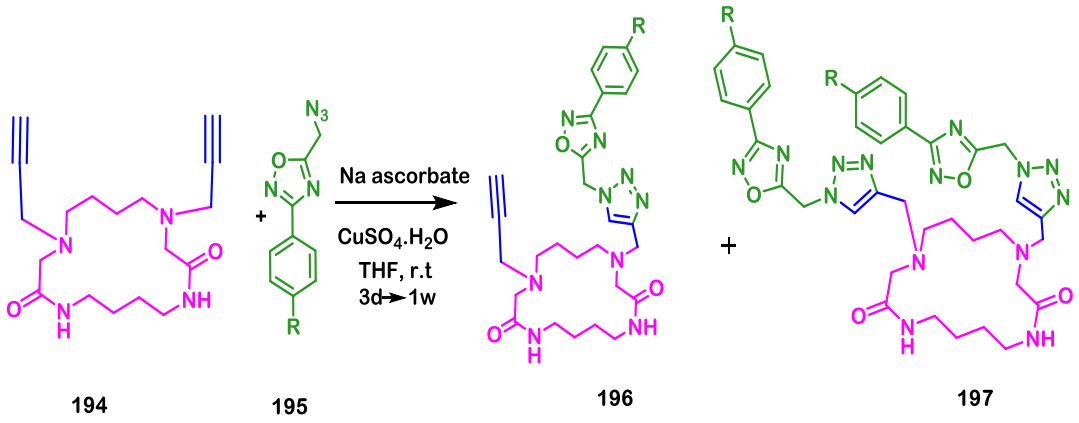


Figure 4.44. ^{13}C NMR spectrum of the compound **194**

Azacrown with acetylenic side chain **194** was then subjected to 1,3-dipolar cycloaddition with azidooxadiazole **195** to yield a mixture of mono and dipropargyl substituted cycloadducts **196, 197** which can easily be separated and purified (Scheme 4.44).



	R	Yield (%) 196	197
a	H	25	73
b	CH_3	44	53
c	F	30	61
d	Cl	40	42
e	Br	38	71
f	NO_2	35	41
g	CH_3O	36	46
h	CH_3S	38	41

Scheme 4.40. Synthesis and cycloadditions of macrotetrazacycles **194** leading to cycloadducts **196a-h, 197a-h**

Among the important spectral characteristics of the novel compounds **196(a-h)** are an acetylenic proton, three CH_2 protons, which are attached to propargyl, oxadiazole, triazole, and a C=CH proton of triazole ring and NH protons which are closer to carbonyl groups exhibiting resonances at around 2.18, 3.82, 5.88, 3.34 and 7.25 and 6.96–6.93 ppm, respectively. Assignments of the protons were shown below (Figure 4.46). As for ^{13}Carbon assignments for these compounds, the carbonyl and acetylenic carbons appeared at around 172–175 and 70–80 ppm range (Figure 4.47). HRMS measurements were also in accordance with the structures.

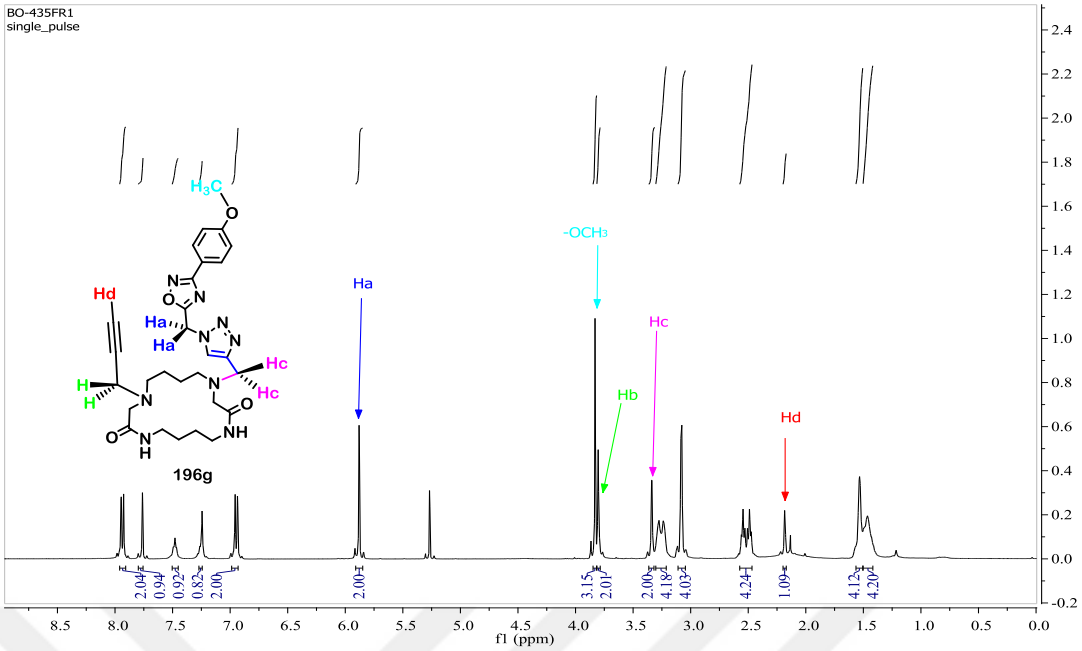


Figure 4.45. ^{1}H NMR spectrum of the compound **196g**

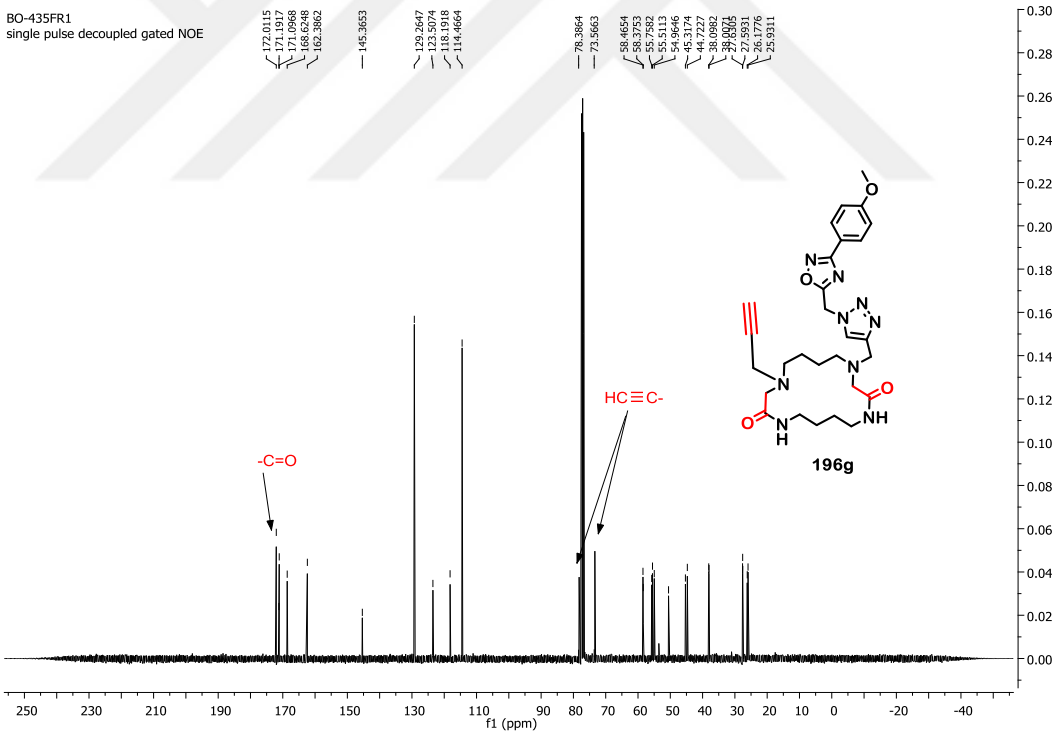


Figure 4.46. ^{13}C NMR spectrum of the compound **196g**

Upon examination of the IR data of **197g**, disappearance of the strong and weak absorptions at around 3327 cm^{-1} and 2096 cm^{-1} of the acetylenic group have been observed (Figure 4.48). ^{1}H NMR spectra also showed the four methylene protons as separate singlet and doublets at around 5.92–5.90 and 3.81–3.76 ppm, six

aromatic protons, also two protons originated from 1,2,3-triazole ring can be seen at around 7.90, 6.92 ppm (Figure 4.49). Carbonyl carbons appeared at 173–172 ppm region (Figure 4.50). HRMS: m/z (ESI-TOF, $[M+H^+]$) calcd for : $C_{38}H_{46}N_{14}O_6$: 795.3803; found: 795.3804 for compound **197g**.

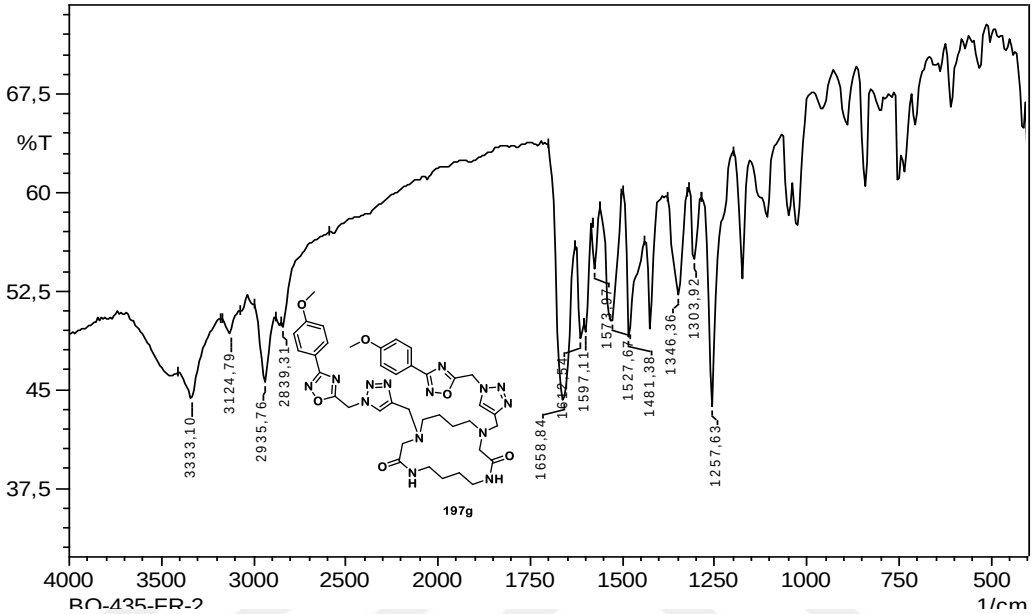


Figure 4.47. IR spectrum of compound **197g**

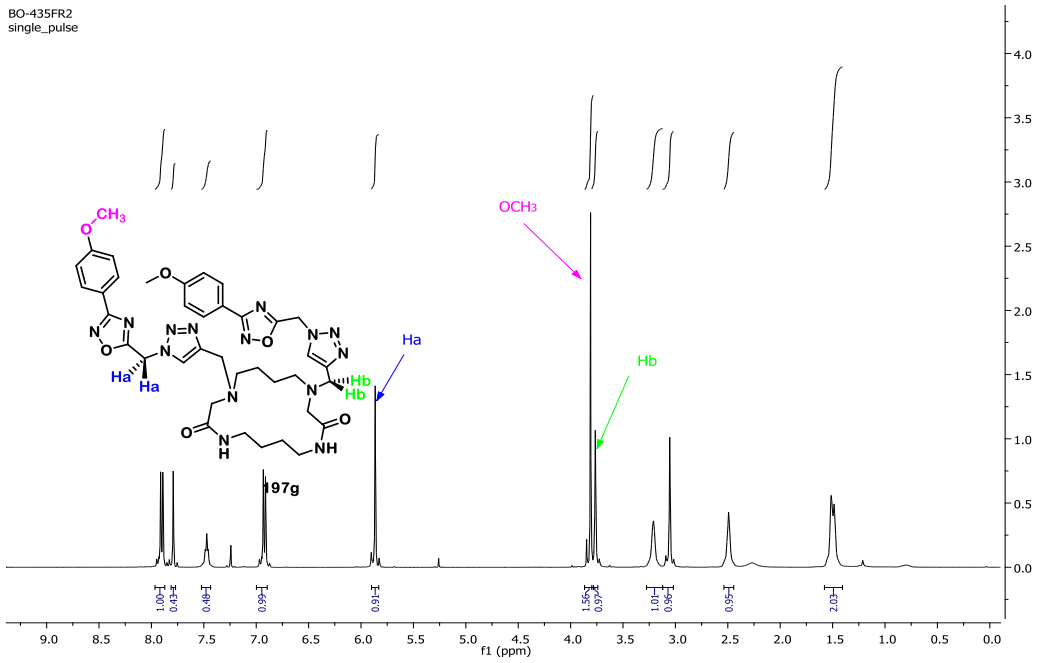


Figure 4.48. ^{1}H NMR spectrum of the compound **197g**

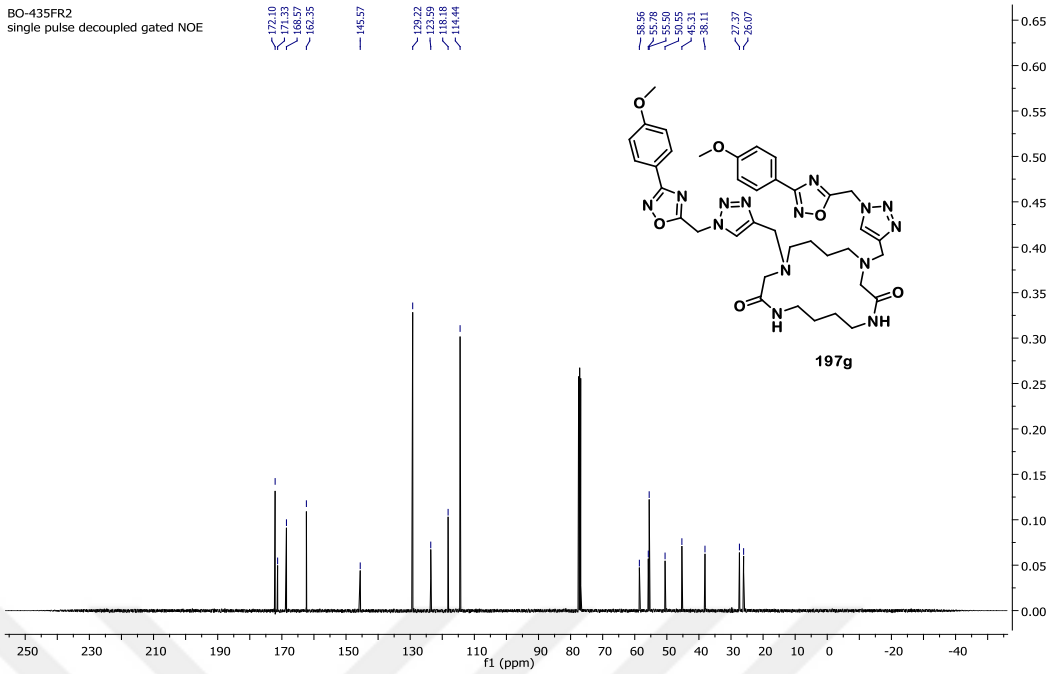
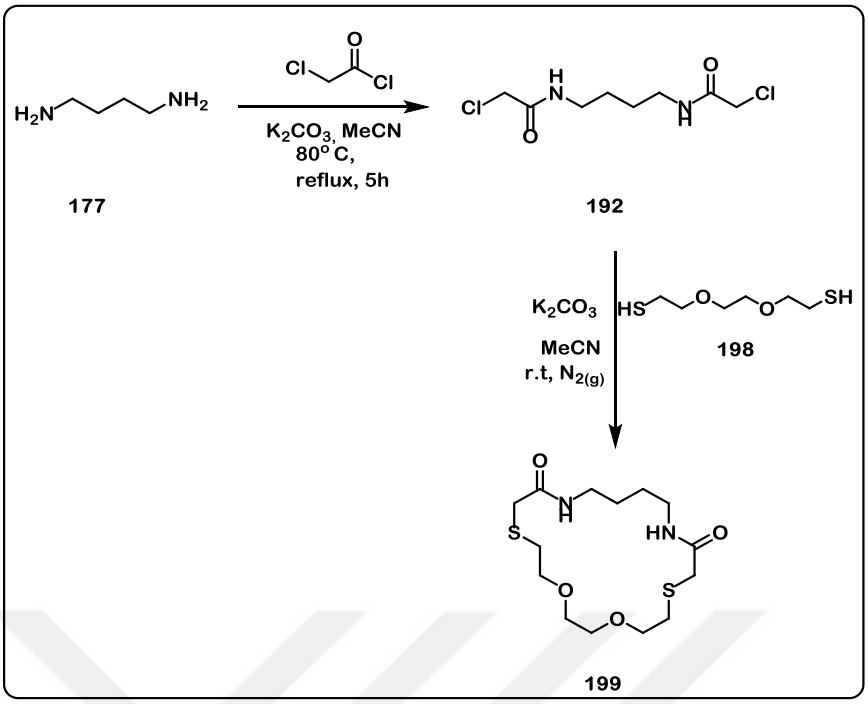


Figure 4.49. ^{13}C NMR spectrum of the compound **197g**

4.4 Synthesis of the Different Types of Crown Ethers

In the direction of our goal we have focused on the synthesis of various type of crown ethers unlike the ones we have mentioned previously. Since the crown ethers have found too many practical usages over the decades starting from their first dicovery in many areas such as material science, pharmaceutical science, and industry due to their affinity towards the metal cations (Mane, et al., 2016; Maciejewski, et al.,2009; Herman, et al., 2003; Wang, 2000; Vaira, et al., 1999). Herein we further introduce the synthesis of the 1,17-dioxa-3,14-dithia-6,11-diazacyclononadecane-5,12-dione **199** (Scheme 4.45). This novel compound **199** was obtained in two steps. The first step was mentioned previously (Scheme 4.43), and in the second step the crablike cyclization occurred between dithiol **198** and the amide **192** (Scheme 4.45).



Scheme 4.41. Synthesis of the 1,17-dioxa-3,14-dithia-6,11-diazacyclonona decane-5,12-dione **199**

Upon the examination of the ^{1}H NMR spectrum of the compound **199**, the protons from amide and methylene protons which are closer to carbonyl resonate as singlet at 7.16 and 3.26 ppm. Further, the methylenic protons originated from 2,2'-(ethane-1,2-diyl bis (oxy))diethanethiol **198** are observed at around 3.70–1.59 ppm (Figure 4.51). Carbonyl carbons can be viewed at 170 ppm in ^{13}C NMR, and the structural elucidation is supported by the LC-MS data which gave $[M+Na]^{+}$ at 373 *m/z* as base peak (Figure 4.52).

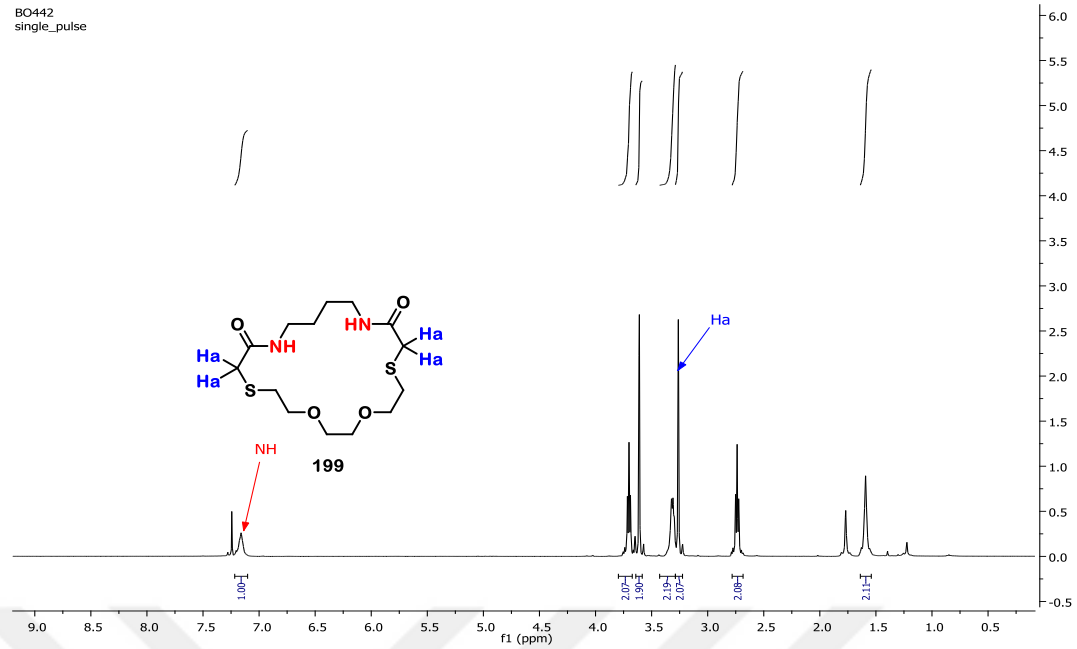


Figure 4.50. ^{1}H NMR spectrum of compound **199**

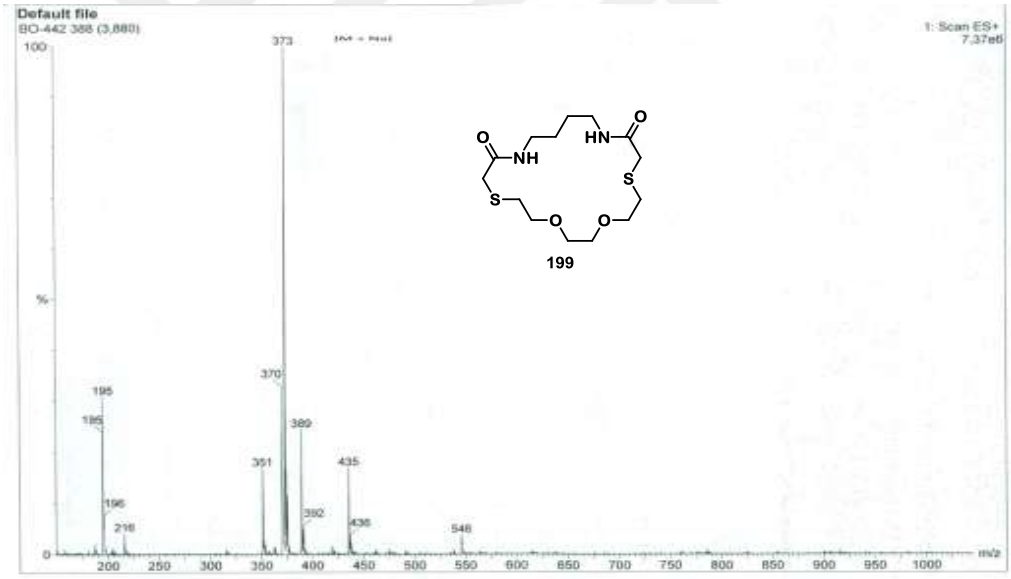
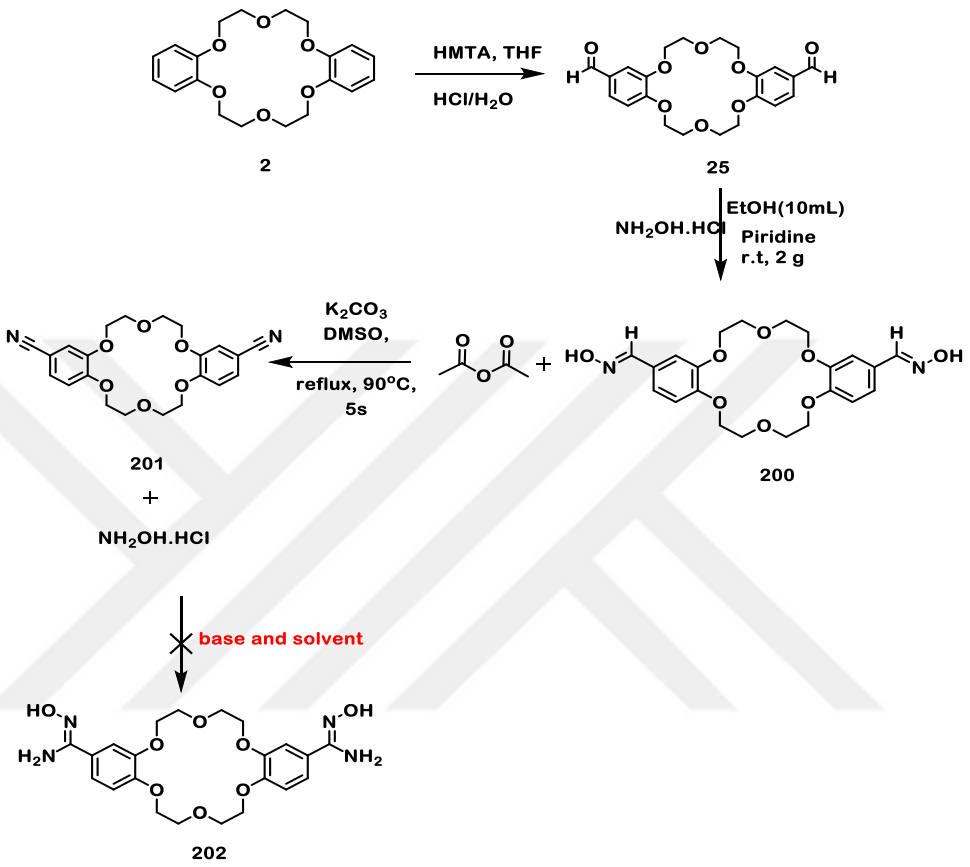


Figure 4.51. LC-MS spectrum of compound **199**

In the literature, Duff and Bills first reported formylation of phenolic compounds by using hexamethylene tetramine (Duff and Bills, 1932, 1934). The formylation of the dibenzo-18-crown-6 were conducted according to Duff reaction conditions by Jagadele and coworkers (Jagadale, et al., 2015). This reaction route encouraged us to synthesize the products **200** and **201** (Scheme 4.46) and then we wanted to transform **201** to **202** by means of $NH_2OH.HCl$, Et_3N in EtOH, but this

trial was unsuccessful. Different reaction conditions were tried (Table 4.2). But any of them did not work at all to convert dinitrile **201** into diamidoxime **202**. Consequently, we were able to generate two crowns identified by IR, (^{1}H, ^{13}C) NMR and LC-MS spectra and also physical data (Figure 4.53–4.57).



Scheme 4.42. Synthesis of the benzocrown ethers with nitrile and aldoxime functionalities **200**, **201.**

Table 4.2. Basic solutions assayed for the synthesis of compound **202**

Type	Base	Solvent	Temperature (^{o}C)	Product
1	Et_3N	EtOH	80	No Reaction
2	Et_3N	MeOH:EtOH	80	No Reaction
3	NaOH	EtOH	80	No Reaction
4	t-BuOK	DMSO	100	No Reaction
5	t-BuOK	PhMe:MeOH	100	No Reaction
6	DABCO	DMSO	100	No Reaction
7	Pyridine	Pyridine	100	No Reaction
8	K_3PO_4	DMF	100	No Reaction
9	NaH	THF	65	No Reaction

When we checked the IR spectrum of the compound **200**, the OH and C=N absorbtions are seen at 3369 and 1600 cm^{-1} respectively (Figure 4.53). The compound **200** have two distinct chemical shifts; NOH at around 10.89 ppm and are iminic proton at around 7.98 ppm (Figure 4.54). This was supported by ^{13}C NMR and LC-MS spectra (Figure 4.55).

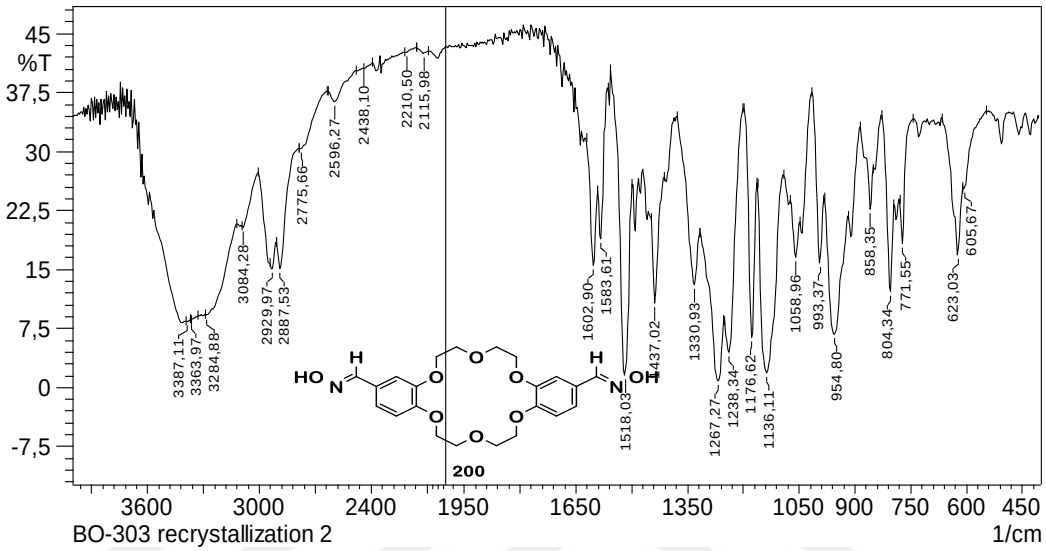


Figure 4.52. IR spectrum of the compound **200**

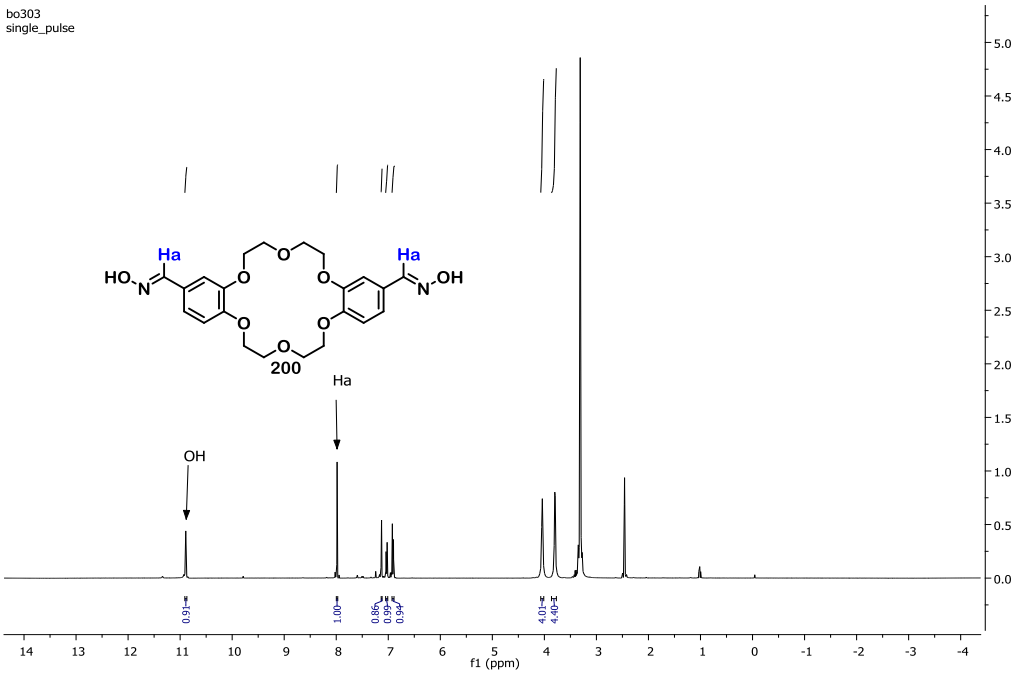


Figure 4.53. ^{1}H NMR spectrum of compound **200**

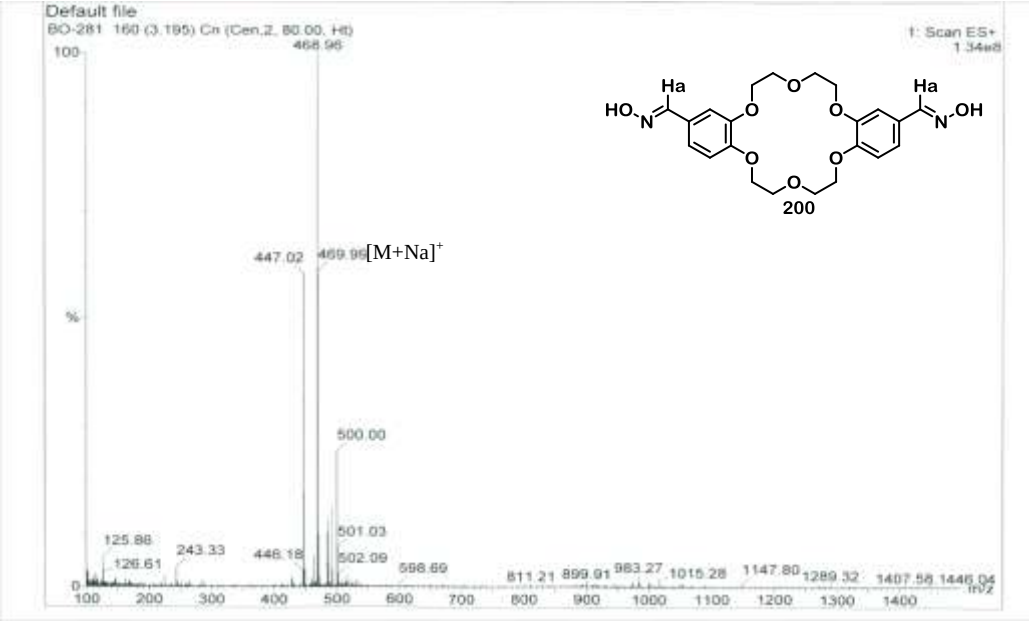


Figure 4.54. LC-MS spectrum of compound **200**

For the compound **201** the first evidence was nitrile absorption in the IR spectrum at 2225 cm^{-1} (Figure 4.56). It was supported by the (^{1}H,^{13}C) NMR and LC-MS spectra (Figures 4.57, 4.58) and physical characteristics.

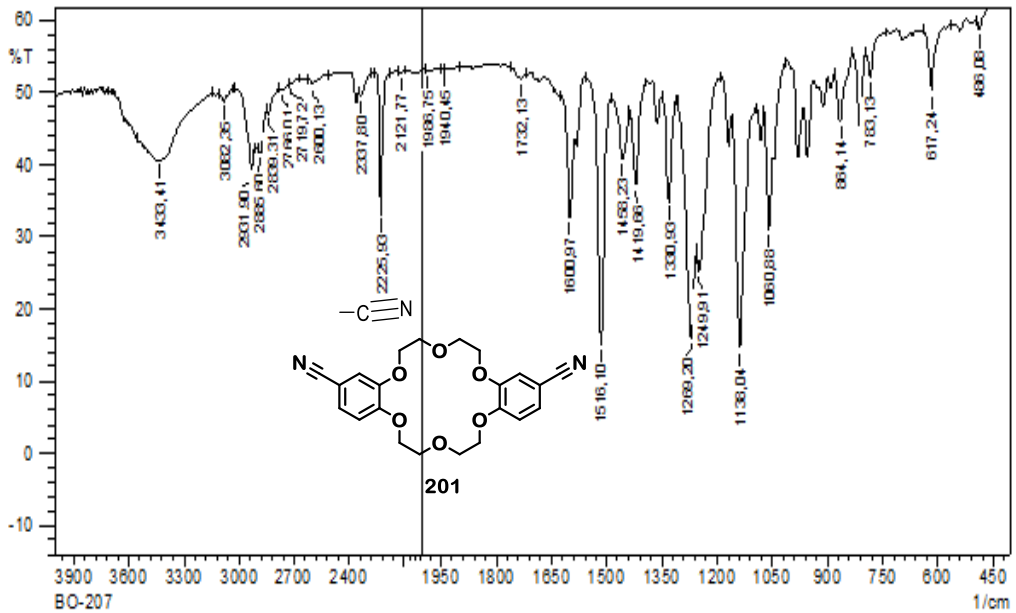


Figure 4.55. IR spectrum of compound **201**

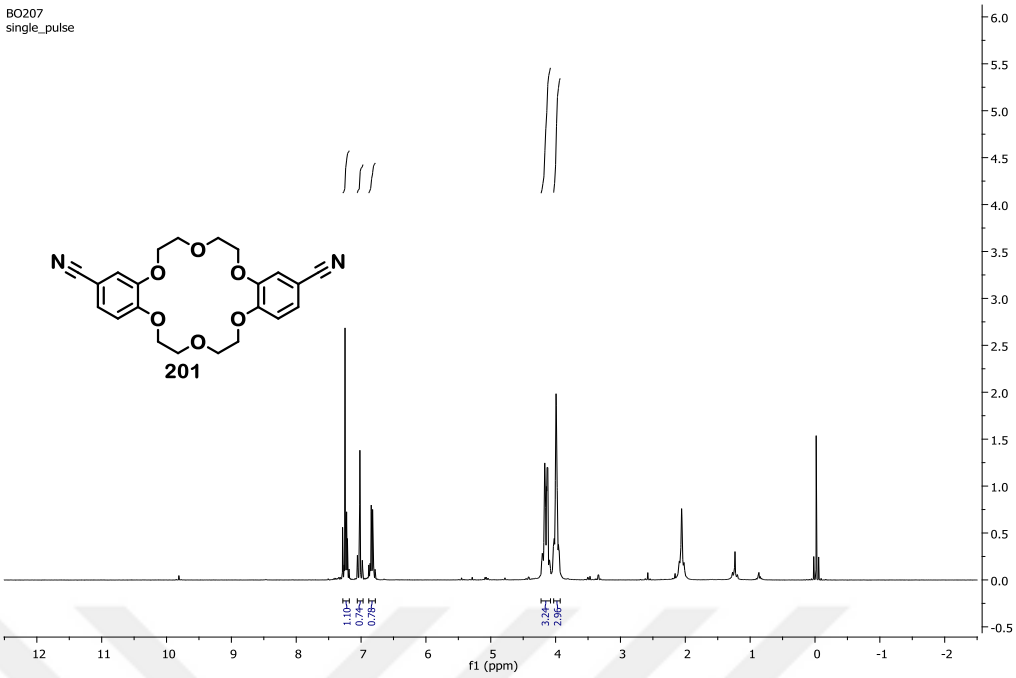


Figure 4.56. ^{1}H NMR spectrum of compound **201**

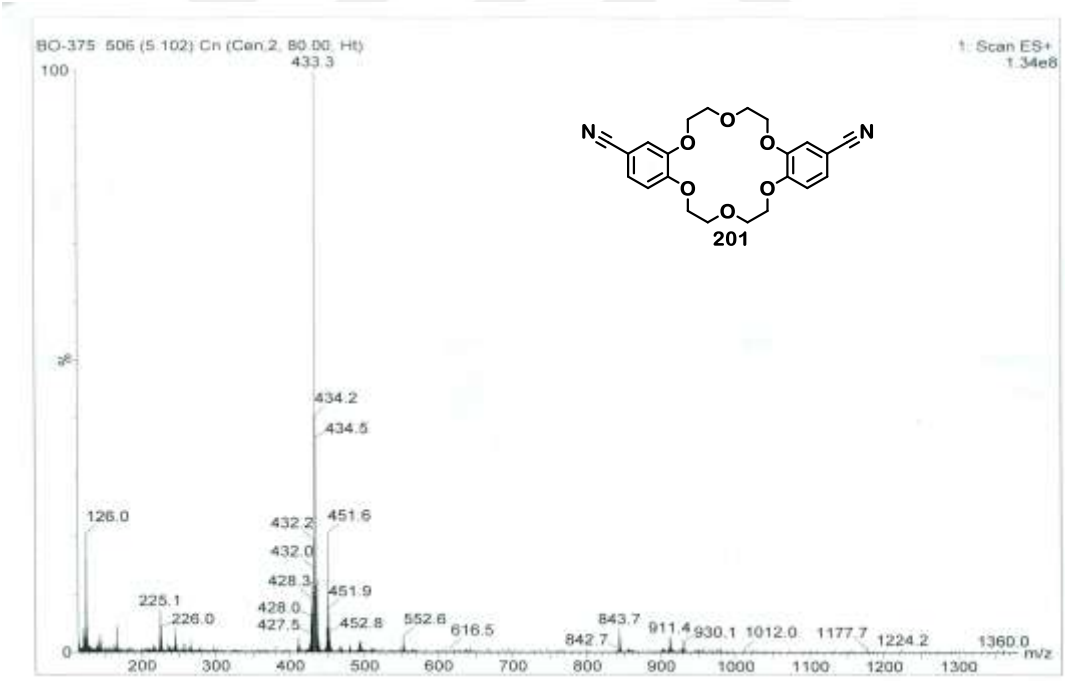


Figure 4.57. LC-MS Spectrum of compound **201**

5. CONCLUSIONS AND RECOMMENDATIONS

In summary, throughout this thesis work, the experiments designated to obtain the target macrocylic ethers were introduced in the following four sections.

In the first part, we have focused on the synthetic sequence for the crown compound **164**. After that 8 novel chloromethyl-1,2,4-oxadiazole substituted aza-crowns **(164a-h)** were constructed. Moreover, 9 novel chloromethyl-1,2,4-oxadiazole substituted benzodioxatriaza crown **168(a-i)** were synthesized. The structures of all the compounds **164**, **(164a-h) and 168(a-i)** were exactly identified by means of ^{1}H NMR, ^{13}C NMR, IR, LC-MS spectra and HRMS measurements.

In the second part, while we tried to synthesize the benzocrown ethers bearing 1,2,4-oxadiazole moiety in different stages, we obtained an unexpected product **181** also we reached our goals for this part. The benzo-crown ethers with 1,2,4-oxadiazole **186** and **191** were synthesized in different six steps. All of these compounds **170, 171, 172, 173, 174, 175, 176, 181, 182, 184,185, 186, 187, 188, 189, 190, 191** have not been reported in the literature, to our best knowledge (Web of Science, SciFinder Scholar), these compounds are elucidated by physical and spectral characteristics.

In the third part, 1,3-dipolar cycloadditions of azamacrocycles carrying acetylenic side chain with azidomethyl 1,2,4-oxadiazoles were accomplished in two protocols. In the first protocol, azamacrocycle **193** and azamacrocycles with acetylenic part **194** were synthesized and characterized by the spectral and physical data. In the second protocol, 1,3-DC reaction between dipoles **195(a-h)** and dipolarophile **194** was carried out and the reaction resulted in a mixture of two different cycloadducts. Thus, 16 novel different cycloadducts **196** in which one of the acetylenic groups underwent cycloaddition, **197(a-h)** in which both acetylenic groups underwent cycloaddition were identified by means of ^{1}H NMR, ^{13}C NMR, LCMS, HRMS and IR spectra.

In the final part, in addition to previously described crown ethers, 3 different crowns **199, 200, 201** were successfully synthesized and identified**.**

As a final remark, to our best knowledge of literature, all of these heterocyclic compounds are novel. Since they can be considered as potential bioactive heterocycles by taking account of their similar analogs in terms of main structural skeleton and existence of oxadiazole, triazole rings along with azamacrocycle, in the near future, it will be arranged to assay a series of biological activity screenings in a collaborative manner with internationally well-known laboratories.

