

**Pd-CATALYZED SYNTHESIS OF SUBSTITUTED
HETEROAROMATIC FLUORANTHENE ANALOGUES
AND STUDIES TOWARDS THE TOTAL SYNTHESIS OF
TRUNCATONE C AND IMELUTEINE**

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By

Merve Yence

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Pd-CATALYZED SYNTHESIS OF SUBSTITUTED HETEROAROMATIC
FLUORANTHENE ANALOGUES AND STUDIES TOWARDS THE TOTAL
SYNTHESIS OF TRUNCATONE C AND IMELUTEINE

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July, 2019

We certify that we have read this thesis and that in my opinion it is fully adequate, in scope and in quality, as a thesis of the degree of Master of Science.

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ABSTRACT

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Fluoranthenes represent an important class of polycyclic aromatic compounds with important applications in modern chemistry and materials science. In addition to being present in the structural core of a variety of fungal natural products, fluoranthenes have also been widely employed as fluorescent probes and in organic electronics. Despite the recent advances in this area, the chemistry of heteroaromatic fluoranthene analogues, in other words, acenaphthylenes fused with heteroaromatic rings such as pyridine, furan, benzofuran, pyrazole, etc. has remained largely unexplored. In this work, we have synthesized a variety of heteroaromatic fluoranthene analogues via a Pd-catalyzed tandem Suzuki-Miyaura and C-H arylation reaction sequence with using different types of boronic acids and esters.

Natural products have an undeniable importance in pharmaceutical chemistry, and for the development of new medicinal drugs, natural products and their derivatives still provide significant contribution. In this project, the total synthesis of natural products truncatone C and imeluteine is targeted.

Keywords: Heteroaromatic fluoranthenes, Natural products, Pd-catalysis

ÖZET

Pd-KATALİZÖRLÜĞÜNDE HETEROAROMATİK SÜBSTİTÜYE FLORANTEN ANALOGLARININ SENTEZİ, TRUNKATON C VE İMELUTEİN TOTAL SENTEZİ ÜZERİNE ÇALIŞMALAR

Merve Yence

Kimya Bölümü, Yüksek Lisans

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Floranten türevleri, çoklu-halkalı (polisiklik) aromatik hidrokarbonlar sınıfına giren bir aromatik bileşik alt-sınıfını oluşturur. Florantenler modern kimya ve malzeme biliminde önemli uygulamalarda kullanılmaktadır. Mantarlardan elde edilen çeşitli doğal ürünlerin yapısında bulunmalarının yanı sıra, florantenler, floresan prob olarak ve organik elektronik alanında kullanılmaktadır. Bu alandaki son gelişmelere rağmen, heteroaromatik floranten analogları, başka bir ifadeyle heteroaromatik halkalarla kaynaşmış asenaftilenler örneğin piridin, furan, benzofuran, pirazol vb. ürünlerin keşifi büyük ölçüde yapılmamıştır. Bu çalışmada, farklı boronik asitler ve esterler kullanarak, Pd katalizörlüğünde birbiri ardına Suzuki-Miyaura tepkimesi ve C-H arilasyon tepkime dizisi vasıtasıyla çeşitli heteroaromatik floranten analogları sentezlendi.

Doğal ürünler, ilaç kimyasında yadsınamaz bir öneme sahiptir ve günümüzde yeni ilaçların geliştirilmesinde, doğal ürünler ve onlardan elde edilen türevler hala büyük bir katkı sunmaktadır. Bu projede, trunkaton C ve imelutein doğal ürünlerinin total sentezi hedeflenmektedir.

Anahtar Kelimeler: Heteroaromatik floranten, Doğal ürünler, Pd-katalizi

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Dedicated to my lovely family...

LIST OF ABBREVIATIONS

Bpin	Pinacolato boronic ester
DMSO	Dimethyl Sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EtOAc	Ethyl Acetate
EtOH	Ethanol
FTIR	Fourier Transform Infra-Red
HRMS	High Resolution Mass Spectrometry
MIDA	<i>N</i> -methylinodiacetic acid
NMR	Nuclear Magnetic Resonance
PAH	Polycyclic Aromatic Hydrocarbon
PIDA	(Diacetoxyiodo)benzene
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
UV	Ultraviolet

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1. Pd-CATALYZED SYNTHESIS OF SUBSTITUTED HETEROAROMATIC FLUORANTHENE ANALOGUES

1.1. INTRODUCTION

1.1.1. Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs), which are also sometimes defined as polynuclear aromatic hydrocarbons (PNAs), condensed ring aromatics, or fused ring aromatics, are a class of organic compounds consisting of two or more fused aromatic rings (Figure 1). Polycyclic aromatic hydrocarbons are generally considered to contain only carbon and hydrogen. The simplest polycyclic aromatic hydrocarbon is naphthalene that contains two fused aromatic rings.

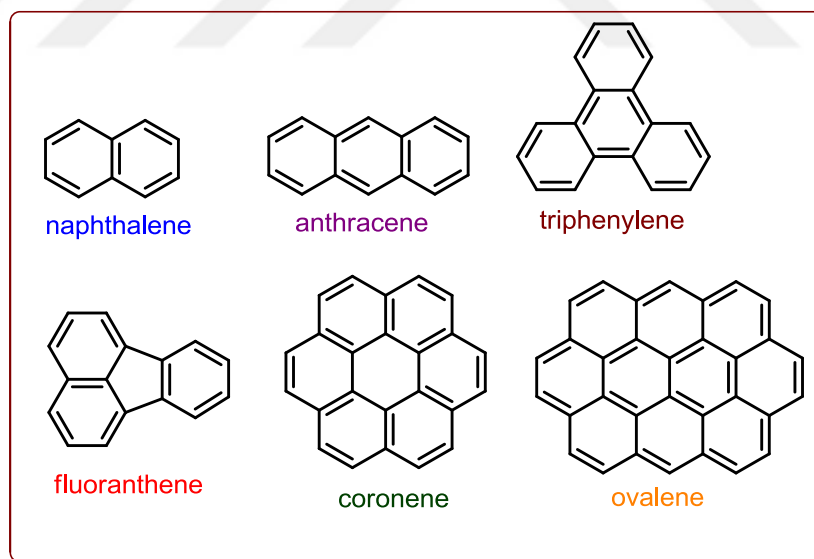


Figure 1. Examples of polycyclic aromatic hydrocarbons.

Polycyclic aromatic hydrocarbons (PAHs) are also considered as a part of environmental contaminants that has long been interest in the fields of organic chemistry, physical chemistry, environmental science and toxicology.²

1.1.1.1. General Applications of Polycyclic Aromatic Hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) have drawn attention due to their biological, electronic and optical features. Triphenylene and truxene derivatives have been studied as active materials in field-effect transistors and light-emitting diodes.³ An alkylated truxene derivative emits strong solid-state fluorescence with high fluorescence quantum yields which makes them light-emitting material.⁴

Pyrene and its derivatives have attracted much attention because of their photo-physical aspects and high stability. Pyrene (**1**) exhibits selective fluorescence quenching for polynitro aromatic compounds (NACs) (Figure 2).⁵ 1-bromopyrene (**2**) as a fluorescence probe⁶ and pyrene-based fluorescent sensor **3** with bulky-trimethylsilyl ethynyl (TMS) groups for NACs were also introduced.⁷

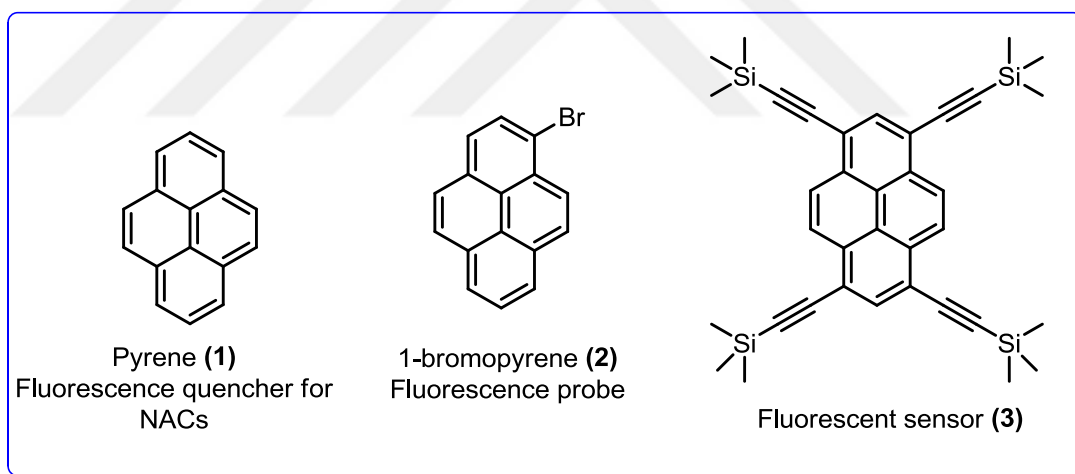


Figure 2. Examples of a few pyrene-based sensors.

PAHs have been used widely as fluorescence probes because of the π -electron-richness, strong photoluminescence and fluorescence features in addition to high chemical stability.

1.1.2. Fluoranthenes and Heteroaromatic Fluoranthene Analogues

Fluoranthenes are one of the smallest and an important subclass of polycyclic aromatic hydrocarbons (PAHs). Fluoranthenes can be defined as naphthalene and benzene rings connected by a five-membered ring. Several fungal natural products have a fluoranthene core in their structures such as hortein⁸ (4) and daldinone E⁹ (5) and they show significant biological activities as indicated in Figure 3. Also, fluoranthenes have been utilized in material science, especially in the field of organic electronics.

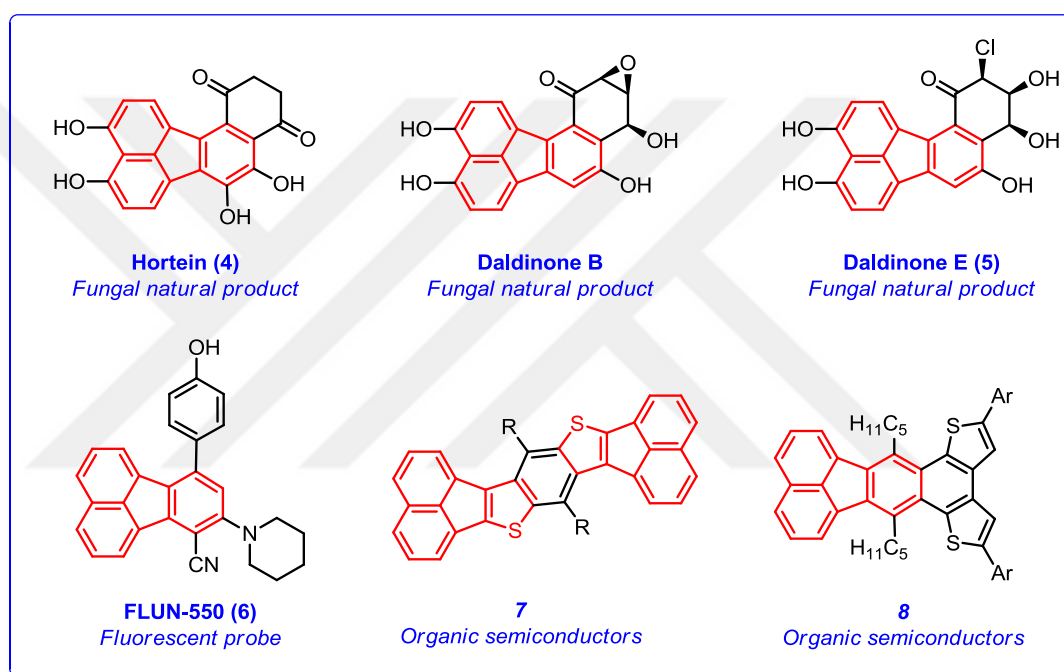


Figure 3. Examples of important fluoranthene analogues.

Heteroaromatic fluoranthene analogues contain heteroatoms such as sulfur, oxygen or nitrogen. Fluoranthene and heteroaromatic fluoranthene analogues have been gaining more importance in recent years due to their unique electronic and optical properties with broad range of applications as functional materials. Therefore, there is an increasing amount of ongoing research on the synthesis of fluoranthene analogues and their practical applications.

1.1.2.1. General Applications of Fluoranthenes and Heteroaromatic

Fluoranthenes

Fluoranthenes are PAHs with a broad range of attractive and practical applications. Fluoranthenes and heteroaromatic fluoranthenes have been utilized in electroluminescent devices,¹¹ fluorescent probes in live cell imaging,¹² and as reporter molecules in drug delivery.¹⁵

Fluoranthenes have attracted great interest particularly in the area of organic electronics as well as sensing, since they show interesting optical properties such as large Stokes shifts, long lifetimes and resistance to air-quenching.¹⁰ For instance, benzo[*k*]fluoranthene-based linear acenes used as the non-doped active layer to fabricate deep blue- to green-emissive organic light emitting diodes (OLEDs) (Figure 4).¹¹

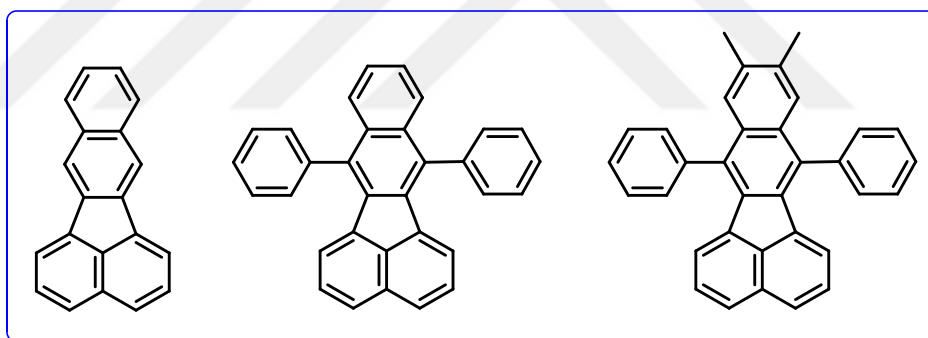


Figure 4. Some benzo[*k*]fluoranthene-based linear acenes.

In 2014, FLUN-550 (**6**) was introduced as a fluoranthene-based fluorescent probe for particular staining of intracellular lipid droplets in vitro cell imaging (Figure 3).¹²

Heteroaromatic fluoranthenes such as diacenaphthylene-fused benzo[1,2-*b*:4,5-*b'*]dithiophenes (**7**) can be used as organic semiconductor and show good field-effect mobility.¹³ Another organic semiconductor example is sulfur-hetero oligoarenes based

on the benzo[*k*]fluoranthene **8** unit which has been developed as an active material for thin-film organic field-effect transistors (Figure 3).¹⁴

In addition, fluoranthenes have been utilized as fluorescent reporters. In 2018, releasing of carbon monoxide (CO) and drug payload was monitored by the increase in characteristic blue fluorescence of the fluoranthene reporter molecule byproduct **9** in cell imaging studies (Figure 5).¹⁵

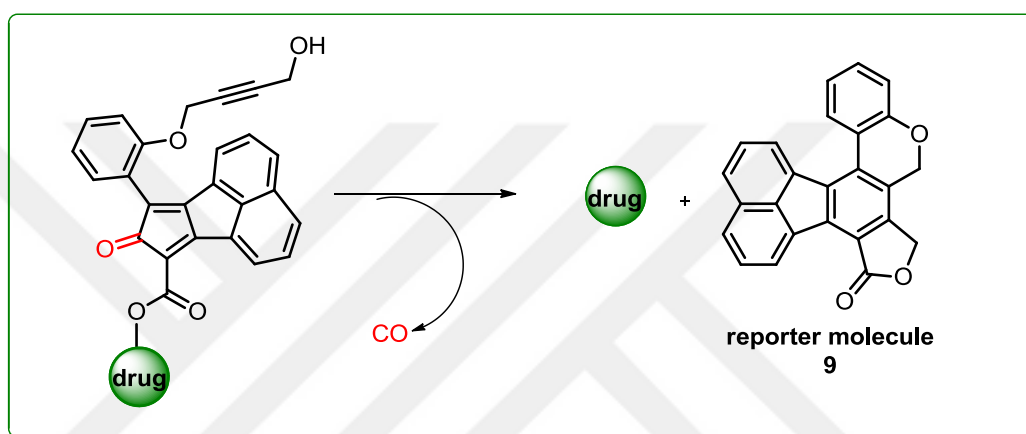


Figure 5. Example of a fluoranthene in drug delivery.

In this transformation, the initial inverse electron-demand Diels-Alder (IEDDA) reaction between the cyclopentadienone moiety and the alkyne followed by the extrusion of carbon monoxide (CO) gives a fluoranthene intermediate. The subsequent spontaneous lactone formation results in the formation of the reporter molecule **9** along with the release of the drug molecule.

In addition, fluoranthene-based materials were employed as fluorescence sensors for the detection of explosive debris (Figure 6).⁵

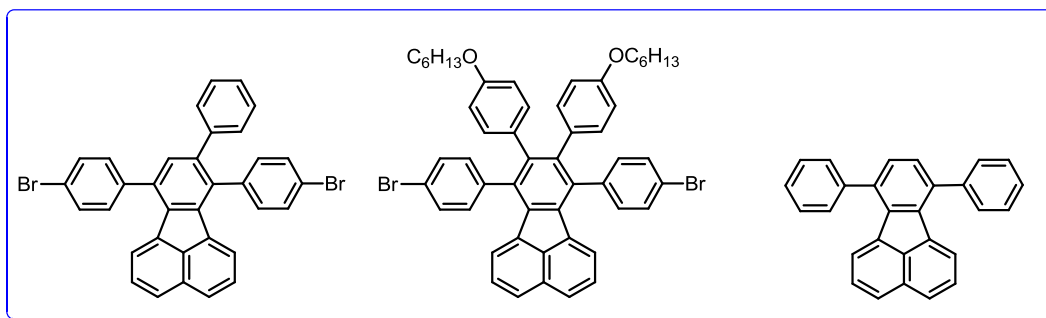


Figure 6. A series of fluoranthene-based sensors.

Recently, fluoranthenes have been applied as a push-pull system in a dye-sensitized solar cell (DSSC) application. Two new fluoranthene-based organic dye sensitizers (**10** and **11**), in which 7,12-diphenylbenzo[*k*]-fluoranthene moiety acts as an electron donor, thiophene and phenylethynyl units act as electron spacers, and carboxylic acid acts as electron acceptor, were accomplished in quasi-solid-state dye-sensitized solar cells (Figure 7).¹⁶

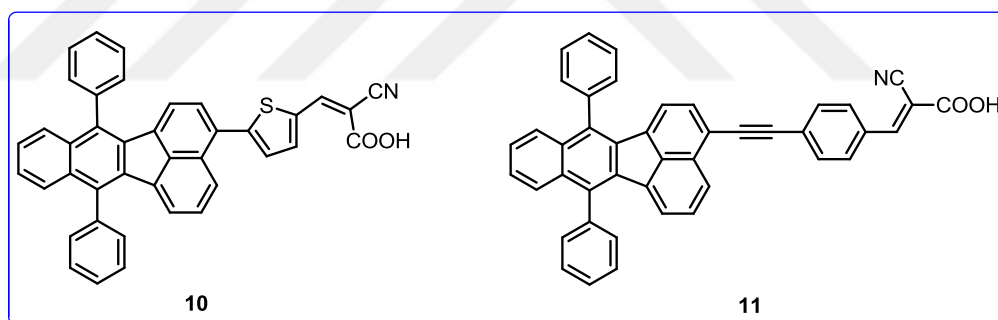


Figure 7. Fluoranthenes based organic dye sensitizers.

Bis(triphenylamine)-substituted fluoranthene derivatives were utilized as organic light emitting diodes (OLEDs) or dye-sensitized solar cell (DSSC) (Figure 8).¹⁷

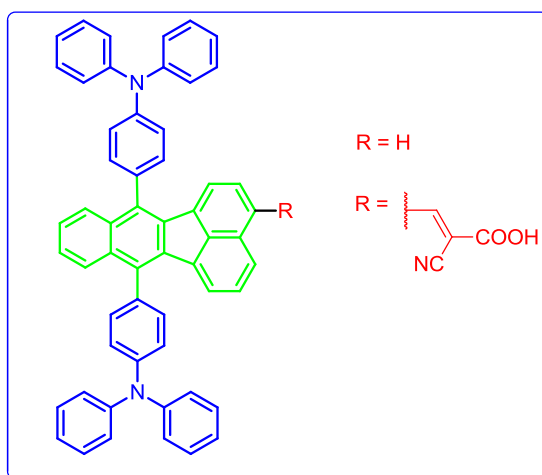


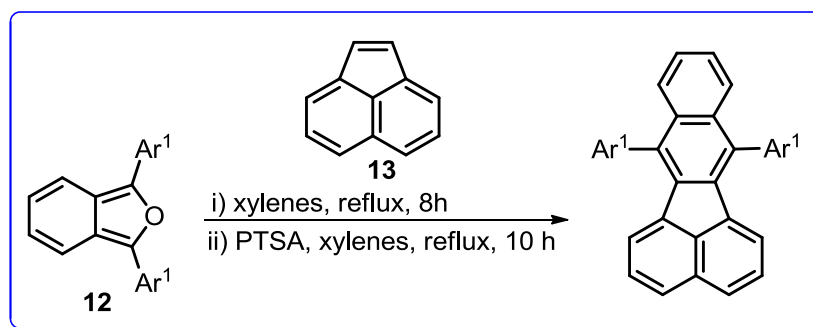
Figure 8. Fluoranthenes as electroluminescent emitters or dye-sensitized solar cells.

1.1.3. Synthesis and Derivatization of Fluoranthenes

A variety of synthetic methodologies are available for the synthesis and derivatization of the fluoranthene derivatives, which mainly include Diels-Alder reaction, transition-metal-catalyzed reactions, and various other cyclization methods.

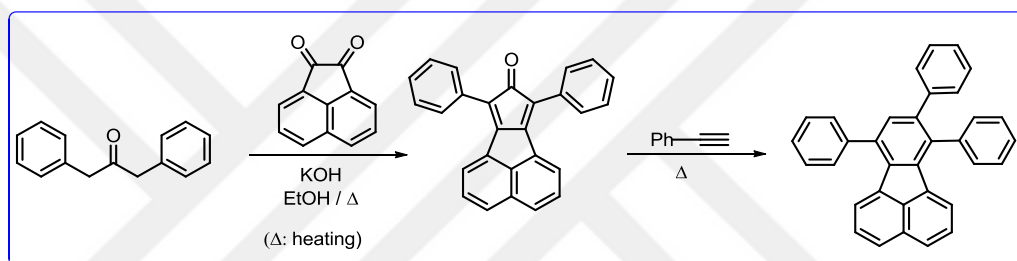
1.1.3.1. Diels-Alder Reactions

Among these methods, Diels-Alder reaction has been the most frequently used transformation. Mohanakrishnan and co-workers outlined a Diels-Alder reaction between symmetrical/unsymmetrical benzo[*c*]furans (**12**) and acenaphthylene (**13**) in xylenes at reflux temperature followed by treatment with p-toluenesulfonic acid (PTSA) to afford benzo[*k*]fluoranthenes (Scheme 1).¹⁸ This methodology successfully was applied to the synthesis of dimeric and trimeric benzo[*k*]fluoranthenes and functionalization of benzo[*k*]fluoranthenes derivatives.



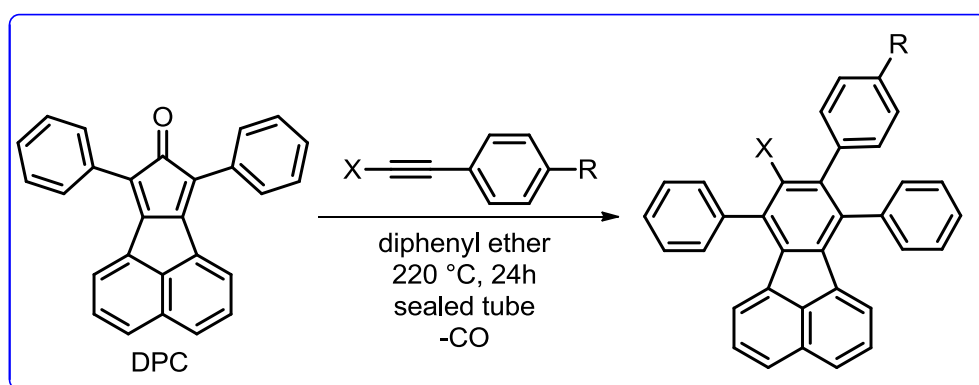
Scheme 1. Diels-Alder reaction of benzo[*c*]furans (**12**) with acenaphthylene (**13**).

With the utilization of a sequence of Knoevenagel and Diels-Alder reactions, 7,8,10-triphenylfluoranthene was synthesized from acenaphthene-quinone, diphenylacetone and phenylacetylene (Scheme 2).¹⁹



Scheme 2. The synthesis of 7,8,10-triphenylfluoranthene.

Also, different types of fluoranthene derivatives were synthesized via the inverse Diels-Alder (IEDDA) cycloaddition reaction of acetylene derivatives with 7,9-diphenyl-8*H*-cyclopenta[*a*]acenaphthylen-8-one (DPC) in diphenyl ether as solvent (Scheme 3).²⁰

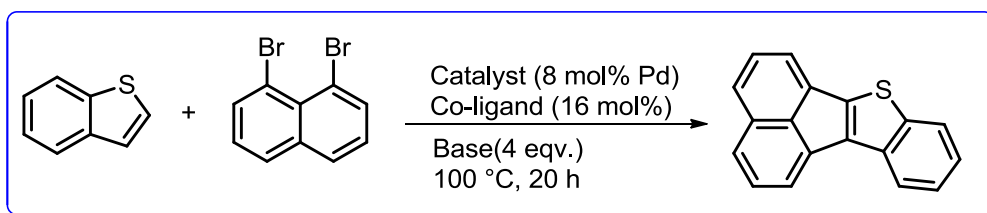


Scheme 3. Synthetic route for preparation of fluoranthene derivatives.

1.1.3.2. Transition Metal-Catalyzed Cross-Coupling and Cyclization

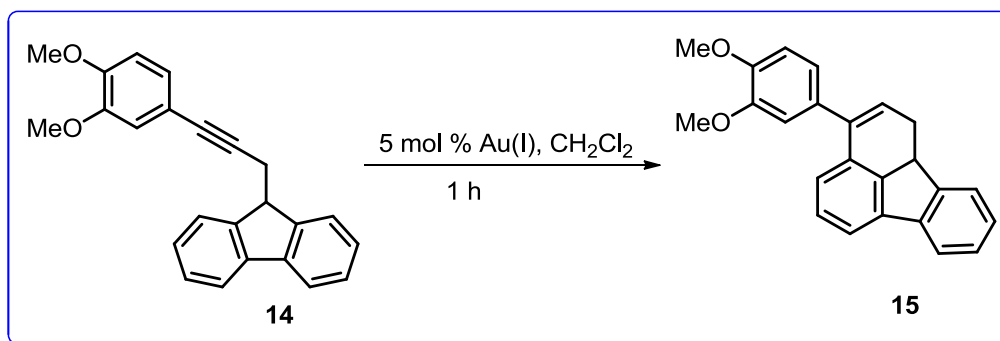
Reactions

Transition metal-catalyzed reactions have also been employed for fluoranthene synthesis. In 2017, Li and co-workers reported on a facile synthesis of thiophene fluoranthene analogue with Pd-catalyzed C-H activation reaction (Scheme 4).¹²



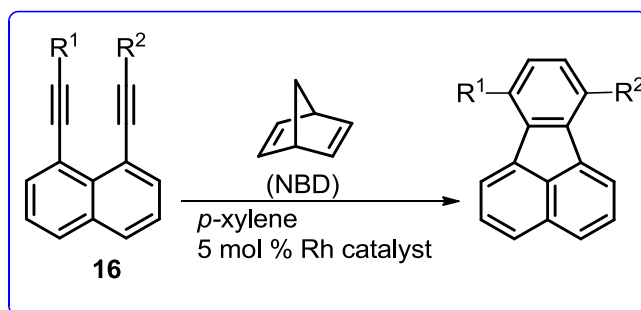
Scheme 4. Pd-catalyzed C-H activation reaction of benzo[*b*]thiophene with 1,8-dibromonaphthalene.

Besides the Pd-catalyzed reactions, related reactions could be carried out with gold(I) and gallium trichloride (GaCl_3) as catalysts. Alkynes can react in the presence of gold-catalyzed Friedel-Crafts-type reactions with arenes to give fluoranthene products (Scheme 5).²¹



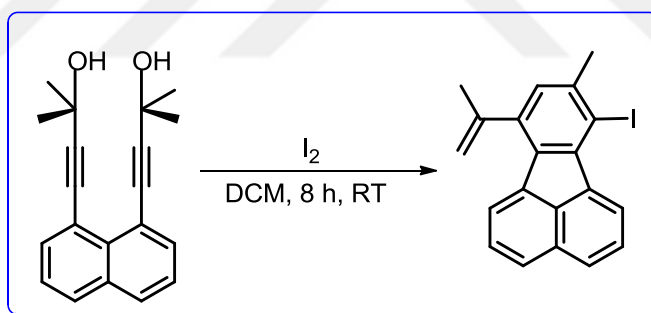
Scheme 5. Gold(I)-catalyzed hydroarylation of **14** to give 1,10b-dihydrofluoranthene (**15**).

