Synthesis and Evaluation of Cannabigerol-Inspired Antimicrobial Compounds

By Eleanor Wong

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Chemical Biology

McMaster University, Master of Chemical Biology (2024) Hamilton, Ontario

Title: Synthesis and Evaluation of Cannabigerol-Inspired Antimicrobial Compounds

Author: Eleanor Wong

Supervisor: Jakob Magolan

Number of Pages: 153

Abstract

With rising rates of antimicrobial resistance, new antibiotics are being investigated to ensure effective treatment options exist, essential for public health. Cannabinoids are a class of prenylated phenolic natural products that have been shown to possess antibiotic potential against Methicillin Resistant *Staphylococcus aureus* (MRSA).[1, 2] Cannabigerol (CBG) a nonpsychotropic cannabinoid was explored as a promising lead for a new antibiotic candidate. CBG and over 40 analogues were synthesized in a medicinal chemistry manner to construct a structure activity relationship (SAR) study. An alumina-mediated phenol geranylation reaction was employed as a key step in the synthesis of analogues. Here we have identified novel CBG analogues with improved physiochemical properties and increased potency against MRSA.

Acknowledgements

First, I would like to thank my supervisor, Dr. Magolan, for his support and guidance over the past 2 years. Thank you for taking a chance on me and for sparking my interest in chemistry. I am grateful to have had the opportunity to be part of your lab.

I would like to thank my mentors, Dr. Jarrod Johnson, Dr. Lauren Irwin, and Dr. Mathew Piotrowski. You are all people who I look up to and have taught me so much.

To professors Dr. Bujold and Dr. Capretta, thank you for taking your time to be on my committee. I appreciate all your insight and encouragement. And to my collaborators in the Brown lab, Maya and Omar.

Thank you to the past and present members of the Magolan lab for making everyday so fun. To my dear friend Nikki Ritchie for sharing a fumehood with me, and the girls who worked on my side, Kaitlyn Breault, Ela Lach, and Meghan Fragis. You are all such talented chemists and wonderful friends.

Lastly, I would like to thank my parents and my sister Suzy for their unconditional support and love. I am so grateful to have you all in my life.

Table of Contents

List of Schemes

List of Figures

List of Tables

List of Abbreviations

Ac	Acetyl
BBr_3	Boron tribromide
Br	Bromine
^oC	Celsius
Cl	Chlorine
CBD	Cannabidiol
CBDA	Cannabidiolic Acid
CBDV	Cannabidivarin
CBG	Cannabigerol
CBGA	Cannabigerolic Acid
CBGV	Cannabigerovarin
CBN	Cannabinol
$CHCl_3$	Chloroform
CF_3	Trifluoromethane
CN	Nitrile
DCE	Dichloroethane
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
F	Fluorine
g	Grams
H	Hydrogen
H_2O	Water
KOAc	Potassium acetate
L	Liter
MIC	Minimum inhibitory concentration
Me	Methyl
MRSA	Methicillin Resistant Staphylococcus aureus
MeCN	Acetonitrile
MeOH	Methanol
Mol	Molar
$NaHCO_3$	Sodium bicarbonate
OMe	Methoxy
Pd/C	Palladium on carbon
$PdCl_2$(dppf)	[1,1-Bis(diphenylphosphino)ferrocene] palladium(II) dichloride
SAR	Structure activity relationship
THC	Tetrahydrocannabinol
THCA	Tetrahydrocannabinolic acid
THCV	Tetrahydrocannabivarin
μM	Micromolar

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public. The academic achievements discussed in this thesis consist of:

Eleanor Wong, Lauren Irwin, Maya Farha, Eric Brown, Jakob Magolan* Synthesis and Evaluation of Cannabigerol Inspired Antibiotics.
The majority of the experimental work was done by Eleanor Wong, with contributions from Dr. L. Iwrin, Dr. N. Jentsch, and Dr. X. Zhang further specified in Chapter 2.

Chapter 1 - Introduction

1.1 Beta-Lactam Antibiotics

Antimicrobial drugs, for the treatment of bacterial infections, play a crucial role in medicine, treating and curing infections and reducing mortality rates worldwide.[3] This advancement significantly contributes to improvements in public health and increased life expectancy.[4] The use of antibiotics mitigates the spread of disease and can ease the severity of disease complications by inhibiting bacteria growth.[4]

The first antibiotic, penicillin, was discovered by Alexander Fleming in 1928.[5] This breakthrough provided the foundation for further development of novel antibiotics and has led to thousands of new penicillin derivates or related molecules, classified as beta-lactam antibiotics.[5] These beta-lactam antibiotics are given their classification due to their beta-lactam ring in their structure shown in Figure 1, which is crucial for antibiotic activity.[6] Today there are eight additional classes of antibiotics however beta-lactam antibiotics are currently the largest class being prescribed as they are well tolerated and effective.[5]

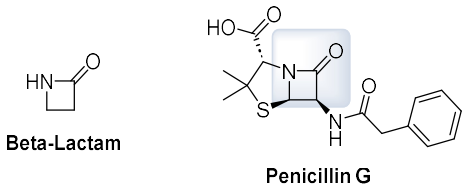


Figure 1 Structure beta-lactam and of Penicillin G with its beta-lactam core highlighted.

Beta-lactam antibiotics work by disrupting cell wall synthesis in both gram positive and gram negative bacteria leading to cell lysis and death.[6] Gram positive bacteria lack an outer membrane but exhibit a thick peptidoglycan layer compared to gram negative bacteria shown in Figure 2.[7] This structural difference affects the bacteria's susceptibility to antibiotics.

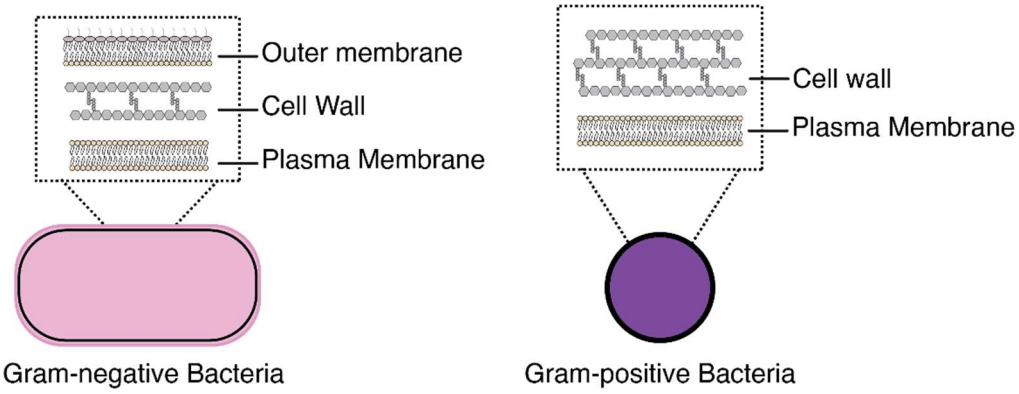


Figure 2 Membranes of gram-negative and gram-positive bacteria.[8]

Broad-spectrum antibiotics are effective against a wide range of both gram-negative and gram-positive bacteria and are invaluable for treating infections, especially when the specific bacteria are unknown. Some beta-lactam antibiotics, such as cephalosporins and carbapenems, possess this broad-spectrum activity.[6] New antibiotics have been developed and are currently being investigated to increase the spectrum of activity, target new bacteria, and combat the emergence of drug-resistant bacteria.[9]

1.2 Antibiotic Crisis

The overuse and inappropriate prescribing of antibiotics has led to a major issue of antibiotic resistance. With an estimated 10 million people dying per year by 2050 as a result of resistance makes this a health crisis as defined by the World Health Organization.[10] *Staphylococcus aureus (S. aureus)*, a gram positive bacteria, is one of the six most problematic pathogenic germs that attributes to the most fatalities from antibiotic resistance with over 100, 000 deaths in 2019.[10] This bacterium is commonly found on the skin and in the nose of healthy individuals but can cause infections, ranging from mild skin infections to more severe and potentially life-threatening conditions.[11]

Methicillin (Figure 3) is a semi-synthetic penicillin antibiotic that was introduced in 1959 to treat gram positive bacteria, specifically infections caused by penicillin-resistant

Staphylococcus aureus.[12] In 1961, just two years after the introduction of methicillin, resistance occurred bringing rise to Methicillin-Resistant *Staphylococcus Aureus* (MRSA).[12] Today, MRSA is now resistant to most β-lactam antibiotics.[13]

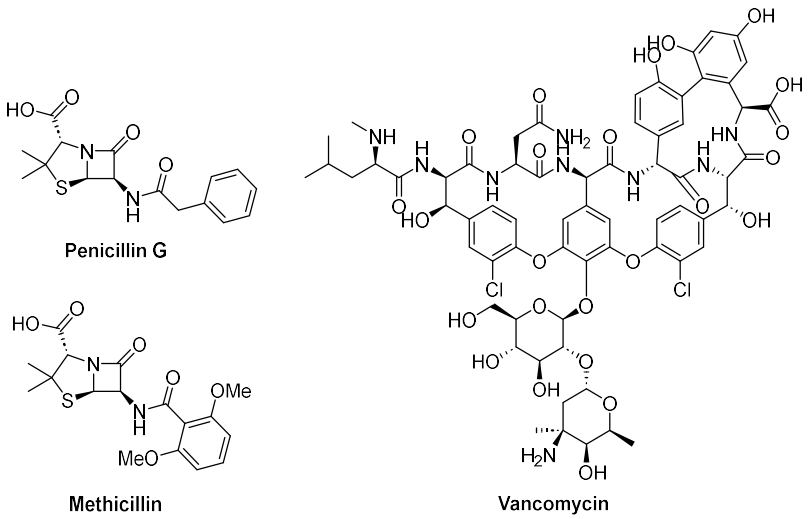


Figure 3 Chemical structures of penicillin G, methicillin, and vancomycin.

MRSA accounts for a major cause of hospital-acquired infections but is also attributed to community and livestock associated MRSA.[11] Typically, vancomycin, a glycopeptide antibiotic (Figure 3), is used as the initial treatment against MRSA.[14] However, in recent years MRSA resistance to vancomycin and other antibiotics has emerged.[14] This resistance is occurring as bacteria are evolving and their genes are mutating lowering their affinity to bind to antibiotics.[13] Bacteria are now harder to treat and is compromising treatments for life-threatening infections.

Along with the lack of antibiotics in the drug discovery pipeline, this antibiotic crisis needs to be addressed where we can rely on natural products for inspiration.

1.3 Natural Products as Drug Leads in the Antibiotic Space

Historically, natural products have been used in traditional medicine for centuries and have since made major contributions to drug discovery and pharmaceuticals.[15] In the antibiotic space, inspiration from nature is significant because plants often have their own evolutionary mechanisms to create their own antibacterial molecules to protect themselves against invaders.[16]

Natural products and natural product derivatives make up over 70% of small molecule antibiotics from 1981 to 2019, with 6 of the 9 classes of antibiotics being naturally occurring.[17] This includes the natural products penicillin and vancomycin that were originally derived from natural sources like soil and fungi bacteria (Figure 3).[17] Natural products exhibit great structural diversity and complexity that is advantageous in drug discovery.

The exploration of natural products as antibiotics leads remains relevant due to the pressing need for new antibiotics to combat the rising levels of resistance.

1.31 Phenols as Antibiotics

A phenol is a chemical compound that consists of a hydroxyl group bonded directly to a benzene ring shown in Figure 4.[18] The structural motif is found in a variety of natural products including the majority of classified antibiotics.[18] An example of this are beta-lactam antibiotics like amoxicillin, cefadroxil, and cefprozil (Figure 4).[18]

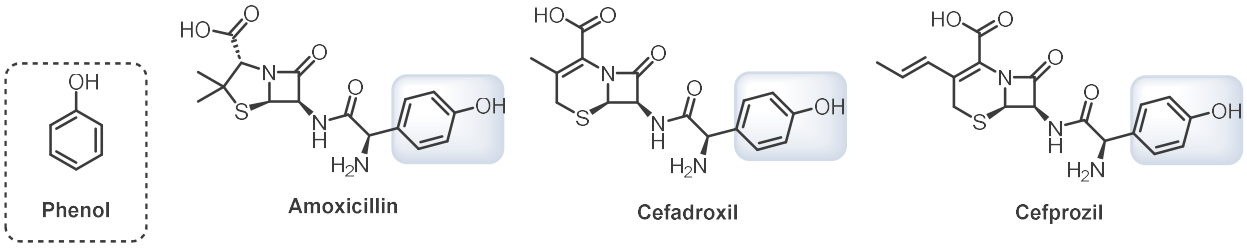


Figure 4 Structure of phenol and beta-lactam antibiotics exhibiting a phenol highlighted in blue.[18]

Other antibiotics like the tetracycline, rifamycin-like, and glycopeptide classes also contain a core phenolic structure with examples shown in Figure 5 where the hydroxyl group(s) have been demonstrated to have great impact on the antibacterial properties of these compounds.[18]

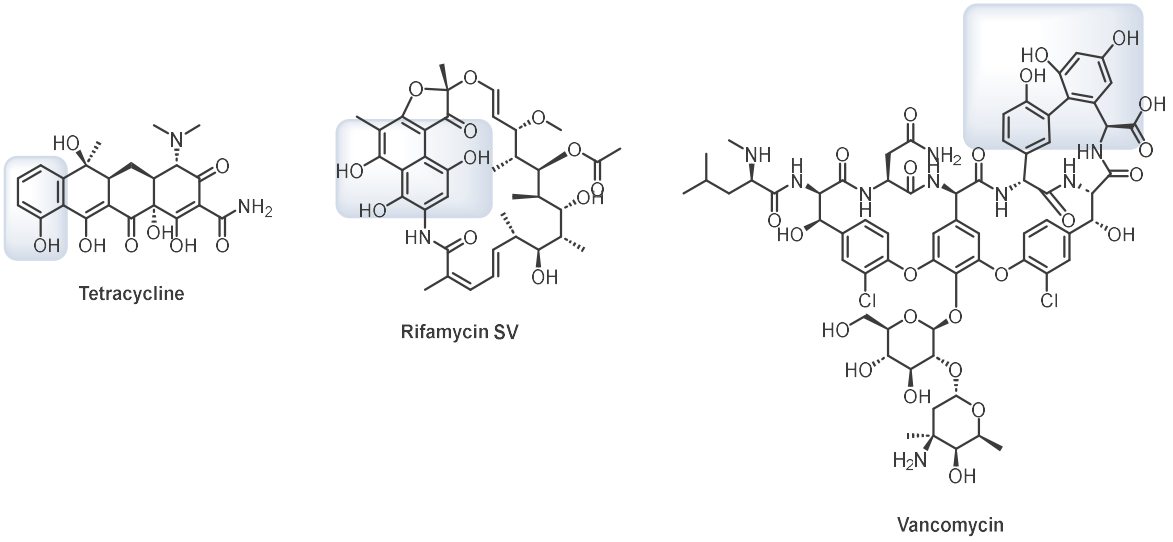


Figure 5 Other classes of antibiotics and their phenols highlighted.

These phenolic natural products are important and should be further investigated for the design of new antibiotics.

Interestingly, the addition of a prenyl, geranyl, or farnesyl chain (Figure 6) to a phenol has been shown to greatly improve activity against bacteria.[19] Incorporation of prenyl chains improve bioactivity over its non-prenylated derivative as it increases the lipophilicity of a molecule and it adds a functional handle that has a strong affinity for biological membranes.[20]

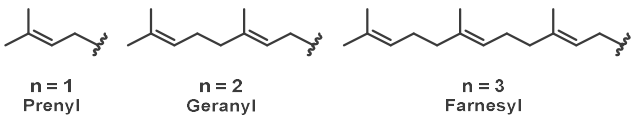


Figure 6 Chemical structures of prenyl chains.

An example of this phenomenon is salicylic acid, a phenolic natural product that is the main aspirin metabolite (Figure 7).[21] This compound exhibits no activity against *S. aureus* with a minimum inhibitory concentration (MIC) of < 500 ug/mL which is the lowest concentration that inhibits the growth of bacteria.[21] Excitingly, when a farnesyl chain is added to salicylic acid, we now see antibacterial activity where the MIC drastically improves to 12.5 ug/mL (Figure 7).[22]

In another example, prenylation of flavonoids showed an improved bacteria inhibition compared to its base phenolic structure. This was observed with the geranylation of naringenin to mimulone which improved the MIC against MRSA by over 1000-fold (Figure 7).[20, 23]

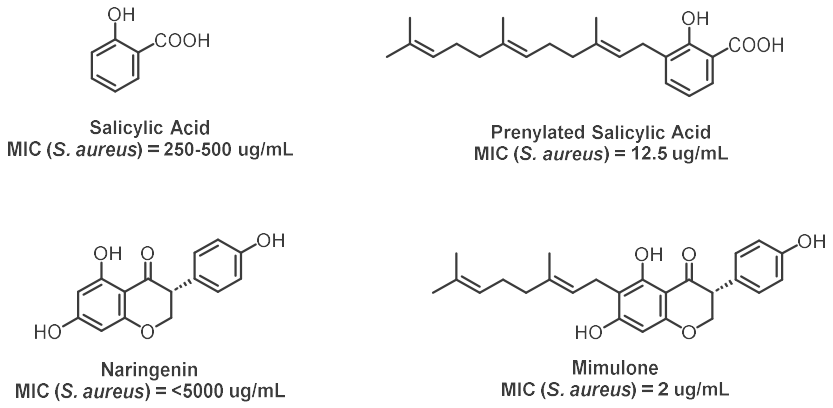


Figure 7 Comparison of phenols and their prenylated derivatives potential against S. aureus.

Consequently, there exists evidence that prenylated phenols act as potent antibiotics.

1.4 Antibiotics found in *Cannabis*

Cannabis sativa is composed of an abundance of bioactive compound called cannabinoids.[24] The medical potential of cannabis and its active constituents has attracted

significant interest due to their diverse biological activities including anti-inflammatory, antioxidant, anticancer, and neuroprotective effects.[2, 24]

Over 100 cannabinoids have been isolated with the major cannabinoids being psychotropic Δ9-tetrahydrocannabinol (THC), and nonpsychoactive cannabinoids cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC) and cannabinol (CBN).[1] These compounds are composed of a phenolic core with a prenyl chain or cyclized prenyl chain derivative shown in Figure 8.

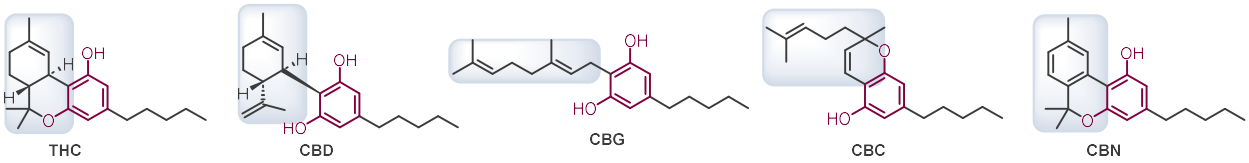
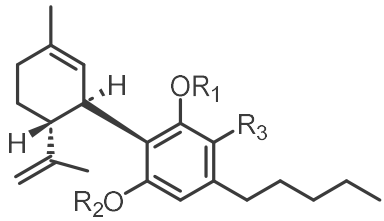
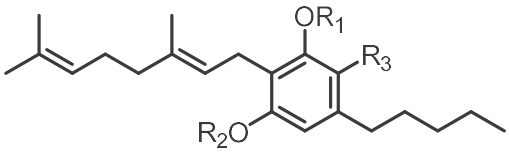


Figure 8 The major cannabinoids with the prenyl chain highlighted in blue and the phenol shown in burgundy.

In the realm of infectious diseases, Appendino *et al*., first showcased the antibacterial activity of the 5 major cannabinoids shown in Figure 8 with MICs ranging from 0.5-2 ug/mL. These potent activities are comparable to conventional antibiotics used for multidrug resistant strains including vancomycin.[25] CBD and CBG were further investigated in a structure-activity relationship (SAR) study due to their nonpsychotropic effects (Figure 9).[1] Methylation and acylation of one or both of the phenols at the R_1 and R_2 position in Figure 9 were explored, along with the acid or ester derivative at R_3.[1] No improvement in MIC's were seen with any of these modifications.[1] However, there is valuable insight in the discovery that free phenols are necessary for activity as well esterification to the acid derivatives (CBGA or CBDA) removes biological activity.[1]



CBD



CBG

	R_1	R_2	R_3	MIC
I-1	Ac	Ac	H	>128 μg/mL
I-2	Me	H	H	>128 μg/mL
I-3	Me	Me	H	>128 μg/mL
CBDA	H	H	COOH	2 μg/mL
I-4	H	H	COOMe	>128 μg/mL

	R_1	R_2	R_3	MIC
I-5	Ac	Ac	H	>128 μg/mL
I-6	Me	H	H	>128 μg/mL
I-7	Me	Me	H	>128 μg/mL
CBGA	H	H	COOH	4 μg/mL
I-8	H	H	COOMe	64 μg/mL

Figure 9 SAR of CBD and CBG by Appendino.

The Brown lab at McMaster University found interest in this initial activity and expanded on the investigation of cannabinoids though exploring the mechanistic insights and *in vivo* activity of these molecule.[2]

The major cannabinoids, along with their carboxylic acid precursors and homologues, were reconfirmed or newly analyzed by the Brown lab for their MIC shown in Figure 10.[2] THC, CBD, CBG and CBN all demonstrated robust activity against MRSA with MICs of 2 ug/mL.[2] The addition of a carboxylic acid functional group (THCA, CBDA, and CBGA) and shortening of the aliphatic chain to 3 carbons (THCV, CBDV, and CBGV) showed moderate to decreased activity.[2]

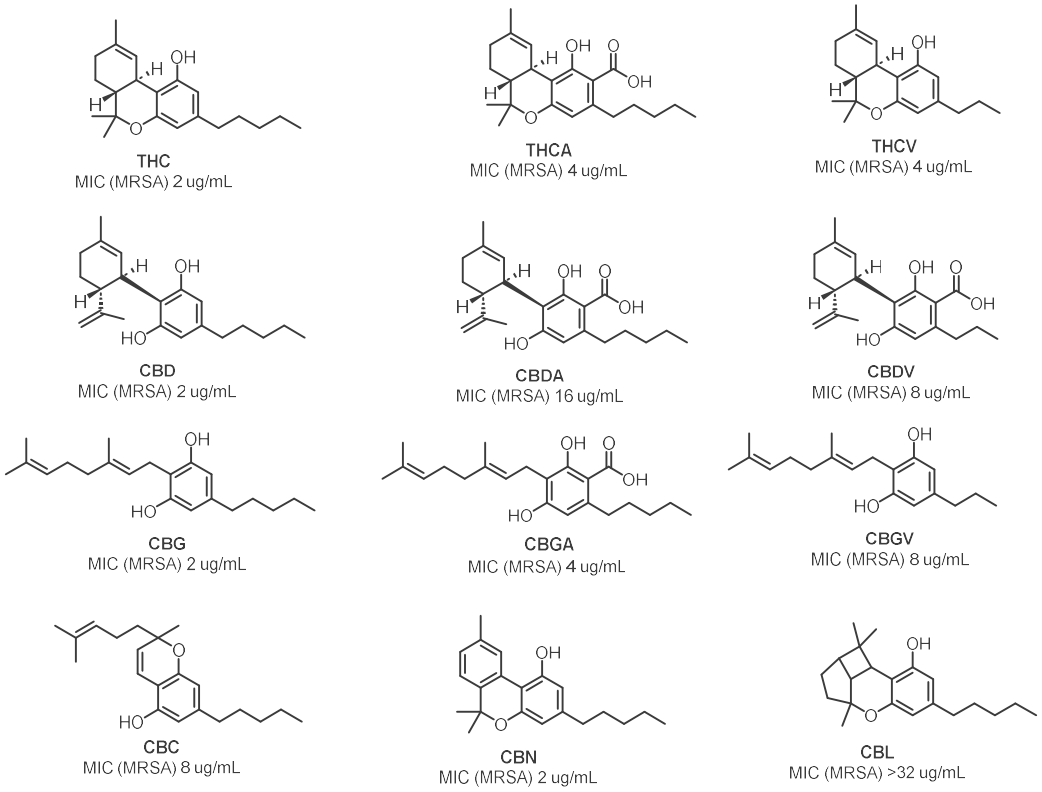


Figure 10 Structure of the major cannabinoids and their antibacterial activity against MRSA.[2]

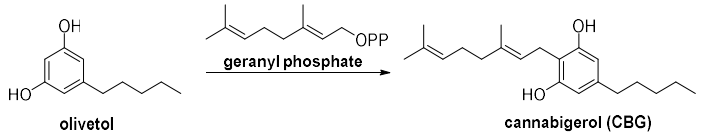
The Brown Lab further investigated the mechanism of these cannabinoids and found that CBG showed the greatest efficacy at inhibiting biofilms and was the most potent cannabinoid against persisters.[2] In addition to its activity, CBG has non-psychoactive effects in humans and was selected for further mechanistic studies and *in vivo* efficacy. It was observed that CBG operates by acting on the cytoplasmic membrane of gram-positive bacteria.[2] A single treatment of 100 mg/kg of CBG in mice resulted in a 2.8 log reduction in bacteria growth at 7 hours in the spleen compared to the vehicle control.[2] This *in vivo* activity was comparable to the antibiotic control, vancomycin administered at a similar dose showing promising levels of efficacy.[2] CBG also showed highly desirable properties for an antibiotic with low rates of resistance and potential as a broad-spectrum antibiotic when the outer membrane of gram-negative bacteria is disrupted.[2]

Overall, CBG conveyed excellent biological activity against MRSA. However, CBG exhibits high lipophilicity and low aqueous solubility.[2] To overcome these challenges, we took to address the structure of CBG, investigating changes in its molecular structure to undergo a medicinal chemistry effort to improve both the physiochemical properties of CBG, as well as its MIC against MRSA.

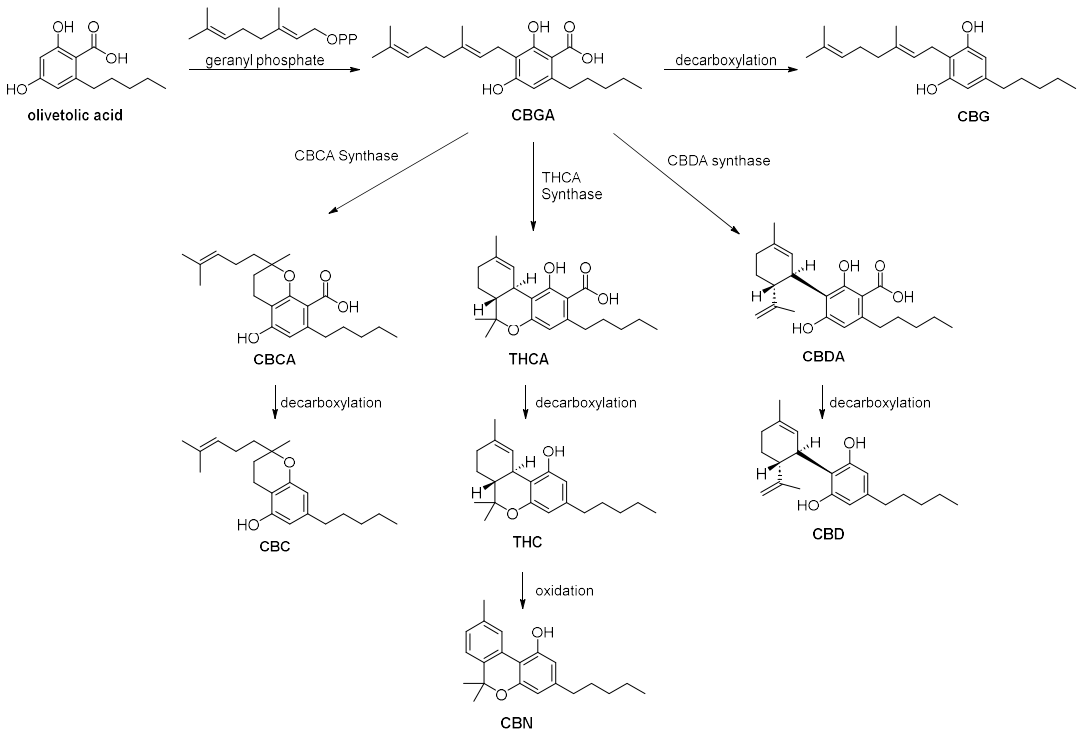
1.5 Synthesis of Cannabigerol

1.5.1 Biosynthesis of Cannabigerol

To synthesize and chemically modify CBG, the plant biosynthesis of the molecule can be understood to motivate the route of chemical synthesis. There are two biosynthetic pathways of CBG including 1) the direct condensation of olivetol and geranyl pyrophosphate (Scheme 1) as well as 2) the condensation of olivetolic acid and geranyl pyrophosphate following an non-enzymatic decarboxylation (Scheme 2).[26] CBGA serves as a direct precursor to CBCA, THCA, and CBDA through enzymatic conversion.[26] These acid derivatives can then undergo a non-enzymatic decarboxylation, typically through heat.[26] Oxidation of THC provides cannabinoid CBN giving 8 cannabinoid derivatives from the same precursor of CBGA.



Scheme 1 Direct biosynthesis of CBG from olivetol and geranyl phosphate.

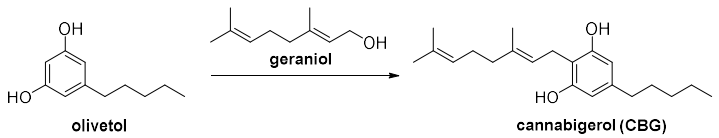


Scheme 2 Biosynthetic pathway of cannabinoids from CBGA. [26].

As CBGA is a precursor to many cannabinoids, it is present in much smaller quantities in Cannabis sativa with less than 1% composition in the plant.[27] A scalable synthesis of CBG is of industrial significance as it can be used for the biosynthesis of other cannabinoids, used in biological studies, as well as provide precursors and insight for medicinal chemistry efforts.[27, 28]

1.5.2 Chemical Synthesis of Cannabigerol

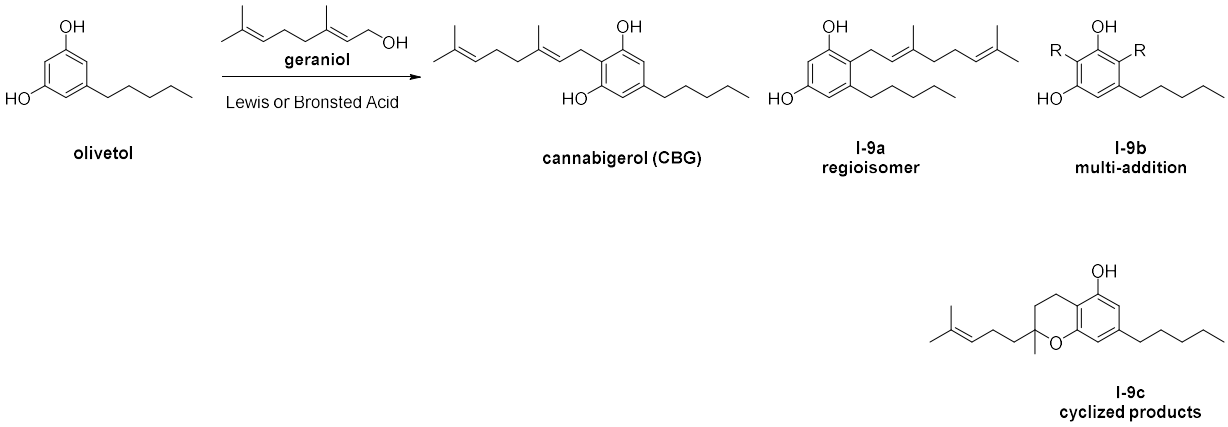
The first structure and synthesis of cannabigerol was published in 1964 with no reported yield by Gaoni and Mechoulam from commercially available and inexpensive olivetol and geraniol inspired by the biosynthetic pathway (Scheme 3).[29]



Scheme 3 Synthesis of CBG from olivetol and geraniol.

Scheme 3. Synthesis of CBG from olivetol and geraniol.

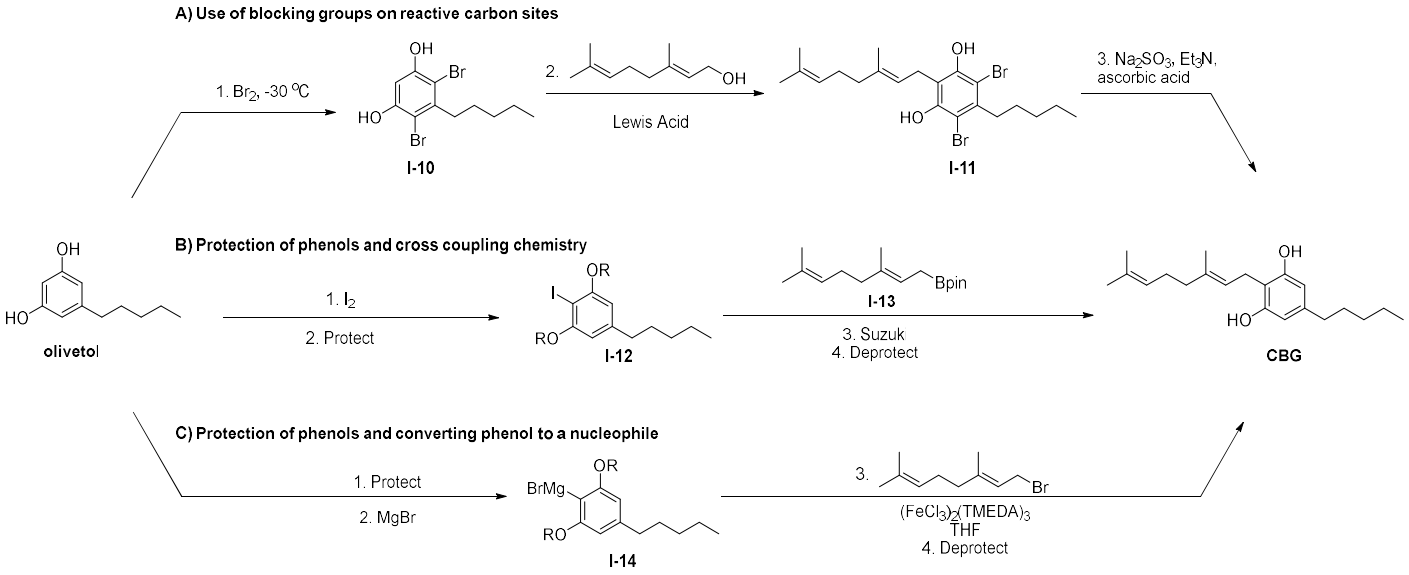
Following this, reported syntheses of CBG from olivetol and geraniol used acidic conditions to help facilitate the reaction to undergo an electrophilic aromatic substitution mechanism. Bronsted and Lewis acids like TsOH and BF_3 etherate resulted in yields of 52% and 29%, respectively.[30-32] The limitation with this acid promoted alkylation method is that the reaction forms complex mixtures of multi-addition (**I-9a**) and cyclized byproducts (**I-9b**) and most significantly, the undesired regioisomer (**I-9a)** as the major product (Scheme 4).[33] This mixture of byproducts also makes purification of the product difficult.[33]



Scheme 4 Synthesis of CBG and its major byproducts including the regioisomer and multi-addition product (R = geranyl and/or H).

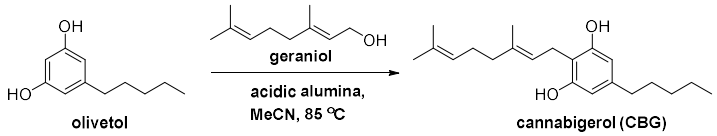
Other reported syntheses of CBG from olivetol are multistep, use protecting groups (**I-12, I-14**) or blocking groups to achieve selectivity (**I-10, I-11**), or were prepared using cross

coupling reactions that include metal catalysts and expensive/inaccessible boronic esters (**I-13**) (Scheme 5).[33-35]



Scheme 5 Synthetic pathways for the synthesis of CBG from olivetol.

A new method for prenylation of phenolic compounds was developed by the Magolan lab using acidic alumina (Scheme 6).[28] Using alumina not only improved selectivity of prenylations to between the two hydroxyl groups and reduced side reactions including double addition and cyclization but also improved yields to 65%.[28] This alumina promoted reaction is continued to be improved for further publication.[36]



Scheme 6 Acidic alumina promoted geranylation of olivetol.

Application of this new methodology leads to a facile one step synthesis of CBG, the synthesis of other cannabinoids, and prenylated phenolic natural products. Additionally, this reaction can support the synthesis of CBG analogues in a medicinal chemistry effort to explore

the potential of CBG as an antibiotic and can address the poor pharmacokinetic properties associated with its chemical structure.

Chapter 2 – Synthesis and Evaluation of Cannabigerol Inspired Antibiotics

2.0 Structure Analysis of CBG

There are three main components of CBG (Figure 11), its phenolic core (1,3-diol), the left-hand side geranyl chain at the 2-position, and the right-hand side 5 carbon aliphatic tail at the 5-position. To explore the full potential of CBG as an antibiotic, the synthesis and evaluation of CBG analogues were investigated, varying substituents at each face of the molecule and expanding the structure-activity relationship to find a suitable antibiotic candidate.

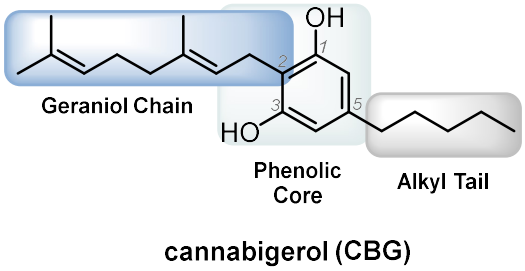


Figure 11 Cannabigerol and its highlighted phenolic core, geraniol chain, and alkyl tail.

Exploration of CBG analogues will allow us to gain insight into each functionality (geraniol chain, phenolic core, and alkyl tail) of CBG and their effects on biological activity. Additionally, modifications are made to improve the physiochemical properties of CBG. This includes modifications to the geranyl chain and aliphatic tail which exhibit high lipophilicity. Shortening the prenyl chain or adding polar functionality which can help overcome the initial poor solubility of CBG. As well, variation at the alkyl chain may also aid in improved solubility.

2.1 Synthesis of Cannabigerol

The synthesis of CBG and CBG analogues are needed to explore its structure activity relationship. Using alumina-templated prenylation chemistry we can access CBG and analogues in a simple manner.

Included in this structure activity relationship are results from reported synthetic CBG derivatives by Appendino *et al.* and Lee *et al.*, with MIC values against MRSA.[1, 37] To further expand the initial SAR, we focused our efforts to synthesize analogues of CBG with diversification at the prenyl chain to understand its role in activity (Figure 12, Figure 14, **II-4, II-5, II-7**). Synthesis of these compounds are from Dr. Nicholas Jentsch and Dr. Xiong Zhang. Synthesis of (Figure 15, **II-20** to **II-26**) are made by Dr. Lauren Irwin. All work is my own unless otherwise indicated.

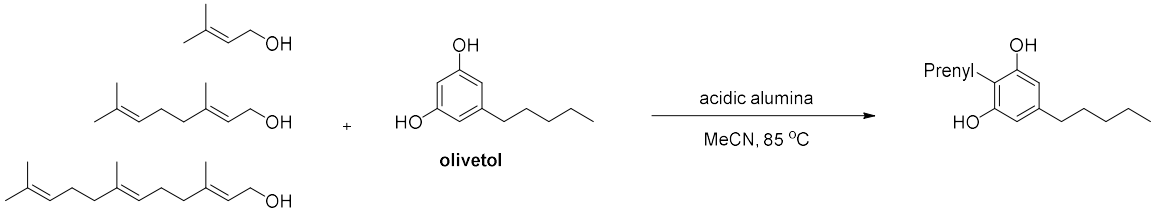


Figure 12 Using acidic alumina to synthesize CBG analogues at the 2-position

2.2 Biological Evaluation of CBG Analogues

CBG and synthetic analogues were tested against conditions of MRSA and *E. coli* for their minimum inhibitory concentration determination by Dr. Maya Farha in the Eric Brown lab at McMaster University.

MRSA as well as MRSA with bicarbonate were evaluated. The addition and combination of bicarbonate with an antibiotic has been shown to improve an antibiotic's efficacy, deeming bicarbonate a potentiator molecule.[38] Bicarbonate acts by disrupting bacterial membrane potential and proton gradient, leading to improved antibiotic uptake and efficacy.[38]

E. coli is a gram-negative bacterium with an outer membrane that needs to be penetrated compared to that of gram-positive MRSA. All CBG analogues were evaluated against E. coli as well as a hyperpermeable strain of *E. coli* (ΔtolC-pore). TolC is an outer membrane

protein in *E. coli* involved in the export of small molecules like antibiotics or toxins across the outer membrane.[39] The deletion of tolC allows *E. coli* to be more susceptible to membrane acting compounds.

These assays were conducted using the guidelines of the Clinical and Laboratory Standards Institute (CLSI) for MIC testing by broth microdilution.[2] The MICs were determined by serial dilutions ranging from 0-256 ug/mL in duplicates for each compound in a 96-well plate with clinical isolates of various bacteria.[2] The plates were incubated at 37 ºC for 18 hours and optical density is read. The MIC is determined at the lowest concentration of a compound showing less than 10% bacteria growth.

2.3 Structure Activity Relationship of CBG

2.31 CBG Analogues at the Phenolic Core

Investigating the core of CBG, Appendino synthesized and evaluated CBG analogues with one or both methylated phenols well as a methyl ester CBGA derivative (Figure 1313).[1]

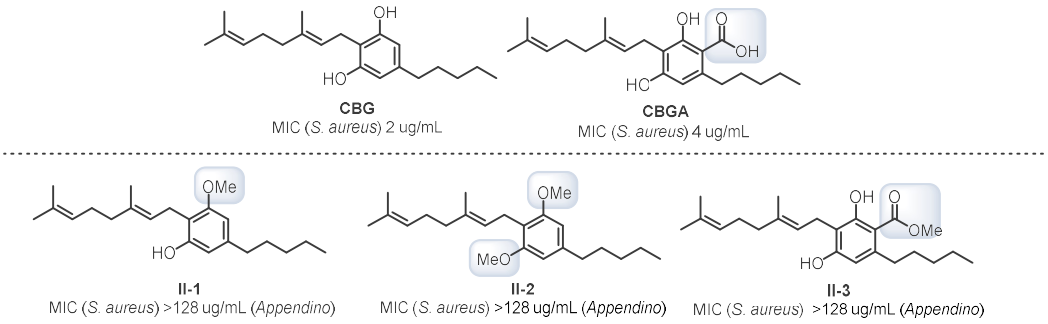


Figure 13 CBG analogues at the phenolic core and their MIC against MRSA.

Methylation of one or both phenols of CBG decreased potency drastically.[1] The MIC of **II-1** and **II-2** increased from 2 ug/mL (CBG) to >128 ug/mL meaning all activity was lost. This indicates that the hydroxyls are important in achieving activity against MRSA.[1] As well, investigating the carboxylated version of CBG (CBGA) showed moderate potency with

an MIC of 4 ug/mL. However, substitution to the methyl ester **II-3** showed no activity with an MIC of >128 ug/mL.[1] This signifies that the phenolic hydroxyl groups cannot be substituted along with ester modification reducing activity.

2.32 CBG Analogues at the Geraniol Chain

Previously, the geraniol chain at the 2-position of CBG was investigated in the Magolan Lab. Synthetic analogues were developed by Dr. Xiong Zhang and Dr. Nicholas Jentsch varying the prenyl chain length (**II-4** and **II-5**) as well as investigating when the prenyl chain is saturated (**II-7**). Dihydroxylation of the prenyl chain was also explored by Appendino (**II-6**) shown in Figure 14.

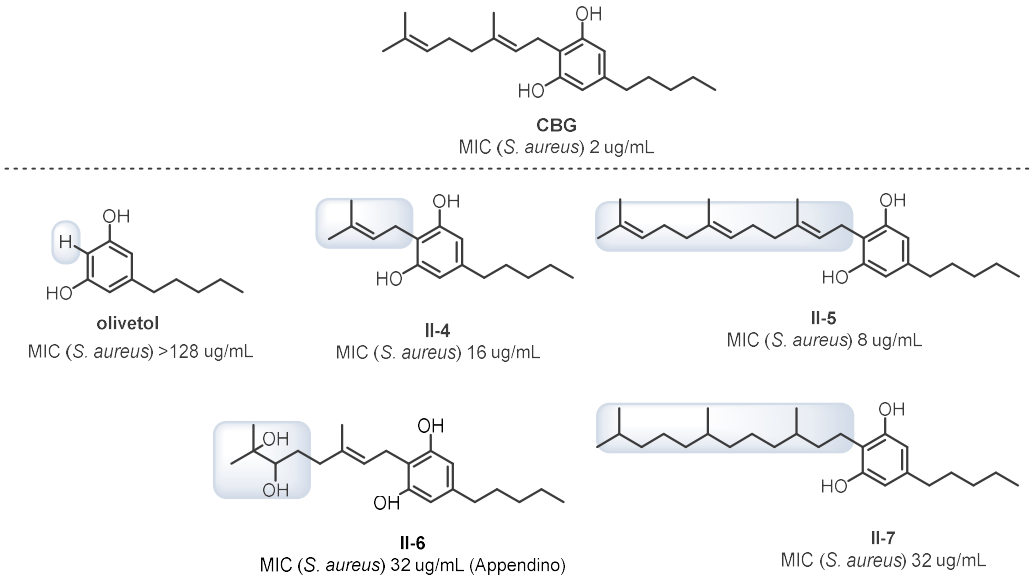


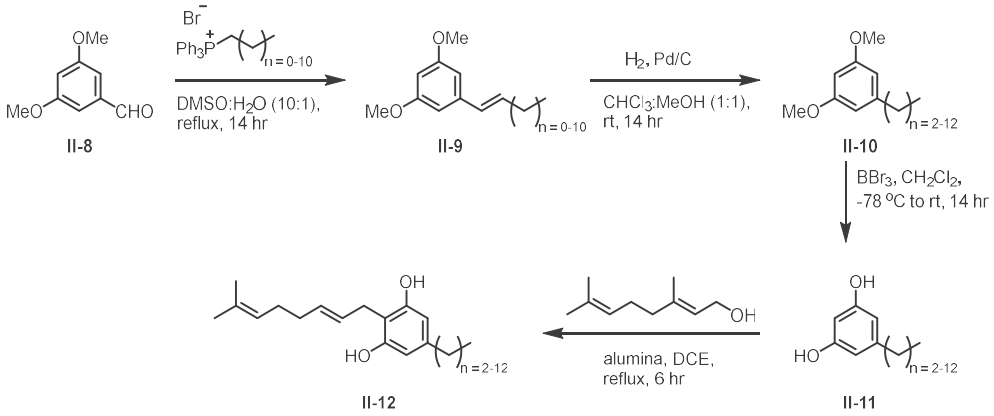
Figure 14 CBG analogues at the geraniol chain and their MIC against MRSA.

Differing the geranyl chain by length to prenyl (**II-4**) and farnesol (**II-5**) did not lead to improvements in activity with increased MICs of 16 ug/mL and 8 ug/mL respectively. Comparing these to olivetol, which has an MIC of >128 ug/mL it signified a requirement of chain substitution. As well, the saturated prenylated chain **II-7** has shown decreased biological activity from its prenylated counterpart where the MIC increased from **II-5** at 8

ug/mL to **II-7** exhibiting an MIC of 32 ug/mL. Lastly, exploring the dihyroxylated prenyl chain **II-6** showed loss of activity with an MIC of 32 ug/mL. This signifies that the geraniol chain of CBG is of importance in achieving a potent MIC with substitution at the prenyl chain decreasing activity.

2.33 CBG Analogues at the Alkyl Tail

CBG has been previously explored by Lee et al., where different alkyl chain lengths were investigated.[37] Carbon chain lengths of 3, 5, 7, 9, and 11 have been synthesized in 4 steps showcased in Scheme 7.[37] The synthetic analogues were then tested against MRSA (Figure 15).



Scheme 7 Synthetic route by Lee et al., towards alkyl CBG analogues.[37]

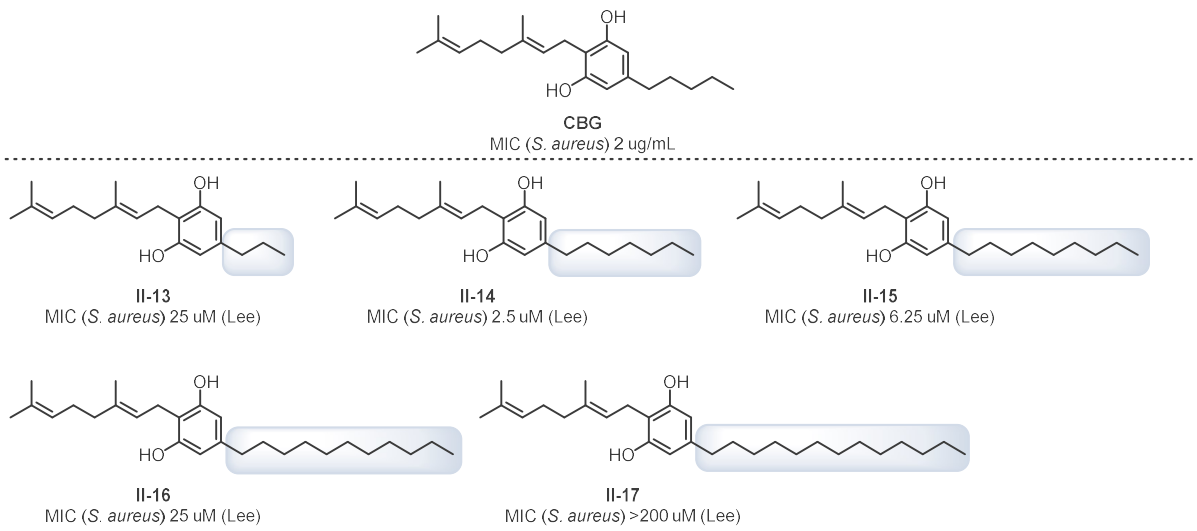


Figure 15 CBG analogues at the alkyl tail and their MIC against MRSA.[37]

Exploring different carbon chain lengths with **II-13** to **II-17** showed activity from 2.5 to >200 uM converted to <1 ug/mL to >128 ug/mL.[37] **II-14** and **II-15** with carbon chains of 7 and 9 showed the most potent activity with **II-13**, **II-16**, and **II-17** exhibiting a decreased MIC.[37]

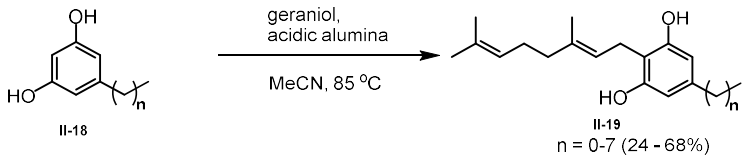
Except for the initial exploration from Lee *et al.,* there has been limited development with diversification at the aliphatic fragment.[37] This has left us with ample room for exploration to unlock the full potential of CBG. With the geraniol chain and phenolic core needed for activity, synthesis of analogues at the 5-position is open for investigation.

