

**SYNTHESIS AND STUDY OF THE DYEING PROPERTIES OF
AURONES
AND
DEVELOPMENT OF A VISIBLE LIGHT-MEDIATED POLYENE
CYCLIZATION METHODOLOGY**

By

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I dedicate this research to my parents, Gangadhar Bhattarai and Saraswati Bhattarai.

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ABSTRACT

Aurones are primarily responsible for pigmentation, imparting yellow and orange hues to flowers and fruits. Despite their proven coloring role in nature, other applications of their pigmentation and photophysical properties have been limited and focused almost entirely on their fluorescent properties. To address this gap, two different color-related projects were explored in this dissertation.

In one project, different dimethyl amino- and ferrocene-appended hydroxy and methoxy substituted aurone derivatives were screened for their dyeing potential using an environmentally sustainable deep eutectic solvent of choline chloride and urea (chapter II). Considering various factors, including solubility, accessibility of the aurones, and their color-imparting ability to different fabrics, only four hydroxy derivatives of dimethylamino-aurones **22-25** were selected for further study. Their dye exhaustion ability, color fastness, color strength, and fixation property on wool fabric were studied. Among the four aurones, 6-OH-DMAA (**22**) showed the highest dye exhaustion, whereas 6,7-diOH-DMAA (**25**) dyed wool showed the lowest value.

In qualitative grey-scale tests, all four aurones showed excellent color fastness against rub, wash, and light exposure, revealing their promising dyeing ability. The color strength (K/S) were calculated using the reflectance values of the dyed fabrics. Fabrics dyed with aurone **22** exhibited high reflectance overall, showing low K/S value for all four tests. Aurones **23** and **25** dyed fabrics showed comparable K/S against rub,

wash, and light tests. Wool fabric dyed with **24** (4,6-diOH-DMAA) showed consistently high K/S for the tests.

The other study sought to employ the aurone scaffold as a versatile organic photocatalyst, looking initially at polyene cyclizations (chapter III). Polyene cyclizations allow easy access to complex polycyclic molecules from acyclic precursors through stereo-controlled multiple C-C bond formation. While this transformation has been used frequently over the years, existing strategies largely demand the use of expensive and toxic transition metal complexes to accomplish the desired reaction. In a highly unusual result, it was discovered that the use of a blue LED enabled a completely catalyst-free cascade cyclization of geranyl phenols containing bromo- and chloro- groups at different positions of the phenolic ring. The desired cyclization products were obtained with high stereoselectivity in the hexafluoro-2-propanol reaction medium. This reaction condition is the simplest option yet reported and has potential for future extension to additional catalyst-free photochemical transformations.

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LIST OF ABBREVIATIONS

μM	Micromolar
AATCC	American Association of Textile Chemists and Colorists
AD	After dyeing
AIBN	Azobisisobutyronitrile
AQ	Anthraquinone
ATCC	American type culture collection
ATRA	Atom transfer radical addition
BCE	Before common era
BD	Before dyeing
BDSB	Bromo(diethyl)sulfoniumbromo(penta)chloroantimonate
BINOL	1,1'-Bi-2-naphthol
Boc	tert-Butyloxycarbonyl
BP	Benzophenone
C.I.	Color index
CDSC	Chlorodiethylsulfonium hexachloroantimonate
CE	Common era
ChCl	Choline chloride
CNF	Cellulose nanofibers
CP	Cercosporin
C-S	Cation-stabilizing
CT	Charge transfer
DABCO	1,4-diazabicyclo[2.2.2]octane
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DCA	9,10-dicyanoanthracene
DCB	1,4-dicyanobenzene
DCM	Dichloromethane
DCN	1,4-dicyanonaphthalene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DES	Deep eutectic solvent

DI	Deionized
DMAA	Dimethylaminoaurone
DMAPP	Dimethylallyl pyrophosphate
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
EDA	Electron-donor-acceptor
EG	Ethylene glycol
EnT	Energy Transfer
ET	Electron Transfer
EtOH	Ethanol
FA	Ferrocenyl aurone
FF	Furfuryl alcohol
FLN	Fluorenone
FPP	Farnesyl pyrophosphate
GES	Glycerin based eutectic solvent
GPP	Geranyl pyrophosphate
HARCP	Hexaacetyl reduced cercosporin
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HPLC	High-Performance Liquid Chromatography
HRMS	High-resonance mass spectrometry
IC	Inhibitory Concentration
IL	Ionic liquid
IPP	Isopentyl pyrophosphate
ISO	International organizations for standardization
KOH	Potassium hydroxide
LBA	Lewis's acid assisted chiral Bronsted acid
LC-MS	Liquid Chromatography-Mass Spectrometry
LED	Light-emitting diode
MB	Methylene blue
MeI	Methyl iodide
MeOH	Methanol
MIC	Minimum Inhibitory Concentration

MK	Michler's ketone
MLCT	Metal-ligand charge-transfer
mM	Millimolar
MRSA	Methicillin-Resistant Staphylococcus aureus
NBS	N-bromosuccinamide
NHC	N-heterocyclic carbene
NIR	Near infra-red
NMQ	N-methyl-quinolinone
NMR	Nuclear magnetic resonance
o.w.f	On weight of fabric
OA	Oxalic acid
ON	Overnight
OVAT	One variable at a time
p- TsOH	p-Toluenesulfoic acid
PCE	Perchloroethylene
PDI	Perylene diimide
PET	Photoinduced electron transfer
PET	Polyethylene terephthalate
PHMB	Polyhexamethylene biguanide
	Poly (1,4-cyclohexane dimethylene isosorbide
PICT	terephthalate)
PLA	Polylactic acid
PQP	Perylene quinonoid pigment
QSAR	Quantitative Structure-Activity Relationship
SET	Single Electron Transfer
TBCO	2,4,4,6-tetrabromo-2,5-cyclohexadione
TBCO	Tetrabromocyclohexadione
TCQB	Tetrachloro-1,4-benzoquinone
T _d	Dyeing transition temperatre
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
T _g	Glass transition temperature

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMPAP	Trimethylphenylammonium perbromide
TMSCl	Trimethylsilyl chloride
TXO	Thioxanthone
U	Urea
UV-Vis	Ultraviolet-visible
XO	Xanthone
YPD	Yeast extract-peptone-dextrose

CHAPTER I

INTRODUCTION

1. Dye: Background

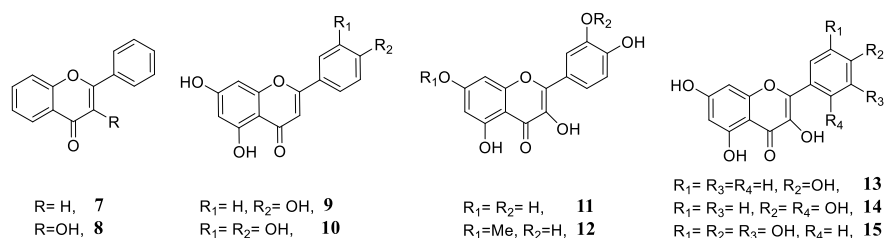
Dyeing is the process of adding color to textile products like fibers, yarns, fabrics, or finished textile products, including garments and apparel. It can be done at any stage of textile manufacturing. Having a long history of more than 4,000 years, textile dyeing is, nevertheless, a rapidly growing industry.¹ Throughout history, people have been using both locally available as well as rare and expensive dyestuffs that add brilliant and permanent hues to textiles. Until the 1850s, the major sources of almost all dyes were natural products obtained from plants, with a few from lichens and invertebrates.¹ Aside from their primary role of coloring fabric, these natural dyes are often associated with great aesthetic and economic values. Based on the colors they provide to the substrate, natural dyes can be classified into four different groups- red, blue, brown/black, and yellow.²

Natural red dyes most commonly contain a quinone scaffold. They have been significantly important in the history of textile dyeing.³ A red dye Alizarin (madder) **1** containing a 1, 2 dihydroxy anthraquinone chromophore was used in antiquity by the ancient Egyptians for coloring textiles. This root extract of the madder plant *Rubia tinctorium* has been reported as one of the most stable red dyes used in ancient history.⁴ Other plant-based red dyes include orchil, redwood, sandalwood, and safflower.⁵ Besides these, animal-originated red dyes, kermes, cochineal, and lac dyes obtained from insects (plant parasites) have also been reported in textile history.⁶⁻⁹ Crimson

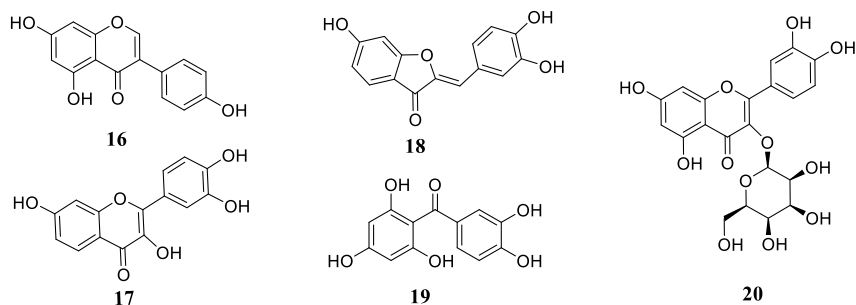
species. Additionally, the extract of logwood found in the heartwood of the tree *Haematoxylon campechianum* also functions as a black dye.

Other historically utilized dyes are the yellow dyes, which have been widely used for fabric dyeing. The largest sources of natural yellow dyes are the natural product flavonoids (a word derived from the Latin root word flavus, meaning yellow). These secondary plant metabolites, which are primarily responsible for pigmentation of flowers, fruits, and leaves, have long historical importance in textile dyeing. Their use as a dyeing agent for various purposes since ancient times has been verified by several composition analysis studies of historic textiles and fabrics using high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS).¹⁷

Based on the absence or presence of the hydroxyl group at position 3 of the skeleton, flavonoids can be categorized into flavones **7** and flavonols **8**, respectively.¹⁸ A plant *Reseda luteola* L, which is also commonly known as weld, is the major source of apigenin **9** and luteolin **10**, which, in combination with alum mordant, produces bright and fast yellow colors in the fabric. For many centuries, this plant remained very popular in Europe and Mediterranean regions for its dyeing efficiency.¹⁹ Further, the HPLC analysis of samples extracted from a yellow fiber of an early 18th-century herald's tabard revealed the presence of luteolin and apigenin with a trace of the methyl ether of luteolin.²⁰



Flavonols (3-hydroxy flavones), which are more susceptible to photooxidation than flavones,¹ mainly contain colorants such as quercetin **11**, rhamnetin **12**, and kaempferol **13** along with morin **14**, myricetin **15**, genistein **16** and fisetin **17**. They are found in a variety of plants, including Persian berries (*Rhamnus* species), young fustic (*Cotinus coggygria*), old fustic (*Chlorophora tinctoria*), and yellow wood (*Solidago virgaurea*). Other sources of flavanols are onion skins (*Allium cepa*), sawwort (*Serratula tinctoria*), dyer's greenweed (*Genista tinctoria*), marigold (*Chrysanthemum* species), dyer's chamomile (*Anthemis tinctoria*), and flax-leaved daphne (*Daphne gnidium*).²¹

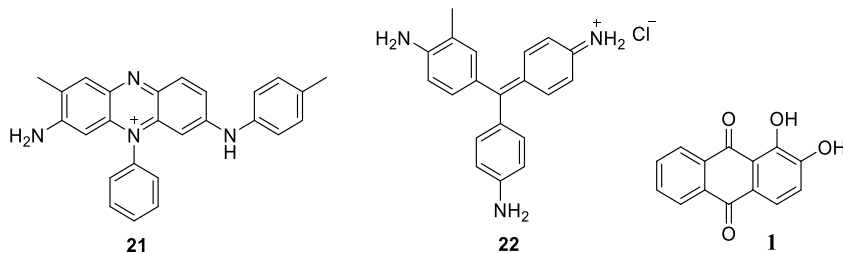


Despite their limitation of photodegradation, there is historical evidence of flavonols being used as a source of yellow dyes. For instance, dyer's broom containing isoflavone genistein **16** has been used for dyeing wool, silk, cotton, and linen since

Roman times. Young fustic (*Cotinus coggygia*) was used to impart dark yellow shades to fabric in the Middle Ages. Study of the fabrics showed myricetin **15** and fisetin **17** together with the aurone sulfuretin **18** being the major yellow colorants.¹⁹

Similarly, the old fustic (*Chlorophora tinctoria*) was first introduced in Europe in the 16th century and was soon widely used as a mordant dye. The main colorants in this source include morin **14** with small amounts of kaempferol **13** and the benzophenone maclurin **19**.²² Analysis of a 16th- 17th century Latin American colonial tapestry from the collection of the Smithsonian's Cooper Hewitt National Design Museum showed that hyperoside **20** was one of the responsible flavonoids for the yellow color of the tapestry.²³ Similarly, quercitron bark, consisting of quercetin **11**, quercitrin, and kaempferol **13** as main constituents, has also been reported as a dye since the late 18th century.²⁴

Until the end of the 19th century, natural dyes were the primary sources of dyes for textiles. The introduction of synthetic dyes after 1857 took over the dyeing industry with their favorable application properties along with the flexibility of colors, larger scale reproducible mass production, and improved quality of dyeing at a lower cost.²⁵ Though there were reports of semi-synthetic dyes- picric acid²⁶ and indigo carmine (prepared by treating the natural indigotin with nitric acid and sulfuric acid, respectively),²⁷ mauveine **21** is the first truly synthetic dye. It was discovered accidentally by William Henry Perkin in 1856 while synthesizing quinine from coal tar. The commercialization of mauveine, also known as aniline purple (1857), tyrian purple (1858), and mauve dye (from 1859) encouraged the exploration and synthesis of several other dyes.²⁸



Fuchsine **22**, a deep red colored dye, was the second commercially successful aniline dye synthesized by August Wilhelm Von Hoffmann in 1858 from aniline and carbon tetrachloride.²⁹ Alizarin **1**, a natural dye, was successfully synthesized from anthracene by two German scientists, Carl Graebe and Carl Liebermann, in 1868.³⁰ Subsequently, in 1869, they succeeded in converting anthracene into alizarin, which, further boosted the importance and economic synthesis of alizarin.^{30,31} The development of more than 400 new dyestuffs within a couple of years, of which 317 were commercially successful, led to a massive industrial revolution in both synthetic dyes' development and pharmaceutical growth.³² Further advancement in chemical techniques enhanced the mass production of high-quality synthetic dyes using inexpensive raw materials. As a result, natural dyes were progressively replaced by synthetic dyes.

1.1. Antimicrobial finishing of textiles

During the last few decades, due to growing consumer demand, there has been interest in the development of textile materials with antimicrobial properties. Estimates have shown that the production of antimicrobial textiles was 30,000 tones in Western Europe and 100,000 tons worldwide in 2000.³³ The large surface area with high moisture retention property of textiles makes them an efficient medium for the growth and rapid multiplication of microorganisms. Natural fibers with proteins and

carbohydrates can provide the required nutrients and energy sources for the microorganisms to grow. Compared to natural fibers, synthetic fibers are more resistant to microorganisms because of their high hydrophobicity. Cellulolytic fungi damage cellulosic fibers such as cotton, linen, jute, and rayon by converting cellulose to soluble sugars. Protein fibers, including wool and silk, are more susceptible to keratinophilic fungi.³⁴

Microbes are transmitted to clothing textiles by direct contact with skin and the environment. Since skin consists of several microbial communities, including Gram-positive bacteria (*Staphylococcus* spp., *Corynebacterium* spp., *Propionibacterium* spp.), Gram-negative bacteria (*Acinetobacter* spp., *E. coli*), and fungi (*Candida* spp., *Malassezia furfur*, *Aspergillus* spp.), these communities are equally common on fabrics.³⁵⁻³⁷ The growth of the microbes may lead to harmful effects on both the user and the textiles, generating unpleasant odors, staining and discoloring the fabric, reducing fabric mechanical strength, and increasing dermal infections and other related diseases.³³ In the clinical setting, the fabrics used play a major role in the chain of infection among patients, health practitioners, and visitors.³⁸ For these reasons, it is highly important to develop antimicrobial textile materials that minimize the growth of microbes on textiles and fibers during their use and storage. Both natural and synthetic, commercially available antimicrobial finishing agents are being used to address the increased demand for antimicrobial textiles.

Study of ancient mummy wraps preserved by the ancient Egyptians using different spices and herbs provides evidence of a long history of antimicrobial finishing of textiles.³⁹ Several plant-based natural products were reported to add antimicrobial finishing to the textiles. However, the immense necessity of antimicrobial finishing of

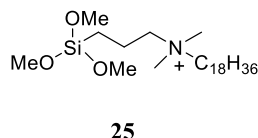
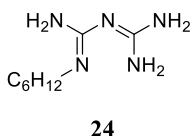
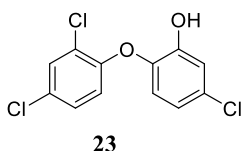
textiles first appeared in 1941 to protect the apparel of military personnel in the South Pacific.⁴⁰ Hot and humid environmental conditions in the region served as ideal conditions for the growth of organisms on natural fiber substrates, which led to damage to the fabrics and the rapid spread of infections among the personnel. During World War II, chemicals such as mixtures of chlorinated waxes, copper, and antimony salts were used to treat the fabrics to stiffen them and give them a distinct odor for protection from microorganisms.⁴¹ However, after the emergence of severe health effects and reported environmental deterioration caused by the overuse of these chemical agents, studies were more focused on the search for effective antimicrobial agents with less toxicity for both human health and the environment.

Besides possessing efficiency against microorganisms, compatibility with textile chemical processing and dyeing, cost-effectiveness, and environmental friendliness are some of the required criteria for any antimicrobial treatment performed on a textile. However, the main challenge is to be non-toxic (cytotoxicity, allergy/irritation, and sensitization) to the consumers. Also, it should not affect the ecology of non-pathogenic flora residing on the skin of the wearer.³³ It should not negatively affect the quality of the textile and should be durable to laundering, dry cleaning, and hot pressing. The most commonly used antimicrobial agents include quaternary ammonium salts, phenolic compounds, polyamines, triclosan **23**, chitosan, halamines, metal ions, antibiotics, and some natural dyes.⁴²⁻⁴⁵

Intermolecular interactions, including covalent bonds, and secondary interactions, such as Van der Waals forces, dipole-dipole interactions, and hydrogen bonding of polymer molecules with the antimicrobial finishing agents, determine the durability of incorporation of antimicrobial agents into fibers. Though the secondary

interactions can contribute to increasing the sustainability of antimicrobial finishing, ionic and covalent bonds are more efficient in adding durable functions to the materials.⁴⁶⁻⁴⁹

Different approaches have been developed to impart antimicrobial functions on fabrics depending on the types of antimicrobial agents and fabric types. For synthetic fibers, integration of antimicrobial agents into the polymer is done prior to extrusion or blended into the fibers during their formation, which increases the durability of the active agents as they are physically embedded in the structure of the fiber.³³ Conventional exhaust and pad-dry-cure processes are applied to incorporate agents such as triclosan **23** and PHMB **24** on some natural and synthetic fibers for their antimicrobial finishing.^{45,50-51} Padding, spraying and foam finishing have been utilized for the assimilation of silicone-based quaternary agent AEM 5700 **25** on the textiles.⁵²



Other reported methods used are the association of nanoparticles with a polymeric matrix to improve the durability of the antimicrobial effect, enzymatic surface modification of textiles for increasing hydrophilicity, and introduction of functional groups on the surface of the fabrics by the sol-gel technique.⁵³⁻⁵⁶ In addition, linking of the active agent onto the fiber using cross-linking and polymerization grafting or micro-encapsulation have also been reported in the literature.⁵⁷⁻⁶¹

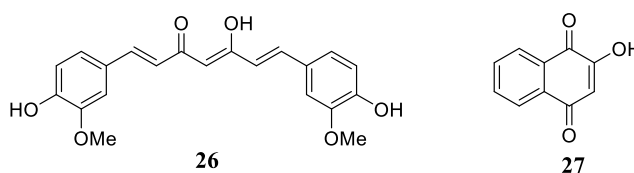
1.2. Antimicrobial natural dyes

Using natural products and natural dyes for the antimicrobial finishing of textiles is not a new concept. Several plant-based compounds such as terpenoids, flavonoids, polypeptides, quinones, tannins, and coumarins with a wide activity spectrum against different fungal and bacterial pathogens have been identified.⁶¹⁻⁷³ Their high compatibility with the environment, lower toxicity, and antimicrobial properties have increased their use in textile coloration. Due to their low fastness and inefficient extraction methods, the use of natural dyes is generally not as efficient as synthetic dyes. Nevertheless, a few attempts have been made to exploit the use of natural dyes as antimicrobial agents on the fibers.

Gupta et al. have studied antimicrobial properties of 11 natural dyes against Gram-positive and Gram-negative bacteria. The presence of tannins was responsible for antimicrobial activity in most of these natural dyes. Cotton fabrics treated with dyes in combination with alum or copper mordants showed 70-90% antimicrobial activity whereas the antimicrobial efficacy of the dyed fabric was decreased to 45-60% without mordanting.⁷⁵ The antimicrobial activities of cotton fabric dyed by extracts obtained from *Ocimum sanctum* and the rind of *Punica granatum* were assessed using AATCC-147 test method by Sathianarayanan et al. Washing durability of fabrics treated with direct application, microencapsulation, resin cross-linking, and their various combinations were also compared. All fabric treatments, except direct application, showed excellent antimicrobial activity as well as good wash durability.⁷⁶

Han and Yang used curcumin to provide color and antimicrobial properties to wool fabric using the conventional pad dyeing process. Very low concentrations of (0.05% - 0.2%) curcumin **26** were found to be effective against the microorganisms *S.*

aureus and *E. coli*, inhibiting their growth by 95%. The antimicrobial efficacy of the dyed fabric was reported even after 30 cycles of home laundering.⁷⁷



Yusuf et al. investigated the dyeing characteristics and antimicrobial efficacy of lawsone **27**, an extract from leaves of henna (*Lawsoma inermis*), applied on woolen yarn. The dyed samples were active against common human pathogens *E. coli*, *S. aureus*, and *C. albicans*.⁷⁸ Similarly, Ghaheh et al. studied colorimetric values, light and wash fastness properties along with antibacterial activity of five different natural dyes obtained from green tea, madder, turmeric, saffron petals, and henna on wool fabric. The results showed that all the natural dyes were considerably active against *S. aureus*, *E. coli*, and *P. aeruginosa*. Pre-treatment of the fabric with aluminum sulfate mordant improved the antibacterial effect.⁷⁹ Similarly, the antimicrobial activity study of catechu-dyed woolen yarn against *E. coli*, *S. aureus*, *C. albicans*, and *C. tropicalis* showed maximum activity at 20% w/v, inhibiting the microbial growth by more than 90%. Most importantly, its hemolytic activity study on human red blood cells indicates the dye being significantly less toxic causing $\leq 20\%$ hemolysis.⁸⁰

In another approach, polyamide fabrics were dyed with walnut shells in a single step dyeing process to evaluate their antimicrobial property. Dyed polyamide fabrics exhibited excellent antibacterial activity against *S. aureus* and *E. coli* with good fastness properties. Pre-treatment of the fabric with mordants ferric sulfate, cupric sulfate, and

potassium aluminum sulfate further increased antimicrobial activity as well as wash durability.⁸¹ Soybean protein fibers were dyed with madder, weld, and walnut seed husk by Jafari et al. The dyed fabric exhibited excellent antimicrobial properties against Gram-positive bacteria with good colorfastness.⁸²

Unripe citrus contains a wide range of flavonoid constituents, including hesperidin, naringin, nobiletin, and tangerine.⁸³ Lee et al. have optimized the dyeing conditions of the unripe citrus extract on silk fabric and evaluated its fastness properties along with antimicrobial activity on the dyed fabric. The antimicrobial activity of the dyed fabric against *S. aureus* and *K. pneumoniae* was investigated quantitatively. Excellent antimicrobial activity > 99% reduction rate against both bacteria was exhibited for all dyed fabrics with good fastness.⁸⁴

1.3. Aurone natural and synthetic dyes

Although natural product dyes are also potentially antimicrobial, one particularly biologically active family of natural products has not been examined in this context – the aurones. Aurones are also responsible for pigmentation in flowers and fruits; like other flavonoids, they possess a wide range of biological properties and have the potential to serve as an antimicrobial dye candidate.⁸⁵

In addition to blue and red color imparting anthocyanins, flavonoids have been the major sources of various yellow natural dyes. Isoflavones, in particular, have been known for their pale-yellow color, whereas the minor flavonoids, particularly aurones are well known for imparting a deep yellow color.⁸⁶ Aurones absorb in the 390-430 nm range, rendering more intense colors than the corresponding chalcones and flavonols.⁸⁷ The minor flavonoid aurones are found in several flowers of Scrophulariaceae and

Compositae families. Yellow Snapdragon flower is one of the best sources for aurones.⁸⁸ Not only limited to flowers, but they are also distributed in the bark, wood, leaves, and seedlings of various plants. Structurally, these small molecule aurones contain a benzofuranone ring A connected to a phenyl ring B by an exocyclic carbon-carbon double bond forming a stable (Z) isomer.⁸⁹⁻⁹² (Figure 1)

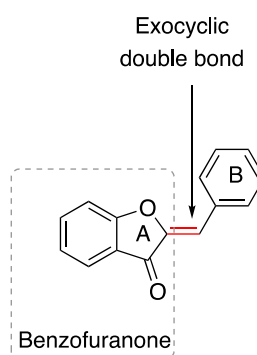


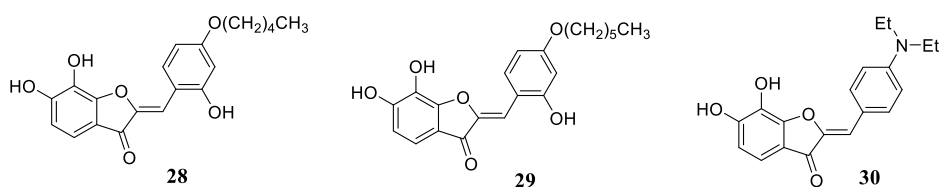
Figure 1: Aurone skeleton

Unlike the other subclasses of the flavonoid family, there is little historical evidence of aurones being used as dyes. A recent preliminary study from the Handy group showed the possibility of aurones as a dyeing agent for some natural fibers,⁹³ but a detailed study to assess their viability as dyes has not been reported. This can be somewhat attributed to their limited natural abundance, raising the necessity of synthesis to access a variety of aurones in reasonable quantities. This limited natural availability has led to the development of numerous synthetic strategies to prepare aurones, which will be discussed in detail in chapter-II.

Aurones are emerging as potential therapeutic heterocyclic scaffolds for the design and development of pharmaceuticals.^{91,94} They are reported to possess a wide

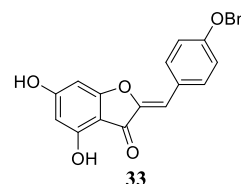
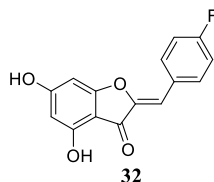
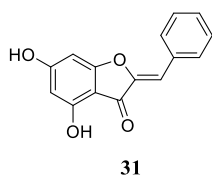
range of bioactivities, including antimicrobial, antiviral, anti-inflammatory, antioxidant, and anticancer properties.^{91,95-102} Focusing on their antimicrobial properties, various natural and synthetic aurones have been reported with antibacterial activities against *E. coli*, *B. subtilis*, *S. aureus*, *K. pneumoniae*, and *P. vulgaris*. They have also been proven to inhibit different fungal strains including *A. fumigatus*, *A. niger*, *A. clavatus*, and *C. albicans*.⁹⁹

Although the benzofuranone moiety itself contributes antimicrobial activity to an aurone molecule, flexibility in diversifying the substitution pattern on both rings of the parent structure has been found to further enhance their biological efficiency.⁹⁴ A study of a series of 6,7- dihydroxy derivatives of aurones with an ortho-hydroxy and a para-alkoxy substituent on the benzylidene ring showed better inhibition of chorismate synthase, an enzyme necessary for the survival of *S. pneumoniae*. Compounds **28** and **29** exhibited improved inhibition efficiency against the bacteria with IC₅₀ values of 0.22 μM and 0.32 μM, respectively, compared to the aurone derivative with a para-diethyl amino group **30** (IC₅₀ 8.0 μM).⁹⁶

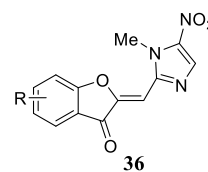
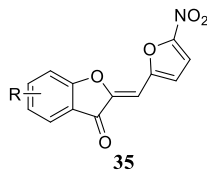
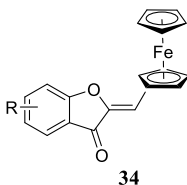


Recently, a set of variously substituted aurones were synthesized and evaluated against both Gram-negative and Gram-positive bacteria, including Methicillin-Resistant *S. aureus* (MRSA) and *P. aeruginosa* and some fungal species. Three compounds **31**, **32**, and **33** with similar 4, 6- dihydroxy substitution patterns in the

benzofuranone rings were selectively effective against most of the Gram-positive bacteria, but only two of them were effective against Gram-negative human pathogens *H. pylori* and *V. alginolyticus*.⁹⁴



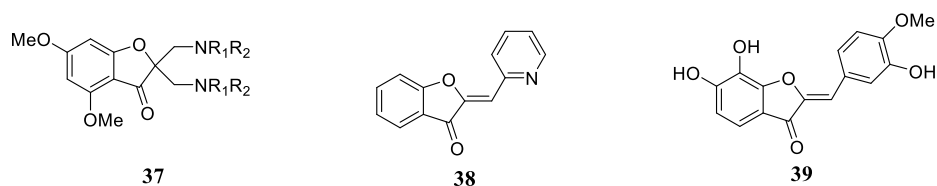
In another study, various ferrocene-substituted aurones **34** were synthesized and evaluated against antibiotic-sensitive and antibiotic-resistant strains of Gram-positive *Staphylococci* and Gram-negative *E. coli*. The results showed significantly lower MIC (minimum inhibitory concentration) ranging from 2-32 mg/L of ferrocenyl aurones compared to ferrocene-substituted chalcone derivatives, confirming the importance of the benzofuranone ring for antibacterial action.¹⁰³ Also, two Quantitative Structure-Activity Relationship (QSAR) studies of aurones showed that substituting the B-ring in aurones by 5-nitrofuran **35** or 5-nitroimidazole rings **36** improved inhibition of the growth of *S. aureus*, *S. epidermidis*, and *B. subtilis*.^{97,104}



Both antibacterial and antifungal activities were exhibited by aurone **37** synthesized by replacing the benzylidene group with a 2,2'-bisaminomethyl moiety. *In vivo* studies of these aurones on mice infected with *C. albicans* led to a significant

increase in the survival time for the treated group (40% death in 16 days) compared to the control (100% death).⁹⁵

Similarly, a study of the inhibitory activity of substituted aurones **38** and **39** against three different species of *Candida* showed that both compounds were effective against the tested fungi with IC₅₀ values below 20 μ M.¹⁰⁵



With all the information on their dual properties (pigmentation and antimicrobial properties), in this research, we envision aurones as potential dyeing candidates for the development of cost-effective and sustainable dyeing agents in the apparel and textile industries. Chapter II describes how we explored the *in situ* synthesis of aurone, and the simultaneous dyeing of fabrics inspired by the proven dyeing ability of many flavonoids and other classes of the flavonoid family.

2. Natural products as a photocatalyst

Including biochemical reactions, many chemical transformations are mediated by catalysts, which can be metallic, enzymatic, or organic. While nature utilizes highly specific biomolecules, called enzymes, to catalyze various biochemical processes, most chemical transformations rely on transition-metal-based catalysts for high selectivity and efficiency. Although organocatalysis by small organic molecules has been known for over a century, transition metal-catalyzed reaction methodologies have remained the prevailing approaches in building organic molecules.

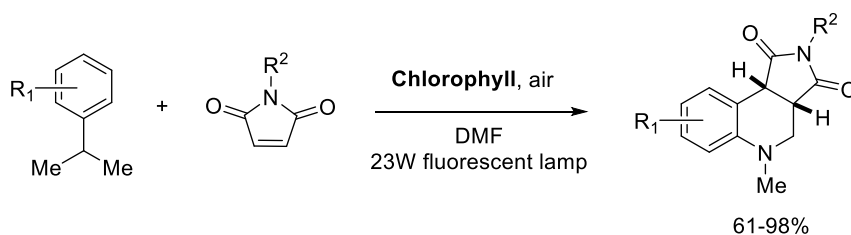
Owing to the sustainability issues related to some transition metals' environmental and toxic effects, organocatalysis, which uses small organic molecules as a catalyst, has gained remarkable attention from the broader chemical synthesis communities since the late 1990s.¹⁰⁶⁻¹⁰⁸ It is evolving as a complementary mode of catalysis, capable of reducing costs, time, and energy consumption in synthetic processes. As most organic molecules are inherently air and moisture-stable, expenses related to handling and storage are significantly lowered. Usually, small organocatalysts are readily accessible to all-scale reactions and are relatively non-toxic and environmentally safer than metal catalysts.¹⁰⁴⁻¹⁰⁶ Some of the well-known organic catalysts include Cinchona alkaloids quinine, L-proline, proline-pyrrolidine-oxyimide, and L-prolinamides.¹⁰⁶⁻¹¹⁰

The concept of organocatalysis expands into the realm of photochemistry, where it is known as photoredox catalysis. It utilizes an inexpensive and endlessly renewable energy source - visible light - to bring about a chemical transformation in the presence of an organic photoredox catalyst or its transition metal counterparts. Like organocatalysis, the photoredox catalysis field has been dominated by transition metal-based photocatalysts, typically ruthenium (Ru) and iridium (Ir) polypyridyl complexes, for decades.^{107,111,112} Although these traditional transition-metal-based catalysts have demonstrated their robustness and versatility in organic synthesis owing to their relatively long-lived excited-state lifetimes, their utility is limited in terms of sustainability as these metals are some of the rarest metals in the earth's crust. Additionally, these metals can be toxic to the environment and human health because of the possible trace metal contamination in the products formed, which limits their use in the pharmaceutical and chemical industries.¹⁰⁶⁻¹⁰⁸

In this context, drawing inspiration from how nature utilizes the natural product chlorophyll for harvesting light during photosynthesis, substantial progress has been made in designing and synthesizing natural products based organic photocatalysts that can potentially match or surpass the performance of transition metal photocatalysts. These advancements have allowed us to achieve distinctive reactivity by enabling the transformation of a broad range of unreactive substrates to some extent.^{111,113}

The essential photophysical properties of photocatalysts, including organic photocatalysts, incorporate the ability to absorb visible light. They show efficient charge separation and charge transfer properties, possess a wide range of redox potentials in the excited state, and have a high electrochemical stability.^{108,114} Organic photocatalysts further offer greater solubility in organic solvents and, most importantly, offer a flexible framework for fine-tuning the photophysical parameters. Some common organic photocatalysts are shown in Figure 2.¹¹¹

Shanmugam et al., in 2015, reported the successful use of chlorophyll as a photocatalyst in developing a photoinduced living radical polymerization methodology under blue and red light. This method allows excellent control over molecular weight and polydispersity.¹²² In another study, Guo et al. reported a green and efficient synthesis of tetrahydroquinolines from *N,N*-dimethylanilines, and maleimides using light energy and chlorophyll as a photosensitizer under an atmosphere of oxygen (Scheme 1).¹²³

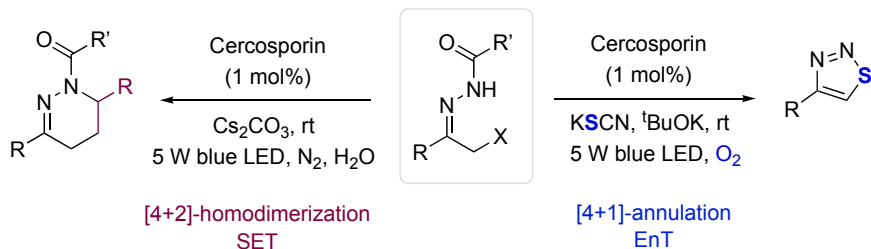


Scheme 1: Chlorophyll-catalyzed visible-light-mediated synthesis of tetrahydroquinolines.

Although not as thoroughly characterized, the perylenequinones, have gained considerable attention in photocatalysis.¹²⁴ They are characterized by a highly conjugated pentacyclic chromophore system, attributed to their photoactivity. Hypocrellins A, Elsinochrome C, and cercosporin (C.P.) are some of the known PQPs (Perylene quinonoid pigment) for their photosensitizing properties arising from energy transfer (EnT) and electron transfer (E.T.) processes.^{125,126}

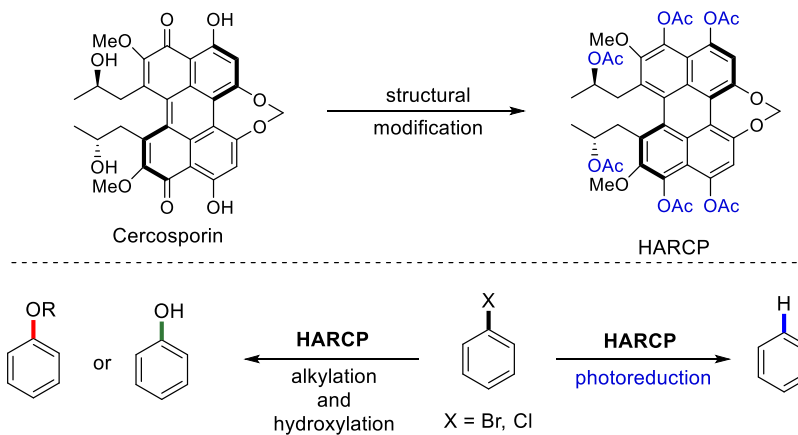
Among them, cercosporin (C.P.) has been successfully employed as an organic photocatalyst in various organic reactions, including oxidation, cycloaddition, and cross-coupling.¹²⁷ Zhang et. al. in 2019 reported photocatalytic [4+1] annulation and

[4+2] cyclodimerization of azoalkenes in the presence of 1 mol% of cercosporin affording N-containing heterocycles, particularly 1,2,3-thiadiazoles and 1,4,5,6-tetrahydropyridazine derivatives.¹²⁸



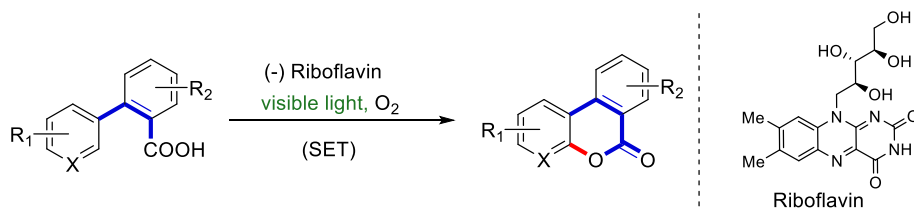
Scheme 2: Cercosporin-catalyzed [4+1] and [4+2] annulations of azo alkenes

Li. et. al. developed a novel and highly efficient perylenephotoreductant, hexaacetyl reduced cercosporin (HARCP), through structural manipulation of cercosporin (C.P.) that can achieve multiple reactions, including photoreduction, alkylation, and hydroxylation constructing C-H and C-O bonds as depicted in Scheme 3.¹²⁷



Scheme 3: HARCP as a novel photocatalyst

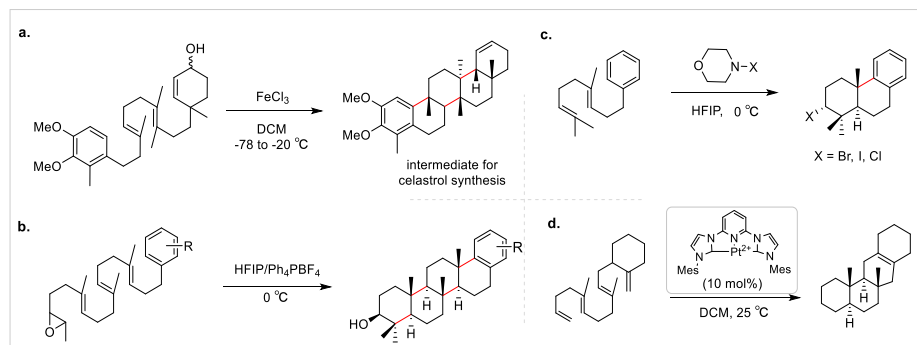
Due to their excellent redox window and better photochemical stability, flavins have been recognized for their photocatalytic property.¹²⁹ Among them, riboflavin (vitamin B2) and its derivatives, which absorb in the blue region of the visible light spectrum, have garnered attention for promoting a variety of organic transformations, including catalytic oxidations, decarboxylative cyanation, nitration, and cyclization¹³⁰⁻¹³⁴. Gilmour et.al reported their one-pot (–)-riboflavin-mediated photocatalytic synthetic strategy for direct cyclization of biaryl carboxylic acids.¹³⁵ (Scheme 4)



Scheme 4: (–) Riboflavin-mediated photocatalytic synthesis of benzocoumarins

Among a myriad of organic reactions, polyene cyclization is a powerful chemical transformation due to its capacity to emulate nature's way of constructing complex polycyclic structures, including cholesterol, from simple acyclic polyene precursors. Since the late 1960s, the scientific community has made astonishing progress in developing the diverse biomimetic synthetic strategies at our disposal.¹³⁶

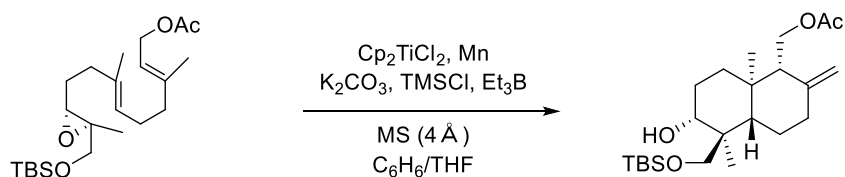
Broadly, these strategies can be categorized into cationic and radical-mediated polyene cyclization. Cationic polyene cyclization can be mediated by Lewis acids (InBr_3 , FeCl_3 , $\text{BF}_3\cdot\text{OEt}_2$, TiCl_4 , $\text{Ti}(\text{O}^i\text{Pr})_4$, Et_2AlCl , SnCl_4 , BBr_3), Bronsted acids ($\text{H}_2\text{O}/\text{HFIP}$, $\text{HFIP}/\text{Ph}_4\text{PBF}_4$, HFeCl_4), halogen electrophiles ($\text{Et}_2\text{SBr}\cdot\text{SbCl}_5\text{Br}$ (BDSB), DBDMH, N-halomorpholines), or sulfur electrophiles.¹³⁶ (Scheme 5)



Scheme 5: Cationic Polyene Cyclization: a) Lewis acid mediated b) Bronsted acid mediated c) Halogen electrophile initiated d) Transition metal mediated.

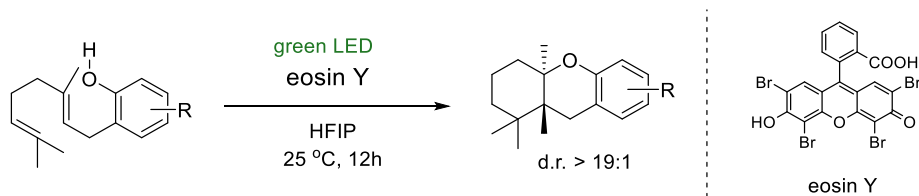
Although cationic polyene cyclizations dominate the literature, radical polyene cyclizations have also been explored and developed since 1960.¹³⁶ The radical polyene cyclization can be achieved either through transition-metal-mediated or photocatalyst-mediated processes. Not surprisingly, most of these reactions utilize transition-metal-

based catalysts, leaving a minimal number of examples relying on photocatalysis. The most common transition metal complexes for this purpose includes titanocene (III) monochloride (Cp_2TiCl) which in many cases is generated *in situ* with a $\text{Cp}_2\text{TiCl}_2/\text{Mn}$ system where Mn acts as a reductant. Other such systems reported include $\text{Mn}(\text{OAc})_3/\text{Cu}(\text{OAc})_2$, and $\text{Fe}(\text{acac})_3/\text{PhSiH}_3$.¹³⁷⁻¹³⁹ (Scheme 6)



Scheme 6: Transition-metal-mediated radical polyene cyclization

On that note, most of the documented photocatalysts depicted in Figure 3, including natural products, have found application in various organic transformations other than polyene cyclization. Among those, xanthene-based eosin Y is the sole reported example utilized in polyene cyclization reactions. In 2015, Yang and coworkers reported an unprecedented reaction protocol using an organic dye eosin Y as a photocatalyst under green light for stereoselective radical cyclization of various polyprenoids and polyene with 1,3-dicarbonyl compounds.¹⁴⁰ (Scheme 7)



Scheme 7: Eosin Y-catalyzed visible-light-mediated polyene cyclization

Having this example at our disposal, we found ourselves motivated by the potential utility of aurones as a photocatalyst for the polyene cyclization reaction. Aurones are a minor sub-class of the flavonoid family. They are well documented for their pigmentation role in imparting dark-yellow color to flowers and fruits.¹⁴¹ Structurally, aurones contain a heterocyclic benzofuranone moiety attached to a phenyl ring via an exocyclic double bond.¹⁴² (Figure 3) The presence of an exocyclic double bond offers an extended conjugation making the structure absorb at a relatively longer wavelength than the corresponding other flavonoids.¹⁴³⁻¹⁴⁴ Despite their promising photophysical properties, they have not been reported for their possible photocatalytic role.

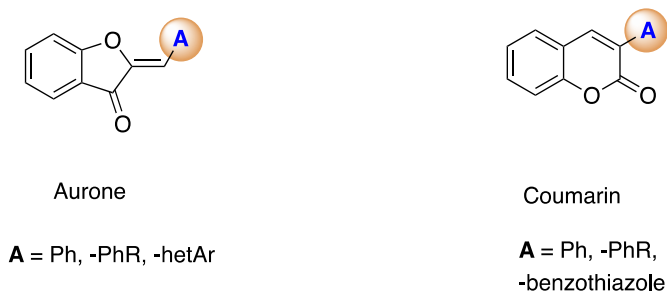
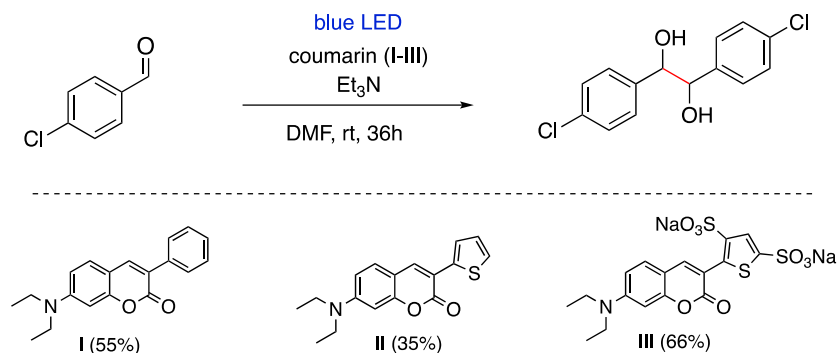


Figure 3: Representation of aurone and coumarin scaffolds

What has been explored is the use of related coumarins. Gualandi and coworkers in 2018 reported an example of coumarin dye derivatives capable of catalyzing the pinacol coupling of aldehyde, ketones, and imines in the presence of blue LEDs.¹⁴⁵ (Scheme 8)



Scheme 8: Pinacol coupling mediated by coumarin in the presence of visible light

Based on this precedent, the initial plan was to utilize their reported coumarins in a polyene cyclization reaction before moving on to exploring aurones. In Chapter III, it will be discussed how this curiosity about the possible utility of natural product aurones as photocatalysts for polyene cyclization led to the development of a blue light-mediated catalyst-free cascade cyclization of geranyl-substituted phenols.

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CHAPTER II

SYNTHESIS AND STUDY OF THE DYEING PROPERTIES OF AURONES

1. Background

Textile dyeing is the process of giving color to a textile. The earliest dyeing, traced back to the bronze age, might have been discovered accidentally through staining by various fruits and plant parts^{1,2} Soon, it became a well-developed form of art that propagated with human civilizations. The dyed fabrics obtained in Egyptian tombs highlight the cultural value of textile dyeing as early as 3000 B.C,³ which soon became an indicator of wealthy social class in some communities, particularly the specific color 'royal purple', whose use was reserved for certain aristocrats.⁴

There are two main sources of dyes: organic/natural and synthetic. Natural dyes are extracted from various plants and animals. Until the 19th century, natural dyes were the only source of textile dyes,⁵ which were subsequently replaced by synthetic dyes prepared from fossil resources.⁶ Accessible synthetic routes, low production cost, flexibility in color variation, and the improved dyeing quality of synthetic dyes became the major factors driving natural dye replacement.⁷ More recently, increasing concerns regarding human health and environmental contamination has raised awareness of the toxicity of synthetic dyes⁸ and driven a resurgent interest in natural dyes and pigments as a sustainable alternative. Gradually, technological upgrading initiatives have been adopted and implemented in various regions of the world to improve the industrial

production of natural dyes and pigments. One prominent attempt has been conducted by the PrisCA project (Italy) to determine the feasibility of using the plant *Reseda luteola*, found in Europe and the Mediterranean region, as a source of yellow dye.⁹⁻¹⁰ The better agronomic potential, brilliant color and an excellent light fastness of its ground powder¹¹ are attributed to a flavonoid called luteolin (Figure 1), which had been found to dye textiles in yellow, dating back to the early 1500s.¹²

2. Aurone as a source of yellow dye

One of the characteristic features that attracts attention in nature is the bright yellow color of flowers, fruits, and leaves of plants. The primary source of this yellow color is a family of natural products called flavonoids.¹³ Flavonoids are responsible for pigmentation in plants and have been employed as a major source of a natural yellow dye for textile dyeing from the ancient era of human civilization. Dye analysis of archaeological textiles dating from the 17th century BCE to the 10th century CE has detected the presence of flavonoids luteolin **1**, rhamnetin **2**, rhamnazin **3**, quercetin **4**, (Figure 4) and their glycosides.¹⁴

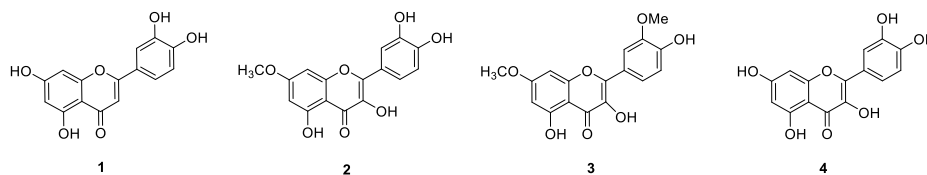


Figure 4: Structure of luteolin, rhamnetin, rhamnazin, and quercetin

Based on their natural abundance, flavonoids, which structurally constitute the C6-C3-C6 skeletal framework, are broadly classified into major and minor categories

(Figure 5). The major flavonoids, including flavone, isoflavone, flavanol, and dihydroflavonol, are abundant in nature and produce yellow shades in plants.¹⁵ The minor flavonoids, aurone and chalcone, are limited in occurrence, but impart deeper yellow-orange hues, giving vibrant golden colors to flowers and fruits.^{16,17}

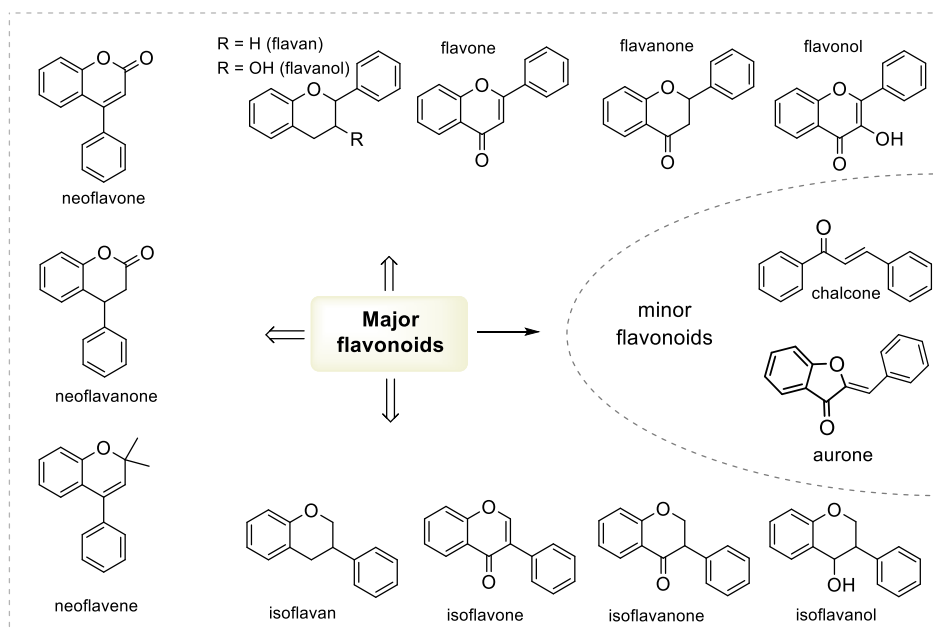


Figure 5: Major and minor flavonoids

This difference in the intensity of the yellow shades is attributed to the inherent light-absorbing properties of the compound dictated by their structural features. Major flavonoids such as flavones, isoflavones, and flavanones possessing a 6:6 chromane system attached to a phenyl ring, generally exhibit UV absorption at 300-350 nm, giving a pale-yellow color, whereas flavonols absorb at 350-385nm. (Figure 6) This absorption range further shifts to 340-390 nm for the minor flavonoid chalcone, adding a darker hue to the yellow color.^{18,19} Unlike other flavonoids, aurones possess a 6:5

benzofuranone core connected with an aryl group by an exocyclic C-C double bond.²⁰ This structural feature extends cross-conjugation between the aryl ring and benzofuranone moiety, extending the absorption range to a lower energy visible region (370-430nm) than the more common flavones.^{18,21} (Figure 6) Overall, this makes aurones the brightest yellow pigments among the flavonoids.

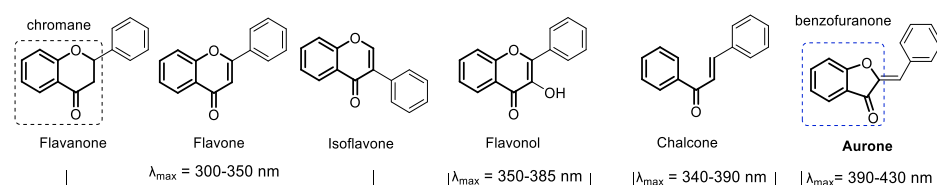


Figure 6: UV-absorption of different flavonoids

More importantly, the absorption properties of aurones can be extrinsically manipulated, which allows flexibility in tuning various photophysical properties. Such tuning can be achieved by aptly substituting electron donating/withdrawing groups in the acceptor (benzofuranone) and donor (phenyl or aryl) moieties of the aurone skeleton. (Figure 7) Studies have shown that the presence of electron-donating groups such as $-NH_2$ at the 4' position on the donor moiety results in a bathochromic (red) shift on the UV-Vis absorption band compared to the unsubstituted aurone due to an extended conjugation.^{21,22} The absorption band of the 4'-aminoaurones (417 nm) was further pushed to 436nm and 510nm, respectively, when electron-withdrawing groups $-CF_3$ and $-NO_2$ were introduced at the 4-position of the acceptor part (benzofuranone). The reason can be explained based on the enhanced push-pull behavior of the molecule when the rings are substituted by electron-donating and electron-withdrawing groups at the opposite sides of the exocyclic double bond.²³ The small structure and relatively

high tunability of light absorption properties of an aurone framework have made it a promising scaffold for fluorescent probes in recent years.²⁴⁻²⁶

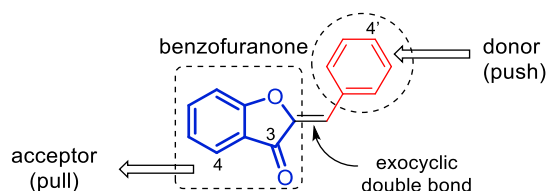
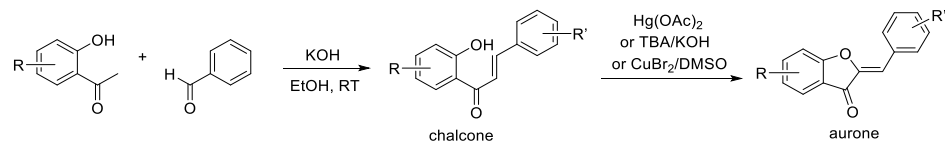


Figure 7: Aurone structure and push-pull effect

3. General methods of aurone synthesis

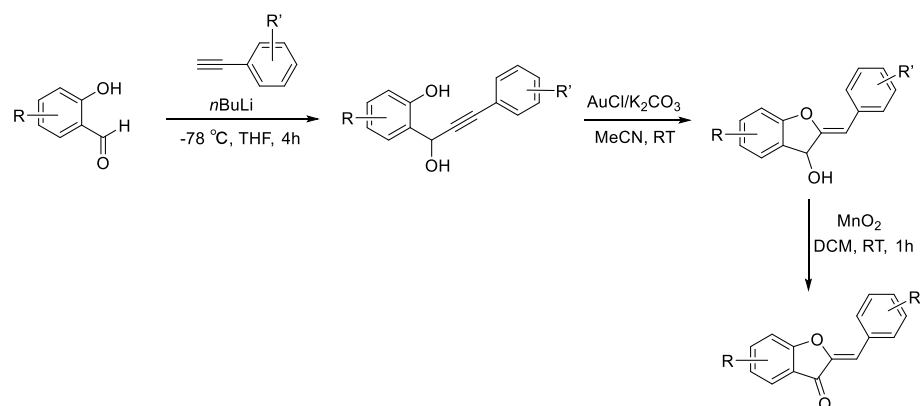
In nature, aurone and its derivatives are biosynthesized by the oxidation and cyclization of chalcones in the presence of enzymes.²⁷ As a secondary metabolite, aurones not only facilitate pollination in plants with their bright yellow color²⁸ but also are well known and studied for their broad range of biological properties, including antibacterial,²⁹⁻³¹ antioxidant,³²⁻³⁴ and antifungal.³⁵ Despite their promising dyeing properties, the study of aurones as a viable dye for textile dyeing is very limited.³⁶ One of the possible reasons could be their limited natural occurrence, which raises the necessity of efficient synthetic approaches to access varieties of aurones.

In this context, three major approaches have been reported in the literature for synthesizing aurones. The first one involves oxidative cyclization of 2'-hydroxychalcones. These pre-synthesized chalcones can be oxidized under various conditions, including using mercury (II) acetate ($\text{Hg}(\text{OAc})_2$),³³ copper (II) bromide (CuBr_2),³⁷ or tetrabutylammonium tribromide.³⁸ (Scheme 9) The oxidative cyclization does suffer from a limited substrate scope.³⁹



Scheme 9: Aurone synthesis via oxidative cyclization of chalcone

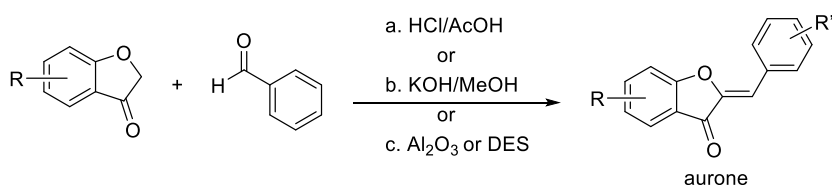
Another approach involves a three-step synthesis from an ortho salicylaldehyde. This low-temperature three-step reaction begins with alkynylation to form a 2-(1-hydroxy prop-2-ynyl) phenol. The phenol is further subjected to an oxidative cyclization to an aurone scaffold in the presence of gold(I) catalyst and then MnO_2 .⁴⁰ (Scheme 10)



Scheme 10: Au(I)-catalyzed aurone synthesis via oxidative cyclization

The most general and versatile method for aurone synthesis is the direct condensation of a benzofuranone with an aromatic aldehyde. This Knoevenagel-type condensation, as depicted in Scheme 11, was first reported by Geissman and Harborne in 1955.⁴¹⁻⁴⁷ Except for some labile functionalities, this strategy tolerates acidic, neutral, and basic reaction conditions.^{41,43,48} Besides regular organic solvents, deep

eutectic mixtures can be employed as neutral reaction media.⁴⁹ Neutral alumina-mediated condensation, another neutral option, is generally suitable for substrates with sensitive functional groups.⁴⁷ This method does not work well with hydroxy-substituted benzofuranone substrates, which, instead prefer acid-catalyzed (HCl) condensation in a glacial acetic acid medium.²⁶



Scheme 11: Aurone synthesis via aldol-type condensation

4. Standardized test methods to determine colorimetric properties of dyed fabrics

Textile items undergo color challenges under external stress factors, including exposure to light, washing with harsh detergents, heat application, perspiration, and many more. To determine the quality of textiles, assess the colorimetric properties of the dyed fabrics, and evaluate their resistance against external factors, several testing methods have been established that can be performed in a controlled laboratory setting by reproducing some real-life challenges that may result in color change of textiles.⁵⁰ These test methods follow a common general method, are easy to perform, and reproducible.^{51,52} Out of all, ISO (International Organizations for Standardization) and AATCC (American Association of Textile Chemists and Colorists) testing methods are commonly used worldwide. Although ISO and AATCC publish their testing protocols

for evaluating textile materials, both share common working principles and evaluation methods for many tests.⁵² Traditionally, assessment and evaluation of color changes in the material were visually assessed with reference to standard grey scales in these test methods.⁵⁰ However, with improved technological advancement, more accurate quantitative results should be possible.

5. Colorimetric properties of a dyed fabric

5.1. Dye exhaustion

Dye exhaustion is (E) the measure of the proportion of the dye absorbed by the fiber in relation to the amount of initially used dye. It is determined spectrophotometrically by measuring the $\lambda_{\max}$ dye absorbance of the dyebath solution before and after dyeing. It is expressed in percentages using the formula depicted below, where A_1 and A_2 are the $\lambda_{\max}$ absorbances of the dye solutions before and after dyeing.^{53,54}

$$\% \text{ Dye Exhaustion} = [(A_1 - A_2) / A_1] \times 100$$

5.2. Color strength

Color strength, quantified by the K/S ratio, is a crucial parameter for assessing the color depth of the dyed fabric. The test measures the reflectance of a fabric at $\lambda_{\max}$ of the dye using a reflectance spectrophotometer. The ratio (K/S) is calculated using the Kubelka-Munk equation, where higher K/S values represent darker and more saturated colors.^{55,56}

$$\frac{K}{S} = (1 - R_{\lambda_{\max}})^2 / 2R_{\lambda_{\max}}$$

Where, K represents the absorption coefficient, S the scattering coefficient, and $R_{\lambda_{\max}}$ is the reflectance value of the fabrics at $\lambda_{\max}$ of the dye.

5.3. Colorfastness

In the textile industry, fading of color has always been a prime concern as the change in depth of shades occurs through various inevitable factors. Colorfastness is the measure of resistance of the level of color change of a material under the influence of external stress factors such as exposure to wash, light, or perspiration.⁵⁷ It simply reflects the color retaining ability of a fabric. Some dyes fade faster and are more prone to color loss via other factors. Several methods have been developed to assess color fastness of the dyed fabrics.

5.3.1. Colorfastness to rubbing/crocking

Rubbing or crocking fastness is the transfer of dyed textile material's color from its surface to a specific test cloth by rubbing.⁵⁸ For rub fastness, the standard methods reported are the ISO 105-X12 test or AATCC 8, using a crock meter on which a dyed fabric, wet or dry, is rubbed against a reference test cloth.^{54,59} Rubbing fastness is influenced by various factors, including dye quality, type of rubbing cloth, the number of strokes, the force applied during rubbing and water content in the fabric.⁶⁰

For the test, two individual fabric specimens of at least 5 cm x 13 cm are required, one each for the dry and the wet tests. During the process, the testing sample is fixed, and the finger of the crock meter covered with a dry cotton rubbing cloth (5 cm × 5 cm dimension) rubs over the sample at least ten times in a back-and-forth direction. The same procedure is repeated with a wet rubbing cloth for the wet rubbing fastness test. The degree of staining of the two cotton rubbing cloths is assessed using

the grey scale for staining 1 (poor)- 5(excellent).⁶¹ Since double rubbing force is applied for the wet testing procedure compared to dry rubbing, wet rubbing fastness usually shows poorer results than the dry ones.⁶² In addition, while using a wet rubbing cloth, part of the dye may be solubilized in water and easily migrate to the surface of the test specimen, which easily stains the rubbing cloth.⁶³

5.3.2. Colorfastness to wash

A fabric's resistance to the loss and change in any color characteristics when subjected to washing is called colorfastness to wash.⁶⁴ It is the most common colorfast test. Unfixed dye molecules on the fabric surface usually come off due to friction from agitation during washing. Similarly, temperature of water, type of detergent and bleaching agents used, and the chemical interaction of these agents with dye molecules are also contributing factors to poor wash fastness.

For washing fastness measurements, samples are tested under appropriate temperature conditions, detergent solution, bleaching, and abrasive action, and evaluation is done according to the standard procedure ISO 105-C06 or AATCC-61.^{54,65} A test sample measuring 10 cm x 4 cm of the textile is stitched between two undyed cotton fabrics of size 5 cm x 4 cm. The attached fabrics are washed at 50°C for 30 mins in a washing solution that contains sodium perborate (1g/L) and ECE phosphate detergent (4.0g/L). The color change in the dyed fabrics and the staining of the adjacent fabric are evaluated by greyscale standards 1(poor) - 5(excellent). The colorfastness to washing should be at least 3-4 for color change and staining.⁶⁴

5.3.3. Colorfastness to light

Light fastness is another key parameter evaluated for the quality of dyed fabric and refers to the ability of the fabric to retain color when exposed to light for an extended period.⁶⁶ The resistance to light depends on the intensity of light, inherent properties of the fabric, season, altitude, and the distance from the equator.⁶⁷ While rub and wash impose mechanical stress on the fabric surface, light usually degrades color through photochemical reactions in the presence of UV and visible light. The extent of color loss due to sunlight or artificial light sources is one of the common problems recognized in the textile industry. The extent depends on how firmly dye molecules are adsorbed on the fabric surface, how well the fabric absorbs UV-light, and how active dye molecules are towards photochemical reactions when exposed to a light source. In this context, the keratin backbone of wool fiber is reported to absorb high UV radiation due to photoactive amino acids, including cysteine, tryptophan, tyrosine, and phenylalanine.⁶⁸⁻⁷⁰

In the presence of UV light, which has higher energy than visible light, the dye molecules undergo electronic excitation to a higher state, which transfers energy to atmospheric triplet state oxygen during the quenching process, generating reactive singlet oxygen. The interaction of excited dye molecules with light also forms reactive superoxide radicals.⁷¹ These reactive species can destroy the dye molecules on a fabric's surface. Also, the excited dye molecules themselves can degrade through photolysis, photo redox, and photosensitization, leading to shade depth fading. The ISO-105-B02 or the AATCC-16 are the commonly employed methods for testing light fastness, which includes exposing the dyed fabric to an artificial light source that mimics the daylight generated by passing xenon arc lamp-generated light through a

series of filters.^{65,72} During the testing process, a small test sample and a series of eight blue wool standard fabrics (reference 1–8) arranged on a suitable backing are exposed to high-intensity xenon-generated light under controlled humidity and temperature conditions. The lightfastness rating system is based on the fading rate of eight blue-dyed wool samples, which are rated from 1 (poor) to 8 (excellent). 4-5 ratings are acceptable values.^{72,73}

6. Factors influencing the colorimetric properties of a dyed fabric

Textile dyeing is a process to apply uniform color to any textile material, including fibers, yarns, and fabrics, not only to enhance the color and design of the dyed material, but also to improve product characteristics in terms of fastness to washing, rubbing, perspiration and light.⁷⁴ A better outcome of the process is the interplay of various external and internal factors. External factors refer to the environmental conditions affecting the product and are less likely to be controlled. Internal factors refer to the firmness of the combination of dye and fiber, concentration of dyes and dyeing auxiliaries, pH of the solution, material to liquor ratio, temperature, and time.^{75,76} These process parameters not only impact the degree of coloration on the fabric, but also evaluate and determine the manufacturing cost linked to the dyeing process.⁷⁷ Since the internal factors can be manipulated, focus must be given on improving these parameters. Some of them are described below.

6.1. Dyeing Process

The dyeing process follows three steps: pre-treatment (preparation), dyeing, and post-treatment (finishing). The success of each step is dependent on the optimum interplay of several variables, including the quality of the fibers, the correct choice of

chemicals, the dyeing method, and the type of equipment used.⁷⁸ Pre-treatments such as de-sizing, scouring, mercerization, degumming, beaching, etc., help to remove any impurities or foreign materials from the fabrics.⁷⁹ Similarly, post-treatments involve permanent press treatments, waterproofing, softening, antistatic protection, and microbial protection.⁸⁰ Both pre-treatments and post-treatments aim to improve the coloration and quality of the fabric. They can be done either by mechanical or chemical methods, depending on the nature of the fabrics used.

Two types of methods, continuous and batch process, are commonly used for dyeing. The continuous dyeing process involves simultaneous dyeing of fabric and fixation of dye in one operation. In this process, dyeing can be done either by immersing a fabric in a dyebath solution, or by spraying dye solution on the fabric. Then the dyed fabric is passed through a squeeze roller to remove excess liquid, a process known as padding. Heat and steam are applied afterward to ensure dye adsorption on the fabric.⁸¹ Batch or exhaust dyeing is another dyeing method that entails submerging a fabric in a dyebath solution and dyeing occurs as dye molecules diffuse onto the fabric's surface through the movement of either dye-liquor or the substrate being dyed.⁸² Exhaust dyeing operates in two phases- a rapid adsorption phase followed by a rate-determining diffusion phase⁷¹ in which the uniform coloration of fabric depends on the uniformity of the dye bath solution, rate of dye adsorption, dyeing temperature, and rate of dyeing.⁸³

6.2. Selection of dyes and fibers

The quality of dyeing materials greatly influences the quality of the dyeing process. For uniform coloration, dye candidates must show a high affinity to fabrics, resist fading when exposed to an external environment, and be relatively inexpensive.⁸⁴

The choice of a dye and its compatibility with the chosen fabric is crucial because different dyes have different chemical or physical binding abilities with the fiber. The strong binding forces enhance the color fixation and fastness of the fabric.⁸⁵ Fixation of the dye molecule to the fiber may involve at least one of the four types of chemical interactions depending on the chemical structure of the dye molecule and the types of functional groups on the fiber: ionic bonding, Van der Waals interaction, hydrogen bonding, and covalent bonding.⁸⁶

Ionic bonds are formed between oppositely charged ions present in the dye and fibers. Wool, silk, and nylon contain positively charged amino groups and negatively charged carboxylic groups in their structure. So, the basic group in the fabric can quickly form ionic bonds with water-soluble acid dyes containing sulphonic ($-\text{SO}_3\text{H}$) or carboxylic ($-\text{COOH}$) groups.⁸⁴ Conversely, cationic or basic dyes can interact with the fiber's carboxylic ($-\text{COOH}$) groups.^{86,87}

The covalent bond is another strong interaction that can be formed between a dye molecule with a reactive electrophilic site and a fiber having nucleophilic functional groups such as $-\text{OH}$, $-\text{NH}_2$, or $-\text{SH}$.⁸⁸ Dyeing cotton fabrics with reactive dyes under alkaline conditions is a typical example of forming such covalent linkage. The alkali used in the process ionizes the hydroxyl groups in cotton, which can interact with a reactive group (mono- or dichloro triazine) within the dye molecule to form a covalent bond.⁸¹

While not as strong, hydrogen bonding between the dye molecule and the fiber is another effective way to retain dyes on fabrics. The dye molecule must have a hydrogen atom bonded to a strongly electronegative atom for H-bonding. This H-atom interacts with free electron pairs of highly electronegative heteroatoms (generally N or

O) present in the structural constituents of a fiber, forming the hydrogen bond. While dyeing hydrophobic polyester fibers with disperse dyes, hydrogen-bonding is the major intermolecular force for strong dye substantivity towards the fiber.⁸⁹

Besides hydrogen-bonding, dyeing of PET fibers with disperse dyes also involves much weaker van der Waals forces as well as dipole-dipole type interactions between the polar dye molecule and the fiber.⁹⁰ Both options rely on the proximity of dye molecules and fiber.^{74,84} Dyeing of PET fabric is generally carried out at high temperatures, which causes swelling of fiber, facilitating diffusion of dye molecules into the empty space. When the fiber returns to its original shape, the dye molecule is trapped and held within the fiber by van der Waals forces.⁹¹

6.3. Selection of dyeing auxiliaries

For effective dyeing, the exhaust dyeing method typically utilizes additional chemicals known as auxiliaries, including surfactants, acids, alkalis, electrolytes, and leveling agents, at various dyeing stages. Although some auxiliaries fulfill more than one function, specific auxiliaries have proven effective for targeted results.⁹² Inorganic electrolytes NaCl and Na₂SO₄ are employed with reactive dyes to enhance dye exhaustion and dye fixation on cellulose fibers by generating an electrically positive bilayer.⁹³ This bilayer drives dye molecules to the cellulose fiber surface, which are otherwise repelled by the negatively charged cellulose surface in an aqueous medium. The process can be further enhanced by adding an alkali auxiliary, which forms cellulosate ions, leading to strong dye-fiber covalent interactions.⁹⁴⁻⁹⁵

Although the addition of alkali during the dyeing of cellulosic fibers with reactive dyes enhances dye-fiber bonding, it also induces the hydrolysis of reactive dyes

depleting dye-fiber fixation efficiency and dye fastness.⁹⁶ The dyed cellulosic fabrics must be treated with additional wash-off agents during the finishing process to improve fastness.⁹⁵ In the case of aqueous dyeing of textiles with water-insoluble disperse dyes, the process demands employing a suitable concentration of dispersing agents, such as lignin sulfonates or polycondesates of aryl sulfonic acids with formaldehyde, to disperse dye aggregates in the form of micelles to the fiber.⁹⁷⁻⁹⁹

6.4. Solvents used for dyeing

Conventional dyeing requires large amounts of water as a dyeing solvent and utilizes several chemicals at various stages of the dyeing process, which generates hazardous effluents.¹⁰⁰ In considering possible replacements, key desirable features include low cost, easily accessibility, innocuous, non-inflammable, non-corrosive, inert to textiles and stable to repeated recovery.¹⁰¹ Although several dyeing and processing techniques have been developed, including using supercritical carbon dioxide dyeing, air-dyeing, plasma processing, and enzymatic surface modification,¹⁰²⁻¹⁰⁵ their broad applicability is restricted by high cost and operational complexities in terms of dye solubility, energy demand, and treatment conditions.^{106,107}

As a part of the solution, organic solvents are used as an alternative to water for dyeing processes.¹⁰⁸⁻¹⁰⁹ Although organic solvents reduce the generation of effluents and control environmental costs,¹¹⁰ their application was mostly limited to wet processing such as de-sizing, scouring, bleaching, and finishing.¹¹¹ In 1920, organic solvents as a dyeing medium were introduced with the introduction of hydrophobic fibers like cellulose acetate, which are not possible to dye in an aqueous solution.¹¹²

Organic solvents, especially hydrophilic ones, act as dyeing solvents and also contribute to dye absorption. Similarly, when mixed in water, hydrophobic organic solvents form a two-phase system that facilitates the movement of dye molecules from the hydrophobic solvent to the aqueous, leading to increased dye adsorption on fabric surfaces.¹¹³ Organic solvents, particularly chlorinated hydrocarbons, such as tetrachloroethylene or perchloroethylene (PCE), trichloroethylene, and 1,1,1-trichloroethane, are employed in dyeing. (Figure 8) Owing to its higher stability to decomposition, PCE is the most common organic solvent used in the dyeing industry.¹¹⁴

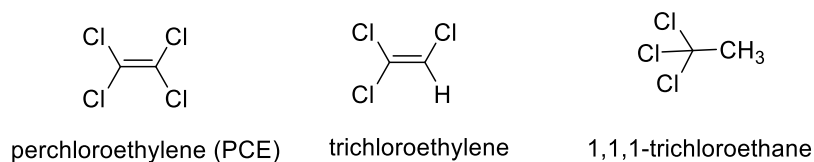


Figure 8: Common organic solvents used in dyeing

The use of organic solvents not only reduces the burden of excessive water usage, which generates a tremendous amount of effluent discharge, but also significantly decreases production-related costs as they require less energy than water for heating and vaporization. Additionally, they offer faster wetting and drying of textiles with less swelling.¹¹⁰ Despite some economic and pragmatic advantages, the higher toxicity of the halogenated organic solvents to living organisms, their poor biodegradability, greater difficulty in recovery, and greater handling challenges due to their low evaporation/flashpoints, have limited their application as dyeing solvents.¹⁰⁴ In addition, some of these solvents require additives to improve stability, which might affect the textile finishing process. In some cases, organic solvents may form hydrogen

bonds with a fabric and the solvent molecule may remain trapped, posing a risk to the consumer's health.¹¹⁶

With the rise in consumer safety awareness, there has been a constant effort to substitute traditional organic solvents with more sustainable alternatives for dyeing. Ionic liquids have been studied as one such alternative. The merit of its solvent properties, including its non-volatile nature with high vapor density and low flammability, high solvation ability for a wide range of compounds, and, remarkably, its recyclability, has added promising value to ionic liquids (IL) as a water-free dye solvent.^{117,118} ILs are salts formed from interactions between a large organic cation and a counter-organic or inorganic anion. Interestingly, studies found that these ionic liquids, which generally melt below 100°C, enhance dye uptake even without auxiliaries with improved color strength.¹¹⁹⁻¹²¹ The generally poor biodegradability of ILs, production of toxic by-products during synthesis, and high production cost have been the limiting factors to their large-scale utility.¹²²

Deep eutectic solvents (DES) are gaining popularity as an alternative to ionic liquids due to their lower production cost, greater availability, and presumed environmental compatibility.¹²³ DES are composed of two or more components and exhibit a dramatic depression in melting point compared to the pure components in the mixture.¹²⁴ DES are easily prepared utilizing inexpensive, less toxic, and often biodegradable starting materials such as quaternary ammonium salts (choline chloride), acids, where one component is a hydrogen bond donor (HBD), and the other one is an acceptor (HBA).¹²³ Some of the common HBAs and HBDs are included in Figure 9.¹²⁵

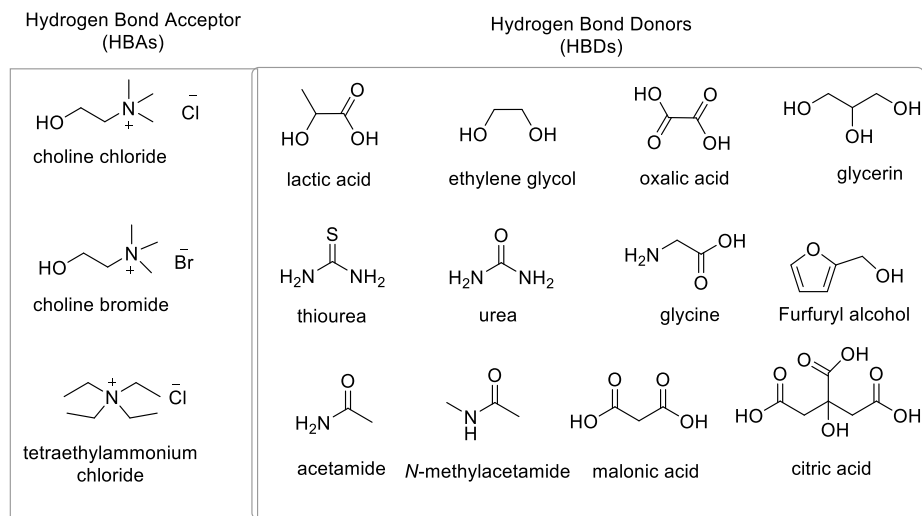


Figure 9: Representative hydrogen bond donors and acceptors used for forming DES

Although DES have a broad application in various fields, including organic synthesis, organic extraction, electrochemistry, pharmaceutical synthesis, bio-analysis, and gas capture,¹²⁶⁻¹³⁵ their usage in the textile industry is mainly limited as a solvent used in electrospinning of fibers and the surface modification of different fabrics, nanofibers, and nanocomposites.¹³⁶⁻¹³⁹ Studies have shown that treatment of ethylene terephthalate (PET) fabrics with DES (mixture of choline chloride and oxalic acid) drastically improved their hydrophilicity without changing the crystal structure and mechanical properties of the fabric.^{137,140} Synthetic and DES treated natural fibers such as wool and cotton have shown significant improvement in their surface properties, including wetting and anti-felting ability and dye absorption.¹⁴¹

Additionally, in another study, a choline chloride and urea eutectic mixture was found to improve cellulose fibers' hydrophilicity by the fabric's cationic functionalization, where all the available hydroxyl groups on cellulose were determined

to be modified.¹³⁶ In addition to the surface modification, DES has been reported to enhance the dispersion of dye molecules in solution by significantly decreasing their particle size.¹⁴² This feature was particularly noted in the case of disperse dyes C.I. Disperse Blue 79 (**5**) and C.I. Disperse Red 343 (**6**), (Figure 10), which normally require dispersing agents to improve their solubility, but were found to dissolve quickly in the DES mixture of choline chloride (ChCl) and ethylene glycol (EG) at room temperature. Not limited to solubility, this same DES also improved the color strength of those dyed fabrics compared to conventionally dyed fabric with the same dyes in the presence of dispersing agents.¹⁰⁰ Besides fabric surface modification and dissolving dyes, DES has shown great potential as a water-free dyeing solvent for textile dyeing.

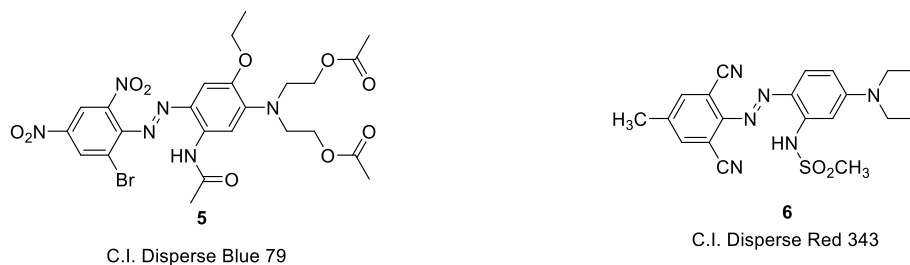


Figure 10: Structure of C.I. Disperse Blue 79 and C.I. Disperse Red 343

The bio-based poly (1,4-cyclohexane dimethylene isosorbide terephthalate) PICT nanofibers, on dyeing with C.I. Disperse Red-167:1 dye (**7**) (Figure 12), utilizing two different DES ChCl/EG and ChCl/furfuryl alcohol (FF) showed better color strength in ChCl/EG solvent, although the nanofibers' color fastness properties were similar, regardless of the dyeing medium employed.¹⁴³ PLA (polylactic acid) is a bio-renewable and bio-degradable material.^{144,145} Despite being a promising alternative to petroleum-based polyethylene, its application in the textile industry is limited due to

poor compatibility with conventional dyeing, as it requires 110°C to obtain a desirable color depth. At this point, its hydrolytic degradation occurs in aqueous medium.¹⁴⁶⁻¹⁵¹ Interestingly, DES [ChCl / oxalic acid (OA)] treated PLA filaments dyed with three disperse dyes, C.I. Disperse Red 167 (**8**), C.I. Disperse Orange 30 (**9**), and C.I. Disperse Blue 79 (**5**), exhibited good color strength and dye uptake property at 90°C, with a better rubbing fastness than PLA filament dyed at 110°C due to surface modification.¹⁵² (Figure 11)

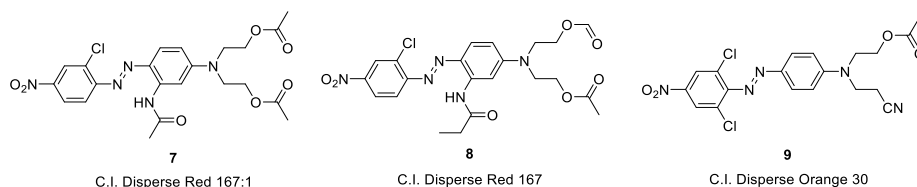


Figure 11: Structure of C.I. Disperse Red 167:1, C.I. Disperse Red 167, and C.I. Disperse Orange

In another study, Disperse Blue 56 (**10**) was utilized in dyeing polyester fabric in a glycerin-based eutectic solvent prepared by mixing ChCl, urea, and glycerin in a fixed proportion. The dyeing performed without dispersing agents demonstrated that the wash, light fastness, and tensile strength of DES (glycerin-based) dyed fabric remained comparable to aqueous dyed fabric. In comparison, sublimation fastness and thermal stability were better than the aqueous dyed fabric.¹⁵³ Similarly, silk fabric dyed with Acid Blue 281 (**11**) and Acid Red 151 (**12**) in the same dyeing medium showed comparable colorimetric properties to the conventional aqueous-dyed fabric. (Figure 12) Rubbing, washing, and light fastness of both fabrics show similar results. However, glycerin-based eutectic mixture dyed silk fabric showed more swelling and gained

better color strength properties even at a lower temperature and in less time than that of aqueous dyed silk fabric.¹⁵⁴ This study supports that besides being a better dyeing medium, DES could also be used as a swelling agent for silk fibers, enhancing their dye uptake capacity.

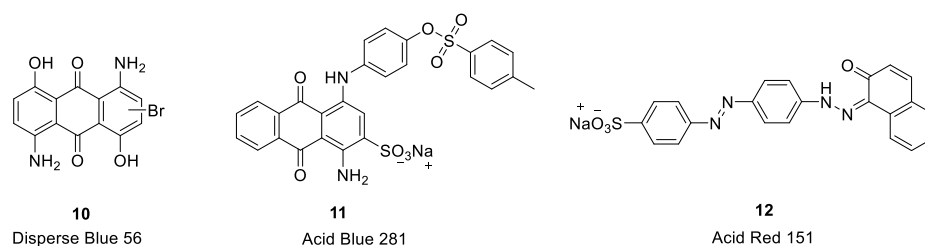


Figure 12: Structure of Disperse Blue 56, Acid Blue 281, and Acid Red 151

Cellulose nanofibers (CNFs) show better mechanical strength and color fastness when dyed with reactive dyes than direct sulfur and vat dyes.^{155,156} However, anionic sulfonic groups (-R-SO₃⁻) in the reactive dyes show lower dye affinity with the negatively charged CNF surfaces. Hence, a high loading of sodium salts/sulfates is required while dyeing them with reactive dyes.¹⁵⁷ Mehdi et al. reported a salt-free dyeing of CNFs with reactive dyes, C.I. reactive blue 19 (**13**) and C.I. reactive red 195 (**14**), utilizing ChCl/EG based DES as a dyeing solvent. (Figure 13) The DES dyed fabric showed enhanced color yield and improved tensile strength and wettability compared to aqueous dye fabric. The improved dye properties can be explained based on the ionic interaction of positively charged nitrogen ions in DES with negatively charged fabric surfaces.¹⁵⁸

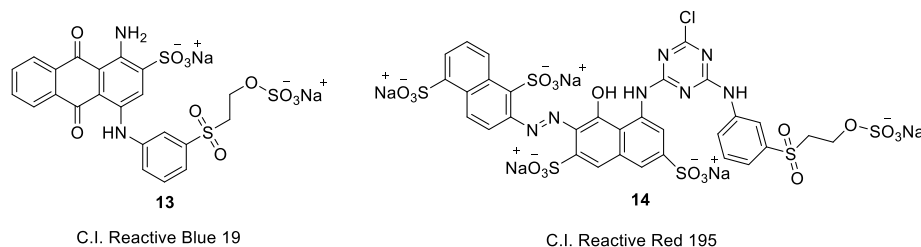


Figure 13: C.I. Reactive Blue 19 and C.I. Reactive Red 195

Woolen fabric shows poor dye absorption properties due to its dense and chemically inert scale present on its surface.¹⁵⁹ Its dyeing process demands a higher temperature at a higher concentration of salts.^{160,161} In addition, wool fabrics must be pre-treated employing chlorine-containing organic reagents to remove the outer scale for better color absorption.¹⁶² In this context, Jiang et al. introduced a 1:1 molar mixture of CHCl_3 with oxalic acid, citric acid, or malic acid as a novel natural DES medium for woolen fabrics. Woolen fabric dyed in this water-free recyclable media exhibited a higher color strength value (K/S) and similar color fastness, even at a lower dye concentration than conventional aqueous dyeing medium. Impressively, even after ten consecutive dyeing cycles, the color strength and fastness of the DES dyed fabric remained intact.¹⁴¹

Recently, Mouro et al. used a natural pigment prodigiosin to dye a multifiber fabric in a novel DES, a 1:2 molar mixture of CHCl_3 and lactic acid. Prodigiosin is a red-colored bacterial pigment with a high potential to replace synthetic dyes owing to its good biodegradability and low toxicity.^{163,164} Among all fabrics, nylon dyed in this DES exhibited enhanced light fastness. The addition of a bio-mordant L-cystine in the dyeing

process further enhanced anti-bacterial activity against *S. aureus* and *P. aeruginosa* compared to the fabric dyed in a medium containing acidified ethanol/distilled water (1:199) and L-cystine.¹⁶⁵

These studies support the role of deep eutectic mixtures or solvents (DES) as efficient, eco-friendly, and water-free alternative dyeing medium.

