REPUBLIC OF TURKEY
BİNGÖL UNIVERSITY
INSTITUTE OF SCIENCE

SYNTHESIS OF WATER-SOLUBLE 2-FORMYLBODIPY DYES

MASTER THESIS

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CHEMISTRY

SUPERVISOR OF THESIS
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BİNGÖL-2017

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This dissertation was accepted by the following committee on 21.09.2017 with the vote unity.

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I confirm the result above

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Director of the institute

ACKOWLEDGEMENT

This thesis documents the input effectuated at the central laboratory at Bingol University from 2015 to 2017. During that time I had the pleasure of interacting and working with a lot of people from whom I gained invaluable knowledge and experience. Numerous fellows have lent their support in innumerable ways from the point when the master level research was merely a thought bubble in my mind to the final dissertation-writing process. It is a great pleasure to thank all those people who made this brain-wrenching task possible.

We thankfully acknowledge the financial support of TÜBİTAK (3501-Career Development Program (CAREER)/114Z806) and BUBAP unit of Bingöl University (BAP-834-255-2015 and BAP-MMF.2016.00.003).

It is difficult to overstate my gratitude to my esteemed master's mentor, Dr. Murat Işik., who cordially accepted me into his research group and trusted in my intellectual capacity. I could not have explored the nadir or reached the zenith and everything in between in my master's route, without his valuable guidance, influential inspiration and unwavering faith in my abilities. His gamut of knowledge, infectious enthusiasm, certitude, earnest endeavors, superb writing skills and diligent work has always helped me broaden my horizon to the amazing world of chemistry. He struck a perfect balance between giving me the liberty to follow my heart while reining in my imagination sporadically and averting me from taking wrong turns. You are an epitome of a great, dedicated Dr. Işik and I am incredibly proud of having worked under your guidance. Thank you very much for dedicating voluntary hours in proofreading innumerable versions of this thesis and help polish a rudimentary piece into something worthy.

Imad M. MOHAMMED TAHIR

Bingöl 2017

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LIST OF SYMBOLS

BODIPY	: 4, 4-difluoro-4-bora-3a,4a-diaza-s-indacene
^{1}H	: Proton NMR
^{13}C	: Carbon-13 NMR
Δ	: Chemical shift
E	: Extinction coefficient
CDCl3	: Deuterated Chloroform
DCM	: Dichloromethane
DCMU	: 3-(3,4-dichlorophenyl)-1,1-dimethylurea
DDQ	: 2, 3-dichloro-5, 6-dicyano-p-benzoquinone
DNA	: Deoxyribonucleic acid
Et	: Ethyl
EtOAc	: Ethyl acetate
EtOH	: Ethanol
HRMS	: High-resolution mass spectrometer
H_2SO_4	: Sulphric acid
HCl	: Hydrochloric acid
HOMO	: Highest Occupied Molecular Orbital
G	: Gram
Me	: Methyl
mg	: Milligram
MHz	:Mega Hertz
min	: Minutes
MS	: Mass Spectrometry
m/z	: Mass to charge ratio
MeI	: Iodomethane

mmol	: Milimole
Me	: Methanol
N	: Nitrogen
nm	: Nanometer
NMR	: Nuclear Magnetic Resonance
n-BuLi	: *n*-Butyl Lithium
NH_4Cl	: Ammonium chloride
NaOH	: Sodium hydroxide
O	: Oxygen
Ph	: Phenyl
ppm	: Parts per million
RT	: Room Temperature
S	: Sulphur
TFA	: Trifluoroacetic Acid
TLC	: Thin Layer Chromatography
TMS	: Tetramethylsilane
UV	: Ultra violet
UV-Vis	: Ultra violet-visible

LIST OF FIGURES

SUDA ÇÖZÜNEN 2-FORMYLBODIPY BOYALARIN SENTEZİ

ÖZET

BODIPY boyaları, 1968 yılından bu yana, yüksek absorpsiyon katsayısı, floresans kuantum verimi ve iyi fotokimyasal kararlılığın yanısıra, uzun süre kararlı kalmalarını sağlayan pH ve yerleştirildikleri ortamın polaritesinden etkilenmeme kabiliyeti gibi diğer faydalı özellikleri nedeniyle birçok uygulamada floresan bileşikler olarak yaygın şekilde kullanılmaktadırlar. Bununla birlikte, BODIPY çekirdekleri hidrofobiktir; dolayısıyla, biyolojik durumlarda etiketlemeyi engellerler. Flüoresan problar biyolojik koşullarda kullanılacaksa eğer suda çözünürlük oldukça önemlidir. Moleküler durumlarda probların uygulanması da suda sönümleme veya agregasyon nedeniyle engellenir. Bu nedenle, yeni suda çözünen BODIPY boyaları geliştirmek önemlidir. Tüm yeni bileşikler Hidrojen-1 nükleer manyetik rezonans (^{1}H NMR), Karbon-13 nükleer manyetik rezonans (^{13}C NMR), yüksek çözünürlüklü kütle spektrometresi (HRMS) ve infrared (kızılötesi) (IR) analizi ile tanımlandı.

Çalışmanın amacı, BODIPY çekirdeğine kuaterner amonyum grupları sokarak yeni bir suda çözünen BODIPY boya sentezlemektir. Kuarterner amonyum grupları ihtiva eden suda çözünen BODIPY boyası, suda çözünmeyi sağlayan grupların mezo pozisyonuna sokulması ve bunu takiben metil iyodür veya 1,3-propansulton kullanılarak kuarterner amonyum gruplarının oluşturulması ile meydana gelmiştir.

Bu çalışmada kullanılan yolda (yöntemde), hidrofilik grupların eklenmesiyle suda çözünen BODIPY boyalarının başarılı sentezi için yeni ve etkin bir teknik genişletilmiş ve en uygun hale getirilmiştir. Ayrıca, bu yeni metodolojinin yardımı ile, hafif çözünürlük koşulları altında orta ila iyi verimlerde suda çözünen BODIPY boyalarının çeşitli türevleri sentezlenmiştir. Buna ek olarak önerilen boyanın suda çözünür olduğu doğrulanmıştır.

Anahtar Kelimeler: BODIPY boyalar, suda çözünürlük, flüoresans, prob.

SYNTHESIS OF WATER-SOLUBLE 2-FORMYLBODIPY DYES

ABSTRACT

Since 1968, BODIPY dyes have been widely used as fluorescence compounds in many applications due to their high absorption coefficient, fluorescence quantum yield, and good photochemical stability as well as other beneficial properties, such as the ability to be unaffected by the pH and polarity of the environment in which they are placed, which enables them to remain stable for long periods of time. However, BODIPY cores are hydrophobic; thus, they impede labeling in biological situations. Solubility in water is critical if fluorescent probes are to be used in biological conditions. The application of probes in molecular situations is also deterred by quenching or aggregation in water. Thus, it is important to develop new water-soluble BODIPY dyes. All the new compounds were characterized by (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR), high resolution mass spectrometry (HRMS) and infrared (IR) analysis.

The study aimed to synthesize a new water-soluble BODIPY dye by introducing quaternary ammonium groups into the BODIPY core. The water-soluble BODIPY dye containing quaternary ammonium groups was created by introducing the water-solubilizing groups onto the meso position followed by formation of the quaternary ammonium groups using methyl iodide or 1,3-propanesultone.

In the route used in this study, a new and competent technique was extended and optimized for the successful synthesis of water-soluble BODIPY dyes via introducing hydrophilic groups. Moreover, with the aid of this new methodology, various derivatives of water-soluble BODIPY dyes were synthesized in moderate to good yields under mild reactions conditions. In addition, the proposed dyes were shown to be soluble in water.

Keywords: BODIPY dyes, water-solubility, fluorescence, probe.

1. INTRODUCTION

Fluorophores play a significant role inflorescence spectroscopy, and imaging. Fluorophores are crucial components that interact with the light and can assist in the absorption of energy a specific wavelength. The electromagnetic spectrum has a natural limit. A peculiarity of the absorption spectra of organic dyes, as opposed to atomic spectra, is the width of the absorption band, which usually covers several tens of nanometers (Kubitscheck et al. 2017).

This is easy to understand recalling that a typical dye molecule is composed of several tens of atoms, giving rise to different vibrations of the skeleton. These vibrations together with their overtones densely cover the spectrum between a few wavenumbers and 3000 cm1 (Barros et al. 2016). Furthermore, most of these vibrations are coupled to the electronic transitions. That is, after electronic excitation the electron density changes, which is associated with a change in bond length.

The drop of fluorescence radiance can be explained by the increased scattering coefficient of the lesion compared to that of sound enamel. Green fluorescence is shown schematically. These unattractive properties very limit the application of BODIPY probes in sensing and cell imaging applications. With the purpose of rising above these disadvantages, we have developed an exceptionally successful strategy to prepare Water-soluble Ionic BODIPY Dyes (Loudet and Burgess 2007).

There are three or more emission bands shown in fluorescence emission spectra in times of low temperatures, and this is having been attributed to various pigments and complexes: There is long wavelength band that is exhibited by young plants at 725 nm and flashed leaves, at 735. Nm by mature chloroplasts of higher plants and at about 715 Nm by many green algae is attributed to PSI except for a small fraction which is due to

the long wavelength tail of the 695 nm emission band. The 695 nm band originates from the core antenna of PSII and the band at 685.

Nm from the LHC a/b. Hence, the fluorescence transients recorded at these three wavelengths can provide information for the three complexes accordingly (tripartite model). Analysis of the Fluorescence Transient 21 A. The Fluorescence Transient at 695 nm The approaches described in Section III utilizes the fact that, in the presence of DCMU at room temperature, the experimental fluorescence induction curve reveals the kinetics of the pure photochemical the normalized treated samples at ambient temperature.

The absorption and fluorescence spectroscopies were both used to investigate photophysical properties of newly discovered and this was done in solutions of dichloromethane that were diluted. We were also interested in the biological activity of these two different carbazole-linked BODIPYs, particularly concerning the capability to inhibit human colon cancer HT29 cell lines (Schmitt et al. 2013).

Advances in the techniques used in imaging have made it possible to accomplish many tasks and studies in the living cells. For example, it is now possible to study the interactions of proteins in living cells in dynamic and average systems. This is possible because of the labels that can be attached to proteins such as antibodies localized to certain organs in the body of the test subjects for imaging (Loudet and Burgess 2007). However, the availability of probes limits the fluorescence imaging events in cells. Few probes can emit radiation at wavelengths greater than 800nm even though living tissues are transparent to the radiation at such wavelengths (Loudet and Burgess 2007).

BODIPY (4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene) dyes are strong UV absorbing small molecules that also emit characteristic sharp fluorescence peaks with high quantum yields (Niu 2011). BODIPY dyes also boast of other properties such as the ability to be unaffected by the pH and polarity of the environment in which they are placed and remain stable for longer periods (Leen 2010). The structures of these dyes can be modified in several ways to enhance their fluorescence activity, a property that has seen

them find numerous application in labeling DNA and proteins (Loudet and Burgess 2007).

1.1. History and Structure of BODIPY Dyes

BODIPY dyes were discovered in 1968 by Treibs and Kreuzer when they noticed that when 2, 4-dimethylpyrrole was acylated with acetic anhydride and boron trifluoride acting as a Lewis acid catalyst, a highly fluorescent compound was formed instead of the expected acylated pyrroles (Leen 2010). This compound resulted from the condensation of pyrroles using an acid catalyst to dipyrrin. This reaction was then followed by complexation of the compound with a unit of the dye with boron difluoride (Leen 2010). The figures below represent the sequence of the reactions described above and the general structure of BODIPY

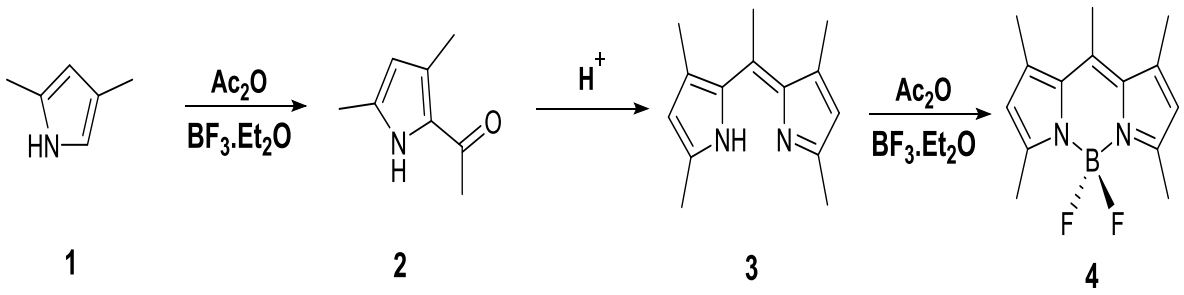


Figure 1.1. Synthesis of boron dipyrrin dye

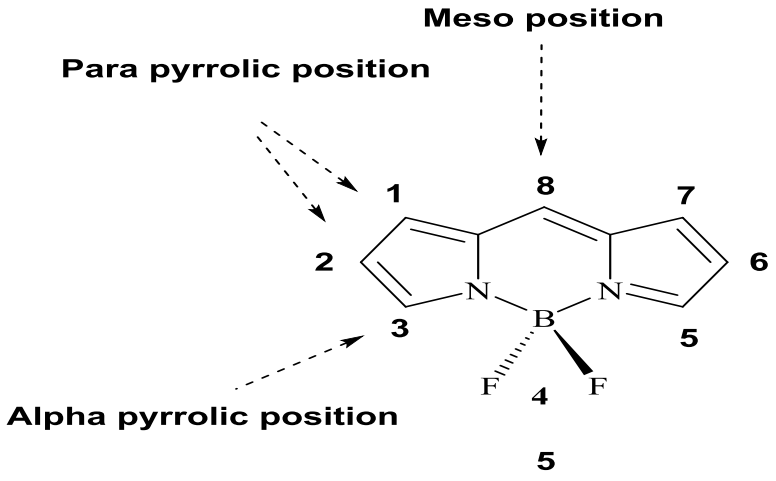


Figure 1.2. General structure of BODIPY

BODIPY dyes absorb light in the visible range, and their profiles of absorbance and emittance have minimal Stokes shift besides being sharp as discussed above. The small Stokes shift presents a challenge on the optimal usage of the dyes in flow cytometry and fluorescence spectroscopy (Zheng et al. 2008). However, this shift can be rectified by covalently attaching an ancillary absorber of light to the BODIPY core to create an energy transfer cassette (Niu 2011). The complexes formed in the dyes are usually stable in physiological ranges of pH and only dissociate in strong acidic and basic environments. The dyes have low toxicity, which in combination with the other properties make them suitable for use as probes in biological systems (Leen 2010). These applications include molecular biolabeling, chemical sensors, cell imaging, and two-photon absorption (Leen 2010).

The post-functionalization at the meso, α, β-pyrrolic or the 4 position on the core of BODIPY makes it possible to extend the emission maximum of the dyes towards the 510-800nm range (Leen 2010). The BODIPY dyes also have high extinction coefficients, often exceeding $\varepsilon > 50.000$, good chemical stability, and photostability (Uppal 2012). Besides the possibility to enhance their absorption and emission spectra, it is also possible to tune their electrochemical signatures by restructuring their pyrrolic core (Hayes 2014). The BODIPY core is, however, hydrophobic and thus poses a setback in labeling in biological situations (Niu 2011). Solubility in water is vital for these fluorescent probes to be used in biological conditions (Niu 2011). The application of the probes in molecular situations is also hindered by quenching or aggressiveness in water (Niu 2011).

1.2. Water-Soluble BODIPY Dyes

BODIPY dyes are synthesized using three methods that use different compounds. One of the strategies begins with the reaction between pyrroles and chlorides of acids (Fan et al. 2014). In an intermediary stage of the reaction, an unstable dipyrromethene hydrochloride salt is formed through condensation and subsequently complexes with boron trifluoride-diethyl etherate in a basic medium (Fan et al. 2014).

The second method involves pyrroles and aldehydes in the initial stage. The pyrrole is subjected to a reaction with the aldehyde and catalyzed by an acid (Niu 2011). To form the intermediate compound, p-chloranil is used to oxidize the mixture and after that, it is complexed with boron trifluoride diethyl etherate (Loudet and Burgess 2007). For the synthesis of unsymmetrical BODIPY dyes, keto pyrroles are used. The latter's intermediate a condensation reaction mediated by a Lewis acid with another pyrrole moiety (Fan et al. 2014). The resultant compound is then complexed with boron trifluoride diethyl etherate is a basic medium. Symmetrical BODIPY dyes can be synthesized by treating pyrrole-2-carbaldehyde with excess $POCl_3$ (Fan et al. 2014).

Hydrophilic groups can also be introduced by a two-step process whereby halogenation is performed at the 2- and 6- positions or at the 2- and 5- positions and then ultimately followed by coupling reaction mediated by palladium (Fan et al. 2014). Fluorine atoms can also be substituted with hydrophilic groups onto the boron atom by using alkynyl Grignard reagents (Fan et al. 2014). The Knoevenagel condensation involving a 3,5-dimethyl-substituted BODIPY and an aldehyde can also be used to introduce hydrophilic groups onto the BODIPY chemical structure (Fan et al. 2014).

The diagram below illustrates some of the methods that can be used to introduce hydrophilic groups onto the BODIPY structure.

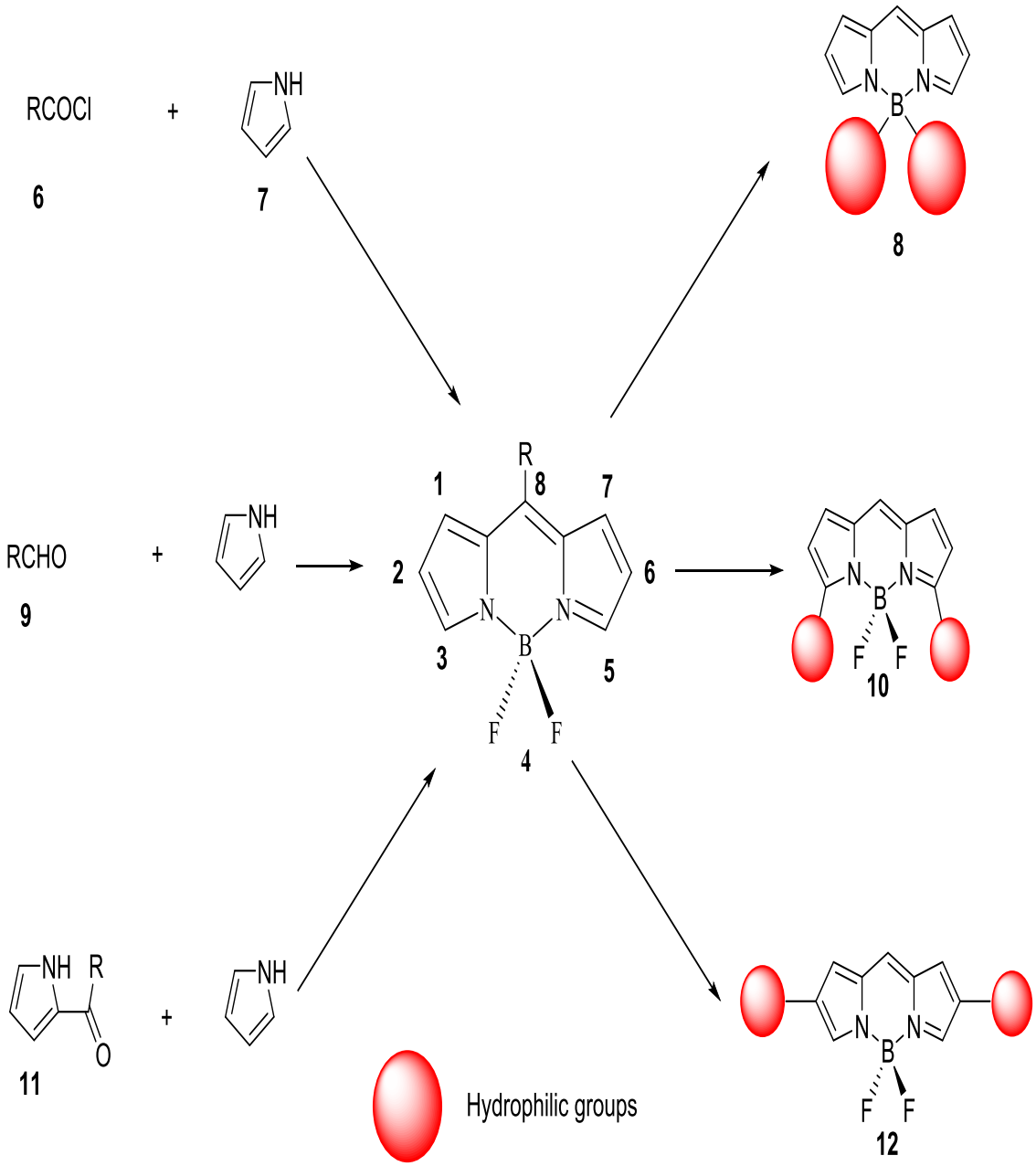


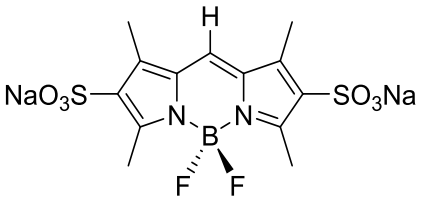
Figure 1.3. Strategies for the synthesis of water-soluble BODIPY dyes. (8) Hydrophilic modifica
Boron atom; 10) Hydrophilic introduction at the 3- and 5- positions; 12) Hydrophilic modificatio
and 6- positions

2. LITERATURE REVIEW

2.1. Water-Soluble BODIPY Dyes

2.1.1. Water-Soluble Dyes Containing Sulfonate Groups

The first BODIPY sulfonate of this kind was developed in 1985 by Worries et al. the BODIPY substituted by 1,3,5,7-tetramethyl was sulfonated with chlorosulfonic acid and then neutralized with sodium hydroxide to give the compound 13 as described in the figure below (Worries et al.1985).