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APPENDICES

7. APPENDICES

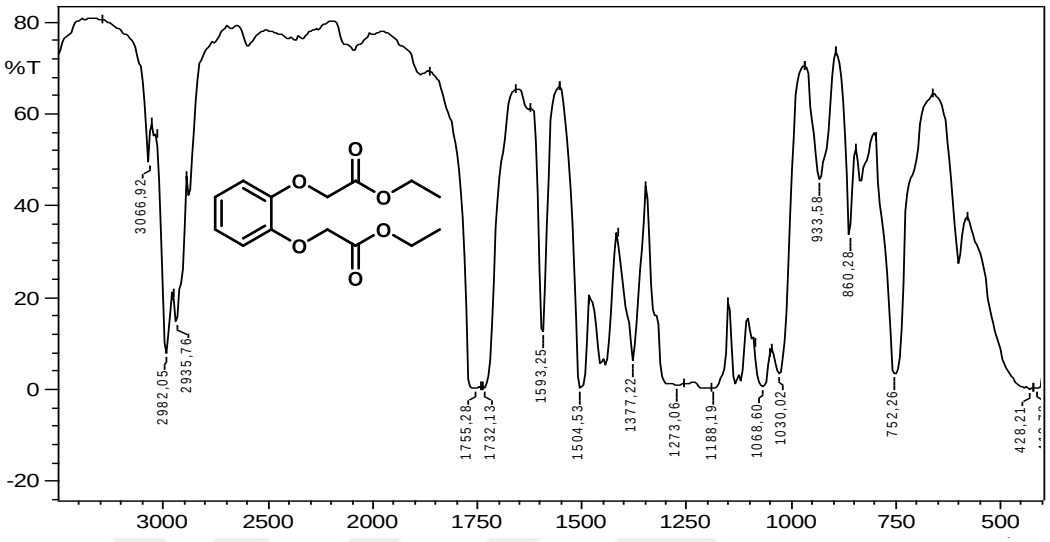

Figure 7.58. IR spectrum of compound **162**

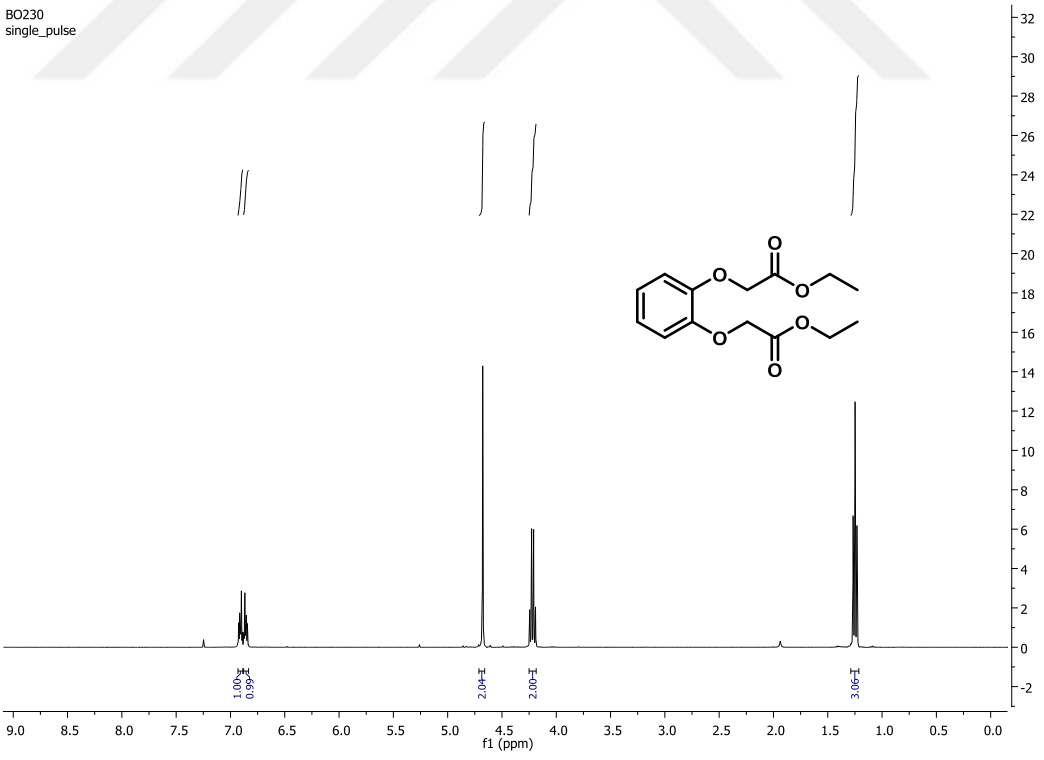

Figure 7.59. ^{1}H NMR spectrum of compound **162**

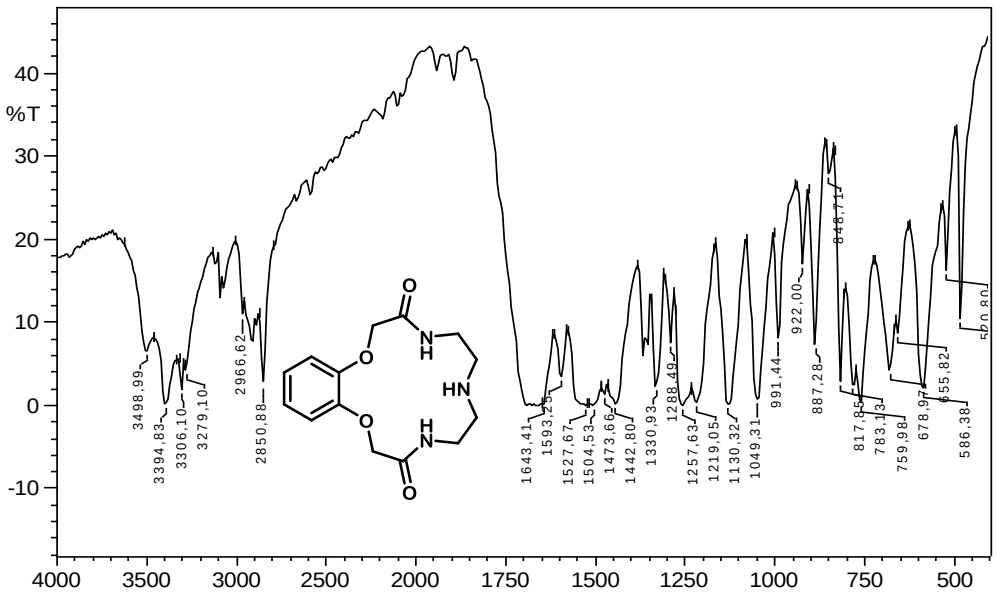

Figure 7.60. IR spectrum of compound **163**

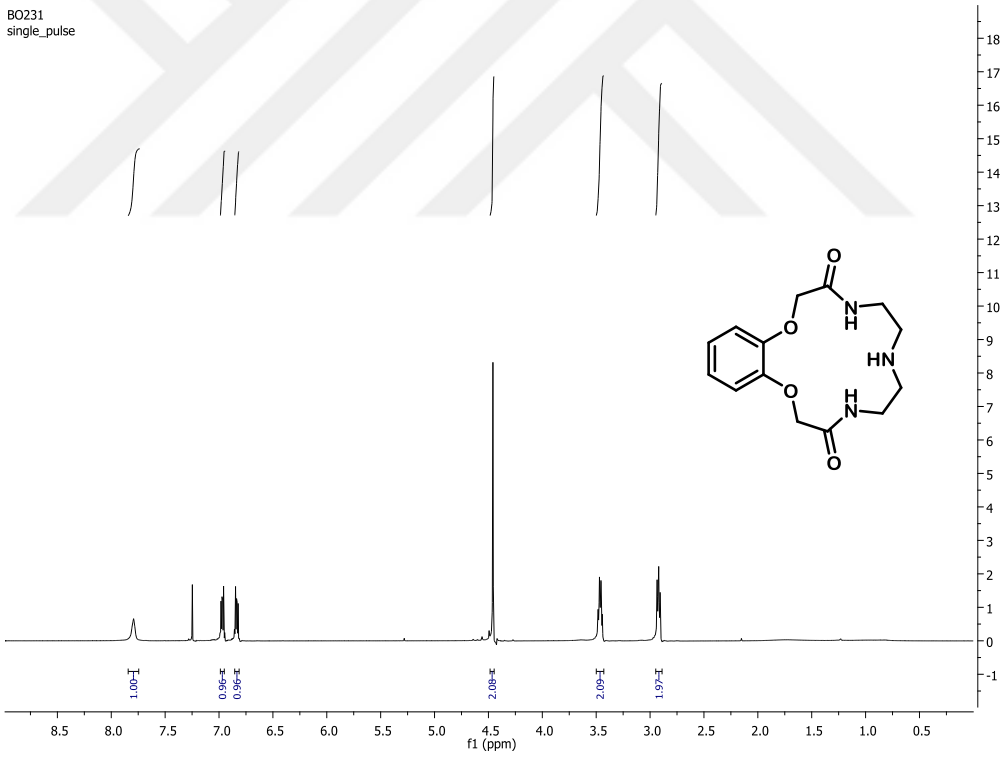

Figure 7.61. ^{1}H NMR spectrum of compound **163**

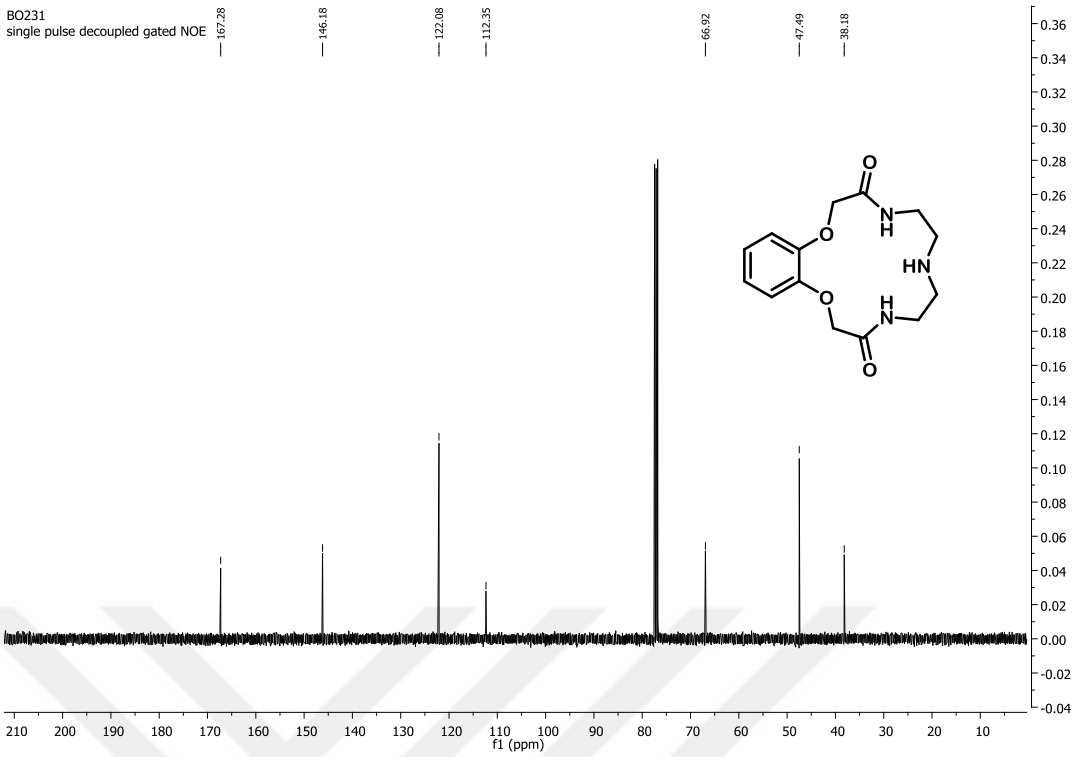

Figure 7.62. ^{13}C NMR spectrum of compound **163**

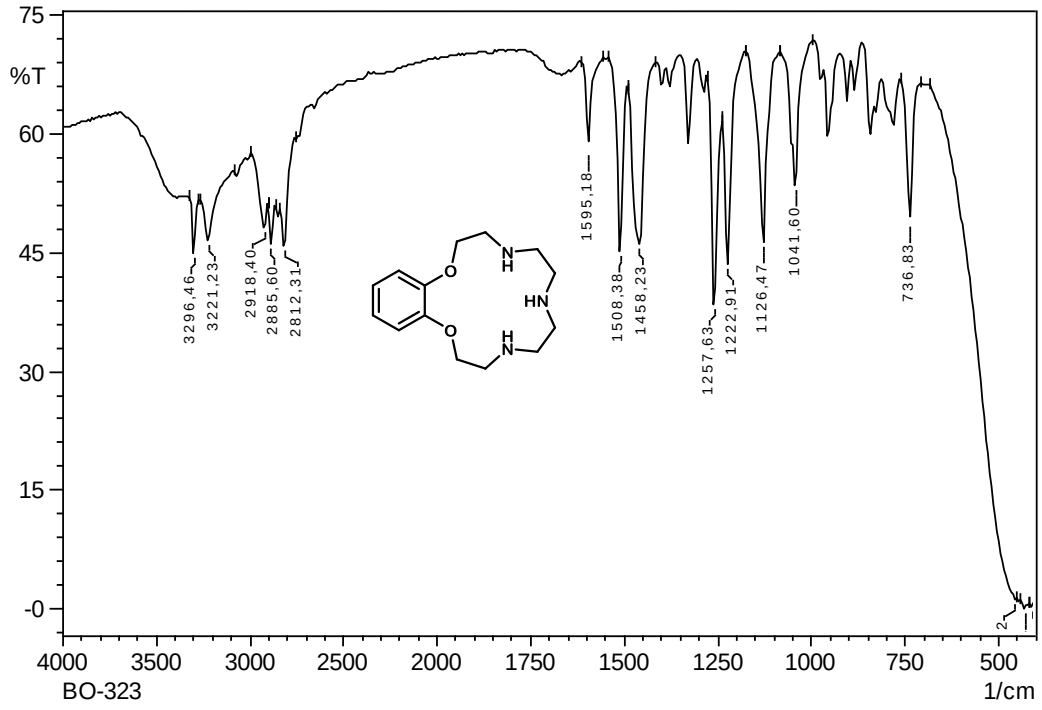

Figure 7.63. IR spectrum of compound **164**

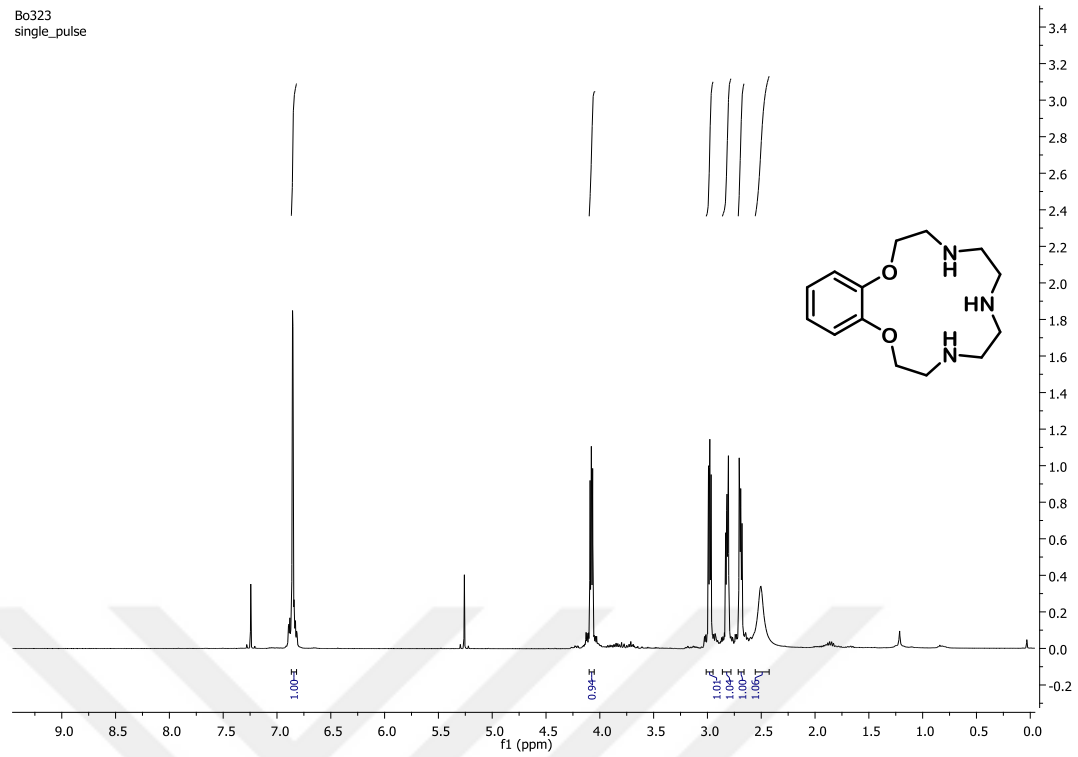

Figure 7.64. ^{1}H NMR spectrum of compound **164**

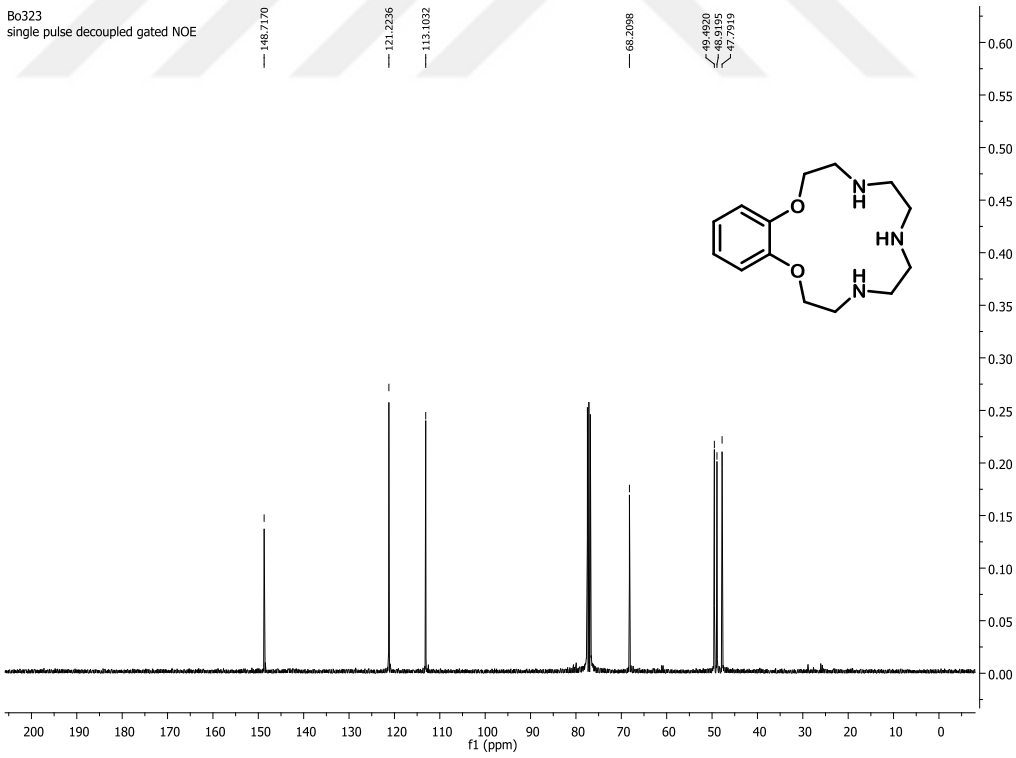

Figure 7.65. ^{13}C NMR spectrum of compound **164**

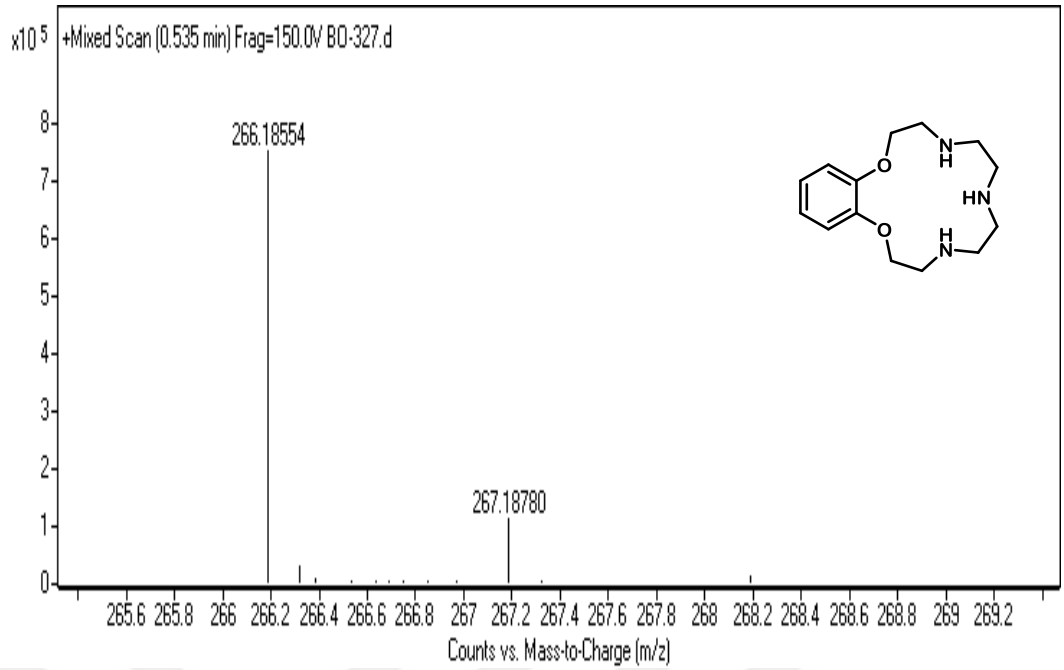

Figure 7.66. HR-MS Spectrum of compound **164**

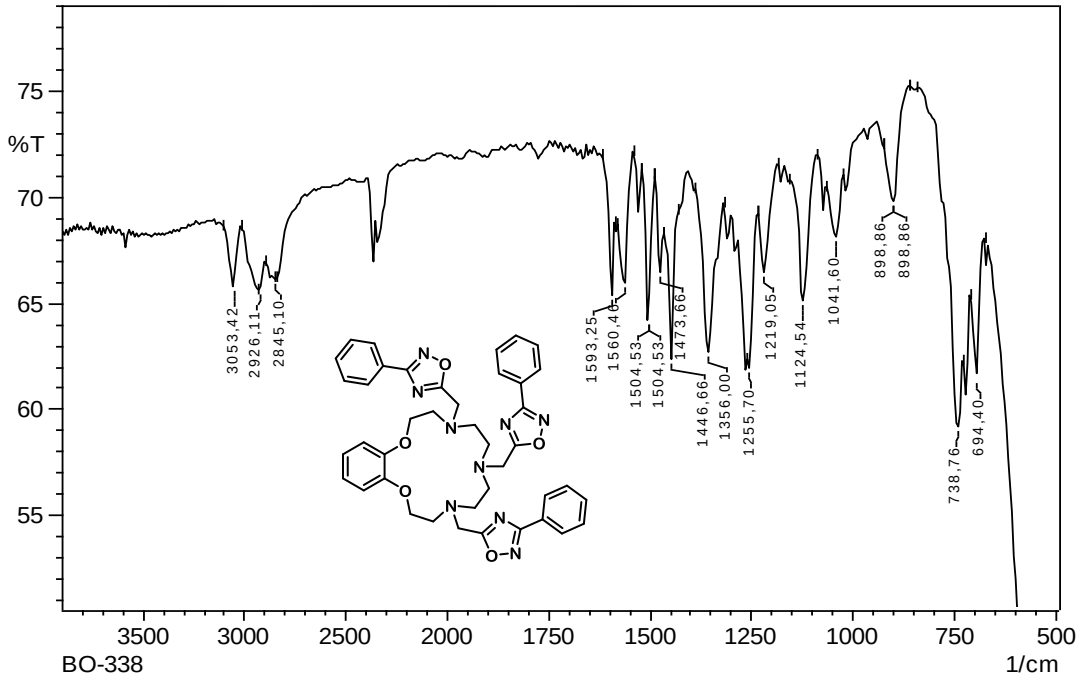

Figure 7.67. IR spectrum of compound **166a**

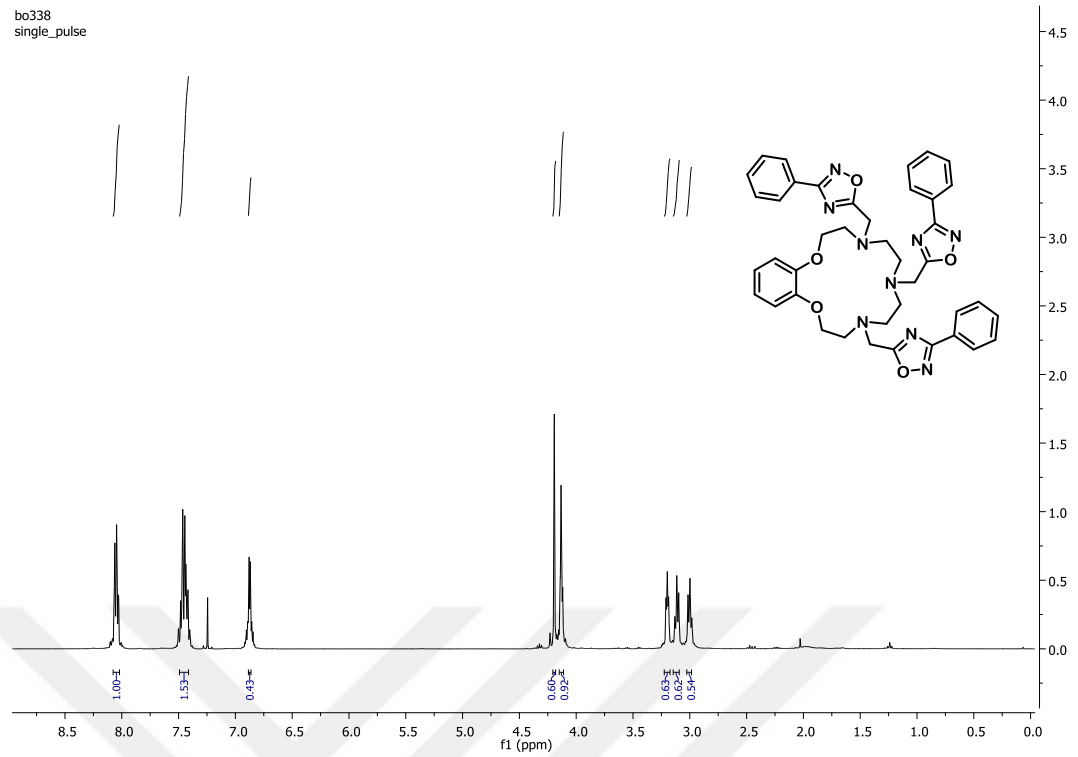

Figure 7.68. ^{1}H NMR spectrum of compound **166a**

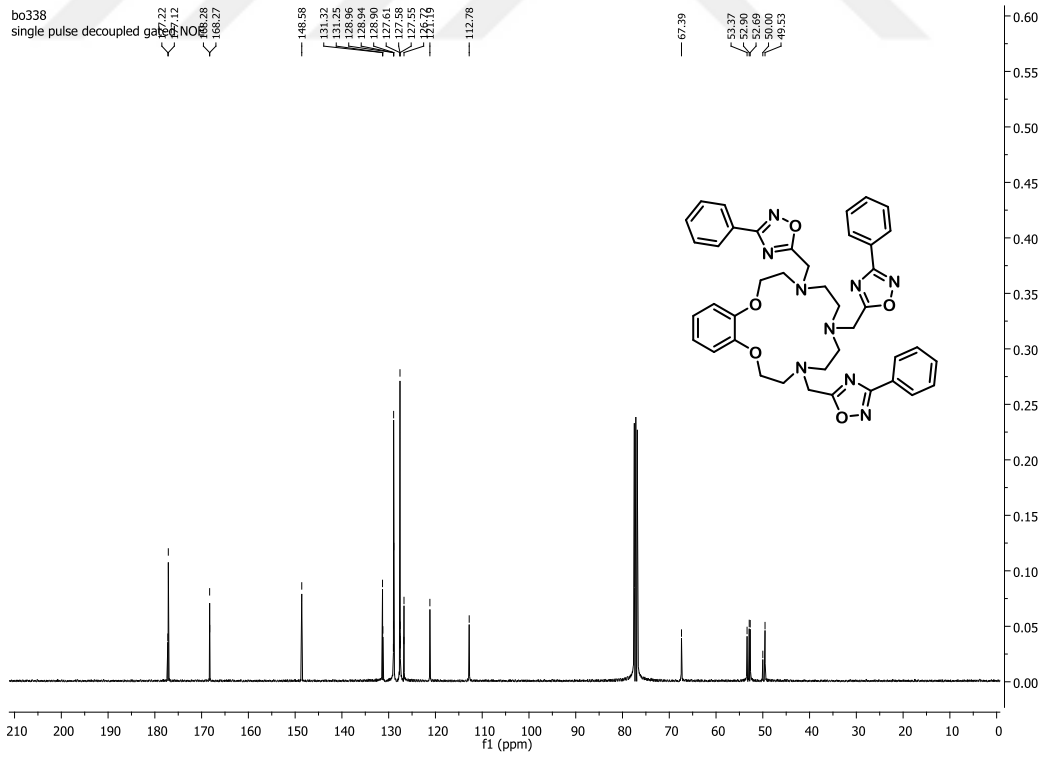

Figure 7.69. ^{13}C NMR spectrum of compound **166a**

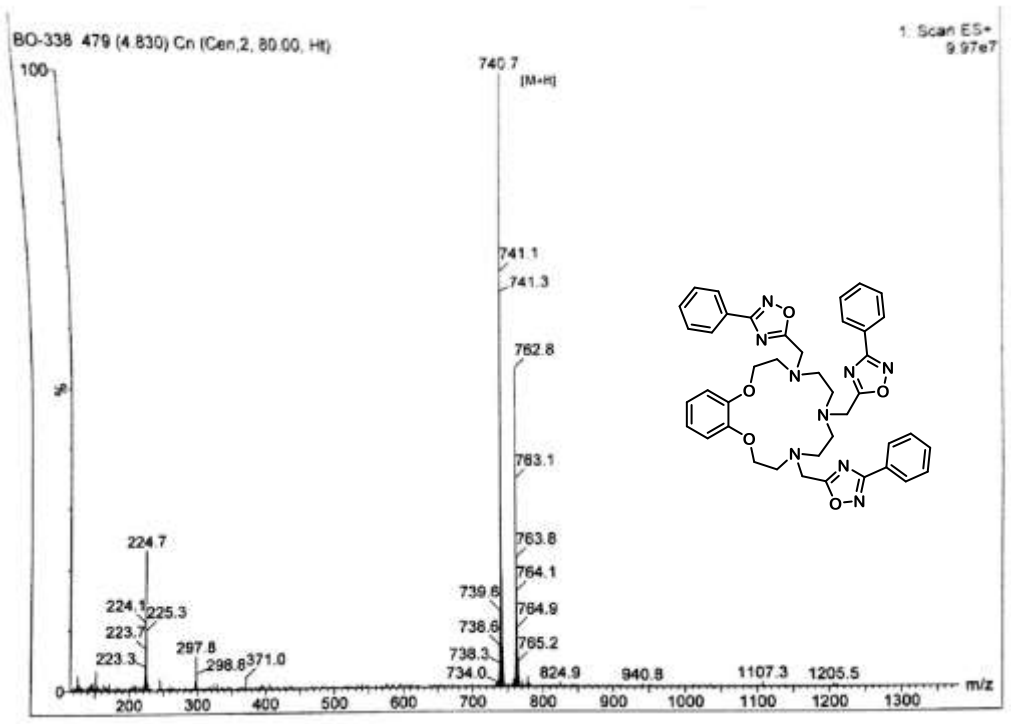

Figure 7.70. LC-MS Spectrum of compound **166a**

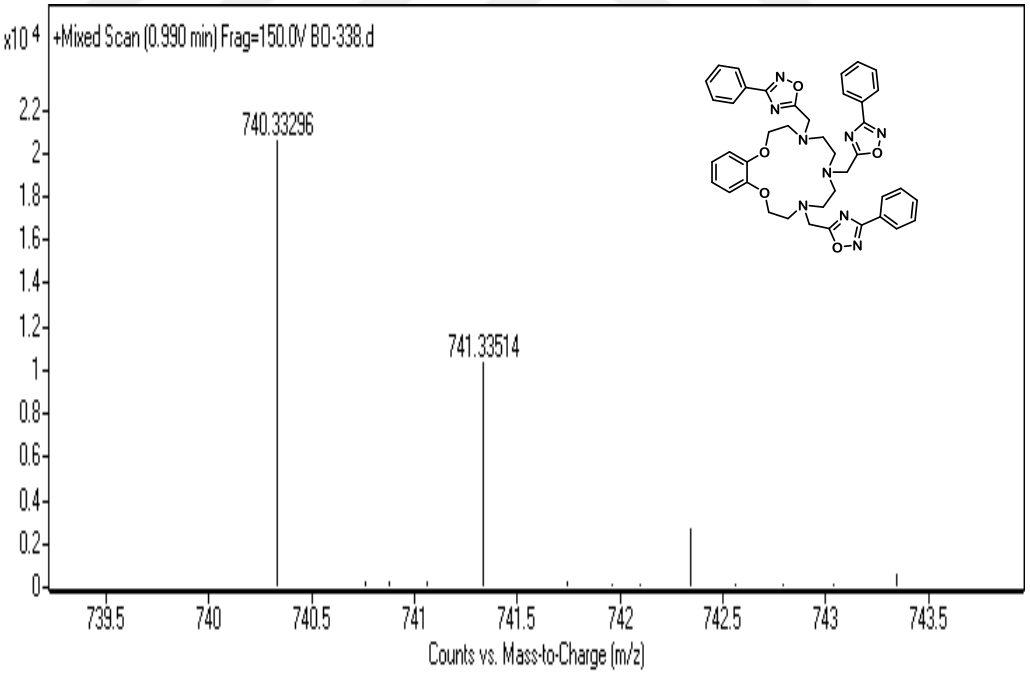

Figure 7.71. HR-MS Spectrum of compound **166a**

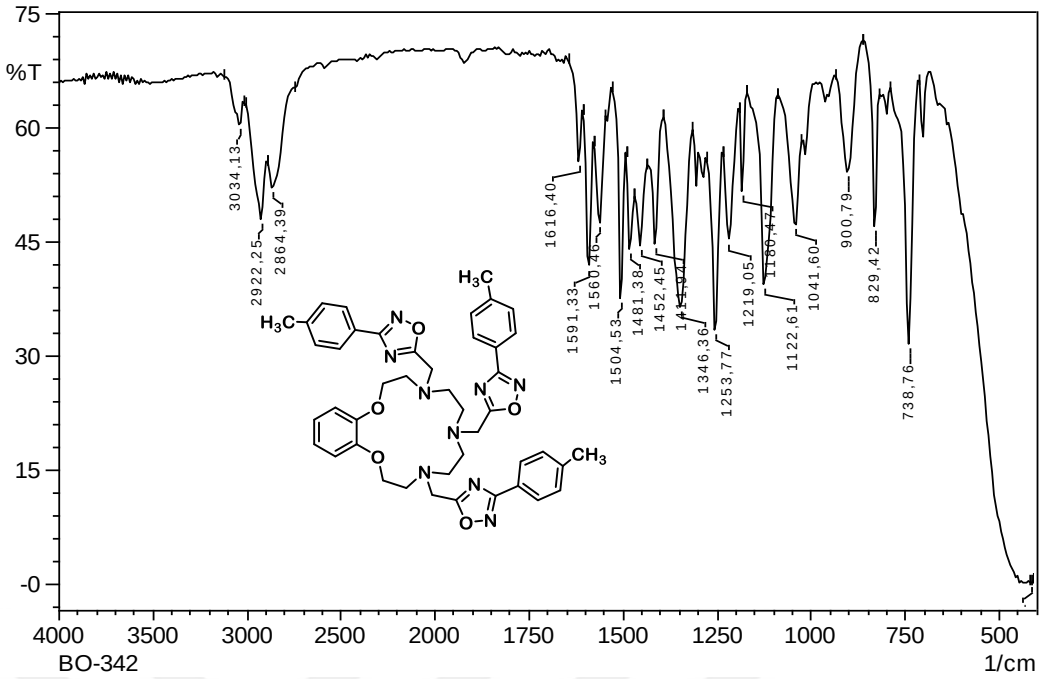

Figure 7.72. IR spectrum of compound **166b**

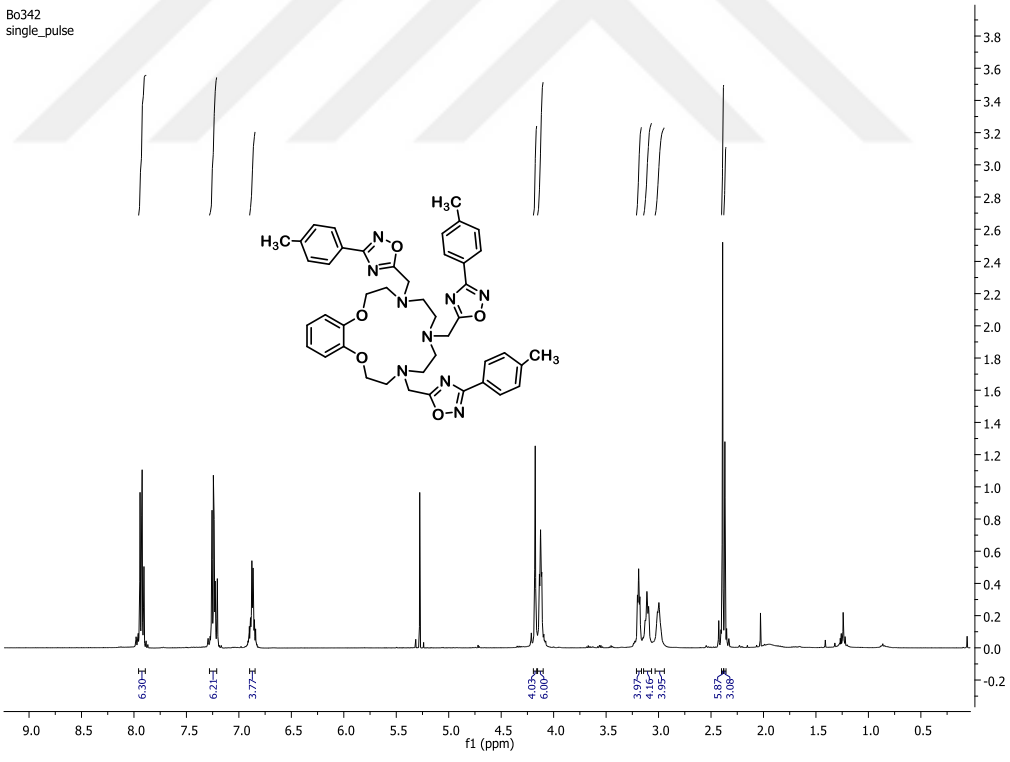

Figure 7.73. ^{1}H NMR spectrum of compound **166b**

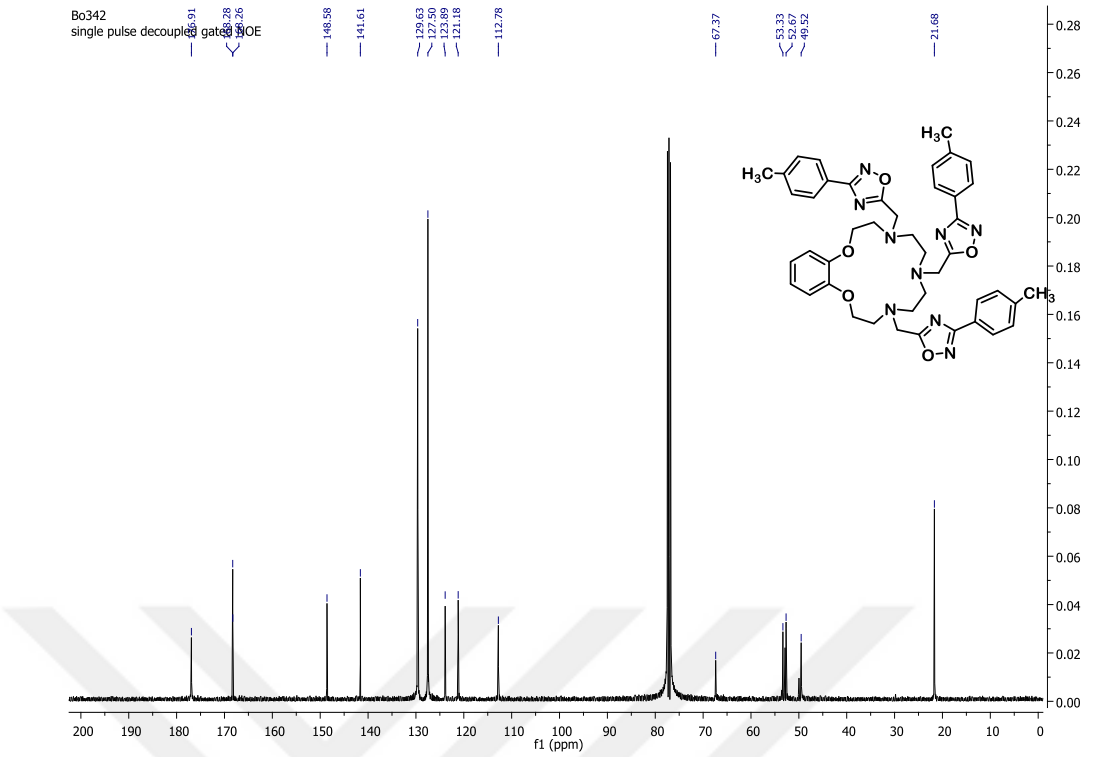

Figure 7.74. ^{13}C NMR spectrum of compound **166b**

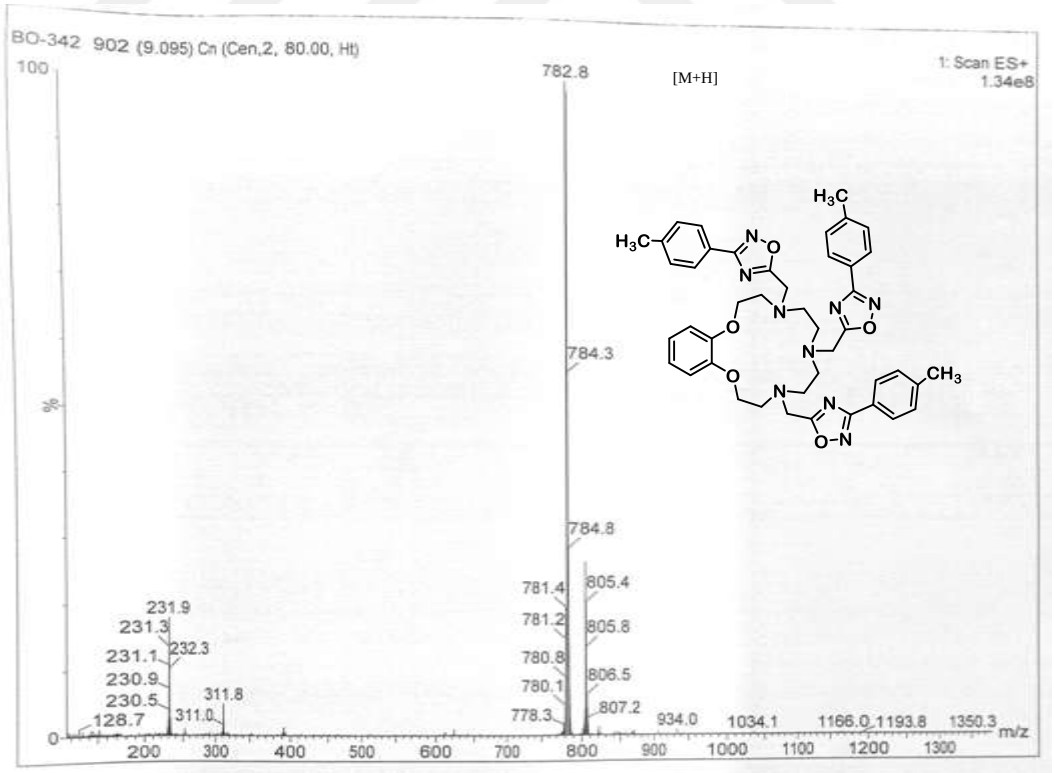

Figure 7.75. LC-MS Spectrum of compound **166b**

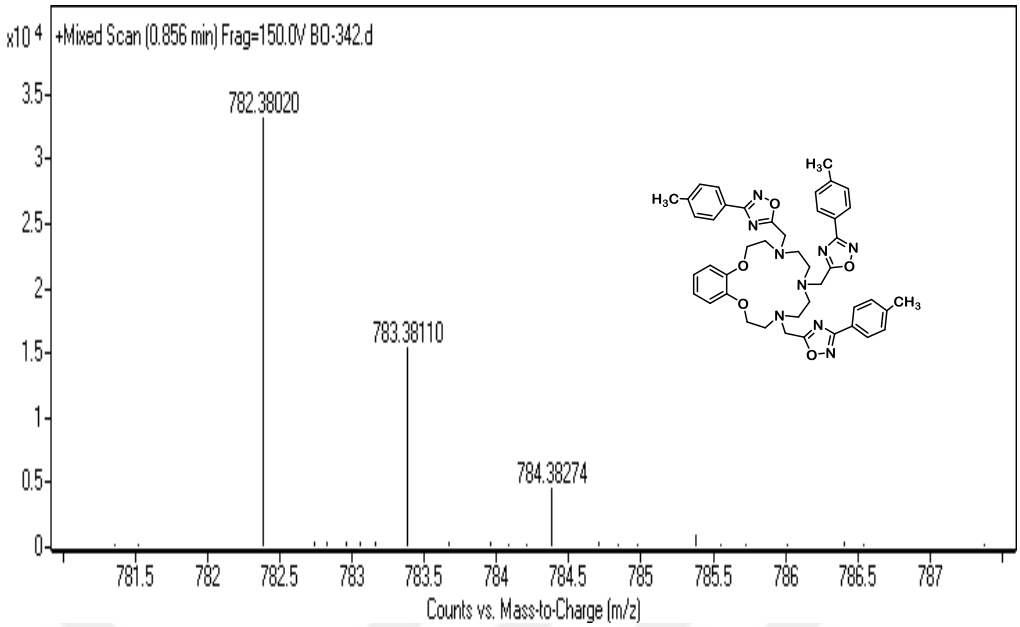

Figure 7.76. HR-MS Spectrum of compound **166b**

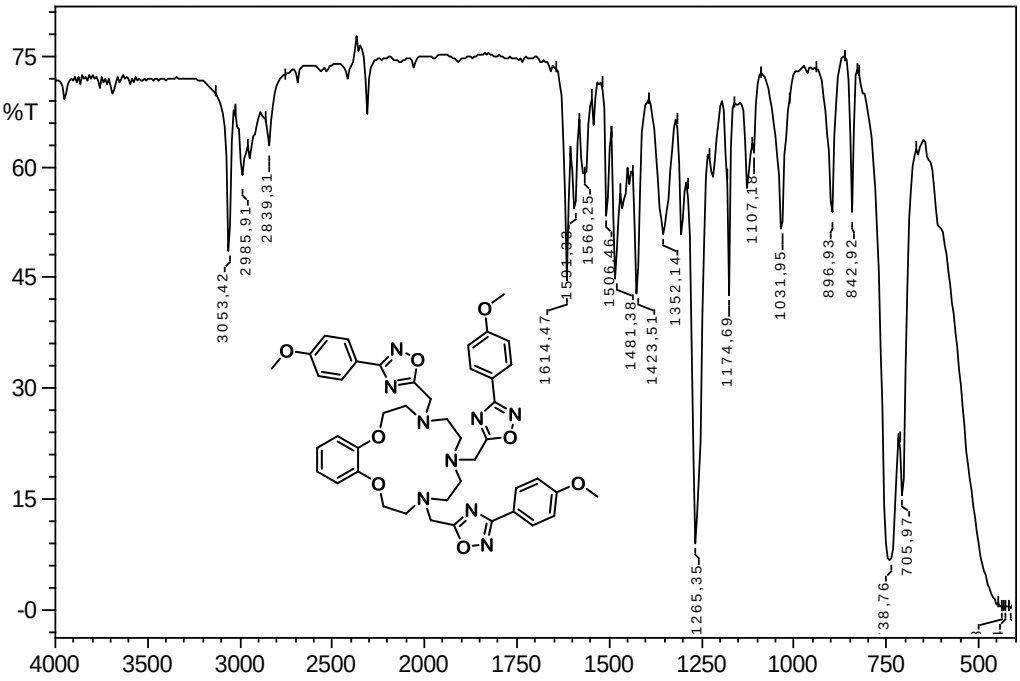

Figure 7.77. IR spectrum of compound **166c**

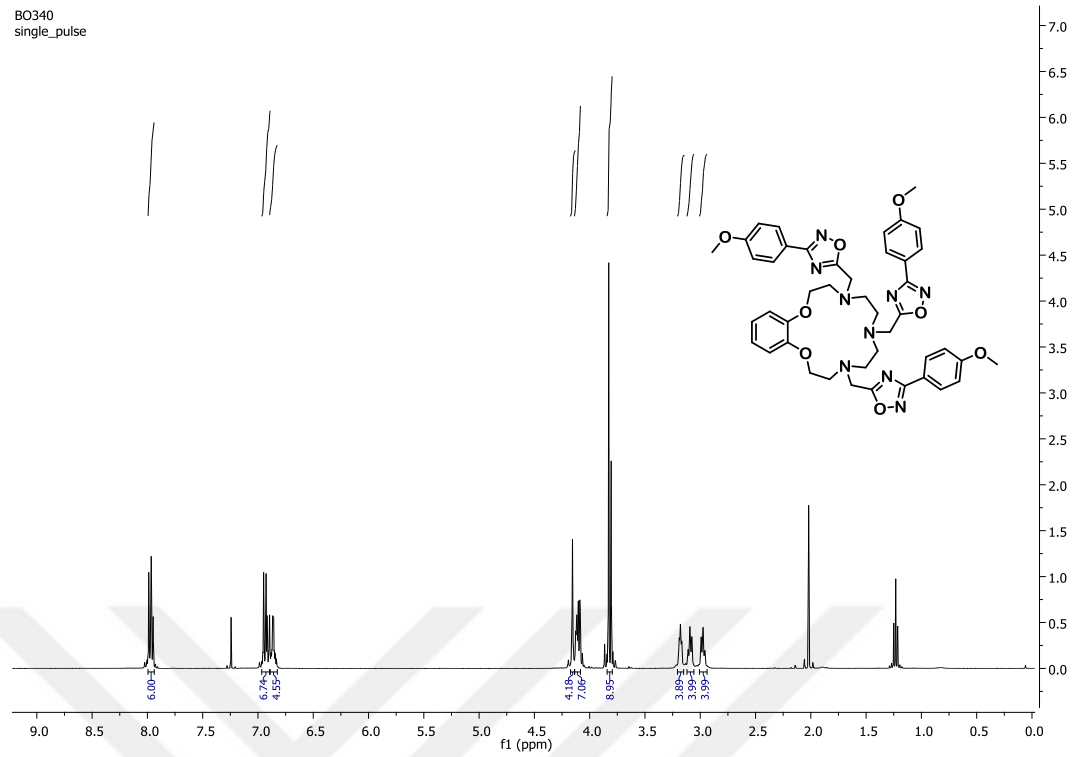

Figure 7.78. ^{1}H NMR spectrum of compound **166c**

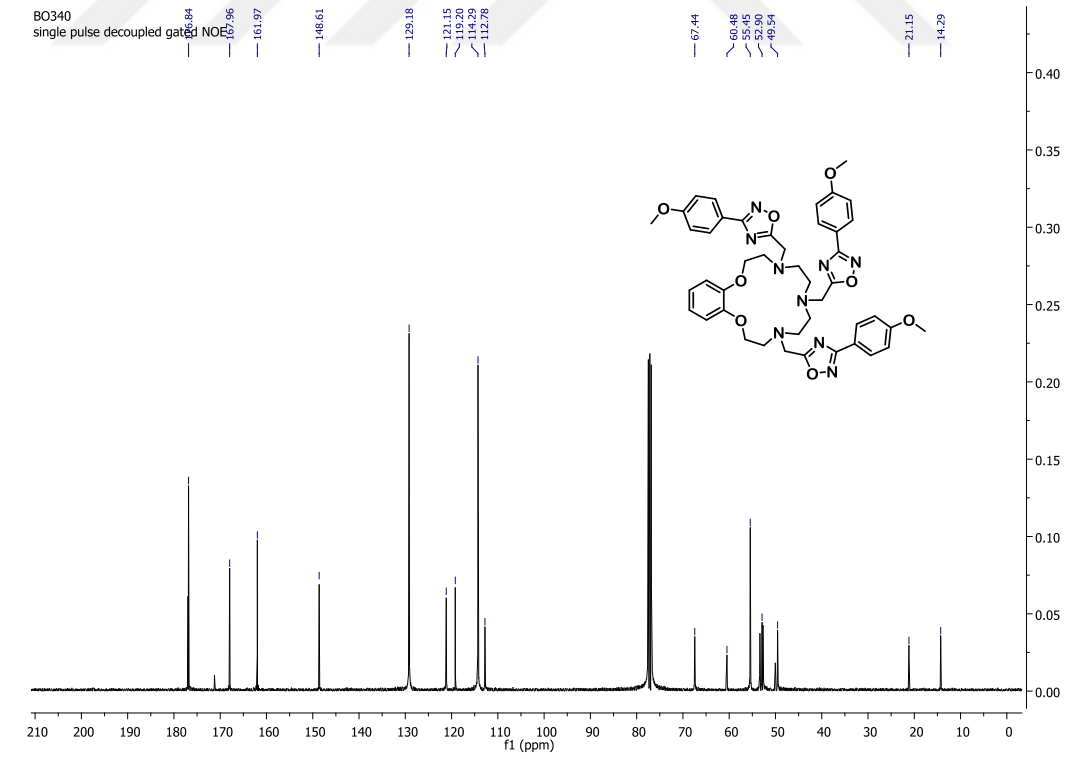

Figure 7.79. ^{13}C NMR spectrum of compound **166c**

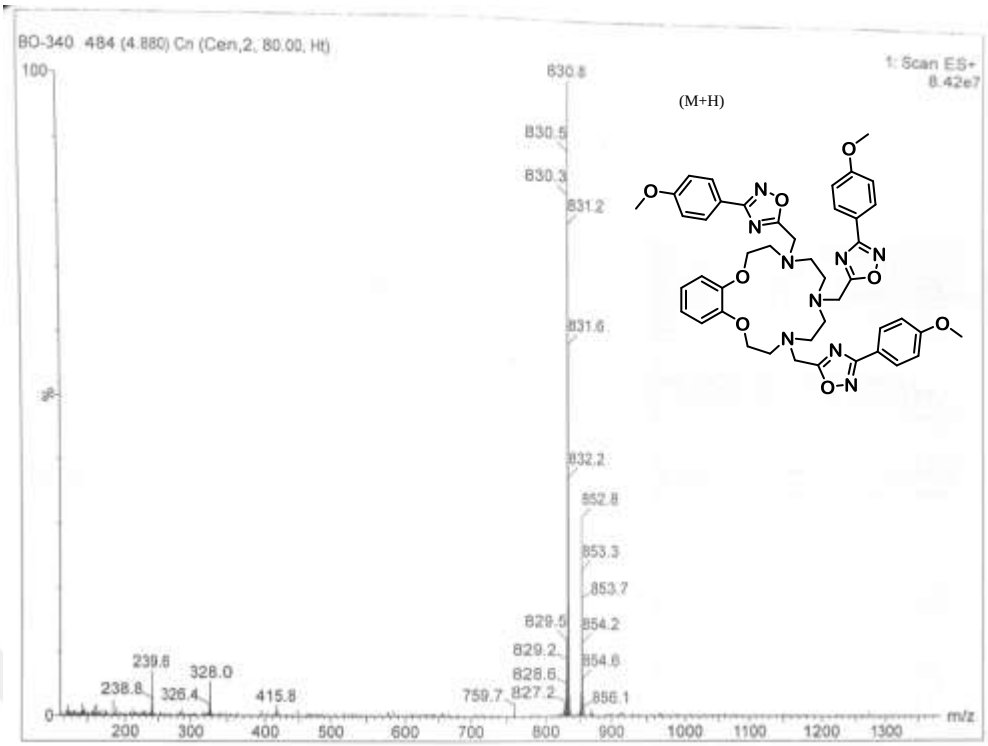

Figure 7.80. LC-MS Spectrum of compound **166c**

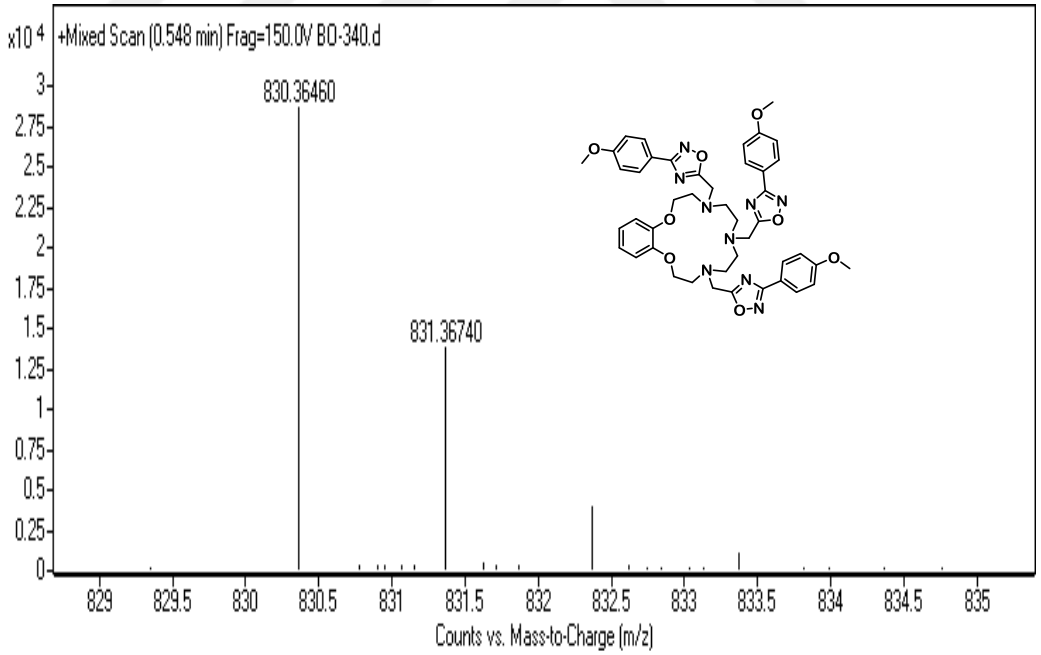

Figure 7.81. HR-MS Spectrum of compound **166c**

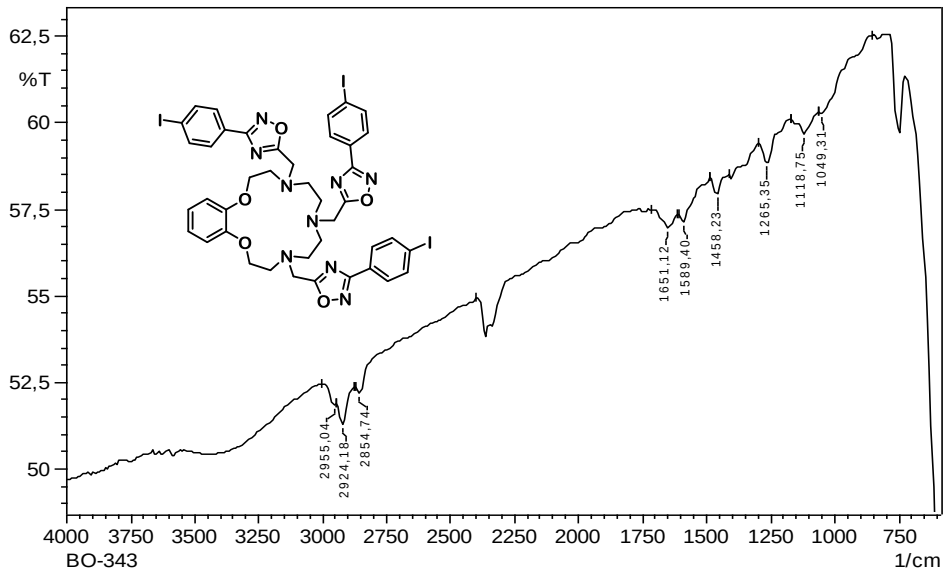

Figure 7.82. IR spectrum of compound 166d

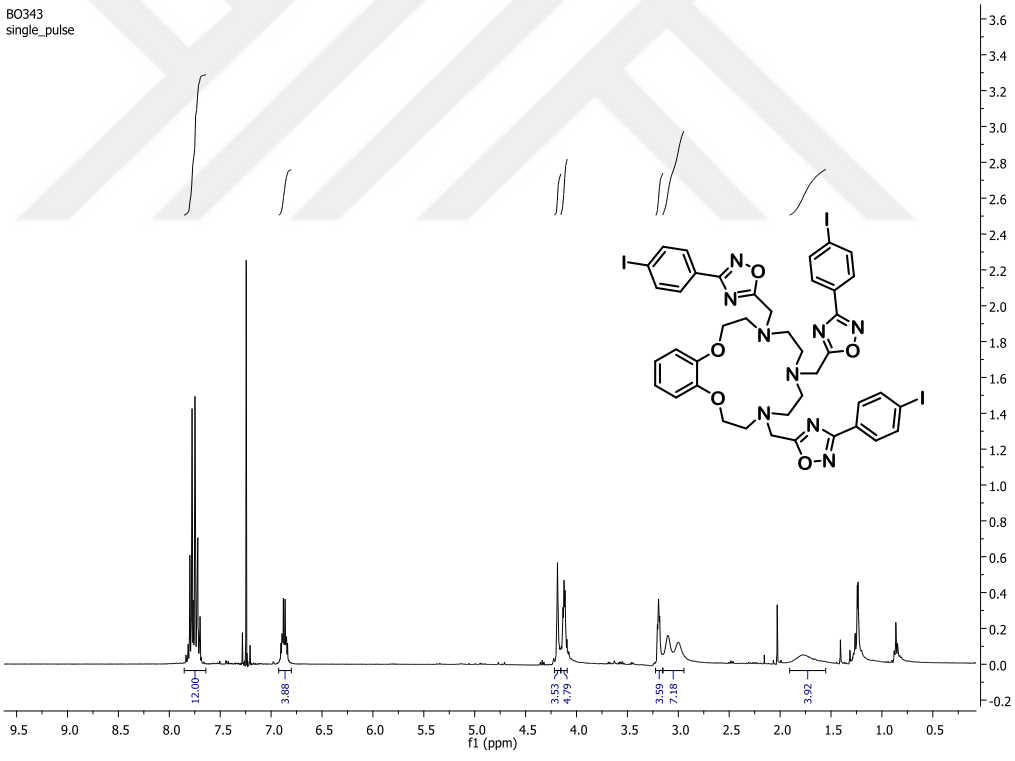

Figure 7.83. ^{1}H NMR spectrum of compound **166d**

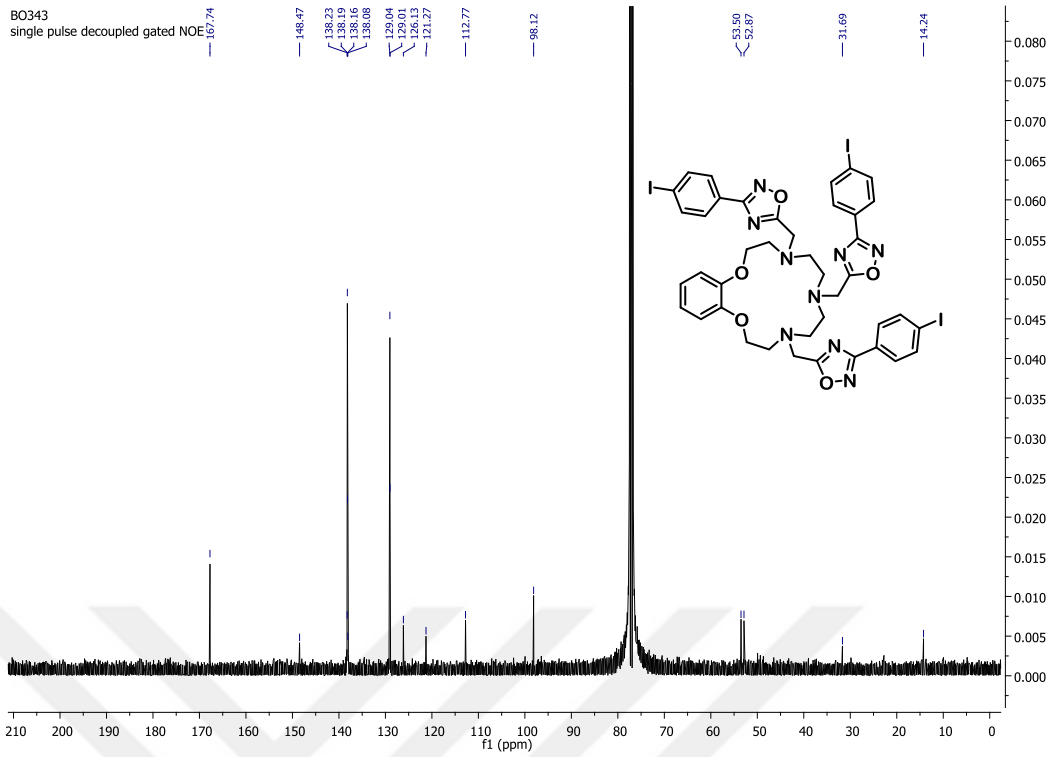

Figure 7.84. ^{13}C NMR spectrum of compound **166d**

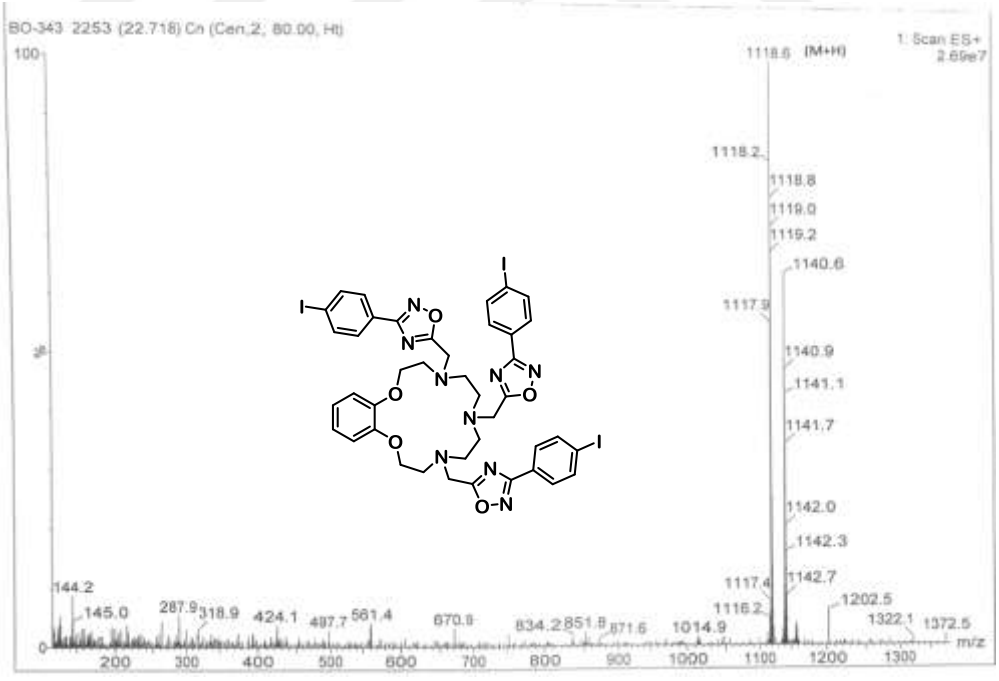

Figure 7.85. LC-MS Spectrum of compound **166d**

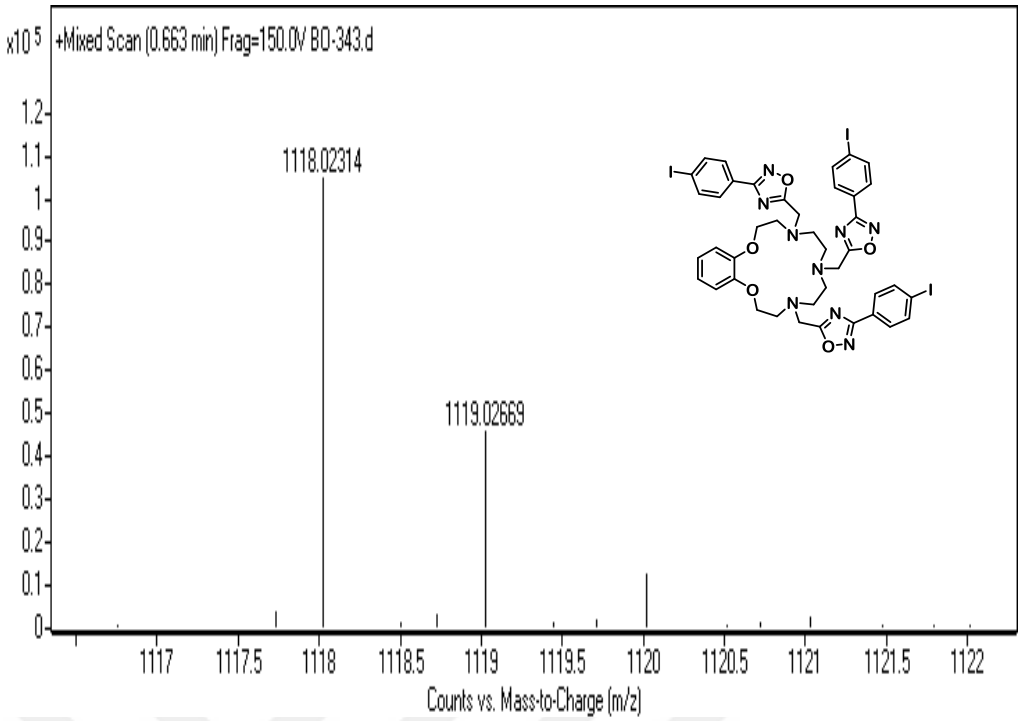

Figure 7.86. HR-MS Spectrum of compound **166d**

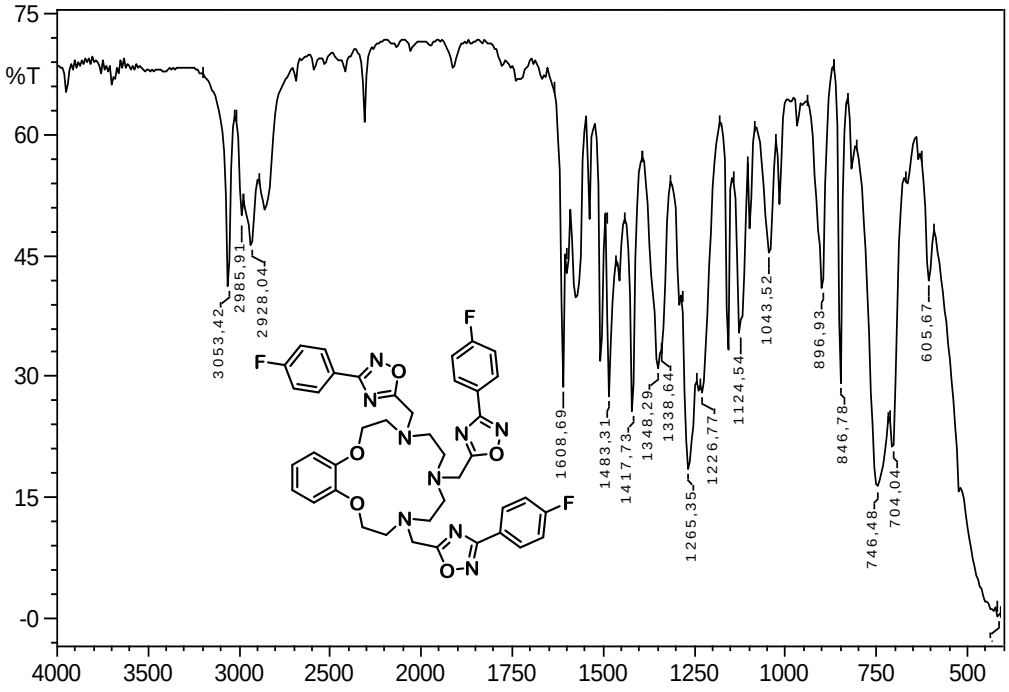

Figure 7.87. IR spectrum of compound **166e**

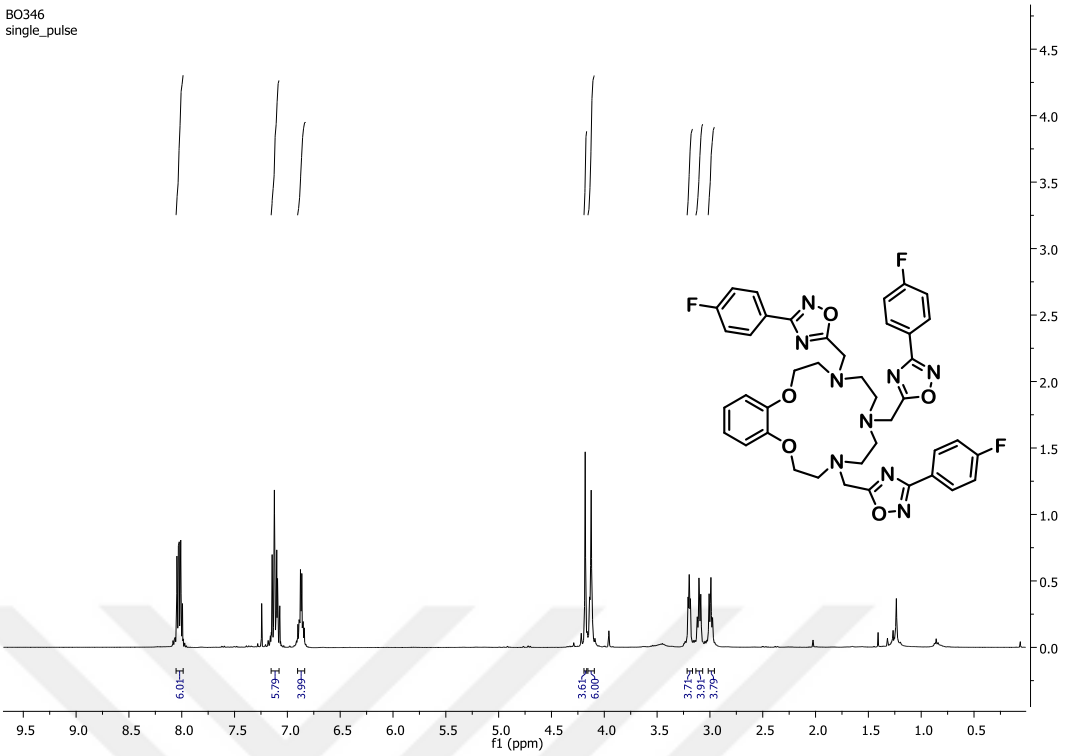

Figure 7.88. ^{1}H NMR spectrum of compound **166e**

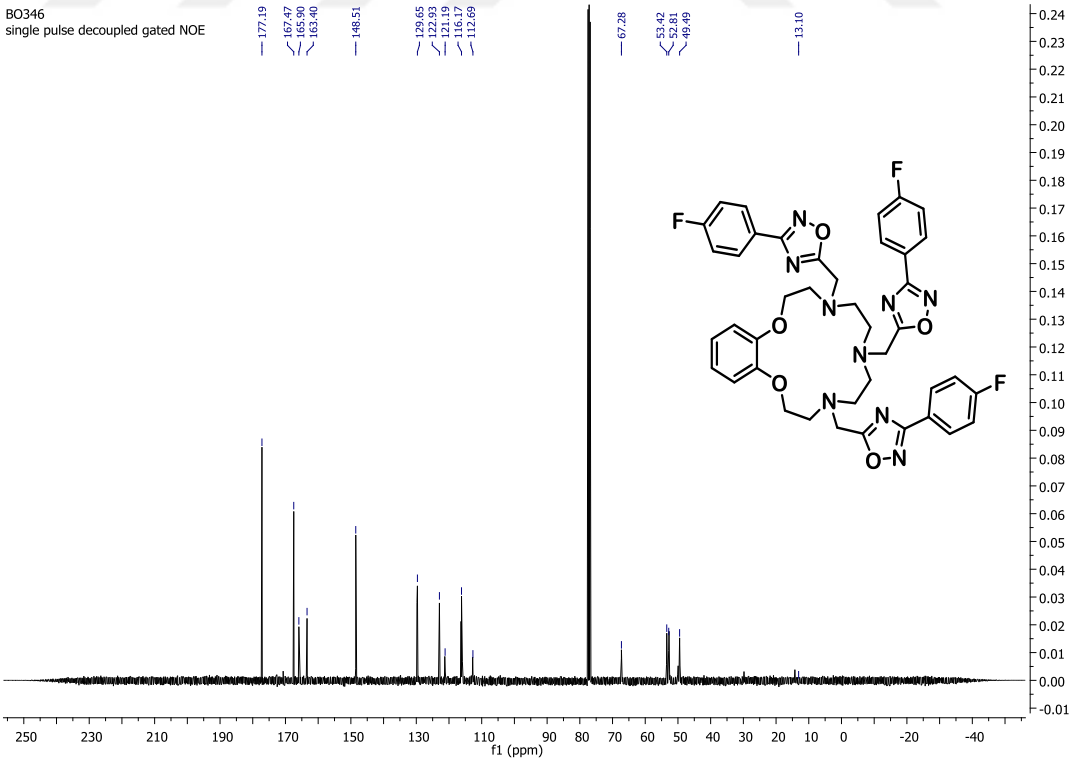

Figure 7.89. ^{13}C NMR spectrum of compound **166e**

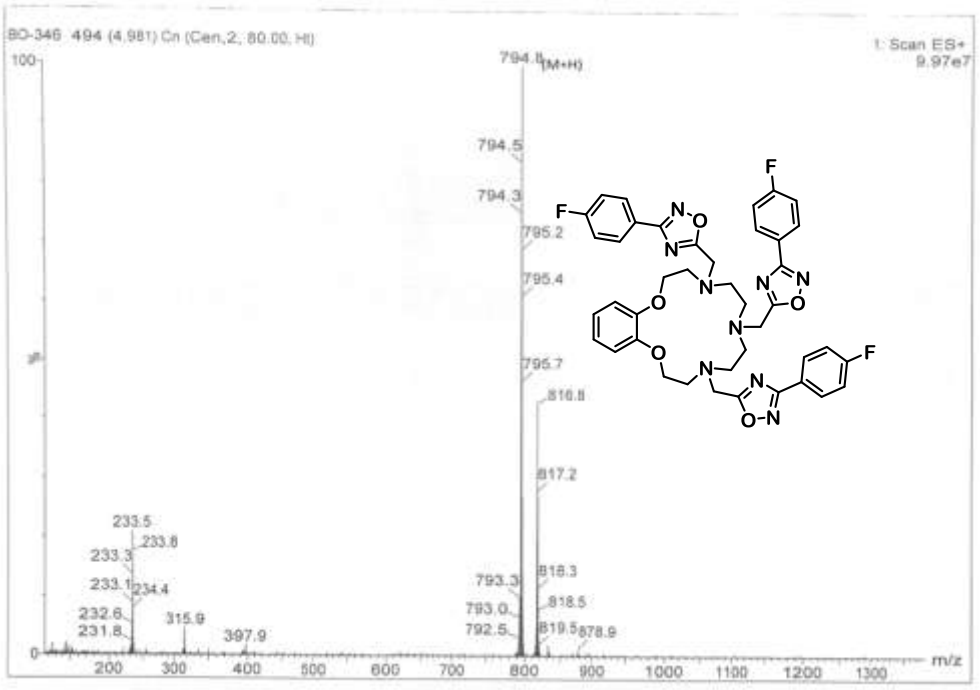

Figure 7.90. LC-MS Spectrum of compound **166e**

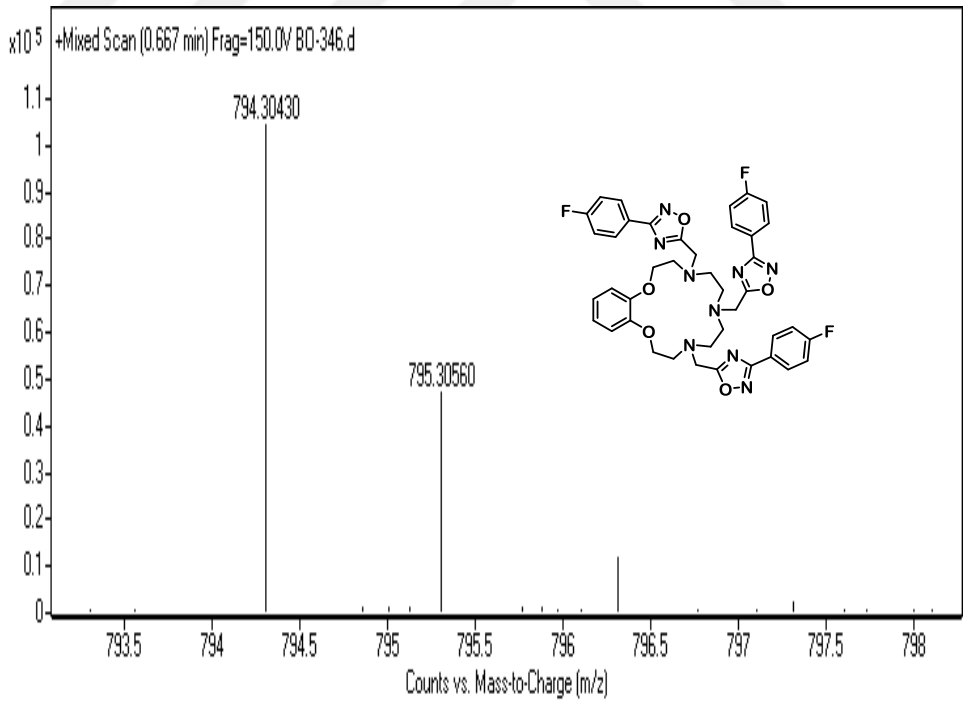

Figure 7.91. HR-MS Spectrum of compound **166e**

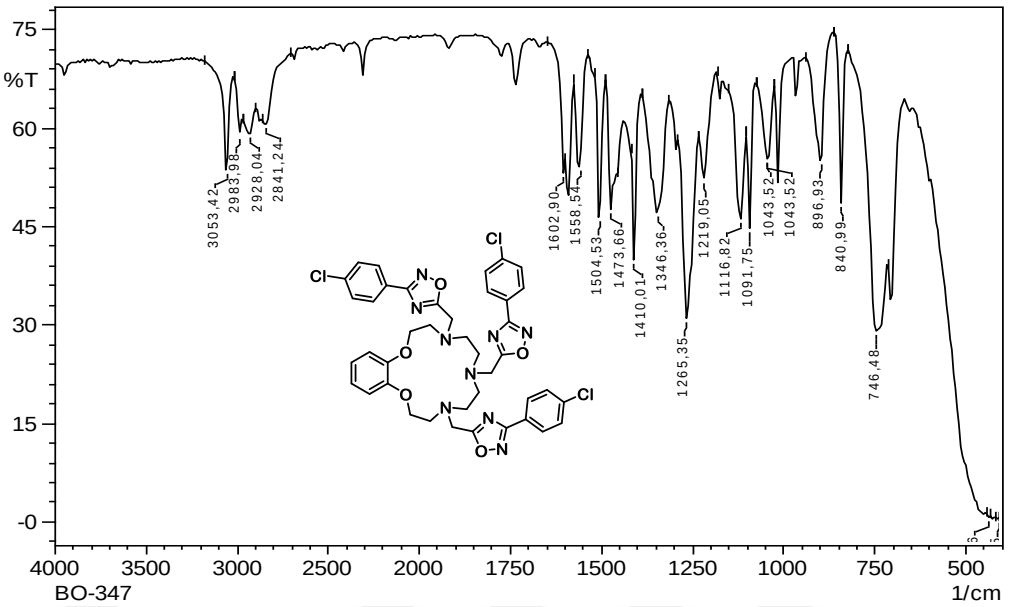

Figure 7.92. IR spectrum of compound **166f**

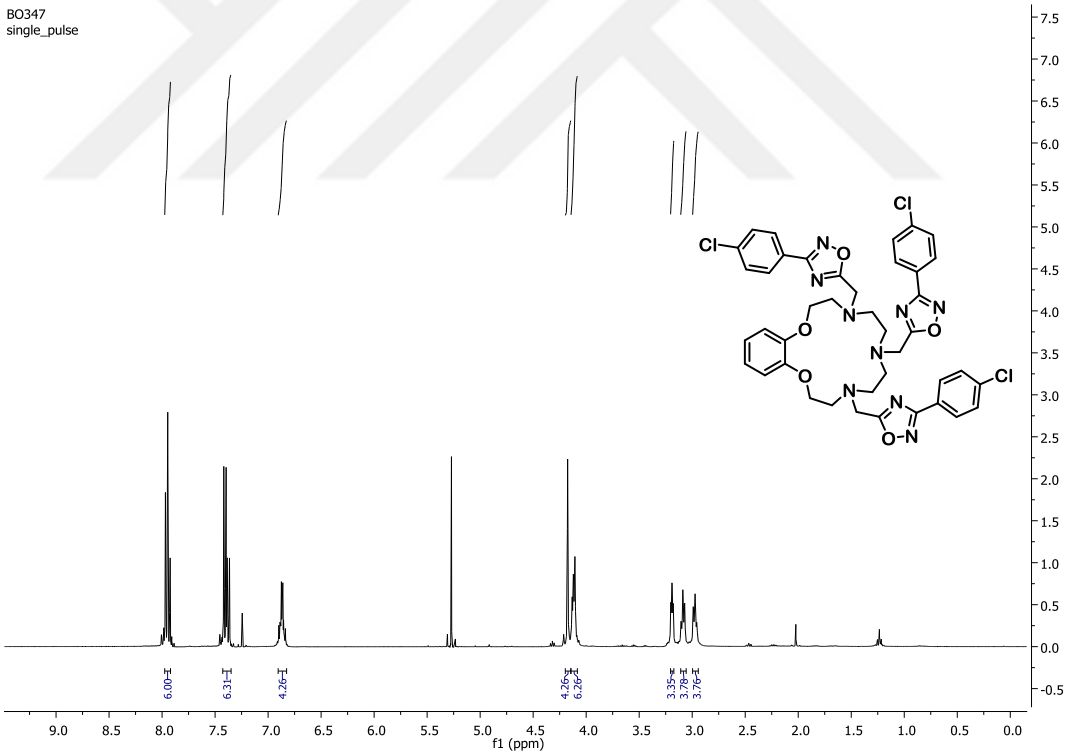

Figure 7.93. ^{1}H NMR spectrum of compound **166f**

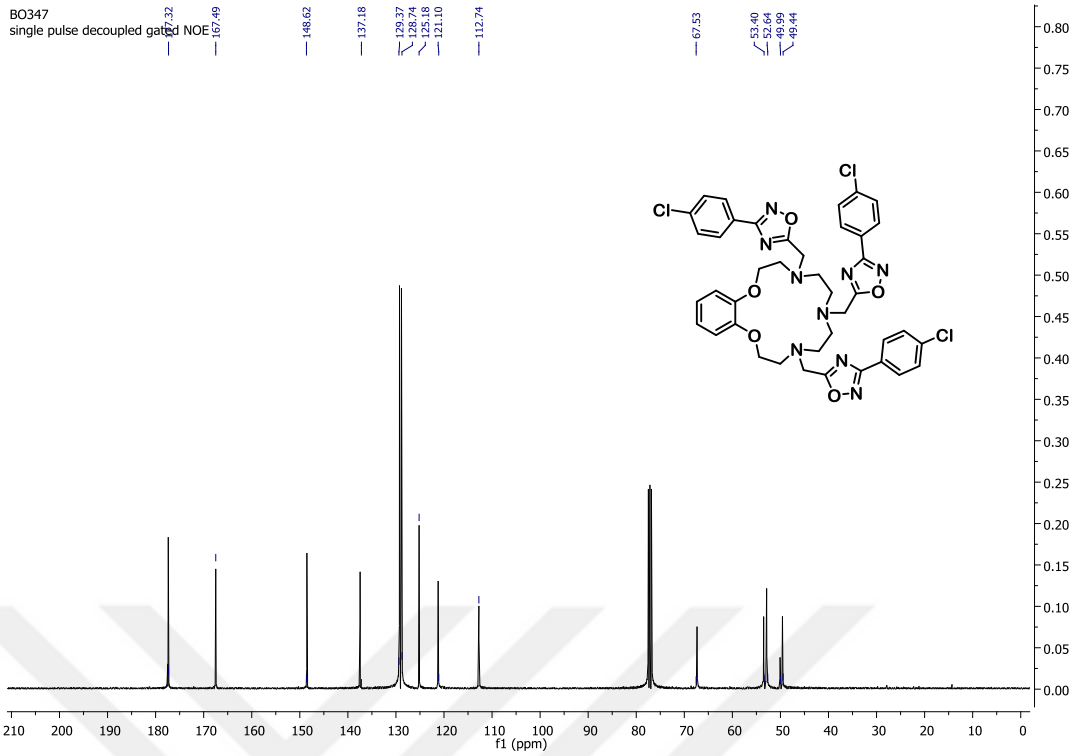