7. Dyeing process optimization

Effective dyeing is the outcome of the combined effect of several operating parameters during the process in which each parameter contributes individually. One effective way to determine the impact of each parameter on the overall process involves the study of the effect of each variable one at a time while keeping others constant.⁷⁷ This approach is commonly known as OVAT (one variable at a time) process optimization. Finding the optimized dyeing condition to save time, effort, energy, and the amount of chemicals required is of utmost importance. Some of the parameters and their effects on the dyeing process are discussed below:

7.1. Effect of dyeing time

Depending on the molecular shape and size of the dye molecule and its affinity towards the fiber, dyeing time varies. The higher the affinity, the faster and more effective is the dyeing process. Generally, dyes with high molecular weight and lower affinity take longer to diffuse and establish bonds with the fiber polymer than counterparts with low molecular weight and higher substrate affinity.⁷⁹ Although, in many cases, longer dyeing duration facilitates dye fixation to the fiber, the linear relation works until an optimum time is reached. Slower dyeing processes can also harm

dye stability (hydrolysis of dye molecules) and fabric quality, particularly at an elevated temperature.¹⁶⁶

Alam et al., in their study of dyeing cotton fabric with reactive dyes, Reactive Red 6B (C.I. no 18852) and Reactive Yellow R.L. (C.I. no. 18200), demonstrated a linear increase in dye adsorption, which reached a maximum at sixty minutes.¹⁶⁷ Similar results were reported for chitosan treated cotton fabric dyed with Reactive Red 120 (**15**) in which the dye adsorption, color strength, and wash fastness reached a plateau at forty-five minutes.¹⁶⁶ (Figure 14) This was true with wool dyeing using natural black rice extract dyes.¹⁶⁸

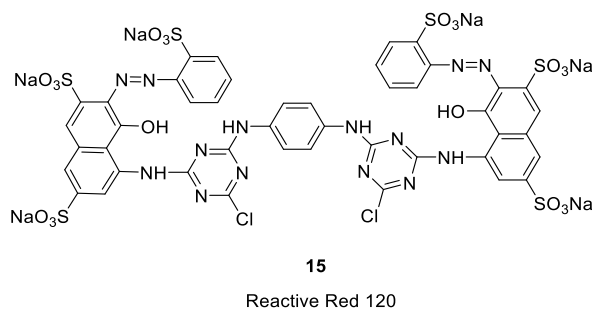


Figure 14: Structure of C.I. Reactive Red 120

The dyeing process must not be too slow or too fast. Quick dyeing results in disproportionate adsorption of dye molecules on the fabric surface, compromising the color fastness due to various factors, including washing, and rubbing.^{166,168} Initially, the diffusion of dye molecules into the fiber occurs rapidly, but with time, it slows down and comes to an equilibrium. This is because, at first, the sites inside the fabrics are easily accessible, so more and more dye molecules can diffuse quickly, enhancing the colorimetric properties. However, as time progresses, dye molecules must find more

remote sites of attachment that slow the dyeing processes, eventually making them constant.¹⁶⁹

7.2. Effect of dyeing temperature

Dyeing temperature has a significant influence on the rate of diffusion of the dye molecules into the fabric surface and hence affects the dye exhaustion, color strength, and color fastness of the dyed fabric. Usually, the rate of dyeing increases with an increase in temperature due to an increase in the kinetic energy of dye molecules in the dye bath solution.¹⁶⁶ This helps more and more dye molecules penetrate the fiber surface, enhancing favorable fixation. Generally, 60-95°C is considered an optimum temperature range for substantial fastness properties.¹⁵⁹ The temperature also depends on the dye fabric affinity. With a good affinity, dyeing can be accomplished at lower temperatures. For example, cold brand dyes (dichloro triazine type- Figure 15), which have a good affinity and reactivity towards cellulosic fibers, can be dyed at 30 °C.⁷⁹

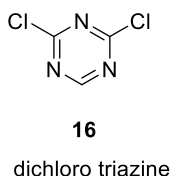


Figure 15: Structure of dichloro triazene

Dyeing temperature influences the solubility of dyes in the dye bath. Some dyes aggregate at lower temperatures and even form micelles. Consequently, their dispersion on the fabric's surface significantly diminishes, which improves with increased temperature as the aggregates break and the dye molecules are released. Ideally, this

enhances the dye exhaustion and color strength.^{81,171} The temperature of the dye bath also affects the fabrics used. Some types of fabrics are more affected than others. Most natural fibers are porous; hence, dyes can quickly diffuse into the bulk of the fibers even at moderate temperatures.⁸¹

Synthetic fibers are generally challenging to dye at temperatures below their glass transition temperature (T_g) due to their confined molecular mobility. As the dyeing temperature gradually increases above T_g , the rotation of the polymer chain starts and reaches the dyeing transition temperature (T_d), which creates a sufficient free volume (space) for the diffusion of dye molecules into the polymer.^{172,173} Thermoplastic synthetic fibers require a temperature above T_d for effective dye exhaustion and color strength. Nylon and acrylic fibers have lower values of T_g and T_d , so that they can be easily dyed at 100°C.⁸¹ In case of PET fibers, despite lower T_g (78°C), their extreme crystallinity and hydrophobicity require temperature of about 130- 140°C for effective dye diffusion.¹⁷⁴

During a study, Li et al. observed maximum K/S values at 95°C for wool/acrylic blended fabric dyed with reactive dyes, which either remained steady or decreased above 100°C due to hydrolysis.¹⁷⁵ In a separate investigation of the adsorption of safflower yellow dye **17** (Figure 16) on wool protein fiber, Yoo et al. reported a slow increase in color strength below 50°C, which gained a maximum value at 90 °C.¹⁷⁶ Wool dyeing at this temperature enables swelling of the wool fiber, opening pores, and helping in the easy diffusion of dye molecules on the wool fiber. This is not possible when dyeing wool at a lower temperature.¹⁷⁷

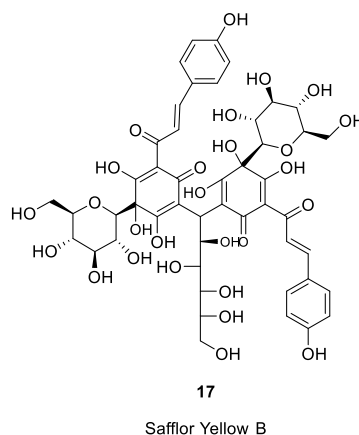


Figure 16: Structure of Safflor Yellow B

7.3. Effect of concentration of dye (Shade percentage)

Shade percentage, expressed as a percentage of the weight of the dry fabric, is the amount of dye used to produce a desired color. For 1% shade, 1.0 g of dye should be used per 100 g of fabric. As the uniformity of color in a dyed fabric or its shade percentage depends on the weight of the dye and fabric, it could be challenging while dyeing hygroscopic protein or cellulosic fibers because they absorb varying amounts of water from the air, which depends upon the relative humidity and temperature, influencing the gross weight of a given amount of fiber.^{178,179} The depth of the shade in a fabric also depends on the amount of dye used. Lower dye concentration gives paler shades, whereas increased dye amount gives deeper color to the material.⁸¹ With higher availability of dye molecules in a dye bath solution, more dye molecules can attach to the fiber, and hence, more diffusion occurs, eventually increasing the shade depth.¹⁸⁰ However, sometimes, at higher concentrations, if the binding between dye molecules

and the fiber is not strong enough, more molecules will only deposit on the fabric's surface, giving it a duller shade with poor color fastness properties.

The shade depth's intensity significantly influences color strength, dye uptake, and colorfastness properties. The dye uptake and color strength of the dyed fabric usually increase with increasing depth of shade. Light fastness is also higher for deeper dyeing since a higher dye concentration means more dye aggregates in the fiber. Hence, a greater amount of dye molecules must be destroyed at a given time for a significant color change of the material. So, paler shades fade fastest because photochemical fading is more pronounced for the smallest aggregates.¹⁸¹

A study on the effect of concentration on the color and physical properties of Remazo Blue RR or Reactive Blue 19 dyed viscose and cotton knitted fabrics at 1-9% shade percentages exhibited a direct relation between the K/S value of the dye concentration. A study was conducted on the effect of dye concentration on the color and physical properties of Remazo Blue RR or Reactive Blue 19 dyed viscose, and cotton knitted fabrics. At 1-9% shade percentages, the study exhibited 36.3% and 31.5% K/S value increases for the respective fabrics. A more rapid increase was observed for the viscose knitted fiber because of its high reactivity and absorption capacity.¹⁸² A similar trend was observed in the case of wool fiber dyed with the extract of *Terminalia chebula* at 0.5 to 15% shade percentages (o.w.f). The color strength significantly increased with the dye concentration, giving deeper shades. However, the change in dye concentration affected none of the fastness properties.¹⁸³

In this context, aurones, despite their promising coloring properties, have not been explored for fabric dyeing. There are only a handful of precedents at our disposal as a reference. In this study, various aurone derivatives were synthesized and used to

dye wool fabric. The dyeing was performed in DES medium, and various colorimetric properties of the dyed wool fabric were studied.

8. Results and discussion

The motivation for this study originated from the dual properties of aurones as an antimicrobial agent and their pigmentation role in fruits and flowers.²⁸ While the biological properties, including antimicrobial, of aurone derivatives have been widely studied and documented, their coloring properties have virtually remained unexplored.³⁶ Relying on the limited colorimetric information available for aurones in the literature,^{21,184} the Handy group has been working on understanding the optical properties of various substituted aurones. In one of their studies on the impact of substitution on the benzofuranone moiety of the aurone framework on its colorimetric properties, they observed the impressive dyeing ability of a few aurone derivatives.

Among a series of hydroxy and halogen-substituted aurones, the 4-hydroxy substituted aurone (Figure 17) imparted a vibrant color to a wide range of natural fibers with an unexpected affinity for polypropylene. The preliminary dyeing studies also revealed a remarkable photobleaching stability of a series of aurones studied, showcasing the dyeing ability of aurones.³⁶

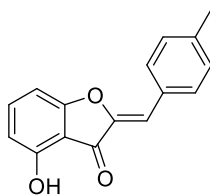


Figure 17: 2-(4-Methylbenzylidene)-1-(4'-hydroxybenzofuran-3-one)

Inspired by these results, we envisioned aurone as an antimicrobial dyeing agent for fabrics. Besides exploring the dyeing capability of various aurone candidates, we were also interested in knowing if the antimicrobial activity of the aurone could be retained on fabric or not after dyeing. Based on their reported antimicrobial properties against *C. albicans*,³⁵ three aurone analogs were selected for a preliminary study. (Figure 18)

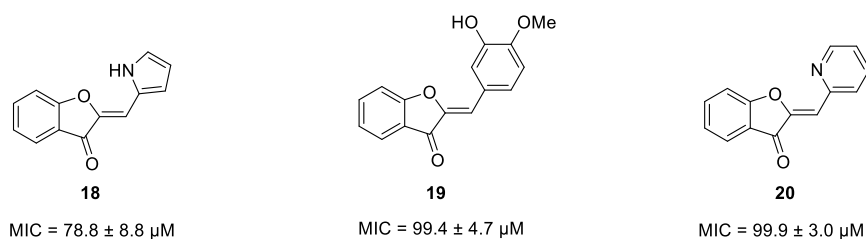


Figure 18: Aurones with antimicrobial activity against *C. albicans*

For proof of concept, the idea was to perform a one-pot synthesis of the aurones followed by the dyeing of fabric in a deep eutectic solvent. The success of this method would reduce the number of operations and cut waste generated. For this purpose, two DES mixtures, a 1:2 molar mixture of choline chloride (ChCl) and urea (U) and a 1:1 molar mixture of choline chloride (ChCl) and oxalic acid (OA), were prepared by agitating the desired proportion of the components at 70 °C overnight.^{185,186} (Figure 19)

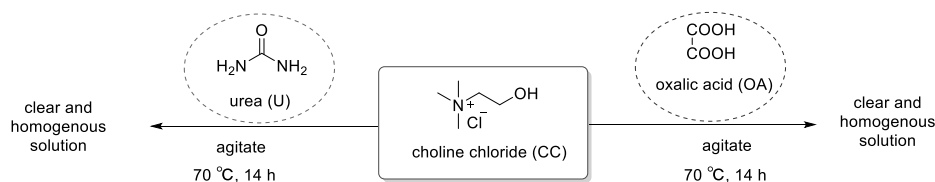


Figure 19: Preparation of DES (ChCl/U and ChCl/OA)

For the study, a thirteen-row multifiber fabric strip constituting acetate rayon, sef, arnel, cotton, creslan, dacron 54, dacron 64, nylon 6.6, orlon 75, silk, polypropylene, viscose rayon, and wool was employed. Aurones **18-20** were synthesized in situ by mixing an equimolar amount of benzofuranone and the corresponding aromatic aldehydes in ChCl/U and ChCl/OA mixtures.⁴⁹ As a multifiber fabric combines different types of fabrics, color is expected to be retained with different intensities on different fabric types. The general strategic outline for dyeing a fabric is depicted in Figure 20.

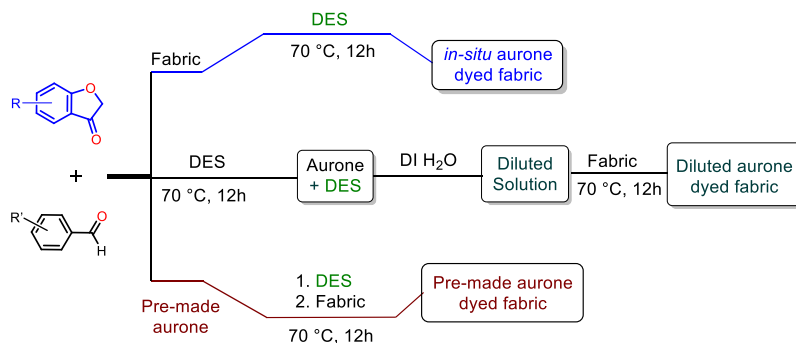


Figure 20: Dyeing strategies for preliminary study a) *in situ* dyeing b) diluting dye bath solution c) dyeing with pre-made aurone.

In situ dyeing was carried out by adding a fabric in the same vial containing starting materials and the deep eutectic solvent and agitated overnight at 70°C. The fabric strip was washed with water several times and air-dried. Interestingly, *in situ* dyeing with aurone **18**, particularly in ChCl/OA medium, imparted black color to the fabric, irrespective of the aurone input sources (*in situ* vs pre-made aurone). It was further confirmed by stirring premade aurone **18** in ChCl/OA solution (without adding a fabric) under the same reaction conditions, which resulted in a dark black solution.

In situ dyeing with aurone **19** imparted a darker yellow shade to the fabric in both solvent mixtures. A similar result was observed with aurone **18** in ChCl/U. Although the retention of yellow shade on the aurone **19** dyed fabric was better in ChCl/OA than ChCl/U, the oxalic acid mixture was found to degrade cotton fiber, limiting its utility. (Figure 21). As aurone **20** did not show promising coloring properties, it was not considered for further study.

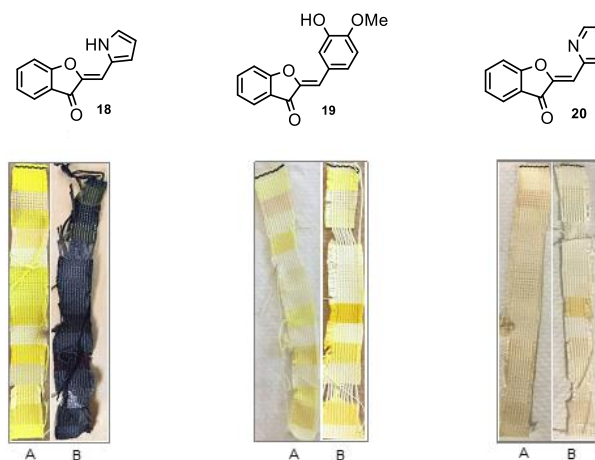


Figure 21: Fabric dyed with **18**, **19**, and **20** in ChCl/U (A) and ChCl/OA (B)

However, *in situ* dyeing technique was ineffective due to the high viscosity of the DES used, which caused an uneven distribution of the color on the fabric. To overcome this issue, the dye bath solution was diluted 20-fold with water and the diluted solution was used for dyeing the fabrics under the previously stated conditions. Using diluted (1:20) DES solutions containing *in situ* synthesized aurones **18** and **19**, a fabric was added and dyed for two hours at 70°C while stirring. The visual observation showed better color retention by the fabric in diluted dye bath solution. One way to quantify this result is by determining % dye exhaustion, which measures the absorbance ratio of dye bath solution before and after dyeing.^{53,54}

$$\% \text{ Dye exhaustion} = [(A_1 - A_2)/A_1] \times 100$$

A₁ and A₂ are the absorbance values of the dye solution before and after dyeing.

Although aurone **18** in ChCl/U solution showed a slight increase in % dye exhaustion after dilution (Table 1, entry 1), it showed poor absorbance in ChCl/OA. Similarly, as aurone **20** did not absorb in the visible region, we could not calculate its dye uptake percentage. In the case of **19**, the dilution of the dye bath solution markedly increased the % dye exhaustion compared to the undiluted one in both deep eutectic mixtures, giving different yellow shades to the multi-fiber fabric. (Table 1)

Table 1: Dye exhaustion study of aurone **18** and **19**

SN	Aurones	DES	% dye exhaustion		λ_{max} (nm)
			Undiluted	Diluted	
1.	18	ChCl/U	65	74	442
2.	19	ChCl /U	24	59	410
3.		ChCl /OA	29	81	410

Next a qualitative assessment of the antifungal activity of these dyed fabrics against *C. albicans* according to the standard procedure described in the AATCC test method 147-2004 (Parallel streak method) was performed.¹⁸⁷ For this purpose, YPD broth was prepared, sterilized, and inoculated with a full loop of *C. albicans* (ATCC strain 90028) and incubated for 72 h at 30°C.¹⁸⁸ The incubated broth was diluted (1:9) with sterile distilled water and streaked on the pre-prepared sterilized YPD agar petri dishes. The aurone **18** and **19** dyed fabrics in ChCl /U were appropriately cut into (2 cm × 3 cm) size and placed transversely over the streaks on the agar surfaces. The plates were then incubated at 35°C for 72 h.¹⁸⁷ The qualitative assessment of antifungal properties against *C. albicans* of dyed fabric in ChCl/U solvent showed aurone **18** had possible activity on the creslan segment, and aurone **19** showed some activity on the cotton segment. (Figure 22)



Figure 22: Qualitative assessment of antifungal properties. Picture 1) *In situ* dyed fabric with aurone **18** in ChCl/ U. Picture 2) Control experiment: Fabric dyed only in ChCl/U DES. Picture3) *In situ* dyed fabric with aurone **19** in ChCl/U.

Based on this preliminary study, the next step was to synthesize and screen more aurone derivatives. For this purpose, eighteen aurone derivatives were selected; half of them with 4-dimethylamino (DMAA) substitution (**21-29**) in the B- ring (phenyl), and the other half (**30-38**) were ferrocenyl-appended aurones (FA) incorporating a ferrocenyl group as a B-ring attached to the exocyclic double bond of the aurone framework (Figure 23). The dimethylamino group in the B-rings are well known to enhance the colorimetric properties of the aurone via extended conjugation.^{21,23} On the other hand, ferrocenyl-appended aurones have been reported for their antimicrobial properties¹⁸⁹, although their colorimetric properties have not been well explored.

In order to learn more about the poorly explored dyeing potential of aurones, the study first focused on assessing the colorimetric and dyeing properties of the aurones. The plan was then to evaluate the antimicrobial activity of the best dyes against different microorganisms and determine if their antimicrobial property would be retained on the dyed fabric.

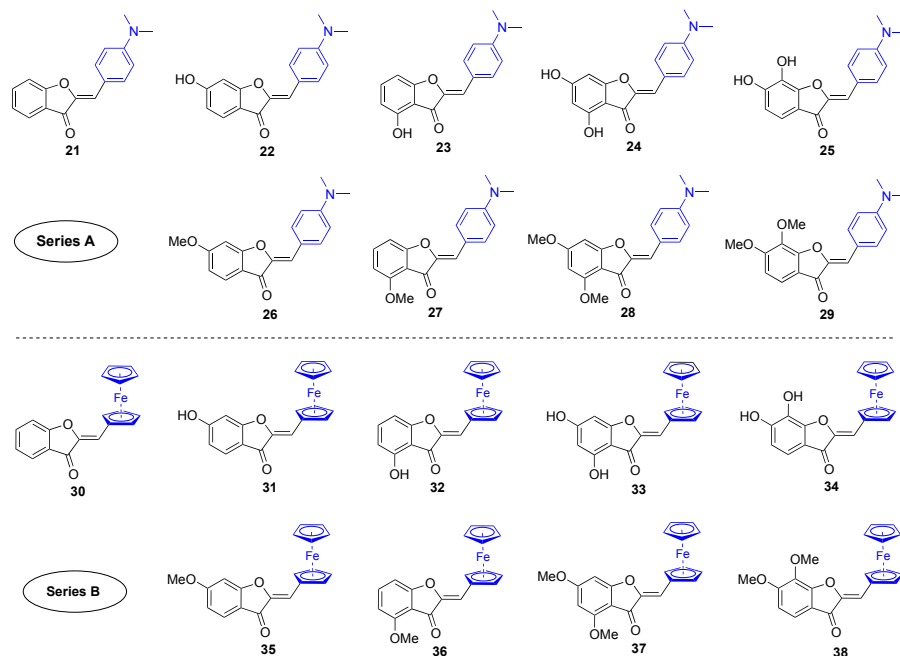
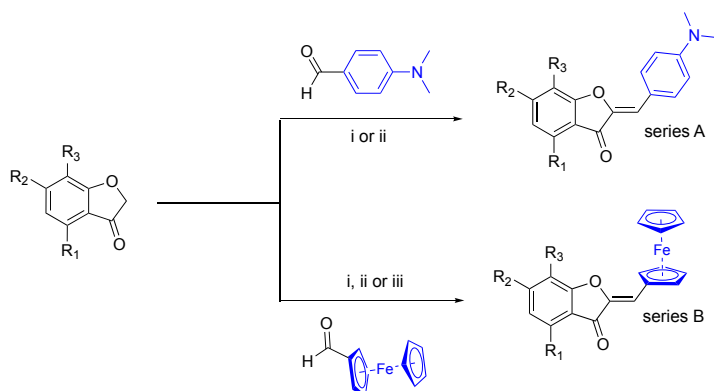


Figure 23: Aurone candidates for the study. Series-A (4'-dimethylaminophenyl: DMAA-series) and Series-B (ferrocenyl-appended aurones)

While performing the *in situ* dyeing, we encountered a major issue with the determination of the yield of the product formed and hence the concentration of the dyebath solution. Further, not all aurones are formed efficiently using a deep eutectic solvent. To avoid this variability, it was decided to synthesize and isolate the aurone candidates and use a quantifiable amount for dyeing. In addition, deep eutectic solvents have high viscosity, which made agitation of the dye bath solution difficult with added fabric inside the dyeing vessel. Without proper agitation, the color distribution on the fabric was uneven. To avoid this problem, dilution of the dye bath solution was required, making the simultaneous synthesis of aurones and dyeing in the diluted solution in one pot impractical.

8.1. Synthesis of aurones

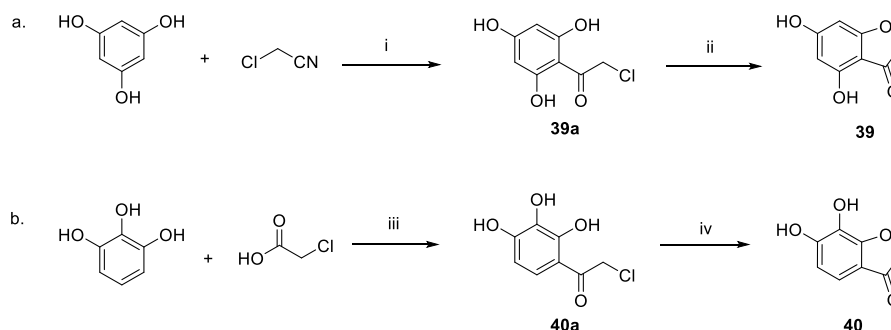
All aurone derivatives were prepared by condensing various substituted benzofuran-3(2*H*)-ones with 4-(dimethylamino)benzaldehyde and ferrocene carboxaldehyde, either under acidic, basic or neutral conditions. Most hydroxy and methoxy-substituted aurones were prepared in acetic acid catalyzed by concentrated HCl.⁴¹ While some products didn't require further purification after filtration, others required flash column chromatography. Unlike most aurones, **24**, **28**, **33**, and **37** required stronger base-catalyzed reaction conditions (KOH/H₂O).⁴³ Compound **30** was prepared using ChCl/U deep eutectic solvent.⁴⁹ (Scheme 12)



Series A: **21**: R₁, R₂, R₃ = H; **22**: R₁, R₃ = H, R₂ = OH; **23**: R₁ = OH, R₂, R₃ = H; **24**: R₁, R₂ = OH, R₃ = H; **25**: R₁ = H, R₂, R₃ = OH; **26**: R₁, R₃ = H, R₂ = OMe; **27**: R₁ = OMe, R₂, R₃ = H; **28**: R₁, R₂ = OMe, R₃ = H; **29**: R₁ = H, R₂, R₃ = OMe; **Series B:** **30**: R₁, R₂, R₃ = H; **31**: R₁, R₃ = H, R₂ = OH; **32**: R₁ = OH, R₂, R₃ = H; **33**: R₁, R₂ = OH, R₃ = H; **34**: R₁ = H, R₂, R₃ = OH; **35**: R₁, R₃ = H, R₂ = OMe; **36**: R₁ = OMe, R₂, R₃ = H; **37**: R₁, R₂ = OMe, R₃ = H; **38**: R₁ = H, R₂, R₃ = OMe;

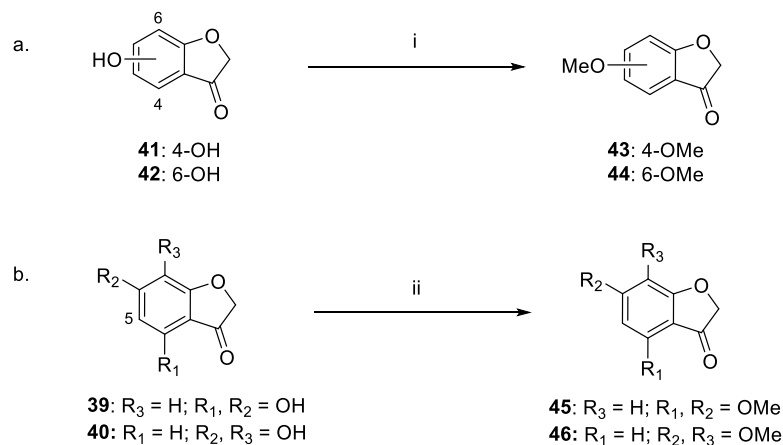
Scheme 12: General synthetic schemes for aurone derivatives **21-38**. Conditions: i) glacial acetic acid, conc. HCl, rt, 0.5-3h; ii) KOH/H₂O (1:1), MeOH, 65°C, 3-4h (only for compounds **24**, **28**, **33**, **34**); iii) ChCl/U (1:2), 80°C, 12 h (only for compound **30**)

The synthesis of dihydroxy aurones required pre-synthesized benzofuranones. While mono-hydroxy substituted benzofuranones **41** and **46** were commercially available, dihydroxy-substituted analogs **39** and **40** were synthesized via a two-step process. First, compound **39a** was obtained through the known Houben-Hoesch reaction of phloroglucinol with chloroacetonitrile in the presence of anhydrous ZnCl_2 followed by cyclization.¹⁹⁰⁻¹⁹² (Scheme 13a) Similarly, compound **40** was synthesized by the ring-closure of the intermediate **40a** obtained by reacting pyrogallol with chloroacetic acid.^{193,194} (Scheme 13b)



Scheme 13: Synthetic strategy for dihydroxy substituted benzofuran-(2H)-one **39** and **40**. Reaction conditions; i) anh ZnCl_2 , anh Et_2O , dry HCl (bubbling), 0°C , 4 h, 1N HCl , reflux, 1 h; ii) NaOMe , MeOH , 65°C , 2 h; iii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, POCl_3 , 50°C , 5 h; iv) NaOAc , EtOH , 70°C , 6 h.

The mono- (**39**, **40**) and dihydroxy benzofuranones (**41**, **42**) were subsequently converted to the corresponding methoxy analogs **43-46** via o-alkylation with methyl iodide (MeI).¹⁹⁵ (Scheme 14a and 14b).



Scheme 14: Synthesis of mono- and dimethoxy benzofuran-(2*H*)-ones. Reaction conditions: i) MeI (2.0 equiv), K₂CO₃ (1.5 equiv), acetone, 35°C, 4 h; ii) MeI (3.0 equiv), K₂CO₃ (2.0 equiv), DMF, Ar, 80°C, 2 h.

8.2. Dye exhaustion study of the selected synthetic aurones

The preliminary dyeing study of aurones **18** and **19** on multifiber fabric exhibited that different fibers have different color and intensity retention properties. Some fibers were dyed better than others. Having these aurones synthesized, we moved to screen them to identify the fabric and aurones offering better absorption and color retention properties. Due to a change in commercial availability, the 13-row multifiber fabric used for the preliminary study was replaced with a 6-row (acetate, cotton, nylon, polyester, acrylic, wool) multifiber fabric for further research. One of the critical dyeing parameters includes the dye solubility in the dye bath, as the availability of the dye molecule for adsorption on the fabric's surface significantly affects the quality of the dyeing outcome.

The screening was intended to identify the right fiber and the aurones for further study. For this purpose, multifiber fabric was dyed with all eighteen synthetic aurones in ChCl/U medium to determine their dye exhaustion property. The study was performed under 1% shade, where the % shade implies the amount of dye employed for a specific fabric weight. The outcome of the study is summarized in Table 2.

Table 2: % Dye exhaustion study of aurone **21-38** in ChCl/U

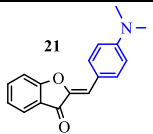
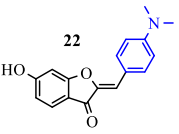
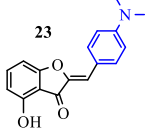
SN	Aurone	$\lambda_{\max}$ (nm)	Trial	Absorbance		%DE	Av. % DE	Fabric after dyeing
				BD	AD			
1.		492	I	0.8485	0.0989	88.34	93.57 ± 4.55	
			II	0.9775	0.0420	95.70		
			III	1.7490	0.0583	96.66		
2.		452	I	2.2782	0.8683	61.89	55.92 ± 5.22	
			II	1.5153	0.7244	52.19		
			III	2.1336	0.9885	53.67		
3.		470	I	1.5925	0.2154	86.47	84.43 ± 4.71	
			II	1.5548	0.1900	87.78		
			III	1.7954	0.3763	79.04		

Table 2: Contd.

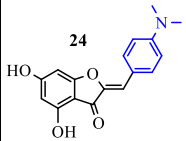
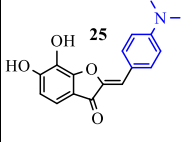
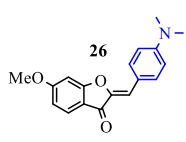
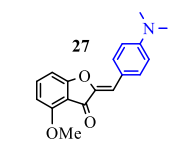
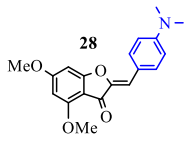
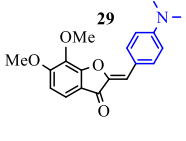
SN	Aurone	$\lambda_{\max}$ (nm)	Trial	Absorbance		%DE	Av. % DE	Fabric after dyeing
				BD	AD			
4.	<chem>Oc1cc(O)c2c(c1)oc(=O)c2C=Cc3ccc(N)cc3</chem> 	446	I	1.5071	1.1672	22.55	27.55 ± 6.04	
			II	1.3363	0.9911	25.83		
			III	1.3235	0.8701	34.26		
5.	<chem>Oc1cc(O)c2c(c1)oc(=O)c2C=Cc3ccc(N)cc3</chem> 	476	I	1.4314	0.9779	31.68	42.24 ± 9.44	
			II	1.0211	0.5121	49.85		
			III	1.1307	0.6196	45.20		
6.	<chem>COc1ccc2c(c1)oc(=O)c2C=Cc3ccc(N)cc3</chem> 	472	I	1.1940	0.1066	91.07	90.13 ± 1.66	
			II	1.0846	0.1224	88.71		
			III	1.0479	0.0983	90.62		
7.	<chem>COc1ccc2c(c1)oc(=O)c2C=Cc3ccc(N)cc3</chem> 	478	I	1.1481	0.1337	88.35	91.24 ± 2.61	
			II	1.0660	0.0857	91.95		
			III	0.8752	0.0576	91.40		
8.	<chem>COc1ccc2c(c1)c(OC)c(=O)c2C=Cc3ccc(N)cc3</chem> 	380	I	0.7731	- 0.1140	114.75	109.11 ± 7.48	
			II	0.9675	- 0.0857	111.96		
			III	0.8106	- 0.0050	100.62		
9.	<chem>COc1ccc2c(c1)c(OC)c(=O)c2C=Cc3ccc(N)cc3</chem> 	476	I	0.8514	0.1749	79.45	86.71 ± 6.61	
			II	0.7209	0.0549	92.38		
			III	0.6747	0.0791	88.28		

Table 2: Contd.

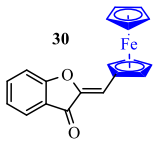
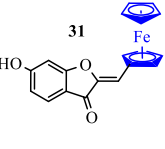
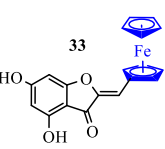
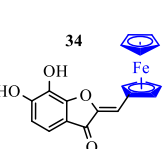
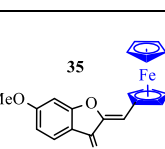
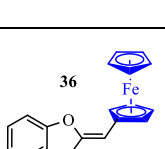
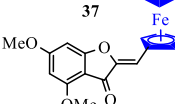
SN	Aurone	$\lambda_{\max}$ (nm)	Trial	Absorbance		%DE	Av. % DE	Fabric after dyeing
				BD	AD			
10.		382	I	0.6079	0.3505	42.43	65.97 ± 28.55	
			II	0.6942	0.2925	57.86		
			III	0.4357	0.0999	97.70		
11.		392	I	0.7988	0.4410	44.79	48.98 ± 15.47	
			II	0.9531	0.3230	66.10		
			III	0.8679	0.5552	36.03		
12.		398	I	0.5222	0.2062	60.51	57.74 ± 3.13	
			II	0.4684	0.2139	54.34		
			III	0.4073	0.1695	58.37		
13.		400	I	0.5354	0.3677	31.33	29.73 ± 5.06	
			II	0.4893	0.3716	24.06		
			III	0.4114	0.2724	33.79		
14.		384	I	0.1876	0.0412	77.92	92.00 ± 16.46	
			II	0.4486	-0.045	110.10		
			III	0.3447	0.0415	87.97		
15.		406	I	0.4855	0.2389	50.79	75.64 ± 22.10	
			II	0.7158	0.1218	82.98		
			III	0.6749	0.0463	93.14		

Table 2: Contd.

SN	Aurone	$\lambda_{\max}$ (nm)	Trial	Absorbance		%DE	Av. % DE	Fabric after dyeing
				BD	AD			
16.	37 	380	I	1.2484	0.1818	85.44	83.21 ± 2.74	
			II	0.3094	0.0494	84.03		
			III	0.5430	0.1078	80.15		
BD = before dyeing; AD = after dyeing; %DE = % dye exhaustion								

The table summarizes the % dye exhaustion of the series A and B aurones when dyeing six-fiber fabric in ChCl/U. One of the major factors that affect the dyeing efficiency and quality is the solubility of the dye candidate in the dyeing medium. Poor solubility leads to an inconsistent dyeing pattern as the dye molecules are not homogeneously distributed in the dye bath. Out of 18 aurone candidates, only hydroxy-substituted aurones, except the 4-hydroxy ferrocenylaurone (**32**), were soluble in ChCl/U, giving a homogenous solution. Since we used multifiber for the initial screening and different compounds have a unique affinity to the various fiber types, the % dye exhaustion represents an average dye exhaustion and not an absolute value for a particular fabric. However, this screening study detailed the solubility, % dye exhaustion, and color retention properties of aurones on various fibers and provided guidance for the next stage.

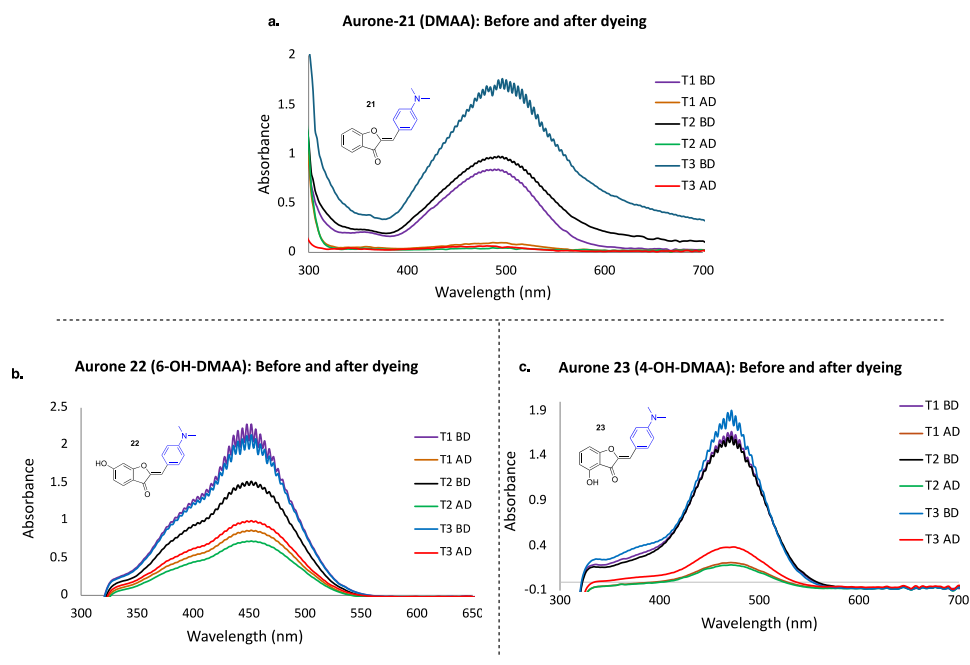


Figure 24: UV-absorption spectra of aurone **21**, **22**, and **23** (before and after dyeing).

While **21** resulted in some precipitate in the dye bath, the aurones **22** and **23** of the series A were highly soluble in ChCl/U bath and resulted in a homogenous solution. Despite the lower solubility, **21** (DMAA) exhibited higher % exhaustion than both **22** (6-OH-DMAA) and **23** (4-OH-DMAA). All three compounds dyed yellow to orange shades to different fibers of the fabric used. **23** (4-OH-DMAA) in particular, demonstrated excellent dyeing ability and color retention after wash. It dyed acetate, nylon and wool fabric with an orange, dark orange, and maroon colors respectively. (Table 2, Entry 3). The UV-absorption of **23** shows less variability among the trials after and before dyeing in comparison to **21** and **22**. (Figure 24)

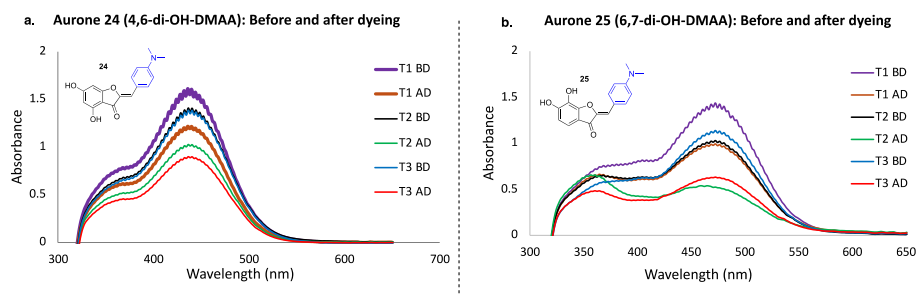


Figure 25: UV-absorption spectra of aurone **24** and **25** (before and after dyeing)

Despite the excellent solubility of the dihydroxy aurones **24** and **25** in the ChCl/U bath, both showed low % dye exhaustion (27.55 ± 6.04 and 42.24 ± 9.44 respectively) compared to the corresponding mono-hydroxy analogs **22** and **23** (55.92 ± 5.22 and 84.43 ± 4.71) (Figure 26) However, both imparted strong yellow, brownish yellow and dark brown colors, specifically to the acetate, nylon, and wool fibers respectively, revealing their promising dyeing properties. (Table 2, entries 2-5). The UV-absorption spectra for **24** and **25** are depicted in Figure 25.

The methoxy-substituted analogs of the series A, except **28** (4,6-dimethoxy-DMAA), were soluble in the dye bath. All of them exhibited high % dye exhaustion ($> 85\%$). Due to limited solubility, aurone **28** was observed to precipitate on the fabric surface, leading to an erroneously high % dye exhaustion. Aurones **26**, **27**, and **29** dyed particularly the acetate, nylon, and wool fibers with yellow, orange, and dark orange, respectively, whereas **28** imparted yellow shades to those fibers. (Table 2, entries 6-9). The UV-absorption spectra are included in Figure 26.

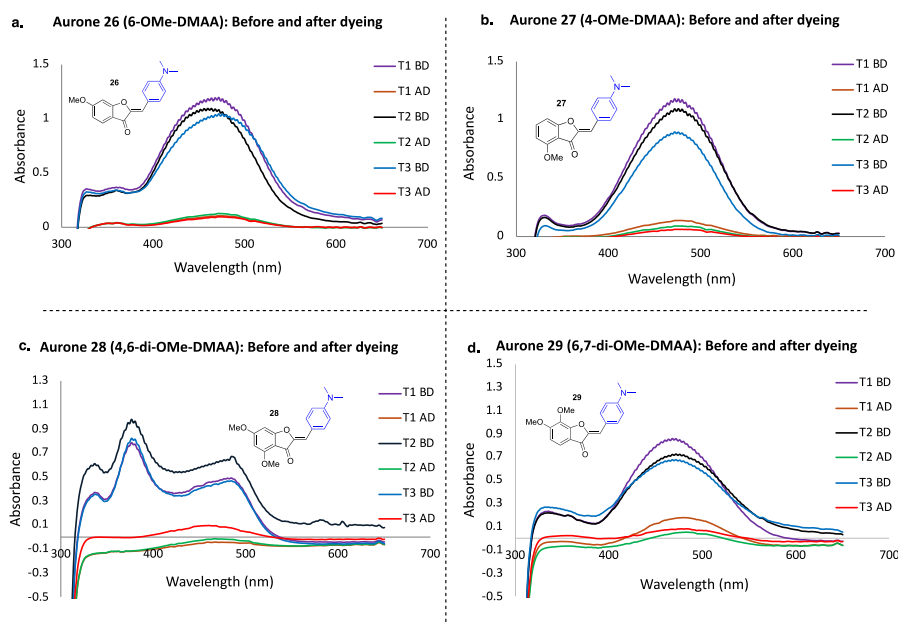


Figure 26: UV-absorption spectra of mono- and di-methoxy substituted DMAA **26-29** (before and after dyeing)

Ferrocenyl compounds typically exhibit two absorbance bands, one in the UV region (around 300 nm) and the other characteristic band in the visible region (above 400 nm).¹⁹⁶ The dye exhaustion of all ferrocenyl-aurones in this study was calculated for the absorbance in the visible region. Only the hydroxy-substituted ferrocenyl-aurones **31** (6-OH-FA), **33** (4,6-diOH-FA), and **34** (6,7-diOH-FA) were soluble and exhibited 48.98 ± 15.47 , 57.74 ± 3.14 , and 29.93 ± 5.06 % dye exhaustion, respectively. (Table 2, Entries 11-13) The unsubstituted ferrocenyl-aurone **30** and **32** (4-OH-FA) were insoluble in the dye bath. Unlike others, **32** did not produce interpretable UV-absorption spectra to calculate % dye exhaustion. However, irrespective of differences in solubility and dye exhaustion, all four effectively dyed the nylon and wool fiber with

a prominent burgundy shade. (Table 2, Entries 11-14). The UV-absorption spectra of all three trials before and after dyeing are included in Figure 27.

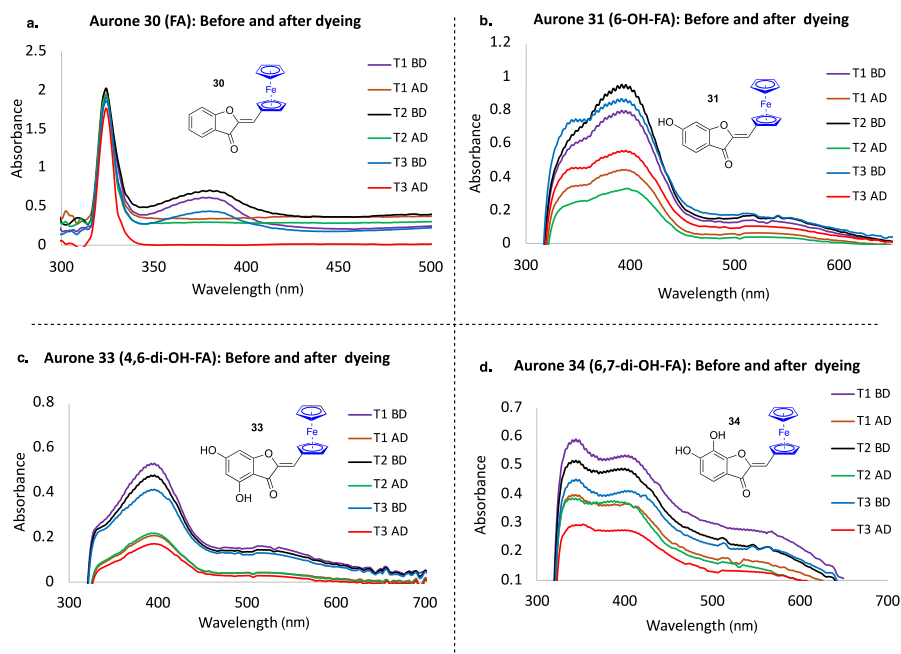


Figure 27: UV-absorption spectra of ferrocenyl-aurones **30**, **31**, **33**, and **34** (before and after dyeing)

All the methoxy-substituted ferrocenyl-aurones were insoluble in CHCl_3/U , leading to precipitation and deposition on the fabric surface and inconsistent UV-absorption patterns, as depicted in Figure 28. Except for aurone **36**, which showed a prominent band at ~ 406 nm, the absorption band in the UV region for others was obscure and unreliable to quantify dye exhaustion, particularly in the case of compound **38**. All four selectively imparted light purple to the acetate fiber and brown color to the wool fiber.

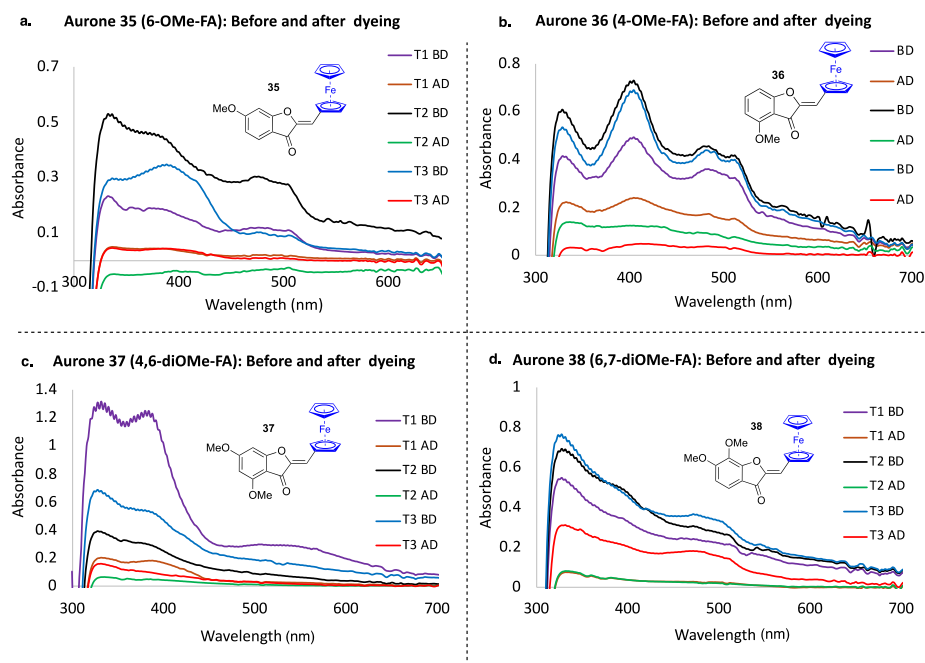


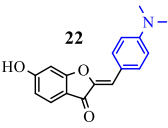
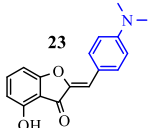
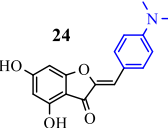
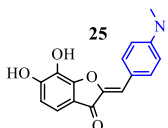
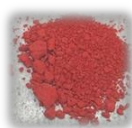
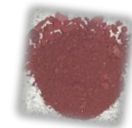
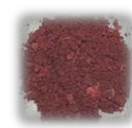
Figure 28: UV-absorption spectra of ferrocenyl-aurones **35-38** (before and after dyeing)

The visual observation of the dyed fabric showed that both series A and B were more selective towards the acetate, nylon, and wool fiber of the multifiber fabric. However, some aurones, including **23-25**, also dyed cotton fabric. The hydroxyderivatives were initially considered for further study by analyzing the various factors, including solubility, % dye exhaustion, and the visual observations of the color intensity on the fiber. However, despite good solubility and dye exhaustion properties, the accessibility of hydroxy-substituted ferrocenyl-aurone analogs was limited by difficult purification, leading to low yield. Also, ferrocenyl-aurone precursors are relatively expensive in terms of sustainability.

Among the methoxy analogs **26-29**, the relevance of **28** (4,6-diOMe-DMAA) was compromised by its poor solubility in the DES mixture. In comparison, aurone **26**

(6-OMe-DMAA), **27** (4-OMe-DMAA), and **29** (6,7-diOMe-DMAA) exhibited excellent solubility in DES and demonstrated encouraging coloring properties towards acetate, nylon, and wool (Table 2, entry: 6, 7, and 9). However, considering the easy and inexpensive access of hydroxy-dimethylaminoaurone (OH-DMAA) candidates **22-25** and a requirement of an additional synthetic step for methoxy substituted aurones, we decided to focus only on them for this study, acknowledging a need for a separate study of OMe-DMAA analogs. The description of the colors of each of these four aurone derivatives imparted on the different fibers is summarized in Table 3.

Table 3: Multifiber fabric dyed with aurone **22-25**

Types of Fibers	 22	 23	 24	 25
				
<i>Acetate</i>	Yellow	Orange	Yellow	Greenish yellow
<i>Cotton</i>	-	Maroon	Brown	Light peach
<i>Nylon</i>	Dark orange	Dark orange	Brownish yellow	Brownish yellow
<i>Ployester</i>	-	Light yellow	-	-
<i>Acrylic</i>	-	Light peach	-	-
<i>Wool</i>	Dark orange	Maroon	Dark brown	Dark brown
				

As observed in the figure, nylon (third stripe from the top) and wool (sixth stripe from the top) showed the most promising color retention properties. We decided to move further with the natural fiber wool for this study. We hypothesized that weekly acidic hydroxyl groups in aurones **22-25** should lead to chemical and physical interactions with the various groups of the polypeptide chain of wool.

Wool is a protein fiber consisting of keratin protein as the main structural constituent. Keratin protein is a collection of separate long chains of amino acids which are further connected to each other by various covalent bonds (crosslinks) and physical interactions, including ionic bonds, hydrogen bonds, and van der Waals' forces.¹⁹⁷ (Figure 29) Disulfide crosslinking is the most common chemical bond that significantly contributes to determining the chemical and physical stability of wool fiber and contributes to its mechanical and physical properties.^{81,198}

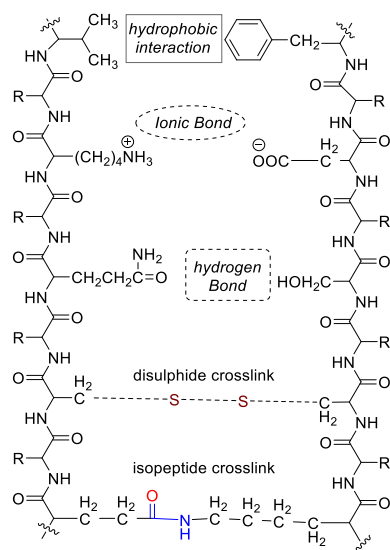


Figure 29: Schematic representation of structure of wool fiber (structure adapted from Rippon, J.A. 2013).

As shown in Figure 29, chemically, the polypeptide strands of the keratin skeleton contain many acidic (carboxylic) and basic (amino) side chains, rendering an amphoteric nature to wool fiber. Acid and reactive dyes are the most used dyes and display a high affinity towards wool fiber. The anionic form of a dye can make ionic interactions with the wool fabric's positively charged (ammonium) active site.¹⁹⁹ Heat-assisted alkaline treatment of wool breaks the polypeptide linkage, causing damage to the keratin structure and causing yellowing of wool by the hydrolysis of aspartic and glutamic residues to aspartic acid and glutamic acid, respectively.²⁰⁰ However, under normal conditions, wool fibers are resistant to acidic conditions. The basic -NH_2 functional groups of wool fiber can be protonated and form -NH_3^+ in the presence of acids, forming a bond with anionic dyes.²⁰¹

Having narrowed the number of aurone candidates to four from eighteen and selected wool fabric for further study, we optimized the dyeing parameters: time, temperature, and shade percentage. For this purpose, aurone **22** was chosen as a model compound because of its straightforward synthesis and purification, ensuring its convenient access for the study in high purity. A representative scheme of optimization is illustrated in Figure 30.

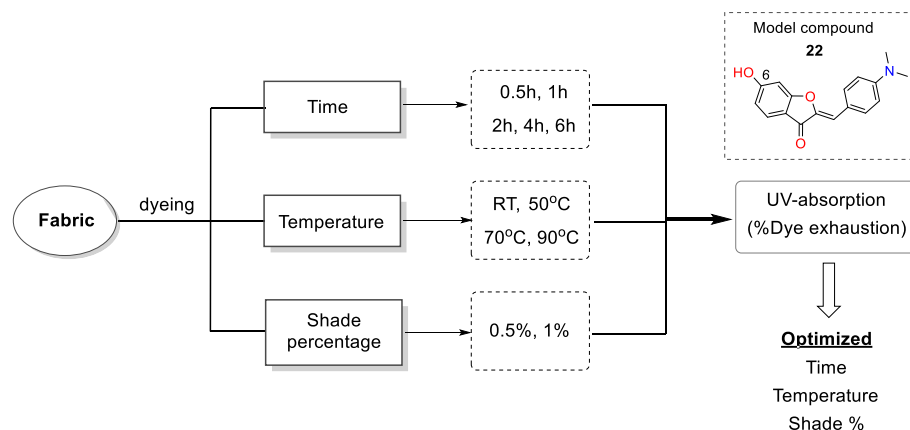


Figure 30: Graphical representation of optimization study strategy

8.3. Optimization of the dyeing parameters

Three variables- time, temperature, and % shade - were studied one at a time while keeping the others constant to optimize the dyeing process. Based on the temperature and shade percentage applied in the preliminary study with the eighteen aurones, the optimum reaction time was determined under 1% shade, keeping the temperature constant at 70°C. Then, the temperature was screened, keeping the shade percentage constant (1%) under the optimized reaction time. Finally, shade percentage was studied for 0.5 and 1%. For the study, a common dye bath solution was prepared for each experiment by dissolving aurone **22** (1% of the weight of the fabric) in DES, which was further diluted to make a dyebath before aliquoting into three equal portions having a material to liquid (MLR) ratio 1:20.

To each of the dye bath solutions, wool fabric was added and stirred under various conditions. Once the dyeing was complete, the dye exhaustion was determined by a comparison of the absorbance at maximum wavelength before and after dyeing.

8.3.1. Dyeing time study

Time is one of the major parameters of the dyeing process. It is crucial to determine the optimum time for the dyeing process, which significantly impacts the cost and the process's effectiveness. Although dye with high molecular weight generally takes a prolonged time to diffuse through the fiber compared to low molecular weight dyeing candidates, it further depends on the bath's temperature and the compound's weight ratio to the fabric. So, optimizing dyeing parameters (time, temperature, and % shade) is vital for effective dyeing outcomes. For time optimization, the dyeing process was carried out for 0.5, 1, 2, 4, and 6 hours at 70 °C and 1% shade. All experiments were performed in triplicate to ensure the accuracy and reliability of results.

The UV-absorption spectra of the time study are shown in Figure 32. The purple curve represents the before-dyeing absorption by the common dye bath solution (50 μM), and after-dyeing absorption trials are represented by red, green, and orange curves. Using a common dye bath solution for all three trials allowed a better comparison to calculate % dye exhaustion. The after-dyeing absorptions for all three trials for each experiment (0.5h to 6h) were found to be highly consistent. (Figure 31)

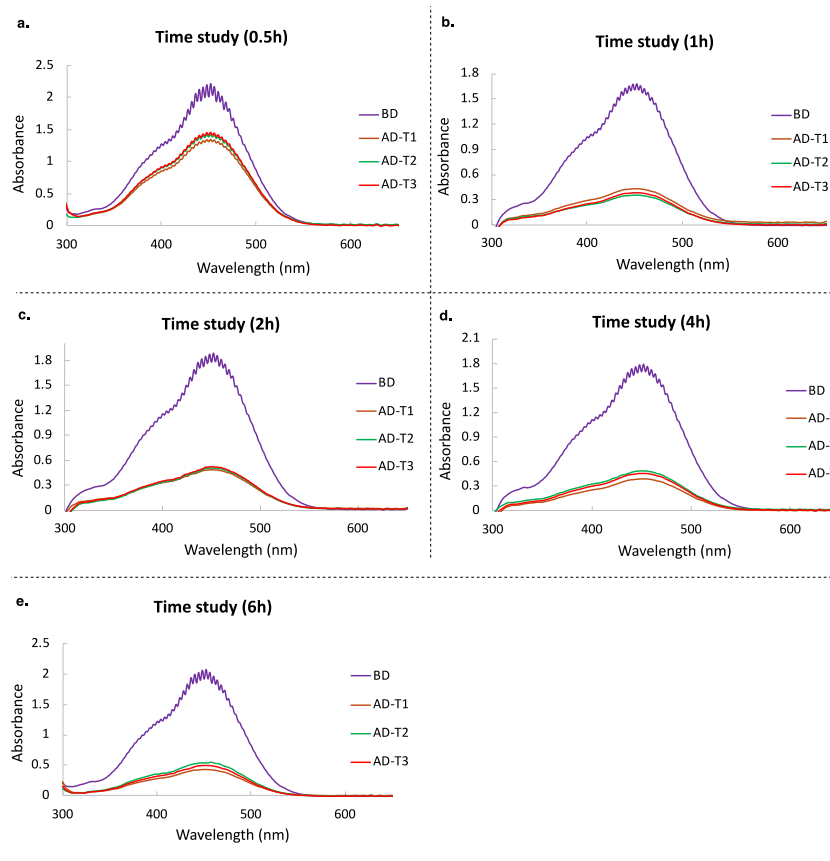


Figure 31: Time optimization study; purple curve represents UV-absorption of the common dye bath before dyeing and green, red, and orange represent UV-absorption of the dye batch solution after-dyeing. For the study dye bath solutions (before and after dyeing) were diluted to 50 μ M with reference to the amount of aurone **22** employed. UV-absorption before and after dyeing in; a) 0.5 h b) 1 h c) 2 h d) 4 h, and e) 6 h.

The study showed that the highest % dye exhaustion (76.9 ± 2.4) of aurone **22** by the wool fiber is one hour. The dye exhaustion at 0.5 h (36.2 ± 2.4) more than doubled at one one-hour time point and remained relatively constant until six hours. About a 3% decrease in dye exhaustion was observed in two hours compared to 1h, after which it gradually increased by $\sim 1\%$ through six hours. Since no significant

increase was observed between 2 and 6 hours, we did not consider more time points for the study. (Figure 32a)

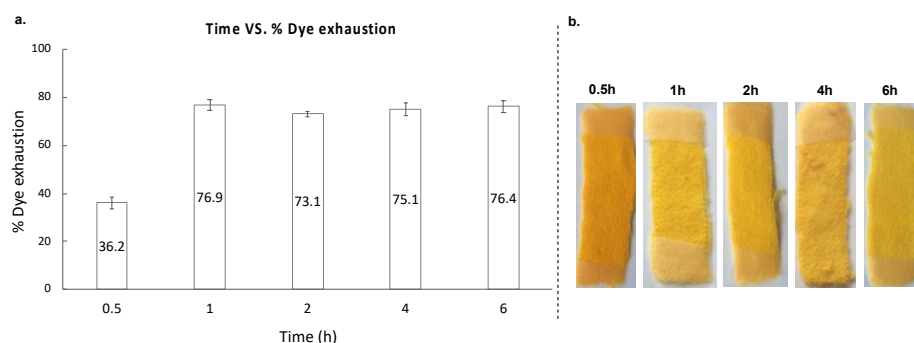


Figure 32: Comparative study of the effectiveness of time in the % dye exhaustion of aurone **22** in ChCl/U. a) The % dye exhaustion is shown in the middle of the bar, with SD represented by error bars. b) Wool fiber dyed for 0.5 to six hours at 70°C and 1% shade and washed with water and soap before air dried.

In addition to % dye exhaustion, the visual observation of the wool fiber dyed for 0.5 h to six hours also showed similar results in terms of color retention. Although the color retention at 0.5 h showed a dark yellow or orange color compared to others, the % dye exhaustion was only 36.2 ± 2.4 in contrast to the fabric kept for a longer time. The color retention at various times is shown in Figure 33b.

8.3.2. Temperature study

Another crucial dyeing parameter is temperature, which affects the dye exhaustion and contributes to the color strength and fastness. An elevated temperature is expected to increase the dye solubility, enhancing dye fixation on the fabric.

However, it also depends on the types of fabric and its morphology and composition. Natural fiber wool is extremely porous morphologically, so the dye is expected to diffuse easily, even at moderate temperatures. To determine the optimum dyeing temperature, we performed experiments at various temperatures ranging from room temperature ($20 \pm 2^\circ\text{C}$) to 90°C .

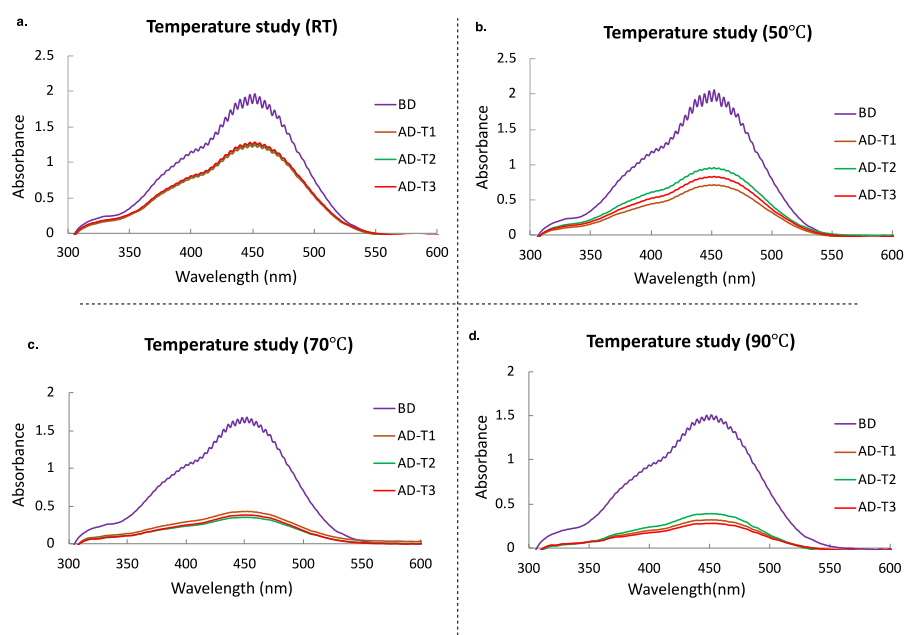


Figure 33: Temperature Optimization Study. UV-absorption spectra for before (purple curve) and after dyeing (green, red, and orange curves) with aurone **22** at various temperature. a) room temperature ($20 \pm 2^\circ\text{C}$) b) 50°C c) 70°C d) 90°C .

All the experiments were run for one hour (optimized time for dyeing) at 1% shade. After 1 hour, fabrics (3 trials) were washed with soap and water and air dried. The % dye exhaustion and visual color retention by the fabric were compared to determine the optimum temperature for the process. The comparison of the dye

exhaustion and color retention is summarized in Figure 34. The study showed a temperature-dependent increase in % dye exhaustion. (Figure 34a) A notable surge in the dye exhaustion was observed with the rise in temperature to 70°C. The exhaustion percentage increased from 35.7 to 59.4 between room temperature to 50°C, which further increased and reached 76.9 at 70°C and remained relatively constant even when subjected to 90°C.

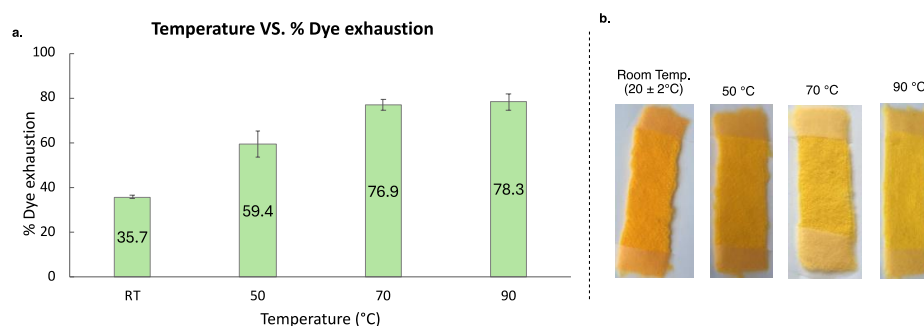


Figure 34: Comparative study of temperature effect in the dye exhaustion of wool fabric dyed with aurone **22** in ChCl/U. a) Temperature VS. % dye exhaustion comparison at different temperature. The % dye exhaustions values are shown in the middle of the bar with SD represented by the error bars. b) Pictures of wool fabric after dyeing at different temperature for 1h and washed with water and soap before air dried.

The picture on the right of the graph (Figure 34b) shows the color retained by the fabrics at different temperature followed by washing with soap and water. Interestingly, despite remarkably low dye exhaustion, the fabric gained a dark orange hue up to 50°C, which adopted a yellow color above 70°C.

Having determined 70°C as the optimum dyeing temperature, we further studied the effect of stirring on the dye exhaustion efficiency of the fiber. An independent experiment conducted at 70°C for one hour without stirring led to 52.3 % dye exhaustion compared to 76.9 % with stirring, reflecting the importance of effective stirring for maximum dye dispersion.

8.3.3. Concentration of dye (Shade percentage) study

The dye concentration employed in a fabric dyeing process is commonly referred to as shade percentage. It is expressed as the amount of dye in relation to the weight of the fabric used. It signifies the depth of a particular shade in a dyed fabric, which generally depends on the amount of dye used. Lower concentrations usually result in paler shades compared to the solution with a higher shade percentage, as higher dye molecule concentration in a dye bath solution is expected to enhance the dye uptake. However, it is not universally applicable, as the amount of dye absorbed and retained by the fiber equally depends on the morphology and chemical composition of a fabric. So, it is crucial to determine the optimum shade percentage or depth of shade for the fiber of interest. The most common shade % reported in the dyeing process ranges from 0.1 to 5. In addition to 1% shade, we studied the dye exhaustion at 0.5 shade percentage. The results are summarized in Figure 35.

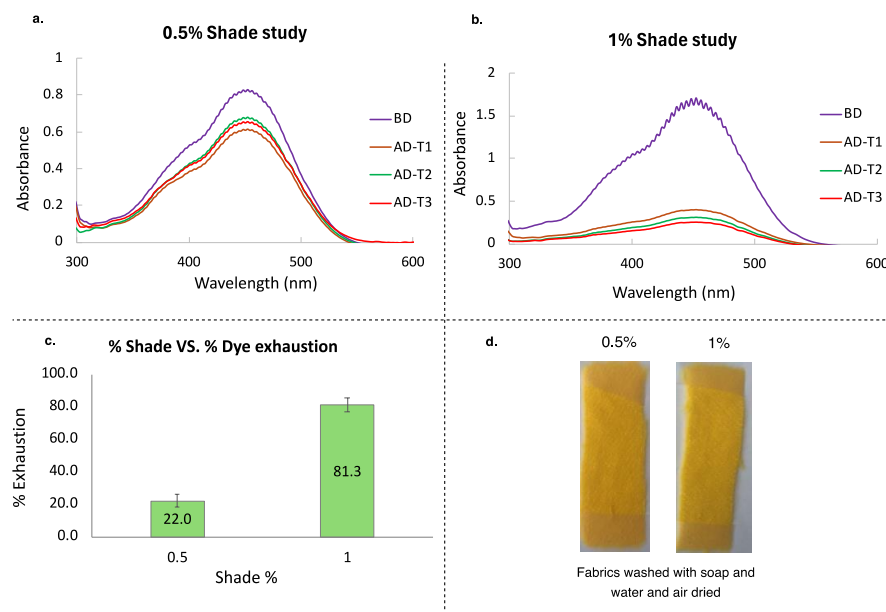


Figure 35: Shade percentage study; a, b) UV-absorption spectra for before (purple curve) and after dyeing (green, red, and orange curves) for 1h at 70°C with aurone **22** in 0.5 and 1% dye concentration, respectively. c) Comparison of % dye exhaustion between 0.5 and 1% shade applied. d) Wool fabric after dyeing in 0.5 and 1% shade concentration for 1h at 70°C and washed with water and soap before air dried.

Although the fabric seemed to gain a darker shade in a dye-bath solution with 0.5 % shade (Figure 35d) compared to the solution with 1% shade, the dye exhaustion for the fabric dyed in 1% shade solution was found to be almost 4-fold higher than the 0.5 % (22 vs. 81.3%). (Figure 35c). This value is comparable to the one obtained for the temperature screening experiment at 70°C (76.9%). (Figure 34a) The UV-absorption spectra utilized to calculate % dye exhaustion of wool fibers dyed in 0.5 and 1% shade concentration of aurone **22** are included in Figure 35. Since a high amount of

dye exhaustion at 1% shade was already obtained and aurone **22** showed poor solubility at a higher % shade in the used volume of DES, higher % shades were not considered.

8.4. Determine and compare color strength and color fastness of aurone 22-25

dyed fabrics

The optimization of dyeing on wool fabric, using aurone **22** as a model compound provided us with optimal dyeing parameters that were applied across all four aurone dyes in this study given the similarities of these compounds. The next stage involved examining the properties of the dyed fabrics, particularly color strength and fastness on wool fabric. All these tests were performed on the fabrics of different dimensions as necessitated by the standard procedures or protocols. ISO 105-X12, ISO 105-C06, and ISO 105-B02 are the common protocols employed in studying rub fastness, wash fastness, and light fastness, respectively.^{54,59} The schematic representation of the study is outlined below in Figure 36.

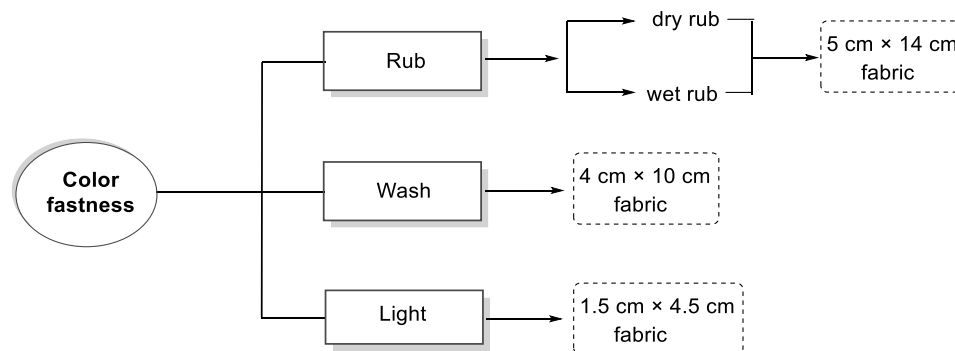


Figure 36: Schematic representation of color fastness study strategy

Colorfastness is a key dyeing parameter that signifies a dyed fabric's resistance to losing its color characteristics. Since dyed textile fabrics are utilized for various purposes, they get exposed to different agents and conditions that deteriorate the color of a fabric, and the most common factors or agents that affect the color stability of a dyed fabric are rub, wash, and light. The ability to resist the effect of these factors plays an instrumental role in making the fabric commercially acceptable. Wool fabric was cut into various dimensions, as specified in Figure 36. For the rub fastness, both wet and dry rub, 5 cm x 14 cm pieces were used, whereas smaller 4 cm x 10 cm wool fabrics were used for the wash fastness study.

Similarly, 1.5 cm x 4.5 cm pieces were used for dyeing to study light fastness. These various dimensions of wool fabrics were dyed with aurones **22-25** in triplicate experiments under the optimized conditions and subsequently subjected to washing with soap and water. All dyed fabrics were air-dried. For each trial, before and after dyeing, the UV absorption of the dye bath solution and the % dye exhaustion were calculated for each experiment. The % dye exhaustion calculated for aurone dyed wool fabric are tabulated below in Table 4, and the corresponding UV spectra are incorporated in Appendix B.

Table 4: Average % dye exhaustion of aurones **22-25** on wool fabric

SN	Aurones	% DE (average of triplicate)				Average (%DE)
		Dry Rub	Wet Rub	Wash	Light	
1.	22 (6-OH)	93.9	90.4	87.3	77.8	87.3
2.	23 (4-OH)	69.8	78.5	74.5	67.3	72.5
3.	24 (4,6-diOH)	79.7	77.3	74.5	80.2	77.9
4.	25 (6,7-diOH)	39.4	47.5	45.5	53.3	46.4
* % DE = % Dye exhaustion Fabric dimensions: Dry rub ((5cm x14cm); Wet rub (5cm x14cm); wash (4cm x10cm); Light (1.0cm x4.5cm)						

The % dye exhaustion obtained for each dimension of dyed wool fabric for the fastness study was averaged for three trials, and the summary is plotted in Figure 37. Among the four candidates, 6-hydroxy substituted aurone (**22**) dyed wool fabric showed the highest dye exhaustion ($87.3 \pm 6.5\%$), whereas 4-hydroxy (**23**) and 4,6-dihydroxy (**24**) analogs showed comparable dye exhaustion, $72.6 \pm 4.9\%$ and $78.0 \pm 2.5\%$, respectively. Despite having dihydroxyl groups, 6,7-dihydroxy substituted analog (**25**) exhibited poor dye exhaustion (only $46.5 \pm 5.7\%$).

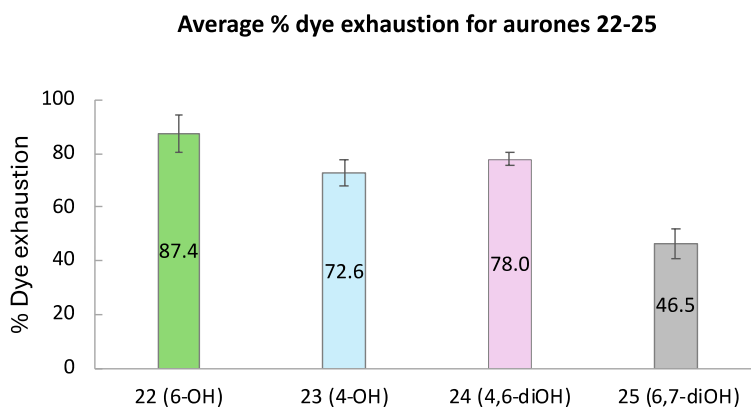
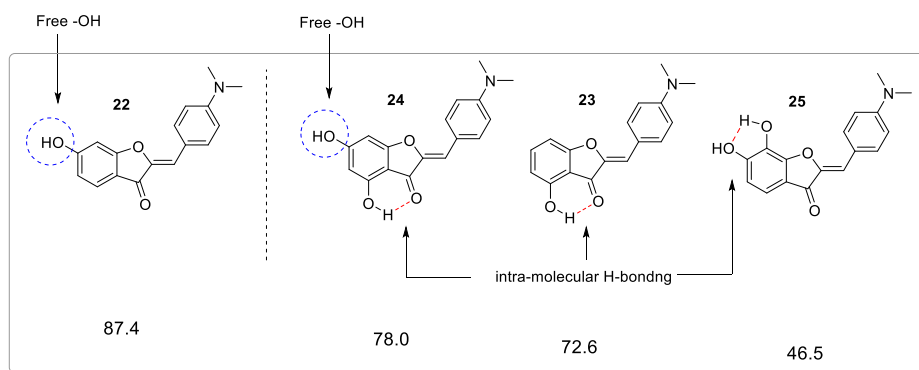


Figure 37: Average % dye exhaustion of aurone **22-25** dyed wool fabrics

Chemically, the presence of both acidic and basic functionalities renders an amphoteric nature to wool. The polypeptide linkage with various functionalities in keratin protein, the main structural constituent of the wool fiber, offers multiple sites for molecular interactions.¹⁹⁹ Likewise, aurones **22-25** also possess multiple active sites for chemical and physical interactions with fabric components.

Among other functionalities, the hydroxyl group, besides enhancing the aurone's solubility in the ChCl/U mixture, can enable strong hydrogen-bonding interactions with fabric as well as the potential for acid-base chemistry and thus ionic interactions. This effect translates and manifests as increased dye adsorption, with % dye exhaustion as one way to quantify and express it. On that note, an increase in the number of -OH substituents is expected to increase the dye-fabric interactions, thus leading to high dye exhaustion. However, among the four hydroxy aurones, the mono hydroxylated analog **22** (6-OH) exhibited the highest % dye exhaustion compared to dihydroxy analogs **24** and **25**. (Figure 37)

Despite two hydroxyl substituents, aurone **25** (6,7-diOH) dyed wool fabric demonstrated the lowest dye exhaustion. It can be attributed to the relative availability of -OH groups in a molecule for the intermolecular interactions with the wool fabric functionalities. As illustrated in Scheme 15, low dye exhaustion of aurones **23**, **24**, and **25** compared to **22** can be attributed to the less accessibility of the hydroxyl group for the intermolecular interactions due to their possible involvement in intra-molecular hydrogen-binding, making them less available for intermolecular interactions.



Scheme 15: Intramolecular H-bonding and its effect in % dye exhaustion of aurones

Additionally, in a slightly basic ChCl/U dyeing medium, these aurones can reside in ionic form, which may participate in both ionic and covalent interactions with the wool fiber. However, % dye exhaustion calculated for the aurones **22-25** is solely based on the optimized conditions for the model compound **22**. Although they share the common aurone framework and functionalities (-NMe₂, carbonyl, and ether), they possess different numbers, if not the position of the hydroxyl group, which can significantly affect their interacting properties with fibers, hence the % dye exhaustion at various time, temperature, and concentration.

8.4.1. Colorfastness study of aurones 22-25 against rub, wash, and light

While grey-scale numerical determinations are the standard method adopted in the textile area, in this research the colorfastness was also evaluated using reflectance spectroscopy. Reflectance of an object denotes the fraction of the illumination reflected by it at each wavelength and determines its color as well as intensity.²⁰² The higher the reflectance value, the less the light at that wavelength is absorbed and thus the lighter the color is. This higher reflectance can be a sign of either dye loss or of a change in hue, a variable that is not considered in standard grey-scale measurements. Comparing the reflectance of a dyed fabric before and after a specific test (rub, wash, and light treatment) is not generally used in the textile area but is a known method for evaluating color shade and intensity in the paint area and would seem to have promise in other dyeing areas as well. Furthermore, the reflectance at the maximum absorption wavelength (λ_{max}) can be used to determine the color strength of a dyed fabric. So, the measure of reflectance of a dyed fabric serves for colorfastness, color strength, and hue evaluation.

In this study, we utilized both grey-scale and reflectance spectroscopy to determine the color fastness of aurone **22-25** dyed fabrics. First, the fabrics of different dimensions were subjected to grey-scale tests against rub, wash, and light, as described in the experimental section, for visual assessment of color change or loss after the test. The results of the grey scale test are tabulated below (Table 5) on a scale of 1-5, with five being excellent and one being poor.

Table 5: Grey scale color fastness assessment of **22-25** dyed fabrics

S.N.	Aurones	*Grey Scale Value (1-5)			
		Dry Rub	Wet Rub	Wash	Light
1	22 (6-OH)	5	4	4	4
2	23 (4-OH)	5	5	4	4
3	24 (4,6-diOH)	5	4	5	5
4	25 (6,7-diOH)	5	4	3	5
*Grey scale value: 5 - excellent; 1 - poor					

All fabrics showed promising color fastness properties against all four stress tests, standard fabric color-depleting stress factors in daily life. Except for aurone **25**, which exhibited a grey-scale value of 3 against wash compared to the other tests (Table 5, entry 4), all other aurones demonstrated high resistance (grey scale value 4-5) towards rub, wash, and light exposure.

In addition to standard grey-scale measurements, the color of the dyed fabrics was evaluated using a reflectance spectrophotometer in the region from 400-700 nm both before and after the appropriate colorfastness test, with each test being performed in triplicate. The results of the reflectance measurement for dyed fabrics are discussed below.

8.4.1.1. Reflectance-based colorfastness study of aurone **22** (6-OH)

The UV-Vis reflectance curves for before and after dry rub and wet rub, wash, and light treatment of aurone **22** dyed fabrics are shown in Figure 38. The plot suggests a high tolerance of the dyed fabric towards dry rub, as indicated by nominal difference in the reflectance value shown by the reflectance curves before and after dry rub.

(Figure 38a). A similar trend was observed for wet rub except for a noticeable reflectance increase near 600 nm. (Figure 38b)

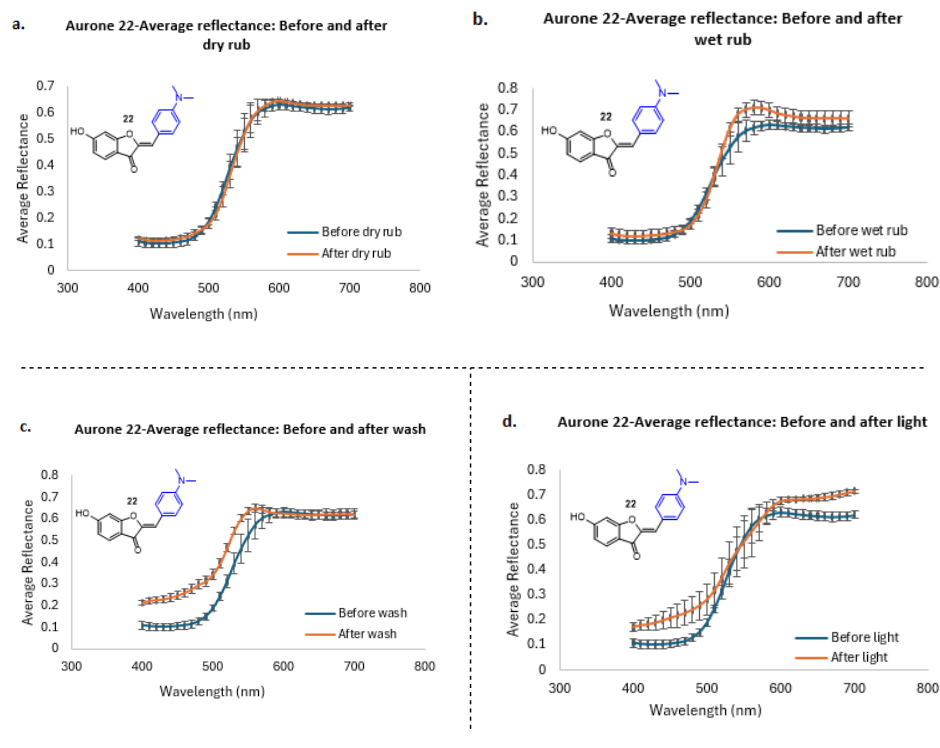


Figure 38: Vis-reflectance spectra of aurone **22** dyed fabrics against a) dry rub b) wet rub c) wash, and d) light treatment. The cyan and orange color curves represent reflectance of the dyed fabric before and after tests, respectively. The results are the average of three separate trials with confidence intervals shown.

The reflectance curve for the wash test, in Figure 38c, showed significantly high reflectance between 400 nm to 550 nm (an average of ~1.9-fold increase in reflectance) for after-wash fabric compared to the unwashed sample, implying a significant color

loss in this region. The after-wash reflectance decreased after 550 nm and followed the reflectance curve for the unwashed fabric from 600-700 nm. Similarly, the fabric exposed to light was also observed to lose color compared to the untreated fabric from 400 nm to 550 nm. The treated and untreated fibers showed similar reflectance from 550 nm to 600 nm. However, the reflectance value increased for light-treated fabric, indicating further color loss above 600 nm (Figure 38d).

8.4.1.2. Reflectance-based colorfastness of aurone **23 (4-OH)**

The 4-hydroxy derivative aurone **23** dyed fabrics showed only a minimal color loss against rub, wash, and light treatment, overall, as depicted in Figure 39. The reflectance curves for before and after dry rub showed almost no difference in the reflectance values from 400 nm to 600 nm, indicating an excellent resistance of the dyed fabric towards dry rub. A similar trend was observed for the wet rub but with a minimal increase in the reflectance throughout the visible region (400-700 nm) compared to the dry rub. (Figure 39b). Overall, the aurone **23** dyed fabric appeared highly resistant to dry and wet rubbing.

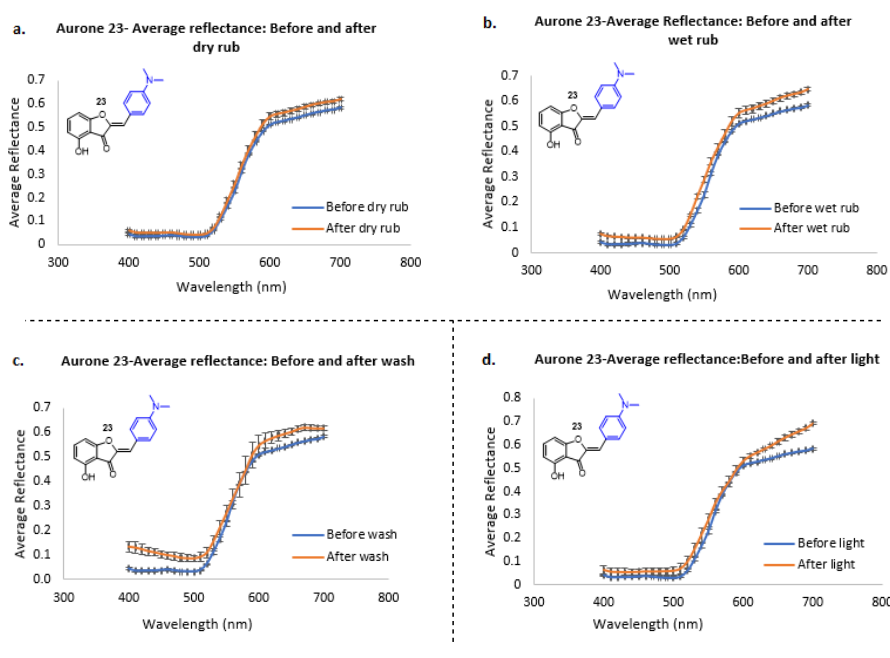


Figure 39: Vis-reflectance spectra of aurone **23** dyed fabrics against a) dry rub b) wet rub c) wash, and d) light treatment. The cyan and orange color curves represent reflectance of the dyed fabric before and after tests, respectively. The results are the average of three separate trials with confidence intervals shown.

The wash test of the dyed fabric showed higher reflectance at ~ 400 nm (0.13 vs. 0.03 unwashed) which gradually decreased and became comparable to that of the unwashed fabric from ~ 530 nm- 600 nm but increased again gradually above 600 nm. (Figure 39c) Although some color loss was observed from 400 nm to ~ 500 nm and 600-700 nm based on the reflectance at various wavelengths, the effect of wash on the colorfastness appeared to be minimal.

The comparison of the reflectance curve for light-treated versus untreated fabric (Figure 39d) suggests high colorfastness of the aurone **23** dyed fabric from 400-600 nm

against the light source. Above 600nm, the fabric showed increased reflectance, inferring a loss of hue.

8.4.1.3. Reflectance-based colorfastness of aurone **24 (4,6-diOH)**

The 4,6-dihydroxy derivative aurone **24** dyed fabrics subjected to rub, wash, and light treatment test exhibited high colorfastness towards dry rub and wash, as demonstrated in Figures 40a and 40c. Although a slight increase in reflectance was observed for the dry rub above ~550nm, the difference appeared to be nominal compared to the reflectance measured for unrubbed fabric. However, the reflectance for pre- and post-wet rub was found to be comparable up to 500 nm, above which the difference increased gradually and became significant. At 600 nm, the reflectance increased by ~ 1.32-fold (0.31 to 0.41) after wet rub indicating a significant color loss. (Figure 40b). A similar, but smaller, result was observed for the wash effect on the colorfastness of the aurone **24** dyed fabric which showed an increased reflectance above 550 nm, although the increase was less significant than the wet rub test.

Interestingly, the plot in Figure 40d revealed almost no effect of light treatment on the colorfastness of the fabric. The reflectance curve for the pre- and post-light treatment virtually appeared to overlap, indicating no color loss from 400-660 nm.

