ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL

SYNTHESIS, CHARACTERIZATION AND APPLICATIONS OF IMINE DERIVATIVES WITH NEAR-INFRARED (NIR) ABSORPTION AND/OR EMISSION PROPERTIES

M.Sc. THESIS

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Thesis Advisor: Assoc. Prof. Ayşe DAUT ÖZDEMİR

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İSTANBUL TEKNİK ÜNİVERSİTESİ ★ LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ

YAKIN KIZILÖTESİ (NIR) ABSORPSİYON VE/VEYA EMİSYON ÖZELLİKLERİNE SAHİP İMİN TÜREVLERİNİN SENTEZİ, KARAKTERİZASYONU VE UYGULAMALARI

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HAZİRAN 2024

Seren MOD, a M.Sc. student of ITU Graduate School of Science and Technology 509211273 successfully defended the thesis entitled "SYNTHESIS, CHARACTERIZATION AND APPLICATIONS OF IMINE DERIVATIVES WITH NEAR-INFRARED (NIR) ABSORPTION AND/OR EMISSION PROPERTIES", which she prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

Thesis Advisor	**:**	**Assoc. Prof. Ayşe DAUT ÖZDEMİR** Istanbul Technical University	**……**
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Date of Submission : 23 May 2024
Date of Defense : 27 June 2024

To my late mother,

FOREWORD

"If you want to find the secrets of the universe, think in terms of energy, frequency and vibration." - Nikola Tesla

My master's journey and my changing thesis topic in my final year showed me how important it is to let go sometimes, and taught me that situations that have the potential to lower our energy actually have the potential to increase our energy when viewed from a different perspective. During my work on this thesis, I learned to shift from blue to purple with the materials I synthesized and to reach higher energy areas by creating new orders within the unexpected irregularities caused by complex structures that have been created. If you expect a material to behave a certain way in a certain direction, that material will of course behave in that direction exactly as expected. However, if that material behaves in a completely different way than expected, perhaps this is exactly what we expected. In this thesis, nothing that has been seen before has been discovered as new, but it has been learned to look at the equations that are already known from a new perspective while working on some points. As Schrödinger said, "The task is not to see what has never been seen before, but to think what has never been thought before about what you see everyday."

I would like to express my gratitude and respect to all my professors, laboratory teammates, and my closest friends and my family who gave me new perspectives during my journey. But most of all, I would like to thank my mother, who has contributed immensely to helping me love my life and my job.

June 2024

Seren MOD

(Chemist)

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ABBREVIATIONS

BODIPY : Boron-dipyrromethene
CC : Column Chromatography
DCE : Dichloroethane
DCM : Dichloromethane
DETA : Diethylenetriamine
DMF : *N,N*–Dimethylformamide
eqv : Equivalent
EtOH : Ethanol
FT-IR : Fourier Transform Infrared Spectroscopy
NMR : Nuclear Magnetic Resonance Spectrometer
NIR : Near – Infrared (region)
TETA : Triethylenetetramine
TLC : Thin Layer Chromatography
UV/Vis : Ultraviolet – Visible Spectroscopy

SYMBOLS

µL **:** Microliter
µM **:** Micromolar
M **:** Metal
mL **:** Mililiter
mM **:** Milimolar
nm **:** Nanometer
λ **:** Wavelength

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SYNTHESIS, CHARACTERIZATION AND APPLICATIONS OF IMINE DERIVATIVES WITH NEAR-INFRARED (NIR) ABSORPTION AND/OR EMISSION PROPERTIES

SUMMARY

The use of organic dyes in a wide range of applications, including high-contrast bioimaging, solar panels, phototherapy, molecular probe design, and biosensors, has led to a significant increase in interest in these dyes (Particulary, λ_{max} = 700-1000 nm) in recent years. Many dye compounds with absorption in the near infrared have been created and developed up to this point. Nevertheless, the majority of these compounds exhibit poor thermal and photostability characteristics.

Organoboron complexes, especially BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) derivatives, exhibit remarkable absorption values, strong fluorescence characteristics, higher photostability, and structural adjustable, turning them extremely attractive structures. Due to these characteristics, BODIPYs have a broad range of potential uses in a variety of research fields, such as fluorescence imaging and sensor applications where they can be used as indicator dyes or laser dyes. To cause the absorption and emission bands of BODIPY compounds to shift to higher wavelengths, a few synthesis techniques and structural modification strategies have been developed. Performing an aza-substitution at the meso-position, wherein the C8-carbon is substituted with an aza-nitrogen atom to form borondifluoride-azadipyrromethene (aza-BODIPY), can also yield higher wavelength values and emissions.

Considering that Schiff bases will increase the conjugation of the structure, starting from the highly conjugated tetra-phenyl aza-BODIPY compound, Schiff bases were synthesized as tri- and tetra-dentate ligand utilizing imine and amine nitrogen atoms. Contrary to our expectation, adding an imine functionality to the structure did not improve conjugation of the tetra-phenyl substituted aza-BODIPY system. Moreover, instead of increasing absorption and emission values, we obtained decreased results on the contrary.

On the other hand, in the UV/Vis spectrum results, it was observed that the highest red-shift in both of the designed ligands occurred in the sample containing copper (II) metal solution. Subsequently, the second and third highest interactions were achieved in zinc (II) and cobalt (II) solutions, respectively. Although the interaction time of mercury (II) metal with the ligands is shorter than that of other metals, the maximum shift in wavelength of the mercury (II) complex had the lowest value among all metals. At the same time, although the maximum wavelength at which the cobalt (II) complex shifts is high, it has been determined that the interaction time is longer than that of other metals.

The measurements also allowed us to make comments about tri- and tetra-dentated ligands (synthesized from DETA, TETA respectively). It was observed that the interactions of the TETA-based ligand with the metal were higher than the interactions

of the DETA-based ligand, although by a small difference. However, it has also been noted that the DETA-based ligand reacts faster with metals in terms of interaction time.

This situation can be explained by the shorter distances between the complexation centres of the tridentate ligand. On the other hand, the higher difference between the binding constant and the dissociation constant of the short-distance tridentate ligand compared to the tetradentate ligand provides an advantage in binding rate. In light of these results and considering all these factors, it is thought that the tetradentate ligand, which is the TETA product providing a wide complexation area, remains kinetically slow in its interaction with the metal due to the bond length.

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ÖZET

Yakın kızılötesi bölgesinde, özellikle de maksimum dalga boyu 700 ila 1000 nm arasında, absorpsiyon ve emisyon veren organik boyalara olan ilgi; moleküler probların tasarımı, yüksek kontrasta sahip biyogörüntüleme, biyosensörler, fototerapi ve güneş panelleri gibi çok çeşitli uygulamalarda kullanım alanlarına sahip olmaları nedeniyle son yıllarda önemli derecede artmıştır. Bugüne kadar yakın kızılötesi bölgesinde absorpsiyona sahip çok fazla sayıda boya bileşikleri tasarlanıp geliştirilmiştir. Siyaninler, ftalosiyaninler, porfirinler, bor-dipirometen(BODIPY)ler, benzoheterosiklikler ve ksantenler yakın kızılötesi bölgesinde aktif olan bileşiklere örnek olarak verilebilir.

Bugüne kadar geliştirilmiş olan pek çok sayıda yakın kızılötesi absorpsiyonuna sahip bileşikler olmasına rağmen, bu bileşikler çoğunlukla termal ve fotostabilite açılarından zayıf özellikler göstermektedir. Organobor kompleksleri, yüksek floresans ve yüksek stabilite özellikleri nedeniyle oldukça dikkat çeken yapılar olmuştur. Organobor komplekslerinin bu özelliklerinin kazanımı; şelat halkalarının boyutları, organik ligandların yapıları ve koordinasyona dahil olan elektron verici atomlar üzerinde yapılan çeşitli düzenlemelerle sağlanabilmektedir. Farklı ligand türleri içerisinden, *O,O-, N,O-* ve *N,N*-bazlı ligandlar diflorobor kompleks yapılarının tasarımında oldukça yaygın bir şekilde kullanılmaktadır.

İyi bilinen diflorobor kompleks yapılarından biri de *N,N*-bazlı bir ligand türü olan BODIPY (4,4-difloro-4-bora-3a,4a-diaza-s-indasen) türevleridir. Diflorobor şelatlı floresans boyarmaddeler arasında porfirin benzeri bir yapı analogu olan BODIPY kompleksleri; olağanüstü absorpsiyon değerlere, güçlü floresans özelliklere, yüksek fotostabiliteye ve yapısal olarak ayarlanabilme yeteneğine sahip olmaları açısından en umut verici yapılardan biridir. Bu özellikler BODIPY'lerin floresans görüntülemede lazer boyaları olarak ve sensör uygulamalarında gösterge boyaları olarak kullanımlarını da içerisine dahil eden birçok çeşitli araştırma alanında geniş bir potansiyel uygulama yelpazesine olanak tanımaktadır.

Buna karşın, rijit bir yapıya sahip olmaları dolayısı ile basit BODIPY kromofor bileşiğinin Stokes kaymaları oldukça küçüktür (Tipik derecede 30 nm'den daha azdır). Bu da floresansın kendi kendine soğurulmasına ve buna bağlı olarak kuantum veriminde önemli ölçüde bir azalmaya neden olmaktadır. Aynı zamanda, BODIPY bileşiğinin spektral özellikleri yakın kızılötesi bölgesine ulaşmayan 505/516 nm (Absorpsiyon ve emisyon) aralığında sınırlı kalmaktadır. Böylelikle, bazı sentez metodları ve yapısal modifikasyon stratejileri, BODIPY bileşiklerinin absorpsiyon ve emisyon bantlarının daha yüksek dalga boylarına kaymalarını sağlayacak şekilde geliştirilmiştir.

Geleneksel strateji, π-konjugasyon sisteminin periferik sübstitüsyon veya pirol grubunun α- veya β-pozisyonlarında bulunan benzen, tiyofen, furan, naftalin gibi aromatik halkaların füzyonu yoluyla genişletilmesi olarak bilinir; bu da absorpsiyon ve floresans emisyon bantlarının önemli ölçüde kırmızı bölgeye doğru kaymasına neden olmaktadır.Alternatif olarak BODIPY yapısının, mezo-pozisyonunda bir aza-sübstitüsyon gerçekleştirilmesi yoluyla değiştirmesi de mümkündür ve C8-karbonunun bir aza-nitrojen atomu ile değiştirilmesiyle borondiflorür azadipirrometen (aza-BODIPY) boyaları sentezlenebilmektedir.

Yakın kızılötesi floresans boyarmaddeler arasında aza-BODIPY yapıları (λ_{max}>650 nm); optik ve elektrokimyasal nitelikler, üstün fotostabilite, kolay sentez aşamaları ve kimyasal yapı modifikasyonlarının uygulanabilirliği gibi son derece çekici avantajlar sergilemektedir. Yapılarında dört fenil grubu içeren ve yüksek konjuge sistemler olarak bilinen aza-BODIPY bileşikleri (5,5-difluoro-1,3,7,9-tetraphenyl-4-bora-3a,4a,8-triaza-s-indacene), yüksek dalga boyunda absorpsiyon vererek, aynı zamanda yüksek floresans emisyon sağlamaktadır. Bu da sensör uygulamalarında oldukça önemli bir özellik sayılan yakın kızılötesi bölgesinde absorpsiyon ve/veya emisyon yapan bileşiklerin elde edilmesi için ideal koşullu bir yapı oluşturmaktadır.

Schiff bazları olarak da bilinen imin bileşikleri, yapılarında bulunan azometin (CH=N) azot donör atomları nedeniyle konjugasyona önemli ölçüde katkısı bulunmaktadır. Aynı zamanda imin bileşiklerinin sahip oldukları azometin azot atomları, metal iyonlarının koordinasyonu açısından da büyük önem arz etmektedir ve etkileşimlerinden güçlü metal kompleks yapılar elde edilebilmektedir.