Figure 7.94. ^{13}C NMR spectrum of compound **166f**

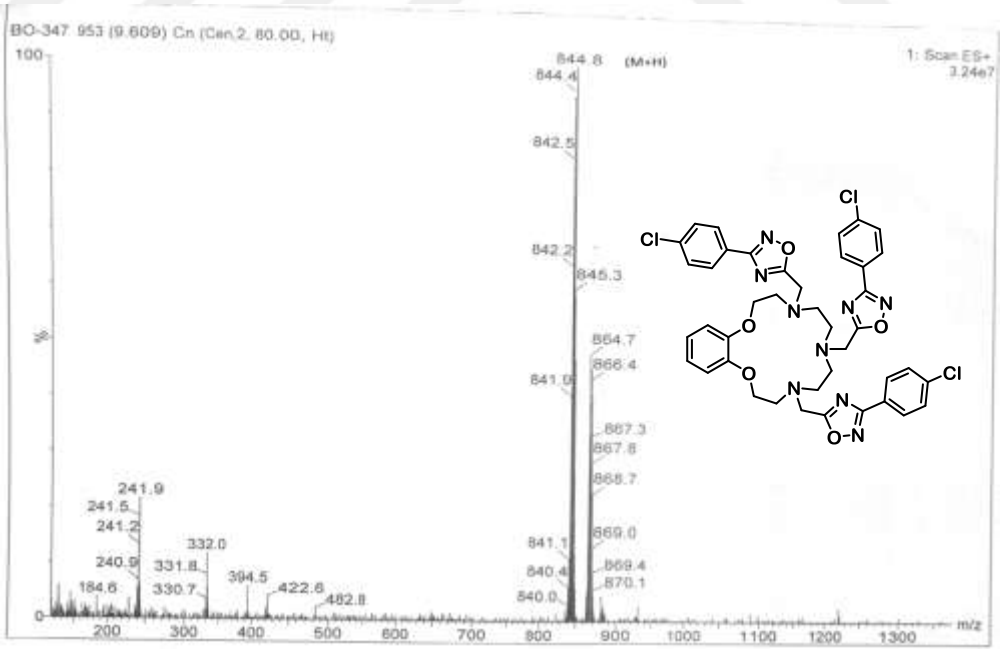

Figure 7.95. LC-MS Spectrum of compound **166f**

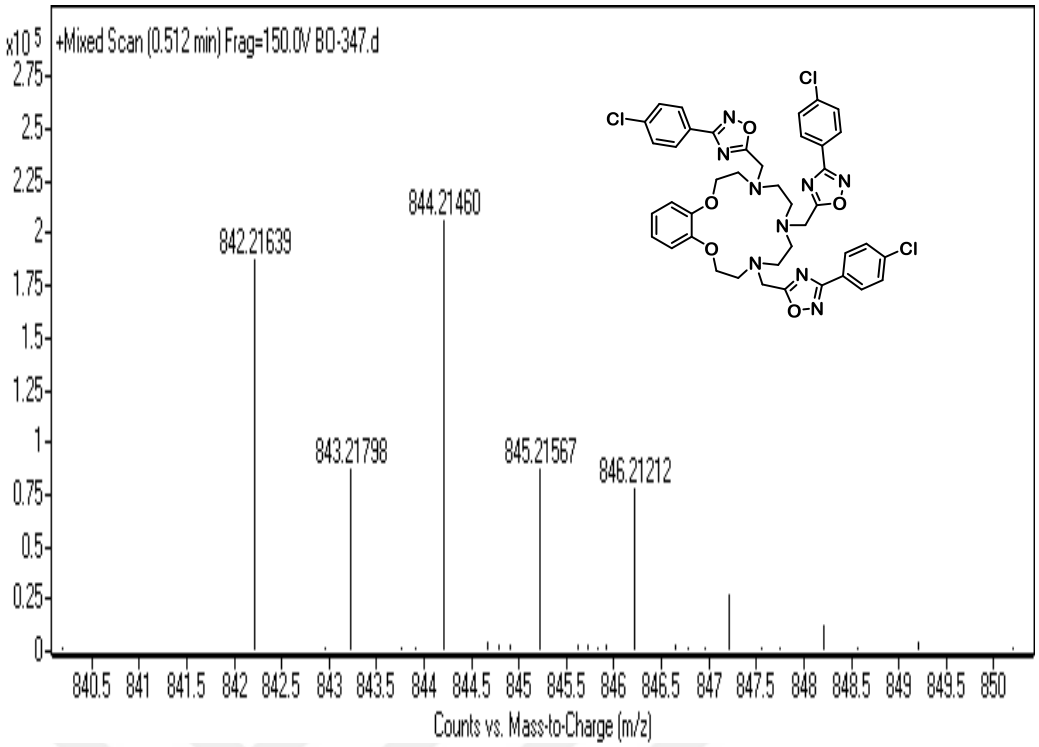

Figure 7.96. HR-MS Spectrum of compound **166f**

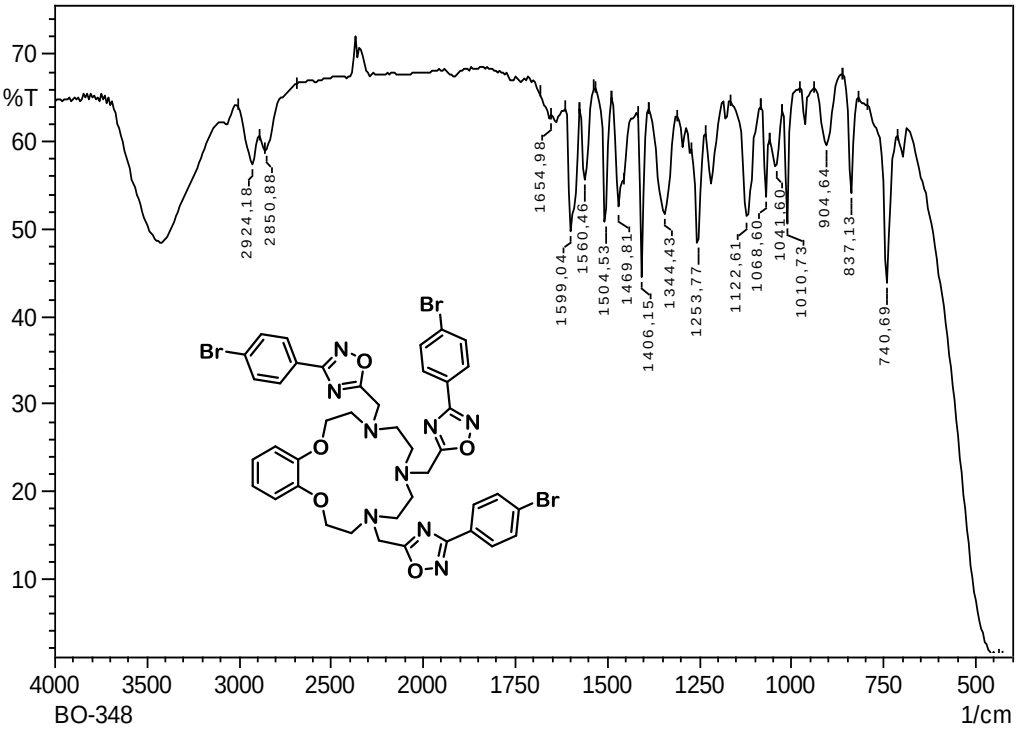

Figure 7.97. IR spectrum of compound **166g**

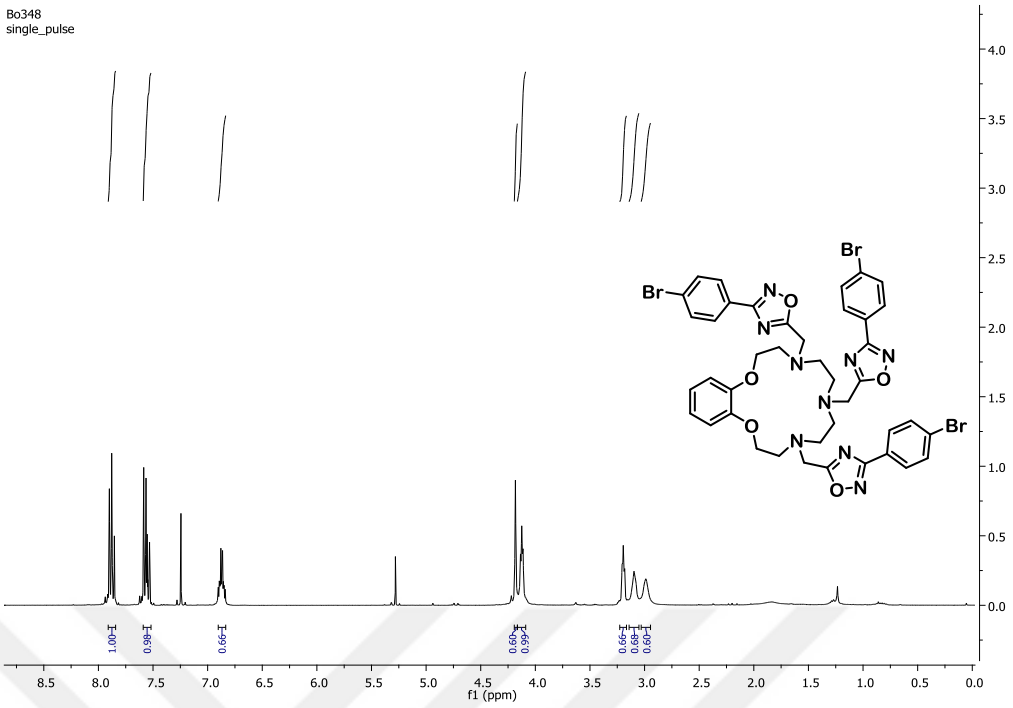

Figure 7.98. ^{1}H NMR spectrum of compound **166g**

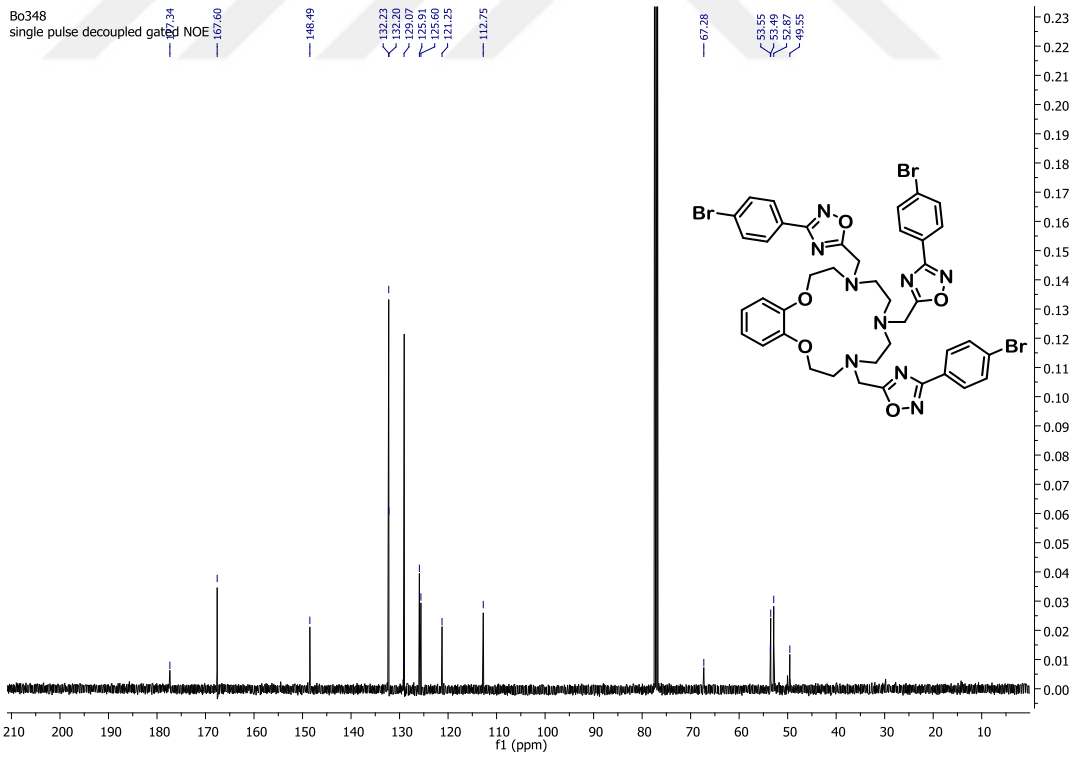

Figure 7.99. ^{13}C NMR spectrum of compound **166g**

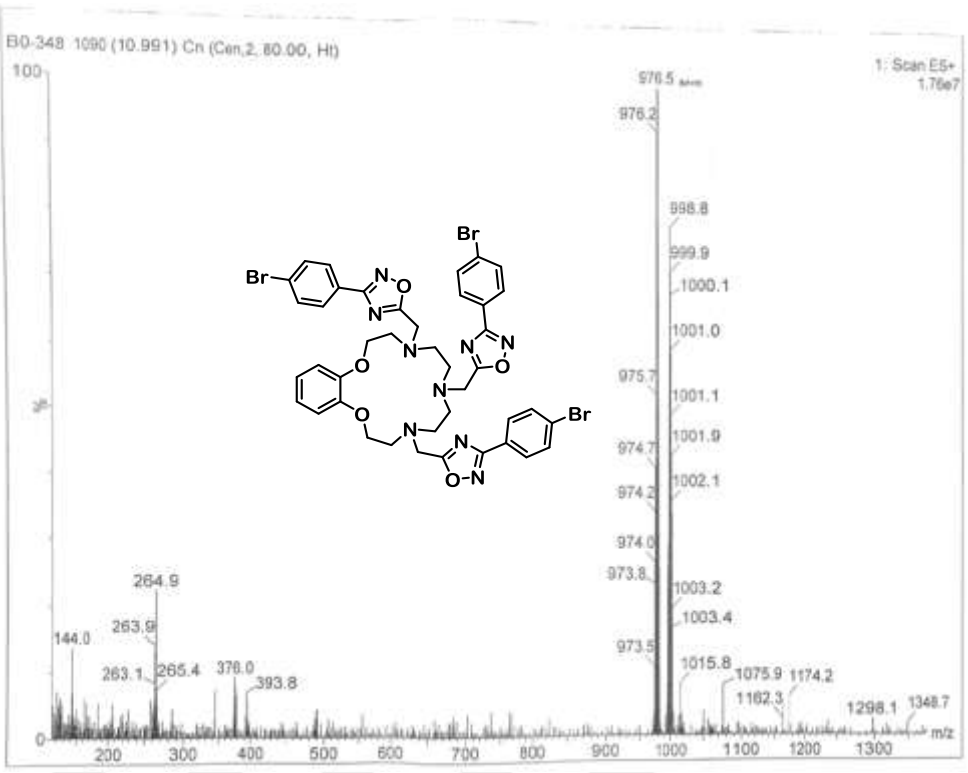

Figure 7.100. LC-MS Spectrum of compound **166g**

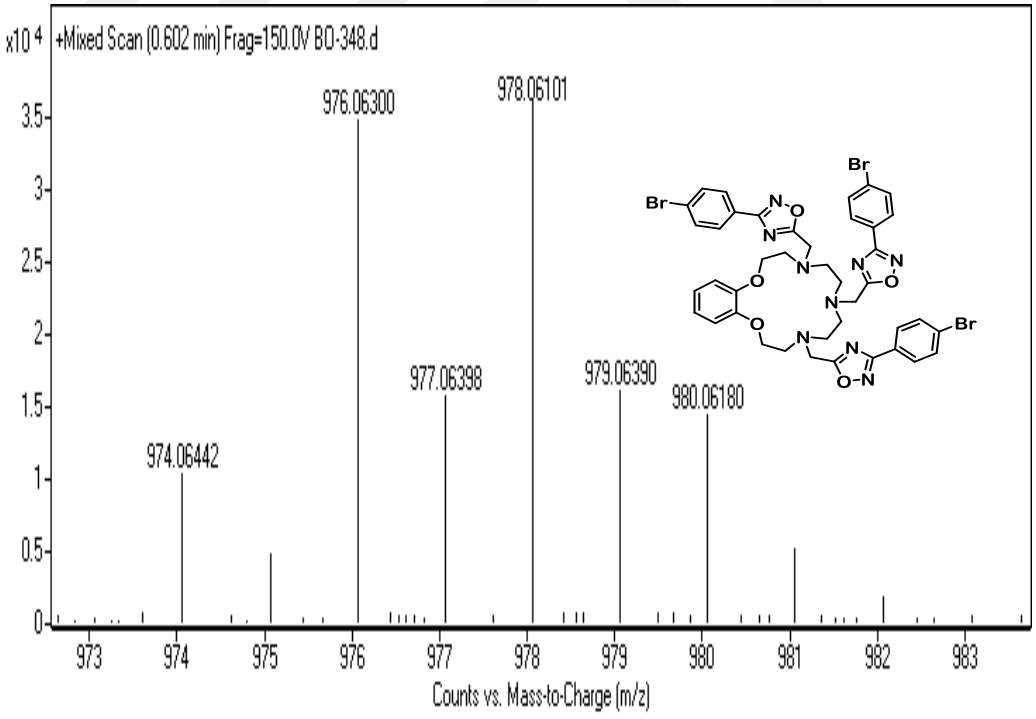

Figure 7.101. HR-MS Spectrum of compound **166g**

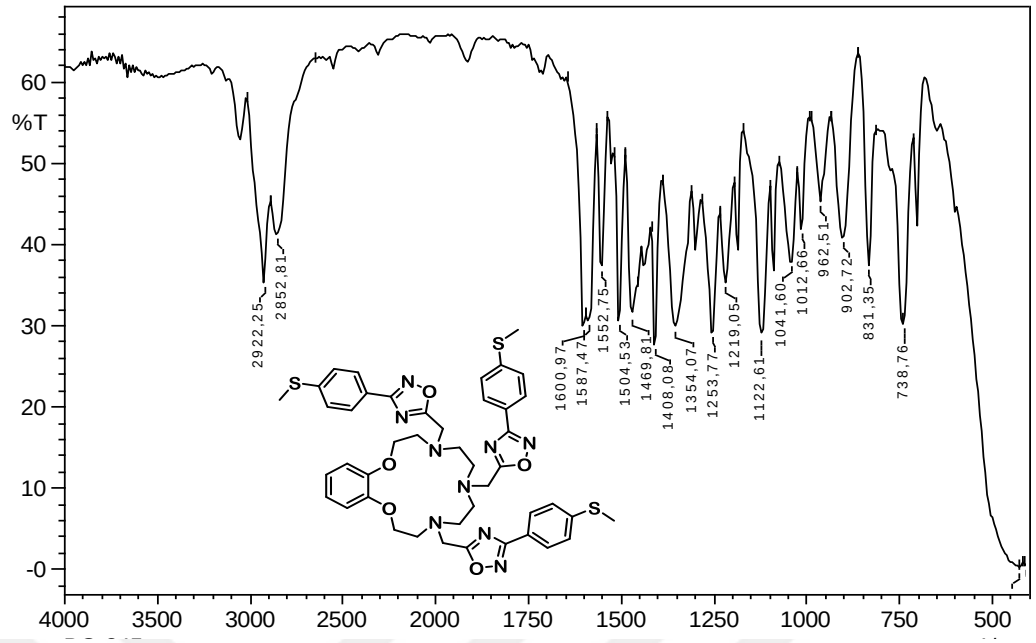

Figure 7.102. IR spectrum of compound **166h**

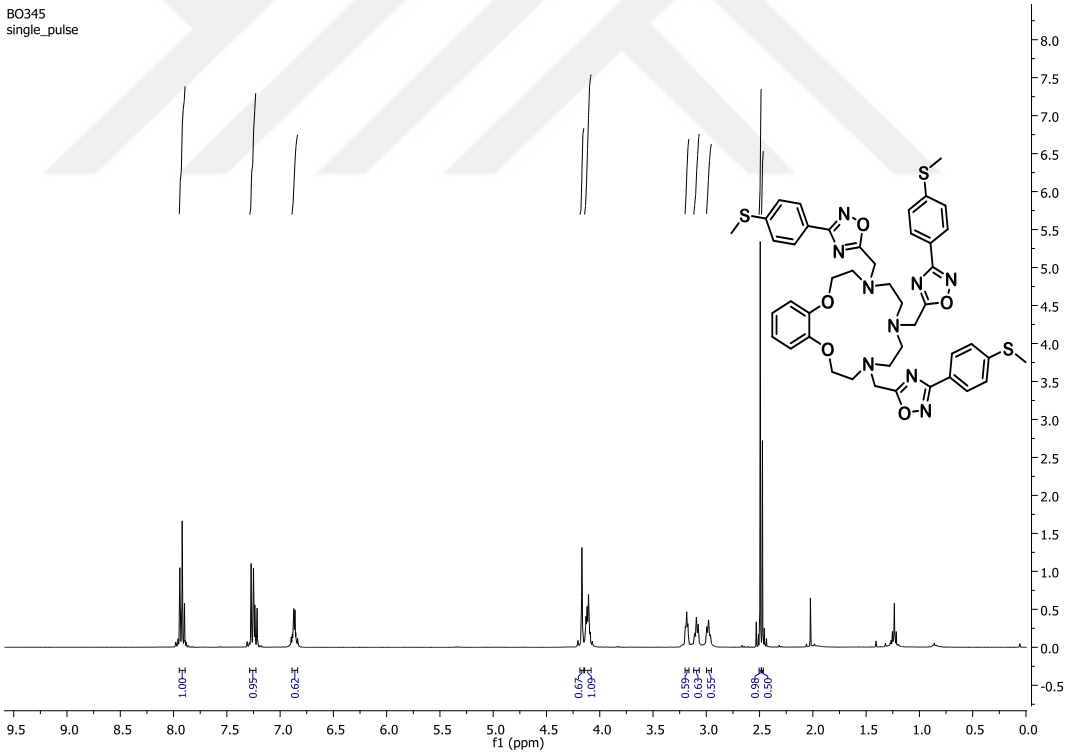

Figure 7.103. ^{1}H NMR spectrum of compound **166h**

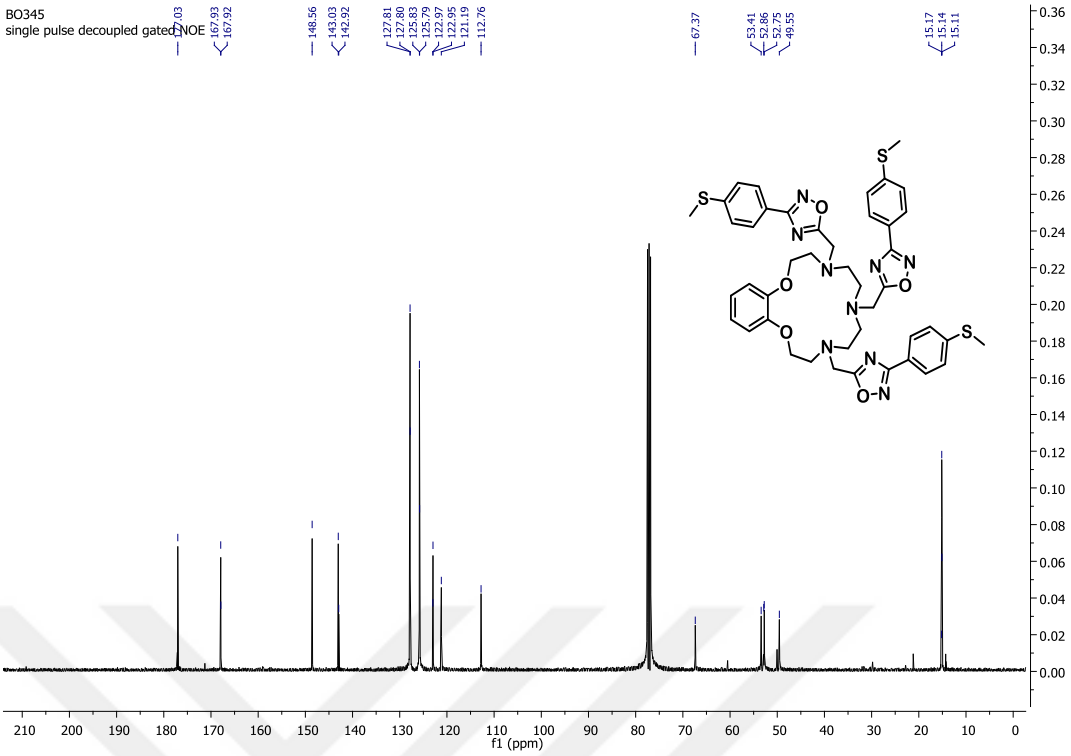

Figure 7.104. ^{13}C NMR spectrum of compound **166h**

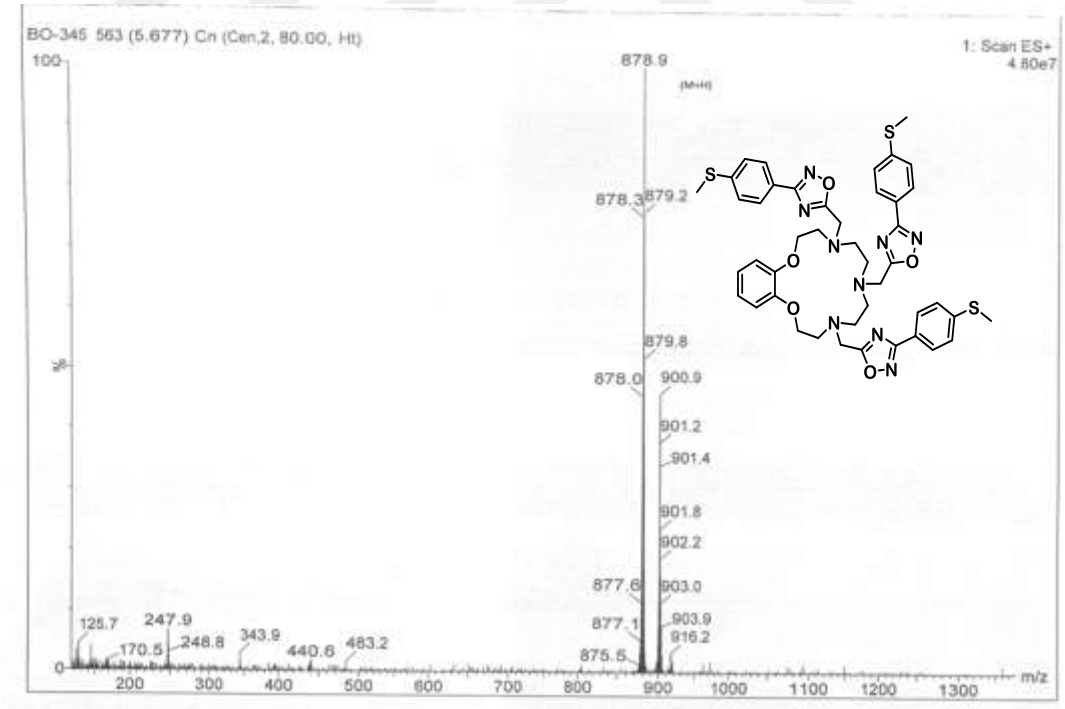

Figure 7.105. LC-MS Spectrum of compound **166h**

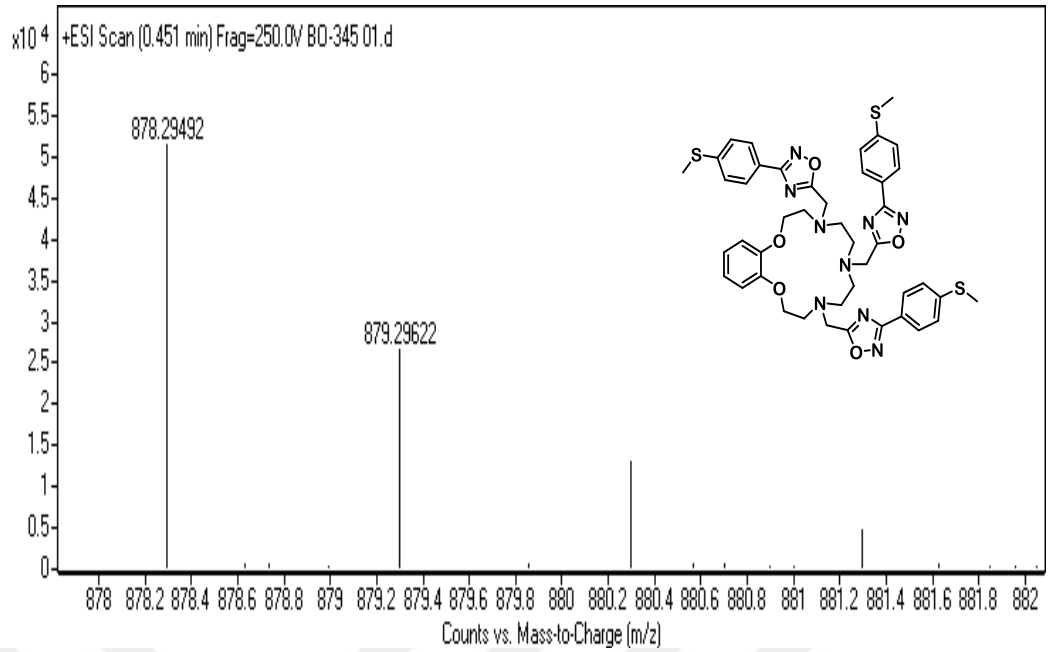

Figure 7.106. HR-MS Spectrum of compound **166h**

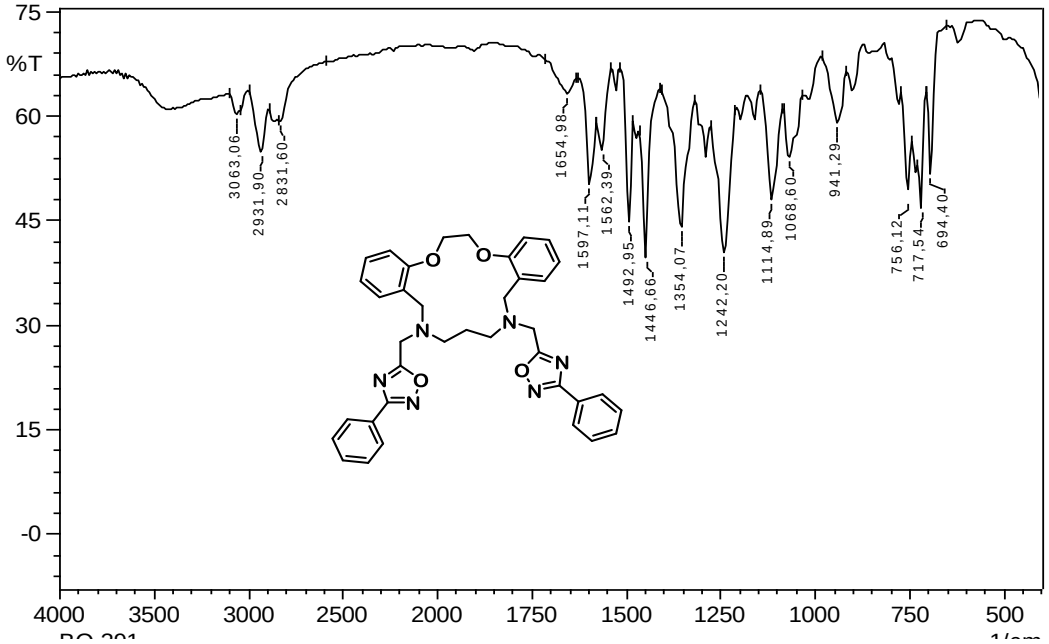

Figure 7.107. IR spectrum of compound **168a**

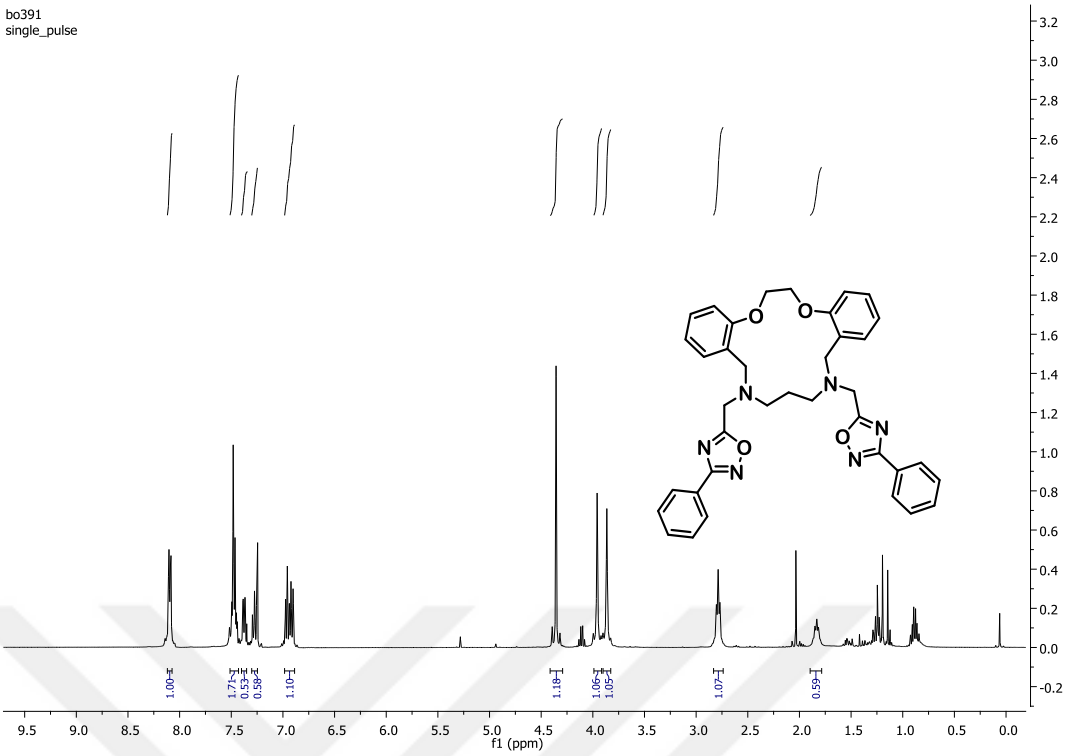

Figure 7.108. ^{1}H NMR spectrum of compound **168a**

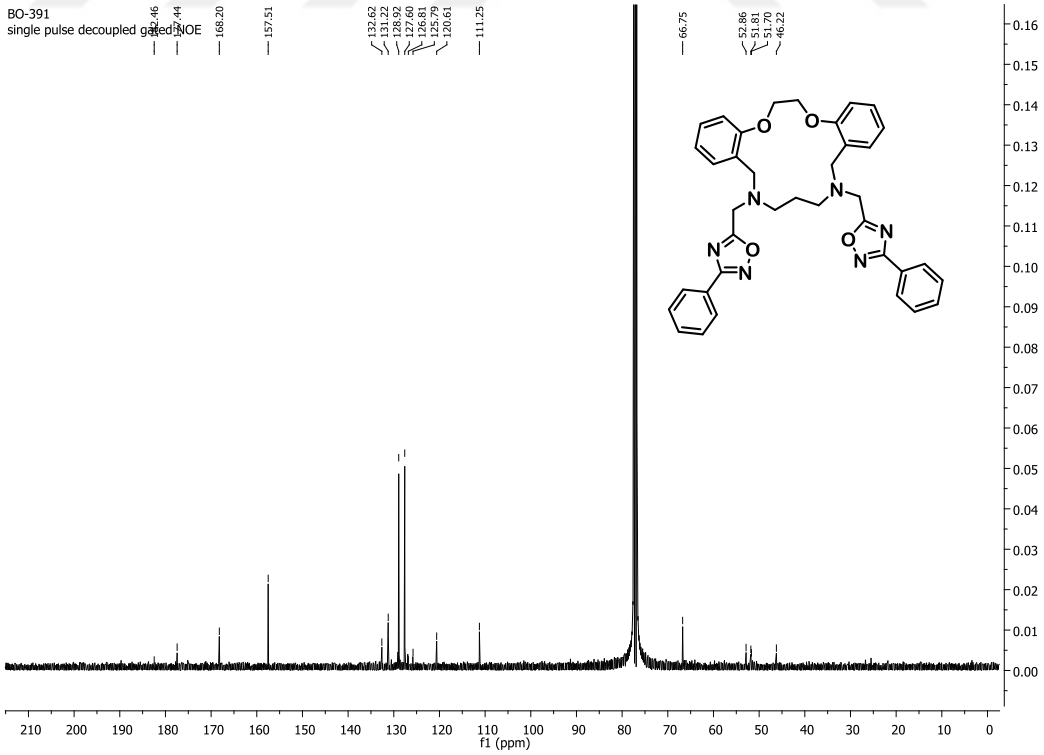

Figure 7.109. ^{13}C NMR spectrum of compound **168a**

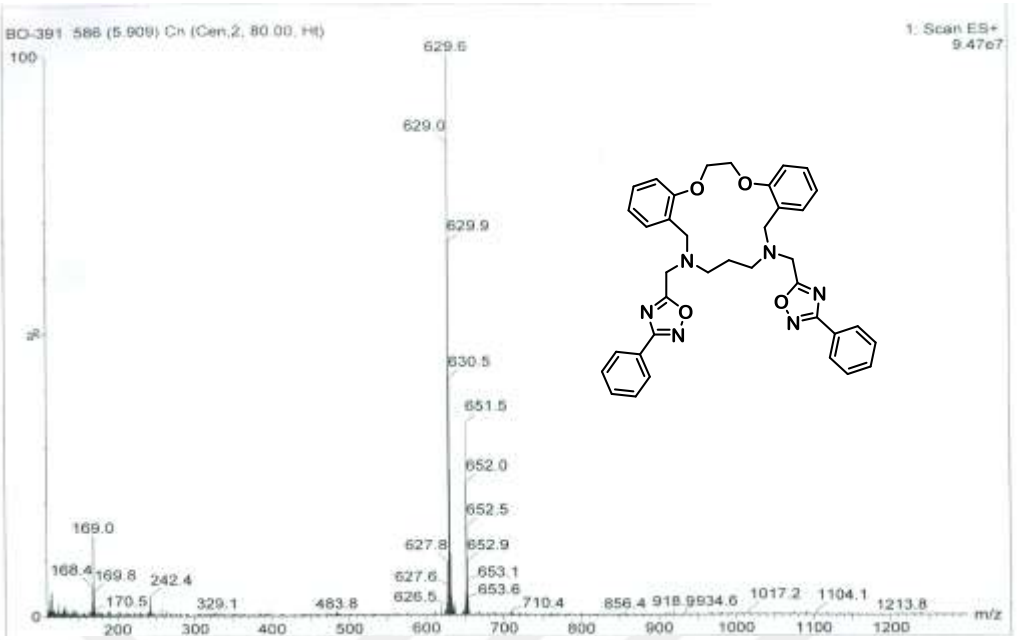

Figure 7.110. LC-MS Spectrum of compound **168**

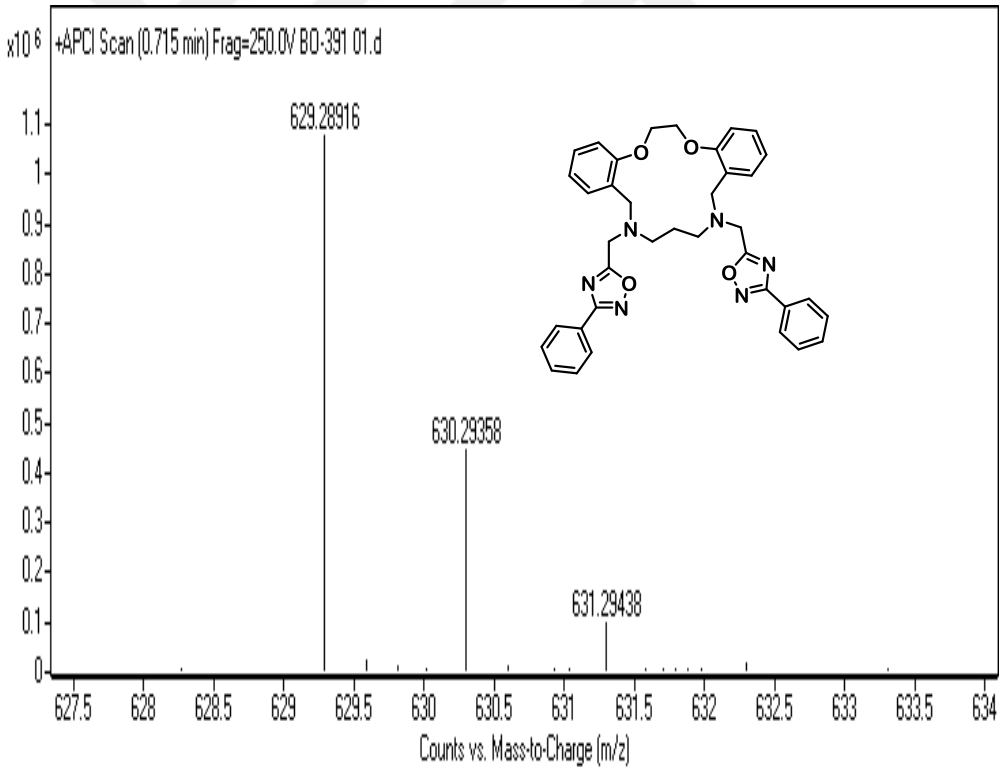

Figure 7.111. HR-MS Spectrum of compound **168a**

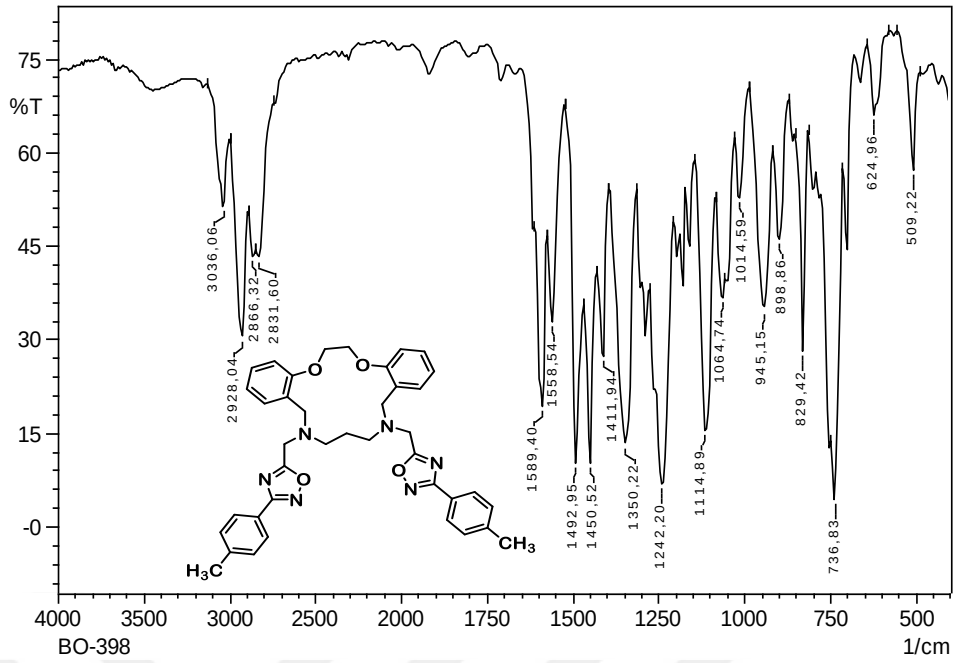

Figure 7.112. IR spectrum of compound **168b**

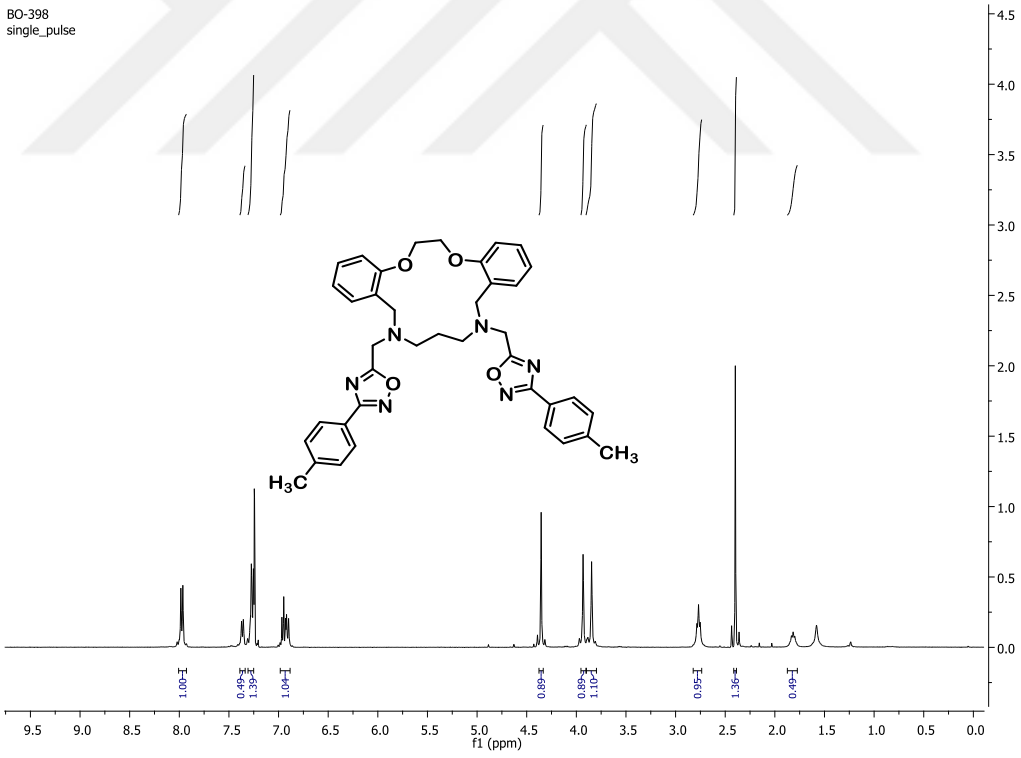

Figure 7.113. ^{1}H NMR spectrum of compound **168b**

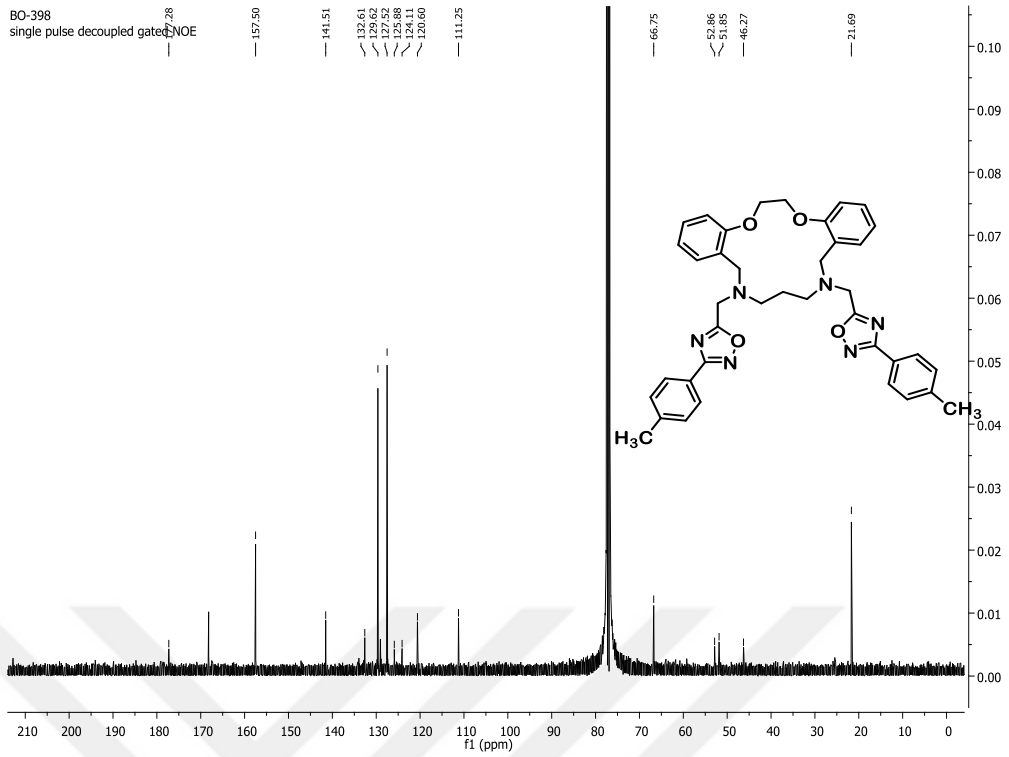

Figure 7.114. ^{13}C NMR spectrum of compound **168b**

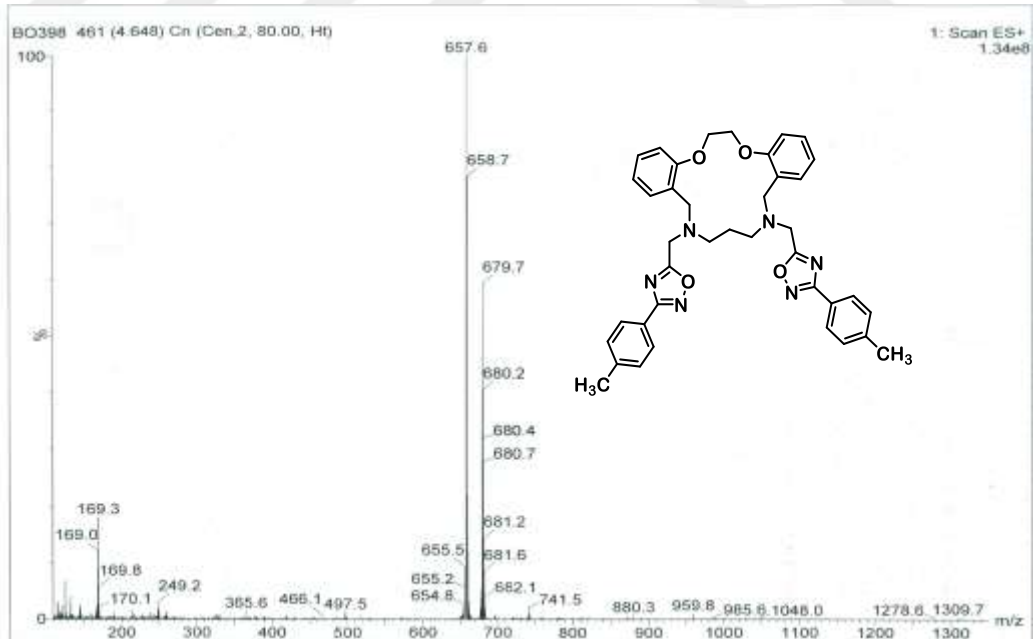

Figure 7.115. LC-MS Spectrum of compound **168b**

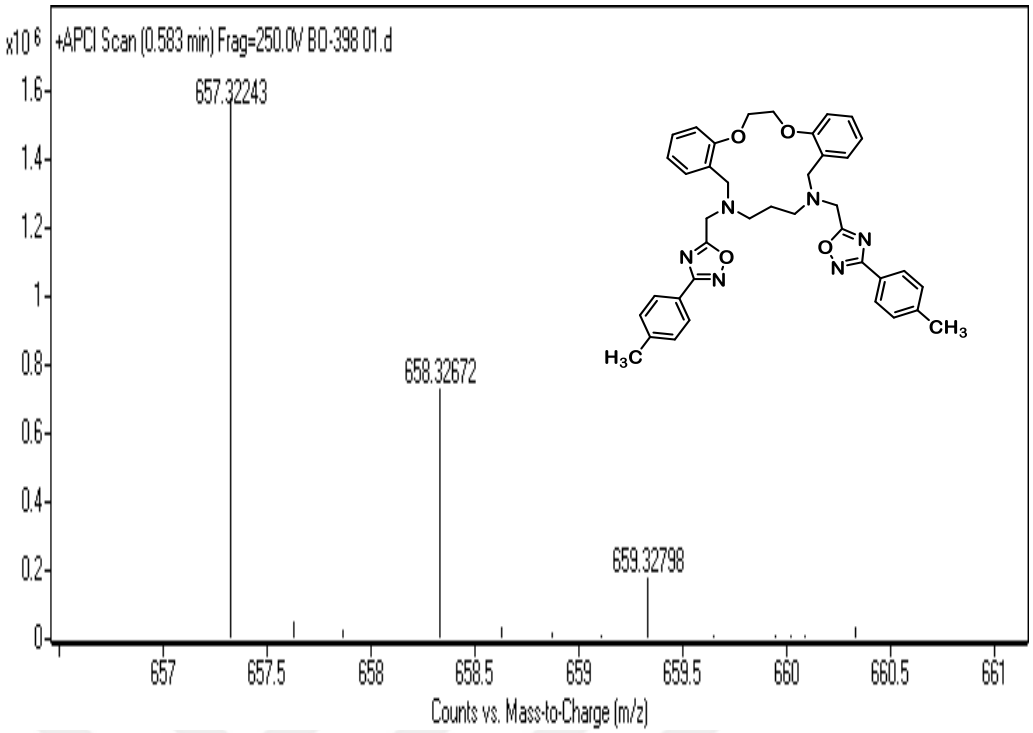

Figure 7.116. HR-MS Spectrum of compound **168b**

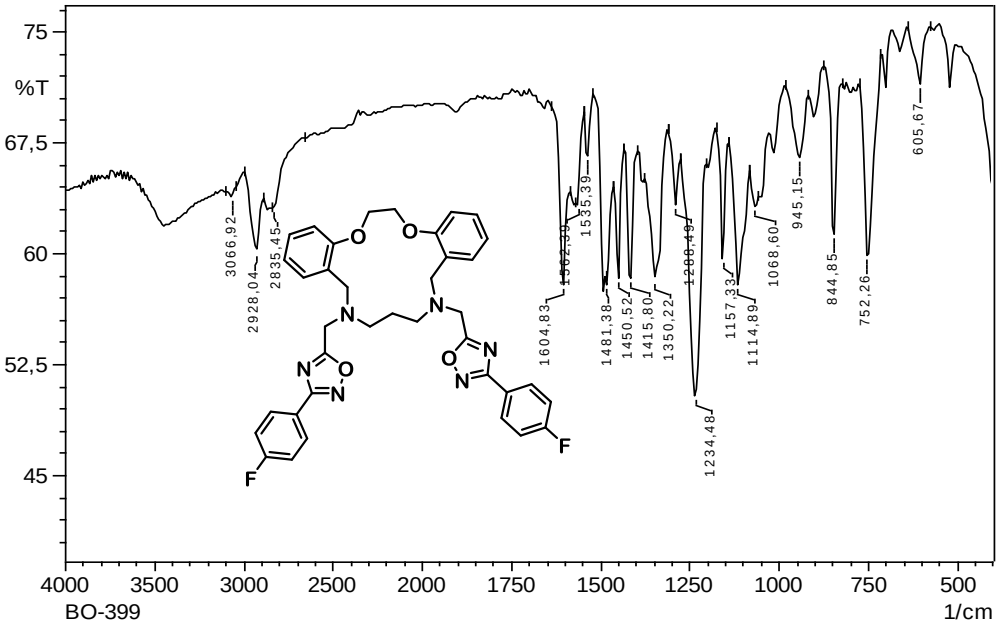

Figure 7.117. IR spectrum of compound **168c**

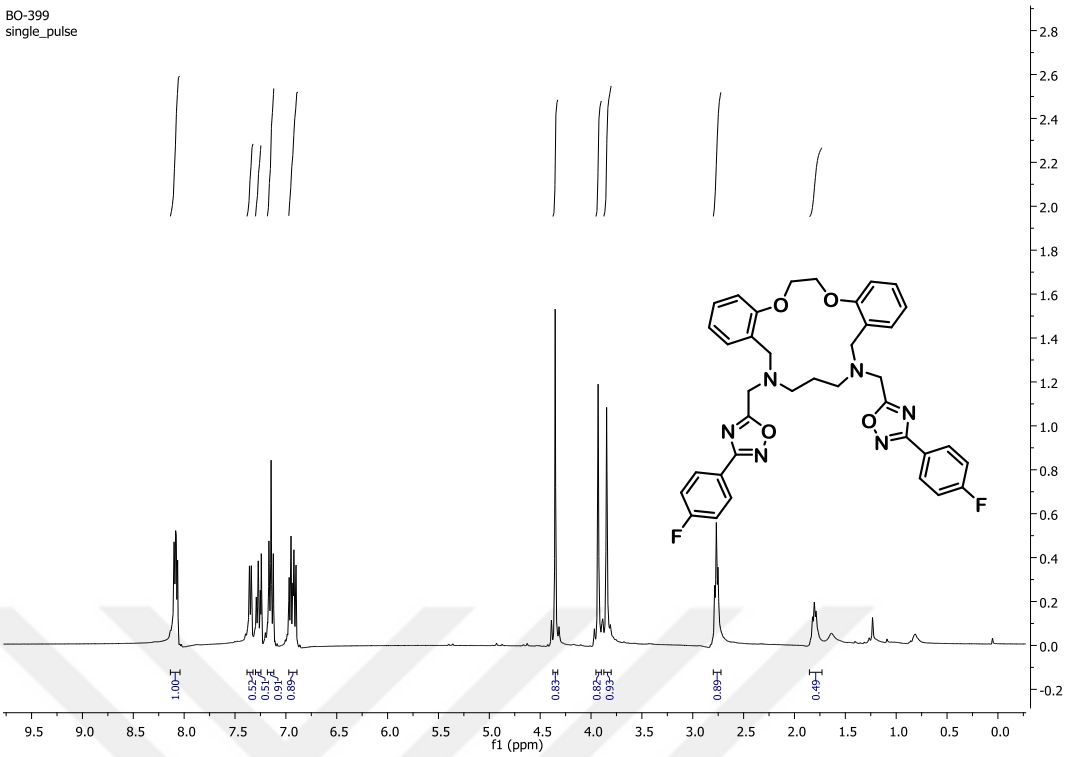

Figure 7.118. ^{1}H NMR spectrum of compound **168c**

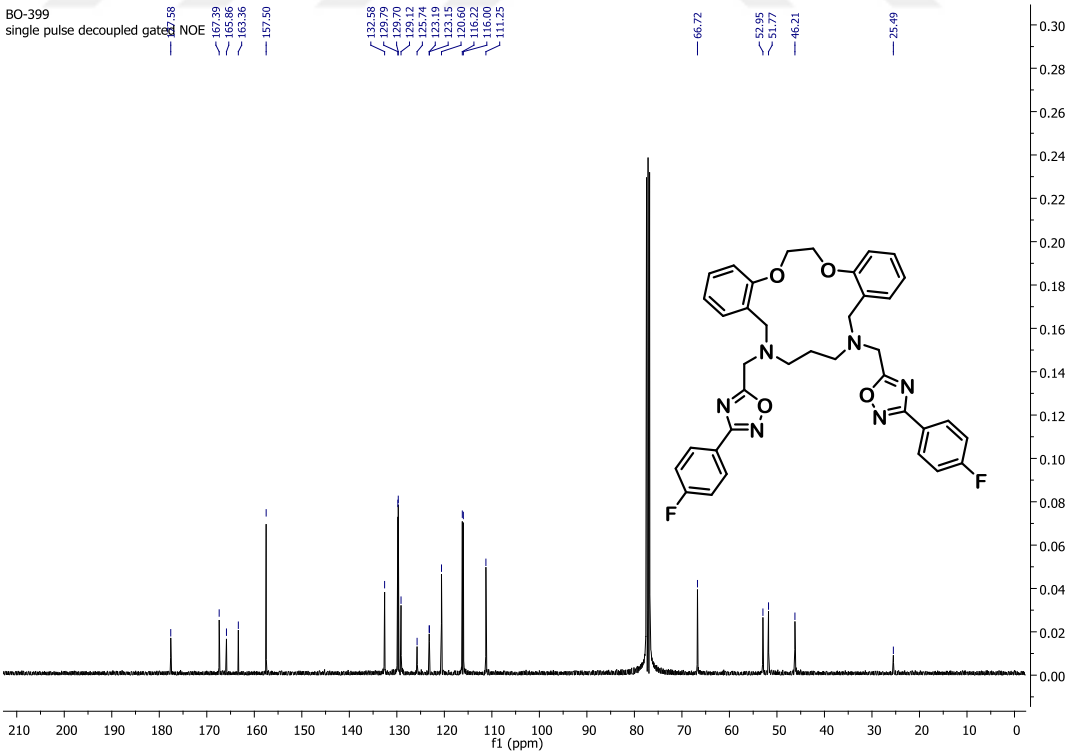

Figure 7.119. ^{13}C NMR spectrum of compound **168c**

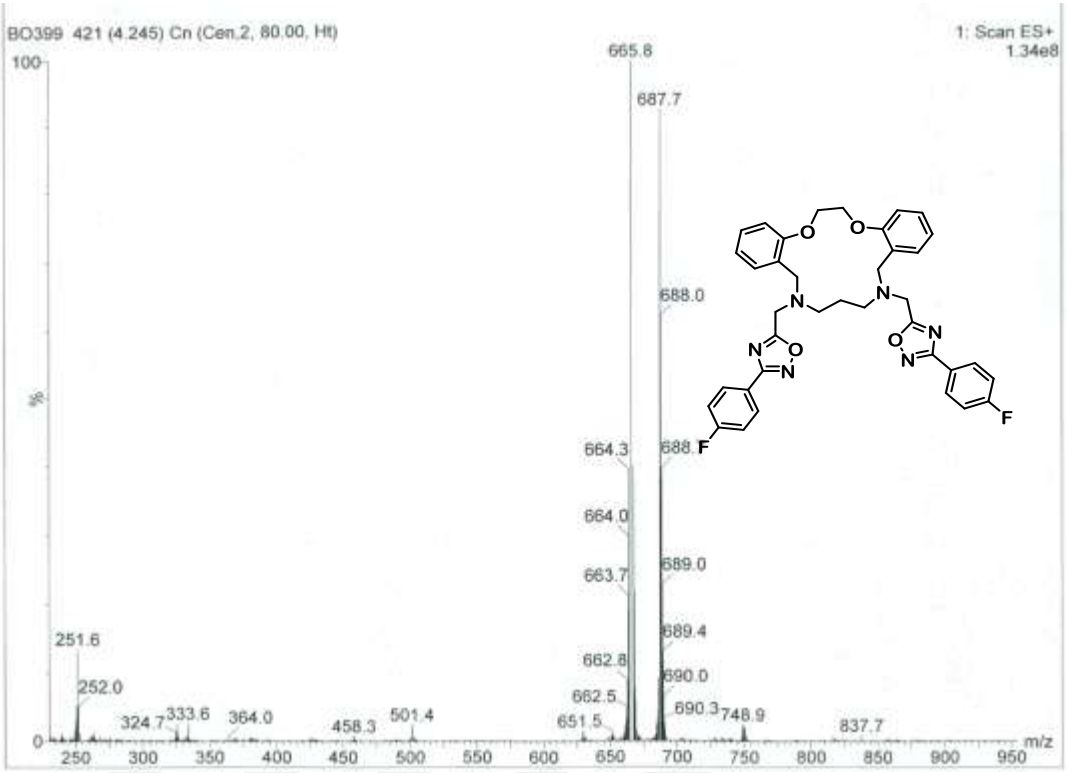

Figure 7.120. LC-MS Spectrum of compound **168c**

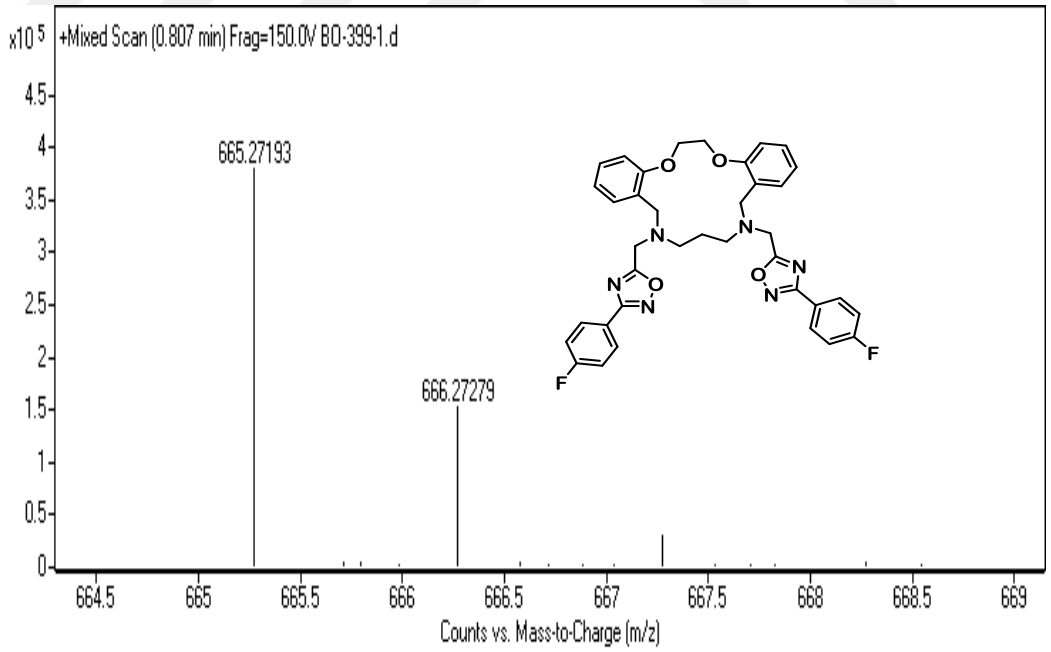

Figure 7.121. HR-MS Spectrum of compound **168c**

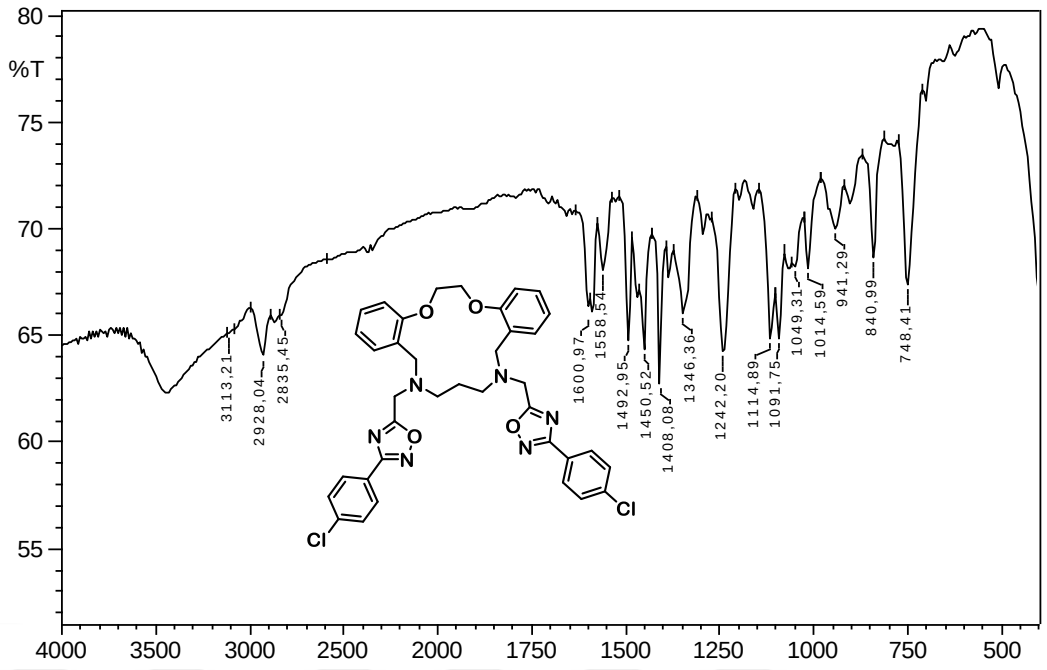

Figure 7.122. IR spectrum of compound **168d**

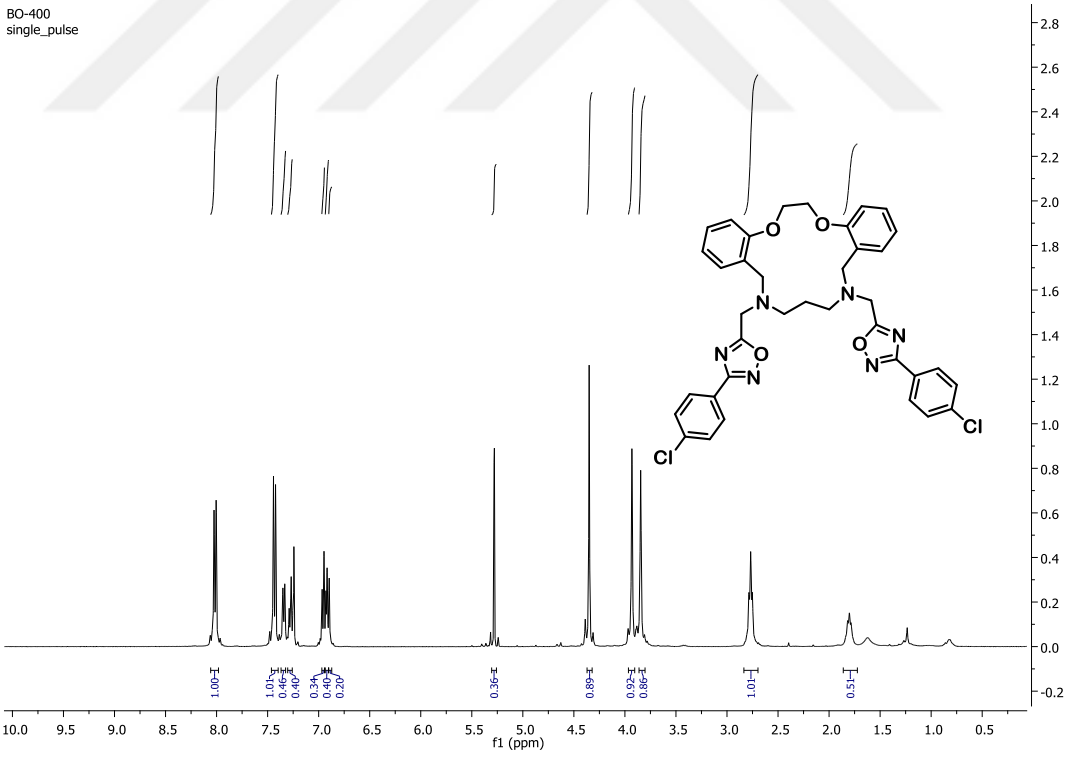

Figure 7.123. ^{1}H NMR spectrum of compound **168d**

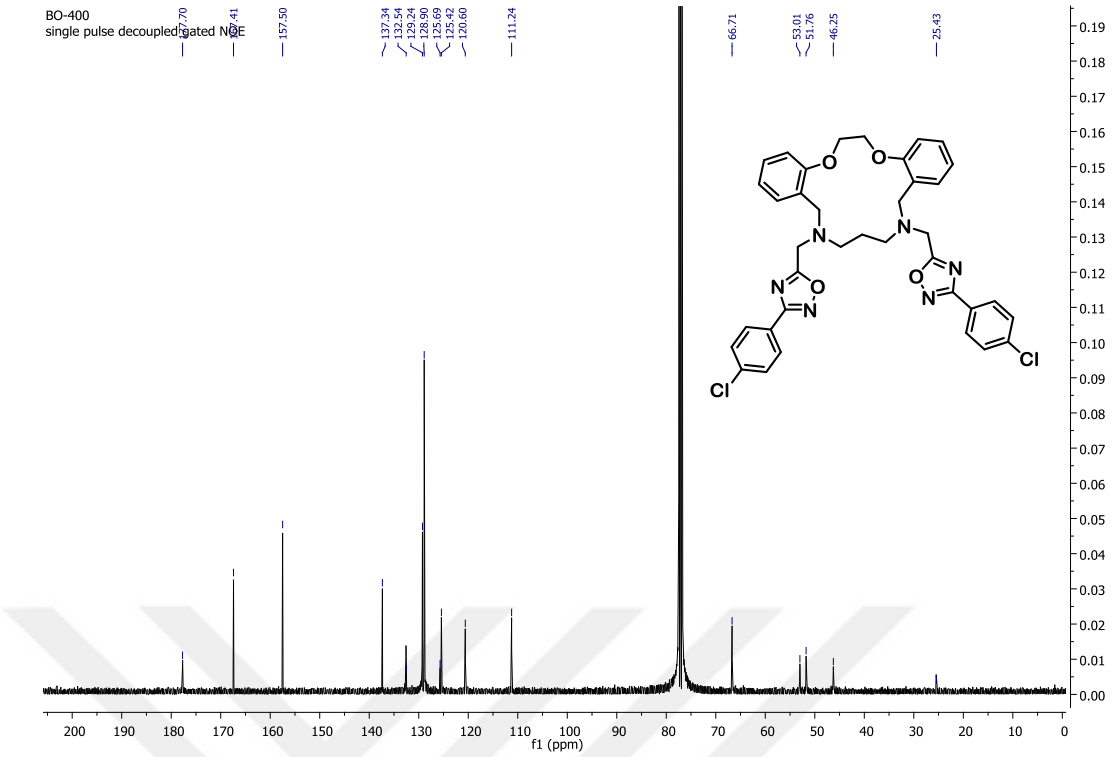

Figure 7.124. ^{13}C NMR spectrum of compound **168d**

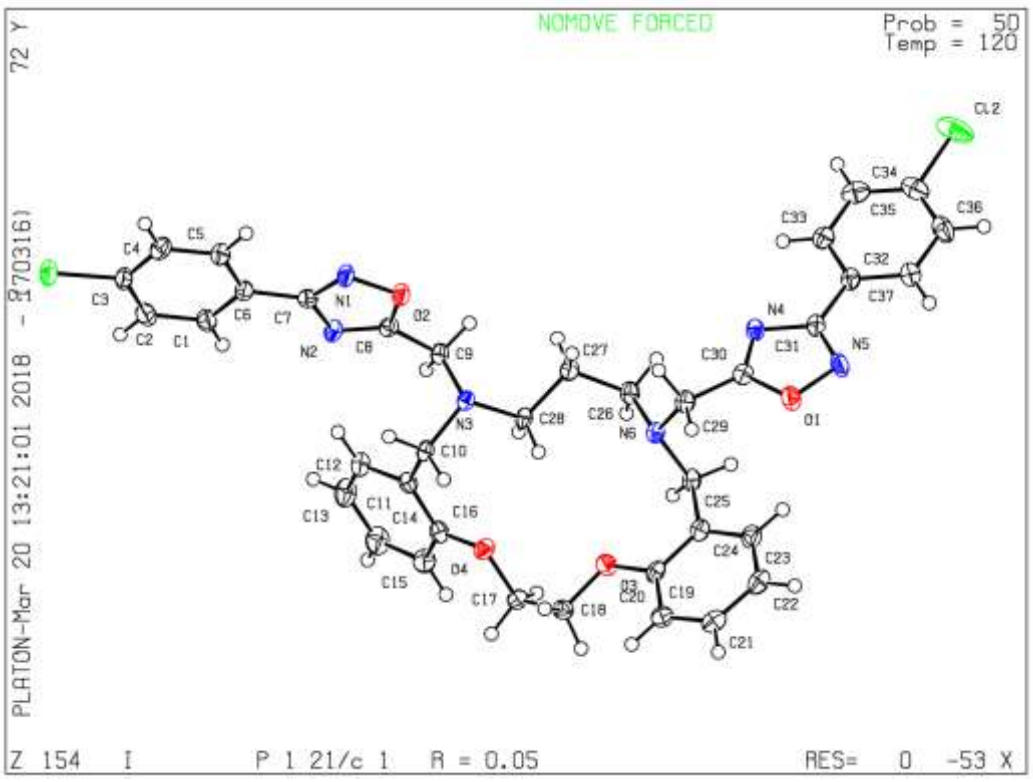

Figure 7.125. X-Ray ORTEP view of compound **168d**

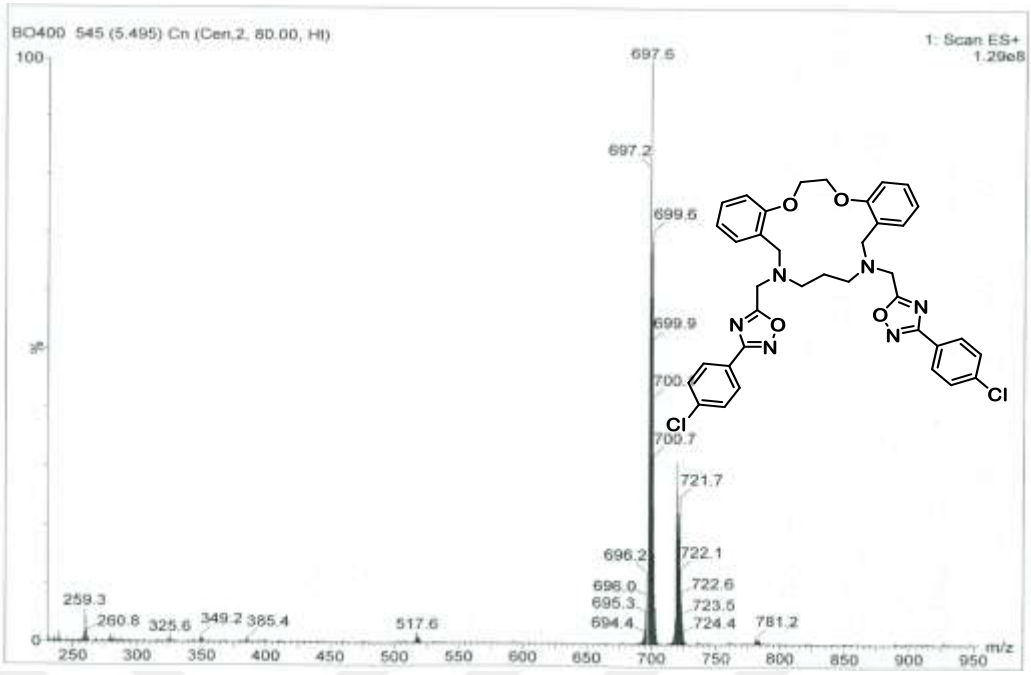

Figure 7.126. LC-MS Spectrum of compound **168d**

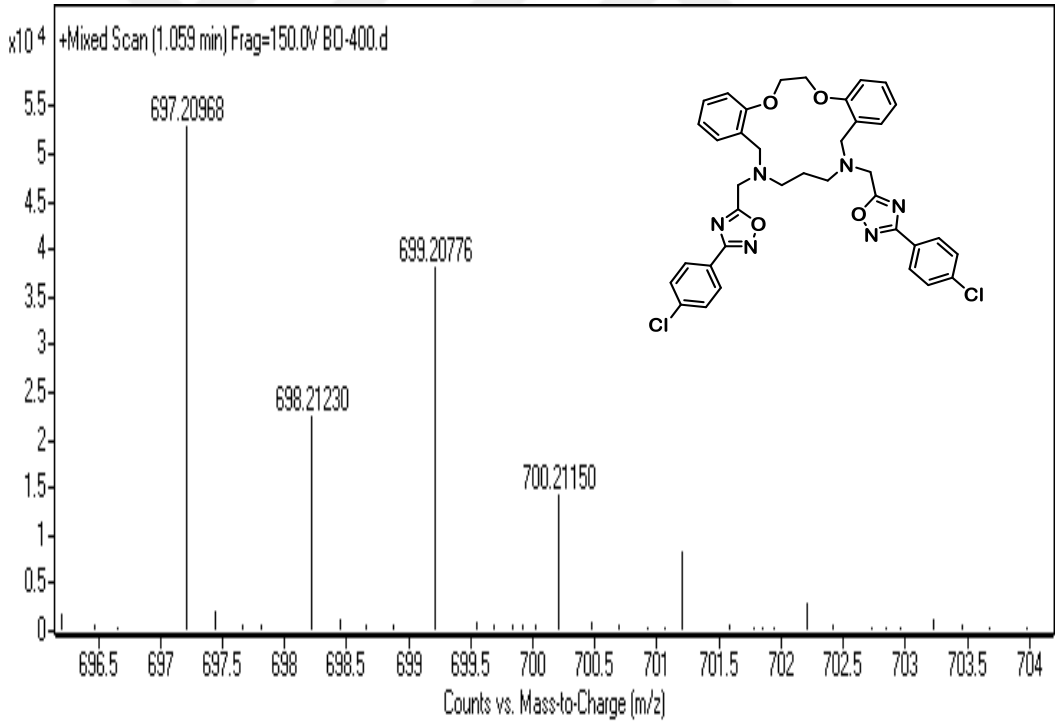

Figure 7.127. HR-MS Spectrum of compound **168d**

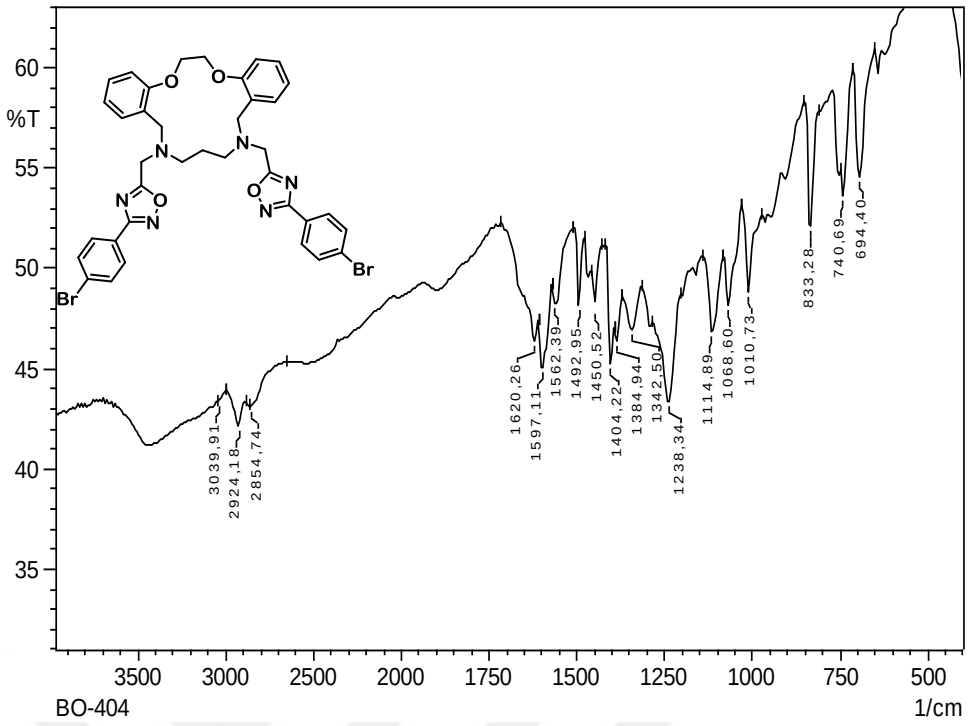

Figure 7.128. IR spectrum of compound **168e**

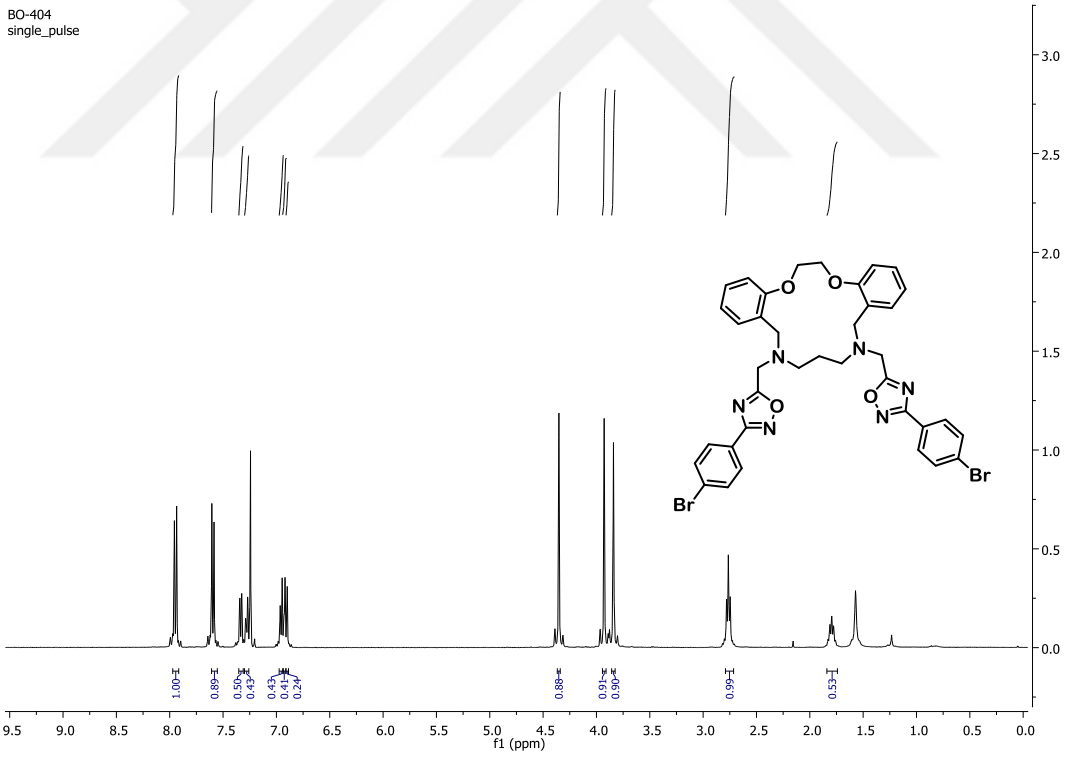

Figure 7.129. ^{1}H NMR spectrum of compound **168e**

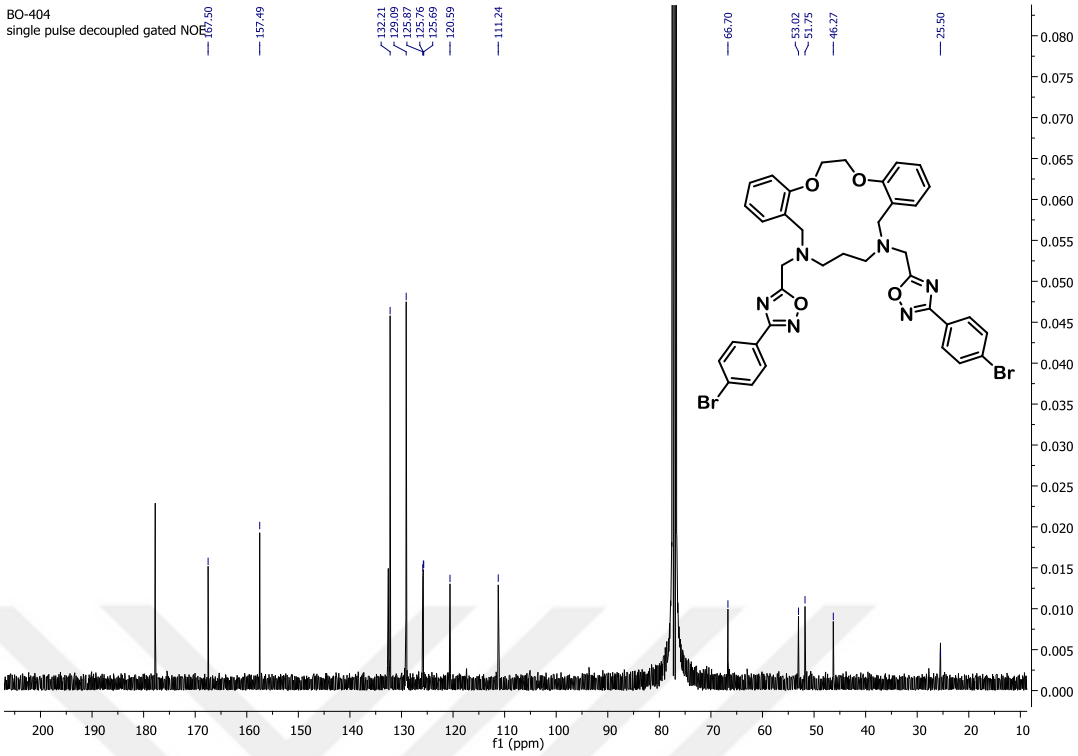

Figure 7.130. ^{13}C NMR spectrum of compound **168e**

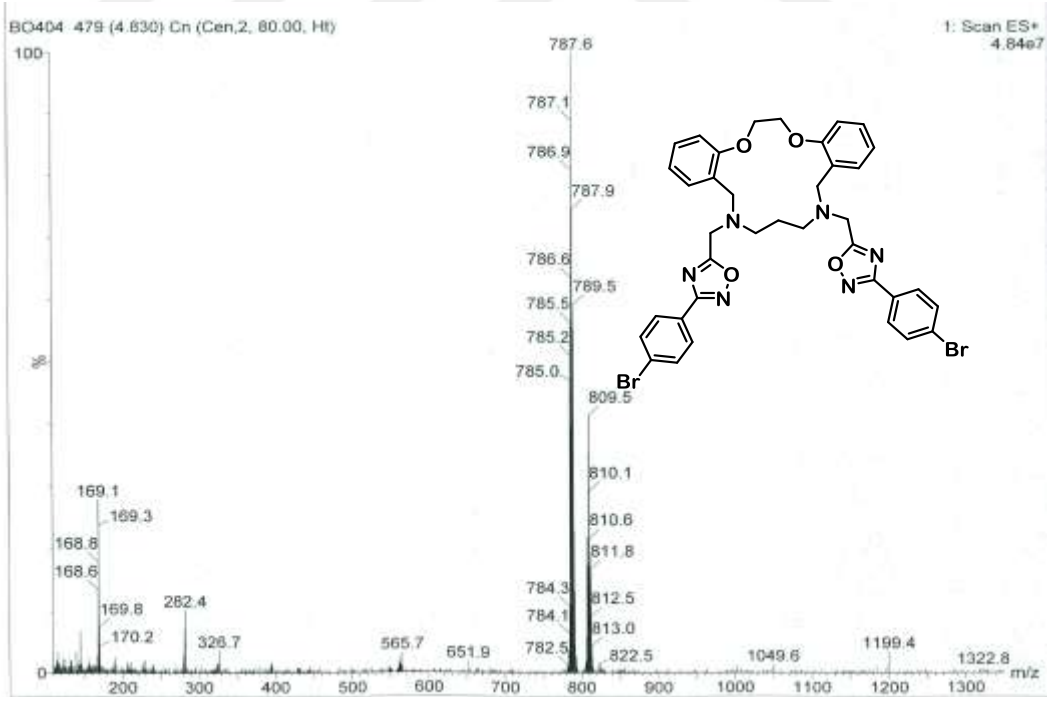

