2007

Synthesis and Evaluation of Derivatives and Analogs of Xanthene Dyes

Xiangyang Xu
Louisiana State University and Agricultural and Mechanical College, xxu3@lsu.edu

SYNTHESIS AND EVALUATION OF DERIVATIVES AND ANALOGS OF XANTHENE DYES

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirement for the degree of
Doctor of Philosophy

in

The Department of Chemistry

By
Xiangyang Xu
B.E., Central South University, 1996
M.E., University of Science and Technology of China, 2002
August, 2007

ACKNOWLEDGMENTS

First, I would like to express my sincere gratitude to my advisor, Dr. Robert M. Strongin, for his guidance, support, and encouragement. His inspiration and patience helped me to stay focused on my goals.

I would also like to thank Dr. William Crowe, Dr. David Spivak, Dr. Robert Cook and Dr. Kenneth Rose being my committee members. I fully appreciate their patience and time reading my dissertation and giving valuable advices.

Then, I would like to thank the members of the Dr. Strongin's Research Group, from the past to the present, Dr. Jorge Escobedo, Dr. Oleksandr Rusin, Dr. Nadia St. Luce, Dr. Rolanda Johnson, Dr. Kyu Kwang Kim, Dr. Weihua Wang, Onur Alpturk, Youjun Yang, Shan Jiang, George Samoei, for their willingness to help me. I enjoyed the time we shared together in LSU. The acknowledgement would also go to Dr. Frank Fronczek, Dr. Dale Trelevean for their help on my research.

Finally, to the rest of my friends and family, thank you for all your support and love.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BBr_3	Boron tribromide
BHC	Brominated hydrocarbon
ºC	Degrees Celsius
CaH_2	Calcium Hydride
Cal.	Calculated
$CDCl_3$	Dueterated Chloroform
CHC	Chlorinated hydrocarbon
C_6H_5Cl	Chlorobenzene
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CH_3OD	Dueterated Methanol
CH_3OH	Methanol
^{13}C NMR	Carbon-13 Neclear Magnetic Resonance
$(CH_3)_4Si$	Tetramethyl silane
CH_3SO_3H	Methanesulfonic acid
CO	Carbon Monoxide
Cys	Cysteine
DCFH	2',7'-Dichlorodihydrofluorescein
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DHR 123	Dihydrorhodamine 123
DHR-6G	Dihydrorhodamine 6G
D_2O	Dueterium oxide
DMACA	4-(Dimethylamino)-cinnamaldehyde
DMF	N-N-Dimethylformamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
FAB	Fast Atom Bombardment
FT-IR	Fourier Transform Infrared
g	Grams
h	Hours
HCL	Hydrochloric acid
HCN	Hydrocyanic Acid
Hcy	Homocysteine
HIV	Human Immunodeficiency Virus
H_2O	Water
H_2O_2	Hydrogen Peroxide
HPLC	High-Performance Liquid Chromatography
^{1}H NMR	1-d Proton Nuclear Magnetic Resonance
HPF	6-hydroxy-9-phenyl-fluorone
HRMS	High-Resolution Mass Spectrometry

H_2SO_4	Sulfuric Acid
ISC	Intersystem Crossing
M	Molar (moles/Liter)
mBrB	Monobromobimane
mM	Millimolar (mmoles/Liter)
$MgSO_4$	Magnesium Sulfate
MALDI	Matrix-Assisted Laser Desorption Ionization
MeOH	Methanol
mg	Milligrams
mL	Milliliters
mmol	Millimoles
MS	Mass Spectrometry
MW	Molecular Weight
$NaBH_4$	Sodium Borohydride
NaOt-Bu	Sodium tert-butoxide
Na_2CO_3	Sodium Carbonate
$NaHCO_3$	Sodium Bicarbonate
NaOH	Sodium Hydroxide
Na_2SO_4	Sodium Sulfate
NBA	N-Bromoacetamide
NBD-F	4-Fluoro-7-Nitrobenzofurazan
NIR	Near-infrared
NMR	Nuclear Magnetic Resonance

O_2	Oxygen
OH	Hydroxide
OPA	O-phthalaldehyde
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PAAm	Polyacrylamide
PBDD	Polybrominated-dibenzon-p-dioxin
PCDD	Polychlorinated dibenzo-p-dioxin
PMMA	Poly-methylmethacrylate
ppm	Parts Per Million
PTZ	Phenothiazene
PXDD	Polyhalogenated dibenzo-p-dioxin
RDS	Rate Determining Step
R_f	Ratio to Solvent Front
ROS	Reactive Oxygen Species
rt	Room Temperature
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCDF	2,3,7,8-tetrachlorodibenzofuran
THF	Tetrahydrofuran
tHcy	Total Homocysteine
TLC	Thin-Layer Chromatography
μM	Micromolar (micromoles/Liter)
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible

XDD	Halogenated dibenzo-p-dioxin
XHC	Halogenated hydrocarbon
$ZnCl_2$	Zinc Chloride
λ	Wavelength

ABSTRACT

Xanthene dyes are one of the oldest synthetic dyes. Fluorescein was first synthesized by von Baeyer in 1871. Since its discovery, it has been extensively studied. Fluorescein can exist as four different ionic forms (cationic form, neutral form, monoanionic form and dianionic form). Under physiological conditions (pH 7.4), fluorescein mainly exists as the dianionic form which grants it large quantum yield and excellent solubility in water. This renders fluorescein and its derivatives useful for studies in biological media.

Cysteine (Cys) and homocysteine (Hcy) are of the few amino acids which contain sulfur and both of them are believed to be related to some diseases. Cardiovascular diseases, Alzheimer's disease and neutral tube defects are reported to be associated with elevated levels of homocysteine in blood plasma. Low levels of cysteine are associated with slowed growth, hair depigmentation, liver damage, etc. The reason for Cys and Hcy being connected with diseases is still unclear. Herein, we designed and synthesized fluorescein-based dyes for detecting Hcy and Cys in the visible spectral region with the highest selectivity.

Optical sensors in the near-infrared (NIR) spectral range have captured the attention of researchers interested in studying chemical and biological processes in live tissues because absorption and scattering by endogenous biomolecules are minimal. Three heptamehtine cyanine-based dyes were designed and synthesized for the detection or labeling of Cys and Hcy. Biocompatible hydrogels have been studied in many fields, e.g., drug delivery system, separation processes or sensors (fluorescent polymers). A

fluorescein-based hydrogel with potential application for detection of Cys and Hcy were designed and underwent synthesized.

Dibenzo-p-dioxin is a structural analog of xanthene but is notorious for the toxicicty of the halogenated members, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Since polyhalogenated dibenzo-p-dioxins (PXDDs) have been shown to be a significant threat to public health, measuring the concentrations of PXDDs in the environment as well as understanding their mechanism of formation and environmental fate is needed. Here we designed a novel synthesis with control halogen substitution patterns in order to result in a large number of PXDDs.

CHAPTER 1

INTRODUCTION

1.1 Definition of Xanthene Dyes

Any dyes that include a xanthene molecule structure (Figure 1.1), an aromatic cyclic ether with an oxygen between the two aromatic rings, are called xanthene dyes.[1-3]

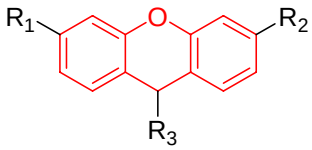


Figure 1.1: General xanthene dye structure, in which R_1, R_2 are normally paired as electron donor and acceptor (e.g., –OH and =O, $-NH_2$ and $–NR_2^+$, R_3 could be any substituent, e.g.,-H -Ph, etc.

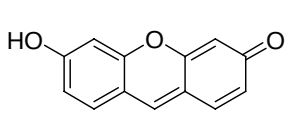
Based on the different electron donor-acceptor pairs on the commonly xanthene dyes. Xanthene dyes can be divided into two subgroups. The first one includes hydroxyl group as donor and keto group as acceptor, such as 3-hydroxy-6-fluorone,[4] fluorescein[5-6] and the related derivatives; e.g., eosin Y,[7] rose Bengal,[8] phloxine[9] and 6-hydroxy-9-phenylfluorone.[10-11] The other subgroup includes amines as electron donor and quaternary ammonium as acceptor. Examples include the pyronine[9] series and rhodamine series of compounds; e.g., rhodamine 110[12] and rhodamine B.[13] Some well known xanthene dyes are shown in Figure 1.2.

1.2 Properties of Xanthene Dyes

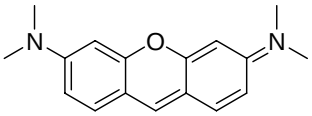
Xanthene dyes include many of the oldest synthetic dyes. Fluorescein was first synthesized by von Baeyer in 1871.[5-6] Since its discovery, it has been extensively studied.[14-19]

1.2.1 Xanthene Dye Spectral Properties

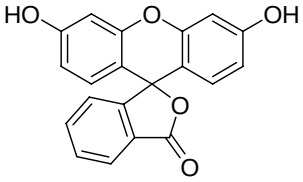
In 1958, Zanker, et al.[16] found that fluorescein can exist in aqueous solutions as four different ionic forms (cationic, neutral, anionic, dianionic) (Figure 1.3). This renders



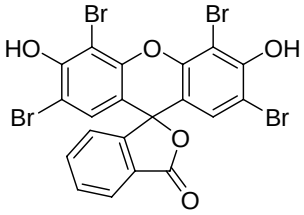
3-Hydroxy-6-Fluorone



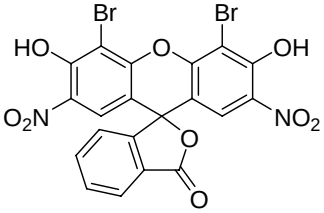
Pyronine Y



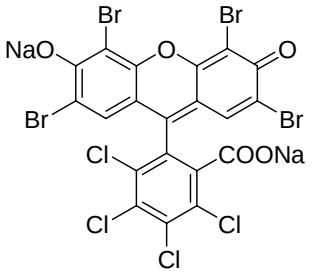
Fluorescein



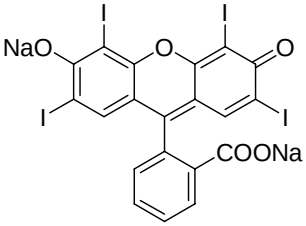
Eosin-Y



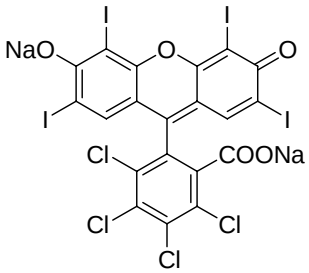
Eosin-B



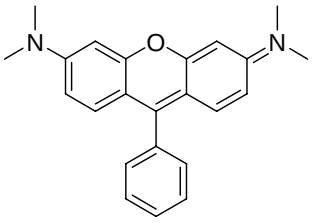
Phloxine-B



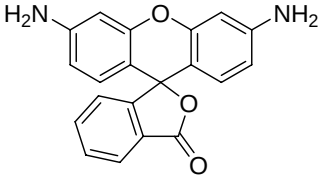
Erythrosin-B



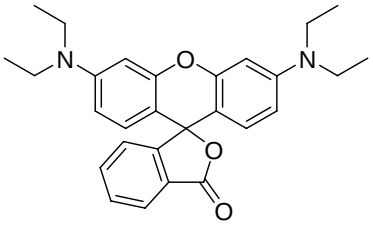
Rose bengal



Rosamine



Rhodamine 110



Rhodamine B

Figure 1.2. Some Well Known Xanthene dyes.

its absorption and fluorescence properties pH dependent.[17-18] Among the four ionic forms, each possesses specific spectral properties. The cationic form and the dianionic form only occur in strongly acidic (pH < 2) or strongly basic (pH > 8) aqueous conditions, respectively. The neutral form exists as three isomers (red quinoid, colorless lactone, and yellow zwitterion) at pH ~3.3. Among the three neutral isomers, the quinoid and lactone forms are believed to be the major forms. When the aqueous solution pH is around 5.5, fluorescein mainly exists as a monoanion (carboxylate monoanion or

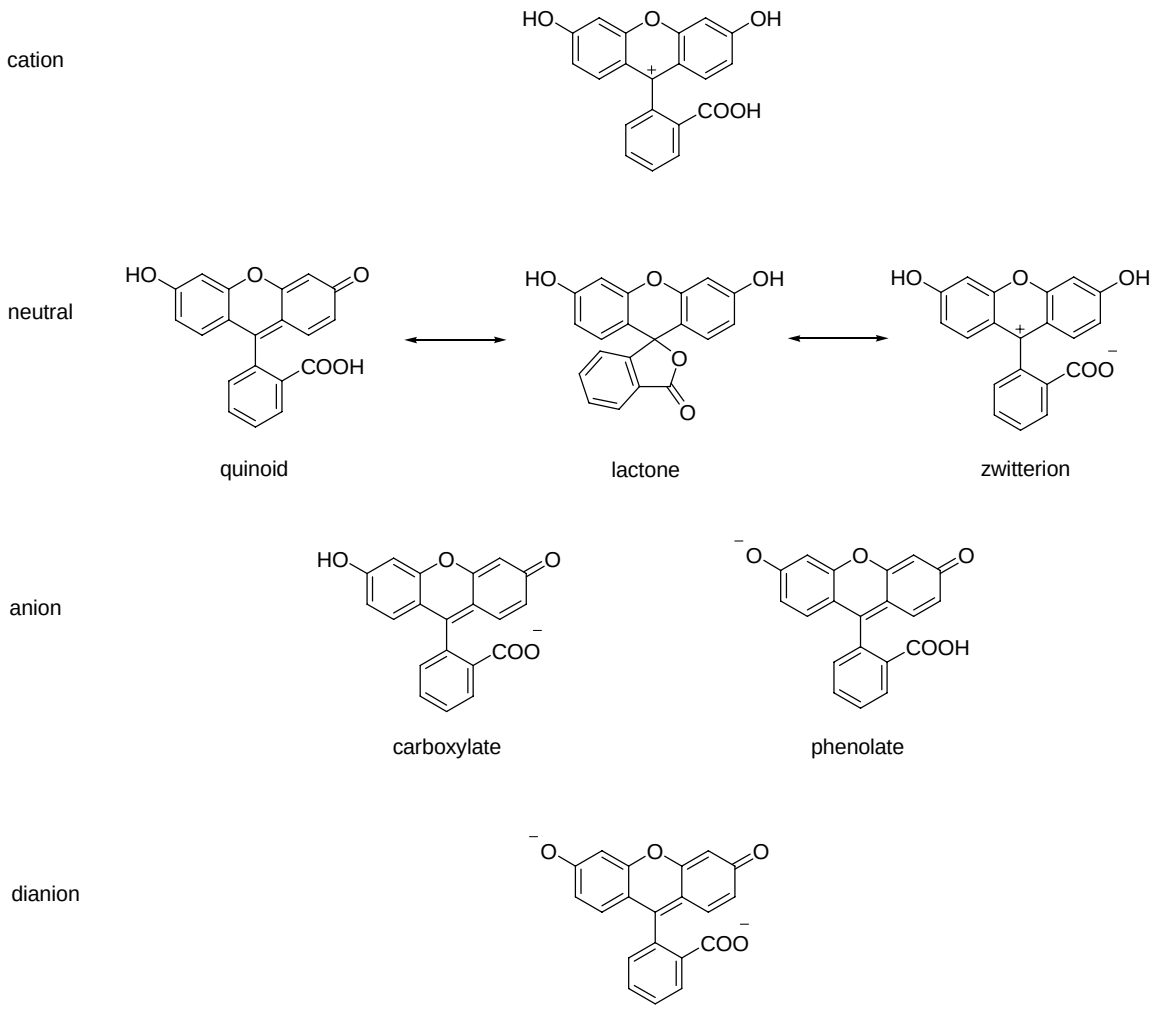


Figure 1.3. Fluorescein's four different ionic forms.

phenoxylate monoanion), between them the carboxylate monoanion is believed to be the major form.

The previous studies also show that the four different fluorescein forms would give different absorption spectra (Figure 1.4).[17-18] Under basic conditions (pH > 8), the dianion displays the greatest absorption at 490 nm and a shoulder at 475 nm. Under mildly acidic conditions (pH ~ 5.5), the monoanion form has relatively weaker absorptions at 472 nm and 453 nm. In highly acidic media (pH < 2), the cationic form shows a specific, low absorption at 437 nm. Under carefully controlled aqueous conditions at pH exactly 3.3, the neutral form shows the relatively weakest absorptions at 434 nm and a shoulder at 472 nm. In strongly acidic conditions, the cationic form is relatively not as highly conjugated which allows the compound to absorb at the shortest wavelength. In the neutral form, fluorescein can exist as a poorly-conjugated lactone and in a conjugated quinonoid form; therefore, the compound can absorb at two different wavelengths. The dianion form is highly conjugated, and thus shows the highest absorption at the longest wavelength. In the monoanion form, there are two isomers. One is the carboxylate form which is similar to the conjugated dianion and shows absorption at longer wavelengths. Another is the phenoxylate form which is similar to the neutral quinonoid form and absorbs at a relatively shorter wavelength (see Figure 1.4 for more quantitative data).

Another type of xanthene dye, 6-hydroxy-9-phenyl-fluorone (HPF),[16-17] was studied by Zanker and Peter in 1958.[16] They reported that HPF can occur in three forms: cationic, neutral and anionic (Figure 1.5). When the pH is < 1.5, HPF exists as a cation. Under strongly basic conditions (pH>10.2), HPF exists as an anion. Under mildly acidic conditions (pH~4.8), HPF mainly exist in the neutral form.

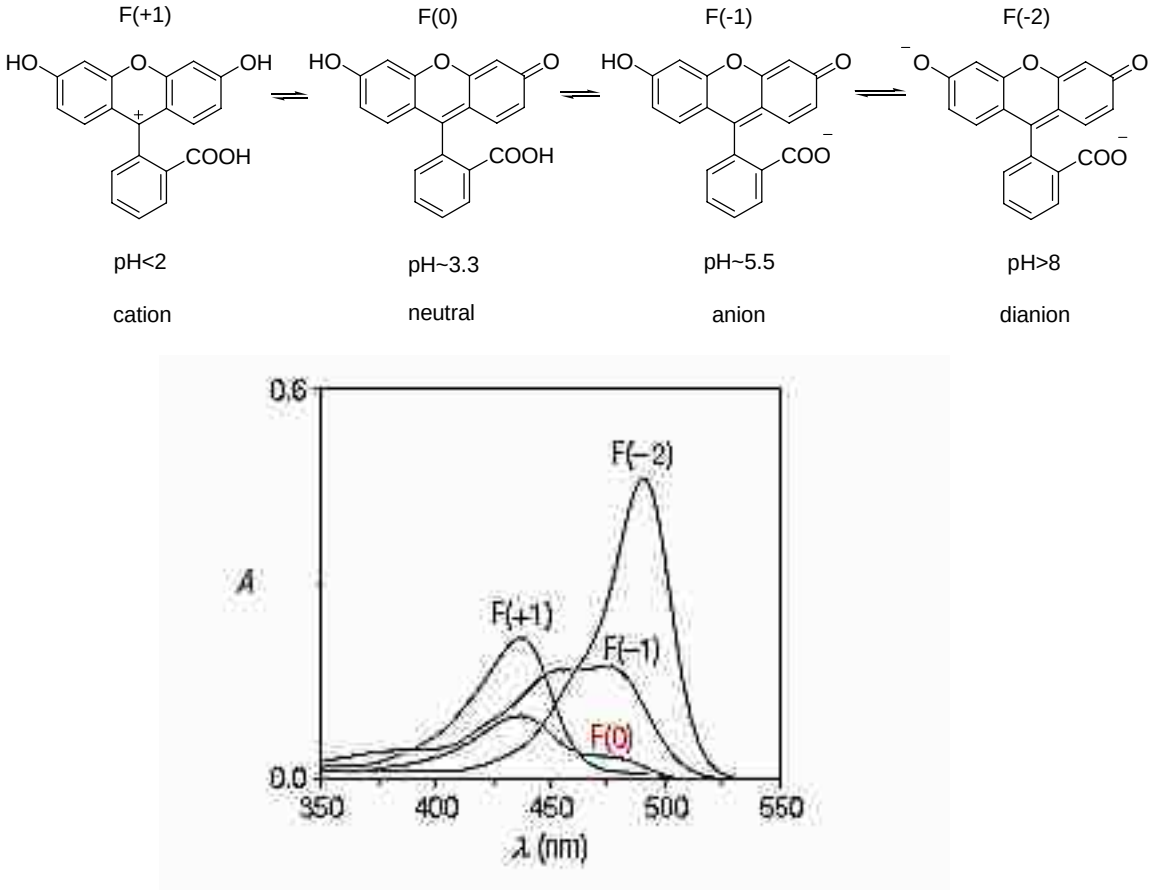


Figure 1.4. Absorption spectra of four different fluorescein ionic forms.[14]

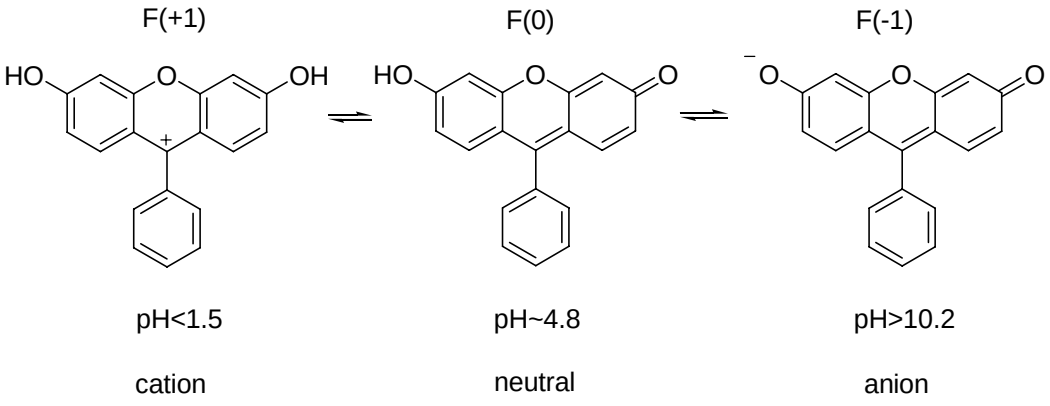


Figure 1.5. 6-Hydroxy-9-phenyl-fluorone's three different ionic forms.

1.2.2 Photochemical Properties of the Xanthene Dyes

Figure 1.6 shows the structures of fluorescein and its derivatives, eosin, rose bengal and erythrosine. The difference among them is that the hydrogen atoms on the xanthene ring, or the 9-phenyl ring of fluorescein, are replaced by halogen atoms and give other various fluorescein derivatives. Eosin is a fluorescein-based dye with bromines on the 2, 4, 5, and 7 positions, and rose bengal has iodines on the 2, 4, 5, 7, and chlorines on 3'-6' positions. Erythrosin is the parent compound of rose bengal with no chlorines on the 3'-6' positions. These halogenated derivatives show unique properties as compared to fluorescein. When exposed to light, the halogenated fluorescein compounds undergo intersystem crossing (ISC) to the triplet state. Thus the halogenated fluoresceins show a large absorbance but very low fluorescence, while fluorescein shows almost a unit fluorescence quantum yield. The photophysical properties[8] of them are shown below. (Table 1.1).

Table 1.1: Photoproperties of fluorescein and its halogenated derivatives [8]

Compound	λ max nm	ϕfl	ϕst
Fluorescein	491	0.93	0.03
Eosin	514	0.63	0.3
Erythrosin	525	0.08	0.6
Rose Bengal	548	0.08	0.76

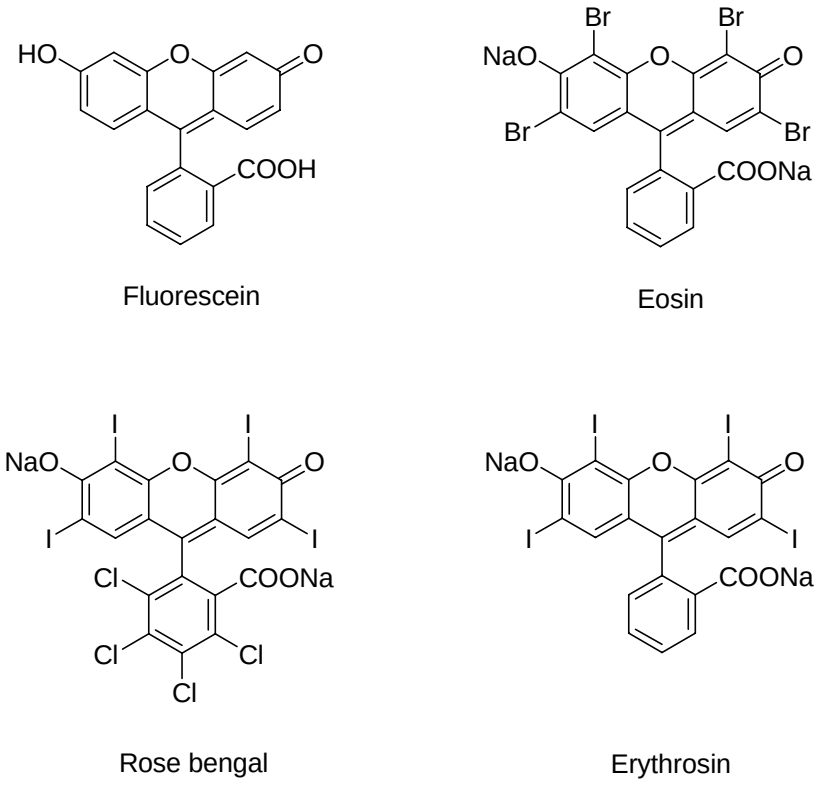
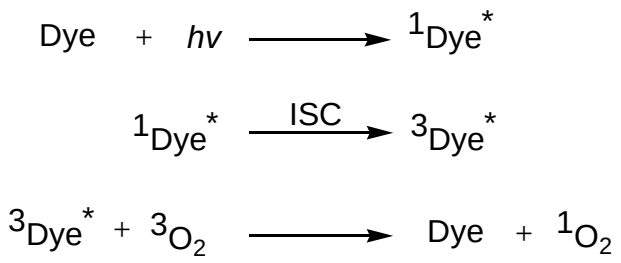


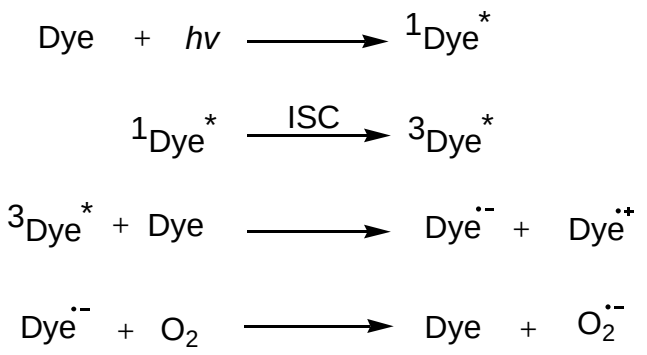
Figure 1.6. Fluorescein and its halogenated derivatives.

- **Quenching of dyes and formation of singlet oxygen and superoxide radical anion**

Because of the halogenated fluorescein dyes' excited triplet state, both singlet oxygen[20] and superoxide radical anion[21] can be formed under the combination of light and oxygen.[22] The ratio of superoxide radical anion to singlet oxygen, which are generated from the reaction, is believed to be around 1:3. Two different mechanisms are responsible for each of them (Scheme 1.1 and 1.2).



Scheme 1.1: Mechanism of formation of singlet oxgen.



Scheme 1.2: Mechanism of formation of superoxide radical anion.

Since Windaus et al.[23] who first reported proof that dyes can be used as a sensitizer in 1928, the halogenated fluoresceins have drawn a lot of attention and found enormous applications, e.g. Rose Bengal already was used as sensitizer to produce singlet oxygen during a photooxidation reaction.[22, 24-25]

The generation of superoxide radical anion from Rose Bengal was first reported

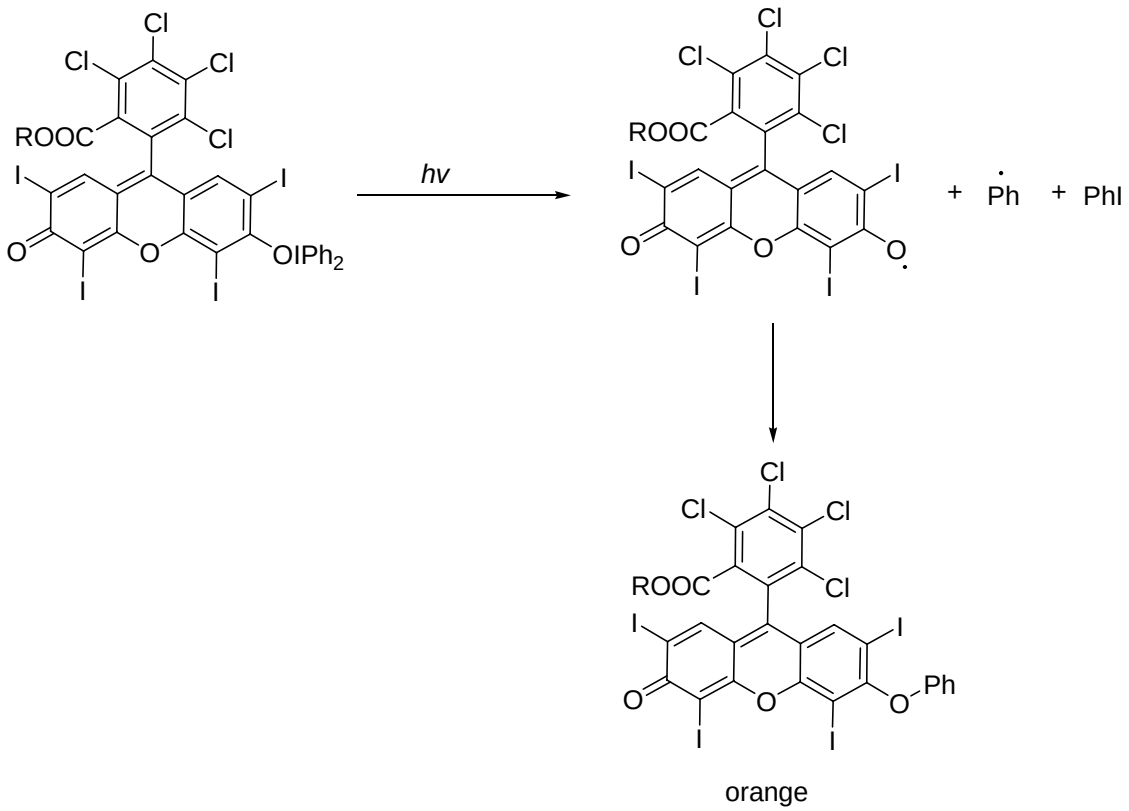
by Neckers et al.[26] However, Kochevar et al. found that the formation of superoxide radical anion in aqueous solution or a biological enviroment is limited to certain conditions, i.e. which needs the concentration O_2 should be low enough not to be quenched by triplet dye to form a single oxygen but high enough to react with the semireduced radical anion dye and form the superoxide radical anion.[27]

- **Radical formation from dye oxidation-photoinitiator**

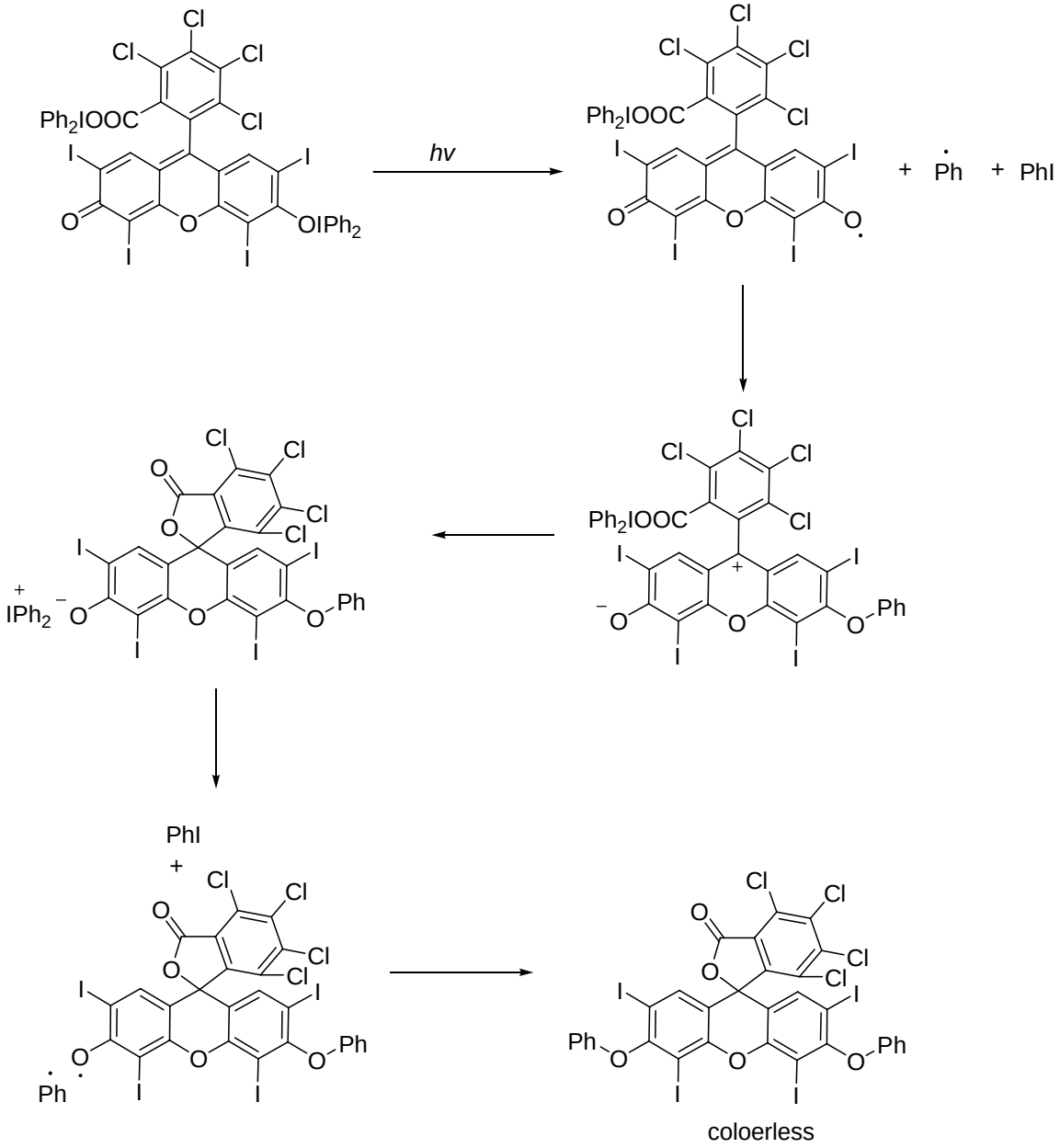
In 1988, Neckers et al. found that the Rose Bengal monoanion or dianion salt including counterions, such as iodonium (IPh_2^+) ion would undergo photobleaching and produce radicals as initiator for polymerization.[28] The reason is that the reduction potential of the counter ion is lower than the oxidation potential of the dye. Thus, a single electron would transfer from the higher potential xanthene dye to the lower potential counter ion. From the observations (color changes and product separation), Neckers et al. thought that dye photobleaching could occur in two ways. The monoanionic rose bengal salt forms a quinoid orange form (Scheme 1.3), and the dianionic rose bengal salt forms a lactone which is colorless (Scheme 1.4). The two different reactions are shown below.

- **Radical formation from dye reduction-photoinitiator**

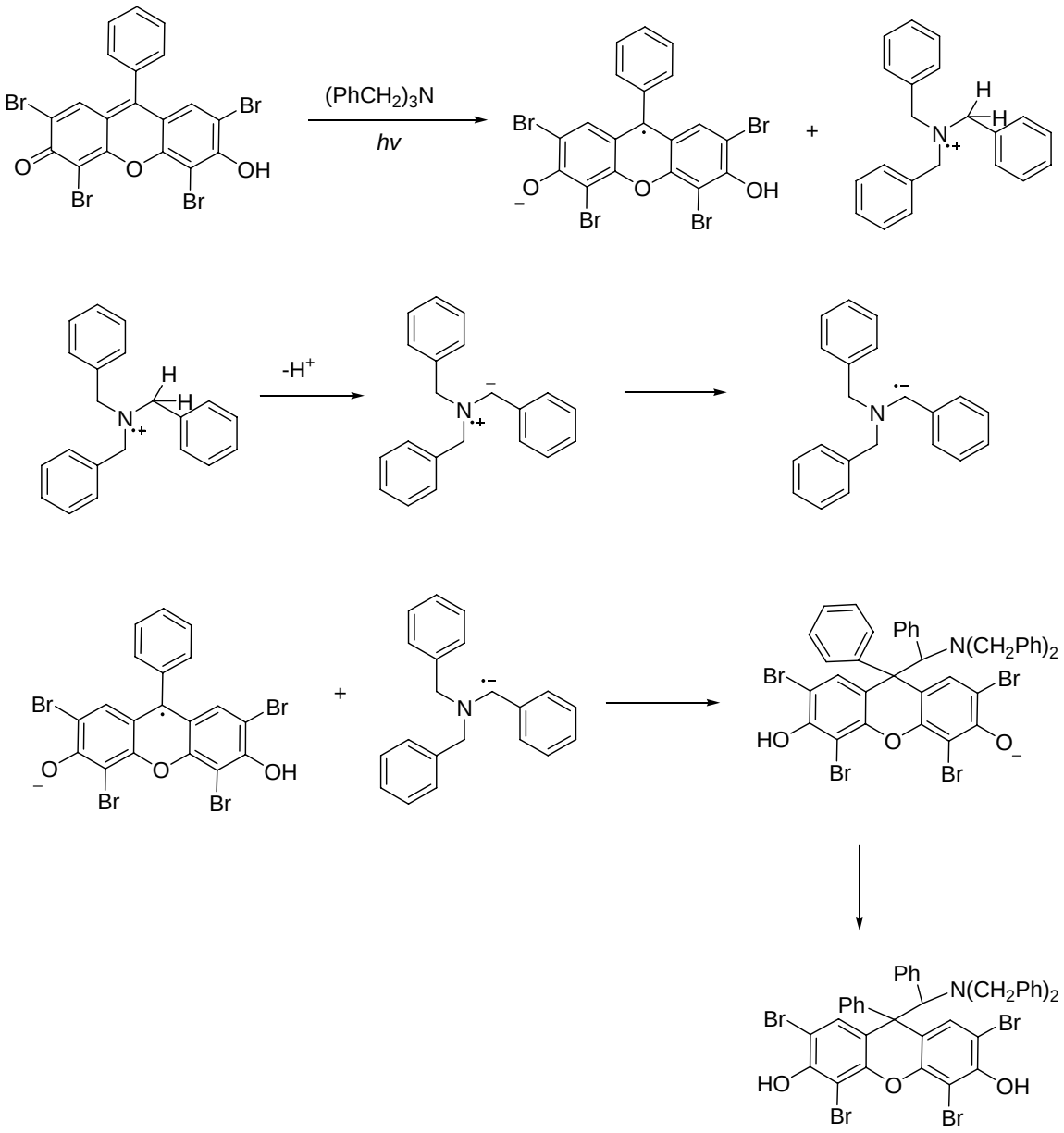
Xanthene dyes also can undergo photoreduction reactions.[29] The reason is also based on the relative electrochemical potential of dye and counter ion. If the electrochemical potential of the counter ion, e.g iodonium ion, is higher than the dye's electrochemical potential, the dye will go through a photooxidation reaction. If the electrochemical potential of the counter ion, e.g. tertiary amine, is lower than the dye's electrochemical potential, a photoreduction reaction will occur. For Rose Bengal, Davidson, Tretheway, and Neckers found that it can be bleached with light and a reducing reagent (tertiary amine or hydride).[29-30] In 1986, Phillips et al.[31] found that



Scheme 1.3: Photobleaching of monoanionic rose bengal iodonium salt.



Scheme 1.4: Photobleaching of dianionic rose bengal iodonium salt.



Scheme 1.5: Photobleaching of decarboxylated eosin under the light with tribenzylamine.

2,4,5,7-tetrabromo-6-hydroxyl-9-phenyl-fluorone, another xanthene-based dye, could also be converted to a colorless form (triarylmethane) when it was irradiated under degassed conditions (in the presence of tribenzylamine). The reaction is shown in Scheme 1.5.

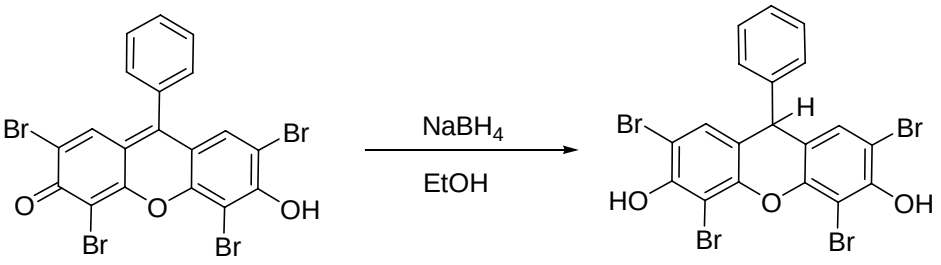
- **Chemical reduction of xanthene derivatives to leuco dye-probes for ROS**

In protic solvents, xanthene dyes mainly exist in the quinonoid form. This makes carbon-9 more electropositive. When xanthene dyes are subjected to reducing reagents, such as $NaBH_4$, they are reduced to the colorless *leuco* form (Scheme 1.6).[29] Normally the *leuco* form is not very stable and is readily oxidized to the starting xanthene dye. Based on this property, the *leuco* dye can be used to detect reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\cdot}OH$) and superoxide radical anion ($O_2^{\cdot-}$).

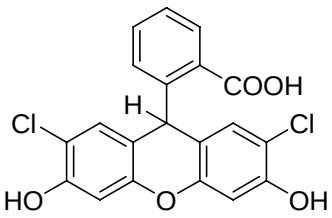
2',7'-Dichlorodihydrofluorescein (DCFH) was first used by Keston et al. in the detection of the hydroperoxide.[32-34] Since then, many dihydroxanthene dyes (Figure 1.7) were invented and used in the detection of some ROS species, e.g. dihydrorhodamine 123 (DHR 123) was invented for the detection of superoxide,[34] dihydrorhodamine 6G (DHR-6G) was designed to detect smoke oxidants[35] and 2,3,4,5,6-pentafluoro-dihydro-tetramethylrosamine (RedoxSensor) was prepared as a fluorogenic indicator for oxidative activity.[36] In the review by Soh, fluorescent probes for the detection of ROS were extensively discussed.[37]

1.3 Synthesis of Xanthene Dyes

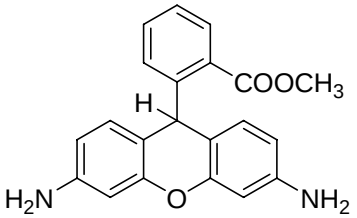
The most common method used to synthesize the xanthene type of dye was discovered by Baeyer in 1871 (Scheme 1.7).[5-6] Normally at high temperature, resorcinol or *m*-aminophenol condense with phthalic anhydride in the presence of an acid catalyst



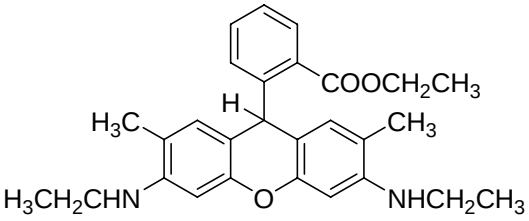
Scheme 1.6: Chemical reduction of decarboxylate eosin with $NaBH_4$.



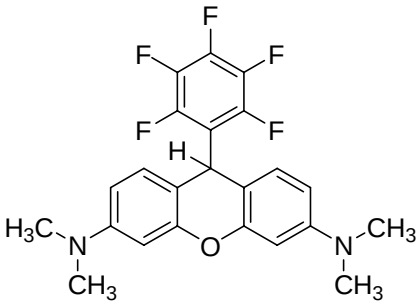
DCFH



DHR 123



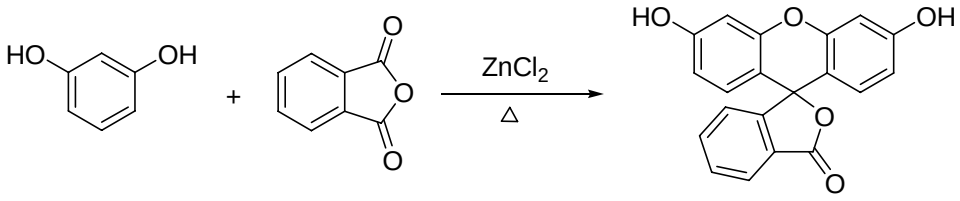
DHR-6G



RedoxSensor

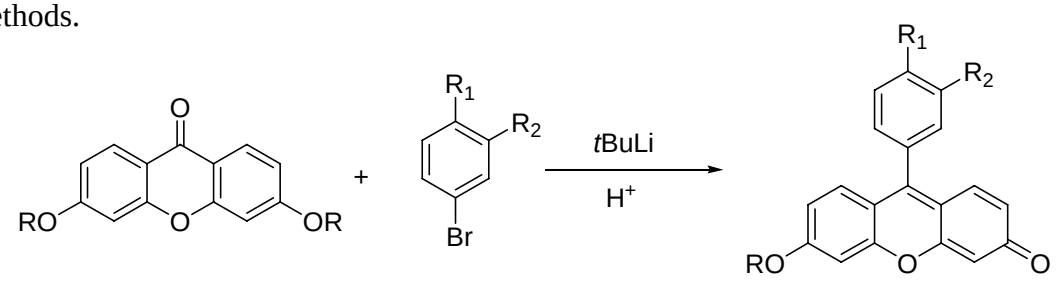
Figure 1.7: Some common xanthene-based fluorescent probes for the detection of ROS.

($ZnCl_2$, H_2SO_4, CH_3SO_3H etc.) to form the desired xanthene dye. This method is straightforward and convenient, but sometimes necessitates troublesome purifications.



Scheme 1.7: Traditional method for synthesis of xanthene dye.

In 2002, the Lawrence group[38] reported using xanthone and a lithium reagent as the precursor to synthesize a xanthene dye (Scheme 1.8). More recently, the Nagano group[39] and the Peterson group[40] have used the Grignard reagent and a xanthone to synthesize two fluorescein analogs Tokyo green and Pennsylvania Green (Figure 1.8). The xanthone reactions are generally more efficient and regioselective than the traditional methods.

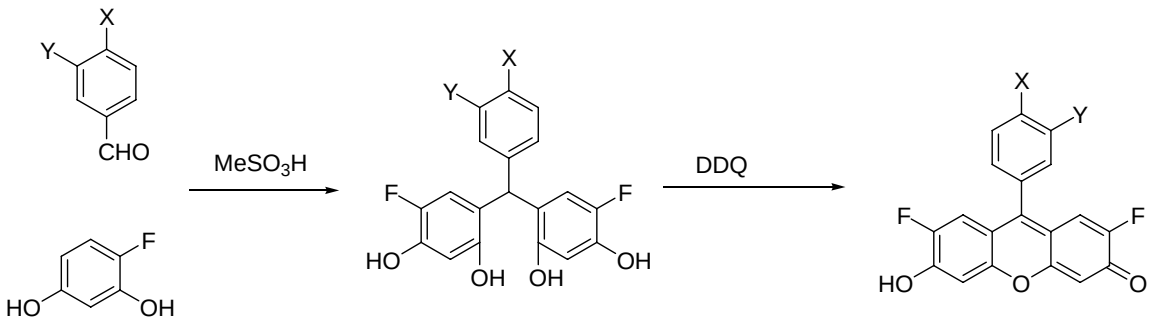


Scheme 1.8: Novel synthesis of xanthene dyes using xanthone as a precursor.

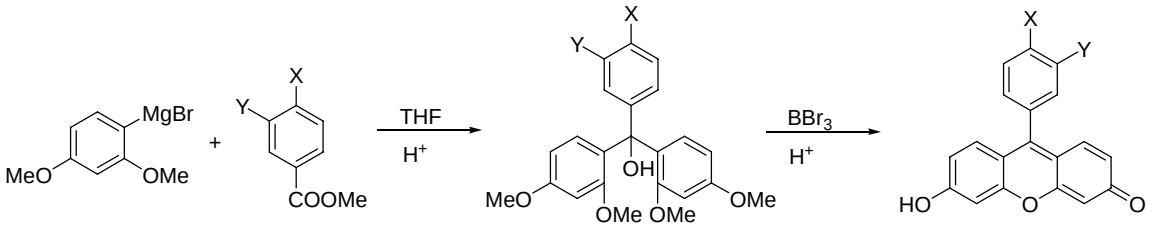
For a specific xanthene, 9-phenyl substituted fluorone, an efficient two-step synthesis was developed by the Vranken group (Scheme 1.9).[41] The first step of the synthesis involved the condensation of an aryl aldehyde with a 4-substitued resorcinol in diluted methanesulfonic acid to form a triarylmethane, followed by cyclization using the oxidant DDQ to give the desired dye. This method is pretty mild and which could give a light to synthesize more xanthene-type dyes.

Tokyo Green Pennsylvania Green

Figure 1.8: Structures of Tokyo Green and Pennsylvania Green.



Scheme 1.9: A convenient two-step synthesis of xanthene dye under mild conditions.



Scheme 1.10: Convenient synthesis of xanthene dye through carbinol as an intermediate.

During the course of developing a new fluorescent sensor for the detection of biomolecules, our group[42-43] also invented a convenient two-step synthesis of 9-arylsubstituted fluorones (Scheme 1.10). In the first step of the synthesis, the Grignard reagent of protected resorcinol readily reacted with a substituted phenyl ester to form a triarylmethane alcohol (triphenylcarbinol), which was then subjected to deprotection with BBr_3. A smooth cyclization occurred.

1.4 Application of Some Xanthene Dyes

The most common uses of xanthene-based dyes have been to dye textiles and cloth, since they first appeared in the 19th century. Rhodamine B and rhodamine 6G have strong fluorescence. They are still the most popular dyes for dyeing cloth.[1]

As stated above, most xanthene dyes exist in several different ionic forms in aqueous solution; e.g. fluorescein can exist as four different ionic forms (cationic form, neutral form, monoanionic form and dianionic form).[14-19] Under physiological conditions (pH 7.4), fluorescein mainly exists as the dianionic form which grants it a high molar absorptivity and large quantum yield (0.92, pH > 8).[44] Also the dianionic form is easily dissolved in water. This renders fluorescein and its derivatives useful for studies in biological media. They can be used as fluorescent probes to track the locations of proteins in the living cell.[45] They also can be used to detect certain biological molecules. Recently, our group successfully applied xanthene-based dyes as fluorescent sensors for homocysteine and cysteine.[46-49] Moreover, we have developed other xanthene-based sensors for the colorimetric or fluorimetric detection of sugars.[50-53]

Another very important use of xanthene dyes is as laser components. The rhodamines are among the most popular organic-dye lasers. Sorokin et al. first applied rhodmine 6G in a flashlamp-pumped dye laser.[54] In 1970, Peterson et al. used rhodamine 6G in the first continuous-wave dye laser.[55] Rhodamine B is used as a photosensitizer[56]

or as a quantum counter.[57] It can be used as a dye laser too.[58] Fluorescein and its derivatives also play important roles in tunable lasers.[58]

1.5 References

1 Neckers, D. C. *J. Chem. Edu*. **1987**, *64(8)*, 649-656.

2 Shi, J. M.; Zhang, X. P.; Neckers, D. C. *J. Org. Chem.* **1992**, *57*, 4418-4421.

3 Shi, J. M.; Zhang, X. P.; Neckers, D. C. *Tetrahedron Lett.* **1993**, *34*, 6013-6016.

4 Tanabe, T.; Torres-Filho, A.; Neckers, D. C. *J. Poly. Sci. Part A: Poly. Chem.* **1995**, *33*, 1691-1703.

5 von Baeyer, A., *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 555-558.

6 von Baeyer, A. *Chem. Ber.* **1871**, *5,* 255.

7 von Hoffmann, A. *W. Ber.* **1875**, *8*, 55.

8 Neckers, D. C. *J. Photochem. Photobio. A, Chem.* **1989**, *47*, 1-29.

9 Gurr. E., *Synthetic dyes in biology, medicine and chemistry,* Academic Press **1971**, London, England.

10 Zulkowsky, C. *Monatsh. Chem.* **1884**, *5*, 221-227.

11 Cohn, G. *Chem. Ber.* **1891**, *24*, 2064.

12 a. Zollinger, H. *Colour Chemistry: Syntheses, Properties, and Applications of Organic Dyes and Pigments, 2nd rev. ed.;* **1991,** VCH: Weinheim, b. Gordon, P. F.; Gregory, P. *Organic Chemistry in Colour*; **1983,** Springer-Verlag: New York, c. Abrahart, E. N. *Dyes and Their Intermediates, 2nd ed*.; **1977**, Edward Arnold: London.

13 Holmes, W. C. *lnd. Eng. Chem.* **1924**, *16*, 35.

14 Margulies, D.; Melman, G.; Shanzer, A. *Nat. Mater.* **2005**, *4*, 768-771.

15 Margulies, D.; Melman, G.; Shanzer, A. *J. Am. Chem. Soc.* **2006**, *128*, 4865-4871.

16 Zanker, V.; Peter, W. *Chem. Ber.* **1958**, *91*, 572-580.

17 Martin, M. M.; Lindqvist, L. *J. Lumin.* **1975**, *10*, 381-390.

18 Sjoback, R.; Nygren, J.; Kubista, M. *Spectrochim. Acta A* **1995**, *51,* L7-L21.

19 Mchedlov-Petrossyan, N. O.; Tychina, O. N.; Berezhnaya, T. A.; Alekseeva, V. I.; Savvina, L. P. *Dyes and Pigments*, **1999**, *43*, 33-46.

20 Lamberts, J. J. M.; Neckers, D. C. *Tetrahedron*, **1985**, *41*, 2183-2190.

21 Lee, P. C. C.; Rodgers, M. A. *J. Photochem. Photobiol.* **1987**, *45*, 79.

22 Neckers, D. C.; Valdes-Aguilera, O. M. *Adv. Photochem.* **1993**, *18*, 315.

23 Windaus, A,; Brunken, J. *Liebigs Ann. Chem.* **1928**, *460*, 225-235

24 Kautsky, H.; Bruijn, H. *Naturwissenschaften*, **1931**, *19*, 1043

25 Foote, C. S.; Wexler, S. *J. Am. Chem. Soc*. **1964**, *86*, 3876

26 Srinivasan, V. S.; Podolski, D.; Westrick, N. J.; Neckers, D. C. *J. Am. Chem. Soc.* **1978**, *100*, 6513-6515.

27 Lambert, C. R.; Kochevar, I. E. *J. Am. Chem. Soc.* **1996**, *118*, 3297-3298.

28 Linden, M. S.; Neckers, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 1257-1260.

29 Zakrzewski, A.; Neckers, D. C. *Tetrahedron*, **1987**, *43*, 4507-4512.

30 Davidson, R. S.; Tretheway, K. R. *J. Chem. Soc. Chem. Comm.* **1975**, *16*, 674-675.

31 Phillips, K.; Read, G. *J. Chem. Soc., Perkin Transactions 1*. **1986**, *4*, 671-673.

32 Keston, A. S.; Brandt, R. B. *Anal. Biochem*. **1965**, *11*, 1-5.

33 Black, M. J.; Brandt, R. B. *Anal. Biochem.* **1974**, *58*, 246-254.

34 Henderson, L. M.; Chappell, J. B. *Eur. J. Biochem.* **1993**, *217*, 973-980.

35 Ou, B.; Huang, D. *Anal. Chem.* **2006**, *78*, 3097-3103.

36 Chen, C.; Gee, K. *Free Radical Biol. Med.* **2000**, *28*, 1266-1278.

37 Soh, N. *Anal. Bioanal. Chem.* **2006**, *386*, 532-543.

38 Chen, C. C.; Yeh, R.H.; Lawrence, D. D. *J. Am. Chem. Soc.* **2002**, *124*, 3840-3841.

39 Urano, Y.; Kamiya, M.; Kanda, K.; Ueno, T.; Hirose, K.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 4888-4894.

40 Mottram, L. F.; Boonyarattannkalin, S.; Kovel, R. E.; Peterson, B. R. *Org. Lett.* **2006**, *8(4)*, 581-584.

41 Bacci, P. J.; Kearney, A.M; Van-Vranken, D. L. *J. Org. Chem.* **2005**, *70*, 9051-9053.

42 Yang, Y.; Escobedo, J. O.; Wong, A.; Schowalter, C. M.; Touchy, M. C.; Jiao, L.; Crowe, W. E.; Fronczek, F. R.; Strongin, R. M. *J. Org. Chem.* **2005**; *70*, 6907-6912.

43 Yang, Y.; Lowry, M.; Schowalter, C. M.; Fakayode, S.O., Escobedo, J. O.; Xu, X.; Zhang, H.; Jensen, T. J.; Fronczek, F. R.; Warner, I.M.; Strongin, R. M. *J. Am. Chem. Soc.* **2006**, *128*, 14081-14092.

44 Guilbault, G. G. *Practical Fluorescence*; Guilbault, G. G., Ed.;Marcel Dekker Inc.: New York, **1990**.

45 *Fluorescent and Luminescent Probes for Biological Activity*; Mason, W.T., Ed.; Academic Press; San Diego, **1999**.

46 Wang, W.; Rusin, O.; Xu, X.; Kim, K. K.; Escobedo, J. O.; Fakayode, S. O.; Fletcher, K. A.; Lowry, M.; Schowalter, C. M.; Lawrence, C. M.; Fronczek, F. R.; Warner, I. M.; Strongin, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 15949-15958.

47 Wang, W.; Escobedo, J. O.; Lawrence, C. M.; Strongin, R. M. *J. Am. Chem. Soc.* **2004**, *126*, 3400-3401.

48 Rusin, O.; Luce, N.; Agbaria, R. A.; Escobedo, J. O.; Jiang, S.; Warner, I. M.; Dawan, F. B.; Lian, K.; Strongin, R. M. *J. Am. Chem. Soc.* **2004**, *126*, 438-439.

49 Escobedo, J. O.; Wang, W.; Strongin, R. M. *Nat. Protocols*, **2007**, *1*, 1-4.

50 Jiang, S.; Escobedo, J. O.; Kim, K. K.; Alpturk, O.; Samoei, G. K.; Fakayode, S. O.; Warner, I. M.; Rusin, O.; Strongin, R. M. *J. Am. Chem. Soc.* **2006**, *128*, 12221-12228.

51 Yang, Y; Lewis, P. T.; Escobedo, J. O.; St Luce, N. N.; Treleaven, W. D.; Cook, R. L.; Strongin, R. M. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1282-1291.

52 He, M.; Johnson, R. J.; Escobedo, J. O.; Beck, P. A.; Kim, K. K., St Luce, N. N.; Davis, C. J.; Lewis, P. T.; Fronczek, F. R.; Melancon, B. J.; Mrse, A. A.; Treleaven, W. D.; Strongin, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 5000-5009.

53 Kim, K. K.; Escobedo, J. O.; St Luce, N. N.; Rusin, O.; Wong, D.; Strongin, R. M. *Org. Lett.* **2003**, *5*, 5007-5010.

54 Sorokin, P. P.; Lankard, J. R.; Moruzzi, V. L.; Hammond, E. C. *J. Chem. Phys.* **1968**, *48*, 4726.

55 Peterson, O. G.; Tuccio, S. A.; Snavely, B. B. *Appl. Phys. Lett.* **1970**, *17*, 245.

56 Kramer, H. E. A.; Mante, A. *Photochem. Photobiol*. **1972**,*15*,25.

57 Demas, J. M.; Crosby, G. A. *J. Phys. Chem.* **1971**, *75*, 911.

58 *Dye Lasers*; Schafer, F. P., Ed.; Springer-Verlag: Berlin, **1973**

CHAPTER 2

COLORIMETRIC AND FLUOROMETRIC DETECTION OF CYSTEINE AND HOMOCYSTEINE *

2.1 Background

Biological thiols are of great interest to public health.[1] Some common biological thiols are shown below (Figure 2.1).

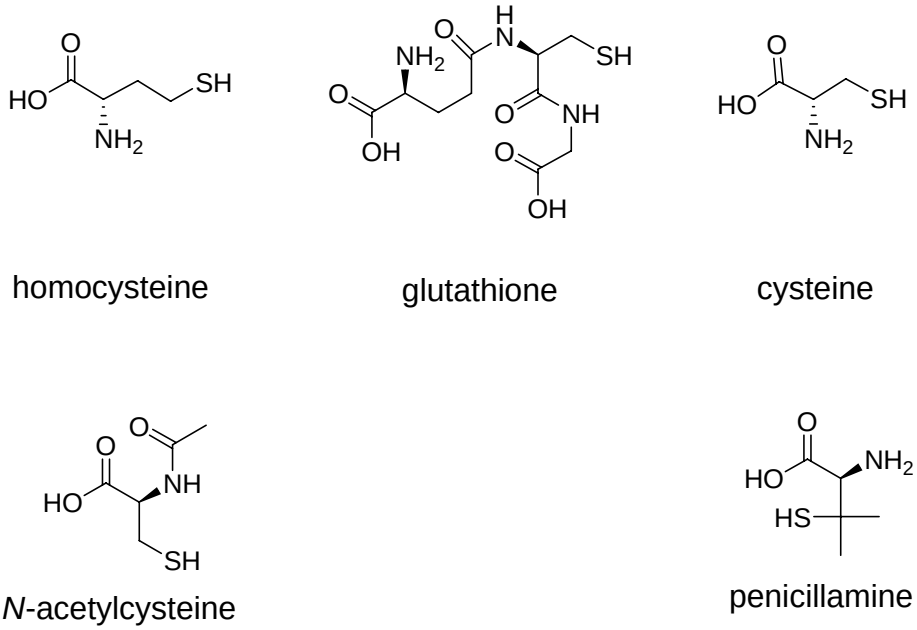


Figure 2.1: Some common biological thiols.

2.1.1 Homocysteine

Homocysteine (Hcy) is a sulfur containing amino acid that is an intermediate in the metabolism of methionine to cysteine (Figure 2.2). Methionine is an essential amino acid and is the only source of homocysteine.[2] If the pathway to ether cysteine or methionine is blocked, the concentration of Hcy will rise and probably result in hyperhomocysteinemia. Hyperhomocysteinemia is the condition where plasma Hcy

* Parts of this chapter have appeared in *Journal of the American Chemical Society*.

concentration exceeds 12-15 μM.[1]

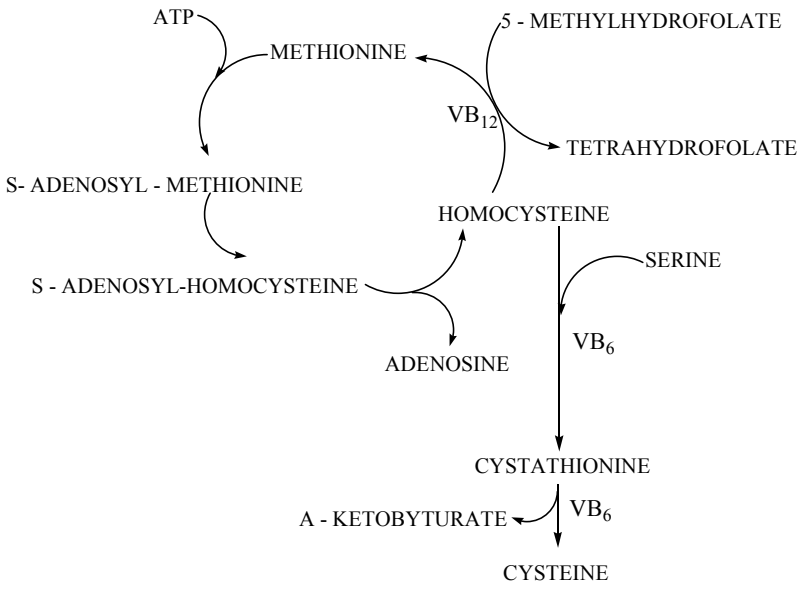


Figure 2.2: Methionine metabolism.

It has been reported that some diseases are related to hyperhomocysteinemia, such as cardiovascular,[1] Alzheimer's disease[1] and neutral tube defects.[3] More recently, osteoporosis[4] and complications during pregnancy,[5] were also reported to be associated with elevated levels of homocysteine in blood plasma, though the reasons are still unclear. It is still unknown if high level Hcy causes diseases or is just a consequence of disease.

2.1.2 Cysteine

Cysteine (Cys) is a nonessential amino acid which can be made by the human body under normal physiologic conditions from essential amino acid. Cysteine is also one of the limited amino acids that contain sulfur. Most cysteine normally appears in proteins, e.g. beta-keratin, one of the main proteins of skin, nails, and hair, while small amounts of free cysteine can be found in body fluids and in plants.

Cysteine is very important to the human body. It is a component of the antioxidant glutathione, which is known for neutralizing free radicals occurred in the

body. In addition, people have found that cysteine is useful to stimulate the healing of erosive gastritis induced by nonsteroidal anti-inflammatory drugs, e.g. aspirin and ibuprofen, and prevent bleeding induced by gastritis.[6] In 1991, Droge et al. reported that cysteine plays a very important role in the immune system.[7] It is also founded that people suffered from HIV have low levels of cysteine and glutathione, the reason could be that a decrease of Cys or glutathione would either lead to, or suffered from, immune system problem related to HIV.[8,9,10]

Like other thiols, cysteine can also be easily oxidized to cystine via disulfide bond formation. The poor water solubility of the cystine reduces its excretion. It can accumulate either in urine, leading to cystinuria[11] or in various organs of the body, forming stones, such as kidney stones.[12]

It has already been reported that the low levels of cysteine are associated with slowed growth, hair depigmentation, edema, lethargy, liver damage, muscle and fat loss, skin lesions and weakness.[13] However, on the other hand, excess cysteine in the human brain has also been associated with significant problems related to neurotoxicity.[14]

2.2 General Thiol Detection Methods

Due to the importance of cysteine and homocysteine, there is a significant need for their detection. Various detection methods have been developed, which mainly include chromatographic separations, immuno- and enzymatic assays, electrochemistry, mass spectrometrometry, etc. Normally, these methods need to be used in combination. For example, HPLC normally needs to be combined with mass spectrometrometry. Electrochemical detection is also a very common detection method. However, it is unselective and oxidizable impurities may result in low selectivity and precision, etc.[15]

For immuno- and enzymatic assays, the enzymes used are normally very expensive, also they have short shelf lives.

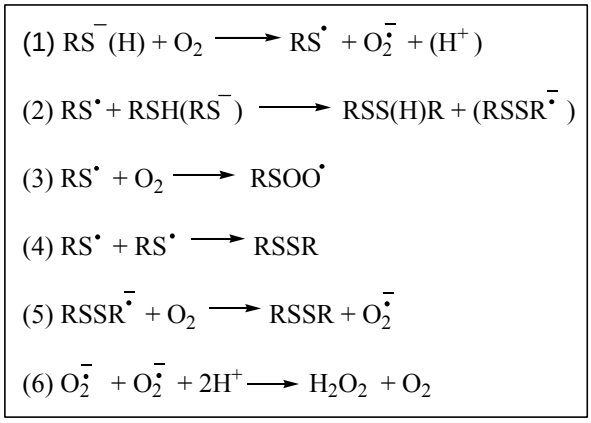


Figure 2.3: Complex chemistry of biological thiols.

Additional challenges include the facts that: 1) thiols are readily prone to oxidation (Figure 2.3); 2) biological thiols have very similar structures; 3) biological thiols are normally colorless and nonfluorescent, which make derivatization a need. Some known derivatization reagents are shown in Figure 2.4.

However, excess derivatization agents must often be removed from reaction mixtures, which can make the detection procedure more complicated. Some derivatives are prone to unwanted further reactions, such as when using 4-fluoro-7-nitrobenzofurazan (NBD-F) to detect penicillamine, an unexpected S-N migration occurred (Figure 2.5).[16]

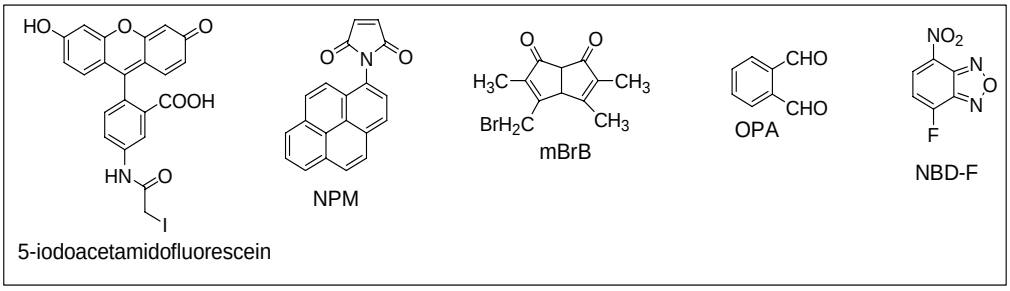


Figure 2.4: Some common known derivatization reagents.

Other thiol-chromophore/fluorophore derivatives also are sensitive to light and hydrolysis, such as O-phthalaldehyde (OPA) which is only stable in the dark.[17] Some derivatization agents themselves are prone to instability, such as monobromobimane (mBrB) .[18]

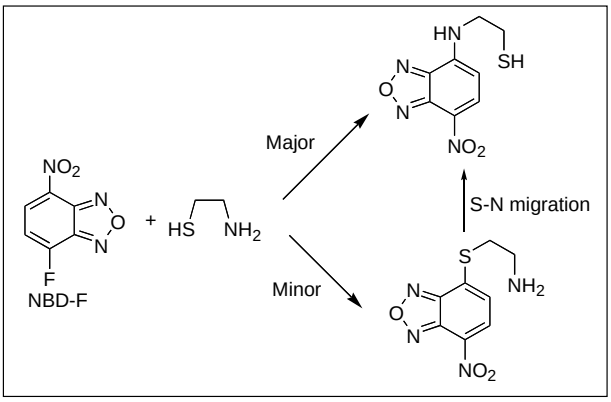
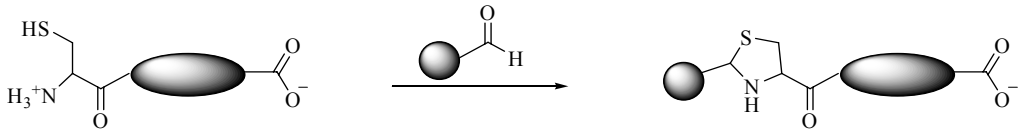


Figure 2.5: S-N migrations and competition in NBD-F reactions.

2.3 Formation of *N*-thiazolidines

It is well known that Cys can react with aldehyde,[19] and that *N*-terminal cysteines can selectively react with aldehydes and form thiazolidines.[20] The product is also stable



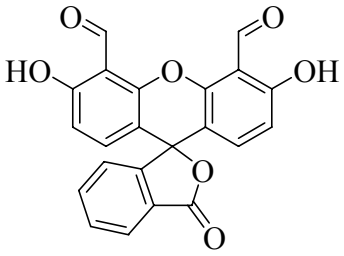
Scheme 2.1: Reaction of cysteine with aldehydes to form thiazolidines.

at slightly acidic aqueous conditions, while *N*-termianl oxazolidines, resulting from the reaction between serine and an aldehyde, are 10^4 times less stable than *N*-terminal thiazolidines.[21] Thiazolidine formation has been used to label and immobilize proteins and peptides[22] (Scheme 2.1).

Based on our group's former research experience with sugar detection via a UV-Vis technique,[23] we reasoned that the reaction of an aldehyde with Cys or Hcy would

promote colorimetric and fluorimetric responses, which also can be easily monitored by UV-Vis or fluorescence techniques. Thus, a highly selective probe, fluorescein dialdehyde (Figure 2.6), was studied. It showed selective colorimetric and fluorometric detection in preliminary research for Hcy and Cys.[24] More comprehensive results are presented below.

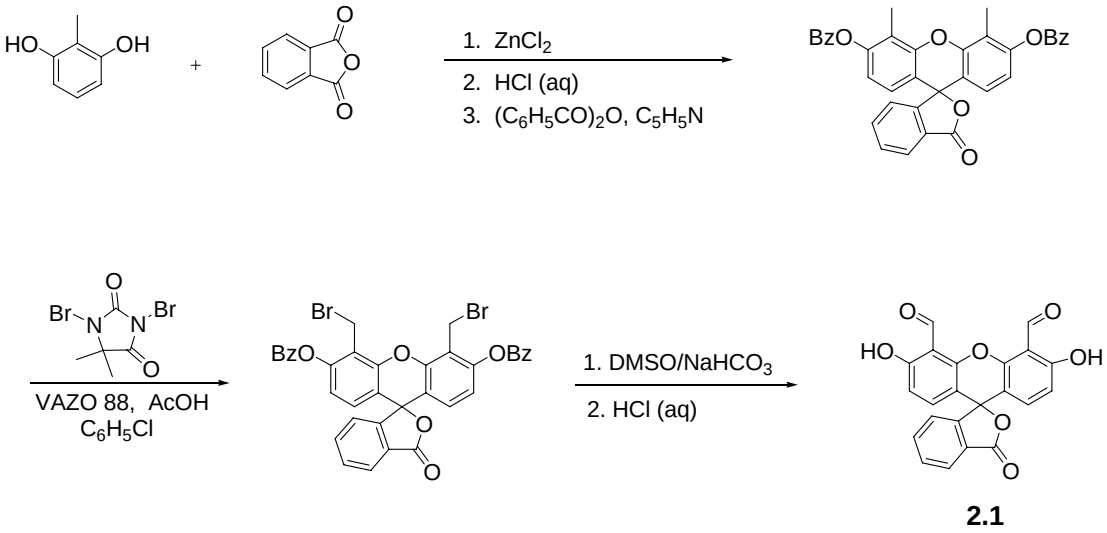
2.4 Multistep Synthesis of Fluorescein Dialdehyde



2.1

Figure 2.6: Fluorescein dialdehyde.

The fluorescein dialdehyde (Compound **2.1** in Figure 2.6) we used to discriminate Cys and Hcy from other amino acids and thiols was derived from the literature.[25] It was in fact an intermediate in a synthesis of a fluorescent sensor for zinc ion. The preparation



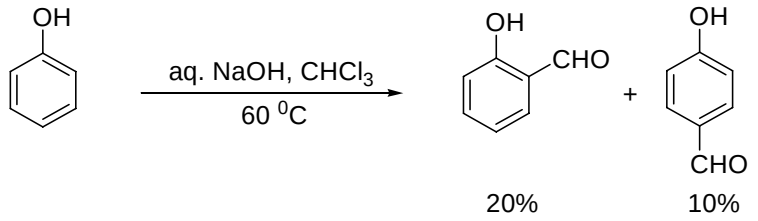
2.1

Scheme 2.2: Multistep synthesis of compound **2.1**. [25]

is a multi-step synthesis (Scheme 2.2) starting from a condensation of 2-methyl resorcinol with phthalic anhydride at high temperature (from 150°C to 230°C) with the aid of anhydrous $ZnCl_2$. This is similar to the traditional fluorescein synthesis invented by von Baeyer.[26] The crude 4,5-dimethyl fluorescein was protected as a benzoate in order to convert it to a less polar compound for easier purification by recrystalliztion. A facile radical bromination reaction produced the dibromo fluorescein in high yield, but a long reaction time is required, i.e. the reaction was conducted over three days. After purification by recrystallization in toluene and EtOH, the dibromo fluorescein was converted to fluorescein dialdehyde by a Kornblum aldehyde synthesis[27] through oxidation with DMSO in the presence of $NaHCO_3$. In order to obtain ~40% yield, it was required to use rigorously dried DMSO distilled over CaH_2 followed by storage over molecular sieves. It was pointed out that undistilled DMSO would cut the yield by more than 50%.[25] During the period of preparation of the fluorescein dialdehyde, I found that the synthesis was time consuming, tedious and used a lot of reagents. I hypothesized that choosing a more convenient synthesis method for preparing fluorescein-based aldehydes would be very useful.

2.5 Reimer-Tiemann Reaction and Its Applications

It is known that there are several methods could be used to directly introduce an aldehyde group to an aromatic compound or a heteroaromatic compound, such as the



Scheme 2.3: Reimer-Tiemann reaction.

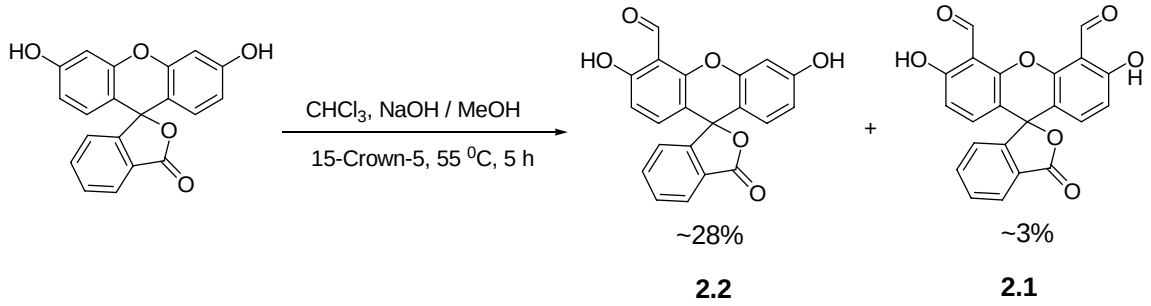
Gattermann reaction,[28] Gattermann-Koch reaction,[29] Vilsmeier-Haack reaction,[30] Duff reaction,[31] and Reimer-Tiemann reactions.[32-35] However, compared to the Reimer-Tiemann reaction, the other reactions have their certain "drawbacks" and Reimer-Tiemann reaction has its own special advantages, though normally the Reimer-Tiemann reaction gives a low yield product. For example, among the other reactions, some formylating agents are very toxic, e.g., the HCN used in Gattermann reaction, the CO used in the Gattermann-Koch reaction, and the phosphrous compounds required in Vilsmeier- Haack reaction. Additionally, some of these formylating reagents (e.g CO) are gaseous and which make the reaction relatively more difficult to perform. The Reimer-Tiemann reaction, in contrast, is conducted under basic conditions and doesn't necessitate anhydrous conditions. Compared with other reactions, the Reimer-Tiemann reaction's advantages are: 1) the reaction is easy to handle and control, 2) the chemicals used in the reaction are cheap, and 3) the reagents are non-toxic or low toxic.

In 1876, two young German chemists, Karl Reimer and Ferdinand Tiemann found that phenol can be directly formylated when it was treated with strong base (such as NaOH) and chloroform.[32-35] Thus this kind of direct formylation of organic compounds is named (Scheme 2.3).

However the Reimer-Tiemann reaction is divided into a normal and an abnormal transformation depending on the reaction products. A normal Reimer-Tiemann reaction is the one in which the active aromatic (such as phenol and some heterocylic compounds, e.g. pyrroles and indoles) are treated with chloroform and strong base and yields one or more aldehydes. The abnormal Reimer-Tiemann reaction products can be further divided into cyclohexadienones and ring-expansion products.[36] Here, we are mainly concerned with the application of the normal Reimer-Tiemann reaction in formylation of fluorescein

and naphthofluorescein.

2.6 Results and Discussion



Scheme 2.4: One step synthesis of fluorescein mono-aldehyde (compound **2.2**) and fluorescein di-aldehyde (compound **2.1**).

- **Synthesis of fluroescein-based aldehyde with Reimer-Tiemann reaction**

Under normal Reimer-Tiemann reaction conditions (Scheme 2.4), commercially availabe fluorescein treated with concentrated NaOH and $CHCl_3$ at 55 °C with the aid of a phase transfer catalyst (15-Crown-5 ether) for 5h to afford fluorescein mono-aldehyde (compound **2.2**) in a single step in a 28.3% yield, and a small amount (3.4%) of fluorescein dialdehyde (compound **2.1**). The single-crystal X-ray structures analysis confirmed the structure assignment. From the single-crystal structure, we can see that both fluorescein-based derivatives exist as lactones (Figure 2.7).

Applying the same reaction conditions to naphthofluorescein (Scheme 2.5), the product naphthofluoresceine monoaldehyde (compound **2.3**) was obtained in 15% yield along with a trace amount of naphthofluorescein dialdehye (compound **2.4**). The single-crystal X-ray structure analysis also confirmed the assignment of the product (Figure 2.8).

