“Design and Synthesis of Donor-Acceptor Based Aza-BODIPY Derivatives”

M.Sc. Thesis

By

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DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY INDORE

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“Design and Synthesis of Donor-Acceptor Based Aza-BODIPY Derivatives”

A THESIS

Submitted in partial fulfilment of the requirements for the award of the degree of

Master of Science

by

Nitish Kumar

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY INDORE

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INDIAN INSTITUTE OF TECHNOLOGY
INDORE
CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in this thesis entitled report entitled "**Design and Synthesis of Donor-Acceptor Based Aza-BODIPY Derivatives**", in the partial fulfilment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted to the **DEPARTMENT OF CHEMISTRY, Indian Institute of Technology Indore,** is an authentic record of my own work carried out during the time period from June, 2022 of joining the M.Sc. program to May 2023 of M.Sc. thesis submission under the supervision of Prof. Rajneesh Misra, Professor, IIT Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Nitish Kumar

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

Prof. Rajneesh Misra

Nitish Kumar has successfully given his M.Sc. Oral Examination held on May ____

Signature of supervisor of M.Sc. thesis
Date: _____

Convener, DPGC
Date: 25/05/2023

Signature of PSPC Member #1
Dr. Amrendra Kumar Singh
Date: _____

Signature of PSPC Member #2
Dr. Debayan Sarkar
Date: _____

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Nitish Kumar

DEDICATED TO MY PARENTS

AND MY FRIENDS……

For their support in every stage of my life!

ABSTRACT

Here, we have designed and synthesised aza-BODIPY dyes **6a** and **6b** by BF_2 complexation using boron trifluoride diethyl etherate ($BF_3.OEt_2$) respectively. The aza-boron dipyrromethene (aza-BODIPY) is a class of BODIPY dyes that contain heteroatoms with a nitrogen atom at *meso* position instead of carbon, displays strong electron accepting nature with near infrared (NIR) absorption, low band gap and low lying LUMO levels. Aza-BODIPY has shown great potential for photothermal therapy (PTT) in organic photosensitizers due to excellent NIR absorption and photothermal conversion efficiency. The photophysical and electrochemical properties as well as their density functional theory (DFT) studies were explored which shows good donor–acceptor interaction and successful tuning of the HOMO-LUMO gap. Aza-BODIPY shows various applications in organic photovoltaics, photodynamic cancer therapy, photothermal properties, organic field-effect transistor (OFET) and organic light emitting diode (OLED).

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LIST OF FIGURES, SCHEMES AND TABLES

ACRONYMS

OLEDs	Organic light-emitting diodes
OFETs	Organic field-effect transistors
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital

1. INTRODUCTION

Near-infrared (NIR) absorbing dyes have been widely used in biomedical applications because of its penetration of NIR light is deep into most biological tissue compared to the visible light.[1] NIR fluorescent dyes displayed superior advantages in both the bioimaging and environmental fields.[2] Recent advances in bioapplications such as phototherapy, photoacoustic (PA) and fluorescence bioimaging have mostly focused on the production of various high-performance organic materials.[3-5] Efficiency of organic dyes is highly altered by light harvesting in the NIR band.[6] These dyes show excellent properties, such as high quantum yield, low photobleaching, and deep tissue penetration.[7-9] NIR dyes have various applications in bioimaging studies.[10]

Invitrogen commercializes boron-dipyrromethene (BODIPY) are an organo-boron fluorescent dye which reflects ultraviolet (UV)-visible light.[11] Mostly at wavelengths below 600 nm, BODIPY strongly absorb UV radiation and then re-emit it in very narrow frequency along with high quantum yield.[12] Many BODIPY derivatives display high fluorescence, small stoke shift, and good photostability.[13-15] BODIPY has several applications in solar cell, supramolecular fluorescent liquid, light harvesting system, and light-emitting sensor.[16-19]

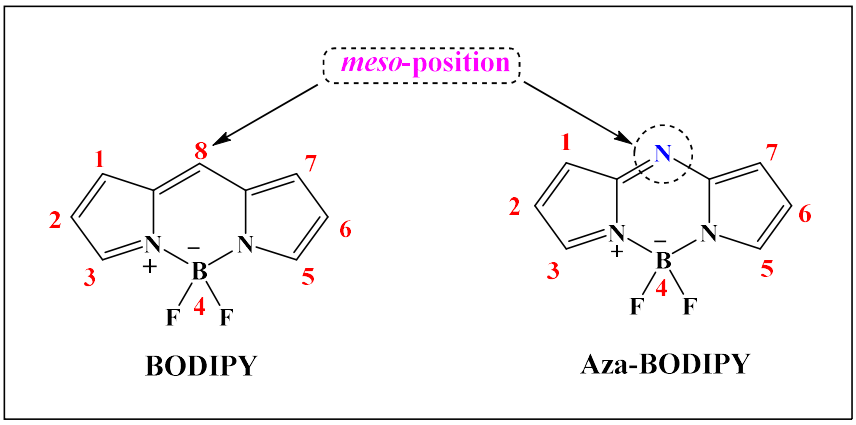


Figure **1**. General structures of BODIPY and aza-BODIPY dyes.

The aza-BODIPY typically has higher wavelength absorption and emission maxima as compared to the BODIPY dyes.[20] Aza-BODIPYs have garnered a lot of attention more lately due to their high transmittance and red shifted absorption.[21] Aza-BODIPY derivatives have a benefit of having red shifted absorption and emission profiles over BODIPY dyes in terms of flexibility for structural change, photostability, and chemical stability.[22] It has been due to the high electronegetivity of nitrogen atom in the aza-BODIPY analogue as compared to *meso*-carbon atoms in the BODIPY analogue.[23]

The aza-BODIPY dyes have found an exponentially increasing number of large applications due to their excellent photophysical properties such as intense absorption/fluorescence into NIR region, high molar extinction coefficient, and relatively high quantum yield with large photostability.[24] These dyes have tremendous potential in fluorescence imaging and phototherapy due to their improved

penetration depth, lower photon scattering, and reduced autofluorescence in biological tissues.[25] Aza-BODIPY red shifted absorption and emission appear to be influenced by the presence of aryl substituent at positions 1, 3, 5, and 7 which make the heterocycles very hydrophobic and prone to aggregation in aqueous conditions.[26] Thus aza-BODIPY shows various applications in fluorescent chemosensors, activated solar cell, photodynamic treatment (PDT), photothermal therapy (PTT), organic field-effect transistor (OFET),[27] organic light emitting diode (OLED),[28] therapeutics, and photosenitizers used in phototherapeutic.[29]