2.4 Alkyl CBG Analogues at the Alkyl Tail

Further investigation to varying alkyl chain lengths is needed to bridge the gap of the work from Lee *et al.,* along with obtaining further biological evaluation.[37]

Alkyl CBG analogues were investigated in the Magolan Lab changing the chain length at the 5-position from 0 to 7 carbons. These analogues were synthesized using the alumina

templated allylation chemistry to install a geraniol chain at the 2-position on varying resorcinols.



Scheme 8 Synthesis of alkyl CBG analogues.

Seven CBG analogues were synthesized by Dr. Lauren Irwin with varying alkyl chain lengths in 24-68% yields and tested against MRSA, MRSA with bicarbonate, *E. coli*, and ΔtolC-pore *E. coli*.

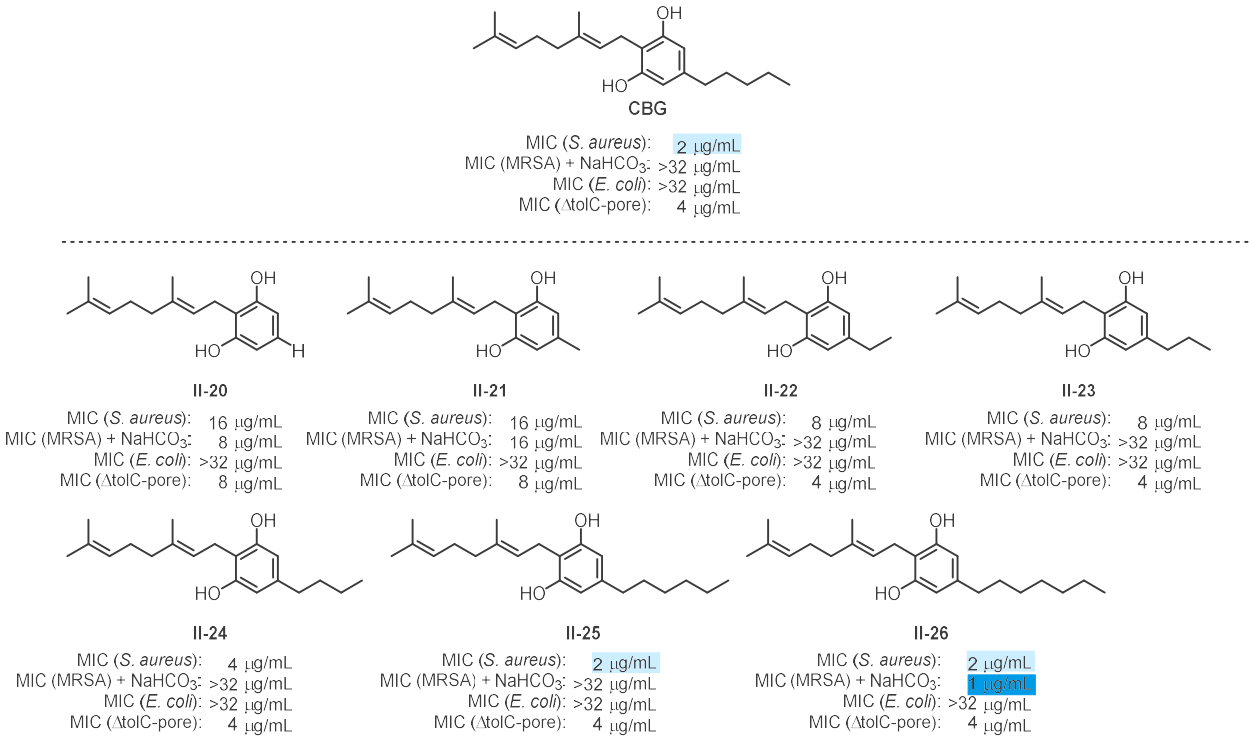


Figure 16 CBG analogues with alkyl chains from 0 to 7 carbons and their antibacterial properties.

When evaluating these alkyl CBG analogues against MRSA, CBG and compounds **II-25** and **II-26** with carbon chain lengths of 5, 6, and 7 showed good activity exhibiting and MIC of 2 ug/mL. Compound **II-20** with no carbon chain exhibited an MIC of 16 ug/mL signifying that

substitution at the 5-position of CBG is needed for bioactivity. Increasing chain length from unsubstituted (**II-20**) to a methyl (**II-21**) showed similar activity with an MIC of 16 ug/mL suggesting that a group larger than a methyl is necessary for improvement of activity against MRSA. Excitingly, we see an improvement in MIC when extending the chain length to 2, 3, and 4 with compounds **II-22** to **II-24** exhibiting MICs of 4-8 ug/mL.

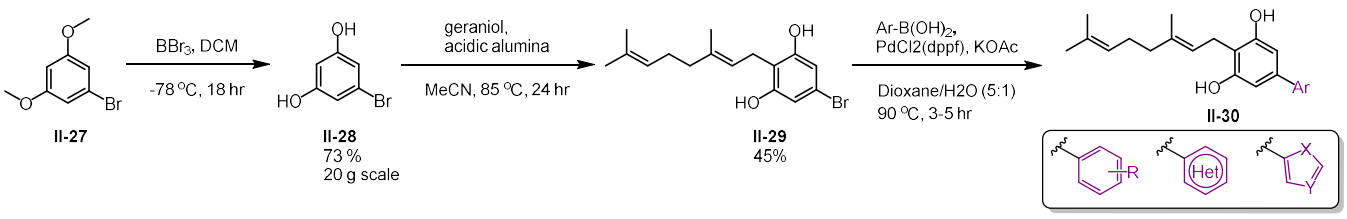
When bicarbonate is used as a potentiator molecule, slight inconsistencies are seen in the data meaning the assay should be redone to confirm MICs.

No activity was seen with alkyl CBG analogues against *E. coli*. This was of no surprise as CBG is a membrane acting compound and therefore unable to cross the outer membrane of gram-negative bacteria. However, in the presence of a tolC deletion, activity was regained. All analogues showed moderate activity against this strain of *E. coli* displaying MICs of 4-8 ug/mL except for compound **II-26** where no activity was regained.

These analogues should be analyzed further to see if the inconsistencies are from the assays or if compound **II-26** undergoes a different mechanism of action compared to that of the other alkyl CBG analogues.

2.5 Aryl CBG Analogues at the Alkyl Tail

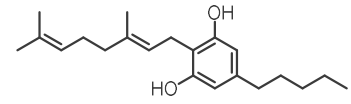
With the alkyl tail explored, we then envisioned diverse aryl CBG analogues to improve lipophilicity by removing the greasy aliphatic chain at the 5-position and further improve potency (Scheme 9). There has been no previously reported syntheses of aryl CBG analogues making this the first of its kind.



Scheme 9 Synthetic route to aryl CBG analogues.

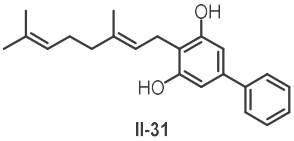
A library of novel analogues was synthesized using our new alumina templated *ortho*-allylation chemistry on 5-bromoresorcinol **II-27**. The geranylated 5-bromoresorcinol bromine can then act as a handle for diversification. Here, a mild Suzuki coupling is used to present aryl CBG analogues in the presence of free phenols with no protecting groups needed. Suzuki couplings are commonplace in medicinal chemistry because they are scalable, reliable, reproducible, and have a large functional group tolerance.[40] Functionalized boronic acids were used in the cross coupling to synthesize CBG analogues in 5-58% yields.

First investigated was a phenyl ring at the 5-position of CBG (**II-31**) shown in Figure 17.



CBG

MIC (*S. aureus*): 2 μg/mL
MIC (MRSA) + $NaHCO_3$: >32 μg/mL
MIC (*E. coli*): >32 μg/mL
MIC (ΔtolC-pore): 4 μg/mL



II-31

MIC (*S. aureus*): 4 μg/mL
MIC (MRSA) + $NaHCO_3$: 2 μg/mL
MIC (*E. coli*): >32 μg/mL
MIC (ΔtolC-pore): 2 μg/mL

Figure 17 Phenyl CBG analogue and its antibacterial activity.

II-31 showed exciting prospective to aryl CBG analogues where potent activity was seen against MRSA with an MIC of 4 ug/mL. With the addition of bicarbonate, an improved MIC was

seen of 2 ug/mL. Like the alkyl CBG analogues, no activity was seen against *E. coli,* but activity was regained when a hyperpermeable strain was used displaying an MIC of 2 ug/mL. The antibacterial activity of the phenyl CBG analogue showed great potential for further exploration of these types of compounds.

2.5.1 Evaluation of methyl substituents on 5-Phenyl CBG

The ortho, meta, and para sites of the phenyl ring were then explored to see if substitution at one of these sites can improve activity further.

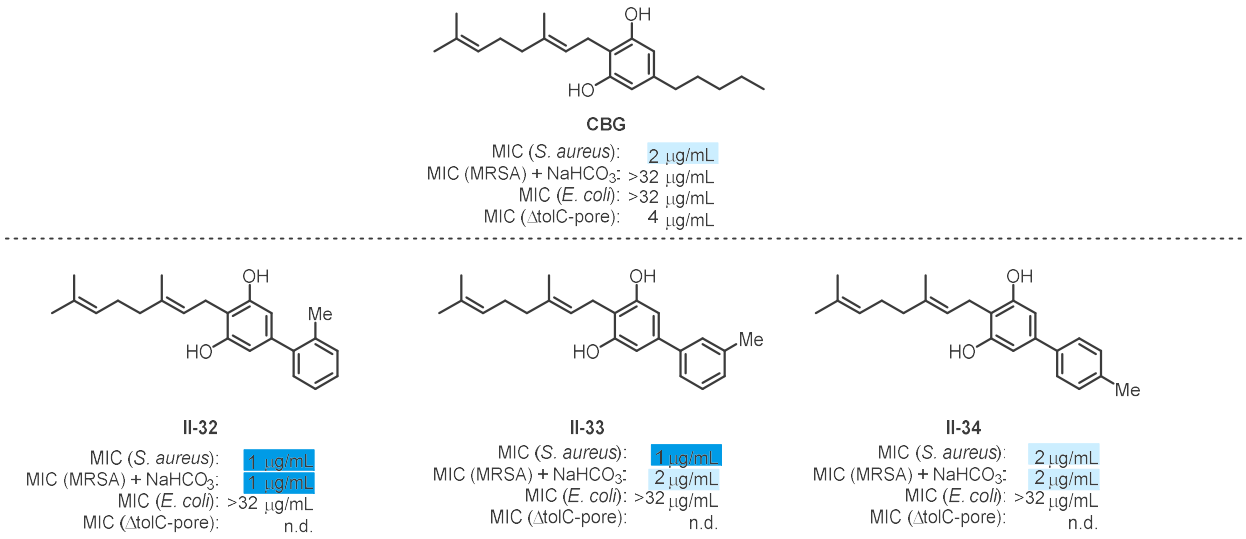


Figure 18 Ortho, meta, and para methyl substitution on phenyl CBG and their antibacterial properties.

Varying the location of methyl substituents at the ortho, meta, and para sites exhibited good activity against MRSA in all cases. **II-32** and **II-33** methyl substituents at the ortho and meta sites displaying an MIC of 1 ug/mL, improving the activity compared to CBG and to that of the unsubstituted phenyl ring **II-31**. With the addition of bicarbonate, the same or decreased activity was seen.

2.5.2 Evaluation of substituents on 5-Phenyl CBG

To further explore substitution, electron withdrawing Cl, F, and CF_3 as well as electron donating OMe substituents were substituted around the attached phenyl ring to investigate electronic effects on activity (Figure 19).

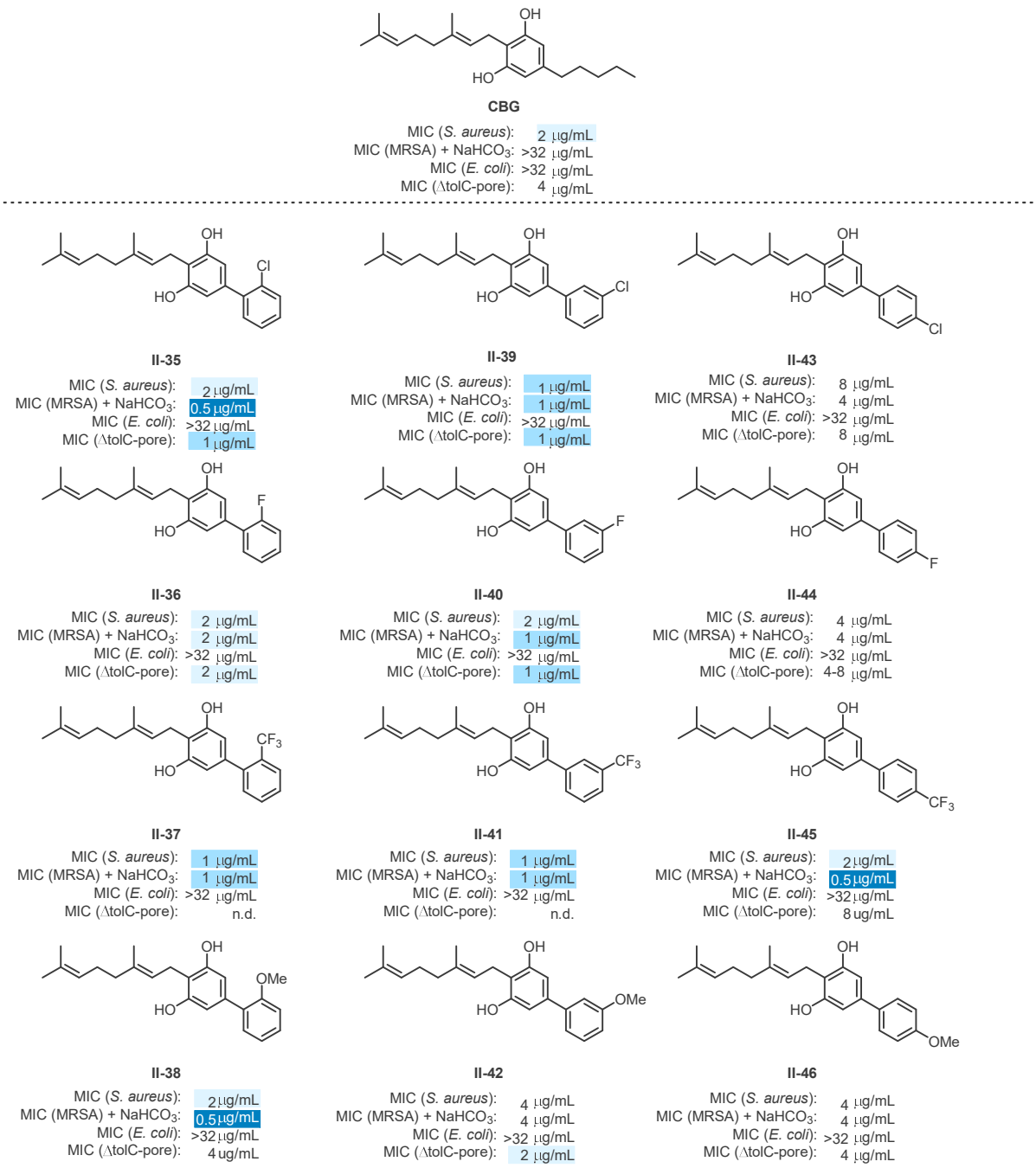


Figure 19 Ortho, meta, and para substitutions on phenyl CBG and their antibacterial properties.

All ortho substituents (**II-35** to **II-38**) exhibited potent antibacterial activity against MRSA with MIC's ranging from 1-2 ug/mL. Specifically, **II-37** the ortho-CF_3 substituent, stood out with its low MIC of 1 ug/mL. When in the presence of the potentiator molecule bicarbonate, it was seen that the activity of the ortho substituents remained the same or improved. Compounds **II-35** and **II-38** improved activity over 2-fold in the presence of bicarbonate displaying MICs of 0.5 ug/mL. Substitution at the ortho-site with any electron withdrawing or donating group improved activity meaning a substituent at the ortho position has steric influence on the mode of action.

At the meta position, electron withdrawing substituents **II-39** to **II-41** showed good activity with MIC's ranging from 1-2 ug/mL. However, electron donating OMe **II-42** showed decrease in potency (4 ug/mL) and has worse activity than CBG itself. The presence of bicarbonate allowed for all meta-analogues to exhibit the same or improved activity and activity was regained in the presence of the tolC-pore strain of *E. coli*. This trend signifies that electron donating effects are non-beneficial for activity.

All para substituents (**II-43** to **II-46**) showed decreased bacterial potential with MICs of 4-8 ug/mL for all substituents except for the para-CF_3 analogue. **II-45** showed an MIC of 2 ug/mL which did not trend for the other para substituent analogues. As well, in the presence of bicarbonate, **II-45** stood out with a further improved MIC to 0.5 ug/mL against MRSA.

Of these analogues, **II-32**, **II-33**, **II-37**, **II-39**, and **II-41** showed improved antibiotic activity exhibiting MICs of 1 ug/mL when compared to CBG (2 ug/mL). Additional ortho and para-analogues were synthesized and evaluated to explore the positions further.

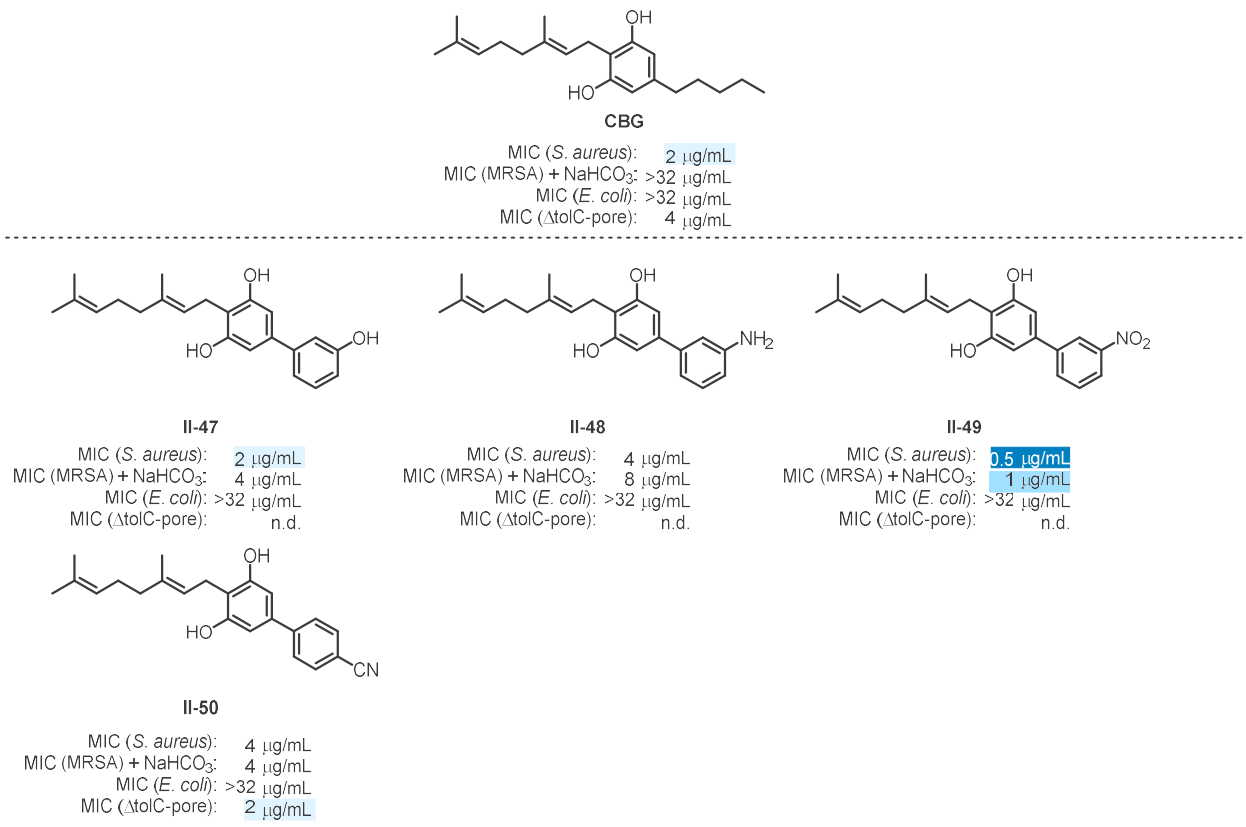


Figure 20 Expansion of ortho and para CBG analogues and their antibacterial properties.

We can confirm through the evaluation of **II-47**, **II-48**, and **II-49** that electron withdrawing substituents in the meta position are favoured. Electron donating hydroxy (**II-47**), and amino (**II-48**) substituents exhibited moderate potential with MICs of 2 and 4 ug/mL against MRSA respectively. We see a drastic improvement in potency with the electron withdrawing nitro substituent **II-49**. However, this nitro group is not favourable and generally avoided in medicinal chemistry due to its poor pharmacokinetic properties and toxicity.[41] The nitro group is comparable in electronics and lipophilicity to a trifluoromethyl substituent. However, comparing **II-49** to **II-41** there was decreased activity.

Lastly, a nitrile substituent at the para site (**II-50**) was investigated to increase the overall hydrophilicity of the compound.[42] However, **II-50** showed moderate potency similar to the other para-analogues investigated in Figure 18.

2.5.3 Evaluation of Disubstituted 5-Phenyl CBG Analogues

As all ortho-substituents showed high activity, a disubstituted effect was investigated. 2,4-disubstituted and 2,6-disubstituted analogues were synthesized and evaluated. As well, a 3,5-disubstituted analogue was investigated due to the potential of electron withdrawing meta substituents showing promising MICs.

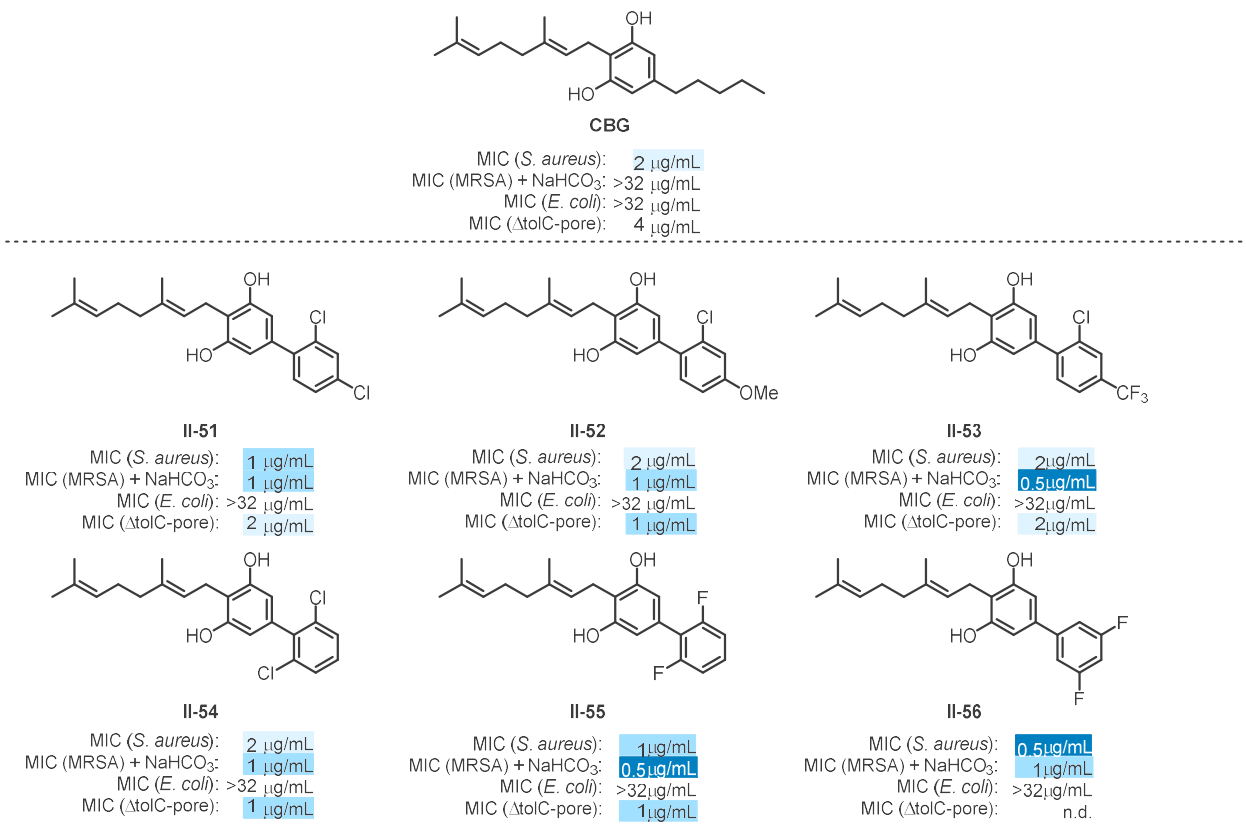


Figure 21 Disubstituted CBG analogues and their antibacterial activities.

This additive effect of an ortho-chloro with a para substituent (**II-51**) showed improved activity compared to the para substituent itself. **II-51** showed excellent potency with an MIC of 1

ug/mL. **II-52** and **II-53** also showed potential with MICs of 2 ug/mL, suggesting that the ortho substituent is of great importance.

Another additive effect was investigated with 2,6-disubstituted analogues. **II-54** and **II-55** were synthesized and evaluated to see if the addition of a second ortho substituent increased activity. **II-54** showed comparable activity to that of **II-35**. Interestingly, we saw improvement with **II-55** increasing its potency by 1-fold compared to **II-36** (2-fluorophenyl) where the MIC improved from 2 ug/mL to 1 ug/mL against MRSA. As well, **II-55** in the presence of bicarbonate displayed a potent MIC of 0.5 ug/mL.

Lastly, the 3,5-difluorinated analogue II-56 was investigated because we had observed good potential with electron withdrawing meta substituents. This additive effect was seen as **II-56** improved its activity 2-fold compared to **II-40**. This potent MIC of **II-56** at 0.5 ug/mL has improved drastically from 2 ug/mL against MRSA.

2.5.4 Evaluation of Heterocyclic-CBG Analogues

Lastly, heterocycles were explored. Introduction of heterocycles can improve pharmacokinetic properties where we are introducing polarity to the compound, introducing hydrogen bonding, and reducing lipophilicity.[43]

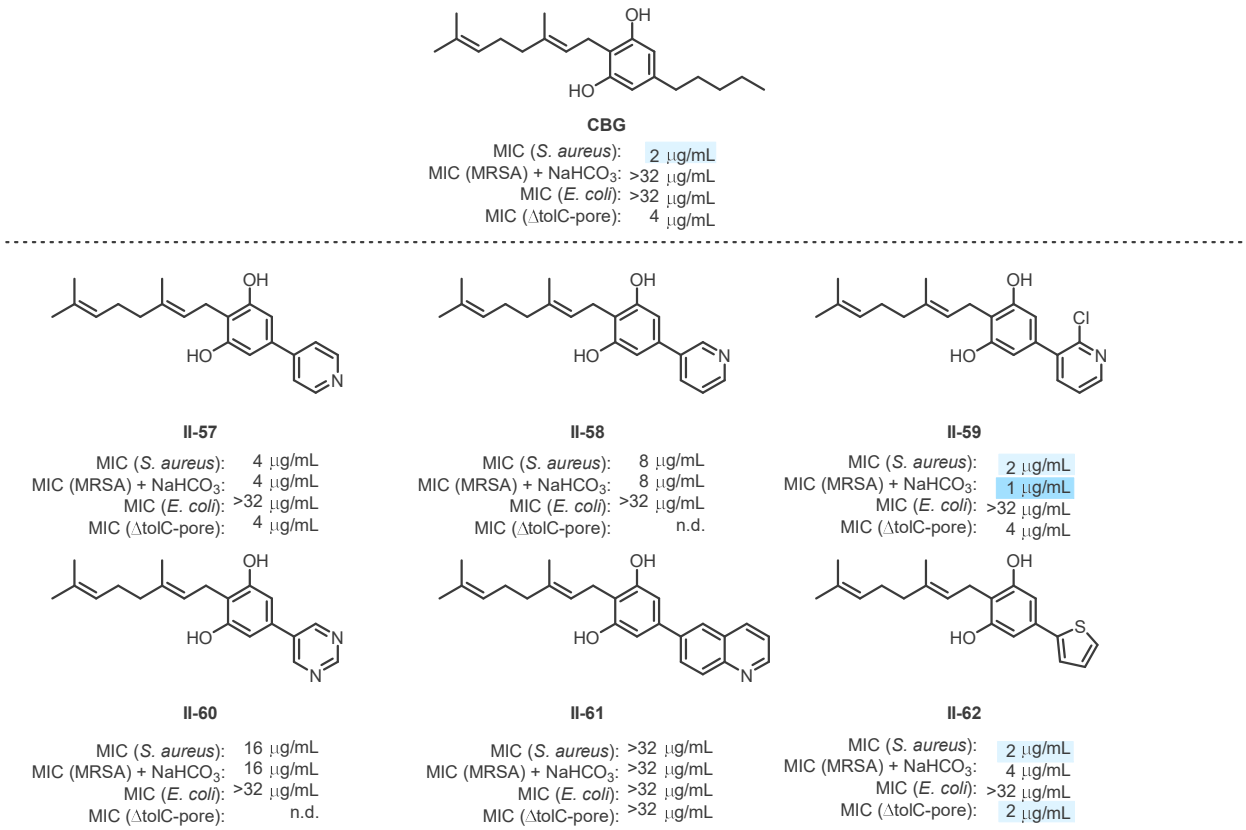


Figure 22 Heterocyclic CBG analogues and their antibacterial activities.

Pyridine type CBG analogues were explored. **II-57** showed moderate activity of 4 ug/mL against MRSA. Moving the nitrogen atom from the 4-position to the 3-position (**II-58**) decreased activity further to 8 ug/mL against MRSA. However, the introduction of a heteroatom (Cl) at the ortho position (**II-59**) showed activity being regained with an MIC of 2 ug/mL against MRSA. Again, this signifies the importance of an ortho substituent on these aryl CBG analogues.

Pyrimidine **II-60** showed further decrease in activity compared to the pyridine compounds with an MIC of 16 ug/mL against MRSA. This indicates that only one heteroatom in the ring can be tolerated. The extension of space to the quinoline (**II-61**) showed no activity with an MIC of >32 ug/mL. Lastly, thiophenyl **II-62** showed moderate potency at 2 ug/mL and should be further explored.

All heterocycles except for **II-59** showed similar or decreased potency when in addition with bicarbonate or against ΔtolC-Pore *E. coli*. **II-59** exhibited an increased potential with bicarbonate possibly due to the ortho-chloro substituent.

2.6 Summary of Structure-Activity Relationship Effects of 5-Position CBG Analogues

CBG and 39 CBG analogues at the alkyl tail were synthesized and evaluated. Nine analogues showed an increased potency compared to CBG against MRSA with MICs of 0.5-1 ug/mL. Fourteen analogues exhibited the same potency to that of CBG (2 ug/mL) and sixteen analogues showed decreased activity.

Of the alkyl analogues, a carbon chain length of 5 (CBG), 6 (**II-25**), and 7 (**II-26**), showed potent activity with MICs of 2 ug/mL against MRSA. Carbon chains smaller than 5 showed decreased activity.

Of the aryl CBG class, **II-56** and **II-49** showed the greatest activity with an MIC of 0.5 ug/mL against MRSA. The meta-nitrophenyl analogue **II-49** was synthesized to confirm electron withdrawing meta substituents are favoured even though nitro groups are not favoured metabolically. Overall, ortho and meta substituents were favoured over para substitution. Disubstituted analogues showed improved potency and heterocycles were tolerated.

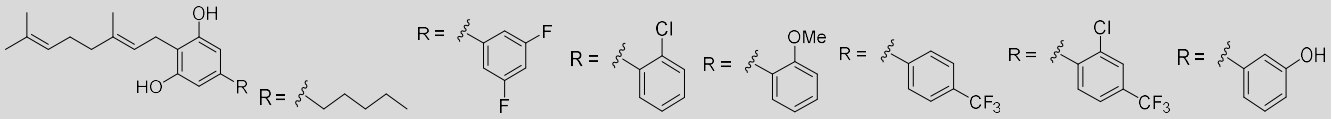
II-35, **II-38**, **II-45**, and **II-53** were of great interest due to their ability to improve their MIC in the presence of bicarbonate from 2 ug/mL to 0.5 ug/mL against MRSA. These analogues should be further investigated.

2.7 Predicted Pharmacokinetic Properties of CBG Analogues

Further analyzing the most potent antibiotic derivatives of CBG discovered, **II-56**, **II-35**, **II-38**, **II-45**, **II-53**, and **II-47** underwent *in silico* predictions by SwissADME to evaluate their

pharmacokinetic properties (Table 1).[44] These compounds were chosen due to their potent MIC against MRSA and improvement when assayed with bicarbonate. **II-47** was also included to compare predicted pharmacokinetic properties with a more polar functional group.

Table 1 Predicted pharmacokinetic properties of CBG analogues predicted by SwissADME

							
	CBG	II-56	II-35	II-38	II-45	II-53	II-47
MIC (ug/mL)	2	0.5	2	2	2	2	2
MW	316.48	358.42	356.89	352.47	390.44	424.88	338.44
Log P	6.74	3.97	3.94	4.02	4.19	4.31	3.51
H-donors	2	2	2	2	2	2	3
H-acceptors	2	2	2	2	2	2	3
Rotatable bonds	9	6	6	7	7	7	6
Rings	1	2	2	2	2	2	2
Predicted Solubility (mg/mL)	0.0003	0.0002	0.0001	0.0003	0.00006	0.00001	0.0005

Predicted from SwissADME

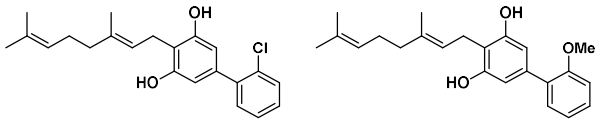
These analogues showed an impressive improvement in lipophilicity while keeping the molecular weight similar and staying within Lipinski's rules. However, the predicted solubility of these compounds is still poor. To improve this, future CBG analogues should investigate an added polar substituent to improve solubility. An addition of a phenol to CBG at position 5 (**II-47**), showed an improvement with a predicted solubility of 0.0005 mg/mL making the compound improve from poor to moderate solubility. This change in lipophilicity and predicted solubility had minimal effect on potency, with **II-47** exhibiting an MIC of 2 ug/mL. Lastly, fluorination of these CBG analogues can better the bioavailability and increases potency of drugs which should be further explored.[45]

Chapter 3 - Future Work

With the synthesized library of CBG analogues, further biological studies are needed. Moreover, additional CBG analogues should be investigated to improve pharmacokinetic properties for the identification of a CBG-derived antibiotic. Lastly, the synthesis of aryl CBG analogues can be used as inspiration for the synthesis of natural products including stilbenoids which warrants further investigation.

3.1 Biological Assays

In vivo studies are currently being investigated using **II-35** and **II-38** in mice. CBG analogues that showed a 2-fold increase in MIC when in the presence of bicarbonate have been chosen for further evaluation. Of these analogues **II-35** and **II-38** are of consideration as they exhibit the best predicted solubilities of the candidates (Figure 23). *In vivo* activity of **II-35** and **II-38** are ongoing.



II-35
MIC (MRSA) = 2 ug/mL
MIC (MRSA) + Bicarb = 0.5 ug/mL
MIC (*E. coli*) = >32 ug/mL
MIC (tolC-Pore *E. coli*) = 1 ug/mL

II-38
MIC (MRSA) = 2 ug/mL
MIC (MRSA) + Bicarb = 0.5 ug/mL
MIC (*E. coli*) = >32 ug/mL
MIC (tolC-Pore *E. coli*) = 4 ug/mL

Figure 23 Candidates for in vivo studies.

As CBG exhibits extensive biological activity with activity beyond MRSA, this library of CBG compounds should also be screened for other bacterial pathogens as well as other therapeutics to explore the full potential of cannabinoids and CBG.

Lastly, the alkyl CBG analogues (**II-20** to **II-26**) should be rescreened against MRSA with bicarbonate and against ΔtolC-Pore *E. coli* due to inconsistencies in the assay results.

3.2 Improving the Pharmacokinetic Properties of CBG

Aryl CBG analogues should be further explored. The newly developed CBG candidates exhibited improved antibacterial activity and lipophilicity. However, the aqueous solubility is still poor. New analogues should be developed to overcome this issue by introducing polar functionalities and sp^3 character to the molecule.[46] Ortho-substituted benzene derivatives should be expanded upon due to it's change in dihedral angle of the bicyclic structure of aryl CBG analogues.[46] Ortho-substitution also decreases molecular symmetry which are factors known to improve solubility.[46]

With the meta-nitrobenzene CBG analogue (**II-49**) being a potent inhibitor of MRSA, exploration of electron withdrawing substituents that are not toxic or metabolically unstable at this site should also be further explored. Bioisosteres are known chemical moieties that can replace a functional group while retaining similar biological activity. Nitro-bioisosteres like sulfonyl groups including sulfonamides can mimic the electron withdrawing properties of nitro groups. Other replacements that can be explored include tetrazoles which are often used to replace carboxylic acids and nitro groups due to their similar electronic distribution.[47]

3.3 Extending Suzuki Coupling to Stilbenoids

Stilbenoids are secondary plant metabolites and the hydroxylated derivatives of stilbenes (Figure 24) which have diverse biological activities and potential therapeutic applications including antibacterial, antioxidant, anti-inflammatory, anticancer, cardioprotective, and neuroprotective effects.[48]

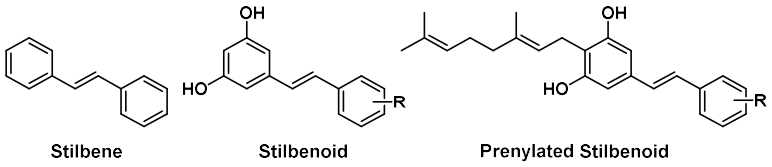
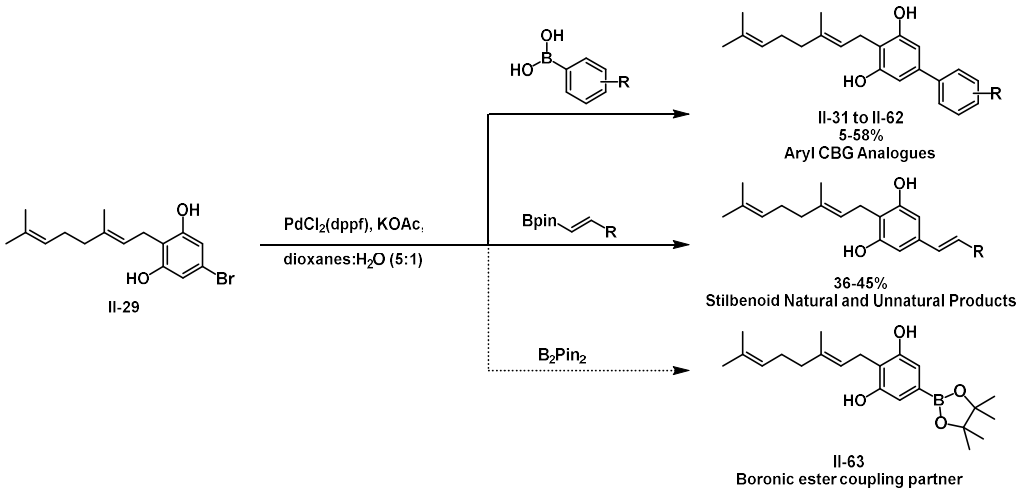


Figure 24 Stilbene, stilbenoid and prenylated stilbenoids

Using the same Suzuki coupling conditions with different coupling partners, we can access a wide variety of complex prenylated natural and unnatural products. This includes aryl CBG analogues explored in Scheme 9, coupling of vinyl boronic esters to access stilbenoid natural products, borylated geranylated resorcinols (**II-63**) for further diversification with complex bromines and other diverse prenylated phenolic compounds. We have demonstrated Suzuki couplings without the use of phenolic protection and in the presence of prenyl chains where we can extend this strategy further.

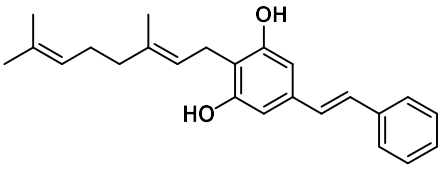


Scheme 10 Using Suzuki-Miyaura reaction conditions to access different prenylated products.

Following the Suzuki coupling conditions, we can access prenylated stilbenoid natural products with the use vinyl boronic esters. This has shown initial promise with the synthesis of amorphastilbol in moderate yields of 46%.

Further investigation into access of borylated geranylated resorcinol **II-63** is needed. This can allow us to synthesize diverse prenylated compounds through Suzuki couplings with alkyl and aryl halides. The boronic ester can be installed using bis(pinacolato)diboron (B_2pin_2) coupled with geranylated bromoresorcinol **II-29**. This Miyaura borylation is known and should be continued to be investigated.[49]

As stilbenoid natural products exhibit significant bioactivity, particularly antibacterial properties, we initially tested amorphastilbol against MRSA (Figure 25).[50] The natural product displayed an MIC of 2 ug/mL against MRSA and a tolC-pore *E. coli* showing initial antibacterial properties that should be further explored for the potential of prenylated stilbenoids using the route in Scheme 10. The introduction of an olefin between the two biphenyl rings can allow for more flexibility of the molecule which can lead to improved solubility over the aryl CBG analogues.



Amorphastilbol
MIC (MRSA) = 2 ug/mL
MIC (MRSA) + Bicarb = 2 ug/mL
MIC (*E. coli*) = >32 ug/mL
MIC (tolC-Pore *E. coli*) = 2 ug/mL

Figure 25 Antibacterial properties of amorphastilbol

With these promising results, prenylated stilbenoid natural and unnatural products should be synthesized and evaluated along with exploration of the synthesis of **II-63**.

Chapter 4 - Conclusion

42 CBG analogues were synthesized and tested for their antibacterial properties. It was found that the geraniol chain and phenolic core is necessary for activity against MRSA (Figure 26).[1] With limited exploration of the 5-poistion of CBG and free patent space, a library of CBG analogues was synthesized using our new alumina mediated ortho-prenylation method and Suzuki couplings. The synthesis and biological evaluation of alkyl and aryl CBG analogues allowed us to study the structure-activity relationship of CBG against MRSA, improve the antibiotic potential of CBG, and improve physiochemical properties (Figure 27). Improvement to the activity and physiochemical properties came from the substitution of the alkyl tail to substituted benzene derivatives. The addition of an ortho substituent or electron withdrawing meta substituent saw great improvement of MIC of up to 0.5-1 ug/mL and decreased lipophilicity.

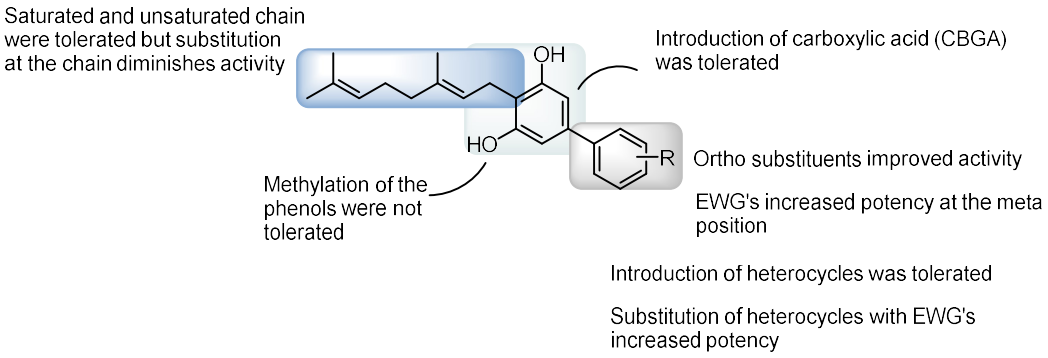


Figure 26 Structure activity relationship summary of aryl CBG analogues

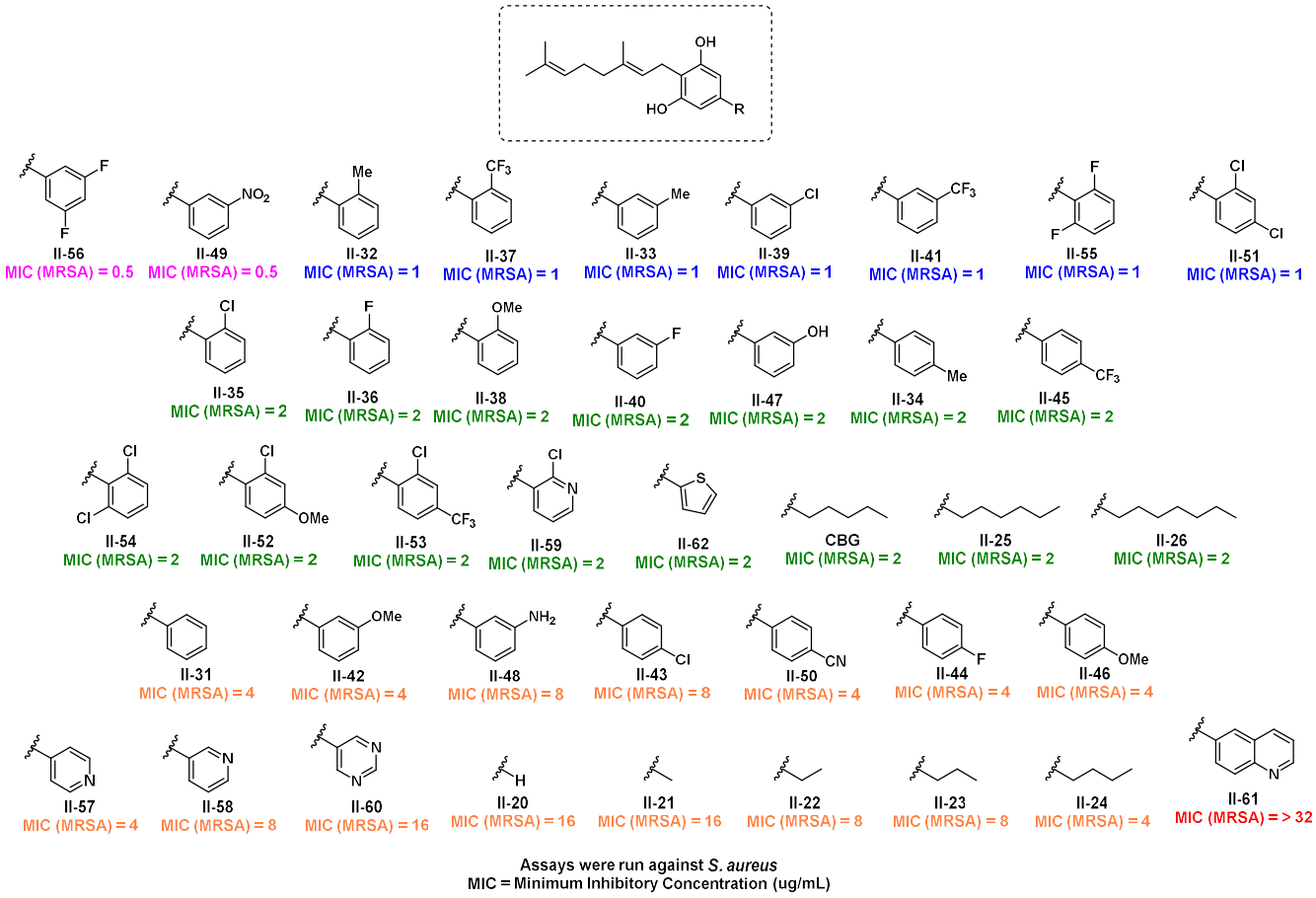


Figure 27 CBG and CBG analogues activity against MRSA.

In addition, *in vivo* studies with II-35 and II-38 are currently in progress and further biological evaluation of the novel analogues against other pathogens and therapeutics should be explored.

To further expand on this protecting group free Suzuki coupling to access aryl CBG analogues, we can also explore a unique method for accessing stilbenoid natural products, which merits additional investigation and antibiotic evaluation.