Figure 7.131. LC-MS Spectrum of compound **168e**

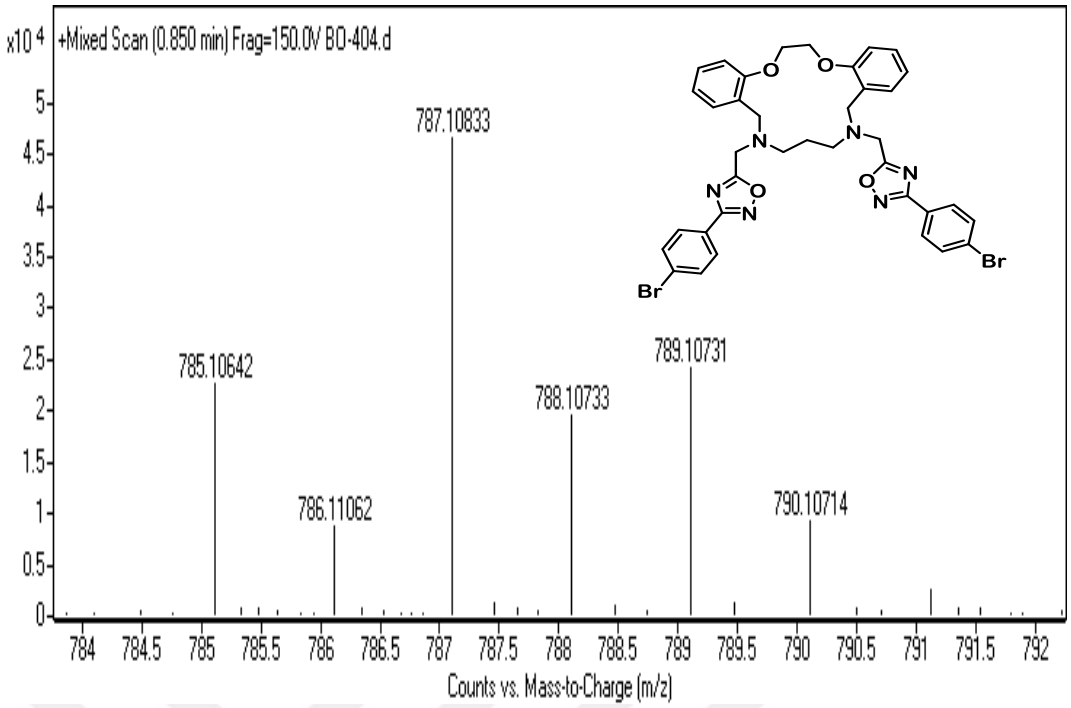

Figure 7.132. HR-MS Spectrum of compound **168e**

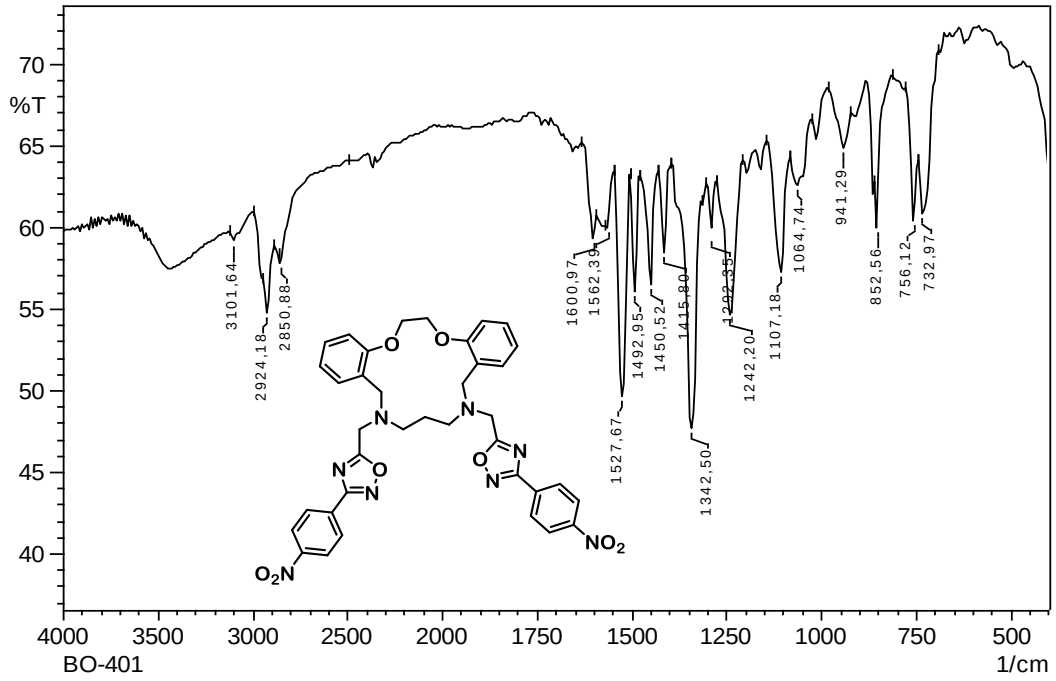

Figure 7.133. IR spectrum of compound **168f**

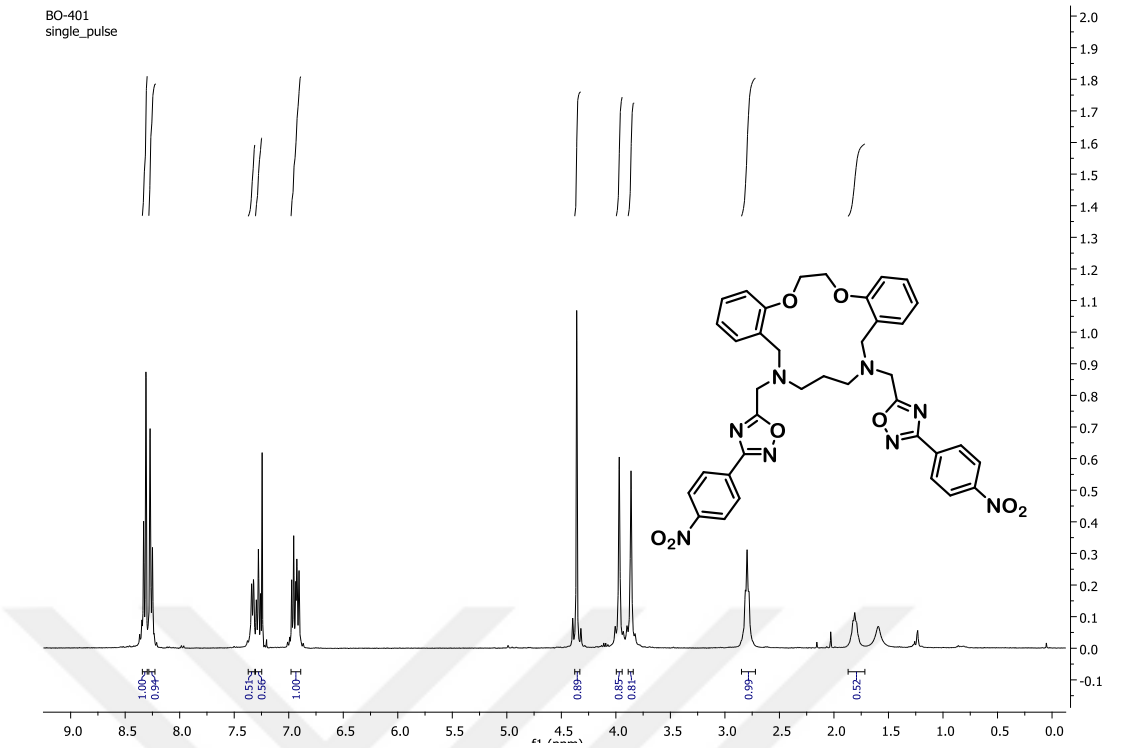

Figure 7.134. ^{1}H NMR spectrum of compound **168f**

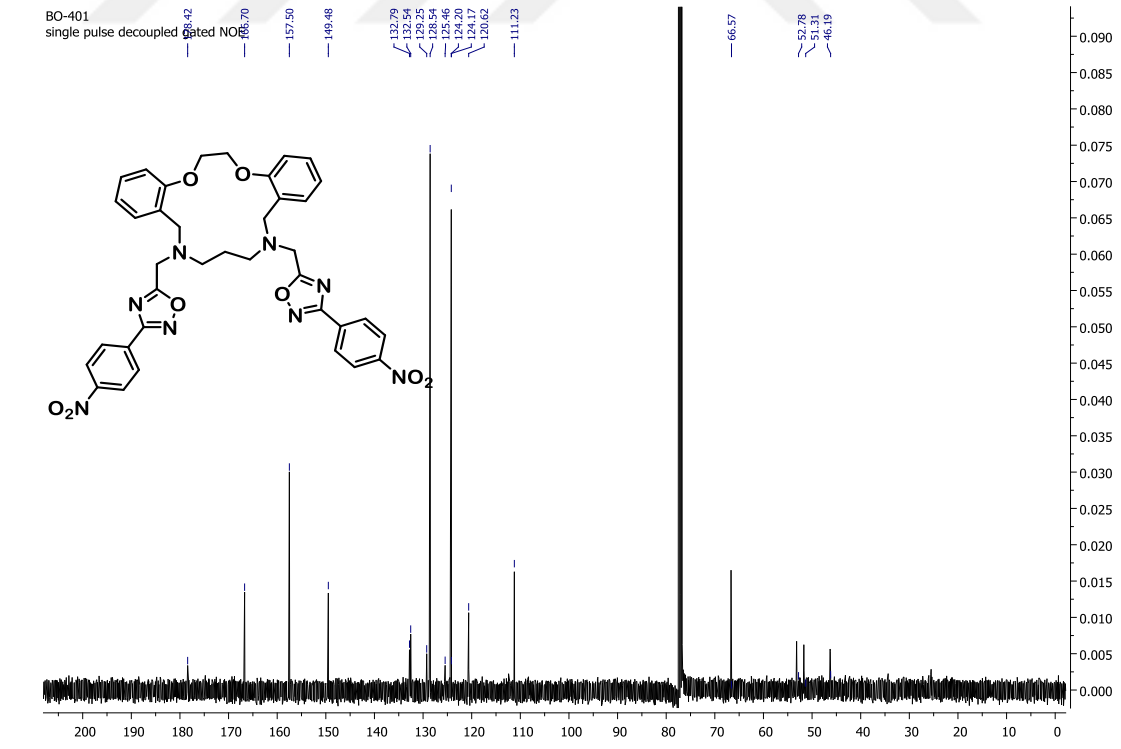

Figure 7.135. ^{13}C NMR spectrum of compound **168f**

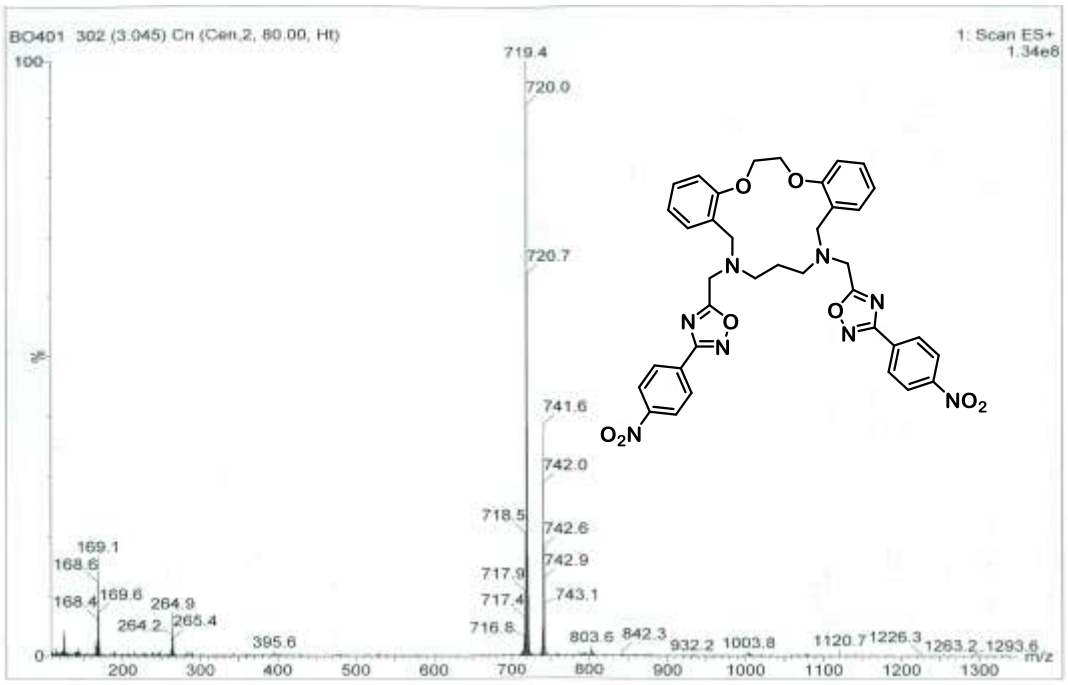

Figure 7.136. LC-MS Spectrum of compound **168f**

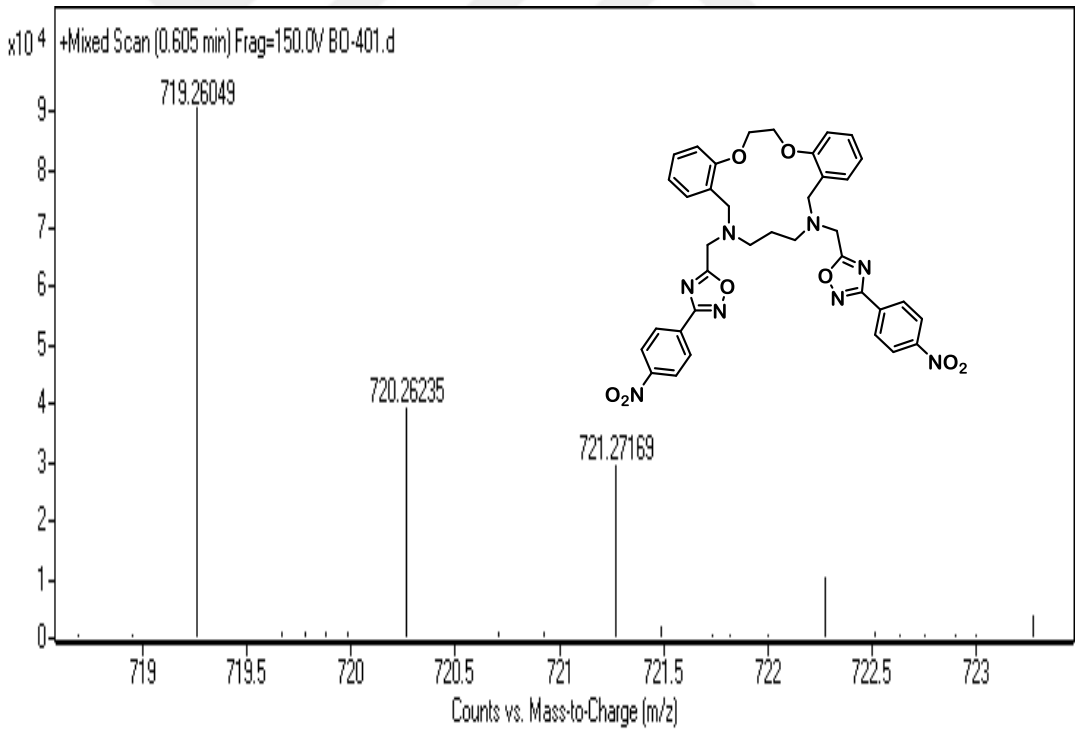

Figure 7.137. HR-MS Spectrum of compound **168f**

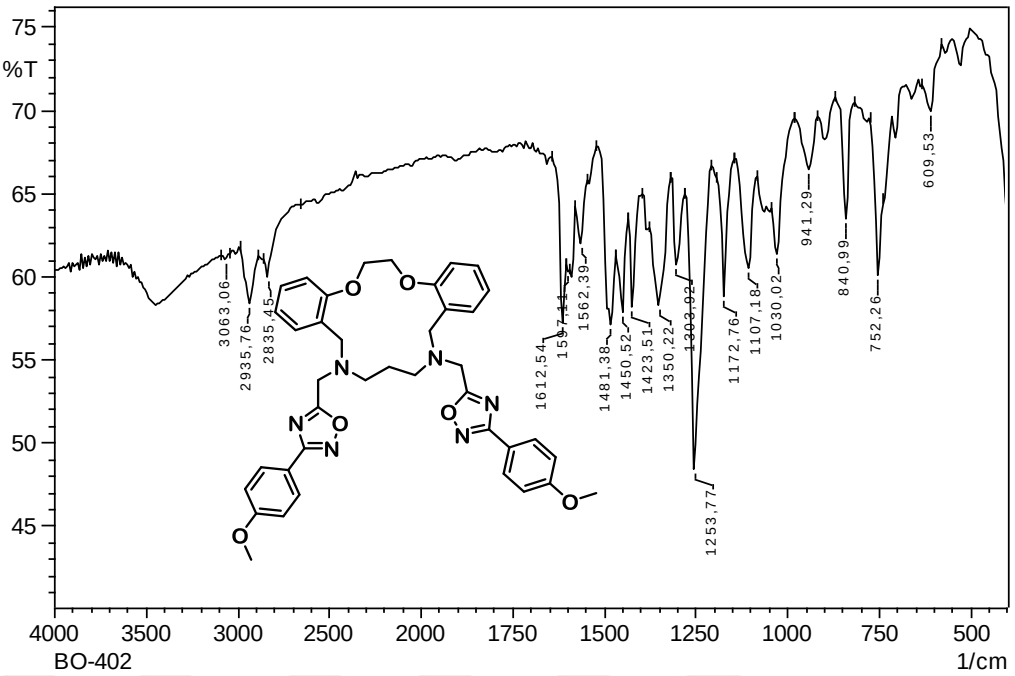

Figure 7.138. IR spectrum of compound **168g**

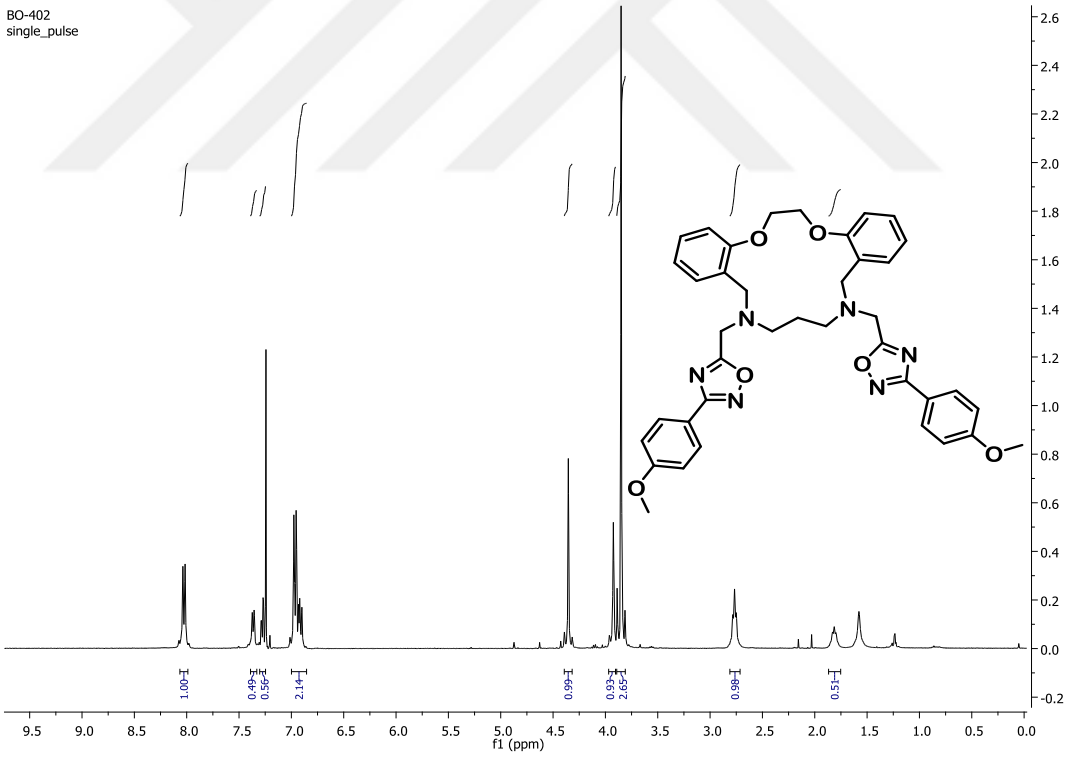

Figure 7.139. ^{1}H NMR spectrum of compound **168g**

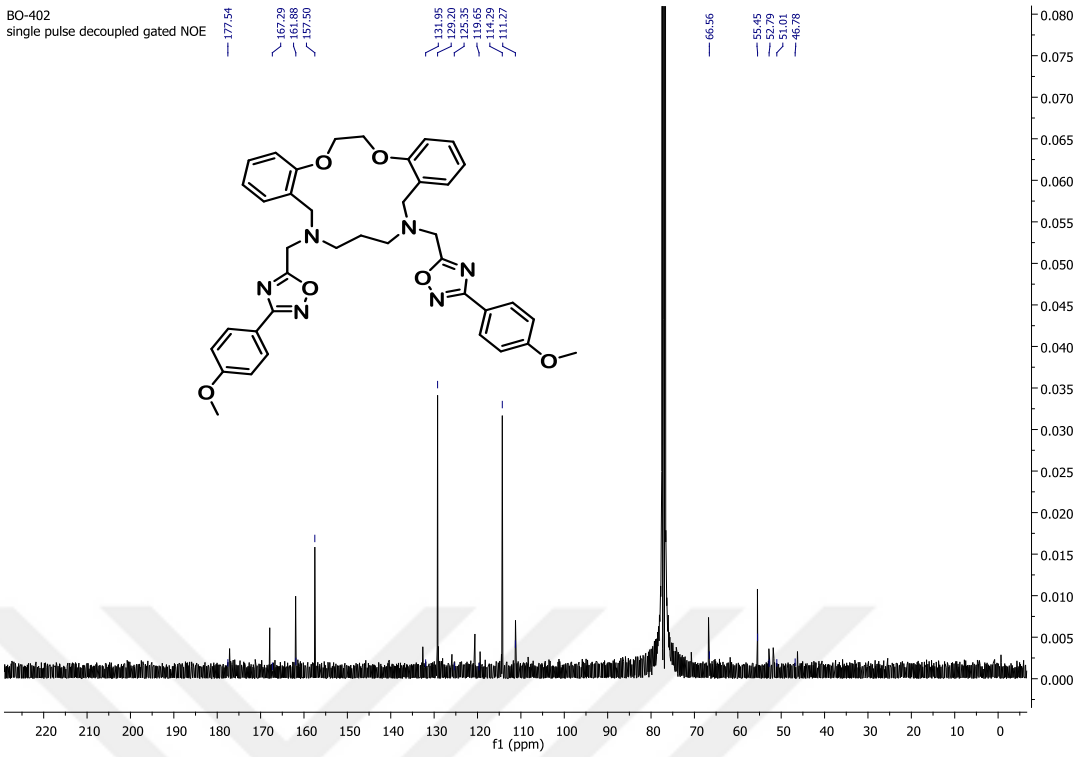

Figure 7.140. ^{13}C NMR spectrum of compound **168g**

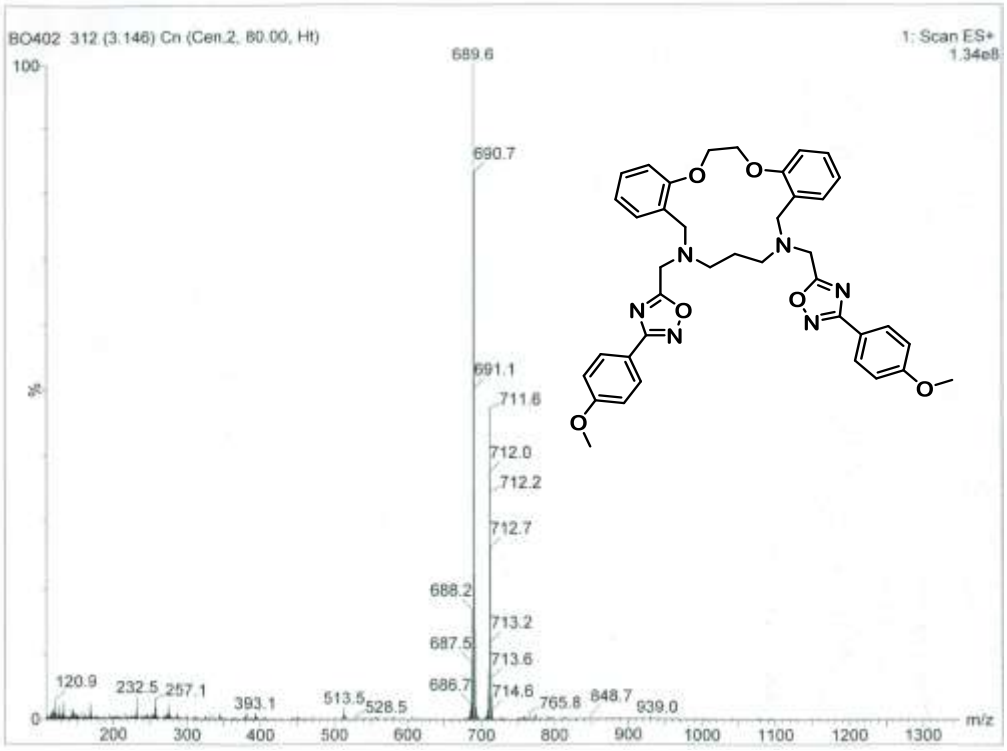

Figure 7.141. LC-MS Spectrum of compound **168g**

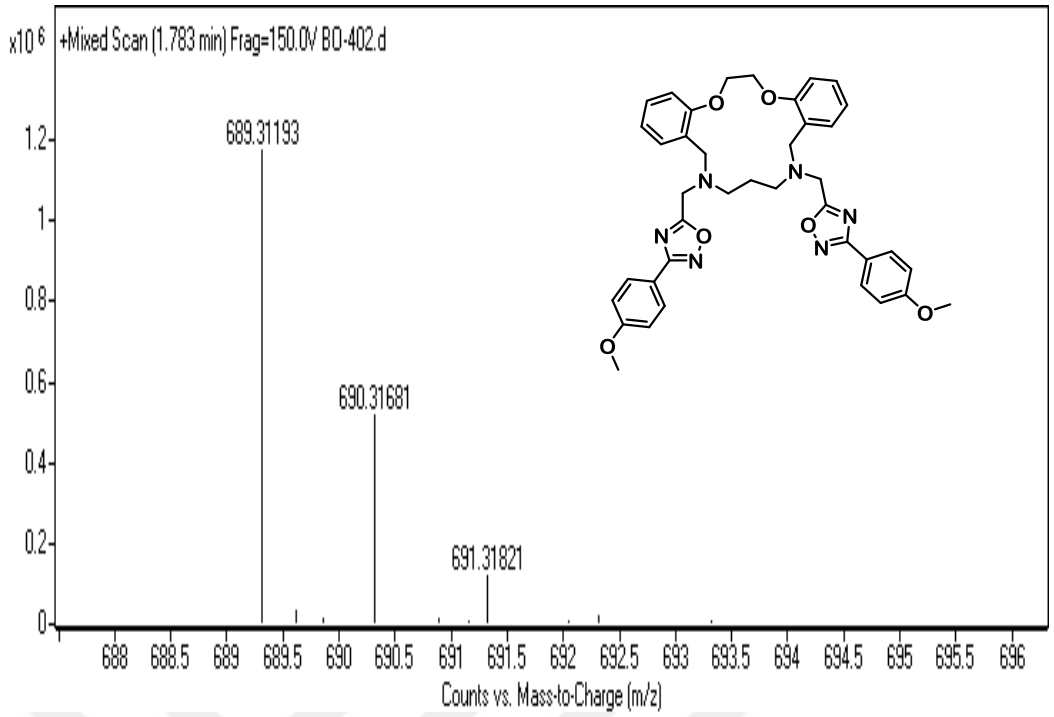

Figure 7.142. HR-MS Spectrum of compound **168g**

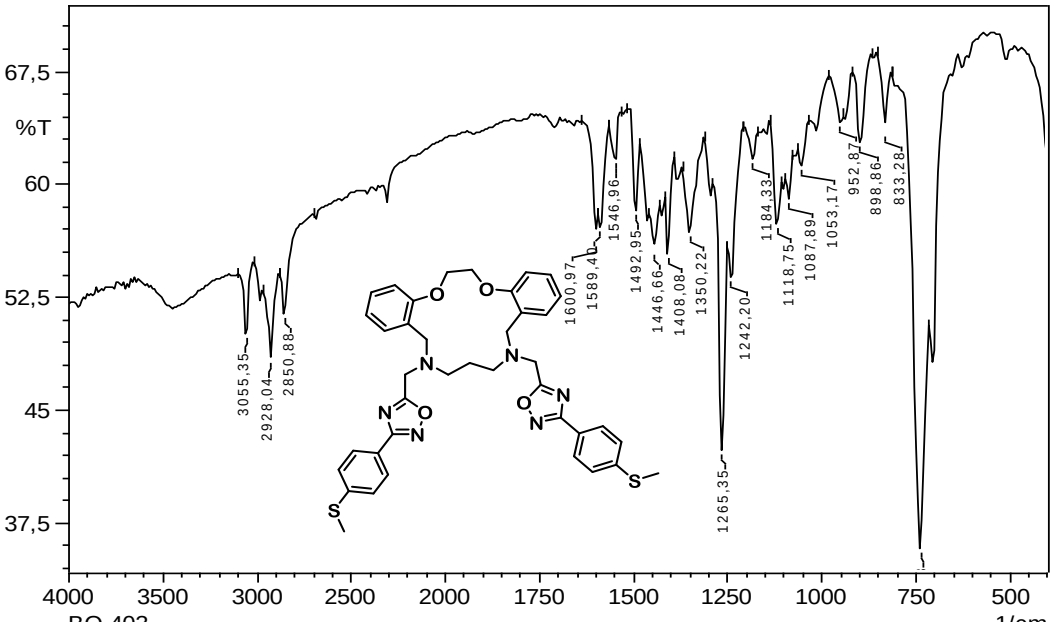

Figure 7.143. IR spectrum of compound **168h**

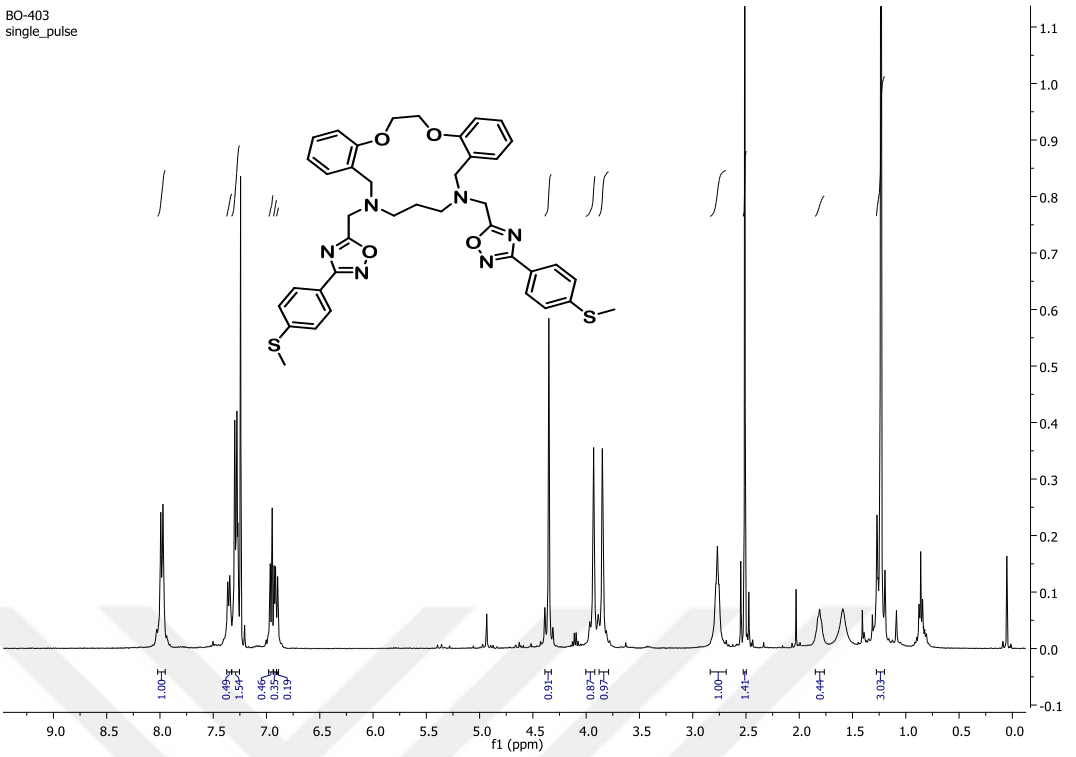

Figure 7.144. ^{1}H NMR spectrum of compound **168h**

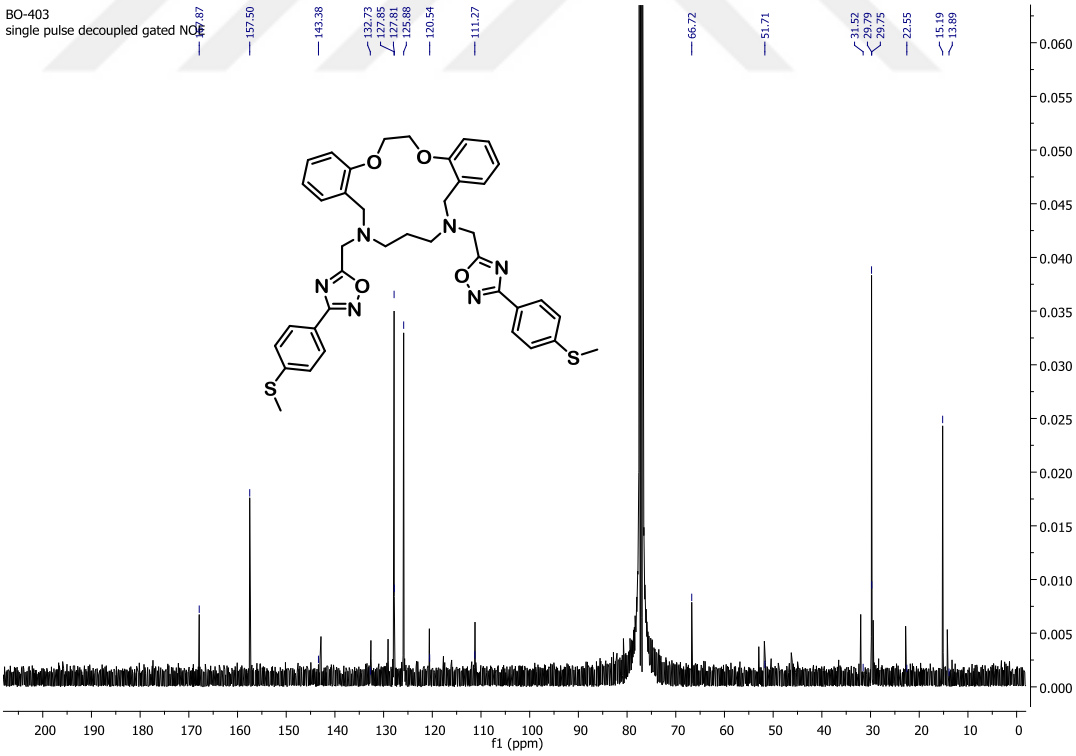

Figure 7.145. ^{13}C NMR spectrum of compound **168h**

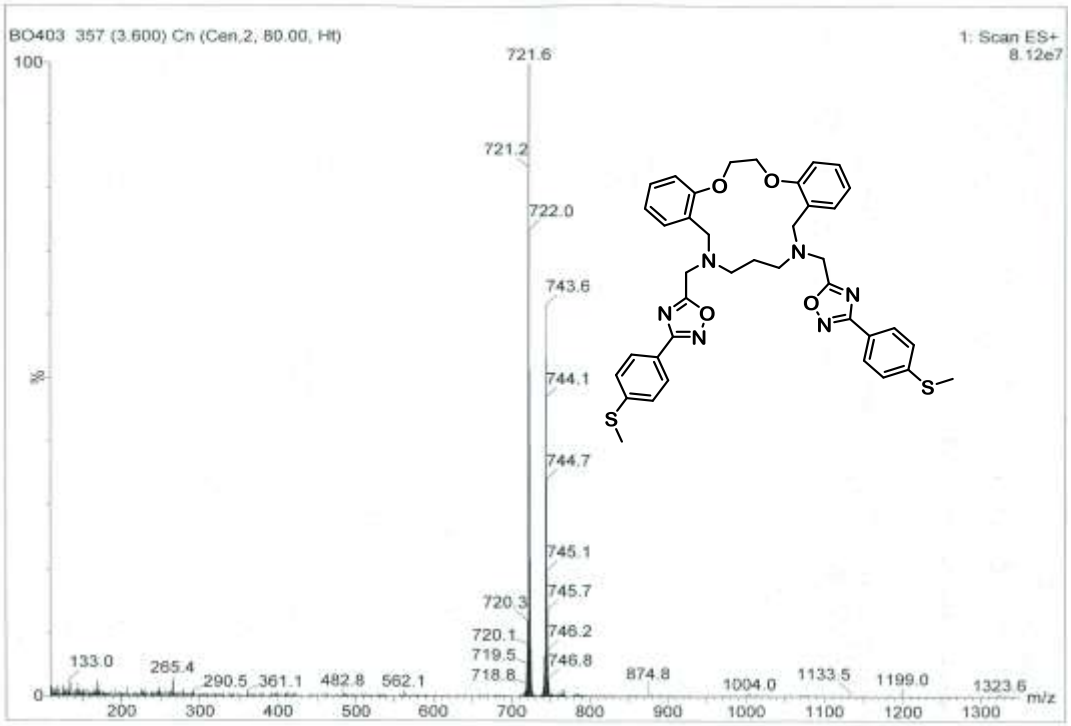

Figure 7.146. LC-MS Spectrum of compound **168h**

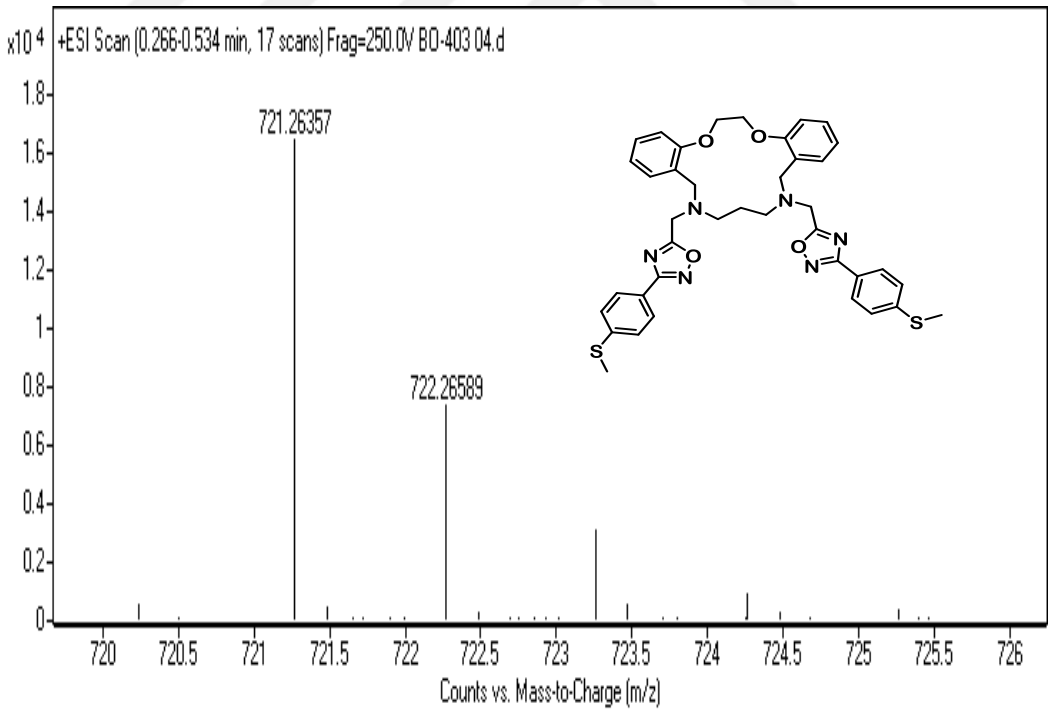

Figure 7.147. HR-MS Spectrum of compound **168h**

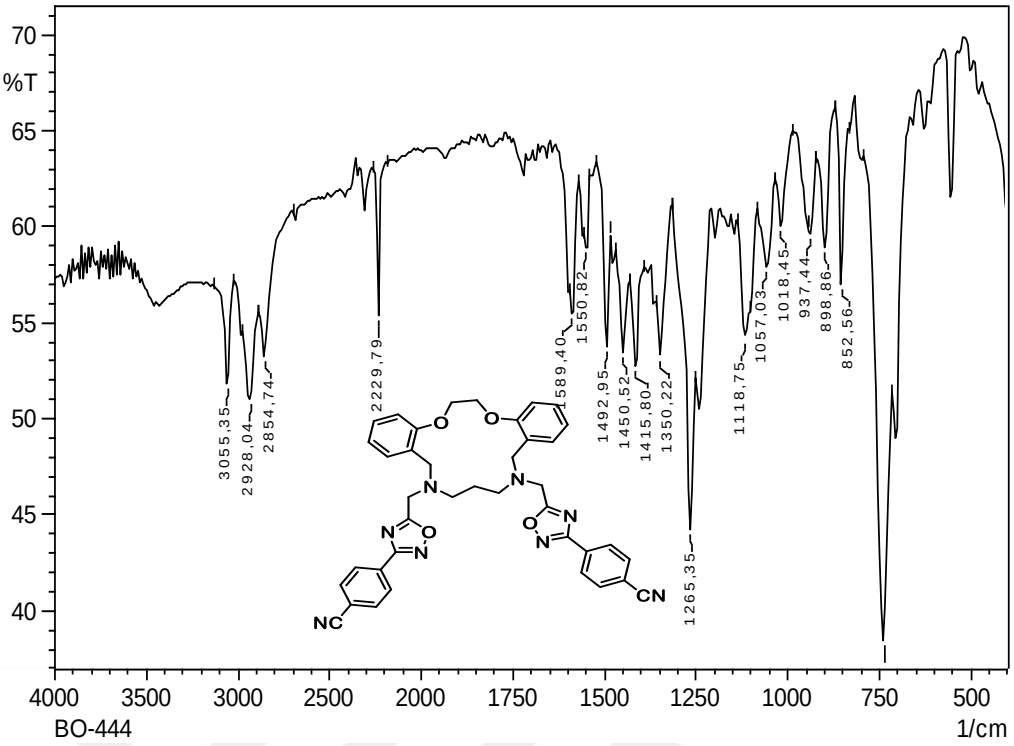

Figure 7.148. IR spectrum of compound **168ı**

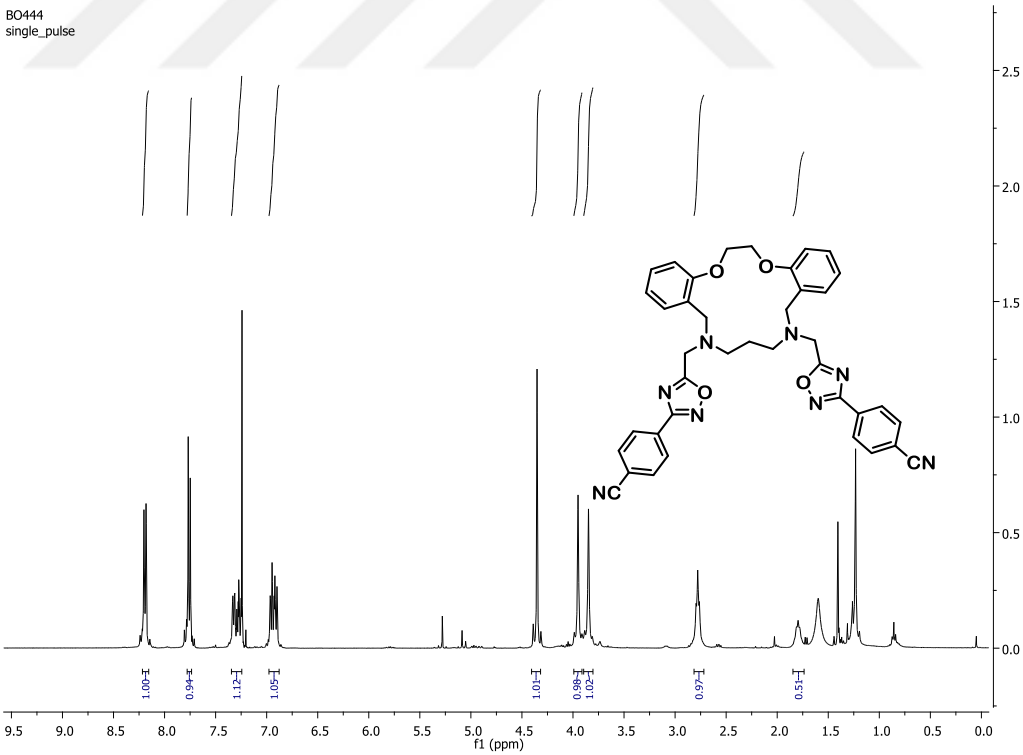

Figure 7.149. ^{1}H NMR spectrum of compound **168ı**

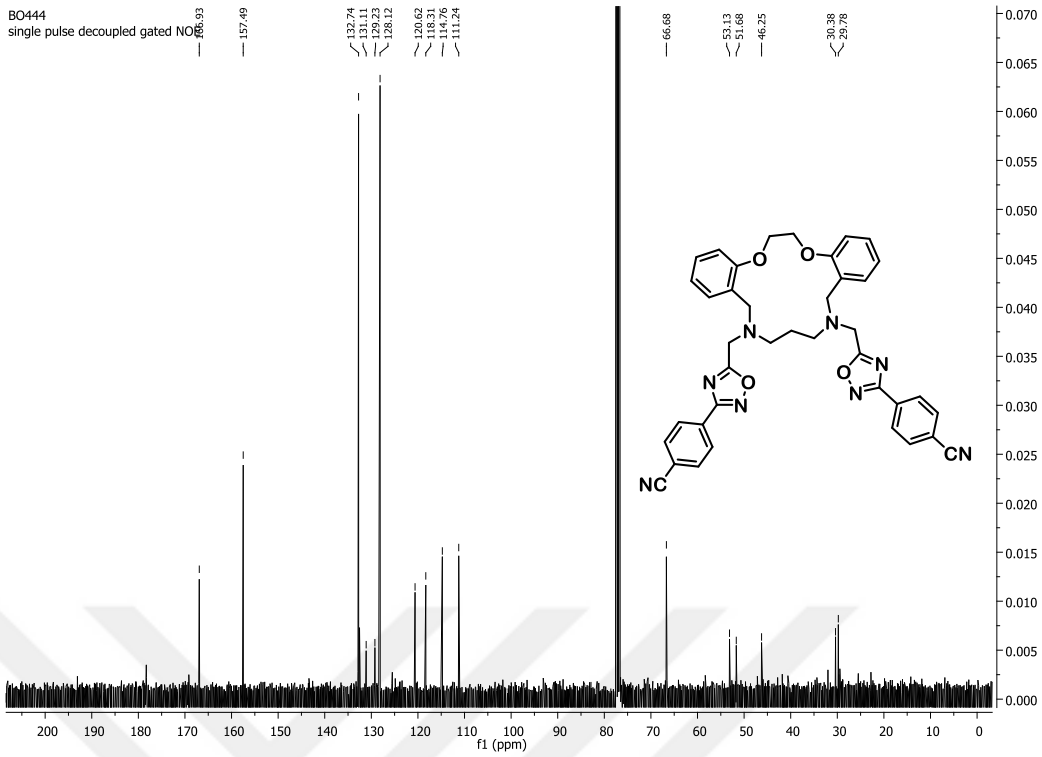

Figure 7.150. ^{13}C NMR spectrum of compound **168ı**

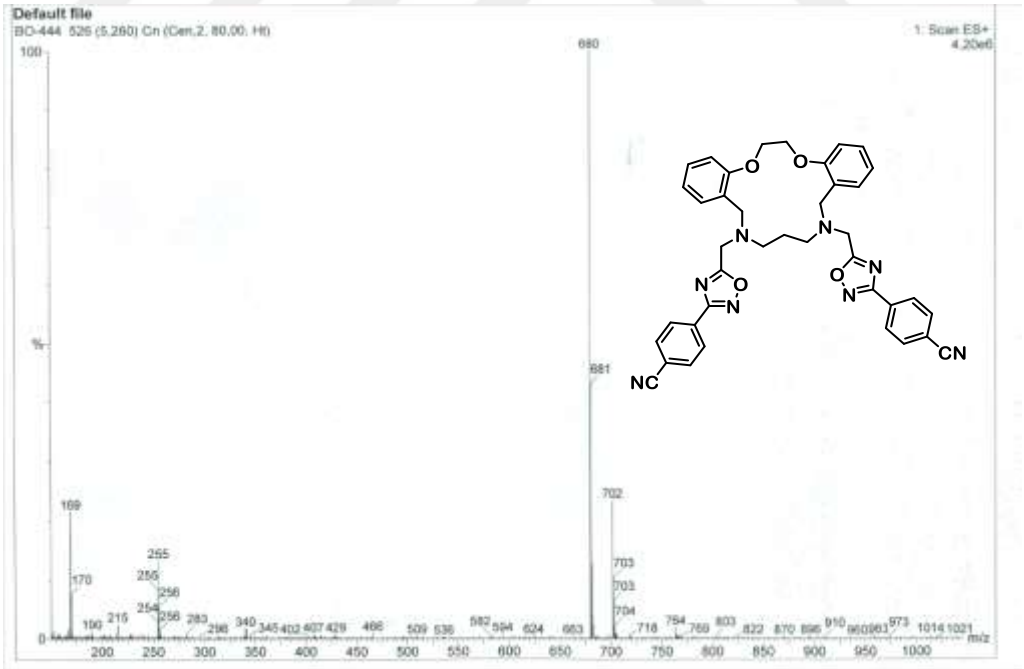

Figure 7.151. LC-MS Spectrum of compound **168ı**

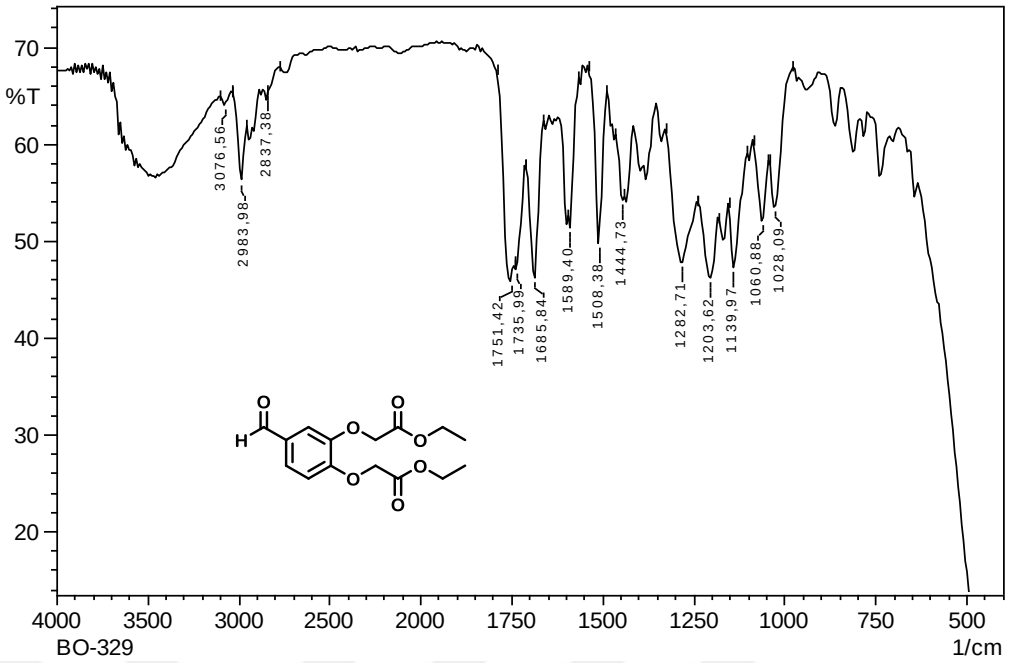

Figure 7.152. IR spectrum of compound **170**

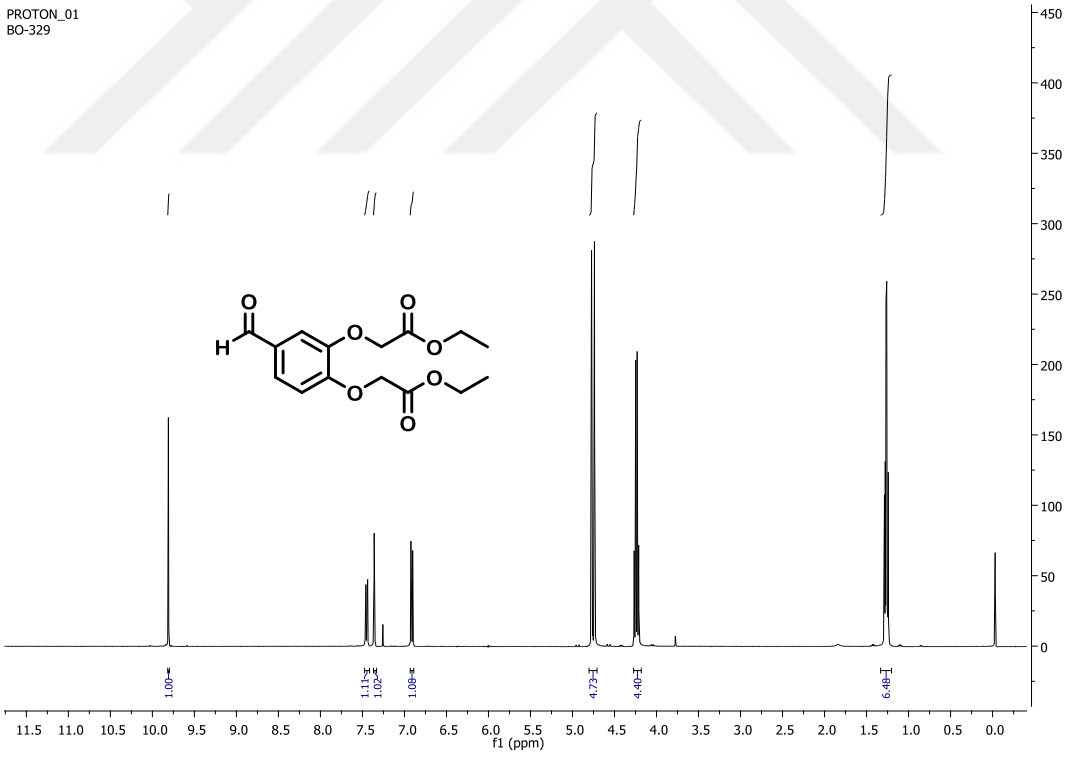

Figure 7.153. ^{1}H NMR spectrum of compound **170**

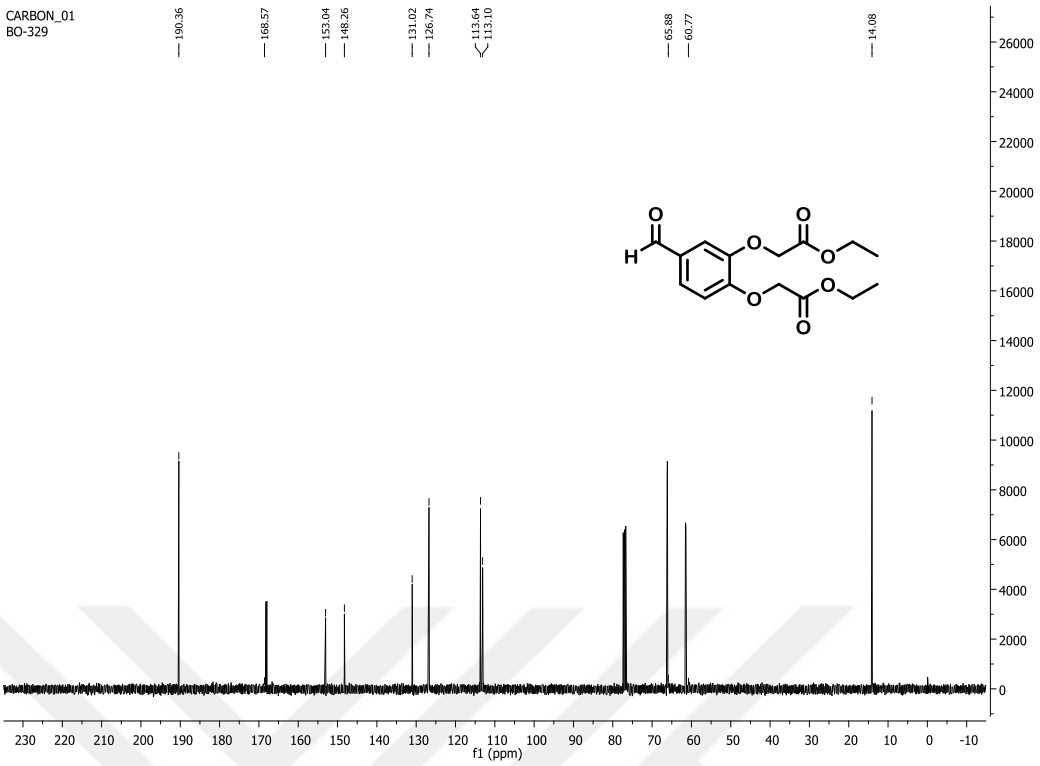

Figure 7.154. ^{13}C NMR spectrum of compound **170**

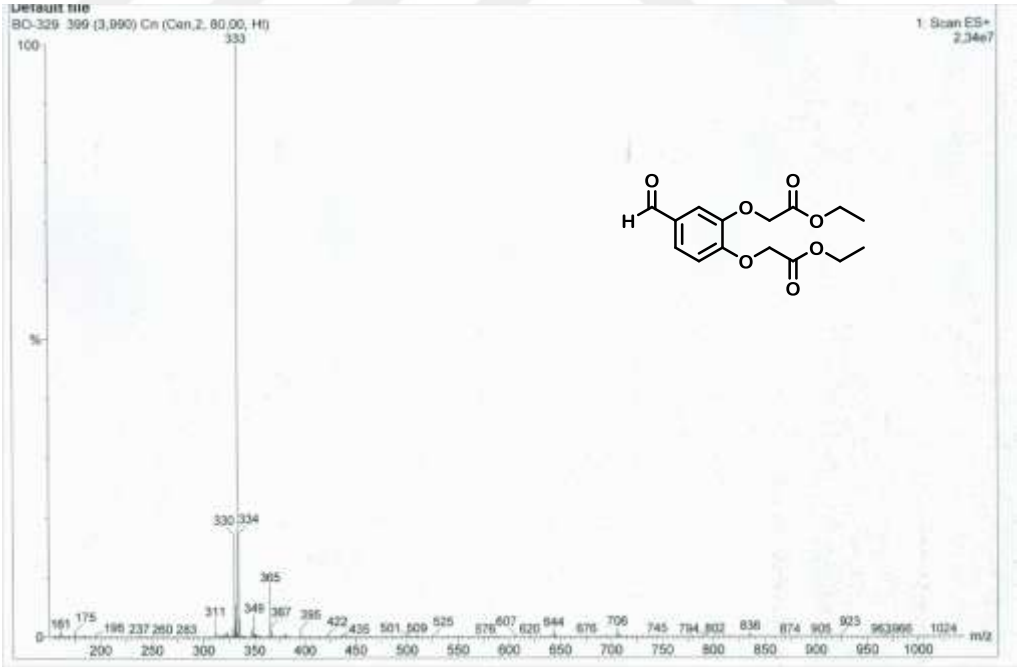

Figure 7.155. LC-MS Spectrum of compound **170**

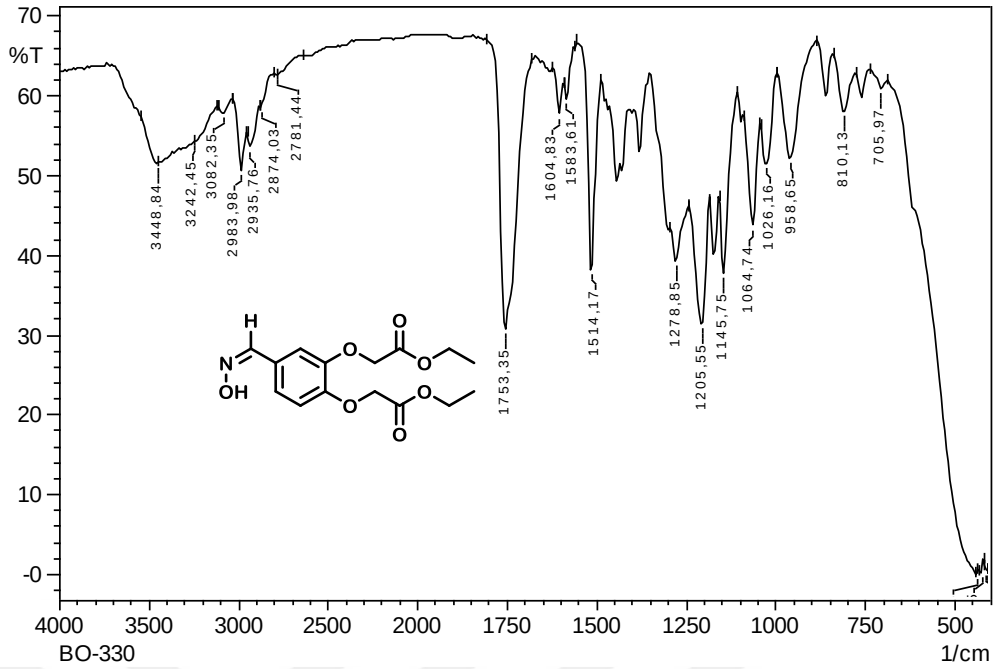

Figure 7.156. IR spectrum of compound **171**

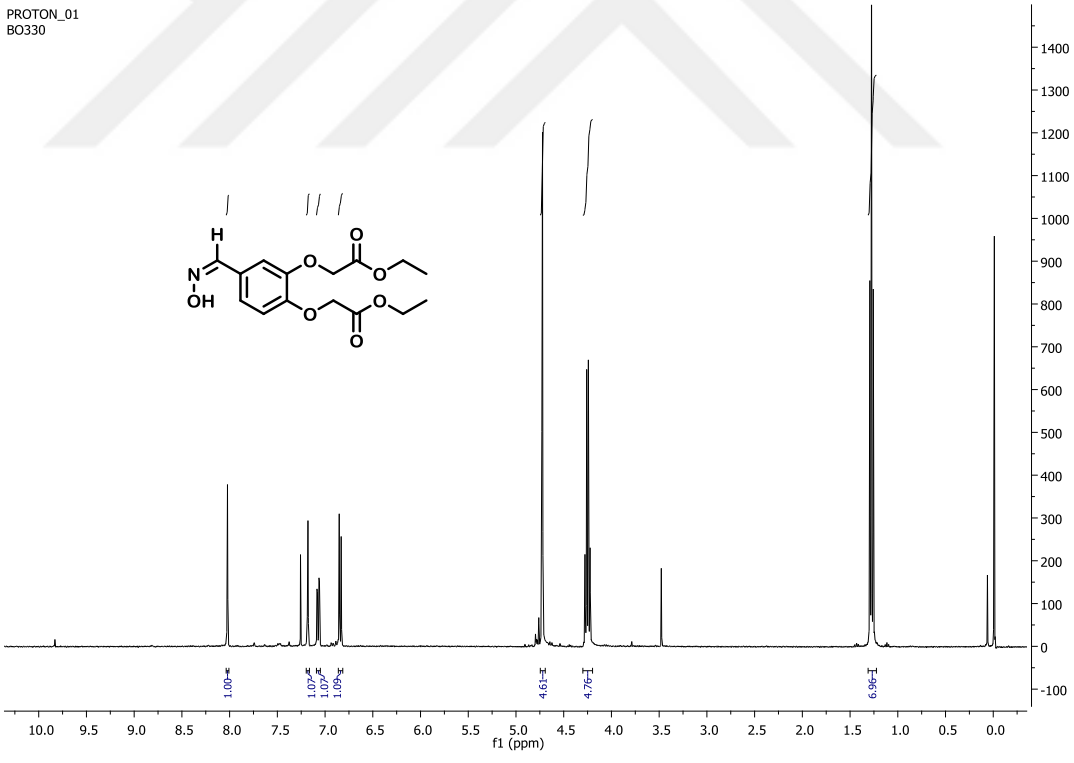

Figure 7.157. ^{1}H NMR spectrum of compound **171**

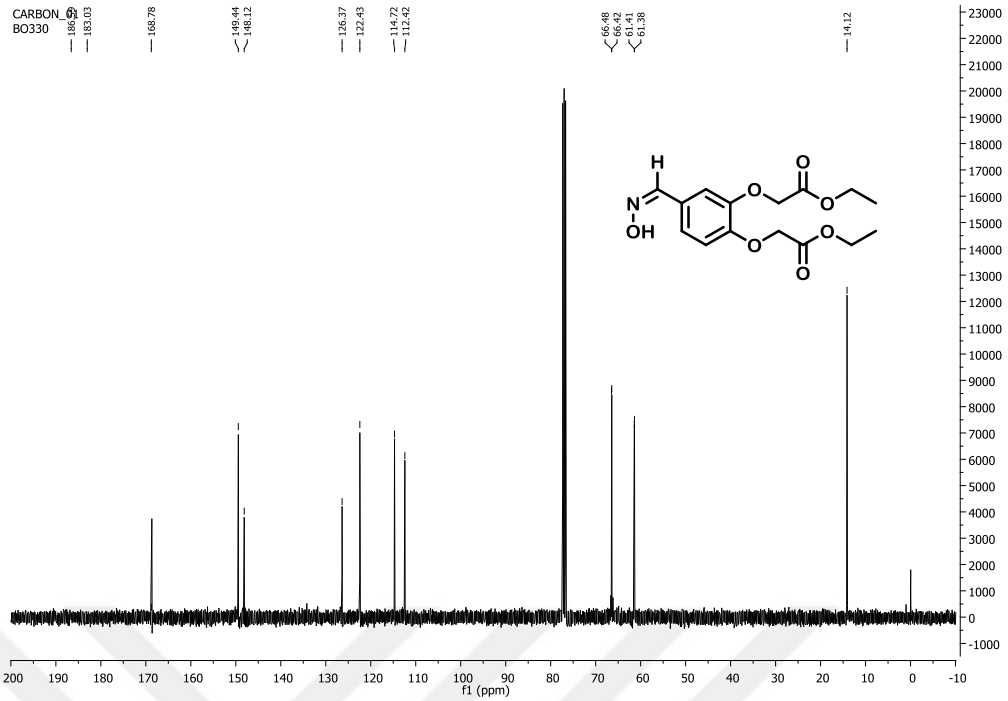

Figure 7.158. ^{13}C NMR spectrum of compound **171**

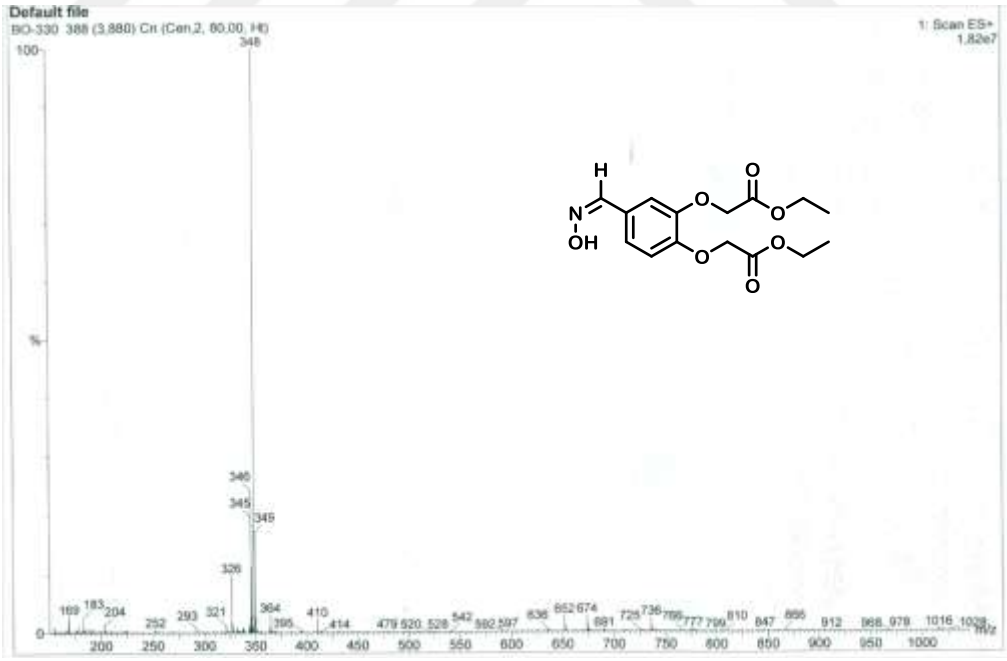

Figure 7.159. LC-MS Spectrum of compound **171**

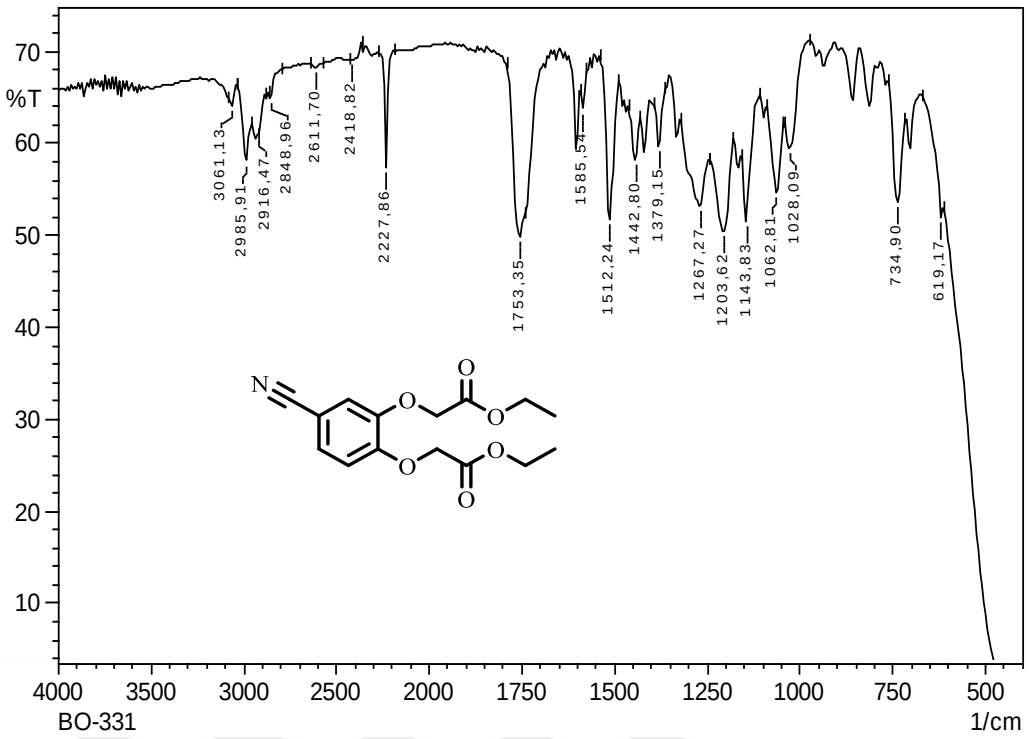

Figure 7.160. IR spectrum of compound **172**

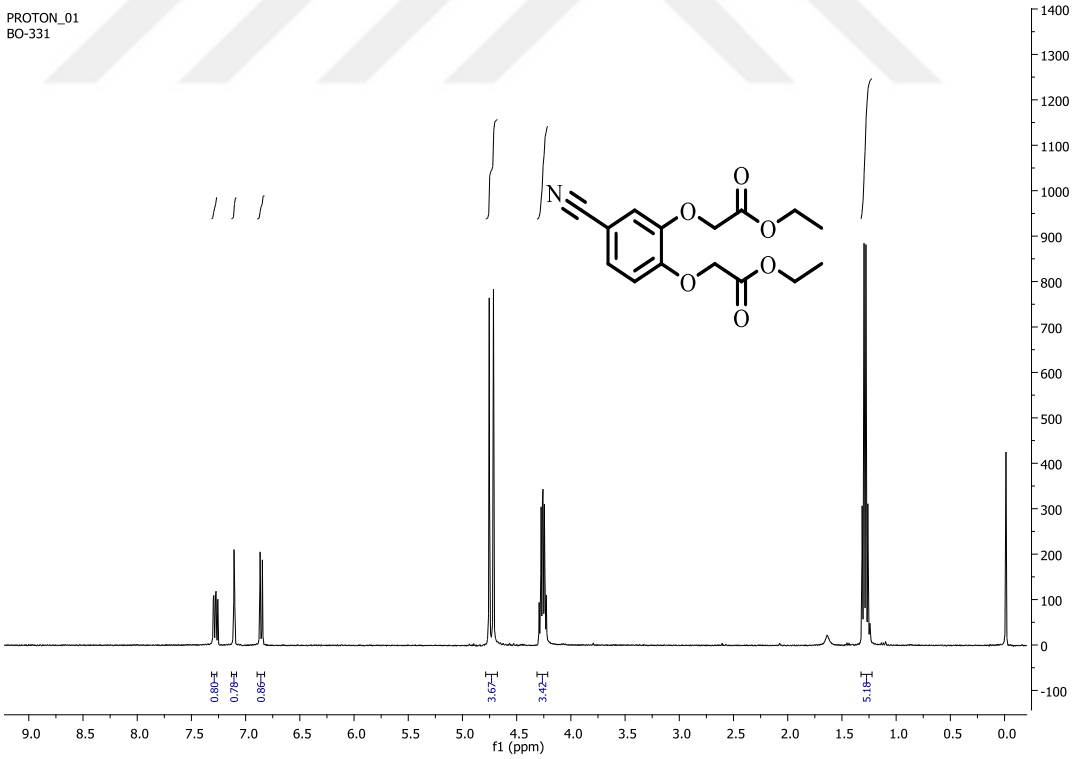

Figure 7.161. ^{1}H NMR spectrum of compound **172**

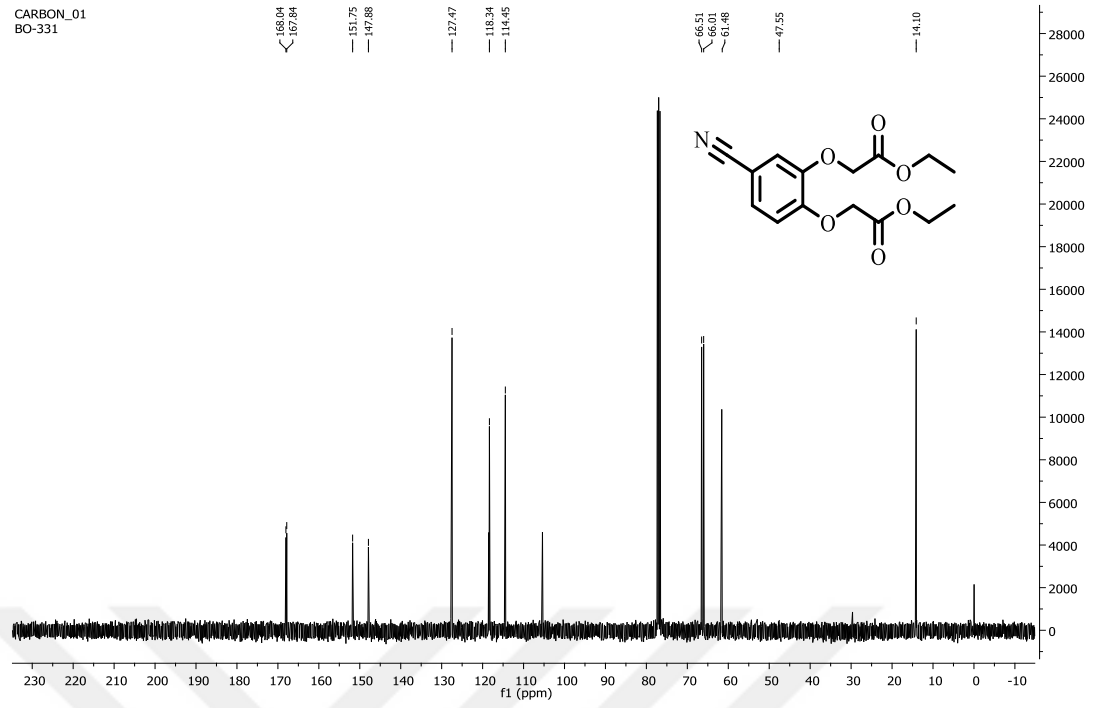

Figure 7.162. ^{13}C NMR spectrum of compound **172**

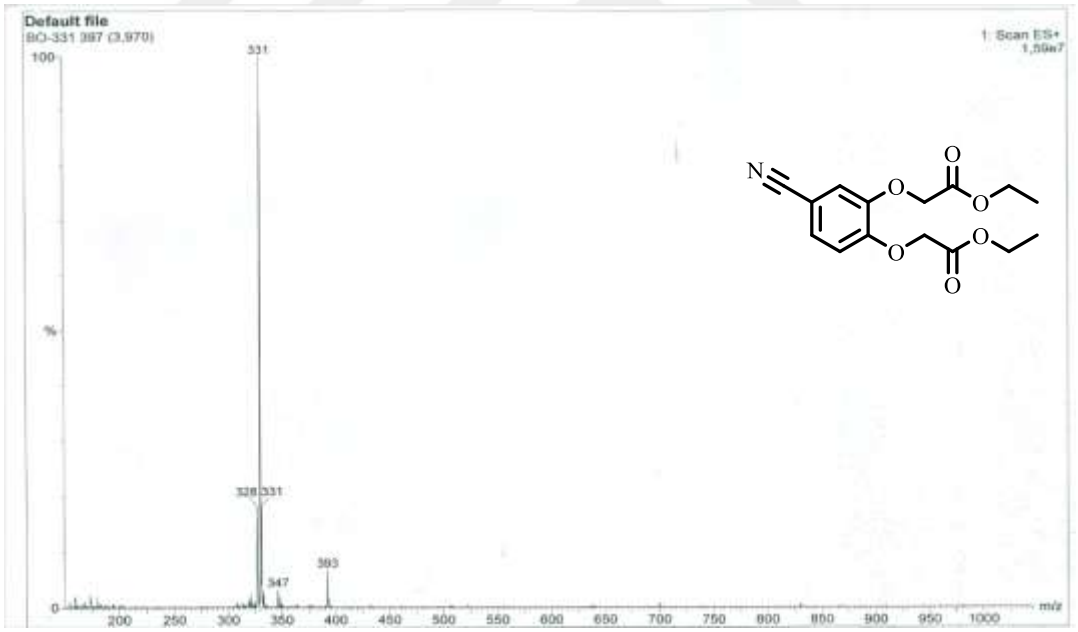

Figure 7.163. LC-MS Spectrum of compound **172**

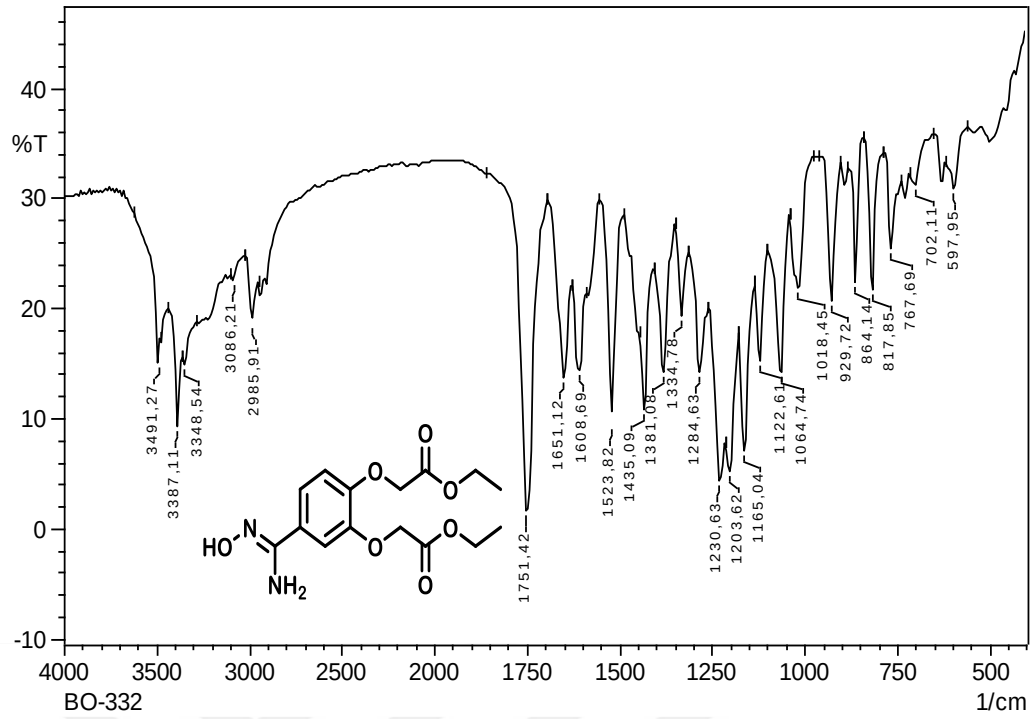

Figure 7.164. IR spectrum of compound **173**

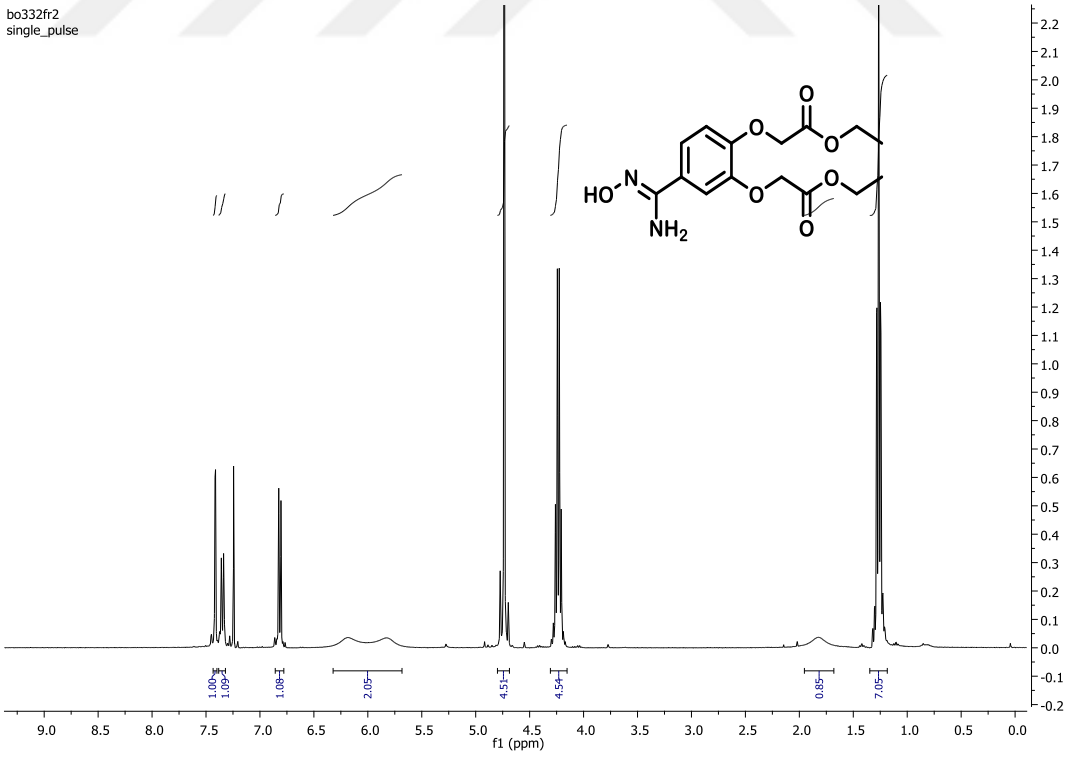

Figure 7.165. ^{1}H NMR spectrum of compound **173**

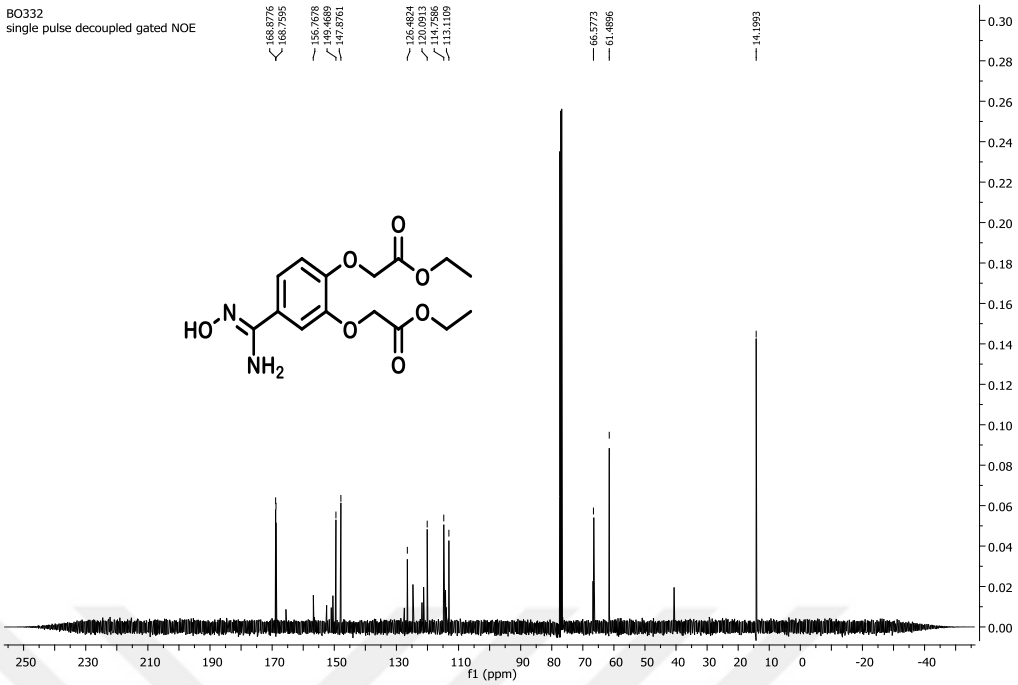

Figure 7.166. ^{13}C NMR spectrum of compound **173**

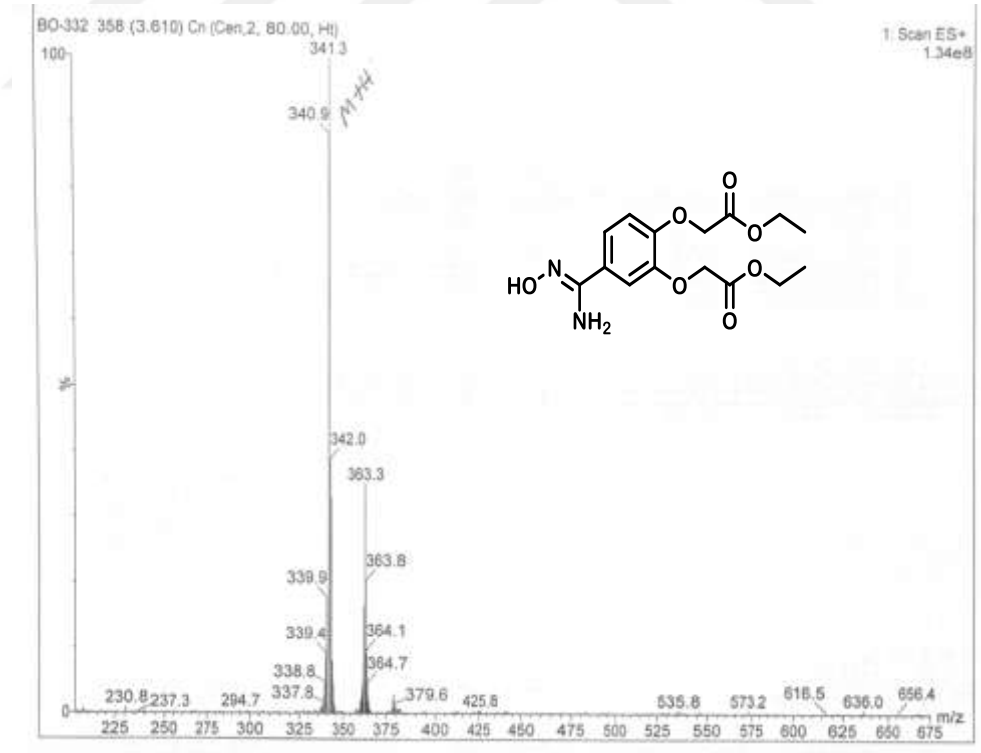

Figure 7.167. LC-MS Spectrum of compound **173**

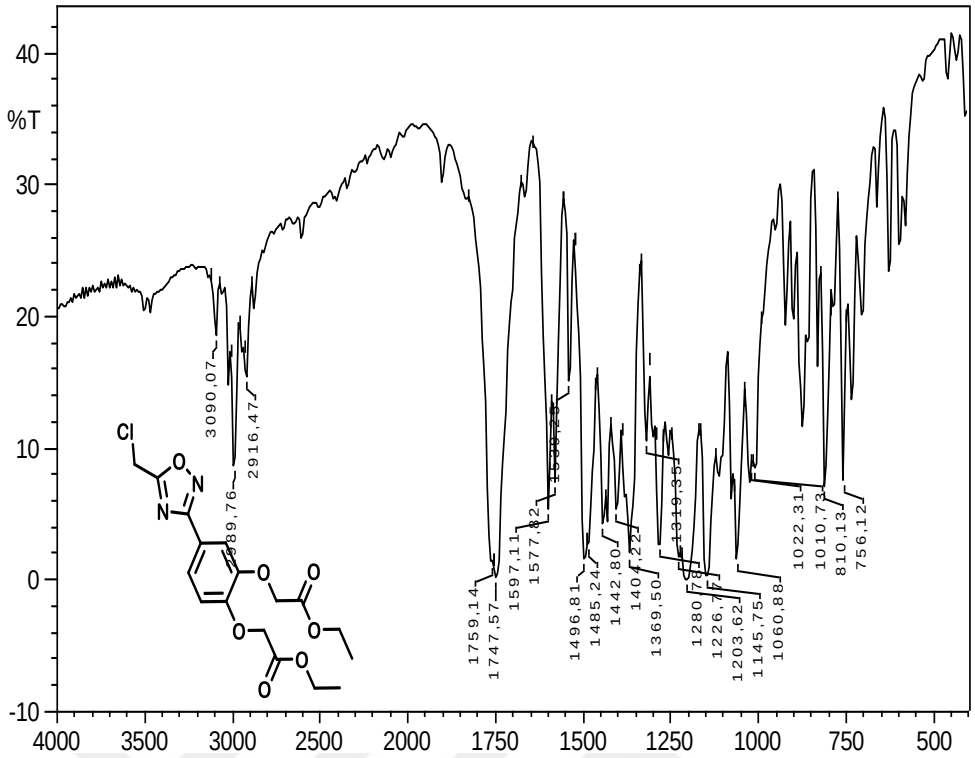