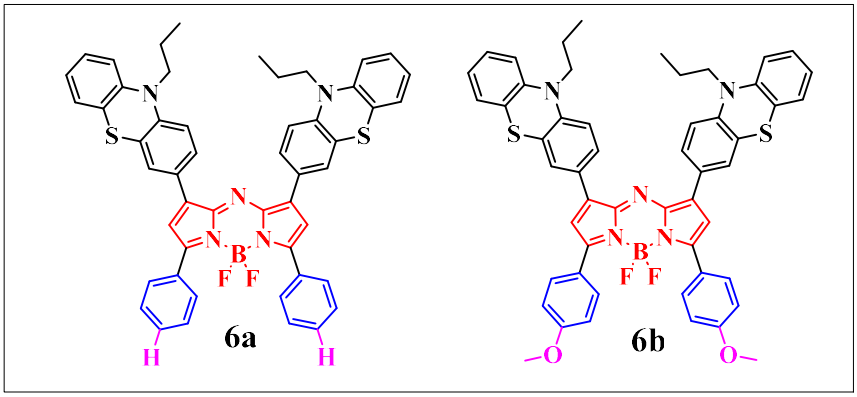


Figure **2**. Chemical structures of aza-BODIPY dyes **6a** and **6b**

Herein, we report the design and synthesis of two different aza-BODIPY dyes **6a** and **6b** to study its photophysical and computational properties.

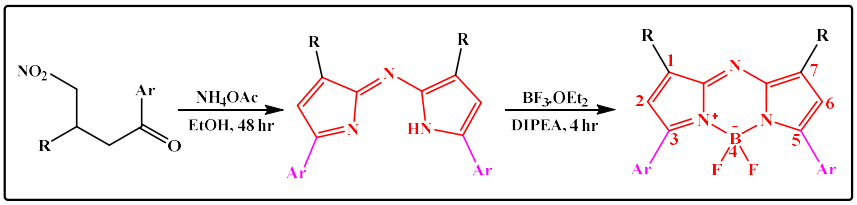
2. LITERATURE REVIEW

Different Synthetic methods for the preparation of aza-BODIPYs analogues:

It has been reported that three different synthetic methods of aza-BODIPY dye have been reported (scheme 1–3) owning to investigations. O'Shea's *et al.* combined a cyclization reaction of substituted ketones and aldehydes with the use of trifluoride complexes to create symmetrical and asymmetrical aza-BODIPY products by employing a method involving a cyclization reaction followed by boron trifluoride complexation to produce the desired product.[30]

O'shea's method:

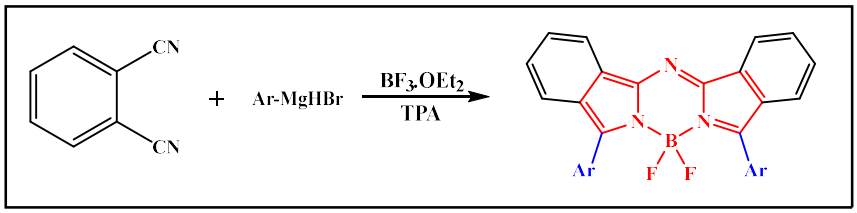
O'Shea's group was the first to develop simple methods for preparing aza-BODIPY compounds.[31] O'shea *et al.* discovered a new and improved synthetic route of symmetric aza-BODIPY derived from 1,3-diaryl-4-nitrobutan-1-one.[32] The key intermediates are formed through 1,4-Michael addition of nitromethane with readily available chalcones *via* aldol condensation reaction between respective benzaldehydes and acetophenones.[33] This key intermediate is further condensed with nitro butanone derivatives in refluxed ethanol in presence of ammonium acetate.[34] Finally, aza-BODIPY dyes is formed when react with BF_2 complexation in presence of diisopropylethylamine for 4 hr (scheme 1).[35] Through the synthesis following this method and the condition used are mild, the yield of the product is low (15-30%).



Scheme 1. O'Shea's method for aza-BODIPY synthesis.

Lukyanets and Shen's method:

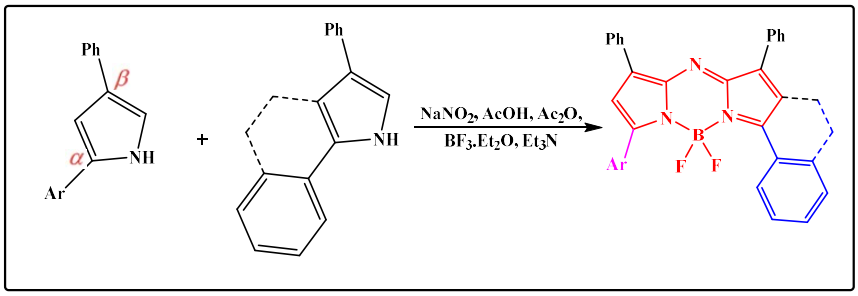
A study shows that aza-BODIPY can be synthesised by reacting phthalonitrile with aryl magnesium bromide as described by Shen and Lukyanets *et al.* method (scheme **2**).[36]



Scheme 2. Lukyanet's method for aza-BODIPY synthesis.

Carreira's method:

Zhao and Carreira *et al.* demonstrated a modern and successful technique of asymmetric symmetric synthesis of aza -BODIPY using a single 2,4-diaryl pyrrole which includes a direct cyclization of substituted pyrrole followed by boron trifluoride complexation (scheme **3**).[37] This implies that the key requirement for the synthesis of aza-BODIPY in Carreira's method is the presence of an aryl unit at the α and β positions in pyrrole ring.[38]



Scheme 3. Carreira's method for aza-BODIPY synthesis.

3. EXPERIMENTAL SECTION:

3.1 General methods

All the chemicals that were used in the experiment were obtained unless indicated specifically. Using the conventional Schlenk method, all moisture responsive reactions were carried out in an argon environment. $CDCl_3$ was used as a solvent to record ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra of both the compounds. The Chemical shifts are measured in parts per million (ppm) in reference to the solvent residual peak ($CDCl_3$, 7.26 ppm). In addition, s (singlet), d (doublet), and m (multiplet) are given in terms of Hz and coupling constants J. The chemical shifts in ^{13}C NMR are measured in reference to the solvent residual peak ($CDCl_3$, 77.36 ppm). The HRMS data were investigated using an ESI-TOF mass spectrometer. In dichloromethane, UV-visible spectrophotometer was used to measure the absorption spectra of aza-BODIPY.