The advantage of this simple new synthesis of fluorescein-based aldehydes and naphthafluorescein-based aldehyde includes convenience and efficiency, but the yield of this reaction is low to moderate. The reason could be that a side reaction occurred

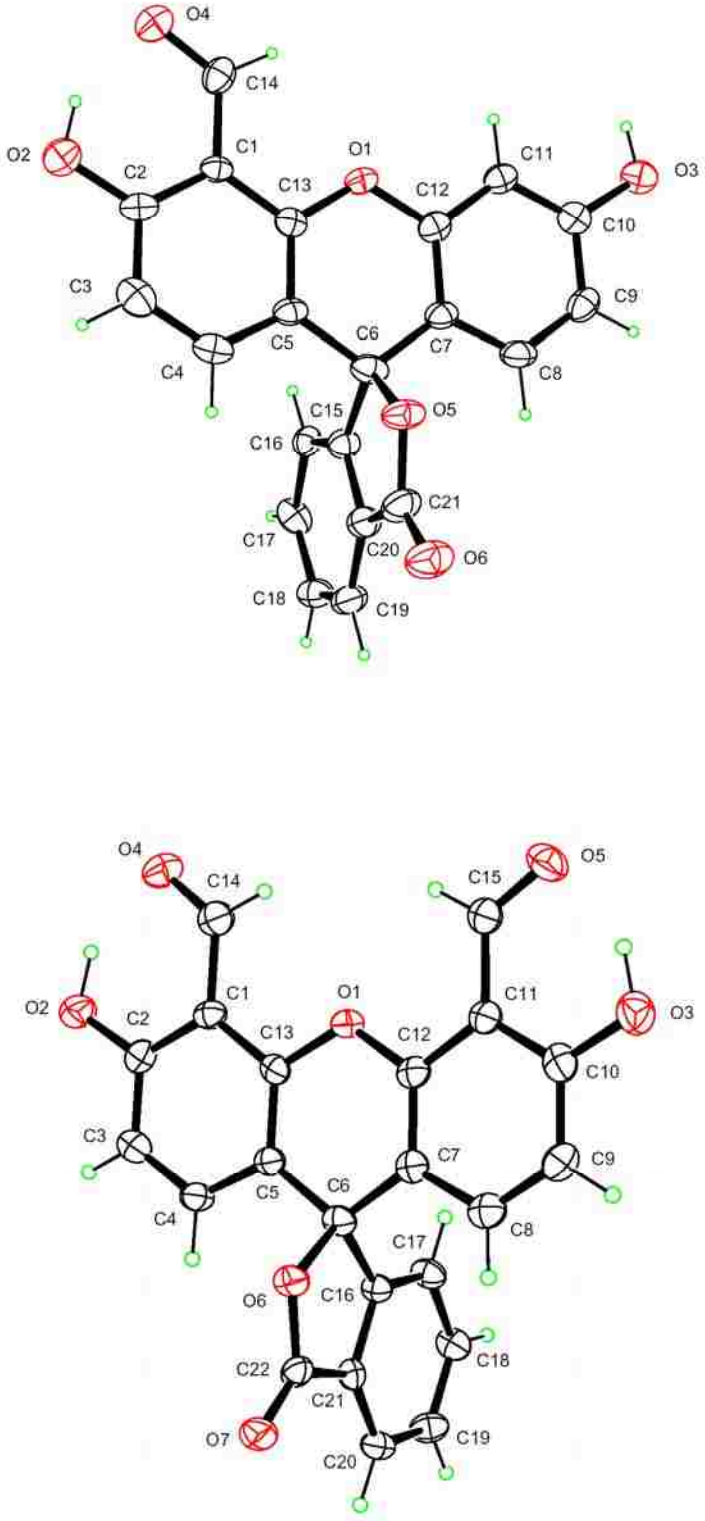
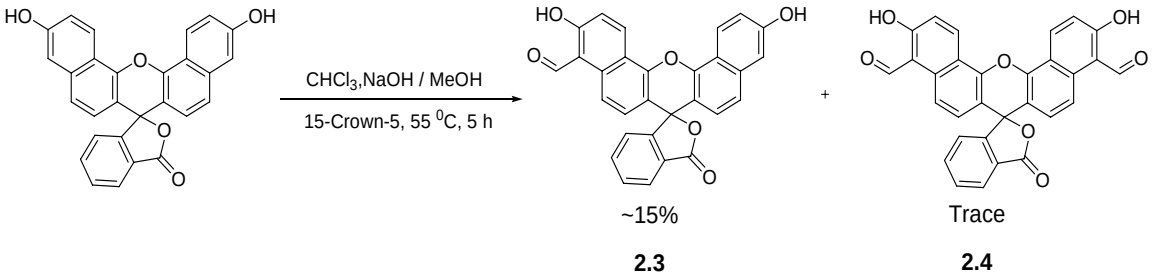


Figure 2.7: Single-crystal X-ray structures of compound **2.1** (top) and compound **2.2** (bottom).



Scheme 2.5: One step synthesis of naphthofluorescein aldehydes

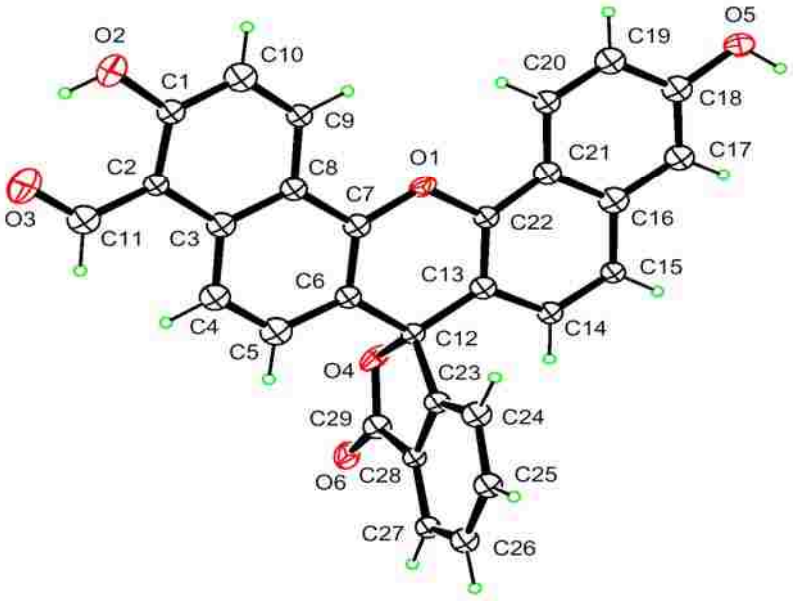


Figure 2.8: Single-crystal X-ray structure of compound **2.3**.

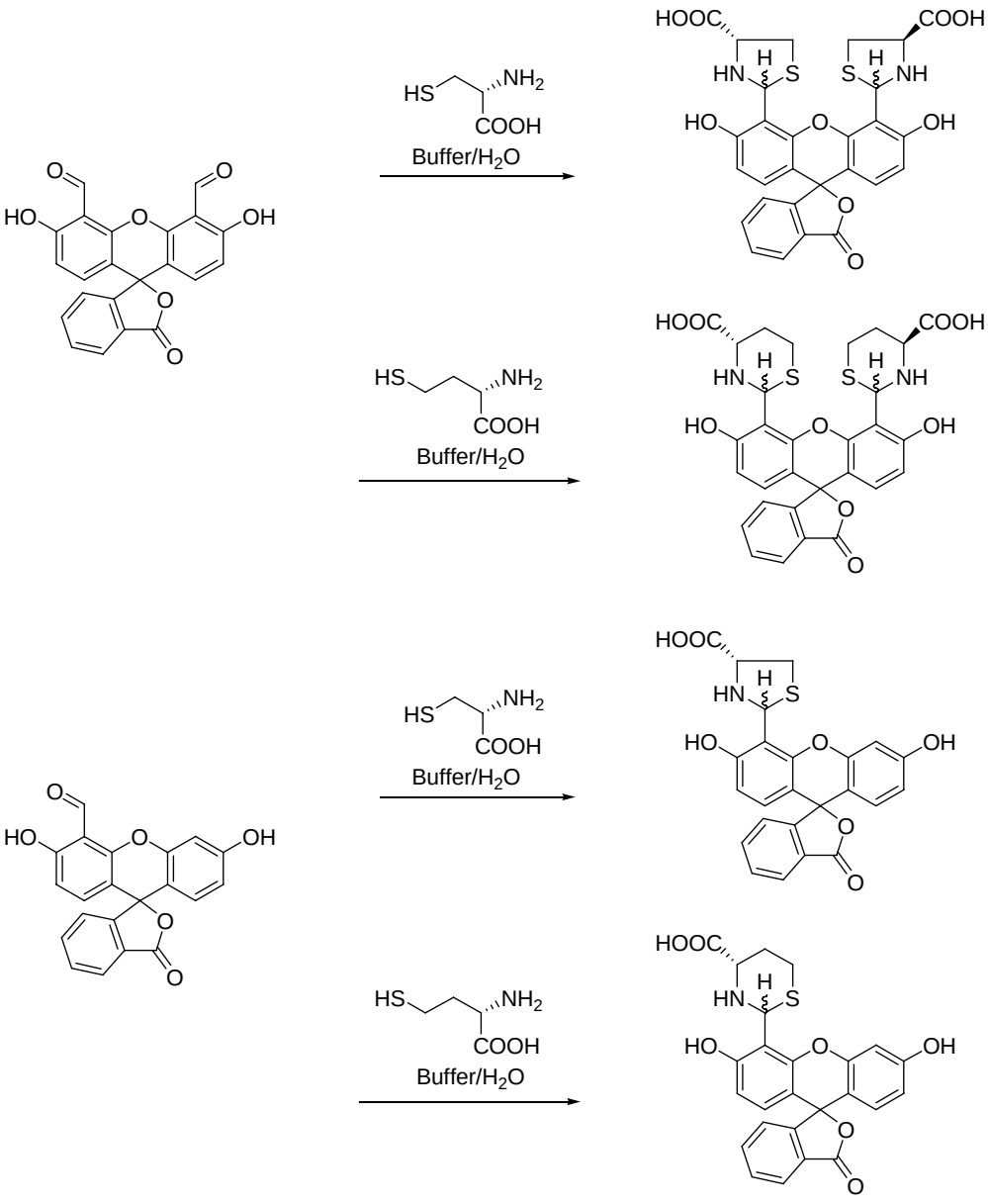
between carbene and water. The large amount of water needed for this reaction is due to the pretty low solubility of fluorescein or naphthafluorescein in organic solvents.

- **Detection of Cys and Hcy with fluorescein-based aldehydes**

The formation of thiazolidinic acids were observed upon the reaction of fluoresceine mono- and dialdehydes with Cys and Hcy in buffered solution (Scheme 2.6). When Cys or Hcy was added to a solution of compound **2.1** (Figure 2.6) (1.0 x 10^{-6} M, pH 9.5), the solution color changed from bright yellow to brownish-orange.[24] Similar color changes were also can be found on reverse phase silica gel.[24] UV-Vis technique showed absorbance changes (a decrease in absorbance at 480 nm followed by a ~ 25 nm red shift) when cysteine was added to the dye solution. Similarly, the addition of Cys or Hcy to solutions of compound **2.1** also resulted in fluorescence quenching because of the formation of thiazolidines or thiazinanes.[24]

It is known that the concentration of total homocysteine (tHcy) in plasma is less than 12~15 μM.[1, 37-38] Cys concentration in plasma is normally 20-30 times of Hcy concentration. In a communication,[24] we reported that compound **2.1** can be used to monitor the low concentration Cys (the cysteine concentration range 10^{-5}-10^{-6} M.).

In order to study the selectivity of the probe for the detection of Cys and Hcy, in the previous work,[24] we also checked the response of fluorescein dialdehyde to some other sulfur-containing molecules (L-methionine, mercaptoethanol, glutathione), other amino acids (L-glutamine, L-serine, L-glycine, L-glutamic acid), and amines (D-glucosamine hydrochloride and n-propylamine (8.0 x 10-4 M, pH 9.5).[24] We found that only a small or no decrease in absorbance at 480 nm is observed and there is no wavelength shift was seen for all of those molecules, though all of these compounds' concentration is as 10 times more than the cysteine used. For example, Figure 2.9



Scheme 2.6: Thiazolidine formation.

illustrates the response of serine to fluorescein dialdehyde at the 2.5 x 10^{-6} *M* concentration. There was no spectral change at first, when serine was continuously added to the solution of fluroescein dialdehyde from 4 x 10^{-5} M to 8 x 10^{-4} *M* and finally only a minor absorbance decrease. When Cys was added from 4 x 10^{-6} *M* to 8 x 10^{-5} *M*, we found a decrease at 480 nm first, and then a 25-nm red shift. The reason for this is that the product *N*-teminal oxazolidine formed from serine and aldehyde is 10^4 times less stable than thiazolidines.[21] So from the above results, we can see that fluorescein dialdehyde is a selective probe for colorimetric and fluorometric detection of Cys and Hcy.

The new probe, fluroescein-monoaldehyde (compound **2.2**), also showed a positive response to the Cys and Hcy (Figure 2. 10). From the absorption spectra, we can see that both Cys and Hcy can produce an obvious decrease of the absorbance at 495 nm but no red shift, which is a slightly different from the behavior of compound **2.1**.

In the fluorescence studies, a different response from each of the two probes was observed. Addition of cysteine or homocysteine to compound **2.1** (1.7 x 10^{-7} *M*) and compound **2.2** (1.7 x 10^{-7} *M*) respectively resulted in the probes showing different magnitudes of fluorescence quenching (Figure 2.11 and Figure 2.12).

In Figure 2.11, it shows that when Cys or Hcy was added to the fluorescein-dialdehyde buffered (0.1 M carbonate buffer, pH=9.5) solution at room temperature, both Cys and Hcy showed a certain degree quenching of fluorescence. Cys showed a little bit greater quench. However, for the fluorescein-monoaldehyde (Figure 2.11), surprisingly Hcy quenched the fluorescence in a less magnitude. Compared to the Hcy, Cys showed a certain selectivity.

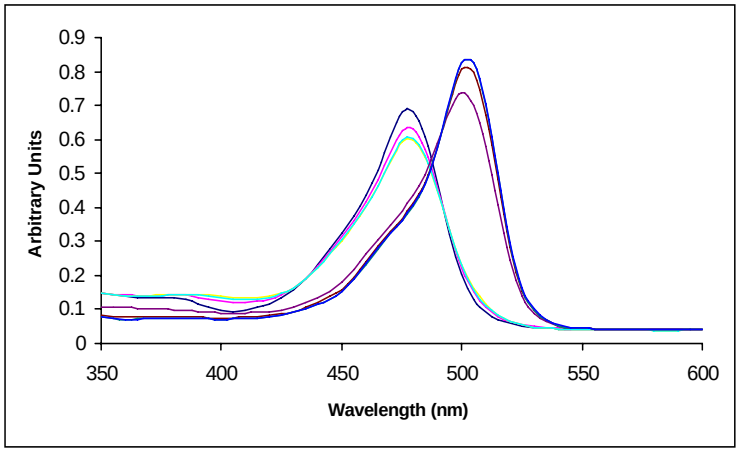


Figure 2.9: Successive addition of L-serine (to final concentrations of 4 x 10^{-5} M to 8 x 10^{-4} M) to an aqueous solution of dialdehyde (2.5 x 10^{-6} M) at pH 9.5 results only in an absorbance change at 480 nm. Addition of L-cysteine (to final concentrations of 4 x 10^{-6} M to 8 x 10^{-5} M) to the L-serine-dialdehyde solution produces an absorbance change at 505 nm**.**

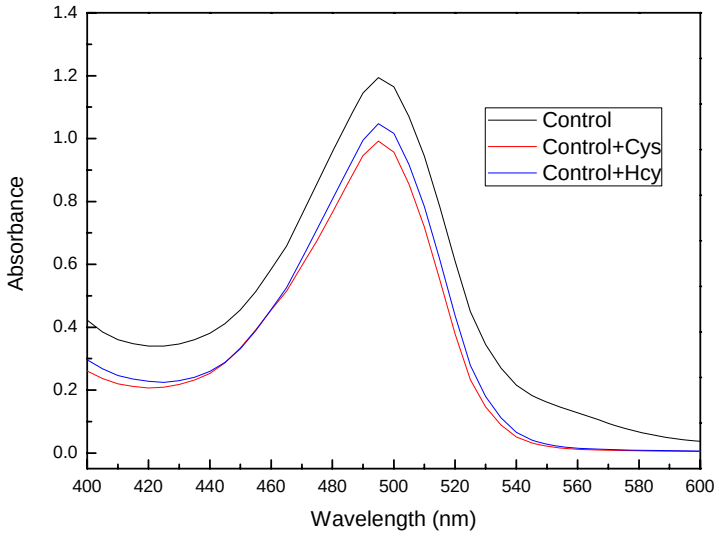
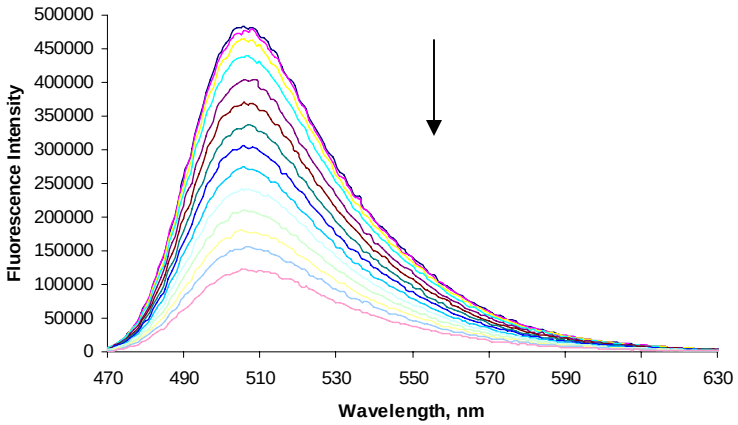
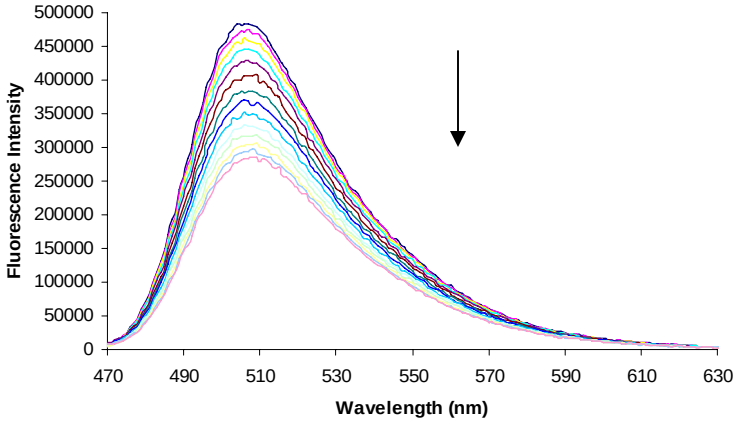


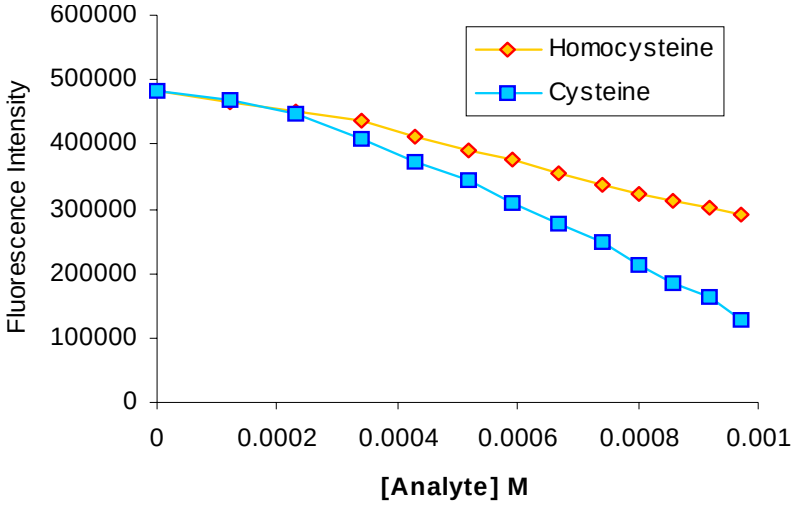
Figure 2.10: L-cysteine (final concentrations of 4 x 10^{-6} M) added to an aqueous solution of compound **2.2** (2.5 x 10^{-6} M) at pH 9.5 results in an absorbance decrease at 495 nm.



a. Fluorescence emission spectra of solutions of compound **2.1** (1.7 x 10^{-7} *M*, 0.1 *M* carbonate buffer, pH 9.5) excited at 460 nm at rt in the various of concentration of Cys.

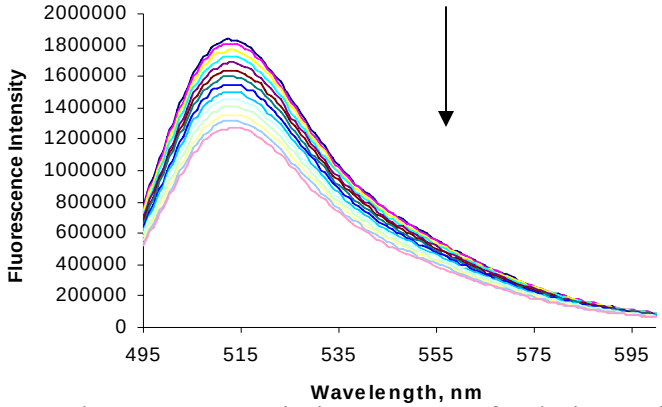


b. Fluorescence emission spectra of solutions of compound **2.1** (1.7 x 10^{-7} *M*, 0.1 *M* carbonate buffer, pH 9.5) excited at 460 nm at rt in the various of concentration of Cys.

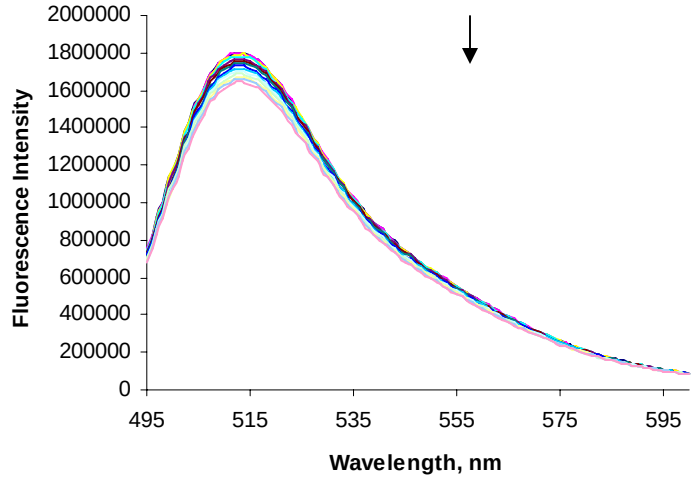


c. Plot of fluorescence intensity of solutions of **2.1** in the presence of various concentrations of Cys and Hcy.

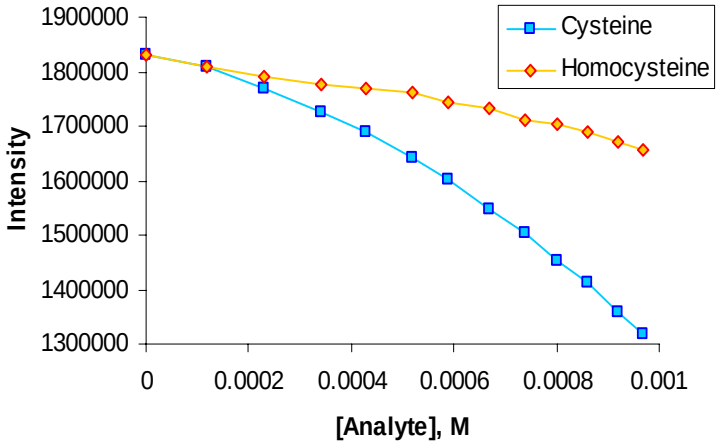
Figure 2.11: Compound **2.1** fluorescence studies.



a. Fluorescence emission spectra of solutions of compound **2.2** (1.7 x 10^{-7} *M*, 0.1 *M* carbonate buffer, pH 9.5) excited at 460 nm at rt in the various of concentration of Cys.



b. Fluorescence emission spectra of solutions of compound **2.2** (1.7 x 10^{-7} *M*, 0.1 *M* carbonate buffer, pH 9.5) excited at 460 nm at rt in the various of concentration of Hcy.



c. Plot of Fluorescence intensity of solutions of **2.2** in the presence of various concentrations of Cys and Hcy.

Figure 2.12: Compound **2.2** fluorescence studies.

2.7 Experimental

General. UV-Visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices). Analytical thin-layer chromatography (TLC) was performed using general-purpose silica gel on glass (Scientific Adsorbants). Chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å). All chemicals were purchased from Sigma or Aldrich and used without further purification. Proton NMR spectra were acquired in either CD_3OD, or DMSO-*d6* on a Bruker DPX-250, DPX-300 spectrometer. All δ values are reported with $(CH_3)_4Si$ at 0.00 ppm or DMSO at 2.49 ppm as references.

- **Formylation of Fluorescein**

2.5g (7.75mmol) Fluorescein and 3mL methanol were placed in a 100mL three-neck round bottom flask. Then 10g of 50% sodium hydroxide solution, 2.42 mL (30mmol) of chloroform and 0.03mL 15-Crown-5 was carefully added while maintaining the mixture temperature at 55ºC. The mixture was stirred at this temperature for 5 h with a condenser attached. After cooling, the mixture was acidified with 10 *M* H_2SO_4, and the product precipitated. The solid was filtered and dried in vacuo overnight. Chromatography on silica gel (15: 85 EtOAC: DCM) yielded the products, white fluorescein di-aldehyde (**2.1**) and light yellow fluorescein mono-aldehyde (**2.2**). TLC: compound **2.1** R_f=0.55 (15: 85 EtOAC: DCM), compound **2.2** R_f=0.28 (15: 85 EtOAC: DCM). Characterization data for compound **2.2**. ^{1}H NMR (DMSO-d_6, 250 MHz) δ (ppm): 6.60 (s, 2H), 6.68 (d, *J* =8.9Hz, 1H), 6.84(s, 1H), 6.92 (d, *J*=8.9 Hz, 1H), 7.29(d, *J*= 7.5 Hz, 1H), 7.69 (td, *J*=1.2,7.5 Hz, 1H), 7.76 (td, *J*=1.2, 7.5Hz, 1H),7.99 (d, *J*= 7.5 Hz, 1H), 10.26(s, 1H), 10.62(s, 1H), 11.87 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 81.92, 102.75, 109.20, 109.27, 109.75, 113.48, 113.63, 124.06, 124.89, 125.97, 129.07, 130.42,

135.91, 136.61, 150.94, 152.25, 152.46, 159.71, 163.04, 168.68, 192.94 FTIR (KBr, cm -1) 1007, 1112,1157, 1227, 1465, 1512, 1593,1648, 1721, 3271 MALDI *m*/*z* for $C_{21}H_{12}O_6$, calcd 360.32, found 361.16 ($M+H^+$), 383.24 ($M+Na^+$)

Collection of X-ray Data. Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with MoKα radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller.

- **Formylation of Naphthofluorescein**

The procedure is similar as above. 2.5g (5.78 mmol) naphthofluorescein and 3mL methanol were placed in a 100 mL three-neck round bottom flask. Then 10g of 50% sodium hydroxide solution, 1.87 mL (23.12mmol) of chloroform and 0.02mL 15-Crown-5 were carefully added while maintaining the mixture temperature at 90 ºC. The mixture was stirred at this temperature for around 5 h with a condenser attached. After cooling, the mixture was acidified with 10M H_2SO_4, and the product was precipitated. The solid was filtered and dried in the vacuo overnight. Chromatography on silica gel (10: 90 EtOAC: DCM) yielded the products, light pink Naphthofluorescein Mono-aldehyde. TLC: R_f=0.57 (15: 85 EtOAC: DCM). Characterization data for compound **2.3.** ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.69 (d, *J* =9Hz, 1H), 6.95 (d, *J* =9Hz, 1H), 7.20 (d, *J* =2Hz, 1H), 7.29 (m, 2H), 7.45 (m, 2H), 7.73 (m, 2H), 8.08 (m, 1H),8.67 (dd, *J*= 7.5 Hz, 3.0 Hz, 2H), 9.04 (d, *J* =9Hz, 1H), 10.18 (s, 1H), 10.77 (s, 1H), 12.07 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ(ppm): 82.47, 109.42, 111.33, 112.98, 117.22, 118.95, 119.32, 119.70, 122.88, 123.84, 124.18, 124.87, 125.64, 127.44, 130.38, 131.56, 133.23, 135.84, 135.99, 145.94, 146.12, 153.10, 157.41, 164.82, 168,81, 192.42 FTIR (KBr, cm -1) 1014, 1086,1156, 1226, 1463, 1516, 1576,1630, 1756, 3425 MALDI *m*/*z* for $C_{29}H_{16}O_6$, calcd 460.43, found 460.91

Collection of X-ray Data. Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with MoKα radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller

2.8 Conclusion

A convenient synthesis of fluorescein-based aldehydes, compound **2.1** and **2.2**, was presented. Both of the two compounds showed the selective detection of cysteine and homocysteine over other biological thiols. A longer wavelength fluorescent sensor, naphthafluorescein mono-aldehyde, compound **2.3**, was also synthesized by the one step reaction and it also possesses potential application on the detection of cysteine or homocysteine.

2.9 References

1. Refsum, H.; Ueland, P. M.; Nygård, O.; Vollset, S. E. *Annu. Rev. Med*. **1989**, *49*, 31.

2. Selhub, J. *Annu. Rev. Nutr.* **1999**, *19*, 217.

3. Steegerstheunissen, R. P. M.; Boers, G. H. J.; Trijbels, F. J. M.; Eskes, T. K. A. B. N. *N. Engl. J. Med*. **1991**, *324*, 199.

4. van Meurs, J. B. J.; Dhonukshe-Rutten, R. A. M.; Pluijm, S. M. F.; van der Klift, M.; de Jonge, R.; Lindemans, J.; de Groot, L. C. P. G. M.; Hofman, A.; Witteman, J. C. M.; van Leeuwen, J. P. T. M.; Breteler, M. M. B.; Lips, P.; Pols, H. A. P.; Uitterlinden, A. G. *N. Engl. J. Med.* **2004,** *350(20)*, 2033-2041.

5. Ueland, P. M.; Vollset, S. E.. *Clin. Chem.* **2004**, *50,* 1293.

6. Salim, A.S. *Can. J. Surg.* 1993, *36*, 53-58.

7. Droge, W.; Eck, H. P.; Gander, H.; Mihm, S. *Am. J. Med.* **1991**, *91*(suppl 3C):S140-S144.

8. Eck, H. P.; Gander, H.; Hartmann, M.; Petzoldt, D.; Daniel, V.; Droge, W. *Biol. Chem. Hoppe. Seyler.* **1989**, *370*, 101–108.

9. Droge, W.; Eck, H. P.; Mihm, S. *Immunol. Today,* **1992**, *13*, 211–4.

10. Droge, W. *Pharmacology,* **1993**, *46*, 61–5.

11. Crawhall, J. C.; Watts, R. W. E. *Am. J. Med.* **1968**, *45*, 736.

12. Berlow, S. *Adv. Clin. Chem.* **1967**, *9*, 165.

13. Shahrokhian, S. *Anal. Chem*. **2001**, *73*, 5972.

14. Klingman, J. G.; Choi, D. W. *Neurology* **1989**, *39*, 397-398.

15. Fahey, R. C. In *Glutathione: Chemical, Biochemical and Medical Aspects* Dolphin, D.; Poulson, R.; Avramovic, O., Ed.; Wiley, New York, 1989; Chapter 9, p. 303.

16. Al-Majed, A. A. *Anal. Chim. Acta* **2000**, *408*, 169.

17. Fermo, I.; Arcellonic, C.; Mazzola, G.; D'angelo, A.; Paroni, R. *J. Chromatogr. B.* **1998**, *719*, 31.

18. Baeyens, W.; Van der Weken, G.; Ling, B.; Lin Moerloose, P. D. *Anal. Lett.* **1988**, *21*, 741

19 (a) Schubert, M.P. *J.Biol. Chem.* **1936**, *114*, 341. (b) Schubert, M.P. *J.Biol. Chem.* **1937**, *121*, 539. (c) Fourneau, J.P.; Efimovsky, O.; Gaignault, J.C.; Jacquier, R.; LeRidant, C. *R. Acad. Sci. Ser. C* **1971**, *272*, 1571.

20 (a) Jencks, W. P. *J. Am. Chem. Soc.* **1959**, *81*, 475. (b) Sayer, J. M.; Peskin, M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 4277.

21 Tam, J. P.; Miao, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9013, and references therein.

22 Zhang, L.; Tam, J. P. *Anal. Biochem.,* **1996,** *233*, 87.

23 (a) Davis, C. J.; Lewis, P. T.; McCarroll, M. E.; Read, M. W.; Cueto, R.; Strongin, R. M. *Org. Lett.* **1999**, *1*, 331. (b) Lewis, P. T.; Davis, C. J.; Cabell, L. A.; He, M.; Read, M. W.; McCarroll, M. E.; Strongin, R. M. *Org. Lett.* **2000**, *2*, 589 (c) He, M., Johnson; R. J.; Escobedo, J. O.; Beck, P. A.; Kim, K. K.; St Luce, N. N.; Davis, C. J.; Lewis, P. T.; Fronczek, F. R.; Melancon, B. J.; Mrse, A. A.; Treleaven, W. D., Strongin, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 5000-5009.

24 (a) Wang, W.; Rusin, O.; Xu, X.; Kim, K. K.; Escobedo, J. O.; Fakayode, S. O.; Fletcher, K. A.; Lowry, M.; Schowalter, C. M.; Lawrence, C. M.; Fronczek, F. R.; Warner, I. M.; Strongin, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 15949-15958. (b) Rusin, O.; St. Luce, N. N.; Agbaria, R. A.; Escobedo, J. O.; Jiang, S.; Warner, I. M.; Dawan, F. B.; Lian, K.; Strongin, R. M.. *J. Am. Chem. Soc*. **2004**, *126(2)*, 438-439.

25 Burdette, S. C.; Walkup, G. K.; Spingler, B.; Tsien, R. Y.; Lippard, S. J. *J. Am. Chem. Soc*. **2001**, *123*, 7831-7841.

26 von Baeyer, A., *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 555-558. (b) von Baeyer, A. *Chem. Ber.* **1871**, *5,* 255.

27 (a) Kornblun, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Kornblun, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.

28 Gattermann, L. *Ber.*, **1898**, *31*, 1149, 1765, 1770.

29 Gattermann, L.; Koch, J. A. *Ber.* **1897**, *30,* 1622.

30 Vilsmeier, A.; Haack, A. *Ber.* **1927**, *60*, *119* -122.

31 Duff, J. C.; Bills, E. J. *J. Chem. Soc*. **1932**, 1987; **1934**, 1305.

32 Reimer, K. *Ber.* **1876**, *9*, 423.

33 Reimer, K.; Tiemann, F. *Ber.* **1876**, *9*, 824.

34 Reimer, K.; Tiemann, F. *Ber.* **1876**, *9*, 1268.

35 Reimer, K.; Tiemann, F. *Ber.* **1876**, *9*, 1285.

36 Wynberg, H.; Meijer, E. W. *Organic Reactions,* **1982**, *28,* 1, New York.

37 Refsum, H.; Ueland, P. M.; Svardal, A. M. *Clin Chem.* **1989**, *35*, 1921–1927.

38 Fiskerstrand, T.; Refsum, H.; Kvalheim, G.; Ueland, P. M. *Clin Chem.* **1993**, *39*, 263–271.

CHAPTER 3

SELECTIVE DETECTION OF CYSTEINE AND DEVELOPMENT OF NIR SENSOR

PART I. SELECTIVE DETECTION OF CYSTEINE

3.1 Background

In recent work,[1] the Strongin group evaluated the selective spectrophotometric

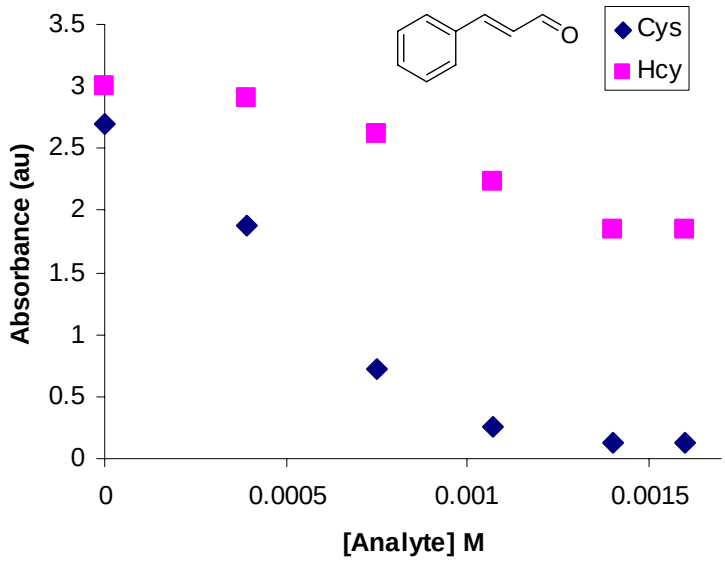


Figure 3.1: Absorbance at 400 nm of solutions of cinnamaldehyde in the presence of various concentrations of Cys and Hcy.

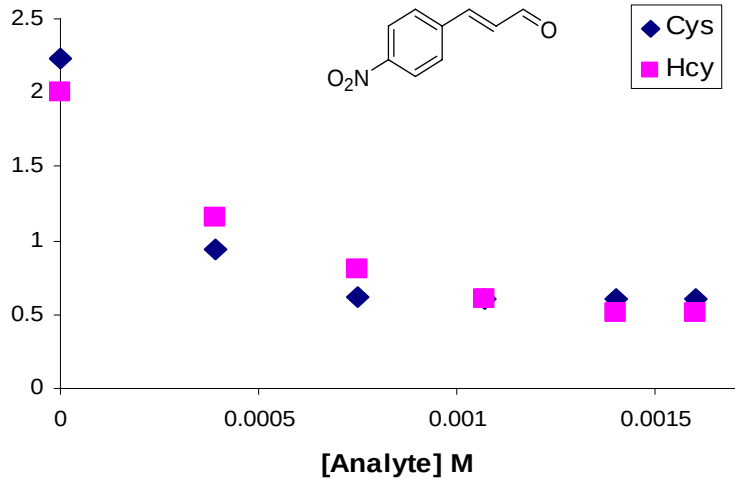


Figure 3.2. Absorbance at 400 nm of solutions of 4-nitrocinnamaldehyde in the presence of various concentrations of Cys and Hcy.

* Parts of this chapter have appeared in *Journal of the American Chemical Society*.

response of some cinnamaldehyde derivatives towards cysteine in the presence of homocysteine and found that commercially available cinnamaldehyde afforded mildly selective detection for Cys. From this result they were able to activate or deactivate the selectivity for cysteine by changing the aromatic ring substituents (Figures 3.1, 3.2 and 3.3). It was found that cinnamaldehyde containing an electron-donating group in the benzene ring, e.g. 4-(dimethylamino)-cinnamaldehyde (DMACA), did show enhanced selective detection for Cys over Hcy. The reason is attributed to the fact that the electron-donating group renders the aldehyde and/or beta carbon less electrophilic.

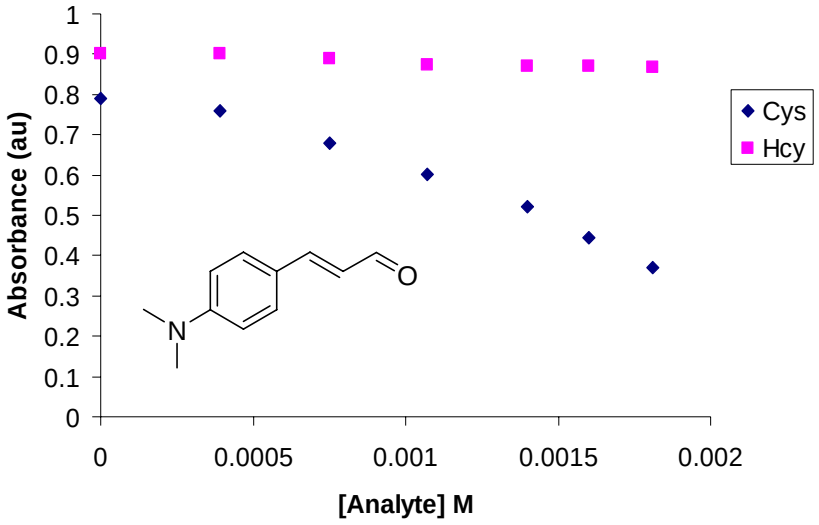
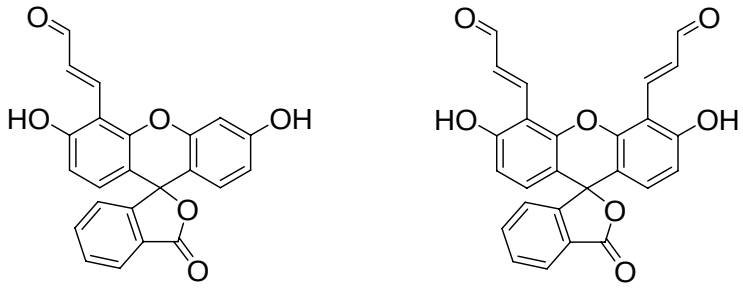


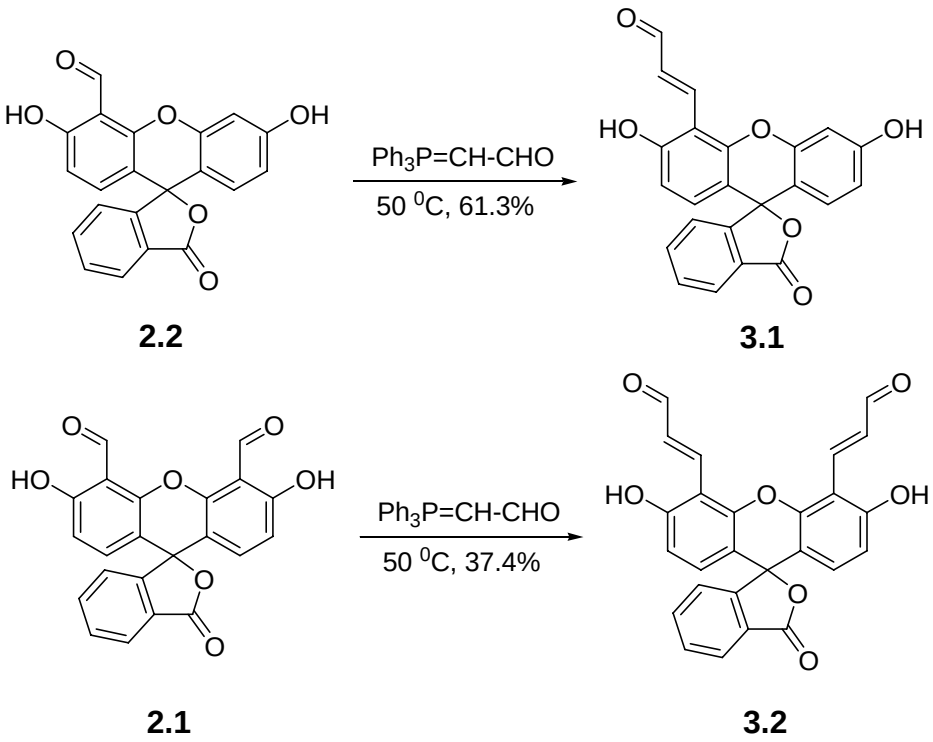
Figure 3.3. Absorbance at 400 nm of solutions of DMACA in the presence of various concentrations of Cys and Hcy.

From the above results, we reasoned that an α,β-unsaturated aldehyde group can be appended to fluorescein, a very common fluorescent dye. Thus, such a modified fluorescent dye may potentially be used in selectively labeling or detecting peptides and proteins via *N*-terminal Cys residues and to selectively detect free cysteine**.** Proposed compounds **3.1** and **3.2** (Figure 3.4) were prepared via Wittig procedures from fluorescein mono- and dialdehydes respectively (see Chapter 2).



3.1 **3.2**

Figure 3.4: mono- and di- α,β-unsaturated fluorescein aldehydes.



2.2 **3.1**

2.1 **3.2**

Scheme 3.1 Synthesis of compound **3.1** and **3.2**.

3.2 Synthesis of Mono- and Di- α,β-unsaturated Fluorescein Aldehydes

Scheme 3.1 depicts a one-step synthesis of compounds **3.1** and **3.2**. The starting material, compound **2.2** (fluorescein monoaldehyde)**,** was synthesized from commercially available fluorescein via a Reimer-Tiemann reaction (Chapter 2) and extended to the unsaturated aldehyde fluorescein by heating fluorescein monoaldehyde with triphenylphosphoranylidene acetaldehyde in $CHCl_3$ at 50 ºC overnight to afford **3.1** in ~60 % yield. Another starting material, compound **2.1** (fluorescein dialdehyde), was prepared according to Lippard's procedure.[2] The di- α,β-unsaturated fluorescein aldehyde (**3.2**) was obtained using the same procedure as with the mono aldehyde with a yield of about 40 %.

3.3 Results and Discussion

3.3.1 Addition of Cysteine to Conjugated Aldehydes

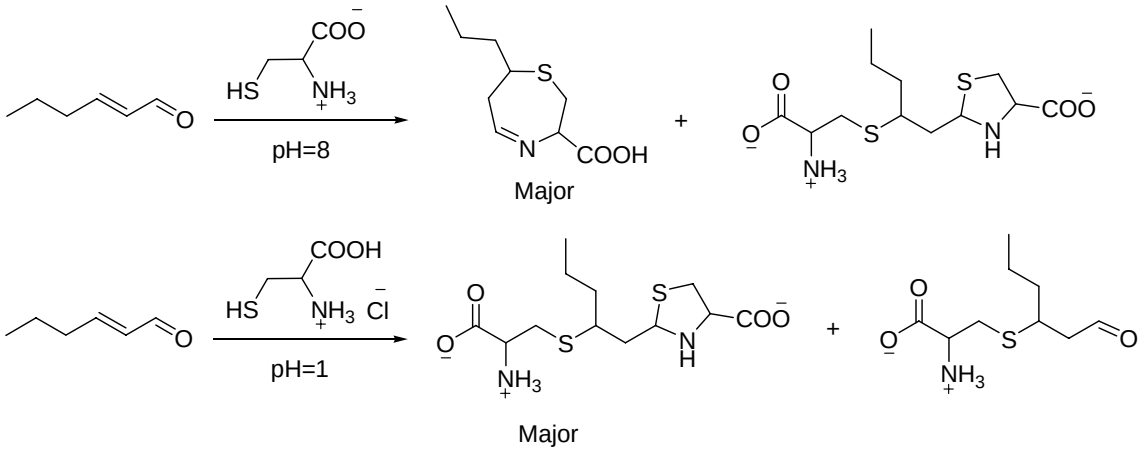
It is known that cysteine can react with α,β-unsaturated aldehydes to generate some important precursors of odorant sulfur compounds in flavors and fragrances.[3-4] Recently, Starkenmann et al.[5-6] studied reactions of cysteine and α,β-unsaturated aldehydes.

- **Addition of Cysteine to α,β-unsaturated aldehydes**

Under basic conditions (pH 8-9), addition of cysteine to non-substituted α,β-unsaturated aldehydes would mainly generate a 7-member ring Schiff base and a bis-adduct containing a thiazolidine (Scheme 3.2), which was reported by Esterbauer et al. as early as in 1976.[7] The reaction was believed to undergo two steps, the first step being the Michael-type addition between cysteine and α,β-unsaturated aldehyde; then the mono-adduct may have reacted intramolecularly leading to the formation of a 7-membered ring Schiff base or an intermolecular reaction with another molecule of cysteine to form a

thiazolidine (Scheme 3.2).[5]

Under acidic conditions (pH=1), non-substituted α,β-unsaturated aldehydes would react with cysteine and mainly form a bis-adduct and some mono-adduct, a saturated aldehyde (Scheme 3.2).[5]

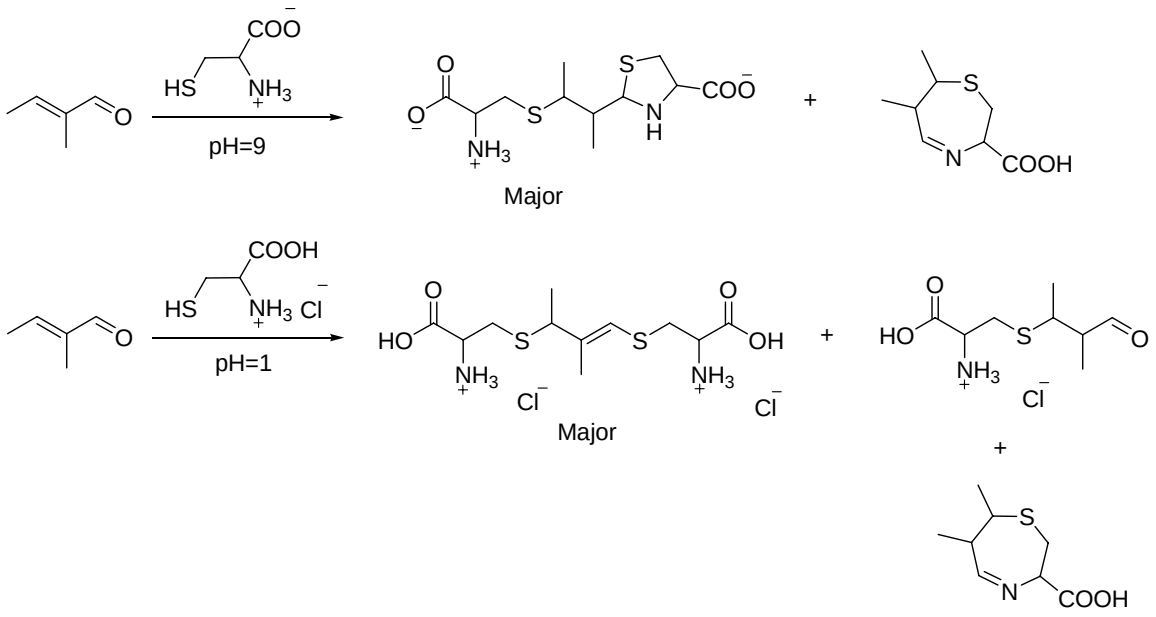


Scheme 3.2. Products from the reaction of cysteine and non-substituted α,β-unsaturated aldehydes.

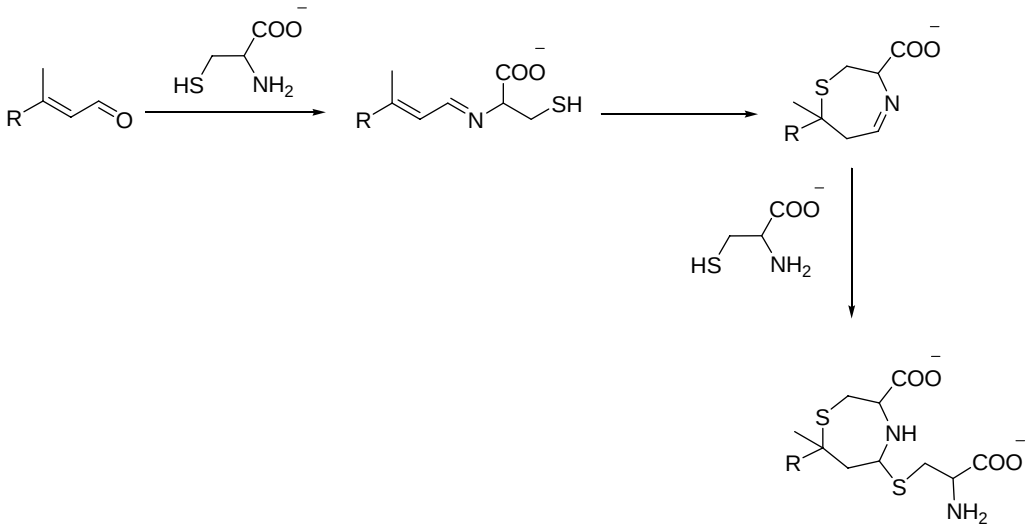
- **Addition of Cysteine to α-alkyl-substituted α,β-unsaturated aldehyde**

An α-substituted α,β-unsaturated aldehyde would give a different result from the non-substituted α,β-unsaturated aldehyde case when it reacts with cysteine. Under basic conditions (pH 8-9), the major product from the reaction between 1 equiv Cys and 1 equiv α-substituted α,β-unsaturated aldehyde is a bis-adduct containing thiazolidine units, and as minor product a 7-member ring Schiff base. In contrast, under acidic conditions, a bis-adduct containing a vinylic sulfide moeity is generated as a major product, and a 7-membered ring Schiff base and a single-adduct as minor products. The non-substituted α,β-unsaturated aldehydes can't generate a bis adduct vinylic sulfide moeity due to the low stability of the less substituted olefin (Scheme 3.3).[5]

- **Addition of Cysteine to β,β-dialkyl α,β-unsaturated Aldehyde**



Scheme 3.3: α-Substituted α,β-unsaturated aldehyde conjugates with cysteine.



Scheme 3.4: β,β -dialkyl α,β-unsaturated aldehyde reacts with Cys affording 7-membered hexahydro-1,4-thiazepine (pH=7).

A β,β-dialkyl α,β-unsaturated aldehyde normally reacts with cysteine (at neutral conditions, pH=7) and yields exclusively one product, a 7-membered ring Schiff base. Starkenmann et al. reported a detailed study of this reaction.[6] They believed that substitution on the β- position would make the Michael addition proceed very slowly, and that the amino group would react with the aldehyde group first and form an α,β-unsaturated imine, then a "7-endo-trig" cyclization would occur (Scheme 3.4).[6]

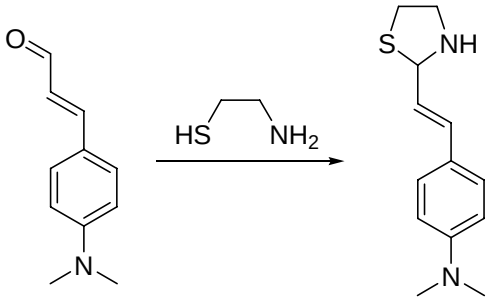
- **Addition of Cysteamine to β,β-dialkyl α,β-unsaturated Aldehyde**

During the mechanistic studies of thiazolidine hydrolysis, Fife et al. prepared 1, 3-thiazolidine derivatives of 4-*N*,*N*-dimethylamino cinnamaldehyde (DMACA) by heating equivalent amounts of DMACA and cysteamine in dry benzene (Scheme 3.5).[8] In this reaction, cysteamine reacts with α,β-unsaturated aldehyde and forms a thiazolidine mono-adduct (5-membered ring). To the best of our knowledge, this is one of the few examples where a mono-adduct thiazolidine is prepared from an α,β-unsaturated aldehyde and an aliphatic aminothiol.

3.3.2. Selective Detection of Cysteine with Fluoresceine-Derived Conjugated Aldehydes

When a solution of cysteine (1.0×10^{-3} *M*) is continuously added to a solution of compound **3.1** or **3.2** (1.0×10^{-6} *M*, 0.1 *M* carbonate buffer, pH 9.5), the fluorescence intensity increases steadily (Figures 3.7 and 3.8a). In contrast, there is no significant fluorescence change observed when Hcy (1.0×10^{-3} *M*) is continuously added to a solution of **3.1** or **3.2** at the same conditions (Figure 3.7 and 3.8b). These results indicate that Cys can be discriminated from Hcy by using **3.1** or **3.2** as fluorophore.

Due to the reversibility of the reaction between cysteine and **3.1** or **3.2** and to the limited amount of these dyes, we were not able to separate the products and to determine



Scheme 3.5. Synthesis of 1,3-thiazolidine from the reaction of DMACA and cysteamine.

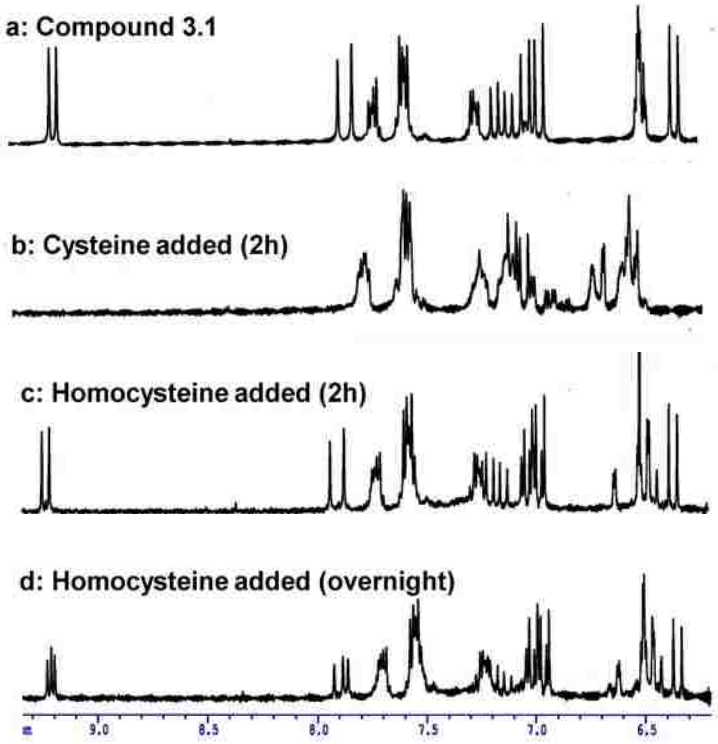


Figure 3.5: (a) ^{1}H NMR of compound **3.1** in D_2O (with one drop of NaOD); (b) 2 h after addition of 10 equiv Cys. (c) 2 h after addition of 10 equiv Hcy. (d) 12 h after addition of 10 equiv Hcy.

exactly what type of reaction occurred. However, based on the extensive research on cysteine conjugated α,β-unsaturated aldehydes[1, 5-8] the ^{1}H NMR shifts before and after the reaction (Figure 3.5) and the mass spectra (see appendix) of the reaction mixture of compound **3.1** and cysteine, we believe that the reason why compounds **3.1** and **3.2** can selectively react with Cys is the same as in the case of 4-*N*,*N*-dimethylamino-cinnamaldehyde. Under our conditions, a strong electron donating group renders the β-carbon less electrophilic which makes the rate-determing step (Michael-type addition)[7] slower. Thus, DMACA would prefer to react with Cys and form an α,β-unsaturated imine first, followed by the formation of a 5-membered thiazolidine, again due to the lower electrophilicity of the β- carbon and, in a lesser extent, form a 7-membered ring Schiff base (Scheme 3.6). If there is Cys still available, it could be added again to the 7-membered Schiff base to form a thiazepine. In contrast, due to the slow formation of the 1,4-Hcy mono- adduct, Hcy will not easily react with the unsaturated aldehyde to form a 6-membered thiazinane. Moreover, Hcy may also react with the unsaturated aldehyde and form a conjugated imine (-CH=CH-CH=N-), but in the cyclization step, the unfavored formation of a 8-membered ring or slow ring closure of 6-membered thiazinane would inhibit this step.

Similarly, as in the case of DMACA, compounds **3.1** or **3.2** would also prefer to react with Cys and form a single-adduct first, leading to a 5-membered thiazolidine or 7-membered ring Schiff base, which in turn, could react with additional cysteine to form thiazepine. On the other hand, Cys may probably also react slowly with **3.1** or **3.2** to form a 1,4-mono-adduct saturated aldehyde, the excess Cys may continuously react and form a thiazolidine (Scheme 3.6). All three cases exhibit the disappearance of the characteristic aldehyde peak (Figure 3.5). In the case of Hcy, it may react with **3.1** or **3.2**

to form an α,β-unsaturated imine as an intermediate, but the unfavored 8-membered ring formation or the slow ring closure of 6-membered thiazinane would prevent a cyclization. Hence, Hcy would prefer to undergo a slow 1,4-addition followed by cyclization to form a thiazinane. From Figure 3.5, we can see that after 2 h, there is not a significant change in the ^{1}H NMR. Surprisingly, after 12 h, the characteristic doublet for the conjugated aldehyde peak decreases and a new singlet for the saturated aldehyde peak appears. We believe that this results indicate that Hcy undergoes a slow 1,4-addition forming a mono-adduct, a saturated aldehyde, which could also further react with additional Hcy and form a thiazinane.

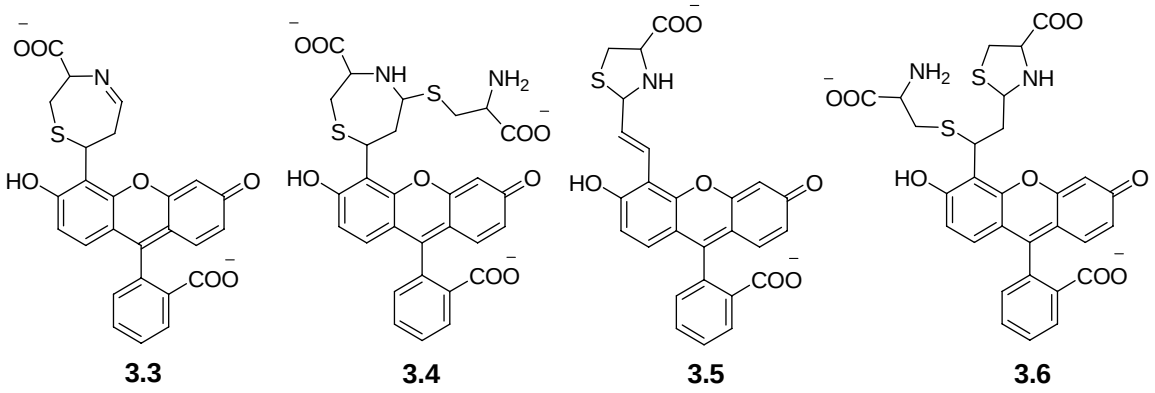
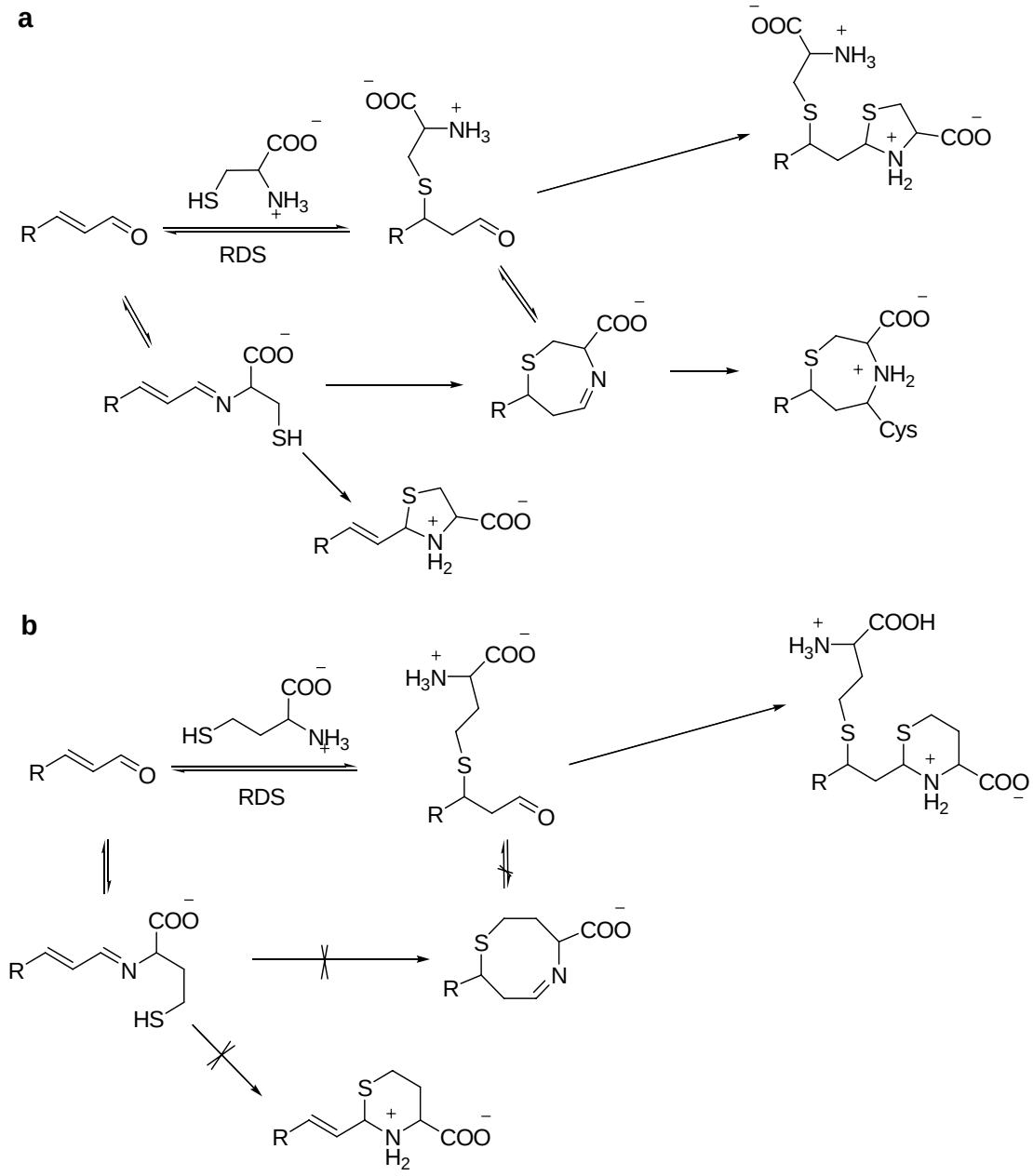


Figure 3.6. The possible products from the reaction of compound **3.1** and cysteine.

Based on the analysis of the reaction of compound **3.1** with cysteine, we hypothesize that the products may contain two different mono-adducts (compound **3.3** or **3.5** in Figure 3.6), the excess cysteine may continuously react with a 7-membered ring Schiff base to form a bis-adduct (compound **3.4** in Figure 3.6), and probably another bis-adduct from the reaction sequence that starts with a Michael addition followed by thiazolidine formation (compound **3.6** in Figure 3.6). The MALDI results of the reaction

mixture revealed the presence of compounds **3.3** and **3.5**, as Na^{+} and K^{+} chelates and compounds **3.4** and **3.6** as their Na^{+} chelates (see appendix).



Scheme 3.6: mono- and di- α, β-unsaturated fluorescein aldehyde conjugated with cysteine (a) or homocysteine (b).

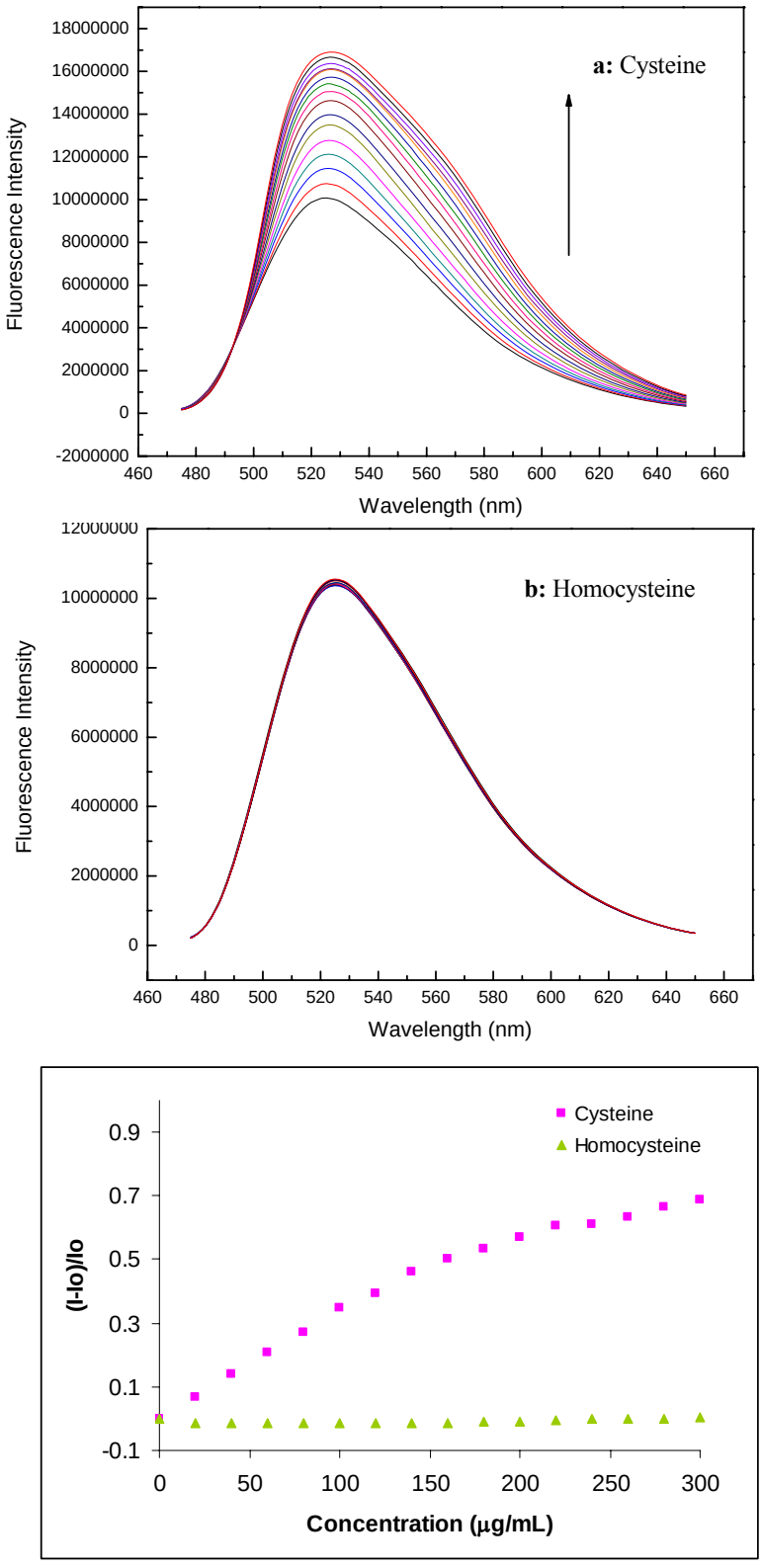


Figure 3.7. Fluorescence emission spectra of solutions of **3.1** (1.7×10^{-6} *M*, 0.1 *M* carbonate buffer, pH 9.5) excited at 485 nm at rt in the presence of various concentrations of Cys (a) and Hcy (b).

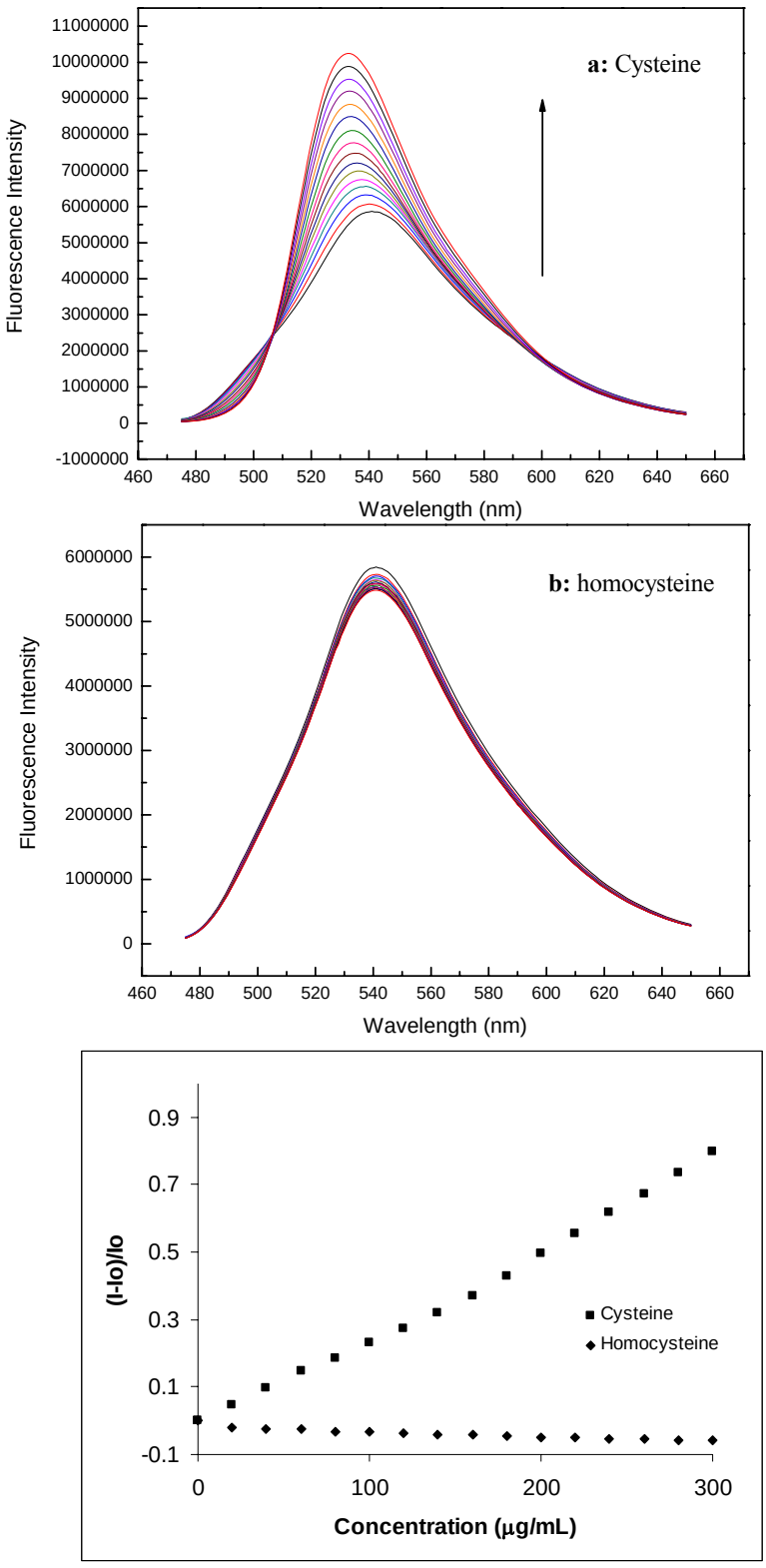


Figure 3.8. Fluorescence emission spectra of solutions of **3.2** (1.7×10^{-6} *M*, 0.1 *M* carbonate buffer, pH 9.5) excited at 485 nm at rt in the presence of various concentrations of Cys (a) and Hcy (b).

3.4 Experimental

General. UV-Visible spectra were recorded at rt on a Spectramax Plus (Molecular Devices). Analytical thin-layer chromatography (TLC) was performed using general-purpose silica gel on glass (Scientific Adsorbants). Chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å). All chemicals were purchased from Sigma-Aldrich and used without further purification. Proton NMR spectra were acquired in either CD_3OD, or DMSO-d_6 on a Bruker DPX-250, DPX-300 spectrometer. All δ values are reported with $(CH_3)_4Si$ at 0.00 ppm or DMSO at 2.49 ppm as references.

- **Synthesis of α,β-unsaturated Fluorescein-mono-aldehyde (3.1)**

To a solution of monoaldehyde **2.2** (144 mg, 0.4 mmol) in $CHCl_3$ (25 mL), triphenylphosphoranylidene acetaldehyde (152 mg, 0.5 mmol) was added forming a red solution. The mixture was stirred at 50 ºC under N_2 for 24 h, cooled to rt and the solvent removed *in vacuo*. The residue was absorbed in silca gel and subjected to column chromatography (10/90 MeOH/CH_2Cl_2 v/v) to afford compound **1** (94.7 mg, 61.3%) as a red solid. Characterization data for compound **3.1**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.59 (s, 2H), 6.68 (s, 2H), 6.84 (s, 1H), 7.22 (m, 1H), 7.30 (d, *J*= 7.4 Hz, 1H), 7.69 (m, 2H), 7.99 (d, *J*= 7.4 Hz, 1H), 8.13 (d, *J*=16.09 Hz, 1H), 9.73 (d, *J*=7.96 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 103.55, 110.41, 111.37, 111.99, 113.51, 113.99, 125.09, 125.57, 127.91, 129.99, 130.88, 132.19, 133.28, 136.10, 143.56, 151.94, 152.86, 153.45, 160.61, 160.68, 169.44, 195.95. MALDI *m*/*z* for $C_{23}H_{14}O_6$, calcd 386.08, found 387.15, 409.18 (M+ Na^+), 431.16 (M+ $2Na^+$).

- **Synthesis of α,β-unsaturated Fluorescein-di-aldehyde (3.2)**

The procedure is similar as above. To a 100 mL three-neck round bottom flask.

194 mg (0.5 mmol) fluorescein dialdehyde (**2.1**) and 182.4 mg (0.6 mmol) triphenylphosphoranylidene acetaldehyde were dissolved in 30 mL MeCN. The mixture was stirred at 50 ºC under N_2 for 24 h, cooled to rt, and the red solution was concentrated under vacuum. The red solid was absorbed on silica gel and subjected to chromatography (10/90 MeOH/CH_2Cl_2 v/v) to afford compound **3.2** (82.3 mg, 37.4%) as a red solid. Characterization data for compound **3.2**. ^{1}H NMR (DMSO-d_6, 250 MHz) δ (ppm): 6.70 (m, 4H), 7.15 (dd, *J* =7.5, 16.0 Hz, 1H), 7.33 (d, *J* =7.5 Hz, 1H), 7.72 (m, 2H), 7.99 (d, *J* =7.5 Hz, 1H), 8.08 (d, *J* =16.0 Hz, 1H), 9.73 (d, *J* =7.5 Hz, 2H), 11.35 (s, 2H). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ (ppm): 82.26, 109.28, 109.66, 113.12, 124.10, 124.77, 125.86, 130.30, 131.13, 132.42, 135.79, 143.01, 149.50, 152.19, 159.51, 168,53, 195.85. MALDI *m*/*z* for $C_{26}H_{16}O_7$, calcd 440.09, found 441.05.

PART II: SYNTHESIS AND CHARACTERIZATION OF NOVEL HEPTAMETHINE CYANINE DYES AND APPLICATION IN THE DETECTION OF CYSTEINE AND HOMOCYSTEINE

3.5 Introduction

Optical sensors in the near-infrared (NIR) spectral range have recently captured the attention of researchers interested in studying chemical and biological processes in live tissues because absorption and scattering by endogenous biomolecules are minimal.[9,10] There is also ongoing interest in some NIR dyes that have applications in high-technology areas, such as photochemistry, molecular biology, clinical chemistry, tumor therapy, laser physics, nonlinear optics, laser sensitive optical recording techniques, optical disks, compact disks, laser printers, optical cards, photoengraving, transparent bar coding, forgery prevention, photoresists, spectrally sensitized photographic materials, thermal transfer printing, and heat shielding materials.[11] Among the NIR dyes, cyanine dyes are the most common ones.

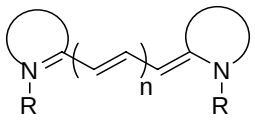


Figure 3.9: General structure of cyanine dyes.

As shown by the general structure (Figure 3.9), cyanine dyes are cationic molecules in which two heterocyclic units are connected by a polymethine chain, which possesses an electron donor in one end and an electron acceptor at the opposite end.[12,13] Their common names depend on the number of methine groups in the polymethine chain. For example, in Figure 3.9, when n=0 and n=3, they are referred to as monomethine and heptamethine respectively. Heptamethines are known to have a strong absorption band in the NIR region.

The main purpose of this project is the synthesis of a subclass of heptamethine cyanine dyes **3.7-3.9** (Figure 3.10) that could potentially be used to detect or label cysteine (Cys) or homocysteine (Hcy).

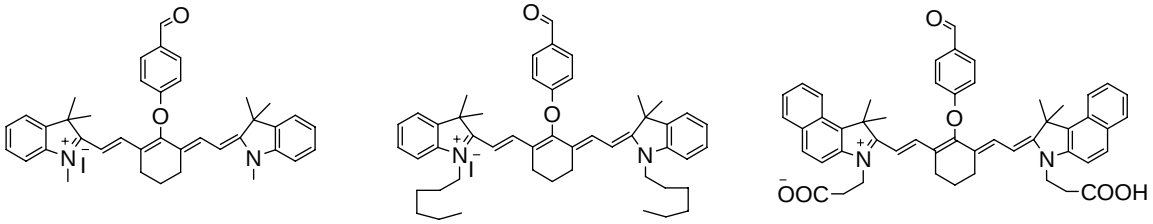
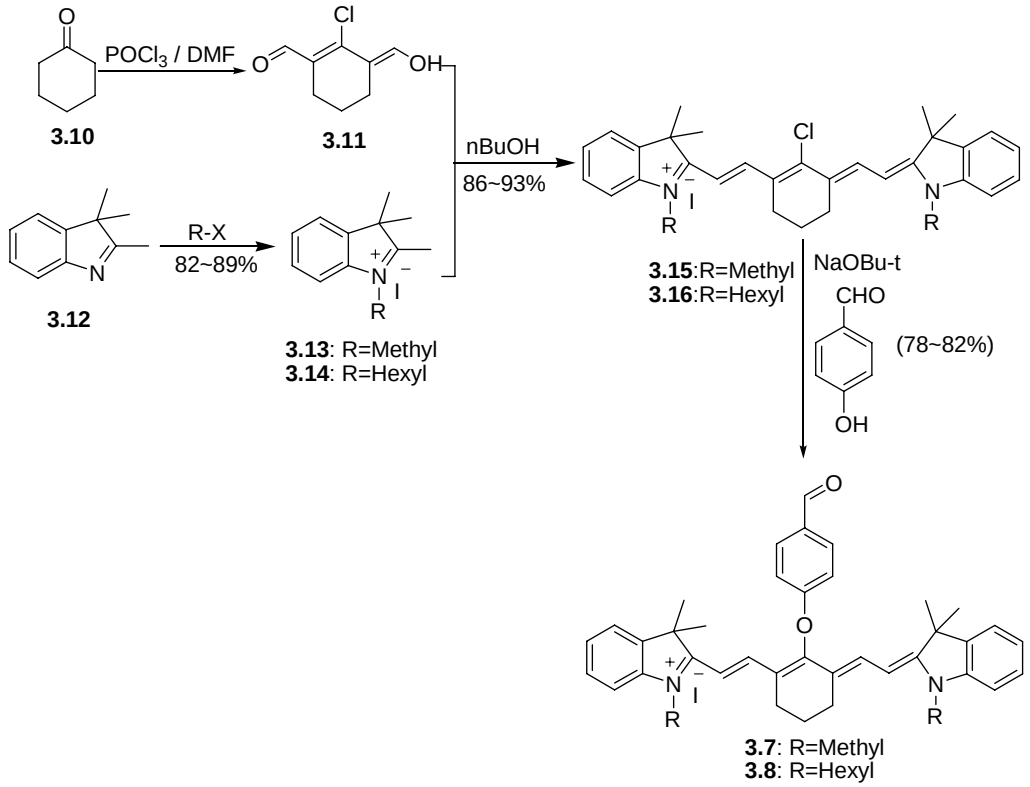


Figure 3.10: NIR probes for the detection of Cys and Hcy.