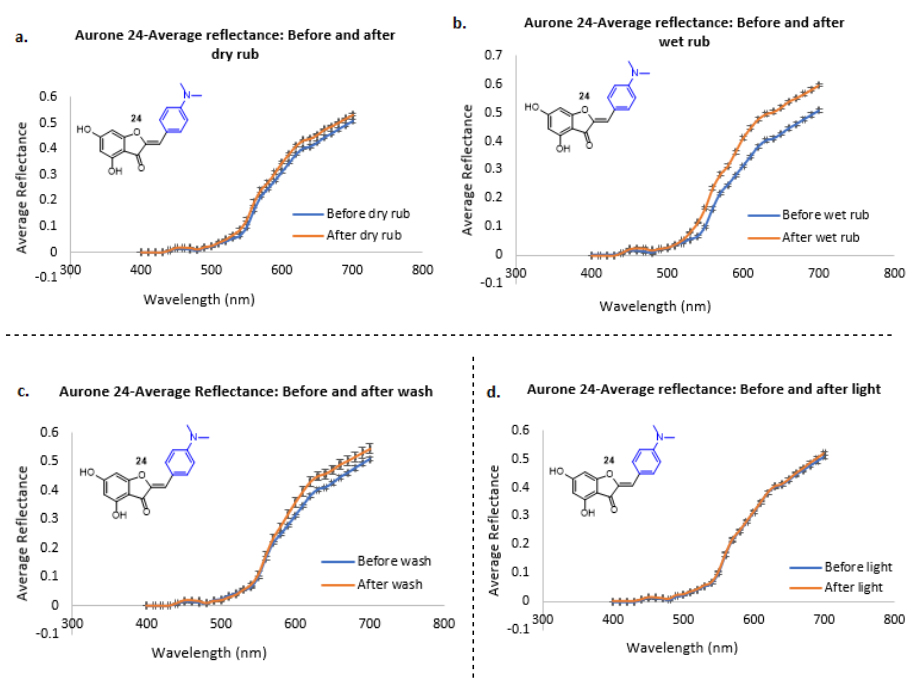


Figure 40: Vis-reflectance spectra of aurone **24** dyed fabrics against a) dry rub b) wet rub c) wash, and d) light treatment. The cyan and orange color curves represent reflectance of the dyed fabric before and after tests, respectively. The results are the average of three separate trials with confidence intervals shown.

8.4.1.4. Reflectance-based colorfastness of aurone **25** (6,7-diOH)

The reflectance curves for aurone **25** dyed fabric against rub, wash, and light exposure are illustrated in Figure 41. The plot in Figure 41c for the wash test showed a ~11-fold reflectance increases at 400 nm after wash (0.011 vs 0.121). Although the increase appeared to be substantial from 400 to ~ 500 nm, the reflectance of post-wash fabric was consistently higher throughout the range of study (400 to 700nm) compared to the unwashed fabric.

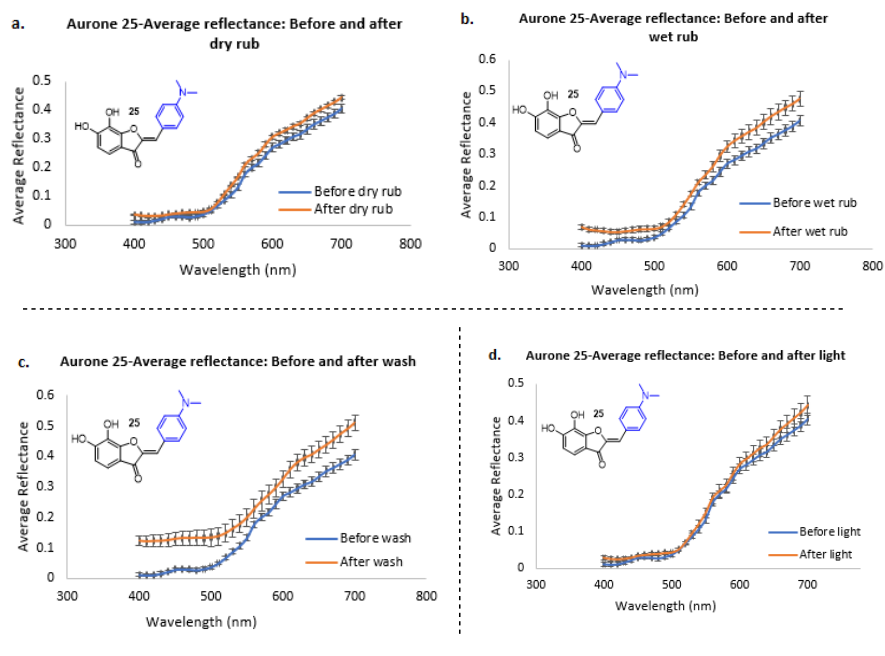


Figure 41: Vis-reflectance spectra of aurone **25** dyed fabrics against a) dry rub b) wet rub c) wash, and d) light treatment. The cyan and orange color curves represent reflectance of the dyed fabric before and after tests, respectively. The results are the average of three separate trials with confidence intervals shown.

The dry rub for aurone **25** showed a comparable reflectance between the pre-rub and post-rub until 500nm, above which, the value gradually and slightly increased for post-rub. However, the effect of rub was observed to be more prominent for wet fabric (Figure 41b) as the post-rubbed fabric constantly exhibited increased reflectance throughout the visible range of the study, indicating more color loss to the wet rub test than the dry rub. The fabric was found to show good tolerance against light effect as indicated by the reflectance curves in Figure 41d. Overall, compounds **23** and **24**

appeared to show comparatively better colorfastness among the four against rub, wash, and light exposure.

8.4.2. Evaluation of color strength

The observed radiant energy from any fabric surface is the combination of hue, saturation, and lightness imparted by the dye, representing the color depth of the fabric surface. Color depth is a critical quality component in the textile industry and is expressed in color strength. Color strength, or the ability of a dye to impart color to a fabric, is quantified as the ratio of absorption coefficient (K) to scattering coefficient (S) using the Kubelka-Munk equation.

$$\frac{K}{S} = (1 - R_{\lambda_{max}})^2 / 2R_{\lambda_{max}}$$

K/S value is associated with the reflectance of a dyed fabric at λ_{max} of the dye.

Using the reflectance curves measured to evaluate colorfastness, we calculated the K/S value for each test (rub, wash, and light exposure). The K/S values were calculated for each test at the respective λ_{max} of each aurone dye candidate and tabulated in Table 6.

Table 6: Color strength (K/S) of aurone **22-25**

Aurone	$K/S = (1-R_{\lambda_{\max}})^2 / 2R_{\lambda_{\max}}$							
	Dry rub		Wet rub		Wash		Light	
	B	A	B	A	B	A	B	A
22 (6-OH) ($\lambda_{\max}$) = 452 nm	3.8	3.3	3.8	3.0	3.8	1.1	3.8	1.5
23 (4-OH) ($\lambda_{\max}$) = 470 nm	12.7	9.4	12.7	7.6	12.7	4.3	12.7	7.9
24 (4,6-OH) ($\lambda_{\max}$) = 446 nm	32.5	26.9	32.5	21.6	32.5	26.2	32.5	36.9
25 (6,7-OH) ($\lambda_{\max}$) = 476 nm	17.2	10.5	17.2	6.9	17.2	2.8	17.2	11.6
A = after, B = before								

Since the K/S value depends on the dyed fabric's reflectance, the numerical value for the compound imparting a pale color will be lower than the one imparting a darker shade to the fabric. In our case, the aurones follow the order **22** < **23** < **24** > **25**, with **22** imparting a pale-yellow shade to the fabric. The K/S values for aurone **22** dyed fabrics subjected to rub, wash, and light treatment showed the lowest color strength for wash (1.1) and light (1.5). Since **22** imparted a pale-yellow shade to the fabrics compared to **23-25**, it is expected to have higher reflectance, contributing to the lower K/S value overall. Like **22**, the aurone **23** showed the highest color strength for dry rub (9.4) and the lowest for wash (4.3). The K/S values for both compounds towards four different tests followed the same order: dry rub > wet rub > light > wash. However, the dihydroxy derivatives **24** and **25** that give dark orange shades to the fabrics showed the highest K/S towards light exposure (36.9 and 11.6). While compound **25** showed the

lowest color strength after wash (2.8), analog **24** exhibited the lowest K/S for wet rub (21.6). (Table 6)

8.4.2.1. % Dye fixation (F%)

We further utilized the K/S values obtained for aurone **22-25** dyed wool fabric, both before and after rub, wash, and light treatment, to determine the amount of fixed dye on the fabric. Fixation is the measure of adherence of coloring matter to fabric and is expressed as % fixation rate (F%). The fixation rate (F%) of a dyed fabric is calculated using the equation;^{203,204}

$$F\% = \frac{\left(\frac{K}{S}\right)_a}{\left(\frac{K}{S}\right)_b} * 100\%$$

Where (K/S)_b and (K/S)_a are the color strength of a dyed fabric before and after the treatment or test.

The F% for aurone **22-25** dyed fabrics are summarized in Table 7.

Table 7: % Dye fixation of aurone **22-25** against rub, wash, and light exposure

Entry	Aurone	Dry rub	Wet rub	Wash	Light
		F%	F%	F%	F%
1.	22 (6-OH)	86.8	78.9	28.9	39.4
2.	23 (4-OH)	74.0	59.8	33.8	62.2
3.	24 (4,6-OH)	82.7	66.4	80.6	113.5
4.	25 (6,7-OH)	61.0	40.1	16.3	67.4

Aurone **22** exhibited the highest fixation (86.8%) on the wool fabric against dry rub compared to wet rub, wash, and light exposure. However, dye fixation was highly

affected by wash, as evidenced by the low F% (28.9%). This suggested a significant dye molecule loss from the fabric surface during the wash. A similar effect was observed when exposed to the light source (F% = 39.4%). Aurone **23** dyed fabric also showed a similar fixation trend. After washing, the fixation was low (33.8%), indicating that the molecules were effectively dislodged from the fabric surface. The F% order can be summarized as dry rub > light > wet rub > wash. (Table 7)

Compound **24** showed a relatively higher F% for all the tests. It exhibited a higher % F (80.6%) for washing compared to **22** and **23**. The % F follows Light > dry rub > wash > wet rub. The data shows an anomaly in the case of light treatment; F% > 100%. One of the possible reasons behind such a high fixation value could be the photoisomerization of **24** in the presence of light converting Z isomer to E form, which may have higher absorption, resulting in a higher K/S value to the fabric after light treatment compared to pre-treatment. (Table 6)

In the case of **25**, the lowest F% was observed for wash treatment (16.3%). It showed comparable F% for both dry and light fastness. The F% order can be summarized as light > dry rub > wet rub > wash. (Table 7) While all aurones exhibited relatively high dye fixation against dry rub, most of them, specifically **22**, **23**, and **25** dyed wool fabrics, were found prone to wash treatment as indicated by their F% values (28.9, 33.8, and 16.3) respectively. (Table 7)

9. Conclusions

In summary, this study demonstrated the dyeing potential of aurone. A library of ferrocene and dimethylamino- appended aurones derivatives was synthesized to explore and evaluate their dyeing potential. While the use of ferrocenyl derivatives was

limited by their poor solubility in CHCl_3/U , four hydroxy derivatives (**22-25**) of the dimethylamino aurones (DMAA) series were evaluated for color fastness, color strength, and fixation ability on wool fabric. An average dye exhaustion for each aurone dyed fabric was determined at their respective λ_{max} for three trials, which followed the order of **22** ($87.3 \pm 6.5\%$) > **24** ($78.0 \pm 2.5\%$) > **23** ($72.6 \pm 4.9\%$) > **25** ($46.5 \pm 5.7\%$). The dyed fabrics were further evaluated for their colorfastness ability against rub, wash, and light, where all of them exhibited high grey-scale values, showing their strong interaction with wool fabric.

Additionally, the dyed fabrics (before and after tests) were spectroanalyzed to determine their reflectance and calculate their color strength or K/S ratios. While aurone **22** exhibited the lowest K/S due to its lighter shades, a consistently high K/S value was obtained for aurone **24** with a darker shade against all four tests compared to **23** and **25**. Further, the K/S values were used to calculate the % dye fixation (F%) which showed high F% against dry rub, however, aurone **22**, **23**, and **25** showed poor results after wash treatment.

10. Experimental

General information: Multifiber test fabric was purchased from Kimble Chase and Ready-to-Dye white wool was purchased from Hobby House. The reactions were done using ACS-grade reagents under an air atmosphere unless otherwise specified. JEOL AS (500 and 300 MHz) NMR instrument was used to record ^1H and ^{13}C NMR. The chemical shifts were recorded in ppm with reference to the tetramethylsilane (TMS), CDCl_3 (Chloroform- d_6), Acetone- d_6 or DMSO- d_6 . The following conventions are used for multiplicities: s, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; *dd*, doublet of doublet;

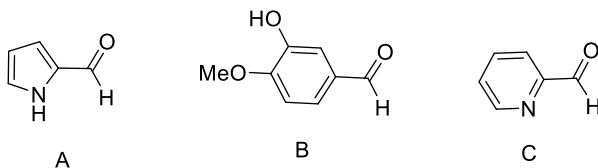
tt, triplet of triplet; *dt*, doublet of triplet; *ddd*, doublet of doublet of doublet; *br*, broad. All extracts were concentrated using a Buchi rotavapor under reduced pressure using a Buchi Rotary Evaporator. Thin Layer Chromatography (TLC) was done on silica-coated TLC plates and monitored by short wavelength (254 nm) UV light. Silica gel column chromatography was used for compound purification. HP-8452A Diode Array Spectrophotometer (Agilent Technologies INC.) was used to record UV-visible absorption spectra.

10.1. Preparation of DES dye bath and in situ dyeing of fabric

Choline chloride-urea (1:2)¹⁸⁵: In a 6-dram vial, 100 mmol (6.0 g) of urea was weighed and to it, 50 mmol (7.0 g) of choline chloride was added. The vial was left in an orbital shaker at 70°C overnight to obtain a homogeneous mixture of DES.

Choline chloride-oxalic acid (1:1)¹⁸⁶: In a 6-dram vial, 70 mmol (8.8 g) of oxalic acid and 70 mmol (9.8 g) of choline chloride were taken and the vial was left in an orbital shaker at 70°C overnight to obtain a homogeneous mixture of DES.

In situ synthesis of aurones and dyeing multifiber fabric in one pot: In a 6-dram vial, 0.1 mmol of aldehyde (A) and 0.1 mmol of benzofuranone were dissolved in 10 mL of the DES and added a strip of 0.45 g multifiber fabric in the same vial. The mixture was stirred overnight at 70°C. Next day, the fabric was washed with de-ionized water several times and air dried. The same process was repeated using aldehydes B and C.



UV- Visible absorption (Sample preparation): 1 mM stock solution was prepared by diluting 1 mL of dyebath solution (before and after dyeing) with 9 mL methanol. 150 μ L of stock solution was further diluted with 2850 μ L of methanol in a 3 mL cuvette to obtain a final concentration of 50 μ M. All the UV-absorption spectra were collected using this concentration.

Dilution of *in situ* dyebath solution for dyeing multifiber fabric: In a vial, 0.1 mmol of the benzofuranone and 0.1 mmol of the aldehyde were taken, and to this added 2 mL of DES. The reaction mixture was stirred overnight at 70°C. Without further purification or characterization, the solution was diluted by adding water. For this, 1 mL of the resulting solution was pipetted out and 19 mL of DI water was added to it, making the concentration of dye bath solution 2.5 mM in a 6-dram vial. With this diluted solution, a 0.5 ± 0.1 g fabric strip was dyed with stirring for about 2h at 70°C in a sand bath.

UV-Vis absorption (Sample preparation): 0.5 mM stock solution was prepared diluting 1 mL of 2.5 mM dyebath solution (before and after dyeing) with 1mL methanol and 3 mL DI water. All UV-absorption spectra were collected using a 50 μ M solution of the compounds in DI water prepared by diluting 300 μ L of stock solution with 2700 μ L of DI water in a 3 mL cuvette.

10.2. % Dye exhaustion

Percent dye exhaustion ($E\%$) was determined by measuring the absorbance values (at wavelength of maximum absorbance, λ_{max}) according to equation (1).

$$\% \text{ Dye Exhaustion} = [(A_0 - A_1)/A_0] \times 100 \dots\dots\dots (1)$$

Where A_0 and A_1 are absorbance of dye before and after dyeing process respectively.

10.3. Determination of Antimicrobial Activity of aurone dyed fabrics

Assessment of the antimicrobial activity was carried out against *C. albicans* according to the standard procedure described in the AATCC test method 147- 2004.¹⁸⁷

Preparation of *C. albicans* inoculum:¹⁸⁸ In a one-liter Erlenmeyer flask, 500 mL of deionized water was taken, and added 25.0 g of YPD broth. The solution was heated for a while until the solid dissolves completely. After that, the flask was closed with aluminum foil and was sterilized in an autoclave at 121 °C for 15 minutes.

5.0 ml of the sterilized broth solution was poured into individual test-tubes and autoclaved. The broth in the test-tube was inoculated with a full loop of *C. albicans* (ATCC strain 90028) and incubated for 18 - 24h at 35°C. After 24h, 1.0 mL of broth culture was transferred into 9.0 mL of sterile distilled water in a test-tube and the solution was mixed properly using agitation.¹⁸⁸

Sterilized YPD agar petri dishes were prepared by dispensing sterilized nutrient agar by pouring 15.0 mL into a standard flat bottomed petri dish. Agar was allowed to gel firmly before inoculating. Using a 10 µL inoculating loop, one loopful of the diluted inoculum was gently streaked on the surface of the sterile agar plate without breaking the surface. In a similar manner, four other streaks were made on the agar surface. The dyed fabrics were cut in (2 cm x 5 cm) sizes. The fabric was gently transversely pressed across the five inoculum streaks, and it was made sure that the fabrics had intimate contact with the agar surface using a sterilized spatula. The plates were then incubated at 35°C for 72 h. The incubated plates were examined for interruption of fungal growth

along the streaks of inoculum, beneath the specimen and for a clear zone of inhibition beyond its edge.¹⁸⁷

10.4. Fabric screening

Multifiber fabric of 0.5 ± 0.1 g was used directly without any pre-treatment. For dyeing, the required amount of aurones (1 % o.w.f) was dissolved in 2 mL DES (ChCl/ urea) in a 6-dram vial by stirring it for about 60 minutes at 70°C. Required volume of water was added to maintain 1:20 MLR (material to liquor ratio) and the solution was further heated at the same temperature for about 15 minutes. Fabric was added to the dye bath solution and was dyed for 4 h at 70°C with constant stirring. The fabric was taken out of the solution and then washed with soap and water and air dried. The dyeing process for each dye was repeated three times.

For 1% shade, amount of dye required= $1/100 \times \text{mass of fabric (g)}$

$1:20 \text{ MLR} = \text{mass of fabric (g)} / \text{Volume of solution (mL)}$

$\text{Volume of solution} = \text{mass of fabric} \times 20$

UV-Vis absorption (Sample preparation)

Stock solution of 0.780 ± 0.150 mM concentration was prepared by diluting 1 mL of 1.57 ± 0.30 mM dye bath solution (before and after dyeing) with 1mL acetone. All the UV-absorption spectra were collected using a 50 μ M solution of the compounds (except where otherwise noted) by diluting stock solution with DI water in a 3 mL cuvette.

Percent dye exhaustion ($E\%$) was determined by measuring the absorbance values (at wavelength of maximum absorbance, λ_{max}) according to equation 1 (Section 10.2).

10.5. Dyeing condition optimization

For this study, dyeing of wool fabric (without any pre-treatment) was carried out with aurone **22** (6-OH-DMAA). To optimize the dyeing process, the effect of three variables- dyeing time, dyeing temperature, and shade percentage were studied respectively.

Three wool fabrics each weighing 0.4 ± 0.05 g were taken. For dyeing, a common dye bath solution was prepared by dissolving 12.2 ± 0.4 mg of aurones (except for 0.5% shade study, in which 6.5 mg of dye was used for the same mass of three fabrics) in 6.0 mL of deep eutectic solvent in a 50 mL round bottomed flask. The solution was stirred for about 60 minutes at 70°C. 24.0 mL of DI water was added to the flask and the diluted solution was stirred for a further 15 minutes at the same temperature. Now, 8 mL of prepared dyebath solution (1:20 MLR) was transferred into three different 6-dram vials and fabrics were added to them individually. The fabrics were then stirred under various conditions.

For time study, the dyeing was carried out for 0.5, 1, 2, 4, 6h at 70°C maintaining 1% shade of dye. For the effect of temperature study, the dyeing was performed for 1 h with 1% shade of dye and the temperature varied from room temperature to 50, 70, and 90°C. At 70°C, dyeing was also carried out by stirring the dyebath solution and without stirring it. Two different shade percentages (0.5% and 1%) were used to study the effect of amount of dye with respect to the fabric weight at 70°C for 1 h.

UV-Vis absorption (Sample preparation): Stock solution of 0.720 ± 0.020 mM concentration was prepared by diluting 1 mL of 1.44 ± 0.040 mM dyebath solution (before and after dyeing) with 1 mL acetone. All the UV-absorption spectra were

collected using 50 μ M solution of the compounds (except otherwise noted) by diluting stock solution with DI water in a 3 mL cuvette.

Percent dye exhaustion ($E\%$) was determined by measuring the absorbance values (at wavelength of maximum absorbance, λ_{max}) according to equation (1). (Section 10.2)

10.6. Colorfastness evaluation

Once the optimization condition was determined, wool fabrics of different dimensions were dyed separately with the four dye candidates **22**, **23**, **24**, and **25**. The size of fabrics were determined according to the intended test methods for evaluating color fastness properties of the dye candidates. For rub fastness, wool fabrics of 5 cm $\times$ 14 cm were cut separately for dry and wet tests. Fabric size of 4 cm $\times$ 10 cm was taken for determining wash fastness and 1.5cm $\times$ 4.5 cm dimension for determining light fastness. All these fabrics were dyed according to the dyeing method explained above.

Dyebath preparation for 5 cm $\times$ 14 cm fabric: Three wool fabrics each weighing 2.00 ± 0.35 g were taken. For dyeing, a common dye bath solution was prepared by dissolving 60 ± 10 mg of aurones in 30 ± 5 mL of deep eutectic solvent in a 250 mL Erlenmeyer flask. The solution was stirred for about 60 minutes at 70°C. 120 ± 20 mL of DI water was added to the flask and the diluted solution was stirred for a further 15 minutes at the same temperature. Now, 40 ± 5 mL of prepared dyebath solution (1:20 MLR) was transferred into three different 125 mL Erlenmeyer flasks and fabrics were added to them individually. The fabrics were then stirred for 1 h at 70°C.

Dyebath preparation for 4 cm $\times$ 10 cm fabric: Three wool fabrics each weighing 1.20 ± 0.20 g were taken. For dyeing, a common dye bath solution was prepared by dissolving 36 ± 5 mg of aurones in 18 ± 2.5 mL of deep eutectic solvent in a 125mL

Erlenmeyer flask. The solution was stirred for about 60 minutes at 70°C. 72 ± 10 mL of DI water was added to the flask and the diluted solution was stirred for a further 15 minutes at the same temperature. Now, 24 ± 3 mL of prepared dyebath solution (1:20 MLR) was transferred into three different 50 mL Erlenmeyer flasks and fabrics were added to them individually. The fabrics were then stirred for 1 h at 70°C.

Dyebath preparation for 1.5cm × 4.5 cm fabric: Three wool fabrics each weighing 0.25 ± 0.02 g were taken. For dyeing, a common dye bath solution was prepared by dissolving 7.5 ± 0.6 mg of aurones in 3.7 ± 0.3 mL of deep eutectic solvent in a 25 mL round bottomed flask. The solution was stirred for about 60 minutes at 70°C. 15 ± 1 mL of DI water was added to the flask and the diluted solution was stirred for a further 15 minutes at the same temperature. Now, 5 ± 0.4 mL of prepared dyebath solution (1:20 MLR) was transferred into three different 6-dram vials and fabrics were added to them individually. The fabrics were then stirred for 1 h at 70°C.

UV-Vis absorption (Sample preparation): Stock solution of 0.68 ± 0.04 mM concentration was prepared by diluting 1 mL of 1.37 ± 0.1 mM dyebath solution (before and after dyeing) with 1 mL acetone. All the UV-absorption spectra were collected using 50 μ M solution of the compounds (except otherwise noted) by diluting stock solution with DI water in a 3 mL cuvette.

Procedures for evaluating color fastness: All the tests were performed in three trials and grey-scale numbers were averaged. The AATCC 8 test method was used for the rub test.

Dry rub: The test sample was rubbed with a dry rubbing cloth (cotton fiber) using a crockmeter for 10 turns with a force of 9 N. The rubbing cloth was assessed for color

transfer and the rubbing cloth was graded using grey-scale method. The rubbed sample was spectroanalyzed.

Wet rub: A separate test sample was rubbed with a wet rubbing cloth (cotton fiber) in the same manner as for dry rubbing and the rubbing cloth was graded by grey-scale method. The rubbed sample was spectroanalyzed.

Color fastness to washing: ISO 105 C06 AS2 test method was used for wash test. The test sample was subjected to agitation in water at 50°C with a peroxide-based bleach for 40 minutes. The sample was then rinsed and air dried and spectroanalyzed.

Color fastness to light: AATCC 16 test method was employed for light exposure test. The test sample was subjected to irradiation using a xenon arc lamp for 10 hours and then the color change in the tested fabric was evaluated by grey-scale method and then spectroanalyzed.

Spectroanalysis: The reflectance spectrum of the dyed fabric was recorded from 400-700 nm using a Variable SpectroPro, both before and after the testing procedure (with 12 hours allowed for drying in the case of color fastness to washing and wet rub). The data was transferred to excel for plotting and averaging.

10.7. Synthesis of benzofuranones

Monomethoxy-substituted benzofuranone:¹⁹⁴ 1.0 mmol of hydroxy substituted benzofuranone was dissolved in 1mL of acetone. To this, added 1.5 equiv. of K₂CO₃ and 2.0 equiv. of methyl iodide. The reaction was stirred for 4 h at 35°C. After the reaction mixture was cooled, acetone was removed using *in vacuo*. DI water was added to the reaction mixture and the organic layer was extracted with ethyl acetate. It was dried over anhydrous magnesium sulfate and solvent was removed *in vacuo*. The

compound was purified by flash chromatography (10% ethyl acetate: hexane). A yellow solid was obtained as the final product (66%).

Synthesis of 4,6-dihydroxybenzofuranone:¹⁹¹ In a 50 mL RB flask, 5 mmol of phloroglucinol was dissolved in 20 mL of anhydrous ether and 1.6 equiv. of chloroacetonitrile was added. The mixture was placed on an ice-bath. Then, 0.75 equiv. of anhydrous ZnCl_2 was added. Dry HCl gas was passed through the reaction mixture for 2 h, maintaining the temperature of the reaction mixture at 0°C. The reaction was left in the refrigerator overnight. The next day, dry HCl gas was passed through the reaction at 0 °C for 2 h. A yellow precipitate was obtained, which was washed with ether 4-5 times. The precipitate was dissolved in 20 mL of 1N HCl and the solution was refluxed at 100°C for about 1 h. The solution was cooled gradually, first to room temperature, and then in an ice-bath. After a while, a brownish white precipitate formed, which was filtered through a Hirsh funnel, washed with DI water several times, and then dried. (Yield 55%)

The precipitate was dissolved in methanol (1 mmol= 5 mL), and 3.6 equiv. of sodium methoxide was added to it. The reaction mixture was refluxed for 2 h. The methanol was removed in *vacuo* and the mixture was acidified with 1N HCl. Water was added and the organic layer was extracted with ethyl acetate, washed with water and brine solution, dried over anhydrous magnesium sulfate, and the solvent was removed in *vacuo*. 60% of brown colored pure product was obtained.

Synthesis of 6,7-dihydroxybenzofuranone:¹⁹² 5 mmol of pyrogallol was added to a 6-dram vial and 1.2 equiv. of chloroacetic acid was added. To the same vial, 4 equiv. of boron trifluoride etherate and 2.5 equiv. of phosphorus oxychloride were added. The reaction mixture was heated for 5 h at 50 °C. After 5 h, the reaction mixture was cooled

down to room temperature, and then was placed on an ice-bath. 4 mL of ice-cooled DI water was slowly added dropwise to the reaction mixture. The reaction mixture was left overnight maintaining at 0 °C. The solid product was filtered, washed with water, and then dried. 39% of the black solid was obtained.

The precipitate was dissolved in ethanol (1 mmol= 5 mL), and 3.0 equiv. of sodium acetate was added. The reaction mixture was heated to reflux for 6h. The ethanol was evaporated *in vacuo*. An equal volume of DI water was added to the reaction mixture, extracted with ethyl acetate, washed with water and brine solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. 79% of a brown colored pure product was obtained.

Synthesis of dimethoxy substituted benzofuranone:¹⁹⁴ 1.0 mmol of dihydroxy substituted benzofuranone was dissolved in 4mL of DMF. To this, was added 2 equiv. of K₂CO₃ and 3 equiv. of methyl iodide. The reaction was stirred for 2 h at 80 °C. After the reaction mixture was cooled, DI water was added, and the product was extracted with ethyl acetate. The extracted layer was washed with water several, and then dried over anhydrous magnesium sulfate, and solvent was removed *in vacuo*. The compound was purified by flash chromatography (20%-50% ethyl acetate: hexane). 43% of yellow solid was obtained as the final product.

10.8. Synthesis of aurones

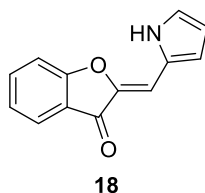
Method 1:⁴⁹ Benzofuranone (0.5 mmol) and aldehyde (0.5 mmol) were dissolved in 1 mL of the deep eutectic solvent formed from a 1:2 molar ratio of choline chloride and urea. The reaction mixture was stirred at 80 °C for 12 h. After cooling to room temperature, it was washed with DI H₂O and extracted with ethyl acetate. The organic

layer was dried over anhydrous MgSO_4 and concentrated *in vacuo* to give the desired aurone. The crude solid was purified by flash column chromatography using 10% ethyl acetate in hexane eluent. Compound 30 was synthesized utilizing this method.

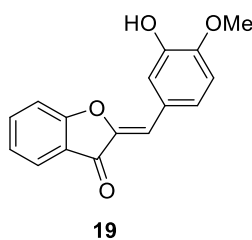
Method 2:⁴¹ 0.57 mmol of benzofuranone was dissolved in 5 mL of glacial acetic acid. To this solution, 0.68 mmol (1.2 equiv.) of aldehyde and 3 drops of concentrated HCl were added. The reaction was stirred at RT for 5 h. After that, the reaction mixture was poured into ice-cooled water. The precipitated products were obtained via filtration and washed with water several times and air dried. Further purification was performed as noted.

Method 3:⁴⁶ In a 3-dram vial, 0.5 mmol of disubstituted benzofuranone was dissolved in 2.5 mL of methanol and 1.4 equiv. of aldehyde was added to it. In a separate vial 0.375 g of KOH and 0.375 g of water were combined. The KOH solution was then added to the reaction vial and this mixture was heated at 65°C for 4h. The reaction mixture was then cooled to room temperature. Once at room temperature, 1N HCl was used to neutralize the KOH solution. The solution was then partitioned between ethyl acetate and water. The ethyl acetate layer was concentrated to dryness *in vacuo* to afford the desired aurone. Further purification was performed as noted.

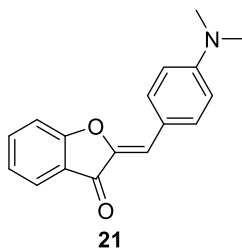
10.9. Characterization data for aurones



(Z)-2-((1H-Pyrrol-2-yl) methylene)benzofuran-3(2H)-one (18)³⁵: (Synthesized using method 3) Yield: 59% (62.2 mg); yellow solid. ¹H NMR (500 MHz, CHLOROFORM-D) δ 8.67 (br, s, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.43 (s, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.04 (s, 1H), 6.89 (dd, J = 4.6, 2.3 Hz, 1H), 6.80 (dd, J = 3.6, 2.2 Hz, 1H).

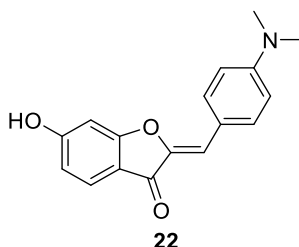


(Z)-2-(3-hydroxy-4-methoxybenzylidene)benzofuran-3(2H)-one(19)³⁵: (Synthesized using method 3) Yield: 46% (61.7 mg); yellow solid. ¹H NMR (500 MHz, CHLOROFORM-D) δ 7.80 (d, J = 7.5 Hz, 1H), 7.69 (s, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.35 (dd, J = 14.8, 8.5 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 5.72 (s, 1H), 3.96 (s, 3H).



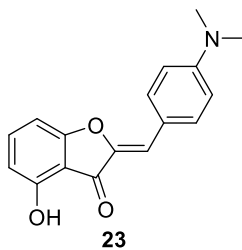
(Z)-2-(4-Dimethylaminobenzylidene)-benzofuran-3(2H)-one (21)²⁰⁵: (Synthesized using method 2) Yield: 63% (95.8 mg); red solid. ¹H NMR (300 MHz, CHLOROFORM-D) δ 7.85 (d, J = 9.1 Hz, 2H), 7.80 (ddd, J = 7.6, 1.4, 0.6 Hz, 1H),

7.61 (ddd, $J = 8.6, 7.3, 1.4$ Hz, 1H), 7.31 (dt, $J = 8.3, 0.7$ Hz, 1H), 7.21 – 7.16 (m, 1H), 6.92 (s, 1H), 6.75 (d, $J = 9.1$ Hz, 2H), 3.07 (s, 6H). ^{13}C NMR (126 MHz, CHLOROFORM- D_3) δ 184.18, 165.42, 151.47, 145.16, 135.95, 133.77, 124.45, 123.01, 122.53, 120.16, 115.43, 112.90, 112.08, 40.05.



***(Z)-2-(4-Dimethylaminobenzylidene)-6-hydroxybenzofuran-3(2H)-one(22)*²⁰⁶:**

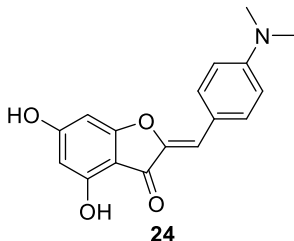
(Synthesized using method 2) Yield: 80% (128.3 mg); orange solid. ^1H NMR (500 MHz, DMSO- D_6) δ 11.04 (s, 1H), 7.80 (d, $J = 8.9$ Hz, 2H), 7.58 (d, $J = 8.5$ Hz, 1H), 6.79 (d, $J = 8.9$ Hz, 2H), 6.77 (d, $J = 1.8$ Hz, 1H), 6.72 (s, 1H), 6.69 (dd, $J = 8.4, 1.9$ Hz, 1H), 3.01 (s, 6H). ^{13}C NMR (126 MHz, DMSO- D_6) δ 180.79, 167.01, 165.72, 151.07, 145.00, 133.01, 125.52, 119.14, 113.60, 112.67, 112.60, 112.01, 98.46.



***(Z)-2-(4-Dimethylaminobenzylidene)-4-hydroxybenzofuran-3(2H)-one(23)*²⁰⁷:**

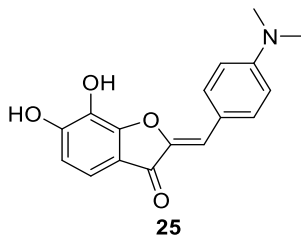
(Synthesized using method 2) Yield: 55% (87.6 mg); dark orange solid. ^1H NMR (500 MHz, DMSO- D_6) δ 10.95 (s, 1H), 7.79 (d, $J = 9.0$ Hz, 2H), 7.48 (t, $J = 8.1$ Hz, 1H),

6.83 (d, $J = 8.0$ Hz, 1H), 6.78 (d, $J = 9.0$ Hz, 2H), 6.70 (s, 1H), 6.60 (d, $J = 8.2$ Hz, 1H), 3.00 (s, 6H). ^{13}C NMR (126 MHz, DMSO- D_6) δ 181.15, 165.90, 157.26, 151.51, 144.66, 138.17, 133.42, 119.73, 112.71, 112.49, 110.55, 110.25, 102.93.



***(Z)-2-(4-Dimethylaminobenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one(24)*²⁰⁸:**

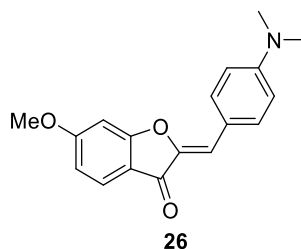
(Synthesized using method 3) Crude product was purified by flash column chromatography using 5% MeOH: DCM. Yield: 46% (47.9 mg); dark brown solid. ^1H NMR (500 MHz, DMSO- D_6) δ 10.80 (s, 2H), 7.73 (d, $J = 8.9$ Hz, 2H), 6.77 (d, $J = 8.9$ Hz, 2H), 6.53 (s, 1H), 6.19 (s, 1H), 6.05 (s, 1H), 2.98 (s, 6H). ^{13}C NMR (126 MHz, DMSO- D_6) δ 179.33, 167.75, 167.16, 158.48, 151.22, 145.78, 132.91, 120.04, 112.50, 110.60, 103.64, 98.02, 90.83.



***(Z)-2-(4-Dimethylaminobenzylidene)-6,7-dihydroxybenzofuran-3(2H)-one(25)*¹⁹⁴:**

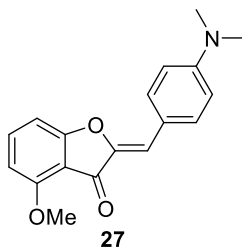
(Synthesized using method 2) Yield: 64% (132.3 mg); dark brown solid. ^1H NMR (500

MHz, DMSO-D6) δ 7.89 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.71 (t, J = 4.0 Hz, 2H), 3.02 (s, 6H). ^{13}C NMR (126 MHz, DMSO-D6) δ 182.08, 155.13, 154.31, 151.54, 145.76, 133.68, 130.57, 119.83, 115.51, 115.43, 113.02, 112.98, 112.46.



(Z)-2-(4-Dimethylaminobenzylidene)-6-methoxybenzofuran-3(2H)-one(26)²⁰⁶:

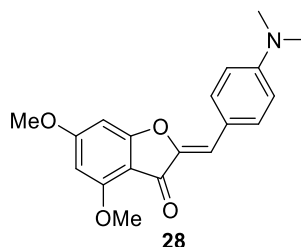
(Synthesized using method 2) Yield: 57% (95.9 mg); yellowish orange solid. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.82 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 8.5 Hz, 1H), 6.84 (s, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.74 (dd, J = 8.6, 1.8 Hz, 3H), 3.92 (s, 3H), 3.06 (s, 6H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 182.72, 167.82, 166.85, 151.28, 146.04, 133.43, 125.60, 120.31, 115.83, 114.07, 112.08, 111.80, 96.64, 56.08, 40.25.



(Z)-2-(4-Dimethylaminobenzylidene)-4-methoxybenzofuran-3(2H)-one(27):

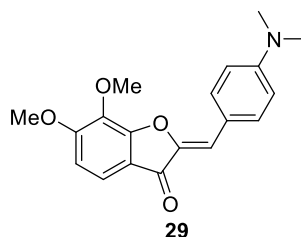
(Synthesized using method 2) Yield: 71% (119.6 mg); bright orange solid. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.79 (dd, J = 7.0, 1.9 Hz, 2H), 7.50 (t, J = 8.2 Hz,

1H), 6.85 (dd, $J = 7.4, 2.0$ Hz, 2H), 6.71 (d, $J = 9.0$ Hz, 2H), 6.56 (d, $J = 8.3$ Hz, 1H), 3.98 (s, 3H), 3.03 (s, 6H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 181.94, 166.37, 158.32, 151.13, 144.95, 137.38, 133.36, 120.14, 114.09, 111.93, 111.59, 104.82, 104.51, 56.24, 40.12.



(Z)-4,6-Dimethoxy-(4'-dimethylaminobenzylidene)benzofuran-3(2H)-one(28)¹⁹²:

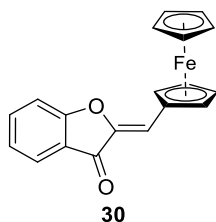
(Synthesized using method 3) Yield: 82% (134.0 mg); yellow solid. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.78 (d, $J = 8.8$ Hz, 2H), 6.78 (s, 1H), 6.72 (d, $J = 8.9$ Hz, 2H), 6.37 (s, 1H), 6.12 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.05 (s, 6H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 180.61, 168.47, 168.30, 159.25, 151.03, 145.92, 133.11, 120.39, 112.85, 112.01, 105.99, 93.77, 89.11, 56.28, 56.15, 40.24.



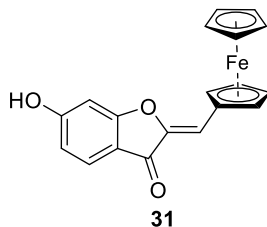
(Z)-2-(4-Dimethylaminobenzylidene)-6,7-methoxybenzofuran-3(2H)-one(29):

(Synthesized using method 2) Yield: 48% (89.1 mg); brown solid. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.83 (d, $J = 9.0$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 1H), 6.87 (s, 1H),

6.79 (d, $J = 8.5$ Hz, 1H), 6.75 (d, $J = 9.0$ Hz, 2H), 4.20 (s, 3H), 3.99 (s, 3H), 3.07 (s, 6H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 182.92, 158.14, 157.00, 151.32, 145.62, 133.95, 133.47, 120.02, 119.33, 117.82, 114.52, 112.10, 107.80, 61.20, 56.86, 40.22.

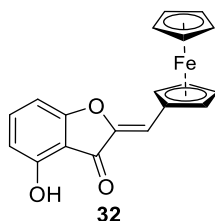


(Z)-2-(Ferrocenylidene)benzofuran-3-one (30)¹⁹⁶: (Synthesized using method 1) Yield: 73% (120.5 mg); purple solid. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.81 (d, $J = 7.5$ Hz, 1H), 7.64 (t, $J = 7.3$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 7.20 (t, $J = 7.4$ Hz, 1H), 6.91 (s, 1H), 4.88 – 4.87 (m, 2H), 4.57 – 4.55 (m, 2H), 4.19 (s, 5H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 183.04, 165.47, 146.07, 136.24, 124.58, 123.18, 122.70, 116.63, 113.06, 75.15, 71.94, 71.60, 70.07.

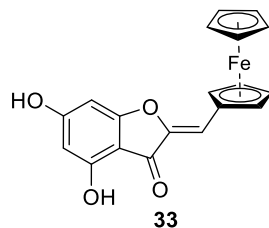


(Z)-2-Ferrocenylidene-6-hydroxy-benzofuran-3-one (31)²⁰⁹: (Synthesized using method 2) Crude Yield: 56% (55 mg); dark purple solid. ^1H NMR (500 MHz, DMSO-

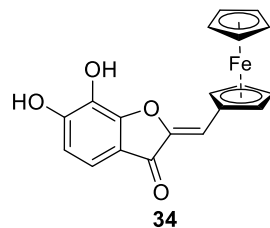
D6) δ 11.08 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.77 (s, 1H), 6.71 (s, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.89 (s, 2H), 4.57 (s, 2H), 4.19 (s, 5H).



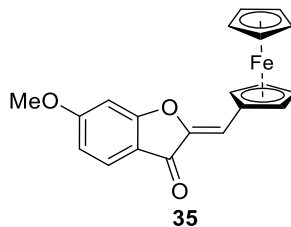
(Z)-2-Ferrocenylidene-4-hydroxy-benzofuran-3-one (32)²⁰⁹: (Synthesized using method 2) Crude Yield: 38% (77.8 mg); dark purple solid. ¹H NMR (301 MHz, DMSO-D6) δ 11.01 (s, 1H), 7.51 (s, 1H), 6.84 (s, 1H), 6.68 (s, 1H), 6.60 (s, 1H), 4.88 (s, 2H), 4.57 (s, 2H), 4.19 (s, 5H).



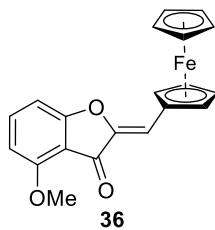
(Z)-4,6-Dihydroxy-2-ferrocenylidene-benzofuran-3-one (33)²⁰⁹: (Synthesized using method 3) Crude yield: 60% (108.2 mg); dark purple solid. ¹H NMR (300 MHz, ACETONE-D6) δ 6.61 (s, 1H), 6.35 (d, J = 1.7 Hz, 1H), 6.14 (d, J = 1.7 Hz, 1H), 4.88 (t, J = 1.8 Hz, 2H), 4.56 – 4.52 (m, 2H), 4.21 (s, 5H).



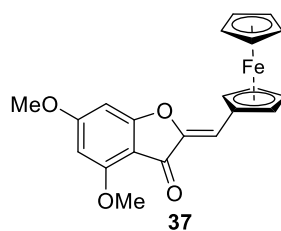
***(Z)*-6,7-Dihydroxy-2-ferrocenylidene-benzofuran-3-one (34):** (Synthesized using method 3) Crude yield: 26% (47.8 mg); purple solid. ^1H NMR (300 MHz, DMSO- D_6) δ 10.53 (s, 1H), 9.54 (s, 1H), 7.12 (s, 1H), 6.70 (s, 2H), 5.01 (s, 2H), 4.58 (s, 2H), 4.18 (s, 5H).



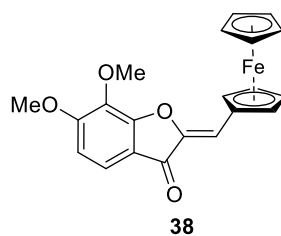
***(Z)*-2-Ferrocenylidene-6-methoxy-benzofuran-3-one (35)¹⁸⁹:** (Synthesized using method 2) Yield: 52% (110.7 mg); brownish purple solid. ^1H NMR (500 MHz, CHLOROFORM- D) δ 7.72 (s, 1H), 6.80 (s, 1H), 6.75 (s, 2H), 4.85 (s, 2H), 4.53 (s, 2H), 4.19 (s, 5H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, CHLOROFORM- D) δ 181.62, 167.81, 166.95, 146.95, 125.65, 115.82, 115.02, 112.03, 96.62, 75.28, 71.60, 71.34, 69.96, 69.74, 56.14.



***(Z)*-2-Ferrocenylidene-4-methoxy-benzofuran-3-one (36)²⁰⁹:** (Synthesized using method 2) Crude yield: 16% (34.7 mg); purple solid. ¹H NMR (500 MHz, CHLOROFORM-D) δ 7.55 (td, J = 8.2, 5.4 Hz, 1H), 6.88 – 6.79 (m, 2H), 6.59 (dd, J = 8.3, 5.0 Hz, 1H), 4.83 (s, 2H), 4.51 (s, 2H), 4.17 (s, 5H), 3.99 (s, 3H).



***(Z)*-4,6-Dimethoxy-2-ferrocenylidene-benzofuran-3-one (37)¹⁸⁹:** (Synthesized using method 2) Crude yield: 69% (154.2 mg); dark brown solid. ¹H NMR (300 MHz, CHLOROFORM-D) δ 6.73 (s, 1H), 6.36 (s, 1H), 6.12 (s, 1H), 4.81 (s, 2H), 4.49 (s, 2H), 4.17 (s, 5H), 3.95 (s, 3H), 3.91 (s, 3H).



(Z)-6,7-Dimethoxy-2-ferrocenylidene-benzofuran-3-one (38): (Synthesized using method 2) Crude yield: 30% (66.9 mg); dark purple solid. ¹H NMR (300 MHz, CHLOROFORM-D) δ 7.52 (d, J = 8.7 Hz, 1H), 6.84 (s, 1H), 6.79 (d, J = 8.3 Hz, 1H), 4.84 (s, 2H), 4.54 (s, 2H), 4.20 (s, 3H), 4.18 (s, 5H), 3.99 (s, 3H).

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CHAPTER III

DEVELOPMENT OF A VISIBLE LIGHT-MEDIATED POLYENE CYCLIZATION METHODOLOGY

1. Background

Polyenes are poly-unsaturated organic compounds possessing multiple carbon-carbon double bonds.¹ Their derivatives are everywhere in living organisms, including bacteria, archaea, plants, animals, and humans.²⁻⁸ They contribute to reinforcing cell membranes, showing adequate light-harvesting capacity, imparting different colors to flowers and fruits, and serving as fluorescent probes for studying lipid-lipid and lipid-protein interaction.⁹⁻¹¹ Structurally, they contain several alkenes within a molecule and various functionalities attached to either end. Unlike alkenes, which absorb light in the ultraviolet region, polyenes absorb longer wavelengths depending on how double bonds in the molecular framework are arranged.

Based on the arrangements of double bonds in the molecules, polyenes can be broadly categorized into conjugated and non-conjugated polyenes. Conjugated polyenes possess more than three carbon-carbon double bonds separated by single bonds, leading to an alternating single and double bond pattern. This structural feature allows pi-pi interaction among the double bonds through conjugation- the upshot being a significant lowering of the energy needed for absorption, causing them to absorb in the visible region of the electromagnetic spectrum.¹² Conjugated polyenes can be isoprenoids or non-isoprenoids, depending on their biosynthetic precursors. Isoprenoids

are biosynthetically built from their biological isoprene precursors- isopentyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP),¹³ where isoprene structurally represents a 3-methyl-1,3-butadiene. (Figure 42)

Isoprenoids, or terpenoids, are the largest group of more than 55,000 natural products identified in bacteria, archaea, and eukaryotes.^{14,15} They are commonly synthesized through the classical mevalonate pathway where the precursors, IPP and DMAPP preferably undergo successive head-to-tail addition generating higher terpenoid precursors including geranyl pyrophosphate (GPP, C₁₀), farnesyl pyrophosphate (FPP, C₁₅). However, squalene (C₃₀) is formed from two FPP units connected tail-to-tail.¹⁶ (Figure 42)

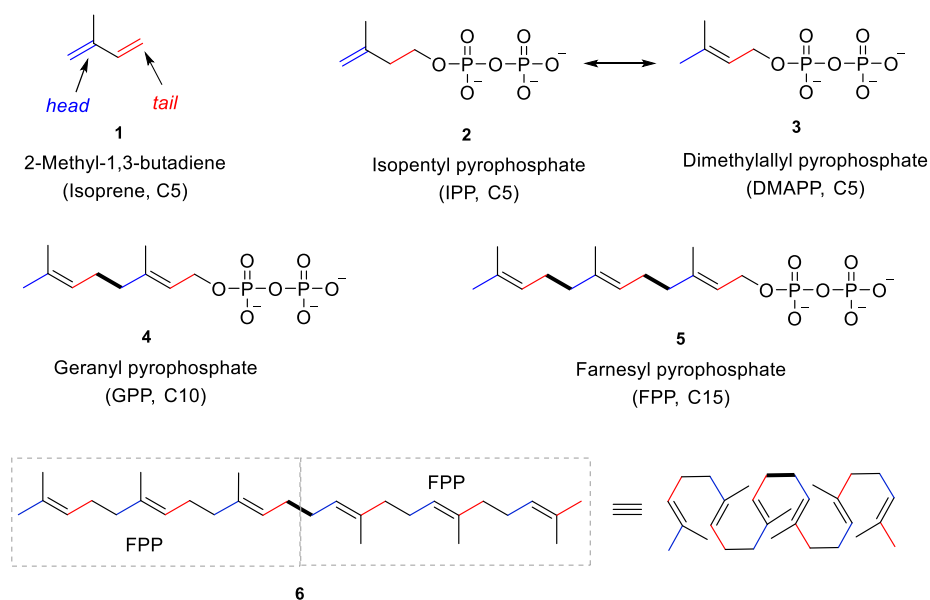


Figure 42: Terpenoids and their building blocks

There are conjugated polyenals and polyolefinic fatty acids identified as non-isoprenoids.¹² Unlike isoprenoids, polyenals (n= 6-14) and polyolefinic fatty acids (n= 6-10) are linear unsaturated polyenes terminated by aldehyde and carboxyl functionality.¹⁷⁻²⁰ Psittacofulvin, a pigmentation molecule found in parrot feathers is a typical example of polyenals. (Figure 43)

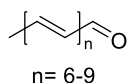


Figure 43: Generic skeleton of Psittacofulvin

Among the common isoprenoids, including retinol (vitamin A), vitamin B, dolichols, and squalene, carotenoids are the most abundant natural products with a polyene framework. Among carotenoids, carotene **7** and lycopene are the common ones found in carrots and tomatoes, respectively, constituting extended conjugation leading to UV-Vis and even NIR (near infra-red) absorption.²¹ Unlike plants and bacteria, which can produce their own carotenoids, the human body must rely on plant sources where it converts carotene into vitamin A (**8, 9**) (Figure 44).²²

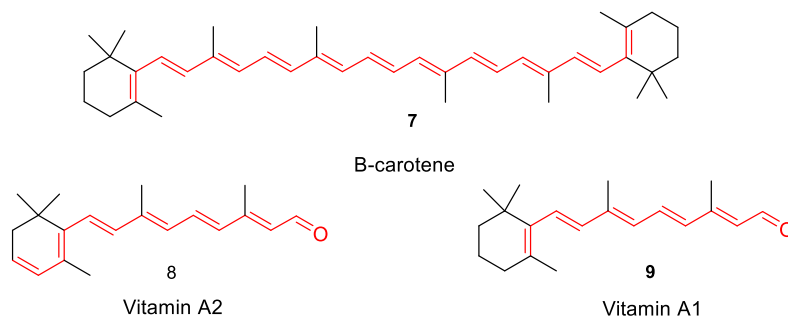
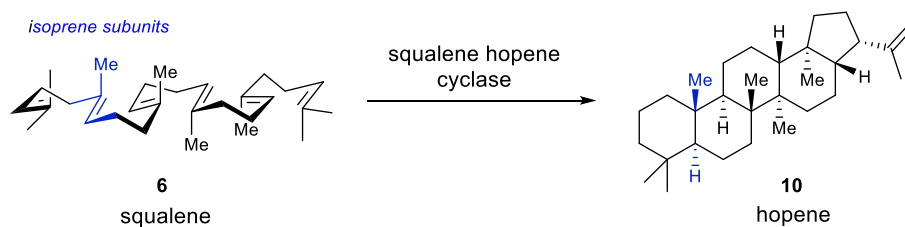


Figure 44: Structures of conjugated isoprenoids (β -carotene and vitamin A)

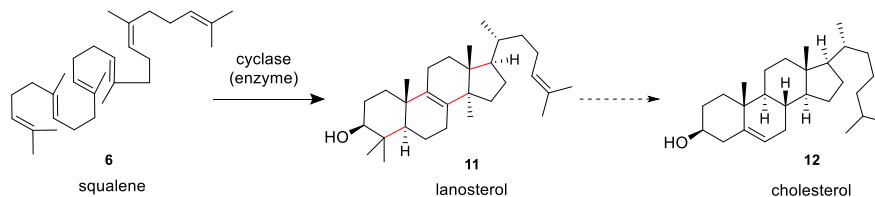
Nature's compelling way of building structurally formidable molecular frameworks has always fascinated and inspired chemists to make strides in developing efficient reaction methodologies. Among the myriad of chemical transformations nature utilizes, cascade polyene cyclization, also referred as terpene cyclization, is one of the most potent reactions enabling complex biomolecule construction from simple acyclic polyene precursors.²³ Polyenes are the biosynthetic precursors of many natural products, typically terpenes, ranging in complexity from menthol to highly complex steroids such as lanosterol and cholesterol. For this, nature utilizes enzyme-catalyzed controlled cyclizations to build up these extraordinarily diverse polycyclic terpenoid structures from linear polyene substrates, such as geranyl pyrophosphate, farnesyl pyrophosphate, and squalene²⁴⁻²⁶. The synthesis of hopene **10** from squalene **6** is one of the prominent examples of such enzyme-catalyzed cyclizations.²⁷ (Scheme 16)



Scheme 16: Enzymatic polyene cyclization of squalene to hopene

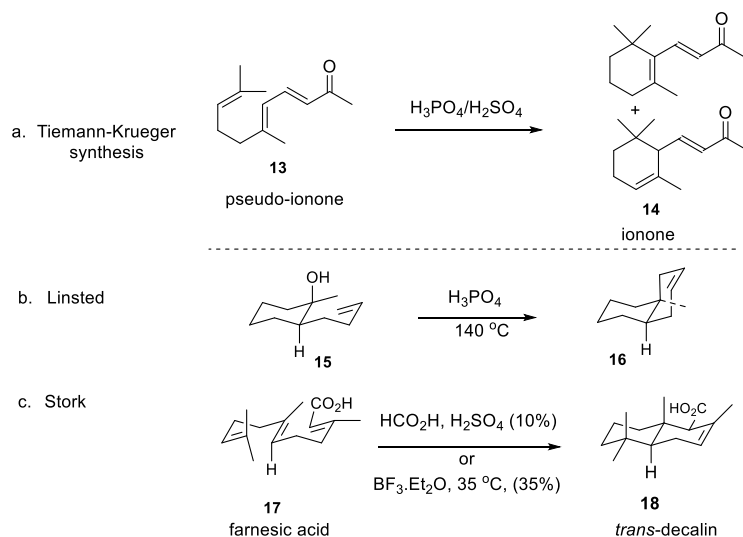
Before 1934, when Robinson proposed squalene as a precursor of cholesterol, fatty acids (e.g., arachidonic acid) were believed to be more viable precursors.²⁸ In 1945, Blotch and Rittenberg, through an isotope labelling experiment, discovered that both squalene and cholesterol derive from acetic acid, supporting their assumption that squalene might be the actual precursor.²⁹ The discovery and structural determination of lanosterol in 1952 established the structural connection among squalene, lanosterol, and

cholesterol, inspiring Bloch and Woodward to further investigate the conversion of squalene to cholesterol by studying the carbon framework arrangement, employing ^{14}C labeled acetate.^{30,31} The result suggested that rearrangement and cyclization of squalene **6** leads to lanosterol **11** first, which, then undergoes structural modification to cholesterol **12**. (Scheme 17)



Scheme 17: Cyclization of squalene and its relation to cholesterol

The substantial contribution from scientific communities in investigating this hypothesis can be traced back to the Tiemann-Krueger synthesis of ionone from pseudo-ionone **13**.^{32,33} (Scheme 18a) Later, Stork extended the synthetic outcome of Linstead's findings (Scheme 18b) to understanding the stereoselectivity of the acid-promoted cyclization through his seminal work on decalin synthesis from farnesic acid **17**.^{28,34,35} (Scheme 18c) However, these early attempts suffered from poor yield and low product selectivity.



Scheme 18: Early studies in polyene cyclization

Despite all the achievements in understanding the fundamentals of polyene cyclization, its applicability was mostly confined to the domain of enzymatic transformation until Johnson (1968) and van Tamelen (1975) demonstrated the profound relevance of polyene cyclization in the total synthesis of natural products.^{36,37} Since then, synthetic chemists have been able to successfully mimic such a robust cascade cyclization in synthesizing various natural products and their analogs (Figure 45),³⁸⁻⁴² tremendously reducing the number of reaction steps and reaction waste.

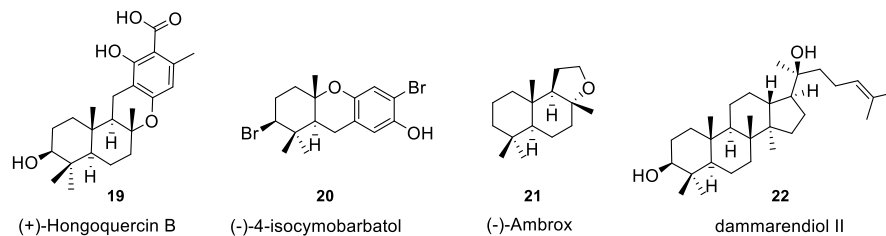
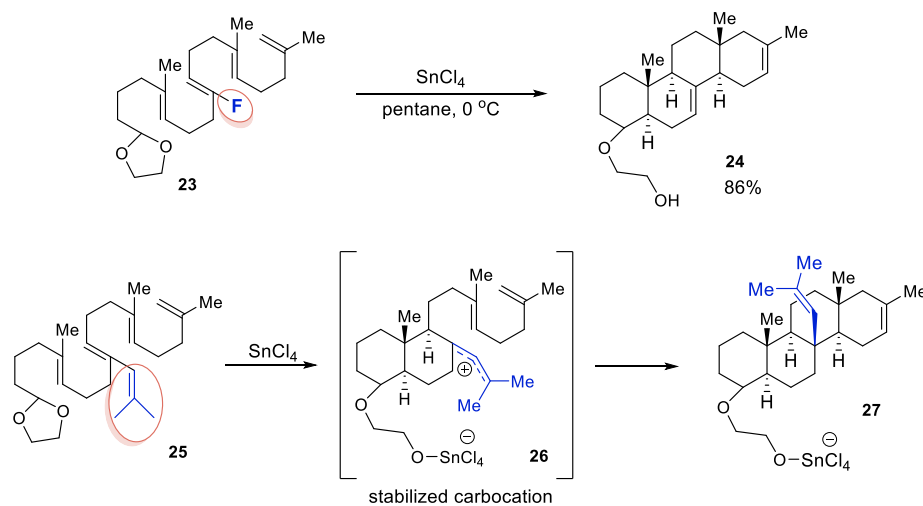


Figure 45: Natural products synthesized via polyene cyclization

In nature, highly stereo-controlled polyene cyclizations are catalyzed by specific cyclase enzymes that facilitate the generation of a cationic intermediate by an asymmetric protonation of a C-C double bond. This intermediate is further stabilized during the cyclization process through hydrogen or alkyl group rearrangement, and finally, the biosynthetically formed intermediate is quenched to give the cyclized product. During the overall process, the carbocation formation step is crucial as it dictates the stereoselectivity of the product.⁴³

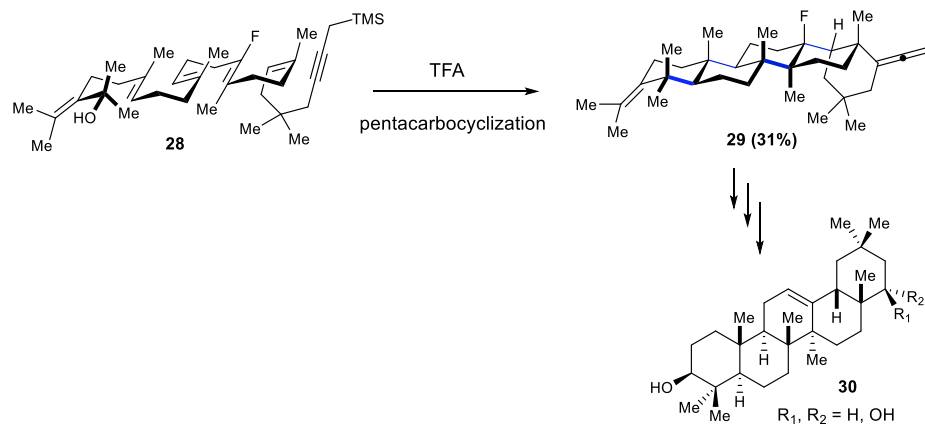
Early polyene cyclization strategies primarily relied upon activating the C-C double bond through protonation or Lewis-acid coordination. These strategies were mostly successful in forming two to three rings from olefinic substrates. But both strategies, unlike the enzymatic process, exhibited suboptimal selectivity. Attempts to synthesize more than four rings suffered miserably in yield and stereoselectivity due to incomplete cyclization and competing side reactions.⁴⁴ Amidst unsuccessful attempts for the high-yield and stereoselective synthesis of tetracyclic products, Johnson, in 1986, introduced a new approach in biomimetic polyene cyclization- Cation-Stabilizing (C-S) Auxiliaries.⁴⁵ He demonstrated that cation-stabilizing auxiliaries, including isobutenyl and fluorine groups, when introduced to a substrate as a double bond

modifier, enhance the propagation of the cyclization process by stabilizing the adjacent carbonium ion, thereby improving the yield and stereoselectivity (Scheme 19)



Scheme 19: Cation-stabilizing auxiliaries; a. fluorine b. isobutenyl group

In 1997, he reported the first non-enzymatic one-step biomimetic pentacyclization of a polyene utilizing fluorine as a cation-stabilizing agent. This formidable transformation was achieved in 31% yield by treatment with trifluoroacetic acid (TFA).⁴⁶ (Scheme 20)

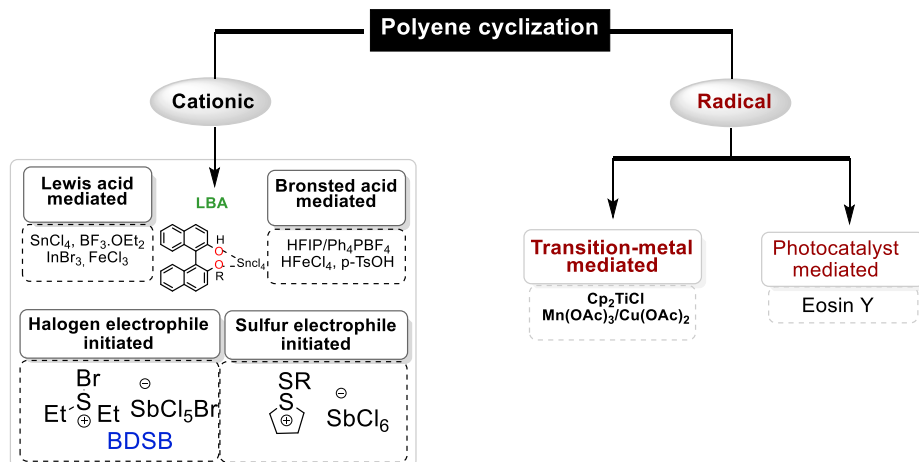


Scheme 20: Pentacarbocyclization by Johnson

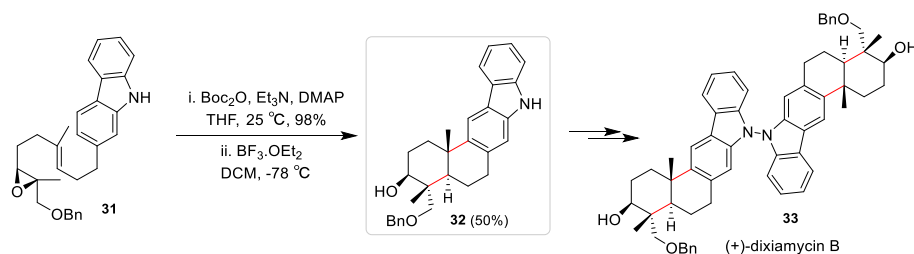
His contribution in developing new initiators (acetal sulfonate esters and allylic alcohols), terminators (alkynes and allyl silanes) and cation-stabilizing auxiliaries (notably fluorine) for cationic mediated polyene cyclization,⁴⁷ broadened the application and robustness of polyene cyclization in natural product synthesis.

2. Classification of polyene cyclizations

Polyene cyclization strategies are commonly mediated by Lewis/Bronsted acids, halogen and sulfur electrophiles, transition metal complexes, and organocatalysts.⁴⁸⁻⁶⁰ Mechanistically, they all can be broadly divided into cationic and radical pathways, which can be further categorized into subtypes. (Figure 46)

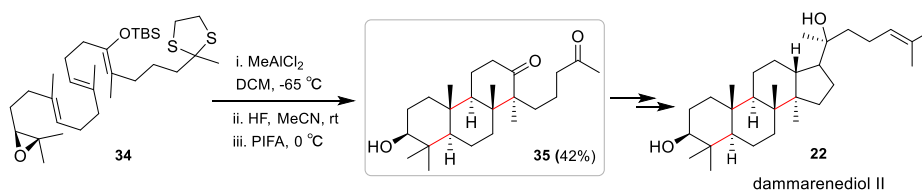


into decalin carboxylic acid **18**.³⁵ (Scheme 18c) Based on this precedent, the Baran group successfully utilized $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to activate the epoxide moiety of N-Boc protected precursor **31**, leading to a pentacyclic intermediate **32** during the synthesis of the natural product (+)-dixiamycin B (**33**).^{23, 61} (Scheme 21)



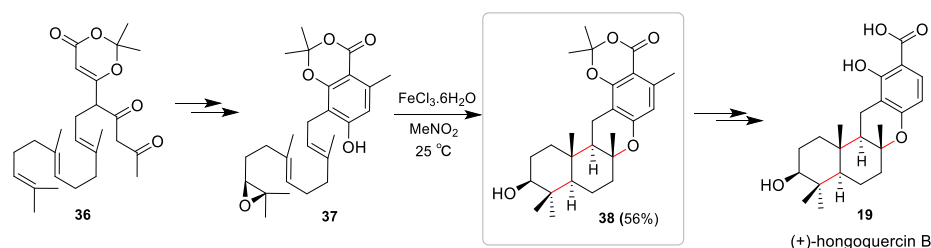
Scheme 21: Synthesis of (+)-dixiamycin B

Other common Lewis acids employed in the literature include, InBr_3 , FeCl_3 , Et_2AlCl , SnCl_4 , and BBr_3 .^{38,39,48,62-65} Corey, in 1996, in his first total synthesis of dammarenediol **22**, utilized a polyene cascade cyclization to construct a tricyclic intermediate.⁴² The cyclization was mediated by methyl-aluminum chloride (MeAlCl_2), which on further de-silylation and thioketal hydrolysis, formed a tricyclic intermediate **35** of dammarenediol II (**22**). (Scheme 22)



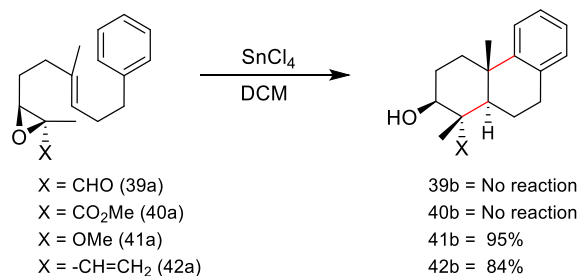
Scheme 22: Corey's epoxide-initiated synthesis of dammarenediol II

Similarly, iron (III) chloride (FeCl_3) was employed by Seigel and co-workers (2015) in their 31-step total synthesis of celastrol to construct the pentacyclic core.⁶² Employing SnCl_4 , the yield of the intermediate was only 15%. The utility of FeCl_3 in polyolefin cyclization was further demonstrated by the Barrett group in a dual biomimetic strategy for the synthesis of (+)-hongoquercin B (**19**). In the presence of iron (III) chloride hexahydrate, resorcyate intermediate **37** provided the pentacyclic precursor **38** of (+)-hongoquercin B in 56% yield and 92% ee.^{23,38,39} (Scheme 23)



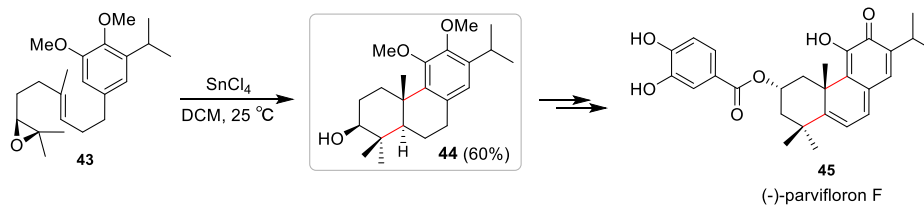
Scheme 23: Barrett biomimetic synthesis of (+)-hongoquercin B using FeCl_3

Another commonly employed Lewis acid is SnCl_4 , which was used by Johnson in as early as 1986 when he introduced the concept of Cation-Stabilizing (C-S) auxiliaries which allowed the construction of long-awaited tetracyclic ring systems.⁴⁵ More recently, Corey, in his systematic study of the cyclization of functionalized unsaturated oxirane substrates, found that the initiator role of SnCl_4 was significantly affected by the types of functional groups in the molecule. The presence of electron-withdrawing groups such as aldehyde **39a** did not lead to cyclization, whereas electron-releasing groups such as methoxy **41a** and vinyl group **42a** in the presence of SnCl_4 resulted in tricyclic compounds.⁶⁴ (Scheme 24)



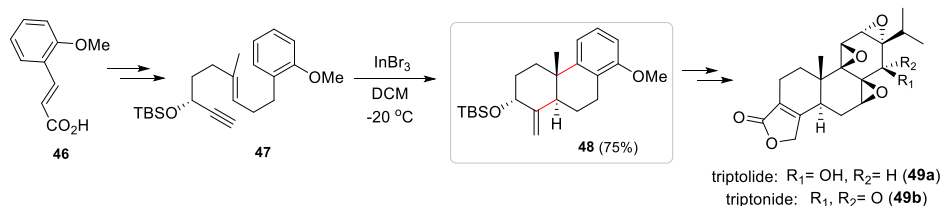
Scheme 24: SnCl_4 catalyzed polyene cyclization

In another study, SnCl_4 was employed as an initiator in the synthesis of (-)-parvifloron F (**45**), a valuable diterpene with promising biological activities. In his total synthesis of (-)-parvifloron F, Nakagawa-Goto accessed the tricyclic core **44** from the epoxide containing precursor **43** in a single-step.^{23,66} (Scheme 25)



Scheme 25: SnCl_4 mediated synthesis of (-)-parvifloron F

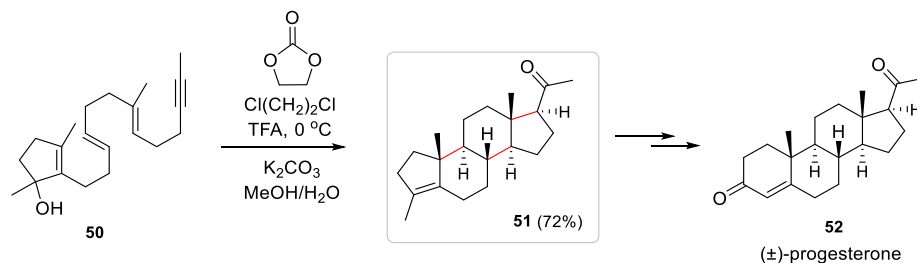
Corey's contribution in developing new initiators and methodology is invaluable. His original indium bromide (InBr_3) mediated cyclization was extended to synthesize triptolide and related analogs.⁴⁹ (Scheme 26)



Scheme 26: InBr_3 initiated synthesis of triptolide and triptonide

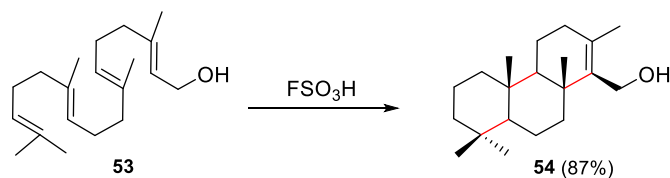
2.1.2. Bronsted acid mediated polyene cyclization

Various Bronsted acids have been studied and employed in developing polyene cyclization methodologies. Common ones include H_3PO_4 , CF_3COOH , $\text{H}_2\text{O}/\text{HFIP}$, $\text{HFIP}/\text{Ph}_4\text{PBF}_4$, and HFeCl_4 .^{50,51,67-69} Linstead used the Bronsted acid, H_3PO_4 , for cyclohexannulation of a tertiary alcohol, leading to a stereoselective formation of cis-decalin in 89% yield.⁶⁷ (Scheme 18b) Similarly, Schinz utilized a mixture of sulfuric acid and formic acid as an initiator for similar purposes.⁷⁰ Johnson, a pioneer in the field of biomimetic synthesis of natural products, used trifluoroacetic acid (TFA) to promote the cascade cyclization of a polyene precursor **50** activated by an allylic alcohol moiety to form a pentacyclic intermediate **51**, that was further transformed into progesterone.⁶⁸ (Scheme 27)



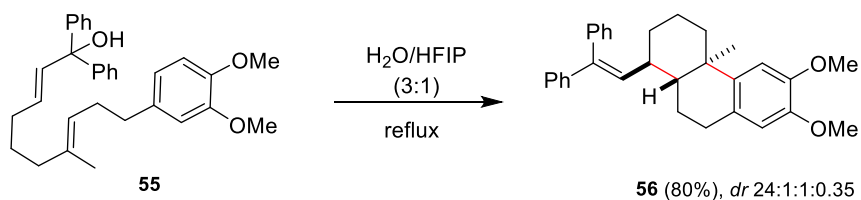
Scheme 27: Johnson's synthesis of progesterone

Similarly, in the 1970s, superacids, typically fluorosulfonic acid, were explored as cyclization promoters. Since this acid is a much stronger acid compared to common mineral acids, it allowed the reactions to be performed at temperatures as low as -78 °C. At such a low temperature, polyene conformational mobility is highly restricted, controlling the selectivity of the outcome.^{71,72} (Scheme 28)



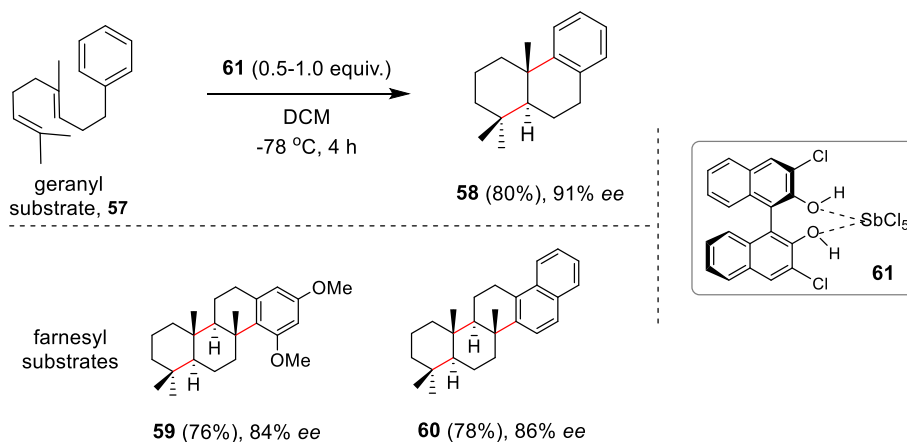
Scheme 28: Super-acid promoted polyene cyclization

At the other extreme, a weak Bronsted acid ($\text{pK}_a = 9.03$) 1,1,1,3,3,3-hexafluoropropan-2-ol, commonly known as HFIP, either in combination with hot water or alone was used as a mildly acidic catalyst promoting cascade polyene cyclization. In a series of experiments, the Qu group utilized HFIP/water (3:1) or neat HFIP alone as a reaction medium in achieving diastereoselective cyclizations of polyene substrates containing allylic alcohols.⁵⁰ This method was further expanded to epoxide-containing analogs using a HFIP/ Ph_4PBF_4 system.⁵¹



Scheme 29: Cyclization promoted by HFIP/hot water

Another strategy was developed by Yamamoto in the late 90s, called the Lewis acid - assisted chiral Bronsted acid (LBA) method, utilizing a Lewis acid SnCl_4 with a BINOL-derived Bronsted acid as a polyene cyclization initiator.⁴¹ This strategy exploits the enhanced acidity of the proton of the chiral Bronsted acid (BINOL-derived) in association with the Lewis acid to achieve high stereoselectivity. A similar strategy was later explored by the Corey group utilizing a sterically demanding Lewis-acid SbCl_5 in combination with an electron-deficient BINOL derivative, which expanded the generality of this method to geranyl- and farnesyl-derived substrates with phenyl terminating groups affording the products in 76–82% yield and 84–90% ee.⁷³ (Scheme 30)



Scheme 30: Enantioselective proton-initiated cyclization

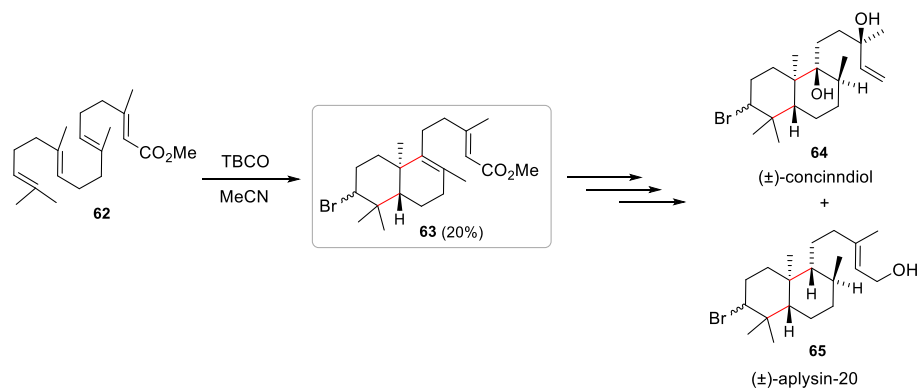
Later in 2018, Zhao and co-workers further improvised the LBA strategy by developing a chiral Bronsted acid N-phosphoramidate from BINOL, that was utilized in an enantioselective cyclization in the synthesis of (-)-ferruginol.⁷⁴

2.1.3. Halogen and Sulfur electrophile-initiated polyene cyclization

The seminal studies and observations by Van Tamelen (1966), Nasipuri (1975) and Faulkner (1975) provided a promising possibility to achieve the biomimetic synthesis of halogenated polycyclic natural products through halogen electrophiles, particularly a bromine-initiated mechanism.⁷⁵⁻⁷⁷ Only a few NBS-mediated polyene cyclization strategies have been successfully used in the total synthesis of natural products, including snyderol from methyl farnesate and luzofuran.^{78,79} Although the use of standard reagents N-bromosuccinamide (NBS) or Br₂ was only partially successful, the results of these findings led to the development of more efficient halonium-generating reagents in the last two decades.

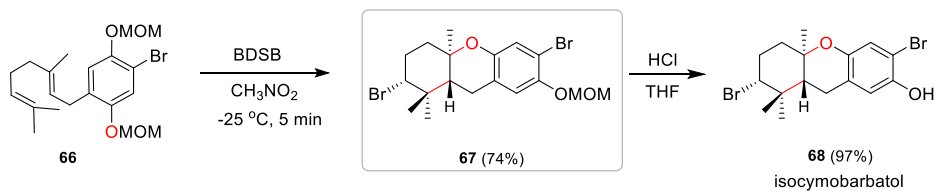
Some of them include 2,4,4,6-tetrabromo-2,5-cyclohexadione (TBCO), bis(pyridine)iodonium tetrafluoroborate, bromo(diethyl)sulfonium bromo(penta)chloroantimonate (BDSB) and its chloro variant (CDSC), and trimethylphenylammonium perbromide (TMPAP).^{53,80-85} All these reagents initiate polyene cyclization utilizing halonium, typically bromonium electrophiles, for the carbocyclization.

The Kato group introduced tetrabromocyclohexadione (TBCO) in 1985, which they employed in the key step for the total synthesis of concinndiol **64** and aplysin-20 (**65**) from a common precursor **62** yielding only 20% of the desired brominated bicyclic product **63**.⁸⁶



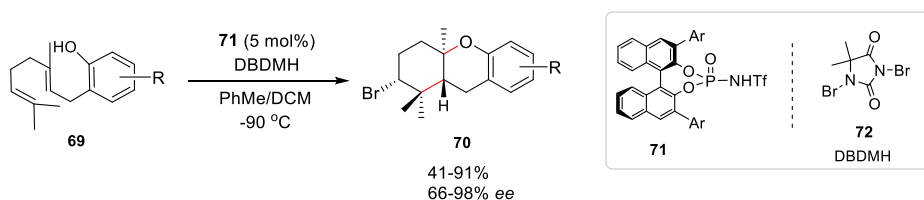
Scheme 31: TBCO mediated bromocyclization employed in the synthesis of aplysin-20 and concinndiol

In this context, the Snyder group in 2009 introduced BDSB as a highly efficient chemoselective reagent for carbocyclization of a range of polyene substrates via a bromonium-mediated pathway. They revealed the superior efficiency of BDSB compared to TBCO while working on the total synthesis of isocymobarbatol **68**, and peyssonol A.^{53,54} (Scheme 32)



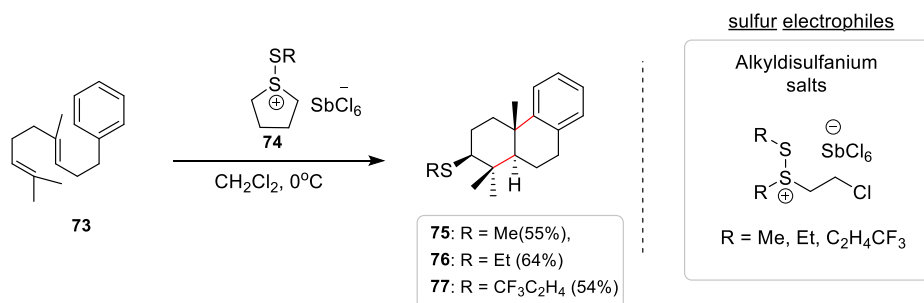
Scheme 32: BDSB mediated bromocyclization involved in the synthesis of isocymobarbatol

A decade after Ishihara's report on the enantioselective halocyclization of simple polyprenoids using a nucleophilic chiral phosphonamidite in the presence of NBS,⁸⁷ Yamamoto, in 2017, reported the first asymmetric bromocyclization of polyenes employing a BINOL-based chiral thiophosphoramidate catalyst **71** in combination with 1,3-dibromo-5,5-dimethylhydantoin **72** (DBDMH).⁸⁸ (Scheme 33)



Scheme 33: DBDMH mediated enantioselective polyene cyclization

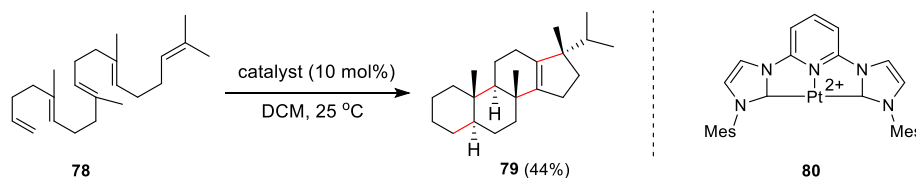
Similarly, the Snyder group introduced alkyldisulfanium salts as sulfur electrophiles for polyene cyclization, as depicted below.^{55,89}(Scheme 34)



Scheme 34: Electrophilic sulfur-promoted polyene cyclization

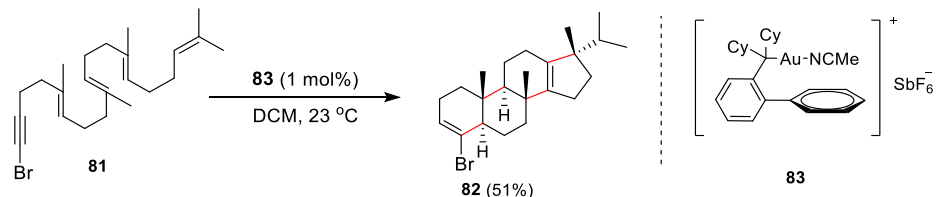
2.1.4. Transition-metal-mediated cationic polyene cyclization

Besides acids and various electrophilic catalysts, transition-metal complexes have also been employed recently for the carbocyclization of polyenes. Platinum (Pt), gold (Au) and iridium (Ir) based complexes have been reported in the literature.^{58,60,90} Advancing their own findings, Gagné and co-workers (2014) introduced a new polyene cyclization strategy using their newly developed N-heterocyclic carbene (NHC) based pincer ligand **80**, which tolerated broad substrate scope.⁹¹ (Scheme 35)



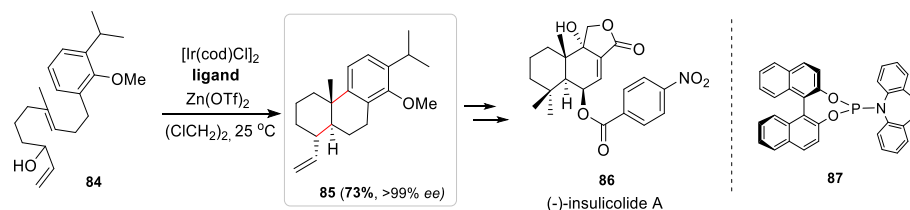
Scheme 35: Pt (II)-mediated polyene cyclization

Echavarren and Rong developed a gold (I)-catalyzed methodology that allows the cascade cyclization of steroid-like compounds containing triple bonds and terminating arene rings.⁶⁰ The strategy was extended to molecules containing alcohol, phenols, and heteroarenes as terminating nucleophiles.⁹² Mechanistically the driving force for cyclization is the preferential formation of kinetically favored gold(I) bound alkynes.⁹³



Scheme 36: Gold(I)-catalyzed polyene cyclization

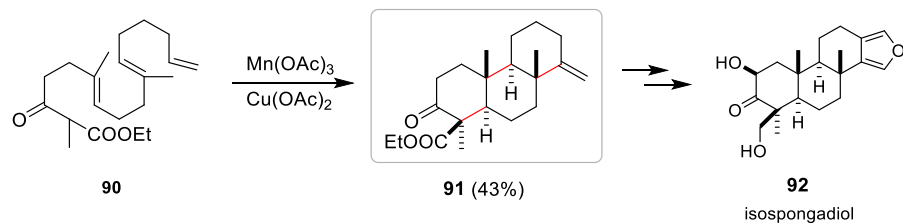
The $[\text{Ir}(\text{cod})\text{Cl}]_2$ catalyzed enantioselective polyene cyclization developed by Carreira⁹⁰ was later utilized by Yang and co-workers in their first synthesis of (-)-Insulicolide A. The tricyclic key intermediate **85** was prepared by employing an $[\text{Ir}(\text{cod})\text{Cl}]_2$ cyclization of **84**.⁹⁴ (Scheme 37)



Scheme 37: $[\text{Ir}(\text{cod})\text{Cl}]_2$ catalyzed synthesis of (-)-insulicolide A

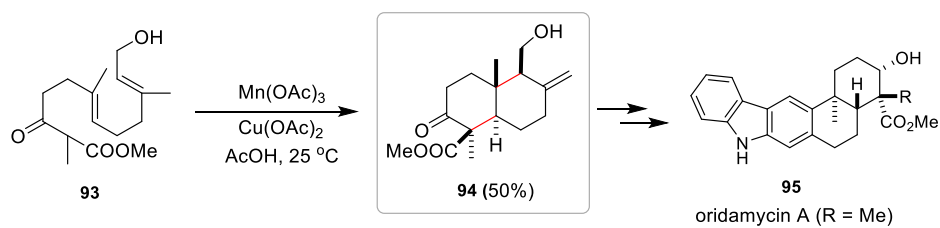
2.2. Radical polyene cyclization

While cationic polyene cyclization dominates the literature, radical polyene cyclization has also been explored and developed. In this context, in 1960, Breslow proposed a radical-mediated polyene cyclization as an alternate biosynthetic pathway for polyene cyclizations. Although his idea was later rejected,²³ his work eventually became the basis for developing radical-mediated strategies. In his work, Breslow demonstrated milder and more efficient ways of constructing terpene frameworks via



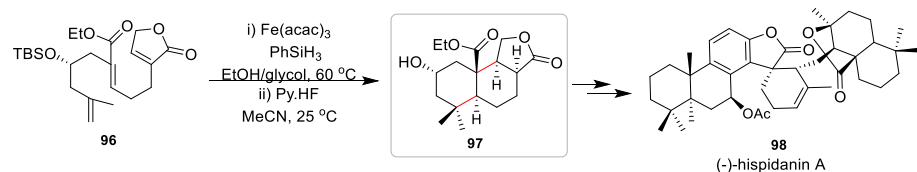
Scheme 39: Mn (III)/Cu (II) promoted polyene cyclization

Trotta and co-workers utilized the Mn (III)/Cu (II) system to synthesize a trans-decalin core of (±)-oridamycin A **95** from a geranyl β-keto ester **93**.¹⁰² (Scheme 40) The Baran group has utilized this catalytic system in the total synthesis of natural products sesquicillin A, higginsianin A, and subglutinol A and B, where the radical cyclization was initiated by an electrochemical method.¹⁰³



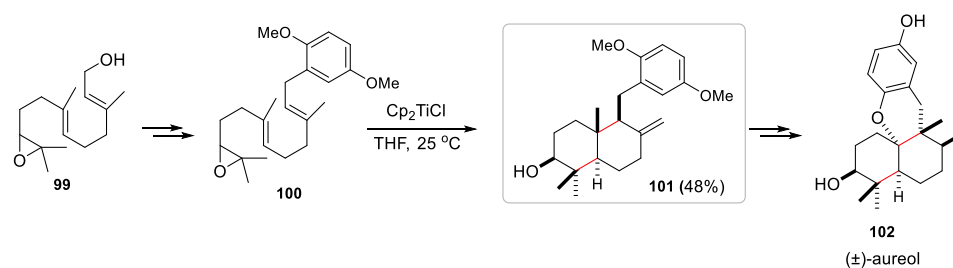
Scheme 40: Total synthesis of (±)-oridamycin A

In 2017, Deng et al. utilized phenylsilane (PhSiH₃) as a hydrogen source in combination with Iron (III) acetylacetonate (Fe(acac)₃) to access a key lactone intermediate **97**, leading to the total synthesis of (-)-hispidanin A **98**.¹⁰⁴ (Scheme 41)



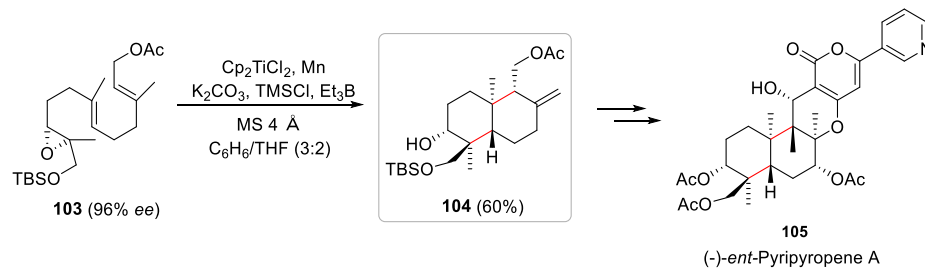
Scheme 41: Fe (III)/PhSiH₃ mediated radical polyene cyclization

Cp_2TiCl is another mild and chemoselective reagent for radical polyene cyclization of various substrates. Due to its air-sensitivity, it is prepared *in situ* from Cp_2TiCl_2 in the presence of Mn or Zinc dust.¹⁰⁵ A titanocene (III)-mediated strategy was utilized by Oltra and co-workers in the synthesis of ($\pm$)-aureol **102** to access the bicyclic key intermediate **101** from a racemic epoxide substrate **99**.¹⁰⁶ (Scheme 42)



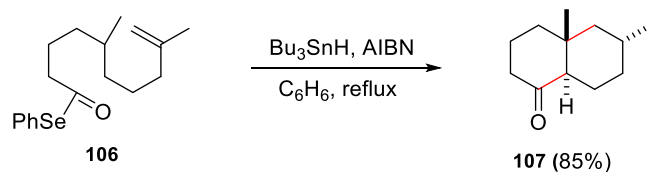
Scheme 42: Cp_2TiCl -mediated synthesis of ($\pm$)-aureol

In another study, Takahashi employed the $\text{Cp}_2\text{TiCl}_2/\text{Mn}$ system to generate Cp_2TiCl *in situ*, which was used to convert an epoxy enantiomer to a bicyclic intermediate **104** that led to the synthesis of (-)-entPyrropyrene A **105**.¹⁰⁷ (Scheme 43) Similarly, Seifert and Gohl utilized Cp_2TiCl together with 2,4,6-collidine and Mn in the synthesis of (-)-3-oxotauranin and (-)-3B-hydroxytauranin.¹⁰⁸



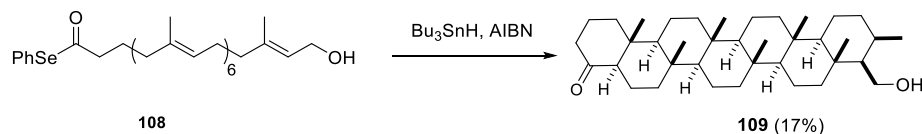
Scheme 43: Synthesis of (-)-ent-Pyripyropene A

The inherent acyl radical generating ability of acyl selenium compounds was exploited by Pattenden and co-workers in developing an acyl/alkyl radical cyclization of polyene-selenoates in the presence of Bu_3SnH -AIBN. The cyclization of phenylselenoester **106** to the corresponding bicyclo decalone **107**, as shown in scheme 44, is initiated by the acyl radical. The stereochemical outcome of cyclization is affected by the alkyl substitutions and the stereochemistry in the olefinic terminus.^{109,110}



Scheme 44: Free-radical cyclization of acyl selenides polyenes

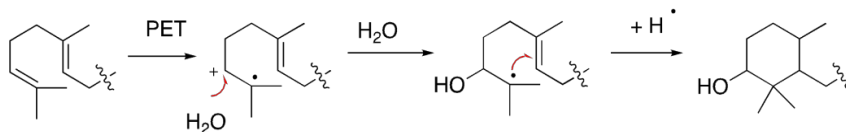
Using this method, they also synthesized azasteroids from polyene enamide selenoesters.¹¹¹ Although they further demonstrated the synthetic ability of this method by preparing a heptacyclic compound **109** from its acyclic polyene precursor **108** in a single step¹¹² (Scheme 45), the difficulty in accessing acyl selenoesters has limited its synthetic application.