3.2 Experimental Procedure

Synthesis of compound 1:

Phenothiazine (0.500 g, 2.5 mmol) and propyl iodide (0.25 ml, 2.5 mmol) were dissolved in dimethyl sulfoxide (DMSO) then sodium hydroxide (NaOH) was added as a base at RT for 24 hr. After completion of reaction compound layer was separated using dichloromethane (DCM) and water. After then solvent was evaporated using rota evaporator. Pure compound was obtained *via* column chromatography using hexane as solvent. Yield: 90%; **^{1}H NMR** (500 MHz, CHLOROFORM-*d*): 7.15 - 7.17 (m, 4 H), 6.92 - 6.94 (d, *J*=7.78

Hz, 4 H), 3.82 (m, 2 H), 1.84 - 1.85 (st *J*=7.29 Hz, 2 H), 1.01 (t, *J*=7.40 Hz, 3 H) **^{13}C NMR** (125 MHz, CHLOROFORM-*d*): 127.3, 127.1, 124.9, 122.4, 115.6, 49.3, 20.0, 11.2; **HRMS** (ESI) m/z $[M + nH]^+$ calcd for $C_{15}H_{16}NS$: 242.0998 found 242.0964.

Synthesis of compound 2:

A 250 ml two neck round bottom (RB) flask was taken and dried. Alkylated Phenothiazine (0.500 g, 2.07 mmol), was added to the RB and some ice was kept around the RB. Dichloroethane (DCE) (40 ml) and *N,N*-dimethylformamide (DMF) (0.64 ml) was added to the reaction mixture. Finally, $POCl_3$ (0.77 ml, 8.20 mmol) was added dropwise to the reaction mixture. After 5 minutes reaction mixture was put on heat bath for 16 hr at 80 ^oC. After 16 hr reaction was stopped and some ice-cold water was added to the RB slowly. Then organic layer was extracted using DCM and ice. After then solvent was dried using rota evaporator. Pure compound was obtained by column chromatography (silica gel, n-hexane: DCM; 1:9) as eluent. Yield: 80%; **^{1}H NMR** (500 MHz, CHLOROFORM-*d*): 9.82 (s, 1 H), 7.61 - 7.66 (m, 2 H), 7.13 - 7.18 (m, 2 H), 6.89 - 6.93 (m, 3 H), 3.88 - 3.91 (m, 2 H) 1.85 - 1.91 (m, 2 H), 1.04 - 1.07 (t, *J*=7.40 Hz, 3 H). **^{13}C NMR** (125 MHz, CHLOROFORM-*d*) :190.0, 170.8, 143.4, 131.0, 128.4, 127.5, 125.0, 123.6, 116.0, 49.7, 20.0, 11.2; **HRMS** (ESI) m/z $[M+nH]^+$ calcd for $C_{16}H_{16}NSO$: 270.0947 found 270.0923.

Synthesis of aza-BODIPY 6a:

In a 250 mL RB, aza-dipyrromethene **5a** (0.500 gm, 0.64 mmol) was dissolved in 100 mL of dry DCM (30 mL). Then, DIPEA (1.5 ml) was added dropwise to this solution over 15 min, and the mixture was stirred for 5 min at RT. Then, $BF_3.OEt_2$ (1.58 ml, 12.8 mmol) was added to the flask, and the resulting solution was stirred for at RT under argon for 4 hr. The organic layer was extracted with DCM, and water. In order to dry the organic layer, sodium sulfate was added and the layer was dried over the sodium sulfate. Pure compound was obtained by column chromatography (silica gel, n-hexane: DCM; 2:3) as eluent. Yield: 45%; **^{1}H NMR** (500 MHz, CHLOROFORM-*d*): 7.96 – 8.01 (m, 5 H), 7.89 (d, *J* = 2.0 Hz, 2 H), 7.45 - 7.48 (m, 5 H), 7.15 - 7.19 (m, 3 H), 7.12 (dd, *J* = 1.4, 7.5 Hz, 3 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 6.89 - 6.95 (m, 6 H), 3.90 - 3.93 (m, 4 H), 1.90 - 1.94 (m, 4 H), 1.05 (t, *J* = 7.4 Hz, 6 H). **^{13}C NMR** (125 MHz, CHLOROFORM-*d*): 158.8, 146.4, 145.5, 144.2, 142.5, 132.0, 130.6, 129.5, 128.9, 128.5, 127.7, 127.4, 127.4, 127.0, 124.6, 124.1, 122.9, 117.0, 115.7, 115.6, 58.5, 49.5, 30.3, 20.2, 18.4, 11.3, 1.0; **HRMS** (ESI) m/z $[M+nH]^+$ calcd for $C_{50}H_{41}BF_2N_5S_2$: 824.2867 found 824.2838.

Synthesis of aza-BODIPY 6b:

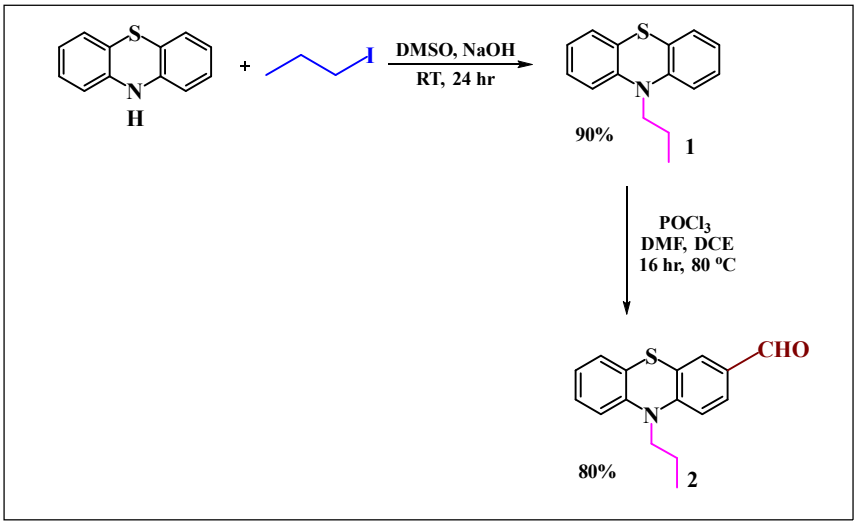
In a 250 mL flat RB, aza-dipyrromethene **5b** (0.500 gm, 0.60 mmol) was dissolved in 100 mL of dry DCM (30 mL). Then, DIPEA (1.5 ml) was added dropwise to this solution over 15 min, and the mixture was stirred for 5 min at RT. Then, $BF_3.OEt_2$ (1.6 mL, 26.7