Schiff bazlarından elde edilen metal komplekslerin sensör uygulamalarının yanı sıra; bu komplekslerin antifungal, antimikrobiyal, antikanser vb. biyolojik aktiviteler sergilediklerini ve bu kompleks yapıların, DNA ile etkileşimlerini gösteren çalışmalar da bulunmaktadır.

Tüm bu gerekçelerden ötürü Schiff bazlarının, aza-BODIPY yapısında güçlendirilmiş konjuge sistem oluşturabilecek potansiyel bileşikler olarak rol oynayabileceği düşünüldü. Bu görüşten yola çıkılarak imin-bazlı metal sensörü geliştirilmesi hedef olarak belirlendi. Böylece dört-fenil grubu içeren aza-BODIPY bileşiğinin sahip olduğu absorpsiyon ve emisyon değerlerinde, Schiff bazı metal komplekslerinin oluşturulmasıyla yakın kızılötesi bölgesine kadar bir kırmızı-kayma sağlanabileceği öngörüldü.

Öte yandan, yapılarında üç ya da dört azot atomu içeren aminlerden oluşan imin yapılarının, geçiş metalleriyle daha güçlü etkileşimleri söz konusudur. Bu nedenle, Schiff bazı ligandlarının tasarımında kullanılan aminlerin üç azot içeren dietilentriamin (DETA) ve dört azot içeren trietilentetramin (TETA) olarak seçilmesine karar verilmiştir.

Formillenmiş aza-BODIPY bileşiğinin, çift taraflı bir Schiff bazı sensörü olarak tasarımı için stokiyometrik olarak 2 mol aldehite 1 diamin bileşiği reaksiyonu gerçekleştirildi. Elde edilen Schiff bazı sensör yapılarının, NMR ve FT-IR spektrum sonuçları alınarak karakterizasyonu yapıldıktan sonra, DMF içerisinde çözeltileri hazırlanarak dalga boylarının ve absorpsiyon yaptığı optimum aralığın belirlenmesi için UV/Vis spektroskopi ölçümleri alındı.

En optimize değerlerin sağlandığı derişim aralığı 0.8 absorbans değeri olarak belirlendi. Metal etkileşimi ölçümleri için bu değeri sağlayan derişimde Schiff bazı çözeltileri hazırlandı ve çeşitli metal çözeltileri kullanılarak (Hg^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+},

Sn^{2+}) UV/Vis spektroskopi ölçümleri alındı. Yapılan ölçümler sırasında ligandın ilgili metalle etkileşme süresi, ulaştığı en yüksek absorpsiyon seviyesi, kaydığı maksimum dalga boyu ve maksimum etkileşimin gerçekleştiği metal derişimi gibi parametreler göz önünde bulundurularak çeşitli veriler elde edildi. Metal-ligand etkileşimlerinin en iyi oranda gerçekleştiği çözeltideki metal ve ligandın mol oranları hesaplanarak, bu çözelti üzerinden zamana-karşı etkileşimlerinin ölçülmesi için otomatik çekimler alındı. Ligandın ilgili metalle etkileştiği en ideal süre, örnek maksimum dalga boyu ve absorpsiyon değerine ulaştığı ana kadar geçen zaman baz alınarak belirlendi. Ölçüm sonuçları üç-dişli ve dört-dişli azot atomu içeren Schiff bazı ligandları arasında derlenerek, tasarlanan sensör yapıları ve sahip oldukları özellikler hakkında yorumlamalar yapılarak genel sonuçlara ulaşıldı.

Her ne kadar tasarlanan sensör yapısının metal etkileşimlerinde kırmızı-bölgeye kayma gözlenmiş olsa da, yakın kızılötesi bölgesine ulaşmaya yetecek kadar bir miktarda elde edilemedi. Dört-fenil grubu içeren aza-BODIPY sisteminin konjugasyonu, tahmin edildiği üzere yapıya bir Schiff bazı eklenerek güçlendirilemedi. Aksine, yapıda imin bağının oluşumu, aza-BODIPY bileşiğinin sahip olduğu konjugasyonda da bir azalma gerçekleştirmiştir; bu da elde edilen imin bileşiklerinin UV/Vis spektrumlarında mavi-bölgeye doğru bir kaymaya sebep olmuştur. Aza-BODIPY üzerinden üç ya da dört-dişli azot atomu içeren bir Schiff bazı oluşturularak elde edilen yapının artacağı düşünülen absorpsiyon ve emisyon değerleri, tam tersine azalmıştır. Ayrıca yapıdaki imin zincirinin uzunluğu arttıkça mavi bölgeye doğru kaymanın daha çok gerçekleştiği de gözlenmiş oldu. Konjugasyonun kesilmesiyle kaydedilen mavi-kaymaların yanında, oluşturulan yapının floresans emisyon özelliklerinin de kaybedildiği sonucuna ulaşılmıştır ve bu sebeple floresans ölçümleri alınamamıştır.

UV/Vis spektrum sonuçları incelendiğinde tasarlanan ligandların her ikisinde de en fazla kaymanın, bakır (II) metal çözeltinin bulunduğu örnekte meydana geldiği gözlenmiştir. Takiben çinko (II) ve kobalt (II) çözeltilerinde en fazla etkileşimin sağlandığı da belirlenmiştir. Cıva (II) metalinin ligand ile etkileşim süresi diğer metallere nazaran her ne kadar daha kısa da olsa; cıva (II) kompleksinin dalga boyundaki maksimum kayma, tüm metallerin içerisinde en düşük değere sahip olmuştur. Aynı zamanda kobalt (II) kompleksinin kaydığı maksimum dalga boyu yüksek olsa da, etkileşim süresinin, diğer metallerinkinden fazla olduğu saptanmıştır.

Yapılan ölçümlerden derlenen tüm sonuçlar, üç-dişli ve dört-dişli ligandlar hakkında yorum yapmamıza da yardımcı olmuştur. Dört-dişli TETA-bazlı ligandın metalle etkileşimlerinin, DETA-bazlı ligandın etkileşimlerinden düşük bir farkla da olsa yüksek olduğu gözlenmiştir. Ancak bunun yanında, etkileşim süresi yönünden DETA-bazlı ligandın metallerle daha hızlı reaksiyon verdiği de kaydedilmiştir. Bu durum, üç-dişli ligandın kompleksleşme merkezleri arasındaki mesafelerin daha kısa olmasıyla açıklanabilir. Benzer şekilde TETA ürünü olan dört-dişli ligandın da bağ uzunluğu nedeniyle metal ile etkileşimlerinde kinetik açıdan yavaş kaldığı düşünülmektedir.

1. INTRODUCTION

The study of new molecular chemo-sensors has received considerable attention due to their potential applications in both biological and environmental contexts (De Castro et al., 2016). The development of chemo-sensors with sensing ability towards metal ions is of particular relevance. Metal ions are needed for correct metabolic activity; however, when present in excess, they are associated with several pathologies.

In terms of sensitive and highly selective detection, optical methods offer fast, reliable user-friendly, and real-time, on-the-sight applications. A wide range of literature showcases small optically active molecules, polymers carrying them, metal–organic frameworks, and nanoparticles (Sadikogullari et al., 2023). Among these, aza-BODIPYs stand out as a candidate for chemo-sensor applications, thanks to their features such as high absorption coefficients, strong chemical- and photo-stability, and sharp fluorescence peaks with high quantum yields well into the near-infrared spectrum.

In this study, we harness the power of aza-BODIPY, embedded in a Schiff base structure for metal detection in water media, via fluorescence spectroscopy. Our results show that, C=N conjugation causes fluorophore molecule to lose its emission due to newly introduced relaxion of C=N isomerization, which causes this thesis topic from fluorescence-based application to UV/Vis based application. On the other hand, fast response and colorimetric detection capabilities show promising results for further investigation, which will be discussed in the thesis. On the context, synthetic detail and characterization will be provided along with the spectrophotometric result.

1.1 Near-Infrared Dyes

In recent years, there has been a significant interest in organic dyes that exhibit absorption and emission in the near-infrared (NIR) spectrum, due to their diverse applications, for instance, in molecular probes, high-contrast bioimaging, biosensors, phototherapy, and solar cells (Zuo et al., 2020).

Up to date, numerous near–infrared dyes have been developed. Cyanines, phthalocyanines, porphyrins, squaraines, borondipyrromethenes (BODIPYs), benzo[c]heterocycles, and xanthenes can be given as dyes which are active in the NIR region (Figure 1.1) (Escobedo, & Rusin, 2010). Despite the large number of NIR dyes that have been developed to date, they often suffer from poor thermal- and photo-stability. Among them, organoboron complexes have attracted attention due to their fluorescence characteristics and stability, which may be controlled by adjusting the size of chelate cycle, the structure of organic ligands, and the chemical nature of the atom donors involved in coordination (Lugovik, Eltyshev, & Suntsova, 2018).

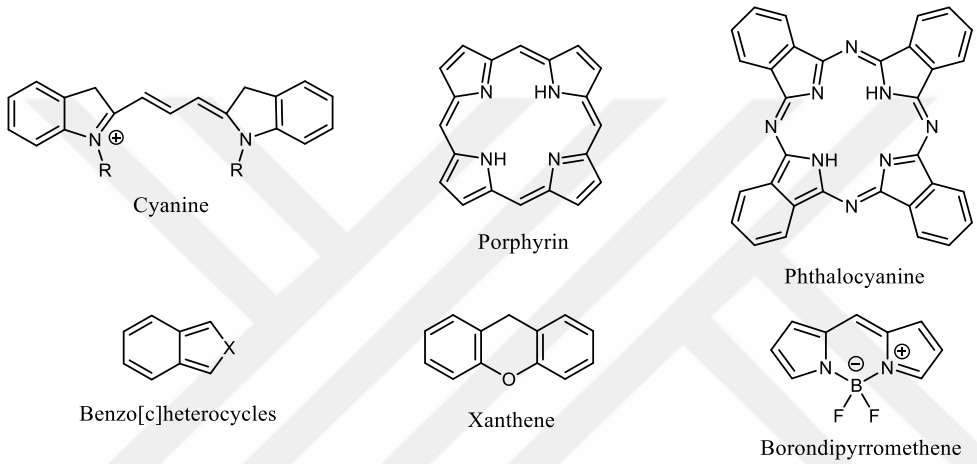

Figure 1.1 : General formulas of cyanines, phthalocyanines, porphyrins, borondipyrromethenes (BODIPYs), benzo[c]heterocycles, and xanthenes as common fluorophore dyes (Barbieri, Bandini, & Monti, 2016).

Among several types of ligands, *O,O*-, *N,O*-, and *N,N*-based ligands are the most widely used in difluoro-boron complexes (Figure 1.2) (Tan et al., 2021). In this study, we focused on one of the *N,N*-based ligands, known as aza-BODIPY (aza-boron-dipyrromethene) due to their relatively high Stokes shifts, pH independent absorbance and emission properties in near-infrared region.

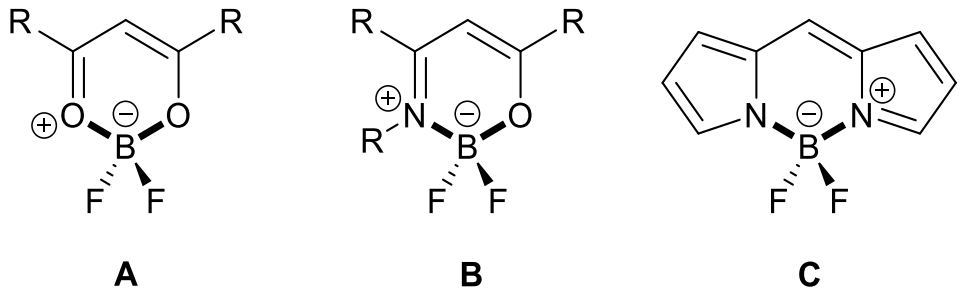

Figure 1.2 : Organic BF_2 complexes based on bidentate ligands: (A) *O,O*-donor ligand, (B) *N,O*-donor ligand, (C) *N,N*-donor ligand (Tan et al., 2021).