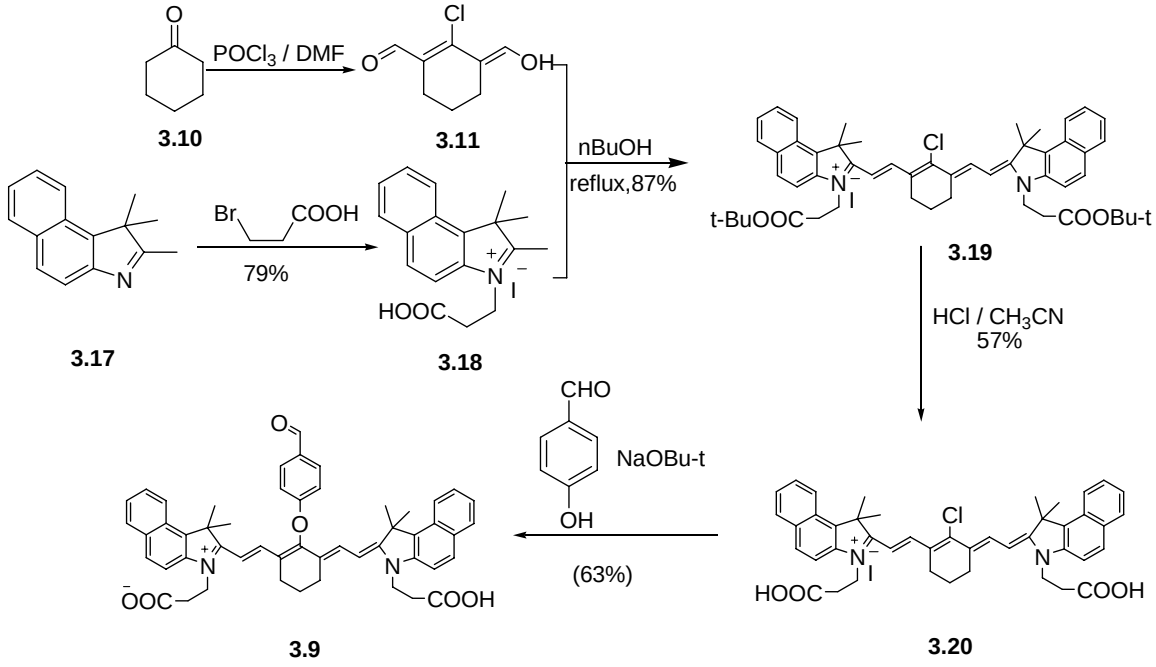
3.6 Results and Discussion

- **Synthesis**

The dyes **3.7** and **3.8** were synthesized according to the general procedures for the synthesis of heptamethine cyanine dyes[14] (Scheme 3.7). As shown in scheme 3.7, the



Scheme 3.7. Synthesis of heptamethine cyanine aldehyde **3.7** and **3.8.**



Scheme 3.8: Synthesis of compound **3.9.**

intermediate **3.11** (2-chloro-1-formyl-3-hydroxymethylenecyclohexene) was prepared according to literature procedures.[15,16] Intermediates **3.13** and **3.14** were made via heating at reflux a solution of alkyl iodides (methyl iodide or hexyl iodide) and **3.12** (2,3,3-trimethylindolenine), in high yield. Normally, the pure salts can be recrystallized from ethanol or methanol. Furthermore, according to Patonay's method,[13] **3.15** and **3.16** can be easily obtained in good yield. The synthesis of heptamethine cyanine aldehyde dyes (**3.7** and **3.8**) were accomplished by stirring 4-hydroxy benzaldehyde and heptamethine chlorides (**3.15** and **3.16**) in DMF in the presence of base (NaO*t*-Bu). Pure product was obtained after column chromatography. Single-crystal X-ray structure data confirms the assignment of **3.7** and **3.8** (Figures 3.11 and 3.13)

The heptamethine cyanine dye **3.9** was prepared according to Scheme 3.8, in which the intermediate **3.11** was synthesized according to a known procedure[15,16] (note: **3.11** is somewhat unstable and needs to be stored in the dark at -20 ºC or convert it to its stable aniline Schiff base). Reaction of **3.17** with 3-bromopropionic acid in 1,2-dichlorobenzene gave compound **3.18**. Condensation of **3.11** and **3.18** in *n*-butanol under azeotropic conditions quantitatively afforded diester **3.19**, which was characterized by ^{1}H NMR and MALDI and showed the same spectra as the published one (see appendix).[15] Diester **3.19** was dissolved in CH_3CN and 1N HCl was slowly added while stirring at 60 ºC overnight. Compound **3.20** precipitated as shining crystals. Pure **3.20** can also be obtained via flash column chromatography. The heptamethine cyanine aldehyde (**3.9**) synthesis was accomplished by stirring 4-hydroxy benzaldehyde and heptamethine chloride (**3.20**) in DMF in the presence of base (NaO*t*-Bu). Purified product was obtained after column chromatography. Single-crystal X-ray structure analysisconfirmed the structure assignment of **3.9** (Figure 3.12).

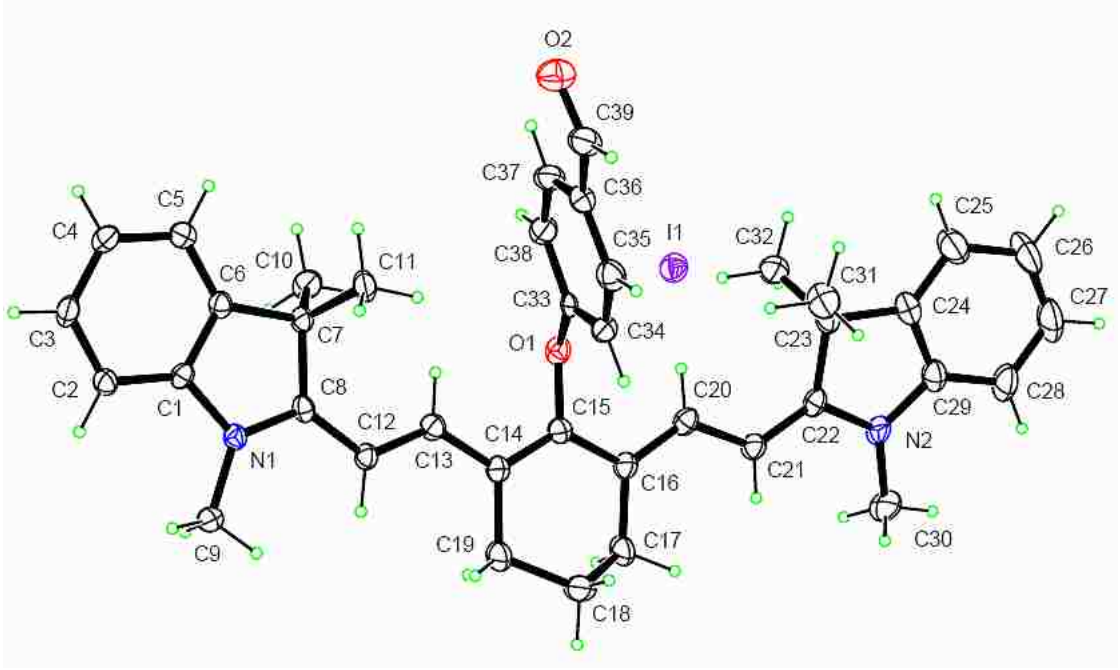


Figure 3.11. Single-crystal X-ray structure of compound **3.7.**

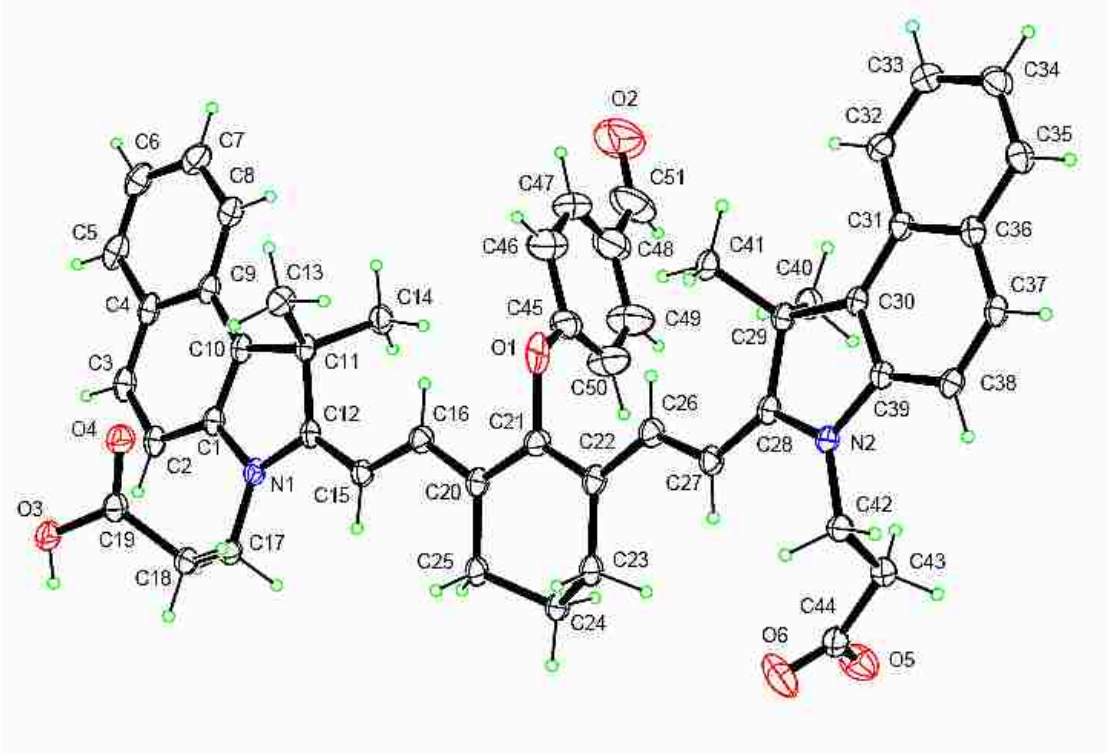


Figure 3.12. Single-crystal X-ray structure of compound **3.9.**

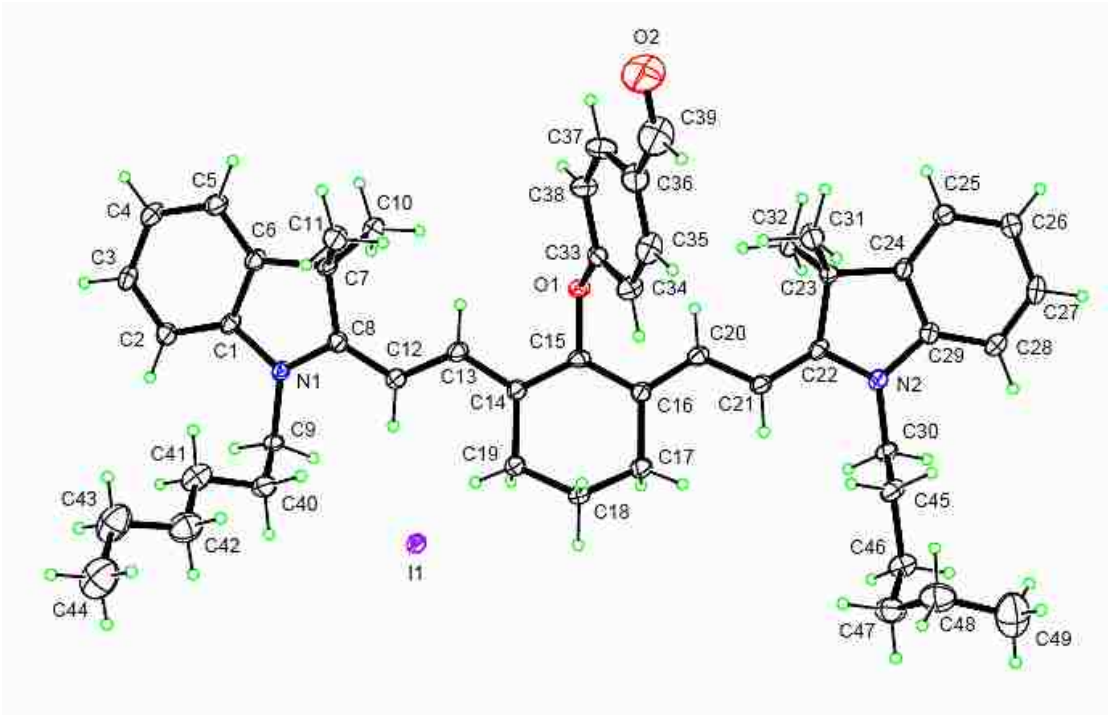


Figure 3.13. Single-crystal X-ray structure of compound **3.8.**

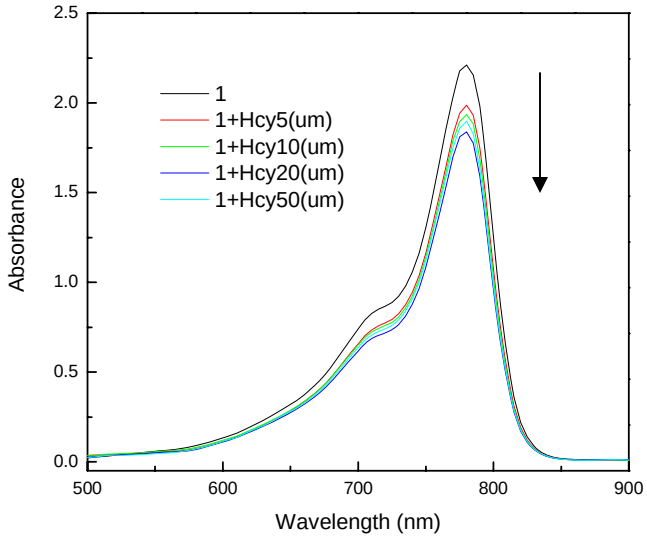


Figure 3.14: Vis-NIR spectra of solutions containing NIR dye **3.7** (1×10^{-6} *M*, 0.1 M carbonate buffer, pH 9.5) and Hcy (5 – 50 μM).

- **Preliminary study of novel NIR sensors for the detection of Cys and Hcy**

Figure 3.14 shows the Vis-NIR spectra of solutions containing NIR dye **3.7** and various concentrations of Hcy. The absorption decreases when the Hcy concentration increases.

3.7 Experimental

- **General procedure**

All chemicals were purchased from Sigma-Aldrich and used without further purification. UV-Visible and Visible-NIR spectra were recorded at rt on a Spectramax Plus (Molecular Devices). Mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with proper matrices. Analytical thin-layer chromatography (TLC) was performed using general-purpose silica gel on glass (Scientific Adsorbants). Chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å). Proton NMR spectra were acquired in either CD_3OD, or DMSO-d_6 on a Bruker DPX-250 or a Bruker DPX-300 spectrometer. All δ values are reported with $(CH_3)_4Si$ at 0.00 ppm or DMSO at 2.49 ppm as references.

Collection of X-ray Data. Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with MoKα radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller.

- **Synthesis of 1,2,3,3-Tetramethyl-3H-indolium iodide (3.13)**

2,3,3-trimethylindolenine (5 g, 31.39 mmol) and iodomethane (8.91 g, 62.78 mmol) were dissolved in 30 mL MeOH. The mixture was heated and refluxed under N_2 for 20 h. and cooled to rt. The solid product was filtered and washed with cold MeOH to give 7.73 g (81.8%) pink crystalline solid. ^{1}H NMR (DMSO-d_6, 250 MHz) δ (ppm): 1.51 (s, 6H), 2.76 (s, 3H), 3.96 (s, 3H), 7.59 (m, 2H), 7.80 (m, 1H), 7.88 (m, 1H)

- **Synthesis of 1-Hexyl-2,3,3-trimethyl-3H-indolium iodide (3.14)**

2,3,3-trimethylindolenine (1 g, 6.3 mmol) and 1-iodohexane (6.68 g, 31.5 mmol) were mixed in a 50 mL round bottom flask. The mixture was heated and refluxed at 100 ºC under N_2 for 15 h and cooled to rt. The solvent was removed under vacuum. The residue was washed with Et_2O followed by MEK to give 2.06 g (88.1%) of a white solid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.85 (t, *J*=7.0 Hz, 3H), 1.30 (m, 6H), 1.67 (s, 6H), 1.92 (m, 2H), 3.13 (s, 3H), 4.65 (t, *J*=7.75 Hz, 2H), 7.58 (m, 4H,) ^{13}C NMR (Acetone-d_6, 62.5 MHz) δ (ppm): 13.77, 15.59, 22.44, 22.59, 26.50, 28.09, 31.58, 49.35, 55.12, 116.25, 124.03, 129.55, 130.10, 141.95, 142.69, 196.99 MALDI *m/z* for $C_{17}H_{22}N^+$, calcd 244.21, found 243.84.

- **Synthesis of 3-(2-carboxyethyl)-1,1,2-trimethyl-1H-benz[e]indolium bromide (3.18)**

1,1,2-Trimethylbenz(e)indole (6.3 g, 30.1 mmol) and 3-bromopropionic acid (5.02 g, 32.8 mmol) were dissolved in 30 mL 1,2-Diclorobenzene. The mixture was heated and refluxed at 110 ºC under N_2 for 15 h and cooled to rt. The precipitate was filtered and washed thoroughly with CH_2Cl_2 to give 8.64 g (79.33%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.74 (s, 6H), 2.95 (s, 3H), 3.00 (t, *J*=5.75 Hz, 2H), 4.74 (t, *J*=5.75 Hz, 2H), 7.37 (d, *J*= 5.0 Hz, 1H), 7.61 (d, *J*= 5.0 Hz, 1H), 7.74 (m, 2H), 8.26 (d, *J*=7.5 Hz, 1H), 8.34 (d, *J*= 7.5 Hz, 1H).

- **Synthesis of 3.15**

Into a round bottom flask equipped with a Dean-Stark trap and a condenser, compound **3.13** (6.02 g, 20 mmol) and compound **3.11** (1.72 g, 10 mmol) were dissolved in a mixture of 100 mL of *n*-butanol and 30 mL of benzene. The mixture was azeotropically refluxed overnight and cooled to rt and a greenish crystalline solid precipitated. The solid was filtered and washed with Et_2O to afford 5.7 g (93.3%) of

compound **3.15**. Characterization data for compound **3.15**. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.70 (s, 6H), 1.95 (m, 2H), 2.72 (t, *J*=6.0 Hz, 4H), 3.73 (s), 6.15 (d, *J*= 14.1 Hz, 2H), 7.17 (d, *J*= 7.5 Hz, 2H), 7.23 (d, *J*= 7.5 Hz, 2H), 7.35 (m, 4H), 8.30 (d, *J*= 14.1 Hz, 2H).

- **Synthesis of 3.16**

The procedure is similar as the one for preparing **3.15**. Into a flask equipped with a Dean-Stark trap, compound **3.14** (3.71 g, 10 mmol) and **3.11** (0.86 g, 5 mmol) were dissolved in a mixture of 100 mL of *n*-butanol and 30 mL of toluene. The mixture was azeotropically refluxed overnight and cooled to rt. A greenish crystalline solid was precipitated. The solid was filtered and washed with Et_2O to give 3.23 g (86.1%) of compound **3.16**. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.85 (t, *J*=7.0 Hz, 6H), 1.31 (m, 12H), 1.69 (s, 12H), 1.81 (m, 6H), 2.66 (t, *J*=6.0 Hz, 4H), 4.14 (t, *J*=7.5 Hz, 4H), 6.12 (d, *J*= 14.0 Hz, 2H), 7.13 (d, *J*= 7.5 Hz, 2H), 7.22 (d, *J*=7.5 Hz, 2H), 7.36 (m, 4H), 8.29 (d, *J*=14.0 Hz, 2H) ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (ppm): 13.81, 20.54, 22.27, 26.48, 27.16, 27.84, 27.97, 31.24, 44.86, 49.20, 101.08, 110.81, 122.16, 125.21, 127.00, 128.66, 140.87, 142.01, 144.13, 150.34, 172.18 MALDI *m/z* for $C_{42}H_{56}ClN_2^+$, calcd 623.41, found 623.00.

- **Synthesis of 3.19**

The procedure is similar as that for making **3.15**. Into a flask equipped with a Dean-Stark trap, 7.24 g (20 mmol) of **3.18** and 1.72 g (10 mmol) of **3.11** were dissolved in a mixture of 100 mL of *n*-butanol and 30 mL of toluene. The mixture was azeotropically refluxed overnight and cooled to rt. A greenish crystalline solid precipitated. The solid was filtered and washed with Et_2O to give 7.77 g (87.1%) of product. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.80 (t, , *J*= 7.25 Hz, 6H), 1.24 (m, 4H),

1.47 (m, 4H), 1.99 (s, 12H), 2.30 (m, 2H), 2.77 (m, 4H), 2.98 (t, *J*= 6.25 Hz, 4H), 3.98 (t, *J*= 6.75 Hz, 4H), 4.70 (t, *J*=6.00 Hz, 4H), 6.33 (d, *J*=14.00 Hz, 2H), 7.44 (d, *J*=8.00 Hz, 2H), 7.58 (m, 4H), 7.91 (m, 4H), 8.08 (d, *J*= 8.00 Hz, 2H), 8.41 (d, *J*= 14.00 Hz, 2H), MALDI *m/z* for $C_{52}H_{60}ClN_2O_4^+$, calcd 811.42, found 810.84.

- **Synthesis of 3.20**

Into a N_2 flushed 100 mL round bottom flask, 500 mg (0.56 mmol) of **3.19** was dissolved in 10 mL of MeCN. 10 mL of 1N HCl was added and the mixture allowed to stir at 60 ºC overnight and cooled to rt. A brown crystalline solid precipitated. The solid was filtered and washed with copious amounts of water to give 287.64 mg (57%) of compound **3.20**. ^{1}H NMR (DMSO-d_6, 250 MHz) δ (ppm): 1.94 (m, 14H), 2.81 (m, 8H), 4.56 (t, *J*=6.25 Hz, 4H), 6.43 (d, *J*=14.0 Hz, 2H), 7.51 (t, *J*=7.5 Hz, 2H), 7.66 (t, *J*=7.5 Hz, 2H), 7.76 (d, *J*=8.7 Hz, 2H), 8.07 (t, *J*=7.5 Hz, 4H), 8.27 (d, *J*=8.7 Hz, 2H), 8.33 (d, *J*= 14.0 Hz, 2H) 12.63 (b, 2H) MALDI *m/z* for $C_{44}H_{43}ClN_2O_4$, calcd 698.29, found 698.85.

- **Synthesis of 3.7**.

To an ice cooled 50 ml three-neck round bottom flask, 4-hydroxybezaldehyde (136.6 mg, 1.12 mmol) and sodium *tert*-butoxide (101.88 mg, 1.06 mmol) were mixed. Anhydrous DMF (20 mL) was added under N_2 while stirring. After 30 min, the solution was allowed to warm to rt and the chloro-dye **3.15** (611 mg, 1 mmol) was added. Three hours later, the reaction was quenched with dry ice, and the solvent was removed under vacuum. The crude product was subjected to column chromatography with CH_2Cl_2/MeOH 9/1 to give 577.86 mg (82%) of a green crystalline solid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.29 (s, 12H), 2.05 (m, 2H), 2.77 (m, 4H), 3.68 (m, 6H), 6.12 (d, *J*= 14.2 Hz, 2H), 7.12 (d, *J*= 8.5 Hz, 2H), 7.22 (m, 6H), 7.34 (m, 2H), 7.73 (d,

J= 14.2 Hz, 2H), 7.92 (d, *J*= 8.5 Hz, 2H), 9.90 (s, 1H) ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (ppm): 20.95, 24.37, 27.67, 31.86, 48.78, 100.88, 110.67, 115.19, 121.87, 122.10, 125.16, 128.70, 131.15, 132.59, 140.68, 141.06, 142.60, 162.10, 163.93, 172.37, 190.46 MALDI m/z for $C_{39}H_{41}N_2O_2^+$, calcd 569.32, found 570.18.

- **Synthesis of 3.8**.

The procedure is similar as above. To an ice-cooled 50 mL three-neck round bottom flask, 4-hydroxybezaldehyde (67.16 mg, 0.55 mmol) and sodium *tert*-butoxide (50.94 mg, 0.53 mmol) were mixed. Anhydrous DMF (20 mL) was added under N_2 with stirring. After 30 min, the solution is allowed to warm to rt and the chloro-dye **3.16** (375.63 mg, 0.50 mmol) was added and stirred for 3 h. The reaction was quenched with dry ice, and the solvent removed under vacuum. The crude product was subjected to column chromatography with CH_2Cl_2/MeOH 90/5 to give 326.61 mg (78%) of a brown crystalline solid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) 0.87 (t, *J*=7.0 Hz, 6H), 1.35 (m, 24H), 1.79 (m, 4H), 2.08 (m, 2H), 2.77 (t, *J*=5.75 Hz, 4H), 4.08 (t, *J*=7.5 Hz, 4H), 6.07 (d, *J*=14.2 Hz, 2H), 7.06 (d, *J*=8.0 Hz, 2H), 7.22 (m, 6H), 7.31 (m, 2H), 7.74 (d, *J*=14.2 Hz, 2H), 7.95 (d, *J*=8.0 Hz 2H), 9.92 (s, 1H) ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (ppm): 13.92, 20.98, 22.39, 24.49, 26.58, 27.22, 27.78, 31.34, 44.78, 48.93, 100.51, 110.68, 115.29, 121.78, 122.09, 125.16, 128.66, 131.18, 132.68, 140.88, 141.16, 142.03, 162.32, 163.88, 171.83, 190.54 MALDI *m/z* for $C_{49}H_{61}N_2O_2^+$, calcd 709.47, found 708.57.

- **Synthesis of 3.9.**

To an ice-cooled 150 mL three-neck round bottom flask, 4-hydroxybezaldehyde (195.39 mg, 1.6 mmol) and sodium *tert*-butoxide (153.78 mg, 1.6 mmol) were mixed. Anhydrous DMF (50 mL) was added under N_2 with stirring. After 30 min, the solution was allowed to warm to rt and the chloro-dye **3.20** (390.09 mg, 0.5 mmol) was added and

stirred for 3 h. The reaction was quenched with dry ice, and the solvent removed under vacuum. The crude product was washed with 1N HCl and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue subjected to column chromatography (CH_2Cl_2/MeOH 86/14 to afford 183.14 mg (63%) of a light brown crystalline solid. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.85 (m, 4H), 1.61 (s, 12H), 2.10 (m, 2H), 2.84 (m, 4H), 4.47 (m, 4H), 6.29 (d, *J*=14.2 Hz, 2H), 7.31 (d, *J*= 8.5 Hz, 2H), 7.43 (t, *J*= 7.5 Hz, 4H), 7.55 (t, *J*= 7.5 Hz, 2H), 7.87 (m, 10H), 9.93 (s, 1H) ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (ppm): 14.11, 24.44, 27.43, 29.68, 33.87, 41.49, 50.67, 70.53, 100.34, 110.68, 115.38, 121.86, 124.97, 127.58, 127.94, 130.13, 130.77, 131.19, 131.86, 132.75, 133.69, 139.27, 140.55, 162.09, 164.13, 173.17, 174.02, 190.53 MALDI *m/z* for $C_{51}H_{48}N_2O_6$, calcd 784.35, found 784.53.

3.8 Conclusion

In summary, two novel fluorescein-based fluorescent sensors, compound **3.1** and **3.2**, were developed. The fluorescence studies of the two α,β-unsaturated fluorescein-based aldehyde show that both of them have highly selective detection of Cys over Hcy. Base on the ^1H NMR shifts before and after the reaction and the mass spectra of the reaction mixture of compound **3.1** and cysteine, a hypothetical mechanism about the selection was also proposed. We believed under the slightly basic conditions the α,β-unsaturated fluorescein-based aldehyde would like to react with cysteine via a kinetic reaction control to form a 5-membered ring or a 7-membered ring containing product, while homocysteine would like to undergo via a thermodynamic reaction control to form a saturated aldehyde. Besides, I also synthesized three heptamethine-based aldehydes, which show a potential application of detection of cysteine and homocysteine in the NIR region.

3.9 References

1 Wang, W.; Rusin, O.; Xu, X.; Kim, K.K.; Escobedo, J. O.; Fakayode, S. O.; Fletcher, K. A.; Lowry, M.; Schowalter; C. M.; Lawrence, C. M.; Fronczek, F. R.; Warner, I. M.; Strongin, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 15949-15958.

2 Burdette, S. C.; Walkup, G. K.; Spingler, B.; Tsien, R. Y.; Lippard, S. J. *J. Am. Chem. Soc*. **2001**, *123*, 7831-7841.

3. Lancaster, J. E.; Boland, M. J. *CRC Onion Allied Crops* **1990**, *3*, 33-68.

4. Block, E. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1135-1178.

5. Starkenmann, C. *J. Agric. Food Chem.* **2003**, *51*, 7146-7155.

6. Starkenmann, C.; Brauchli, R.; Maurer, B. *J. Agric. Food Chem.* **2005**, *53*, 9244-9248.

7. Esterbauer, H.; Ertl, A.; Scholz, N. *Tetrahedron* **1976**, *32*, 285-289.

8. Fife, T. H.; Natarajan, R.; Shen, C. C.; Bembi, R. *J. Am. Chem. Soc*. **1991**, *113*, 3071-3079.

9. Ntziachristos, V.; Tung, C. H.; Bremer, C.; Weissleder, R. *Nat. Med*. **2002**, *8*,75.

10. Hawrysz, D. J.; Sevick-Muraca, E. M., *Neoplasia* **2002**, *2*, 388.

11. Daehne, S.; Resch-Genger, U.; Wolfbeis, O. S. *Near-Infrared Dyes for High Technology Applications*, June **1998**.

12. Tyutyulkov, N.; Fabian, J.; Mehlhorn, A.; Dietz, F.; Tadjer, A. *Polymethine Dyes: Structure and properties*; St. Kliment Ohridski University Press: Sofia, Bulgaria, **1991**.

13. Fabian, J.; Nakazumi, H.; Matsuoka, M. *Chem. Rev*. **1992**, *92*, 1197-1226.

14. Narayanan, N.; Patonay, G. *J. Org. Chem.* **1995**, *60*, 2391-2395.

15. Reynolds, G. A.; Drexhage, K. H. *J. Org. Chem.* **1977**, *42*, 885-888.

16. Zhang, Z.; Achilefu, S. *Org. Lett.* **2004**, *6*, 2067-2070.

CHAPTER 4

A HYDROGEL FOR BIOMEDICAL APPLICATION

4.1 Introduction

Hydrogels are composed of three-dimensional cross-linked hydrophilic polymer networks that can contain a large amount of water.[1-5] Many hydrogels are biocompatible and have been studied in many fields. For example, based on responses to temperature changes, hydrogels have been used in drug delivery systems,[6-11] e.g., Hoffman et. al have developed a system for delivering vitamin B12.[11] Hydrogels also undergo swelling and contraction in response to environmental factors such as type of solvent,[12] ion concentration,[13] pH[14] etc. Recently, in our group, we have systematically added specific functional groups to poly-methylmethacrylate (PMMA). The derivatized PMMA can selectively contract in the presence of glucose over other sugars, at physiological levels in human blood plasma.[15] Other hydrogel applications include contact lenses,[16] and separation processes.[17,18]

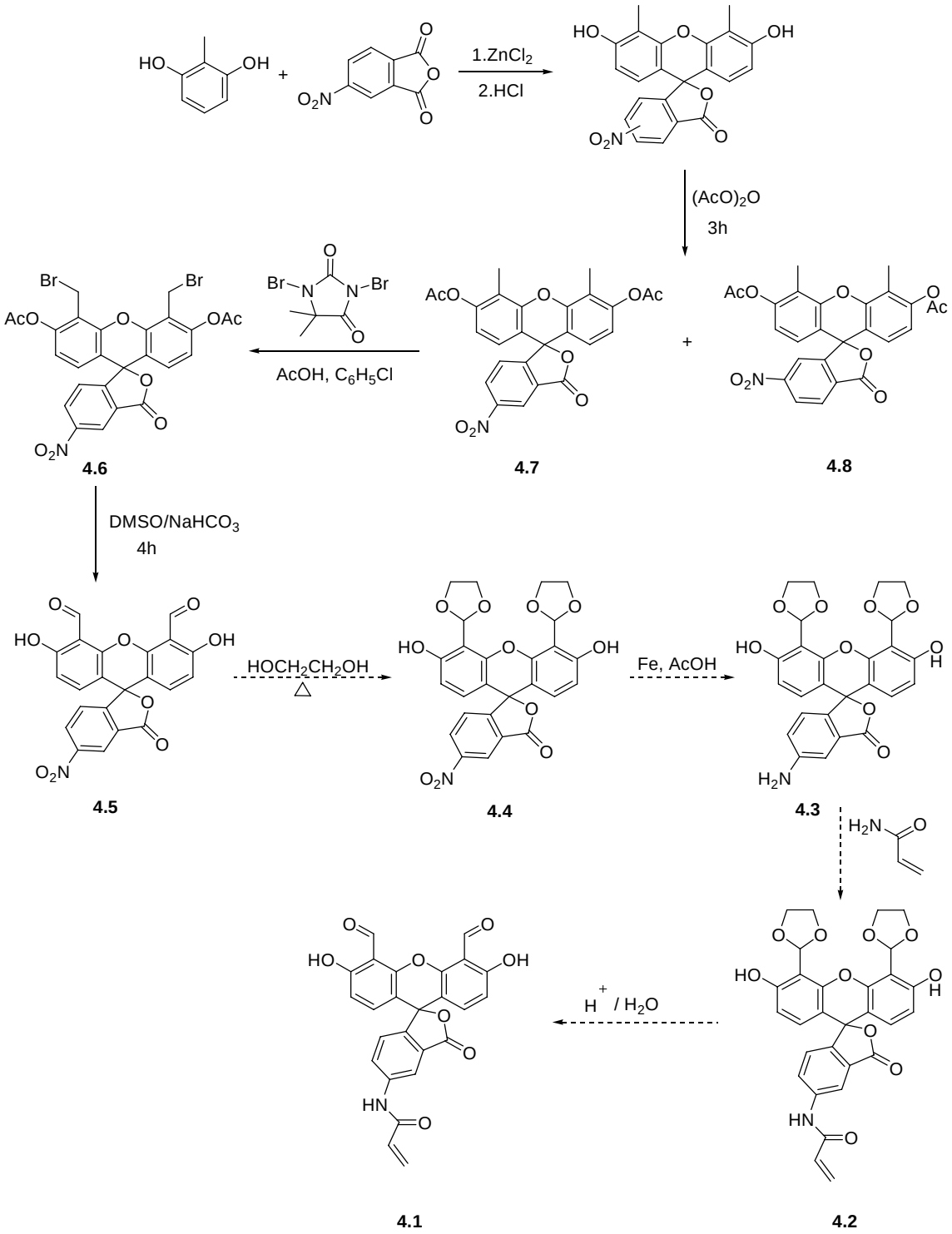
Polyacrylamide (PAAm) hydrogels are some of the most common hydrogels.[16-18] They are normally made from acrylamide subunits which are very easily polymerized.

In the first part of this work we tried to synthesize a fluorescein-based polyacrylamide polymer which can have potential application for cysteine or homocysteine detection (Scheme 4.1).

4.2 Results and Discussion

- **Synthesis of compound 4.1**

Compound **4.5** (4-nitro-4',5'-fluorescein dialdehyde) was synthesized according to the procedure shown in Scheme 4.1 starting from the condensation of commercially



Scheme 4.1: Synthesis of 5'-acryloylamidofluorescein dialdehyde (**4.1**).

available 2-methyl resorcinol and 4-nitrophthalic anhydride in the presence of $ZnCl_2$ at high temperatures (150-230 ºC). ^1H NMR analysis indicated that the crude product contained *ca*. a 1.3:1 ratio of 4-nitro-4',5'-dimethylfluorescein to 5–nitro-4',5'-dimethylfluorescein.

Without any further separation, the mixture was allowed to react with excess acetic anhydride under reflux in pyridine for 3 h. This afforded the acetylated mixture of both 4-nitro-4'-5'-dimethylfluorescein and 5-nitro-4'-5'-dimethylfluorescein diacetates (compounds **4.7** and **4.8** respectively). Recrystallization from EtOAc produced pure compound **4.7**. The filtrate was concentrated and recrystallized from toluene to afford pure isomer **4.8**.

Under mild bromination conditions, 4-nitro-4',5'-bis(bromomethyl)fluorescein diacetate (**4.6**) can be generated from compound **4.7** in high yields. Figure 4.1 shows the single crystal X-ray structure of **4.6**.

A Kornblum reaction[19] was used to convert the dibromo fluorescein (**4.6**) to 4-nitro fluorescein dialdehyde (**4.5**) via oxidation of compound **4.6** with DMSO in the presence of excess $NaHCO_3$ at 130 ºC for 4 h.

Exhaustive attempts to directly reduce the nitro group in the presence of an unprotected aldehyde group are still ongoing. An alternative method to reduce the nitro group to an amino is shown in scheme 4.1. After condensation of amino compound **4.3** with acryloyl chloride, ethylene acetal **4.2** can be deprotected to obtain dialdehyde monomer **4.1**.

4.3 Experimental

General. UV-Visible spectra were recorded at rt on a Spectramax Plus 384 (Molecular Devices). Analytical thin-layer chromatography (TLC) was performed using

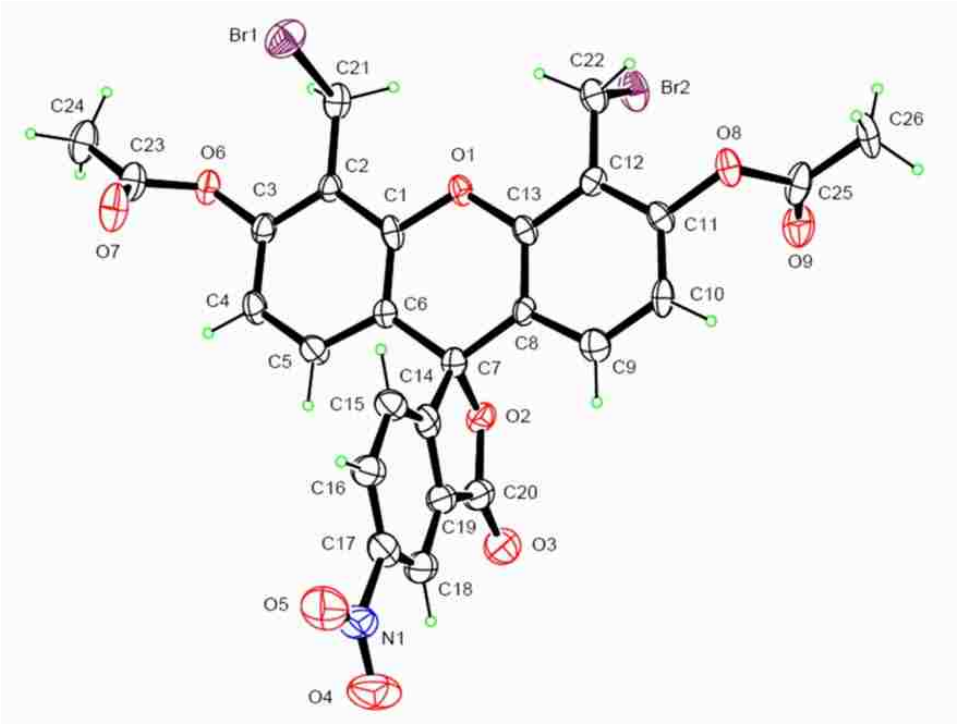


Figure **4**.**1**. single crystal X-ray structure of compound **4.6**, 4-nitro-4',5'-bis(bromomethyl)fluorescein diacetate.

general-purpose silica gel on glass (Scientific Adsorbants). Chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å). All chemicals were purchased from Sigma-Aldrich and used without further purification. ^{1}H NMR spectra were acquired in either CD_3OD, or DMSO-d_6 on a Bruker DPX-250 or DPX-300 spectrometer. All δ values are reported with $(CH_3)_4Si$ at 0.00 ppm or DMSO at 2.49 ppm as references.

Collection of X-ray Data. Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with MoKα radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller.

- **Syntheis of 4-Nitro-4',5'-Dimethylfluorescein Diacetate (4.7) and 5–Nitro-4', 5'-Dimethylfluorescein Diacetate (4.8)**

A mixture of 4-nitrophthalic anhydride (10 g, 51.78 mmol) and 2-methylresorcinol (11.57 g, 93.20 mmol) was heated until complete liquification (around 150 ºC) and 5 g fused $ZnCl_2$ was added portionwise. The temperature was gradually increased to 230 ºC until the mixture solidified. The solid was allowed to cool to rt, crushed and added to 200 mL 3M HCl. The mixture was boiled for 1 h. The crude product was filtered, flushed with copious amounts of water and dried under vacuum overnight. Without any purification, acetic anhydride (40 mL) was added to the mixture and dissolved in 100 mL pyridine and heated under reflux for 3 h. The mixture was cooled to rt and the solvent removed in vacuum. The residue was dissolved in the least amount of EtOAc and 4-Nitro-4',5'-Dimethylfluorescein Diacetate (**4.7**) recrystallized out. The pure pale yellow **4.7** can be obtained by 2 or 3 consecutive recrystallizations from EtOAc. The mother liquor was concentrated and redissolved in toluene, and 5–Nitro-4',5'-Dimethylfluorescein Diacetate (**4.8**) can be recrystallized out. The more pure

purple **4.8** can be obtained by 2 or 3 consecutive recrystallizations from Toluene. ^{1}H NMR for 4-Nitro-4',5'-Dimethylfluorescein Diacetate (**4.7**) ($CDCl_3$, 250 MHz) δ (ppm): 2.36 (s, 12H), 6.63 (d, *J* =8.7 Hz, 2H), 6.79 (d, *J* =8.7 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 1H), 8.49 (dd, *J*=2.0, 8.4 Hz, 1H), 8.83 (d, *J*=2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (ppm): 9.98, 21.19, 83.47, 115.14, 118.60, 120.13, 121.37, 125.57, 126.12, 128.15, 130.38, 149.84, 150.35, 151.22, 158.15, 167.07, 169.15. MALDI *m*/*z* for $C_{26}H_{19}NO_9$, calcd 489.11, found 490.59 (M+ H^+).

^{1}H NMR for 5-Nitro-4',5'-Dimethylfluorescein Diacetate (**4.8**) ($CDCl_3$, 300 MHz) δ (ppm): 2.37 (s, 12H), 6.66 (d, *J* =8.64 Hz, 2H), 6.82 (d, *J* =8.64 Hz, 2H), 8.03 (d, *J*=1.68 Hz, 1H), 8.21 (d, *J*=8.34 Hz, 1H) , 8.46 (dd, *J*=1.68, 8.34 Hz, 1H).

- **Synthesis of 4-Nitro-4', 5'-Bis(bromomethyl)fluorescein Diacetate (4.6)**

Into a 500 mL round bottom flask was added C_6H_5Cl (90 mL), 4-nitro-4',5'-dimethylfluorescein diacetate (1 g, 2.04 mmol), 1,3-dibromo-5,5-dimethylhydantoin (0.7 g, 2.45 mmol), 1,1'-azobis(cyclohexanecarbonitrile) (0.16 g, 0.08 mmol) and acetic acid (0.03 mL). The mixture was stirred at 40 ºC for 72 h, cooled to rt and washed 3 times with hot H_2O. The organic layer was collected and dried over $MgSO_4$. A pale yellow product was obtained after solvent removal in vacuo. The X-ray analysis of a single crystal confirmed the expected structure. ^{1}H NMR for 4-nitro-4',5'-bis(bromomethyl)fluorescein diacetate ($CDCl_3$, 300 MHz) δ (ppm): 2.42 (s, 6H), 4.81 (s, 4H), 6.76 (d, *J* =8.7 Hz, 2H), 6.94 (d, *J* =8.7 Hz, 2H), 7.44 (d, *J*=8.4 Hz, 1H), 8.54 (dd, *J*=1.9, 8.4 Hz, 1H), 8.86 (d, *J*=8.4 Hz,1H).

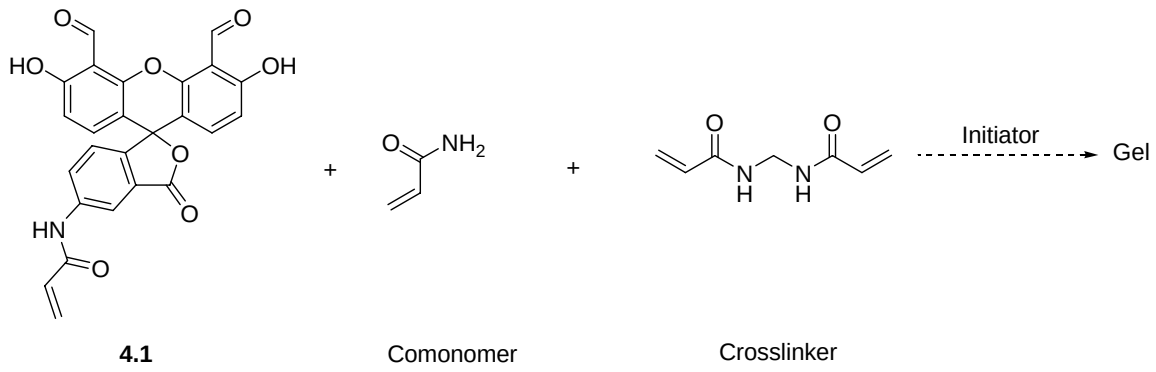
- **Synthesis of 4-Nitro-4', 5'-Fluorescein Dialdehyde (4.5)**

4-Nitro-4',5'-bis(bromomethyl)fluorescein diacetate (500 mg, 0.77 mmol) and $NaHCO_3$ (500 mg, 6.0 mmol) were dissolved in DMSO (50 mL). The solution was

stirred at 130 ºC for 4 h and cooled to rt. To the resulting mixture 2N HCl (200 mL) was added and stirred for 30 min producing a red solid precipitate. The solid was filtered, dried and subjected to flash column chromatography on silica gel (EtOAc:CH_2Cl_2 8:2). A pale yellow solid was obtained (yield: 113 mg, 33.7%). ^{1}H NMR for 4-nitro-4',5'-fluorescein dialdehyde (DMSO, 300 MHz) δ (ppm): 6.78 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 8.60 (dd, *J*=1.8, 8.4 Hz, 1H), 8.69 (d, *J*=1.8 Hz, 1H), 10.70 (s, 2H), 11.86 (s, 2H). MALDI *m*/*z* for $C_{22}H_{11}NO_9$, calcd 433.04, found 434.19 ($M+H^+$), 460.28 ($M+ Na^+ +4H^+$).

4.4 Future Work

- **Synthesis of water-soluble fluorescein-based polymer**



Scheme 4.2: Synthesis of polyacrylamide hydrogel.

Scheme 4.2 shows a proposed synthesis of polyacrylamino-fluorescein dialdehyde. During the synthesis acrylamide is used a comonomer and *N*,*N*'-methylenebis–acrylamide is used as the crosslinker. The hydrogel can be prepared via free radical polymerization or a chemical polymerization according to a well established protocol.[20]

4.5 Conclusion

I have successfully synthesized a new fluorescein-based dye, compound **4.5**,

which was a important intermediate towards the preparation of a fluorescein-based hydrogel. The single crystal X-ray structure of compound **4.6** confirmed the correct assignment of the intermediate. The rest of the synthesis is currently being done in our laboratory. The hydrogel would show a potential application of the detection of cysteine and homocysteine.

4.6 References

1. Guilherme, M. R.; Silva, R.; Girotto, E. M.; Rubira, A. F.; Muniz, E. C. *Polymer* **2003,** *44,* 4213.

2. Muta, H.; Miwa, M.; Satoh, M. *Polymer,* **2001,** *42,* 6313.

3. Zhang, X.; Hu, Z.; Li, Y. *Polymer* **1998**, *39*, 2783.

4. Garcia, D. M.; Escobar, J. L.; Bada, N.; Casquero, J.; Hernandez, E.; Katime, I. *Eur. Polym. J.* **2004**, *40*, 1637.

5. Aouada, F.; Moura, M. R.; Fernandes, P. R.; Rubira, A. F.; Muniz, E. C. *Eur. Polym. J.* **2005**, 41, 2134.

6. Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163.

7. Tanaka, T.; Filmore, D. J. *J. Chem. Phys.* **1979**, *70*, 1214.

8. Muniz, E. C.; Geuskens, G. *Macromolecules* **2001**, *14*, 4480.

9. Muniz, E. C.; Geuskens, G. *J. Mater. Sci. Mater. M.* **2000**, *12*, 879.

10. Muniz, E. C.; Geuskens, G. *J Membr Sci,* **2000**, *172*, 287.

11. Afrassiabi, A.; Hoffman. A. S. L. *J. Membr. Sci.* **1987**, *33*, 191.

12. Philippova, O. E.; Pieper, T. G.; Sitnikova, N. L.; Starodoubtsev, S. G.; Khokhlov, A. R.; Kilian, H. G. *Macromolecules* **1995**, *28*, 3925.

13. Starodoubtsev, S. G.; Khokhlov, A. R.; Sokolov, E. L.; Chu, B. *Macromolecules*, **1995**, *28*, 3930.

14. Firestone, B. A.; Siegel, R. A. *Polym. Commun.* **1988**, *29*, 204-208.

16. J. Kopecek *Euro. J. Pharm. Sci.* **2003**, *20*, 1.

15. Samoei, G.; Wang, W.; Escobedo, J. O.; Xu, X.; Schneider, H.; Strongin, R. M. *Angew. Chem. Int. Ed*. **2006**, *45*, 5319-5322

17. Park, C.-H.; Orozco-Avila, I. *Biotechnol. Prog.* **1992**, *8*, 521.

18. Park, C.-H.; Orozco-Avila, I. *Biotechnol. Prog.* **1993**, *9*, 640.

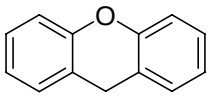
19. (a) Kornblun, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Kornblun, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.

20. Biorad. *Acrylamide Polymerization – A Practical Approach*, Bulletin 1156, also available at http://www.biocompare.com/technicalarticle/1089/Acrylamide-Polymerization-%E2%80%94-A-Practical-Approach-from-Bio-Rad.html.

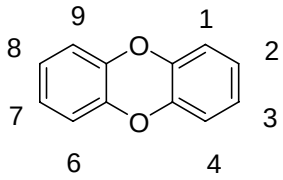
CHAPTER 5

NOVEL SYNTHESIS OF POLYHALOGENATED DIBENZO-P-DIOXINS

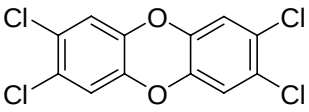
5.1 Background



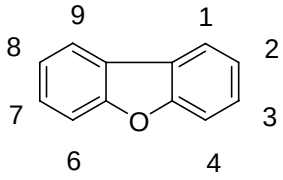
Xanthene



Dibenzo-p-dioxin



2, 3, 7, 8-tetrachloro-Dibenzo-dioxin



Dibenzofuran

Figure 5.1: Structures of xanthene and dibenzo-*p*-dioxins.

Dibenzo-p-dioxin is a structural analog of xanthene. Each are planar tricyclic aromatic ethers. Dibenzo-p-dioxin has one more C-O-C bridge existing between the two benzene rings (Figure 5.1). Dibenzo-p-dioxin is notorious particularly because of the chlorinated-members of its class, for example, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is regarded as one of the most toxic chemicals known. It is reported that 0.6 μg of TCDD per kg of body weight can kill a guinea pig.[1] It is important to note that the toxicity of 2,3,7,8-tetrachlorodibenzofuran (TCDF),[2] and the toxicity of the polybrominated-dibenzon-p-dioxins (PBDD) has also been shown to be similar to the

analogous of polychlorinated dibenzo-p-dioxin (PCDD).[3,4]

- **Significance and purpose**

Since polyhalogenated dibenzo-p-dioxins (PXDDs) have been shown to be a significant threat to public health,[3, 4] a need exists for measuring the concentrations of PXDDs in the environment as well as understanding their mechanism of formation and environmental fate. Mixed bromo/chloro PXDDs have been found, for example, in emissions from electronic wastes and waste carpets. According to the US-EPA Office of Solid Wastes, at least 2.1 million tons of electronic waste (e-waste) was generated in 2000 alone. At least 91 % of this waste entered US landfills or incinerators. Because there are hundreds of congeners of PXDDs and related compounds, there is currently a lack of available standards to allow for the proper identification and health assessment of these materials.[5-15] Upon combustion and thermal degradation, simple halogenated hydrocarbons (XHCs) can form a wide range of PXDD and related XHC emissions and reaction intermediates.

A laboratory reactor study is a practical method for understanding these complex reactions. Because of the multitude of environmentally relevant reaction products, we will synthesize a library of PXDD standards. Using carbon-13 labeling, we can study their mechanism of formation in both gas-phase and CuO-mediated surface processes under both pyrolytic and oxidative conditions. We will develop methods to examine racemic and chiral waste by-products. To the best of our knowledge, there are no reports which focus, for instance, on the formation of new stereocenters during

combustion or on the specific stereochemical fate of chiral molecules during combustion.

- **Related Synthesis**

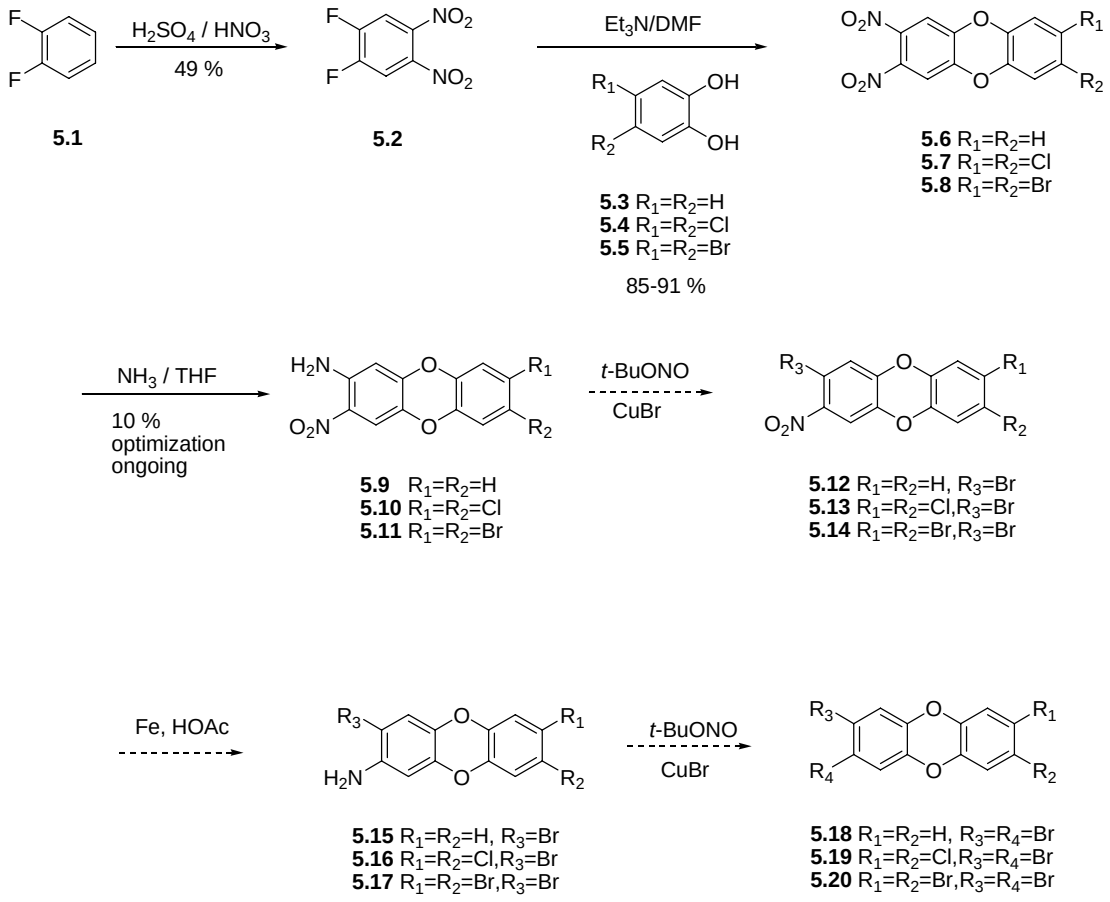
In actual waste processes, both chlorinated and brominated (e.g., flame retardant) materials are incinerated together. Importantly, progress on the origin, environmental fate, and biological activity of BHC and mixed XHCs has been hindered by a lack of available standards. There are no commercial standards of the mixed halogenated dibenzodioxins or dibenzofurans. Moreover, there have only been limited reports describing any attempted controlled syntheses of these compounds. A relatively recent related synthesiss was reported by Jay and Stieglitz.[16, 17] They used, for instance, non-halogenated dioxins as substrates which were heated at 260 – 300 °C in the presence of copper bromide and copper chloride in an inert gas flow.[17] This method of course afforded a mixture of products and little or no control over halogen substitution patterns. Older studies by Kende et al. showed that certain individual halogenated dibenzo-p-dioxins (XDDs) (including just one mixed bromo/chloro XDD) could be synthesized, isolated and characterized via carbon-13 NMR; however, there were structural isomers that were indistinguishable. Their pioneering methodology, while quite impressive during that time period, was not general towards the formation of large classes of specific mixed bromo/chloro XDD.[18]

We propose to conduct a controlled, laboratory study of the thermal reactions of PXDD precursors. This novel approach should result in large numbers of PXDDs that can be formed; the types of mixed chlorinated hydrocarbon (CHC), brominated

hydrocarbon (BHC), and XHC precursors that can form them.

5.2 Results and Discussion

- **Syntheses**



Shceme 5.1: Novel syntheses of polyhalogenated dibenzo-p-dioxins.

1,2-Difluoro-4,5-dinitrobenzene (**5.2**) was synthesized according to a published procedure with minor modification.[19] The commercially available compound 1,2-difluorobenzene (**5.1**) was carefully added neat to a pre-cooled (0 ºC), concentrated mixture of H_2SO_4 and fuming HNO_3. Because the beginning of the reaction is

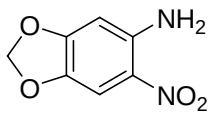
extremely exothermic, one should never let the temperature exceed 5 ºC.

After addition of compound **5.1**, the mixture was kept cooled with an ice bath and stirred for 30 min, warmed to rt and stirred for another 2 h. The reaction mixture was heated at 100 ºC overnight. Less time (e.g. 2 h, according to the literature procedure) at higher temperatures led to no reaction. Longer time is needed likely since fluoride is a weak deactivator for nitration of the benzene ring. When cooled to rt, the mixture was poured into an ice-H_2O mixture resulting in the formation of white crystals. The crystals were filtered and rinsed with copious amounts of cold H_2O. An analytical sample was recrystallized according to the published procedure.[19]

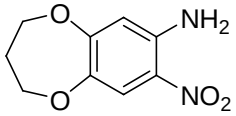
The nucleophilic aromatic substitution of fluorine in **5.2** by a catechol phenoxy group[20] (as in **5.3**, **5.4** and **5.5**) occurs smoothly in DMF in the presence of Et_3N at 60 ºC , affording yellow 6,7-dinitro substituted benzodioxin (**5.6**, **5.7** and **5.8**) in good yield (~85%-91%).

Conversion of 6,7-dinitro substituted benzodioxins (**5.6**, **5.7** and **5.8**) to *o*-amino nitro compounds **5.9**, **5.10** and **5.11** involved the substitution of one nitro group with NH_3. This method was chosen since Boyer et al.[21] reported in 1955 the selective substitution of only one of the *o*-nitro groups in 3,4-dintrotoluene with NH_3 gas when he prepared 3-amino-4-nitrotoluene. Despite the general belief that electron donating groups deactivate the aromatic ring for the S_NAr substitution of NO_2 groups, there is evidence that they have been synthesized successfully by this method; e.g., compounds **5.21**,[22] and **5.22** (Figure 5.2).[23] In the synthesis of compound **5.9** under mild conditions, i.e. heated

1,2-dinitrobenzodioxin (**5.6**) in THF saturated with NH_3 gas at 60 ºC for 6 h, the ^1H NMR spectrum showed that part of the starting materials has one nitro group replaced by amino. The preliminary result (first try to date) gave a 10 % yield based on ^1H NMR integration. The optimization of this step is ongoing. This is very encouraging. These successes demonstrate the feasibility of our proposed (i) highly facile new synthesis of the dioxin skeletal framework and (ii) selective manipulation of functional groups.



5.21



5.22

Figure 5.2: *o*-amino nitro compounds (**5.21 and 5.22**) prepared from *o*-nitro compounds via a S_NAr reaction.

5.3 Experimental

- **Synthesis of 1,2-difluoro-4,5-dinitrobenzene** (**5.2**)

60 mL conc. H_2SO_4 and 40 mL fuming HNO_3 were added to a 500 mL three-neck round bottom flask immersed in an ice bath. 5 g (44 mmol) 1, 2-difluorobenzene was added dropwise at a rate that kept the temperature below 5 ºC. The mixture was continually stirred over the ice bath for 30 min. The system was warmed to rt and stirred for 2 h. The mixture was heated at 100 ºC overnight. After cooling to rt, the mixture was poured into 1 Kg crushed ice. A white precipitate was collected by filtration and washed with copious amounts of H_2O and dried under vacuum overnight,

yield: 4.44g (48.5%). ^{1}H NMR (250 MHz, CD_2Cl_2) δ (ppm): 7.88 (t, J = 7.6 Hz, 2H); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ (ppm): 115.90, 150.33, 154.55.

- **Synthesis of 6, 7-dinitrodibenzodioxin** (**5.6**)

500 mg catechol (2.45 mmol) and 269.8 mg of 1,2-difluoro -4,5-dinitrobenzene (**2**) (2.45 mmol) were dissolved in 100 mL DMF at rt. Triethylamine (1.38 mL, 9.8 mmol) was added dropwise. The resulting light yellow solution was heated at 60 °C overnight. The solvent was removed under vacuum, and the crude product extracted using CH_2Cl_2 and H_2O (3 × 100 mL), dried over $MgSO_4$ and filtered. The solvent was removed under vacuum. Yield: 570 mg (84.9%). ^{1}H NMR (250 MHz, acetone-d_6) δ (ppm): 7.05 (m, 4H), 7.70 (s, 2H); ^{13}C NMR (62.5 MHz, acetone-d_6) δ (ppm): 114.475, 117.73, 126.66, 141.08, 146.24.

Compounds **5.7** and **5.8** were also synthesized according to the above procedure. However, **5.7** and **5.8** are insoluble in CH_2Cl_2, and both were suspended in CH_2Cl_2 after evaporation of DMF. The products were filtered by suction and washed with CH_2Cl_2. The mother liquor was concentrated and suspended in a small amount of CH_2Cl_2 and filtered again. The products were dried in a vacuum oven overnight. Yields for compound **5.7** and compound **5.8** were 764.9 mg (91%) and 699.0 mg (87%) respectively.

Characterization data for compound **5.7**: ^{1}H NMR (250 MHz, THF-d_8) δ (ppm): 7.29 (s, 2H), 7.75 (s, 2H); ^{13}C NMR (62.5 MHz, THF-d_8) δ114.62, 119.09, 128.84, 140.73, 145.33.

Characterization data for compound **5.8**: ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm): 7.53 (s, 2H), 7.90 (s, 2H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ (ppm): 113.67, 118.86, 120.96, 138.22, 139.91, 144.28.

5.4 Conclusion

We presented a novel synthesis of PXDDs. The new synthesis can be used to conduct a controlled, laboratory study of the thermal reactions of PXDD precursors.

5.5 References

1. Sparschu, G. L.; Dunn, F. L.; Rowe, V. K. *Food Cosmet. Toricol.* **1971**, *9*, 405.

2. Moore, J. A.; McConnell, E. E.; Dalgard, D. W.; Harris, M. W. *Ann. N.Y. Acad. Sci.* **1979**, *320*, 151-163.

3. Mennear, J. H.; Lee, C. C. *Environ. Health Perspect.* **1994,** *102*, 265-274.

4. Weber, L. W. D.; Greim, H., *J. Toxicol. Environ. Health*, **1997,** *50*, 195-215.

5. Vehlow, J.; Bergfeldt, B.; Jay, K.; Seifert, H.; Wanke, T.; Mark, F. *Waste Manage. Res.* **2000**, *18(2)*, 131-140.

6. Bhaskar, T.; Murai, K.; Brebu, M.; Matsui, T.; Uddin, M.; Muto, A.; Sakata, Y. *Green Chem.* **2002**, *4(6)*, 603-606.

7. Bhaskar, T.; Matsui, T.; Kaneko, J.; Uddin, M.; Muto, A.; Sakata, Y. *Green Chem.* **2002**, *4(4)*, 372-375.

8. Uddin, M.; Bhaskar, T.; Kaneko, J.; Muto, A.; Sakata, Y.; Matsui, T., *Fuel*, **2002**, *81(14)*, 1819-1825.

9. Vehlow, J.; Bergfeldt, B.; Hunsinger, H.; Seifert, H.; Mark, F. E. *Environ. Sci. & Pollut. Res.* **2003**, *10(5)*, 329-334.

10. Watanabe, I.; Sakai, S. *Environment International*, **2003**, *29(6)*, 665-682.

11. Weber, R.; Kuch, B. *Environment International*, **2003**, *29(6)*, 699-710.

12. Bhaskar, T.; Matsui, T.; Uddin, M. A.; Kaneko, J.; Muto, A.; Sakata, Y. *Appl. Catal. Part B: Environ.* **2003**, *43(3)*, 229-241.

13. de Boer, J.; Wester, P. G.; van der Horst, A.; Leonards, P. E. G. *Environmental Pollution,* **2003**, *122(1)*, 63-74.

14. Soderstrom, G.; Marklund, S. *Environ. Sci. Technol.* **2004**, *38(3)*, 825-830.

15. Schuler, D.; Jager, J. *Chemosphere* **2004**, *54(1)*, 49-59.

16. Jay, K.; Stieglitz, L. *Chemosphere* **1996**, *33*, 1041-1045.

17. Jay, K.; Stieglitz, L. *Chemosphere* **1991**, *22*, 987-996.

18. Kende, A. S.; Wade, J. J.; Ridge, D.; Poland, A. *J. Org. Chem.* **1974**, *39*, 931-937.

19. Kazimierczuk, Z.; Dudycz, L.; Stolarski, R.; Shugar, D. *J. Carbohydr. Nucleoside, Nucleotides* **1981**, *8,* 101-117.

20. (a) Cram, D. J.; Choi, H. J.; Bryant, J. A.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7748-7765; (b) Rudkevich, D. M.; Hilmersson, G.; Rebek, J. *J. Am. Chem. Soc.* **1998**, *120*, 12216-12225; (c) Butterfield, S. M.; Rebek, J. *J. Am. Chem. Soc.* **2006**, *128*, 15366-15367.