mmol) was added to the flask, and the resulting solution was stirred for at RT under argon for 4 hr. The organic layer was extracted with DCM, and water. In order to dry the organic layer, sodium sulfate was added and the layer was dried over the sodium sulfate. Pure compound was obtained by column chromatography (silica gel, n-hexane: DCM; 2:3) as eluent. Yield: 40%; **^{1}H NMR** (500 MHz, CHLOROFORM-*d*): 7.98 - 8.03 (m, 4 H), 7.92 (dd, *J* = 2.0, 8.5 Hz, 2 H), 7.81 (d, *J* = 2.0 Hz, 2 H), 7.10 - 7.16 (m, 2 H), 7.04 (dd, *J* = 1.4, 7.6 Hz, 2 H), 6.92 - 6.98 (m, 6 H), 6.86 - 6.91 (m, 2 H), 6.79 - 6.85 (m, 4 H), 3.85 (s, 6 H), 3.81 - 3.84 (m, 4 H), 1.78 - 1.93 (m, 4 H), 1.00 (t, *J* = 7.3 Hz, 6 H). **^{13}C NMR** (125 MHz, CHLOROFORM-*d*) :161.6, 157.4, 146.0, 145.1, 144.2, 141.3, 131.5, 131.4, 131.4, 129.0, 127.5, 127.3, 127.2, 127.0, 124.4, 124.3, 124.1, 116.6, 115.5, 115.4, 55.4, 49.4, 32.0, 30.3, 23.7, 20.1, 11.32; **HRMS** (ESI) m/z $[M+nH]^+$ calcd for $C_{52}H_{44}BF_2N_5O_2S_2$: 884.3079 found 884.3056.

4. RESULTS AND DISCUSSION

4.1 Synthesis

The phenothiazine and propyl iodide dissolve in DMSO was added in 100 ml two-necked RB and then added NaOH at RT for 24 hr. The compound layer was separated using DCM and water. Crude oils obtained by removing the remaining solvent were purified *via* column chromatography to obtain compound **1**.

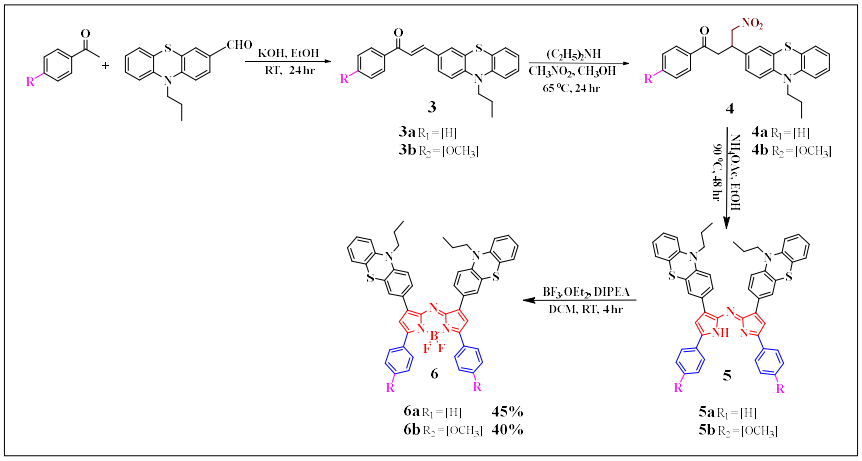


Scheme 4. Synthetic route of compound **1**

The $POCl_3$ was added dropwise to distilled DMF at 0 °C. A solution of compound **1** in DMF was added slowly to the $POCl_3$/DMF complex at 0 °C. The reaction mixture was stirred at 80 °C for 16 hr. After the completion of reaction (monitoring TLC), the reaction mixture was cooled down to RT and poured into an ice–water solution. The crude product was purified *via* column chromatography to obtain compound **2**.

Synthetic scheme 2

To synthesize the donor-acceptor functionalized aza-BODIPY dyes, nitrochalcones are required as the precursors. An aldol condensation of 10-propyl-10*H*-phenothiazine-3-carbaldehyde and 4-methoxy acetophenone in ethanol under basic conditions using potassium hydroxide (KOH) at RT for 24 hr followed by recrystallization generates chalcone. Further, chalcone was subjected to nitration with nitromethane under basic conditions using diethyl amine in methanol solvent at 70 ºC *via* Michael addition produces nitrochalcone (Scheme **5**).



Scheme 5. Synthetic route of aza-BODIPY dyes **6a** and **6b**

Now, further nitrochalcones and ammonium acetate were added to ethanol solvent to reflux for 48 hr at 80 ºC to give aza-dipyrromethene **5**. It was kept at RT for half an hour and after that excess solvent was removed. After that aza-dipyrromethene was dissolved in DCM and treated with DIPEA as a base followed by dropwise addition of boron

trifluoride diethyl etherate ($BF_3.OEt_2$) at RT of for 4 hr to give aza-BODIPY dyes **6a**, and **6b**.

The final compounds were purified *via* column chromatography using hexane and DCM as eluent to obtain the pure product. The aza-BODIPY dyes **6a**, and **6b** were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. These dyes are soluble in various organic solvents such as DCM, chloroform, toluene etc.

4.2. PHOTOPHYSICAL PROPERTIES

The absorption spectra of donor-acceptor functionalized aza-BODIPY dyes **6a** and **6b** were recorded in DCM at room temperature (RT) and are shown in Figure 3. The corresponding data is listed in Table 1.

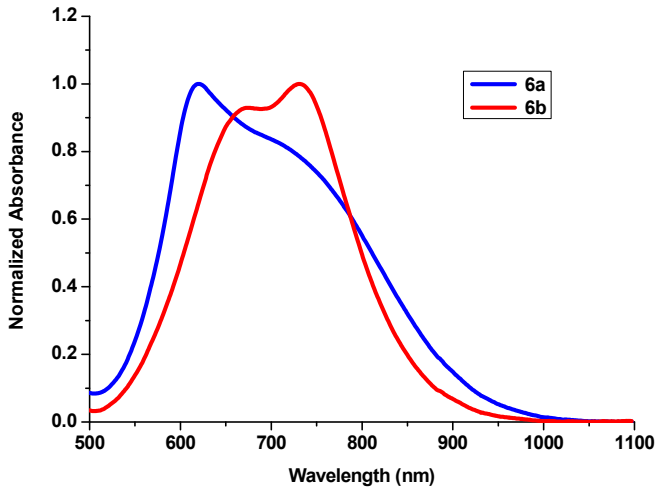


Figure 3. The normalized electronic absorption spectra of donor-acceptor functionalized aza-BODIPY derivatives **6a** and **6b** in DCM (1×10^{-5}M).