1.1.1 Borondipyrromethanes (BODIPYs)

BODIPYs are the well-known BF_2 chelated compounds which are based on *N,N*-ligands in their structures (Figure 1.3) (Lugovik et al., 2018). BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) complexes are one of the most promising structures by virtue of their excellent absorption, strong fluorescence, high photostability properties, and ability to be structurally tuned, which enables an extensive range of potential applications in a variety of research fields (Kubo, & Nozawa, 2021). These characteristics led to the employment of BODIPYs as laser dyes in fluorescence imaging and as indicator dyes in sensor applications (Lu, & Mack, 2014).

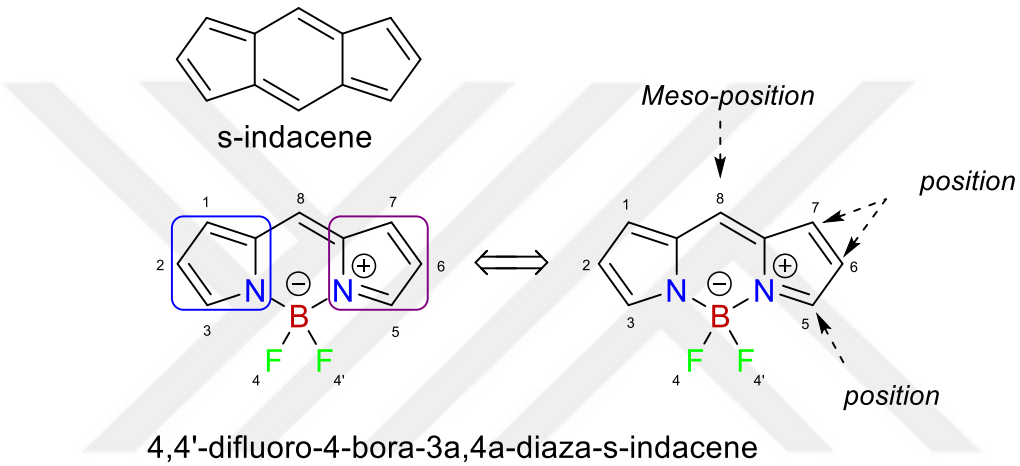

Figure 1.3 : The IUPAC naming and numbering of the fluorophore "BODIPY" (4,4'-difluoro-4-bora-3a,4a-diaza-s-indacene) based on s-indacene. Pyrrole ring left boxes, azafulvene right boxes. Formal charges are provided for the delocalized resonance structures of BODIPY (Squeo, & Pasini, 2020).

Nevertheless, because of their rigid structures, the Stokes shifts of ordinary BODIPY chromophore are very small, typically less than 30 nm, resulting in significant fluorescence self-absorption and an associated decrease in quantum yield (Lugovik et al., 2018). Also, its spectral properties are limited to the absorption maxima at 505/516 nm region (absorption and emission) (Zuo et al., 2020), which is not in the NIR region. Therefore, some synthesis methods and structural modification strategies have been developed to shift the main absorption and fluorescence emission bands to longer wavelengths (Lu, & Mack, 2014).

1.1.2 Borondifluoride Azadipyrromethenes (Aza-BODIPYs)

Aza-BODIPYs have attracted a lot of research interest due to their strong absorption properties in the NIR region (λ>650 nm) (Cui, & Sheng, 2017). And among the NIR dyes, aza-BODIPYs exhibit highly attractive advantages, including optical and electrochemical qualities, facile synthesis and chemical modification, and superior photostability (Zuo et al., 2020) (see Figure 1.4).

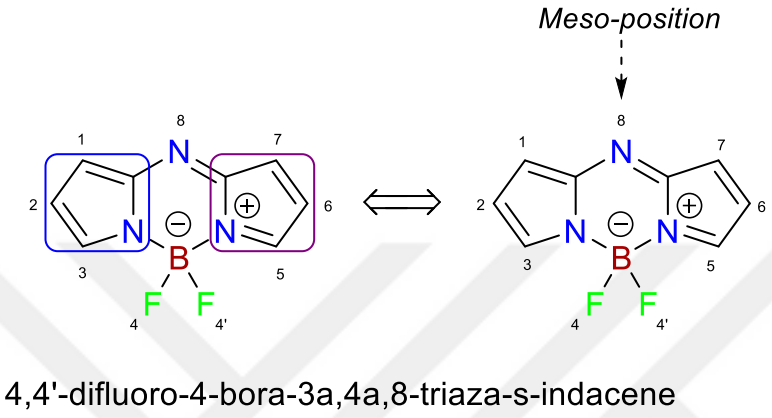

Figure 1.4 : IUPAC numbering of basic aza-BODIPY (4,4'-difluoro-4-bora-3a,4a,8-triaza-s-indacene) structure (Schellhammer et al., 2017).

Examples belong to BODIPY (1, 2, 3) and aza-BODIPY (4, 5, 6) are given in Figure 1.5, including their absorption/emission values.

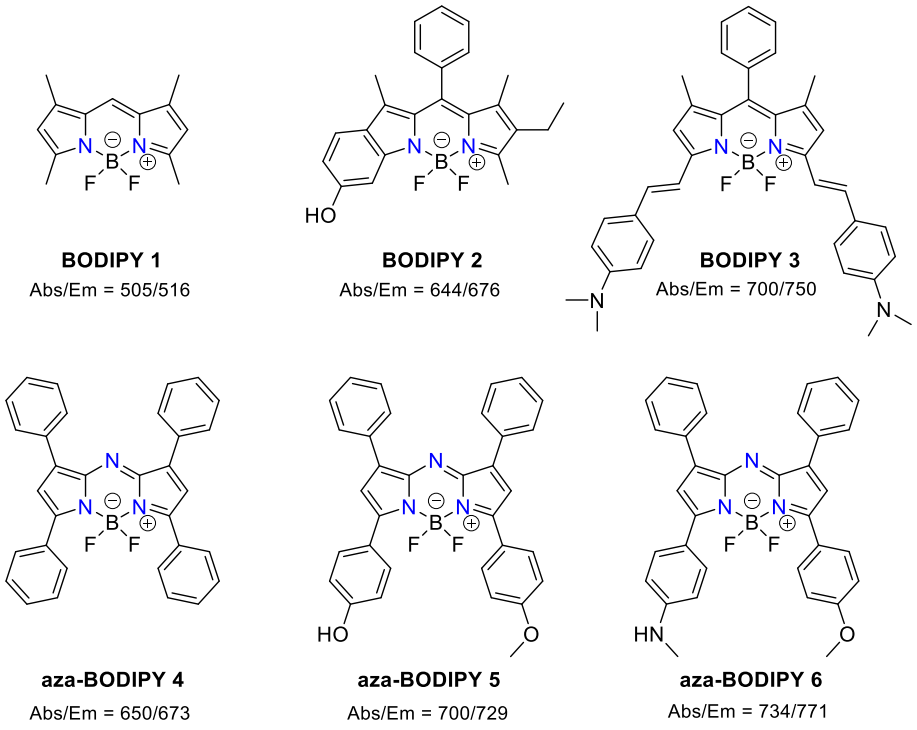

Figure 1.5 : Chemical structure examples of BODIPY (1, 2, 3) and aza-BODIPYs (4, 5, 6), and their absorption/emission values (Ding et al., 2023).

Aza-BODIPY synthesis was first developed by O'Shea *et al.* in which synthesis of *E*–chalcone was firstly done via Claisen Schimdt condensation. Than nitromethane addition to *E*–chalcone via nucleophilic Michael addition is performed followed by an condensation with ammonium acetate to obtain aza dipyrromethene ring. The last step of the method was BF_2 chelating of aza–dipyrromethene via $BF_3{\cdot}Et_2O$ (Figure 1.6) (Killoran, & O'Shea, 2005).

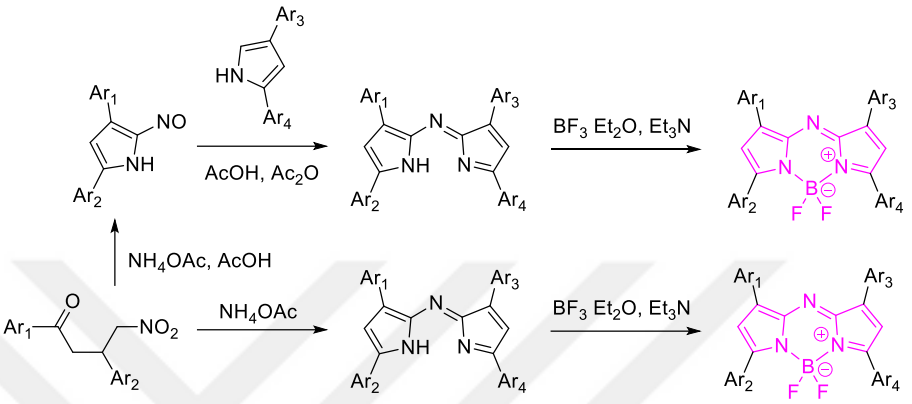

Figure 1.6 : Synthesis of aza-BODIPY compound (Killoran, & O'Shea, 2005).

1.2 Schiff Bases (Imines)

Carbonyl moieties of aldehydes or ketones have electrophilic carbon atoms that are suitable for the attack of nucleophilic amine compounds. By the condensation reaction of a primary amine and a carbonyl compound (ketone or aldehyde), an imine compound (C=N), which is also known as Schiff base, is formed. While the Schiff bases of aliphatic aldehydes are moderately unstable, those of aromatic aldehydes are more consistent by means of their active conjugation system.

Schiff bases are a significant class that have been thoroughly studied due to their azomethine nitrogen atoms in the structure. Schiff bases are also remarkable ligands, mostly bi- or tri-dentate, that have been thoroughly studied due to their coordination with metal ions through azomethine nitrogen. They are the subject of extensive research, because of their sensitivity, synthetic flexibility, and selectivity to the central metal atom, as well as the presence of an azomethine group that helps reveal the biological mechanism underlying the transformation reaction (More, & Yoshi, 2019).

Several auxiliaries, such as Schiff bases (C=N, imines), organoboron derivatives (e.g., BODIPY dyes), benzimidazole quinoline, etc., have been described for the selective

detection of transition metals in samples by using spectral analysis techniques, such as FT-IR, UV/Vis, and fluorescence spectroscopy (Korzec, & Senkała, 2019).

One of the reasons that imines attract special attention in studies is their facile synthesis, easy availability, and electronic properties. It is stated that metal complexes of imine bases are important in terms of biological activities such as antifungal, antimicrobial, anticancer, etc., and there are also some reports that show the interactions between Schiff bases and DNA structure (Abdel-Rahman et al., 2016).

The design of Schiff base ligands containing three or four nitrogen atoms provides a structure that is favourable for strong interactions with transition metals. The fact that imines have such properties allows them to be easily used as sensors or probes in applications.

1.3 Foundational Studies

Azomethine derivatives, by containing a C=N bond that is essential for biological activity, have been shown to have antifungal, antibacterial, antiviral, antimalarial, cytostatic, anti-inflammatory, and antipyretic properties. A number of pharmaceuticals containing an azomethine group in their structures are currently used in medicine, such as thioacetazone and nifuroxazide, as oral antibacterial medicines. Such compounds assure an attractive research field for novel drug discovery because of their wide range of activities and synthetic techniques that facilitate the simple multidirectional modification of Schiff base structures. And their metal complexes, in addition to their uses in medicinal chemistry, are also widely used in analytical and catalysis chemistry, as well as in the food industry, dye industry, and agroindustry (Prakash et al., 2011).