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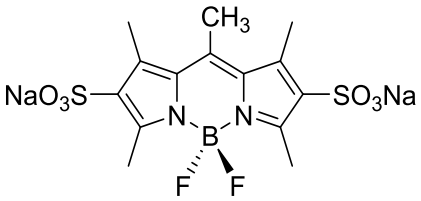

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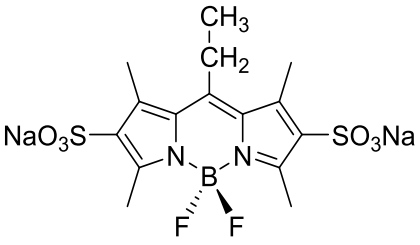

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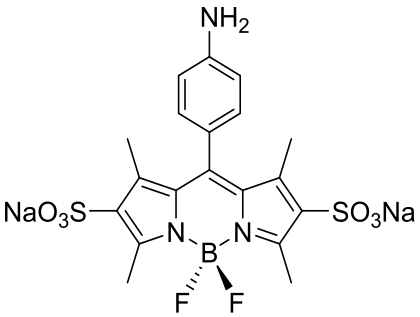

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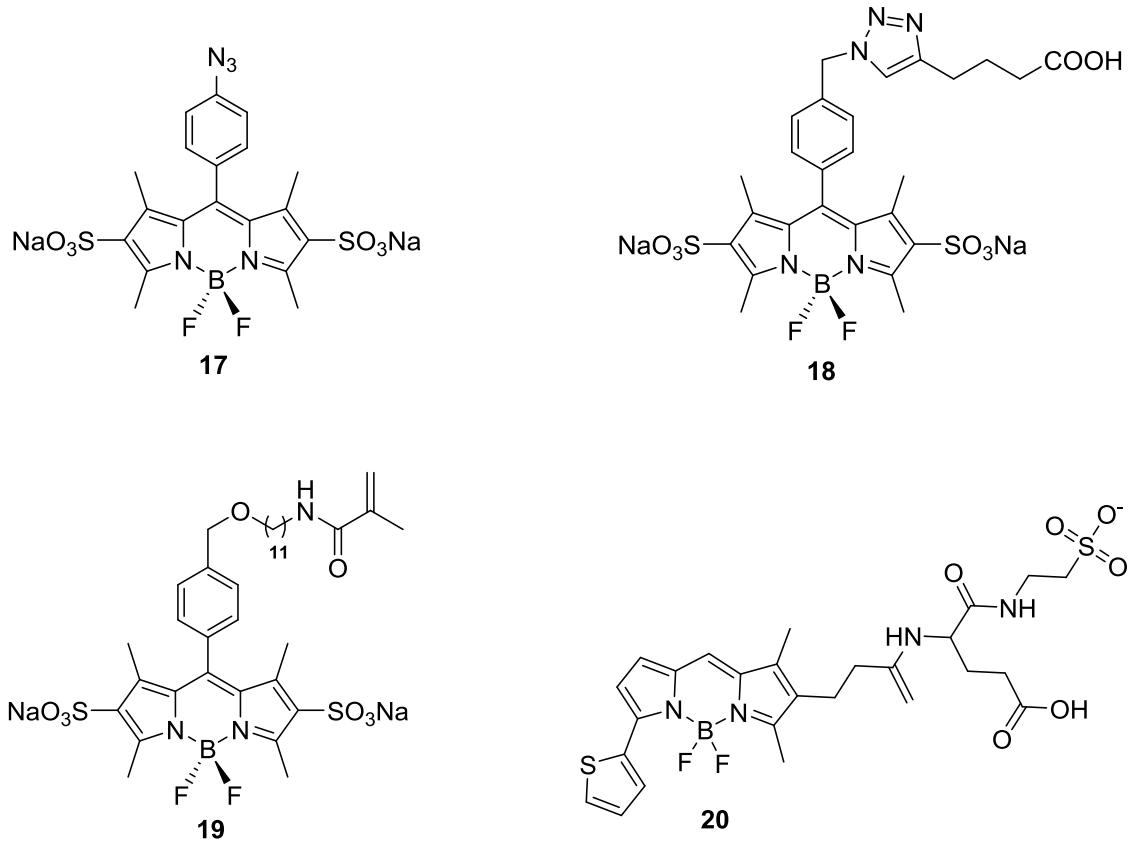


Figure 2.1. Water-soluble structures of BODIPY derivatives (13-20) having sulfonate groups

The dye 13 is reported to have a high fluorescence quantum yield in water (Worries et al. 1985). Its absorption and emission maxima are very similar to those belonging to non-sulfonated precursor having hydrogen atoms at the 2- and 6- positions (Hayes 2014). It is possible to achieve a mono-sulfonated dye by performing the sulfonation reaction using equimolar quantities of chlorosulfonic acid and the precursor (Mirri et al. 2016). The water-soluble dyes 14 and 15 as shown in Figure 2.1 above are examples of other sulfonated BODIPY dyes that have been synthesized (Leen 2010). These dyes bear a methyl or ethyl group at their meso-positions respectively. The downside to using these two dyes is that they have a lower fluorescence quantum yield as compared to dye 13 (Fan et al. 2014).

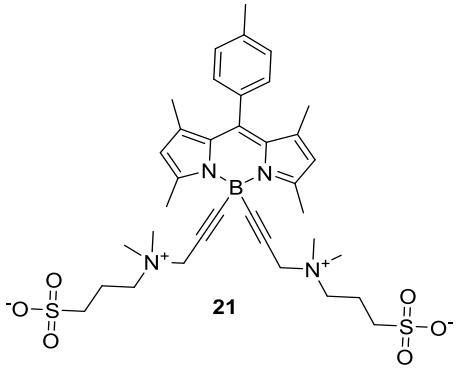
Dye 16 can undergo acylation reactions that result in coupling it with biomolecules. When the same dye is treated to a diazotization reaction, it forms a derivative of the fifth dye (17) in Figure 2.1 above (Li et al. 2008). Dye 19 can be formed from a click reaction

involving azide 5 and hexynoic acid. It is possible to couple the dye with an amino group on a protein or any derivative of DNA. These dyes are also capable of releasing strong fluorescence in water and polar solvents such as methanol. These characteristics make them suitable for biological labeling (Worrieset al. 1985).

2.1.2. Water-Soluble BODIPY Dyes Containing Quaternary Ammonium Groups

A study has also been conducted that reports of water soluble BODIPY dye (21) as shown in Figure 2.2 below. The dye contained quaternary ammonium groups. It was possible to make the dye soluble in water because of the introduction of water-solubilizing groups onto the boron by a sequential addition of fluorine atoms using an alkynyl Grignard reagent followed by the formation of quaternary ammonium groups using 1,3-propanesultone (Fan et al. 2014).

The dye so formed was found to be highly fluorescent in water. When a phosphate buffer saline was used, the dye exhibited two absorption bands at 522 and 567 nm signaling the formation of an aggregate of the dye (Fan et al. 2014). The aggregate disappeared when ethanol was added. Dye 24 as shown in Figure 2.2 below also has quaternary ammonium group and it was synthesized through Sonogashira coupling reaction that constituted of 2,6-diiodo-substituted BODIPY precursor and 3-dimethylamino-1-propyne (Komatsu et al. 2009). The reaction was then followed by another reaction with 1,3-propanesultone (Bura and Ziessel 2011). In yet another experiment conducted by Bura and Ziessel, the synthesis of red-emitting BODIPY dyes that were soluble in water was reported (Bura and Ziessel 2011). These researchers introduced several water-solubilizing groups onto the molecule of the dye in an attempt tosuppress the self-aggregation of the dyes in water as illustrated in Figure 2.2 below (Bura and Ziessel 2011).



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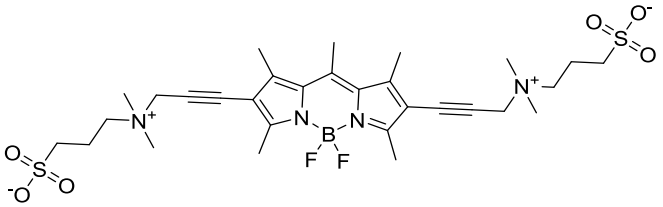

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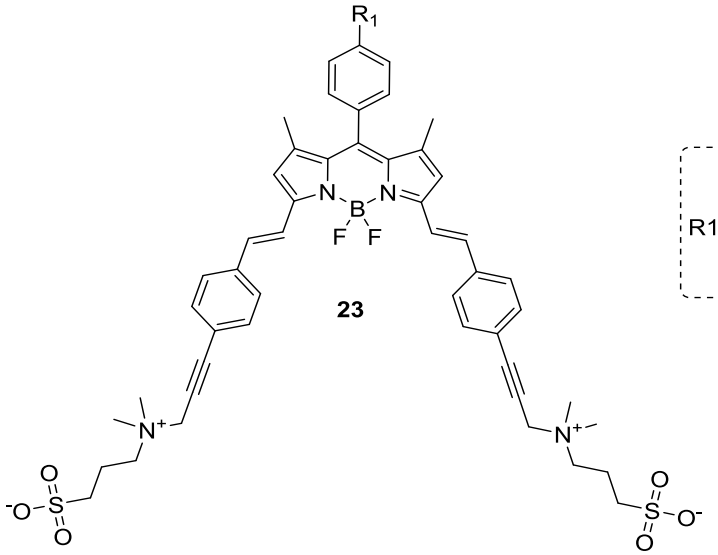

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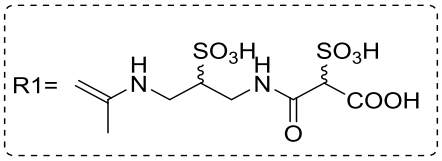

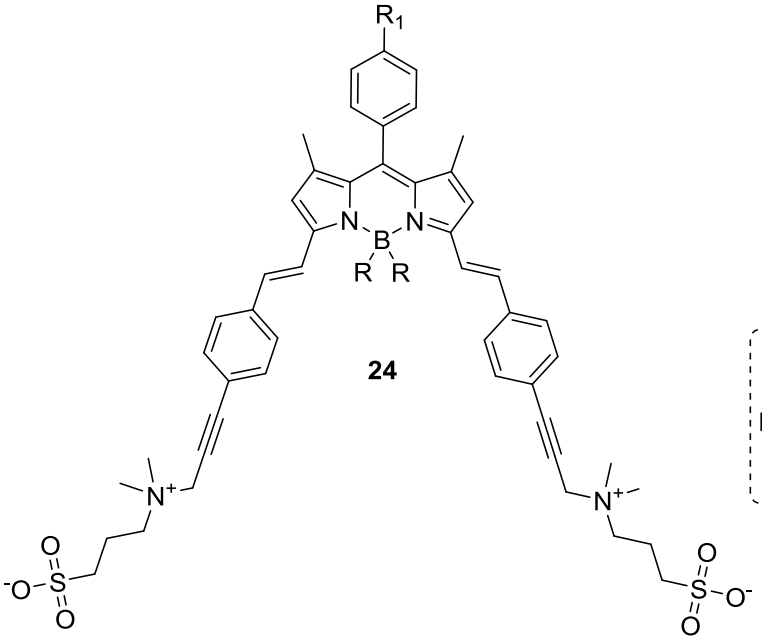

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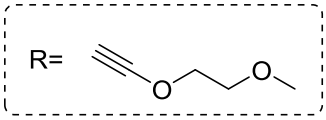
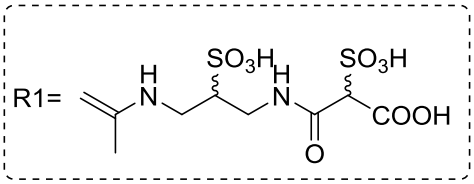




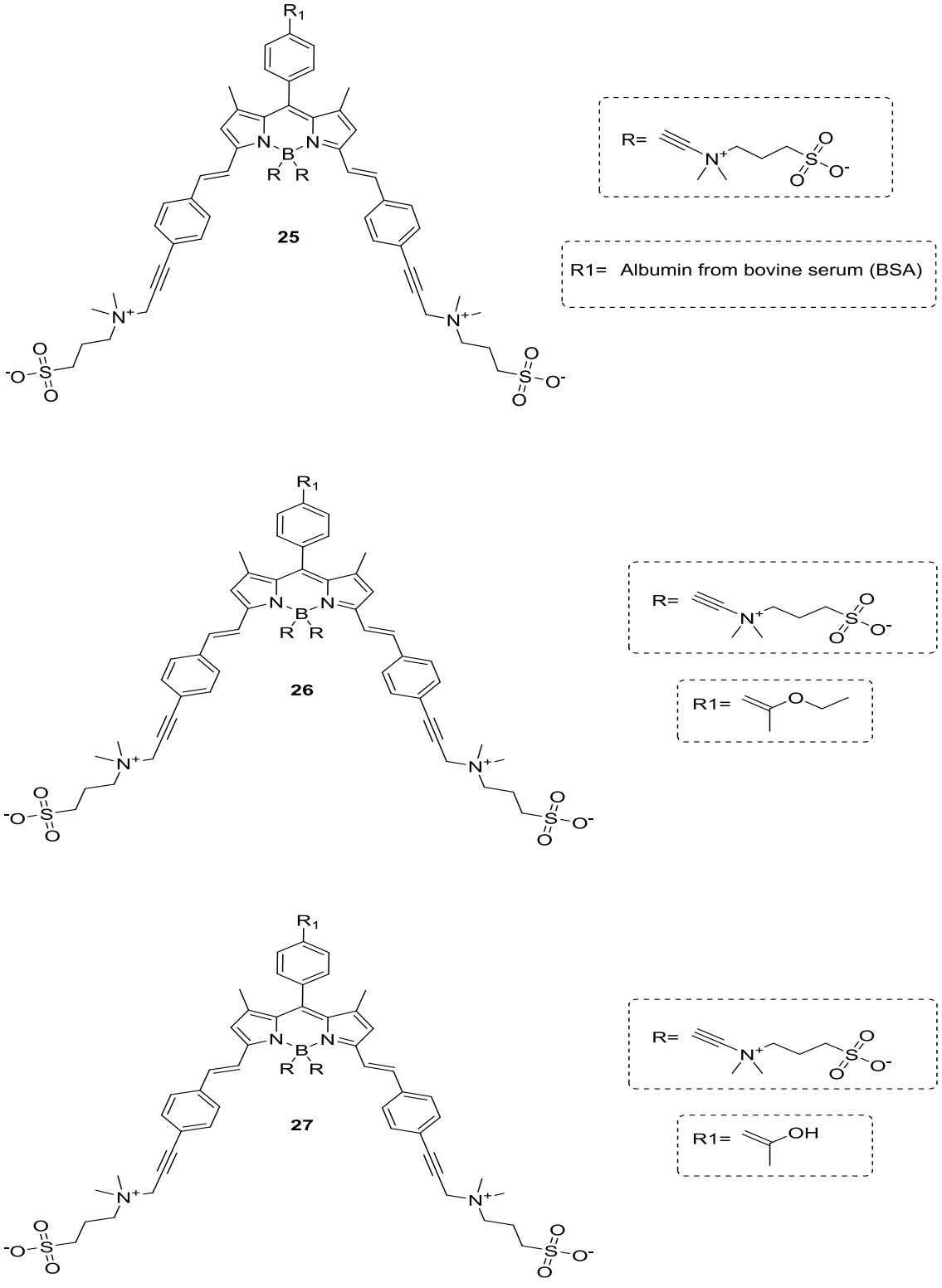
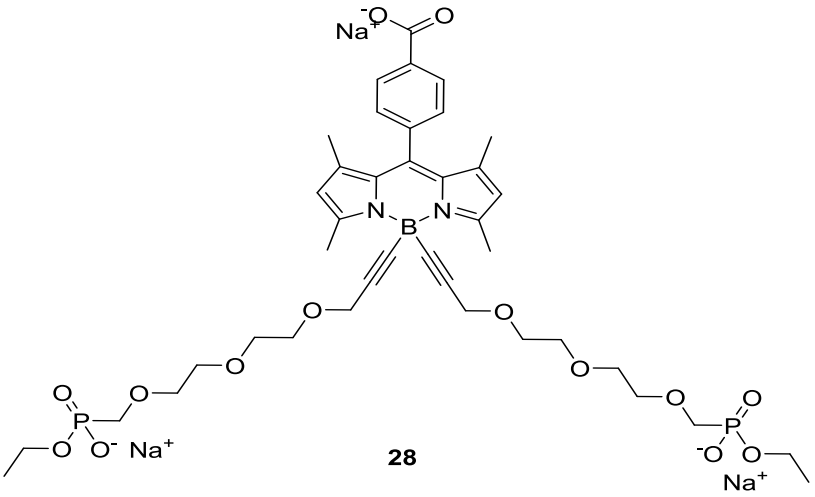


Figure 2.2. Structures of water-soluble BODIPYs (21-27) having quaternary ammonium groups

2.1.3. Water-soluble BODIPY Dyes Containing Phosphonate Groups

The introduction of phosphate groups into the structures of the dye molecules can help to improve the solubility of the BODIPY dyes in water (Bura and Ziessel 2011). Some intermediates have been synthesized before and have been found to contain alcoholic or phenolic hydroxyl groups (Fan et al. 2014). The latter underwent a series of modifications using phosphonate groups to create dyes 28-30 as shown in Figure 2.3 below. The initial oligo ethyleneglycol hydrophilic formed a chain with triisopropylsilyloxy before they were introduced to the boron atom (Bura and Ziessel 2011). The ultimate step involved cleaving of the siloxy groups with 2M HCl (Fan et al. 2014).



