UNIVERSITY OF NAIROBI

ANTICANCER AND ANTIBACTERIAL PROPERTIES OF SECONDARY METABOLITES FROM THREE SELECTED *MACARANGA* SPECIES AND PHYTOCHEMISTRY OF *FICUS THONNINGII*

BY

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2023

DECLARATION

I declare that this thesis is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work or my own work has been used, this has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.

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DEDICATION

This thesis is dedicated to Almighty Allah (SWA) for His infinite mercy in my life, without who nothing is possible.

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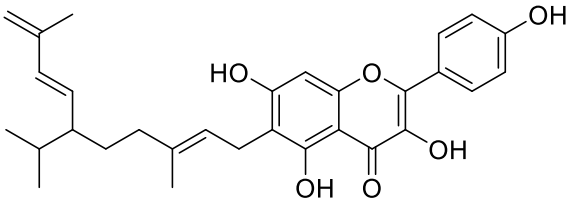
ABSTRACT

Medicinal plants are essential in human ailment therapy even before modern civilization. The quest for and utilization of these medicinal plants has continued to receive increased interest. Cancer is a major global health issue affecting all communities irrespective of their development status. Bacteria, in addition to triggering cancer progression, continue to be a significant source of morbidity and fatality in cancer patients. The rising prevalence of drug resistance by cancerous cells and bacteria and the diverse undesirable side effects have necessitated the search for lead compounds that may be exploited in developing novel therapeutic drugs with better efficacy and less toxicity. Therefore, dichloromethane/methanol (1:1) extracts of different parts of *Macaranga conglomerata, Macaranga capensis, Macaranga kilimandscharica*, and *Ficus thonningii* were phytochemically investigated, and the isolated compounds evaluated for anticancer and antibacterial potencies. To identify and purify pure compounds, several chromatographic procedures were utilized, including column chromatography (CC) using silica gel, Sephadex LH-20, and Chromatotron. The structures of the isolated compounds were determined using spectroscopic (NMR, UV, IR, optical rotation) and spectrometric (HRESIM) techniques. Phytochemical analysis of all the plant samples led to the isolation of twenty-two compounds, out of which one is novel. Phytochemical analysis of *M. conglomerata* leaves afforded five compounds, including three flavonoids (**245** – **247**) and two ellagic acid derivatives (**248** – **249**). The stem bark of *M. conglomerata* yielded a triterpenoid (**250**). A triterpenoid (**251**), two coumarins (**252** – **253**), one ellagic acid derivative (**254**), and three flavonoids (**255** – **257**) were isolated from the stem bark of *M. capensis*. Chemical analysis of the root extract of *M. Capensis* afforded a sterol (**258**) and a phenolic oxirane (**259**). The stem bark of *F. thonningii* yielded seven compounds, including four flavonoids (**260** – **263**), one phenolic acid (**264**), one sugar (**265**), and one sterol (**266**). 6-[(2(*E*),7(*E*))-6-Isopropyl-3,9-dimethyldeca-2,7,9-trienyl] kaempferol (trivially named as conglomeratin) (**245**) is new, while 2,2′-(((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(methylene))bis(oxirane) (**259**) has not been isolated from nature before now. Saccharose (**265**) is reported from the genus *Ficus* for the first time. Methyl thiazol tetrazolium (MTT) assay was used to assess the cytotoxicity of the isolated compounds to determine their anticancer potential. Among the tested compounds, conglomeratin (**245**) displayed the highest cytotoxic potency against liver (HepG2) (IC_{50} = 13.1 µM) and breast (MCF-7) (IC_{50} = 16.2 µM) cancerous cells. Compound **259** also showed moderate cytotoxic potential against HepG2 (IC_{50} = 15.6 µM) and MCF-7 (IC_{50} = 28.2 µM), respectively, while

compound **251** displayed moderate activity (IC_{50} = 42.9 µM) only against the HepG2 cell line. The IC_{50} values for the reference drug doxorubicin were 0.69 µM (MCF-7) and 0.81 µM (HepG2). Using the iodonitrotetrazolium (INT) colorimetric test, the antibacterial properties of the extracts and pure compounds were assessed. The minimal inhibitory concentration (MIC) values for the three *Macaranga* species (*M. conglomerata*, *M. capensis*, and *M. kilimandscharica*) extracts ranged from 4 to 128 µg/mL against Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli, Enterobacter aerogenes, Klebsiella pneumoniae, Providencia stuartii* and *Pseudomonas aeruginosa*) microorganisms. Almost all the extracts displayed a bactericidal impact on the tested bacteria with a minimal bactericidal concentration (MBC)/minimal inhibitory concentration (MIC) ratio of less than 4. Compound **245** showed significant and moderate activities towards *P. aeruginosa* (MIC = 7.8 µg/mL) and *S. aureus, E. coli* and *K. pneumoniae* (MIC = 62.5 µ/mL), while compound **248** displayed selectivity for *K. pneumoniae* (MIC = 7.8 µg/mL), and compound **246** was potent against *P. aeruginosa* (MIC = 1.0 µg/mL). The MIC values for the reference drug ciprofloxacin ranges from 1.0 – 15.6 µg/mL for all the microorganisms. The current study has revealed that compounds from the *Macarana* species exhibited strong to moderate anticancer potentials and broad-spectrum antibacterial activities. Hence, they should be exploited as candidates for therapeutic agents in drug development.



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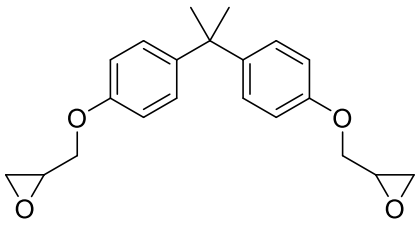

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LIST OF ABBREVIATIONS/ACRONYMS AND SYMBOLS

A549	Human Lung Adenocarcinoma Cells	MCF-7	Human Breast Carcinoma Cells
CC	Column Chromatography	HepG2	Human Liver cancer Cells
CD_3OD	Deuterated Methanol	*m*	Multiplet
$CDCl_3$	Deuterated Chloroform	*m*/*z*	Mass to Charge Ratio
CH_2Cl_2	Dichloromethane	MeOH	Methanol
COSY	Correlation Spectroscopy	MHz	Mega Hertz
d	Doublet	MS	Mass Spectrometry
dd	Double Doublets	NMR	Nuclear Magnetic Resonance
DEPT	Distortionless Enhancement by Polarization Transfer	NOESY	Nuclear Overhauser and Exchange Spectroscopy
TEDFund	Tertiary Education Trust Fund	TLC	Thin Layer Chromatography
HMBC	Heteronuclear Multiple Bond Correlation	UV	UltraViolet
HRESIMS	High-Resolution Electrospray Ionization Mass Spectrometry	WHO	World Health Organization
HSQC	Heteronuclear Single Quantum Correlation	δ	Chemical Shift
Hz	Hertz	µg/mL	Microgram Per Milliliter
IC_{50}	Half-maximum Inhibitory Concentration	*s*	Singlet
IR	Infrared Radiation	µM	Micro Molar
MTT	Methyl Thiazol Tetrazolium	MIC	Minimal Inhibitory Concentration
DMSO-*d*6	Deuterated Dimethylsulfoxide	MBC	Minimal Bactericidal Concentration
MDR	Multi-Drug Resistant	CCM	Complete Culture Medium
EMEM	Eagle's Minimum Essential Medium	ATCC	American Type Culture Collection
INT	Iodonitrotetrazolium	MHB	Mueller Hinton Broth
MHK	Ministry of Health Kenya	AMP	Ampicillin
CYP	Cyprofloxacin	ATM	Aztreonam
CEF	Cefepime	CHL	Chloramphenicol
KAN	Kanamycin	NAL	Nalidixic acid

NOR	Norfloxacin	STR	Streptomycin
TET	Tetracycline	FLX	Flomoxef
IM/CS	Imipenem/Cilastatin Sodium	GEN	Gentamicin
brs	Broad singlet		

LIST OF PUBLICATIONS

Ibrahim Hashim, Leonidah Kerubo Omosa, Vaderament-Alexe Nchiozem-Ngnitedem, John Mmari Onyari, Shital Mahindra Maru, Michel-Gael Fofack Guefack, Armelle Tsafack Mbaveng and Victor Kuete (2021). Antibacterial Activities and Phytochemical Screening of Crude Extracts from Kenyan *Macaranga* Species Towards MDR Phenotypes Expressing Efflux Pumps. *Pharmacognosy Communications*, 11(2): 119-126, DOI: 10.5530/pc.2021.2.22

Ibrahim Hashim, John Mmari Onyari, Leonidah Kerubo Omosa, Shital Mahindra Maru, Vade rament-A Nchiozem-Ngnitedem and Rajshekhar Karpoormath (2022). Conglomeratin: a new antibacterial flavonol derivative from *Macaranga conglomerata* Brenan (Euphorbiaceae). *Natural Product Research*, 36(23): 6012-6020, DOI: 10.1080/14786419.2022.2061481

Ibrahim Hashim, Leonidah Kerubo Omosa, John Mmari Onyari, Shital Mahindra Maru and Justus Mukavi (2022). Chemical constituents from the stem bark of *Ficus thonningii* and their chemotaxonomic significance. *European Journal of Medicinal Plants*, 33(10): 19-27, DOI: 10.9734/EJMP/2022/v33i1030493

CHAPTER 1: INTRODUCTION

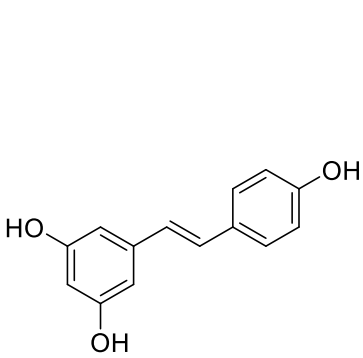
1.1: Background

Medicinal plants have been essential in human ailment therapy even before moderncivilization. The quest for and utilization of these medicinal plants has continued to receive increased interest, particularly in developing countries. Medicinal herbs are increasingly being used in industrialized nations for therapeutic and preventative purposes, particularly for the treatment of hard-to-treat diseases. In fact, almost 60 % of people worldwide utilize herbal medicines to meet their health needs (El-Seedi *et al.*, 2013; Alves-Silva *et al.*, 2017). These developments are related to medicinal herbs' availability and affordability in emerging nations and the accessibility of traditional medicine practitioners to the population. These phenomena are observable in rural areas where patients can pay for the services of herbal practitioners as local standard practice stipulates. The primary elements influencing the rising interest in medicinal plants in industrialized countries are their natural origin and lower or non-existent toxicity when compared to the adverse consequences of manufactured medications (Lowe *et al.*, 2021). In Africa, nearly 80 % of the population resort to fork remedies for diseases, including pain, malaria, infertility, diabetes, cancers, and microbial infections (Ozioma and Chinwe, 2019). Njoroge *et al.* (2010) stated that about 90 % of Kenyans had utilized medicinal plants to treat one ailment or the other at least once in their lifetime. This is invariably connected to the cultural acceptability and effectiveness of the plants in improving hard-to-treat diseases besides their cheapness and local availability.

Plants generate a vast array of phytochemicals with a wide range of structures. These phytochemicals are referred to as secondary metabolites, as opposed to primary metabolites, needed in the development of plants. Phytochemicals (natural products) such as alkaloids, phenolic compounds and terpenoids all contribute significantly to how plants interact with their

surrounding ecosystems. They may function as hormones or substances that defend plants from pathogens and phytophagous or as floral pigments capable of enticing pollinators. Natural products facilitate basic plant development processes and are historically utilized for medications (Springob and Kutchan, 2009).

Phenolic compounds such as resveratrol (**1**) and epigallocatechin-3-gallate (**2**) found in *Arachis hypogea* and green tea, respectively, were both reported to be effective anticancer and antibacterial agents (Vestergaard and Ingmer, 2019; Priya and Satheeshkumar, 2020; Wu and Brown, 2021). Plant-derived secondary metabolites such as Urgineanin A (**3**) and homoisopogon A (**4**) isolated from *Urginea depressa* and *Ophiopogon japonicus*, respectively, revealed promising anticancer activities against multidrug-resistant cancerous cells (Dai *et al.,* 2013; Dang *et al.*, 2017; Bitchagno *et al.*, 2020). Furthermore, ferruginin A (**5**) and candidone (**6**) from *Harungana madagascariensis* and *Milicia excelsa*, respectively, were found to display significant antibacterial activities against multidrug-resistant bacteria (MIC = 4 – 64 µg/mL) (Mbaveng *et al.,* 2015; Tankeo *et al.*, 2016).



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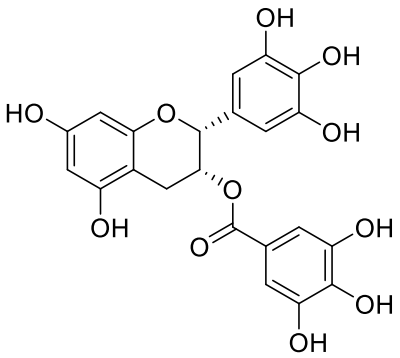

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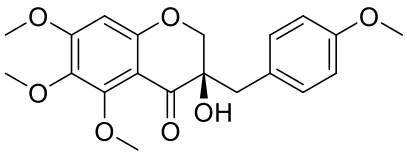

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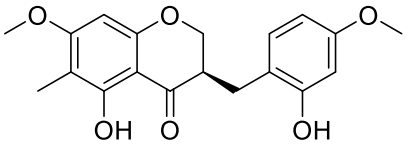

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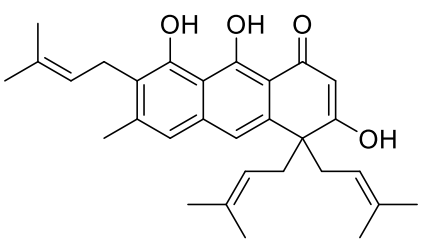

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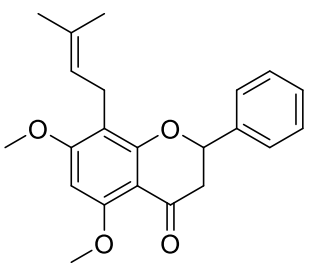

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Many other plants traditionally utilized for cancer and bacterial infection treatment may be sources of lead compounds needed to develop medications against these diseases. Plants in the genera *Macaranga* and *Ficus* are examples of such plants. Prenylated flavonoids, which possess diverse pharmacological activities, including anticancer and antibacterial properties, are commonly found in *Macaranga* and *Ficus* genera plants (Kuete *et al.,* 2011; Mai *et al.,* 2020; Vu *et al.,* 2021; Pagna *et al.,* 2022). In this study, therefore, crude extracts and isolated compounds from three *Macaranga* species, *Macaranga conglomerata*, *Macaranga capensis*, and *Macaranga kilimandscharica* found in Kenya, were examined for potential utilization in cancer and bacterial infection treatment. Additionally, *Ficus thonningii* was phytochemically investigated.

1.2: Statement of the Problem

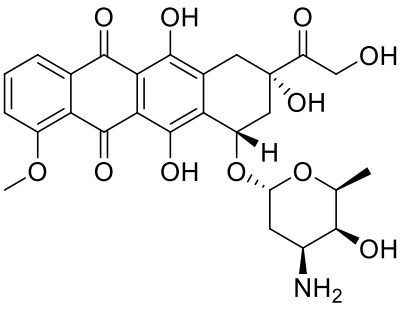
Cancer is a major global health issue affecting all communities irrespective of their development status. Globally, the burden of cancer has been rising in terms of new cases and fatalities. In 2020, for instance, the global total cancer deaths increased to about 10 million (Sung *et al.*, 2021) from 9.6 million mortality recorded in 2018 (Bray *et al.*, 2018). Moreover, cancer and cardiovascular diseases are presently considered the main causes of mortality globally (Bray *et al.*, 2021). The prevalence rate of cancer in developing nations such as Kenya has shown a steady increase despite the government's strategic plans to control the menace of cancer. In 2017, for instance, the Kenyan Ministry of Health reported about 39,000 new cancer patients and 27,000 cancer mortality (MHK, 2017; 2022). However, within one year, the indices of cancer in Kenya had risen to 47,887 and 32,987 for new cancer patients and mortality, respectively (WHO, 2018). The most common malignancy among women was breast cancer, responsible for 15.5 % of cancer fatalities globally among female patients in 2020 (Sung *et al.*, 2021). It was the leading type of cancer in females in Africa and Kenya, with an estimated incidence of 186,598 and 6,799, respectively, in 2020. In Kenya, breast cancer

accounted for 11.5% (3,107) of all cancer-related fatalities, making it the second most common cancer-related cause of death. Nevertheless, one of the most typical tumours among men is liver cancer. In 2020, it accounted for 10.4 % of overall cancer mortality in males (Ferlay *et al.,* 2021). Liver cancer was reported as the third leading cause of mortality in Africa (66,944) (GLOBOCAN, 2020; Ferlay *et al.,* 2021; Sung *et al.,* 2021; MHK, 2022).

Microbes such as bacteria are among the main components that exponentially contribute to cancer initiation and development. Infectious agents, especially bacteria, account for 16.1 % of malignant tumors globally (Khatun *et al.,* 2021). Chronic inflammation brought on by bacterial infections causes cancer to develop and ultimately results in death. For instance, *Helicobacter pylori,* a bacterium found in the stomach, attacks the DNA of the host cells, controls the immune system, and induces inflammation that can activate cell growth and result in stomach cancer (Dekaboruah *et al.,* 2020; Khatun *et al.,* 2021). Another noteworthy illustration is *Fusobacterium nucleatum* which is associated with colorectal and oral cancers (Sethi *et al.,* 2019; Harrandah *et al.,* 2021). The bacterium was found to be capable of releasing toxins and carcinogenic metabolites and is responsible for inflammatory diseases of the digestive tract (dos Reis *et al.,* 2019). Apart from triggering the cancer progression, bacteria remain a significant source of mortality and fatality in cancer patients.

Chemotherapeutic drugs are the most commonly available and frequently utilized cancer therapy option, yet these drugs are not selective and can damage normal cells. Moreover, most chemotherapy drugs such as doxorubicin (**7**) now in use cause significant side effects, leading to increased mortality (Elasbali *et al.,* 2022) and treatment resistance in malignant cells (Lu *et al.,* 2015; Christowitz *et al.,* 2019; Li *et al.,* 2021). Further, antibiotic efficacy loss due to bacterial antibiotic resistance has hampered the cancer therapeutic effectiveness (Nanayakkara

et al., 2021). Ciprofloxacin is an example of such antibiotic (**8**) (Hamed *et al.*, 2018; Pang *et al.*, 2019). Due to the rising prevalence of drug resistance by cancerous cells and bacteria, it has become imperative to identify lead compounds that may be exploited in developing novel therapeutic drugs. This can be achieved by investigating the potential of historically used medicinal plants such as *Macaranga* and *Ficus* species. Most of these compounds derived from natural sources, particularly medicinal plants, are effective and selective against malignant cells and bacteria, with little or no side effects (Kuete *et al.*, 2011; Vu *et al.*, 2021).



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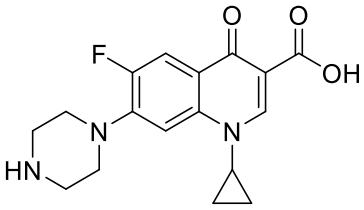

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1.3: Objectives of the Study

1.3.1: General Objective

This study's general objective was to isolate the secondary metabolites from three selected *Macaranga* species and *Ficus thonningii* with potential anticancer and antibacterial applications.

1.3.2: Specific Objectives

The specific objectives of this study were:

i) To determine the secondary metabolites of *Macaranga conglomerata*, *Macaranga capensis*, *Macaranga kilimandscharica*, and *Ficus thonningii*.

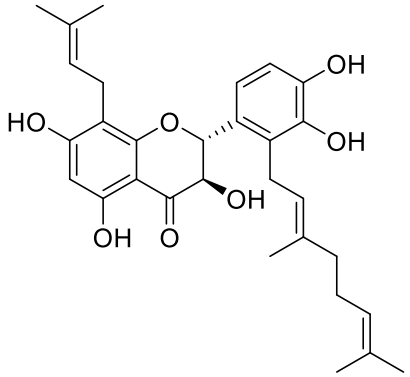
ii) To assess the cytotoxic potency of the isolated compounds from the selected *Macaranga* species.

iii) To evaluate the antibacterial activities of the selected *Macaranga* species's crude extracts and isolated compounds.

1.4: Justification of the Study

Prenylated flavonoids and stilbenes have recently received increasing interest in cancer chemoprevention and chemotherapy due to their characteristic structures' diversity and broad-ranging bioactivities on multi-target tissues (Nema *et al.,* 2012; Chen *et al.,* 2014). The high antioxidant, anti-inflammatory, and apoptosis-inducing ability of these metabolites are linked to their pharmacological potentials with minimal side effects(Sirerol *et al.,* 2016). Furthermore, natural metabolites (such as flavonoids) have the capability of interacting with the different constituents of bacterial cell structure, making them better antibacterial agents (Pistelli and Giorgi, 2012; Borges *et al.,* 2016).

Previous investigation revealed that the genera *Macaranga* and *Ficus* contain prenylated flavonoids and stilbenes with potent pharmacological activities. Diterpenes, coumarins, and tannins were also reported from the two genera (Kamarozaman *et al.,* 2019; Insanu *et al.,* 2020; Salehi *et al.,* 2021). The cancer cell line A2780 was sensitive to macarecurvatin B (**9**) (IC_{50} = 0.83 µM) isolated from *M. recurvate* (Tanjung *et al.,* 2012). Lonchocarpol A (**10**) from *M. Hurifolia* demonstrate potent antibacterial efficacy with MIC values of 7.65 and 0.18 µM towards *S. typhi* and *K. pneumoniae*, respectively (Pagna *et al.,* 2022).



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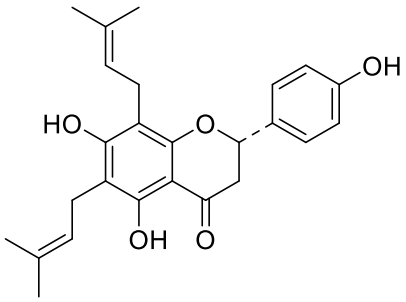

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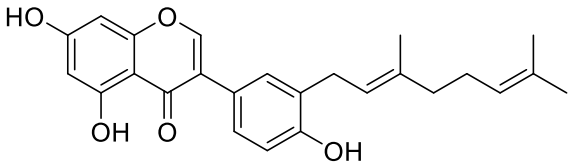

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Furthermore, myrsininone A (**11**) isolated from the fruits of *F. aurata* exhibited broad-spectrum antibacterial properties, with MIC ranges between 1.25 to 20.00 µg/mL (Shao *et al.*, 2022).

Although several *Macaranga* species have been recognized to have pharmacological potential and a variety of traditional uses, the anticancer and antibacterial efficacy of crude extracts and compounds from the three selected *Macaranga* species have not received any attention. Furthermore, a literature survey indicated that little has been done to isolate secondary metabolites in *F. thonningii*. The antibacterial activity of *Ficus thonningii* leaves extract was reported by Kone and his colleagues (Koné *et al.*, 2004). However, the systematic phytochemical studies of *F. thonningii* from East Africa has hitherto not been reported. Based on the established paucity of data, the anticancer and antibacterial potentials of the selected *Macaranga* species and the phytochemical constituents of *F. thonningii* were investigated.

CHAPTER 2: LITERATURE REVIEW

2.1: Cancer

In a broader perspective, an assembly of syndromes known as cancer are defined by uncontrolled and abnormal cell development capable of invading and spreading to different bodily regions. Cancer is considered the leading cause of fatality and a global impediment to longevity (WHO, 2020; Sung *et al.*, 2021). Globally, about 10 million cancer deaths and over 19 million new cases of the disease were reported in 2020 (Sung *et al.*, 2021). The rapid and growing cancer occurrence and lethality are associated with the prevalence of the risk factors that are linked to socio-economic development (Lortet-tieulent *et al.*, 2020). Malignant diseases have emerged as a public health menace in Africa. Africa, in 2020, accounted for 1.1 million of the World's cancer cases and 712 800 cancer deaths (which equates to approximately 2000 cancer mortality per day).

In contrast to other World regions (except Asia), the share of cancer mortality in Africa (7.2 %) is higher than that of the incidence (5.7 %) (Sung *et al.*, 2021). Barriers to early detection and quality cancer treatment, less healthy diets and cancer types are the main contributing factors associated with Africa's high cancer fatality rate. Infectious diseases, smoking, diet, unhealthy lifestyles, occupational and behavioural risks, and obesity are attributed to Africa's rising cancer rate (Sylla and Wild, 2012; Makhafola and McGaw, 2017). The most diagnosed form of cancer in the African region are the female breast, lung colorectum, prostate and stomach, with female breast cancer leading the cause of cancer incidence (186 598), whereas lung cancer account for the highest cancer mortality (Sung *et al.*, 2021).

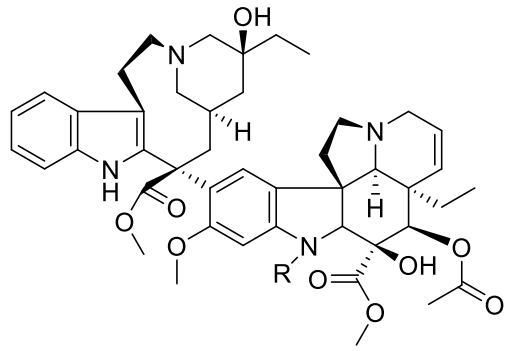
To stem the ever-growing burden of cancer on the public's health system, particularly in Africa, affordable and quality treatment modalities are required, besides early detection and diagnosis policies. Treatments and palliative care are the essential components of a comprehensive cancer

management approach. Whereas surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, or their combination are the leading cancer treatment strategies worldwide, palliative care aims to improve cancer patients' life quality through surgical and radiological palliation and pain management (Ngoma, 2006; Yildizhan *et al.,* 2018). However, these treatment strategies are often associated with different side effects; the most notable being severe pain and secondary cancer formation (Huang *et al.,* 2017). Chemotherapy remains the most promising option in cancer management, but the regimen is confronted with drug resistance by different cancerous cells. The resistance is borne either by increasing medication release outside the cells or by reducing its cell's absorption (Mansoori *et al.,* 2017). The drug resistance results in tumour relapse, followed by a metastatic process (Kuczynski *et al.,* 2013; Housman *et al.,* 2014). Therefore, it has become necessary to look for selective chemo-agents from natural sources, especially those with low disease resistance, fewer side effects, high medicinal attributes, and cost-effectiveness.

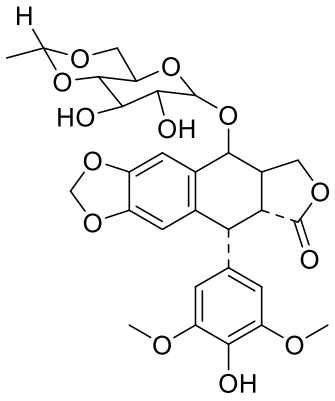
2.1.1: Anticancer Drugs of Natural Origin

Bioactive molecules derived from various natural sources have the potential to be medicinally significant. The utilization of medication from natural sources, predominantly plants, is as old as human civilization across the globe. Nature remains a trove of possible chemotherapeutic medicines and lead compounds (Khazir *et al.,* 2014). More than 60 % of today's cancer medications originate from plants or microbes (Newman and Cragg, 2012). Potent analogues and prodrugs are developed using phytochemicals isolated from natural sources as a paradigm via chemical techniques such as total or combinatorial synthesis (Basmadjian *et al.,* 2014; Cragg and Pezzuto, 2016). As of 2012, approximately 80 % of the 236 new chemical entities approved as chemotherapeutic drugs were derived from or inspired by natural products (Khazir *et al.,* 2014).

Plant-derived agents like vincristine (**12**) and vinblastine (**13**) from *Catharanthus roseus*, as well as etoposide (**14**) from *Podophyllum peltatum* (Lee and Xiao, 2011) are among the most effective cancer chemotherapeutics on the market today (Cragg and Pezzuto, 2016). Other anticancer agents of plant origin in clinical use include gimatecan (**15**) from *Camptotheca acuminate* (Pecorelli *et al.,* 2010) and cabazitaxel (**16**) from *Taxus brevifolia* (Paller and Antonarakis, 2011).



	R
12	CHO
13	CH_3



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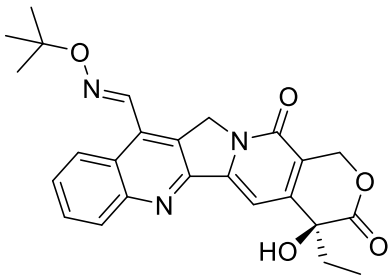

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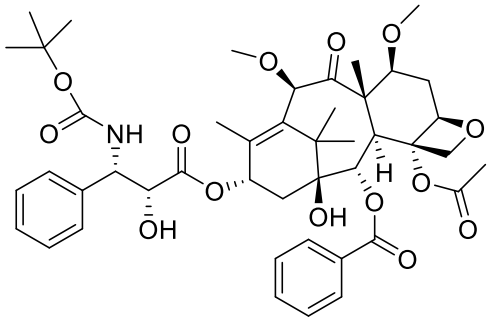
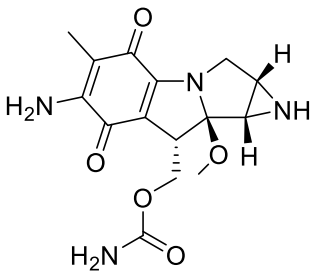


16

Microorganisms are also regarded as promising sources of natural chemotherapeutic agents due to their vast dispersion and diversity. Furthermore, harsh environment-resistant microbes release compounds that may have medicinal uses. Mitomycin (**17**), epirubicin (**18**), and valrubin (**19**) are all *Streptomyces sp.* derived anticancer agents used to treat breast and bladder cancers (Ormrod *et al.,* 1999; Kuznetsov *et al.,* 2001; Khazir *et al.,* 2014).



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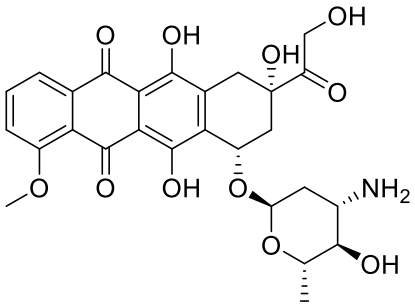

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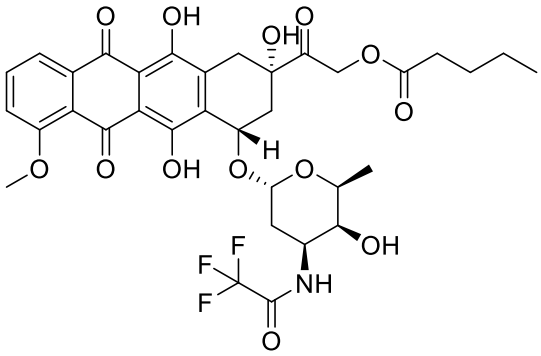
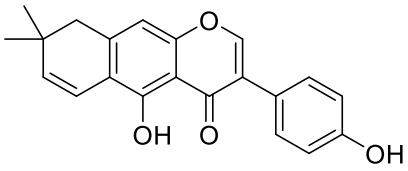


19

2.1.2: Phytochemicals with Anticancer Potentials

Scientific evidence suggests that phytochemicals and derivatives are promising options for improving treatment efficiency and reducing adverse reactions in cancer patients. Several of these metabolites have been evaluated for cytotoxicity. By scavenging free radicals, suppressing tumour growth, and acting as anti-angiogenic agents, they have overlapping and supporting mechanisms that slow cancer development (Choudhari *et al.,* 2020; Khan *et al.,* 2022). Among them was alpinumisoflavone (**20**) (IC_{50} = 9.60 µM), a pyranoisoflavone isolated from *Ficus chlamydocarpa,* which induced apoptosis in drug-sensitive drugs CCRF-CEM leukaemia cells (Kuete *et al.,* 2016). Morusin (**21**) (IC_{50} = 0.64 µM), atalantoflavone (**22**) (IC_{50} = 1.25 µM), and 3′-geranyl-3-prenyl-2′,4′,5,7- tetrahydroxyflavone (**23**) (IC_{50} = 1.32 µM), all reported from *Morus alba*'s leaves, demonstrated potent cytotoxic efficacy against human cervical cancer cells (HeLa) (Dat *et al.,* 2010).



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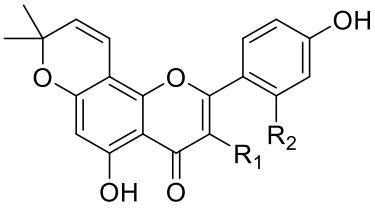
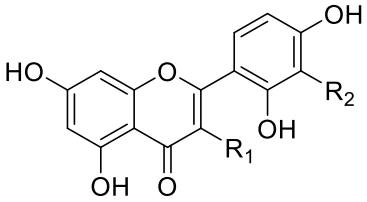
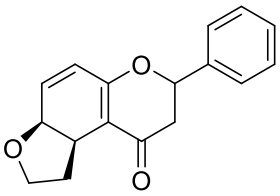


	R_1	R_2
21	Prenyl	OH
22	H	H



23: R_1 = Prenyl, R_2 = Geranyl

Chou *et al.* (2010) isolated cryptocaryanone A (**24**) from *Cryptocarya chinensis* which showed cytotoxic activities against MCF-7 (IC_{50} = 5.1 µM), SF-268 (IC_{50} = 5.0 µM), and NCI-H460 (IC_{50} = 4.3 µM). Two isoflavones, durmilone (**25**) and 6,7,3′-trimethoxy-4′,5′-methylenedioxyisoflavone (**26**) from *Lonchocarpus bussei* displayed significant cytotoxic activities against leukaemia CCRF-CEM cells with IC_{50} = 0.54 and 6.27 µM, respectively (Adem *et al.*, 2019).



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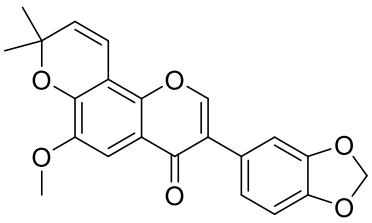
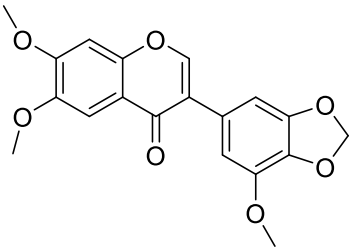


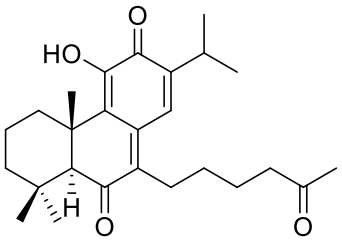
25



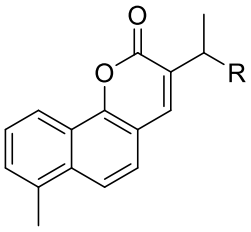
26

A diterpene, 7-(2-oxohexyl)-11-hydroxy-6,12-dioxo-7,9(11),13-abietatriene[=7-(2-oxohexyl)-taxodione] (**27**), isolated from *Salvia austriaca*, was tested using MTT assays for its cytotoxicity effect against three tumour cancerous cells (Kuźma *et al.*, 2012). The compound

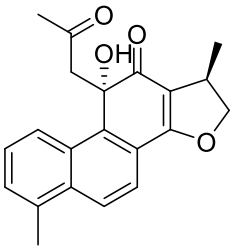
had a considerable impact in preventing the proliferation of all the tested tumour cells, considering the IC_{50} values of 0.63 µM (HL-60), 0.66 µM (NALM-6) and 0.72 µM (WM-115). Antiproliferative activities of diterpenoids from *Salvia yunnanensis* against HeLa cells: salyunnanin D (**28**) (IC_{50} = 7.92 µM), salyunnanin E (**29**) (IC_{50} = 0.86 µM), and danshenol A (**30**) (IC_{50} = 5.74 µM) were reported (Wu *et al.,* 2014). Bourjotinolone B (**31**) was evaluated for cytotoxicity against A-549 cell lines after its isolation from *Toona sinensis* (Tang *et al.,* 2016). It displayed potent inhibition and selectivity on A-549 cells, including inducing apoptosis.



27

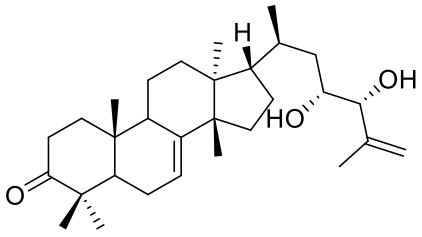


	R
28	CH_3
29	CH_2OH

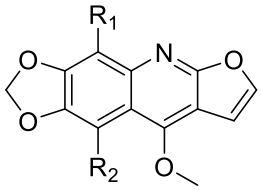


30

Three alkaloids, maculine (**32**) (IC_{50} = 9.5 µM), 5-methoxymaculine (**33**) (IC_{50} = 7.9 µM), and flindersiamine (**34**) (IC_{50} = 8.9 µM), reported from *Oricia suaveolens* inhibited the activities of lung adenocarcinoma A-549 cell line (Wansi *et al.,* 2008).



31



	R_1	R_2
32	H	H
33	H	OCH_3
34	OCH_3	H

2.2: Bacterial Infections

Infectious diseases caused by bacteria and viruses continue to pose a serious threat to public health, claiming 500,000 individual lives annually and accounting for 25 % of all deaths worldwide (Nii-trebi, 2017; Sebola *et al.,* 2020). In developing countries, infectious diseases account for about 45 % of mortality, and approximately 90 % of these deaths are mainly due to bacterial infections (Al-judaibi, 2014; Nii-trebi, 2017). Infections resulting from antibiotic-resistant pathogens have become a significant concern. The WHO has identified antibiotic resistance as a serious problem to global health, with an estimated 700,000 fatalities annually (Aslam *et al.,* 2018; Koulenti *et al.,* 2019). Fighting pathogen-caused diseases and complications arising from chemotherapy, dialysis, or organ transplanting has been impaired due to the continuing trend of loss of effective antibiotics.

Resistance-causing bacterial infections have become more common, and certain bacteria strains are now almost immune to antibiotics (Breijyeh *et al.,* 2020). According to research, certain bacteria have been linked to human cancers, and bacterial infection is responsible for about 15% of cancers globally, making it a serious health concern (Mager, 2006; Sebola *et al.,* 2020). For instance, *Helicobacter pylori, Salmonella typhi, Chlamydia pneumoniae, Chlamydia trachomatis,* and *Streptococcus bovis* are associated with gastric cancer (Nokhandani *et al.,* 2021), gallbladder cancer (Kumar *et al.,* 2006), lung cancer (Littman *et al.,* 2004; Manton *et al.,* 2009), cervical carcinoma (Castanheiraa *et al.,* 2021), and colon cancer (Cheng *et al.,* 2020), respectively. Chronic infections, immune evasion and suppression, and in some cases, producing toxins that alter the normal cell growth, which results in tumour initiation and promotion, thereby causing and facilitating mutations, are the mechanisms by which bacterial agents can cause cancer (Mager, 2006; Elsland and Neefjes, 2018).

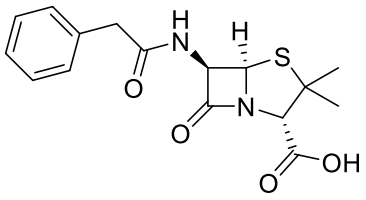
2.2.1: Multidrug resistance in Bacteria

Bacterial resistance to antibiotic drugs has become a major health challenge in both developing and developed nations due to an increased rate of disease incidents, death, and prolonged hospital stay or medical procedures (Sebola *et al.*, 2020). Overuse of antibiotics, lack of quality and affordable medicine, increase in the number of immunodepressed patients, and incorrect prescriptions are contributing factors in the emergence of resistant bacterial strains (Sebola *et al.*, 2020; WHO, 2017). Bacteria can acquire antibiotic resistance from other bacteria or via genetic mutation. Through mutations, bacteria can produce enzymes or other chemically active substances that can render antibiotics ineffective. In some instances, the mutations enable the bacteria to remove the antibiotic-attacked target cells or block the entrance points via which the antibiotics enter the cells (Tanwar *et al.*, 2014; Reygaert, 2018; Breijyeh *et al.*, 2020).

Six dangerous bacteria species, including *Enterobacteriaceae* (mainly *E. coli*, *Salmonella spp.*, and *Klebsiella pneumoniae*), *Acinetobacter spp.*, *Pseudomonas aeruginosa*, *Enterococcus spp.*, *Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae*, are resistant to almost all antibiotics (WHO, 2014, 2017). *Staphylococcus aureus* is also classified as a highly antibiotic-resistant pathogenic bacteria (Chua and Gubler, 2013; WHO, 2017).

2.2.2: Natural Product Derived Antibiotic Drugs

Natural products are used to develop therapeutic agents for almost every disease (Patridge *et al.*, 2016). Plant metabolites have remained the origin of potent therapeutics against pathogenic microbes (Rossiter *et al.*, 2017). Only three of the nine classes of antibiotics (sulfonamides, fluoroquinolones, and oxazolidinones) are synthetically developed, leaving the other six isolated from nature. These classes of antibiotic drugs from nature include penicillin G (**35**), tetracycline (**36**), erythromycin (**37**), gentamicin (**38**), and clindamycin (**39**) (Patridge *et al.*, 2016; Rossiter *et al.*, 2017).



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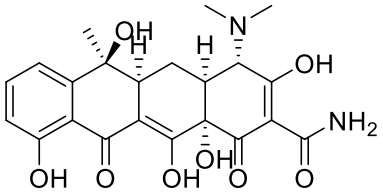

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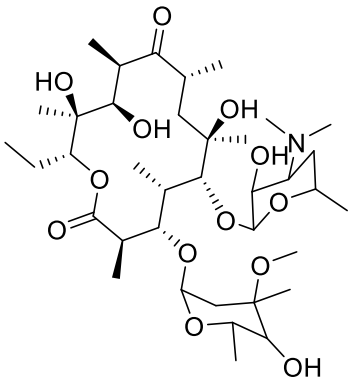

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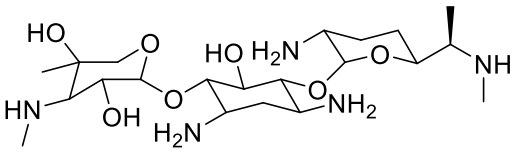

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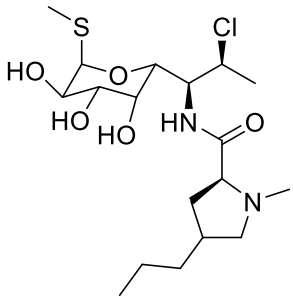


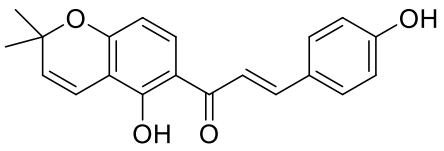
39

Bacterial resistance to these drugs and their derivatives has increased due to their frequent prescription for nonbacterial infections, such as viral infections, and unregulated use, resulting in sublethal doses, allowing resistance to spread quickly (Ventola, 2015). Therefore, the need for new medications with novel biochemical interactions to fight infections caused by resistant bacteria is critical. Phytochemicals have the potential to act as effective antimicrobial agents. They can equally improve the efficacy of conventional antibiotics when used in combination therapy.

2.2.3: Phytochemicals with Antibacterial Potentials

Plant-derived compounds can interact with the pathogenic processes, thereby decreasing the bacteria's ability to develop resistance. These compounds, including flavonoids (especially prenylated), terpenoids, alkaloids, and essential oils, have proven efficacy against drug-resistant bacteria (Savoia, 2012; Barbieri *et al.*, 2017; Gorniak *et al.*, 2019). For example, 6,8-diprenyleriodictyol (**40**), isobavachalcone (**41**) and 4-hydroxylonchocarpin (**42**), isolated from

Dorstenia species, showed potency towards methicillin-resistant *S. aureus* strain, displaying MIC of 0.5 – 4.0 µg/mL (Dzoyem *et al.,* 2013).



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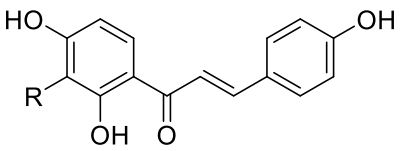
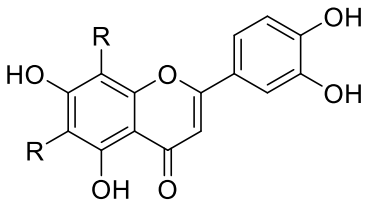
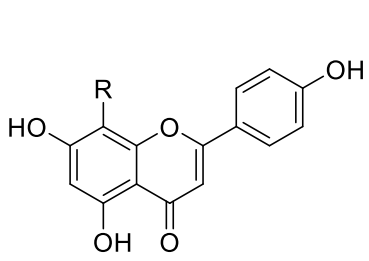


41: R = Prenyl

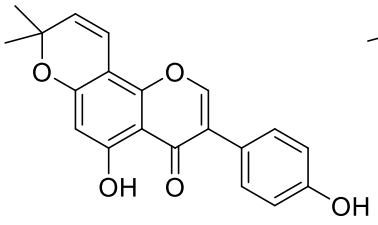


42: R = Prenyl

Licoflavone C (**43**) and derrone (**44**) from *Retama raetam* manifested good activities against *E. coli* (MIC = 7.81 µg/mL) (Edziri *et al.*, 2012). Neocyclomorusin (**45**), candidone (**46**), and neobavaisoflavone (**47**) were evaluated by Mbaveng *et al.* (2015) for their potency towards *E. coli* and *K. pneumoniae*. The compounds' MIC ranged between 4 to 8 µg/mL. 3′-*O*-methyldiplacol (**48**) and mimulone (**49**) were isolated from *P. tomentosa* fruits and screened against five MRSA strains (1903, 3202, 62097, 67755, 1679). The compounds' MICs (2 – 8 µg/mL) confirmed their strong activity (Navrátilová *et al.,* 2016).



43: R = Prenyl



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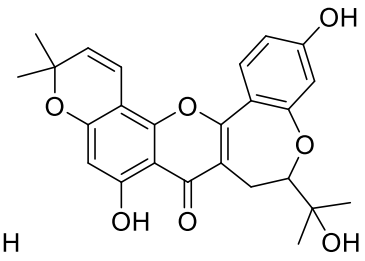

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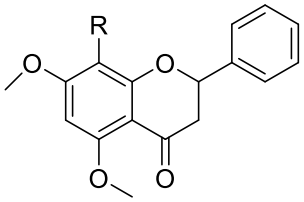
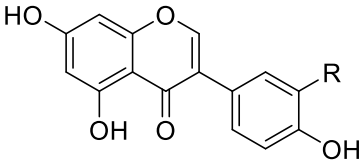
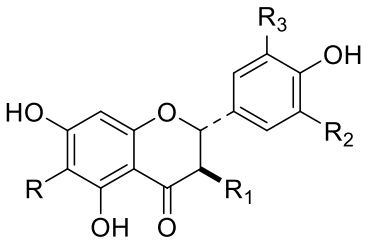


46: R = Prenyl



47: R = Prenyl



	R	R_1	R_2	R_3
48	Geranyl	OH	OCH_3	H
49	Geranyl	H	H	H

2.3: Bacteria and Cancer

Bacterial and viral inflammatory microenvironments have been proven to cause carcinogenesis. The interaction of immune systems with some microorganisms leads to the generation of persistent inflammation that aids in cancer development (Mager, 2006). Previous research has shown an important link between gastric cancer and infection caused by *H. pylori* (Wroblewski *et al.*, 2010). Furthermore, *B. fragilis* and *E. coli* play an integral part in colon cancer development by causing chronic inflammation. Due to their poisons and metabolites, among others, bacteria can also cause cancer (Nokhandani *et al.*, 2021). Chronic activation of reactive oxygen species (ROS), interleukin-8 (IL-8), cyclooxygenase-2 (COX-2) and nitric oxide (NO), as well as environmental variables, has been demonstrated to contribute considerably to the carcinogenesis process (Sears and Garrett, 2014).

2.4: The Family Euphorbiaceae

With approximately 300 genera and 7,500 species, Euphorbiaceae (the spurge family) is a well known flowering family that includes a wide variety of plants, from simple weeds to woody trees. Most of the members of this family inhabit tropical climates, while others occur as rainforest trees and herbs (Rahman and Akter, 2013). The family includes economically important species such as castor oil plants, rubber trees, and poisonous weeds like *Euphorbia esula* and *Euphorbia maculata.* As a result, Euphorbiaceae is considered a complex family with great research potential (Mwine and van Damme, 2011).

2.4.1: The Genus Macaranga

Macaranga genus consists of over 300 species, with about 200 species found in tropical Asia and New Guinea (Siregar and Sambas, 2000). It belongs to the Euphorbiaceae family, and it's a soft-wooded tree that rapidly grows to about 15 – 30 m tall (Zakaria *et al.,* 2008; Magadula, 2014; Koter *et al.,* 2019). *Macaranga* species are known to form symbioses with ants. While the ants provide herbivore protection to the trees, the trees serve as nesting space and provide nutrients to the ants (Feldhaar *et al.,* 2000). Some *Macaranga* species are features of secondary forests and are regarded as index species for the extent of forest intrusion (Slik *et al.,* 2003). Seven species of *Macaranga* were reported to be native to the East African forests. *Macaranga conglomerata, Macaranga capensis, Macaranga kilimandscharica*, and *Macaranga schweinfurthii* are found in Kenya within 300 – 2100 m altitudes (Ngangao, Kakamega, and Kieni forests, Taita Hills) (Beentje, 1994; Zakaria *et al.,* 2008; Dharani and Yenesew, 2022).

2.4.1.1: Macaranga conglomerata **Brenan**

Native to Kenya (Taita Hills) and Tanzania (West Usambara Mountain), *Macaranga conglomerata* (commonly called 'Dundu' by Taita people in Kenya) is a medium-sized tree (up to 32 m) with long-stalked inflorescence. Its leaves are slightly pulvinate at the base, held in

a drooping position with the margins incurved, and a leaf-blades ovate shape that is often broadly. The species is restricted to the mentioned montane forests within the elevation of 1400 – 2000 m (Lovett *et al.,* 2005; Lovett and Clarke, 2020).

2.4.1.2: Macaranga capensis (Baill) Sim.

Macaranga capensis (commonly called 'Bwabwa' by Chichewa or 'Mbawa' (Swahili) in Kenya) is a deciduous tree with pale grey bark, spirally arranged, broadly ovate leaves, and short thorns on young stems. It has a densely yellowish-green dehiscent fruit and purplish-brown to blackish seeds. *M. capensis*, an habitant of evergreen forest (305 – 2133 m), is regarded as an indicator of forest invasion. It is found along the lake and stream banks of East Africa (Kenya, Ethiopia) to South Africa and can grow up to 30 meters long (Beentje, 1994; Grace *et al.,* 2003; Wursten *et al.,* 2017).

2.4.1.3: Macaranga kilimandscharica Pax

It is a semi-deciduous tree (4.5 – 27 m) with young branches pubescent. The stems are ascending when young but become a broad spreading crown as it grows old. *M. kilimandscharica* (commonly called 'Mukuhakuha' by Kikuyu in Kenya) is similar to *M. capensis* but with leaves blades rhombic-ovate and rounded or slightly cordate base, in addition to the absence of spines in its branches. The species inhabit mountainous evergreen forests (1300 – 3000 m) and vigorously regenerate in forest edges and disturbed places. The species is native to the East African region (Bussmann and Beck, 1995; Orwa *et al.,* 2009).

2.5: The Family Moraceae

Moraceae (mulberry) consists of 37 genera and about 1100 species, most of which are tropical trees characterized by milky and, in some instances, watery sap. Moraceae species have pinnately veined, simple, and alternate leaves. Both the inflorescences and the unisexual

blooms occur in various sizes and forms. A fleshy structure known as a syncarp surrounds the typically drupaceous fruits. The seeds are huge when there is no endosperm but are microscopi with it. The Moraceae family is found throughout the planet, from tropical to temperate climates. Species such as breadfruit and jackfruit (*Artocarpus*), African breadfruit (*Treculia*), and *Ficus carica* (*Ficus*) produce edible fruits that are not only beneficial to humankind but also the animals. *Morus* and *Maclura* genera from the Moraceae family are involved with silk production, whereas other species from *Broussonetia* and *Artocarpus* find applications in furniture (Berg and Corner, 2005; Zerega *et al.,* 2005; Tamokou *et al.,* 2017).

2.5.1: The Genus Ficus

Ficus genus (Moraceae) consists of over 850 species found worldwide in tropics and subtropics zones (Al-Musayeib *et al.*, 2017). Regarding growth habits, *Ficus* is among the leading diversified plant genera. It includes creepers, climbers, and stranglers. It also has free-standing deciduous and evergreen trees. *Ficus* species are distinguished by their distinctive syconium-like inflorescence and symbiotic connection with Agaonidae wasps, which pollinate their species exclusively (Novotny *et al.*, 2002; Ramírez-benavides, 2016; Khadivi *et al.*,2018; Teixeira *et al.,* 2019; Salehi *et al.,* 2021). About 511 and 132 species of *Ficus* are widely distributed in Indo-Australasian and Neotropical regions, respectively (Kumar *et al.,* 2018). In the African region, 112 species of *Ficus* are recognized currently (Noort *et al.,* 2007), with 37 being distributed in Kenya within 0 – 2300 m altitude, including *Ficus thonningii* (Berg and Hijman, 1989; Maundu *et al.*, 2005; Karangi, 2008).

2.5.1.1: Ficus thonningii

Ficus thonningii Blume (commonly called 'Mugumo' by Kikuyu in Kenya) has a dense, rounded to spreading crown, often epiphytically initially, and is multi-stemmed, evergreen, or short deciduous. The shiny green leaves of *F. thonningii* are alternate, oval (up to 12 cm) with

rounded tip and tapering base, whereas the young leaves are pale and finely hairy. The aerial roots are frequently present, and the bark is greyish. As a flowering tree, both sexual and asexual means of propagation are employed to grow *F. thonningii*, and wasps pollinate it through symbiotic relationships (Dangarembizi *et al.,* 2013, 2014). *F. thonningii* tree grows well in bright, deep, and well-drained soils and is mainly found in tropical and subtropical Africa's upland forests. In Kenya, it can be found in upland forests, dry forest remnants, open or forested grassland, and riverbanks within the altitudes of 300 – 2300 m (Danthu *et al.,* 2002; Maundu *et al.,* 2005).

2.6: Ethnomedicinal uses of *Macaranga* species

In Asia, Eastern and Southern Africa, *Macaranga* species are employed commonly as decoction to manage stomachache, bilharzia, coughing, swallowed poison, fever, dysentery, inflammation, and jaundice. Externally, leaves, resin, and red gum of species from the genus are used in wounds, sores, and boils healing (Kokwaro, 1993; Mahidol *et al.,* 2002; Khatun *et al.,* 2014; Qi *et al.,* 2017).

Traditionally, *M. capensis* stem bark has long been used in KwaZulu-Natal in treating different skin conditions (Grace *et al.,* 2003; Mhlongo and Van Wyk, 2019). Washambaa people of Tanzania utilize the *M. capensis* leaves to manage allergies (Lovett *et al.,* 2005). In Burundi, Ethiopia, and Zimbabwe, the roots (fresh, powdered, or boiled decoction) of *M. Capensis* are used to treat coughs and cold, male impotence, and bilharzia (Grace *et al.,* 2003; Maroyi, 2013). A decoction of *M. kilimandscharica*'s leaves is employed in Kenya and Tanzania to remedy stomach ailments, while its roots extract is used to treat cough, cold, and bilharzia (Kokwaro, 1993; Lovett *et al.,* 2005). Ethnomedicinal uses of some *Macaranga* species are highlighted in Table 2.1.

Table 2.1: Ethnomedicinal uses of some *Macaranga* species

***Macaranga* Species**	**Part(s)**	**Uses**	**Country**	**Reference**
M. aleuritoides	Fruit/Seed and bark	Treatment of abdominal pains, cough, boils, and breast abscesses	Papua New Guinea	Waruruai *et al.,* 2011
M. deheiculata	Leaves	Treatment of jaundice	China	Qi *et al.,* 2017
M. denticulate	Stem and leaves decoction	Prevention of infections after childbirth.	Thailand	Sutthivaiyakit *et al.,* 2002
M. gigantean	Young shoot	Management of fungal infections	Indonesia	Grosvenor *et al.,* 1995
M. indica	Redgum	Healing of wounds	India	Khatun *et al.,* 2014
M. pruinose	Leaves decoction	Treatment of stomach aches	Indonesia	Grosvenor *et al.,* 1995
M. tanarius	Root decoction	Fever relief, suppress coughing, antipyretic, antitussive	Malaysia	Lim *et al.,* 2009
	Leaves extract	Healing of wounds, relieve inflammation	Thailand	Phommart *et al.,* 2005
	Dried root	Emetic agent	Thailand	Mahidol *et al.,* 2002

2.7: Ethnomedicinal uses of *Ficus* species

Indigenous medicinal practices, including Ayurveda, traditionally utilized *Ficus* species. In addition to being used as anticancer, antioxidant, astringent, and carminative agents, *Ficus* species are employed in managing diabetes, ulcers, dysentery, diarrhoea, stomachaches, and haemorrhoids (Kokwaro, 1993; Joseph and Raj, 2010; Badgujar *et al.,* 2014).

Traditional healers have utilized macerated *F. thonningii* to cure diabetes mellitus, gonorrhoea and diarrhoea (Njoroge and Kibunga, 2007; Dangarembizi *et al.,* 2013). In Angola, wounds are treated using the leaves decoction of *F. thonningii*. In the case of gingivitis, the gums that are

bleeding are massaged with leaves while the sores are cleansed with leaf extract. Bronchitis, urinary tract infections, and jaundice are also treated with *F. thonningii*'s leaf extracts (Cousins and Huffman, 2002; Ahur and Madubunyi, 2012; Dangarembizi *et al.,* 2013). An infusion of crushed *F. thonningii'*s stem bark is employed in managing inflammation, arthritis, and sore throats, while the roots are utilised in the treatment of dental aches and malaria, as well as induce lactation (Kokwaro, 1993; Teklehaymanot and Giday, 2007; Ahur and adubunyi, 2012; Dangarembizi *et al.,* 2014). Table 2.2 highlights some of the *Ficus* species' traditional uses.

Table 2.2: Ethnomedicinal uses of some *Ficus* species

***Ficus* Species**	**Part(s)**	**Uses**	**Country**	**Reference(s)**
F. abutilifolia	Leaves	Management of edema.	Nigeria	Dambatta and Aliyu, 2011
F. asperifolia	Dry fruit decoction	Treatment of sterility.	Cameroon	Ngadjui *et al.*, 2013
	Leaf extract	Purgative agent.		Watcho *et al.*, 2009
	Stem bark	Management of diabetes.	Nigeria	Omoniwa *et al.*, 2014
F. capensis	Root	Remedy for cough	Kenya	Kokwaro, 1993
	Bark	Treatment of stomach upsets.		
F. carica	Leaves decoction	Treatment blood deficiency	Nigeria	Nebedum *et al.*, 2010
	Bark	Management of inflammation.	Iran	Ramazani *et al.*, 2010
	Latex	Treatment of sore throat and diabetes.	South Africa	Masevhe *et al.*, 2015
F. exasperate	Leaves	Treatment of inflammation, ulcers, and stomachache.	Nigeria	Ahmed *et al.*, 2012
F. natalensis	Bark	Bark is chewed and the juice swallowed to induce lactation.	Kenya	Kokwaro, 1993
F. platyphylla	Bark	Treatment of psychoses, depression, epilepsy, pain and inflammation.	Nigeria	Chindo *et al.*, 2010
F. racemose	Fruits	Relief of dysentery.	India	Bheemachari *et al.*, 2007
	Bark	Treatment of hematuria, menorrhagia, and hemoptysis.	Bangladesh	Mohiuddin and Lia, 2020
	Root	Chewed to treat tonsillitis.		

2.8: Phytochemistry of the genus *Macaranga*

Previous reports identify *Macaranga* species as rich sources of prenylated flavonoids and stilbenes, many of which have biological activities that encompass almost the entire pharmacological sciences (Magadula, 2014; Vu *et al.*, 2018). Other phytochemicals like

terpenes and tannins were also reported from the genus, even though few (< 10%) of the 300 species in the genus have been investigated phytochemically (Magadula, 2014).

2.8.1: Flavonoids of Macaranga genus

Flavonoids are a group of polyphenolic metabolites with a distinctive C6 - C3 - C6 structure (Alvarez, 2014). These flavonoids are found in different parts of plants, tea, and wine (Batra and Sharma, 2013). The genus *Macaranga* was found to include Flavonols (**I**), flavanones (**II**), flavanonols (**III**), flavones (**IV**), and chalcones (**V**).

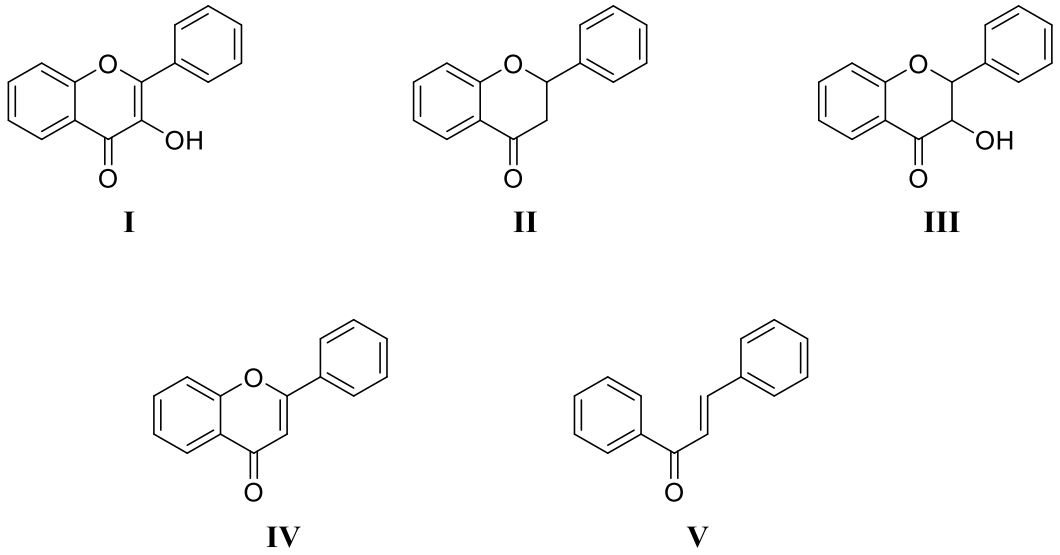


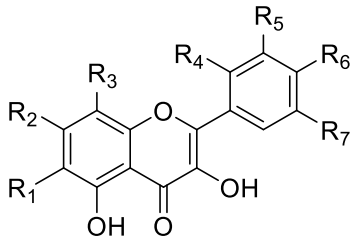
Figure 2.4: The basic skeleton of classes of flavonoids found in *Macaranga* species

2.8.1.1: Flavonols from Macaranga genus

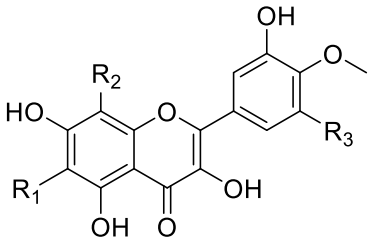
Flavonols are subclass of flavonoids having α, β – unsaturated double bond in ring C with hydroxy group attached to C-3 of the same ring. Flavonols isolated from *Macaranga* species are characterized by prenyl, geranyl or farnesyl group or their modified unit attached to ring A at C-6 or C-8 position. Table 2.3 below summarizes the flavonols reported from the genus *Macaranga*.