Fluoranthenes were also shown to be synthesized by a transition metal-mediated cascade reaction in which 1,8-dialkynynaphthalenes (**16**) and norbornadiene (NBD) were reacted in the presence of a rhodium catalyst (Scheme 6).²²



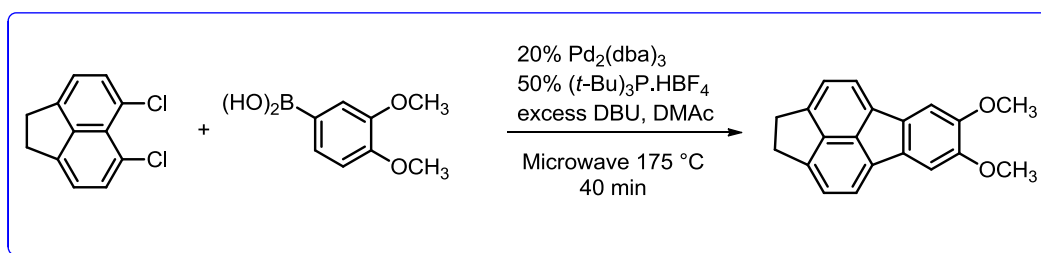
Scheme 6. Preparation of fluoranthenes from Diynes and NBD.

In another study reported in 2011, fluoranthenes were synthesized by the iodine-mediated cyclization of the rigid parallel triple bonds mapped from 1,8-dialkynyl naphthalenes with iodine under mild conditions (Scheme 7).²³



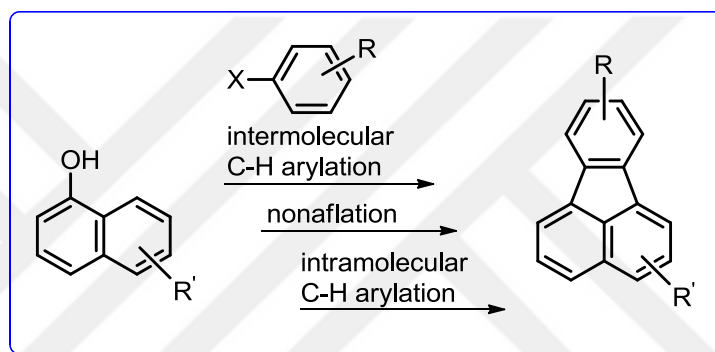
Scheme 7. Synthesis of a fluoranthene via iodine-mediated cyclizations.

In 2019, Quimby and Scott reported a Suzuki-Heck-type coupling reaction between 1,8-dichloronaphthalenes and arylboronic acids in the presence of high catalyst loading (20 mol % $Pd_2(dba)_3$) and under high reaction temperature (175 °C) (Scheme 8).²⁴



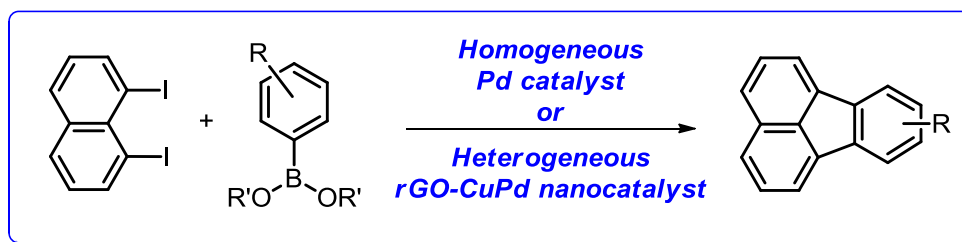
Scheme 8. Fluoranthene synthesis by a Suzuki-Heck-type coupling cascade.

A three-step synthetic sequence for the preparation of fluoranthenes, involving Miura's intermolecular C-H arylation, nonaflation, and intramolecular C-H arylation, has been developed by Manabe and co-workers in 2016 (Scheme 9).²⁵



Scheme 9. Three step synthesis of fluoranthenes.

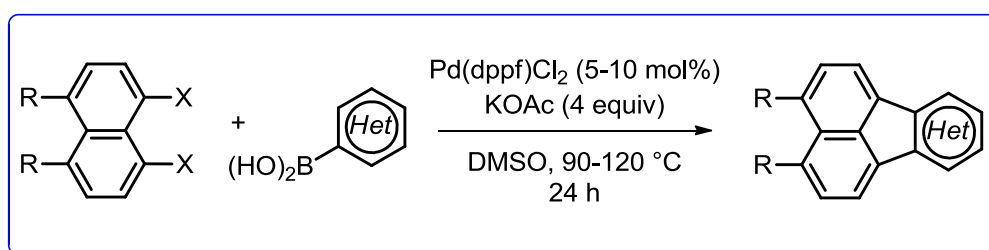
In a collaborative work with the Metin group in 2017, our group developed a catalytic method for the synthesis of substituted fluoranthenes that operates via tandem Suzuki-Miyaura and intramolecular C-H arylation reactions. Notably, both $\text{Pd}(\text{dppf})\text{Cl}_2$ as a homogeneous Pd catalyst and reduced graphene oxide-assembled CuPd alloy nanoparticles (rGO-CuPd) as a heterogeneous Pd catalyst were discovered to be highly effective catalysts for this transformation. In these reactions, high functional group tolerance was observed where arylboronic acids and esters that possess electron-withdrawing and donating substituents gave fluoranthene analogues in moderate to high yields (Scheme 10).²⁶



Scheme 10. Synthesis of fluoranthene derivatives via tandem Suzuki-Miyaura and intramolecular C-H arylation.

1.1.4. The Aim of This Work

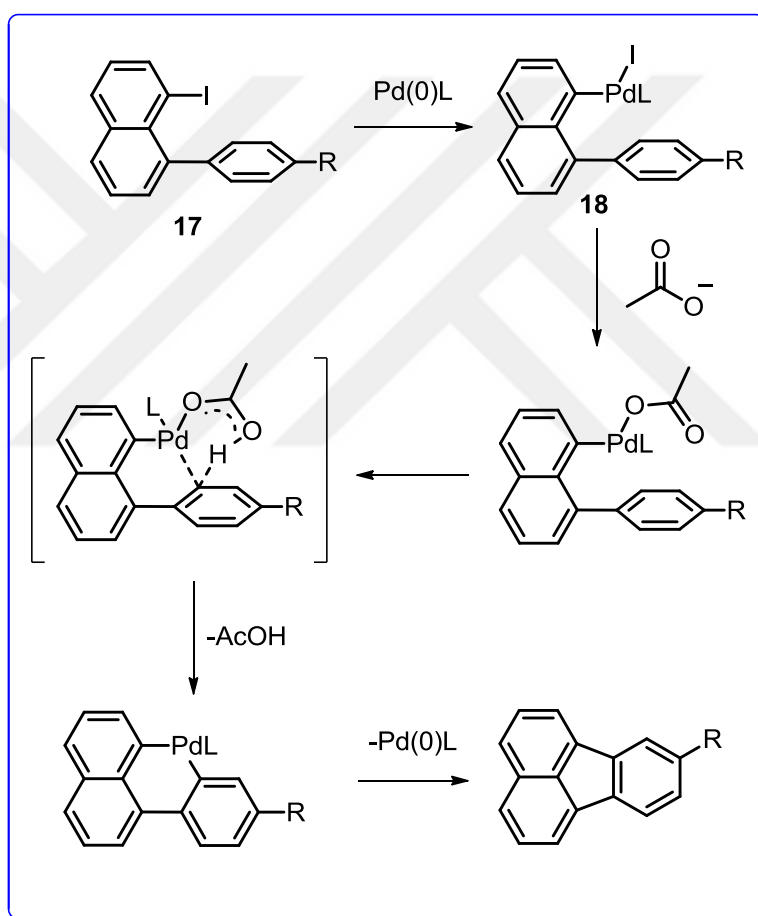
The aim of this work was synthesis of a broad range of heteroaromatic fluoranthene analogues via the Pd-catalyzed tandem Suzuki-Miyaura and C-H arylation reaction sequence based on our methodology.²⁶ Using this methodology, Sujit et al., demonstrated aromatic fluoranthenes synthesis with only the unsubstituted diiodonaphthalene as starting material. Our purpose was to show the efficiency of this methodology, which could be used in the synthesis of a broad range of aromatic and heteroaromatic fluoranthene analogues. Therefore, in this work, using two different 1,8-dihalonaphthalenes and a variety of boronic acids/esters, a wide range of heteroaromatic fluoranthene analogues were synthesized (Scheme 11).



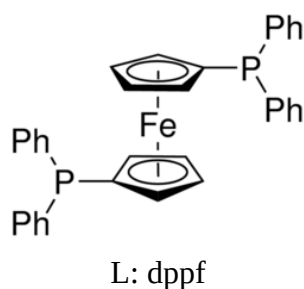
Scheme 11. The synthesis of heteroaromatic fluoranthene analogues.

The proposed reaction mechanism of the fluoranthene synthesis is given in Scheme 12. According to this mechanism, the initial Suzuki-Miyaura coupling between 1,8-diiodonaphthalene and boronic acid/ester affords the Suzuki-Miyaura monoarylation product **17**. The oxidative addition of the Pd(0) catalyst is expected to give intermediate **18** which may undergo a ligand exchange with an acetate anion (AcO⁻

) present in the reaction medium. The intramolecular C-H-activation step is proposed to occur via the insertion of the Ar-Pd-OAc moiety to the aromatic C-H bond along with the concomitant deprotonation of this C-H hydrogen assisted by the acetate group acting as a base. Kinetic isotope effect (KIE) studies indicated that this C-H activation step is unlikely to be the rate-determining step in the overall transformation.²⁶ Finally, the reductive elimination of intermediate **18** is proposed to give fluoranthene product along with the regeneration of Pd(0) catalyst.



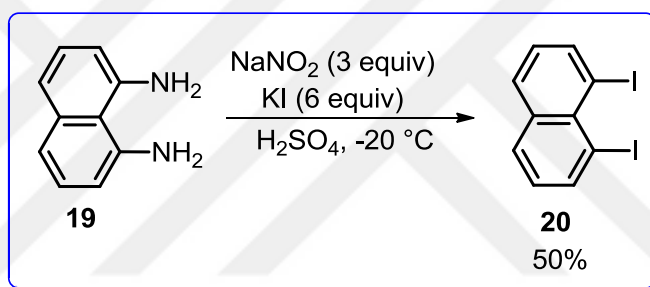
Scheme 12. Proposed reaction mechanism.



1.2. RESULTS & DISCUSSION

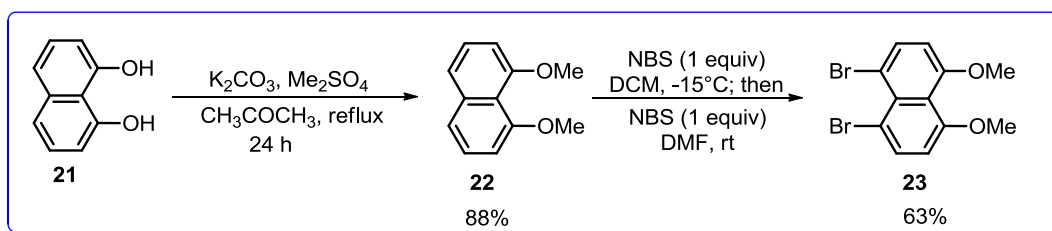
1.2.1. Synthesis of 1,8-Dihalonaphthalenes

In this section, two different 1,8-dihalonaphthalenes, which were used as starting materials for the synthesis of the heteroaromatic fluoranthenes, were prepared. 1,8-diiodonaphthalene (**20**) was synthesized by the Sandmeyer reaction starting from commercially available 1,8-diaminonaphthalene (**19**) on gram scale. Firstly, the treatment of 1,8-diaminonaphthalene (**19**) with sodium nitrite resulted in the formation of diazonium salt, which was subsequently reacted with potassium iodide to afford 1,8-diiodonaphthalene (**20**) in 50% yield as indicated in Scheme 13.



Scheme 13. The synthesis of 1,8-diiodonaphthalene (**20**).

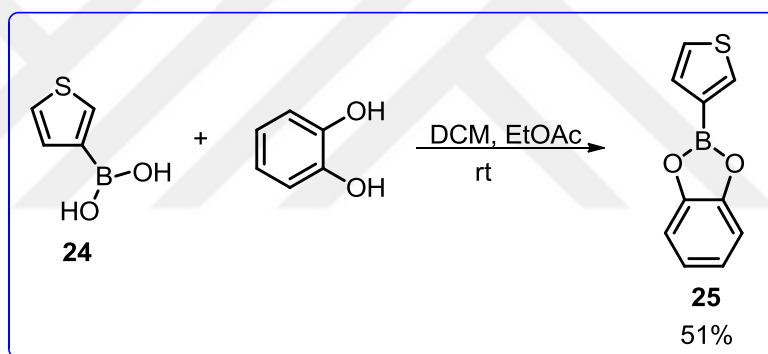
Our other objective was to show that substituted 1,8-dihalonaphthalene (**23**) could be used in fluoranthene synthesis, and in order to achieve this goal, 1,8-dibromo-4,5-dimethoxynaphthalene (**23**) was prepared. Its synthesis began with dimethylation of 1,8-dihydroxynaphthalene (**21**) using excess potassium carbonate as base and dimethyl sulfate as the methylating agent to obtain 1,8-dimethoxynaphthalene (**22**) in 88% yield. Additionally, 1,8-dimethoxynaphthalene (**22**) was reacted with N-bromosuccinimide (NBS) to afford 1,8-dibromo-4,5-dimethoxynaphthalene (**23**) in 63% yield (Scheme 14).



Scheme 14. The synthesis of 1,8-dibromo-4,5-dimethoxynaphthalene (**23**).

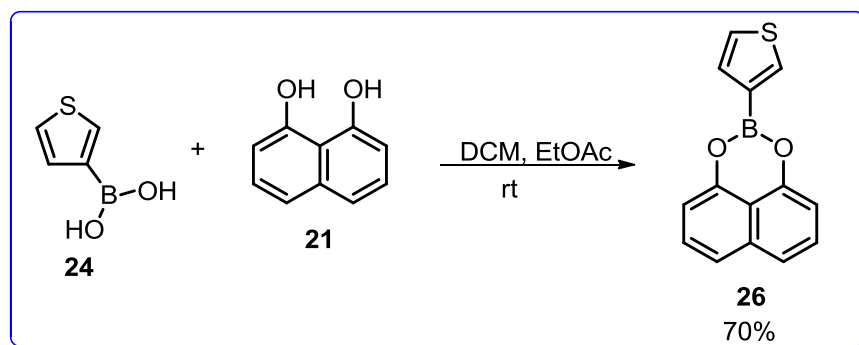
1.2.2. Synthesis of Catechol Boronic Ester and Boronic Ester of 26

In order to be utilized in fluoranthene synthesis, two different types of boronic esters were synthesized. First, when 3-thiophene-boronic acid (**24**) was reacted with catechol, catechol boronic ester **25** was obtained in 51% yield after recrystallization (Scheme 15).



Scheme 15. The synthesis of catechol boronic ester (**25**).

Afterwards, boronic ester **26** was obtained in pure form after recrystallization from reaction between 3-thiophene-boronic acid (**24**) and 1,8-dihydroxynaphthalene (**21**) under mild conditions in 70% yield (Scheme 16).

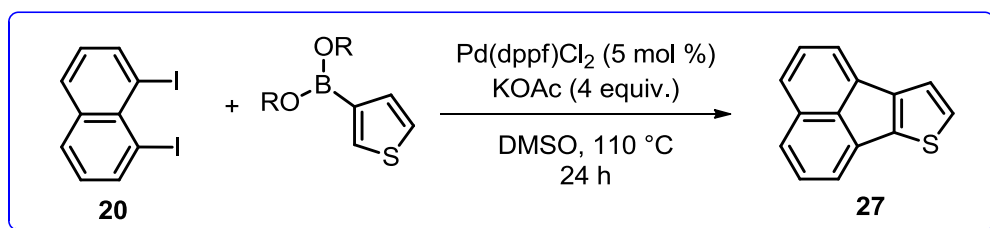


Scheme 16. The synthesis of boronic ester (26).

1.2.3. Investigation of Boronic Esters

There are some examples of the most common types boron reagents which are catechol boronic ester, MIDA boronate and pinacol boronic ester used in Suzuki Miyaura coupling reactions.²⁷

In this section, our objective was to show that a broad range of boronic esters in addition to boronic acids could be used in the fluoranthene synthesis methodology. For this reason, different types of boronic esters, which were pinacolato boronic ester (Bpin), catechol boronic esters (Bcat) and MIDA boronic ester (BMIDA) were investigated. For the synthesis of **27**, boronic esters were reacted with diiodonaphthalene (**20**) under Pd catalysis (Scheme 17).

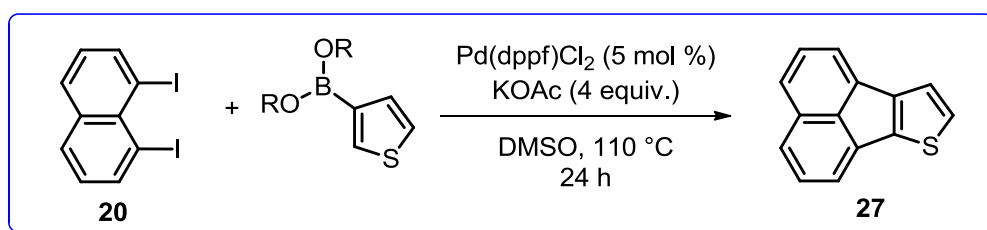


Scheme 17. The synthesis of compound **27** from boronic esters.

Generally, high yields of **27** was obtained from boronic esters as indicated in Table 1. When 3-thiophene-boronic acid (**24**) and pinacolato boronic ester (**28**) were investigated, fluoranthene analogue **27** was obtained in 78% yield in both reactions (entries 1 and 2). When catechol boronic ester **25** was tested, **27** was isolated in 69%

yield (entry 3). It should be noted that, to the best of our knowledge, boronic esters that have a 1,8-naphthalenediol moiety **26** have not been used as boronic esters in cross-coupling reactions and thus, boronic ester **26** has been introduced in this work as a new form of boronic esters to be used in cross-coupling reactions. Pleasingly, when boronic ester (**26**) was explored, fluoranthene analogue **27** was obtained in 84% yield (entry 4).

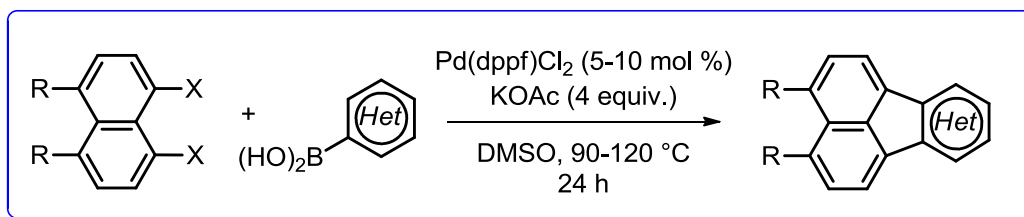
When thiophene-3-boronic acid MIDA boronic ester (**29**) was explored, formation of the fluoranthene product **27** was not observed (Entry 5). MIDA boronates are not expected to undergo the transmetallation step in the Suzuki Miyaura coupling since boron is not available for the coordination of the base. Therefore, our expectation was supported with this experiment. It is hypothesized that a vacant and Lewis asidic boron p-orbital is necessary for transmetallation of a boronic acid in cross-coupling conditions. According to this hypothesis, removing this p-orbital via rehybridizing an sp^2 -hybrized to its sp^3 -hybridized boronate via complexation with a trivalent heteroaromatic ligand such as MIDA boronic ester (**29**) would reduce reactivity towards cross-coupling.²⁸ Due to this reduction of cross-coupling, fluoranthene product **27** was not observed.

Table 1. Boronic esters investigation

Entry	Boronic Acid or Ester	Yield of Fluoranthene (%)
1	 24	78
2	 28	78
3	 25	69
4	 26	84
5	 29	-

1.2.4. Substrate Scope

The scope of the heteroaromatic fluoranthene synthesis was investigated using the 1,8-dihalonaphthalenes along with a variety of boronic acids and esters (Scheme 18).



Scheme 18. The synthesis of fluoranthene analogues.

As described in Table 2, nine different heteroaromatic fluoranthene analogues were synthesized in this section, and high functional group tolerance was observed in all these transformations.

The reaction tolerates the presence of thiophene and furan groups, affording fluoranthene products **27** and **30** in 78% and 54% yield, respectively (entries 1 and 2). Benzofuran group was also tested and fluoranthene analogue product **31** was isolated in 86% yield (Entry 3).

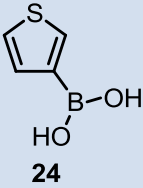
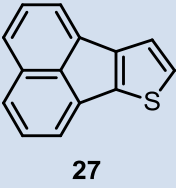
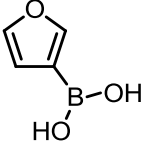
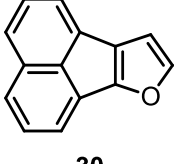
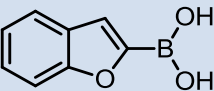
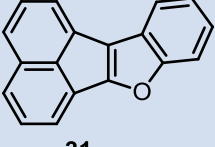
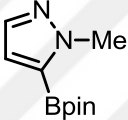
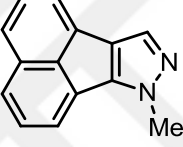
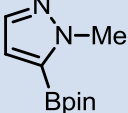
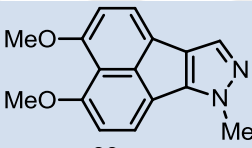
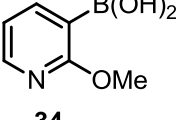
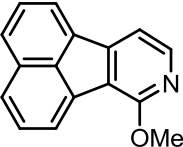
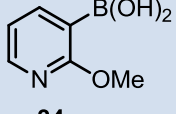
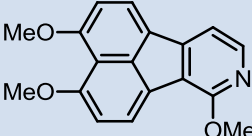
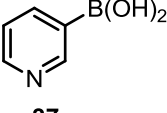
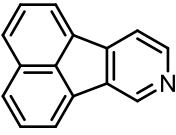
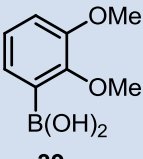
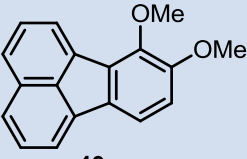
Nitrogen-containing heterocycles play a crucial role for the development of new drugs. Studies indicate that almost all pharmaceuticals containing heterocyclic structure have also at least one nitrogen atom.²⁹ Therefore, five different azo-fluoranthene analogues were synthesized. Pyrazole group was tested with the two 1,8-dihalonaphthalenes, affording fluoranthene product **32** and dimethoxy-substituted fluoranthene product **33** in good yields, (80% and 73% yield, respectively) (entries 4 and 5). We next investigated the Pd-catalyzed reactions of 2-methoxy-3-pyridinylboronic acid (**34**) with the 1,8-dihalonaphthalenes **20** and **23**. Both reactions proved to work well under the optimized conditions giving aza-fluoranthene products **35** and **36** in 90% and 56% yield, respectively (entries 6 and 7). When 3-pyridylboronic acid (**37**) was tested as substrate, aza-fluoranthene **38** was isolated as the major product of the reaction in 45% yield (entry 8). Whereas the other regioisomer was also observed to form as a minor product of the reaction, it could not be isolated in pure form. In

addition, determination of the ratio of the major and minor products in the crude reaction mixture proved to be very difficult due to overlapping signals in its ^1H -NMR spectrum.

Finally, the use of the electron-rich 2,3-dimethoxy-phenylboronic acid (**39**) afforded fluoranthene product **40** in 76% yield (entry 9). While this is not a heteroaromatic fluoranthene analogue, we investigated the formation of this product due to its structural resemblance to the skeleton of the natural product hortein (**4**).⁸

The full characterization of all heteroaromatic fluoranthene analogues prepared in this section has been conducted by ^1H - and ^{13}C -NMR spectroscopy, high-resolution mass spectrometry (HRMS) and FTIR spectroscopy.

Table 2. Scope of heteroaromatic fluoranthene synthesis as shown in scheme 18

Entry	ArB(OR) ₂	Product	Yield (%)
1			78
2			54
3			86
4			80
5			73
6			90
7			56
8			45
9			76

1.3. CONCLUSION

Synthesis of two different starting materials, unsubstituted and substituted dihalonaphthalenes were accomplished successfully. Boronic ester **26** has been introduced in this work as a new form of boronic esters to be used in cross-coupling reactions, and fluoranthene analogue **27** was synthesized.

Using two different 1,8-dihalonaphthalenes and a variety of boronic acids/esters, nine different heteroaromatic fluoranthenes were synthesized in 45-90% yield. Therefore, the efficiency of our methodology was shown by via both aromatic and heteroaromatic fluoranthene synthesis.

2. STUDIES TOWARDS THE TOTAL SYNTHESIS OF TRUNCATONE C AND IMELUTEINE

2.1. INTRODUCTION

2.1.1. Natural Products and Their Bioactivities

In organic chemistry terminology, natural products are generally defined as secondary metabolites synthesized by living organisms. Natural products have high structural variety and special pharmacological or biological activities because of the natural selection and evolutionary processes.³⁰

Natural products have an undeniable importance in pharmaceutical chemistry, and for the development of new medicinal drugs, natural products, and their derivatives still provide significant contributions.^{31,32} Natural product-based drugs include compounds from plants (including elliptinium (**41**) galantamine (**42**)), (daptomycin (**43**)) and synthetic or semi-synthetic compounds based on natural products (tigecycline (**44**)) as indicated in Figure 9. They cover a range of therapeutic applications: anti-cancer, anti-infective, anti-diabetic activities, among others, and they exhibit a significant diversity of chemical structures.³¹

Total synthesis has a key role in the investigation of the biological activities and drug properties of natural products, which generally can be obtained only in small quantities from various organisms. Total syntheses of such natural products not only provide their production in large scales, but also enable the ability to make synthetic modifications to synthesize their derivatives.

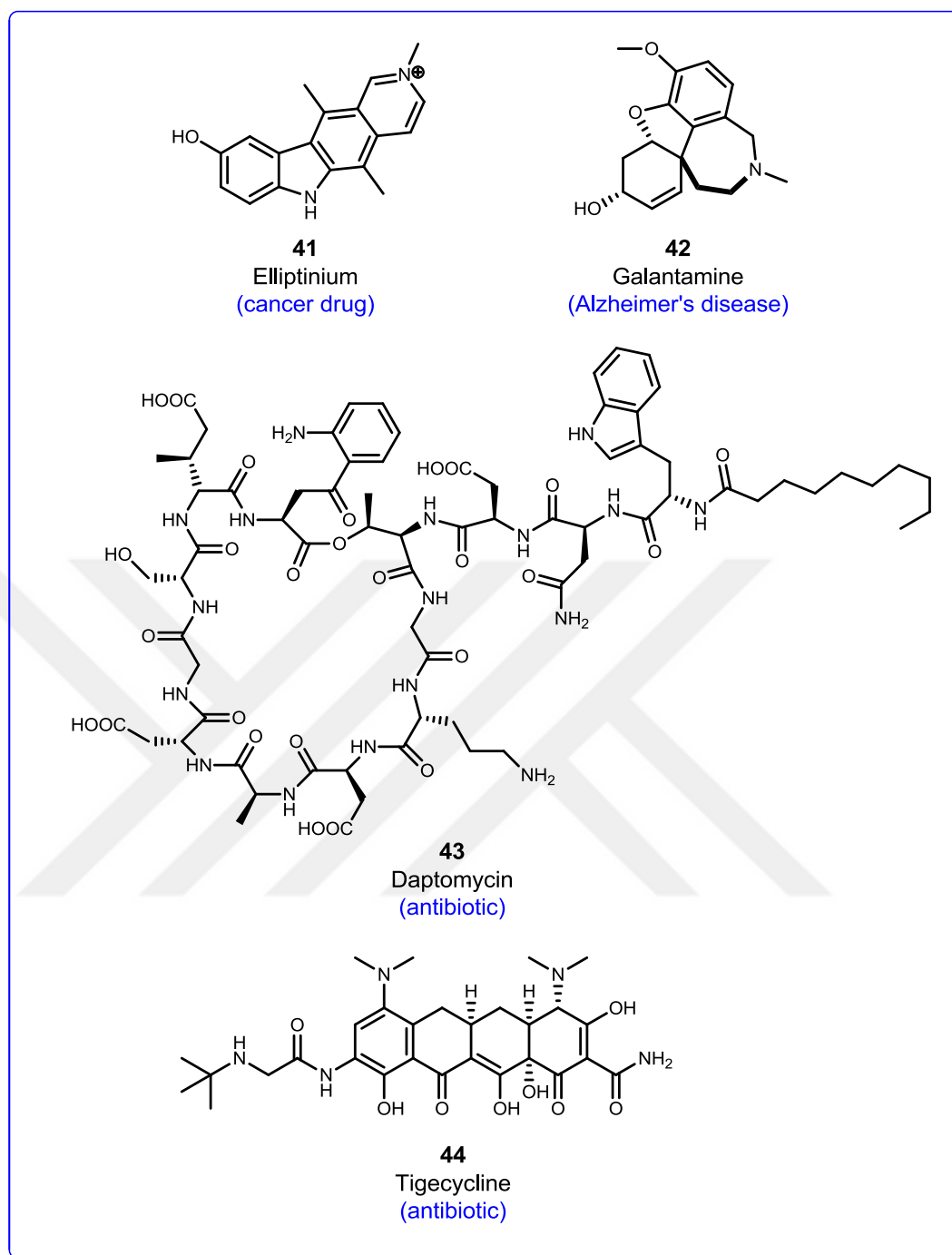


Figure 9. Examples of some important natural products.

Total synthesis of natural products has always been a challenge for chemists. However, it is still attractive to enhance facile and modular methods for the total synthesis of natural products due to their benefits in chemistry, biochemistry and medicine.