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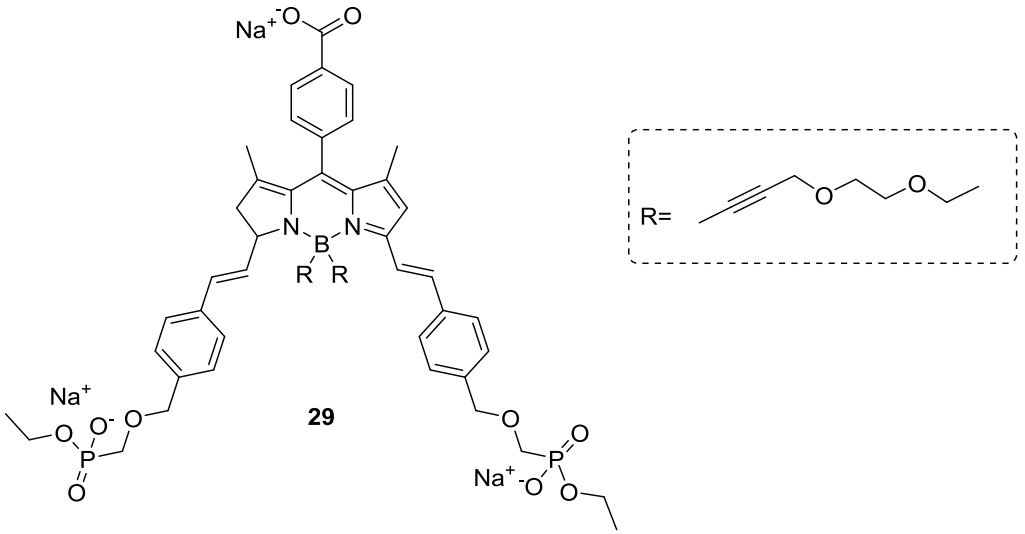

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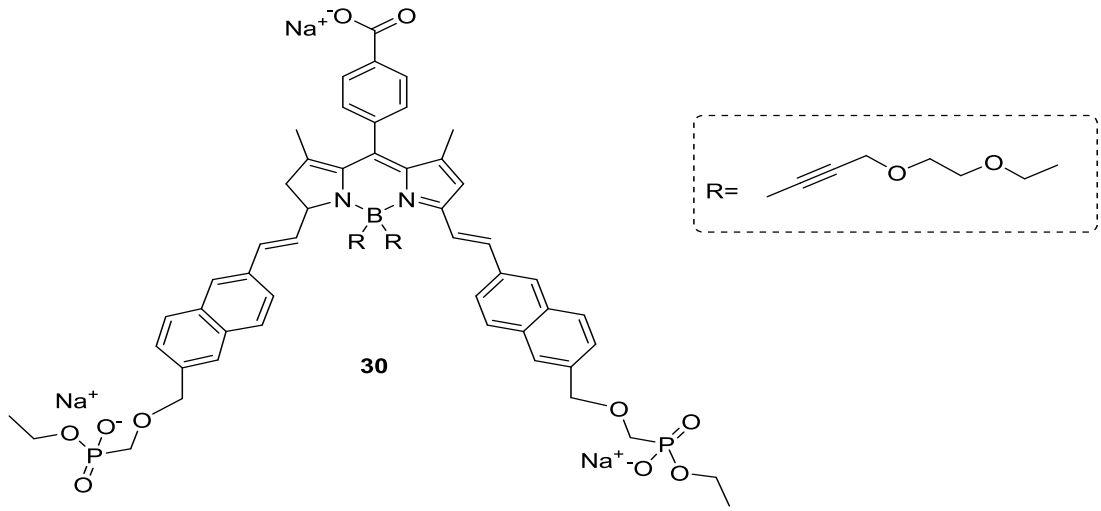


Figure 2.3. Structures of water-soluble BODIPY (28-30) dyes with phosphonate groups

The Knoevenagel condensation reaction was used to form the precursors of dyes 29 and 30 at the 3- and 5-methyl groups and then deprotected with the base. The three dyes have good solubility in water besides being fluorescent. The quantum yields are in the range of 0.23-0.61 and have emission wavelengths ranging between 509 nm and 667 nm (Fan et al. 2014).

2.1.4. Water-soluble BODIPY Dyes Containing Carboxylate Groups

Komatsu et al. first synthesized BODIPY 31 (2, 6-dicarboxylate) and its amide and ester derivatives. The benzyl ester derivative was used to synthesize Dye 32 through catalytic hydrogenation (Fan et al. 2014). It was also noted that the fluorophore could be destroyed when the alkyl ester derivative underwent hydrolysis in a basic medium (Matsui et al. 2011). This particular dye exhibits a green fluorescence and its emission band is liable to a bathochromic shift at 20nm as compared to its ester derivatives. This phenomenon is attributed to lower capacity of the COO^- group to withdraw electrons (Mirri et al. 2016).

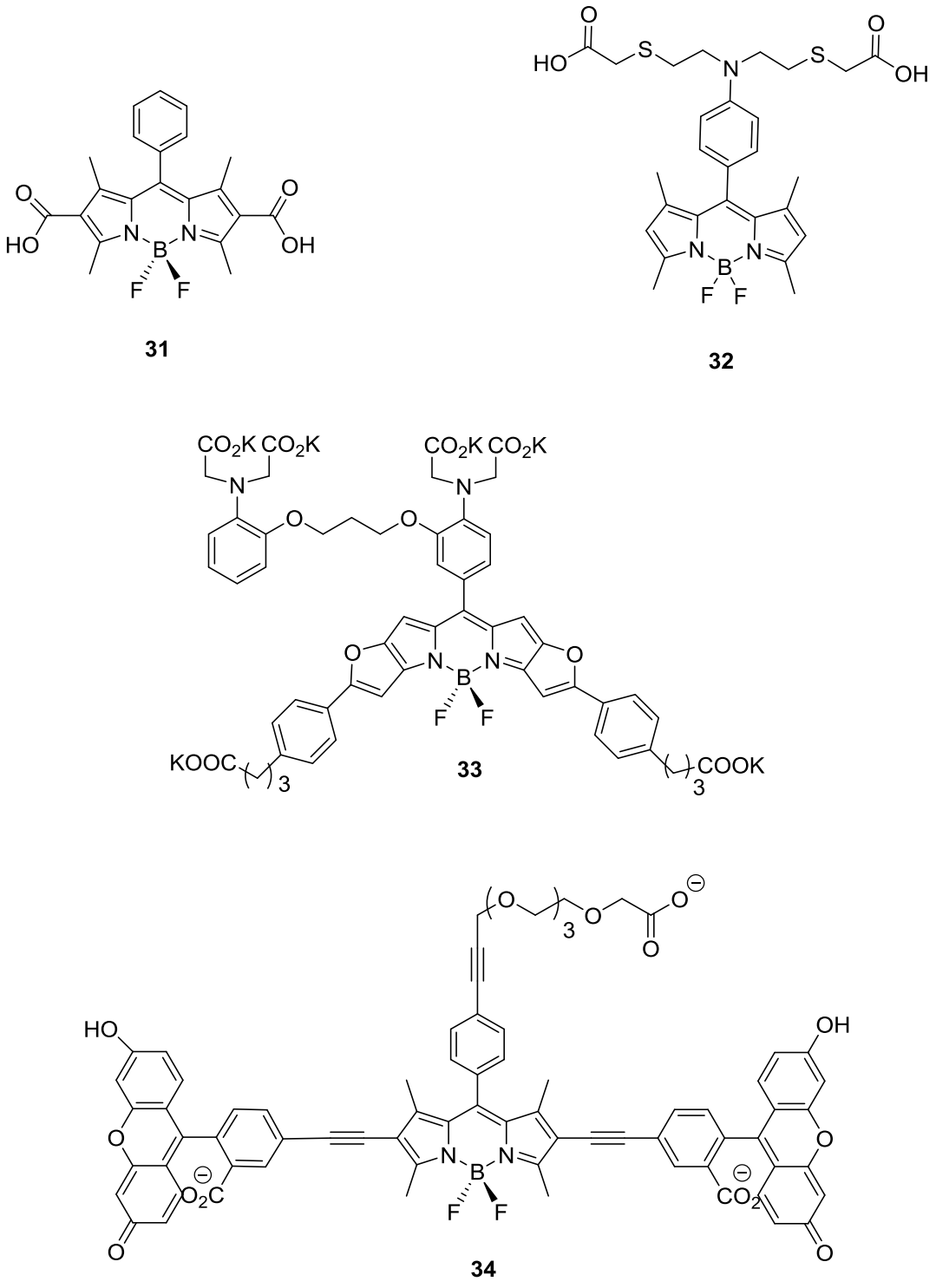


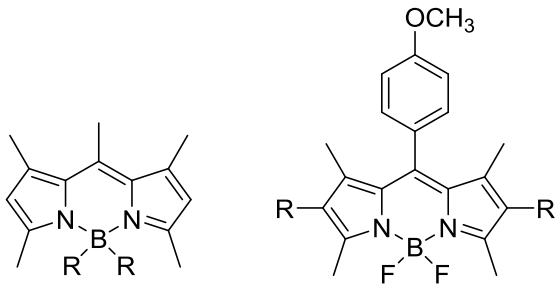
Figure 2.4. Structures of water-soluble BODIPY dyes (31-34) having carboxylate groups

Figure 2.4 also gives the structure of a red fluorescent calcium probe (compound 33) that has a much longer emission maximum and longer wavelength as compared to dye 33 (Matsui et al. 2011). Dye 34, on the other hand, has a BODIPY core and an N/O/S

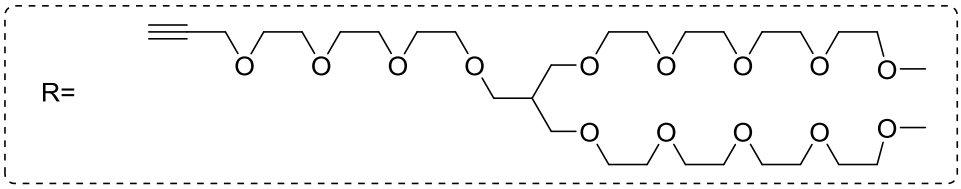
receptor group that can identify ions, a trait that has seen it being used as a chemosensor for Ni^{2+} (Fan et al. 2014). Dye 36 was synthesized by Han et al and it has a conjugated (D-A-D) donor-acceptor-donor structure synthesized through the Sonogashira coupling method by reacting 2,6-diiodi-substituted BODIPY precursor and alkynyl fluorescein building blocks (Komatsu et al. 2009).

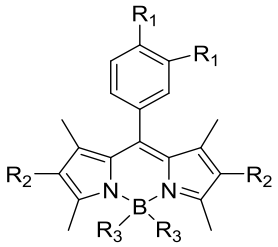
2.1.5. Water-soluble BODIPY Dyes Containing Oligo-Ethyleneglycol Chains

Water-soluble BODIPY dyes containing neutral oligo-ethylene glycol hydrophilic chains have also been synthesized besides those containing charged hydrophilic groups. There are BODIPY dyes (35-44) that have a linear or branched oligo-ethylene glycol chain (Fan et al. 2014). These chains are hydrophilic and contribute to the enhancement of the dyes' solubility in water (Zhu et al. 2011). The chains also reduce the aggregate of the dyes because of their steric hindrance effect (Wu and Burgess 2008). These traits make the dyes strongly fluorescent especially when placed in water. Dyes 35, 36, and 37 have absorption and emission spectra that are not affected by the alkynyl groups that are attached to the boron atoms (Fan et al. 2014). However, this attachment and specifically on the 2- and 6- positions of the BODIPY core resulted in bathochromic shifts in the emission and absorption maxima in dyes 36 and 40 (Niu et al. 2009). Knoevenagel condensations were responsible for the synthesis of dyes 43 and 42 using dye 38 and the corresponding aldehyde (Fan et al. 2014).



35 **36**





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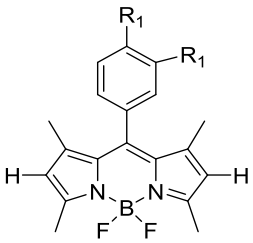

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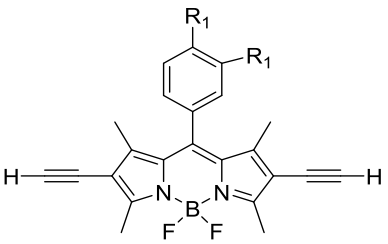

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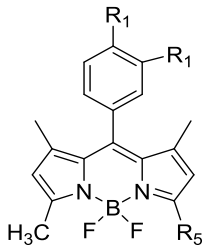

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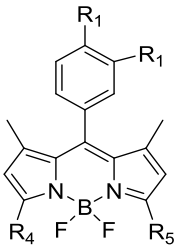

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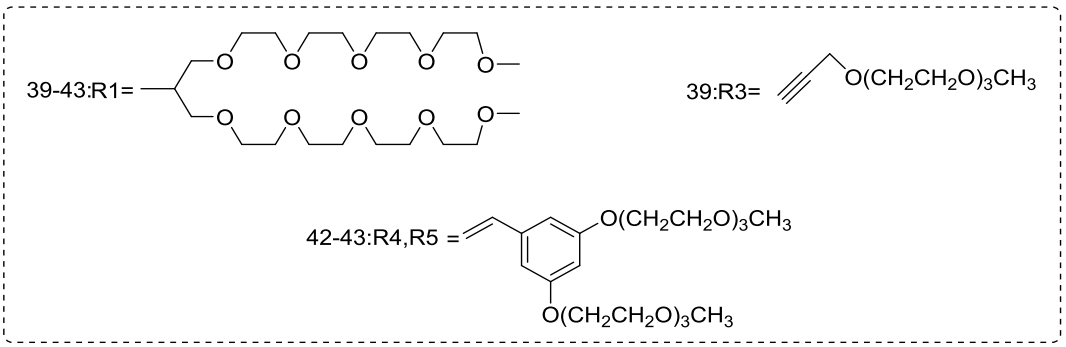

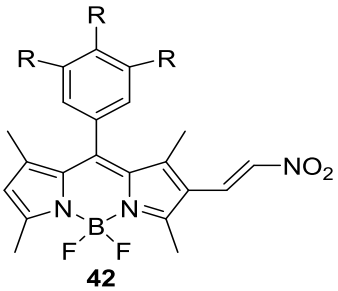

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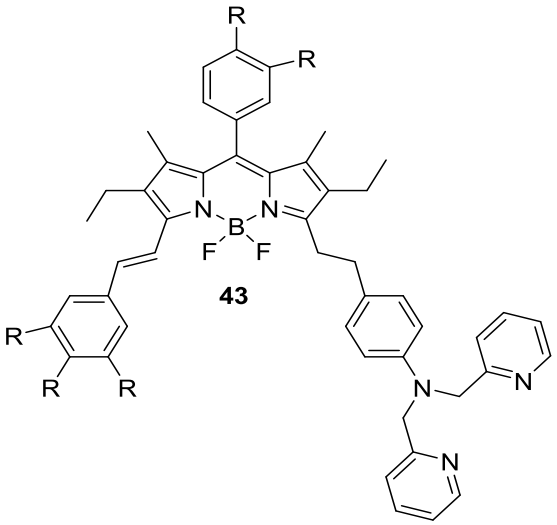


43

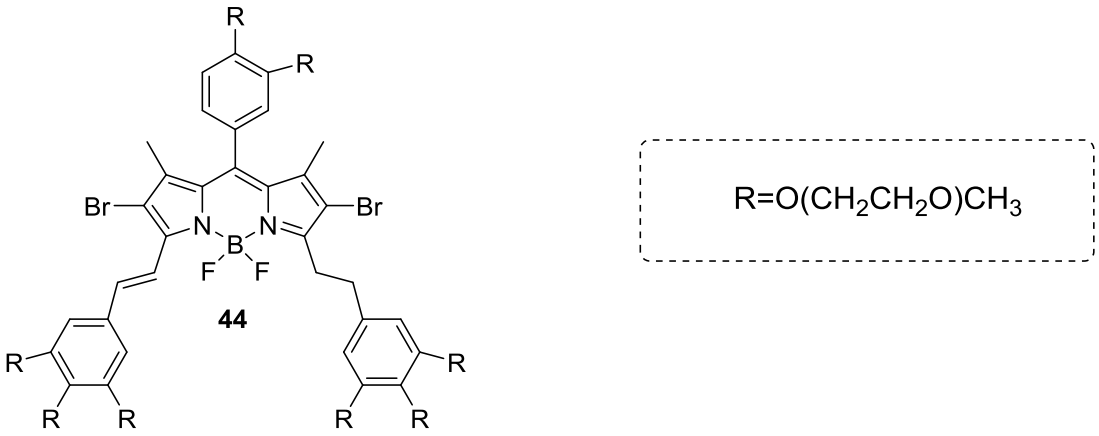


Figure 2.5. Structure of water-soluble BODIPY dyes (35-44) containing oligo-ethyleneglycol hydrophilic groups

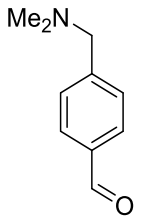
3. MATERIALS AND METHODS

3.1. Materials

The Chemicals and Reagents are atmosphere and moisture-sensitive. The reactions were completed under argon atmosphere in glassware. The glassware was dried in an oven. Ordinary reagents were attained from commercial supply and were utilized without any purification. Dry solvents were also used in the reaction. Thin layer chromatography (TLC) was used for determining the composition of the probes. Column Chromatography was also used and silica gel was used in the glass columns. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400 (working at 400MHz and 100 MHz for ^{1}H NMR and ^{13}C NMR) in chloroform-d with Tetramethylsilane (TMS) as the interior solvent. Moreover, IR spectroscopy was utilized for characterization.

3.2. Methods

3.2.1. 4-((Dimethylamino) methyl)benzaldehyde (48)



48

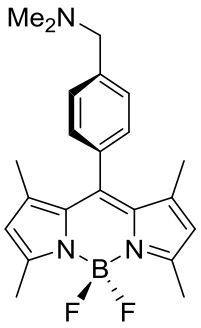
Figure 3.1. Structure of 4-((Dimethylamino) methyl)benzaldehyde

100 mmol of terephthalaldehyde, 500 mM of methylamine hydrochloride, and 400 mmol of NaOH are dissolved in methanol in an ice bath and allowed to reach room temperature. The solution stirred at this temperature for one day, and then was added in three portions with 35 mmol of the $NaBH_3CN$ as reducing agent. The solution was stirred at room temperature for one day. The TLC analysis of solution was showed that the starting material was gone, and the reaction was terminated by the addition of 1 M hydrochloric acid (250 mL). The solution was evaporated and then was extracted by ether (100 mL) three times to remove unreacted staring materials. The acidic aqueous solution was brought to pH 8-9 by adding solid sodium hydroxide and extracted with ether. The organic phase was dried by addition of sodium sulphate, and filtered through filter paper. The ether phase was evaporated under vacuum on a rotary evaporator then purified by flash column chromatography with a 98: 2 triethylamine: ethyl acetate. Eluent system gave the pure product as yellowish orange oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.99 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 3.51 (s, 2H), 2.26 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 146.1, 135.5, 129.8, 129.5, 63.9, 45.4. HRMS (ESI) $C_{10}H_{12}NO$ için hesaplanan, $[M - H]^+$ 162.0919, bulunan 162.0926. IR (neat) 2975, 2943, 2818, 2771, 1695, 1606, 1577, 1455 cm^{-1}.

The synthesis of the 4 - ((Dimethylamino) methyl)benzaldehyde (48) was also carried out with Method B, which was a long, but secures (patented) method because Method A is somewhat low yielding and because our NMR access is difficult. TLC comparison of the obtained products and TLC comparison of the aldehyde-derived BODIPY stains obtained by each method showed that they are the same product.

3.2.2. Synthesis of BODIPY Dyes (49)



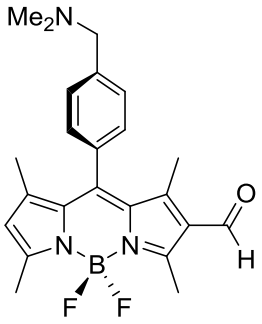
49

Figure 3.2. Structure of BODIPY dyes

A solution of 10 mmol of pure 4 - ((Dimethylamino) methyl)benzaldehyde in 0.01 M dichloromethane (DCM) was prepared and the oxygen was removed from the solution by passing argon through it for half an hour. 2.2 equivalents of 2, 4-dimethylpyrrole (22 mmol) were then added via the aid of a micropipette and finally, a catalytic amount of trifluoroacetic acid (25%) was added with the syringe and the homogeneous solution was left stirring under argon and at room temperature. The formation of the product was detected by TLC chromatography. The appropriate conversion was achieved by stirring for one day with 1.1 equivalents of para-chloranil added to the reaction medium. This was allowed to stir about 1 hour. The solution was left in the ice bath and stirring continued. At this temperature, 5 mL of triethylamine was added dropwise and allowed to stir for 15 minutes. Immediately thereafter, 5 mL of boron trifluoride was again added dropwise and the mixture is allowed to stir at room temperature. The reaction is allowed to stir at room temperature full day. Basic extraction was then carried out with bicarbonate solution. This process was repeated 3 times and all organic phases are combined and the product is dried over dried sodium sulphate. After filtration through filter paper the product concentrated was under vacuum to give final product as a bright green solid via flash column chromatography. Eluant: 95: 5 Dichloromethane: Methanol. Yield: 12%.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.99 (s, 2H), 3.67 (s, 2H), 2.56 (s, 6H), 2.37 (s, 6H), 1.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 143.0, 141.4, 134.5, 130.9, 130.3, 129.5, 128.8, 128.2, 121.3, 63.4, 44.7, 14.6, 14.3. HRMS (ESI) $C_{22}H_{27}BF_2N_3$calcfor, $[M + H]^+$ 382.2266, found 382.2279. IR (neat) 2926, 2857, 2760, 2600, 1723, 1541, 1507, 1462, 1406 cm^{-1}.