Table 2.3: Flavonols from *Macaranga* genus

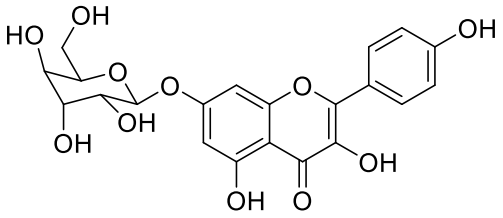
***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. pruinose	Macapruinosin C (**50**)	Leaves	Syah and Ghisalberti, 2010
	Papyriflavonol A (**51**)		
M. rhizinoids	Macarhizinoidin A (**52**)	Leaves	Tanjung *et al.*, 2010
	Macarhizinoidin B (**53**)		
M. hurifolia	Macafolia A (5**4**)	Fruits	Pagna *et al.*, 2022
	Macafolia B (**55**)		
M. pruinose	Macapruinosin F (**56**)	Leaves	Syah and Ghisalberti, 2012
	Glysperin A (**57**)		
M. kurzii	Izalpinin (**58**)	Leaves	Thanh *et al.*, 2012
	Glepidotin A (**59**)		
	8-Prenylgalangin (**60**)		
	Galangin (**61**)		
M. recurvata	Broussoflavonol F (**62**)	Leaves	Tanjung *et al.*, 2012
M. kurzii	Icaritin (**63**)	Twigs	Yang *et al.*, 2014
	6,8-Diprenylgalangin (**64**)		
	Licoflavonol (**65**)		
M. hispida	5,7,3′,4′-Tetrahydroxy-6-geranylflavonol (**66**)	Leaves	Megawati *et al.*, 2015
	Kaemferol 7-*O*-β-glucoside (**67**)		
M. siamensis	Macasiamenol A (**68**)	Leaves and twigs	Pailee *et al.*, 2015
	Macasiamenol B (**69**)		
M. indica	Macarindicin A (**70**)	Twigs	Yang *et al.*, 2015a
	Macarindicin B (**71**)		
M. denticulata	Denticulatin D (**72**)	fronds	Yang *et al.*, 2015b
	Denticulatin E (**73**)		
M. trichocarpa	4′-*O*-Methylmacagigantin (**74**)	Leaves	Tanjung *et al.*, 2018
M. indica	Macarindicin D (**75**)	Leaves	Huonga *et al.*, 2019
	Macarindicin E (**76**)		
	Macarindicin F (**77**)		
M. denticulata	3′-Dihydroxy-solophenol C (**78**)	Fruits	Le *et al.*, 2021
M. barteri	8-Prenylkaempferol (**79**)	Leaves	Segun *et al.*, 2019
	Isomacarangin (**80**)		
M. indica	Macarindicin I (**81**)	Leaves	Vu *et al.*, 2021
	Macarindicin II (**82**)		
	Macarindicin III (**83**)		
	Macarindicin IV (**84**)		



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
50	Prenyl	OH	H	Geranyl	OH	OH	H
51	Prenyl	OH	H	H	OH	OH	Prenyl
52	Geranyl	OH	H	H	H	OCH_3	H
53	H	OH	H	Geranyl	OH	OCH_3	H
56	Geranyl	OH	H	H	H	OH	Prenyl
57	Prenyl	OH	H	H	H	OH	Prenyl
58	H	OCH_3	H	H	H	H	H
59	Prenyl	OH	H	H	H	H	H
60	H	OH	Prenyl	H	H	H	H
61	H	OH	H	H	H	H	H
62	H	OH	Prenyl	H	H	OH	Prenyl
63	H	OH	Prenyl	H	H	OCH_3	H
64	Prenyl	OH	Prenyl	H	H	H	H
65	Prenyl	OH	H	H	H	OH	H
66	Geranyl	OH	H	H	H	OH	OH
68	H	OH	Prenyl	H	H	OCH_3	Prenyl
69	H	OH	H	H	H	OCH_3	Prenyl
70	Geranyl	OH	H	H	OH	OH	Prenyl
71	Farnesyl	OH	H	H	OH	OH	H
73	H	OH	H	H	OH	OH	Geranyl
74	Farnesyl	OH	H	H	H	OCH_3	H
75	Prenyl	OH	H	H	H	OH	CHO
79	H	OH	Prenyl	H	H	OH	H
80	H	OH	Geranyl	H	H	OH	H



54: R_1 = Prenyl R_2 = H R_3 = Prenyl
55: R_1 = R_2 = R_3 = Prenyl



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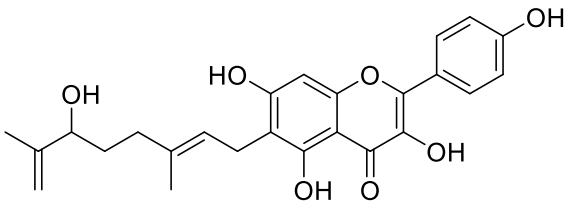

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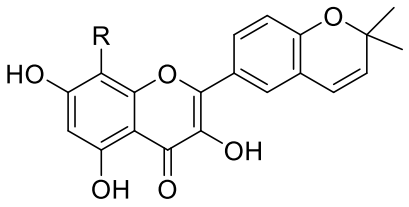
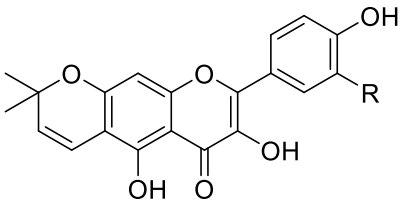
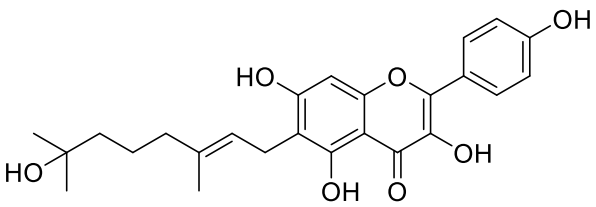


76: R = Prenyl



77: R = Prenyl



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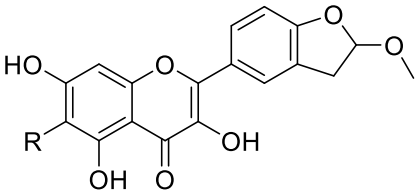
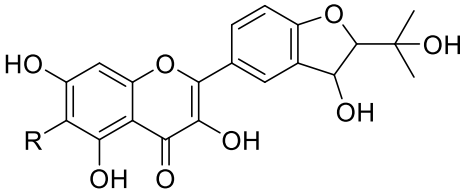
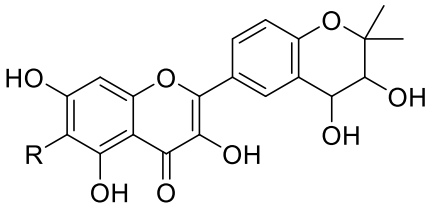


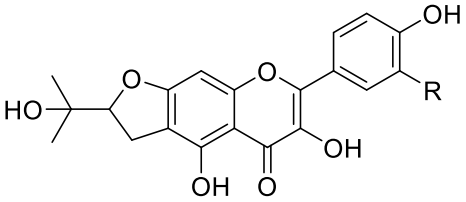
81: R = Prenyl



82: R = Prenyl



83: R = Prenyl



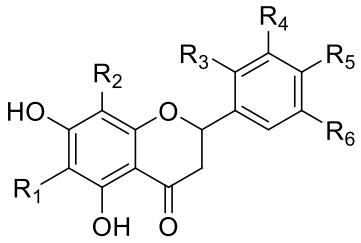
84: R = Prenyl

2.8.1.2: Flavanones from Macaranga genus

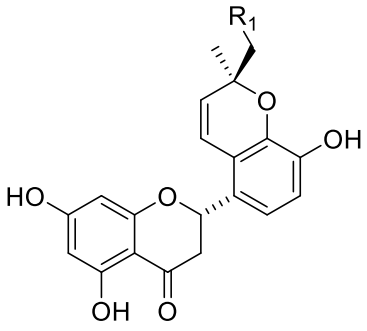
Flavanones belong to the subclass of flavonoids characterized by a saturated C ring. Prenylation at C-6 and/or C-8 of ring A is a common feature of flavanones reported from the genus. Flavanones isolated from the genus *Macaranga* are summarized in Table 2.4 below.

Table 2.4: Flavanones from *Macaranga* genus

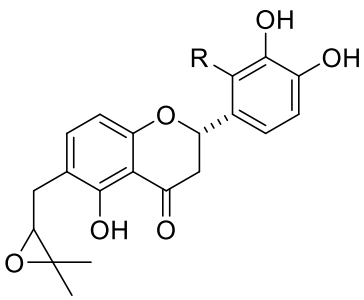
***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. tribola	6-Prenyl-3′-methoxy-eriodictyol (**85**)	Flower	Zakaria *et al.*, 2010
	6-Farnesyl-3′,4′,5,7-tetrahydroxy flavanone (**86**)		
	Nymphaeol B (**87**)		
	Nymphaeol C (**88**)		
M. lowii	4′-*O*- Methyl-8-isoprenylnaringenin (**89**)	Leaves	Agustina *et al.*, 2012
M. kurzii	5,7-Dihydroxy-6-prenylflavanone (**90**)	Leaves	Thanh *et al.*, 2012
	Glabranin (**91**)		
M. tribola	Malaysianone A (**92**)	Inflorescences	Zakaria *et al.*, 2012
M. kurzii	Isosakuranetin (**93**)	Twigs	Yang *et al.*, 2014
	8-Prenylnaringenin (**94**)		
M. tanarius	Epoxynymphaeol C (**95**)	Leaves	Syah and Ghisalberti, 2015
M. indica	Macarindicin C (**96**)	Twigs	Yang *et al.*, 2015a
M. denticulata	Bonannione A (**97**)	Twigs and leaves	Zhang *et al.*, 2016
M. hosei	4′-*O*-Methyl-8-isoprenyl eriodictyol (**98**)	Leaves	Marliana *et al.*, 2018
	6-Isoprenyl eriodictyol (**99**)		
M. tanarius	Propolin C (**100**)	Fruits	Lee *et al.*, 2019
	Propolin D (**101**)		
	Propolin F (**102**)		
	Propolin G (**103**)		
	Propolin H (**104**)		
M. balansae	Propolin I (**105**)	Fruits	Mai *et al.*, 2020
	6,8-Diprenyl-4′-methylnaringenia (**106**)		
M. denticulata	8-Dimethlallylisosakuranetin (**107**)	Fruits	Le *et al.*, 2021



	R_1	R_2	R_3	R_4	R_5	R_6
85	Prenyl	H	H	OCH_3	OH	H
86	Farnesyl	H	H	OH	OH	H
87	H	H	Generyl	OH	OH	H
88	Prenyl	H	Generyl	OH	OH	H
89	H	Prenyl	H	H	OCH_3	H
90	Prenyl	H	H	H	H	H
91	H	Prenyl	H	H	H	H
93	H	H	H	H	OCH_3	H
94	H	Prenyl	H	H	OH	H
96	Farnesyl	H	H	H	OH	H
97	Geranyl	H	H	H	OH	H
98	H	Prenyl	H	OH	OCH_3	H
99	Prenyl	H	H	H	OH	OH
100	Geranyl	H	H	OH	OH	H
101	H	H	Geranyl	OH	OH	H
102	H	H	H	OH	OH	H
103	Prenyl	H	Geranyl	OH	OH	H
104	H	H	H	H	OH	Geranyl
105	Farnesyl	H	H	OH	H	OH
106	Prenyl	Prenyl	H	H	OCH_3	H
107	H	Prenyl	H	H	OCH_3	H



92: R = Prenyl



95: R = Geranyl

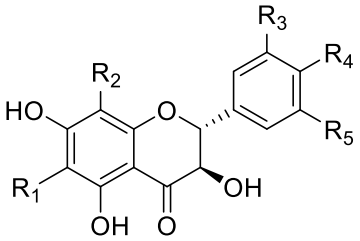
2.8.1.3: Flavanonols from Macaranga genus

Flavanonols are flavonoids with a 3-hydroxy-2,3-dihydro-2-phenylchromen-4-one backbone.

Listed in Table 2.5 below are some flavanonols from the *Macaranga* genus.

Table 2.5: Flavanonols from *Macaranga* genus

***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. lowii	Macalowiinin (**108**)	Leaves	Agustina *et al.*, 2012
M. recurvata	Macarecurvatin A (**109**)	Leaves	Tanjung *et al.*, 2012
	6,8-Diisoprenylaromadendrin (**110**)		
M. kurzii	Kurzphenol B (**111**)	Twigs	Yang *et al.*, 2014
	Glepidotin B (**112**)		
M. denticulata	Bonanniol A (**113**)	Twigs and leaves	Zhang *et al.*, 2016
M. balansae	4′-Methyl-8-prenyltaxifolin (**114**)	Fruits	Mai *et al.*, 2020
	6,8-Diprenylaromadendrin (**115**)		
M. denticulata	Diplacol (**116**)	Fruits	Le *et al.*, 2021



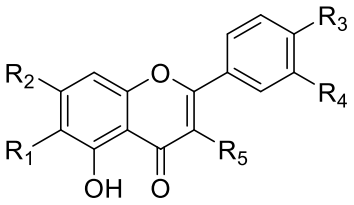
	R_1	R_2	R_3	R_4	R_5
108	H	Prenyl	H	OCH_3	H
109	Prenyl	Prenyl	H	OH	OH
110	Prenyl	Prenyl	H	OH	H
111	Prenyl	Prenyl	H	H	H
112	H	Prenyl	H	H	H
113	Geranyl	H	H	OH	H
114	H	Prenyl	OH	OCH_3	H
115	Prenyl	Prenyl	H	OH	H
116	Geranyl	H	H	OH	OH

2.8.1.4: Flavones from Macaranga genus

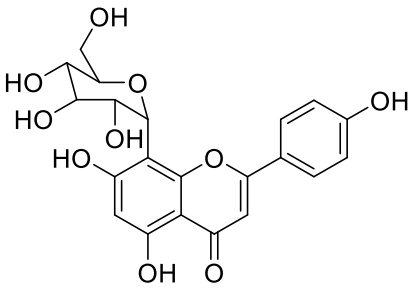
Flavones are flavonoids with chromanone backbone, and a phenyl group attached to C-2. Table 2.6 below lists the flavones isolated from the genus.

Table 2.6: Flavones from *Macaranga* genus

***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. lowii	4′-*O*- Methyl-5,7,4′-trihydroxyflavone (**117**)	Leaves	Agustina *et al.*, 2012
M. gigantifolia	5,7,3′,4′- Tetrahydroxy-3,6-diprenylflavone (**118**)	Leaves	Darmawan *et al.*, 2015
	Apigenin (**119**)		Fajriah, 2016
	Apigenin-8-*C*-glycoside (**120**)		Primahana and Darmawan, 2017
M. hosei	5-Hydroxy-6,7,4′-trimethoxyflavone (**121**)	Leaves	Salleh *et al.*, 2017
M. indica	Isovitex (**122**)	Leaves	Vu *et al.*, 2021



	R_1	R_2	R_3	R_4	R_5
117	H	OH	OCH_3	H	H
118	Prenyl	OH	OH	OH	Prenyl
119	H	OH	OH	H	H
121	OCH_3	OCH_3	OCH3	H	H



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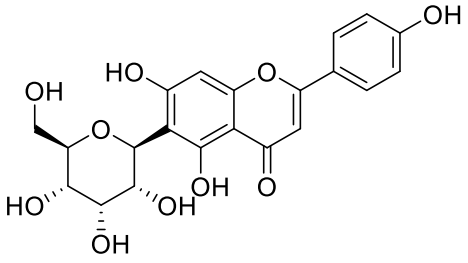


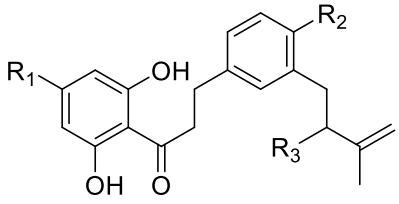
122

2.8.2: Chalcones from Macaranga genus

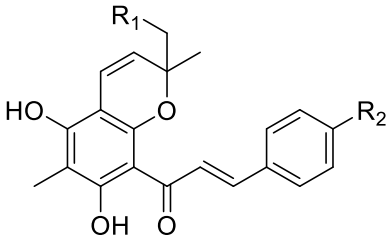
Chalcones are polyphenolic compounds characterized by α, β-unsaturated ketones. They serve as precursors for flavonoids biosynthesis in plants (Gaonkar and Vignesh, 2017). Table 2.7 below highlights examples of isolated chalcones from *Macaranga* genus.

Table 2.7: Chalcone from *Macaranga* genus

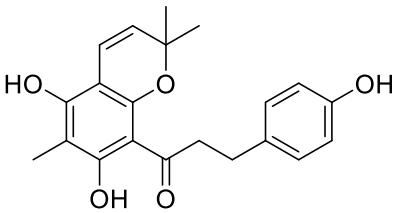
***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. trichocarpa	Oxymacatrichocarpin C (**123**)	Leaves	Fareza *et al.*, 2014
	Isomacatrichocarpin C (**124**)		
	Flavokawain C (**125**)		Tanjung *et al.*, 2018
	Helichrysetin (**126**)		
M. denticulata	Dentichalcone A (**127**)	Twigs and leaves	Zhang *et al.*, 2016
	Dentichalcone B (**128**)		
	Dentichalcone C (**129**)		



	R_1	R_2	R_3
123	OH	OCH_3	OH
124	OCH_3	OH	H



	R_1	R_2
127	H	OH
129	OH	H



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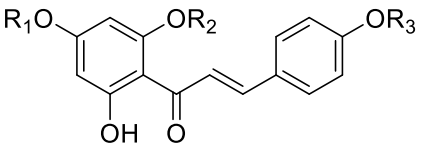


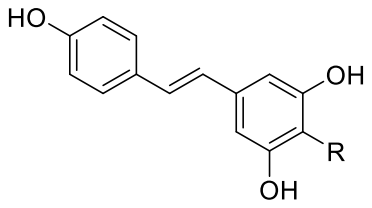
	R_1	R_2	R_3
125	CH_3	CH_3	H
126	H	CH_3	H

2.8.3: Stilbenes from the genus Macaranga

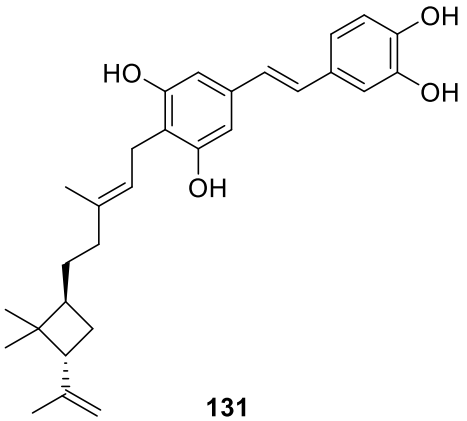
Stilbenes are polyphenolic compounds that have two phenyl rings bridged by an ethylene. They are also described to contain C6 – C2 – C6 carbon skeleton or 1,2-diphenylethylene nucleus. Stilbenes are the second main type of metabolites isolated from *Macaranga* genus (Table 2.8).

Table 2.8: Stilbenes from *Macaranga* genus

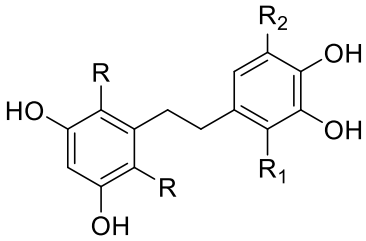
***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. schweinfuethii	Schweinfurthin J (**130**)	Leaves	Klausmeyer *et al.*, 2010
M. ruinosa	Macapruinosin (**131**)	Leaves	Syah and Ghisalberti, 2010
M. javanica	Laevifolin A (**132**)	Leaves	Ilmiawati *et al.* 2015
M. denticulata	Denticulatain A (**133**)	Fronds	Yang *et al.*, 2015b
M. siamensis	Macasiamenene L (**134**)	Leaves and twigs	Pailee *et al.*, 2015
	Macasiamenene M (**135**)		
M. rubiginosa	Macarubiginosin A (**136**)	Leaves	Tanjung *et al.*, 2017
M. tanarius	Schweinfurthin K (**137**)	Fruits	Péresse *et al.*, 2017
	Schweinfurthin L (**138**)		
M. trichocarpa	Macatrichocarpin H (**139**)	Leaves	Tanjung *et al.*, 2018
M. barteri	Macabartebene A (**140**)	Leaves	Segun *et al.*, 2019
	Macabartebene B (**141**)		
	Macabartebene C (**142**)		
M. heynei	Malayheyneiin D (**143**)	Leaves	Kamarozaman *et al.*, 2019
M. balansae	4′-Deprenyl-4-methoxymappain (**144**)	Fruits	Mai *et al.*, 2020
M. denticulata	4′-Deprenylmappain (**145**)	Fruits	Le *et al.*, 2021
M. barteri	Schweinfurthin G (**146**)	Leaves	Segun *et al.*, 2021
	Mappain (**147**)		



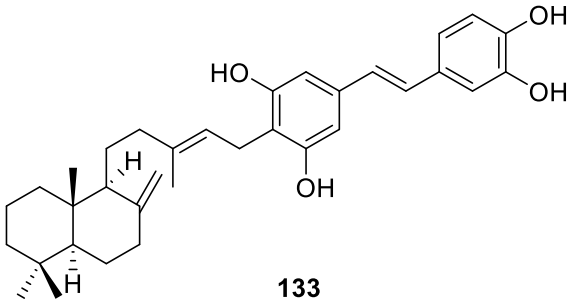
130: R = Farnesyl



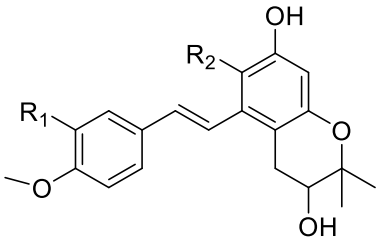
131



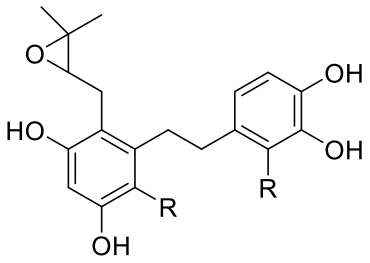
132: R = R_1 = Prenyl, R_2 = H



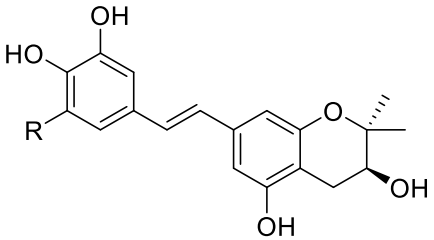
133



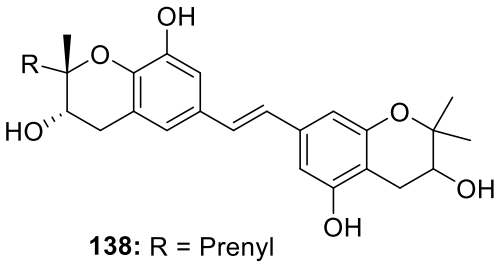
134: R_1 = H, R_2 = Prenyl
135: R_1 = OH, R_2 = Prenyl



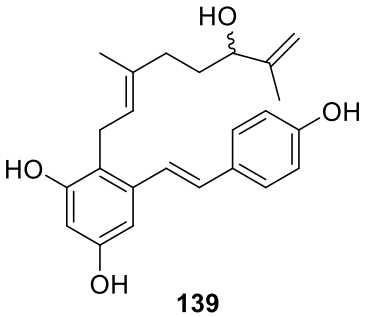
136: R = Prenyl



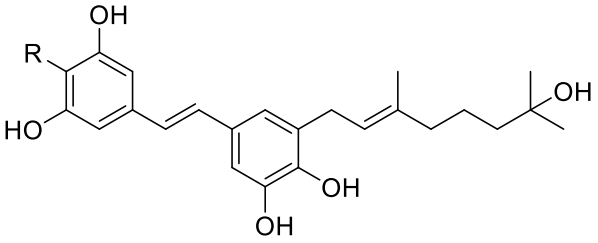
137: R = Geranyl



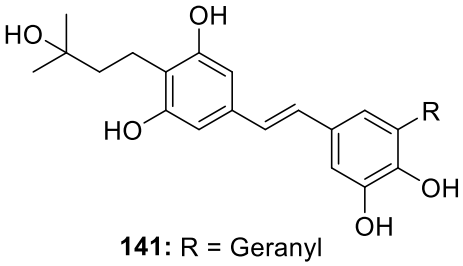
138: R = Prenyl



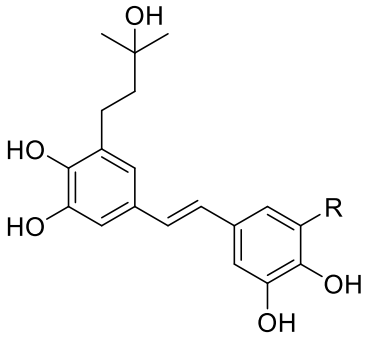
139



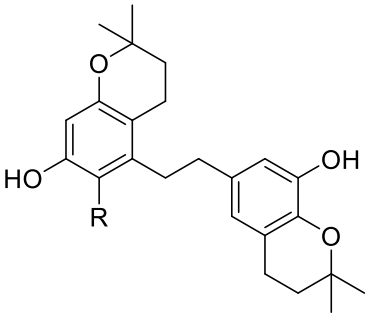
140: R = Prenyl



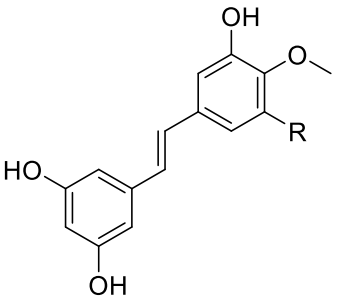
141: R = Geranyl



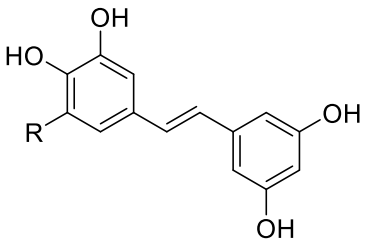
142: R = Geranyl



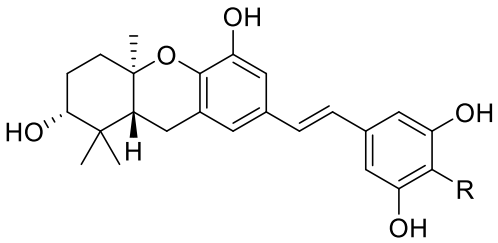
143: R = Prenyl



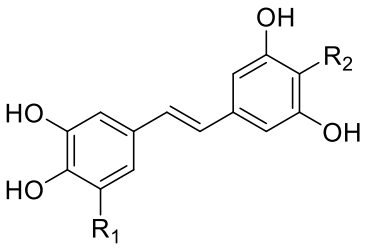
144: R = Geranyl



145: R = Geranyl



146: R = Prenyl



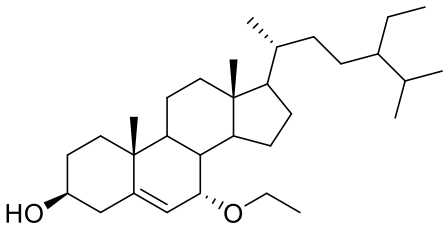
147: R_1 = Geranyl, R_2 = Prenyl

2.8.4: Terpenoids from the genus Macaranga

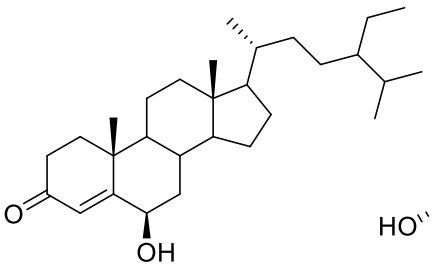
The genus *Macaranga* also yielded terpenoids such as taraxerol and its derivatives and cembranoids, in addition to the flavonoids and stilbenes (Yang *et al.*, 2015b; Qi *et al.*, 2017; Le *et al.*, 2021). Table 2.9 below highlights some of the terpenoids isolated from *Macaranga* genus.

Table 2.9: Terpenoids from *Macaranga* genus

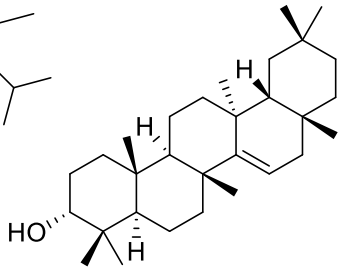
***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. denticulata	3β-Hydroxy-7α-24β-ethylcholest-5-ene (**148**)	Fronds	Yang *et al.*, 2015b
	(24*R*)-6β-Hydroxy-24-ethylcholest-4-en-3-one (**149**)		
	Epitaraxerol (**150**)		
M. hosei	Lupenone (**151**)	Leaves	Salleh *et al.*, 2017
	β-Sitostenone (**152**)		
M. constricta	Taraxerone (**153**)	Leaves	
	Taraxerol (**154**)		
	β-Amyrin (**155**)		
M. deheiculata	Deheiculatin J (**156**)	Leaves and twigs	Qi *et al.*, 2017
	Deheiculatin K (**157**)		
	Deheiculatin L (**158**)		
M. pustulata	Deheiculatin M (**159**)	Twigs	Luo *et al.*, 2018
	Deheiculatin N (**160**)		
	Deheiculatin O (**161**)		
M. balansae	Stigmastane 3β,5α,6β-triol (**162**)	Stem	Thang *et al.*, 2018
M. denticulata	Poilaneic acid (**163**)	Fruits	Le *et al.*, 2021



148



149



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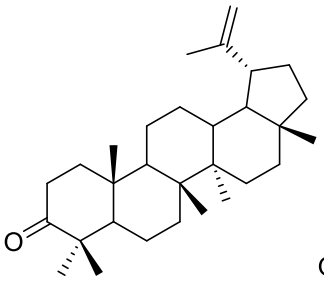

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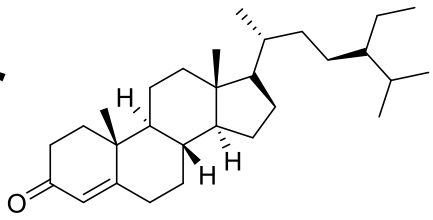

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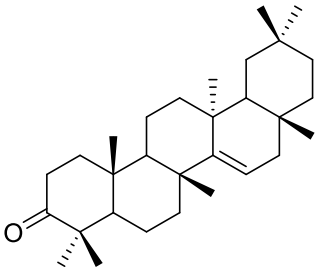

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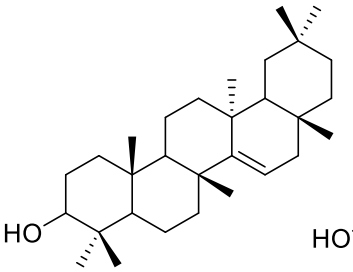

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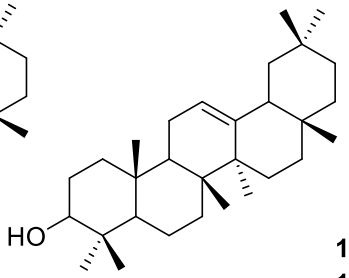

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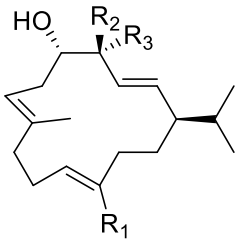
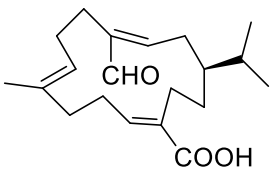


156: R_1 = COOH, R_2 = CH_3, R_3 = OCH_3
157: R_1 = COOH, R_2 = OCH_3, R_3 = CH_3
158: R1 = CH_2OH, R_2 = OH, R_3 = CH_3



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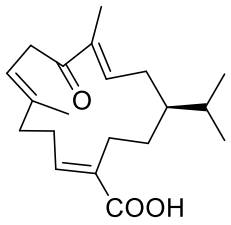

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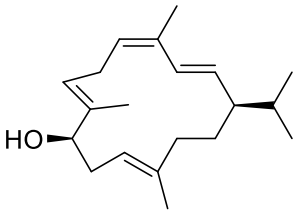

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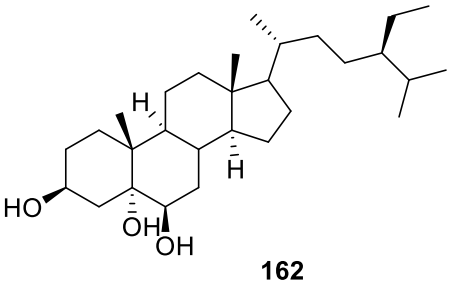
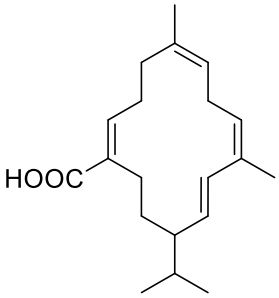


162



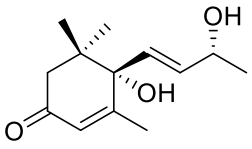
163

2.8.5: Coumarins, Ellagic acids and Phenanthrenes from the genus Macaranga

Other classes of compounds isolated from the genus *Macaranga* includes coumarins (Yang *et al.*, 2014), ellagic acids (Yang *et al.*, 2015a; Thang *et al.*, 2018), and phenanthrenes (Ilmiawati *et al.*, 2015) (Table 2.10).

Table 2.10: Other compounds from *Macaranga* genus

***Macaranga* species**	**Compound**	**Plant part**	**Reference**
M. kurzii	Blumenol A (**164**)	Twigs	Yang *et al.*, 2014
	Scopeletin (**165**)		
	Salicylic acid (**166**)		
M. indica	Ellagic acid (**167**)	Twigs	Yang *et al.*, 2015a
M. denticulate	α-Tocopherolquinone (**168**)	Fronds	Yang *et al.*, 2015b
	Boehmanan (**169**)		
M. javanica	Macajavanicin A (**170**)	Leaves	Ilmiawati *et al.*, 2015
	Macajavanicin B (**171**)		
	Macajavanicin C (**172**)		
M. sampsonii	Maltol β-*D*-glucopyranoside (**173**)	Fruits	Quynh *et al.*, 2018
	Methyl brevifolincarboxylate (**174**)		
	3,5-Dihydroxy-4-methoxy benzoic acid (**175**)		
	Gallic acid (**176**)		
M. balansae	Dehydroxycubebin (**177**)	Stems	Thang *et al.*, 2018



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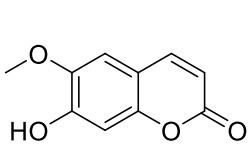

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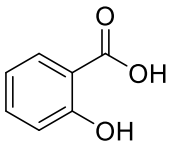

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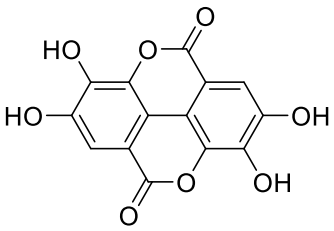

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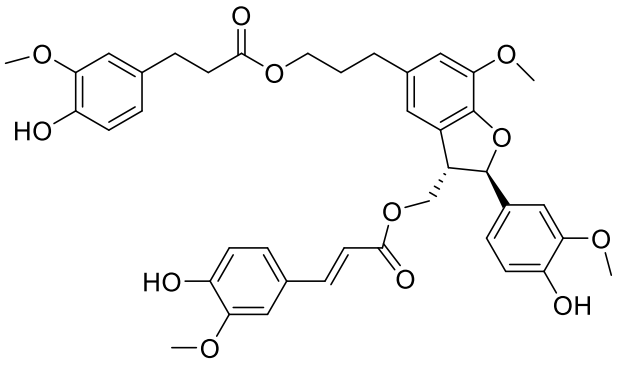

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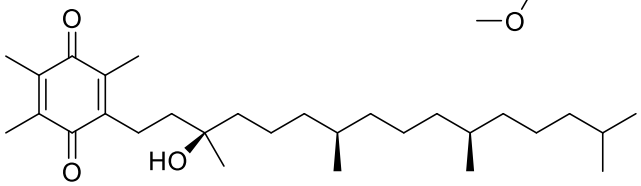

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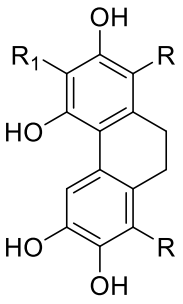
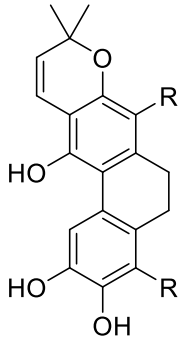


170: R = Prenyl, R_1 = H
171: R = R_2 = Prenyl



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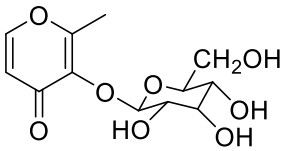

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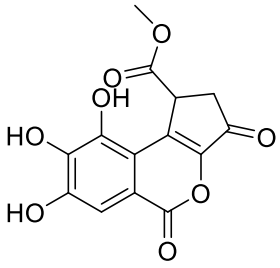

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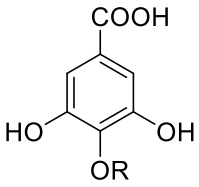
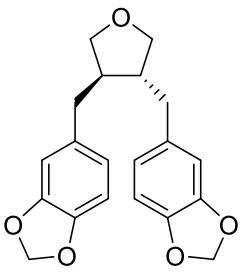


175: R = CH3
176: R = H



177

2.9: Phytochemistry of the genus *Ficus*

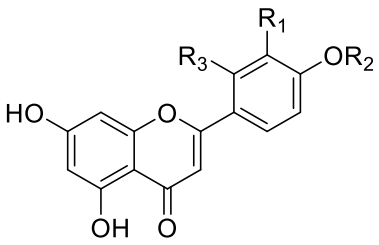
Following the phytochemical analyses of various *Ficus* species parts, secondary metabolites including flavonoids, terpenoids, alkaloids, and coumarins were identified and characterized (Chaware *et al.,* 2020; Putra *et al.,* 2020; Murugesu *et al.,* 2021; Salehi *et al.,* 2021).

2.9.1: Flavonoids from the Ficus genus

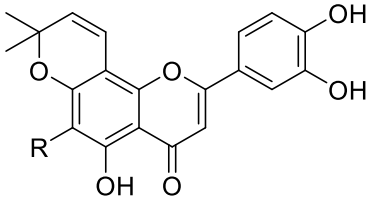
Flavonoids are among the predominant phytoconstituents found in the *Ficus* genus. Flavones, isoflavones, flavanones, and flavanonols were isolated from the *Ficus* genus.

2.9.1.1: Flavones from the Ficus genus

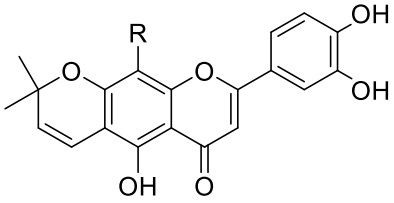
Flavones isolated from the genus *Ficus* include luteolin (**178**), chrysoeriol (**179**), 5,6,7-trihydroxy-4′-methoxy-flavone (**180**) and 5,7,2′,4′-tetrahydroxyflavone (**181**) from *F. tsiangii* (Wang *et al.,* 2014), ficubee A (**182**) and ficubee B (**183**) from *F. beecheyana* (Lee *et al.,* 2004), and carpachromene (**184**) from *F. nervosa* (Chen *et al.,* 2010).



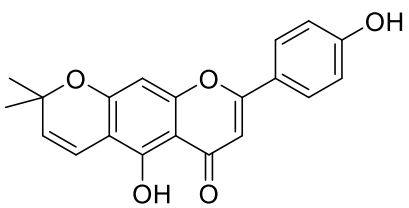
	R_1	R_2	R_3
178	OH	H	H
179	OCH_3	H	H
180	H	CH_3	H
181	H	H	OH



182: R = Prenyl



183: R = Prenyl



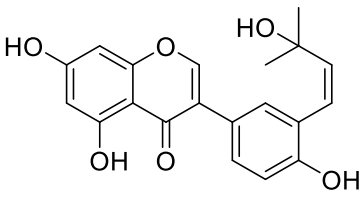
184

2.9.1.2: Isoflavones from the Ficus genus

Isoflavones are the major class of flavonoids reported from *Ficus* species. Table 2.11 below summarizes the isoflavones isolated from the genus *Ficus.*

Table 2.11: Isoflavones from the *Ficus* genus

***Ficus* species**	**Compound**	**Plant part**	**Reference**
F. auriculata	(*Z*)-5,7,4′-Trihydroxy-3′-[3-hydroxy-3-methyl-1-butenyl]isoflavone (**185**)	Fruits	Shao *et al.*, 2022
	5,7,4′-Trihydroxy-3′-[7-hydroxy-3,7-dimethyl-2(*E*)-octenyl]isoflavone (**186**)		
	5,7,4′-Trihydroxy-3′-[6,7-dihydroxy-3,7-dimethyl-2(*E*)-octenyl] isoflavone (**187**)		
	Isowigtheone (**188**)		
F. nervosa	Parvisoflavone B (**189**)	Roots	Chen *et al.*, 2010
	Alpinumisoflavone (**190**)		
	2′-Hydroxygenistein (**191**)		
F. tikoua	Wighteone (**192**)	Stem bark	Wei *et al.*, 2012
	Lupiwighteone (**193**)		
F. tsiangii	Genistein (**194**)	Leaves	Wang *et al.*, 2014
	Prunetin (**195**)		



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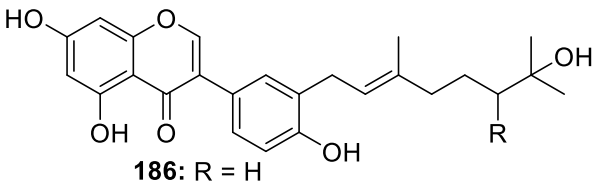
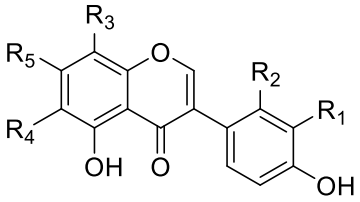
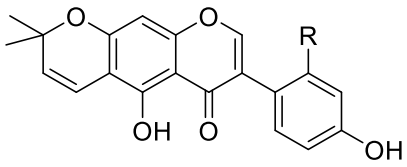


186: R = H
187: R = OH



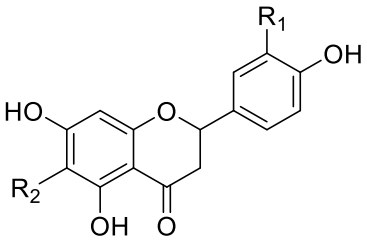


189: R = H
190: R = OH

	R1	R2	R3	R4	R5
188	Prenyl	H	H	H	OH
191	H	OH	H	H	OH
192	H	H	H	Prenyl	OH
193	H	H	Prenyl	H	OH
194	H	H	H	H	OH
195	H	H	H	H	OCH_3

2.9.1.3: Flavanones from the Ficus genus

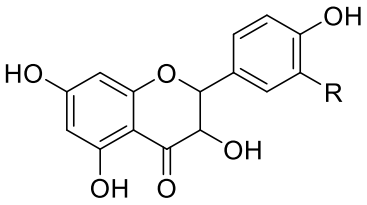
Examples of flavanones reported from *Ficus* species include naringenin (**196**), eriodictyol (**197**), isocarthamidin (**198**) found in *F. tsiangii*'s stems (Wang *et al.*, 2014), and 6 – prenylnaringenin (**199**) from the *F. tikoua* (Wei *et al.*, 2012).



	R_1	R_2
196	H	H
197	OH	H
198	H	OH
199	H	Prenyl

2.9.1.4: Flavanonols from the Ficus genus

Few flavanonols, including taxifolin (**200**) and dihydrokaempferol (**201**), were isolated from *F. tsiangii* (Wang *et al.*, 2014).



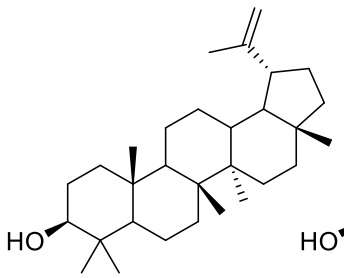
200: R = OH
201: R = H

2.9.2: Terpenoids from the Ficus genus

Terpenoids are the major class of plant metabolites reported from the *Ficus* genus. Table 2.12 below summarizes the terpenoids isolated from the genus *Ficus.*

Table 2.12: Terpenoids from *Ficus* genus

***Ficus* species**	**Compound**	**Plant part**	**Reference**
F. benjamina	Lupeol (**202**)	Leaves	Singh *et al.*, 2019
	Ursolic acid (**203**)		
F. sycomorus	Lupeol acetate (**204**)	Root	Muktar *et al.*, 2018
F. exasperata	Betulinic acid (**205**)	Stem bark	Tameye *et al.*, 2021
	β-Amyrin (**206**)		
F. cordata	3β-Acetoxy-8,26-cyclo-ursan-20β-ol (**207**)	Stem bark	Poumale *et al.*, 2008
	8,26-Cyclo-urs-21-en-3β,20β-diol (**208**)		
	Oleanolic acid (**209**)		
	α-Amyrin (**210**)		
F. nervosa	Friedelinol (**211**)	Leaves	Ragasa *et al.*, 2014
	Squalene (**212**)		
	Cycloeucalenol (**213**)		
F. pandurata	β-Amyrone (**214**)	Stem bark	Ramadan *et al.*, 2009
	α-Amyrin acetate (**215**)		
F. retusa	Moretenone (**216**)	Aerial	Sarg *et al.*, 2011



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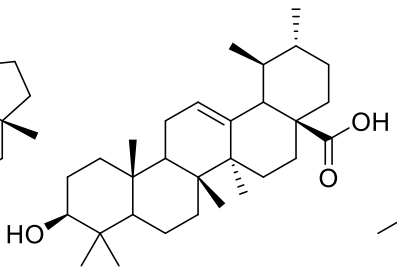

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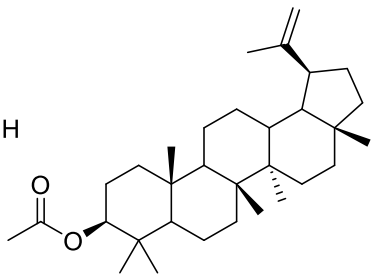

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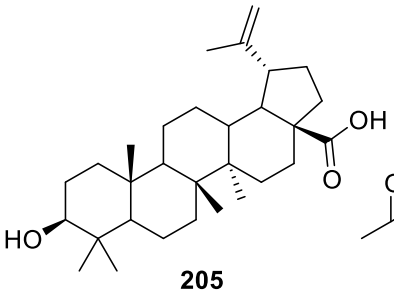

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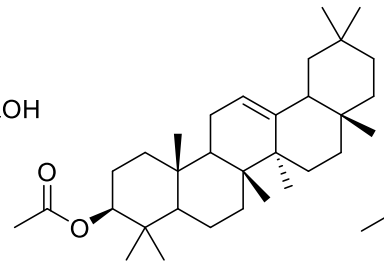

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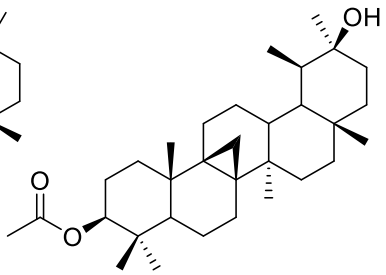

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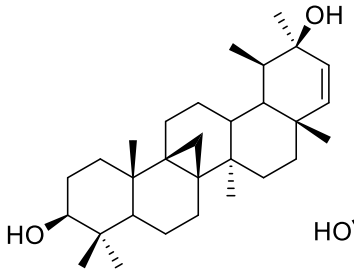

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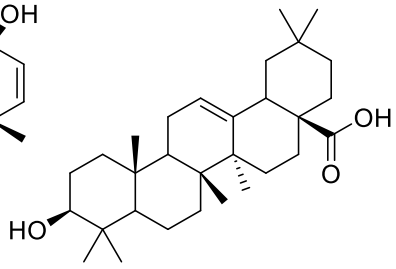

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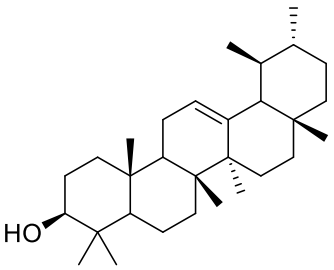

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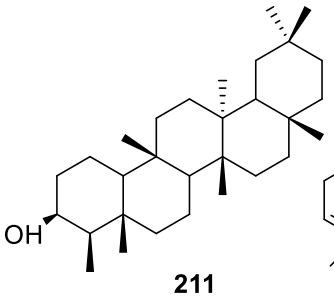

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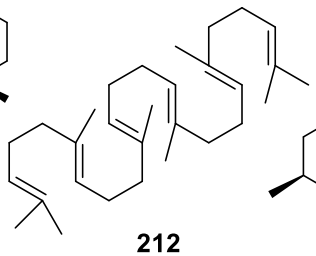

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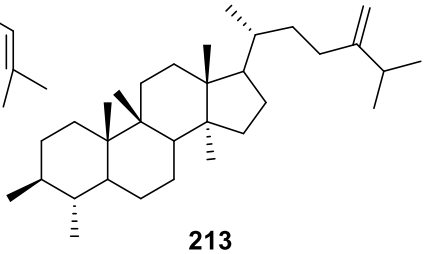

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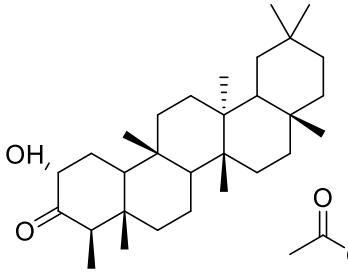

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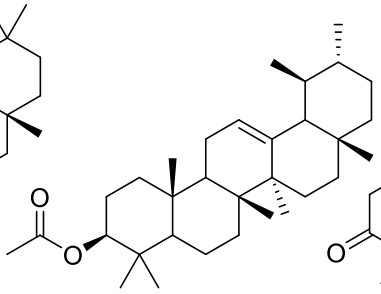

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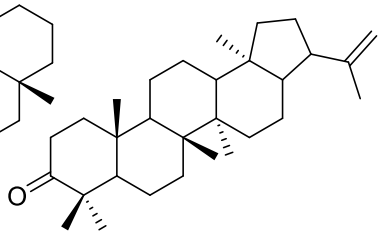
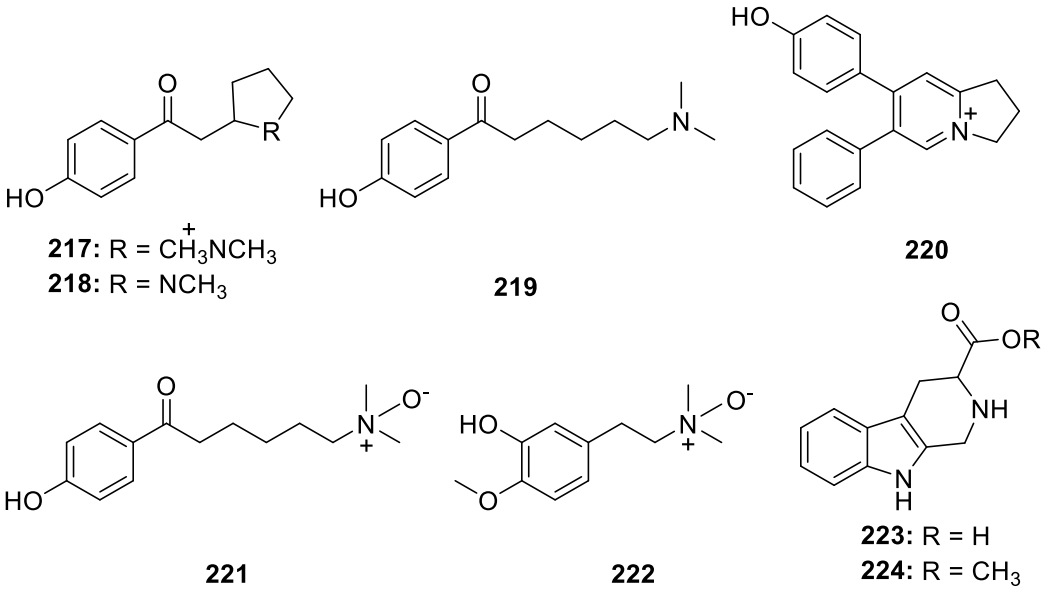


216

2.9.3: Alkaloids from the Ficus genus

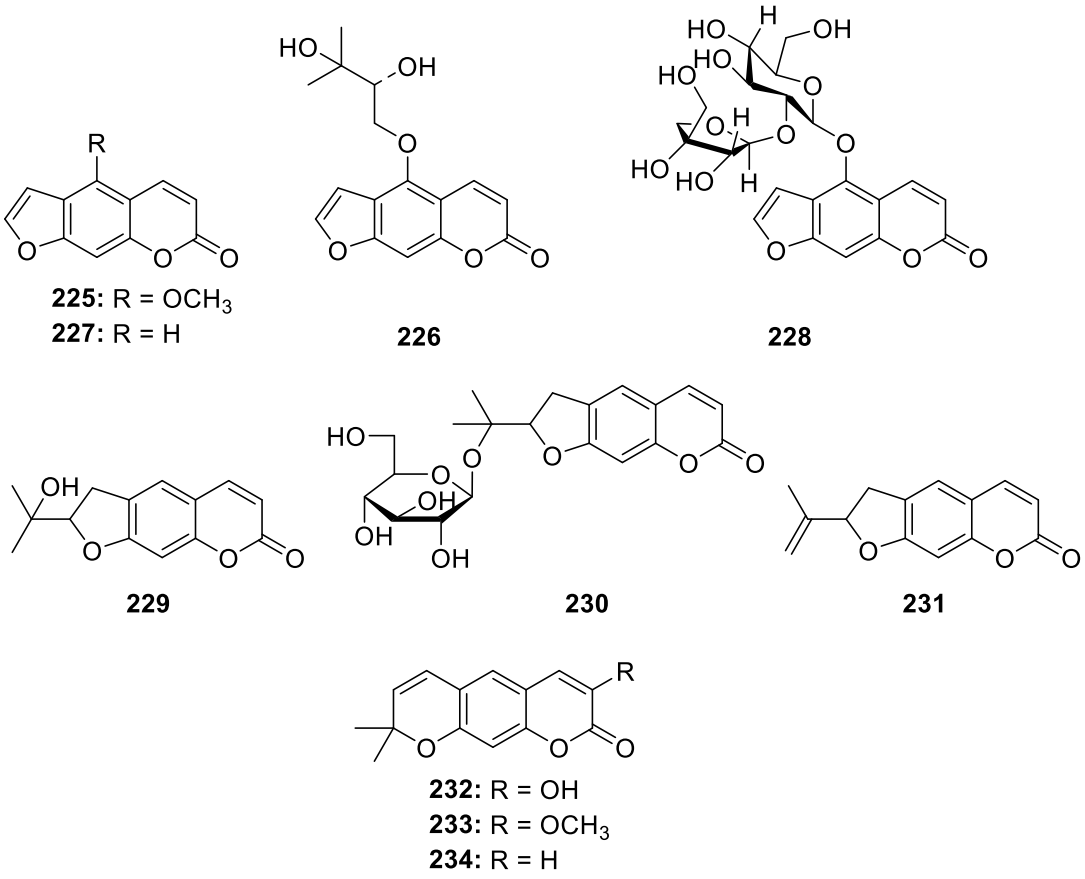
Alkaloids are organic compounds containing at least one nitrogen atom in an amine-type structure. Alkaloids isolated from the genus *Ficus* include ficushispimines A (**217**), B (**218**) and C (**219**), ficushispidine (**220**) and ficuhismines C (**221**) and D (**222**) (Shi *et al.*, 2016; Jia *et al.*, 2020). 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (**223**) and methyl 1-methyl-1,2,3,4-tetrahydro-*β*-carboline-3-carboxylate (**224**) were reported from *F. hirta* (Wan *et al.*, 2017) .



2.9.4: Coumarins from the Ficus genus

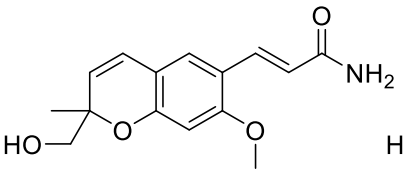
Coumarins are chromenones with a keto group located at the 2-position. They are an essential class of C6 – C3 plant metabolites with various pharmacological potentials. Coumarins isolated from the genus *Ficus* include bergapten (**225**) and oxypeucedanin hydrate (**226**) from *F. exasperata* (Amponsah *et al.,* 2013), psoralen (**227**) from *F. carica* (Chunyan *et al.,* 2009), 5-*O*-[β-*D*-apiofuranosyl-(1→2)-β-*D*-glucopyranosyl]-bergaptol (**228**) from *F. hitra* (Dai *et al.,* 2018), nodakenetin (**229**), 4′-O-b-glucopyranosyl-3′-hydroxy-nodakenetin (**230**), and isoangenomalin (**231**) from *F. tsiangii* (Wang *et al.,* 2014). 3-hydroxyxanthyletin (**232**), 3-

methoxyxanthyletin (**233**) and xanthyletin (**234**) were also reported from *F. nervosa* (Chen *et al.,* 2010).



2.9.5: Miscellaneous compounds from the Ficus genus

Cinnamic acid derivatives, including ficusanolides A (**235**) and B (**236**) and ficusanol (**237**), were reported from *F. exasperata* (Tameye *et al.,* 2021). Among the sphingolipids that have been identified from various species of *Ficus* include gynuramide II (**238**) (Mbougnia *et al.,* 2021), mucusamide (**239**) (Bankeu *et al.,* 2010), mucusoside (**240**) (Hassan *et al.,* 2020), and lutaoside (**241**) (Poumale *et al.,* 2011).



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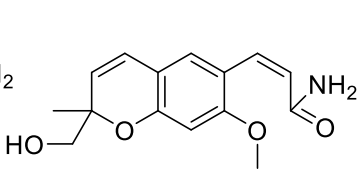

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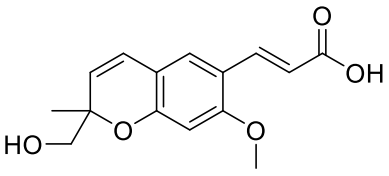

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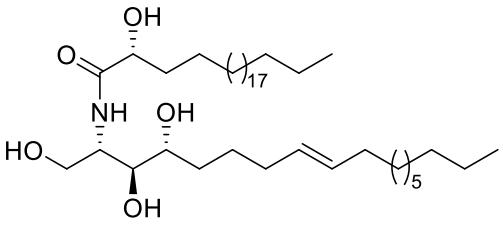

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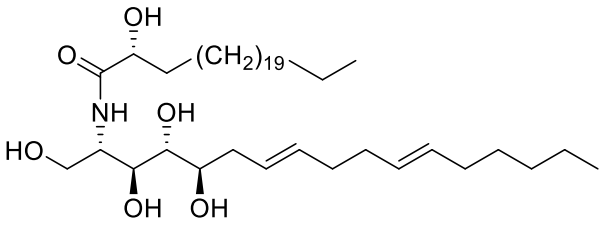
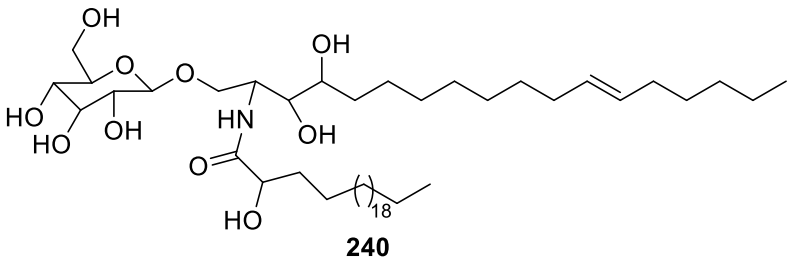
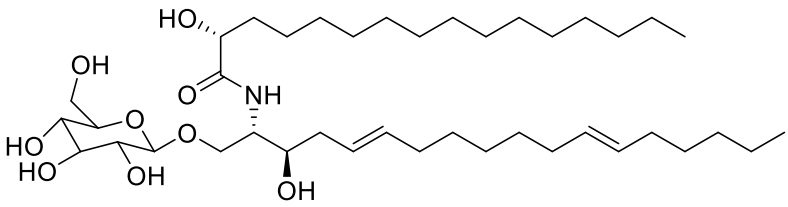


239

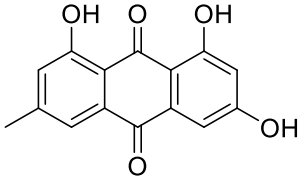


240

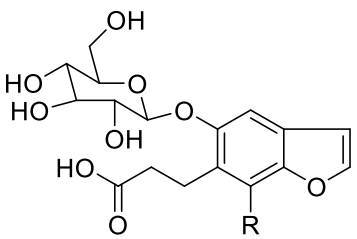


241

Anthraquinones such as emodin (**242**) was reported from *F. natalensis* stem bark (Mbougnia *et al.*, 2021). Benzofurans isolated from the genus *Ficus* include 6-carboxyethyl -5-hydroxybenzofuran 5-*O*-β-*D*-glucopyranoside (**243**) and 6-carboxyethyl-7-methoxyl-5-hydroxy-benzofuran 5-*O*-β-*D*-glucopyranoside (**244**) reported from the *F. tikoua* stem bark (Wei *et al.*, 2011).



242



243: R = OCH_3
244: R = H

2.10: Pharmacological Activities of Phytochemicals from *Macaranga* species

Different researchers have exploited the phytochemicals from *Macaranga* species for various biological applications. The isolated bioactive compounds from the genus *Macaranga* displayed a spectrum of pharmacological properties, including antimalaria (Zakaria *et al.,* 2012), antioxidant (Pailee *et al.,* 2015), antimicrobial (Lee *et al.,* 2019), and cytotoxicity (Doan *et al.,* 2019; Mai *et al.,* 2020). Anticancer and antibacterial properties of the genus's phytoconstituents are highlighted below.

2.10.1: Anti-cancer and Antibacterial Activities of Phytochemicals from Macaranga species

Macarhizinoidin A (**52**), a flavonol, was reported from *M. denticulata* and showed strong cytotoxic effects on MCF-7, Lu-1, HepG-2, and KB cancerous cells (IC_{50} = 0.60 – 1.30 µM) (Le *et al.*, 2021). Laevifolin A (**132**), a dihydrostilbene, was found to be active (IC_{50} = 4.3 µM) when evaluated for cytotoxic potential towards murine leukaemia (P-388) cells (Tanjung *et al.,* 2017). Macasiamenene L (**134**) (IC_{50} = 0.66 µM) and Macasiamenene M (**135**) (IC_{50} = 1.22 µM) reported from *M. siamensis* were strongly active against acute lymphoblastic leukaemia (MOLT-3) cell line (Pailee *et al.*, 2015). Macabartebenes A (**140**), B (**141**), and C (**142**) were isolated from *M. barteri*'s leaves and exhibited significant anticancer potential (IC_{50} = 0.60 – 1.81 µM) against A549, MCF-7, HeLa, and PC3 cancerous cells (Segun *et al.*, 2019). Schweinfurthin G (**146**) reported from *M. tanarius*'s fruits demonstrated a strong cytotoxicity against KB cells (IC_{50} = 0.06 µM) (Huong *et al.,* 2020).

Macafolias A (**54**) and B (**55**) isolated from *M. hurifolia*'s fruits were evaluated for inhibitory potential towards different bacterial strains. With the MIC value range of 24.03 – 27.67 µM, the compounds moderately inhibit the growth of *K. pneumoniae, P. aeruginosa, S. typhi,* and *E. coli*. Lonchocarpol A (**101**) showed significant antibacterial potential towards *K. pneumoniae* (MIC = 7.65 µM) and *S. typhi* (MIC = 0.18 µM) (Pagna *et al.*, 2022).