Scheme 45: Preparation of heptacyclic compound from an acyl selenide

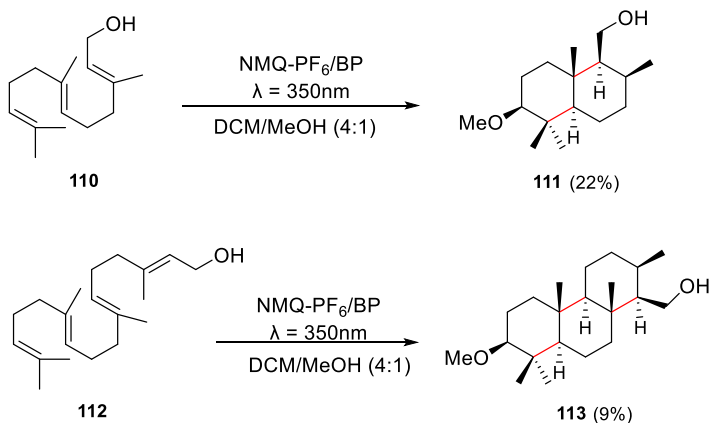
2.2.2. Photocatalyst-mediated polyene cyclization

Remarkable achievements have been obtained in developing photocatalytic transformations for carbon-carbon (C-C, C=C) and carbon-heteroatom (C-N, C-S, C-O, C-Cl) bonds formation, α -amine functionalization, alkene functionalization, decarboxylative coupling reactions, cycloadditions, and atom transfer radical addition reactions (ATRA).¹¹⁵⁻¹²⁵ Even though the photocatalytic functionalization of basic alkenes has been well explored, its extension to polyene cyclization remains limited.¹¹⁴ This can be attributed to the possible nucleophilic capture of the radical intermediate, thereby disrupting the cascade bond movement. Demuth and co-workers reported their seminal work on photochemically induced electron transfer (PET) polyene cyclization in 1993. Mechanistically, the PET-generated reactive radical-cation is trapped by a nucleophile (e.g., H₂O or MeOH) to give a redox-neutral intermediate that triggers the cascade cyclization, resulting in a trans-anti-trans product.^{126,127} (Scheme 46).



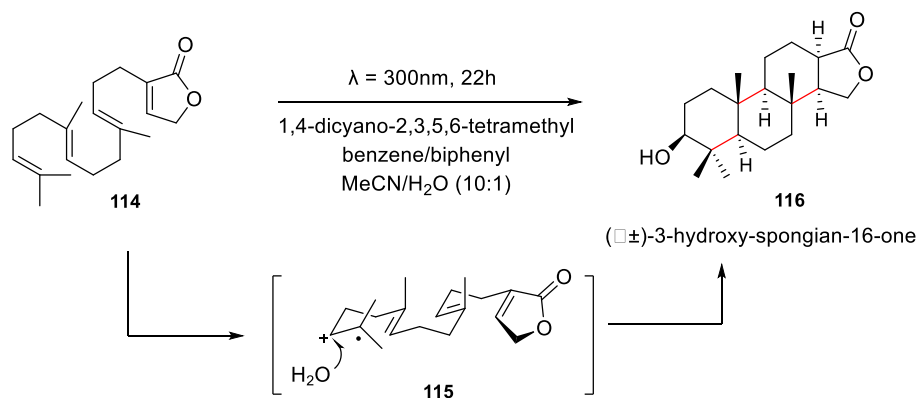
Scheme 46: Graphical representation of PET mediated polyene cyclization

Interestingly, farnesol and geranyl geraniol polyenes in the presence of N-methylquinolinium hexafluorophosphate/biphenyl (NMQ-PF₆/BP) (an electron-acceptor couple), cyclized to give exclusively trans-fused cyclohexane rings.¹²⁸ However, its applicability was limited by very low yields.



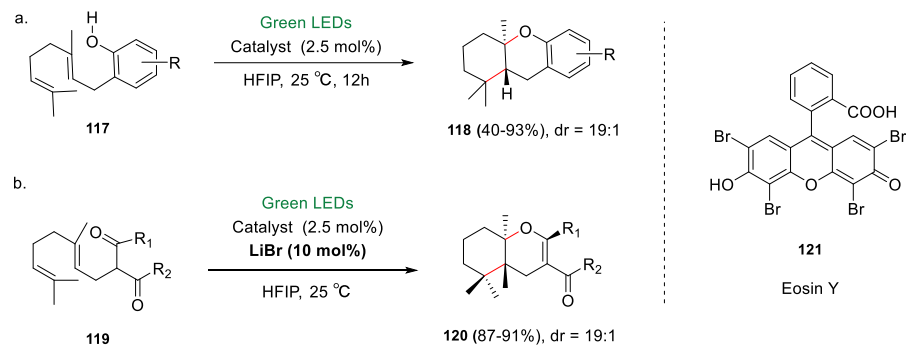
Scheme 47: Polyene cyclization via PET

The same group further demonstrated the effectiveness of this method by extending it to construct tricyclic and tetracyclic steroidal natural products, including (±)-3-hydroxy-spongian-16-one **116**^{129,130} (Scheme 48), but the non-oxidative cyclization process prevented olefin formation in the final step, limiting its applicability in natural terpene synthesis.¹³¹



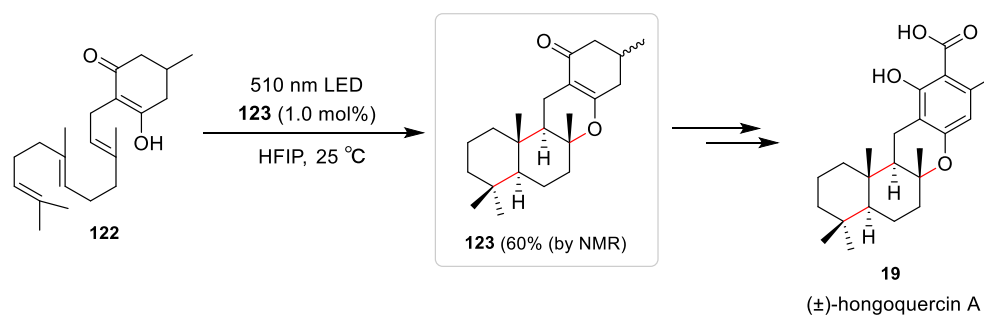
Scheme 48: PET strategy in the synthesis of steroidal natural products

Despite their effort, the photocatalyst-mediated polyene cyclization remains in its infancy. There are only a handful of visible-light-mediated photocatalytic polyene cyclization strategies reported in the literature. Yang et al. reported one using eosin Y **121** as an organic photocatalyst in hexafluoro-2-propanol (HFIP) solvent.¹³² This system allowed a mild and efficient way of constructing polycyclic terpene scaffolds from a wide range of geranyl and farnesyl substituted phenol substrates with high stereochemical control, leading to an excellent diastereoselective outcome. The further extension of this visible-light-mediated organic photocatalytic method to polyenes with a 1,3-ketocarbonyl terminating group required LiBr as an additive. (Scheme 49)



Scheme 49: Visible-light-mediated photocatalytic cyclization of polyenes

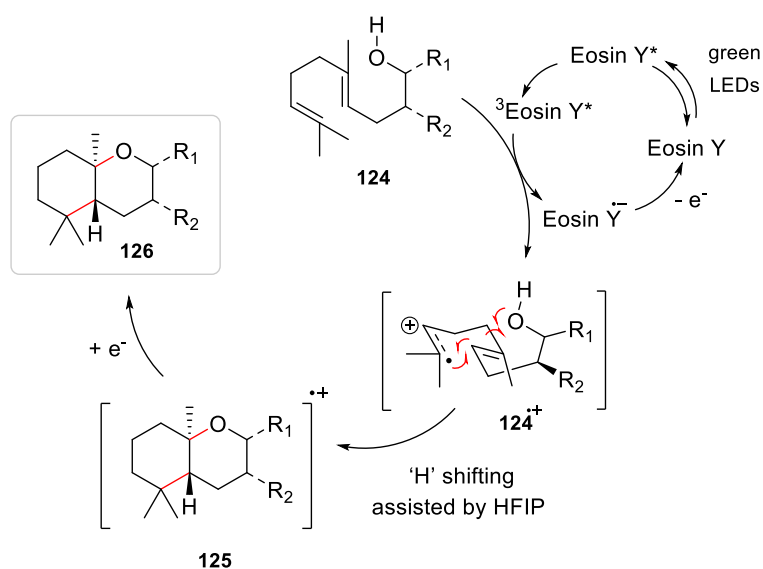
Zhang and co-workers further utilized this strategy to access the tetracyclic core **123** in the total synthesis of (±)-hongoquercin A **19**.¹³³ (Scheme 50)



Scheme 50: Synthesis of (±)-hongoquercin A

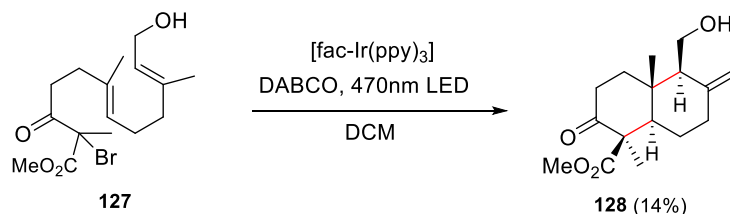
This reaction did not occur in the presence of a radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). Based on this result and Stern-Volmer experiments, they proposed a catalytic cycle, as depicted in Scheme 51. The photo-induced electron transfer from a substrate **124** to the triplet eosin Y generates the radical

cation intermediate **124⁺**, which is highly stabilized by HFIP solvent.¹³³⁻¹³⁶ HFIP further assists the proton transfer process, leading to the desired cyclized product **126**.



Scheme 51: Light-mediated eosin Y catalyzed polyene cyclization (adapted from Yang, Z. et al. 2017)

Besides this sole example of light-mediated cascade polyene cyclization method, Trotta reported a transition metal-based cyclization using [*fac*-Ir(ppy)₃]. (Scheme 52) Although the yield was low, the photocatalyst led to the cyclization of α -bromo- β -keto ester **127** to trans-decalin **128** with an axial methoxy ester.¹³⁷



Scheme 52: $[\text{fac-Ir(ppy)}_3]$ catalyzed light mediated polyene cyclization

2.3. Catalyst-free organic transformations

Most radical-mediated strategies demand the use of stoichiometric activators or initiators, typically transition metal complexes, and suffer from inefficient conversion leading to complex mixtures accompanied by low isolated yields.¹³² Although the successful use of an organic photocatalyst in the presence of visible light has provided a promising alternative to the transition-metal-mediated radical polyene cyclization, catalyst-free visible-light-mediated conditions are still more interesting and highly desired in terms of simplicity, cost-effectiveness, and environmental sustainability.

The visible-light mediated catalyst-free reactions can proceed either by a single electron transfer process (SET) in which one component of a reaction absorbs light and is excited to form a reactive cation and anion radical species, or through the formation of an electron donor-acceptor complex (EDA) as shown in the Figure 47.¹³⁸

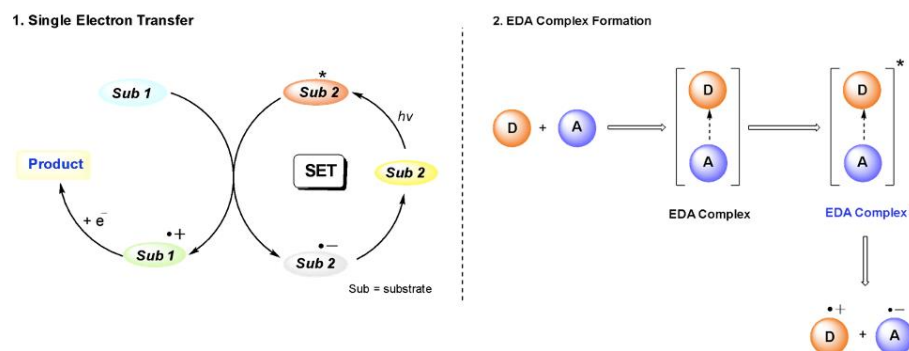


Figure 47: Mechanistic overview of visible light-mediated catalyst-free cyclization

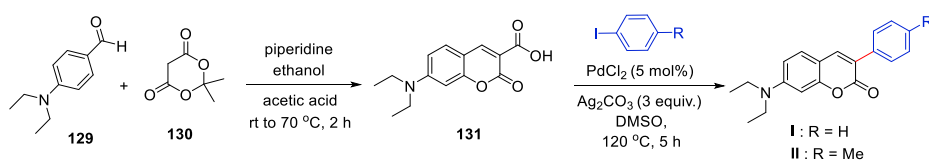
Despite remarkable achievements in developing catalyst-free reaction methodologies in the last decade, its extension to polyene cyclization has not yet been explored. In this context, we developed a catalyst-free methodology while exploring a visible-light-mediated organocatalyst-catalyzed polyene cyclization strategy for geranyl-substituted phenols. Under a blue LED light, the reaction offered the desired cyclized products with high stereoselectivity in hexafluoro-2-propanol.

3. Results and discussion

Inspired by Luo's findings on the successful use of eosin Y as a photocatalyst (Scheme 49) and the light-harvesting property of flavonoids in the lower wavelength region of the visible spectrum (typically blue and green),¹³⁹ we became interested in the possible use of a major flavonoid as a photocatalyst for polyene cyclization.

Flavonoids are an interesting but largely unexplored option for organic photocatalysts. They are readily available both from natural sources as well as synthetically.¹⁴⁰ Further, their photophysical properties, particularly in terms of

absorption can be readily tuned by systematic alteration of the parent structure. The one existing application of flavonoids to photocatalysis was reported by Gualandi and Cozzi who reported the successful application to several different reactions but did not include any polyene cyclizations.¹⁴¹ To explore this gap, flavonoids **I** and **II** were first synthesized employing a reported procedure.^{142,143} (Scheme 53)



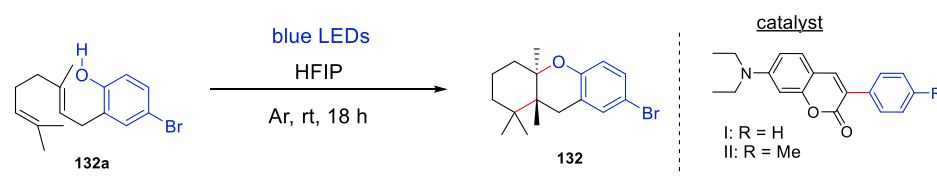
Scheme 53: Synthesis of flavonoids **I** and **II**

Flavonoids **I** and **II** were then applied in the direct cyclization of the model substrate geranyl substituted phenol **2a** in hexafluoro-2-propanol (HFIP) solvent. In the presence of blue LED light, **I** and **II** resulted in the desired cyclized product **132** in 62% and 66% yield, respectively, after 24 hours. No reaction was observed in the absence of blue light. Interestingly, the reaction also failed using a green LED light with either **I** or **II**, doubtless due to the poor match of their absorption maxima with the emission spectrum of the green LED lamp.

An important question is if **I** or **II** is essential for cyclization. Surprisingly, the control reaction of **132a** in HFIP in the presence of blue LED light (Table 8 entry 5) led to the formation of the cyclized product, revealing that the transformation does not require a photocatalyst. The reaction afforded 64% of the cyclized product with high diastereoselectivity (>19:1) after 18 h at room temperature resulting in a new blue-light-mediated catalyst-free reaction protocol for the cyclization of various geranyl

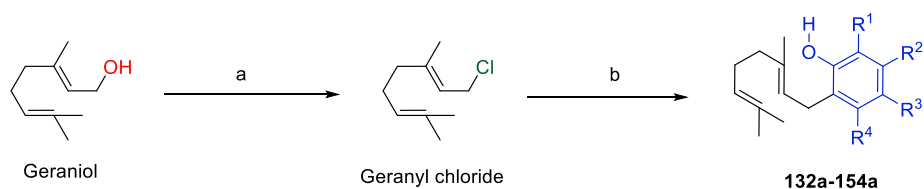
substituted phenols. Notably, no reaction occurred using a green LED light in the absence of a photocatalyst, just as was reported by Luo (Table 8).

Table 8: Reaction condition study



Entry	Modified conditions	Yield ^a (%)	d.r.
1.	I (5 mol%), 24 h, rt	62	> 19:1
2.	II (5 mol%), 24 h, rt	66	> 19:1
3.	I or II (5 mol%), w/o blue LEDs, 24 h, rt	NR	
4.	I or II (5 mol%), with green LEDs, 24 h, rt	NR	
5.	blue LED, 18 h, rt	64	> 19:1
6.	green LED, 18 h, rt	NR	
7.	blue LED, 18 h, 35 °C	63	> 19:1

With this result in hand, the generality of the reaction protocol was explored. For this purpose, various geranyl substituted phenol derivatives were synthesized as depicted in Scheme 54. The geranyl chloride was obtained by treating geraniol with SOCl₂ in the presence of tributylamine at ice-cold temperature.¹⁴⁴ The resulting chloride was reacted with a NaH treated solution of substituted phenols to give the geranyl substituted phenols (**132a-154a**).



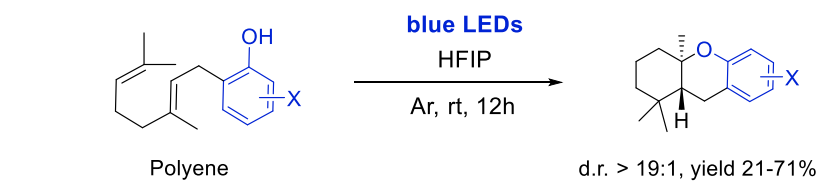
132a: R³ = Br; **133a:** R¹ = OMe, R³ = Br; **134a:** R¹ = Br; **135a:** R⁴ = Br; **136a:** R² = Br; **137a:** R² = Br, R⁴ = OH; **138a:** R³ = Cl; **139a:** R¹ = Me, R³ = Cl; **140a:** R¹ = Cl; **141a:** R¹ = Cl, R³ = Me; **142a:** R² = Cl; **143a:** R⁴ = Cl; **144a:** R⁴ = F; **145a:** R³ = F; **146a:** R² = I; **147a:** R³ = I; **148a:** R³ = OCF₃; **149a:** R³ = Me; **150a:** R³ = OMe; **151a:** R⁴ = COMe; **152a:** R⁴ = CO₂Me; **153a:** R⁴ = CHO; **154a:** R⁴ = OCF₃

Scheme 54: Synthetic route to compounds **132a-154a**. Reagents and conditions: (a) Bu₃N, SOCl₂, Et₂O, 0 °C; (b) geranyl chloride solution added to phenol, NaH, toluene 0 °C to rt, ON.

Under the standard catalyst-free reaction conditions, a series of cascade cyclizations were investigated (Table 9). Initially, variations in the location of a bromine on the phenol ring were explored. Moving the bromine to the ortho position (**134a**) resulted in cyclization and afforded product **134** in 62% yield. For the meta positions (**135a** and **136a**), only-**135a** cyclized in 45% yield.

Changing the halogen to chlorine resulted in similar trends. The para isomer (**138a**) cyclized in 71% yield and the ortho isomer (**140a**) cyclized in 47% yield. Interestingly, neither of the two meta isomers (**142a** and **143a**) cyclized even though one of the two bromo substituted phenols did.

Table 9: Substrate scope study



Entry	Polyene	Cyclized product
1.	132a	132 (64%)
2.	133a	133 (64%)
3.	134a	134 (62%)
4.	135a	135 (45%)
5.	136a 5-Br	NR

Table 9 Contd.

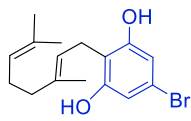
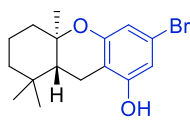
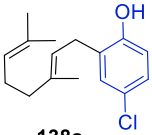
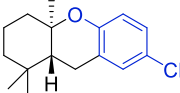
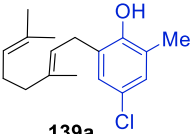
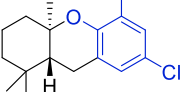
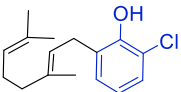
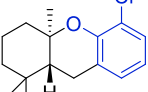
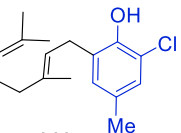
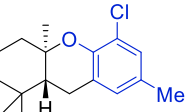
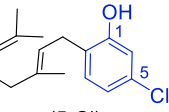
Entry	Polyene	Cyclized product
6.	 137a	 137 (55%)
7.	 138a	 138 (71%)
8.	 139a	 139 (35%)
9.	 140a	 140 (47%)
10.	 141a	 141 (55%)
11.	 (5-Cl) 142a	NR

Table 9 Contd.

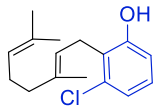
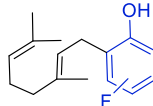
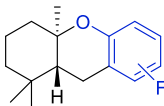
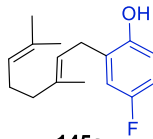
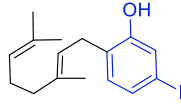
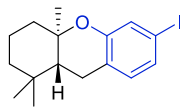
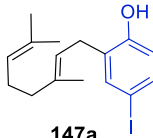
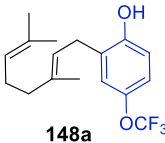
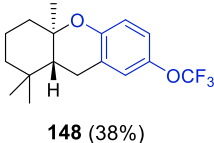
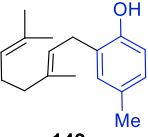
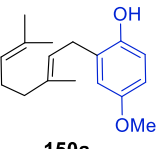
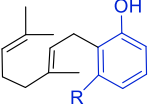
Entry	Polyene	Cyclized product
12.	 (3-Cl) 143a	NR
13	 144a	 144 (40%)
14	 145a	NR
15	 146a	 146 (21%)
16	 147a	NR

Table 9 Contd.

Entry	Polyene	Cyclized product
17	 148a	 148 (38%)
18	 149a	NR
19	 150a	NR
20	 151a R = COMe 152a R = CO ₂ Me 153a R = CHO 154a R = OCF ₃	NR

Further exploring halogen substituted phenols, surprisingly neither the para fluoro or iodo substrates (**145a** and **147a**) cyclized, indicating that the presence of a halogen was not sufficient for cyclization. For the meta isomers (**144a** and **146a**), only the iodo compound could be cleanly prepared, while the corresponding fluoro substrate afforded an inseparable mixture of isomeric precursors. The meta iodophenol yielded

21% pure cyclized product, while the mixture of meta fluoro phenols did cyclize to a similar mixture of isomers in a modest 40% yield. Attempts to prepare the ortho iodo and fluoro phenols failed to afford any geranylated products.

Curious as to what would happen when moving past halogen substituted phenols, para trifluoromethoxy, methyl, and methoxy substrates (**148a**, **149a**, **150a**) were studied, with only the trifluoromethoxy compound cyclizing in a very modest 38%. For the meta series (**151a-154a**), none cyclized, affording simply recovered starting material.

This lack of reaction for the non-halogenated compounds as well as the iodo and fluoro ones was quite unexpected given the generally good yields observed by Luo for para fluoro, iodo, and methoxy substrates under Eosin-Y conditions.¹³⁹ To examine if the presence of halogen was sufficient, additional bromo and chloro substituted compounds that contained not only the halogen, but also methyl, methoxy, or additional hydroxy functionality. These reactions were all successful, with the combination of a methoxy and a bromine in compound-**133a** affording the cyclization product in the same yield as **132a** which lacks the methoxy. Similarly, chlorine with methyl as in substrate **141a** affords the cyclization product in very similar yield to the corresponding ortho chloro substrate **140a**. For another combination of chloro and methyl (substrate **139a**), the yield is significantly reduced compared to the simple para chloro compound **138a**. Finally, bromoresorcinol **137a** cyclized in 55% yield, even though the corresponding meta bromo phenol **136a** did not cyclize. As a result, it did appear that the presence of bromine or chlorine was important for the general success of these photocatalyst free cyclizations.

In considering possible explanations for the success or failure of cyclization, one possibility was the acidity of the phenol. Assuming that the influence of the gernanyl group would be comparable in all substrates, the reported pKa values of the simple phenols were compared, as well as the σ value (Table 10) of the substituents as a surrogate for acidity (Table 10).¹⁴⁵⁻¹⁴⁸ In terms of pKa, while the bromo and chlorophenols are more acidic than the fluorophenols, simple acidity is not a satisfactory explanation since the equally or even more acidic formyl and acetyl substituted phenols failed to cyclize. Similarly, the σ values do not provide an adequate way to predict the success or failure of cyclization. The values for the para substituted phenols offer consistency, with the identical values for bromine and chlorine both cyclizing. In the case of meta substituted phenols, however, there is no consistent pattern, with numerous substrates with values between those of chlorine and bromine failing to cyclize.

Table 10: *pKa* and σ values for halo substituted phenols

Substituent	<i>pKa</i>			σ	
	<i>o</i>	<i>m</i>	<i>p</i>	<i>m</i>	<i>p</i>
Bromo	8.45	9.03	9.37	0.39	0.23
Chloro	8.56	9.02	9.38	0.37	0.23
Fluoro		9.28	9.95	0.34	0.06
Iodo				0.35	0.18
Methyl		10.08	10.14	-0.07	-0.17
Methoxy		9.65	10.21	0.12	-0.27
Trifluoromethoxy				0.38	0.35
Formyl		8.00	8.05	0.25	0.42
Acetyl		9.19	8.05	0.28	0.50
Carboxymethyl				0.37	0.45
<i>o</i> = ortho; <i>m</i> = meta, <i>p</i> = para					

A second option is the possibility of an EDA complex process. A growing number of photocatalyst free reactions have been reported.¹⁴⁹ Indeed, a number of addition reactions to alkenes have been reported that proceed well in the presence of 2-bromophenol as an EDA catalyst.¹⁵⁰ Nonetheless, UV spectra of substrates **132a** and **138a** which cyclized and substrates **145a** and **147a** which did not reveal longer wavelength absorptions that might be expected as evidence of a donor/acceptor complex.

4. Conclusions

In conclusion, we have developed a set of photocatalyst-free polyene cyclizations that afford the products in good yield and high selectivity. The presence of bromine or chlorine on the aryl ring is important for successful cyclization, but this requirement is beneficial as bromine can be readily converted into a wide range of other functional groups or removed entirely. This work also serves to reinforce the importance of exploring various wavelengths of light in the absence of photocatalyst when developing photo-mediated chemistry.

5. Experimental

General Information: All the reactions were done under an air atmosphere unless otherwise specified. ¹H and ¹³C NMR of all the compounds were recorded on JEOL AS (500 and 300 MHz) NMR instrument and chemical shifts were recorded in ppm. All the chemical shifts were recorded using CDCl₃ (Chloroform-d₆) as a standard reference. The following conventions are used for multiplicities: *s*, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; *dd*, doublet of doublet; *tt*, triplet of triplet; *dt*, doublet of triplet; *ddd*,

doublet of doublet of doublet; *br*, broad. All extracts were concentrated under reduced pressure using a Buchi Rotary Evaporator. During the purification and identification of compounds, Thin Layer Chromatography (TLC) was performed on silica-coated TLC plates and monitored by short wavelength (254 nm) UV light. Products were purified by silica gel column chromatography. ACS-grade reagents were employed during the experiments. The blue lamp used for all cyclizations was an ABI PAR38 12W LED grow light with a reported emission of 450-460 nm.

5.1. General method for synthesis of flavonoids I and II

Synthesis of Coumarin-3-carboxylic acid (131):¹⁴² To a solution of 0.5 mmol 4-(diethylamino)-2-hydroxybenzaldehyde (**129**) in 1 mL of ethanol in a 3-dram glass vial, 0.5 mmol of Meldrum's acid (**130**) was added in a dropwise manner. To the solution, 2 drops of piperidine and 1 drop of acetic acid were added. The solution was stirred at room temperature for 20 minutes and then heated to reflux for 2 h. After cooling, the resulting orange colored precipitate was filtered, washed with ice-cooled ethanol and dried.

Decarboxylative arylation of 131:¹⁴³ In a 3-dram vial, compound **131** (0.25 mmol), aryl iodide (1.3 equiv), PdCl₂ (5 mol %), and Ag₂CO₃ (0.75 mmol) were dissolved in 3 mL of DMSO. The resulting solution was heated at 120 °C for 5 h. The reaction mixture was cooled, washed with DI water, and then extracted with ethyl acetate several times. The extracted organic layer was further washed with DI water multiple times and dried over anhydrous MgSO₄. Solvent was removed using a rotatory evaporator to obtain crude product, which, further was purified by flash chromatography using 10 % ethyl acetate in hexane.

5.2. General method for the synthesis of geranyl chloride¹⁴⁴

To a solution of geraniol and tributylamine (1.0 mmol) in 3 mL diethyl ether in a 3-dram glass vial placed in an ice-bath at 0 °C, 1.0 mmol of SOCl₂ was added dropwise over 10 minutes. Once the SOCl₂ addition was completed, the reaction was stirred at room temperature for 2 h. After the reaction (monitored by TLC), the reaction mixture was acidified with 1N HCl, washed with DI water, and then extracted with diethyl ether. The organic fraction was dried over anhydrous MgSO₄, filtered and the solvent was removed using a rotatory evaporator to obtain the crude mixture. This mixture was loaded onto a silica-packed glass pipette and eluted with hexane to obtain the desired product as a clear oil, which was used for the next step without further purification.

5.3. Synthesis of geranyl substituted phenols¹³²

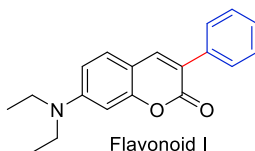
In a 3-dram glass vial, 0.5 mmol (64.3 mg) p-chlorophenol and 2 mL toluene were mixed at 0 °C. To this solution was added 0.5 mmol sodium hydride (12 mg). Then the reaction mixture was brought to room temperature and stirred. After 1 h, crude geranyl chloride (0.45 mmol, 78.3 mg) dissolved in 2 mL of toluene was added and the reaction was stirred overnight. Completion of the reaction was determined by TLC using 10% ethyl acetate in hexane solvent system. The reaction was quenched with saturated NH₄Cl (cold) and diluted with DI water. The mixture was extracted with ethyl acetate, and the organic fraction was washed with brine solution, dried over anhydrous MgSO₄, filtered, and concentrated *in-vacuo*. The crude reaction mixture was purified by flash column chromatography using 2% ethyl acetate in hexane eluent to give the product which was characterized by HRMS and NMR.

5.4. Cyclization of geranyl substituted phenols¹³²

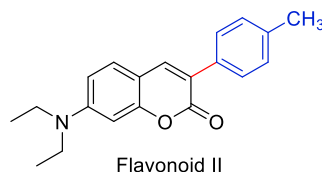
0.05 mmol of geranyl substituted phenol was dissolved in 0.5 mL of hexafluoroisopropanol (HFIP) in a 1-dram vial. The vial was then flushed with argon gas and stirred inside a closed box while being irradiated with a blue light for 18 h. The reaction mixture slowly turned brown. After completion of the reaction, as determined by TLC, the solvent was removed *in vacuo*, and 0.5 mL DCM was added to it, followed by silica. Once the crude reaction mixture was adsorbed on the silica, DCM was removed *in vacuo* to prepare a dry load for column chromatography. The dry powder was loaded on the top of a dry silica-packed glass pipette and eluted with hexane to afford the desired cyclized product as a clear oil.

5.5. Characterization data of the synthesized compounds

5.5.1. Characterization data for flavonoids I and II:

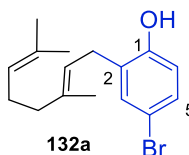


7-(Diethylamino)-3-phenyl-2H-chromen-2-one (I).¹⁴³ Yield: 34% (25.4 mg); bright yellow solid. ¹H NMR (500 MHz, CHLOROFORM-D) ¹H NMR (500 MHz, CHLOROFORM-D) δ 7.70 (d, *J* = 2.1 Hz, 2H), 7.69 (d, *J* = 1.1 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.36 – 7.30 (m, 2H), 6.60 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 3.43 (q, *J* = 7.1 Hz, 4H), 1.23 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (126 MHz, CHLOROFORM-D) δ 162.04, 156.57, 150.85, 140.93, 136.18, 129.26, 128.66, 128.60, 128.07, 121.25, 109.45, 109.27, 97.49, 45.21, 12.82.

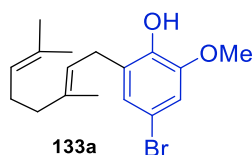


7-(Diethylamino)-3-(4-methylphenyl)-2H-chromen-2-one. Yield: 34% (25.4 mg); bright yellow solid. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.67 (s, 1H), 7.59 (d, J = 6.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 6.59 (dd, J = 8.8, 2.5 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 3.42 (q, J = 7.1 Hz, 4H), 2.38 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 161.86, 156.19, 150.44, 140.08, 137.67, 132.99, 129.10, 128.89, 128.19, 121.02, 109.26, 108.96, 97.23, 44.93, 21.32, 12.56.

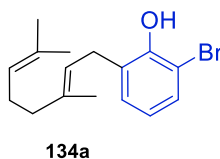
5.5.2. Characterization data for phenol-substituted polyenes:



(E)-4-bromo-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (132a):¹³² Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 42% (58.3 mg); pale yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.22 – 7.17 (m, 2H), 6.68 (d, J = 7.8 Hz, 1H), 5.28 (t, J = 7.2 Hz, 1H), 5.20 – 5.04 (m, 2H), 3.32 (d, J = 7.2 Hz, 2H), 2.16 – 2.04 (m, 4H), 1.75 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 153.65, 139.41, 132.53, 132.23, 130.24, 129.31, 123.78, 120.82, 117.59, 112.75, 39.74, 29.59, 26.41, 25.83, 17.84, 16.31.

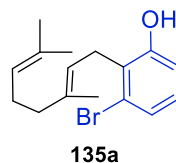


(E)-4-bromo-6-methoxy-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (133a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 25% (37.6 mg); brown oil. ^1H NMR (500 MHz, CDCl_3) δ 6.87 (d, $J = 2.2$ Hz, 1H), 6.83 (d, $J = 2.2$ Hz, 1H), 5.61 (s, 1H), 5.28 (td, $J = 7.4, 1.2$ Hz, 1H), 5.10 (t, $J = 6.8$ Hz, 1H), 3.86 (s, 3H), 3.32 (d, $J = 7.3$ Hz, 2H), 2.11 (dd, $J = 14.4, 7.2$ Hz, 2H), 2.07 – 2.02 (m, 2H), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.95, 142.58, 137.14, 131.58, 129.31, 124.58, 124.26, 121.34, 111.87, 111.18, 56.34, 39.79, 27.70, 26.66, 25.79, 17.78, 16.19. HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{24}\text{BrO}_2$ 339.0959; found 339.0963.

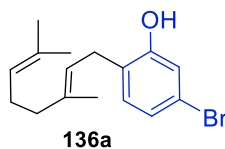


(E)-6-bromo-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (134a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 45% (63.0 mg); pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.30 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.07 (d, $J = 7.4$ Hz, 1H), 6.73 (t, $J = 15.5$ Hz, $J = 7.5$ Hz, 1H), 5.61 (s, 1H), 5.31 (t, $J = 7.4$ Hz, 1H), 5.09 (t, $J = 6.5$ Hz, 1H), 3.39 (d, $J = 7.3$ Hz, 2H), 2.14 – 2.04 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.29, 137.48, 131.67,

129.64, 129.36, 129.17, 124.25, 121.49, 121.43, 110.45, 39.81, 29.21, 26.63, 25.78, 17.78, 16.18. HRMS (ESI): calculated for C₁₆H₂₂BrO 309.0854; found 309.0849.

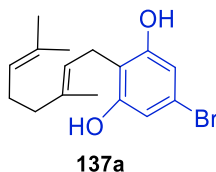


(E)-3-bromo-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (135a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 24% (33.7 mg); colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.13 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.64 – 5.49 (m, 1H), 5.20 (t, *J* = 6.6 Hz, 1H), 5.05 (t, *J* = 6.7 Hz, 1H), 3.59 (d, *J* = 6.9 Hz, 2H), 2.13 – 2.01 (m, 4H), 1.81 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H). ¹³C NMR (126 MHz, CHLOROFORM-D) δ 155.50, 138.85, 132.08, 128.17, 127.24, 125.14, 123.88, 120.56, 115.30, 77.38, 77.13, 76.87, 39.77, 29.87, 26.46, 25.79, 17.82, 16.49. HRMS (ESI): calculated for C₁₆H₂₂BrO 309.0854; found 309.0856.

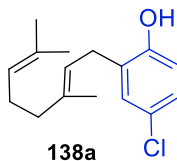


(E)-5-bromo-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (136a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 32.4% (45.1 mg); colorless oil. ¹H NMR (500 MHz, CHLOROFORM-D) δ 7.00 – 6.96 (m, 2H),

6.95 (d, $J = 7.9$ Hz, 1H), 5.43 – 5.17 (m, 2H), 5.06 (t, $J = 6.5$ Hz, 1H), 3.30 (d, $J = 7.2$ Hz, 2H), 2.09 (tt, $J = 10.8, 5.5$ Hz, 4H), 1.75 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H).

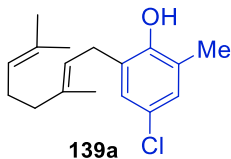


(E)-5-bromo-3-hydroxy-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (137a): Reaction (0.5 mmol of phenol (94.5 mg, 2 equivalent of NaH (24.0 mg) and 0.9 mmol geranyl chloride (157.0mg)) were used was stirred overnight under the standard reaction conditions. Yield: 37% (33.7 mg); pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 6.58 (s, 2H), 5.96 – 5.85 (m, 2H), 5.23 (t, $J = 7.9$ Hz, 1H), 5.04 (t, $J = 6.4$ Hz, 1H), 3.37 (d, $J = 7.1$ Hz, 2H), 2.15 – 1.99 (m, 4H), 1.79 (s, 3H), 1.67 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 155.92, 139.54, 132.24, 123.77, 121.11, 119.53, 113.03, 111.67, 60.95, 39.75, 26.40, 25.76, 22.32, 21.01, 17.78, 16.28. HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{22}\text{BrO}_2$ 325.0803; found 325.0807.

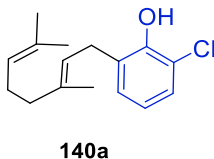


(E)-4-chloro-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (138a):¹³² Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 56% (67.3 mg); pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.05 (dt, $J = 8.3, 2.5$ Hz, 2H), 6.72 (d, $J = 8.3$ Hz, 1H), 5.29 – 5.26 (m, 2H), 5.08 – 5.05 (m, 1H), 3.31 (d, $J = 7.2$ Hz,

2H), 2.15 – 2.07 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 153.11, 139.31, 132.20, 129.62, 128.81, 127.23, 125.34, 123.80, 120.84, 117.04, 39.74, 29.56, 26.41, 25.81, 17.82, 16.29.

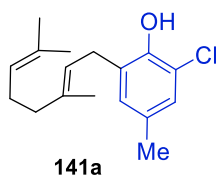


(E)-4-chloro-6-methyl-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (139a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 73% (91.2 mg); pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 6.97 (d, $J = 2.4$ Hz, 1H), 6.92 (d, $J = 2.6$ Hz, 1H), 5.29-5.24 (m, 1H), 5.15 (s, 1H), 5.06 (t, $J = 6.8$ Hz, 1H), 3.31 (d, $J = 7.2$ Hz, 2H), 2.19 (s, 3H), 2.14- 2.08 (m, 4H), 1.77 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.41, 138.43, 131.12, 127.46, 126.69, 126.03, 125.17, 123.56, 122.62, 119.97, 38.61, 29.03, 25.22, 24.65, 16.67, 15.11, 14.75. HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{24}\text{ClO}$ 279.1516; found 279.1520.

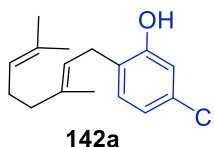


(E)-6-chloro-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (140a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction condition. Yield: 42% (49.8 mg); colorless oil ^1H NMR (500 MHz, CDCl_3) δ 7.17 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.04 (d, $J = 7.1$ Hz, 1H), 6.79 (t, $J = 7.8$ Hz, 1H), 5.64 (s, 1H), 5.32 (t, $J = 7.9$ Hz, 1H), 5.10

(t, $J = 6.2$ Hz, 1H), 3.38 (d, $J = 7.3$ Hz, 2H), 2.15 – 2.04 (m, 4H), 1.72 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.60, 137.42, 131.70, 129.35, 128.41, 126.57, 124.26, 121.47, 120.81, 119.87, 39.83, 28.86, 26.63, 25.82, 17.81, 16.18. HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{22}\text{ClO}$ 265.1359; found 265.1355.

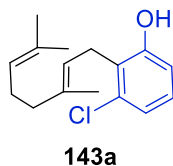


(E)-6-chloro-4-methyl-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (141a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 69% (86.6 mg); pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 6.97 (s, 1H), 6.82 (s, 1H), 5.46 (s, 1H), 5.30 (t, $J = 7.3$ Hz, 1H), 5.10 (t, $J = 6.9$ Hz, 1H), 3.34 (d, $J = 7.3$ Hz, 2H), 2.23 (s, 3H), 2.13 – 2.02 (m, 4H), 1.72 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.11, 137.12, 131.59, 130.28, 129.16, 128.95, 126.74, 124.24, 121.69, 119.47, 39.80, 29.03, 26.65, 25.75, 20.50, 17.76, 16.19. HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{24}\text{ClO}$ 279.1516; found 279.1513.

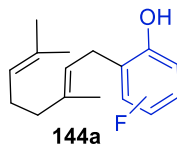


(E)-5-chloro-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (142a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 28.4% (37.6 mg); colorless oil. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.01 (d, $J = 7.9$ Hz, 1H), 6.85 – 6.80 (m, 2H), 5.27 (ddd, $J = 7.9, 6.9, 2.8$ Hz, 2H), 5.06 (t, $J = 6.8$ Hz, 1H), 3.32

(d, $J = 7.3$ Hz, 2H), 2.09 (ddd, $J = 20.2, 13.2, 7.0$ Hz, 4H), 1.75 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H).

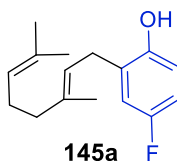


(*E*)-3-chloro-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (143a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 19% (25.5 mg); colorless oil. ^1H NMR (500 MHz, CHLOROFORM- D) δ 7.01 (t, $J = 8.0$ Hz, 1H), 6.96 (dd, $J = 8.0, 1.1$ Hz, 1H), 6.72 (dd, $J = 8.0, 1.1$ Hz, 1H), 5.33 (s, 1H), 5.21 (td, $J = 6.9, 1.0$ Hz, 1H), 5.05 (t, $J = 6.8$ Hz, 1H), 3.56 (d, $J = 7.0$ Hz, 2H), 2.13 – 1.97 (m, 4H), 1.81 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H).

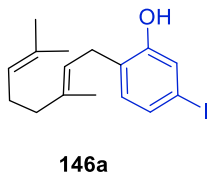


(*E*)-3-fluoro-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (144a): Reaction (0.68 mmol scale, 117.0 mg) was stirred overnight under the standard conditions. Yield: 66% (112.0 mg); colorless oil. Mixture of regioisomers. ^1H NMR (500 MHz, CDCl_3) δ 7.03 (dd, $J = 15.0, 8.1$ Hz, 1H), 6.59 (ddd, $J = 20.2, 17.6, 9.4$ Hz, 2H), 5.41 (d, $J = 17.2$ Hz, 1H), 5.33 – 5.22 (m, 1H), 5.06 (d, $J = 6.8$ Hz, 1H), 3.37 (dd, $J = 45.4, 7.0$ Hz, 2H), 2.14 – 2.04 (m, 4H), 1.78 (d, $J = 19.5$ Hz, 3H), 1.68 (d, $J = 9.2$ Hz, 3H), 1.60 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.11, 137.12, 131.59, 130.28, 129.16, 128.95,

126.74, 124.24, 121.69, 119.47, 39.80, 29.03, 26.65, 25.75, 20.50, 17.76, 16.19. HRMS (ESI): calculated for C₁₆H₂₂FO 249.1671; found 249.1675.

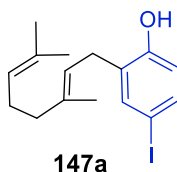


(E)-4-fluoro-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (145a)¹³²: Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 33% (36.3 mg); colorless oil. ¹H NMR (500 MHz, CHLOROFORM-D) δ 6.82 (dd, J = 9.3, 3.2 Hz, 1H), 6.78 (dd, J = 8.2, 3.1 Hz, 1H), 6.73 (dd, J = 8.7, 4.8 Hz, 1H), 5.32 – 5.25 (m, 1H), 5.10 – 5.04 (m, 1H), 4.98 (s, 1H), 3.33 (d, J = 7.2 Hz, 2H), 2.11 (tt, J = 9.9, 4.9 Hz, 4H), 1.75 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H).

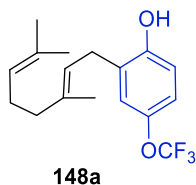


(E)-5-iodo-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (146a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 15% (23.7 mg); colorless oil. ¹H NMR (301 MHz, CDCl₃) δ 7.20 – 7.15 (m, 2H), 6.82 (d, J = 7.3 Hz, 1H), 5.29 – 5.21 (m, 2H), 5.05 (s, 1H), 3.30 (d, J = 7.2 Hz, 2H), 2.20 – 2.05 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 155.30, 139.29, 132.19, 131.48, 129.87, 126.88, 124.87, 123.82, 120.99, 91.22, 39.74, 29.48,

26.41, 25.79, 17.80, 16.26. HRMS (ESI): calculated for C₁₆H₂₂IO 357.0715; found 357.0712.

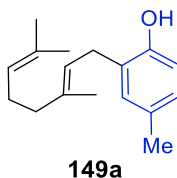


(E)-4-iodo-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (147a)¹³²: Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 68% (109.6 mg); colorless oil. ¹H NMR (500 MHz, CHLOROFORM-D) δ 7.38 (dd, *J* = 8.6, 2.3 Hz, 2H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.26 (dd, *J* = 16.6, 10.5 Hz, 2H), 5.07 (t, *J* = 6.6 Hz, 1H), 3.30 (d, *J* = 7.2 Hz, 2H), 2.17 – 2.03 (m, 4H), 1.75 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H).

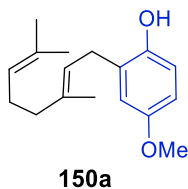


(E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-4-(trifluoromethoxy)phenol (148a)¹³²: Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 41% (58.1 mg); pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 6.96 (d, *J* = 7.7 Hz, 2H), 6.78 (dd, *J* = 5.9, 4.9 Hz, 1H), 5.33–5.28 (m, 2H), 5.07 (t, *J* = 6.1 Hz, 1H), 3.35 (d, *J* = 7.2 Hz, 2H), 2.1–2.07 (m, 4H), 1.75 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 152.01, 141.63, 138.64, 131.21, 127.34, 122.71,

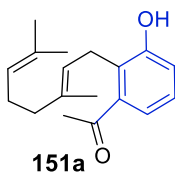
121.76, 119.59, 119.19, 115.39, 38.69, 28.63, 25.37, 24.70, 16.73, 15.21. HRMS (ESI): calculated for C₁₇H₂₂F₃O 264.1655; found 264.1658.



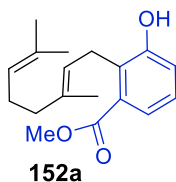
(E)-4-methyl-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (149a): Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 67% (74.2 mg); colorless oil. ¹H NMR (500 MHz, CHLOROFORM-D) δ 6.94 (t, *J* = 7.3 Hz, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 5.40 – 5.32 (m, 1H), 5.15 (dd, *J* = 29.1, 11.3 Hz, 2H), 3.37 (t, *J* = 6.5 Hz, 2H), 2.29 (s, 3H), 2.19 – 2.07 (m, 4H), 1.80 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H).



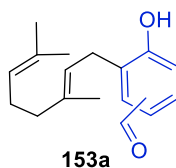
(E)-4-methoxy-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (150a)¹³²: Reaction (0.45 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 32% (34.5 mg); colorless oil. ¹H NMR (500 MHz, CHLOROFORM-D) δ 6.73 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 6.65 (dd, *J* = 8.6, 3.0 Hz, 1H), 5.31 (t, *J* = 7.0 Hz, 1H), 5.07 (t, *J* = 6.6 Hz, 1H), 4.85 (s, 1H), 3.75 (s, 3H), 3.33 (d, *J* = 7.2 Hz, 2H), 2.11 (dt, *J* = 13.2, 7.3 Hz, 4H), 1.76 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H).



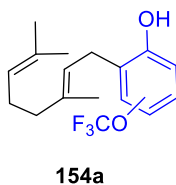
(E)-3-acetyl-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (151a): Reaction (0.5 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 23.3% (31.7 mg); colorless oil. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.54 – 7.46 (m, 2H), 7.35 (td, J = 8.0, 2.9 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 5.48 (s, 1H), 5.08 (s, 1H), 4.58 (d, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.16 – 2.04 (m, 4H), 1.74 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H).



(E)-3-acetyl-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (152a): Reaction (0.5 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 34% (49.1 mg); colorless oil. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.61 (d, J = 7.6 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.09 (dd, J = 8.2, 2.4 Hz, 1H), 5.47 (t, J = 6.6 Hz, 1H), 5.07 (t, J = 6.5 Hz, 1H), 4.56 (d, J = 6.6 Hz, 2H), 3.89 (s, 3H), 2.13 – 2.05 (m, 4H), 1.74 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H).

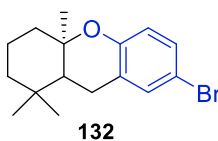


(E)-3-acetyl-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (153a): Reaction (0.5 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 10.3% (13.3 mg); colorless oil. ^1H NMR (301 MHz, CHLOROFORM-D) δ 9.97 (s, 1H), 7.47 – 7.43 (m, 2H), 7.42 – 7.40 (m, 1H), 7.23 – 7.16 (m, 1H), 5.49 (t, J = 6.5 Hz, 1H), 5.10 (s, 1H), 4.60 (d, J = 6.5 Hz, 2H), 2.17 – 2.04 (m, 4H), 1.76 (s, 3H), 1.68 (s, 4H), 1.61 (s, 3H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 192.30, 159.51, 141.99, 137.83, 131.97, 130.08, 123.78, 123.50, 122.32, 118.93, 113.03, 65.22, 39.63, 26.35, 25.77, 17.79, 16.81.



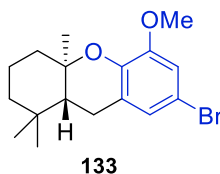
(E)-3-acetyl-2-(3,7-dimethylocta-2,6-dien-1-yl)phenol (154a): Reaction (0.5 mmol scale) was stirred overnight under the standard reaction conditions. Yield: 21.5% (33.9 mg); colorless oil. ^1H NMR (500 MHz, CHLOROFORM-D) δ 7.08 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 9.7 Hz, 2H), 5.63 (s, 1H), 5.29 (t, J = 7.3 Hz, 1H), 5.06 (t, J = 5.9 Hz, 1H), 3.34 (d, J = 7.2 Hz, 2H), 2.10 (dt, J = 13.5, 7.0 Hz, 1H), 1.75 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H).

5.5.3. Characterization data for the cyclized products:



trans-(4a,9a)-7-Bromo-1,1,4a-tetramethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene

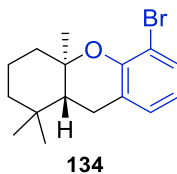
(132):¹³² Reaction (0.04 mmol scale, 11.7 mg) was stirred for 18 hours under the standard reaction conditions. Yield: 64% (7.5 mg); (trans/ cis > 95%) colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.19 – 7.11 (m, 2H), 6.63 (d, *J* = 8.6 Hz, 1H), 2.67 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.57 (dd, *J* = 16.5, 13.3 Hz, 1H), 1.95 (d, *J* = 10.9 Hz, 1H), 1.66 (dd, *J* = 13.1, 4.9 Hz, 2H), 1.59 – 1.46 (m, 4H), 1.19 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 152.57, 132.19, 130.07, 124.93, 118.92, 111.65, 77.69, 47.87, 41.50, 39.95, 33.46, 32.10, 23.26, 20.68, 19.82, 19.80.



trans-(4a,9a)-7-bromo-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-

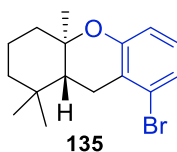
xanthene (133): Reaction (0.03 mmol scale, 12.0 mg) was stirred for 18 hours under standard conditions. Yield: 64% (7.7 mg); (trans/ cis > 95%) pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 6.82 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 3.81 (s, 3H), 2.65 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.57 (dd, *J* = 16.5, 13.1 Hz, 1H), 2.07 (d, *J* = 11.7 Hz, 1H), 1.70 – 1.63 (m, 3H), 1.59 – 1.45 (m, 3H), 1.21 (s, 3H), 0.98 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 149.67, 142.20, 125.03, 124.16, 112.76, 111.04, 78.08, 56.27, 47.82, 41.48, 39.86, 33.49, 32.12, 23.33, 20.68, 19.84, 19.74. HRMS (ESI): calculated for $\text{C}_{17}\text{H}_{24}\text{BrO}_2$ 339.0959; found 339.0961.



trans-(4a,9a)-5-Bromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene

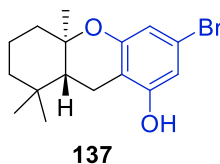
(134): Reaction (0.05 mmol scale, 15.4 mg) was stirred for 18 hours under the standard reaction conditions. Yield: 62% (9.6 mg); (trans:cis = 75:25) colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, J = 5.6 Hz, 1H), 6.99 (d, J = 6.1 Hz, 1H), 6.70–6.64 (m, 1H), 2.67 (dd, J = 36.5, 14.6 Hz, 2H), 2.05 (d, J = 9.9 Hz, 1H), 1.73–1.65 (m, 3H), 1.62–1.47 (m, 3H), 1.22 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.24, 130.85, 128.80, 124.43, 120.33, 111.46, 78.69, 48.08, 41.50, 39.76, 33.46, 32.12, 23.63, 20.66, 20.07, 19.82. HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{22}\text{BrO}$ 309.0854; found 309.0856.



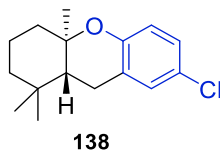
trans-(4a,9a)-8-Bromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene

(135): Reaction (0.04 mmol scale, 13.2 mg) was stirred for 18 hours under the standard reaction conditions. Yield: 45% (5.9 mg); (trans:cis > 95%) white waxy solid. ^1H NMR

(500 MHz, CDCl₃) δ 7.09 (dd, J = 7.6, 3.2 Hz, 1H), 6.94 (td, J = 8.0, 3.6 Hz, 1H), 6.72 (dd, J = 8.0, 3.1 Hz, 1H), 2.78 (d, J = 17.0 Hz, 1H), 2.40 (t, J = 15.2 Hz, 1H), 1.97 (d, J = 9.2 Hz, 1H), 1.67 (dd, J = 8.6, 4.3 Hz, 2H), 1.60 – 1.47 (m, 4H), 1.18 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 154.59, 127.94, 125.44, 123.70, 123.04, 116.43, 77.49, 48.30, 41.58, 39.74, 33.50, 32.14, 24.98, 20.62, 19.80, 19.71. HRMS (ESI): calculated for C₁₆H₂₂BrO 309.0854; found 309.0858.

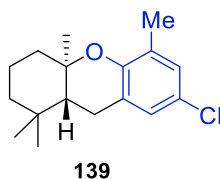


***trans*-(4a,9a)-6-Bromo-8-hydroxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (137):** Reaction (0.05 mmol scale, 18.0 mg) was stirred for 18 hours under standard conditions. Yield: 55% (10.0 mg); (*trans*:*cis* > 95%) brownish oil. ¹H NMR (500 MHz, CDCl₃) δ 6.57 (d, J = 1.6 Hz, 1H), 6.49 (d, J = 1.7 Hz, 1H), 4.87 (s, 1H), 2.65 (dd, J = 16.5, 4.9 Hz, 1H), 2.24 (dd, J = 16.4, 13.3 Hz, 1H), 1.97 – 1.93 (m, 1H), 1.69–1.54 (m, 6H), 1.19 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 155.14, 154.47, 119.48, 113.18, 109.63, 109.24, 77.85, 47.53, 41.54, 39.80, 33.56, 32.13, 20.67, 19.79, 19.71, 17.70. HRMS (ESI): calculated for C₁₆H₂₂BrO₂ 325.0803; found 325.0800.



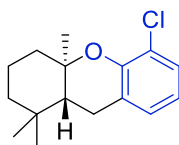
trans-(4a,9a)-7-Chloro-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene

(138):¹³² Reaction (0.1 mmol scale, 27.8 mg) was stirred for 18 hours under the standard reaction conditions. Yield: 71% ((19.8 mg); (trans:cis > 95%) colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.04–6.99 (m, 2H), 6.67 (d, *J* = 8.5 Hz, 1H), 2.66 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.60–2.53 (m, 1H), 1.95 (d, *J* = 11.5 Hz, 1H), 1.66 (dd, *J* = 13.1, 5.1 Hz, 2H), 1.61–1.46 (m, 4H), 1.19 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 152.03, 129.24, 127.17, 124.31, 118.41, 77.66, 47.89, 41.51, 39.96, 33.46, 32.11, 23.31, 20.69, 19.82.



trans-(4a,9a)-7-Chloro-5-methyl-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-

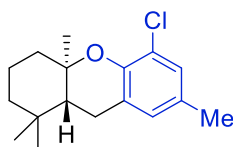
xanthene (139): Reaction (0.08 mmol scale, 22.7 mg) was stirred for 18 hours under standard conditions. Yield: 35% (8.0 mg); (trans:cis > 95%) white waxy solid. ¹H NMR (500 MHz, CDCl₃) δ 6.88 (d, *J* = 13.9 Hz, 2H), 2.73 – 2.51 (m, 2H), 2.10 (s, 3H), 1.95 (d, *J* = 11.0 Hz, 1H), 1.56 (ddd, *J* = 36.6, 31.0, 14.4 Hz, 6H), 1.16 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 150.16, 127.98, 127.94, 126.57, 123.51, 123.48, 77.33, 48.00, 41.58, 40.00, 33.42, 32.09, 23.45, 20.64, 20.07, 19.83, 15.99. HRMS (ESI): calculated for C₁₇H₂₄ClO 279.1516; found 279.1513.



140

trans-(4a,9a)-5-Chloro-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene

(140): Reaction (0.06 mmol scale, 16.2 mg) was stirred for 18 hours under the standard reaction conditions. Yield: 47% (7.6 mg); (trans:cis > 95%) white waxy solid. ^1H NMR (500 MHz, CDCl_3) δ 7.15 (d, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 7.2$ Hz, 1H), 6.73 (t, $J = 7.7$ Hz, 1H), 2.71 (dd, $J = 16.5, 5.0$ Hz, 1H), 2.61 (dd, $J = 16.5, 13.2$ Hz, 1H), 2.06 (d, $J = 11.7$ Hz, 1H), 1.73 – 1.65 (m, 3H), 1.60 – 1.47 (m, 3H), 1.22 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.35, 128.03, 127.78, 124.45, 121.95, 119.70, 78.57, 47.99, 41.49, 39.78, 33.49, 32.12, 23.54, 20.67, 20.04, 19.84. HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{22}\text{ClO}$ 265.1359; found 265.1362.

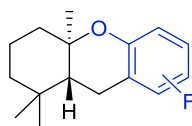


141

trans-(4a,9a)-5-Chloro-7-methyl-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-

xanthene (141): Reaction (0.1 mmol scale, 28.9 mg) was stirred for 18 hours under standard conditions. Yield: 55% (15.8 mg); (trans:cis > 95%) white waxy solid. ^1H NMR (300 MHz, CDCl_3) δ 6.98 (s, 1H), 6.77 (s, 1H), 2.74 – 2.51 (m, 2H), 2.21 (s, 3H), 2.04 (d, $J = 10.9$ Hz, 1H), 1.74 – 1.66 (m, 3H), 1.56 – 1.47 (m, 3H), 1.20 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.01, 129.16, 128.53, 128.24,

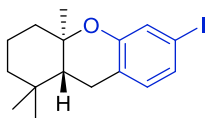
124.04, 121.41, 78.29, 48.08, 41.51, 39.79, 33.46, 32.12, 23.52, 20.66, 20.33, 19.96, 19.84. HRMS (ESI): calculated for C₁₇H₂₄ClO 279.1516; found 279.1515.



144

trans-(4a,9a)-8-Fluoro-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene

(144): Reaction (0.16 mmol scale, 39.1 mg) was stirred for 18 hours under the standard reaction conditions. Yield: 40% (15.9 mg); colorless oil Mixture of isomers. ¹H NMR (500 MHz, CDCl₃) δ 7.03 – 6.92 (m, 1H), 6.59 – 6.45 (m, 2H), 2.73 (ddd, *J* = 72.7, 16.4, 4.9 Hz, 1H), 2.57 – 2.36 (m, 1H), 1.98 – 1.93 (m, 1H), 1.69 – 1.46 (m, 6H), 1.21 (d, *J* = 5.5 Hz, 3H), 1.01 (d, *J* = 12.5 Hz, 3H), 0.91 (d, *J* = 12.9 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 130.36, 130.29, 127.22, 118.33, 112.60, 106.86, 106.69, 106.04, 105.87, 104.14, 103.95, 77.79, 77.66, 48.05, 47.33, 41.57, 41.51, 39.92, 33.50, 32.15, 22.78, 20.75, 20.69, 19.90, 19.82, 19.75, 17.17 HRMS (ESI): calculated for C₁₆H₂₂FO 249.1671; found 249.1669.

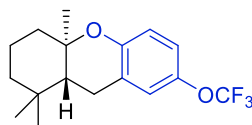


146

trans-(4a,9a)-6-Iodo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (146):

Reaction (0.05 mmol scale, 19.4 mg) was stirred for 18 hours under the standard reaction conditions. Yield: 21% (4.0 mg); (trans:cis = 85:15) colorless oil. ¹H NMR

(500 MHz, CDCl₃) δ 7.11 (dd, J = 5.2, 1.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 1H), 2.63 (dd, J = 14.3, 7.0 Hz, 1H), 2.55–2.48 (m, 1H), 1.94 (d, J = 8.8 Hz, 1H), 1.64 (dd, J = 13.2, 4.8 Hz, 2H), 1.57–1.43 (m, 4H), 1.19 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 153.30, 130.26, 127.73, 125.16, 121.59, 89.95, 76.93, 46.98, 40.53, 38.98, 32.56, 31.19, 22.11, 19.78, 18.98, 18.86. HRMS (ESI): calculated for C₁₆H₂₂IO 357.0715; found 357.0711.



148

***trans*-(4a,9a)-1,1,4a-trimethyl-7-(trifluoromethoxy)-2,3,4,4a,9,9a-hexahydro-1H-xanthene (148)**¹³²: Reaction (0.05 mmol scale, 16.7 mg) was stirred for 18 hours under standard conditions. Yield: 38% (6.3 mg); (*trans*:*cis* > 95%) colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 6.92 (s, 2H), 6.74–6.70 (m, 1H), 2.77–2.65 (m, 1H), 2.63–2.55 (m, 1H), 1.95 (d, J = 11.4 Hz, 1H), 1.67 (dd, J = 11.8, 5.7 Hz, 2H), 1.59–1.47 (m, 4H), 1.20 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 151.95, 141.92, 123.70, 122.25, 120.31, 117.82, 77.76, 47.80, 41.48, 39.94, 33.46, 32.13, 23.48, 20.70, 19.88, 19.81, CF₃ signal buried under CDCl₃. HRMS (ESI): calculated for C₁₇H₂₂F₃O 264.1655; found 264.1659.

6. References

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CHAPTER IV

CONCLUSIONS

Aurones have gained significant interest in drug discovery due to their wide range of bioactivity against various pathogens and diseases. Additionally, their ability to impart colors to flowers and fruits has been successfully utilized to explore their fluorogenic aspects, leaving their potential dyeing ability virtually unexplored. Motivated by this gap, this work has demonstrated that the potential of aurones extends far beyond their biological and fluorescent properties. Although further efforts are required to achieve their full potential, some clear guidance and encouraging signs have been obtained.

The first project has furnished some interesting results and observations on the dyeing ability of aurones in textiles. Although the attempt to develop an *in situ* synthesis of aurones accompanied by fabric dyeing in one pot displayed some practical issues, the study demonstrated the utility and significance of deep eutectic solvents in dissolving aurone dye candidates, which otherwise are insoluble in water. Determining the dye properties of a compound is time consuming, which makes it important to design a screening process focused on the specific application, including the type of textile, biological properties, color intensity, colorfastness, etc. Utilizing the multifiber fabric for screening the eighteen aurone derivatives (**21-38**) enabled us to compare the color retention of different dye molecules in various fabrics and how the same compound imparts different hues and intensities in other fabrics. Most of the aurone candidates were deemed suitable for acetate, nylon, and wool fabrics. Also, the effect

of various substitutions in the aurone appeared to manifest in terms of variation of hues imparted on the fabrics. While dimethylamino-substituted aurones mostly showed vibrant yellow to dark orange color, in contrast, ferrocene-substituted aurones showed light purple to dark purple coloration to the fabric, although their utility was limited due to their poor aqueous solubility.

In this study, dyeing wool with four hydroxy-substituted dimethylamino aurones (**22-25**) displayed satisfactory colorimetric properties. Among them, the 4,6-dihydroxylated compound **24** was generally the most resistant to color loss for the rubbing, photostability, or washing tests. This is likely to be attributed to the possibility of forming hydrogen bonding by the compound with the polar groups in wool fabric, which explains its better colorfastness. Although this study provides a comparative study on various dyeing properties of four selected aurones (**22-25**) on wool fabrics, it solely relies on the dyeing parameters optimized for aurone **22** (taken as a model compound for optimization). Since each aurone has different λ_{max} and physical properties, their dyeing parameters would need to be optimized individually.

Similarly, inspired by a report that utilized flavonoids in photocatalysis, the other project explored aurones as photocatalysts in polyene cyclization, one of the fascinating chemical transformations observed in nature. It allows access to structurally and stereochemically challenging polycyclic frameworks from acyclic precursors. Most existing methods, however, predominantly use expensive and toxic transition metal-based catalysts. So, there has been an interest in developing organocatalyzed methodologies.

While working in this direction, employing synthetic flavonoids as catalysts for the cyclization of a geranyl-substituted bromophenol substrate, an even more

interesting blue-light mediated catalyst-free polyene cyclization methodology was discovered. This methodology allows one-step cascade cyclization of geranyl-substituted phenols in hexafluoro-2-propanol (HFIP). Under the optimized reaction conditions, the generality of the reaction was studied on various geranyl substituted phenols. Among the halogen-substituted phenolic substrates, bromo-substitution in ortho, meta, and para led to the corresponding cyclized products, while only ortho and para-chloro afforded cyclization. Interestingly, neither iodo nor fluoro derivatives in the para position cyclized. In the meta position, iodo compound cyclized to give the product in poor yield, but fluoro derivatives only yielded an inseparable mixture of cyclized isomers.

A range of other substituents were explored, including methyl, methoxy, aldehyde, ester, and trifluoromethoxy substituted substrates. With the exception of trifluoromethoxy, none cyclized, signifying the essential role of halogens on the aryl ring for the successful cyclization. Several possible reasons for this halogen requirement have been explored, but the exact role remains unclear. The possibility of increased acidity in the excited state remains one explanation that has not been fully explored.

A key lesson learned from this project is the importance of studying various wavelengths of light when developing photochemical transformations since green light requires a catalyst, while blue light does not.

Future opportunities:

Both studies, exploring aurone as a dyeing agent and developing a blue-light mediated catalyst free-cyclization, provide a plentiful direction for future efforts. As virtually no precedent is available in the literature for the use of aurones in dyeing, the

future remains wide open. Evaluating the antimicrobial efficacy of pure aurones and comparing their effect in solution with that after dyeing the fabrics can help determine if solution activity serves as an effective guide for antimicrobial textile dyeing. If the same trend holds, then the non-textile studies could be used to screen and guide the selection of antimicrobial aurone dyes.

Similarly, further study on the influence of benzofuranone substitution could also be beneficial in developing effective dyes for hydrophobic fabrics, including polyester and acrylic. The methoxy derivatives, also part of the fabric screening (in Chapter II), or even new alkyl-substituted benzofuranones may be good options for this purpose.

The application of aurones as photocatalysts remains unexplored and certainly remains an interesting opportunity to make use of their easy synthesis, small size, and the easy ability to tune their photophysical properties. Determining the property responsible for the catalyst-free photocyclizations is also important as this could lead to the rational design of future photocatalyst-free transformations. Finally, the halogen-substituted cyclized products obtained from the photocyclizations methodology offer a unique opportunity for functionalization via cross-coupling chemistry, extending application in drug discovery and offering another direction for future efforts.

APPENDICES

APPENDIX – A

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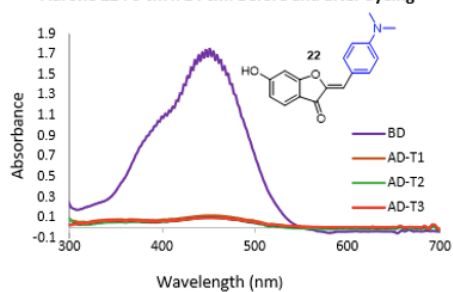
1. Chapter III reproduced from;
 - Bhattarai, S.; Kafle, A.; Handy, S.T. “Catalyst-free light-mediated polyene cyclization” *Tetrahedron* **2024**, *156*, 133910.

APPENDIX - B

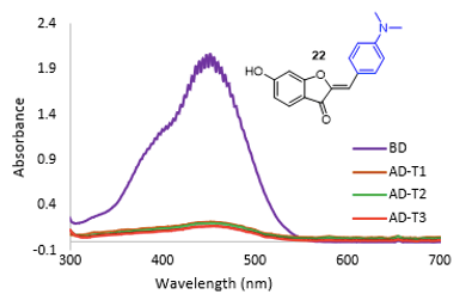
Colorfastness test: UV-Vis absorption (before and after dyeing)

1. Aurone **22** (6-OH-DMAA)

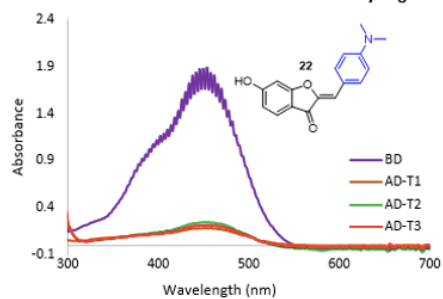
a. Aurone **22** : 5 cm x 14 cm: Before and after dyeing



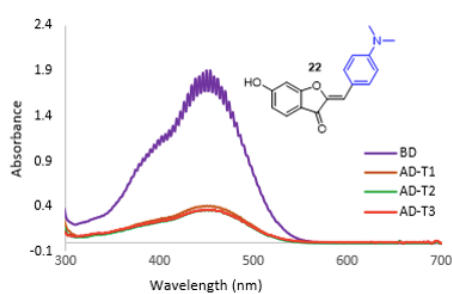
b. Aurone **22** : 5 cm x 14 cm: Before and after dyeing



c. Aurone **22** : 4 cm x 10 cm: Before and after dyeing

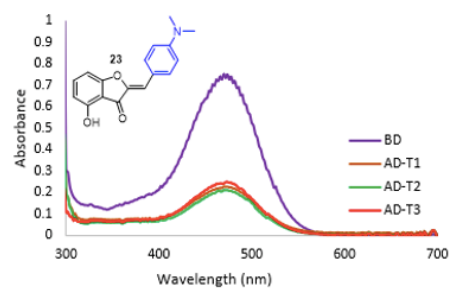


d. Aurone **22** : 1.5 cm x 4.5 cm: Before and after dyeing

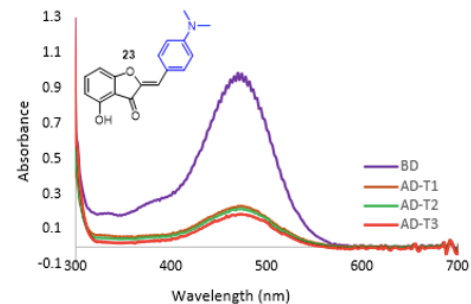


2. Aurone 23 (4-OH-DMAA)

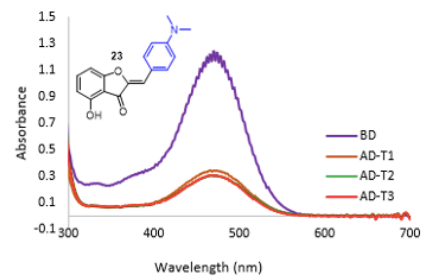
a. Aurone 23: 5 cm x 14 cm: Before and after dyeing



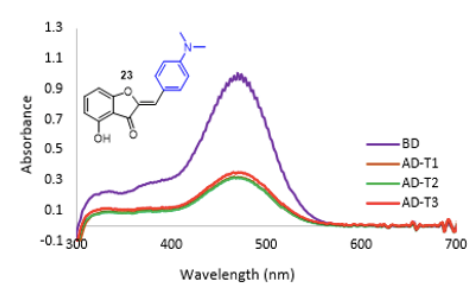
b. Aurone 23: 5 cm x 14 cm: Before and after dyeing



c. Aurone 23: 4 cm x 10 cm: Before and after dyeing

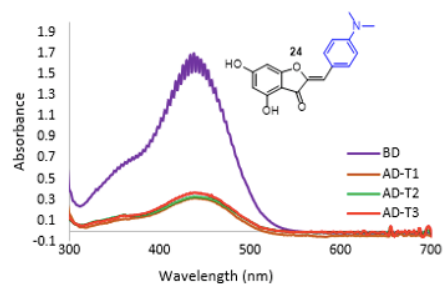


d. Aurone 23: 1.5 cm x 4.5 cm: Before and after dyeing

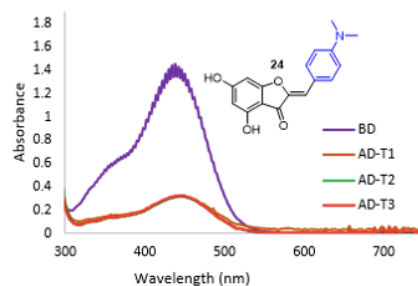


3. Aurone 24 (4, 6-diOH-DMAA)

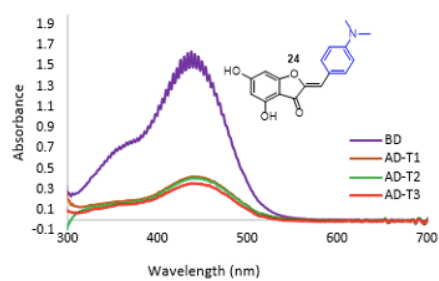
a. Aurone 24: 5 cm x 14 cm: Before and after dyeing



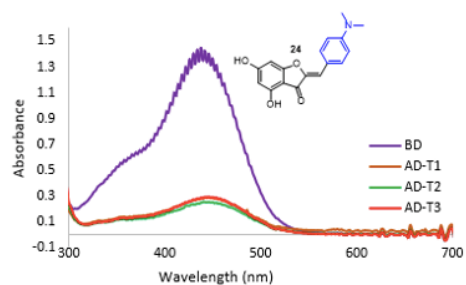
b. Aurone 24: 5 cm x 14 cm: Before and after dyeing



c. Aurone 24: 4 cm x 10 cm: Before and after dyeing

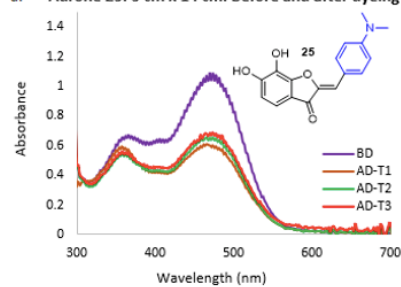


d. Aurone 24: 1.5 cm x 4.5 cm: Before and after dyeing

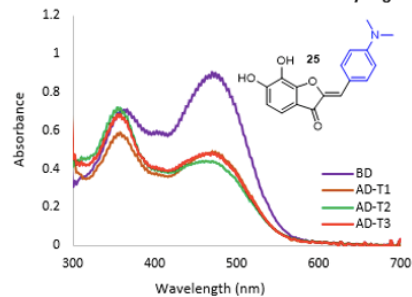


4. Aurone **25** (6,7-diOH-DMAA)

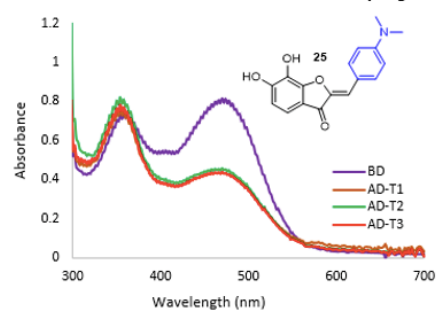
a. Aurone **25**: 5 cm x 14 cm: Before and after dyeing



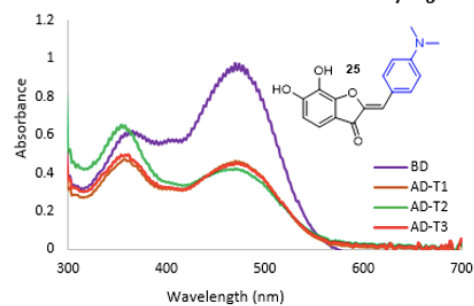
b. Aurone **24**: 5 cm x 14 cm: Before and after dyeing



c. Aurone **24**: 4 cm x 10 cm: Before and after dyeing



d. Aurone **25**: 1.5 cm x 4.5 cm: Before and after dyeing

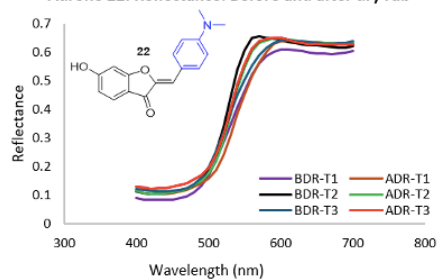


APPENDIX - C

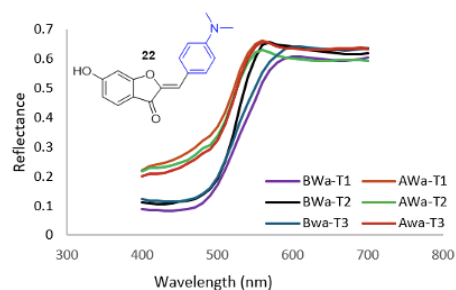
Colorfastness test: Reflectance measured (before and after dyeing)

1. Aurone 22 (6-OH-DMAA)

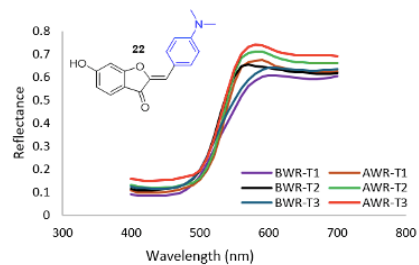
a. Aurone 22: Reflectance: Before and after dry rub



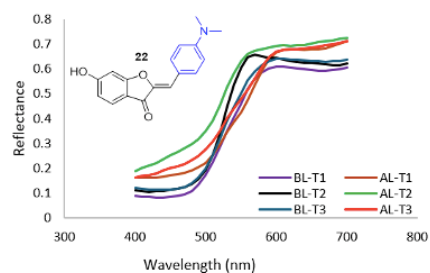
c. Aurone 22: Reflectance: Before and after wash



b. Aurone 22: Reflectance: Before and after wet rub

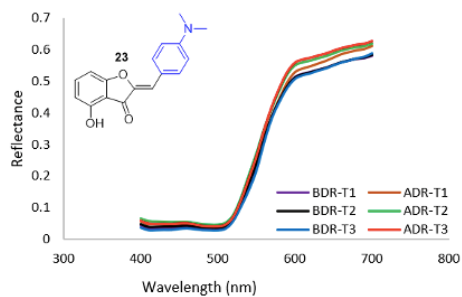


d. Aurone 22: Reflectance: Before and after light

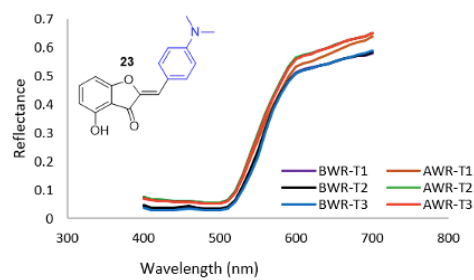


2. Aurone 23 (6-OH-DMAA)

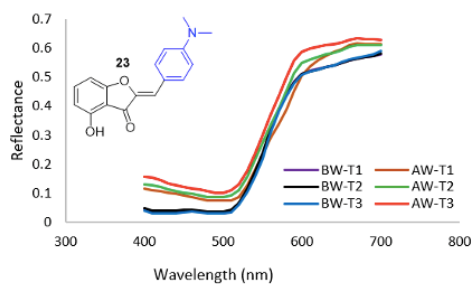
a. Aurone 23: Reflectance: Before and after dry rub



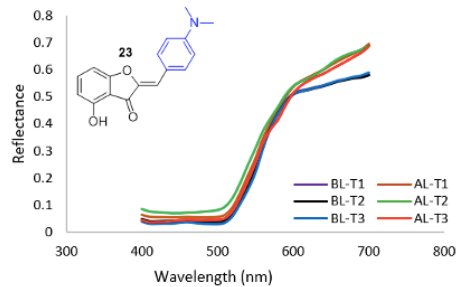
b. Aurone 23: Reflectance: Before and after wet rub



c. Aurone 23: Reflectance: Before and after wash

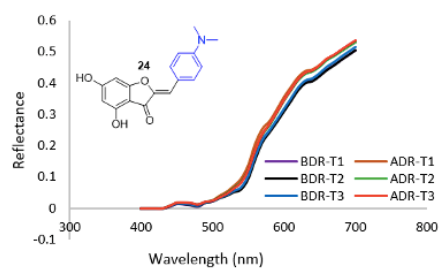


d. Aurone 23: Reflectance: Before and after light

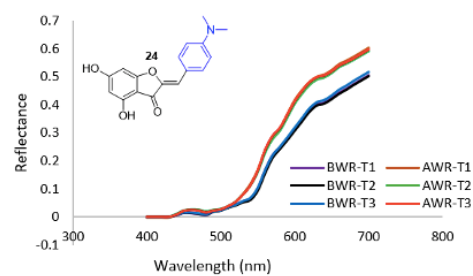


3. Aurone 24 (4, 6-diOH-DMAA)

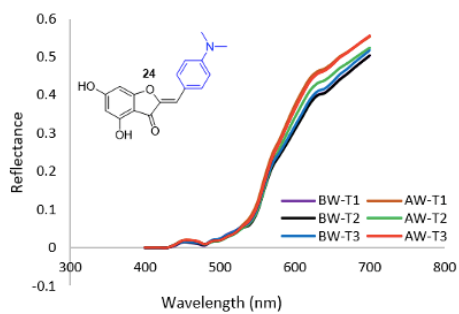
a. Aurone 24: Reflectance: Before and after dry rub