5.0 References

(1) Appendino, G.; Gibbons, S.; Giana, A.; Pagani, A.; Grassi, G.; Stavri, M.; Smith, E.; Rahman, M. M. Antibacterial Cannabinoids from Cannabis sativa: A Structure−Activity Study. *Journal of Natural Products* **2008**, *71* (8), 1427-1430. DOI: 10.1021/np8002673.
(2) Farha, M. A.; El-Halfawy, O. M.; Gale, R. T.; MacNair, C. R.; Carfrae, L. A.; Zhang, X.; Jentsch, N. G.; Magolan, J.; Brown, E. D. Uncovering the Hidden Antibiotic Potential of Cannabis. *ACS Infect Dis* **2020**, *6* (3), 338-346. DOI: 10.1021/acsinfecdis.9b00419 From NLM Medline.
(3) Hariyanto, H.; Yahya, C. Q.; Cucunawangsih, C.; Pertiwi, C. L. P. ANTIMICROBIAL RESISTANCE AND MORTALITY. *Afr J Infect Dis* **2022**, *16* (2), 13-20. DOI: 10.21010/Ajid.v16i2.2 From NLM.
(4) Hutchings, M. I.; Truman, A. W.; Wilkinson, B. Antibiotics: past, present and future. *Current opinion in microbiology* **2019**, *51*, 72-80.
(5) Bush, K.; Bradford, P. A. beta-Lactams and beta-Lactamase Inhibitors: An Overview. *Cold Spring Harb Perspect Med* **2016**, *6* (8). DOI: 10.1101/cshperspect.a025247 From NLM Medline.
(6) Bush, K.; Bradford, P. A. β-Lactams and β-Lactamase Inhibitors: An Overview. *Cold Spring Harb Perspect Med* **2016**, *6* (8). DOI: 10.1101/cshperspect.a025247 From NLM.
(7) Silhavy, T. J.; Kahne, D.; Walker, S. The bacterial cell envelope. *Cold Spring Harb Perspect Biol* **2010**, *2* (5), a000414. DOI: 10.1101/cshperspect.a000414 From NLM.
(8) Klein, T. A.; Ahmad, S.; Whitney, J. C. Contact-Dependent Interbacterial Antagonism Mediated by Protein Secretion Machines. *Trends in Microbiology* **2020**, *28* (5), 387-400. DOI: https://doi.org/10.1016/j.tim.2020.01.003.
(9) Ventola, C. L. The antibiotic resistance crisis: part 1: causes and threats. *P t* **2015**, *40* (4), 277-283. From NLM.
(10) Ali Alghamdi, B.; Al-Johani, I.; Al-Shamrani, J. M.; Musamed Alshamrani, H.; Al-Otaibi, B. G.; Almazmomi, K.; Yusnoraini Yusof, N. Antimicrobial resistance in methicillin-resistant staphylococcus aureus. *Saudi J Biol Sci* **2023**, *30* (4), 103604. DOI: 10.1016/j.sjbs.2023.103604 From NLM PubMed-not-MEDLINE.
(11) Tong, S. Y.; Davis, J. S.; Eichenberger, E.; Holland, T. L.; Fowler, V. G., Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev* **2015**, *28* (3), 603-661. DOI: 10.1128/CMR.00134-14 From NLM Medline.
(12) Mark C Enright; Robinson, D. A.; Randle, G.; Feil, E. J.; Grundmann, H.; Spratt, B. G. The evolutionary history of methicillin-resistant Staphylococcus aureus (MRSA). *Proc Natl Acad Sci U S A* **2022**, *28* (99), 7687-7692. DOI: 10.1073/pnas.122108599.
(13) Lee, A. S.; de Lencastre, H.; Garau, J.; Kluytmans, J.; Malhotra-Kumar, S.; Peschel, A.; Harbarth, S. Methicillin-resistant Staphylococcus aureus. *Nat Rev Dis Primers* **2018**, *4*, 18033. DOI: 10.1038/nrdp.2018.33 From NLM Medline.
(14) Cong, Y.; Yang, S.; Rao, X. Vancomycin resistant Staphylococcus aureus infections: A review of case updating and clinical features. *J Adv Res* **2020**, *21*, 169-176. DOI: 10.1016/j.jare.2019.10.005 From NLM PubMed-not-MEDLINE.

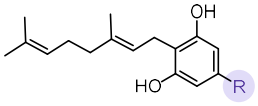
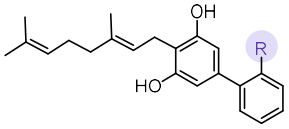
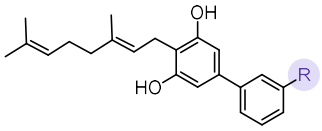
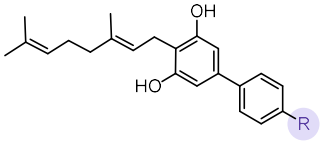
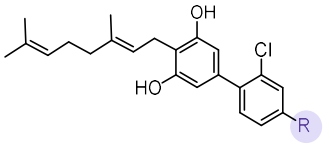
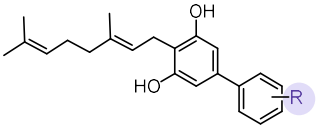
(15) Yuan, H.; Ma, Q.; Ye, L.; Piao, G. The Traditional Medicine and Modern Medicine from Natural Products. *Molecules* **2016**, *21* (5). DOI: 10.3390/molecules21050559 From NLM.
(16) Rossiter, S. E.; Fletcher, M. H.; Wuest, W. M. Natural Products as Platforms To Overcome Antibiotic Resistance. *Chem Rev* **2017**, *117* (19), 12415-12474. DOI: 10.1021/acs.chemrev.7b00283 From NLM.
(17) Schneider, Y. K. Bacterial Natural Product Drug Discovery for New Antibiotics: Strategies for Tackling the Problem of Antibiotic Resistance by Efficient Bioprospecting. *Antibiotics* **2021**, *10*, 842. DOI: 10.3390/antibiotics10070842.
(18) Scott, K. A.; Cox, P. B.; Njardarson, J. T. Phenols in Pharmaceuticals: Analysis of a Recurring Motif. *Journal of Medicinal Chemistry* **2022**, *65* (10), 7044-7072. DOI: 10.1021/acs.jmedchem.2c00223.
(19) Škovranová, G.; Čulenová, M.; Treml, J.; Dzurická, L.; Marova, I.; Sychrová, A. Prenylated phenolics from Morus alba against MRSA infections as a strategy for wound healing. *Front Pharmacol* **2022**, *13*, 1068371. DOI: 10.3389/fphar.2022.1068371 From NLM.
(20) Navrátilová, A.; Schneiderová, K.; Veselá, D.; Hanáková, Z.; Fontana, A.; Dall'Acqua, S.; Cvačka, J.; Innocenti, G.; Novotná, J.; Urbanová, M.; et al. Minor C-geranylated flavanones from Paulownia tomentosa fruits with MRSA antibacterial activity. *Phytochemistry* **2013**, *89*, 104-113. DOI: https://doi.org/10.1016/j.phytochem.2013.01.002.
(21) Adamczak, A.; Ożarowski, M.; Karpiński, T. M. Antibacterial Activity of Some Flavonoids and Organic Acids Widely Distributed in Plants. *J Clin Med* **2019**, *9* (1). DOI: 10.3390/jcm9010109 From NLM.
(22) Rüegg, T.; Calderón, A. I.; Queiroz, E. F.; Solís, P. N.; Marston, A.; Rivas, F.; Ortega-Barría, E.; Hostettmann, K.; Gupta, M. P. 3-Farnesyl-2-hydroxybenzoic acid is a new anti-Helicobacter pylori compound from Piper multiplinervium. *Journal of Ethnopharmacology* **2006**, *103* (3), 461-467. DOI: https://doi.org/10.1016/j.jep.2005.09.014.
(23) Lee, K. A.; Moon, S.-H.; Lee, J.-Y.; Kim, K.-T.; Park, Y.-S.; Paik, H.-D. Antibacterial activity of a novel flavonoid, 7-O-butyl naringenin, against methicillin-resistant Staphylococcus aureus (MRSA). *Food Science and Biotechnology* **2013**, *22* (6), 1725-1728. DOI: 10.1007/s10068-013-0272-9.
(24) Calapai, F.; Cardia, L.; Esposito, E.; Ammendolia, I.; Mondello, C.; Giudice, R. L.; Gangemi, S.; Calapai, G.; Mannucci, C. Pharmacological Aspects and Biological Effects of Cannabigerol and its Synthetic Derivatives. *Evidence-Based Complementary and Alternative Medicine* **2022**, *2022*, 3336516. DOI: 10.1155/2022/3336516.
(25) Choo, E. J.; Chambers, H. F. Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia. *Infection & Chemotherapy* **2016**, *48* (4). DOI: 10.3947/ic.2016.48.4.267.
(26) Jastrzab, A.; Jarocka-Karpowicz, I.; Skrzydlewska, E. The Origin and Biomedical Relevance of Cannabigerol. *Int J Mol Sci* **2022**, *23* (14). DOI: 10.3390/ijms23147929 From NLM Medline.
(27) Perez, E.; Fernadez, J. R.; Fitzgerald, C.; Rouzard, K.; Tamura, M.; Savile, C. In vitro and clinical evaluation of Cannabigerol (CBG) produced via yeast biosynthesis: A cannabinoid with a broad range of anti-inflammatory and skin health-boosting properties. *Molecules* **2022**, *27*, 491. DOI: https://doi.org/10.3390/molecules27020491.

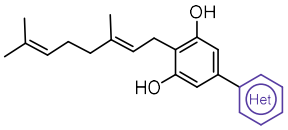
(28) Jentsch, N. G.; Zhang, X.; Magolan, J. Efficient Synthesis of Cannabigerol, Grifolin, and Piperogalin via Alumina-Promoted Allylation. *Journal of Natural Products* **2020**, *83* (9), 2587-2591. DOI: 10.1021/acs.jnatprod.0c00131.
(29) Gaoni, Y.; Mechoulam, R. The stucture and synthesis of Cannabigerol, a New Hashish Constituent. *Proceedings of the Chemical Society* **1964**, *March*, 82.
(30) Seung-Hwa Baek; Yook, C. N.; Han, D. S. Boron Trifluoride Etherate on Alumina-A Modified Lewis Acid Reagent(V) A Convinient Single-step Synthesis of Cannabinoids. *Bulletin of the Korean Chemical Society* **1994**, *16* (3), 293-296.
(31) Futoshi Tuara; Satoshi Morimoto; Shoyama, Y. Purification and Characterization of Cannabidiolic-acid Synthase from Cannabis sativa L. *The Journal of Biological Chemistry* **1996**, *271* (29), 17411-17416. DOI: https://doi.org/10.1074/jbc.271.29.17411.
(32) Mechoulam, R.; Yagen, S. Stereoselective cyclizations of cannabinoid 1,5 dienes. *Tetrahedron Lett.* **1969**, (60), 5349-5352. DOI: https://doi.org/10.1016/S0040-4039(01)88961-9.
(33) ROBERT, D.; JACOB, B.; THOMAS, S.; SEAN, C. METHODS OF SYNTHESIZING HALOGENATED CANNABINOIDS AND DERIVATIVES OF CANNABINOIDS. 2022.
(34) CHENGUO, F.; JIANGUO, F.; GUOQIANG, L.; JIANGE, Z.; RUIXIANG, L.; MAOQI, Y.; JUNJIE, W. Method for preparing cannabinoid phenol and analogues thereof. 2021.
(35) THOMAS, S.; ROBERT, D.; SEAN, C.; JACOB, B. SYNTHESIS OF CANNABIGEROL. 2020.
(36) Piotrowski, M. L. I., L. C.; Darveau, P.; Zhang, X.; Jentsch, N. G.; Hoford, S.; Vemulapalli, S.; Johnson, J. W.; Dudding, T.; Magolan, J. . Alumina-Templated ortho-Allylation of Phenols. *Manuscript in Preperation 2023*.
(37) Lee, Y.-E.; Kodama, T.; Morita, H. Novel insights into the antibacterial activities of cannabinoid biosynthetic intermediate, olivetolic acid, and its alkyl-chain derivatives. *Journal of Natural Medicines* **2023**, *77* (2), 298-305. DOI: 10.1007/s11418-022-01672-9.
(38) Farha, M. A.; French, S.; Stokes, J. M.; Brown, E. D. Bicarbonate Alters Bacterial Susceptibility to Antibiotics by Targeting the Proton Motive Force. *ACS Infectious Diseases* **2018**, *4* (3), 382-390. DOI: 10.1021/acsinfecdis.7b00194.
(39) Zgurskaya, H. I.; Krishnamoorthy, G.; Ntreh, A.; Lu, S. Mechanism and Function of the Outer Membrane Channel TolC in Multidrug Resistance and Physiology of Enterobacteria. *Front Microbiol* **2011**, *2*, 189. DOI: 10.3389/fmicb.2011.00189 From NLM.
(40) Buskes, M. J.; Blanco, M. J. Impact of Cross-Coupling Reactions in Drug Discovery and Development. *Molecules* **2020**, *25* (15). DOI: 10.3390/molecules25153493 From NLM.
(41) Nepali, K.; Lee, H.-Y.; Liou, J.-P. Nitro-Group-Containing Drugs. *Journal of Medicinal Chemistry* **2019**, *62* (6), 2851-2893. DOI: 10.1021/acs.jmedchem.8b00147.
(42) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-containing pharmaceuticals: efficacious roles of the nitrile pharmacophore. *J Med Chem* **2010**, *53* (22), 7902-7917. DOI: 10.1021/jm100762r From NLM.
(43) Jampilek, J. Heterocycles in Medicinal Chemistry. *Molecules* **2019**, *24* (21). DOI: 10.3390/molecules24213839 From NLM.
(44) Daina, A.; Michielin, O.; Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports* **2017**, *7* (1), 42717. DOI: 10.1038/srep42717.

(45) Chandra, G.; Singh, D. V.; Mahato, G. K.; Patel, S. Fluorine-a small magic bullet atom in the drug development: perspective to FDA approved and COVID-19 recommended drugs. *Chem Zvesti* **2023**, 1-22. DOI: 10.1007/s11696-023-02804-5 From NLM.
(46) Ishikawa, M.; Hashimoto, Y. Improvement in Aqueous Solubility in Small Molecule Drug Discovery Programs by Disruption of Molecular Planarity and Symmetry. *Journal of Medicinal Chemistry* **2011**, *54* (6), 1539-1554. DOI: 10.1021/jm101356p.
(47) Neochoritis, C. G.; Zhao, T.; Dömling, A. Tetrazoles via Multicomponent Reactions. *Chemical Reviews* **2019**, *119* (3), 1970-2042. DOI: 10.1021/acs.chemrev.8b00564.
(48) Akinwumi, B. C.; Bordun, K. M.; Anderson, H. D. Biological Activities of Stilbenoids. *Int J Mol Sci* **2018**, *19* (3). DOI: 10.3390/ijms19030792 From NLM.
(49) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters. *The Journal of Organic Chemistry* **1995**, *60* (23), 7508-7510. DOI: 10.1021/jo00128a024.
(50) de Bruijn, W. J. C.; Araya-Cloutier, C.; Bijlsma, J.; de Swart, A.; Sanders, M. G.; de Waard, P.; Gruppen, H.; Vincken, J.-P. Antibacterial prenylated stilbenoids from peanut (Arachis hypogaea). *Phytochemistry Letters* **2018**, *28*, 13-18. DOI: https://doi.org/10.1016/j.phytol.2018.09.004.

6.0 Appendix

Table 2 Antibacterial properties of CBG analogues

CBG Analogue		Minimum Inhibitory Concentration (ug/mL)			
		MRSA	MRSA + Bicarbonate	*E. coli*	ΔTolC-pore *E. coli*
	R = pentyl (CBG)	2	> 32	> 32	4
	R = H	16	8	> 32	8
	R = methyl	16	16	> 32	8
	R = ethyl	8	> 32	> 32	4
	R = propyl	8	> 32	> 32	4
	R = butyl	4	> 32	> 32	4
	R = hexyl	2	> 32	> 32	4
	R = heptyl	2	1	> 32	> 32
	R = phenyl	4	2	> 32	2
	R = Me	1	1	> 32	n.d.
	R = Cl	2	0.5	> 32	1
	R = F	2	2	> 32	2
	R = CF_3	1	1	> 32	n.d.
	R = OMe	2	0.5	> 32	4
	R = Me	1	2	> 32	n.d.
	R = Cl	1	1	> 32	1
	R = F	2	1	> 32	1
	R = CF_3	1	1	> 32	n.d.
	R = OMe	4	4	> 32	2
	R = OH	2	4	> 32	n.d.
	R = NH_2	4	8	> 32	n.d.
	R = NO_2	0.5	1	> 32	n.d.
	R = Me	2	2	> 32	n.d.
	R = Cl	8	4	> 32	8
	R = F	4	4	> 32	4-8
	R = CF_3	2	0.5	> 32	8
	R = OMe	4	4	> 32	4
	R = CN	4	4	> 32	2
	R = Cl	1	1	> 32	2
	R = OMe	2	1	> 32	1
	R = CF_3	2	0.5	> 32	2
	R = 2,6-Cl_2	2	1	> 32	1
	R = 2,6-F_2	1	0.5	> 32	1
	R = 3,5-F_2	0.5	1	> 32	n.d.
	R = 4-pyridinyl	4	4	> 32	4



R = 3-pyridinyl	8	8	> 32	n.d.
R = 2-Cl-pyridin-3-yl	2	1	> 32	4
R = 5-pyrimidinyl	16	16	> 32	n.d.
R = 6-quinolinyl	> 32	> 32	> 32	> 32
R = 2-thiophenyl	2	4	> 32	2

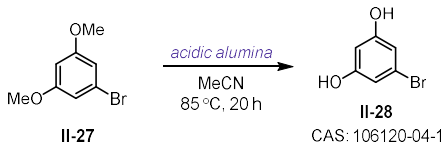
6.1 General Considerations

Reagents, substrates, and solvents were purchased from commercial suppliers and used without purification unless otherwise specified. Reaction progress was monitored by analytical thin-layer chromatography, which was precoated aluminum-backed plates (silica gel F254 SiliCycle Inc.), visualized under UV light, and plates were developed using iodine vapour. An automated flash chromatography system (Teledyne CombiFlash Rf 200) was used for the purification of compounds on silica gel (40–60 μM particle size). NMR spectra were recorded at 25 °C using either a Bruker AVIII 700 (^{1}H at 700 MHz and DEPTQ ^{13}C at 176 MHz) or Bruker NEO 400 (^{1}H at 400 MHz and DEPTQ ^{13}C at 101 MHz). Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) with reference to residual solvents as follows: Chloroform-*d* (referenced to 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Coupling constants (J) are reported in hertz and peak multiplicities are reported using the following abbreviations: m = multiplet; s = singlet; d = doublet; t = triplet; q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, td = triplet of doublets, tq = triplet of quartets, qd = quartet of doublets, br = broad signal. Infrared spectroscopy (IR) experiments were recorded on a Thermo Scientific Nicolet iS5 FT-IR Spectrometer paired with the Thermo Scientific iD7 ATR Accessory. High-Resolution Mass Spectrometry (HRMS) experiments were recorded on a Brüker microTOF II mass spectrometer with electrospray ionization (ESI) and paired with an Agilent HPLC and UV detector. Low-Resolution Mass Spectrometry (LRMS) experiments were recorded on an Advion expression^{S} CMS with atmospheric-pressure chemical ionization (APCI).

6.2 Experimental Procedures and Characterization Data

1. Synthesis of Resorcinol

5-bromoresorcinol (II-28)

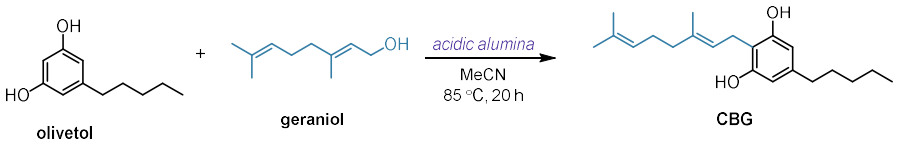


To an oven-dried and desiccator cooled 2-neck round bottom flask, was added 1-bromo-3,5-dimethoxybenzene (**II-27**) (10 g, 46.0 mmol, 1 eq) and dichloromethane (25 mL). The solution was cooled to -78 °C before dropwise addition of boron tribromide (13.3 mL, 138.2 mmol, 3 eq). The reaction was slowly warmed to room temperature and stirred overnight for a total of 18 h. The reaction was cooled to 0 °C then quenched with a dropwise addition of methanol (15 mL) over 60 min. The solution was diluted with water (25 mL) and the resultant white slurry was vacuum filtered through a Celite plug. The filtrate was collected and the phases split. The aqueous phase was extracted with dichloromethane (3 x 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. The crude mixture was concentrated *in vacuo* and purified by flash column chromatography eluting with EtOAc/Hex (10%→20% EtOAc/Hex) yielding 2-bromoresorcinol as a white crystalline solid (6.35 g, 46.0 mmol,

73%). R_f = 0.31 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.60 (d, *J* = 2.2 Hz, 2H), 6.28 (t, *J* = 2.2 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.46, 123.05, 111.77, 102.19. HRMS (ESI) *m/z*: [M − H]$^-$ calcd for $C_6H_5BrO_2$ 186.9400; Found 186.9407.

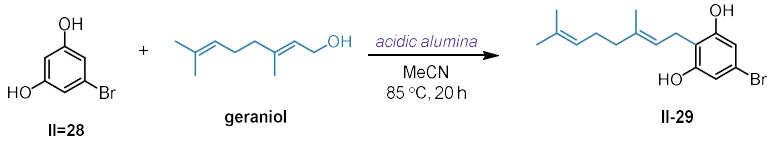
2. Synthesis of Prenylated Resorcinol

2-geranyl-5-pentylresorcinol (CBG)



To an oven-dried and desiccator cooled round bottom, was added geraniol (85.6 mg, 0.55 mmol, 0.5 eq), olivetol (200 mg, 1.11 mmol, 1.0 eq) and acidic alumina (1.1 g, 2g/mmol, relative to geraniol). Acetonitrile (1.8 mL, 0.3 M) was added to the reagents and the reaction stirred at reflux for 20 h. At which point TLC indicated complete consumption of geraniol (25% EtOAc, stain: vanillin). The crude mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with subsequent 10-15 mL volumes of boiling ethyl acetate and the residual solvent on the funnel outlet monitored by TLC for presence of products (10-15 rinses). Once products were no longer detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The collected crude mixture was purified by silica gel chromatography, eluting with EtOAc/Hex (0%→10% EtOAc/Hex) yielded 2-geranyl-5-pentylresorcinol (CBG) as a white crystalline solid (52.1 mg, 0.55 mmol, 30%). R_f = 0.62 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 2H), 5.31 – 5.24 (m, 1H), 5.09 – 5.02 (m, 1H), 5.02 – 4.98 (m, 2H), 3.39 (d, *J* = 7.2 Hz, 2H), 2.48 – 2.42 (m, 2H), 2.15 – 2.03 (m, 4H), 1.81 (s, 3H), 1.68 (s, 3H), 1.59 (m, 5H, singlet CH_3 overlapping m), 1.37 – 1.24 (m, 4H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.95, 142.91, 139.14, 132.21, 123.90, 121.84, 110.71, 108.51, 39.85, 35.66, 31.64, 30.89, 26.54, 25.82, 22.69, 22.41, 17.85, 16.34, 14.17. HRMS (ESI) *m/z*: [M − H]$^-$ calcd for $C_{21}H_{32}O_2$ 315.2330; Found 315.2342

2-geranyl-5-bromoresorcinol (II-29)



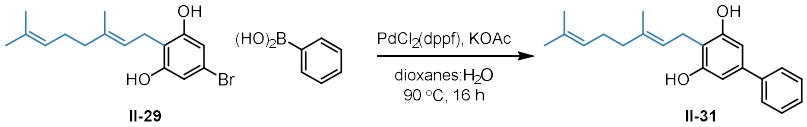
To an oven-dried and desiccator cooled round bottom, was added geraniol (694 mg, 4.50 mmol, 1.0 eq), 5-bromoresorcinol (1.7 g, 9.0 mmol, 3 eq) and acidic alumina (9.0 g, 2g/mmol, relative to geraniol). Acetonitrile (15.0 mL, 0.3 M) was added to the reagents and the reaction stirred at reflux for 20 h. At which point TLC indicated complete consumption of geraniol (25% EtOAc, stain: vanillin). The crude mixture was vacuum-filtered hot over a sintered glass funnel (4-6 micron porosity). The collected alumina was rinsed thoroughly with subsequent 10-15 mL volumes of boiling ethyl acetate and the residual solvent on the funnel outlet monitored by TLC for presence of products (10-15 rinses). Once products were no longer

detectable by TLC, the hot ethyl acetate rinses were stopped, and the collected organic fraction concentrated *in vacuo*. The collected crude mixture was purified by silica gel chromatography, eluting with EtOAc/Hex (0%→10% EtOAc/Hex) yielded 2-geranyl-5-bromoresorcinol (**II-29**) as a clear oil (267 mg, 0.77 mmol, 52%). R_f = 0.58 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.58 (s, 2H), 5.31 – 5.19 (m, 3H), 5.05 (t, 1H), 3.37 (d, *J* = 7.1, 2H), 2.15 – 2.02 (m, 4H), 1.80 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.80, 140.09, 132.41, 123.72, 120.89, 119.67, 112.87, 111.94, 39.80, 26.42, 25.82, 22.38, 17.85, 16.36. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{16}H_{21}BrO_2$ 323.0652; Found 323.0659.

General Procedure A – Synthesis of Aryl CBG Derivatives II-31 – II-62

To an oven-dried and desiccator cooled round bottom flask, was added 2-geraniol-5-bromoresorcinol (**II-29**) (1 equiv), desired boronic acid (1.5 equiv) and KOAc (4 equiv). A 5:1 ratio of dioxanes to water (6 mL) was added to the flask. The flask was purged with Argon and $PdCl_2$(dppf) (10 mol %) was added. The reaction was heated to 80 °C and progress was monitored by TLC (25% EtOAc/Hex, stain: vanillin) for complete consumption of 2-geraniol-5-bromoresorcinol (EtOAc/Hex, stain: vanillin). Upon completion of the reaction, the mixture was filtered over celite washing with DCM (15 mL). The DCM was then washed with water (5 mL), then brine (5 mL). The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The collected crude mixture was purified by flash-column chromatography, eluting with EtOAc/Hex.

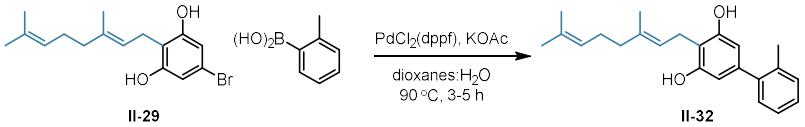
2-geranyl-5-phenylresorcinol (II-31)



II-29 II-31

According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), phenyl boronic acid (45 mg, 0.369 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-phenylresorcinol (**II-31**) as a clear oil (25 mg, 0.246 mmol, 32%). R_f = 0.53 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 10.3 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 6.66 (s, 2H), 5.34-5.29 (m, 1H), 5.16 (br s, 2H), 5.05-5.08 (m, 1H), 3.47 (d, *J* = 7.1 Hz, 2H), 2.15-2.06 (m, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 155.43, 140.90, 140.59, 139.61, 132.30, 128.83, 127.53, 126.99, 123.84, 121.43, 112.71, 107.34, 39.85, 26.51, 25.83, 22.53, 17.86, 16.39. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{26}O_2$ 321.1860; Found 321.1871.

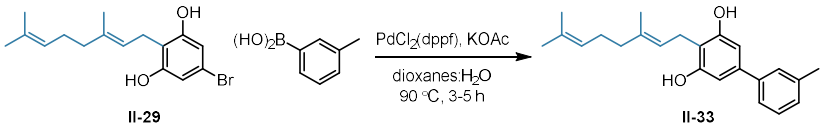
2-geranyl-5-(2-methylphenyl)resorcinol (II-32)



II-29 II-32

According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-methylphenylboronic acid (58 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-methylphenyl)resorcinol (**II-32**) as a clear oil (22.7mg, 0.246 mmol, 28%). R_f = 0.50 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 6.92 (m, 2H), 6.37 (s, 1H), 5.36-5.34 (m, 1H), 5.19 (br s, 2H), 5.09-5.05 (m, 1H), 3.48 (d, *J* = 7.2 Hz, 2H), 2.29 (s, 2H), 2.19 – 2.06 (m, 1H), 1.85 (s, 1H), 1.69 (s, 1H), 1.61 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.77, 141.55, 141.43, 139.43, 135.43, 132.27, 130.39, 129.62, 127.37, 125.78, 123.87, 121.60, 112.08, 109.52, 39.86, 26.52, 25.82, 22.53, 20.58, 17.86, 16.37. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{28}O_2$ 335.2017; Found 335.2022.

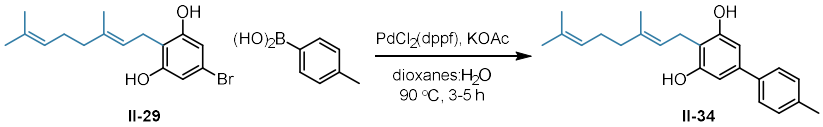
2-geranyl-5-(3-methylphenyl)resorcinol (II-33)



II-29 II-33

According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 3-methylphenylboronic acid (58 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-methylphenyl)resorcinol (**II-33**) as a yellow oil (8.1 mg, 0.246 mmol, 10%). R_f = 0.50 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 3H), 7.14 (d, *J* = 7.1 Hz, 1H), 6.65 (s, 2H), 5.36 – 5.28 (m, 1H), 5.16 (s, 2H), 5.12 – 5.02 (m, 1H), 3.47 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.14-2.06 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.25, 140.90, 140.44, 139.44, 138.27, 132.16, 128.60, 128.16, 127.67, 123.96, 123.72, 121.33, 112.44, 107.21, 39.73, 26.38, 25.71, 22.40, 21.54, 17.73, 16.26. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{28}O_2$ 335.2017; Found 335.2016.

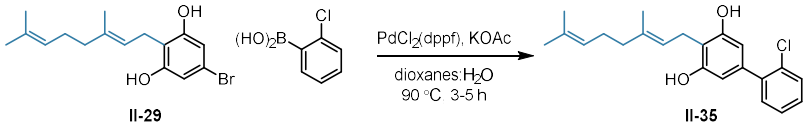
2-geranyl-5-(4-methylphenyl)resorcinol (II-34)



II-29 II-34

According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 4-methylphenylboronic acid (58 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(4-methylphenyl)resorcinol (**II-34**) as a clear oil (22.7 mg, 0.246 mmol, 27%). R_f = 0.53 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 6.64 (s, 2H), 5.35 – 5.27 (m, 1H), 5.14 (s, 2H), 5.10 – 5.03 (m, 1H), 3.46 (d, J = 7.1 Hz, 2H), 2.38 (s, 3H), 2.17 – 2.05 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.60 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.27, 140.71, 139.40, 137.57, 137.21, 132.15, 129.04, 126.68, 123.72, 120.79, 112.25, 107.00, 39.73, 26.38, 25.70, 22.39, 21.11, 17.73, 16.25. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{28}O_2$ 335.2017; Found 335.2016.

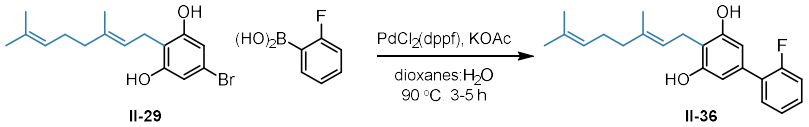
2-geranyl-5-(2-chlorophenyl)resorcinol (II-35)



II-29 II-35

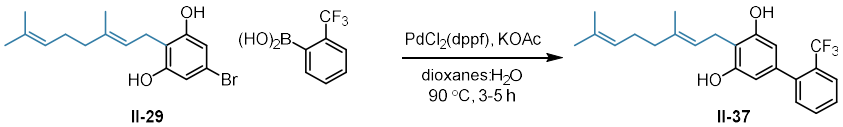
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-chlorophenylboronic acid (58 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-chlorophenyl)resorcinol (**II-35**) as a yellow oil (43.3 mg, 0.246 mmol, 49%). R_f = 0.53 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 7.44 (dd, J = 7.2, 2.1 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.25 (dd, J = 7.2, 2.1 Hz, 1H), 6.51 (s, 2H), 5.37 – 5.32 (m, 1H), 5.29 (s, 2H), 5.09-5.07 (m, 1H), 3.49 (d, J = 7.2 Hz, 2H), 2.15 – 2.08 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 154.73, 139.96, 139.56, 138.78, 132.43, 132.29, 131.30, 130.06, 128.62, 126.86, 123.85, 121.42, 113.10, 39.83, 26.49, 25.81, 22.58, 17.85, 16.36. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{25}ClO_2$ 355.1470; Found 355.1480.

2-geranyl-5-(2-fluorophenyl)resorcinol (II-36)



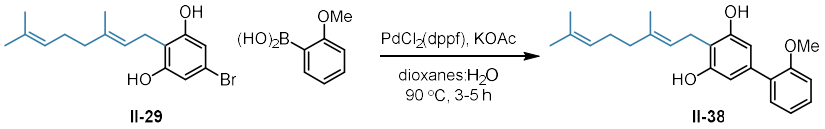
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-fluorophenylboronic acid (52 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-fluorophenyl)resorcinol (**II-36**) as a clear oil (49.0 mg, 0.246 mmol, 58%). R_f = 0.52 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 8.02 (td, J = 7.7, 1.8 Hz, 1H), 7.95 – 7.88 (m, 1H), 7.83 – 7.71 (m, 2H), 5.95 (t, J = 7.2 Hz, 1H), 5.89 (s, 2H), 5.70 (t, J = 6.8 Hz, 1H), 4.11 (d, J = 7.2 Hz, 2H), 2.79 – 2.69 (m, 4H), 2.47 (s, 3H), 2.32 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 160.52, 159.11, 155.07, 139.58, 135.14, 132.29, 130.59 (d, J = 3.9 Hz), 129.07 (d, J = 8.3 Hz), 128.45 (d, J = 12.7 Hz), 124.41 (d, J = 3.9 Hz), 123.85, 121.36, 116.19 (d, J = 22.9 Hz), 113.29, 109.26, 39.84, 26.49, 25.81, 22.55, 17.85, 16.37. ^{19}F NMR (377 MHz, $CFCl_3$) δ -117.84. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{25}FO_2$ 339.1766; Found 339.1771.

2-geranyl-5-(2-trifluoromethylphenyl)resorcinol (II-37)



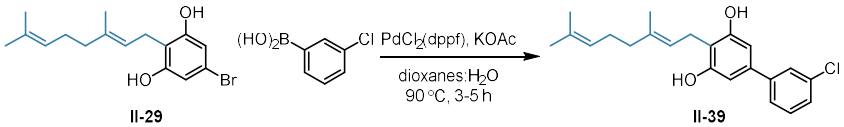
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-trifluoromethylphenylboronic acid (52 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-trifluromethylphenyl)resorcinol (**II-37**) as a clear oil (18.9 mg, 0.246 mmol, 19%). R_f = 0.50 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 9.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 6.9 Hz, 1H), 6.39 (s, 2H), 5.36-5.32 (m, 1H), 5.13 (br s, 2H) 5.09 – 5.05 (m, 3H), 3.48 (d, *J* = 7.1 Hz, 2H), 2.16-2.07 (m, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.46, 139.60, 139.28, 132.31, 131.96, 131.38, 127.46, 126.17 (q, J = 5.0 Hz), 125.63, 123.84, 122.91, 121.45, 112.96, 109.54, 77.48, 77.16, 76.84, 39.85, 26.51, 25.81, 22.56, 17.86, 16.39. ^{19}F NMR (377 MHz, $CFCl_3$) δ -57.37. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{25}F_3O_2$ 389.1734; Found 389.1748.

2-geranyl-5-(2-methoxyphenyl)resorcinol (II-38)



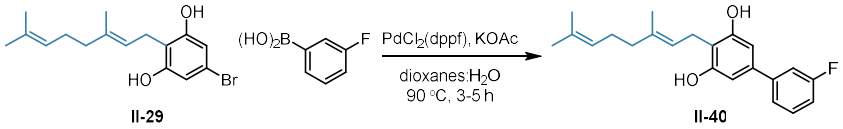
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-methoxyphenylboronic acid (56 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-methoxyphenyl)resorcinol (**II-38**) as a yellow oil (13.0 mg, 0.246 mmol, 15%). R_f = 0.50 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 7.30 (t, J = 7.8 Hz, 2H), 7.02 – 6.95 (m, 2H), 6.61 (s, 2H), 5.33 (t, J = 7.2 Hz, 1H), 5.10 (s, 2H), 5.09 – 5.05 (m, 1H), 3.81 (s, 3H), 3.46 (d, J = 7.6 Hz, 2H), 2.15 – 2.06 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 156.53, 154.71, 139.21, 137.95, 132.23, 130.76, 130.08, 128.76, 123.91, 121.64, 120.92, 112.47, 111.35, 109.80, 55.72, 39.87, 26.54, 25.83, 22.57, 17.86, 16.38. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{28}O_3$ 351.1966; Found 351.1973.

2-geranyl-5-(3-chlorophenyl)resorcinol (II-39)



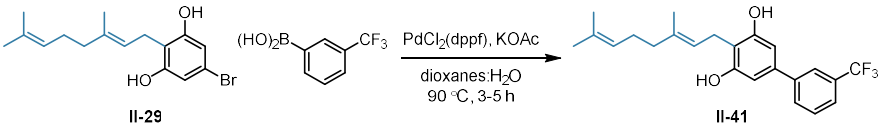
According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 3-chlorophenylboronic acid (29 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-chlorophenyl)resorcinol (**II-39**) as a white powder (19.2 mg, 0.123 mmol, 44%). R_f = 0.48 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 1.9 Hz, 1H), 7.38 (dt, *J* = 7.2, 1.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 6.62 (s, 2H), 5.33-5.28 (m, 3H), 5.08-5.05 (m, 1H), 3.47 (d, *J* = 7.1 Hz, 2H), 2.16-2.06 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.55, 142.44, 139.80, 139.37, 134.68, 132.33, 130.04, 127.49, 127.11, 125.11, 123.80, 121.24, 113.39, 107.28, 39.83, 26.47, 25.83, 22.54, 17.85, 16.38. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{25}ClO_2$ 355.1470; Found 335.1476.

2-geranyl-5-(3-fluorophenyl)resorcinol (II-40)



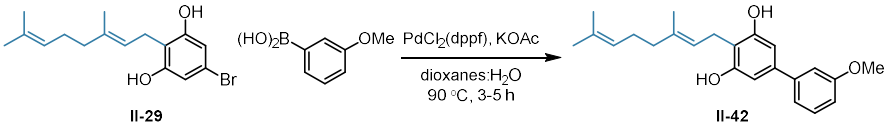
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 3-fluorophenylboronic acid (52 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-fluorophenyl)resorcinol (**II-40**) as a clear oil (8.1 mg, 0.246 mmol, 10%). R_f = 0.57 (25% EtOAc/Hex).^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.36 (td, *J* = 8.0, 5.9 Hz, 1H), 7.30 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.22 (dt, *J* = 10.3, 2.2 Hz, 1H), 7.01 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.63 (s, 2H), 5.30 (t, *J* = 7.1 Hz, 1H), 5.18 (s, 2H), 5.06 (d, *J* = 6.5 Hz, 1H), 3.47 (d, *J* = 7.4 Hz, 2H), 2.11 (dq, *J* = 16.3, 8.9, 8.4 Hz, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 163.81, 162.42, 155.40, 142.75 (d, J = 7.7 Hz), 139.71, 139.42, 132.21, 130.14 (d, J = 8.3 Hz), 123.66, 122.45, 121.09, 113.95 (dd, J = 21.1, 74.4 Hz), 113.15, 107.16, 77.20, 77.02, 77.00, 76.84, 39.72, 26.35, 25.70, 22.41, 17.73, 16.27. ^{19}F NMR (377 MHz, $CFCl_3$) δ -113.72. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{25}FO_2$ 339.1766; Found 339.1776.

2-geranyl-5-(3-trifluoromethylphenyl)resorcinol (II-41)



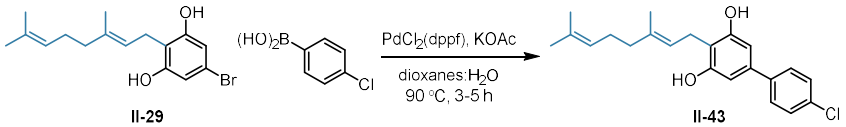
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 3-trifluoromethylphenylboronic acid (86 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-trifluromethylphenyl)resorcinol (**II-41**) as a clear oil (30.3 mg, 0.123 mmol, 32 %). R_f = 0.68 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.70 (d, *J* = 11.1 Hz, 1H), 7.60 – 7.49 (m, 2H), 6.66 (s, 2H), 5.35 – 5.28 (m, 1H), 5.23 (s, 2H), 5.09 – 5.04 (m, 1H), 3.48 (d, *J* = 7.8 Hz, 2H), 2.18 – 2.07 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.53, 141.24, 139.85, 139.21, 132.23, 131.25, 130.93, 130.59, 130.09, 129.17, 123.85 (dq, J = 4.0, 43.4 Hz), 123.65, 121.00, 113.36, 107.24, 39.72, 26.35, 25.70, 22.41, 17.73, 16.28. ^{19}F NMR (377 MHz, $CFCl_3$) δ -63.16. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{25}F_3O_2$ 389.1734; Found 389.1747.

2-geranyl-5-(3-methoxyphenyl)resorcinol (II-42)



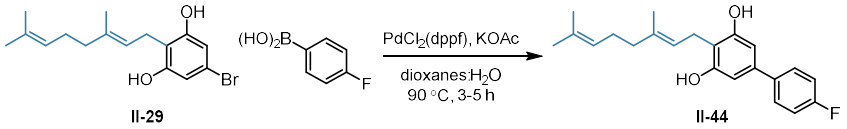
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 3-methoxyphenylboronic acid (56 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-methoxyphenyl)resorcinol (**II-42**) as a clear oil (13.1 mg, 0.246 mmol, 15%). R_f = 0.45 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.31 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 6.7 Hz, 1H), 7.06 (s, 1H), 6.88 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.65 (s, 2H), 5.31 (t, *J* = 7.2 Hz, 1H), 5.19 (s, 2H), 5.07 (t, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 3.47 (d, *J* = 7.1 Hz, 2H), 2.10 (dt, *J* = 24.7, 7.3 Hz, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.60 (s, 4H). 13C NMR (176 MHz, CDCl3) δ 159.99, 155.41, 142.15, 140.77, 139.64, 132.30, 129.82, 123.84, 121.40, 119.52, 113.08, 112.90, 112.66, 107.38, 26.51, 25.83, 22.54, 17.86, 16.39. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{28}O_3$ 351.1966; Found 351.1970.

2-geranyl-5-(4-chlorophenyl)resorcinol (II-43)



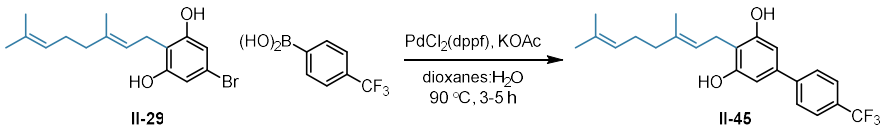
According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 4-chlorophenylboronic acid (29 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(4-chlorophenyl)resorcinol (**II-43**) as a yellow oil (19.6 mg, 0.123 mmol, 45%). R_f = 0.57 (25% EtOAc/Hex).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.61 (s, 2H), 5.32-5.28 (m, 1H), 5.23 (s, 2H), 5.08-5.04 (m, 1H), 3.46 (d, *J* = 7.1 Hz, 2H), 2.13-2.07 (m, 4H), 1.83 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.42, 139.70, 139.46, 138.90, 133.42, 132.21, 128.84, 128.08, 123.67, 121.12, 111.81, 107.04, 40.12, 26.36, 25.70, 22.40, 17.73, 16.26. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{25}ClO_2$ 355.1470; Found 355.1476.

2-geranyl-5-(4-fluorophenyl)resorcinol (II-44)



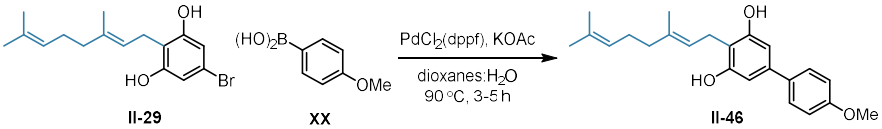
According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 4-fluorophenylboronic acid (17 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(4-fluorophenyl)resorcinol (**II-44**) as a clear oil (12.8 mg, 0.123 mmol, 30%). R_f = 0.48 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 7.50 – 7.47 (m, 2H), 7.09 (t, J = 8.7 Hz, 2H), 6.60 (s, 2H), 5.30 (t, J = 7.1 Hz, 1H), 5.17 (s, 2H), 5.06 (t, J = 6.8 Hz, 1H), 3.46 (d, J = 7.2 Hz, 2H), 2.10 (dt, J = 23.8, 7.2 Hz, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 163.19, 161.79, 155.36, 139.77, 139.63, 136.57 (d, J = 5.3 Hz), 132.19, 128.38 (d, J = 8.8 Hz), 123.67, 121.18, 115.56 (d, J = 21.1 Hz), 112.50, 111.83, 107.10, 39.72, 26.36, 25.70, 22.37, 17.73, 16.26. ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.05. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{25}FO_2$ 339.1766; Found 339.1772.

2-geranyl-5-(4-trifluoromethylphenyl)resorcinol (II-45)



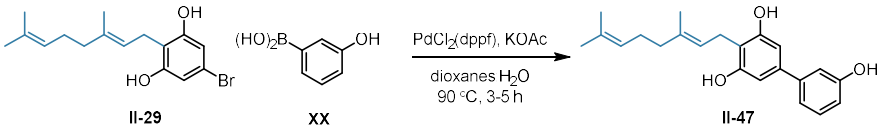
According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 4-trifluoromethylphenylboronic acid (23 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(4-trifluromethylphenyl)resorcinol (**II-45**) as a clear oil (10.2 mg, 0.123 mmol, 22%). R_f = 0.68 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 13.4, 8.7 Hz, 5H), 6.66 (s, 2H), 5.45 (s, 2H), 5.30 (t, *J* = 7.2 Hz, 1H), 5.06 (d, *J* = 6.3 Hz, 1H), 3.48 (d, *J* = 7.1 Hz, 2H), 2.11 (dt, *J* = 23.2, 7.2 Hz, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.58, 144.03, 139.74, 139.15, 132.21, 129.66 (q, J = 31.7 Hz), 127.11, 125.64 (q, J = 3.5 Hz), 123.66, 121.06, 113.58, 107.26, 39.72, 26.35, 25.70, 22.43, 17.73, 16.27. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.94. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{25}F_3O_2$ 389.1734; Found 389.1740.

2-geranyl-5-(4-methoxyphenyl)resorcinol (II-46)



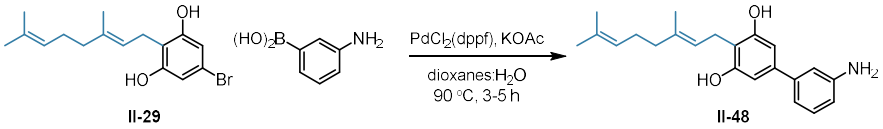
According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 4-methoxyphenylboronic acid (28 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(4-methoxyphenyl)resorcinol (**II-46**) as a white powder (13.5 mg, 0.123 mmol, 32%). R_f = 0.28 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.61 (s, 2H), 5.31 (t, *J* = 6.4 Hz, 1H), 5.22 (s, 2H), 5.06 (d, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 3.46 (d, *J* = 7.1 Hz, 2H), 2.10 (t, *J* = 6.4 Hz, 4H), 1.83 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.32, 155.43, 140.87, 139.48, 133.16, 132.20, 128.00, 123.86, 121.53, 114.25, 112.47, 106.89, 77.36, 55.49, 39.85, 26.52, 25.83, 22.49, 17.85, 16.38. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{28}O_3$ 351.11966; Found 351.1978.

2-geranyl-5-(3-hydroxyphenyl)resorcinol (II-47)



According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 3-hydroxyphenylboronic acid (25 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-hydroxyphenyl)resorcinol (**II-47**) as a clear oil (13.8 mg, 0.123 mmol, 33%). R_f = 0.13 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 2H), 5.30 (t, *J* = 6.4 Hz, 3H), 5.09 – 5.02 (m, 1H), 3.46 (d, *J* = 7.2 Hz, 2H), 2.17 – 2.03 (m, 4H), 1.83 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.75, 155.27, 142.21, 140.21, 139.53, 132.18, 129.94, 123.71, 121.25, 119.45, 114.38, 113.79, 112.92, 107.19, 26.37, 25.70, 22.43, 17.73, 16.25. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{26}O_3$ 337.1809; Found 337.1821.

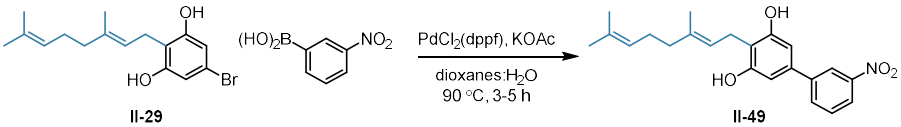
2-geranyl-5-(3-aminophenyl)resorcinol (II-48)



II-29 II-48

According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 3-aminophenylboronic acid (25 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-aminophenyl)resorcinol (**II-48**) as a clear oil (14.3 mg, 0.246 mmol, 35%). R_f = 0.14 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 8.9 Hz, 1H), 6.82 (s, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.58 (s, 2H), 5.30 (t, J = 7.1 Hz, 1H), 5.13 – 5.03 (m, 1H), 3.45 (d, J = 7.1 Hz, 2H), 2.21 – 2.00 (m, 2H), 1.83 (s, 3H), 1.68 (s, 2H), 1.60 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.22, 146.36, 141.78, 140.86, 139.30, 132.06, 129.63, 123.74, 121.39, 117.68, 114.42, 113.83, 112.60, 107.14, 39.73, 26.39, 25.70, 22.41, 17.73, 16.25. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{27}NO_2$ 336.1969; Found 336.1975.

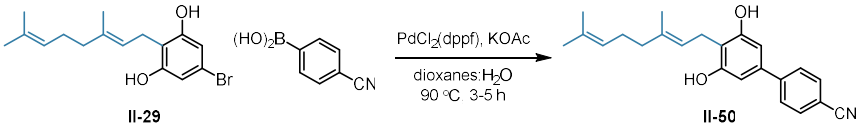
2-geranyl-5-(3-nitrophenyl)resorcinol (II-49)



II-29 II-49

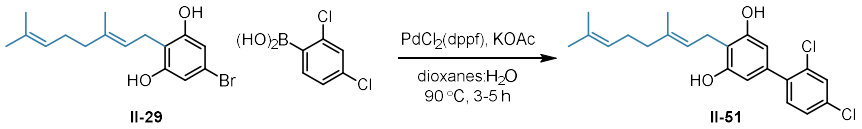
According to General Procedure A, 2-geraniol-5-bromoresorcinol (35 mg, 0.108 mmol), 3-nitrophenylboronic acid (27 mg, 0.162 mmol) and KOAc (42 mg, 0.432 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (3 mg, 0.011 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3-nitrophenyl)resorcinol (**II-49**) as a clear oil (9.7 mg, 0.108 mmol, 24%). R_f = 0.40 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (t, J = 2.0 Hz, 1H), 8.17 (ddd, J = 8.3, 2.3, 1.1 Hz, 1H), 7.85 (d, J = 9.6 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 6.69 (s, 2H), 5.37 (s, 2H), 5.33 – 5.27 (m, 1H), 5.10 – 5.03 (m, 1H), 3.48 (d, J = 7.2 Hz, 2H), 2.14-2.07 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.70, 148.67, 142.15, 140.04, 138.03, 132.73, 132.27, 129.66, 123.62, 122.13, 121.69, 120.84, 113.92, 107.20, 39.72, 26.33, 25.71, 22.44, 17.74, 16.29. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{25}NO_4$ 366.1711; Found 366.1720.