2.11: Pharmacological Activities of Phytochemicals from *Ficus* species

Several researchers have investigated the potential of phytochemicals from *Ficus* species for different biological uses. Antiplasmodial (Singh *et al.,* 2019), antifungal (Wan *et al.,* 2017), antioxidant (Wei *et al.,* 2011), inflammation inhibition (Jia *et al.,* 2020), cytotoxicity (Tameye *et al.,* 2021), and antibacterial (Rusli *et al.,* 2019) effects were shown in isolated bioactive compounds from the genus *Ficus*.

2.11.1: Anti-cancer and Antibacterial Activities of Phytochemicals from Ficus species

Ursolic acid (**203**) isolated from *F. exasperata* displayed a moderate cytotoxic potential on colon (HT-29) and cervix (KB-3-1) cancerous cells with IC_{50s} of 34.4 and 50.9 µM respectively (Tameye *et al.,* 2021). Oleanolic acid (**209**) and friedelin (**211**) isolated from *F. drupacea*'s stem bark were cytotoxic against MCF-7 and HeLa cells (IC_{50} = 16.26 – 22.81 µg/mL) (Yessoufou *et al.,* 2015).

An isoflavone, 5,7,4′-trihydroxy- 3′ -[6,7-dihydroxy- 3,7-dimethyl-2(E)-octenyl]isoflavone (**187**) (MIC = 1.25 - 20.00 µg/mL), reported from *F. aurata* significantly inhibit the development of *B. cereus, S. albus, E. coli P. aeruginosa,* and *S. epidermidis* (Shao *et al.,* 2022). Naringenin (**196**) isolated from the roots of *F. nervosa* displayed potent activity (MIC = 2.8 µg/mL) against *Mycobaterium tuberculosis* (Chen *et al.,* 2010). The root bark of *F. sycomorus* was examined phytochemically, and lupeol acetate (**204**) was isolated. The compound was effective (MIC = 12.5 µg/mL) in the inhibition of *S. typhi, S. aureus* and *B. subtilis* growth (Muktar *et al.,* 2018).

2.12: Gaps in Knowledge

Despite the wide-range of ethnomedicinal applications and potential pharmacological activities of secondary metabolites from *Macaranga* species reported in the literature, the

phytochemical investigations (isolation of secondary metabolites) and biological activities such as anticancer and antibacterial efficacy of compounds from the selected species of *Macaranga* have not been reported in the literature. Additionally, the systematic phytochemical study of *F. thonningii* from East Africa has hitherto not been reported in the literature.

CHAPTER 3: MATERIALS AND METHODS

3.1: Plants Materials

Macaranga conglomerata (Figure 3.1) and *Macaranga capensis* (Figure 3.2) were collected in March 2019 (Ngangao forest), while *Macaranga kilimandscharica* (Figure 3.3) and *Ficus thonningii* (Figure 3.4) were harvested in February (Kieni forest) and August (Riverside Drive, Nairobi) 2020, respectively. Each plant material was identified by Taxonomist from the Department of Biology, Faculty of Science and Technology (FST), University of Nairobi, where a voucher specimen of each sample was deposited (Table 3.1). Samples of each plant were air-dried under shade, powdered, weighed, and stored for subsequent use.

Figure 3.1: Leaves of *Macaranga conglomerata*
(Photo taken by Ibrahim, March 2019)

Figure 3.2: Stem bark of *Macaranga capensis*
(Photo taken by Ibrahim, March 2020)

Figure 3.3: Leaves of *Macaranga kilimandscharica*
(Photo taken by Ibrahim, March 2020)

Figure 3.4: Stem barks of *Ficus thonningii*
(Photo taken by Ibrahim, October 2021)

Table 3.1: Plant sample voucher number and collection location

Plant Name	Voucher Number	GPRS	Collection location
Macaranga conglomerata	HIUON 2019/001	3°25′ S, 38°20′ E	Ngangao forest
Macaranga kilimandscharica	HIUON 2020/002	0°85′ S, 36°67′ E	Kieni forest
Macaranga capensis	HIUON 2020/003	3°25′ S, 38°20′ E	Ngangao forest
Ficus thonningii	HIUON 2021/004	1°16′ 19.2″ S, 36°48′ 07.6″ E	Riverside Drive, Nairobi

3.2: Chromatography

Silica gel 60 – 120, 100 – 200, 70 – 230, and 230 – 400 meshes as solid phases for column chromatography (CC), and Sephadex LH–20 (25 – 100 μm, Sigma Aldrich) were used. Thin Layer Chromatography (TLC) was carried out on pre-coated silica gel 60 plates (0.25 mm;

Merck, Darmstadt, Germany). Compounds were visualized under UV light and further by spraying with H_2SO_4–H_2O (5 %, v/v).

3.3: Spectroscopy and Spectrometry

NMR spectra were performed on Bruker 400 MHz spectrometer and Bruker Avance III 600 MHz spectrometer using standard pulse sequences and referenced to residual solvent signals. Bruker-Alpha FT-IR spectrometer (SN 100964) with single reflection ATR (cricket, Harrick Scientific) was used in performing the IR analysis. UV absorbance was obtained on Shimadzu UV-1800 UV/Visible Scanning Spectrophotometer (UV-1800 240V). A Waters Synapt G2 Quadrupole time-of-flight (qTOF) mass spectrometer (MS) connected to a Waters Acquity ultra-performance liquid chromatograph (UPLC) (Waters, Milford, MA, USA) was used for direct infusion high-resolution MS analysis. Specific rotation was recorded on ADP410 Polarimeter (Bellingham Stanley Ltd).

3.4: Extraction and Isolation of Compounds

3.4.1: Isolated compounds from the Leaves of Macaranga conglomerata

Extensive extraction with CH_3OH/CH_2Cl_2 (1:1, 6 L) was done on 1.8 kg of air-dried powdered leaves at room temperature for three days. The solvents were concentrated under a vacuum usin g a rotary evaporator to yield 200.3 g of leaves crude extract. The crude extract (200.0 g) was fra ctionated in a chromatographic column (CC) using silica gel (60 – 120) as an adsorbent eluting with CH_2Cl_2/*n*-hexane (0:10, 1:1 and 10:0) followed by EtOAc/*n*-hexane (1:1 and 10:0) and finally, CH_2Cl_2/CH_3OH (1:1 and 0:10) to yield seven fractions (F_{A-G}). Size exclusion chromatography on fraction D (20.0 g) with CH_3OH/CH_2Cl_2 (1:1) eluting solvent yielded five s ubfractions (Fr_{D1-5}). Subfraction Fr_{D4} (2.4 g) was purified in CC using silica gel (100 – 200 mesh) eluting with a gradient of EtOAc/*n*-hexane (0.5:19.5 to 10:0) to provide conglomeratin **245** (11.2 mg) and macarangin **246** (3.6 mg).

Fraction E (15.0 g) was subjected to silica gel CC (100 – 200) eluting with *n*-hexane/EtOAc (10:0 to 0:10), resulting in 334 fractions of 100 mL each. Based on their TLC profiles, the fracti ons were combined into four main subfractions (Fr_{E1-4}). Subfraction Fr_{E2} (81.9 mg) was purified by silica gel CC (70 – 230) eluting with EtOAc/*n*-hexane (10:0 to 0:10) to afford quercetin **247** (5.3 mg). 3,3′,4′-Trimethoxyellagic acid **248** (6.0 mg) was obtained when subfraction Fr_{E3} (67.8 mg) was subjected to silica gel (100 – 200) CC eluting with EtOAc/*n*-hexane (1.5:8.5) isocratically. Fr_{E4} (201.4 mg) was purified in Sephadex LH-20 CC using CH_3OH/CH_2Cl_2 (1:1) as mobile phase to yield 3,3′-trimethoxyellagic acid **249** (7.3 mg).

3.4.2: Isolated compounds from the Stem bark of Macaranga conglomerata

Thorough extraction of the dried powdered stem (3.9 kg) using CH_3OH/CH_2Cl_2 (1:1, 9 L, 24 h × 3) produced 450.9 g of crude extract at room temperature. 200.0 g of stem's crude extract was subjected to silica gel (60 – 120) CC eluting with EtOAc/*n*-hexane (0:10 to 10:0), resulting in 645 fractions of 500 mL each. These fractions were, however, combined based on their TLC pr ofiles into nine fractions (F_{H-P}). Fraction I (470.0 mg) was loaded onto a silica gel column (70 – 230) and eluted with a binary system of CH_2Cl_2/*n*-hexane (2:8) to afford 3-acetylaleuritolic acid **250** (12.4 mg).

3.4.3: Isolated compounds from the Stem of Macaranga capensis

The maceration extraction technique was used to obtain 65.9 g of crude extract from *Macaranga capensis*'s stem bark (0.6 Kg). The process was carried out at room temperature using CH_3OH/CH_2Cl_2 (1:1, 3L, 24 h × 3). 60.0 g of stem bark crude extract was subjected to silica gel (60 – 120) CC eluting with EtOAc/*n*-hexane (0:10 to 10:0), resulting in 350 fractions of 100 mL each. These fractions were, however, combined based on their TLC profiles into six fractions (F_{A-F}). Isocratic system of EtOAc/*n*-hexane (3:7) was used to elute

fraction C (580.5 mg), which yielded betulin **251** (18.7mg) and three sub-fractions coded Fr_{C1-3}, after being chromatographed on silica gel (100 – 200) CC. Scopoletin **252** (1.5 mg), 3-hexyl-8-hydroxy-6-methoxy-1*H*-isochromen-1-one **253** (4.0 mg), and 3,3′-di-*O*-methyl ellagic acid-4′-*O*-α-*L*-rhamnopyranoside **254** (2.5 mg) were isolated when Fr_{C2} (83.2 mg) was purified in a chromatotron (EtOAc/*n*-hexane (1:9 to 10.0)). Repeated chromatotron of sub-fraction Fr_{C3} (43.2 mg) using ternary system of CH_3OH/EtOAc/*n*-hexane (0.5:2.5:7) led to the isolation of chrysoeriol **255** (2.3 mg) and a mixture (1.9 mg) of isorhamnetin **256** and kaempferol **257**.

3.4.4: Isolated compounds from the Roots of Macaranga capensis

Maceration technique was employed at room temperature using CH_3OH/CH_2Cl_2 (1:1, 3 L, 24 h × 3) to obtain 50.7 g of crude extract from dried powdered roots (0.8 Kg) of *Macaranga capensi s*. 40 g of root's crude extract was subjected to silica gel (60 – 120) CC eluting with EtOAc/*n*-hexane (0:10 to 10:0), resulting in 432 fractions of 100 mL each. These fractions were, however, combined based on their TLC profiles into eight fractions (F_{G-N}). A binary system of EtOAc/*n*-hexane (2:8) was used when fraction J (47 mg) was subjected to silica gel (70 – 230) CC to afford β-sitosterol **258** (13.8 mg). Purification of fraction U (89 mg) using silica gel (100 – 200) CC eluting with EtOAc/*n*-hexane (1:20 to 10:0) yielded 2,2′-(((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(methylene))bis(oxirane) **259** (40.5 mg).

3.4.5: Isolated compounds from the Stem bark of Ficus thonningii

Dried powdered stem bark of *Ficus thonningii* (1.7 Kg) was extracted at room temperature with CH_2Cl_2/CH_3OH (1:1, 6 L, 24 h × 3) by maceration to afford 85.7 g of crude extract. 80 g of the stem bark crude extract was fractionated in a chromatographic column using silica gel (60 – 120) as an adsorbent eluting with EtOAc/*n*-hexane (0:10, 1:9, 1.5:8.5, 2:8, 3:7, 3.5:6.5, 4:6, 4.5:5.5, 1:1 and 10:0) followed by CH_3OH/EtOAc (1:9 and 2:8) to yield twelve fractions (HIF_{A-}

$_L$). Fraction HIF_I (2.8 g) was subjected to silica gel (70 – 230) CC eluting with EtOAc/*n*-hexane (1:9 to 10:0), resulting in the isolation of yukovanol **260** (5.1 mg) and 5,7,4′-trihydroxy-3′-(2-hydroxy-3-methyl-3-butenyl) isoflavone **261** (3.0 mg). Purification of fraction HIF_J (2.81 g) using silica gel (70 – 230) CC eluting with a gradient of EtOAc/*n*-hexane (0.5:9.5 to 10:0), resulted in 85 fractions of 30 mL each. The fractions were pooled based on their TLC profiles in to two main subfractions (HIF_{J1-2}).

Subfraction HIF_{J1} (700 mg) was subjected to silica gel (230 – 400) CC eluting with a gradient polarity of EtOAc/*n*-hexane (0:10 to 1.5:8.5) to afford a semi-pure compound. The semi-pure compound was purified on a chromatotron using a gradient EtOAc/*n*-hexane (2:8 to 10:0) to yield cajanin **262** (13.41 mg). Subfraction HIF_{J2} (900 mg) was also purified using silica gel (230 – 400) CC eluting with a gradient of EtOAc/*n*-hexane (1:9 to 6:4) to afford taxifolin **263** (1.06 mg) and protocatechuic acid **264** (2.82 mg). Fraction HIF_L (3.5 g) afforded brown crystals which, after filtration and recrystallization in CH_3OH, saccharose **265** (43.2 mg) was obtained. Similarly, stigmasterol **266** (33.6 mg) was crystallized in fraction HIF_F (1.02 g), and the crystals were repeatedly washed with *n*-hexane to obtain the compound.

3.5: Biological Activities

3.5.1: Cytotoxicity Assay by MTT technique

The MTT test looks at cellular metabolic activity to assess the cytotoxicity, cell viability, and cell growth. In this colourimetricassay, metabolically active cells convert the yellow tetrazolium salt (methyl thiazol tetrazolium or MTT) into purple formazan crystals. NAD(P)H-dependent oxidoreductase enzymes in live cells convert MTT to formazan. The formazan crystals are dissolved, and the solution is measured at 500 – 600 nm with a multi-well spectrophotometer (Ndlovu *et al.,* 2021).

3.5.1.1: Cell culture and Stock Preparation

In a complete culture medium (CCM) made up of Eagle's Minimum Essential Medium (EMEM) supplemented with 10 % foetal calf serum, 1 % penicillin-streptomycin-fungizone, and 1 % L-glutamine, MCF-7 and HepG2 cells were each cultured in a monolayer (106 cells per 25 cm^3 culture flask) until they were about 60 % confluent. Dimethyl Sulphoxide (DMSO; 1 % v/v benchmark DMSO) was used to prepare a stock solution of 50 mM of each sample and reference drug (doxorubicin), and diluted in CCM to achieve the concentrations used in subsequent experiments (Ndlovu *et al.,* 2021).

3.5.1.2: Cell viability Assay

The Methyl Thiazol Tetrazolium (MTT) test was used to assess each compound's effect on MCF-7 and HepG2 cells viability, and the IC_{50} was calculated in accordance to published protocols (Ndlovu *et al.,* 2021).

3.5.2: In-vitro Antibacterial Assay

Antibacterial activities of nine crude extracts from *Macaranga conglomerata*, *Macaranga kilimandscharica* and *Macaranga capensis,* and the isolated compounds were determined again st 13 bacterial strains expressing multidrug resistance (MDR) phenotypes.

3.5.2.1: Culture media and microbial strains for susceptibility assays

The studied micro-organisms were cultured overnight on Mueller Hinton Agar for 24 hrs before assaying. Mueller Hinton Broth (MHB) was used as liquid culture medium for susceptibility ass ays. A panel of six pathogenic microbes, sensitive and multidrug resistant Gram-negative (*Escherichia coli, Enterobacter aerogenes, Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Providencia stuartii*) and Gram-positive (*Staphylococcus aureus*) bacterial

strains expressing efflux pumps were provided by the American Type Culture Collection (ATCC). Their bacterial features are depicted in Table 3.2.

Table 3.2: Characteristics of bacterial strains and features

Bacterial species	Types	Relevant features
Escherichia coli		
	ATTC 10536	Reference strain (Kuete *et al.*, 2010)
	AG102	AG 100 over-expression of pumps *Acr AB* (Chevalier *et al.*, 2000)
Enterobacter aerogenes		
	ATCC 13048	Reference strain (Kuete *et al.*, 2010)
	EA27	Clinical strain present efflux energy-dependant of chloramphenicol norfloxacin and KAN^r, AMP^r, NAL^r, STR^r, TET^r (Ghisalberti *et al.*, 2005)
Klebsiella pneumoniae		
	ATCC 11296	Reference strain (Kuete *et al.*, 2010)
	Kp55	Clinical MDR isolate: TET^r, AMP^r, ATM^r, CEF^r (Kuete *et al.*, 2010)
Providencia stuartii		
	PS2636	*AcrAB-TolcC* associate of porines of types OMPF and OMPC (Kuete *et al.*, 2010)
	NEA16	Clinical isolate of *P. stuartii AcrAB-TolC* (Kuete *et al.*, 2010)
Pseudomonas aeruginosa		
	PA01	Reference strain (Kuete *et al.*, 2010)
	PA124	Clinical strain multi-resistant *MexAB-OprM* (Lorenzi *et al.*, 2009)
Staphylococcus aureus		
	ATCC 25923	Reference strain
	MRSA 3	Clinical isolate: $Ofxa^r$, Kan^r, Tet^r, Erm^r (Paudel *et al.*, 2012)
	MRSA 6	Clinical isolate: $Ofxa^r$, Flx^r, Kan^r, Tet^r, Cyp^r, IM/Cs^r, Chl^r, Gen^r, Nis^r, Amp^r (Paudel *et al.*, 2012; Dzoyem *et al.*, 2013)

AMP^r, ATM^r, CEF^r, CHL^r, KAN^r, NAL^r, NOR^r, STR^r and TET^r: resistant (r) to ampicillin, aztreonam, cefepime, chloramphenicol, kanamycin, nalidixic acid, norfloxin, streptomycin and tetracycline, respectively; *AcrAB-TolC, MexAB-OprM:* Efflux pump; $Ofxa^r$, Kan^r, Tet^r, Flx^r, Cyp^r, IM/Cs^r, Chl^r, Gen^r, Nis^r, Amp^r and Erm^r: resistant (r) to Ofloxacine, Kanamycin, Tetracy

clin, Flomoxef, Cyprofloxacin, Imipenem/Cilastatin sodium, chloramphenicol, Gentamicin, Ampicillin, Nisin, and Erythromycin, respectively.

3.5.2.2: Determination of bacterial susceptibility of crude extracts and Isolated compounds

Iodonitrotetrazolium (INT) colourimetric assay (Eloff, 1998; Mativandlela *et al.,* 2006) was performed to assess the minimal inhibitory concentrations (MICs) of crude extracts, isolated compounds and ciprofloxacin against a panel of 13 Gram-negative and Gram-positive bacteria. Briefly, each crude extract and isolated compound (1 mg/mL each) was first dissolved in DMSO/MHB mixture. The solution obtained was then added to MHB and serially diluted two-fold in triplicate to different concentratios (in a 96-well microplate). One hundred microlitres (100 µL) of inoculum (1.5×106 CFU/mL) prepared in MHB was then added. The plates were covered with a sterile plate sealer, then agitated to mix the contents of the wells using a shaker and incubated at 37 °C for 18 h. The final concentration of DMSO was lower than 2.5% and did not affect microbial growth. Wells containing MHB, 100 µL of inoculum, and DMSO at a final concentration of 2.5 % served as a negative control. Ciprofloxacin was used as a reference antibiotic. The MICs of crude extracts were determined after 18 h of incubation at 37 °C, following the addition of (40 µL) of 0.2 mg/mL INT and incubation at 37 °C for 30 minutes (Kuete *et al.,* 2008). Viable bacteria reduced the colourless dye to pink. MIC was defined as the lowest sample concentration that prevented this change and exhibited complete inhibition of microbial growth. All assays were performed in triplicate as described by Kuete *et al.* (2008).

For the minimal bactericidal concentrations (MBCs) determination, a volume of 150 µL of MHB was introduced in a new 96-well microplate, following addition of 50 µL of the previous well microplate contents where no microbial growth was observed, and which did not receive an INT (during the reading of MICs). After an incubation period of 48 hrs at 37 °C, the MBC of each crude extract was determined and defined by adding 40 µL of 0.2 mg/mL INT as previously described (Kuete *et al.,* 2010).

CHAPTER 4: RESULTS AND DISCUSSION

Phytochemical investigation of the selected *Macaranga* and *Ficus* species resulted in isolating twenty-twoisecondary metabolites, one of which was novel. Furthermore, this is the first time the phytochemicals from the studied *Macaranga* species (*M. conglomerata* and *M. capensis*) have been reported. Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), Infrared radiation (IR), Polarimeter, and Mass Spectrometry (MS) analyses were employed for structure elucidation of the isolated compounds. The MTT technique was utilized to evaluate the anti-cancer activities of the isolated compounds. INT colourimetric test was used to assess the antibacterial efficacy of isolated compounds and crude extracts (to determine the MICs). In the following sections, the findings of this investigation will be discussed.

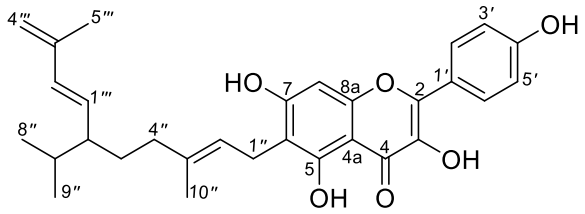
4.1: Compounds from *Macaranga conglomerata*'s leaves

One novel compound: 6-[(2(*E*),7(*E*))-6-isopropyl-3,9-dimethyldeca-2,7,9-trienyl] kaempferol (trivially named as conglomeratin) (**245**) along with four other reported compounds known as macarangin (**246**), quercetin (**247**), 3,3′,4-trimethoxyellagic acid (**248**), and 3,3′-dimethoxyellagic acid (**249**) were isolated and identified.

4.1.1: Conglomeratin (245)

Compound **245** was obtained as a yellow solid with $[\alpha]_D^{25}$ = +55.8 (*c* 0.53, MeOH) optical rotation. Its molecular formula, $C_{30}H_{34}O_6$ (fourteen indices of hydrogen deficiency), was deduced from the deprotonated ion peak observed in the (–)-HRESIMS at *m/z* 489.2271 [M - H]$^-$ (calcd. for $C_{30}H_{33}O_6^-$, 489.2277). Its IR spectrum displayed absorption bands attributable to hydroxyl groups (3317 cm^{-1}) and α, β-unsaturated ketone moiety (1655 cm^{-1}). The UVλ_{max} (370 nm) and ^{13}C NMR (δ_C 147.8 (C-2), 135.7 (C-3) and 178.3 (C-4) spectra of compound **245** exhibited signature of C-ring of flavonol framework (Le *et al.*, 2021; Nchiozem-Ngnitedem *et*

al., 2021). The NMR data (Table 4.1, Appendix 1) also displayed three signals in the aromatic region attributable to that of C-6 (δ_C 112.3) substituted kaempferol moiety similar to 3′-dehydroxy-solophenol C (Le *et al.*, 2021) and denticulatain D (Yang *et al.*, 2015b) isolated from *M. denticulata*. Besides signals observed for the kaempferol core, the ^{1}H and ^{13}C NMR also showed 15 carbons assigned to a modified geranyl [δ_H 3.21 (2H, *m*, H-1″), 5.10 (1H, *t*, *J* = 7.3 Hz, H-2″), 1.79 (2H, *m*, H-4″), 1.48 (2H, *m*, H-5″), 1.69 (1H, *m*, H-6″), 1.44 (1H, *m*, H-7″), 0.70 (3H, *d*, *J* = 6.8 Hz, H-8″), 0.73 (3H, *d*, *J* = 6.8 Hz, H-9″) and 1.65 (3H, *s*, H-10″); δ_C 22.1 (C-1″), 123.9 (C-2″), 135.6 (C-3″), 38.6 (C-4″), 31.4 (C-5″), 49.8 (C-6″), 33.3 (C-7″), 19.5 (C-8″), 21.2 (C-9″) and 16.1 (C-10″)] and isoprenyl [δ_H 5.24 (1H, *dd*, *J* = 15.9, 9.5 Hz, H-1‴), 5.82 (1H, *d*, *J* = 15.9 Hz, H-2‴), 4.65 and 4.60 (2H, *brs*, H-4‴) and 1.68 (3H, *s*, H-5‴); δ_C 133.7 (C-1‴), 135.4 (C-2‴), 143.3 (C-3‴), 114.5 (C-4‴) and 18.9 (C-5‴)] units. These signals are typical of a highly prenylated flavonol from the genus *Macaranga*. The large coupling constant ($^{3}J_{\text{H-1‴, H-2‴}}$ = 15.9 Hz) indicate the *trans* orientation of the $\Delta^{1'''(2''')}$ olefinic bond. The ^{13}C NMR, HSQC and DEPT spectra (Appendix 1) showed 30 carbons with different functionalities including 1 α, β-unsaturated carbonyl group, 20 sp^2 and 9 sp^3 hybrid carbons. The interconnectivity of the two aliphatic chains was established from the HMBC cross-peaks (Appendix 1) observed from H-2‴ (δ_H 5.82) to C-3‴ (δ_C 143.3), C-4‴ (δ_C 114.5), C-5‴ (δ_C 18.9) and C-6″ (δ_C 49.8). The location of the isoprenyl substituent at the said position was further confirmed based on ^{1}H-^{1}H COSY between H-1‴/H-2‴ and H-1‴/H-6″. The transoid conformation of the isoprenyl unit was established as observed in the NOESY spectrum (Appendix 1) between H-1‴ and H-5‴. Based on these spectral data and by comparison with prenylated flavonoids reported in the literature, compound **245** was systematically named as 6-[(2(*E*),7(*E*))-6-isopropyl-3,9-dimethyldeca-2,7,9-trienyl] kaempferol (trivially named as conglomeratin).



245

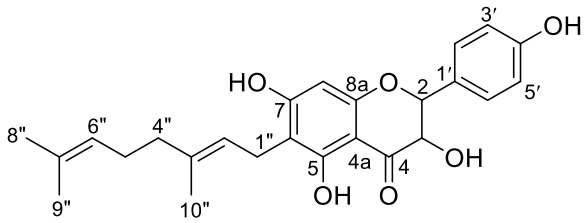
Table 4.1: Compound **245** NMR data (CD_3OD, 400 MHz)

	245		
Position	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	147.8	-	-
3	135.7	-	-
4	178.3	-	-
4a	104.4	-	-
5	158.2	-	-
6	112.3	-	-
7	163.6	-	-
8	93.6	6.33 *s*	C-4a, C-6, C-8a
8a	156.3	-	-
1′	124.1	-	-
2′/6′	130.6	7.98 *d* (8.4)	C-2, C-2′/6′, C-4′
3′/5′	116.3	6.79 *d* (8.4)	C-1′, C-3′/5′, C-4′
4′	160.3	-	-
1″	22.1	3.21 *m*	-
2″	123.9	5.10 *t* (7.3)	-
3″	135.6	-	-
4″	38.6	1.79 *m*	-
5″	31.4	1.48 *m*	-
6″	49.8	1.69 *m*	-
7″	33.3	1.44 *m*	-
8″	19.5	0.70 *d* (6.8)	C-6″, C-7″, C-9″
9″	21.2	0.73 *d* (6.8)	C-6″, C-7″, C-8″
10″	16.1	1.65 *s*	C-2″, C-3″, C-4″
1‴	133.7	5.24 *dd* (15.9, 9.5)	C-3‴
2‴	135.4	5.82 *d* (15.9)	C-3‴, C-4‴, C-5‴, C-6″
3‴	143.3	-	-
4‴	114.5	4.65 and 4.60 *brs*	-
5‴	18.9	1.68, *s*	C-3‴, C-4‴

4.1.2: Macarangin (246)

Compound **246** was obtained as a yellow solid. The ^{1}H NMR spectrum (Table 4.2.Appendix 2) revealed a pair of doublets at δ_H 7.98 (2H, *d*, *J* = 8.5 Hz) for 2′/6′ and 6.81 (2H, *d*, *J* = 8. 5 Hz) for 3′/5′ and a singlet at δ_H 6.34 (1H, *s*). The signals are attributable to that of C-6 (δ_C

112.4) substituted kaempferol moiety. The ^{1}H NMR also displayed two olefinic signals at δ_H 5.15 (1H, *t*, *J* = 7.3 Hz) for H-2″ and 4.96 (1H, m) for H-6″, an allylic proton signal at δ_H 3.21 (2H, *brs*) for H-1″, a pair of multiplets at δ_H 1.86 (2H, *m*) for H-4" and 1.95 (2H, *m*) for H-5″, and three methyl group signals at δ_H 1.50 (3H, *s*) for H-8″, 1.46 (3H, *s*) for H-9″ and 1.69 (3H, *s*) for H-10″, indicating the presence a geranyl group. Based on the HMBC correlation of H-1″ (δ_H 3.21) to C-5 (δ_C 159.6), C-6 (δ_C 112.4), C-7 (δ_C 163.7), C-2″ (δ_C 123.8) and (Appendix 2), the geranyl group was assigned to C-6. Using the NMR (1D and 2D) data and in comparison, with the available literature (Sutthivaiyakit *et al.*, 2002), compound **246** was identified as macarangin.



246

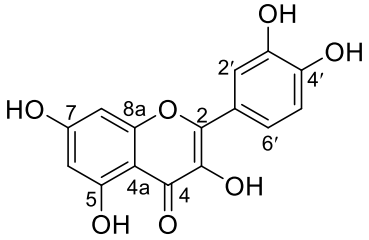
Table 4.2: Compound **246** NMR data (CD_3OD, 400 MHz)

C-position	**246**		
	δ_C	δ_H Mult (*J* in *Hz*)	HMBC (H→C)
2	147.7	-	-
3	135.1	-	-
4	178.1	-	-
4a	105.1	-	-
5	159.6	-	-
6	112.4	-	-
7	163.7	-	-
8	93.6	6.34 *s*	C-4a, C-6, C-7, C-8a
8a	156.2	-	-
1′	124.5	-	-
2′/6′	130.6	7.98 *d* (8.5)	C-4′
3′/5′	116.3	6.81 *d* (8.5)	C-1′
4′	161.2	-	-
1″	22.2	3.21 *brs*	C-5, C-6, C-7, C-2″, C-3″
2″	123.8	5.15 *t* (7.3)	-
3″	135.6	-	-
4″	40.9	1.86 *m*	-
5″	27.4	1.95 *m*	-
6″	125.4	4.96 *m*	-
7″	132.2	-	-
8″	25.8	1.50 *s*	C-6″, C-7″, C-9″
9″	17.7	1.46 *s*	C-6″, C-7″, C-8″
10″	16.3	1.69 *s*	C-2″, C-3″, C-4″

4.1.3: 3,3',4',5,7-Pentahydroxyflavone (Quercetin) (247)

Compound **247** was obtained as a yellow solid. The ^{1}H NMR spectrum (Table 4.3. Appendix 3) revealed a pair of doublet signals that are meta-coupled at δ_H 6.19 (1H, *d*, *J* = 2.0 Hz) for H-6 and 6.39 (1H, *d*, *J* = 2.0 Hz) for H-8, with an AX spin system. An ABX spin system was observed at δ_H 7.74 (1H, *d*, *J* = 2.2 Hz) for H-2′, 6.89 (1H, *d*, *J* = 8.5 Hz) for H-5′, and 7.64 (1H, *dd*, *J* = 8.5, 2.2 Hz) for H-6′. The ^{13}C NMR (Table 4.3) revealed a total of fifteen carbon signals, five of which were methines and ten of which were quaternary carbons. The HMBC correlation between C-2 (C 148.8) and H-2′ (Appendix 3) led the placement of the AX protons in ring A and the ABX system in ring B. The NMR data (1D and 2D) of

compound **247** were comparable with a similar compound known as quercetin previously isolated from *Lagerstroemia speciosa* (Saraswathi *et al.*, 2017).



247

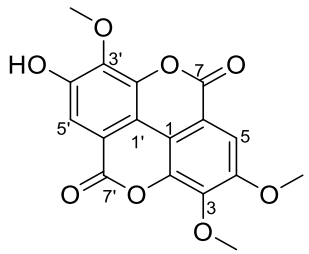
Table 4.3: Compound **247** NMR data (CD_3OD, 600 MHz)

C-position	**247**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	148.8	-	-
3	137.2	-	-
4	177.3	-	-
4a	104.5	-	-
5	162.5	-	-
6	99.3	6.19 *d* (2.0)	C-4a, C-5, C-7, C-8
7	165.8	-	-
8	94.4	6.39 *d* (2.0)	C-4a, C-6, C-7, C-8a
8a	158.3	-	-
1′	124.2	-	-
2′	116.0	7.74 *d* (2.2)	C-2, C-4′, C-5′
3′	146.2	-	-
4′	148.0	-	-
5′	116.2	6.89 *d* (8.5)	C-1′, C-3′
6′	121.7	7.64 *dd* (8.5, 2.2)	C-1′, C-4′

4.1.4: 3,3',4-Trimethoxyellagic acid (248)

The ^1H NMR data (Table 4.4, Appendix 4) of compound **248** (an amorphous white solid) displayed two signals at δ_H 8.21 and 7.63 (1H, *s* each), typical for ellagic acid derivatives. Furthermore, three methoxy signals were observed at δ_H 4.10, 4.03, and 3.99 (3H, *s* each). Table 4.4 revealed 17 carbons signals found in the ^{13}C NMR spectrum, among which are two carbonyl groups of an *α,* β unsaturated lactones at δ_C 158.5 (C-7) and 158.4 (C-7′). Spectra from HSQC together with HMBC (Appendix 4) were used in assigning the three methoxy groups to C-3 (δ_C 140.9), C-4 (δ_C 154.4), and C-3′ (δ_C 143.3), respectively. The two methoxy

groups at δ_C 61.4 and 61.5 (Table 4.4) were downfield shifted, indicating that they were di-*ortho* substituted. This agrees with their placement at δ_C 140.9 and 143.3, respectively. The NMR data (1D and 2D) were comparable with a similar compound known as 3,3′,4-trimethoxyellagic acid previously isolated from *Dipentodon sinicus* (Ye *et al.,* 2007).



248

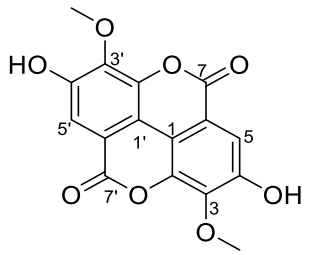
Table 4.4: Compound **248** NMR data (CD_2Cl_2, 500 MHz)

C-position	**248**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1	112.9	-	-
2	111.6	-	-
3	140.9	-	-
4	154.4	-	-
5	107.5	7.63 *s*	C-1, C-3, C-4, C-6, C-7
6	113.0	-	-
7	158.5	-	-
1′	114.2	-	-
2′	111.6	-	-
3′	143.3	-	-
4′	147.6	-	-
5′	117.6	8.21 *s*	C-1′, C-3′, C-4′, C-6′, C-7′
6′	141.4	-	-
7′	158.4	-	-
CH_3O-3	61.5	4.03 *s*	C-3
CH_3O-3′	61.4	4.10 *s*	C-3′
CH_3O-4	56.8	3.99 *s*	C-4

4.1.5: 3,3'-Dimethoxyellagic acid (249)

The ^1H and ^{13}C NMR spectra of compound **249** (a whitish solid) (Table 4.5, Appendix 5) are comparable to those of compound **248**, with the molecular formula of **249** having 30 amu (atomic mass unit) less than **248** indicating the neutral loss of formaldehyde (CH_2O) group

in **249** to form its 3,3′-dimethoxy derivative. The above findings were further supported as a pair of methoxy signals that were di-*ortho* by being downfield shifted were observed in the spectra. On the basis of the NMR (1D and 2D) results together with the published literature, compound **249** was identified as 3,3′-dimethoxyellagic acid (Nkainsa *et al.*, 2020).



249

Table 4.5: Compound **249** NMR data (CD_2Cl_2, 500 MHz)

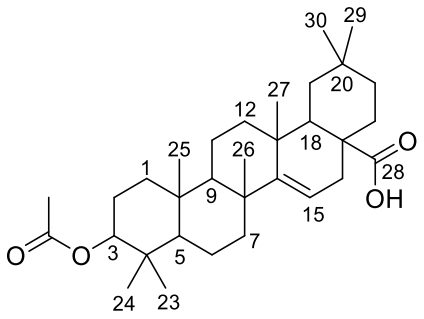
C-position	**249**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1	114.2	-	-
2	141.1	-	-
3	141.7	-	-
4	150.2	-	-
5	112.0	7.77 *s*	C-3, C-4, C-6, C-7
6	112.8	-	-
7	158.5	-	-
1′	114.2	-	-
2′	141.1	-	-
3′	141.9	-	-
4′	140.3	-	-
5′	111.7	7.49 *s*	C-4′, C-6′, C-7′
6′	112.8	-	-
7′	158.4	-	-
CH_3O-3	61.7	4.04 *s*	C-3
CH_3O-3′	61.0	4.03 *s*	C-3′

4.2: Compounds from *Macaranga conglomerata*'s stem bark

One compound identified as 3-acetylaleuritolic acid (**250**) was isolated from *M. conglomerata*'s stem bark.

4.2.1: 3-Acetylaleuritolic acid (250)

Compound **250** was found to be an amorphous white solid. Its ^{1}H NMR data (Table 4.6) revealed a doublet of a doublet signal be attributed to the olefinic proton H-15 at δ_H 5.52 (1H, *dd*, *J* = 8.1, 3.5 Hz). A singlet signal of an acetoxy group at δ_H 2.04 (3H, *s*) was observed. The ^{1}H NMR spectrum (Appendix 6) also displayed a doublet of a doublet signal for proton on the carbon atom bearing the acetoxy group (H-3) at δ_H 4.47 (1H, *dd*, *J* = 10.4, 5.6 Hz). Additionally, a characteristic methine signal at δ_H 2.27 (1H, m) for H-18 was also observed. Furthermore, seven signals attributable to tertiary methyl groups were observed at δ_H 0.85, 0.88, 0.91, 0.92, 0.93, 0.95, and 1.63 (3H, s, each) for H-23, H-24, H-30, H-27, H-29, H-25, and H-26, respectively. ^{13}C NMR spectrum displayed signals at δ_C 183.7 and 171.2, which were assigned to the carboxylic acid (C-28) and acetoxy groups (-C(=O)-O-), respectively. On the basis of the NMR (1D and 2D) results together with the published literature (Rumzhum *et al.*, 2012), compound **250** was found to be 3-acetyl aleuritolic acid.



250

Table 4.6: Compound **250** NMR data ($CDCl_3$, 500 MHz)

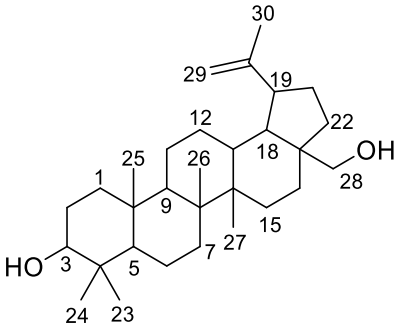
C-position	**250**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1	37.8	1.04	C-2, C-5, C-10, C-25
2	23.6	1.63	C-1, C-3, C-4
3	81.0	4.47 *dd* (10.4, 5.6)	C-1, C-2, C-5, C-4, C-24, COOH
4	37.5	-	-
5	55.7	0.89 *m*	-
6	18.9	1.49 *m*, 1.60 *m*	C-24
7	40.9	1.97 *m*, 1.30 *m*	C-5
8	39.2	-	-
9	49.2	1.43 *m*	C-8, C-10, C-11, C-25, C-26
10	38.1	-	-
11	17.5	1.48 *m*	C-9, C-12
12	33.5	1.61 *m*, 1.78 *m*	C-11, C-13, C-27
13	37.5	-	-
14	160.7	-	-
15	116.9	5.52 *dd* (8.0, 3.5)	C-8, C-13, C-16, C-17
16	31.5	1.93 *m*, 2.37 *m*	C-14, C-21, C-28
17	51.7	-	-
18	41.6	2.27 *m*	C-13, C-16, C-17, C-19, C-20, C-27, C-28
19	35.4	1.10 *m*, 1.24 *m*	C-17, C-18, C-20
20	29.4	-	-
21	30.8	1.42 *m*, 1.70 *m*	C-17, C-23, C-30
22	33.8	1.16 *m*, 1.06 *m*	C-20, C-21
23 Me	28.1	0.85 *s*	C-3, C-4, C-5, C-24
24 Me	16.7	0.88 *s*	C-3, C-4, C-23
25 Me	15.8	0.95 *s*	C-5, C-9
26 Me	26.3	1.63 *s*	C-7, C-8, C-9, C-14
27 Me	22.6	0.92 *s*	C-13, C-14, C-18
28	183.7	-	-
29 Me	32.1	0.93 *s*	C-19, C-22
30 Me	28.8	0.91 *s*	C-19, C-20, C-29
-C(=O)-O-	171.2	-	-
$COOCH_3$	21.5	2.04 *s*	C-3, -C(=O)-O-

4.3: Compounds from *Macaranga capensis*'s stem bark

Seven compounds identified as: betulin (**251**), scopoletin (**252**), 3-hexyl-8-hydroxy-6-methoxy-1*H*-isochromen-1-one **(253),** 3,3′-di-*O*-methylellagic acid-4′-*O*-α-*L*-rhamnopyranoside (**254**), chrysoeriol **(255),** isorhamnetin (**256**), and kaempferol (**257**) were isolated from *M. capensis*'s stem bark.

4.3.1: Betulin (251)

The ^{1}H NMR spectrum (Appendix 7) of compound **251** (a whitish crytal) displayed the existence of diastereotopic protons signals for a methylene group at δ_H 3.33 (1H, *d*, *J* = 10.8 Hz) and 3.79 (1H, *dd*, *J* = 10.9, 2.0 Hz) for H_a-28 and H_b-28, respectively. Six methyl group signals were also observed at δ_H 0.75, 0.82, 0.96, 0.97, 1.01, and 1.67 (each 3H, *s*) for H-29, H-27, H-20, H-30, H-28, and H-25, respectively. Additionally, two exocyclic methylene protons at δ_H 4.57 (1H, *m*) for H_a-29 and 4.64 (1H, *d*, *J* = 2.3 Hz) for H_b-29 were observed. These signals are typical for a lupane skeleton (Ayatollahi *et al.*, 2009). ^{13}C NMR spectrum displayed 30 carbon signals comprising 1 exomethylene, 6 quaternary, 6 methine, 11 methylene, and 6 methyl carbons (Table 4.7). An isopropenyl moiety was implied by the existence of an exocyclic olefinic carbon. On the basis of the NMR (1D and 2D) results together with the published literature (Kaur *et al.*, 2022), compound **251** was identified as betulin.



251

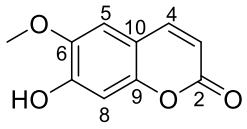
Table 4.7: Compound **251** NMR data ($CDCl_3$, 500 MHz)

C-position		**251**		
		δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1		38.8	1.67 *m*	C-3, C-5
2		27.5	1.63 *m*	C-3, C-4, C-5, C-10
3		79.1	3.18 *dd* (11.2, 4.9)	C-4, C-23, C-24
4		39.0	-	-
5		55.4	0.68 *m*	C-3, C-6, C-9, C-23, C-24
6		18.4	1.52 *m*	C-10
7		34.4	1.38 *m*	C-8, C-27
8		41.0	-	-
9		50.5	1.25 *m*	C-5, C-7, C-10, C-11, C-12, C-27
10		37.4	-	-
11		21.0	1.38 *m*	C-8
12		25.3	1.62 *m*	C-14, C-18
13		37.3	1.63 *m*	C-15
14		42.8	-	-
15		27.2	1.02 *m*	C-8, C-14
16		29.3	1.22 *m*	C-15, C-28
17		56.4	-	-
18		48.9	1.58 *m*	C-13, C-16, C-19, C-20, C-28
19		47.9	2.36 *td* (10.8, 5.8)	C-13, C-18, C-20, C-21, C-29
20		150.6	-	-
21		29.9	1.93 *m*, 1.49 *m*	C-18, C-19
22		34.1	1.86 *m*, 1.01 *m*	C-18, C-21, C-28
23	Me	28.1	0.96 *s*	C-3, C-4, C-5, C-24
24	Me	15.5	0.75 *s*	C-3, C-5, C-23
25	Me	16.2	0.82 *s*	C-5, C-9, C-10
26	Me	16.1	1.02 *s*	C-7, C-8, C-9, C-14
27	Me	14.9	0.97 *s*	C-8, C-14, C-15
28		60.7	3.79 *dd* (10.9, 2.0), 3.33 *d* (10.8)	C-16, C-22
29		109.8	4.64 *s*, 4.57 *s*	C-19, C-30
30	Me	19.2	1.67 *s*	C-19, C-20, C-29

4.3.2: Scopoletin (252)

Compound **252** was isolated as a white solid. Its ^1H NMR data (Table 4.8; Appendix 8) showed signals that were typical of a 6,7-dioxygenated coumarin. Two doublets at δ_H 6.27 (1H, *d*, *J* = 9.5 Hz) and δ_H 7.60 (1H, *d*, *J* = 9.5 Hz), corresponding to H-4 and H-3 of a coumarin's pyrone ring, respectively, were observed (Darmawan *et al.*, 2012; Khan and

Hossain, 2015). A methoxy group at δ_H 3.95 (3H, *s*) and two aromatic proton singlets at δ_H 6.85 for H-5 and 6.92 for H-8, were also noted in the proton spectrum. There were ten signals in the ^{13}C NMR spectrum, including a phenolic hydroxyl group, 1 methoxy group, 4 methines, and 5 quaternary carbons. The NMR data (1D and 2D) were comparable with a similar compound known as 7-hydroxy-6-methoxy coumarin (scopoletin) previously isolated from *Ipomoea digitata* (Khan and Hossain, 2015).



252

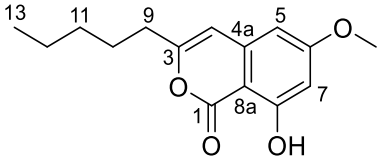
Table 4.8: Compound **252** NMR data ($CDCl_3$, 600 MHz)

C-position	**252**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	161.6	-	-
3	143.4	7.60 *d* (9.5)	C-1, C-10, C-5
4	113.6	6.27 *d* (9.5)	C-1, C-9
5	107.6	6.85 *s*	C-6, C-7
6	144.1	-	-
7	150.4	-	-
8	103.4	6.92 *s*	C-6, C-7, C-9, C-10
9	111.7	-	-
10	149.8	-	-
6-OCH_3	56.6	3.95 *s*	C-6

4.3.3: 8-Hydroxy-6-methoxy-3-pentyl-1H-isochromen-1-one (253)

The ^1H NMR data (Table 4.9, Appendix 9) of compound **253** (an amorphous white solid) showed a methyl signal at δ_H 0.91 (3H, *s*) for H-13, four methylene signals at δ_H 2.48, 1.69, 1.34, and 1.35 (2H, *m* each) for H-9, H-10, H-12, and H-13, respectively. An olefinic singlet signal together with two aromatic doublet signals typical for isocoumarin were observed at δ_H 6.17 (1H, *s*) for H-4, 6.31 (1H, *d*, *J* = 2.3 Hz) for H-5, and 6.46 (1H, *d*, *J* = 2.3Hz) for H-7, respectively (Araújo *et al.*, 2017). A methoxy group (3H, *s*) signal at δ_H 3.87 was also

noted in the ^{1}H NMR spectrum. Three methines (δ_C 104.1, 101.2, and 100.3), five methylenes (δ_C 33.4, 31.3, 26.7, and 22.5), two methyls (δ_C 55.8 and 14.1), and six quaternary carbons (δ_C 166.9, 166.7, 163.8, 158.2, and 100.1), were seen in compound **253**'s ^{13}C NMR spectrum. The presence of a polysubstituted phenyl moiety was revealed by the aromatic signals (δ_C 100.1 – 166.9) (Gao *et al.,* 2021). The HSQC spectrum was used in assigning each proton to the relevant carbon atom. The interconnectivity of the aliphatic chain was established from the HMBC (Appendix 9) cross-peaks observed from H-9 (δ_H 2.48) to C-3 (δ_C 158.2), C-4 (δ_C 104.1), C-10 (δ_C 26.7) and C-11 (δ_C 31.3). Furthermore, the presence of a methoxy group at the C-6 position was established by the long-range correlation between the proton at δ_H 3.87 and C-6 (δ_C 166.9). Based on these spectral data and by comparison with isocoumarins reported in the literature (Kihampa *et al.,* 2009), compound **253** was identified as 8-Hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one.



253

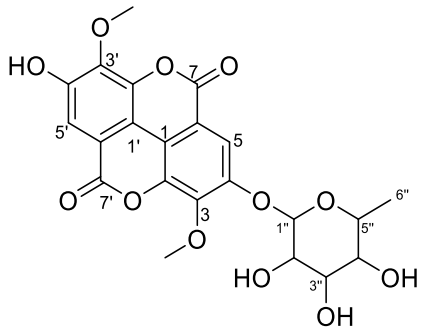
Table 4.9: Compound **253** NMR data ($CDCl_3$, 600 MHz)

C-position	**253**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1	166.7	-	-
3	158.2	-	-
4	104.1	6.17 *s*	C-3, C-8a, C-9
4a	139.6	-	-
5	101.2	6.31 *d* (2.3)	C-4, C-7, C-8a
6	166.9	-	-
7	100.3	6.46 *d* (2.3)	C-5
8	163.8	-	-
8a	100.1	-	-
9	33.4	2.48 *m*	C-3, C-4, C-10, C-11
10	26.7	1.69 *m*	C-11, C-12
11	31.3	1.34 *m*	C-12
12	22.5	1.35 *m*	C-11
13	14.1	0.91 *m*	C-12
6-OCH_3	55.8	3.87 *s*	C-6

4.3.4: 3,3′-Di-O-methylellagic acid-4′-O-α-L-rhamnopyranoside (254)

Compound **254** was isolated as a white amorphous solid. The ^{1}H NMR data (Table 4.10, Appendix 10) displayed in the aromatic region two singlets at δ_H 7.78 and 7.50 attributable to H-5′ and H-5, respectively of ellagic acid derivatives (Nkainsa *et al.*, 2020). Furthermore, signals of two methoxy groups at δ_H 4.03 (3H, *s*) and 4.02 (3H, *s*), and one glycosyl at δ_H 5.55 (1H, *d*, *J* = 1.8 Hz) were observed. The ^{13}C NMR spectrum revealed 22 carbons signals (Table 4.10), among which were two carbonyl groups of an *α, β* unsaturated lactones at δ_C 158.6 (C-7) and 158.4 (C-7′), which are characteristics of ellagic acid (Nkainsa *et al.*, 2020). Spectra from HSQC and HMBC (Appendix 10) were used in assigning the two methoxy groups to C-3 (δ_C 141.9) and C-3′ (δ_C 140.3), respectively. The two methoxy groups at δ_C 61.7 and 61.0 (Table 4.10) were downfield shifted, indicating that they were di-*ortho* substituted. This is consistent with their positioning at δ_C 141.9 and 140.3, respectively. The anomeric proton of the sugar at δ_H 5.55, for H-1″ in the HMBC spectrum of **254** also revealed a correlation between C-4′ (δ_C 152.6) of ellagic acid which established the glycosidic linkage. These results clearly

demonstrated that compound **254** is 3,3′-di-*O*-methylellagic acid-4′-*O*-α-*L*-rhamnopyranoside by comparison with literature (Ye *et al.*, 2007).



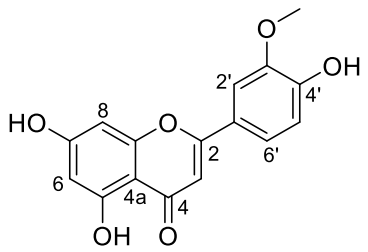
254

Table 4.10: Compound **254** NMR data (CD_2Cl_2, 600 MHz)

C-position	**254**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1	112.0	-	-
2	141.1	-	-
3	141.9	-	-
4	150.2	-	-
5	111.7	7.78 *s*	C-1, C-3, C-4, C-6, C-7
6	114.2	-	-
7	158.6	-	-
1′	112.8	-	-
2′	141.1	-	-
3′	140.3	-	-
4′	141.7	-	-
5′	111.8	7.50 *s*	C-3′, C-7′
6′	114.2	-	-
7′	158.4	-	-
CH_3O-3	61.7	4.03 *s*	C-3
CH_3O-3′	61.0	4.02 *s*	C-3′
1″	99.8	5.55 *d* (1.8)	C-4, C-3″, C-5″
2″	71.6	3.33	
3″	70.1	3.93 *d* (2.7)	
4″	70.5	3.68 *dd* (9.2, 3.5)	
5″	70.3	3.49 *dd* (9.4, 6.2)	
6″	17.9	1.11 *d* (6.2)	

4.3.5: Chrysoeriol (255)

The aromatic proton signals at δ_H 7.53 (1H, *s*) for H-2′, 6.90 (1H, *d*, *J* = 8.8) for H-5′, and 7.52 (1H, *d*, *J* = 1.6 Hz) for H-6′ in the ^{1}H NMR spectrum of compound **255** (a yellowish solid) suggest the 3′,4′-disubstitution pattern for the B ring (Table 4.11; Appendix 11) (Sahin *et al.,* 2004). With a coupling constant of 2.1 Hz, two aromatic signals occurred as meta-coupled doublets at δ_H 6.16 (1H, *d*, *J* = 2.1 Hz) for H-6 and 6.48 (1H, *d*, *J* = 2.1 Hz) for H-8, respectively. This indicated that positions 5 and 7 of ring A contained substituents (Sahin *et al.,* 2004). The characteristic proton signal of H-3 (δ_H 6.86) for a flavone was also observed. Six methines (δ_C 120.4, 115.8, 110.2, 103.2, 98.9, and 94.1), one methoxy (δ_C 56.0), and nine quaternary carbons (δ_C 181.8, 164.2, 163.7, 161.5, 157.4, 150.8, 148.1, 121.5, and 103.7), were observed in the ^{13}C NMR spectrum of compound **255**. The methoxy group was assigned to C-3′ due to the HMBC cross-peak (Appendix 11) observed from H-7′ (δ_H 3.90) to C-3′ (C 148.6). These results clearly demonstrated that compound **255** is chrysoeriol by comparison with literature (Vestena *et al.,* 2019).



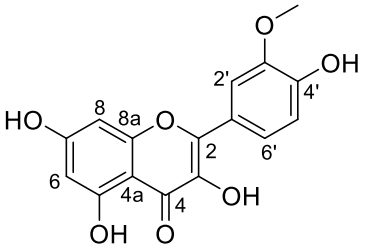
255

Table 4.11: Compound **255** NMR data ($CDCl_3$, 600 MHz)

C-position	**255**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	163.7	-	-
3	103.2	6.86 *s*	C-2, C-4, C-4a, C-1′
4	181.8	-	-
4a	103.7	-	-
5	161.5	-	-
6	98.9	6.16 *d* (2.1)	C-4a, C-5, C-7, C-8
7	164.2	-	-
8	94.1	6.48 *d* (2.1)	C-4a, C-6, C-7, C-8a
8a	157.4	-	-
1′	121.5	-	-
2′	110.2	7.53 *s*	C-2, C-3′, C-4′, C-6′
3′	148.1	-	-
4′	150.8	-	-
5′	115.8	6.90 *d* (8.8)	C-1′, C-3′, C-4′
6′	120.4	7.52 *d* (1.6)	C-2, C-2′, C-4′
3′-OCH_3	56.0	3.86 *s*	C-3′

4.3.6: Isorhamnetin (256)

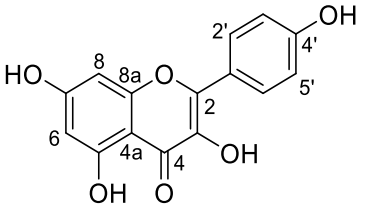
The yellowish solid compound **256**'s ^{1}H-NMR data (Table 4.12, Appendix 12) exhibited aromatic proton signals at δ_H 7.72 (1H, *d*, *J* = 2.2 Hz) for H-2′, 6.89 (1H, *d*, *J* = 9.0 Hz) for H-5′, and 7.65 (1H, *dd*, *J* = 2.2, 9.0 Hz) for H-6′ due to ring B's 3′,4′-disubstitution (Su *et al.*, 2008). A typical meta-coupled pattern signals for ring A were also observed for H-6 and H-8 protons at δ_H 6.14 and 6.39 (1H, *d*, *J* = 2.0 Hz each), respectively. A methoxy group (3H, *s*) signal at δ_H 3.81 was also noted in the ^{1}H NMR spectrum. Five methines (δ_C 121.7, 115.5, 111.7 , 98.3, and 93.5), one methyl (δ_C 55.8), and ten quaternary carbons (δ_C 175.9, 164.1, 160.7, 156. 2, 148.8, 147.4, 146.8, 135.7, 122.0, and 103.0), were observed in the ^{13}C NMR spectrum of compound **256**. The methoxy group was assigned to C-3′ due to the HMBC cross-peaks (Appendix 12) observed from δ_H 3.81 to C-3′ (δ_C 147.4). These results clearly demonstrated that compound **256** is isorhamnetin by comparison with literature (Su *et al.*, 2008 ; Rajvaidhya *et al.*, 2014).



256

4.3.7: Kaempferol (257)

Compound **257's** ^{1}H and ^{13}C NMR spectra (Table 4.12; Appendix 12) were strikingly similar to those of compound **256**. The two compounds were isolated as a mixture. The key distinction was that compound **257** lacked the methoxy signal at δ_H 3.86 (3H, *s*) and δ_C 55.8 (C-3″) which is observed in compound **256**. Also, the existence of the 1′,4′-disubstituted ring B in compound **257** was evident, where the protons at 2′ and 6′ were in the same chemical environment as well as the protons at 3′ and 5′ (Table 4.12). These resonances were consistent with that of kaempferol reported from *Tapinanthus globiferus* (Tukur *et al.*, 2022).



257

Table 4.12: Compounds **256** and **257** NMR data (DMSO, 600 MHz)

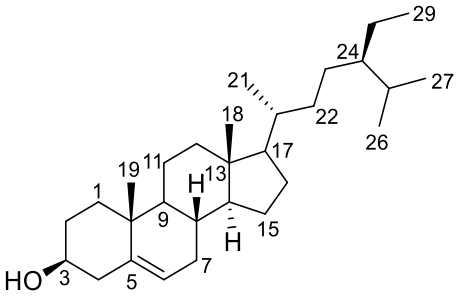
C-position	**256**			**257**		
	δ_C	$\delta_{H\ Mult}$ (*J* in Hz)	HMBC (H→C)	δ_C	$\delta_{H\ Mult}$ (*J* in Hz)	HMBC (H→C)
2	146.8	-	-	146.8	-	-
3	135.7	-	-	135.7	-	-
4	175.9	-	-	175.9	-	-
4a	103.0	-	-	103.0	-	-
5	160.7	-	-	160.7	-	-
6	98.3	6.14 *d* (2.1)	C-4a, C-5, C-7, C-8	98.3	6.14 *d* (2.1)	C-4a, C-5, C-7, C-8
7	164.1	-	-	164.1	-	-
8	93.5	6.39 *d* (2.1)	C-4a, C-6, C-7, C-8a	93.5	6.39 *d* (2.1)	C-4a, C-6, C-7, C-8a
8a	156.2	-	-	156.2	-	-
1′/1′	122.0	-	-	122.0	-	-
2′/6′	-	-	-	129.5	8.00 *d* (9.0)	C-2, C-4′
3′/5′	-	-	-	115.5	6.89 *d* (9.0)	C-1′, C-4′
4′	-	-	-	159.2	-	-
2′	111.7	7.72 *d* (2.2)	C-1′, C-3′, C-6′	-	-	-
3′	147.4	-	-	-	-	-
4′	148.8	-	-	-	-	-
5′	115.5	6.89 *d* (9.0)	C-3′, C-6′	-	-	-
6′	121.7	7.65 *dd* (9.0, 2.2)	C-2, C-2′, C-4′	-	-	-
3′-OCH_3	55.8	3.81 *s*	C-3′	-	-	-

4.4: Compounds from *Macaranga capensis*'s roots

Two compounds identified as β-sitosterol (**258**) and 2,2′-(((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(methylene))bis(oxirane) (**259**) were obtained from *M. capensis*'s roots extract.

4.4.1: β-Sitosterol (258)

The ^{1}H NMR data of compound **258** (a whitish powder) (Table 4.13, Appendix 13) indicated a hydroxymethine proton signal at δ_H 3.53 (1H, m) for H-3 and olefinic proton signal at δ_H 5.35 (1H, *dt*, *J* = 4.9, 2.5 Hz) for H-6. Additionally, six methyl group signals at δ_H 0.67 (3H, *s*), 1.01 (3H, *s*), 0.82 (3H, *m*), 0.92 (3H, *s*), 0.81 (3H, *s*), and 0.84 (3H, *s*) for H-18, H-19, H-21, H-26, H-27, and H-29, respectively, were observed. From the ^{13}C NMR data (Table 4.13), 29 signals were identified. Carbon oxymetic and olefinic carbon signals were observed at δ_c 72.0 (C-3), and 140.9 (C-5) and 121.9 (C-6), respectively. These results indicated that compound **258** is β-sitosterol by comparison with literature (Erwin *et al.*, 2020).



258

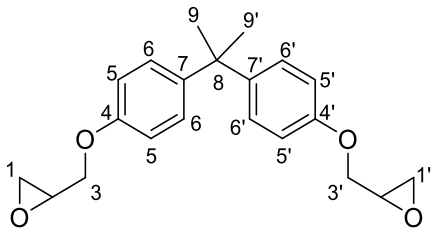
Table 4.13: Compound **258** NMR data ($CDCl_3$, 500 MHz)

C-position		**258**		
		δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1		37.4	1.84 *m*, 1.07 *m*	C-3, C-5, C-10
2		31.8	1.84 *m*, 1.48 *m*	C-3
3		72.0	3.53 *m*	-
4		42.5	2.27 *m*	C-3, C-5, C-6, C-10
5		140.9	-	-
6		121.9	5.35 *dd* (4.9, 2.5)	C-4, C-7, C-10
7		31.8	1.84 *m*	C-5, C-6, C-14
8		32.1	1.99 *m*	C-9, C-13
9		50.3	0.92 *m*	-
10		36.7	-	-
11		21.2	1.50 *m*	C-10, C-13
12		39.9	1.99 *m*, 1.14 *m*	C- 9, C-13, C-14
13		42.5	-	-
14		56.9	1.01 *m*	C-17
15		24.5	1.56 *m*	C-14, C-17
16		29.9	1.25 *m*	C-13, C-17
17		56.2	1.11 *m*	C-13, C-18, C-21, C-22
18	Me	12.1	0.67 *s*	C-13, C-14, C-17
19	Me	19.5	1.01 *s*	C-5, C-9, C-10
20		36.3	1.35 *m*	-
21	Me	20.0	0.82 *m*	C-14, C-20, C-23
22		34.1	1.35 *m*	C-17, C-21, C-23, C-24
23		26.2	1.15 *m*	C-20, C-22, C-24, C-25
24		46.0	0.92 *m*	C-23, C-25
25		29.3	1.66 *m*	C-23, C-24, C-27, C-28
26	Me	18.9	0.92 *s*	C-24, C-25
27	Me	19.2	0.81 *s*	C-24, C-25, C-26
28		23.2	1.25 *m*	C-24, C-25
29	Me	12.0	0.84 *s*	C-28

4.4.2: 2,2'-(((Propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(methylene))bis(oxirane) (259)

Compound **259** was isolated as light brown paste. Compound **259**'s ^{1}H NMR data (Table 4.14; Appendix 14) showedcharacteristic aromatic signals of bisphenol moiety at δ_H 6.82 (4H, *d*, *J* = 8.5 Hz) and 7.13 (4H, *d*, *J* = 8.5 Hz) for H-5/5′ and H-6/6′, respectively (Perrin *et ai.*, 2006). A methyl proton signal at δ_H 1.63 for H-9/9′ was also observed. Resonance peaks at δ_H 4.17

(2H, *dd*, *J* = 11.0, 3.3 Hz) and 3.95 (2H, *dd*, *J* = 11.0, 5.6 Hz), 3.34 (2H, *m*), 2.74 (2H, *dd*, *J* = 5.3, 2.6 Hz) and 2.89 (2H, *t*, *J* = 4.6 Hz), for H-3/3′, H-2/2′, and H-1/1′, respectively, were typical of glycidyl terminal group protons (Teh *et al.*, 2009). In ^{13}C NMR (Table 4.14), a quaternary carbon of bisphenol A moiety was observed at δ_C 41.9. Glycidyl terminal groups carbons were indicated by the signals displayed at δ_C 44.9 (C-1), 50.3 (C-2), and 68.9 (C-3). Compound **259** was identified as 2,2′-(((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(methylene))bis(oxirane) by comparing the results with the published literature (Teh *et al.*, 2009). This compound has not been isolated from nature before now.