3.2.3. Synthesis of 2-formyl BODIPY Dyes (50)



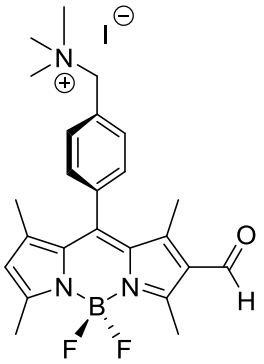
50

Figure 3.3. Structure of 2-formyl BODIPY dye

1 mL of $POCl_3$ was added dropwise to 1 mL of anhydrous DMF at 0°C and allowed to warm to room temperature under argon. It was allowed to mix more strongly for half an hour at room temperature. Then, 0.1 M 1,2-dichloroethane solution and 1 mmol of BODIPY dye 49 was added to mixture, and the mixture was heated to 60 °C, and stirred at that temperature for 3 hours then allowed to cool to room temperature. Then, DCM was added and basic extraction was carried out with carbonate solution. This process was repeated 3 times and all organic phases are combined and the product was dried over sodium sulphate. After filtration through filter paper, it is concentrated under vacuum and purified using flash column chromatography. Eluant: 95: 5 Dichloromethane: Methanol.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.00 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 1H), 3.52 (s, 2H), 2.81 (s, 3H), 2.61 (s, 3H), 2.26 (s, 6H), 1.66 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.9, 161.6, 156.4, 147.2, 143.6, 142.8, 140.4, 134.1, 132.9, 130.2, 128.77, 127.64, 126.26, 123.9, 63.9, 45.2, 15.1, 14.8,

13.0, 11.6. HRMS (ESI) $C_{23}H_{27}BF_2N_3O$ calcfor, $[M + H]^+$ 410.2215, found 410.2210. IR (neat) 1655, 1542, 1517, 1468, 1405 cm^{-1}.

3.2.4. Synthesis MeI Salt of BODIPY (51)



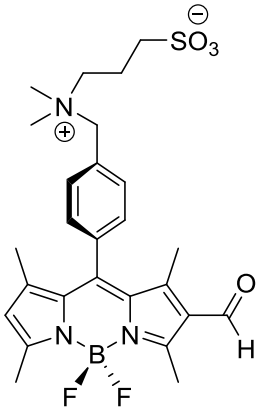
51

Figure 3.4. Structure of MeI salt of BODIPY dyes

To the argon-depleted 1 M ethyl acetate solution of 0.125 mmol 53 of BODIPY dye was added dropwise 10 equivalents of methyl iodide by syringe at 0 °C and the mixture was left to stir at 60 °C for 1 h. When the quartenary salt in the suspension reaches the appropriate conversion was purified by precipitation by centrifugation. At this stage the solution was mixed five times more to get rid of the unreacted starting materials then precipitated again by centrifugation. The product was left to dry after decantation develops a brown solid appearance. Yield: 63%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.78 (dd, J = 8.0, 2.5 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 6.49 (s, 1H), 4.69 (d, J = 8.0 Hz, 2H), 3.08 (s, 9H), 2.72 (s, 3H), 2.57 (s, 3H), 1.61 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.1, 162.6, 155.8, 147.6, 142.90, 142.07, 135.9, 134.3, 133.72, 130.1, 129.24, 129.09, 126.4, 125.2, 67.7, 52.5, 15.26, 15.10, 13.1, 11.8. HRMS (ESI) $C_{24}H_{29}BF_2N_3O$ calcfor, $[M - I]^+$ 424.2372, found 424.2370.IR (neat) 3675, 2971, 2901, 1657, 1543, 1517, 1468, 1405, 1385 cm^{-1}.

3.2.5. Synthesis 1,3-Propanesultone Salt of BODIPY (52)



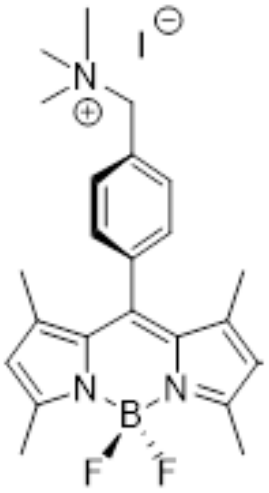
52

Figure 3.5. Structure of 1,3-Propanesultone salt BODIPY dyes

To the argon-depleted 1 M ethyl acetate solution of 0.1125 mmol 53 of BODIPY dye was added dropwise at 0 °C with 10 equivalents of 1, 3-propanesultone by syringe, and the mixture was left to stir for 1 day at 60 °C. when the quaternary salt in the suspension reaches the appropriate conversion level, it is purified by precipitation by centrifugation. At this stage, the solution was mixed five times more to get rid of the unreacted starting materials then precipitated again by centrifugation. The product left to dry after decantation develops a brown solid appearance. Yield: 45%

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.81 (d, J = 7.7 Hz, 2H), 7.60 (d, J = 7.7 Hz, 2H), 6.48 (s, 1H), 4.65 (s, 2H), 3.49 (t, J = 8.4 Hz, 2H), 3.44 – 3.36 (m, 2H), 2.97 (s, 6H), 2.72 (s, 3H), 2.56 (s, 3H), 2.24 – 2.13 (m, 2H), 1.62 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.1, 162.6, 155.8, 147.6, 142.9, 142.2, 135.8, 134.5, 133.7, 129.9, 129.3, 128.9, 126.5, 125.1, 65.9, 63.9, 49.8, 48.2, 19.6, 15.24, 15.11, 13.1, 11.8. HRMS (ESI) $C_{26}H_{33}BF_2N_3O_4S$ calcfor, $[M + H]^+$ 532.2253, found 532.2244.IR (neat) 3675, 3523, 2972, 1657, 1542, 1516, 1469, 1405,1310 cm^{-1}.

3.2.6. (MeI Salt) Compound 53



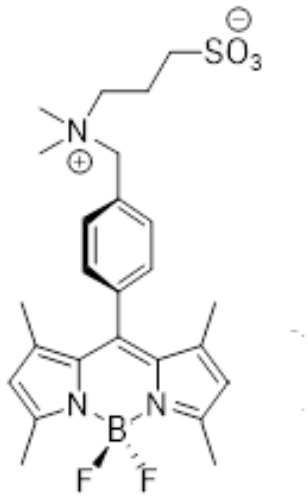
53

Figure 3.6. Structure of MeI salt of BODIPY dyes

To an argon-purged dichloromethane solution (1 M) of 1 mmol BODIPY 49 stiring in an ice-bath was added ten equiv methyl iodide (10 mmol) dropwise. This solution was left to stir at rt for 2 days. The product precipitated out was repeatedly centrifuged and washed several times (5 to 10 times) until the color of the liquor becomes pale orange. The product 53 was obtained as a orange solid which darkens standing at rt. (85%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 7.7 Hz, 2H), 6.18 (s, 2H), 4.63 (s, 2H), 3.03 (s, 9H), 2.43 (s, 6H), 1.32 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6, 143.1, 141.2, 136.5, 134.1, 130.8, 129.6, 129.1, 122.1, 67.7, 52.3, 14.69, 14.55.

3.2.7. (Sultone Salt) Compound 54



54

Figure 3.7. Structure of 1,3-Propanesultone salt BODIPY dyes

To an argon-purged dichloromethane solution (1 M) of 1 mmol BODIPY 49 stiring in an ice-bath was added ten equiv 1,3-propanesulton (10 mmol) dropwise. This solution was left to stir at rt for 2 days. The product precipitated out was repeatedly centrifuged and washed several times (5 to 10 times) until the color of the liquor becomes pale orange. The product 54 was obtained as a orange solid which darkens standing at rt. (56%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 7.4 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 6.17 (s, 2H), 4.61 (s, 2H), 2.93 (s, 6H), 2.43 (s, 7H), 2.13 (t, J = 7.9 Hz, 2H), 1.32 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6, 143.2, 141.2, 136.4, 134.3, 130.9, 129.4, 128.9, 122.0, 60.7, 49.7, 48.1, 29.1, 19.5, 14.67, 14.56.

4. RESULTS AND DISCUSSION

4.1. Syntheses

4,4-Difluoro-3a,4a-diaza-s-indacene, usually referred to as BODIPY dyes, have attracted considerable attention due to their intriguing physicochemical and spectral properties, including high absorption coefficient, fluorescence quantum yield, and good photochemical stability. Because of this reason, improvement of a new and simple method to get different derivatives of BODIPY dyes is high in the order. The main concern of thesis studies its build original methods for synthesis of Water-soluble Ionic BODIPY Dyes.

4.1.1. Synthesis of Water-soluble Ionic BODIPY Dyes

The synthesis of the compounds was carried out in alignment with the recommended synthetic approaches and procedures. Some of the compounds present difficulties in their synthesis and hence require minor technical modifications; however, they remain true to the generally recommended methods. Correspondingly, Proton (^{1}H) and (^{13}C) NMR spectroscopy, high-resolution mass spectroscopy (HRMS) and infrared spectroscopy (IR) analysis were performed for each substance on each step of the synthetic experiment and thus full structural characterization was achieved.

During the experimental process of this study, a new method to synthesize Water-soluble Ionic BODIPY Dyes was developed. The synthetic route planned for the synthesis of the target 2- formyl BODIPY probes (51, 52,53 and 54) as proposed under this project is presented in Figure 4.1 below.

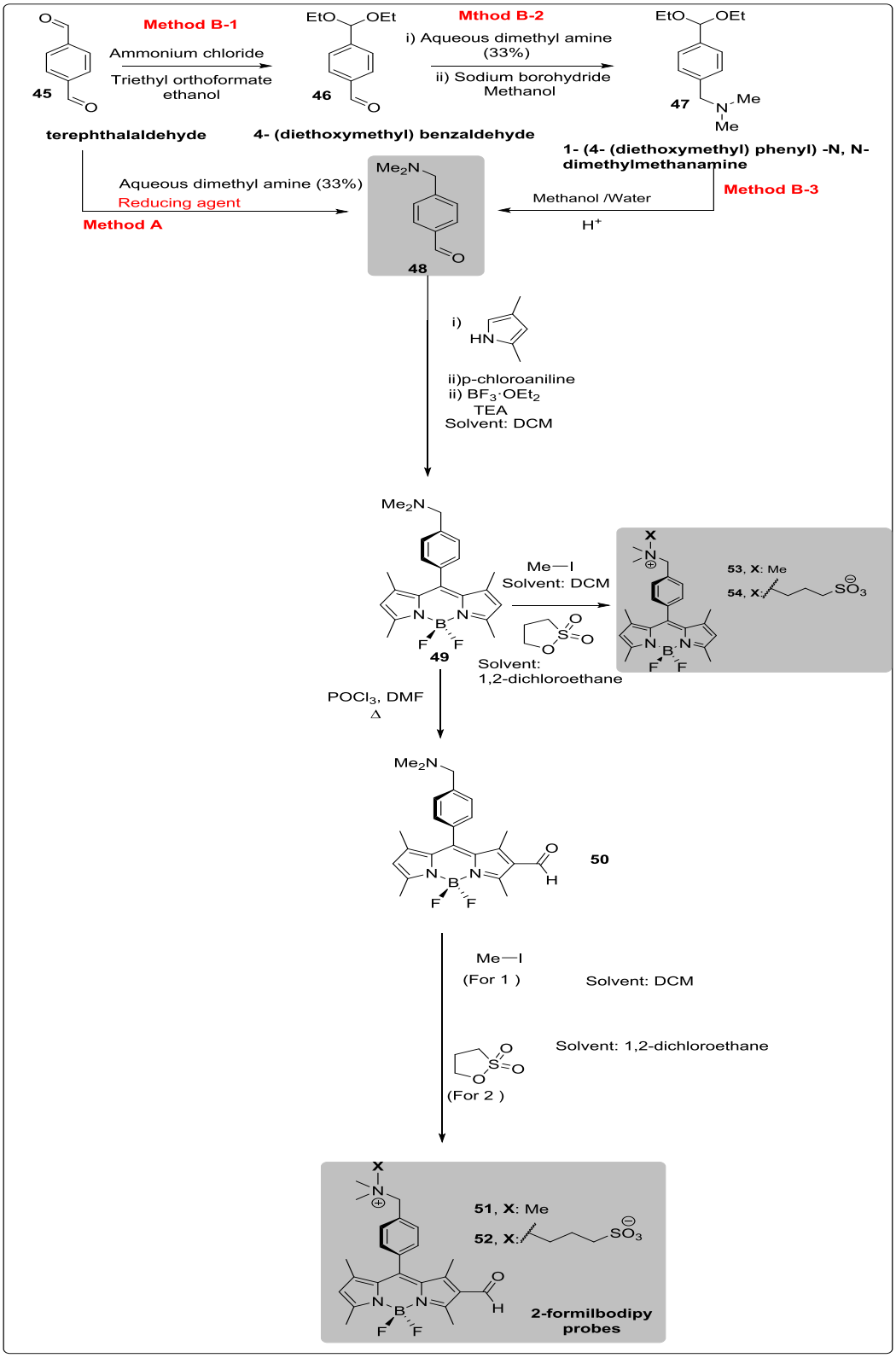


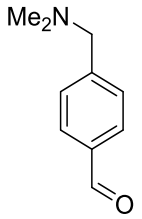
Figure 4.1. Synthesis route of the water-soluble 2-formylBODIPY

4.2. Characterization

4.2.1. ^{1}H and ^{13}C NMR and HRMS Spectroscopy

Nuclear magnetic resonance spectroscopy, more commonly known as NMR, has emerged as the most extraordinary technique that determines the structure of organic compounds. In the current study, for all spectroscopic methods, only one of the totals analysed is normally expected and the entire spectrum is explained. NMR spectroscopy is non-destructive and in the process, excellent data with new instruments is obtained, perhaps in milligrams of the sample, as the sample is required for mass spectroscopy in larger quantities.

4.2.2. ^{1}H and ^{13}C NMR and HRMS Spectroscopy of 4-((Dimethylamino) methyl)benzaldehyde



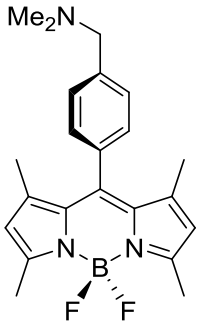
48

Figure 4.2. Characterization of 4-((Dimethylamino) methyl)benzaldehyde

The ^{1}H and ^{13}C NMR spectra of 4-((Dimethylamino) methyl)benzaldehyde were recorded to assess the hydrogen-carbon interactions. The ^{1}H and ^{13}C spectra 4-((Dimethylamino) methyl)benzaldehyde are shown in Figure A.1 and Figure A.2 respectively. The signal appearing at δ = 9.99 ppm in the ^{1}H-NMR spectrum is due to the C=N moiety of the compound. The two doublets present at δ = 7.85 ppm and 7.50 ppm are assigned to protons in the aromatic rings. Protons in the methyl groups are confirmed by the intense signal at 2.26ppm. The presence of carbon in the benzaldehyde group in the ^{13}C-NMR spectrum is confirmed by the intense signal at δ = 191.97 ppm. The intense peak at δ = 45.38 ppm confirms the presence of methyl carbon moiety of 4-((Dimethylamino)

methyl)benzaldehyde. The mass of the compound was confirmed by the high-resolution mass spectrum (Figure B.1). The mass of the molecular ion of 4-((Dimethylamino) methyl)benzaldehyde was confirmed at 162.0926 amu.

4.2.3. ^{1}H and ^{13}C NMR and HRMS Spectroscopy of BODIPY

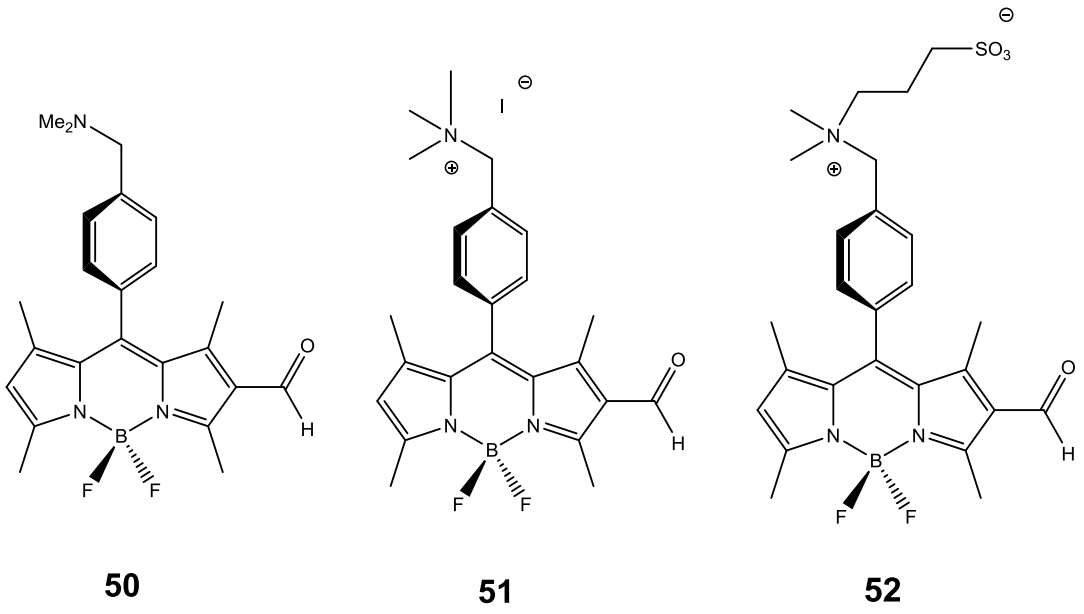


49

Figure 4.3. Characterization of BODIPY dyes

Figure A.3 and Figure A.4 show the ^{1}H and ^{13}C NMR spectra of BODIPY respectively. In the ^{1}H NMR spectrum, two distinct signals corresponding to the 1, 3, 5, 7-tetramethyls (Figure A.3). The intense signal at δ = 1.39 ppm confirmed the presence of the 3, 5-dimethyls while the signal at δ = 2.56 ppm is assigned the 1,7-dimethyls. The tertbutyl groups appear as singlets at δ = 2.37 ppm, whereas the methoxy groups could be found at δ = 3.67 ppm. The signal peaks between δ = 6.40 and δ = 7.53 ppm correspond to the phenyl hydrogen. In the ^{13}C-NMR spectrum, the presence of carbon is confirmed by the intense signal at δ = 155.49 ppm. Mass spectroscopy confirmed the molecular mass of BODIPY at 383.98604amu (Figure B.2).

4.2.4. ^{1}H and ^{13}C NMR and HRMS Spectroscopy of BODIPY Derivatives



50 **51** **52**

Figure 4.4. Characterization of BODIPY derivatives

BODIPY and its derivatives (2-FormylBodipy (50), MeI salt of BODIPY (51), and 1,3-Propanesultone salt of BODIPY(52)) were characterized by ^{1}H-NMR, ^{13}C-NMR, and HRMS. Comparison with ^{1}H-NMR data shows the same profiles of signal peaks for indolylstyryl- and p-methoxyphenylstyryl- aromatic protons, and the peaks for the remaining 1,5,7- and 1,7-methyl groups. Formylation effect of BODIPY is observed as two duplets between δ = 11.50 ppm and δ = 15.10 ppm (Figure A.5). The same effect is seen in Mel salt of BODIPY and 1,3-Propanesultone salt of BODIPY (Figure 3.4 and Figure 3.5 respectively). High-resolution mass spectrometry (HRMS) of 2-formyl BODIPY shows an increase in molecular mass to 411.22463 amu due to an additional oxygen molecule, carbon, and hydrogen (Figure B.3). There is also a significant change in molecular weight as Mel salt, and 1,3-Propanesultone salt are formed (Figure B.4 and Figure B.5 respectively). The ^{1}H-NMR spectra of BODIPY and its compounds shows notable differences (presence of chemical shifts) in the corresponding peaks of the β-hydrogens.

4.3. IR Spectroscopy

IR spectroscopy is often used for full characterization of compounds and what makes this possible is the presence of the infrared MPCs spectra. These are collected at a wide range of about 430 to about 4050 cm−1. The spectra of IR are majorly obtained mainly for GNPs. On doing a similarity check, with both levels of energy it was discovered that there was no major transformation structurally and in terms of the compositional. The spectra of IR indicated absorptions some visible vibrations. From C4 onwards are the side chains and are shown by the asymmetric CH2stretches.

4.3.1 IR Spectrum of 4-((Dimethylamino)methyl)benzaldehyde

The IR spectrum 4-((Dimethylamino)methyl)benzaldehyde is shown in Figure C.1. As can be seen, the spectrum presents strongly overlapped bands between 2500 cm^{-1} and 3000 cm^{-1}. The most distinctive band is around 2771 cm-1, attributed to the N-H stretching. 4-((Dimethylamino) methyl)benzaldehyde showed a strong band at 1695 cm^{-1} (stretching vibration of the carbonyl group). In addition, three overlapping bands were observed at 855, 815 and 782 cm-1, which are attributable to bending vibrations out-of-plane of the aromatic ring.