2-geranyl-5-(4-cyanophenyl)resorcinol (II-50)



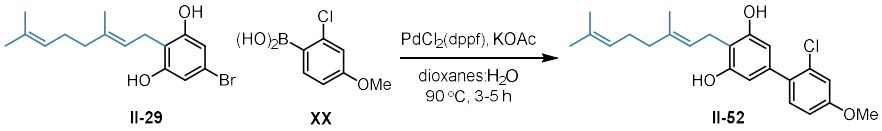
According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), 4-cyanophenylboronic acid (27 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(4-cyanophenyl)resorcinol (**II-50**) as a white powder (9.1 mg, 0.123 mmol, 21%). R_f = 0.32 (25% EtOAc/Hex).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 6.65 (s, 2H), 5.42 (s, 2H), 5.29 (t, *J* = 6.4 Hz, 1H), 5.06 (t, 1H), 3.47 (d, *J* = 7.1 Hz, 2H), 2.11 (m, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 155.81, 145.18, 140.10, 138.63, 132.68, 132.38, 127.57, 123.75, 120.98, 119.09, 114.28, 110.97, 107.35, 77.36, 39.84, 26.46, 25.83, 22.59, 17.86, 16.41. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{23}H_{25}NO_2$ 346.1813; Found 346.1821.

2-geranyl-5-(2,4-dichlorophenyl)resorcinol (II-51)



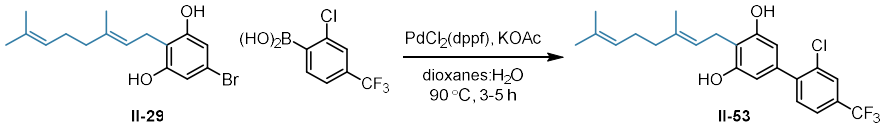
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2,4-dichlorophenylboronic acid (52 mg, 0.368 mmol) and KOAc (97 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2,4-dichlorophenyl)resorcinol (**II-51**) as a clear oil (31.6 mg, 0.246 mmol, 34%). R_f = 0.32 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 7.45 (d, J = 2.1 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.22 (d, J = 8.3 Hz, 1H), 6.46 (s, 2H), 5.34 – 5.30 (m, 1H), 5.26 (s, 2H), 5.06 (t, J = 6.8 Hz, 1H), 3.47 (d, J = 7.2 Hz, 2H), 2.15 – 2.07 (m, 4H), 1.83 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 154.86, 139.77, 138.53, 137.65, 133.77, 133.19, 132.32, 132.02, 129.77, 127.20, 123.80, 121.25, 113.40, 109.65, 39.84, 26.49, 25.82, 22.58, 17.86, 16.38. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{24}Cl_2O_2$ 389.1081; Found 389.1088.

2-geranyl-5-(2-chloro-4-methoxyphenyl)resorcinol (II-52)



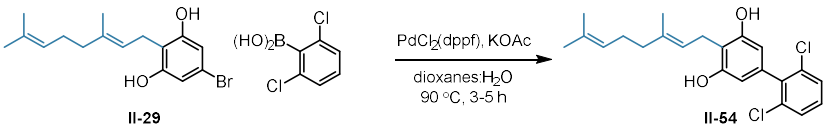
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-chloro-4-methoxyphenylboronic acid (58 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-chloro-4-methoxyphenyl)resorcinol (**II-52**) as a yellow oil (26.5 mg, 0.246 mmol, 28%). R_f = 0.50 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, CDCl3) δ 7.21 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.83 (dd, J = 8.6, 2.7 Hz, 1H), 6.48 (s, 2H), 5.33 (t, J = 6.5 Hz, 1H), 5.19 (s, 2H), 5.07 (t, J = 5.4 Hz, 1H), 3.83 (s, 3H), 3.47 (d, J = 7.1 Hz, 2H), 2.17 – 2.05 (m, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 159.39, 154.71, 139.48, 138.57, 132.92, 132.44, 132.27, 131.83, 123.86, 121.48, 115.25, 113.11, 112.73, 109.90, 55.72, 39.85, 26.52, 25.83, 22.57, 17.86, 16.37. HRMS (ESI) m/z: [M − H]− calcd for $C_{23}H_{27}ClO_3$ 385.1576; Found 385.1579.

2-geranyl-5-(2-chloro-4-trifluoromethylphenyl)resorcinol (II-53)



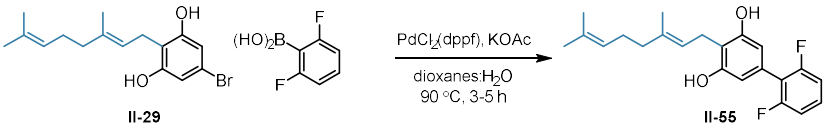
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-chloro-4-trifluoromethanephenylboronic acid (83 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-chloro-4-trifluoromethylphenyl)resorcinol (**II-53**) as a clear oil (38.2 mg, 0.246 mmol, 37%). R_f = 0.45 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 7.71 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.49 (s, 2H), 5.37 – 5.31 (m, 3H), 5.09 – 5.05 (m, 1H), 3.49 (d, J = 7.2 Hz, 2H), 2.16 – 2.08 (m, 4H), 1.84 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.85, 143.42, 139.82, 137.27, 133.01, 132.25, 131.58, 130.80 (q, J = 33.4 Hz), 127.03 (q, J = 3.5 Hz), 123.60 (q, J = 3.5 Hz), 121.01, 113.73, 109.43, 39.72, 26.35, 25.69, 22.49, 17.73, 16.25. ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.21. HRMS (ESI) m/z: [M − H]− calcd for $C_{23}H_{24}ClFO_2$ 423.1344; Found 423.1347.

2-geranyl-5-(2,6-dichlorophenyl)resorcinol (II-54)



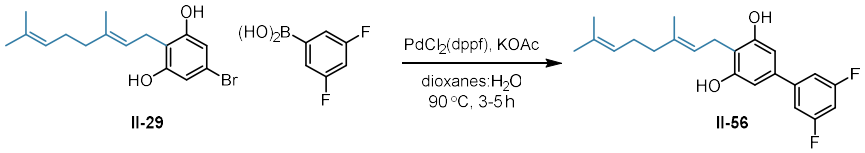
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2,6-dichlorophenylboronic acid (70 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (96 mg, 0.984 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2,6-dichlorophenyl)resorcinol (**II-54**) as a clear oil (4.3 mg, 0.246 mmol, 5%). R_f = 0.57 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 7.36 (d, J = 8.1 Hz, 2H), 7.20 (t, J = 8.1 Hz, 1H), 6.31 (s, 2H), 5.36 (t, J = 7.7 Hz, 1H), 5.18 (s, 2H), 5.07 (t, J = 6.8 Hz, 1H), 3.49 (d, J = 7.2 Hz, 2H), 2.12 (dq, J = 15.6, 8.9, 8.4 Hz, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 155.05, 139.64, 139.07, 136.23, 135.02, 132.31, 129.08, 128.13, 123.84, 121.45, 113.47, 109.71, 39.85, 26.50, 25.83, 22.70, 17.87, 16.40. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{24}Cl_2O_2$ 389.1081; Found 389.1083.

2-geranyl-5-(2,6-difluorophenyl)resorcinol (II-55)



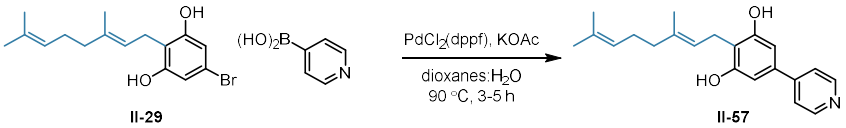
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2,6-difluorophenylboronic acid (27 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2,6-difluorophenyl)resorcinol (**II-55**) as a clear oil (12.4 mg, 0.246 mmol, 14%). R_f = 0.47 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, CDCl3) δ 7.28-7.21 (m, 1H), 6.95 (t, J = 7.9 Hz, 2H), 6.53 (s, 2H), 5.33 (t, J = 7.8 Hz, 1H), 5.23 (s, 2H), 5.07 (t, J = 7.2, 1H), 3.48 (d, J = 7.2 Hz, 2H), 2.15 – 2.07 (m, 4H), 1.84 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 160.22 (dd, J = 7.0, 248.2 Hz), 154.94, 139.59, 132.31, 128.91 (t, J = 6.0 Hz), 128.22, 123.84, 121.29, 118.14, 117.98 (t, J = 11.1 Hz), 113.93, 111.74 (dd, J = 5.3, 21.1 Hz), 110.54, 39.84, 26.50, 25.81, 22.61, 17.85, 16.37. ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.30. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{22}H_{24}F_2O_2$ 357.1672; Found 357.1684.

2-geranyl-5-(3,5-difluorophenyl)resorcinol (II-56)



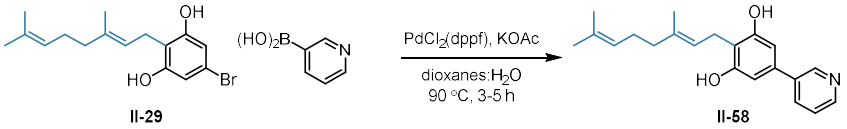
According to General Procedure A, 2-geraniol-5-bromoresorcinol (100 mg, 0.308 mmol), 3,5-difluorophenylboronic acid (73.1 mg, 0.462 mmol) and KOAc (121 mg, 1.23 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (22.7 mg, 0.03 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(3,5-difluorophenyl)resorcinol (**II-56**) as a clear oil (41.4 mg, 0.308 mmol, 38%). R_f = 0.71 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10f – 6.92 (m, 1H), 6.75 (tt, *J* = 8.8, 2.3 Hz, 1H), 6.60 (s, 1H), 5.32-5.28 (m, 1H), 5.07-5.04 (m, 1H), 5.06 (d, *J* = 5.7 Hz, 0H), 3.47 (d, *J* = 7.1 Hz, 1H), 2.15-2.08 (m, 4H), 1.84 (s, 1H), 1.69 (s, 1H), 1.60 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.34 (dd, J = 13.1, 248.5 Hz), 155.60, 143.93 (t, J = 9.1 Hz), 140.06, 138.44 (t, J = 2.0), 132.38, 123.76, 121.04, 113.99, 109.76 (dd, J = 7.1, 19.2 Hz), 107.22, 102. 67 (t, J = 26.3 Hz), 39.83, 26.45, 25.80, 22.57, 17.84, 16.38. ^{19}F NMR (377 MHz, $CFCl_3$) δ -110.38. HRMS (ESI) m/z: [M − H]− calcd for $C_{22}H_{24}F_2O_2$ 357.1672; Found 357.1682.

2-geranyl-5-(pyridin-4-yl)resorcinol (II-57)



According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), pyridin-4-ylboronic acid (23 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(pyridin-4-yl)resorcinol (**II-57**) as a yellow oil (19.1 mg, 0.123 mmol, 48%). R_f = 0.32 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, Chloroform-d) δ 8.60 (d, J = 4.8 Hz, 2H), 7.47 (d, J = 4.8 Hz, 2H), 6.71 (s, 2H), 5.33 (t, J = 6.6 Hz, 1H), 5.07 (t, J = 6.3 Hz, 1H), 3.53 (d, J = 7.1 Hz, 2H), 2.11 (dq, J = 15.7, 8.8, 8.1 Hz, 4H), 1.85 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 156.50, 149.42, 149.20, 139.75, 137.12, 132.30, 123.85, 122.01, 121.28, 115.29, 106.77, 39.88, 26.52, 25.84, 22.70, 17.87, 16.43. HRMS (ESI) *m/z*: [M − H]$^-$ calcd for $C_{21}H_{25}NO_2$ 322.1813; Found 322.1814.

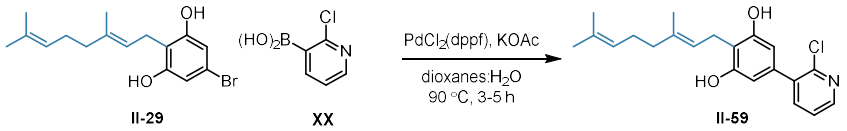
2-geranyl-5-(pyridin-3-yl)resorcinol (II-58)



II-29 II-58

According to General Procedure A, 2-geraniol-5-bromoresorcinol (100 mg, 0.308 mmol), 2-chloro-pyridin-3-ylboronic acid (57 mg, 0.462 mmol) and KOAc (121 mg, 1.23 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (22.7 mg, 0.03 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(pyridin-3-yl)resorcinol (**II-58**) as a clear oil (9.2 mg, 0.308 mmol, 9%). R_f = 0.40 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.58 (s, 1H), 7.96 – 7.83 (m, 3H), 7.44-7.40 (m, 1H), 6.78 (s, 2H), 5.41 – 5.31 (m, 1H), 5.14 – 5.04 (m, 1H), 3.56 (d, J = 7.1 Hz, 2H), 2.14-2.07 (m, 4H), 1.87 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.89, 147.46, 147.20, 139.33, 136.36, 135.33, 132.19, 123.95, 121.70, 114.45, 106.69, 39.90, 26.57, 25.84, 22.64, 17.87, 16.44. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{21}H_{25}NO_2$ 322.1813; Found 322.1825.

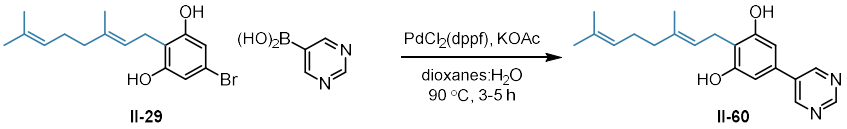
2-geranyl-5-(2-chloro-pyridin-3-yl)resorcinol (II-59)



II-29 XX II-59

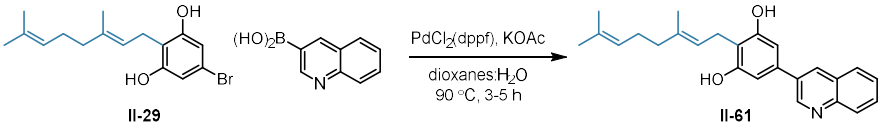
According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-chloro-pyridin-3-ylboronic acid (58.2 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-chloro-pyridin-3-yl)resorcinol (**II-59**) as a white powder (28.2 mg, 0.246 mmol, 32%). R_f = 0.32 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, CDCl3) δ 8.33 (dd, J = 4.8, 2.0 Hz, 1H), 7.64 (dd, J = 7.6, 1.9 Hz, 1H), 7.29 – 7.26 (m, 1H), 6.51 (s, 2H), 6.26 (s, 2H), 5.34 (t, J = 7.8 Hz, 1H), 5.10 – 5.03 (m, 1H), 3.50 (d, J = 7.1 Hz, 2H), 2.17 – 2.05 (m, 4H), 1.84 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 155.00, 149.51, 148.28, 139.75, 139.60, 136.57, 136.51, 132.22, 123.66, 122.49, 121.05, 113.75, 109.40, 77.02, 39.73, 26.35, 25.70, 22.48, 17.73, 16.27. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{21}H_{24}ClNO_2$ 356.1423; Found 356.1432.

2-geranyl-5-(pyrimidin-5-yl)resorcinol (II-60)



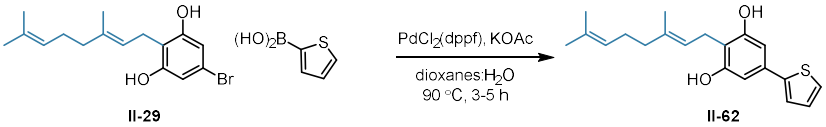
According to General Procedure A, 2-geraniol-5-bromoresorcinol (100 mg, 0.308 mmol), 5-pyrimidinylboronic acid (96 mg, 0.462 mmol) and KOAc (121 mg, 1.23 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (22.7 mg, 0.03 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(pyrimidin-5-yl)resorcinol (**II-60**) as a white powder (36.9 mg, 0.308 mmol, 37%). R_f = 0.32 (100% EtOAc). ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.97 (s, 2H), 6.66 (s, 2H), 6.29 (s, 2H), 5.32-5.30 (m, 1H), 5.10 – 5.05 (m, 1H), 3.52 (d, J = 7.2 Hz, 2H), 2.16 – 2.08 (m, 4H), 1.85 (s, 3H), 1.69 (s, 3H), 1.60 (s, 4H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.30, 156.53, 154.83, 140.13, 134.41, 133.20, 132.37, 123.78, 120.96, 115.02, 106.85, 39.86, 26.48, 25.84, 22.60, 17.87, 16.45. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{20}H_{24}N_2O_2$ 323.1765; Found 323.1778.

2-geranyl-5-(quinolin-3-yl))resorcinol (II-61)



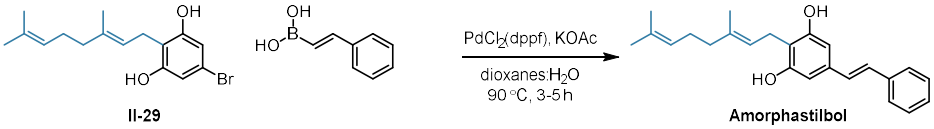
According to General Procedure A, 2-geraniol-5-bromoresorcinol (40 mg, 0.123 mmol), quinolin-3-ylboronic acid (32 mg, 0.184 mmol) and KOAc (48 mg, 0.492 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (9 mg, 0.025 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(quinolin-3-yl)resorcinol (**II-61**) as a white powder (3.3 mg, 0.123 mmol, 10%). R_f = 0.32 (25% EtOAc/Hex). ^{1}H NMR (400 MHz, CDCl3) δ 9.42 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.63 (t, J = 6.9 Hz, 1H), 6.96 (s, 2H), 5.43 (t, J = 7.1 Hz, 1H), 5.15 – 5.06 (m, 1H), 3.65 (d, J = 7.0 Hz, 2H), 2.24 – 2.10 (m, 4H), 1.92 (s, 3H), 1.72 (s, 4H), 1.64 (s, 3H). ^{13}C NMR (176 MHz, CDCl3) δ 156.91, 149.21, 146.64, 139.42, 136.57, 134.11, 133.95, 132.24, 129.98, 128.45, 128.30, 128.27, 127.61, 123.95, 121.73, 114.36, 107.00, 39.94, 26.59, 25.86, 22.71, 17.89, 16.47. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{25}H_{27}NO_2$ 372.1969; Found 372.1976.

2-geranyl-5-(2-thiophene)resorcinol (II-62)



According to General Procedure A, 2-geraniol-5-bromoresorcinol (80 mg, 0.246 mmol), 2-thiopheneboronic acid (45 mg, 0.368 mmol) and KOAc (96 mg, 0.984 mmol) were added to an oven-dried round bottom flask. A 5:1 mixture of dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (18 mg, 0.05 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-(2-thiophene)resorcinol (**II-62**) as a brown powder (12.9 mg, 0.246 mmol, 16%). R_f = 0.47 (25% EtOAc/Hex) ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.25 – 7.21 (m, 2H), 7.06 – 7.03 (m, 1H), 6.69 (s, 2H), 5.28 (d, *J* = 6.5 Hz, 1H), 5.13 (s, 2H), 5.06 (d, *J* = 6.8 Hz, 1H), 3.44 (d, *J* = 7.1 Hz, 2H), 2.10 (dq, *J* = 26.0, 8.8, 8.3 Hz, 5H), 1.83 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). 13C NMR (176 MHz, CDCl3) δ 155.45, 143.92, 139.78, 133.88, 132.32, 128.02, 124.77, 123.81, 123.17, 121.26, 113.04, 106.29, 39.84, 26.50, 25.84, 22.56, 17.86, 16.40. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{20}H_{24}O_2S$ 327.1424; Found 327.1431.

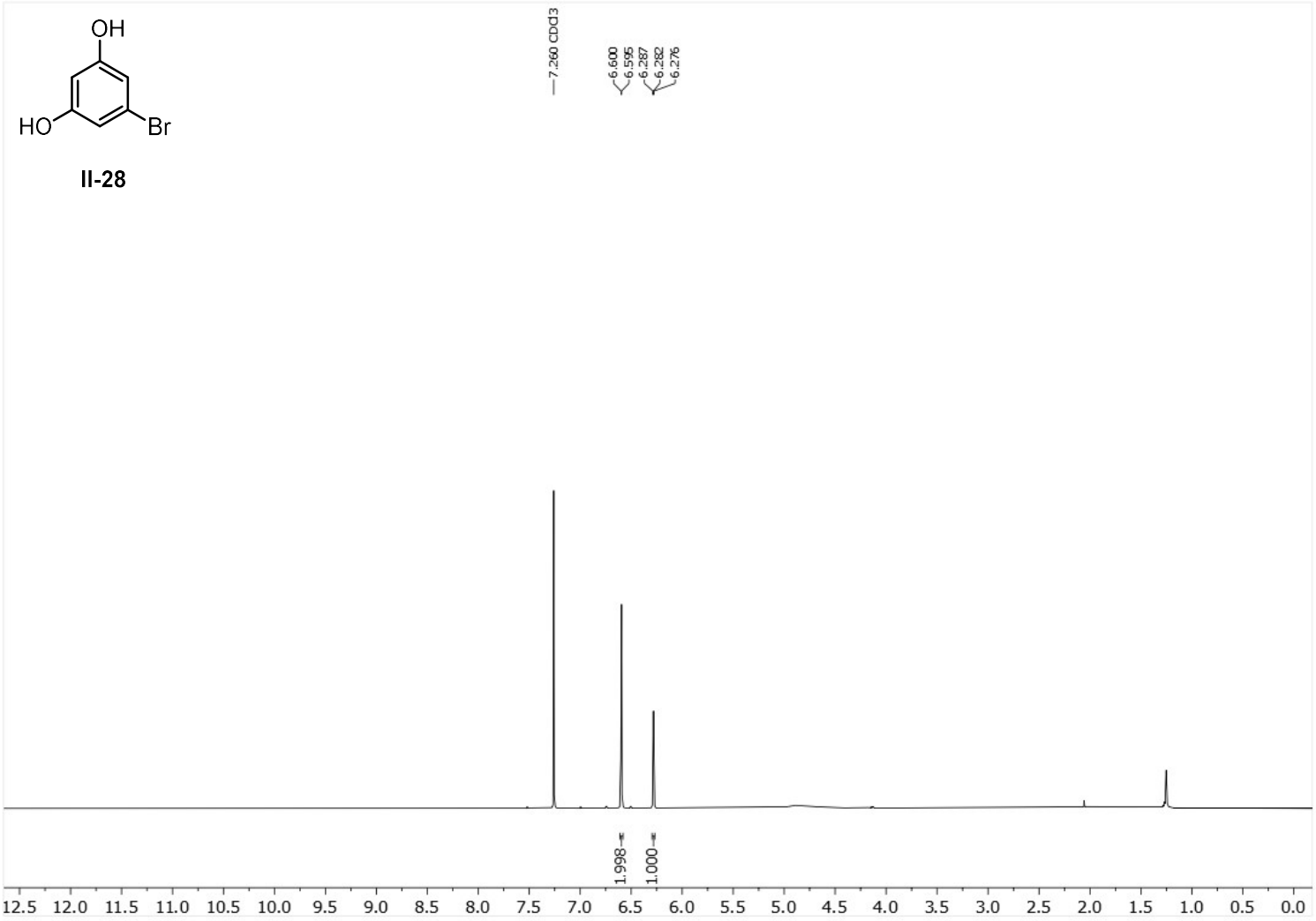
2-geranyl-5-((E)-styryl)resorcinol (Amorphastibol)



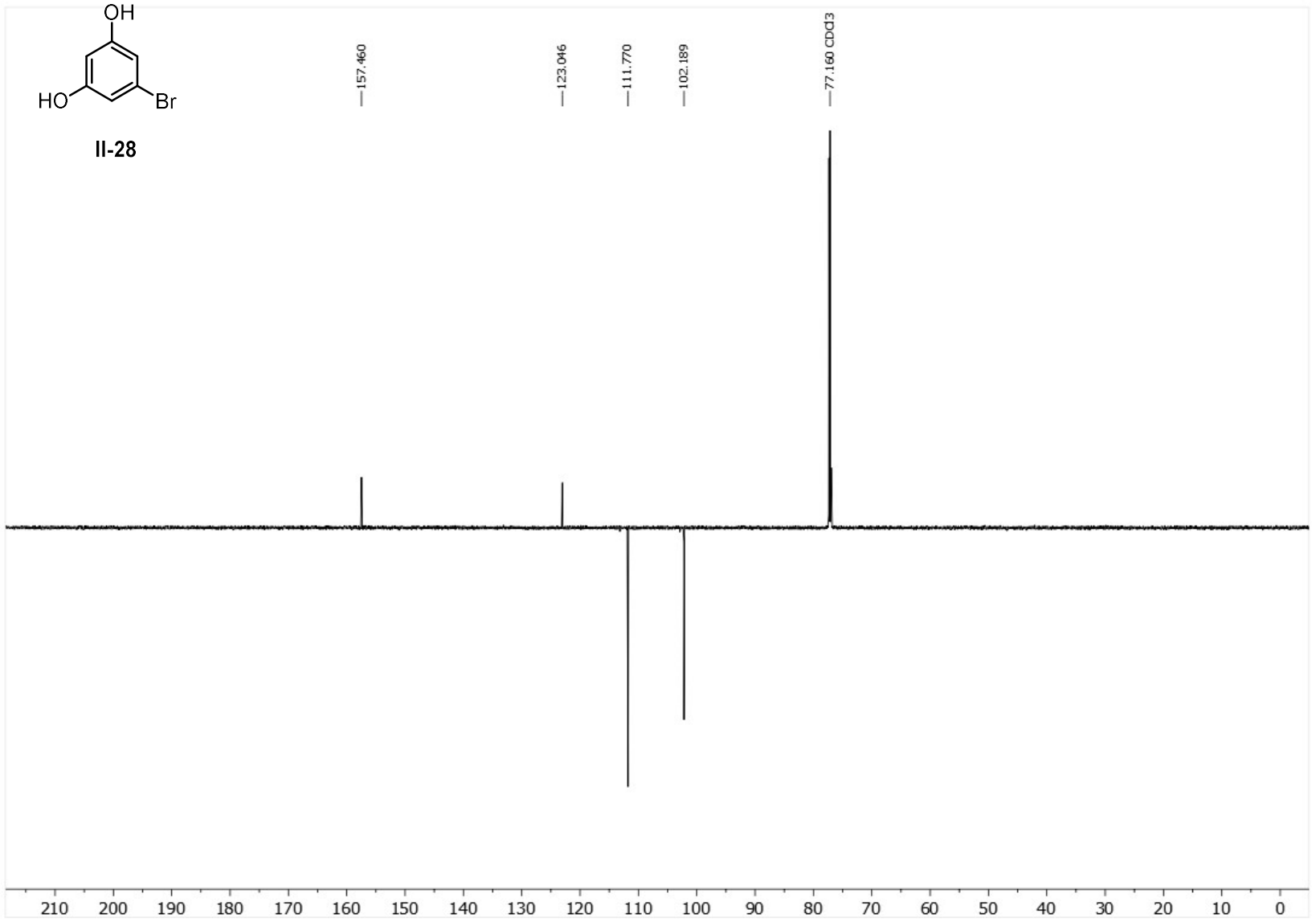
According to General Procedure A, 2-geraniol-5-bromoresorcinol (100 mg, 0.308 mmol), B_2pin_2 (68 mg, 0.463) dioxanes:water was added to the reagents and purged with Argon. $PdCl_2$(dppf) (23 mg, 0.03 mmol) was added and the reaction stirred at 85 °C for 16 h. At which point TLC indicated complete consumption of 2-geraniol-5-bromoresorcinol (25% EtOAc, stain: vanillin). The crude mixture was purified by silica gel chromatography (0%→10% EtOAc/Hex) yielded 2-geranyl-5-((E)-styryl)resorcinol as a white powder (48.5 mg, 0.308 mmol, 46%). R_f = 0.57 (25% EtOAc/Hex). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.26-7.24 (m, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 6.94 (d, *J* = 16.3 Hz, 1H), 6.59 (s, 2H), 5.30 – 5.27 (m, 1H), 5.07 (d, *J* = 16.2 Hz, 3H), 3.44 (d, *J* = 7.2 Hz, 2H), 2.15 – 2.07 (m, 4H), 1.83 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 155.34, 139.65, 137.33, 137.03, 132.30, 128.85, 128.82, 128.16, 127.79, 126.66, 123.84, 121.35, 113.36, 106.70, 39.85, 26.51, 25.84, 22.66, 17.87, 16.40. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{24}H_{28}O_2$ 324.2017; Found 324.2021.

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

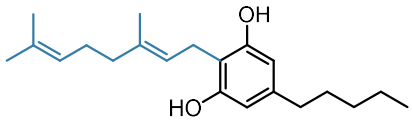
5-bromoresorcinol (**II-28**) (^{1}H NMR; 400 MHz; $CDCl_3$)



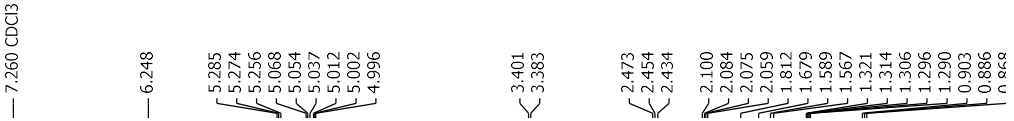
5-bromoresorcinol (**II-28)** (^{13}C NMR; 101 MHz; $CDCl_3$)

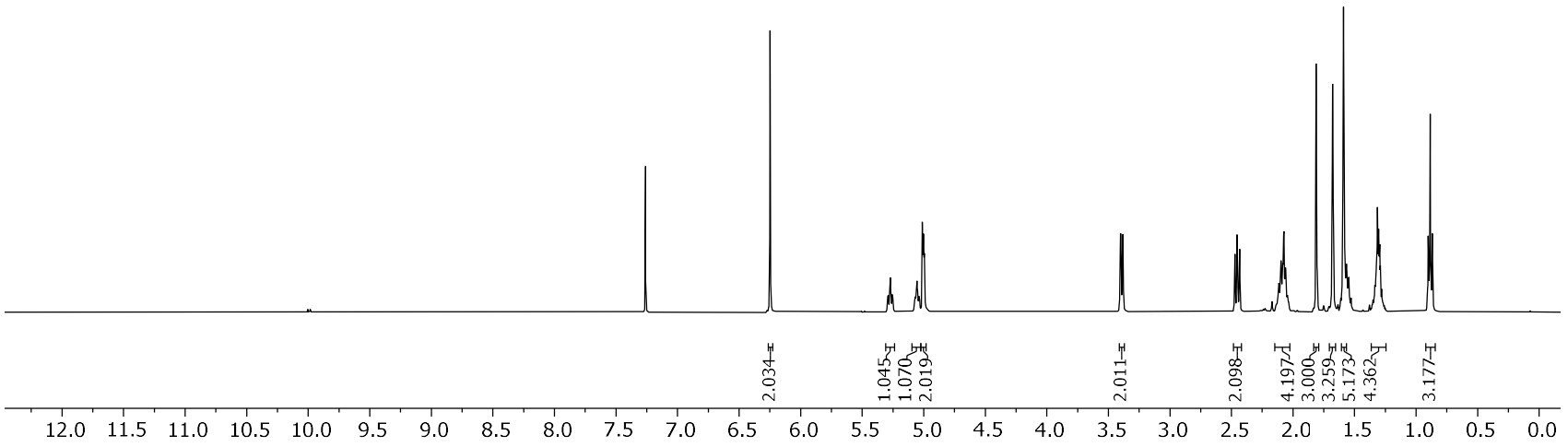


Cannabigerol (**CBG)** (^{1}H NMR; 400 MHz; $CDCl_3$)

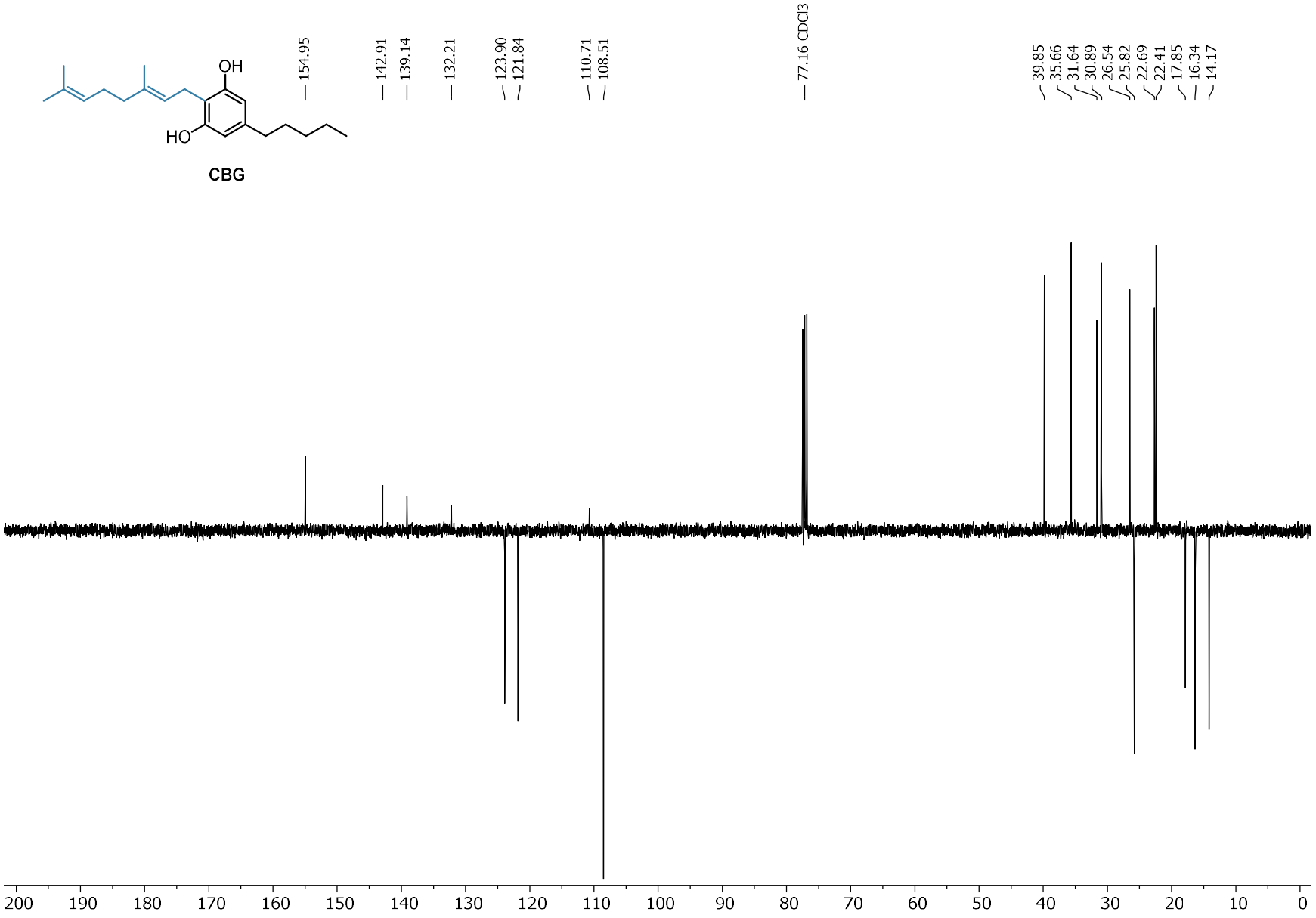


CBG

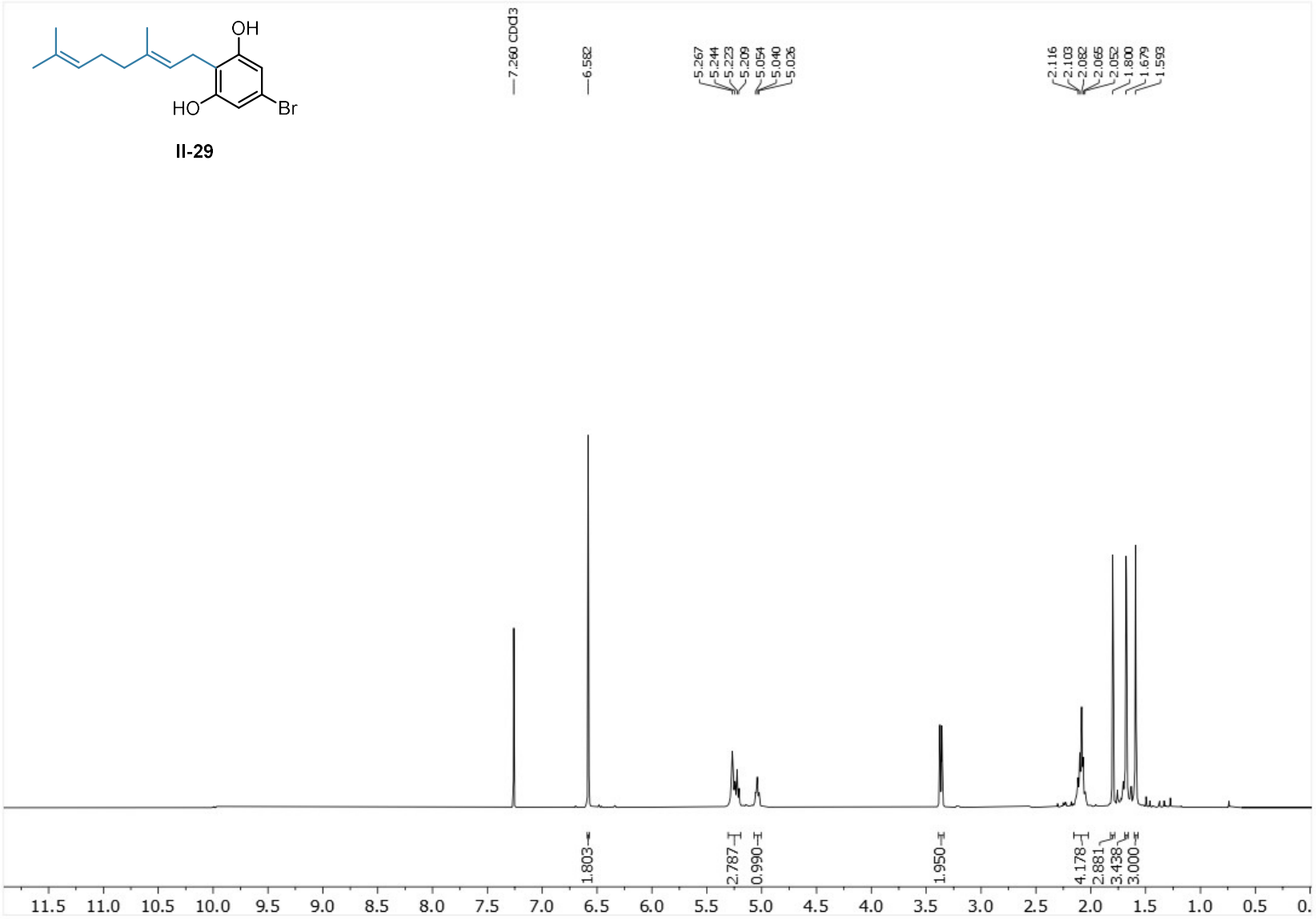




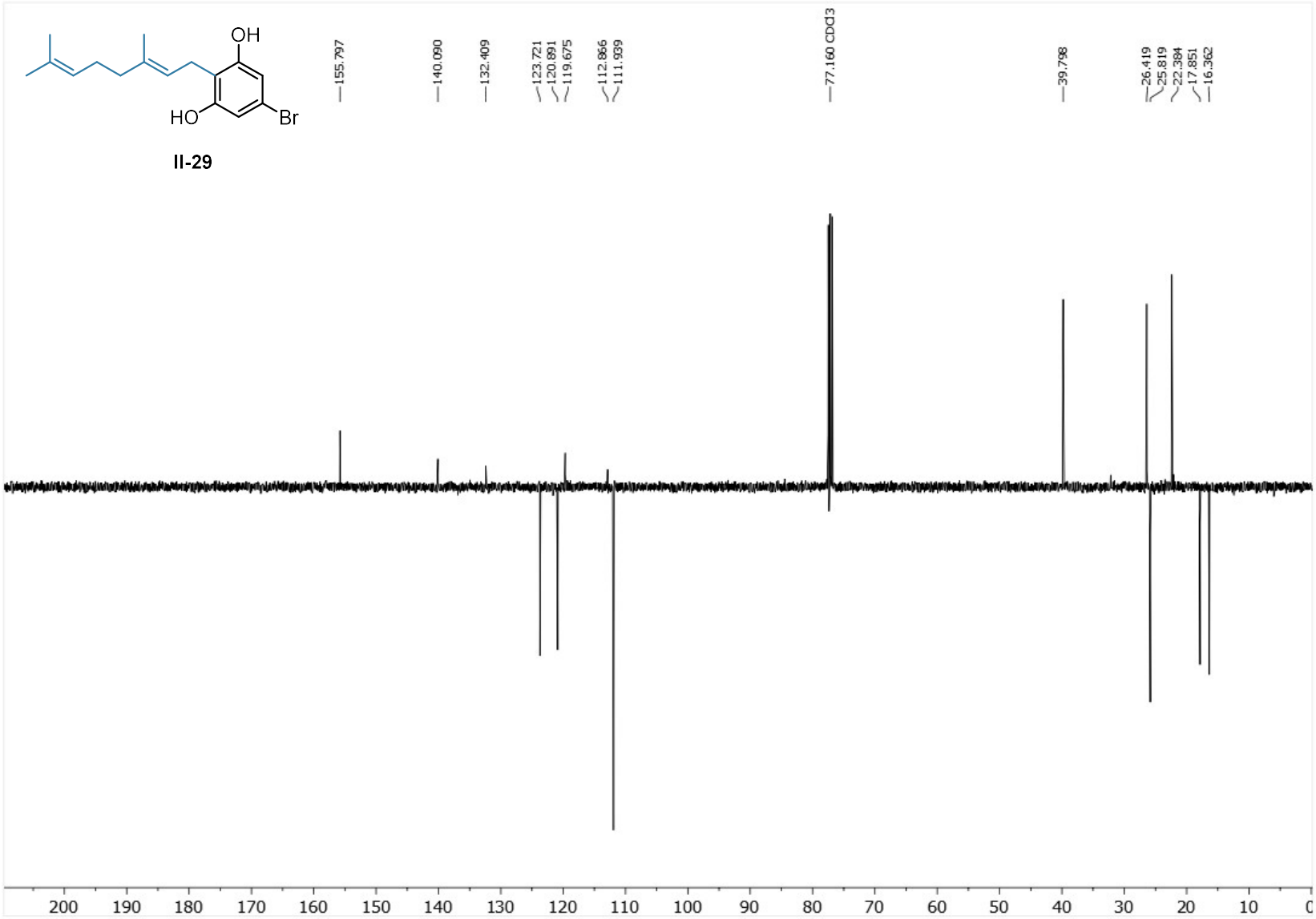
Cannabigerol (**CBG)** (^{13}C NMR; 101 MHz; $CDCl_3$)



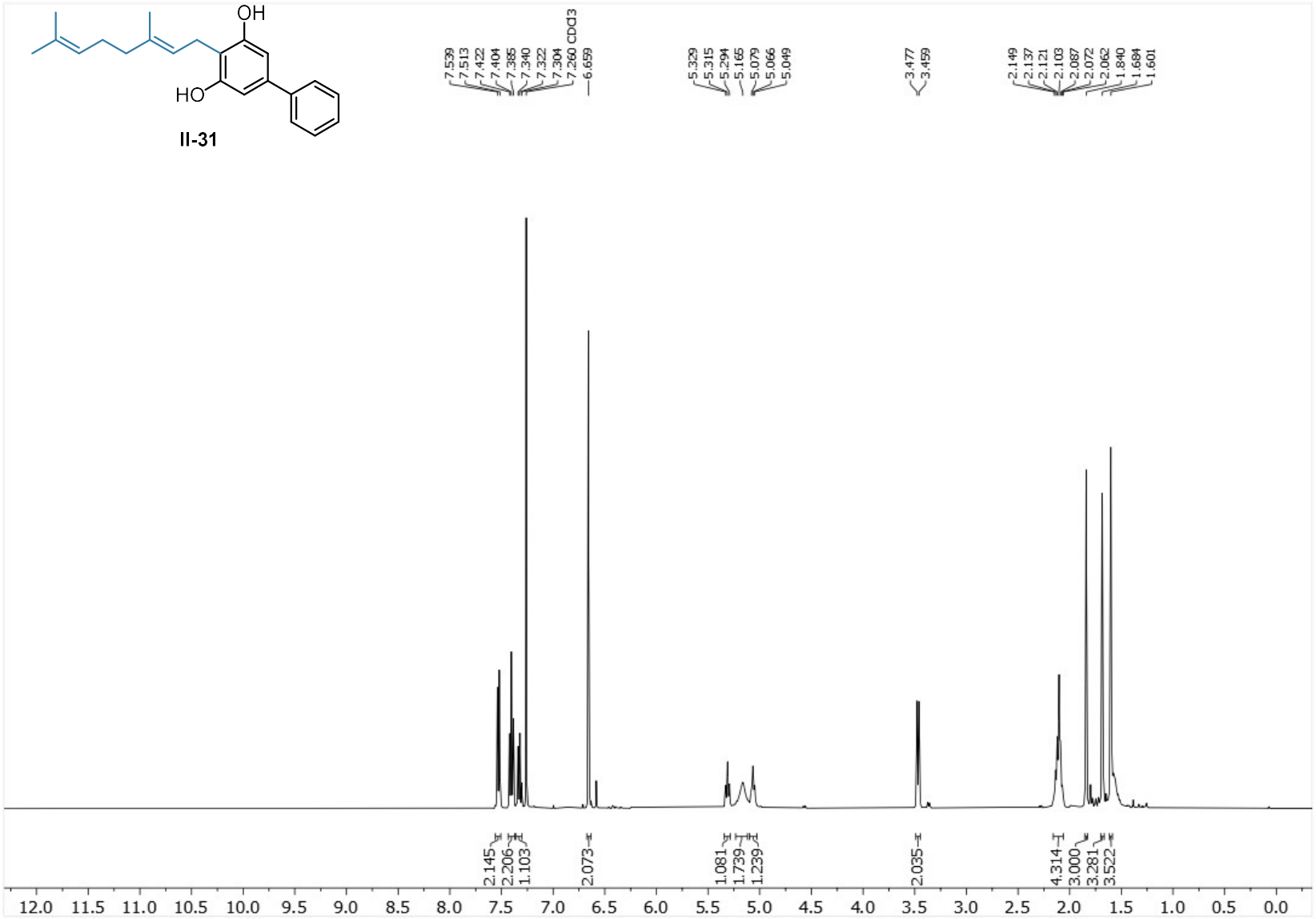
2-geranyl-5-bromoresorcinol **(II-29)** (^{1}H NMR; 400 MHz; $CDCl_3$)



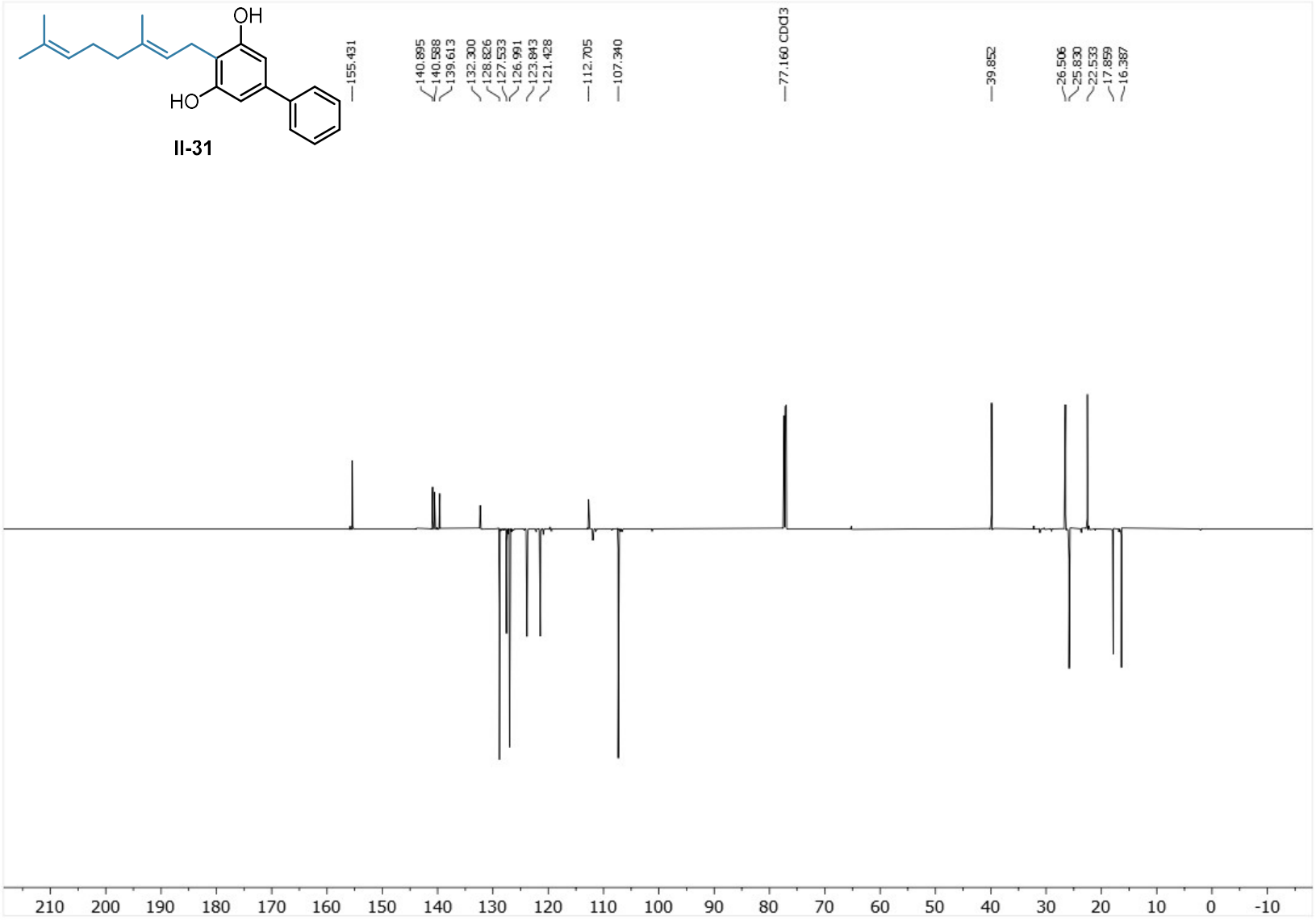
2-geranyl-5-bromoresorcinol **(II-29)** (^{13}C NMR; 101 MHz; $CDCl_3$)