Schiff bases have drawn a lot of interest by having superior biological activity, while their metal complexes can also exhibit strong biological activity (Abdel-Rahman et al., 2019). It is stated that by designing the structure of Schiff base complexes, it is possible to affect the coordination geometry and planarity, as well as their capability to bind to DNA and chemotherapeutic activity (Fang, & Yan, 2019).

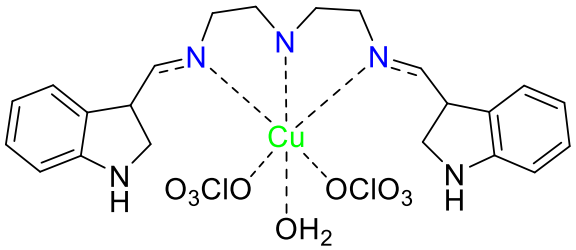

Figure 1.7 : Representative Schiff base complex in the presence of copper (II) metal ion on diethylenetriamine-based tridentate ligand derived from indole-3-carboxaldehyde (Fang, & Yan, 2019).

Schiff bases synthesized from *β*-keto esters and *o*-aminobenzoic acid exhibit biocidal activity against several bacterium types. Additionally, biocidal properties have been studied in metal-ligand complexes of Ni^{2+}, Cu^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, and Zn^{2+} with 2-hydroxyacetophenone derived imines from either ethylenediamine or *o*-phenylenediamine (Figure 1.8) (Uddin et al., 2020).

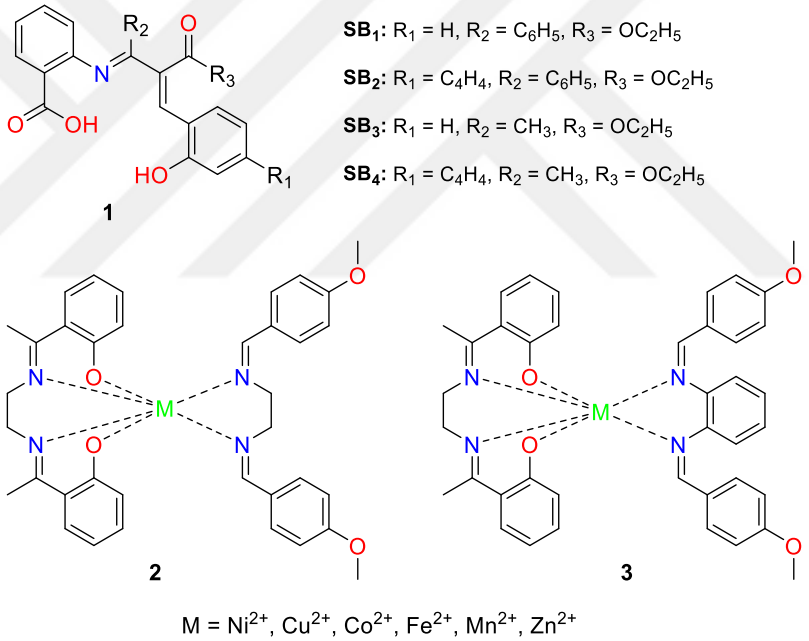

Figure 1.8 : Schiff base metal complexes that reported as anti-bacterial properties (Uddin et al., 2020).

The coordination chemistry of poly-chelates has been developed toward transition metal chelates, which are formed from poly-Schiff bases. By alternating aromatic molecules with the incorporation of a metal-containing chain, coordination polymer materials that show semiconductor behavior can be obtained (Suganya, & Xavier, 1998). It has also been reported that the incorporation of metal ions with polymers can be very useful in applications; such as adhesives, elastomers, and resins (Chantarasiri et al., 2004).

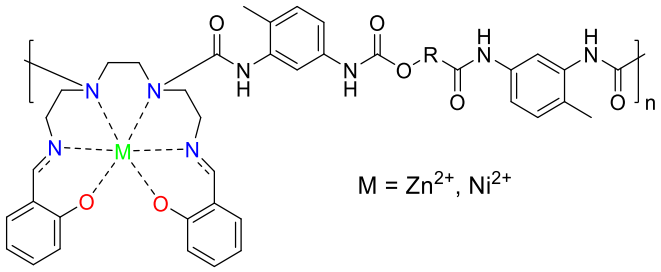

Figure 1.9 : Representative hexadentate Schiff base metal complex including in the structure of polyurethane-ureas (Chantarasiri et al., 2004).

In this thesis, we explore the chelating capabilities of Schiff bases to detect metals in a sample. Although this approach has been studied extensively in the literature, near-infrared-based Schiff bases have not been as widely adopted. For example, a study done by Ozmen *et al.* utilizes Rhodamine-based Schiff base with vinyl-benzaldehyde. In the study, poly (vinyl benzaldehyde-co-divinylbenzene) dense cross-linked polymer structure was prepared and the dye "rhodamine hydrazide" was conjugated to the surface *via* imine bond. The synthesized polymeric structure shows great against Cu^{2+} and Fe^{2+} with rapid fluorescence enhancement (Figure 1.10) (Ozmen et al., 2022).

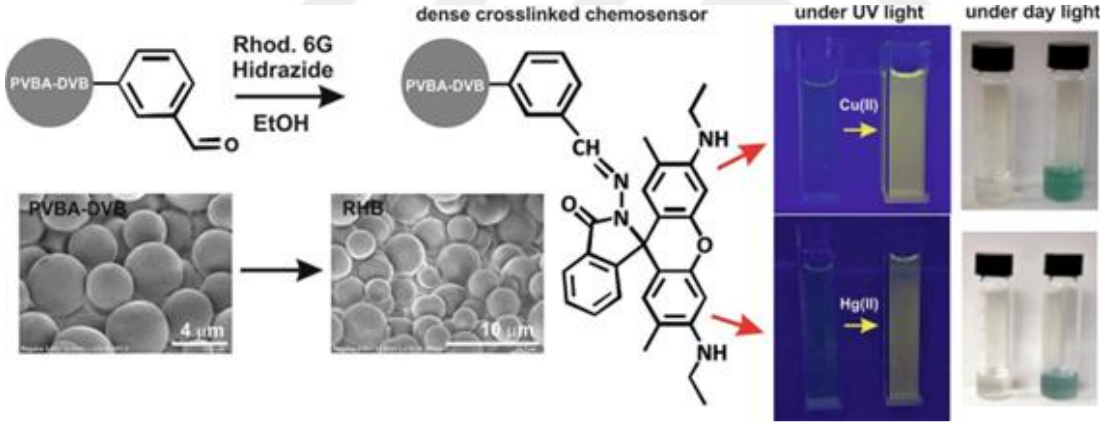

Figure 1.10 : Fe(II) and Cu(II) selective fluorescence sensor (Ozmen et al., 2022).

Another example utilizes 2,2′-thiobisethylamine and diethylenetriamine to form a Schiff base using pyrene-1-carbaldehyde as a fluorophore to optically detect the presence of metal in water media. The results of Schiff bases performing selectively towards Ag^{+} and Pb^{2+} metals are shown in Figure 1.11 (De Castro et al., 2016).

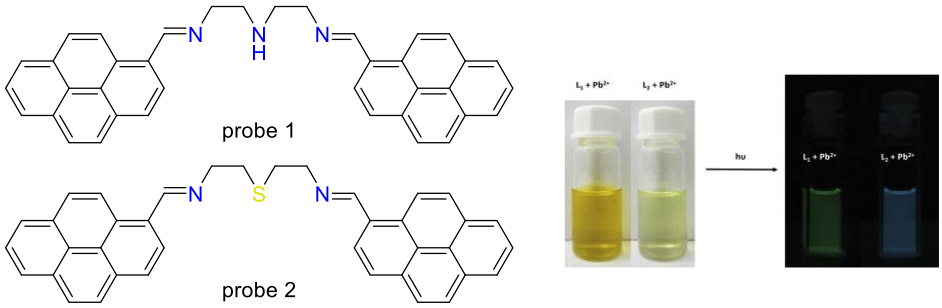

Figure 1.11 : Schematic representation of probes and Pb^{2+} interacted solutions. (De Castro et al., 2016).

With these examples in mind, this thesis aims to synthesize the very first aza-BODIPY-based Schiff base, utilizing tetraphenyl-substituted-aza-BODIPY and several amine derivatives to detect metals in solution. This innovative sensor study is anticipated to provide a robust foundation for the further complexation of aza-BODIPY-based Schiff bases. Such advancements could have significant for applications in therapeutic studies and serve as highly effective ion displacement sensors.

2. EXPERIMENTAL PART

2.1 Materials and Instrumentation

In spectroscopic studies, ^{1}H-NMR and ^{13}C-NMR spectrum were recorded using a 500 MHz Agilent VNMRS NMR spectrometer (Downfield ppm from TMS). FT-IR spectra were saved using a Perkin Elmer 1600. UV/Visible measurements were taken by using PG Instruments T80+ UV/Vis Spectrometer.

In synthetic and titration studies, all chemicals used directly as it is purchased and all solvents were distilled before use. For TLC (Thin Layer Chromatography) Silica gel F254 (Merck 5554) precoated plates, and for column chromatography (CC) Silica gel 60 (Merck 7743) were used. For UV active compounds, the spots were detected under the UV lamp for TLC.

2.2 Synthesis of Aza-BODIPY bearing Schiff Bases

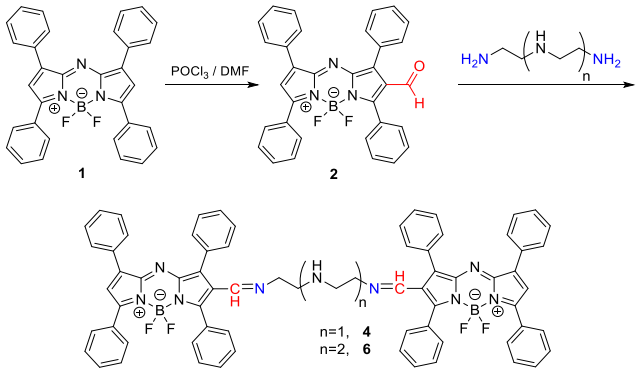

Figure 2.1 : Overview of experimental studies.

Two different Schiff bases were synthesized as probes for metal sensing purposes (Figure 2.1). Firstly, a *β*-formyl aza-BODIPY (2) was synthesized through Vilsmeier-Haack formylation of tetraphenyl substituted aza-BODIPY (1) using $POCl_3$ and DMF under inert conditions. The obtained dye was then reacted with diethylenetriamine (3) resulting with the DETA product (4) and triethylenetetramine (5) yielding TETA product (6) via a classical Schiff base reaction. This approach allowed for the creation of specialized probes aimed at enhancing metal detection in various solutions.

2.2.1 Synthesis of *β*–formyl Aza-BODIPY (2)

0.042 mol (3.33 mL) of DMF and 0.036 mol (3.33 mL) of $POCl_3$ were added to a 3-necked round bottom flask saturated with N_2 gas to provide an inert medium. After stirring for 10 minutes to form Vilsmeier-Haack reagent, a solution of 0.18 mmol (100 mg) of aza-BODIPY dye (1) in dichloroethane (1,2-DCE) was added to the reaction flask drop-wise at room temperature. Heat was turned to 70 degrees, and the reaction was left for 2 hours in reflux (Jiao, Yu, & Li, 2009). The reaction was monitored by TLC. The eluting solvent for TLC was Hex/DCM (3:2, v/v).