259

Table 4.14: Compound **259** NMR data ($CDCl_3$, 600 MHz)

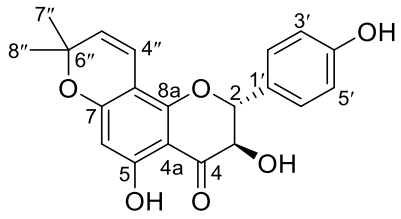
C-position	**259**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1/1′	44.9	2.74 *dd* (5.3, 2.6)	C-2
		2.89 *t* (4.6)	C-2, C-3
2/2′	50.3	3.34 *m*	-
3/3′	68.9	3.95 *dd* (11.0, 5.6)	C-1, C-2, C-4
		4.17 *dd* (11.0, 3.3)	C-1, C-2, C-4
4/4′	156.5	-	-
5/5′	114.1	6.82 *d* (8.5)	C-4, C-7
6/6′	127.9	7.13 *d* (8.5)	C-4, C-8
7/7′	143.8	-	-
8	41.9	-	-
9/9′-CH_3	31.2	1.63 *s*	C-7, C-8

4.5: Compounds from *Ficus thonningii*'s stem bark

Eight compounds identified as yukovanol (**260**), 5,7,4′-trihydroxy-3′-(2-hydroxy-3-methyl-3-butenyl) isoflavone (**261**), cajanin (**262**), taxifolin (**263**), protocatechuic acid (**264**), saccharose (**265**), and stigmasterol (**266**) were isolated from the stem bark of *F. thonningii.*

4.5.1: Yukovanol (260)

The ^{1}H NMR data of compound **260** (an amorphous yellow powder) (Table 4.15, Appendix 15) revealed the presence of a 1,2,3,4,5-penta-substituted benzene ring at δ_H 5.91 (1H, *s*) for H-6, a 1,4-di-substituted benzene ring at δ_H 7.37 (2H, *d*, *J* = 8.5 Hz) for H-2′/6′ and 6.85 (2H, *d*, *J* = 8.5 Hz) for H-3′/5′, and two oxygenated methines at δ_H 5.02 (1H, *d*, *J* = 11.6 Hz) and 4.60 (1H, *d*, *J* = 11.6 Hz) for H-2 and H-3, respectively. Two doublet signals assignable to tertiary-methyl moieties were observed both at δ_H 1.44 (6H, *d*, *J* = 2.4 Hz) for H-7″ and H-8″ and a pair of cis coupled olefinic doublets at δ_H 6.62 (1H, *d*, *J* = 10.1 Hz) and 5.62 (1H, *d*, *J* = 10.1 Hz) for H-4″ and H-5″, respectively (Table 4.15). An oxygen-bearing quaternary sp^3 carbon signal at δ_H 79.5 was seen in ^{13}C NMR (Table 4.15). Based on spectroscopic data, compoun **260** was recognized as a flavanonol derivative containing a 2,2-dimethyl-2*H*-pyran ring either at C-6, C-7 or C-7, C-8 (Zong *et al.*, 2014). The B-ring's hydroxyl group was identified to be at C-4′ because H-2′/6′ and H-3′/5′ of the B-ring had correlations with C-2 and C-1′ respectively, in the HMBC spectrum. Based on the HMBC correlations of H-4″ and H-5″ with C-8a and C-8, respectively (Appendix 15), the 2,2-dimethyl-2*H*-pyran ring was attached to C-7 and C-8 of the A-ring. Based on the NMR (1D and 2D) results together with the reported literature (Sasaki *et al.*, 2012), compound **260** was found to be yukovanol.



260

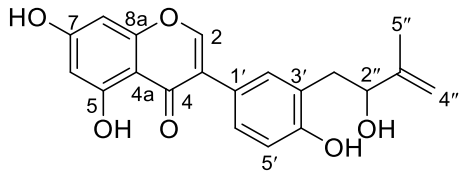
Table 4.15: Compound **260** NMR data (CD_3OD, 500 MHz)

C-position	**260**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	85.1	5.02 *d* (11.6)	C-3, C-4, C-2′/6′
3	73.7	4.60 *d* (11.6)	C-2, C-4
4	199.2	-	-
4a	102.4	-	-
5	163.9	-	-
6	97.1	5.91 *s*	-
7	163.6	-	-
8	104.1	-	-
8a	159.2	-	-
1′	129.1	-	-
2′/6′	130.4	7.37 *d* (8.5)	C-2, C-4′, C-2′/6′
3′/5′	116.2	6.85 *d* (8.5)	C-1′, C-3′/5′, C-4′
4′	159.3	-	-
4″	116.0	6.62 *d* (10.1)	C-8a, C-6″
5″	127.7	5.62 *d* (10.1)	C-8, C-6″, C-7″, C-8″
6″	79.5	-	-
7″	28.6	1.44 *d* (2.4)	C-4″, C-6″, C-8″
8″	28.5	1.44 *d* (2.4)	C-4″, C-6″, C-7″

4.5.2: 5,7,4′-Trihydroxy-3′-(2-hydroxy-3-methyl-3-butenyl) isoflavone (261)

Compound **261** was found to be yellow powder. Its ^{1}H NMR spectrum (Table 4.16, Appendix 16) contained a characteristic signal at δ_H 7.87 (1H, *s*) for H-2 of isoflavone. Two doublet signals of ring A were observed at δ_H 6.37 (1H, *d*, *J* = 2.2 Hz) and 6.28 (1H, *d*, *J* = 2.2 Hz) for H-8 and H-6, respectively. Additionally, a pair of doublet signals at δ_H 7.23 (1H, *d*, *J* = 2.3 Hz) for H-2′ and 6.94 (1H, *d*, *J* = 8.3 Hz) for H-5′, and a doublet of doublet signal at δ_H 7.28 (1H, *dd*, *J* = 8.3, 2.3 Hz) for H-6′ were observed. The correlations between H-2 and C-4, C-8a, and C-1′, as observed in the HMBC spectrum, confirmed the isoflavone skeleton. Additional

long-range correlations were found between H-8 and C-6, C-7, and C-4a. Additionally, signals at δ_C18.4 (CH_3) (δ_H 1.83, (3H, *s*)), 38.4 (CH_2) (δ_H 2.86, 2.99, (2H, *dd*, *J* = 14.7, 8.8, 2.3)), 78.4 (CH-O) (δ_H 4.44 (1H, *m*), 111.2 (=CH_2) (δ_H 4.89 (2H, s)), and 147.2 (=C) indicated 2-hydroxy-3-methyl-3-butenyl as a side chain (Elsohly *et al.*, 2001; Li *et al.*, 2002). Using the HMBC spectrum, the side chain was attached to C-3′ of the B-ring as the correlation between H-1″ and C-3′ was observed. Compound **261** was found to be 5,7,4′-trihydroxy-3′-(2-hydroxy-3-methyl-3-butenyl) isoflavone on the basis of the NMR (1D and 2D) results together with the published literature (Li *et al.*, 2002).



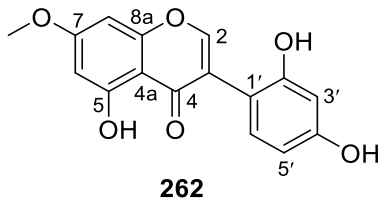
261

Table 4.16: Compound **261** NMR data (CD_2Cl_2, 500 MHz)

C-position	**261**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	153.0	7.87 *s*	C-4, C-8a, C-1′
3	123.5		-
4	180.9	-	-
4a	106.2	-	-
5	162.7	-	-
6	99.6	6.28 *d* (2.2)	C-5, C-7, C-8, C-4a
7	163.4	-	-
8	94.3	6.37 *d* (2.2)	C-6, C-7, C-4a
8a	158.2	-	-
1′	123.0	-	-
2′	132.5	7.23 *d* (2.3)	C-5′, C-1′, C-6′, C-4′, C1″
3′	126.2	-	-
4′	156.7	-	-
5′	117.5	6.94 *d* (8.3)	C-1′
6′	129.4	7.28 *dd* (8.3, 2.3)	C-2′
1″	38.4	2.86 *dd* (14.7, 2.3) 2.99 *dd* (14.7, 8.8)	C-2′, C-3′, C-2″
2″	78.4	4.44 *m*	C-4″, C-5″
3″	147.2	-	
4″	111.2	4.89 *s*	
5″	18.4	1.83 *s*	

4.5.3: Cajanin (262)

The ^{1}H NMR spectrum of compound **262** (a yellow solid) indicated the presence of six aromatic protons (Appendix 17). A characteristic signal at δ_H 8.07 (1H, *s*) assignable to H-2 of isoflavone was observed. The spectrum also revealed a multiplet and doublet signals of ring A at δ_H 6.38 (1H, *m*) and 6.57 (1H, *d*, *J* = 2.3 Hz) for H-6 and H-8, respectively. Additionally, a methoxy signal at δ_H 3.89 (3H, *s*) was observed. A pair of multiplet signals at δ_H 6.40 (1H, *m*) for H-3′ and 6.36 (1H, *m*) for H-5′, and a doublet signal at δ_H 7.05 (1H, *d*, *J* = 8.2 Hz) for H-6′ were also observed. In the HMBC spectrum (Appendix 17), the isoflavone skeleton was confirmed by the correlations of H-2 to C-3, C-4, C-8a, and C-1″. The ^{13}C NMR (Table 4.17) revealed a methoxy carbon signal in addition to fifteen carbon signals, six of which were methines and nine of which were quaternary carbons. The methoxy and hydroxy groups at C-7, 2′ and 4′ were confirmed based on the HMBC correlations. Compound **262** was identified as cajanin on the basis of the NMR (1D and 2D) results together with the published literature (Awouafack *et al.*, 2011).



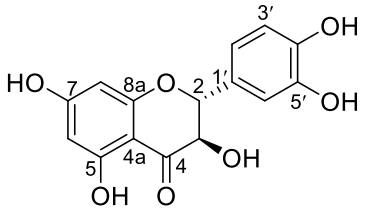
262

Table 4.17: Compound **262** NMR data (CD_3OD, 500 MHz)

C-position	**262**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	157.8	8.07 s	C-3, C-4, C-8a, C-1′
3	122.8	-	-
4	182.8	-	-
4a	107.1	-	-
5	163.5	-	-
6	99.3	6.38 *m*	C-5, C-7, C-8
7	167.3	-	-
8	93.2	6.57 *d* (2.3)	C-6, C-7, C-4a, C-8a
8a	159.7	-	-
OCH_3	56.5	3.89 *s*	C-7
1′	110.6	-	-
2′	157.0	-	-
3′	104.2	6.40 *m*	C-1′, C-4′
4′	160.3	-	-
5′	108.1	6.36 *m*	C-1′
6′	133.2	7.05 *d* (8.2)	C-3, C-4′

4.5.4: Taxifolin (263)

The ^1H NMR spectrum of compound **263** (a yellow solid) (Appendix 18) indicated two meta coupled proton signals at δ_H 5.92 (1H, *d*, *J* = 2.1 Hz) for H-6 and 5.88 (1H, *d*, *J* = 2.1 Hz) for H-8. The proton signals of ring C occurred at δ_H 4.91 (1H, *d*, *J* = 11.5 Hz) and 4.50 (1H, *d*, *J* = 11.5 Hz) for H-2 and H-3, respectively. Ring B displayed three aromatic protons signals at δ_H 6.85 (1H, *dd*, *J* = 8.1, 2.0 Hz) for H-2′, 6.80 (1H, *d*, *J* = 8.1 Hz) for H-3′ and 6.96 (1H, *d*, *J* = 2.0 Hz) for H-6′ which was in the form of an ABX spin-system indicating a flavonol skeleton. The ^{13}C spectrum (Table 4.18) revealed fifteen carbon signals, seven of which were methines and eight of which were quaternary carbons. Compound **263** was identified as taxifolin on the basis of the NMR (1D and 2D) results together with the published literature (Usman *et al.*, 2021).



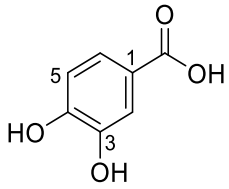
263

Table 4.18: Compound **263** NMR data (CD_3OD, 500 MHz)

C-position	**263**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
2	85.1	4.91 *d* (11.5)	C-3, C-4, C-1′, C-2′, C-6′
3	73.7	4.50 *d* (11.5)	C-2, C-4, C-1′
4	198.4	-	-
4a	101.8	-	-
5	164.5	-	-
6	97.4	5.92 *d* (2.1)	C-7, C-8, C-4a
7	165.3	-	-
8	96.3	5.88 *d* (2.1)	C-6, C-4a
8a	164.5	-	-
1′	129.9	-	-
2′	120.9	6.85 *dd* (8.1, 2.0)	C-6′
3′	116.1	6.80 *d* (8.1)	C-1′, C-4′, C-5′
4′	147.2	-	-
5′	146.3	-	-
6′	115.9	6.96 *d* (2.0)	C-1′, C-2′, C-4′

4.5.5: Protocatechuic acid (264)

The ^{1}H NMR data (Table 4.19) of compound **264** (an amorphous whitish solid) displayed in the aromatic region, three signals at δ_H 7.43 (1H, *d*, *J* = 1.9 Hz) for H-2, 6.77 (1H, *d*, *J* = 8.2 Hz) for H-5, and 7.41 (1H, *dd*, *J* = 8.2, 1.9 Hz) for H-6, suggesting a 1,3,4-substituted benzene ring. ^{13}C NMR spectrum (Appendix 19) revealed signals at δ_C 117.7 (CH, C-2), 145 (C, C-3), 150.9 (C, C-4), 115.6 (CH, C-5), and 123.7 (CH, C-6), corresponding to aromatic carbons. The HMBC spectrum of this compound (Appendix 19) displayed a clear correlation between the two meta-coupled protons with a signal at δ_C 172.3, which is typical of the carbonyl group of carboxylic acid. Therefore, compound **264** was identified, on the basis of the NMR (1D and 2D) results together with the published literature (Erukainure *et al.*, 2017; Nurhamidah *et al.*, 2021), as protocatechuic acid.



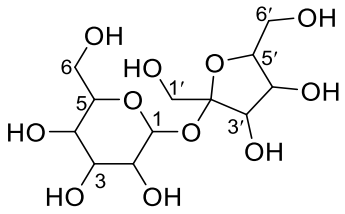
264

Table 4.19: Compound **264** (CD_3OD, 500 MHz)

C-position	**264**		
	δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1	125.0	-	-
2	117.7	7.43 *d* (1.9)	C-3, C-4, C-6, C-7
3	145.9	-	-
4	150.9	-	-
5	115.6	6.77 *d* (8.2)	C-1, C-3, C-4
6	123.7	7.41 *dd* (8.2, 1.9)	C-2, C-7
CO	172.0	-	-

4.5.6: Saccharose (265)

Compound **265** was isolated as colorless crystals. The ^{1}H NMR (Table 4.20, Appendix 20) displayed an anomeric proton signal at δ_H 5.40 (1H, *d*, *J* = 3.8 Hz) for H-1 which was a typical characteristic of α-*D*-glucopyranosyl moiety. Additionally, diagnostic signals typical for β-*D* fructofuranosyl moiety at δ_H 4.20 (1H, *d*, *J* = 8.8 Hz) and 4.04 (1H, *t*, *J* = 8.6 Hz) for H-3′ and H-4′, respectively, were observed. Presence of α-*D*-glucopyranosyl and β-*D*-fructofuranosyl moieties were also indicated from the ^{13}C NMR data by the characteristic resonances at δ_C 92.1 (C-1) and 103.6 (C-2′), respectively (De Bruyn, 1991). The long-range correlation identified in the HMBC spectrum (Appendix 20) flanked by the signal at δ_H 5.40 (H-1) with carbon at δ_C 103.6 (C-2′) indicated the inter-glycosidic linkage of the two monosaccharides as (1 → 2′). Based on the foregoing data from 1D and 2D NMR, and in comparison, with the reported data, compound **265** was identified as saccharose, which was previously reported from *Echinophora platyloba* (Valizadeh *et al.*, 2014).



265

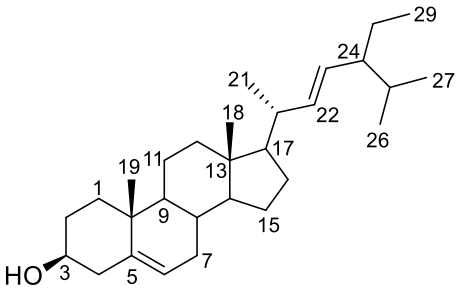
Table 4.20: Compound **265** NMR data (D_2O, 500 MHz)

C-position	**265**		
	δ_C	$\delta_{H\ Mult}$ (*J* i *Hz*)	HMBC (H→C)
1	92.1	5.40 *d* (3.8)	C-3, C-5, C-2′
2	71.0	3.54 *dd* (10.0, 3.8)	C-3
3	72.5	3.75 *dd* (10.0, 9.1)	C-2, C-4
4	69.1	3.46 *t* (9.5)	C-3, C-5, C-6
5	72.3	3.83 *m*	C-6
6	60.0	3.80 *m*	C-4, C-5
1′	61.2	3.66 *s*	C-2′, C-3′
2′	103.6	-	
3′	76.3	4.20 *d* (8.8)	C-1′, C-4′, C-5′
4′	73.9	4.04 *t* (8.6)	C-3′, C-6′
5′	81.3	3.87 *m*	C-2′, C-4′, C-6′
6′	62.3	3.80 *m*	C-5′

4.5.7: Stigmasterol (266)

The ^{1}H NMR data of compound **266** (a whitish powder) (Table 4.21, Appendix 21) revealed three doublet of doublets signals at δ_H 5.34 (1H, *dd*, *J* = 5.5, 1.9 Hz) for H-6, 5.14 (1H, *dd*, *J* = 15.1, 8.6 Hz) for H-22, and 5.02 (1H, *dd*, *J* = 15.1, 8.6 Hz) for H-23, typical characteristics for steroidal skeleton and olefinic protons, respectively. The signal at δ_H 3.52 (1H, *dd*, *J* = 11.6, 4.9 Hz) for H-3 indicated the presence of a hydroxymethine proton. Two singlet signals at 0.68 (3H, *s*) and 1.00(3H, *s*) for H-18 and H-19 were assigned to tertiary methyl groups. Two methyl doublets signals were also observed at δ_H 1.02 (3H, *d*, *J* = 6.7 Hz) and 0.92 (3H, *d*, *J* = 6.4 Hz) for H-21 and H-26, respectively. The ^{13}C NMR data (Table 4.21) data revealed 29 signals. The signals at δ_C 140.9, 121.9, 138.5, and 129.4 corresponded to olefinic carbons at C-5, C-6, C-22, and C-23, respectively. The oxymethine carbon (C-sp^3) signal for C-3 was observed at δ_C 72.0.

Based on the NMR (1D and 2D) results together with the reported literature (Ayele *et al.*, 2022), compound **266** was found to be stigmasterol.



266

Table 4.21: Compound **266** NMR data ($CDCl_3$, 500 MHz)

C-position		**266**		
		δ_C	$\delta_{H\ Mult}$ (*J* in *Hz*)	HMBC (H→C)
1		37.4	1.84 *m*, 1.06 *m*	C-3, C-5, C-10
2		31.8	1.99 *m*, 1.83 *m*	C-3
3		72.0	3.52 *tt* (11.6, 4.9)	C-1, C-2, C-4
4		42.4	2.28 *m*	C-3, C-5, C-6, C-10
5		140.9	-	-
6		121.9	5.34 *dt* (5.5, 1.9)	C-4, C-7, C-10
7		31.8	1.50 *m*	C-5, C-6, C-19, C-14
8		32.1	1.43 *m*	C-9, C-13
9		50.3	0.92 *m*	-
10		36.6	-	-
11		21.2	1.47 *m*, 1.02 *m*	C-10, C-13
12		39.9	2.01 *m*, 1.15 *m*	C-9, C-13, C-14, C-18
13		42.5	-	-
14		56.9	0.99 *m*	C-17
15		24.4	1.84 *m*, 1.56 *m*	C-14, C-17
16		29.9	1.25 *m*	C-13, C-17
17		56.2	1.10 *m*	C-13, C-18, C-21, C-22
18	Me	12.0	0.68 *s*	C-12, C-13, C-14, C-17
19	Me	19.5	1.00 *s*	C-1, C-5, C-9, C-10
20		40.6	2.03 *m*	-
21	Me	21.4	1.02 *d* (6.7)	C-14, C-20, C-23
22		138.5	5.14 *dd* (15.1, 8.6)	C-17, C-20, C-21, C-23, C-24
23		129.4	5.02 *dd* (15.1, 8.6)	C-20, C-22, C-24, C-25, C-28
24		51.4	1.52 *m*	C-23, C-25
25		32.0	1.46 *m*	-
26	Me	18.9	0.92 *d* (6.4)	C-24, C-25
27	Me	19.2	0.81 *d* (8.3)	C-24, C-25, C-26
28		26.2	1.60 *m*	C-24, C-25
29	Me	12.1	0.84 *t* (8.3)	C-24

4.6: Cytotoxicity of Compounds from *M. conglomerata* and *M. capensis*

The toxicity of isolated compounds towards MCF-7 (human breast adenocarcinoma) and HepG2 (human liver cancer) cell lines was evaluated using the MTT test. These malignant cells were selected due to their prevalence and the demand for efficient and less toxic medications. For instance, the most common malignancy among women was breast cancer, responsible for 15.5 % of cancer fatalities among female patients in 2020 (Sung *et al.*, 2021). Nevertheless, one of the most typical tumours among men is liver cancer. In 2020, it accounted for 10.4 % of overall cancer mortality in males (Ferlay *et al.*, 2021). An IC_{50} threshold of ≤ 10 µM is considered a good cytotoxic activity for a pure compound. The activity is moderate, if $10 < IC_{50} < 50$ µM (Kuete and Efferth, 2015). According to their IC_{50} values (Table 4.22), the tested compounds showed different potency against the selected cancerous cells. Compounds **245** and **259** exhibited moderate cytotoxic potentials against the carcinoma cells under investigation with IC_{50} values range of 13.1 – 28.2 µM, while compound **250** displayed activity moderately (IC_{50} = 42.9 µM) only against the HepG2 cell line. The IC_{50} values for the reference drug doxorubicin were 0.69 µM (MCF-7) and 0.81 µM (HepG2). Compounds **245** and **246** are prenylated flavonoids; however, compound **245** showed the highest cytotoxicity, suggesting that its activity is enhanced by the modified geranyl group attached to ring A. All the tested compounds displayed lower cytotoxic effects on MCF-7 and HepG2 cancer cell lines compared with the reference drug (doxorubicin).

Table 4.22: Cytotoxicity of compounds isolated from *M. conglomerata* and *M. capensis*

Compounds	**Cytotoxicity** (IC_{50}, μM)	
	MCF-7	**HepG2**
245	16.2	13.1
246	81.4	56.2
247	98.4	76.7
248	52.6	76.7
249	67.9	67.5
250	89.9	42.9
259	28.2	15.6
Doxorubicin	0.69	0.81

4.7: Antibacterial Activity of Crude Extracts from *Macaranga* Species

The antibacterial activity of *M. conglomerata* (leaves, stem, and root), *M. Capensis* (leaves, stem, and root), and *M. kilimandscharica* (leaves, stem, and root) towards 13 micro-organisms including drug-sensitive and multidrug-resistant were evaluated (Table 4.23). All plant extracts displayed good activities with MIC values ranging from 4 to 128 μg/mL. Crude extracts from *M. capensis* showed potent activity against 13/13 bacteria tested. Most of the extracts from *M. conglomerata* and *M. Kilimandscharica* showed a large spectrum of activities against MDR phenotypes. Their inhibition potencies were observed against 12/13 (92.3%) bacterial strains. Ciprofloxacin, a standard antibiotic, was used as a reference and was effective against all bacterial strains with MICs values as low as 1 to 4 μg/mL. It is noteworthy that most of the extracts showed bactericidal effects against *E. coli, E. aerogenes, K. pneumoniae, P. stuartii, P. aeruginosa,* and *S. aureus,* with MBC/MIC ratio ≤ 4.

When referring to crude extracts derived from plants, many authors defined the antibacterial activity to be strong when MIC is less than 100 μg/mL, moderate when MIC is between 100 and 625 μg/mL, and low when MIC is more than 625 μg/mL (Kuete, 2010; Kuete and Efferth, 2010). Based on this cutoff point, all crude extracts (MIC = 4 – 128 μg/mL) displayed strong

to moderate antibacterial activities against most bacterial strains, with the lowest MIC value recorded at 4 μg/mL. It is important to note that the activity of these plant extracts against bacterial strains was more or less the same. This led to the conclusion that the chemical compositions of all the plant materials are similar. The pronounced antibacterial activities of all the tested crude extracts could be attributed to the presence of flavonoids, stilbenes, terpenoids, and coumarins, which are the predominant phytochemicals reported from *Macaranga* species. These phytochemicals may be acting synergistically or additively to exert the noted strong antibacterial activities. Gram-negative bacteria of the species *E. coli* (ATTC10536 and AG102) and *P. aeruginosa* (PA01 and PA124), known for their multi-resistance to drugs, were less resistant to all crude extracts (MIC $\leq$ 128 μg/mL). Previous reports identified *Macaranga* species as rich sources of prenylated flavonoids and stilbenes, many of which have biological activities (including antibacterial properties) that encompass almost the entire area of pharmacological sciences (Ngoumfo *et al.*, 2008; Magadula, 2014).

Table 4.23: MIC and MBC (in µg/mL) of crude extracts from *Macaranga* species and ciprofloxacin against a panel of 13 bacteria strains

Bacterial strains	MCPL		MCPS		MCPR		MKL		MKS		MKR		MCL		MCS		MCR		Ciprofloxacin	
	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R	MIC (MBC)	R
E. coli																				
ATTC10536	16 (64)	4	16 (64)	2	4 (16)	4	32 (64)	2	32 (64)	2	16 (64)	4	128 (512)	4	8 (16)	2	16 (64)	4	1 (4)	4
AG102	32 (128)	4	32 (64)	2	4 (8)	2	128 (512)	4	16 (32)	2	16 (32)	2	16 (128)	8	8 (16)	2	64 (128)	2	1 (2)	2
E. aerogenes																				
ATCC13048	32 (128)	4	8 (64)	8	16 (32)	2	32 (64)	2	32 (128)	4	8 (32)	4	-	nd	32 (64)	2	64 (128)	2	1 (8)	8
EA27	128 (256)	2	8 (32)	4	4 (16)	4	64 (128)	2	32 (64)	2	16 (256)	16	128 (256)	2	8 (32)	4	64 (128)	2	1 (4)	4
K. pneumoniae																				
ATCC11296	32 (128)	2	32 (64)	2	8 (16)	2	16 (32)	2	8 (32)	4	8 (32)	4	32 (64)	2	8 (32)	4	128 (256)	2	2 (4)	2
KP55	32 (64)	2	16 (32)	2	8 (16)	2	64 (128)	2	32 (64)	2	8 (16)	2	16 (64)	4	16 (32)	2	-	nd	1 (1)	1
P. stuartii																				
PS2636	16 (32)	2	8 (32)	4	32 (64)	2	64 (128)	2	32 (64)	2	8 (64)	8	32 (128)	4	32 (64)	2	32 (64)	2	2 (8)	4
NEA16	16 (32)	2	16 (64)	4	8 (32)	4	-	nd	32 (64)	2	32 (64)	2	32 (128)	4	16 (64)	4	64 (128)	2	1 (4)	4
P. aeruginosa																				
PA01	32 (64)	2	32 (128)	4	32 (64)	2	128 (256)	2	16 (64)	4	16 (64)	4	128 (512)	4	32 (64)	2	64 (128)	2	4 (16)	4
PA124	64 (128)	2	32 (128)	4	32 (64)	2	128 (256)	2	32 (64)	2	16 (32)	2	32 (128)	4	16 (64)	4	64 (256)	4	2 (16)	8
S. aureus																				
ATCC25923	8 (32)	4	4 (16)	4	8 (16)	2	16 (32)	2	8 (16)	2	4 (32)	8	8 (32)	4	8 (32)	4	8 (16)	2	1 (1)	1
MRSA3	4 (16)	4	8 (32)	4	8 (64)	8	8 (16)	2	8 (16)	2	16 (32)	2	16 (64)	4	16 (32)	2	16 (32)	2	1 (4)	4
MRSA6	4 (16)	4	4 (16)	4	4 (16)	4	16 (32)	2	8 (16)	2	8 (32)	4	16 (64)	4	8 (32)	4	16 (32)	2	2 (16)	8

MIC: minimal inhibitory concentration; MBC: minimal bactericidal concentration; R: MBC/MIC ratio (a sample is considered as bacteriostatic or bactericidal when R >4 or ≤4 respectively); (-) : MIC or MBC > 512 µg/mL for crude extract; nd : not determined (as no MIC and MBC values were not observed till 512 µg/mL). MCPL: *M. capensis* leaves; MCPS: *M. capensis* stem; MCP R: *M. capensis* root; MKL: *M. kilimandscharica* leaves; MKS: *M. kilimandscharica* stem; MKR: *M. kilimandscharica* root; MCL: *M. conglomerata* leaves; MCS: *M. conglomerata* stem; MCR: *M. conglomerata* root

4.8: Antibacterial Activity of Compounds from *Macaranga conglomerata*

The isolated compounds from *Macaranga conglomerata*'s stem and leaves were evaluated for their antibacterial activities against 4 bacteria, that is *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 31488. Ciprofloxacin was used as a reference drug (Table 4.24). Compound **245 – 247** (flavonol derivatives) demonstrated broad-spectrum activities against all the tested bacteria strains (MIC = 1.0 – 500 µg/mL), while compounds **248** – **250** only showed varying degrees of inhibitory activities against *K. pneumoniae* ATCC 31488 (MIC = 7.8 – 500 µg/mL) (Table 4.22). Among the isolates, compound **245** was mostly active, exhibiting potent and moderate activities (MIC = 7.8 – 62.5 µg/mL) against all tested bacteria. Moreover, compounds **245** (MIC = 7.8 µg/mL) and **246** (MIC = 1.0 µg/mL) were 2 and 16-folds more active, respectively than ciprofloxacin (MIC = 15.6 µg/mL) against Gram-negative *P. aeruginosa* ATCC 27853. The strong activities of compounds **245** and **246** could be attributed to their prenylated nature. It has been reported that prenylation improves the lipophilic properties of the phenolic compounds, which may be important in structure-activity relation, thereby increasing their antibacterial activities (Botta *et al.,* 2005; Fukai *et al.,* 2005; Eerdunbay aer *et al.,* 2014; Kirmizibekmez *et al.,* 2015).

The influence of prenylation can be observed when comparing the MICs values of compounds **245** – **247**, all with flavonol nuclei. Compound **247** (which lacks prenylation) was found to have relatively weak/low antibacterial activity (MIC = 500 µg/mL) against all the tested bacteria; therefore, it was considered inactive (Jepkoech *et al.,* 2021). Additionally, Gram-negative *K. pneumoniae* has long been recognized as a possible cause of community-acquired pneumonia. Compound **248** (MIC = 7.8 µg/mL) displayed strong activity against *K. pneumoniae* ATCC 31488.

Table 4.24: Antibacterial activity of compounds isolated from *Macaranga conglomerata*

	Antibacterial Activity MIC (µg/mL)			
Compounds	***S. a.***	***E. c.***	***P. a.***	***K. p.***
245	62.5	62.5	7.8	62.5
246	250.0	125.0	1.0	500.0
247	500.0	500.0	500.0	500.0
248	NA	NA	NA	7.8
249	NA	NA	NA	500.0
250	NA	NA	NA	500.0
Ciprofloxacin	15.6	1.0	15.6	2.0

S. a. = *Staphylococcus aureus* ATCC 25923; *E. c.* = *Escherichia coli* ATCC 25922; *P. a.* = *Pseudomonas aeruginosa* ATCC 27853; *K. p.* = *Klebsiella pneumoniae* ATCC 31488; NA: Not active

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1: Conclusions

Three *Macaranga* species (*Macaranga conglomerata*, *Macaranga capensis*, and *Macaranga kilimandscharica*) and *Ficus thonningii* were explored phytochemically in this study. The anticancer and antibacterial properties of the crude extracts and isolated compounds were investigated. The study's findings are summarized in this section.

Fifteen compounds were isolated from the three *Macaranga* species (leaves, stem/bark and roots) and characterized, among which 6-[(2(*E*),7(*E*))-6-isopropyl-3,9-dimethyldeca-2,7,9-trienyl] kaempferol (trivially named as conglomeratin) (**245**) is novel, while 2,2′-(((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(methylene))bis(oxirane) (**259**) has not been isolated from nature before now. Seven compounds were isolated from *Ficus thonningii*'s stem bark and characterized in which saccharose (**265**) is reported from the genus *Ficus* for the first time.

In the anticancer assay, among the evaluated compounds, compounds **245** and **259** showed the most potent cytotoxic activities against liver (HepG2) and breast (MCF-7) cancer cell lines with IC_{50} values range of 13.1 and 28.2 µM. When compared to the reference drug, doxorubicin, all of the compounds tested had lower cytotoxic effects on MCF-7 and HepG2 cancer cell lines.

Crude extracts from different parts of the three *Macaranga* species exhibited good antibacterial activities with MIC values ranging from 4 – 128 µg/mL against Gram-positive and Gram-negative compared with ciprofloxacin. Among the compounds evaluated, compound **245** was significantly active against *P. aeruginosa* (MIC = 7.8 µg/mL) and moderately active towards *S. aureus*, *E. coli* and *K. pneumoniae* (MIC = 62.5 µ/mL). Compound **246** showed potency against *P. aeruginosa* (MIC = 1.0 µg/mL) while **248** was selective towards *K. pneumoniae* (MIC = 7.8 µg/mL).

5.2: Recommendations

Based on the results obtained, the study suggests that:

i. Phytochemical investigation of other parts of the studied plants should be explored, as this work resulted in isolating structurally unique compounds with potent anticancer and antibacterial properties.

ii. To enhance the anticancer and antibacterial potency of the active metabolites, particularly the novel compound, their diverse analogues should be prepared and tested.

iii. The isolated phytochemicals should be further evaluated for synergisms.

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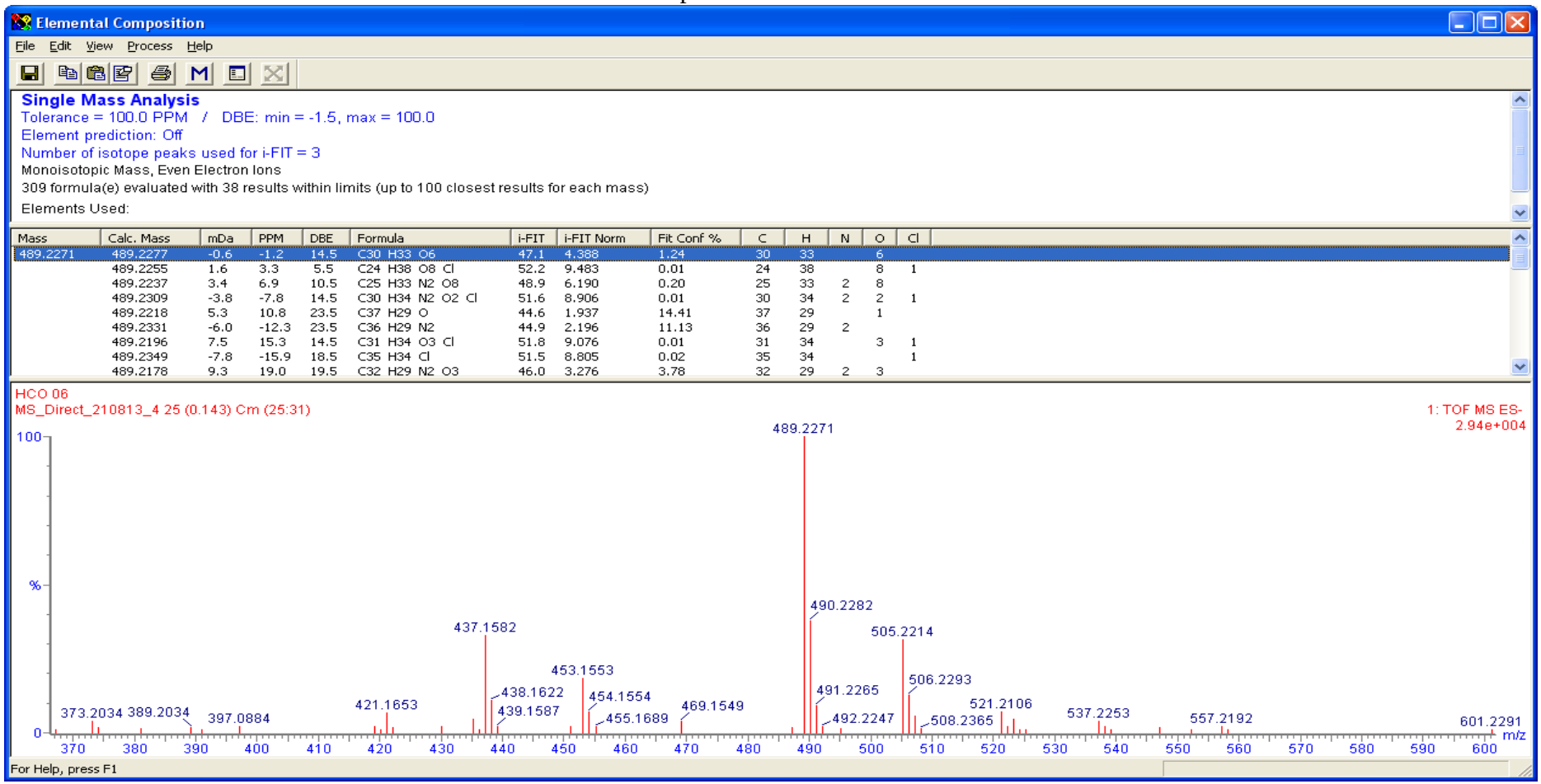
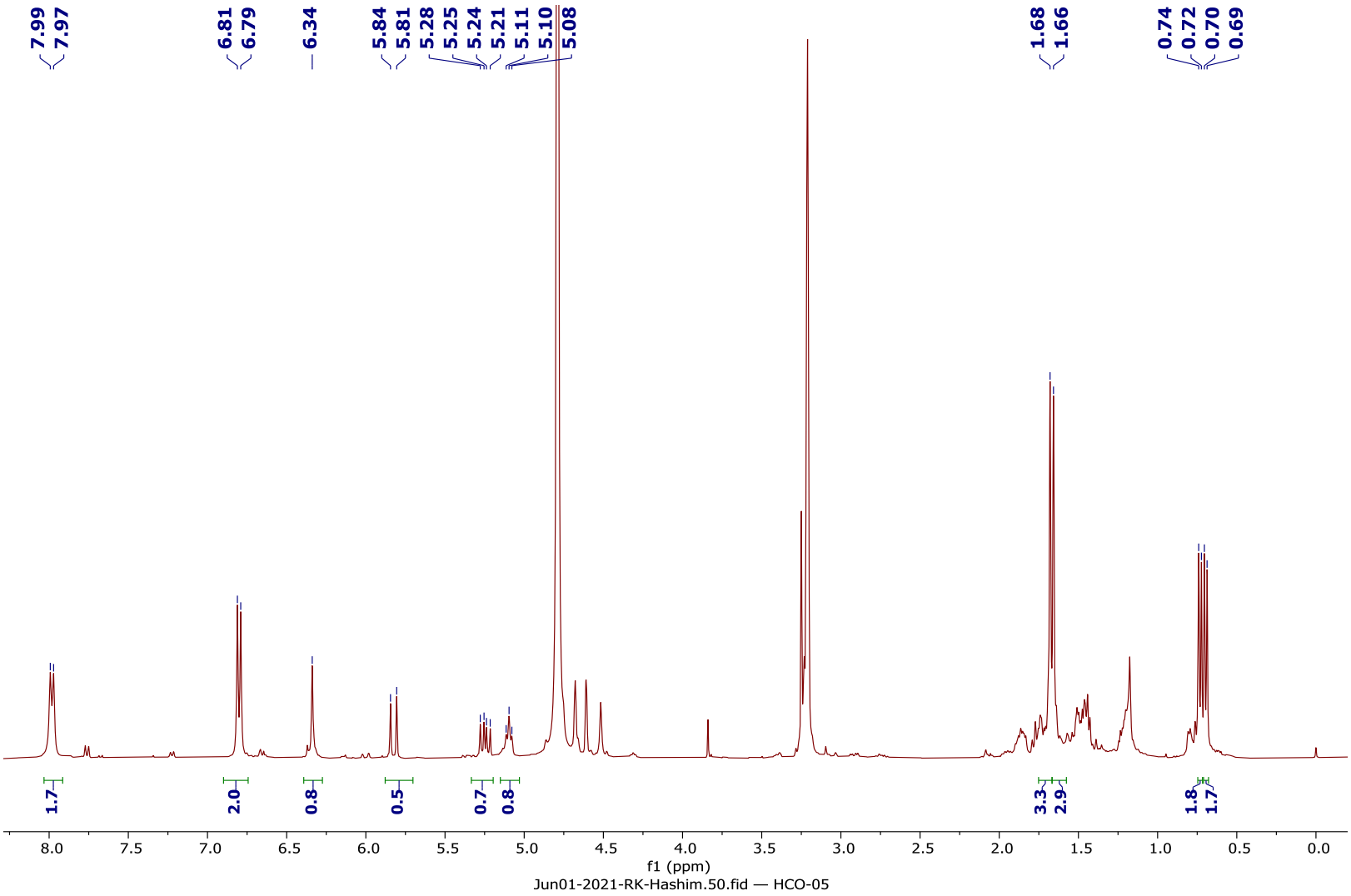
APPENDICES

Appendix 1: Spectra of conglomeratin (**245**)

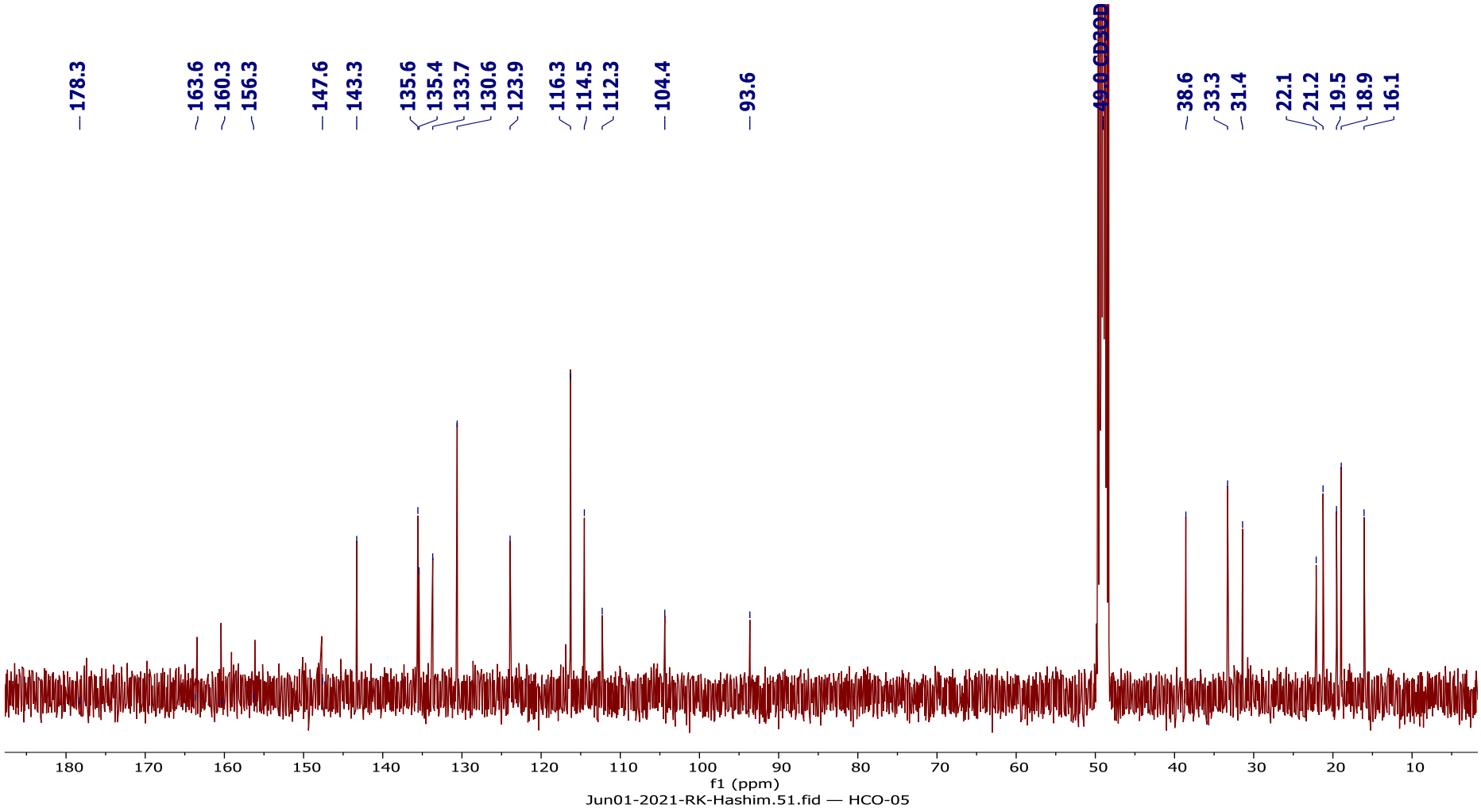
Compound **245** HRESIMS



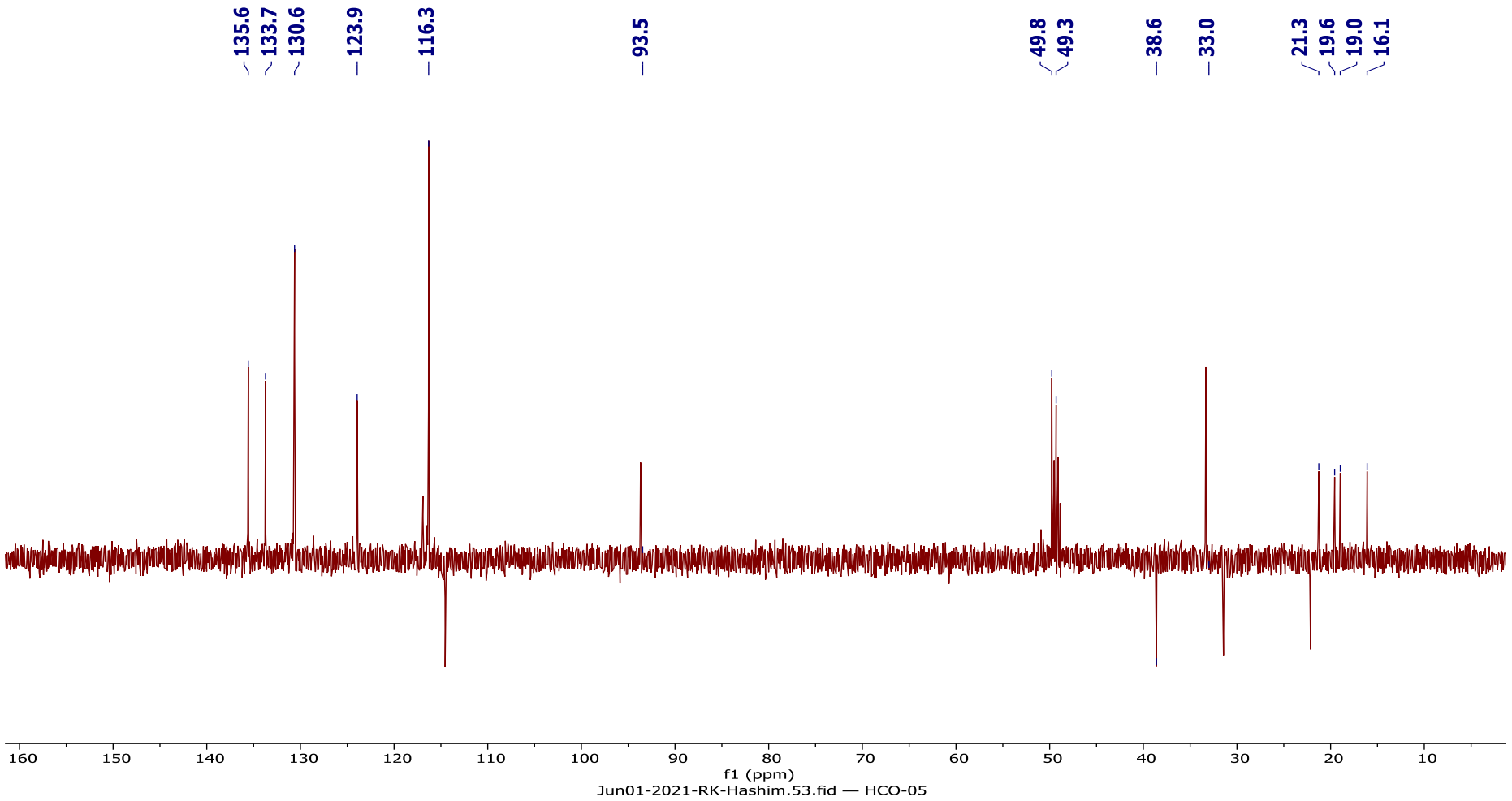
Compound **245** ^{1}H NMR spectrum (CD_3OD, 400 MHz)



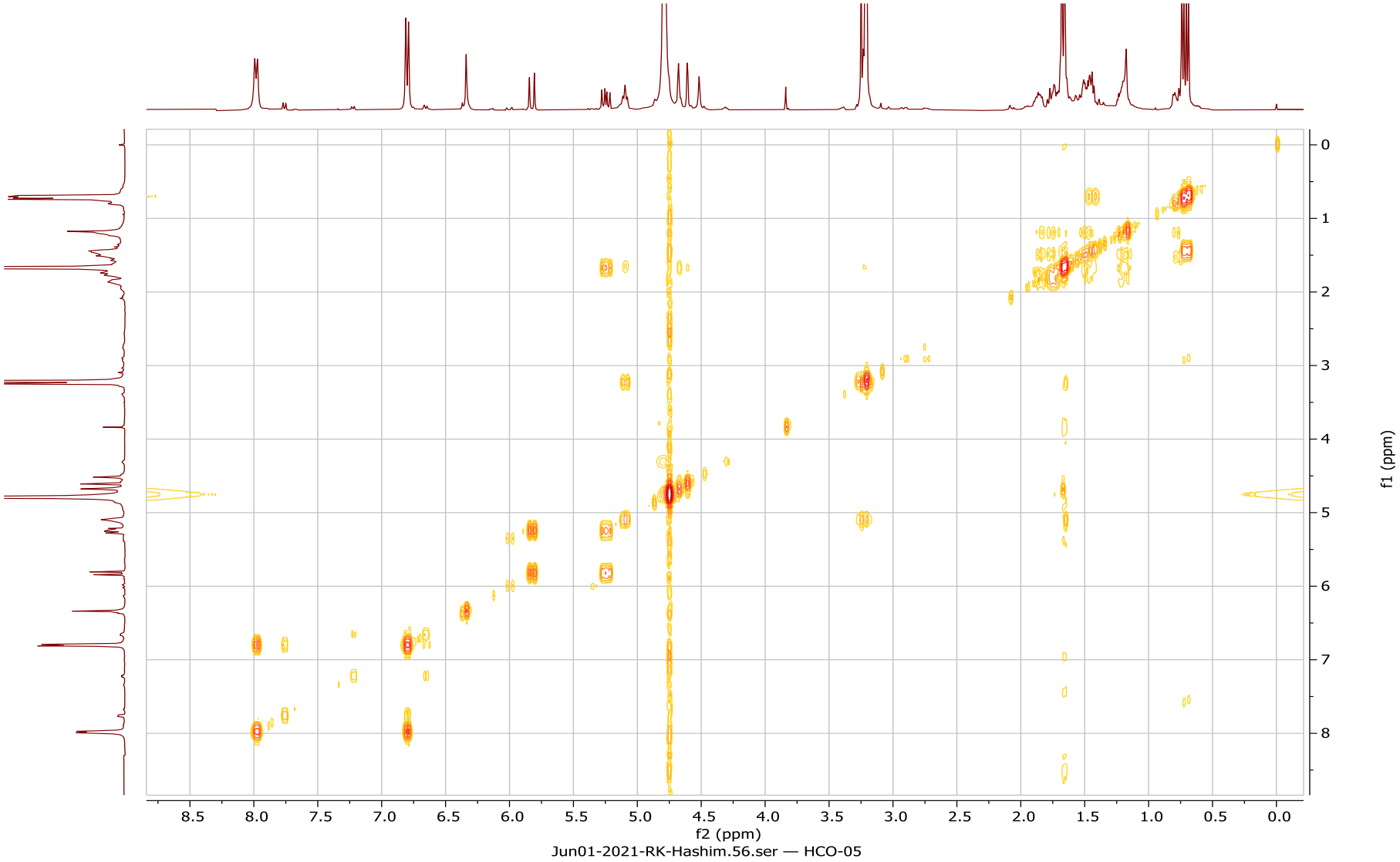
Compound **245** ^{13}C NMR spectrum (CD_3OD, 100 MHz)



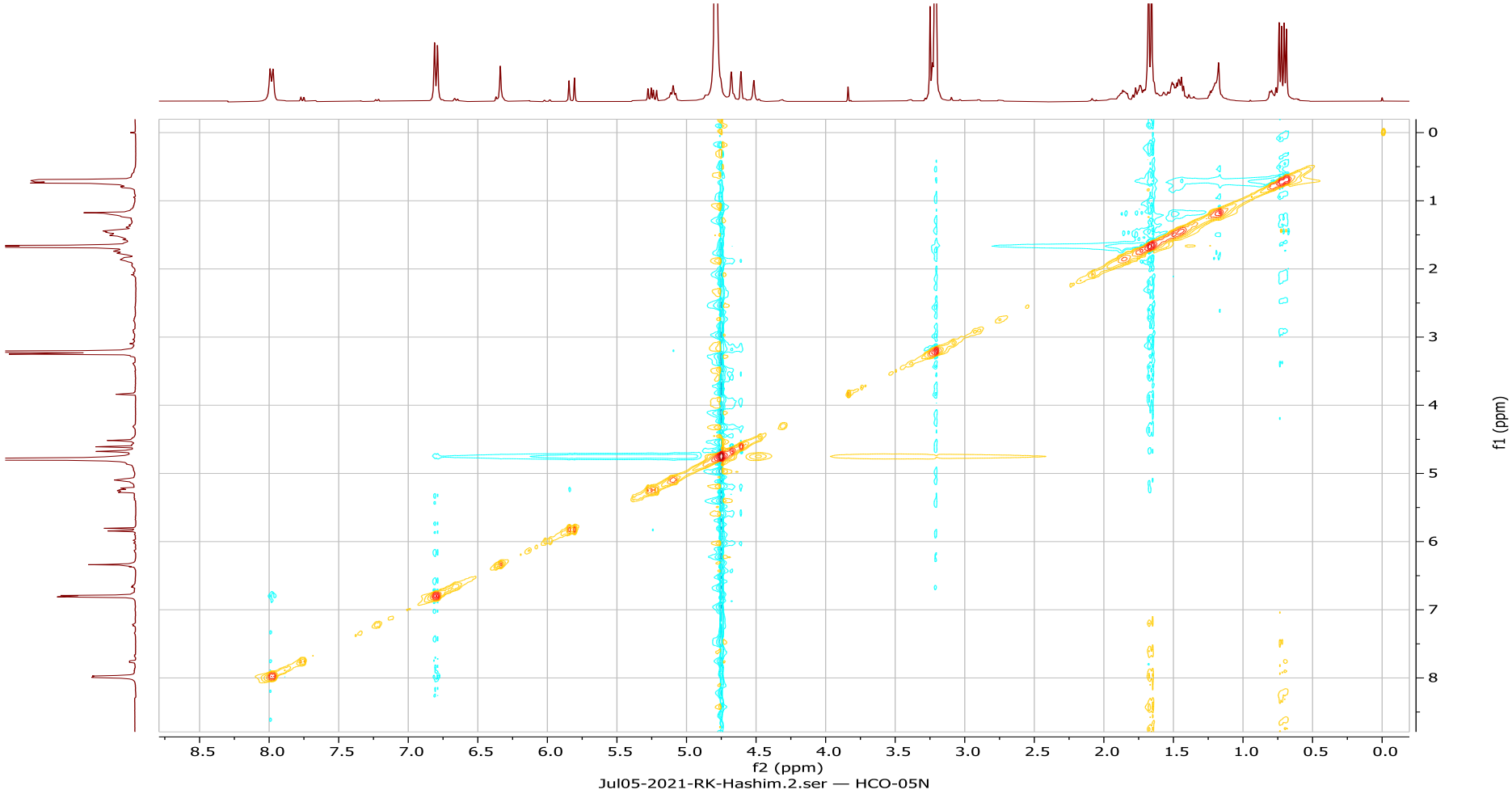
Compound **245** DEPT spectrum (CD_3OD)



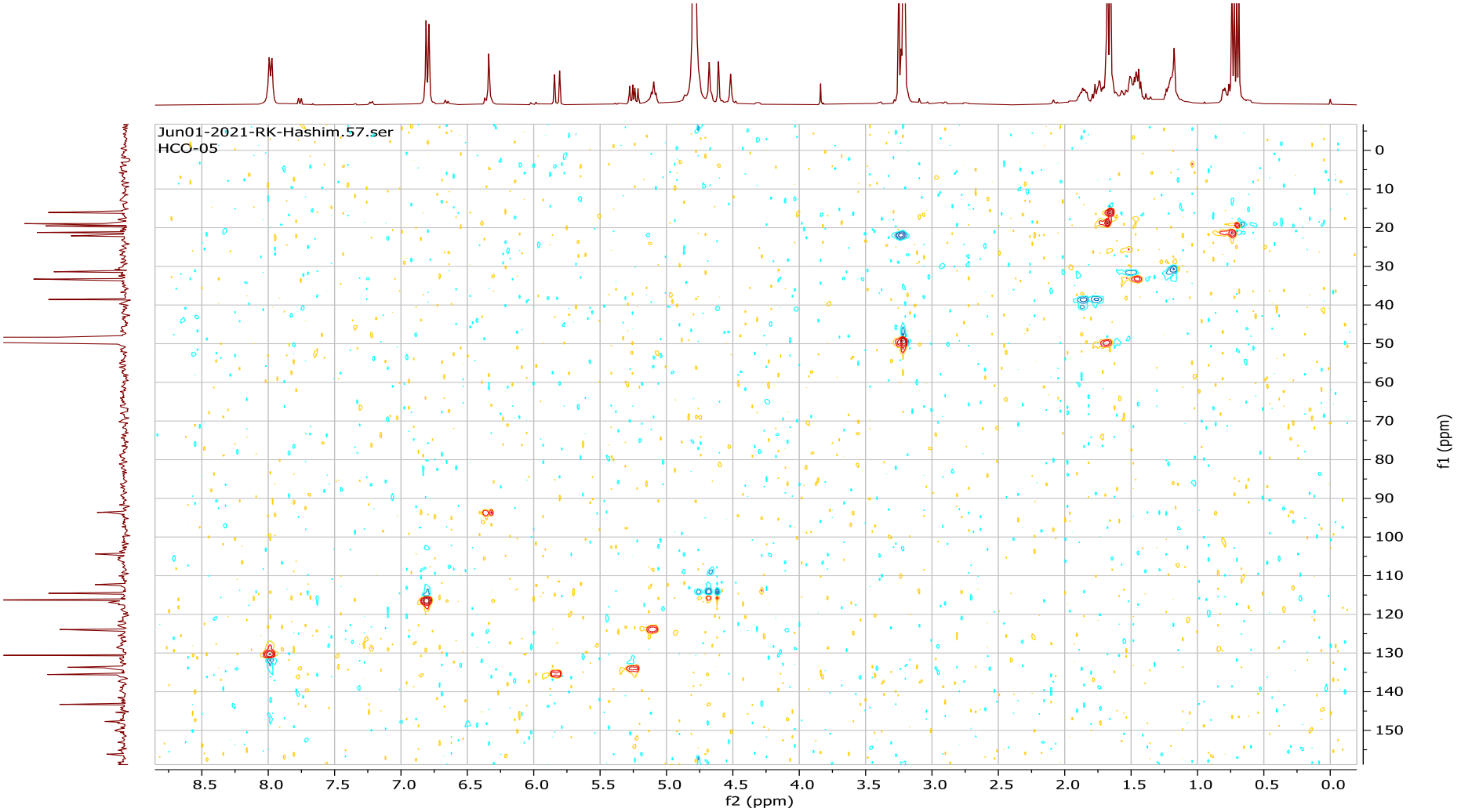
Compound **245** ^{1}H-^{1}H COSY spectrum (CD_3OD)



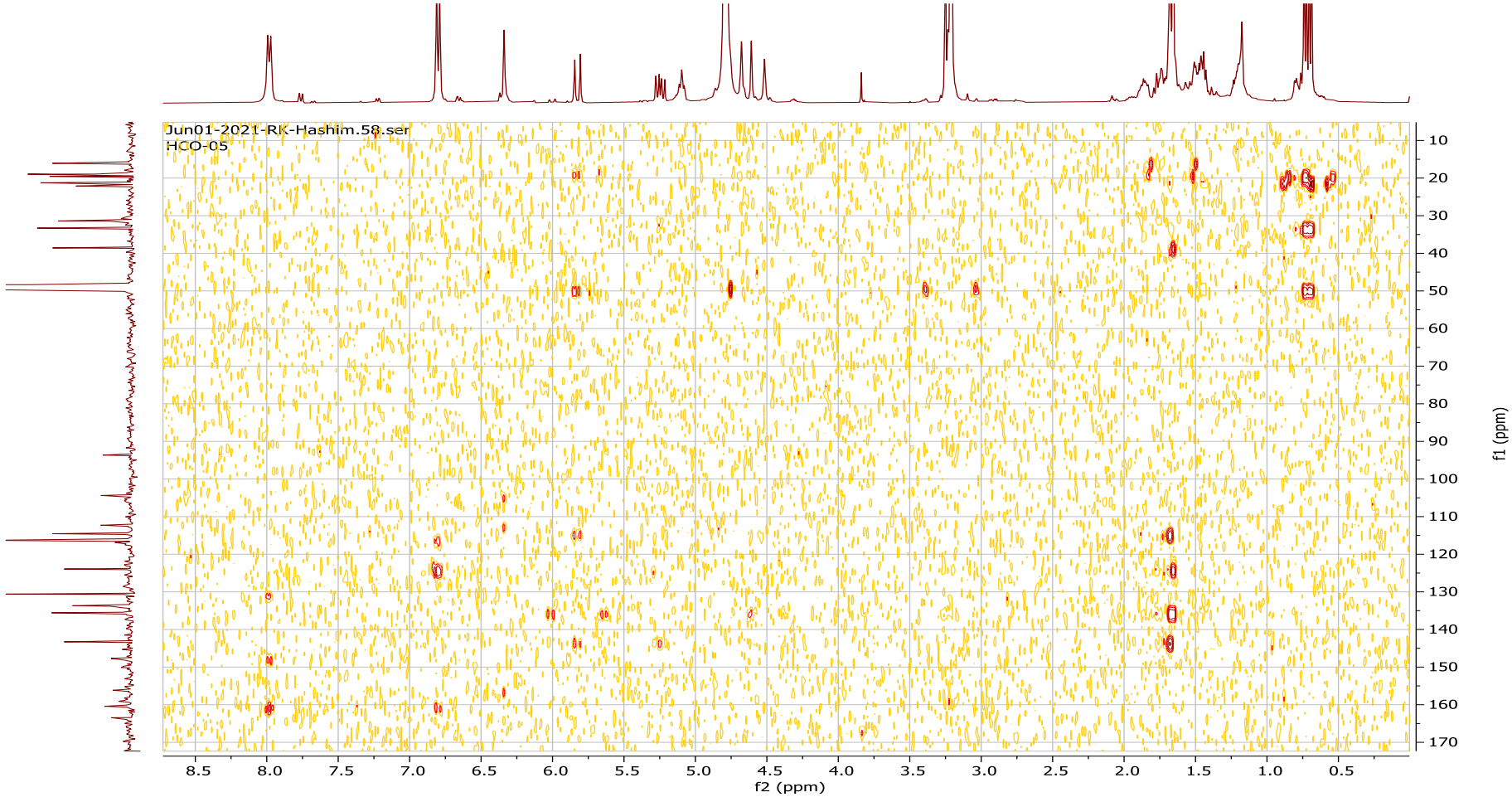
Compound **245** NOESY spectrum (CD_3OD)