The absorption spectra of aza-BODIPY dyes **6a** and **6b** exhibited absorption peaks in the vis-NIR region. The aza-BODIPY **6a** showed dual absorption maximum in NIR region (600-800 nm) while aza-BODIPY **6b** showed dual absorption in NIR region (650-800 nm). Aza-BODIPY **6b** shows red shifted absorption spectra as compared to the aza-BPODIPY **6a** due to the methoxy donor unit. The molar extinction

coefficients for aza-BODIPY dyes **6a** and **6b** are 26,266 and 24,549 M^{-1} cm^{-1} respectively.

Table 1. Photophysical and theoretical properties of aza-BODIPY dyes **6a** and **6b**

Dye	**λ_{abs} (nm)**[a]	**ε ($M^{-1}.cm^{-1}$)**[a]	**E_g**[b] **(eV)**
6a	620	26,266	1.82
6b	732	24,549	1.86

[a]Absorbance measured in DCM at a concentration of 1×10^{-5} M, ε; molar extinction coefficient, [b]Theoretical values of the HOMO-LUMO gap calculated from the DFT calculation.

4.3 DENSITY FUNCTIONAL THEORY

The geometry and electronic structure of the aza-BODIPY dyes **6a** and **6b** were studied with DFT calculations using Gaussian 09W program at the B3LYP/6-31G(d, p) level. Structure optimization was carried out in gas phase to estimate the structure as well as electronic properties. Figure **5** shows the calculated FMO diagram of aza-BODIPY **6a** and **6b**.

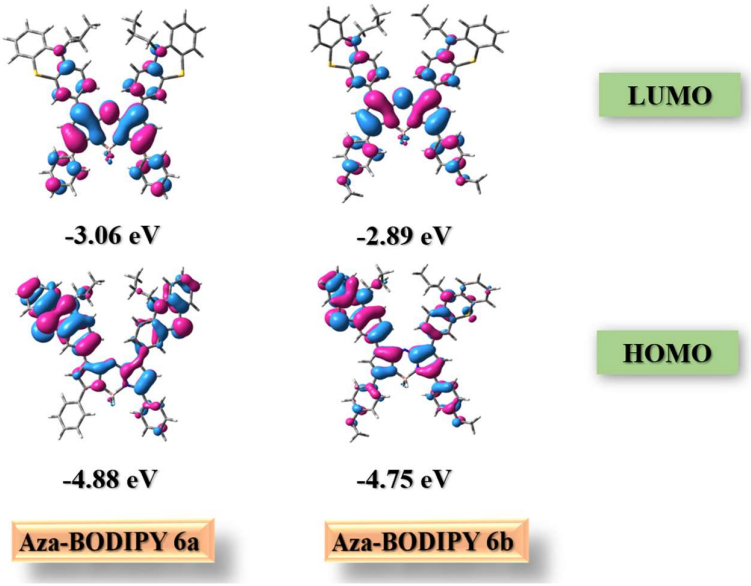


Figure 4. The FMOs of aza-BODIPY dyes **6a** and **6b** at the B3LYP/6-31G(d, p) level.

The optimized structures of aza-BODIPY dyes **6a** and **6b** have distorted geometry. In the aza-BODIPYs **6a** and **6b**, the HOMO orbital electron density is localised on the donor and aza-BODIPY unit, while the LUMO is localised on the aza-BODIPY core. The DFT calculations of aza-BODIPYs **6a** and **6b**, the HOMO energy level values are -4.88 eV, -4.75 eV and the corresponding LUMO energy level values are -

3.06 eV, -2.89 eV respectively. Theoretical calculations reveal that aza-BODIPY **6a** display a band gap of 1.82 eV while, aza-BODIPY **6b** display a band gap of 1.86 eV. Aza-BODIPY **6a** shows a lower band gap as compared to the aza-BODIPY **6b**.

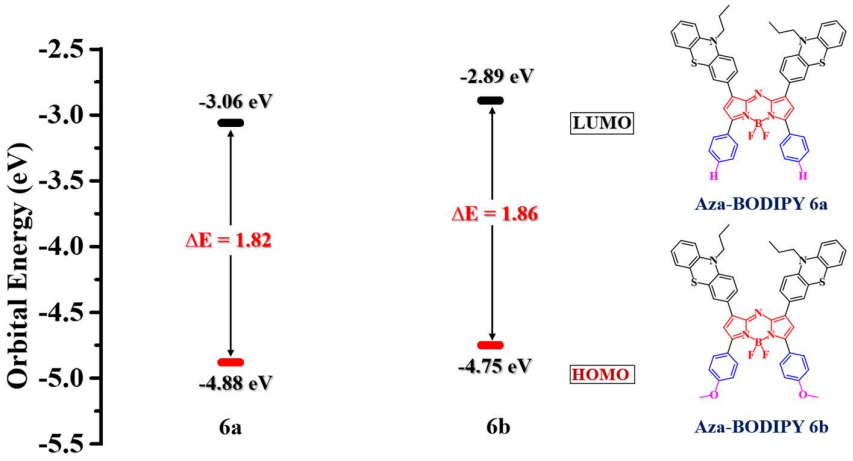


Figure 5. Energy level diagram of aza-BODIPY dyes **6a** and **6b**.

TD–DFT calculations were performed on aza-BODIPY dyes **6a** and **6b** at the B3LYP/6-31G(d, p) level to obtain correlation with absorption studies. The TD-DFT calculations provided the determined electronic transition in aza-BODIPYs **6a** and **6b**, as well as their composition and oscillator strength. The DFT predicted energy level diagram has shown in figure 6. Furthermore, the TD–DFT approach was employed to determine the excitation energies of the aza-BODIPY dyes **6a** and **6b**. According to TD–DFT calculations in the vis-NIR region, aza-BODIPY dye **6a** shows two main electronic transitions in HOMO-2→ LUMO, and HOMO-6→ LUMO whereas aza-BODIPY **6b** shows two main electronics transitions in HOMO-2→ LUMO-7, and HOMO-7 → LUMO transitions.

5. Conclusion

In summary, aza-BODIPY dyes **6a** and **6b** were synthesized by BF_2 complexation reaction using boron trifluoride diethyl etherate ($BF_3.OEt_2$). The effects of the donor and acceptor groups on the photonic and electrochemical properties of the aza-BODIPY dyes **6a** and **6b** were explored. In contrast to photophysical properties, aza-BODIPY dyes **6a** and **6b** shows absorption in UV-visible NIR region. According to DFT study in the aza-BODIPYs **6a**, and **6b** the HOMO is localised on the donor and aza-BODIPY unit, while the LUMO is localised on the aza-BODIPY core. The UV-visible absorption spectra of aza-BODIPY can be further shifted to NIR region by attaching various strong donor substituents such as methoxy, methyl, ether, thiol etc. Thus, the synthesized aza-BODIPY dyes molecule can be used in various optoelectronic applications such as optoelectronic devices, sensing, etc.