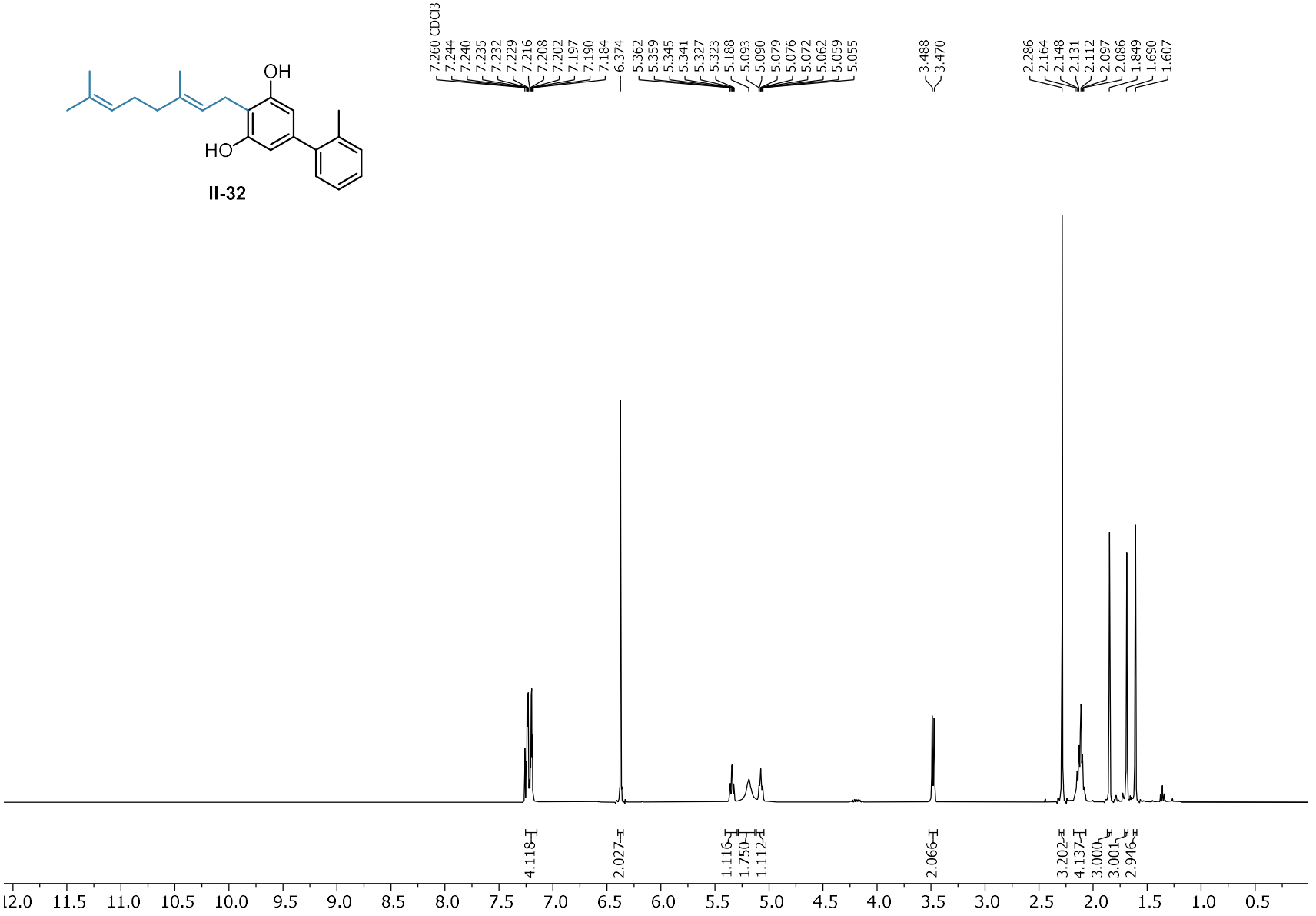
2-geranyl-5-phenylresorcinol (**II-31)** (^{1}H NMR; 400 MHz; $CDCl_3$)



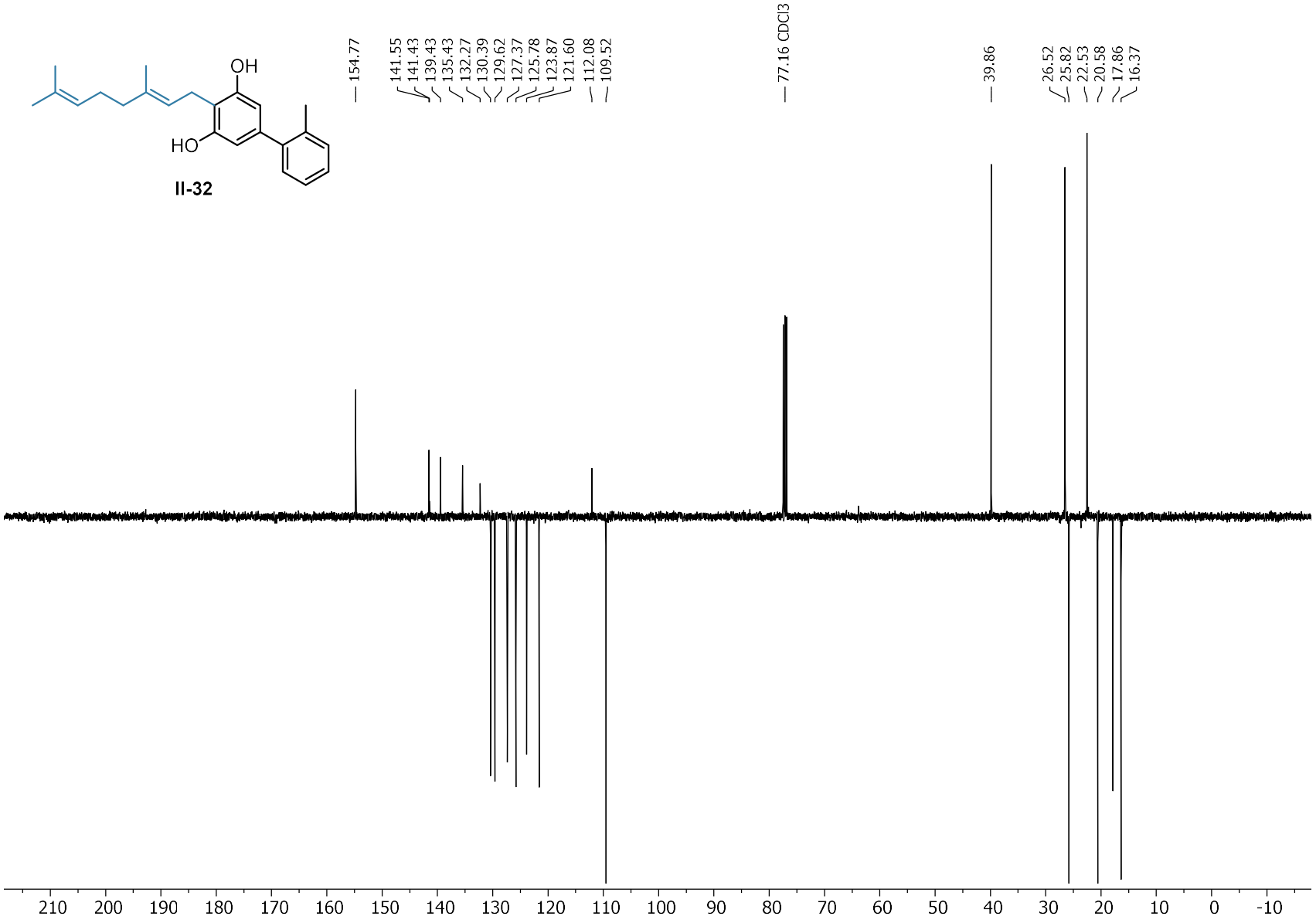
2-geranyl-5-phenylresorcinol (**II-31)** (^{13}C NMR; 101 MHz; $CDCl_3$)



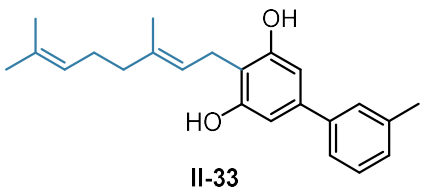
2-geranyl-5-(2-methylphenyl)resorcinol **(II-32)** (^{1}H NMR; 400 MHz; $CDCl_3$)



2-geranyl-5-(2-methylphenyl)resorcinol (**II-32)** (^{13}C NMR; 101 MHz; $CDCl_3$)

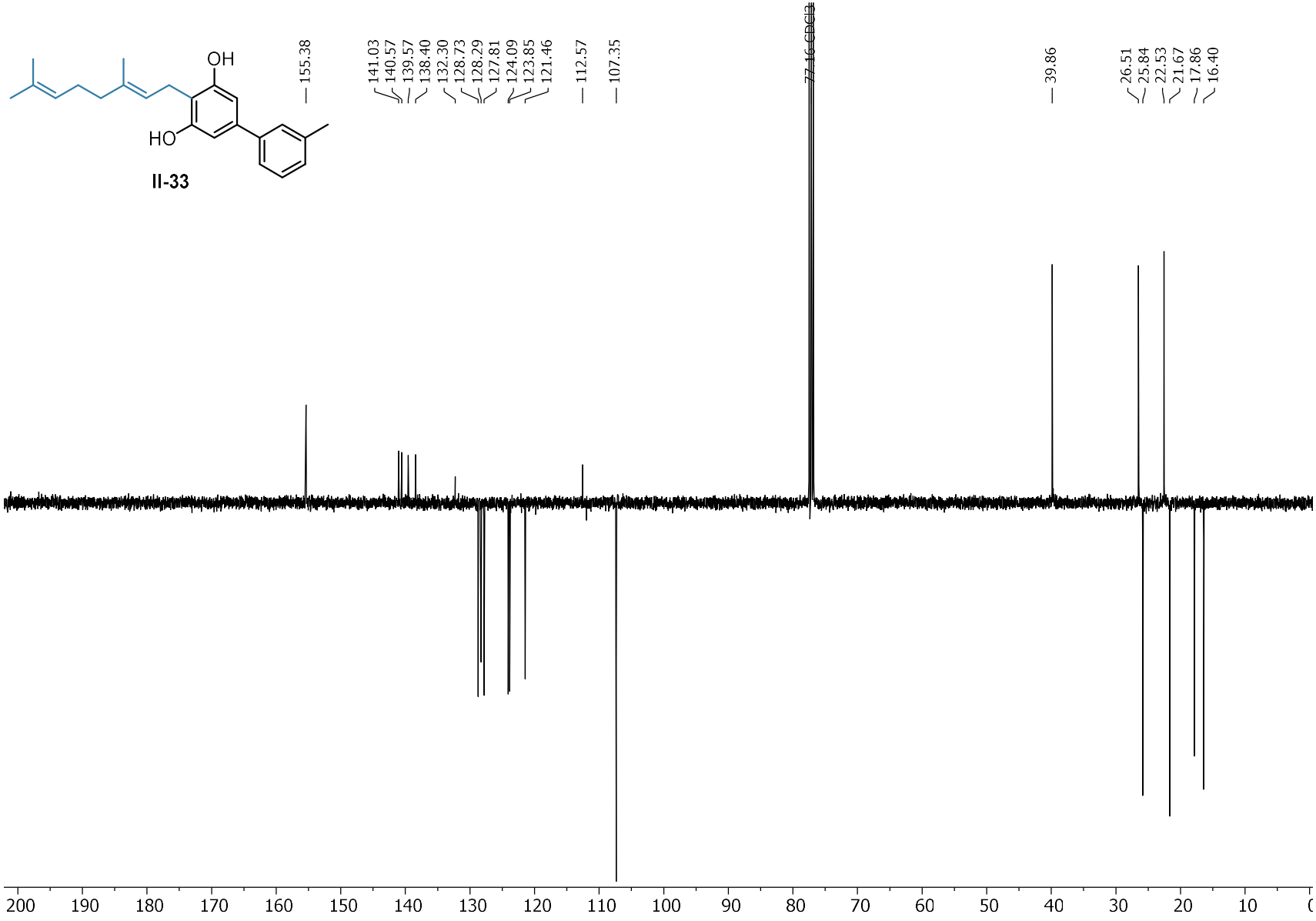


2-geranyl-5-(3-methylphenyl)resorcinol **(II-33)** (^{1}H NMR; 400 MHz; $CDCl_3$)

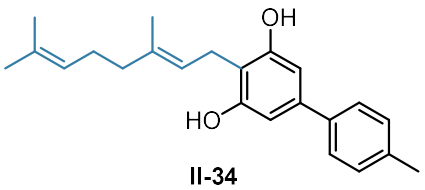


II-33

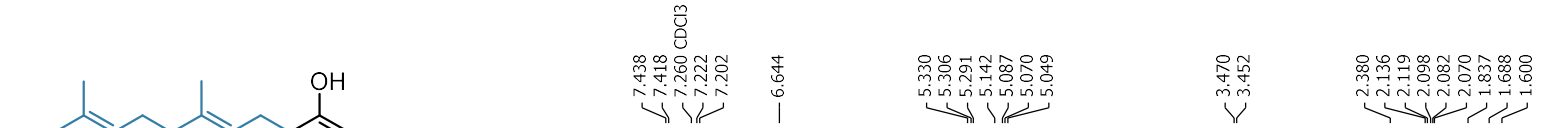
2-geranyl-5-(3-methylphenyl)resorcinol **(II-33)** (^{13}C NMR; 101 MHz; $CDCl_3$)

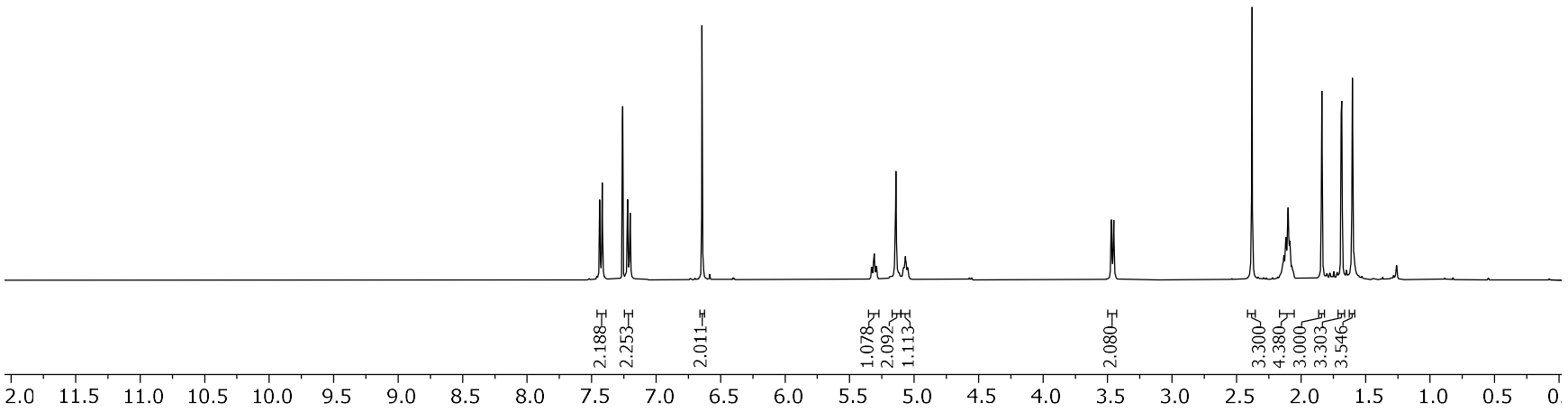


2-geranyl-5-(4-methylphenyl)resorcinol **(II-34)** (^{1}H NMR; 400 MHz; $CDCl_3$)

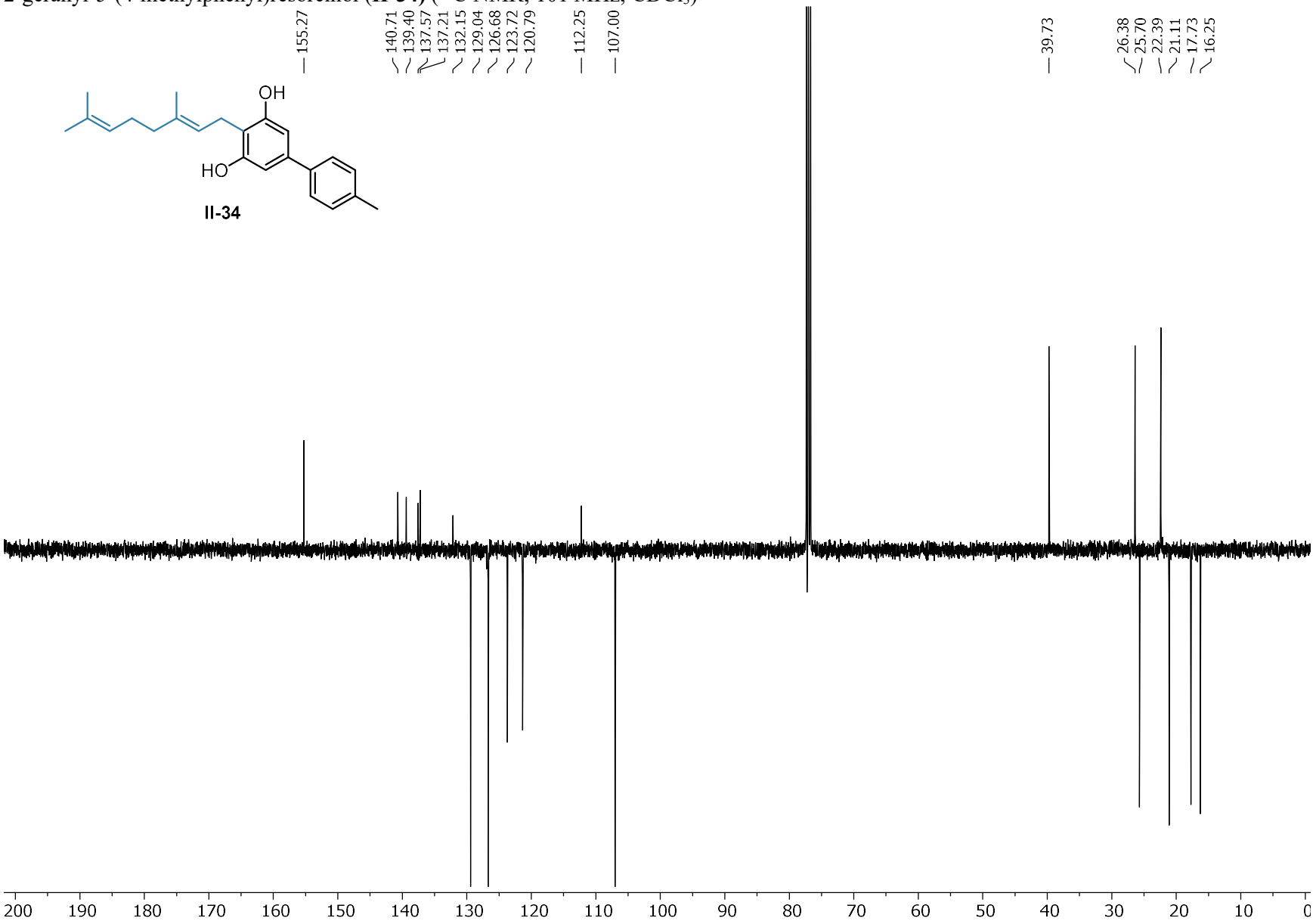


II-34

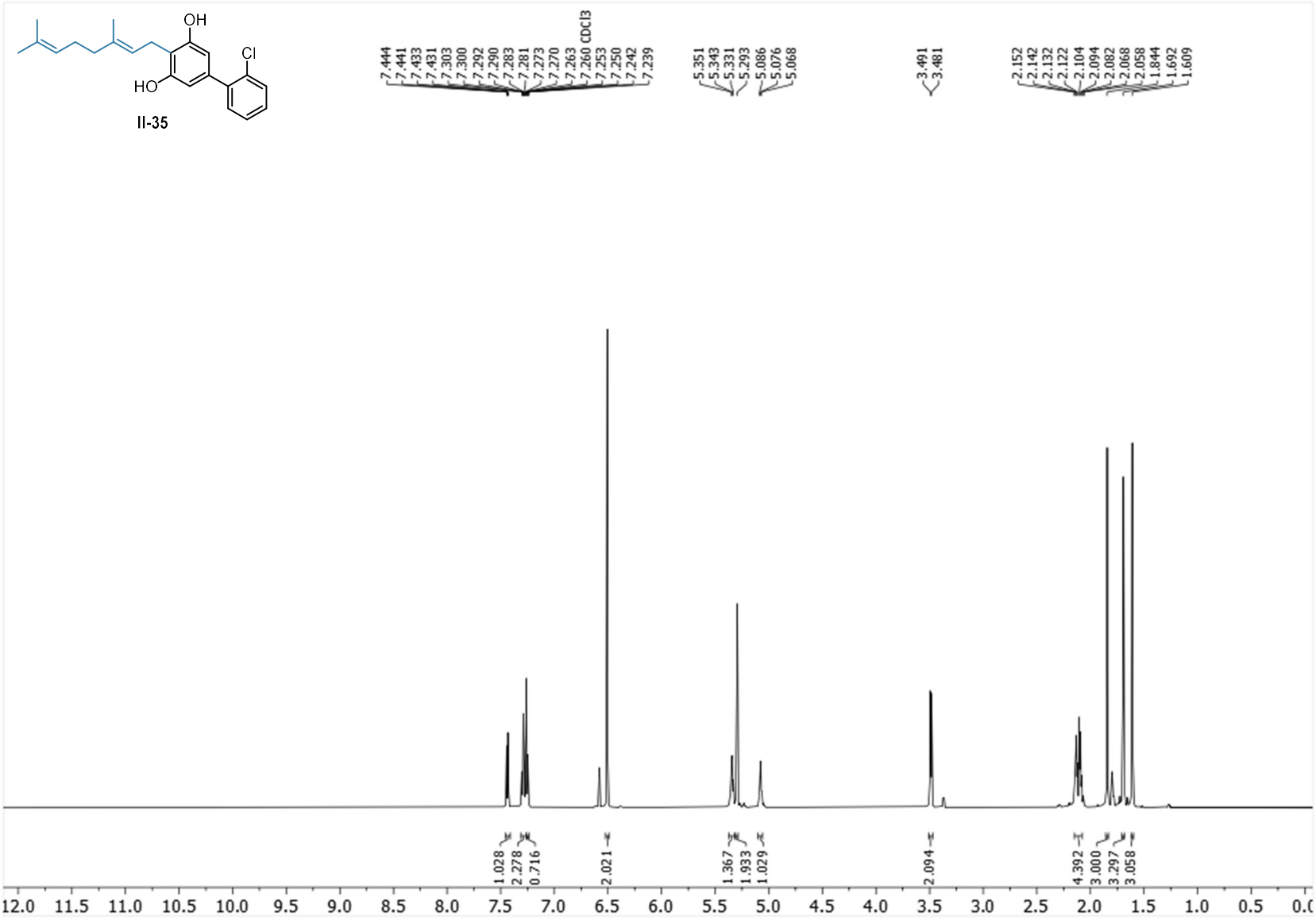




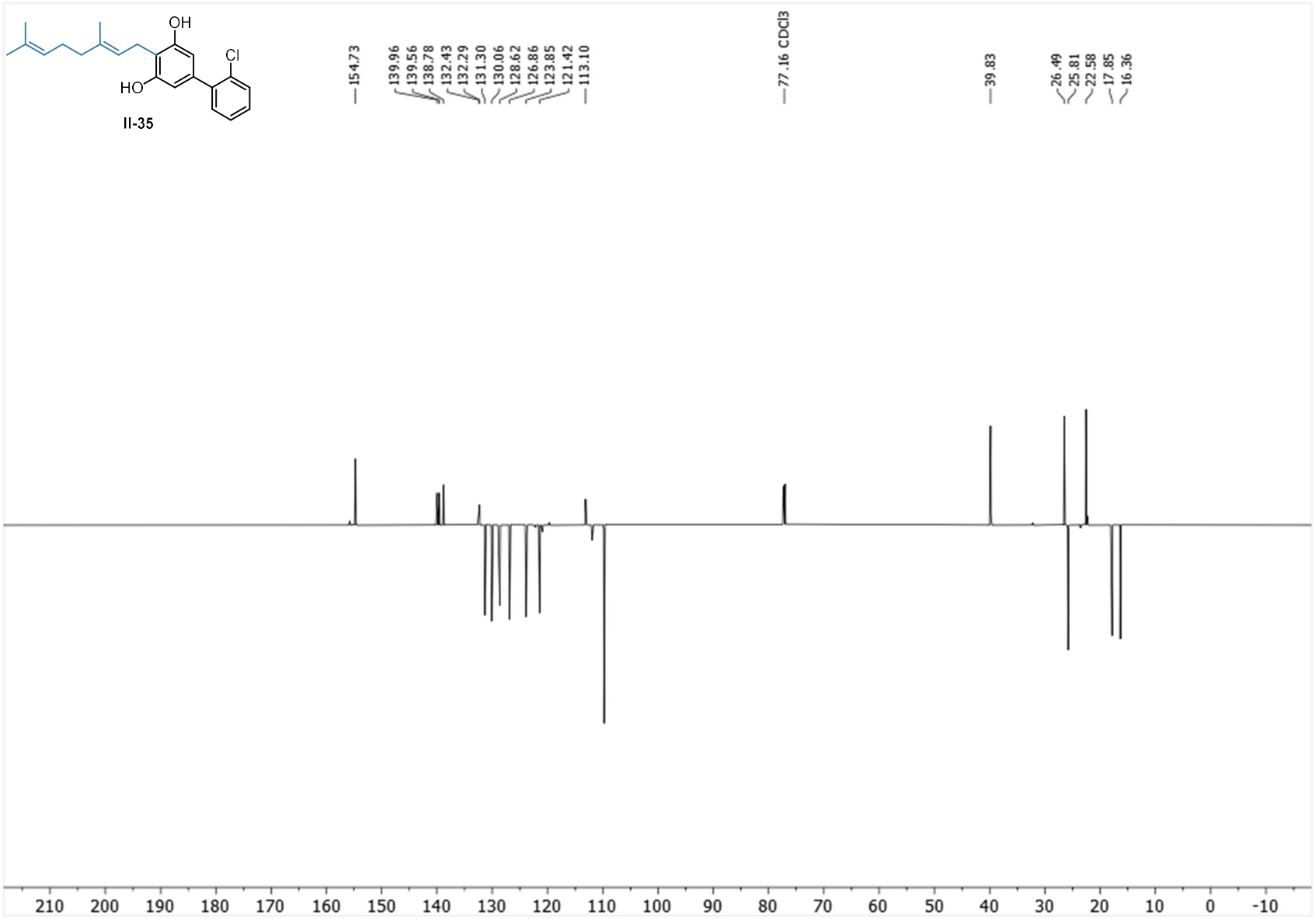
2-geranyl-5-(4-methylphenyl)resorcinol **(II-34)** (^{13}C NMR; 101 MHz; $CDCl_3$)



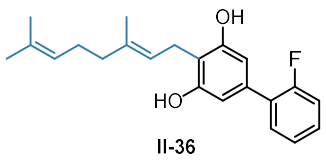
2-geranyl-5-(2-chlorophenyl)resorcinol (**II-35)** (^{1}H NMR; 700 MHz; $CDCl_3$)



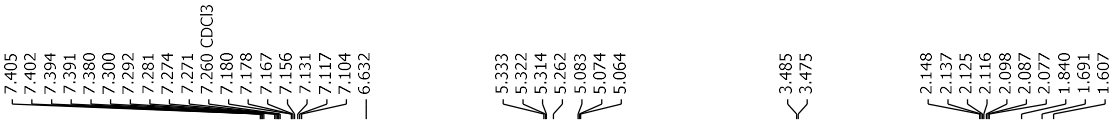
2-geranyl-5-(2-chlorophenyl)resorcinol (**II-35)** (^{13}C NMR; 176 MHz; $CDCl_3$)

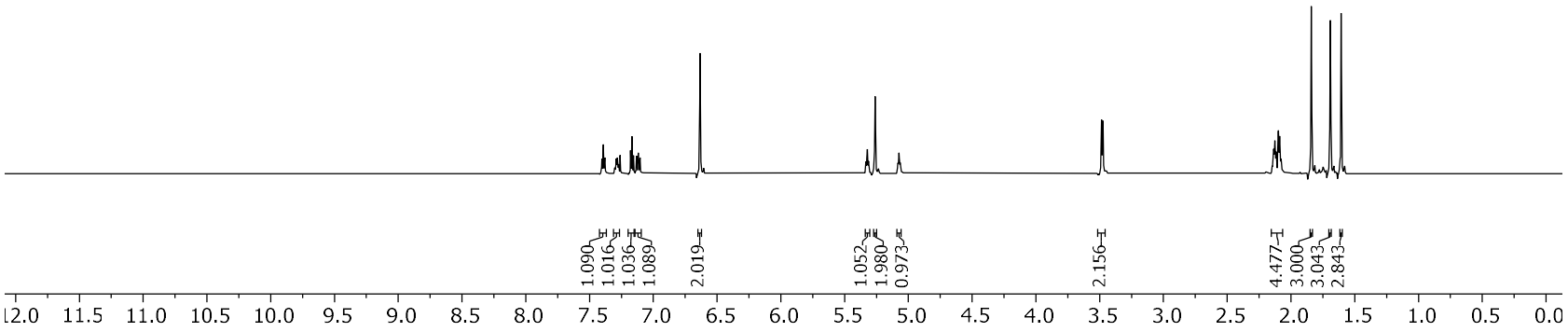


2-geranyl-5-(2-fluorophenyl)resorcinol (**II-36)** (^{1}H NMR; 400 MHz; $CDCl_3$)

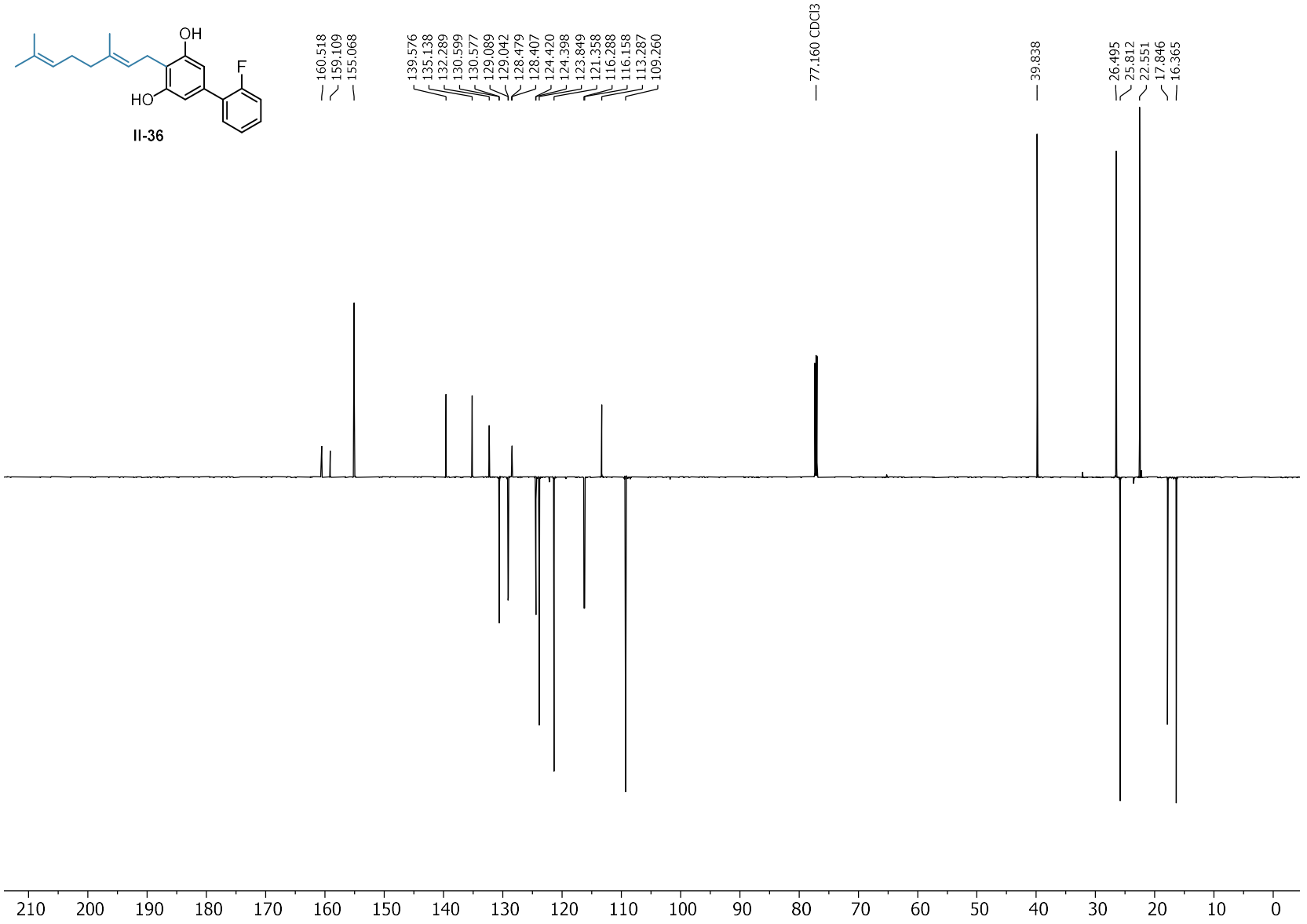


II-36

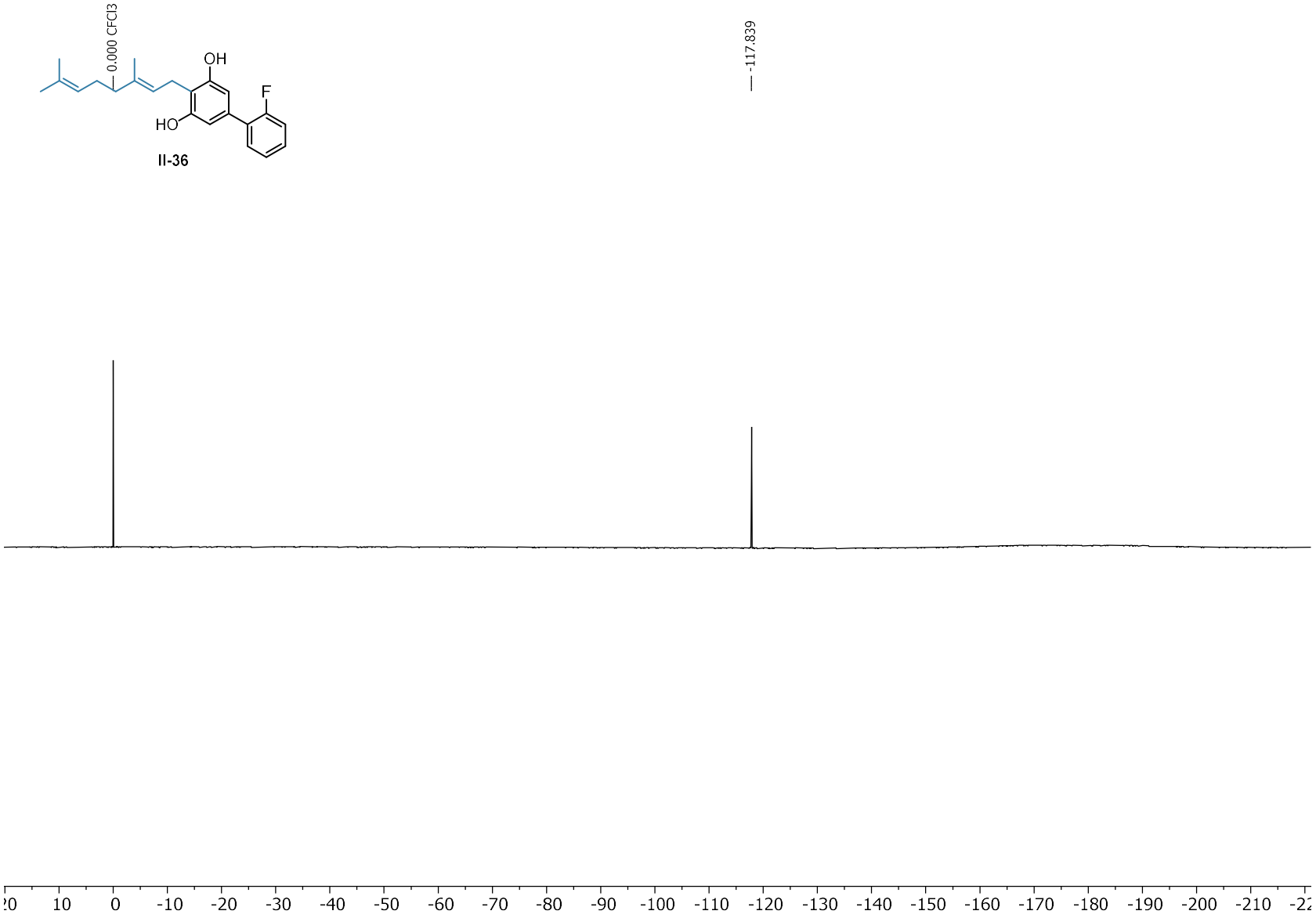




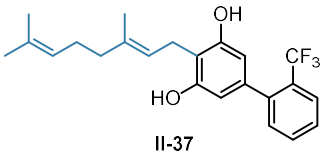
2-geranyl-5-(2-flurophenyl)resorcinol (**II-36)** (^{13}C NMR; 101 MHz; $CDCl_3$)



2-geranyl-5-(2-flurophenyl)resorcinol (**II-36)** (^{19}F NMR; 377 MHz; $CFCl_3$)

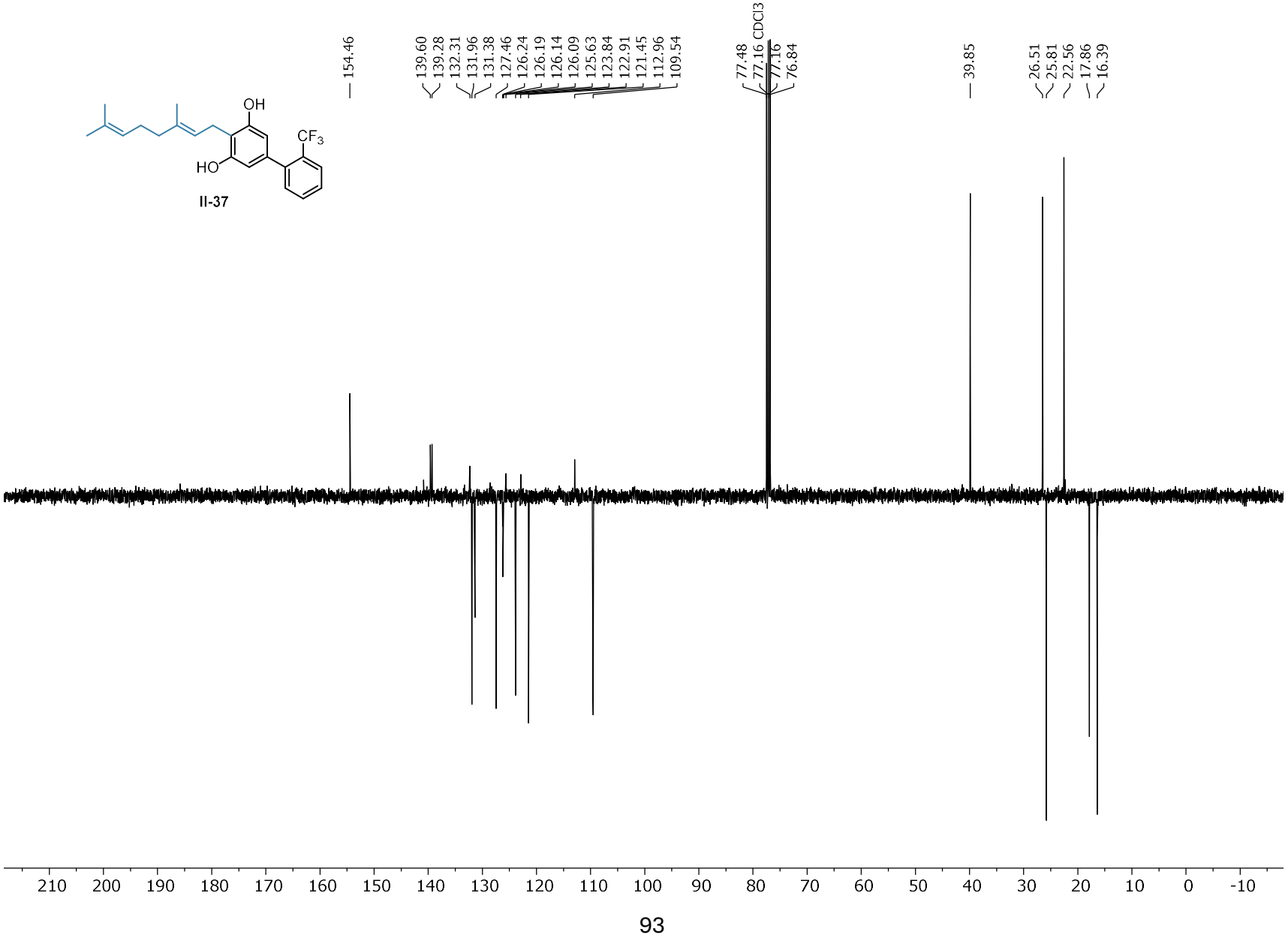


2-geranyl-5-(2-trifluoromethylphenyl)resorcinol **(II-37)** (^{1}H NMR; 400 MHz; $CDCl_3$)

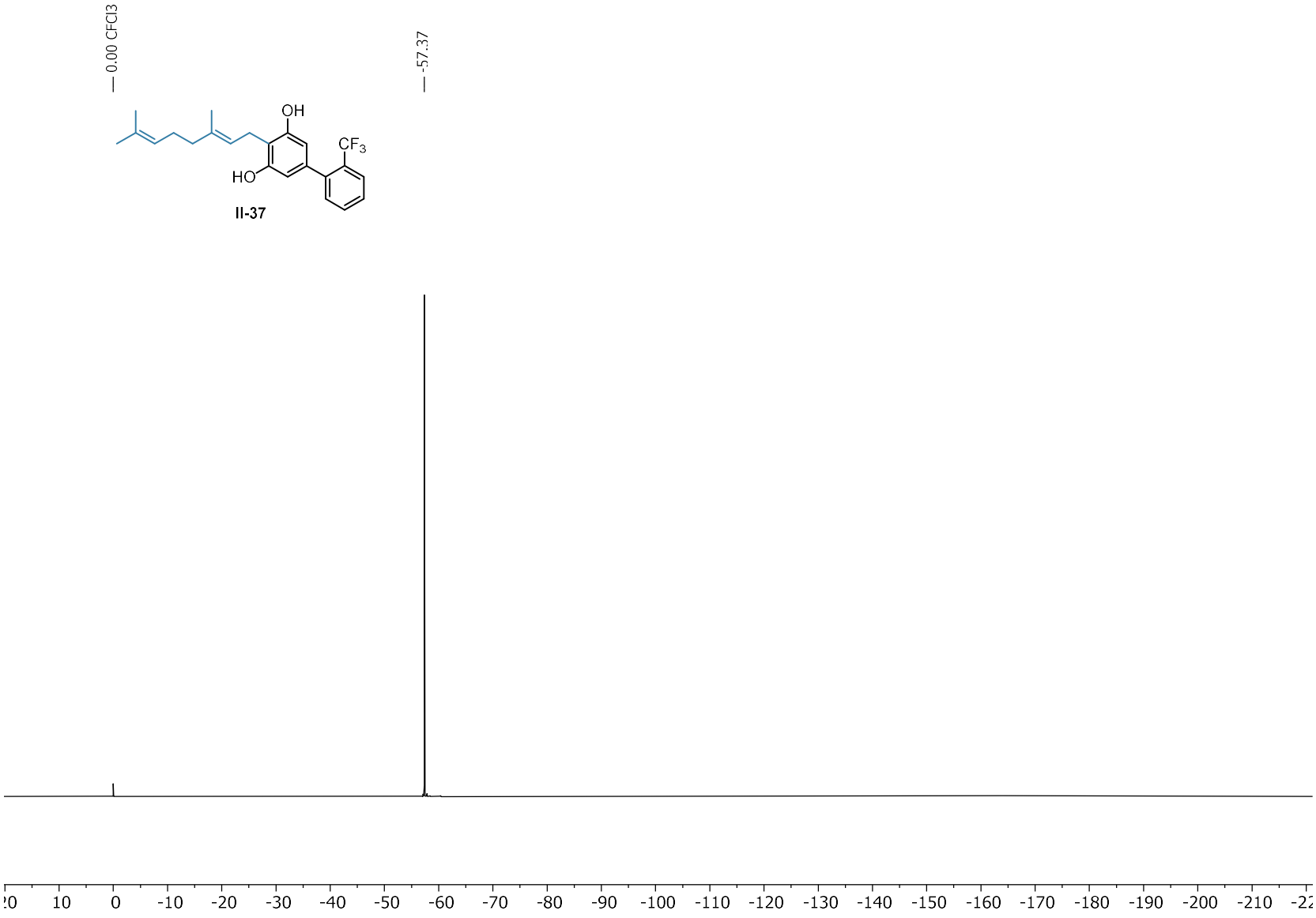


II-37

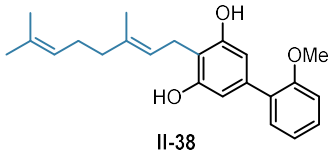
2-geranyl-5-(2-trifluromethylphenyl)resorcinol **(II-37)** (^{13}C NMR; 101 MHz; $CDCl_3$)



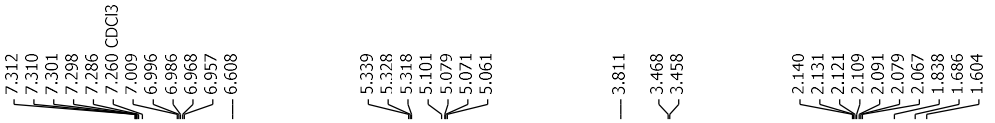
2-geranyl-5-(2-trifluromethylphenyl)resorcinol **(II-37)** (^{19}F NMR (377 MHz, $CFCl_3$)

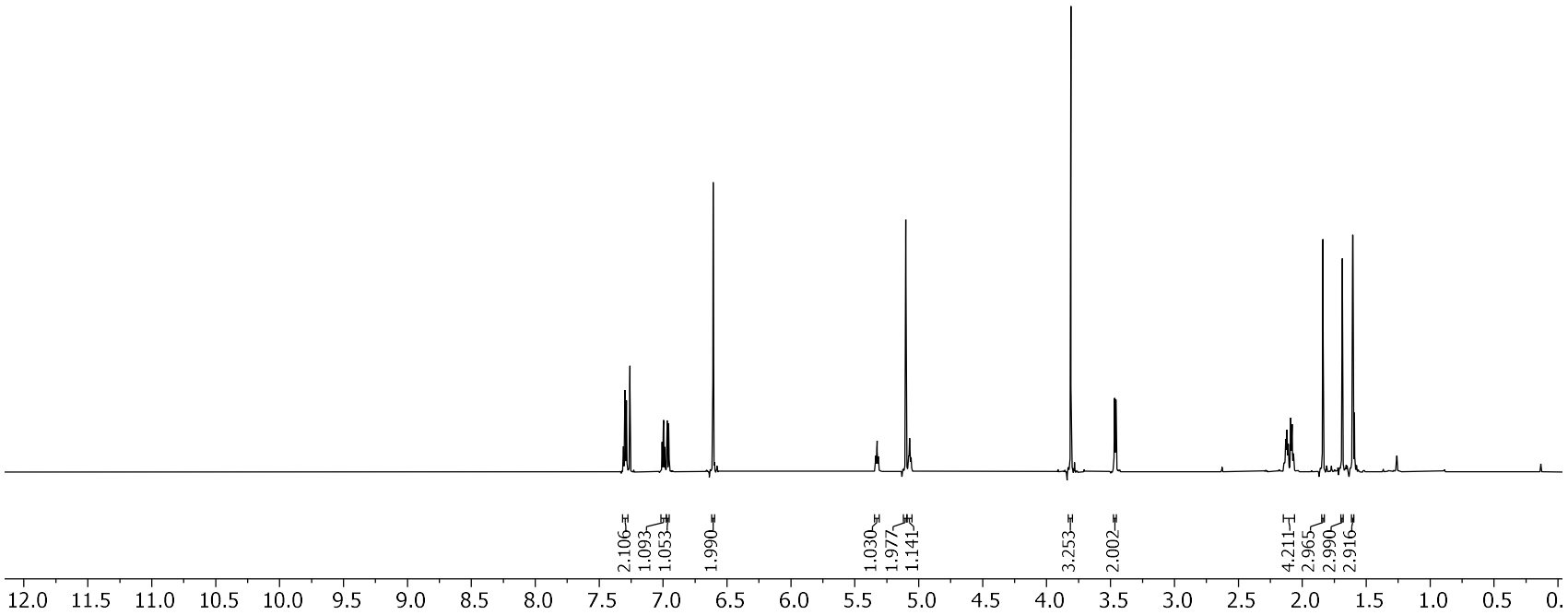


2-geranyl-5-(2-methoxyphenyl)resorcinol (**II-38**) (^{1}H NMR; 400 MHz; $CDCl_3$)