4.3.2 IR Spectrum for BODIPY and Its Derivatives

IR spectra for BODIPY (49) and its derivatives (50, 51, 52) show complex overlapping bands. Figure C.2 indicates strong bands between 2500 cm^{-1} and 3500 cm^{-1} (attributed to the stretching vibration of C=C-H) as well as a strong band at 1723 cm^{-1}(carbonyl group). Mel salt of BODIPY (Figure C.4) showed strong bands at 1655 cm^{-1} (stretching vibration C=C groups), 2901 and 2972 cm-1 (alkyl groups stretching). Figure C.3 and Figure C.4 exhibit similar spectral profiles.

5. CONCLUSION

The BODIPY water-soluble dyes present application potentials in cell imaging, labelling of bio-macromolecules, chemosensors, pH indicators, and photodynamic therapy. It is a general feeling that for them to be effective in application their optical properties and biocompatibility need to be enhanced and optimized by robust molecular design. Particularly, the developments of BODIPY dyes that are fluorescent in the NIR range are of specific interest because of the numerous advantages that the NIR region of the electromagnetic spectrum has to offer. In addition, we believe that our target BODIPY dye can also offer future application potential in the determination of the sulphide in live-cell as well as water.

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APPENDICES

APPENDIX A

^{1}H NMR and ^{13}C NMR Spectra of Compounds

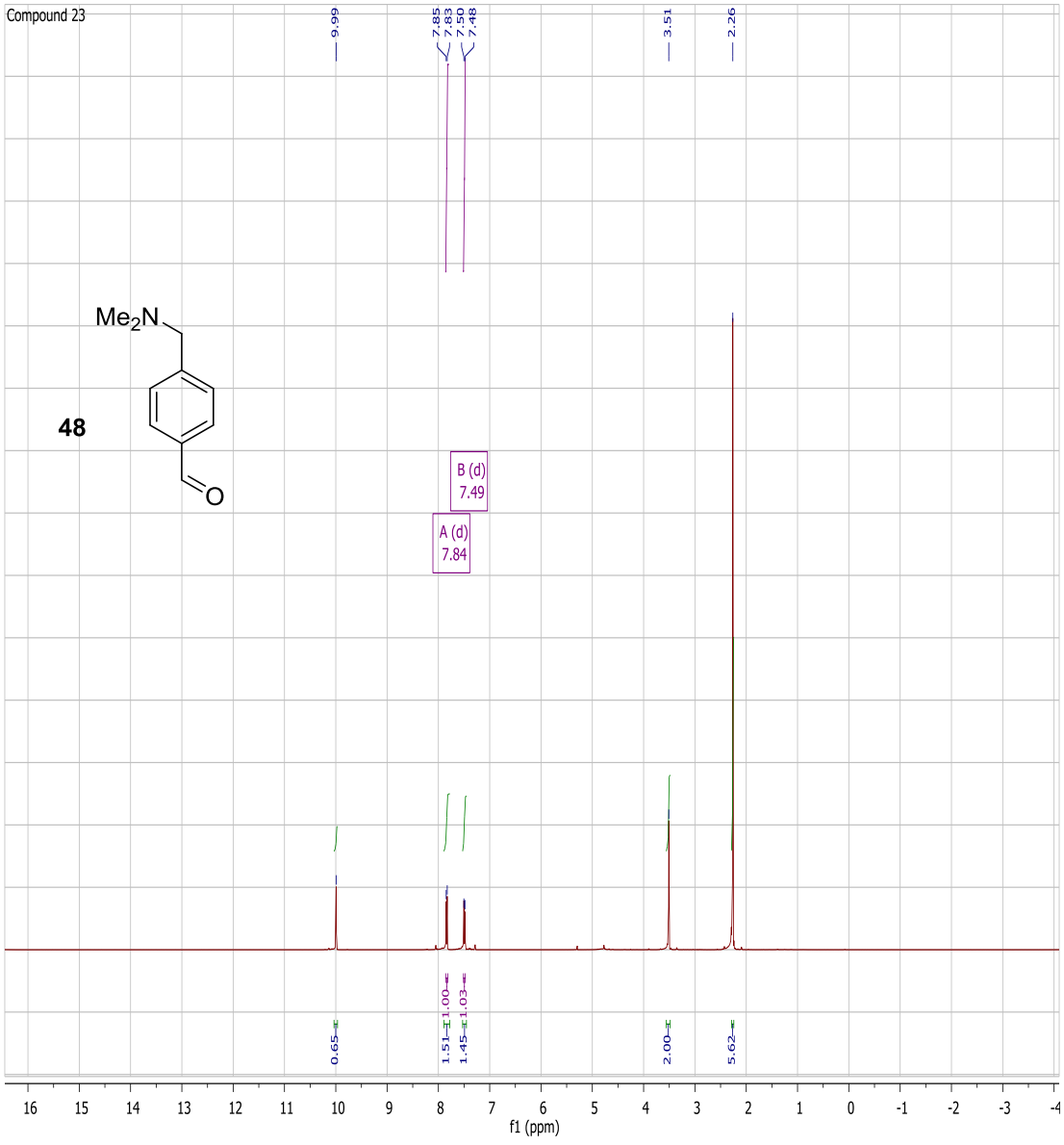

Figure A.1. ^{1}H NMR 4-((Dimethylamino)methyl)benzaldehyde

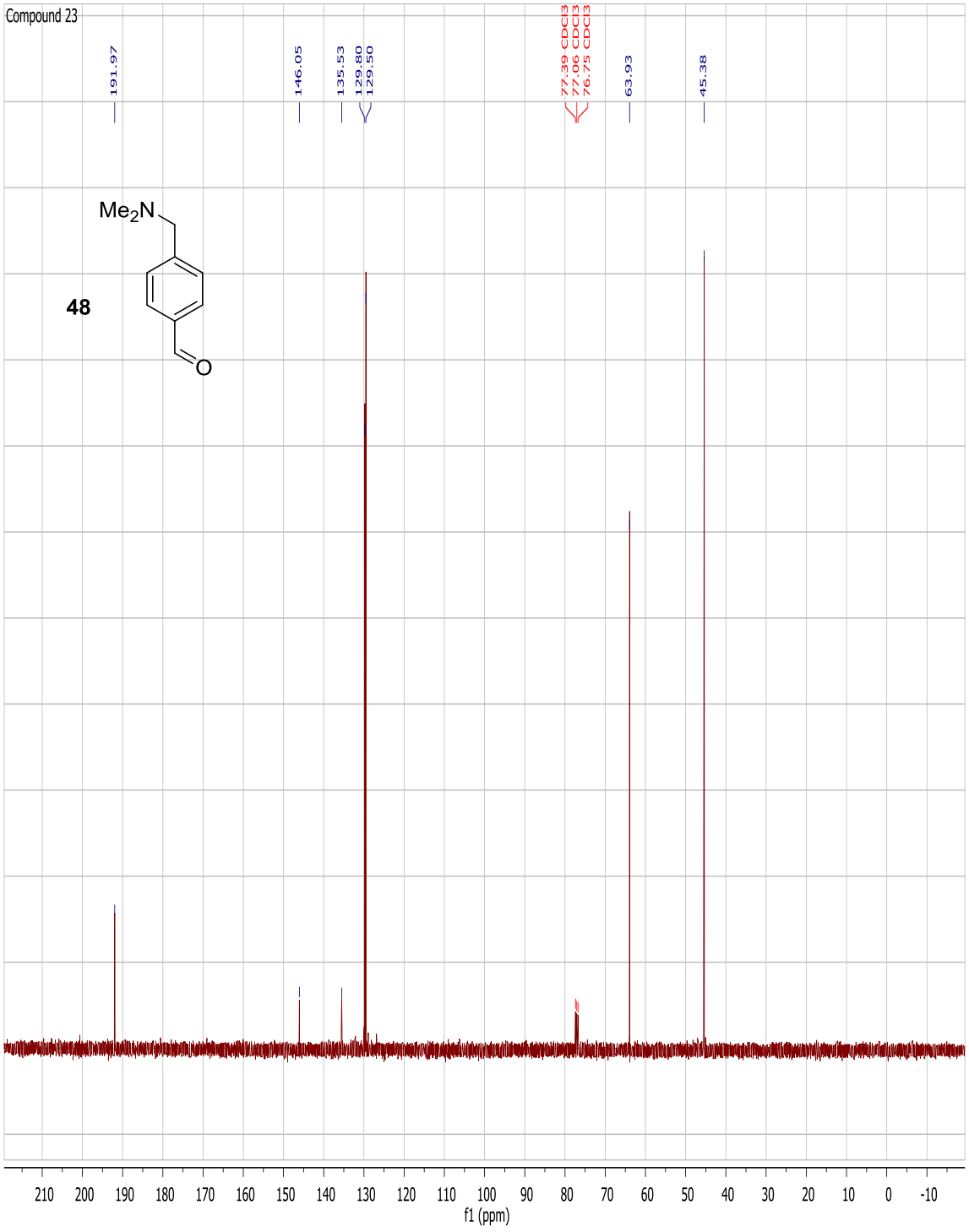

Figure A.2. ^{13}C NMR of 4-((Dimethylamino)methyl)benzaldehyde

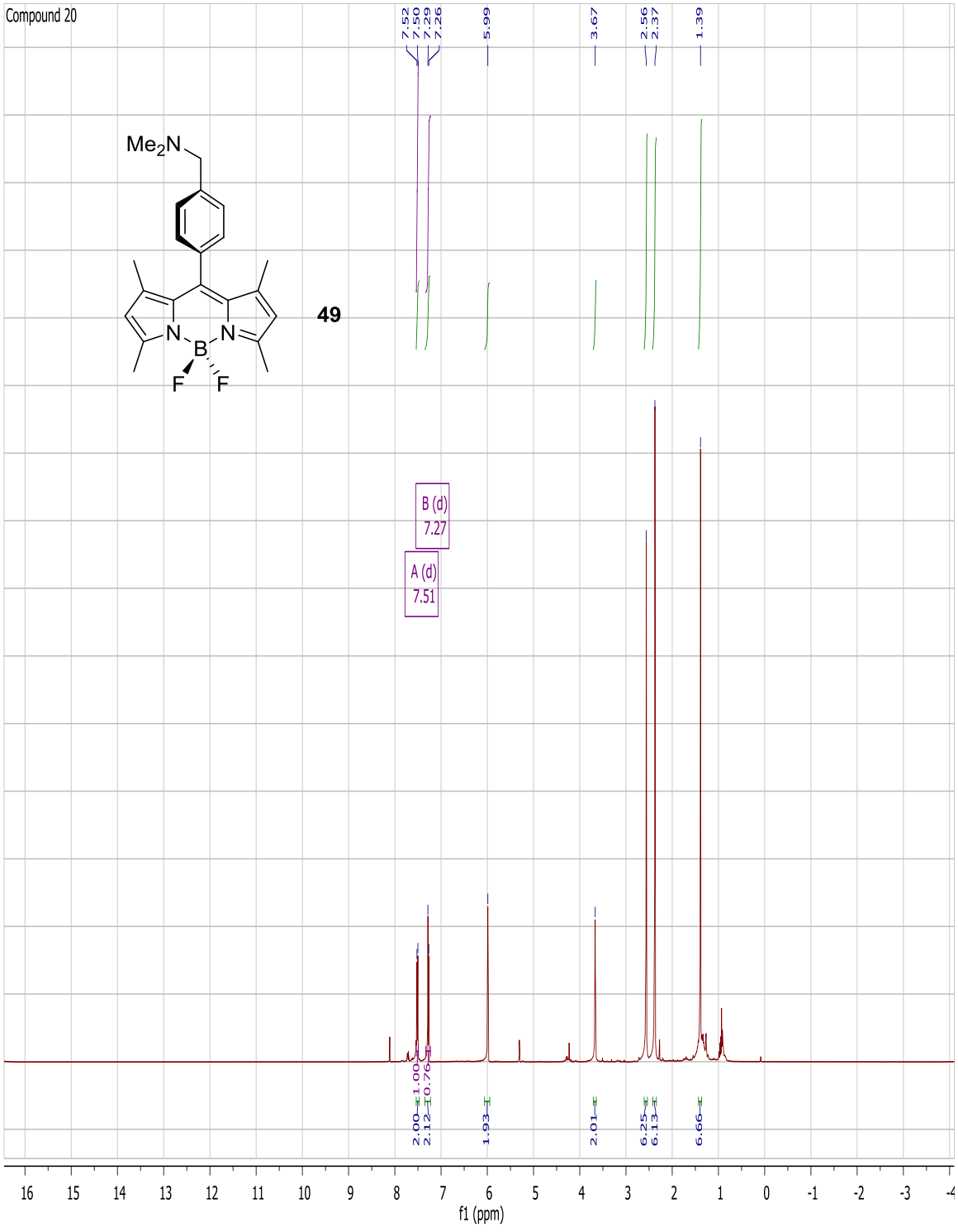

Figure A.3. ^{1}H NMR of BODIPY dye

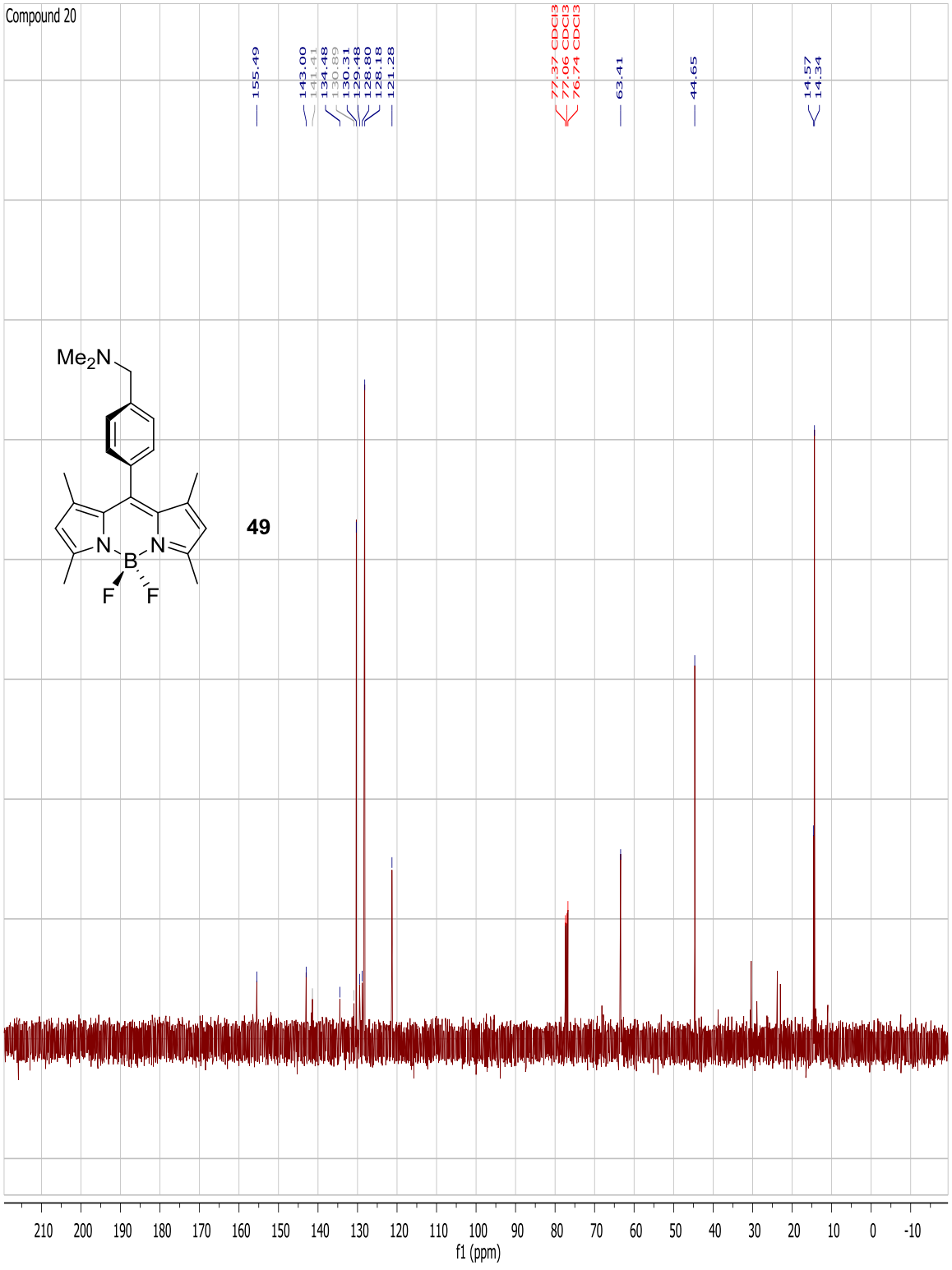

Figure A.4. ^{13}C NMR spectres of BODIPY dye

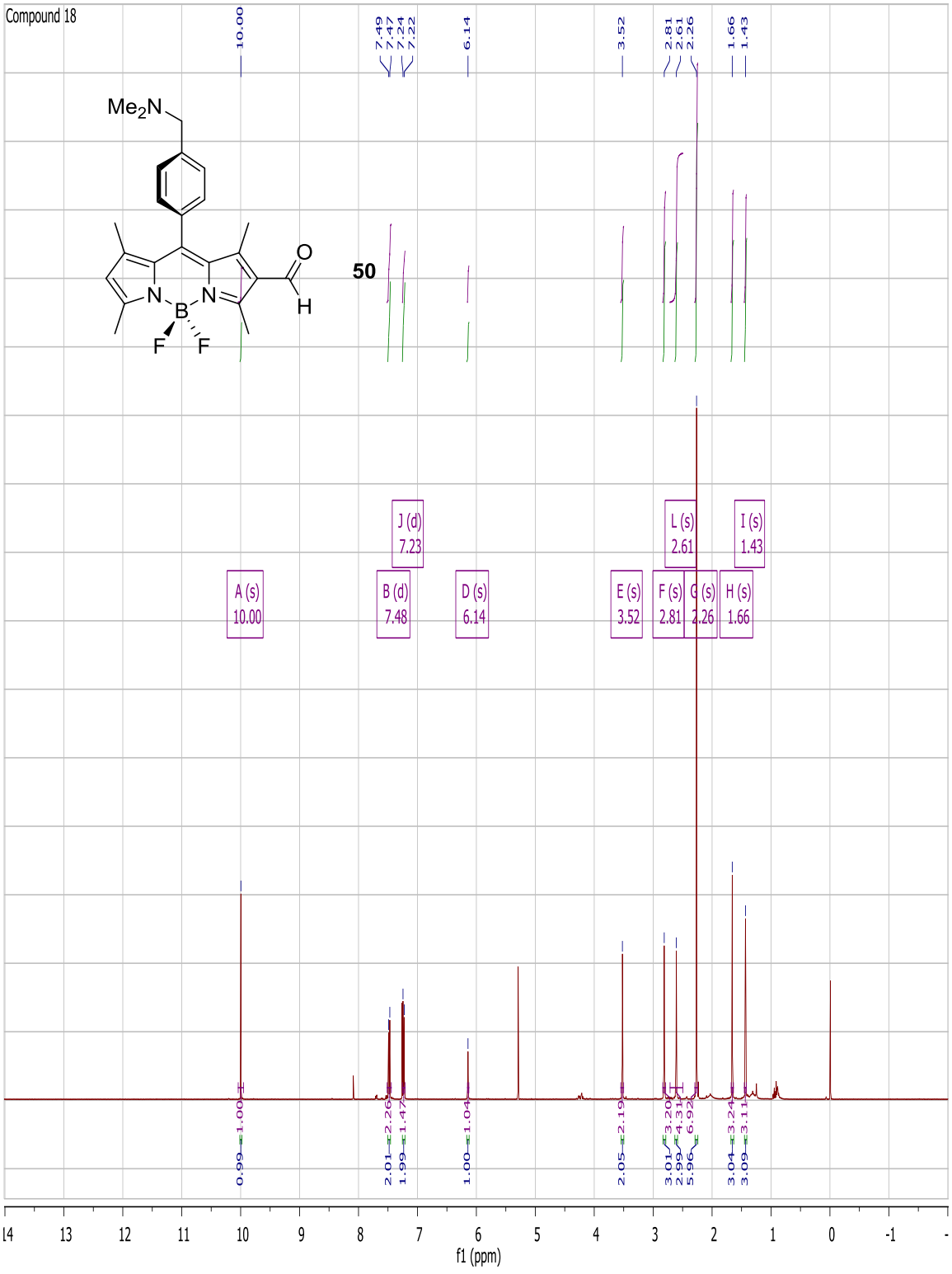

Figure A.5. ^{1}H NMR of 2-FormylBodipy

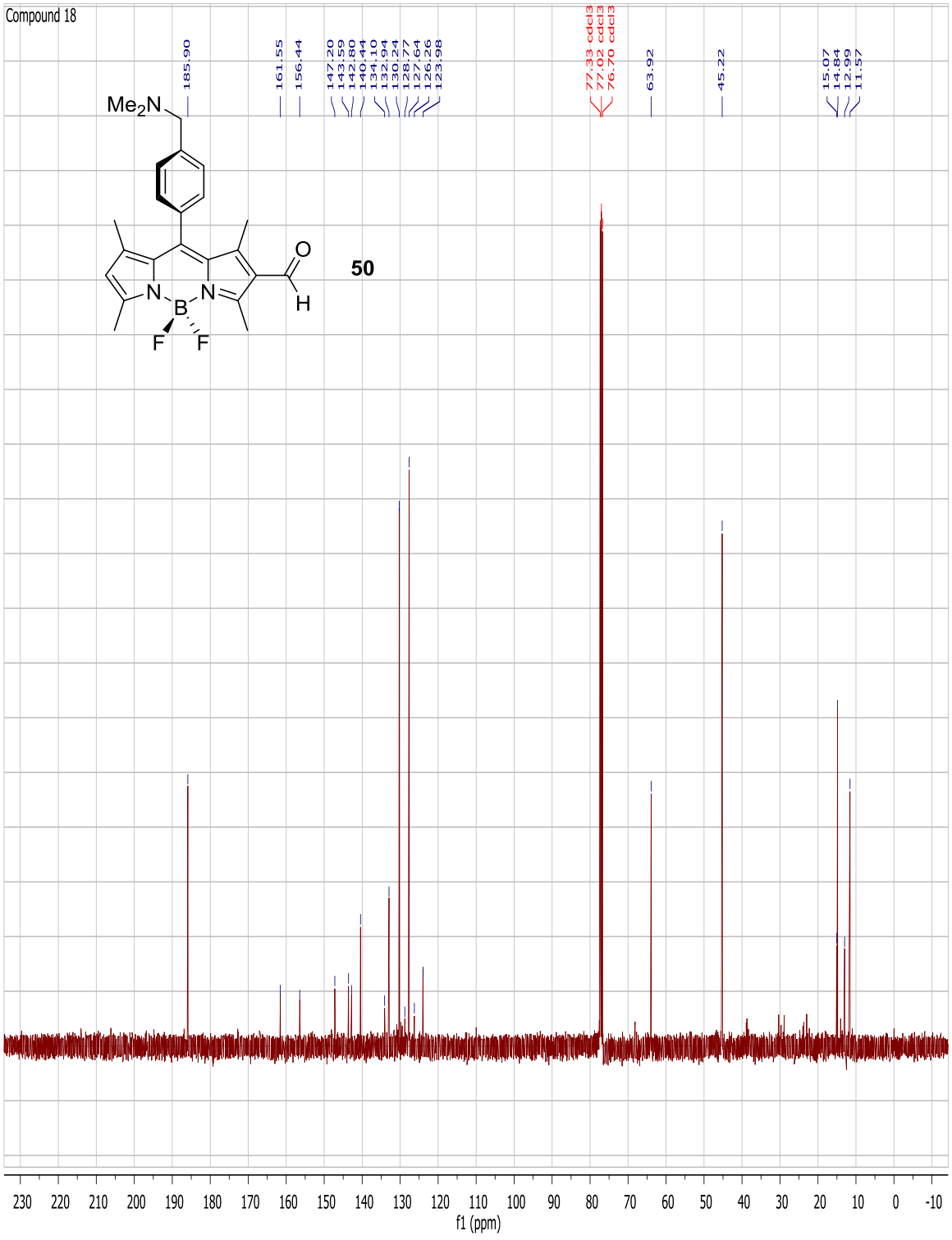

Figure A.6. ^{13}C NMR specters of 2-FormylBodipy

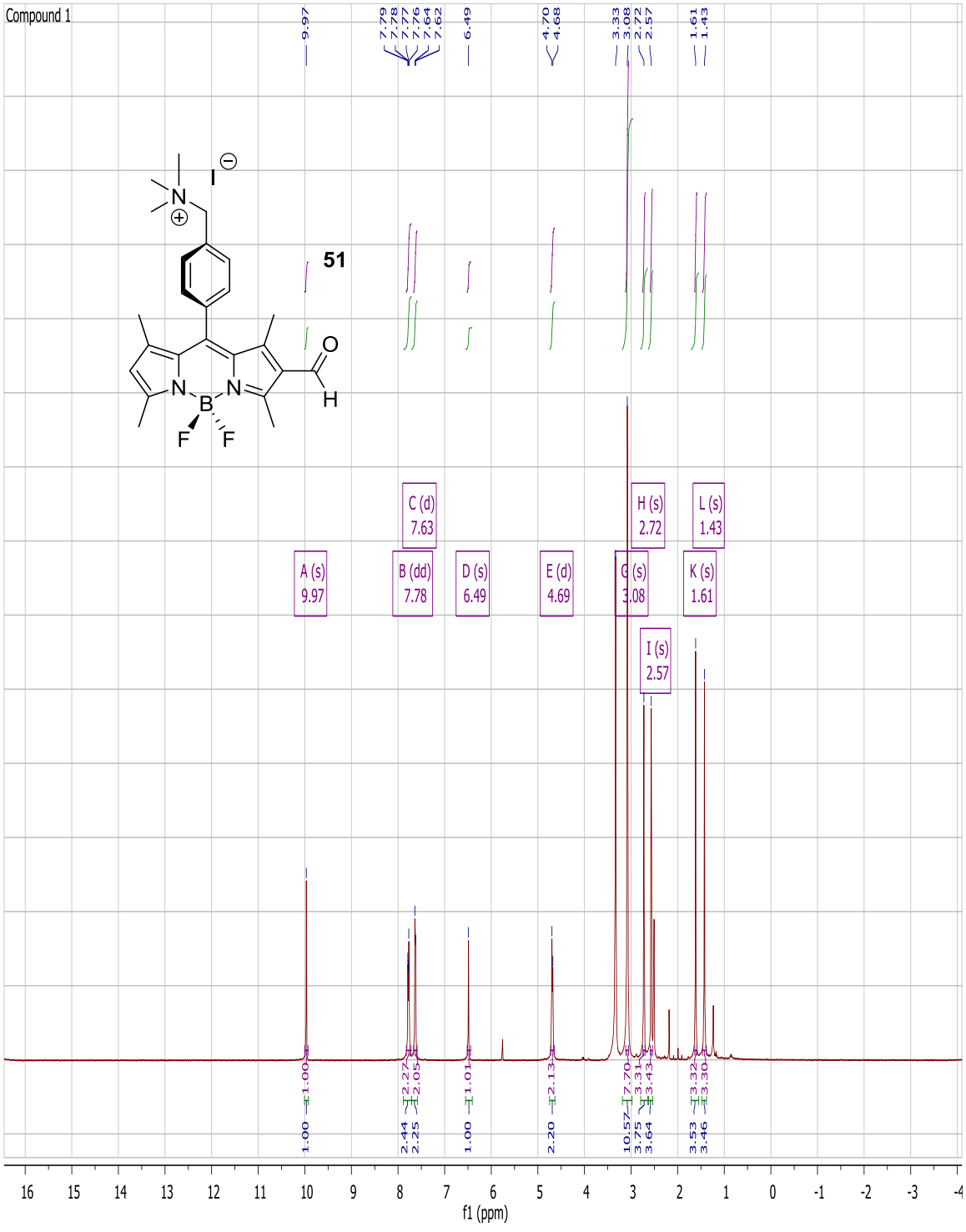

Figure A.7. ^{1}H NMR of MeI salt of BODIPY dyes

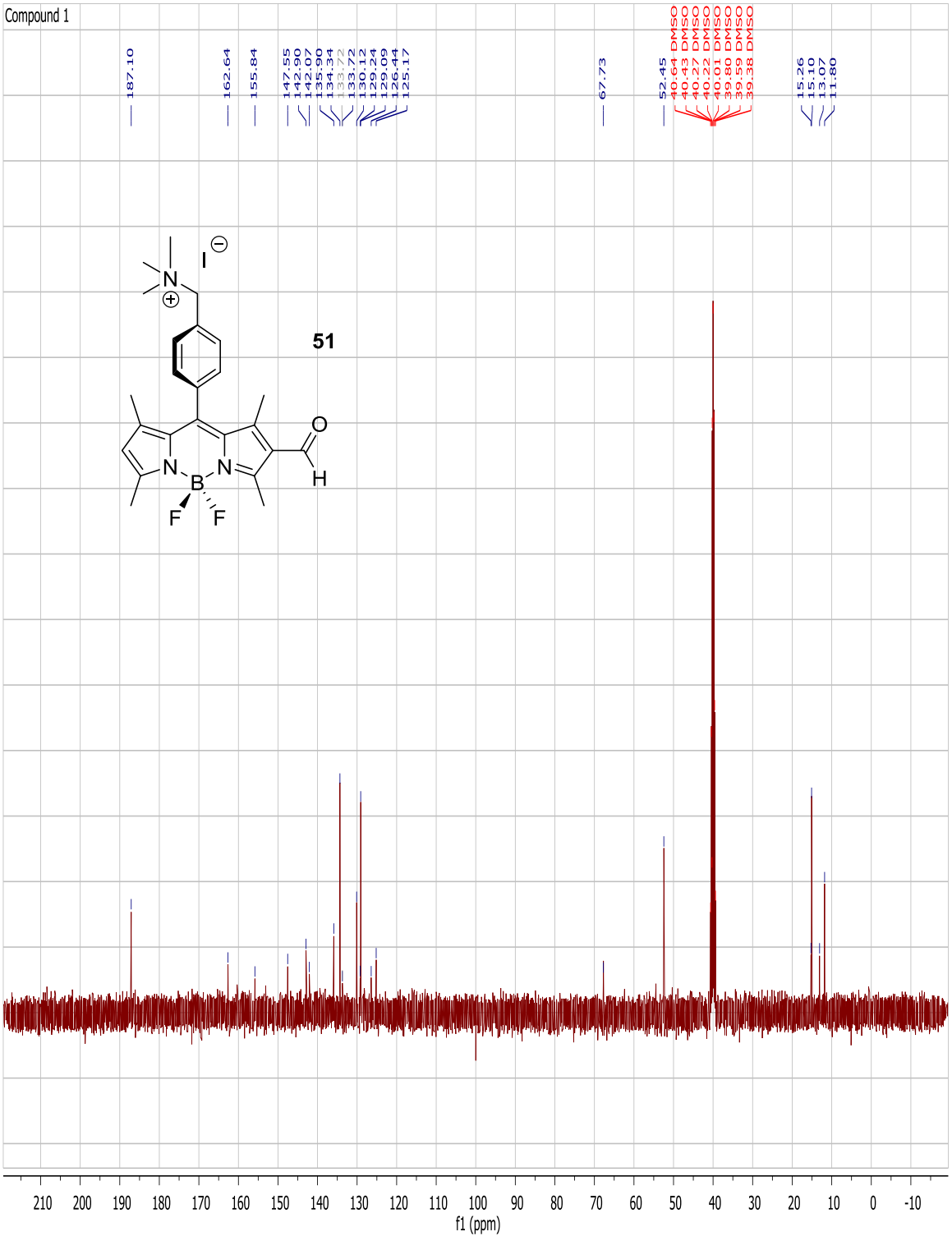