2.1.2. Benzo[j]fluoranthene Natural Products and Their Synthesis

Approximately thirty natural products exist all of which have been isolated from fungi, and which have benzo[j]fluoranthene skeleton with various oxidation states and which possess multiple, oxygenated functional groups. During the isolation studies of these natural products, the biological activities of most of them were investigated and some were found to have significant activities. Some natural products with benzo[j]fluoranthene framework, such as daldinone B (**45**), daldinone C (**46**) and hypoxylonol F (**47**) were isolated from several species with special biological features shown in Figure 10.³³

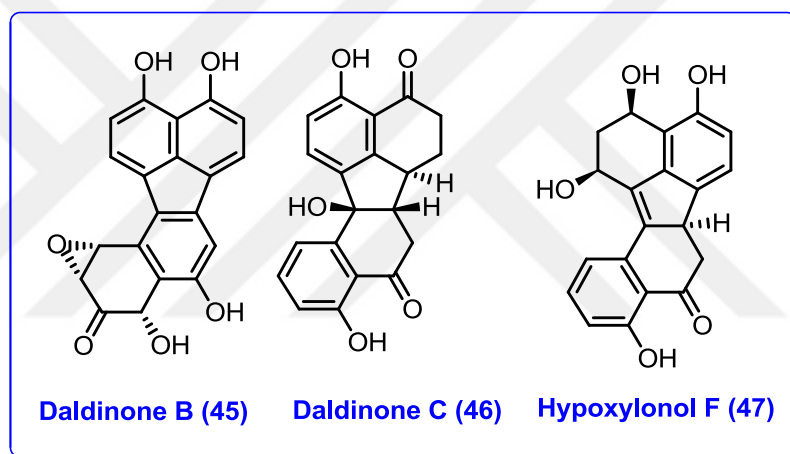
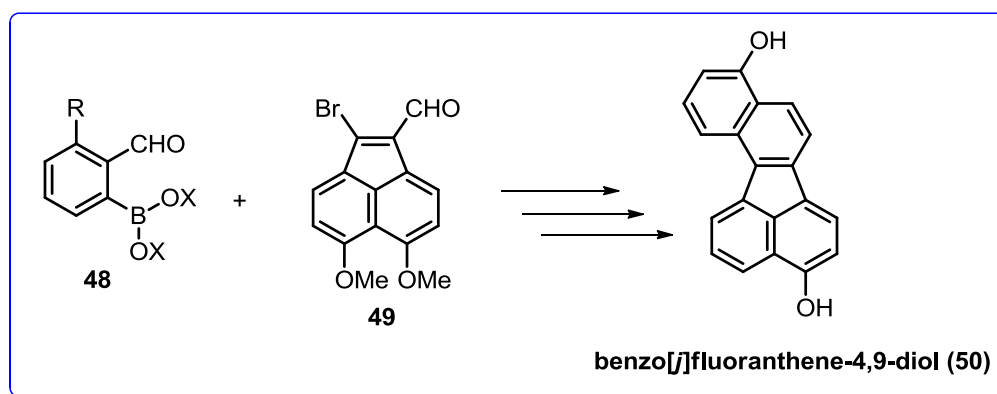


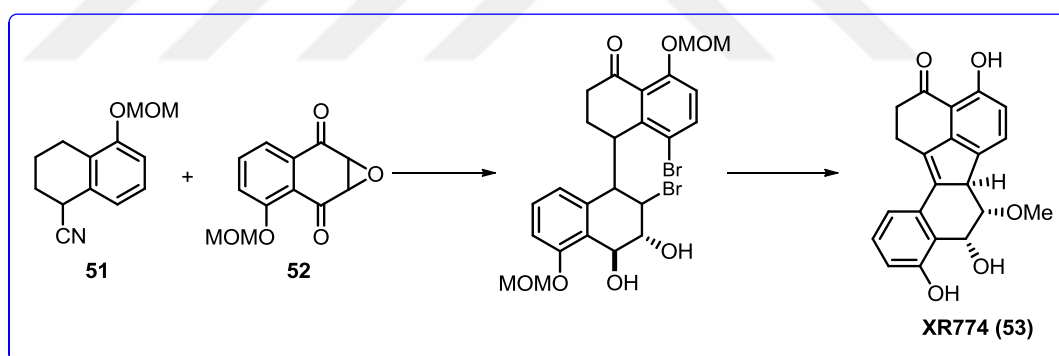
Figure 10. Some natural products with benzo[j]fluoranthene framework.

Despite their structural variations and promising activities, there has been only two synthetic studies towards this benzo[j]fluoranthene natural product class. In the first work reported in this area, Dallavalle and co-workers completed the first total synthesis of the recently isolated natural product benzo[j]fluoranthene-4,9-diol (**50**). The crucial steps of this sequence consist of a Suzuki coupling between appropriately substituted 2-bromo-acenaphthylene-1-carbaldehyde (**49**) and 2-formylbenzeneboronates (**48**) followed by McMurry ring closure (Scheme 19).³⁴



Scheme 19. Synthesis of benzo[j]fluoranthene-4,9-diol (**50**).

The second synthetic study on this class of natural products was reported in 2018 by Hosokawa and co-workers which describes the total synthesis and structural determination of XR774 (**53**), a tyrosine kinase inhibitor. The benzo[j]fluoranthene skeleton has been formed by regioselective coupling between tetraline **51** and tetralone **52** followed by Birch reduction, simultaneous bromination of vinylic and aromatic moieties, and the nickel-mediated intramolecular coupling reaction (Scheme 20).³⁵



Scheme 20. The synthesis of XR774 (**53**).

2.1.3. The Aim of This Work

In this work, the total synthesis of two natural products, imeluteine (**70**) and truncatone C (**61**), that have azafluoranthene and benzo[j]fluoranthene skeletons, was targeted (Figure 11). Truncatone C (**61**) was isolated from stromata (fruiting bodies) in 2016 by Sudarman and co-workers. Truncatone C (**61**) was tested for both antimicrobial and antifungal activity also for cytotoxicity against the mouse fibroblast cell line L929.

Truncatone C (**61**) showed moderate antiproliferative effects against L-929 with IC50 values of 7.0 μM .³⁶ Imeluteine (**70**) is an example of natural azafluoranthene alkaloids. Biological activities of azafluoranthene alkaloids have not been investigated yet in detail due to their low natural abundance. Cytotoxicity of imeluteine (**70**) was found against HCT-116 colon adenocarcinoma, ACHN renal carcinoma, and A549 lung carcinoma at IC50 values of 20.0, 10.2 and 31.0 μM , respectively.³⁷

During these syntheses, a Pd-catalyzed fluoranthene synthesis methodology developed by our group was planned to be utilized for the construction of benzo[j]fluoranthene and azafluoranthene units present in these natural products.²⁶

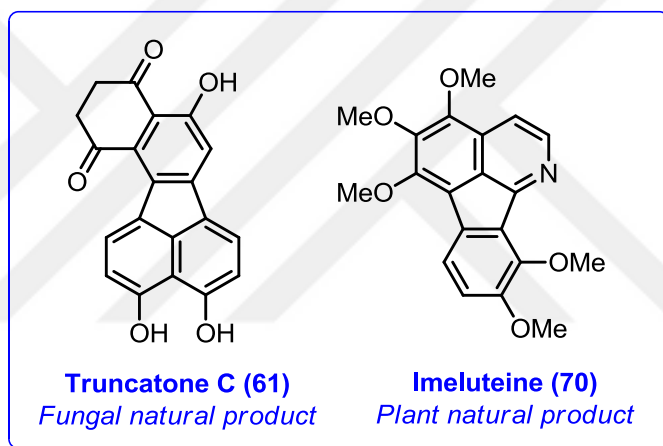


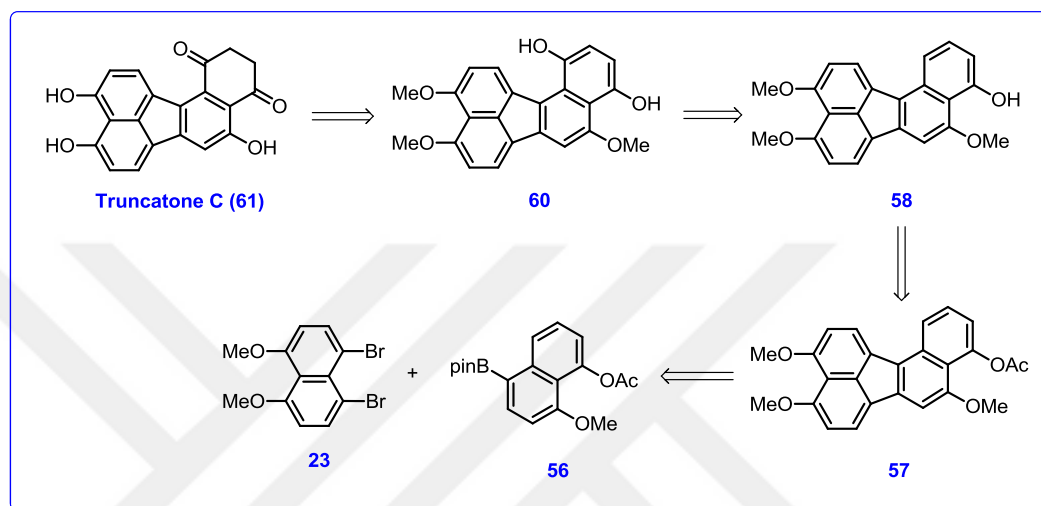
Figure 11. Targeted natural products.

RESULTS & DISCUSSION

2.2.1. Studies Towards Total Synthesis of Truncatone C

2.2.1.1. Retrosynthetic Analysis of Truncatone C

The retrosynthetic strategy towards the synthesis of truncatone C (**61**) is presented in Scheme 21.

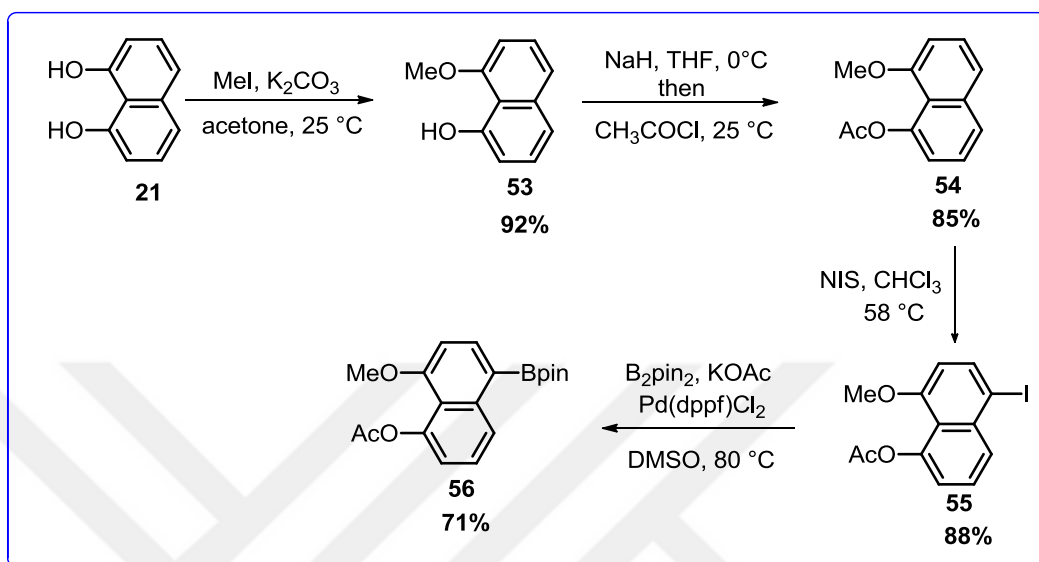


Scheme 21. Retrosynthetic analysis of truncatone C (**61**).

According to its designed retrosynthetic analysis, truncatone C (**61**) would be synthesized by the global demethylation of intermediate **60** containing three methyl-protected naphthol groups. Compound **60** was planned to be obtained by oxidation of phenol derivative **58**. **58** was intended to be prepared by hydrolysis of the acetate group in the intermediate **57** in basic medium. Compound **57** that has benzo[*j*]fluoranthene unit skeleton would be synthesized via the Pd-catalyzed fluoranthene synthesis methodology.²⁶ For this purpose, arylboronic ester **56** would be reacted with 1,8-dibromo-4,5-dimethoxynaphthalene (**23**) to yield **57**. Therefore, truncatone C (**61**) synthesis can be divided into 3 stages which are arylboronic ester synthesis, benzo[*j*]fluoranthene synthesis and transformation of **57** to truncatone C (**61**).

2.2.1.2. Arylboronic Ester Synthesis

The first stage of the truncatone C (**61**) synthesis was the synthesis of arylboronic ester **56** (Scheme 22).



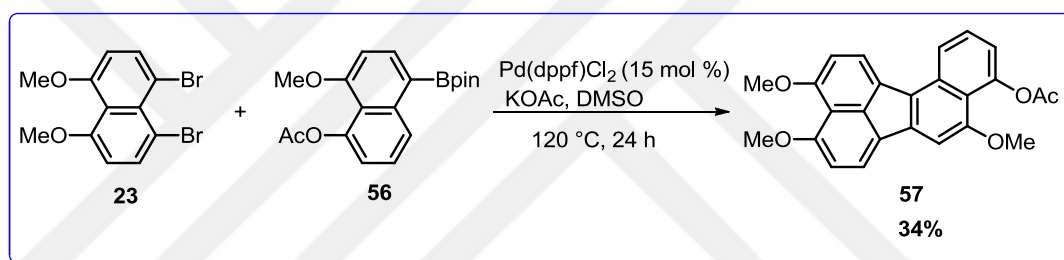
Scheme 22. Synthesis of arylboronic ester.

Our synthesis of arylboronic ester commenced with the monomethylation of the commercially available 1,8-dihydroxynaphthalene (**21**) under mild conditions. Compound **53** was deprotonated with sodium hydride (NaH), followed by the treatment with acetyl chloride resulting in **54** in 85% yield. Afterwards, we investigated the iodination of compound **54** with *N*-iodosuccinimide (NIS). Initial attempts for this iodination step resulted in incomplete conversion to the product with unreacted starting material left. Then, optimization studies were conducted based on changing the equivalents of NIS, solvent, and temperature. After substantial optimization efforts, we succeeded to obtain **55** in 88% isolated yield by employing 4.4 equivalents of NIS, and performing the reaction in chloroform at 58 °C. Since methoxy (OMe) group is a more electron donating group than acetate (OAc) group, the reaction occurs predominantly at the para position of the methoxy group. Final step was borylation of **55** with the use of

B₂pin₂ as borylation reagent and Pd(dppf)Cl₂ as catalyst which resulted in the formation of arylboronic ester **56** in 71% yield.³⁸

2.2.1.3. Benzo[j] Fluoranthene Synthesis

The key step of the truncatone C (**61**) synthesis was benzo[j]fluoranthene synthesis. It was achieved by the Suzuki coupling/intramolecular C-H arylation sequence between arylboronic ester **56** and 1,8-dibromo-4,5-dimethoxynaphthalene (**23**). We were pleased to find that at 120 °C and with the use of 15 mol % Pd(dppf)Cl₂ catalyst, the desired product **57** was obtained in 34% isolated yield after purification by column chromatography (Scheme 23).

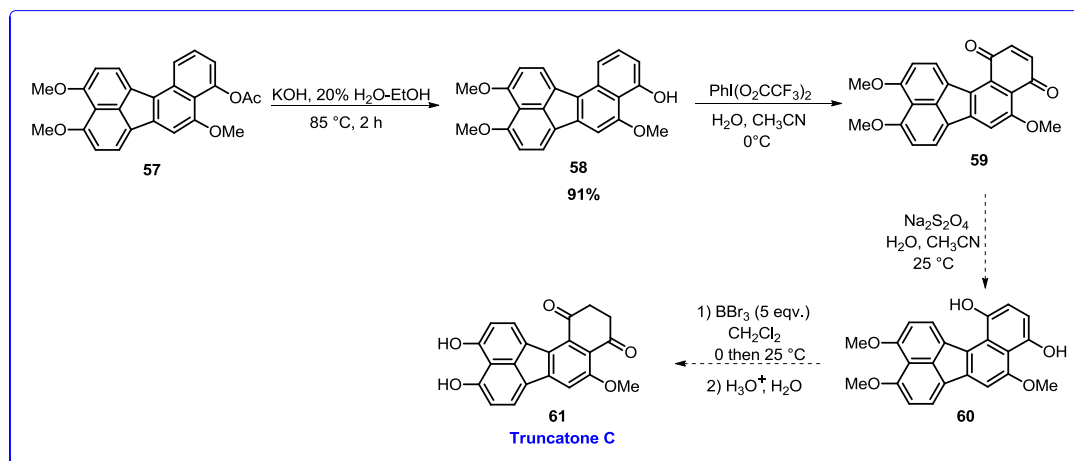


Scheme 23. Synthesis of benzo[j]fluoranthene.

The relatively low yield of the desired product can be attributed to the lower reactivity of aryl bromides (ArBr) in cross-coupling reactions compared to aryl iodides (ArI), in addition to the deactivating effect of the electron-rich -OMe groups in the oxidative addition step of cross-coupling reactions.

2.2.1.4. Studies on the Transformation of **57** to Truncatone C

The synthesis scheme for the conversion of benzo[j]fluoranthene derivative **57** to truncatone C (**61**) shown in Scheme 24.

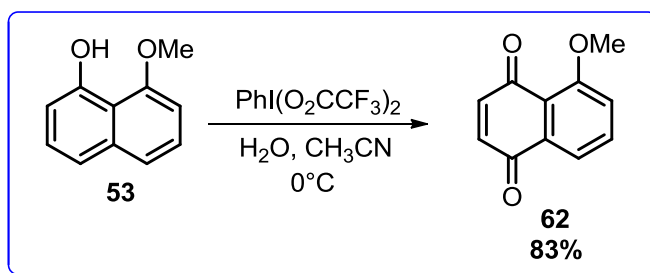


Scheme 24. The planned synthesis of truncatone C.

According to this plan firstly, acetate group (-OAc) in **57** was hydrolyzed under basic conditions to produce **58**. Upon exposure to heated aqueous potassium hydroxide in ethanol resulted in the formation of the phenol **58** in 91% yield. The next step was oxidation of phenol **58** to *para*-quinone **59**. In the literature, there are examples of oxidation of phenols to quinones by bis(trifluoroacetoxy)iodobenzene.³⁹ Quinone **59** was then planned to be reduced to hydroquinone **60**, followed by the global demethylation of **60** to give truncatone C (**61**) as the targeted natural product. For the oxidation of the naphthol **58** to quinone **59** step, various conditions were tried (Table 3).

2.2.1.5. Oxidation Studies of the Naphthol 58

As a preliminary model study, oxidation of naphthol **53** to quinone **62** was examined using a methodology described in the literature for phenol derivatives (Scheme 25).³⁹



Scheme 25. Preliminary study of oxidation of the phenol **53**.

After the initial successful attempt on a small scale, this reaction was carried out once more on 100 mg scale and quinone **62** was obtained in 83% yield after purification by column chromatography. Having conducted this preliminary study, same conditions were applied to oxidation of **58**. However, the desired product **59** was not observed since solubility of **58** is less in acetonitrile at 0°C . Then many conditions were tried as shown in the Table 3. Dichloromethane (DCM) was added and experiment was conducted at room temperature, but **58** was observed as the only product of the reaction. In the next trial, solvent was changed to acetone. Again preliminary study was tried with acetone, oxidation of **53** was achieved so the same conditions were applied to **58**, unfortunately the product **59** could not be observed, only the starting material **58** was observed. It was believed that increase in reaction temperature could solve the solubility problem. Increasing temperature to 60°C led to the formation of overoxidation product **63** (Figure 12). However, it should be noted that even though the ^1H -NMR spectrum of this compound supports the structure of **63**, its full characterization could not be achieved due to its low amount.

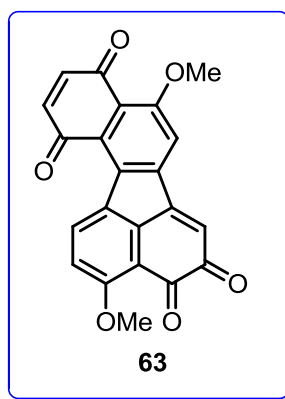
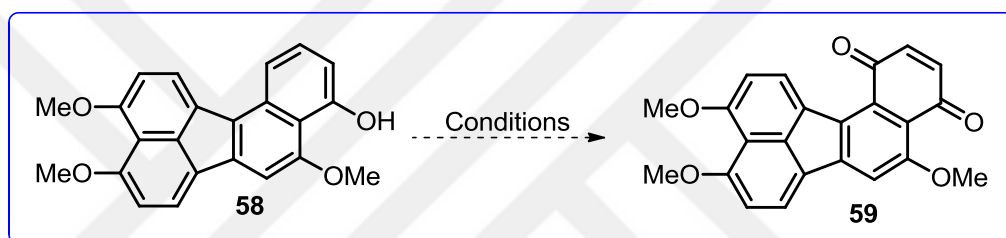


Figure 12. Overoxidation product **63**.

Table 3. Oxidation Studies of the Naphthol **58**



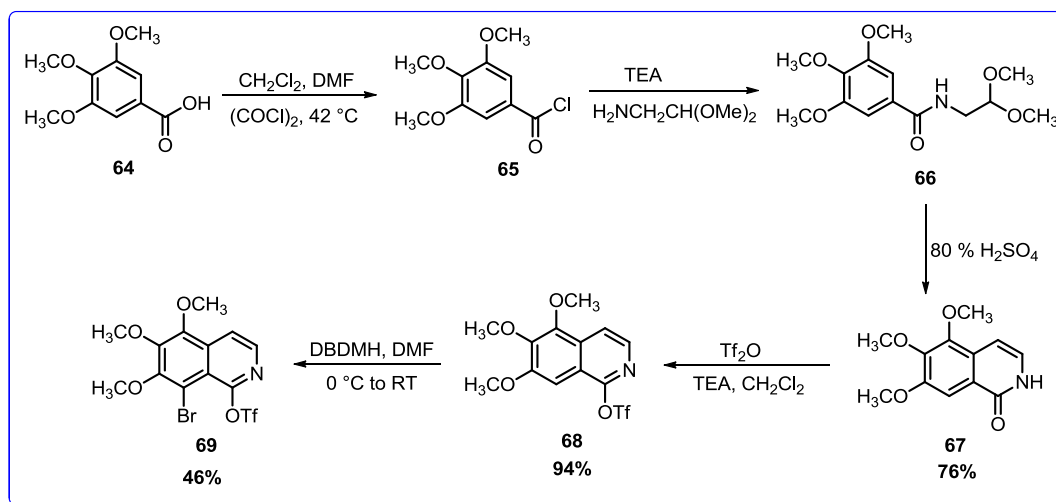
Solvent	Temperature	Oxidant	Result
MeCN-H ₂ O	0 °C	PIFA PhI(O ₂ CCF ₃) ₂	SM (58)
DCM, MeCN-H ₂ O	rt	PIFA	SM (58)
Acetone- H ₂ O	rt	PIFA	SM (58)
Acetone- H ₂ O	60 °C	PIFA	Overoxidation product (63)
DMF-H ₂ O	rt to 50 °C	PIFA	SM (58)
Acetone-H ₂ O	rt to 50 °C	PIDA PhI(O ₂ CCH ₃) ₂	SM (58)

Another solution to the solubility problem of **58** was proposed to be the use of a more polar solvent such as dimethylformamide (DMF), however, this solvent change did not result in the synthesis of **59**. Then, another oxidant which was (diacetoxyiodo)benzene hypervalent iodine reagent was tried, but unfortunately quinone product **59** was not obtained. In conclusion, all our attempts to optimize solvent, temperature, and oxidant were not met with success.

2.2.2. Studies Towards Total Synthesis of Imeluteine

2.2.2.1. Starting Material Synthesis of Imeluteine

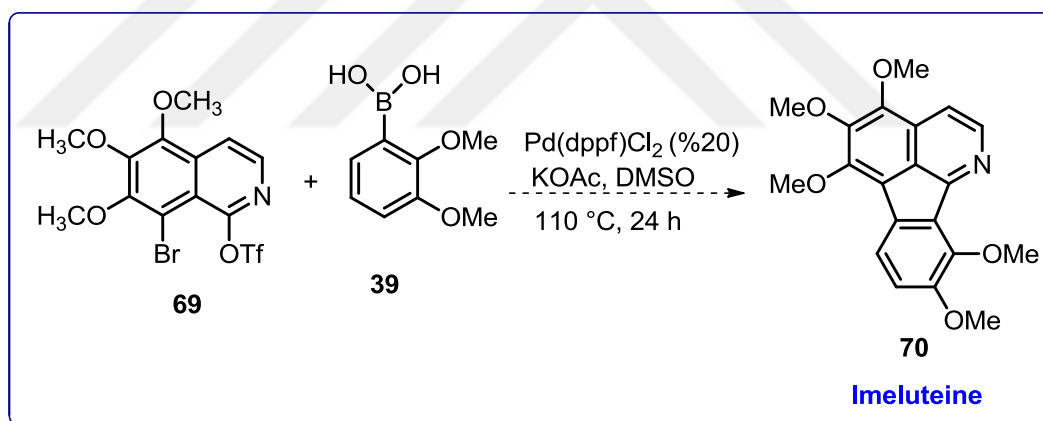
Synthesis of the targeted starting material of imeluteine was achieved in 5 steps starting from the commercially available 3,4,5-trimethoxybenzoic acid (**64**) (Scheme 26). Treatment of benzoic acid **64** with oxalyl chloride produced acyl chloride product **65**.⁴⁰ Amidation of **65** with 2,2-dimethoxyethylamine and triethylamine as a base yielded amide **66**. Amide **66** was in turn cyclized to isoquinolone derivative **67** with the use of aqueous sulfuric acid in 76% yield over two steps. Triflation of isoquinolone **67** afforded **68** in 94% yield. Bromination of triflate **68** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave the corresponding brominated triflate product **69** at 0 °C in the absence of light. Overall, the targeted precursor for the fluoranthene synthesis step was obtained in 46% yield following a literature procedure.⁴¹



Scheme 26. The synthesis of the starting material of imeluteine.

2.2.2.2. Studies for the Synthesis of Imeluteine

After synthesis of starting material of the imeluteine, we focused on the azafluoranthene synthesis (Scheme 27).



Scheme 27. Planned imeluteine synthesis.

The standard reaction condition resulted in decomposition of **69**, which involved hydrolysis of the triflate group, giving the amide product **71** (Figure 13).

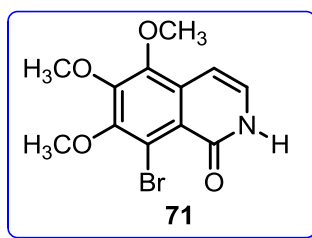


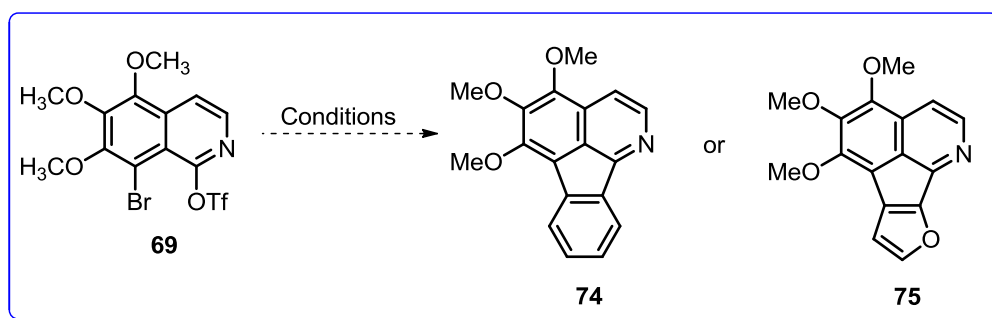
Figure 13. Hydrolysis product **71**.

In order to prevent the hydrolysis of the aryl triflate moiety, we next ran the reaction at 70 °C for 4 hours, using 10% of Pd(dppf)Cl₂. Unfortunately, the hydrolysis product **71** was again the major product observed. We then turned our attention to other reaction conditions reported in the literature for Suzuki coupling reactions.^{42,43} When cesium carbonate (Cs₂CO₃) as a base and toluene-ethanol as a solvent were tried at 100 °C, Suzuki coupling between **69** and 2,3-dimethoxyphenyl boronic acid (**39**) was observed but imeluteine formation could not be achieved as the intramolecular C-H arylation step did not take place.

Despite our efforts to complete the total synthesis of imeluteine resulted in the decomposition of triflate group in **69**. It was believed that imeluteine synthesis was challenging process with 2,3-dimethoxyphenyl boronic acid (**39**) because of its steric and electronic properties. Therefore, our attention was turned to other fluoranthene synthesis.

2.2.2.3. Studies for the Different Fluoranthene Synthesis with **69**

It was considered that unsubstituted boronic acids 2-furyl boronic acid (**72**) and phenyl-boronic acid (**73**) could make fluoranthene synthesis easier so these fluoranthene syntheses **74** and **75** were planned, respectively (Scheme 28).



Scheme 28. Planned fluoranthene syntheses.

In order to achieve two different fluoranthene syntheses, some Suzuki coupling conditions were tried as shown in the Table 4.

Table 4. Optimization studies for fluoranthene **74** and **75**

Entry	ArB(OH) ₂	Temperature	Base	Catalyst
1	 72	100 °C	Cs ₂ CO ₃	Pd(dppf)Cl ₂
2	 73	90 °C	NaHCO ₃	Pd(dppf)Cl ₂
3	 73	90 °C	Na ₂ CO ₃	Pd(dppf)Cl ₂
4	 73	90 °C	NaHCO ₃	Pd(PPh ₃) ₄

These optimization studies resulted in either unknown compound or complex mixture. Despite our best efforts, the desired fluoranthenes either **74** or **75** syntheses were not succeeded.

2.3. CONCLUSION

A six-step sequence has been developed towards the total synthesis of truncatone C. This sequence features highly efficient iodination and Pd-catalyzed borylation steps in addition to a challenging Pd-catalyzed benzo[j]fluoranthene formation reaction. The oxidation of naphthol **58** to the corresponding quinone proved to be difficult and could not be achieved despite many attempts.