6. Supporting Figure

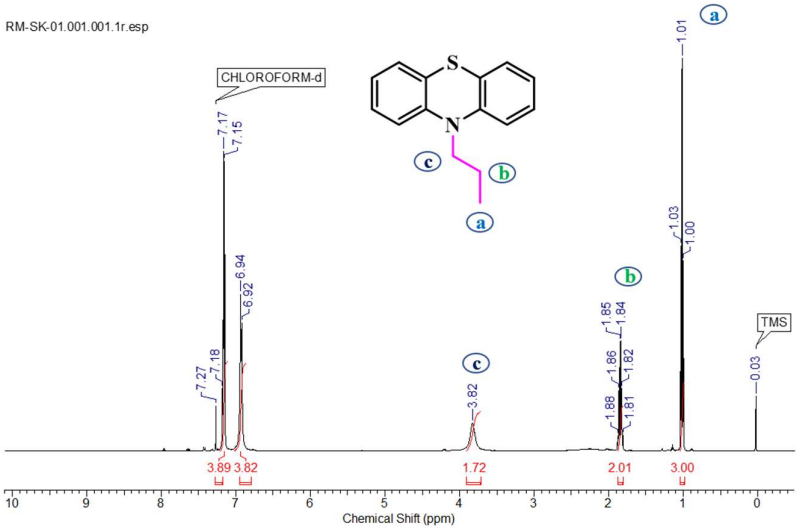


Fig. 6 ^{1}H NMR spectrum of compound **1**

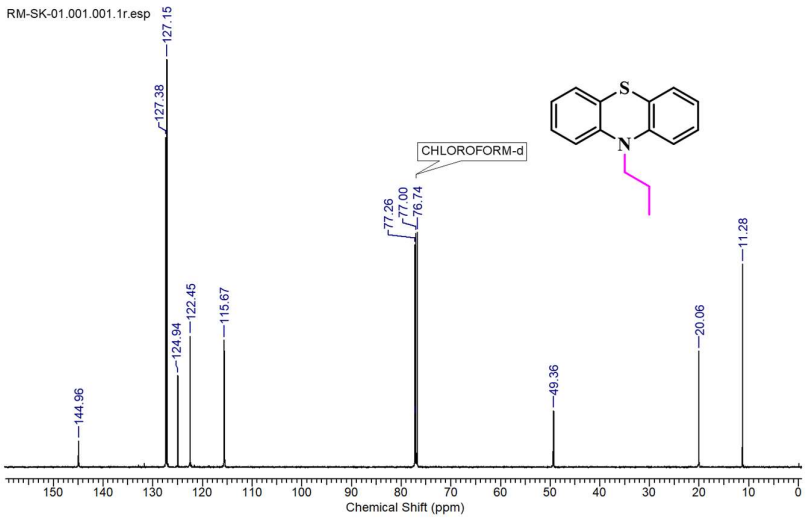


Fig. 7 ^{13}C NMR spectrum of compound **1**

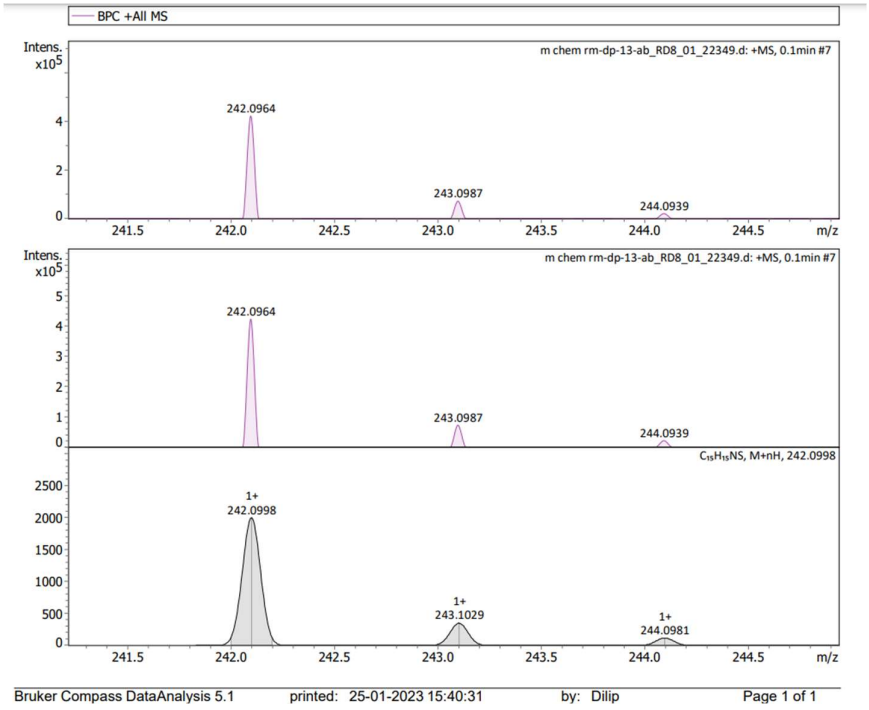


Fig. 8 HRMS of compound **1**

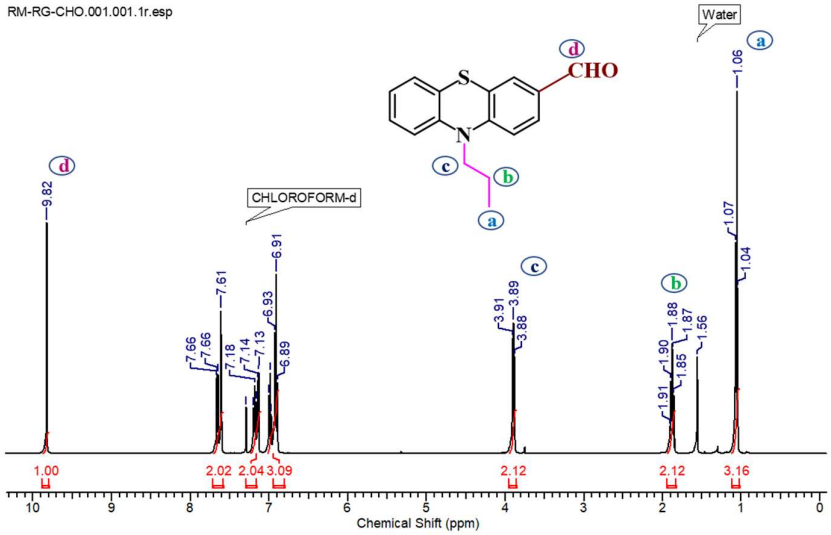


Fig. 9 ^{1}H NMR spectrum of compound **2**