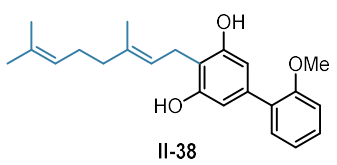


II-38



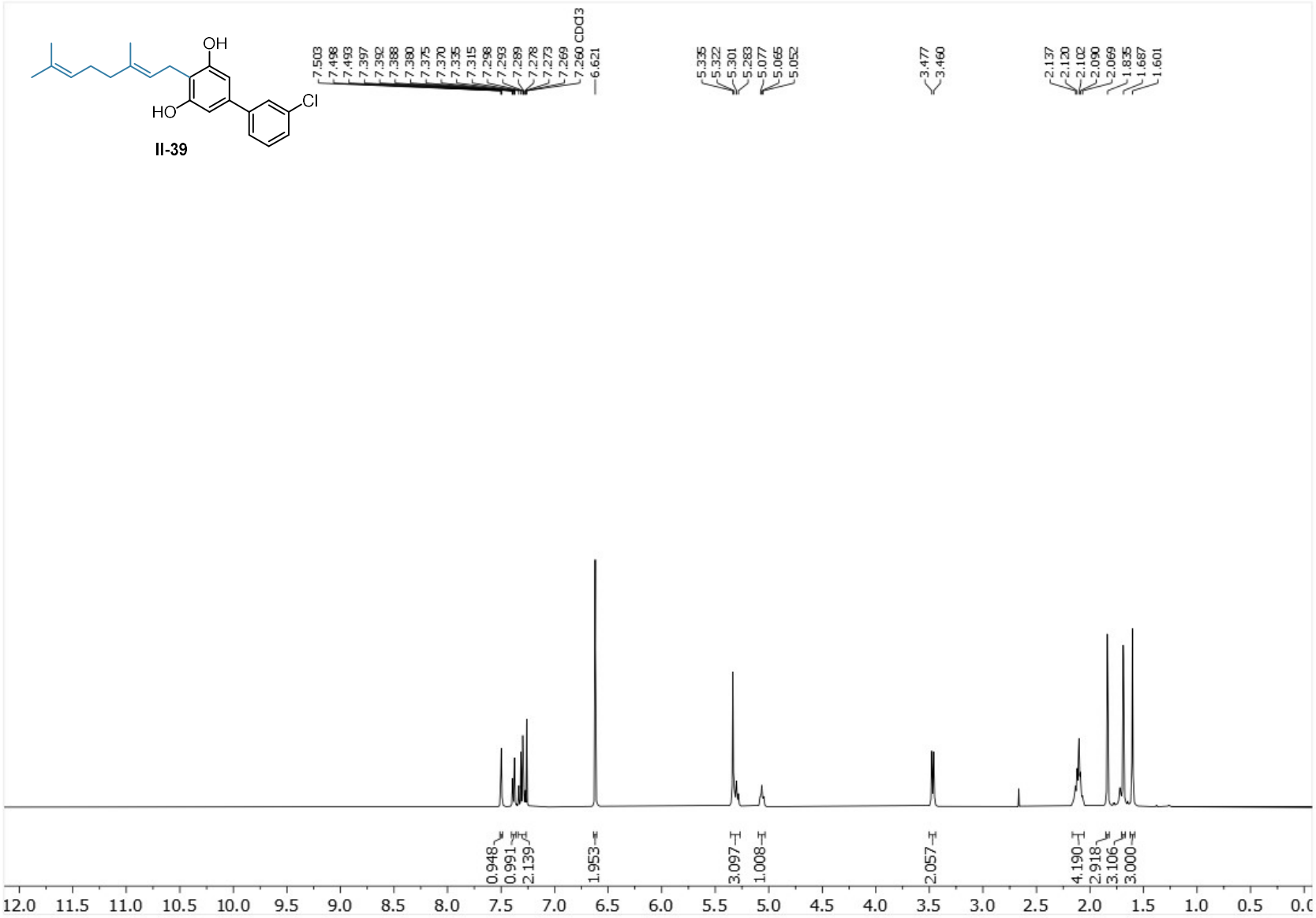


2-geranyl-5-(2-methoxyphenyl)resorcinol (**II-38**) (^{13}C NMR; 101 MHz; $CDCl_3$)

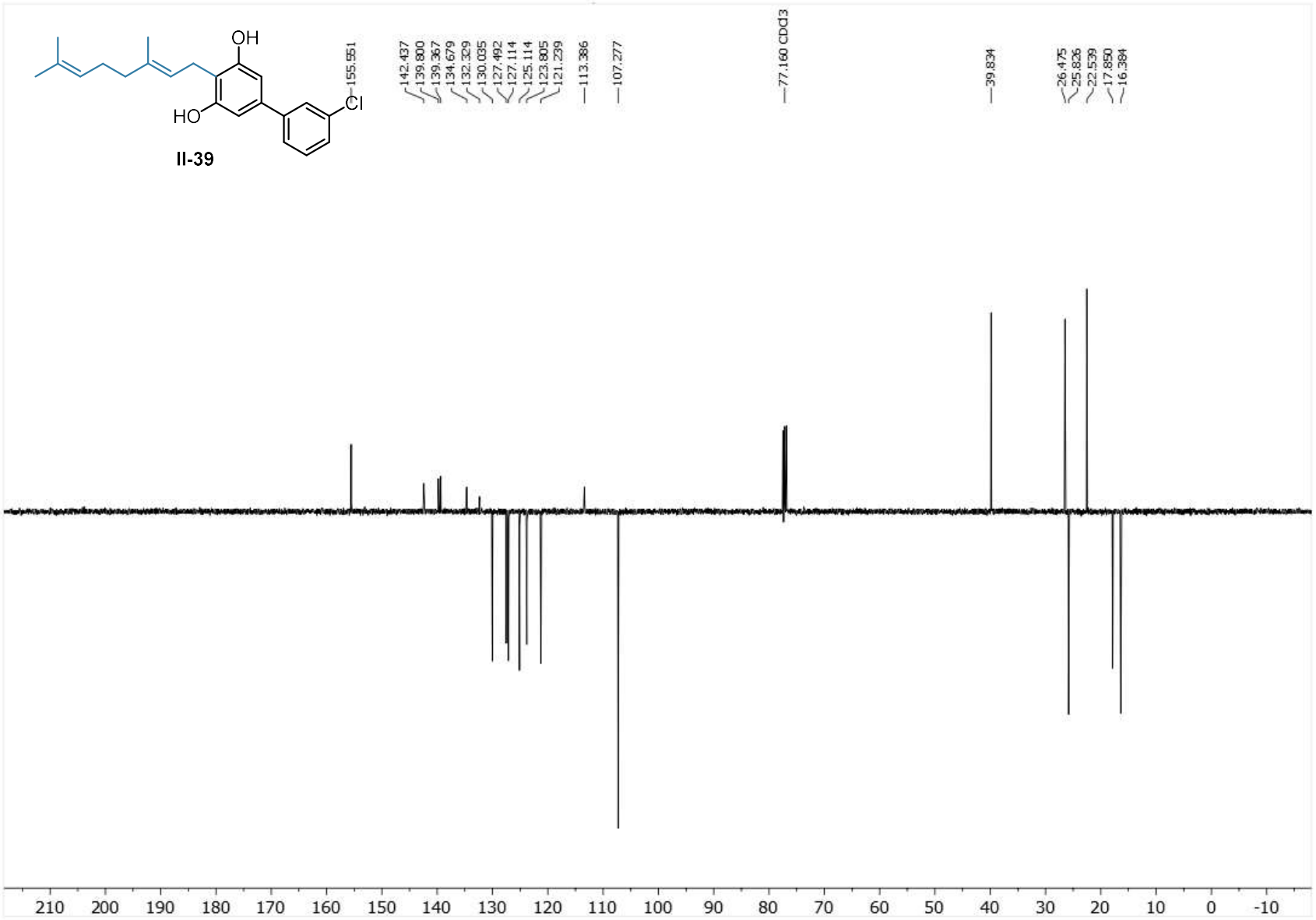


II-38

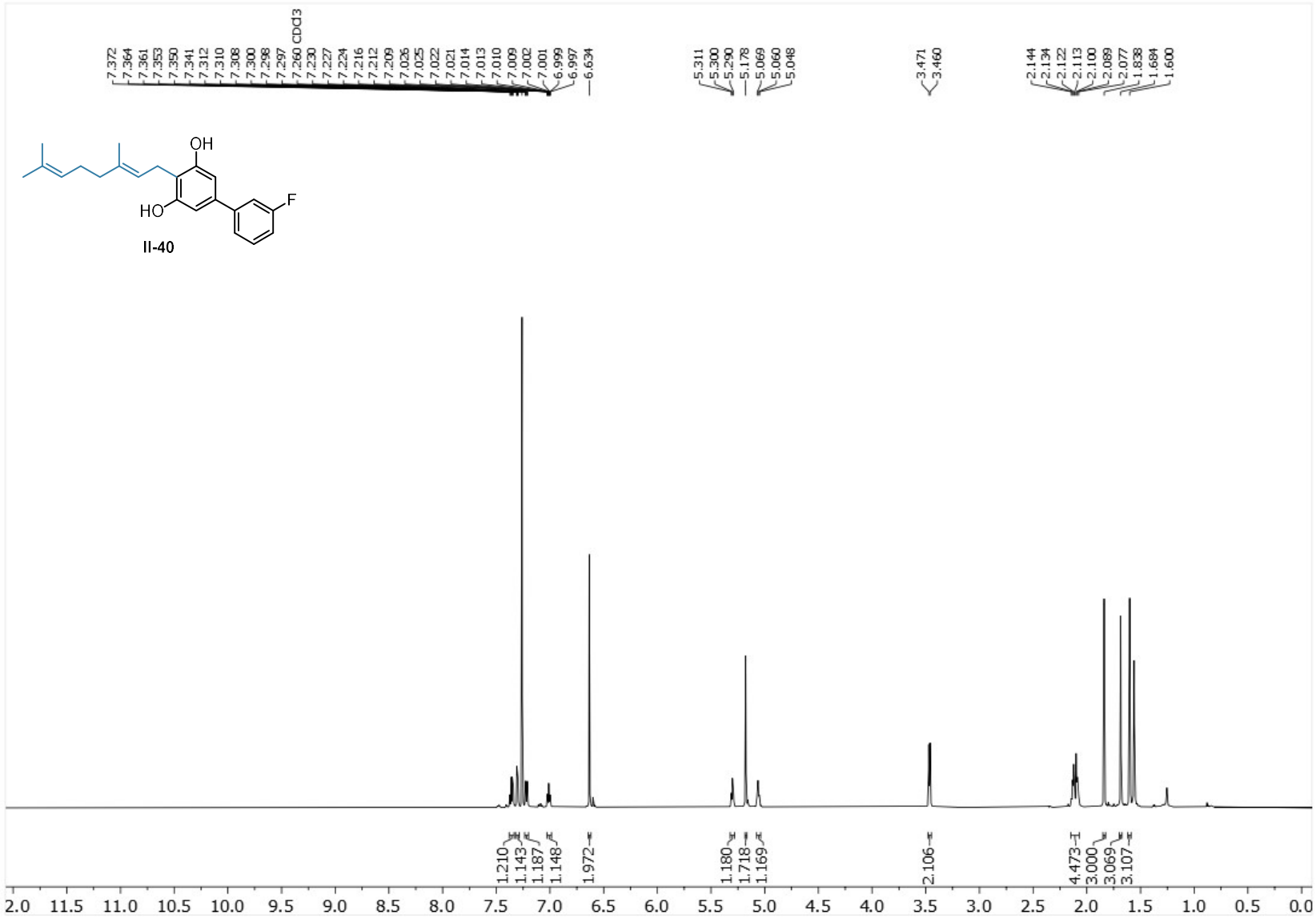
2-geranyl-5-(3-chlorophenyl)resorcinol (**II-39)** (^{1}H NMR; 400 MHz; $CDCl_3$)



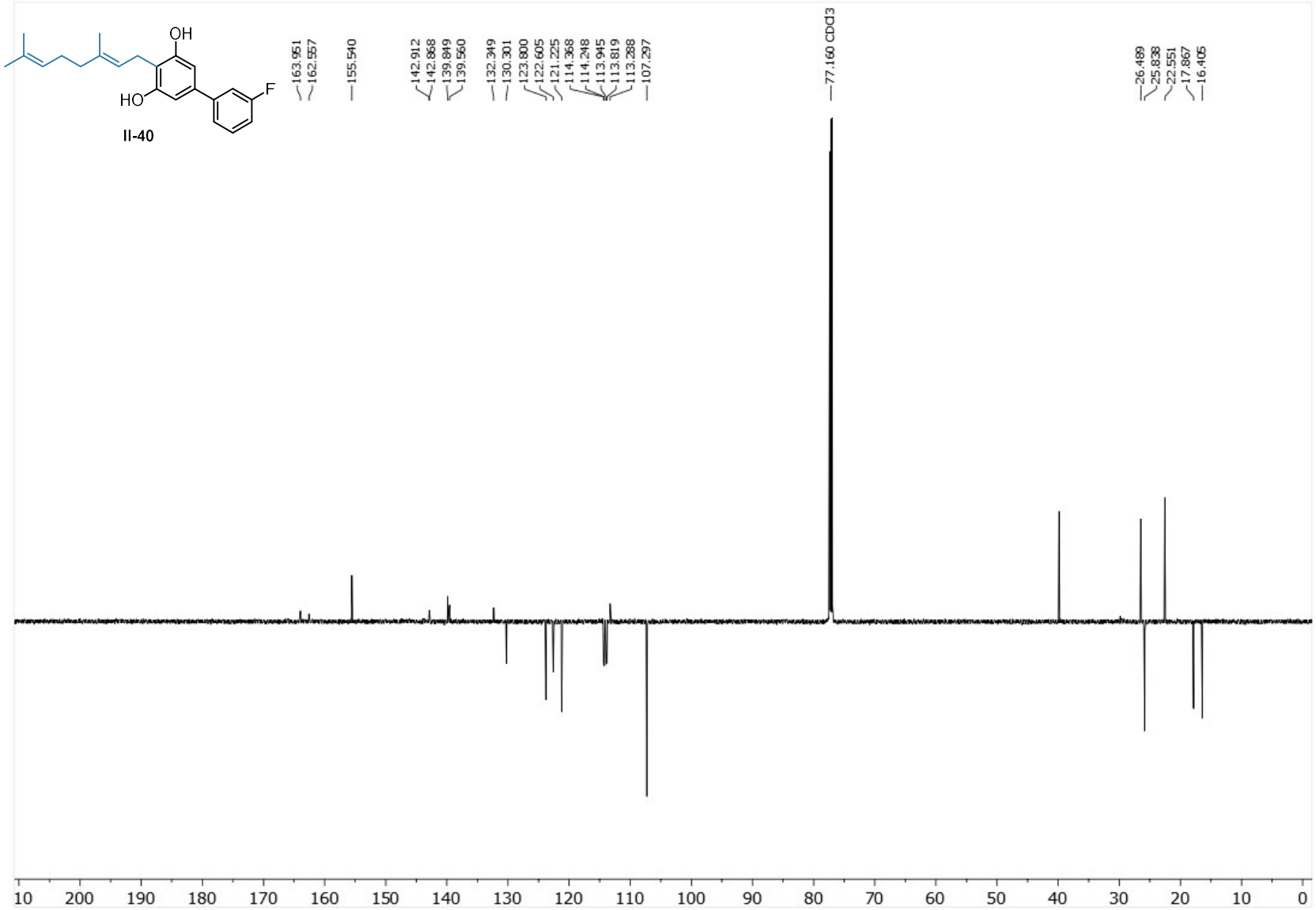
2-geranyl-5-(3-chlorophenyl)resorcinol (**II-39)** (^{13}C NMR; 101 MHz; $CDCl_3$)



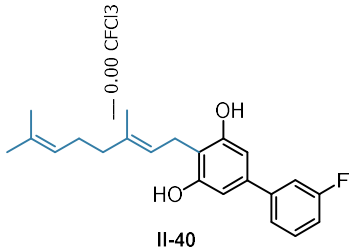
2-geranyl-5-(3-fluorophenyl)resorcinol (**II-40)** (^{1}H NMR; 400 MHz; $CDCl_3$)



2-geranyl-5-(3-flurophenyl)resorcinol (**II-40)** (^{13}C NMR; 101 MHz; $CDCl_3$)

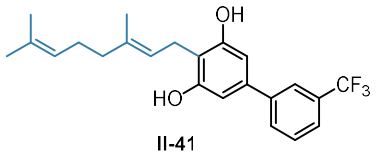


2-geranyl-5-(3-flurophenyl)resorcinol (**II-40) (**^{19}F NMR (377 MHz, $CFCl_3$)



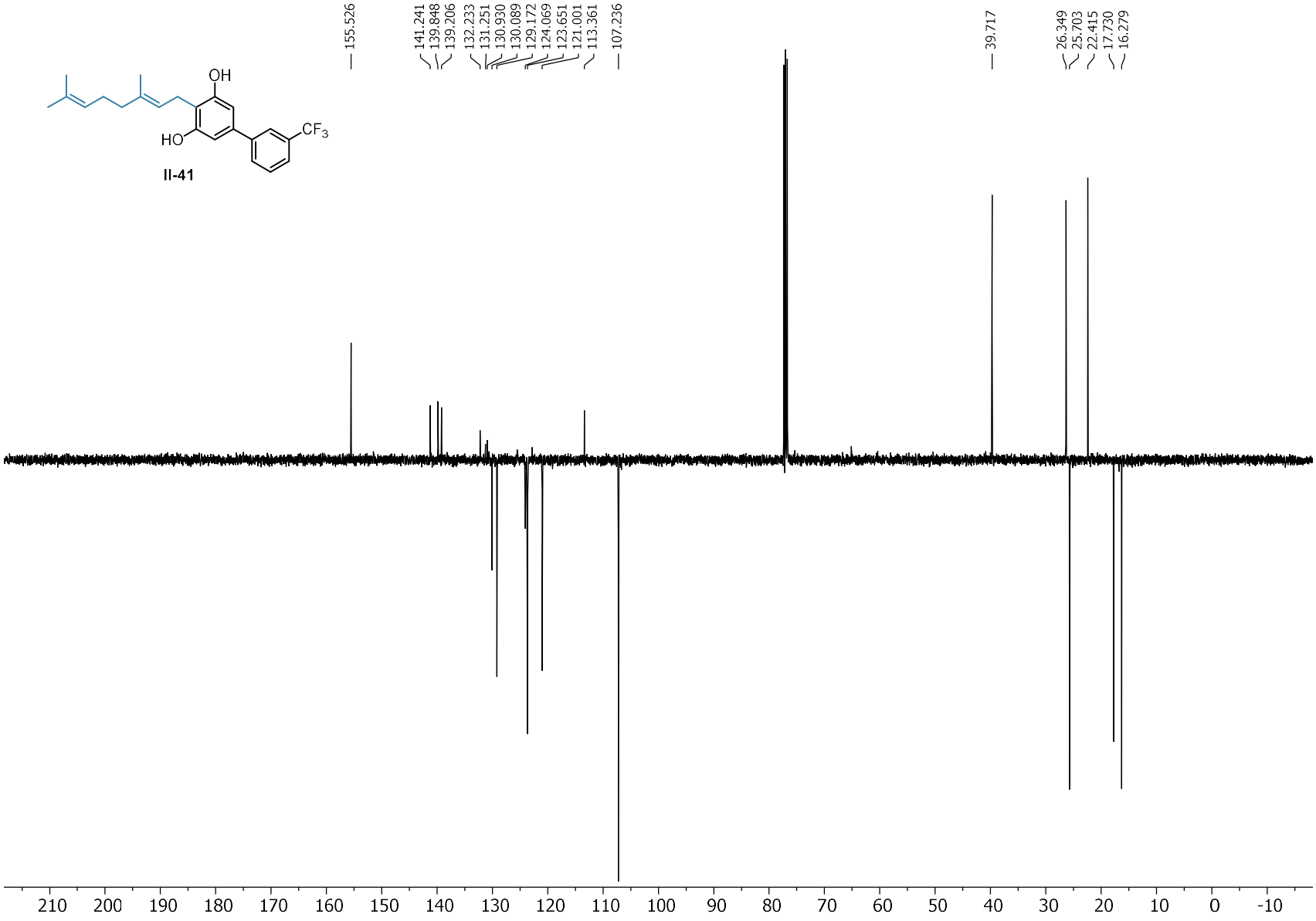
II-40

2-geranyl-5-(3-trifluoromethylphenyl)resorcinol **(II-41)** (^{1}H NMR; 400 MHz; $CDCl_3$)



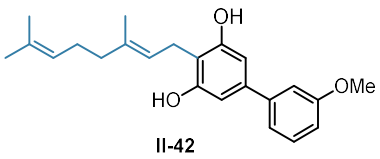
II-41

2-geranyl-5-(3-triflurophenyl)resorcinol (**II-41**) (^{13}C NMR; 101 MHz; $CDCl_3$)

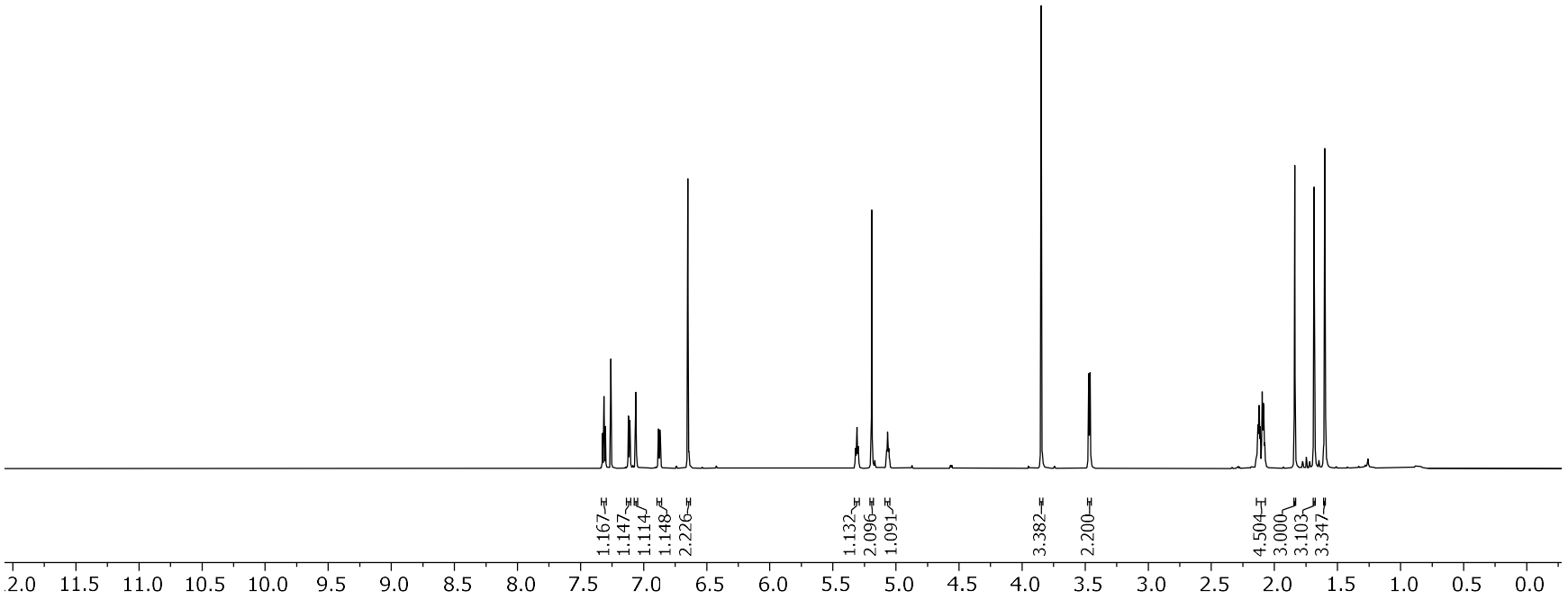


2-geranyl-5-(3-triflurophenyl)resorcinol (**II-41**) (^{19}F NMR, 377 MHz, $CFCl_3$)

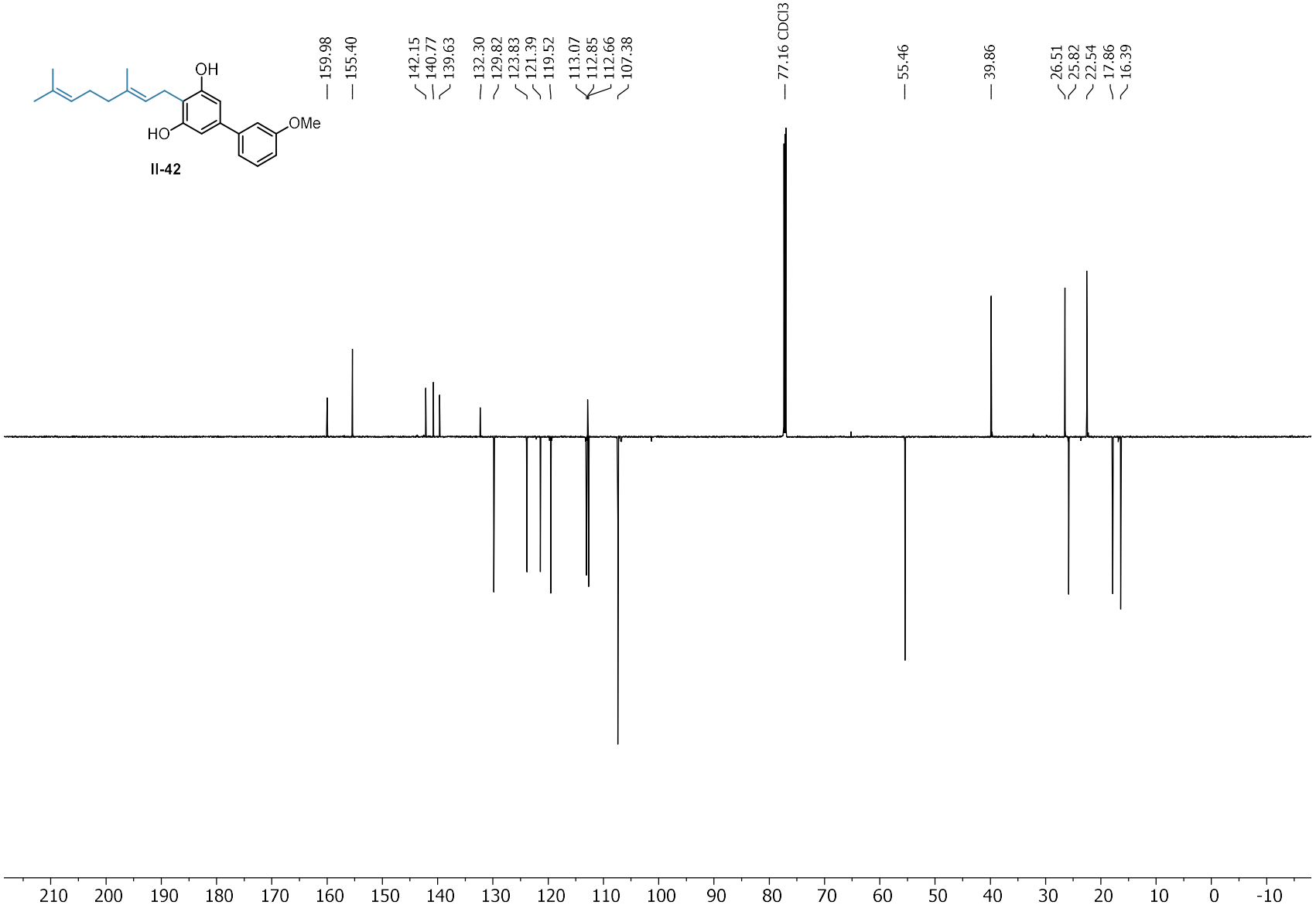
2-geranyl-5-(3-methoxyphenyl)resorcinol (**II-42)** (^{1}H NMR; 400 MHz; $CDCl_3$)



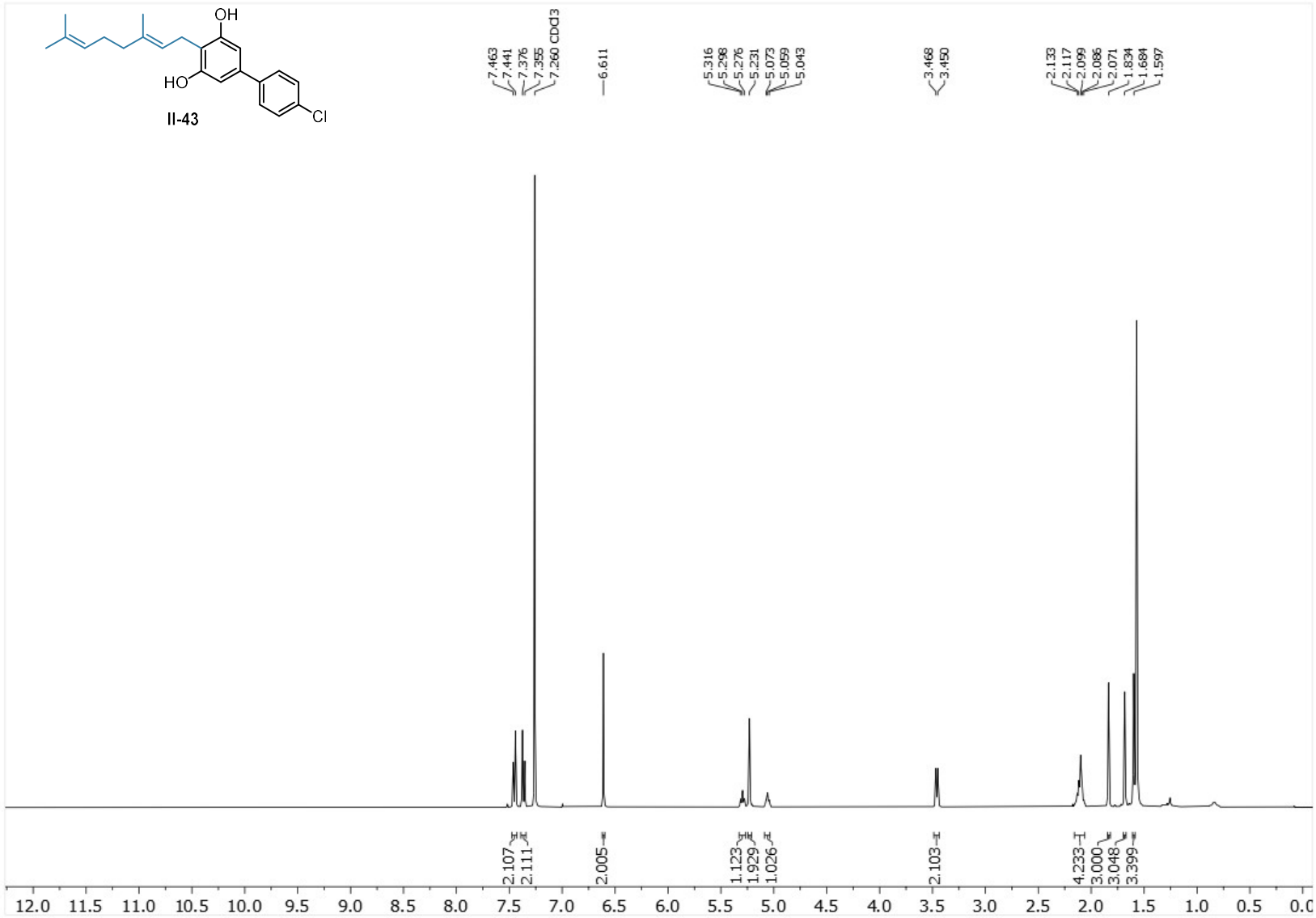
II-42



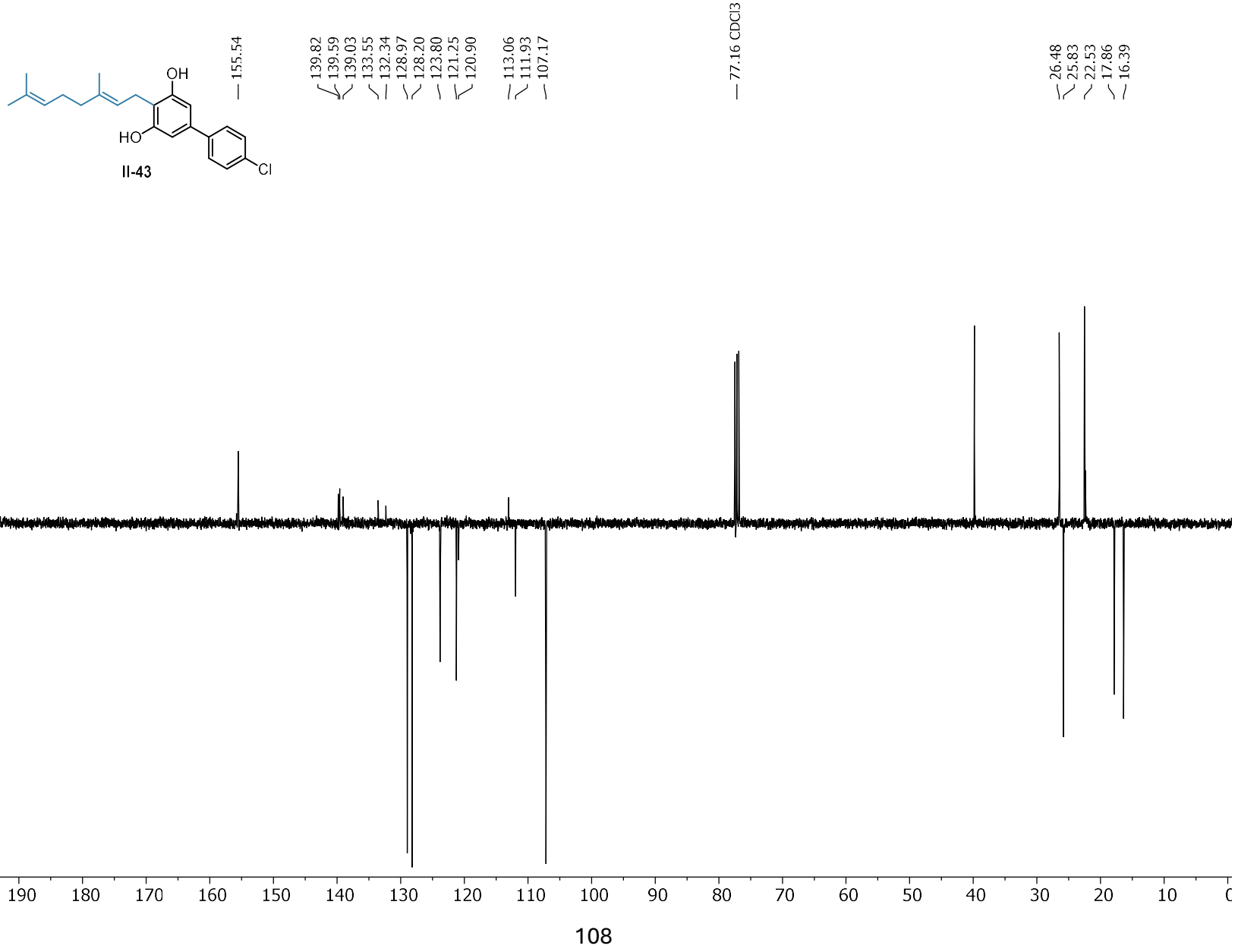
2-geranyl-5-(3-methoxyphenyl)resorcinol (**II-42)** (^{13}C NMR; 101 MHz; $CDCl_3$)



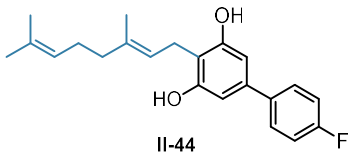
2-geranyl-5-(4-chlorophenyl)resorcinol (**II-43)** (^{1}H NMR; 400 MHz; $CDCl_3$)



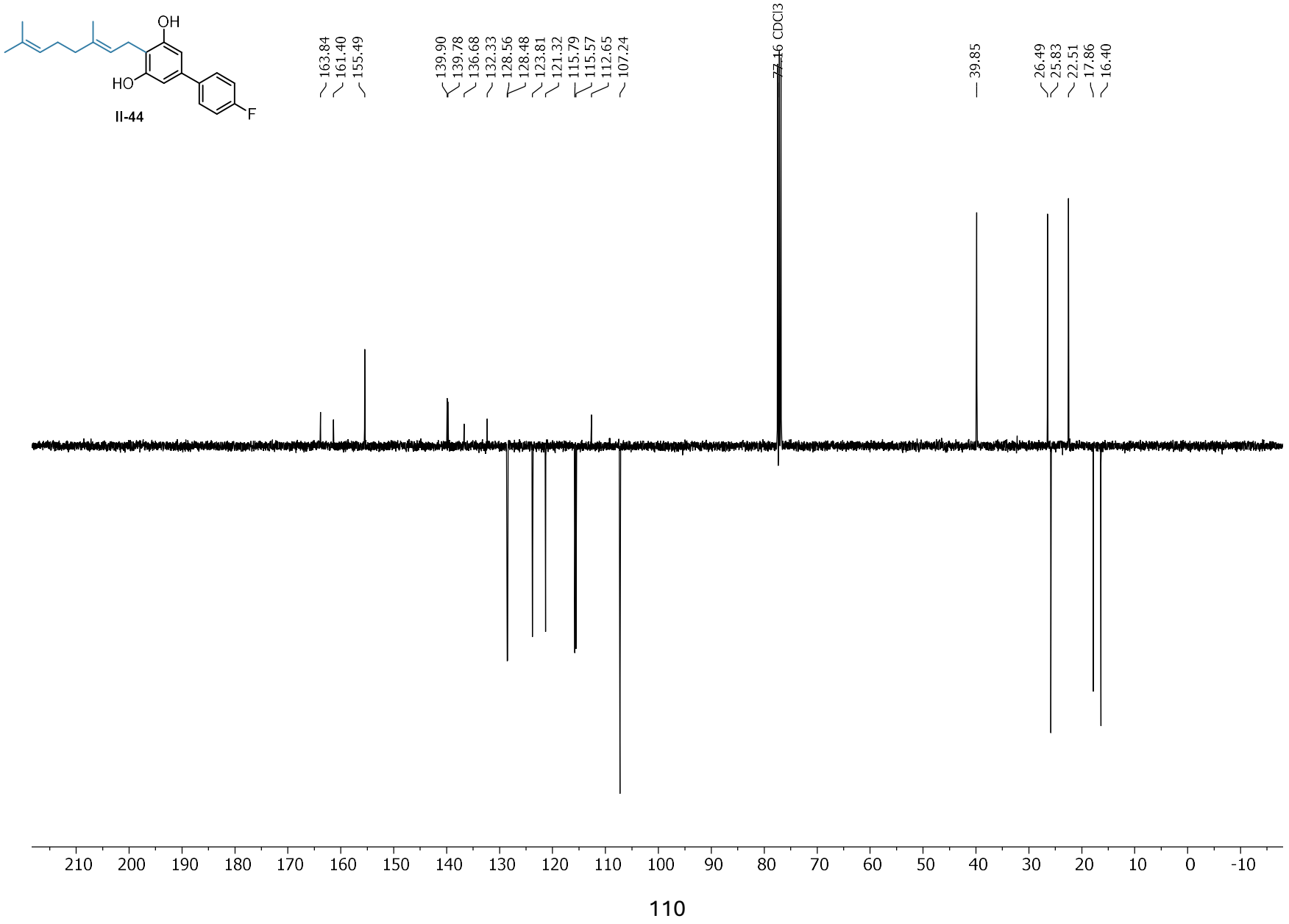
2-geranyl-5-(4-chlorophenyl)resorcinol (**II-43)** (^{13}C NMR; 101 MHz; $CDCl_3$)



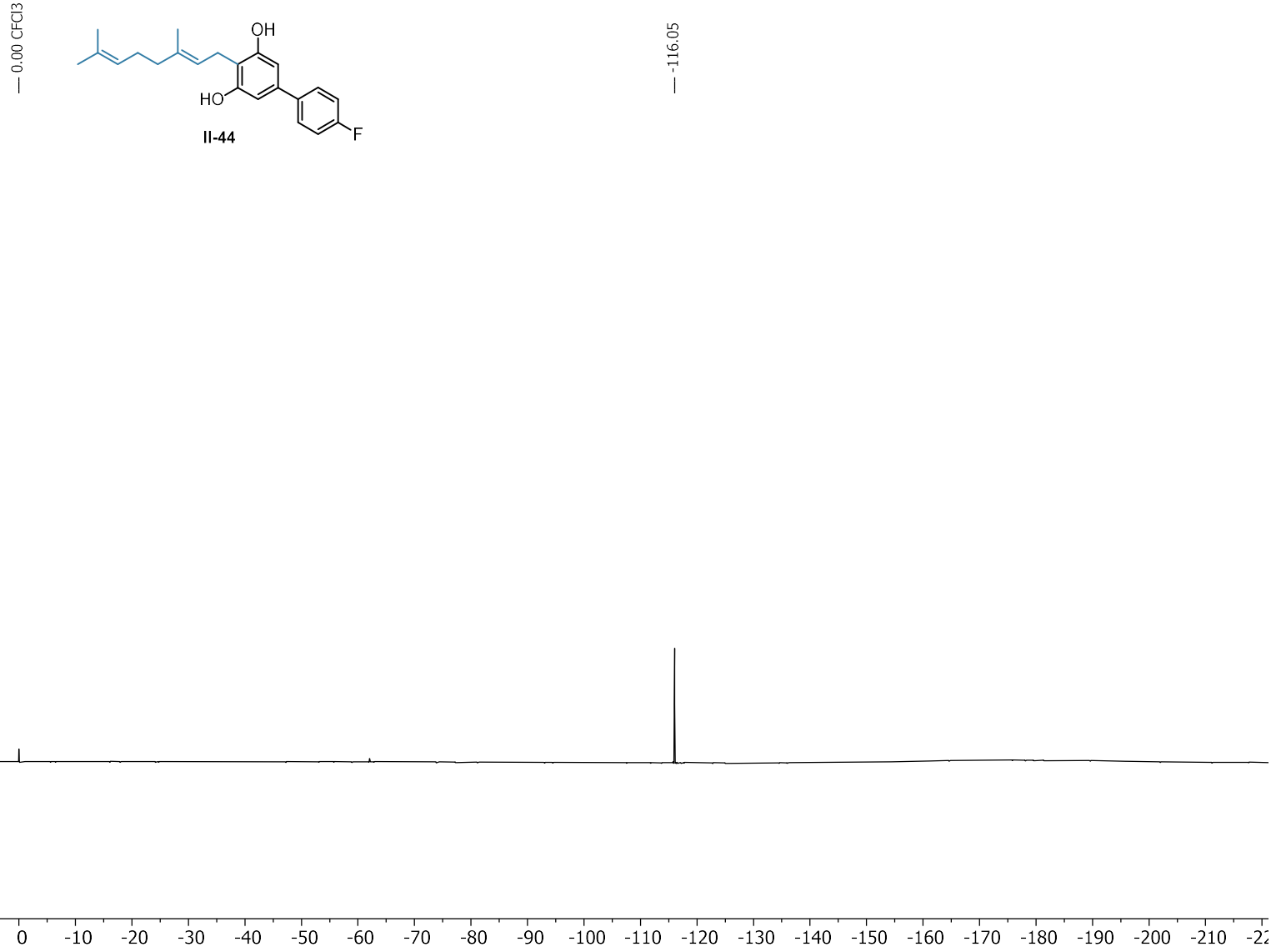
2-geranyl-5-(4-fluorophenyl)resorcinol (**II-44)** (^{1}H NMR; 400 MHz; $CDCl_3$)



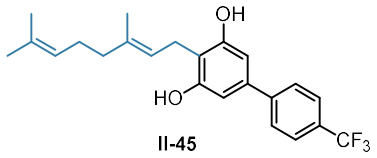
2-geranyl-5-(4-flurophenyl)resorcinol (**II-44)** (^{13}C NMR; 101 MHz; $CDCl_3$)



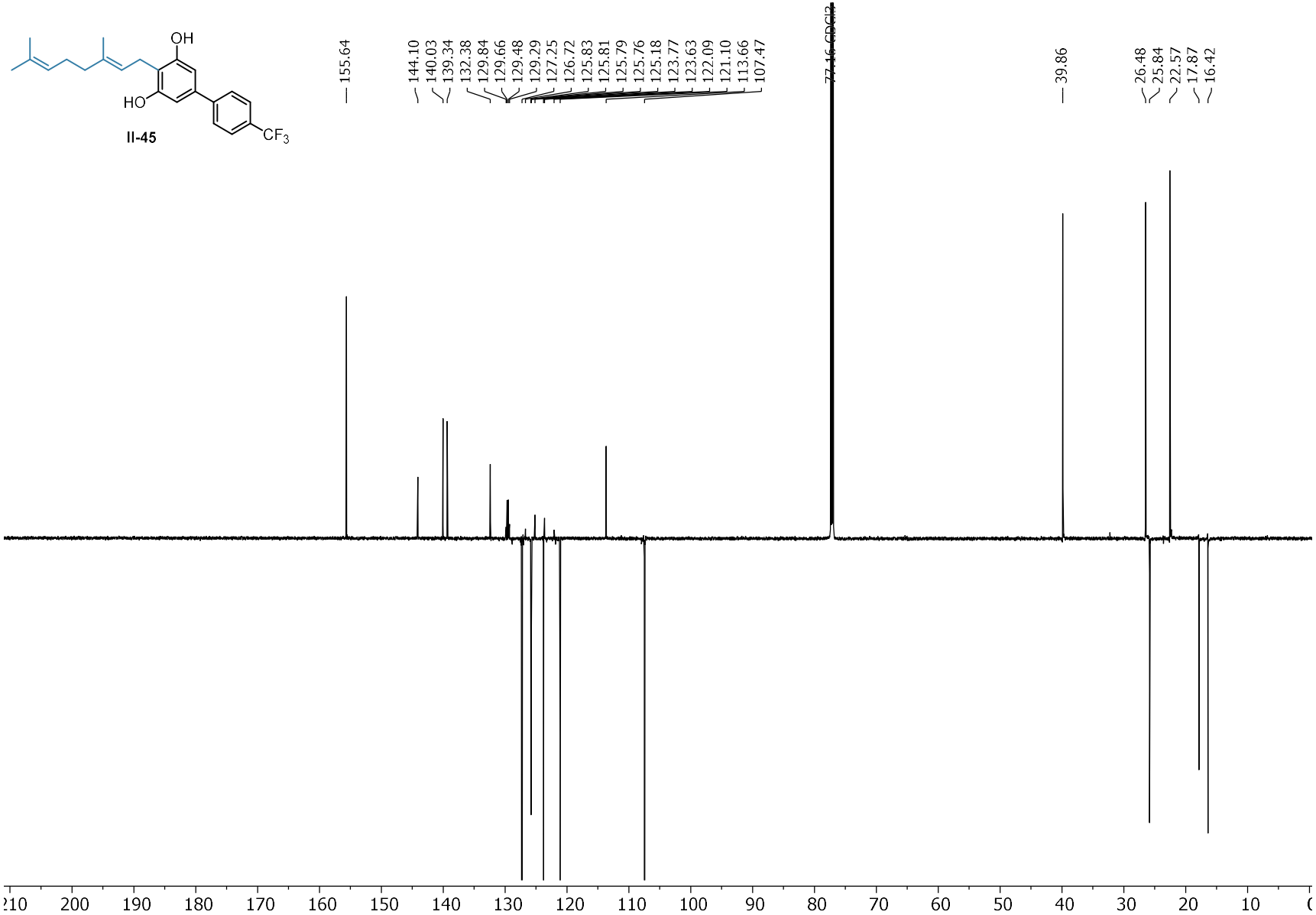
2-geranyl-5-(4-flurophenyl)resorcinol (**II-44)** (^{19}F NMR, 377 MHz, $CFCl_3$)



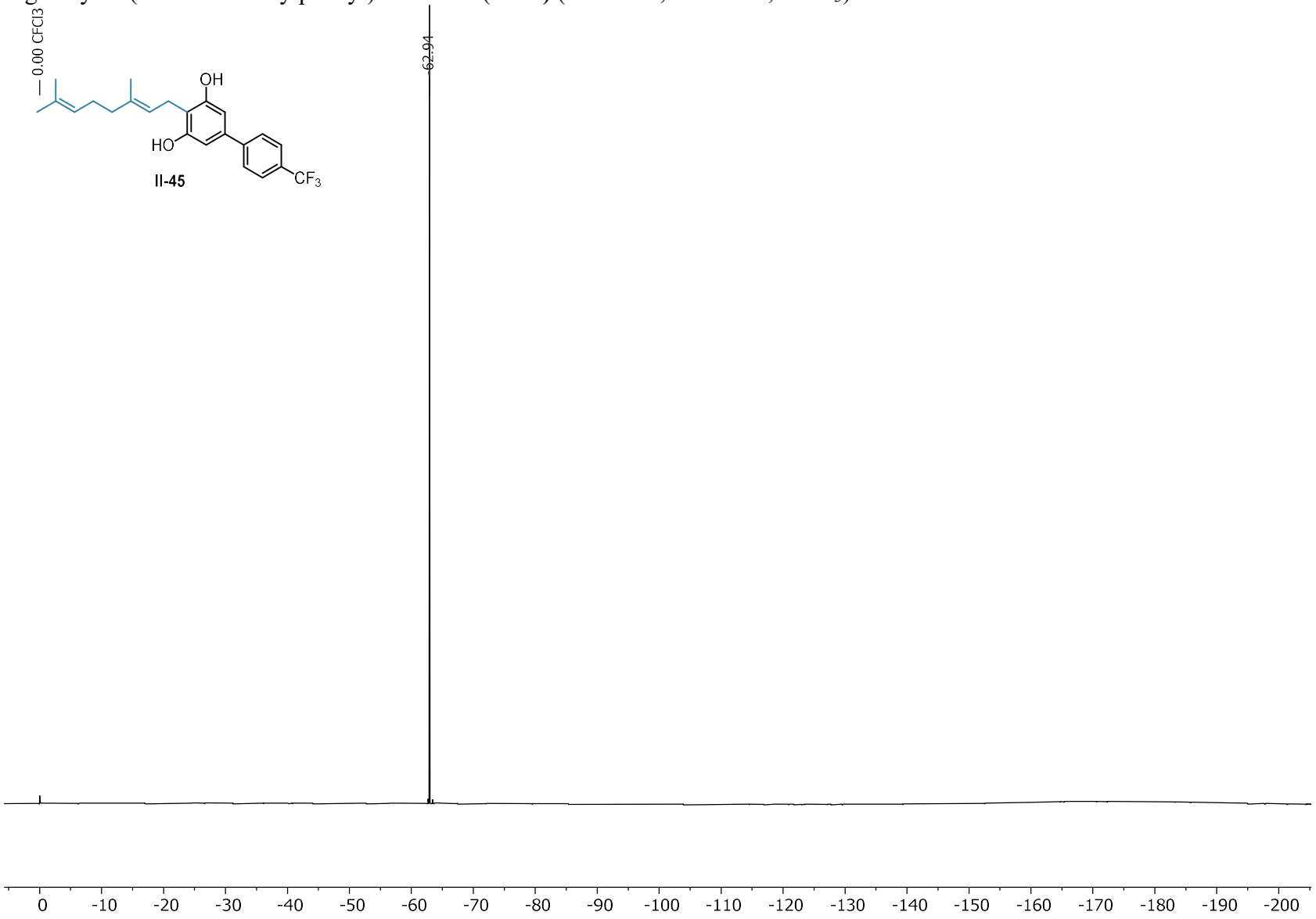
2-geranyl-5-(4-trifluoromethylphenyl)resorcinol **(II-45)** (^{1}H NMR; 400 MHz; $CDCl_3$)