Figure 7.168. IR spectrum of compound **174**

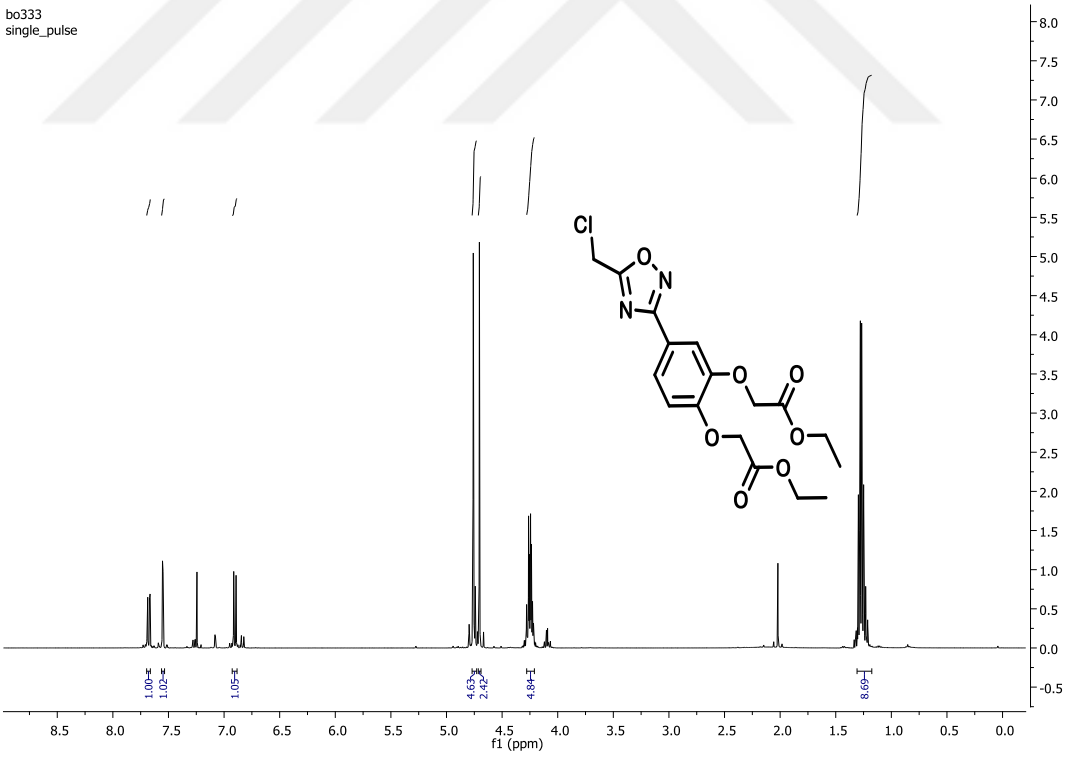

Figure 7.169. ^{1}H NMR spectrum of compound **174**

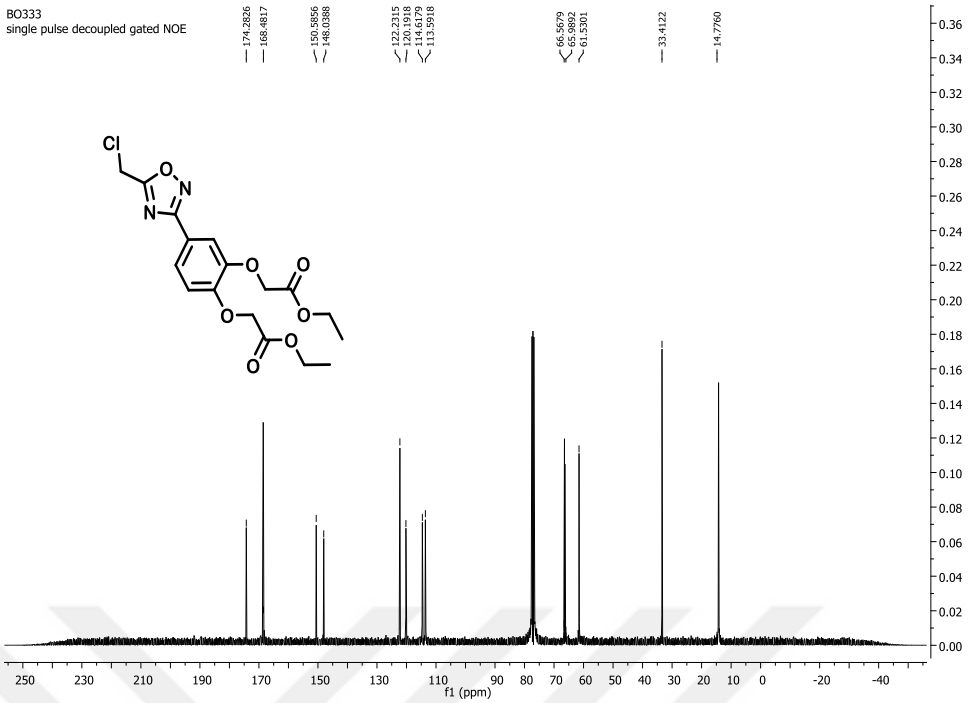

Figure 7.170. ^{13}C NMR spectrum of compound **174**

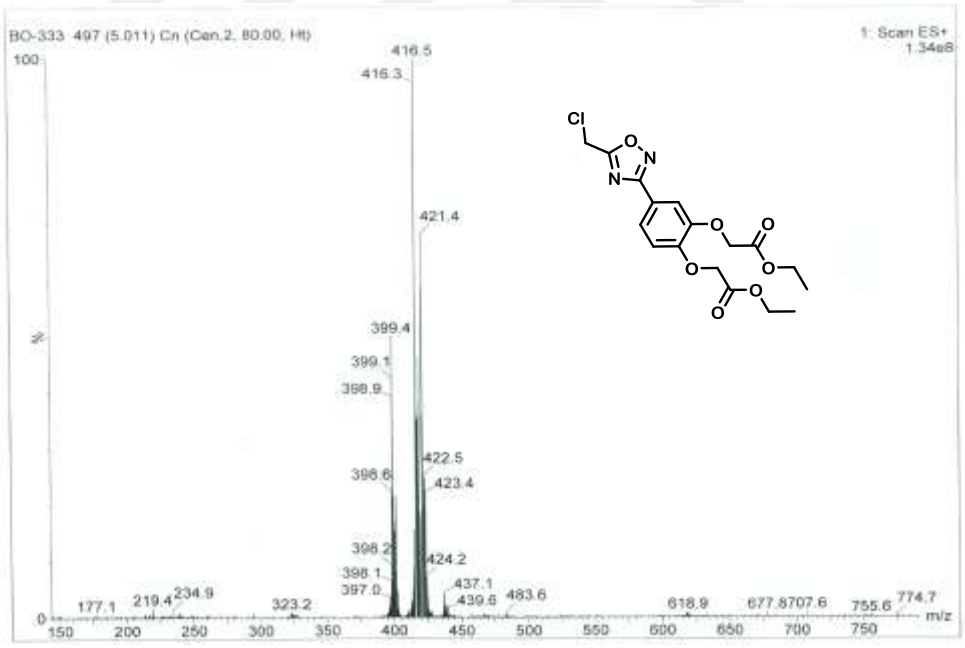

Figure 7.171. LC-MS Spectrum of compound **174**

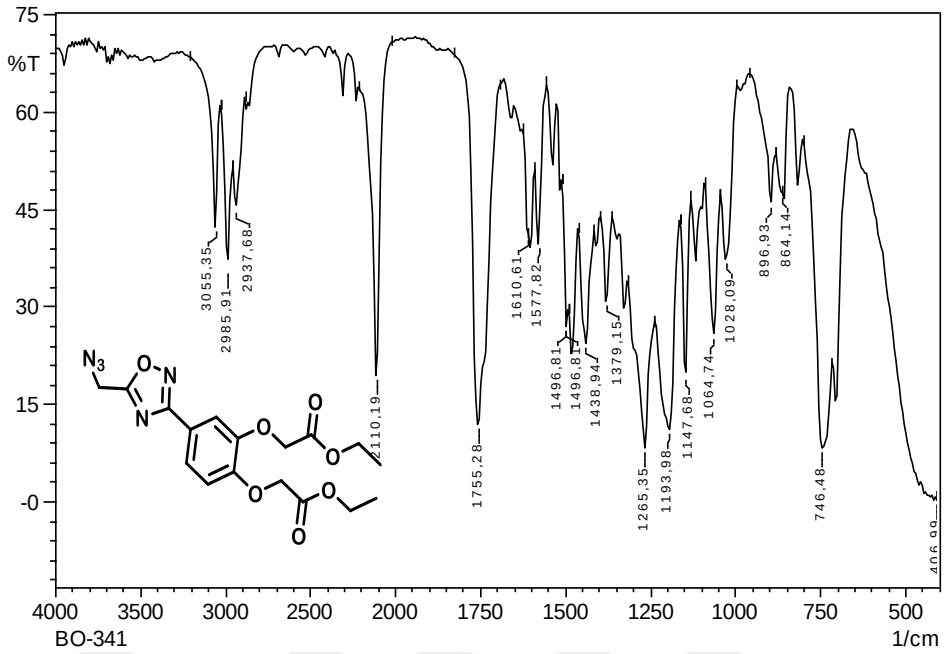

Figure 7.172. IR spectrum of compound **175**

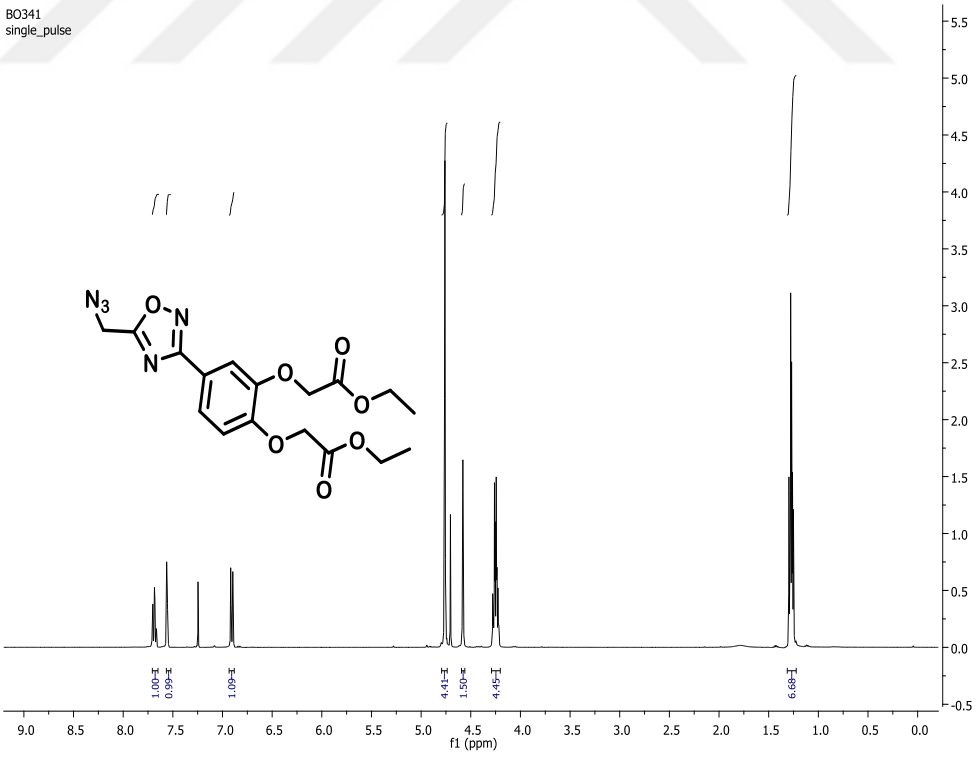

Figure 7.173. ^{1}H NMR spectrum of compound **175**

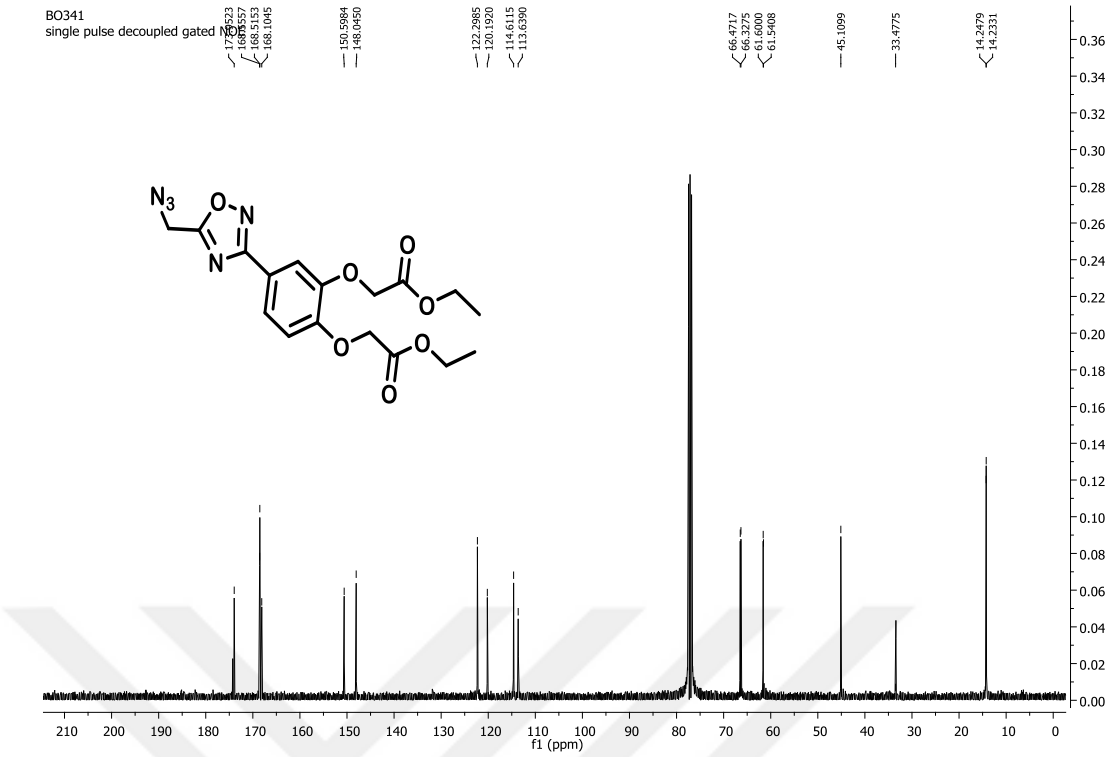

Figure 7.174. ^{13}C NMR spectrum of compound **175**

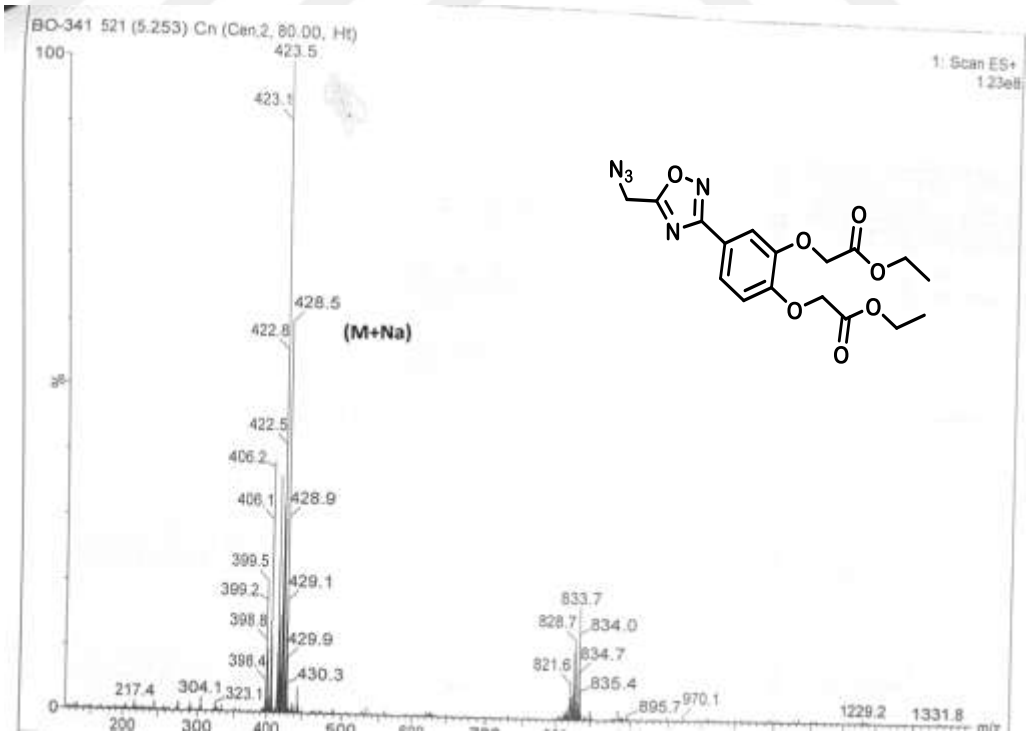

Figure 7.175. LC-MS Spectrum of compound **175**

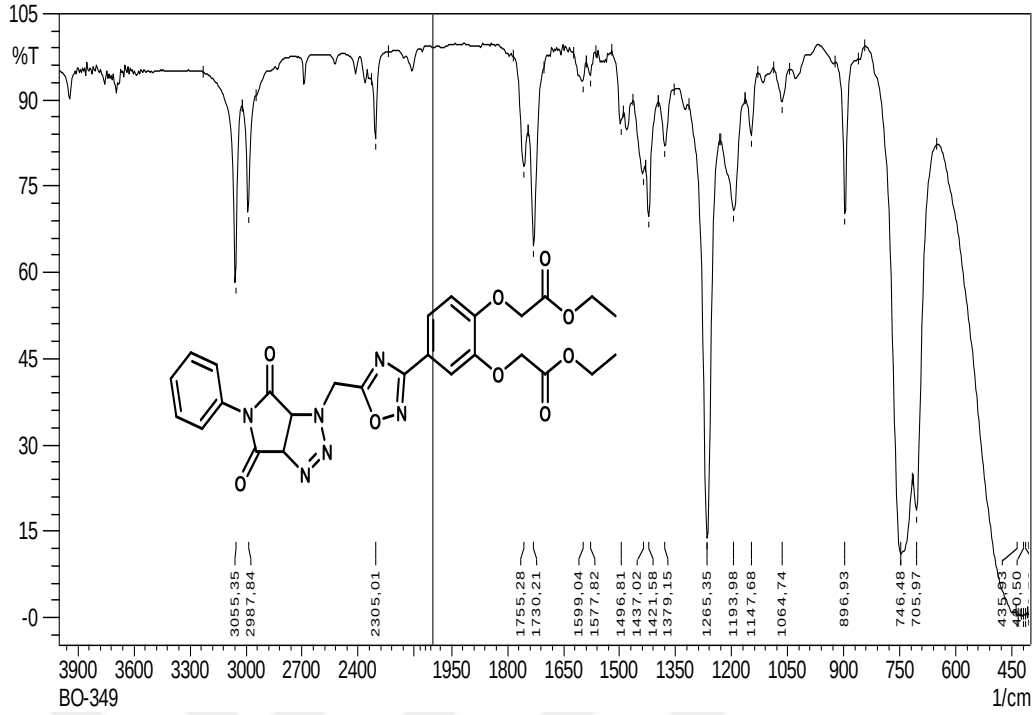

Figure 7.176. IR spectrum of compound **176**

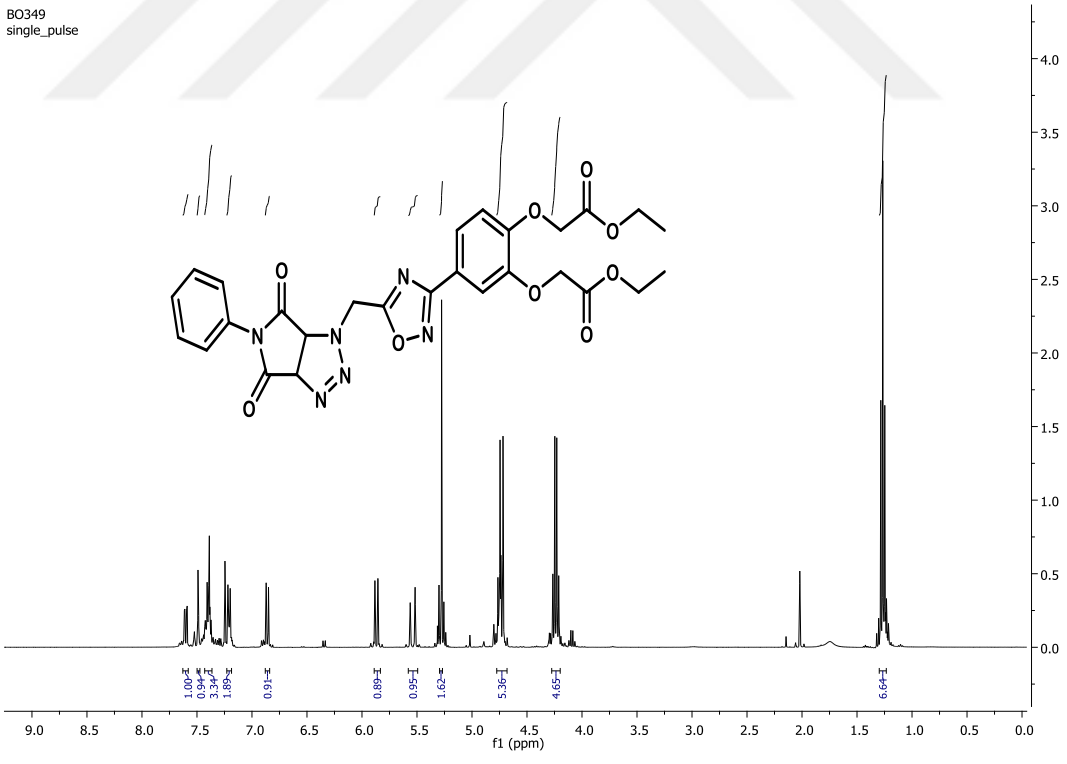

Figure 7.177. ^{1}H NMR spectrum of compound **176**

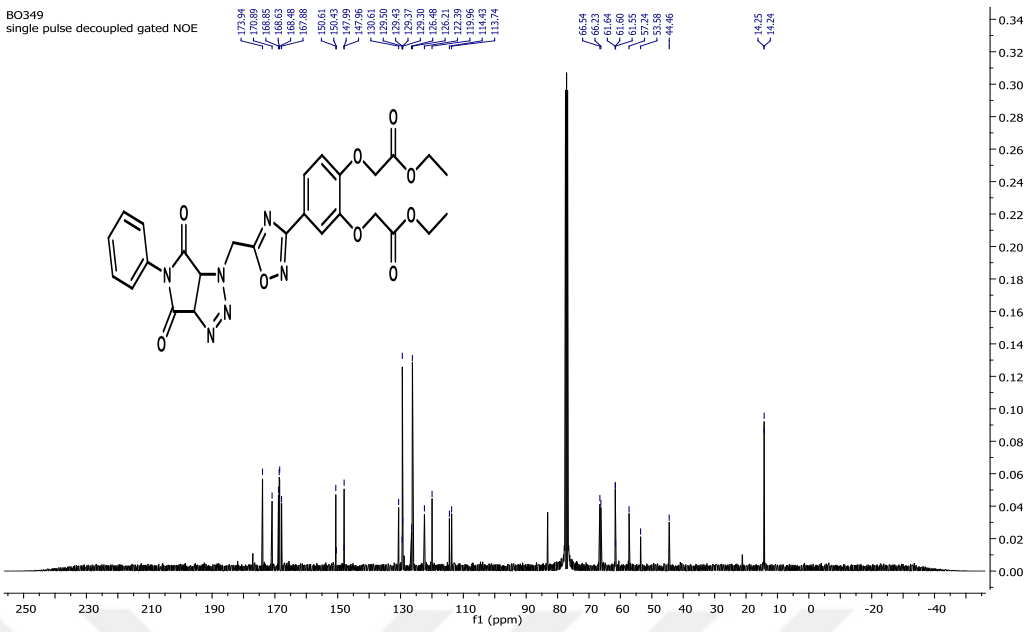

Figure 7.178. ^{13}C NMR spectrum of compound **176**

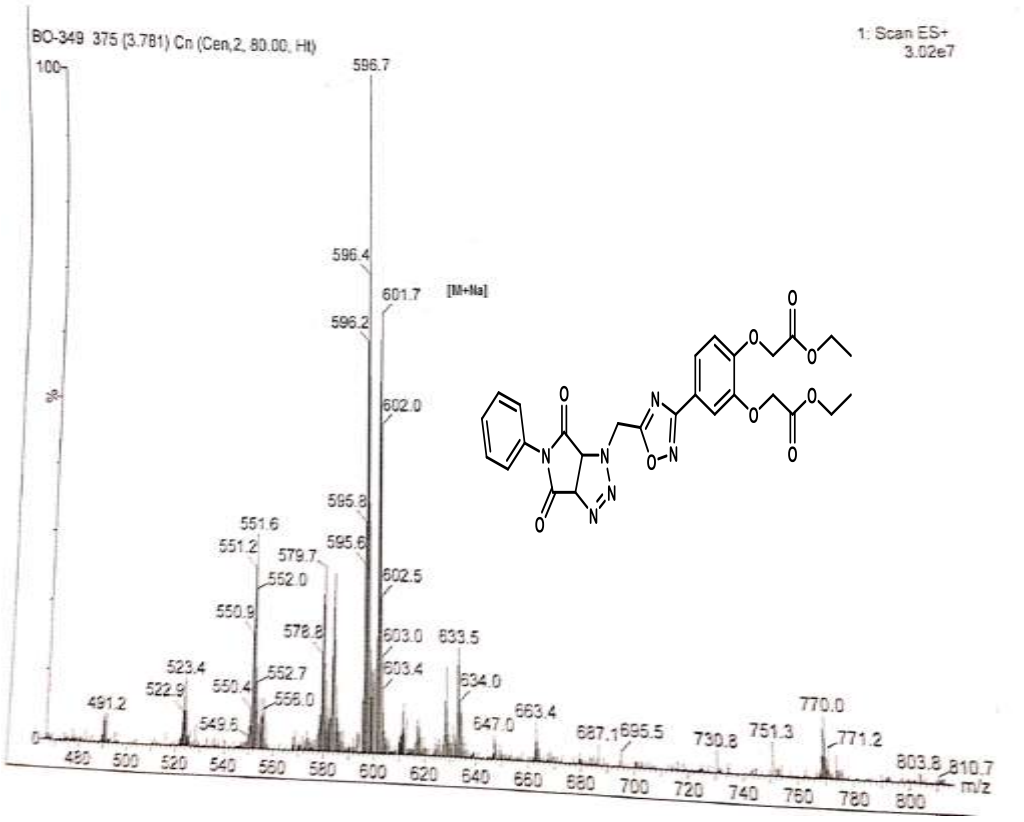

Figure 7.179. LC-MS Spectrum of compound **176**

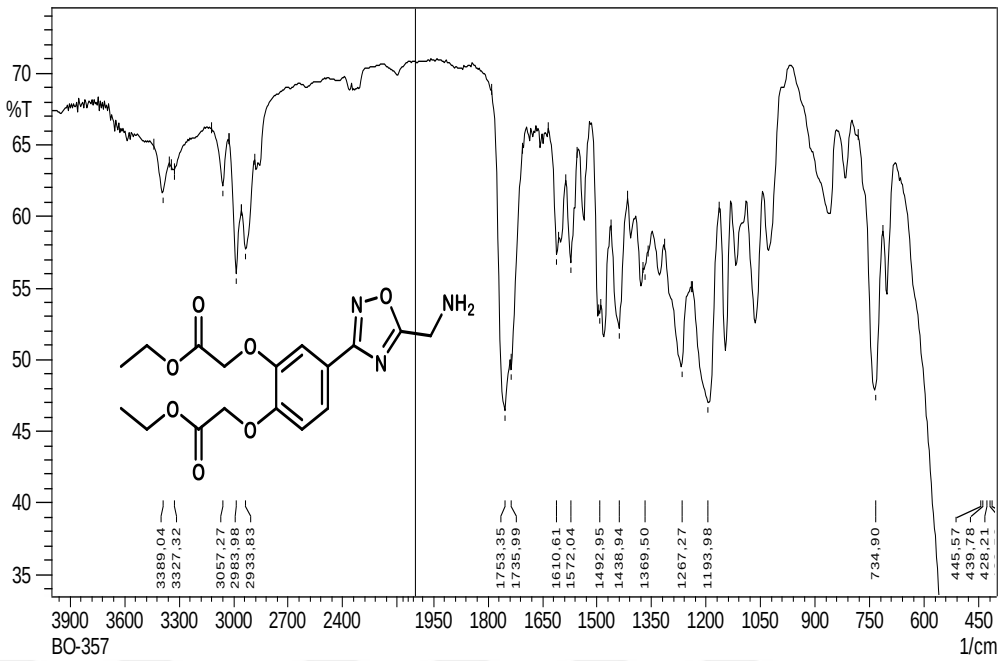

Figure 7.180. IR spectrum of compound **181**

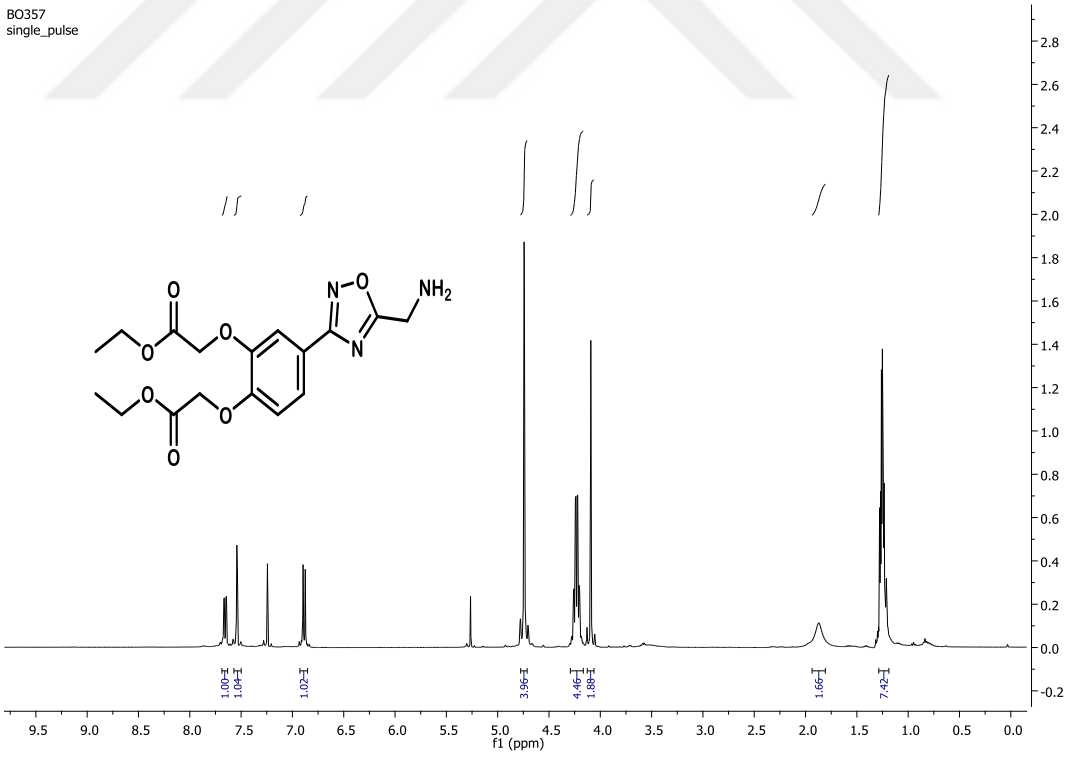

Figure 7.181. ^{1}H NMR spectrum of compound **181**

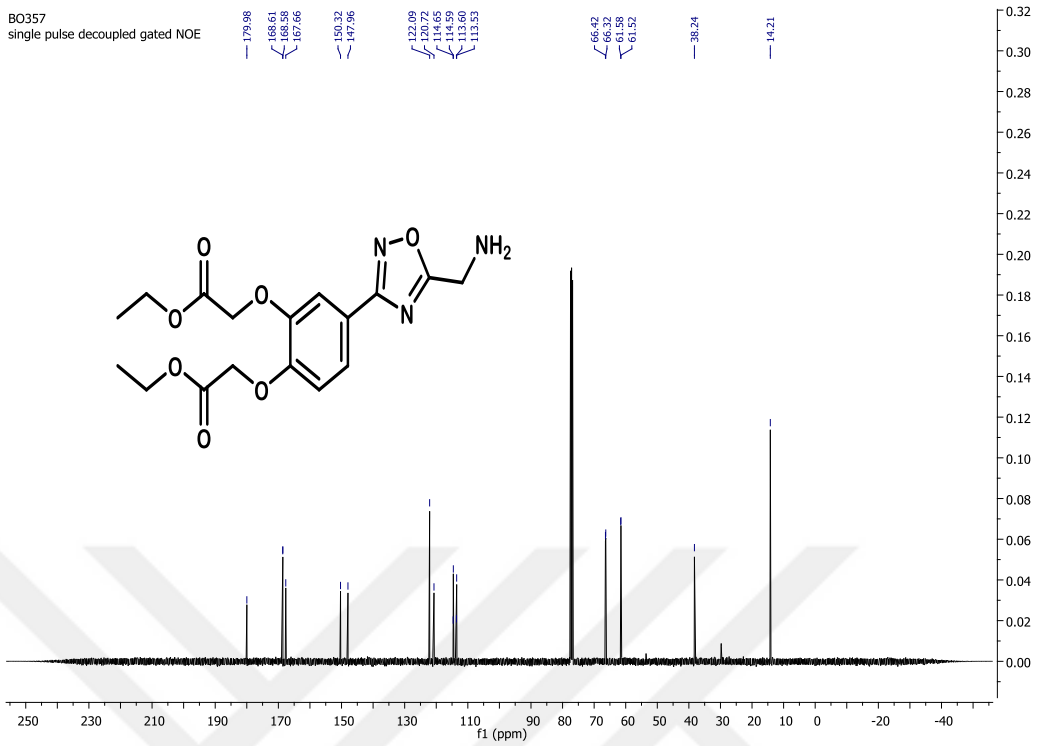

Figure 7.182. ^{13}C NMR spectrum of compound **181**

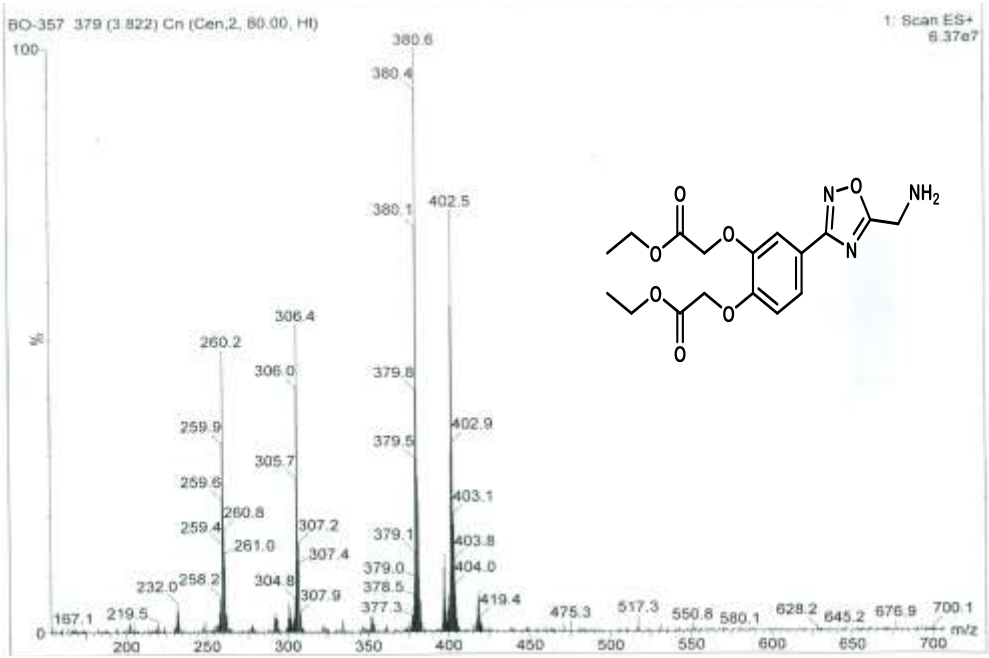

Figure 7.183. LC-MS Spectrum of compound **181**

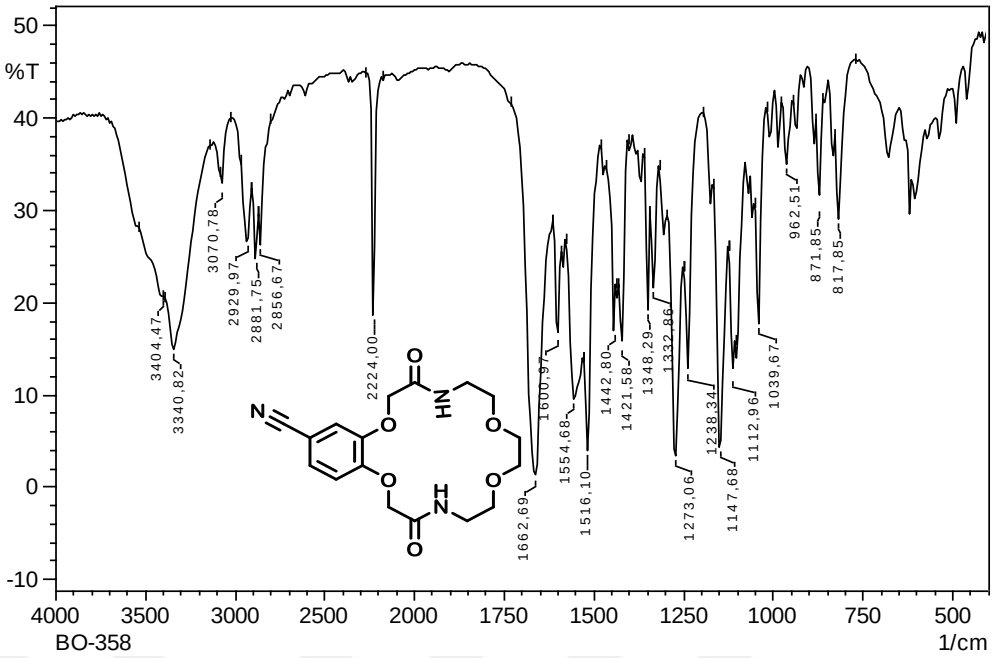

Figure 7.184. IR spectrum of compound **182**

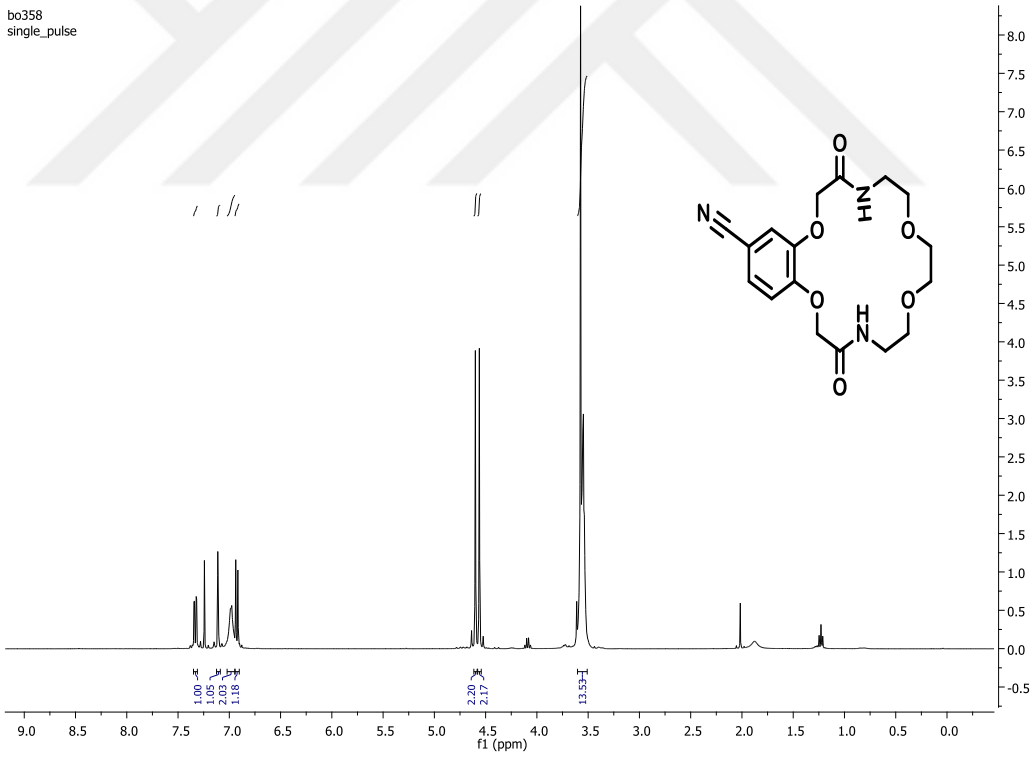

Figure 7.185. ^{1}H NMR spectrum of compound **182**

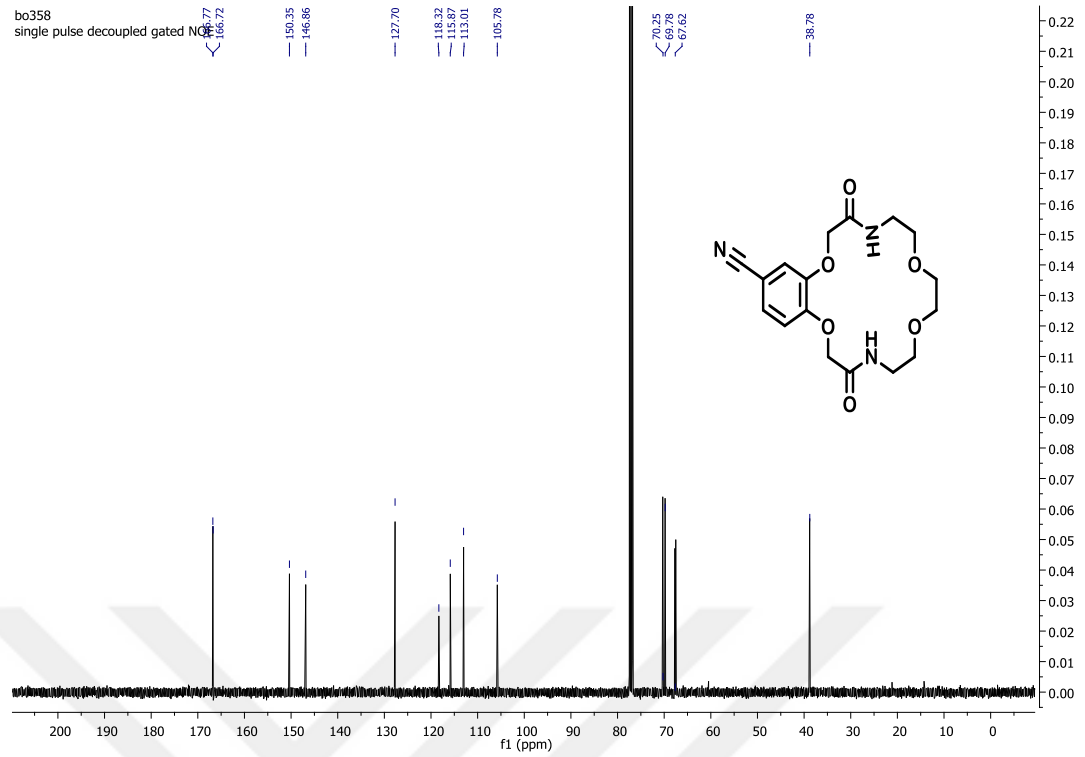

Figure 7.186. ^{13}C NMR spectrum of compound **182**

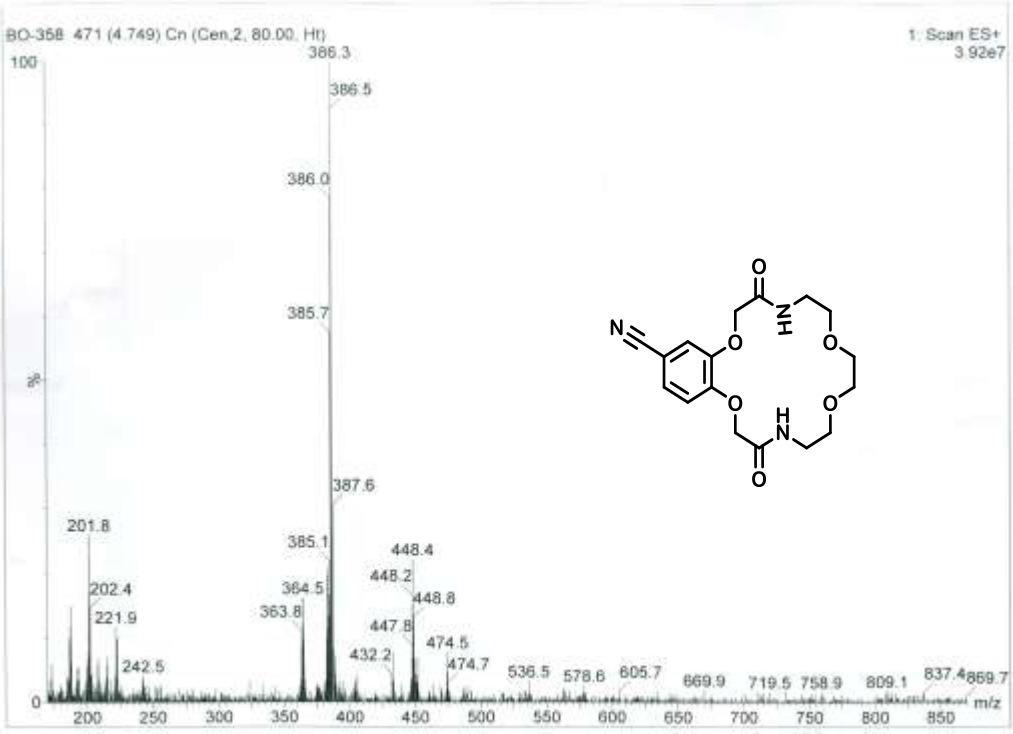

Figure 7.187. LC-MS Spectrum of compound **182**

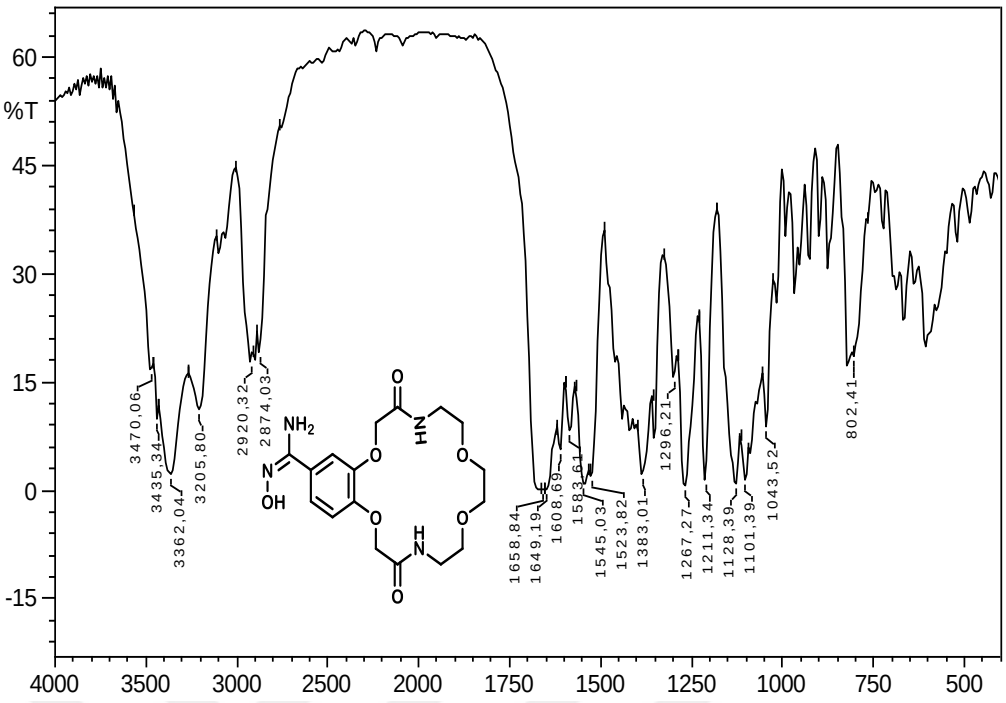

Figure 7.188. IR spectrum of compound **184**

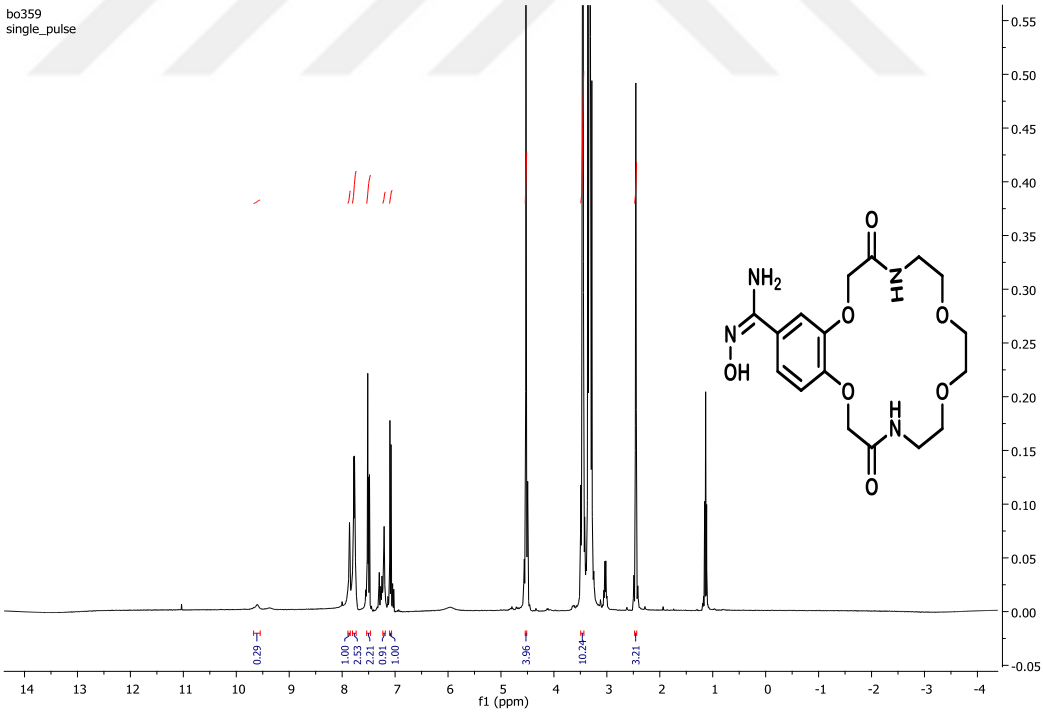

Figure 7.189. ^{1}H NMR spectrum of compound **184**

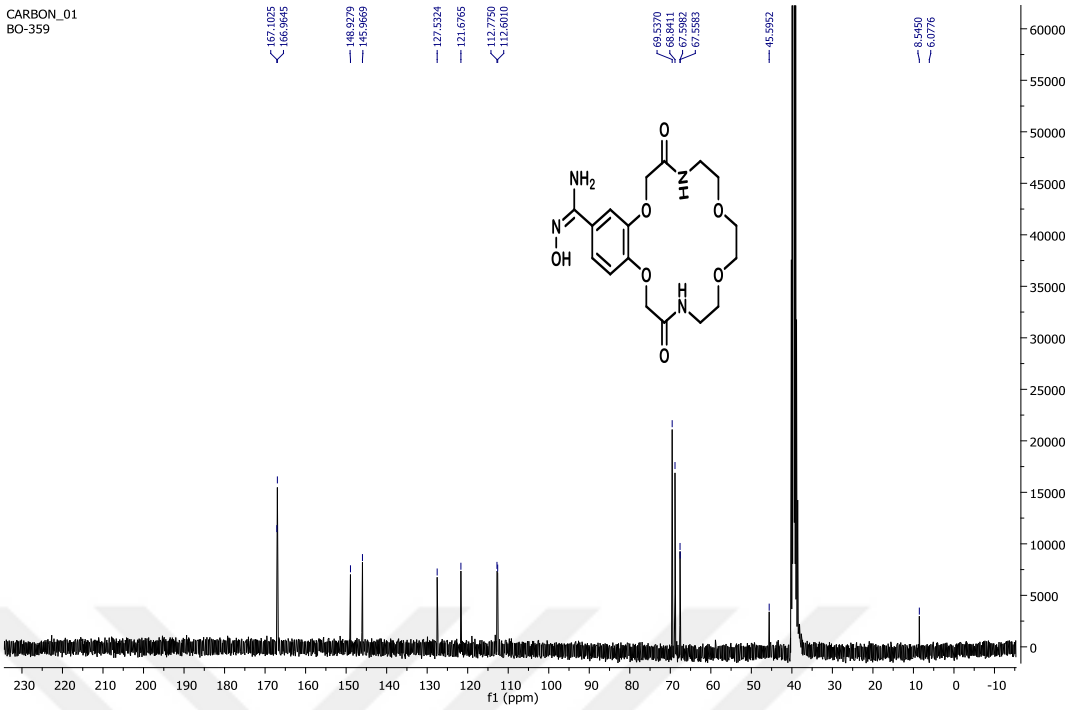

Figure 7.190. ^{13}C NMR spectrum of compound **184**

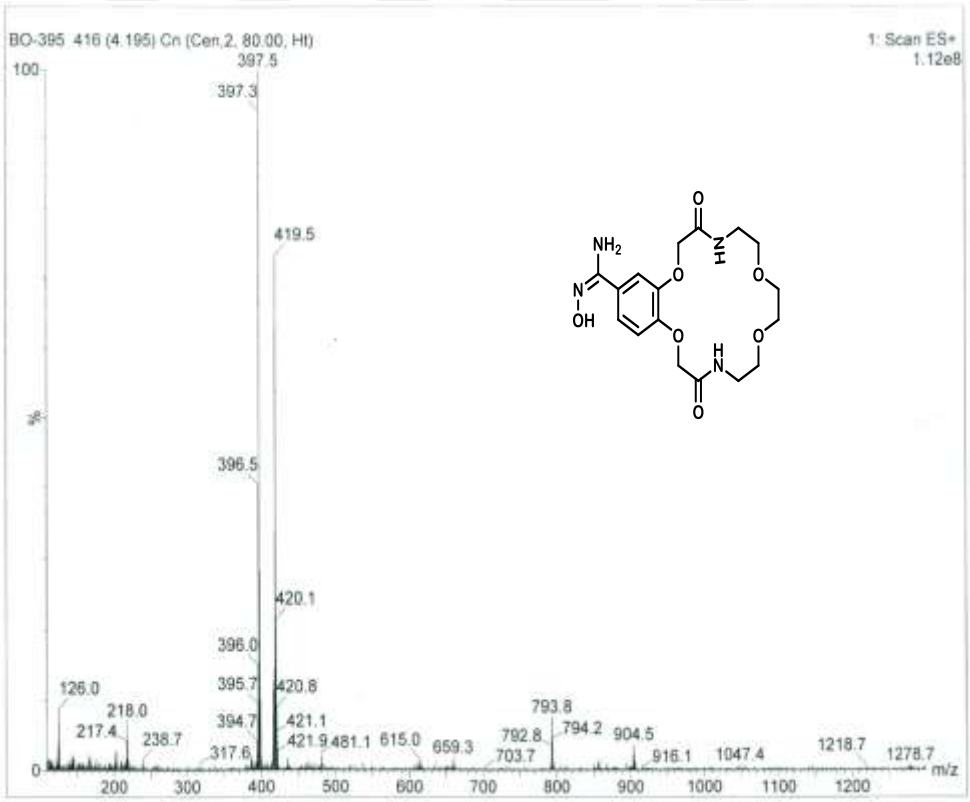

Figure 7.191. LC-MS Spectrum of compound **184**

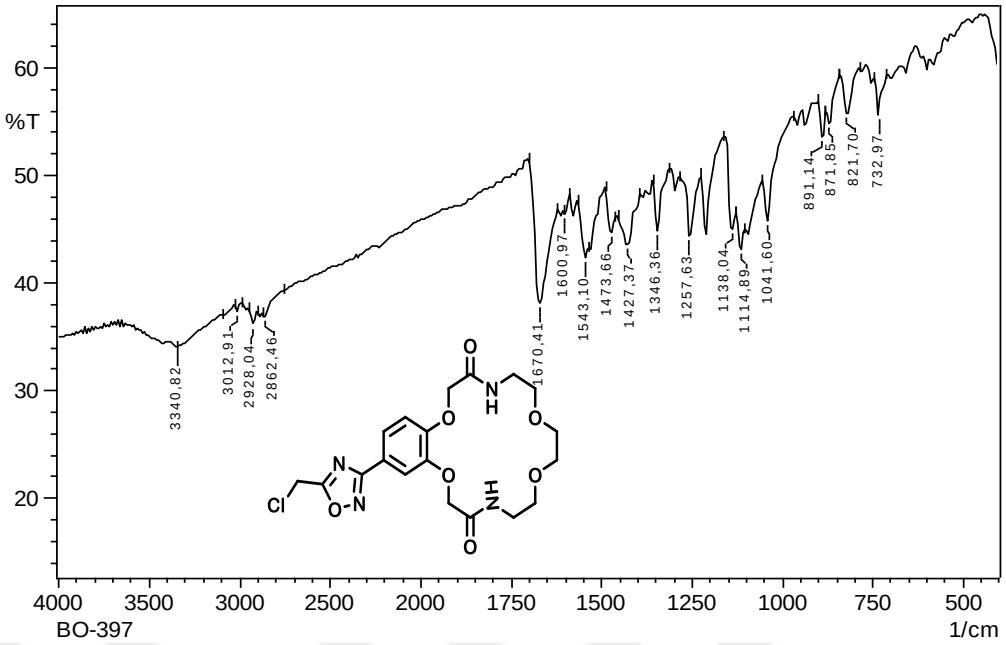

Figure 7.192. IR spectrum of compound **185**

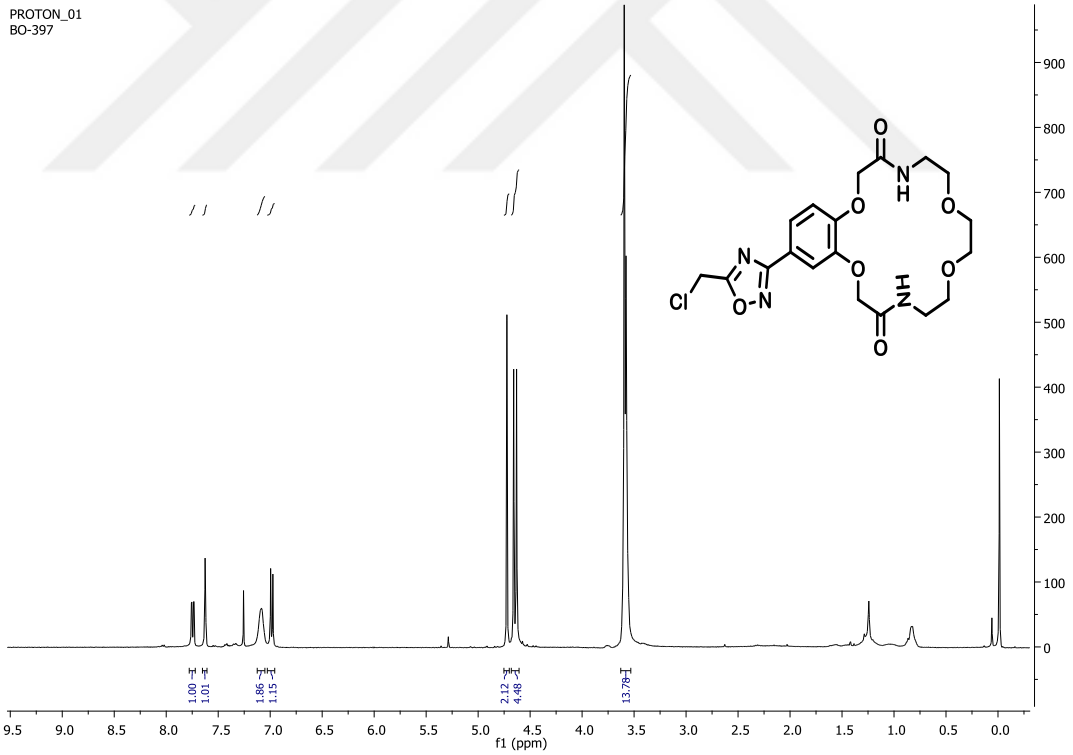

Figure 7.193. ^{1}H NMR spectrum of compound **185**

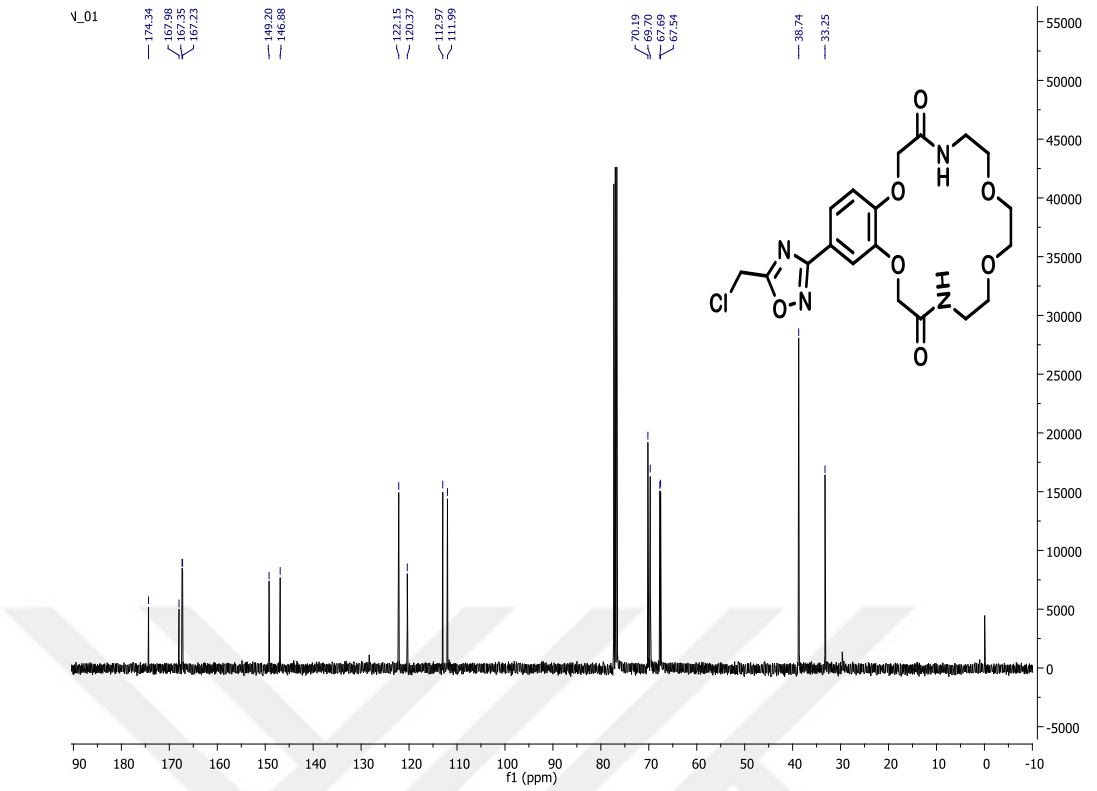

Figure 7.194. ^{13}C NMR spectrum of compound **185**

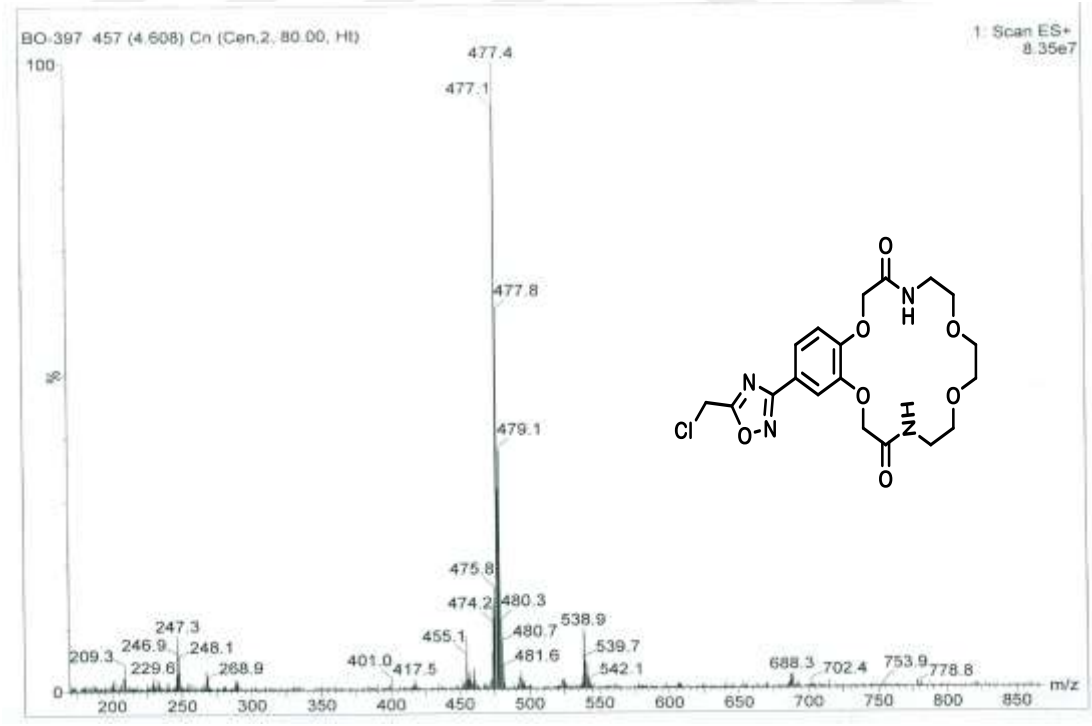

Figure 7.195. LC-MS Spectrum of compound **185**

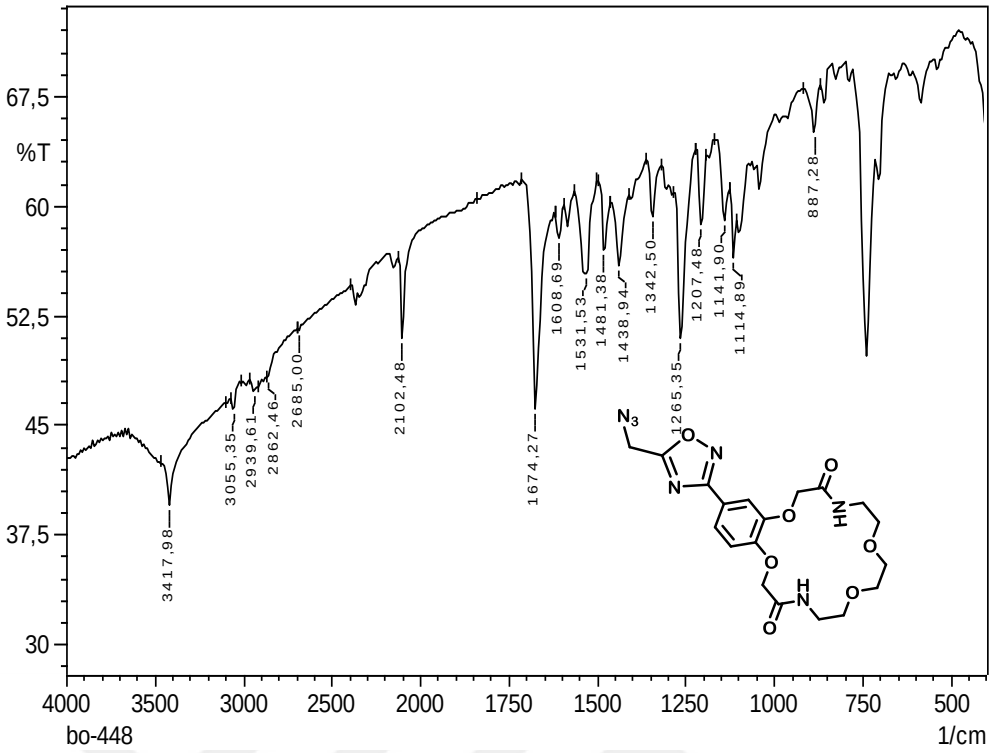

Figure 7.196. IR spectrum of compound **186**

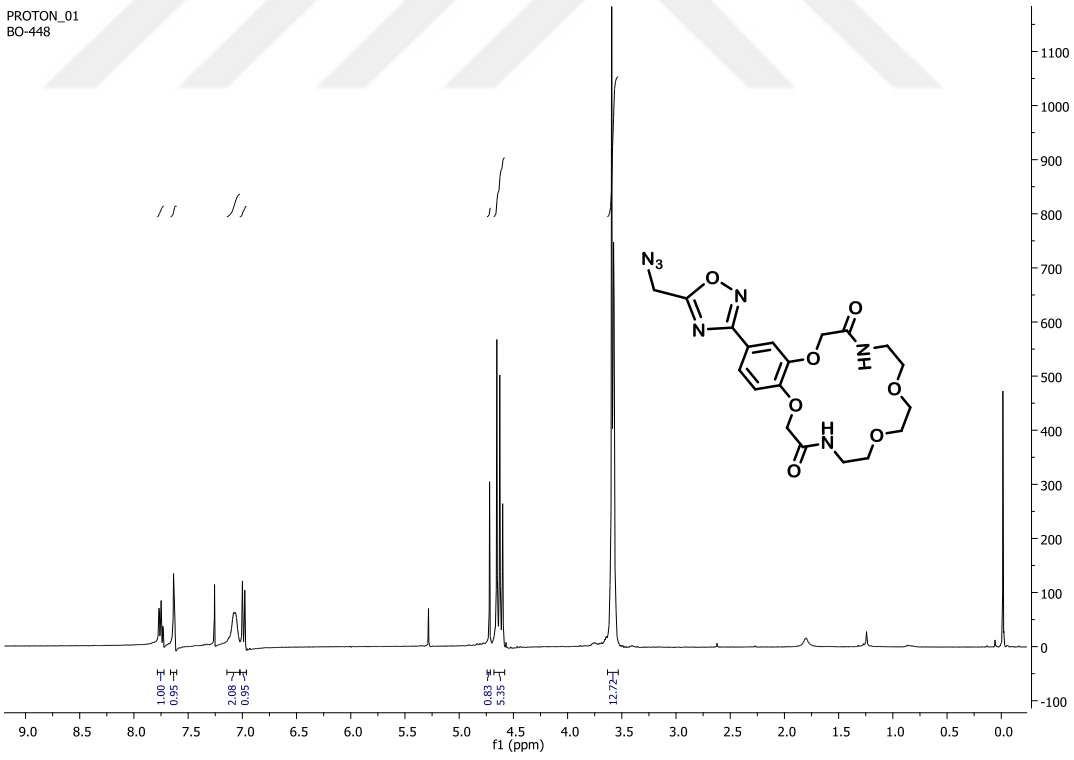

Figure 7.197. ^{1}H NMR spectrum of compound **186**

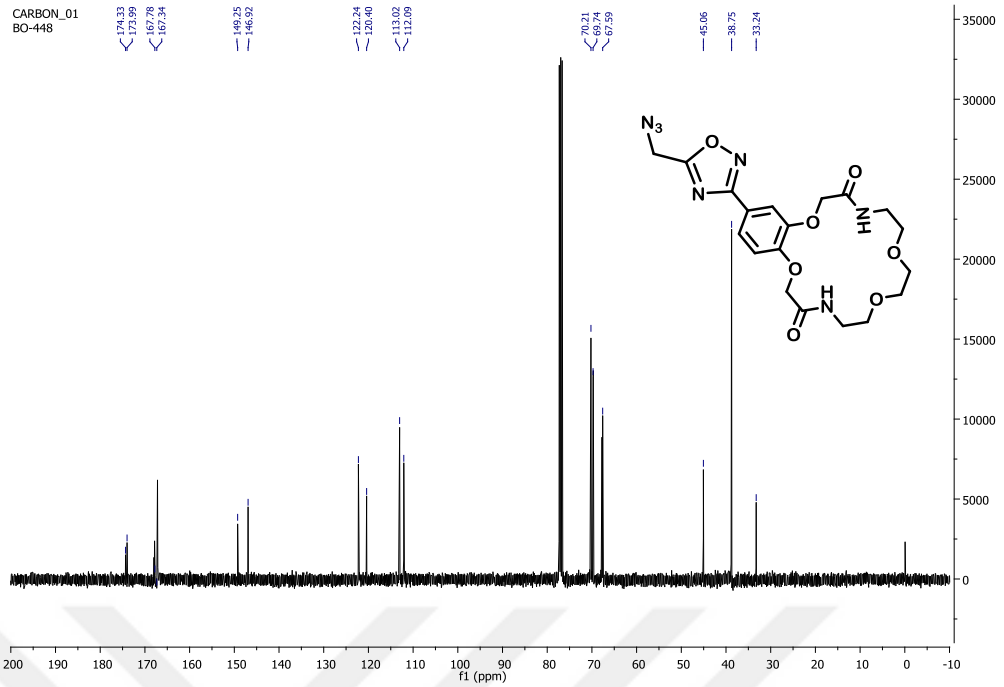

Figure 7.198. ^{13}C NMR spectrum of compound **186**

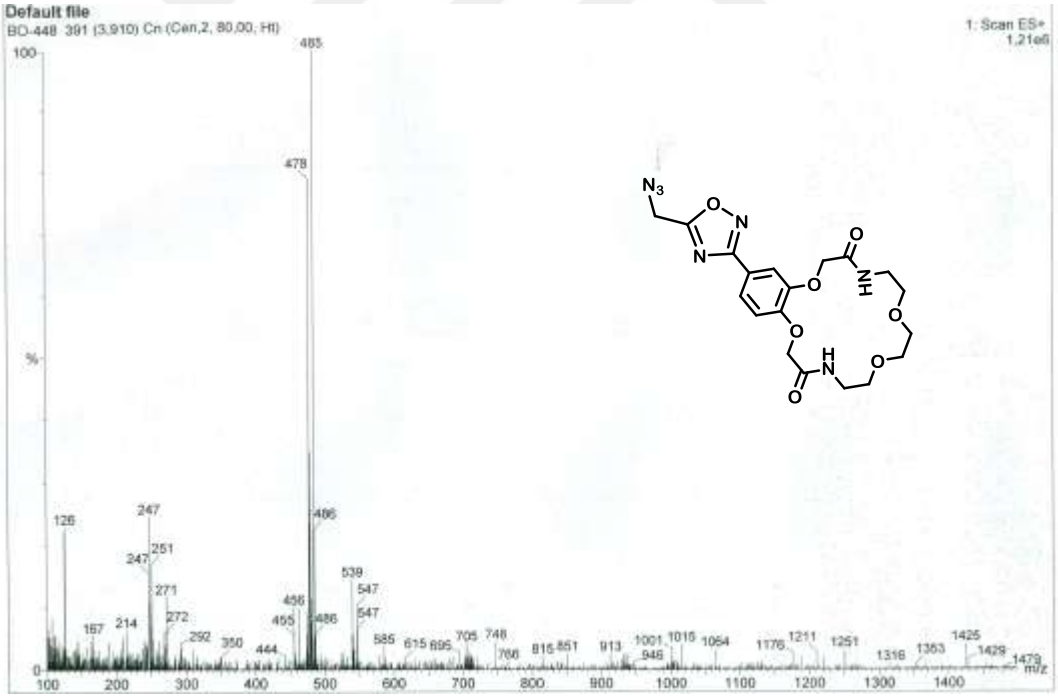

Figure 7.199. LC-MS Spectrum of compound **186**

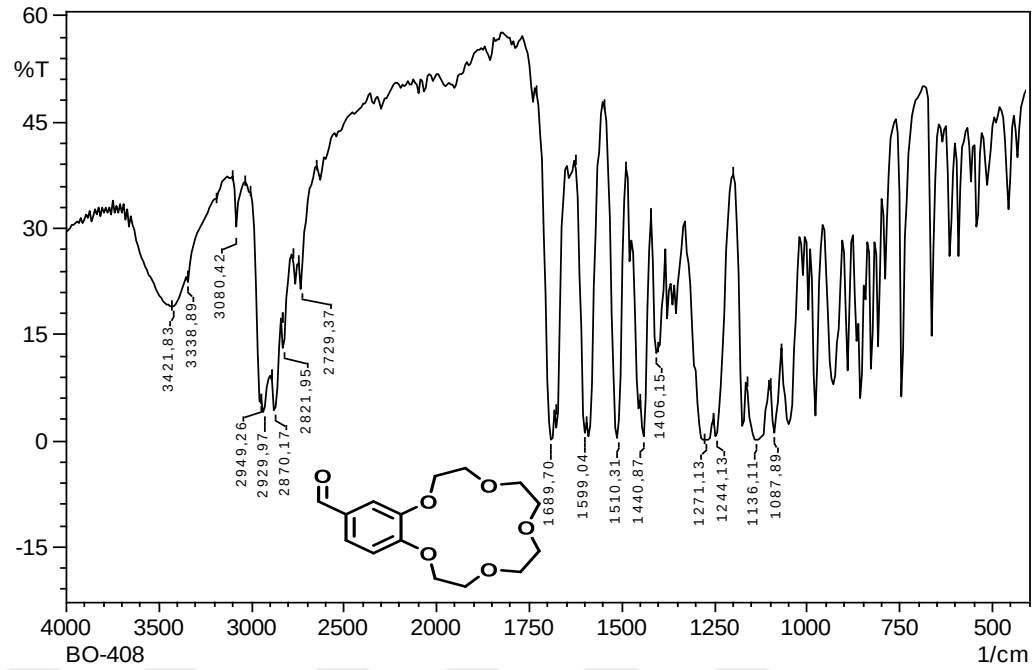

Figure 7.200. IR spectrum of compound **29**

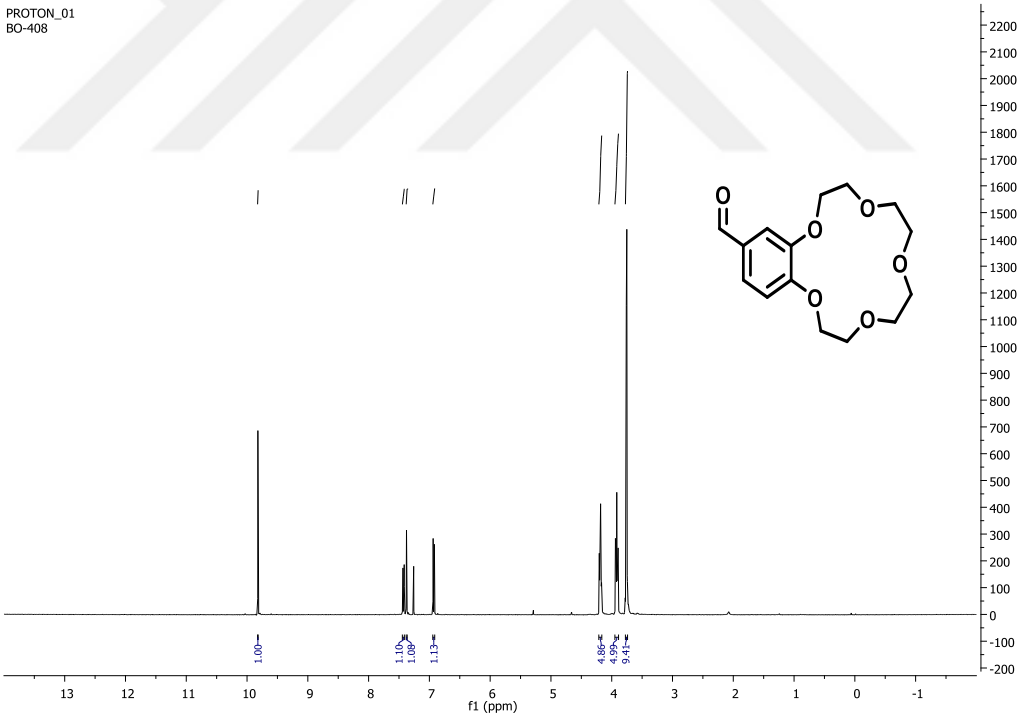

Figure 7.201. ^{1}H NMR spectrum of compound **29**

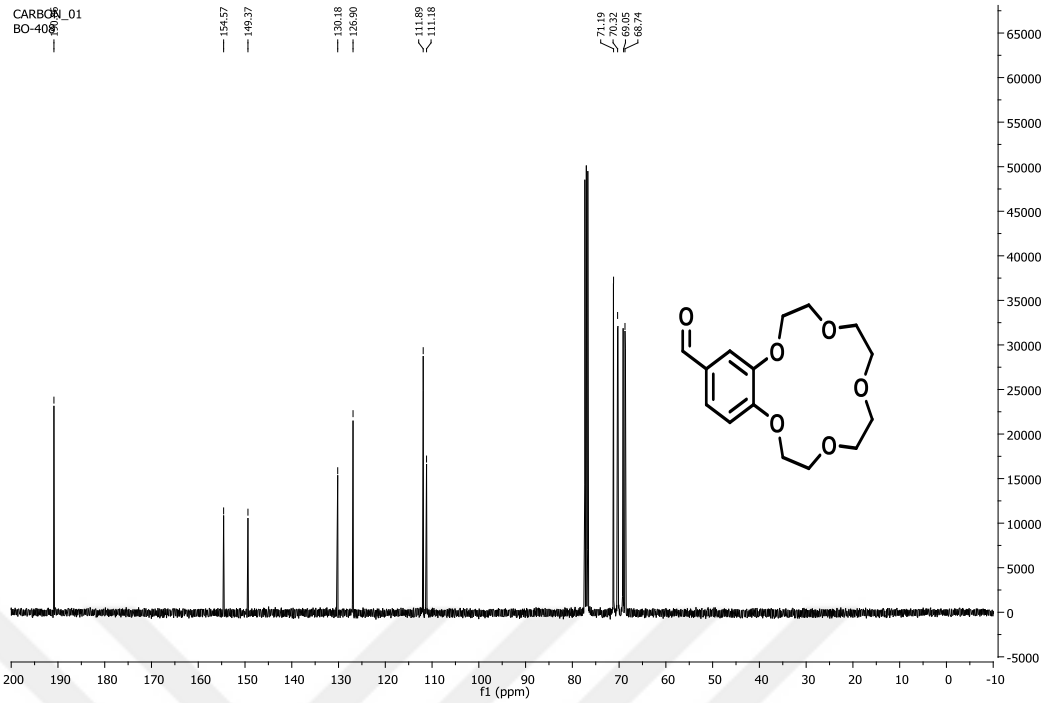

Figure 7.202. ^{13}C NMR spectrum of compound **29**

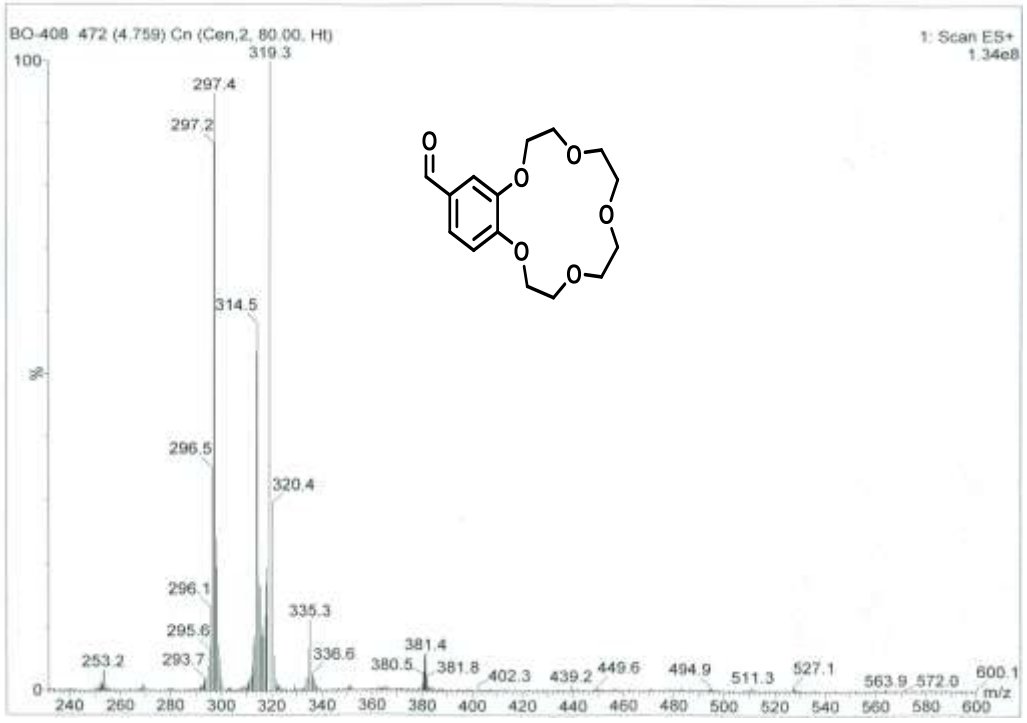

Figure 7.203. LC-MS Spectrum of compound **29**

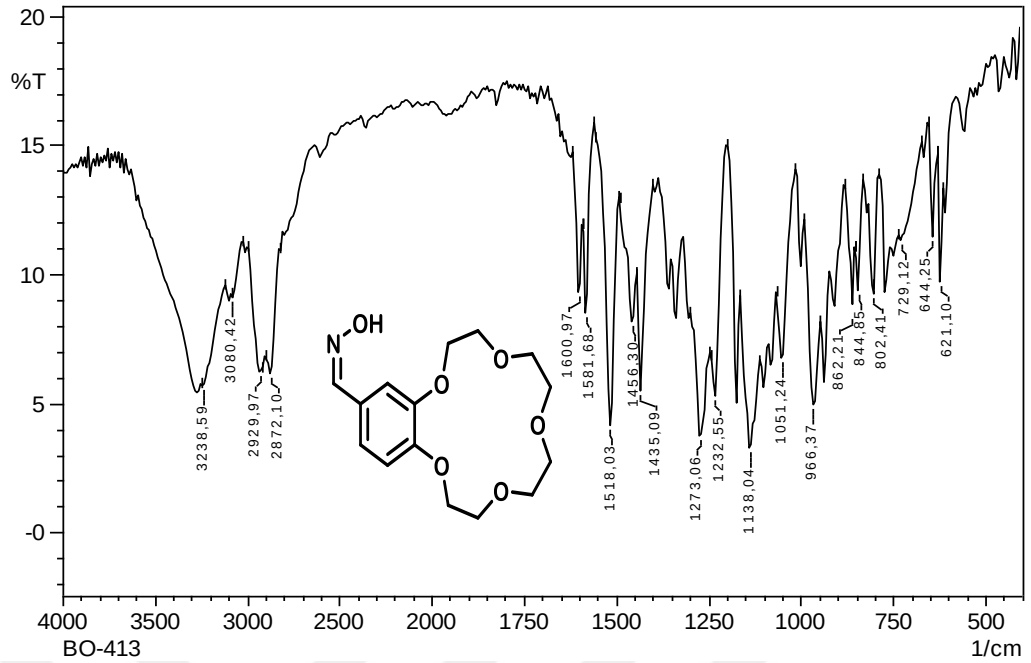

Figure 7.204. IR spectrum of compound **187**

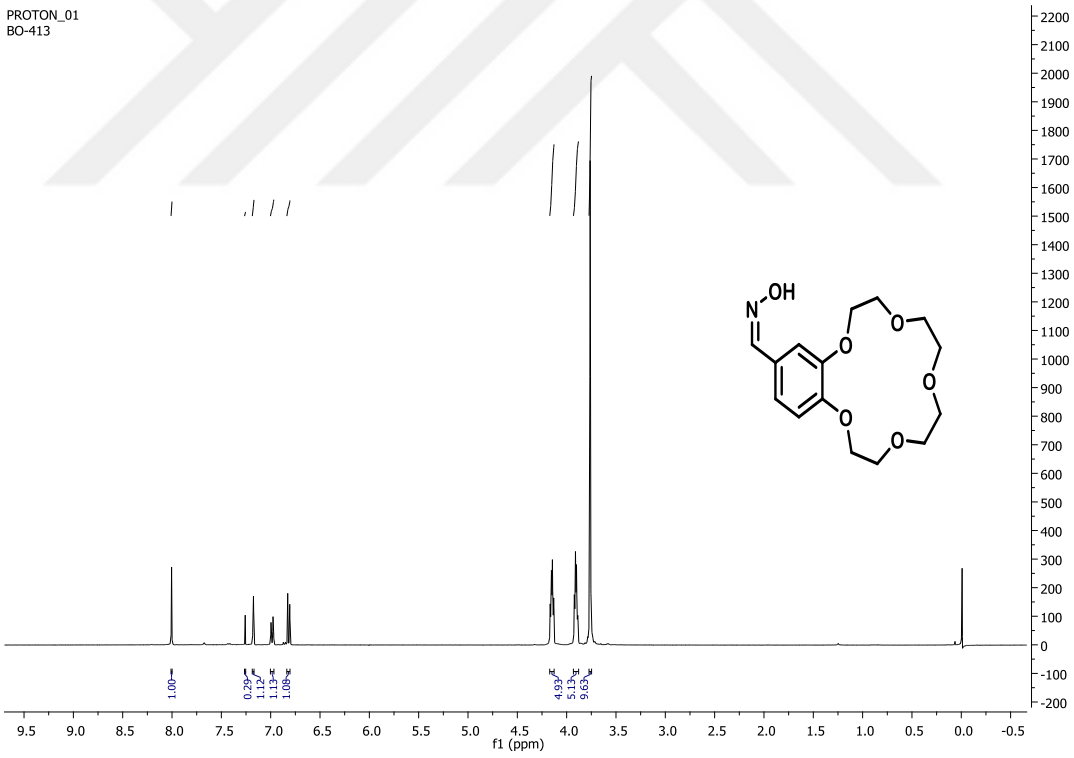

Figure 7.205. ^{1}H NMR spectrum of compound **187**