After reaction was done, the mixture was added on iced water, and stirred for an additional 10 minutes. Extraction funnel was used for separation of organic and aqueous phases of the reaction mixture. The organic phase was collected, dried in anhydrous $MgSO_4$ by stirring for 1 hour, and filtered through an extra fine filter paper. Residues were washed with DCM, and remaining solution was evaporated under vacuum to obtain β-formylated aza-BODIPY product (2). After the solid product was washed with diethyl ether, it was left to dry (Yielded in 86%) (Figure 2.2).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 9.78 ppm s (1H); δ = 8.08 ppm d (J = 8.14, 4H); δ = 7.88 ppm dd (J = 6.00, 2H); 7.73 ppm dd (J= 6.00, 2H); δ = 7.42 – 7.58 ppm m (12H); δ = 7.23 ppm s (1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm = 186.17, 166.28, 159.35, 148.82, 147.47, 143.15, 142.17, 132.76, 132.02, 130.92, 130.77, 130.69, 130.35, 130.34, 130.21, 129.83, 129.59, 128.95, 128.85, 127.99, 127.76, 121.54.

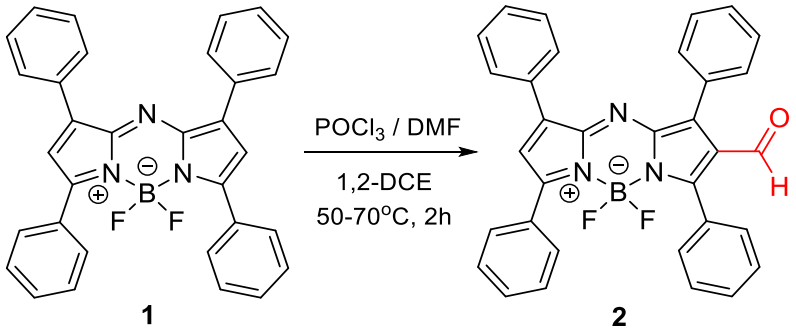

Figure 2.2 : Vilsmeier-Haack reaction scheme of an aza-BODIPY dye formylation in reflux (50-70°C), in the presence of DMF/$POCl_3$ as Vilsmeier reagent, and 1,2-dichloroethane (1,2-DCE) as a solvent (Jiao, Yu, & Li, 2009).

2.2.2 Synthesis of (4) by the reaction of diethylenetriamine (DETA) and 4-formylated-aza-BODIPY compound

0.28 mmol (150 mg) of aza-BODIPY aldehyde was dissolved in ethanol, and 0.14 mmol (15 µL) of DETA was added on the reaction mixture. Heat was set to 70 degrees. 30 minutes after the reflux started, dark blue color of the reaction was turned to dark purple. It was shown on TLC results that aldehyde amount was decreasing by time. An additional hour was kept to ensure the completion of the reaction. In the end of the period, reaction was left to cool, and precipitates were separated from the solvent through using the centrifuge device washing 3 times with EtOH. The solid was prepared for column chromatography.

Column chromatography was used for the purification of obtained imine product. The condition of the solvent system for CC was stoichiometrically 3:2 Hex/DCM. Obtained product (77% yield) was prepared to use for the further spectroscopic measurement methods (Figure 2.3).

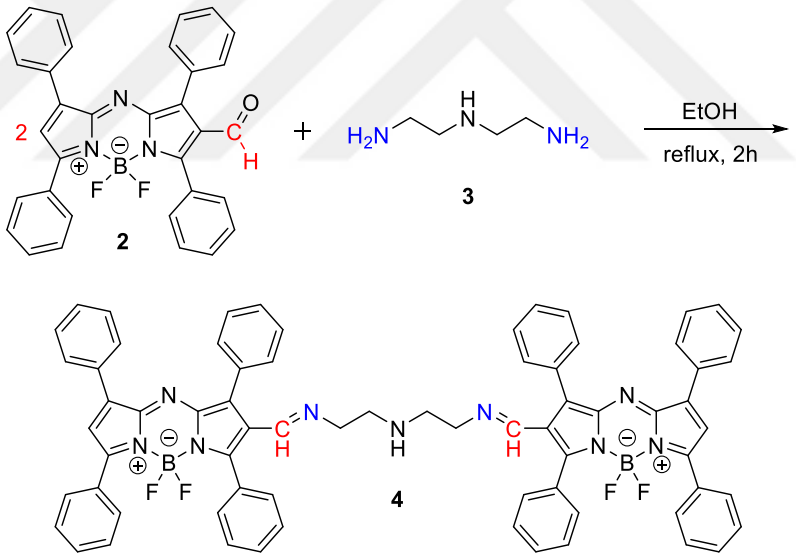

Figure 2.3 : Formation of aza-BODIPY-linked DETA imine product **(4)** by the reaction of *β*-formylated aza-BODIPY **(2)** and diethylenetriamine **(3)**, stoichiometrically 2:1, in the presence of ethanol as solvent in reflux.

2.2.3 Synthesis of (6) by the reaction of triethylenetetramine (TETA) and 4-formylated-aza-BODIPY compound

β-formylated aza-BODIPY (0.28 mmol, 150 mg) was dissolved in EtOH. After the temperature was set to 70 degrees, TETA (0.14 mmol, 20 µL) was added to the reaction flask. The reaction was followed up by TLC, and continued to stir until the aza-BODIPY spot was observed to disappear. The liquid phase was separated from the

solid product by using centrifuge method. The further purification process was carried out using column chromatography method (3:2, Hex/DCM) to obtain the solid TETA imine product (83%). After the characterization of the product was done, it was prepared for the spectroscopic evaluations**.**

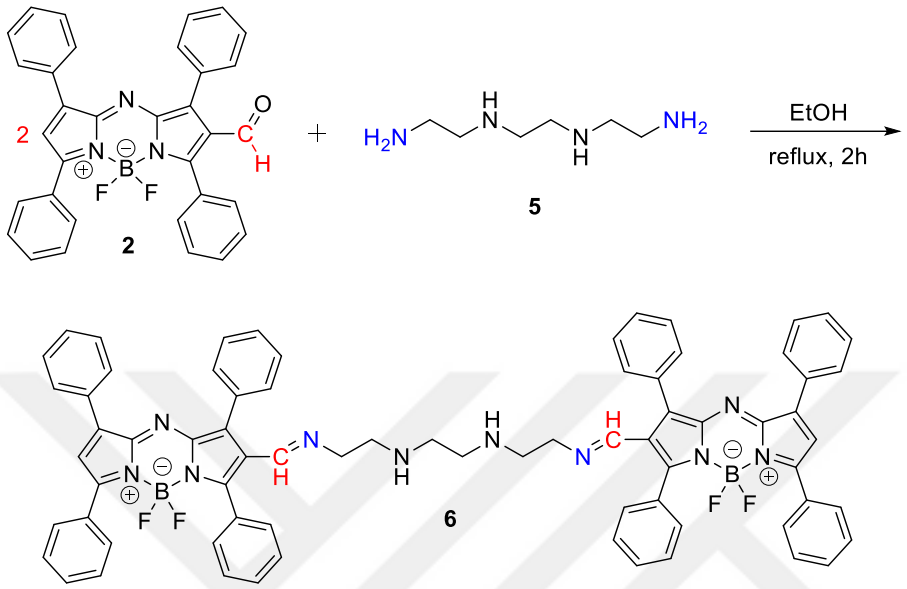

Figure 2.4 : Formation of aza-BODIPY-linked TETA imine product **(6)** by the reaction of β-formylated aza-BODIPY **(2)** and triethylenetetramine **(5)**, stoichiometrically 2:1, in the presence of ethanol as solvent in reflux.

2.3 Spectrophotometric Studies

To investigate the binding capabilities and probe potential of the synthesized aza-BODIPY bearing Schiff bases, UV/Vis spectroscopy was used. For that purpose, firstly 1 mM concentrated ligand solutions (DETA and TETA products) were prepared in DMF and calibration of the ligands were obtained. After ideal concentration solutions were set for ligands, various metal solutions, namely $HgCl_2$, $ZnCl_2$, $CuSO_4$, $Co(OAc)_2$, $SnCl_2$, were prepared in DMF solution for the next step UV/Vis spectroscopy measurements, and optimization of titration were established as 0.02 mM for the DETA and TETA product solutions, and 0.5 mM for each metal solution.

3. RESULTS AND DISCUSSION

In this section, we present and analyse the findings of our study on the synthesis and sensor applications of newly developed ligands. The synthesis results detail the procedures and outcomes of creating the ligands, including their structural characterization and purity assessment. Following this, the titration studies explore the sensor capabilities of the synthesized ligands, highlighting their effectiveness in detecting specific analytes and their potential applications in various fields. By examining both the synthetic process and the practical applications, we aim to provide a comprehensive overview of the ligands' properties and their utility as chemical sensors.

3.1 Reaction of Diamines with β-Formylated Aza-BODIPY Compound

When we carried out an imine reaction between DETA (3) and aza-BODIPY aldehyde (2) (Figure 2.3), the formation of the DETA imine product (4) took place in a very short time (30 min). The most distinguishing feature that shows the reaction was done was the colour changing from blue to purple. The reason for using a centrifuge after the reaction is that the precipitates in the reaction solution are not able to be filtered because of their adsorption on the paper. In addition, it was not possible to evaporate the solvent due to the azeotropic formation of ethanol and the release of water from the reaction (Abdel-Magid, 2014). Therefore, the separation of the precipitates from the liquid phase was done by using a centrifuge device. Column chromatography was used for the purification of the product from the impurities of the starting material.

When we tried TETA as an amine for this reaction, we observed that its reaction process, TLC results, purification methods, and characterization were similar to those of the DETA product. The reaction time was approximately the same, and the colour of the product was also purple. TLC results showed that this product was in the exact same spot as the DETA product.

This radical color changes can be attributed to (i) manipulation of conjugation and (ii) solvatochromism. Aza-BODIPY compounds are known for their strong absorption and

emission in the visible region due to their highly conjugated structure. The formation of an imine changes the electronic structure of the aza-BODIPY core. When the imine forms, it extends the conjugation or alters the electronic distribution within the molecule. This can result in a shift in the absorption maxima, leading to a visible color change. The transition from blue to purple suggests a change in the energy levels of the electronic transitions, likely indicating a new or extended conjugated system.

Furthermore, an essential point of the synthesis and purification lies in addressing the solubility of aza-BODIPY moieties. The limited solubility of the products in aprotic solvents significantly complicates the purification of aza-BODIPY imines.

In line of these findings, it would be valuable to point out the mechanism underlying the formation of Schiff bases from 4-formylated aza-BODIPY. The process of forming imine compounds includes protonation, attack by nucleophiles, removal of water in a slightly acidic medium, and deprotonation as the final step (Figure 3.1) (Abdel-Magid, 2014).

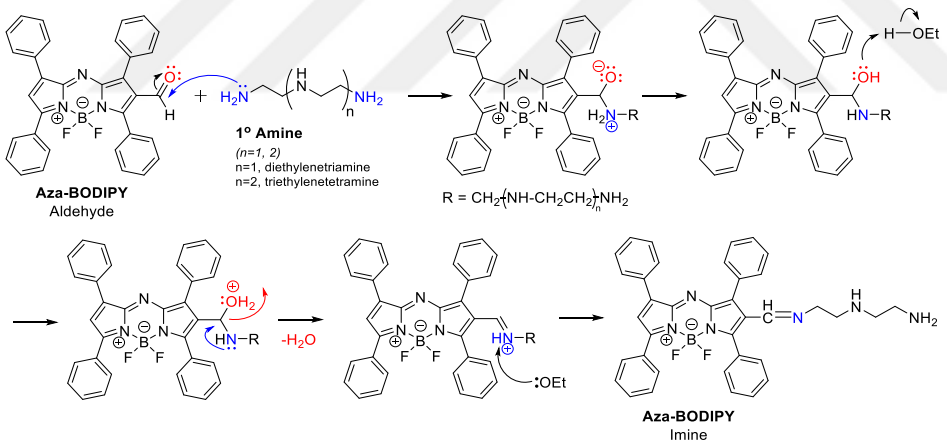

Figure 3.1 : Formation mechanism of imines starting with a *β*-formylated-aza-BODIPY in the presence of a diamine (diethylenetriamine or triethylenetetramine), as a first step. (Representative imine mechanism via aza-BODIPY aldehyde adapted from Ciaccia, & Di Stefano, 2014).