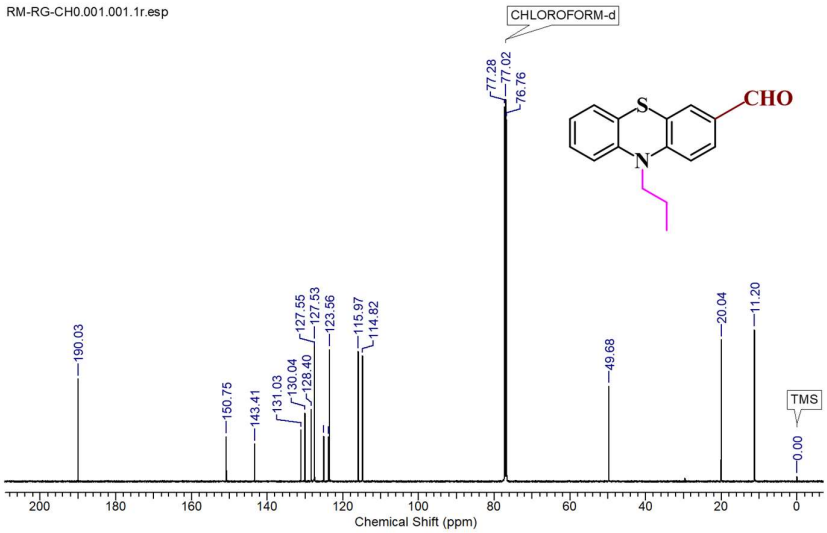


Fig. 10 ^{13}C NMR spectrum of compound **2**

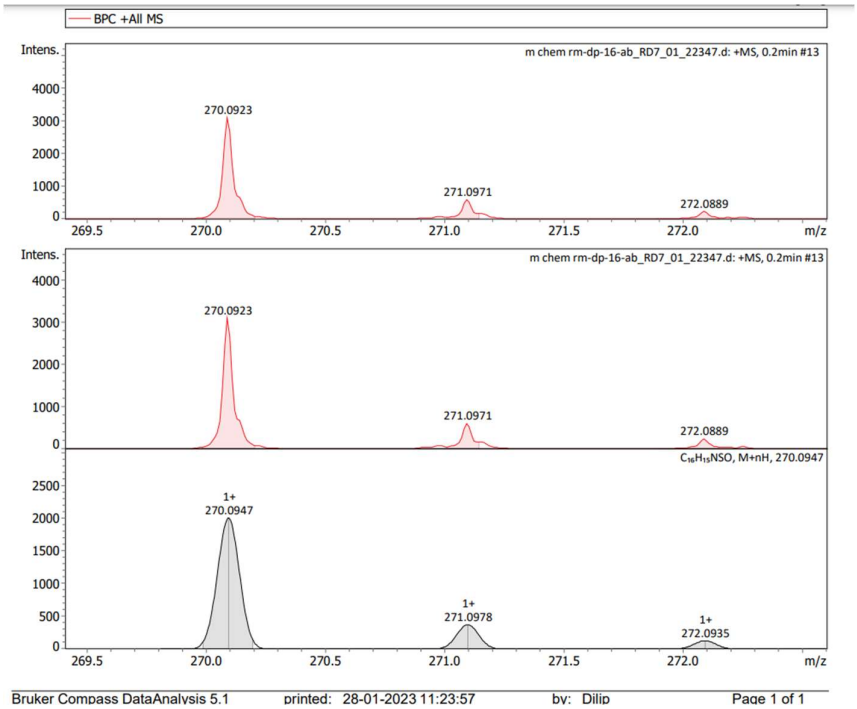


Fig. 11 HRMS of compound **2**

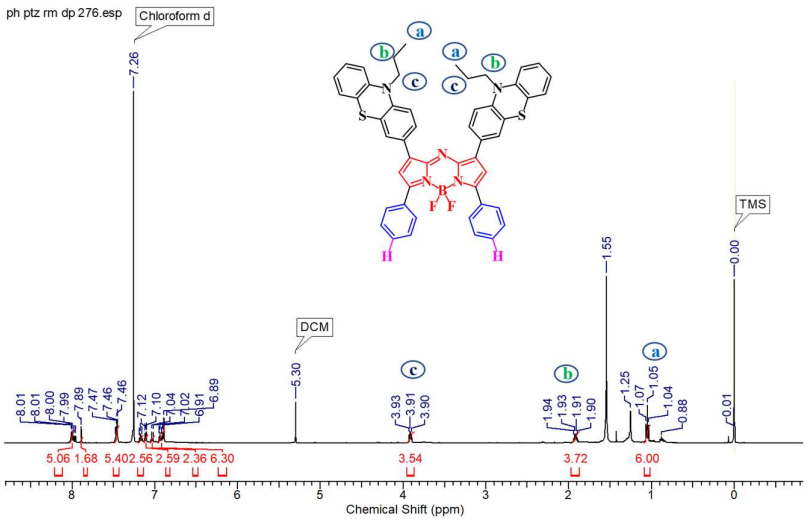


Fig. 12 ^{1}H NMR of aza-BODIPY **6a**

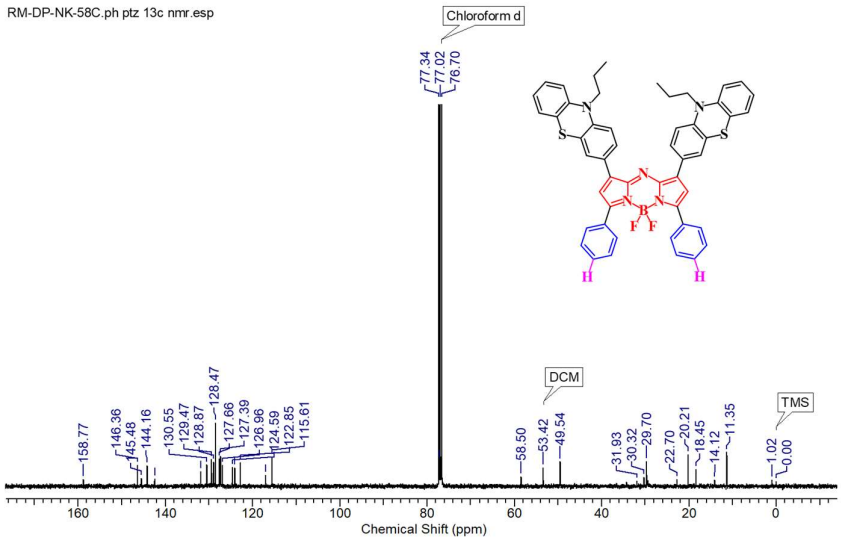


Fig. 13 ^{13}C NMR of aza-BODIPY **6a**