In the second part of this section, the total synthesis of the azafluoranthene natural product imeluteine was targeted using the Pd-catalyzed fluoranthene synthesis methodology. The isoquinoline derivative **69** was prepared successfully in five steps. However, this compound was observed to be extremely resilient towards the Pd-catalyzed azafluoranthene formation reaction, possibly due to the high steric congestion around the reaction centers as well as the highly electron-rich nature of the isoquinoline ring.

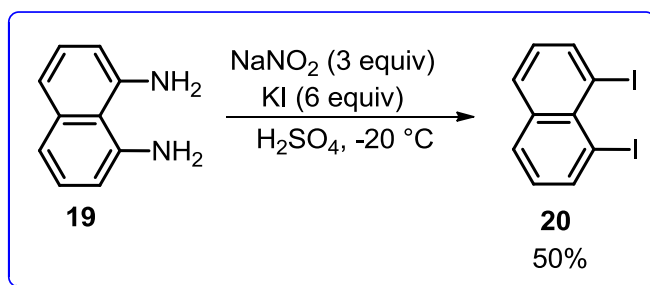
3. EXPERIMENTAL SECTION

3.1. General Information

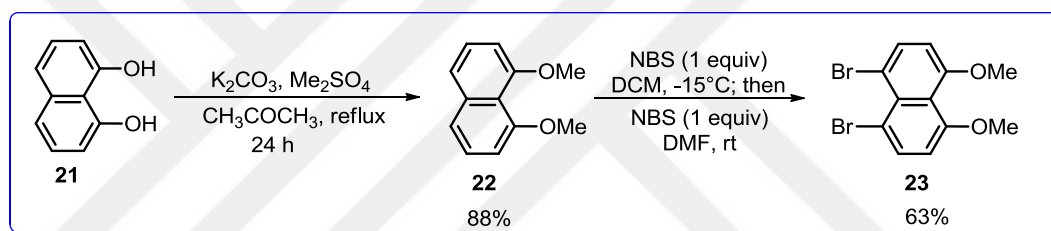
All reactions were performed using oven-dried glassware under an inert atmosphere of nitrogen. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed plates pre-coated with silica gel (Merck, Silica Gel 60 F₂₅₄). UV light and KMnO₄ staining solutions were used for TLC visualization. Flash column chromatography was performed on Silicycle 40-63 μm (230-400 mesh) flash silica gel. NMR spectra were measured on a Bruker spectrometer at 400 MHz for ¹H-NMR spectra and 100 MHz for ¹³C-NMR spectra and calibrated from internal standard (TMS, 0 ppm) or residual solvent signals (chloroform at 7.26 ppm for ¹H spectra, and at 77.16 ppm and for ¹³C spectra). ¹H-NMR data are reported as follows: chemical shift (parts per million, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad, coupling constant (Hz). Infrared (FTIR) spectra were recorded on a Bruker Alpha-Platinum-ATR spectrometer with only selected peaks reported. Mass spectral analyses were performed at UNAM-National Nanotechnology Research Center and Institute of Materials Science and Nanotechnology, Bilkent University.

3.2. Data for Chapter 1

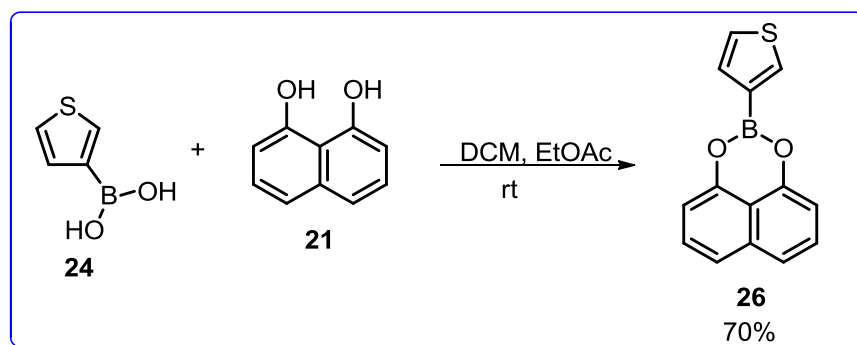
3.2.1. Preparation of Dihalonaphthalene Substrates



1,8-Diiodonaphthalene (**20**)⁴⁴ and 1,8-dibromo-4,5-dimethoxynaphthalene (**23**)^{45,46} were prepared according to reported procedures.

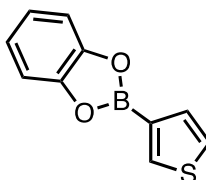


3.2.2. Preparation of Catechol Boronic Ester



Catechol (43 mg, 0.39 mmol) was added to a solution of 3-thiopheneboronic acid (**24**) (50 mg, 0.39 mmol) in anhydrous CH_2Cl_2 (1.3 mL). Ethyl acetate was added dropwise until a homogeneous solution was obtained. The resulting solution was stirred overnight at room temperature. Afterwards, anhydrous Na_2SO_4 was added, and the

resulting mixture was filtered and washed with EtOAc. The resulting solution was concentrated under vacuum to give a pale yellow solid. Recrystallization by slow evaporation from a CH₂Cl₂ solution afforded pure catechol boronic ester **25** as white crystals (81 mg, 51% yield).



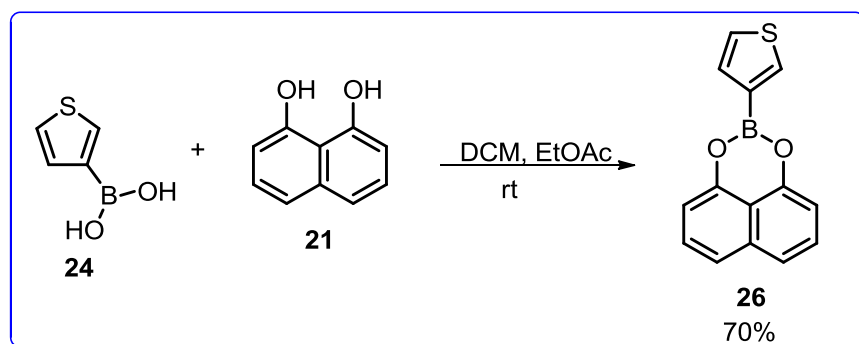
¹H NMR (400 MHz; CDCl₃) δ : 8.26 (1H, dd, J = 2.7, 1.0 Hz), 7.68 (1H, dd, J = 4.9, 1.1 Hz), 7.48 (1H, dd, J = 4.8, 2.7 Hz), 7.36-7.29 (2H, m), 7.16-7.12 (2H, m).

¹³C NMR (100 MHz; CDCl₃) δ : 148.5, 138.3, 131.9, 126.4, 122.9, 112.7

FTIR ν_{max} (ATR, solid)/cm⁻¹ 3091, 2923, 2853, 1521, 1470, 1413, 1300, 1233.

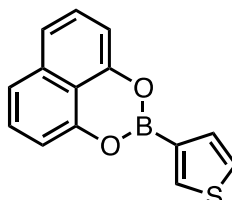
HRMS (-APCI) Calcd for C₁₁H₁₀BO₃S [M+OCH₃]⁺ 233.0449, found: 233.0403.

3.2.3. Preparation of Boronic Ester 26



1,8-Naphthalenediol (**21**) (126 mg, 0.78 mmol) was added to a solution of 3-thiopheneboronic acid (**24**) (100 mg, 0.78 mmol) in anhydrous CH₂Cl₂ (2.6 mL). Ethyl acetate was added dropwise until a homogeneous solution was obtained. The resulting solution was stirred overnight at room temperature. Afterwards, anhydrous Na₂SO₄ was

added, and the resulting mixture was filtered and washed with EtOAc. The resulting solution was concentrated under vacuum to give a pale yellow solid. Recrystallization by slow evaporation from a CH₂Cl₂ solution afforded pure boronic ester **26** as white crystals (138 mg, 70% yield).



¹H NMR (400 MHz; CDCl₃) δ : 8.25 (1H, dd, J = 2.7, 1.0 Hz), 7.67 (1H, dd, J = 4.9, 1.1 Hz), 7.45-7.42 (3H, m), 7.38 (1H, d, J = 8.4 Hz), 7.36 (1H, d, J = 8.4 Hz), 6.97-6.95 (2H, m).

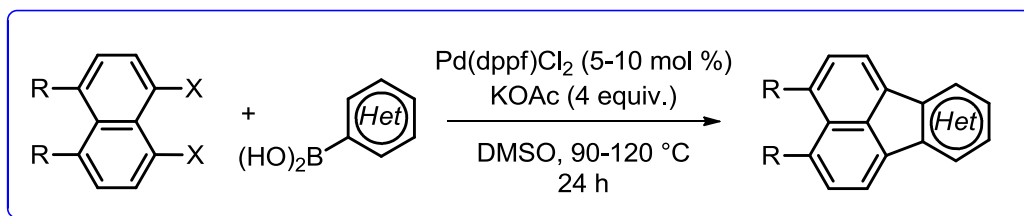
¹³C NMR (100 MHz; CDCl₃) δ : 147.9, 138.1, 135.3, 132.0, 127.9, 125.8, 121.1, 117.7, 109.6.

FTIR ν_{max} (ATR, solid)/cm⁻¹ 1633, 1609, 1517, 1409, 1371, 1296, 1277.

HRMS (+APCI) Calcd for C₁₄H₁₀BO₂S [M+H]⁺ 253.0490, found: 253.0491.

3.2.4. Synthesis of Heteroaromatic Fluoranthenes

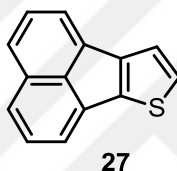
General Procedure



A 25 mL oven-dried, round-bottomed flask was charged with DMSO (2 mL) under nitrogen atmosphere. The solution was deoxygenated by bubbling nitrogen gas

through the solution for 5 min. Dihalonaphthalenes (1.0 equiv), arylboronic acids or boronic esters (1.1 equiv), Pd(dppf)Cl₂•CH₂Cl₂ (5 or 10 mol%) and KOAc (4 equiv) were added sequentially to the solution. The flask was then sealed with a glass stopper, and the reaction mixture was stirred at 110 °C for 24 h. The progress of the reaction was monitored by TLC. After cooling to room temperature, brine (ca. 10 mL) was added to the reaction mixture, and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. The viscous crude product was purified by flash column chromatography (SiO₂) to give the desired product.

Compound 27



Fluoranthene analogue **27** was prepared according to General Procedure using 1,8-diiodonaphthalene (50 mg, 0.13 mmol), 3-thiopheneboronic acid (19 mg, 0.15 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (5.4 mg, 0.006 mmol) and KOAc (52 mg, 0.53 mmol). Purification by flash column chromatography (only hexanes) gave **27** as a yellow solid in 78% yield (21.2 mg).

M.P. = 69.7-70.5 °C

R_f = 0.50 (only hexanes)

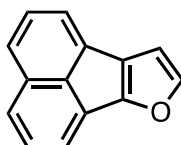
¹H NMR (400 MHz; CDCl₃) δ: 7.76-7.71 (4H, m), 7.56-7.52 (2H, m), 7.41 (1H, d, *J* = 4.8 Hz), 7.37 (1H, d, *J* = 4.9 Hz).

¹³C NMR (100 MHz; CDCl₃) δ: 145.9, 141.6, 134.0, 133.8, 133.6, 129.6, 128.4, 127.80, 127.78, 126.6, 126.3, 120.9, 120.5, 120.2

FTIR $\nu_{\max}$ (ATR,solid)/ cm^{-1} 2922, 2851, 1475, 1431, 1408, 1370, 1185, 1119, 1083.

HRMS (+APCI) Calcd for $\text{C}_{14}\text{H}_9\text{S}$ $[\text{M}+\text{H}]^+$ 209.0420, found: 209.0430.

Compound 30



30

Fluoranthene analogue **30** was prepared according to General Procedure using 1,8-diiodonaphthalene (50 mg, 0.13 mmol), 3-furanylboronic acid (16 mg, 0.15 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (5.4 mg, 0.006 mmol) and KOAc (52 mg, 0.53 mmol). Purification by flash column chromatography (only hexanes) gave **30** as a dark brown oil in 54% yield (13.6 mg).

$R_f = 0.76$ (only hexanes)

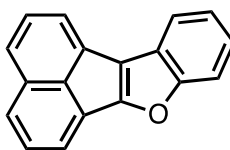
^1H NMR (400 MHz; CDCl_3) δ : 7.72 (1H, dd, $J = 4.1, 0.5$ Hz), 7.71-7.68 (2H, m), 7.64 (1H, dd, $J = 6.8, 0.6$ Hz), 7.54-7.48 (3H, m), 6.78 (1H, d, $J = 2.0$ Hz).

^{13}C NMR (100 MHz; CDCl_3) δ : 146.9, 143.0, 131.5, 130.7, 129.5, 127.7, 127.6, 127.4, 127.01, 126.97, 126.6, 121.9, 119.2, 106.9

FTIR $\nu_{\max}$ (ATR, neat)/ cm^{-1} 3049, 2921, 2851, 1708, 1664, 1478, 1466, 1434.

HRMS (+APCI) Calcd for $\text{C}_{14}\text{H}_9\text{O}$ $[\text{M}+\text{H}]^+$ 193.0648, found: 193.0639.

Compound 31



31

Fluoranthene analogue **31** was prepared according to General Procedure using 1,8-diiodonaphthalene (50 mg, 0.13 mmol), 2-benzofuranylboronic acid (24 mg, 0.15 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (10.8 mg, 0.013 mmol) and KOAc (52 mg, 0.53 mmol). Purification by flash column chromatography (only hexanes) gave **31** as a orange solid in 86% yield (27.5 mg). The spectral data of Compound **31** is in accordance with the reported data in the literature.⁴⁷

M.P. = 78.7-80.0 °C

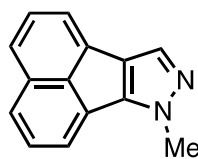
R_f = 0.55 (only hexanes)

¹H NMR (400 MHz; CDCl₃) δ: 7.85-7.80 (4H, m), 7.74 (1H, d, *J* = 8.3 Hz), 7.62-7.54 (3H, m), 7.37-7.29 (2H, m).

FTIR ν_{max} (ATR, solid)/cm⁻¹ 3051, 2923, 2852, 1708, 1665, 1604, 1571, 1478, 1467, 1435.

HRMS (+APCI) Calcd for C₁₈H₁₁O [M+H]⁺ 243.0805, found: 243.0812.

Compound 32



32

Fluoranthene analogue **32** was prepared according to General Procedure using 1,8-diiodonaphthalene (50 mg, 0.13 mmol), 1-Methyl-1H-pyrazole-5-boronic acid pinacol ester (30 mg, 0.15 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (5.4 mg, 0.0060 mmol) and

KOAc (52 mg, 0.53 mmol). Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave **32** as a yellow solid in 80% yield (22 mg).

M.P. = 113.2-114.3 °C

R_f = 0.68 (EtOAc:hexanes = 1:1)

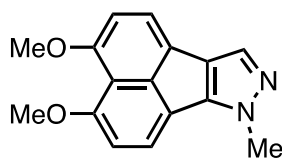
¹H NMR (400 MHz; CDCl₃) δ: 7.79 (1H, dd, *J* = 8.2, 0.4 Hz), 7.68-7.66 (2H, m), 7.65 (1H, s), 7.62 (1H, dd, *J* = 6.8, 0.6 Hz), 7.54 (1H, dd, *J* = 8.2, 7.0 Hz), 7.51 (1H, dd, *J* = 8.2, 6.9 Hz), 4.14 (3H, s).

¹³C NMR (100 MHz; CDCl₃) δ: 148.3, 134.8, 131.8, 131.0, 130.5, 128.2, 127.7, 127.10, 127.05, 126.7, 125.1, 120.9, 119.7, 38.1

FTIR ν_{max} (ATR, solid)/cm⁻¹ 2925, 2851, 1616, 1549, 1478, 1411.

HRMS (+APCI) Calcd for C₁₄H₁₁N₂ [M+H]⁺ 207.0917, found: 207.0928.

Compound 33



33

Fluoranthene analogue **33** was prepared according to General Procedure using 1,8-dibromo-4,5-dimethoxynaphthalene (50 mg, 0.15 mmol), 1-Methyl-1H-pyrazole-5-boronic acid pinacol ester (33 mg, 0.16 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (10.8 mg, 0.013 mmol) and KOAc (57 mg, 0.58 mmol). Purification by flash column chromatography (EtOAc:hexanes = 1:1 to only EtOAc) gave **33** as a yellow solid in 73% yield (28 mg).

M.P. = 241-244°C (decomposition)

$R_f = 0.42$ (only EtOAc)

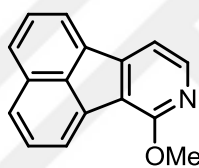
^1H NMR (400 MHz; CDCl_3) δ : 7.64 (1H, d, $J = 7.8$ Hz), 7.58 (1H, s), 7.56 (1H, d, $J = 7.8$ Hz), 6.87 (1H, d, $J = 7.9$ Hz), 6.83 (1H, d, $J = 7.8$ Hz), 4.13 (3H, s), 4.05 (3H, s), 4.02 (3H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 158.6, 156.5, 147.2, 137.9, 130.6, 125.9, 123.2, 122.1, 121.2, 119.2, 115.7, 106.7, 106.0, 56.6, 56.5, 37.9

FTIR ν_{max} (ATR, solid)/ cm^{-1} 2921, 2838, 1592, 1552, 1454, 1417, 1262, 1244.

HRMS (+APCI) Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 267.1129, found: 267.1138.

Compound 35



35

Fluoranthene analogue **35** was prepared according to General Procedure using 1,8-diiodonaphthalene (50 mg, 0.13 mmol), 2-methoxypyridine-3-boronic acid (22 mg, 0.15 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (5.4 mg, 0.006 mmol) and KOAc (52 mg, 0.53 mmol). Purification by flash column chromatography (EtOAc:hexanes = 1:9) gave **35** as a yellow solid in 90% yield (28 mg).

M.P. = 123.3-123.9 °C

$R_f = 0.61$ (EtOAc:hexanes = 1:9)

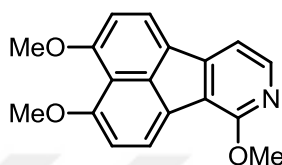
^1H NMR (400 MHz; CDCl_3) δ : 8.24 (1H, d, $J = 5.2$ Hz), 8.14 (1H, d, $J = 6.9$ Hz), 8.02 (1H, d, $J = 7.0$ Hz), 7.96 (1H, d, $J = 8.2$ Hz), 7.84 (1H, d, $J = 8.3$ Hz), 7.68-7.64 (2H, m), 7.47 (1H, d, $J = 5.2$ Hz), 4.22 (3H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 160.5, 149.0, 146.3, 135.2, 134.6, 131.7, 130.0, 129.3, 128.7, 127.8, 126.7, 124.2, 122.8, 120.3, 111.1, 53.6

FTIR ν_{max} (ATR, solid)/ cm^{-1} 2941, 2890, 2851, 1602, 1555, 1422, 1410, 1355.

HRMS (+APCI) Calcd for $\text{C}_{16}\text{H}_{12}\text{NO}$ $[\text{M}+\text{H}]^+$ 234.0914, found: 234.0928.

Compound 36



36

Fluoranthene analogue **36** was prepared according to General Procedure using 1,8-dibromo-4,5-dimethoxynaphthalene (50 mg, 0.15 mmol), 2-methoxypyridine-3-boronic acid (24 mg, 0.16 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (10.8 mg, 0.013 mmol) and KOAc (57 mg, 0.58 mmol). Purification by flash column chromatography (EtOAc:hexanes = 1:4 to EtOAc:hexanes = 1:1) gave **36** as a yellow solid in 56% yield (24 mg).

R_f = 0.77 (EtOAc:hexanes = 1:1)

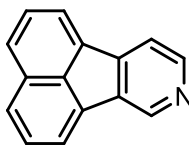
^1H NMR (400 MHz; CDCl_3) δ : 8.14 (1H, d, J = 5.2 Hz), 8.11 (1H, d, J = 7.8 Hz), 8.00 (1H, d, J = 7.8 Hz), 7.42 (1H, d, J = 5.2 Hz), 6.98 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 7.6 Hz), 4.20 (3H, s), 4.09 (3H, s), 4.08 (3H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 160.1, 159.9, 158.1, 147.6, 144.3, 134.8, 127.1, 126.5, 125.9, 124.7, 119.6, 110.3, 107.2, 106.8, 56.63, 56.57, 53.5

FTIR ν_{max} (ATR, solid)/ cm^{-1} 2940, 2835, 1597, 1556, 1500, 1450, 1423.

HRMS (+APCI) Calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 294.1125, found: 294.1140.

Compound 38



38

Fluoranthene analogue **38** was prepared according to General Procedure using 1,8-diiodonaphthalene (50 mg, 0.13 mmol), pyridine-3-boronic acid (18 mg, 0.15 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (5.4 mg, 0.006 mmol) and KOAc (52 mg, 0.53 mmol). Purification by flash column chromatography gave (EtOAc:hexanes = 1:3 to EtOAc:hexanes = 1:1) fluoranthene **38** as a dark green solid in 45% yield (12.0 mg).

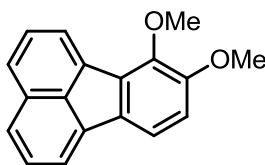
R_f = 0.35 (only EtOAc)

¹H NMR (400 MHz; CDCl₃) δ: 9.19 (1H, s), 8.66 (1H, d, *J* = 5.0 Hz), 8.09 (1H, d, *J* = 6.9 Hz), 8.06 (1H, d, *J* = 6.9 Hz), 8.01 (1H, d, *J* = 8.2 Hz), 7.93 (1H, d, *J* = 8.2 Hz), 7.83 (1H, dd, *J* = 5.0, 0.9 Hz), 7.76-7.66 (2H, m).

FTIR *v*_{max} (ATR, solid)/cm⁻¹ 3040, 2923, 2852, 1602, 1556, 1454, 1425.

HRMS (+APCI) Calcd for C₁₅H₁₀N [M+H]⁺ 204.0808, found: 204.0816.

Compound 40



40

Fluoranthene derivative **40** was prepared according to General Procedure using 1,8-diiodonaphthalene (50 mg, 0.13 mmol), 2,3-dimethoxyphenylboronic acid (26 mg, 0.15 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (5.4 mg, 0.006 mmol) and KOAc (52 mg, 0.53

mmol). Purification by flash column chromatography gave (EtOAc:hexanes = 1:9) fluoranthene **40** as a yellow solid in 76% yield (26 mg).

R_f = 0.45 (EtOAc:hexanes = 9:1)

^1H NMR (400 MHz; CDCl_3) δ : 8.18 (1H, d, J = 6.9 Hz), 7.84-7.82 (2H, m), 7.78 (1H, d, J = 8.2 Hz), 7.67-7.58 (3H, m), 6.92 (1H, d, J = 8.1 Hz), 4.10 (3H, s), 3.97 (3H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 153.2, 146.2, 137.1, 135.6, 133.6, 133.0, 132.5, 130.1, 128.3, 127.9, 126.6, 125.7, 123.4, 119.2, 117.4, 111.6

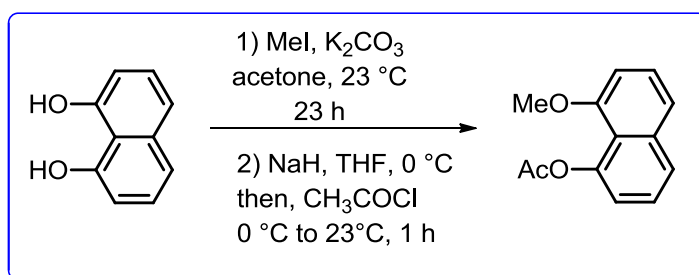
FTIR ν_{max} (ATR, solid)/ cm^{-1} 2922, 2850, 1496, 1445, 1427, 1416.

HRMS (+APCI) Calcd for $\text{C}_{18}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$ 263.1067, found: 263.1076.

3.3. Data for Chapter 2

3.3.1. Arylboronic Ester Synthesis

Compound 54

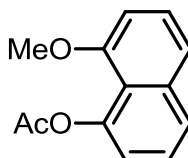


1,8-Naphthalenediol (**21**) (1.00 g, 6.24 mmol) was dissolved in 50 mL of acetone in a 100-mL round-bottomed flask at 23 °C under air. After the sequential addition of K_2CO_3 (1.035 g, 7.49 mmol) and CH_3I (583 μL , 9.37 mmol), the resulting heterogeneous mixture was stirred at 23 °C for 23 h. TLC analysis indicated the full consumption of 1,8-naphthalenediol. The reaction mixture was quenched with saturated

NH₄Cl solution (50 mL) and H₂O (50 mL). The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phase was washed once with brine (70 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a brown solid (1.052 g). This material was used directly in the next step without further purification.

8-Methoxy-1-naphthol (**53**) (1.052 g, obtained via the above procedure) was dissolved in 30 mL of anhydrous THF at rt under nitrogen. The clear solution was cooled to 0 °C and stirred for 10 min. NaH (290 mg, 7.25 mmol, 60% dispersion in mineral oil) was added carefully in portions to the reaction mixture, and vigorous gas evolution was observed. After 10 min, acetyl chloride (CH₃COCl) (647 µL, 9.06 mmol) was slowly added. After an additional stirring of 10 min at 0 °C, the ice bath was removed, and the reaction mixture was stirred at 23 °C for 1 h. TLC analysis indicated the full consumption of 8-methoxy-1-naphthol (**53**). The reaction mixture was quenched with 20 mL of H₂O, and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexanes = 1:9 to 1:4) afforded pure **54** (1.059 g, 85% over two steps) as a white solid.

The ¹H-NMR spectral data are in accordance with the reported data in the literature.⁴⁸



53

M.P. = 82-83 °C

R_f = 0.28 (EtOAc:hexanes = 1:9)

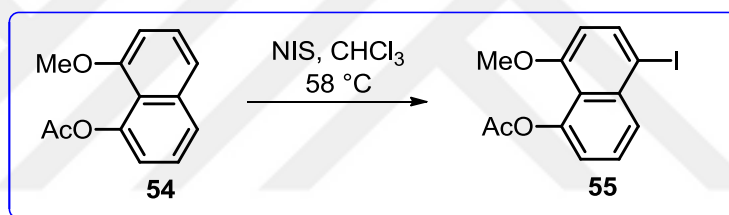
¹H NMR (400 MHz; CDCl₃) δ: 7.70 (1H, dd, *J* = 8.3, 1.1 Hz), 7.47-7.41 (2H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.08 (1H, dd, *J* = 7.4, 1.2 Hz), 6.85 (1H, d, *J* = 7.7 Hz), 3.93 (3H, s), 2.38 (3H, s).

¹³C NMR (100 MHz; CDCl₃) δ: 170.4, 155.3, 146.7, 137.1, 126.54, 126.52, 126.2, 121.2, 119.4, 119.3, 106.3, 56.2, 21.1

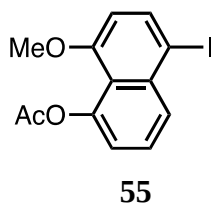
FTIR ν_{max} (ATR, solid)/cm⁻¹ 2968, 2935, 2842, 1742, 1599, 1579, 1462, 1368, 1267, 1206.

HRMS (APCI+) Calcd for C₁₃H₁₃O₃ [M+H]⁺ 217.0860, found: 217.0866.

Compound 55



8-Methoxy-1-acetoxynaphthalene (**54**) (200 mg, 0.93 mmol) was dissolved in 2 mL of chloroform (CHCl₃) in a 25-mL round-bottomed flask at room temperature. After the addition of *N*-iodosuccinimide (916 mg, 4.07 mmol) and additional CHCl₃ (5 mL), the resulting mixture was stirred at 58 °C for 4 h with air-condenser. Afterwards, the reaction mixture was quenched with saturated aqueous Na₂S₂O₃ solution (5 mL) and brine (10 mL). The aqueous phase was extracted with EtOAc (2×10 mL). The combined organic phase was washed once with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexanes = 1:9) afforded pure **55** (279 mg, 88%) as a white solid.



M.P. = 135.1-136.2 °C

R_f = 0.40 (EtOAc:hexanes = 1:5)

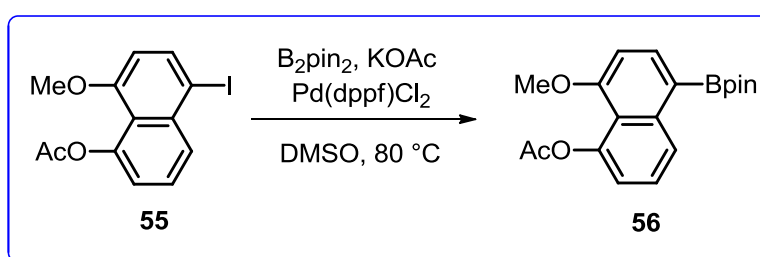
¹H NMR (400 MHz; CDCl₃) δ: 8.02 (1H, dd, *J* = 8.6, 1.2 Hz), 7.98 (1H, d, *J* = 8.3 Hz), 7.53 (1H, dd, *J* = 8.6, 7.5 Hz), 7.15 (1H, dd, *J* = 7.5, 1.2 Hz), 6.62 (1H, d, *J* = 8.3 Hz), 3.92 (3H, s), 2.37 (3H, s).

¹³C NMR (100 MHz; CDCl₃) δ: 170.3, 156.3, 146.7, 137.9, 136.7, 131.2, 127.7, 120.4, 120.2, 107.8, 88.8, 56.4, 21.1

FTIR ν_{max} (ATR, solid)/cm⁻¹ 2963, 2919, 2850, 1744, 1587, 1566, 1502, 1455, 1362, 1311, 1254, 1207.

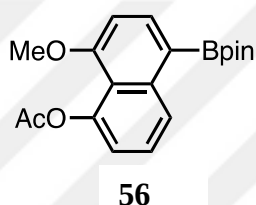
HRMS (APCI+) Calcd for C₁₃H₁₂IO₃ [M+H]⁺: 342.9826, found: 342.9837.