3.2 Structure Analysis of the Synthesized Products

Structural characterization of *β*–formyl aza-BODIPY (2), and Schiff bases (4, 6) (DETA and TETA products respectively) were carried out through ^{1}H-NMR (in $CDCl_3$). According to obtained spectrum, *β*–formyl aza-BODIPY was successfully synthesized, and all individual protons assigned illustrated in Figure 3.2. For further investigation proton NMR of aza-BODIPY and *β*–formyl aza-BODIPY (2) was studied together to enlighten formylation over aza-BODIPY (Figure 3.5).

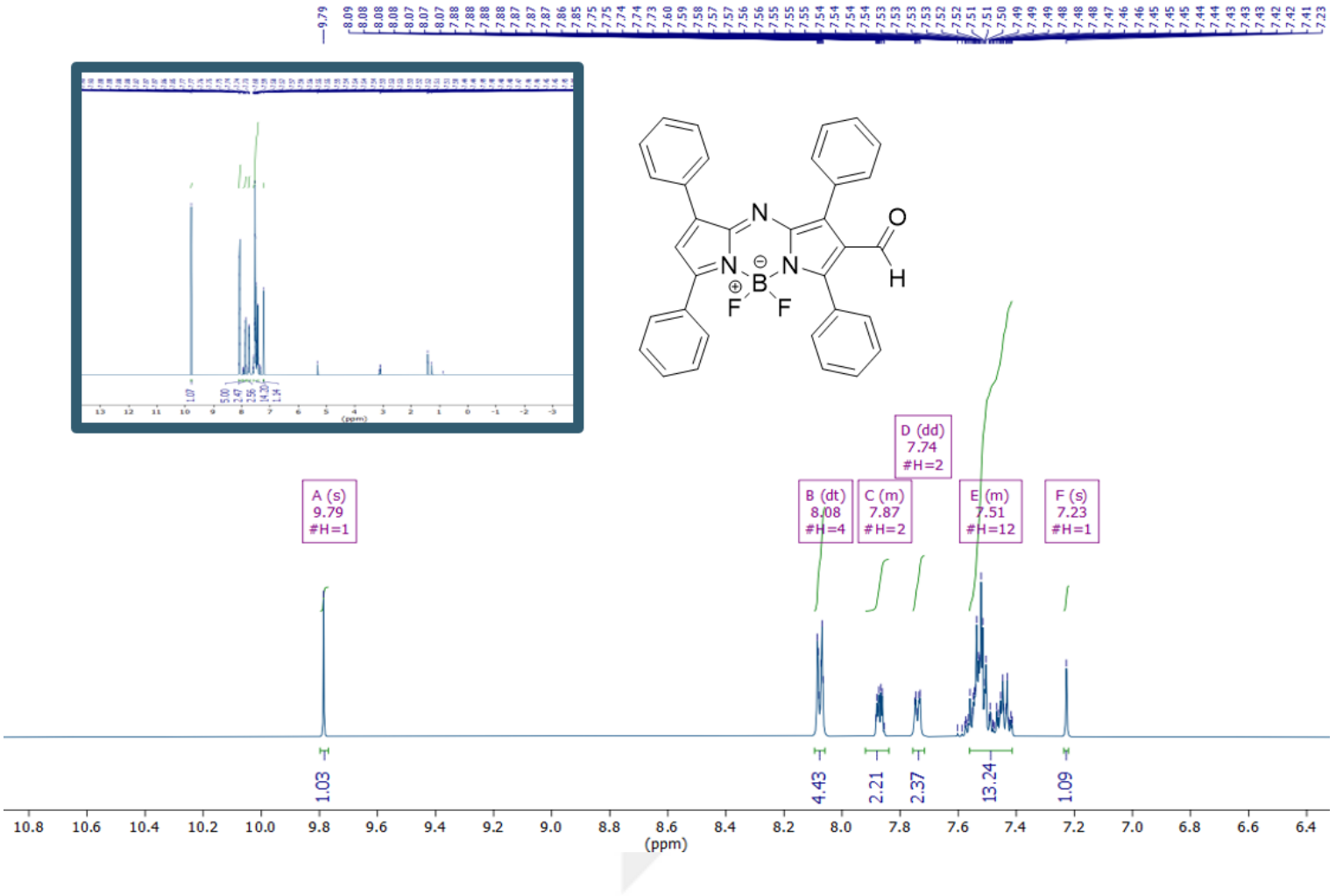

Figure 3.2 : ^{1}H-NMR of *β*–formyl azaBODIPY **(2)** (in $CDCl_3$).

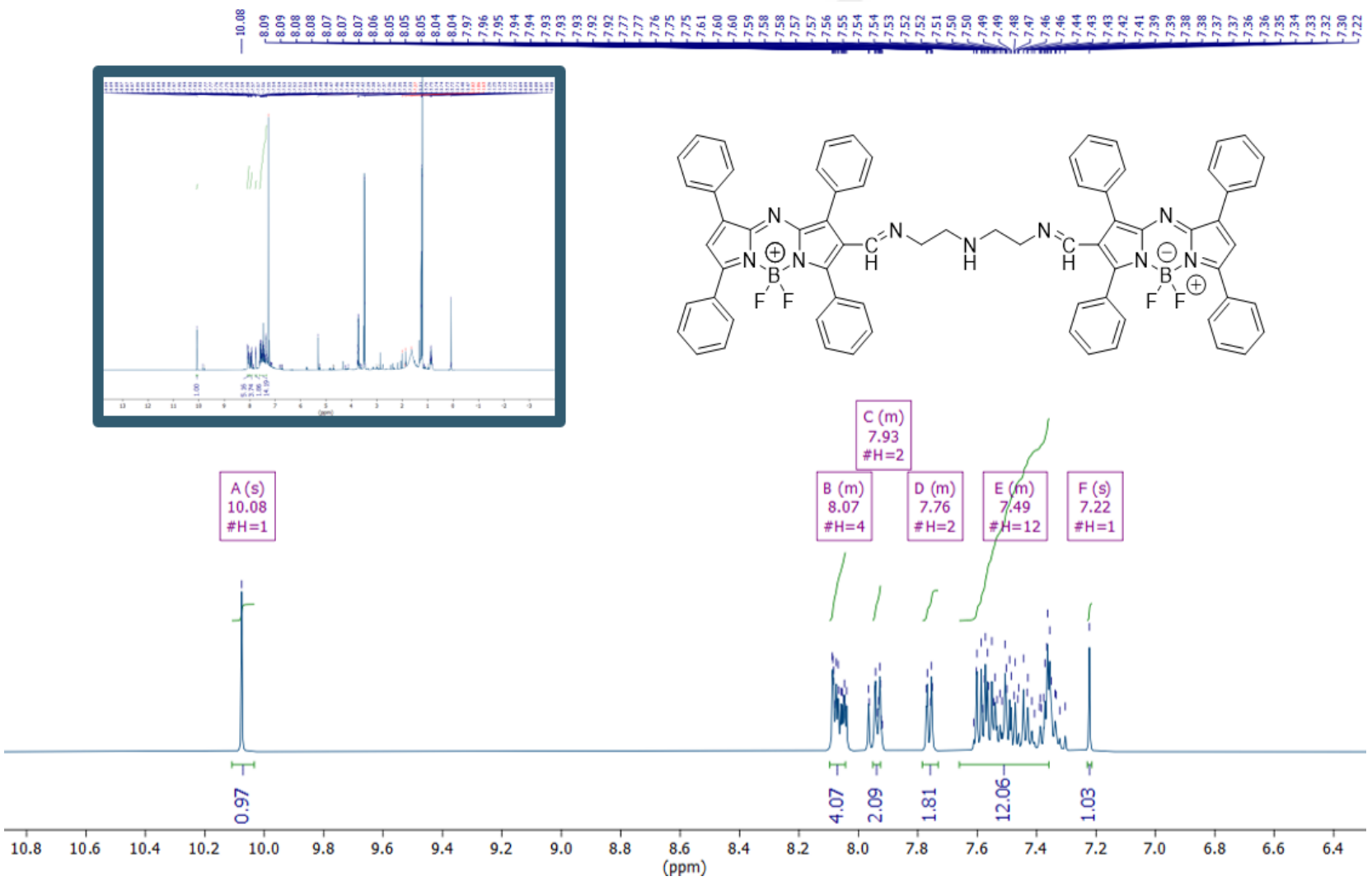

Figure 3.3 : ^{1}H-NMR of DETA-based Schiff base product **(4)** (in $CDCl_3$).

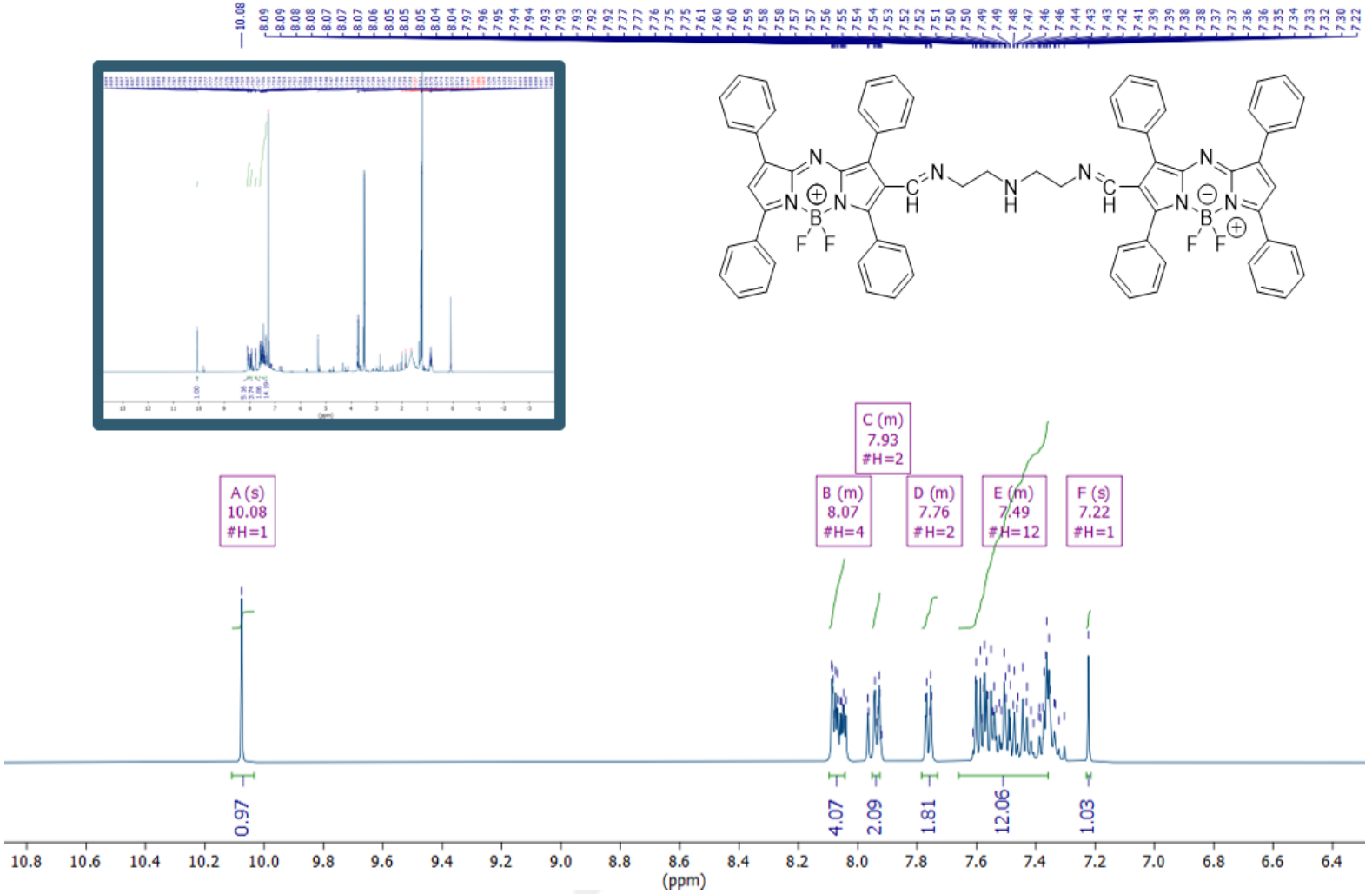

Figure 3.4 : ^{1}H-NMR of TETA-based Schiff base product **(6)** (in $CDCl_3$).