21. Boyer, J. H.; Reinisch, R.F; Danzig, M. J.; Stoner, G. A; Sahhar, F. *J. Am. Chem. Soc.* **1955**, *77*, 5688-5689.

22. Junino, A.; Lang, G.; Genet, A. *Ger. Patent* 3612665, **1986.**

23. Hadjimihalakis, P. M. *J. Heter. Chem.* **1991**, *28*, 1111-1114.

APPENDIX A: CHARACTERIZATION DATA FOR COMPOUND 2.2

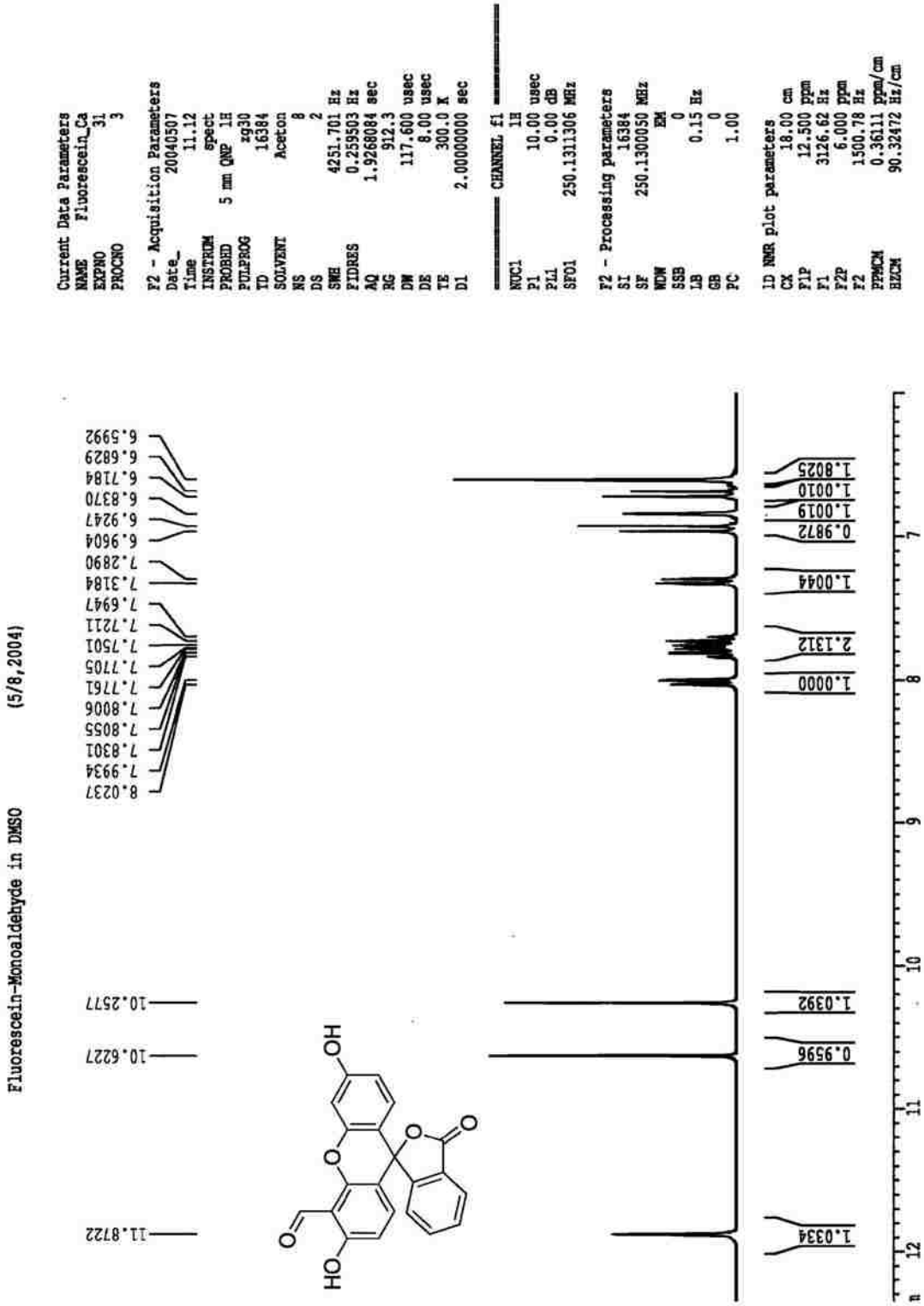


Figure A.1. ^{1}H NMR of compound **2.2**

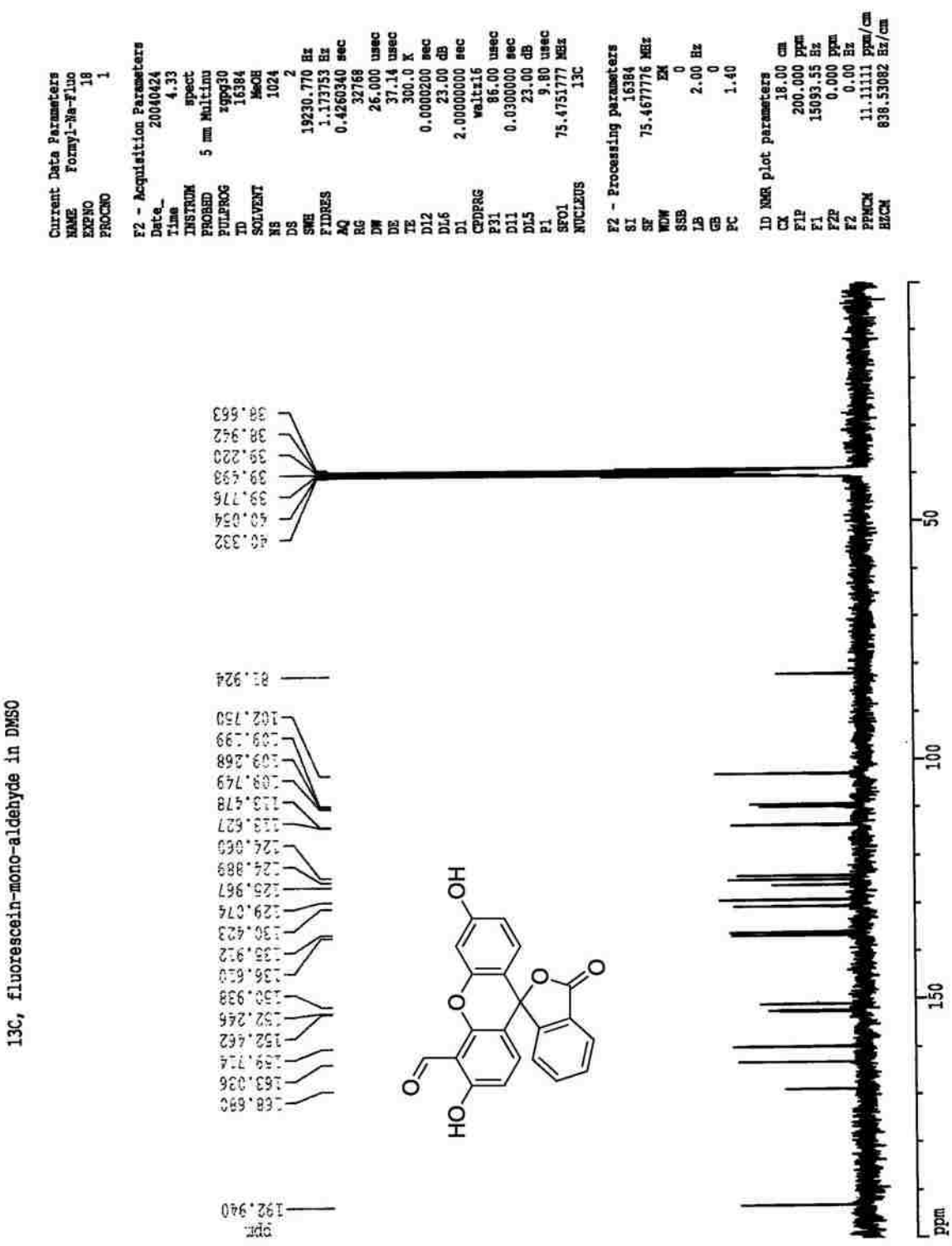


Figure A.2. ^{13}C NMR of compound **2.2**

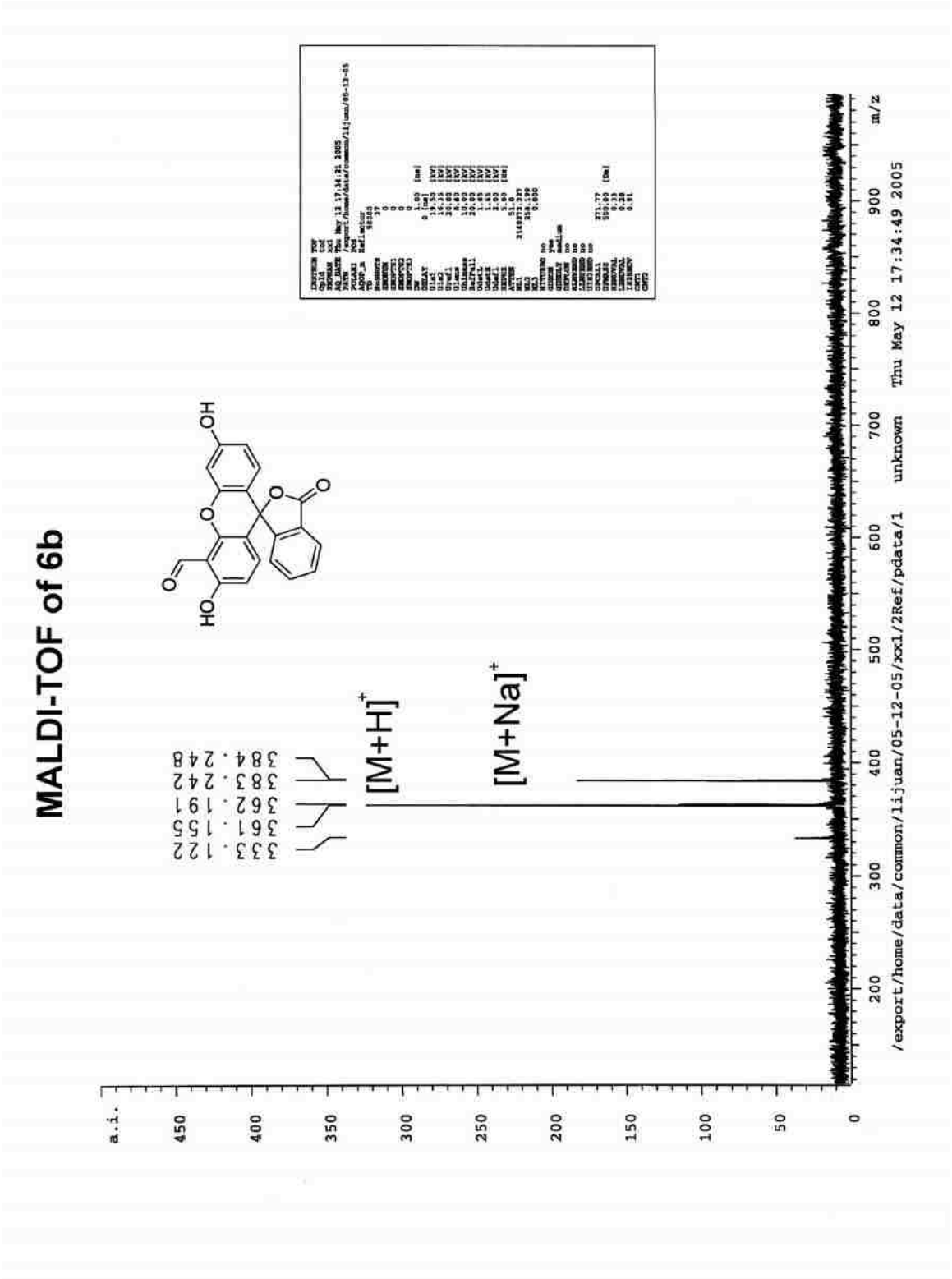


Figure A.3. MALDI MS of compound **2.2**

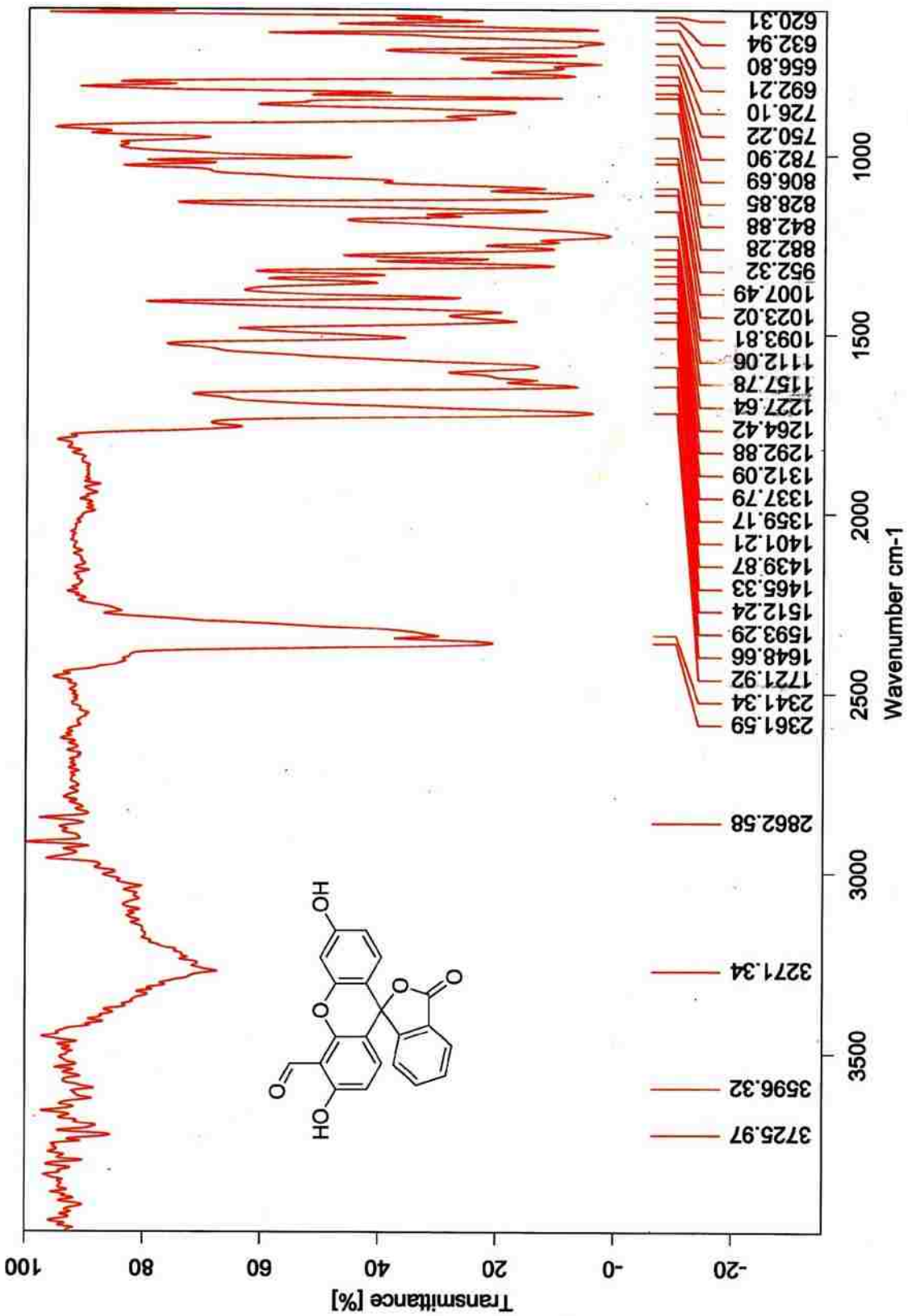


Figure A.4. FTIR of compound **2.2**

APPENDIX B: CHARACTERIZATION DATA FOR COMPOUND 2.3

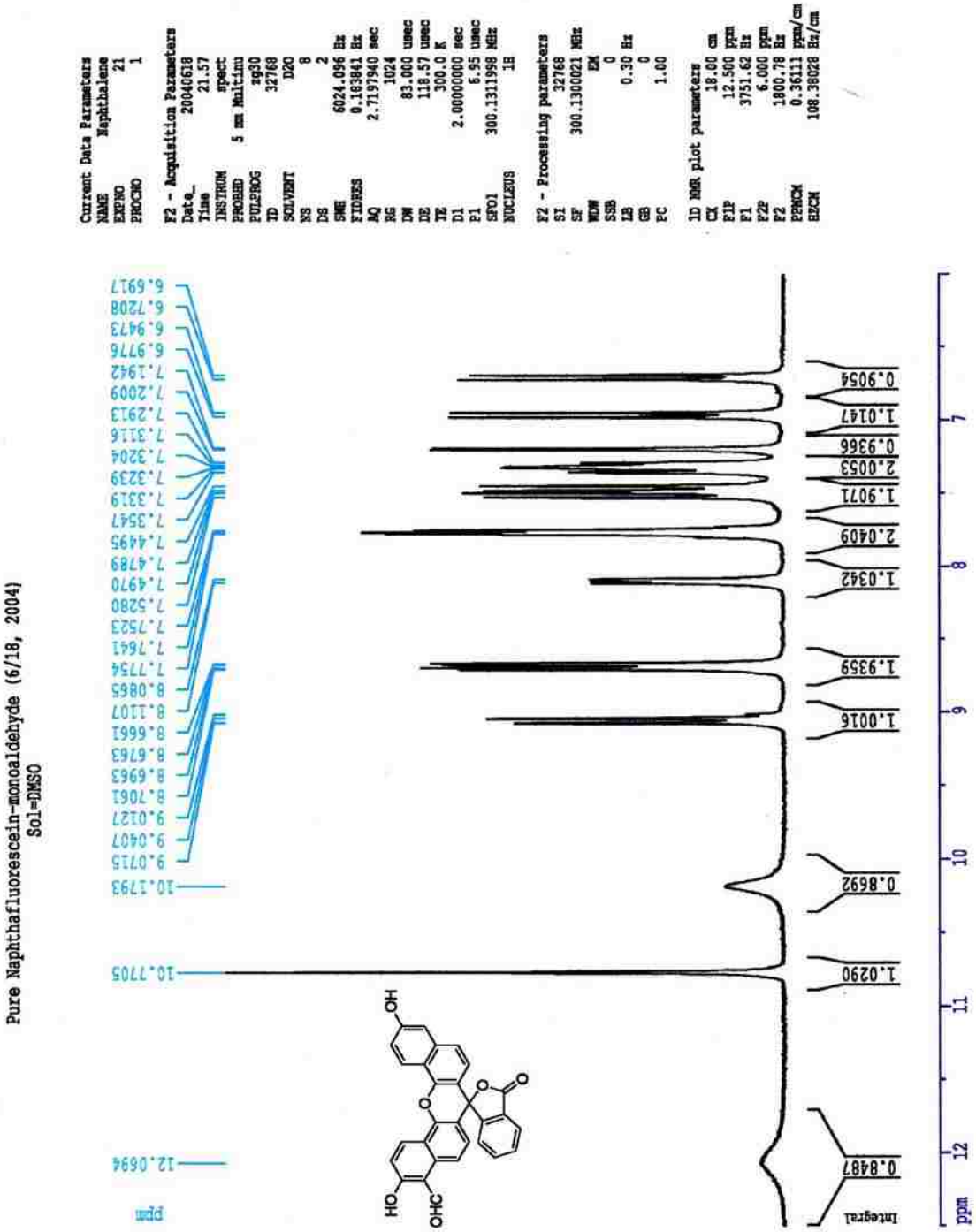


Figure B.1. ^{1}H NMR of compound **2.3**

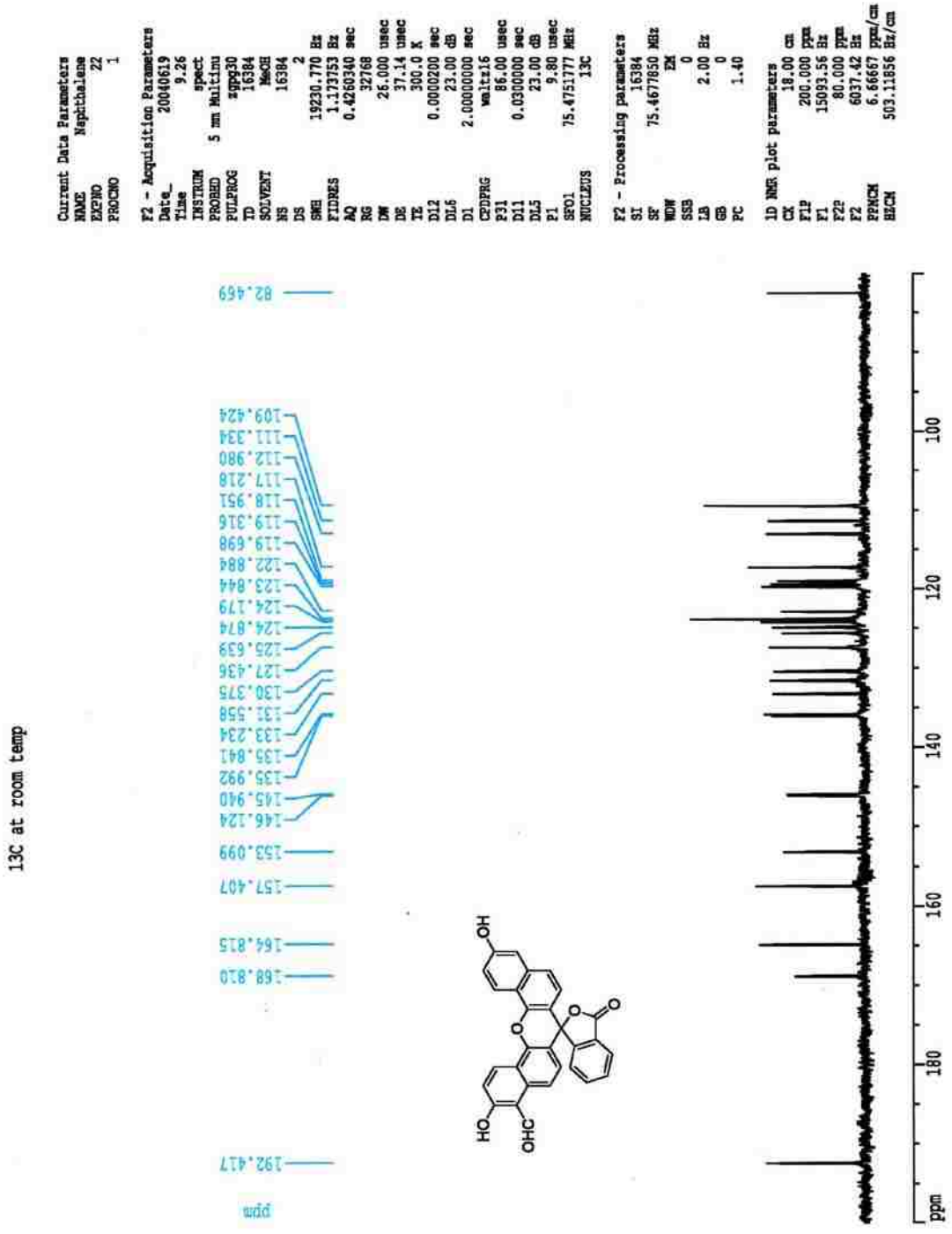


Figure B.2. ^{13}C NMR of compound **2.3**

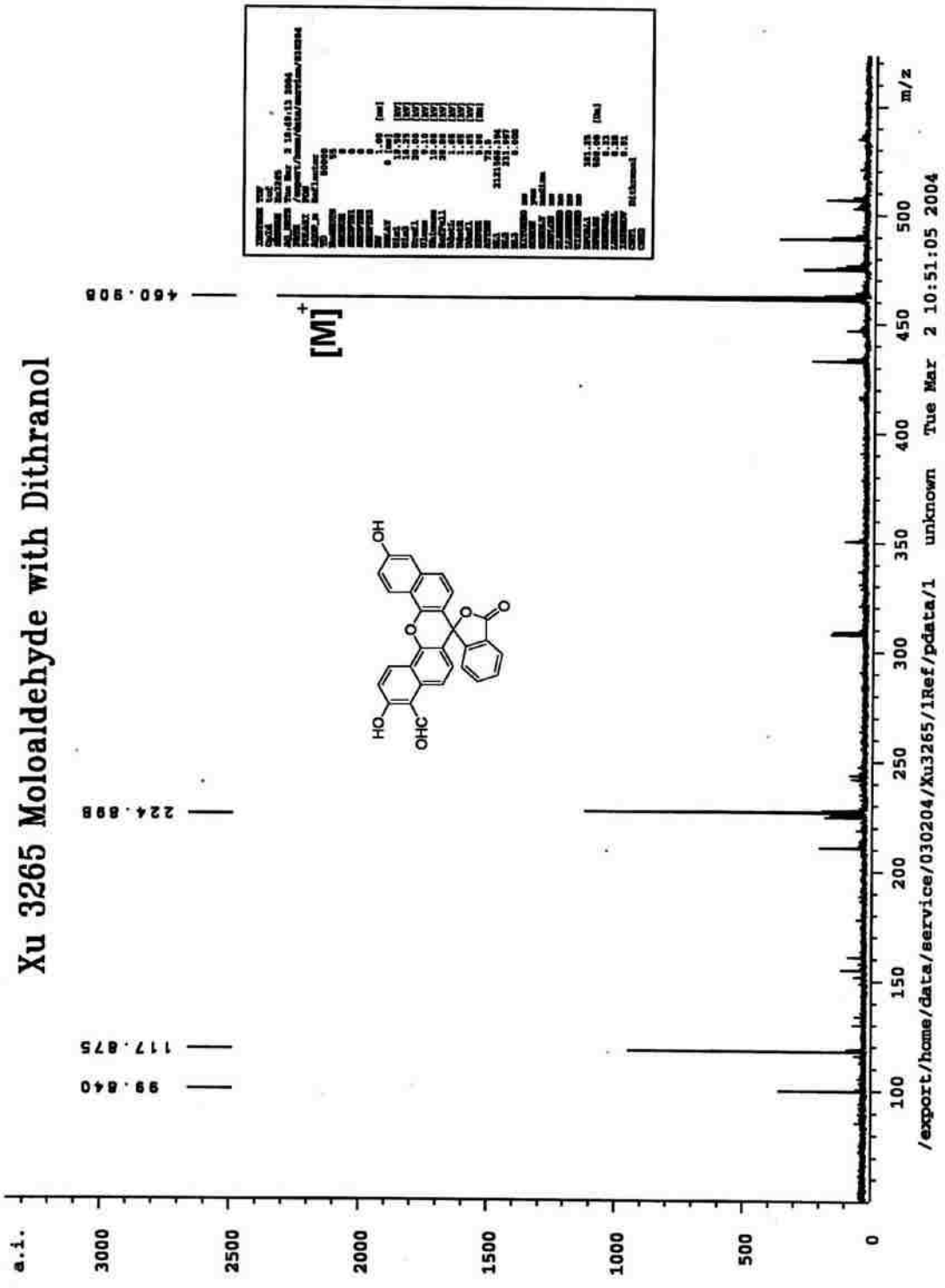


Figure B.3. MALDI MS of compound **2.3**

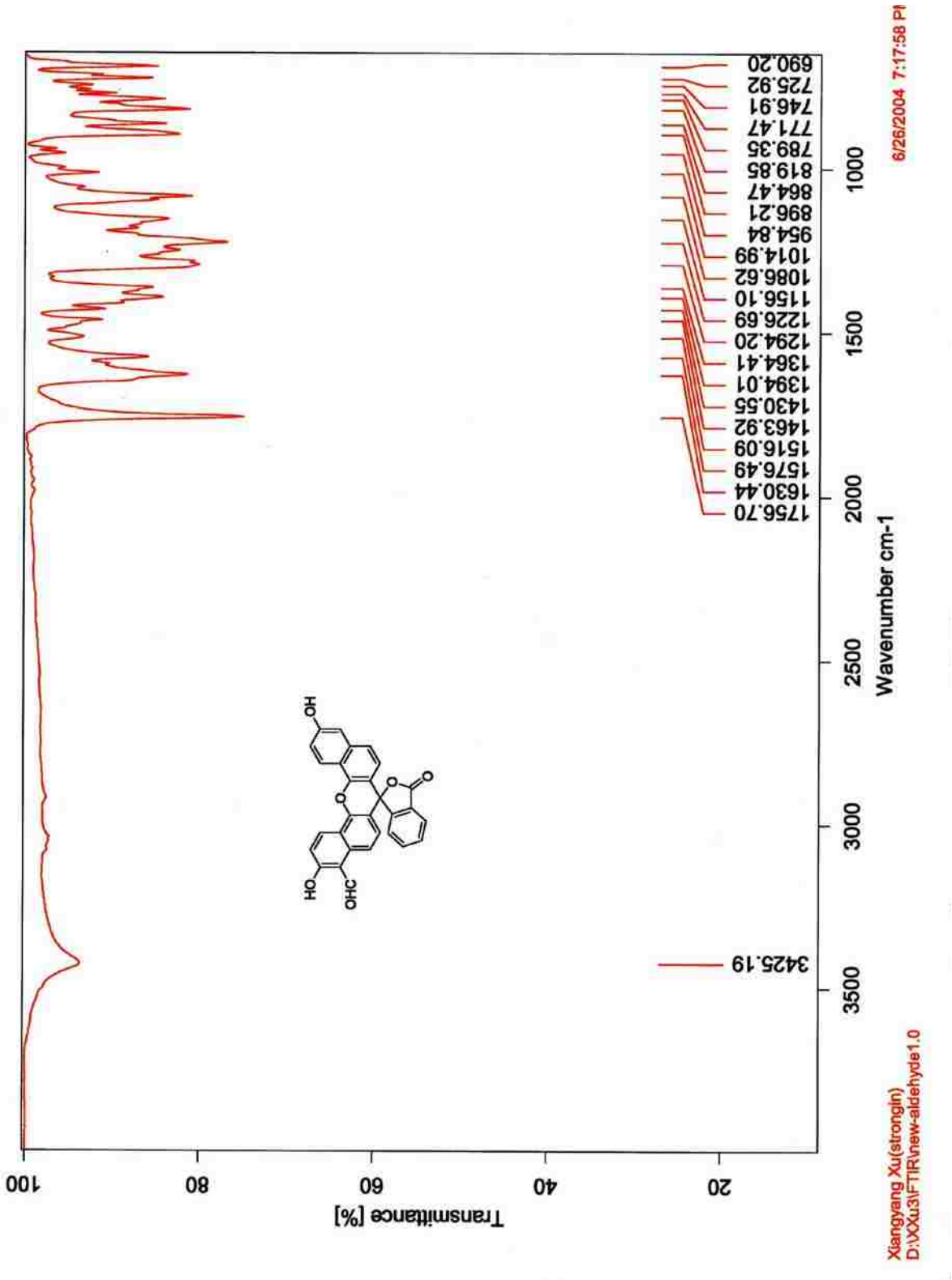


Figure B.4. FTIR of compound **2.3**

APPENDIX C: CHARACTERIZATION DATA FOR COMPOUND 3.1

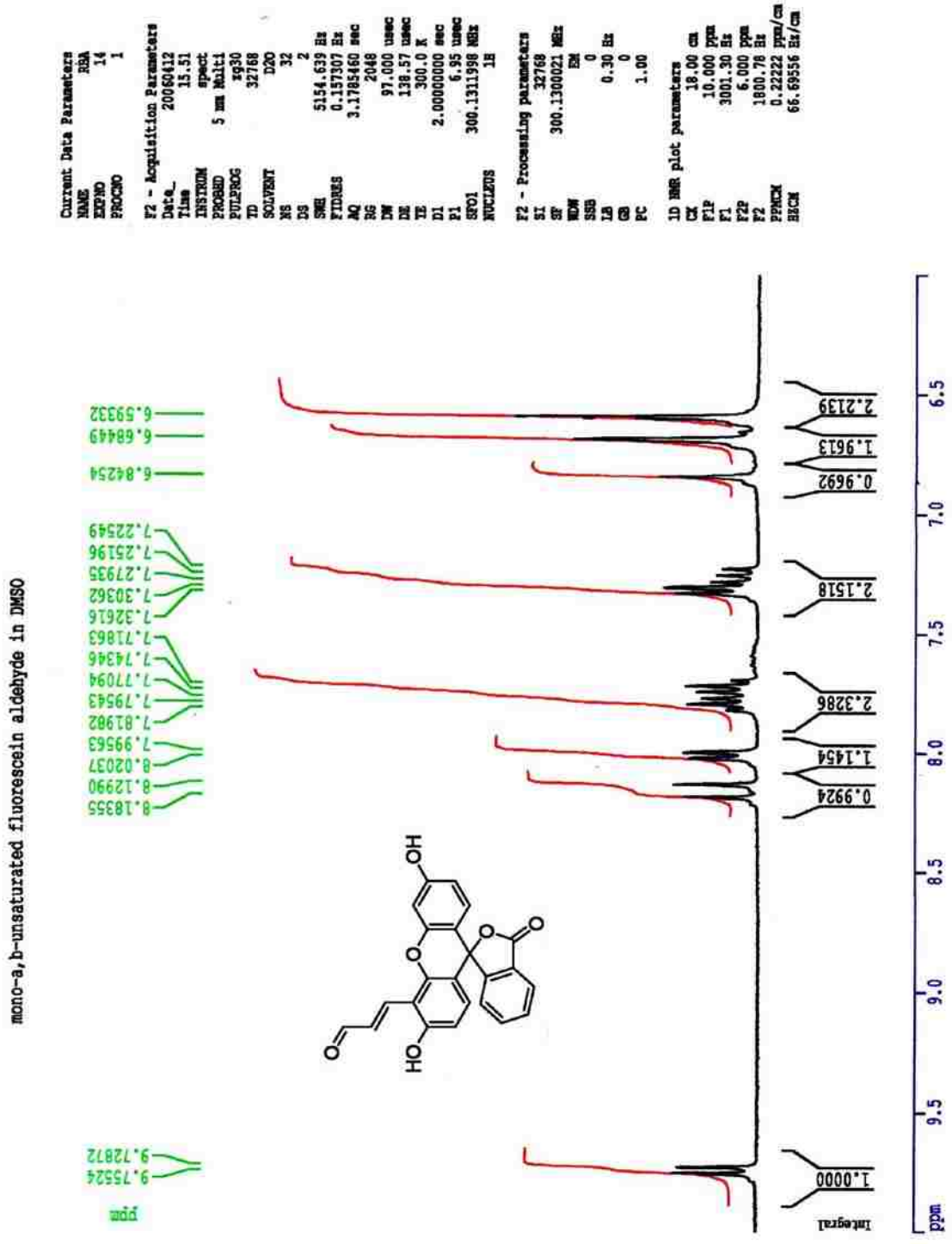


Figure C.1. ^{1}H NMR of compound **3.1**

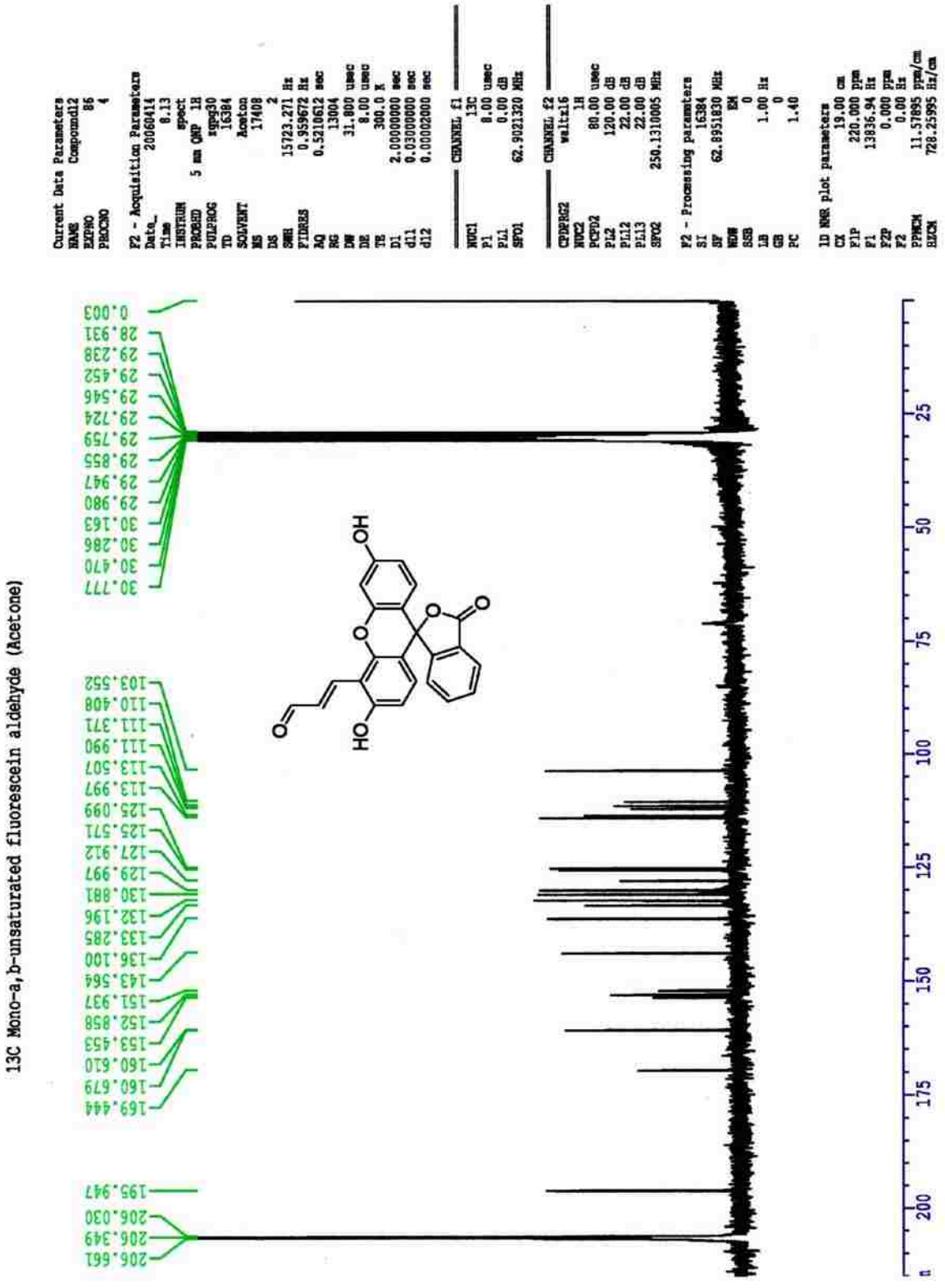


Figure C.2. ^{13}C NMR of compound **3.1**

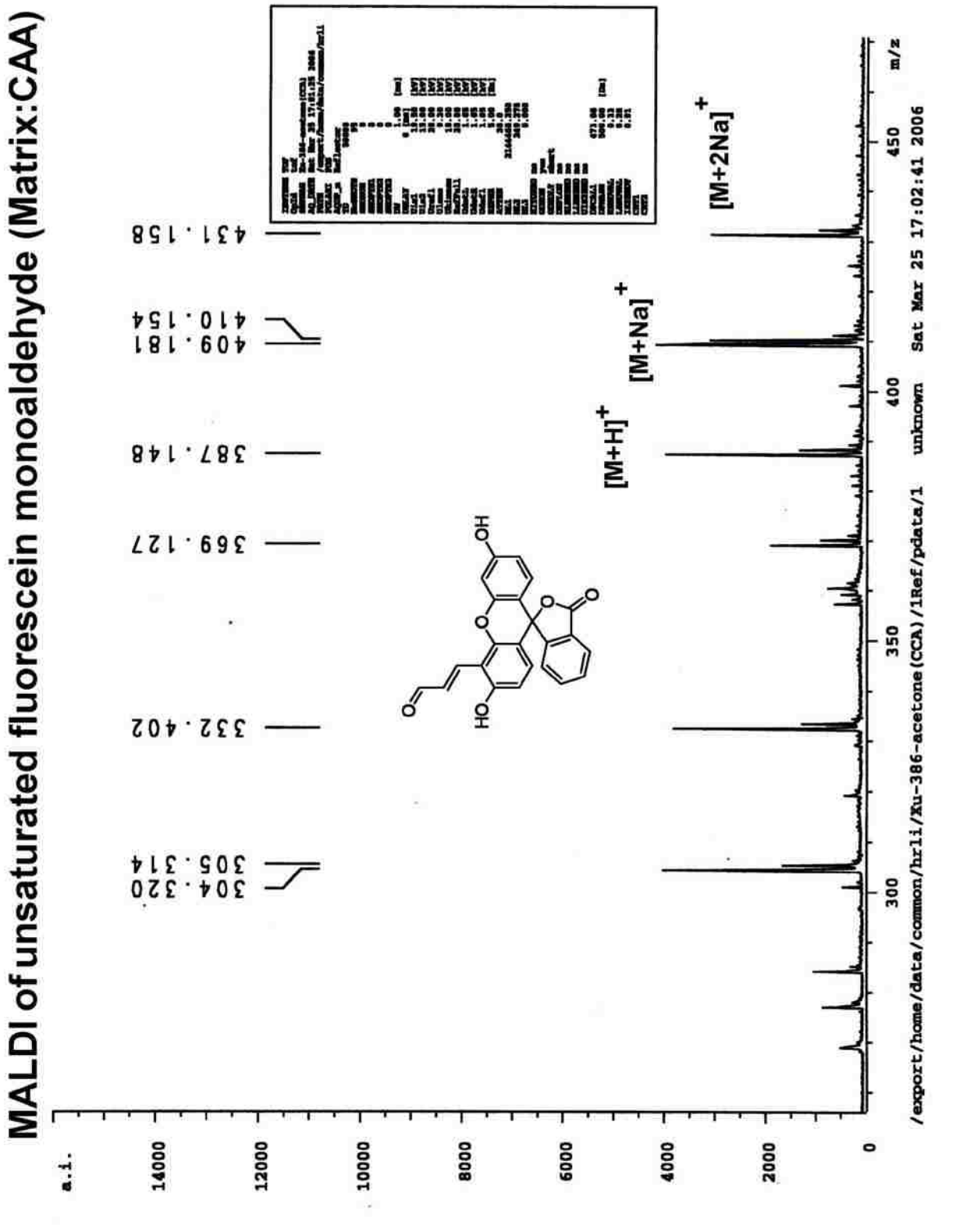


Figure C.3. MALDI MS of compound **3.1**

APPENDIX D: CHARACTERIZATION DATA FOR COMPOUND 3.2

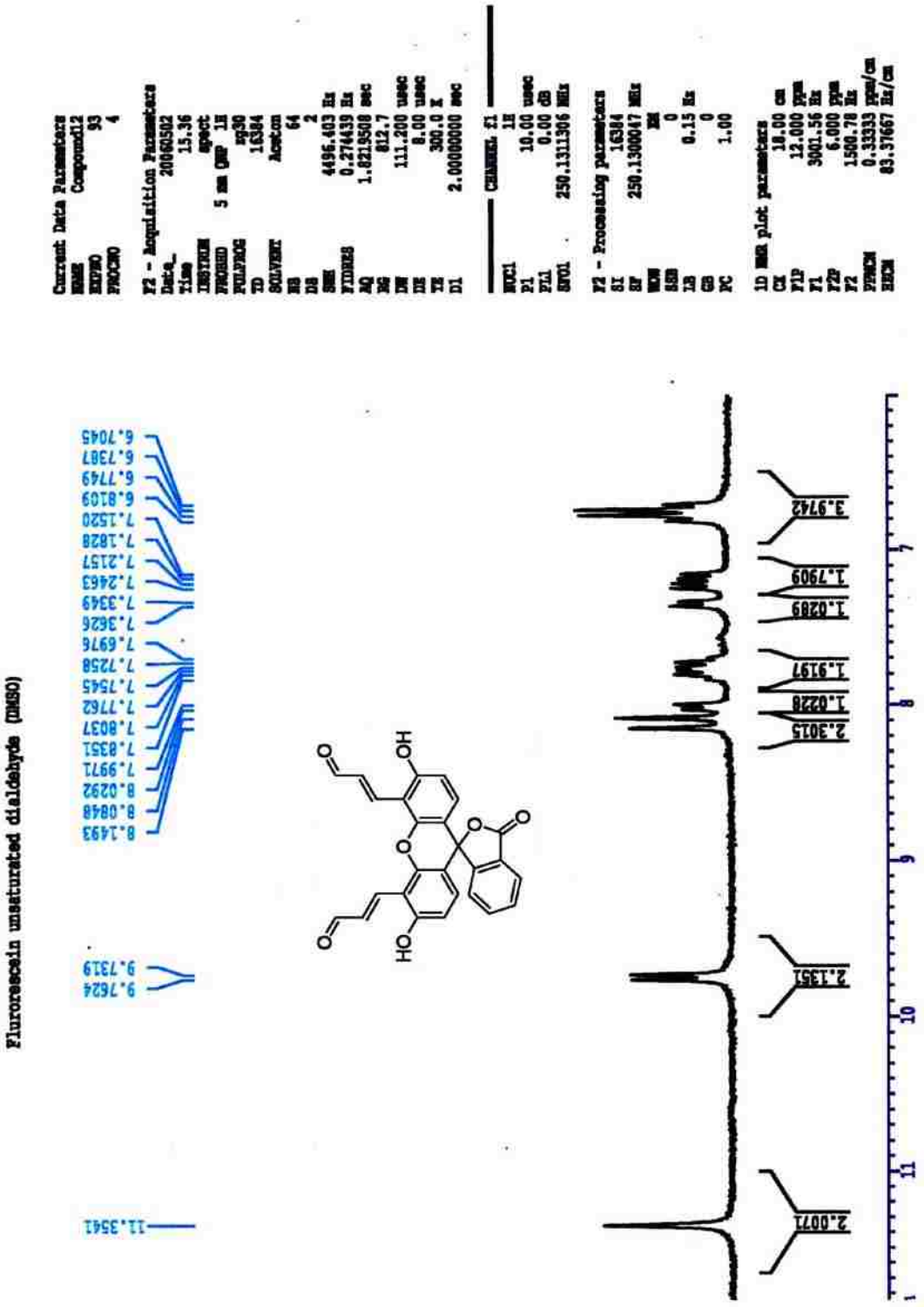


Figure D.1. ^{1}H NMR of compound **3.2**

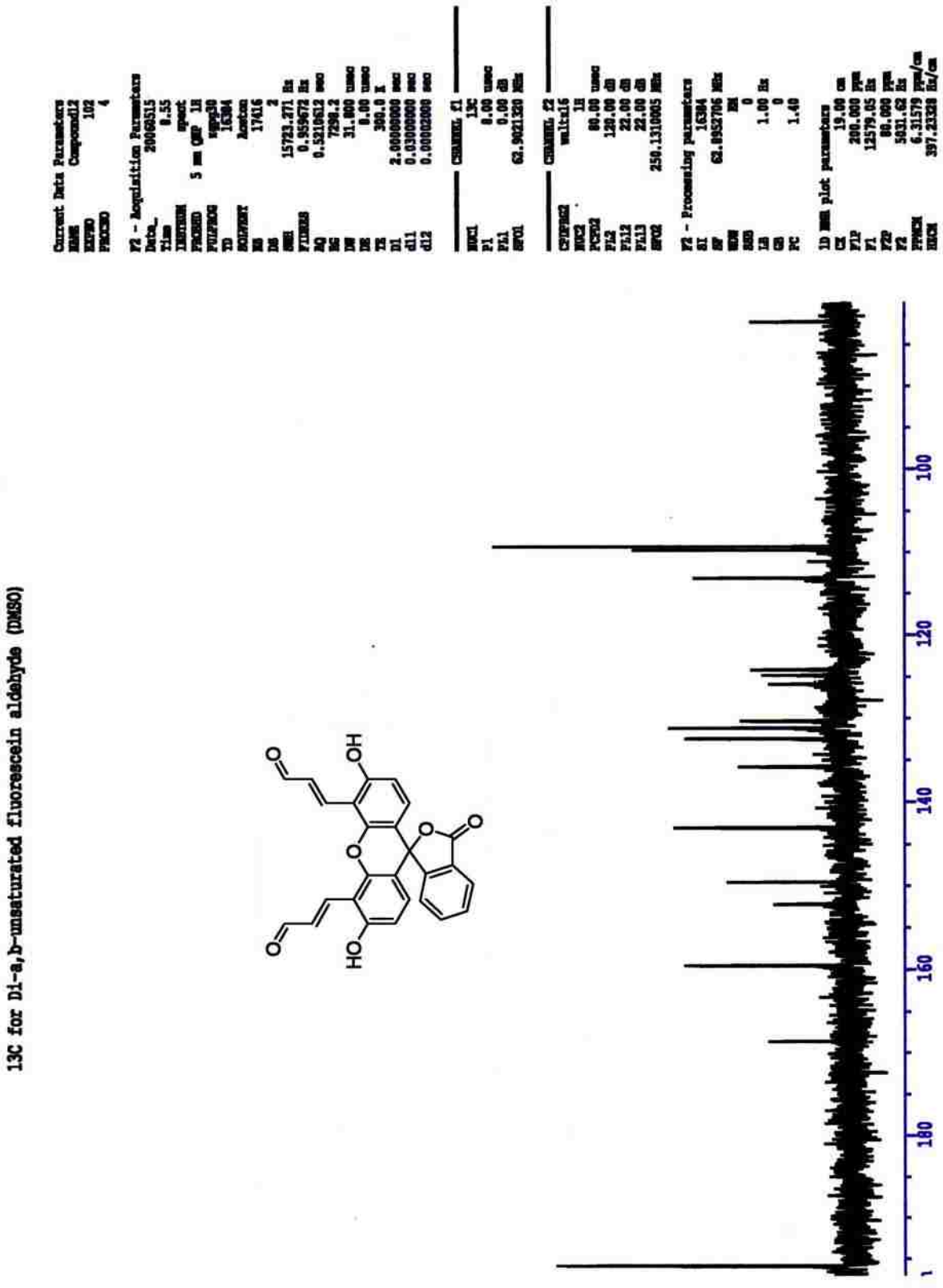


Figure D.2. ^{13}C NMR of compound **3.2**

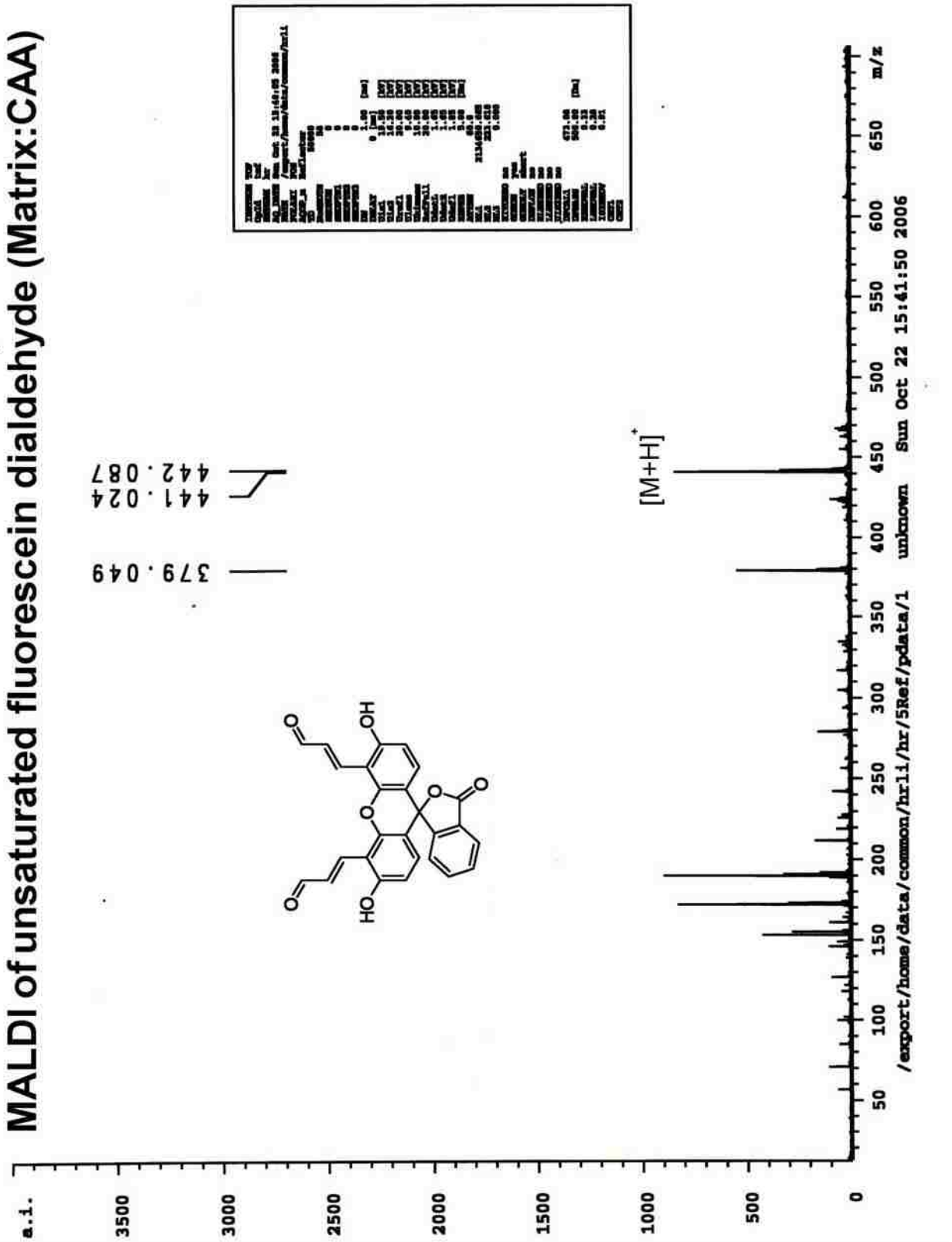
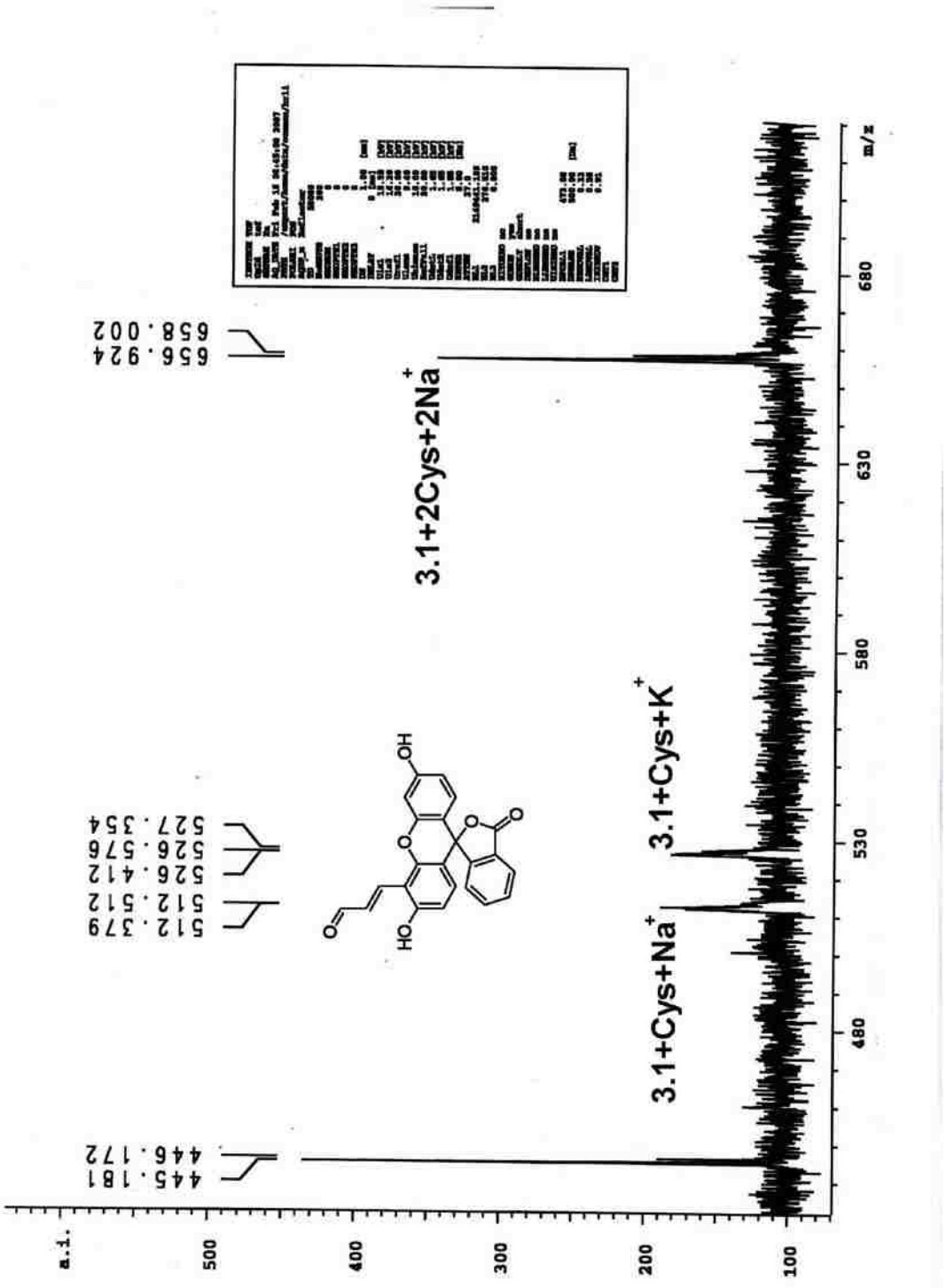
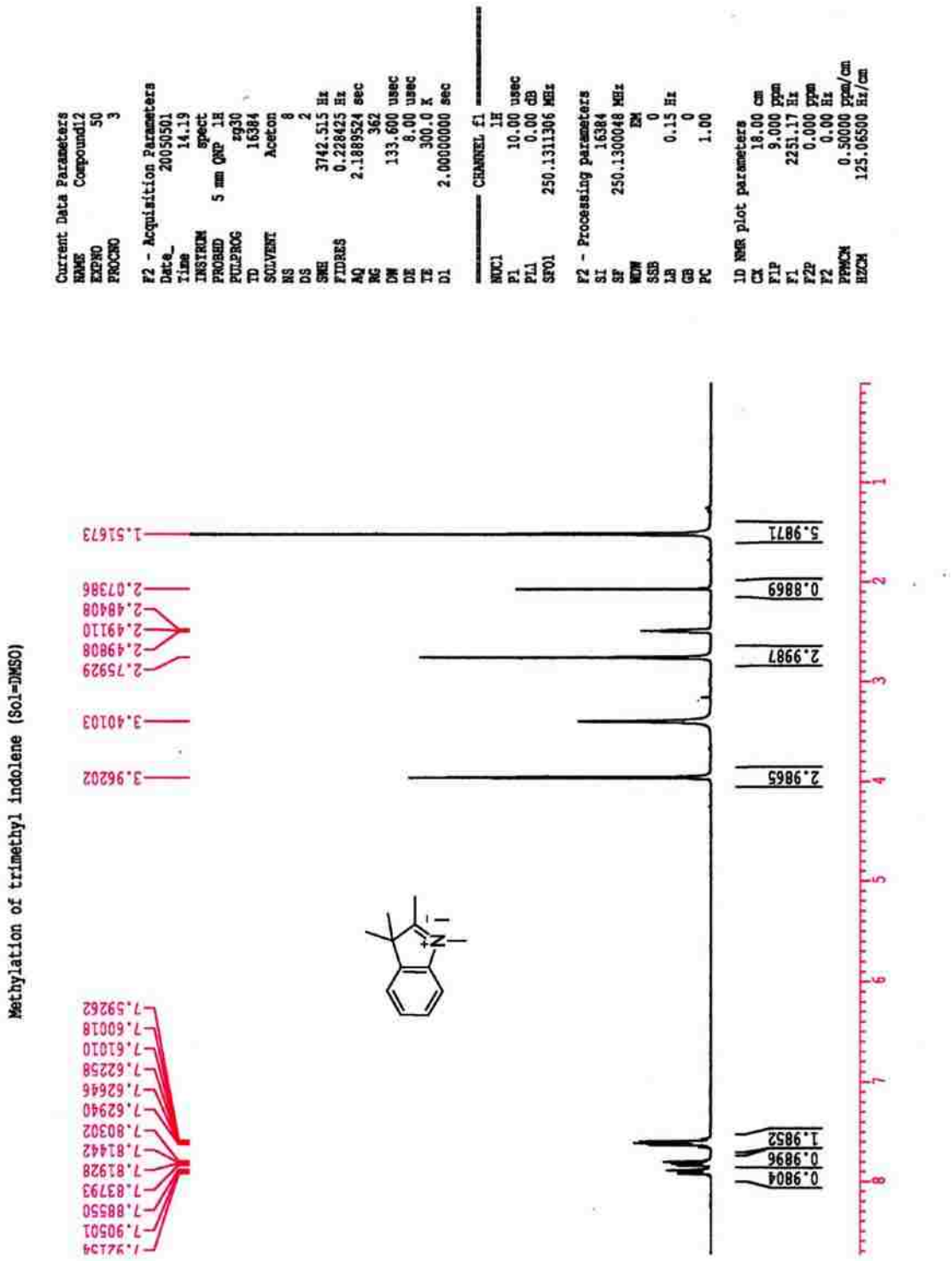


Figure D.3. MALDI MS of compound **3.2**

APPENDIX E: MALDI MS OF REACTION MIXTURE OF COMPOUND 3.1 AND CYS



APPENDIX F: ^{1}H NMR OF COMPOUND 3.13



APPENDIX G: CHARACTERIZATION DATA FOR COMPOUND 3.14

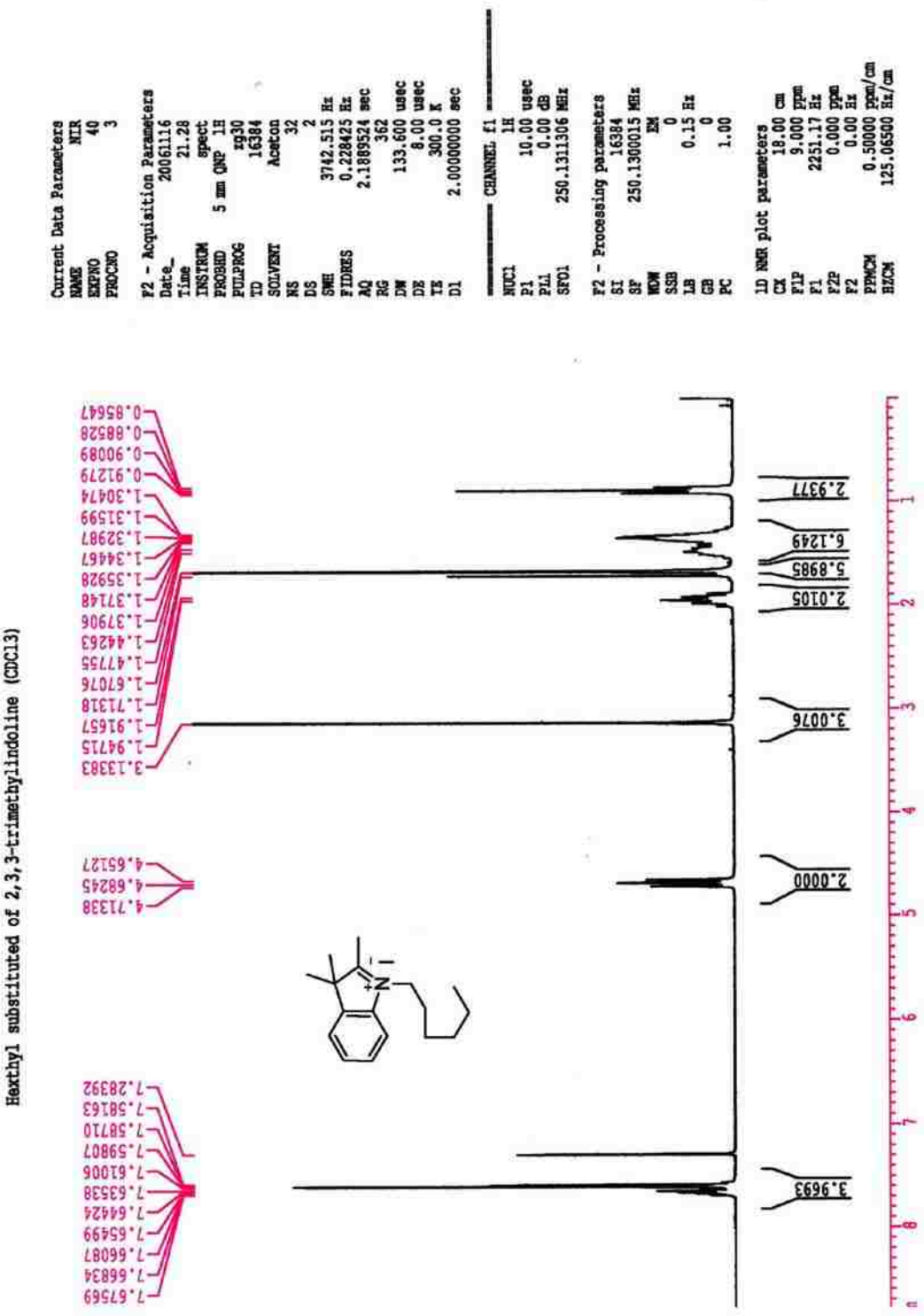


Figure G.1. ^{1}H NMR of compound **3.14**

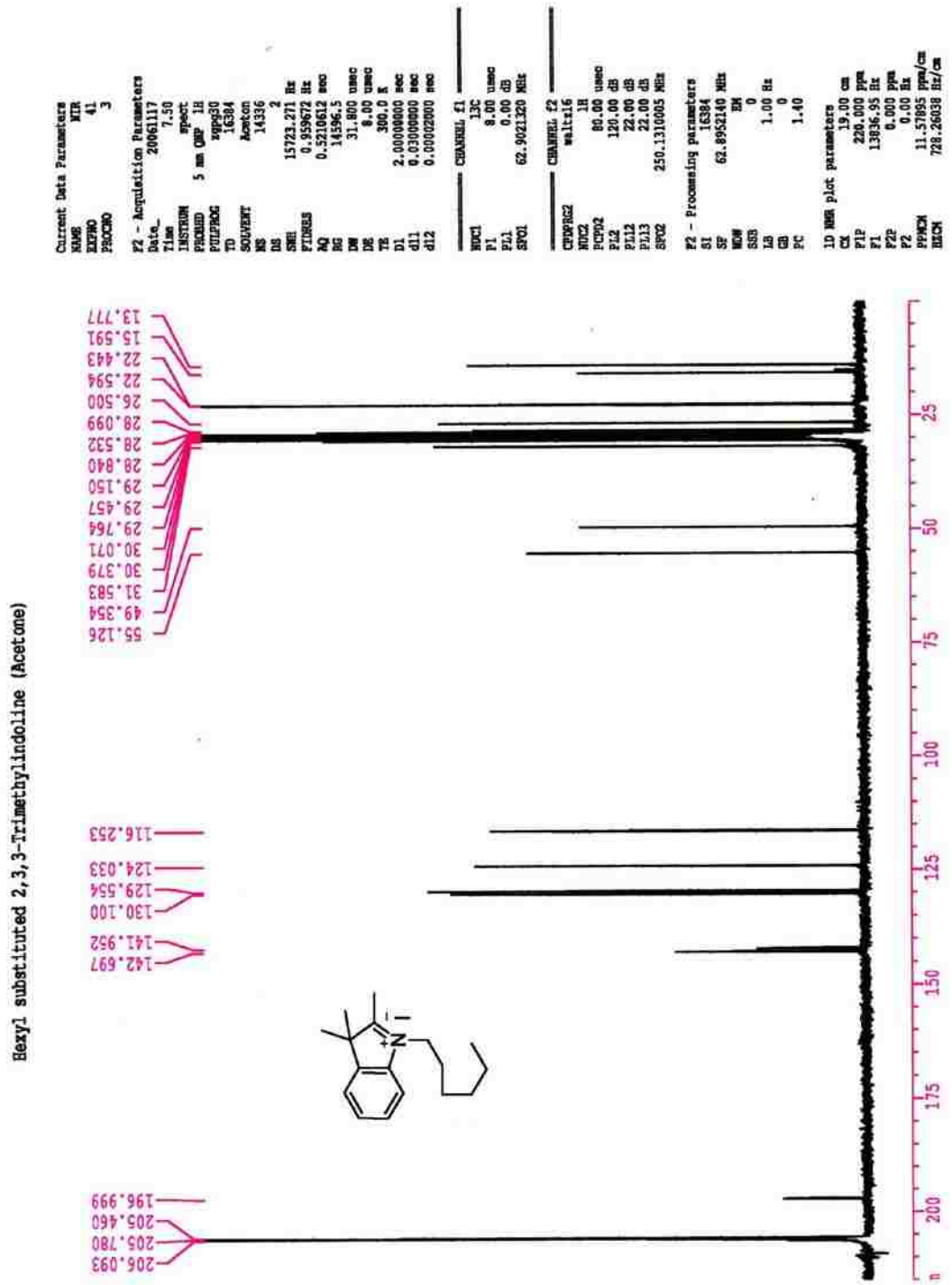


Figure G.2. ^{13}C NMR of compound **3.14**

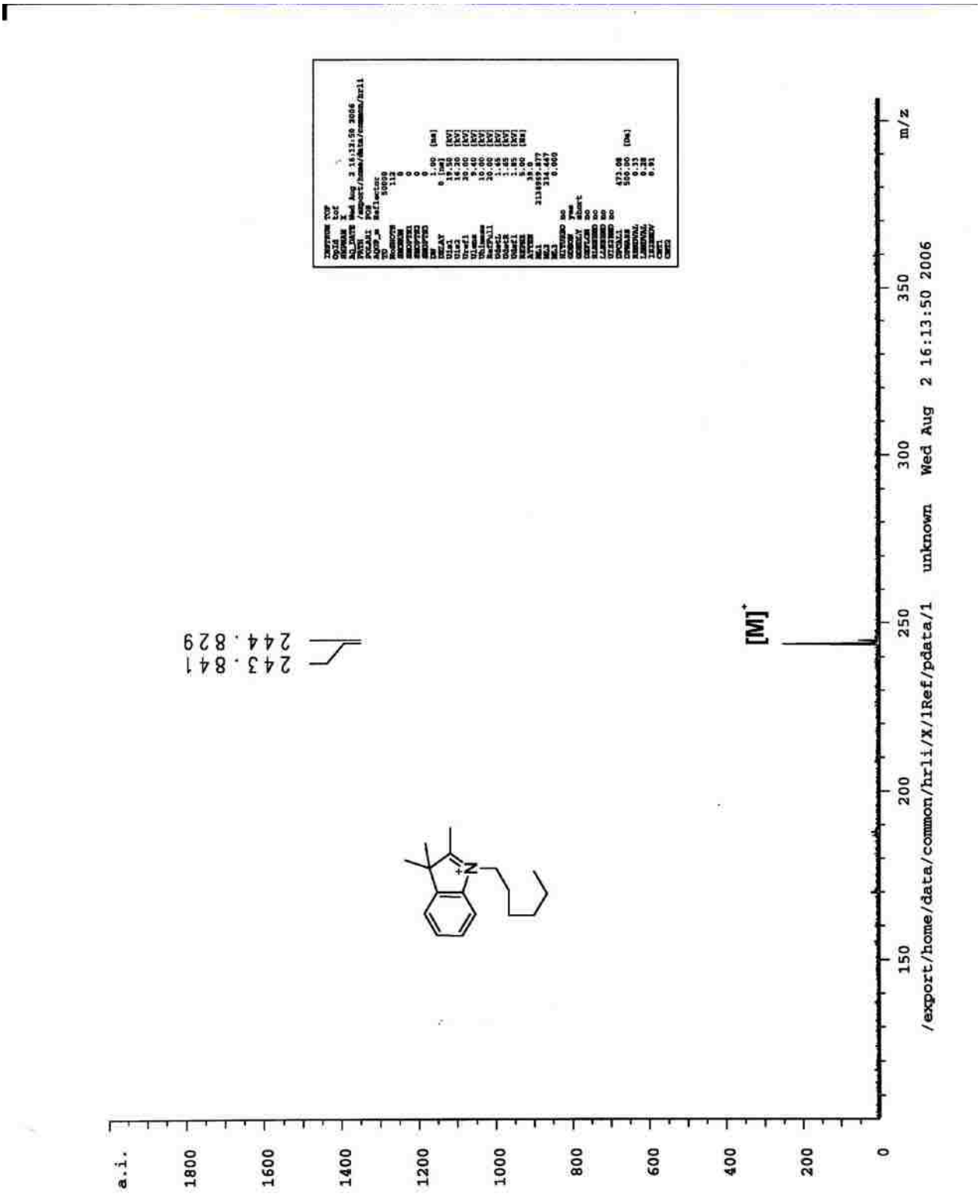
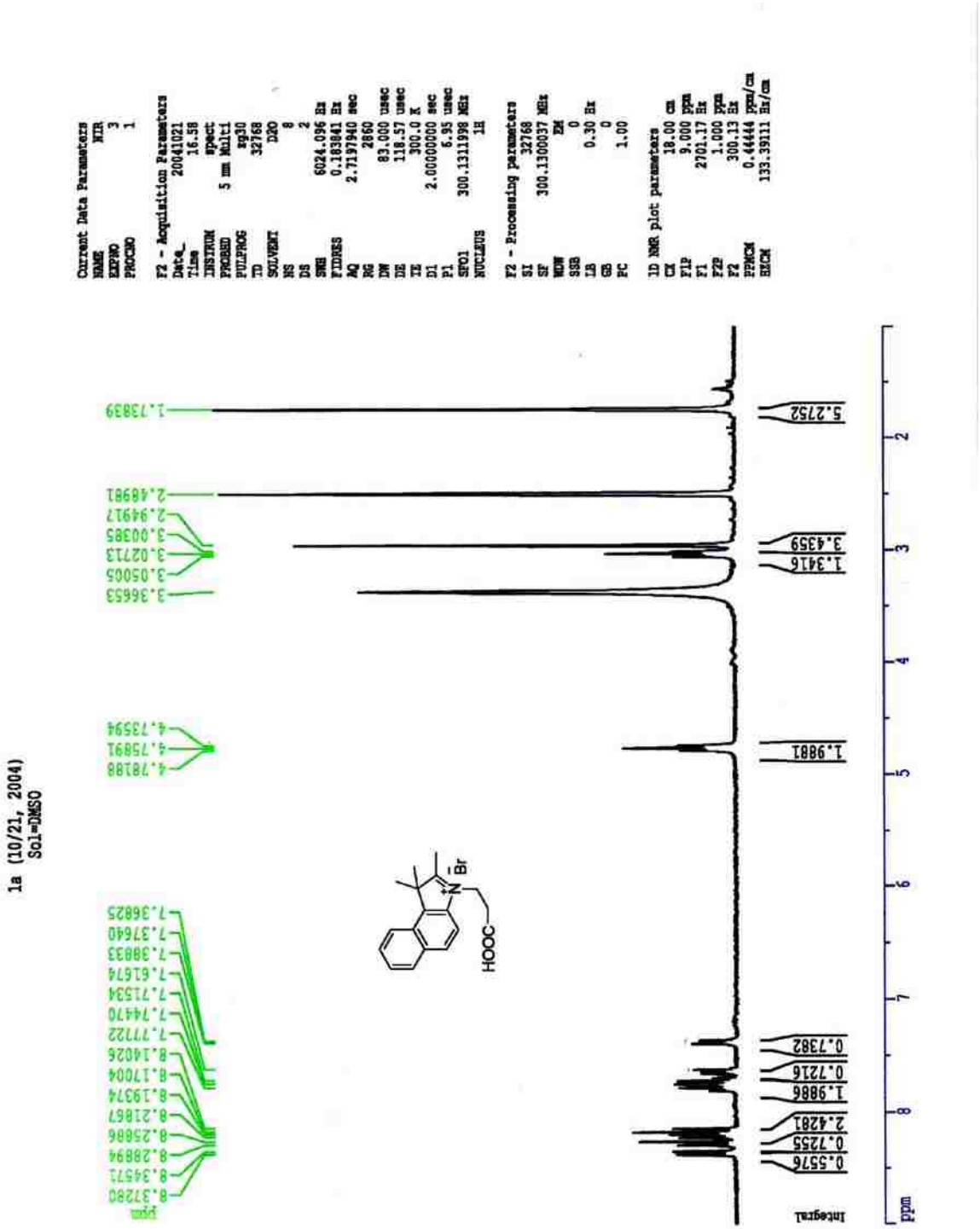
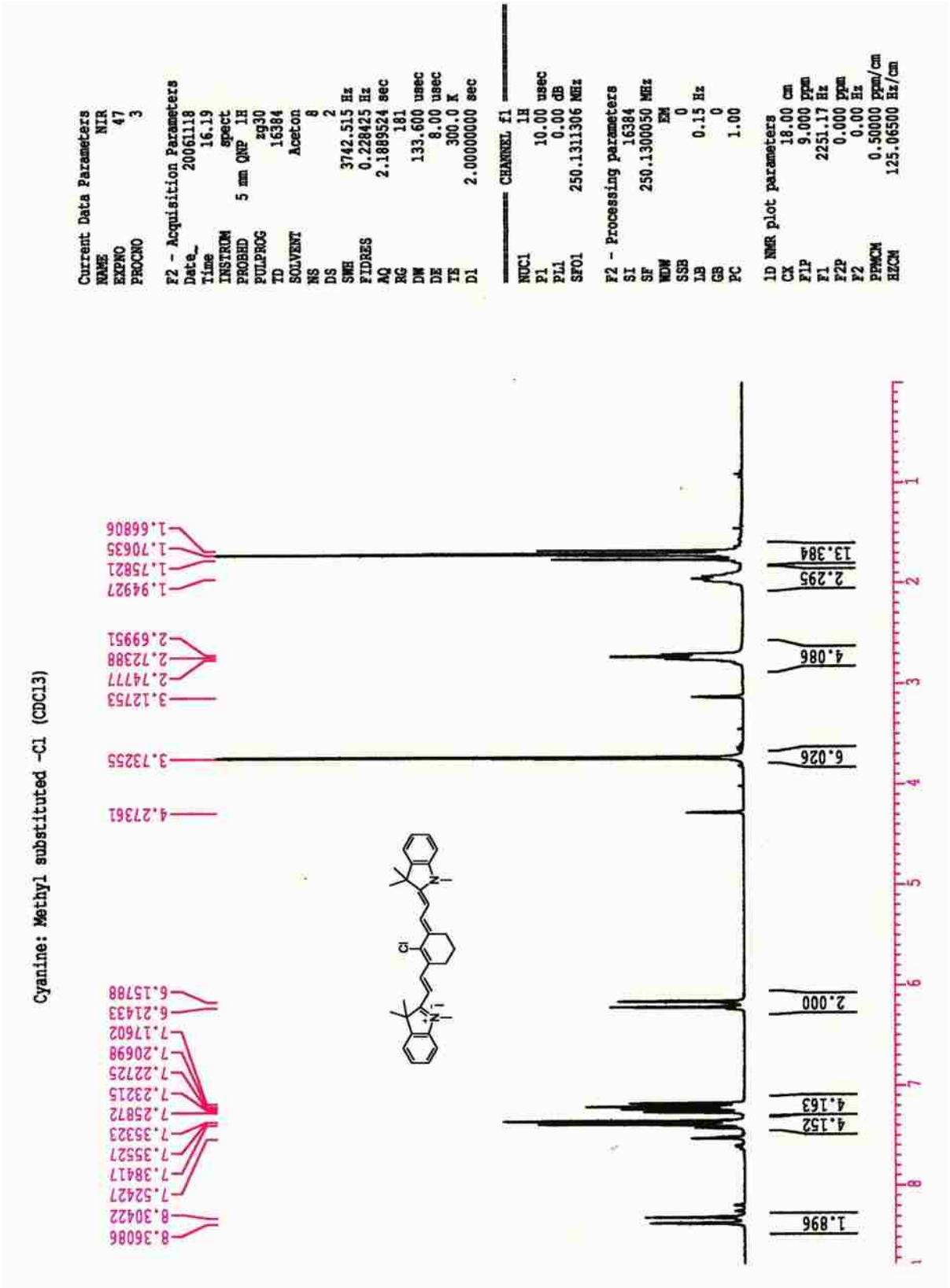