Compound 56



The procedure for the preparation of boronic ester **56** was adapted from the work of Miyaura.³⁸ A 25 mL oven-dried, round-bottomed flask was charged with DMSO (5 mL) under nitrogen atmosphere. The solution was deoxygenated by bubbling nitrogen gas through the solution for 5 min. Iodonaphthalene **55** (400 mg, 1.17 mmol), B₂pin₂ (326 mg, 1.29 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (48 mg, 0.058 mmol) and KOAc (344 mg,

3.51 mmol) were added sequentially to the solution. The flask was then sealed with a glass stopper, and the reaction mixture was stirred at 80 °C for 100 min. TLC analysis at the end of this time indicated full consumption of the starting material. After cooling to room temperature, brine (ca. 10 mL) was added to the reaction mixture, and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. Purification by flash column chromatography (CH₂Cl₂:hexanes = 1:1 to only CH₂Cl₂) afforded boronic ester **56** (282 mg, 71% yield) as a white solid.



M.P. = 168.6-169.8 °C

R_f = 0.41 (EtOAc:hexanes = 1:5)

¹H NMR (400 MHz; CDCl₃) δ: 8.72 (1H, dd, *J* = 8.6, 1.2 Hz), 8.03 (1H, d, *J* = 7.9 Hz), 7.48 (1H, dd, *J* = 8.5, 7.5 Hz), 7.06 (1H, dd, *J* = 7.4, 1.2 Hz), 6.84 (1H, d, *J* = 8.0 Hz), 3.95 (3H, s), 2.36 (3H, s), 1.40 (12H, s).

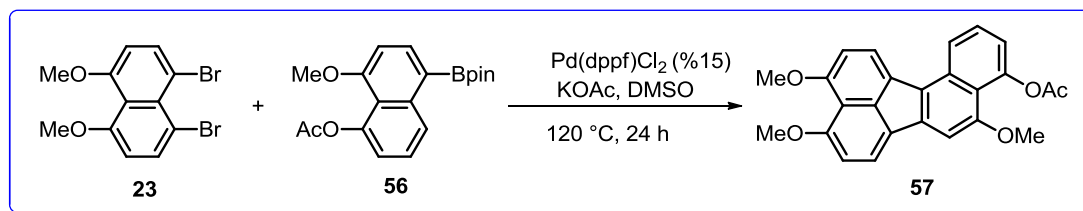
¹³C NMR (100 MHz; CDCl₃) δ: 170.4, 158.1, 146.7, 140.8, 137.4, 127.2, 126.6, 119.3, 119.2, 105.5, 83.7, 56.2, 25.1, 21.2

FTIR ν_{max} (ATR, solid)/cm⁻¹ 2975, 1756, 1587, 1511, 1459, 1360, 1332, 1255, 1218.

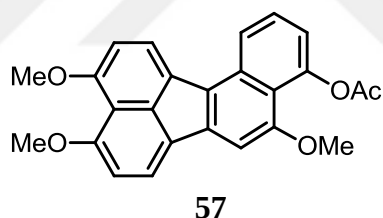
HRMS (APCI+) Calcd for C₁₉H₂₄BO₅ [M+H]⁺: 343.1712, found: 343.1737.

3.3.2. Benzo[j]Fluoranthene Synthesis

Compound 57



Benzo[j]fluoranthene derivative **58** was prepared according to General Procedure I using 1,8-dibromo-4,5-dimethoxynaphthalene (50 mg, 0.15 mmol), arylboronic ester **56** (54 mg, 0.16 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (17.8 mg, 0.021 mmol) and KOAc (57 mg, 0.58 mmol). The reaction mixture was stirred at 120 °C for 24 h. Purification by flash column chromatography (EtOAc:hexanes = 1:3 to only EtOAc) gave fluoranthene **57** as a yellow solid in 34% yield (20 mg).



R_f = 0.55 (EtOAc:hexanes = 1:1)

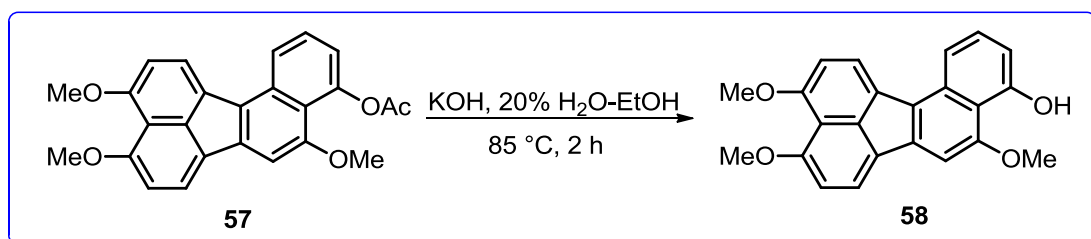
¹H NMR (400 MHz; CDCl₃) δ : 8.53 (1H, d, J = 8.5 Hz), 8.26 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J = 7.8 Hz), 7.55 (1H, dd, J = 8.3, 7.5 Hz), 7.40 (1H, s), 7.04 (1H, dd, J = 7.4, 1.0 Hz), 6.97 (1H, d, J = 7.4 Hz), 6.95 (1H, d, J = 7.6 Hz), 4.09 (6H, s), 4.07 (3H, s), 2.41 (3H, s).

¹³C NMR (100 MHz; CDCl₃) δ : 170.4, 159.1, 157.4, 155.0, 147.7, 137.6, 135.4, 133.3, 130.0, 129.1, 127.0, 126.4, 124.5, 122.6, 122.4, 118.6, 118.5, 114.5, 107.0, 106.7, 100.6, 56.64, 56.59, 56.57, 21.2

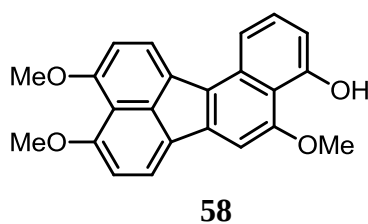
FTIR $\nu_{\max}$ (ATR, solid)/ cm^{-1} 2968, 1836, 1758, 1589, 1459, 1427, 1404, 1363.

HRMS (+APCI) Calcd for $\text{C}_{25}\text{H}_{21}\text{O}_5$ $[\text{M}+\text{H}]^+$: 401.1384, found: 401.1390.

3.3.3. Naphthol 58 Synthesis



KOH (6.5 mg, 0.11 mmol) was added to a solution of benzo[*j*]fluoranthene **57** (15 mg, 0.038 mmol) in 20% H₂O-EtOH mixture (2 mL) at room temperature, and the mixture was heated at 85 °C for 2 h. It was then cooled down to ambient temperature and quenched with 1.0 M aqueous HCl solution, followed by the addition of 4 mL of saturated aqueous NH₄Cl solution. The aqueous phase was extracted CH₂Cl₂ (3×4 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated under vacuum. Purification by flash column chromatography (EtOAc:hexanes = 1:1) gave hydrolysis product **58** as a dark yellow solid (12 mg, 91% yield).



R_f = 0.61 (EtOAc:hexanes = 1:1)

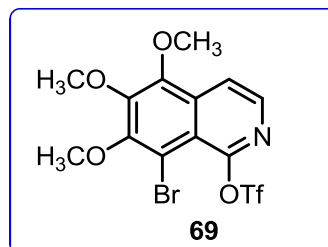
¹H NMR (400 MHz; CDCl₃) δ : 9.64 (1H, s), 8.28 (1H, d, J = 8.0 Hz), 8.11 (1H, d, J = 8.7 Hz), 7.91 (1H, d, J = 7.7 Hz), 7.48 (1H, t, J = 8.0 Hz), 7.35 (1H, s), 6.97 (1H, d, J = 8.3 Hz), 6.95 (1H, d, J = 8.2 Hz), 6.87 (1H, d, J = 7.6 Hz), 4.21 (3H, s), 4.09 (6H, s).

FTIR $\nu_{\max}$ (ATR, solid)/ cm^{-1} 3360, 2922, 2851, 1587, 1454, 1422, 1397, 1368.

HRMS (+APCI) Calcd for C₂₃H₁₉O₄ [M+H]⁺: 359.1278, found: 359.1285.

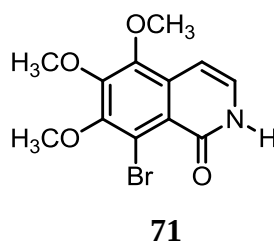
3.3.4. Studies for the Synthesis of Imeluteine

Isoquinoline derivative **69** was prepared according to reported procedures.^{40,41}



Imeluteine (**70**) was attempted to be synthesized following General Procedure using isoquinoline derivative **69** (30 mg, 0.067 mmol), 2,3-dimethoxyphenylboronic acid (13.5 mg, 0.074 mmol), Pd(dppf)Cl₂•CH₂Cl₂ (5.5 mg, 0.006 mmol) and KOAc (26.4 mg, 0.27 mmol). The reaction mixture was stirred at 70 °C for 4 h. After cooling to ambient temperature, brine was added to the reaction mixture, and the aqueous phase was extracted with EtOAc (2×10 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under vacuum. Purification by flash column chromatography (EtOAc:hexanes = 1:2 to EtOAc:hexanes = 1:1) gave only hydrolysis product **71**.

Compound 71



R_f = 0.33 (EtOAc:hexanes = 1:1)

¹H NMR (400 MHz; CDCl₃) δ : 10.61 (1H, br s), 7.11 (1H, d, J = 7.1 Hz), 6.79 (1H, d, J = 7.3 Hz), 4.04 (3H, s), 3.95 (3H, s), 3.93 (3H, s).

^{13}C NMR (100 MHz; CDCl_3) δ : 162.3, 151.3, 150.0, 147.1, 132.8, 120.1, 112.9, 100.3, 61.6, 61.4, 61.0

FTIR ν_{max} (ATR, solid)/ cm^{-1} 3173, 2939, 2848, 1656, 1644, 1581, 1464, 1449, 1398, 1373.

HRMS (+APCI) Calcd for $\text{C}_{12}\text{H}_{13}^{79}\text{BrNO}_4$ $[\text{M}+\text{H}]^+$: 314.0023, found: 314.0032; calcd for $\text{C}_{12}\text{H}_{13}^{81}\text{BrNO}_4$ $[\text{M}+\text{H}]^+$: 316.0002, found: 316.0013.



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5. APPENDIX

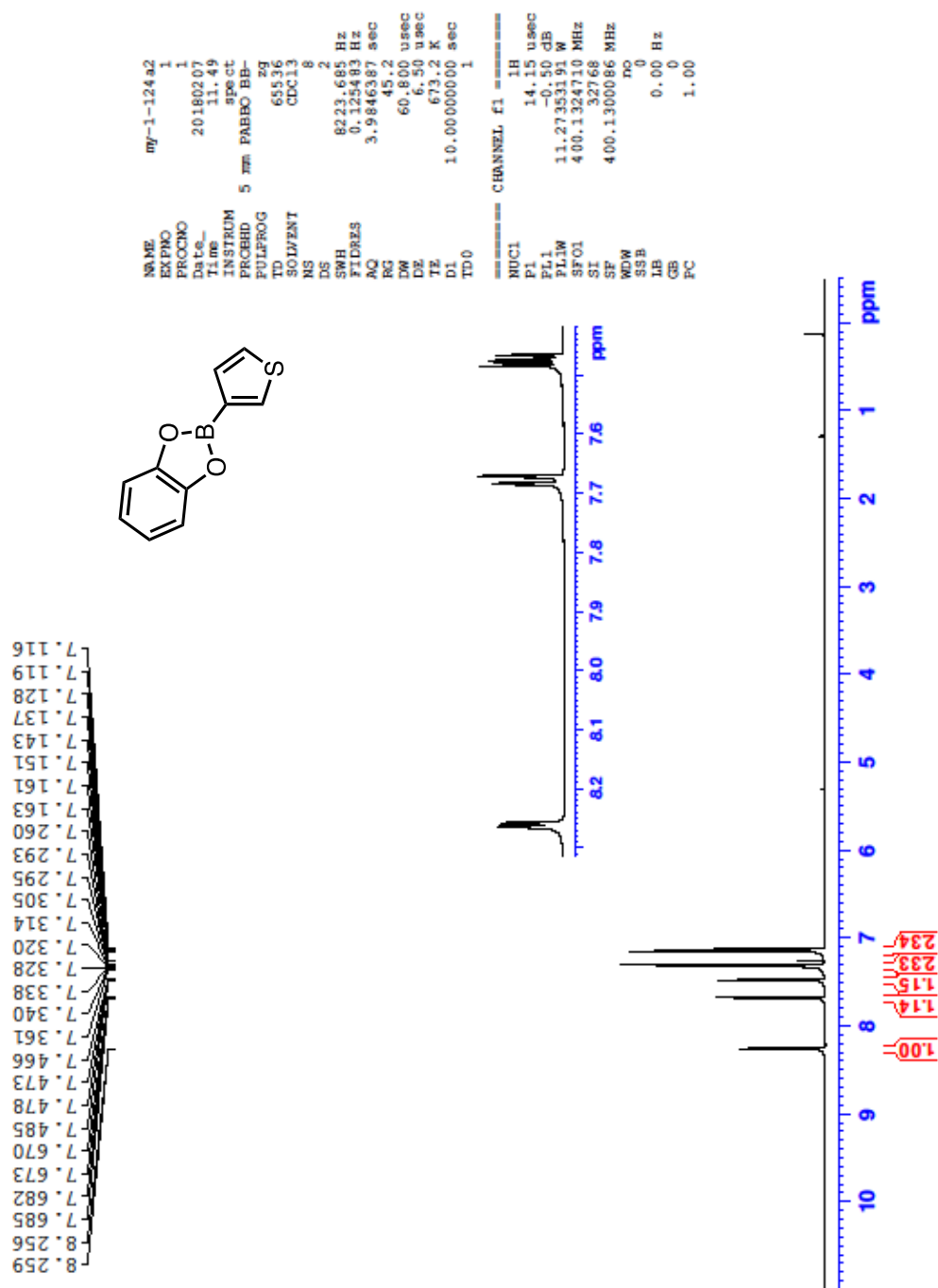


Figure 14. ^1H -NMR spectrum of compound 25.

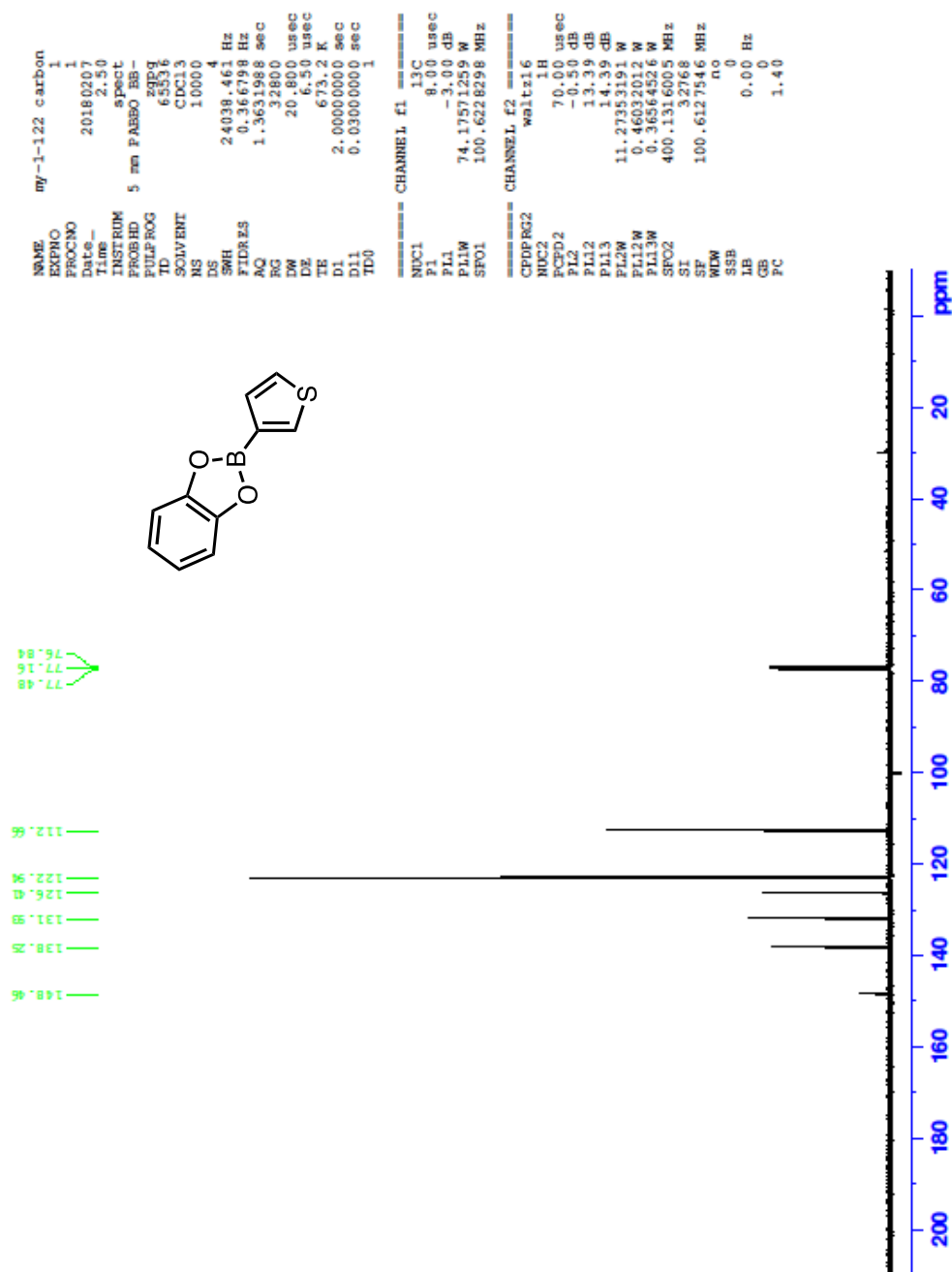


Figure 15. ¹³C-NMR spectrum of compound 25.

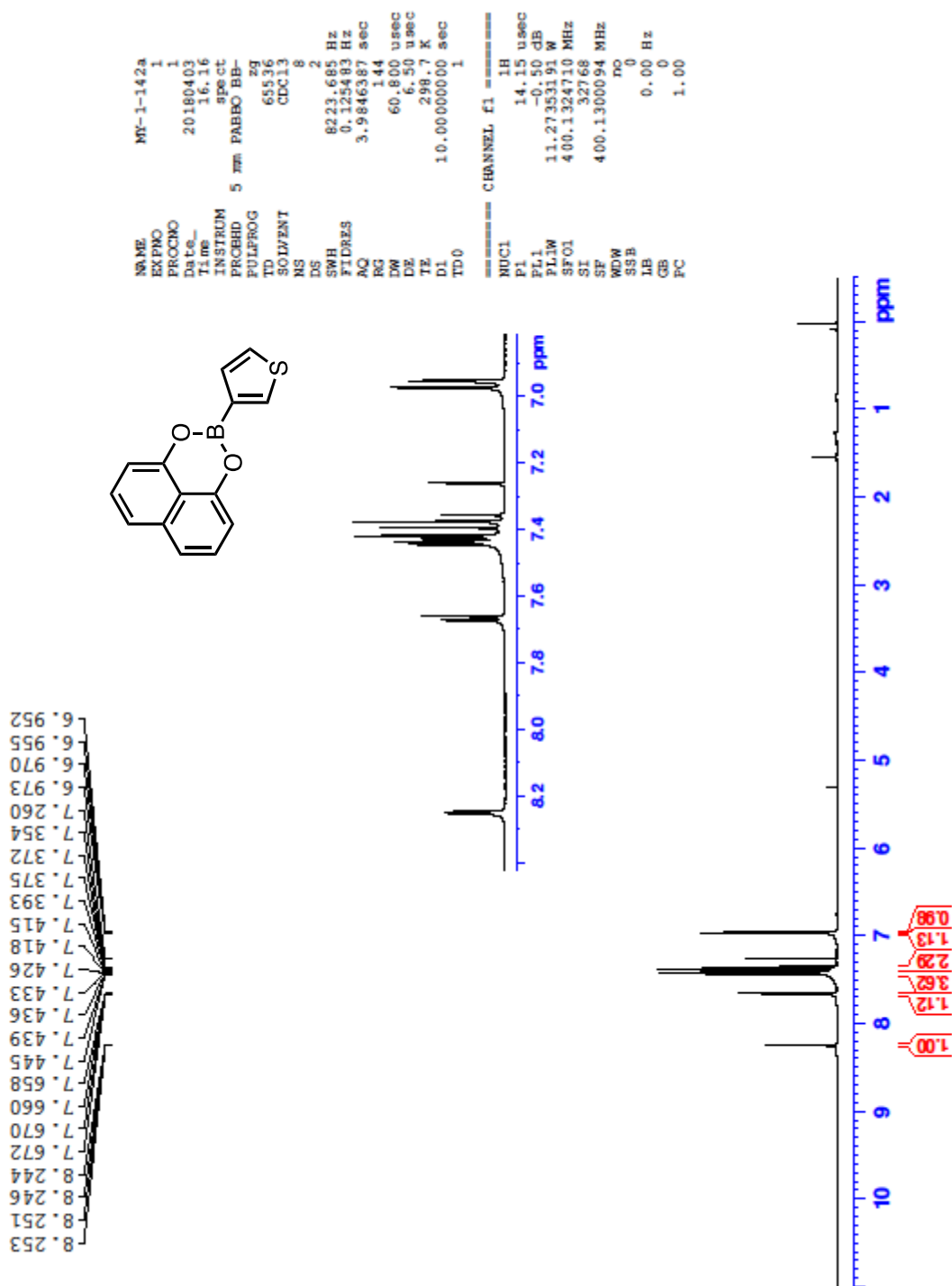


Figure 16. ^1H -NMR spectrum of compound 26.

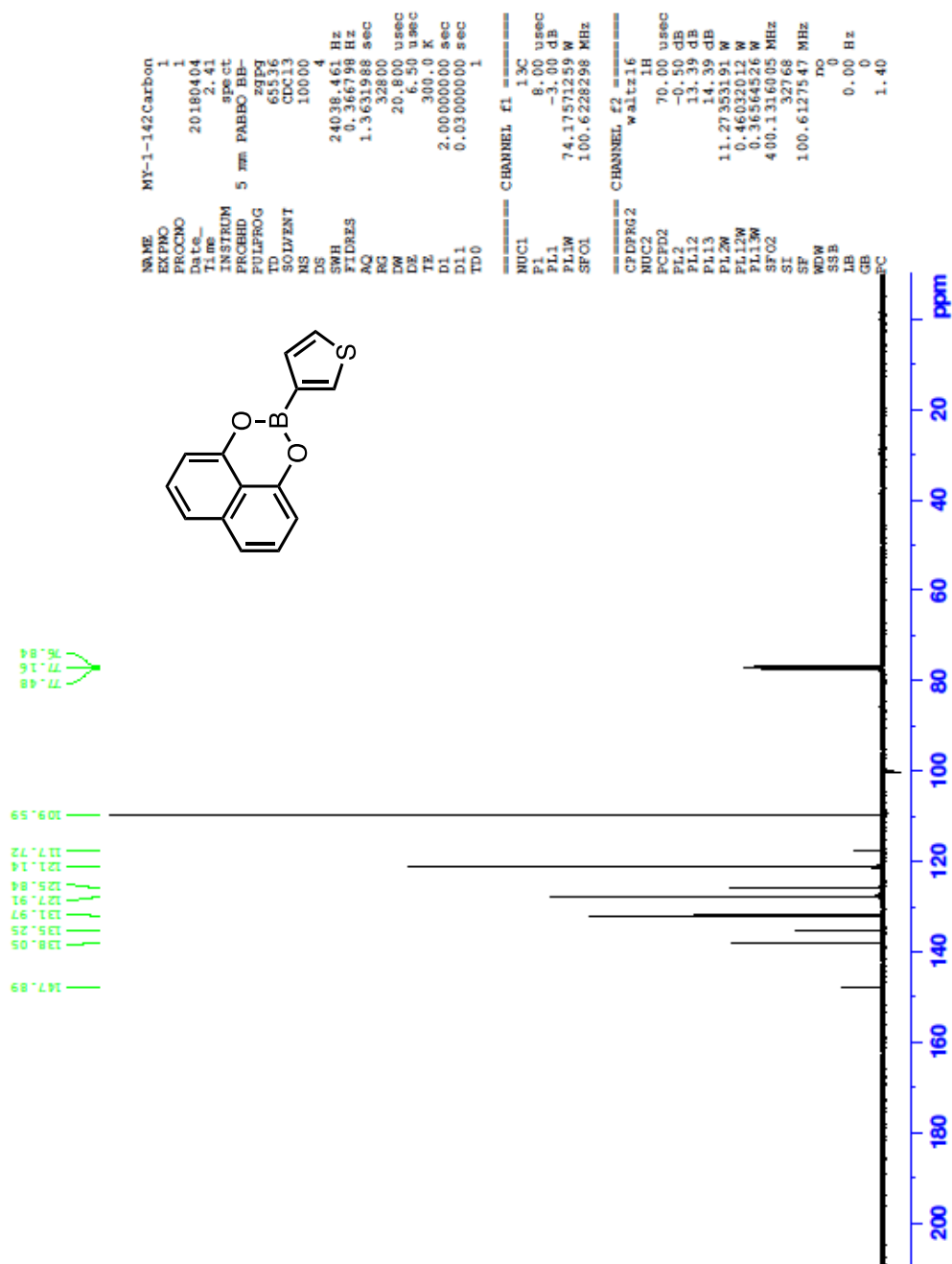


Figure 17. ^{13}C -NMR spectrum of compound 26.

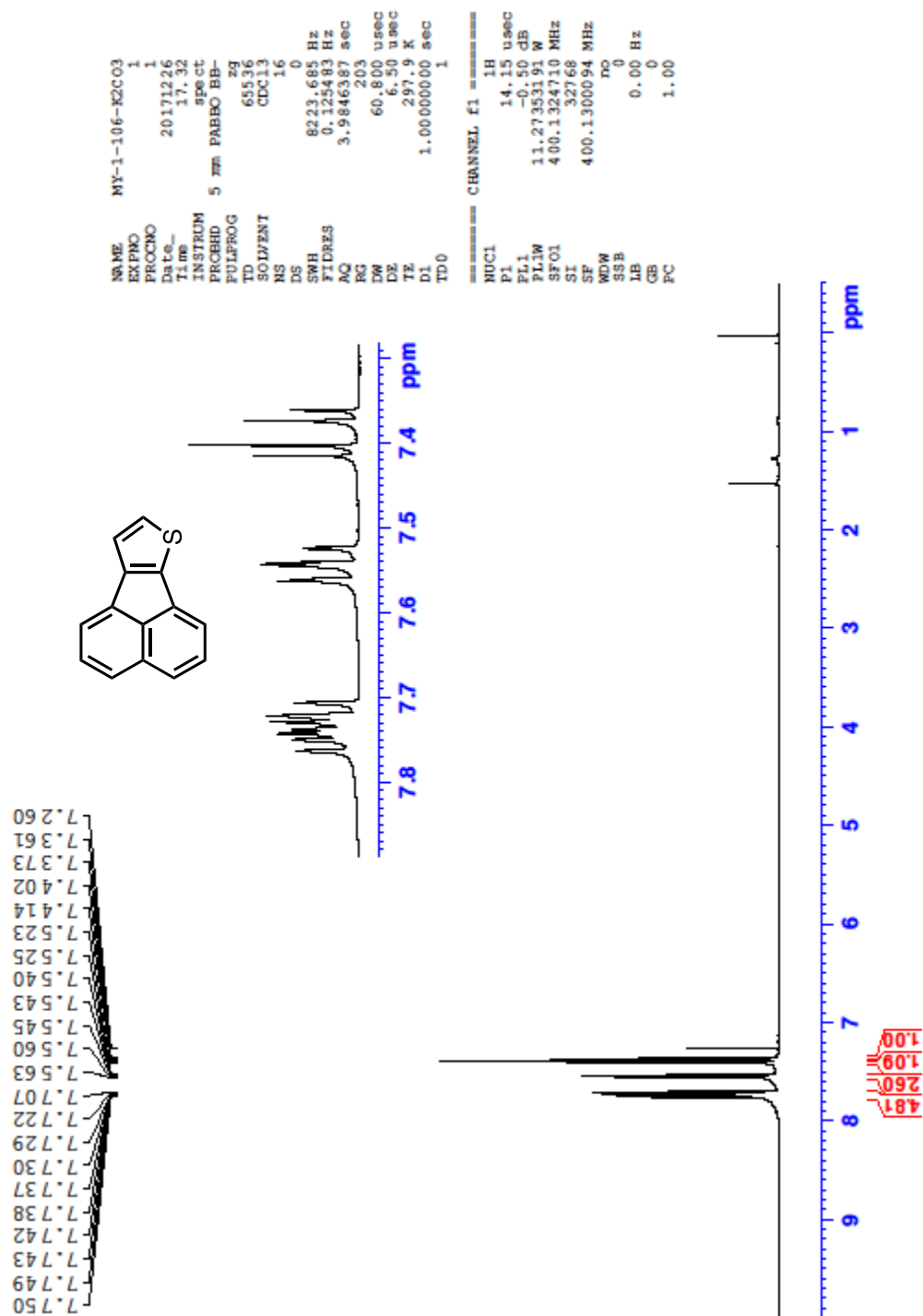
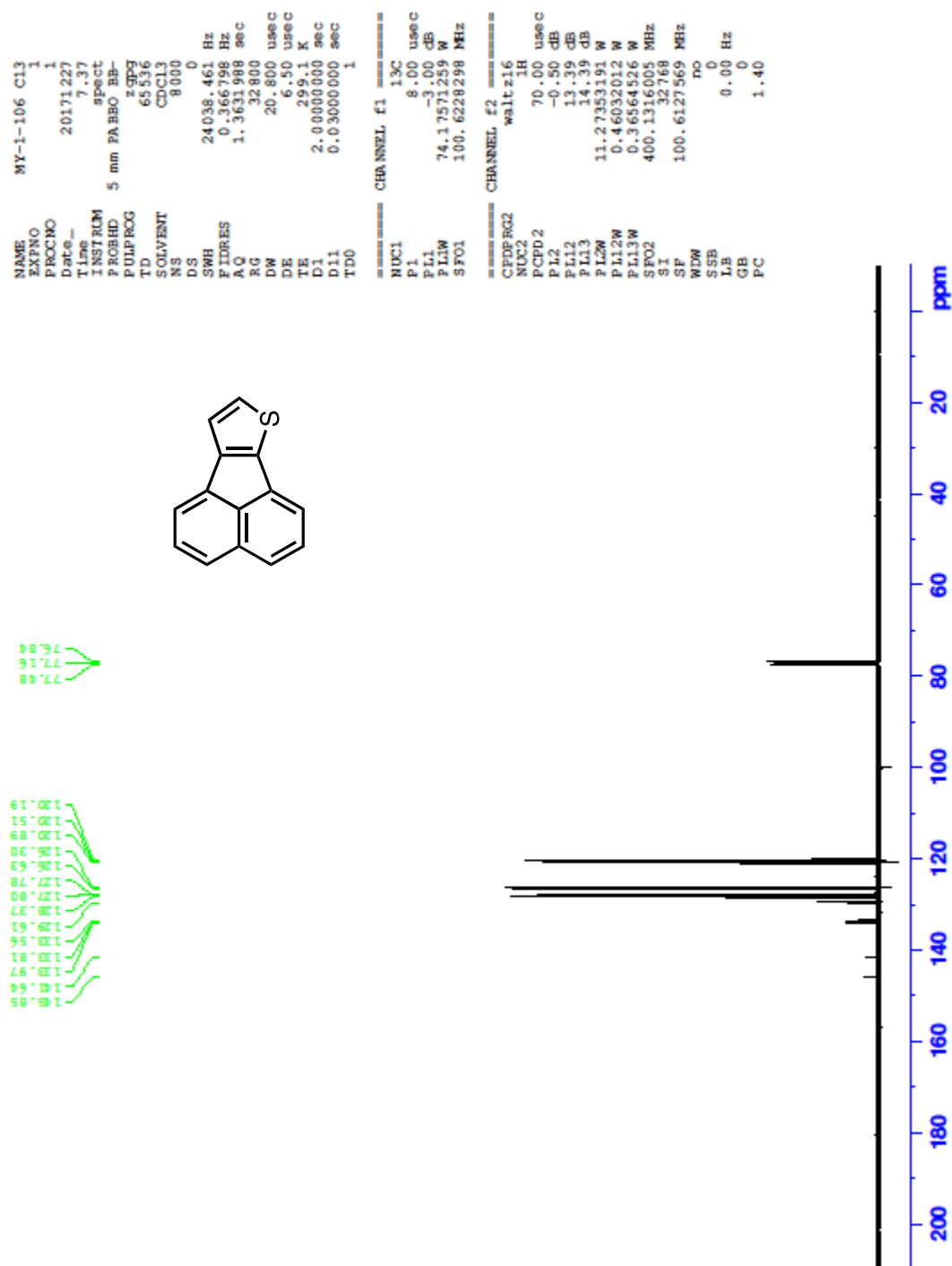


Figure 18. ¹H-NMR spectrum of compound 27.