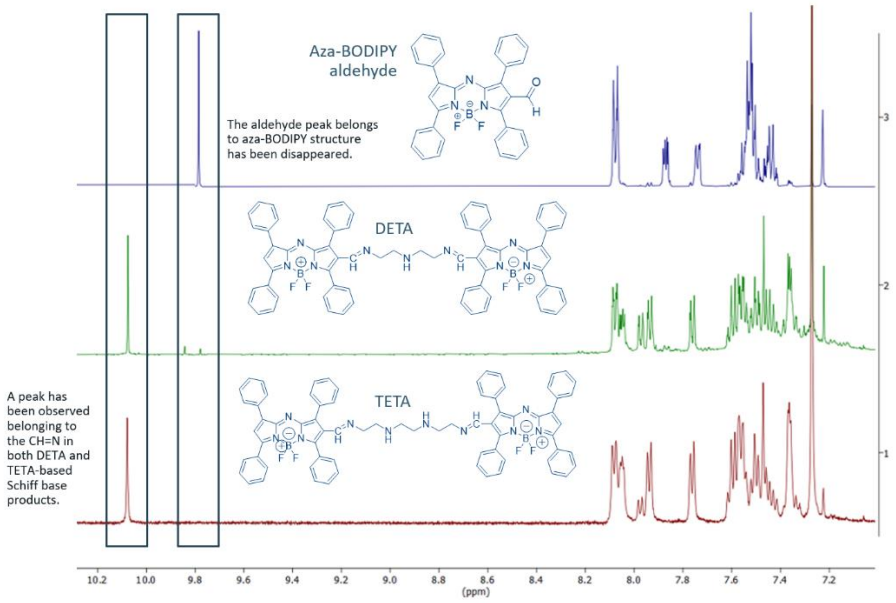

Figure 3.5 : Comparative ^{1}H-NMR spectra of **(1)**, **(4)** and **(6)**.

As for DETA- and TETA-based Schiff bases, a comparative spectrum was provided against each other and the starting material β-formyl aza-BODIPY in Figure 3.5 : Comparative ^{1}H-NMR spectra of (1), (4) and (6). It is evident that the purification of the target sensor was incomplete, as the proton peak of the aldehyde remains present in the spectrum as seen at the spectrum of DETA. As previously noted, due to the entirely symmetrical structures and low solubility of aza-BODIPY moieties in nonpolar solvents, purification via column chromatography becomes challenging. Fortunately, the hydrogens of H-C=N can be readily observed at 10.08 ppm, indicating the successful formation of the target product. Addition to provided NMR spectrums FT-IR analysis were conducted for better information (see Figure 3.6). Unfortunately, the overlap of stretchings for H-C=O and H-C=N results in the characterized peaks being prevented.

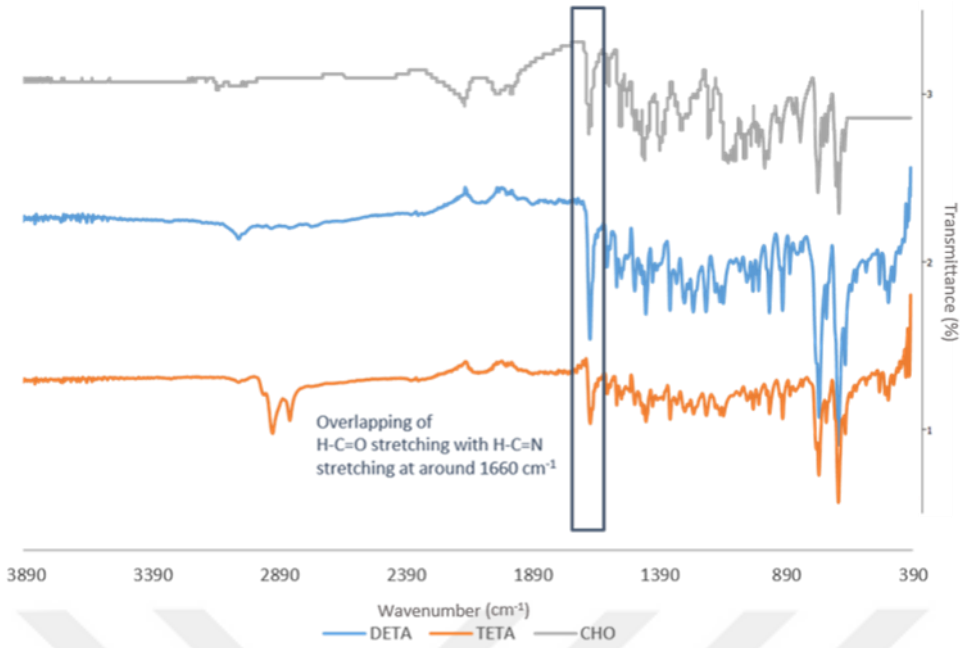

Figure 3.6 : Comparison of FT-IR spectra of **(1)**, **(4)** and **(6)**.

3.3 Optical Analysis and Interaction with Metals

DETA and TETA product solutions in DMF provide a good linear calibration in the 5–30 µM range (Figure 3.7). The absorption maxima were 554 and 544 nm respectively, showing hypsochromic shifts compared to formylated aza-BODIPY (620 nm). To explain, it would be insufficient to consider only the conversion of the aldehyde to an imine. In molecules containing a C=N bond, the HOMO energy is generally higher due to the lower electronegativity of nitrogen, which can lead to a lower energy transition. Contrary to our results, suggesting an overall change in the electron configuration of the molecule.

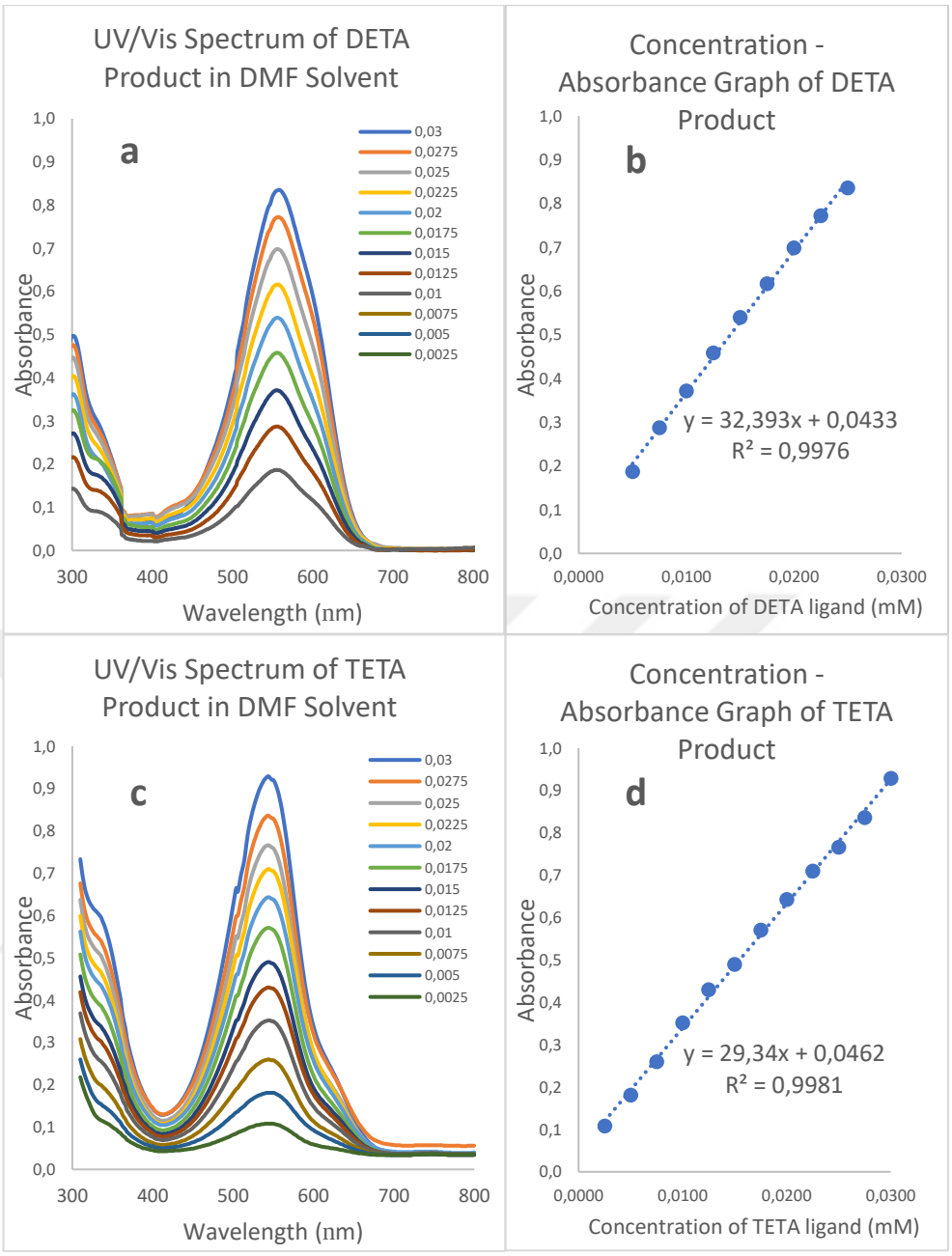

Figure 3.7 : UV/Vis spectrum and calibration curves of **4** (a, b) and **6** (c, d).

A similar situation is observed in fluorescence spectroscopy. While formylated aza-BODIPY shows an emission peak around 640 nm, the Schiff bases do not exhibit any emission. This can be attributed to C=N isomerization, which causes relaxation in the molecule, resulting in diminished light-emitting properties. Due to no emission seen in the DETA and TETA products, fluorescence analyses were not conducted after several trials.

Lastly different metals have been interacted with the DETA and TETA products to determine the following parameters: Schiff base complex formation time, and the amount of change in their shifts in the presence of increasing metal concentration. Predicted complex structures are shown in Figure 3.7.

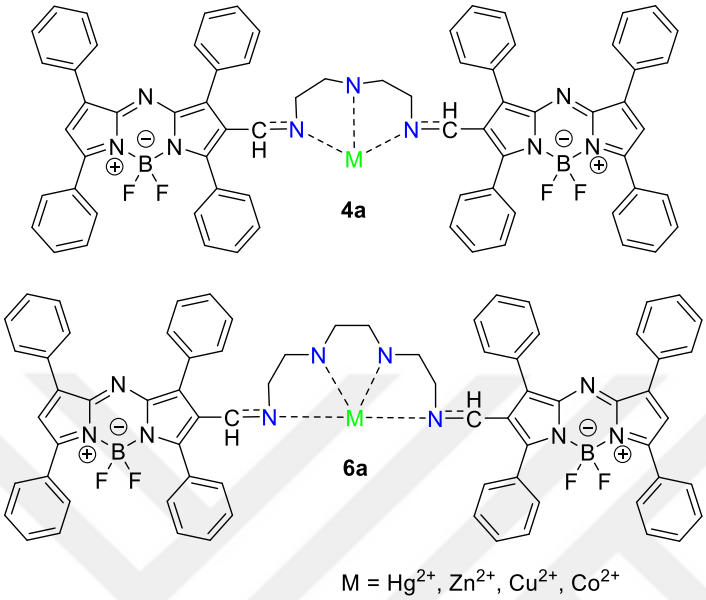

Figure 3.8 : The scheme of expected interaction between the metal ions and the tridentate DETA- and tetradentate TETA-based imine products.