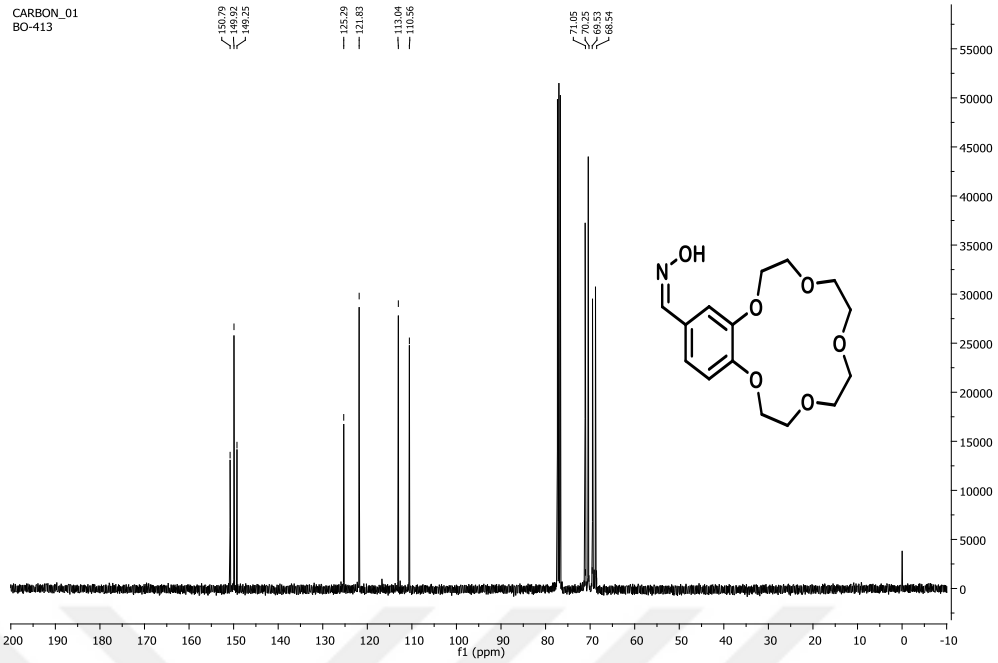

Figure 7.206. ^{13}C NMR spectrum of compound **187**

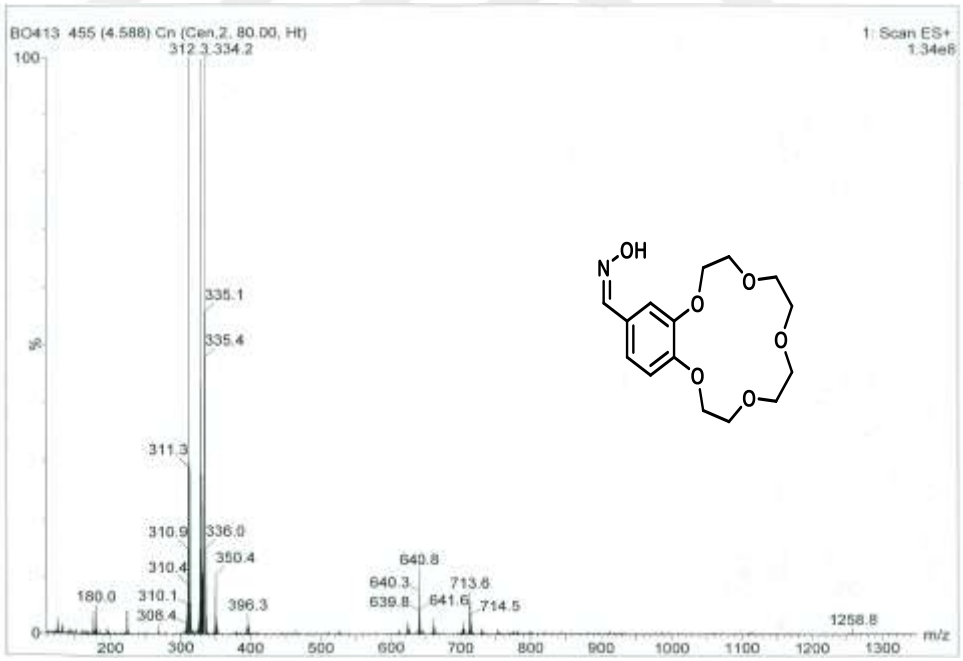

Figure 7.207. LC-MS Spectrum of compound **187**

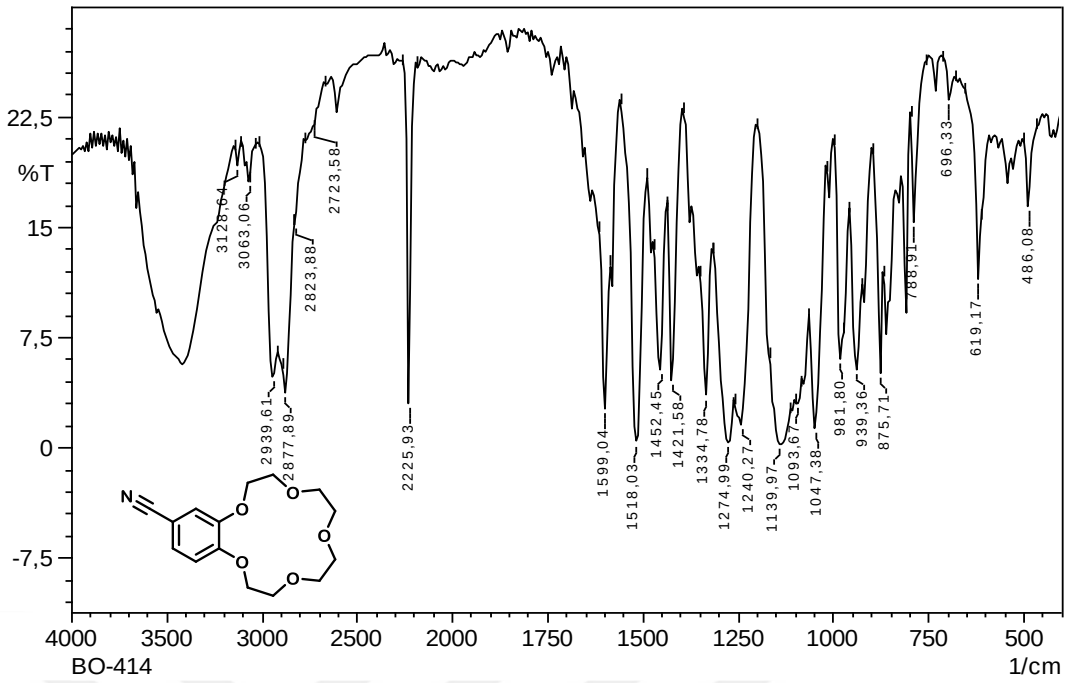

Figure 7.208. IR spectrum of compound **188**

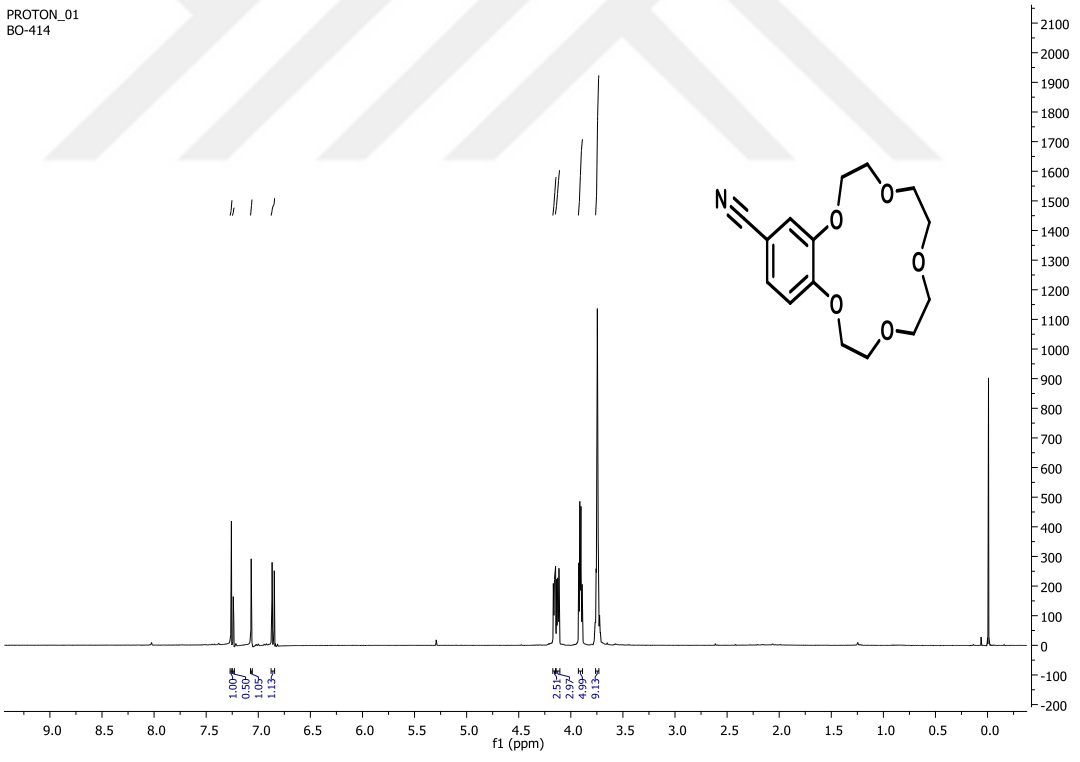

Figure 7.209. ^{1}H NMR spectrum of compound **188**

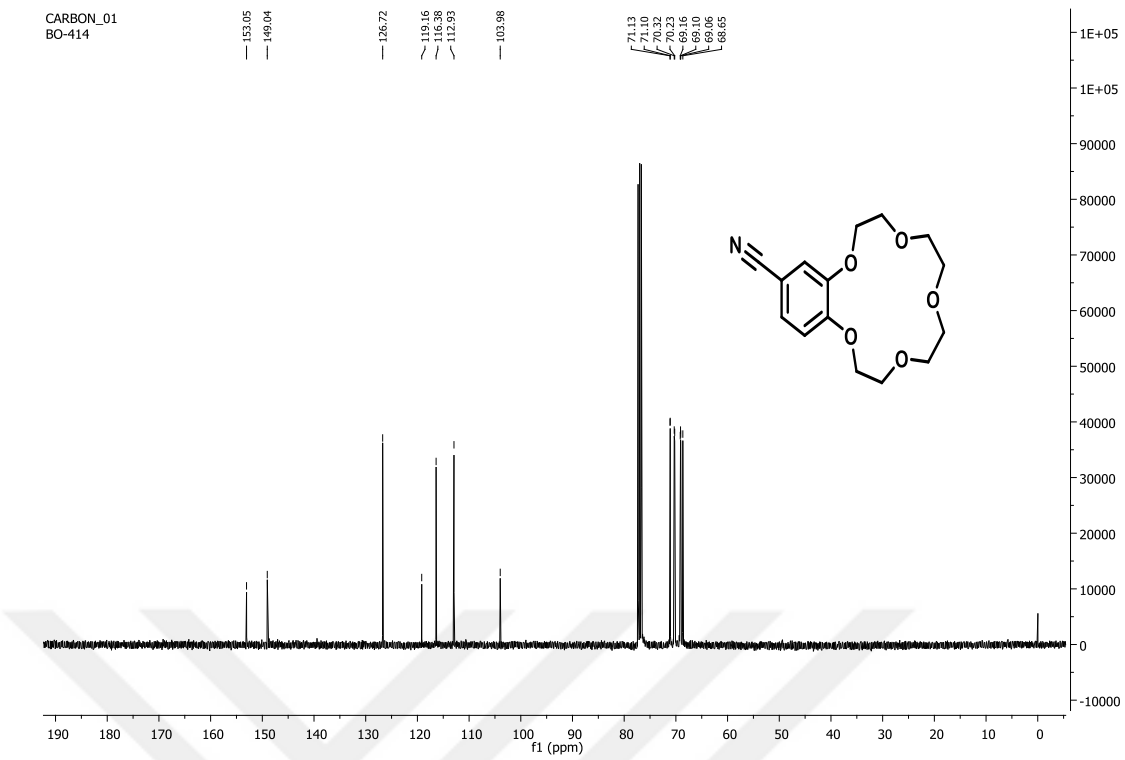

Figure 7.210. ^{13}C NMR spectrum of compound **188**

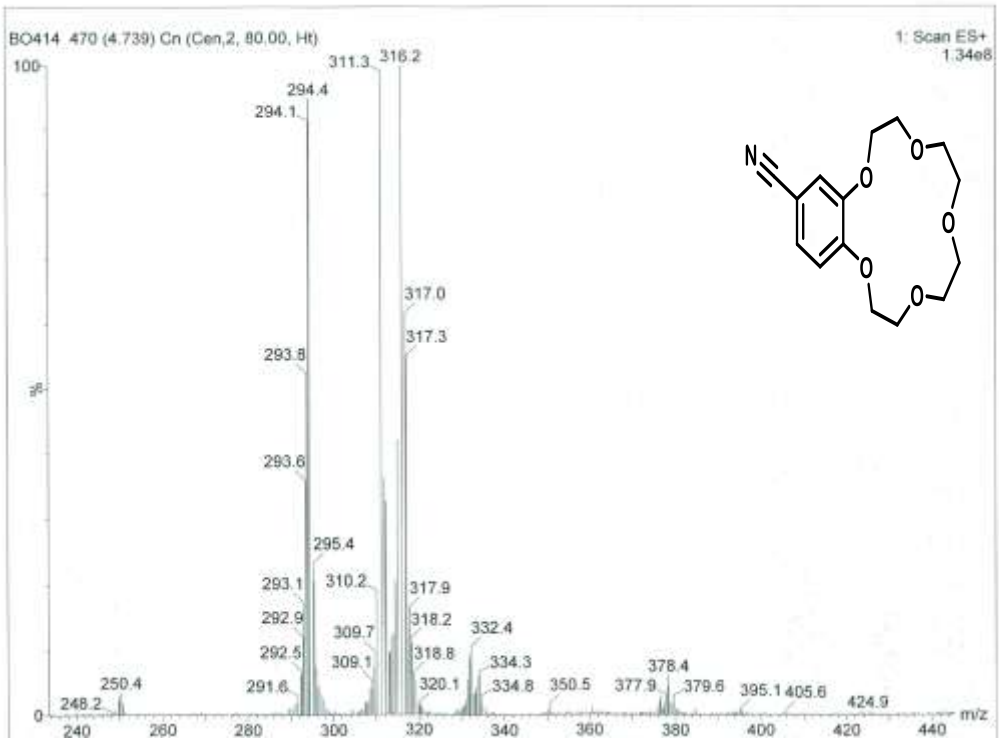

Figure 7.211. LC-MS Spectrum of compound **188**

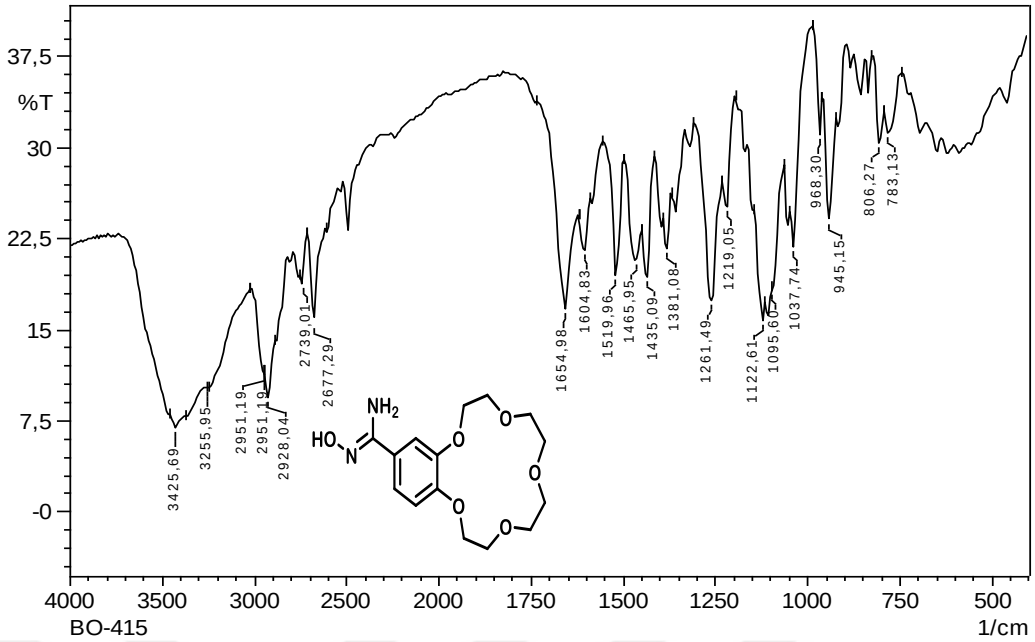

Figure 7.212. IR spectrum of compound **189**

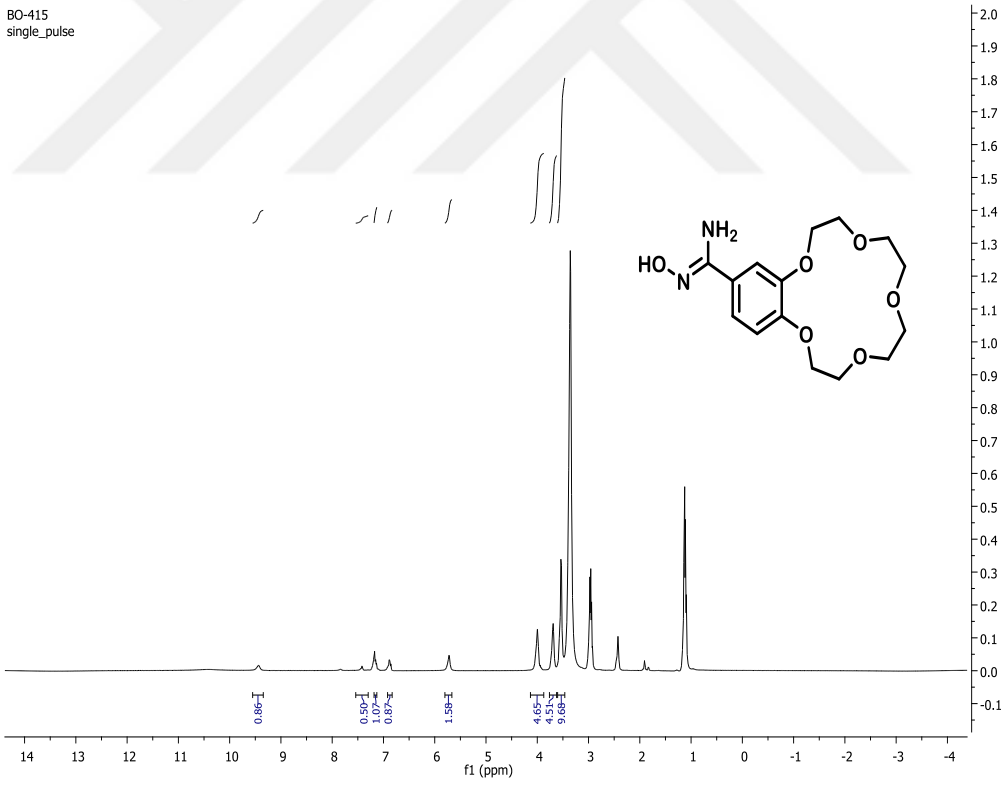

Figure 7.213. ^{1}H NMR spectrum of compound **189**

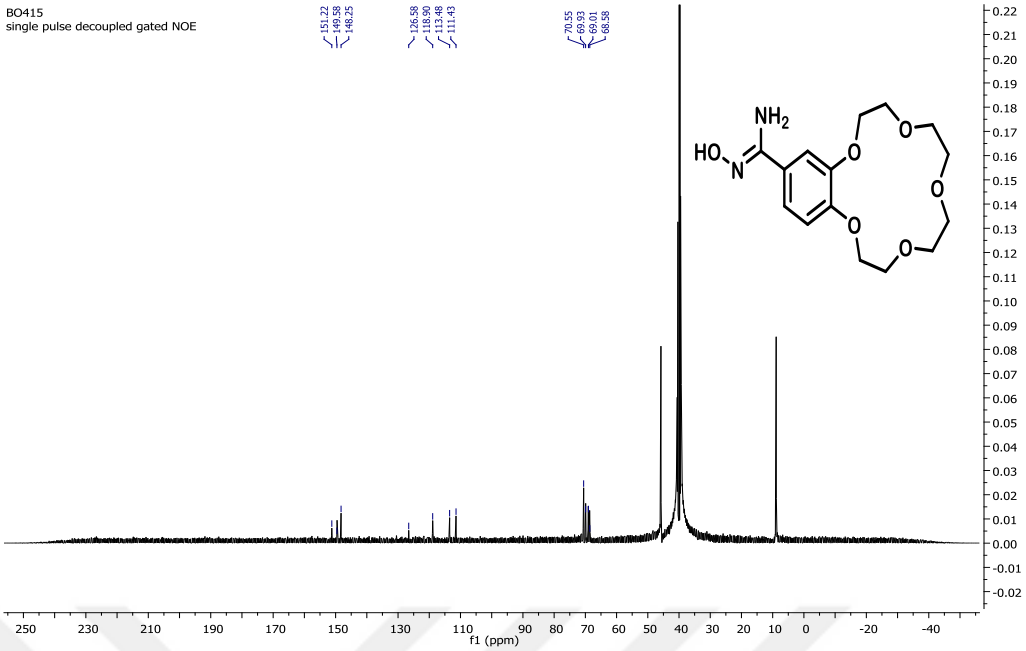

Figure 7.214. ^{13}CNMR spectrum of compound **189**

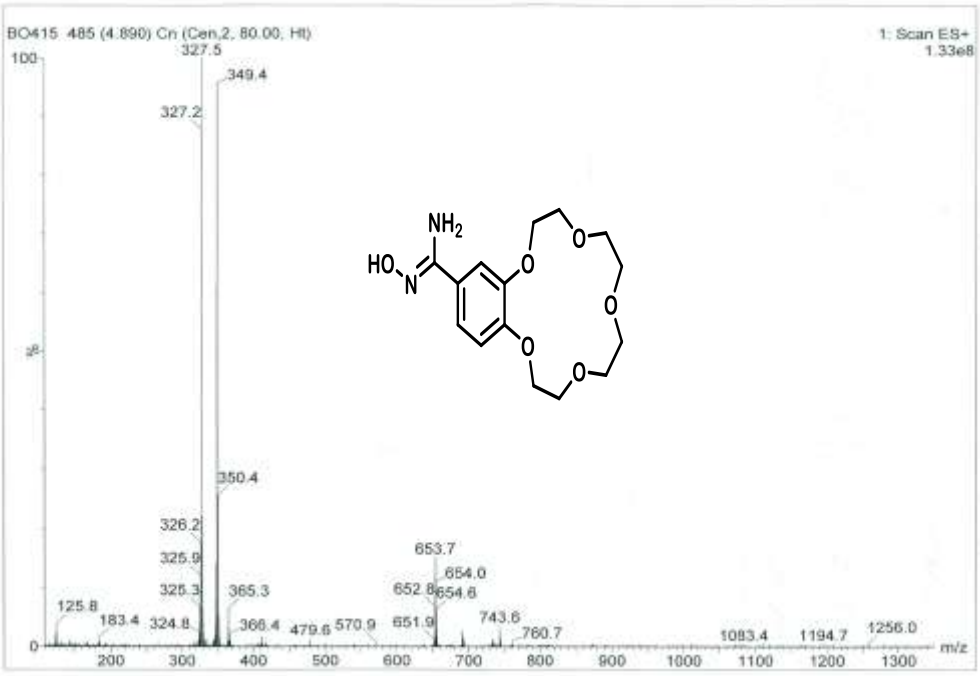

Figure 7.215. LC-MS Spectrum of compound **189**

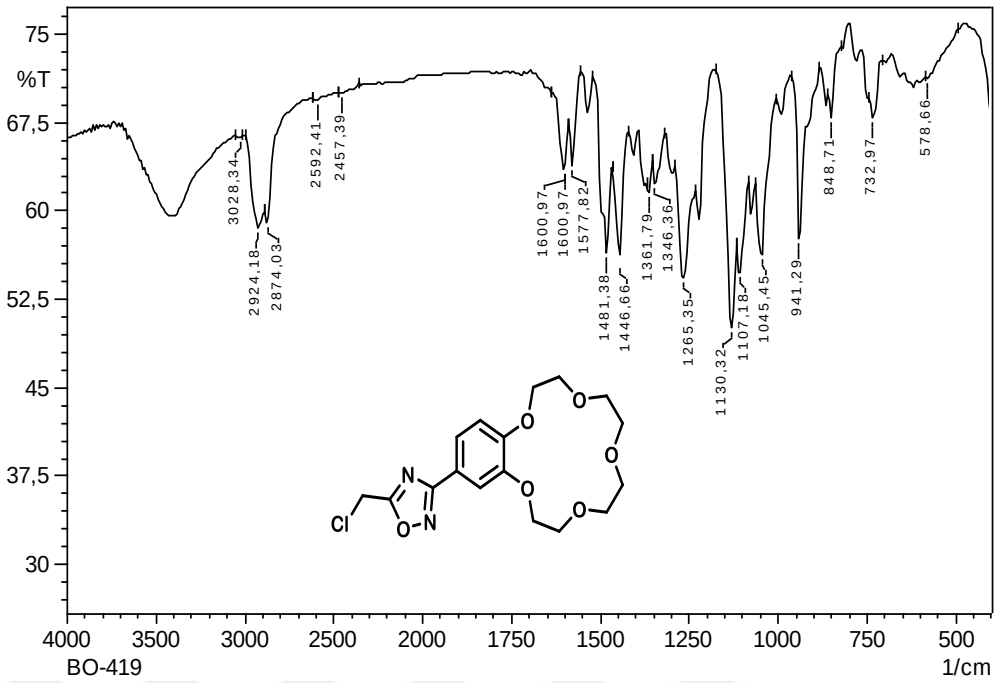

Figure 7.216. IR spectrum of compound **190**

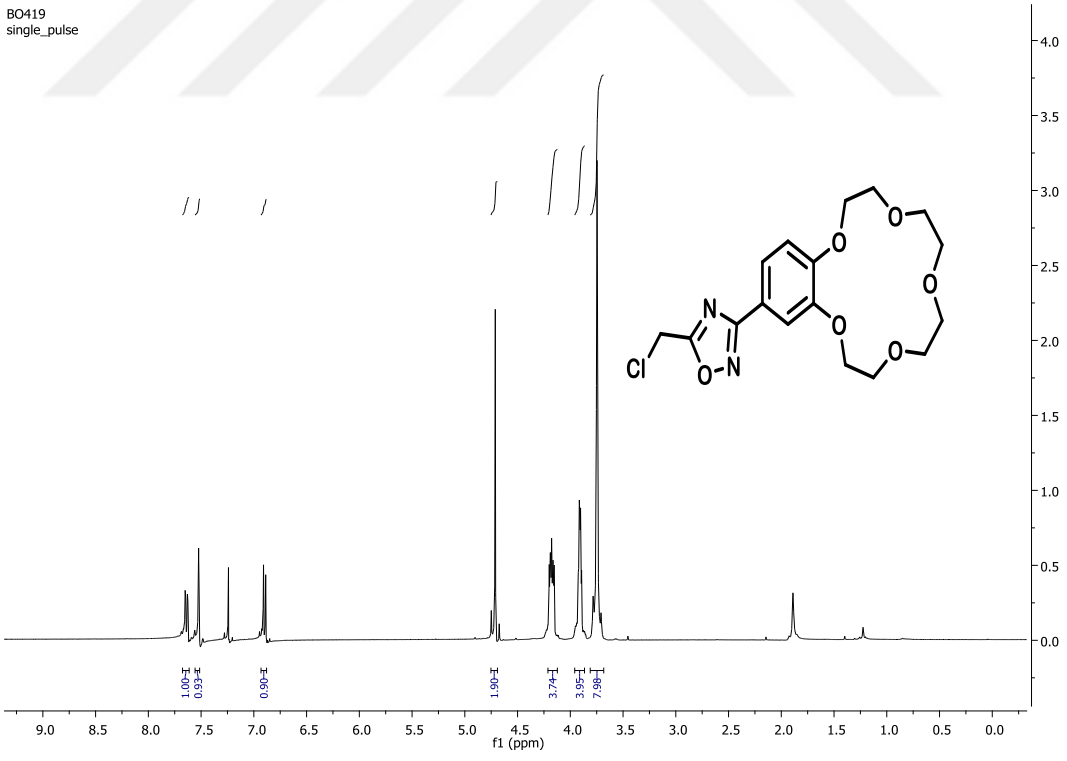

Figure 7.217. ^{1}H NMR spectrum of compound **190**

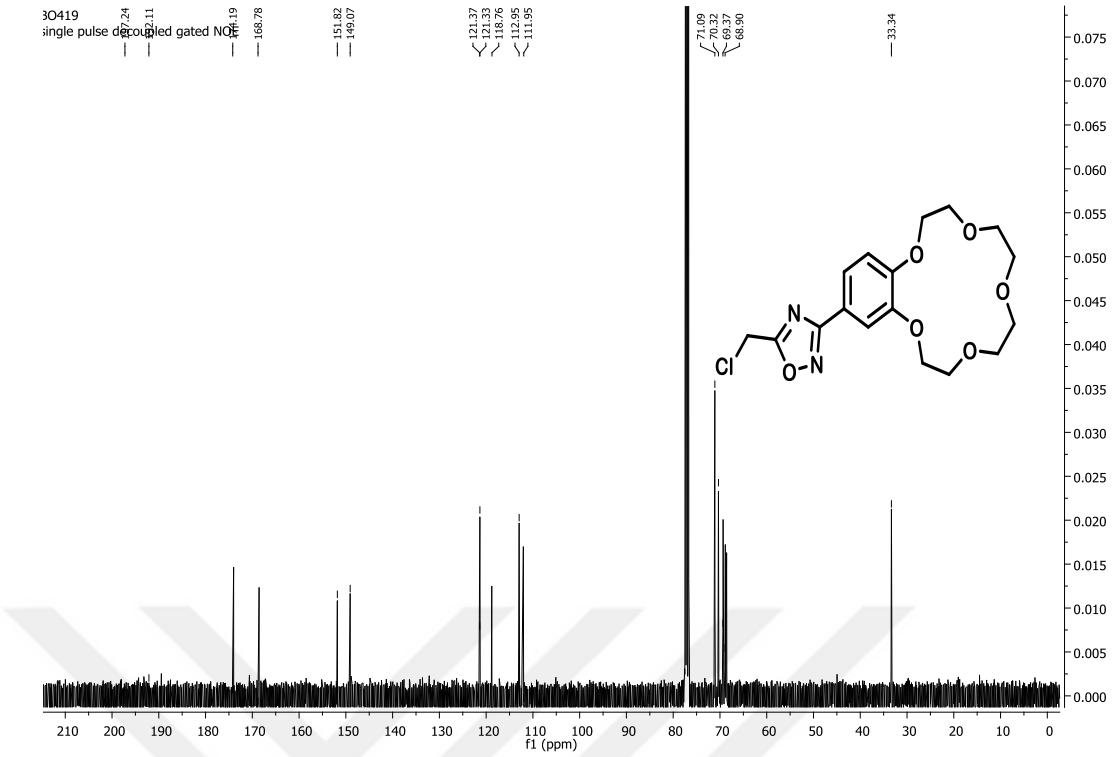

Figure 7.218. ^{13}C NMR spectrum of compound **190**

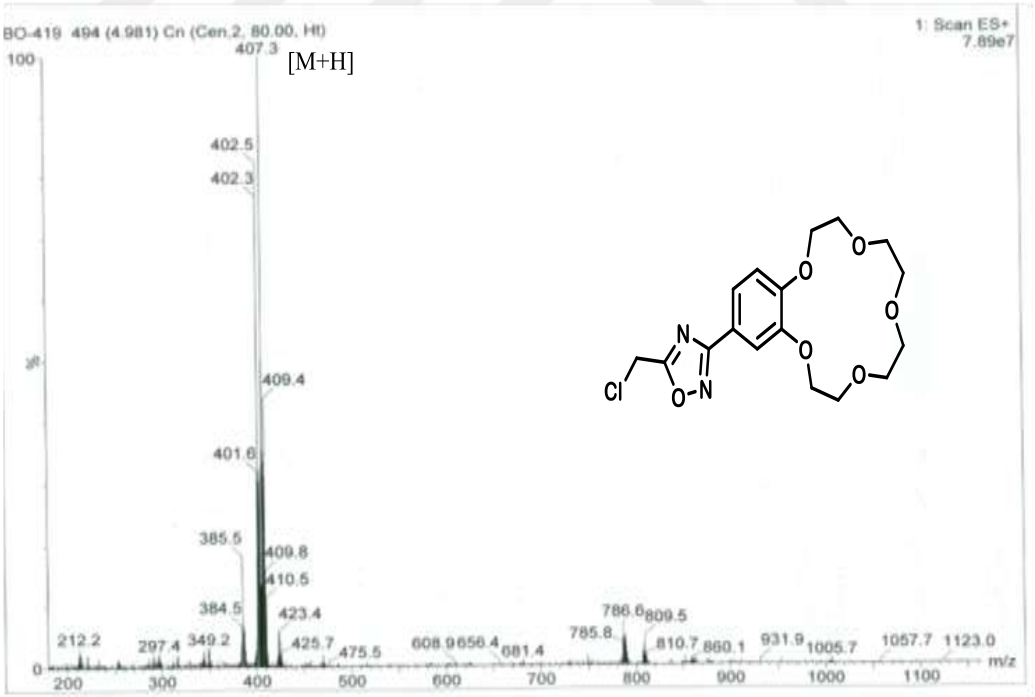

Figure 7.219. LC-MS Spectrum of compound **190**

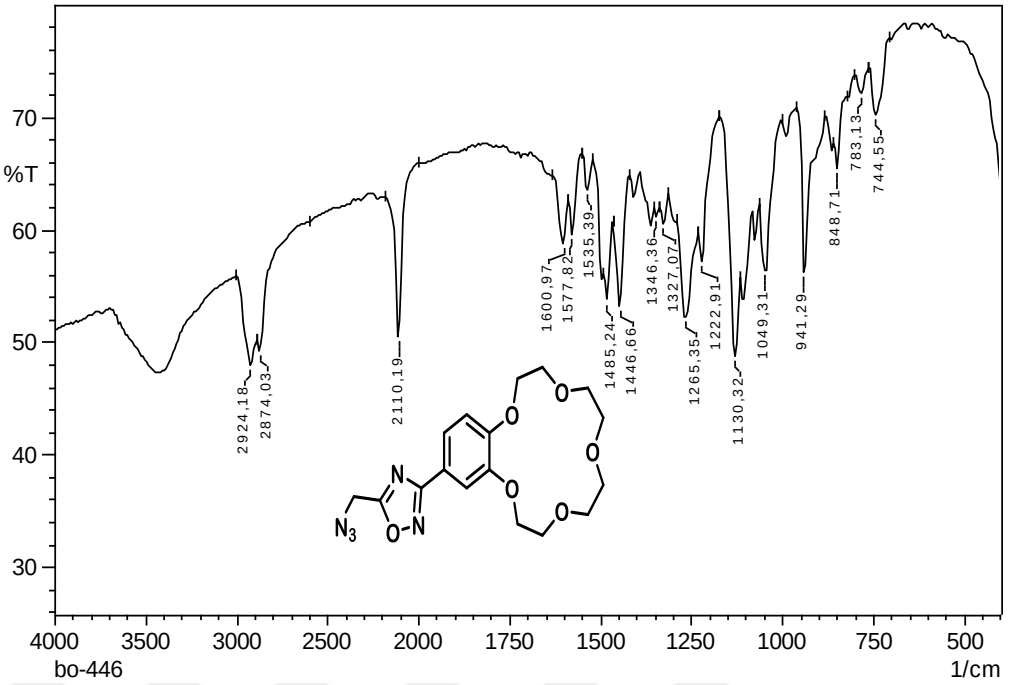

Figure 7.220. IR spectrum of compound **191**

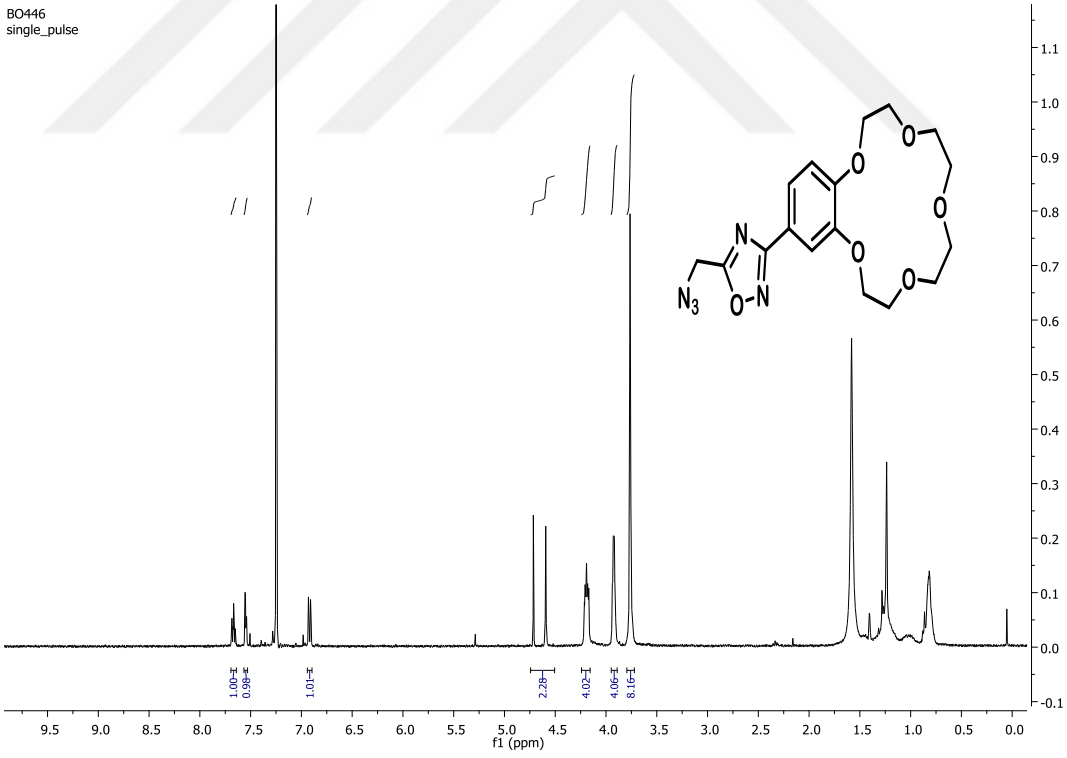

Figure 7.221. ^{1}H NMR spectrum of compound **191**

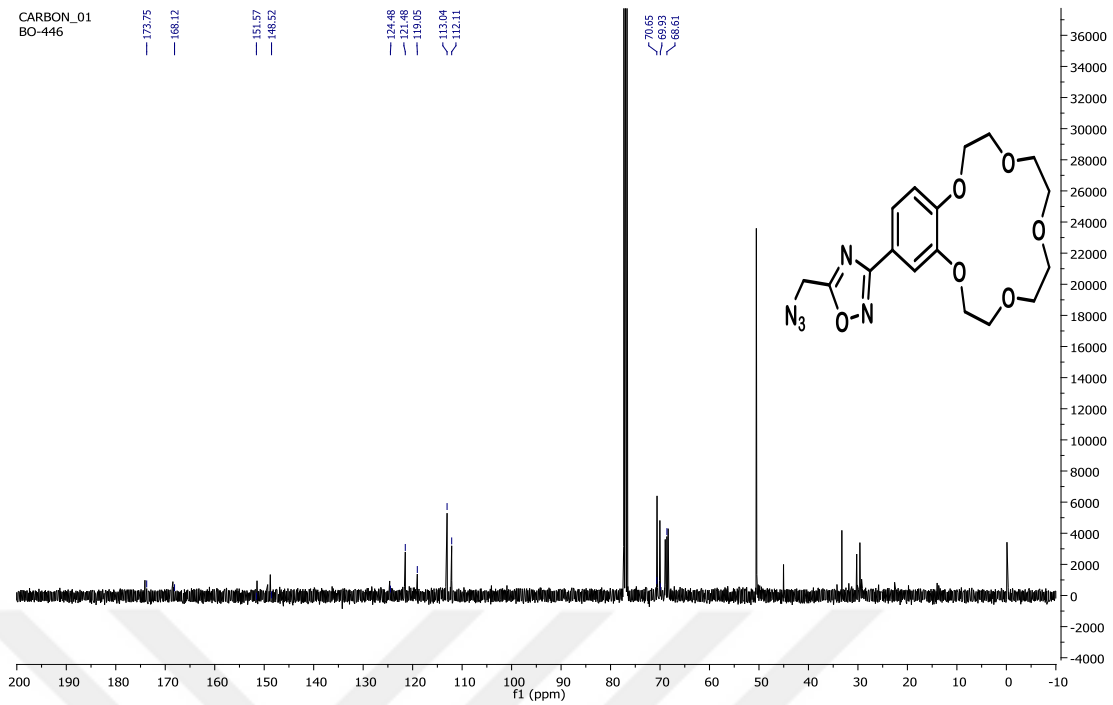

Figure 7.222. ^{13}C NMR spectrum of compound **191**

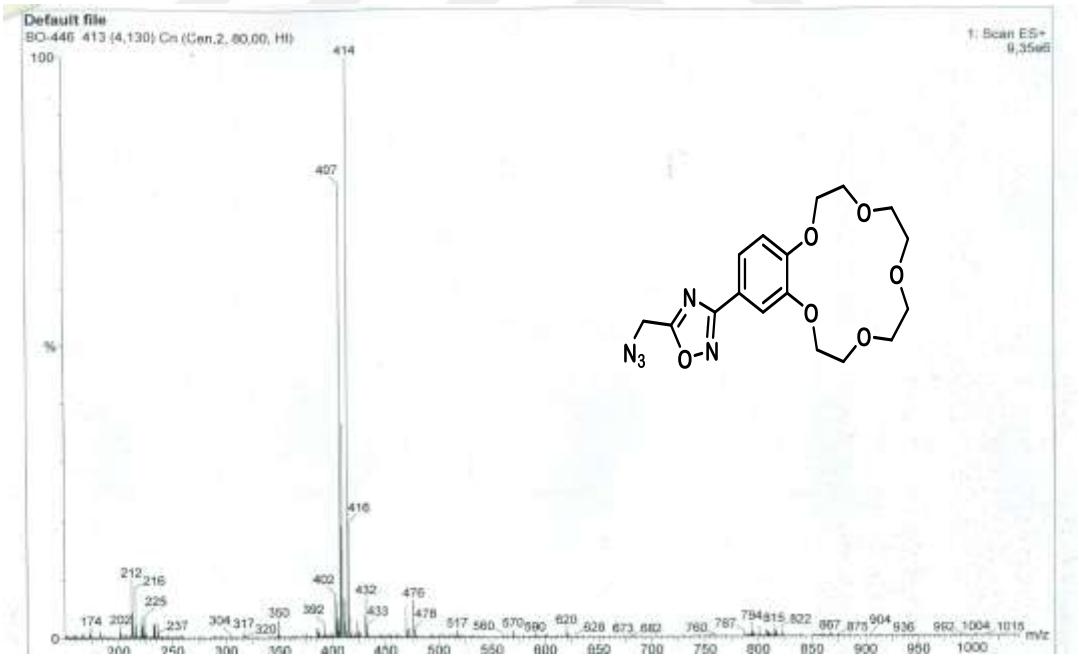

Figure 7.223. LC-MS Spectrum of compound **191**

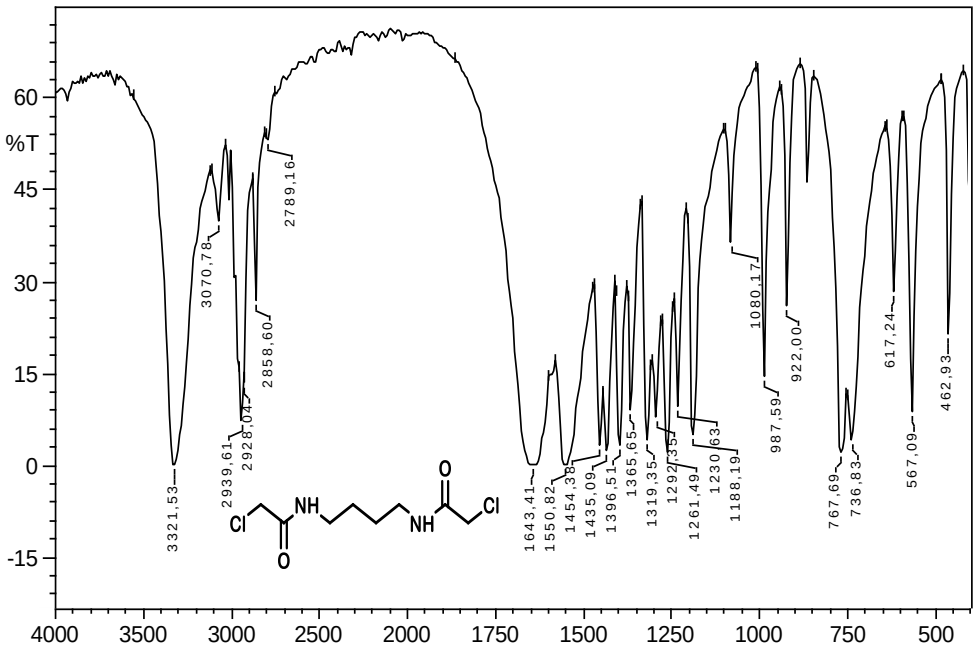

Figure 7.224. IR spectrum of compound **192**

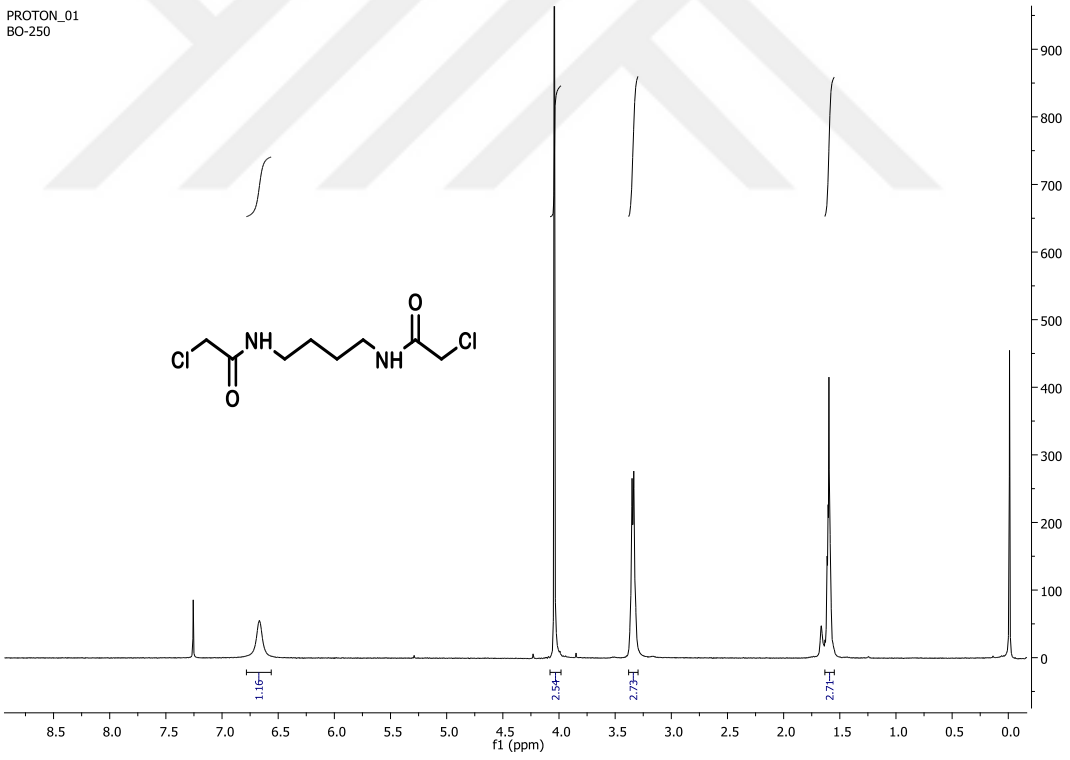

Figure 7.225. ^{1}H NMR spectrum of compound **192**

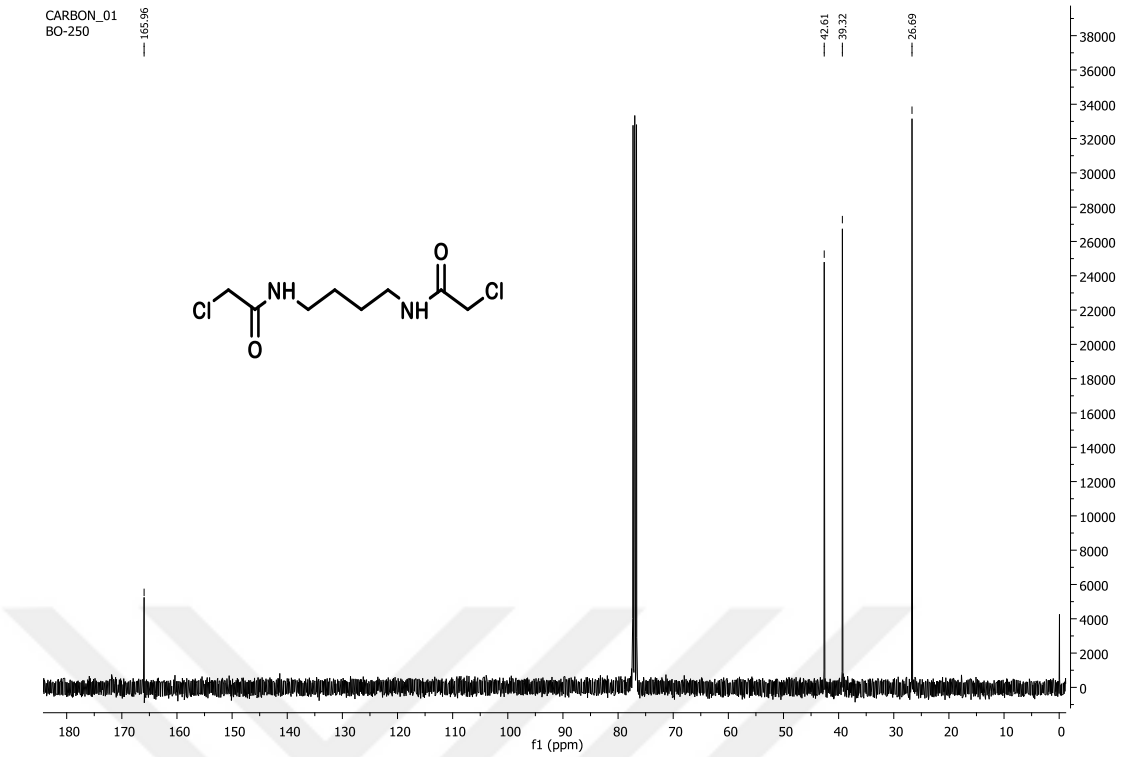

Figure 7.226. ^{13}C NMR spectrum of compound **192**

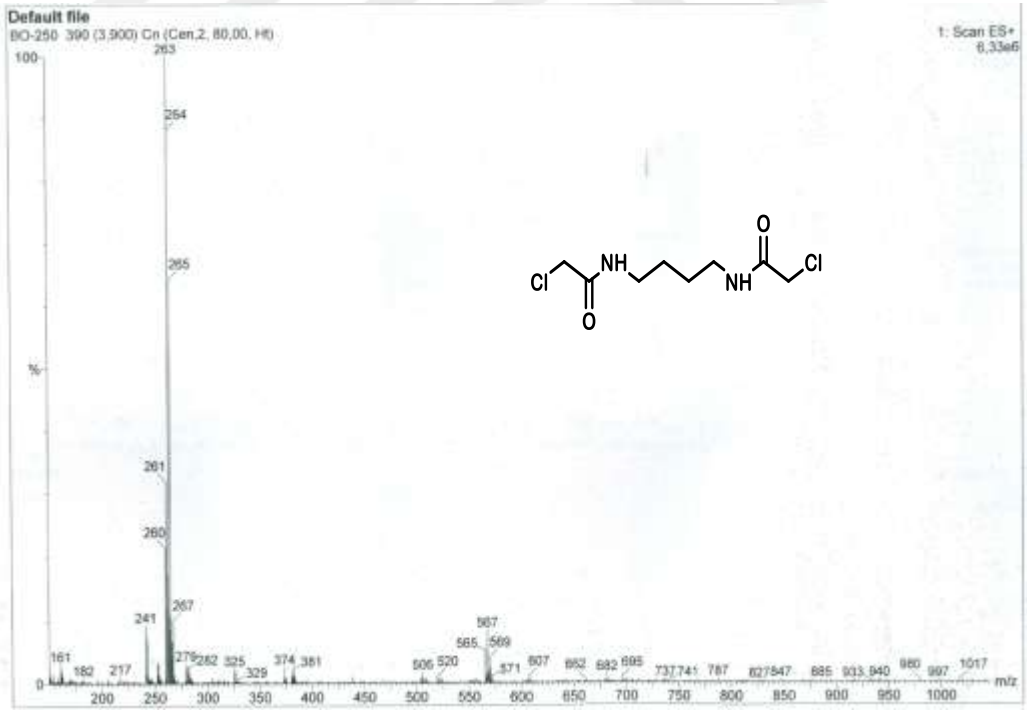

Figure 7.227. LC-MS Spectrum of compound **192**

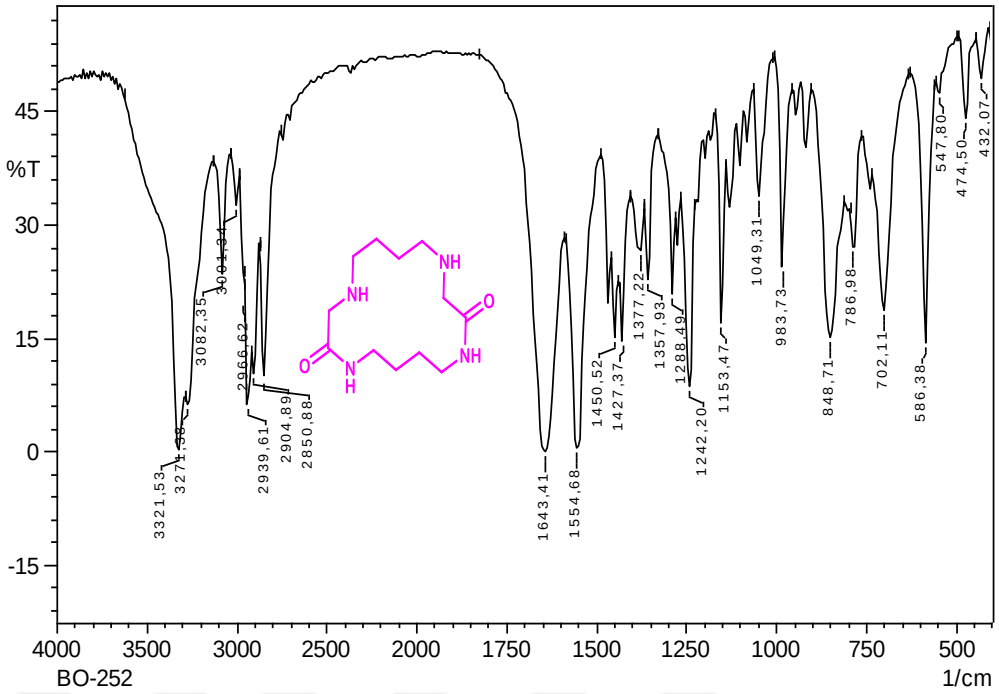

Figure 7.228. IR spectrum of compound **193**

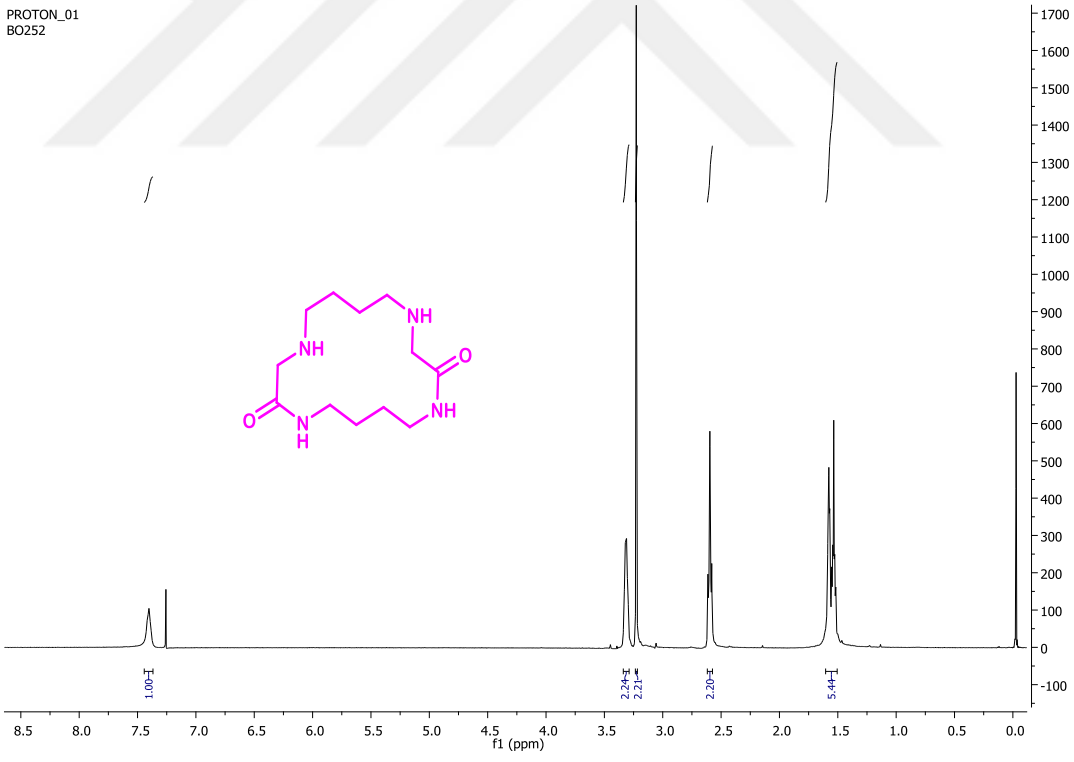

Figure 7.229. ^{1}H NMR spectrum of compound **193**

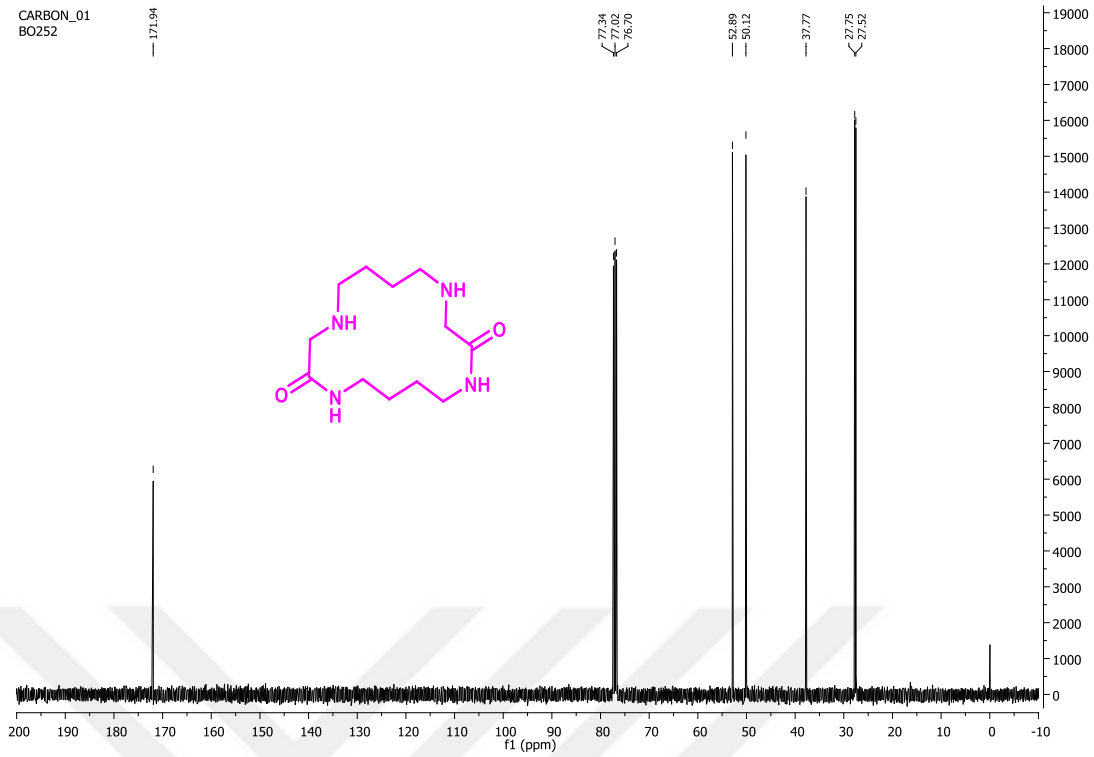

Figure 7.230. ^{13}C NMR spectrum of compound **193**

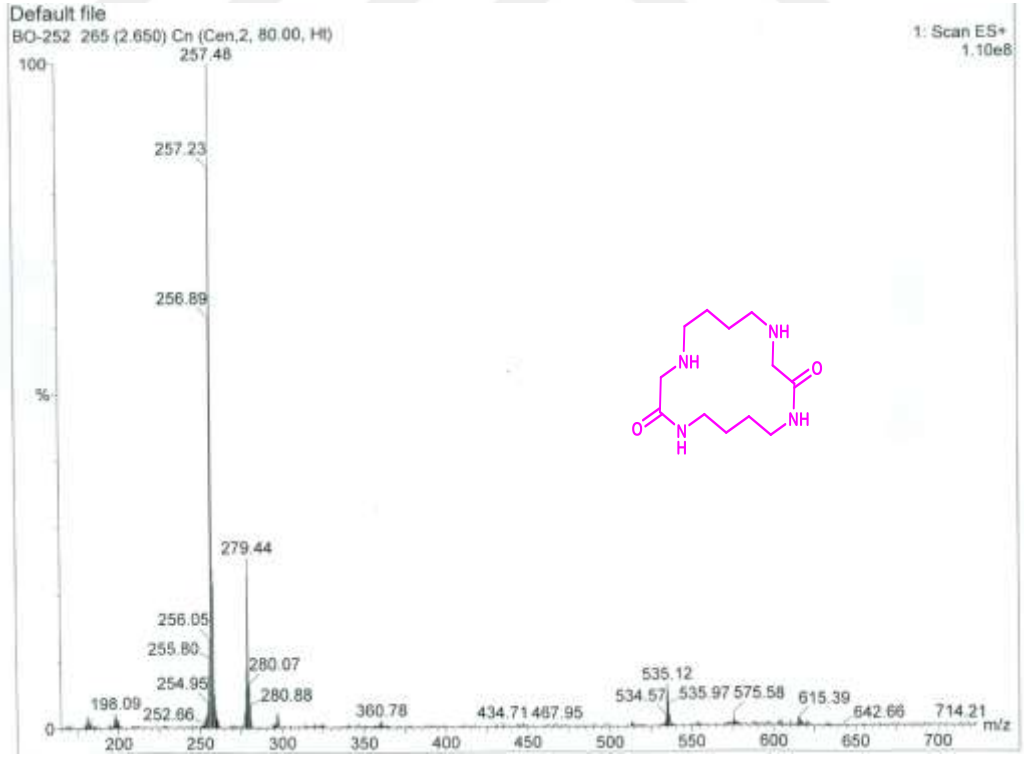

Figure 7.231. LC-MS Spectrum of compound **193**

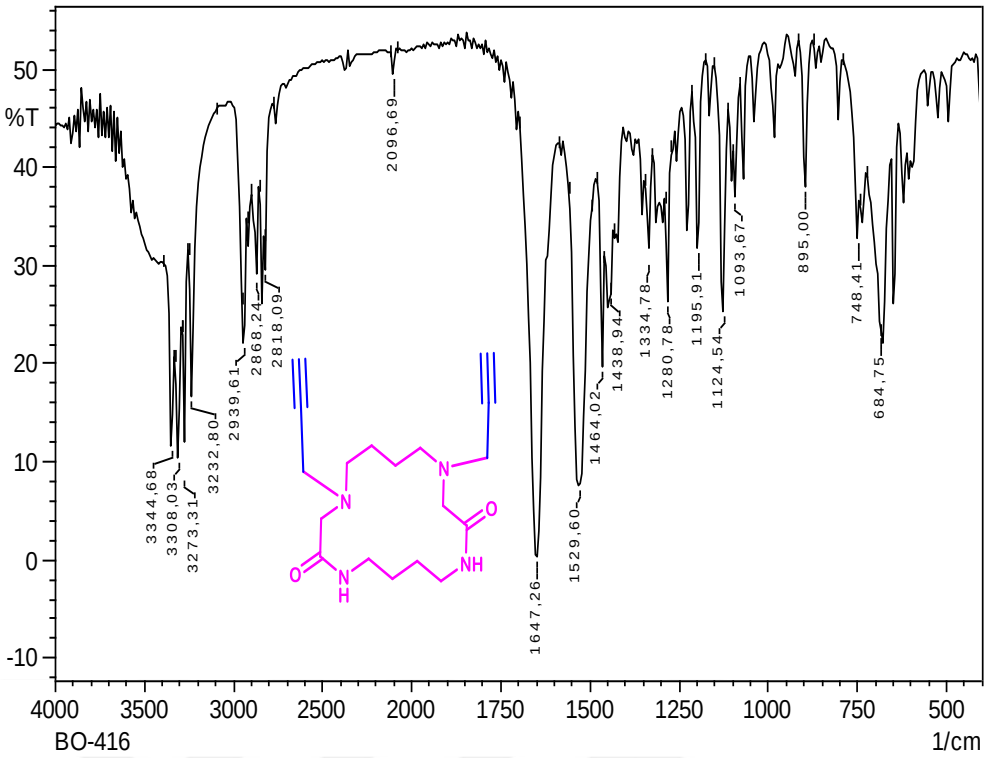

Figure 7.232. IR spectrum of compound **194**

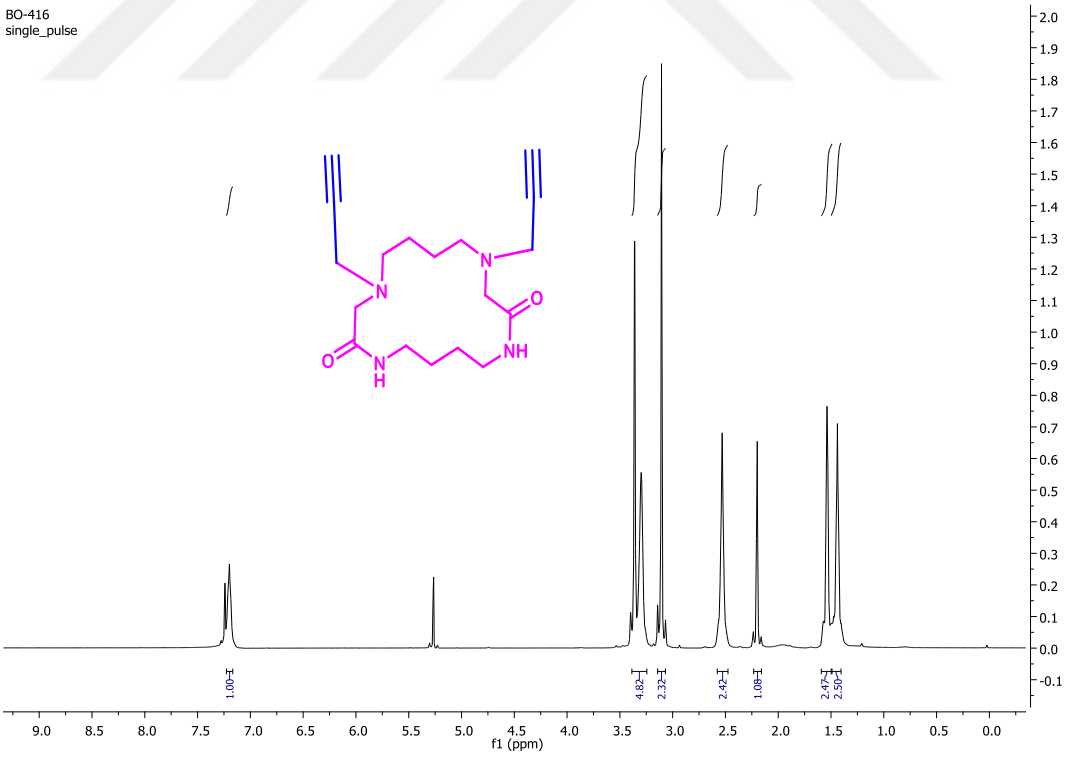

Figure 7.233. ^{1}H NMR spectrum of compound **194**

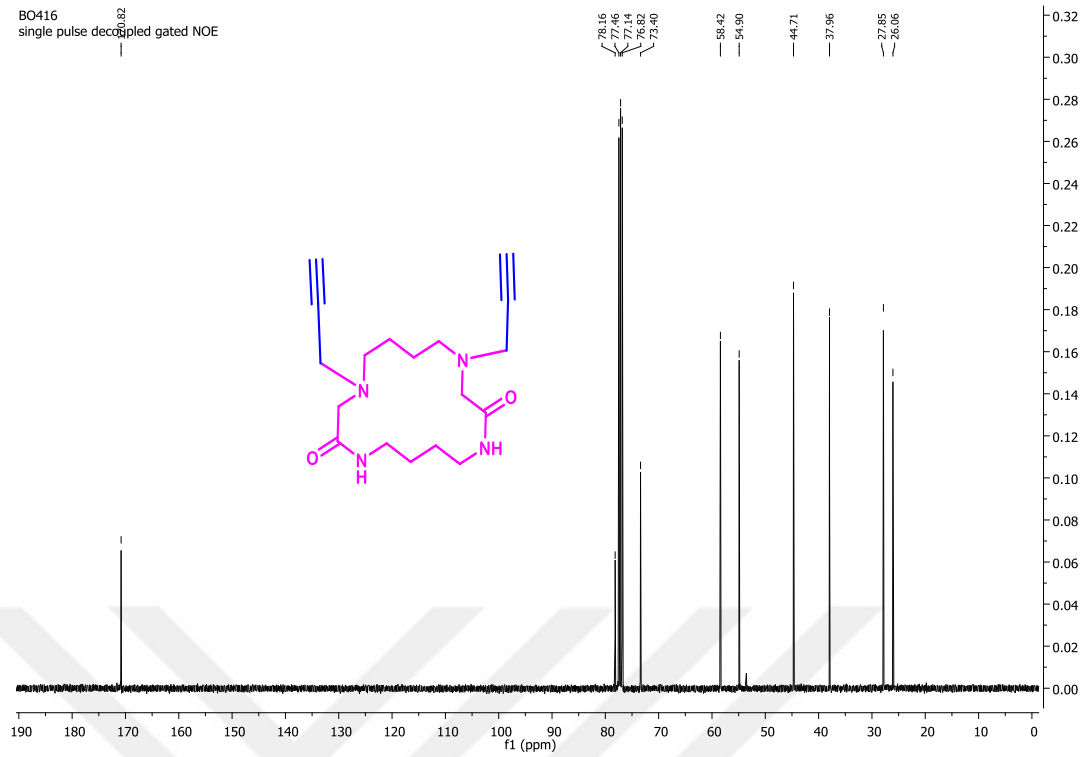

Figure 7.234. ^{13}C NMR spectrum of compound **194**

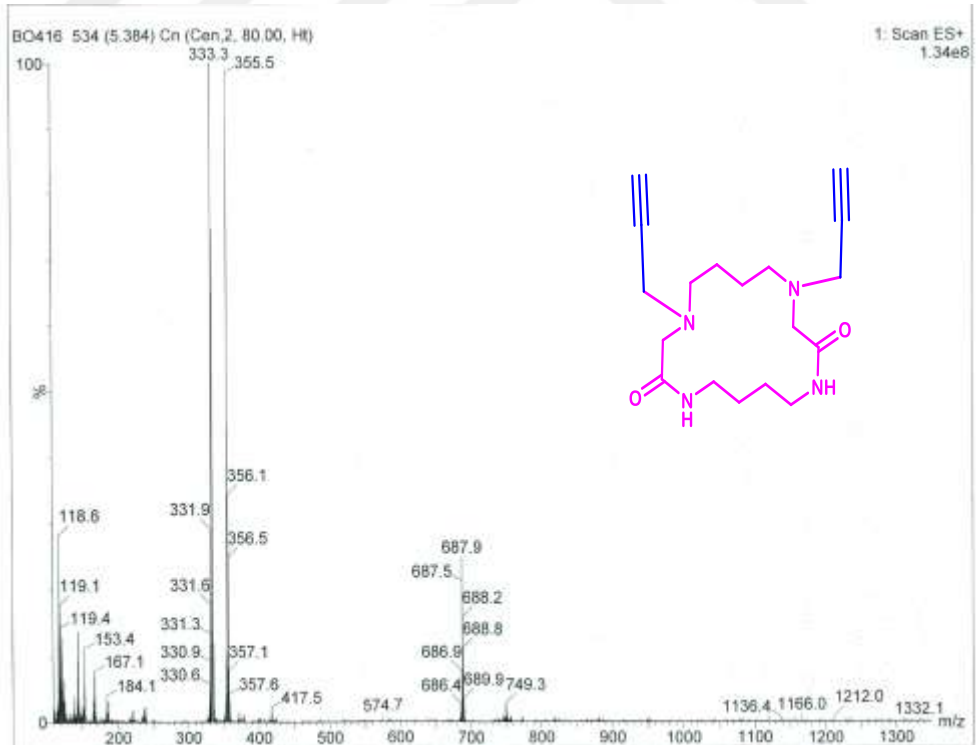

Figure 7.235. LC-MS Spectrum of compound **194**

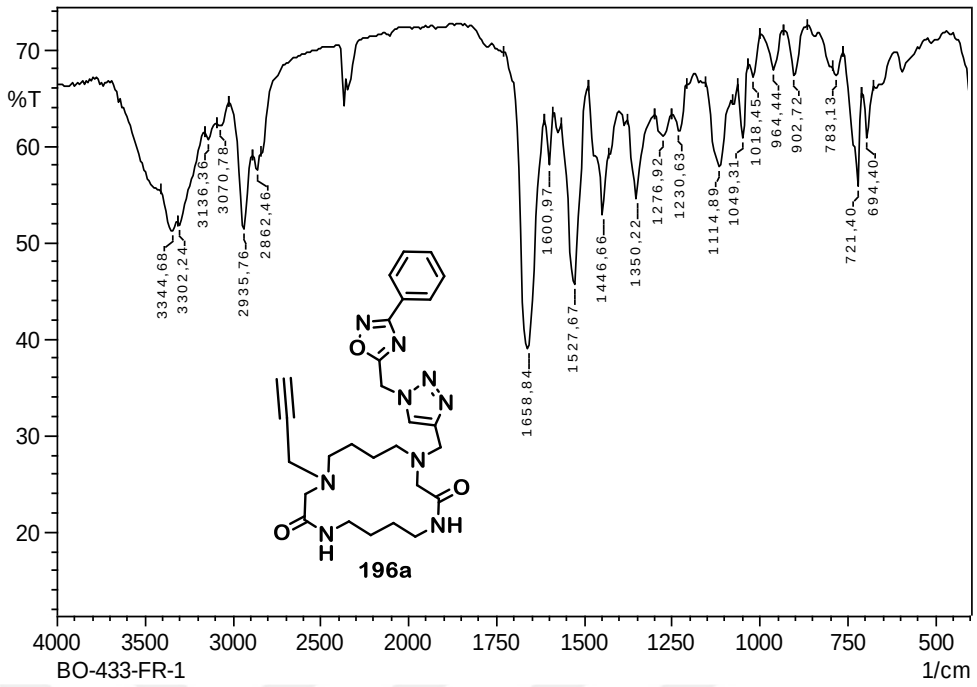

Figure 7.236. IR spectrum of compound **196a**

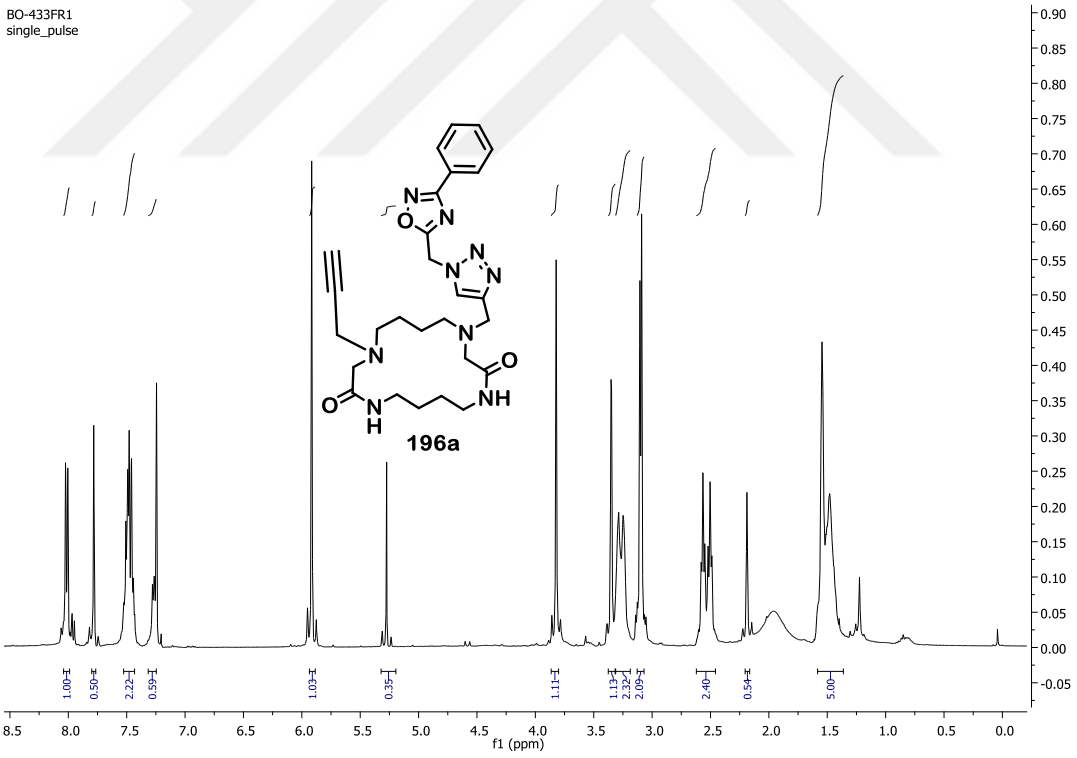

Figure 7.237. ^{1}H NMR spectrum of compound **196a**

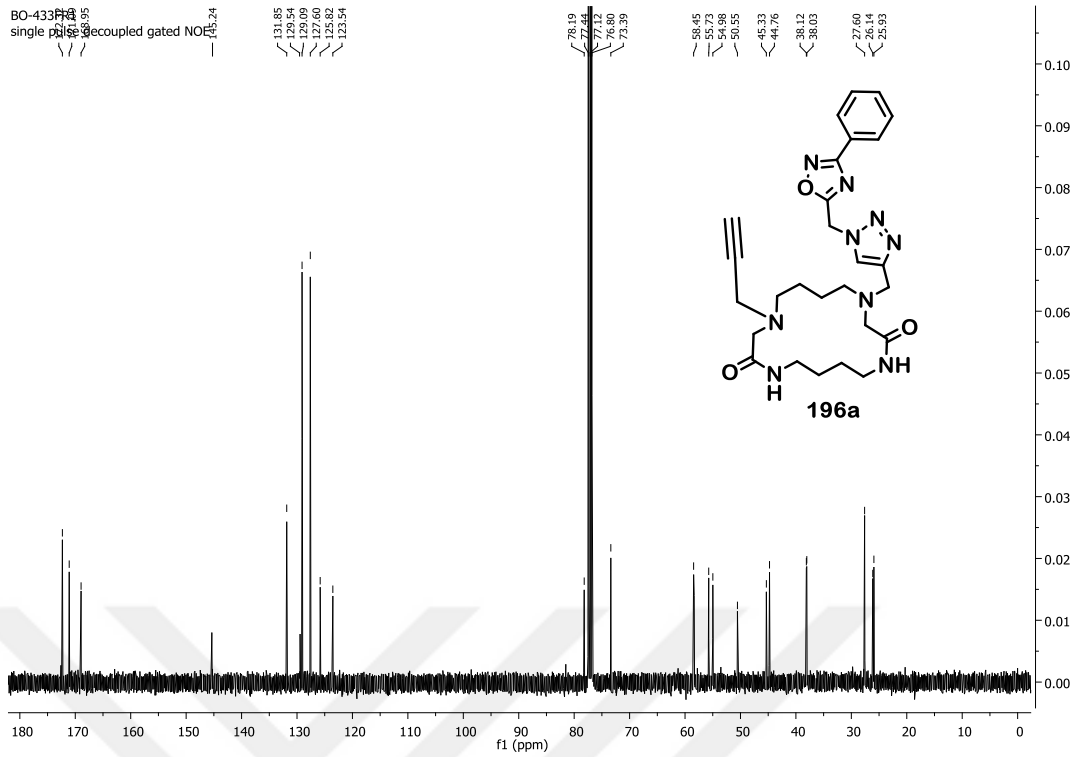

Figure 7.238. ^{13}C NMR spectrum of compound **196a**

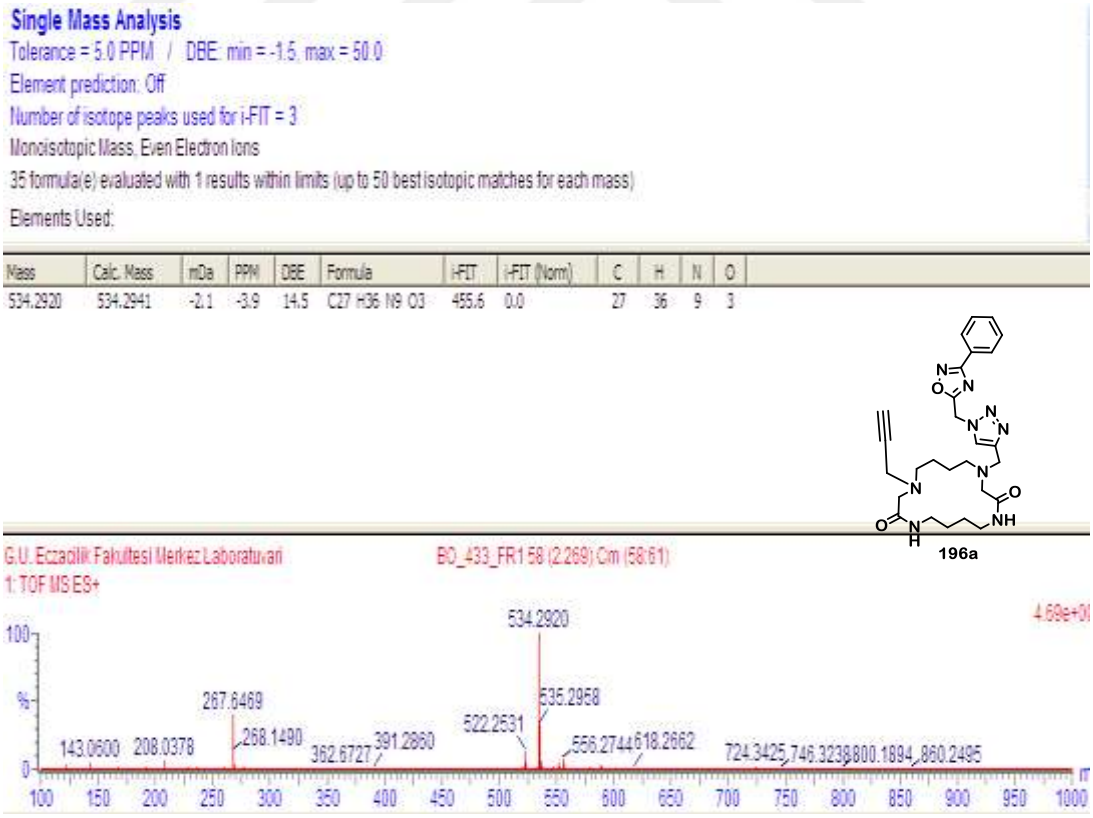

Figure 7.239. HR-MS Spectrum of compound **196a**

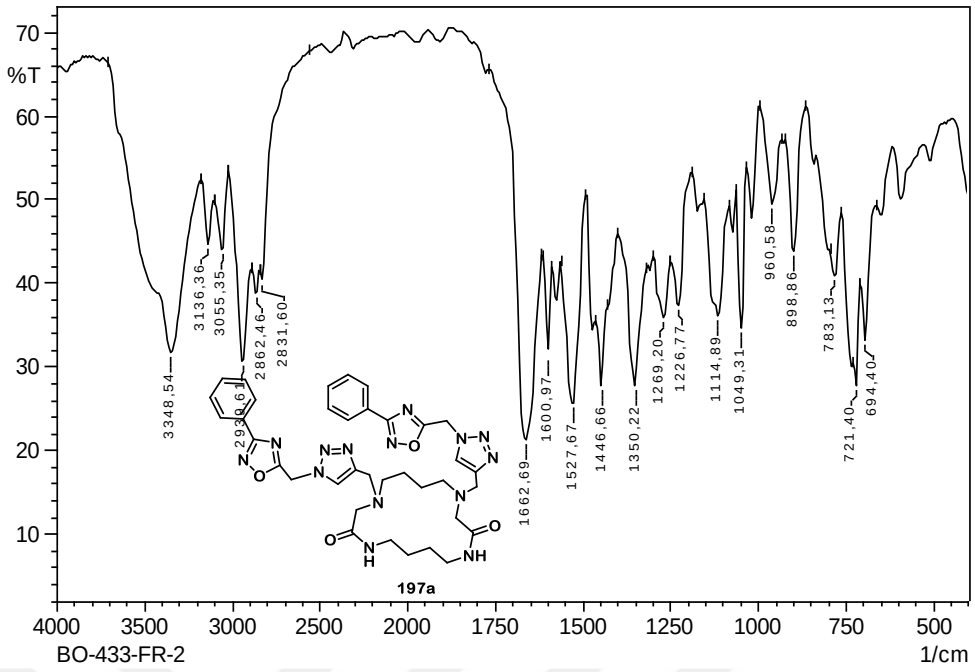

Figure 7.240. IR spectrum of compound **197a**

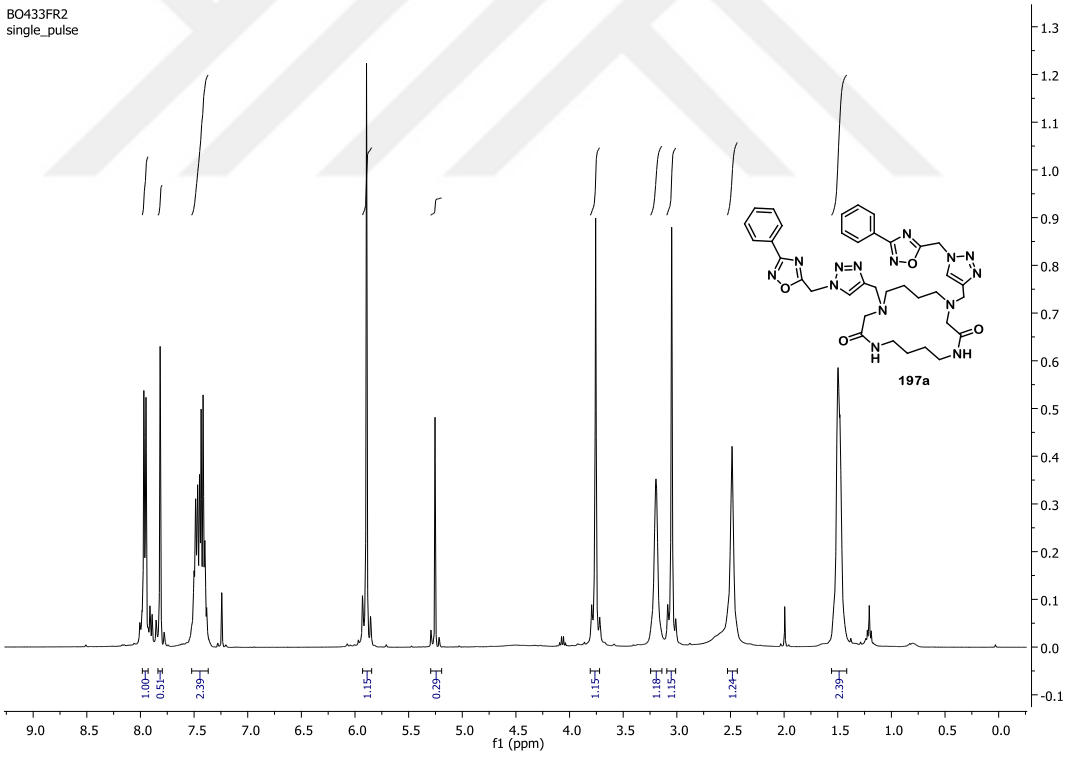

Figure 7.241. ^{1}H NMR spectrum of compound **197a**

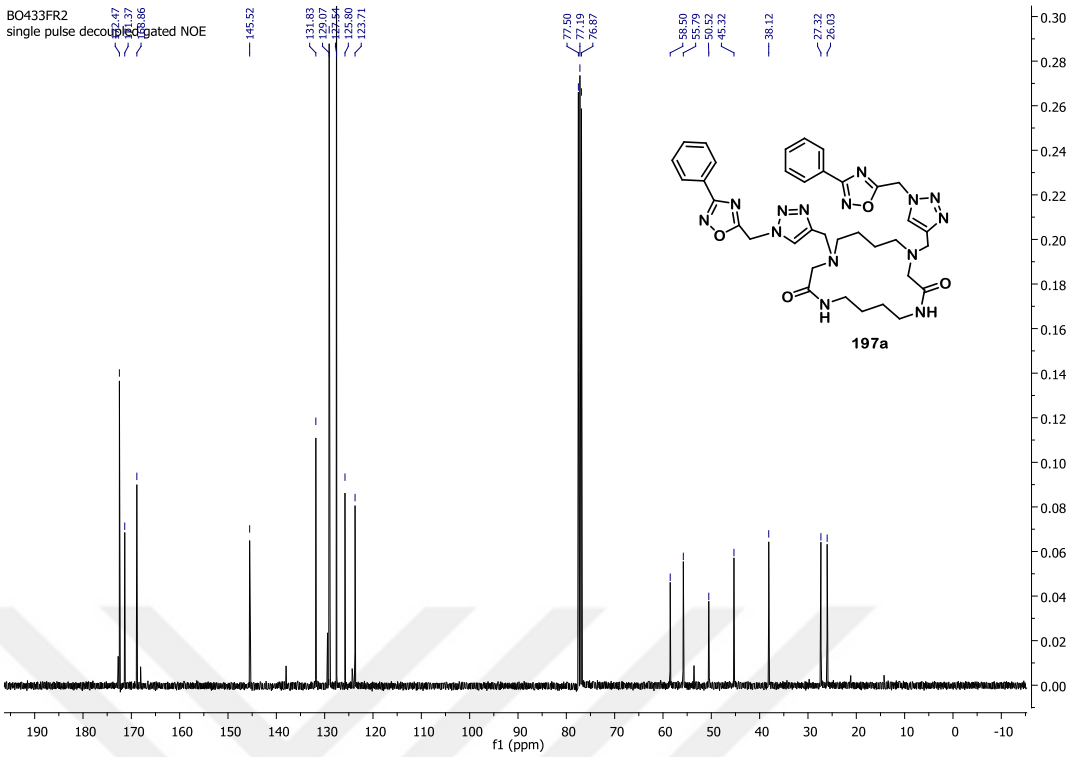

Figure 7.242. ^{13}C NMR spectrum of compound **197a**