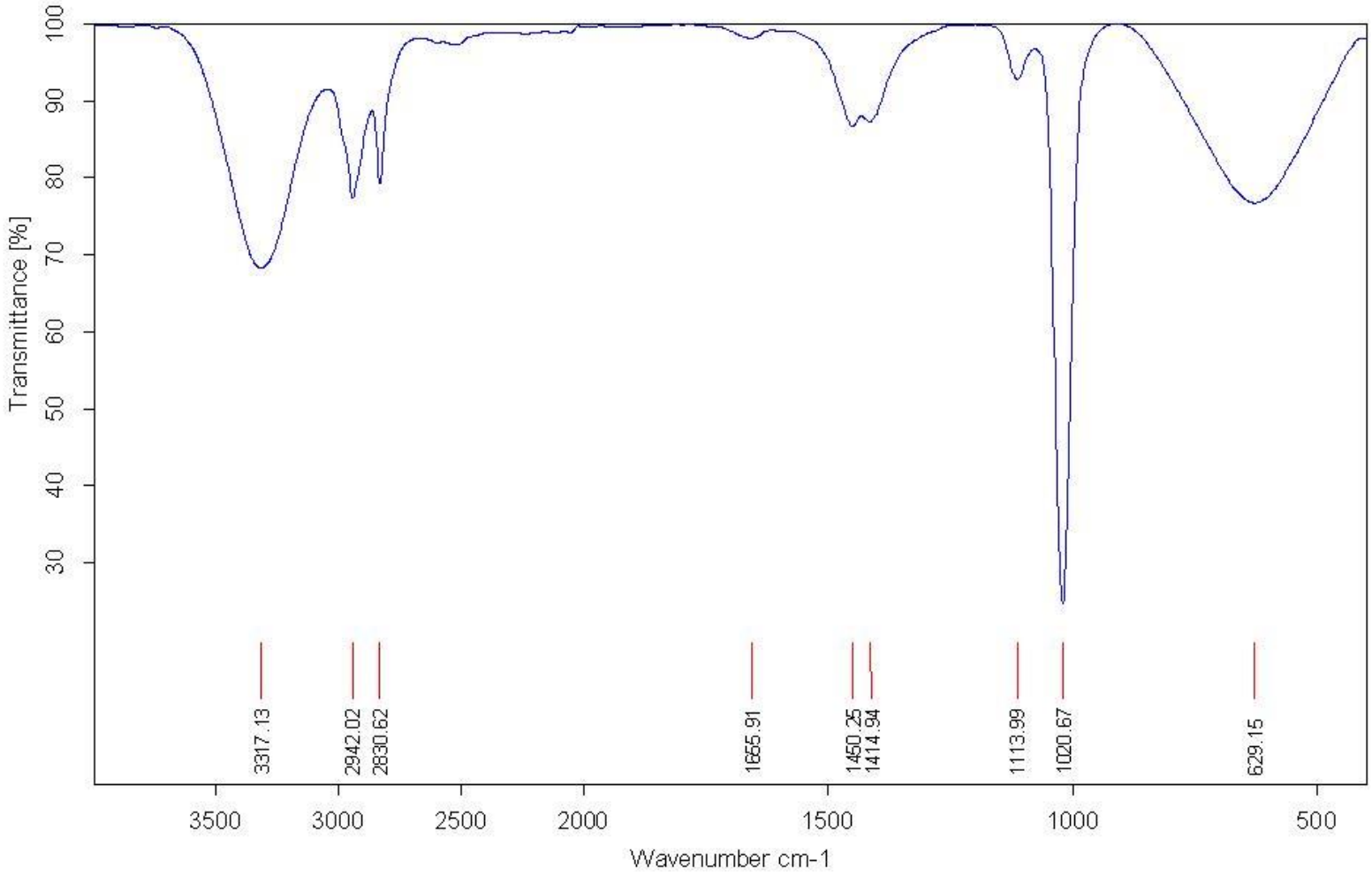
Compound **245** HSQC spectrum (CD_3OD)



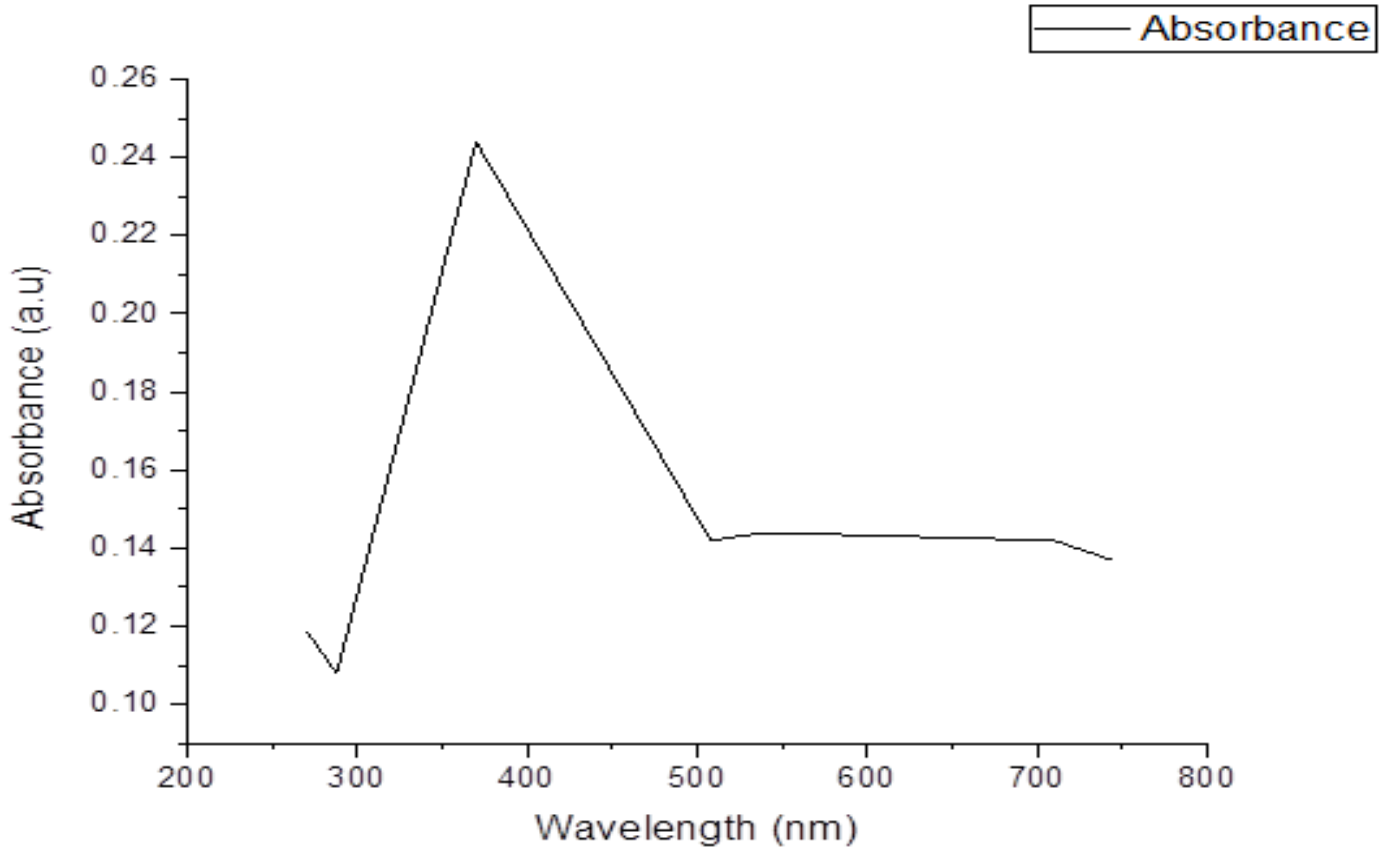
Compound **245** HMBC spectrum (CD_3OD)



IR spectrum of compound **245**

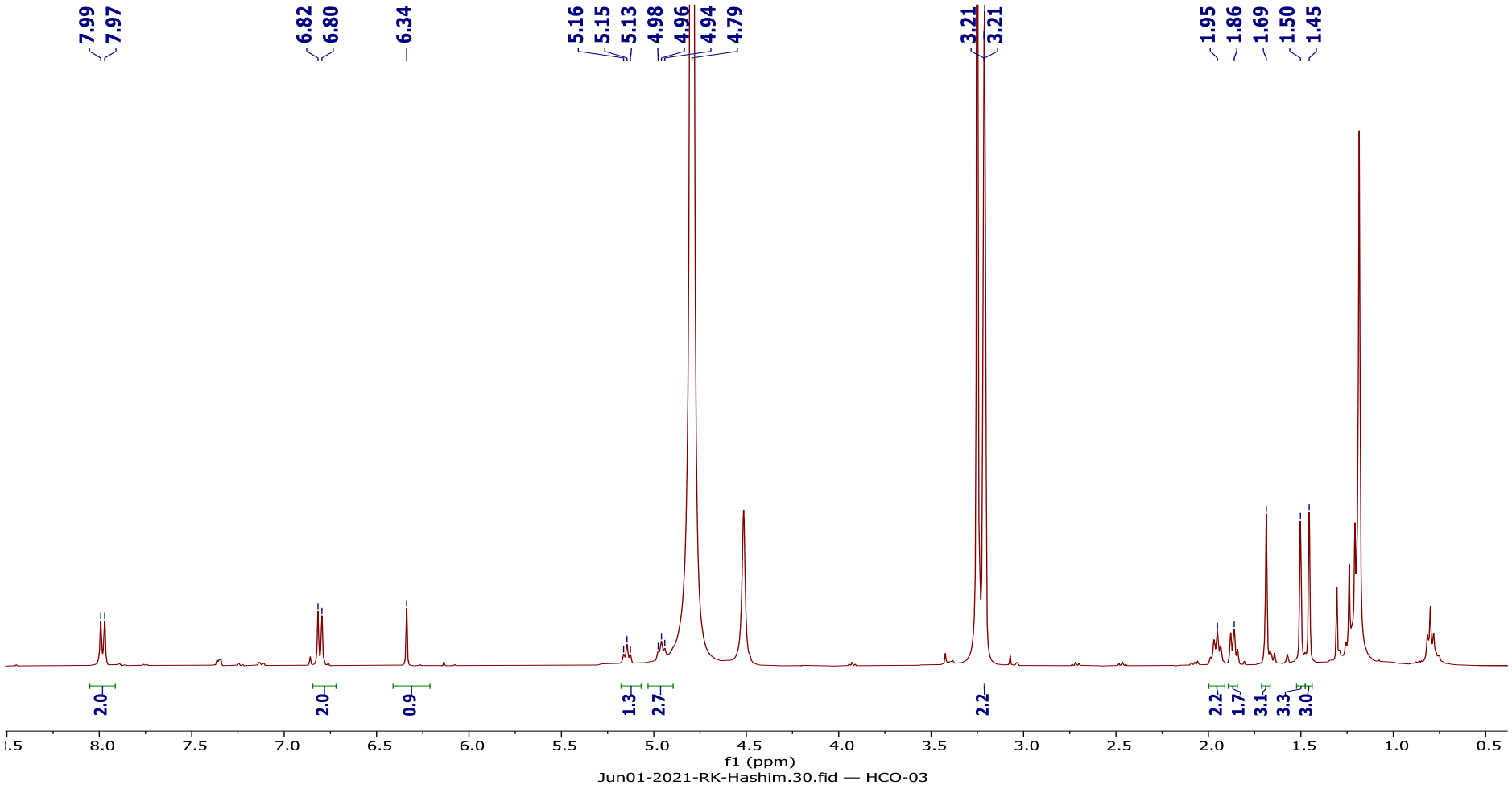


UV spectrum of compound **245**

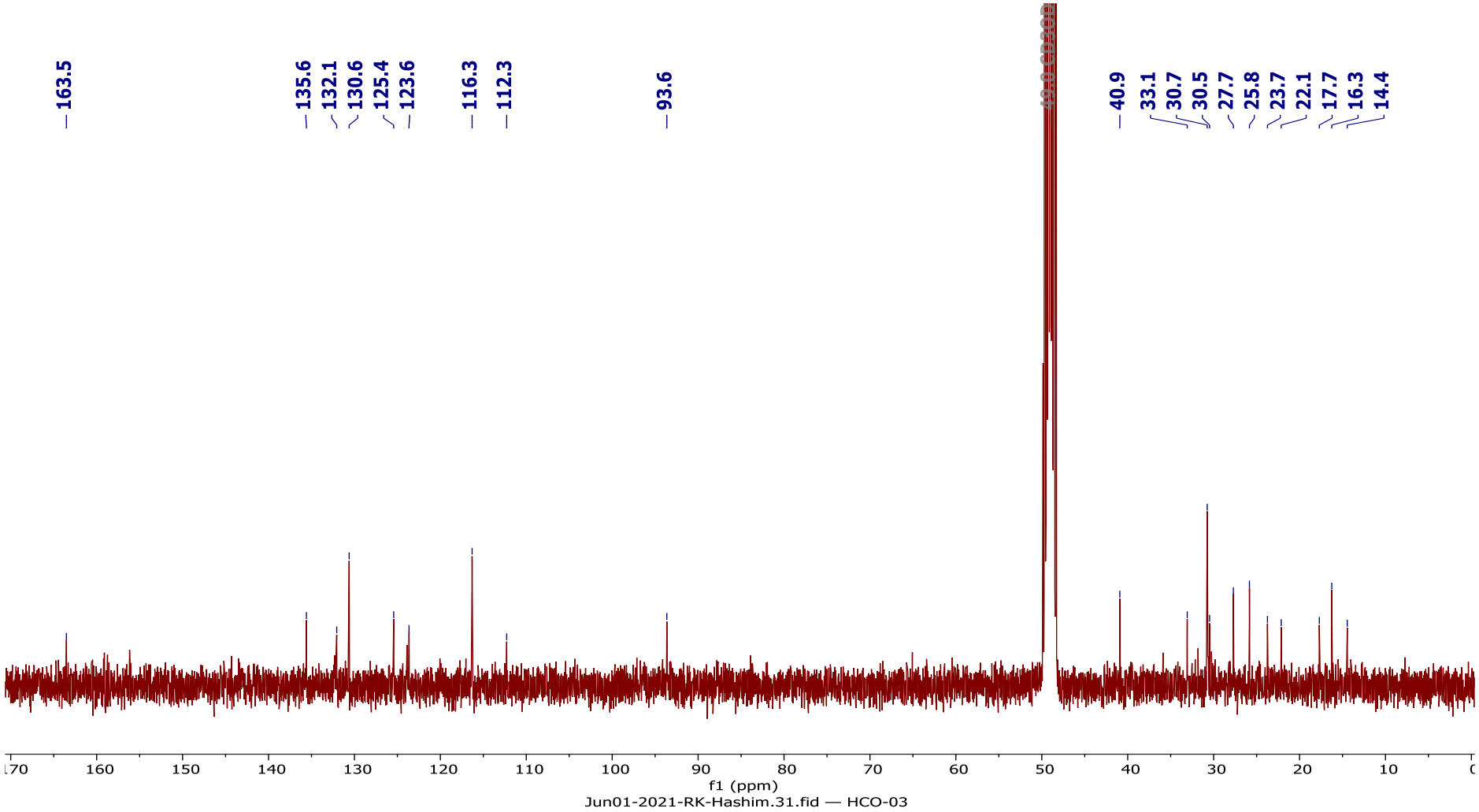


Appendix 2: Spectra of macarangin (**246**)

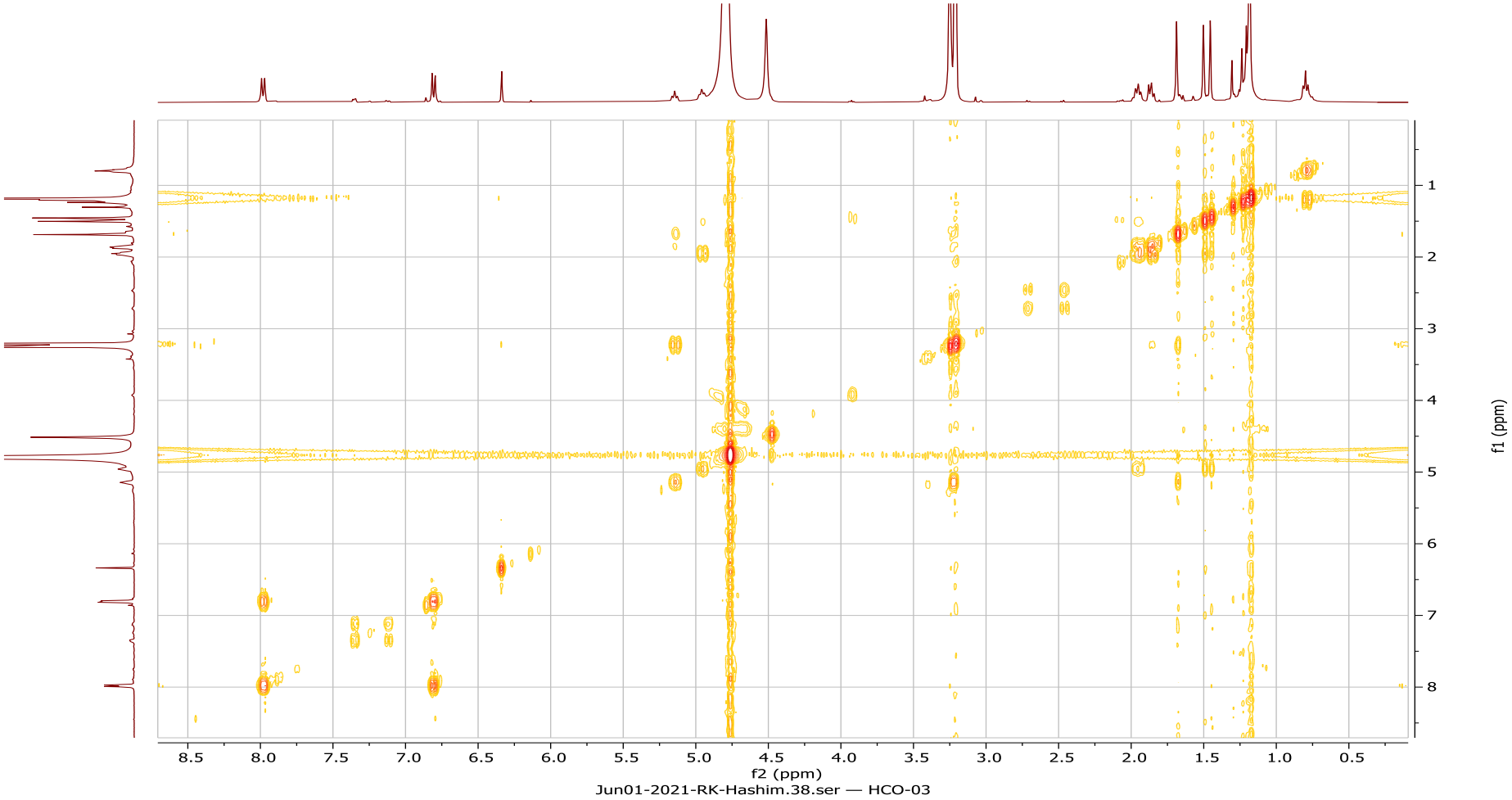
Compound **246** ^{1}H NMR spectrum (CD_3OD, 400 MHz)



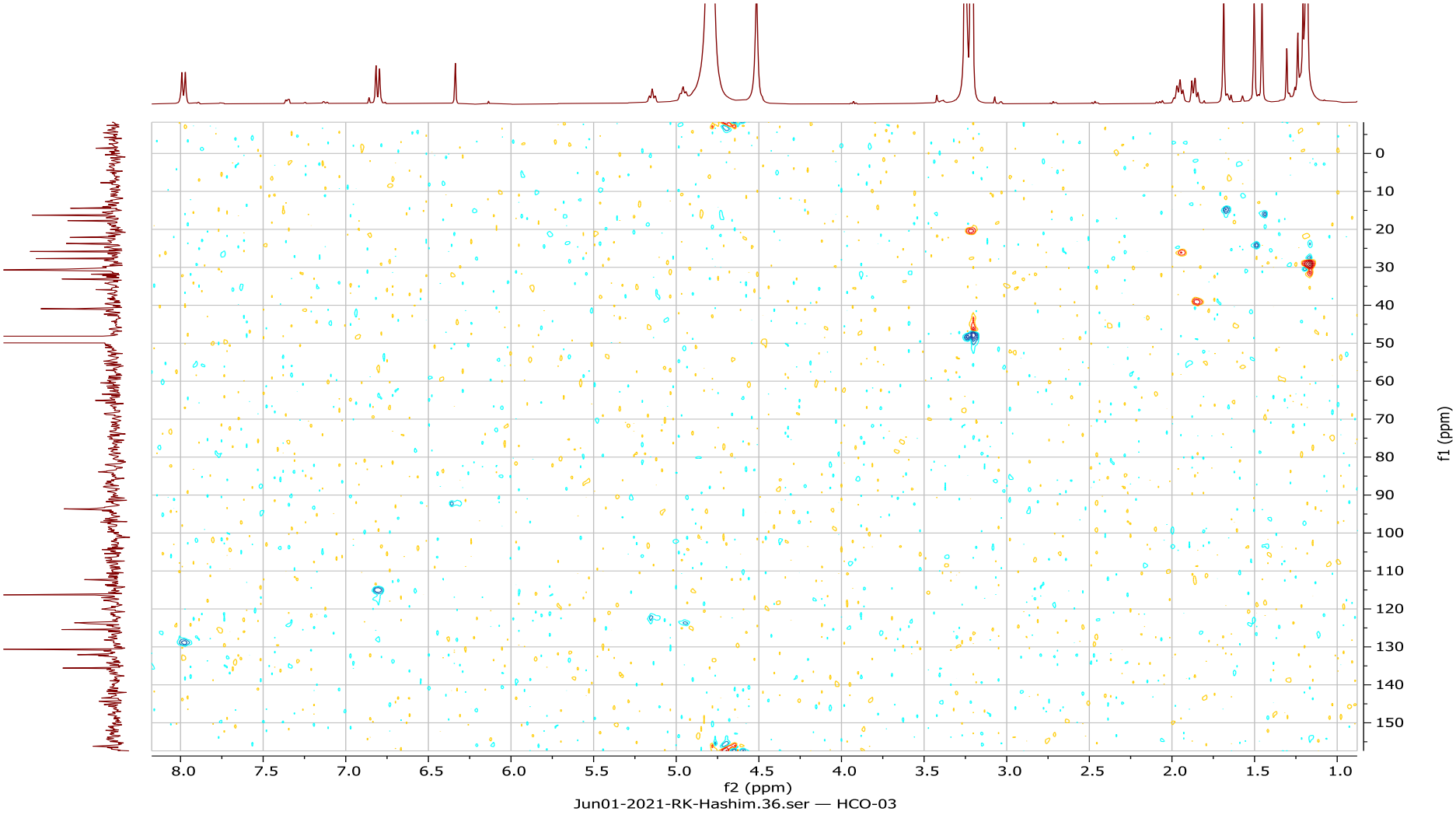
Compound **246** ^{13}C NMR spectrum (CD_3OD, 100 MHz)



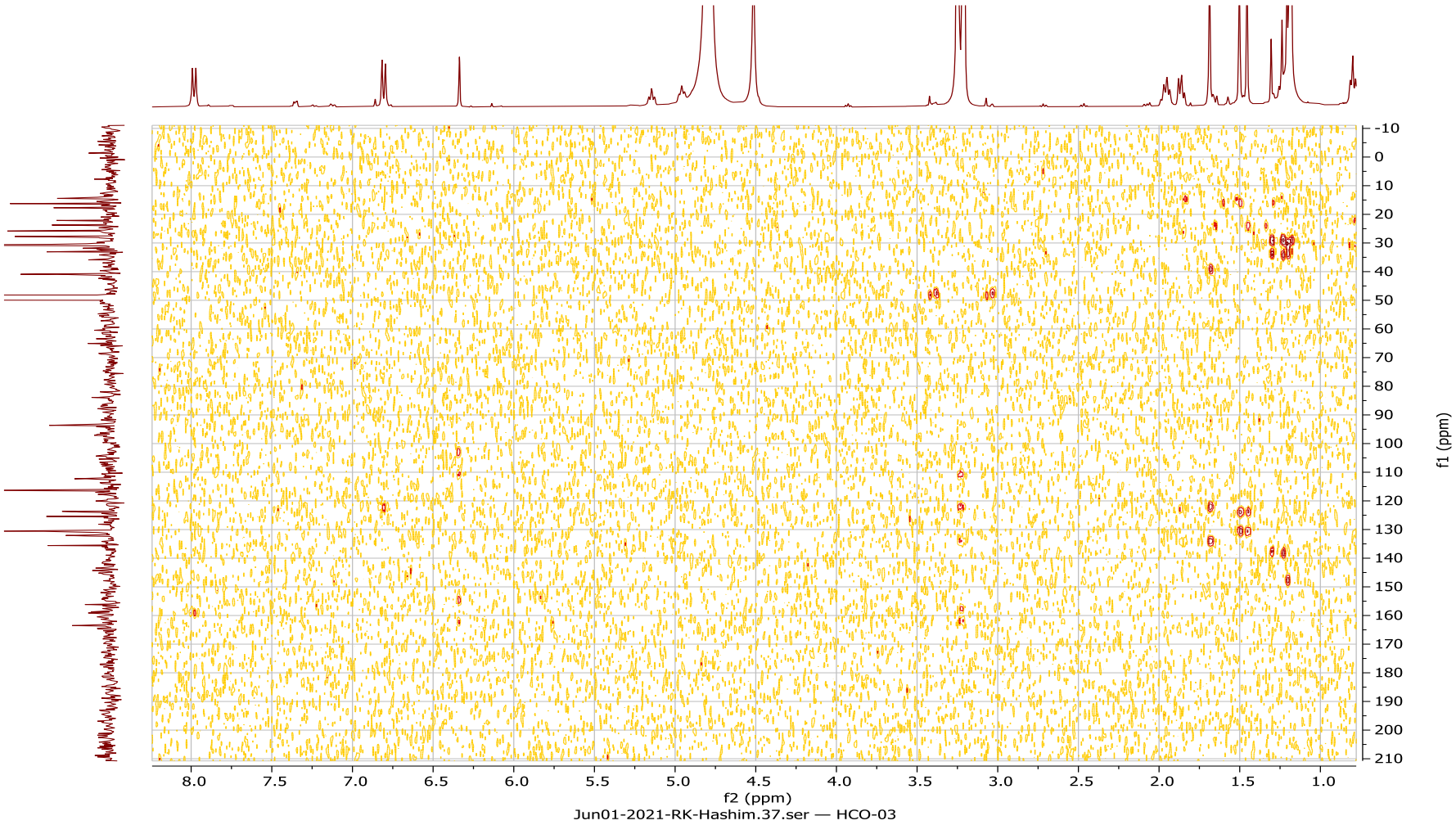
Compound **246** ^{1}H-^{1}H COSY spectrum (CD_3OD)



Compound **246** HSQC spectrum (CD_3OD)

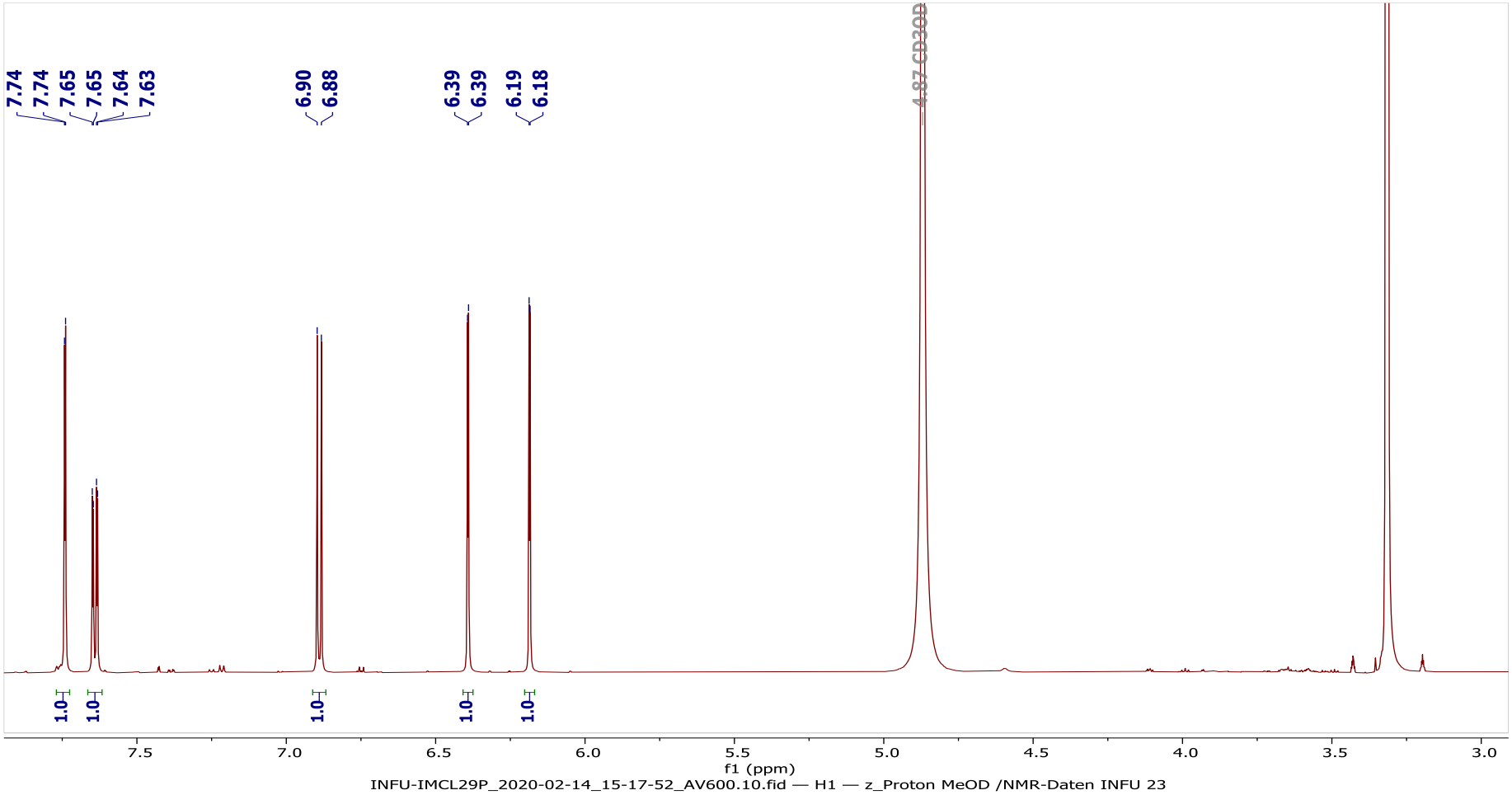


Compound **246** HMBC spectrum (CD_3OD)

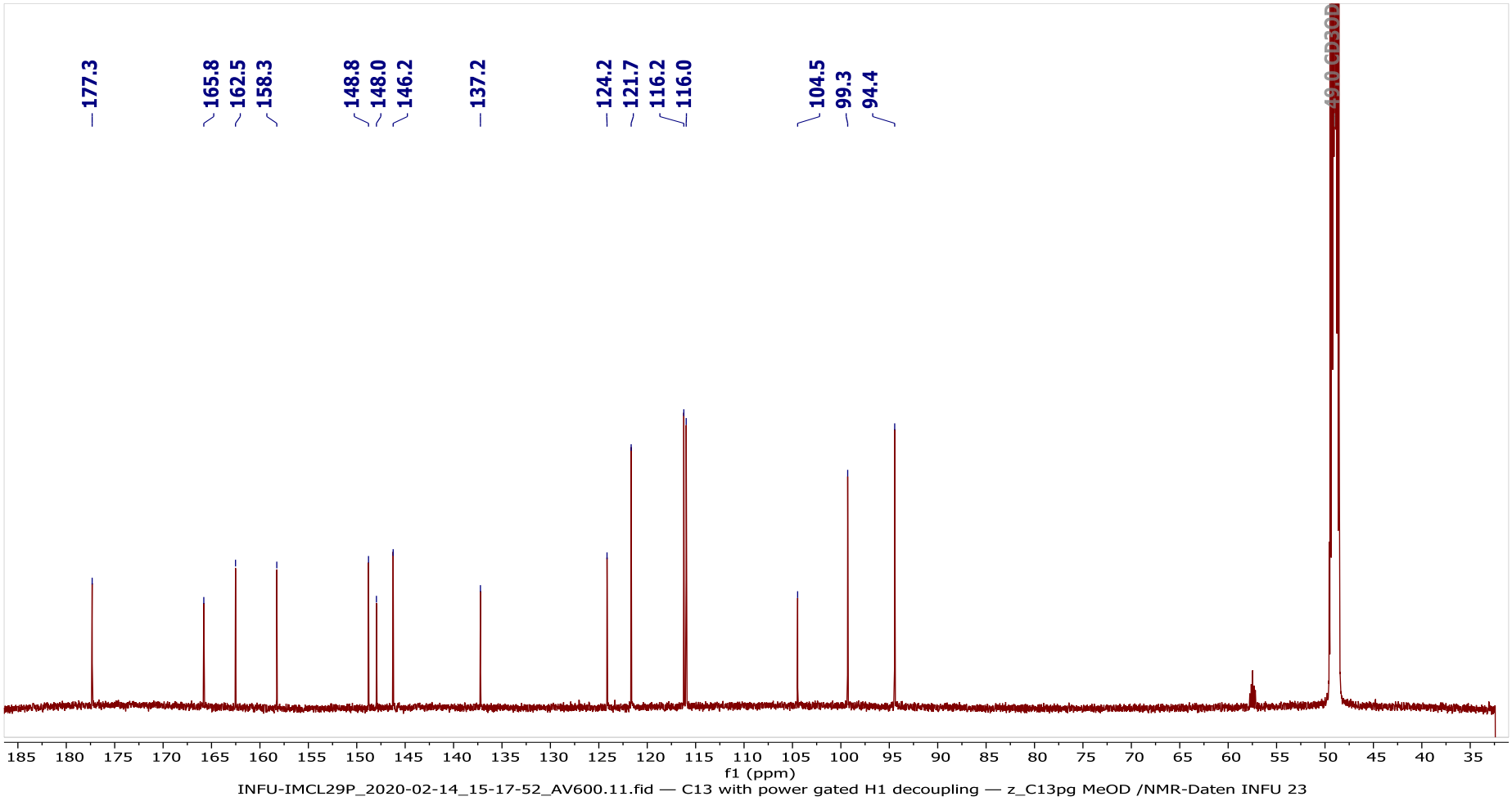


Appendix 3: Spectra of quercetin (**247**)

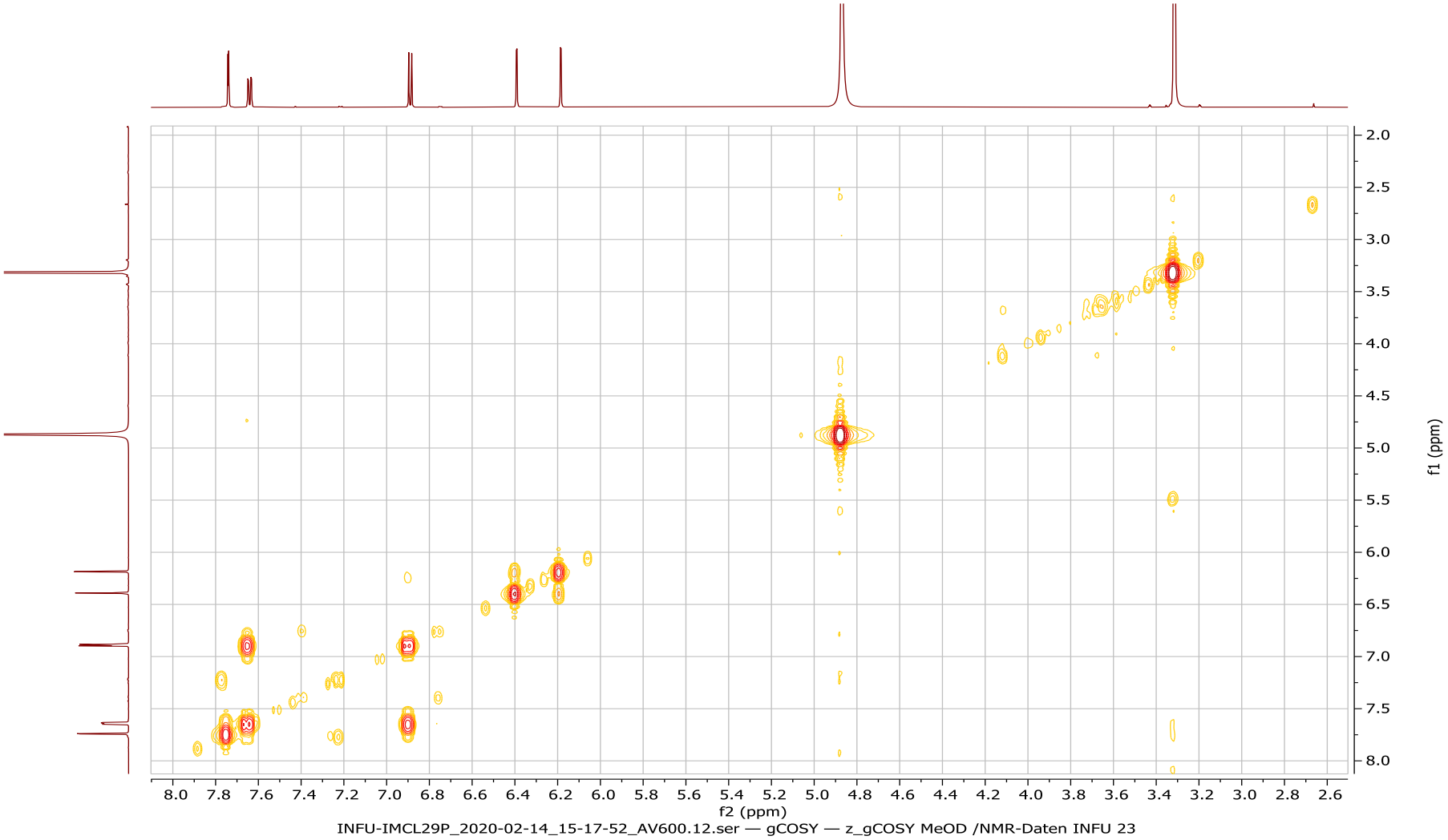
Compound **247** ^{1}H NMR spectrum (CD_3OD, 600 MHz)



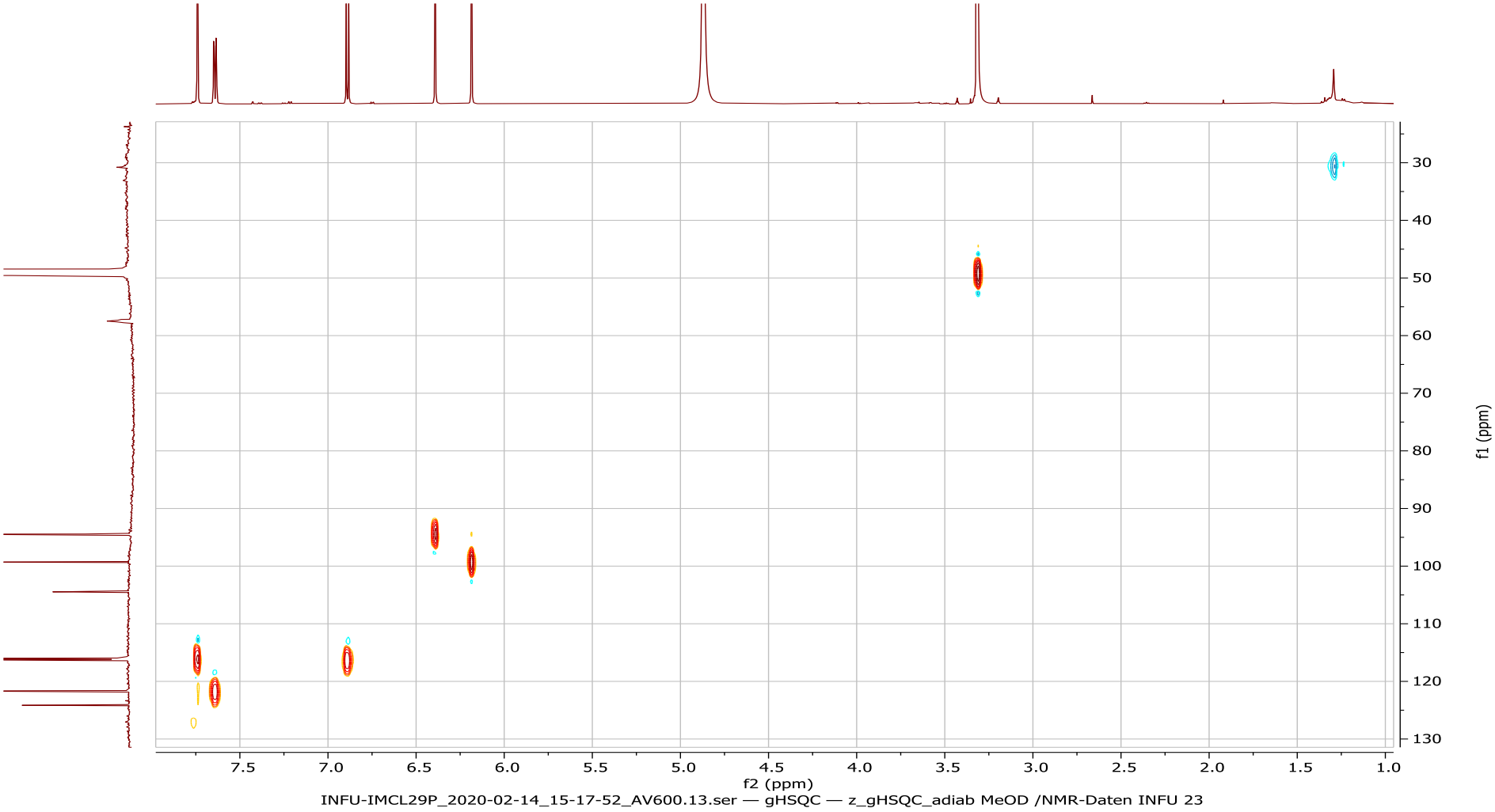
Compound **247** ^{13}C NMR spectrum (CD_3OD, 150 MHz)



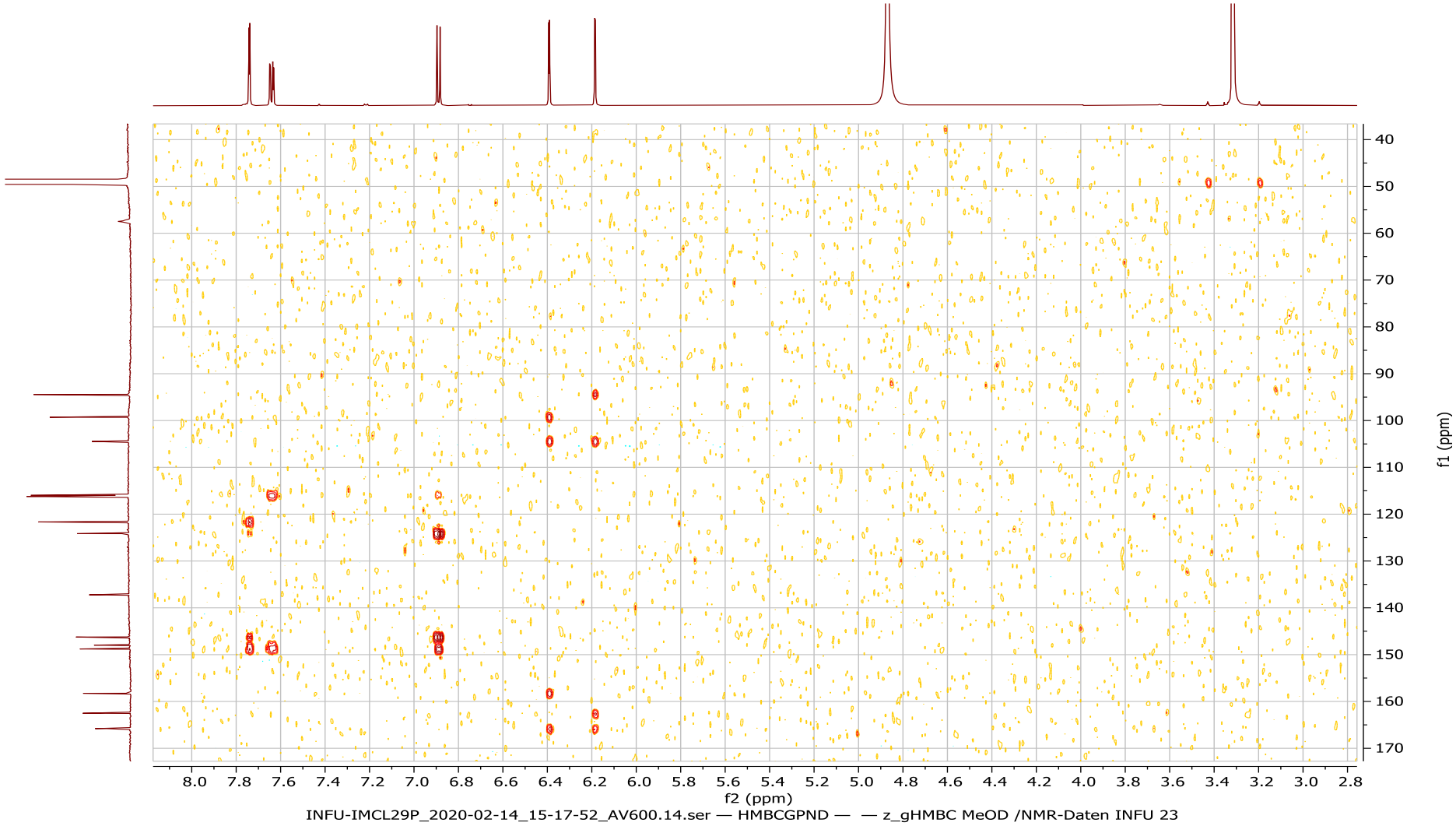
Compound **247** ^{1}H-^{1}H COSY spectrum (CD_3OD)



Compound **247** HSQC spectrum (CD_3OD)

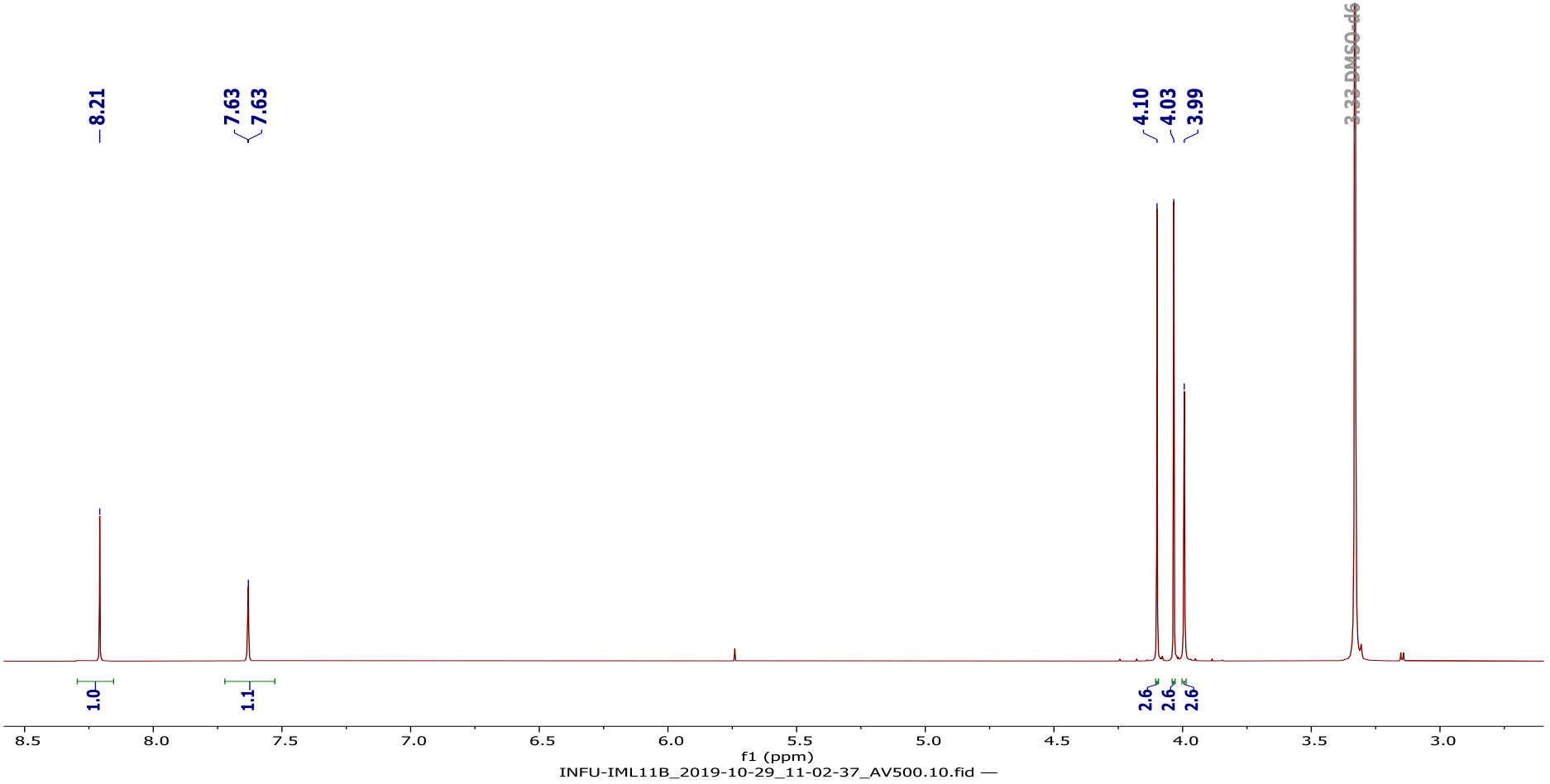


Compound **247** HMBC spectrum (CD_3OD)

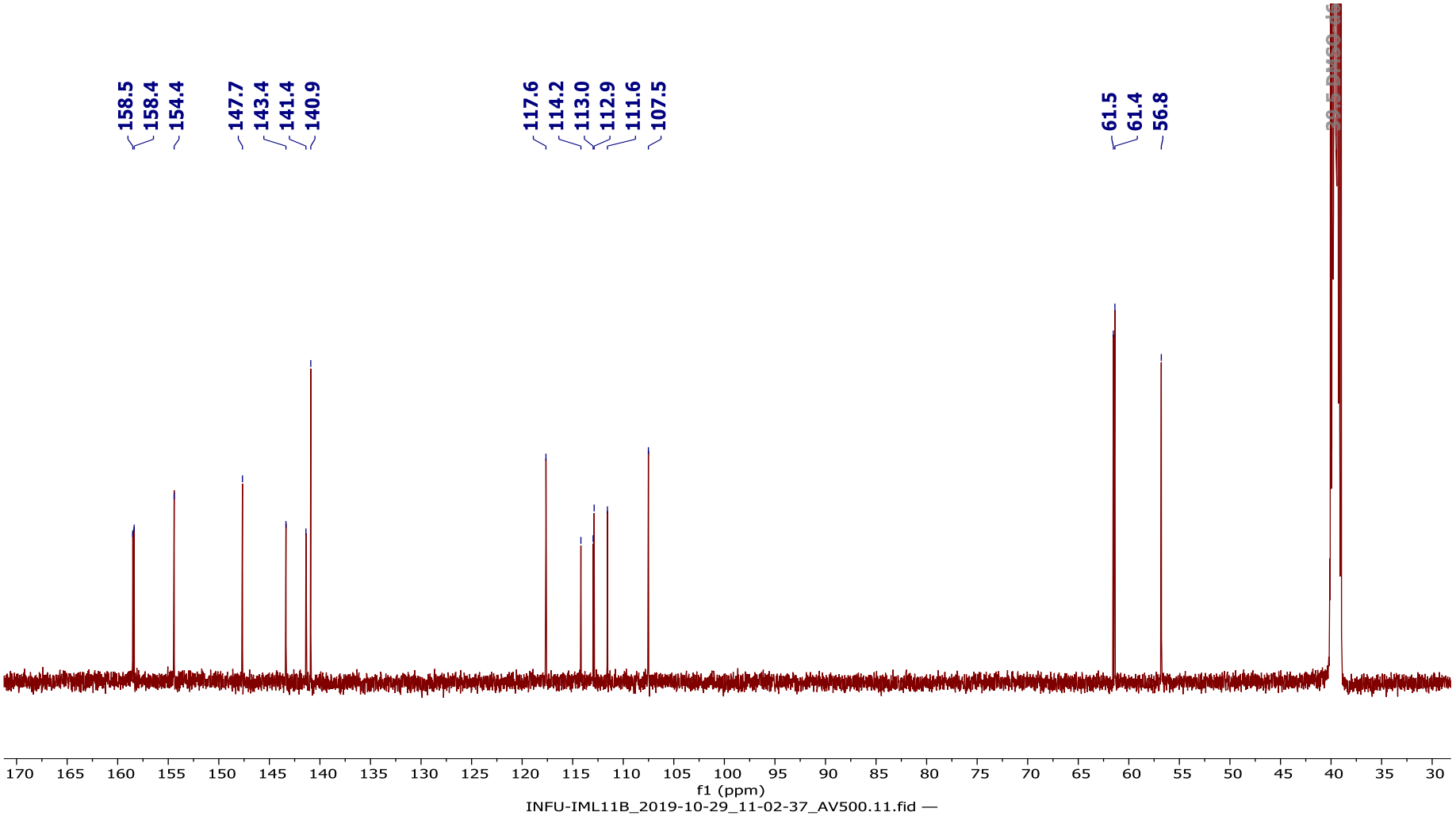


Appendix 4: Spectra of 3,3′,4-trimethoxyellagic acid (**248**)

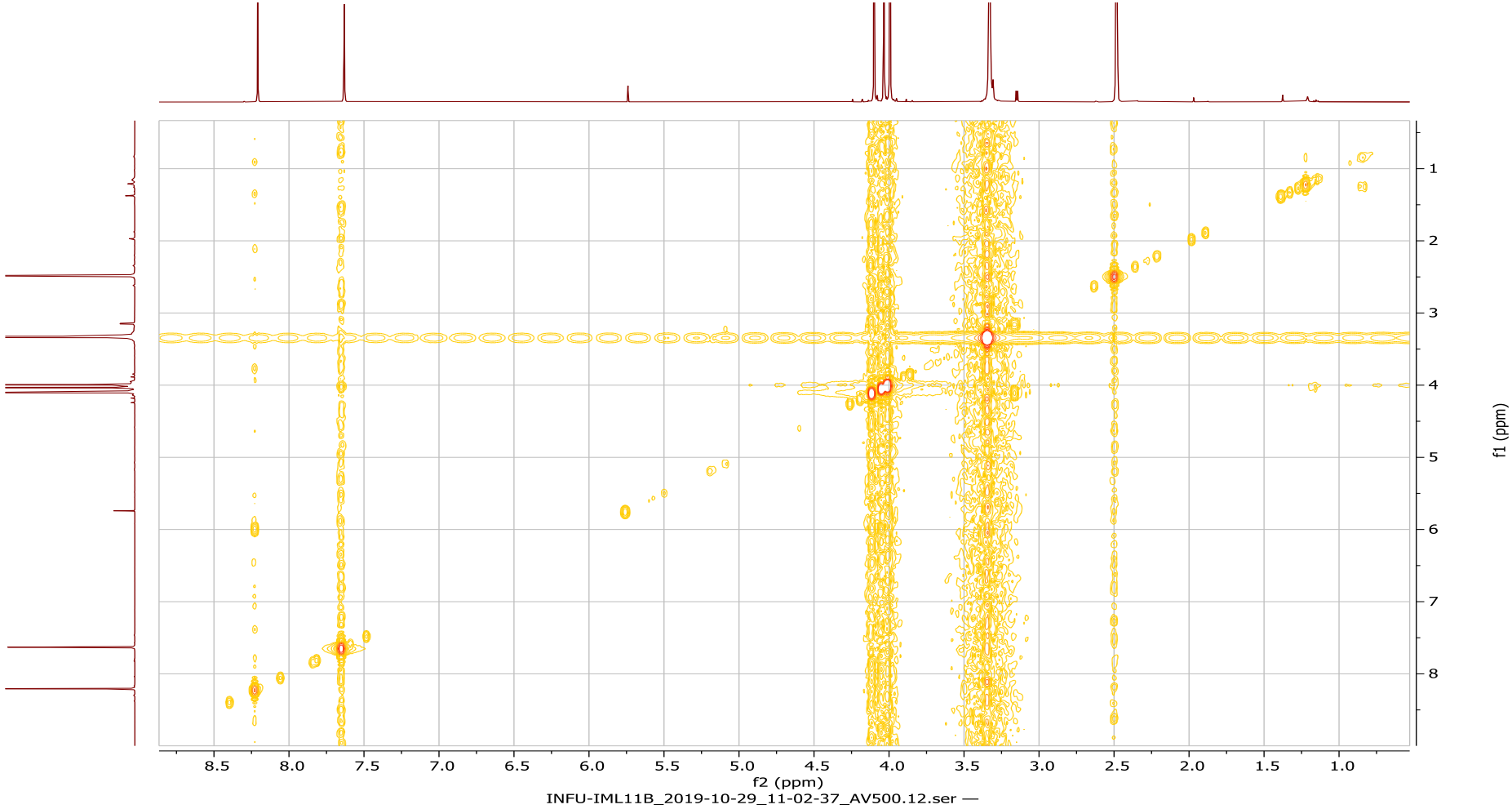
Compound **248** ^{1}H NMR spectrum (DMSO, 500 MHz)



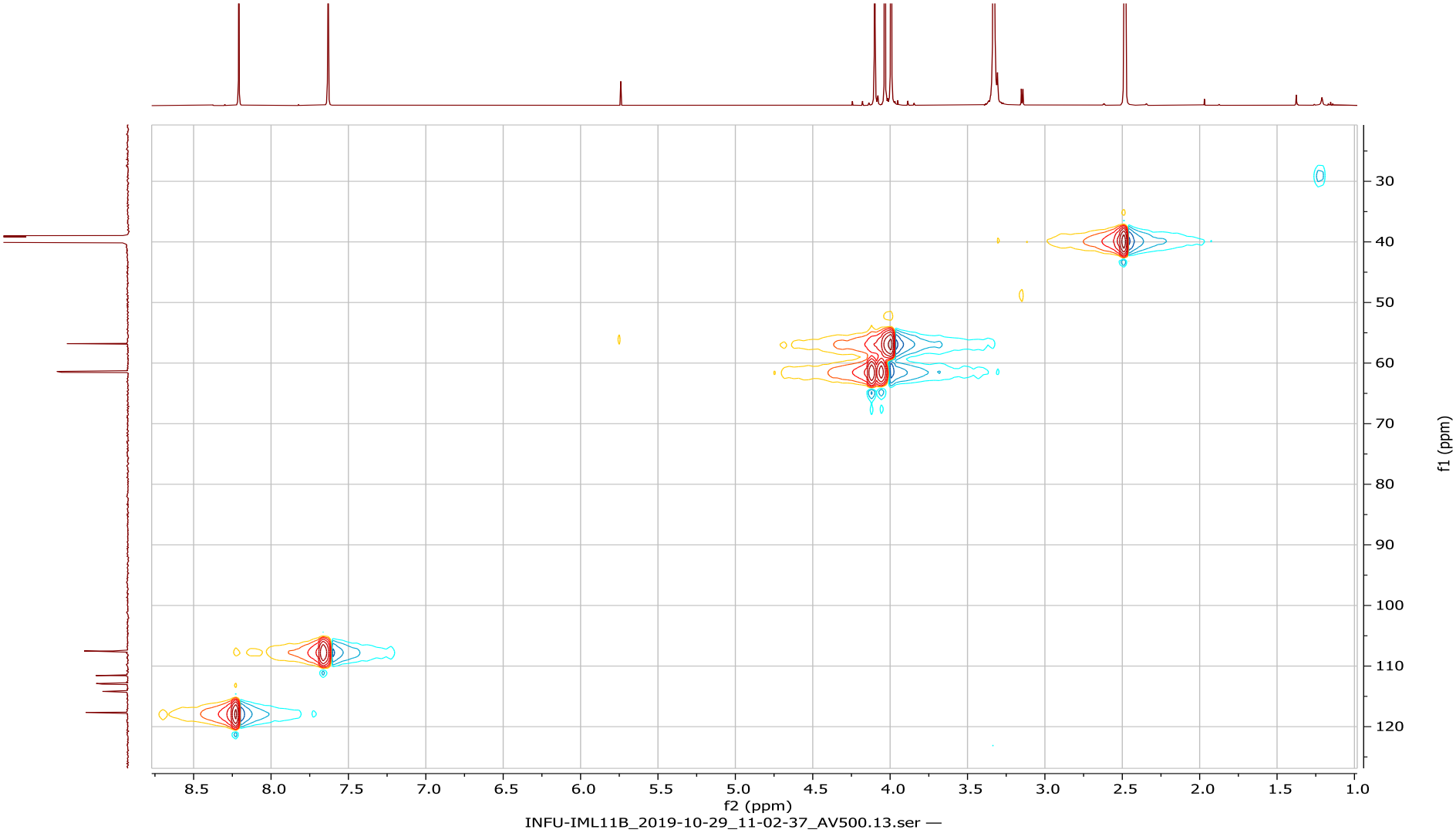
Compound **248** ^{13}C NMR spectrum (DMSO, 125 MHz)