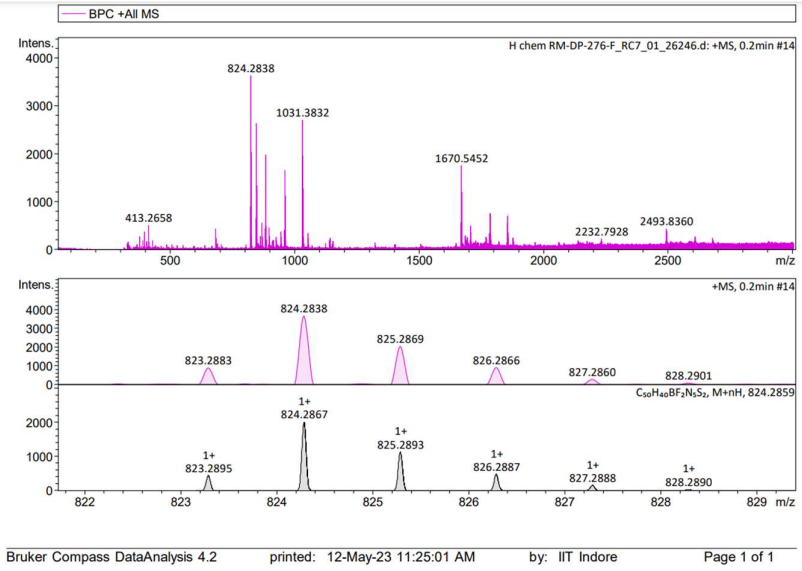


Fig. 14 HRMS of aza-BODIPY **6a**

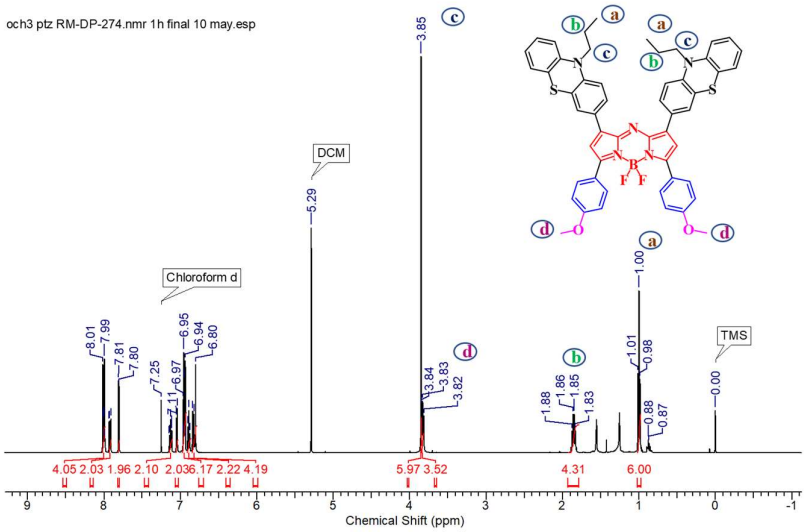


Fig. 15 ^{1}H NMR of aza-BODIPY **6b**

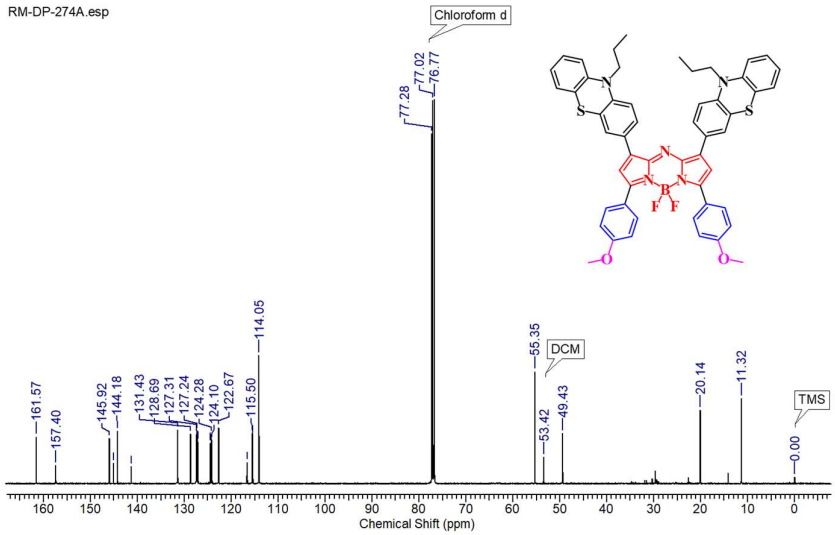


Fig. 16 ^{13}C NMR of aza-BODIPY **6b**

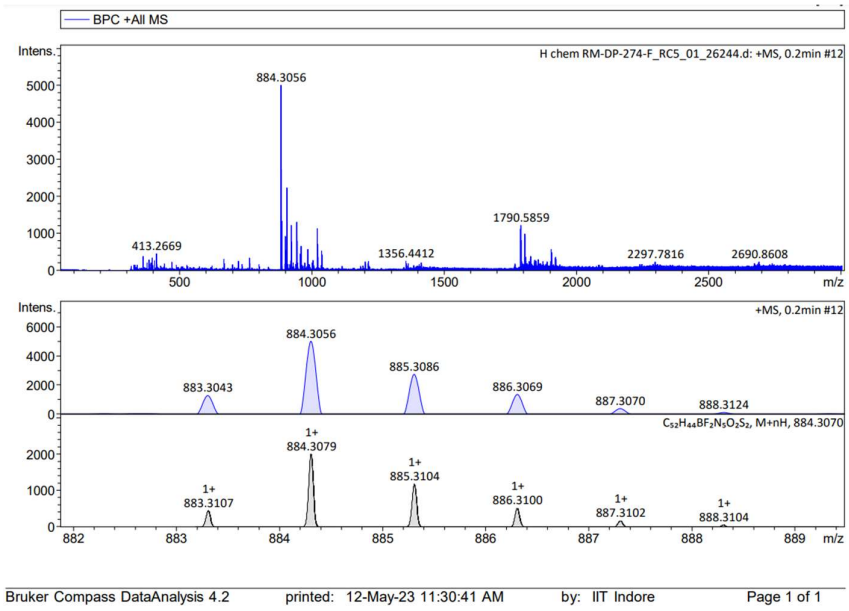


Fig. 17 HRMS of aza-BODIPY **6b**

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