Figure A.8. ^{13}C NMR of MeI salt of BODIPY dyes

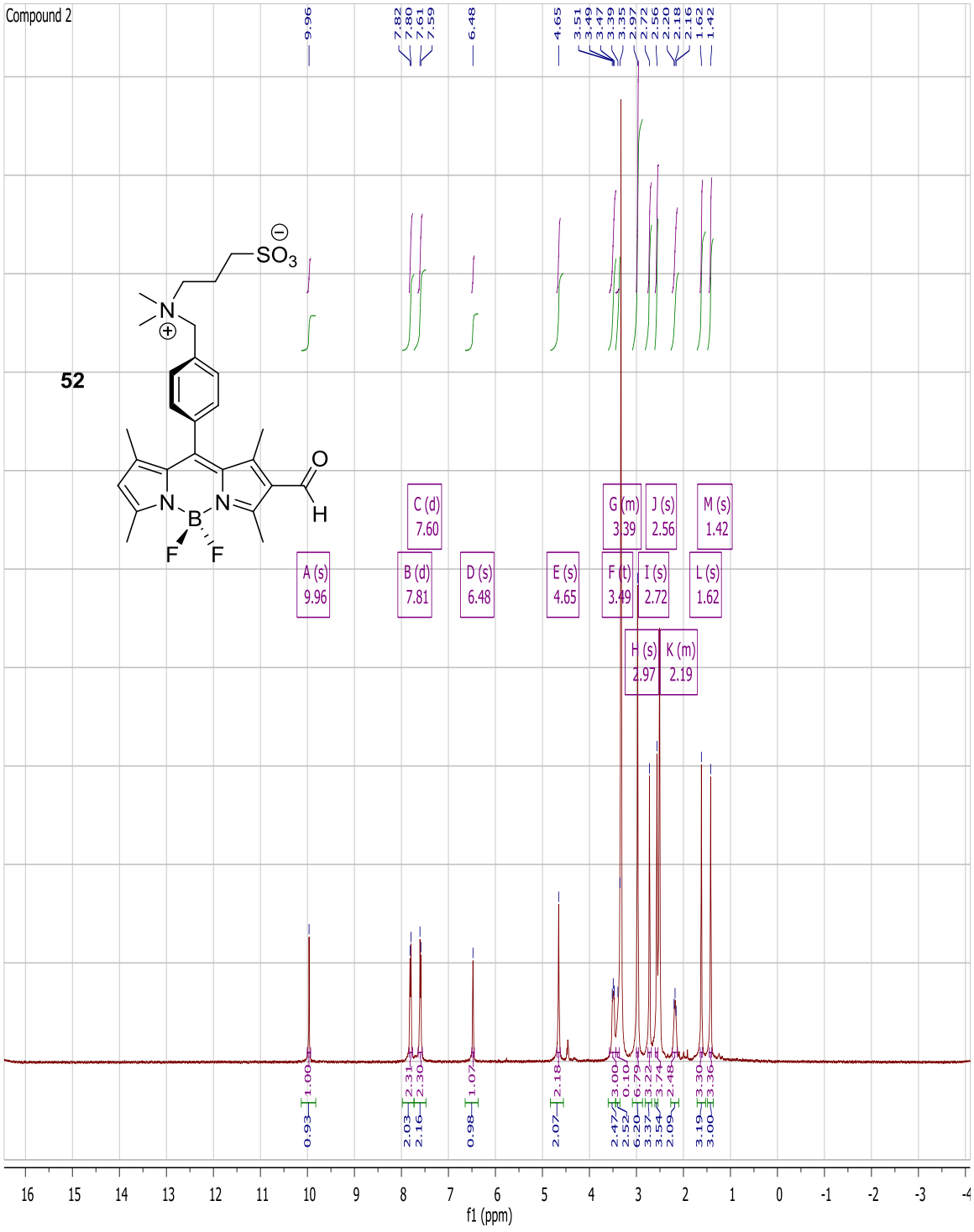

Figure A.9. ^{1}H NMR spectres of 1,3-Propanesultone salt BODIPY dyes

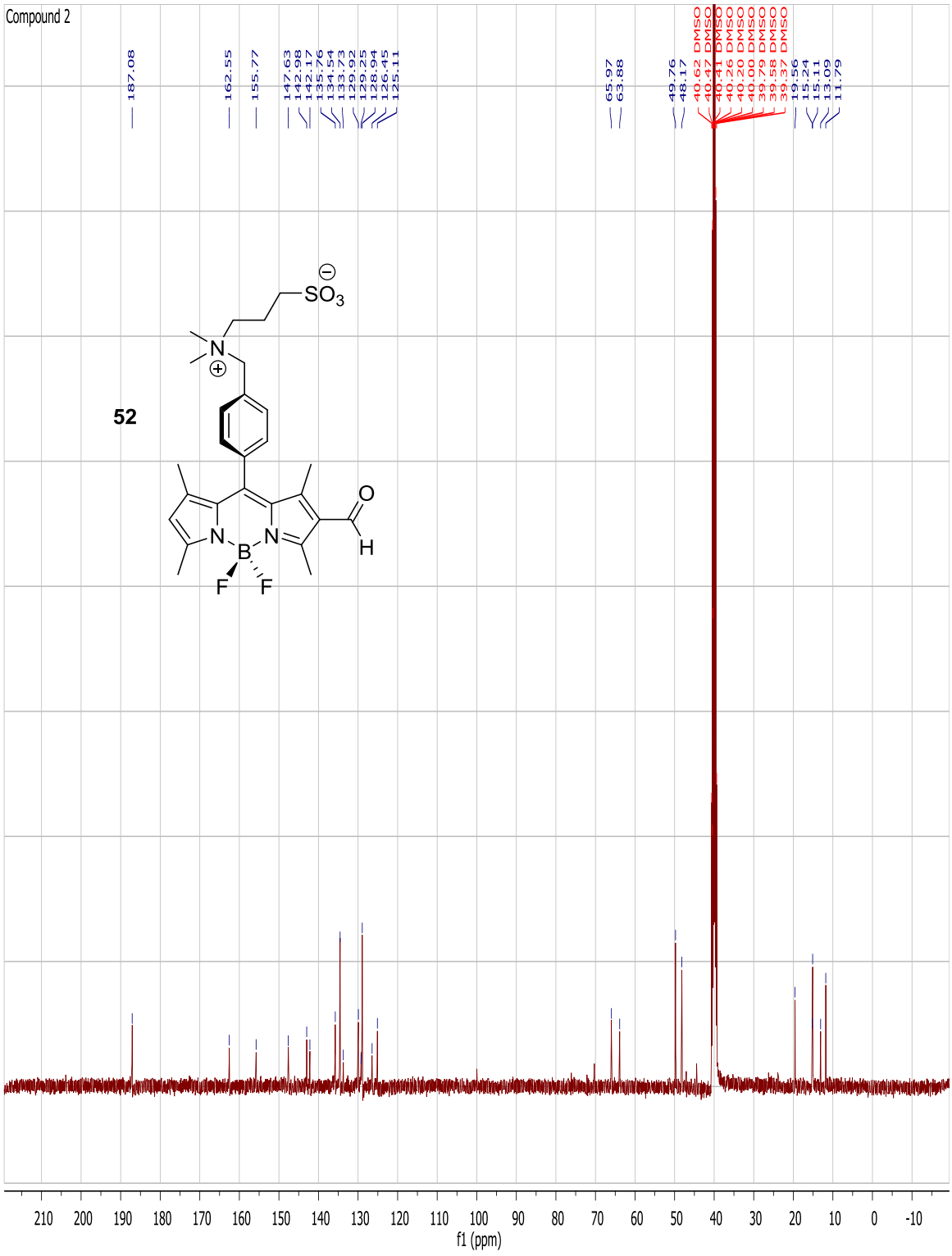

Figure A.10. ^{13}C NMR specters of 1,3-Propanesultone salt BODIPY dyes

Figure A.11. ^{1}H NMR of MeI salt Compound 53

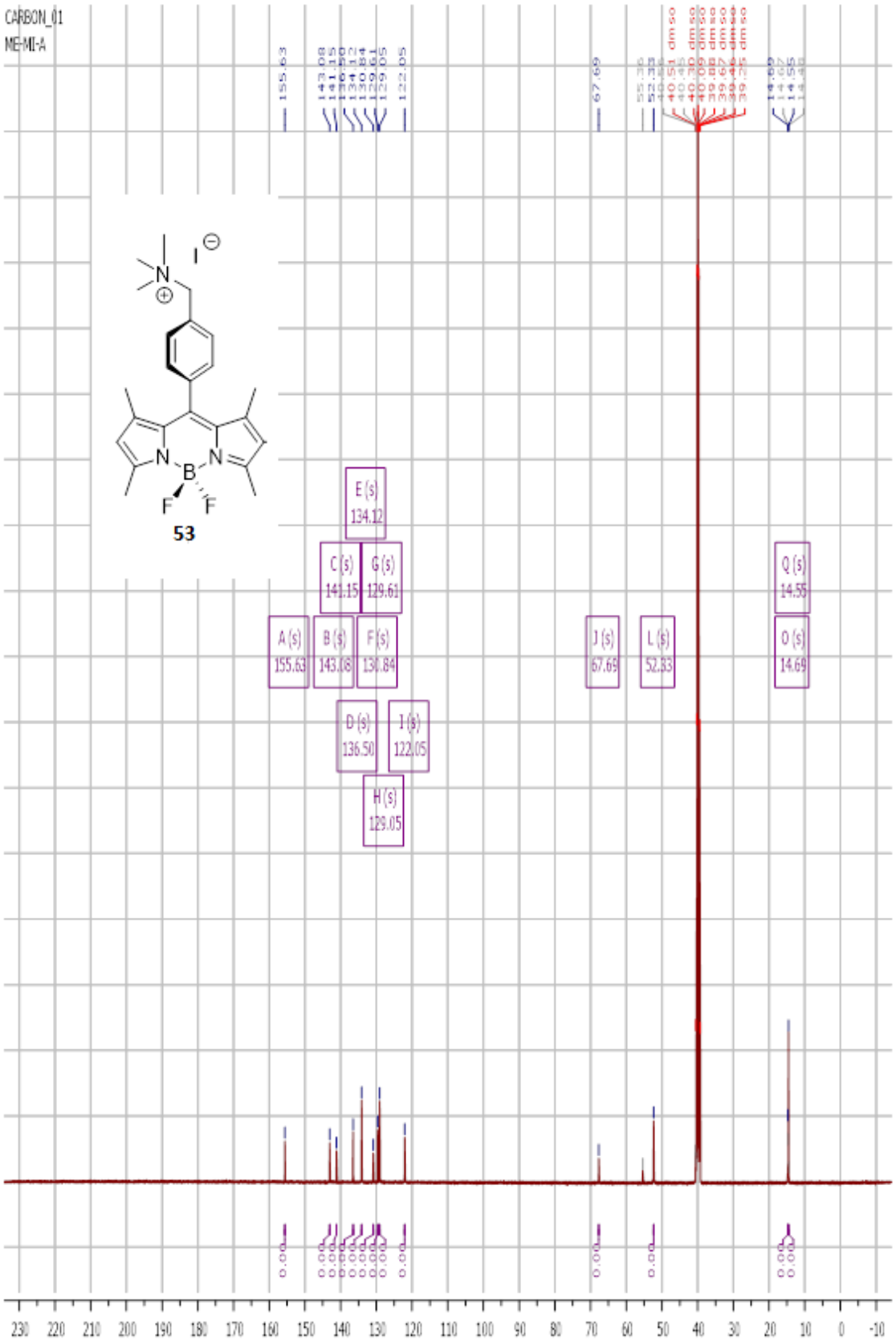

Figure A.12. ^{13}C NMR of (MeI salt) Compound 53

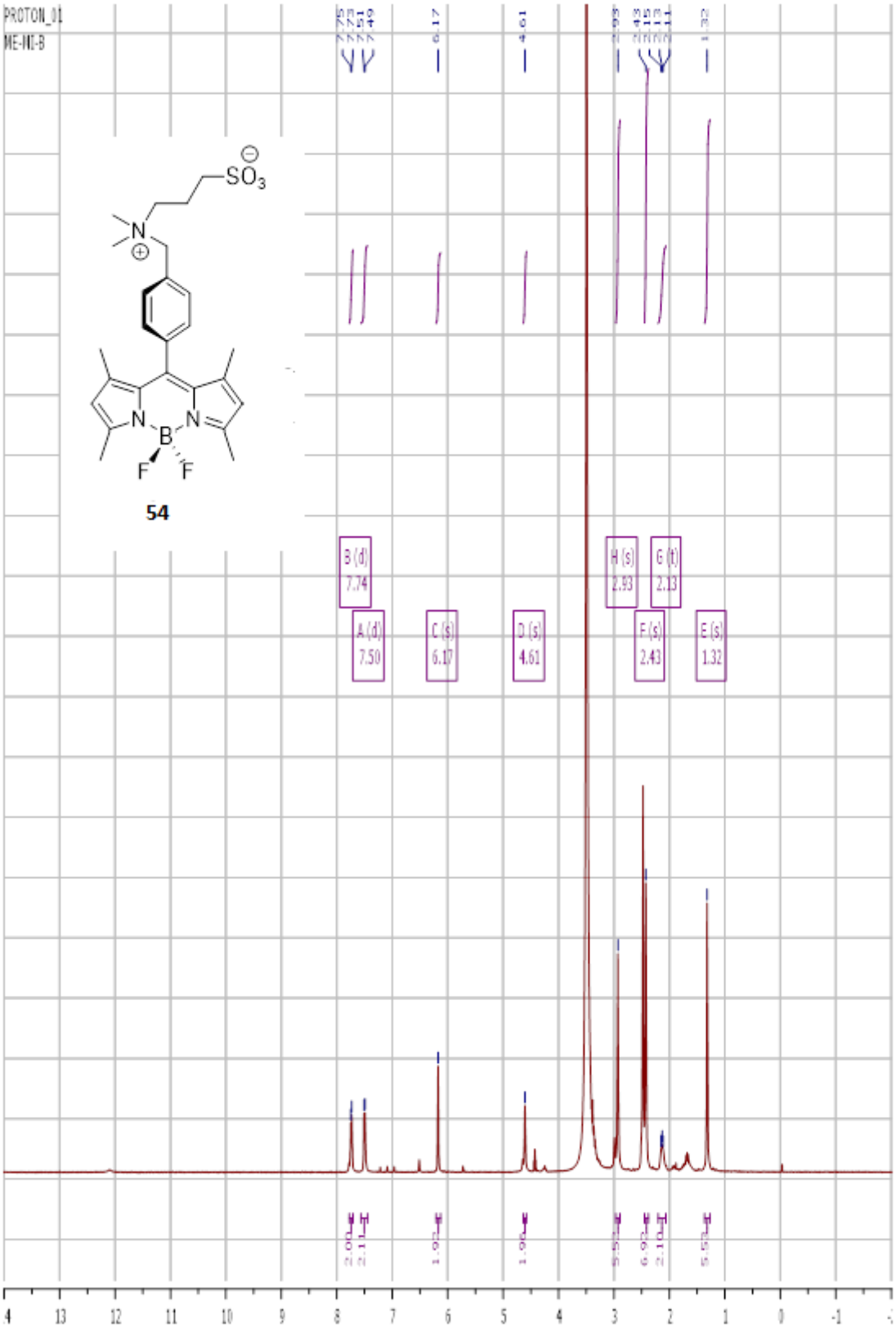

Figure A.13. ^{1}H NMR of Sultone salt Compound 54

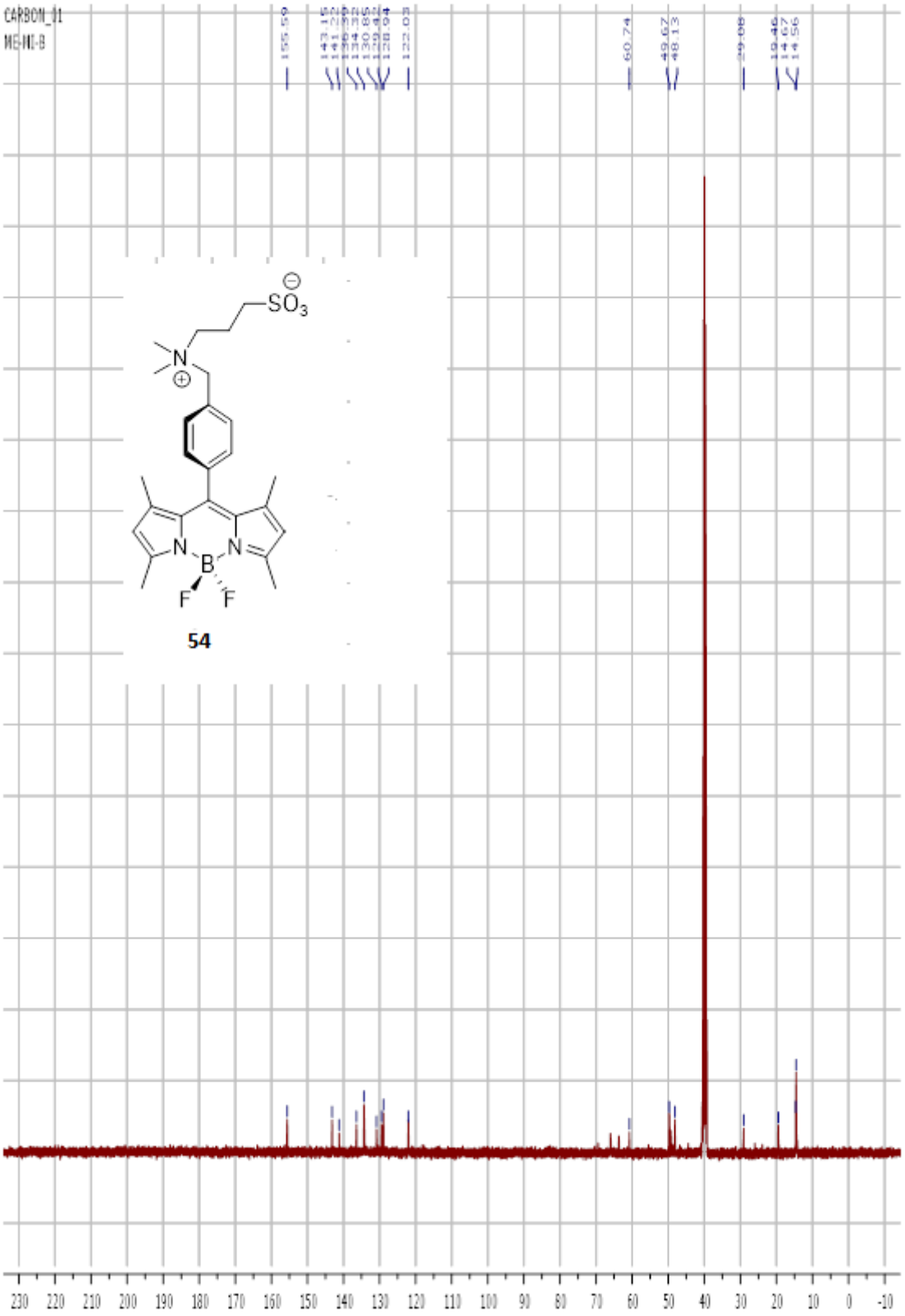

Figure A.14. ^{13}C NMR of Sultone salt Compound 54

APPENDIX B

High Resolution Mass Spectra (HRMS) of Compounds

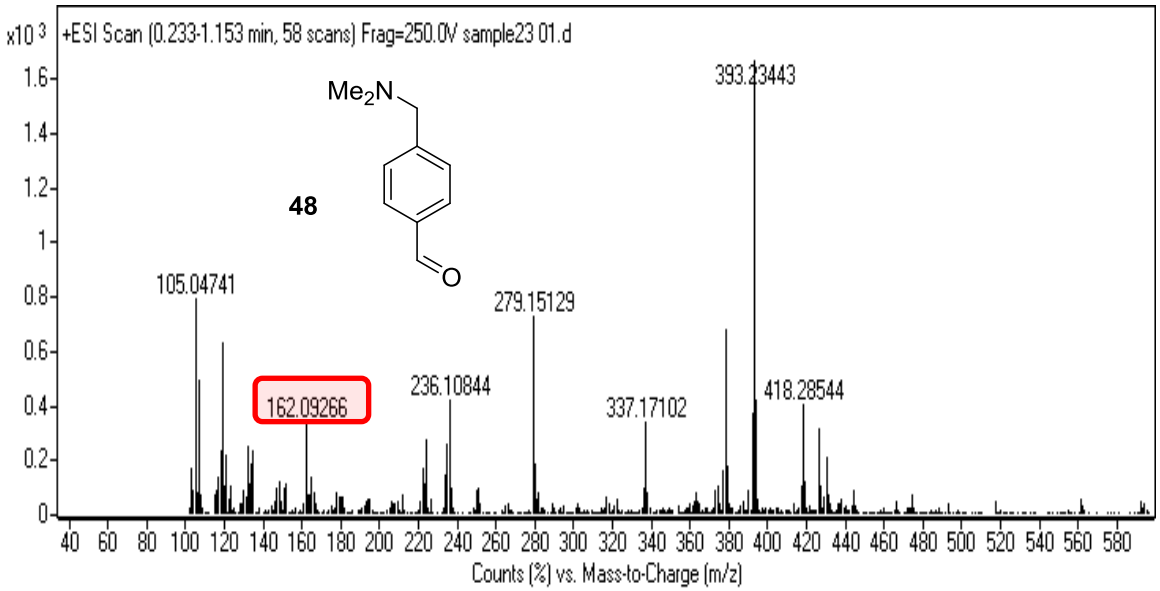

Figure B.1. HRMS of 4-((Dimethylamino)methyl)benzaldehyde

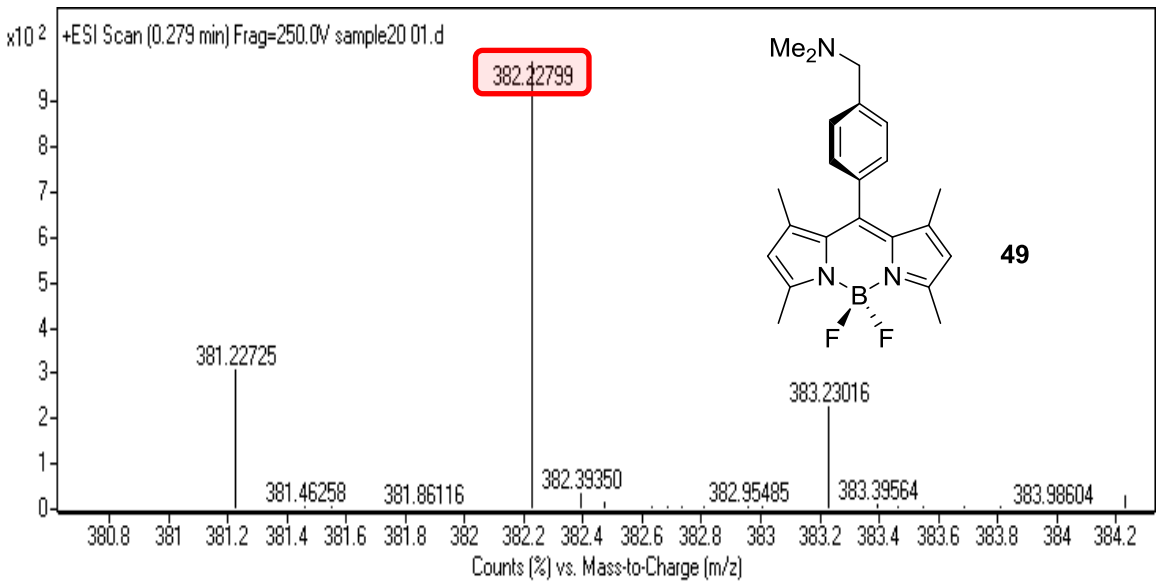

Figure B.2. HRMS of BODIPY

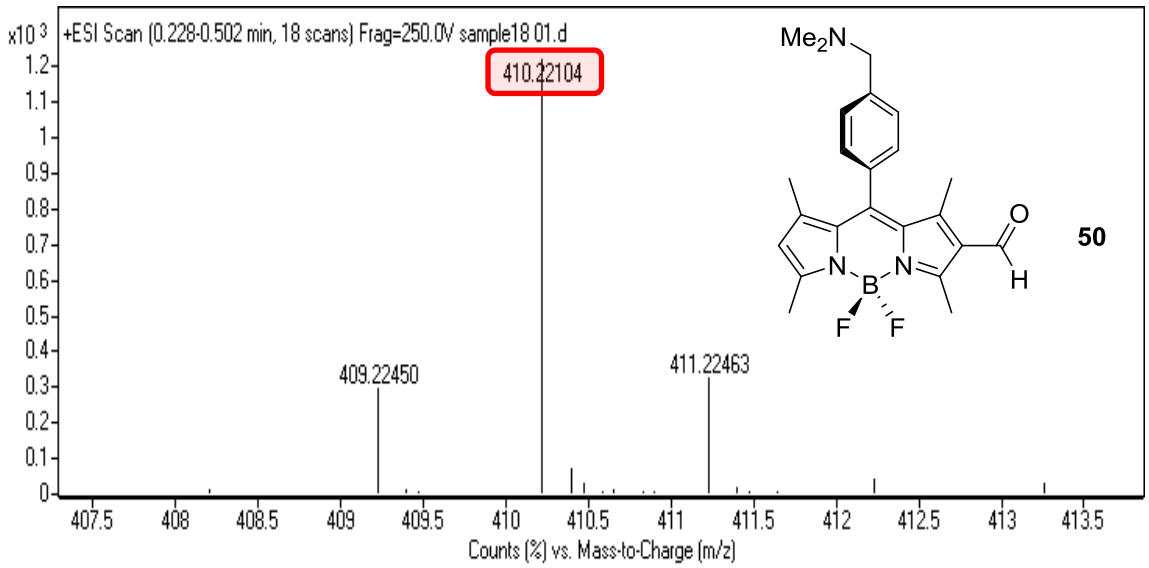

Figure B.3. HRMS of 2-formyl BODIPY

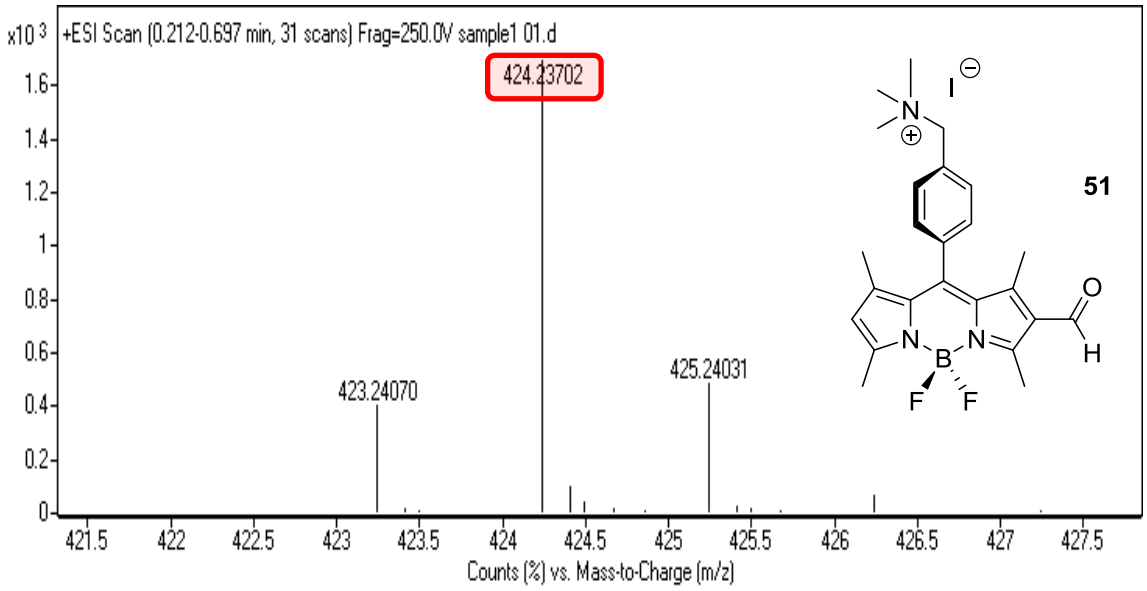

Figure B.4. HRMS of MeI salt of BODIPY