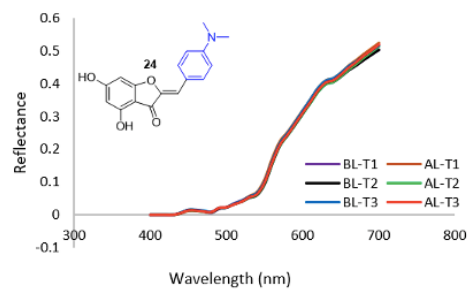
b. Aurone 24: Reflectance: Before and after wet rub



c. Aurone 24: Reflectance: Before and after wash

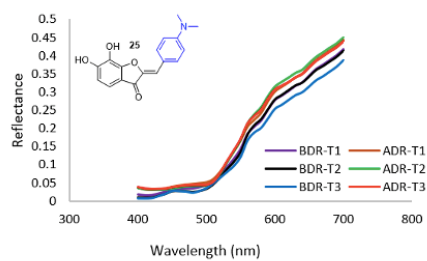


d. Aurone 24: Reflectance: Before and after light

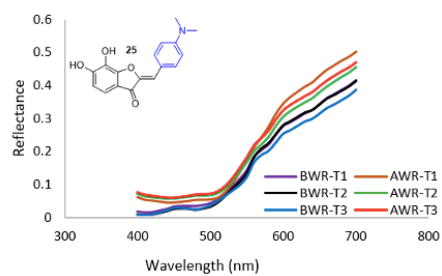


4. Aurone 25 (6,7-diOH-DMAA)

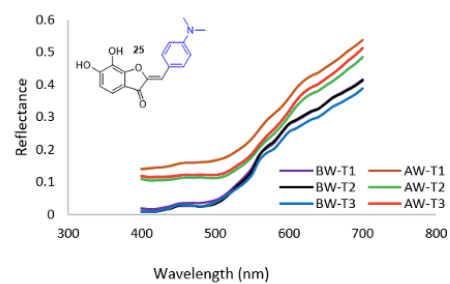
a. Aurone 25: Reflectance: Before and after dry rub



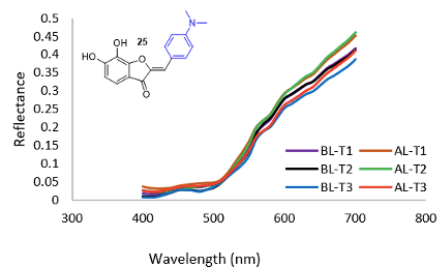
b. Aurone 25: Reflectance: Before and after wet rub



c. Aurone 25: Reflectance: Before and after wash



d. Aurone 25: Reflectance: Before and after light

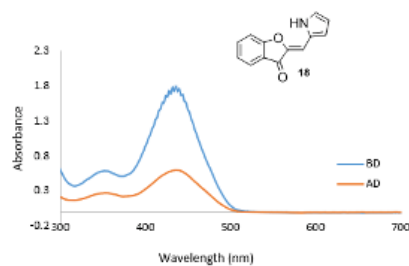


APPENDIX - D

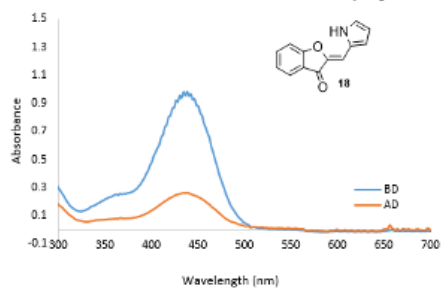
Preliminary dyeing study: UV-Vis absorption of aurone 18-20

(before and after dyeing) - Chapter II

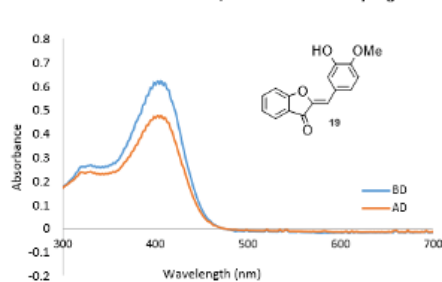
a. Aurone 18: Undiluted ChCl/U: Before and after dyeing



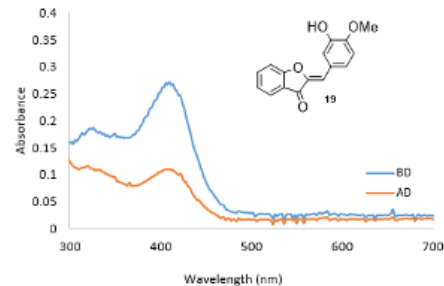
b. Aurone 18: Diluted ChCl/U: Before and after dyeing



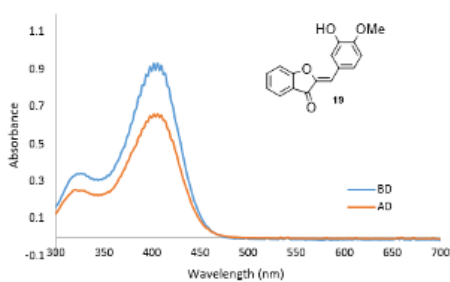
a. Aurone 19: Undiluted ChCl/U: Before and after dyeing



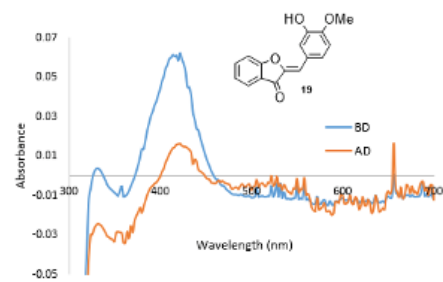
b. Aurone 19: Diluted ChCl/U: Before and after dyeing



a. Aurone 19: Undiluted ChCl/OA: Before and after dyeing



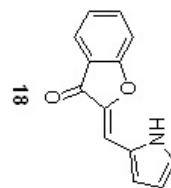
b. Aurone 19: Diluted ChCl/OA: Before and after dyeing



APPENDIX – E

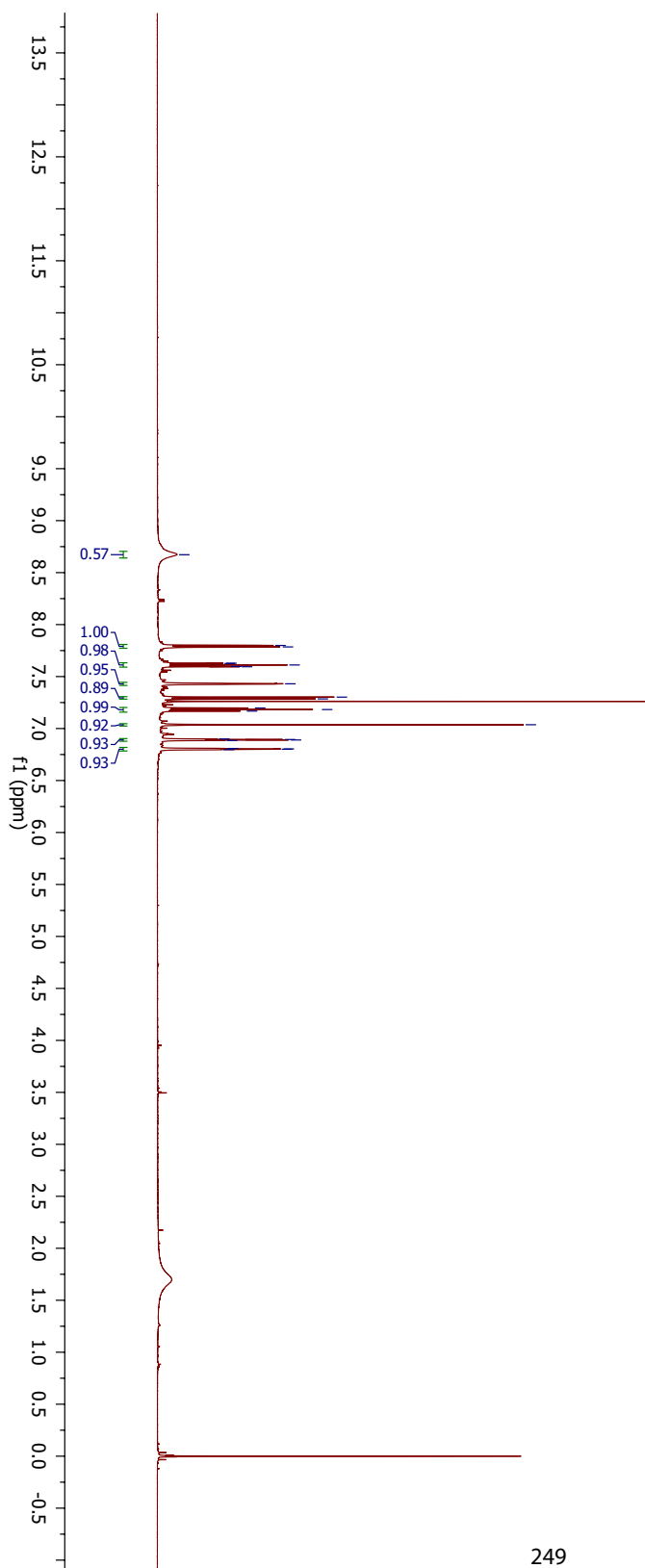
NMR Spectra

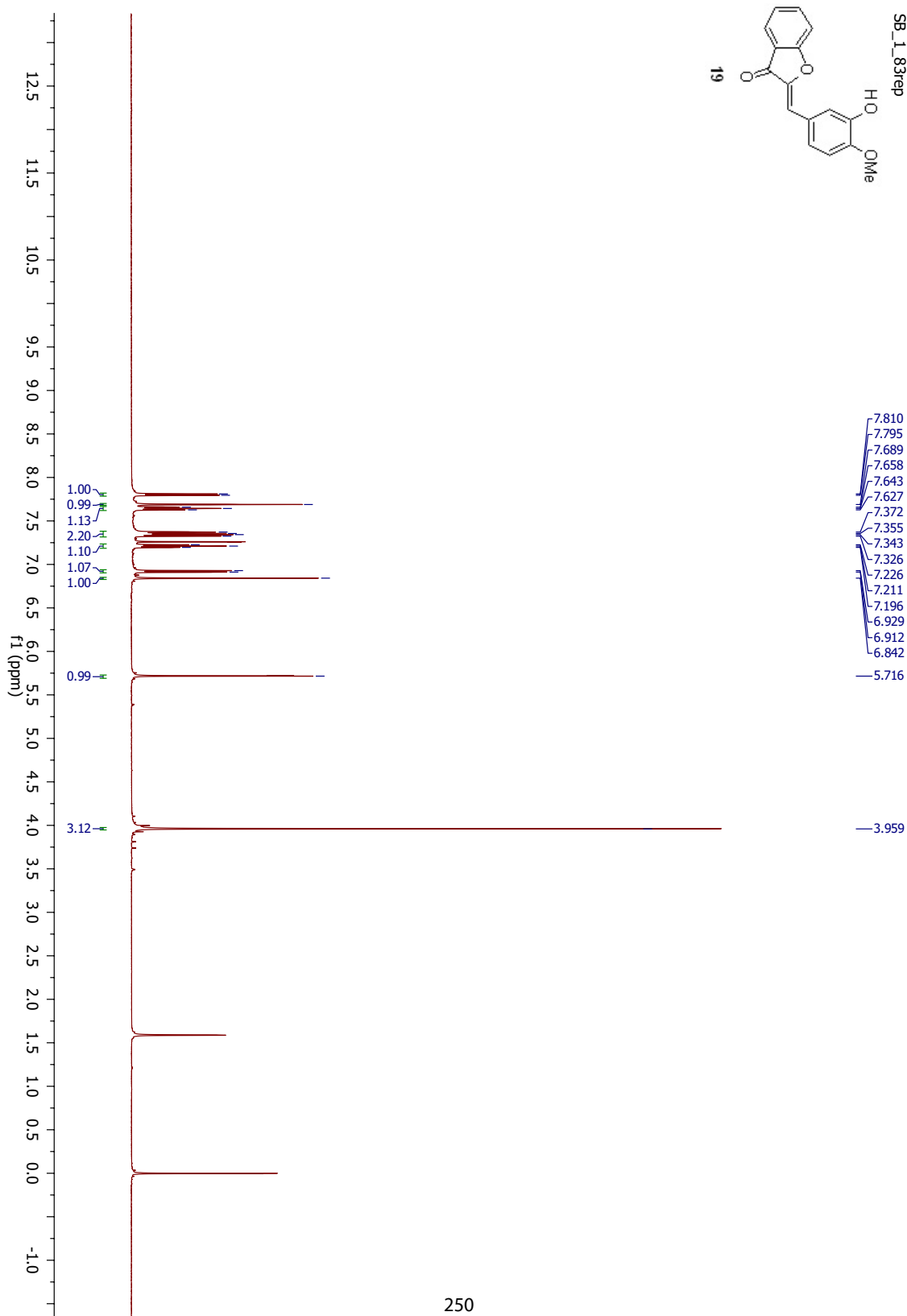
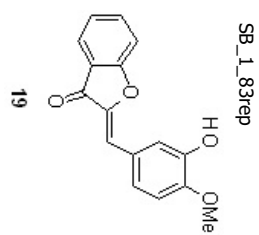
SB-1-74



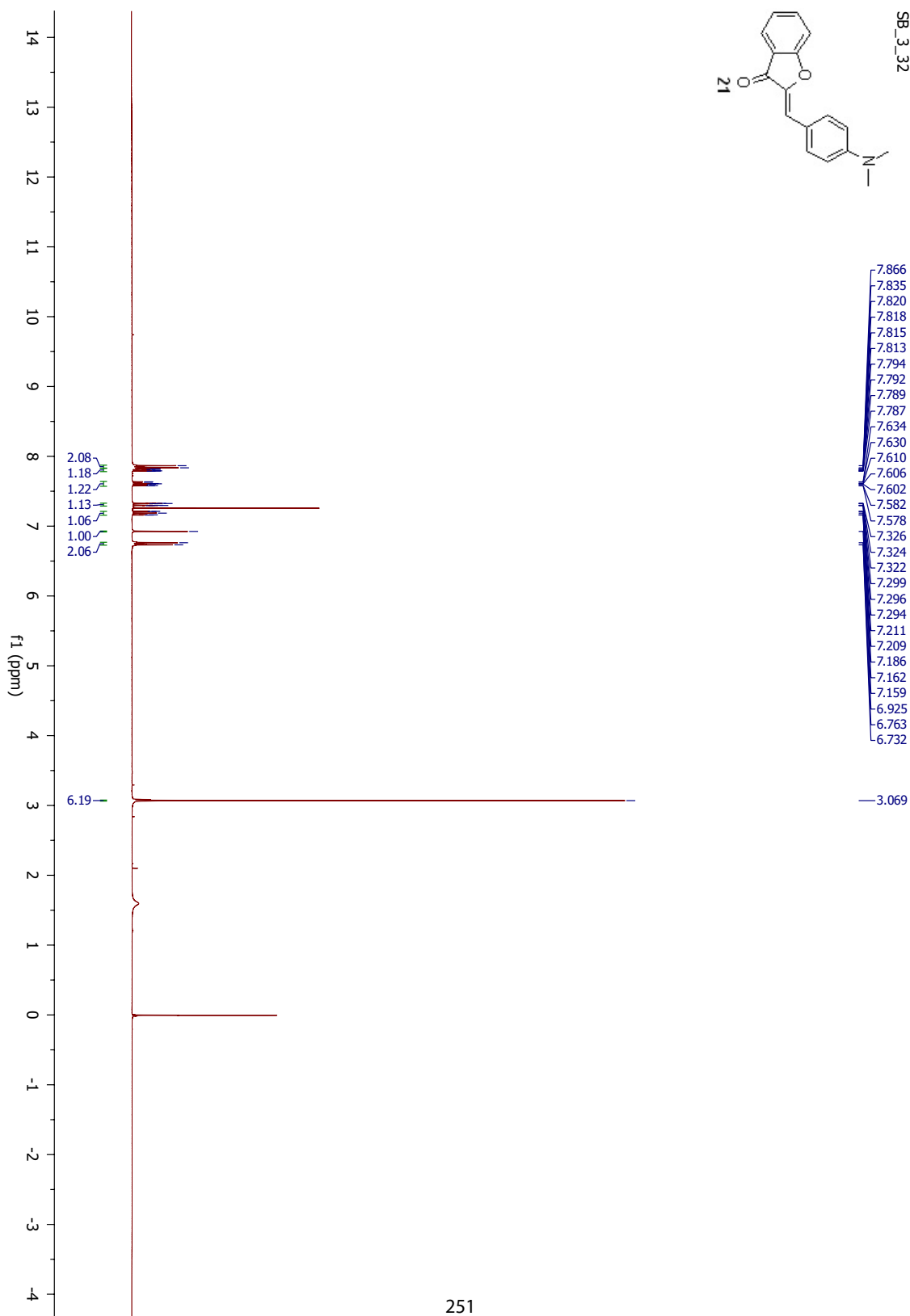
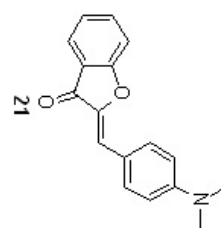
18

8.672
7.799
7.785
7.628
7.626
7.611
7.597
7.594
7.430
7.302
7.285
7.198
7.183
7.168
7.037
6.899
6.894
6.890
6.885
6.808
6.804
6.801
6.797

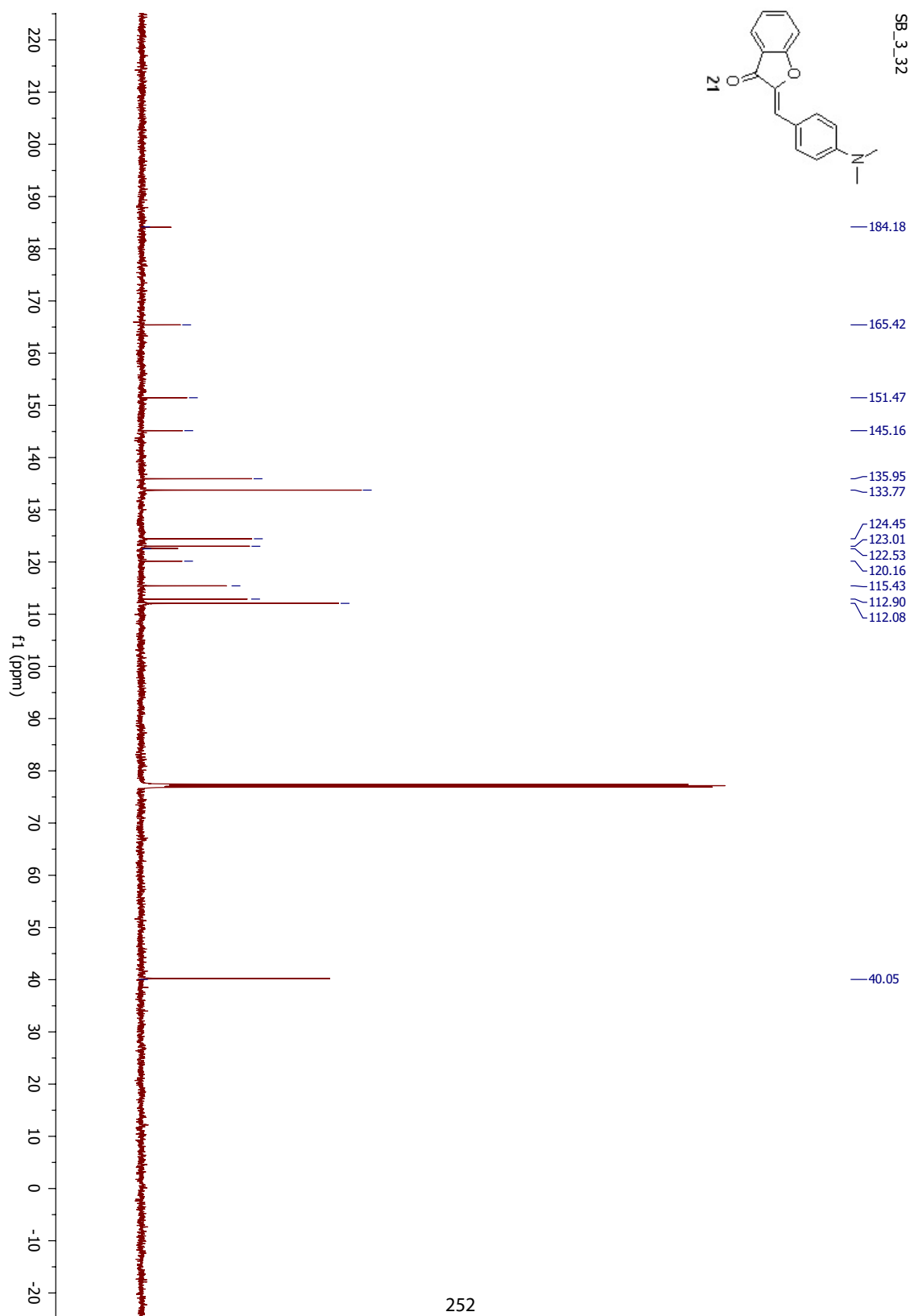
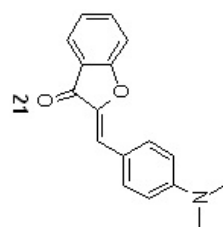


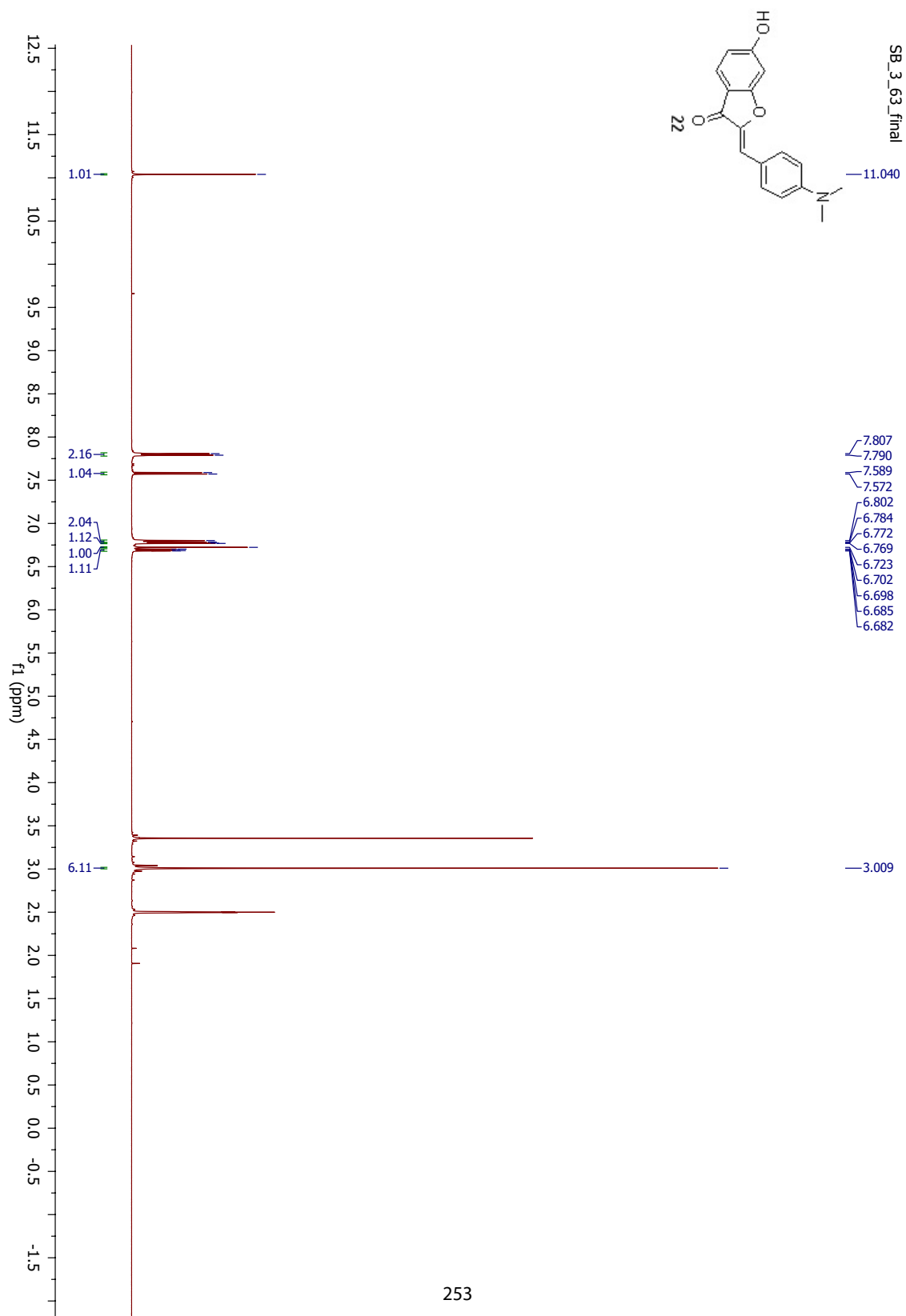


SB_3_32

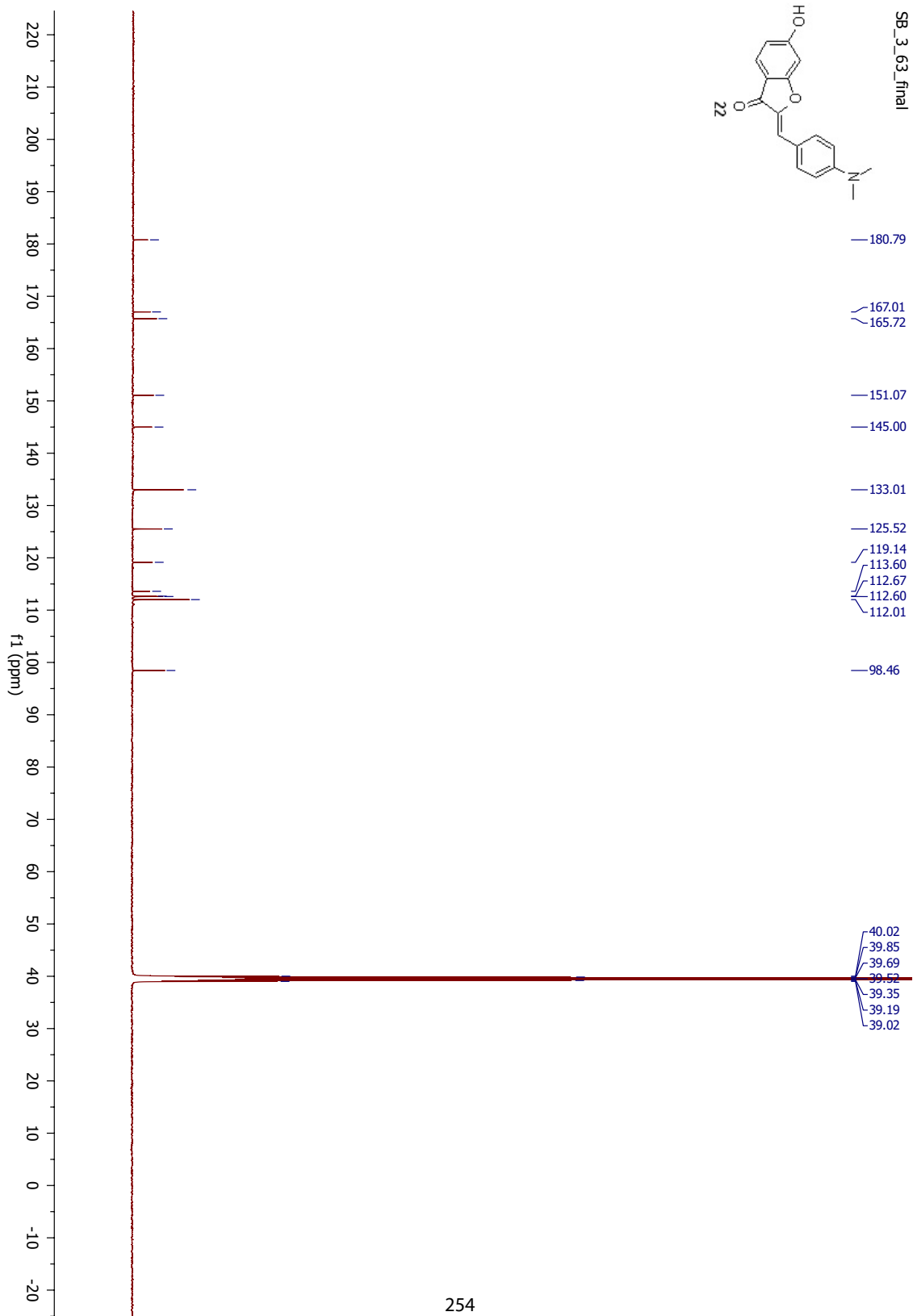
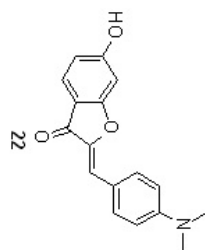


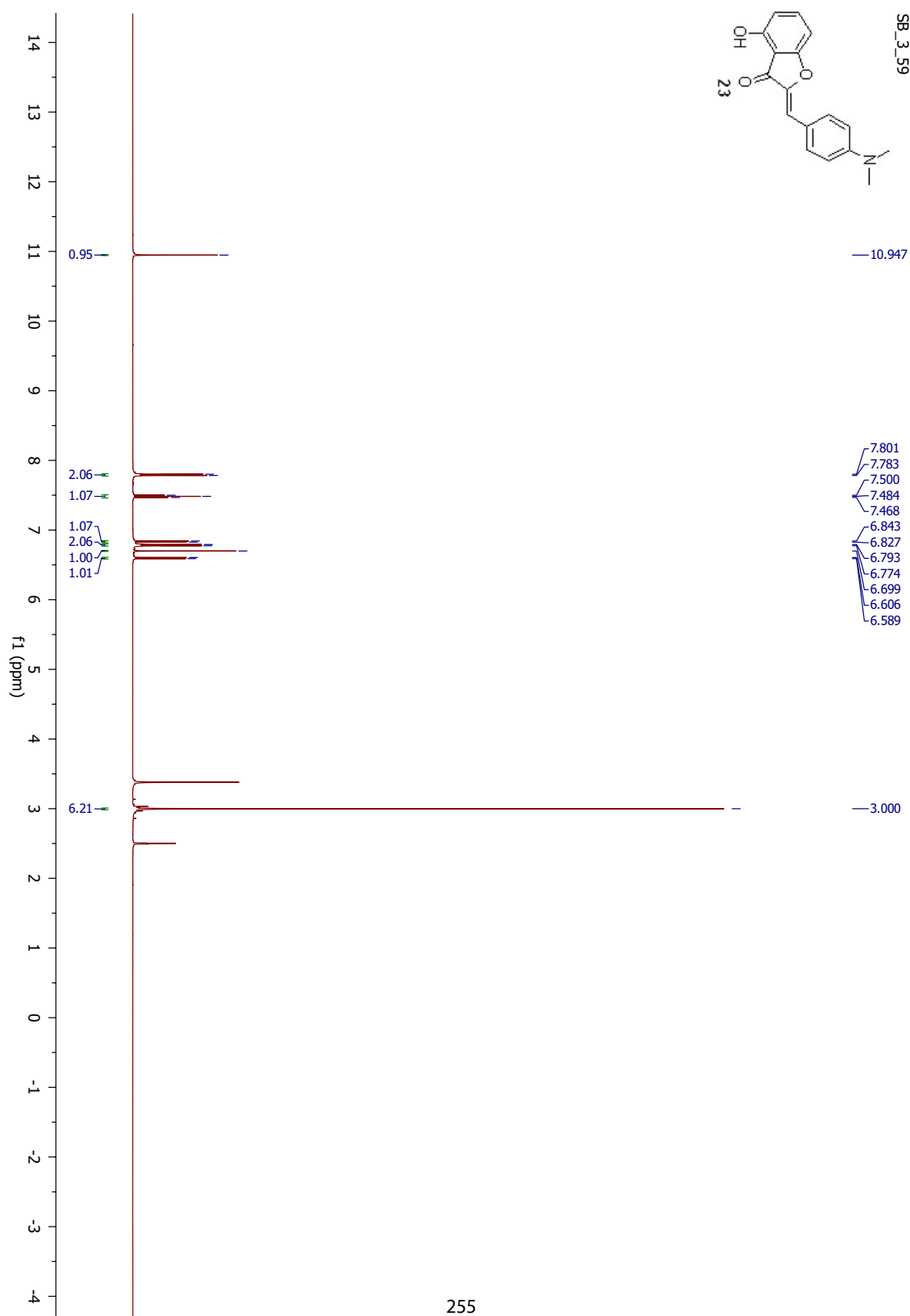
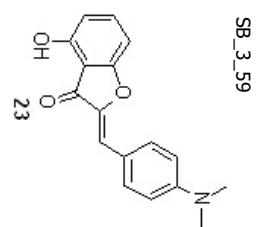
SB_3_32



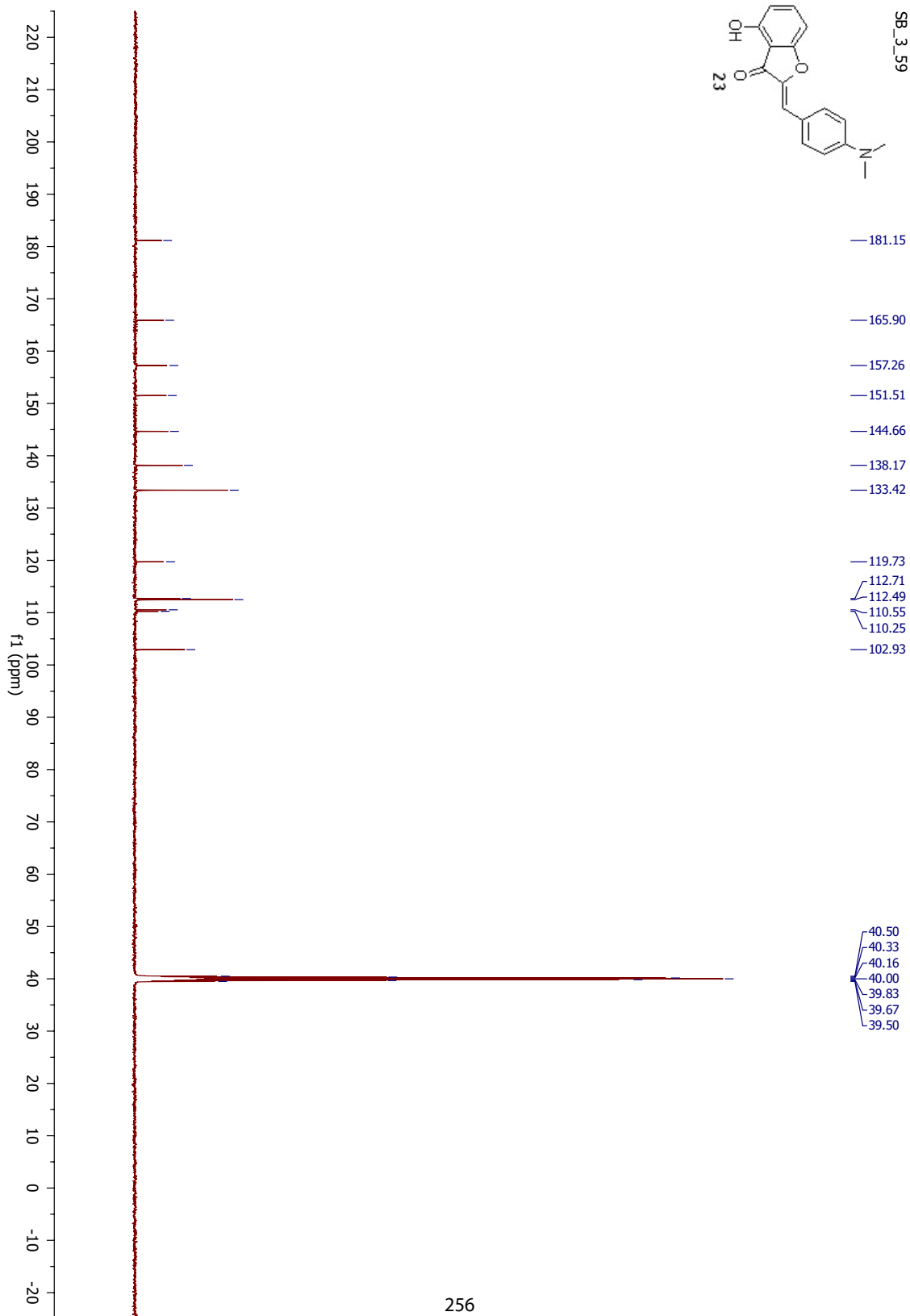
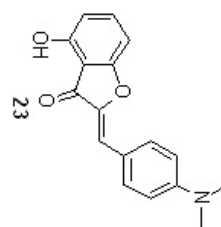


SB_3_63_final

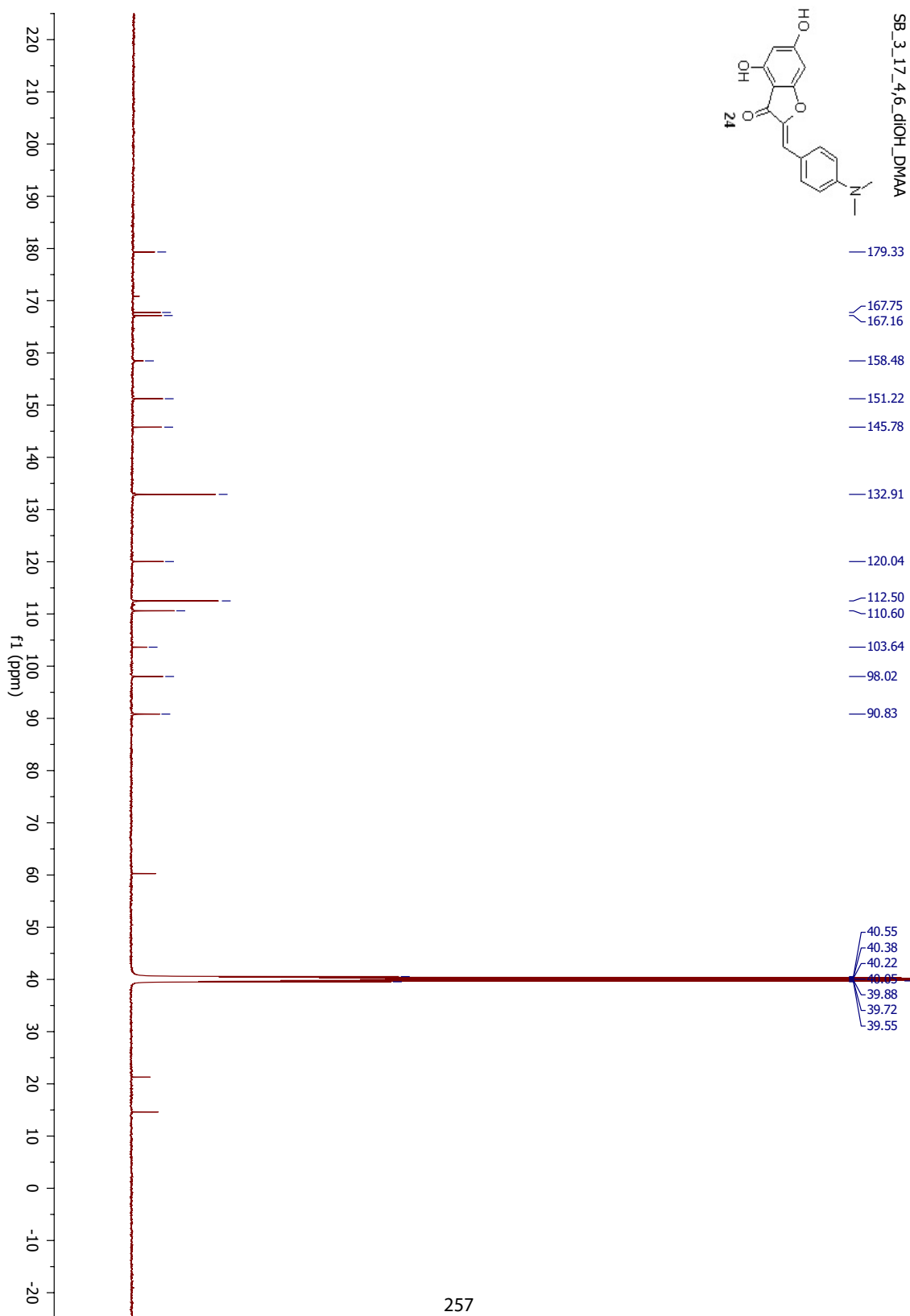
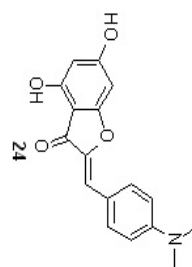




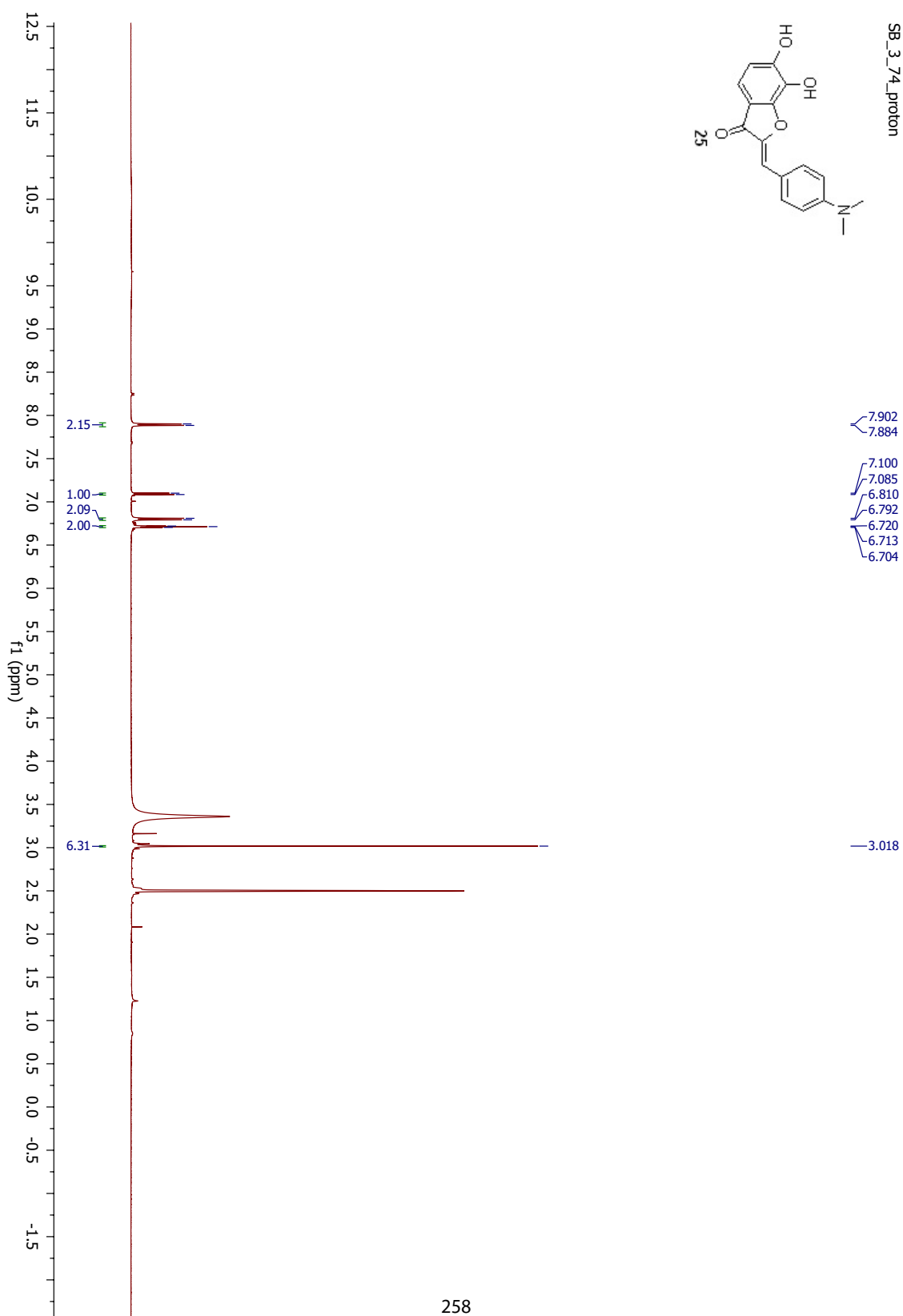
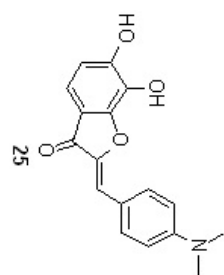
SB_3_59

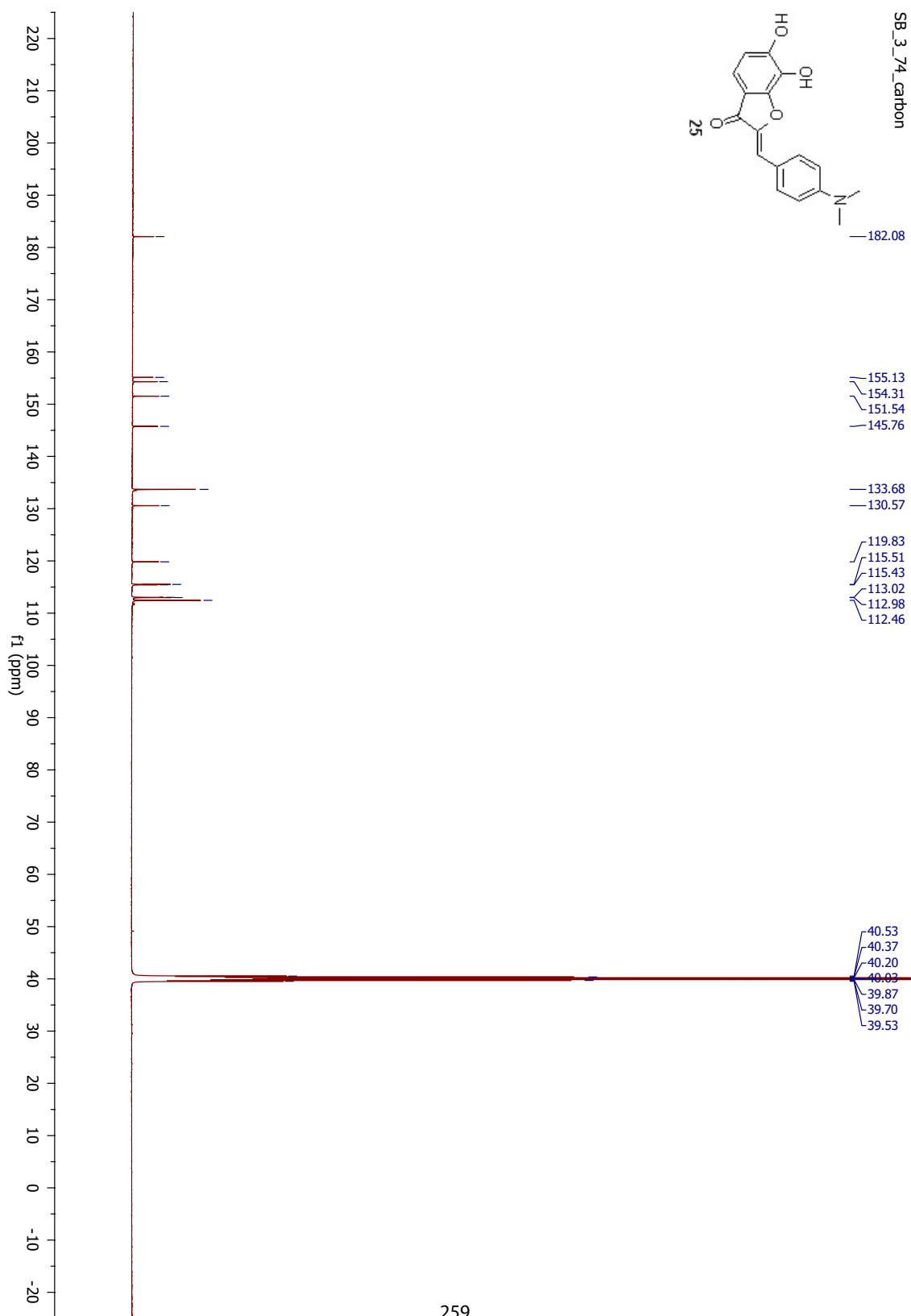


SB_3_17_4,6_diolH_DMAA

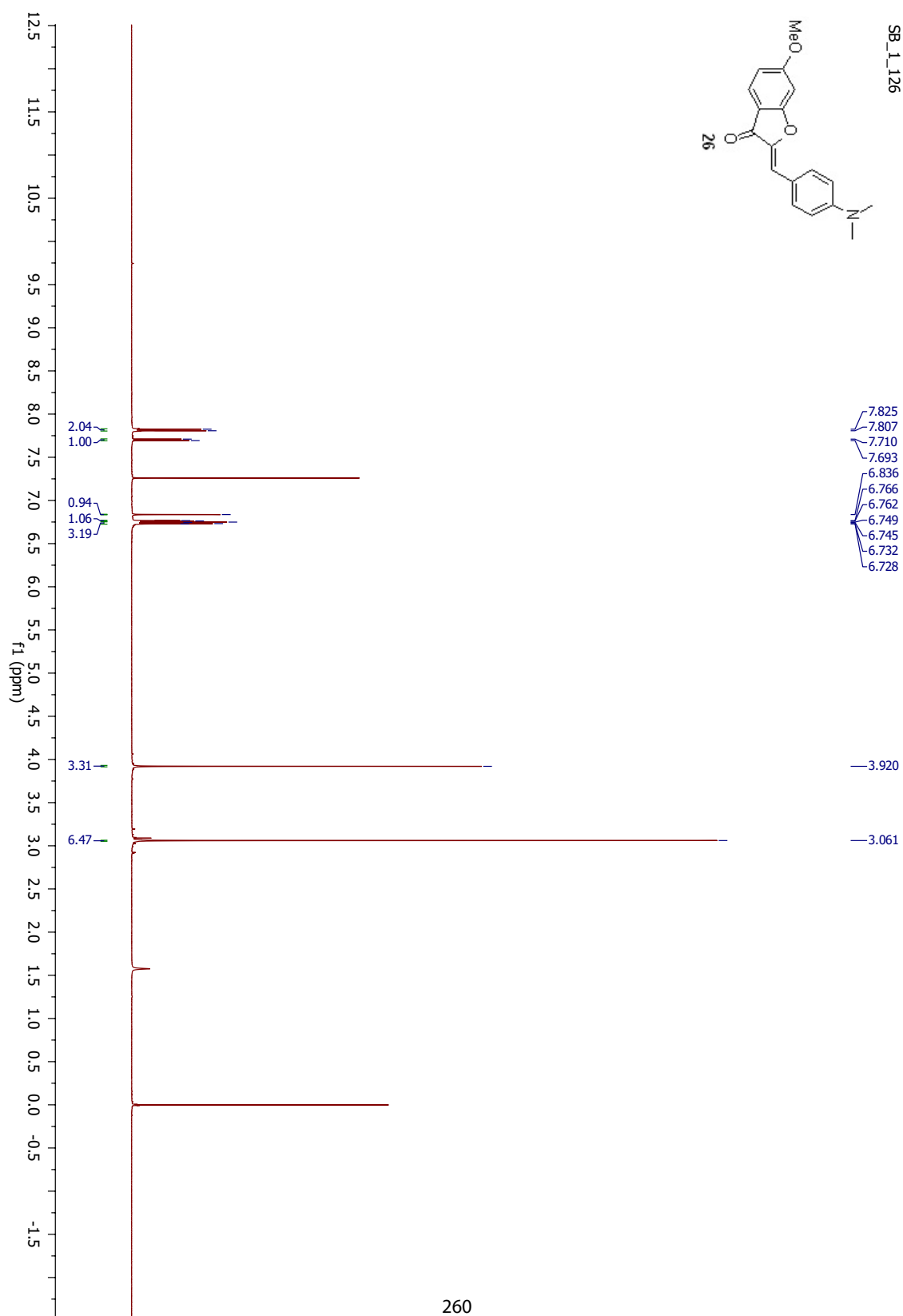
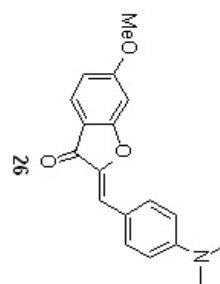


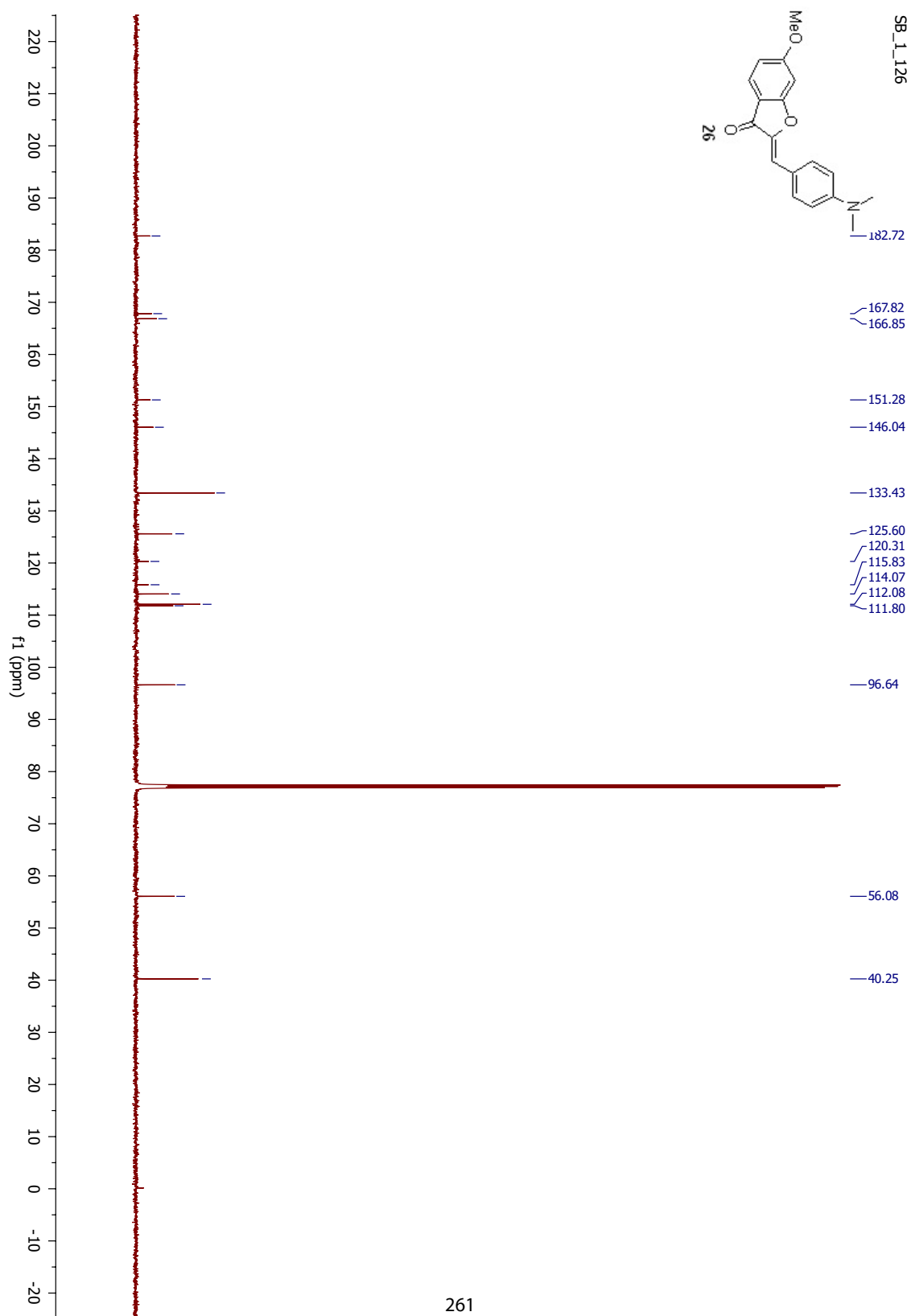
SB_3_74_proton



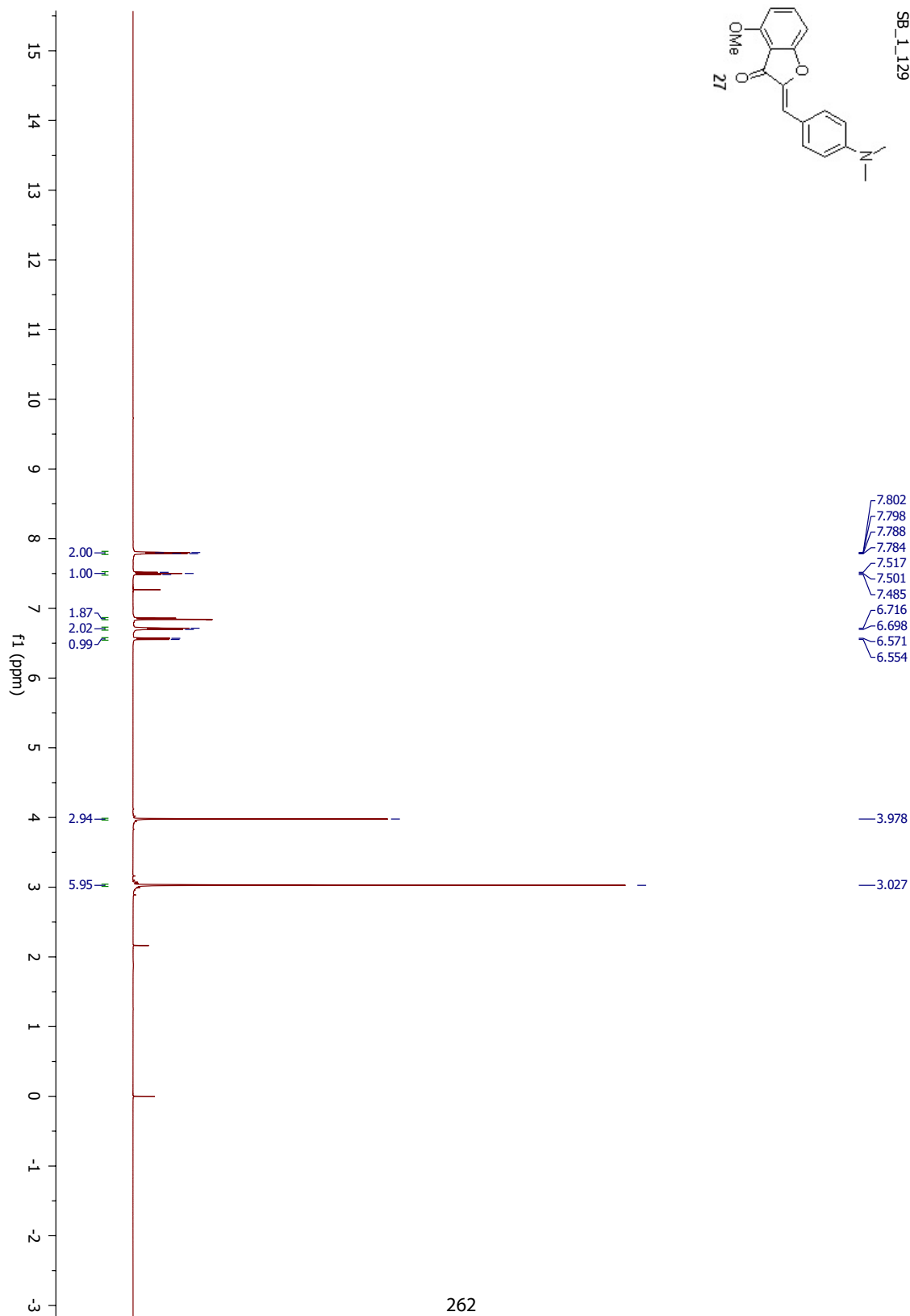
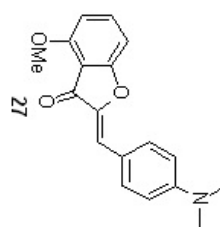


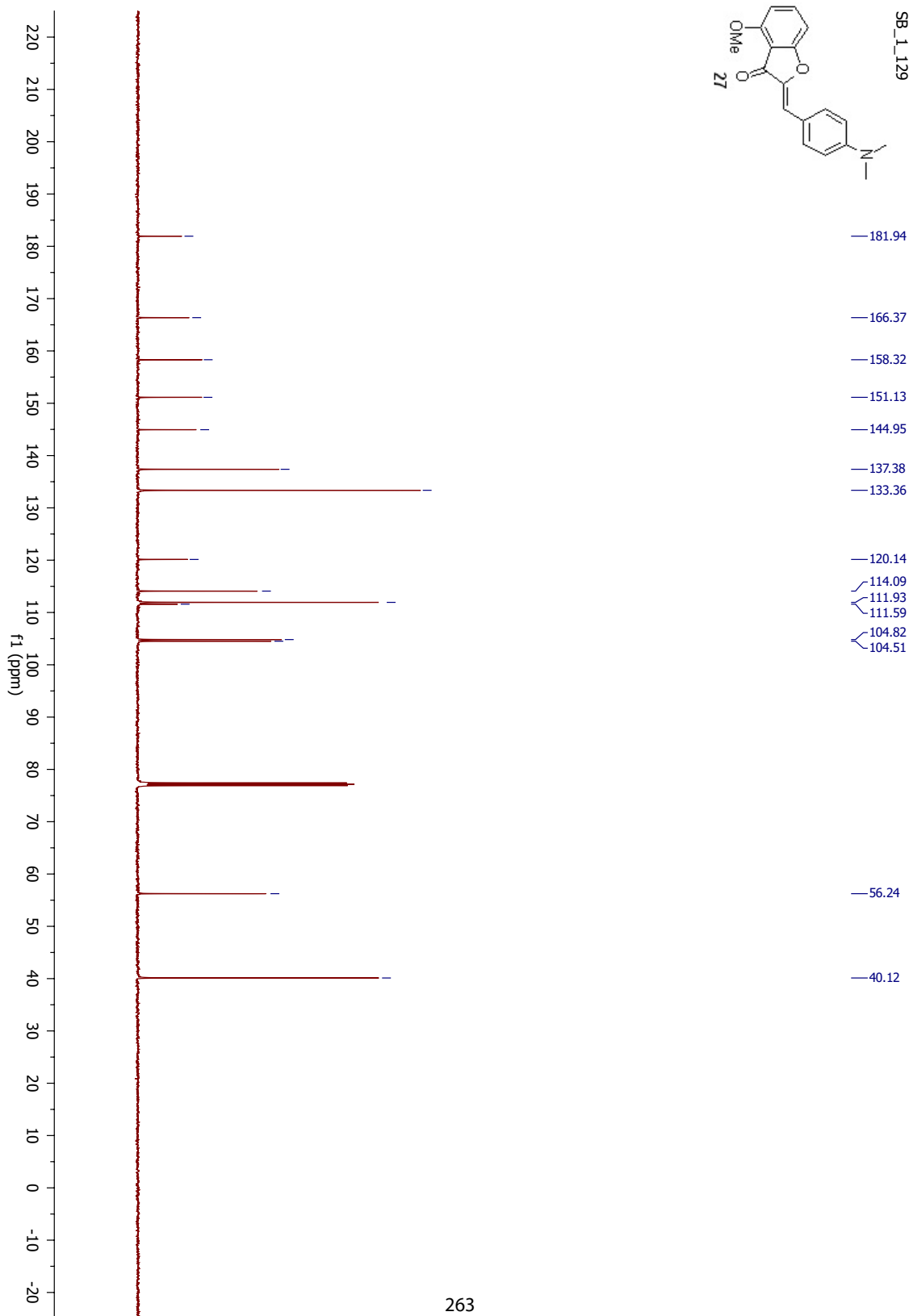
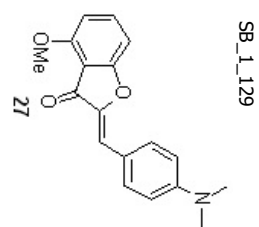
SB_1_126



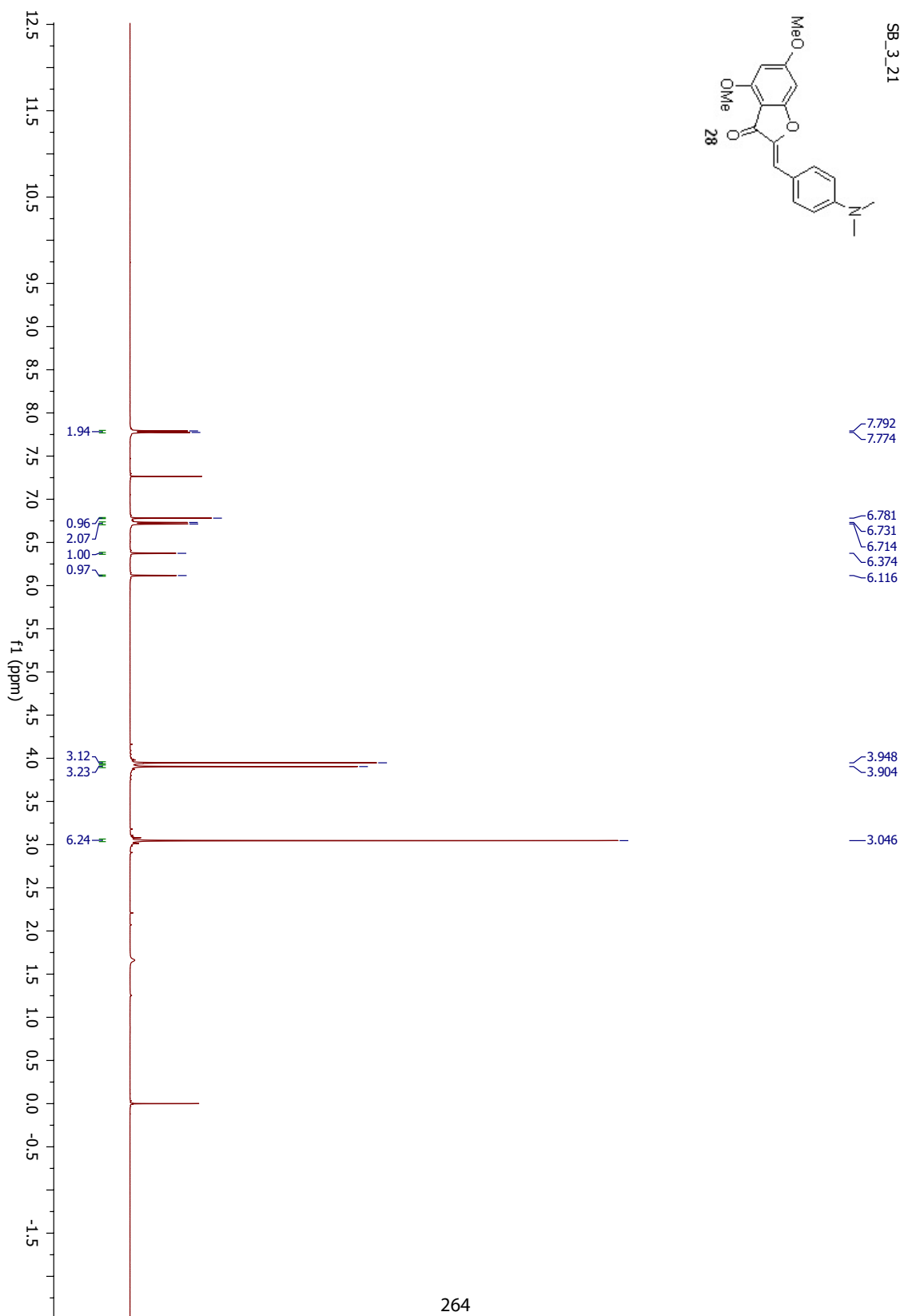
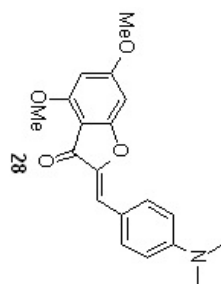


SB_1_129

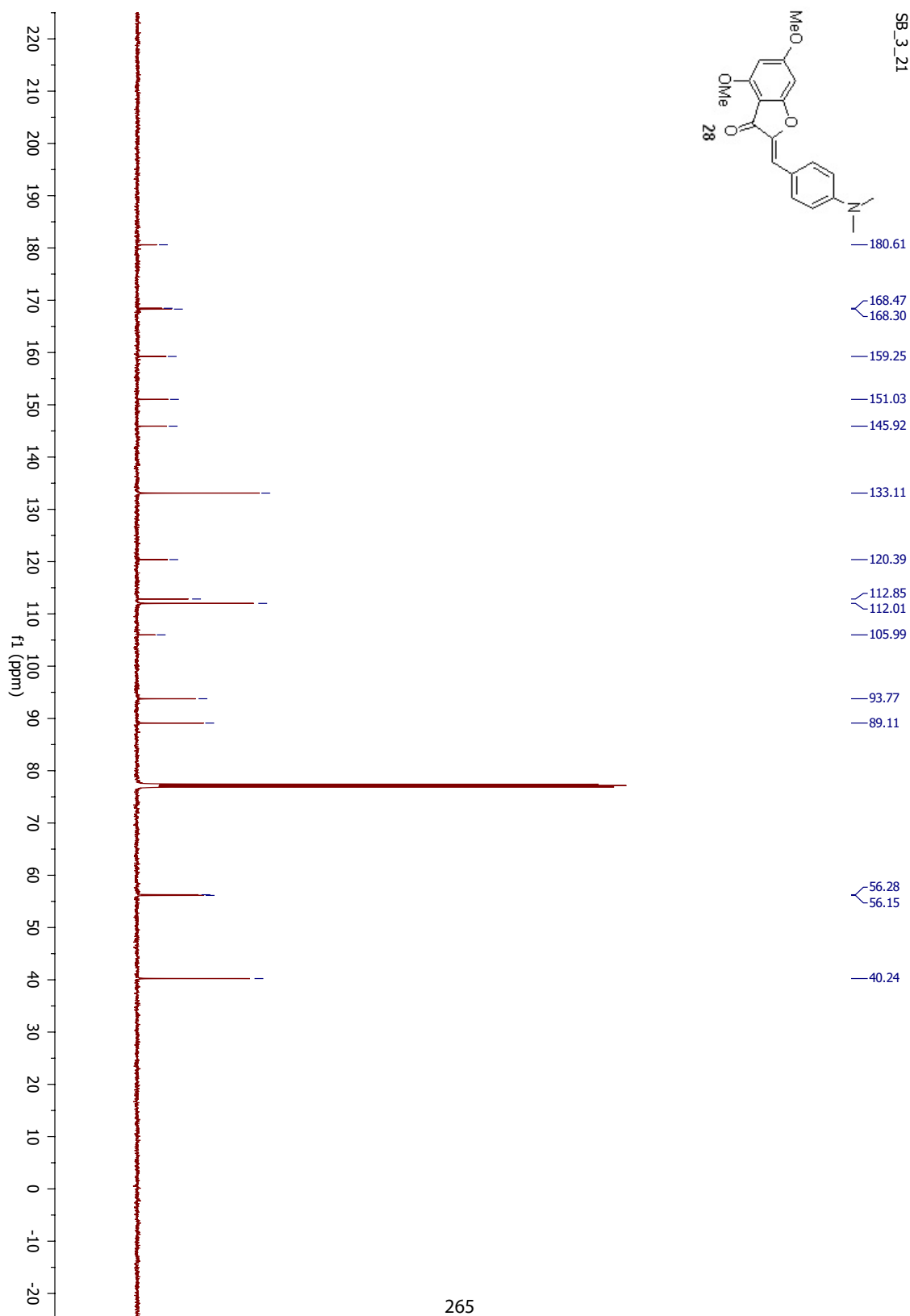
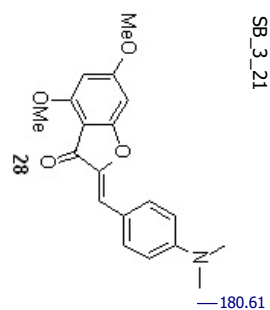




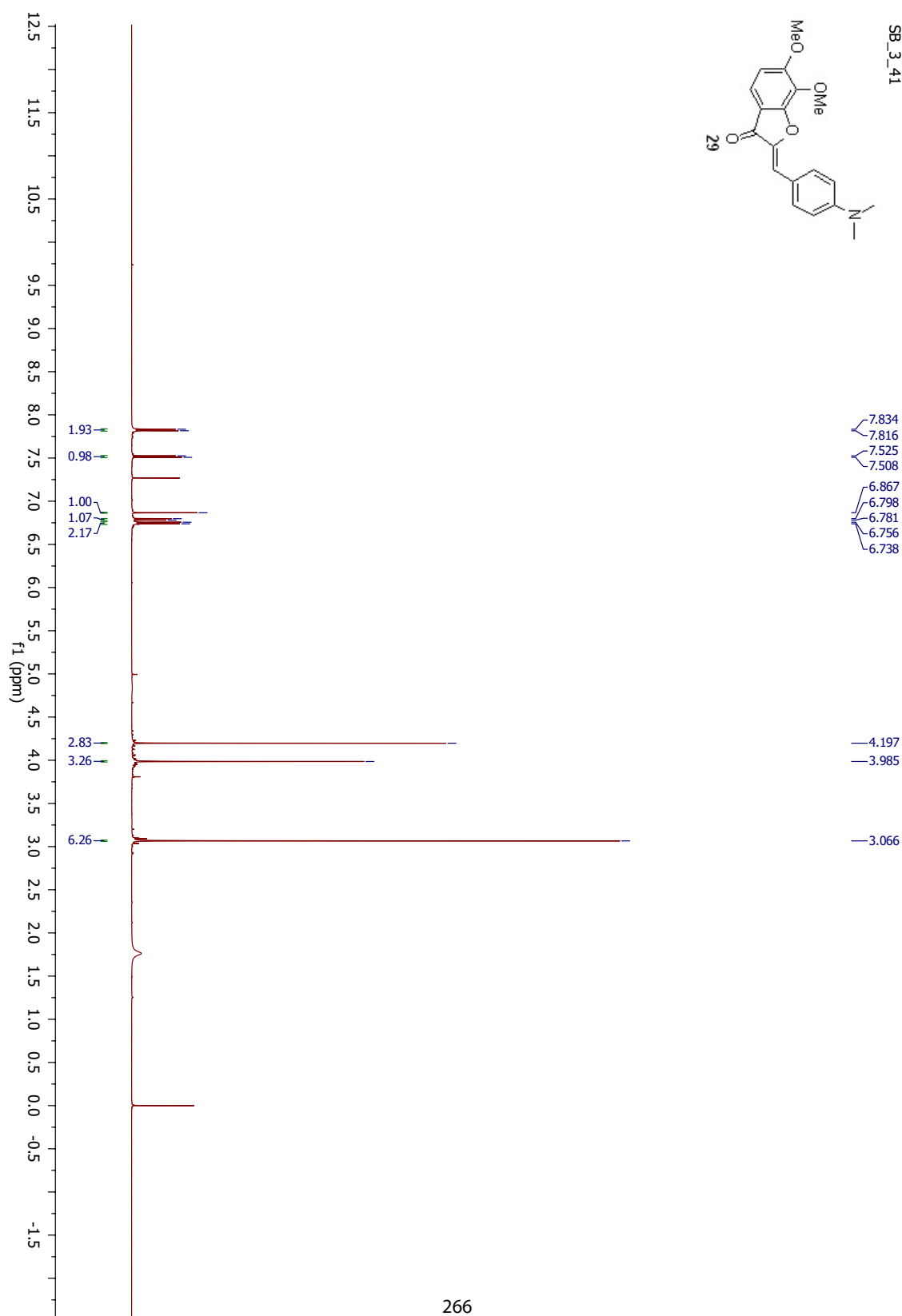
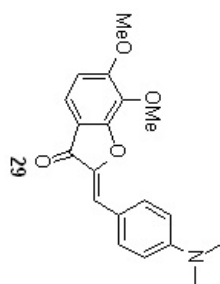
SB_3_21



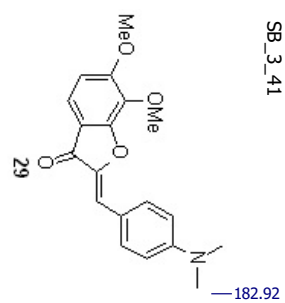
SB_3_21



SB_3_41



SB_3_41



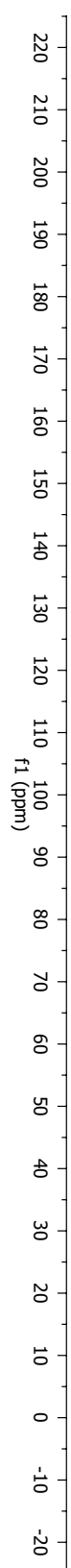
158.14
157.00
151.32
145.62

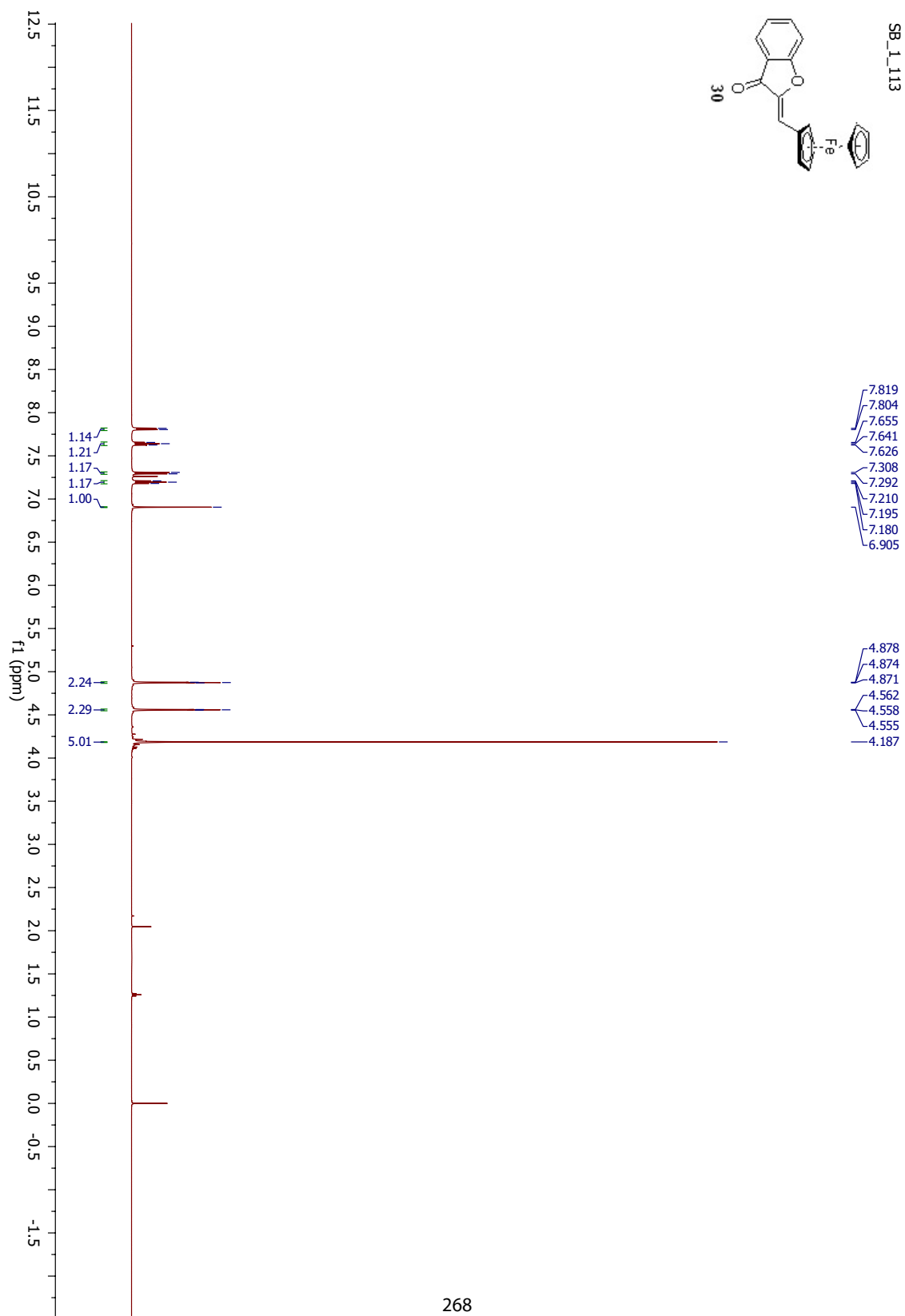
133.95
133.47

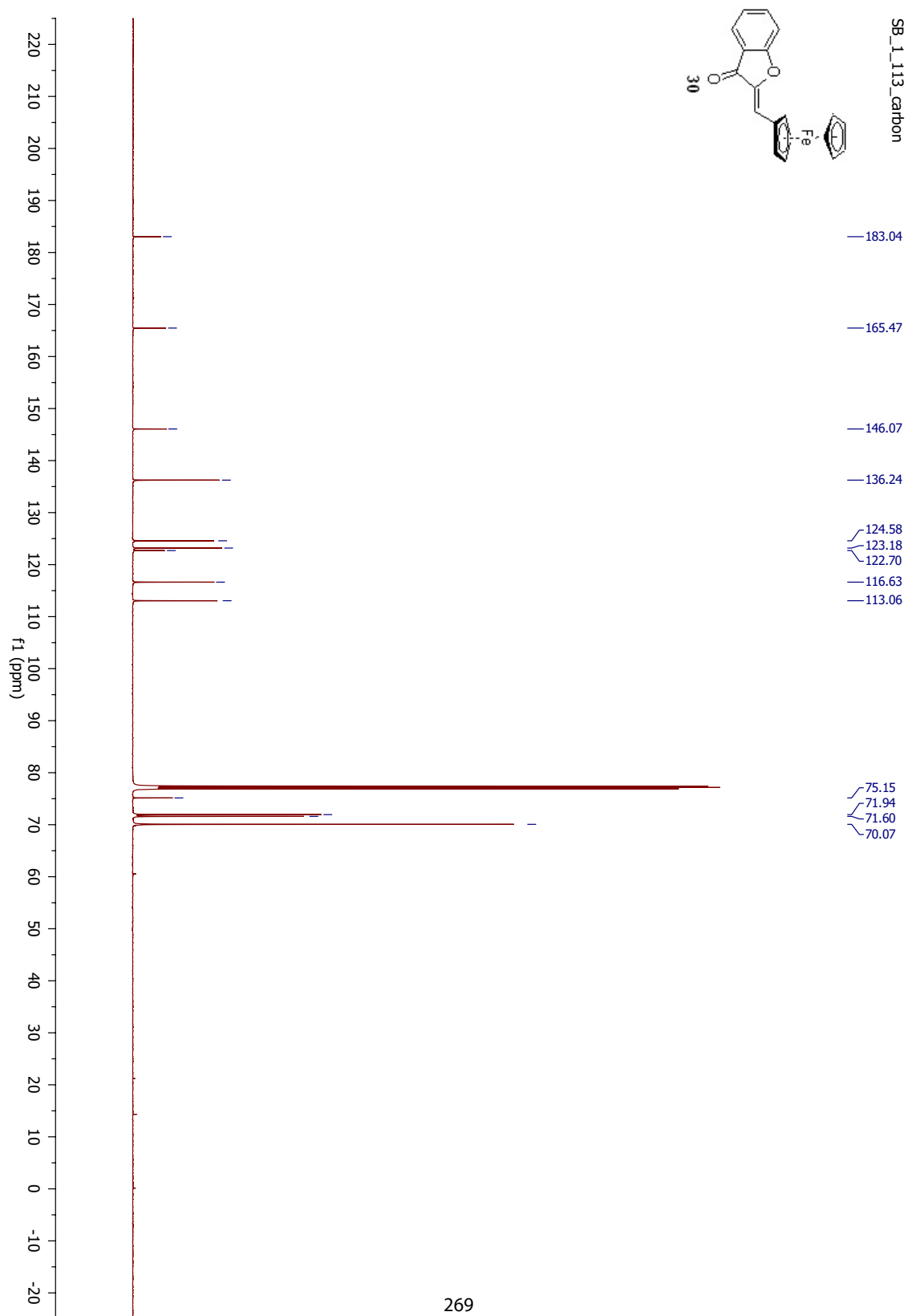
120.02
119.33
117.82
114.52
112.10
107.80

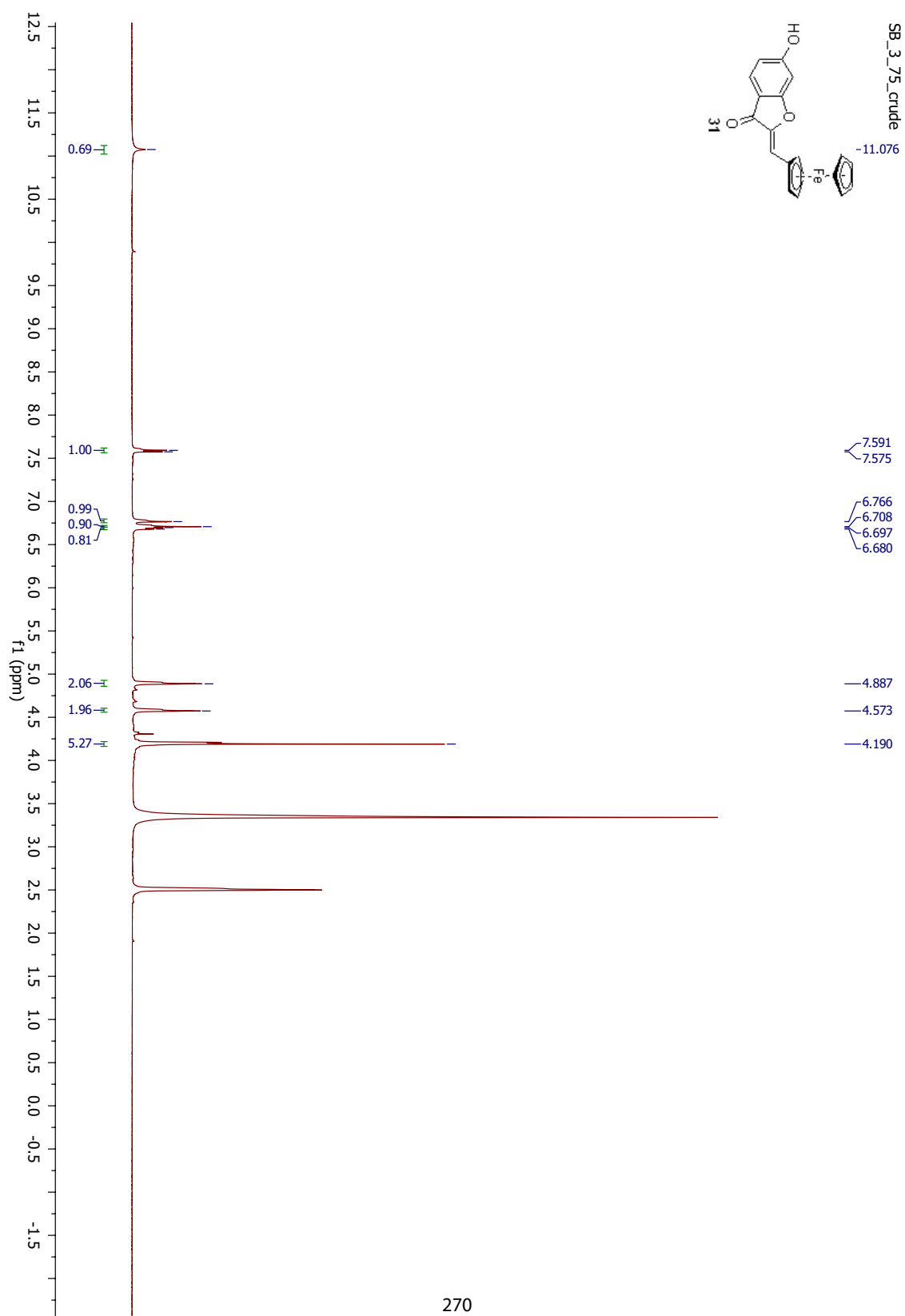
61.20
56.86

40.22

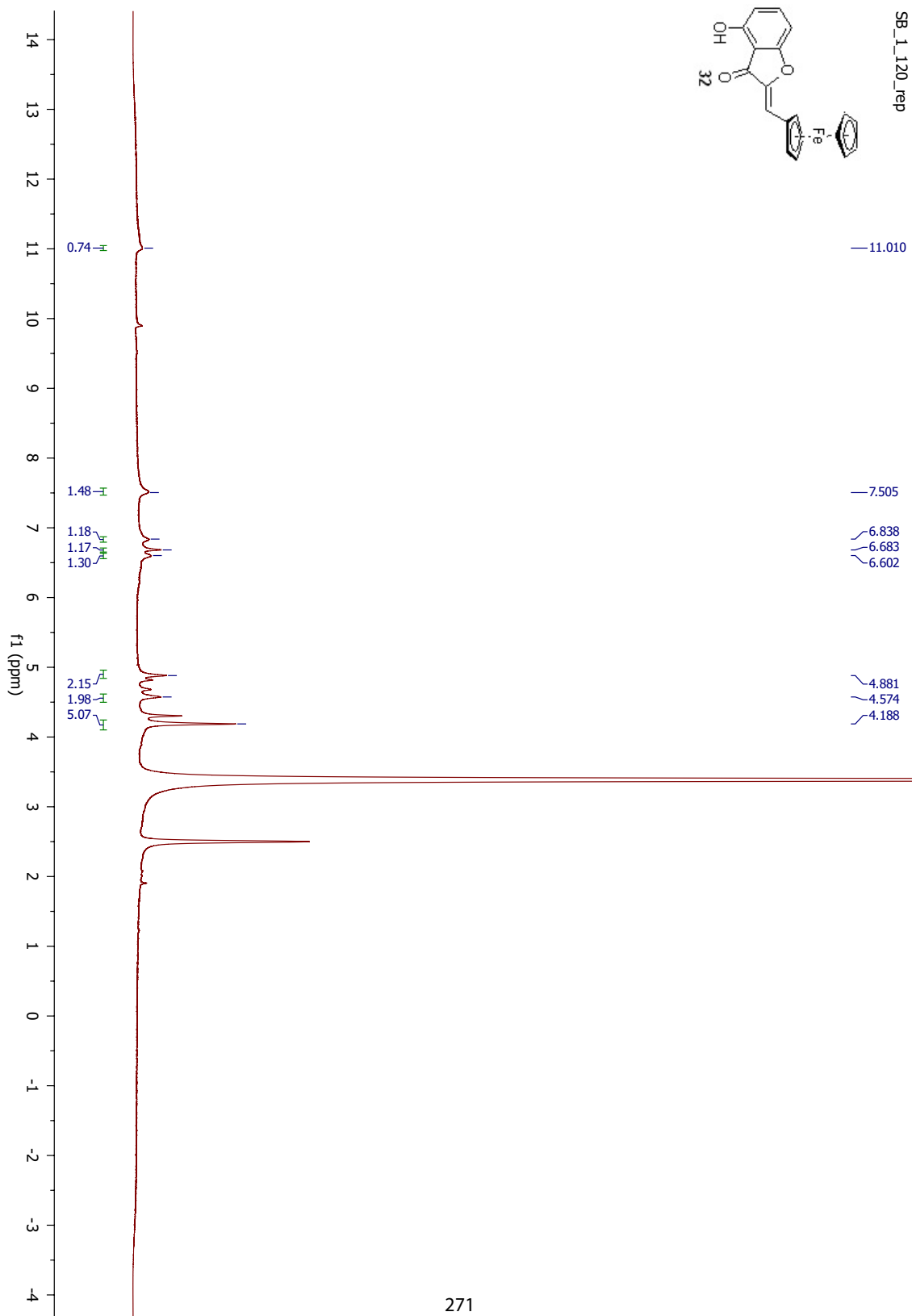
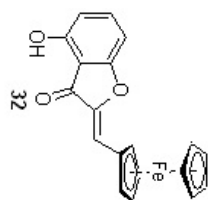