Figure G.3. MALDI MS of compound **3.14**

APPENDIX H: ^{1}H NMR OF COMPOUND 3.18



APPENDIX I: ^{1}H NMR OF COMPOUND 3.15



APPENDIX J: CHARACTERIZATION DATA FOR COMPOUND 3.16

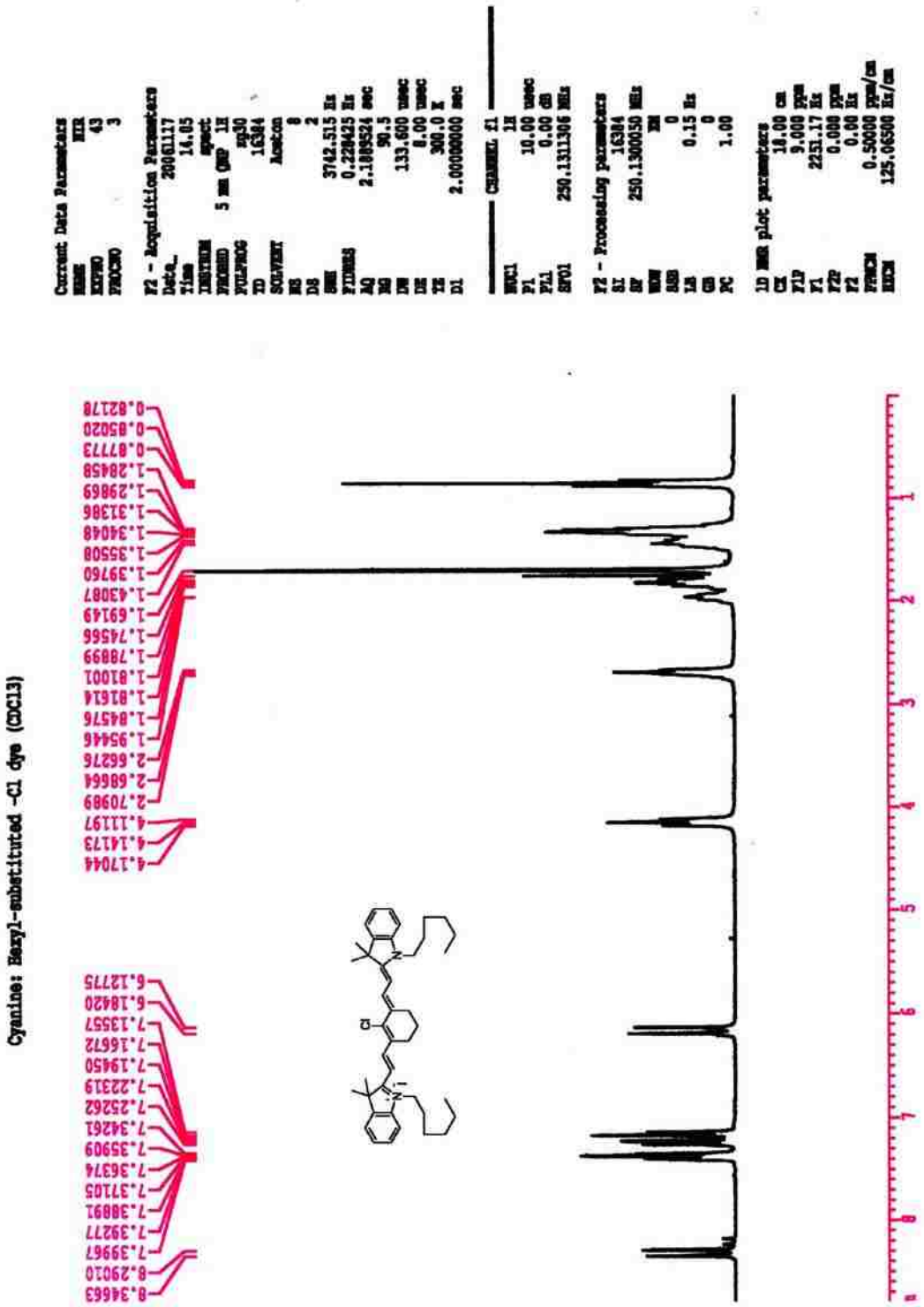


Figure J.1. ^{1}H NMR of compound **3.16**

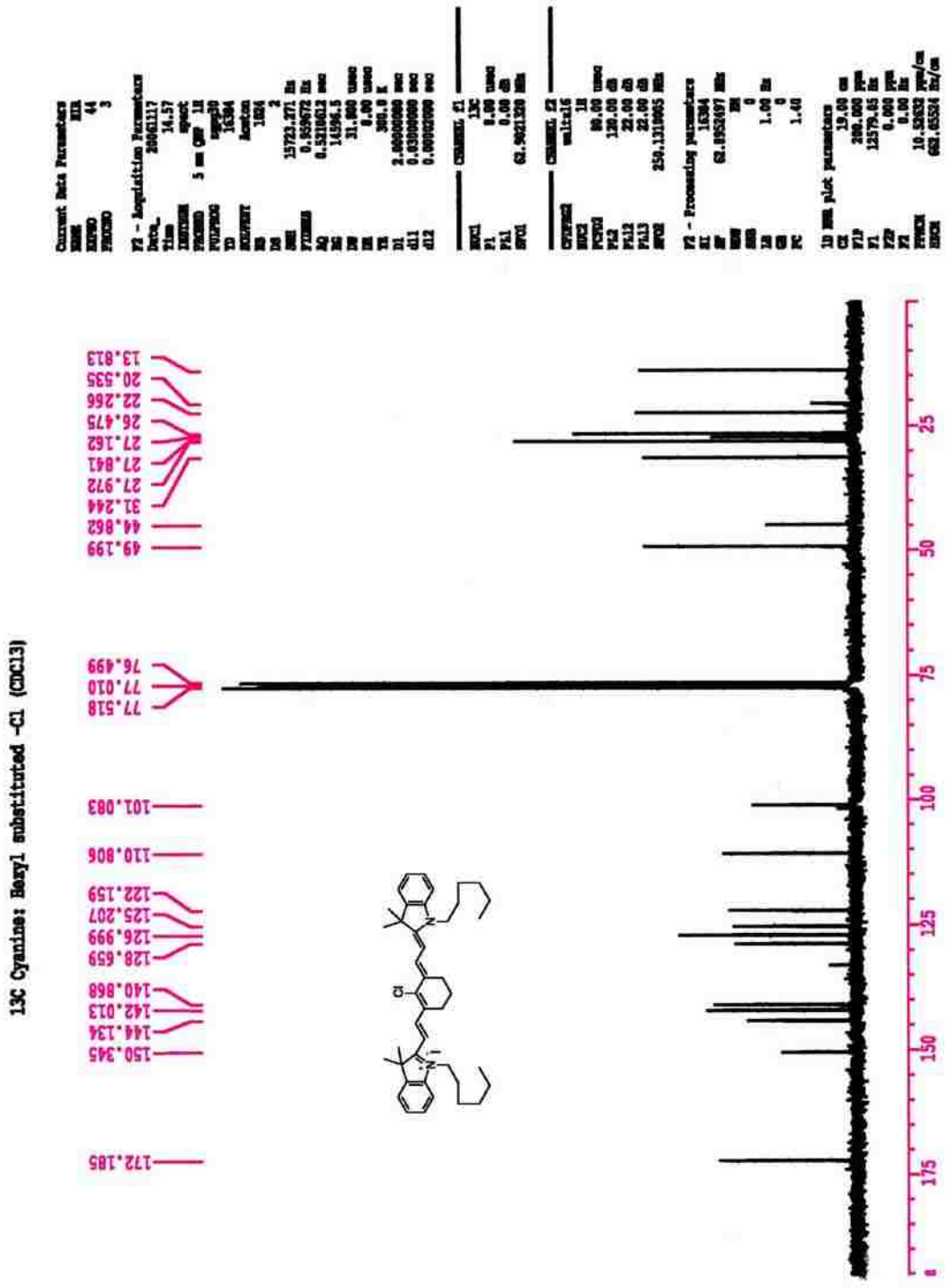


Figure J.2. ^{13}C NMR of compound **3.16**

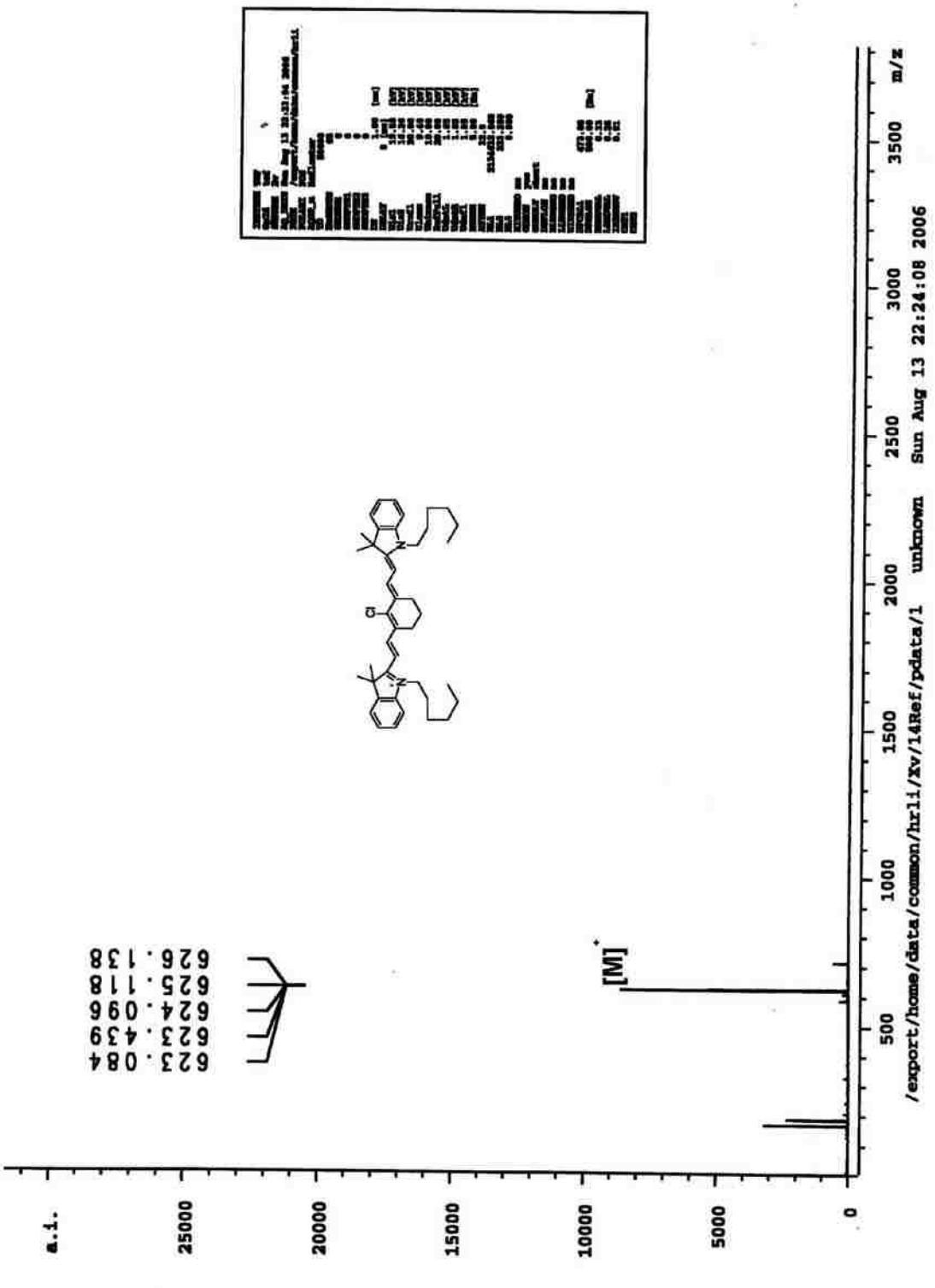


Figure J.3. MALDI MS of compound **3.16**

APPENDIX K: CHARACTERIZATION DATA FOR COMPOUND 3.19

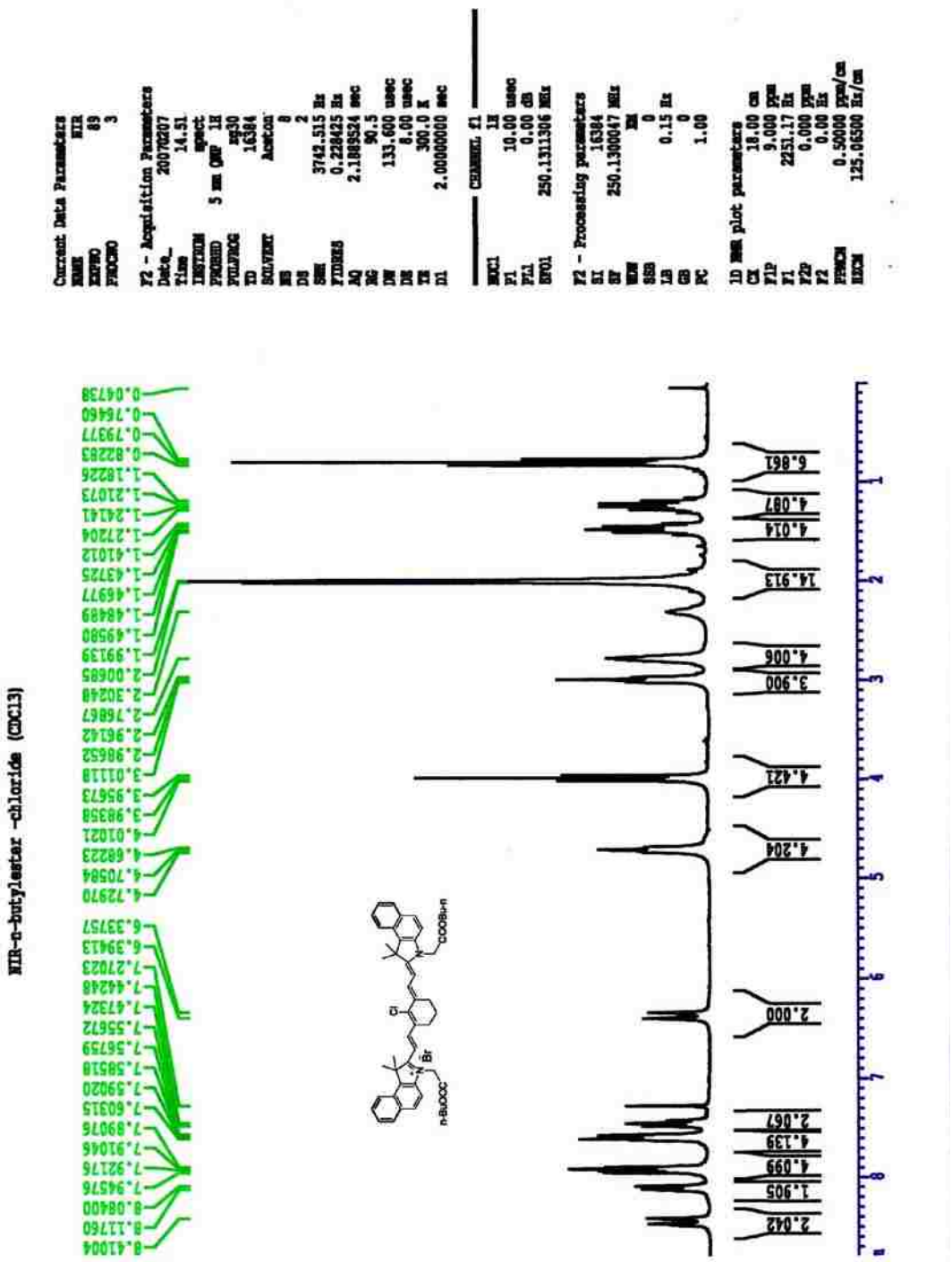


Figure K.1. ^{1}H NMR of compound **3.19**

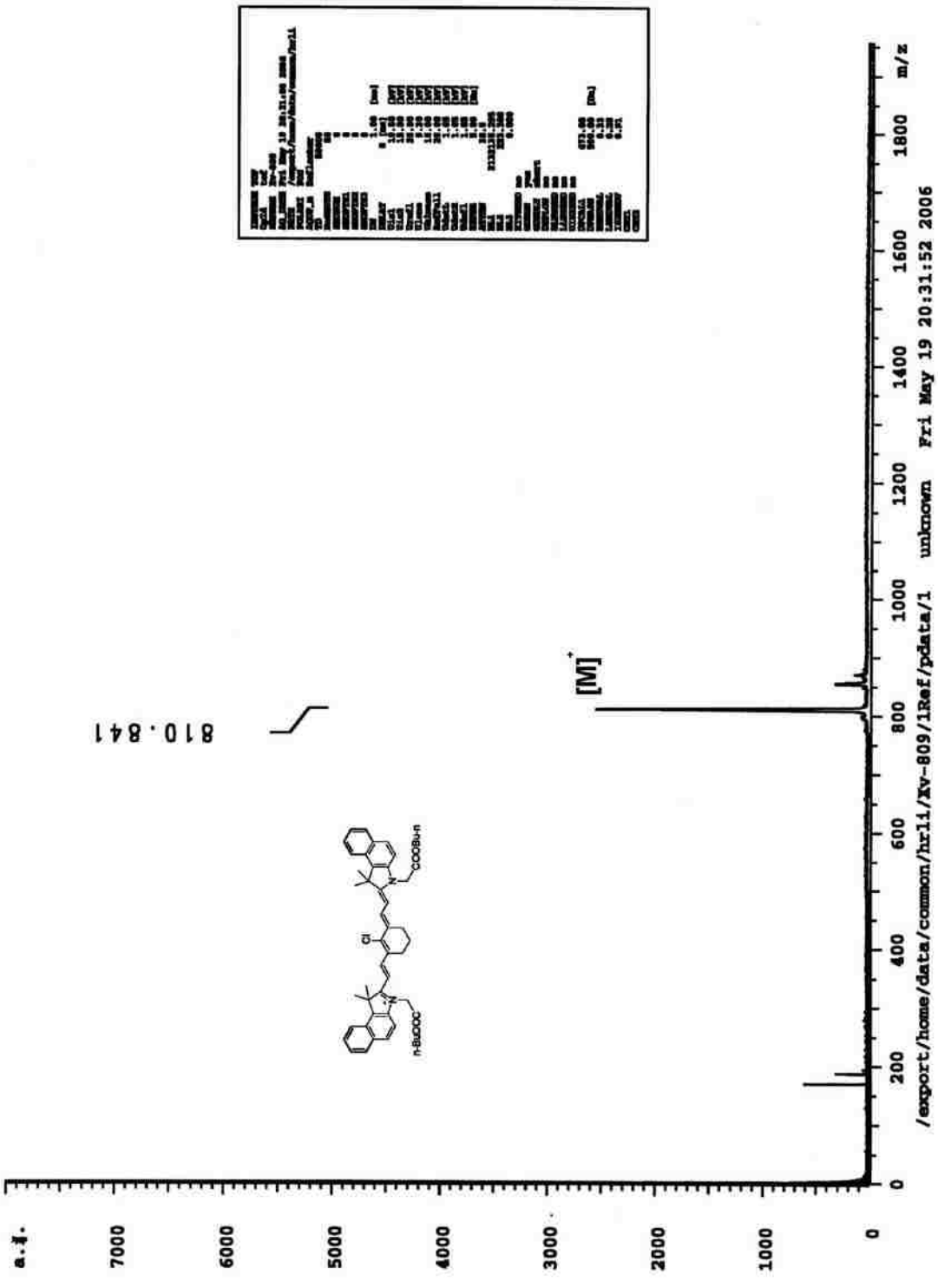


Figure K.2. MALDI MS of compound **3.19**

APPENDIX L: CHARACTERIZATION DATA FOR COMPOUND 3.20

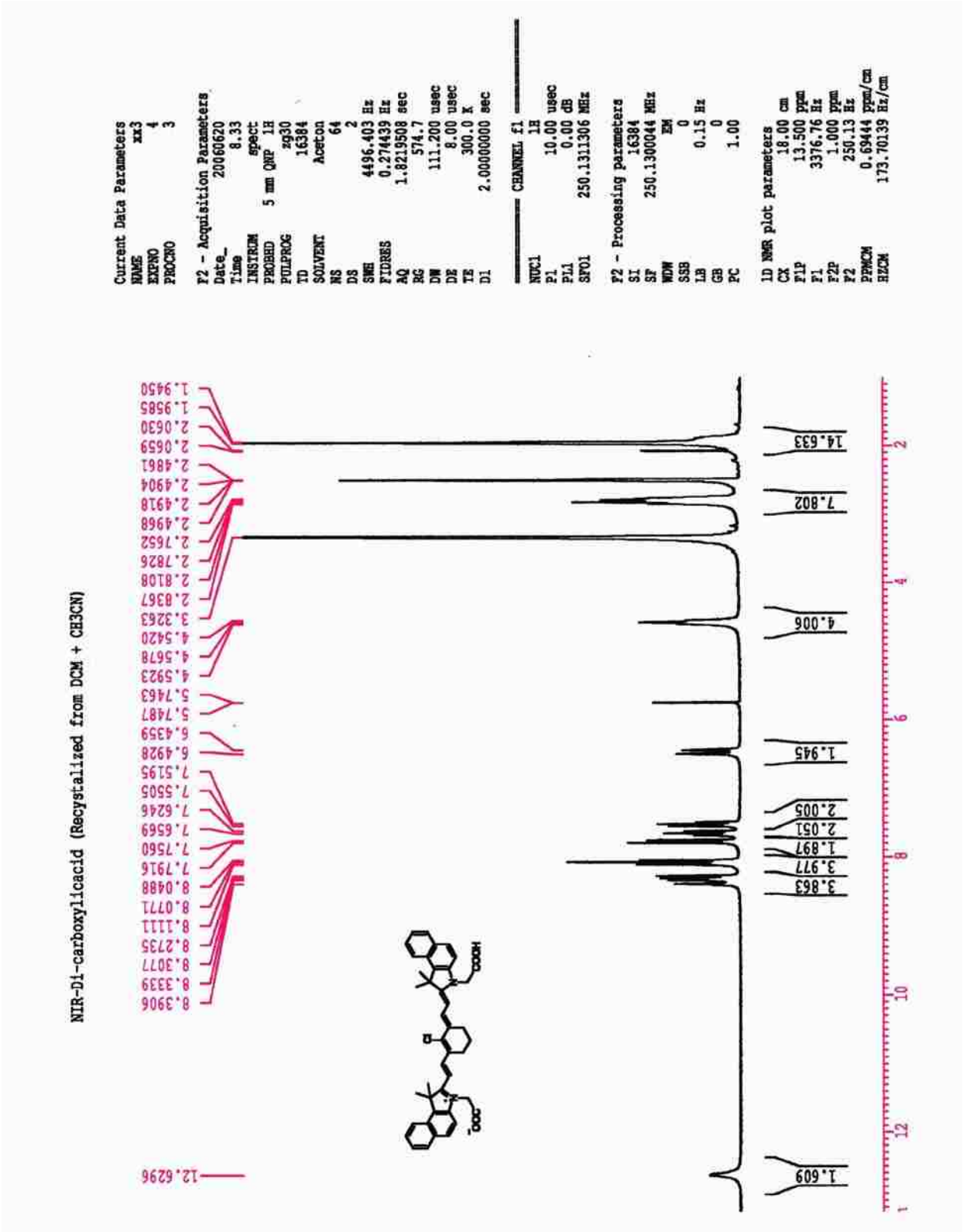


Figure L.1. ^{1}H NMR of compound **3.20**

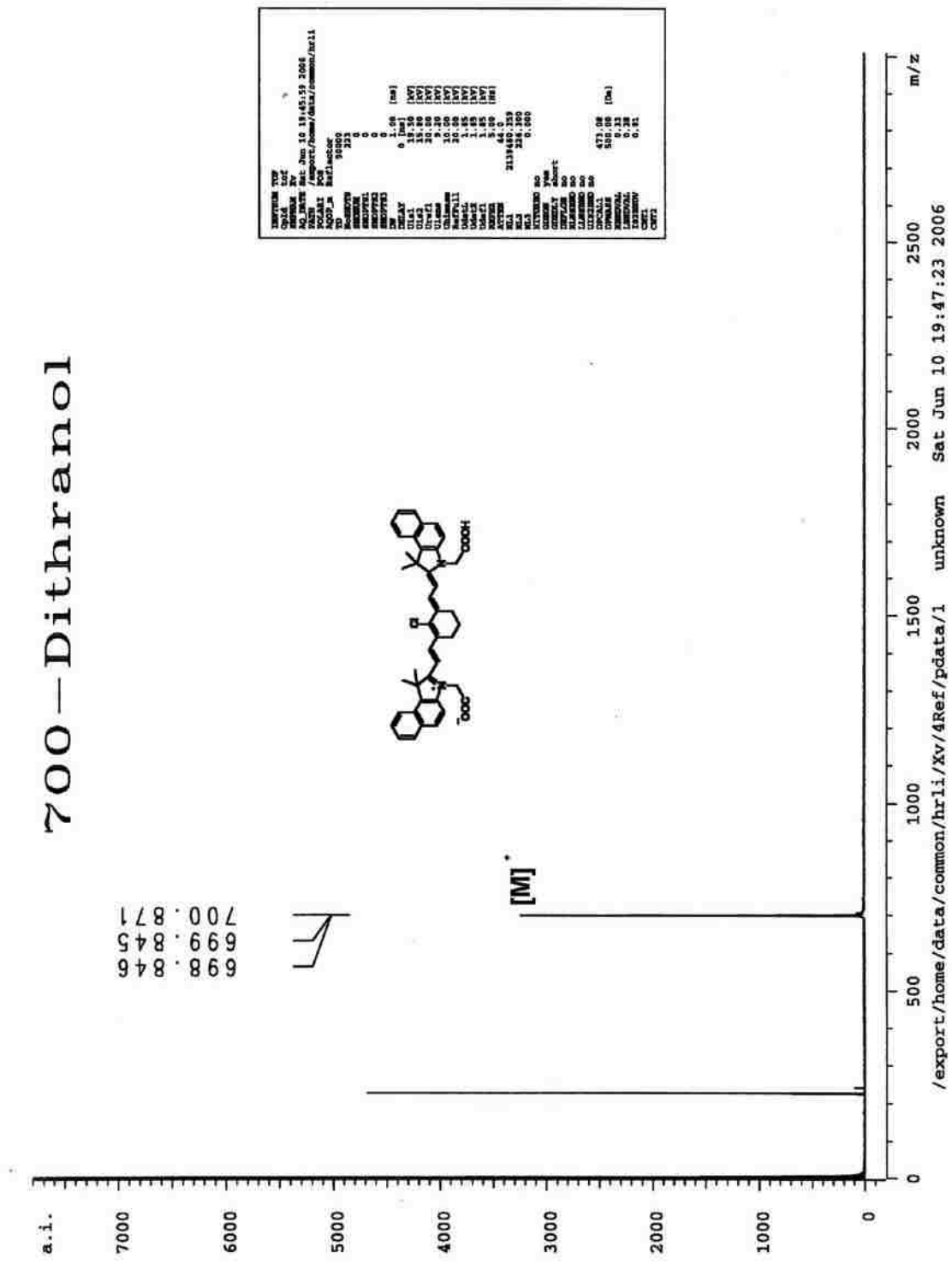


Figure L.2. MALDI MS of compound **3.20**

APPENDIX M: CHARACTERIZATION DATA FOR COMPOUND 3.7

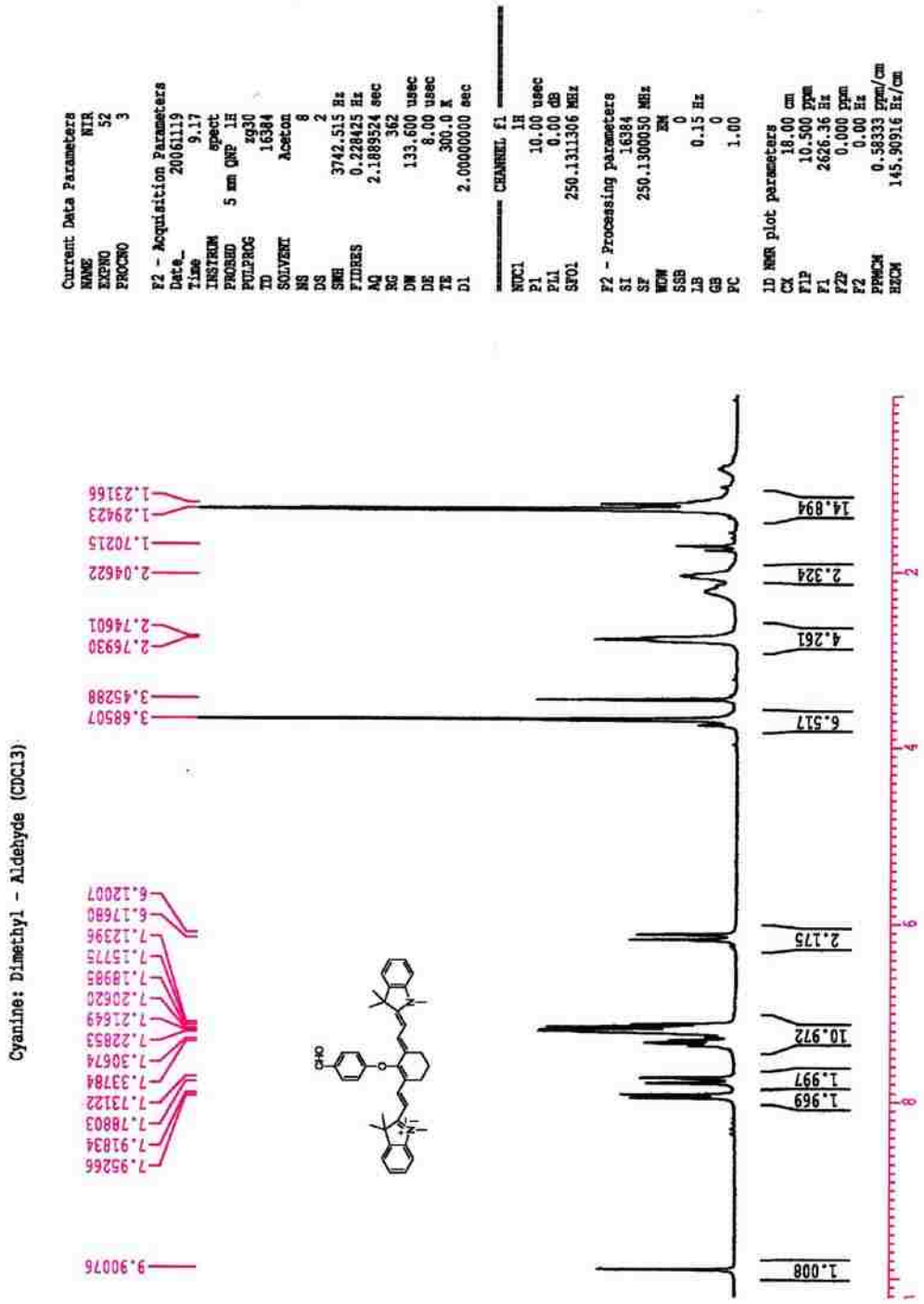


Figure M.1. ^{1}H NMR of compound **3.7**

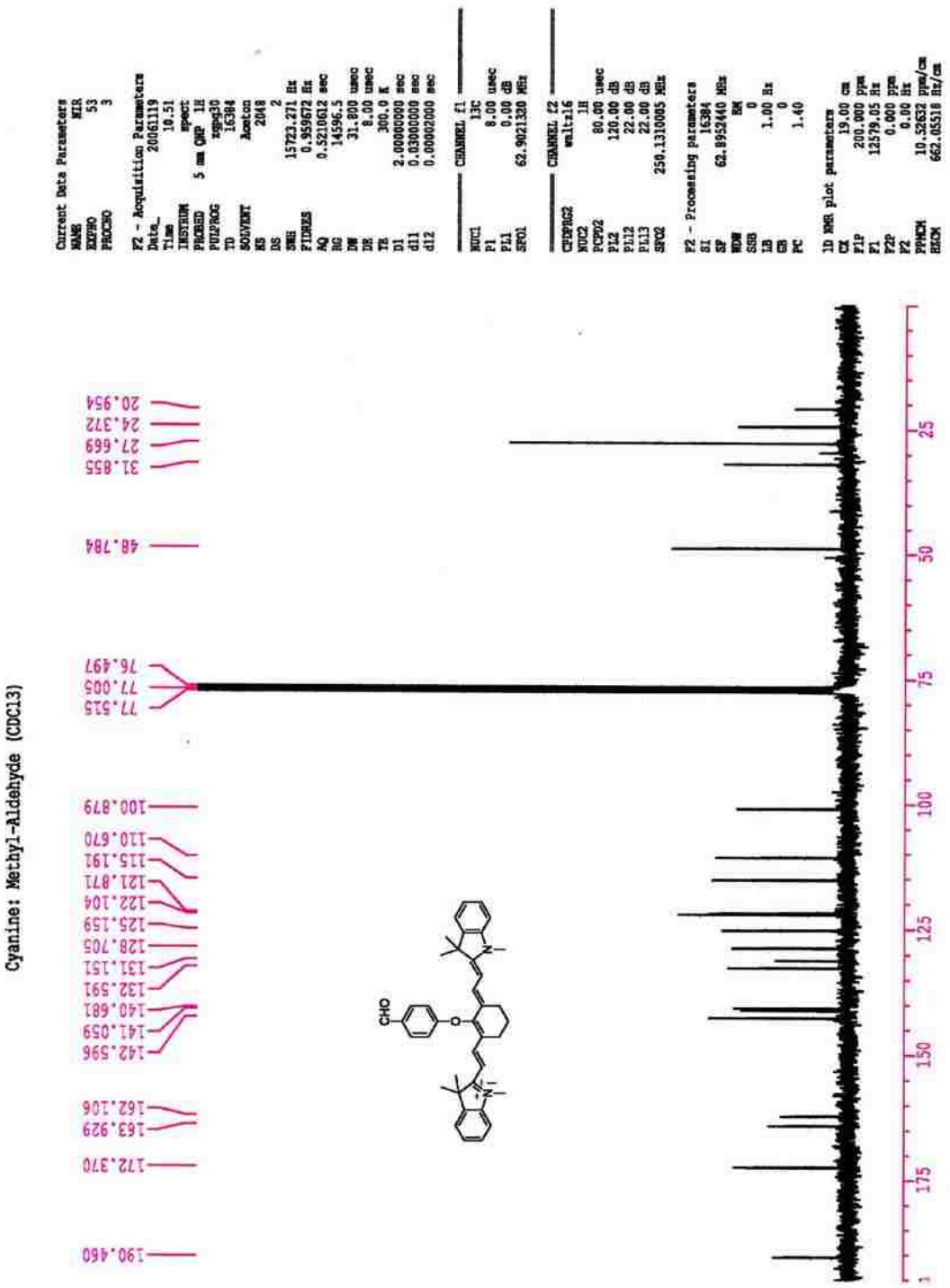


Figure M.2. ^{13}C NMR of compound **3.7**

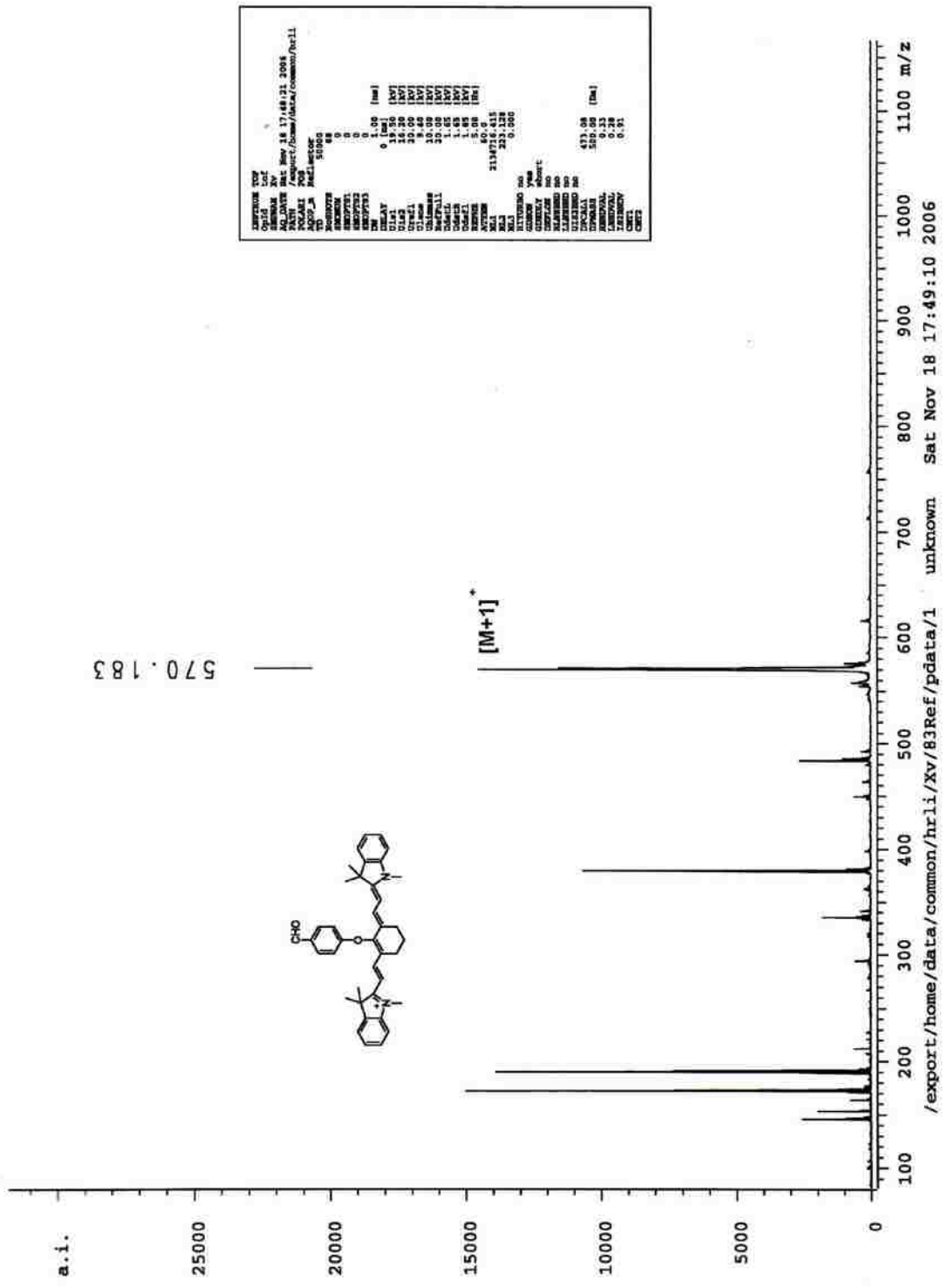


Figure M.3. MALDI MS of compound **3.7**

APPENDIX N: CHARACTERIZATION DATA FOR COMPOUND 3.8

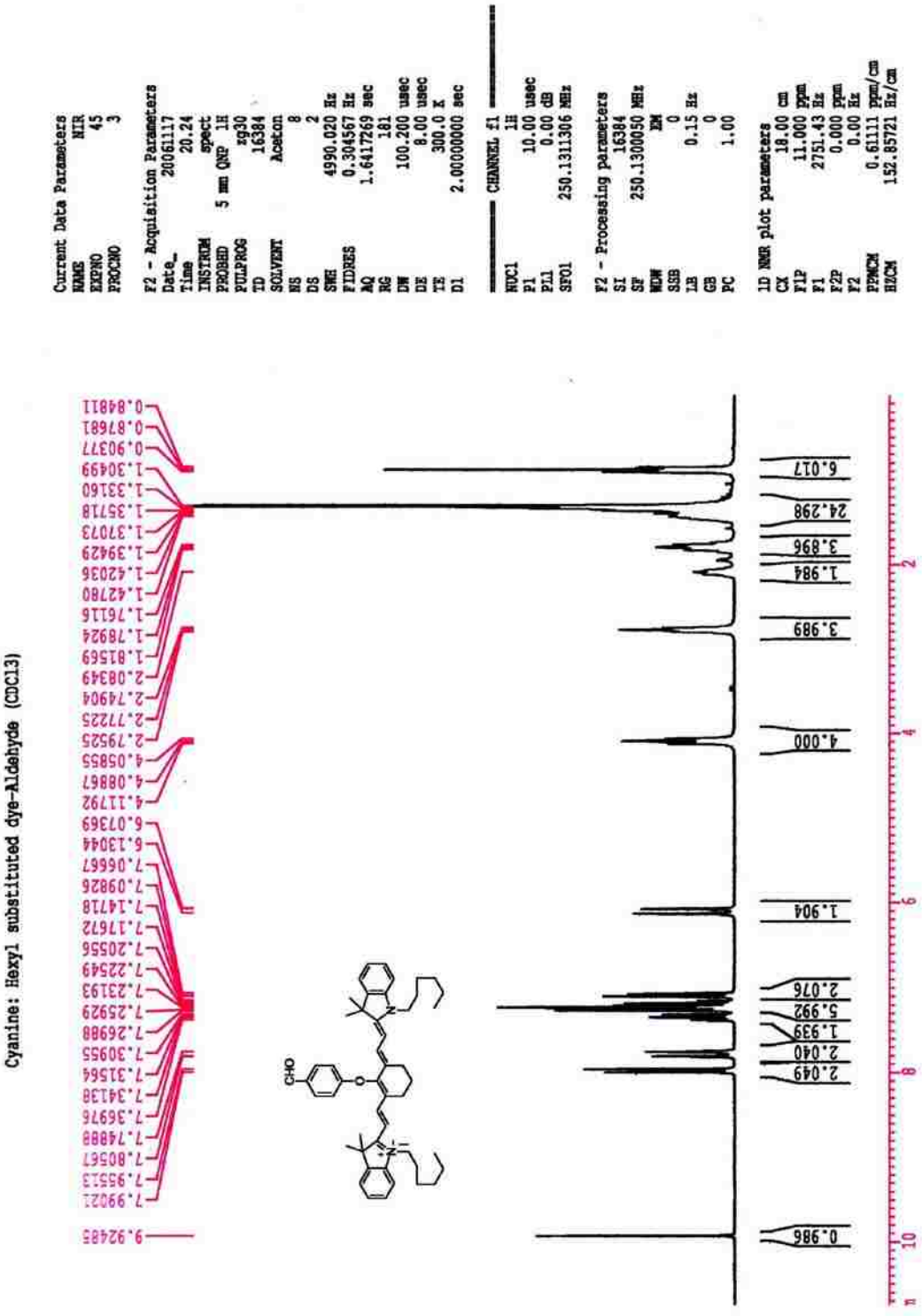


Figure N.1. ^{1}H NMR of compound **3.8**

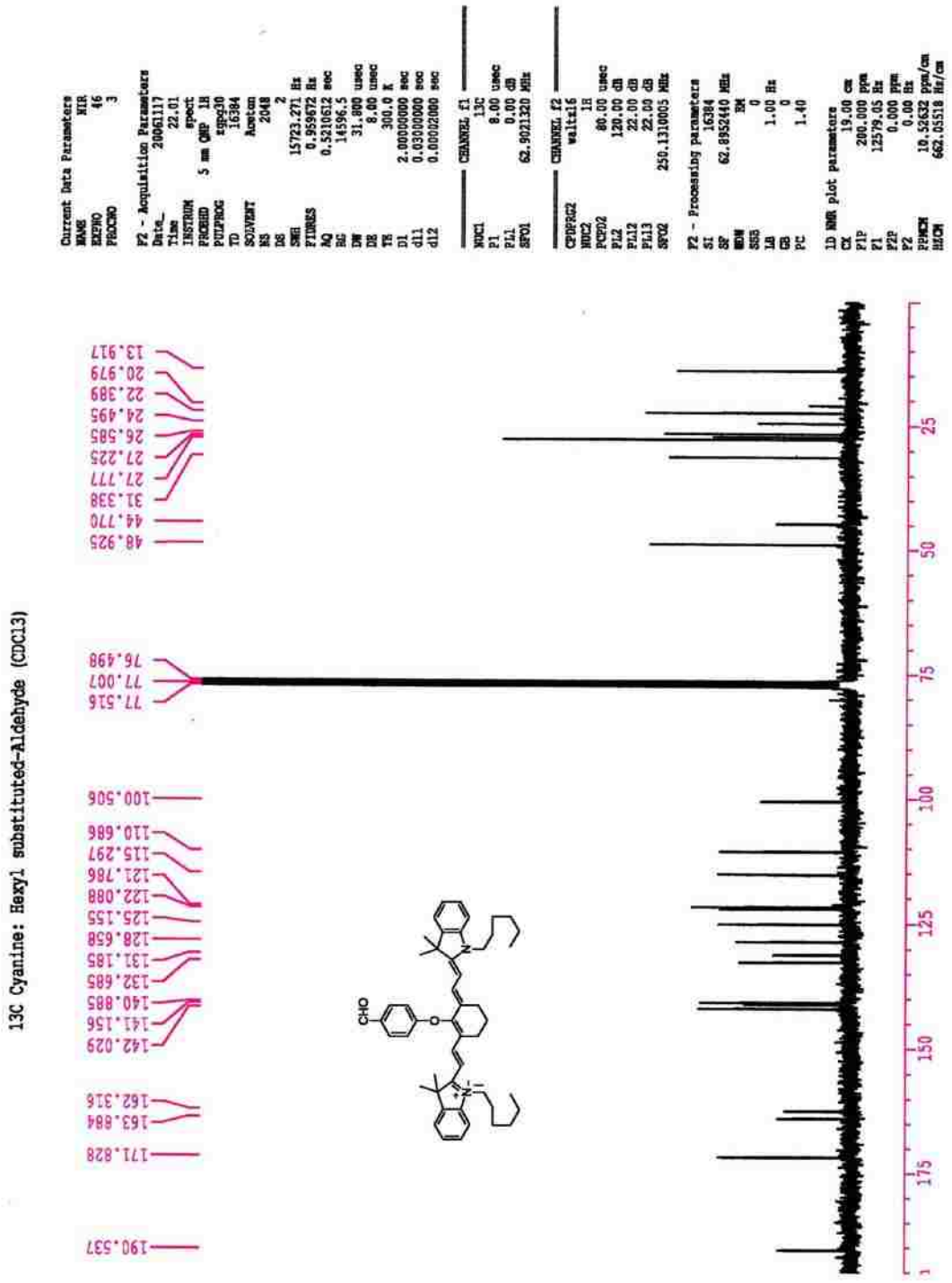


Figure N.2. ^{13}C NMR of compound **3.8**

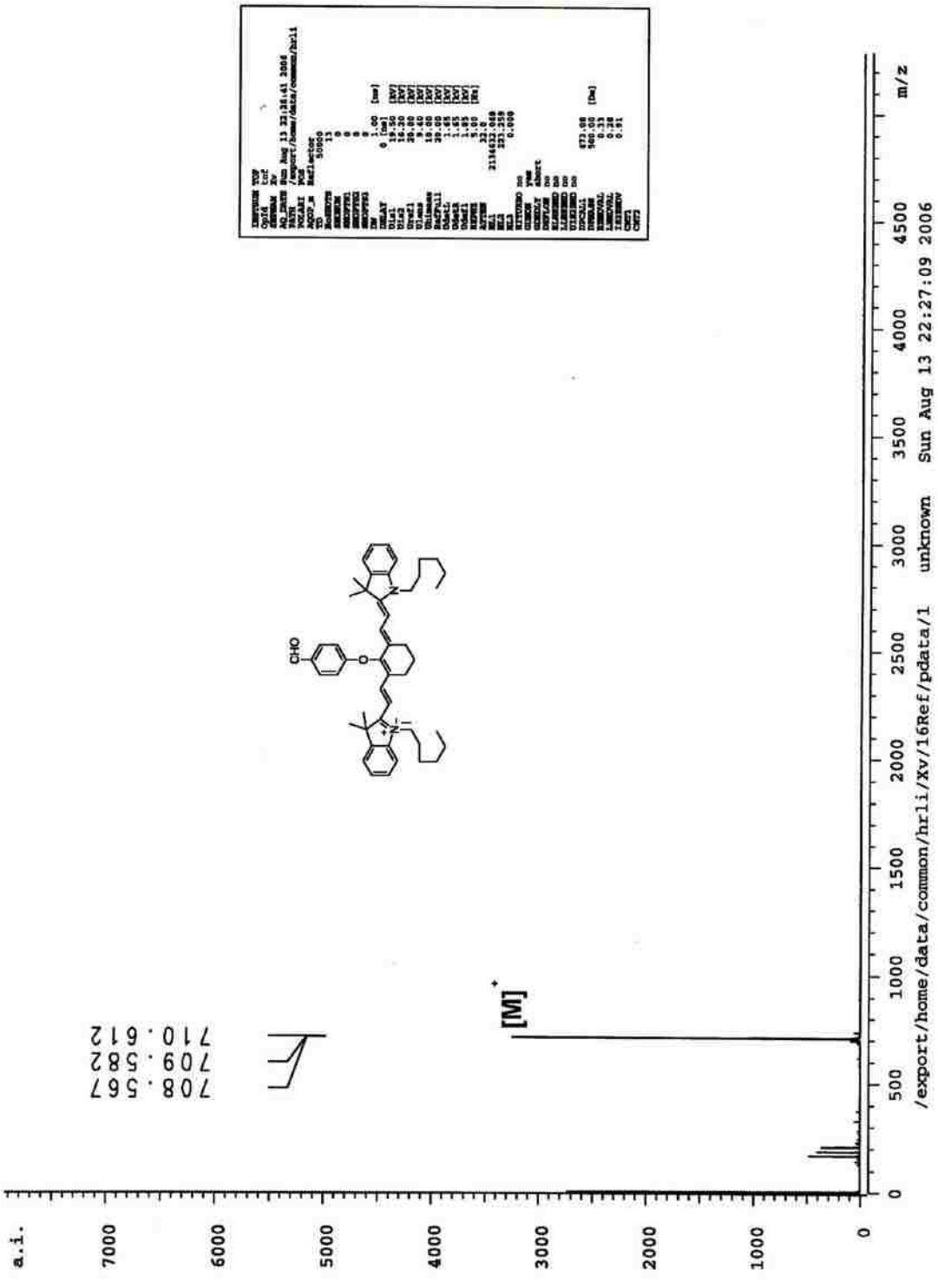


Figure N.3. MALDI MS of compound **3.8**

APPENDIX O: CHARACTERIZATION DATA FOR COMPOUND 3.9

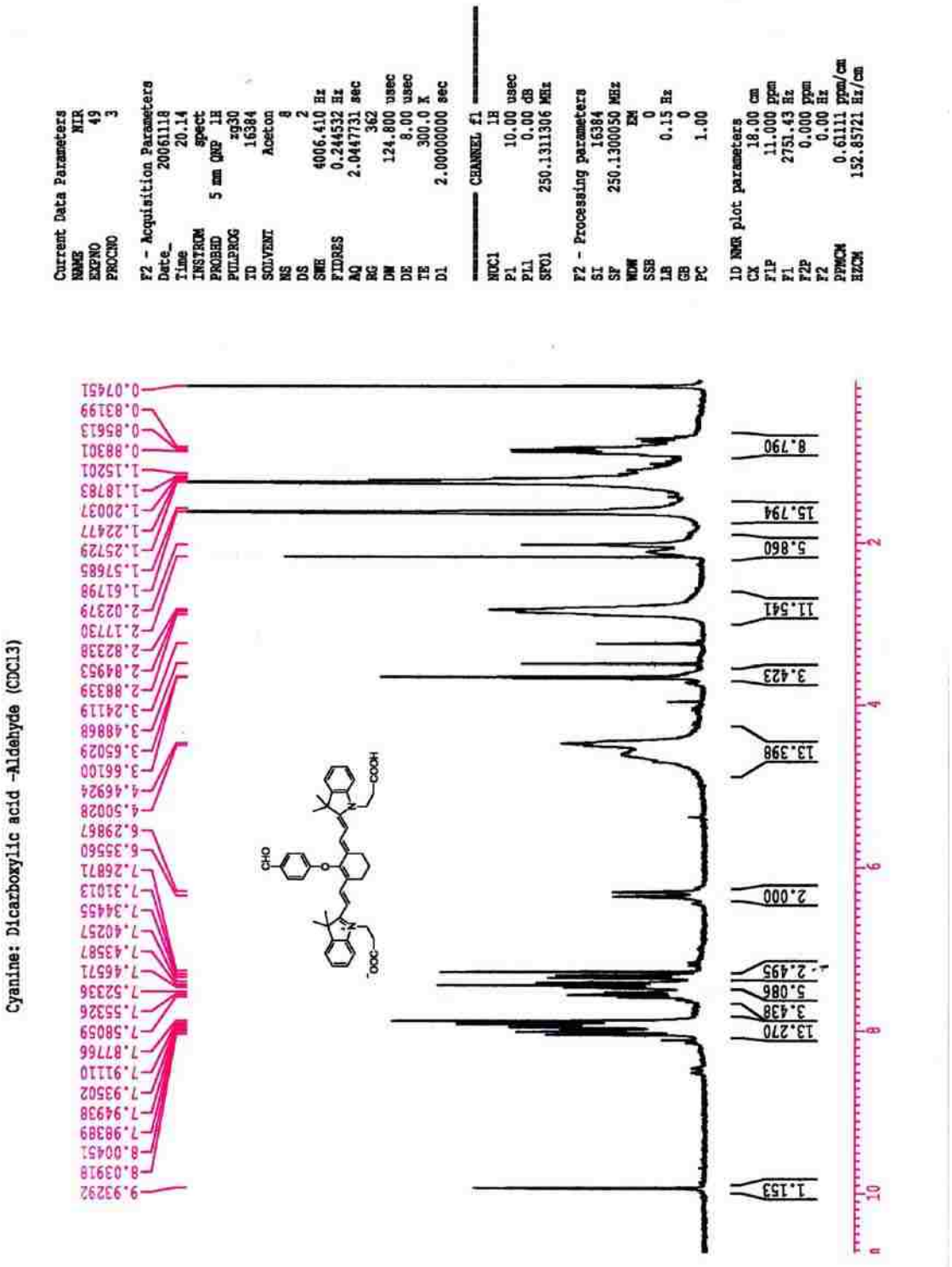


Figure O.1. ^{1}H NMR of compound **3.9**

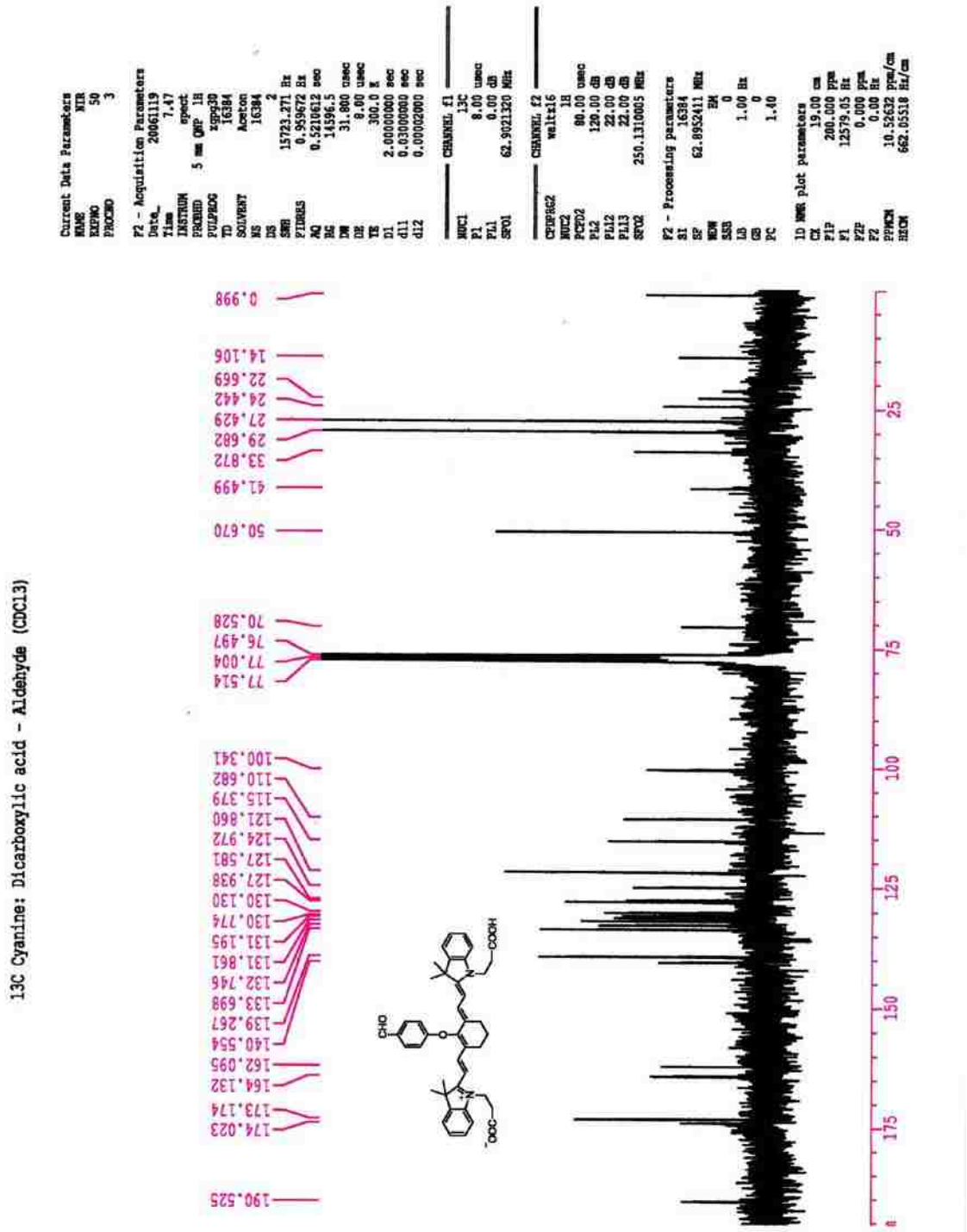


Figure O.2. ^{13}C NMR of compound **3.9**

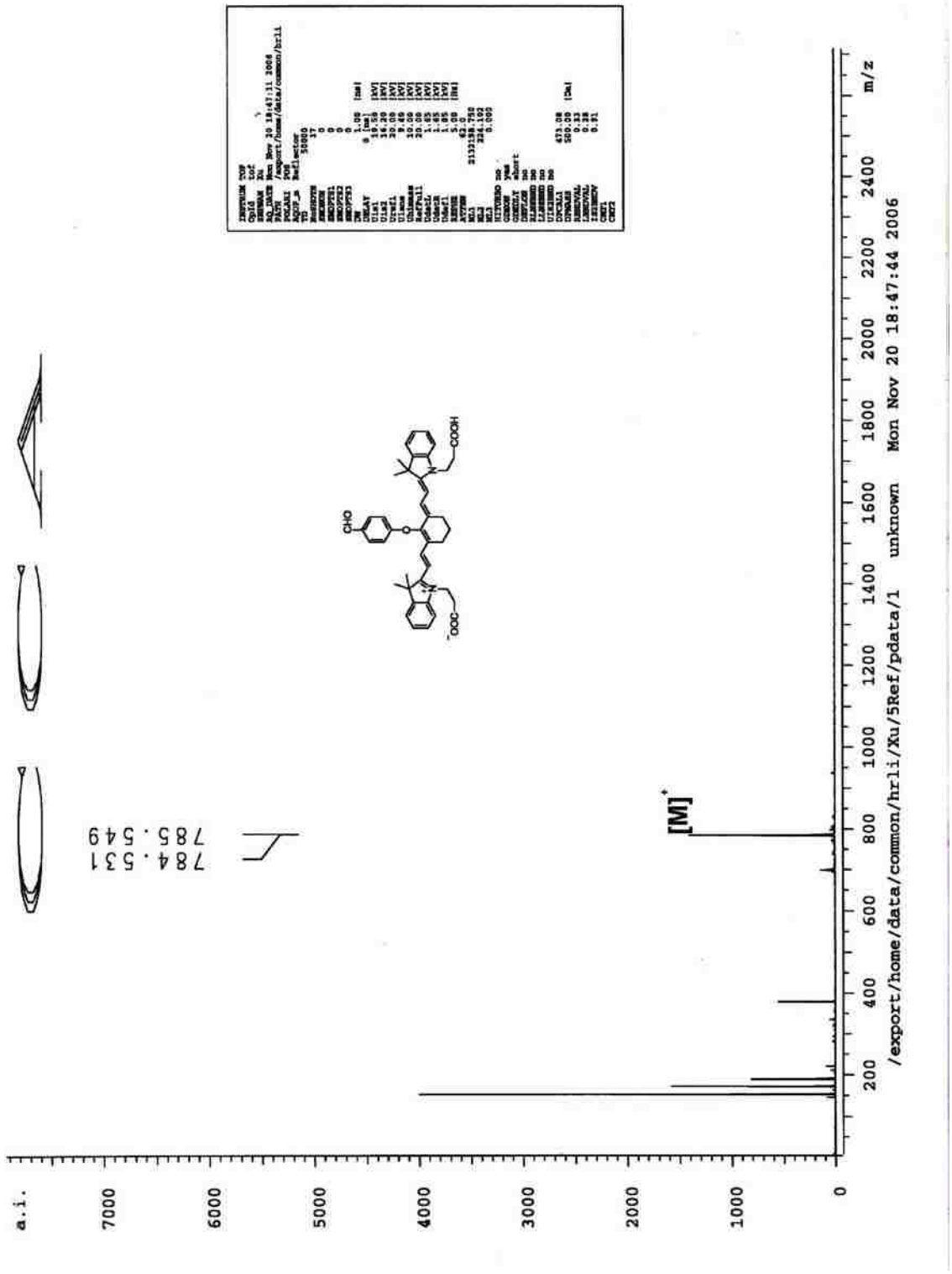


Figure O.3. MALDI MS of compound **3.9**

APPENDIX P: CHARACTERIZATION DATA FOR COMPOUND 4.7

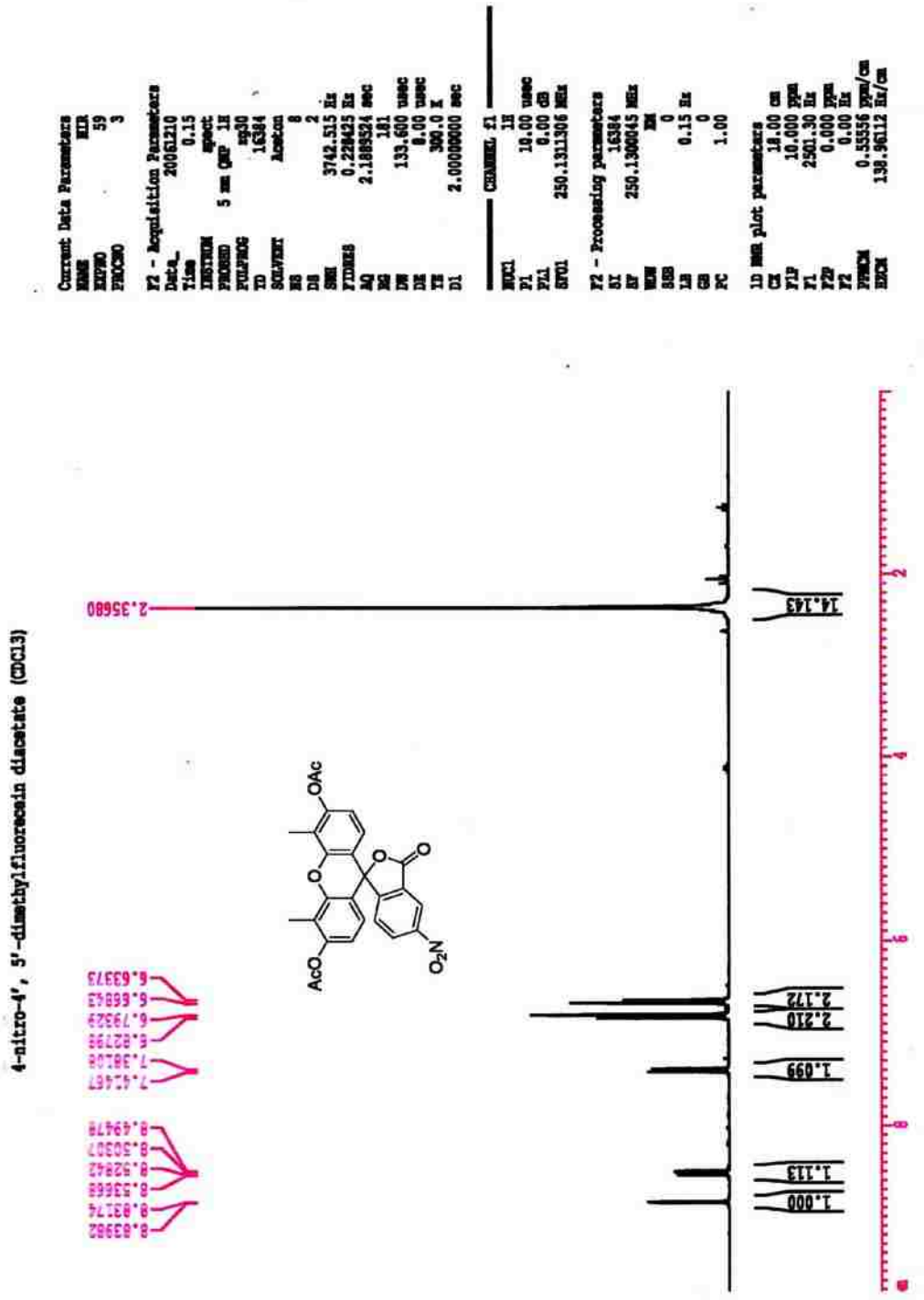


Figure P.1. ^{1}H NMR of compound **4.7**

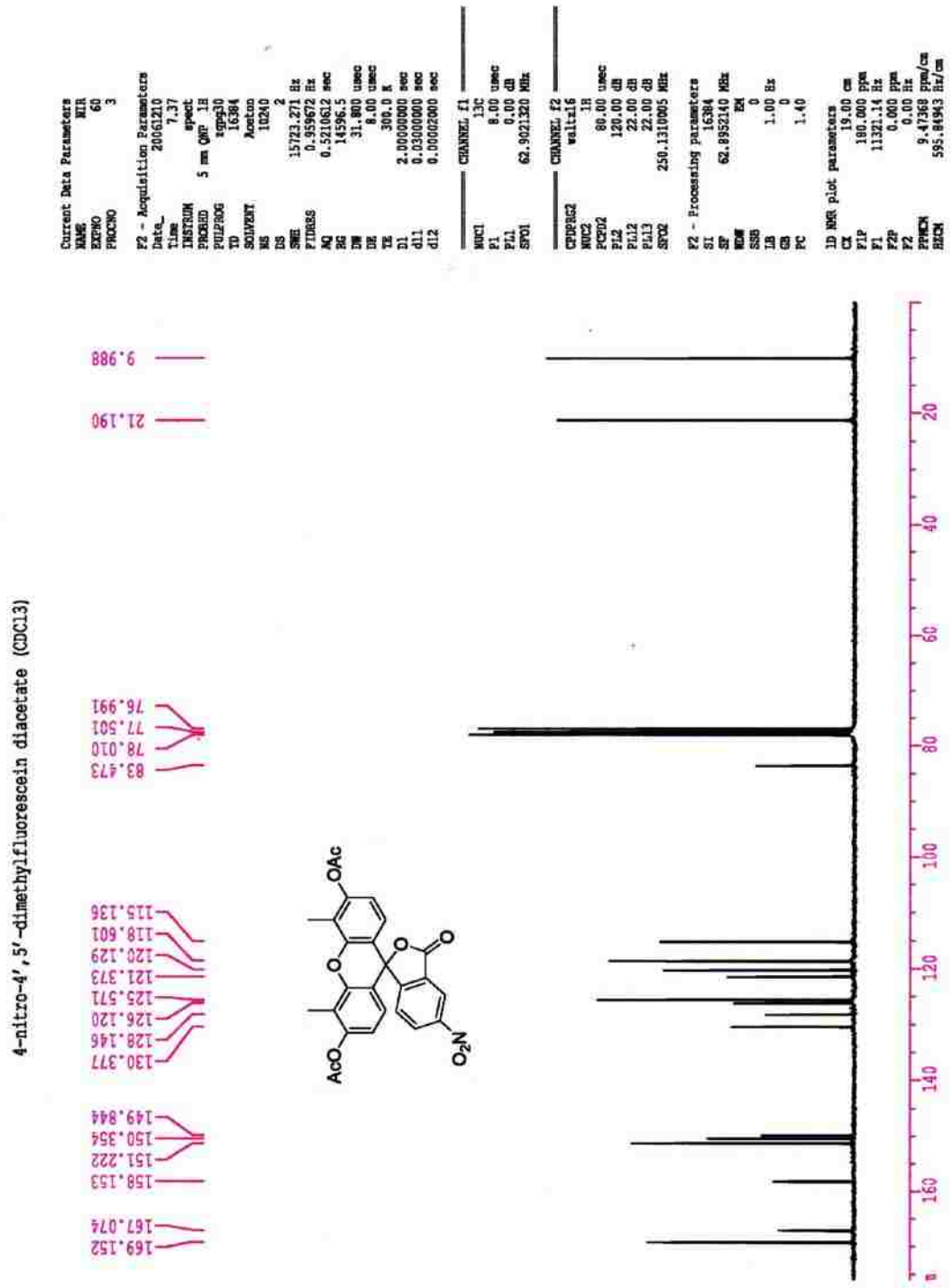


Figure P.2. ^{13}C NMR of compound **4.7**

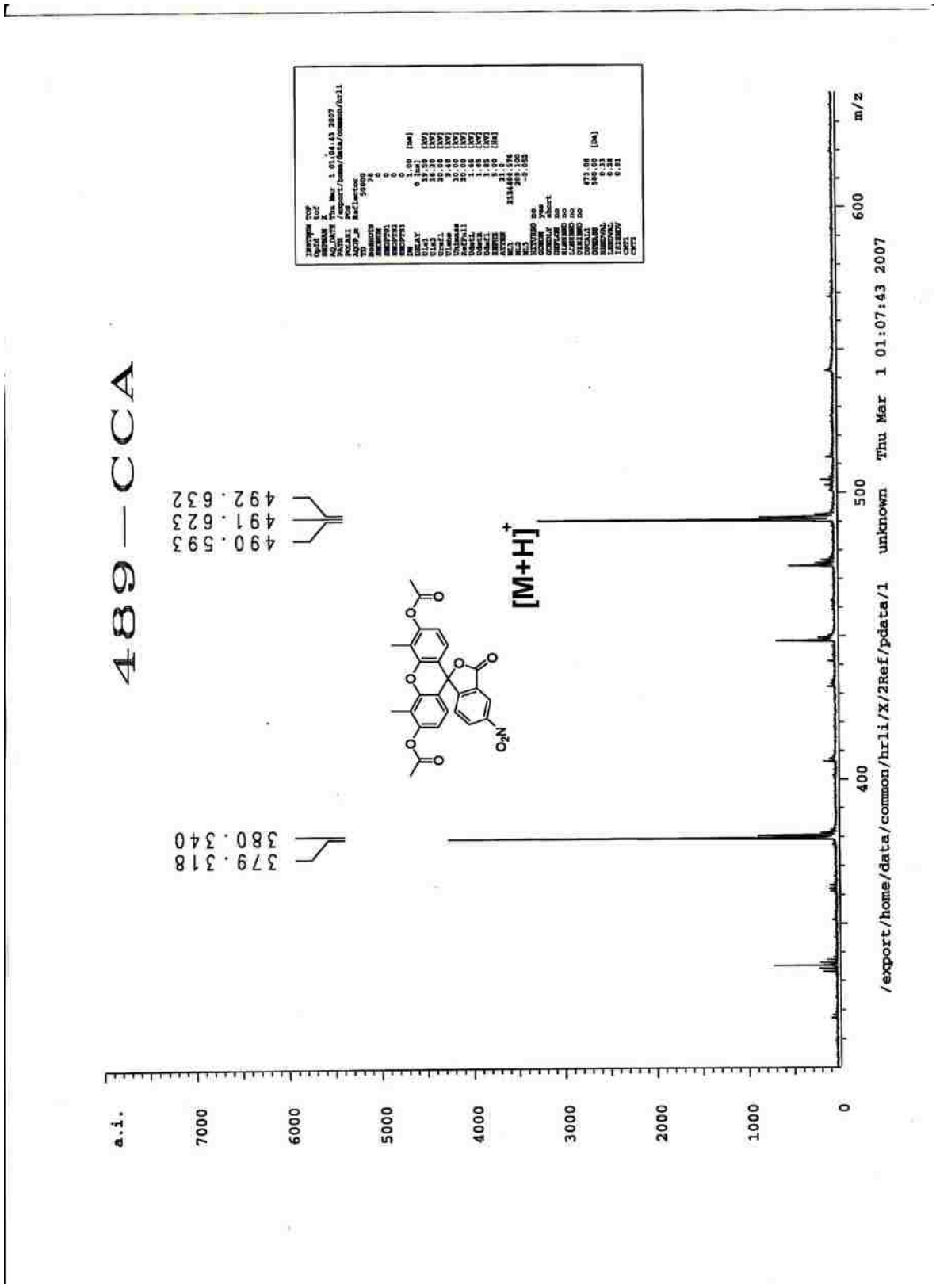
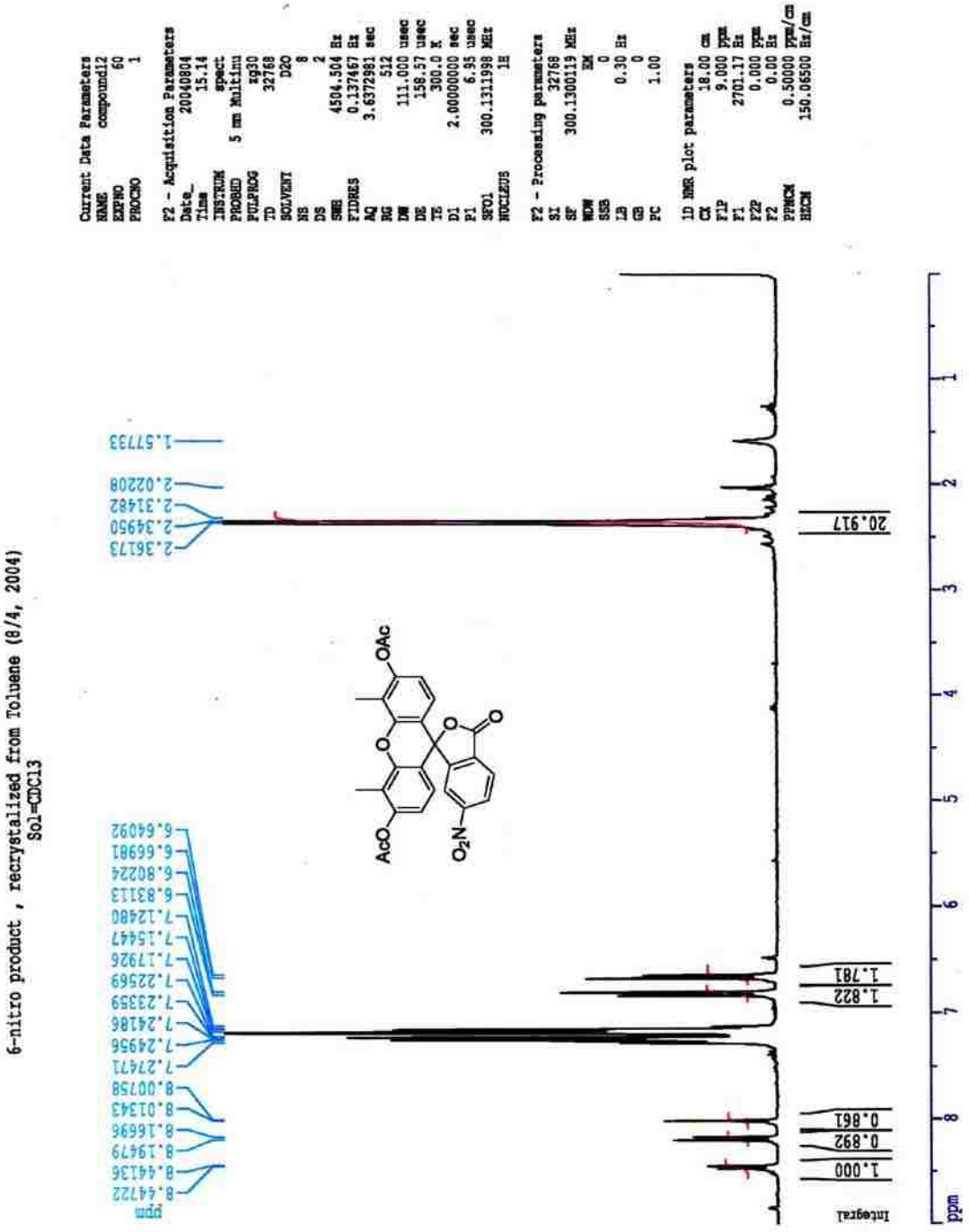
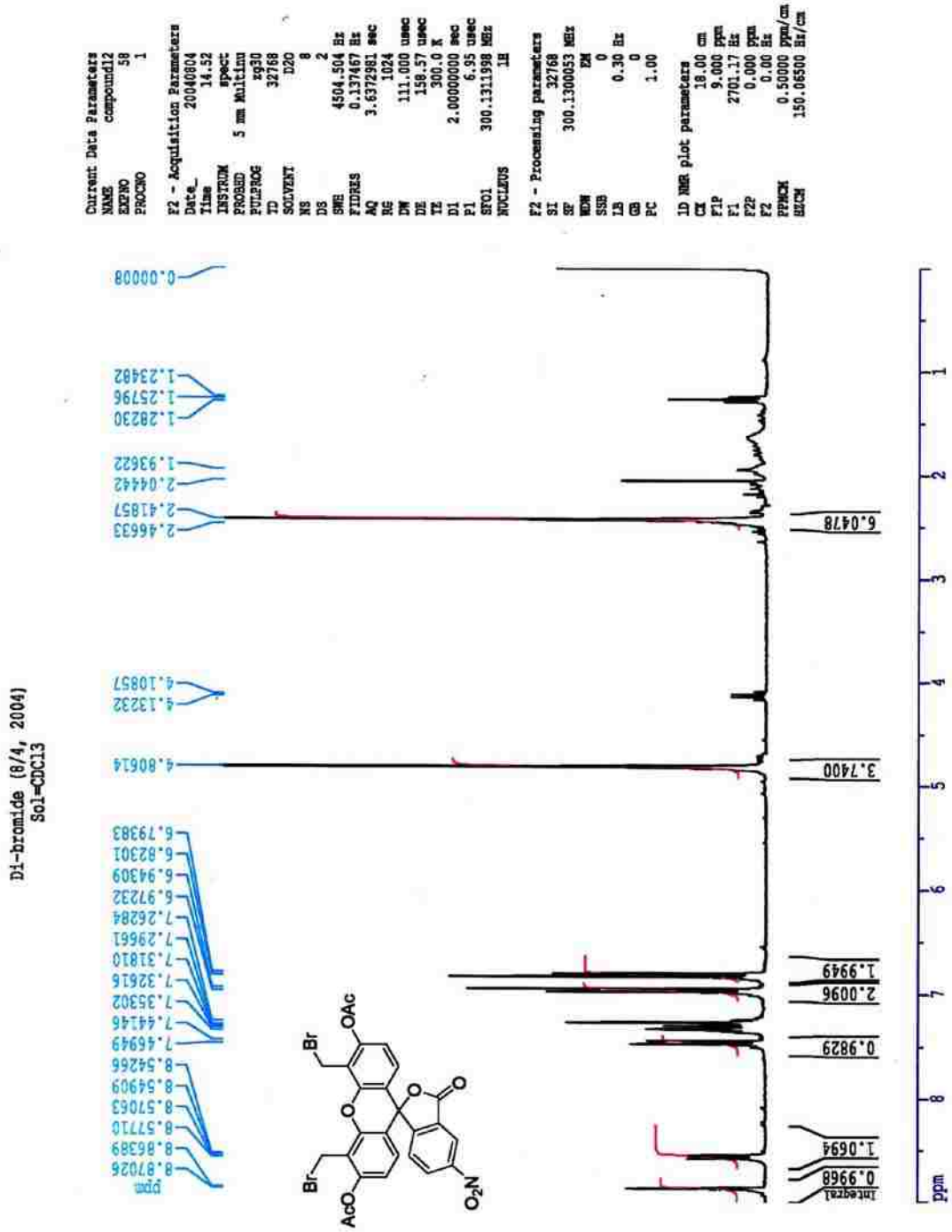