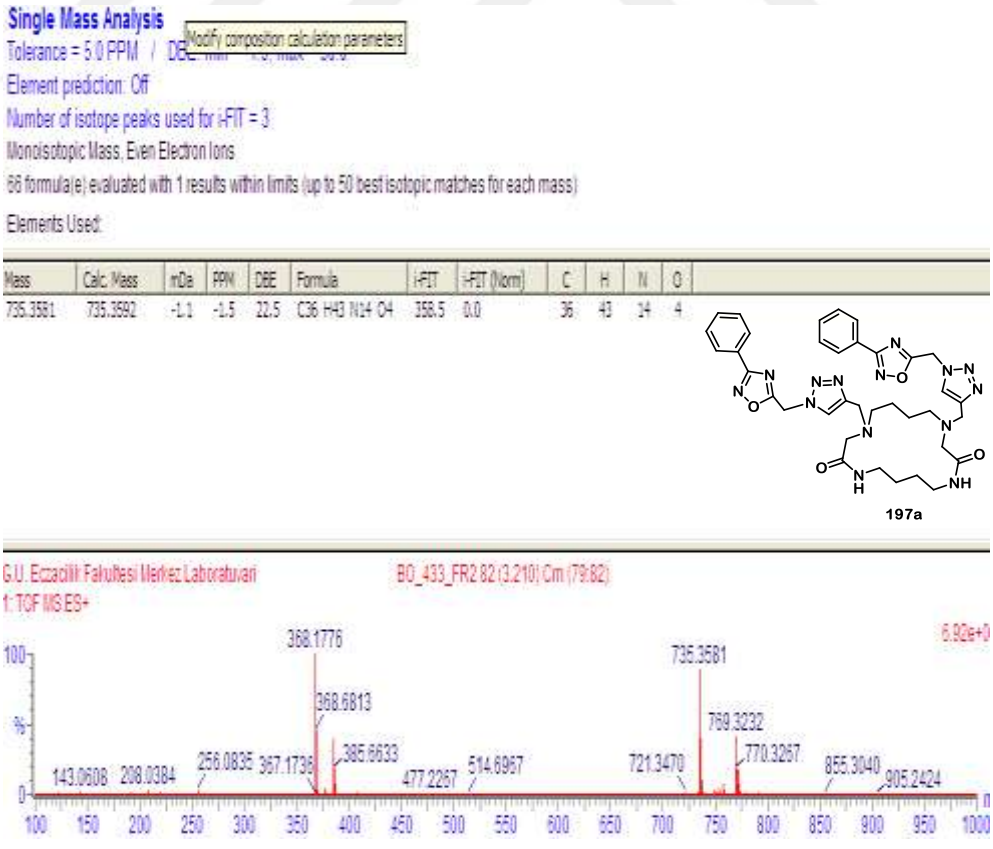

Figure 7.243. HR-MS Spectrum of compound **197a**

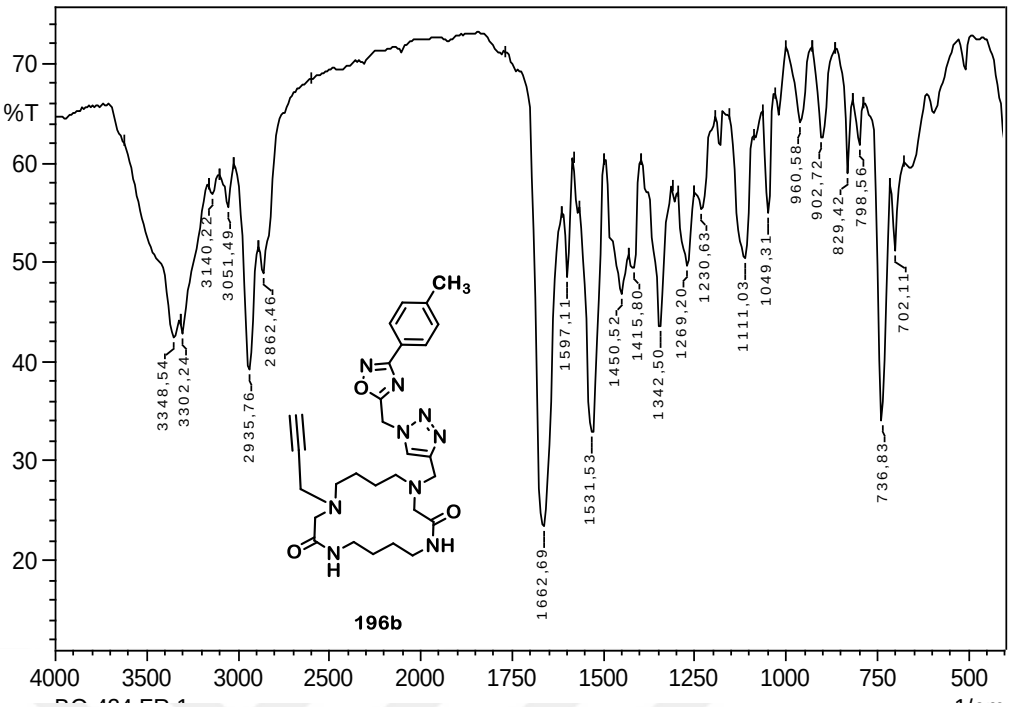

Figure 7.244. IR spectrum of compound **196b**

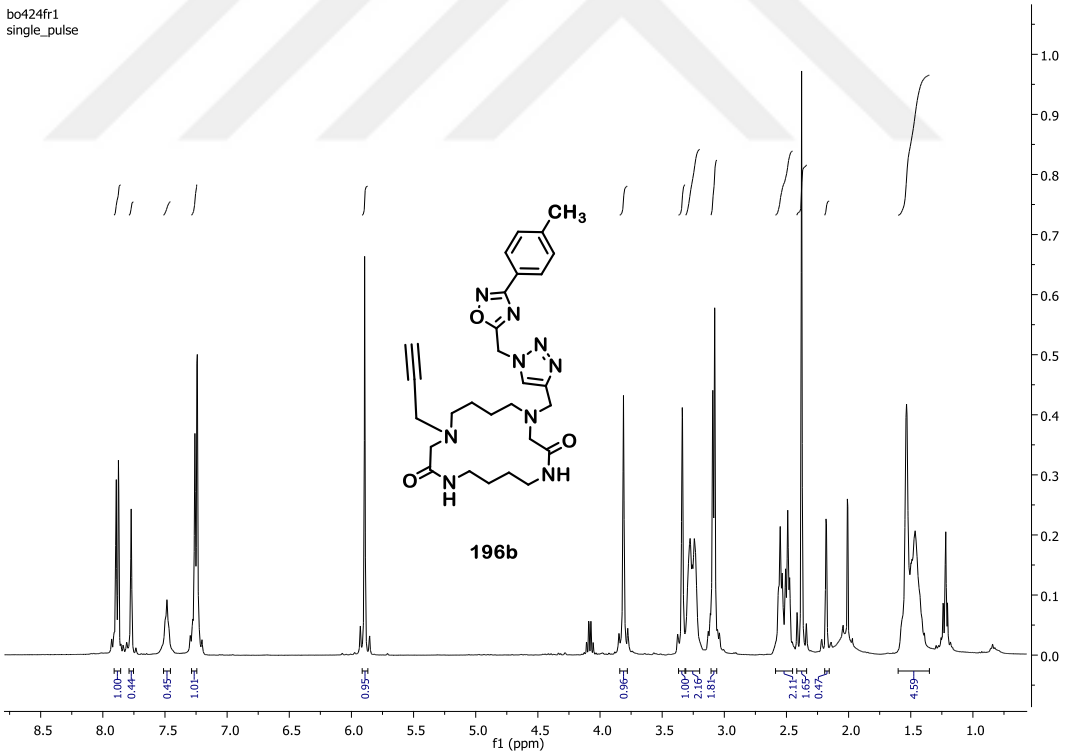

Figure 7.245. ^{1}H NMR spectrum of compound **196b**

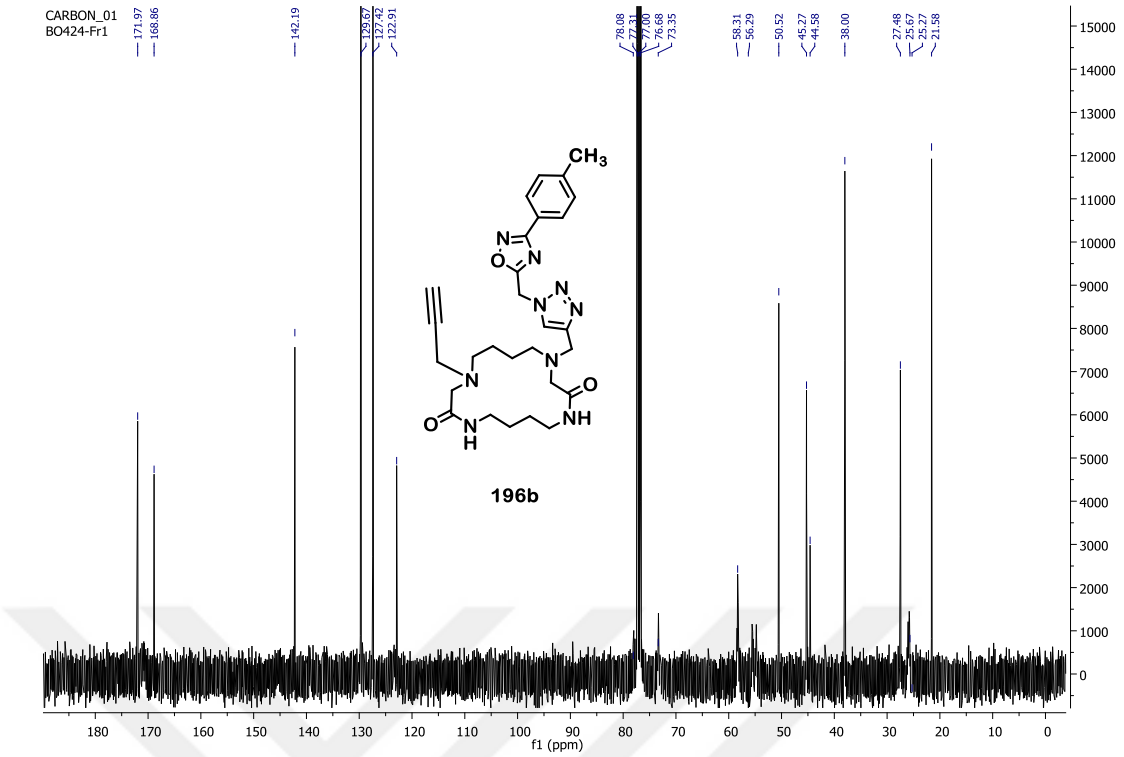

Figure 7.246. ^{13}C NMR spectrum of compound **196b**

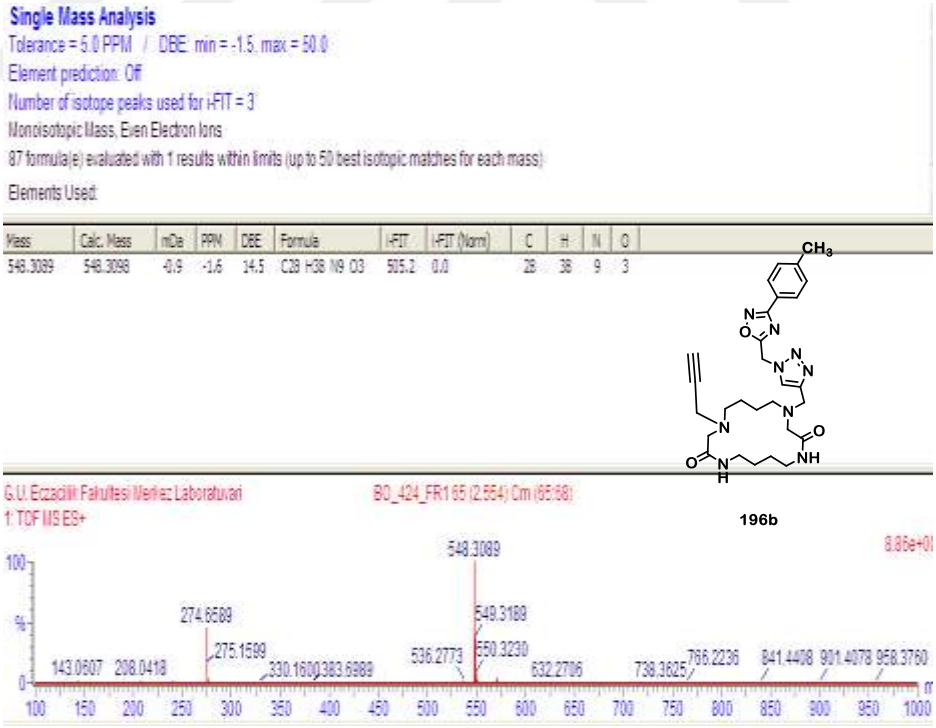

Figure 7.247. MASS Spectrum of compound **196b**

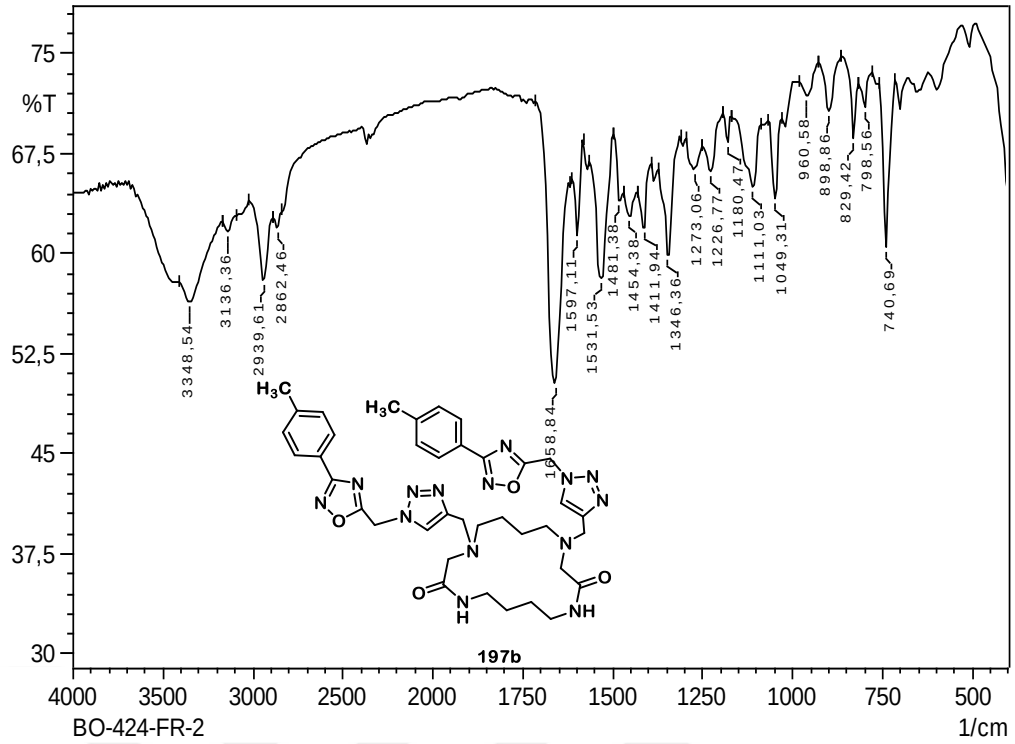

Figure 7.248. IR spectrum of compound **197b**

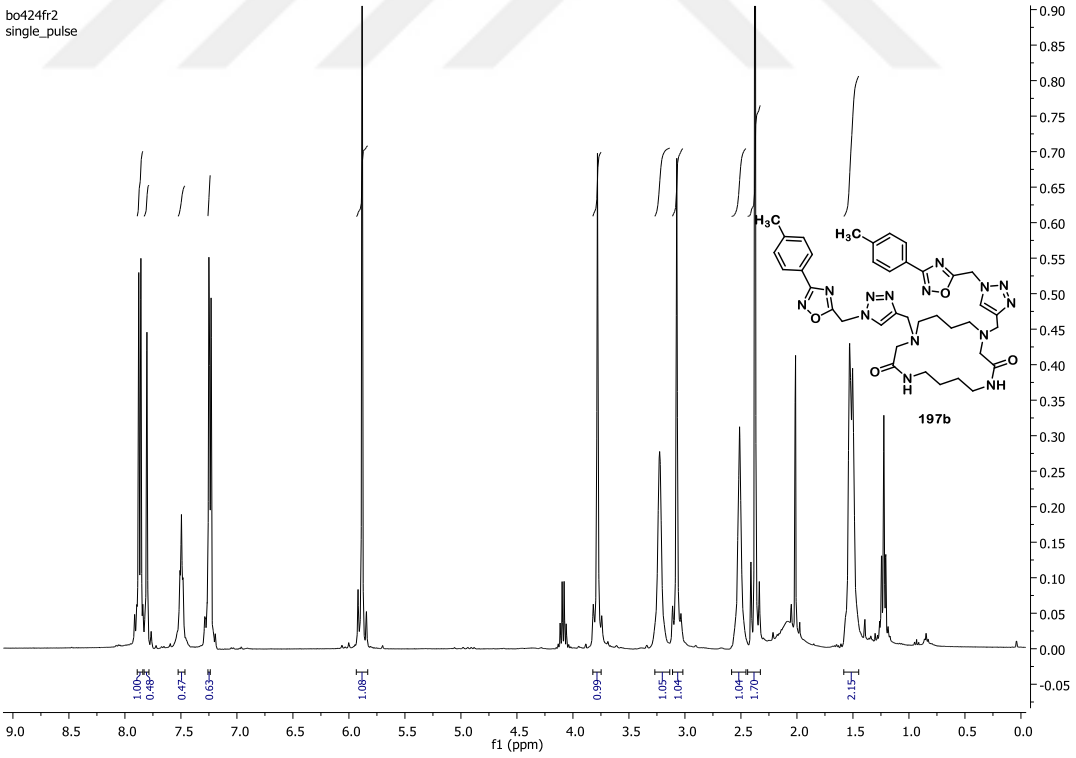

Figure 7.249. ^{1}H NMR spectrum of compound **197b**

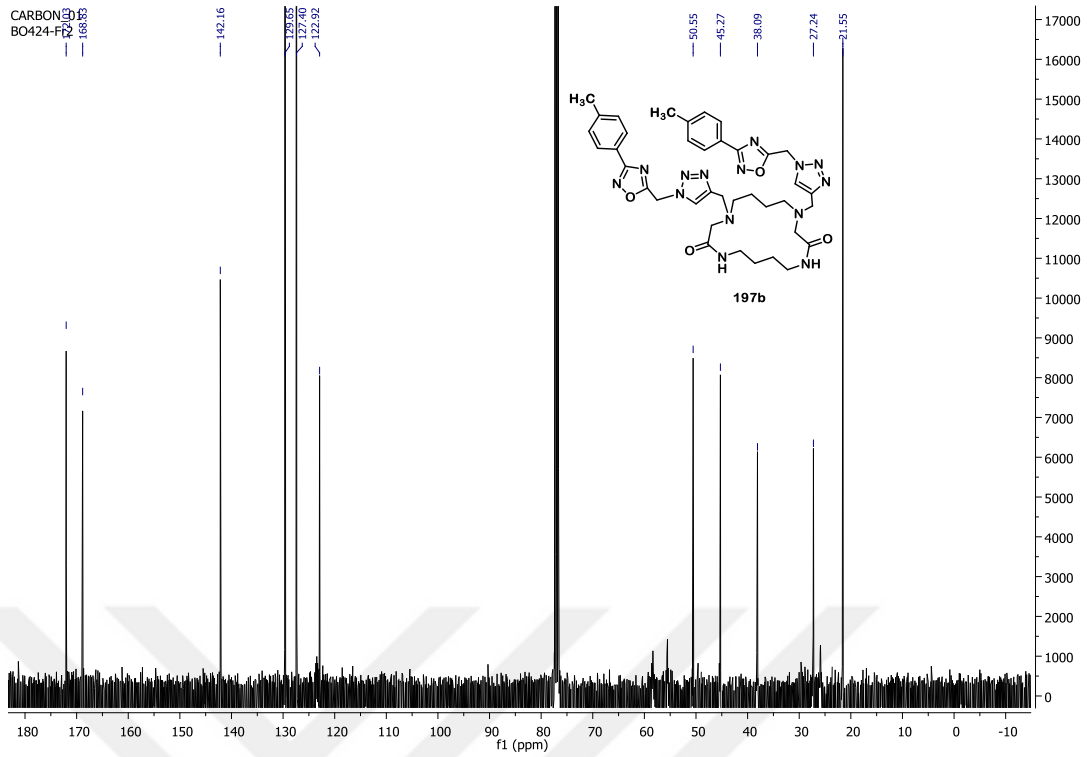

Figure 7.250. ^{13}C NMR spectrum of compound **197b**

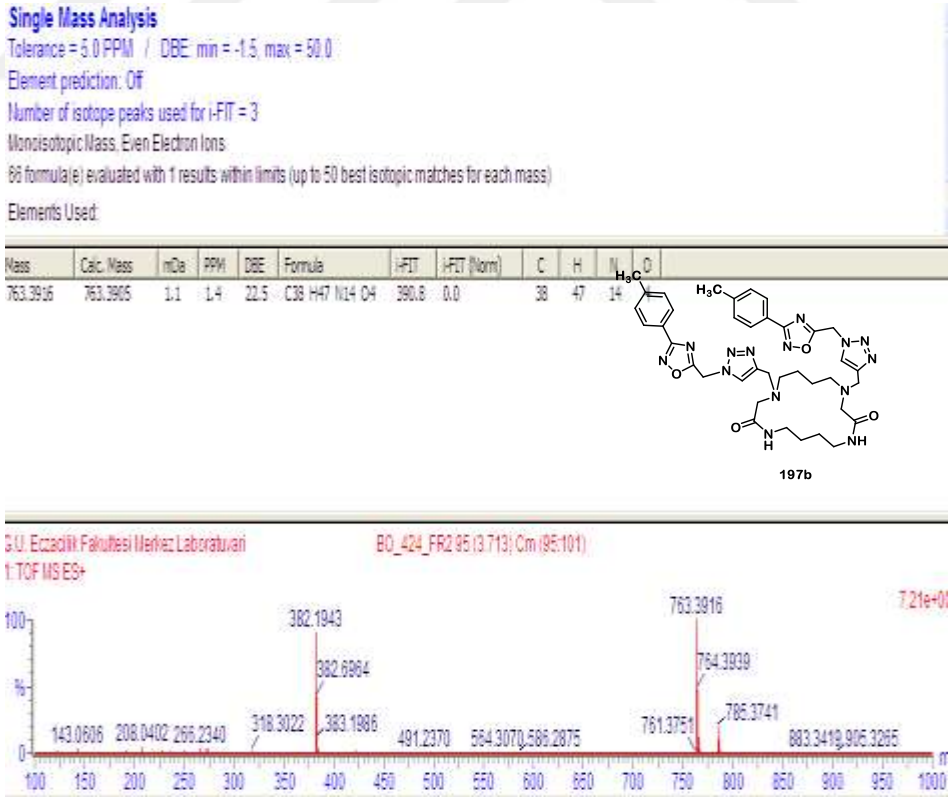

Figure 7.251. HR-MS Spectrum of compound **197b**

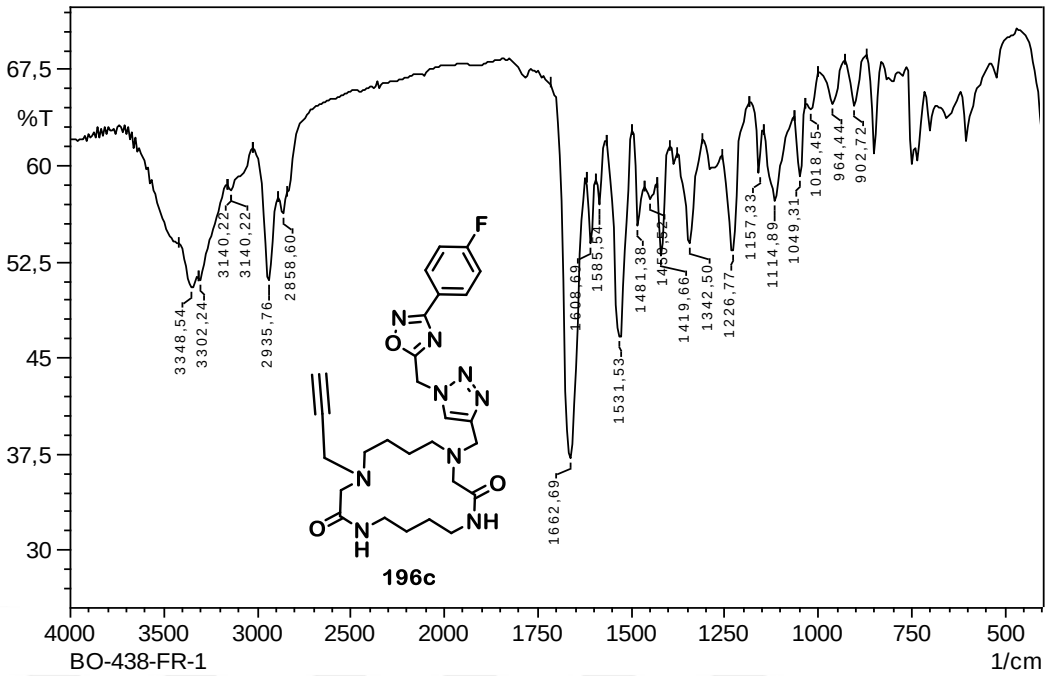

Figure 7.252. IR spectrum of compound **196c**

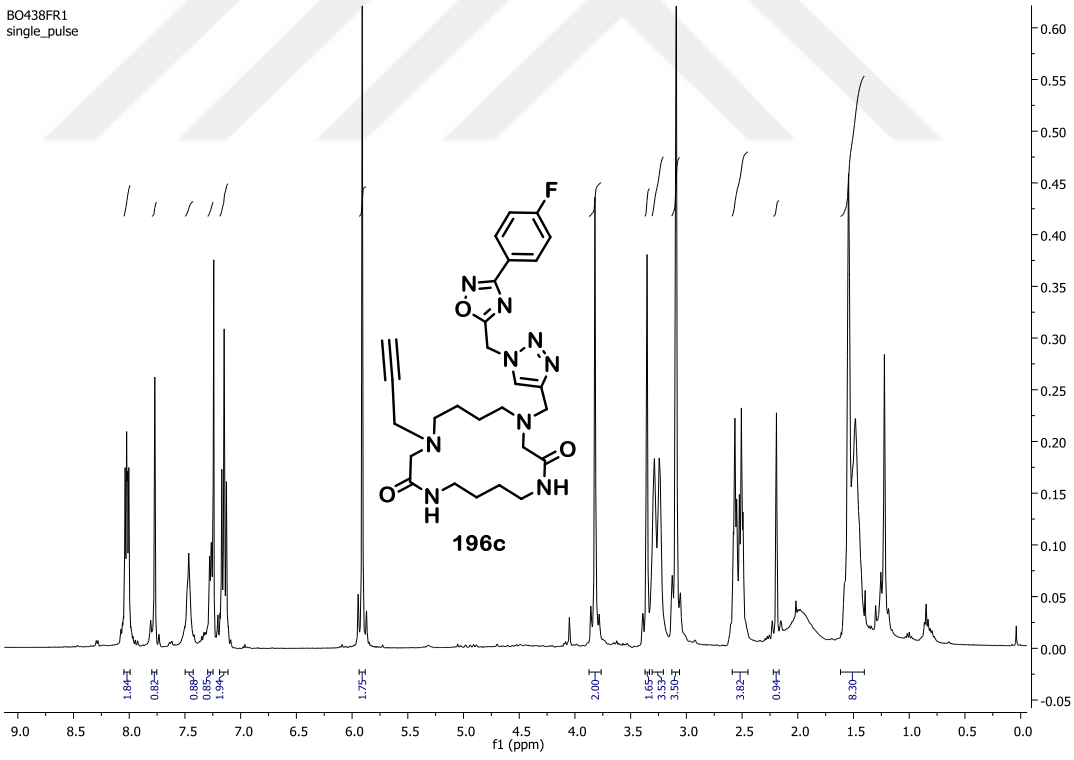

Figure 7.253. ^{1}H NMR spectrum of compound **196c**

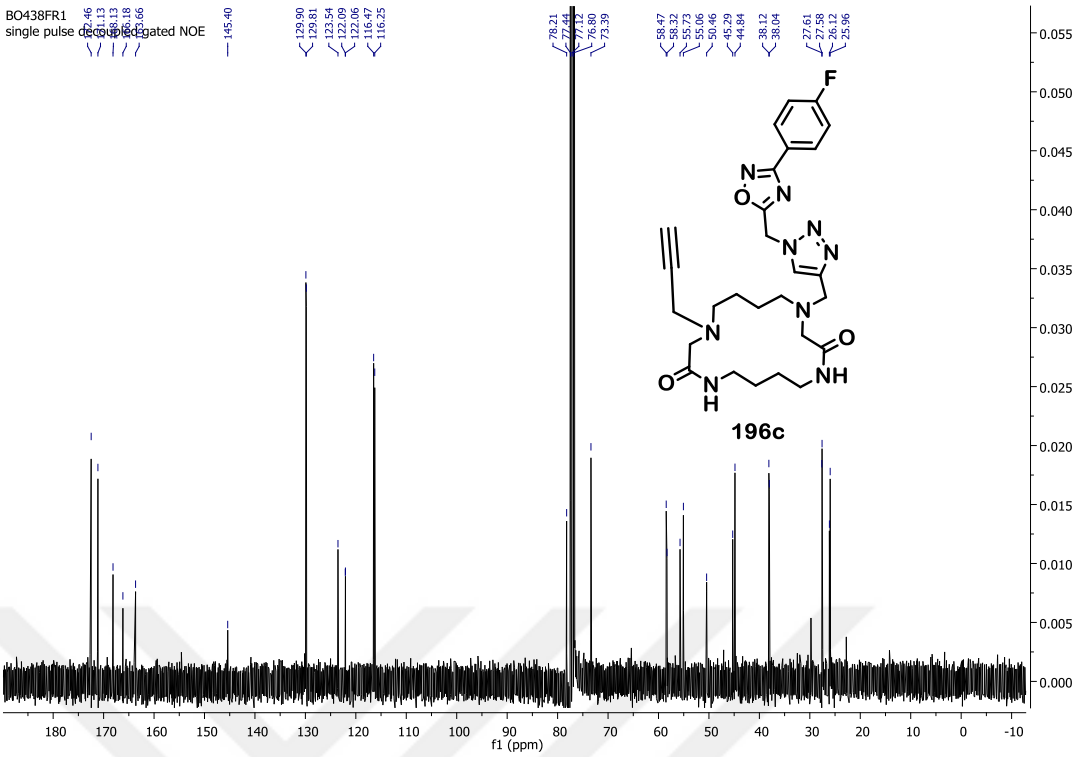

Figure 7.254. ^{13}C NMR spectrum of compound **196c**

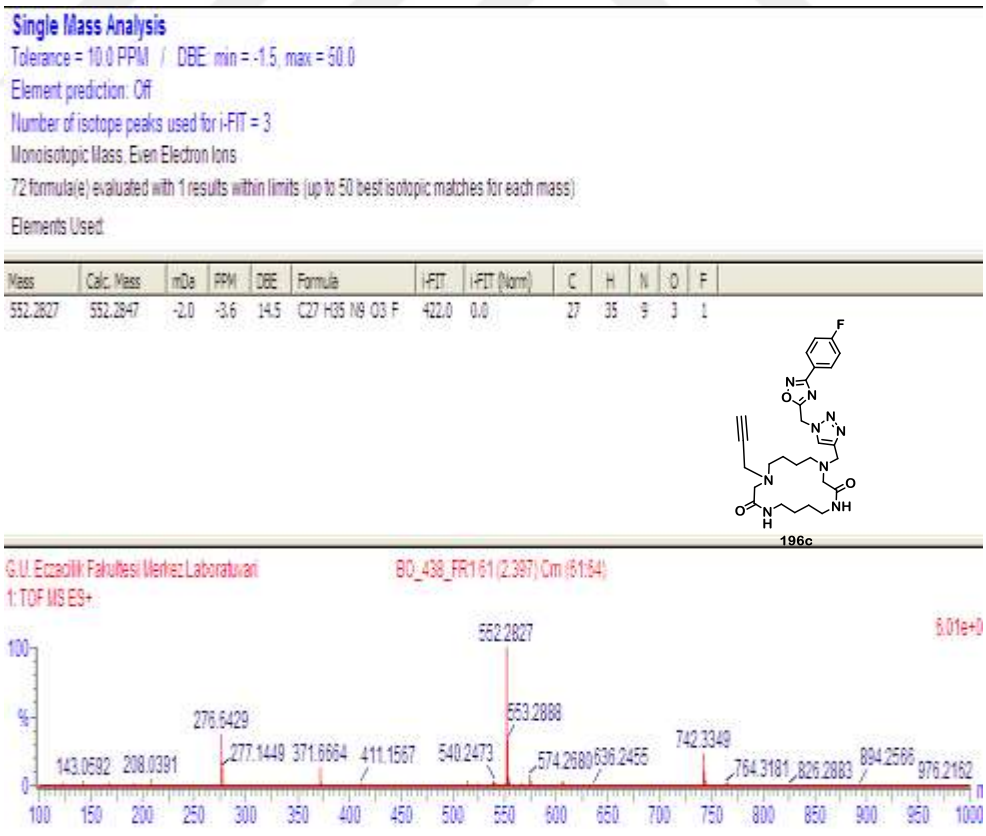

Figure 7.255. HR-MS Spectrum of compound **196c**

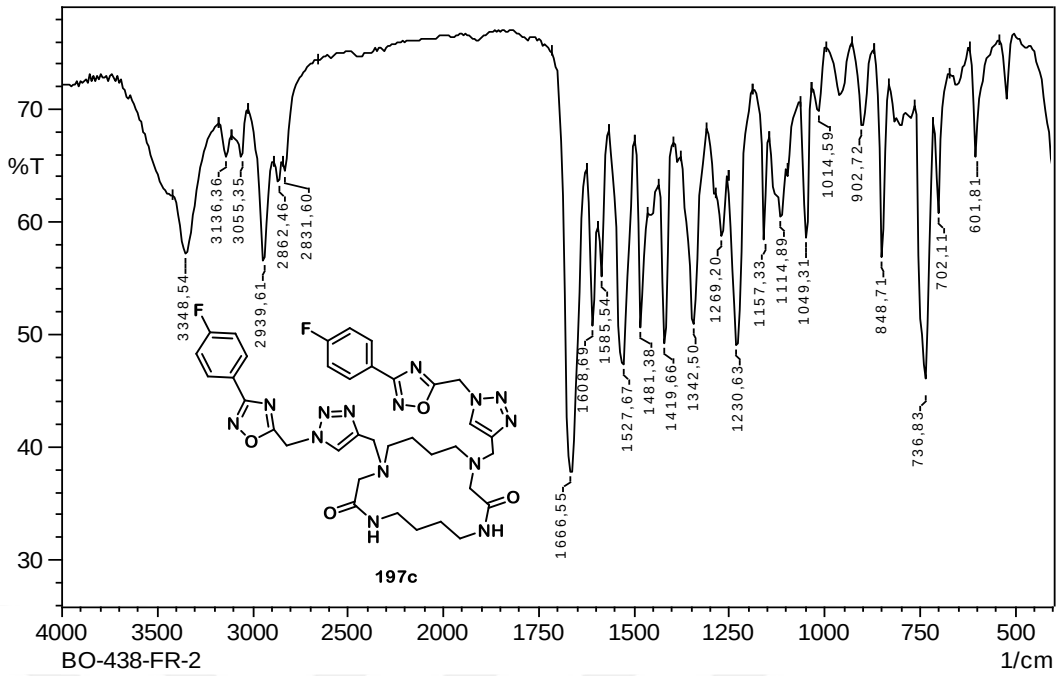

Figure 7.256. IR spectrum of compound **197c**

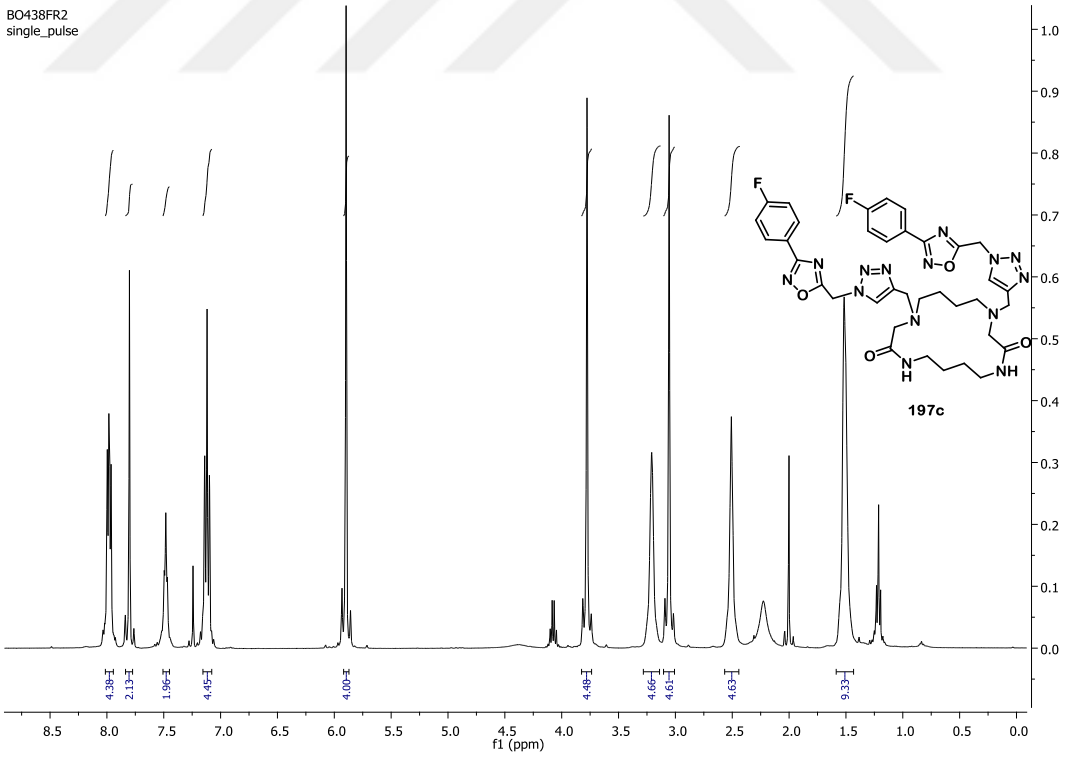

Figure 7.257. ^{1}H NMR spectrum of compound **197c**

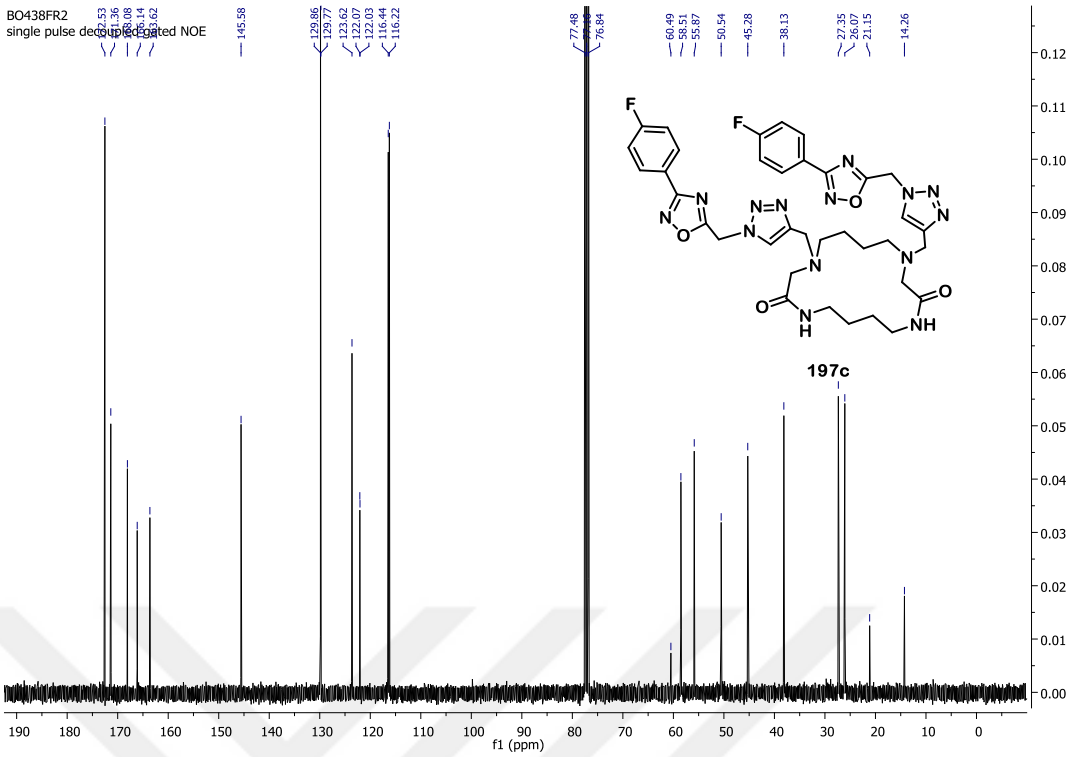

Figure 7.258. ^{13}C NMR spectrum of compound **197c**

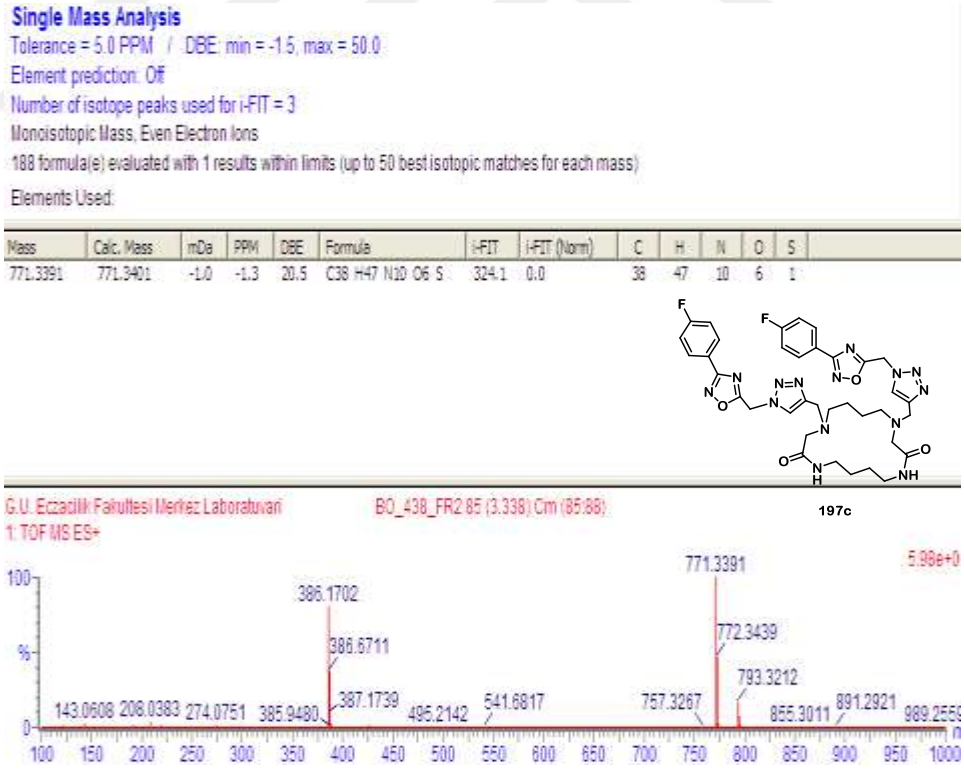

Figure 7.259. HR-MS Spectrum of compound **197c**

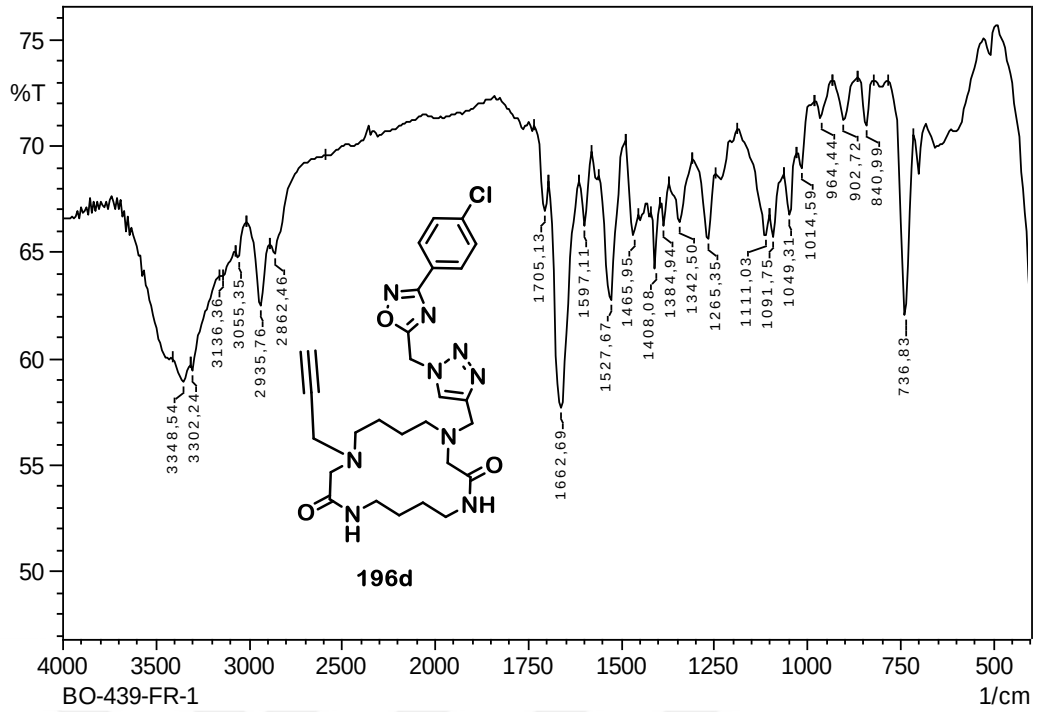

Figure 7.260. IR spectrum of compound **196d**

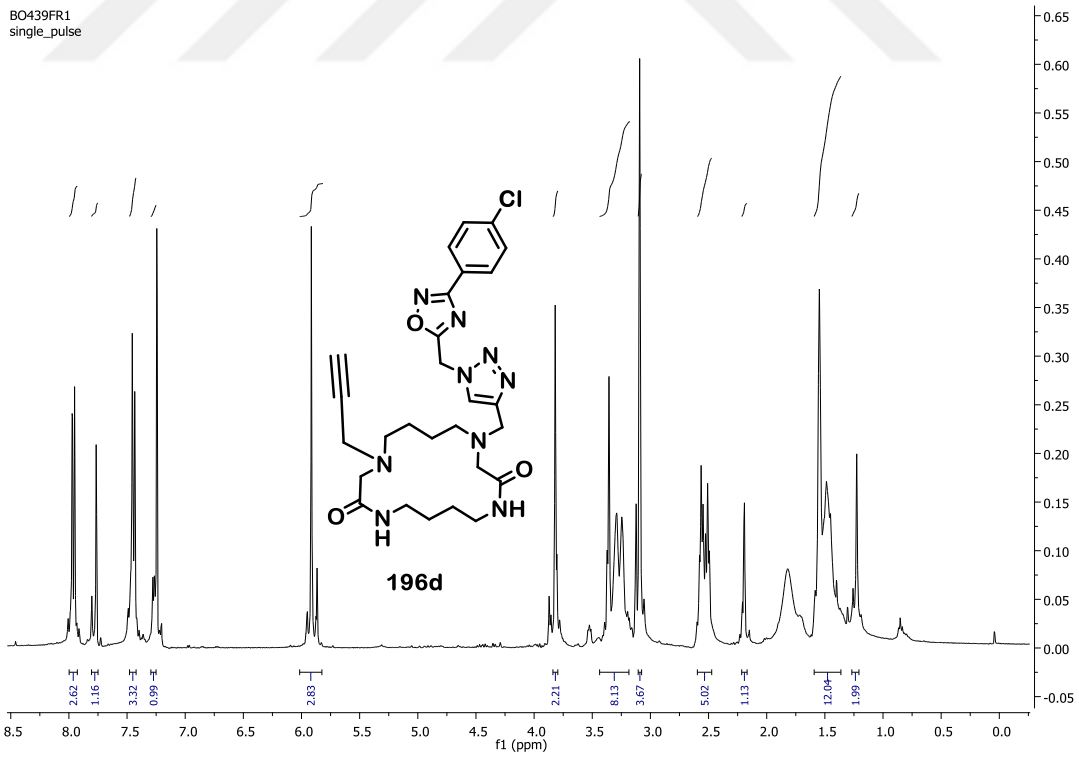

Figure 7.261. ^{1}H NMR spectrum of compound **196d**

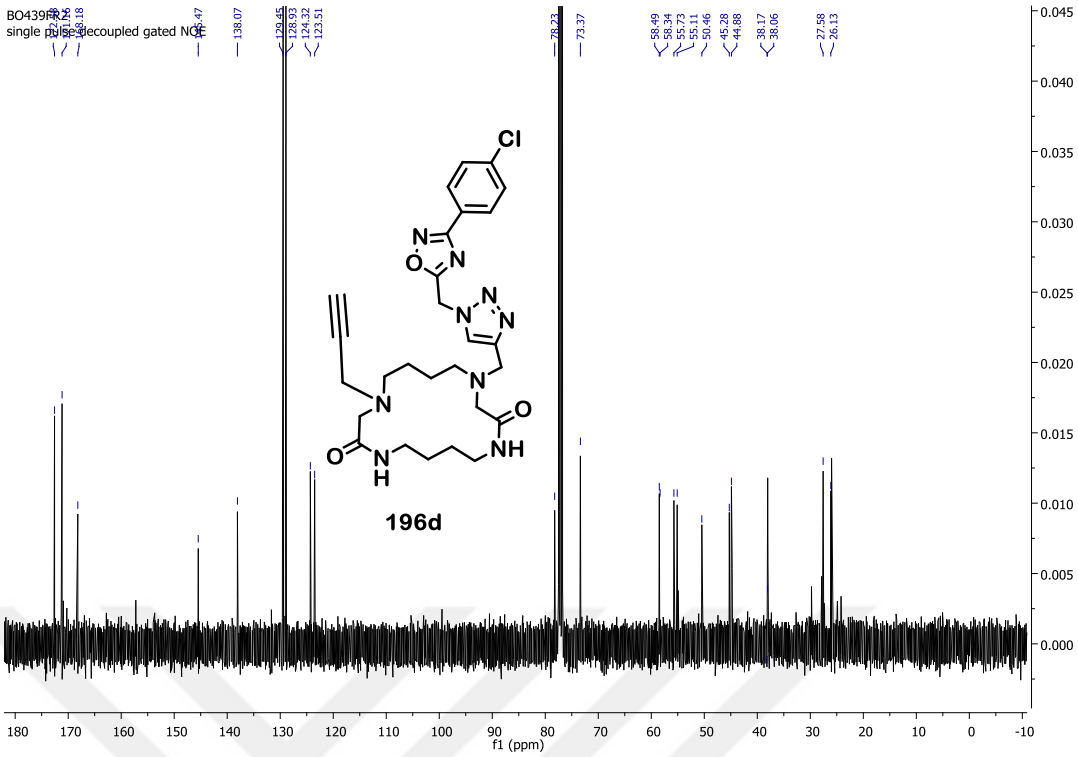

Figure 7.262. ^{13}C NMR spectrum of compound **196d**

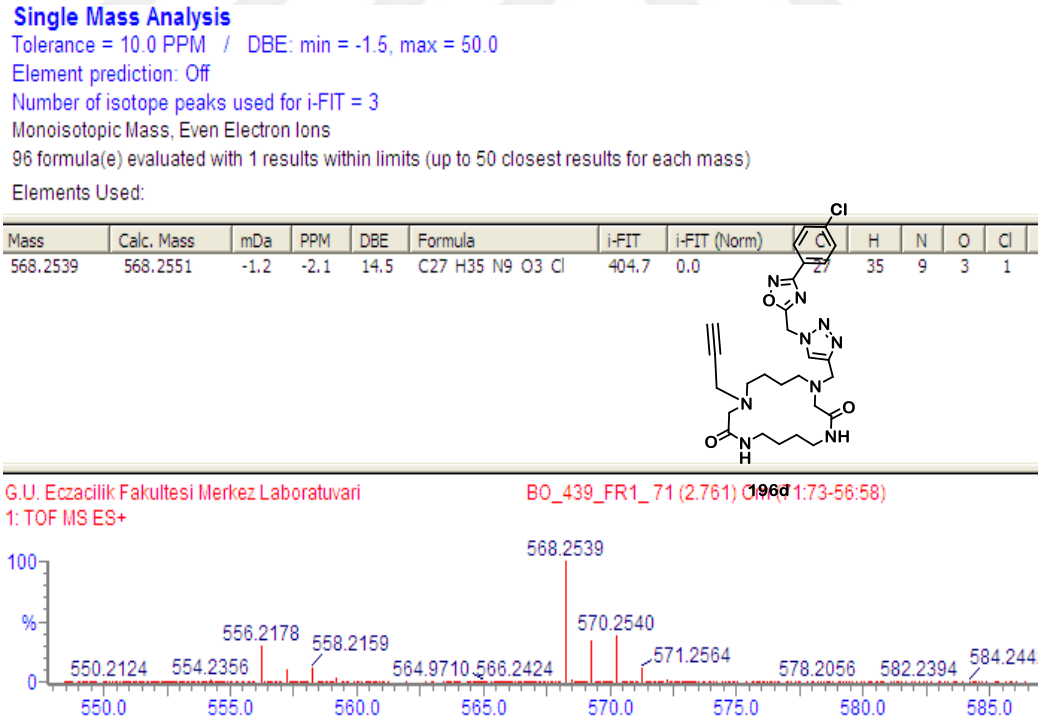

Figure 7.263. HR-MS Spectrum of compound **196d**

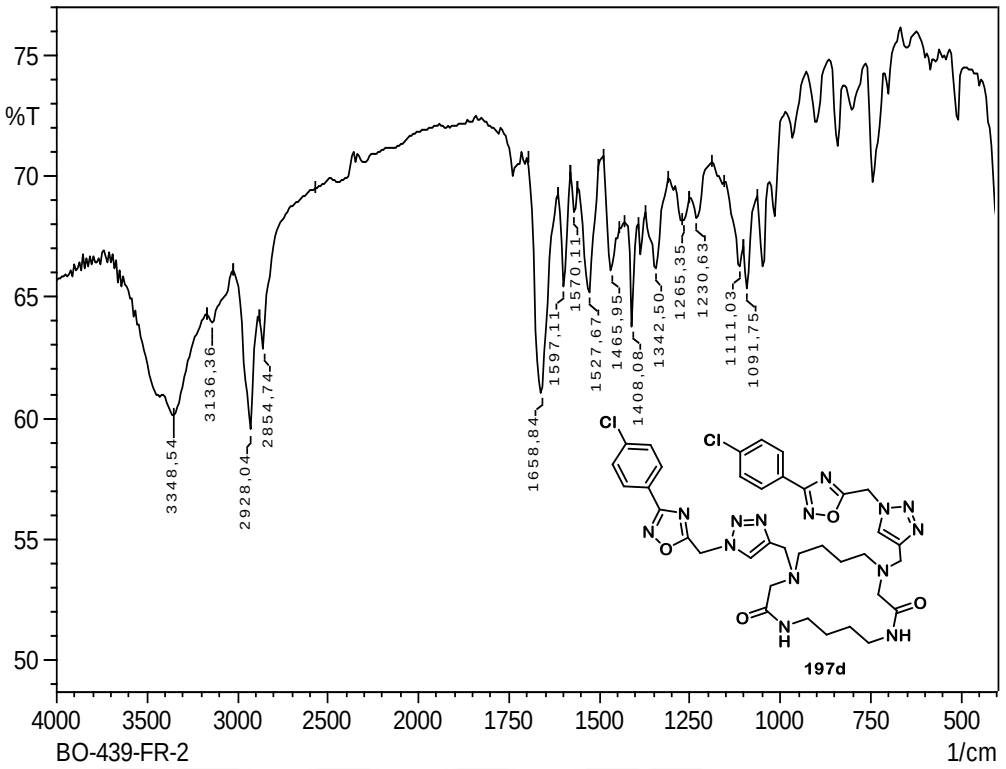

Figure 7.264. IR spectrum of compound **197d**

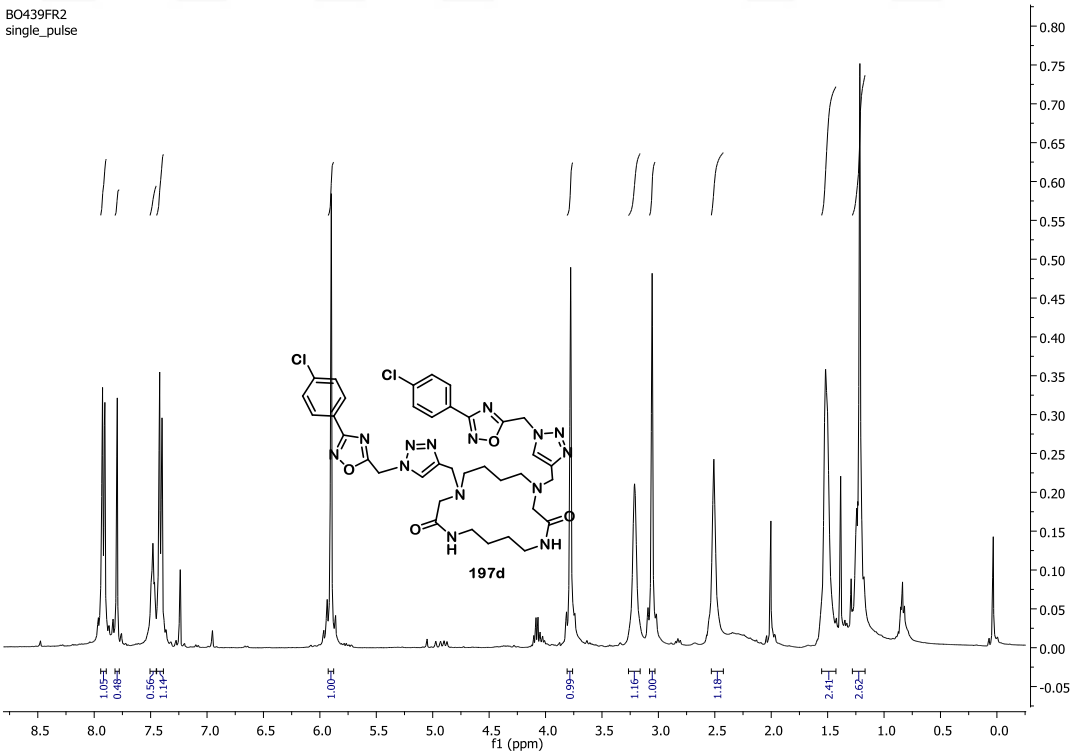

Figure 7.265. ^{1}H NMR spectrum of compound **197d**

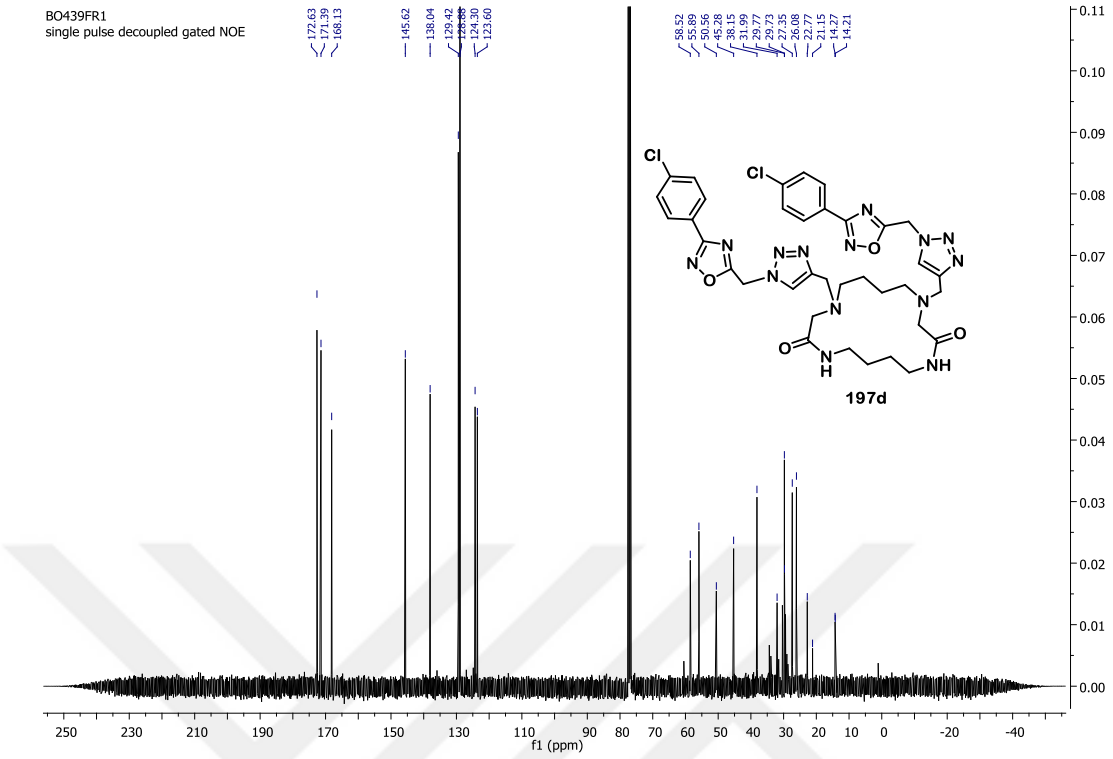

Figure 7.266. ^{13}C NMR spectrum of compound **197d**

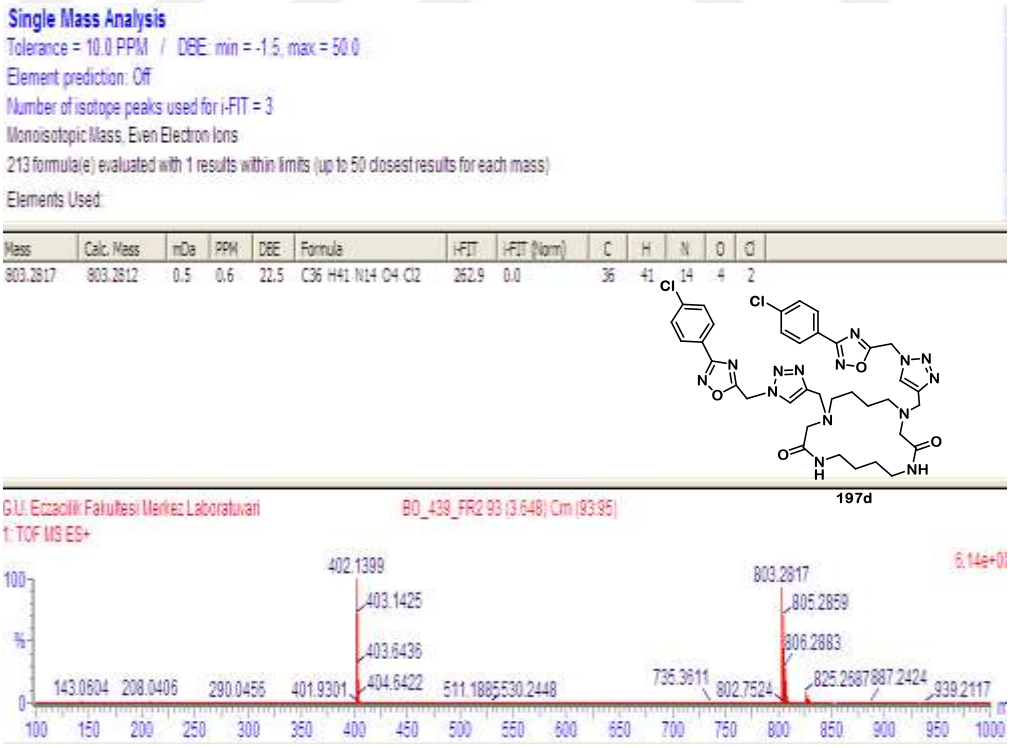

Figure 7.267. HR-MS spectrum of compound **197d**

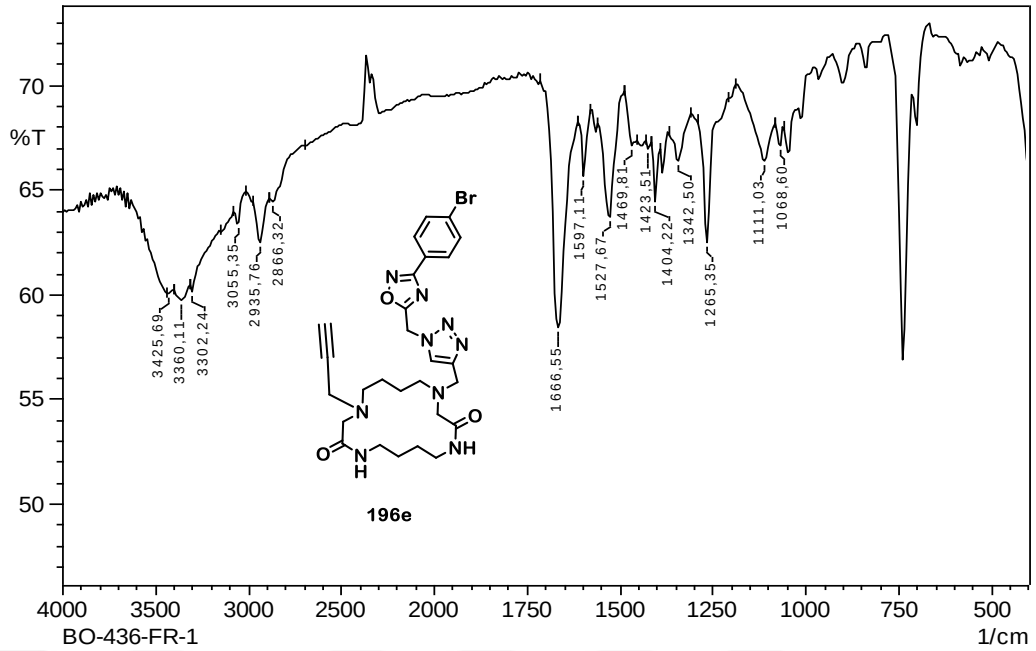

Figure 7.268. IR spectrum of compound **196e**

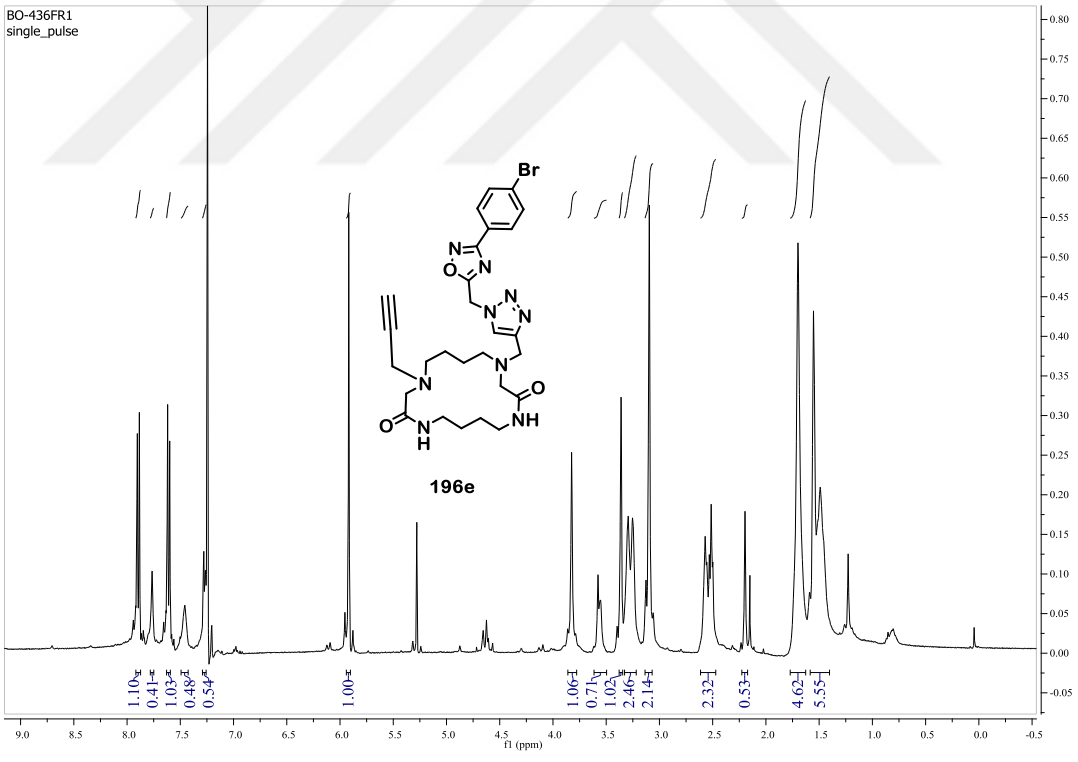

Figure 7.269. ^{1}H NMR spectrum of compound **196e**

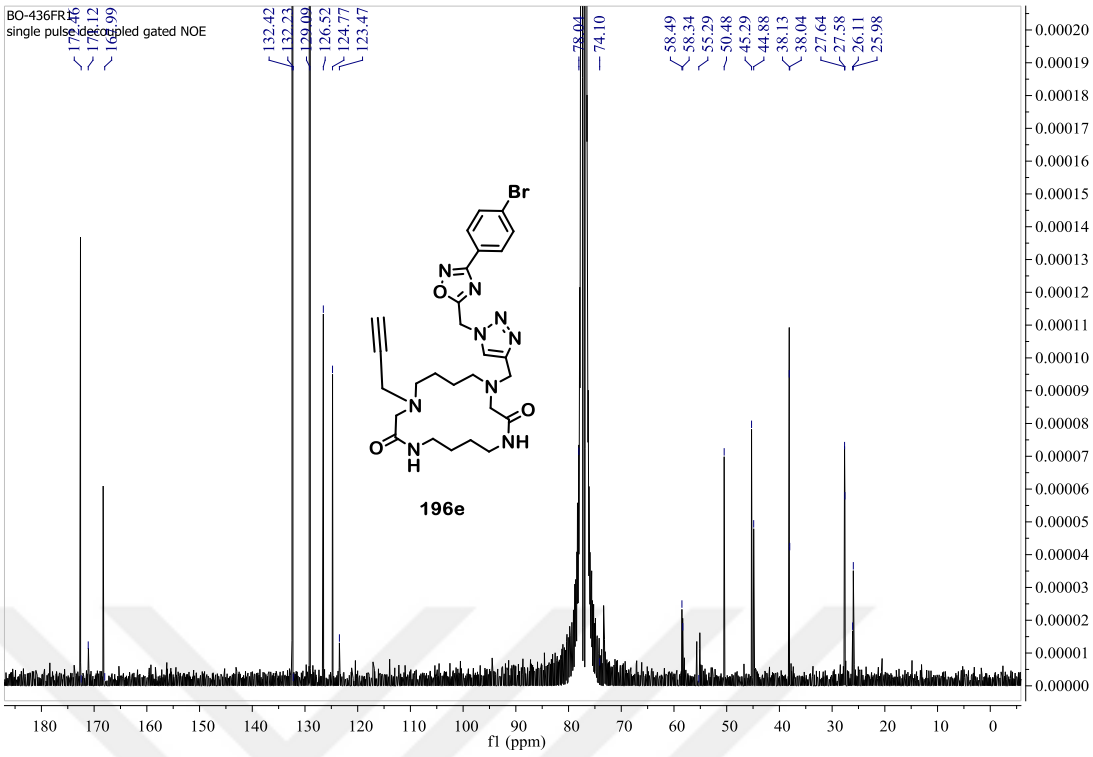

Figure 7.270. ^{13}C NMR spectrum of compound **196e**

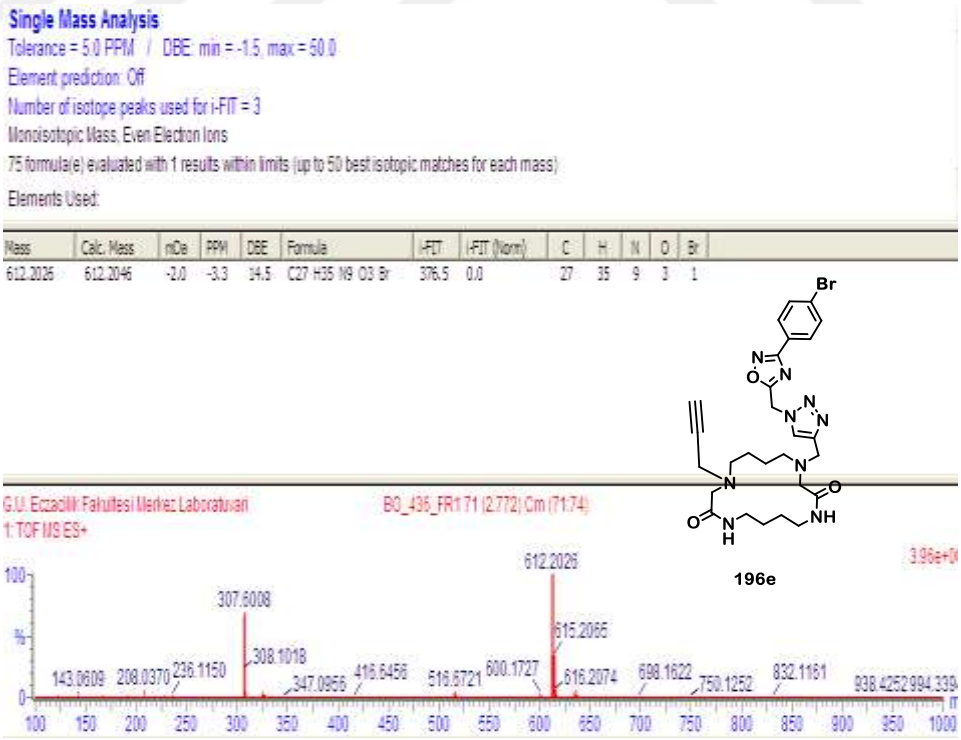

Figure 7.271. HR-MS Spectrum of compound **196c**

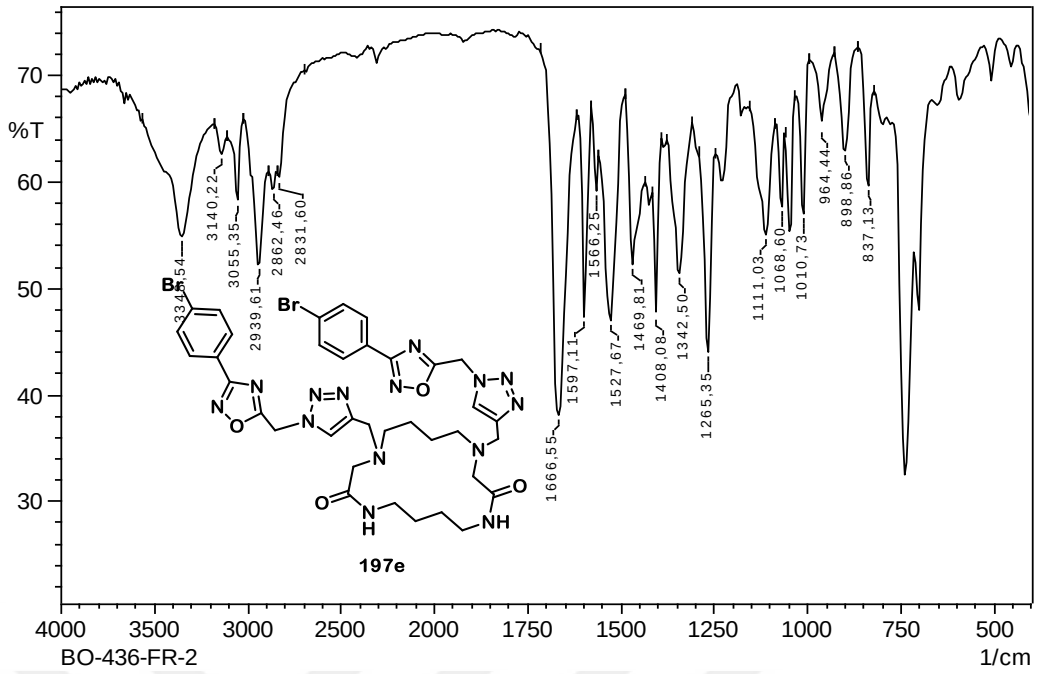

Figure 7.272. IR spectrum of compound **197e**

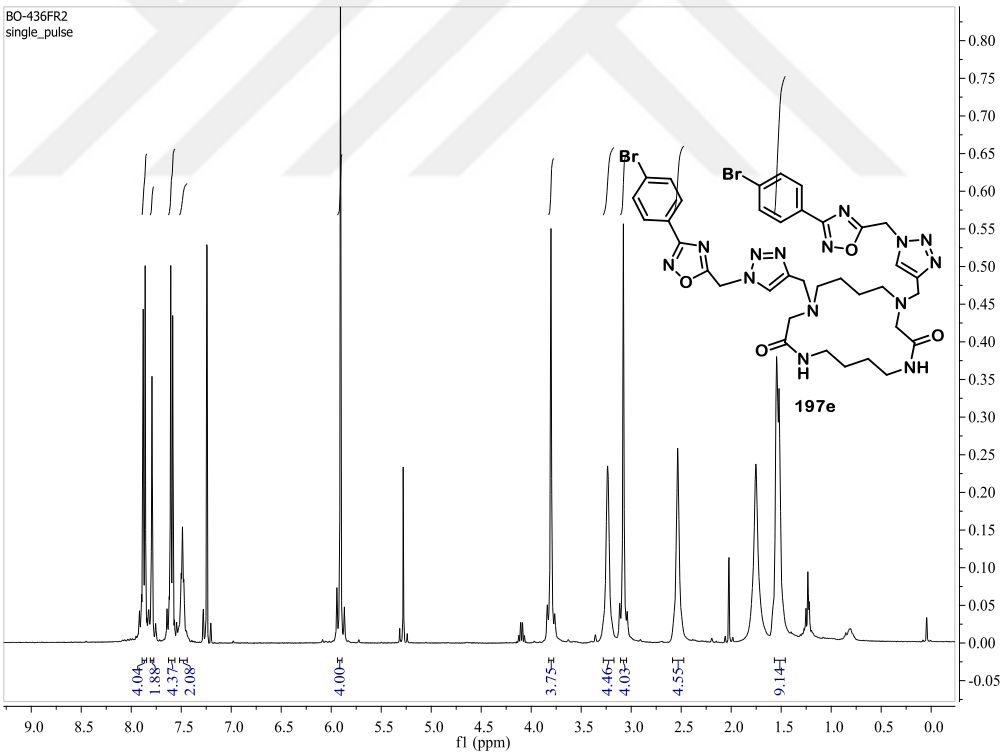

Figure 7.273. ^{1}H NMR spectrum of compound **197e**

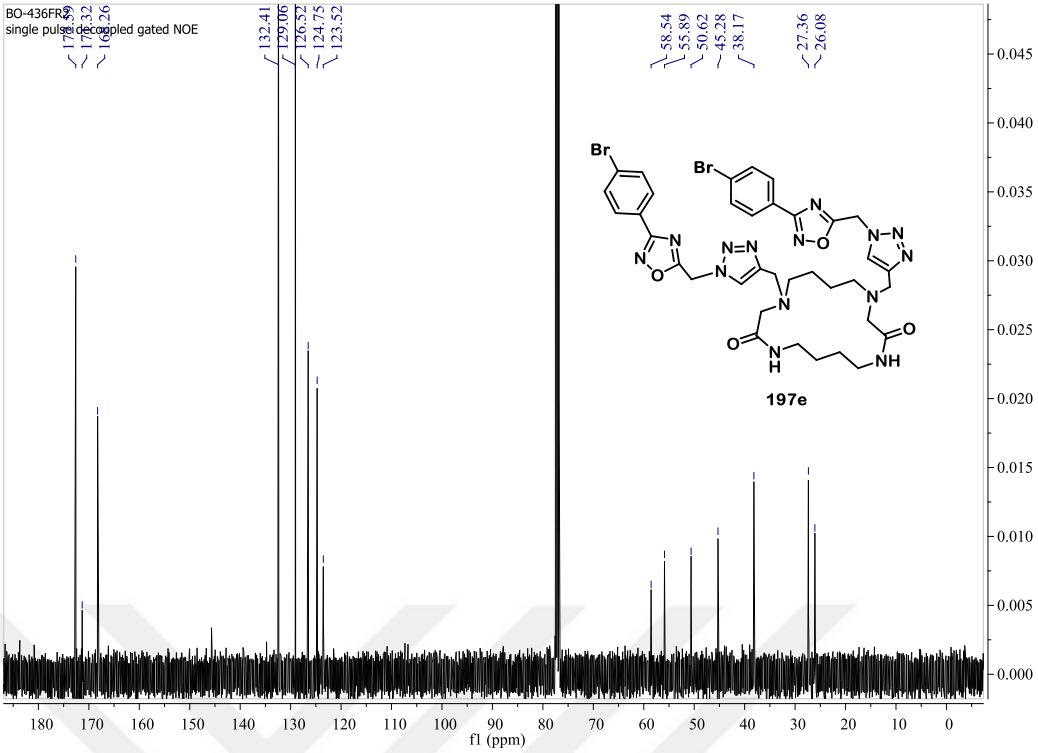

Figure 7.274. ^{13}C NMR spectrum of compound **197e**

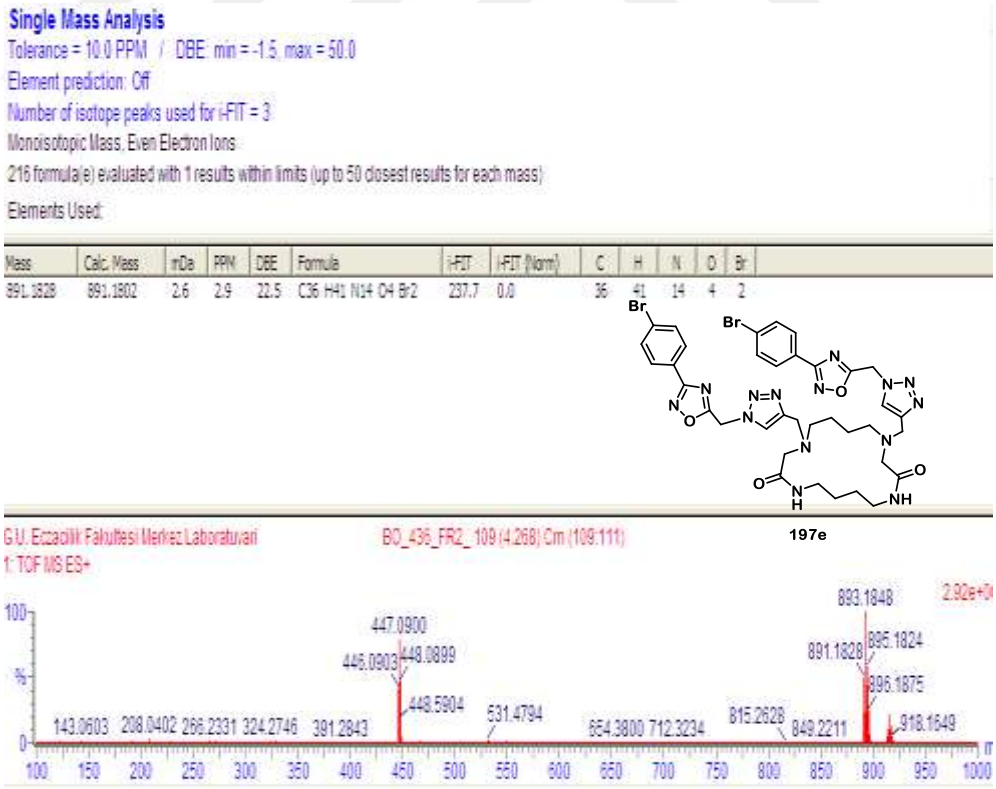

Figure 7.275. HR-MS Spectrum of compound **197e**

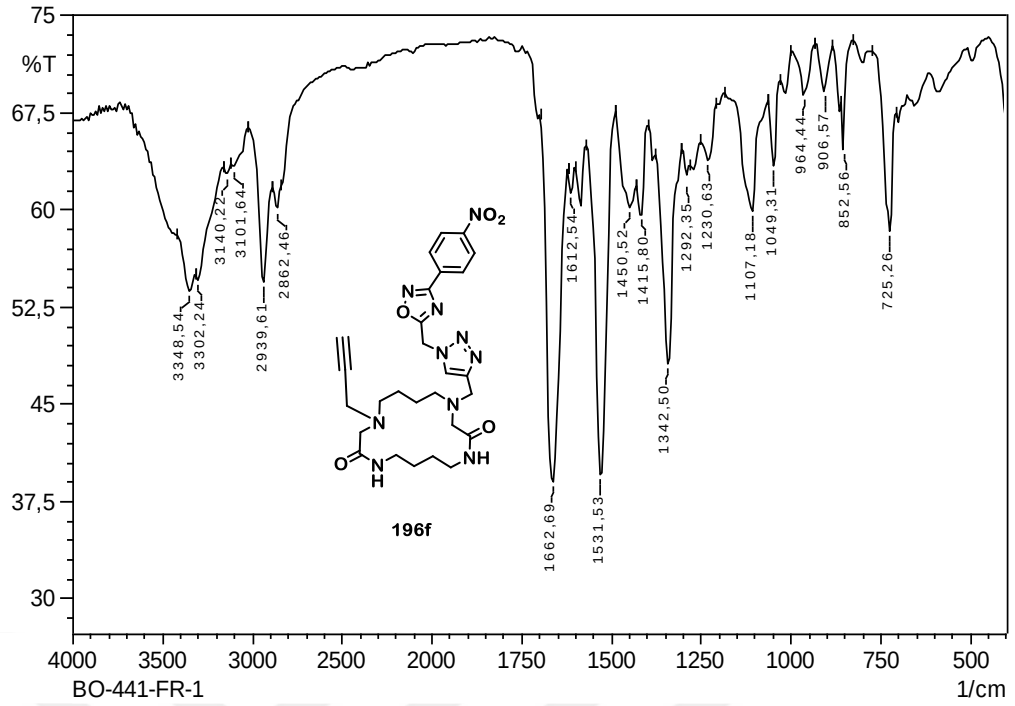

Figure 7.276. IR spectrum of compound **196f**

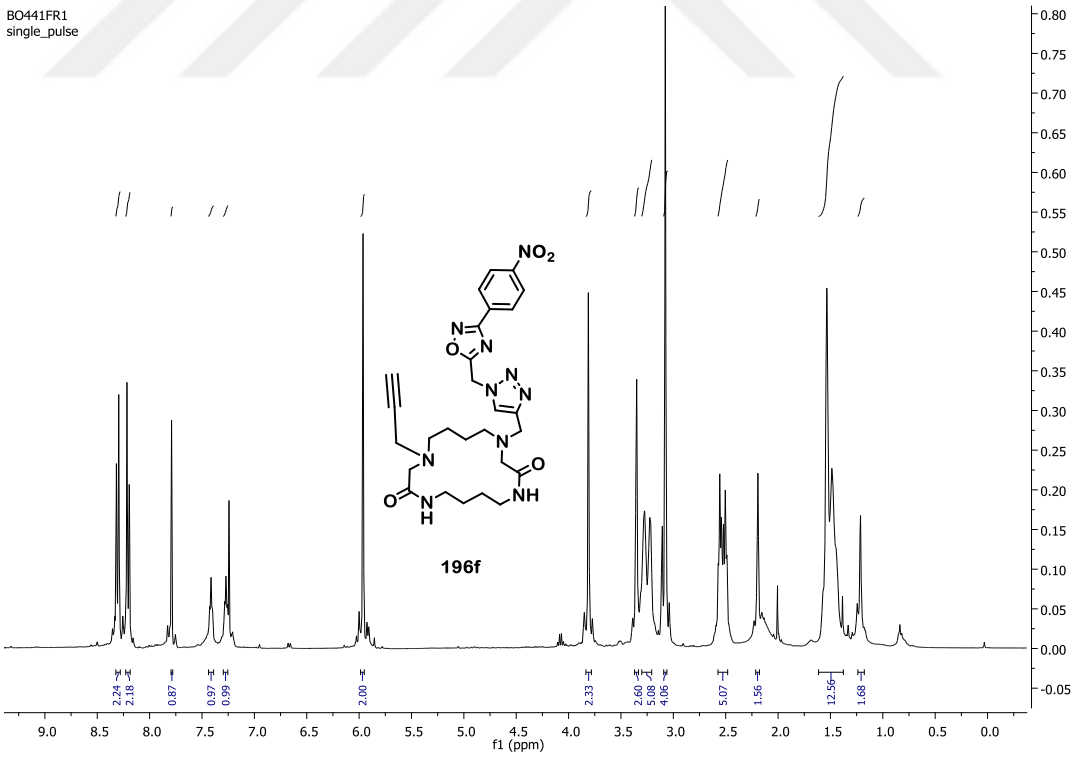

Figure 7.277. ^{1}H NMR spectrum of compound **196f**

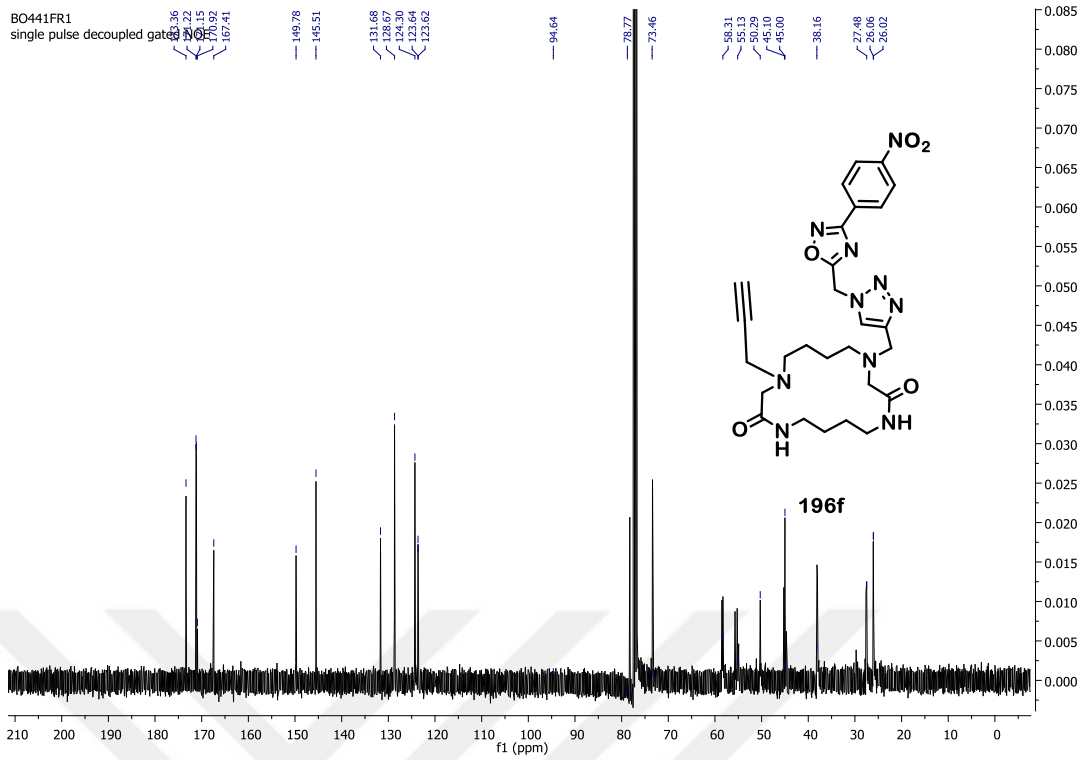

Figure 7.278. ^{13}C NMR spectrum of compound **196f**

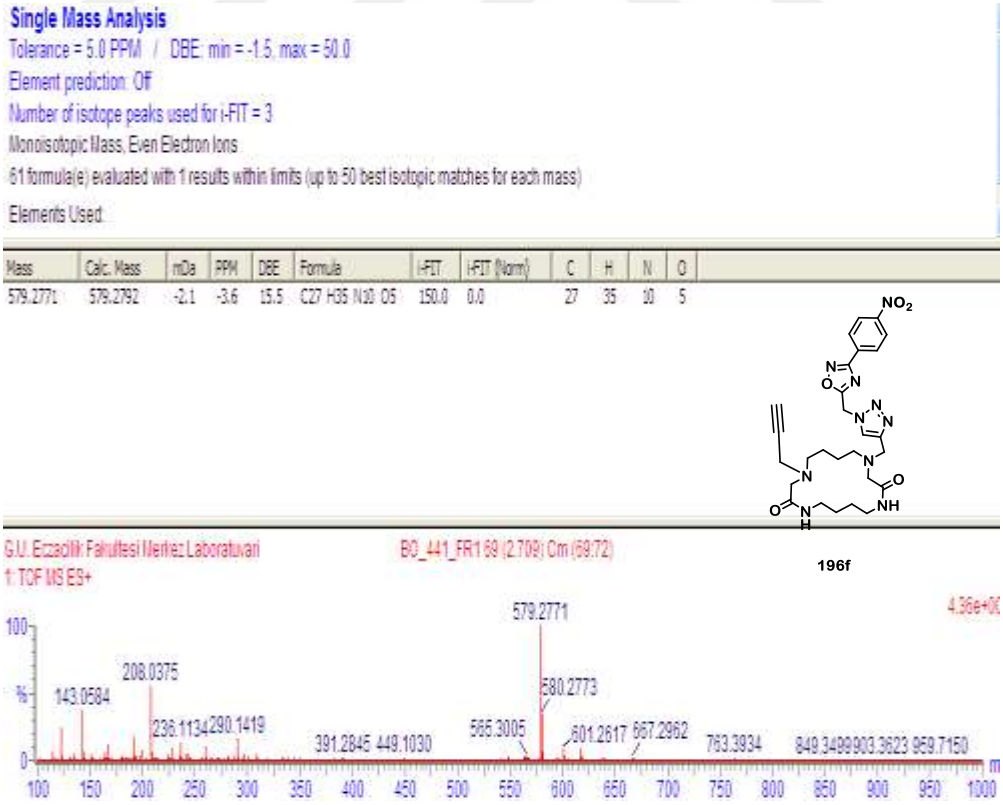