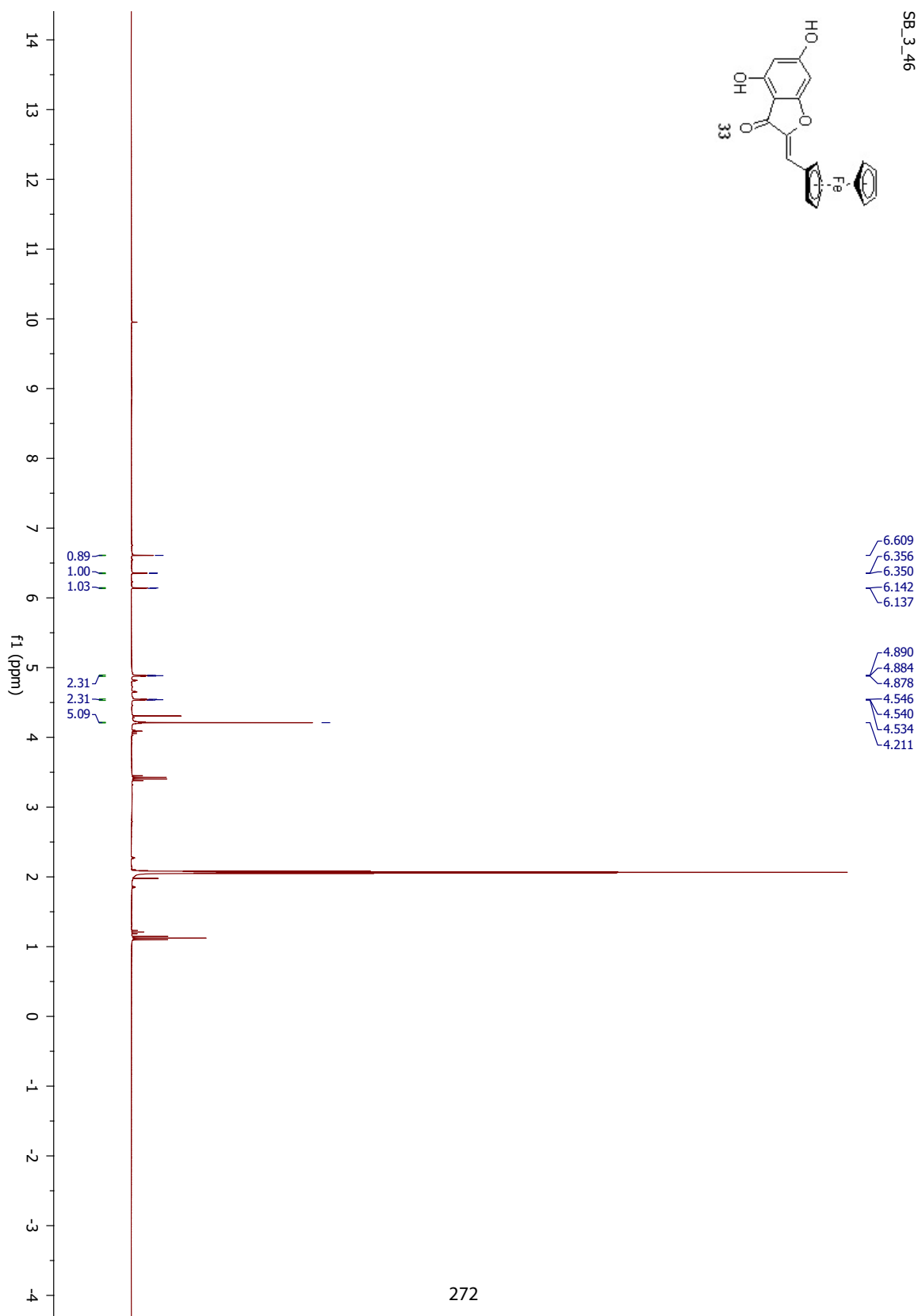
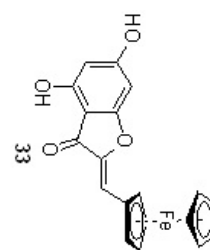




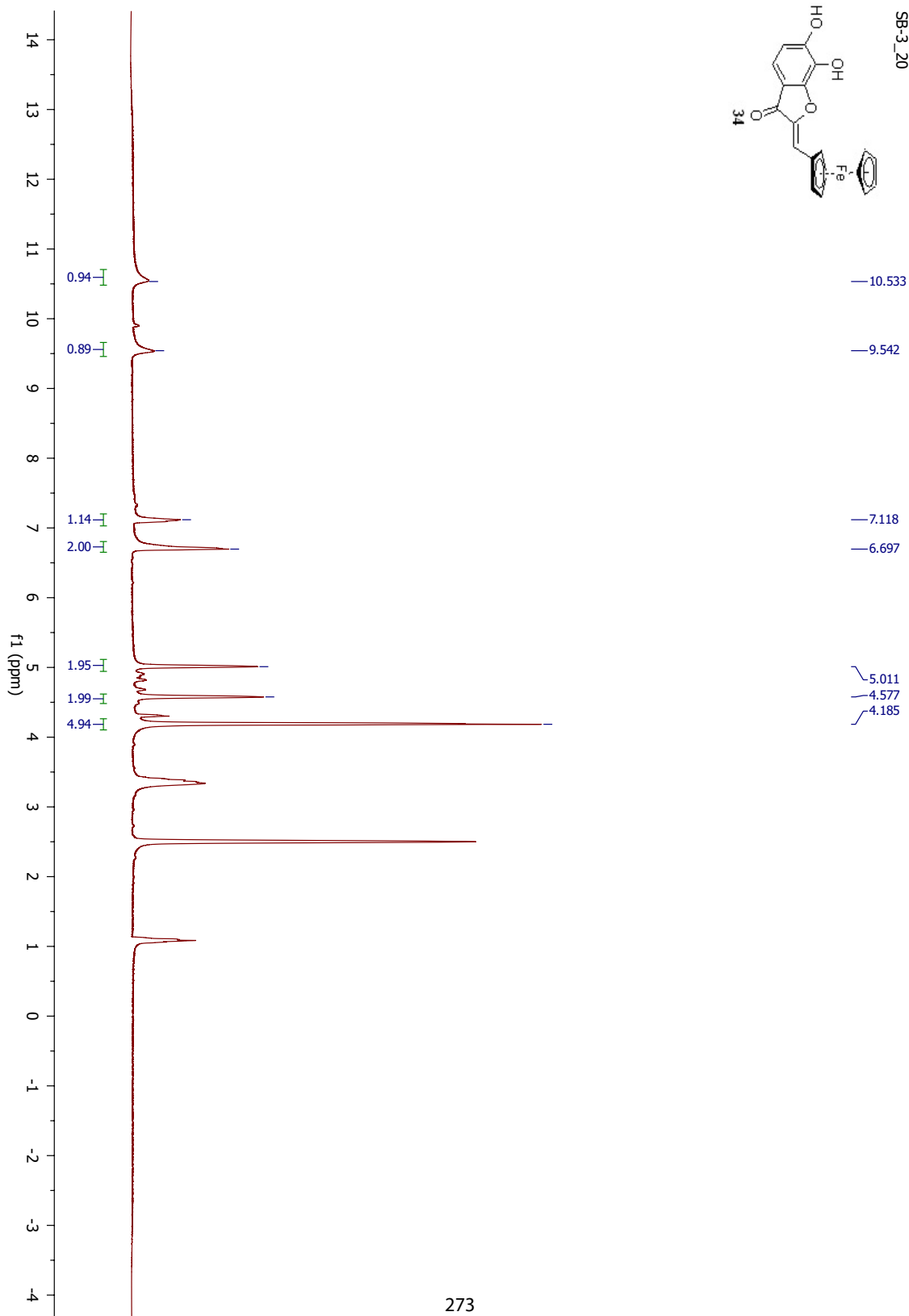
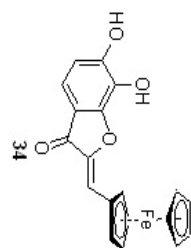
SB_1_120_rep



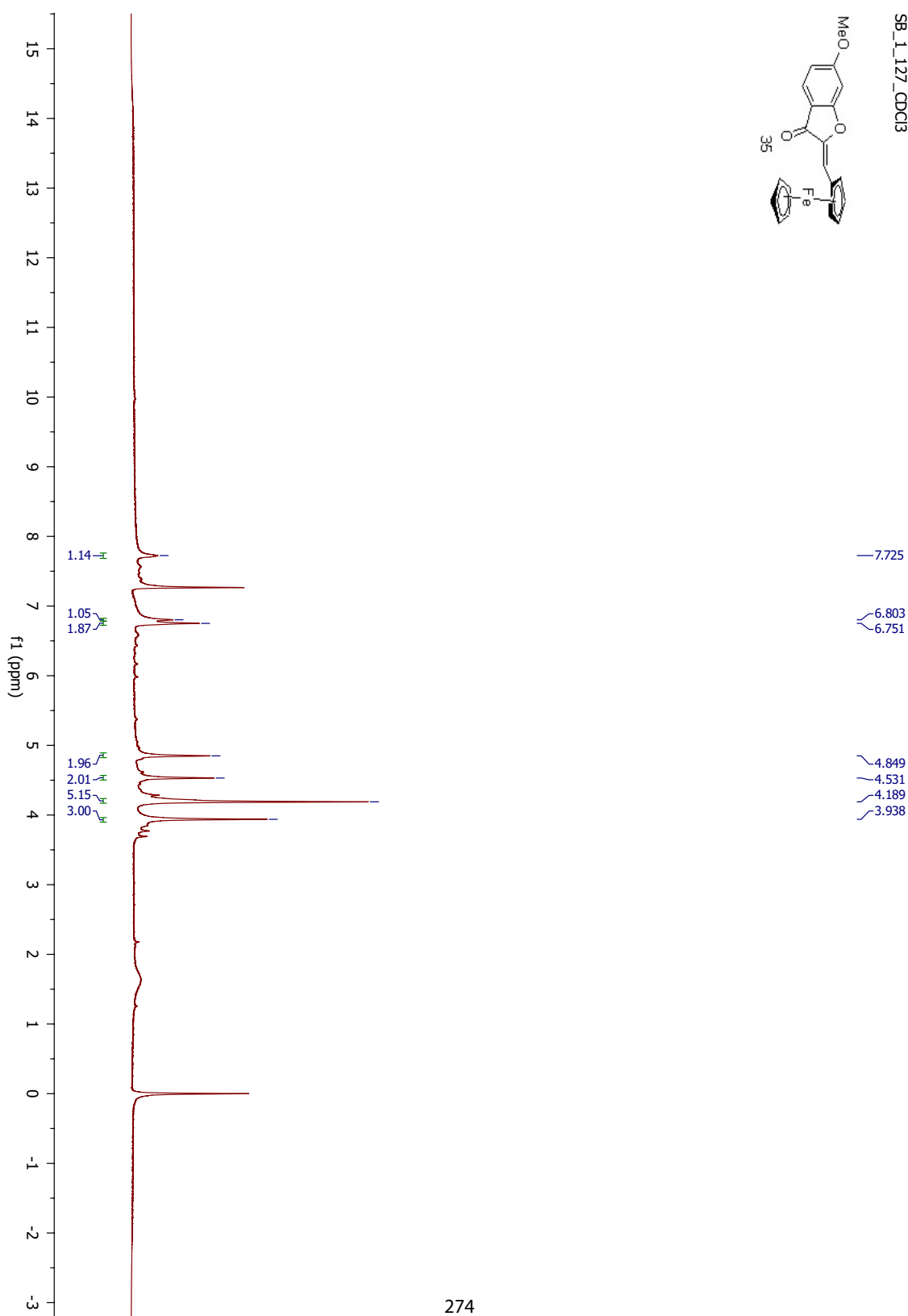
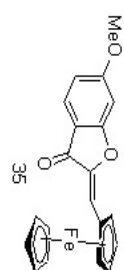
SB_3_46

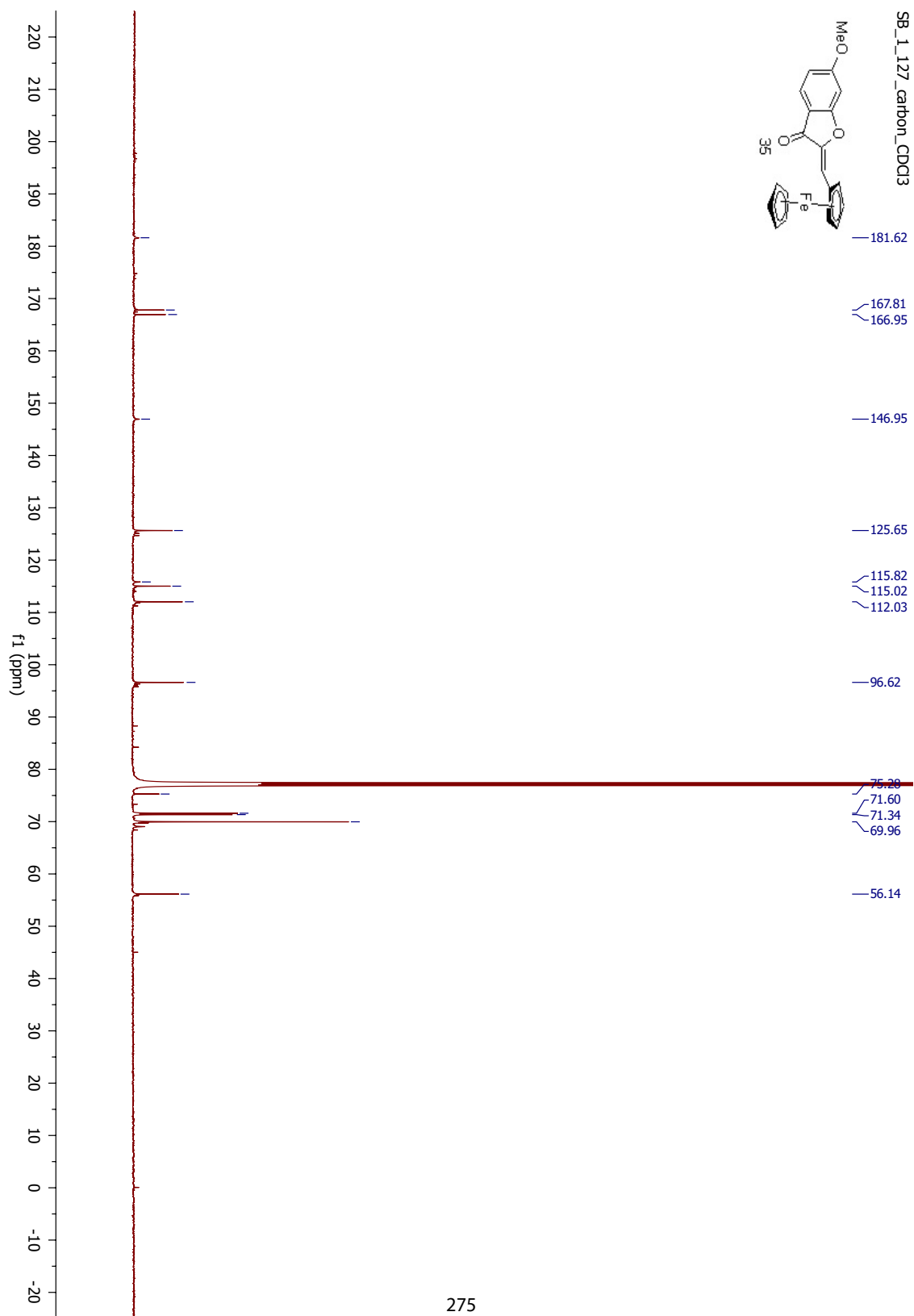


SB-3_20

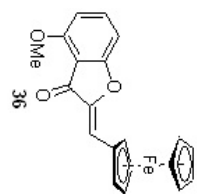


SB_1_127_CDCl3

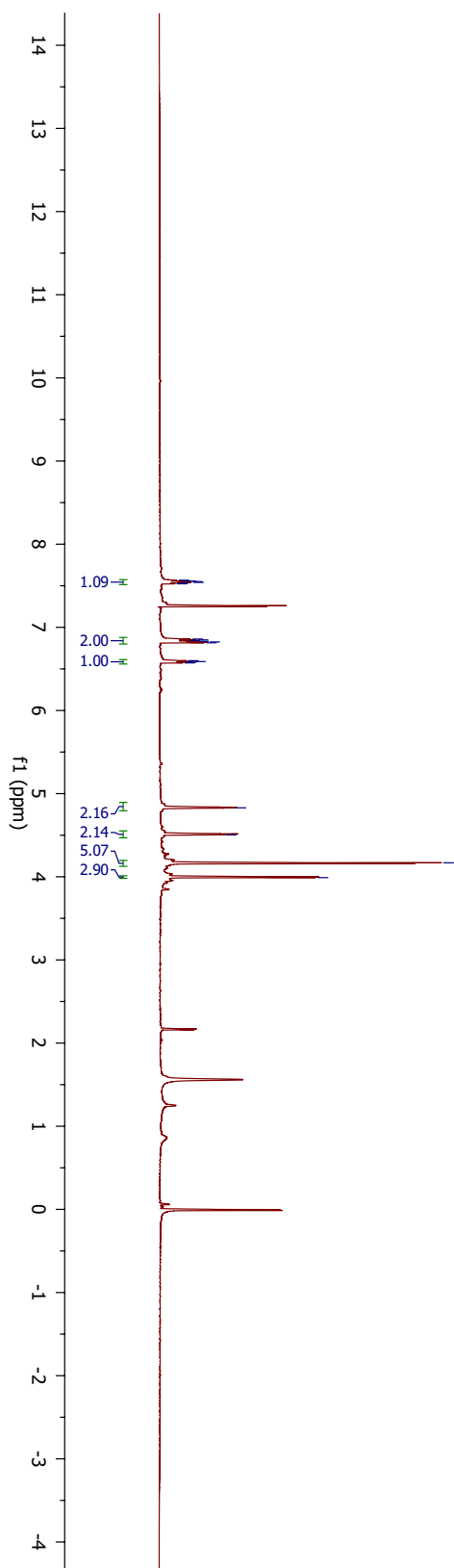




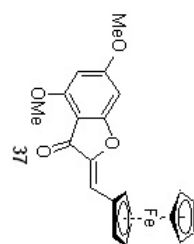
SB_1_131_rep



7.567
7.556
7.551
7.540
7.534
7.524
6.859
6.849
6.843
6.832
6.824
6.814
6.599
6.589
6.582
6.572
4.830
4.506
4.168
3.990

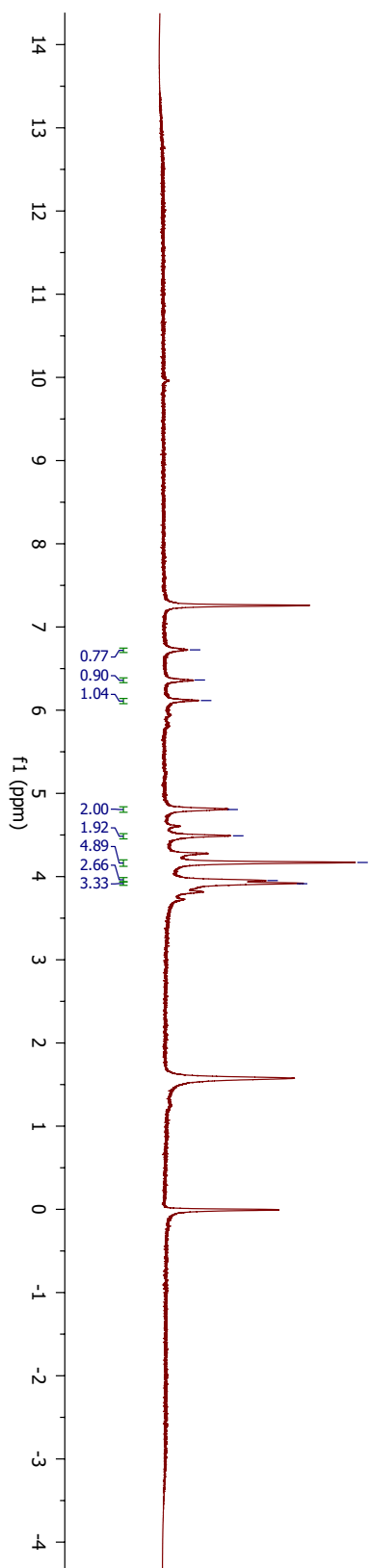


SB_3_34

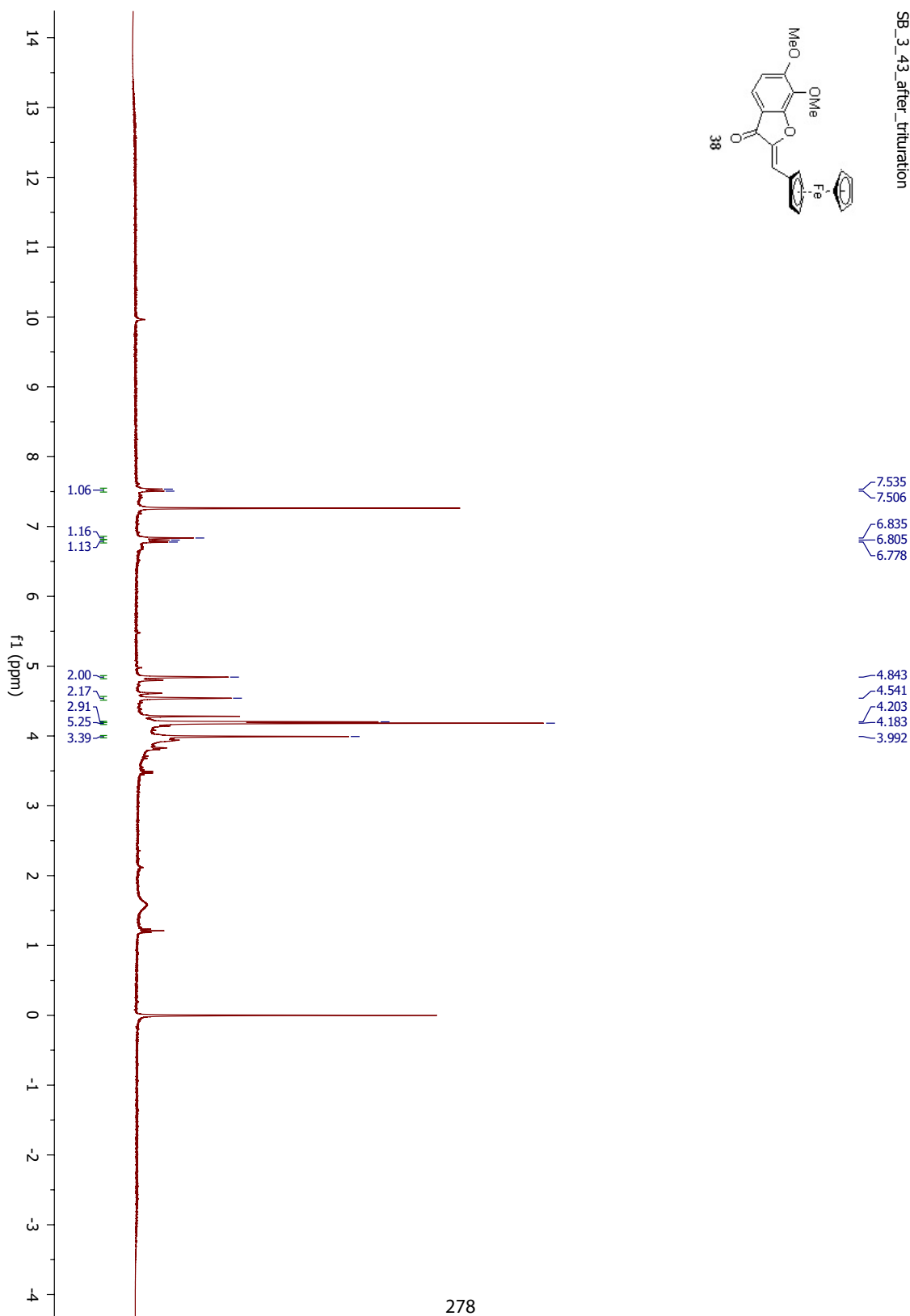
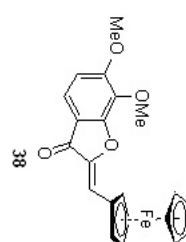


6.725
6.363
6.116

4.806
4.490
4.169
3.952
3.914



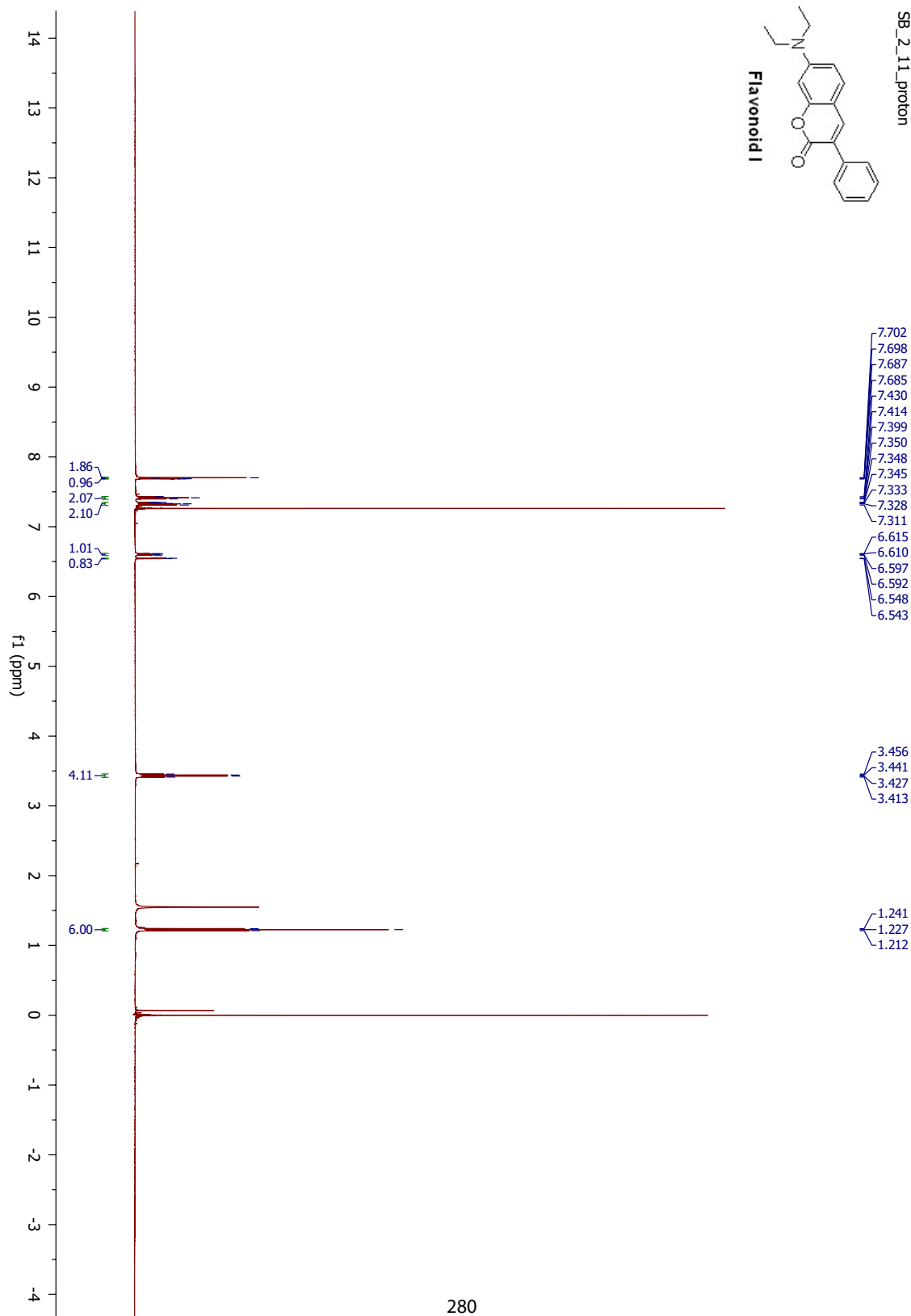
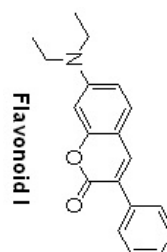
SB_3_43_after_trituration



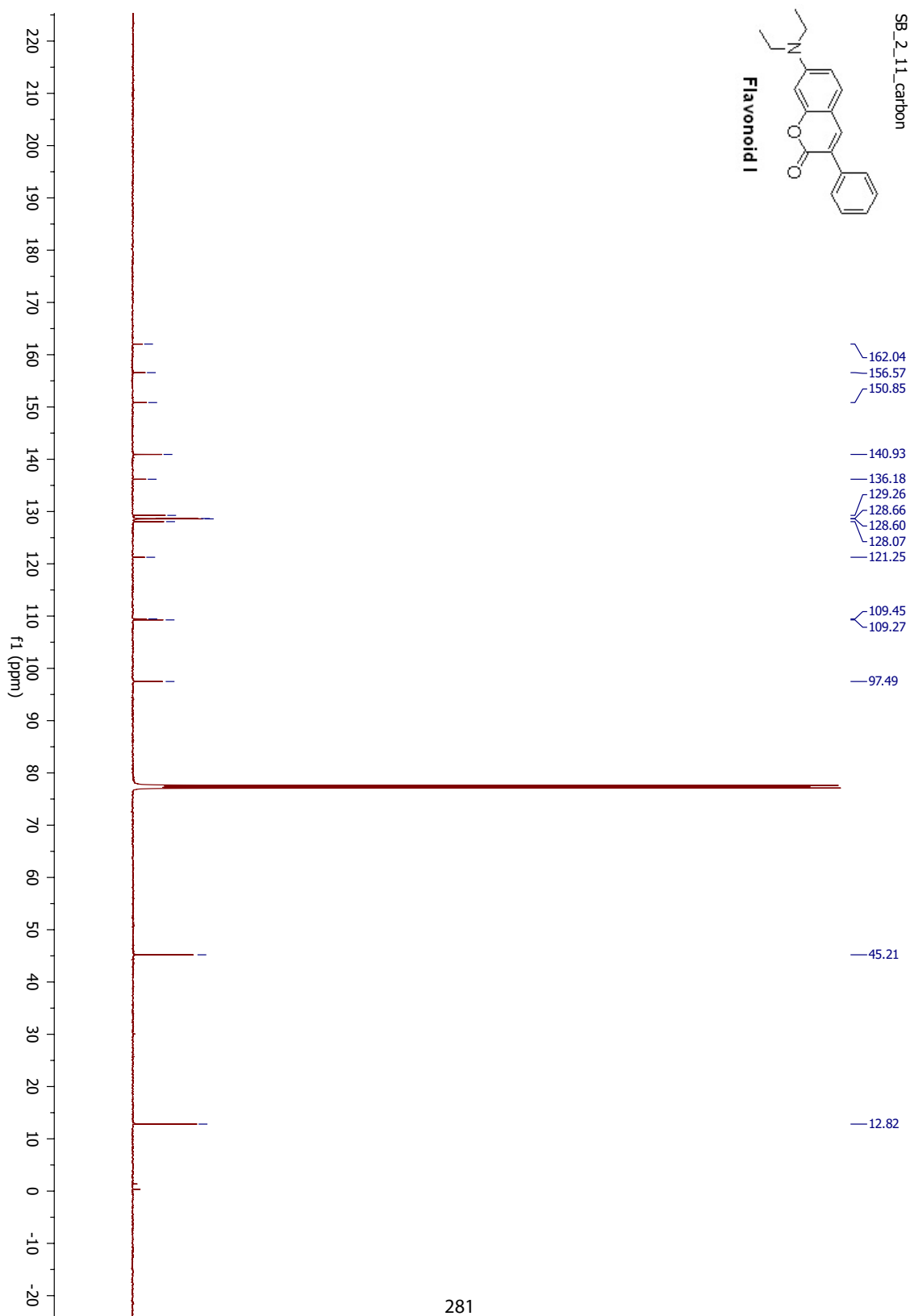
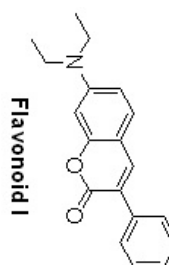
NMR Spectra

Chapter III

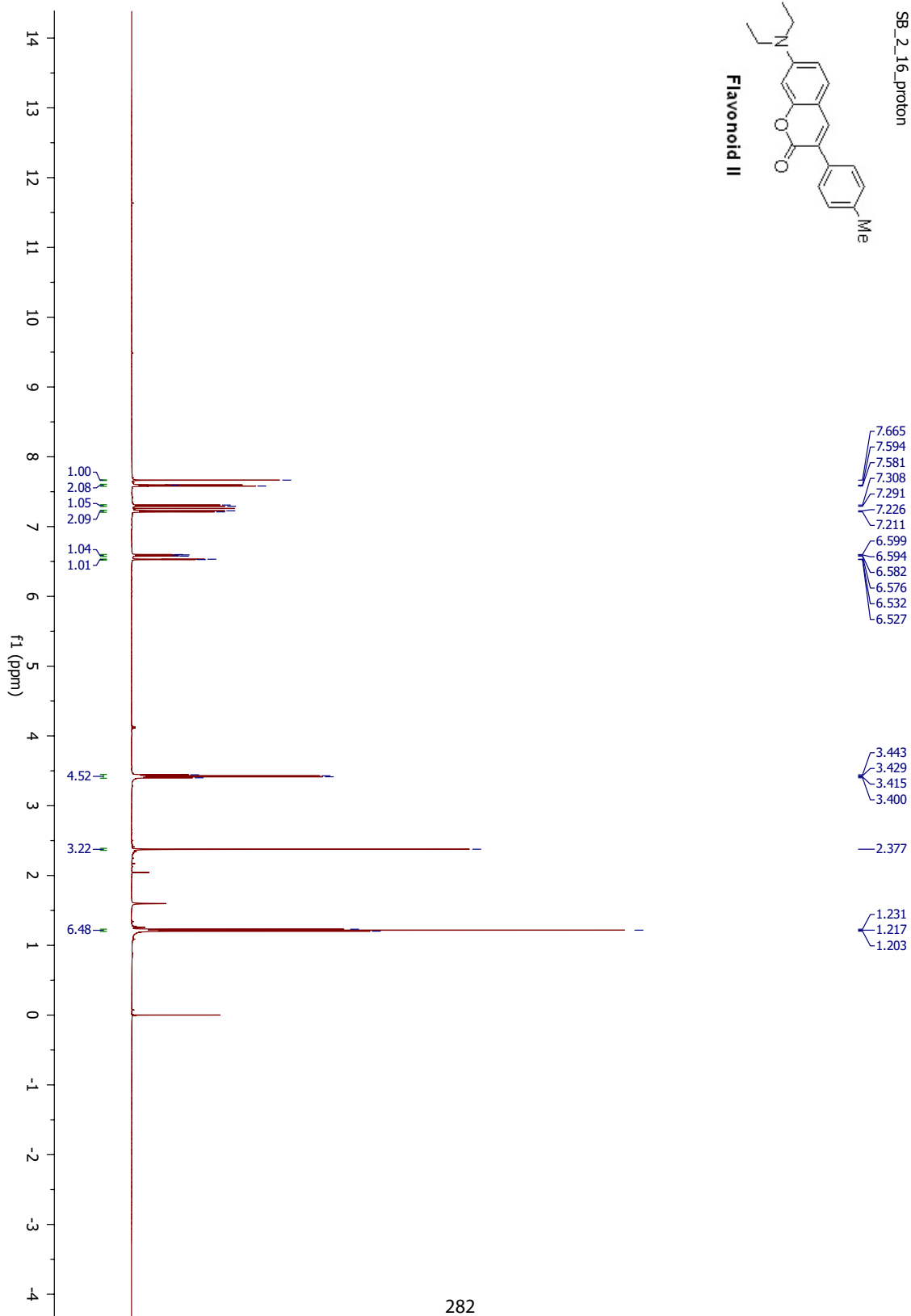
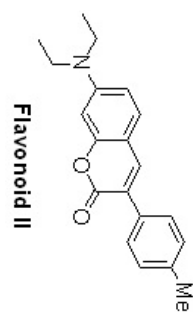
SB_2_11_proton



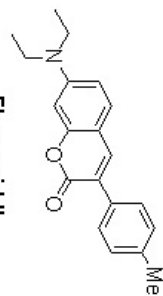
SB_2_11_carbon



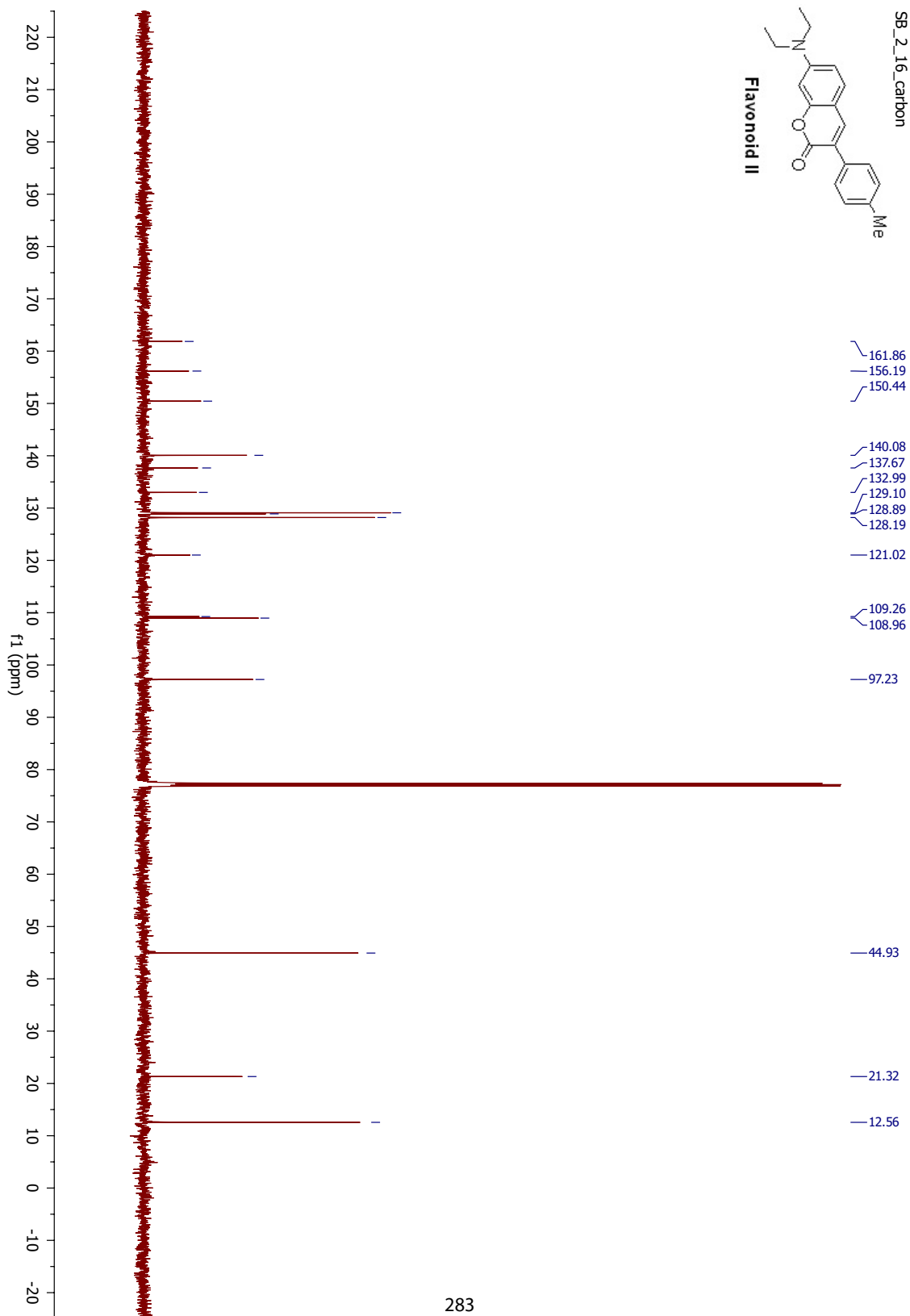
SB_2_16_proton



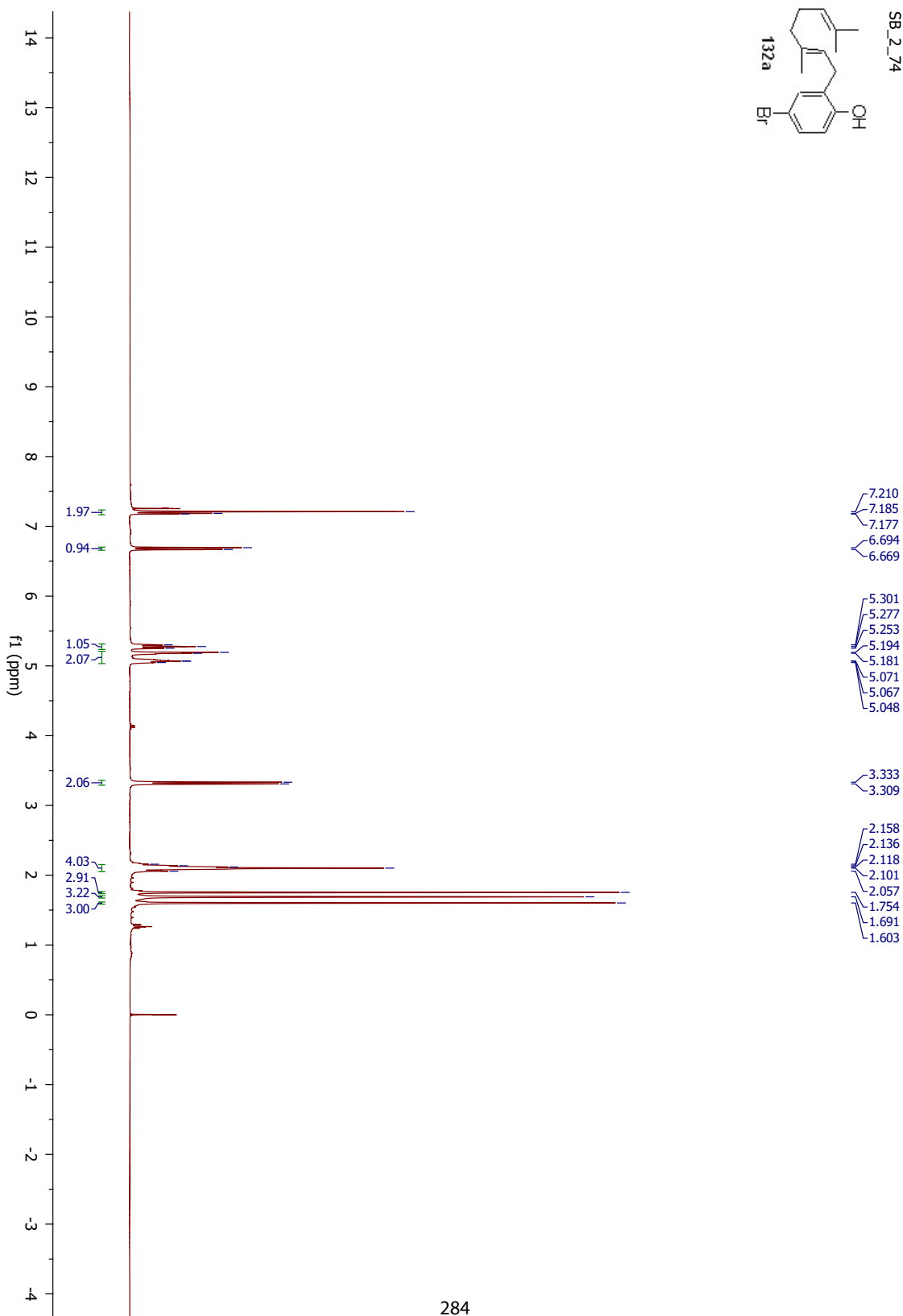
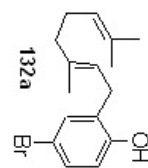
SB_2_16_carbon



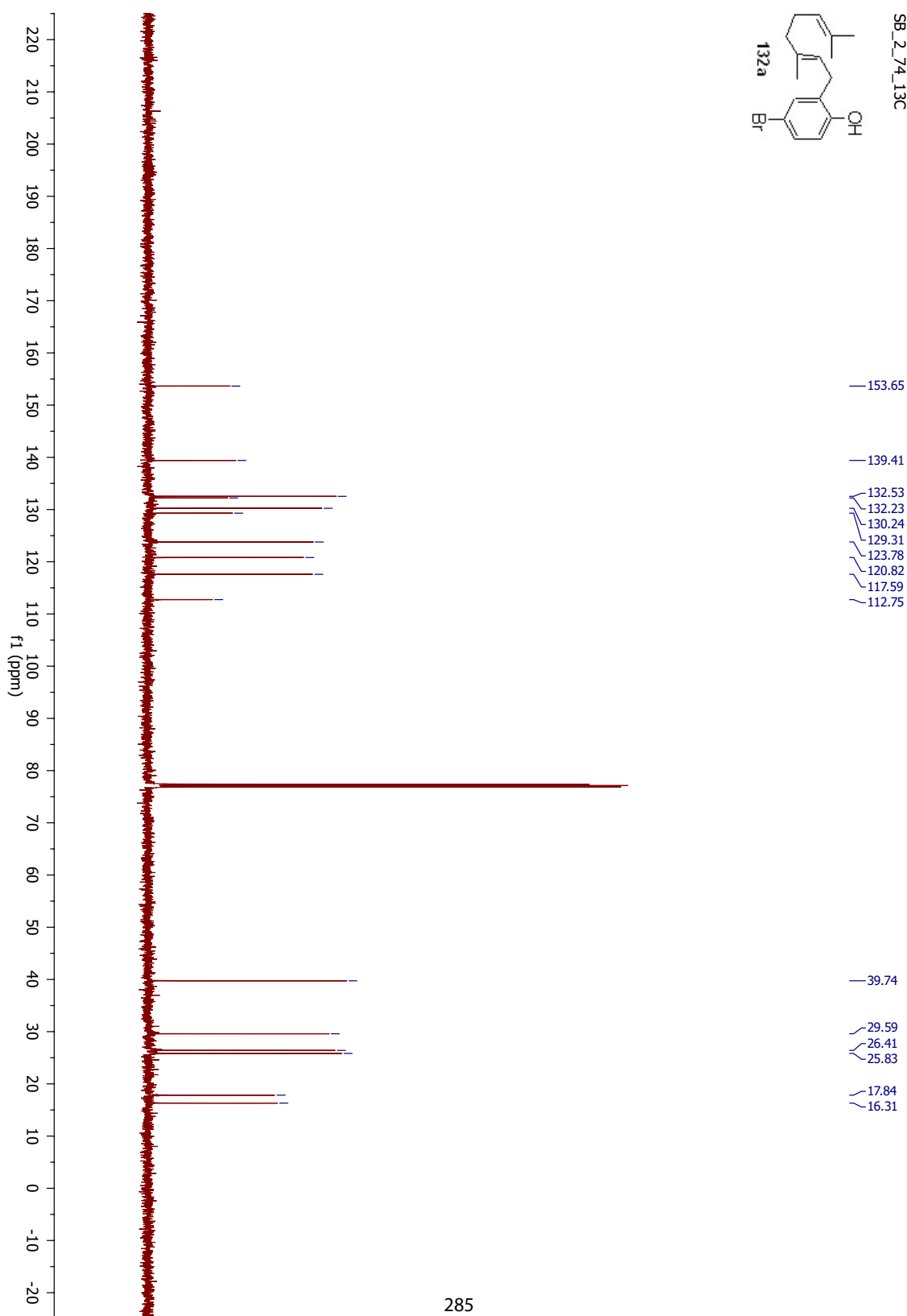
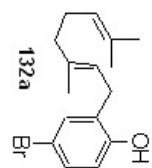
Flavonoid II



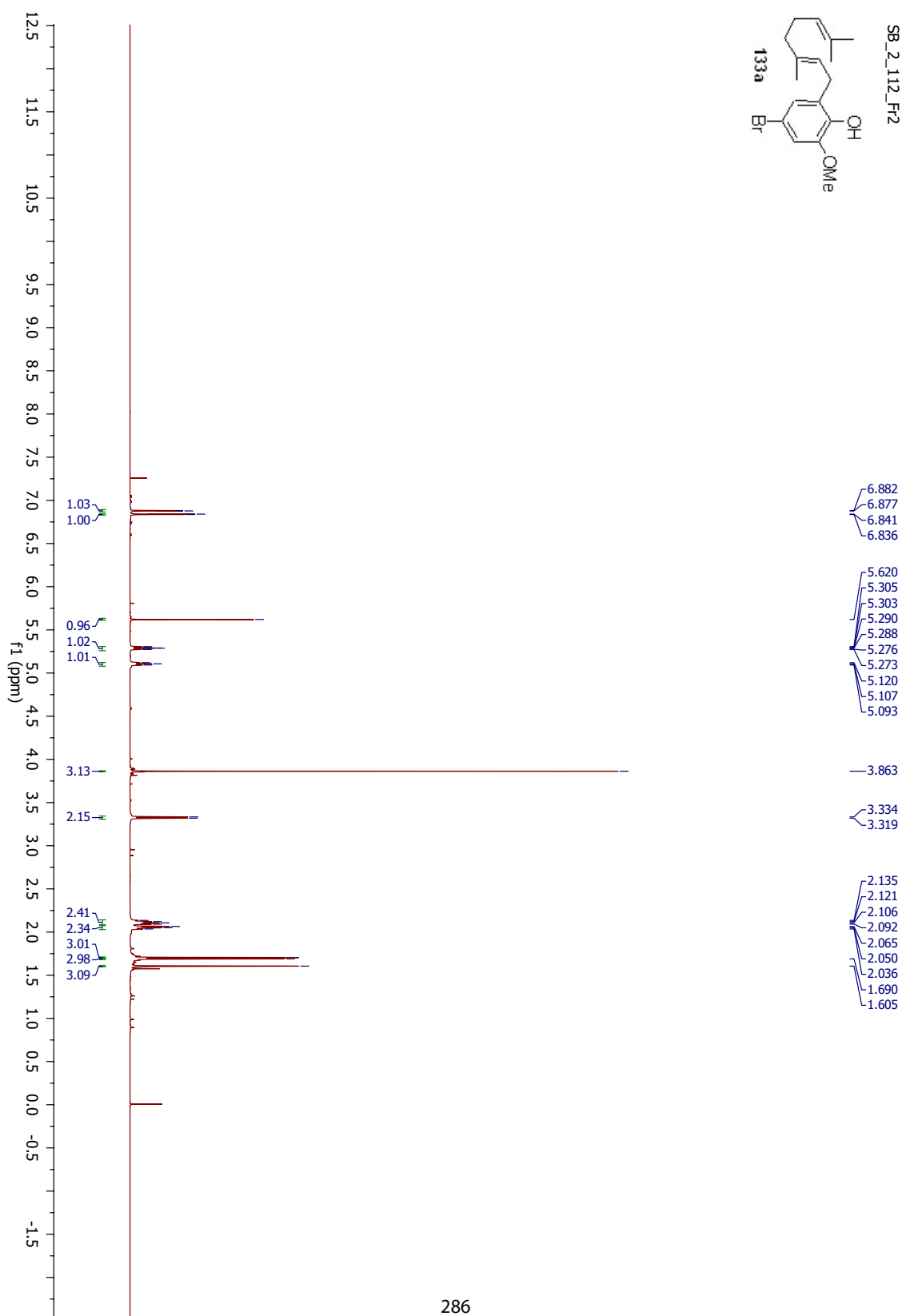
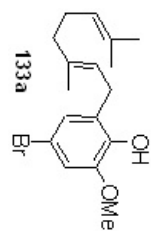
SB_2_74



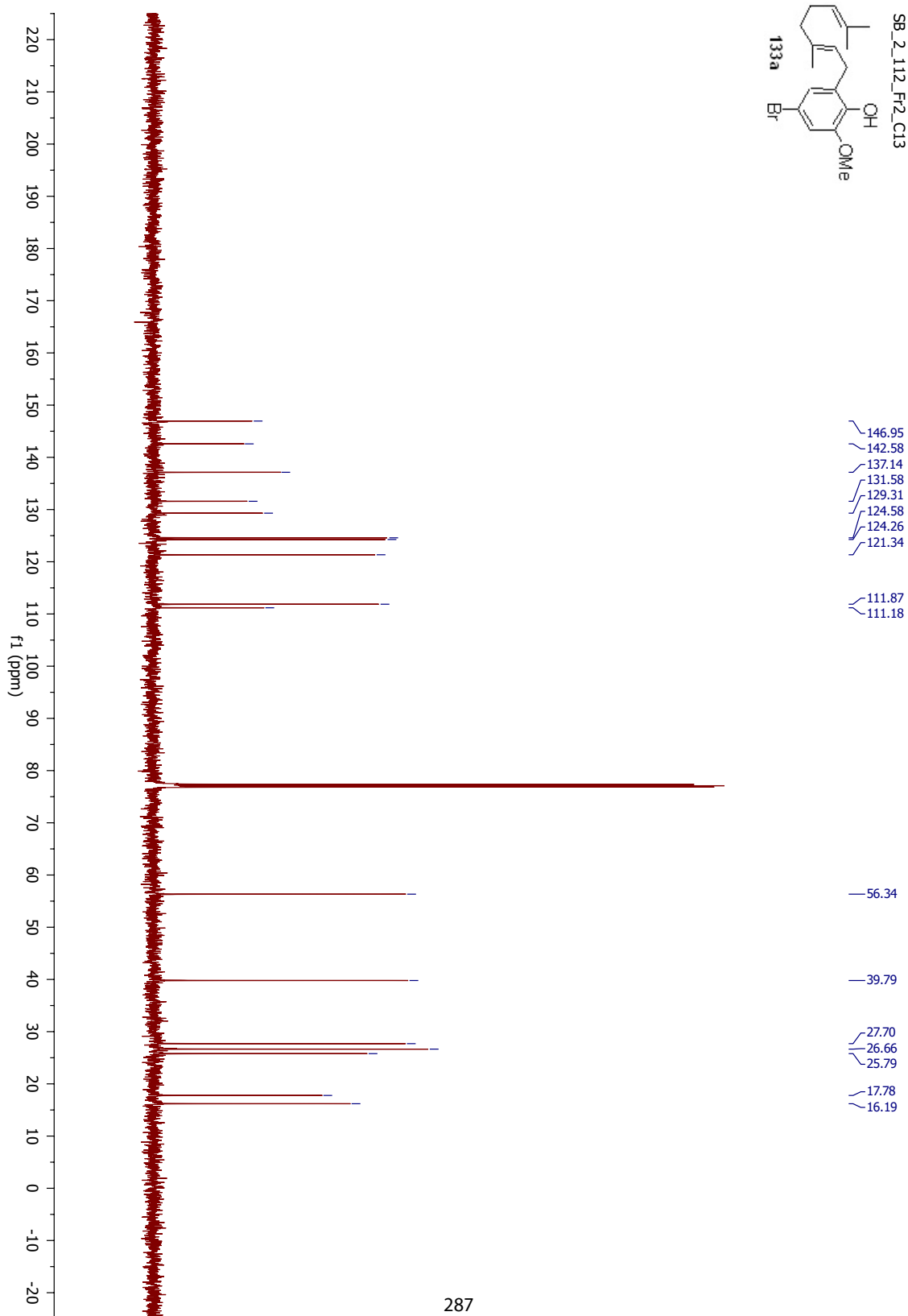
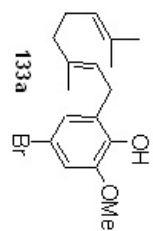
SB_2_74_13C

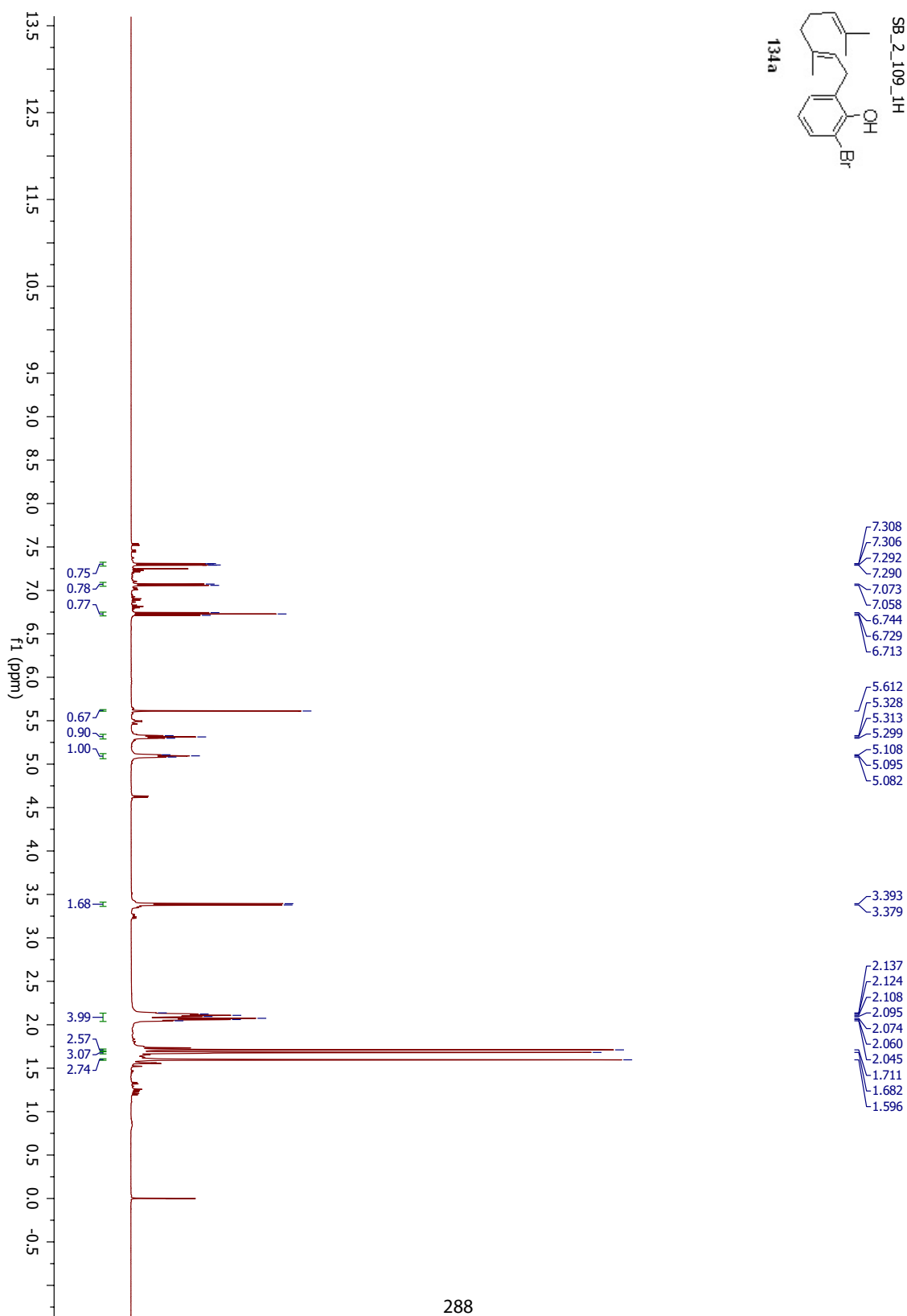
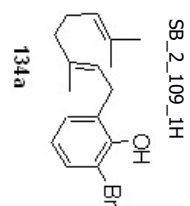


SB_2_112_F12

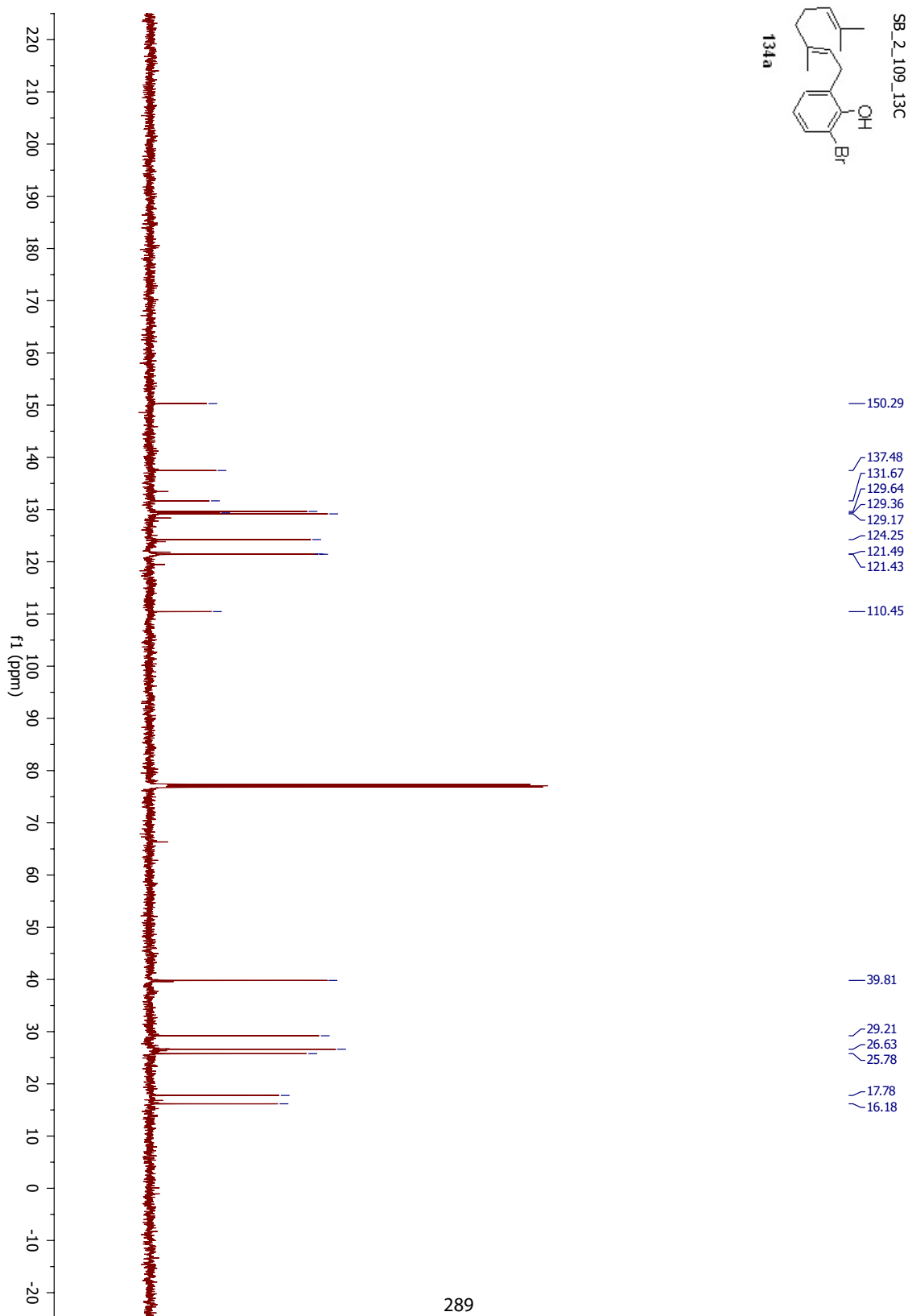
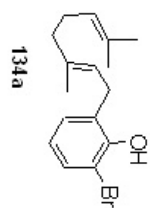


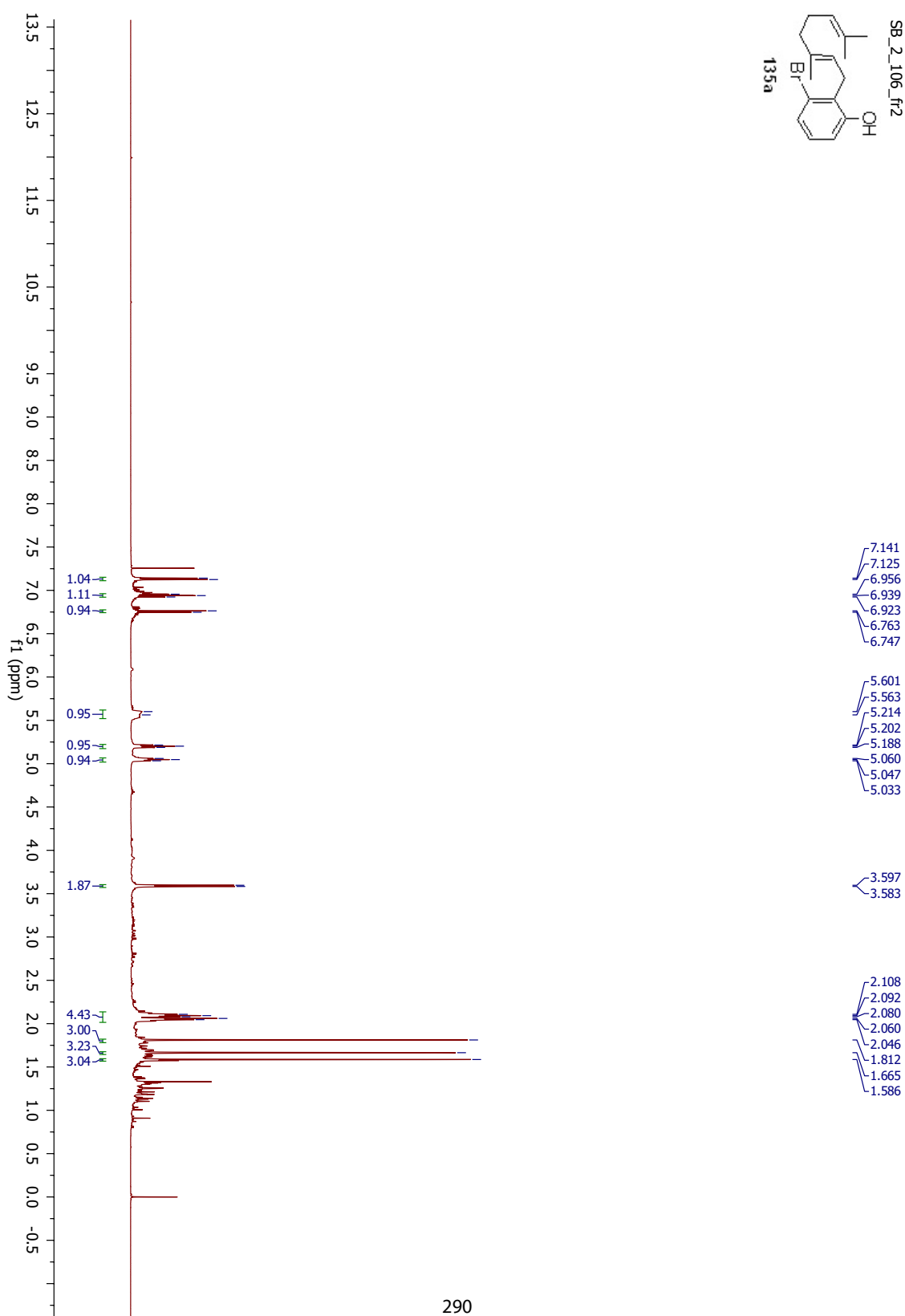
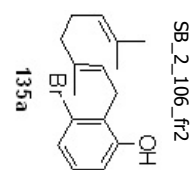
SB_2_112_F12_C13



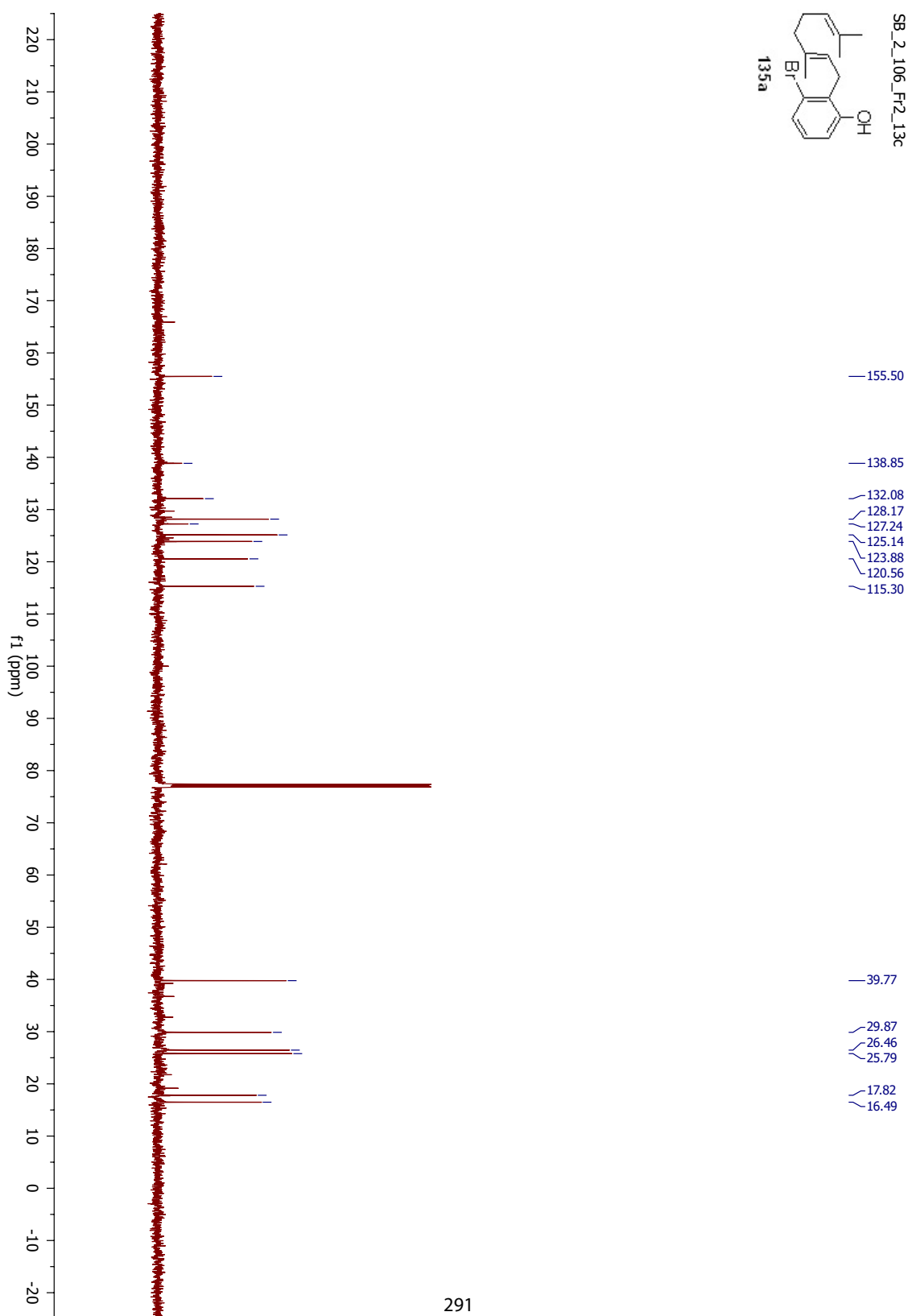
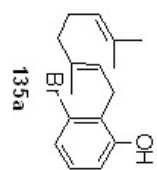


SB_2_109_13C

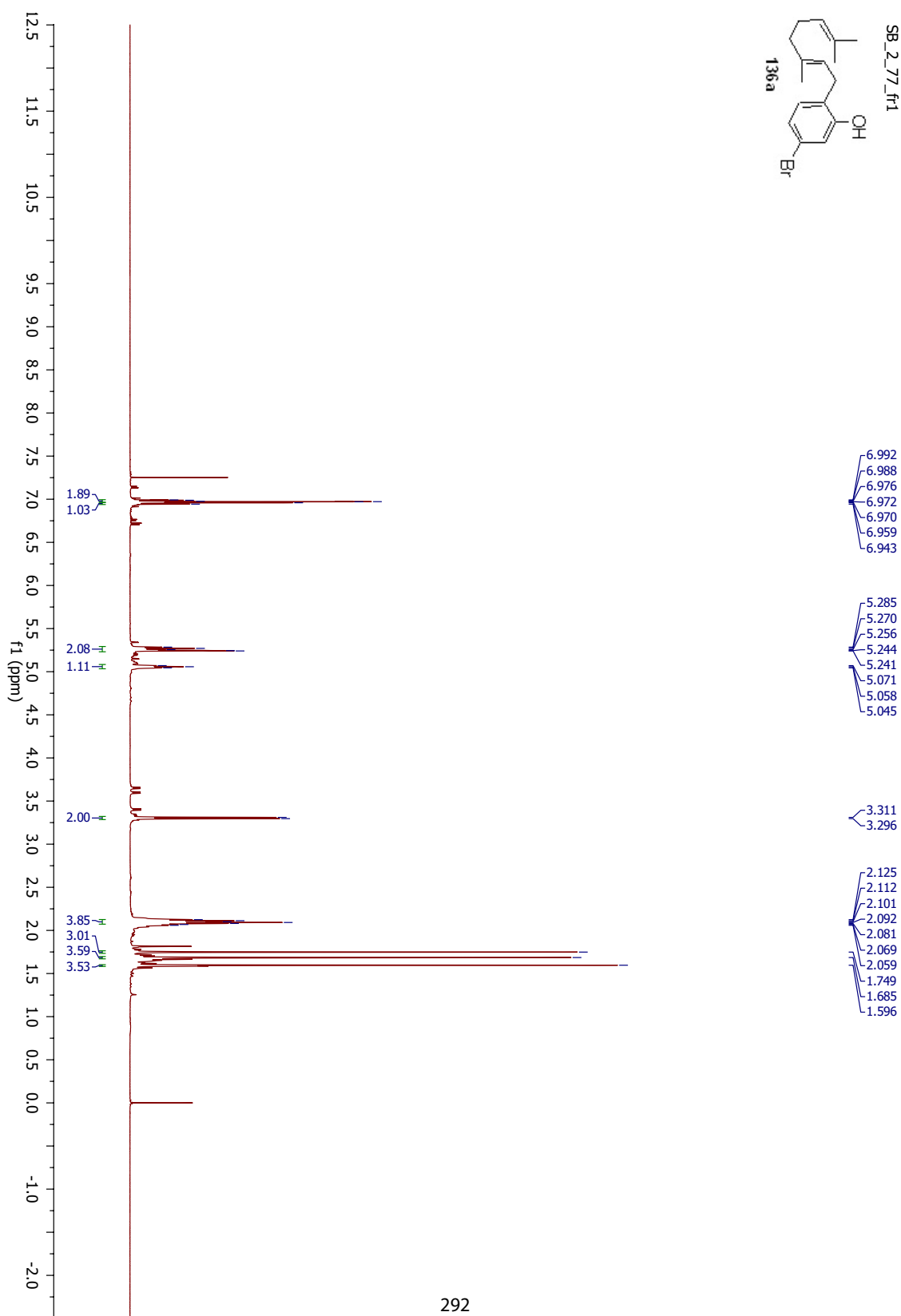
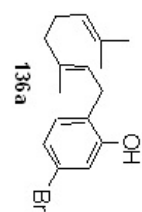


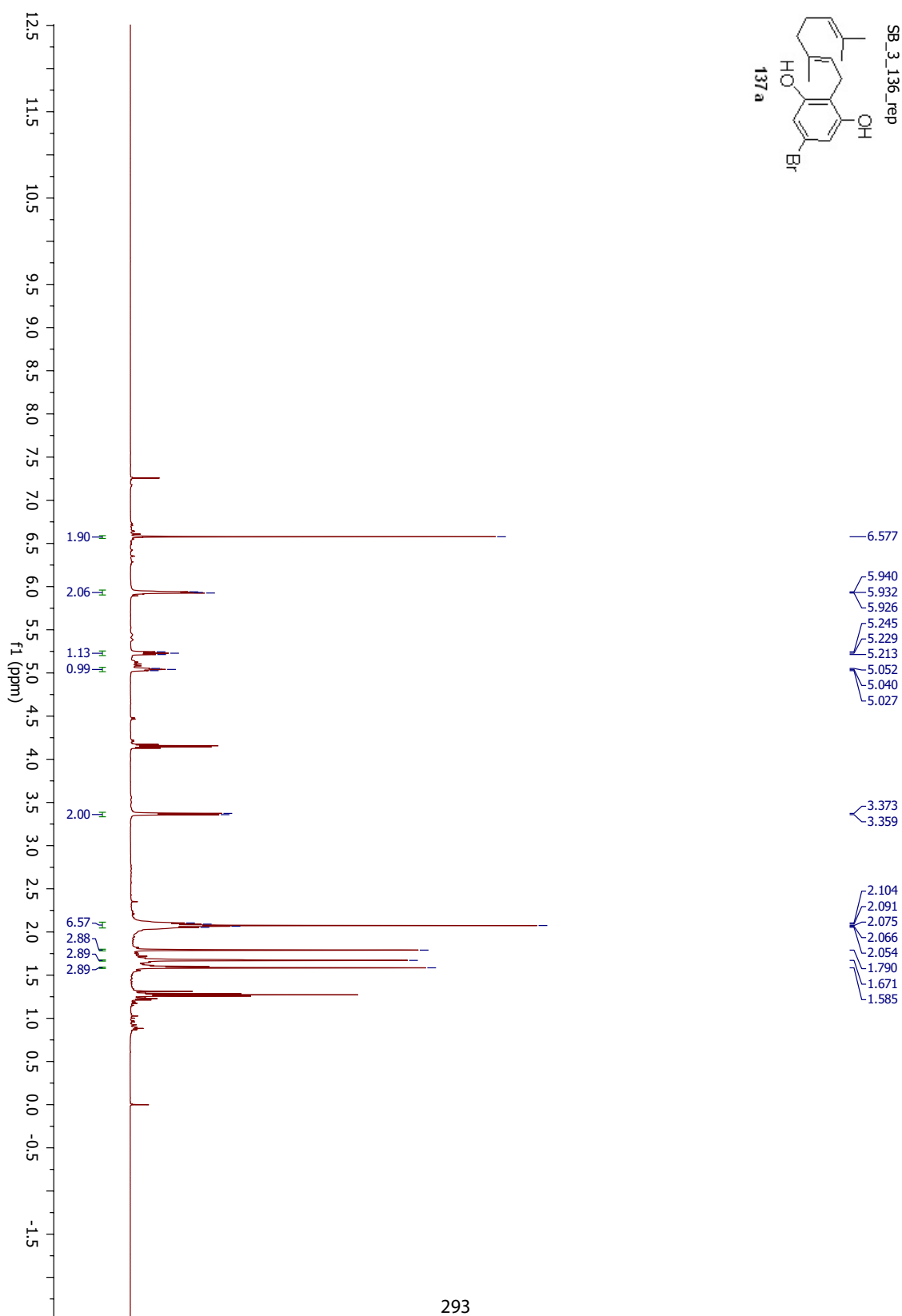
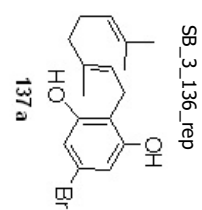


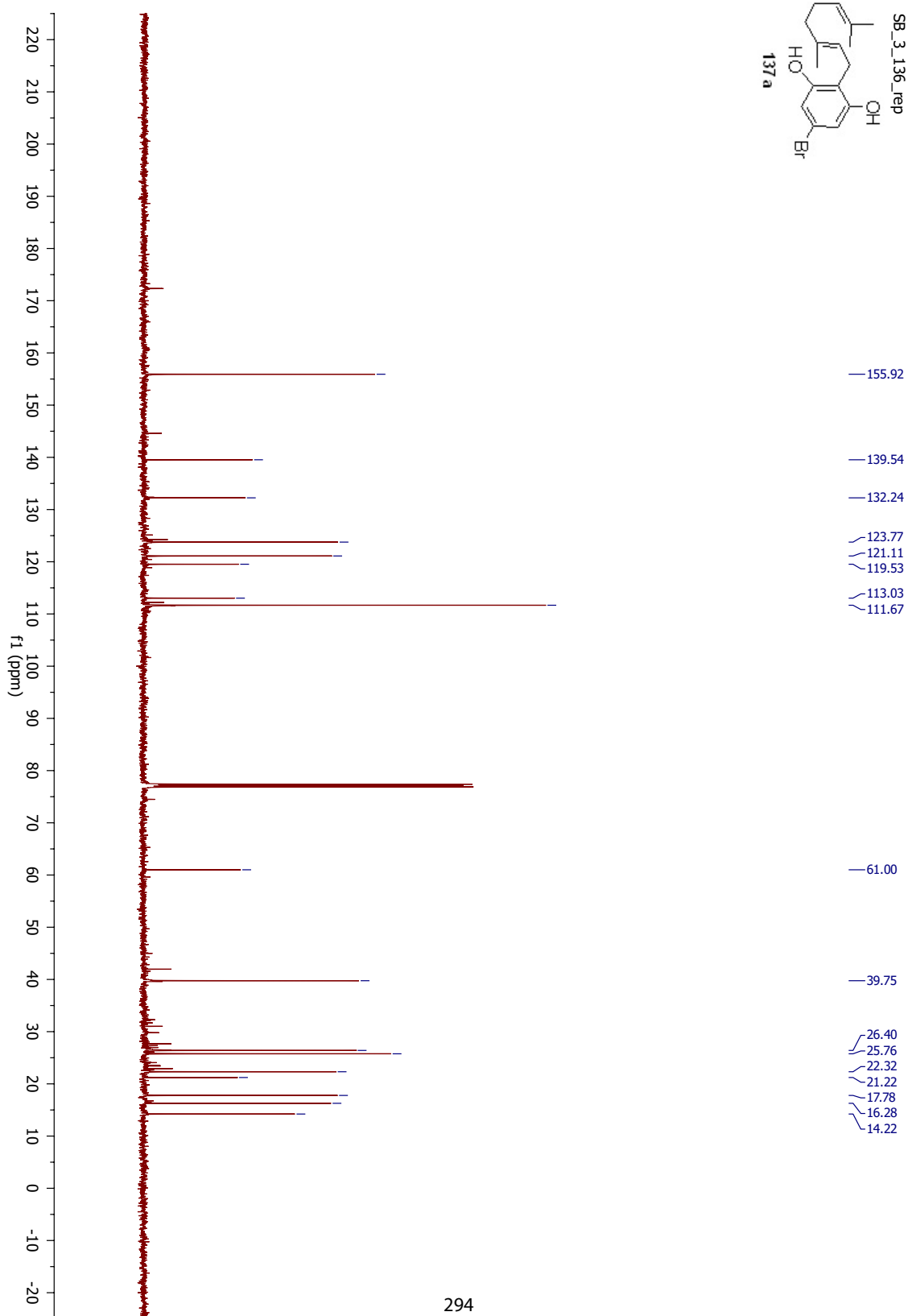
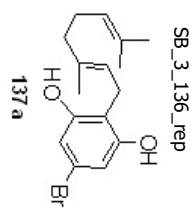
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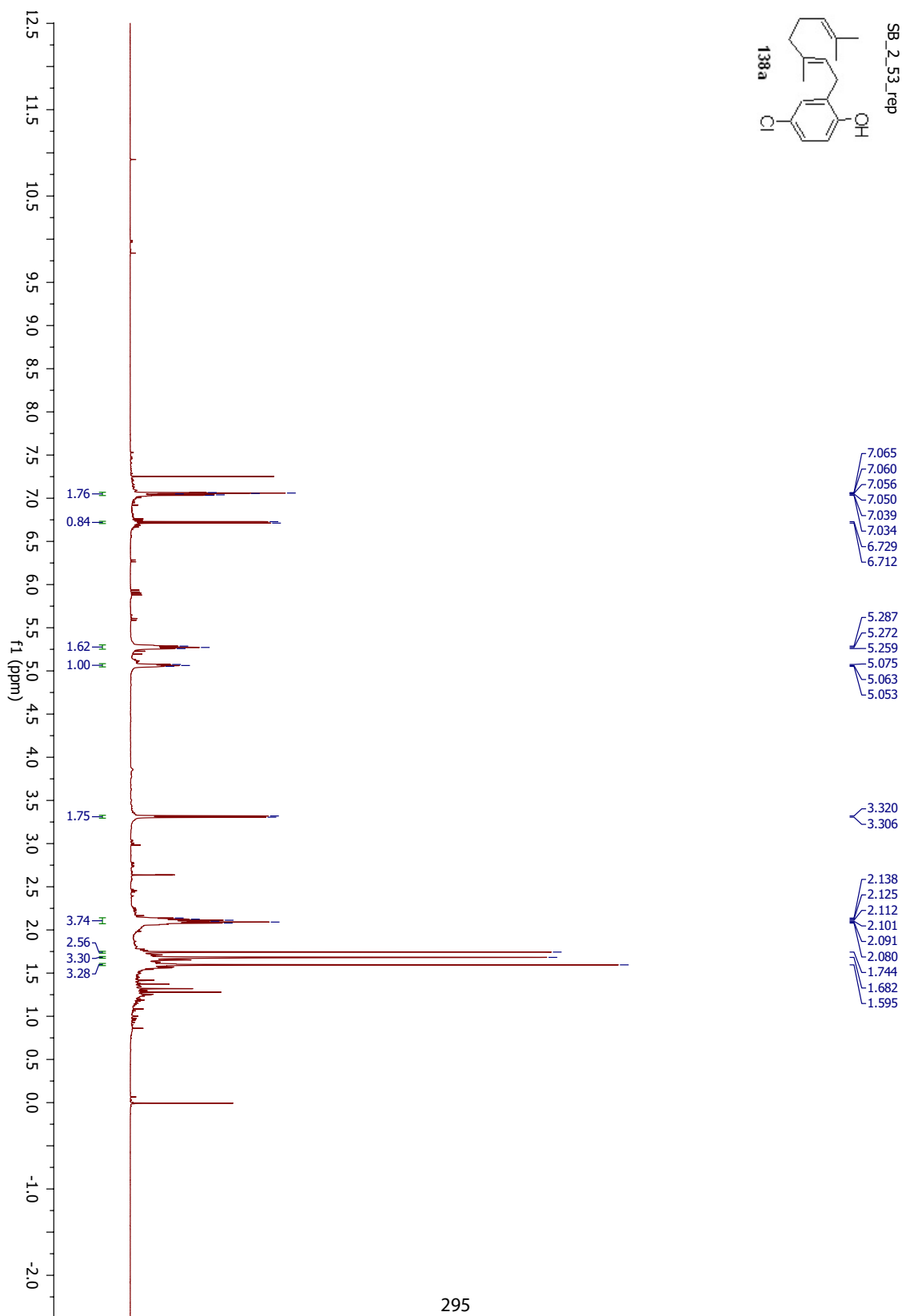
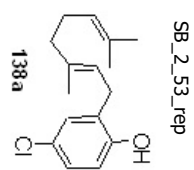