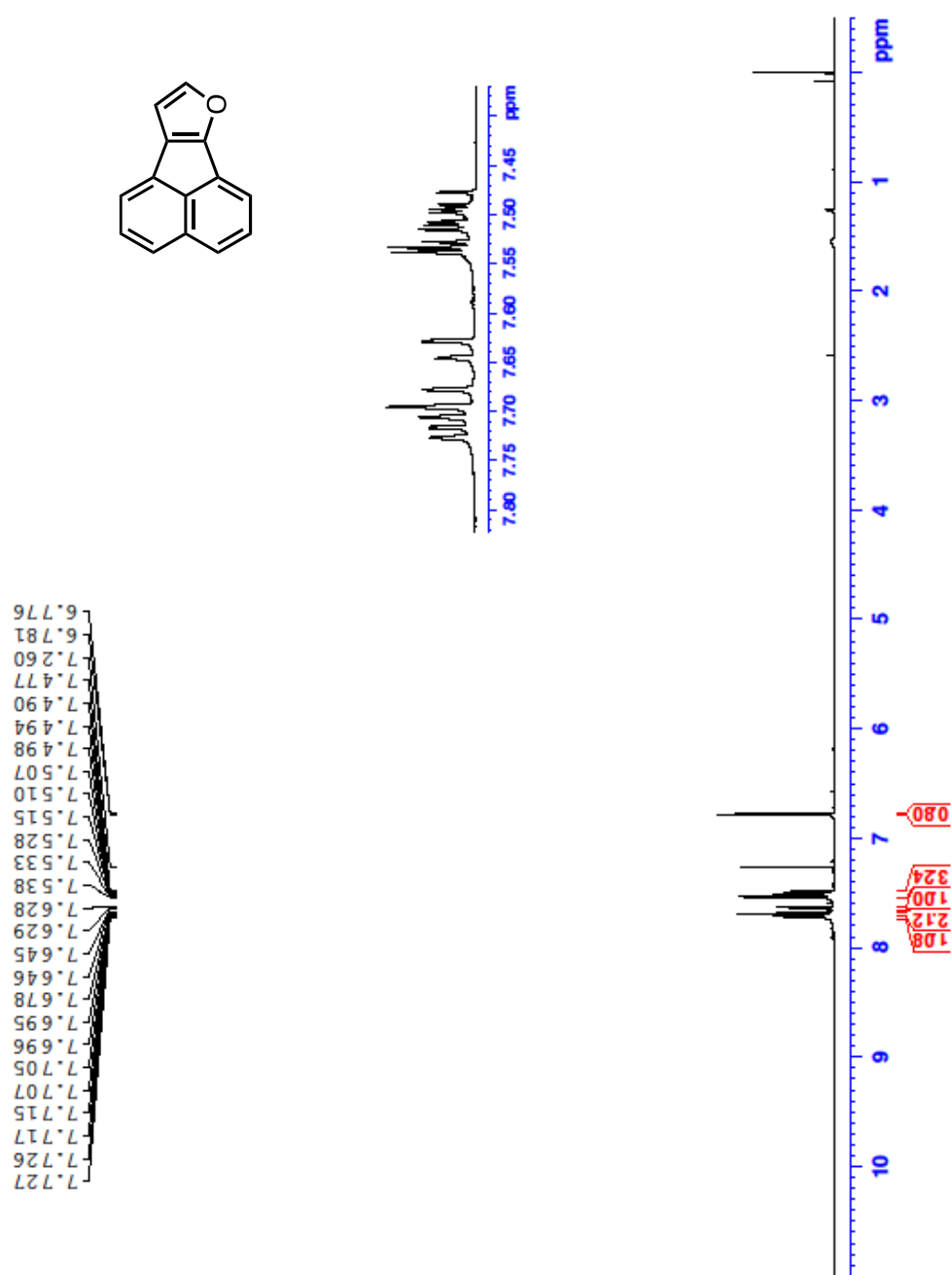


Figure 20. ^1H -NMR spectrum of compound 30.



Figure 21. ^{13}C -NMR spectrum of compound 30.

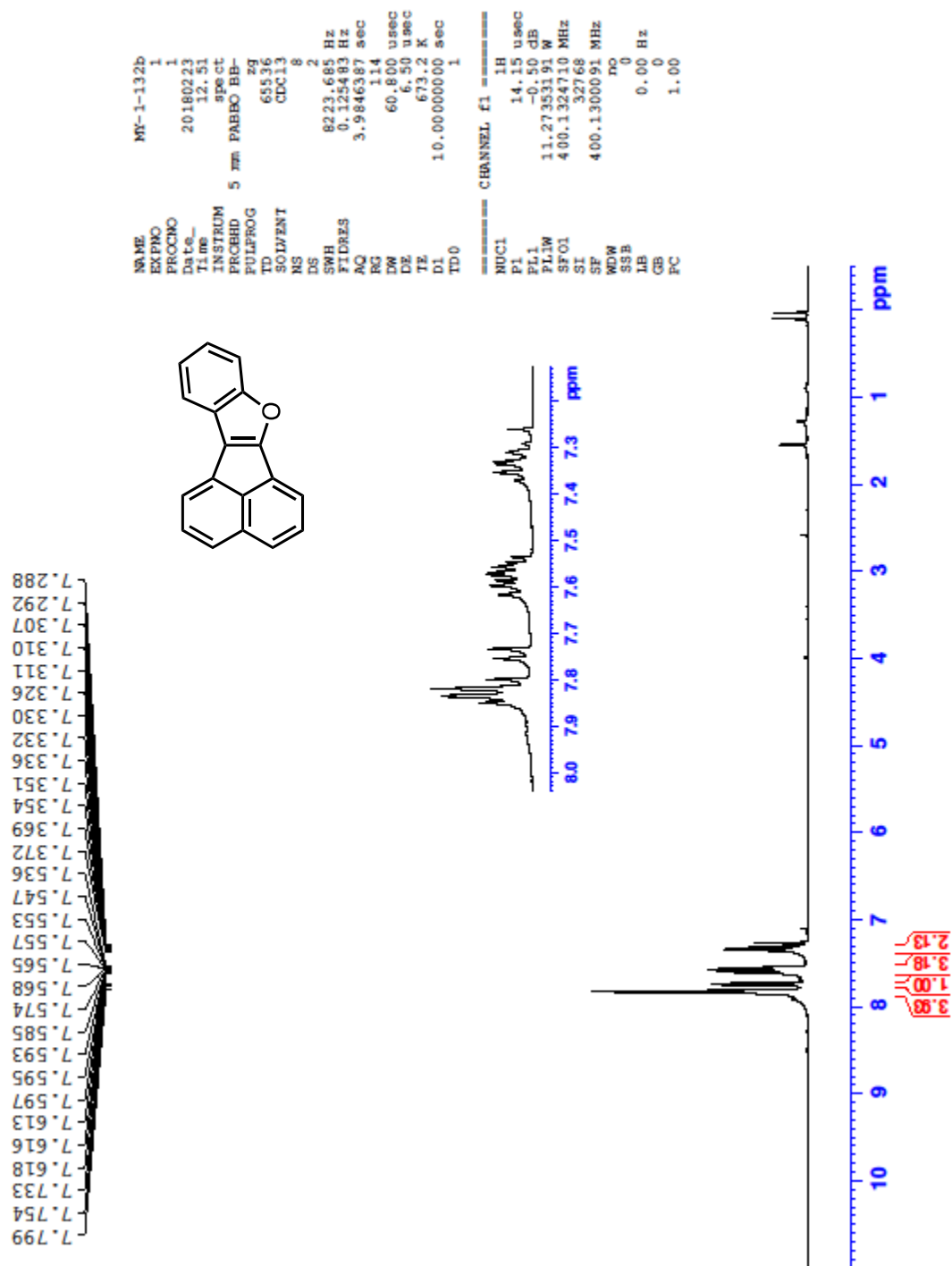


Figure 22. ¹H-NMR spectrum of compound 31.

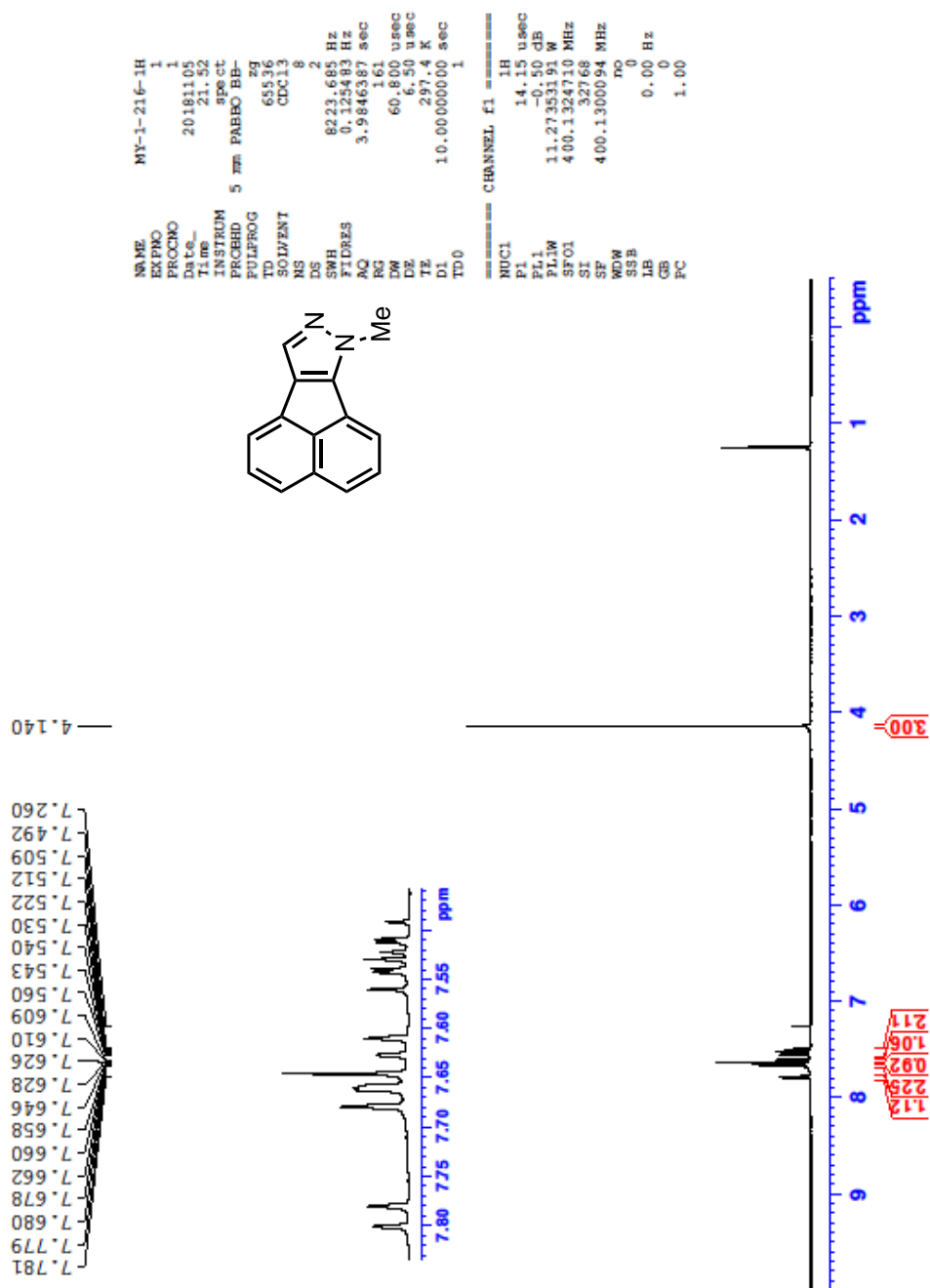


Figure 23. ^1H -NMR spectrum of compound 32.

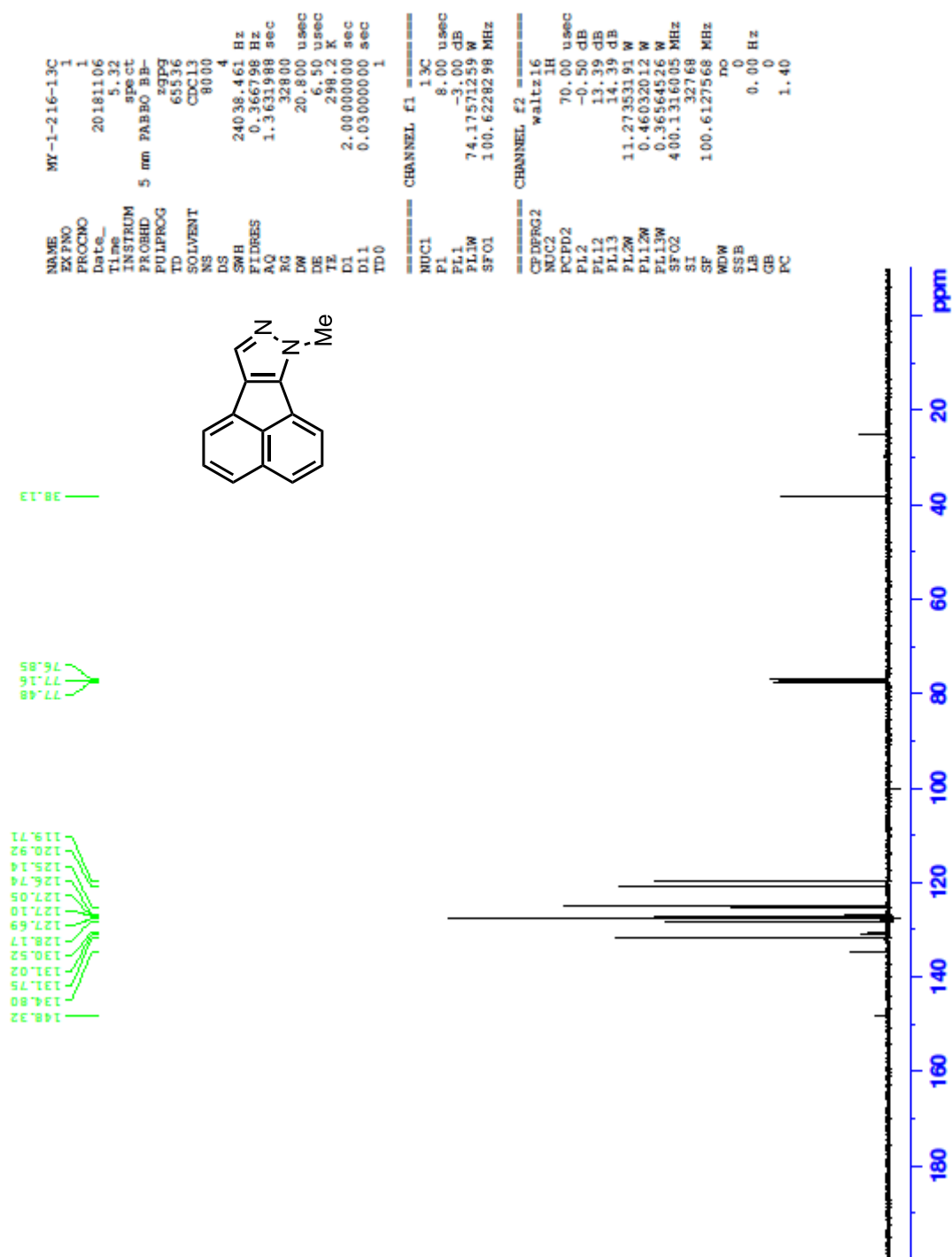


Figure 24. ^{13}C -NMR spectrum of compound **32**.

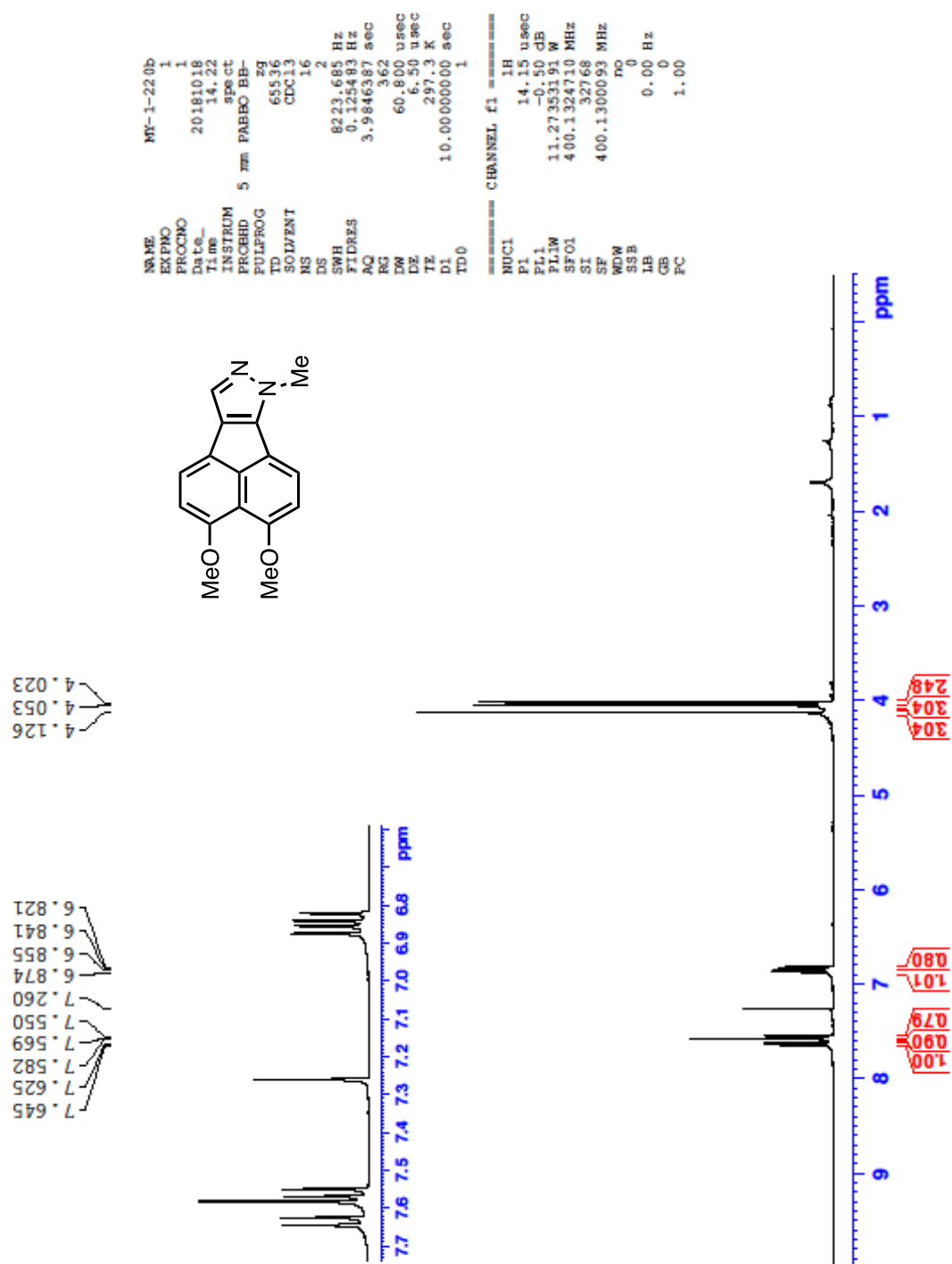


Figure 25. ¹H-NMR spectrum of compound 33.

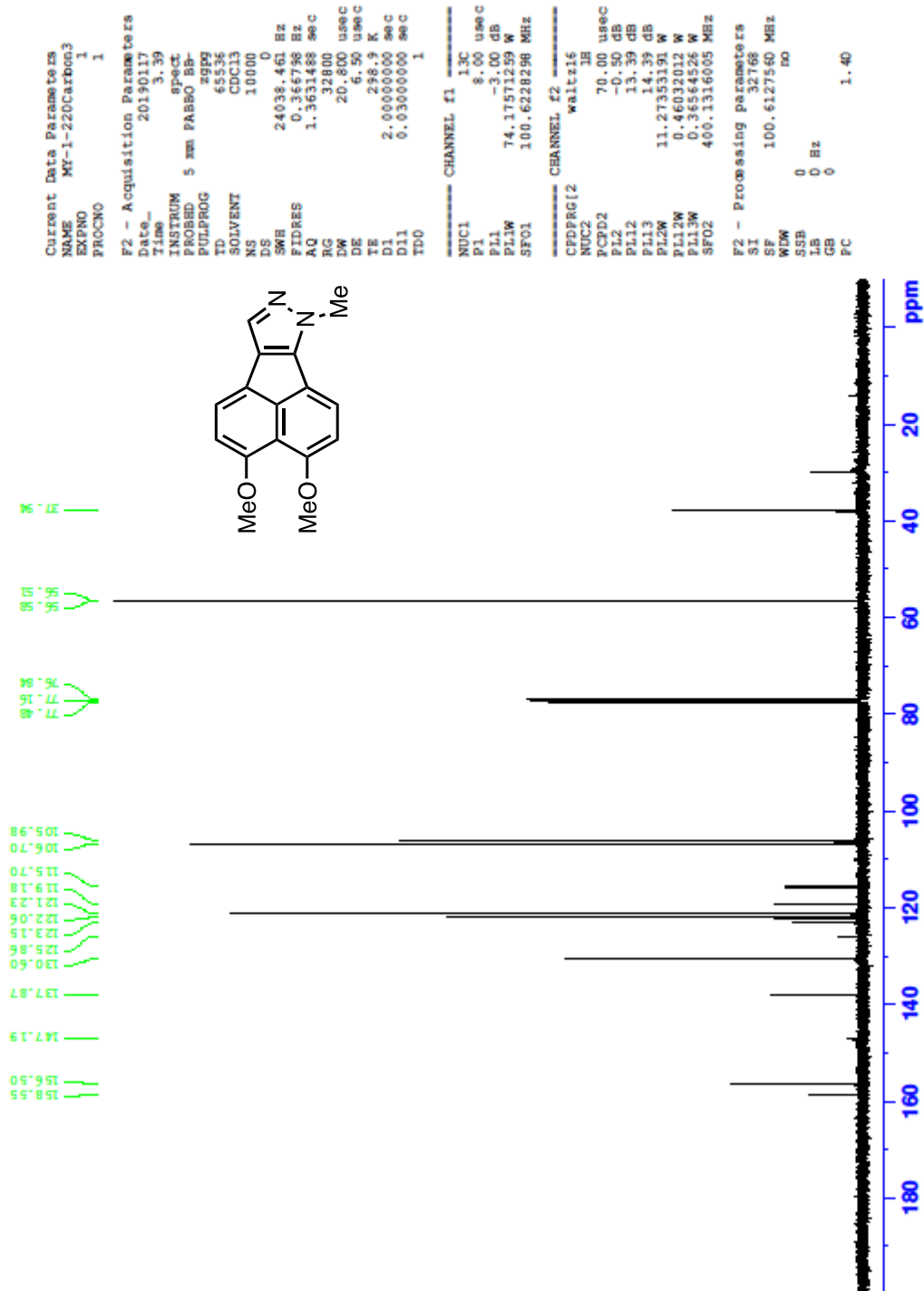


Figure 26. ^{13}C -NMR spectrum of compound 33.

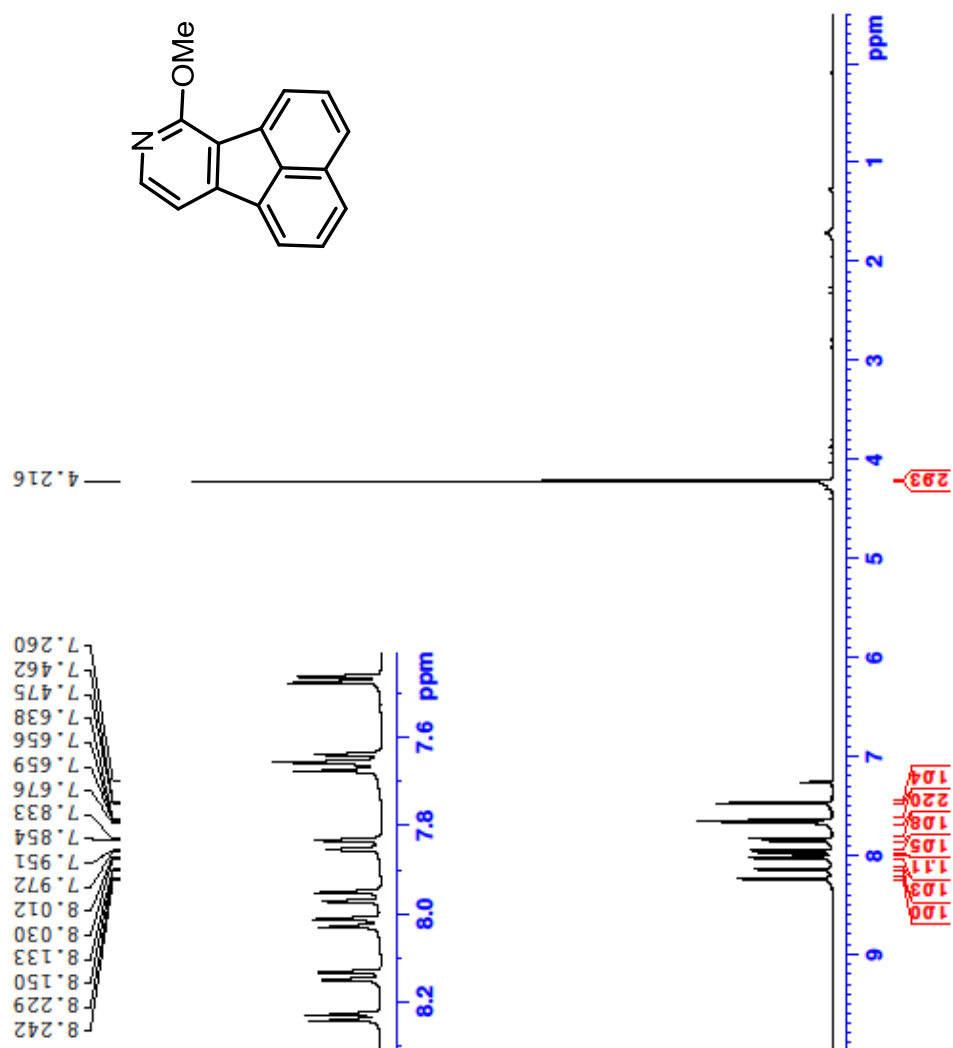


Figure 27. ^1H -NMR spectrum of compound 35.