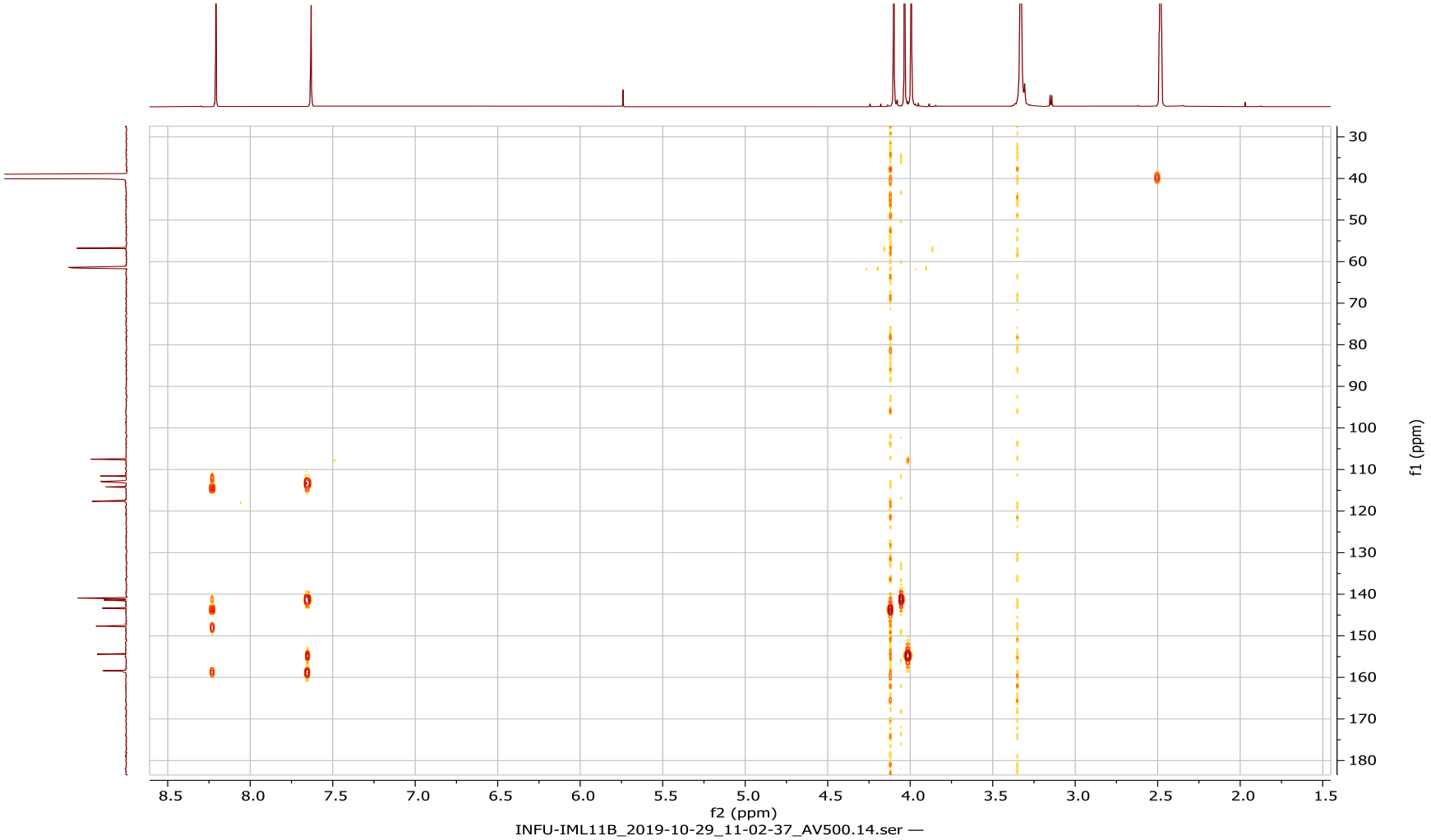
Compound **248** ^{1}H-^{1}H COSY spectrum (DMSO)



Compound **248** HSQC spectrum (DMSO)

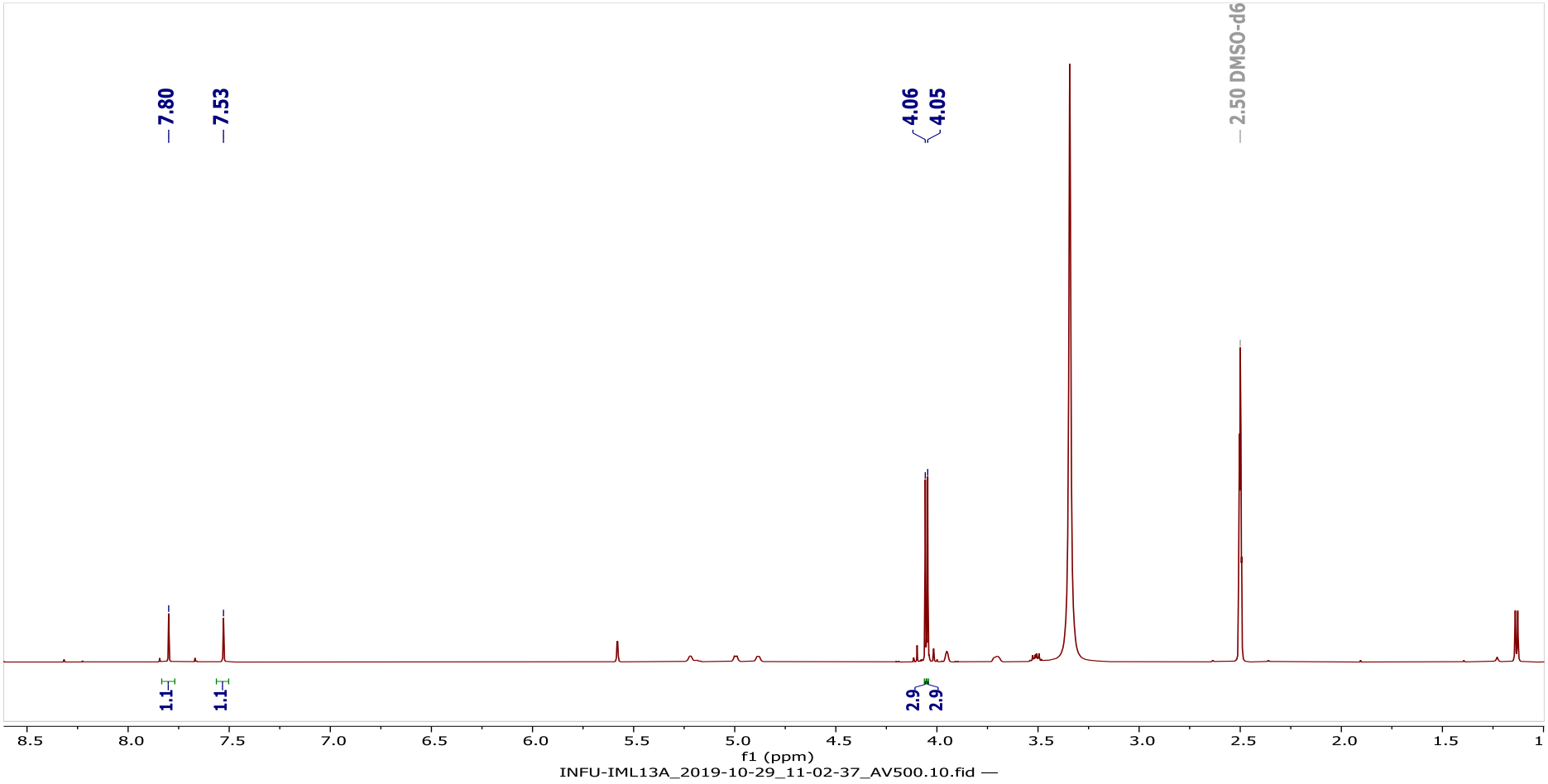


Compound **248** HMBC spectrum (DMSO)

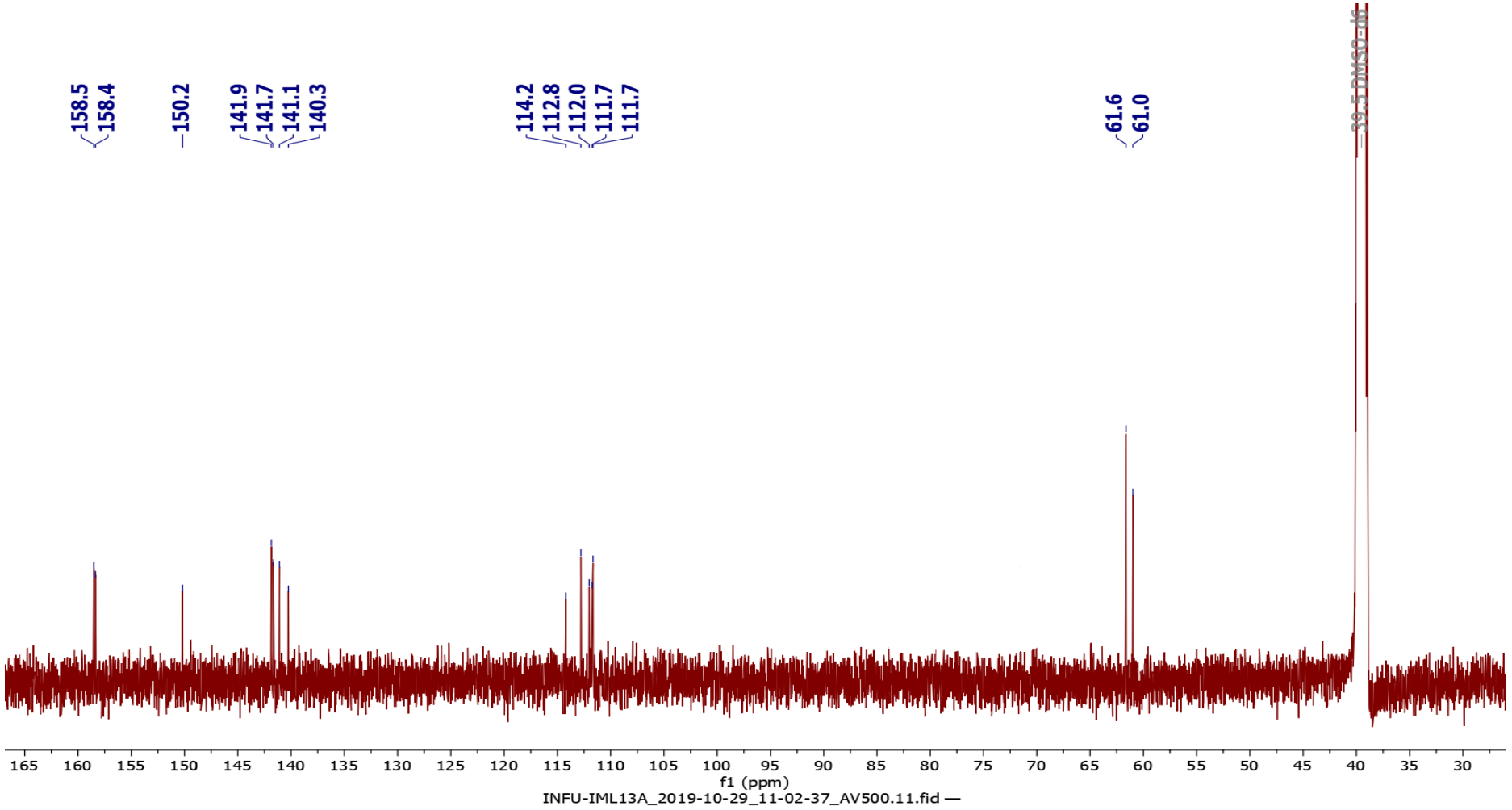


Appendix 5: Spectra of 3,3′-dimethoxyellagic acid (**249**)

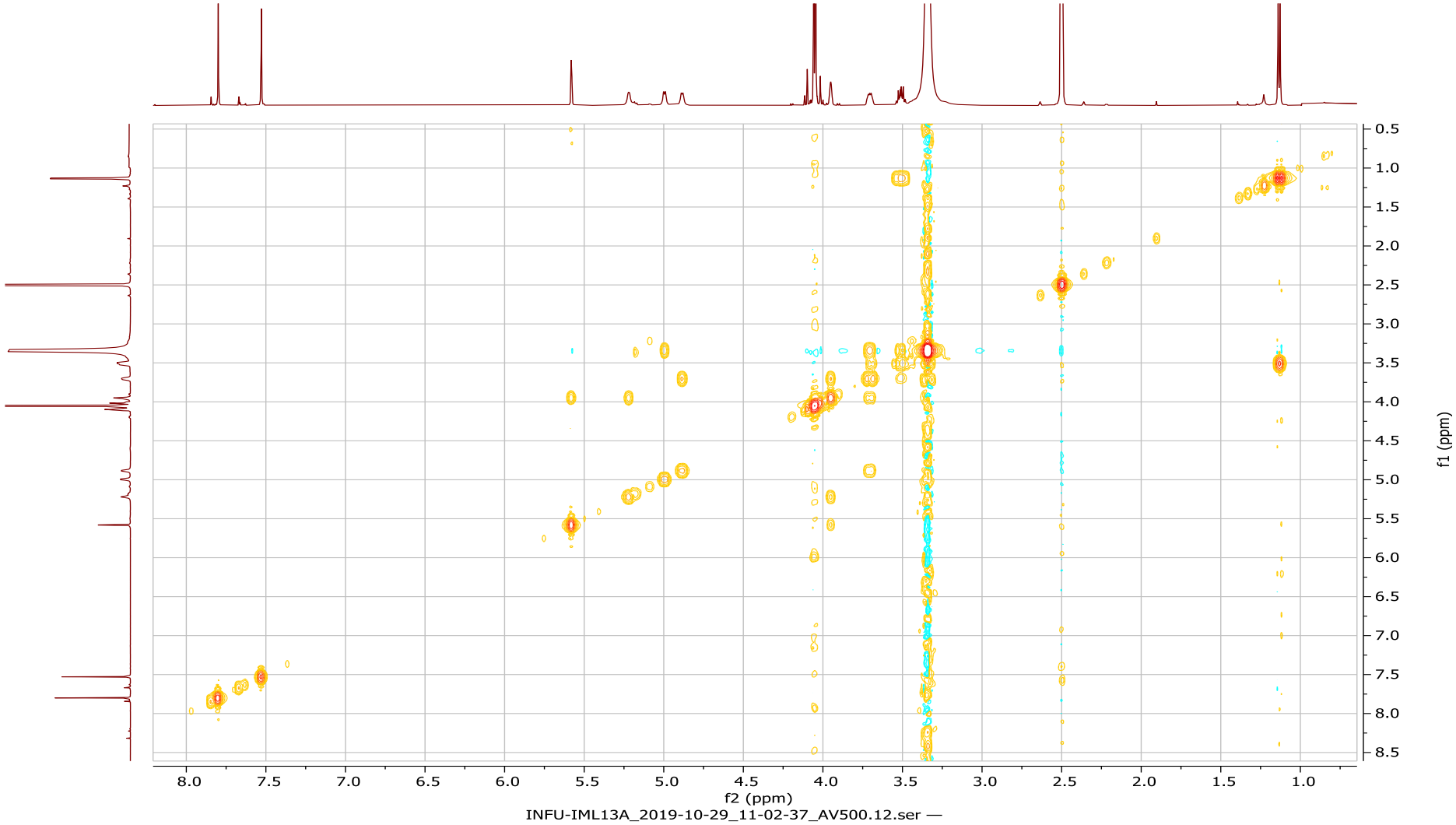
Compound **249** ^{1}H NMR spectrum (DMSO, 500 MHz)



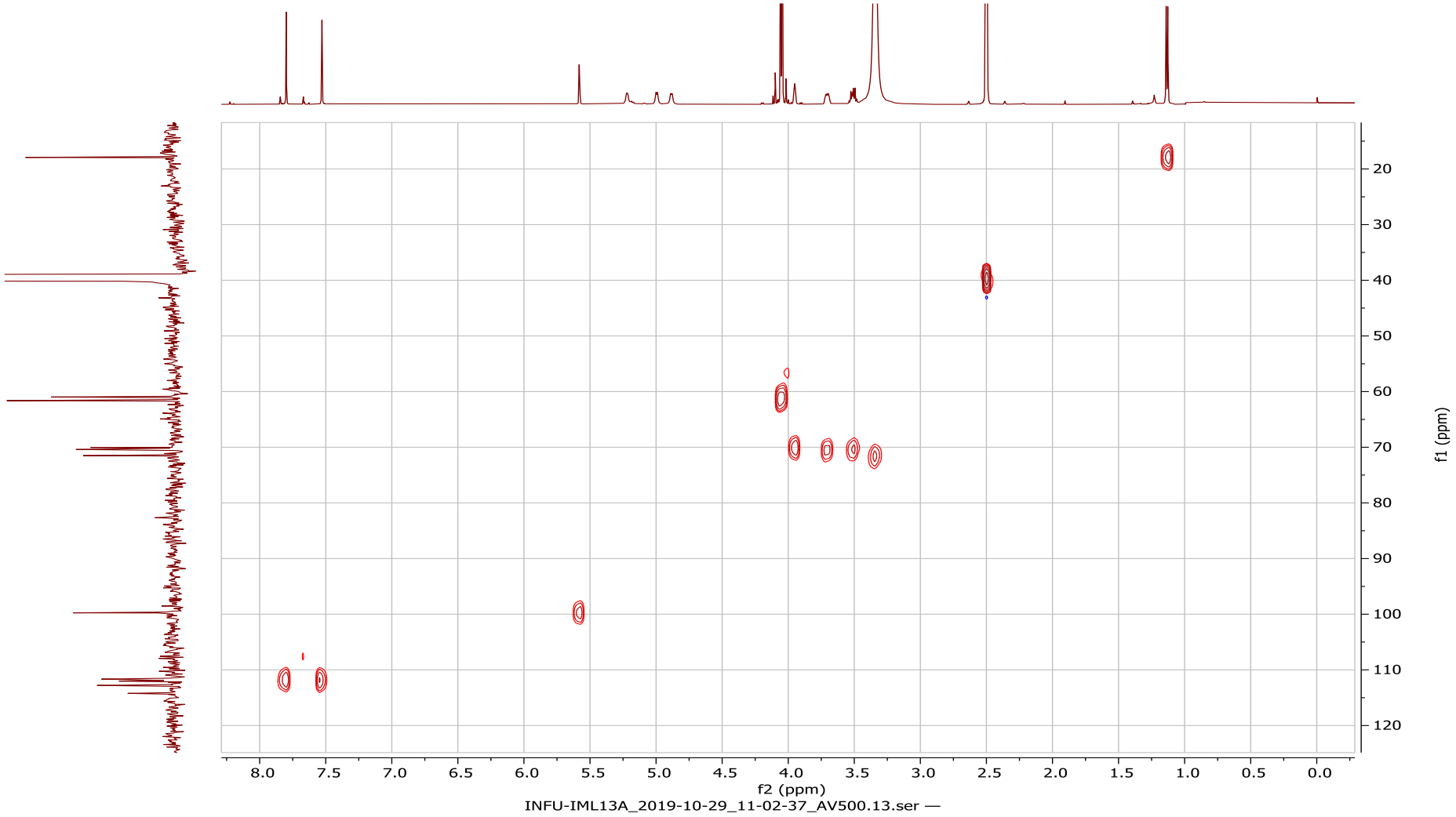
Compound **249** ^{13}C NMR spectrum (DMSO, 125 MHz)



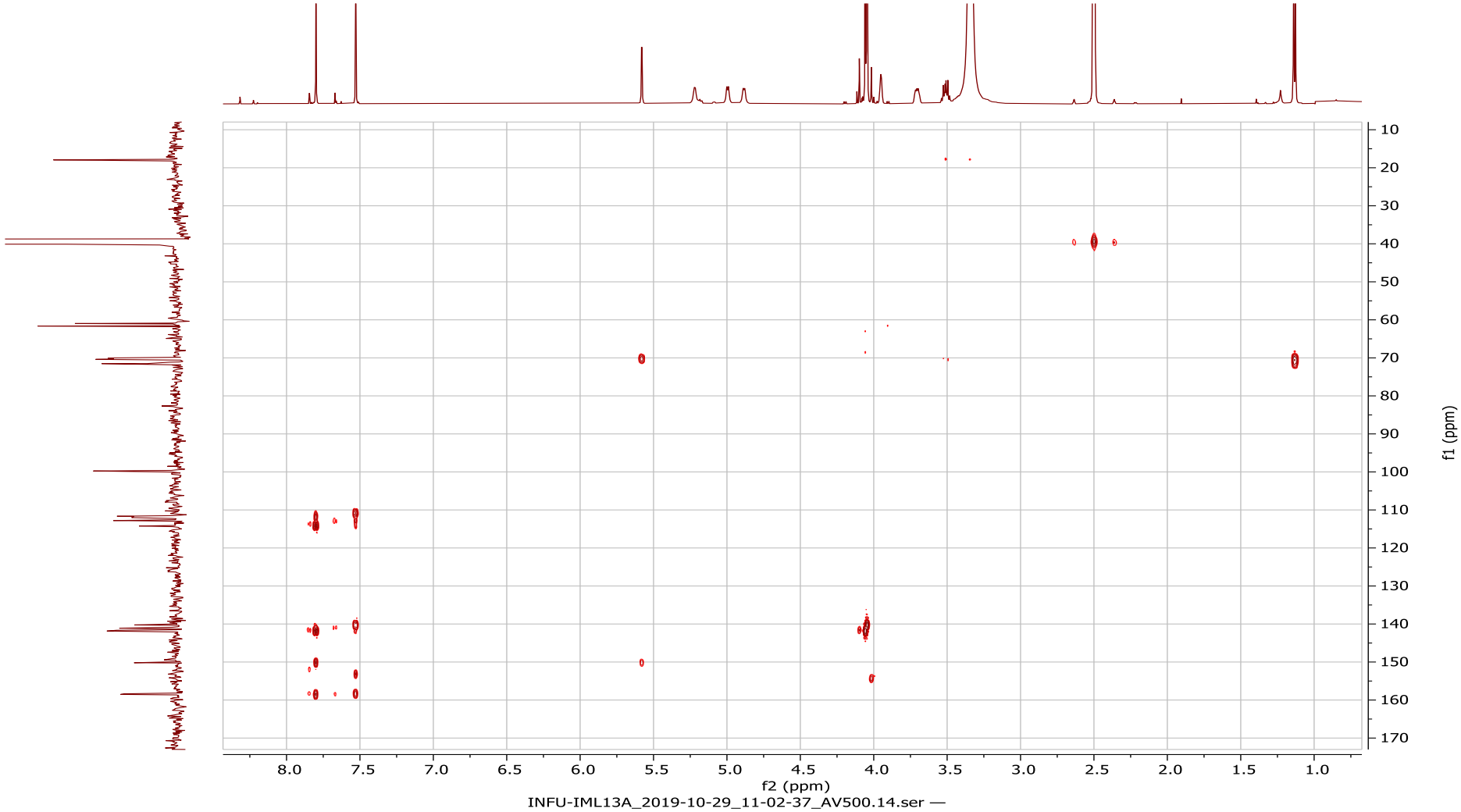
Compound **249** ^{1}H-^{1}H COSY spectrum (DMSO)



Compound **249** HSQC spectrum (DMSO)

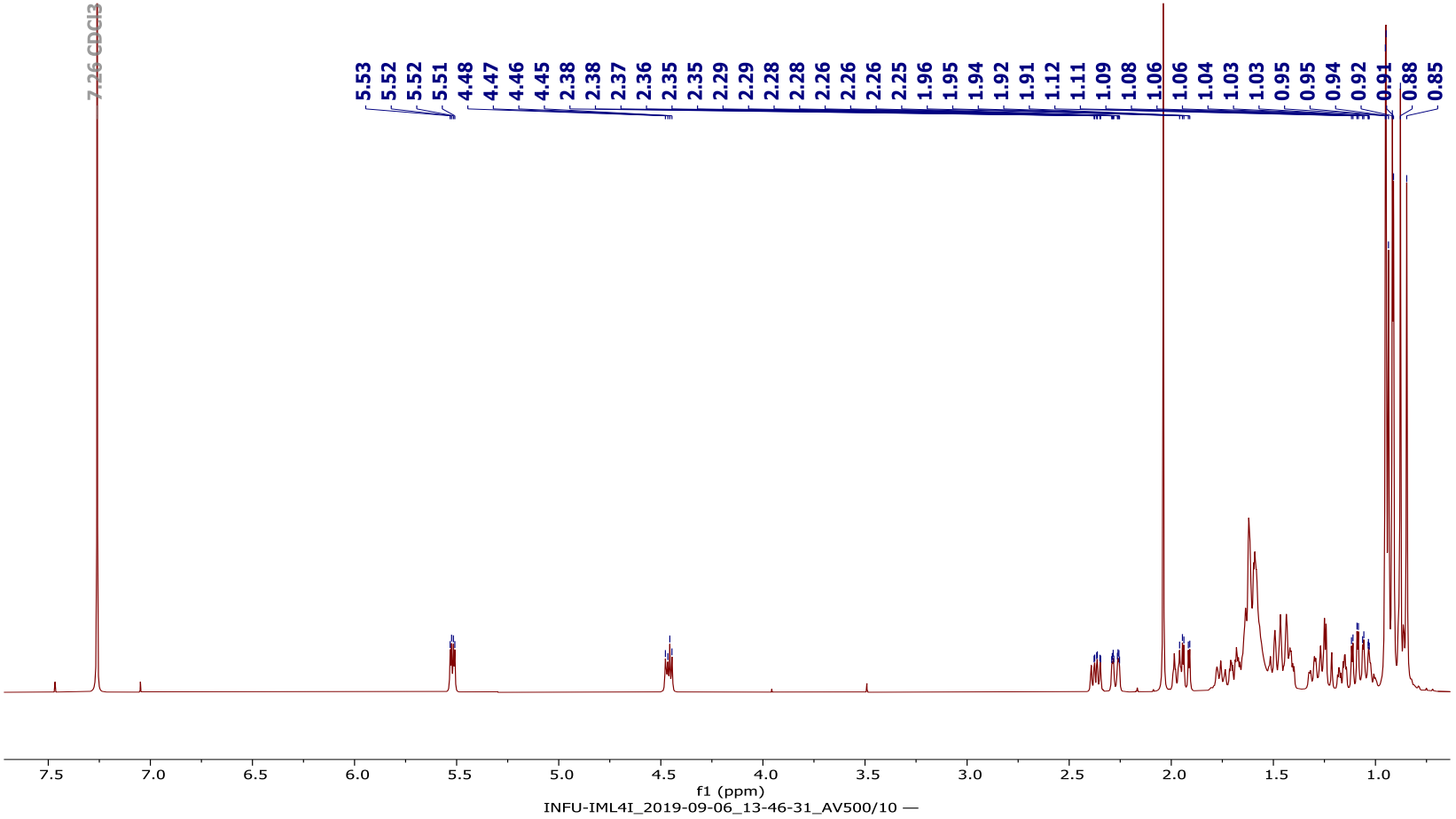


Compound **249** HMBC spectrum (DMSO)

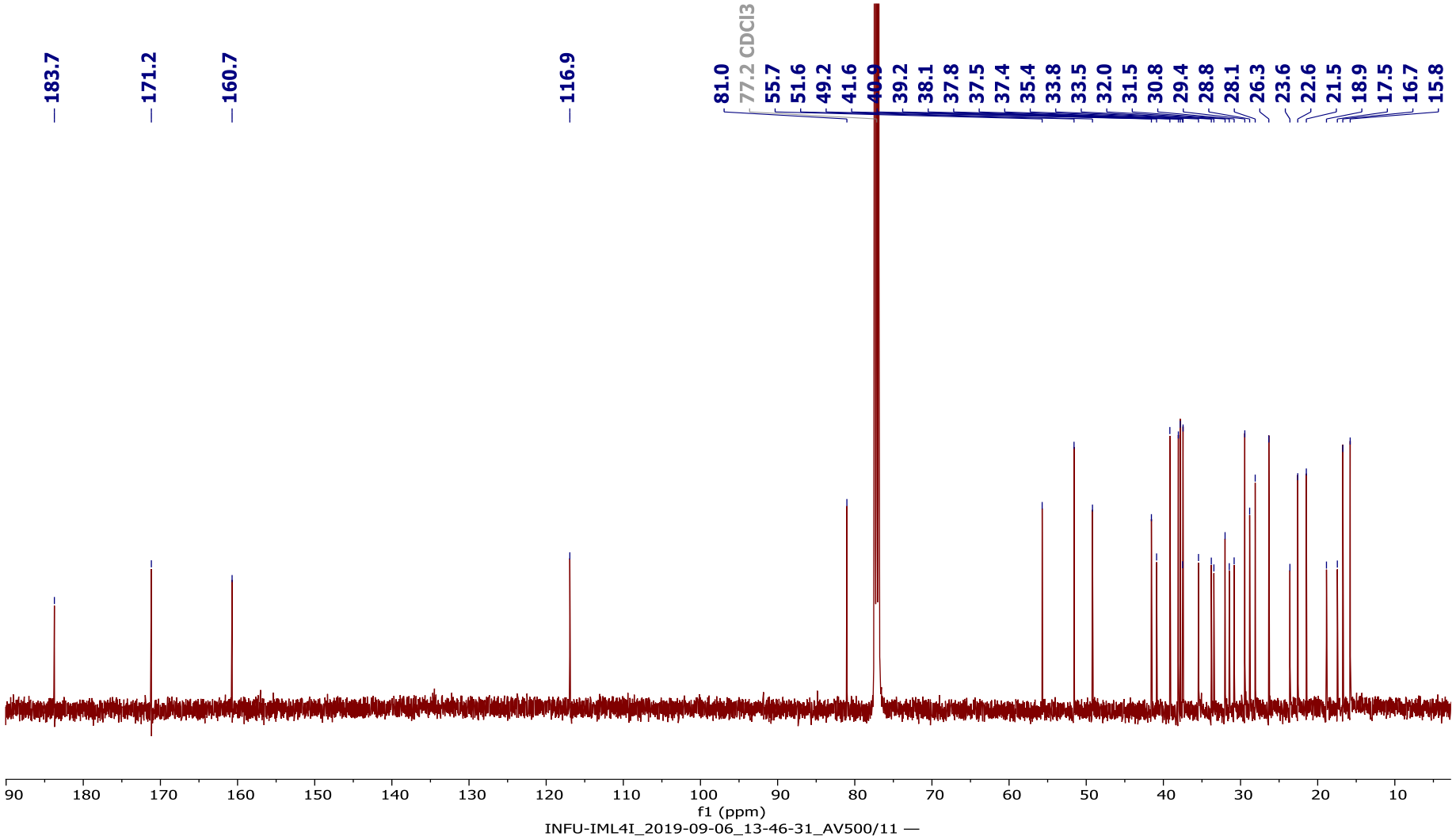


Appendix 6: Spectra of 3-acetyaleuritolic acid (**250**)

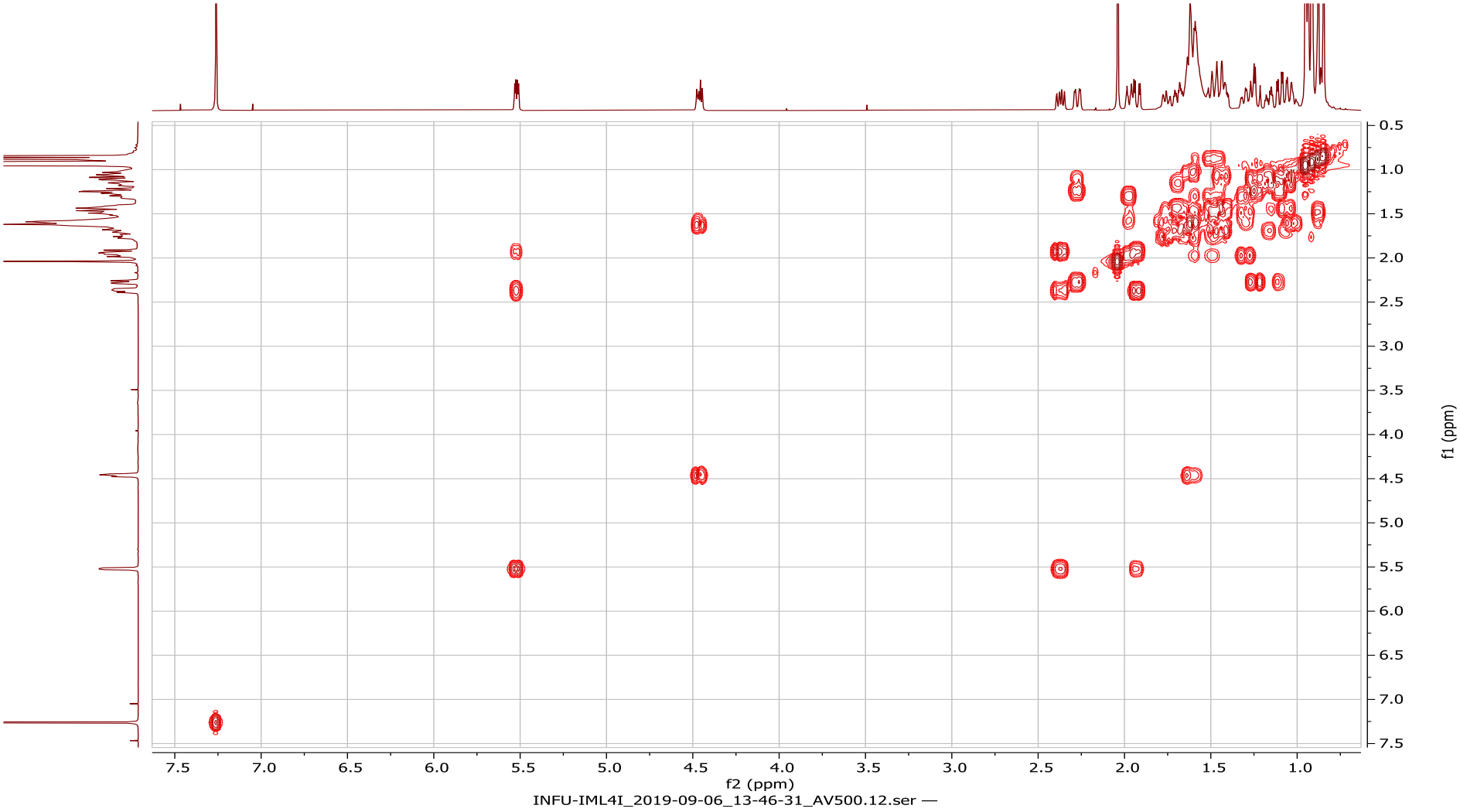
Compound **250** ^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



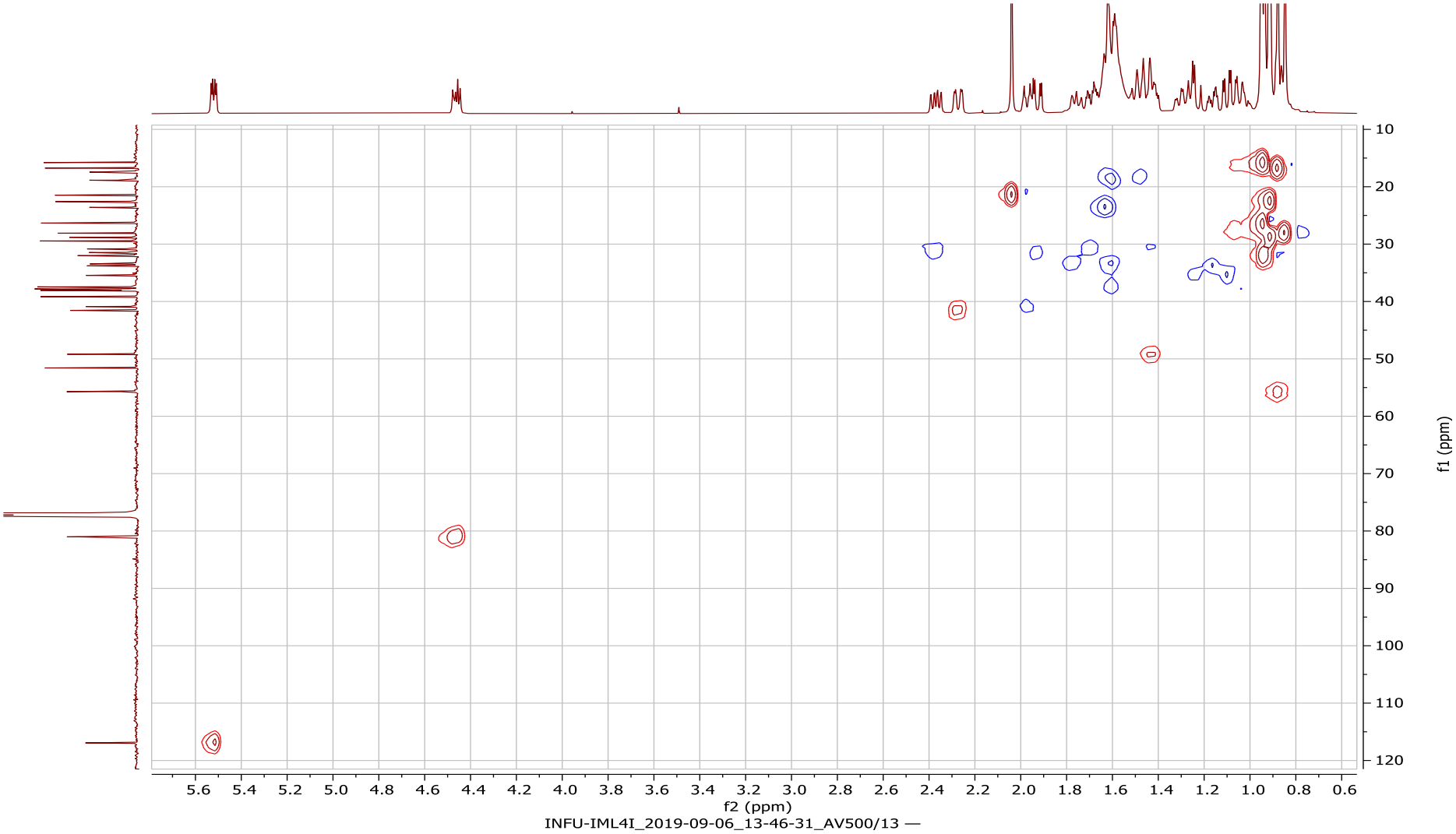
Compound **250** ^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



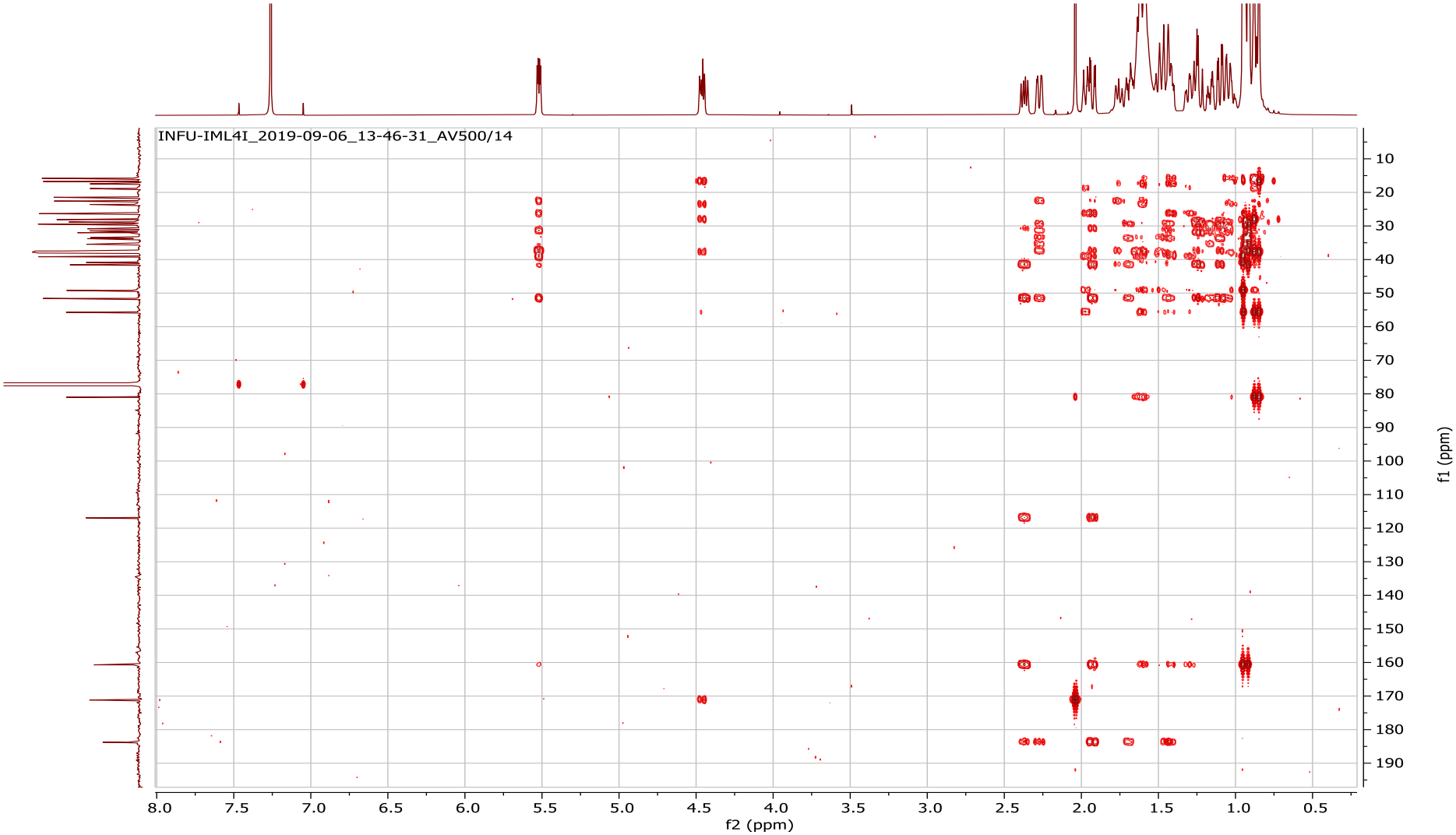
Compound **250** ^{1}H-^{1}H COSY spectrum ($CDCl_3$)



Compound **250** HSQC spectrum ($CDCl_3$)

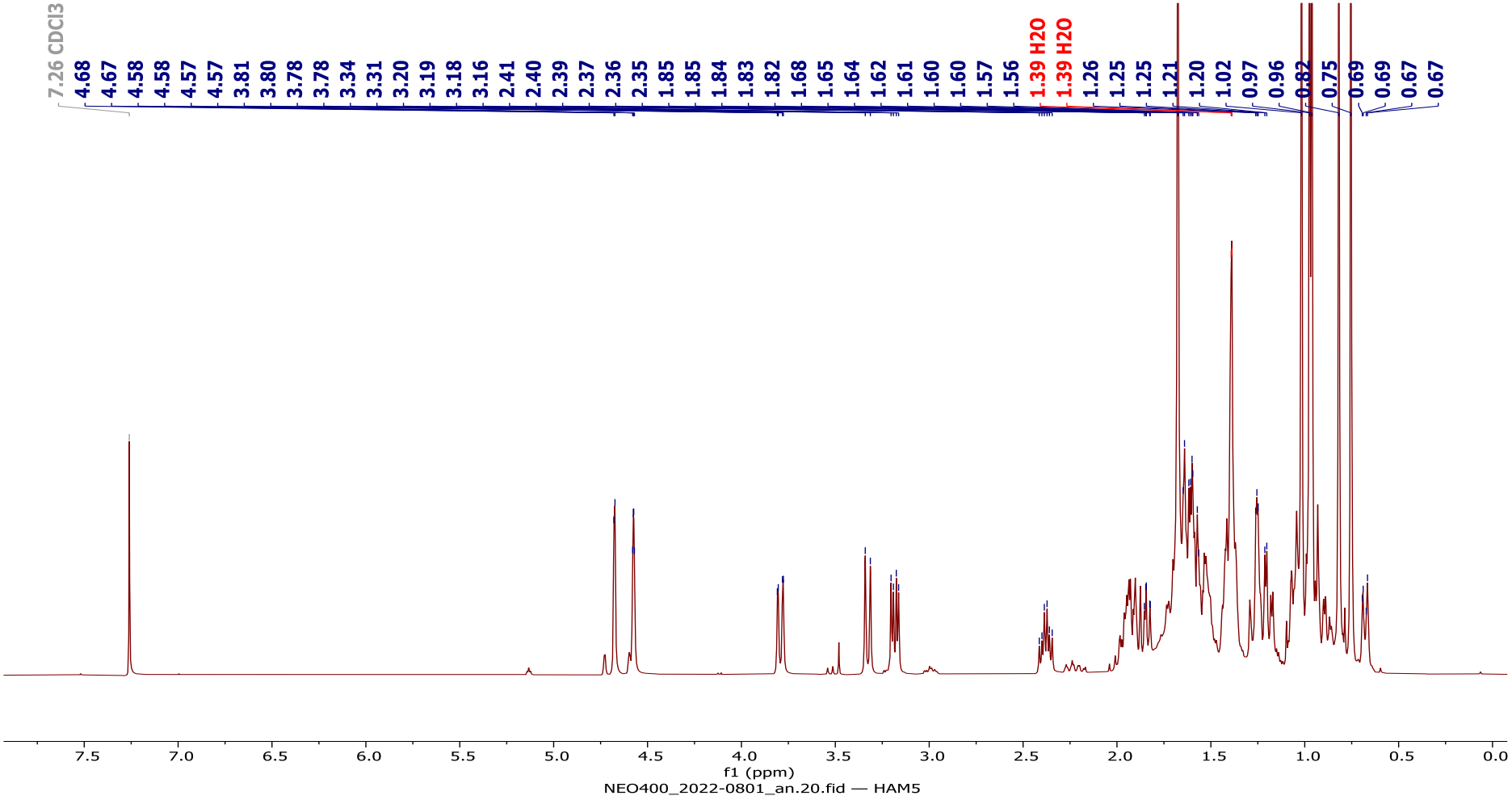


Compound **250** HMBC spectrum ($CDCl_3$)

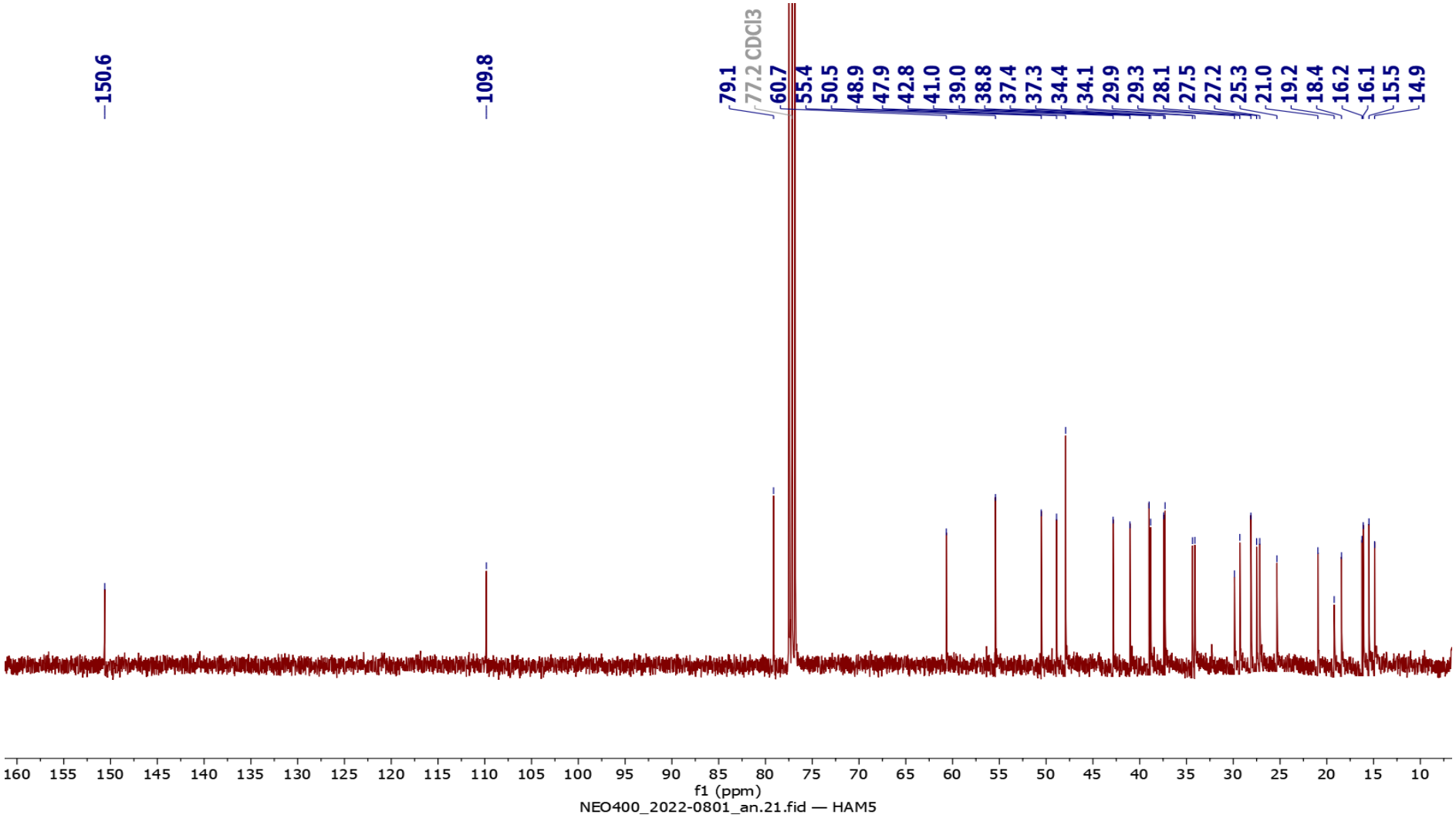


Appendix 7: Spectra of betulin (**251**)

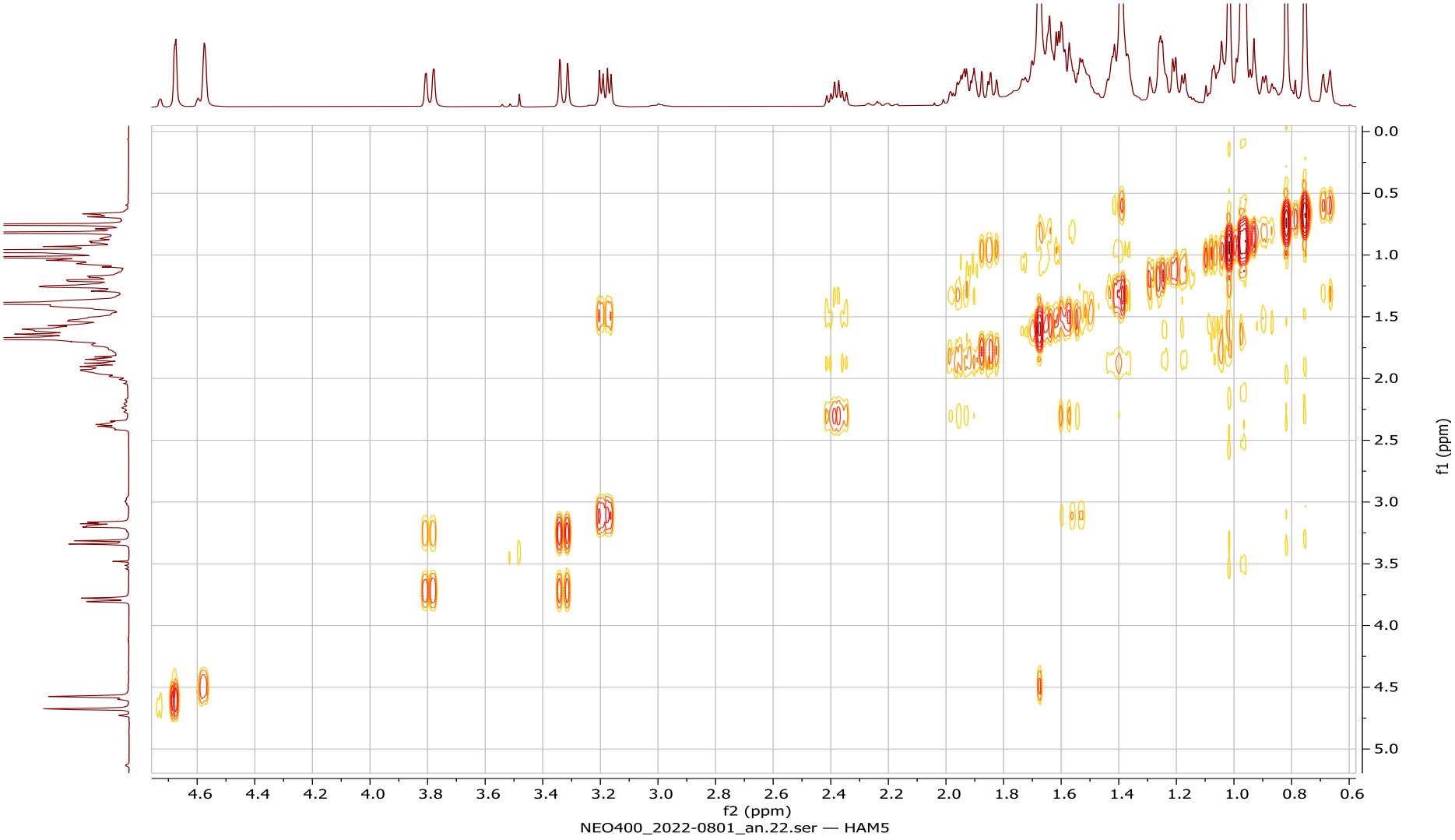
Compound **251** ^{1}H NMR spectrum ($CDCl_3$, 400 MHz)



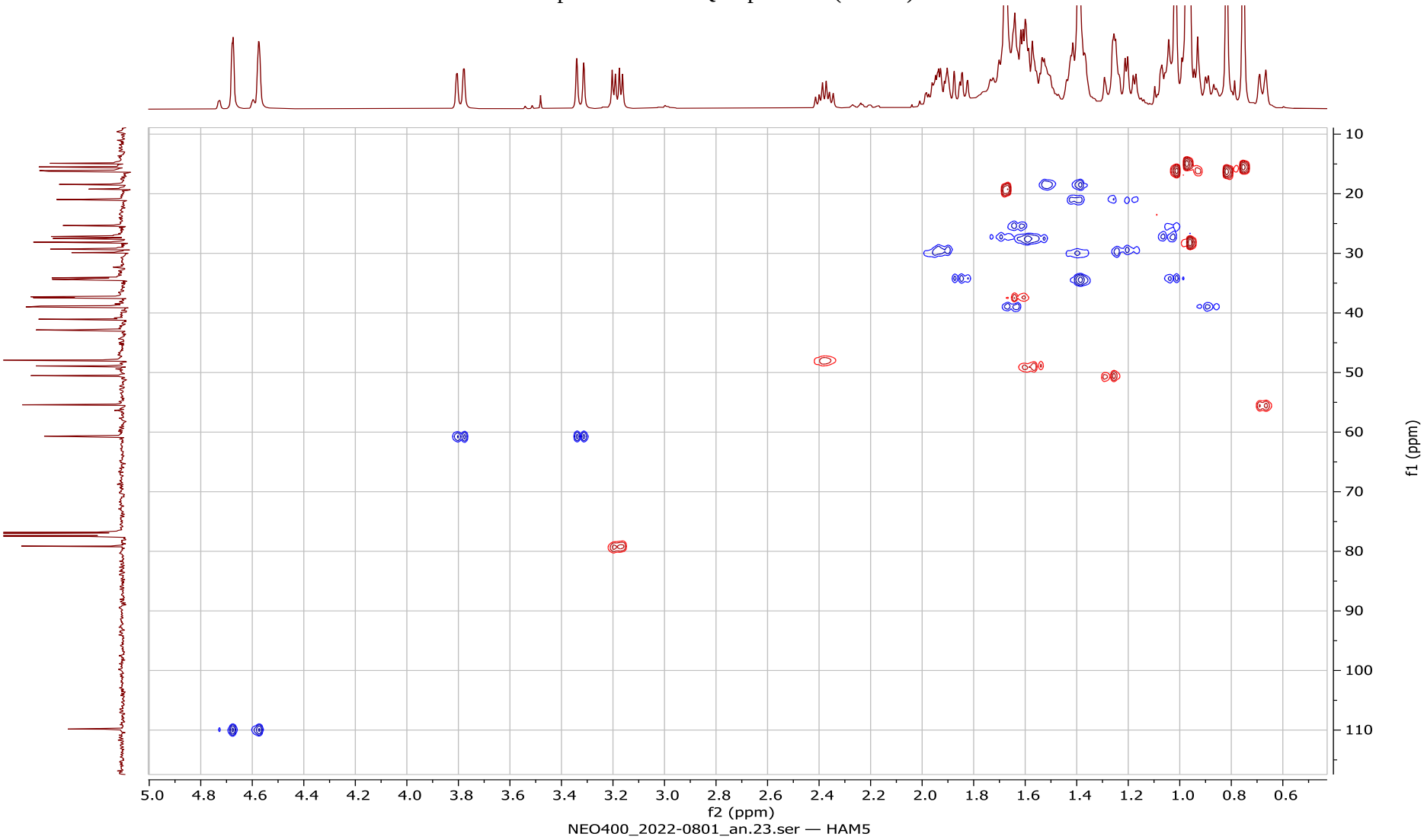
Compound **251** ^{1}C NMR spectrum ($CDCl_3$, 100 MHz)



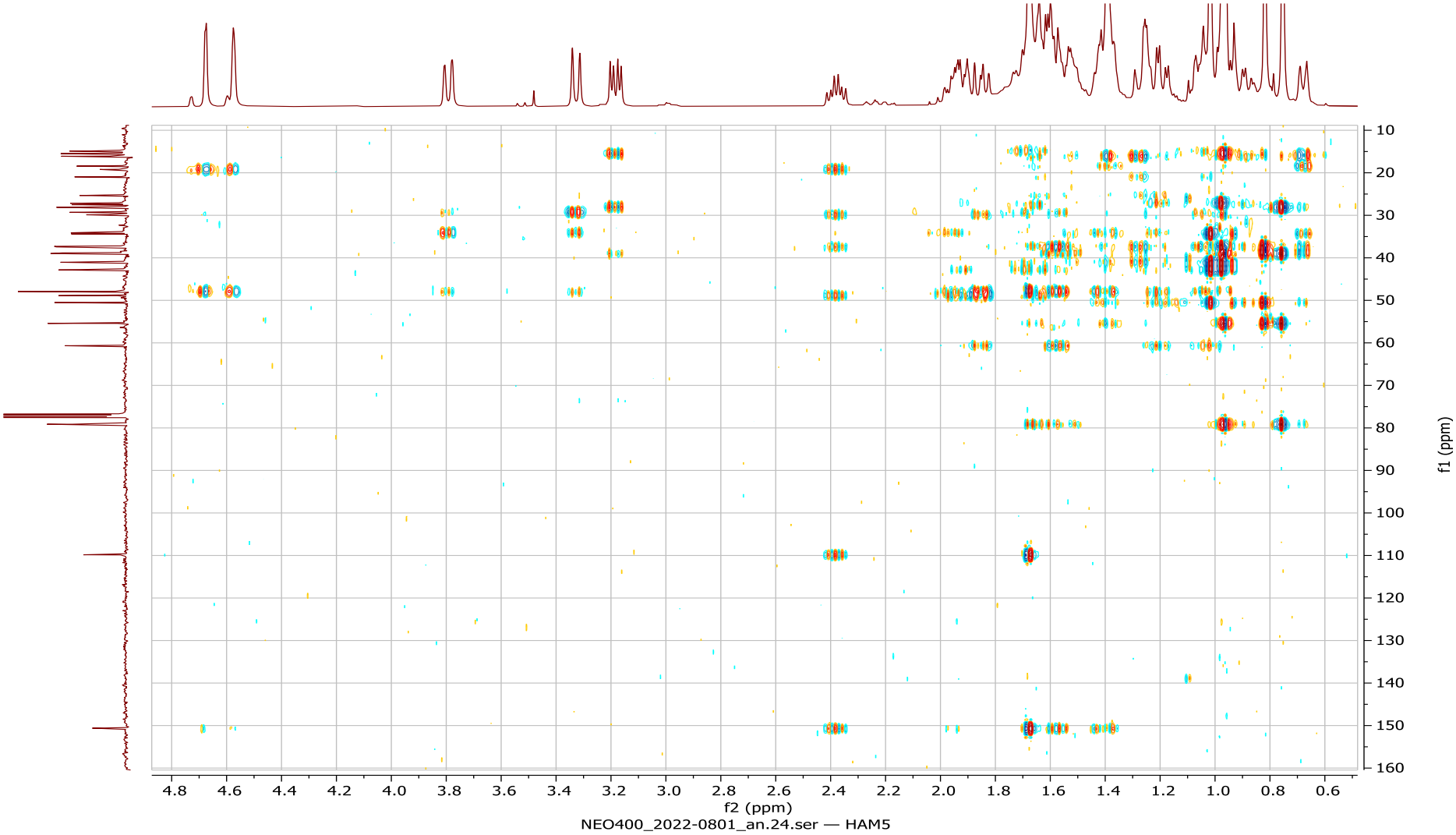
Compound **251** ^{1}H-^{1}H COSY spectrum ($CDCl_3$)



Compound **251** HSQC spectrum ($CDCl_3$)

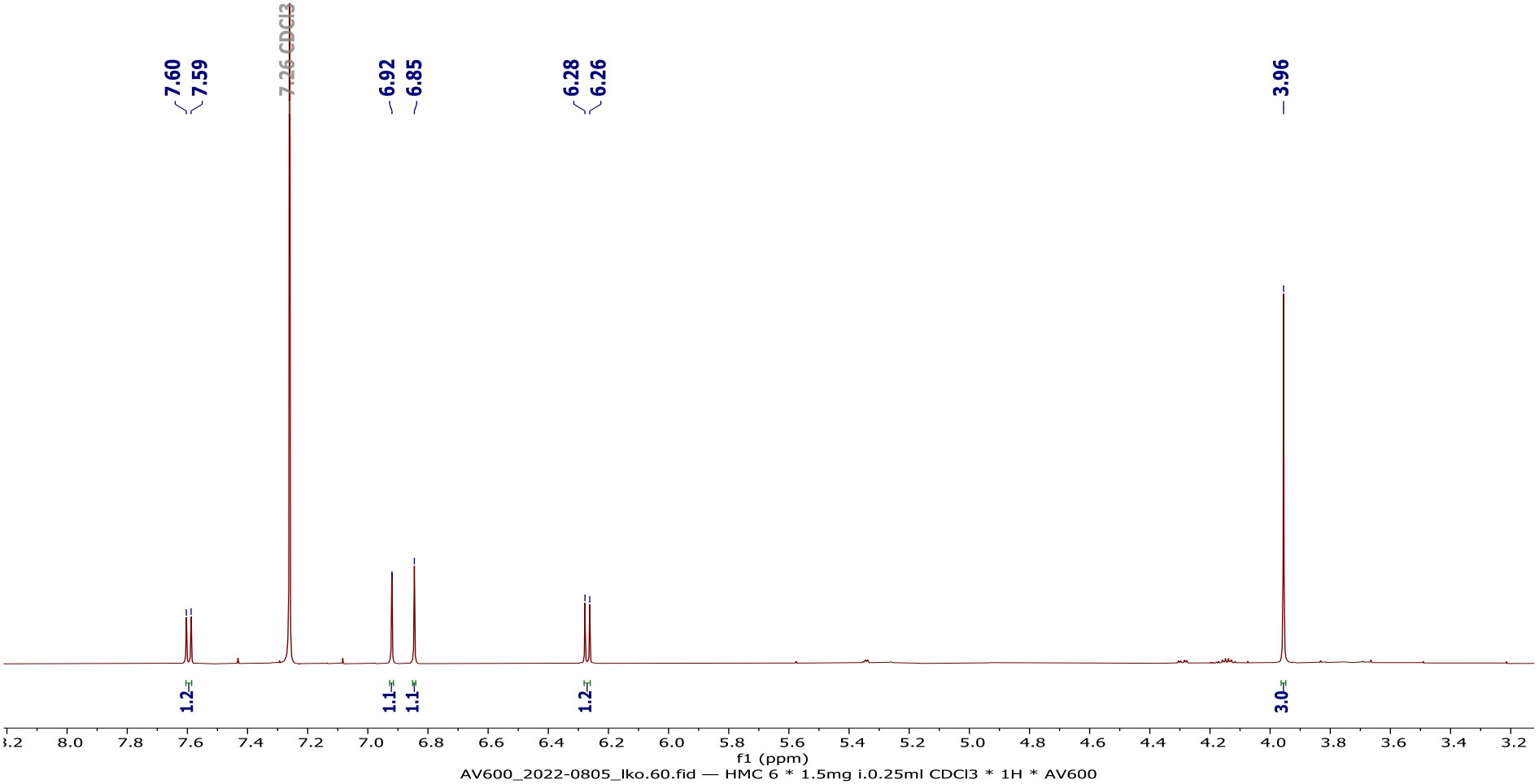


Compound **251** HMBC spectrum ($CDCl_3$)