SB_2_77_fr1

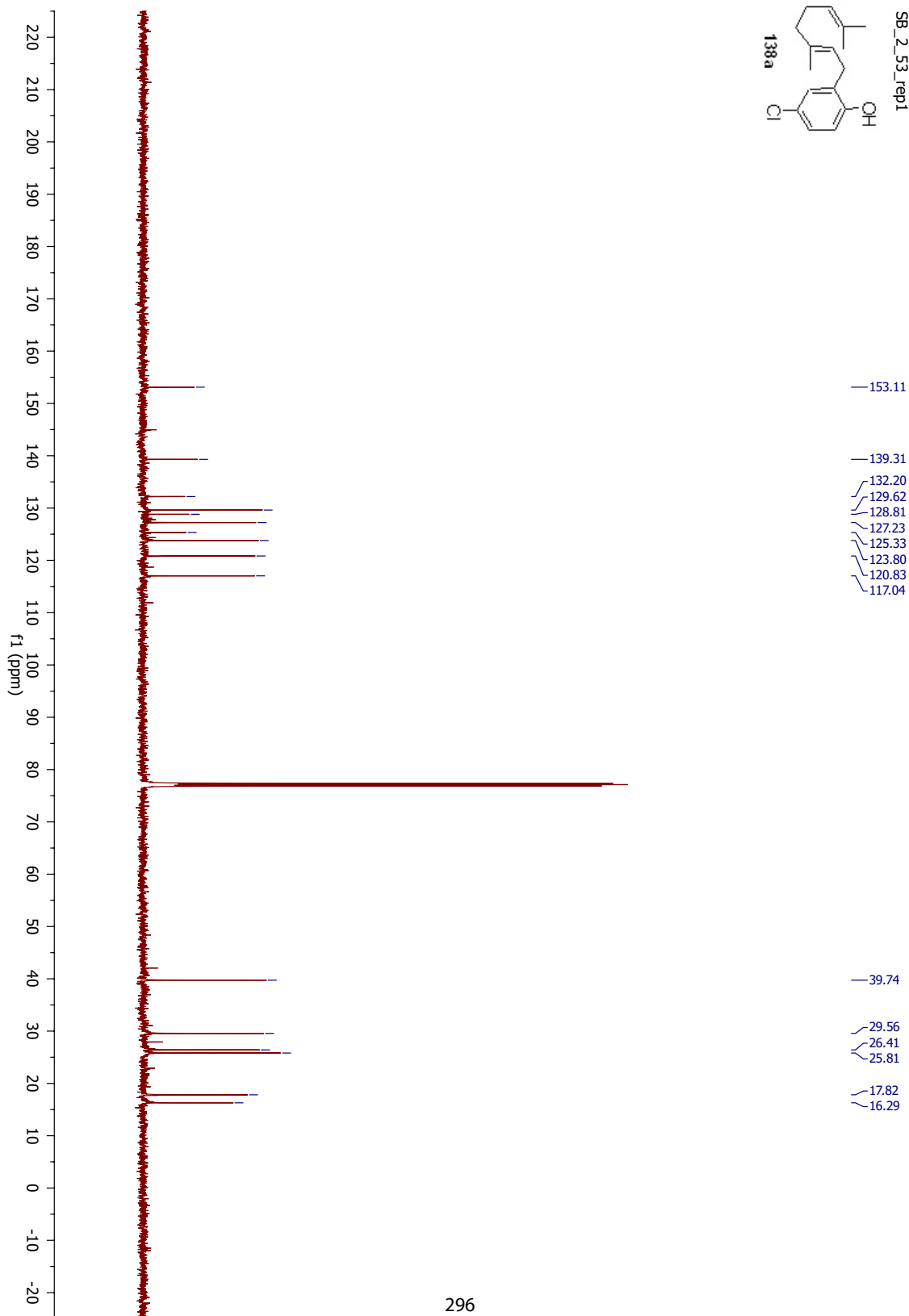
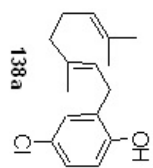




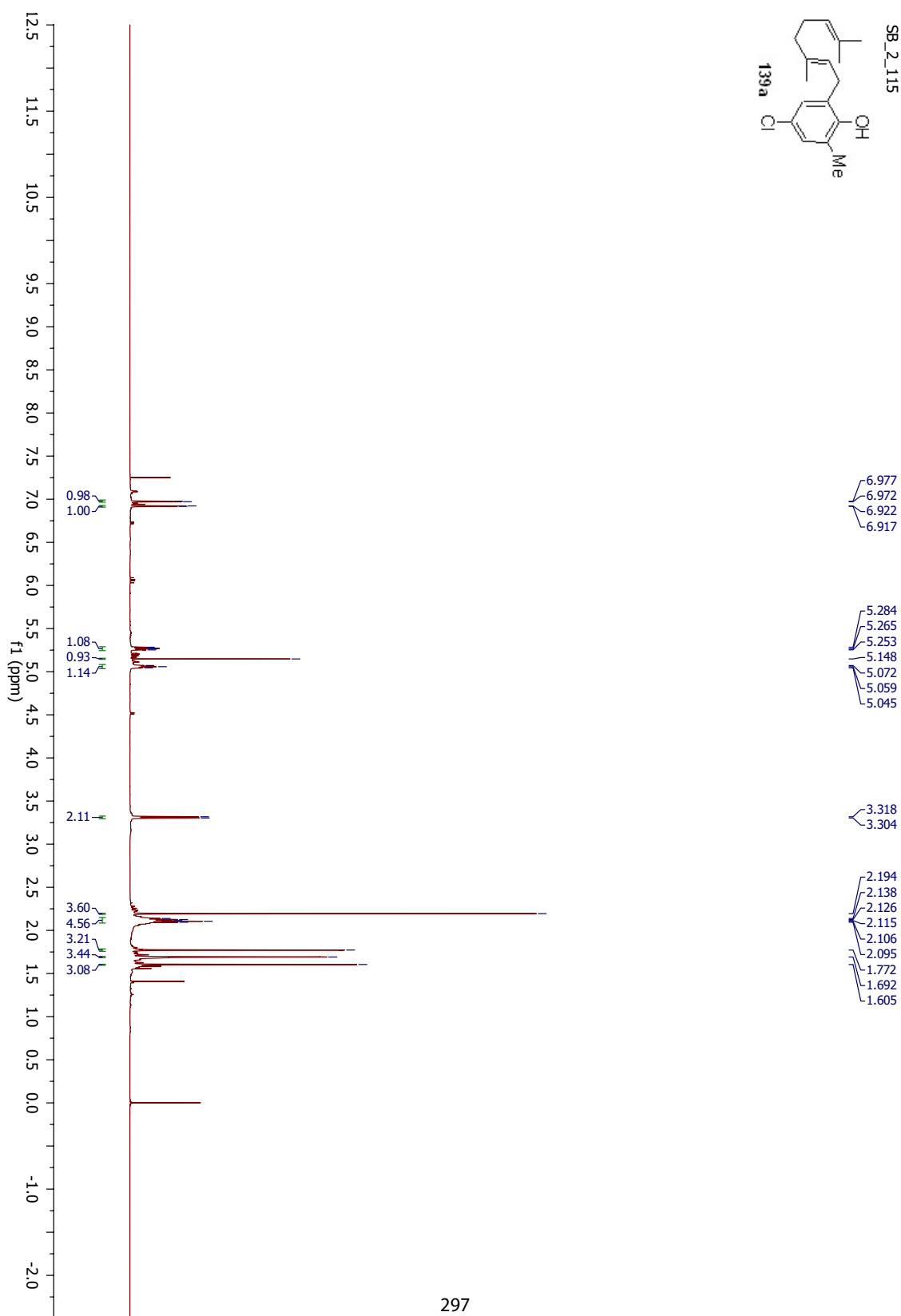
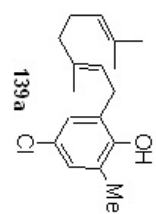


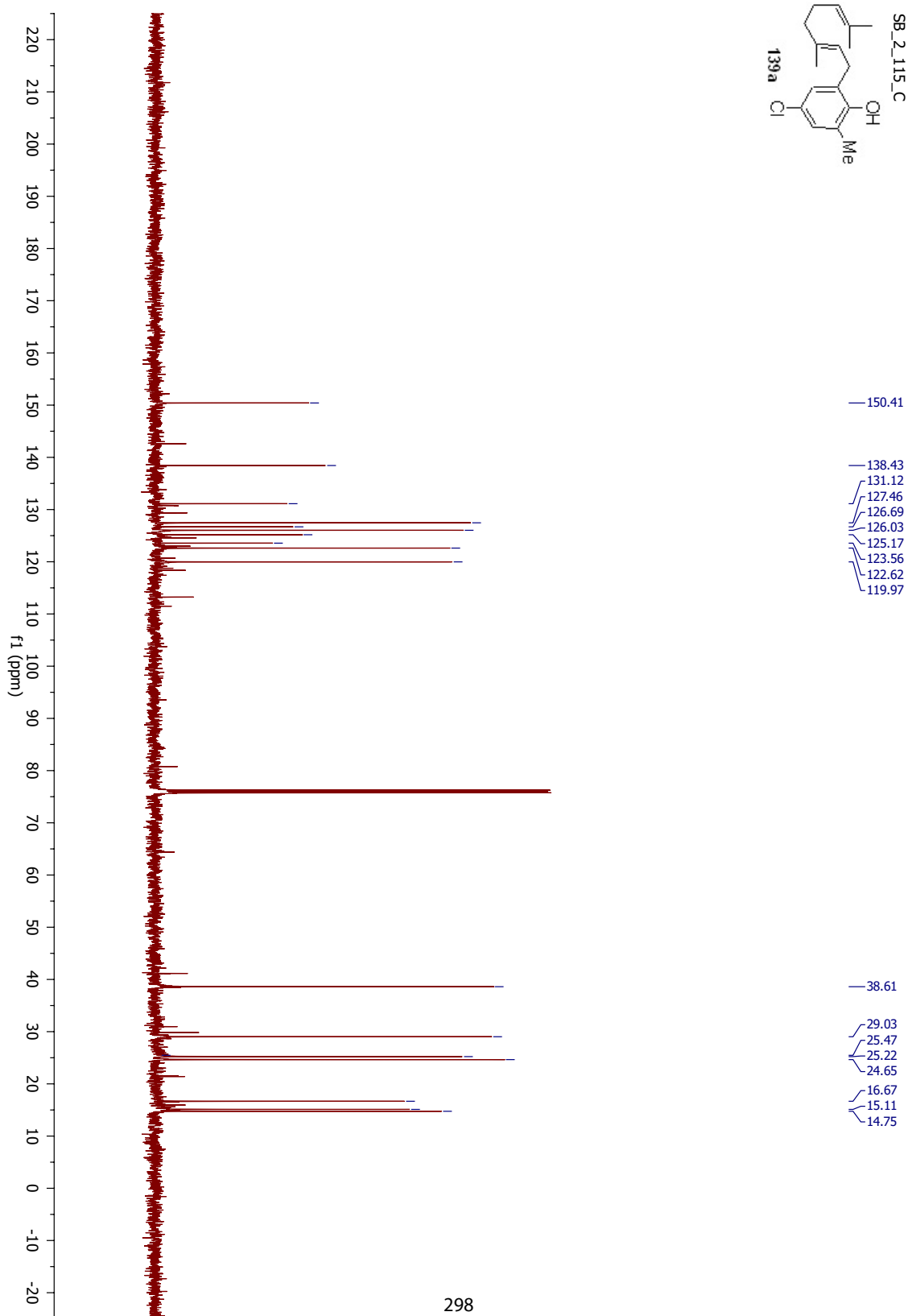
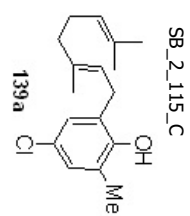


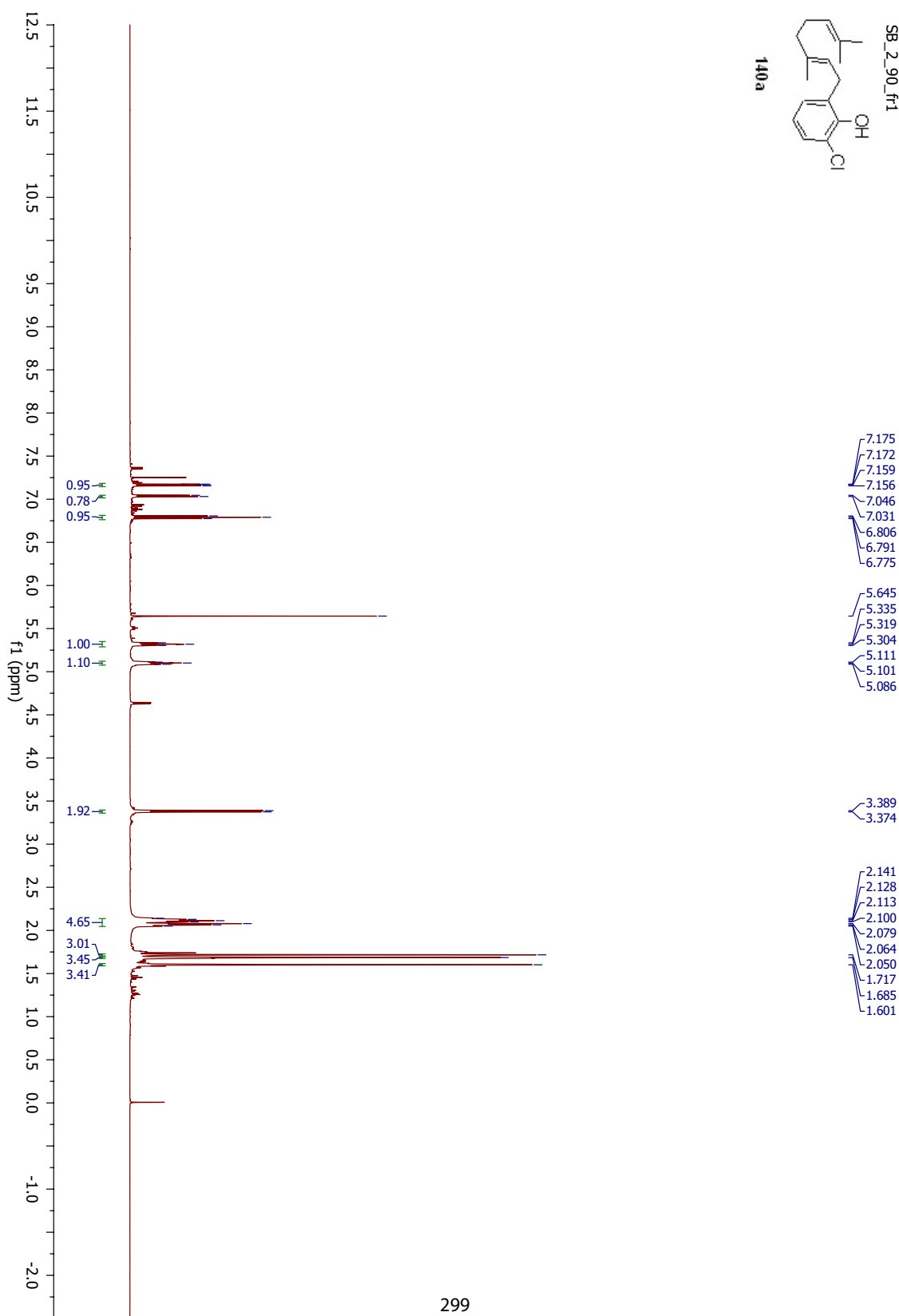
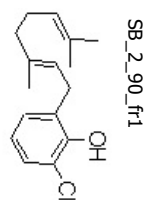
SB_2_53_rep1

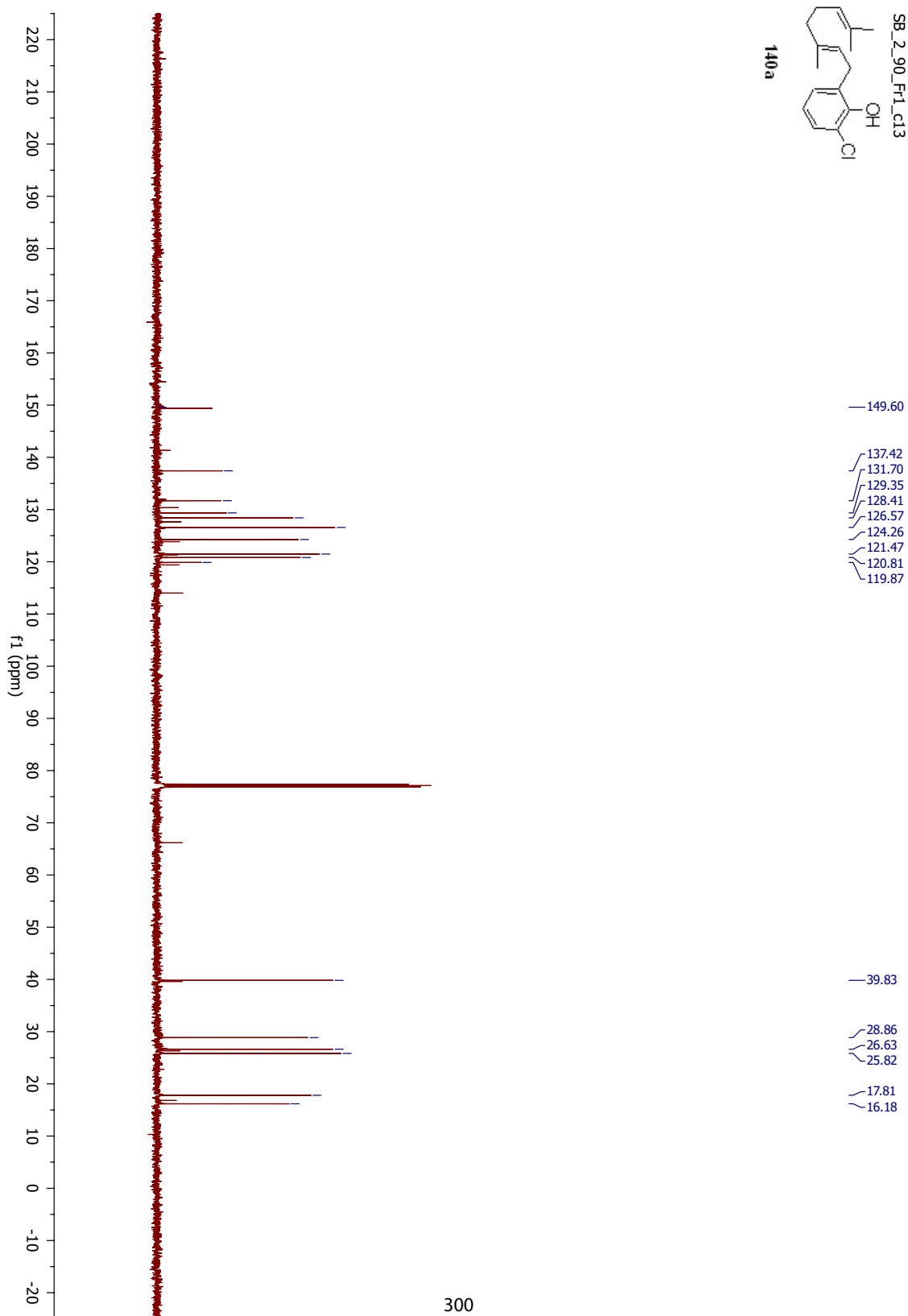
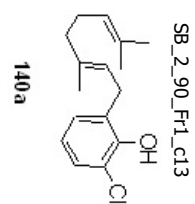


SB_2_115

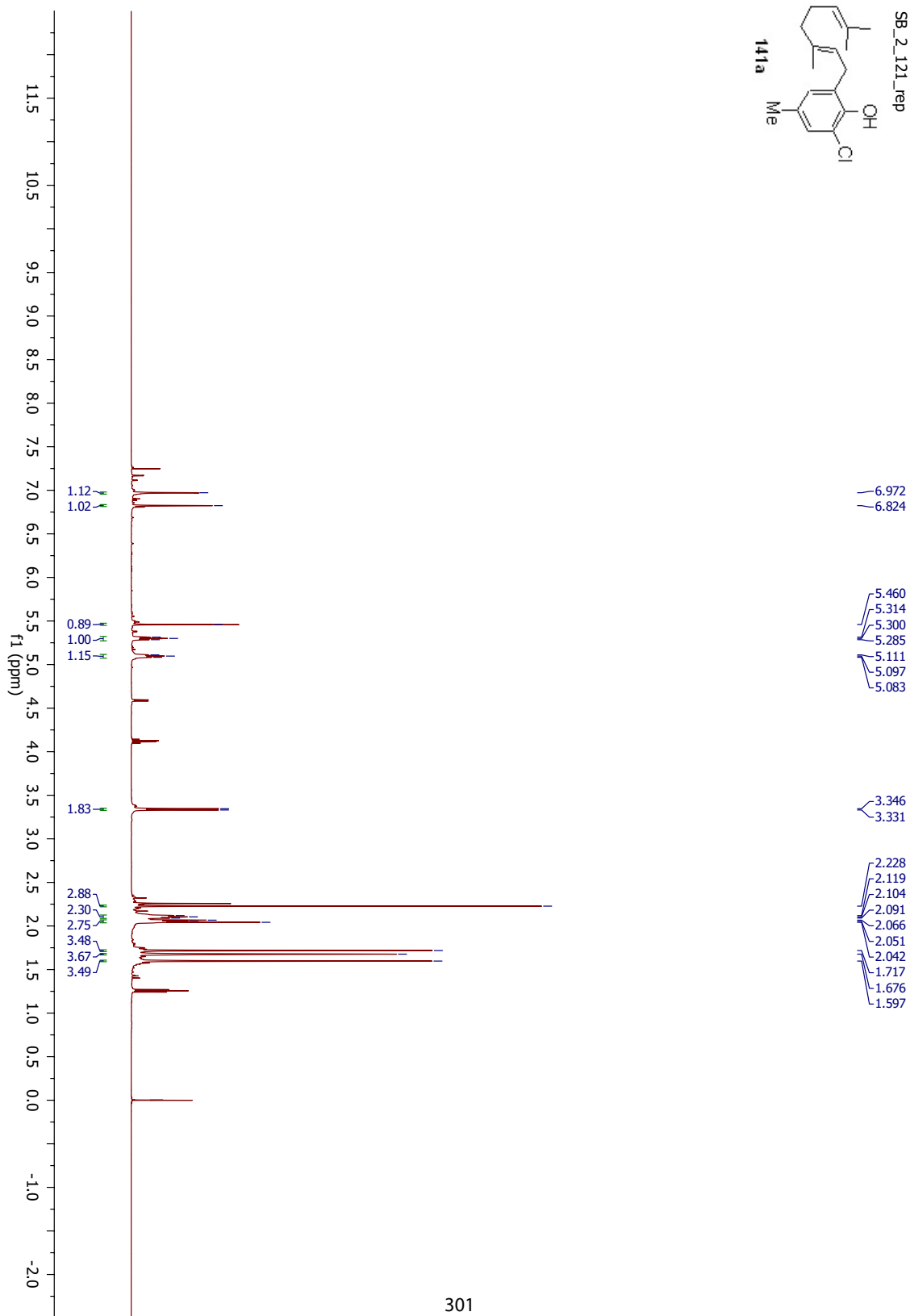
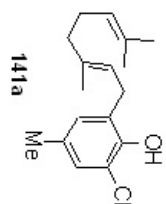


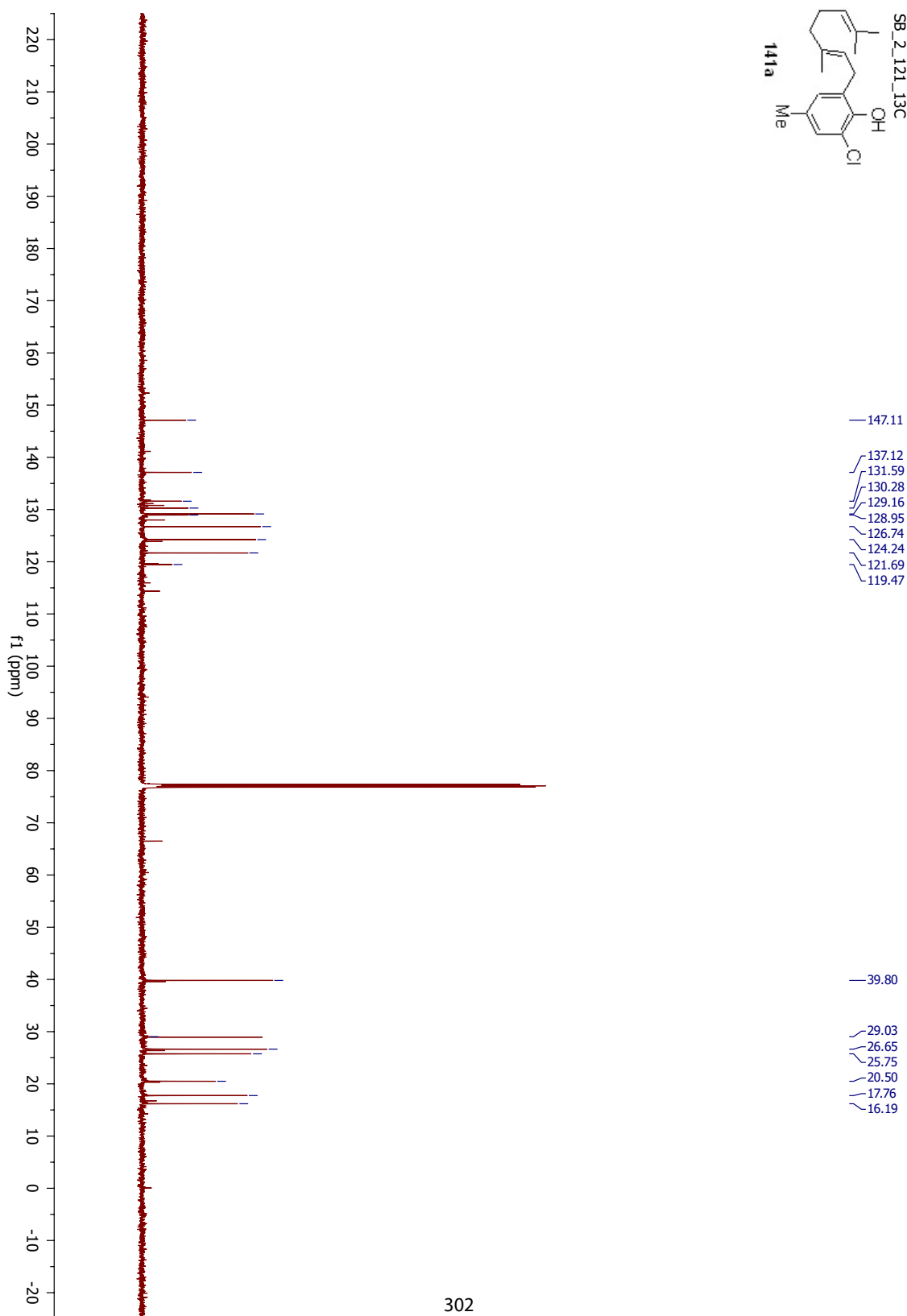
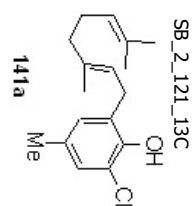


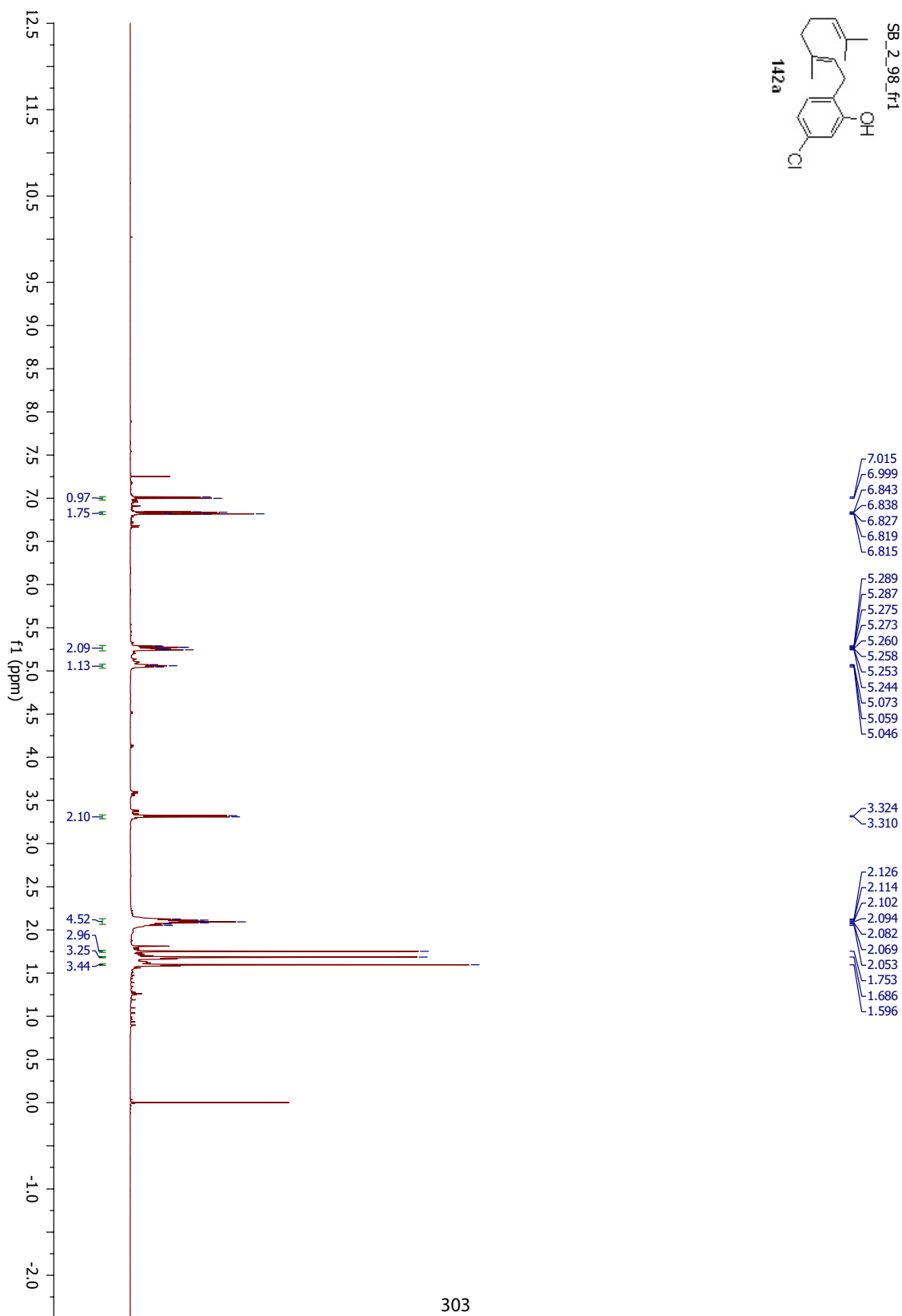
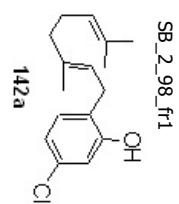




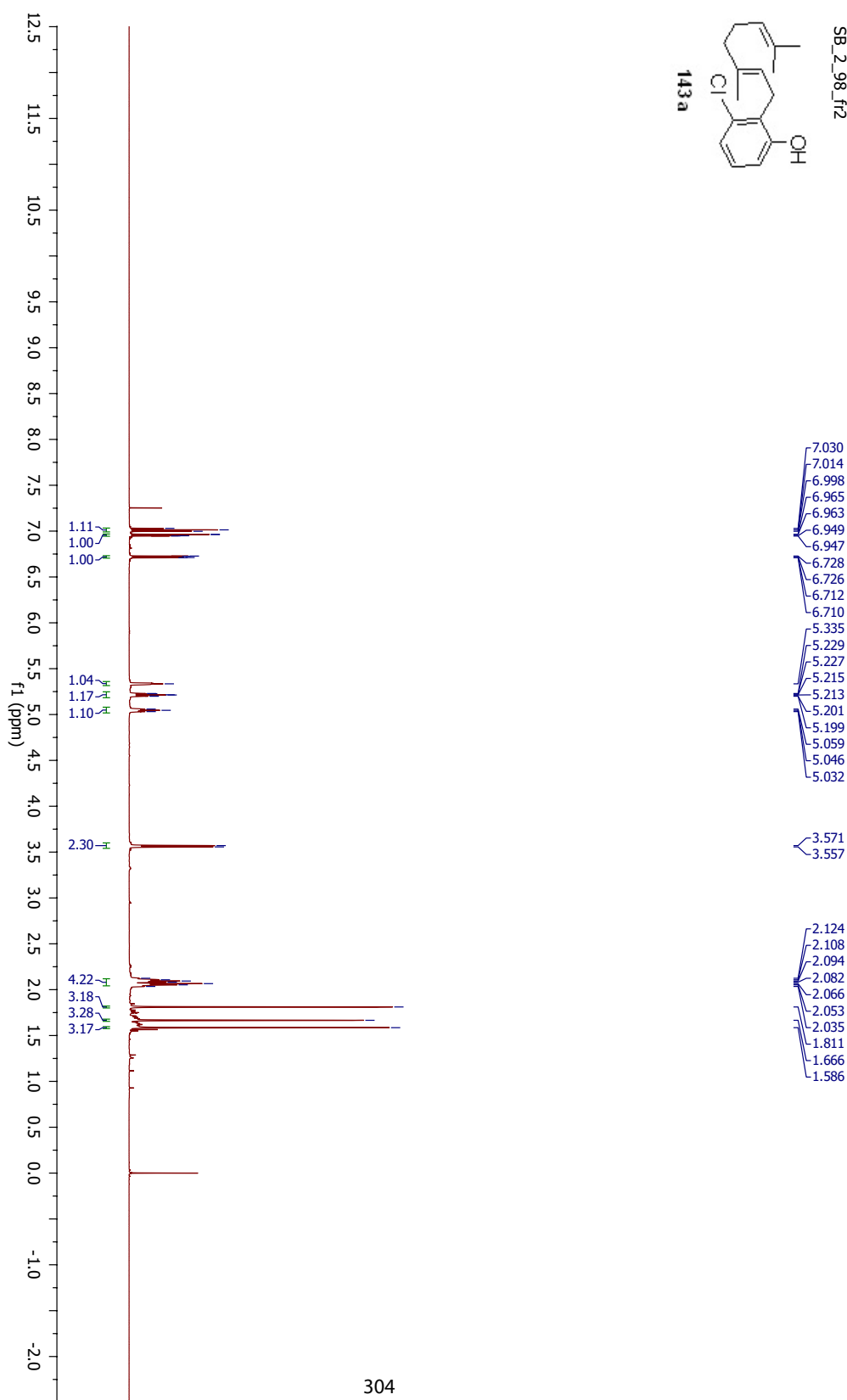
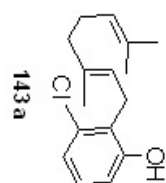
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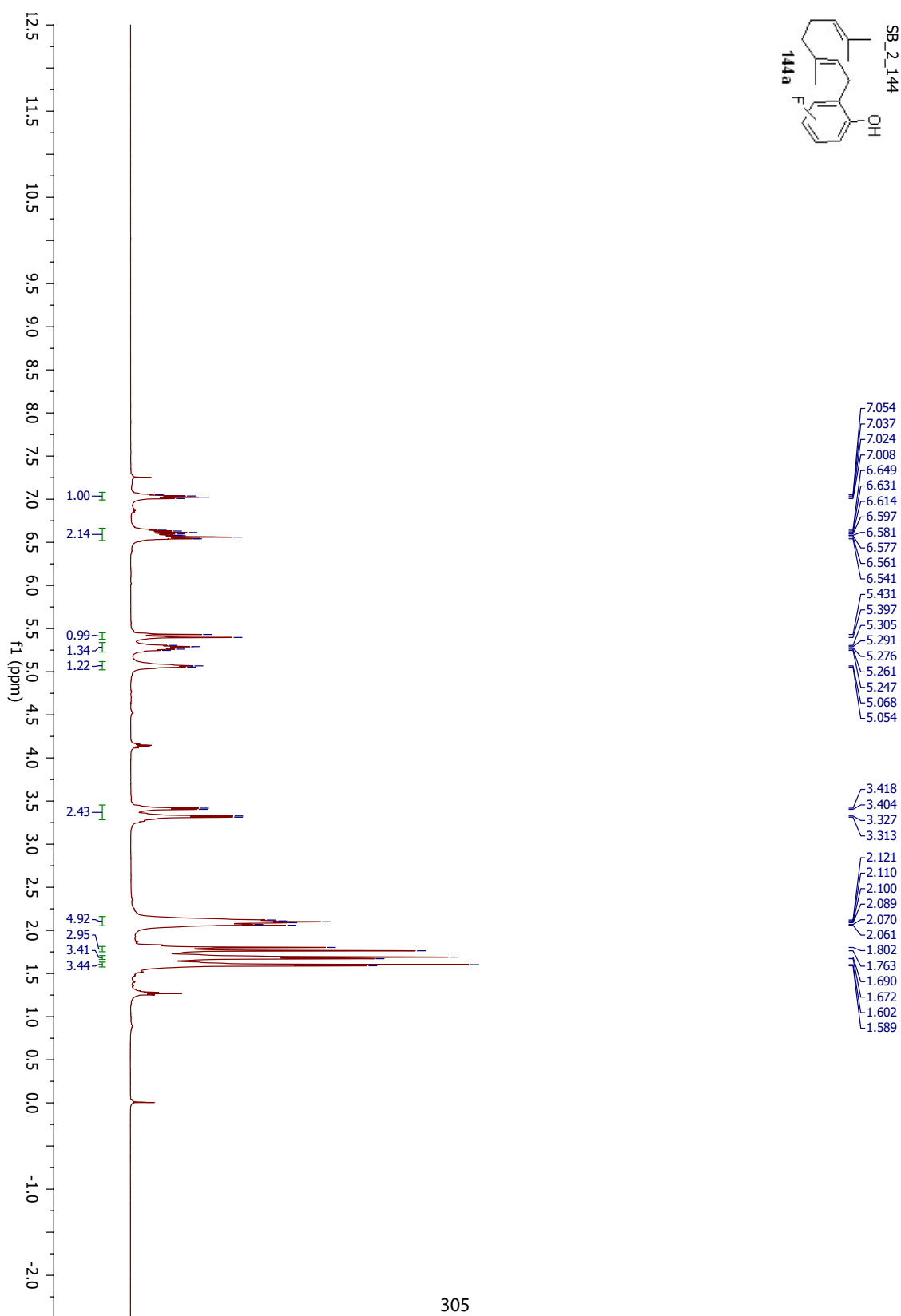
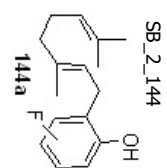


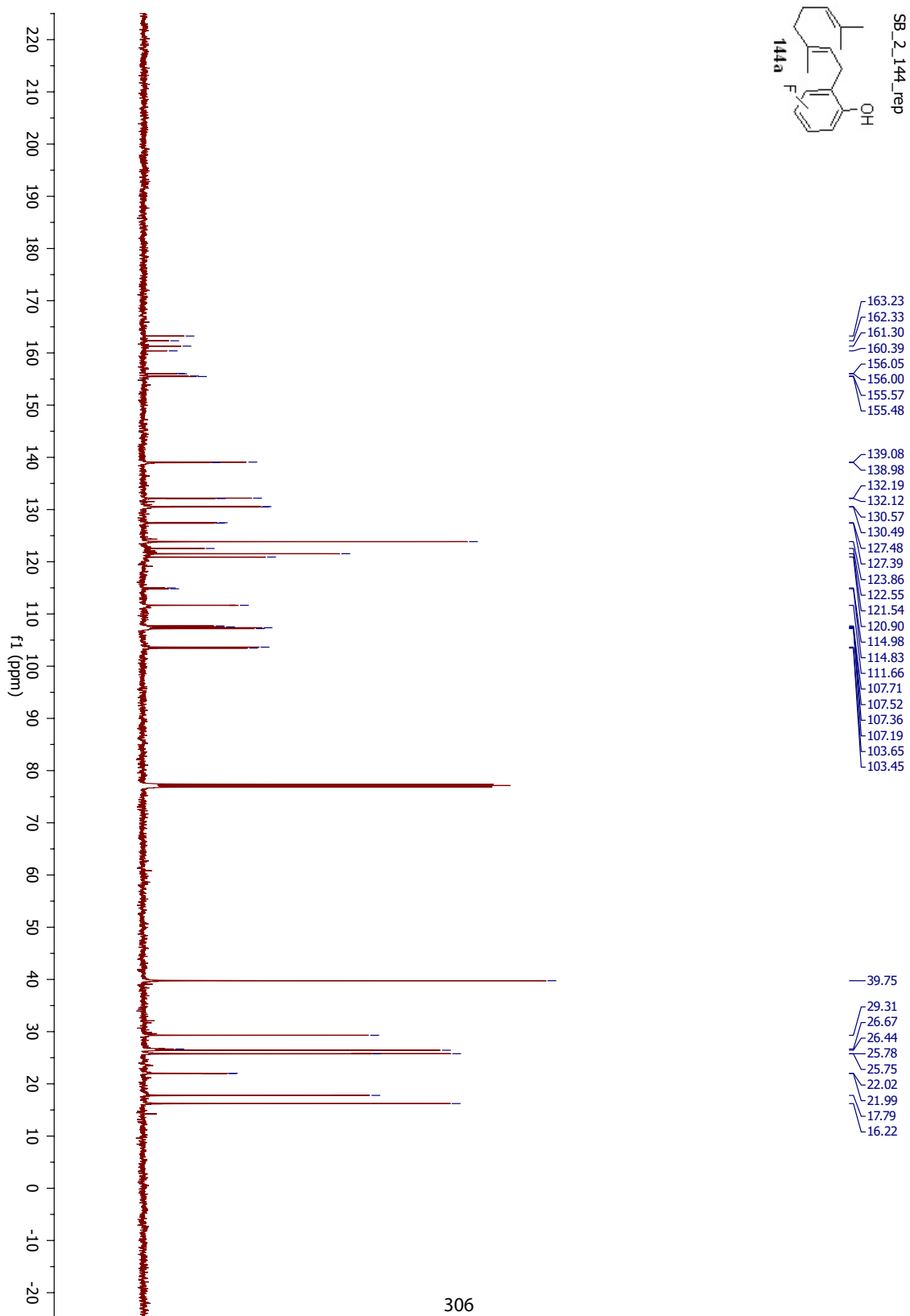
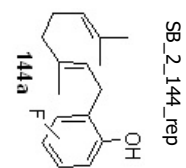


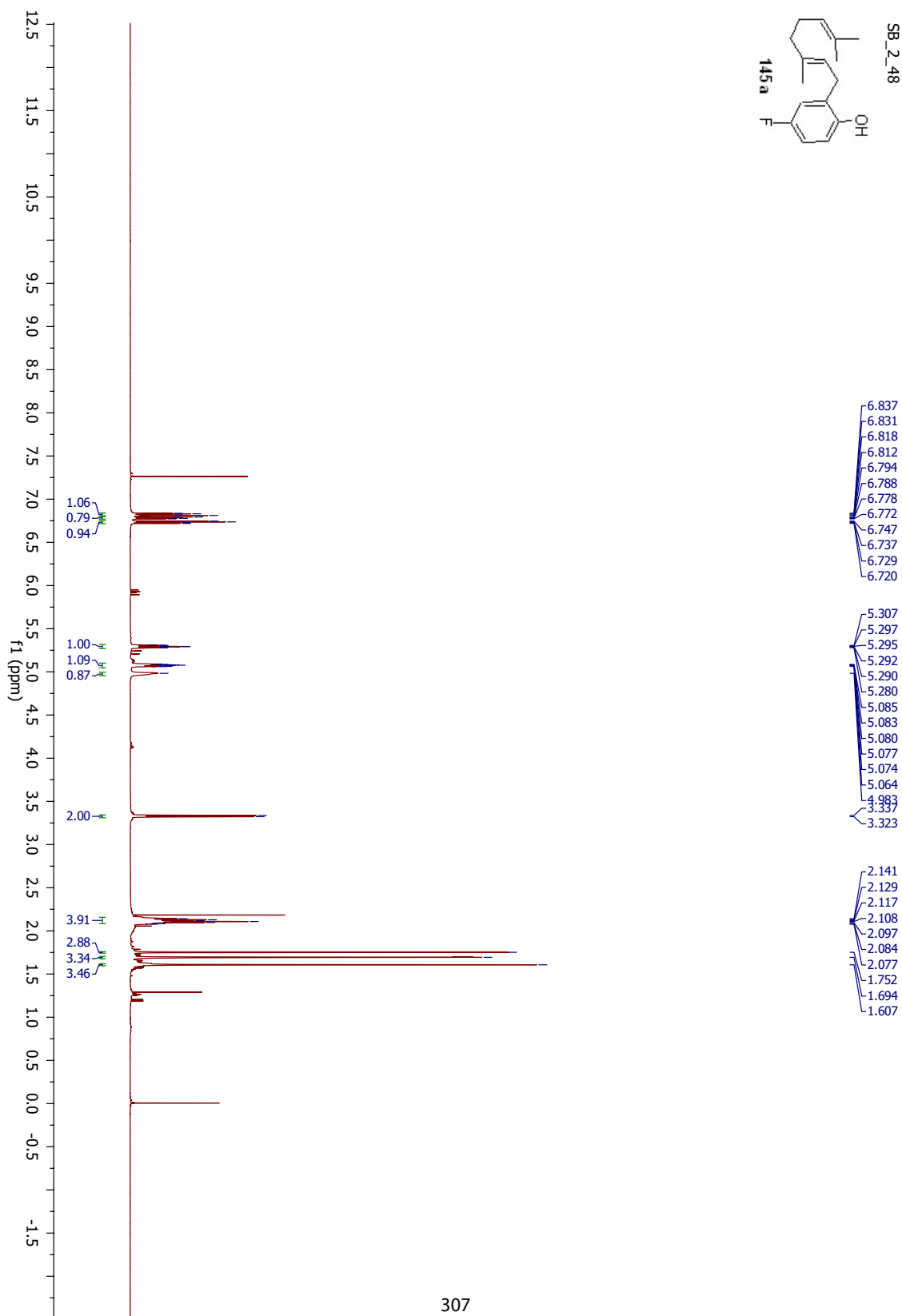
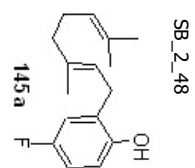


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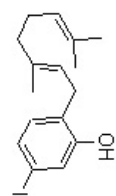




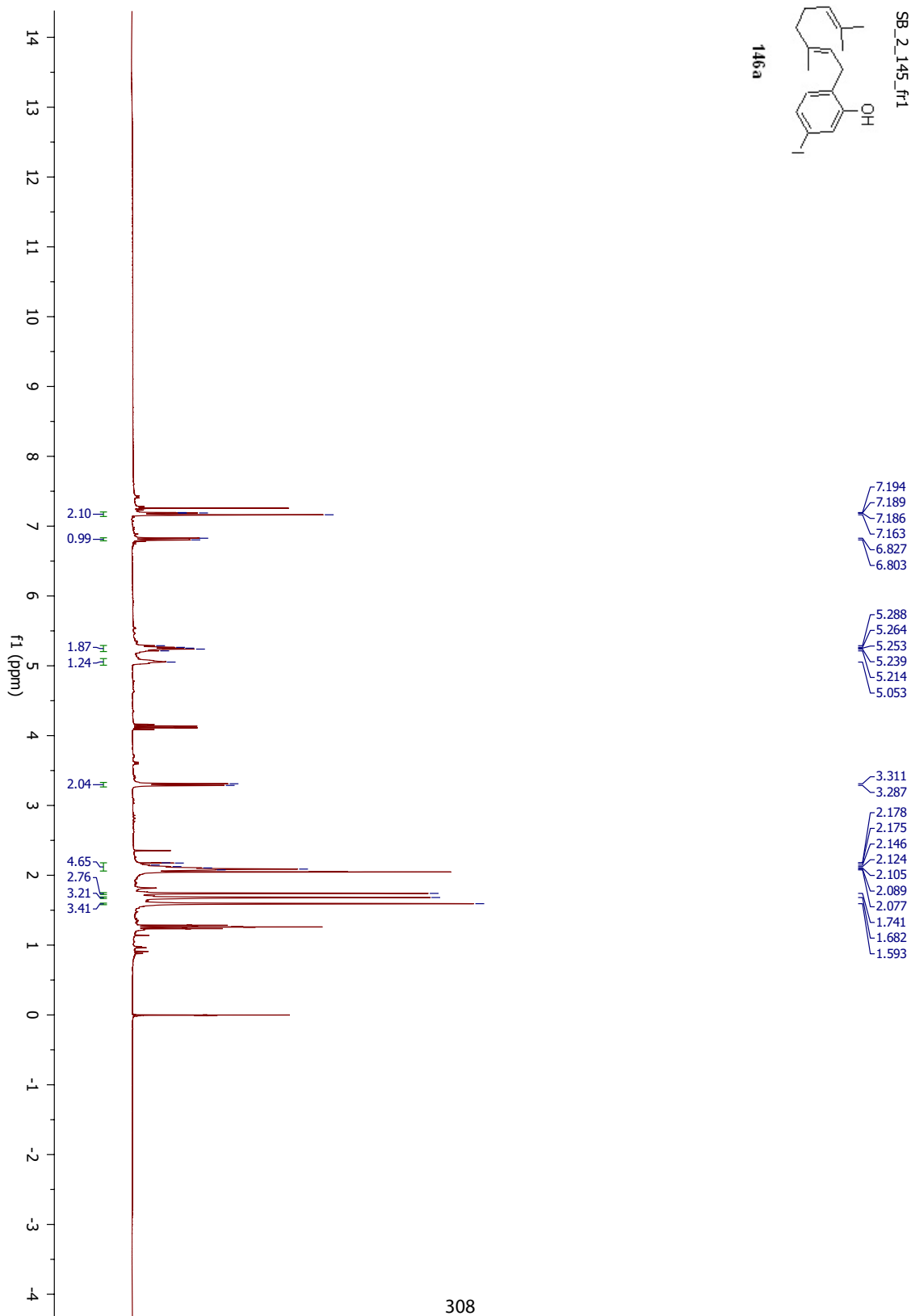




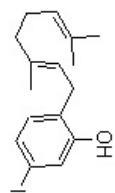
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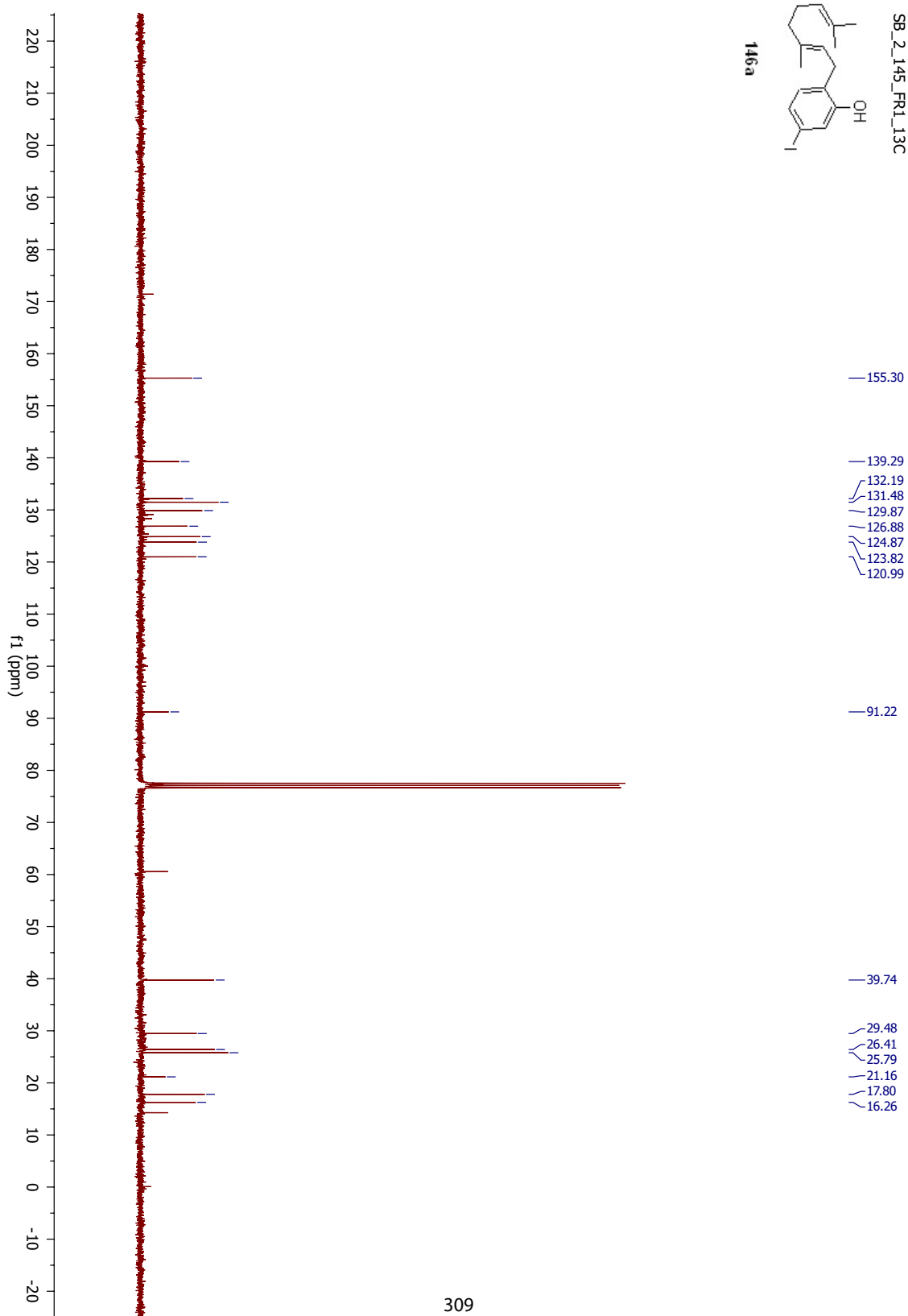
146a



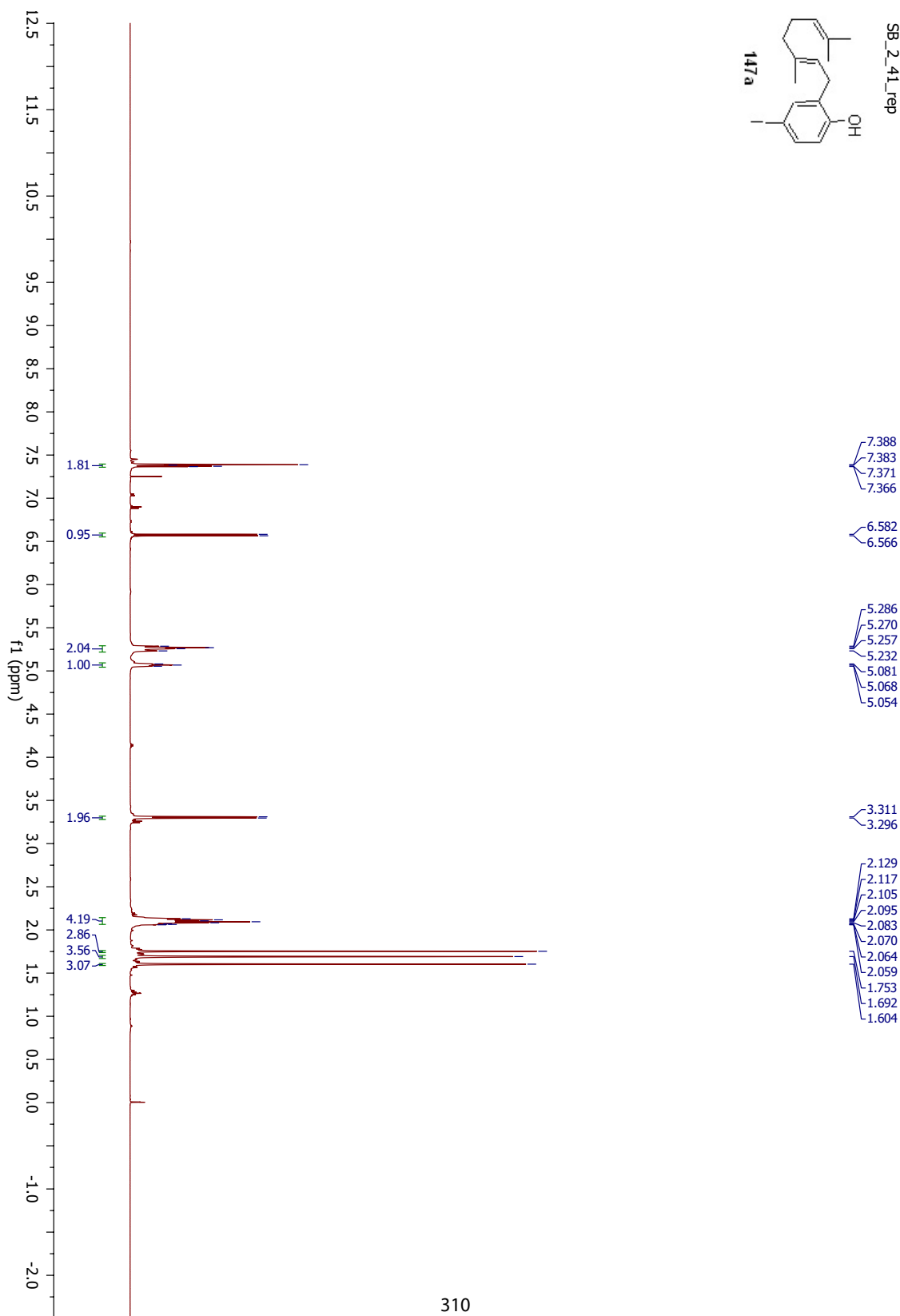
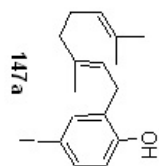
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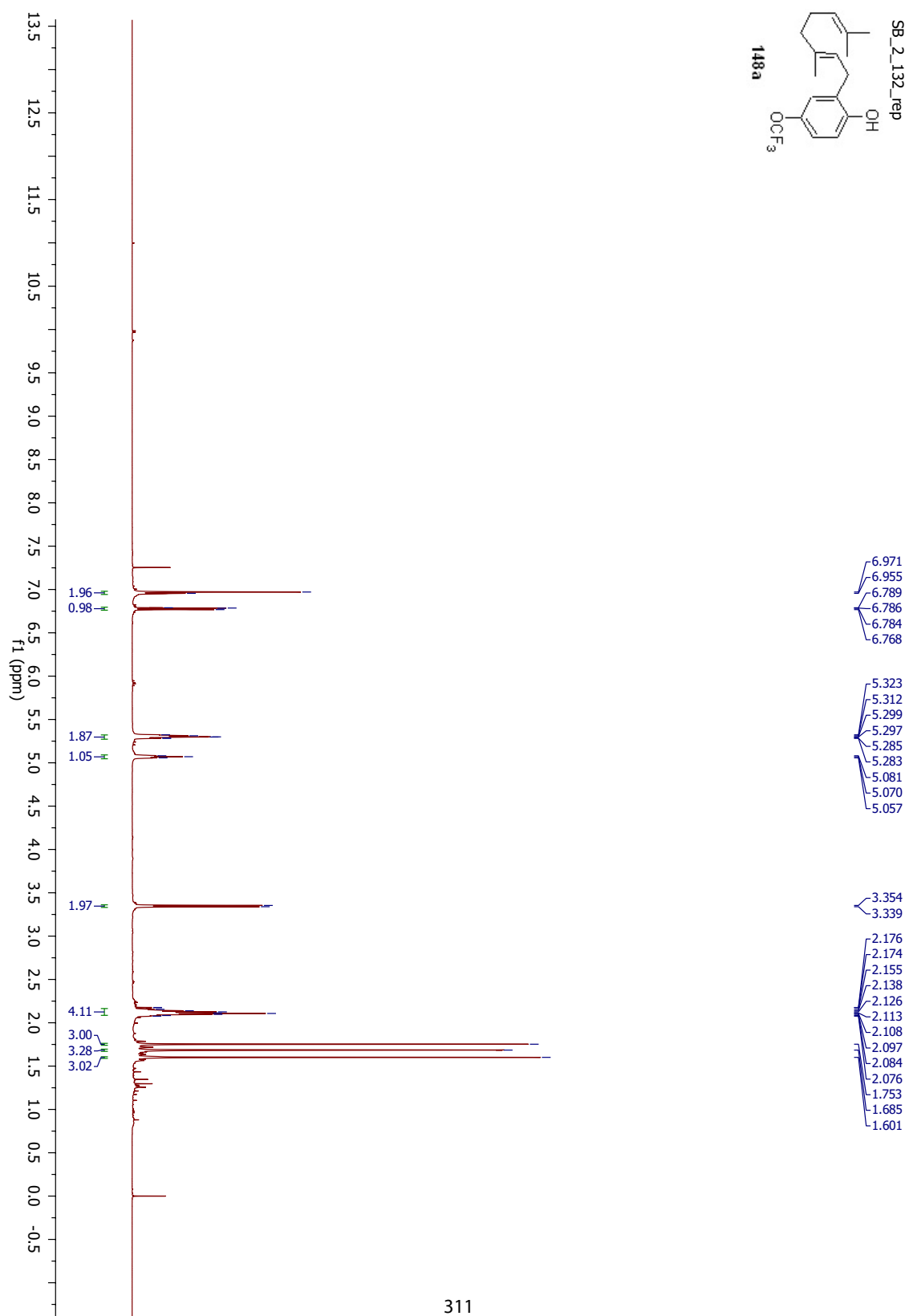
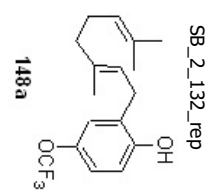


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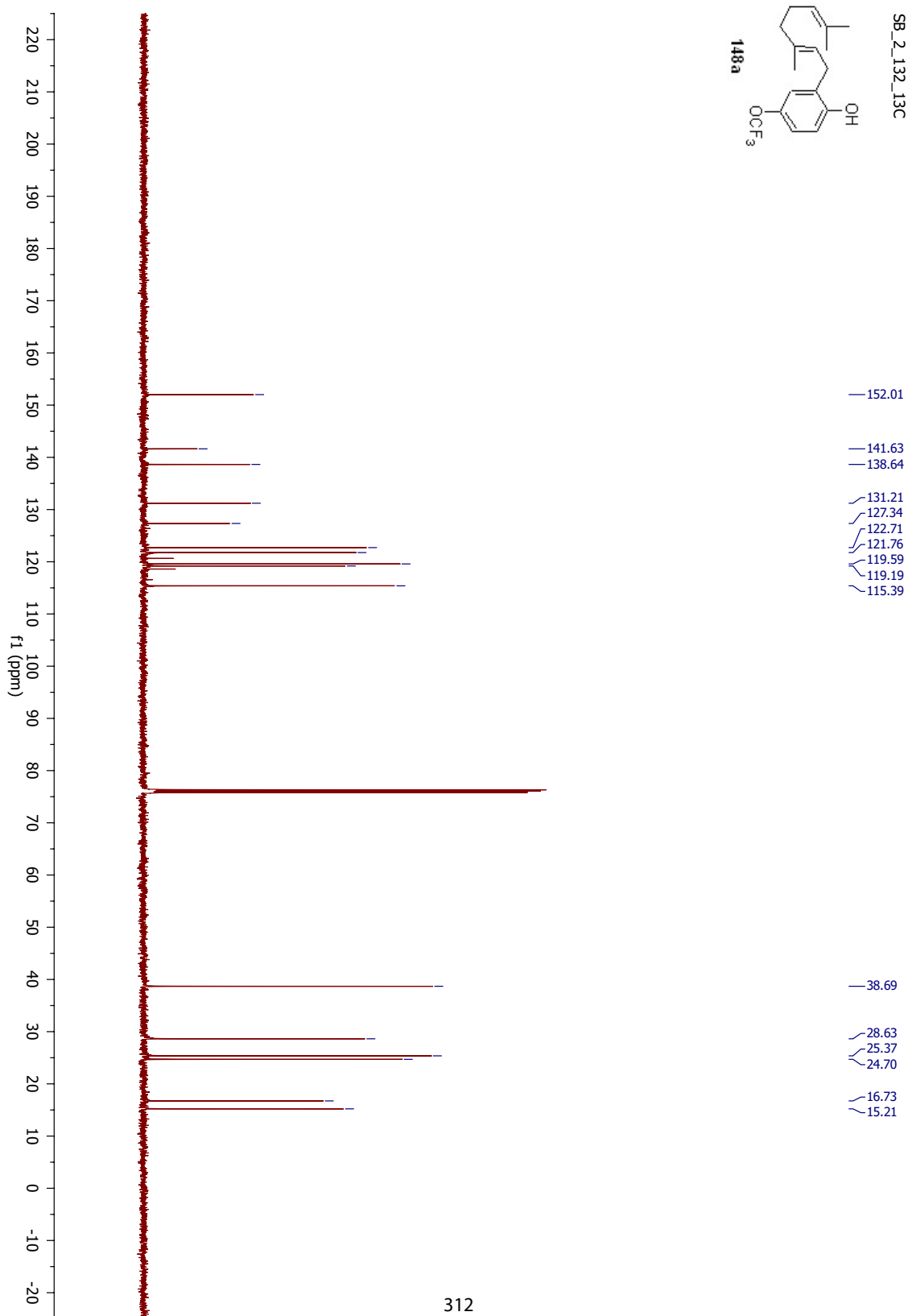
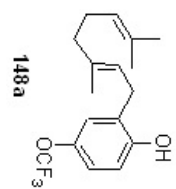


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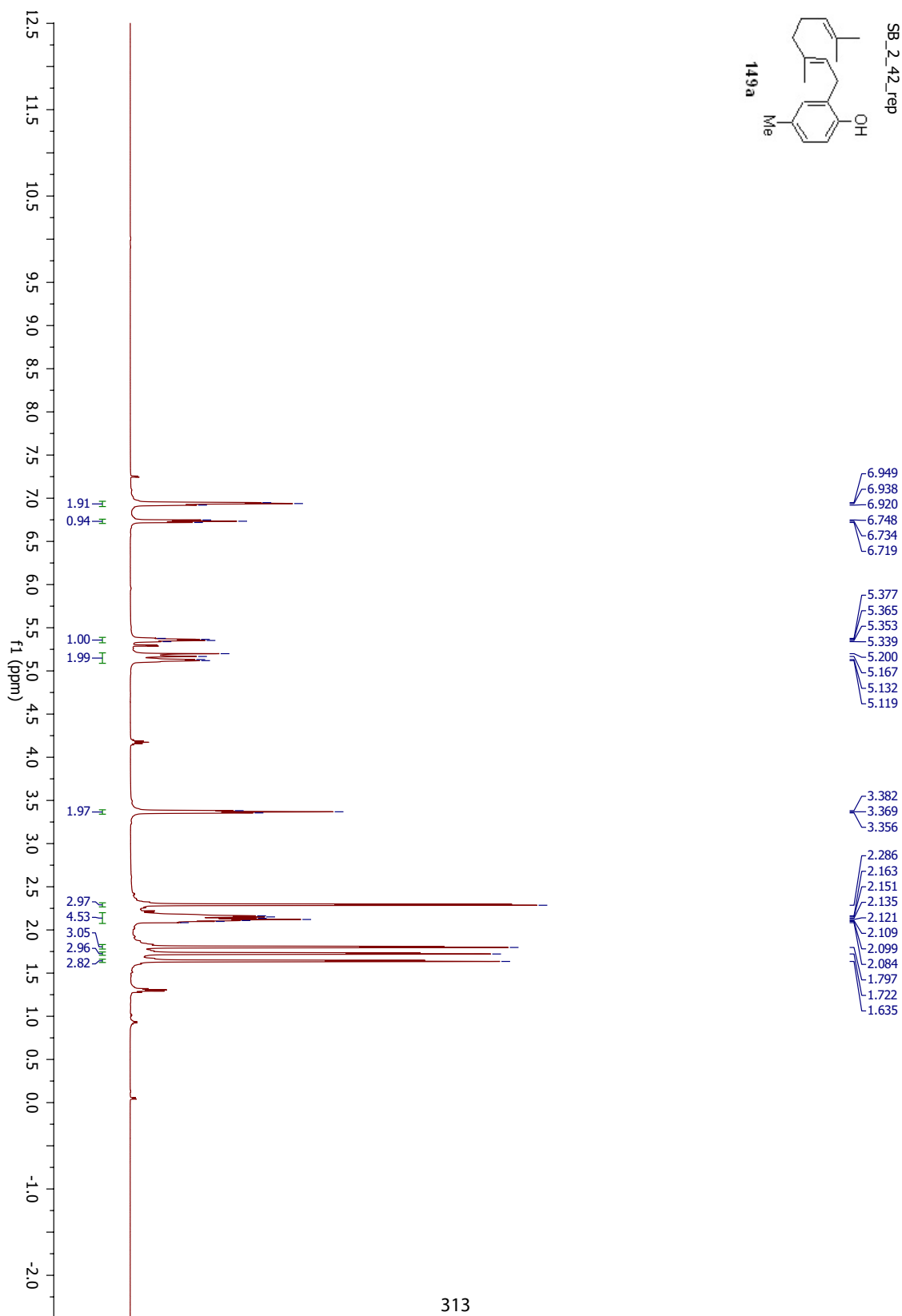
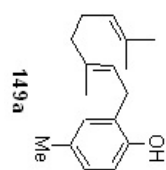


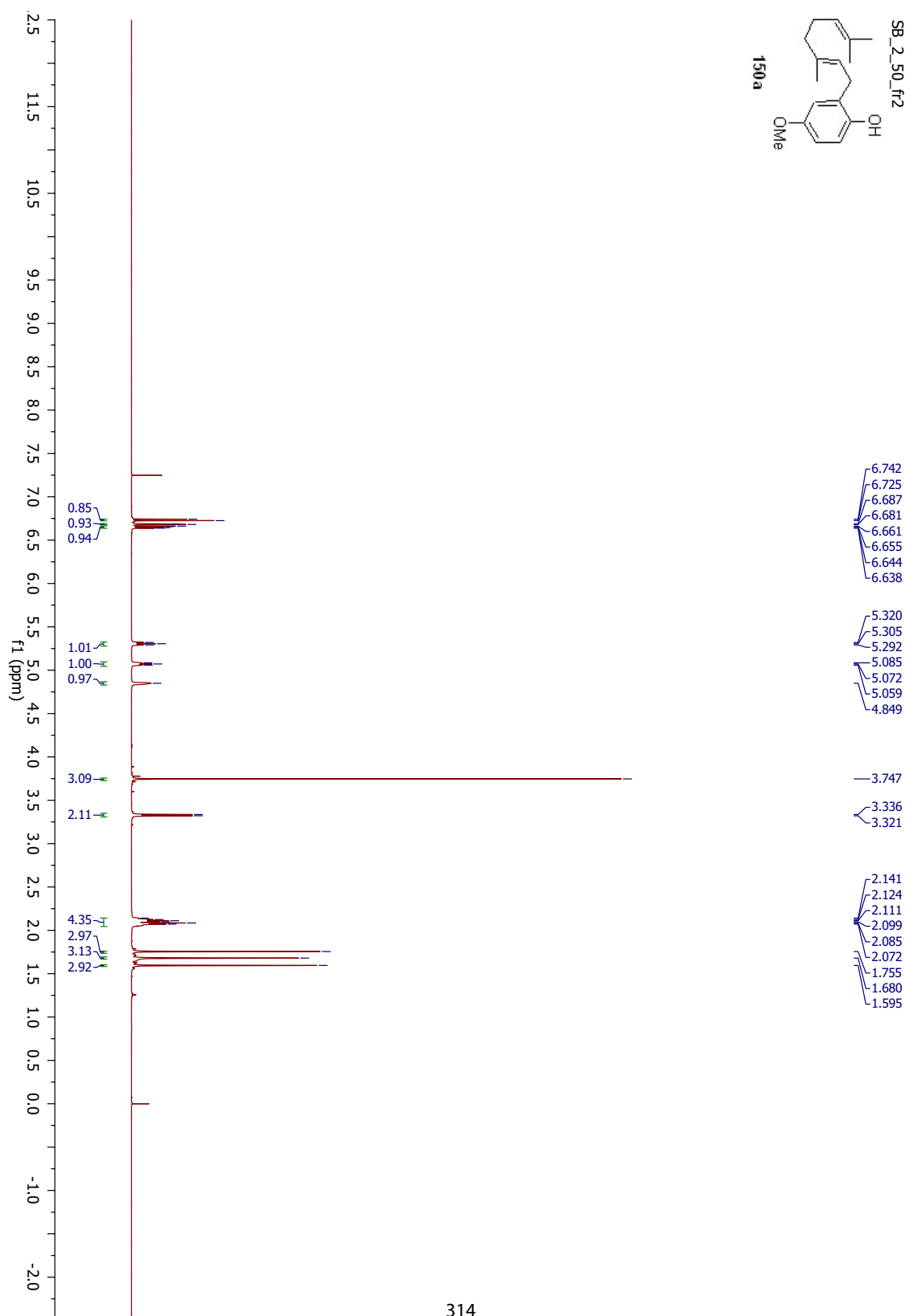
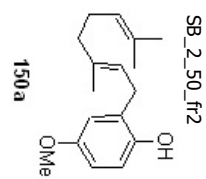


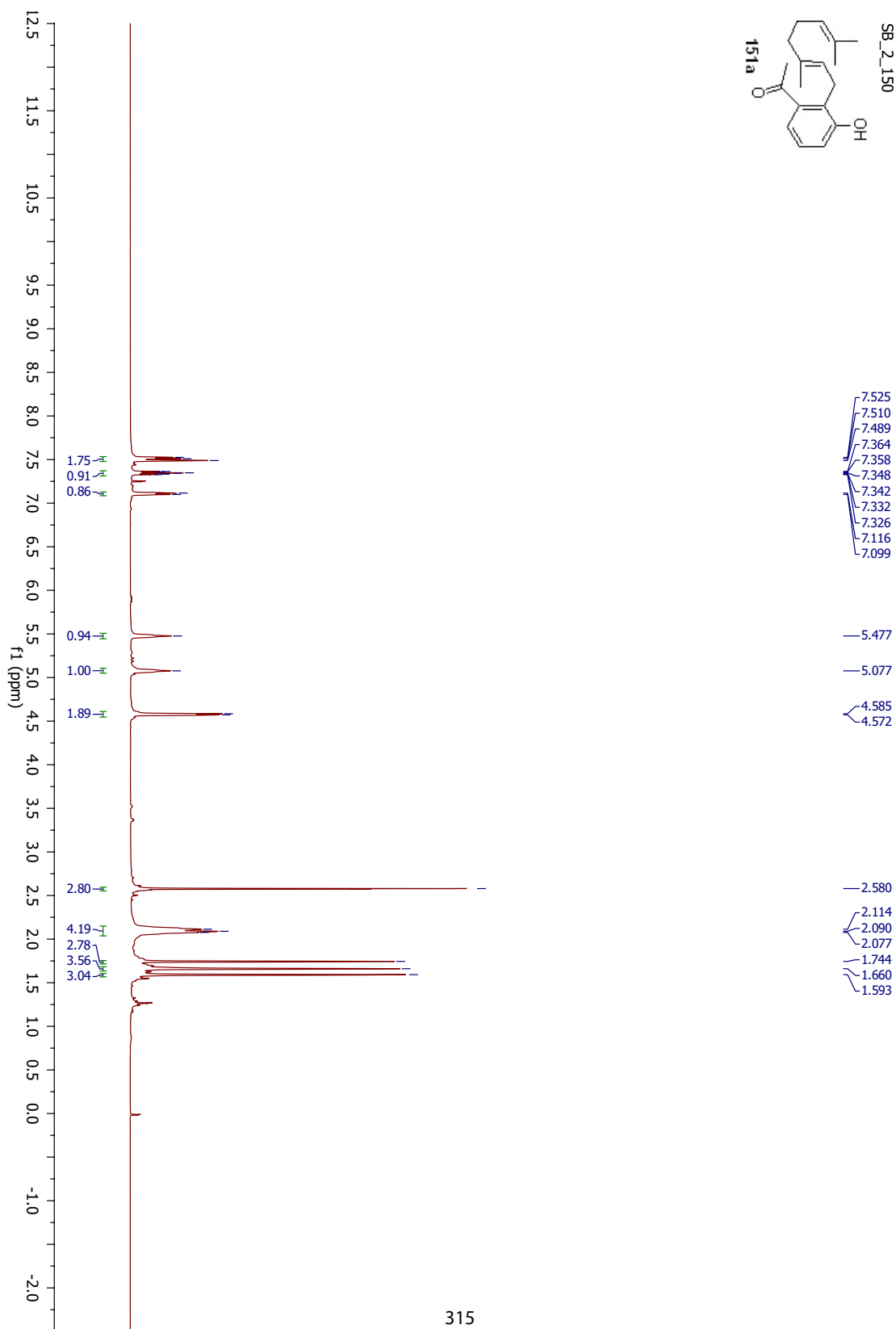
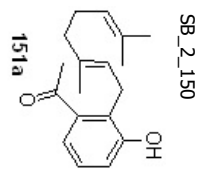
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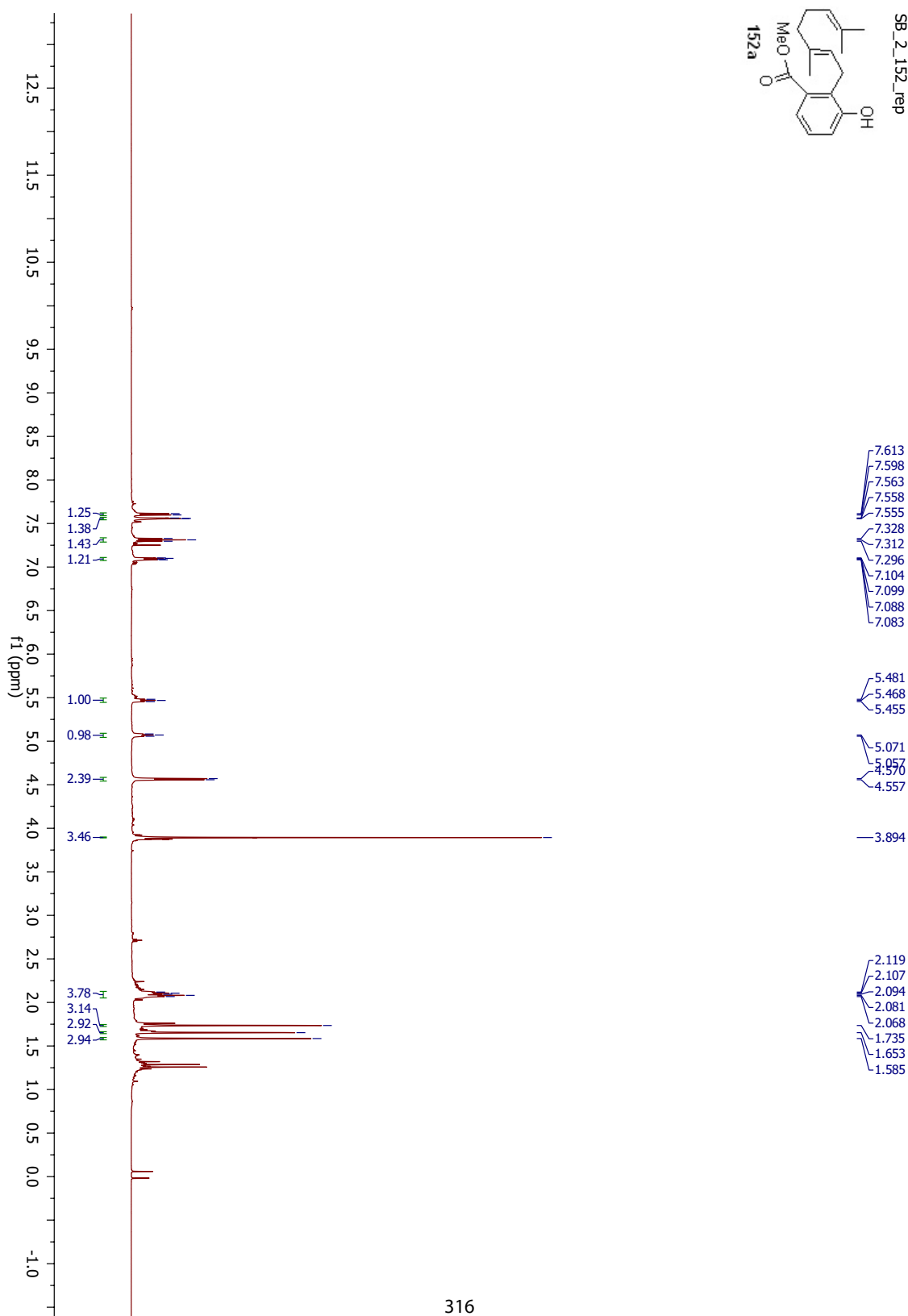
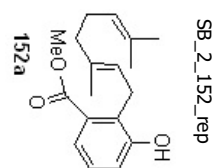


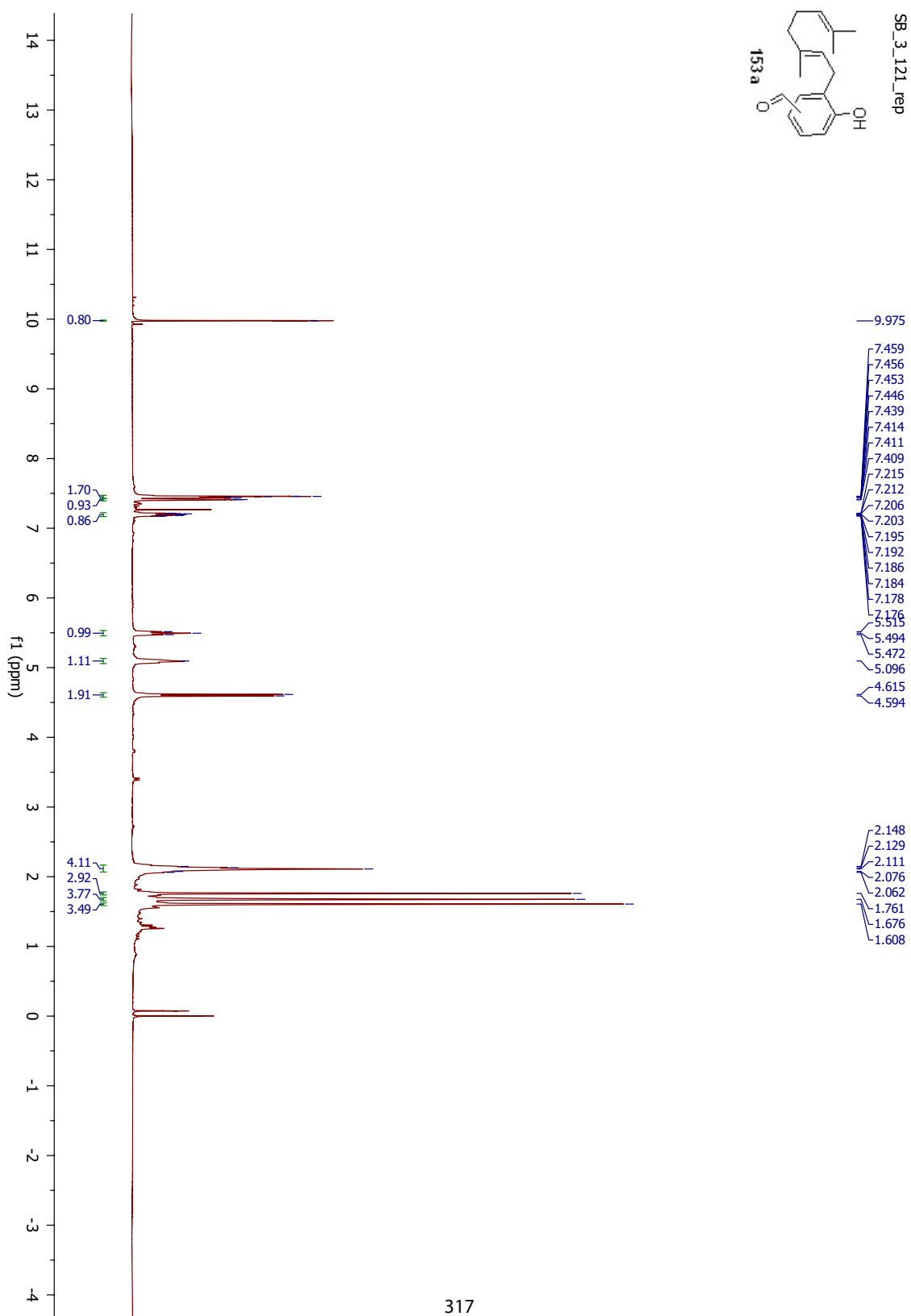
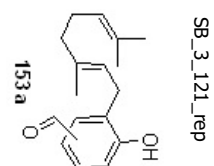
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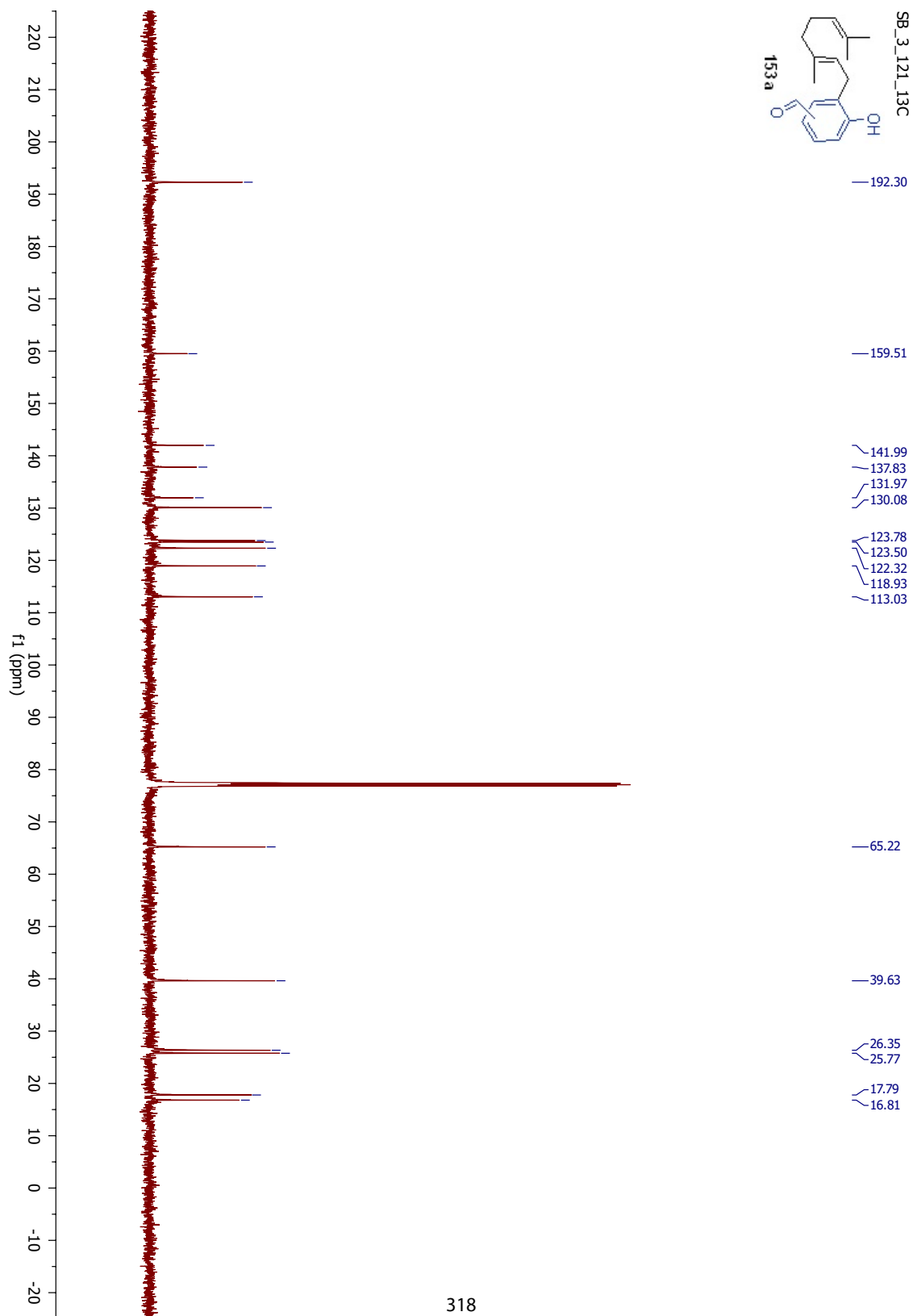


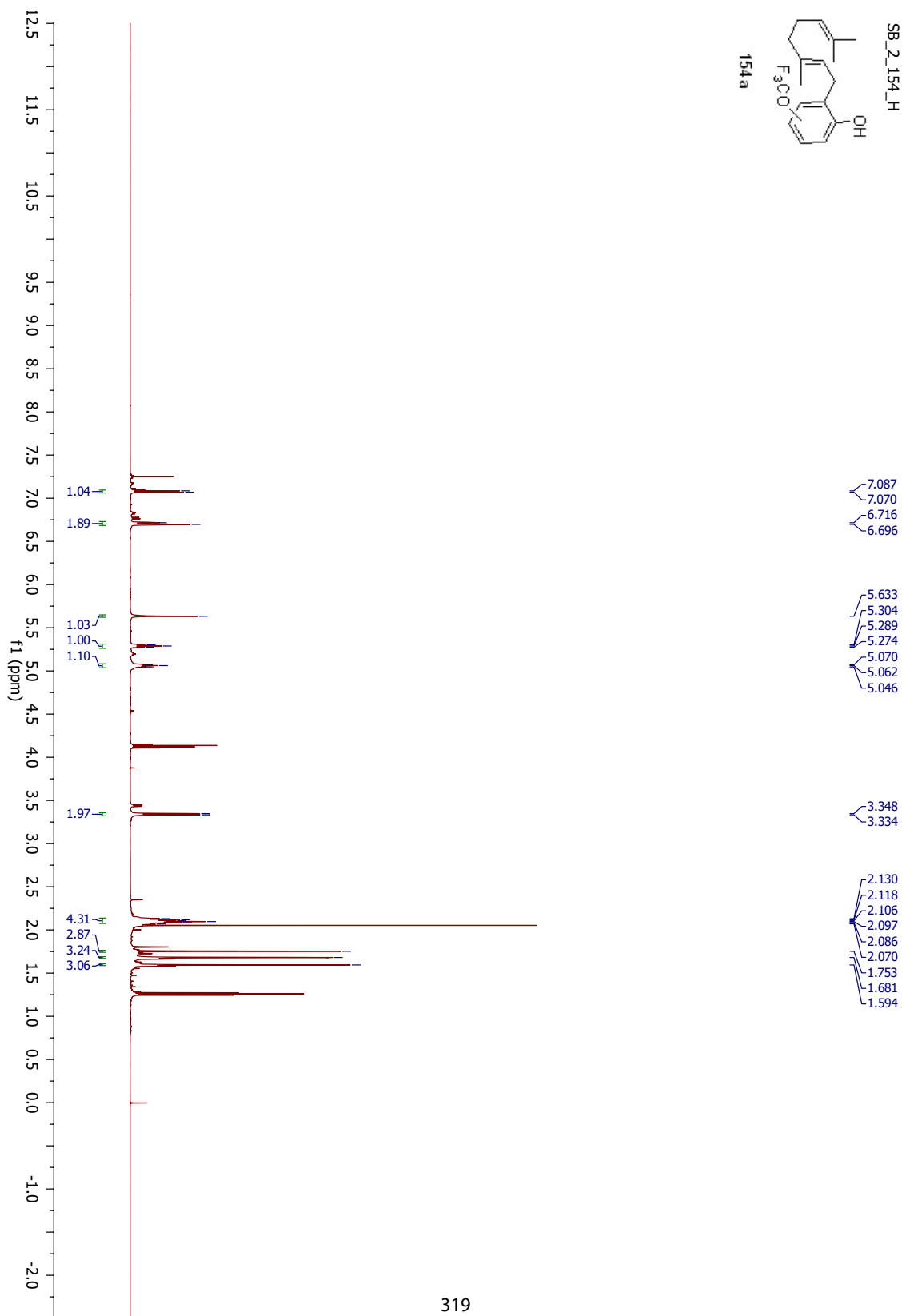
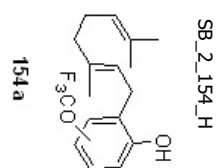