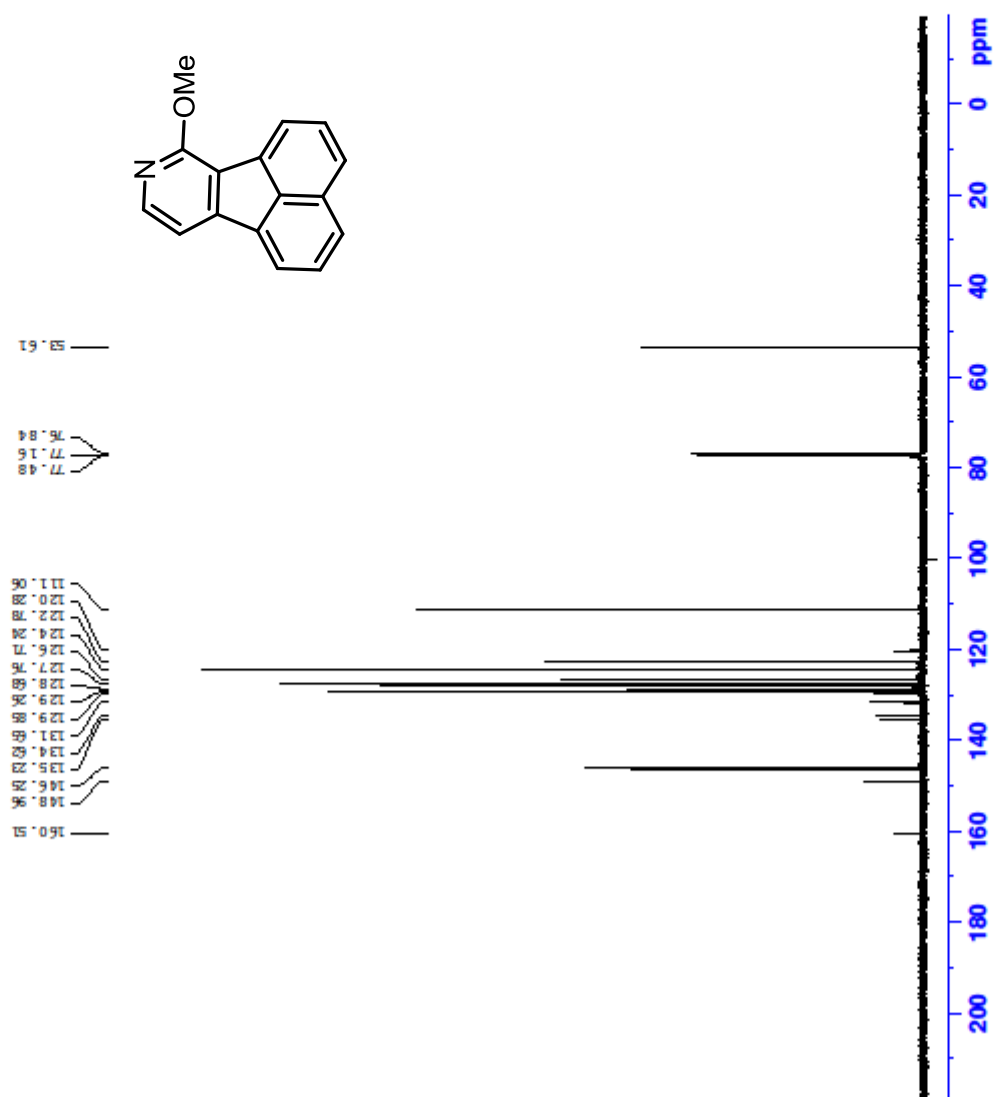


Figure 28. ¹³C-NMR spectrum of compound 35.

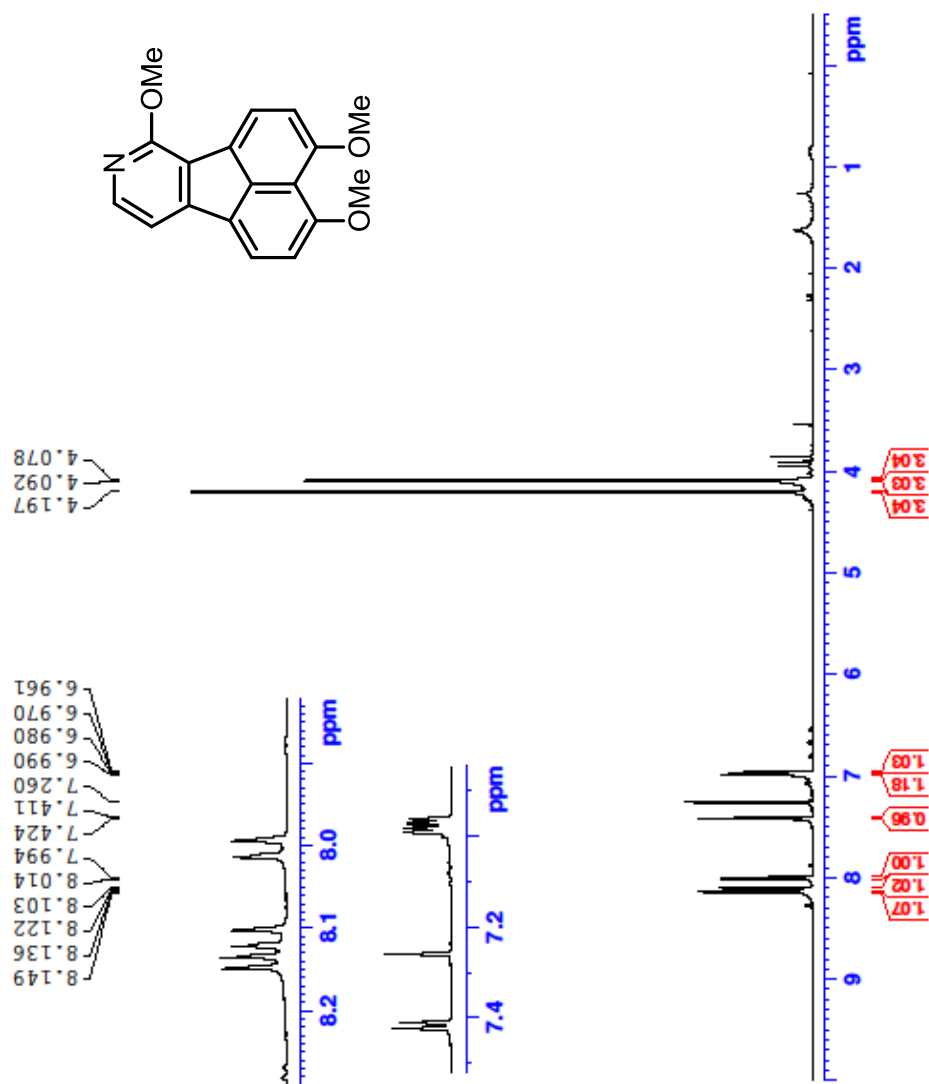


Figure 29. ^1H -NMR spectrum of compound 36.

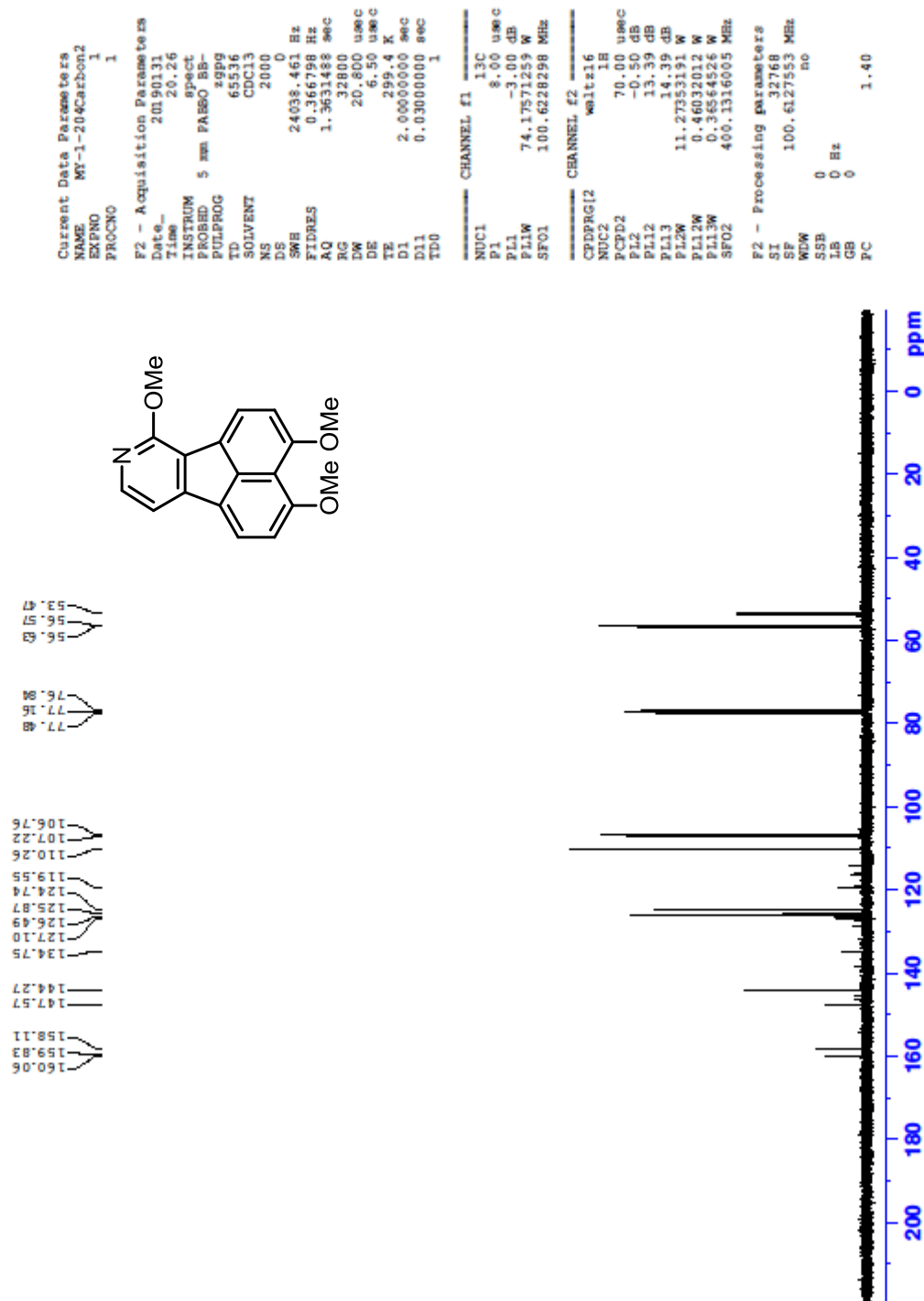


Figure 30. ^{13}C -NMR spectrum of compound 36.

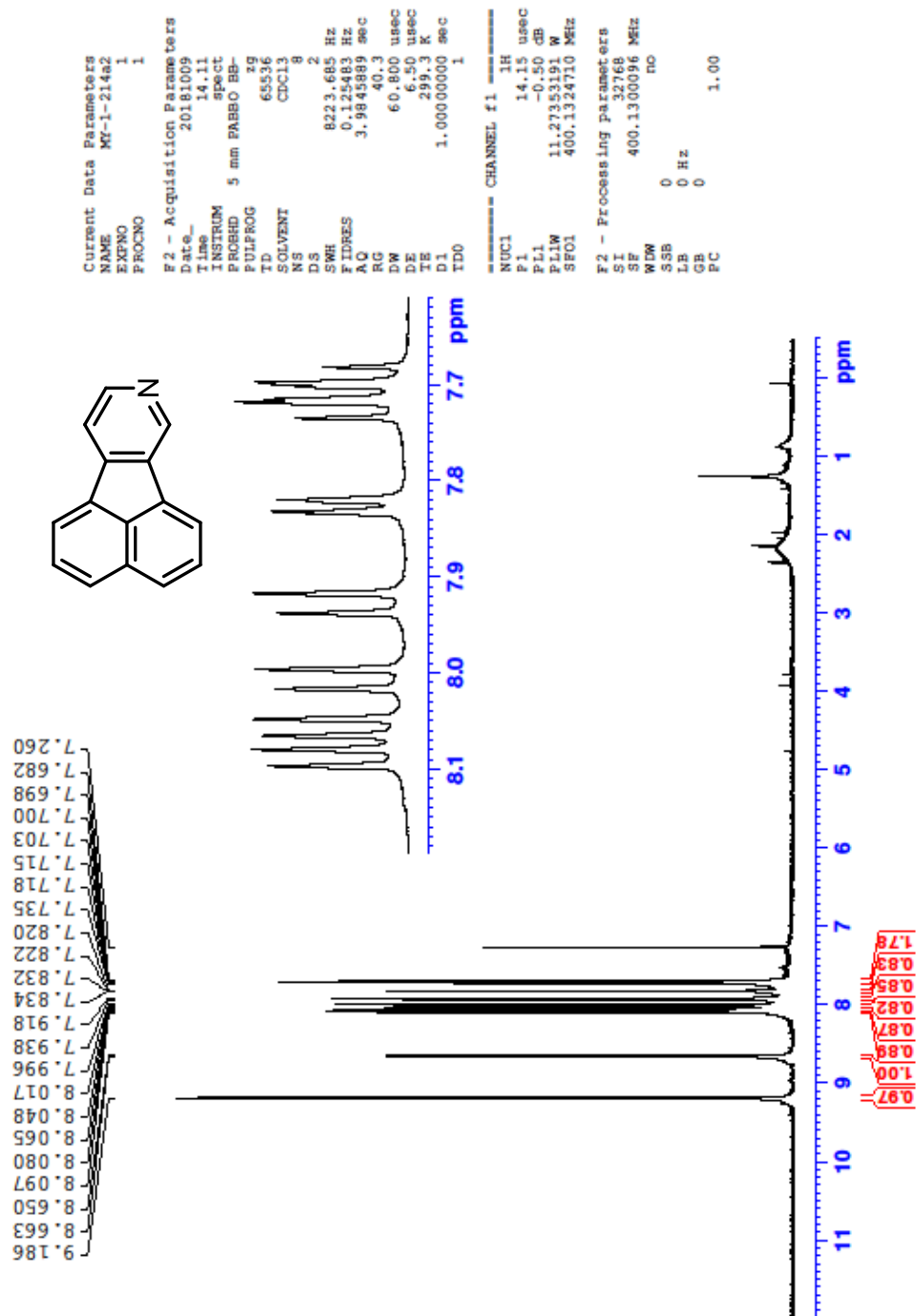


Figure 31. ^1H -NMR spectrum of compound 38.

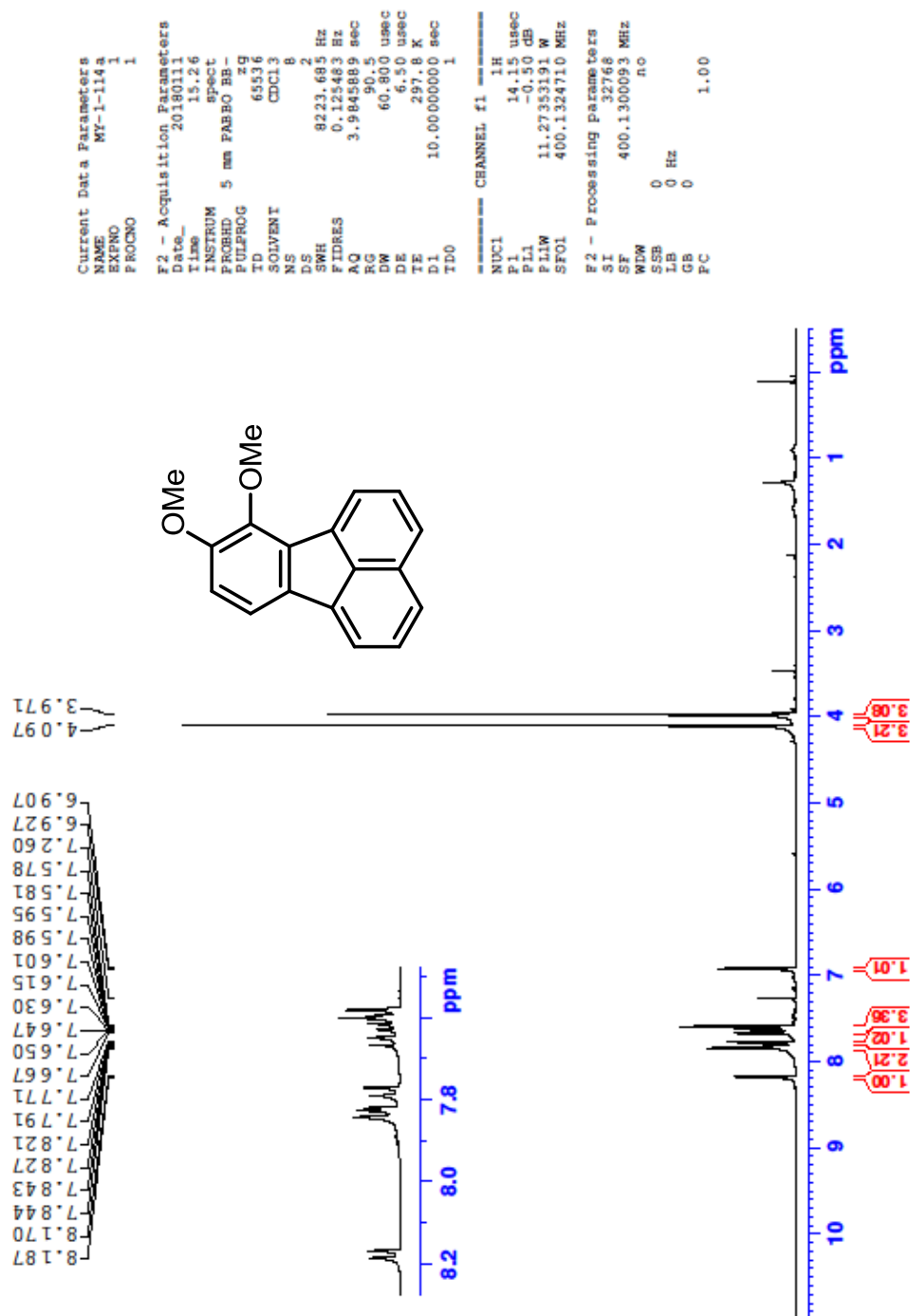


Figure 32. ^1H -NMR spectrum of compound 40.

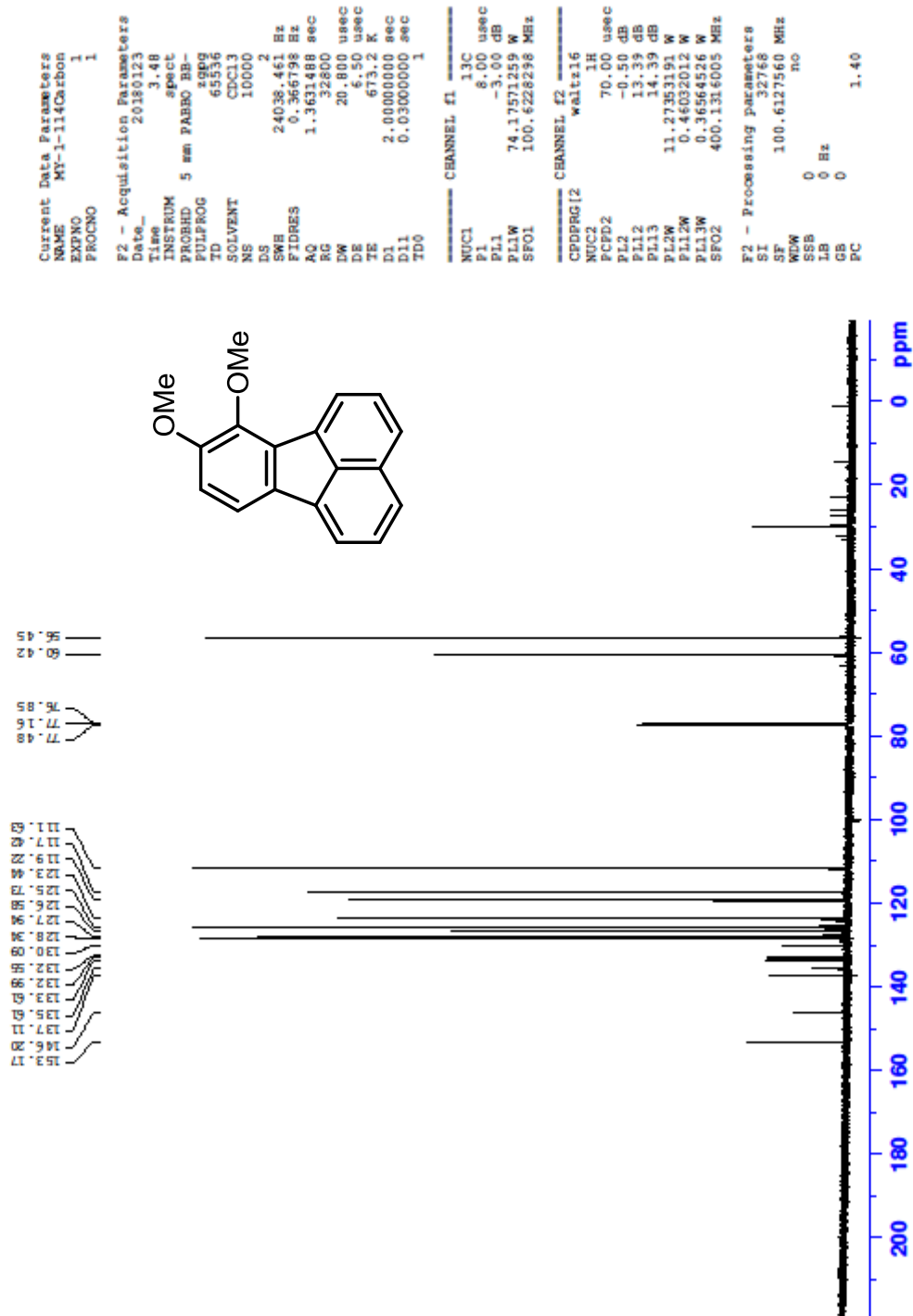


Figure 33. ^{13}C -NMR spectrum of compound 40.

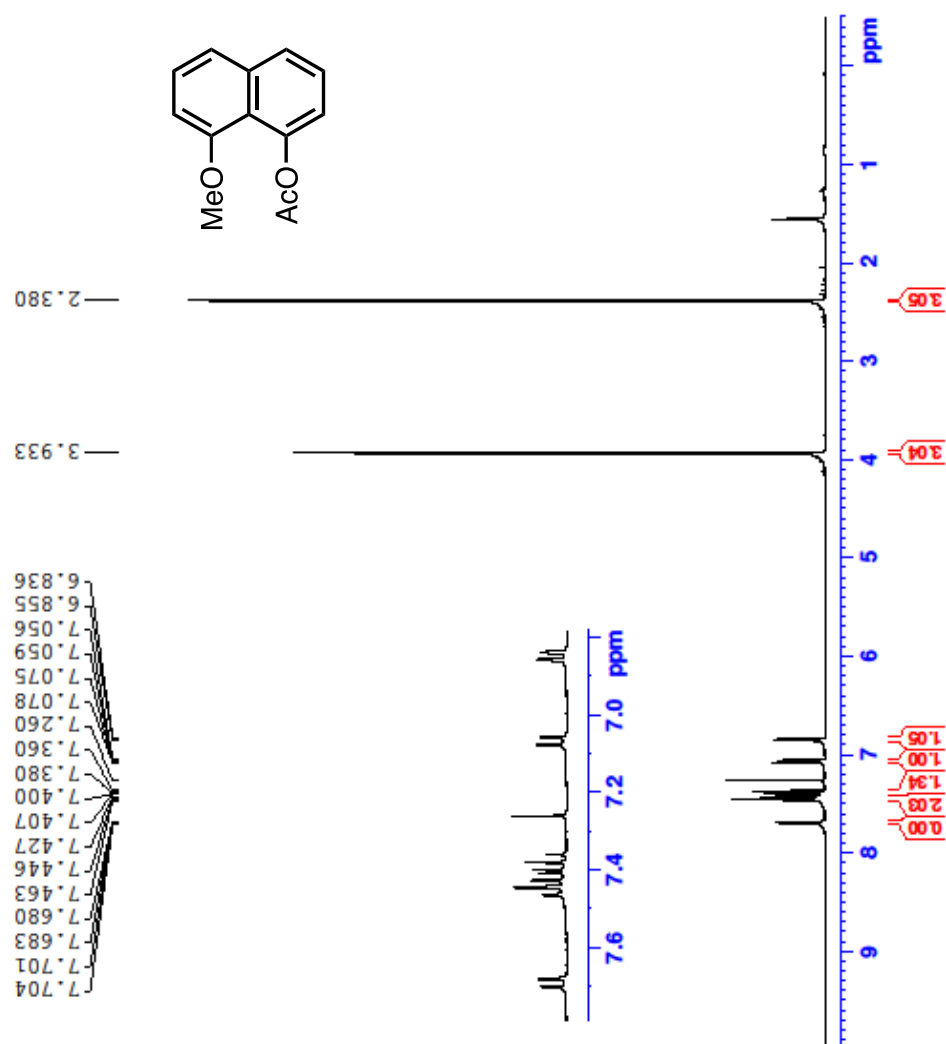


Figure 34. ¹H-NMR spectrum of compound 54.

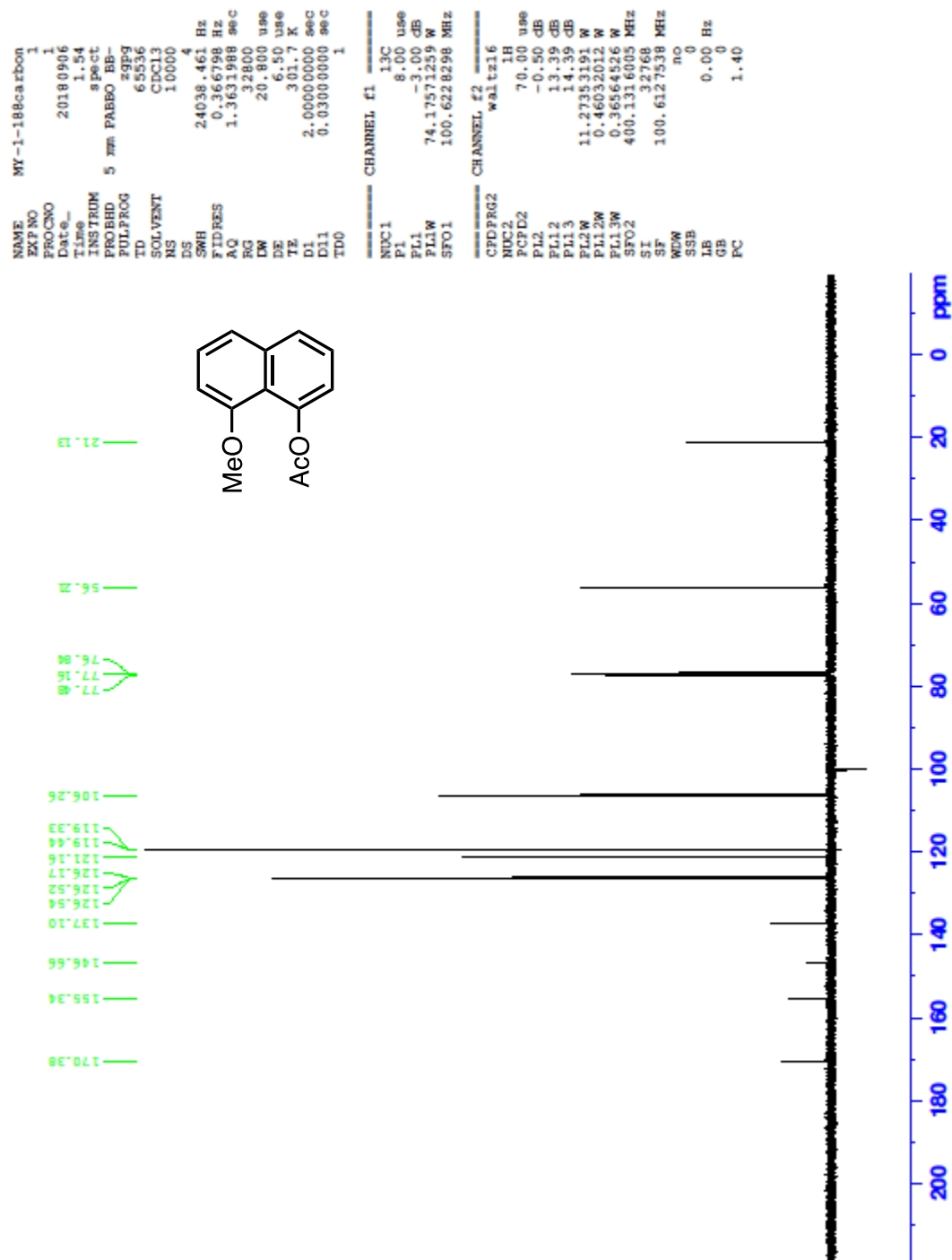


Figure 35. ¹³C-NMR spectrum of compound 54.