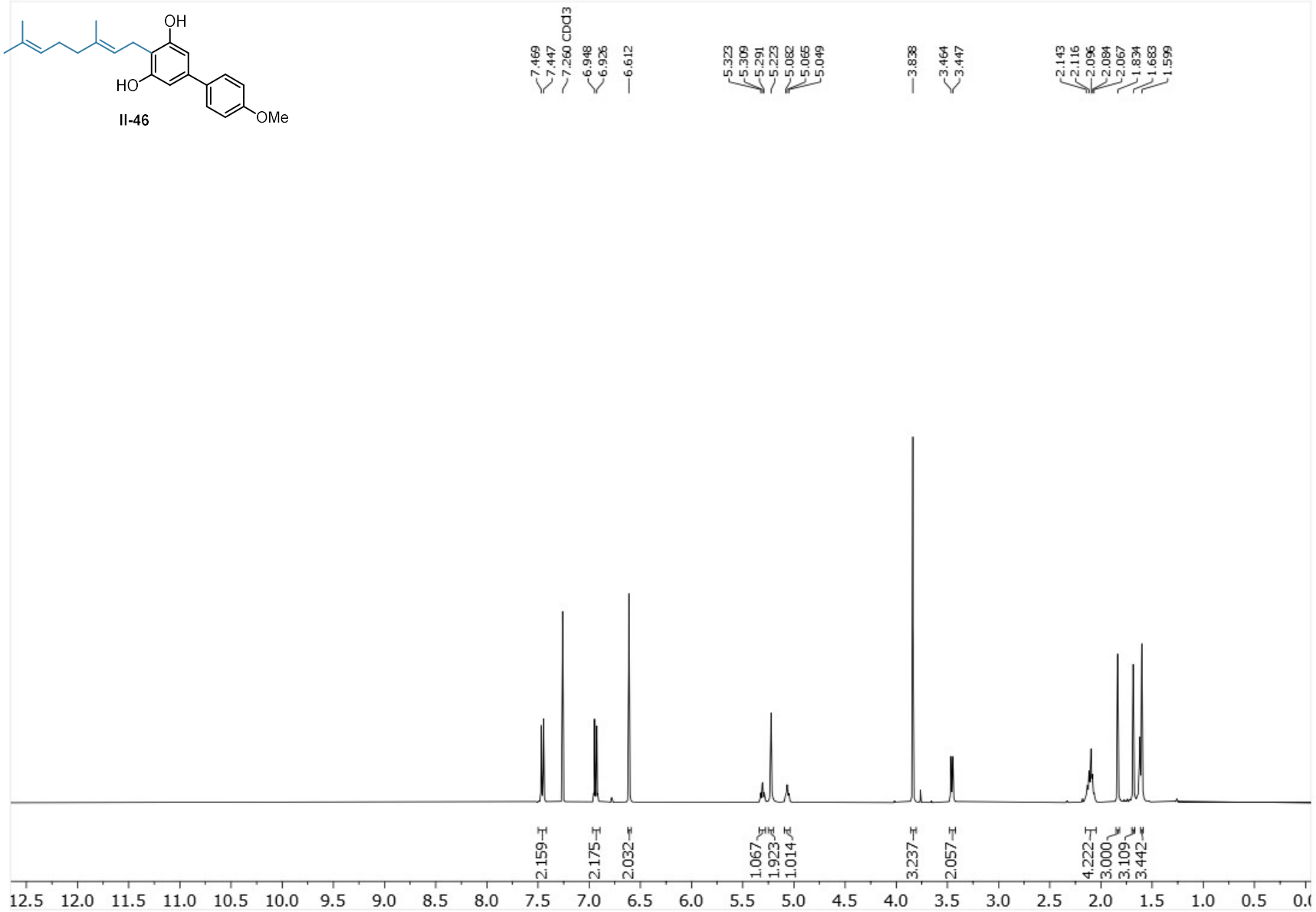
2-geranyl-5-(4-trifluromethylphenyl)resorcinol **(II-45)** (^{13}C NMR; 101 MHz; $CDCl_3$)



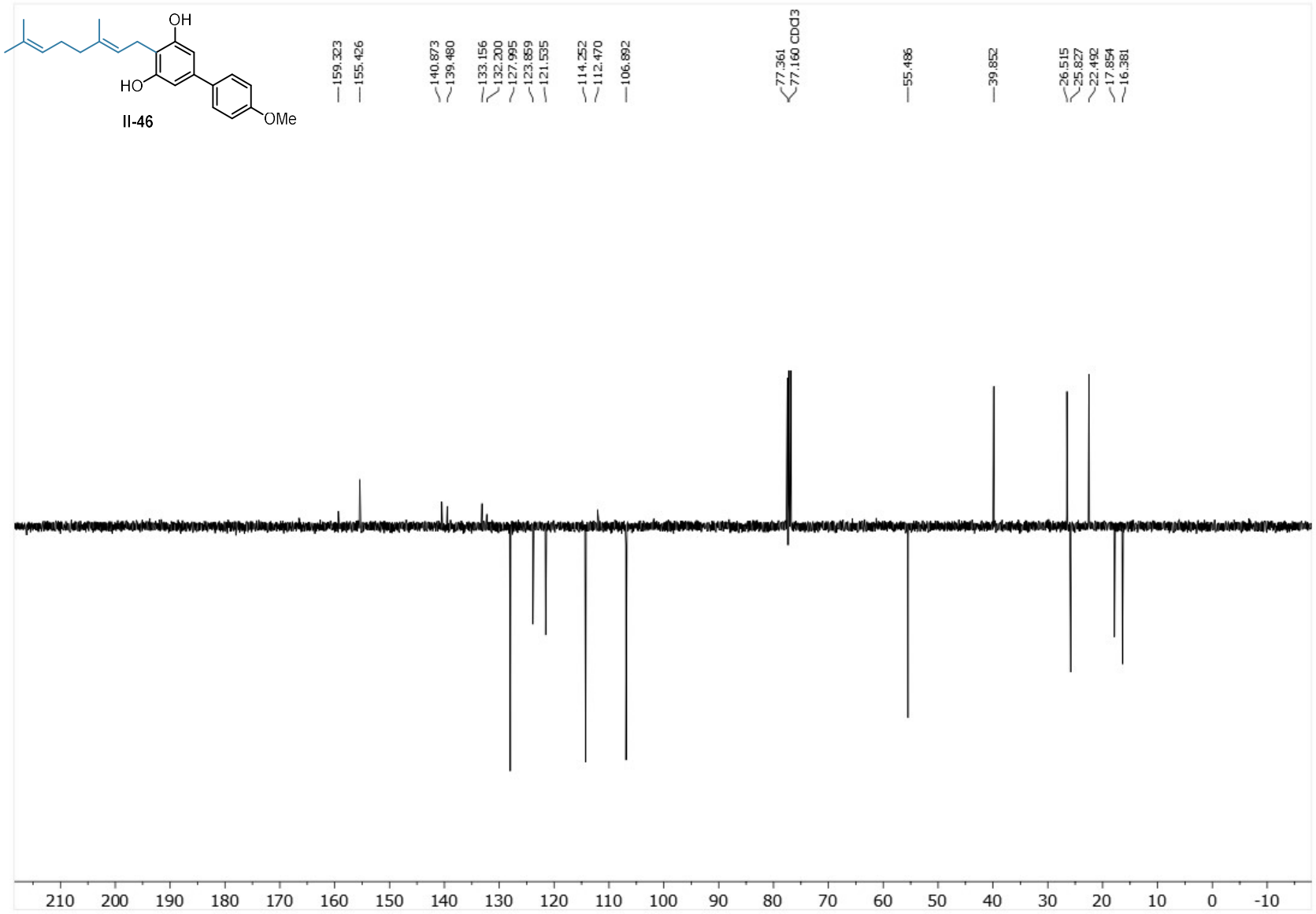
2-geranyl-5-(4-trifluromethylphenyl)resorcinol **(II-45)** (^{19}F NMR, 377 MHz, $CFCl_3$)



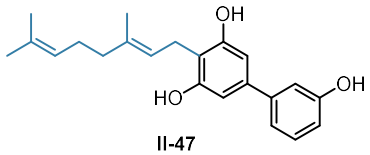
2-geranyl-5-(4-methoxyphenyl)resorcinol (**II-46)** (^{1}H NMR; 400 MHz; $CDCl_3$)



2-geranyl-5-(4-methoxyphenyl)resorcinol (**II-46)** (^{13}C NMR; 101 MHz; $CDCl_3$)

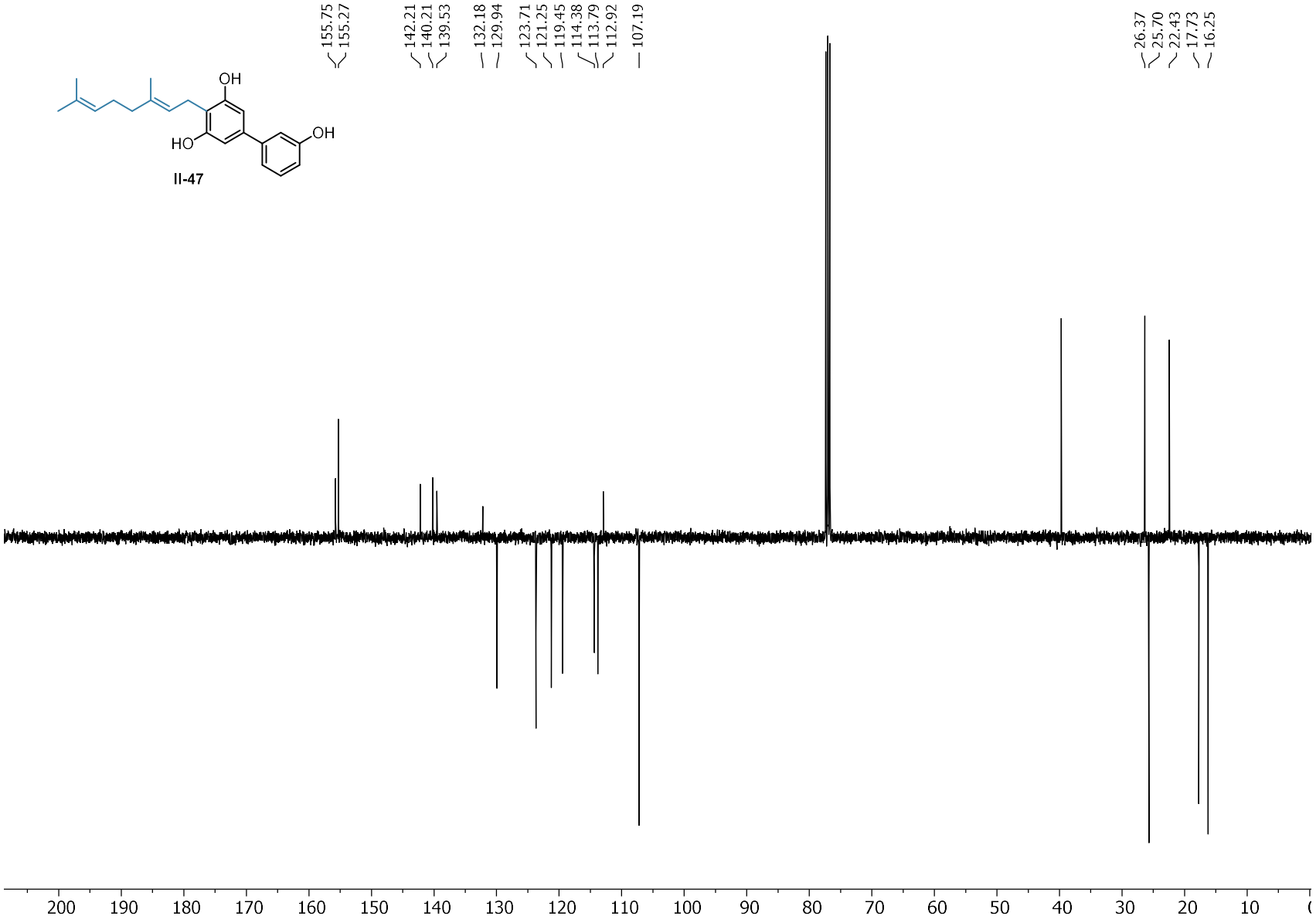


2-geranyl-5-(3-hydroxyphenyl)resorcinol (**II-47)** (^{1}H NMR; 400 MHz; $CDCl_3$)

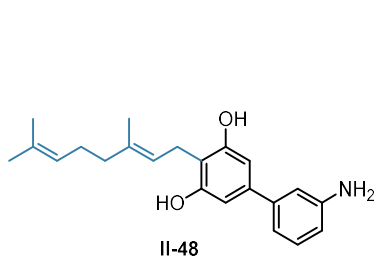


II-47

2-geranyl-5-(3-hydroxyphenyl)resorcinol **(II-47)** (^{13}C NMR; 101 MHz; $CDCl_3$)

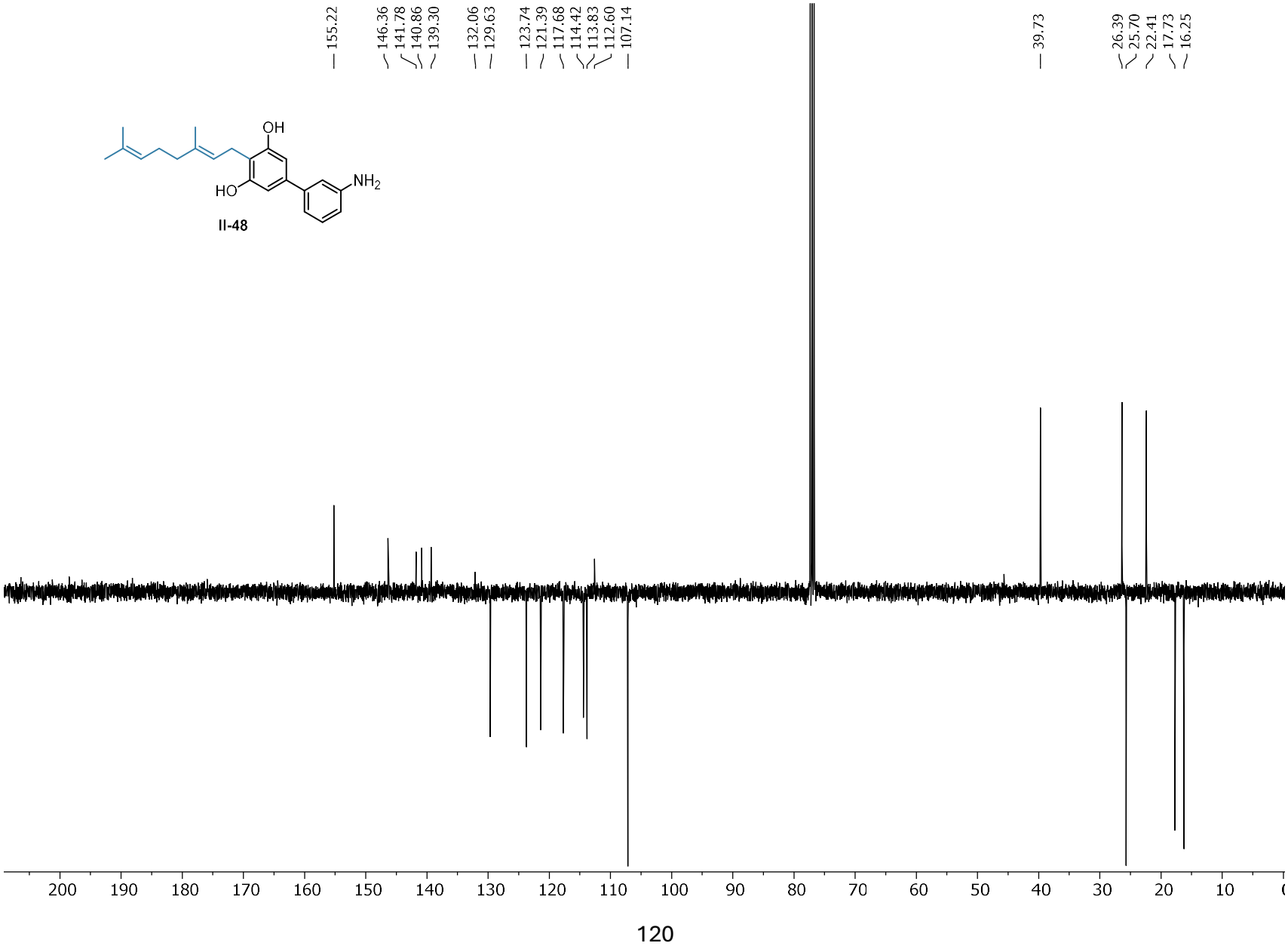


2-geranyl-5-(3-aminophenyl)resorcinol (**II-48)** (^{1}H NMR; 400 MHz; $CDCl_3$)

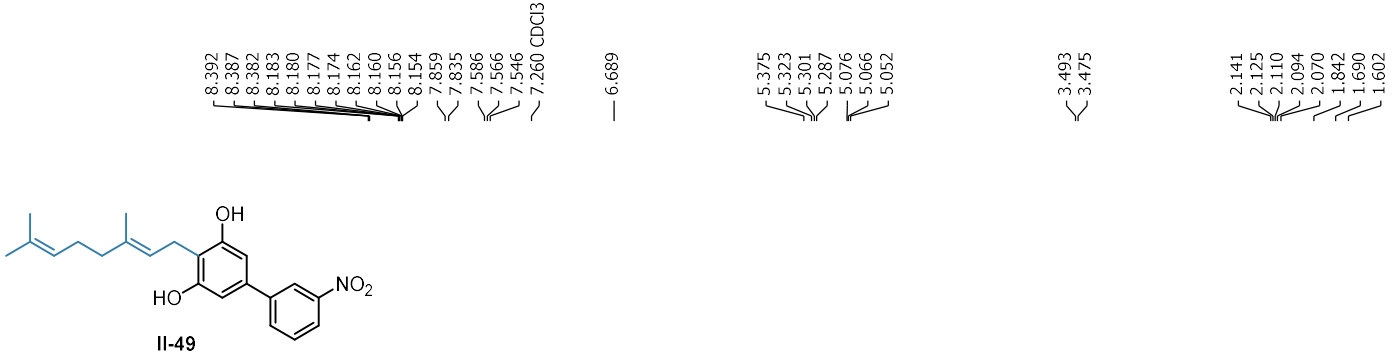


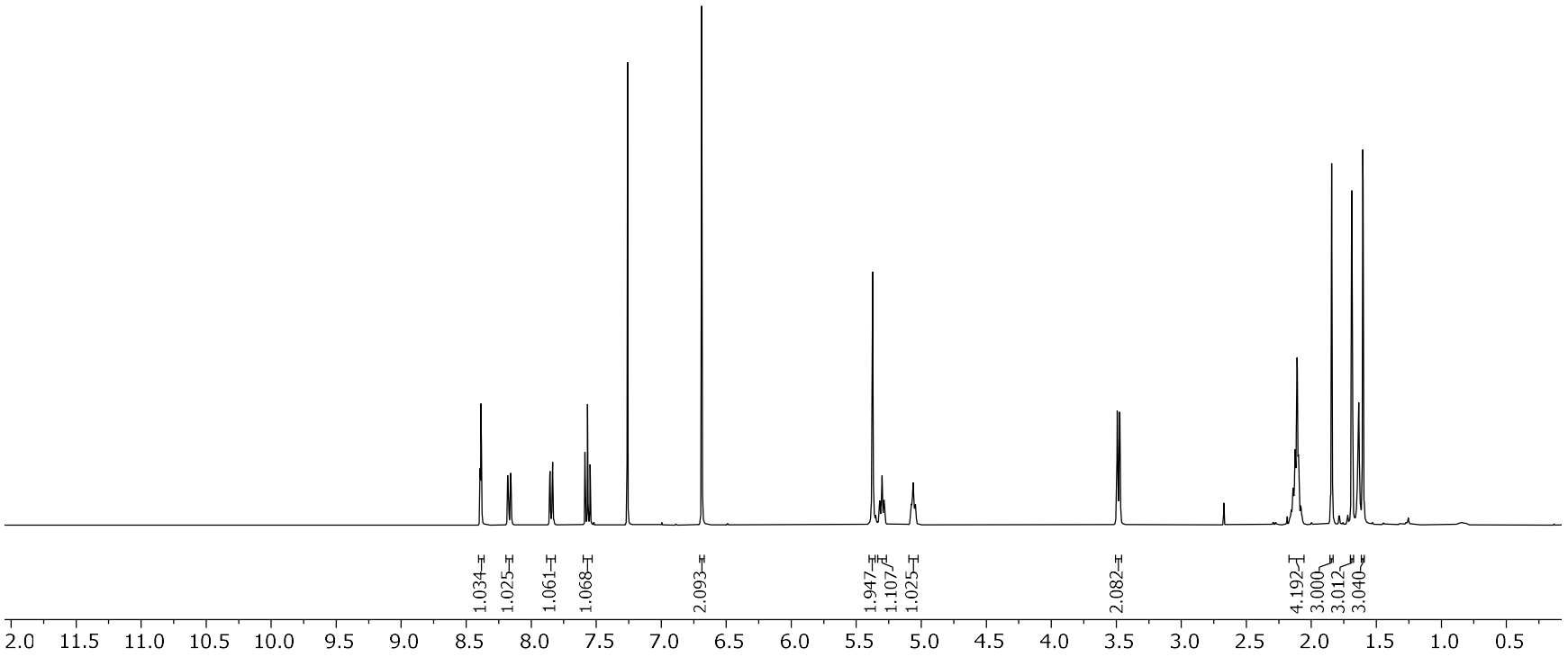
II-48

2-geranyl-5-(3-aminophenyl)resorcinol (**II-48)** (^{13}C NMR; 101 MHz; $CDCl_3$)

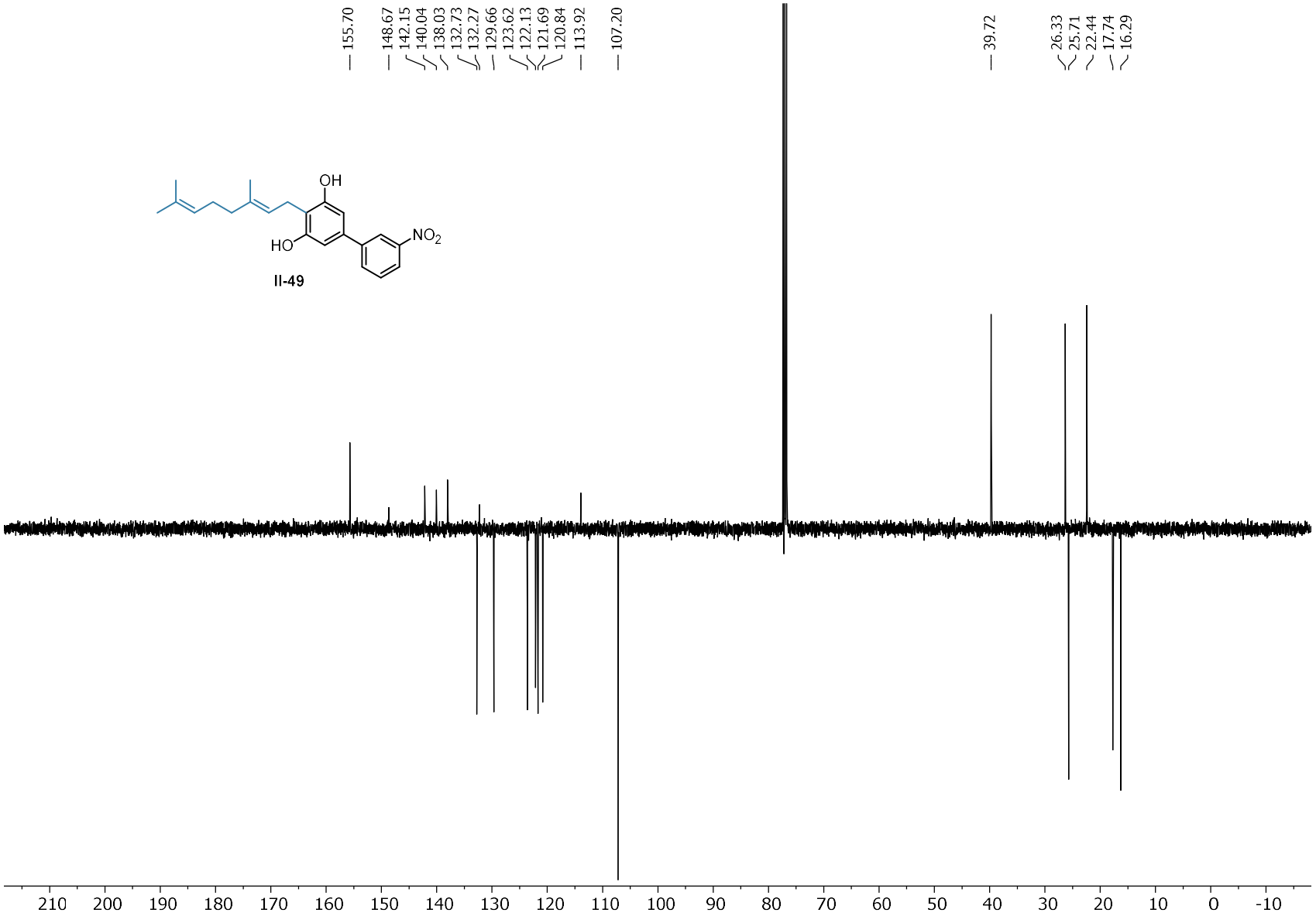


2-geranyl-5-(3-nitrophenyl)resorcinol (**II-49)** (^{1}H NMR; 400 MHz; $CDCl_3$)

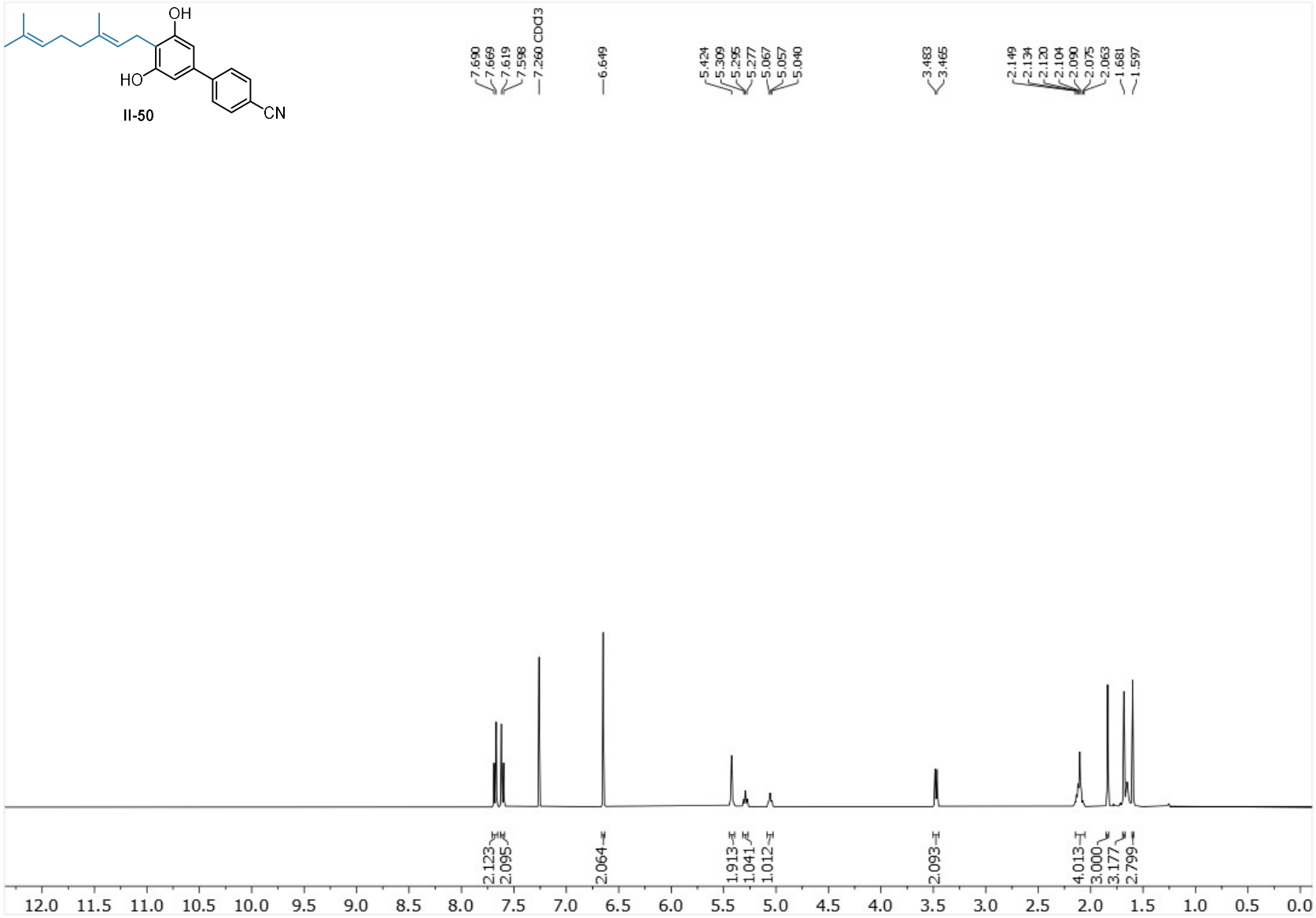




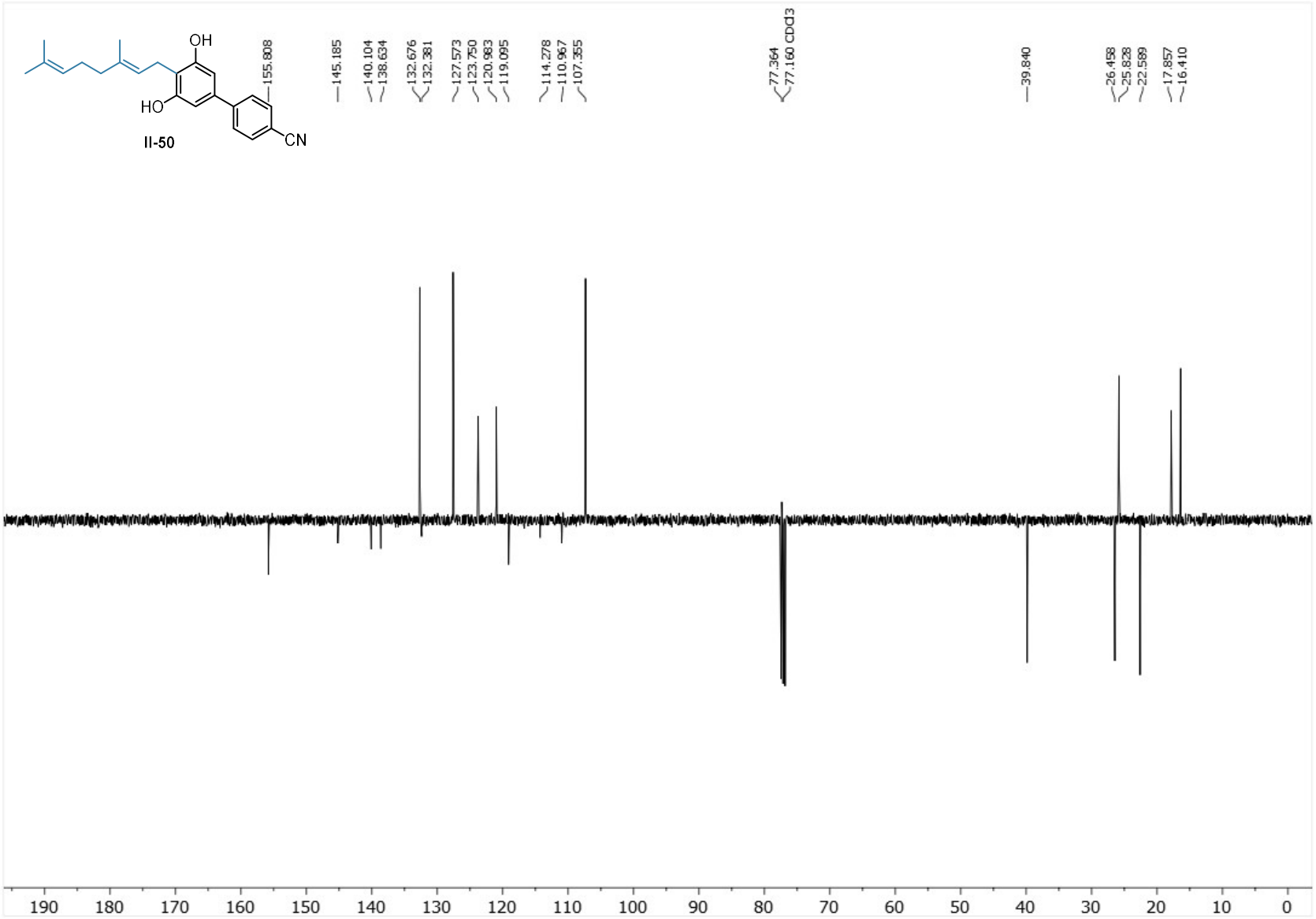
2-geranyl-5-(3-nitrophenyl)resorcinol (**II-49**) (^{13}C NMR; 101 MHz; $CDCl_3$)



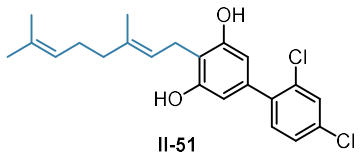
2-geranyl-5-(4-cyanophenyl)resorcinol (**II-50)** (^{1}H NMR; 400 MHz; $CDCl_3$)



2-geranyl-5-(4-cyanophenyl)resorcinol (**II-50)** (^{13}C NMR; 101 MHz; $CDCl_3$)

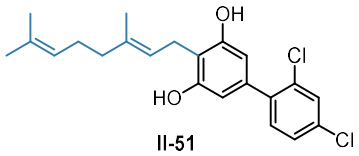


2-geranyl-5-(2,4-dichlorophenyl)resorcinol **(II-51)** (^{1}H NMR; 700 MHz; $CDCl_3$)

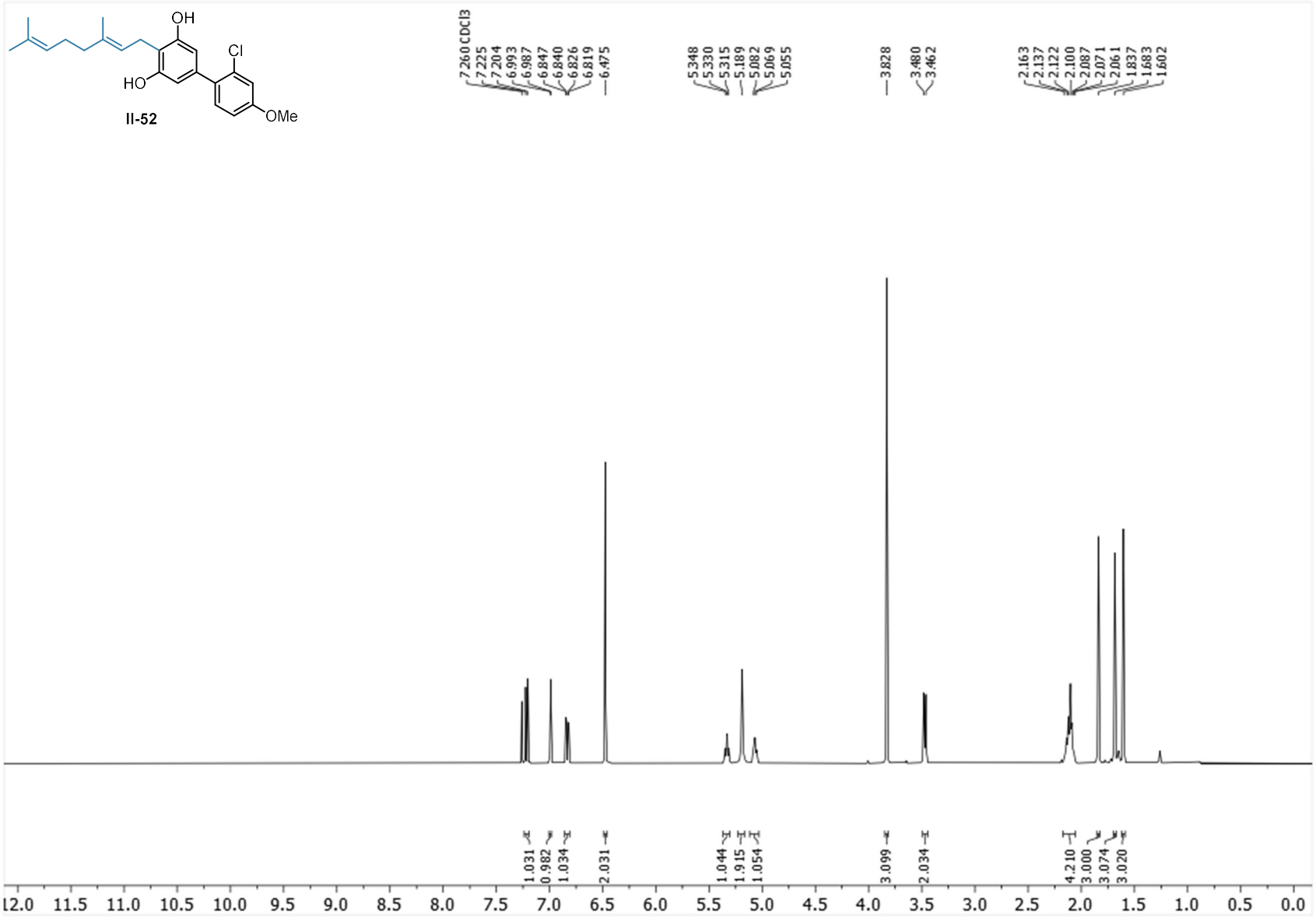


II-51

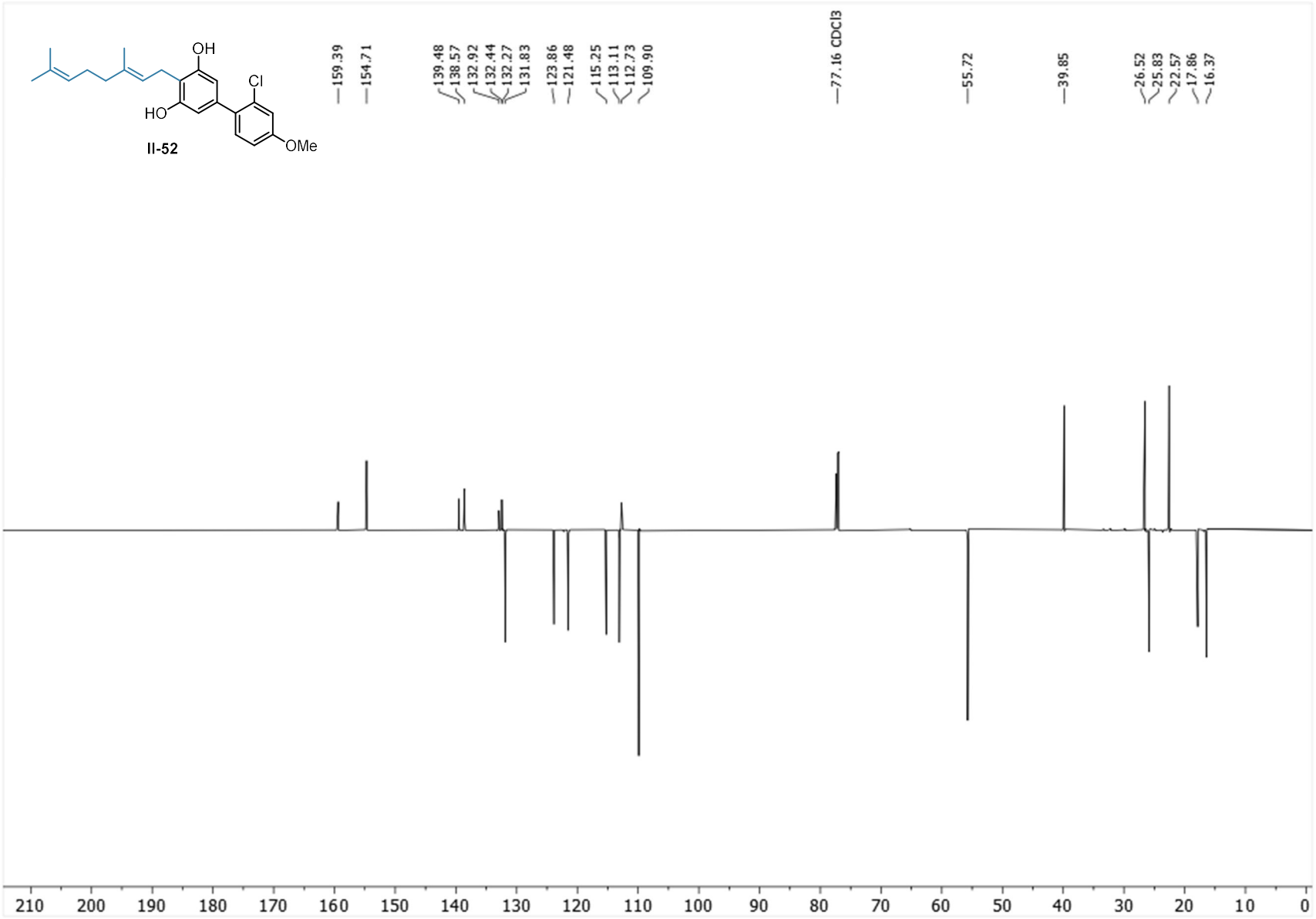
2-geranyl-5-(2,4-dichlorophenyl)resorcinol **(II-51)** (^{13}C NMR; 176 MHz; $CDCl_3$)



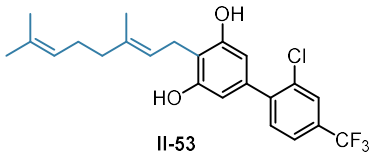
2-geranyl-5-(2-chloro-4-methoxyphenyl)resorcinol (**II-52)** (^{1}H NMR; 700 MHz; $CDCl_3$)



2-geranyl-5-(2-chloro-4-methoxyphenyl)resorcinol (**II-52)** (^{13}C NMR; 176 MHz; $CDCl_3$)

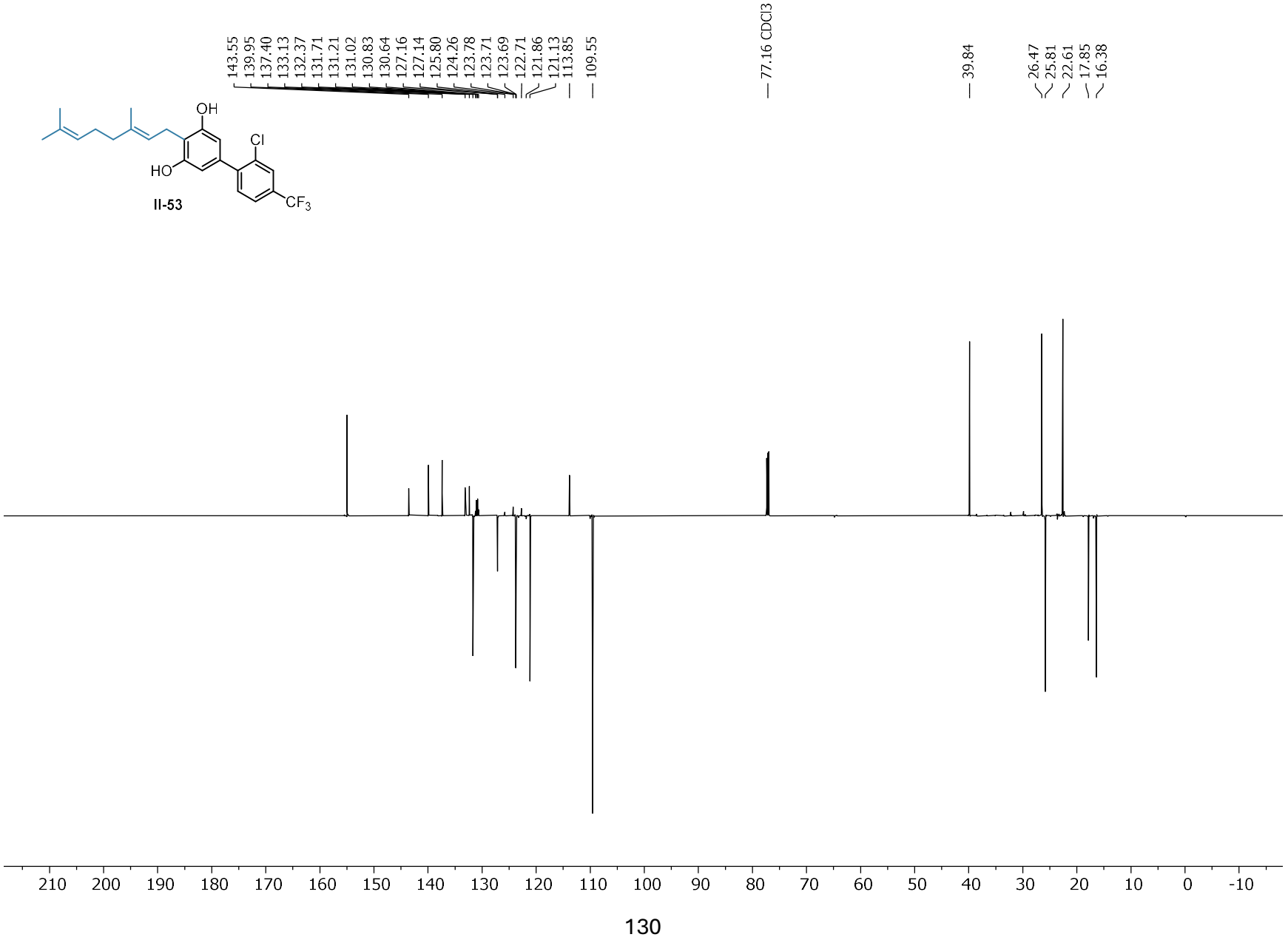


2-geranyl-5-(2-chloro-4-trifluoromethylphenyl)resorcinol **(II-53)** (^{1}H NMR; 700 MHz; $CDCl_3$)

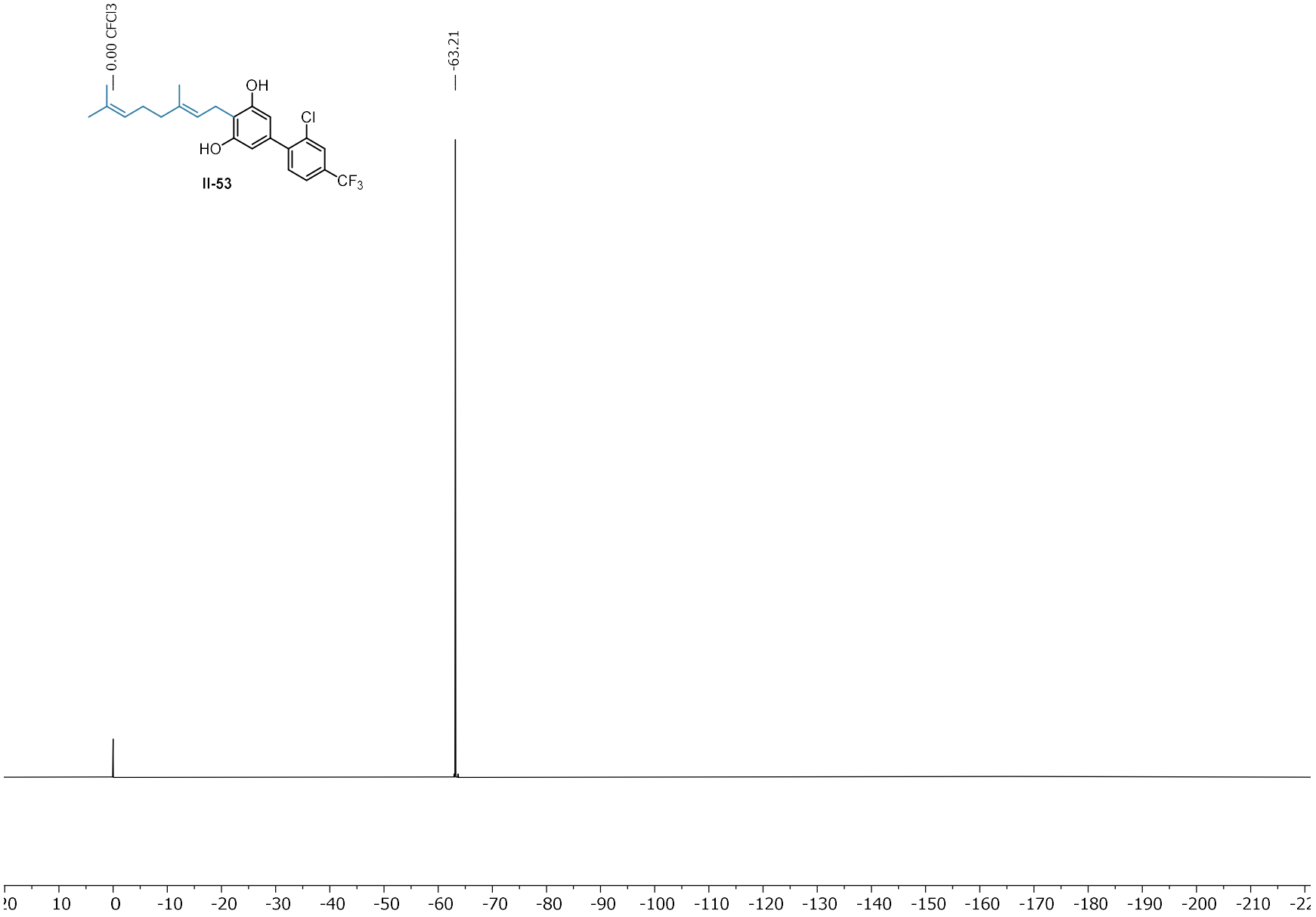


II-53

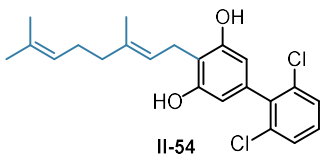
2-geranyl-5-(2-chloro-4-trifluoromethylphenyl)resorcinol **(II-53)** (^{13}C NMR; 176 MHz; $CDCl_3$)



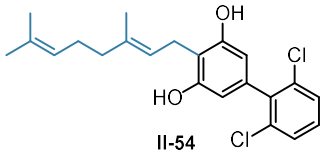
2-geranyl-5-(2-chloro-4-trifluoromethylphenyl)resorcinol **(II-53)** (^{19}F NMR, 377 MHz, $CDCl_3$)



2-geranyl-5-(2,6-dichlorophenyl)resorcinol **(II-54)** (^{1}H NMR; 700 MHz; $CDCl_3$)