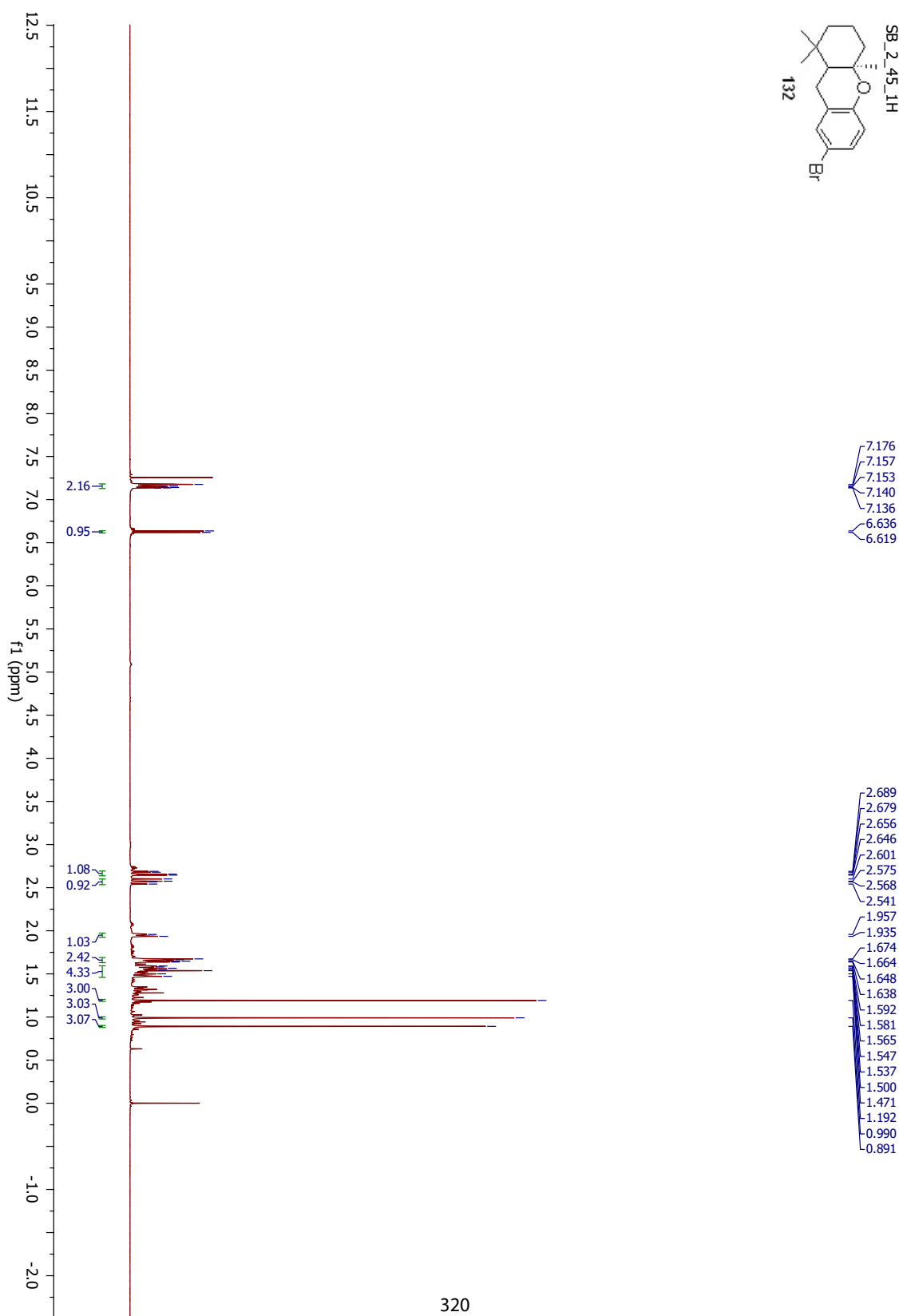
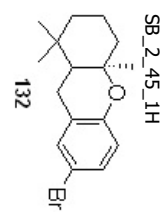


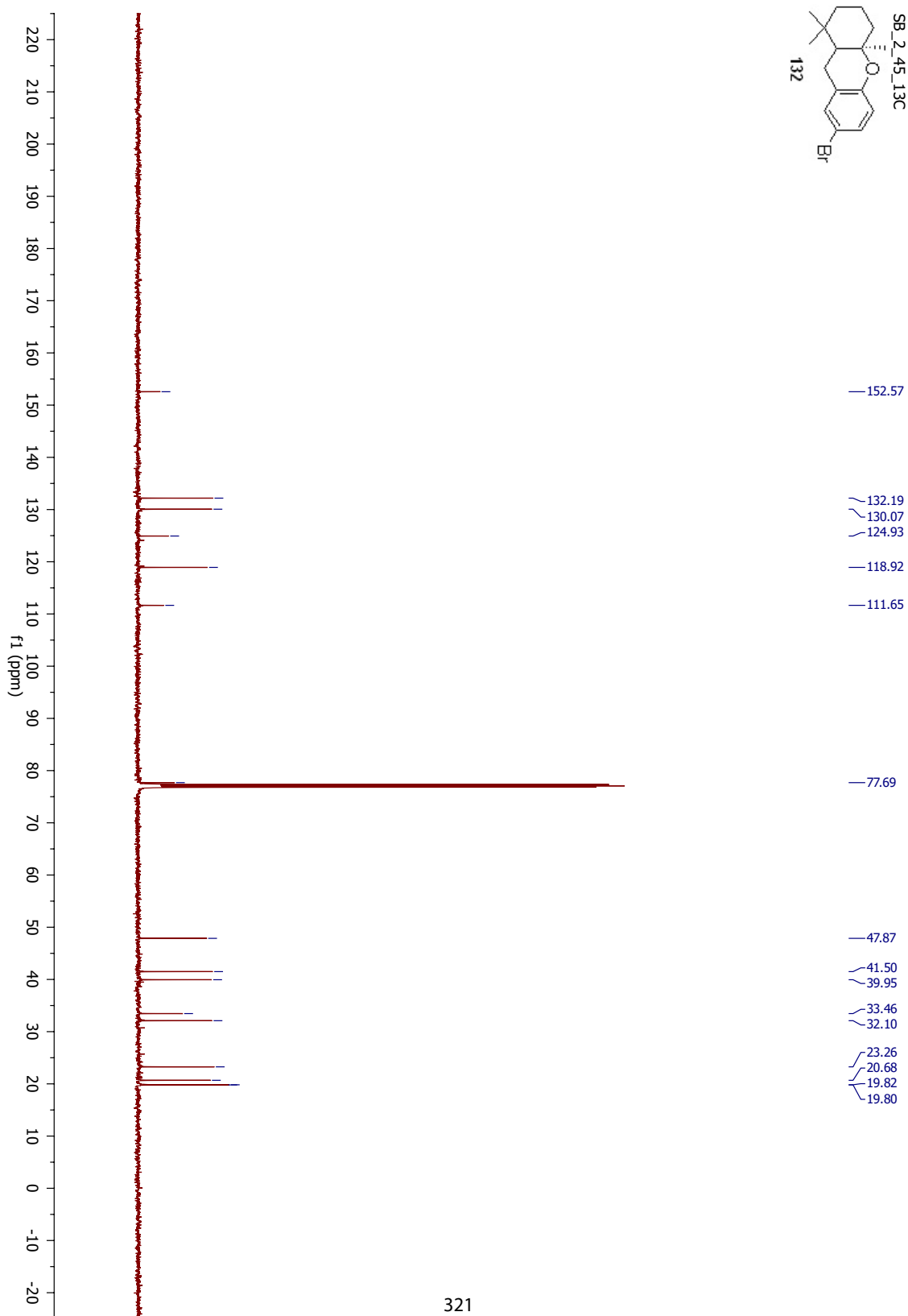
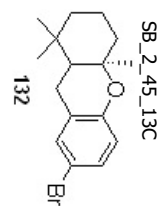


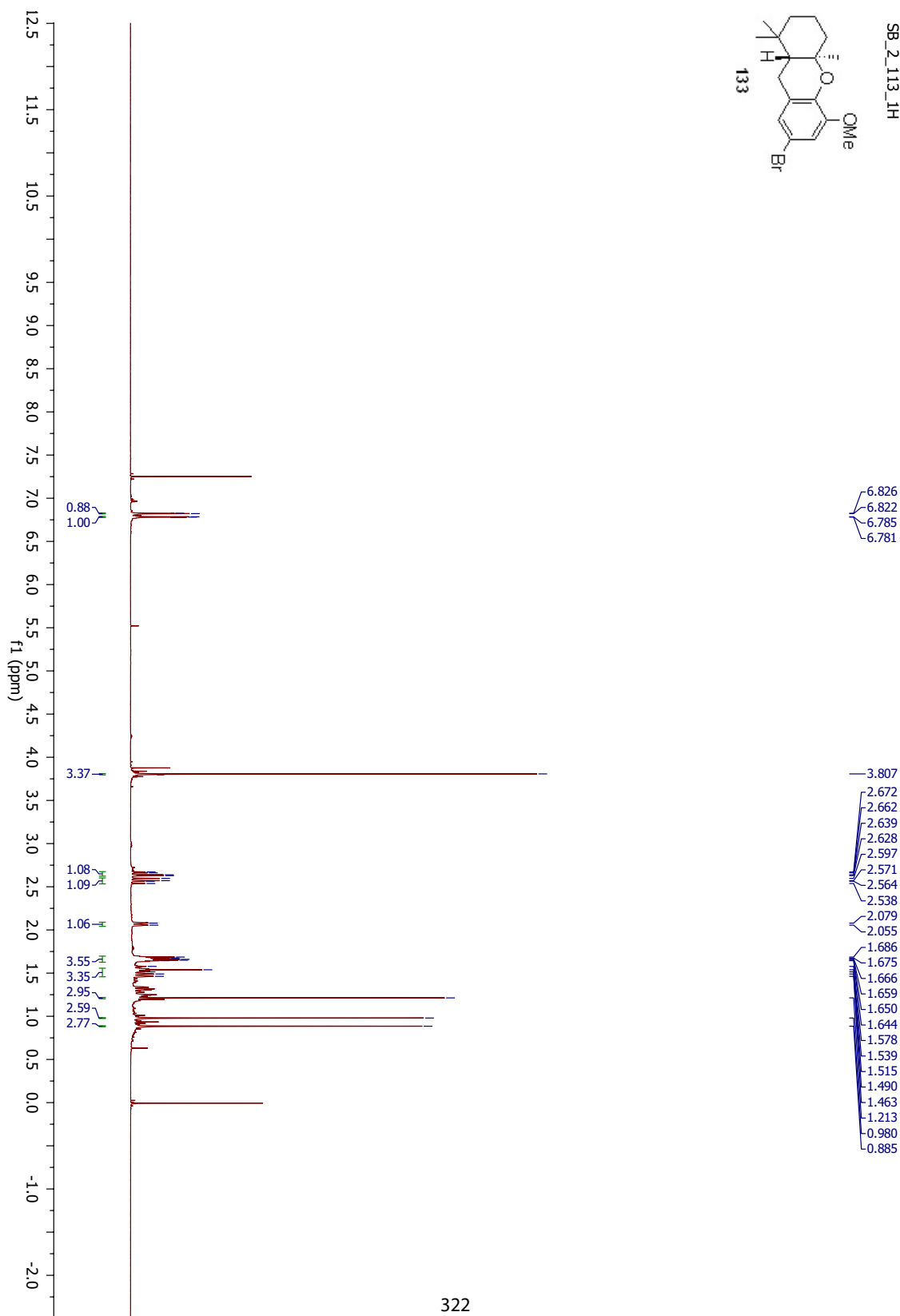
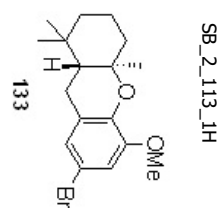




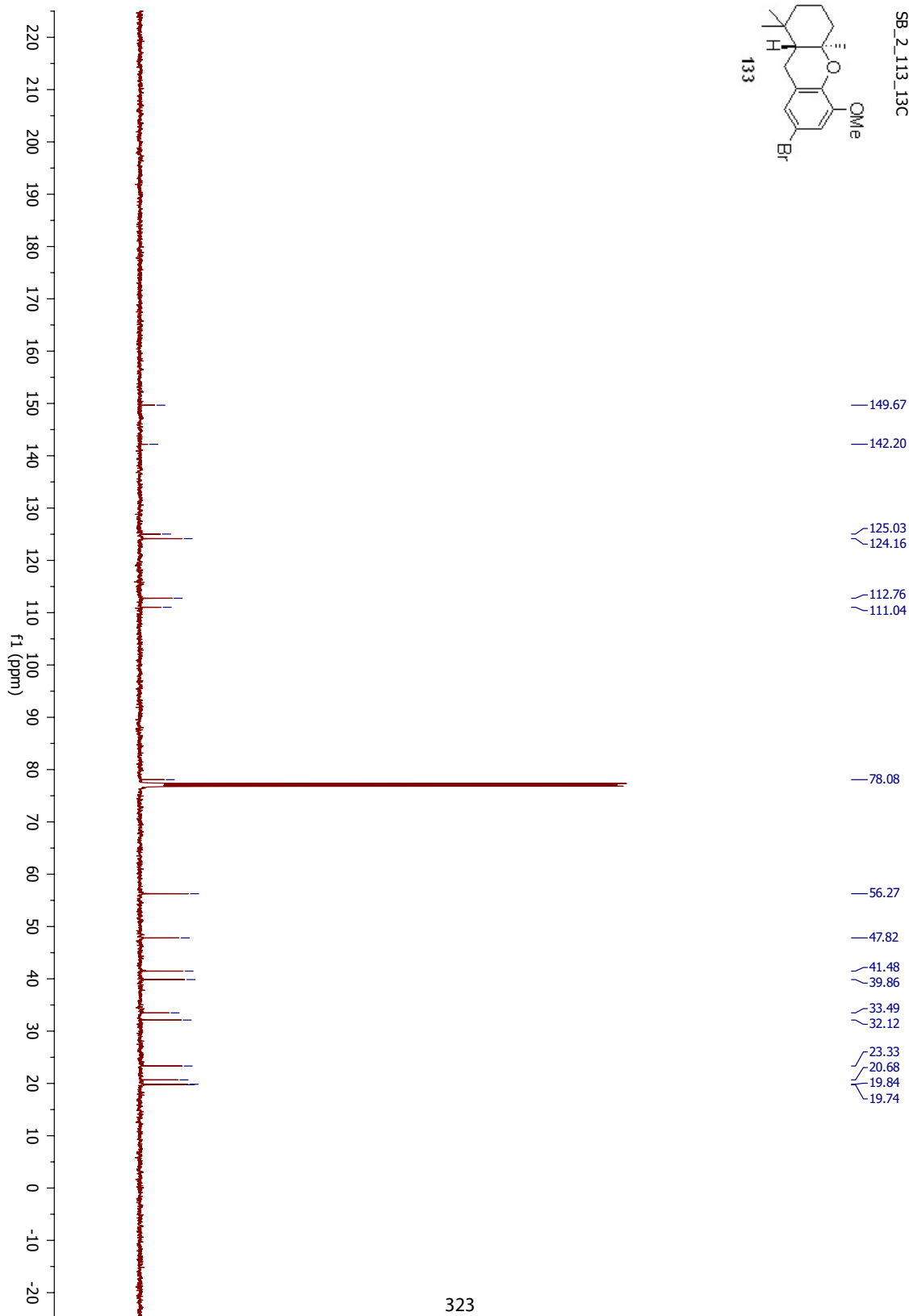
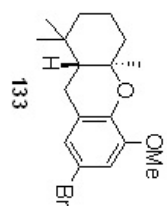


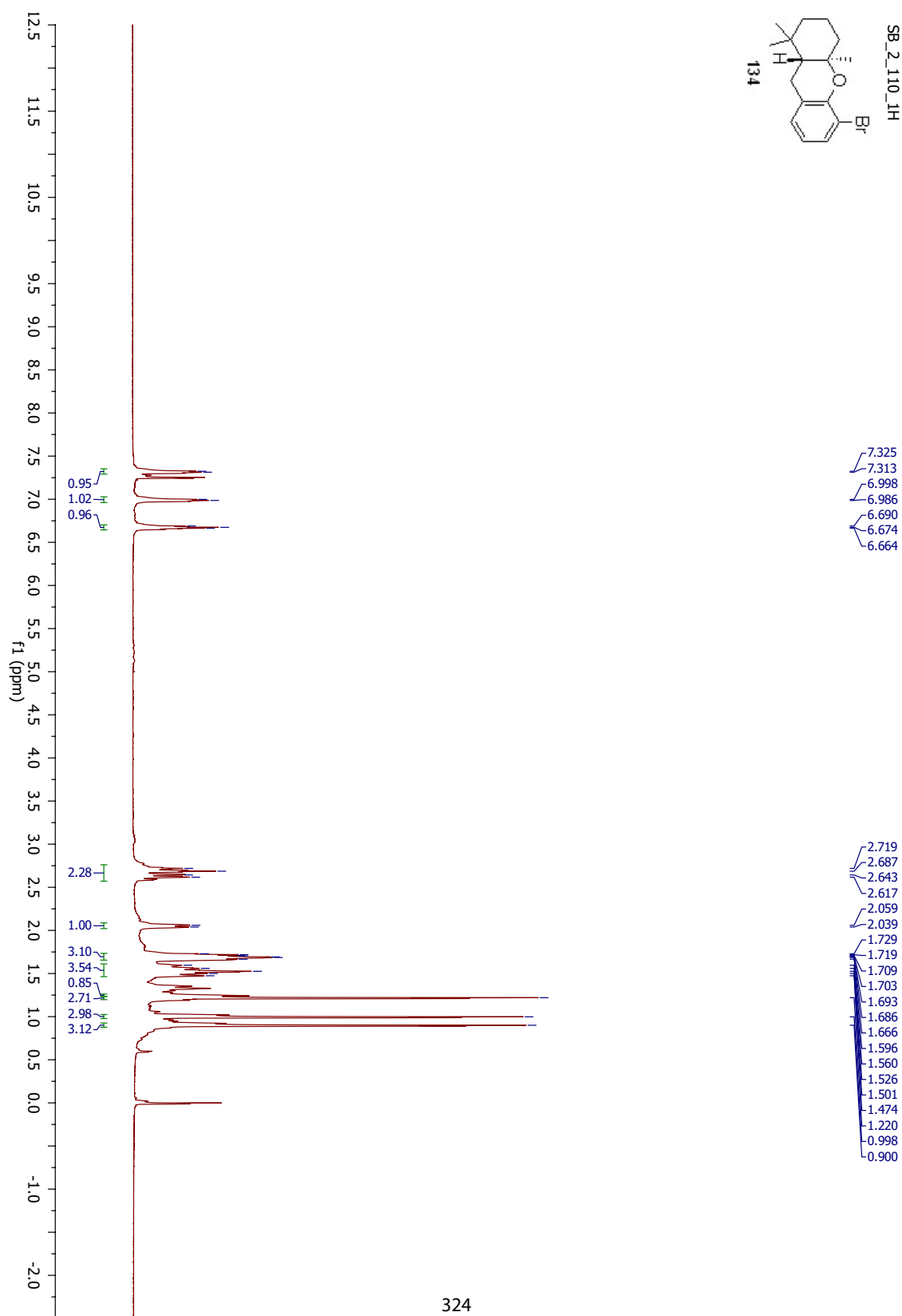
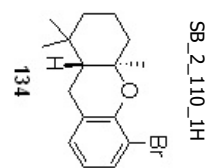




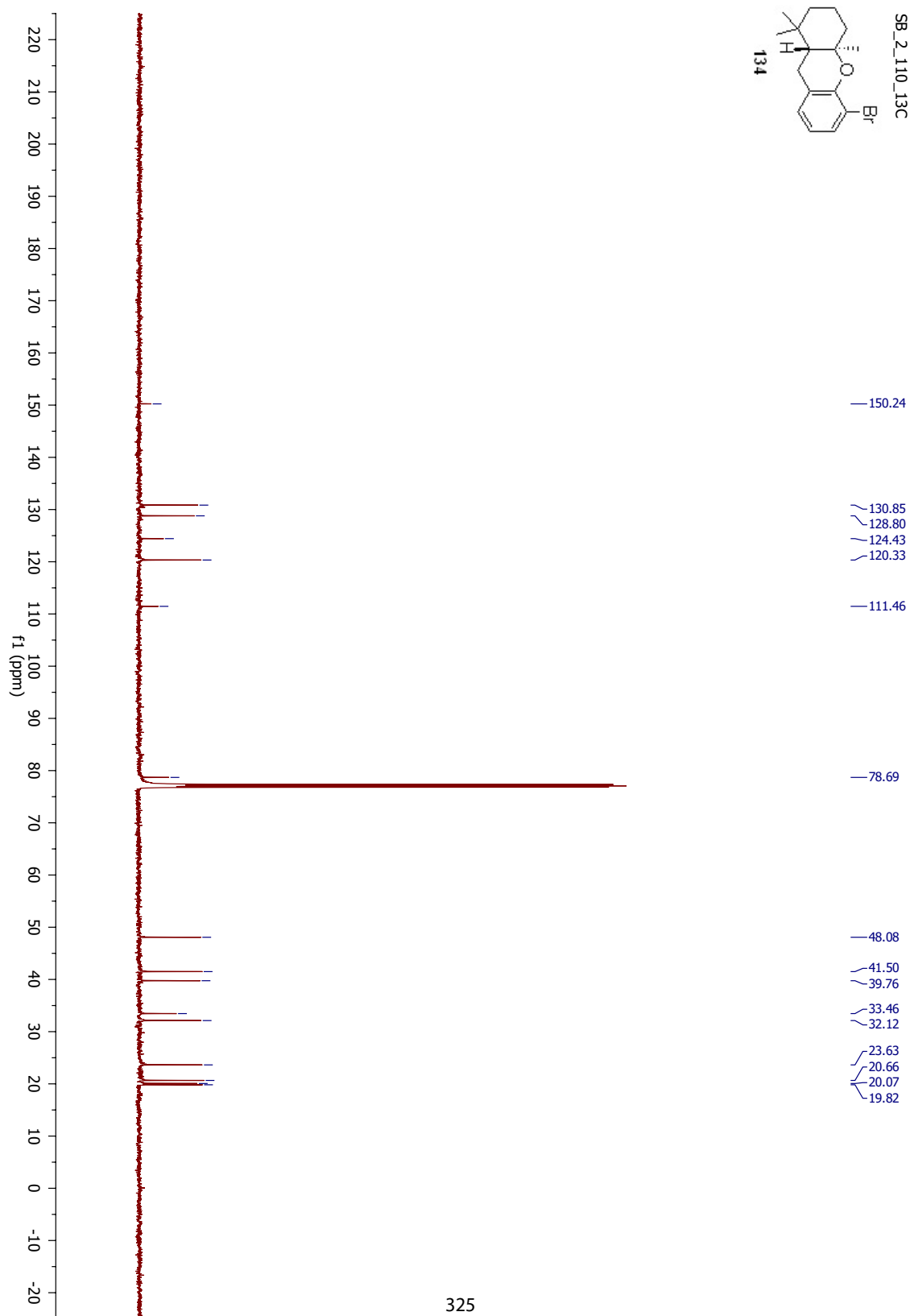
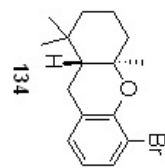


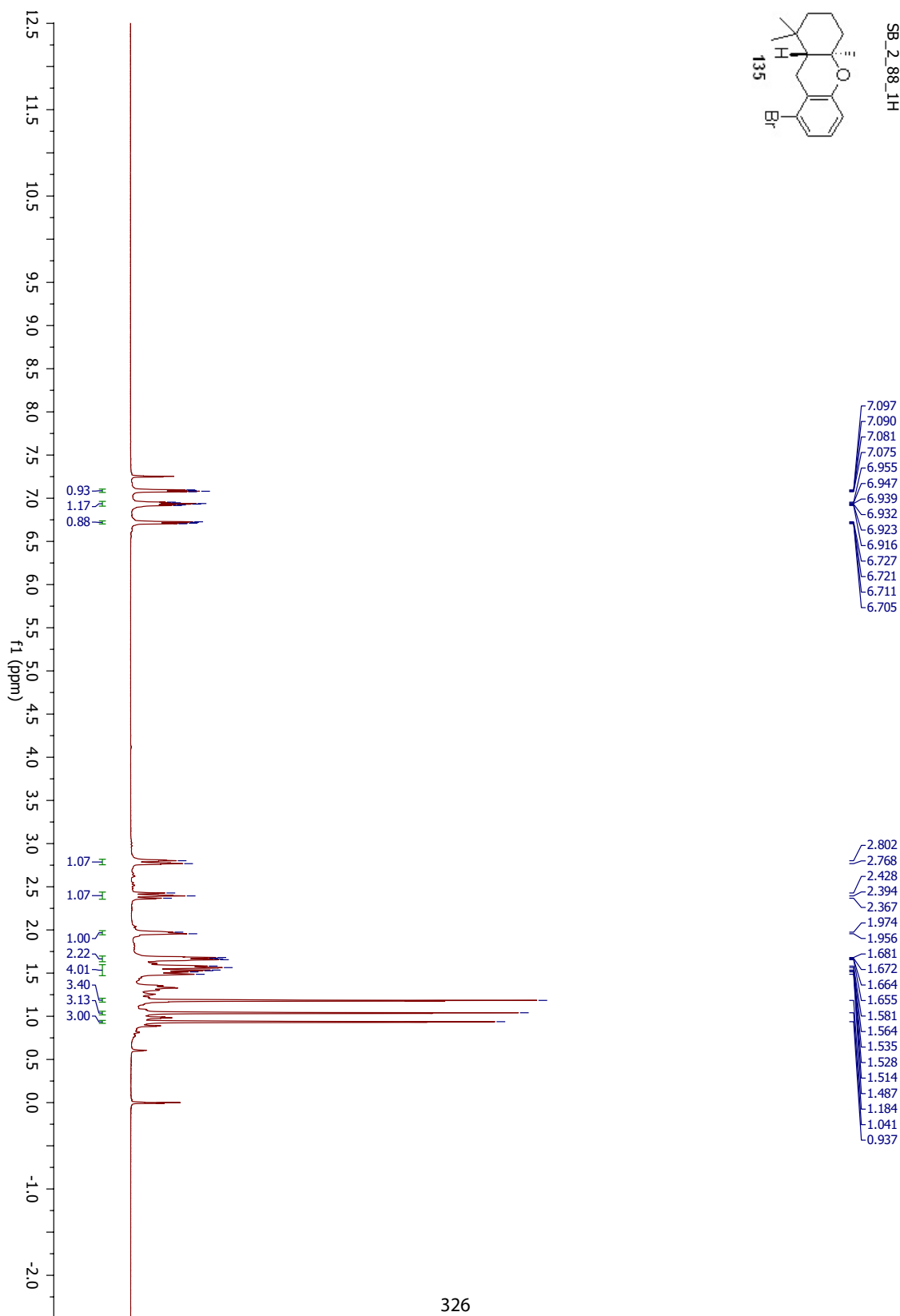
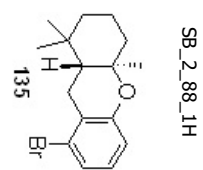
SB_2_113_13C



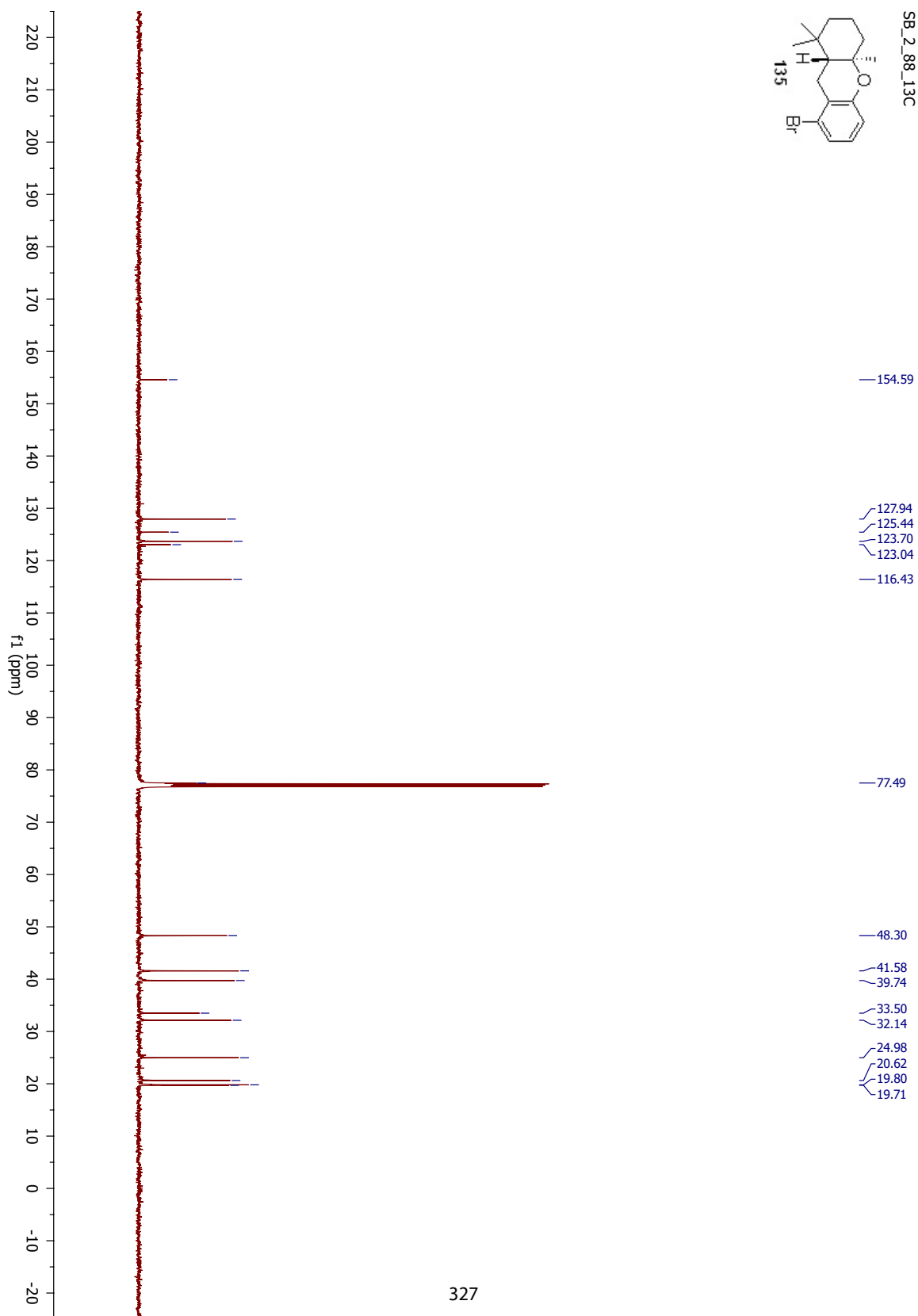
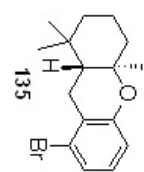


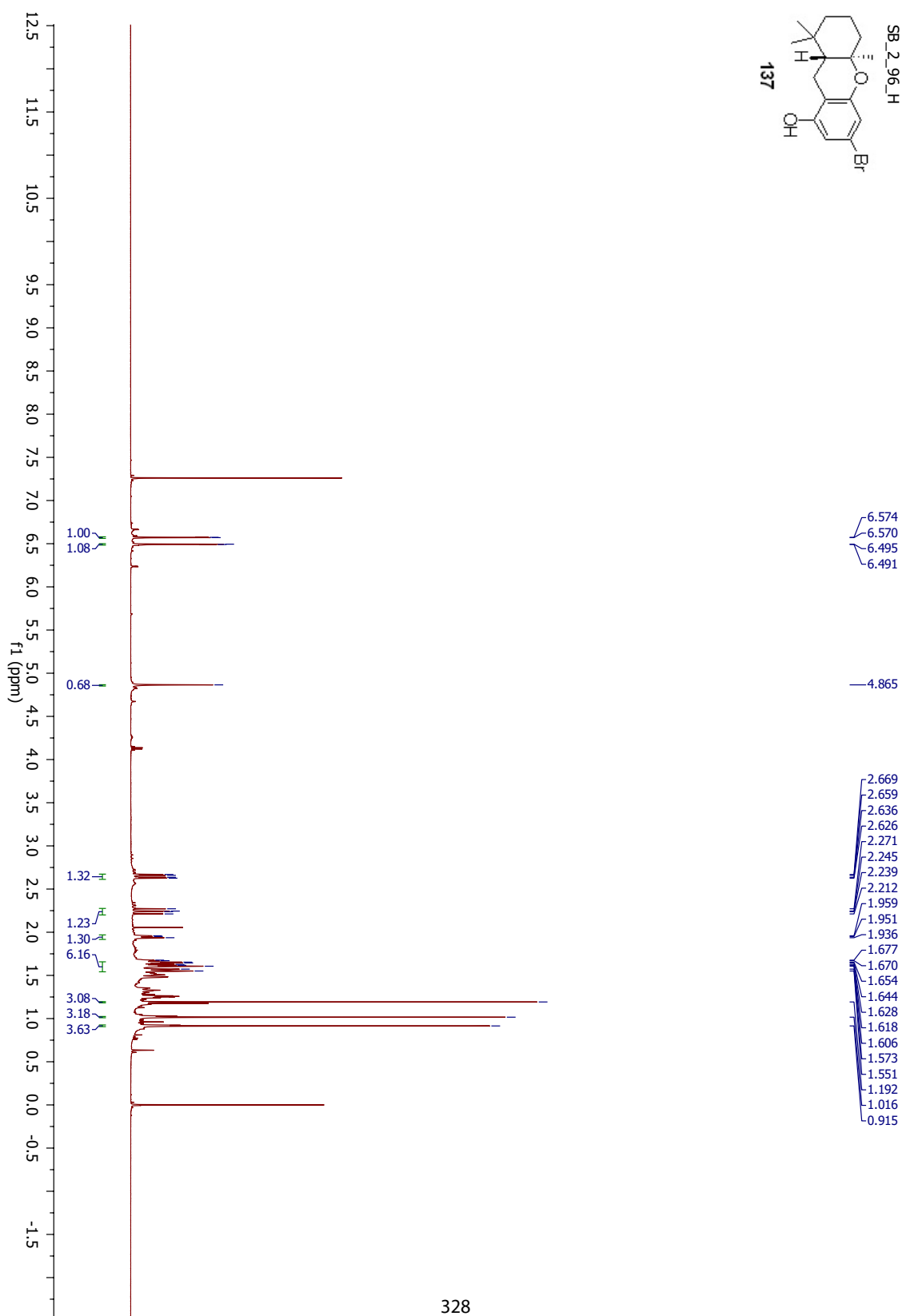
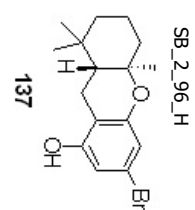
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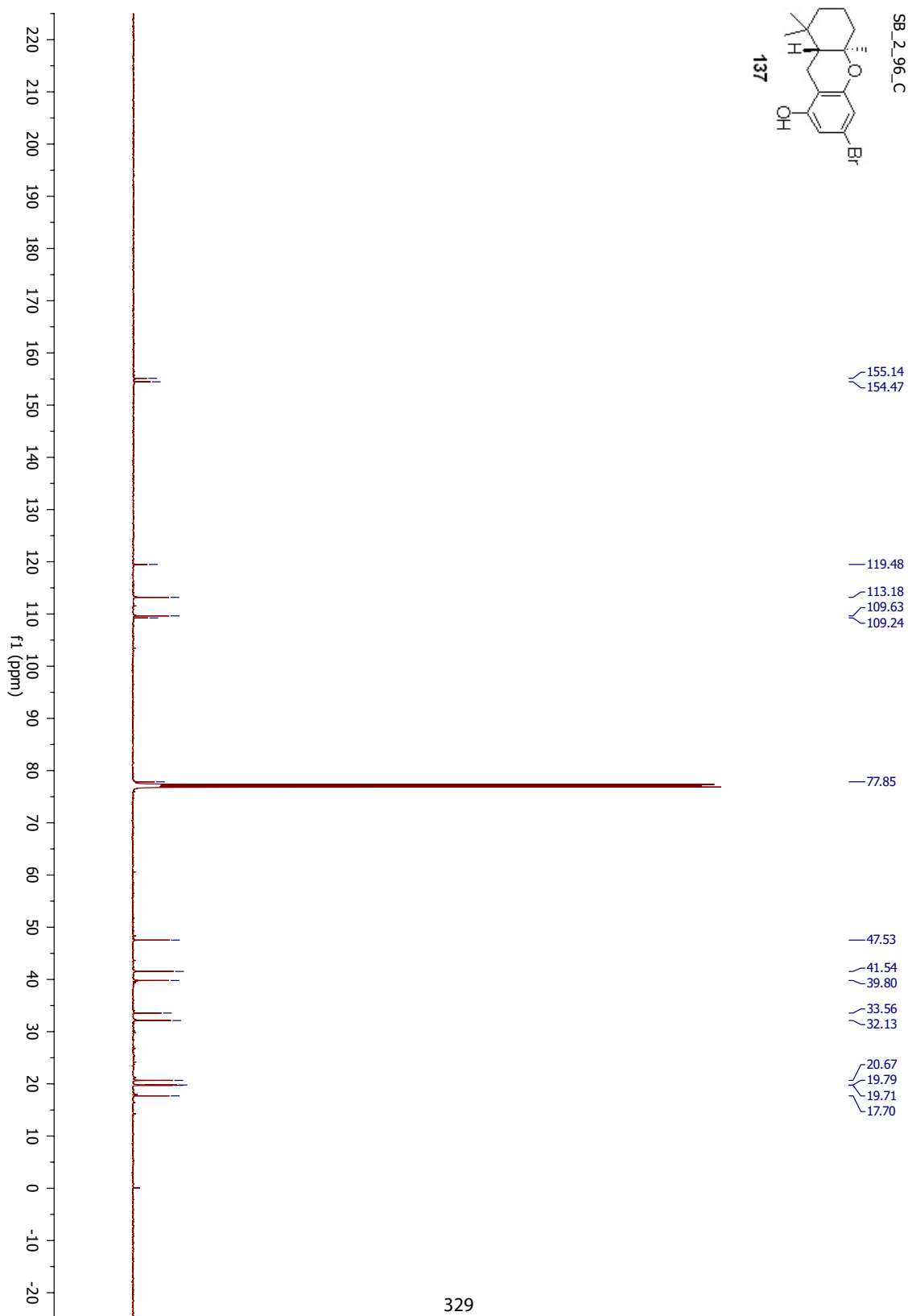
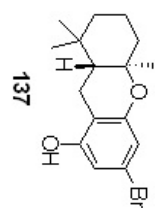


SB_2_88_13C

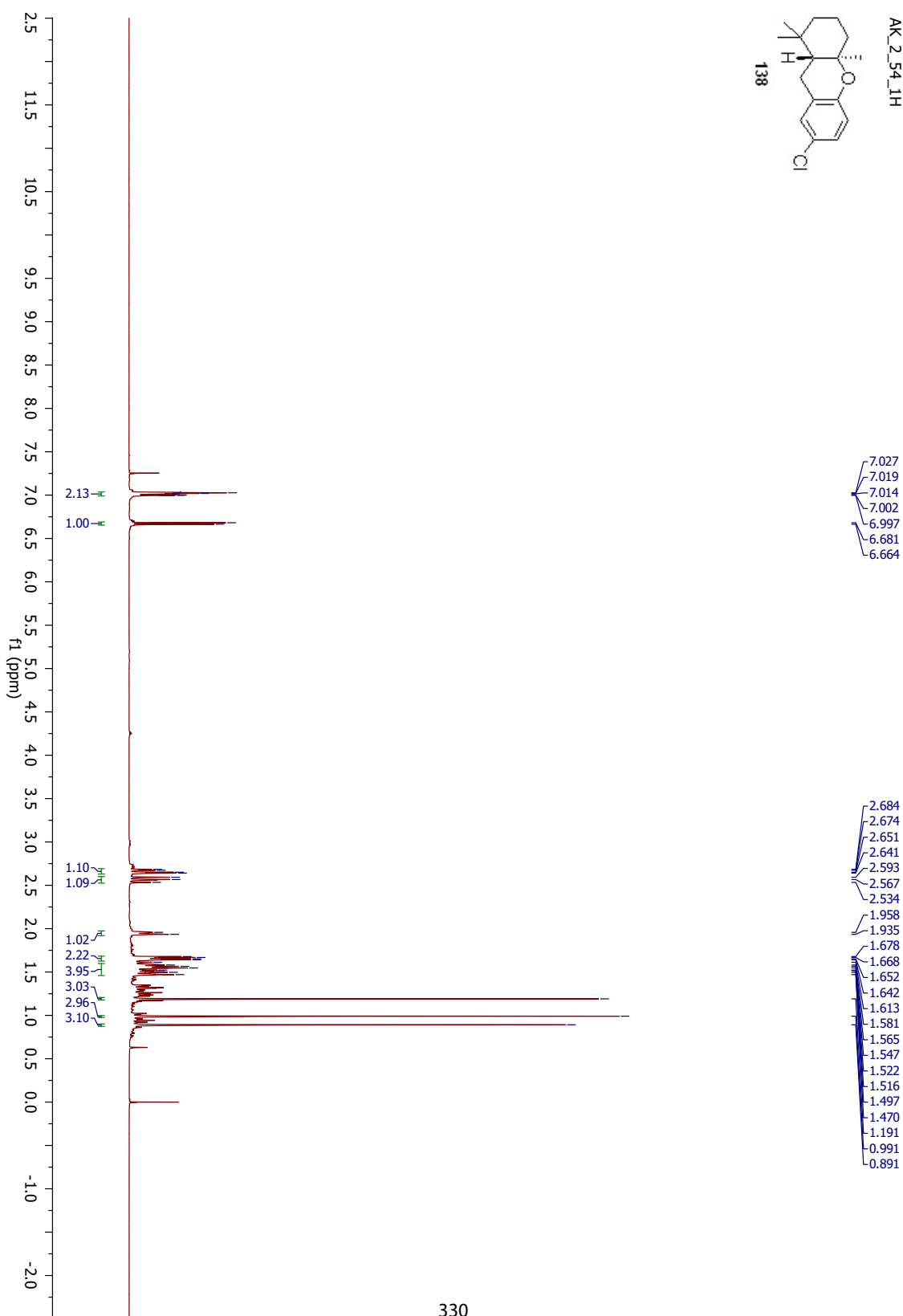
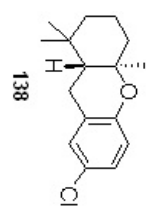




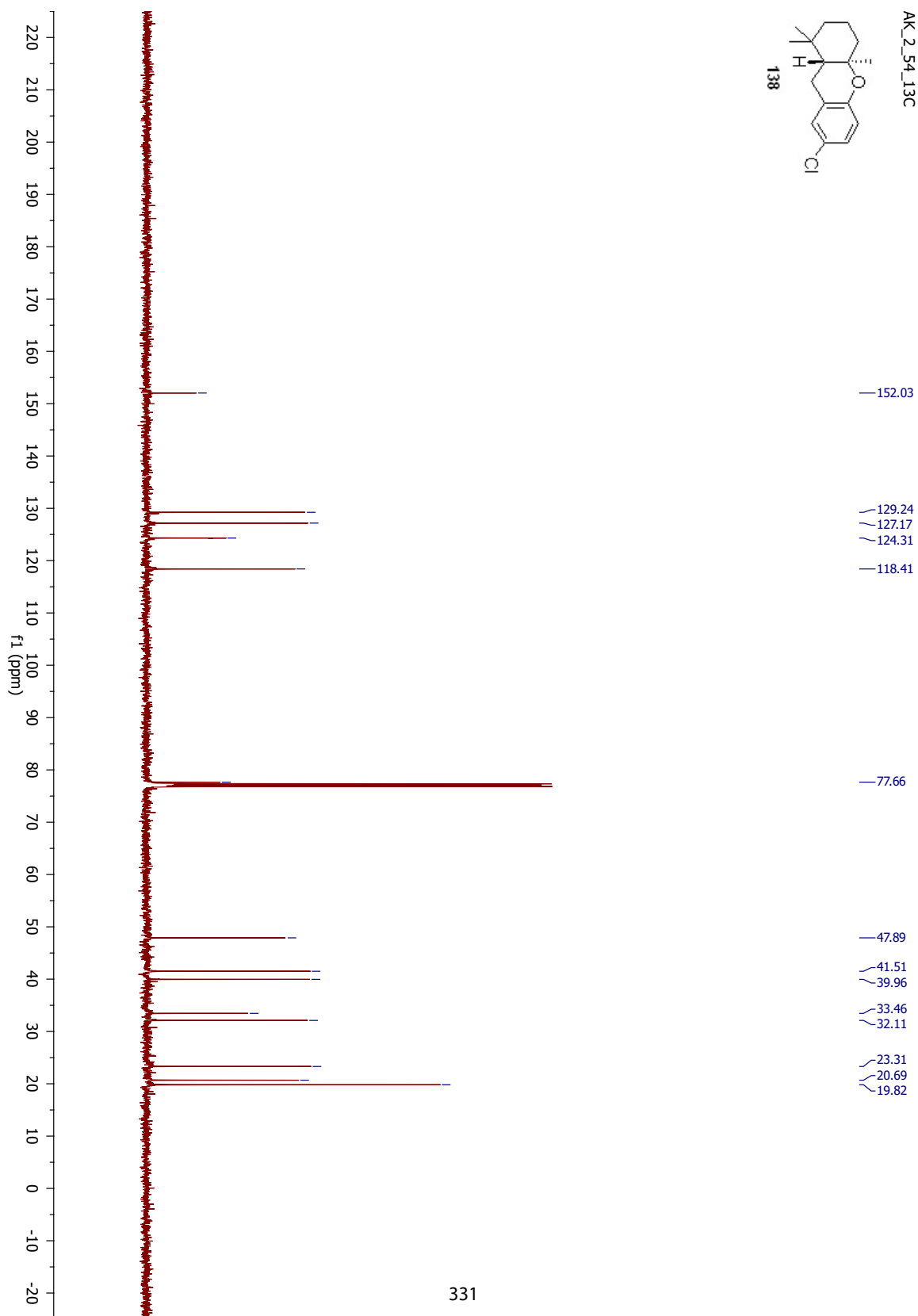
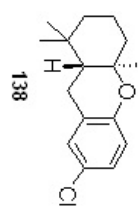
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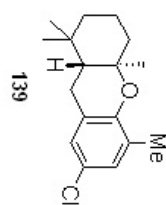
AK_2_54_1H



AK_2_54_13C



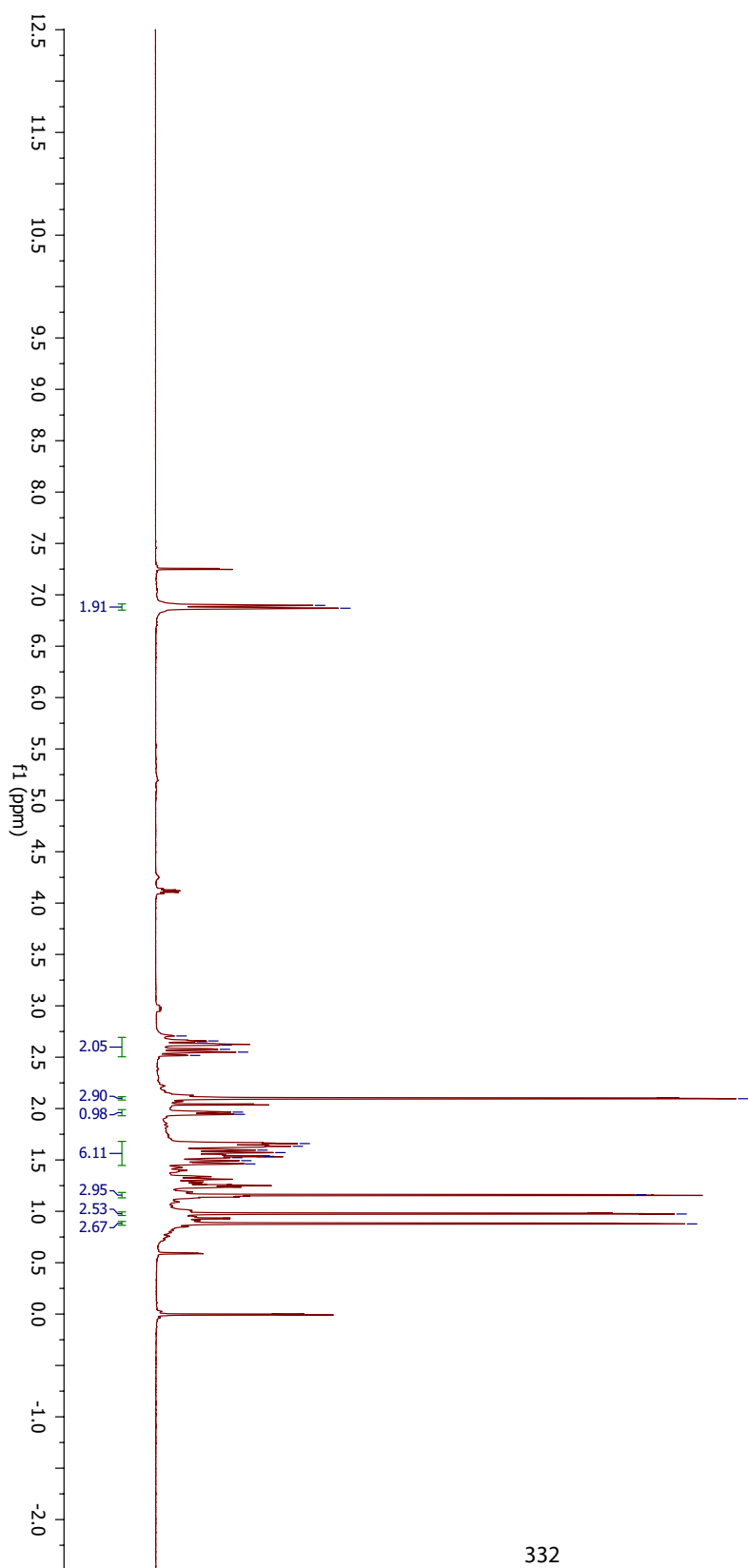
SB_2_122



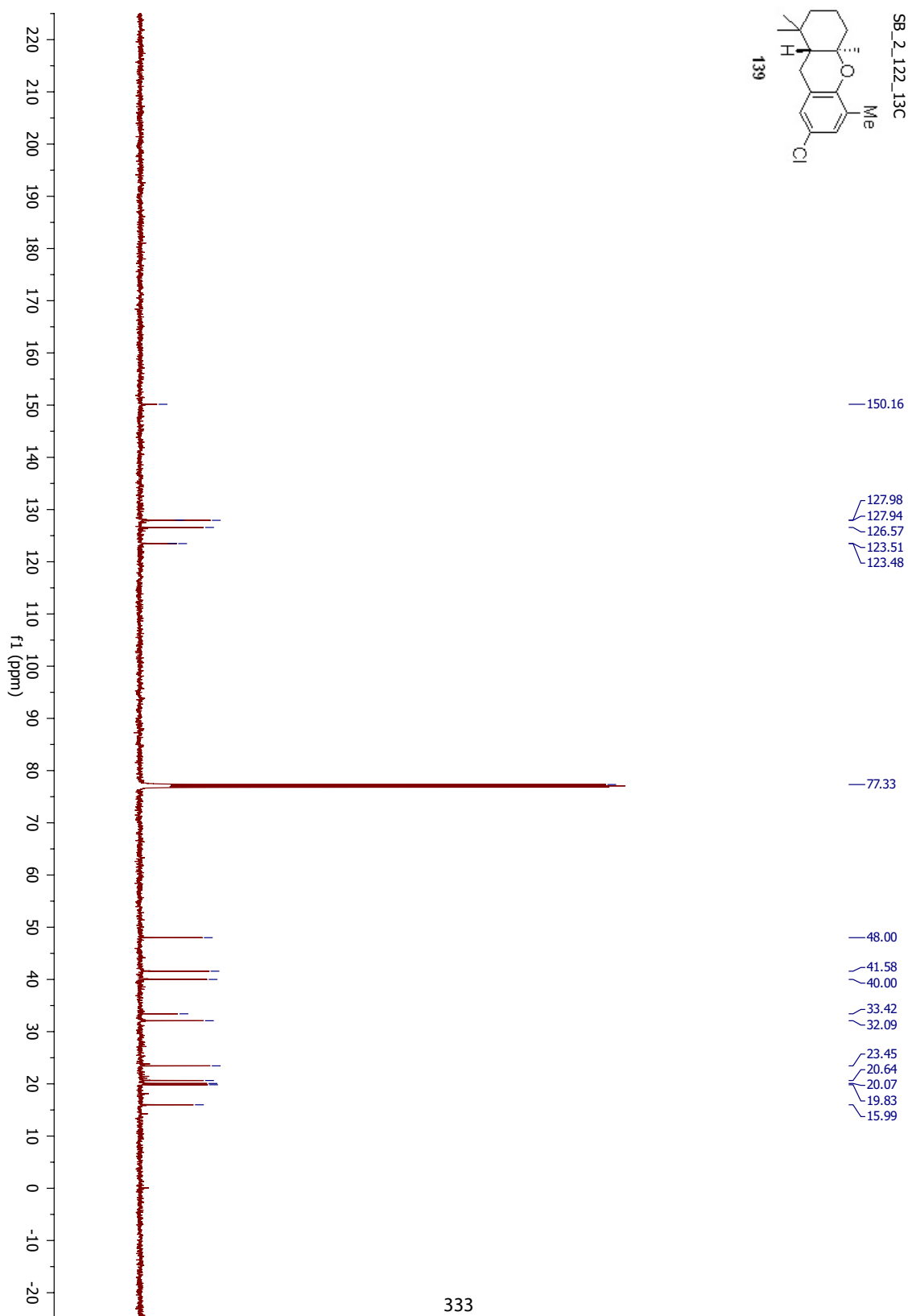
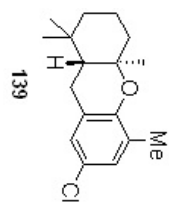
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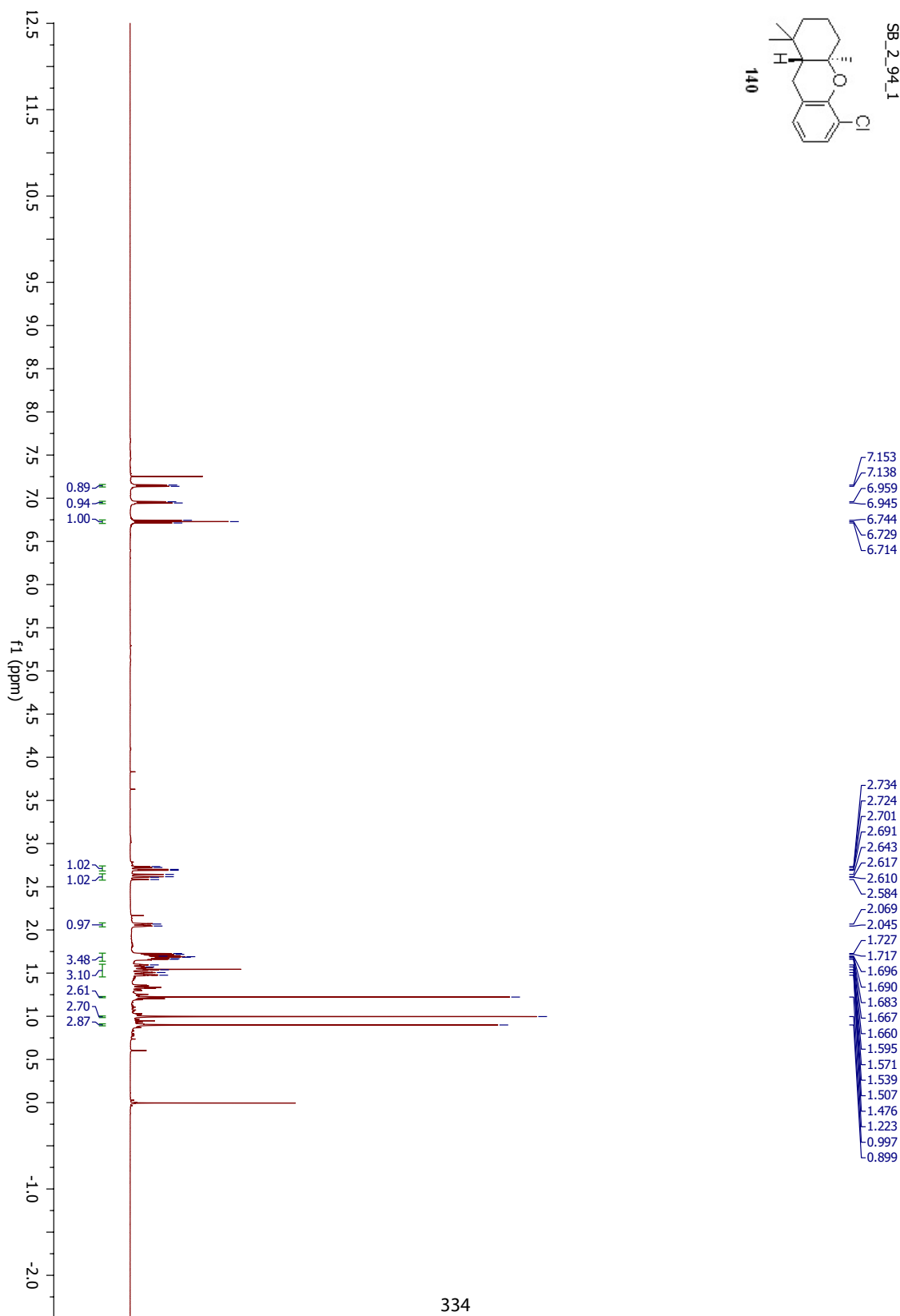
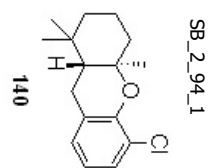
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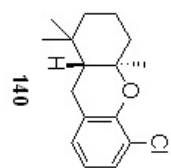


SB_2_122_13C

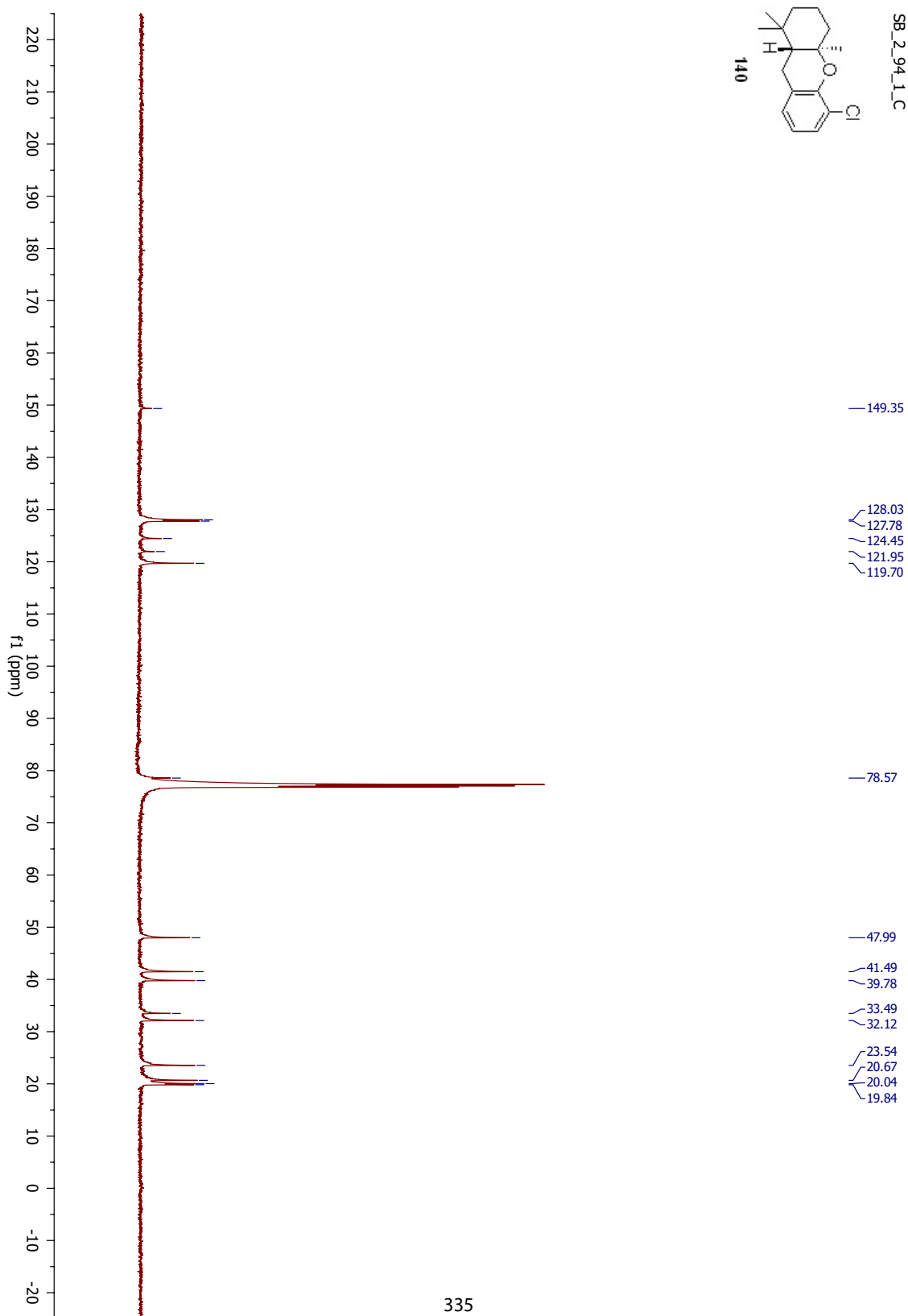




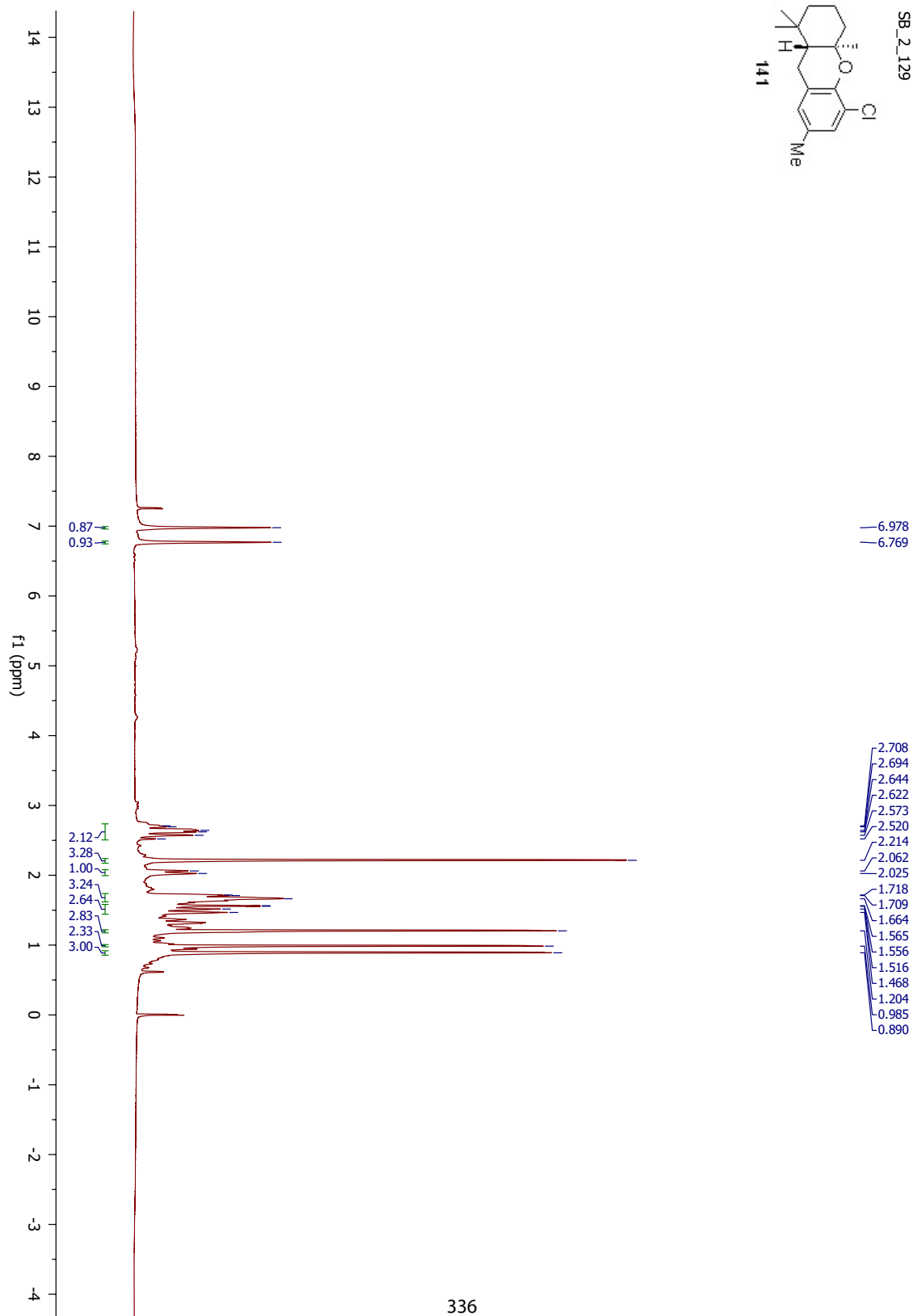
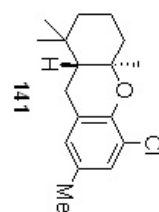
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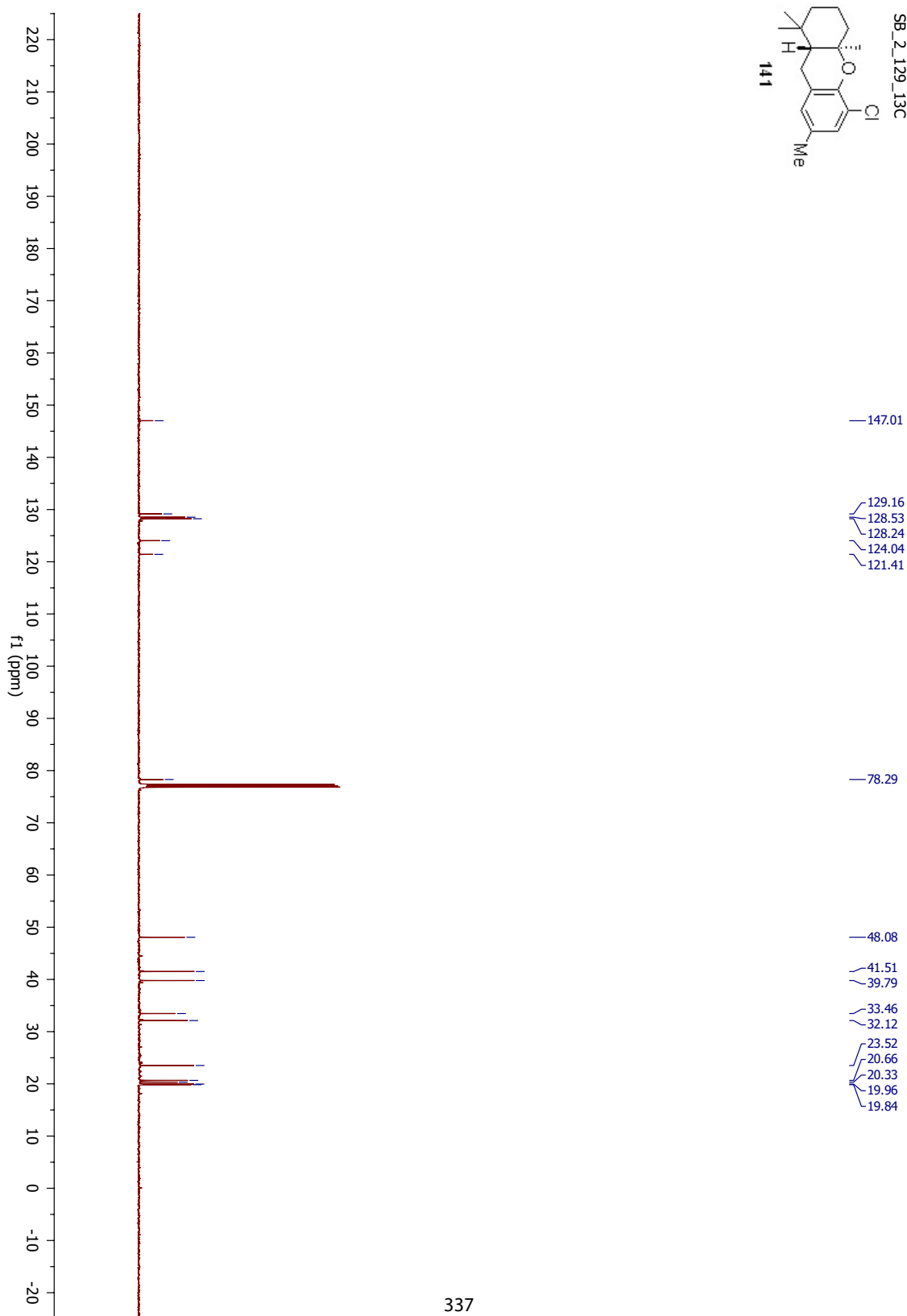
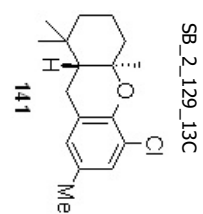


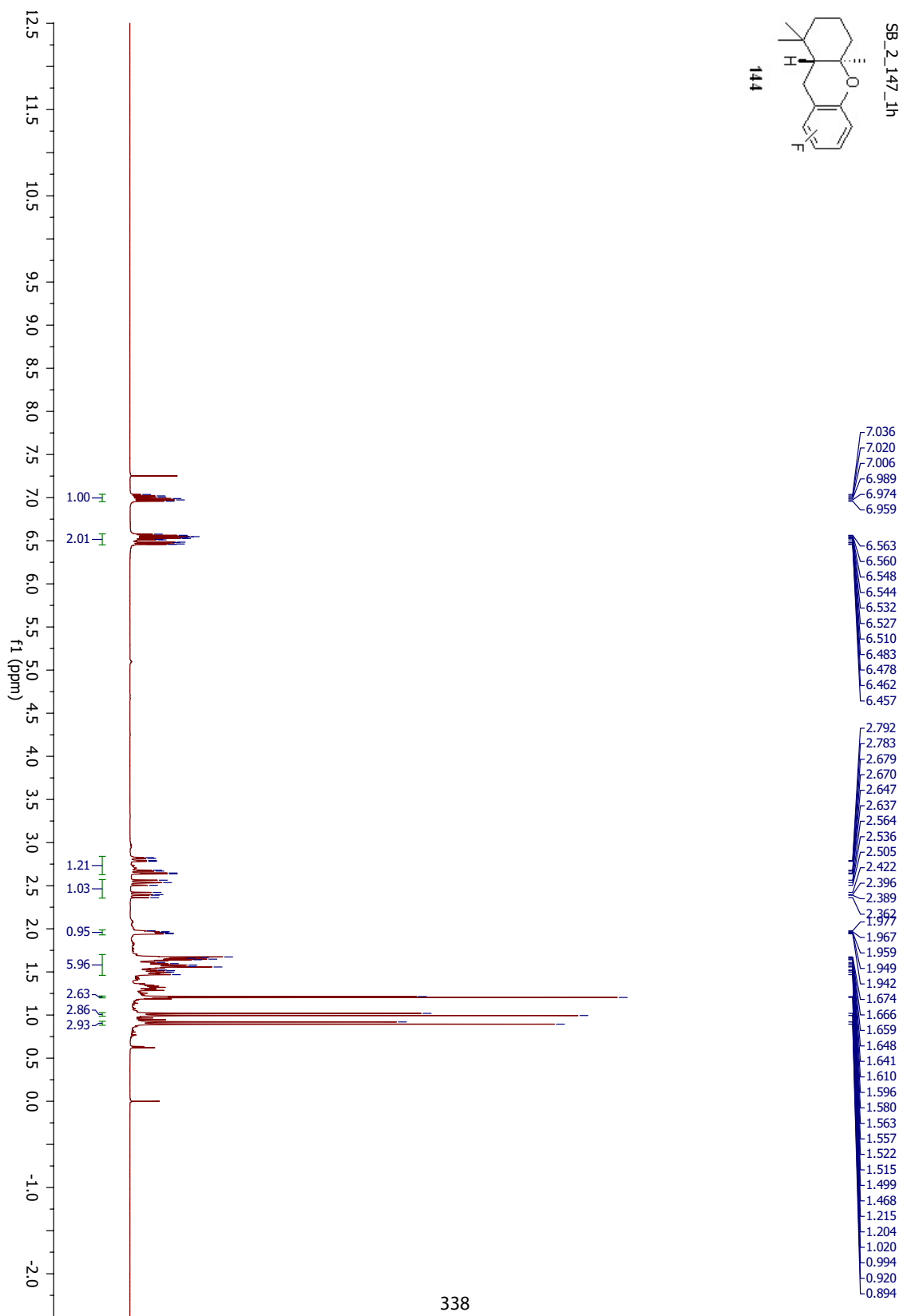
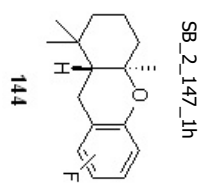
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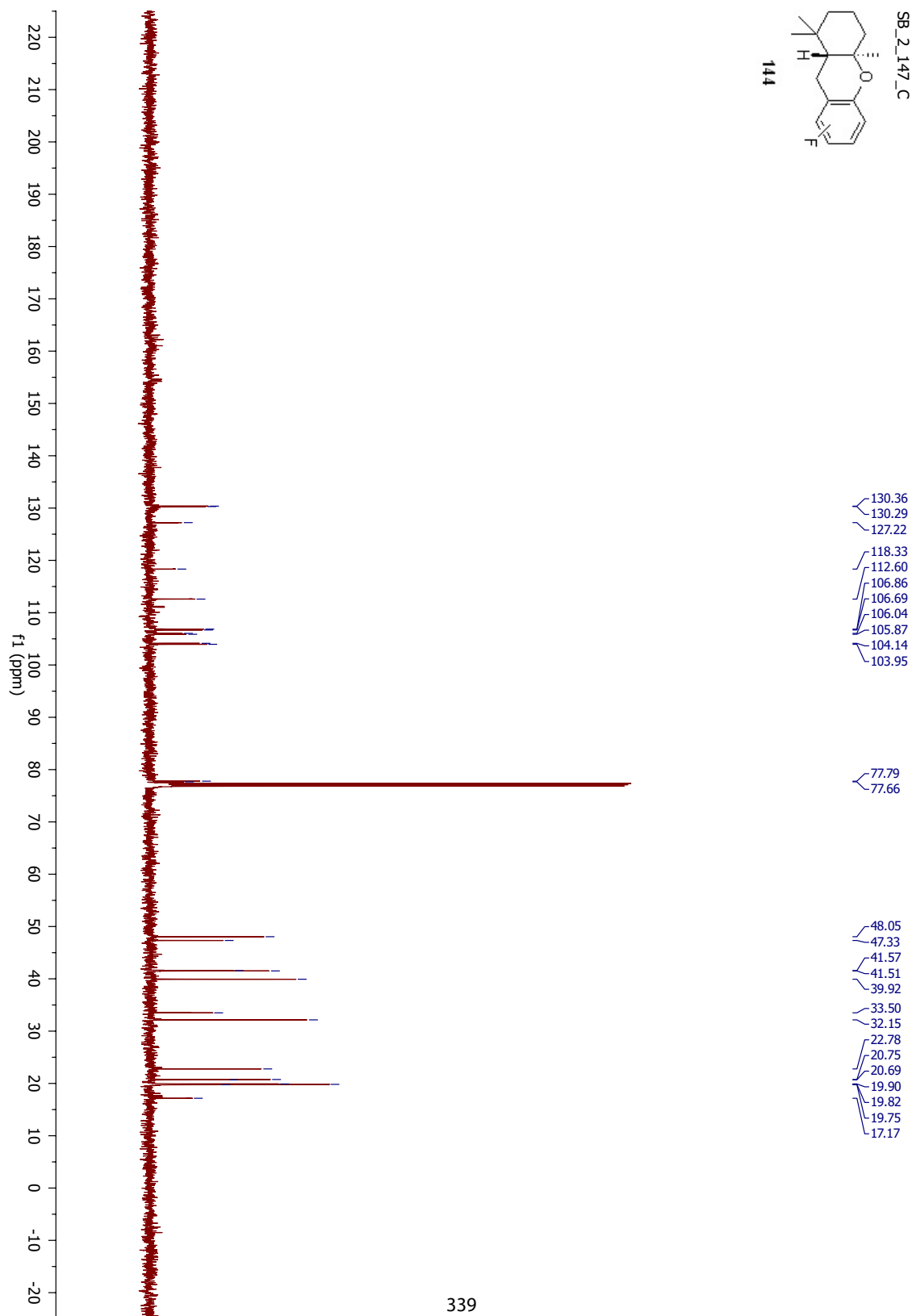
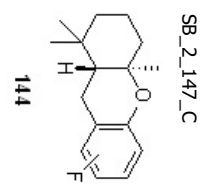


SB_2_129

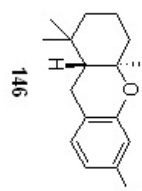






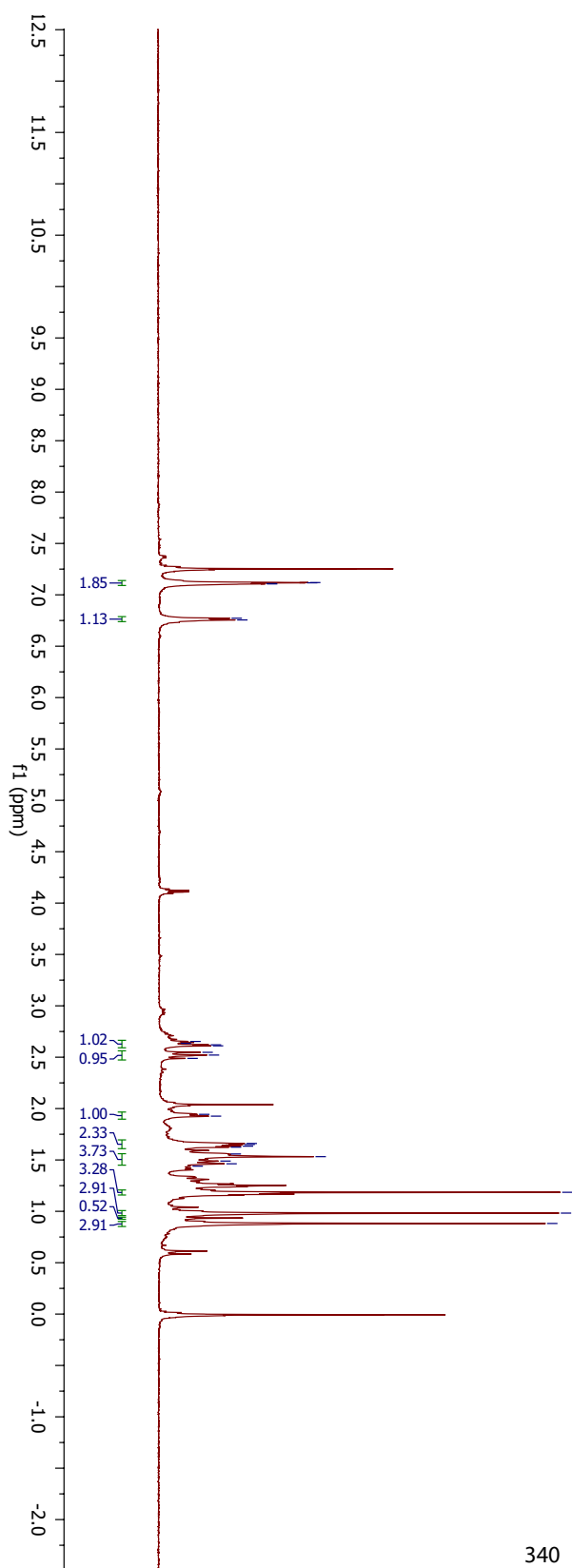


SB_2_146_fr1

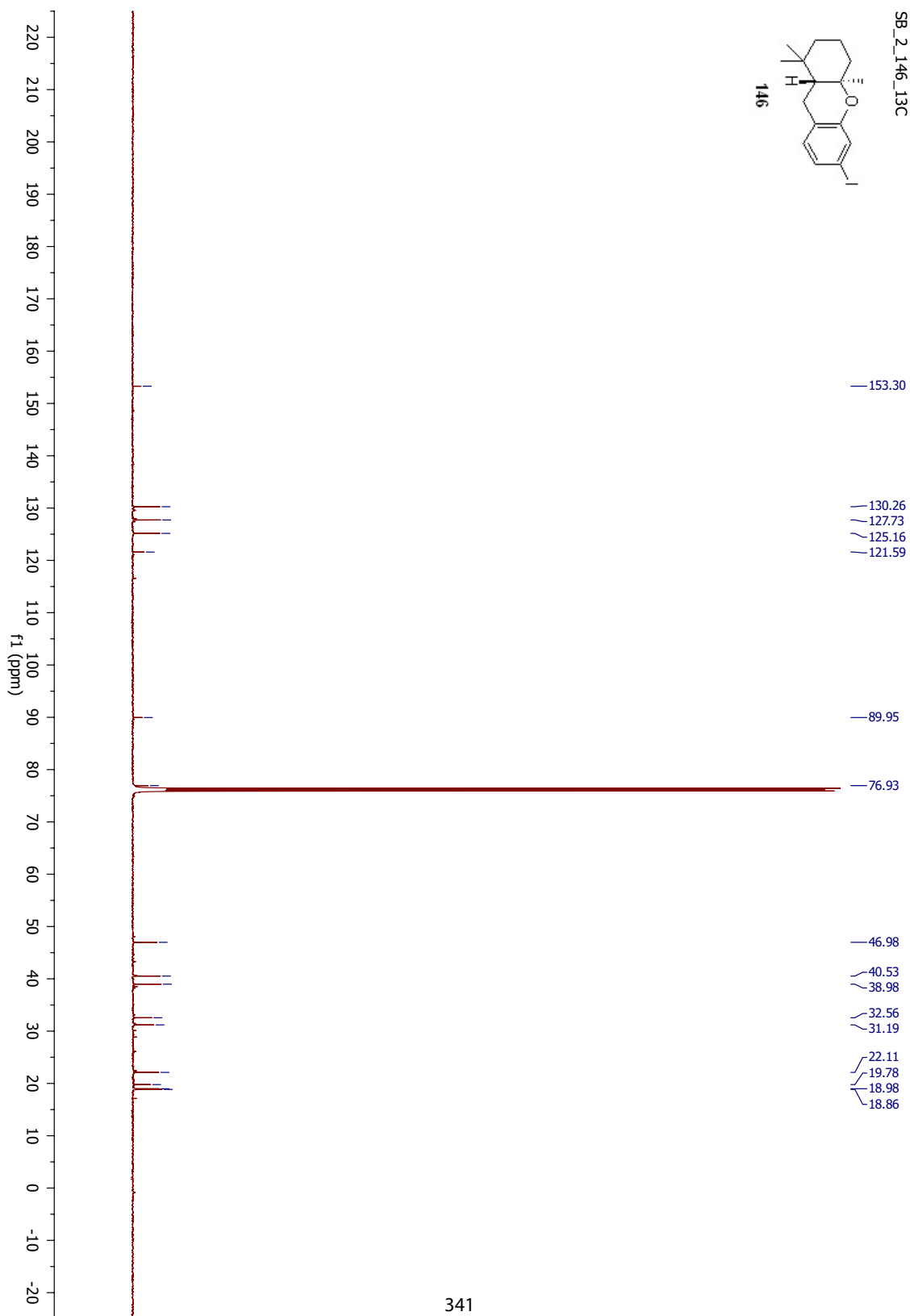
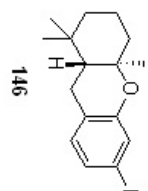


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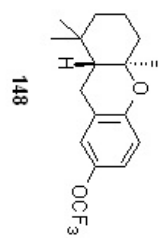
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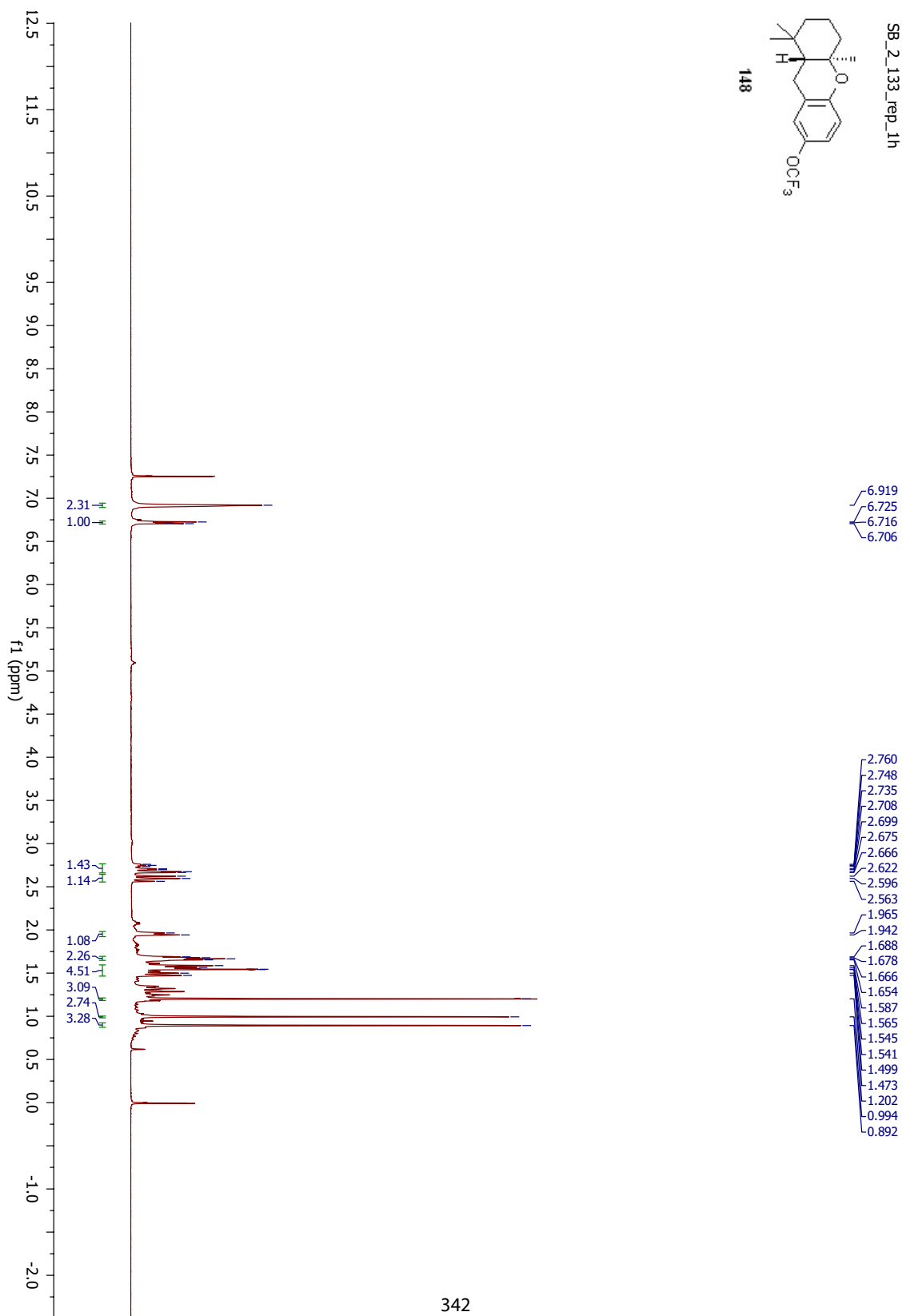
SB_2_146_13C



SB_2_133_rep_1h



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SB_2_133_rep_13c