Figure P.3. MALDI MS of compound **4.7**

APPENDIX Q: ^{1}H NMR OF COMPOUND 4.8



APPENDIX R: ^{1}H NMR OF COMPOUND 4.6



APPENDIX S: CHARACTERIZATION DATA FOR COMPOUND 4.5

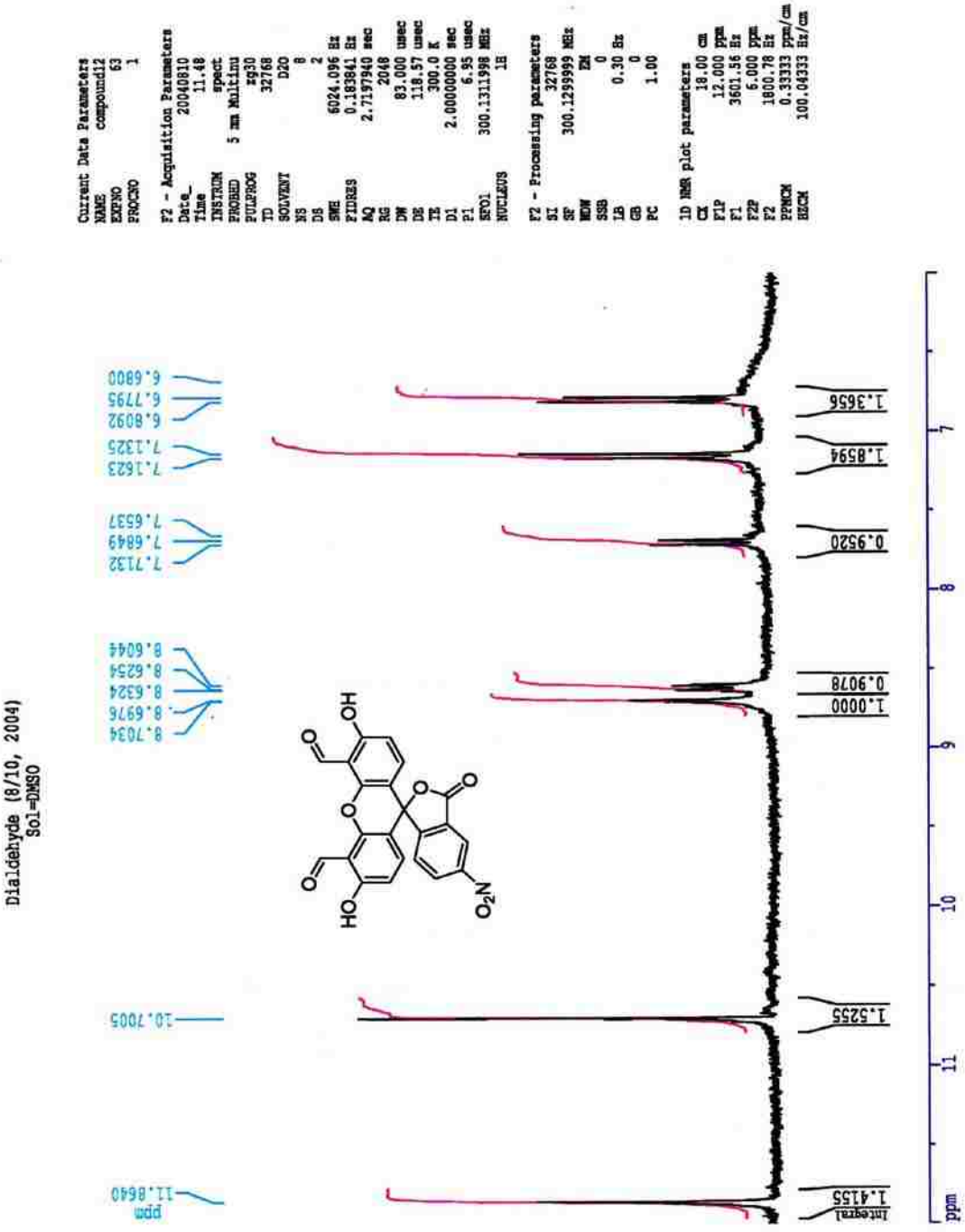


Figure S.1. ^{1}H NMR of compound **4.5**

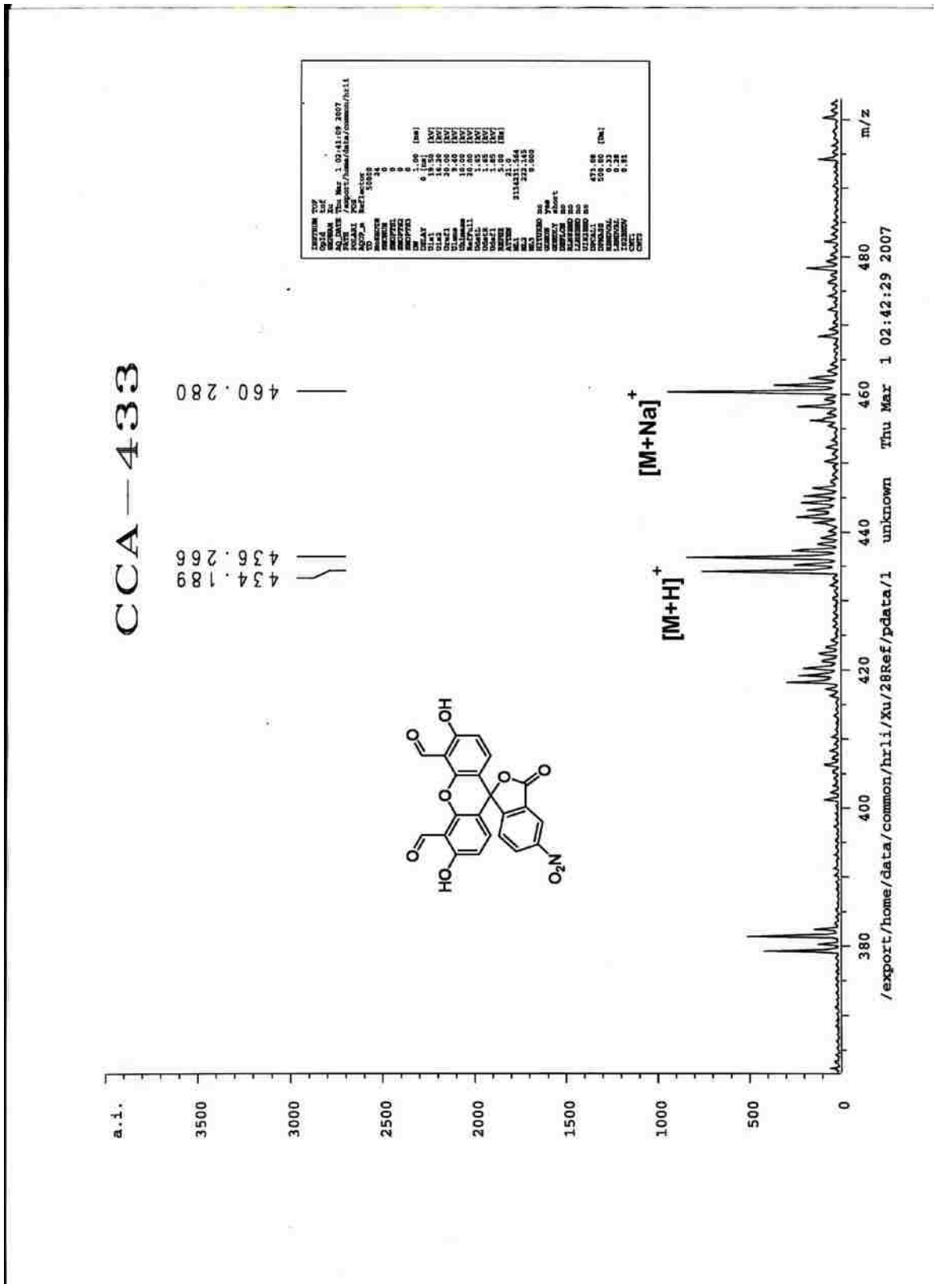


Figure S.2. MALDI MS of compound **4.5**

APPENDIX T: CHARACTERIZATION DATA FOR COMPOUND 5.2

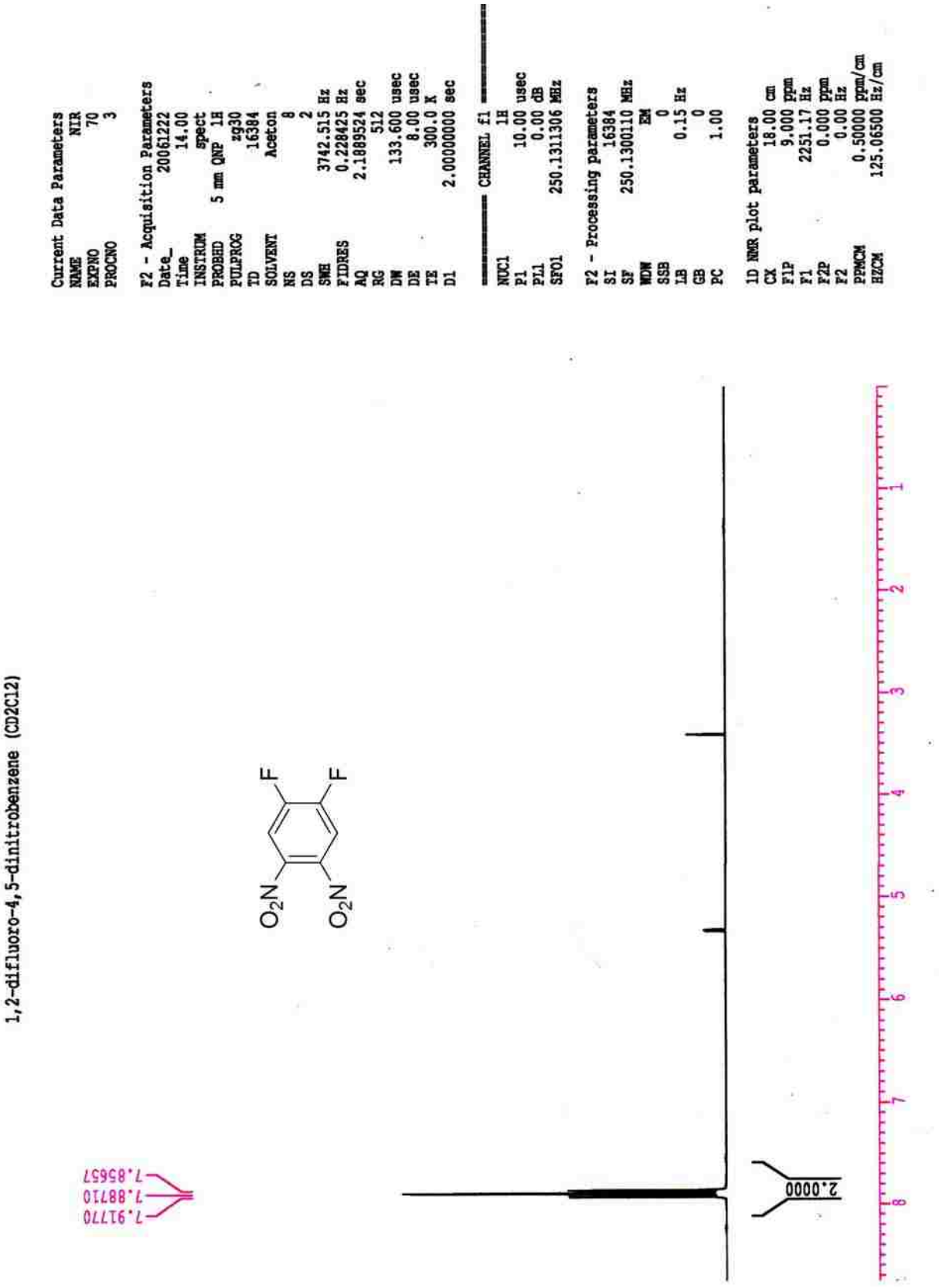


Figure T.1. ^{1}H NMR of compound **5.2**

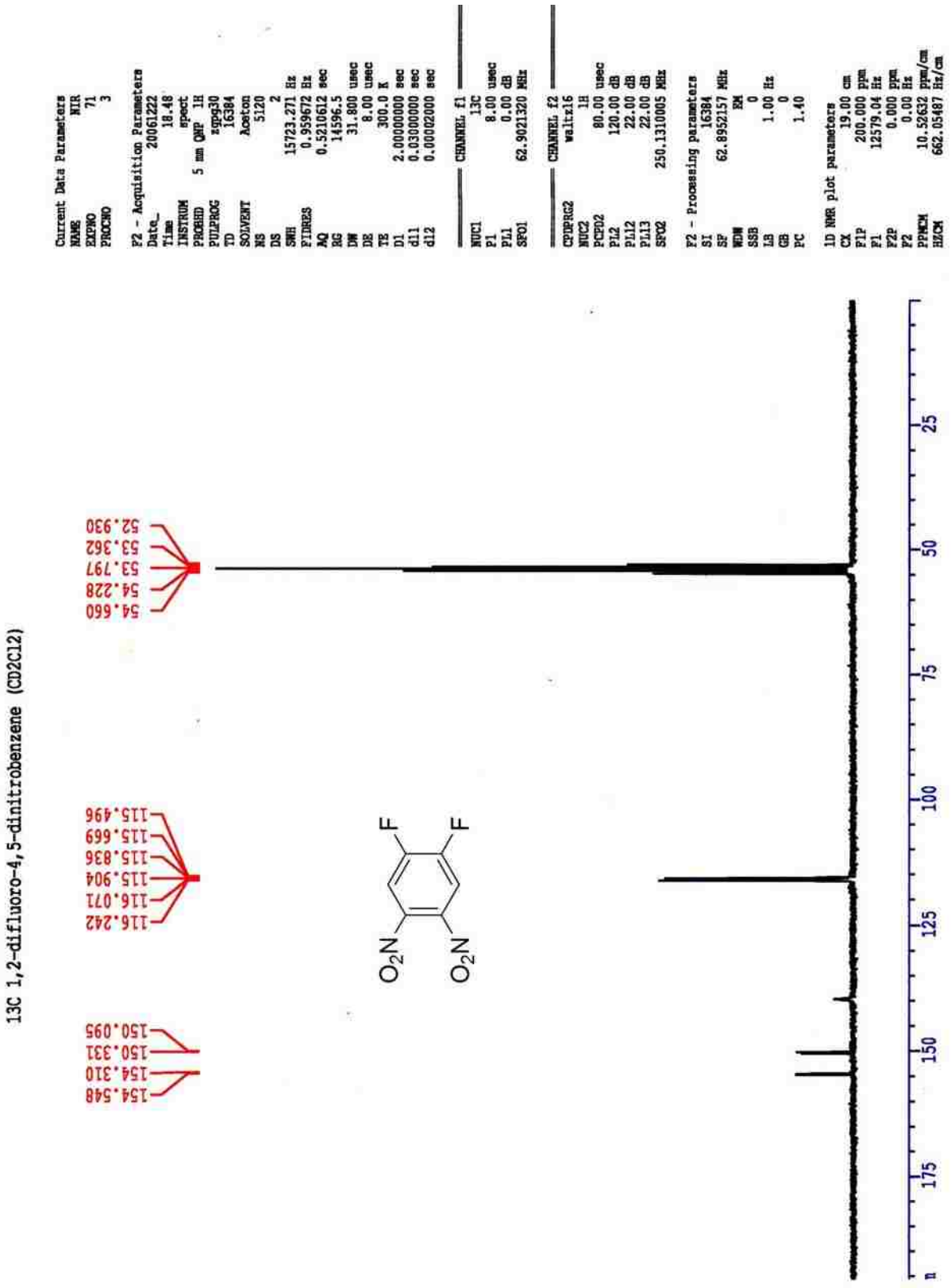


Figure T.2. ^{13}C NMR of compound **5.2**

APPENDIX U: CHARACTERIZATION DATA FOR COMPOUND 5.6

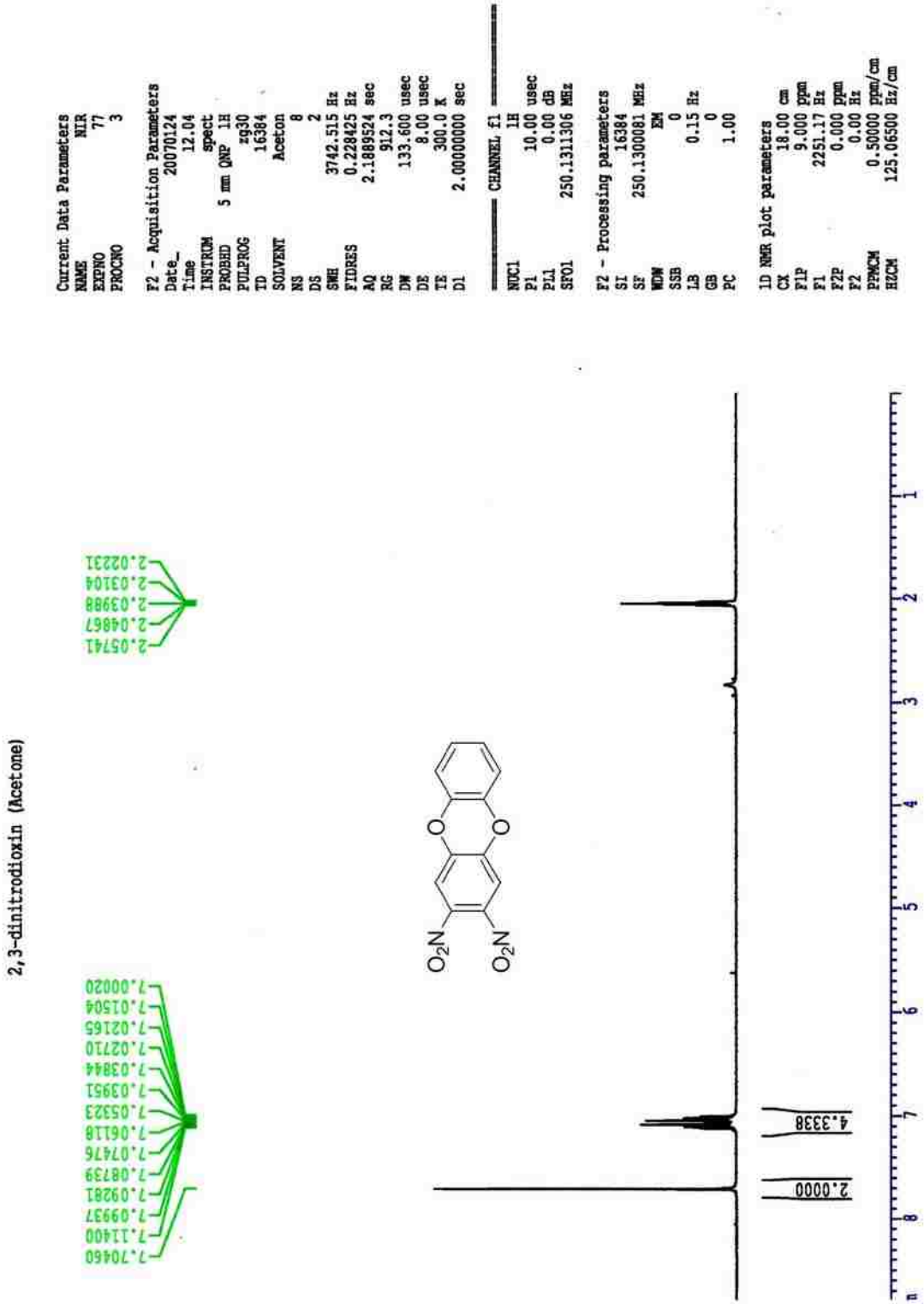


Figure U.1. ^{1}H NMR of compound **5.6**

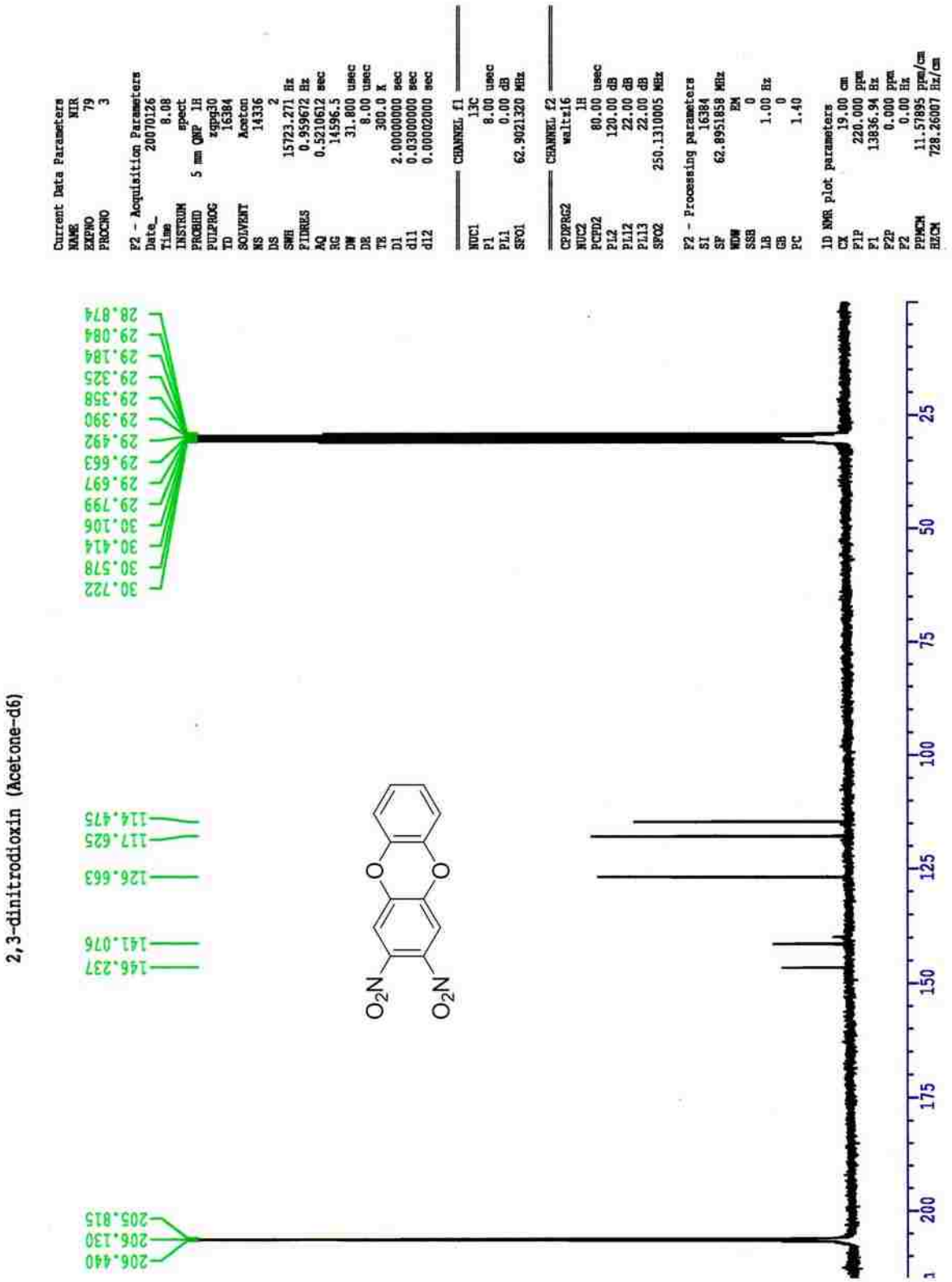


Figure U.2. ^{13}C NMR of compound **5.6**

APPENDIX V: CHARACTERIZATION DATA FOR COMPOUND 5.7

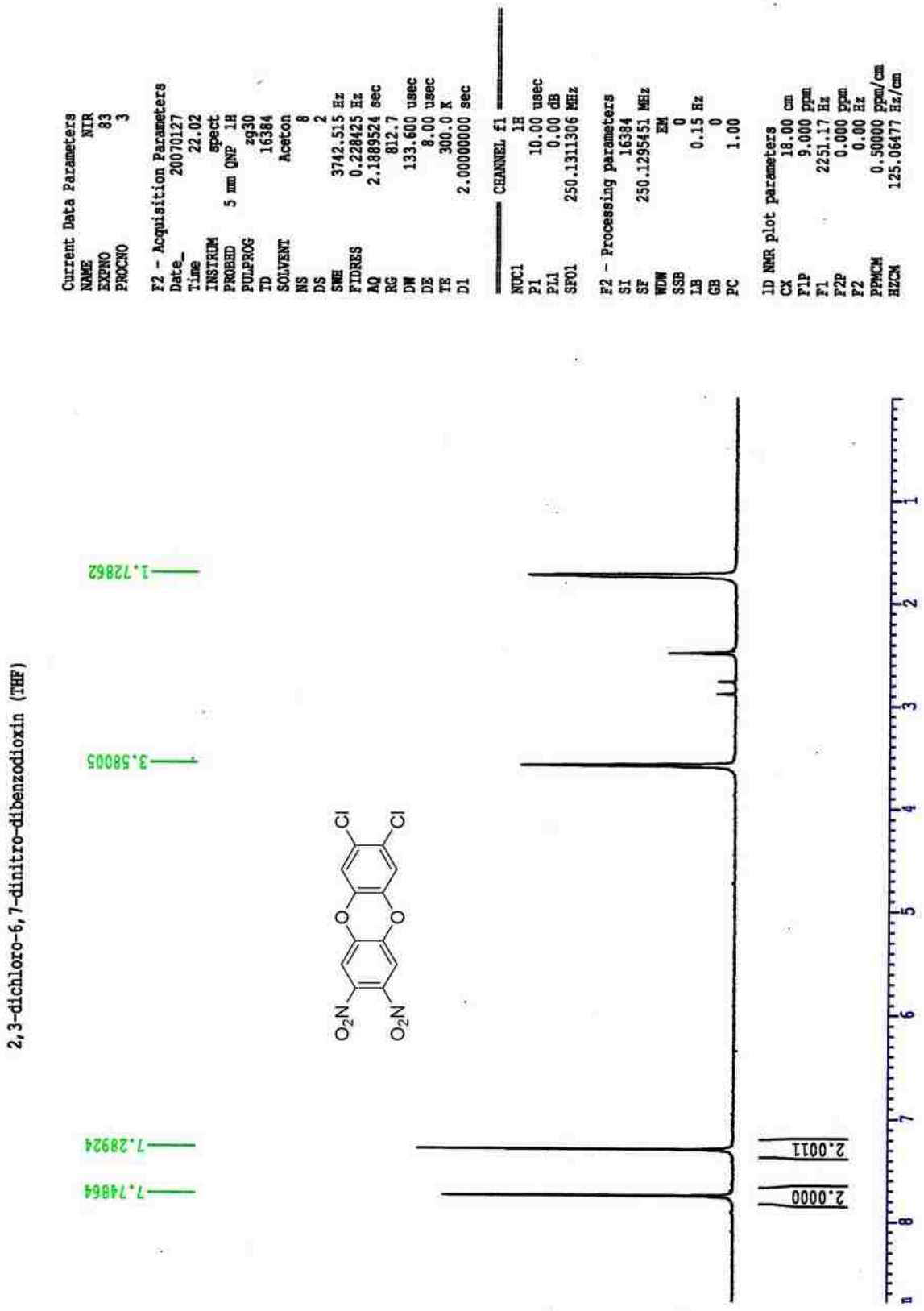


Figure V.1. ^{1}H NMR of compound **5.7**

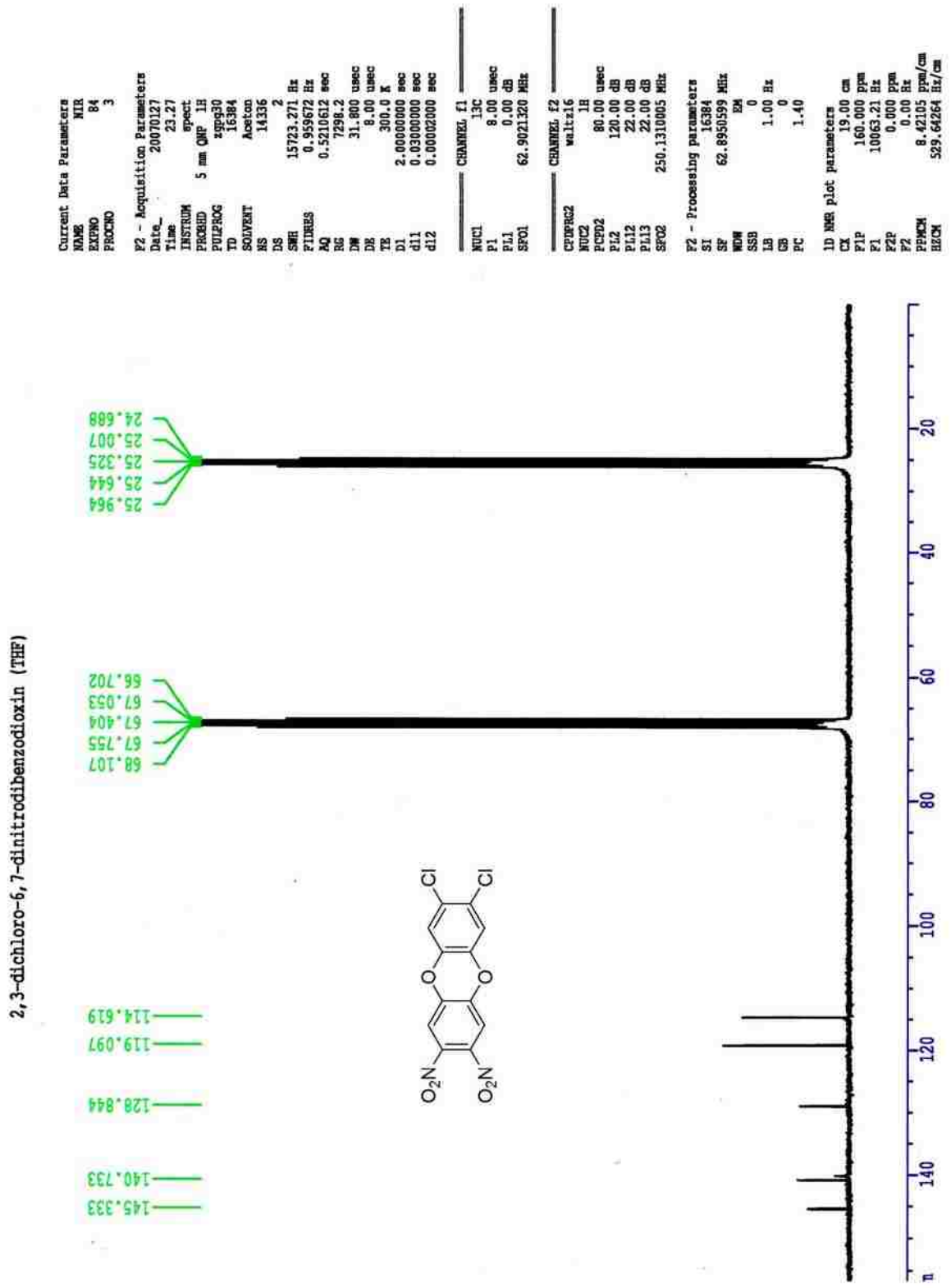


Figure V.2. ^{13}C NMR of compound **5.7**

APPENDIX W: CHARACTERIZATION DATA FOR COMPOUND 5.8

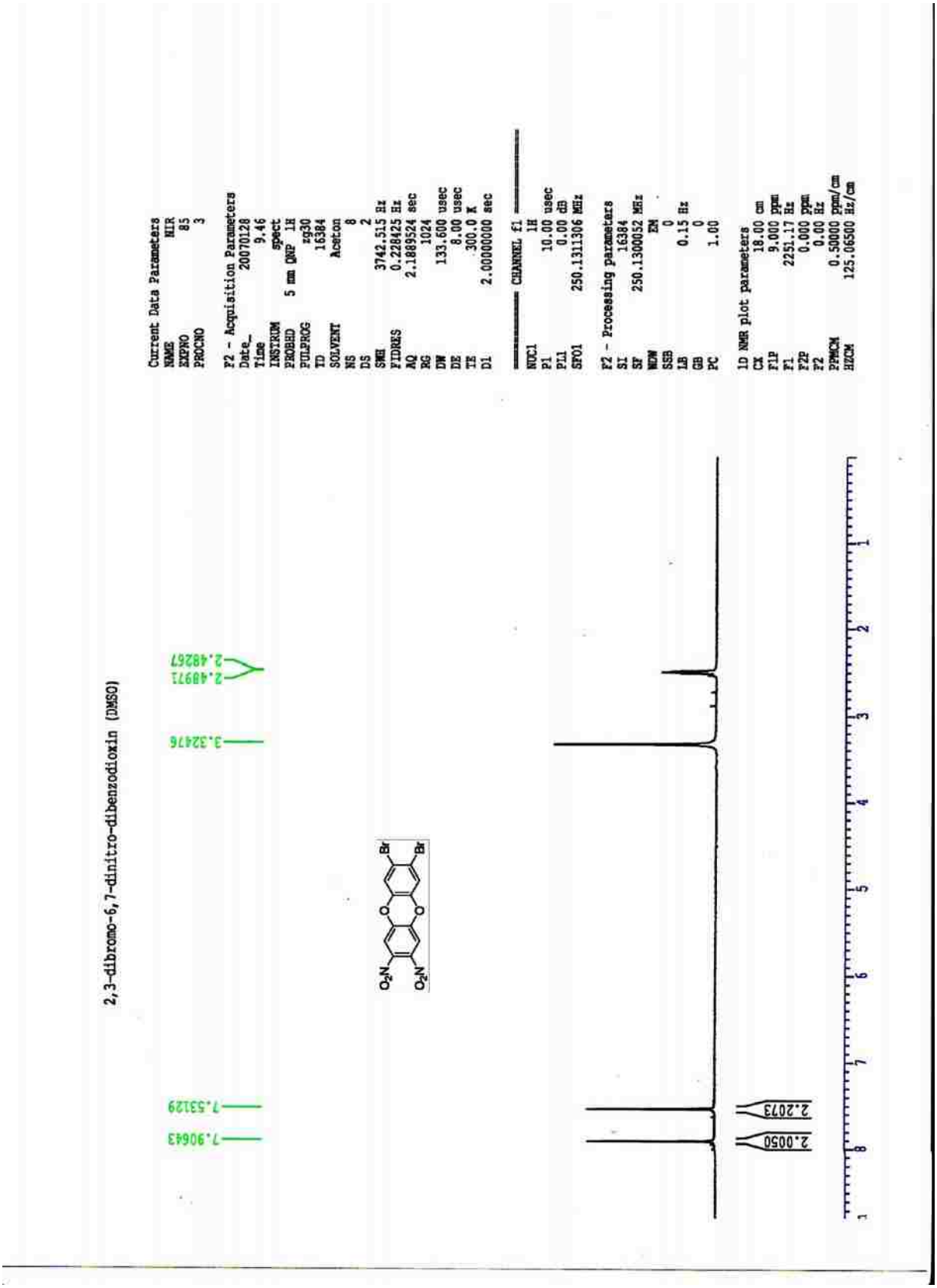


Figure W.1. ^{1}H NMR of compound **5.8**

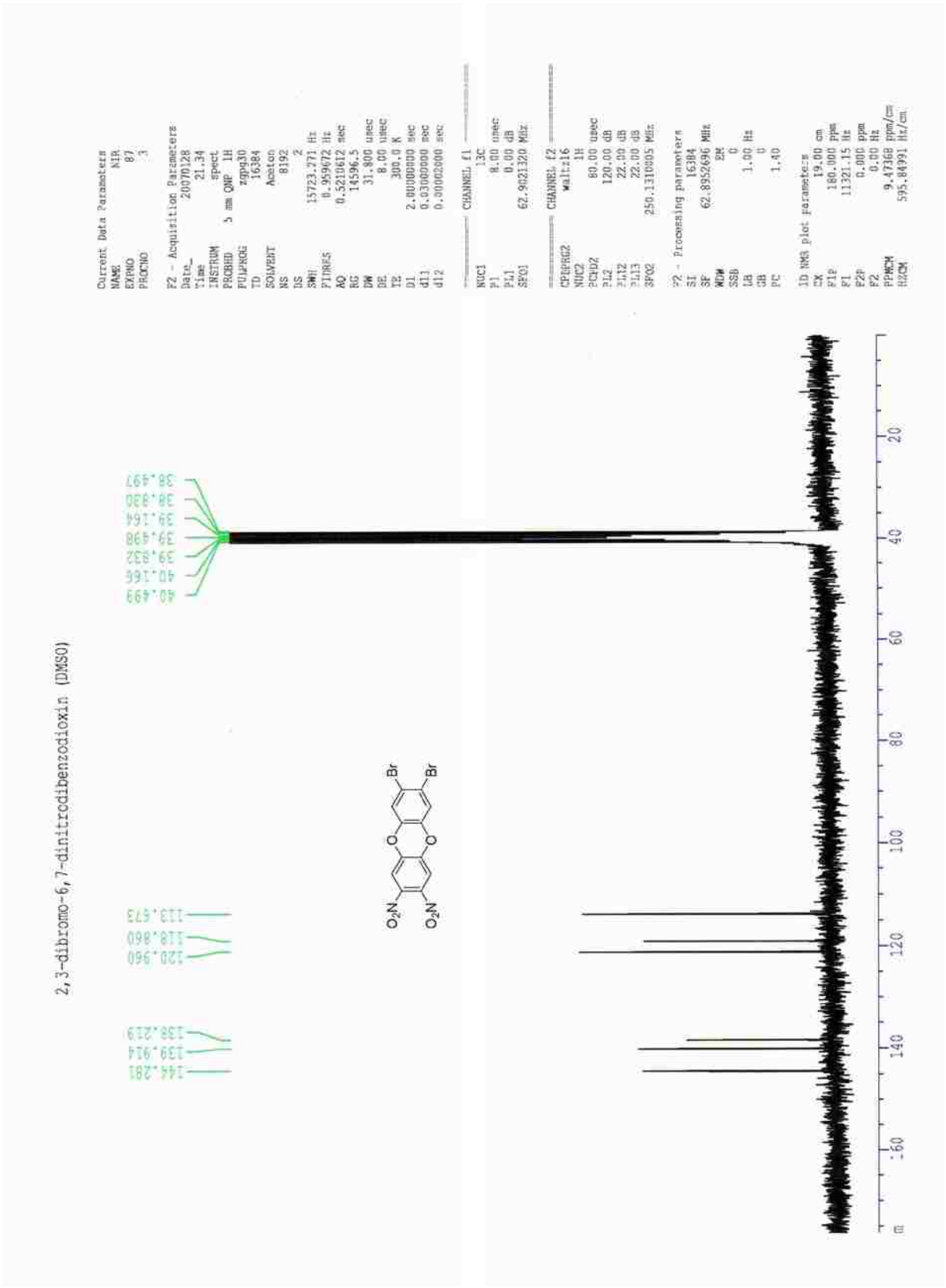
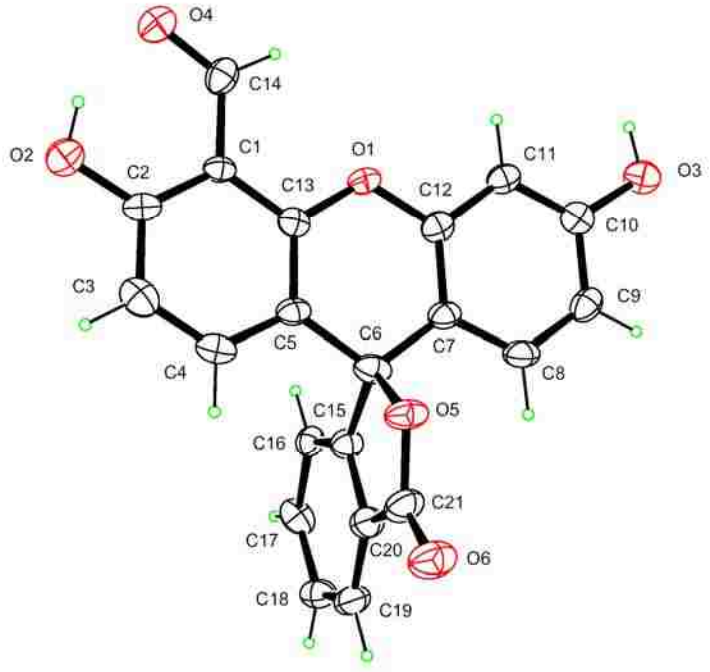


Figure W.2. ^{13}C NMR of compound **5.8**

APPENDIX X: CRYSTALLOGRAPHIC DATA FOR COMPOUND 2.2




```
data_XXu2

_audit_creation_method            SHELXL-97
_chemical_name_systematic
;
 ?
;
_chemical_name_common             ?
_chemical_melting_point           ?
_chemical_compound_source         'local laboratory'
_chemical_formula_moiety      'C21 H12 O6'
_chemical_formula_sum         'C21 H12 O6'
_chemical_formula_weight          360.31

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
```

```
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_space_group_name_H-M 'P 21/c         '
_symmetry_space_group_name_Hall     '-P 2ybc'
_symmetry_cell_setting 'Monoclinic'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x, -y-1/2, z-1/2'

_cell_length_a                    7.891(6)
_cell_length_b                    21.304(15)
_cell_length_c                    9.977(8)
_cell_angle_alpha                 90.00
_cell_angle_beta                  104.80(3)
_cell_angle_gamma                 90.00
_cell_volume                      1622(2)
_cell_formula_units_Z             4
_cell_measurement_temperature     105
_cell_measurement_reflns_used     2673
_cell_measurement_theta_min        2.5
_cell_measurement_theta_max        25.0

_exptl_crystal_description        lath
_exptl_crystal_colour             yellow
_exptl_crystal_size_max           0.32
_exptl_crystal_size_mid           0.15
_exptl_crystal_size_min           0.05
_exptl_crystal_density_meas       ?
_exptl_crystal_density_diffrn     1.476
_exptl_crystal_density_method     'not measured'
_exptl_crystal_F_000              744
_exptl_absorpt_coefficient_mu     0.110
_exptl_absorpt_correction_type    none
_exptl_absorpt_correction_T_min   ?
_exptl_absorpt_correction_T_max   ?
_exptl_absorpt_process_details    ?

_exptl_special_details
;
 ?
;

_diffrn_ambient_temperature       105
_diffrn_radiation_wavelength      0.71073
_diffrn_radiation_type            MoK\a
```

```
_diffrn_radiation_source          'fine-focus sealed tube'
_diffrn_radiation_monochromator   graphite
_diffrn_measurement_device  'KappaCCD (with Oxford Cryostream)'
_diffrn_measurement_method       ' \w scans with \k offsets'
_diffrn_detector_area_resol_mean  ?
_diffrn_standards_number          0
_diffrn_standards_interval_count  ?
_diffrn_standards_interval_time   ?
_diffrn_standards_decay_%         <2
_diffrn_reflns_number             10081
_diffrn_reflns_av_R_equivalents   0.098
_diffrn_reflns_av_sigmaI/netI     0.1942
_diffrn_reflns_limit_h_min        -9
_diffrn_reflns_limit_h_max        9
_diffrn_reflns_limit_k_min        -25
_diffrn_reflns_limit_k_max        22
_diffrn_reflns_limit_l_min        -11
_diffrn_reflns_limit_l_max        11
_diffrn_reflns_theta_min          2.6
_diffrn_reflns_theta_max          25.0
_reflns_number_total              2842
_reflns_number_gt                 1112
_reflns_threshold_expression      I>2\s(I)

_computing_data_collection        'COLLECT (Nonius, 2000)'
_computing_cell_refinement        'HKL Scalepack (Otwinowski & Minor 1997)'
_computing_data_reduction   'HKL Denzo and Scalepack (Otwinowski & Minor 1997)'
_computing_structure_solution     'SIR97 (Altomare  et al., 1999)'
_computing_structure_refinement   'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics     'ORTEP-3 for Windows (Farrugia, 1997)'
_computing_publication_material   'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
;

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type            full
_refine_ls_weighting_scheme       calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.1300P)^2^] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary      direct
```

```
_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
_refine_ls_hydrogen_treatment     constr
_refine_ls_extinction_method      none
_refine_ls_extinction_coef        ?
_refine_ls_number_reflns          2842
_refine_ls_number_parameters      246
_refine_ls_number_restraints      0
_refine_ls_R_factor_all           0.235
_refine_ls_R_factor_gt            0.088
_refine_ls_wR_factor_ref          0.269
_refine_ls_wR_factor_gt           0.202
_refine_ls_goodness_of_fit_ref    0.966
_refine_ls_restrained_S_all       0.966
_refine_ls_shift/su_max           0.000
_refine_ls_shift/su_mean          0.000

loop_
 _atom_site_label
 _atom_site_type_symbol
 _atom_site_fract_x
 _atom_site_fract_y
 _atom_site_fract_z
 _atom_site_U_iso_or_equiv
 _atom_site_adp_type
 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
 _atom_site_calc_flag
 _atom_site_refinement_flags
 _atom_site_disorder_assembly
 _atom_site_disorder_group
O1 O 0.3013(5) 0.5298(2) 0.5371(4) 0.0389(11) Uani 1 1 d . . .
O2 O -0.0278(6) 0.3645(2) 0.2795(4) 0.0555(13) Uani 1 1 d . . .
H20 H -0.0116 0.3493 0.3595 0.083 Uiso 1 1 calc R . .
O3 O 0.6368(6) 0.6841(2) 0.8308(5) 0.0501(13) Uani 1 1 d . . .
H30 H 0.6057 0.6626 0.8909 0.075 Uiso 1 1 calc R . .
O4 O 0.0311(6) 0.3731(2) 0.5446(4) 0.0536(13) Uani 1 1 d . . .
O5 O 0.5116(5) 0.5751(2) 0.2299(4) 0.0509(13) Uani 1 1 d . . .
O6 O 0.6207(6) 0.6078(2) 0.0536(5) 0.0687(16) Uani 1 1 d . . .
C1 C 0.1391(7) 0.4478(3) 0.4102(6) 0.0329(15) Uani 1 1 d . . .
C2 C 0.0665(8) 0.4184(3) 0.2856(7) 0.0416(16) Uani 1 1 d . . .
C3 C 0.0930(9) 0.4415(3) 0.1627(7) 0.0540(19) Uani 1 1 d . . .
H3 H 0.0471 0.4201 0.0776 0.065 Uiso 1 1 calc R . .
C4 C 0.1875(8) 0.4964(3) 0.1665(7) 0.0486(18) Uani 1 1 d . . .
H4 H 0.2047 0.5126 0.0822 0.058 Uiso 1 1 calc R . .
C5 C 0.2584(7) 0.5288(3) 0.2888(6) 0.0364(16) Uani 1 1 d . . .
C6 C 0.3589(8) 0.5896(3) 0.2887(6) 0.0428(17) Uani 1 1 d . . .
C7 C 0.4276(8) 0.6144(3) 0.4320(6) 0.0390(17) Uani 1 1 d . . .
C8 C 0.5271(8) 0.6696(3) 0.4560(7) 0.0480(18) Uani 1 1 d . . .
```

```
H8 H 0.5489 0.6919 0.3797 0.058 Uiso 1 1 calc R . .
C9 C 0.5944(8) 0.6923(3) 0.5900(7) 0.0469(18) Uani 1 1 d . . .
H9 H 0.6614 0.7299 0.6041 0.056 Uiso 1 1 calc R . .
C10 C 0.5642(8) 0.6602(3) 0.7035(7) 0.0435(17) Uani 1 1 d . . .
C11 C 0.4649(8) 0.6061(3) 0.6826(7) 0.0401(17) Uani 1 1 d . . .
H11 H 0.4422 0.5841 0.7590 0.048 Uiso 1 1 calc R . .
C12 C 0.3980(7) 0.5842(3) 0.5471(6) 0.0397(17) Uani 1 1 d . . .
C13 C 0.2356(7) 0.5029(3) 0.4097(6) 0.0338(15) Uani 1 1 d . . .
C14 C 0.1153(8) 0.4223(3) 0.5383(7) 0.0461(18) Uani 1 1 d . . .
H14 H 0.1664 0.4439 0.6221 0.055 Uiso 1 1 calc R . .
C15 C 0.2580(8) 0.6369(3) 0.1867(6) 0.0401(16) Uani 1 1 d . . .
C16 C 0.0978(7) 0.6654(3) 0.1834(6) 0.0377(16) Uani 1 1 d . . .
H16 H 0.0332 0.6555 0.2491 0.045 Uiso 1 1 calc R . .
C17 C 0.0381(8) 0.7091(3) 0.0780(6) 0.0478(19) Uani 1 1 d . . .
H17 H -0.0703 0.7298 0.0720 0.057 Uiso 1 1 calc R . .
C18 C 0.1316(9) 0.7236(3) -0.0186(6) 0.0470(18) Uani 1 1 d . . .
H18 H 0.0865 0.7542 -0.0877 0.056 Uiso 1 1 calc R . .
C19 C 0.2838(9) 0.6952(3) -0.0163(7) 0.0498(18) Uani 1 1 d . . .
H19 H 0.3465 0.7048 -0.0833 0.060 Uiso 1 1 calc R . .
C20 C 0.3467(8) 0.6513(3) 0.0876(6) 0.0459(18) Uani 1 1 d . . .
C21 C 0.5035(9) 0.6124(3) 0.1153(7) 0.055(2) Uani 1 1 d . . .

loop_
 _atom_site_aniso_label
 _atom_site_aniso_U_11
 _atom_site_aniso_U_22
 _atom_site_aniso_U_33
 _atom_site_aniso_U_23
 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
O1 0.042(2) 0.041(3) 0.039(3) 0.007(2) 0.019(2) -0.002(2)
O2 0.062(3) 0.045(3) 0.059(3) 0.002(3) 0.014(3) -0.002(3)
O3 0.055(3) 0.055(3) 0.044(3) -0.003(2) 0.021(2) 0.004(2)
O4 0.052(3) 0.050(3) 0.061(3) 0.004(3) 0.021(2) -0.004(3)
O5 0.045(3) 0.062(3) 0.053(3) 0.020(3) 0.026(2) 0.014(2)
O6 0.056(3) 0.083(4) 0.073(4) 0.024(3) 0.029(3) 0.010(3)
C1 0.034(3) 0.037(4) 0.030(4) 0.005(3) 0.013(3) 0.005(3)
C2 0.049(4) 0.040(4) 0.039(4) 0.010(4) 0.018(3) 0.007(4)
C3 0.059(4) 0.051(5) 0.048(5) -0.003(4) 0.006(4) 0.013(4)
C4 0.056(4) 0.052(5) 0.038(4) 0.012(4) 0.013(3) 0.010(4)
C5 0.036(4) 0.035(4) 0.040(4) 0.012(3) 0.012(3) 0.009(3)
C6 0.039(4) 0.056(5) 0.037(4) 0.009(3) 0.017(3) 0.013(3)
C7 0.039(4) 0.035(4) 0.043(4) 0.012(3) 0.010(3) 0.005(3)
C8 0.046(4) 0.054(5) 0.044(5) 0.021(4) 0.012(3) 0.007(4)
C9 0.038(4) 0.036(4) 0.067(5) 0.008(4) 0.014(4) 0.001(3)
C10 0.042(4) 0.045(5) 0.045(4) -0.002(4) 0.014(3) 0.007(4)
C11 0.040(4) 0.039(4) 0.046(4) 0.004(3) 0.019(3) 0.004(3)
C12 0.035(4) 0.043(4) 0.045(4) 0.000(4) 0.018(3) 0.004(3)
C13 0.026(3) 0.039(4) 0.036(4) 0.004(3) 0.008(3) 0.010(3)
```

```
C14 0.037(4) 0.040(4) 0.062(5) -0.001(4) 0.014(3) 0.000(3)
C15 0.040(4) 0.040(4) 0.041(4) 0.004(3) 0.012(3) 0.003(3)
C16 0.037(4) 0.032(4) 0.044(4) 0.001(3) 0.009(3) -0.001(3)
C17 0.045(4) 0.046(5) 0.046(4) 0.000(4) 0.001(4) 0.020(3)
C18 0.064(5) 0.037(5) 0.043(4) 0.004(3) 0.019(4) 0.001(4)
C19 0.054(4) 0.050(5) 0.049(4) 0.011(4) 0.020(4) -0.005(4)
C20 0.040(4) 0.052(5) 0.045(4) 0.008(4) 0.011(3) 0.000(4)
C21 0.045(4) 0.067(6) 0.059(5) 0.012(4) 0.026(4) -0.003(4)

_geom_special_details
;
 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
;

loop_
 _geom_bond_atom_site_label_1
 _geom_bond_atom_site_label_2
 _geom_bond_distance
 _geom_bond_site_symmetry_2
 _geom_bond_publ_flag
O1 C13 1.369(7) . ?
O1 C12 1.378(7) . ?
O2 C2 1.361(7) . ?
O2 H2O 0.8400 . ?
O3 C10 1.353(7) . ?
O3 H3O 0.8400 . ?
O4 C14 1.250(7) . ?
O5 C21 1.380(7) . ?
O5 C6 1.501(7) . ?
O6 C21 1.239(7) . ?
C1 C2 1.379(8) . ?
C1 C13 1.400(8) . ?
C1 C14 1.444(8) . ?
C2 C3 1.385(9) . ?
C3 C4 1.382(9) . ?
C3 H3 0.9500 . ?
C4 C5 1.389(8) . ?
C4 H4 0.9500 . ?
C5 C13 1.379(8) . ?
C5 C6 1.520(9) . ?
C6 C7 1.490(8) . ?
C6 C15 1.507(8) . ?
C7 C12 1.387(8) . ?
C7 C8 1.400(9) . ?
```

```
C8 C9 1.393(8) . ?
C8 H8 0.9500 . ?
C9 C10 1.395(8) . ?
C9 H9 0.9500 . ?
C10 C11 1.378(9) . ?
C11 C12 1.400(8) . ?
C11 H11 0.9500 . ?
C14 H14 0.9500 . ?
C15 C20 1.384(8) . ?
C15 C16 1.395(8) . ?
C16 C17 1.394(8) . ?
C16 H16 0.9500 . ?
C17 C18 1.390(8) . ?
C17 H17 0.9500 . ?
C18 C19 1.339(8) . ?
C18 H18 0.9500 . ?
C19 C20 1.390(8) . ?
C19 H19 0.9500 . ?
C20 C21 1.457(9) . ?

loop_
 _geom_angle_atom_site_label_1
 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
C13 O1 C12 119.4(5) . . ?
C2 O2 H2O 109.5 . . ?
C10 O3 H3O 109.5 . . ?
C21 O5 C6 109.4(5) . . ?
C2 C1 C13 118.6(6) . . ?
C2 C1 C14 120.6(6) . . ?
C13 C1 C14 120.8(6) . . ?
O2 C2 C1 121.3(6) . . ?
O2 C2 C3 117.7(6) . . ?
C1 C2 C3 121.0(6) . . ?
C4 C3 C2 118.6(7) . . ?
C4 C3 H3 120.7 . . ?
C2 C3 H3 120.7 . . ?
C3 C4 C5 122.5(6) . . ?
C3 C4 H4 118.7 . . ?
C5 C4 H4 118.7 . . ?
C13 C5 C4 117.2(6) . . ?
C13 C5 C6 121.7(6) . . ?
C4 C5 C6 121.1(6) . . ?
C7 C6 O5 108.4(5) . . ?
C7 C6 C15 114.3(6) . . ?
```

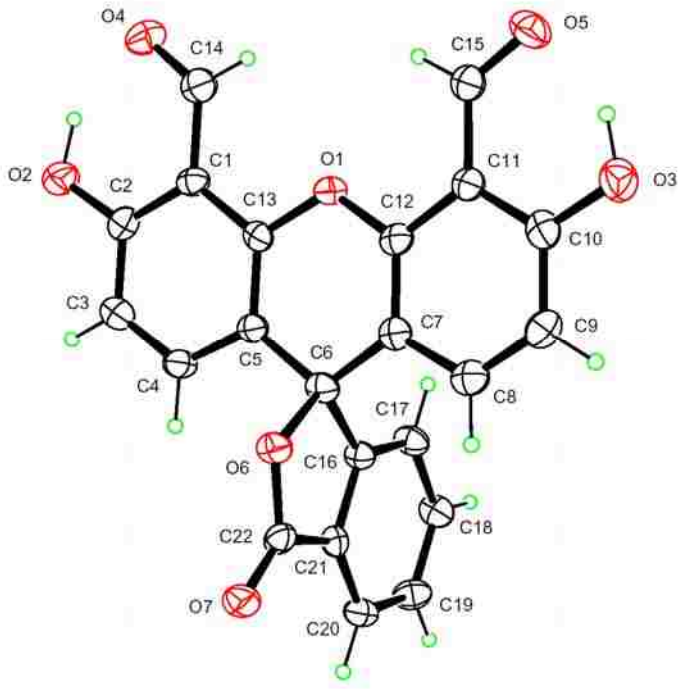
O5 C6 C15 102.3(5) . . ?
C7 C6 C5 111.4(5) . . ?
O5 C6 C5 107.2(5) . . ?
C15 C6 C5 112.7(5) . . ?
C12 C7 C8 116.9(6) . . ?
C12 C7 C6 122.2(6) . . ?
C8 C7 C6 120.9(6) . . ?
C9 C8 C7 121.1(6) . . ?
C9 C8 H8 119.5 . . ?
C7 C8 H8 119.5 . . ?
C8 C9 C10 120.4(6) . . ?
C8 C9 H9 119.8 . . ?
C10 C9 H9 119.8 . . ?
O3 C10 C11 123.0(6) . . ?
O3 C10 C9 117.2(6) . . ?
C11 C10 C9 119.8(6) . . ?
C10 C11 C12 118.9(6) . . ?
C10 C11 H11 120.6 . . ?
C12 C11 H11 120.6 . . ?
O1 C12 C7 122.5(6) . . ?
O1 C12 C11 114.5(5) . . ?
C7 C12 C11 122.9(6) . . ?
O1 C13 C5 122.8(6) . . ?
O1 C13 C1 115.2(5) . . ?
C5 C13 C1 122.0(6) . . ?
O4 C14 C1 123.4(6) . . ?
O4 C14 H14 118.3 . . ?
C1 C14 H14 118.3 . . ?
C20 C15 C16 120.5(6) . . ?
C20 C15 C6 110.8(5) . . ?
C16 C15 C6 128.7(5) . . ?
C17 C16 C15 116.0(6) . . ?
C17 C16 H16 122.0 . . ?
C15 C16 H16 122.0 . . ?
C18 C17 C16 122.3(6) . . ?
C18 C17 H17 118.9 . . ?
C16 C17 H17 118.9 . . ?
C19 C18 C17 121.4(6) . . ?
C19 C18 H18 119.3 . . ?
C17 C18 H18 119.3 . . ?
C18 C19 C20 117.6(6) . . ?
C18 C19 H19 121.2 . . ?
C20 C19 H19 121.2 . . ?
C15 C20 C19 122.2(6) . . ?
C15 C20 C21 107.3(6) . . ?
C19 C20 C21 130.5(6) . . ?
O6 C21 O5 118.9(6) . . ?
O6 C21 C20 131.0(7) . . ?
O5 C21 C20 110.0(5) . . ?

```
loop_
 _geom_torsion_atom_site_label_1
 _geom_torsion_atom_site_label_2
 _geom_torsion_atom_site_label_3
 _geom_torsion_atom_site_label_4
 _geom_torsion
 _geom_torsion_site_symmetry_1
 _geom_torsion_site_symmetry_2
 _geom_torsion_site_symmetry_3
 _geom_torsion_site_symmetry_4
 _geom_torsion_publ_flag
C13 C1 C2 O2 179.6(5) . . . . ?
C14 C1 C2 O2 -0.6(9) . . . . ?
C13 C1 C2 C3 2.2(9) . . . . ?
C14 C1 C2 C3 -178.1(6) . . . . ?
O2 C2 C3 C4 179.6(6) . . . . ?
C1 C2 C3 C4 -2.8(9) . . . . ?
C2 C3 C4 C5 0.7(10) . . . . ?
C3 C4 C5 C13 1.9(9) . . . . ?
C3 C4 C5 C6 -178.9(6) . . . . ?
C21 O5 C6 C7 -117.6(6) . . . . ?
C21 O5 C6 C15 3.5(6) . . . . ?
C21 O5 C6 C5 122.1(5) . . . . ?
C13 C5 C6 C7 1.2(7) . . . . ?
C4 C5 C6 C7 -178.0(5) . . . . ?
C13 C5 C6 O5 119.6(5) . . . . ?
C4 C5 C6 O5 -59.5(7) . . . . ?
C13 C5 C6 C15 -128.7(6) . . . . ?
C4 C5 C6 C15 52.2(8) . . . . ?
O5 C6 C7 C12 -118.3(6) . . . . ?
C15 C6 C7 C12 128.4(6) . . . . ?
C5 C6 C7 C12 -0.7(8) . . . . ?
O5 C6 C7 C8 61.2(7) . . . . ?
C15 C6 C7 C8 -52.1(8) . . . . ?
C5 C6 C7 C8 178.8(5) . . . . ?
C12 C7 C8 C9 0.8(9) . . . . ?
C6 C7 C8 C9 -178.7(6) . . . . ?
C7 C8 C9 C10 0.2(9) . . . . ?
C8 C9 C10 O3 178.5(5) . . . . ?
C8 C9 C10 C11 -0.9(9) . . . . ?
O3 C10 C11 C12 -178.7(5) . . . . ?
C9 C10 C11 C12 0.8(9) . . . . ?
C13 O1 C12 C7 2.1(8) . . . . ?
C13 O1 C12 C11 -177.4(5) . . . . ?
C8 C7 C12 O1 179.6(5) . . . . ?
C6 C7 C12 O1 -0.9(9) . . . . ?
C8 C7 C12 C11 -1.0(9) . . . . ?
C6 C7 C12 C11 178.5(5) . . . . ?
```

```
C10 C11 C12 O1 179.7(5) . . . . ?
C10 C11 C12 C7 0.2(9) . . . . ?
C12 O1 C13 C5 -1.5(8) . . . . ?
C12 O1 C13 C1 -180.0(5) . . . . ?
C4 C5 C13 O1 179.0(5) . . . . ?
C6 C5 C13 O1 -0.1(8) . . . . ?
C4 C5 C13 C1 -2.6(8) . . . . ?
C6 C5 C13 C1 178.2(5) . . . . ?
C2 C1 C13 O1 179.1(5) . . . . ?
C14 C1 C13 O1 -0.7(8) . . . . ?
C2 C1 C13 C5 0.6(8) . . . . ?
C14 C1 C13 C5 -179.1(5) . . . . ?
C2 C1 C14 O4 0.5(9) . . . . ?
C13 C1 C14 O4 -179.7(5) . . . . ?
C7 C6 C15 C20 113.1(6) . . . . ?
O5 C6 C15 C20 -3.8(7) . . . . ?
C5 C6 C15 C20 -118.5(6) . . . . ?
C7 C6 C15 C16 -66.6(8) . . . . ?
O5 C6 C15 C16 176.5(6) . . . . ?
C5 C6 C15 C16 61.8(8) . . . . ?
C20 C15 C16 C17 -1.4(9) . . . . ?
C6 C15 C16 C17 178.2(6) . . . . ?
C15 C16 C17 C18 0.2(9) . . . . ?
C16 C17 C18 C19 1.0(10) . . . . ?
C17 C18 C19 C20 -0.9(10) . . . . ?
C16 C15 C20 C19 1.6(10) . . . . ?
C6 C15 C20 C19 -178.1(6) . . . . ?
C16 C15 C20 C21 -177.5(6) . . . . ?
C6 C15 C20 C21 2.8(8) . . . . ?
C18 C19 C20 C15 -0.4(10) . . . . ?
C18 C19 C20 C21 178.5(7) . . . . ?
C6 O5 C21 O6 178.9(6) . . . . ?
C6 O5 C21 C20 -2.0(7) . . . . ?
C15 C20 C21 O6 178.5(8) . . . . ?
C19 C20 C21 O6 -0.5(13) . . . . ?
C15 C20 C21 O5 -0.5(8) . . . . ?
C19 C20 C21 O5 -179.5(6) . . . . ?

loop_
 _geom_hbond_atom_site_label_D
 _geom_hbond_atom_site_label_H
 _geom_hbond_atom_site_label_A
 _geom_hbond_distance_DH
 _geom_hbond_distance_HA
 _geom_hbond_distance_DA
 _geom_hbond_angle_DHA
 _geom_hbond_site_symmetry_A
O2 H20 O4  0.84 1.86 2.572(6) 141.6 .
O3 H30 O6  0.84 1.98 2.783(7) 160.2 1_556
```

```
_diffrn_measured_fraction_theta_max    0.989
_diffrn_reflns_theta_full              25.05
_diffrn_measured_fraction_theta_full   0.989
_refine_diff_density_max    0.76
_refine_diff_density_min   -0.30
_refine_diff_density_rms    0.071
# END OF CIF
```

APPENDIX Y: CRYSTALLOGRAPHIC DATA FOR COMPOUND 2.1




```
data_XXu3

_audit_creation_method            SHELXL-97
_chemical_name_systematic
;
 ?
;
_chemical_name_common             ?
_chemical_melting_point           ?
_chemical_compound_source          'local laboratory'
_chemical_formula_moiety    'C22 H12 O7, 0.5(C3 H6 O)'
_chemical_formula_sum    'C23.50 H15 O7.50'
_chemical_formula_weight          417.36

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
```

```
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_space_group_name_H-M 'C 2/c          '
_symmetry_space_group_name_Hall   '-C 2yc'
_symmetry_cell_setting 'Monoclinic'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x, y, -z+1/2'
 'x+1/2, y+1/2, z'
 '-x+1/2, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x, -y, z-1/2'
 '-x+1/2, -y+1/2, -z'
 'x+1/2, -y+1/2, z-1/2'

_cell_length_a                    19.388(6)
_cell_length_b                    7.897(2)
_cell_length_c                    24.479(9)
_cell_angle_alpha                 90
_cell_angle_beta                  91.407(10)
_cell_angle_gamma                 90
_cell_volume                      3746.8(18)
_cell_formula_units_Z             8
_cell_measurement_temperature     105
_cell_measurement_reflns_used     3259
_cell_measurement_theta_min        2.5
_cell_measurement_theta_max        26.4

_exptl_crystal_description        needle
_exptl_crystal_colour             colorless
_exptl_crystal_size_max           0.37
_exptl_crystal_size_mid           0.07
_exptl_crystal_size_min           0.05
_exptl_crystal_density_meas       ?
_exptl_crystal_density_diffrn     1.480
_exptl_crystal_density_method     'not measured'
_exptl_crystal_F_000              1728
_exptl_absorpt_coefficient_mu     0.112
_exptl_absorpt_correction_type    none
_exptl_absorpt_correction_T_min   ?
_exptl_absorpt_correction_T_max   ?
_exptl_absorpt_process_details    ?

_exptl_special_details
;
 ?
;
```

```
_diffrn_ambient_temperature       105
_diffrn_radiation_wavelength      0.71073
_diffrn_radiation_type            MoK\a
_diffrn_radiation_source          'fine-focus sealed tube'
_diffrn_radiation_monochromator   graphite
_diffrn_measurement_device  'KappaCCD (with Oxford Cryostream)'
_diffrn_measurement_method       ' \w scans with \k offsets'
_diffrn_detector_area_resol_mean  ?
_diffrn_standards_number          0
_diffrn_standards_interval_count  ?
_diffrn_standards_interval_time   ?
_diffrn_standards_decay_%         <2
_diffrn_reflns_number             10686
_diffrn_reflns_av_R_equivalents   0.058
_diffrn_reflns_av_sigmaI/netI     0.0881
_diffrn_reflns_limit_h_min        -23
_diffrn_reflns_limit_h_max        24
_diffrn_reflns_limit_k_min        -6
_diffrn_reflns_limit_k_max        9
_diffrn_reflns_limit_l_min        -30
_diffrn_reflns_limit_l_max        30
_diffrn_reflns_theta_min          2.6
_diffrn_reflns_theta_max          26.4
_reflns_number_total              3802
_reflns_number_gt                 2255
_reflns_threshold_expression      I>2\s(I)

_computing_data_collection  'COLLECT (Nonius 1999)'
_computing_data_reduction  'Denzo and Scalepack (Otwinowski & Minor, 1997)'
_computing_cell_refinement    'Denzo and Scalepack (Otwinowski & Minor, 1997)'
_computing_structure_solution   'Direct_methods (SIR, Altomare, et al., 1994)'
_computing_structure_refinement   'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics          'ORTEP-3 for Windows (Farrugia, 1997)'
_computing_publication_material   'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
;

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type            full
```

```
_refine_ls_weighting_scheme       calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.0602P)^2^+1.1371P] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary      direct
_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
_refine_ls_hydrogen_treatment     constr
_refine_ls_extinction_method      none
_refine_ls_extinction_coef        ?
_refine_ls_number_reflns          3802
_refine_ls_number_parameters      300
_refine_ls_number_restraints      0
_refine_ls_R_factor_all           0.120
_refine_ls_R_factor_gt            0.058
_refine_ls_wR_factor_ref          0.141
_refine_ls_wR_factor_gt           0.119
_refine_ls_goodness_of_fit_ref    1.023
_refine_ls_restrained_S_all       1.023
_refine_ls_shift/su_max           0.000
_refine_ls_shift/su_mean          0.000

loop_
 _atom_site_label
 _atom_site_type_symbol
 _atom_site_fract_x
 _atom_site_fract_y
 _atom_site_fract_z
 _atom_site_U_iso_or_equiv
 _atom_site_adp_type
 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
 _atom_site_calc_flag
 _atom_site_refinement_flags
 _atom_site_disorder_assembly
 _atom_site_disorder_group
O1 O 0.47740(9) 0.23881(19) 0.52159(8) 0.0232(5) Uani 1 1 d . . .
O2 O 0.30624(10) 0.3479(2) 0.65314(9) 0.0341(5) Uani 1 1 d . . .
H2O H 0.2810(16) 0.291(4) 0.6249(14) 0.051 Uiso 1 1 d . . .
O3 O 0.63095(11) 0.1534(2) 0.37665(9) 0.0349(5) Uani 1 1 d . . .
H3O H 0.5910(17) 0.103(4) 0.3620(14) 0.052 Uiso 1 1 d . . .
O4 O 0.28030(10) 0.1844(2) 0.56100(9) 0.0350(5) Uani 1 1 d . . .
O5 O 0.50498(10) 0.0415(2) 0.37446(9) 0.0341(5) Uani 1 1 d . . .
O6 O 0.59402(9) 0.60806(18) 0.58466(8) 0.0241(5) Uani 1 1 d . . .
O7 O 0.65989(9) 0.8015(2) 0.62792(9) 0.0316(5) Uani 1 1 d . . .
C1 C 0.39099(13) 0.2906(3) 0.58571(12) 0.0222(6) Uani 1 1 d . . .
C2 C 0.37151(13) 0.3584(3) 0.63593(12) 0.0247(7) Uani 1 1 d . . .
C3 C 0.41903(15) 0.4413(3) 0.66984(13) 0.0299(7) Uani 1 1 d . . .
H3 H 0.4054 0.4855 0.7040 0.036 Uiso 1 1 calc R . .
C4 C 0.48591(14) 0.4588(3) 0.65350(13) 0.0270(7) Uani 1 1 d . . .
```

```
H4 H 0.5180 0.5158 0.6769 0.032 Uiso 1 1 calc R . .
C5 C 0.50857(13) 0.3956(3) 0.60336(12) 0.0208(6) Uani 1 1 d . . .
C6 C 0.58165(13) 0.4222(3) 0.58599(12) 0.0219(6) Uani 1 1 d . . .
C7 C 0.59272(13) 0.3523(3) 0.53013(12) 0.0216(6) Uani 1 1 d . . .
C8 C 0.65709(14) 0.3701(3) 0.50484(12) 0.0272(7) Uani 1 1 d . . .
H8 H 0.6931 0.4292 0.5237 0.033 Uiso 1 1 calc R . .
C9 C 0.66947(14) 0.3055(3) 0.45432(12) 0.0274(7) Uani 1 1 d . . .
H9 H 0.7132 0.3210 0.4383 0.033 Uiso 1 1 calc R . .
C10 C 0.61724(14) 0.2162(3) 0.42633(12) 0.0257(7) Uani 1 1 d . . .
C11 C 0.55264(14) 0.1940(3) 0.44979(12) 0.0223(6) Uani 1 1 d . . .
C12 C 0.54227(14) 0.2654(3) 0.50154(12) 0.0221(6) Uani 1 1 d . . .
C13 C 0.46062(13) 0.3120(3) 0.57062(11) 0.0201(6) Uani 1 1 d . . .
C14 C 0.34128(15) 0.2072(3) 0.54940(13) 0.0297(7) Uani 1 1 d . . .
H14 H 0.3564 0.1682 0.5150 0.036 Uiso 1 1 calc R . .
C15 C 0.49829(15) 0.1019(3) 0.42052(13) 0.0264(7) Uani 1 1 d . . .
H15 H 0.4553 0.0874 0.4378 0.032 Uiso 1 1 calc R . .
C16 C 0.63539(13) 0.3636(3) 0.62782(11) 0.0206(6) Uani 1 1 d . . .
C17 C 0.65180(14) 0.2009(3) 0.64428(12) 0.0249(7) Uani 1 1 d . . .
H17 H 0.6275 0.1058 0.6299 0.030 Uiso 1 1 calc R . .
C18 C 0.70511(14) 0.1815(3) 0.68265(12) 0.0261(7) Uani 1 1 d . . .
H18 H 0.7178 0.0708 0.6943 0.031 Uiso 1 1 calc R . .
C19 C 0.74050(14) 0.3201(3) 0.70453(12) 0.0280(7) Uani 1 1 d . . .
H19 H 0.7762 0.3032 0.7312 0.034 Uiso 1 1 calc R . .
C20 C 0.72379(14) 0.4830(3) 0.68747(12) 0.0265(7) Uani 1 1 d . . .
H20 H 0.7478 0.5785 0.7019 0.032 Uiso 1 1 calc R . .
C21 C 0.67116(13) 0.5017(3) 0.64884(12) 0.0212(6) Uani 1 1 d . . .
C22 C 0.64437(13) 0.6550(3) 0.62185(12) 0.0234(7) Uani 1 1 d . . .
O1S O 0.0323(3) 0.7551(5) 0.2483(2) 0.0693(19) Uani 0.50 1 d P . .
C1S C 0.0000 0.6134(5) 0.2500 0.0483(14) Uani 1 2 d S . .
C2S C 0.0552(4) 0.4588(9) 0.2544(3) 0.052(2) Uani 0.50 1 d P . .
C3S C 0.0699(4) 0.5824(13) 0.2499(3) 0.058(2) Uani 0.50 1 d P . .

loop_
 _atom_site_aniso_label
 _atom_site_aniso_U_11
 _atom_site_aniso_U_22
 _atom_site_aniso_U_33
 _atom_site_aniso_U_23
 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
O1 0.0209(10) 0.0250(9) 0.0235(12) -0.0021(8) -0.0034(9) -0.0017(7)
O2 0.0253(12) 0.0405(11) 0.0367(14) -0.0062(10) 0.0028(10) -0.0055(9)
O3 0.0355(12) 0.0421(11) 0.0271(13) -0.0025(10) 0.0017(10) 0.0061(9)
O4 0.0251(12) 0.0401(11) 0.0396(14) 0.0004(10) -0.0014(10) -0.0057(9)
O5 0.0426(13) 0.0332(10) 0.0260(13) -0.0062(10) -0.0069(11) 0.0046(9)
O6 0.0255(10) 0.0129(8) 0.0336(13) 0.0035(8) -0.0058(9) -0.0008(7)
O7 0.0272(11) 0.0161(9) 0.0515(15) -0.0029(9) -0.0042(10) -0.0029(8)
C1 0.0218(15) 0.0192(12) 0.0253(17) 0.0026(12) -0.0046(13) -0.0011(10)
C2 0.0220(16) 0.0245(13) 0.0278(18) 0.0038(13) 0.0018(13) 0.0011(11)
```

```
C3 0.0322(18) 0.0286(14) 0.0288(19) -0.0055(13) -0.0002(15) -0.0013(12)
C4 0.0255(17) 0.0241(13) 0.0311(19) -0.0044(13) -0.0050(14) -0.0023(11)
C5 0.0216(15) 0.0140(11) 0.0266(17) 0.0014(12) -0.0041(13) 0.0009(10)
C6 0.0258(16) 0.0132(11) 0.0265(18) 0.0025(12) -0.0034(13) -0.0010(10)
C7 0.0245(15) 0.0163(11) 0.0237(17) 0.0046(12) -0.0014(13) 0.0020(11)
C8 0.0274(16) 0.0230(13) 0.0308(19) 0.0043(13) -0.0056(14) 0.0020(11)
C9 0.0232(16) 0.0303(14) 0.0286(19) 0.0057(14) 0.0013(14) 0.0016(12)
C10 0.0312(17) 0.0238(12) 0.0219(18) 0.0034(12) -0.0036(14) 0.0097(12)
C11 0.0235(15) 0.0191(12) 0.0242(17) 0.0024(12) -0.0038(13) 0.0043(11)
C12 0.0223(15) 0.0181(12) 0.0257(18) 0.0043(12) -0.0048(13) 0.0028(11)
C13 0.0250(15) 0.0152(12) 0.0199(16) 0.0013(11) -0.0038(13) 0.0034(10)
C14 0.0292(18) 0.0249(13) 0.035(2) 0.0020(13) -0.0026(15) -0.0003(12)
C15 0.0288(16) 0.0202(13) 0.0299(19) 0.0011(13) -0.0051(14) 0.0065(11)
C16 0.0213(14) 0.0201(12) 0.0201(16) 0.0001(11) -0.0020(12) -0.0010(10)
C17 0.0311(16) 0.0171(12) 0.0262(18) 0.0008(12) -0.0047(14) -0.0017(11)
C18 0.0323(17) 0.0222(13) 0.0236(17) 0.0031(12) -0.0053(14) 0.0021(11)
C19 0.0273(16) 0.0329(14) 0.0233(18) 0.0041(13) -0.0076(14) -0.0035(12)
C20 0.0256(16) 0.0256(13) 0.0281(18) -0.0048(13) -0.0040(14) -0.0032(11)
C21 0.0207(15) 0.0182(12) 0.0247(17) -0.0019(12) 0.0011(13) 0.0025(11)
C22 0.0178(14) 0.0196(13) 0.0327(19) 0.0007(12) 0.0013(13) -0.0020(11)
O1S 0.130(6) 0.044(2) 0.034(3) -0.003(3) -0.007(5) -0.025(3)
C1S 0.103(5) 0.030(2) 0.011(3) 0.000 -0.001(3) 0.000
C2S 0.063(5) 0.045(4) 0.049(5) -0.006(4) 0.010(4) 0.027(4)
C3S 0.033(5) 0.101(7) 0.039(5) 0.001(5) -0.001(4) -0.002(5)

_geom_special_details
;
 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
;

loop_
 _geom_bond_atom_site_label_1
 _geom_bond_atom_site_label_2
 _geom_bond_distance
 _geom_bond_site_symmetry_2
 _geom_bond_publ_flag
O1 C12 1.377(3) . ?
O1 C13 1.378(3) . ?
O2 C2 1.346(3) . ?
O2 H20 0.95(3) . ?
O3 C10 1.346(3) . ?
O3 H30 0.93(3) . ?
O4 C14 1.236(3) . ?
O5 C15 1.234(3) . ?
```

```
O6 C22 1.369(3) . ?
O6 C6 1.487(3) . ?
O7 C22 1.204(3) . ?
C1 C2 1.401(4) . ?
C1 C13 1.418(4) . ?
C1 C14 1.453(4) . ?
C2 C3 1.389(4) . ?
C3 C4 1.373(4) . ?
C3 H3 0.9500 . ?
C4 C5 1.405(4) . ?
C4 H4 0.9500 . ?
C5 C13 1.381(3) . ?
C5 C6 1.504(4) . ?
C6 C7 1.495(4) . ?
C6 C16 1.515(3) . ?
C7 C12 1.373(4) . ?
C7 C8 1.414(4) . ?
C8 C9 1.365(4) . ?
C8 H8 0.9500 . ?
C9 C10 1.399(4) . ?
C9 H9 0.9500 . ?
C10 C11 1.402(4) . ?
C11 C12 1.405(4) . ?
C11 C15 1.455(4) . ?
C14 H14 0.9500 . ?
C15 H15 0.9500 . ?
C16 C17 1.381(3) . ?
C16 C21 1.384(3) . ?
C17 C18 1.388(4) . ?
C17 H17 0.9500 . ?
C18 C19 1.392(3) . ?
C18 H18 0.9500 . ?
C19 C20 1.388(4) . ?
C19 H19 0.9500 . ?
C20 C21 1.382(4) . ?
C20 H20 0.9500 . ?
C21 C22 1.468(3) . ?
O1S O1S 1.258(11) 2 ?
O1S C1S 1.283(5) . ?
O1S C3S 1.546(10) . ?
C1S O1S 1.283(5) 2 ?
C1S C3S 1.377(8) 2 ?
C1S C3S 1.377(8) . ?
C1S C2S 1.625(7) 2 ?
C1S C2S 1.625(7) . ?
C2S C3S 1.024(9) . ?

loop_
 _geom_angle_atom_site_label_1
```

```
 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
C12 O1 C13 118.9(2) . . ?
C2 O2 H2O 106(2) . . ?
C10 O3 H3O 109(2) . . ?
C22 O6 C6 111.41(18) . . ?
C2 C1 C13 117.5(2) . . ?
C2 C1 C14 121.4(3) . . ?
C13 C1 C14 121.1(3) . . ?
O2 C2 C3 117.2(3) . . ?
O2 C2 C1 121.8(2) . . ?
C3 C2 C1 121.0(3) . . ?
C4 C3 C2 119.4(3) . . ?
C4 C3 H3 120.3 . . ?
C2 C3 H3 120.3 . . ?
C3 C4 C5 122.4(3) . . ?
C3 C4 H4 118.8 . . ?
C5 C4 H4 118.8 . . ?
C13 C5 C4 117.2(2) . . ?
C13 C5 C6 121.9(3) . . ?
C4 C5 C6 120.9(2) . . ?
O6 C6 C7 108.5(2) . . ?
O6 C6 C5 107.34(19) . . ?
C7 C6 C5 111.4(2) . . ?
O6 C6 C16 101.97(19) . . ?
C7 C6 C16 113.2(2) . . ?
C5 C6 C16 113.8(2) . . ?
C12 C7 C8 116.9(3) . . ?
C12 C7 C6 122.3(2) . . ?
C8 C7 C6 120.8(2) . . ?
C9 C8 C7 122.4(3) . . ?
C9 C8 H8 118.8 . . ?
C7 C8 H8 118.8 . . ?
C8 C9 C10 119.4(3) . . ?
C8 C9 H9 120.3 . . ?
C10 C9 H9 120.3 . . ?
O3 C10 C9 118.1(3) . . ?
O3 C10 C11 121.5(3) . . ?
C9 C10 C11 120.4(3) . . ?
C10 C11 C12 117.9(2) . . ?
C10 C11 C15 120.3(3) . . ?
C12 C11 C15 121.8(3) . . ?
C7 C12 O1 122.7(3) . . ?
C7 C12 C11 123.0(3) . . ?
O1 C12 C11 114.4(2) . . ?
```

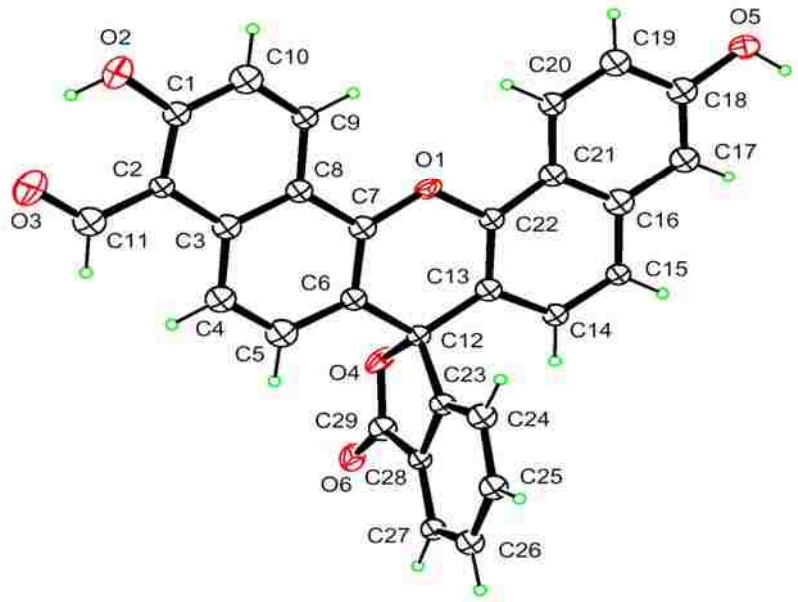
O1 C13 C5 122.4(2) . . ?
O1 C13 C1 115.1(2) . . ?
C5 C13 C1 122.5(3) . . ?
O4 C14 C1 123.3(3) . . ?
O4 C14 H14 118.3 . . ?
C1 C14 H14 118.3 . . ?
O5 C15 C11 123.5(3) . . ?
O5 C15 H15 118.2 . . ?
C11 C15 H15 118.2 . . ?
C17 C16 C21 121.0(2) . . ?
C17 C16 C6 129.1(2) . . ?
C21 C16 C6 109.9(2) . . ?
C16 C17 C18 117.5(2) . . ?
C16 C17 H17 121.2 . . ?
C18 C17 H17 121.2 . . ?
C17 C18 C19 121.7(2) . . ?
C17 C18 H18 119.2 . . ?
C19 C18 H18 119.2 . . ?
C20 C19 C18 120.2(3) . . ?
C20 C19 H19 119.9 . . ?
C18 C19 H19 119.9 . . ?
C21 C20 C19 117.9(2) . . ?
C21 C20 H20 121.1 . . ?
C19 C20 H20 121.1 . . ?
C20 C21 C16 121.7(2) . . ?
C20 C21 C22 130.0(2) . . ?
C16 C21 C22 108.3(2) . . ?
O7 C22 O6 120.9(2) . . ?
O7 C22 C21 130.7(3) . . ?
O6 C22 C21 108.34(19) . . ?
O1S O1S C1S 60.7(3) 2 . ?
O1S O1S C3S 117.9(4) 2 . ?
C1S O1S C3S 57.4(3) . . ?
O1S C1S O1S 58.7(5) 2 . ?
O1S C1S C3S 71.0(5) 2 2 ?
O1S C1S C3S 129.5(6) . 2 ?
O1S C1S C3S 129.5(6) 2 . ?
O1S C1S C3S 71.0(5) . . ?
C3S C1S C3S 159.5(9) 2 . ?
O1S C1S C2S 109.6(4) 2 2 ?
O1S C1S C2S 166.9(4) . 2 ?
C3S C1S C2S 38.8(4) 2 2 ?
C3S C1S C2S 120.8(7) . 2 ?
O1S C1S C2S 166.9(4) 2 . ?
O1S C1S C2S 109.6(4) . . ?
C3S C1S C2S 120.8(7) 2 . ?
C3S C1S C2S 38.8(4) . . ?
C2S C1S C2S 82.6(6) 2 . ?
C3S C2S C1S 57.4(6) . . ?

```
C2S C3S C1S 83.8(7) . . ?
C2S C3S O1S 135.3(9) . . ?
C1S C3S O1S 51.7(4) . . ?

loop_
 _geom_torsion_atom_site_label_1
 _geom_torsion_atom_site_label_2
 _geom_torsion_atom_site_label_3
 _geom_torsion_atom_site_label_4
 _geom_torsion
 _geom_torsion_site_symmetry_1
 _geom_torsion_site_symmetry_2
 _geom_torsion_site_symmetry_3
 _geom_torsion_site_symmetry_4
 _geom_torsion_publ_flag
C13 C1 C2 O2 178.4(2) . . . . ?
C14 C1 C2 O2 0.8(4) . . . . ?
C13 C1 C2 C3 -0.8(4) . . . . ?
C14 C1 C2 C3 -178.5(2) . . . . ?
O2 C2 C3 C4 -178.5(2) . . . . ?
C1 C2 C3 C4 0.8(4) . . . . ?
C2 C3 C4 C5 -0.1(4) . . . . ?
C3 C4 C5 C13 -0.6(4) . . . . ?
C3 C4 C5 C6 177.9(2) . . . . ?
C22 O6 C6 C7 -122.6(2) . . . . ?
C22 O6 C6 C5 116.9(2) . . . . ?
C22 O6 C6 C16 -2.9(3) . . . . ?
C13 C5 C6 O6 120.3(2) . . . . ?
C4 C5 C6 O6 -58.3(3) . . . . ?
C13 C5 C6 C7 1.6(3) . . . . ?
C4 C5 C6 C7 -176.9(2) . . . . ?
C13 C5 C6 C16 -127.7(2) . . . . ?
C4 C5 C6 C16 53.8(3) . . . . ?
O6 C6 C7 C12 -122.1(2) . . . . ?
C5 C6 C7 C12 -4.2(3) . . . . ?
C16 C6 C7 C12 125.5(2) . . . . ?
O6 C6 C7 C8 59.4(3) . . . . ?
C5 C6 C7 C8 177.3(2) . . . . ?
C16 C6 C7 C8 -53.0(3) . . . . ?
C12 C7 C8 C9 0.3(4) . . . . ?
C6 C7 C8 C9 178.9(2) . . . . ?
C7 C8 C9 C10 -0.8(4) . . . . ?
C8 C9 C10 O3 -179.8(2) . . . . ?
C8 C9 C10 C11 0.3(4) . . . . ?
O3 C10 C11 C12 -179.2(2) . . . . ?
C9 C10 C11 C12 0.6(4) . . . . ?
O3 C10 C11 C15 -0.1(4) . . . . ?
C9 C10 C11 C15 179.7(2) . . . . ?
C8 C7 C12 O1 179.9(2) . . . . ?
```

C6 C7 C12 O1 1.3(4) . . . . ?
C8 C7 C12 C11 0.8(4) . . . . ?
C6 C7 C12 C11 -177.8(2) . . . . ?
C13 O1 C12 C7 4.6(3) . . . . ?
C13 O1 C12 C11 -176.3(2) . . . . ?
C10 C11 C12 C7 -1.2(4) . . . . ?
C15 C11 C12 C7 179.7(2) . . . . ?
C10 C11 C12 O1 179.6(2) . . . . ?
C15 C11 C12 O1 0.6(3) . . . . ?
C12 O1 C13 C5 -7.2(3) . . . . ?
C12 O1 C13 C1 174.6(2) . . . . ?
C4 C5 C13 O1 -177.4(2) . . . . ?
C6 C5 C13 O1 4.0(4) . . . . ?
C4 C5 C13 C1 0.6(4) . . . . ?
C6 C5 C13 C1 -177.9(2) . . . . ?
C2 C1 C13 O1 178.3(2) . . . . ?
C14 C1 C13 O1 -4.0(3) . . . . ?
C2 C1 C13 C5 0.1(4) . . . . ?
C14 C1 C13 C5 177.8(2) . . . . ?
C2 C1 C14 O4 -3.1(4) . . . . ?
C13 C1 C14 O4 179.3(2) . . . . ?
C10 C11 C15 O5 -1.0(4) . . . . ?
C12 C11 C15 O5 178.0(2) . . . . ?
O6 C6 C16 C17 -175.8(3) . . . . ?
C7 C6 C16 C17 -59.5(4) . . . . ?
C5 C6 C16 C17 68.9(4) . . . . ?
O6 C6 C16 C21 2.3(3) . . . . ?
C7 C6 C16 C21 118.7(2) . . . . ?
C5 C6 C16 C21 -112.9(2) . . . . ?
C21 C16 C17 C18 0.2(4) . . . . ?
C6 C16 C17 C18 178.2(3) . . . . ?
C16 C17 C18 C19 0.8(4) . . . . ?
C17 C18 C19 C20 -1.2(4) . . . . ?
C18 C19 C20 C21 0.5(4) . . . . ?
C19 C20 C21 C16 0.6(4) . . . . ?
C19 C20 C21 C22 -177.3(3) . . . . ?
C17 C16 C21 C20 -0.9(4) . . . . ?
C6 C16 C21 C20 -179.3(3) . . . . ?
C17 C16 C21 C22 177.3(3) . . . . ?
C6 C16 C21 C22 -1.0(3) . . . . ?
C6 O6 C22 O7 -177.5(3) . . . . ?
C6 O6 C22 C21 2.5(3) . . . . ?
C20 C21 C22 O7 -2.8(5) . . . . ?
C16 C21 C22 O7 179.2(3) . . . . ?
C20 C21 C22 O6 177.1(3) . . . . ?
C16 C21 C22 O6 -0.9(3) . . . . ?
C3S O1S C1S O1S 176.1(7) . . . 2 ?
O1S O1S C1S C3S 4.8(8) 2 . . 2 ?
C3S O1S C1S C3S -179.12(16) . . . 2 ?

```
O1S O1S C1S C3S -176.1(7) 2 . . . ?
O1S O1S C1S C2S 29(2) 2 . . 2 ?
C3S O1S C1S C2S -155.0(18) . . . 2 ?
O1S O1S C1S C2S -173.3(5) 2 . . . ?
C3S O1S C1S C2S 2.8(5) . . . . ?
O1S C1S C2S C3S -30(2) 2 . . . ?
O1S C1S C2S C3S -4.2(8) . . . . ?
C3S C1S C2S C3S 177.5(3) 2 . . . ?
C2S C1S C2S C3S 170.8(10) 2 . . . ?
C1S C2S C3S O1S 4.7(9) . . . . ?
O1S C1S C3S C2S 171.5(6) 2 . . . ?
O1S C1S C3S C2S 175.8(8) . . . . ?
C3S C1S C3S C2S -6.1(6) 2 . . . ?
C2S C1S C3S C2S -10.6(11) 2 . . . ?
O1S C1S C3S O1S -4.3(8) 2 . . . ?
C3S C1S C3S O1S 178.1(3) 2 . . . ?
C2S C1S C3S O1S 173.6(5) 2 . . . ?
C2S C1S C3S O1S -175.8(8) . . . . ?
O1S O1S C3S C2S -2.0(17) 2 . . . ?
C1S O1S C3S C2S -5.9(12) . . . . ?
O1S O1S C3S C1S 3.9(7) 2 . . . ?

loop_
 _geom_hbond_atom_site_label_D
 _geom_hbond_atom_site_label_H
 _geom_hbond_atom_site_label_A
 _geom_hbond_distance_DH
 _geom_hbond_distance_HA
 _geom_hbond_distance_DA
 _geom_hbond_angle_DHA
 _geom_hbond_site_symmetry_A
O2 H20 O4  0.95(3) 1.77(3) 2.637(3) 149(3) .
O3 H30 O5  0.93(3) 1.77(3) 2.597(3) 146(3) .

_diffrn_measured_fraction_theta_max    0.993
_diffrn_reflns_theta_full              26.4
_diffrn_measured_fraction_theta_full   0.993
_refine_diff_density_max    0.33
_refine_diff_density_min   -0.23
_refine_diff_density_rms    0.057
# END OF CIF
```

APPENDIX Z: CRYSTALLOGRAPHIC DATA FOR COMPOUND 2.3




```
data_XXu4

_audit_creation_method            SHELXL-97
_chemical_name_systematic
;
 ?
;
_chemical_name_common             ?
_chemical_melting_point           ?
_chemical_compound_source          'local laboratory'
_chemical_formula_moiety      'C29 H16 O6, 2(C3 H6 O)'
_chemical_formula_sum     'C35 H28 O8'
_chemical_formula_weight          576.57

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
```

```
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_space_group_name_H-M 'P -1          '
_symmetry_space_group_name_Hall   '-P 1'
_symmetry_cell_setting 'Triclinic'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x, -y, -z'

_cell_length_a                    7.338(5)
_cell_length_b                    12.459(9)
_cell_length_c                    16.247(13)
_cell_angle_alpha                 81.00(3)
_cell_angle_beta                  80.19(3)
_cell_angle_gamma                 73.69(3)
_cell_volume                      1395.5(18)
_cell_formula_units_Z             2
_cell_measurement_temperature     105
_cell_measurement_reflns_used     4614
_cell_measurement_theta_min        2.5
_cell_measurement_theta_max        25.6

_exptl_crystal_description        plate
_exptl_crystal_colour             yellow
_exptl_crystal_size_max           0.10
_exptl_crystal_size_mid           0.10
_exptl_crystal_size_min           0.02
_exptl_crystal_density_meas       ?
_exptl_crystal_density_diffrn     1.372
_exptl_crystal_density_method     'not measured'
_exptl_crystal_F_000              604
_exptl_absorpt_coefficient_mu     0.097
_exptl_absorpt_correction_type    none
_exptl_absorpt_correction_T_min   ?
_exptl_absorpt_correction_T_max   ?
_exptl_absorpt_process_details    ?

_exptl_special_details
;
 ?
;

_diffrn_ambient_temperature       105
_diffrn_radiation_wavelength      0.71073
_diffrn_radiation_type            MoK\a
_diffrn_radiation_source          'fine-focus sealed tube'
_diffrn_radiation_monochromator   graphite
```

```
_diffrn_measurement_device  'KappaCCD (with Oxford Cryostream)'
_diffrn_measurement_method       ' \w scans with \k offsets'
_diffrn_detector_area_resol_mean  ?
_diffrn_standards_number          0
_diffrn_standards_interval_count  ?
_diffrn_standards_interval_time   ?
_diffrn_standards_decay_%         <2
_diffrn_reflns_number             15953
_diffrn_reflns_av_R_equivalents   0.310
_diffrn_reflns_av_sigmaI/netI     0.501
_diffrn_reflns_limit_h_min        -8
_diffrn_reflns_limit_h_max        8
_diffrn_reflns_limit_k_min        -15
_diffrn_reflns_limit_k_max        14
_diffrn_reflns_limit_l_min        -19
_diffrn_reflns_limit_l_max        19
_diffrn_reflns_theta_min          2.5
_diffrn_reflns_theta_max          25.5
_reflns_number_total              5053
_reflns_number_gt                 1306
_reflns_threshold_expression      I>2\s(I)

_computing_data_collection  'COLLECT (Nonius 1999)'
_computing_data_reduction  'Denzo and Scalepack (Otwinowski & Minor, 1997)'
_computing_cell_refinement    'Denzo and Scalepack (Otwinowski & Minor, 1997)'
_computing_structure_solution   'Direct_methods (SIR, Altomare, et al., 1994)'
_computing_structure_refinement   'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics           'ORTEP-3 for Windows (Farrugia, 1997)'
_computing_publication_material   'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
;

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type            full
_refine_ls_weighting_scheme       calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.0877P)^2^] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary      direct
_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
```

```
_refine_ls_hydrogen_treatment     constr
_refine_ls_extinction_method      none
_refine_ls_extinction_coef        ?
_refine_ls_number_reflns          5053
_refine_ls_number_parameters      219
_refine_ls_number_restraints      0
_refine_ls_R_factor_all           0.393
_refine_ls_R_factor_gt            0.140
_refine_ls_wR_factor_ref          0.331
_refine_ls_wR_factor_gt           0.233
_refine_ls_goodness_of_fit_ref    0.997
_refine_ls_restrained_S_all       0.997
_refine_ls_shift/su_max           0.001
_refine_ls_shift/su_mean          0.000

loop_
 _atom_site_label
 _atom_site_type_symbol
 _atom_site_fract_x
 _atom_site_fract_y
 _atom_site_fract_z
 _atom_site_U_iso_or_equiv
 _atom_site_adp_type
 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
 _atom_site_calc_flag
 _atom_site_refinement_flags
 _atom_site_disorder_assembly
 _atom_site_disorder_group
O1 O 0.7059(9) 0.5139(6) 0.5378(4) 0.0244(19) Uani 1 1 d . . .
O2 O 0.5903(12) 0.0423(6) 0.6941(5) 0.036(2) Uani 1 1 d . . .
H2OH H 0.5640 0.0254 0.7460 0.054 Uiso 1 1 calc R . .
O3 O 0.4150(11) 0.0888(7) 0.8383(5) 0.046(2) Uani 1 1 d . . .
O4 O 0.6710(9) 0.7124(6) 0.7088(5) 0.029(2) Uani 1 1 d . . .
O5 O 1.0674(11) 0.6836(6) 0.1819(5) 0.038(2) Uani 1 1 d . . .
H5OH H 1.0415 0.7523 0.1634 0.057 Uiso 1 1 calc R . .
O6 O 0.6301(10) 0.8246(6) 0.8091(4) 0.035(2) Uani 1 1 d . . .
C1 C 0.5999(15) 0.1534(10) 0.6785(7) 0.026(3) Uiso 1 1 d . . .
C2 C 0.5158(14) 0.2253(9) 0.7405(7) 0.021(3) Uiso 1 1 d . . .
C3 C 0.5244(15) 0.3433(9) 0.7200(7) 0.028(3) Uiso 1 1 d . . .
C4 C 0.4505(15) 0.4253(9) 0.7758(7) 0.032(3) Uiso 1 1 d . . .
H4 H 0.3924 0.4044 0.8306 0.038 Uiso 1 1 calc R . .
C5 C 0.4597(15) 0.5337(10) 0.7539(7) 0.035(3) Uiso 1 1 d . . .
H5 H 0.4103 0.5863 0.7939 0.042 Uiso 1 1 calc R . .
C6 C 0.5403(14) 0.5692(9) 0.6736(7) 0.023(3) Uiso 1 1 d . . .
C7 C 0.6202(15) 0.4908(9) 0.6166(7) 0.025(3) Uiso 1 1 d . . .
C8 C 0.6104(14) 0.3769(9) 0.6394(7) 0.024(3) Uiso 1 1 d . . .
C9 C 0.6913(13) 0.2931(8) 0.5834(7) 0.022(3) Uiso 1 1 d . . .
H9 H 0.7521 0.3152 0.5295 0.027 Uiso 1 1 calc R . .
```

```
C10 C 0.6865(16) 0.1851(10) 0.6022(7) 0.036(3) Uiso 1 1 d . . .
H10 H 0.7427 0.1324 0.5627 0.043 Uiso 1 1 calc R . .
C11 C 0.4146(16) 0.1891(11) 0.8176(7) 0.036(3) Uiso 1 1 d . . .
H11 H 0.3446 0.2432 0.8543 0.043 Uiso 1 1 calc R . .
C12 C 0.5536(14) 0.6879(8) 0.6496(6) 0.020(3) Uiso 1 1 d . . .
C13 C 0.6466(15) 0.7075(9) 0.5615(7) 0.024(3) Uiso 1 1 d . . .
C14 C 0.6727(14) 0.8157(9) 0.5265(6) 0.023(3) Uiso 1 1 d . . .
H14 H 0.6313 0.8759 0.5603 0.028 Uiso 1 1 calc R . .
C15 C 0.7547(13) 0.8345(9) 0.4465(6) 0.021(3) Uiso 1 1 d . . .
H15 H 0.7623 0.9085 0.4239 0.026 Uiso 1 1 calc R . .
C16 C 0.8309(16) 0.7433(10) 0.3949(7) 0.033(3) Uiso 1 1 d . . .
C17 C 0.9196(14) 0.7613(10) 0.3103(7) 0.031(3) Uiso 1 1 d . . .
H17 H 0.9334 0.8337 0.2866 0.037 Uiso 1 1 calc R . .
C18 C 0.9848(16) 0.6708(10) 0.2641(7) 0.032(3) Uiso 1 1 d . . .
C19 C 0.9740(15) 0.5631(10) 0.2995(7) 0.033(3) Uiso 1 1 d . . .
H19 H 1.0271 0.5015 0.2673 0.039 Uiso 1 1 calc R . .
C20 C 0.8883(14) 0.5452(9) 0.3797(7) 0.025(3) Uiso 1 1 d . . .
H20 H 0.8773 0.4719 0.4024 0.029 Uiso 1 1 calc R . .
C21 C 0.8160(15) 0.6349(9) 0.4290(7) 0.026(3) Uiso 1 1 d . . .
C22 C 0.7238(14) 0.6225(9) 0.5093(7) 0.022(3) Uiso 1 1 d . . .
C23 C 0.3599(14) 0.7712(8) 0.6705(6) 0.023(3) Uiso 1 1 d . . .
C24 C 0.1897(14) 0.7888(9) 0.6365(7) 0.029(3) Uiso 1 1 d . . .
H24 H 0.1827 0.7489 0.5924 0.035 Uiso 1 1 calc R . .
C25 C 0.0324(15) 0.8671(9) 0.6704(7) 0.027(3) Uiso 1 1 d . . .
H25 H -0.0865 0.8792 0.6500 0.033 Uiso 1 1 calc R . .
C26 C 0.0404(15) 0.9288(9) 0.7329(6) 0.027(3) Uiso 1 1 d . . .
H26 H -0.0717 0.9824 0.7535 0.033 Uiso 1 1 calc R . .
C27 C 0.2067(13) 0.9140(8) 0.7657(6) 0.021(3) Uiso 1 1 d . . .
H27 H 0.2127 0.9564 0.8085 0.026 Uiso 1 1 calc R . .
C28 C 0.3670(13) 0.8339(8) 0.7335(6) 0.019(3) Uiso 1 1 d . . .
C29 C 0.5617(15) 0.7952(9) 0.7547(7) 0.028(3) Uiso 1 1 d . . .
O1S O 0.9151(11) 0.1042(7) 0.8757(5) 0.051(3) Uani 1 1 d . . .
O2S O 0.8009(14) -0.3425(8) 1.0212(6) 0.070(3) Uani 1 1 d . . .
C1S C 0.7996(17) 0.0755(10) 0.9375(8) 0.035(3) Uiso 1 1 d . . .
C2S C 0.7792(17) -0.0419(10) 0.9562(8) 0.046(4) Uiso 1 1 d . . .
H2S1 H 0.6601 -0.0450 0.9381 0.069 Uiso 1 1 calc R . .
H2S2 H 0.7757 -0.0654 1.0168 0.069 Uiso 1 1 calc R . .
H2S3 H 0.8884 -0.0925 0.9259 0.069 Uiso 1 1 calc R . .
C3S C 0.6796(18) 0.1646(11) 0.9907(8) 0.059(4) Uiso 1 1 d . . .
H3S1 H 0.7018 0.2377 0.9664 0.089 Uiso 1 1 calc R . .
H3S2 H 0.7146 0.1465 1.0478 0.089 Uiso 1 1 calc R . .
H3S3 H 0.5439 0.1679 0.9927 0.089 Uiso 1 1 calc R . .
C4S C 0.8410(18) -0.3770(11) 0.9525(9) 0.046(4) Uiso 1 1 d . . .
C5S C 0.7278(18) -0.4439(10) 0.9257(8) 0.055(4) Uiso 1 1 d . . .
H5S1 H 0.6039 -0.4341 0.9616 0.083 Uiso 1 1 calc R . .
H5S2 H 0.7978 -0.5237 0.9308 0.083 Uiso 1 1 calc R . .
H5S3 H 0.7069 -0.4182 0.8671 0.083 Uiso 1 1 calc R . .
C6S C 1.0122(17) -0.3596(10) 0.8933(8) 0.050(4) Uiso 1 1 d . . .
H6S1 H 1.0835 -0.3222 0.9202 0.075 Uiso 1 1 calc R . .
```

```
H6S2 H 0.9706 -0.3125 0.8422 0.075 Uiso 1 1 calc R . .
H6S3 H 1.0948 -0.4326 0.8786 0.075 Uiso 1 1 calc R . .

loop_
 _atom_site_aniso_label
 _atom_site_aniso_U_11
 _atom_site_aniso_U_22
 _atom_site_aniso_U_33
 _atom_site_aniso_U_23
 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
O1 0.017(4) 0.019(4) 0.030(5) -0.001(4) 0.001(4) 0.003(3)
O2 0.034(5) 0.029(5) 0.043(5) 0.005(4) -0.011(5) -0.007(4)
O3 0.053(6) 0.031(5) 0.056(6) 0.006(5) -0.015(5) -0.016(4)
O4 0.024(4) 0.018(4) 0.045(5) -0.002(4) -0.018(4) -0.001(3)
O5 0.032(5) 0.036(5) 0.033(5) -0.004(4) 0.003(4) 0.008(4)
O6 0.049(5) 0.030(5) 0.027(5) -0.001(4) -0.019(4) -0.002(4)
O1S 0.052(6) 0.053(6) 0.042(6) -0.009(5) 0.015(5) -0.015(5)
O2S 0.089(7) 0.070(7) 0.048(7) -0.031(6) -0.014(6) -0.001(6)

_geom_special_details
;
 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
;

loop_
 _geom_bond_atom_site_label_1
 _geom_bond_atom_site_label_2
 _geom_bond_distance
 _geom_bond_site_symmetry_2
 _geom_bond_publ_flag
O1 C7 1.353(13) . ?
O1 C22 1.395(12) . ?
O2 C1 1.386(12) . ?
O2 H2OH 0.8400 . ?
O3 C11 1.242(13) . ?
O4 C29 1.355(11) . ?
O4 C12 1.510(10) . ?
O5 C18 1.374(13) . ?
O5 H5OH 0.8400 . ?
O6 C29 1.234(11) . ?
C1 C10 1.348(15) . ?
C1 C2 1.400(13) . ?
C2 C11 1.420(15) . ?
```

```
C2 C3 1.473(14) . ?
C3 C4 1.404(13) . ?
C3 C8 1.408(15) . ?
C4 C5 1.358(15) . ?
C4 H4 0.9500 . ?
C5 C6 1.397(15) . ?
C5 H5 0.9500 . ?
C6 C7 1.389(14) . ?
C6 C12 1.495(14) . ?
C7 C8 1.428(14) . ?
C8 C9 1.427(13) . ?
C9 C10 1.341(14) . ?
C9 H9 0.9500 . ?
C10 H10 0.9500 . ?
C11 H11 0.9500 . ?
C12 C13 1.492(14) . ?
C12 C23 1.526(13) . ?
C13 C22 1.394(13) . ?
C13 C14 1.430(14) . ?
C14 C15 1.349(14) . ?
C14 H14 0.9500 . ?
C15 C16 1.445(13) . ?
C15 H15 0.9500 . ?
C16 C21 1.404(15) . ?
C16 C17 1.430(15) . ?
C17 C18 1.381(14) . ?
C17 H17 0.9500 . ?
C18 C19 1.393(15) . ?
C19 C20 1.361(14) . ?
C19 H19 0.9500 . ?
C20 C21 1.405(13) . ?
C20 H20 0.9500 . ?
C21 C22 1.370(14) . ?
C23 C28 1.397(12) . ?
C23 C24 1.399(13) . ?
C24 C25 1.382(13) . ?
C24 H24 0.9500 . ?
C25 C26 1.383(13) . ?
C25 H25 0.9500 . ?
C26 C27 1.367(12) . ?
C26 H26 0.9500 . ?
C27 C28 1.396(12) . ?
C27 H27 0.9500 . ?
C28 C29 1.456(13) . ?
O1S C1S 1.275(14) . ?
O2S C4S 1.218(13) . ?
C1S C2S 1.491(15) . ?
C1S C3S 1.498(15) . ?
C2S H2S1 0.9800 . ?
```

```
C2S H2S2 0.9800 . ?
C2S H2S3 0.9800 . ?
C3S H3S1 0.9800 . ?
C3S H3S2 0.9800 . ?
C3S H3S3 0.9800 . ?
C4S C5S 1.483(15) . ?
C4S C6S 1.492(16) . ?
C5S H5S1 0.9800 . ?
C5S H5S2 0.9800 . ?
C5S H5S3 0.9800 . ?
C6S H6S1 0.9800 . ?
C6S H6S2 0.9800 . ?
C6S H6S3 0.9800 . ?

loop_
 _geom_angle_atom_site_label_1
 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
C7 O1 C22 120.0(9) . . ?
C1 O2 H2OH 109.5 . . ?
C29 O4 C12 109.7(7) . . ?
C18 O5 H5OH 109.5 . . ?
C10 C1 O2 116.5(10) . . ?
C10 C1 C2 124.5(12) . . ?
O2 C1 C2 118.9(11) . . ?
C1 C2 C11 122.0(11) . . ?
C1 C2 C3 116.9(11) . . ?
C11 C2 C3 120.9(11) . . ?
C4 C3 C8 117.6(11) . . ?
C4 C3 C2 124.0(12) . . ?
C8 C3 C2 118.4(10) . . ?
C5 C4 C3 122.0(12) . . ?
C5 C4 H4 119.0 . . ?
C3 C4 H4 119.0 . . ?
C4 C5 C6 121.2(11) . . ?
C4 C5 H5 119.4 . . ?
C6 C5 H5 119.4 . . ?
C7 C6 C5 119.1(11) . . ?
C7 C6 C12 119.4(11) . . ?
C5 C6 C12 121.4(10) . . ?
O1 C7 C6 124.8(11) . . ?
O1 C7 C8 115.4(10) . . ?
C6 C7 C8 119.8(11) . . ?
C3 C8 C9 117.9(11) . . ?
C3 C8 C7 120.2(10) . . ?
```

C9 C8 C7 121.9(11) . . ?
C10 C9 C8 124.0(12) . . ?
C10 C9 H9 118.0 . . ?
C8 C9 H9 118.0 . . ?
C9 C10 C1 118.3(12) . . ?
C9 C10 H10 120.8 . . ?
C1 C10 H10 120.8 . . ?
O3 C11 C2 121.9(11) . . ?
O3 C11 H11 119.0 . . ?
C2 C11 H11 119.0 . . ?
C13 C12 C6 112.7(9) . . ?
C13 C12 O4 108.8(9) . . ?
C6 C12 O4 107.8(8) . . ?
C13 C12 C23 114.2(9) . . ?
C6 C12 C23 111.0(9) . . ?
O4 C12 C23 101.6(7) . . ?
C22 C13 C14 115.0(11) . . ?
C22 C13 C12 123.5(11) . . ?
C14 C13 C12 121.4(10) . . ?
C15 C14 C13 121.8(10) . . ?
C15 C14 H14 119.1 . . ?
C13 C14 H14 119.1 . . ?
C14 C15 C16 120.6(11) . . ?
C14 C15 H15 119.7 . . ?
C16 C15 H15 119.7 . . ?
C21 C16 C17 119.6(11) . . ?
C21 C16 C15 118.9(11) . . ?
C17 C16 C15 121.5(11) . . ?
C18 C17 C16 118.3(12) . . ?
C18 C17 H17 120.8 . . ?
C16 C17 H17 120.8 . . ?
O5 C18 C17 120.8(11) . . ?
O5 C18 C19 117.7(10) . . ?
C17 C18 C19 121.4(12) . . ?
C20 C19 C18 120.7(11) . . ?
C20 C19 H19 119.7 . . ?
C18 C19 H19 119.7 . . ?
C19 C20 C21 120.2(11) . . ?
C19 C20 H20 119.9 . . ?
C21 C20 H20 119.9 . . ?
C22 C21 C16 117.5(11) . . ?
C22 C21 C20 122.8(11) . . ?
C16 C21 C20 119.7(11) . . ?
C21 C22 C13 126.0(12) . . ?
C21 C22 O1 114.5(10) . . ?
C13 C22 O1 119.4(11) . . ?
C28 C23 C24 120.3(9) . . ?
C28 C23 C12 110.6(8) . . ?
C24 C23 C12 129.1(9) . . ?