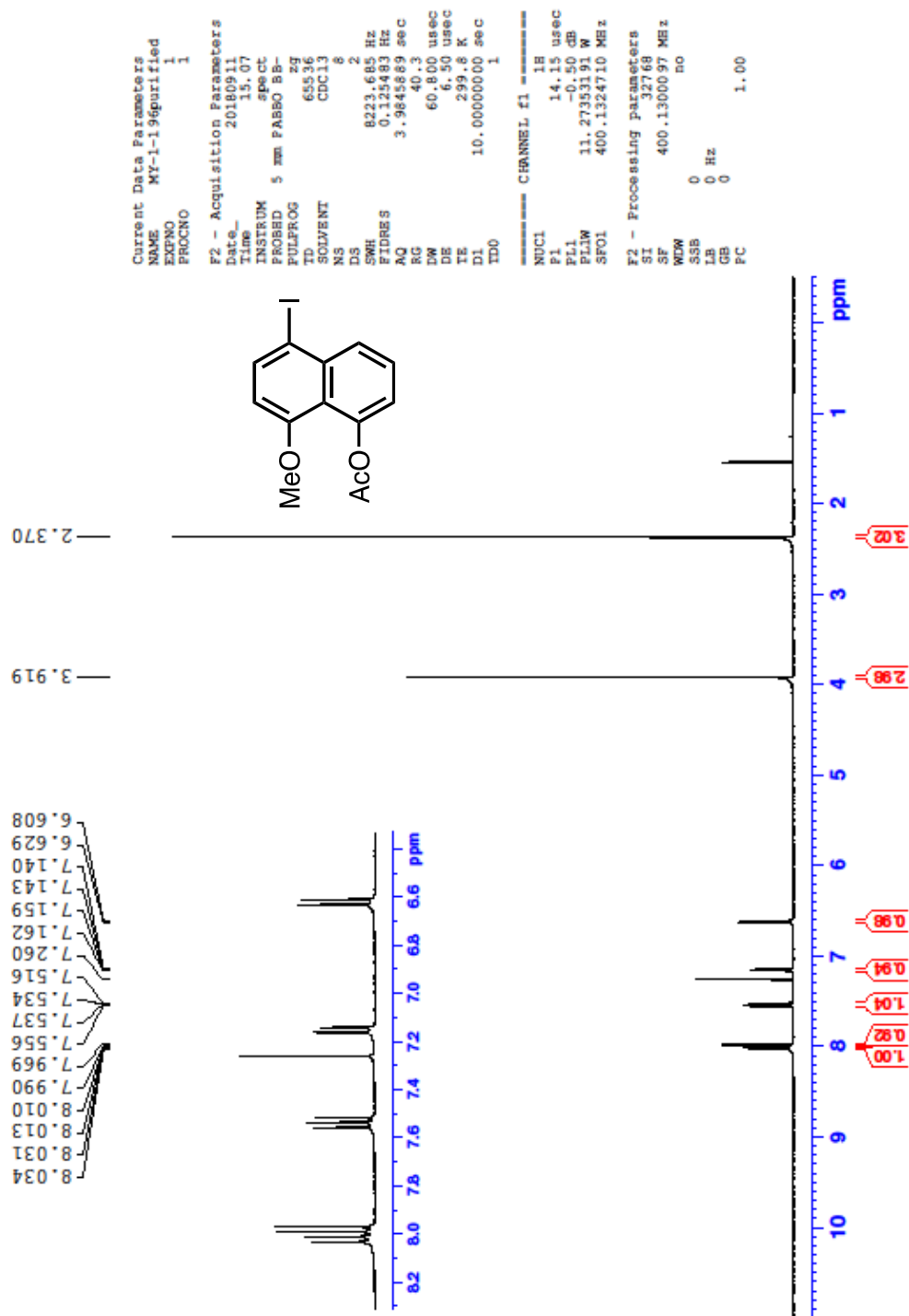


Figure 36. ^1H -NMR spectrum of compound 55.

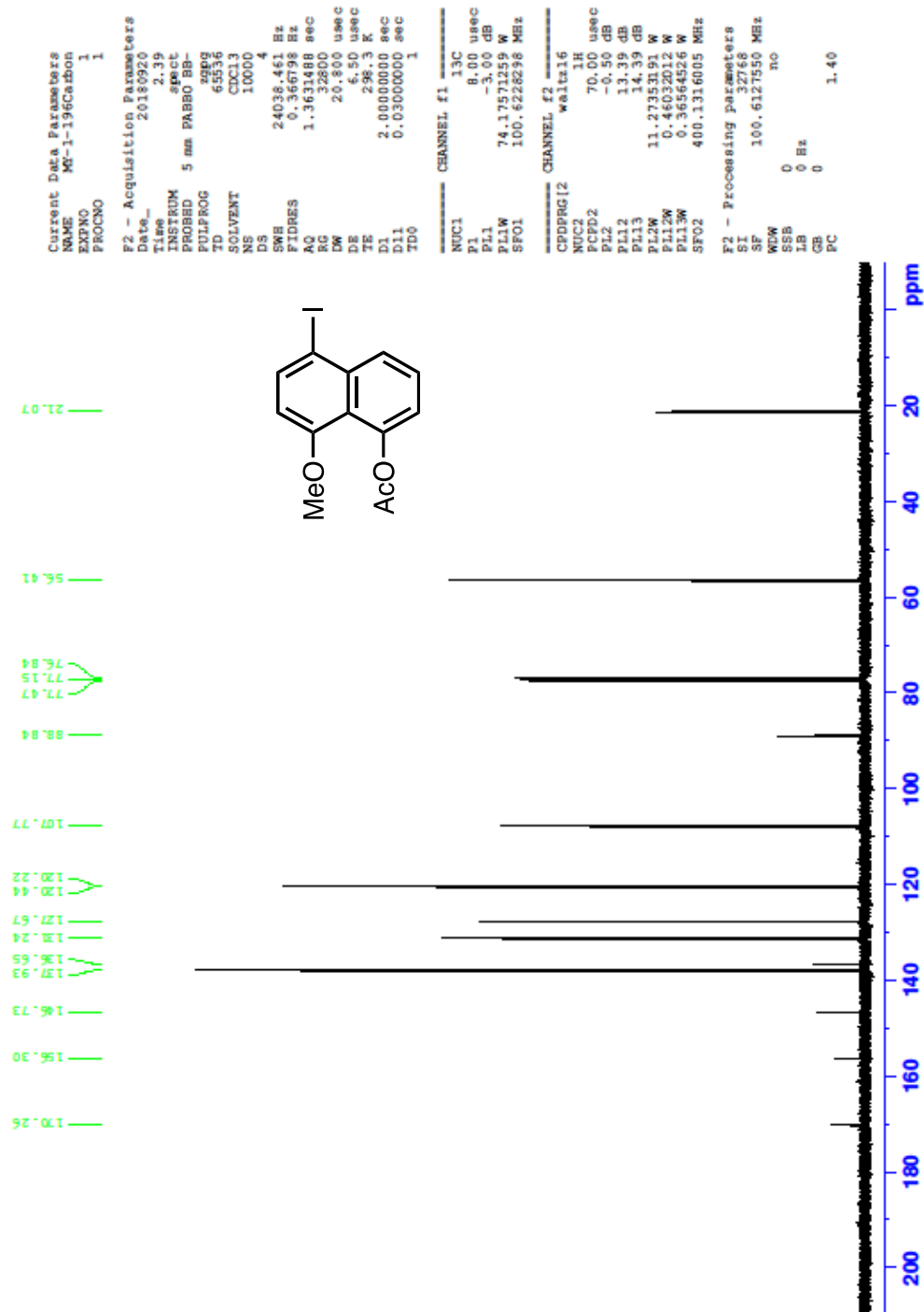


Figure 37. ^{13}C -NMR spectrum of compound 55.

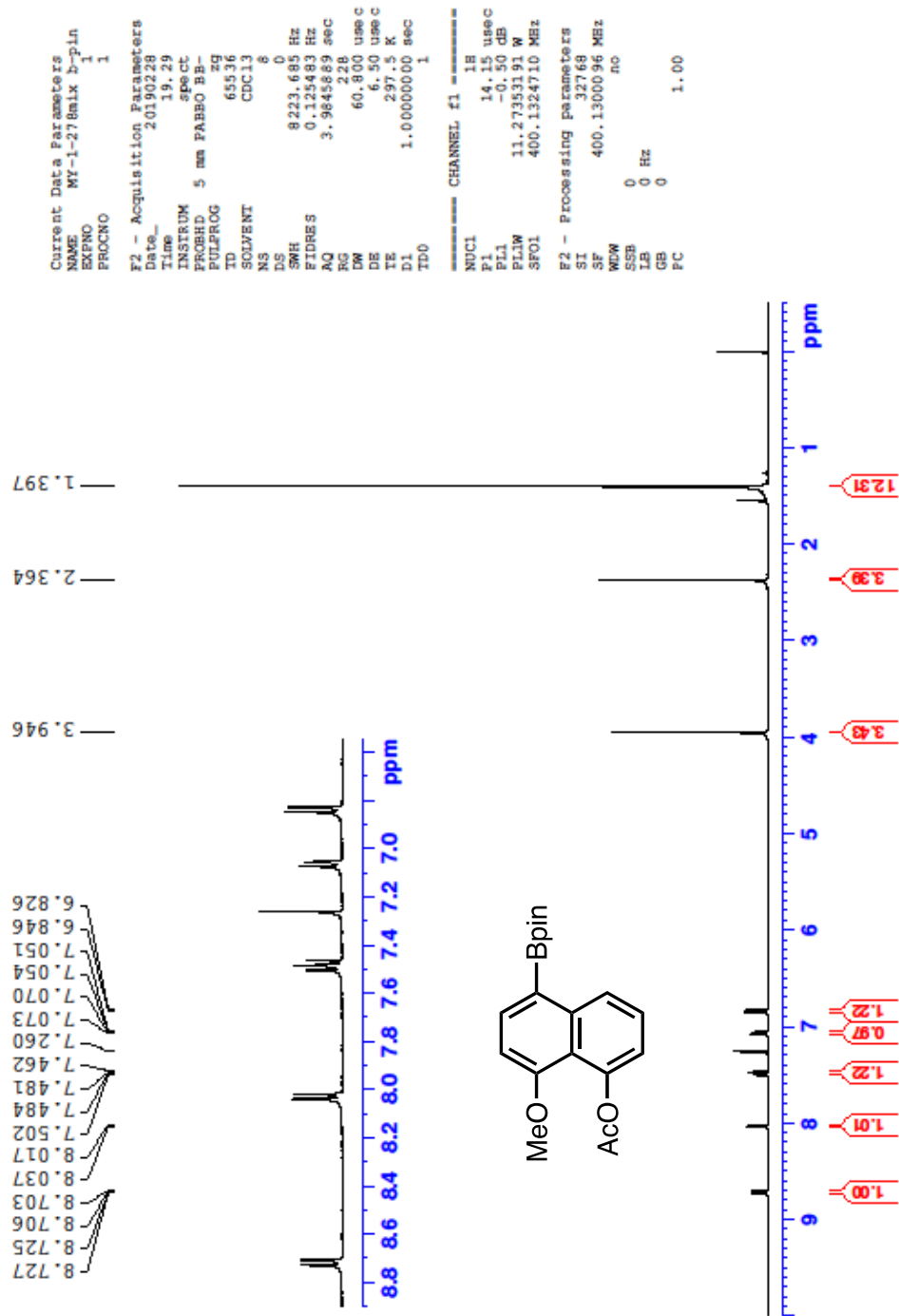


Figure 38. ^1H -NMR spectrum of compound 56.

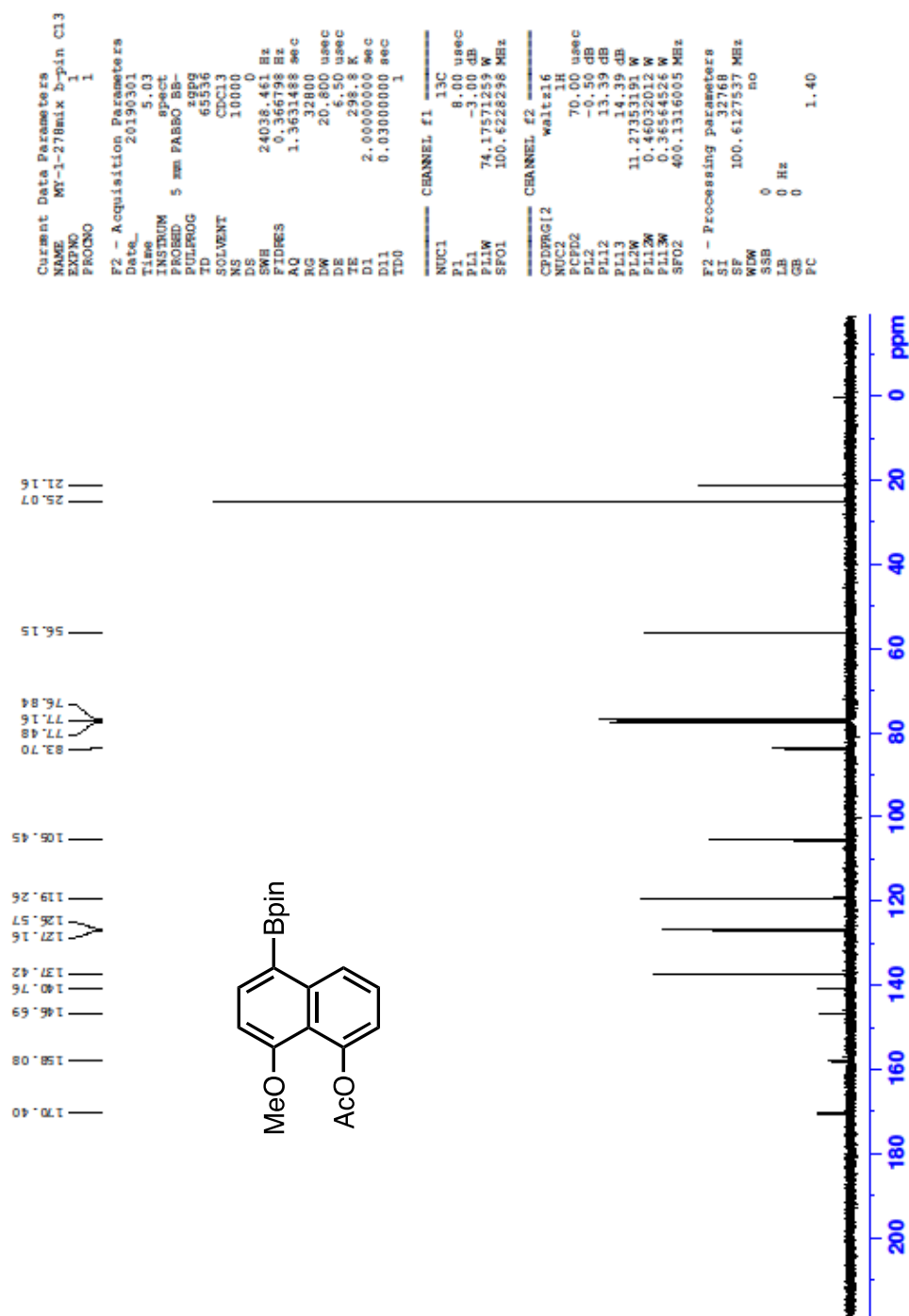


Figure 39. ^{13}C -NMR spectrum of compound 56.

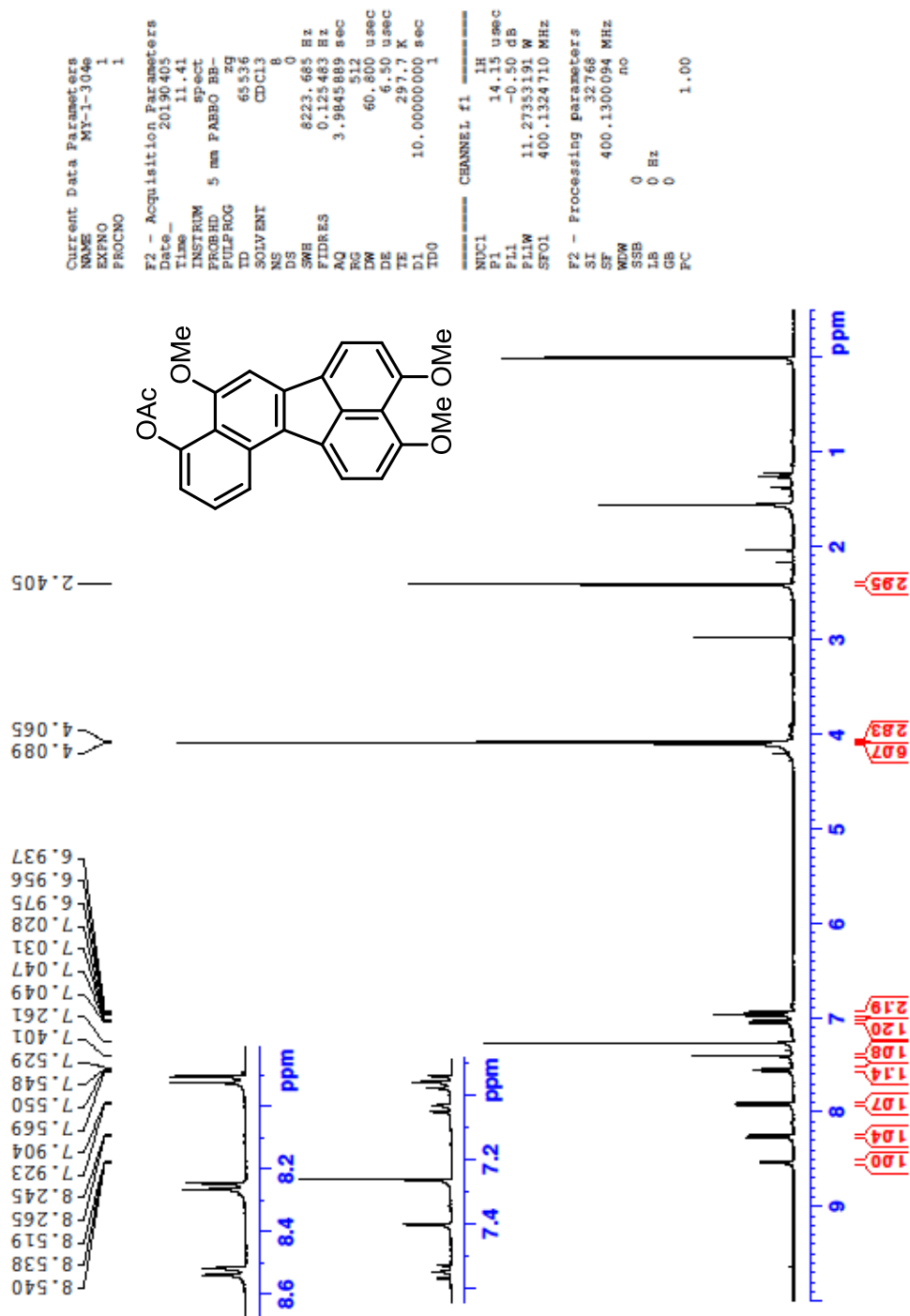


Figure 40. ^1H -NMR spectrum of compound 57.

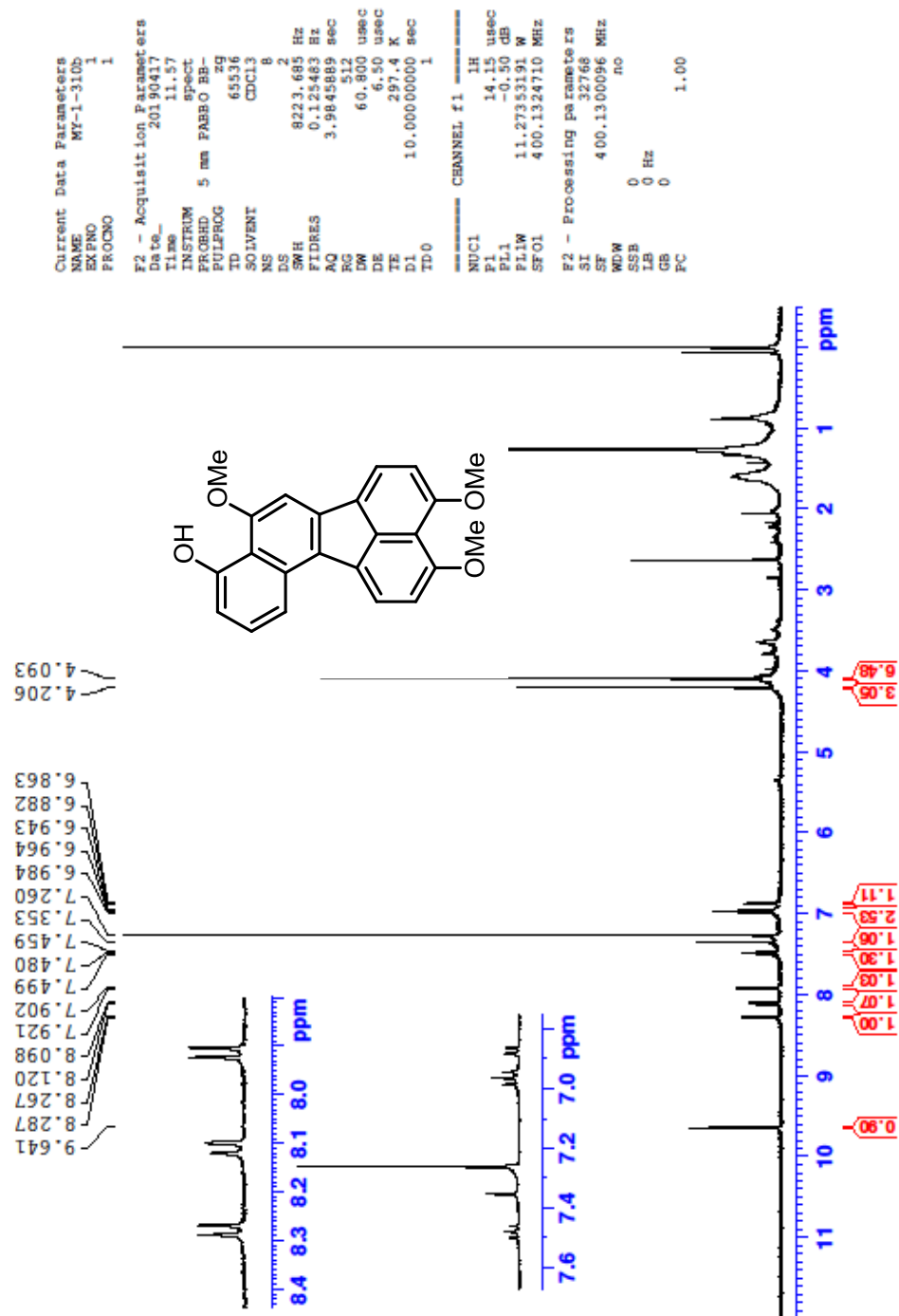


Figure 42. ^1H -NMR spectrum of compound 58.

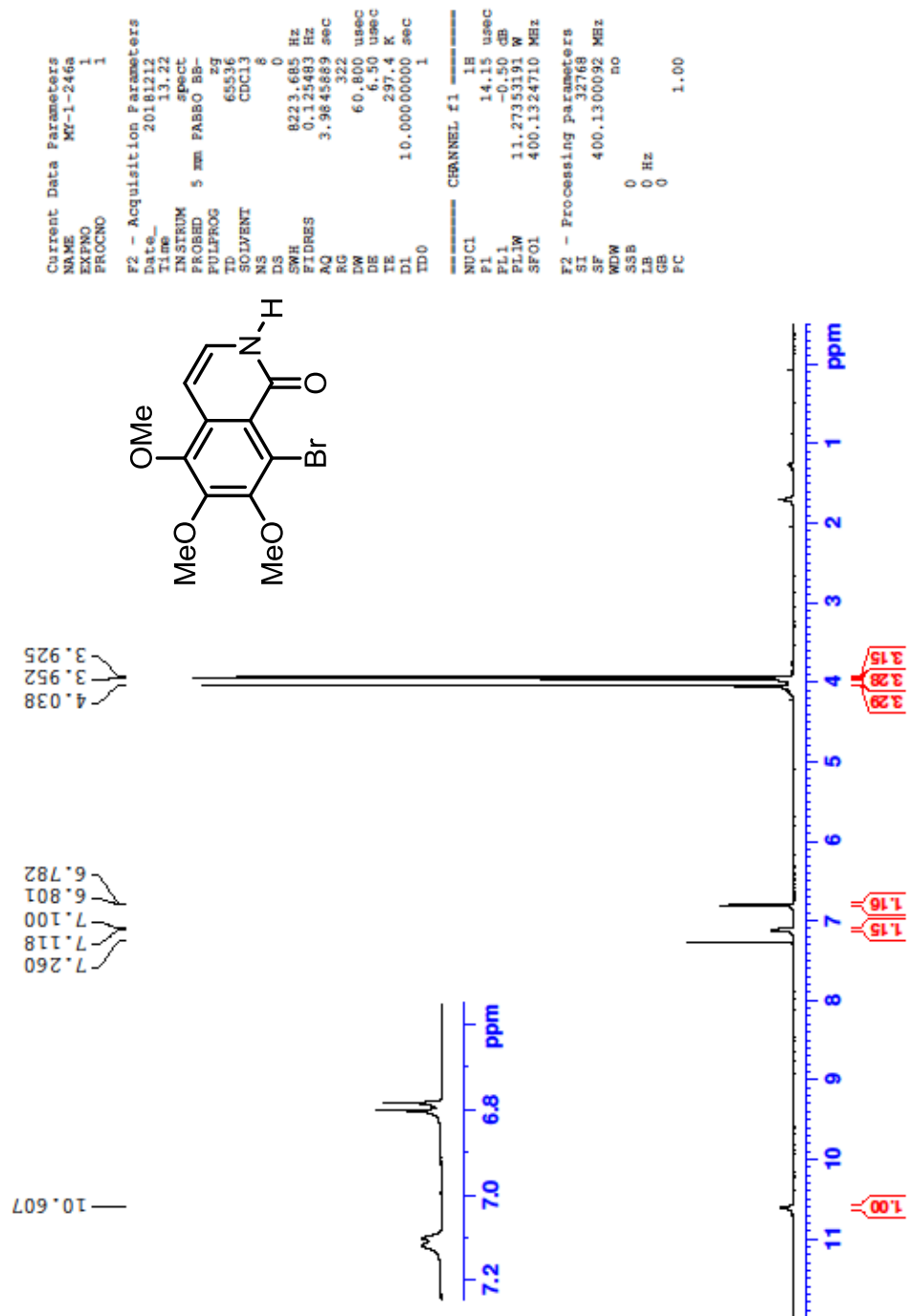


Figure 43. ¹H-NMR spectrum of compound 71.

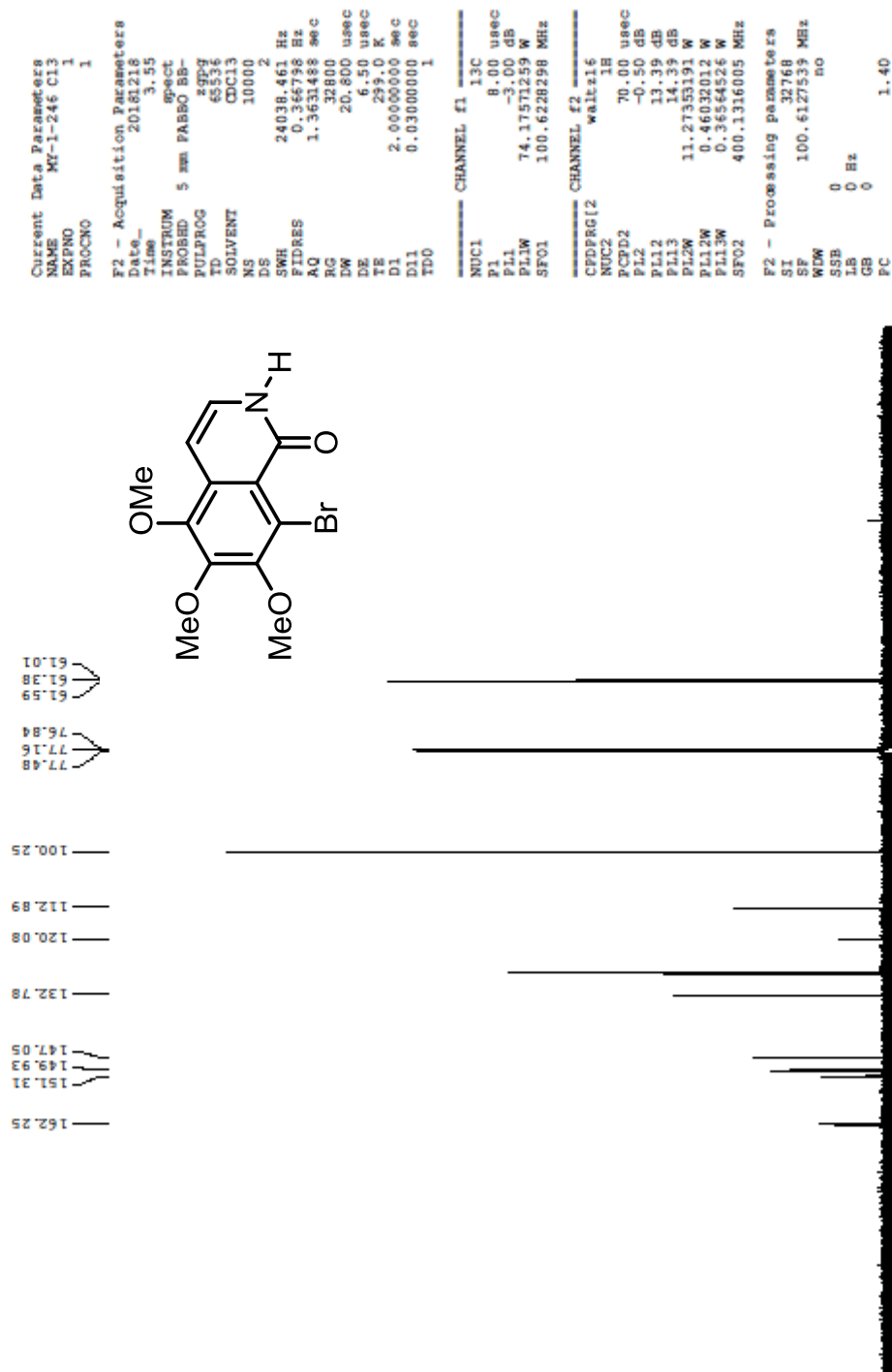


Figure 44. ^{13}C -NMR spectrum of compound 71.