Figure 7.279. HR-MS Spectrum of compound **196f**

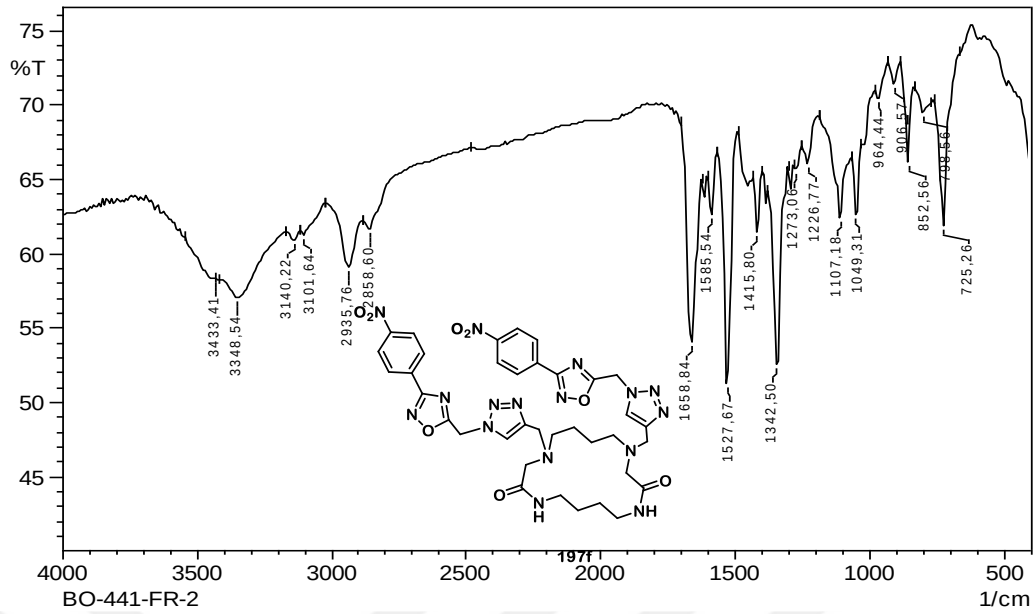

Figure 7.280. IR spectrum of compound **197f**

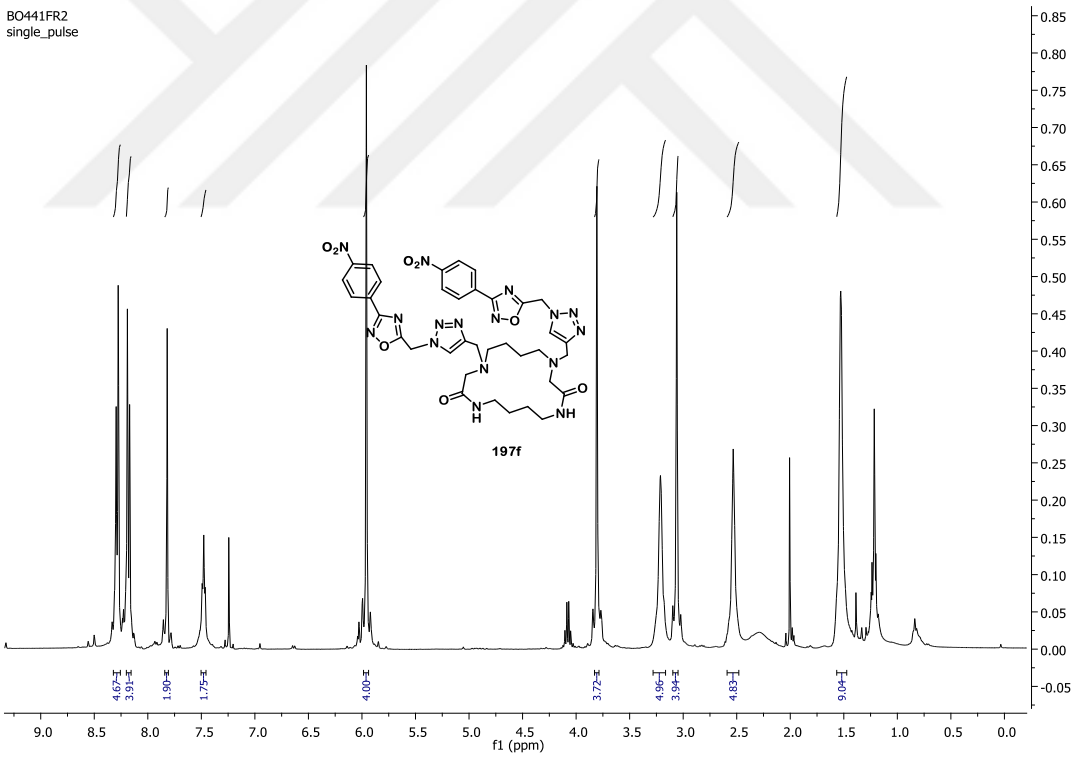

Figure 7.281. ^{1}H NMR spectrum of compound **197f**

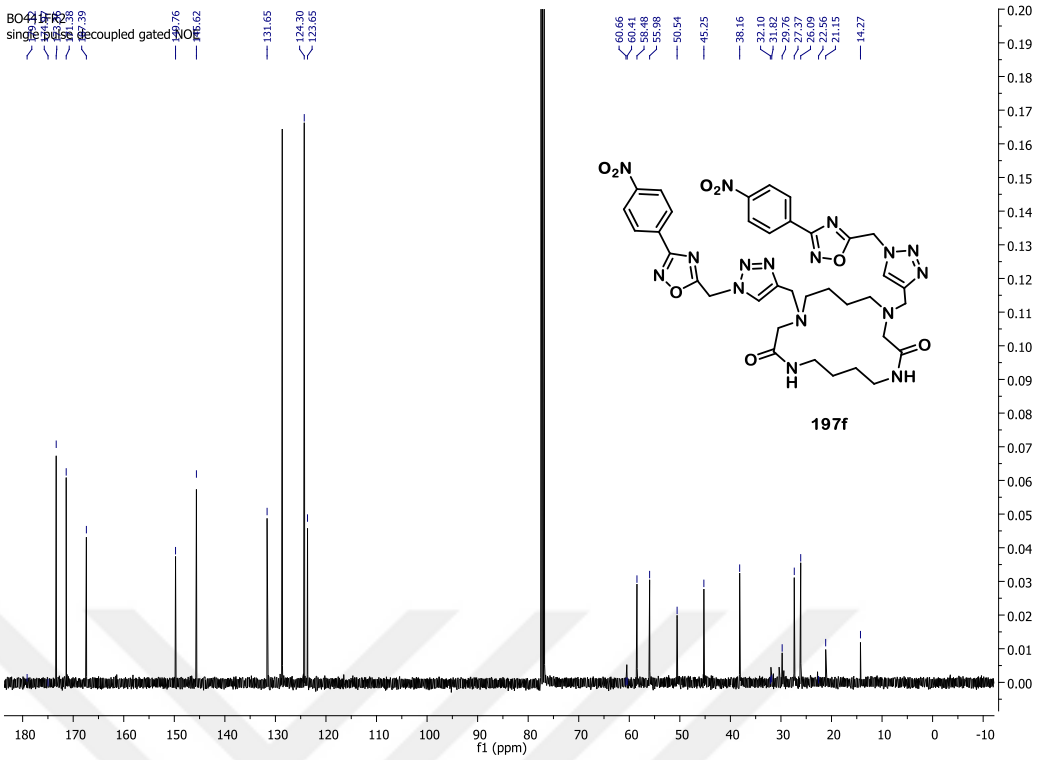

Figure 7.282. ^{13}C NMR spectrum of compound **197f**

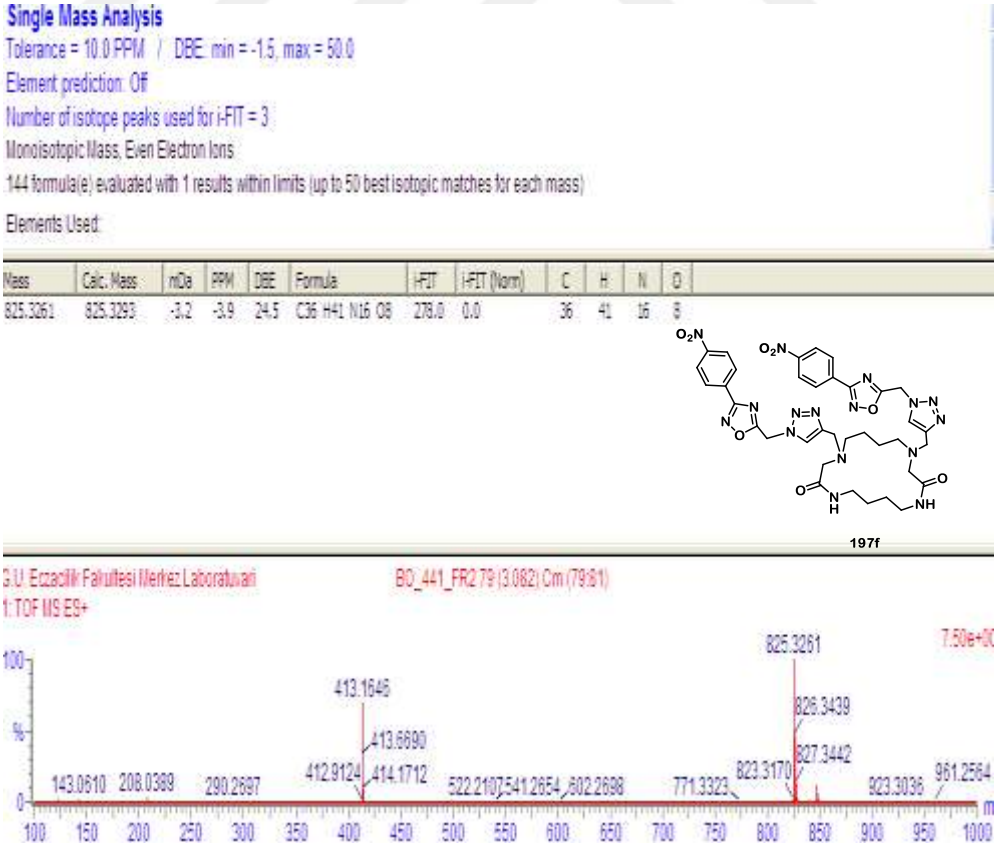

Figure 7.283. HR-MS Spectrum of compound **197f**

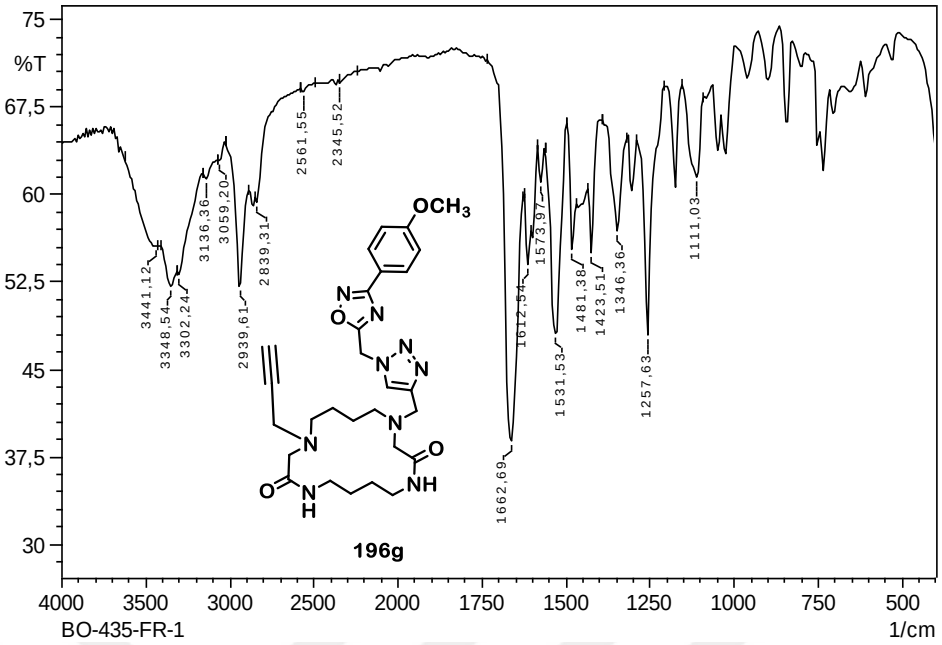

Figure 7.284. IR spectrum of compound **196g**

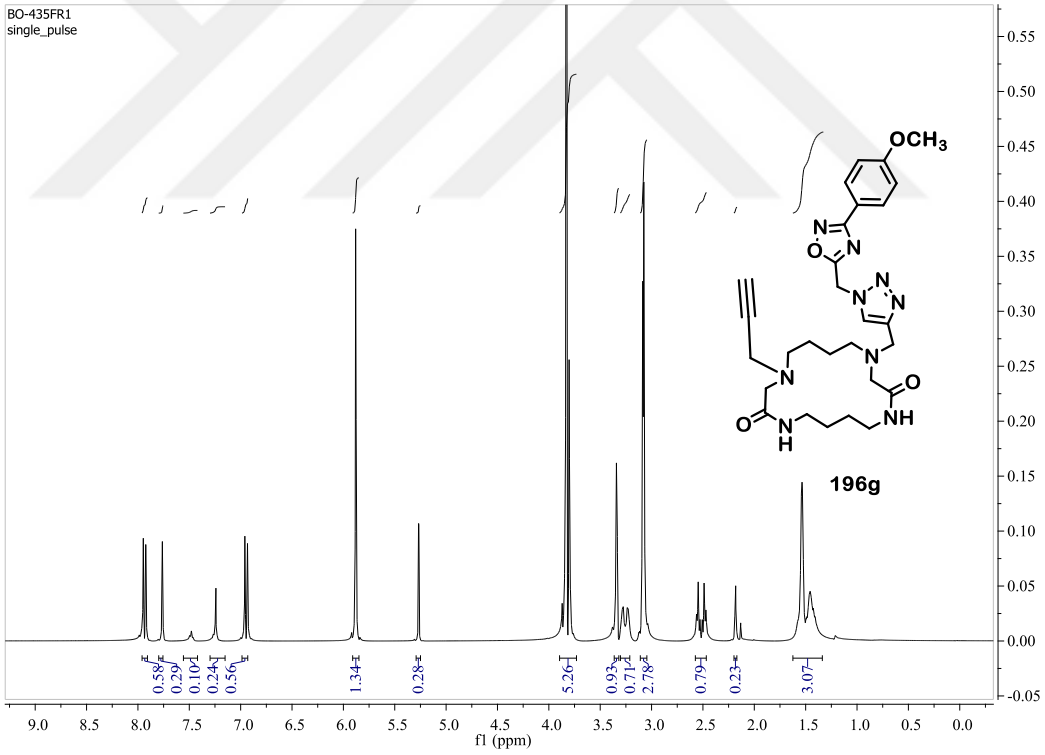

Figure 7.285. ^{1}H NMR spectrum of compound **196g**

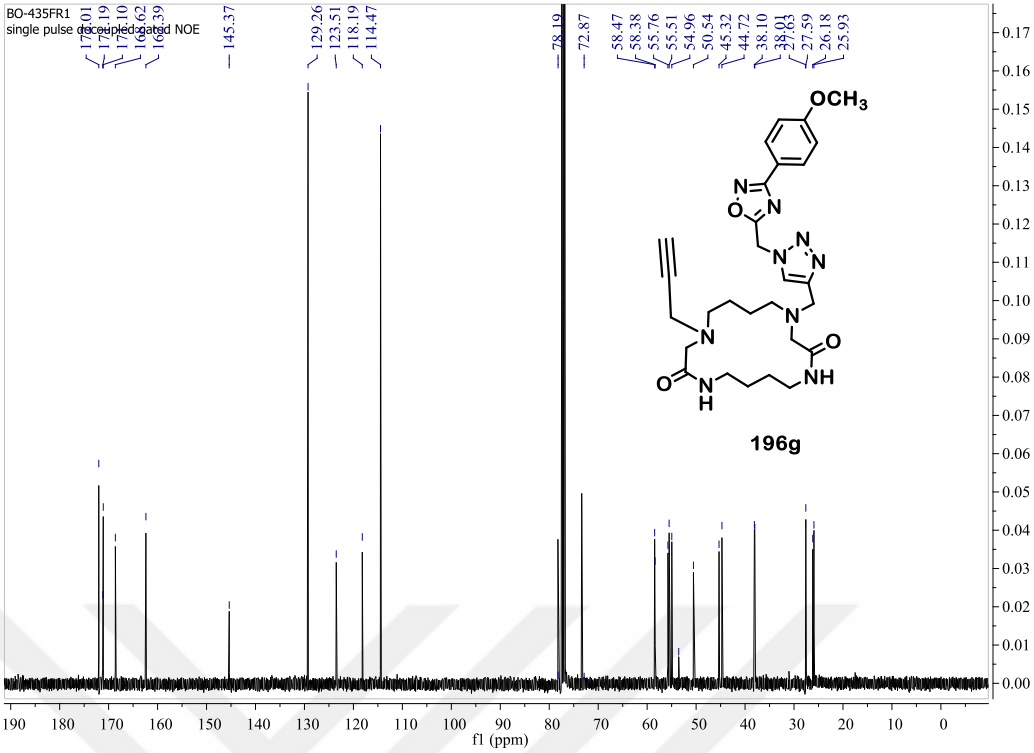

Figure 7.286. ^{13}C NMR spectrum of compound **196g**

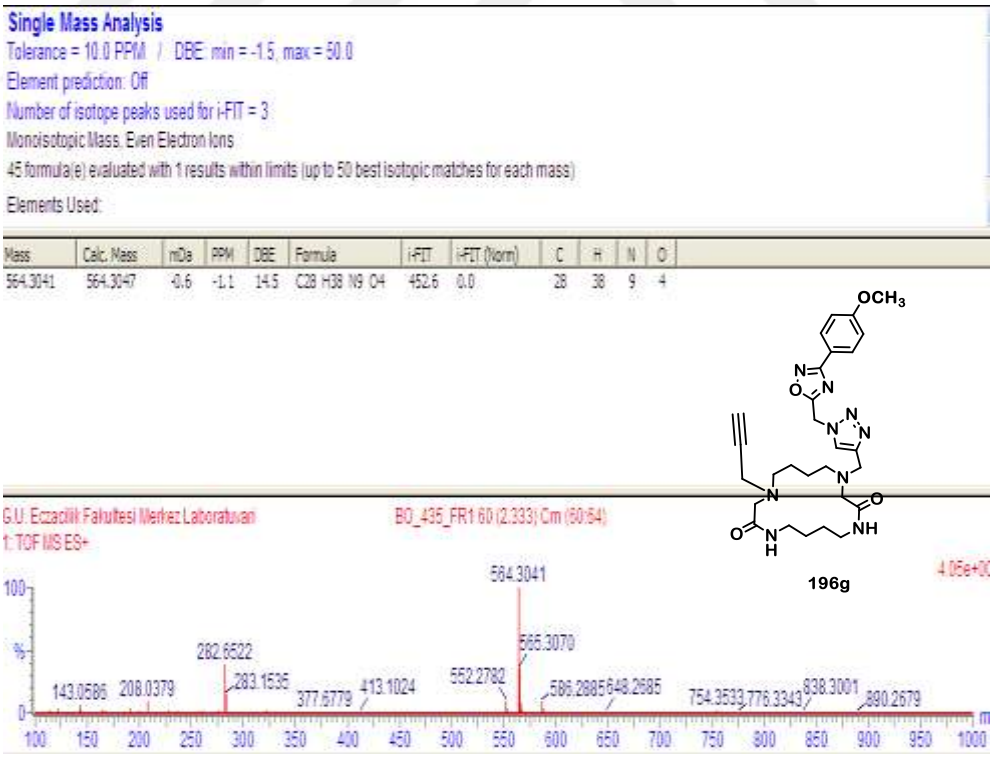

Figure 7.287. HR-MS Spectrum of compound **196g**

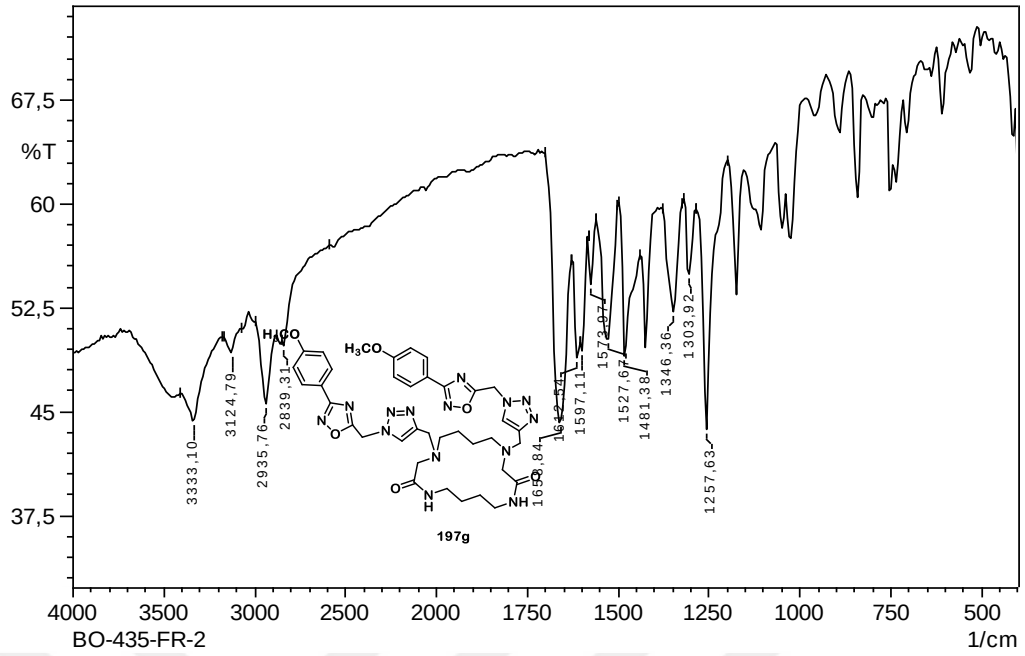

Figure 7.288. IR spectrum of compound **197g**

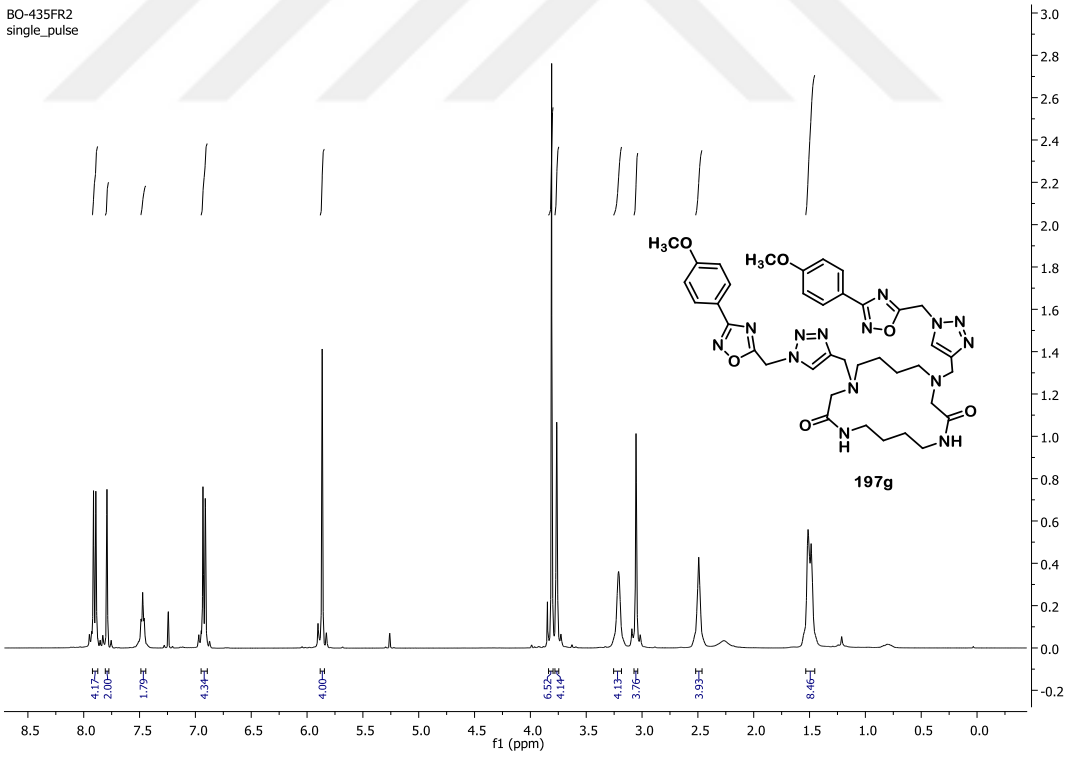

Figure 7.289. ^{1}H NMR spectrum of compound **197g**

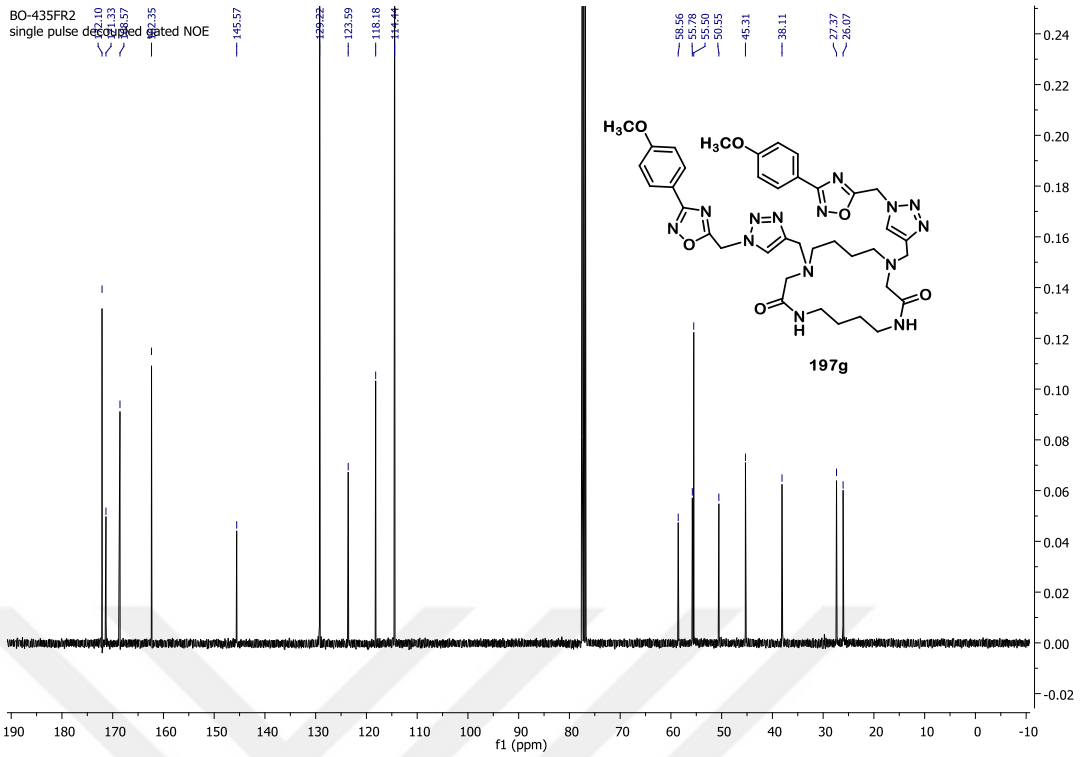

Figure 7.290. ^{13}C NMR spectrum of compound **197g**

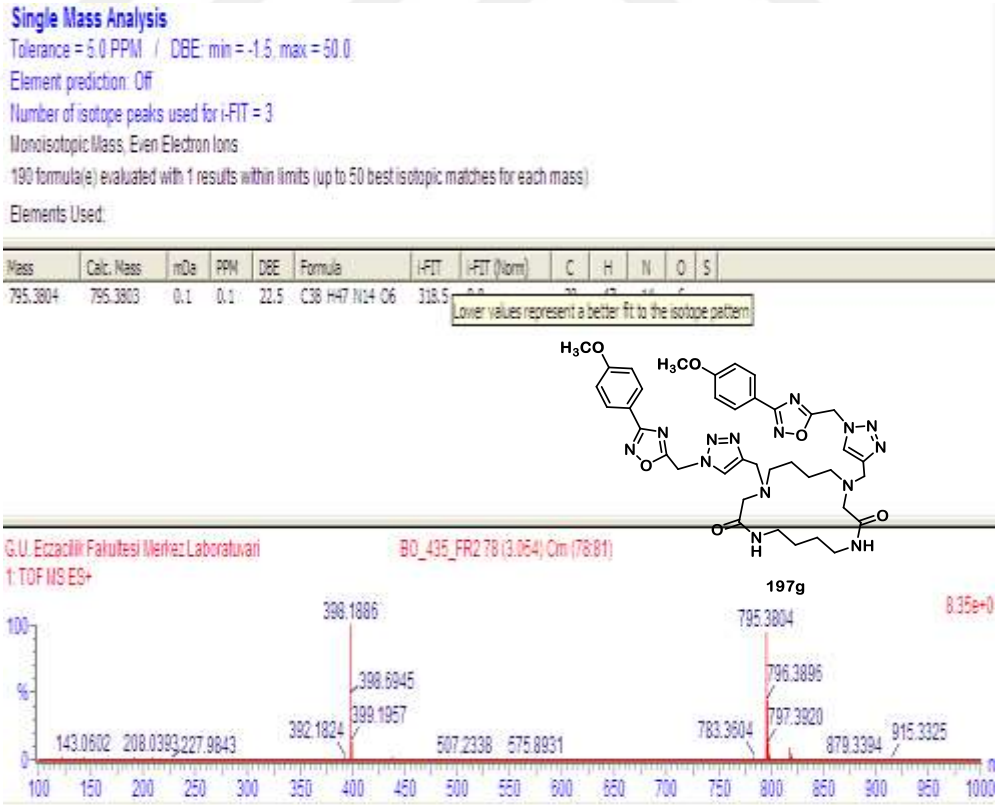

Figure 7.291. HR-MS Spectrum of compound **197g**

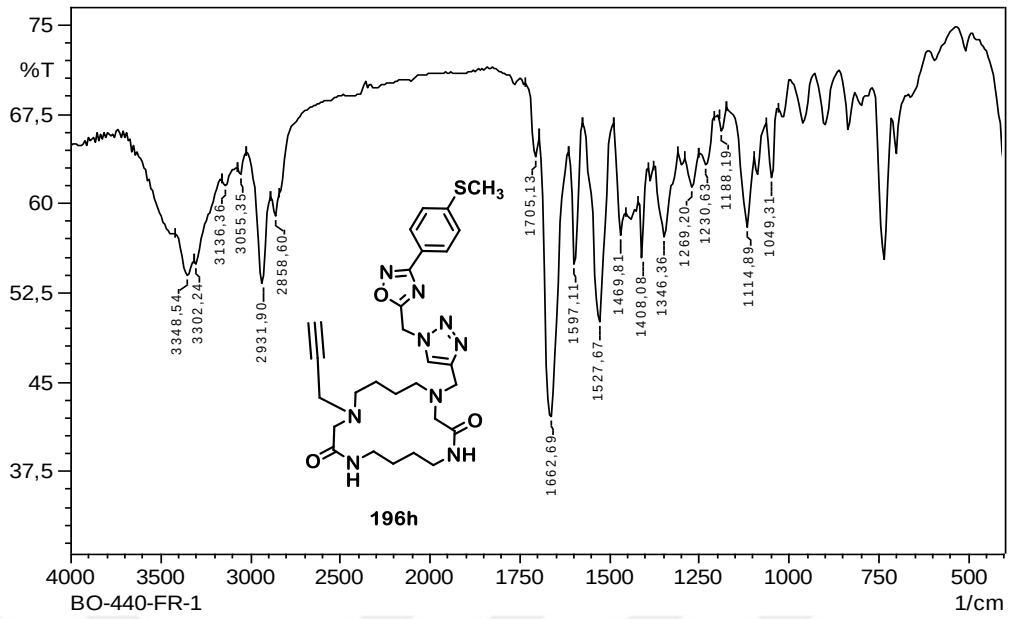

Figure 7.292. IR spectrum of compound **196h**

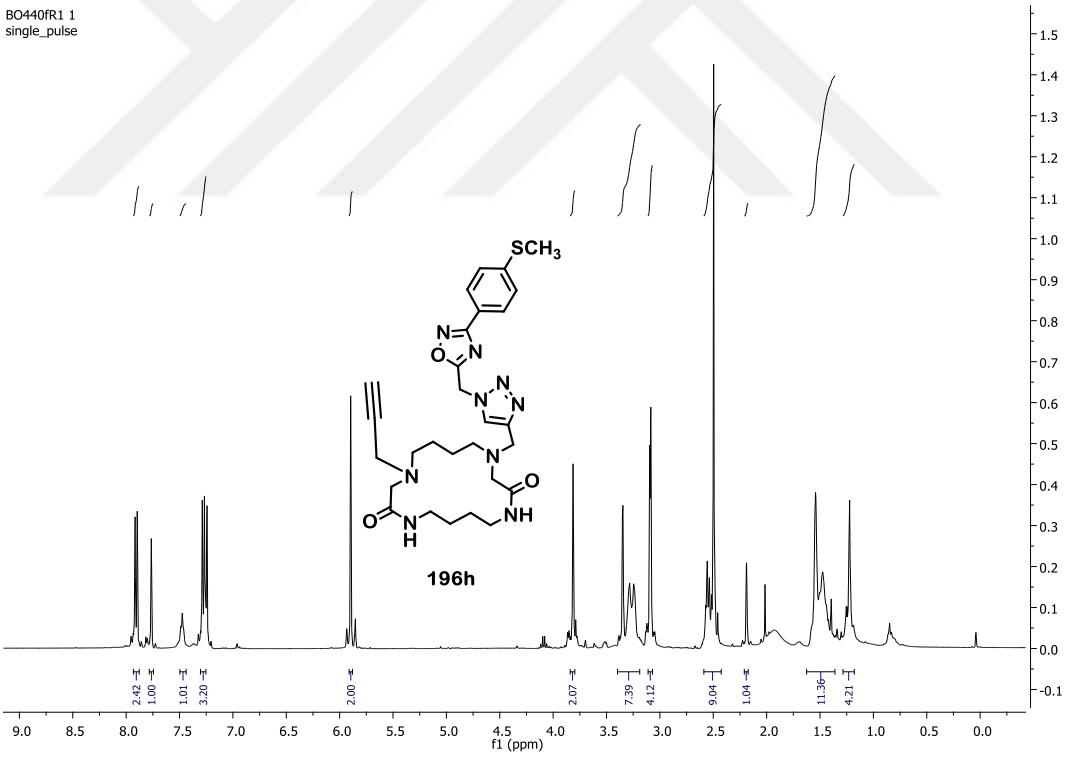

Figure 7.293. ^{1}H NMR spectrum of compound **196h**

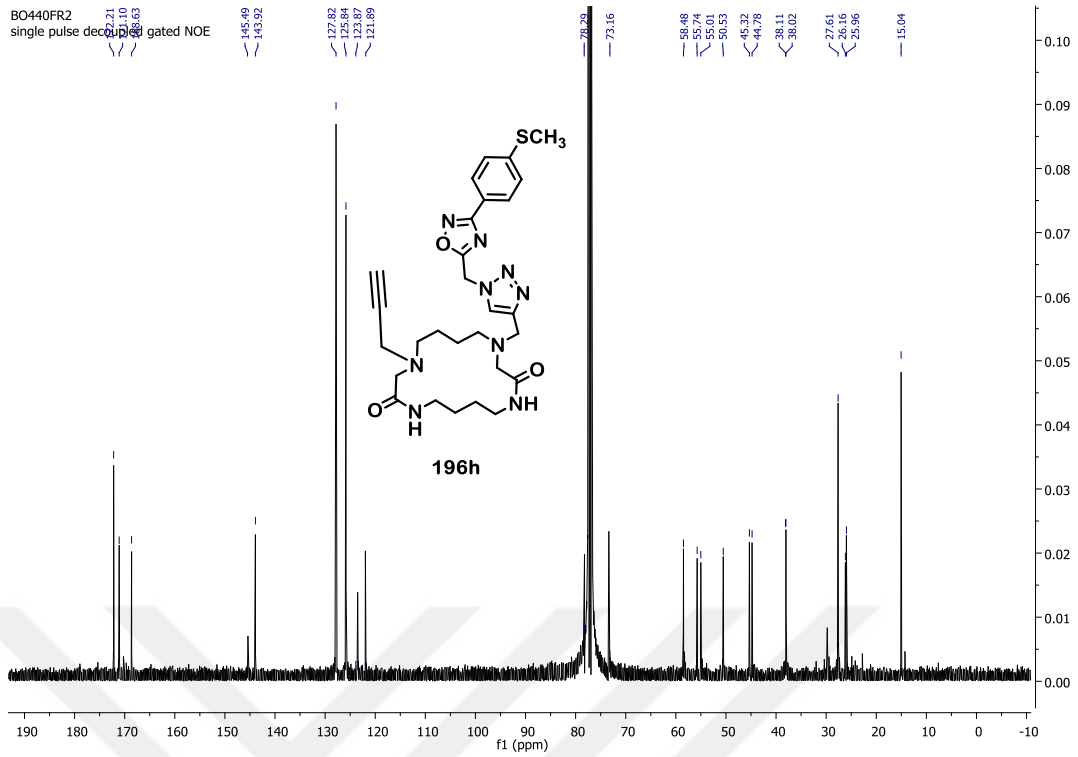

Figure 7.294. ^{13}C NMR spectrum of compound **196h**

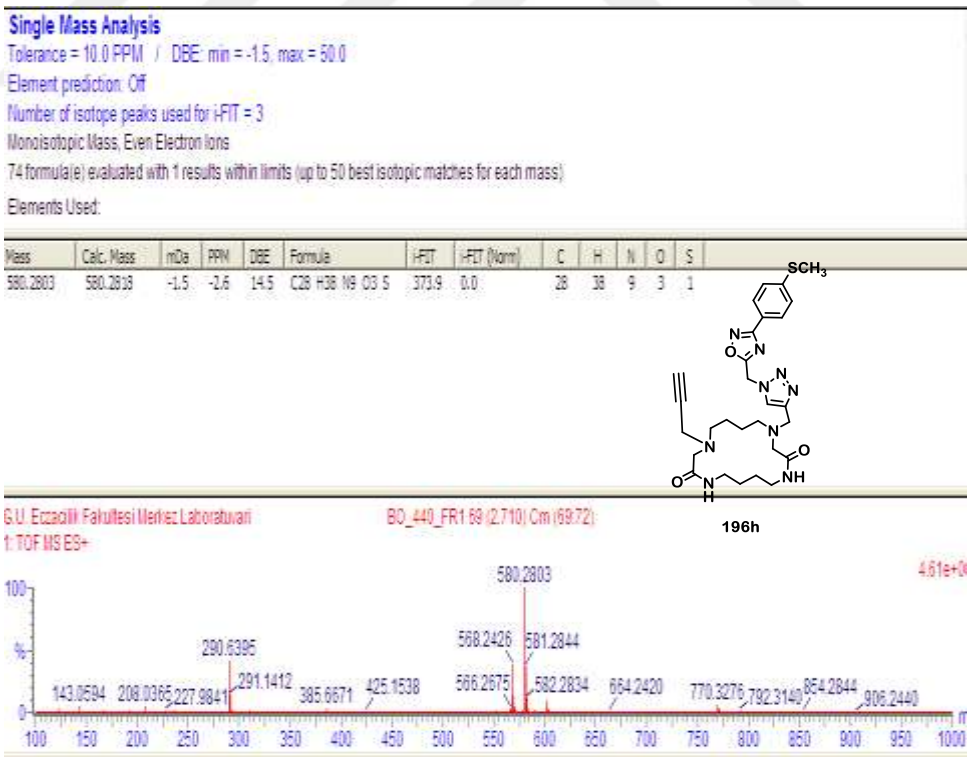

Figure 7.295. HR-MS Spectrum of compound **196h**

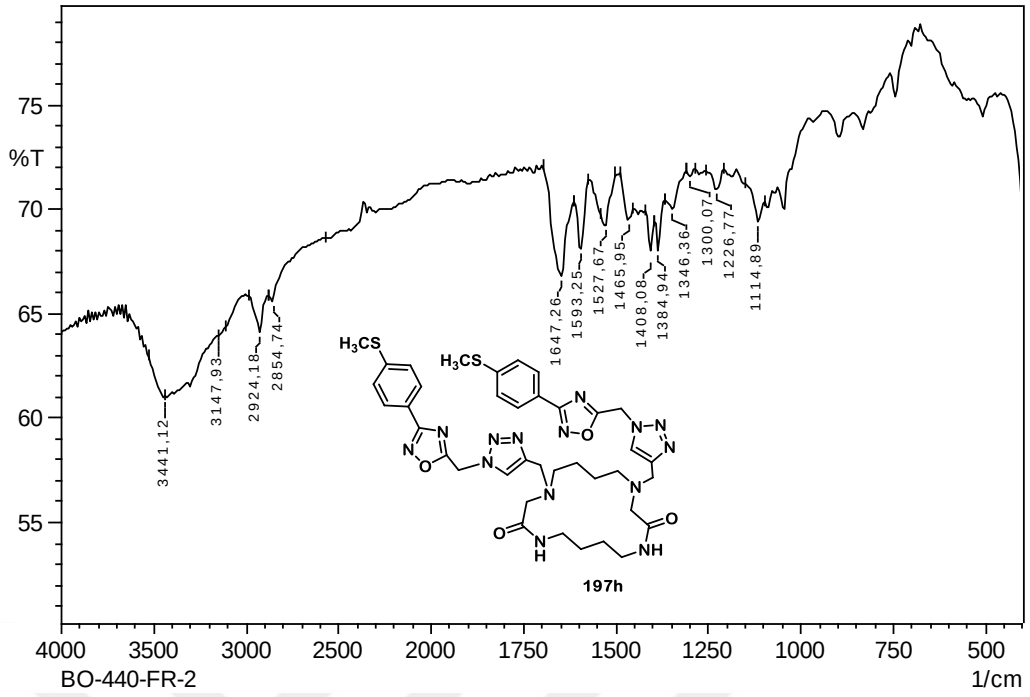

Figure 7.296. IR spectrum of compound **197h**

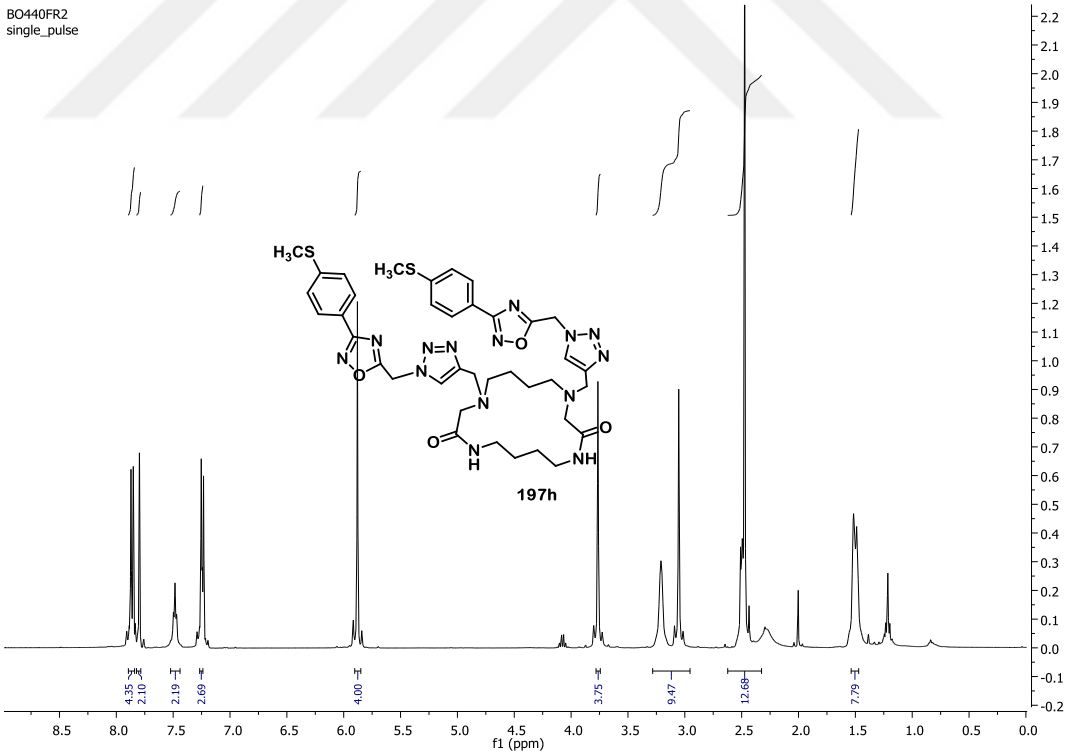

Figure 7.297. ^{1}H NMR spectrum of compound **197h**

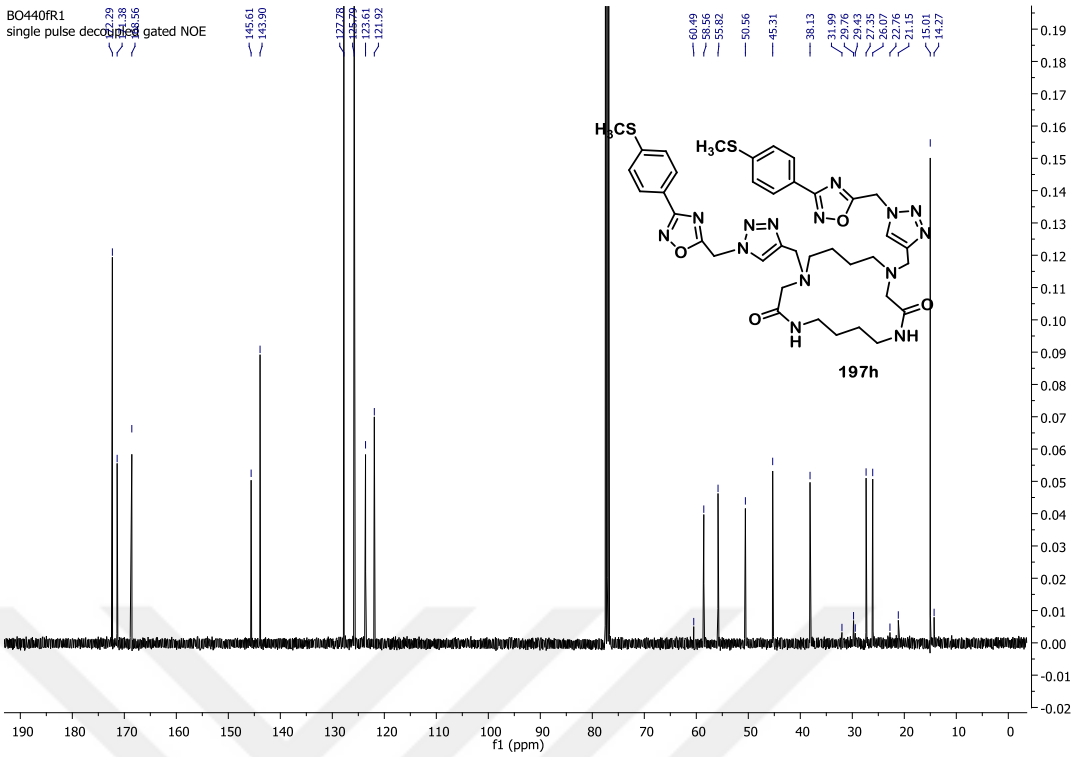

Figure 7.298. ^{13}C NMR spectrum of compound **197h**

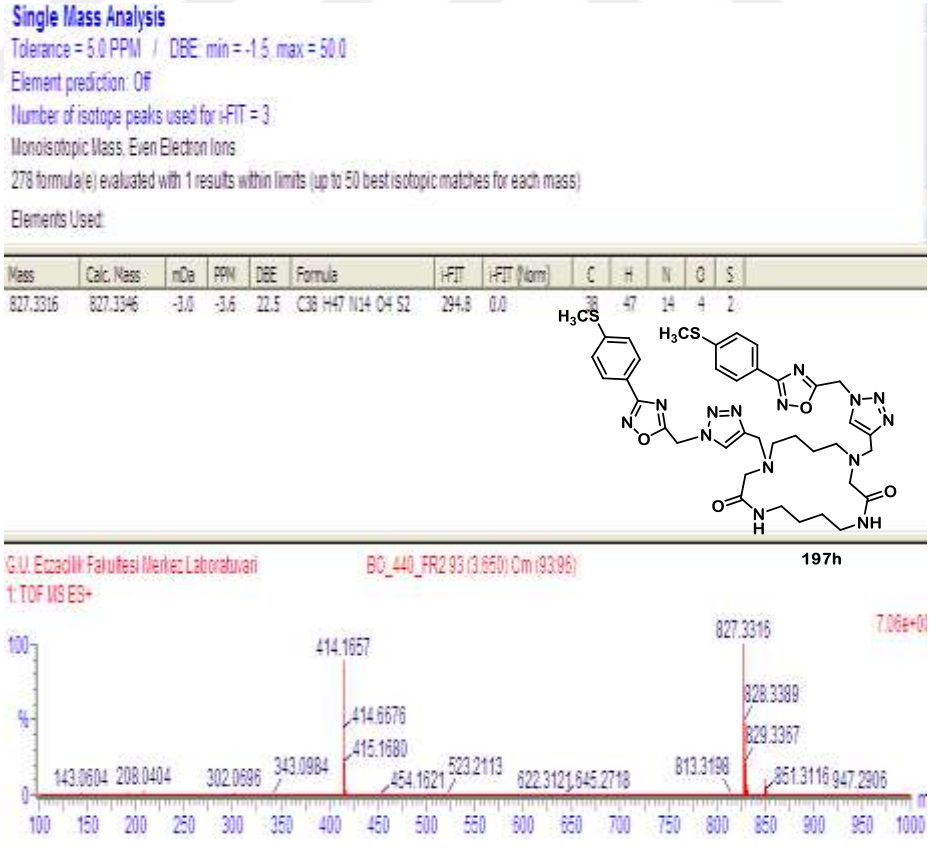

Figure 7.299. HR-MS Spectrum of compound **197h**

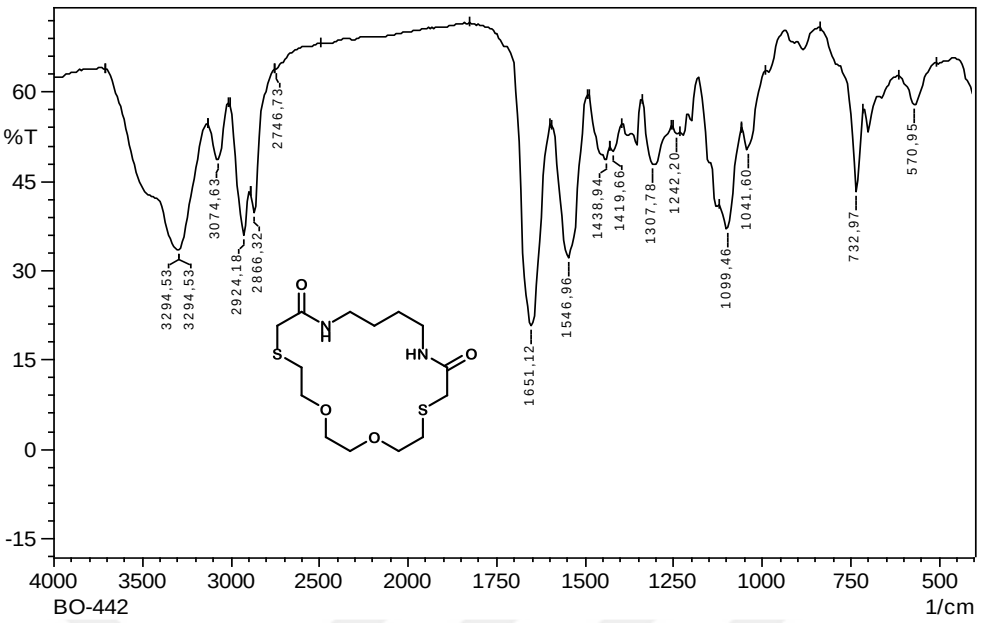

Figure 7.300. IR spectrum of compound **199**

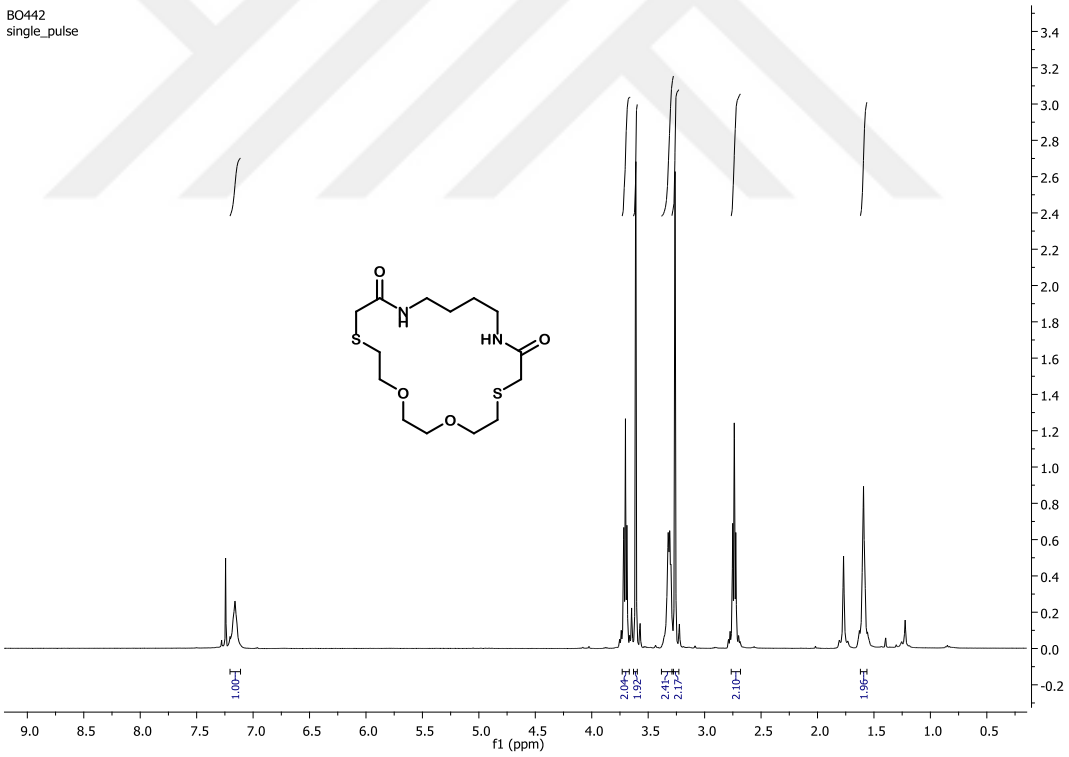

Figure 7.301. ^{1}H NMR spectrum of compound **199**

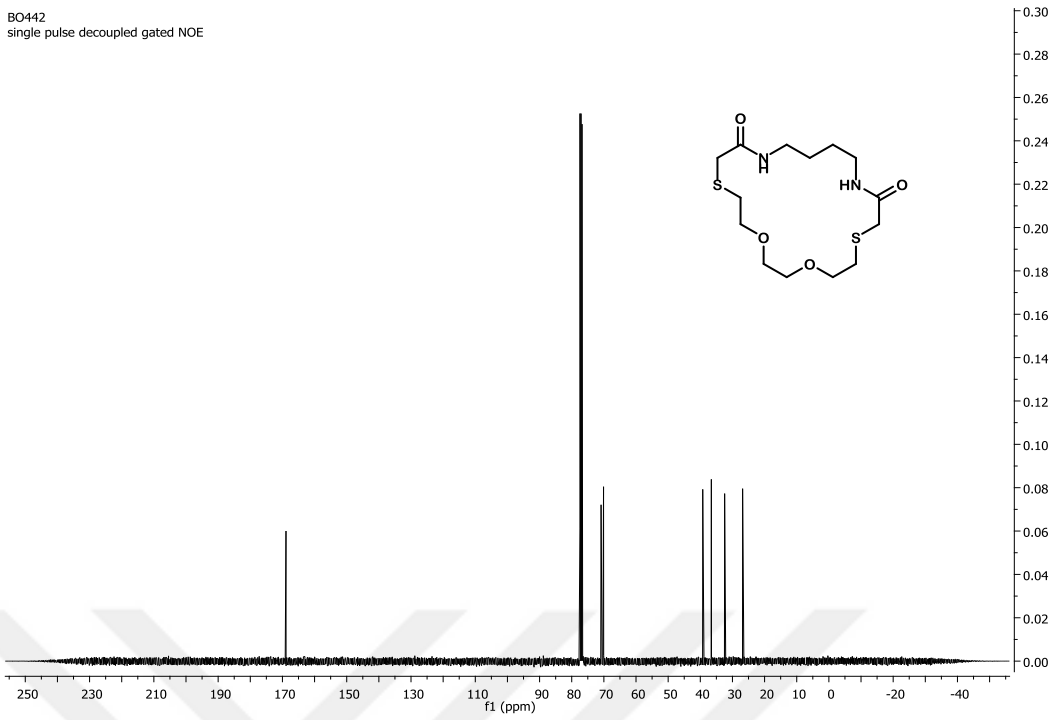

Figure 7.302. ^{13}C NMR spectrum of compound **199**

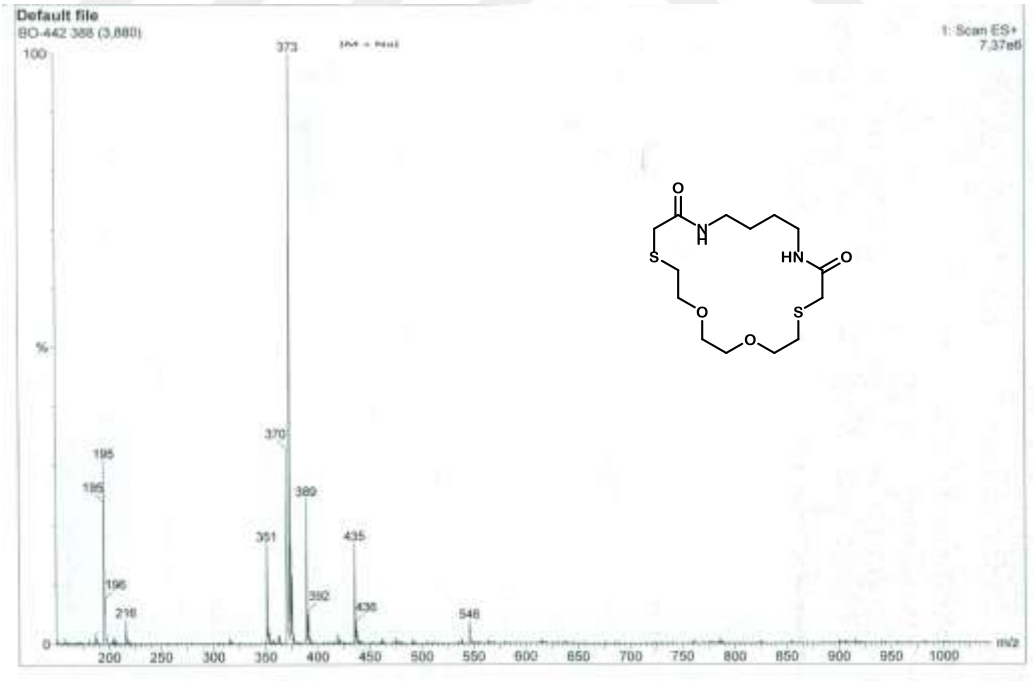

Figure 7.303. LC-MS Spectrum of compound **199**

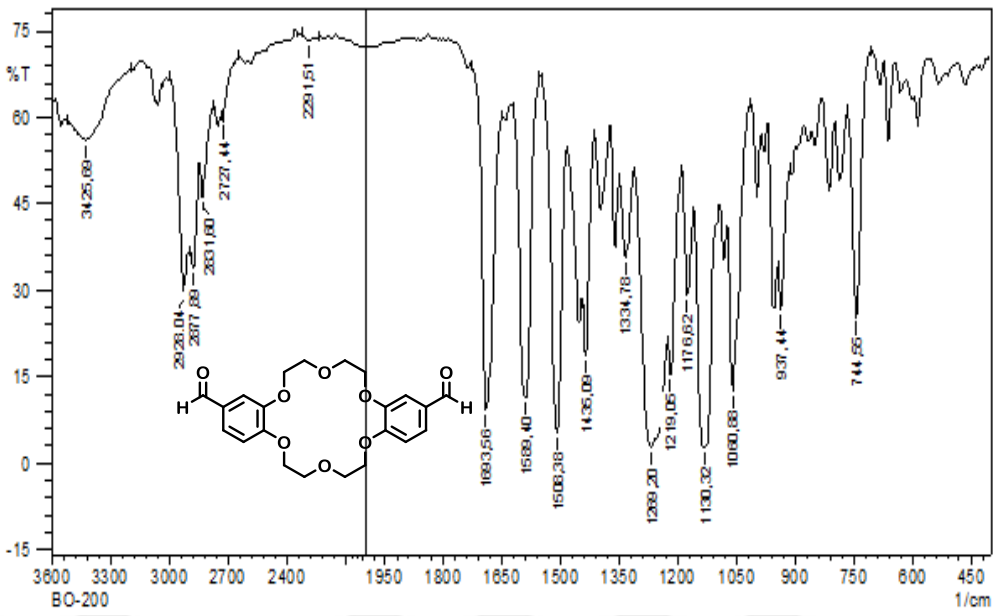

Figure 7.304. IR spectrum of compound **25**

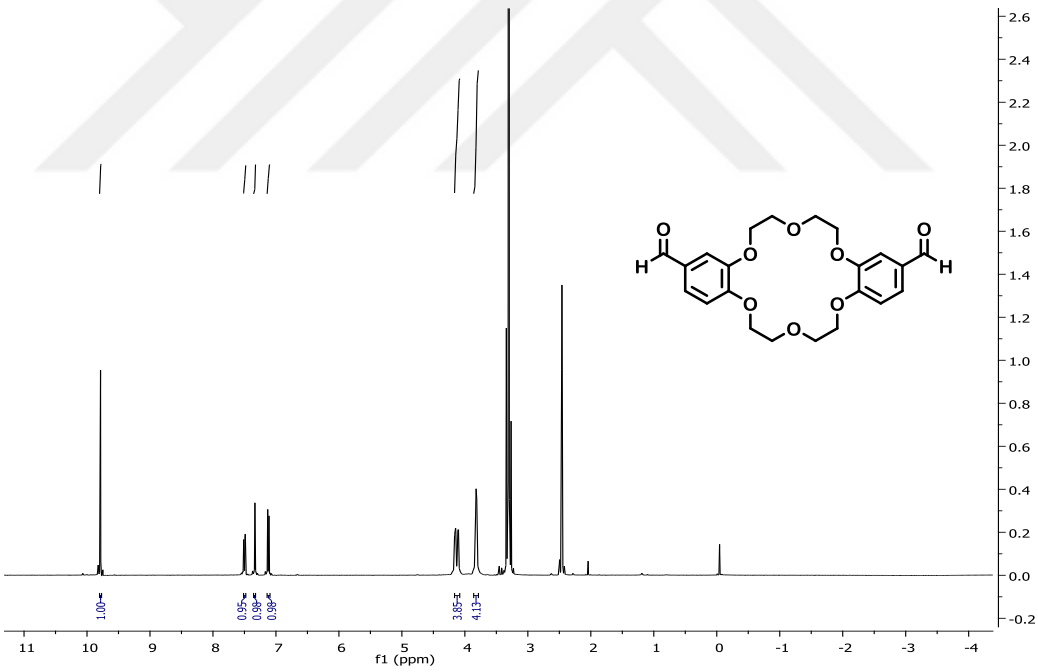

Figure 7.305. ^{1}H NMR spectrum of compound **25**

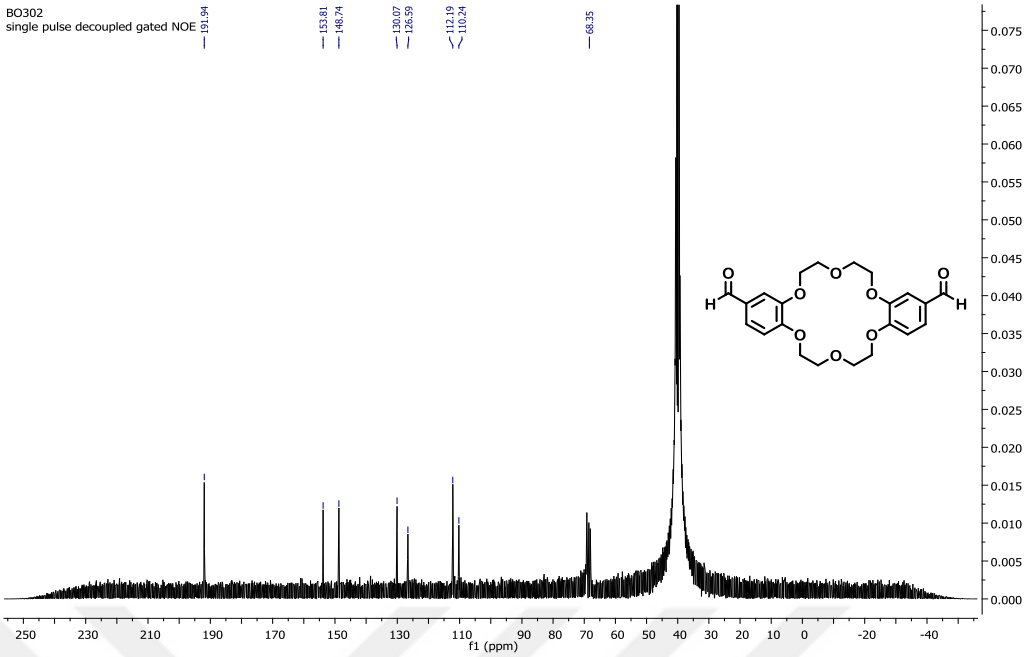

Figure 7.306. ^{13}C NMR spectrum of compound **25**

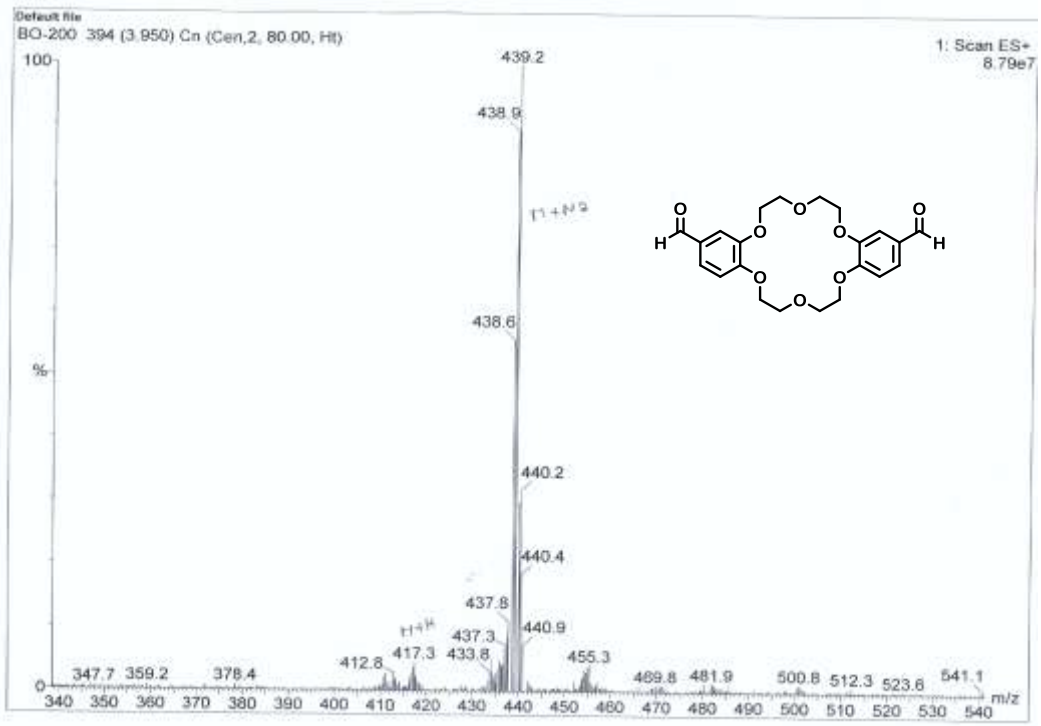

Figure 7.307. LC-MS Spectrum of compound **25**

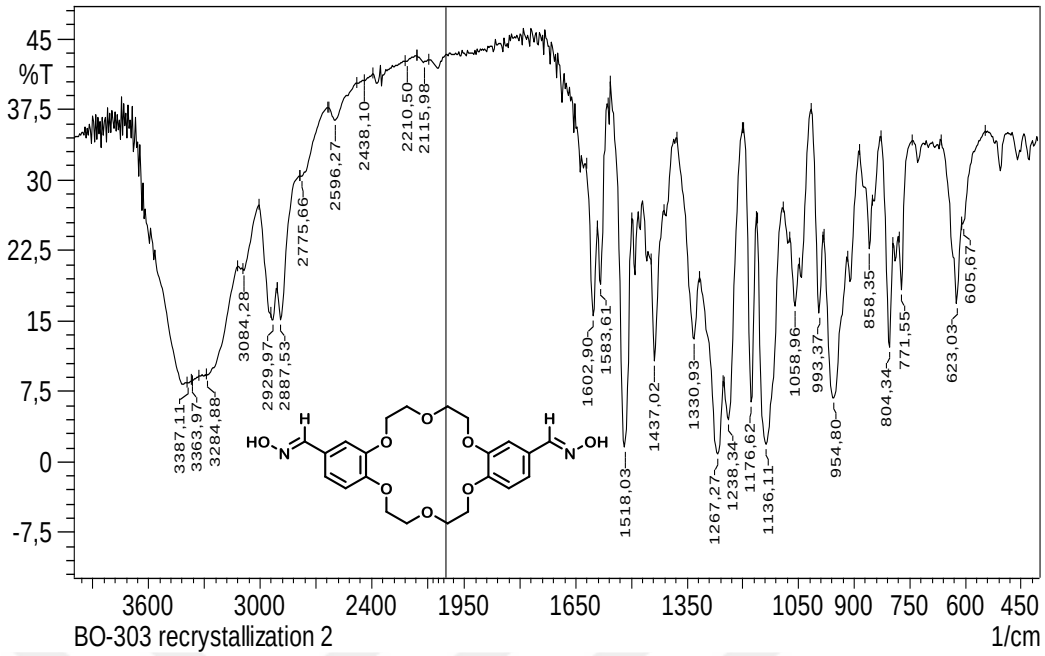

Figure 7.308. IR spectrum of compound **200**

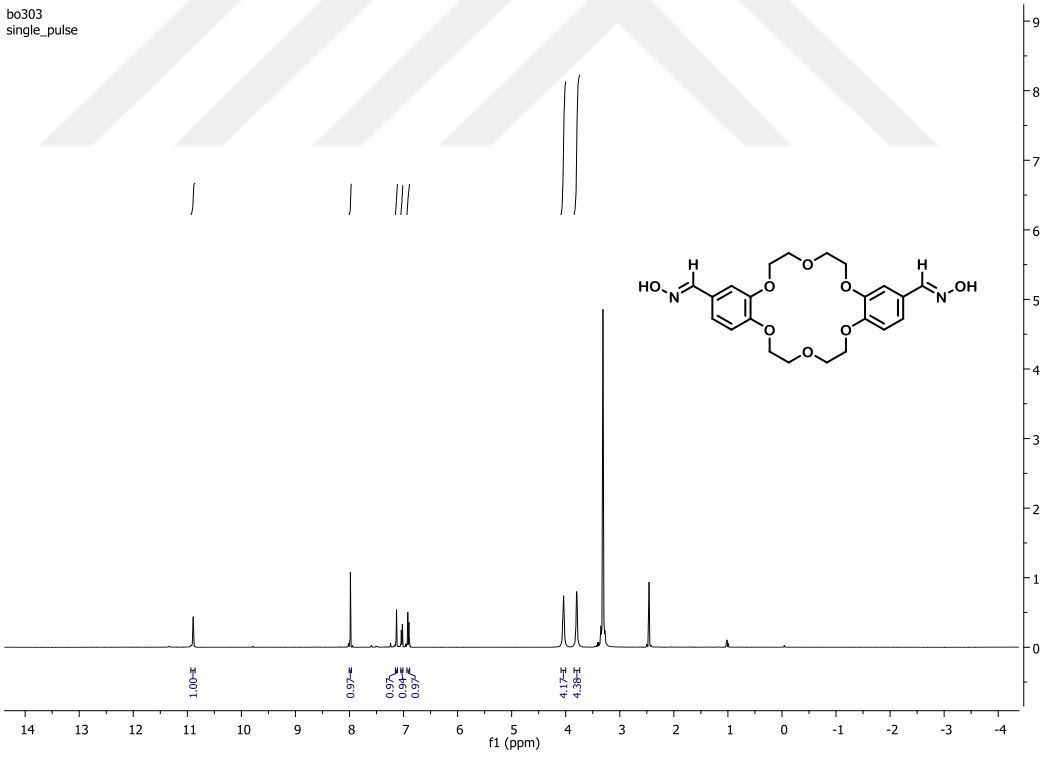

Figure 7.309. ^{1}H NMR spectrum of compound **200**

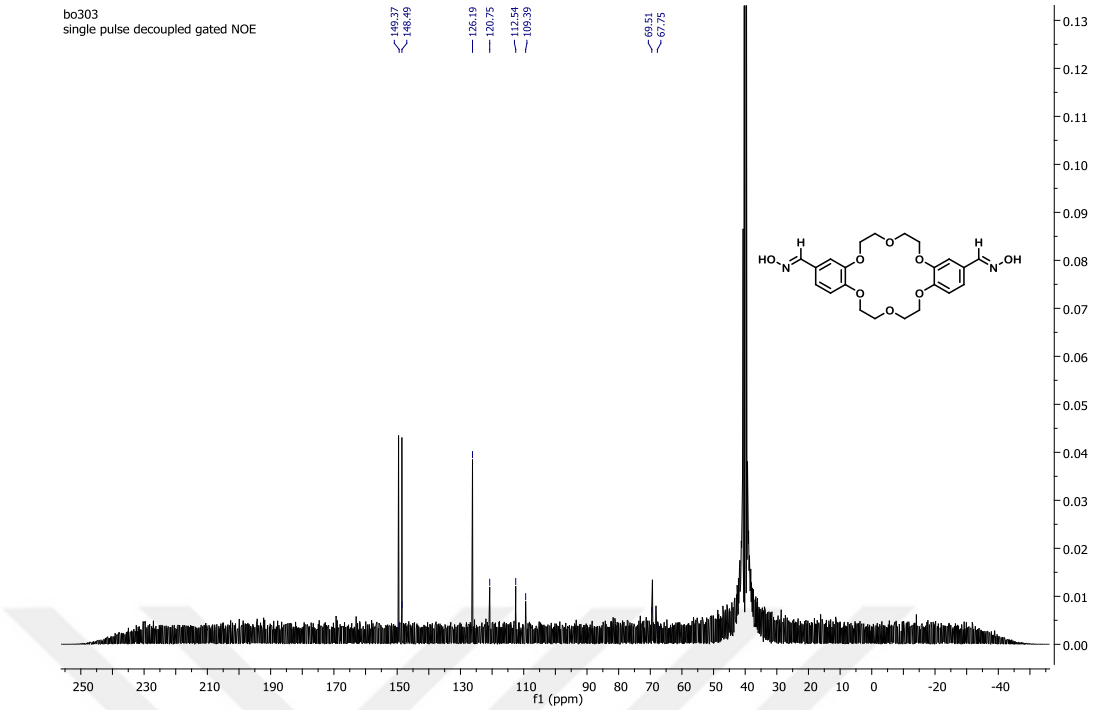

Figure 7.310. ^{13}C NMR spectrum of compound **200**

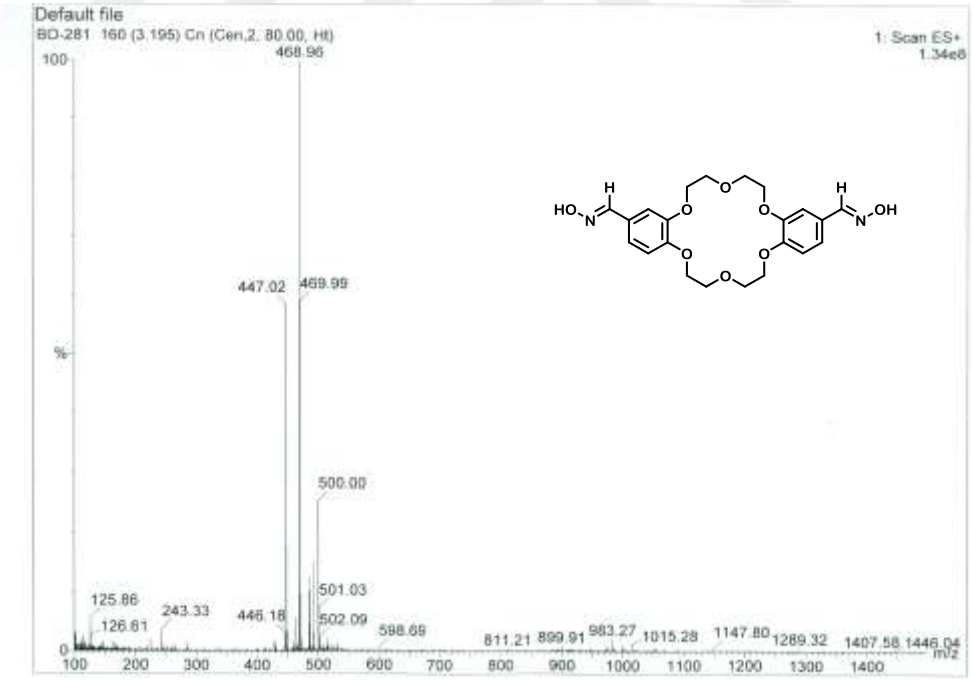

Figure 7.311. LC-MS Spectrum of compound **200**

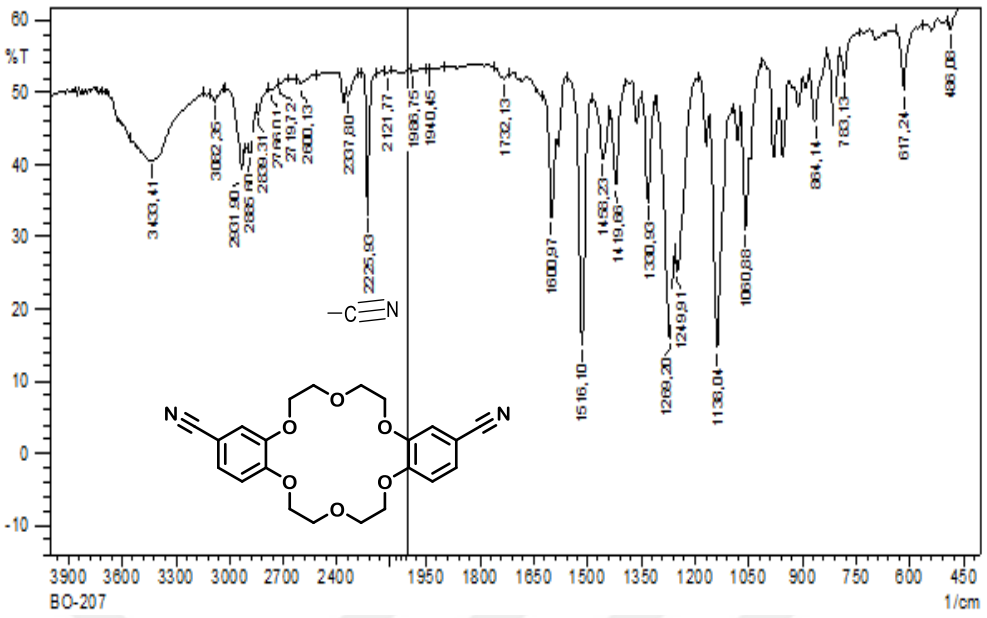

Figure 7.312. IR spectrum of compound **201**

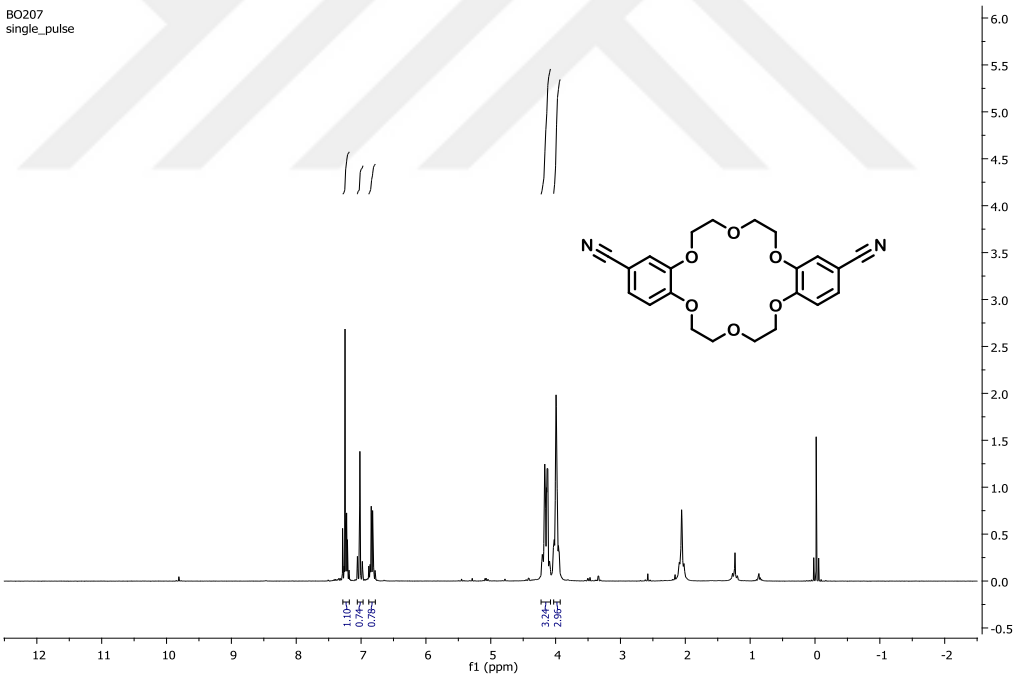

Figure 7.313. ^{1}H NMR spectrum of compound **201**

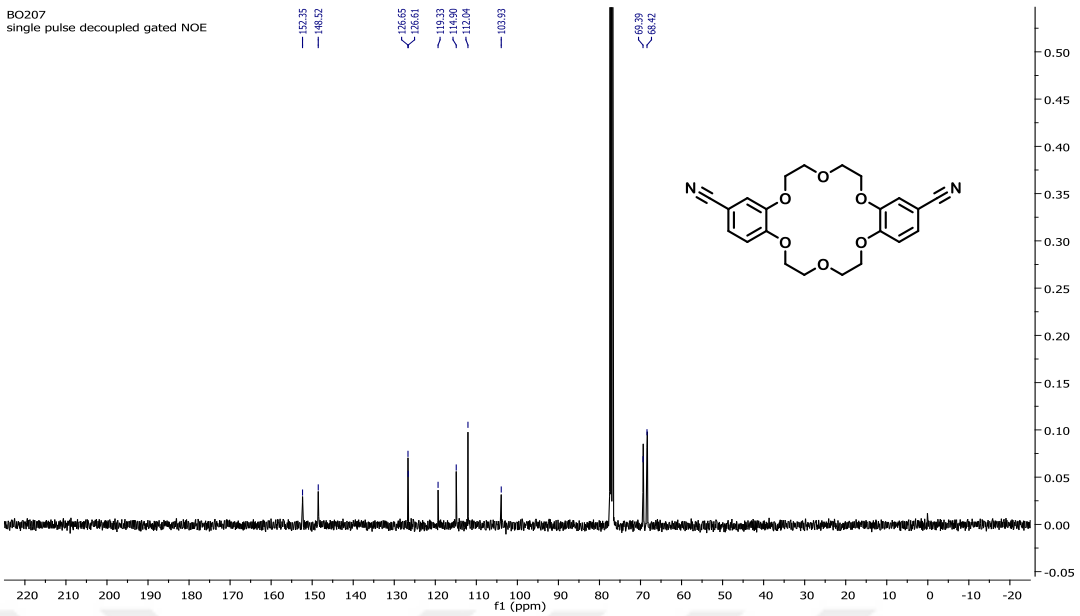

Figure 7.314. ^{13}C NMR spectrum of compound **201**

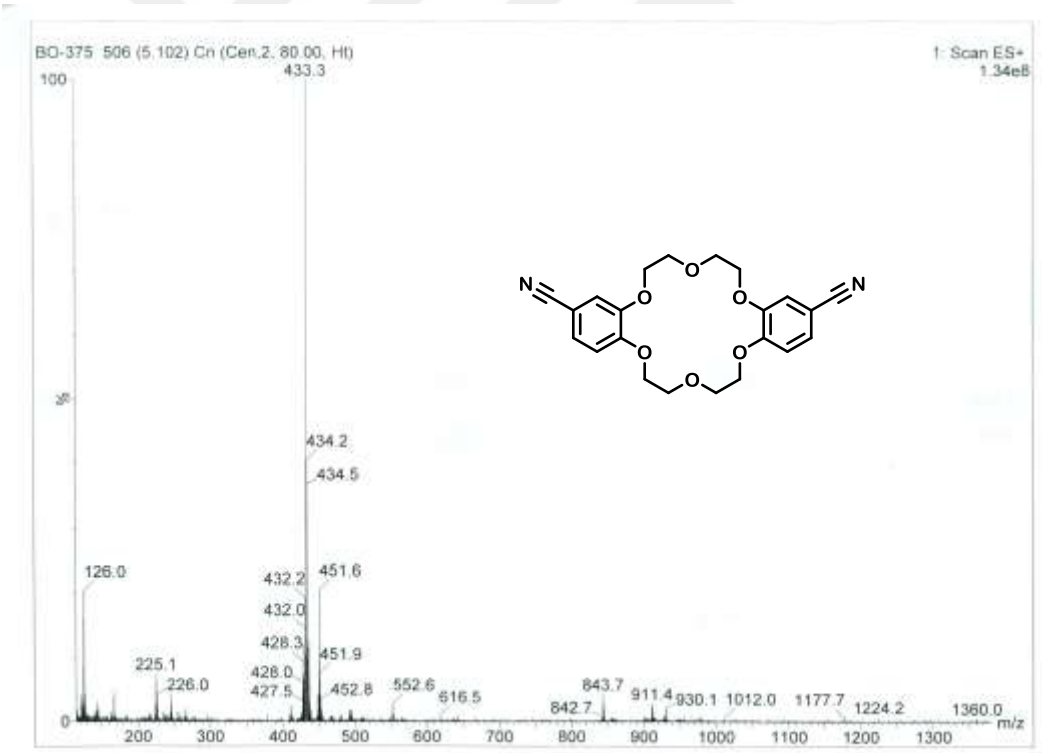

Figure 7.315. LC-MS Spectrum of compound **201**

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