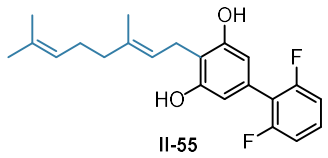


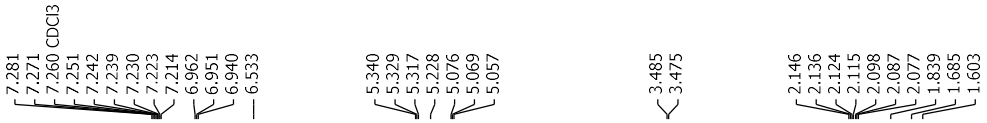
2-geranyl-5-(2,6-dichlorophenyl)resorcinol **(II-54)** (^{13}C NMR; 176 MHz; $CDCl_3$)

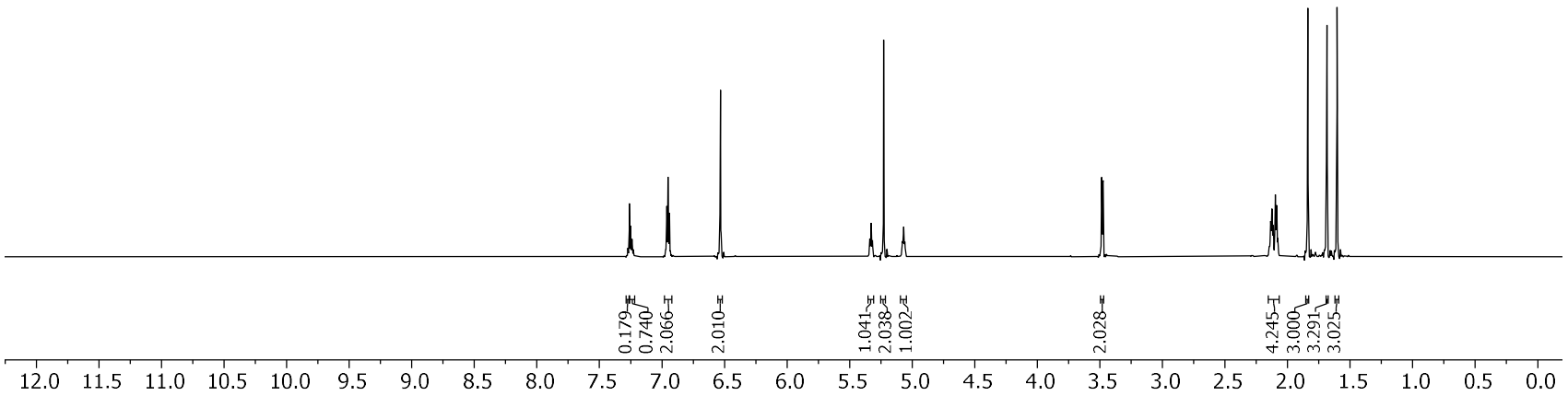


II-54

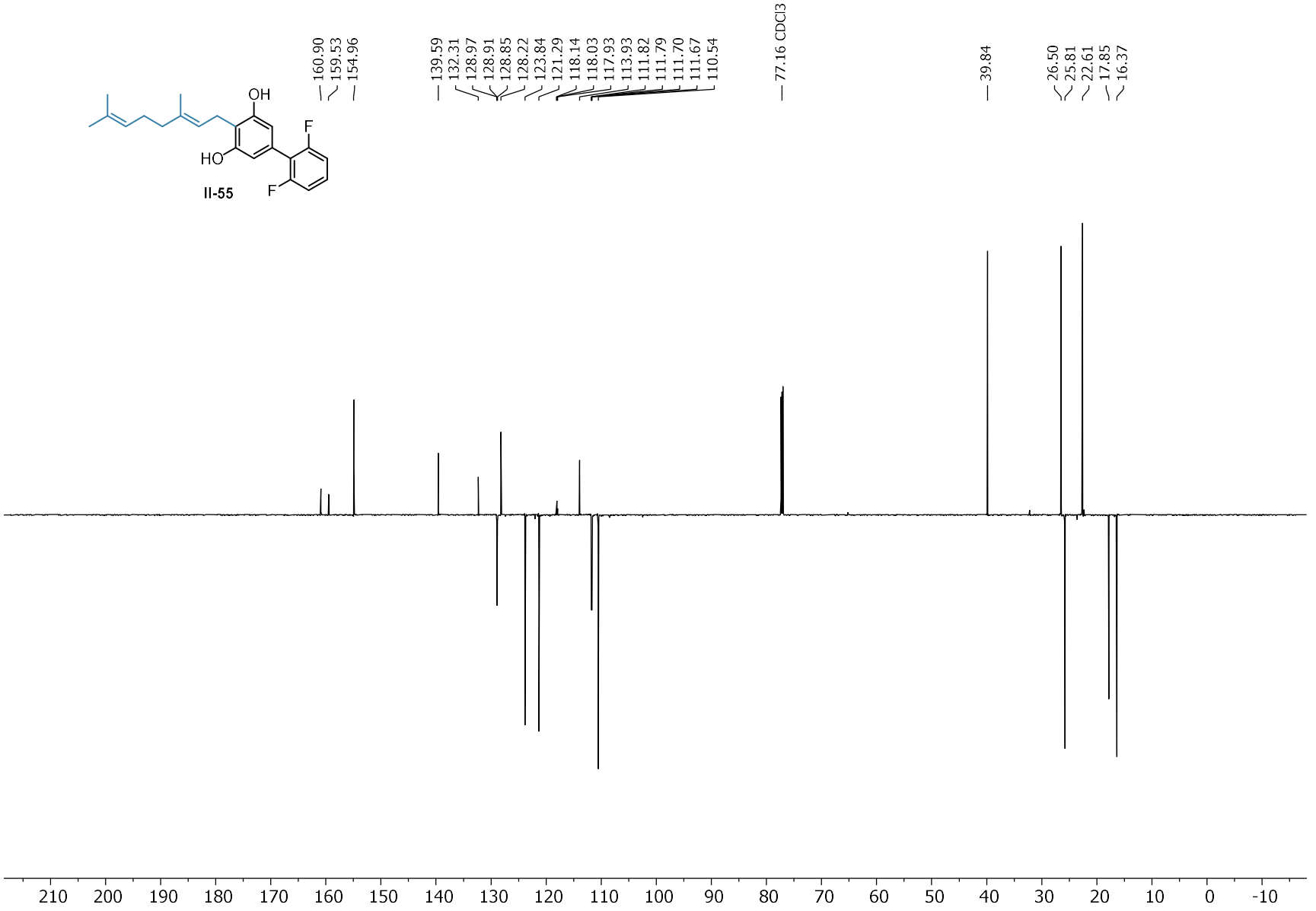
2-geranyl-5-(2,6-difluorophenyl)resorcinol (**II-55)** (^{1}H NMR; 700 MHz; $CDCl_3$)



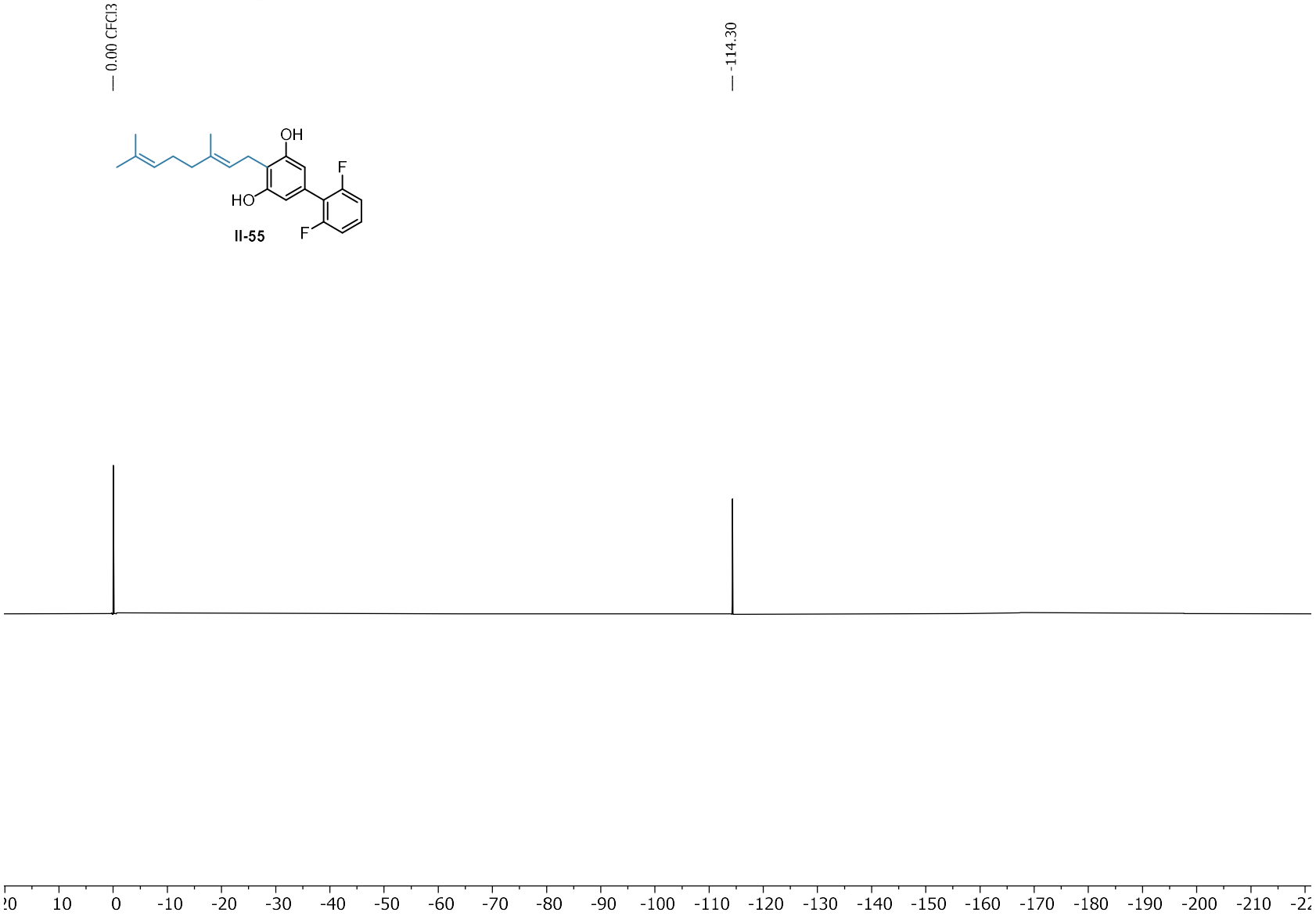




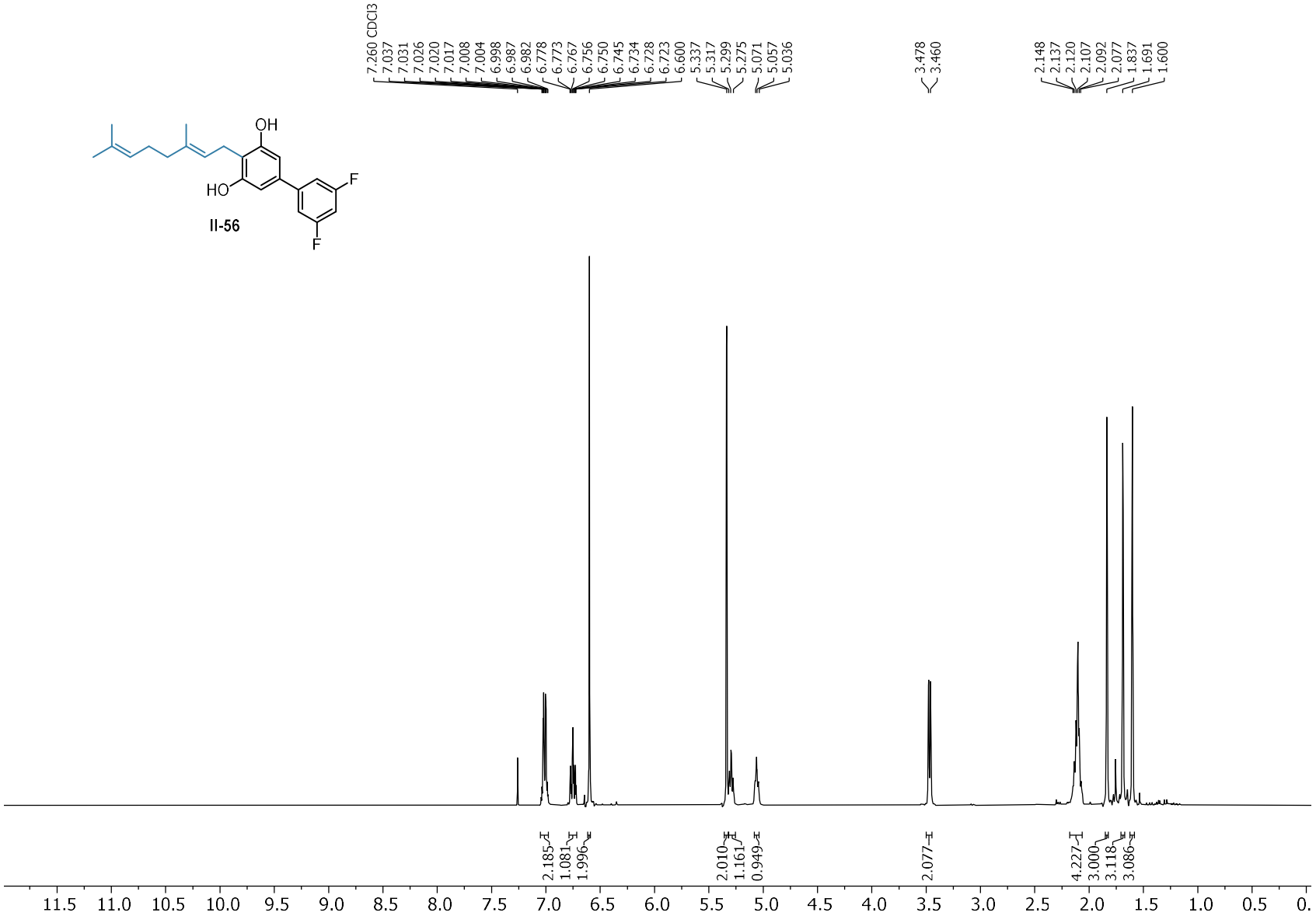
2-geranyl-5-(2,6-difluorophenyl)resorcinol (**II-55)** (^{13}C NMR; 176 MHz; $CDCl_3$)



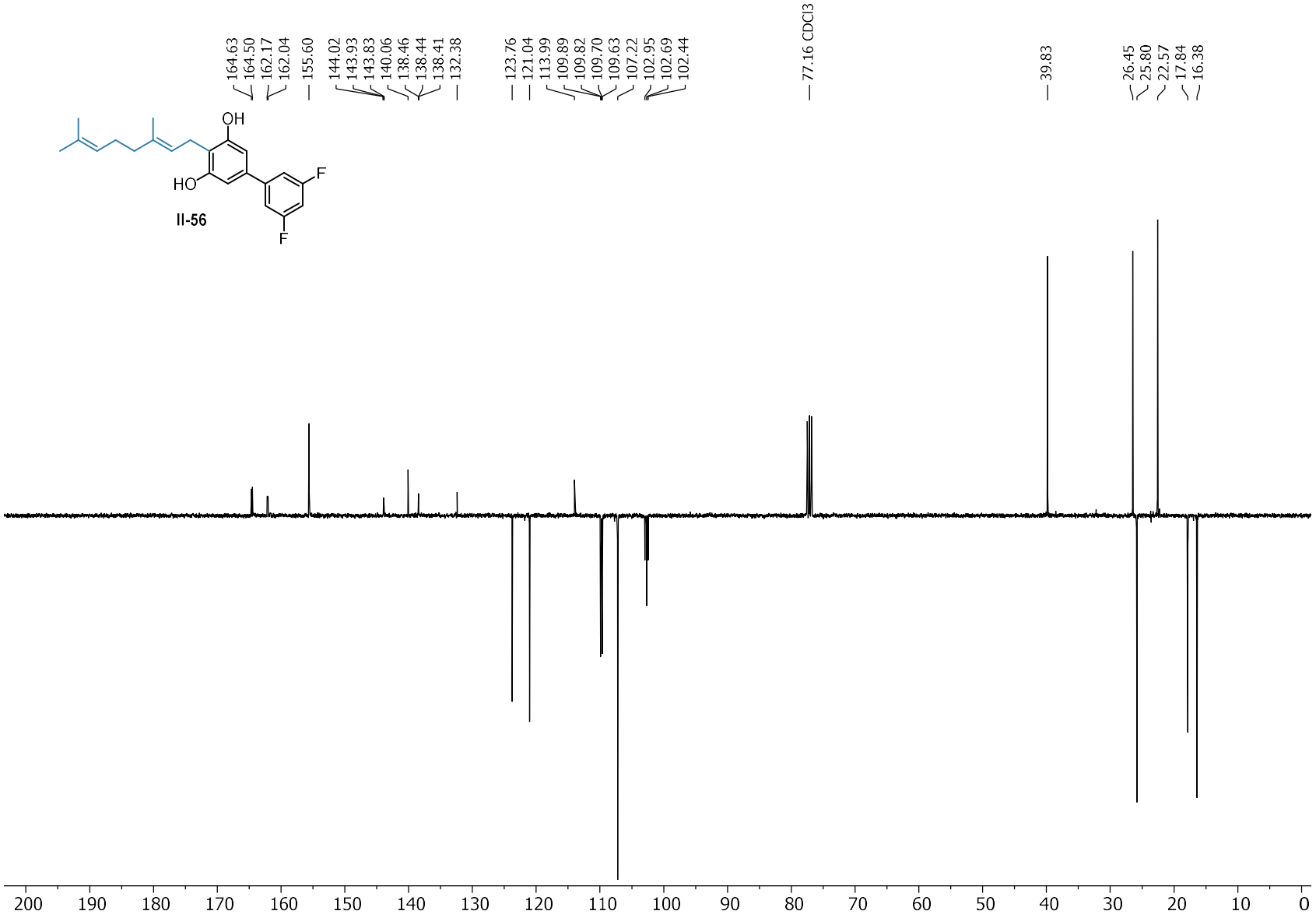
2-geranyl-5-(2,6-difluorophenyl)resorcinol **(II-55)** (^{19}F NMR, 377 MHz, $CDCl_3$)



2-geranyl-5-(3,5-difluorophenyl)resorcinol (**II-56)** (^{1}H NMR; 400 MHz; $CDCl_3$)

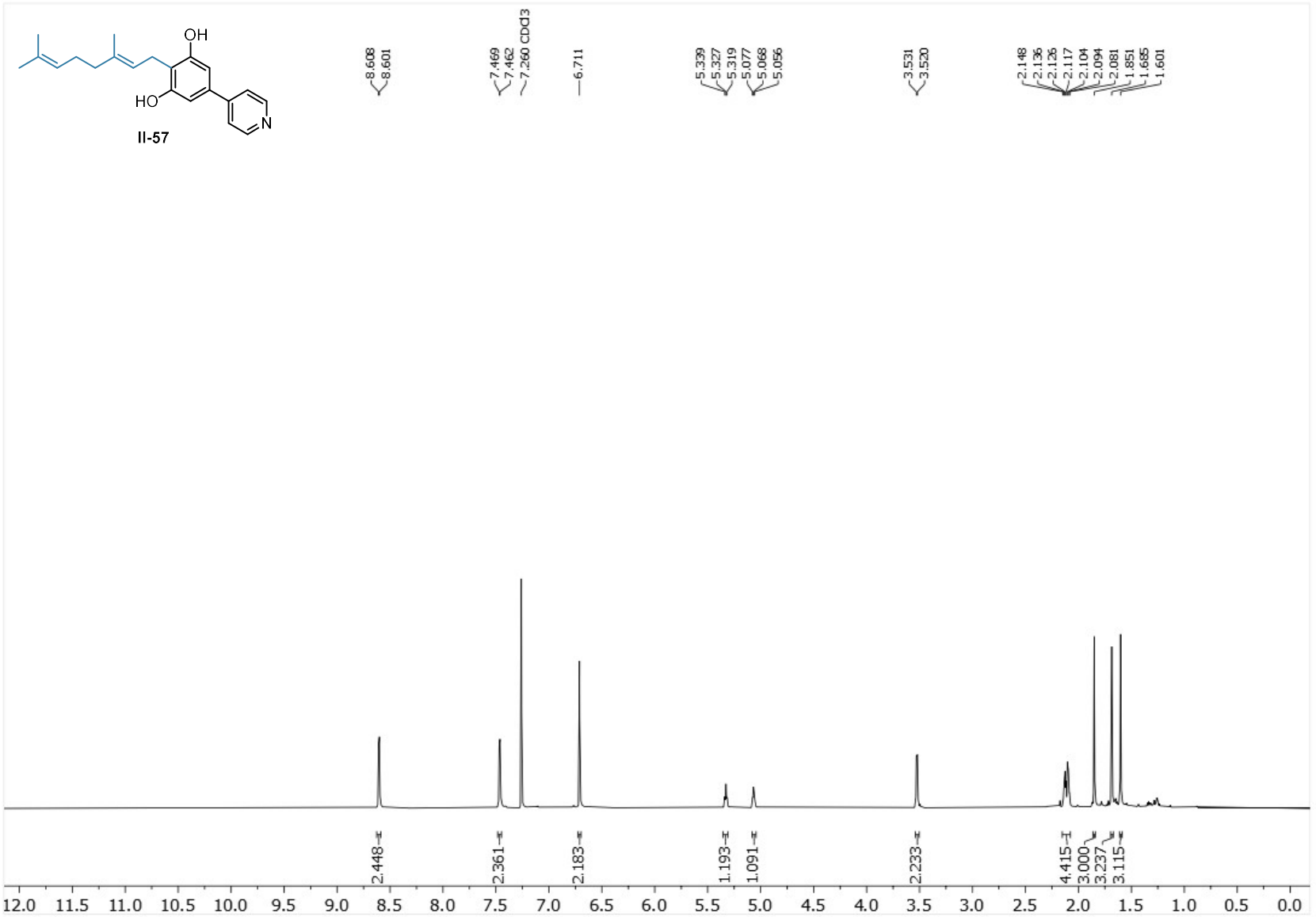


2-geranyl-5-(3,5-difluorophenyl)resorcinol (**II-56)** (^{13}C NMR; 101 MHz; $CDCl_3$)

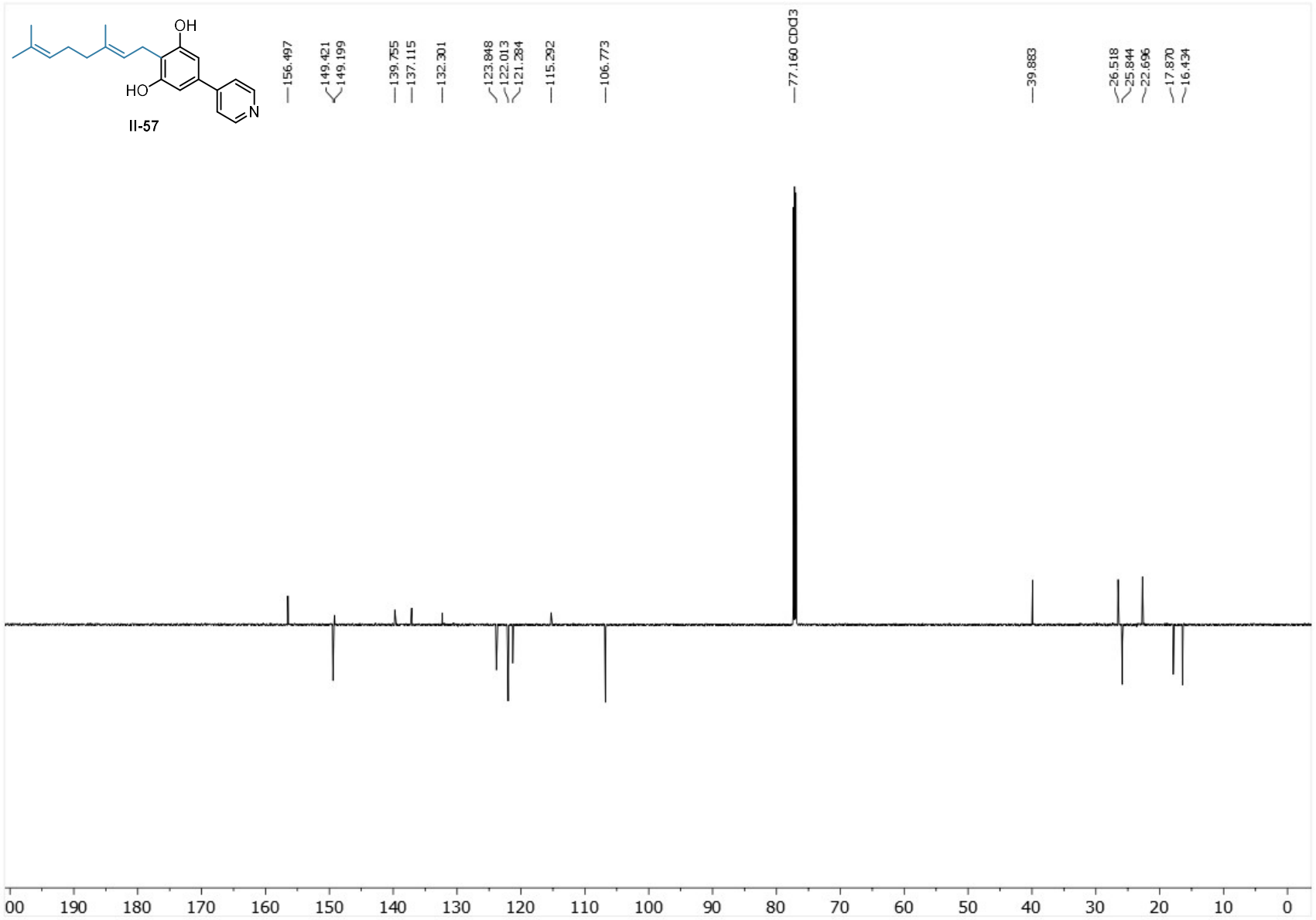


2-geranyl-5-(3,5-difluorophenyl)resorcinol **(II-56)** (^{19}F NMR, 377 MHz, $CDCl_3$)

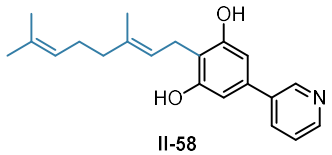
2-geranyl-5-(4-pyridinyl)resorcinol (**II-57)** (^{1}H NMR; 700 MHz; $CDCl_3$)



2-geranyl-5-(4-pyridinyl)resorcinol (**II-57)** (^{13}C NMR; 176 MHz; $CDCl_3$)

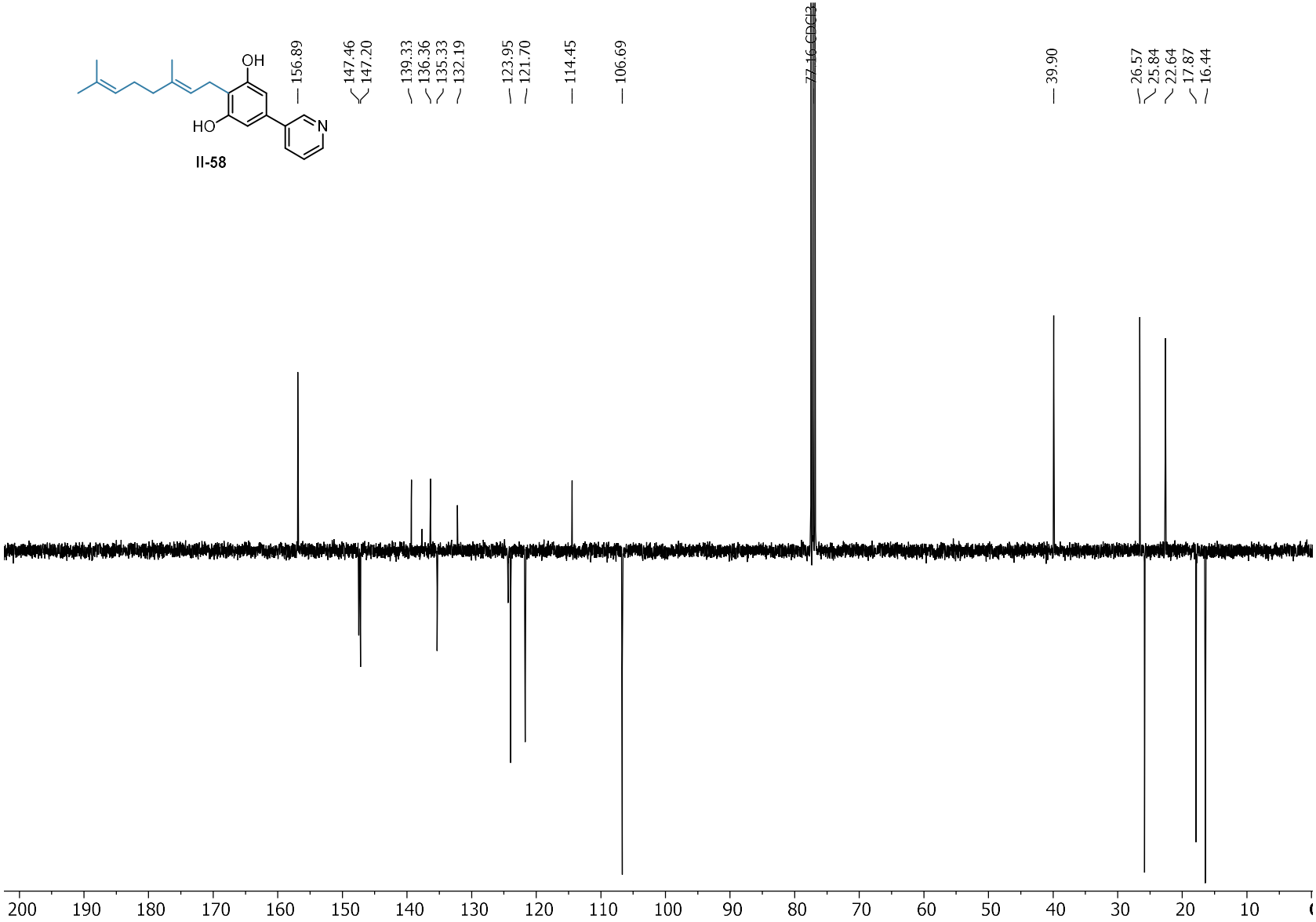


2-geranyl-5-(3-pyridinyl)resorcinol (**II-58)** (^{1}H NMR; 400 MHz; $CDCl_3$)

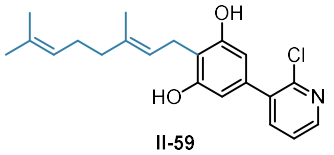


II-58

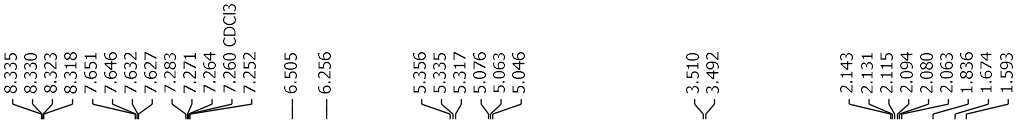
2-geranyl-5-(3-pyridinyl)resorcinol (**II-58)** (^{13}C NMR; 101 MHz; $CDCl_3$)

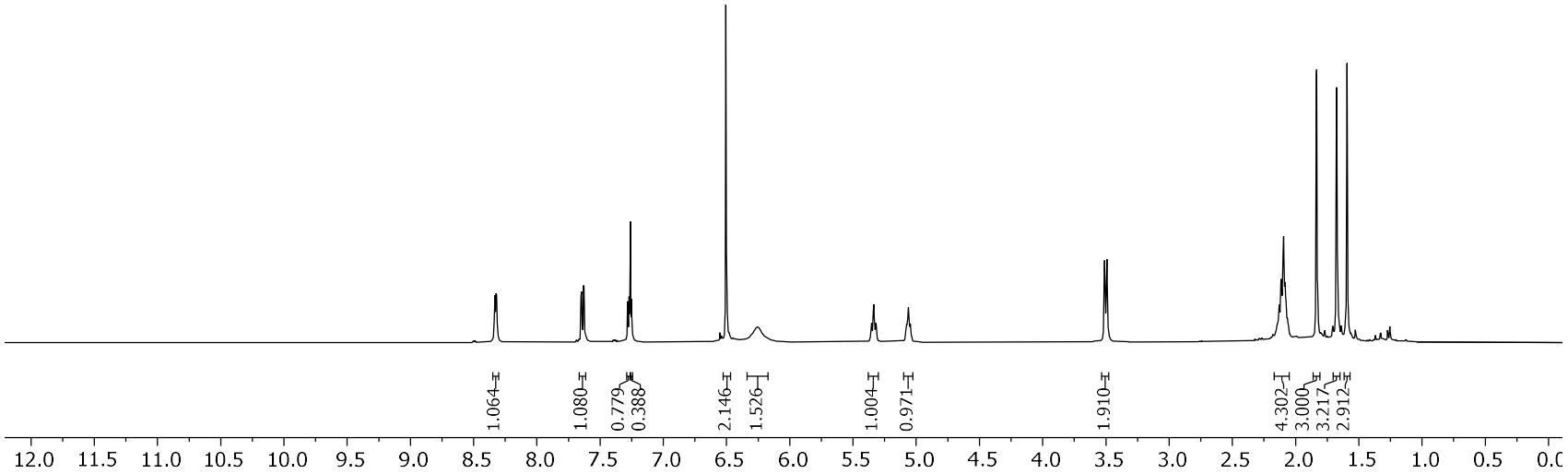


2-geranyl-5-(2-chloropyridin-3-yl)resorcinol **(II-59)** (^{1}H NMR; 700 MHz; $CDCl_3$)

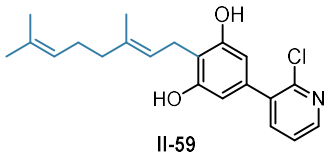


II-59



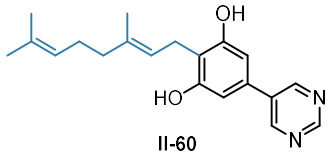


2-geranyl-5-(2-chloropyridin-3-yl)resorcinol (**II-59**) (^{13}C NMR; 176 MHz; $CDCl_3$)



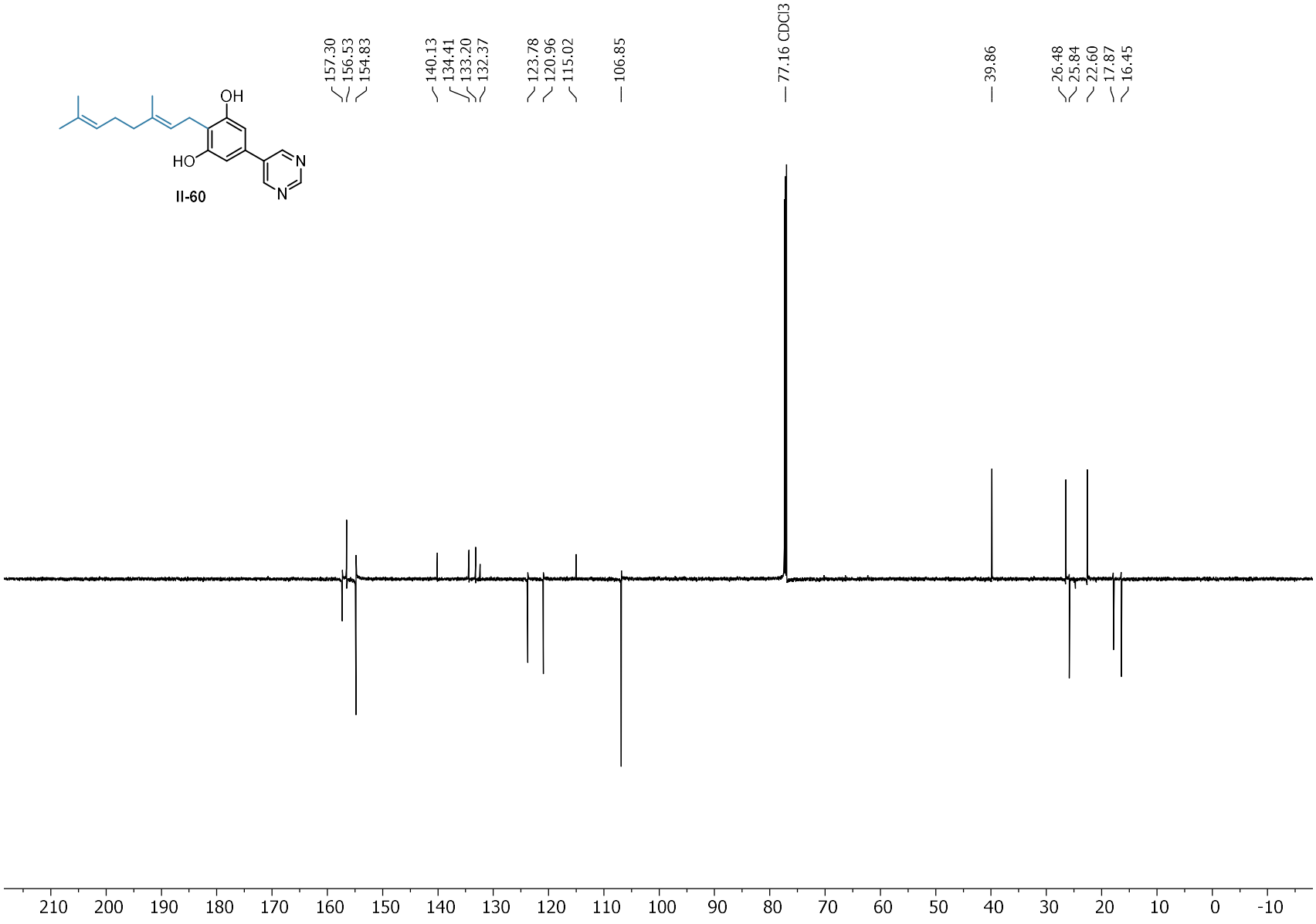
II-59

2-geranyl-5-(5-pyrimidinyl)resorcinol (**II-60)** (^{1}H NMR; 700 MHz; $CDCl_3$)

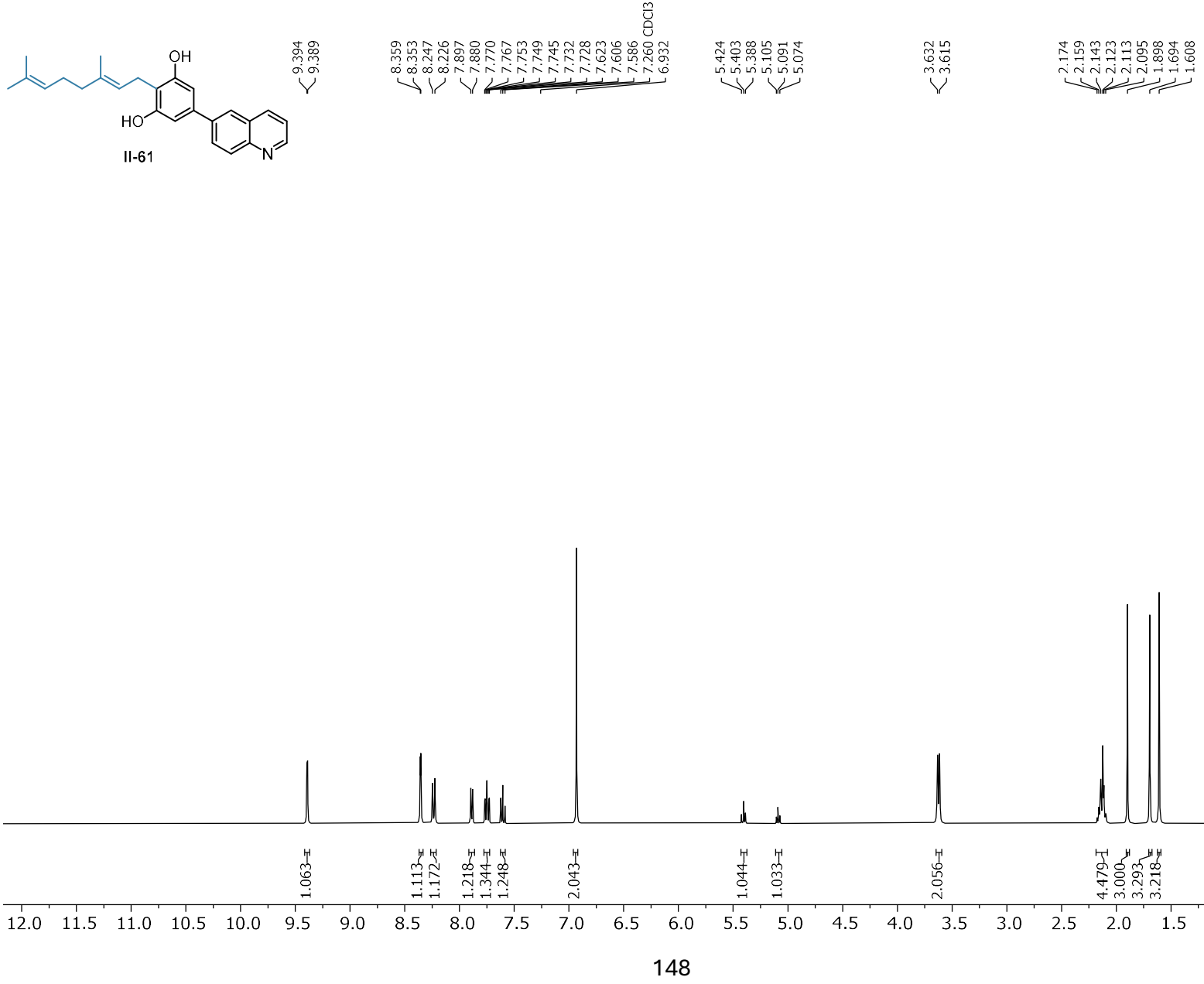


II-60

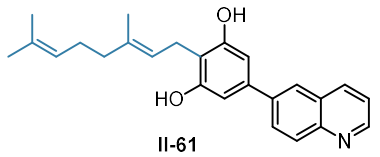
2-geranyl-5-(5-pyrimidinyl)resorcinol (**II-60)** (^{13}C NMR; 176 MHz; $CDCl_3$)



2-geranyl-5-(3-quinolinyl)resorcinol (**II-61**) (^{1}H NMR; 700 MHz; $CDCl_3$)

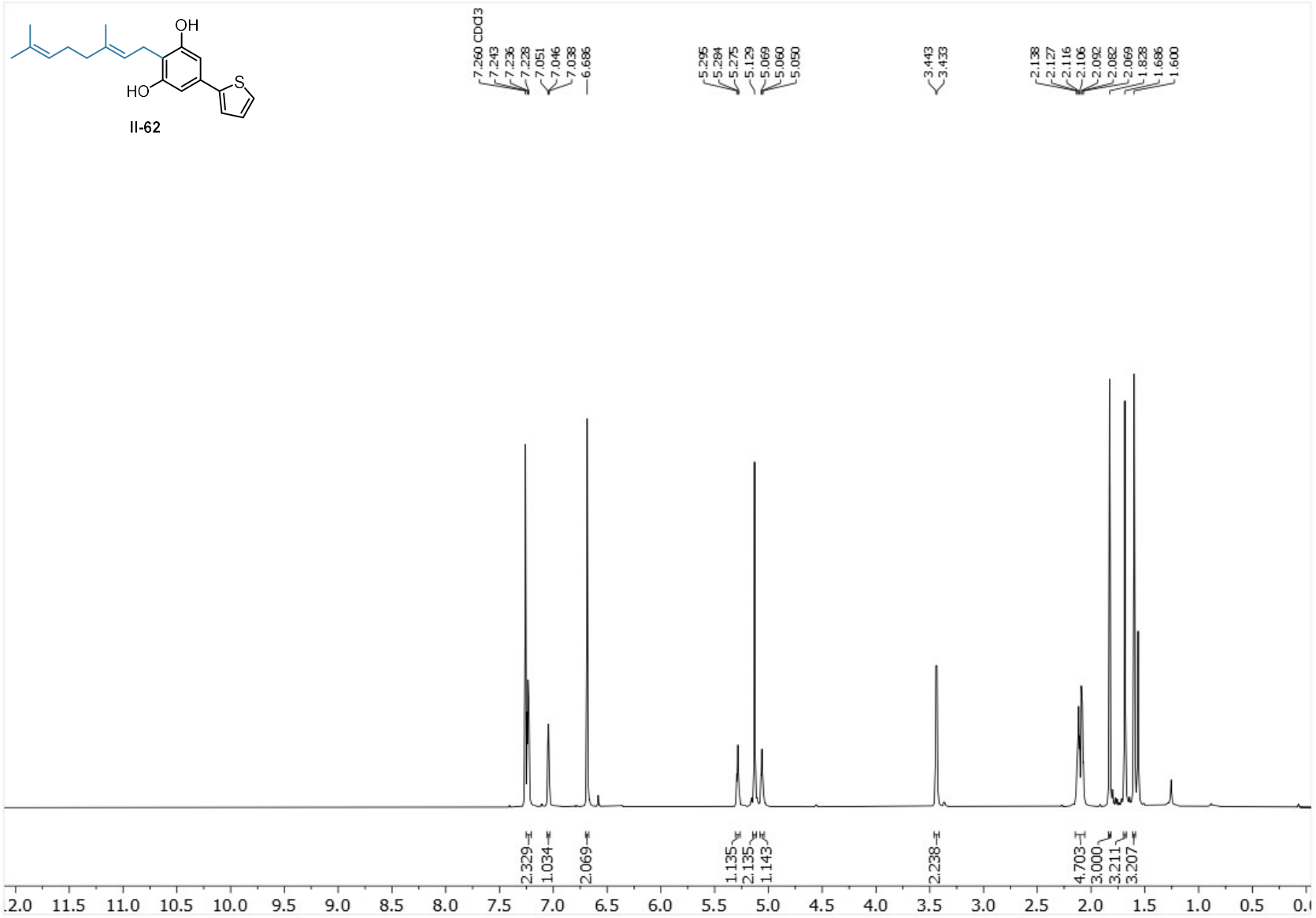


2-geranyl-5-(3-quinolinyl)resorcinol (**II-61)** (^{13}C NMR; 176 MHz; $CDCl_3$)

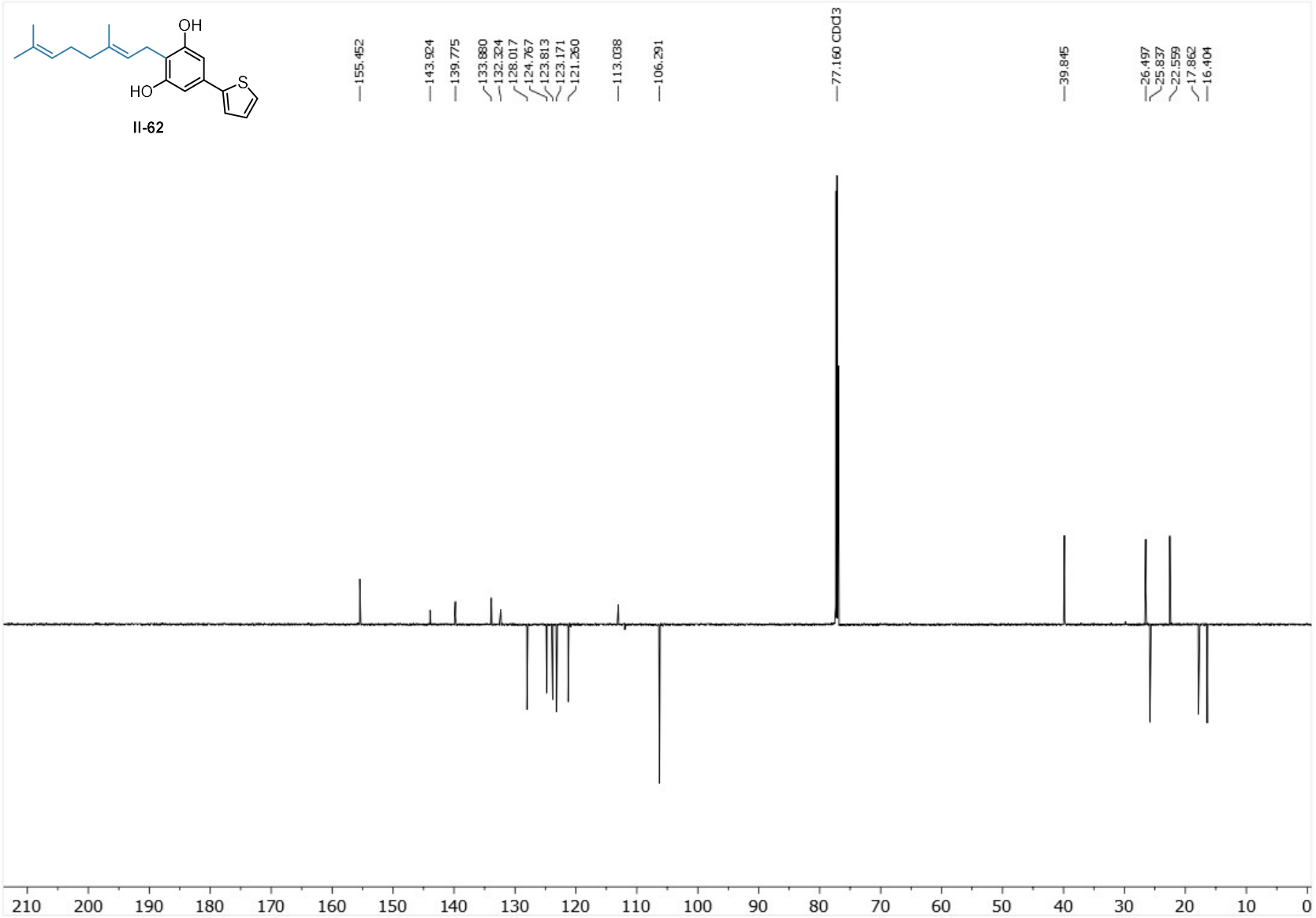


II-61

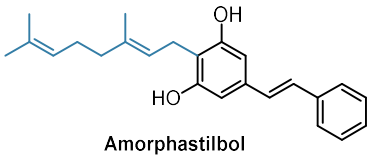
2-geranyl-5-(2-thiophene)resorcinol **(II-62)** (^{1}H NMR; 700 MHz; $CDCl_3$)



2-geranyl-5-(2-thiophene)resorcinol **(II-62)** (^{13}C NMR; 176 MHz; $CDCl_3$)



2-geranyl-5-((E)-styryl)resorcinol (**amorphastilbol**) (^{1}H NMR; 700 MHz; $CDCl_3$)



Amorphastilbol

2-geranyl-5-((E)-styryl)resorcinol **(amorphastilbol)** (^{13}C NMR; 176 MHz; $CDCl_3$)