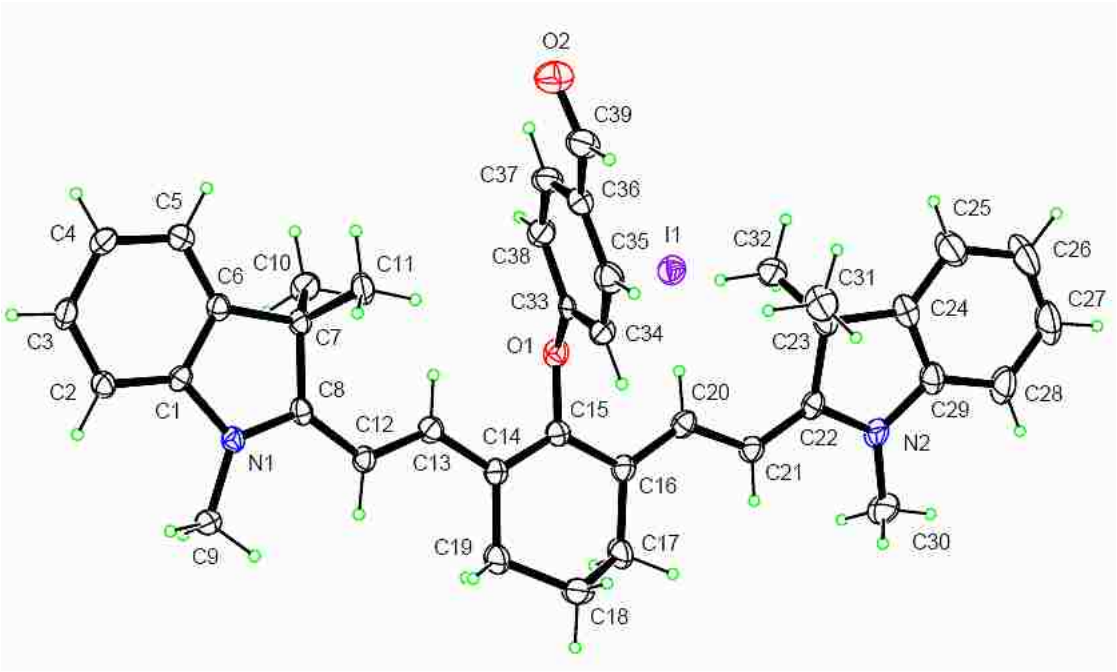
```
C25 C24 C23 116.6(10) . . ?
C25 C24 H24 121.7 . . ?
C23 C24 H24 121.7 . . ?
C24 C25 C26 122.8(10) . . ?
C24 C25 H25 118.6 . . ?
C26 C25 H25 118.6 . . ?
C27 C26 C25 121.3(10) . . ?
C27 C26 H26 119.4 . . ?
C25 C26 H26 119.4 . . ?
C26 C27 C28 117.1(9) . . ?
C26 C27 H27 121.5 . . ?
C28 C27 H27 121.5 . . ?
C27 C28 C23 122.0(9) . . ?
C27 C28 C29 131.6(9) . . ?
C23 C28 C29 106.4(9) . . ?
O6 C29 O4 119.6(9) . . ?
O6 C29 C28 128.6(10) . . ?
O4 C29 C28 111.7(9) . . ?
O1S C1S C2S 121.8(11) . . ?
O1S C1S C3S 117.9(12) . . ?
C2S C1S C3S 120.3(12) . . ?
C1S C2S H2S1 109.5 . . ?
C1S C2S H2S2 109.5 . . ?
H2S1 C2S H2S2 109.5 . . ?
C1S C2S H2S3 109.5 . . ?
H2S1 C2S H2S3 109.5 . . ?
H2S2 C2S H2S3 109.5 . . ?
C1S C3S H3S1 109.5 . . ?
C1S C3S H3S2 109.5 . . ?
H3S1 C3S H3S2 109.5 . . ?
C1S C3S H3S3 109.5 . . ?
H3S1 C3S H3S3 109.5 . . ?
H3S2 C3S H3S3 109.5 . . ?
O2S C4S C5S 121.4(13) . . ?
O2S C4S C6S 121.7(12) . . ?
C5S C4S C6S 116.8(11) . . ?
C4S C5S H5S1 109.5 . . ?
C4S C5S H5S2 109.5 . . ?
H5S1 C5S H5S2 109.5 . . ?
C4S C5S H5S3 109.5 . . ?
H5S1 C5S H5S3 109.5 . . ?
H5S2 C5S H5S3 109.5 . . ?
C4S C6S H6S1 109.5 . . ?
C4S C6S H6S2 109.5 . . ?
H6S1 C6S H6S2 109.5 . . ?
C4S C6S H6S3 109.5 . . ?
H6S1 C6S H6S3 109.5 . . ?
H6S2 C6S H6S3 109.5 . . ?
```

```
loop_
 _geom_torsion_atom_site_label_1
 _geom_torsion_atom_site_label_2
 _geom_torsion_atom_site_label_3
 _geom_torsion_atom_site_label_4
 _geom_torsion
 _geom_torsion_site_symmetry_1
 _geom_torsion_site_symmetry_2
 _geom_torsion_site_symmetry_3
 _geom_torsion_site_symmetry_4
 _geom_torsion_publ_flag
C10 C1 C2 C11 175.4(10) . . . . ?
O2 C1 C2 C11 -2.5(14) . . . . ?
C10 C1 C2 C3 -0.2(15) . . . . ?
O2 C1 C2 C3 -178.1(9) . . . . ?
C1 C2 C3 C4 -178.6(9) . . . . ?
C11 C2 C3 C4 5.7(15) . . . . ?
C1 C2 C3 C8 1.9(13) . . . . ?
C11 C2 C3 C8 -173.8(9) . . . . ?
C8 C3 C4 C5 0.3(15) . . . . ?
C2 C3 C4 C5 -179.2(10) . . . . ?
C3 C4 C5 C6 1.2(16) . . . . ?
C4 C5 C6 C7 -2.9(15) . . . . ?
C4 C5 C6 C12 -179.0(10) . . . . ?
C22 O1 C7 C6 1.9(13) . . . . ?
C22 O1 C7 C8 -179.7(9) . . . . ?
C5 C6 C7 O1 -178.6(9) . . . . ?
C12 C6 C7 O1 -2.5(15) . . . . ?
C5 C6 C7 C8 3.0(14) . . . . ?
C12 C6 C7 C8 179.1(9) . . . . ?
C4 C3 C8 C9 178.0(9) . . . . ?
C2 C3 C8 C9 -2.5(13) . . . . ?
C4 C3 C8 C7 -0.1(14) . . . . ?
C2 C3 C8 C7 179.4(9) . . . . ?
O1 C7 C8 C3 179.9(9) . . . . ?
C6 C7 C8 C3 -1.5(14) . . . . ?
O1 C7 C8 C9 1.9(13) . . . . ?
C6 C7 C8 C9 -179.6(9) . . . . ?
C3 C8 C9 C10 1.5(15) . . . . ?
C7 C8 C9 C10 179.6(10) . . . . ?
C8 C9 C10 C1 0.2(16) . . . . ?
O2 C1 C10 C9 177.1(9) . . . . ?
C2 C1 C10 C9 -0.8(16) . . . . ?
C1 C2 C11 O3 8.9(15) . . . . ?
C3 C2 C11 O3 -175.6(10) . . . . ?
C7 C6 C12 C13 3.2(13) . . . . ?
C5 C6 C12 C13 179.3(9) . . . . ?
C7 C6 C12 O4 -116.8(10) . . . . ?
C5 C6 C12 O4 59.2(12) . . . . ?
```

C7 C6 C12 C23 132.8(10) . . . . ?
C5 C6 C12 C23 -51.2(13) . . . . ?
C29 O4 C12 C13 120.7(9) . . . . ?
C29 O4 C12 C6 -116.8(10) . . . . ?
C29 O4 C12 C23 0.0(11) . . . . ?
C6 C12 C13 C22 -4.0(13) . . . . ?
O4 C12 C13 C22 115.5(10) . . . . ?
C23 C12 C13 C22 -131.8(10) . . . . ?
C6 C12 C13 C14 179.9(9) . . . . ?
O4 C12 C13 C14 -60.6(11) . . . . ?
C23 C12 C13 C14 52.1(13) . . . . ?
C22 C13 C14 C15 4.4(14) . . . . ?
C12 C13 C14 C15 -179.2(9) . . . . ?
C13 C14 C15 C16 -4.2(14) . . . . ?
C14 C15 C16 C21 0.9(14) . . . . ?
C14 C15 C16 C17 -179.5(10) . . . . ?
C21 C16 C17 C18 1.3(15) . . . . ?
C15 C16 C17 C18 -178.3(9) . . . . ?
C16 C17 C18 O5 178.6(9) . . . . ?
C16 C17 C18 C19 -3.2(15) . . . . ?
O5 C18 C19 C20 -177.9(9) . . . . ?
C17 C18 C19 C20 3.9(16) . . . . ?
C18 C19 C20 C21 -2.5(15) . . . . ?
C17 C16 C21 C22 -177.7(9) . . . . ?
C15 C16 C21 C22 1.9(15) . . . . ?
C17 C16 C21 C20 0.0(15) . . . . ?
C15 C16 C21 C20 179.6(9) . . . . ?
C19 C20 C21 C22 178.2(10) . . . . ?
C19 C20 C21 C16 0.6(14) . . . . ?
C16 C21 C22 C13 -1.5(15) . . . . ?
C20 C21 C22 C13 -179.2(9) . . . . ?
C16 C21 C22 O1 177.1(9) . . . . ?
C20 C21 C22 O1 -0.6(14) . . . . ?
C14 C13 C22 C21 -1.5(14) . . . . ?
C12 C13 C22 C21 -177.8(10) . . . . ?
C14 C13 C22 O1 180.0(8) . . . . ?
C12 C13 C22 O1 3.6(14) . . . . ?
C7 O1 C22 C21 178.9(9) . . . . ?
C7 O1 C22 C13 -2.3(12) . . . . ?
C13 C12 C23 C28 -117.2(10) . . . . ?
C6 C12 C23 C28 114.1(10) . . . . ?
O4 C12 C23 C28 -0.3(11) . . . . ?
C13 C12 C23 C24 63.5(15) . . . . ?
C6 C12 C23 C24 -65.2(15) . . . . ?
O4 C12 C23 C24 -179.6(11) . . . . ?
C28 C23 C24 C25 -2.1(16) . . . . ?
C12 C23 C24 C25 177.1(11) . . . . ?
C23 C24 C25 C26 2.1(17) . . . . ?
C24 C25 C26 C27 -0.9(18) . . . . ?

```
C25 C26 C27 C28 -0.2(16) . . . . ?
C26 C27 C28 C23 0.1(16) . . . . ?
C26 C27 C28 C29 -178.3(11) . . . . ?
C24 C23 C28 C27 1.1(17) . . . . ?
C12 C23 C28 C27 -178.2(10) . . . . ?
C24 C23 C28 C29 179.9(10) . . . . ?
C12 C23 C28 C29 0.5(12) . . . . ?
C12 O4 C29 O6 177.4(10) . . . . ?
C12 O4 C29 C28 0.4(12) . . . . ?
C27 C28 C29 O6 1(2) . . . . ?
C23 C28 C29 O6 -177.3(12) . . . . ?
C27 C28 C29 O4 178.0(11) . . . . ?
C23 C28 C29 O4 -0.6(12) . . . . ?

loop_
 _geom_hbond_atom_site_label_D
 _geom_hbond_atom_site_label_H
 _geom_hbond_atom_site_label_A
 _geom_hbond_distance_DH
 _geom_hbond_distance_HA
 _geom_hbond_distance_DA
 _geom_hbond_angle_DHA
 _geom_hbond_site_symmetry_A
O2 H2OH O3  0.84 1.84 2.542(12) 139.7 .
O5 H5OH O1S  0.84 1.90 2.694(12) 157.9 2_766

_diffrn_measured_fraction_theta_max    0.972
_diffrn_reflns_theta_full              25.5
_diffrn_measured_fraction_theta_full   0.972
_refine_diff_density_max    0.445
_refine_diff_density_min   -0.37
_refine_diff_density_rms    0.089
#END OF CIF
```

APPENDIX AA: CRYSTALLOGRAPHIC DATA FOR COMPOUND 3.7




```
data_XXu10

_audit_creation_method            SHELXL-97
_chemical_name_systematic
;
 ?
;
_chemical_name_common             ?
_chemical_melting_point           ?
_chemical_compound_source          'local laboratory'
_chemical_formula_moiety  'C39 H41 N2 O2 1+, I 1-'
_chemical_formula_sum    'C39 H41 I N2 O2'
_chemical_formula_weight          696.64

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'    0.0033    0.0016
```

```
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'I'  'I'  -0.4742   1.8119
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'N'  'N'   0.0061   0.0033
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_space_group_name_H-M 'P 21/c        '
_symmetry_space_group_name_Hall     '-P 2ybc'
_symmetry_cell_setting 'Monoclinic'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x, -y-1/2, z-1/2'

_cell_length_a                    20.111(3)
_cell_length_b                    9.721(2)
_cell_length_c                    18.261(3)
_cell_angle_alpha                 90
_cell_angle_beta                  103.354(4)
_cell_angle_gamma                 90
_cell_volume                      3473.5(11)
_cell_formula_units_Z             4
_cell_measurement_temperature     110
_cell_measurement_reflns_used     7540
_cell_measurement_theta_min        2.5
_cell_measurement_theta_max        27.9

_exptl_crystal_description        plate
_exptl_crystal_colour             'blue-bronze'
_exptl_crystal_size_max           0.42
_exptl_crystal_size_mid           0.18
_exptl_crystal_size_min           0.03
_exptl_crystal_density_meas       ?
_exptl_crystal_density_diffrn     1.332
_exptl_crystal_density_method     'not measured'
_exptl_crystal_F_000              1432
_exptl_absorpt_coefficient_mu     0.957
_exptl_absorpt_correction_type 'multi-scan'
_exptl_absorpt_correction_T_min   0.689
_exptl_absorpt_correction_T_max   0.972
_exptl_absorpt_process_details  'HKL Scalepack (Otwinowski & Minor 1997)'
```

```
_exptl_special_details
;
 ?
;

_diffrn_ambient_temperature       110
_diffrn_radiation_wavelength      0.71073
_diffrn_radiation_type            MoK\a
_diffrn_radiation_source          'fine-focus sealed tube'
_diffrn_radiation_monochromator   graphite
_diffrn_measurement_device  'KappaCCD (with Oxford Cryostream)'
_diffrn_measurement_method       ' \w scans with \k offsets'
_diffrn_detector_area_resol_mean  ?
_diffrn_standards_number          0
_diffrn_standards_interval_count  ?
_diffrn_standards_interval_time   ?
_diffrn_standards_decay_%         <2
_diffrn_reflns_number             39781
_diffrn_reflns_av_R_equivalents   0.053
_diffrn_reflns_av_sigmaI/netI     0.0836
_diffrn_reflns_limit_h_min        -26
_diffrn_reflns_limit_h_max        26
_diffrn_reflns_limit_k_min        -11
_diffrn_reflns_limit_k_max        12
_diffrn_reflns_limit_l_min        -23
_diffrn_reflns_limit_l_max        24
_diffrn_reflns_theta_min          2.7
_diffrn_reflns_theta_max          27.9
_reflns_number_total              8271
_reflns_number_gt                 5606
_reflns_threshold_expression      I>2\s(I)

_computing_data_collection        'COLLECT (Nonius, 2000)'
_computing_cell_refinement        'HKL Scalepack (Otwinowski & Minor 1997)'
_computing_data_reduction   'HKL Denzo and Scalepack (Otwinowski & Minor 1997)'
_computing_structure_solution     'SIR97 (Altomare  et al., 1999)'
_computing_structure_refinement   'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics     'ORTEP-3 for Windows (Farrugia, 1997)'
_computing_publication_material   'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
```

```
;

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type            full
_refine_ls_weighting_scheme       calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.0373P)^2^+2.2694P] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary      direct
_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
_refine_ls_hydrogen_treatment     constr
_refine_ls_extinction_method      none
_refine_ls_extinction_coef        ?
_refine_ls_number_reflns          8271
_refine_ls_number_parameters      403
_refine_ls_number_restraints      0
_refine_ls_R_factor_all           0.088
_refine_ls_R_factor_gt            0.047
_refine_ls_wR_factor_ref          0.101
_refine_ls_wR_factor_gt           0.089
_refine_ls_goodness_of_fit_ref    1.016
_refine_ls_restrained_S_all       1.016
_refine_ls_shift/su_max           0.001
_refine_ls_shift/su_mean          0.000

loop_
 _atom_site_label
 _atom_site_type_symbol
 _atom_site_fract_x
 _atom_site_fract_y
 _atom_site_fract_z
 _atom_site_U_iso_or_equiv
 _atom_site_adp_type
 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
 _atom_site_calc_flag
 _atom_site_refinement_flags
 _atom_site_disorder_assembly
 _atom_site_disorder_group
I1 I 0.157473(11) 0.93298(2) 0.540838(13) 0.02793(8) Uani 1 1 d . . .
O1 O 0.30592(11) 0.2663(2) 0.73597(14) 0.0282(5) Uani 1 1 d . . .
O2 O 0.11754(15) 0.4823(3) 0.43042(16) 0.0461(7) Uani 1 1 d . . .
N1 N 0.03128(13) 0.2755(3) 0.84314(15) 0.0232(6) Uani 1 1 d . . .
N2 N 0.61844(14) 0.3990(3) 0.77448(18) 0.0319(7) Uani 1 1 d . . .
C1 C -0.03016(16) 0.2346(3) 0.79227(19) 0.0218(7) Uani 1 1 d . . .
C2 C -0.09522(17) 0.2255(3) 0.8048(2) 0.0268(8) Uani 1 1 d . . .
H2 H -0.1040 0.2427 0.8529 0.032 Uiso 1 1 calc R . .
C3 C -0.14706(18) 0.1900(3) 0.7432(2) 0.0306(8) Uani 1 1 d . . .
H3 H -0.1927 0.1836 0.7492 0.037 Uiso 1 1 calc R . .
```

```
C4 C -0.13398(18) 0.1637(3) 0.6735(2) 0.0313(8) Uani 1 1 d . . .
H4 H -0.1706 0.1396 0.6326 0.038 Uiso 1 1 calc R . .
C5 C -0.06799(17) 0.1722(3) 0.6626(2) 0.0289(8) Uani 1 1 d . . .
H5 H -0.0589 0.1539 0.6148 0.035 Uiso 1 1 calc R . .
C6 C -0.01594(16) 0.2078(3) 0.72327(19) 0.0237(7) Uani 1 1 d . . .
C7 C 0.05994(16) 0.2277(3) 0.72901(19) 0.0249(8) Uani 1 1 d . . .
C8 C 0.08407(16) 0.2741(3) 0.81084(19) 0.0223(7) Uani 1 1 d . . .
C9 C 0.03236(18) 0.3073(4) 0.92199(19) 0.0315(8) Uani 1 1 d . . .
H9A H 0.0395 0.2224 0.9517 0.047 Uiso 1 1 calc R . .
H9B H -0.0113 0.3489 0.9251 0.047 Uiso 1 1 calc R . .
H9C H 0.0696 0.3718 0.9418 0.047 Uiso 1 1 calc R . .
C10 C 0.09212(18) 0.0886(3) 0.7157(2) 0.0347(9) Uani 1 1 d . . .
H10A H 0.0860 0.0226 0.7542 0.052 Uiso 1 1 calc R . .
H10B H 0.1410 0.1012 0.7186 0.052 Uiso 1 1 calc R . .
H10C H 0.0698 0.0534 0.6657 0.052 Uiso 1 1 calc R . .
C11 C 0.07064(18) 0.3399(4) 0.6730(2) 0.0340(9) Uani 1 1 d . . .
H11A H 0.0497 0.3105 0.6216 0.051 Uiso 1 1 calc R . .
H11B H 0.1197 0.3547 0.6780 0.051 Uiso 1 1 calc R . .
H11C H 0.0494 0.4259 0.6840 0.051 Uiso 1 1 calc R . .
C12 C 0.15120(16) 0.3125(3) 0.84881(19) 0.0241(7) Uani 1 1 d . . .
H12 H 0.1584 0.3475 0.8986 0.029 Uiso 1 1 calc R . .
C13 C 0.20589(16) 0.3011(3) 0.8167(2) 0.0264(8) Uani 1 1 d . . .
H13 H 0.1970 0.2644 0.7672 0.032 Uiso 1 1 calc R . .
C14 C 0.27506(17) 0.3384(3) 0.84942(19) 0.0261(8) Uani 1 1 d . . .
C15 C 0.32398(17) 0.3229(3) 0.80854(19) 0.0258(8) Uani 1 1 d . . .
C16 C 0.39572(16) 0.3485(3) 0.8363(2) 0.0272(8) Uani 1 1 d . . .
C17 C 0.41796(18) 0.3847(4) 0.9183(2) 0.0390(9) Uani 1 1 d . . .
H17A H 0.4610 0.4382 0.9270 0.047 Uiso 1 1 calc R . .
H17B H 0.4271 0.2992 0.9484 0.047 Uiso 1 1 calc R . .
C18 C 0.36389(19) 0.4683(5) 0.9442(2) 0.0445(11) Uani 1 1 d . . .
H18A H 0.3577 0.5575 0.9174 0.053 Uiso 1 1 calc R . .
H18B H 0.3793 0.4872 0.9987 0.053 Uiso 1 1 calc R . .
C19 C 0.29605(18) 0.3923(4) 0.9291(2) 0.0357(9) Uani 1 1 d . . .
H19A H 0.2996 0.3143 0.9646 0.043 Uiso 1 1 calc R . .
H19B H 0.2602 0.4552 0.9384 0.043 Uiso 1 1 calc R . .
C20 C 0.43803(16) 0.3426(3) 0.7877(2) 0.0266(8) Uani 1 1 d . . .
H20 H 0.4175 0.3207 0.7369 0.032 Uiso 1 1 calc R . .
C21 C 0.50982(16) 0.3661(3) 0.8055(2) 0.0270(8) Uani 1 1 d . . .
H21 H 0.5320 0.3769 0.8570 0.032 Uiso 1 1 calc R . .
C22 C 0.54918(16) 0.3741(3) 0.7539(2) 0.0264(8) Uani 1 1 d . . .
C23 C 0.52814(17) 0.3627(4) 0.6684(2) 0.0286(8) Uani 1 1 d . . .
C24 C 0.5959(2) 0.3887(4) 0.6467(2) 0.0364(9) Uani 1 1 d . . .
C25 C 0.6113(2) 0.3938(5) 0.5776(3) 0.0522(12) Uani 1 1 d . . .
H25 H 0.5771 0.3787 0.5329 0.063 Uiso 1 1 calc R . .
C26 C 0.6797(3) 0.4224(5) 0.5747(3) 0.0669(14) Uani 1 1 d . . .
H26 H 0.6916 0.4267 0.5273 0.080 Uiso 1 1 calc R . .
C27 C 0.7287(3) 0.4438(5) 0.6389(3) 0.0605(13) Uani 1 1 d . . .
H27 H 0.7741 0.4636 0.6355 0.073 Uiso 1 1 calc R . .
C28 C 0.7137(2) 0.4373(4) 0.7090(3) 0.0462(11) Uani 1 1 d . . .
```

```
H28 H 0.7480 0.4512 0.7538 0.055 Uiso 1 1 calc R . .
C29 C 0.64664(19) 0.4096(4) 0.7114(2) 0.0344(9) Uani 1 1 d . . .
C30 C 0.65612(19) 0.4133(4) 0.8515(2) 0.0465(11) Uani 1 1 d . . .
H30A H 0.6408 0.4961 0.8734 0.070 Uiso 1 1 calc R . .
H30B H 0.7050 0.4211 0.8530 0.070 Uiso 1 1 calc R . .
H30C H 0.6482 0.3324 0.8803 0.070 Uiso 1 1 calc R . .
C31 C 0.4757(2) 0.4726(4) 0.6325(2) 0.0437(10) Uani 1 1 d . . .
H31A H 0.4929 0.5639 0.6503 0.066 Uiso 1 1 calc R . .
H31B H 0.4323 0.4555 0.6467 0.066 Uiso 1 1 calc R . .
H31C H 0.4685 0.4686 0.5776 0.066 Uiso 1 1 calc R . .
C32 C 0.5021(2) 0.2178(4) 0.6435(2) 0.0394(9) Uani 1 1 d . . .
H32A H 0.4945 0.2103 0.5887 0.059 Uiso 1 1 calc R . .
H32B H 0.4591 0.2009 0.6584 0.059 Uiso 1 1 calc R . .
H32C H 0.5361 0.1496 0.6674 0.059 Uiso 1 1 calc R . .
C33 C 0.27210(15) 0.3422(3) 0.67663(18) 0.0230(7) Uani 1 1 d . . .
C34 C 0.26866(18) 0.4866(4) 0.6756(2) 0.0294(8) Uani 1 1 d . . .
H34 H 0.2918 0.5391 0.7177 0.035 Uiso 1 1 calc R . .
C35 C 0.23053(19) 0.5506(4) 0.6115(2) 0.0341(9) Uani 1 1 d . . .
H35 H 0.2281 0.6482 0.6097 0.041 Uiso 1 1 calc R . .
C36 C 0.19596(18) 0.4749(4) 0.5499(2) 0.0300(8) Uani 1 1 d . . .
C37 C 0.20149(18) 0.3330(4) 0.5519(2) 0.0334(9) Uani 1 1 d . . .
H37 H 0.1790 0.2804 0.5095 0.040 Uiso 1 1 calc R . .
C38 C 0.23918(18) 0.2672(4) 0.6145(2) 0.0317(8) Uani 1 1 d . . .
H38 H 0.2426 0.1697 0.6151 0.038 Uiso 1 1 calc R . .
C39 C 0.1523(2) 0.5433(4) 0.4838(2) 0.0379(9) Uani 1 1 d . . .
H39 H 0.1513 0.6410 0.4829 0.045 Uiso 1 1 calc R . .

loop_
 _atom_site_aniso_label
 _atom_site_aniso_U_11
 _atom_site_aniso_U_22
 _atom_site_aniso_U_33
 _atom_site_aniso_U_23
 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
I1 0.02452(12) 0.03092(13) 0.02691(13) 0.00382(10) 0.00299(9) -0.00146(10)
O1 0.0206(12) 0.0297(13) 0.0353(15) -0.0030(11) 0.0083(11) 0.0013(10)
O2 0.0522(18) 0.0462(16) 0.0366(17) 0.0001(14) 0.0035(15) 0.0011(14)
N1 0.0194(15) 0.0250(14) 0.0263(16) -0.0016(12) 0.0078(12) 0.0007(11)
N2 0.0172(15) 0.0413(18) 0.0381(19) -0.0070(14) 0.0081(14) -0.0035(12)
C1 0.0199(17) 0.0180(16) 0.0266(19) -0.0010(14) 0.0036(15) -0.0007(13)
C2 0.0256(19) 0.0276(18) 0.030(2) -0.0066(15) 0.0128(16) -0.0030(14)
C3 0.0225(19) 0.0300(19) 0.040(2) -0.0036(17) 0.0096(17) -0.0076(15)
C4 0.0256(19) 0.036(2) 0.030(2) -0.0024(16) 0.0006(16) -0.0064(15)
C5 0.0269(19) 0.035(2) 0.025(2) -0.0010(15) 0.0064(16) -0.0010(15)
C6 0.0224(18) 0.0205(16) 0.030(2) -0.0025(15) 0.0101(15) -0.0008(13)
C7 0.0186(17) 0.0294(18) 0.029(2) -0.0051(15) 0.0094(15) -0.0005(14)
C8 0.0231(18) 0.0176(16) 0.0293(19) 0.0003(14) 0.0123(15) 0.0008(13)
C9 0.0250(19) 0.043(2) 0.027(2) -0.0085(17) 0.0066(16) -0.0051(16)
```

```
C10 0.0259(19) 0.036(2) 0.043(2) -0.0154(17) 0.0108(17) 0.0011(15)
C11 0.0253(19) 0.046(2) 0.033(2) 0.0067(18) 0.0118(17) -0.0067(16)
C12 0.0187(17) 0.0274(18) 0.0267(19) 0.0008(15) 0.0060(15) 0.0000(14)
C13 0.0235(18) 0.0263(18) 0.031(2) -0.0044(15) 0.0086(16) 0.0007(14)
C14 0.0208(17) 0.0302(19) 0.028(2) -0.0008(15) 0.0073(15) -0.0008(14)
C15 0.0239(18) 0.0282(18) 0.026(2) -0.0005(15) 0.0070(15) -0.0001(14)
C16 0.0196(18) 0.0323(19) 0.030(2) -0.0024(16) 0.0062(15) -0.0013(14)
C17 0.0211(19) 0.065(3) 0.032(2) 0.0025(19) 0.0082(17) -0.0048(18)
C18 0.031(2) 0.072(3) 0.031(2) -0.016(2) 0.0083(18) -0.005(2)
C19 0.0228(19) 0.052(2) 0.034(2) -0.0012(18) 0.0104(17) -0.0013(16)
C20 0.0198(17) 0.0255(18) 0.033(2) -0.0019(15) 0.0030(15) 0.0010(14)
C21 0.0207(18) 0.0309(18) 0.029(2) -0.0029(16) 0.0050(15) -0.0003(14)
C22 0.0162(17) 0.0268(17) 0.035(2) -0.0008(16) 0.0043(15) 0.0003(14)
C23 0.0222(18) 0.0332(19) 0.031(2) 0.0028(16) 0.0080(16) -0.0005(15)
C24 0.036(2) 0.038(2) 0.040(2) 0.0056(18) 0.0180(19) -0.0007(17)
C25 0.046(3) 0.072(3) 0.044(3) 0.008(2) 0.020(2) -0.001(2)
C26 0.061(3) 0.090(4) 0.064(3) 0.013(3) 0.045(3) -0.003(3)
C27 0.047(3) 0.066(3) 0.082(4) 0.001(3) 0.041(3) -0.010(2)
C28 0.028(2) 0.049(2) 0.066(3) -0.009(2) 0.020(2) -0.0085(19)
C29 0.029(2) 0.033(2) 0.045(2) -0.0013(17) 0.0161(18) -0.0012(15)
C30 0.0188(19) 0.073(3) 0.045(3) -0.012(2) 0.0006(18) -0.0029(19)
C31 0.034(2) 0.052(2) 0.044(3) 0.011(2) 0.0074(19) 0.0078(19)
C32 0.037(2) 0.046(2) 0.037(2) -0.0102(19) 0.0129(19) -0.0050(18)
C33 0.0101(15) 0.038(2) 0.0227(19) -0.0030(16) 0.0082(14) -0.0044(14)
C34 0.0264(19) 0.0325(19) 0.030(2) -0.0078(16) 0.0092(16) -0.0056(15)
C35 0.036(2) 0.031(2) 0.038(2) -0.0013(18) 0.0144(18) 0.0001(17)
C36 0.028(2) 0.035(2) 0.030(2) -0.0030(16) 0.0123(16) -0.0019(15)
C37 0.032(2) 0.041(2) 0.027(2) -0.0083(17) 0.0070(17) 0.0005(17)
C38 0.028(2) 0.033(2) 0.035(2) -0.0077(17) 0.0092(17) -0.0008(15)
C39 0.047(2) 0.038(2) 0.030(2) -0.0024(18) 0.0113(19) -0.0009(18)

_geom_special_details
;
 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
;

loop_
 _geom_bond_atom_site_label_1
 _geom_bond_atom_site_label_2
 _geom_bond_distance
 _geom_bond_site_symmetry_2
 _geom_bond_publ_flag
O1 C33 1.357(4) . ?
O1 C15 1.403(4) . ?
```

```
O2 C39 1.214(4) . ?
N1 C8 1.328(4) . ?
N1 C1 1.420(4) . ?
N1 C9 1.468(4) . ?
N2 C22 1.378(4) . ?
N2 C29 1.399(5) . ?
N2 C30 1.441(5) . ?
C1 C6 1.380(4) . ?
C1 C2 1.382(4) . ?
C2 C3 1.389(5) . ?
C2 H2 0.9500 . ?
C3 C4 1.381(5) . ?
C3 H3 0.9500 . ?
C4 C5 1.389(5) . ?
C4 H4 0.9500 . ?
C5 C6 1.380(5) . ?
C5 H5 0.9500 . ?
C6 C7 1.518(4) . ?
C7 C8 1.529(5) . ?
C7 C10 1.543(5) . ?
C7 C11 1.544(5) . ?
C8 C12 1.418(4) . ?
C9 H9A 0.9800 . ?
C9 H9B 0.9800 . ?
C9 H9C 0.9800 . ?
C10 H10A 0.9800 . ?
C10 H10B 0.9800 . ?
C10 H10C 0.9800 . ?
C11 H11A 0.9800 . ?
C11 H11B 0.9800 . ?
C11 H11C 0.9800 . ?
C12 C13 1.365(4) . ?
C12 H12 0.9500 . ?
C13 C14 1.428(5) . ?
C13 H13 0.9500 . ?
C14 C15 1.374(4) . ?
C14 C19 1.512(5) . ?
C15 C16 1.436(5) . ?
C16 C20 1.364(5) . ?
C16 C17 1.503(5) . ?
C17 C18 1.517(5) . ?
C17 H17A 0.9900 . ?
C17 H17B 0.9900 . ?
C18 C19 1.520(5) . ?
C18 H18A 0.9900 . ?
C18 H18B 0.9900 . ?
C19 H19A 0.9900 . ?
C19 H19B 0.9900 . ?
C20 C21 1.423(4) . ?
```

```
C20 H20 0.9500 . ?
C21 C22 1.366(5) . ?
C21 H21 0.9500 . ?
C22 C23 1.523(5) . ?
C23 C24 1.526(5) . ?
C23 C32 1.535(5) . ?
C23 C31 1.538(5) . ?
C24 C25 1.367(5) . ?
C24 C29 1.387(5) . ?
C25 C26 1.417(6) . ?
C25 H25 0.9500 . ?
C26 C27 1.363(7) . ?
C26 H26 0.9500 . ?
C27 C28 1.382(6) . ?
C27 H27 0.9500 . ?
C28 C29 1.386(5) . ?
C28 H28 0.9500 . ?
C30 H30A 0.9800 . ?
C30 H30B 0.9800 . ?
C30 H30C 0.9800 . ?
C31 H31A 0.9800 . ?
C31 H31B 0.9800 . ?
C31 H31C 0.9800 . ?
C32 H32A 0.9800 . ?
C32 H32B 0.9800 . ?
C32 H32C 0.9800 . ?
C33 C38 1.382(5) . ?
C33 C34 1.405(5) . ?
C34 C35 1.390(5) . ?
C34 H34 0.9500 . ?
C35 C36 1.388(5) . ?
C35 H35 0.9500 . ?
C36 C37 1.384(5) . ?
C36 C39 1.477(5) . ?
C37 C38 1.375(5) . ?
C37 H37 0.9500 . ?
C38 H38 0.9500 . ?
C39 H39 0.9500 . ?

loop_
 _geom_angle_atom_site_label_1
 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
C33 O1 C15 120.9(3) . . ?
C8 N1 C1 111.7(3) . . ?
```

```
C8 N1 C9 127.3(3) . . ?
C1 N1 C9 120.9(3) . . ?
C22 N2 C29 111.4(3) . . ?
C22 N2 C30 123.7(3) . . ?
C29 N2 C30 125.0(3) . . ?
C6 C1 C2 122.9(3) . . ?
C6 C1 N1 108.5(3) . . ?
C2 C1 N1 128.5(3) . . ?
C1 C2 C3 116.4(3) . . ?
C1 C2 H2 121.8 . . ?
C3 C2 H2 121.8 . . ?
C4 C3 C2 121.6(3) . . ?
C4 C3 H3 119.2 . . ?
C2 C3 H3 119.2 . . ?
C3 C4 C5 120.8(3) . . ?
C3 C4 H4 119.6 . . ?
C5 C4 H4 119.6 . . ?
C6 C5 C4 118.2(3) . . ?
C6 C5 H5 120.9 . . ?
C4 C5 H5 120.9 . . ?
C1 C6 C5 120.1(3) . . ?
C1 C6 C7 109.3(3) . . ?
C5 C6 C7 130.7(3) . . ?
C6 C7 C8 101.1(3) . . ?
C6 C7 C10 109.2(3) . . ?
C8 C7 C10 111.3(3) . . ?
C6 C7 C11 109.6(3) . . ?
C8 C7 C11 112.2(3) . . ?
C10 C7 C11 112.8(3) . . ?
N1 C8 C12 123.3(3) . . ?
N1 C8 C7 109.3(3) . . ?
C12 C8 C7 127.4(3) . . ?
N1 C9 H9A 109.5 . . ?
N1 C9 H9B 109.5 . . ?
H9A C9 H9B 109.5 . . ?
N1 C9 H9C 109.5 . . ?
H9A C9 H9C 109.5 . . ?
H9B C9 H9C 109.5 . . ?
C7 C10 H10A 109.5 . . ?
C7 C10 H10B 109.5 . . ?
H10A C10 H10B 109.5 . . ?
C7 C10 H10C 109.5 . . ?
H10A C10 H10C 109.5 . . ?
H10B C10 H10C 109.5 . . ?
C7 C11 H11A 109.5 . . ?
C7 C11 H11B 109.5 . . ?
H11A C11 H11B 109.5 . . ?
C7 C11 H11C 109.5 . . ?
H11A C11 H11C 109.5 . . ?
```

H11B C11 H11C 109.5 . . ?
C13 C12 C8 122.6(3) . . ?
C13 C12 H12 118.7 . . ?
C8 C12 H12 118.7 . . ?
C12 C13 C14 127.1(3) . . ?
C12 C13 H13 116.4 . . ?
C14 C13 H13 116.4 . . ?
C15 C14 C13 119.7(3) . . ?
C15 C14 C19 119.0(3) . . ?
C13 C14 C19 121.3(3) . . ?
C14 C15 O1 119.6(3) . . ?
C14 C15 C16 125.2(3) . . ?
O1 C15 C16 114.9(3) . . ?
C20 C16 C15 119.4(3) . . ?
C20 C16 C17 124.8(3) . . ?
C15 C16 C17 115.8(3) . . ?
C16 C17 C18 111.5(3) . . ?
C16 C17 H17A 109.3 . . ?
C18 C17 H17A 109.3 . . ?
C16 C17 H17B 109.3 . . ?
C18 C17 H17B 109.3 . . ?
H17A C17 H17B 108.0 . . ?
C17 C18 C19 111.2(3) . . ?
C17 C18 H18A 109.4 . . ?
C19 C18 H18A 109.4 . . ?
C17 C18 H18B 109.4 . . ?
C19 C18 H18B 109.4 . . ?
H18A C18 H18B 108.0 . . ?
C14 C19 C18 112.5(3) . . ?
C14 C19 H19A 109.1 . . ?
C18 C19 H19A 109.1 . . ?
C14 C19 H19B 109.1 . . ?
C18 C19 H19B 109.1 . . ?
H19A C19 H19B 107.8 . . ?
C16 C20 C21 126.7(3) . . ?
C16 C20 H20 116.7 . . ?
C21 C20 H20 116.7 . . ?
C22 C21 C20 124.8(3) . . ?
C22 C21 H21 117.6 . . ?
C20 C21 H21 117.6 . . ?
C21 C22 N2 122.1(3) . . ?
C21 C22 C23 129.4(3) . . ?
N2 C22 C23 108.5(3) . . ?
C22 C23 C24 101.6(3) . . ?
C22 C23 C32 111.4(3) . . ?
C24 C23 C32 109.8(3) . . ?
C22 C23 C31 112.8(3) . . ?
C24 C23 C31 109.8(3) . . ?
C32 C23 C31 111.0(3) . . ?

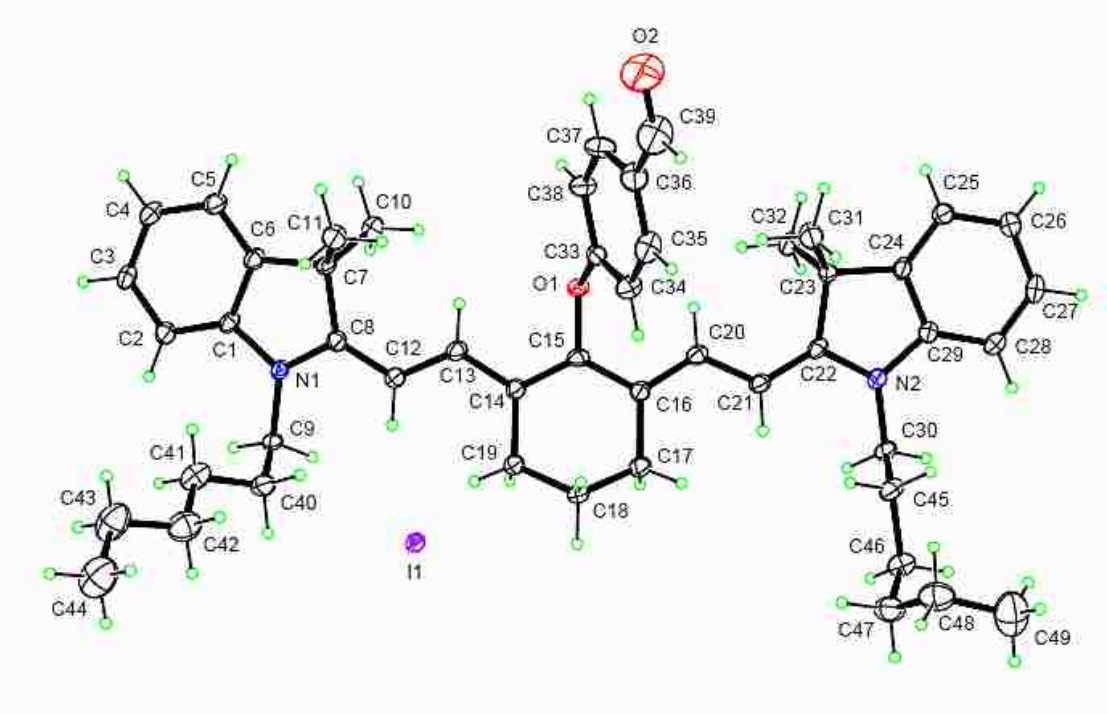
C25 C24 C29 120.2(4) . . ?
C25 C24 C23 130.6(4) . . ?
C29 C24 C23 109.1(3) . . ?
C24 C25 C26 118.0(5) . . ?
C24 C25 H25 121.0 . . ?
C26 C25 H25 121.0 . . ?
C27 C26 C25 120.8(4) . . ?
C27 C26 H26 119.6 . . ?
C25 C26 H26 119.6 . . ?
C26 C27 C28 121.5(4) . . ?
C26 C27 H27 119.3 . . ?
C28 C27 H27 119.3 . . ?
C27 C28 C29 117.4(4) . . ?
C27 C28 H28 121.3 . . ?
C29 C28 H28 121.3 . . ?
C28 C29 C24 122.1(4) . . ?
C28 C29 N2 128.5(4) . . ?
C24 C29 N2 109.4(3) . . ?
N2 C30 H30A 109.5 . . ?
N2 C30 H30B 109.5 . . ?
H30A C30 H30B 109.5 . . ?
N2 C30 H30C 109.5 . . ?
H30A C30 H30C 109.5 . . ?
H30B C30 H30C 109.5 . . ?
C23 C31 H31A 109.5 . . ?
C23 C31 H31B 109.5 . . ?
H31A C31 H31B 109.5 . . ?
C23 C31 H31C 109.5 . . ?
H31A C31 H31C 109.5 . . ?
H31B C31 H31C 109.5 . . ?
C23 C32 H32A 109.5 . . ?
C23 C32 H32B 109.5 . . ?
H32A C32 H32B 109.5 . . ?
C23 C32 H32C 109.5 . . ?
H32A C32 H32C 109.5 . . ?
H32B C32 H32C 109.5 . . ?
O1 C33 C38 115.1(3) . . ?
O1 C33 C34 124.6(3) . . ?
C38 C33 C34 120.2(3) . . ?
C35 C34 C33 118.3(3) . . ?
C35 C34 H34 120.8 . . ?
C33 C34 H34 120.8 . . ?
C36 C35 C34 121.3(3) . . ?
C36 C35 H35 119.3 . . ?
C34 C35 H35 119.3 . . ?
C37 C36 C35 119.0(3) . . ?
C37 C36 C39 119.9(3) . . ?
C35 C36 C39 121.0(3) . . ?
C38 C37 C36 120.7(3) . . ?

```
C38 C37 H37 119.6 . . ?
C36 C37 H37 119.6 . . ?
C37 C38 C33 120.3(3) . . ?
C37 C38 H38 119.9 . . ?
C33 C38 H38 119.9 . . ?
O2 C39 C36 124.0(4) . . ?
O2 C39 H39 118.0 . . ?
C36 C39 H39 118.0 . . ?

loop_
 _geom_torsion_atom_site_label_1
 _geom_torsion_atom_site_label_2
 _geom_torsion_atom_site_label_3
 _geom_torsion_atom_site_label_4
 _geom_torsion
 _geom_torsion_site_symmetry_1
 _geom_torsion_site_symmetry_2
 _geom_torsion_site_symmetry_3
 _geom_torsion_site_symmetry_4
 _geom_torsion_publ_flag
C8 N1 C1 C6 -1.0(4) . . . . ?
C9 N1 C1 C6 -178.3(3) . . . . ?
C8 N1 C1 C2 -178.9(3) . . . . ?
C9 N1 C1 C2 3.8(5) . . . . ?
C6 C1 C2 C3 -1.2(5) . . . . ?
N1 C1 C2 C3 176.3(3) . . . . ?
C1 C2 C3 C4 0.7(5) . . . . ?
C2 C3 C4 C5 -0.1(5) . . . . ?
C3 C4 C5 C6 -0.1(5) . . . . ?
C2 C1 C6 C5 1.0(5) . . . . ?
N1 C1 C6 C5 -176.9(3) . . . . ?
C2 C1 C6 C7 179.8(3) . . . . ?
N1 C1 C6 C7 1.8(3) . . . . ?
C4 C5 C6 C1 -0.3(5) . . . . ?
C4 C5 C6 C7 -178.8(3) . . . . ?
C1 C6 C7 C8 -1.8(3) . . . . ?
C5 C6 C7 C8 176.8(3) . . . . ?
C1 C6 C7 C10 115.5(3) . . . . ?
C5 C6 C7 C10 -65.9(5) . . . . ?
C1 C6 C7 C11 -120.4(3) . . . . ?
C5 C6 C7 C11 58.2(4) . . . . ?
C1 N1 C8 C12 179.0(3) . . . . ?
C9 N1 C8 C12 -3.9(5) . . . . ?
C1 N1 C8 C7 -0.2(3) . . . . ?
C9 N1 C8 C7 176.9(3) . . . . ?
C6 C7 C8 N1 1.2(3) . . . . ?
C10 C7 C8 N1 -114.6(3) . . . . ?
C11 C7 C8 N1 118.0(3) . . . . ?
C6 C7 C8 C12 -178.0(3) . . . . ?
```

C10 C7 C8 C12 66.2(4) . . . . ?
C11 C7 C8 C12 -61.2(4) . . . . ?
N1 C8 C12 C13 175.1(3) . . . . ?
C7 C8 C12 C13 -5.8(5) . . . . ?
C8 C12 C13 C14 179.1(3) . . . . ?
C12 C13 C14 C15 -178.6(3) . . . . ?
C12 C13 C14 C19 2.6(5) . . . . ?
C13 C14 C15 O1 -2.1(5) . . . . ?
C19 C14 C15 O1 176.7(3) . . . . ?
C13 C14 C15 C16 -176.0(3) . . . . ?
C19 C14 C15 C16 2.8(5) . . . . ?
C33 O1 C15 C14 76.9(4) . . . . ?
C33 O1 C15 C16 -108.6(3) . . . . ?
C14 C15 C16 C20 -173.4(3) . . . . ?
O1 C15 C16 C20 12.4(5) . . . . ?
C14 C15 C16 C17 4.8(5) . . . . ?
O1 C15 C16 C17 -169.4(3) . . . . ?
C20 C16 C17 C18 143.6(4) . . . . ?
C15 C16 C17 C18 -34.5(5) . . . . ?
C16 C17 C18 C19 56.8(5) . . . . ?
C15 C14 C19 C18 20.0(5) . . . . ?
C13 C14 C19 C18 -161.2(3) . . . . ?
C17 C18 C19 C14 -49.3(5) . . . . ?
C15 C16 C20 C21 179.5(3) . . . . ?
C17 C16 C20 C21 1.5(6) . . . . ?
C16 C20 C21 C22 -172.5(3) . . . . ?
C20 C21 C22 N2 179.0(3) . . . . ?
C20 C21 C22 C23 0.8(6) . . . . ?
C29 N2 C22 C21 -176.9(3) . . . . ?
C30 N2 C22 C21 2.6(5) . . . . ?
C29 N2 C22 C23 1.6(4) . . . . ?
C30 N2 C22 C23 -178.9(3) . . . . ?
C21 C22 C23 C24 177.0(4) . . . . ?
N2 C22 C23 C24 -1.4(3) . . . . ?
C21 C22 C23 C32 -66.1(5) . . . . ?
N2 C22 C23 C32 115.5(3) . . . . ?
C21 C22 C23 C31 59.6(5) . . . . ?
N2 C22 C23 C31 -118.8(3) . . . . ?
C22 C23 C24 C25 -179.2(4) . . . . ?
C32 C23 C24 C25 62.7(5) . . . . ?
C31 C23 C24 C25 -59.6(5) . . . . ?
C22 C23 C24 C29 0.6(4) . . . . ?
C32 C23 C24 C29 -117.4(3) . . . . ?
C31 C23 C24 C29 120.2(3) . . . . ?
C29 C24 C25 C26 -0.7(6) . . . . ?
C23 C24 C25 C26 179.1(4) . . . . ?
C24 C25 C26 C27 0.2(7) . . . . ?
C25 C26 C27 C28 0.6(8) . . . . ?
C26 C27 C28 C29 -0.7(7) . . . . ?

```
C27 C28 C29 C24 0.1(6) . . . . ?
C27 C28 C29 N2 -179.4(4) . . . . ?
C25 C24 C29 C28 0.6(6) . . . . ?
C23 C24 C29 C28 -179.3(3) . . . . ?
C25 C24 C29 N2 -179.8(4) . . . . ?
C23 C24 C29 N2 0.3(4) . . . . ?
C22 N2 C29 C28 178.3(4) . . . . ?
C30 N2 C29 C28 -1.1(6) . . . . ?
C22 N2 C29 C24 -1.2(4) . . . . ?
C30 N2 C29 C24 179.3(3) . . . . ?
C15 O1 C33 C38 -161.0(3) . . . . ?
C15 O1 C33 C34 18.5(4) . . . . ?
O1 C33 C34 C35 -178.3(3) . . . . ?
C38 C33 C34 C35 1.2(5) . . . . ?
C33 C34 C35 C36 0.6(5) . . . . ?
C34 C35 C36 C37 -2.0(5) . . . . ?
C34 C35 C36 C39 176.4(3) . . . . ?
C35 C36 C37 C38 1.6(5) . . . . ?
C39 C36 C37 C38 -176.7(3) . . . . ?
C36 C37 C38 C33 0.1(5) . . . . ?
O1 C33 C38 C37 178.0(3) . . . . ?
C34 C33 C38 C37 -1.5(5) . . . . ?
C37 C36 C39 O2 3.1(6) . . . . ?
C35 C36 C39 O2 -175.2(4) . . . . ?

_diffrn_measured_fraction_theta_max    0.994
_diffrn_reflns_theta_full              27.9
_diffrn_measured_fraction_theta_full   0.994
_refine_diff_density_max    1.59
_refine_diff_density_min   -1.06
_refine_diff_density_rms    0.097
# END OF CIF
```

APPENDIX BB: CRYSTALLOGRAPHIC DATA FOR COMPOUND 3.8




```
data_NIR-3

_audit_creation_method            SHELXL-97
_chemical_name_systematic
;
 ?
;
_chemical_name_common             ?
_chemical_melting_point           ?
_chemical_compound_source          'local laboratory'
_chemical_formula_moiety    'C49 H61 N2 O2 1+, I 1-'
_chemical_formula_sum       'C49 H61 I N2 O2'
_chemical_formula_weight          836.90

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
```

```
 'I'  'I'  -0.4742   1.8119
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'N'  'N'   0.0061   0.0033
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_space_group_name_H-M 'P 21/n        '
_symmetry_space_group_name_Hall     '-P 2yn'
_symmetry_cell_setting 'Monoclinic'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x+1/2, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x-1/2, -y-1/2, z-1/2'

_cell_length_a                    15.066(2)
_cell_length_b                    19.470(3)
_cell_length_c                    16.580(2)
_cell_angle_alpha                 90
_cell_angle_beta                  112.441(7)
_cell_angle_gamma                 90
_cell_volume                      4495.2(11)
_cell_formula_units_Z             4
_cell_measurement_temperature     90
_cell_measurement_reflns_used     9378
_cell_measurement_theta_min        2.5
_cell_measurement_theta_max        27.1

_exptl_crystal_description        plate
_exptl_crystal_colour             'blue-green/bronze dichroic'
_exptl_crystal_size_max           0.27
_exptl_crystal_size_mid           0.23
_exptl_crystal_size_min           0.05
_exptl_crystal_density_meas       ?
_exptl_crystal_density_diffrn     1.237
_exptl_crystal_density_method     'not measured'
_exptl_crystal_F_000              1752
_exptl_absorpt_coefficient_mu     0.751
_exptl_absorpt_correction_type 'multi-scan'
_exptl_absorpt_correction_T_min   0.823
_exptl_absorpt_correction_T_max   0.963
_exptl_absorpt_process_details  'HKL Scalepack (Otwinowski & Minor 1997)'

_exptl_special_details
;
 ?
```

```
;

_diffrn_ambient_temperature       90
_diffrn_radiation_wavelength      0.71073
_diffrn_radiation_type            MoK\a
_diffrn_radiation_source          'fine-focus sealed tube'
_diffrn_radiation_monochromator   graphite
_diffrn_measurement_device  'KappaCCD (with Oxford Cryostream)'
_diffrn_measurement_method       ' \w scans with \k offsets'
_diffrn_detector_area_resol_mean  ?
_diffrn_standards_number          0
_diffrn_standards_interval_count  ?
_diffrn_standards_interval_time   ?
_diffrn_standards_decay_%         <2
_diffrn_reflns_number             37226
_diffrn_reflns_av_R_equivalents   0.036
_diffrn_reflns_av_sigmaI/netI     0.0570
_diffrn_reflns_limit_h_min        -19
_diffrn_reflns_limit_h_max        19
_diffrn_reflns_limit_k_min        -24
_diffrn_reflns_limit_k_max        23
_diffrn_reflns_limit_l_min        -21
_diffrn_reflns_limit_l_max        21
_diffrn_reflns_theta_min          2.5
_diffrn_reflns_theta_max          27.1
_reflns_number_total              9881
_reflns_number_gt                 7440
_reflns_threshold_expression      I>2\s(I)

_computing_data_collection        'COLLECT (Nonius, 2000)'
_computing_cell_refinement        'HKL Scalepack (Otwinowski & Minor 1997)'
_computing_data_reduction   'HKL Denzo and Scalepack (Otwinowski & Minor 1997)'
_computing_structure_solution     'SIR97 (Altomare  et al., 1999)'
_computing_structure_refinement   'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics     'ORTEP-3 for Windows (Farrugia, 1997)'
_computing_publication_material   'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
;

_refine_ls_structure_factor_coef  Fsqd
```

```
_refine_ls_matrix_type           full
_refine_ls_weighting_scheme      calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.0335P)^2^+4.8374P] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary     direct
_atom_sites_solution_secondary   difmap
_atom_sites_solution_hydrogens   geom
_refine_ls_hydrogen_treatment    constr
_refine_ls_extinction_method     SHELXL
_refine_ls_extinction_coef       0.00129(13)
_refine_ls_extinction_expression
 'Fc^*^=kFc[1+0.001xFc^2^\l^3^/sin(2\q)]^-1/4^'
_refine_ls_number_reflns         9881
_refine_ls_number_parameters     494
_refine_ls_number_restraints     0
_refine_ls_R_factor_all          0.065
_refine_ls_R_factor_gt           0.039
_refine_ls_wR_factor_ref         0.089
_refine_ls_wR_factor_gt          0.080
_refine_ls_goodness_of_fit_ref   1.009
_refine_ls_restrained_S_all      1.009
_refine_ls_shift/su_max          0.003
_refine_ls_shift/su_mean         0.000

loop_
 _atom_site_label
 _atom_site_type_symbol
 _atom_site_fract_x
 _atom_site_fract_y
 _atom_site_fract_z
 _atom_site_U_iso_or_equiv
 _atom_site_adp_type
 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
 _atom_site_calc_flag
 _atom_site_refinement_flags
 _atom_site_disorder_assembly
 _atom_site_disorder_group
I1 I 0.151479(13) 0.595518(9) 0.128776(11) 0.01932(7) Uani 1 1 d . . .
O1 O 0.57552(13) 0.43045(9) 0.35942(12) 0.0169(4) Uani 1 1 d . . .
O2 O 0.9361(2) 0.24256(15) 0.3985(2) 0.0631(9) Uani 1 1 d . . .
N1 N 0.18082(16) 0.35305(11) 0.06228(15) 0.0181(5) Uani 1 1 d . . .
N2 N 0.80668(17) 0.67725(12) 0.60286(14) 0.0184(5) Uani 1 1 d . . .
C1 C 0.14040(19) 0.28656(14) 0.05482(17) 0.0169(6) Uani 1 1 d . . .
C2 C 0.0485(2) 0.26512(14) 0.00100(18) 0.0192(6) Uani 1 1 d . . .
H2 H 0.0038 0.2954 -0.0392 0.023 Uiso 1 1 calc R . .
C3 C 0.0261(2) 0.19663(14) 0.00955(18) 0.0200(6) Uani 1 1 d . . .
H3 H -0.0355 0.1796 -0.0261 0.024 Uiso 1 1 calc R . .
C4 C 0.0917(2) 0.15273(15) 0.06896(19) 0.0227(6) Uani 1 1 d . . .
```

H4 H 0.0738 0.1065 0.0736 0.027 Uiso 1 1 calc R . .
C5 C 0.1830(2) 0.17537(15) 0.12174(19) 0.0218(6) Uani 1 1 d . . .
H5 H 0.2278 0.1452 0.1621 0.026 Uiso 1 1 calc R . .
C6 C 0.2070(2) 0.24305(14) 0.11383(18) 0.0192(6) Uani 1 1 d . . .
C7 C 0.29867(19) 0.28296(14) 0.16244(18) 0.0188(6) Uani 1 1 d . . .
C8 C 0.27080(19) 0.35475(14) 0.12277(17) 0.0180(6) Uani 1 1 d . . .
C9 C 0.1273(2) 0.41364(14) 0.01406(18) 0.0214(6) Uani 1 1 d . . .
H9A H 0.1386 0.4526 0.0551 0.026 Uiso 1 1 calc R . .
H9B H 0.0577 0.4032 -0.0092 0.026 Uiso 1 1 calc R . .
C10 C 0.3202(2) 0.28301(15) 0.26136(18) 0.0240(6) Uani 1 1 d . . .
H10A H 0.3815 0.3063 0.2925 0.036 Uiso 1 1 calc R . .
H10B H 0.3241 0.2356 0.2822 0.036 Uiso 1 1 calc R . .
H10C H 0.2688 0.3072 0.2721 0.036 Uiso 1 1 calc R . .
C11 C 0.3831(2) 0.25275(16) 0.1442(2) 0.0265(7) Uani 1 1 d . . .
H11A H 0.3692 0.2553 0.0816 0.040 Uiso 1 1 calc R . .
H11B H 0.3925 0.2047 0.1631 0.040 Uiso 1 1 calc R . .
H11C H 0.4414 0.2790 0.1764 0.040 Uiso 1 1 calc R . .
C12 C 0.3243(2) 0.41555(14) 0.14422(18) 0.0203(6) Uani 1 1 d . . .
H12 H 0.2965 0.4554 0.1112 0.024 Uiso 1 1 calc R . .
C13 C 0.41407(19) 0.42215(14) 0.20950(18) 0.0185(6) Uani 1 1 d . . .
H13 H 0.4447 0.3818 0.2397 0.022 Uiso 1 1 calc R . .
C14 C 0.46307(19) 0.48509(14) 0.23414(17) 0.0180(6) Uani 1 1 d . . .
C15 C 0.54248(19) 0.49106(14) 0.31197(17) 0.0165(6) Uani 1 1 d . . .
C16 C 0.58543(19) 0.55393(14) 0.35052(17) 0.0165(6) Uani 1 1 d . . .
C17 C 0.5535(2) 0.61829(14) 0.29596(18) 0.0207(6) Uani 1 1 d . . .
H17A H 0.6097 0.6486 0.3068 0.025 Uiso 1 1 calc R . .
H17B H 0.5067 0.6434 0.3137 0.025 Uiso 1 1 calc R . .
C18 C 0.5075(2) 0.60161(14) 0.19858(18) 0.0205(6) Uani 1 1 d . . .
H18A H 0.4816 0.6442 0.1653 0.025 Uiso 1 1 calc R . .
H18B H 0.5568 0.5829 0.1787 0.025 Uiso 1 1 calc R . .
C19 C 0.4267(2) 0.54947(14) 0.18035(19) 0.0237(7) Uani 1 1 d . . .
H19A H 0.3743 0.5699 0.1946 0.028 Uiso 1 1 calc R . .
H19B H 0.4003 0.5375 0.1176 0.028 Uiso 1 1 calc R . .
C20 C 0.65164(19) 0.55527(14) 0.43533(17) 0.0174(6) Uani 1 1 d . . .
H20 H 0.6685 0.5128 0.4655 0.021 Uiso 1 1 calc R . .
C21 C 0.6959(2) 0.61523(14) 0.48032(17) 0.0180(6) Uani 1 1 d . . .
H21 H 0.6761 0.6578 0.4509 0.022 Uiso 1 1 calc R . .
C22 C 0.76536(19) 0.61719(14) 0.56308(17) 0.0166(6) Uani 1 1 d . . .
C23 C 0.8090(2) 0.55746(14) 0.62676(18) 0.0191(6) Uani 1 1 d . . .
C24 C 0.88296(19) 0.59508(15) 0.70392(17) 0.0186(6) Uani 1 1 d . . .
C25 C 0.9466(2) 0.57044(16) 0.78297(18) 0.0228(6) Uani 1 1 d . . .
H25 H 0.9495 0.5228 0.7961 0.027 Uiso 1 1 calc R . .
C26 C 1.0069(2) 0.61722(15) 0.84332(19) 0.0239(7) Uani 1 1 d . . .
H26 H 1.0514 0.6013 0.8980 0.029 Uiso 1 1 calc R . .
C27 C 1.0016(2) 0.68700(16) 0.82340(18) 0.0239(7) Uani 1 1 d . . .
H27 H 1.0434 0.7180 0.8648 0.029 Uiso 1 1 calc R . .
C28 C 0.9371(2) 0.71234(15) 0.74484(17) 0.0200(6) Uani 1 1 d . . .
H28 H 0.9334 0.7600 0.7318 0.024 Uiso 1 1 calc R . .
C29 C 0.87823(19) 0.66515(14) 0.68599(17) 0.0172(6) Uani 1 1 d . . .

```
C30 C 0.7768(2) 0.74577(13) 0.56621(18) 0.0186(6) Uani 1 1 d . . .
H30A H 0.7968 0.7797 0.6143 0.022 Uiso 1 1 calc R . .
H30B H 0.7058 0.7470 0.5381 0.022 Uiso 1 1 calc R . .
C31 C 0.8597(2) 0.50405(16) 0.5908(2) 0.0320(8) Uani 1 1 d . . .
H31A H 0.9061 0.5273 0.5718 0.048 Uiso 1 1 calc R . .
H31B H 0.8120 0.4801 0.5411 0.048 Uiso 1 1 calc R . .
H31C H 0.8934 0.4707 0.6366 0.048 Uiso 1 1 calc R . .
C32 C 0.7319(2) 0.52400(16) 0.65398(19) 0.0286(7) Uani 1 1 d . . .
H32A H 0.7624 0.4909 0.7009 0.043 Uiso 1 1 calc R . .
H32B H 0.6847 0.5003 0.6037 0.043 Uiso 1 1 calc R . .
H32C H 0.6996 0.5596 0.6746 0.043 Uiso 1 1 calc R . .
C33 C 0.65907(19) 0.40165(14) 0.35907(16) 0.0169(5) Uani 1 1 d . . .
C34 C 0.7232(2) 0.43566(16) 0.33065(18) 0.0240(6) Uani 1 1 d . . .
H34 H 0.7100 0.4809 0.3076 0.029 Uiso 1 1 calc R . .
C35 C 0.8070(2) 0.40207(17) 0.3367(2) 0.0285(7) Uani 1 1 d . . .
H35 H 0.8517 0.4249 0.3182 0.034 Uiso 1 1 calc R . .
C36 C 0.8262(2) 0.33585(17) 0.3692(2) 0.0290(7) Uani 1 1 d . . .
C37 C 0.7603(2) 0.30230(16) 0.39593(19) 0.0278(7) Uani 1 1 d . . .
H37 H 0.7724 0.2564 0.4169 0.033 Uiso 1 1 calc R . .
C38 C 0.6777(2) 0.33534(15) 0.39214(18) 0.0233(6) Uani 1 1 d . . .
H38 H 0.6338 0.3128 0.4120 0.028 Uiso 1 1 calc R . .
C39 C 0.9151(3) 0.3017(2) 0.3742(3) 0.0478(10) Uani 1 1 d . . .
H39 H 0.9590 0.3273 0.3575 0.057 Uiso 1 1 calc R . .
C40 C 0.1559(2) 0.43522(16) -0.0617(2) 0.0295(7) Uani 1 1 d . . .
H40A H 0.1279 0.4809 -0.0828 0.035 Uiso 1 1 calc R . .
H40B H 0.2267 0.4399 -0.0394 0.035 Uiso 1 1 calc R . .
C41 C 0.1243(3) 0.38569(17) -0.1383(2) 0.0342(8) Uani 1 1 d . . .
H41A H 0.0543 0.3778 -0.1577 0.041 Uiso 1 1 calc R . .
H41B H 0.1569 0.3411 -0.1187 0.041 Uiso 1 1 calc R . .
C42 C 0.1465(3) 0.41163(19) -0.2155(2) 0.0392(8) Uani 1 1 d . . .
H42A H 0.2169 0.4160 -0.1971 0.047 Uiso 1 1 calc R . .
H42B H 0.1184 0.4580 -0.2317 0.047 Uiso 1 1 calc R . .
C43 C 0.1082(3) 0.3653(2) -0.2960(2) 0.0486(10) Uani 1 1 d . . .
H43A H 0.1408 0.3202 -0.2812 0.058 Uiso 1 1 calc R . .
H43B H 0.0388 0.3575 -0.3111 0.058 Uiso 1 1 calc R . .
C44 C 0.1223(3) 0.3940(2) -0.3752(3) 0.0559(11) Uani 1 1 d . . .
H44A H 0.0922 0.4394 -0.3893 0.084 Uiso 1 1 calc R . .
H44B H 0.0926 0.3631 -0.4250 0.084 Uiso 1 1 calc R . .
H44C H 0.1911 0.3981 -0.3627 0.084 Uiso 1 1 calc R . .
C45 C 0.8188(2) 0.76662(14) 0.49936(19) 0.0221(6) Uani 1 1 d . . .
H45A H 0.7978 0.7335 0.4503 0.026 Uiso 1 1 calc R . .
H45B H 0.8898 0.7651 0.5268 0.026 Uiso 1 1 calc R . .
C46 C 0.7866(2) 0.83934(15) 0.46425(19) 0.0260(7) Uani 1 1 d . . .
H46A H 0.7172 0.8444 0.4520 0.031 Uiso 1 1 calc R . .
H46B H 0.8217 0.8732 0.5098 0.031 Uiso 1 1 calc R . .
C47 C 0.8041(3) 0.85534(18) 0.3811(2) 0.0335(8) Uani 1 1 d . . .
H47A H 0.7672 0.8221 0.3354 0.040 Uiso 1 1 calc R . .
H47B H 0.7784 0.9017 0.3606 0.040 Uiso 1 1 calc R . .
C48 C 0.9083(3) 0.85293(19) 0.3907(2) 0.0389(9) Uani 1 1 d . . .
```

```
H48A H 0.9113 0.8582 0.3324 0.047 Uiso 1 1 calc R . .
H48B H 0.9353 0.8073 0.4137 0.047 Uiso 1 1 calc R . .
C49 C 0.9701(3) 0.9084(2) 0.4512(3) 0.0603(12) Uani 1 1 d . . .
H49A H 0.9411 0.9536 0.4315 0.091 Uiso 1 1 calc R . .
H49B H 1.0347 0.9073 0.4502 0.091 Uiso 1 1 calc R . .
H49C H 0.9742 0.9001 0.5108 0.091 Uiso 1 1 calc R . .

loop_
 _atom_site_aniso_label
 _atom_site_aniso_U_11
 _atom_site_aniso_U_22
 _atom_site_aniso_U_33
 _atom_site_aniso_U_23
 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
I1 0.01561(10) 0.01293(9) 0.02478(11) 0.00072(8) 0.00253(7) -0.00016(8)
O1 0.0118(9) 0.0131(9) 0.0249(10) 0.0028(8) 0.0061(8) 0.0022(8)
O2 0.0407(16) 0.0445(18) 0.102(2) -0.0049(16) 0.0246(16) 0.0201(14)
N1 0.0122(11) 0.0122(11) 0.0250(12) -0.0012(10) 0.0016(10) -0.0010(9)
N2 0.0180(12) 0.0144(12) 0.0211(12) -0.0013(9) 0.0055(10) -0.0023(10)
C1 0.0154(13) 0.0128(13) 0.0240(14) -0.0029(11) 0.0093(12) 0.0003(11)
C2 0.0148(13) 0.0174(14) 0.0238(15) -0.0019(11) 0.0055(12) 0.0006(11)
C3 0.0163(14) 0.0171(14) 0.0269(15) -0.0065(12) 0.0086(12) -0.0043(11)
C4 0.0245(16) 0.0144(14) 0.0308(16) -0.0033(12) 0.0122(13) -0.0027(12)
C5 0.0205(14) 0.0154(14) 0.0285(16) 0.0003(12) 0.0081(13) 0.0014(12)
C6 0.0152(13) 0.0155(14) 0.0264(15) -0.0015(12) 0.0075(12) -0.0016(11)
C7 0.0150(13) 0.0120(13) 0.0252(15) -0.0011(11) 0.0031(12) 0.0015(11)
C8 0.0124(13) 0.0171(14) 0.0223(14) -0.0013(11) 0.0041(11) 0.0006(11)
C9 0.0169(14) 0.0112(14) 0.0277(15) 0.0014(11) -0.0011(12) 0.0025(11)
C10 0.0235(15) 0.0191(15) 0.0261(15) 0.0000(12) 0.0059(13) -0.0051(13)
C11 0.0169(14) 0.0226(16) 0.0365(17) -0.0031(13) 0.0064(13) 0.0024(12)
C12 0.0176(14) 0.0150(15) 0.0240(15) 0.0013(11) 0.0031(12) -0.0009(11)
C13 0.0141(13) 0.0142(14) 0.0257(15) 0.0019(11) 0.0057(12) 0.0004(11)
C14 0.0129(13) 0.0146(14) 0.0238(15) -0.0003(11) 0.0041(11) 0.0000(11)
C15 0.0154(13) 0.0130(13) 0.0216(14) 0.0026(11) 0.0077(11) 0.0041(11)
C16 0.0126(13) 0.0143(14) 0.0219(14) -0.0014(11) 0.0058(11) 0.0009(11)
C17 0.0201(14) 0.0138(13) 0.0254(15) -0.0016(11) 0.0056(12) 0.0012(11)
C18 0.0203(14) 0.0129(13) 0.0239(14) 0.0023(11) 0.0035(12) 0.0007(12)
C19 0.0190(15) 0.0154(14) 0.0282(16) 0.0026(12) -0.0005(13) -0.0014(12)
C20 0.0147(14) 0.0139(14) 0.0244(15) 0.0010(11) 0.0086(12) 0.0005(11)
C21 0.0189(14) 0.0123(13) 0.0227(14) 0.0011(11) 0.0081(12) 0.0007(11)
C22 0.0167(14) 0.0121(13) 0.0226(14) -0.0032(11) 0.0094(12) -0.0002(11)
C23 0.0152(14) 0.0132(14) 0.0234(15) -0.0005(11) 0.0013(12) 0.0007(11)
C24 0.0160(13) 0.0151(13) 0.0227(14) -0.0049(12) 0.0051(11) -0.0022(12)
C25 0.0180(15) 0.0174(14) 0.0292(16) 0.0020(12) 0.0048(13) -0.0004(12)
C26 0.0194(15) 0.0249(16) 0.0235(15) -0.0001(12) 0.0040(13) -0.0017(12)
C27 0.0208(15) 0.0256(16) 0.0243(15) -0.0088(12) 0.0075(13) -0.0080(13)
C28 0.0229(15) 0.0153(14) 0.0231(15) -0.0020(12) 0.0101(12) -0.0022(12)
C29 0.0158(14) 0.0169(14) 0.0187(14) -0.0024(11) 0.0065(11) -0.0010(11)
```

```
C30 0.0215(14) 0.0106(13) 0.0228(14) -0.0010(11) 0.0075(12) 0.0010(11)
C31 0.0269(17) 0.0210(16) 0.0361(18) -0.0109(14) -0.0013(14) 0.0098(14)
C32 0.0300(17) 0.0219(16) 0.0270(16) 0.0026(13) 0.0031(14) -0.0102(14)
C33 0.0179(13) 0.0163(13) 0.0145(12) -0.0020(11) 0.0039(11) 0.0036(12)
C34 0.0263(16) 0.0192(15) 0.0276(16) 0.0002(12) 0.0114(13) 0.0010(13)
C35 0.0255(16) 0.0280(17) 0.0360(17) -0.0075(14) 0.0161(14) -0.0031(15)
C36 0.0241(17) 0.0277(17) 0.0337(17) -0.0058(14) 0.0095(14) 0.0053(13)
C37 0.0305(17) 0.0229(16) 0.0306(17) 0.0070(13) 0.0125(14) 0.0109(14)
C38 0.0241(16) 0.0198(15) 0.0269(16) 0.0060(12) 0.0107(13) 0.0033(13)
C39 0.0304(19) 0.044(2) 0.073(3) -0.011(2) 0.0236(19) 0.0061(18)
C40 0.0249(16) 0.0202(16) 0.0351(18) 0.0076(14) 0.0022(14) -0.0029(13)
C41 0.039(2) 0.0243(17) 0.0423(19) 0.0002(14) 0.0184(17) -0.0035(15)
C42 0.039(2) 0.036(2) 0.046(2) 0.0031(16) 0.0205(17) -0.0014(17)
C43 0.059(3) 0.043(2) 0.054(2) -0.0089(19) 0.033(2) -0.014(2)
C44 0.076(3) 0.050(3) 0.054(2) -0.011(2) 0.039(2) -0.009(2)
C45 0.0236(15) 0.0145(14) 0.0296(16) -0.0008(12) 0.0118(13) -0.0006(12)
C46 0.0301(17) 0.0197(15) 0.0301(16) 0.0022(13) 0.0136(14) 0.0016(13)
C47 0.043(2) 0.0286(18) 0.0285(17) 0.0061(14) 0.0125(15) 0.0038(16)
C48 0.050(2) 0.040(2) 0.0327(18) 0.0080(16) 0.0224(17) 0.0033(18)
C49 0.058(3) 0.081(3) 0.046(2) -0.005(2) 0.024(2) -0.024(3)

_geom_special_details
;
 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
;

loop_
 _geom_bond_atom_site_label_1
 _geom_bond_atom_site_label_2
 _geom_bond_distance
 _geom_bond_site_symmetry_2
 _geom_bond_publ_flag
O1 C33 1.380(3) . ?
O1 C15 1.400(3) . ?
O2 C39 1.221(5) . ?
N1 C8 1.344(3) . ?
N1 C1 1.416(3) . ?
N1 C9 1.480(3) . ?
N2 C22 1.370(3) . ?
N2 C29 1.408(3) . ?
N2 C30 1.464(3) . ?
C1 C6 1.390(4) . ?
C1 C2 1.394(4) . ?
C2 C3 1.396(4) . ?
```

```
C2 H2 0.9500 . ?
C3 C4 1.390(4) . ?
C3 H3 0.9500 . ?
C4 C5 1.391(4) . ?
C4 H4 0.9500 . ?
C5 C6 1.386(4) . ?
C5 H5 0.9500 . ?
C6 C7 1.521(4) . ?
C7 C11 1.532(4) . ?
C7 C8 1.533(4) . ?
C7 C10 1.545(4) . ?
C8 C12 1.400(4) . ?
C9 C40 1.534(4) . ?
C9 H9A 0.9900 . ?
C9 H9B 0.9900 . ?
C10 H10A 0.9800 . ?
C10 H10B 0.9800 . ?
C10 H10C 0.9800 . ?
C11 H11A 0.9800 . ?
C11 H11B 0.9800 . ?
C11 H11C 0.9800 . ?
C12 C13 1.378(4) . ?
C12 H12 0.9500 . ?
C13 C14 1.408(4) . ?
C13 H13 0.9500 . ?
C14 C15 1.390(4) . ?
C14 C19 1.515(4) . ?
C15 C16 1.418(4) . ?
C16 C20 1.379(4) . ?
C16 C17 1.513(4) . ?
C17 C18 1.529(4) . ?
C17 H17A 0.9900 . ?
C17 H17B 0.9900 . ?
C18 C19 1.524(4) . ?
C18 H18A 0.9900 . ?
C18 H18B 0.9900 . ?
C19 H19A 0.9900 . ?
C19 H19B 0.9900 . ?
C20 C21 1.409(4) . ?
C20 H20 0.9500 . ?
C21 C22 1.372(4) . ?
C21 H21 0.9500 . ?
C22 C23 1.539(4) . ?
C23 C24 1.525(4) . ?
C23 C31 1.539(4) . ?
C23 C32 1.542(4) . ?
C24 C25 1.381(4) . ?
C24 C29 1.392(4) . ?
C25 C26 1.400(4) . ?
```