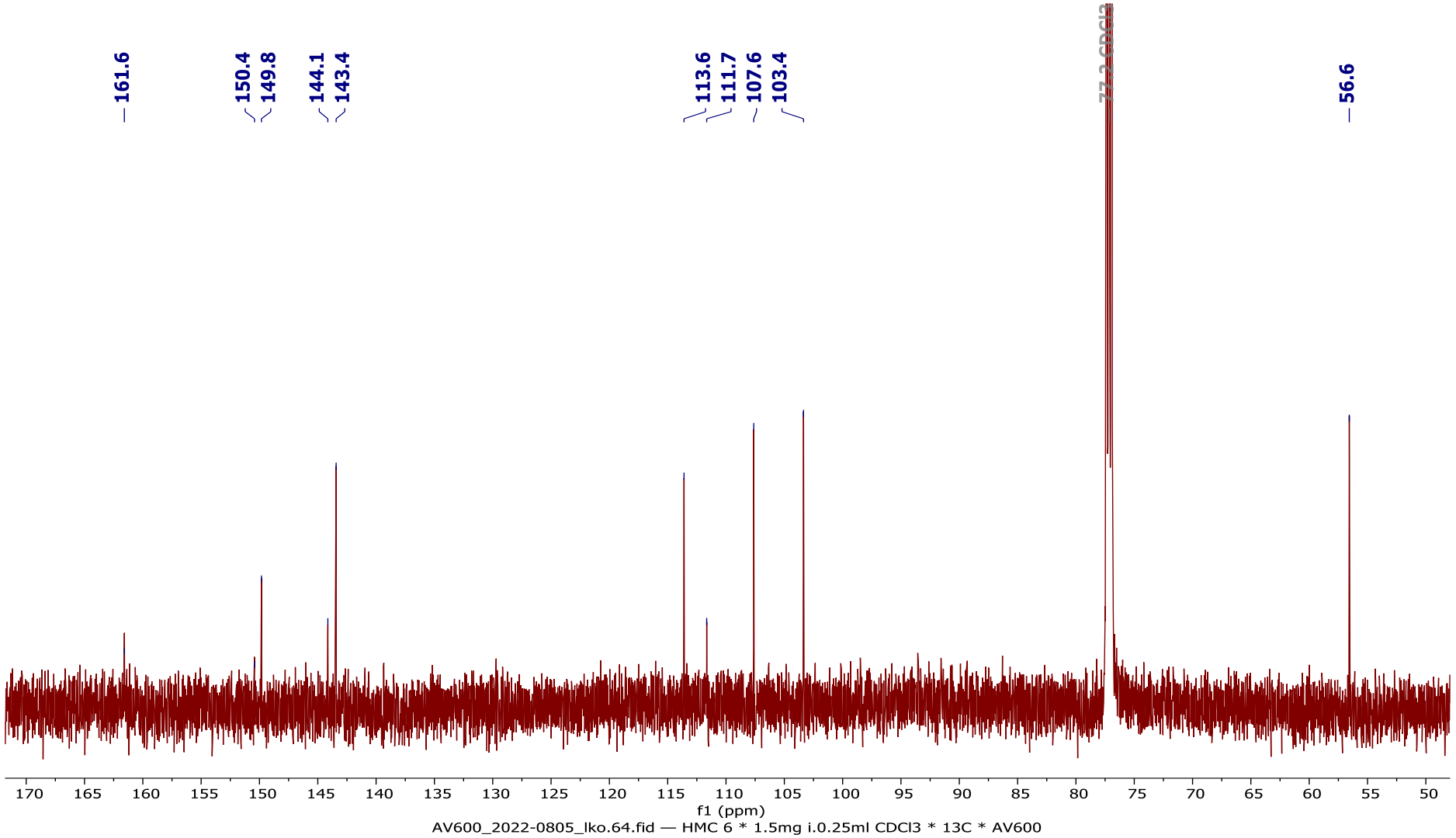


Appendix 8: Spectra of scopoletin (**252**)

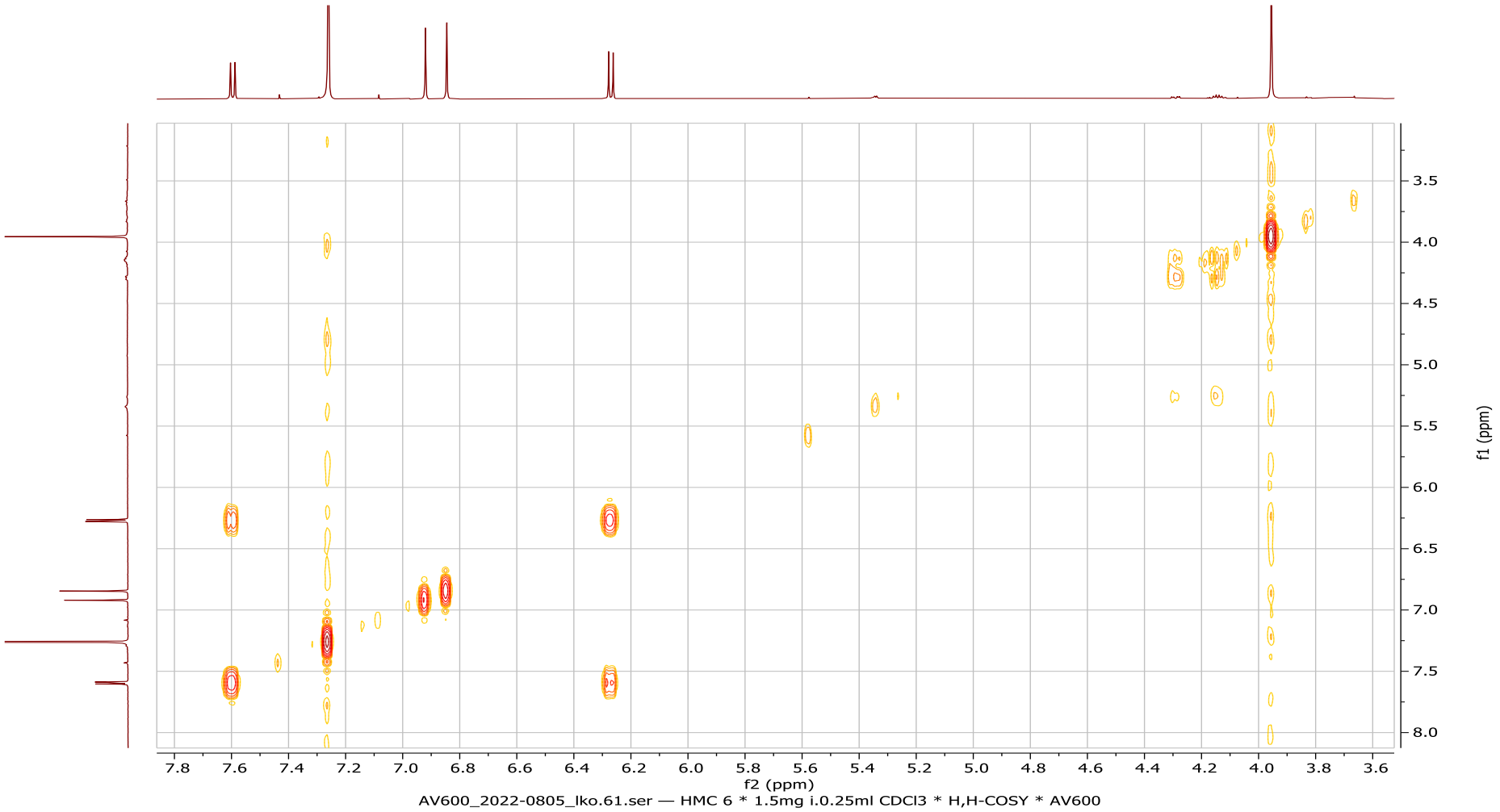
Compound **252** ^{1}H NMR spectrum ($CDCl_3$, 600 MHz)



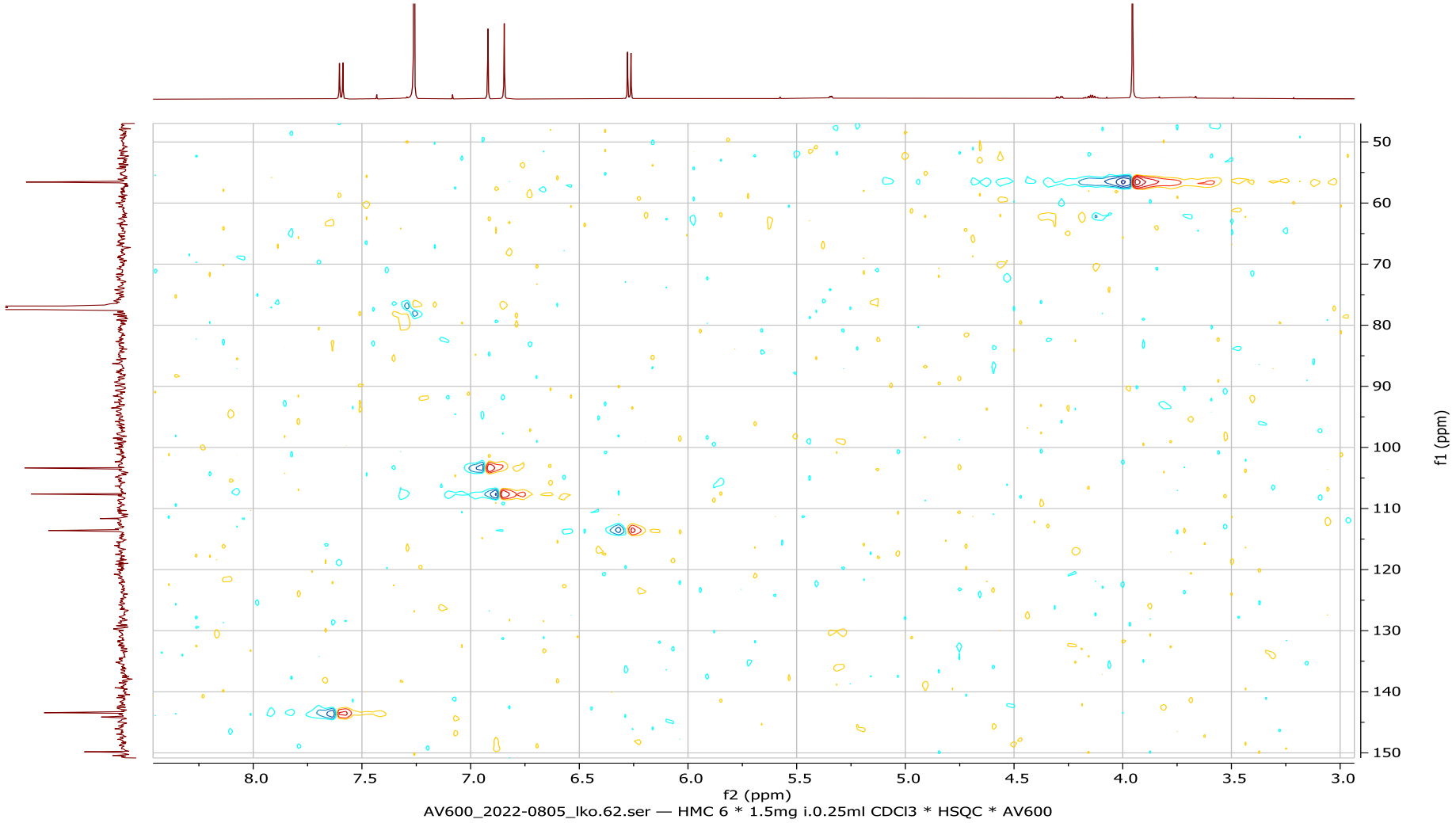
Compound **252** ^{13}C NMR spectrum ($CDCl_3$, 150 MHz)



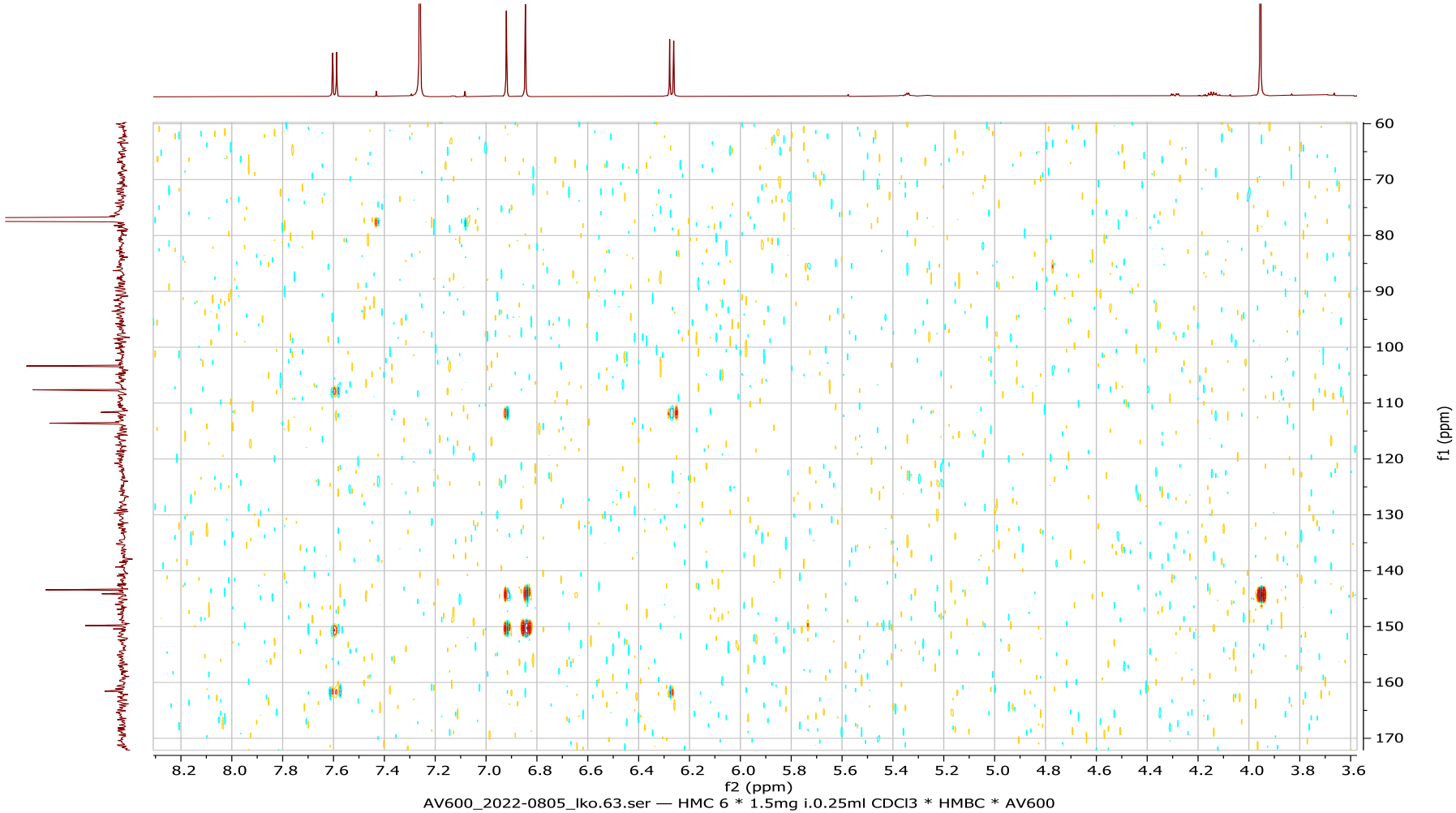
Compound **252** ^{1}H-^{1}H COSY spectrum ($CDCl_3$)



Compound **252** HSQC spectrum ($CDCl_3$)

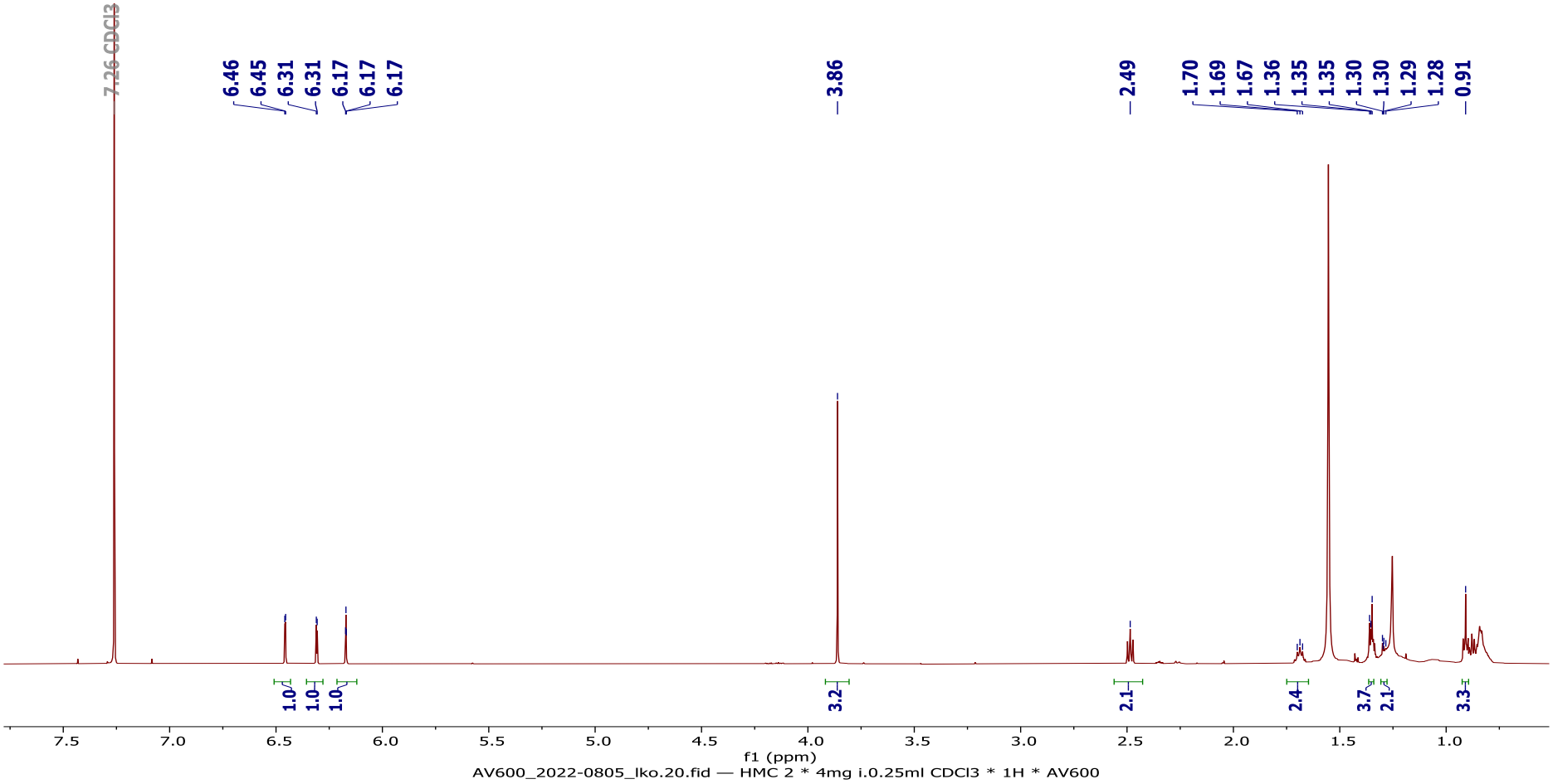


Compound **252** HMBC spectrum ($CDCl_3$)

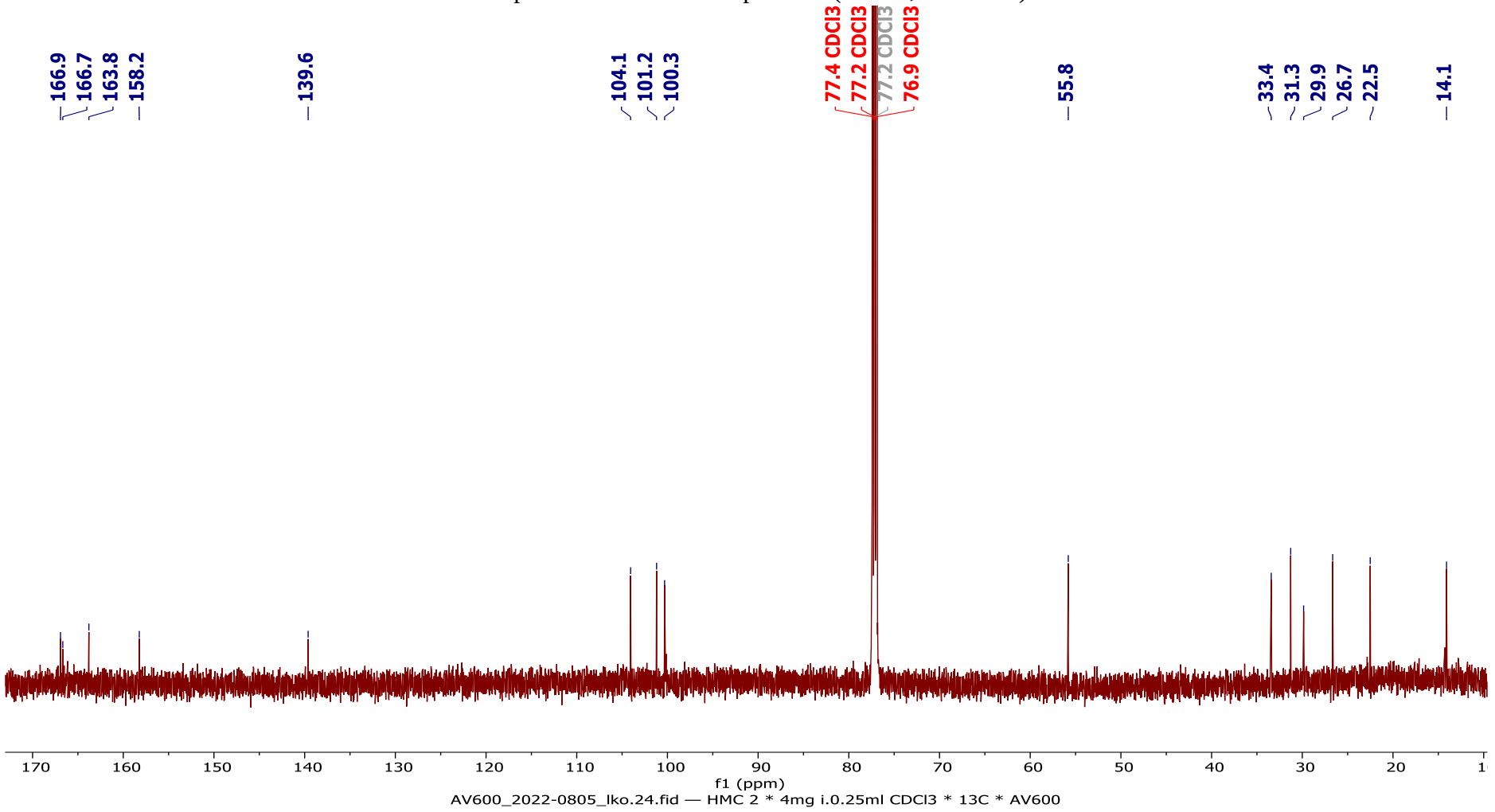


Appendix 9: Spectra of 8-Hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (**253**)

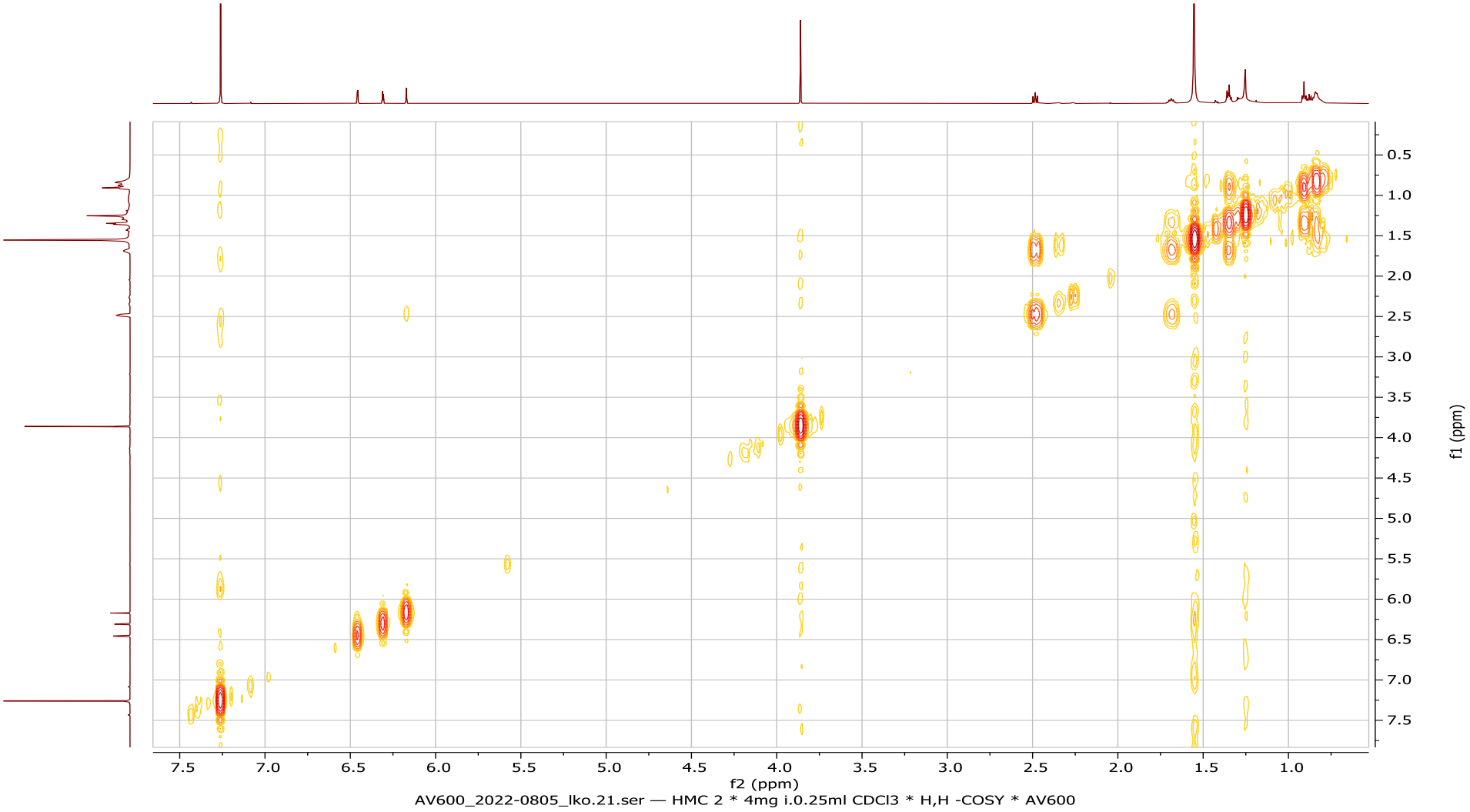
Compound **253** ^{1}H NMR spectrum ($CDCl_3$, 600 MHz)



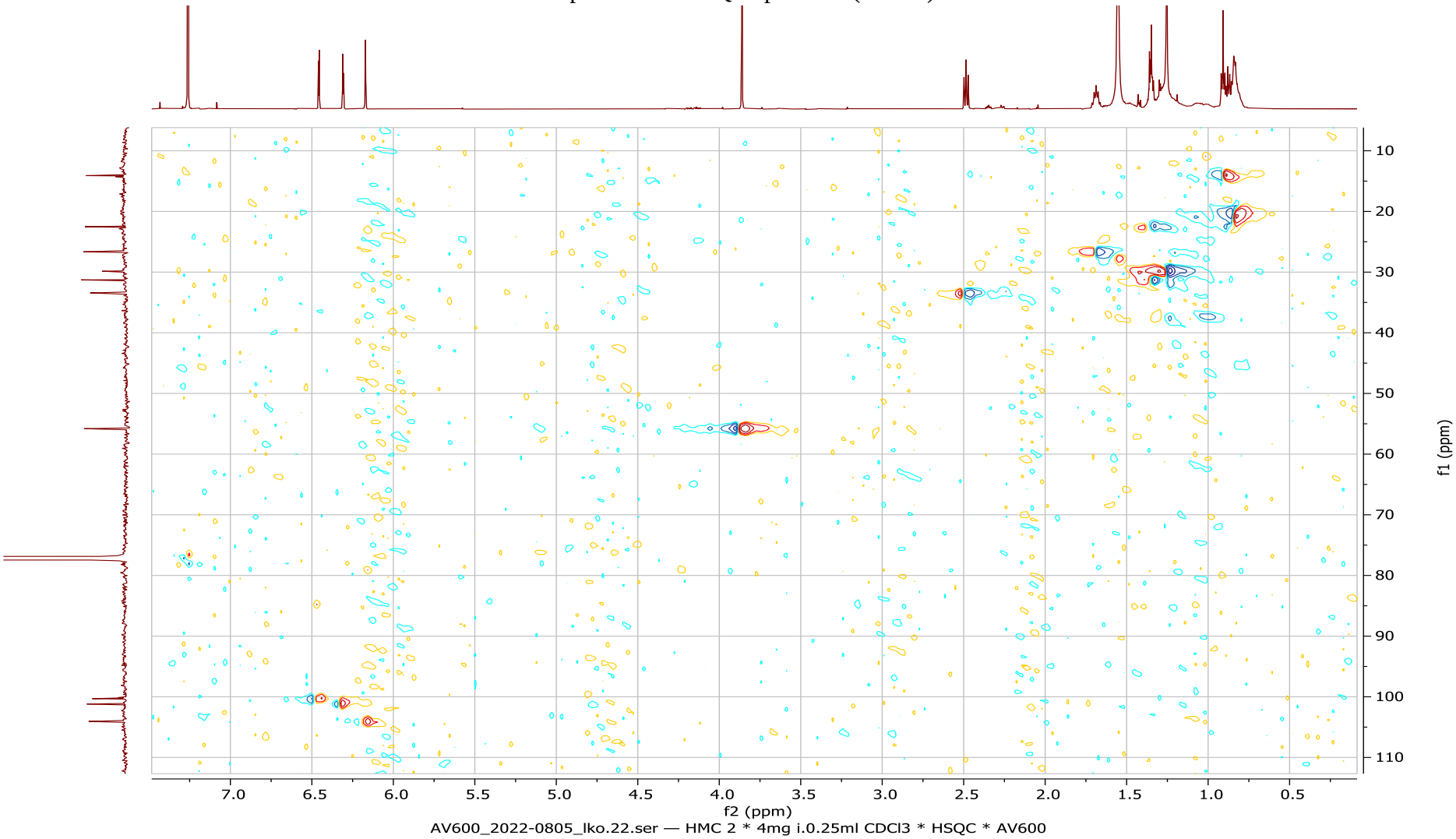
Compound **253** ^{13}C NMR spectrum ($CDCl_3$, 150 MHz)



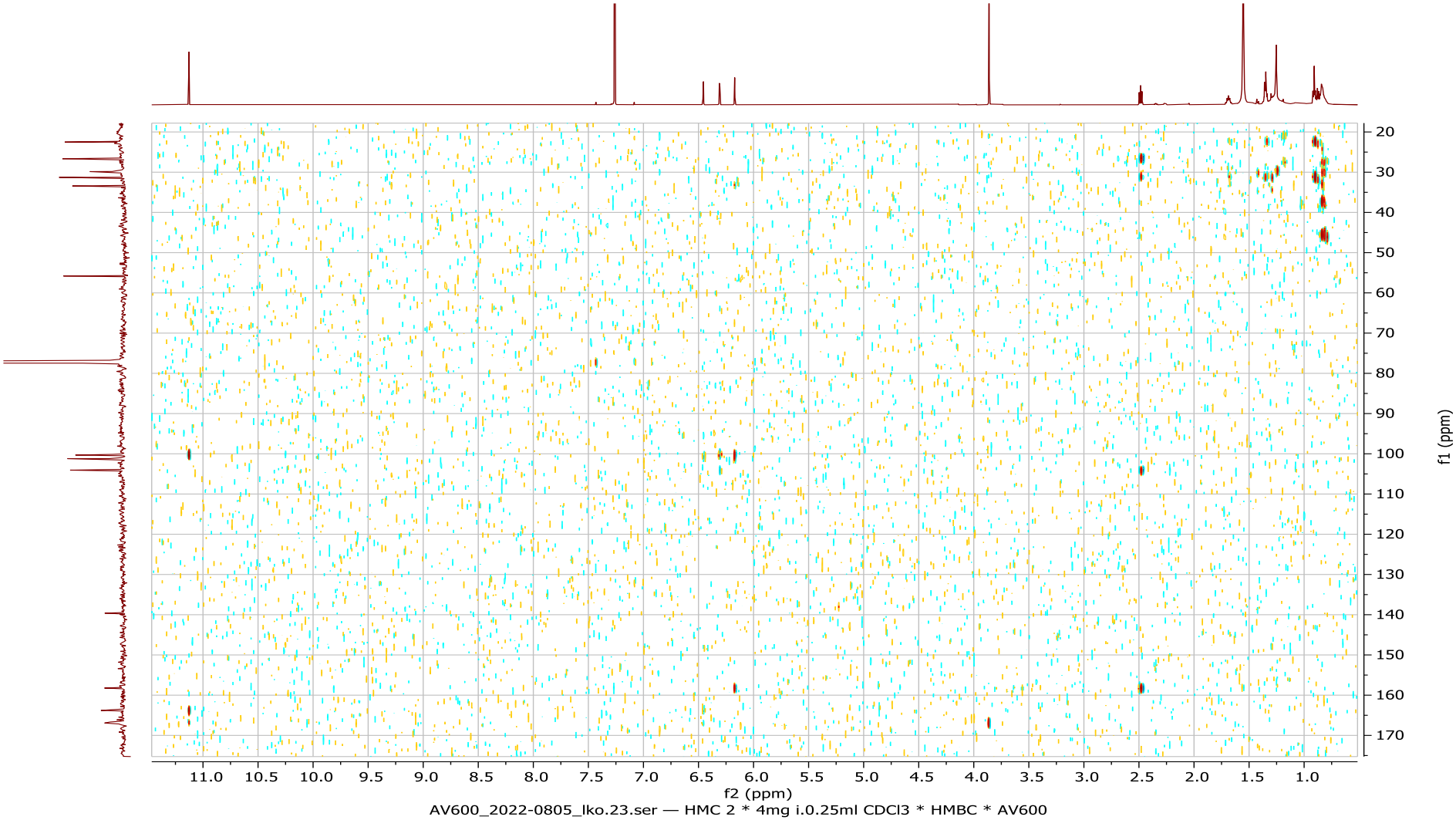
Compound **253** ^{1}H-^{1}H COSY spectrum ($CDCl_3$)



Compound **253** HSQC spectrum ($CDCl_3$)

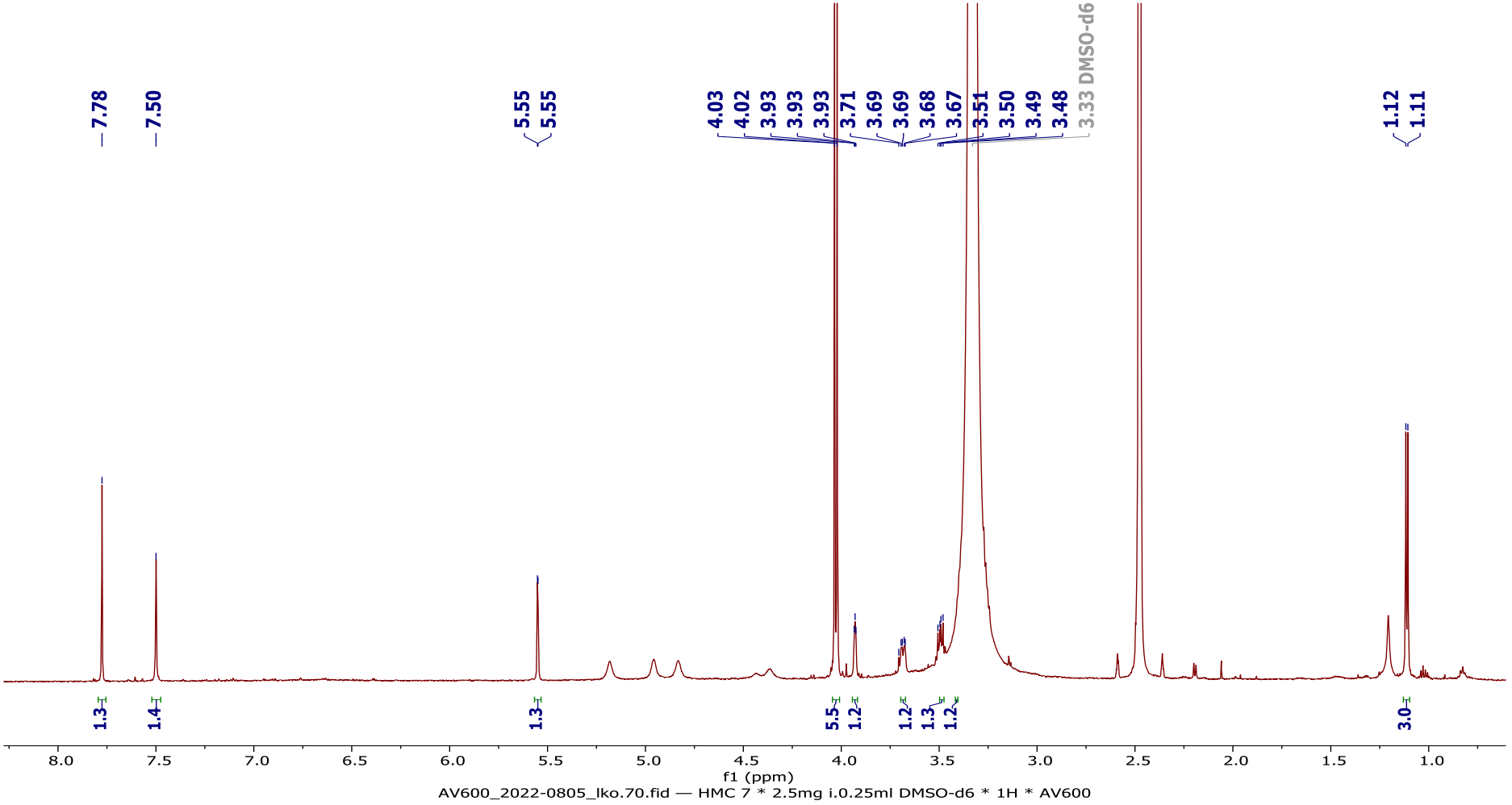


Compound **253** HMBC spectrum ($CDCl_3$)

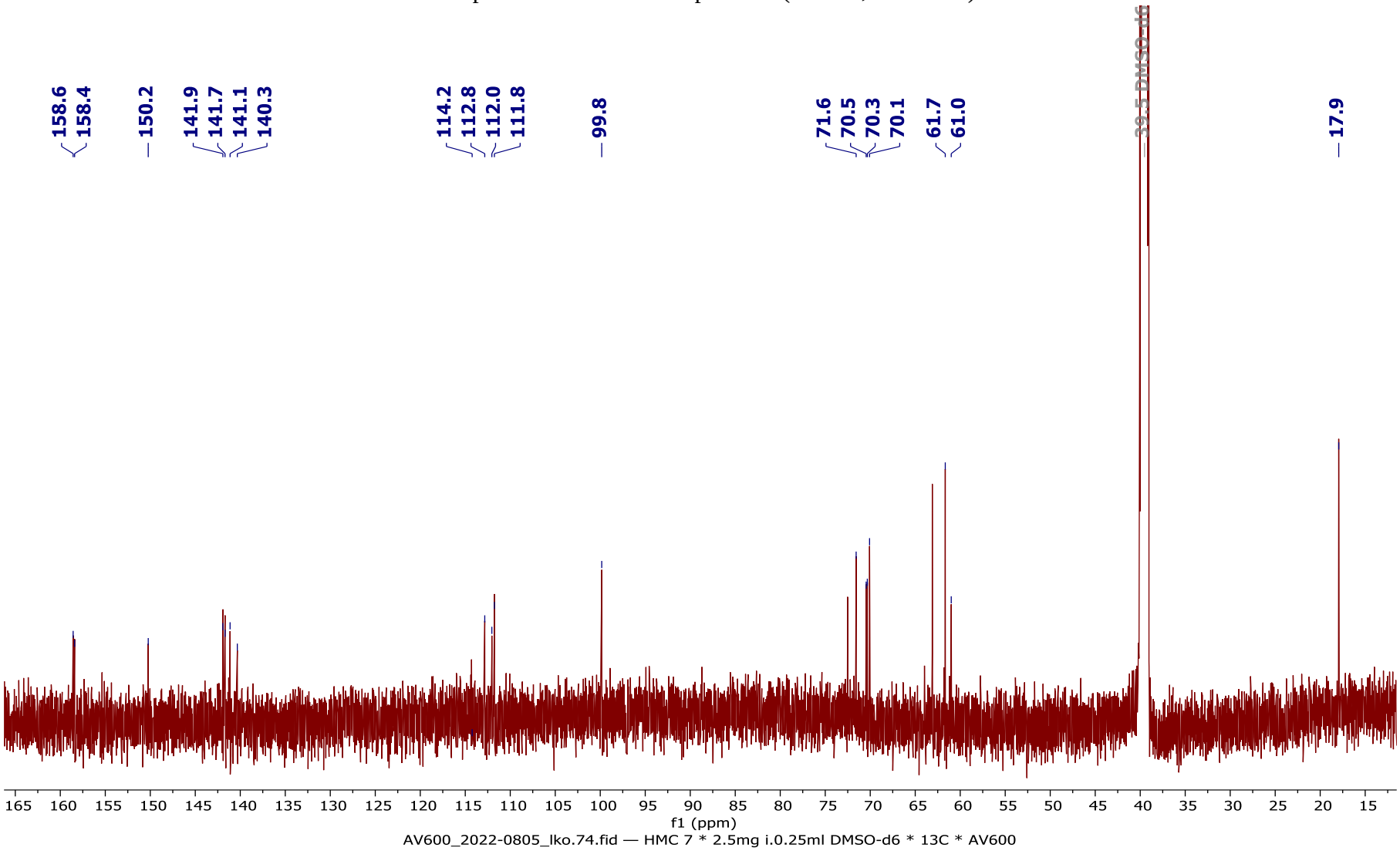


Appendix 10: Spectra of 3,3′-Di-*O*-methylellagic acid-4′-*O*-α-*L*-rhamnopyranoside (**254**)

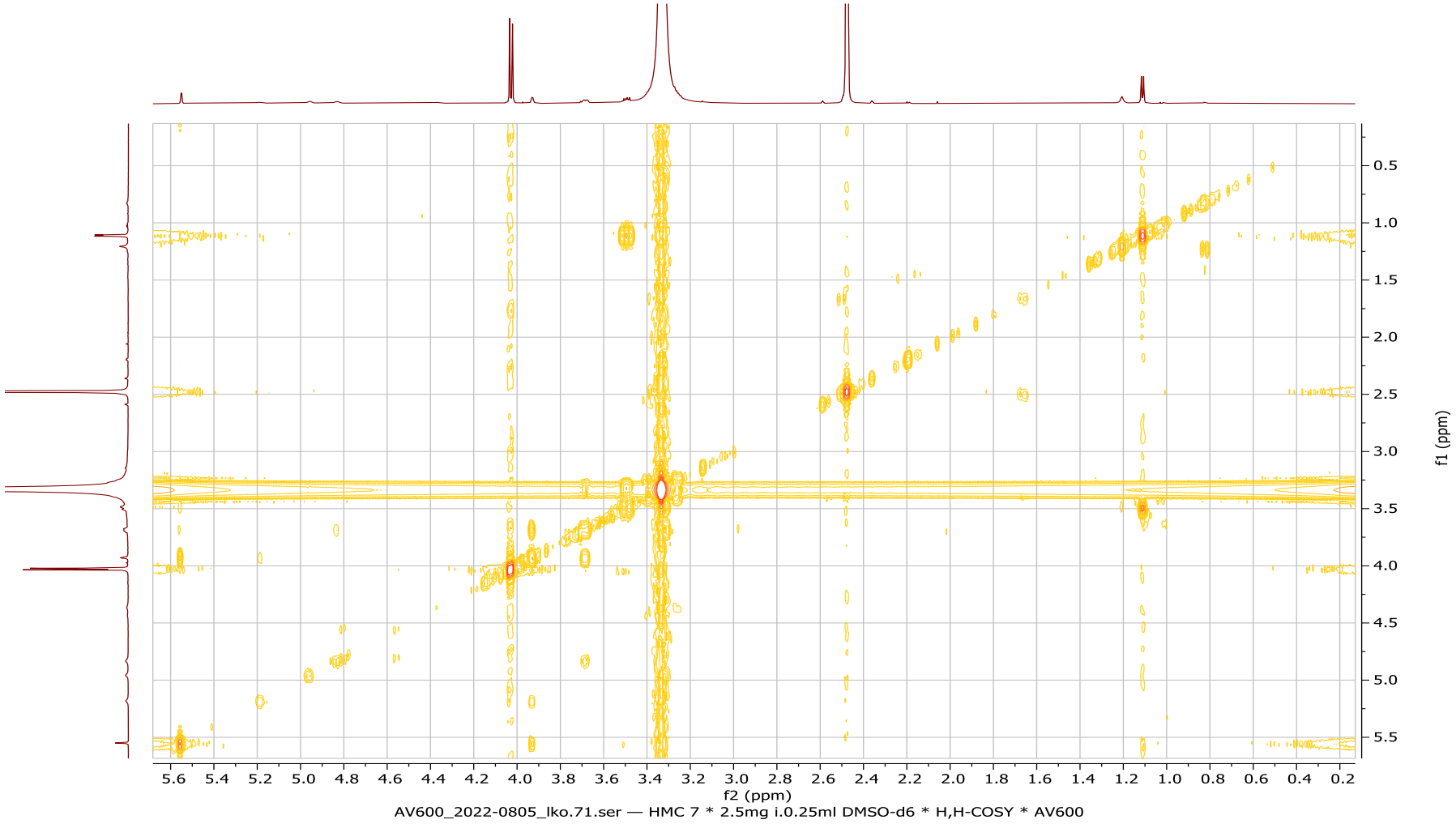
Compound **254** ^{1}H NMR spectrum (DMSO, 600 MHz)



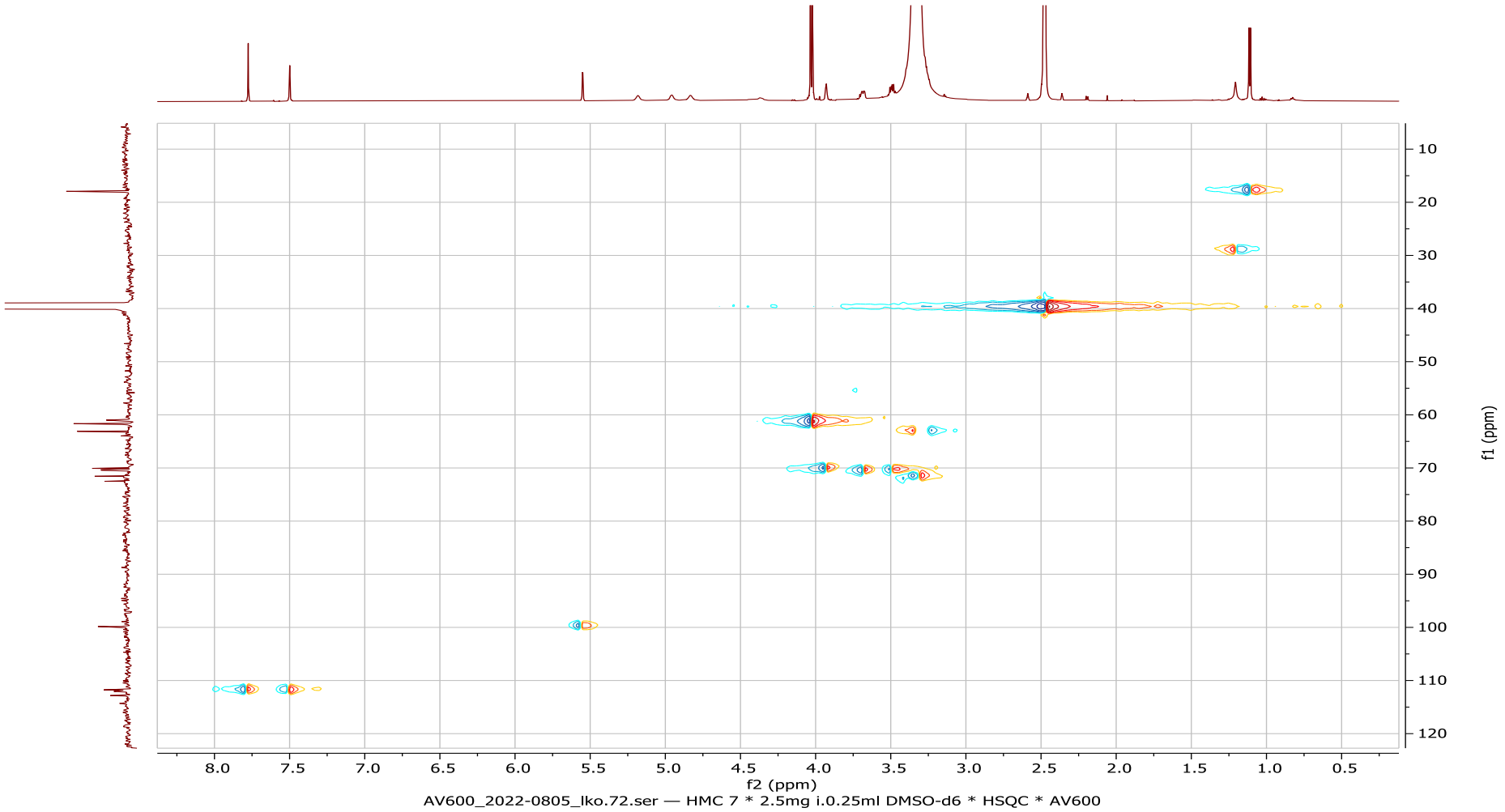
Compound **254** ^{13}C NMR spectrum (DMSO, 150 MHz)



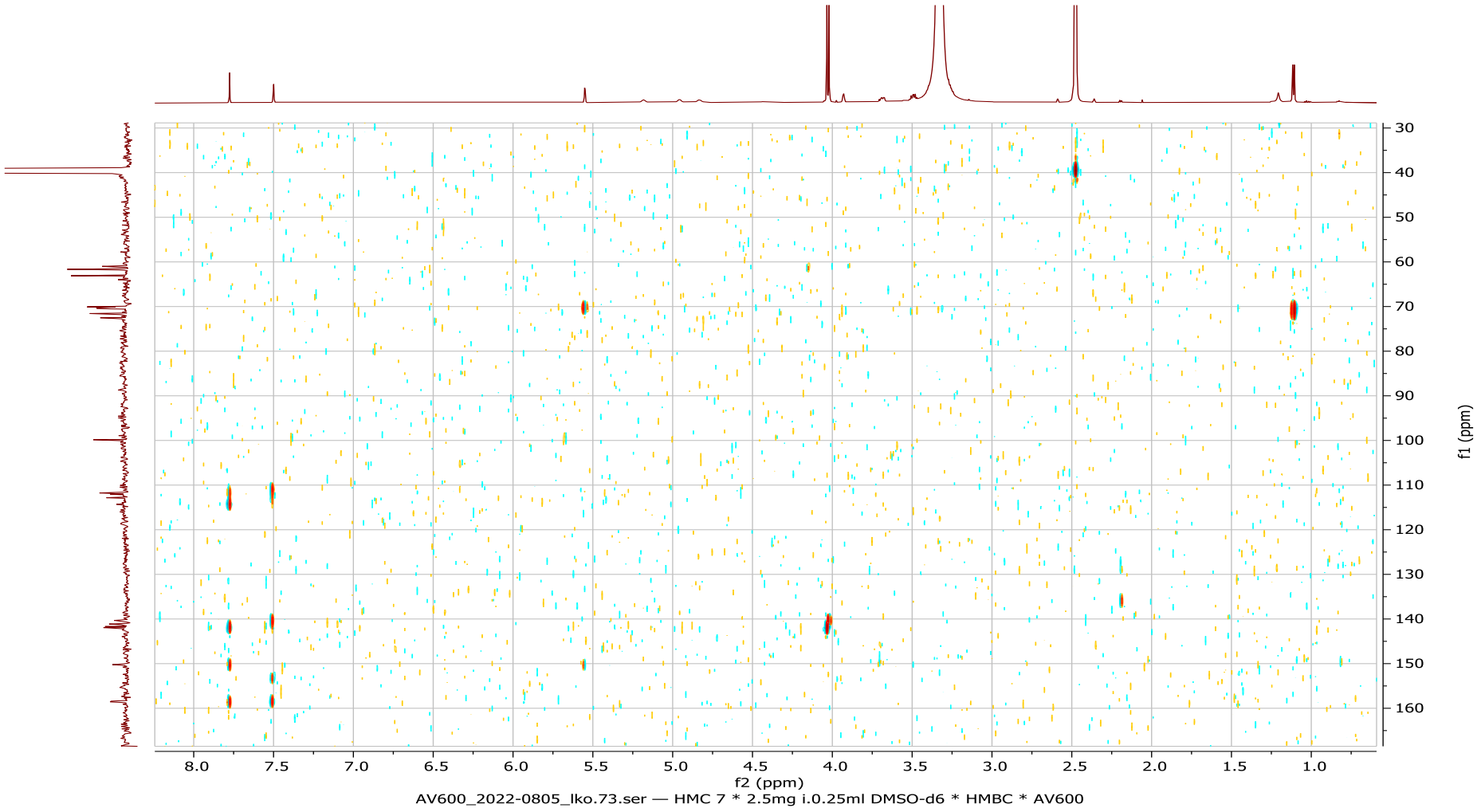
Compound **254** ^{1}H-^{1}H COSY spectrum (DMSO)



Compound **254** HSQC spectrum (DMSO)

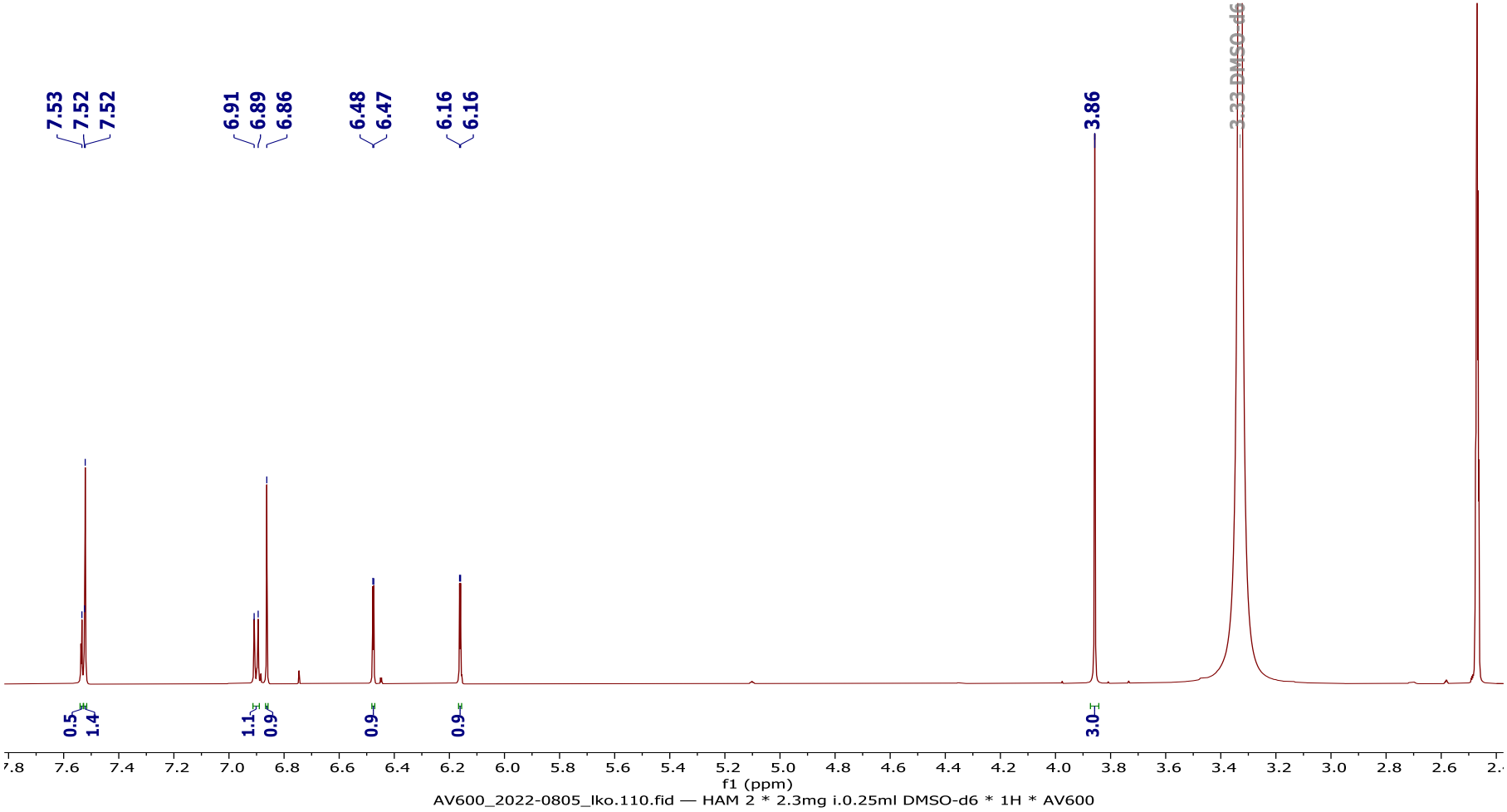


Compound **254** HMBC spectrum (DMSO)

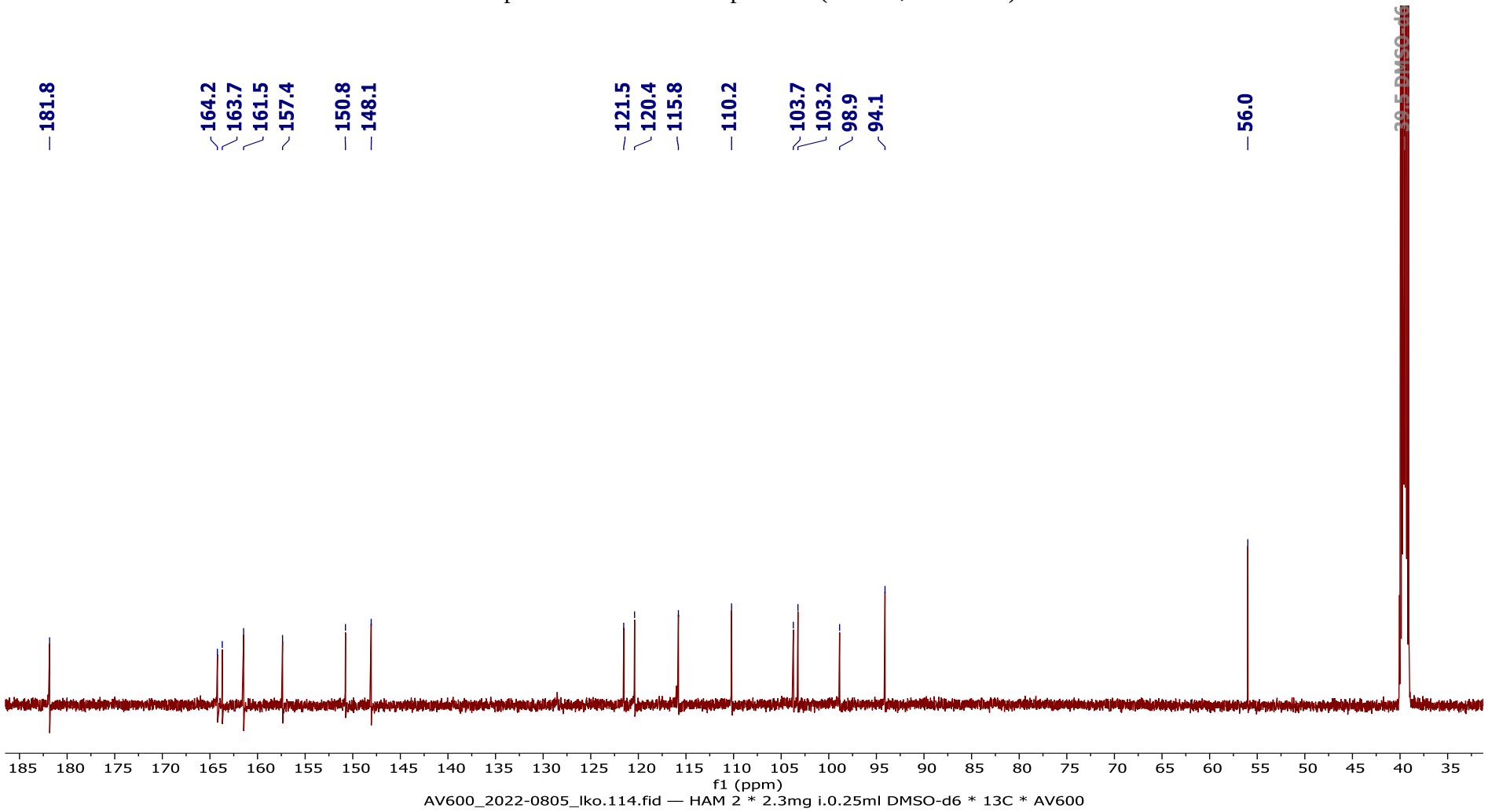


Appendix 11: Spectra of chrysoeriol (**255**)