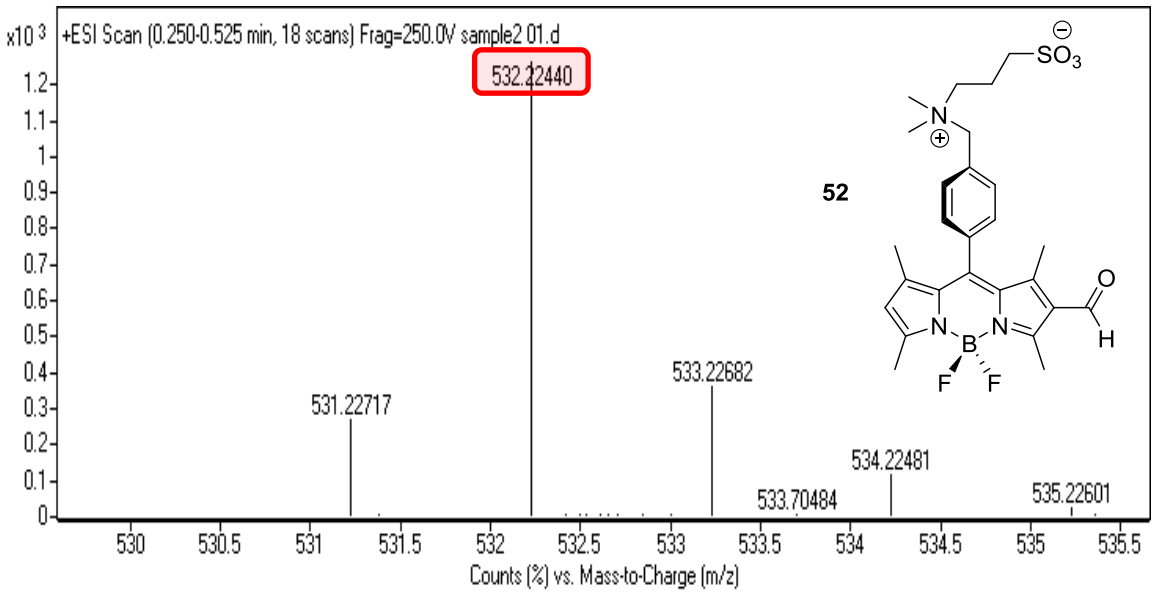

Figure B.5. HRMS of 1, 3-Propanesultone salt of BODIPY

APPENDIX C

IR Spectra of Compounds

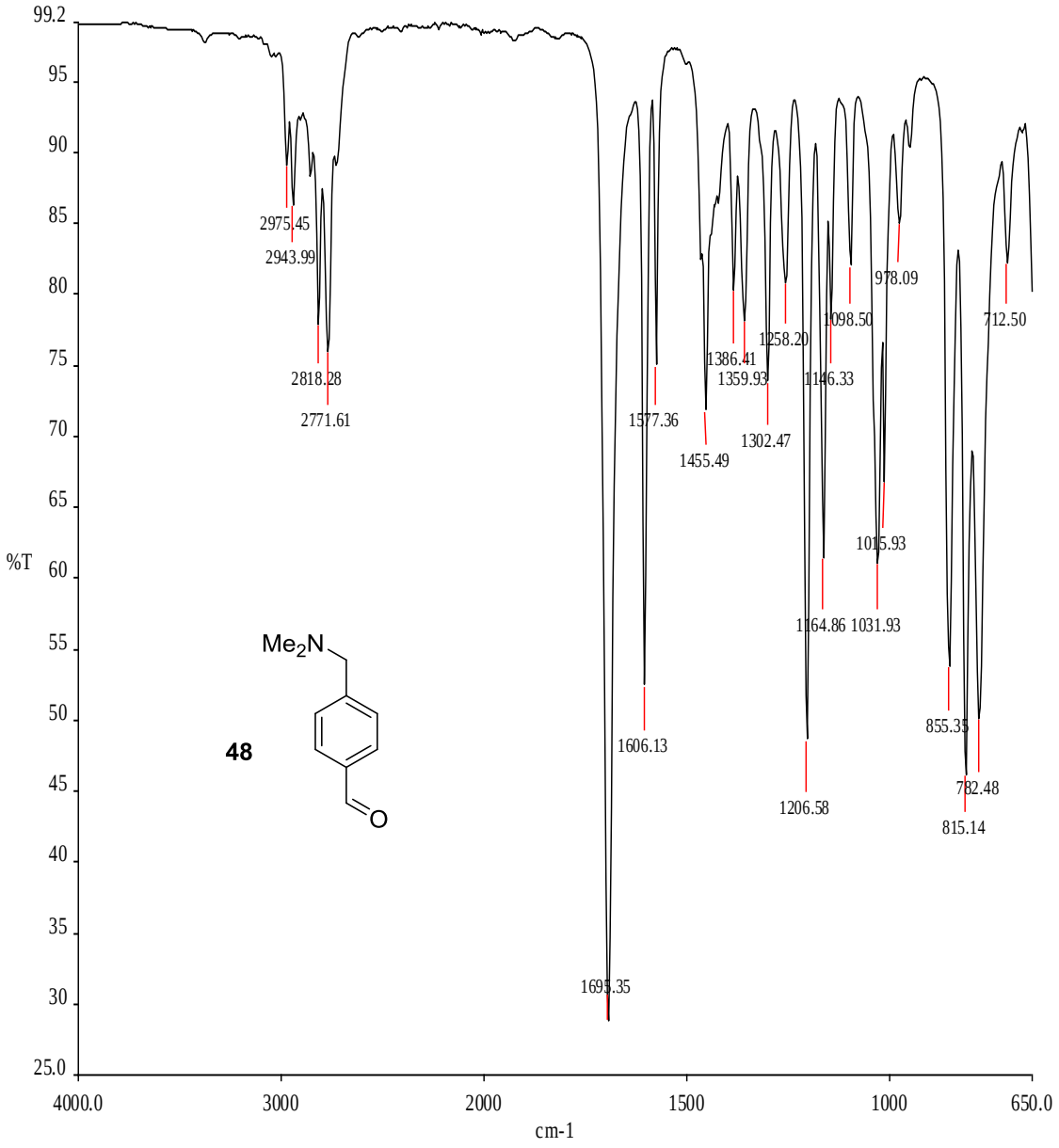

Figure C.1. IR spectrum of 4-((dimethyl amino)methylbenzaldehyde

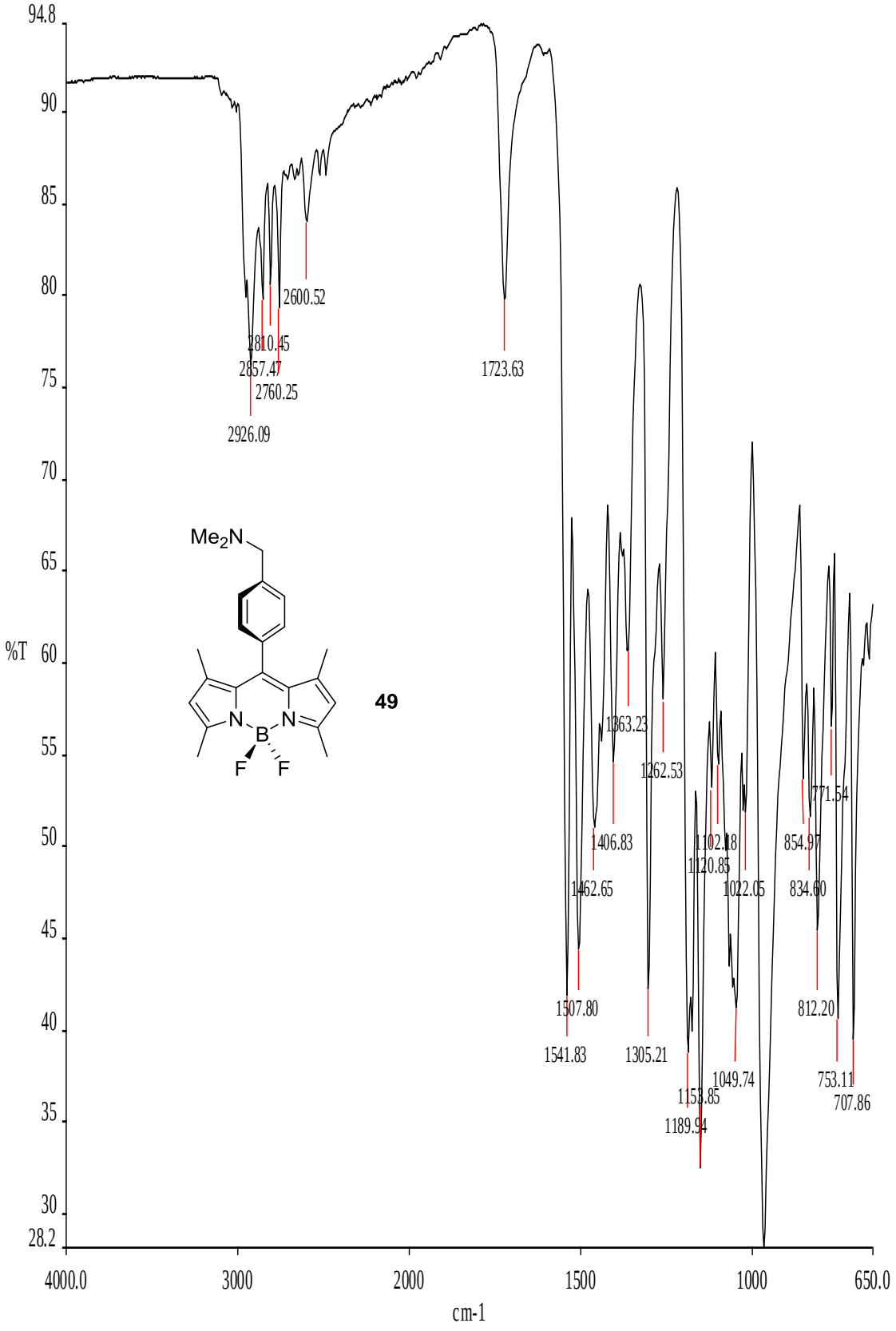

Figure C.2. IR Spectrum of BODIPY

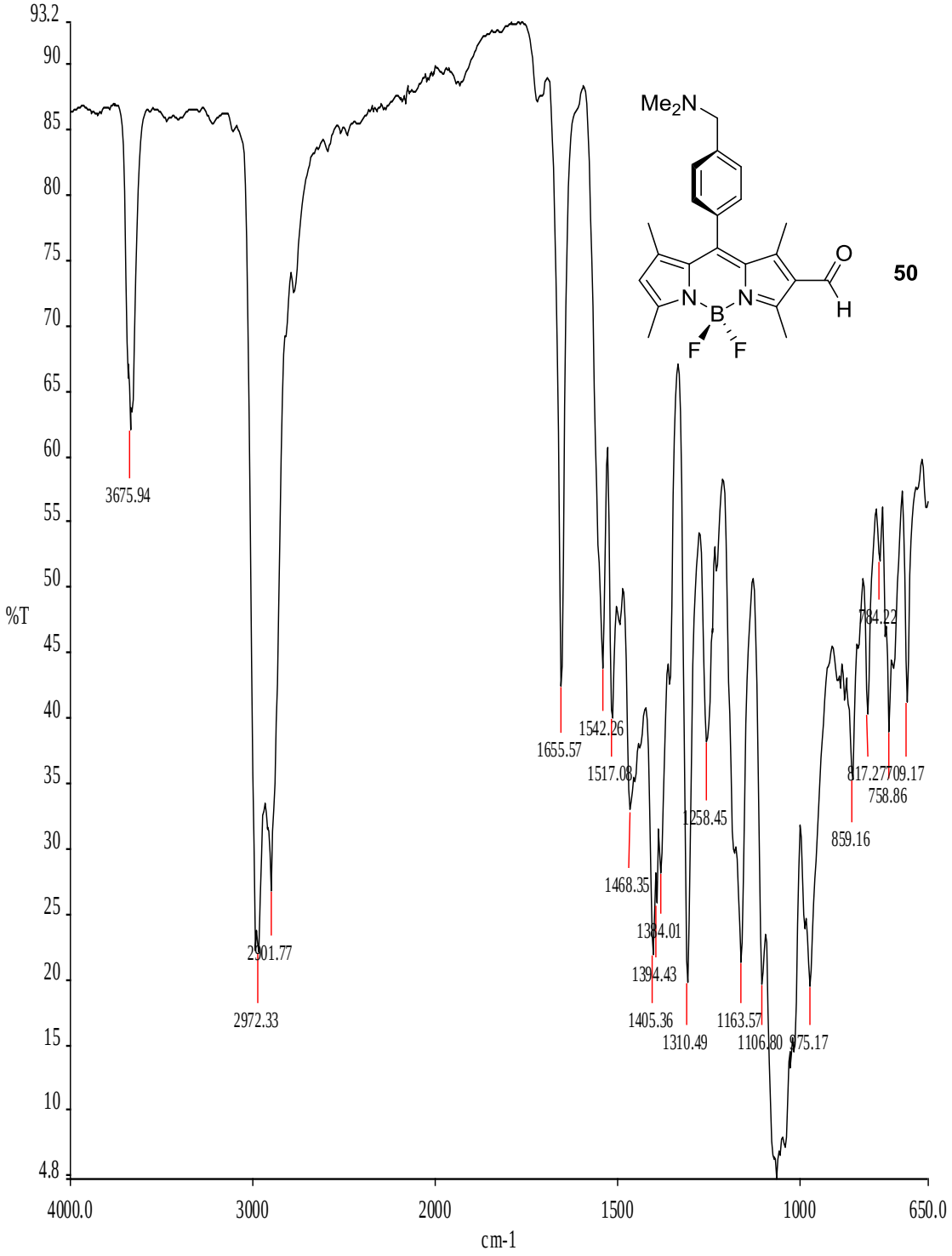

Figure C.3. IR spectrum of 2-formyl BODIPY dye

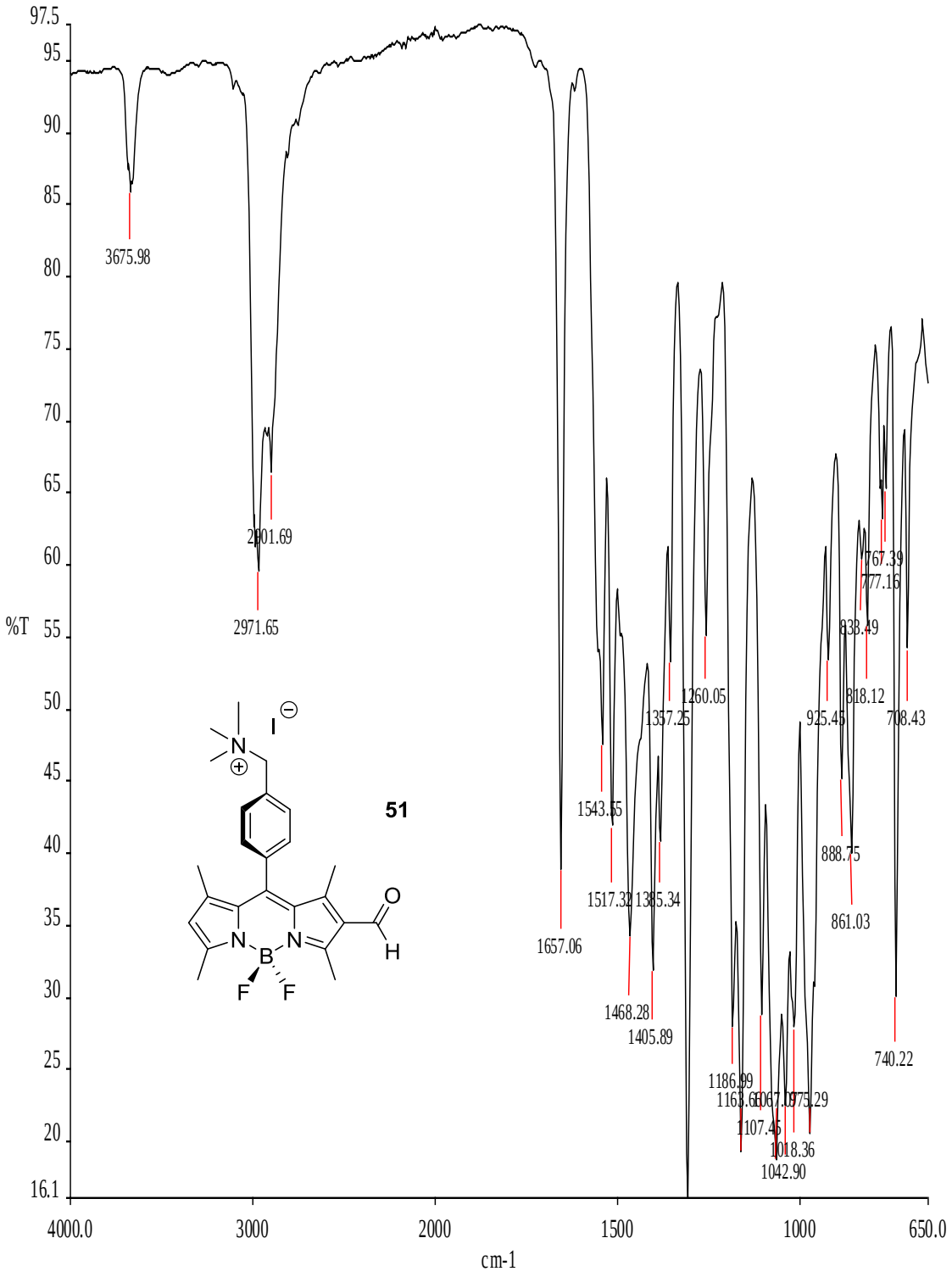

Figure C.4. IR Spectrum of Mel Salt of BODIPY

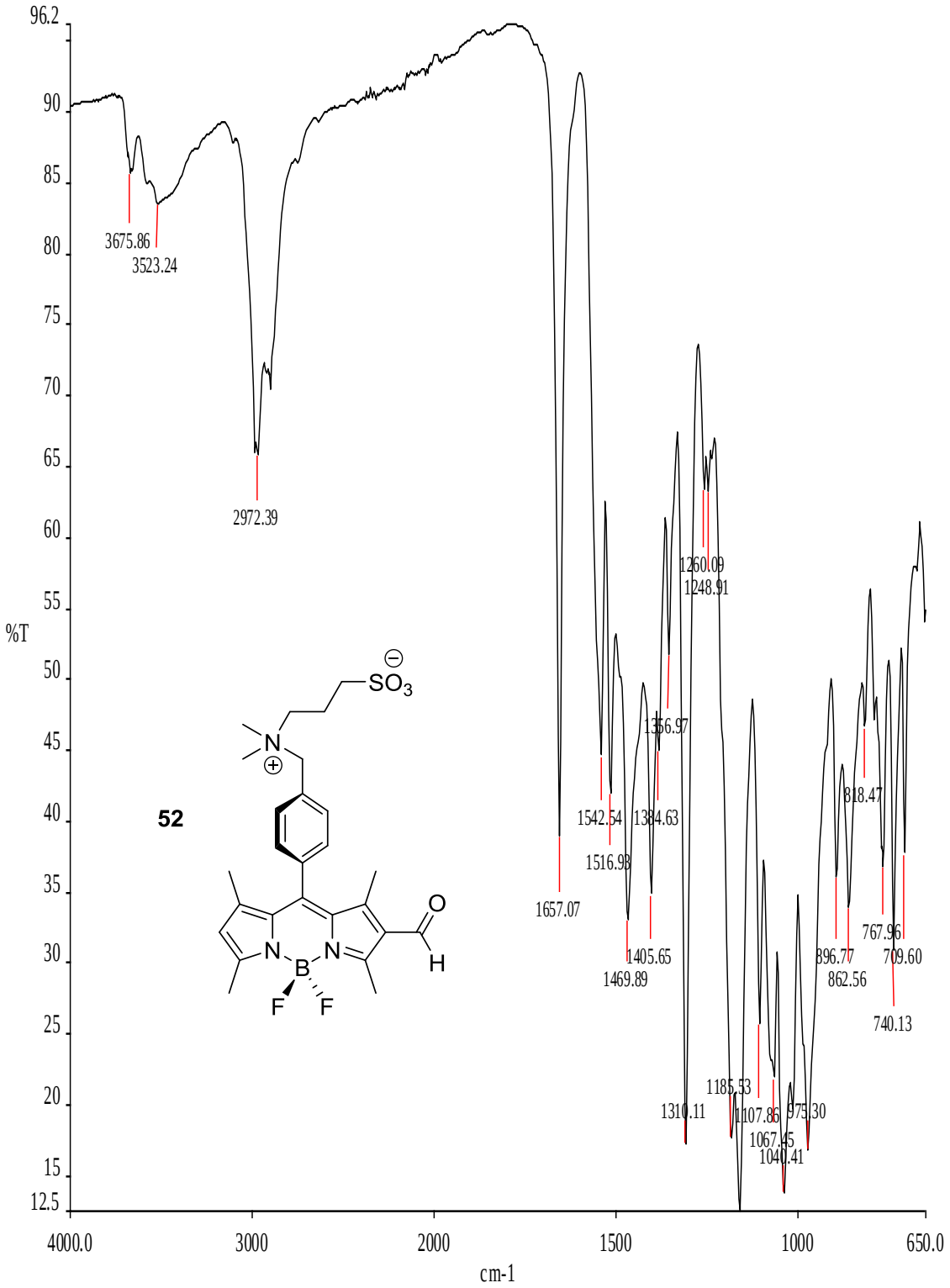

Figure C.5. IR Spectrum of 1, 3-Propanesultone salt of BODIPY

PERSONAL BACKGROUND

He was born in Mosel city in 1983. After receiving primary education in Mosel and Karama town, he graduated from secondary school in IRAQ. Before coming to Bingol, he received a B.Sc. in chemistry science (2007) from Mosel University. Later, he completed M.A postgraduate programme in organic chemistry at Bingol University, Turkey. He is working in Quality control in Zakho District of the Dohuk Governorate of Iraqi Kurdistan.