C25 H25 0.9500 . ?
C26 C27 1.393(4) . ?
C26 H26 0.9500 . ?
C27 C28 1.385(4) . ?
C27 H27 0.9500 . ?
C28 C29 1.387(4) . ?
C28 H28 0.9500 . ?
C30 C45 1.526(4) . ?
C30 H30A 0.9900 . ?
C30 H30B 0.9900 . ?
C31 H31A 0.9800 . ?
C31 H31B 0.9800 . ?
C31 H31C 0.9800 . ?
C32 H32A 0.9800 . ?
C32 H32B 0.9800 . ?
C32 H32C 0.9800 . ?
C33 C38 1.389(4) . ?
C33 C34 1.394(4) . ?
C34 C35 1.391(4) . ?
C34 H34 0.9500 . ?
C35 C36 1.385(5) . ?
C35 H35 0.9500 . ?
C36 C37 1.394(5) . ?
C36 C39 1.468(5) . ?
C37 C38 1.382(4) . ?
C37 H37 0.9500 . ?
C38 H38 0.9500 . ?
C39 H39 0.9500 . ?
C40 C41 1.520(4) . ?
C40 H40A 0.9900 . ?
C40 H40B 0.9900 . ?
C41 C42 1.527(5) . ?
C41 H41A 0.9900 . ?
C41 H41B 0.9900 . ?
C42 C43 1.529(5) . ?
C42 H42A 0.9900 . ?
C42 H42B 0.9900 . ?
C43 C44 1.515(5) . ?
C43 H43A 0.9900 . ?
C43 H43B 0.9900 . ?
C44 H44A 0.9800 . ?
C44 H44B 0.9800 . ?
C44 H44C 0.9800 . ?
C45 C46 1.537(4) . ?
C45 H45A 0.9900 . ?
C45 H45B 0.9900 . ?
C46 C47 1.531(4) . ?
C46 H46A 0.9900 . ?
C46 H46B 0.9900 . ?

```
C47 C48 1.518(5) . ?
C47 H47A 0.9900 . ?
C47 H47B 0.9900 . ?
C48 C49 1.526(5) . ?
C48 H48A 0.9900 . ?
C48 H48B 0.9900 . ?
C49 H49A 0.9800 . ?
C49 H49B 0.9800 . ?
C49 H49C 0.9800 . ?

loop_
 _geom_angle_atom_site_label_1
 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
C33 O1 C15 118.0(2) . . ?
C8 N1 C1 111.4(2) . . ?
C8 N1 C9 124.8(2) . . ?
C1 N1 C9 123.7(2) . . ?
C22 N2 C29 111.5(2) . . ?
C22 N2 C30 124.5(2) . . ?
C29 N2 C30 123.9(2) . . ?
C6 C1 C2 122.8(3) . . ?
C6 C1 N1 109.0(2) . . ?
C2 C1 N1 128.2(2) . . ?
C1 C2 C3 116.1(3) . . ?
C1 C2 H2 121.9 . . ?
C3 C2 H2 121.9 . . ?
C4 C3 C2 121.7(3) . . ?
C4 C3 H3 119.2 . . ?
C2 C3 H3 119.2 . . ?
C3 C4 C5 121.0(3) . . ?
C3 C4 H4 119.5 . . ?
C5 C4 H4 119.5 . . ?
C6 C5 C4 118.2(3) . . ?
C6 C5 H5 120.9 . . ?
C4 C5 H5 120.9 . . ?
C5 C6 C1 120.1(3) . . ?
C5 C6 C7 130.7(3) . . ?
C1 C6 C7 109.1(2) . . ?
C6 C7 C11 110.7(2) . . ?
C6 C7 C8 101.2(2) . . ?
C11 C7 C8 112.2(2) . . ?
C6 C7 C10 110.1(2) . . ?
C11 C7 C10 110.8(2) . . ?
C8 C7 C10 111.5(2) . . ?
```

N1 C8 C12 122.0(2) . . ?
N1 C8 C7 109.3(2) . . ?
C12 C8 C7 128.7(2) . . ?
N1 C9 C40 113.2(2) . . ?
N1 C9 H9A 108.9 . . ?
C40 C9 H9A 108.9 . . ?
N1 C9 H9B 108.9 . . ?
C40 C9 H9B 108.9 . . ?
H9A C9 H9B 107.7 . . ?
C7 C10 H10A 109.5 . . ?
C7 C10 H10B 109.5 . . ?
H10A C10 H10B 109.5 . . ?
C7 C10 H10C 109.5 . . ?
H10A C10 H10C 109.5 . . ?
H10B C10 H10C 109.5 . . ?
C7 C11 H11A 109.5 . . ?
C7 C11 H11B 109.5 . . ?
H11A C11 H11B 109.5 . . ?
C7 C11 H11C 109.5 . . ?
H11A C11 H11C 109.5 . . ?
H11B C11 H11C 109.5 . . ?
C13 C12 C8 125.2(3) . . ?
C13 C12 H12 117.4 . . ?
C8 C12 H12 117.4 . . ?
C12 C13 C14 123.9(3) . . ?
C12 C13 H13 118.1 . . ?
C14 C13 H13 118.1 . . ?
C15 C14 C13 120.8(2) . . ?
C15 C14 C19 117.9(2) . . ?
C13 C14 C19 121.2(2) . . ?
C14 C15 O1 116.5(2) . . ?
C14 C15 C16 125.0(2) . . ?
O1 C15 C16 118.1(2) . . ?
C20 C16 C15 120.3(2) . . ?
C20 C16 C17 122.4(2) . . ?
C15 C16 C17 117.4(2) . . ?
C16 C17 C18 111.6(2) . . ?
C16 C17 H17A 109.3 . . ?
C18 C17 H17A 109.3 . . ?
C16 C17 H17B 109.3 . . ?
C18 C17 H17B 109.3 . . ?
H17A C17 H17B 108.0 . . ?
C19 C18 C17 110.9(2) . . ?
C19 C18 H18A 109.5 . . ?
C17 C18 H18A 109.5 . . ?
C19 C18 H18B 109.5 . . ?
C17 C18 H18B 109.5 . . ?
H18A C18 H18B 108.0 . . ?
C14 C19 C18 110.6(2) . . ?

C14 C19 H19A 109.5 . . ?
C18 C19 H19A 109.5 . . ?
C14 C19 H19B 109.5 . . ?
C18 C19 H19B 109.5 . . ?
H19A C19 H19B 108.1 . . ?
C16 C20 C21 124.6(3) . . ?
C16 C20 H20 117.7 . . ?
C21 C20 H20 117.7 . . ?
C22 C21 C20 125.4(3) . . ?
C22 C21 H21 117.3 . . ?
C20 C21 H21 117.3 . . ?
N2 C22 C21 122.6(2) . . ?
N2 C22 C23 108.5(2) . . ?
C21 C22 C23 128.9(2) . . ?
C24 C23 C31 109.7(2) . . ?
C24 C23 C22 101.3(2) . . ?
C31 C23 C22 113.0(2) . . ?
C24 C23 C32 110.4(2) . . ?
C31 C23 C32 111.6(3) . . ?
C22 C23 C32 110.3(2) . . ?
C25 C24 C29 120.2(3) . . ?
C25 C24 C23 130.5(3) . . ?
C29 C24 C23 109.3(2) . . ?
C24 C25 C26 118.6(3) . . ?
C24 C25 H25 120.7 . . ?
C26 C25 H25 120.7 . . ?
C27 C26 C25 120.2(3) . . ?
C27 C26 H26 119.9 . . ?
C25 C26 H26 119.9 . . ?
C28 C27 C26 121.7(3) . . ?
C28 C27 H27 119.1 . . ?
C26 C27 H27 119.1 . . ?
C27 C28 C29 117.2(3) . . ?
C27 C28 H28 121.4 . . ?
C29 C28 H28 121.4 . . ?
C28 C29 C24 122.2(2) . . ?
C28 C29 N2 128.5(3) . . ?
C24 C29 N2 109.3(2) . . ?
N2 C30 C45 113.4(2) . . ?
N2 C30 H30A 108.9 . . ?
C45 C30 H30A 108.9 . . ?
N2 C30 H30B 108.9 . . ?
C45 C30 H30B 108.9 . . ?
H30A C30 H30B 107.7 . . ?
C23 C31 H31A 109.5 . . ?
C23 C31 H31B 109.5 . . ?
H31A C31 H31B 109.5 . . ?
C23 C31 H31C 109.5 . . ?
H31A C31 H31C 109.5 . . ?

H31B C31 H31C 109.5 . . ?
C23 C32 H32A 109.5 . . ?
C23 C32 H32B 109.5 . . ?
H32A C32 H32B 109.5 . . ?
C23 C32 H32C 109.5 . . ?
H32A C32 H32C 109.5 . . ?
H32B C32 H32C 109.5 . . ?
O1 C33 C38 115.0(2) . . ?
O1 C33 C34 124.0(3) . . ?
C38 C33 C34 120.9(3) . . ?
C35 C34 C33 118.7(3) . . ?
C35 C34 H34 120.7 . . ?
C33 C34 H34 120.7 . . ?
C36 C35 C34 121.0(3) . . ?
C36 C35 H35 119.5 . . ?
C34 C35 H35 119.5 . . ?
C35 C36 C37 119.4(3) . . ?
C35 C36 C39 119.6(3) . . ?
C37 C36 C39 120.9(3) . . ?
C38 C37 C36 120.4(3) . . ?
C38 C37 H37 119.8 . . ?
C36 C37 H37 119.8 . . ?
C37 C38 C33 119.5(3) . . ?
C37 C38 H38 120.2 . . ?
C33 C38 H38 120.2 . . ?
O2 C39 C36 124.2(4) . . ?
O2 C39 H39 117.9 . . ?
C36 C39 H39 117.9 . . ?
C41 C40 C9 114.5(3) . . ?
C41 C40 H40A 108.6 . . ?
C9 C40 H40A 108.6 . . ?
C41 C40 H40B 108.6 . . ?
C9 C40 H40B 108.6 . . ?
H40A C40 H40B 107.6 . . ?
C40 C41 C42 113.1(3) . . ?
C40 C41 H41A 109.0 . . ?
C42 C41 H41A 109.0 . . ?
C40 C41 H41B 109.0 . . ?
C42 C41 H41B 109.0 . . ?
H41A C41 H41B 107.8 . . ?
C41 C42 C43 113.9(3) . . ?
C41 C42 H42A 108.8 . . ?
C43 C42 H42A 108.8 . . ?
C41 C42 H42B 108.8 . . ?
C43 C42 H42B 108.8 . . ?
H42A C42 H42B 107.7 . . ?
C44 C43 C42 114.1(3) . . ?
C44 C43 H43A 108.7 . . ?
C42 C43 H43A 108.7 . . ?

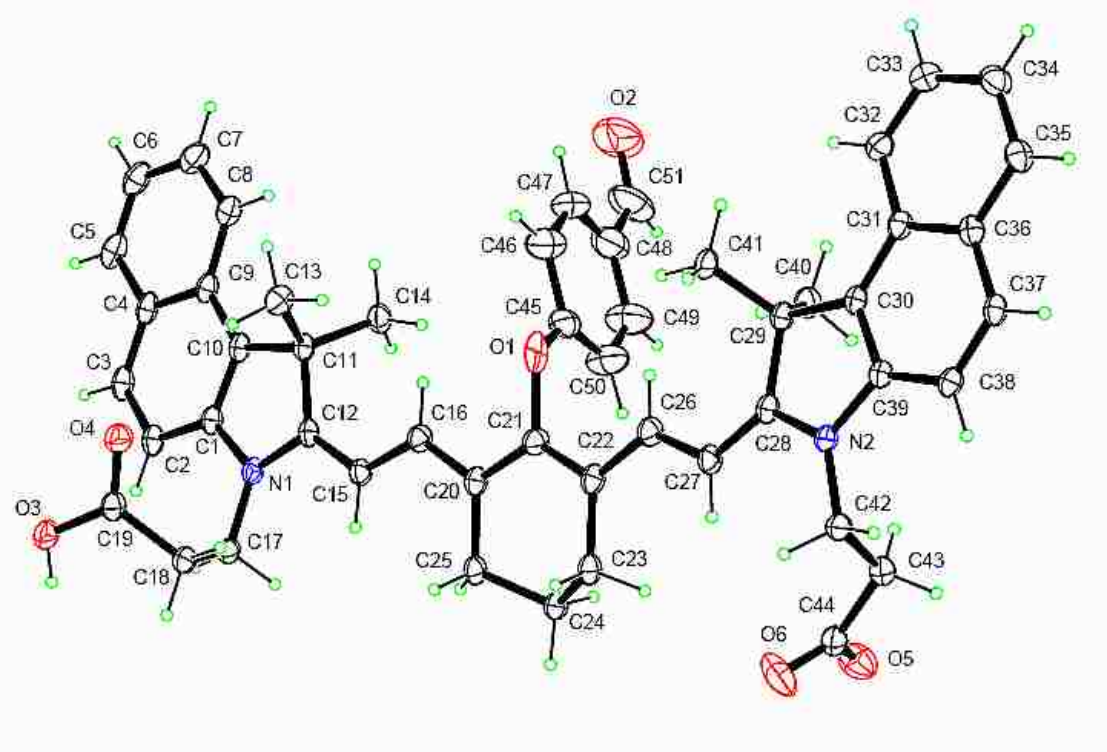
```
C44 C43 H43B 108.7 . . ?
C42 C43 H43B 108.7 . . ?
H43A C43 H43B 107.6 . . ?
C43 C44 H44A 109.5 . . ?
C43 C44 H44B 109.5 . . ?
H44A C44 H44B 109.5 . . ?
C43 C44 H44C 109.5 . . ?
H44A C44 H44C 109.5 . . ?
H44B C44 H44C 109.5 . . ?
C30 C45 C46 111.2(2) . . ?
C30 C45 H45A 109.4 . . ?
C46 C45 H45A 109.4 . . ?
C30 C45 H45B 109.4 . . ?
C46 C45 H45B 109.4 . . ?
H45A C45 H45B 108.0 . . ?
C47 C46 C45 113.0(3) . . ?
C47 C46 H46A 109.0 . . ?
C45 C46 H46A 109.0 . . ?
C47 C46 H46B 109.0 . . ?
C45 C46 H46B 109.0 . . ?
H46A C46 H46B 107.8 . . ?
C48 C47 C46 115.3(3) . . ?
C48 C47 H47A 108.5 . . ?
C46 C47 H47A 108.5 . . ?
C48 C47 H47B 108.5 . . ?
C46 C47 H47B 108.5 . . ?
H47A C47 H47B 107.5 . . ?
C47 C48 C49 113.2(3) . . ?
C47 C48 H48A 108.9 . . ?
C49 C48 H48A 108.9 . . ?
C47 C48 H48B 108.9 . . ?
C49 C48 H48B 108.9 . . ?
H48A C48 H48B 107.7 . . ?
C48 C49 H49A 109.5 . . ?
C48 C49 H49B 109.5 . . ?
H49A C49 H49B 109.5 . . ?
C48 C49 H49C 109.5 . . ?
H49A C49 H49C 109.5 . . ?
H49B C49 H49C 109.5 . . ?

loop_
 _geom_torsion_atom_site_label_1
 _geom_torsion_atom_site_label_2
 _geom_torsion_atom_site_label_3
 _geom_torsion_atom_site_label_4
 _geom_torsion
 _geom_torsion_site_symmetry_1
 _geom_torsion_site_symmetry_2
 _geom_torsion_site_symmetry_3
```

```
 _geom_torsion_site_symmetry_4
 _geom_torsion_publ_flag
C8 N1 C1 C6 0.5(3) . . . . ?
C9 N1 C1 C6 -175.1(2) . . . . ?
C8 N1 C1 C2 178.4(3) . . . . ?
C9 N1 C1 C2 2.8(4) . . . . ?
C6 C1 C2 C3 0.2(4) . . . . ?
N1 C1 C2 C3 -177.4(3) . . . . ?
C1 C2 C3 C4 0.5(4) . . . . ?
C2 C3 C4 C5 -0.7(4) . . . . ?
C3 C4 C5 C6 0.2(4) . . . . ?
C4 C5 C6 C1 0.4(4) . . . . ?
C4 C5 C6 C7 178.8(3) . . . . ?
C2 C1 C6 C5 -0.7(4) . . . . ?
N1 C1 C6 C5 177.4(3) . . . . ?
C2 C1 C6 C7 -179.3(3) . . . . ?
N1 C1 C6 C7 -1.3(3) . . . . ?
C5 C6 C7 C11 63.9(4) . . . . ?
C1 C6 C7 C11 -117.6(3) . . . . ?
C5 C6 C7 C8 -177.0(3) . . . . ?
C1 C6 C7 C8 1.5(3) . . . . ?
C5 C6 C7 C10 -58.9(4) . . . . ?
C1 C6 C7 C10 119.5(3) . . . . ?
C1 N1 C8 C12 -177.5(3) . . . . ?
C9 N1 C8 C12 -2.0(4) . . . . ?
C1 N1 C8 C7 0.5(3) . . . . ?
C9 N1 C8 C7 176.0(2) . . . . ?
C6 C7 C8 N1 -1.2(3) . . . . ?
C11 C7 C8 N1 116.9(3) . . . . ?
C10 C7 C8 N1 -118.2(3) . . . . ?
C6 C7 C8 C12 176.7(3) . . . . ?
C11 C7 C8 C12 -65.3(4) . . . . ?
C10 C7 C8 C12 59.7(4) . . . . ?
C8 N1 C9 C40 79.3(3) . . . . ?
C1 N1 C9 C40 -105.7(3) . . . . ?
N1 C8 C12 C13 175.3(3) . . . . ?
C7 C8 C12 C13 -2.3(5) . . . . ?
C8 C12 C13 C14 -174.8(3) . . . . ?
C12 C13 C14 C15 165.5(3) . . . . ?
C12 C13 C14 C19 -9.8(5) . . . . ?
C13 C14 C15 O1 5.7(4) . . . . ?
C19 C14 C15 O1 -178.9(2) . . . . ?
C13 C14 C15 C16 -167.5(3) . . . . ?
C19 C14 C15 C16 8.0(4) . . . . ?
C33 O1 C15 C14 105.9(3) . . . . ?
C33 O1 C15 C16 -80.5(3) . . . . ?
C14 C15 C16 C20 167.4(3) . . . . ?
O1 C15 C16 C20 -5.7(4) . . . . ?
C14 C15 C16 C17 -10.9(4) . . . . ?
```

```
O1 C15 C16 C17 176.0(2) . . . . ?
C20 C16 C17 C18 161.2(3) . . . . ?
C15 C16 C17 C18 -20.5(4) . . . . ?
C16 C17 C18 C19 53.4(3) . . . . ?
C15 C14 C19 C18 26.0(4) . . . . ?
C13 C14 C19 C18 -158.6(3) . . . . ?
C17 C18 C19 C14 -56.1(3) . . . . ?
C15 C16 C20 C21 -177.9(3) . . . . ?
C17 C16 C20 C21 0.4(4) . . . . ?
C16 C20 C21 C22 -176.6(3) . . . . ?
C29 N2 C22 C21 -177.7(3) . . . . ?
C30 N2 C22 C21 5.6(4) . . . . ?
C29 N2 C22 C23 3.1(3) . . . . ?
C30 N2 C22 C23 -173.6(2) . . . . ?
C20 C21 C22 N2 179.1(3) . . . . ?
C20 C21 C22 C23 -1.9(5) . . . . ?
N2 C22 C23 C24 -2.8(3) . . . . ?
C21 C22 C23 C24 178.1(3) . . . . ?
N2 C22 C23 C31 -120.1(3) . . . . ?
C21 C22 C23 C31 60.8(4) . . . . ?
N2 C22 C23 C32 114.2(3) . . . . ?
C21 C22 C23 C32 -64.9(4) . . . . ?
C31 C23 C24 C25 -60.3(4) . . . . ?
C22 C23 C24 C25 180.0(3) . . . . ?
C32 C23 C24 C25 63.1(4) . . . . ?
C31 C23 C24 C29 121.2(3) . . . . ?
C22 C23 C24 C29 1.6(3) . . . . ?
C32 C23 C24 C29 -115.3(3) . . . . ?
C29 C24 C25 C26 -1.1(4) . . . . ?
C23 C24 C25 C26 -179.4(3) . . . . ?
C24 C25 C26 C27 0.3(4) . . . . ?
C25 C26 C27 C28 0.6(5) . . . . ?
C26 C27 C28 C29 -0.7(4) . . . . ?
C27 C28 C29 C24 -0.2(4) . . . . ?
C27 C28 C29 N2 179.3(3) . . . . ?
C25 C24 C29 C28 1.1(4) . . . . ?
C23 C24 C29 C28 179.7(3) . . . . ?
C25 C24 C29 N2 -178.5(3) . . . . ?
C23 C24 C29 N2 0.1(3) . . . . ?
C22 N2 C29 C28 178.4(3) . . . . ?
C30 N2 C29 C28 -4.9(4) . . . . ?
C22 N2 C29 C24 -2.1(3) . . . . ?
C30 N2 C29 C24 174.6(2) . . . . ?
C22 N2 C30 C45 -81.7(3) . . . . ?
C29 N2 C30 C45 102.1(3) . . . . ?
C15 O1 C33 C38 -167.7(2) . . . . ?
C15 O1 C33 C34 14.2(4) . . . . ?
O1 C33 C34 C35 177.5(2) . . . . ?
C38 C33 C34 C35 -0.5(4) . . . . ?
```

```
C33 C34 C35 C36 0.8(4) . . . . ?
C34 C35 C36 C37 0.3(5) . . . . ?
C34 C35 C36 C39 179.7(3) . . . . ?
C35 C36 C37 C38 -1.6(5) . . . . ?
C39 C36 C37 C38 179.0(3) . . . . ?
C36 C37 C38 C33 1.9(4) . . . . ?
O1 C33 C38 C37 -179.0(2) . . . . ?
C34 C33 C38 C37 -0.8(4) . . . . ?
C35 C36 C39 O2 -176.8(4) . . . . ?
C37 C36 C39 O2 2.5(6) . . . . ?
N1 C9 C40 C41 70.0(3) . . . . ?
C9 C40 C41 C42 175.1(3) . . . . ?
C40 C41 C42 C43 -175.4(3) . . . . ?
C41 C42 C43 C44 174.8(3) . . . . ?
N2 C30 C45 C46 -179.0(2) . . . . ?
C30 C45 C46 C47 -164.8(3) . . . . ?
C45 C46 C47 C48 -61.4(4) . . . . ?
C46 C47 C48 C49 -65.5(4) . . . . ?

_diffrn_measured_fraction_theta_max    0.995
_diffrn_reflns_theta_full              25.0
_diffrn_measured_fraction_theta_full   0.999
_refine_diff_density_max    0.57
_refine_diff_density_min   -0.48
_refine_diff_density_rms    0.086
# END OF CIF
```

APPENDIX CC: CRYSTALLOGRAPHIC DATA FOR COMPOUND 3.9




```
data_NIR-2Aldehyde

_audit_creation_method            SHELXL-97
_chemical_name_systematic
;
 ?
;
_chemical_name_common             ?
_chemical_melting_point           ?
_chemical_compound_source          'local laboratory'
_chemical_formula_moiety     'C51 H48 N2 O6, C H4 O'
_chemical_formula_sum     'C52 H52 N2 O7'
_chemical_formula_weight          816.96

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
```

```
 'H'  'H'    0.0000    0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'N'  'N'    0.0061    0.0033
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'    0.0106    0.0060
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_space_group_name_H-M 'P 21/n        '
_symmetry_space_group_name_Hall     '-P 2yn'
_symmetry_cell_setting 'Monoclinic'

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x+1/2, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x-1/2, -y-1/2, z-1/2'

_cell_length_a                    13.9436(11)
_cell_length_b                    11.5410(10)
_cell_length_c                    25.5730(15)
_cell_angle_alpha                 90
_cell_angle_beta                  90.840(5)
_cell_angle_gamma                 90
_cell_volume                      4114.8(5)
_cell_formula_units_Z             4
_cell_measurement_temperature     90
_cell_measurement_reflns_used     9450
_cell_measurement_theta_min        2.5
_cell_measurement_theta_max        27.8

_exptl_crystal_description        fragment
_exptl_crystal_colour             'blue-green/bronze dichroic'
_exptl_crystal_size_max           0.40
_exptl_crystal_size_mid           0.35
_exptl_crystal_size_min           0.20
_exptl_crystal_density_meas       ?
_exptl_crystal_density_diffrn     1.319
_exptl_crystal_density_method     'not measured'
_exptl_crystal_F_000              1736
_exptl_absorpt_coefficient_mu     0.087
_exptl_absorpt_correction_type    none
_exptl_absorpt_correction_T_min   ?
_exptl_absorpt_correction_T_max   ?
_exptl_absorpt_process_details    ?

_exptl_special_details
;
 ?
```

```
;

_diffrn_ambient_temperature       90
_diffrn_radiation_wavelength      0.71073
_diffrn_radiation_type            MoK\a
_diffrn_radiation_source          'fine-focus sealed tube'
_diffrn_radiation_monochromator   graphite
_diffrn_measurement_device  'KappaCCD (with Oxford Cryostream)'
_diffrn_measurement_method       ' \w scans with \k offsets'
_diffrn_detector_area_resol_mean  ?
_diffrn_standards_number          0
_diffrn_standards_interval_count  ?
_diffrn_standards_interval_time   ?
_diffrn_standards_decay_%         <2
_diffrn_reflns_number             52149
_diffrn_reflns_av_R_equivalents   0.029
_diffrn_reflns_av_sigmaI/netI     0.0410
_diffrn_reflns_limit_h_min        -18
_diffrn_reflns_limit_h_max        18
_diffrn_reflns_limit_k_min        -15
_diffrn_reflns_limit_k_max        14
_diffrn_reflns_limit_l_min        -33
_diffrn_reflns_limit_l_max        33
_diffrn_reflns_theta_min          2.7
_diffrn_reflns_theta_max          27.9
_reflns_number_total              9790
_reflns_number_gt                 7182
_reflns_threshold_expression      I>2\s(I)

_computing_data_collection        'COLLECT (Nonius, 2000)'
_computing_cell_refinement        'HKL Scalepack (Otwinowski & Minor 1997)'
_computing_data_reduction   'HKL Denzo and Scalepack (Otwinowski & Minor 1997)'
_computing_structure_solution     'SIR97 (Altomare  et al., 1999)'
_computing_structure_refinement   'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics     'ORTEP-3 for Windows (Farrugia, 1997)'
_computing_publication_material   'SHELXL-97 (Sheldrick, 1997)'

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR and
 goodness of fit S are based on F^2^, conventional R-factors R are based
 on F, with F set to zero for negative F^2^. The threshold expression of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
 not relevant to the choice of reflections for refinement.  R-factors based
 on F^2^ are statistically about twice as large as those based on F, and R-
 factors based on ALL data will be even larger.
;

_refine_ls_structure_factor_coef  Fsqd
```

```
_refine_ls_matrix_type           full
_refine_ls_weighting_scheme      calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.1270P)^2^+4.7080P] where P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary     direct
_atom_sites_solution_secondary   difmap
_atom_sites_solution_hydrogens   geom
_refine_ls_hydrogen_treatment    constr
_refine_ls_extinction_method     SHELXL
_refine_ls_extinction_coef       0.0021(10)
_refine_ls_extinction_expression
 'Fc^*^=kFc[1+0.001xFc^2^\l^3^/sin(2\q)]^-1/4^'
_refine_ls_number_reflns         9790
_refine_ls_number_parameters     556
_refine_ls_number_restraints     0
_refine_ls_R_factor_all          0.104
_refine_ls_R_factor_gt           0.076
_refine_ls_wR_factor_ref         0.232
_refine_ls_wR_factor_gt          0.213
_refine_ls_goodness_of_fit_ref   1.034
_refine_ls_restrained_S_all      1.034
_refine_ls_shift/su_max          0.000
_refine_ls_shift/su_mean         0.000

loop_
 _atom_site_label
 _atom_site_type_symbol
 _atom_site_fract_x
 _atom_site_fract_y
 _atom_site_fract_z
 _atom_site_U_iso_or_equiv
 _atom_site_adp_type
 _atom_site_occupancy
 _atom_site_symmetry_multiplicity
 _atom_site_calc_flag
 _atom_site_refinement_flags
 _atom_site_disorder_assembly
 _atom_site_disorder_group
O1 O 0.79700(13) 0.30307(18) 0.62131(9) 0.0385(5) Uani 1 1 d . . .
O2 O 0.7677(3) 0.2107(4) 0.86245(14) 0.1037(13) Uani 1 1 d . . .
O3 O 0.25898(14) -0.04821(16) 0.48078(8) 0.0328(4) Uani 1 1 d . . .
H3O H 0.2231 0.0050 0.4695 0.049 Uiso 1 1 calc R . .
O4 O 0.40202(14) -0.06441(16) 0.51789(8) 0.0326(4) Uani 1 1 d . . .
O5 O 0.87840(16) 0.9286(2) 0.55528(9) 0.0485(6) Uani 1 1 d . . .
O6 O 0.90351(18) 0.8352(2) 0.48080(11) 0.0642(8) Uani 1 1 d . . .
N1 N 0.36428(14) 0.12461(18) 0.59966(8) 0.0239(4) Uani 1 1 d . . .
N2 N 1.11397(14) 0.65644(17) 0.55084(8) 0.0221(4) Uani 1 1 d . . .
C1 C 0.32923(17) 0.0312(2) 0.62954(9) 0.0232(5) Uani 1 1 d . . .
C2 C 0.23471(18) -0.0131(2) 0.62807(10) 0.0273(5) Uani 1 1 d . . .
```

```
H2 H 0.1867 0.0187 0.6056 0.033 Uiso 1 1 calc R . .
C3 C 0.21597(19) -0.1039(2) 0.66067(10) 0.0296(6) Uani 1 1 d . . .
H3 H 0.1530 -0.1354 0.6609 0.036 Uiso 1 1 calc R . .
C4 C 0.28689(19) -0.1527(2) 0.69396(10) 0.0277(6) Uani 1 1 d . . .
C5 C 0.2665(2) -0.2492(2) 0.72659(10) 0.0337(6) Uani 1 1 d . . .
H5 H 0.2037 -0.2810 0.7261 0.040 Uiso 1 1 calc R . .
C6 C 0.3346(2) -0.2969(2) 0.75847(11) 0.0373(7) Uani 1 1 d . . .
H6 H 0.3189 -0.3607 0.7802 0.045 Uiso 1 1 calc R . .
C7 C 0.4282(2) -0.2519(3) 0.75928(11) 0.0380(7) Uani 1 1 d . . .
H7 H 0.4755 -0.2857 0.7817 0.046 Uiso 1 1 calc R . .
C8 C 0.4524(2) -0.1597(2) 0.72808(10) 0.0305(6) Uani 1 1 d . . .
H8 H 0.5164 -0.1313 0.7288 0.037 Uiso 1 1 calc R . .
C9 C 0.38326(19) -0.1066(2) 0.69482(9) 0.0254(5) Uani 1 1 d . . .
C10 C 0.40090(17) -0.0113(2) 0.66165(9) 0.0236(5) Uani 1 1 d . . .
C11 C 0.49255(17) 0.0577(2) 0.65210(9) 0.0235(5) Uani 1 1 d . . .
C12 C 0.45743(17) 0.1469(2) 0.61169(9) 0.0227(5) Uani 1 1 d . . .
C13 C 0.56884(19) -0.0207(2) 0.62678(11) 0.0298(6) Uani 1 1 d . . .
H13A H 0.5836 -0.0859 0.6501 0.045 Uiso 1 1 calc R . .
H13B H 0.6273 0.0243 0.6209 0.045 Uiso 1 1 calc R . .
H13C H 0.5440 -0.0503 0.5933 0.045 Uiso 1 1 calc R . .
C14 C 0.5301(2) 0.1171(2) 0.70218(10) 0.0292(6) Uani 1 1 d . . .
H14A H 0.4787 0.1635 0.7175 0.044 Uiso 1 1 calc R . .
H14B H 0.5842 0.1677 0.6936 0.044 Uiso 1 1 calc R . .
H14C H 0.5514 0.0582 0.7274 0.044 Uiso 1 1 calc R . .
C15 C 0.50613(17) 0.2389(2) 0.58926(9) 0.0240(5) Uani 1 1 d . . .
H15 H 0.4704 0.2872 0.5660 0.029 Uiso 1 1 calc R . .
C16 C 0.60215(18) 0.2671(2) 0.59757(10) 0.0256(5) Uani 1 1 d . . .
H16 H 0.6401 0.2162 0.6185 0.031 Uiso 1 1 calc R . .
C17 C 0.31112(18) 0.1758(2) 0.55524(10) 0.0260(5) Uani 1 1 d . . .
H17A H 0.3192 0.2610 0.5559 0.031 Uiso 1 1 calc R . .
H17B H 0.2420 0.1587 0.5588 0.031 Uiso 1 1 calc R . .
C18 C 0.34582(19) 0.1289(2) 0.50276(10) 0.0275(5) Uani 1 1 d . . .
H18A H 0.3065 0.1627 0.4741 0.033 Uiso 1 1 calc R . .
H18B H 0.4133 0.1525 0.4976 0.033 Uiso 1 1 calc R . .
C19 C 0.33874(18) -0.0027(2) 0.50059(10) 0.0259(5) Uani 1 1 d . . .
C20 C 0.64633(18) 0.3657(2) 0.57713(10) 0.0247(5) Uani 1 1 d . . .
C21 C 0.74383(18) 0.3871(2) 0.58747(10) 0.0269(5) Uani 1 1 d . . .
C22 C 0.79732(18) 0.4782(2) 0.56566(10) 0.0260(5) Uani 1 1 d . . .
C23 C 0.74601(18) 0.5595(2) 0.52856(10) 0.0253(5) Uani 1 1 d . . .
H23A H 0.7524 0.5306 0.4923 0.030 Uiso 1 1 calc R . .
H23B H 0.7763 0.6370 0.5306 0.030 Uiso 1 1 calc R . .
C24 C 0.64010(18) 0.5699(2) 0.54158(10) 0.0257(5) Uani 1 1 d . . .
H24A H 0.6074 0.6184 0.5148 0.031 Uiso 1 1 calc R . .
H24B H 0.6336 0.6087 0.5759 0.031 Uiso 1 1 calc R . .
C25 C 0.59161(18) 0.4507(2) 0.54350(10) 0.0247(5) Uani 1 1 d . . .
H25A H 0.5261 0.4597 0.5573 0.030 Uiso 1 1 calc R . .
H25B H 0.5858 0.4195 0.5075 0.030 Uiso 1 1 calc R . .
C26 C 0.89421(18) 0.4889(2) 0.57873(10) 0.0272(5) Uani 1 1 d . . .
H26 H 0.9195 0.4361 0.6039 0.033 Uiso 1 1 calc R . .
```

```
C27 C 0.95766(17) 0.5701(2) 0.55815(10) 0.0257(5) Uani 1 1 d . . .
H27 H 0.9334 0.6237 0.5331 0.031 Uiso 1 1 calc R . .
C28 C 1.05444(17) 0.5773(2) 0.57218(9) 0.0233(5) Uani 1 1 d . . .
C29 C 1.11085(17) 0.5081(2) 0.61372(9) 0.0232(5) Uani 1 1 d . . .
C30 C 1.21036(17) 0.5608(2) 0.60942(9) 0.0216(5) Uani 1 1 d . . .
C31 C 1.29799(18) 0.5344(2) 0.63588(9) 0.0235(5) Uani 1 1 d . . .
C32 C 1.30884(19) 0.4459(2) 0.67424(10) 0.0276(5) Uani 1 1 d . . .
H32 H 1.2552 0.3998 0.6833 0.033 Uiso 1 1 calc R . .
C33 C 1.3958(2) 0.4265(2) 0.69813(11) 0.0335(6) Uani 1 1 d . . .
H33 H 1.4019 0.3667 0.7235 0.040 Uiso 1 1 calc R . .
C34 C 1.4760(2) 0.4939(3) 0.68562(11) 0.0339(6) Uani 1 1 d . . .
H34 H 1.5362 0.4788 0.7022 0.041 Uiso 1 1 calc R . .
C35 C 1.46801(18) 0.5811(2) 0.64974(10) 0.0283(5) Uani 1 1 d . . .
H35 H 1.5225 0.6273 0.6422 0.034 Uiso 1 1 calc R . .
C36 C 1.37957(17) 0.6039(2) 0.62348(9) 0.0238(5) Uani 1 1 d . . .
C37 C 1.37118(17) 0.6940(2) 0.58603(9) 0.0234(5) Uani 1 1 d . . .
H37 H 1.4260 0.7396 0.5786 0.028 Uiso 1 1 calc R . .
C38 C 1.28707(17) 0.7175(2) 0.56029(9) 0.0233(5) Uani 1 1 d . . .
H38 H 1.2825 0.7775 0.5349 0.028 Uiso 1 1 calc R . .
C39 C 1.20741(17) 0.6487(2) 0.57299(9) 0.0217(5) Uani 1 1 d . . .
C40 C 1.06942(19) 0.5356(2) 0.66800(10) 0.0287(5) Uani 1 1 d . . .
H40A H 1.1116 0.5032 0.6953 0.043 Uiso 1 1 calc R . .
H40B H 1.0054 0.5012 0.6707 0.043 Uiso 1 1 calc R . .
H40C H 1.0650 0.6197 0.6725 0.043 Uiso 1 1 calc R . .
C41 C 1.11137(19) 0.3769(2) 0.60188(10) 0.0261(5) Uani 1 1 d . . .
H41A H 1.1322 0.3642 0.5659 0.039 Uiso 1 1 calc R . .
H41B H 1.0466 0.3456 0.6060 0.039 Uiso 1 1 calc R . .
H41C H 1.1556 0.3377 0.6262 0.039 Uiso 1 1 calc R . .
C42 C 1.08424(18) 0.7471(2) 0.51396(10) 0.0274(5) Uani 1 1 d . . .
H42A H 1.0406 0.7135 0.4871 0.033 Uiso 1 1 calc R . .
H42B H 1.1413 0.7778 0.4960 0.033 Uiso 1 1 calc R . .
C43 C 1.0330(2) 0.8467(2) 0.54196(12) 0.0345(6) Uani 1 1 d . . .
H43A H 1.0328 0.8295 0.5799 0.041 Uiso 1 1 calc R . .
H43B H 1.0707 0.9184 0.5371 0.041 Uiso 1 1 calc R . .
C44 C 0.9302(2) 0.8697(2) 0.52395(12) 0.0337(6) Uani 1 1 d . . .
C45 C 0.7811(2) 0.3131(3) 0.67190(13) 0.0403(7) Uani 1 1 d . . .
C46 C 0.8135(3) 0.2152(4) 0.69925(16) 0.0625(10) Uani 1 1 d . . .
H46 H 0.8430 0.1527 0.6814 0.075 Uiso 1 1 calc R . .
C47 C 0.8013(3) 0.2116(3) 0.75387(16) 0.0609(11) Uani 1 1 d . . .
H47 H 0.8242 0.1465 0.7731 0.073 Uiso 1 1 calc R . .
C48 C 0.7579(3) 0.2990(4) 0.77939(15) 0.0563(10) Uani 1 1 d . . .
C49 C 0.7278(3) 0.3951(4) 0.75197(15) 0.0638(11) Uani 1 1 d . . .
H49 H 0.6980 0.4571 0.7700 0.077 Uiso 1 1 calc R . .
C50 C 0.7404(3) 0.4031(3) 0.69804(14) 0.0556(9) Uani 1 1 d . . .
H50 H 0.7206 0.4708 0.6797 0.067 Uiso 1 1 calc R . .
C51 C 0.7419(3) 0.2907(5) 0.83581(16) 0.0744(14) Uani 1 1 d . . .
H51 H 0.7092 0.3527 0.8523 0.089 Uiso 1 1 calc R . .
C1S C 0.5077(3) 0.5988(4) 0.88101(19) 0.1071(13) Uani 1 1 d . . .
O1S O 0.5602(6) 0.5067(6) 0.8531(3) 0.108(2) Uani 1 1 d . . .
```

```
loop_
 _atom_site_aniso_label
 _atom_site_aniso_U_11
 _atom_site_aniso_U_22
 _atom_site_aniso_U_33
 _atom_site_aniso_U_23
 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
O1 0.0181(9) 0.0391(11) 0.0586(13) -0.0103(10) 0.0131(8) -0.0199(8)
O2 0.118(3) 0.109(3) 0.083(2) 0.048(2) -0.036(2) -0.018(2)
O3 0.0286(10) 0.0245(10) 0.0451(11) 0.0000(8) -0.0036(8) -0.0054(8)
O4 0.0290(10) 0.0289(10) 0.0400(10) 0.0020(8) -0.0010(8) -0.0025(8)
O5 0.0352(12) 0.0590(15) 0.0512(13) -0.0039(11) -0.0034(10) 0.0092(10)
O6 0.0461(14) 0.0670(17) 0.0784(18) -0.0384(15) -0.0337(13) 0.0195(13)
N1 0.0205(10) 0.0211(10) 0.0301(10) -0.0012(8) 0.0009(8) -0.0064(8)
N2 0.0192(10) 0.0210(10) 0.0262(10) 0.0031(8) 0.0013(8) -0.0052(8)
C1 0.0219(12) 0.0230(12) 0.0247(11) -0.0043(9) 0.0056(9) -0.0058(9)
C2 0.0233(12) 0.0268(13) 0.0319(13) -0.0062(10) 0.0046(10) -0.0073(10)
C3 0.0267(13) 0.0296(14) 0.0330(13) -0.0090(11) 0.0104(10) -0.0111(11)
C4 0.0342(14) 0.0239(13) 0.0252(12) -0.0072(10) 0.0107(10) -0.0089(10)
C5 0.0451(16) 0.0262(14) 0.0302(13) -0.0048(11) 0.0166(11) -0.0096(12)
C6 0.0563(19) 0.0251(14) 0.0310(14) -0.0008(11) 0.0141(12) -0.0069(13)
C7 0.0565(19) 0.0266(14) 0.0310(14) -0.0009(11) 0.0044(12) 0.0007(13)
C8 0.0371(15) 0.0254(13) 0.0291(13) -0.0035(10) 0.0041(11) -0.0041(11)
C9 0.0316(13) 0.0221(12) 0.0227(11) -0.0052(9) 0.0071(9) -0.0054(10)
C10 0.0240(12) 0.0226(12) 0.0243(11) -0.0046(9) 0.0053(9) -0.0064(9)
C11 0.0212(12) 0.0225(12) 0.0268(12) -0.0020(9) 0.0018(9) -0.0053(9)
C12 0.0194(11) 0.0228(12) 0.0261(11) -0.0051(10) 0.0021(9) -0.0051(9)
C13 0.0260(13) 0.0288(13) 0.0348(13) 0.0016(11) 0.0075(10) -0.0016(10)
C14 0.0304(14) 0.0290(13) 0.0282(12) -0.0008(11) -0.0012(10) -0.0083(11)
C15 0.0219(12) 0.0234(12) 0.0267(11) -0.0006(10) -0.0010(9) -0.0051(9)
C16 0.0215(12) 0.0246(12) 0.0307(12) 0.0010(10) 0.0021(9) -0.0041(10)
C17 0.0219(12) 0.0207(12) 0.0352(13) 0.0004(10) -0.0025(10) -0.0034(9)
C18 0.0279(13) 0.0232(12) 0.0312(13) 0.0034(10) -0.0029(10) -0.0076(10)
C19 0.0248(13) 0.0269(13) 0.0260(12) -0.0003(10) 0.0041(9) -0.0065(10)
C20 0.0220(12) 0.0237(12) 0.0285(12) -0.0019(10) 0.0037(9) -0.0065(10)
C21 0.0225(12) 0.0245(12) 0.0338(13) 0.0038(10) 0.0019(10) -0.0023(10)
C22 0.0228(12) 0.0242(12) 0.0311(12) -0.0012(10) 0.0047(9) -0.0060(10)
C23 0.0227(12) 0.0260(13) 0.0274(12) -0.0005(10) 0.0042(9) -0.0081(10)
C24 0.0217(12) 0.0249(12) 0.0305(12) 0.0038(10) 0.0002(9) -0.0063(10)
C25 0.0221(12) 0.0254(12) 0.0267(12) 0.0003(10) 0.0019(9) -0.0081(10)
C26 0.0219(12) 0.0262(13) 0.0335(13) 0.0017(10) 0.0025(10) -0.0050(10)
C27 0.0204(12) 0.0260(13) 0.0308(12) 0.0006(10) 0.0017(9) -0.0066(10)
C28 0.0225(12) 0.0215(12) 0.0259(11) -0.0005(9) 0.0039(9) -0.0063(9)
C29 0.0232(12) 0.0216(12) 0.0249(11) 0.0003(9) 0.0035(9) -0.0053(9)
C30 0.0213(12) 0.0192(11) 0.0243(11) -0.0020(9) 0.0036(9) -0.0045(9)
C31 0.0238(12) 0.0211(11) 0.0257(11) -0.0030(9) 0.0024(9) -0.0008(9)
C32 0.0290(13) 0.0245(13) 0.0293(12) 0.0024(10) 0.0008(10) -0.0015(10)
```

```
C33 0.0360(15) 0.0286(14) 0.0357(14) 0.0036(11) -0.0013(11) 0.0018(11)
C34 0.0262(13) 0.0376(15) 0.0379(14) -0.0012(12) -0.0039(11) 0.0031(11)
C35 0.0209(12) 0.0332(14) 0.0310(13) -0.0048(11) 0.0035(9) -0.0014(10)
C36 0.0221(12) 0.0254(12) 0.0239(11) -0.0060(10) 0.0037(9) -0.0012(9)
C37 0.0193(11) 0.0226(12) 0.0283(12) -0.0046(10) 0.0051(9) -0.0051(9)
C38 0.0234(12) 0.0207(11) 0.0260(11) 0.0001(9) 0.0053(9) -0.0046(9)
C39 0.0210(11) 0.0201(11) 0.0239(11) -0.0018(9) 0.0017(9) -0.0026(9)
C40 0.0279(13) 0.0302(13) 0.0281(12) 0.0017(11) 0.0051(10) -0.0068(11)
C41 0.0275(13) 0.0203(12) 0.0305(12) 0.0010(10) 0.0017(10) -0.0076(10)
C42 0.0229(12) 0.0251(13) 0.0342(13) 0.0061(10) -0.0034(10) -0.0048(10)
C43 0.0313(14) 0.0254(13) 0.0465(16) -0.0005(12) -0.0119(12) -0.0026(11)
C44 0.0288(14) 0.0251(13) 0.0469(16) -0.0005(12) -0.0069(12) -0.0034(11)
C45 0.0244(14) 0.0413(17) 0.0549(18) 0.0135(14) -0.0078(12) -0.0063(12)
C46 0.070(3) 0.052(2) 0.066(2) 0.0044(19) -0.0187(19) 0.0149(19)
C47 0.074(3) 0.044(2) 0.064(2) 0.0155(18) -0.026(2) 0.0074(19)
C48 0.049(2) 0.065(3) 0.055(2) 0.0144(18) -0.0134(16) -0.0037(18)
C49 0.076(3) 0.069(3) 0.0464(19) 0.0114(19) -0.0033(18) 0.023(2)
C50 0.067(2) 0.050(2) 0.0491(19) 0.0129(17) -0.0014(17) 0.0129(18)
C51 0.070(3) 0.104(4) 0.048(2) 0.031(2) -0.0196(19) -0.010(3)
C1S 0.087(3) 0.081(3) 0.153(4) 0.024(3) -0.011(2) -0.006(2)
O1S 0.149(6) 0.077(4) 0.097(4) -0.002(3) 0.031(4) -0.012(4)

_geom_special_details
;
 All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix.  The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry.  An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.
;

loop_
 _geom_bond_atom_site_label_1
 _geom_bond_atom_site_label_2
 _geom_bond_distance
 _geom_bond_site_symmetry_2
 _geom_bond_publ_flag
O1 C45 1.321(4) . ?
O1 C21 1.490(3) . ?
O2 C51 1.200(5) . ?
O3 C19 1.324(3) . ?
O3 H30 0.8400 . ?
O4 C19 1.213(3) . ?
O5 C44 1.283(4) . ?
O6 C44 1.226(4) . ?
N1 C12 1.355(3) . ?
N1 C1 1.413(3) . ?
N1 C17 1.471(3) . ?
```

N2 C28 1.354(3) . ?
N2 C39 1.416(3) . ?
N2 C42 1.465(3) . ?
C1 C10 1.375(4) . ?
C1 C2 1.413(3) . ?
C2 C3 1.367(4) . ?
C2 H2 0.9500 . ?
C3 C4 1.412(4) . ?
C3 H3 0.9500 . ?
C4 C5 1.422(4) . ?
C4 C9 1.445(4) . ?
C5 C6 1.359(4) . ?
C5 H5 0.9500 . ?
C6 C7 1.405(4) . ?
C6 H6 0.9500 . ?
C7 C8 1.375(4) . ?
C7 H7 0.9500 . ?
C8 C9 1.417(4) . ?
C8 H8 0.9500 . ?
C9 C10 1.412(3) . ?
C10 C11 1.528(3) . ?
C11 C12 1.534(4) . ?
C11 C14 1.538(3) . ?
C11 C13 1.546(4) . ?
C12 C15 1.389(3) . ?
C13 H13A 0.9800 . ?
C13 H13B 0.9800 . ?
C13 H13C 0.9800 . ?
C14 H14A 0.9800 . ?
C14 H14B 0.9800 . ?
C14 H14C 0.9800 . ?
C15 C16 1.391(3) . ?
C15 H15 0.9500 . ?
C16 C20 1.399(3) . ?
C16 H16 0.9500 . ?
C17 C18 1.532(4) . ?
C17 H17A 0.9900 . ?
C17 H17B 0.9900 . ?
C18 C19 1.522(4) . ?
C18 H18A 0.9900 . ?
C18 H18B 0.9900 . ?
C20 C21 1.403(3) . ?
C20 C25 1.505(4) . ?
C21 C22 1.409(3) . ?
C22 C26 1.392(4) . ?
C22 C23 1.507(4) . ?
C23 C24 1.523(3) . ?
C23 H23A 0.9900 . ?
C23 H23B 0.9900 . ?

C24 C25 1.534(3) . ?
C24 H24A 0.9900 . ?
C24 H24B 0.9900 . ?
C25 H25A 0.9900 . ?
C25 H25B 0.9900 . ?
C26 C27 1.397(3) . ?
C26 H26 0.9500 . ?
C27 C28 1.394(3) . ?
C27 H27 0.9500 . ?
C28 C29 1.536(4) . ?
C29 C30 1.520(3) . ?
C29 C40 1.544(3) . ?
C29 C41 1.545(3) . ?
C30 C39 1.377(3) . ?
C30 C31 1.421(3) . ?
C31 C32 1.423(4) . ?
C31 C36 1.431(3) . ?
C32 C33 1.368(4) . ?
C32 H32 0.9500 . ?
C33 C34 1.404(4) . ?
C33 H33 0.9500 . ?
C34 C35 1.366(4) . ?
C34 H34 0.9500 . ?
C35 C36 1.420(4) . ?
C35 H35 0.9500 . ?
C36 C37 1.417(4) . ?
C37 C38 1.364(3) . ?
C37 H37 0.9500 . ?
C38 C39 1.407(3) . ?
C38 H38 0.9500 . ?
C40 H40A 0.9800 . ?
C40 H40B 0.9800 . ?
C40 H40C 0.9800 . ?
C41 H41A 0.9800 . ?
C41 H41B 0.9800 . ?
C41 H41C 0.9800 . ?
C42 C43 1.536(4) . ?
C42 H42A 0.9900 . ?
C42 H42B 0.9900 . ?
C43 C44 1.522(4) . ?
C43 H43A 0.9900 . ?
C43 H43B 0.9900 . ?
C45 C50 1.364(5) . ?
C45 C46 1.400(5) . ?
C46 C47 1.410(6) . ?
C46 H46 0.9500 . ?
C47 C48 1.349(6) . ?
C47 H47 0.9500 . ?
C48 C49 1.375(5) . ?

```
C48 C51 1.466(5) . ?
C49 C50 1.396(5) . ?
C49 H49 0.9500 . ?
C50 H50 0.9500 . ?
C51 H51 0.9500 . ?
O1S C1S 1.481(8) . ?

loop_
 _geom_angle_atom_site_label_1
 _geom_angle_atom_site_label_2
 _geom_angle_atom_site_label_3
 _geom_angle
 _geom_angle_site_symmetry_1
 _geom_angle_site_symmetry_3
 _geom_angle_publ_flag
C45 O1 C21 115.0(2) . . ?
C19 O3 H3O 109.5 . . ?
C12 N1 C1 111.1(2) . . ?
C12 N1 C17 124.7(2) . . ?
C1 N1 C17 123.3(2) . . ?
C28 N2 C39 111.2(2) . . ?
C28 N2 C42 124.9(2) . . ?
C39 N2 C42 123.55(19) . . ?
C10 C1 N1 109.9(2) . . ?
C10 C1 C2 123.8(2) . . ?
N1 C1 C2 126.2(2) . . ?
C3 C2 C1 116.6(3) . . ?
C3 C2 H2 121.7 . . ?
C1 C2 H2 121.7 . . ?
C2 C3 C4 122.3(2) . . ?
C2 C3 H3 118.8 . . ?
C4 C3 H3 118.8 . . ?
C3 C4 C5 121.4(2) . . ?
C3 C4 C9 120.3(2) . . ?
C5 C4 C9 118.2(3) . . ?
C6 C5 C4 121.7(3) . . ?
C6 C5 H5 119.1 . . ?
C4 C5 H5 119.1 . . ?
C5 C6 C7 120.0(3) . . ?
C5 C6 H6 120.0 . . ?
C7 C6 H6 120.0 . . ?
C8 C7 C6 120.9(3) . . ?
C8 C7 H7 119.6 . . ?
C6 C7 H7 119.6 . . ?
C7 C8 C9 120.9(3) . . ?
C7 C8 H8 119.6 . . ?
C9 C8 H8 119.6 . . ?
C10 C9 C8 125.1(2) . . ?
C10 C9 C4 116.6(2) . . ?
```

C8 C9 C4 118.3(2) . . ?
C1 C10 C9 120.3(2) . . ?
C1 C10 C11 108.7(2) . . ?
C9 C10 C11 130.9(2) . . ?
C10 C11 C12 101.41(19) . . ?
C10 C11 C14 112.0(2) . . ?
C12 C11 C14 111.3(2) . . ?
C10 C11 C13 110.1(2) . . ?
C12 C11 C13 109.0(2) . . ?
C14 C11 C13 112.4(2) . . ?
N1 C12 C15 121.6(2) . . ?
N1 C12 C11 108.7(2) . . ?
C15 C12 C11 129.7(2) . . ?
C11 C13 H13A 109.5 . . ?
C11 C13 H13B 109.5 . . ?
H13A C13 H13B 109.5 . . ?
C11 C13 H13C 109.5 . . ?
H13A C13 H13C 109.5 . . ?
H13B C13 H13C 109.5 . . ?
C11 C14 H14A 109.5 . . ?
C11 C14 H14B 109.5 . . ?
H14A C14 H14B 109.5 . . ?
C11 C14 H14C 109.5 . . ?
H14A C14 H14C 109.5 . . ?
H14B C14 H14C 109.5 . . ?
C12 C15 C16 126.2(2) . . ?
C12 C15 H15 116.9 . . ?
C16 C15 H15 116.9 . . ?
C15 C16 C20 124.2(2) . . ?
C15 C16 H16 117.9 . . ?
C20 C16 H16 117.9 . . ?
N1 C17 C18 111.8(2) . . ?
N1 C17 H17A 109.2 . . ?
C18 C17 H17A 109.2 . . ?
N1 C17 H17B 109.2 . . ?
C18 C17 H17B 109.2 . . ?
H17A C17 H17B 107.9 . . ?
C19 C18 C17 111.3(2) . . ?
C19 C18 H18A 109.4 . . ?
C17 C18 H18A 109.4 . . ?
C19 C18 H18B 109.4 . . ?
C17 C18 H18B 109.4 . . ?
H18A C18 H18B 108.0 . . ?
O4 C19 O3 120.6(2) . . ?
O4 C19 C18 121.7(2) . . ?
O3 C19 C18 117.6(2) . . ?
C16 C20 C21 120.3(2) . . ?
C16 C20 C25 121.4(2) . . ?
C21 C20 C25 118.3(2) . . ?

```
C20 C21 C22 125.0(2) . . ?
C20 C21 O1 117.8(2) . . ?
C22 C21 O1 117.0(2) . . ?
C26 C22 C21 119.2(2) . . ?
C26 C22 C23 123.1(2) . . ?
C21 C22 C23 117.7(2) . . ?
C22 C23 C24 111.4(2) . . ?
C22 C23 H23A 109.4 . . ?
C24 C23 H23A 109.4 . . ?
C22 C23 H23B 109.4 . . ?
C24 C23 H23B 109.4 . . ?
H23A C23 H23B 108.0 . . ?
C23 C24 C25 111.4(2) . . ?
C23 C24 H24A 109.3 . . ?
C25 C24 H24A 109.3 . . ?
C23 C24 H24B 109.3 . . ?
C25 C24 H24B 109.3 . . ?
H24A C24 H24B 108.0 . . ?
C20 C25 C24 112.5(2) . . ?
C20 C25 H25A 109.1 . . ?
C24 C25 H25A 109.1 . . ?
C20 C25 H25B 109.1 . . ?
C24 C25 H25B 109.1 . . ?
H25A C25 H25B 107.8 . . ?
C22 C26 C27 125.9(2) . . ?
C22 C26 H26 117.1 . . ?
C27 C26 H26 117.1 . . ?
C28 C27 C26 124.0(2) . . ?
C28 C27 H27 118.0 . . ?
C26 C27 H27 118.0 . . ?
N2 C28 C27 122.2(2) . . ?
N2 C28 C29 108.6(2) . . ?
C27 C28 C29 129.1(2) . . ?
C30 C29 C28 101.57(19) . . ?
C30 C29 C40 109.7(2) . . ?
C28 C29 C40 108.7(2) . . ?
C30 C29 C41 111.8(2) . . ?
C28 C29 C41 112.2(2) . . ?
C40 C29 C41 112.3(2) . . ?
C39 C30 C31 119.8(2) . . ?
C39 C30 C29 109.0(2) . . ?
C31 C30 C29 131.2(2) . . ?
C30 C31 C32 124.4(2) . . ?
C30 C31 C36 117.0(2) . . ?
C32 C31 C36 118.6(2) . . ?
C33 C32 C31 120.7(2) . . ?
C33 C32 H32 119.7 . . ?
C31 C32 H32 119.7 . . ?
C32 C33 C34 120.8(3) . . ?
```

C32 C33 H33 119.6 . . ?
C34 C33 H33 119.6 . . ?
C35 C34 C33 120.2(3) . . ?
C35 C34 H34 119.9 . . ?
C33 C34 H34 119.9 . . ?
C34 C35 C36 121.1(2) . . ?
C34 C35 H35 119.5 . . ?
C36 C35 H35 119.5 . . ?
C37 C36 C35 121.2(2) . . ?
C37 C36 C31 120.2(2) . . ?
C35 C36 C31 118.6(2) . . ?
C38 C37 C36 122.3(2) . . ?
C38 C37 H37 118.9 . . ?
C36 C37 H37 118.9 . . ?
C37 C38 C39 116.9(2) . . ?
C37 C38 H38 121.5 . . ?
C39 C38 H38 121.5 . . ?
C30 C39 C38 123.8(2) . . ?
C30 C39 N2 109.6(2) . . ?
C38 C39 N2 126.7(2) . . ?
C29 C40 H40A 109.5 . . ?
C29 C40 H40B 109.5 . . ?
H40A C40 H40B 109.5 . . ?
C29 C40 H40C 109.5 . . ?
H40A C40 H40C 109.5 . . ?
H40B C40 H40C 109.5 . . ?
C29 C41 H41A 109.5 . . ?
C29 C41 H41B 109.5 . . ?
H41A C41 H41B 109.5 . . ?
C29 C41 H41C 109.5 . . ?
H41A C41 H41C 109.5 . . ?
H41B C41 H41C 109.5 . . ?
N2 C42 C43 111.3(2) . . ?
N2 C42 H42A 109.4 . . ?
C43 C42 H42A 109.4 . . ?
N2 C42 H42B 109.4 . . ?
C43 C42 H42B 109.4 . . ?
H42A C42 H42B 108.0 . . ?
C44 C43 C42 115.6(2) . . ?
C44 C43 H43A 108.4 . . ?
C42 C43 H43A 108.4 . . ?
C44 C43 H43B 108.4 . . ?
C42 C43 H43B 108.4 . . ?
H43A C43 H43B 107.4 . . ?
O6 C44 O5 124.6(3) . . ?
O6 C44 C43 119.2(3) . . ?
O5 C44 C43 116.1(3) . . ?
O1 C45 C50 128.6(3) . . ?
O1 C45 C46 111.2(3) . . ?

```
C50 C45 C46 120.2(3) . . ?
C45 C46 C47 118.4(4) . . ?
C45 C46 H46 120.8 . . ?
C47 C46 H46 120.8 . . ?
C48 C47 C46 121.3(3) . . ?
C48 C47 H47 119.4 . . ?
C46 C47 H47 119.4 . . ?
C47 C48 C49 119.5(4) . . ?
C47 C48 C51 120.2(4) . . ?
C49 C48 C51 120.3(4) . . ?
C48 C49 C50 121.1(4) . . ?
C48 C49 H49 119.5 . . ?
C50 C49 H49 119.5 . . ?
C45 C50 C49 119.5(3) . . ?
C45 C50 H50 120.2 . . ?
C49 C50 H50 120.2 . . ?
O2 C51 C48 124.1(5) . . ?
O2 C51 H51 118.0 . . ?
C48 C51 H51 118.0 . . ?

loop_
 _geom_torsion_atom_site_label_1
 _geom_torsion_atom_site_label_2
 _geom_torsion_atom_site_label_3
 _geom_torsion_atom_site_label_4
 _geom_torsion
 _geom_torsion_site_symmetry_1
 _geom_torsion_site_symmetry_2
 _geom_torsion_site_symmetry_3
 _geom_torsion_site_symmetry_4
 _geom_torsion_publ_flag
C12 N1 C1 C10 -1.0(3) . . . . ?
C17 N1 C1 C10 169.0(2) . . . . ?
C12 N1 C1 C2 178.2(2) . . . . ?
C17 N1 C1 C2 -11.8(4) . . . . ?
C10 C1 C2 C3 -0.5(4) . . . . ?
N1 C1 C2 C3 -179.6(2) . . . . ?
C1 C2 C3 C4 -0.6(4) . . . . ?
C2 C3 C4 C5 -178.3(2) . . . . ?
C2 C3 C4 C9 0.4(4) . . . . ?
C3 C4 C5 C6 179.6(2) . . . . ?
C9 C4 C5 C6 0.8(4) . . . . ?
C4 C5 C6 C7 -0.8(4) . . . . ?
C5 C6 C7 C8 -0.1(4) . . . . ?
C6 C7 C8 C9 0.9(4) . . . . ?
C7 C8 C9 C10 179.6(2) . . . . ?
C7 C8 C9 C4 -0.9(4) . . . . ?
C3 C4 C9 C10 0.8(3) . . . . ?
C5 C4 C9 C10 179.6(2) . . . . ?
```

C3 C4 C9 C8 -178.8(2) . . . . ?
C5 C4 C9 C8 0.0(3) . . . . ?
N1 C1 C10 C9 -179.0(2) . . . . ?
C2 C1 C10 C9 1.7(4) . . . . ?
N1 C1 C10 C11 -1.0(3) . . . . ?
C2 C1 C10 C11 179.8(2) . . . . ?
C8 C9 C10 C1 177.7(2) . . . . ?
C4 C9 C10 C1 -1.8(3) . . . . ?
C8 C9 C10 C11 0.2(4) . . . . ?
C4 C9 C10 C11 -179.3(2) . . . . ?
C1 C10 C11 C12 2.4(2) . . . . ?
C9 C10 C11 C12 -179.9(2) . . . . ?
C1 C10 C11 C14 121.1(2) . . . . ?
C9 C10 C11 C14 -61.1(3) . . . . ?
C1 C10 C11 C13 -113.0(2) . . . . ?
C9 C10 C11 C13 64.8(3) . . . . ?
C1 N1 C12 C15 -176.6(2) . . . . ?
C17 N1 C12 C15 13.5(4) . . . . ?
C1 N1 C12 C11 2.6(3) . . . . ?
C17 N1 C12 C11 -167.3(2) . . . . ?
C10 C11 C12 N1 -3.0(2) . . . . ?
C14 C11 C12 N1 -122.2(2) . . . . ?
C13 C11 C12 N1 113.2(2) . . . . ?
C10 C11 C12 C15 176.2(2) . . . . ?
C14 C11 C12 C15 56.9(3) . . . . ?
C13 C11 C12 C15 -67.7(3) . . . . ?
N1 C12 C15 C16 -177.8(2) . . . . ?
C11 C12 C15 C16 3.1(4) . . . . ?
C12 C15 C16 C20 -175.1(2) . . . . ?
C12 N1 C17 C18 70.1(3) . . . . ?
C1 N1 C17 C18 -98.6(3) . . . . ?
N1 C17 C18 C19 56.6(3) . . . . ?
C17 C18 C19 O4 -85.3(3) . . . . ?
C17 C18 C19 O3 92.3(3) . . . . ?
C15 C16 C20 C21 -179.9(2) . . . . ?
C15 C16 C20 C25 -0.2(4) . . . . ?
C16 C20 C21 C22 174.7(2) . . . . ?
C25 C20 C21 C22 -4.9(4) . . . . ?
C16 C20 C21 O1 -1.0(4) . . . . ?
C25 C20 C21 O1 179.3(2) . . . . ?
C45 O1 C21 C20 -77.5(3) . . . . ?
C45 O1 C21 C22 106.4(3) . . . . ?
C20 C21 C22 C26 -179.2(2) . . . . ?
O1 C21 C22 C26 -3.4(4) . . . . ?
C20 C21 C22 C23 0.3(4) . . . . ?
O1 C21 C22 C23 176.1(2) . . . . ?
C26 C22 C23 C24 -150.9(2) . . . . ?
C21 C22 C23 C24 29.6(3) . . . . ?
C22 C23 C24 C25 -54.3(3) . . . . ?

C16 C20 C25 C24 159.5(2) . . . . ?
C21 C20 C25 C24 -20.8(3) . . . . ?
C23 C24 C25 C20 50.1(3) . . . . ?
C21 C22 C26 C27 176.1(3) . . . . ?
C23 C22 C26 C27 -3.4(4) . . . . ?
C22 C26 C27 C28 -179.6(3) . . . . ?
C39 N2 C28 C27 177.8(2) . . . . ?
C42 N2 C28 C27 4.2(4) . . . . ?
C39 N2 C28 C29 0.7(3) . . . . ?
C42 N2 C28 C29 -172.9(2) . . . . ?
C26 C27 C28 N2 179.2(2) . . . . ?
C26 C27 C28 C29 -4.4(4) . . . . ?
N2 C28 C29 C30 -1.9(2) . . . . ?
C27 C28 C29 C30 -178.7(2) . . . . ?
N2 C28 C29 C40 113.7(2) . . . . ?
C27 C28 C29 C40 -63.1(3) . . . . ?
N2 C28 C29 C41 -121.4(2) . . . . ?
C27 C28 C29 C41 61.7(3) . . . . ?
C28 C29 C30 C39 2.5(3) . . . . ?
C40 C29 C30 C39 -112.4(2) . . . . ?
C41 C29 C30 C39 122.3(2) . . . . ?
C28 C29 C30 C31 -178.0(2) . . . . ?
C40 C29 C30 C31 67.1(3) . . . . ?
C41 C29 C30 C31 -58.2(3) . . . . ?
C39 C30 C31 C32 179.8(2) . . . . ?
C29 C30 C31 C32 0.3(4) . . . . ?
C39 C30 C31 C36 1.2(3) . . . . ?
C29 C30 C31 C36 -178.3(2) . . . . ?
C30 C31 C32 C33 -179.6(2) . . . . ?
C36 C31 C32 C33 -1.0(4) . . . . ?
C31 C32 C33 C34 0.4(4) . . . . ?
C32 C33 C34 C35 0.8(4) . . . . ?
C33 C34 C35 C36 -1.5(4) . . . . ?
C34 C35 C36 C37 -179.7(2) . . . . ?
C34 C35 C36 C31 0.9(4) . . . . ?
C30 C31 C36 C37 -0.4(3) . . . . ?
C32 C31 C36 C37 -179.1(2) . . . . ?
C30 C31 C36 C35 179.0(2) . . . . ?
C32 C31 C36 C35 0.4(3) . . . . ?
C35 C36 C37 C38 180.0(2) . . . . ?
C31 C36 C37 C38 -0.6(4) . . . . ?
C36 C37 C38 C39 0.8(3) . . . . ?
C31 C30 C39 C38 -1.1(4) . . . . ?
C29 C30 C39 C38 178.6(2) . . . . ?
C31 C30 C39 N2 178.2(2) . . . . ?
C29 C30 C39 N2 -2.2(3) . . . . ?
C37 C38 C39 C30 0.0(4) . . . . ?
C37 C38 C39 N2 -179.0(2) . . . . ?
C28 N2 C39 C30 1.0(3) . . . . ?

```
C42 N2 C39 C30 174.7(2) . . . . ?
C28 N2 C39 C38 -179.8(2) . . . . ?
C42 N2 C39 C38 -6.1(4) . . . . ?
C28 N2 C42 C43 76.1(3) . . . . ?
C39 N2 C42 C43 -96.8(3) . . . . ?
N2 C42 C43 C44 -119.9(3) . . . . ?
C42 C43 C44 O6 -20.8(4) . . . . ?
C42 C43 C44 O5 161.7(3) . . . . ?
C21 O1 C45 C50 -15.6(4) . . . . ?
C21 O1 C45 C46 165.1(3) . . . . ?
O1 C45 C46 C47 -179.6(3) . . . . ?
C50 C45 C46 C47 1.1(6) . . . . ?
C45 C46 C47 C48 1.3(6) . . . . ?
C46 C47 C48 C49 -2.3(6) . . . . ?
C46 C47 C48 C51 177.1(4) . . . . ?
C47 C48 C49 C50 0.9(7) . . . . ?
C51 C48 C49 C50 -178.5(4) . . . . ?
O1 C45 C50 C49 178.4(3) . . . . ?
C46 C45 C50 C49 -2.5(6) . . . . ?
C48 C49 C50 C45 1.5(7) . . . . ?
C47 C48 C51 O2 2.0(7) . . . . ?
C49 C48 C51 O2 -178.6(5) . . . . ?

loop_
 _geom_hbond_atom_site_label_D
 _geom_hbond_atom_site_label_H
 _geom_hbond_atom_site_label_A
 _geom_hbond_distance_DH
 _geom_hbond_distance_HA
 _geom_hbond_distance_DA
 _geom_hbond_angle_DHA
 _geom_hbond_site_symmetry_A
O3 H3O O5  0.84 1.72 2.524(3) 158.9 3_666

_diffrn_measured_fraction_theta_max    0.996
_diffrn_reflns_theta_full              25.0
_diffrn_measured_fraction_theta_full   0.998
_refine_diff_density_max    1.00
_refine_diff_density_min   -0.63
_refine_diff_density_rms    0.078
# END OF CIF
```

APPENDIX DD: LETTERS OF PERMISSION

Karen Buehler

From: Xiangyang Xu [xxu3@lsu.edu]
Sent: Sunday, February 11, 2007 10:33 PM
To: Copyright
Subject: Ask for a permission

To whom it may Concern:

I am a graduate student in the Department of Chemistry at Louisisana State University. I am writing to obtain permission for the use of my contribution to the article published in " The Journal of the American Chemical Society". I am one of the authors on the article. The article is:

"Detection of Homocysteine and Cysteine" *J. Am. Chem. Soc.* , **2005**, *127(45)*, 15949-15958.

Thank you for your consideration of this request.

Sincerely

Xiangyang Xu

Phone: (225)-578-3573

Fax: (225)-578-3458

LSU Chemistry Department

Room 232 Choppin Hall

Baton Rouge, La, 70803

2/12/2007

American Chemical Society

Publications Division
Copyright Office

1155 Sixteenth Street, NW
Washington, DC 20036
Phone: (1) 202-872-4368 or -4367
Fax: (1) 202-776-8112 E-mail: copyright@acs.org

VIA FAX: 225-578-3458 DATE: February 15, 2007

TO: Xiangyang Xu, Chemistry Department. Louisiana State University
Room 232 Choppin Hall, Baton Rouge, LA 70803

FROM: C. Arleen Courtney, Copyright Associate C. Arleen Courtney

Thank you for your request for permission to include your paper(s) or portions of text from your paper(s) in your thesis. Permission is now automatically granted; please pay special attention to the implications paragraph below. The Copyright Subcommittee of the Joint Board/Council Committees on Publications approved the following:

Copyright permission for published and submitted material from theses and dissertations
ACS extends blanket permission to students to include in their theses and dissertations their own articles, or portions thereof, that have been published in ACS journals or submitted to ACS journals for publication, provided that the ACS copyright credit line is noted on the appropriate page(s).

Publishing implications of electronic publication of theses and dissertation material
Students and their mentors should be aware that posting of theses and dissertation material on the Web prior to submission of material from that thesis or dissertation to an ACS journal may affect publication in that journal. Whether Web posting is considered prior publication may be evaluated on a case-by-case basis by the journal's editor. If an ACS journal editor considers Web posting to be "prior publication", the paper will not be accepted for publication in that journal. If you intend to submit your unpublished paper to ACS for publication, check with the appropriate editor prior to posting your manuscript electronically.

If your paper has not yet been published by ACS, we have no objection to your including the text or portions of the text in your thesis/dissertation in **print and microfilm formats**; please note, however, that electronic distribution or Web posting of the unpublished paper as part of your thesis in electronic formats might jeopardize publication of your paper by ACS. Please print the following credit line on the first page of your article: "Reproduced (or 'Reproduced in part') with permission from [JOURNAL NAME], in press (or 'submitted for publication'). Unpublished work copyright [CURRENT YEAR] American Chemical Society." Include appropriate information.

If your paper has already been published by ACS and you want to include the text or portions of the text in your thesis/dissertation in **print or microfilm formats**, please print the ACS copyright credit line on the first page of your article: "Reproduced (or 'Reproduced in part') with permission from [FULL REFERENCE CITATION.] Copyright [YEAR] American Chemical Society." Include appropriate information.

Submission to a Dissertation Distributor: If you plan to submit your thesis to UMI or to another dissertation distributor, you should not include the unpublished ACS paper in your thesis if the thesis will be disseminated electronically, until ACS has published your paper. After publication of the paper by ACS, you may release the entire thesis (**not the individual ACS article by itself**) for electronic dissemination through the distributor; ACS's copyright credit line should be printed on the first page of the ACS paper.

Use on an Intranet: The inclusion of your ACS unpublished or published manuscript is permitted in your thesis in print and microfilm formats. If ACS has published your paper you may include the manuscript in your thesis on an intranet that is not publicly available. Your ACS article cannot be posted electronically on a publicly available medium (i.e. one that is not password protected), such as but not limited to, electronic archives, Internet, library server, etc. The only material from your paper that can be posted on a public electronic medium is the article abstract, figures, and tables, and you may link to the article's DOI or post the article's author-directed URL link provided by ACS. This paragraph does not pertain to the dissertation distributor paragraph above. 06/07/06

VITA

The author, Xiangyang Xu, was born in Qianshan, Anhui, China, on July 1, 1973. He grew up and spent most of the time at his southern hometown until he joined the Central South University in Changsha, China, where he received his bachelor of engineering degree in ore separation engineering in 1996. After graduation, he worked as an assistant engineer at Hefei Steel & Iron Co. Ltd.

In August, 1999, he returned to school again and joined the graduate program in the Department of Materials Science and Engineering at the University of Science and Technology of China and earned a master of engineering degree in 2002.

That same year he traveled to the United States and joined Professor Robert M. Strongin's group at Louisiana State University to pursue his doctoral degree in organic chemistry. While at LSU, he designed and synthesized dioxins and chromophoric reagents for the detection of biological molecules as well as evaluating the potential applications of these compounds under the direction of Professor Strongin.