A table displaying the UV/Vis measurement values is listed in Table 3.1 along with the visualization of the study done.

Table 3.1 : UV/Vis measurement results of the DETA and TETA products when reacted with various metal ions (Hg^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+}, Sn^{2+}).

	Imines in DMF	**Metal** in DMF **(0.5 mM)**	**Time** *(sec)*	**Time-depended Δλ**	**[M]-depended Δλ**	**λ_{max}** *(nm)*
4a	DETA product **(0.02 mM)** λ_{max} : 554 nm	$HgCl_2$	90	34	34	580
		$ZnCl_2$	120	42	38	596
		$CuSO_4$	90	50	50	604
		$Co(OAc)_2$	210	40	40	594
		$SnCl_2$	2000	2	-	556
6a	TETA product **(0.02 mM)** λ_{max} : 544 nm	$HgCl_2$	150	38	38	584
		$ZnCl_2$	210	56	50	602
		$CuSO_4$	150	64	62	606
		$Co(OAc)_2$	390	52	50	598

Figure 3.9 : TETA ligand solution in decreasing concentrations, respectively; 0.02; 0.0175; 0.015; 0.0125; 0.01; 0.075; 0.05; 0.025 mM solutions in DMF.

Figure 3.10 : The changes in color 10 minutes after the addition of the metal solution (0.5 mM $ZnCl_2$) in increasing volumes (from 0 up to 3.5 mL) into decreasing volumes of ligand solution (0,02 mM TETA product): Respectively horizantal; 4.0:0.0 ; 3.5:0.5 ; 3.0:1.0 ; 2.5:1.5 ; 2.0:2.0 ; 1.5:2.5 ; 1.0:3.0 ; 0.5:3.5 mL of Ligand/Metal solutions.

Titration spectra of the DETA product (Figure 3.11) and TETA product Figure 3.12were achieved with the interaction of Hg^{2+}, Zn^{2+}, Cu^{2+}, and Co^{2+} metals, respectively. The initial λ_{max} values of the blank ligand samples were set to approximately 0.8 in all samples. Spectral measurements have been continued until the sample reaches the maximum wavelength and absorbance.

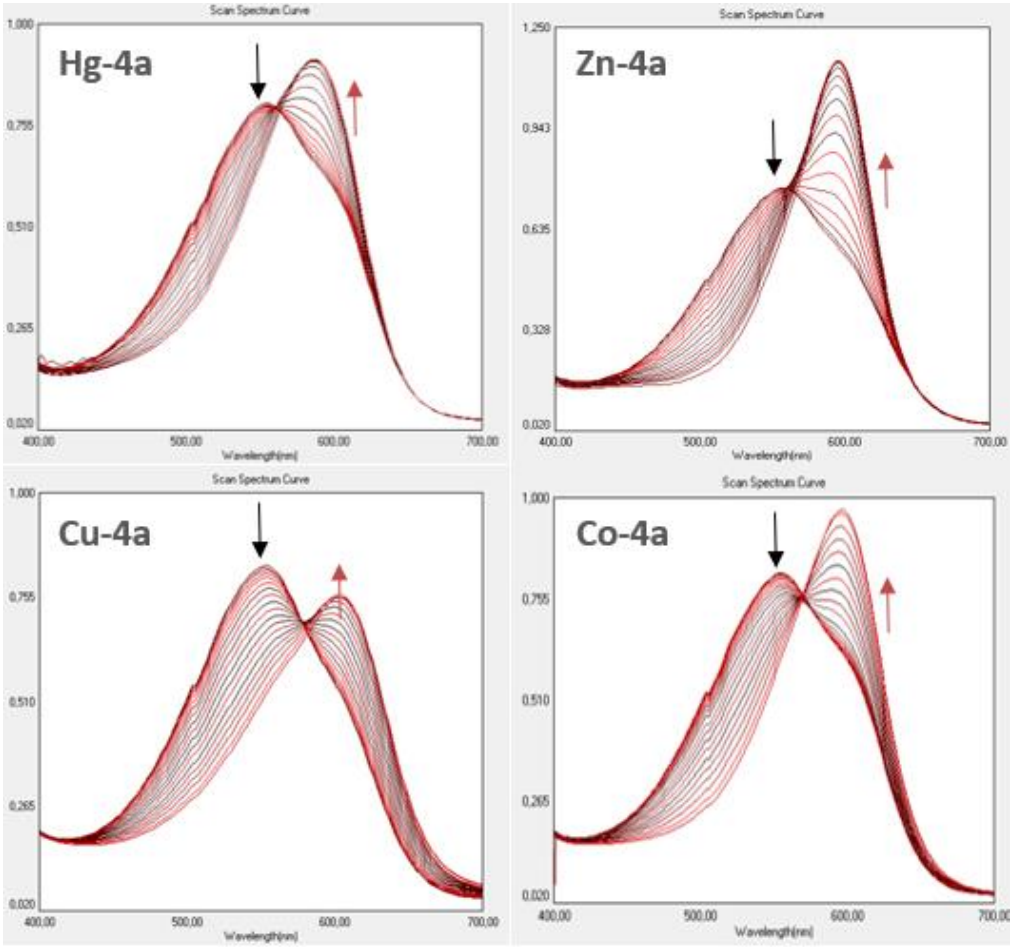

Figure 3.11 : UV/Vis spectra results, displaying the red-shift of the DETA product **(4a)** while interacting with different metals (Hg^{2+}, Zn^{2+}, Cu^{2+}, and Co^{2+}) in the sample cuvette until it reaches its maximum wavelength and absorption values. The offset after each addition was established according to the measured interaction time with the corresponding metal shown in Table 3.1. While the black arrows represent the decrease in absorbance of the DETA product, the red arrows show the increase in absorption caused by the increasing metal concentration in the solution.

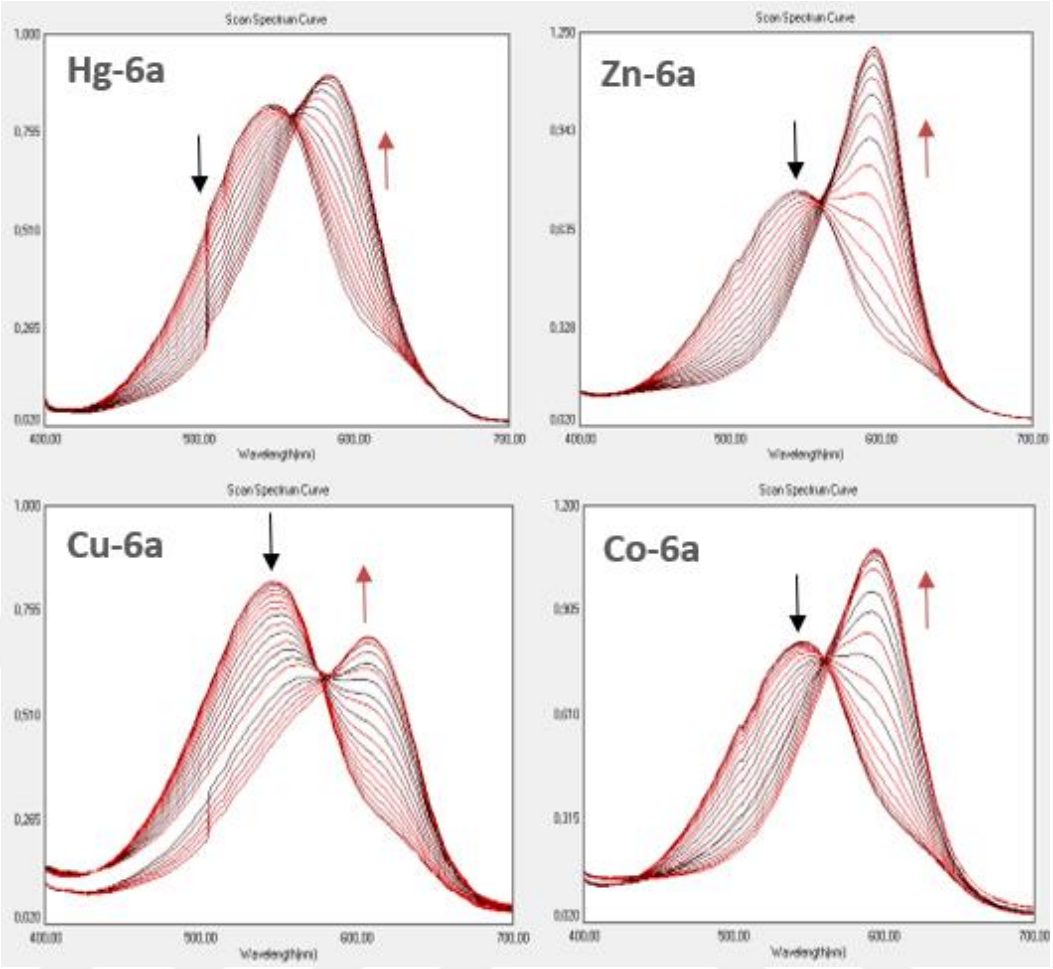

Figure 3.12 : UV/Vis spectra results showing the red-shift caused by the interaction of the TETA product **(6a)** with various metals (Hg^{2+}, Zn^{2+}, Cu^{2+}, and Co^{2+}) until reaching the maximum wavelength and absorption values. The offset was determined based on the measured interaction time with the corresponding metal depicted in Table 3.1. Black and red arrows represent the absorbance changes upon increasing metal concentration in the sample quvette.

3.4 Discussion and Future Aims

Aza-BODIPY moieties have an increasing attention as promising organic compounds, having Vis/NIR absorption and emission properties. On the other hand, bis-Schiff bases of aza-BODIPY that we synthesized new and interesting structures. Although there are studies on metal complexes of Schiff bases with three or four nitrogen donor sides, aza-BODIPY containing Schiff bases have not been studied much.

Since aza-BODIPY (and also 4-formylated-aza-BODIPY) have absorption at high wavelengths ($650<\lambda<734$ nm) and high fluorescence emissions ($673<\lambda<771$ nm) (see Figure 1.3), we expected to obtain higher absorption and emission results by adding a

C=N moiety to the aza-BODIPY structure. Thus, the double-sided aza-BODIPY imine compound could be used as a fluorescent sensor in the NIR region.

Unexpectedly, while we expected a shift towards the red region in UV/Vis measurements, a shift towards the blue region was observed. Moreover, although the new imine compound was predicted to result in increased emission, on the contrary, the emission in the aza-BODIPY (and 4-formylated-aza-BODIPY) compounds completely disappeared. These UV/Vis measurement results led us to speculate that there may be a potential for cession of conjugation with a double-sided imine bond (C=N) in the structure of the designed sensor. We also noted that this loss in fluorescence emission of the obtained imine products could not be regained, even though the shifting to the red region was observed on UV/Vis measurements with the addition of metal to the imine solution.

However, it was noted in the UV/Vis spectrum results that the sample containing the copper (II) metal solution had the highest red-shift for both of the designed ligands. It was then discovered that the solutions containing zinc (II) and cobalt (II) had the second and third highest interaction. Despite having a shorter interaction time with the ligand than the other metals, mercury (II) complex had the lowest maximum wavelength shift of all the metals. In addition, even though the cobalt (II) complex has a high maximum wavelength at which it shifts, it has been discovered that it has a longer interaction time than other metals.

When we compare ligands types (DETA and TETA) and their effects on the interaction with metals, it was found that the interactions between TETA-based ligand and the metal were higher than those of DETA ligand, although by a small difference. However, it has also been noted that the DETA-based ligand reacts faster with metals in terms of interaction time.

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