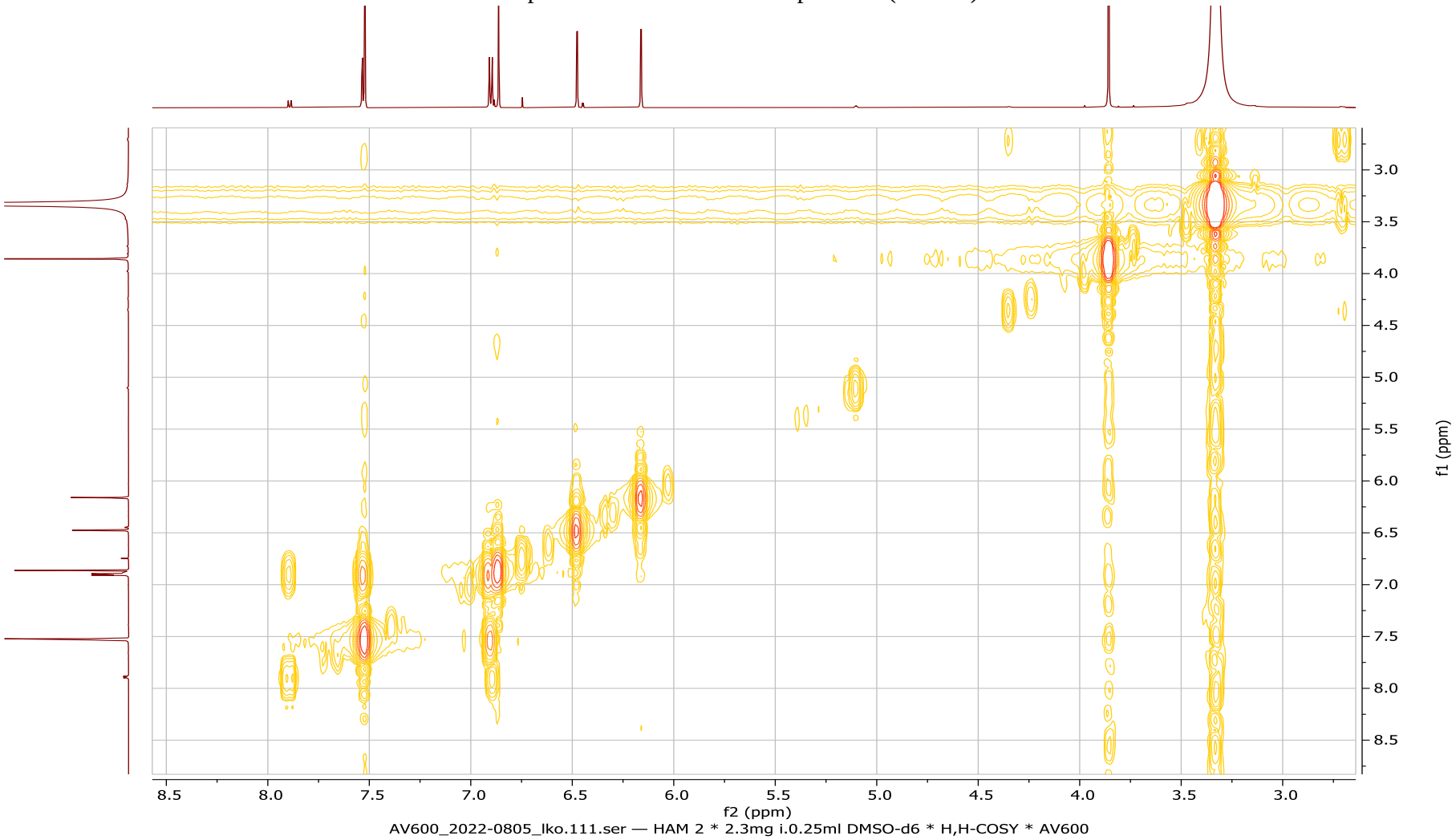
Compound **255** ^{1}H NMR spectrum (DMSO, 600 MHz)



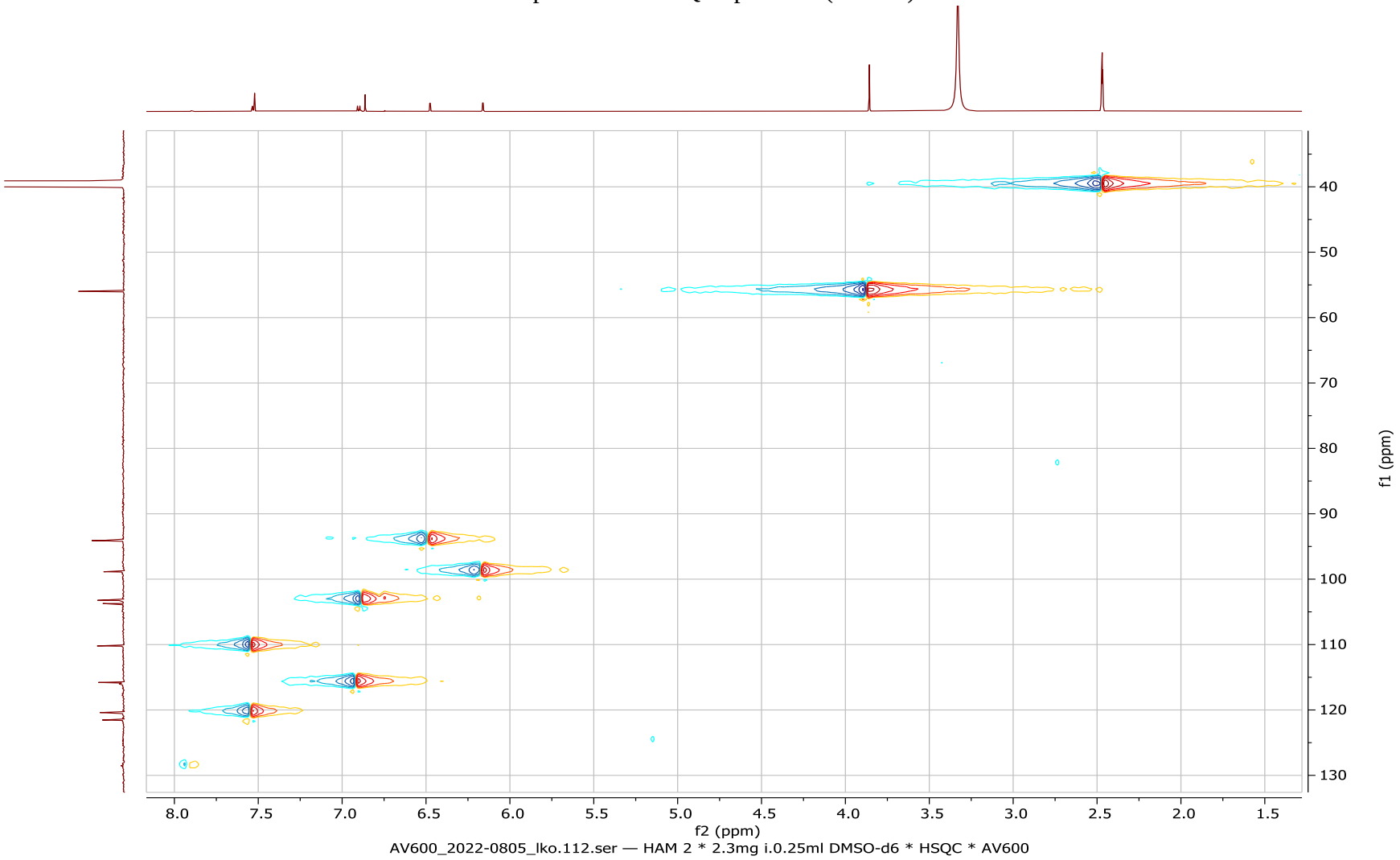
Compound **255** ^{13}C NMR spectrum (DMSO, 150 MHz)



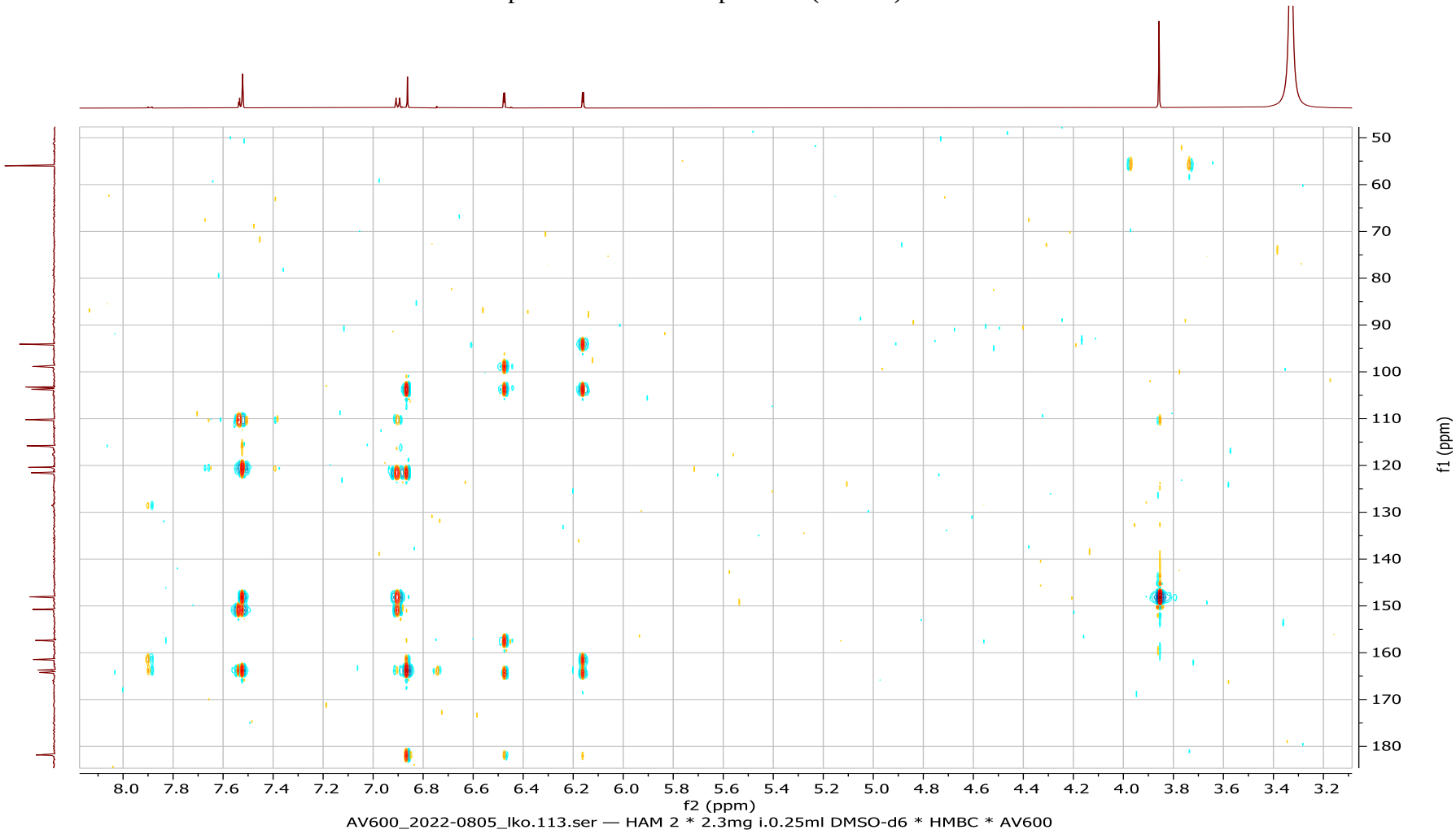
Compound **255** ^{1}H-^{1}H COSY spectrum (DMSO)



Compound **255** HSQC spectrum (DMSO)

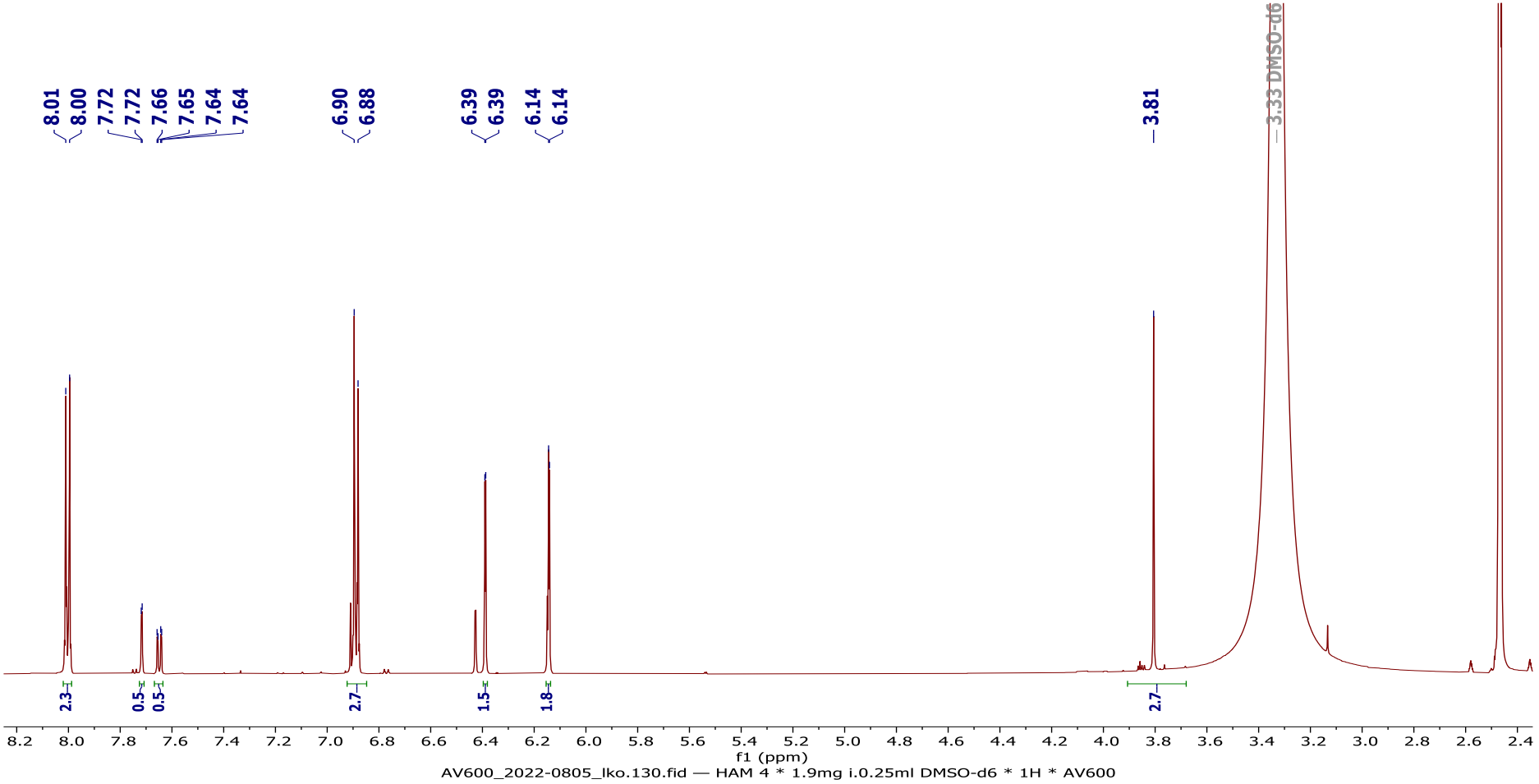


Compound **255** HMBC spectrum (DMSO)

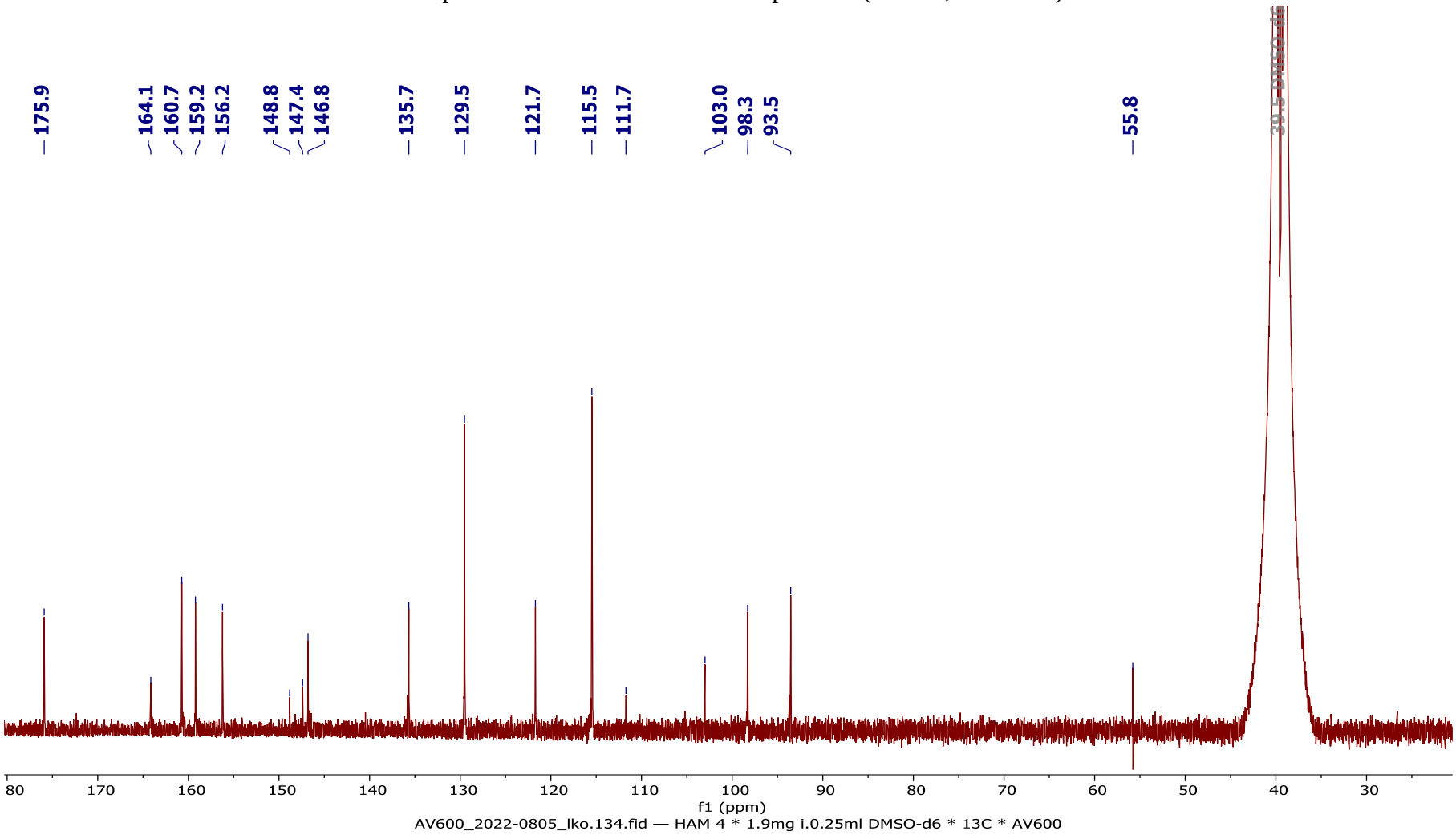


Appendix 12: Spectra of isorhamnetin (**256**) and kaempferol (**257**)

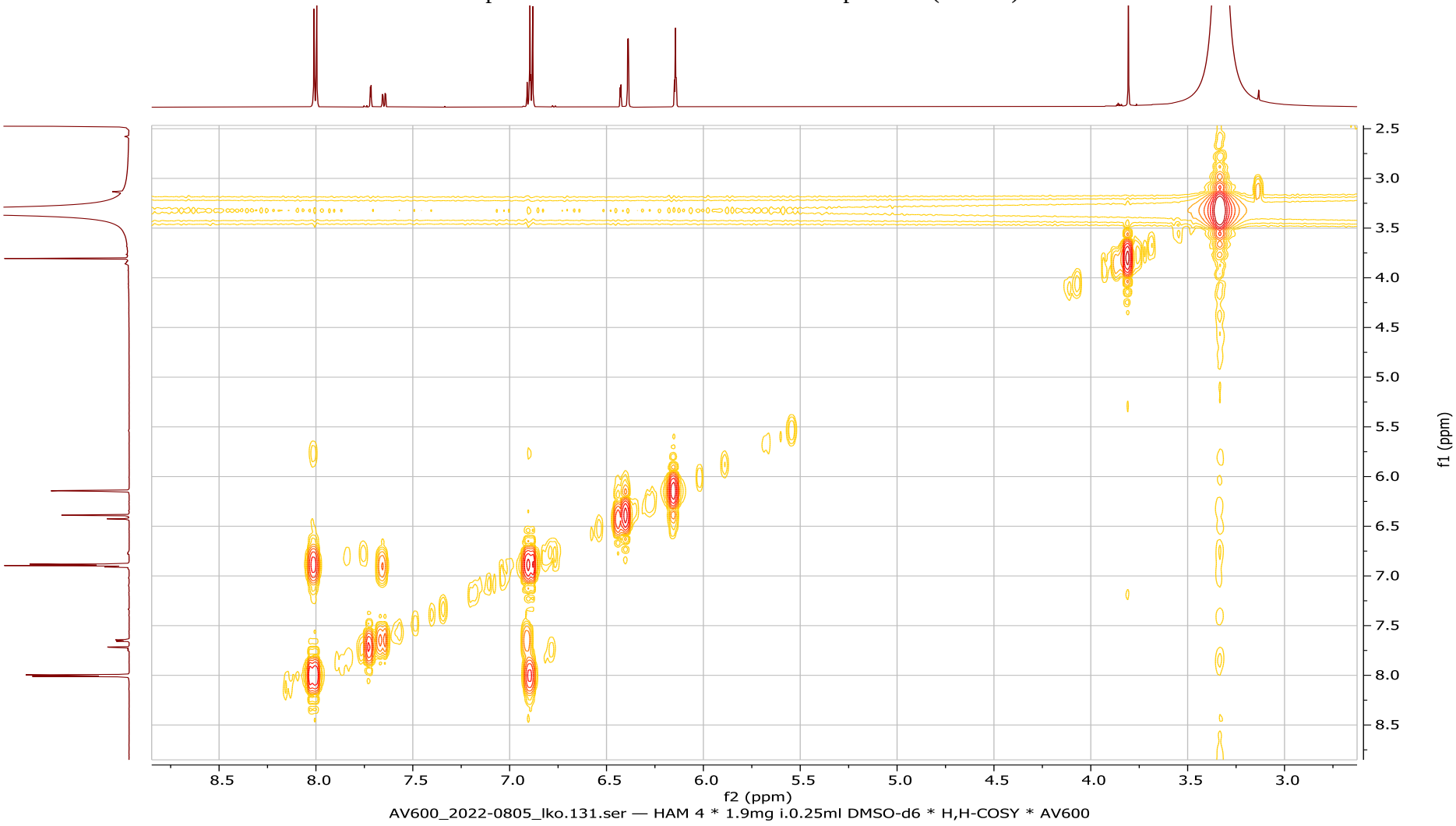
Compounds **256** and **257** ^{1}H NMR spectrum (DMSO, 600 MHz)



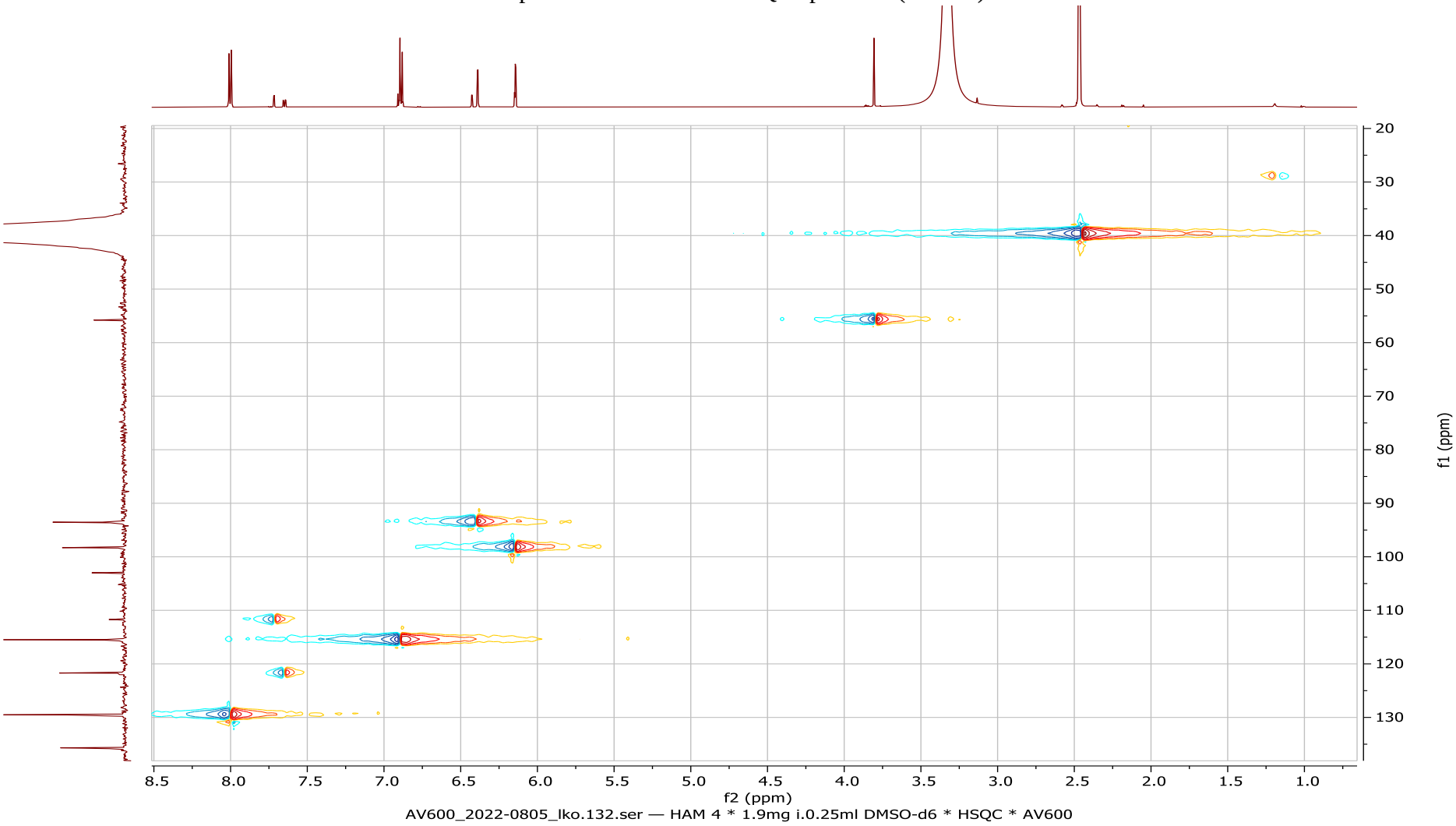
Compounds **256** and **257** ^{13}C NMR spectrum (DMSO, 150 MHz)



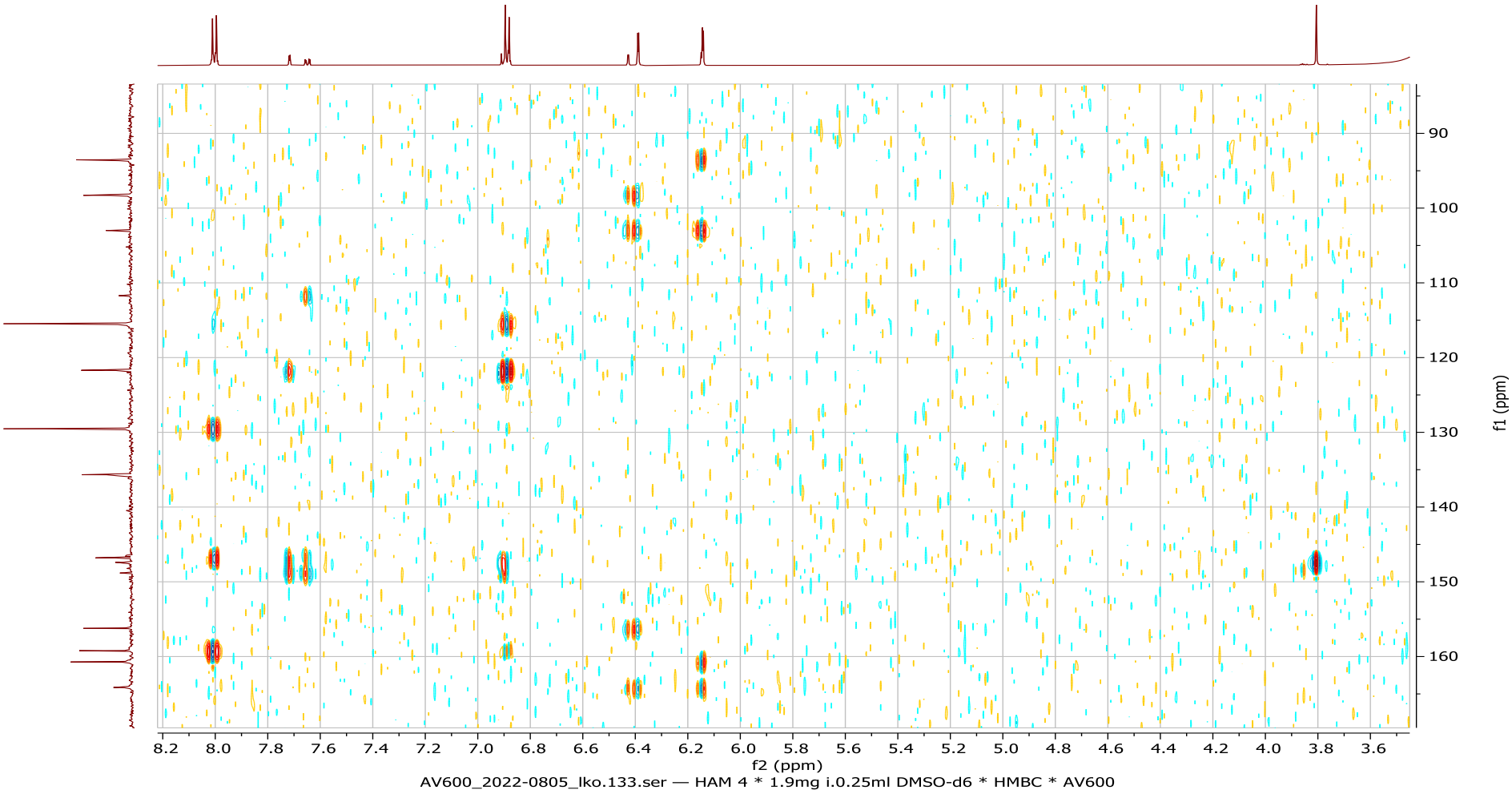
Compounds **256** and **257** ^{1}H-^{1}H COSY spectrum (DMSO)



Compounds **256** and **257** HSQC spectrum (DMSO)

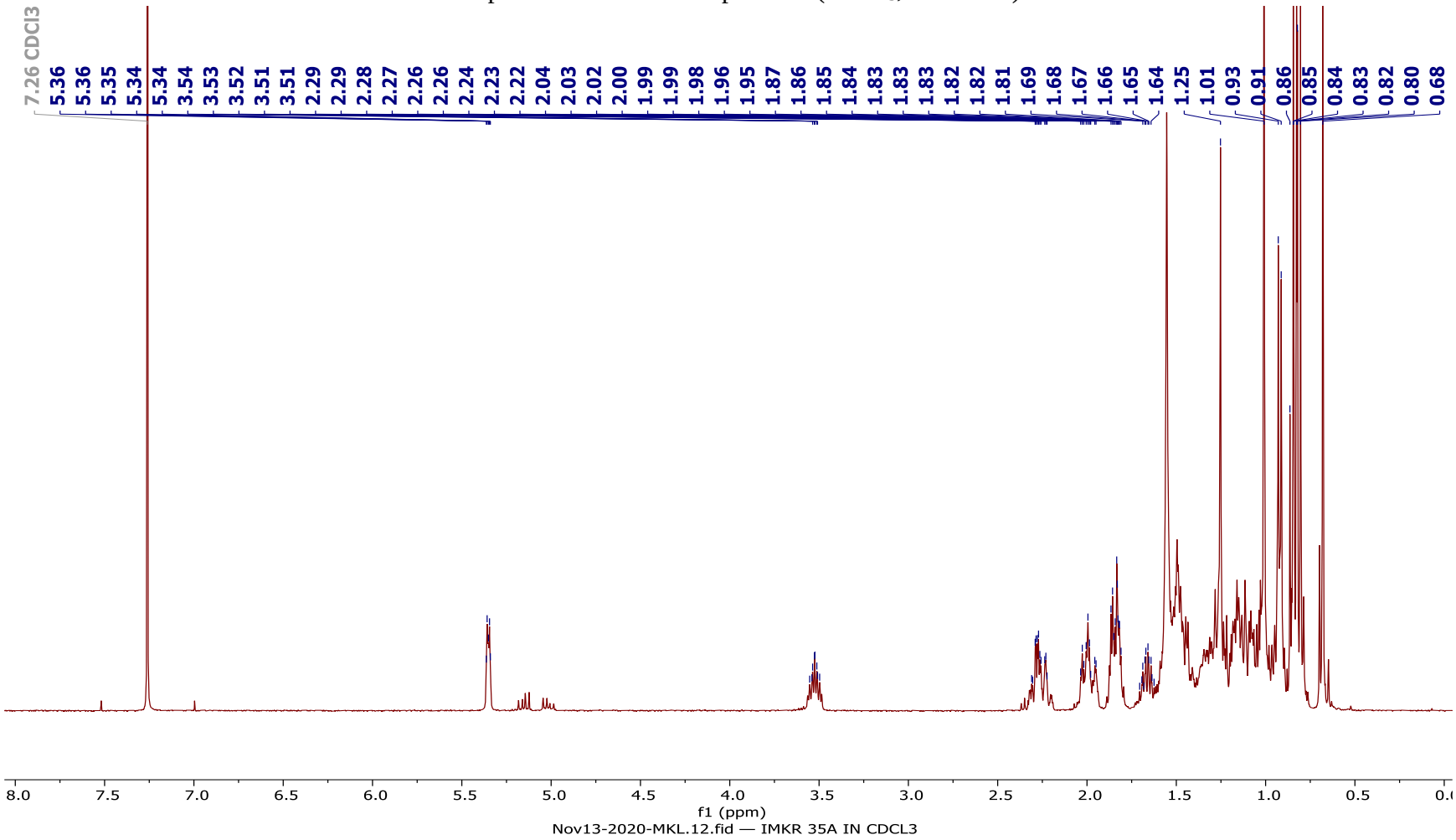


Compounds **256** and **257** HMBC spectrum (DMSO)

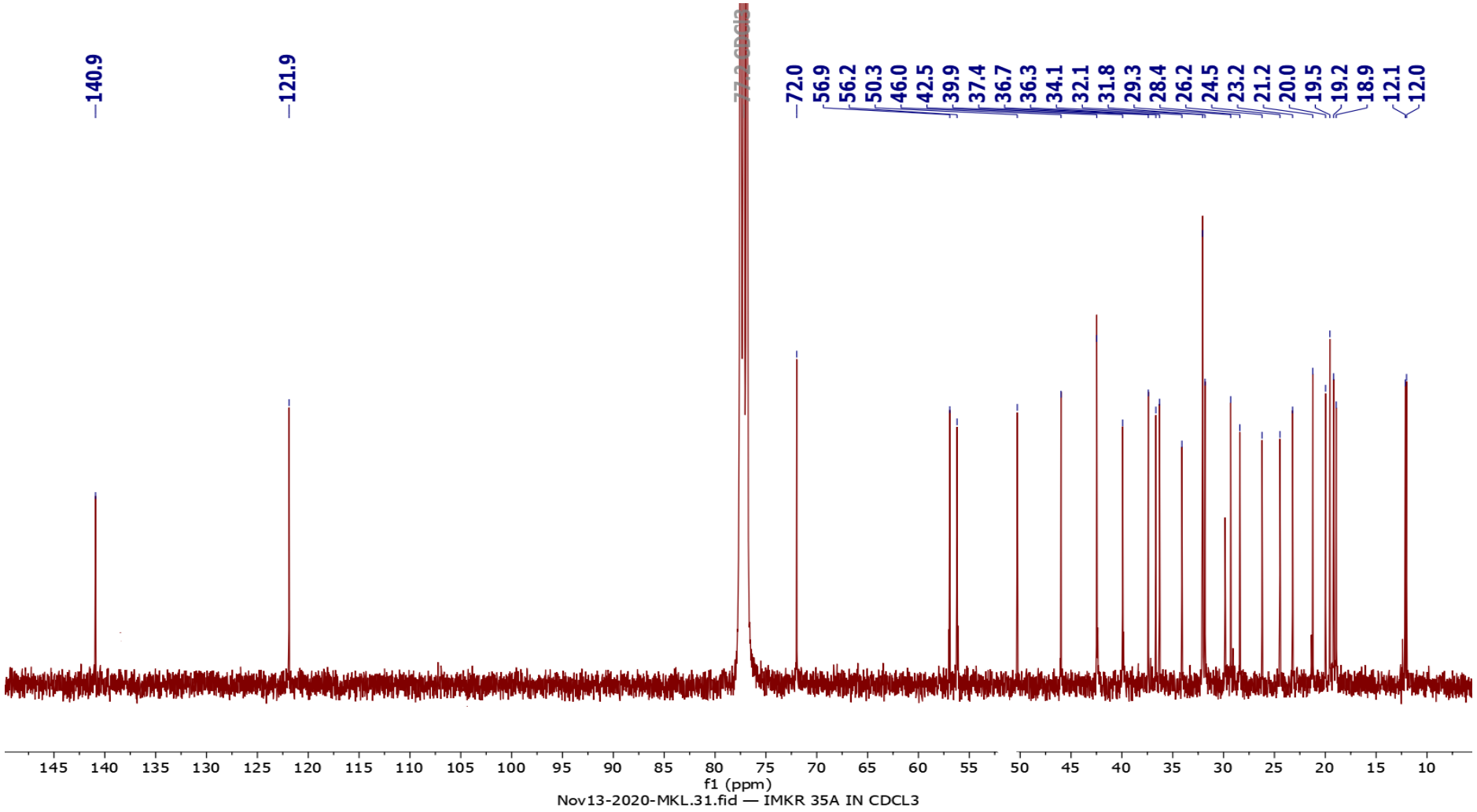


Appendix 13: Spectra of β-sitosterol (**258**)

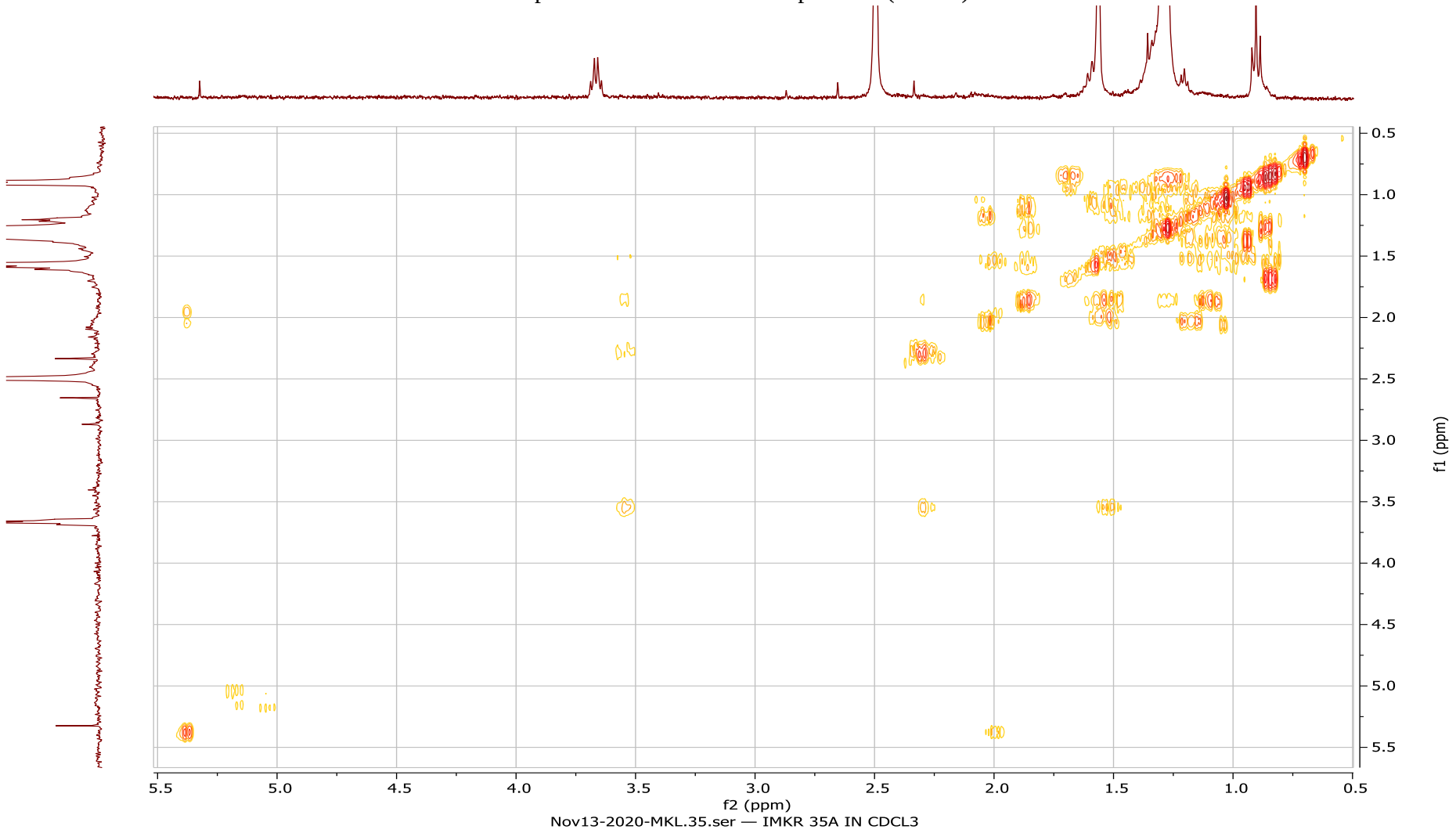
Compound **258** ^{1}H NMR spectrum ($CDCl_3$, 400 MHz)



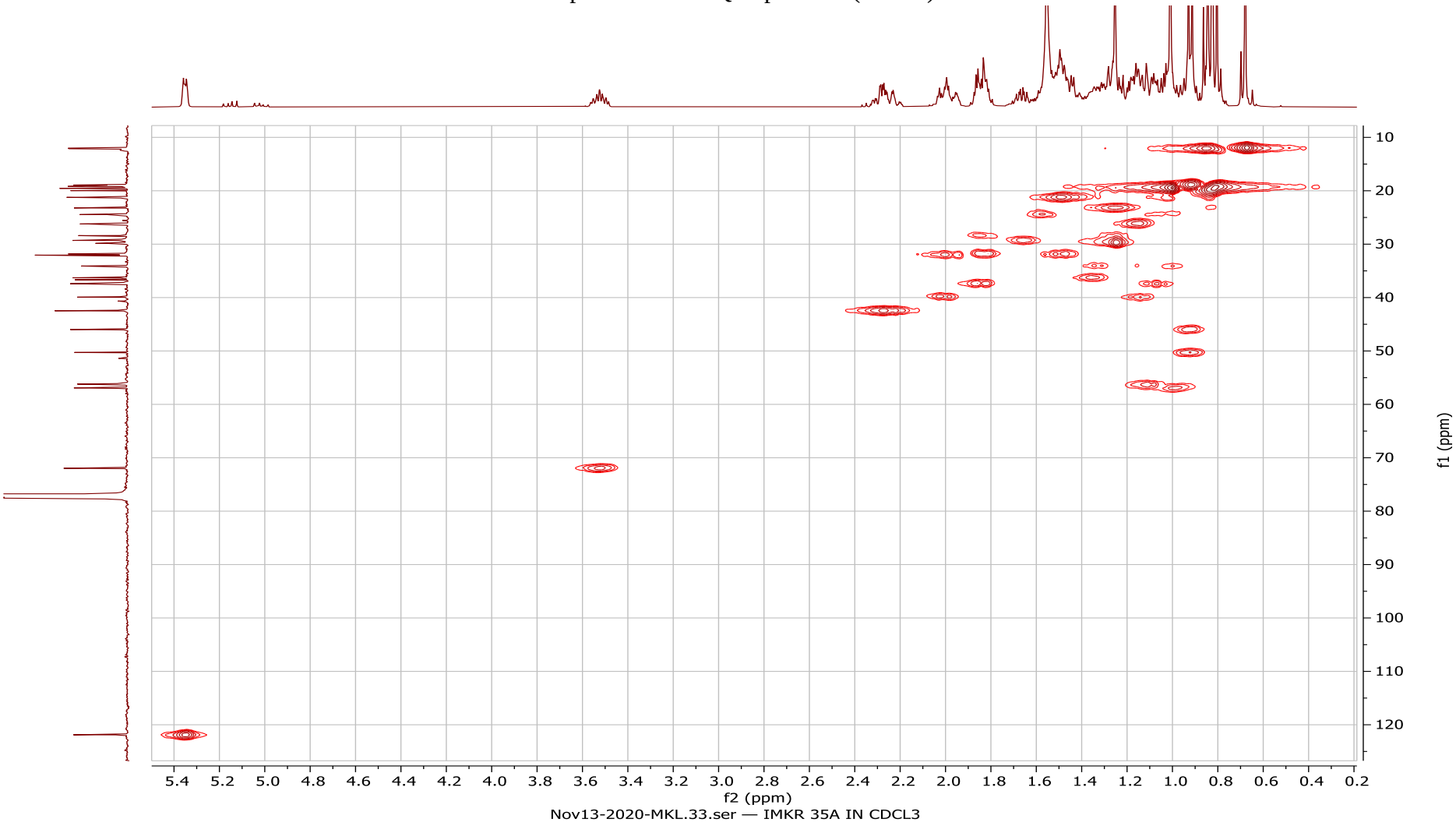
Compound **258** ^{13}C NMR spectrum ($CDCl_3$, 100 MHz)



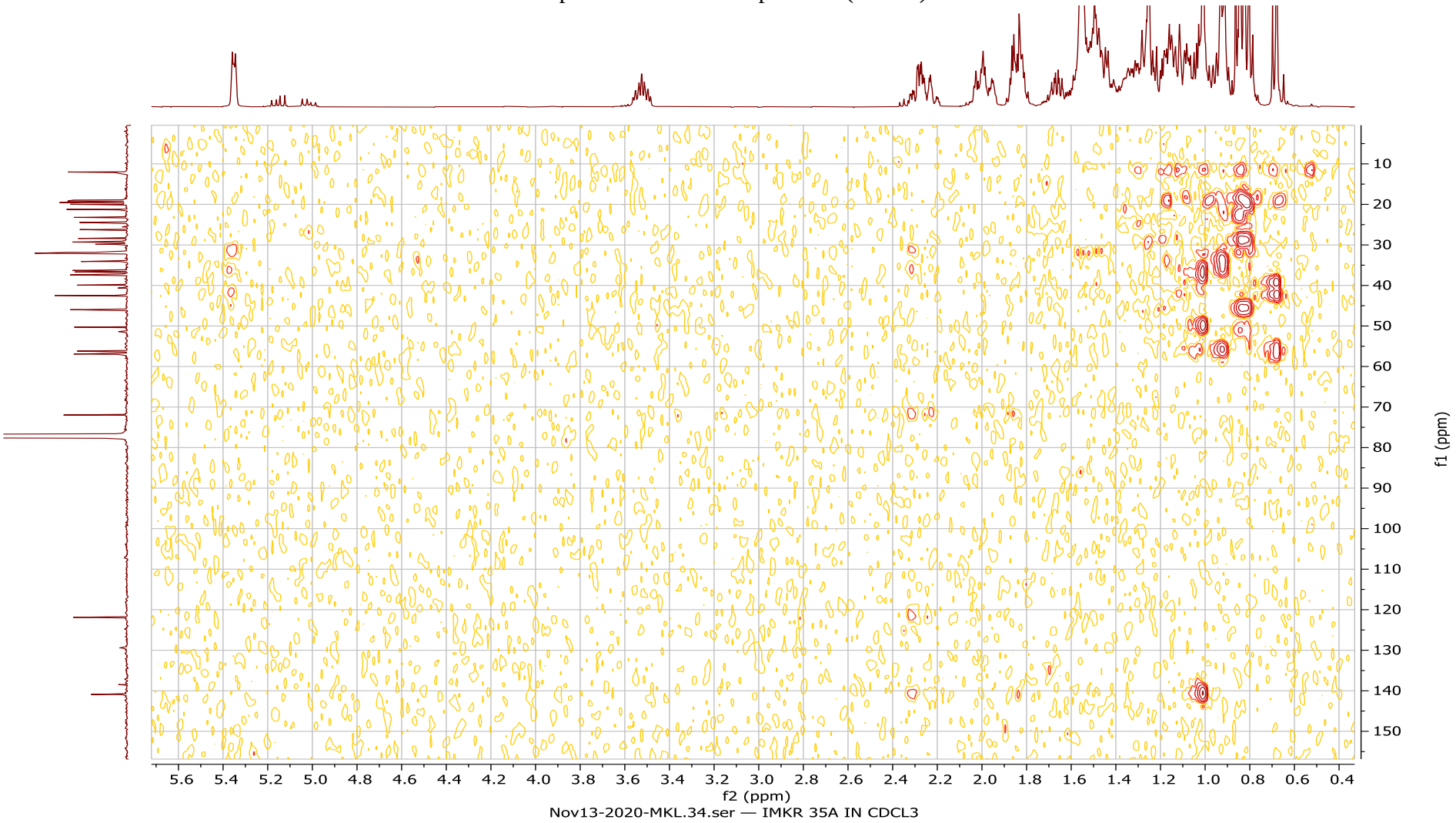
Compound **258** ^{1}H-^{1}H COSY spectrum ($CDCl_3$)



Compound **258** HSQC spectrum ($CDCl_3$)

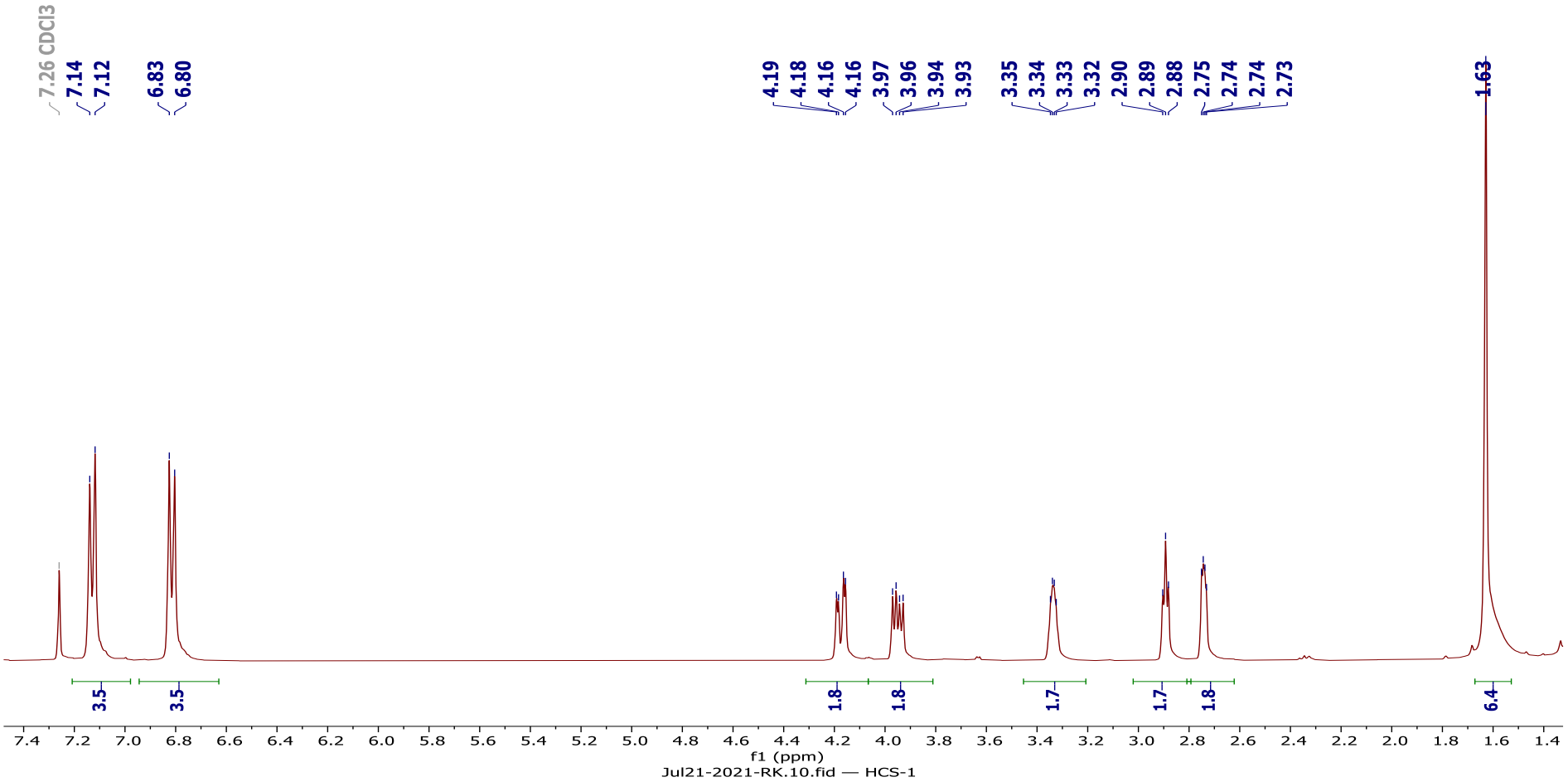


Compound **258** HMBC spectrum ($CDCl_3$)

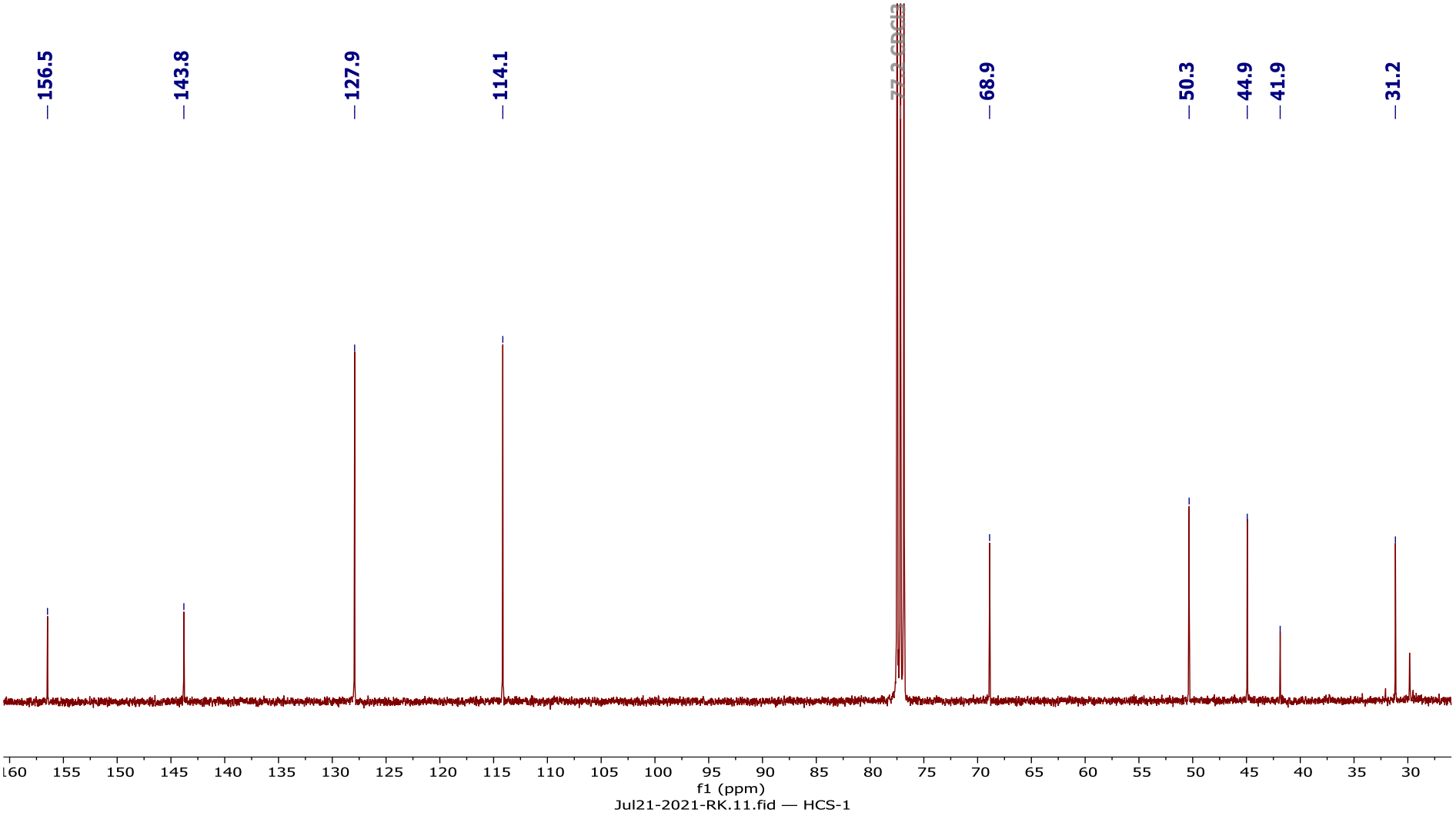


Appendix 14: Spectra of 2,2′-(((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(methylene))bis(oxirane) (**259**)

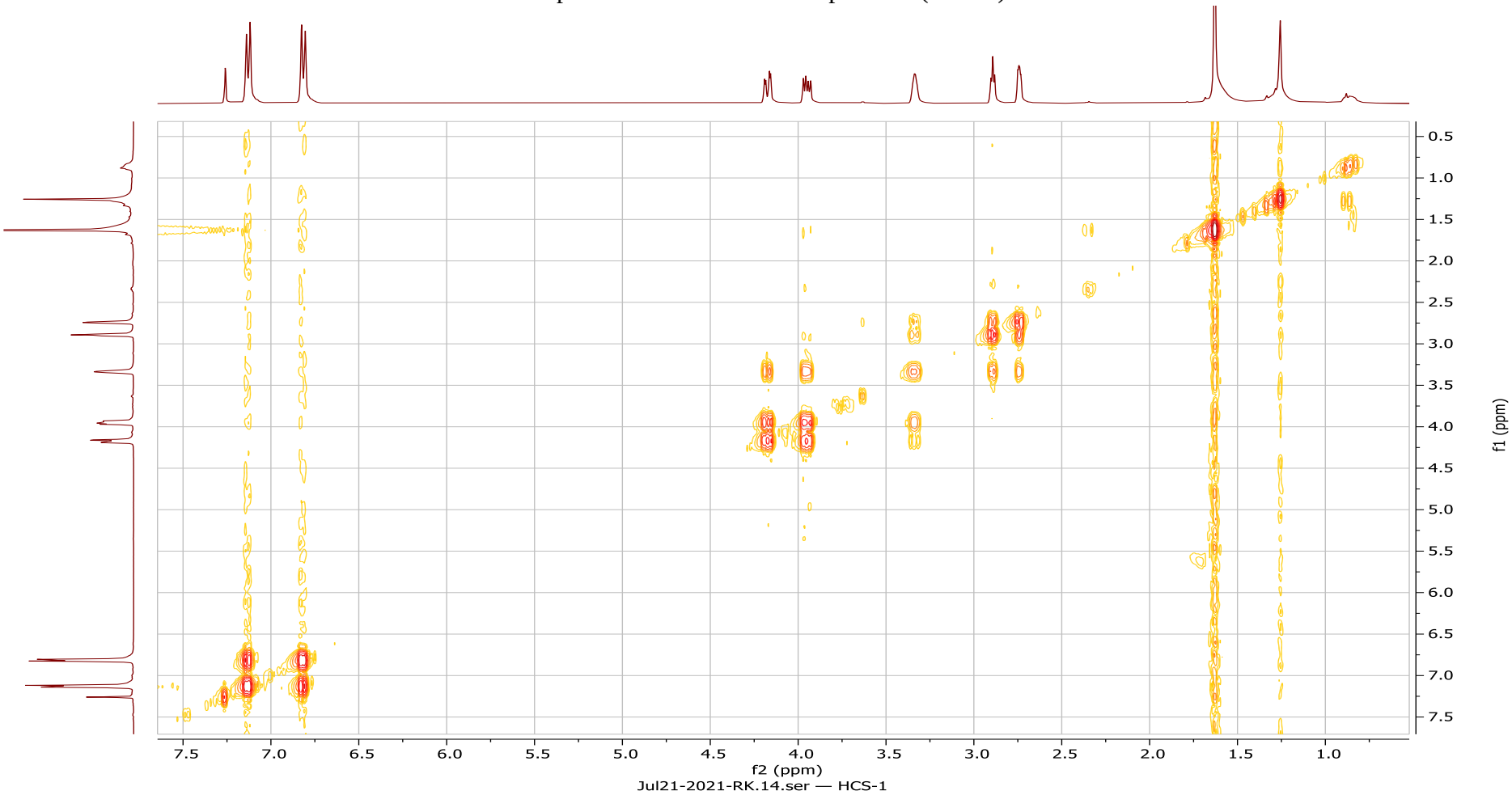
Compound **259** ^{1}H NMR spectrum ($CDCl_3$, 400 MHz)



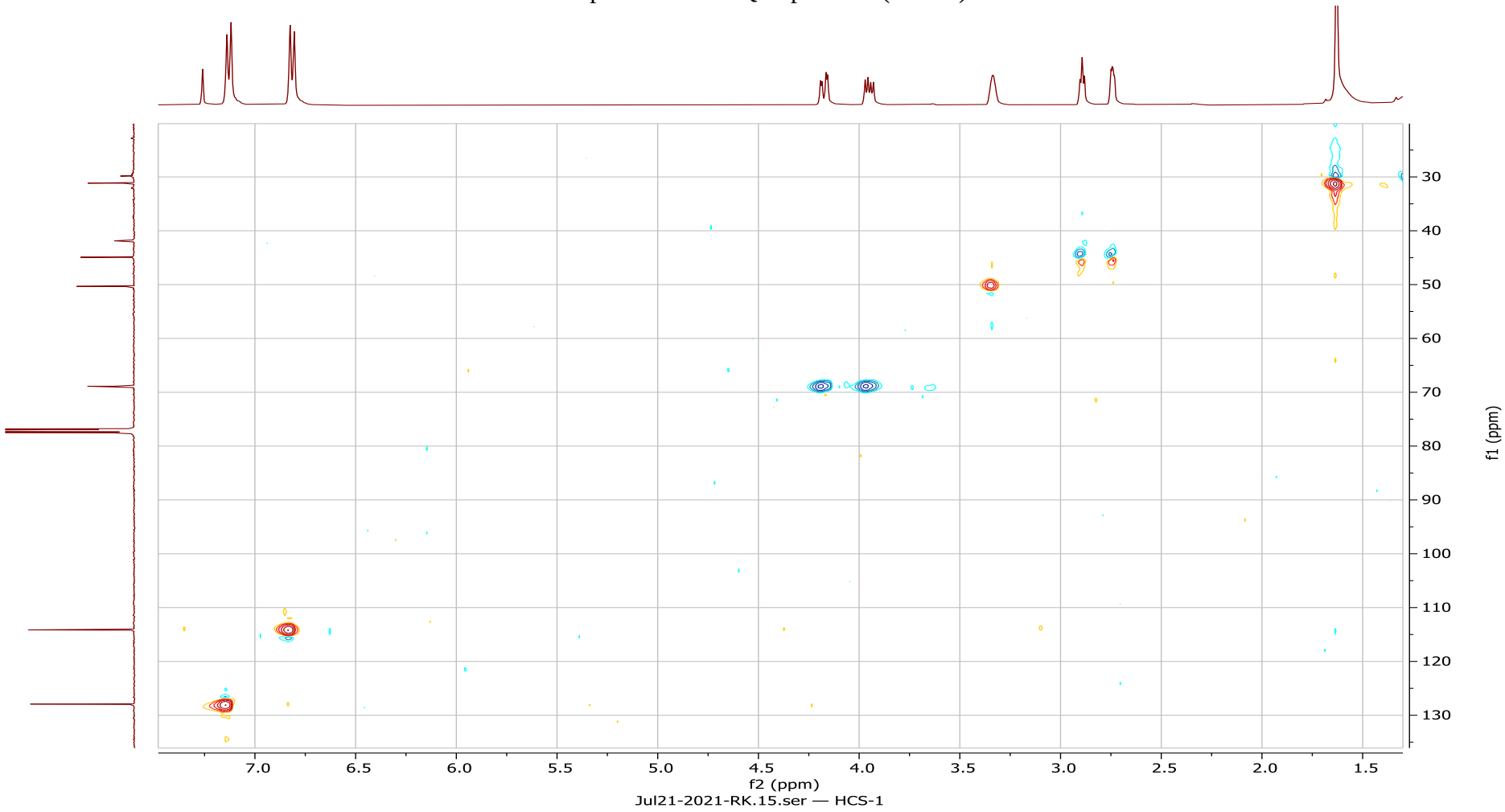
Compound **259** ^{13}C NMR spectrum ($CDCl_3$, 100 MHz)



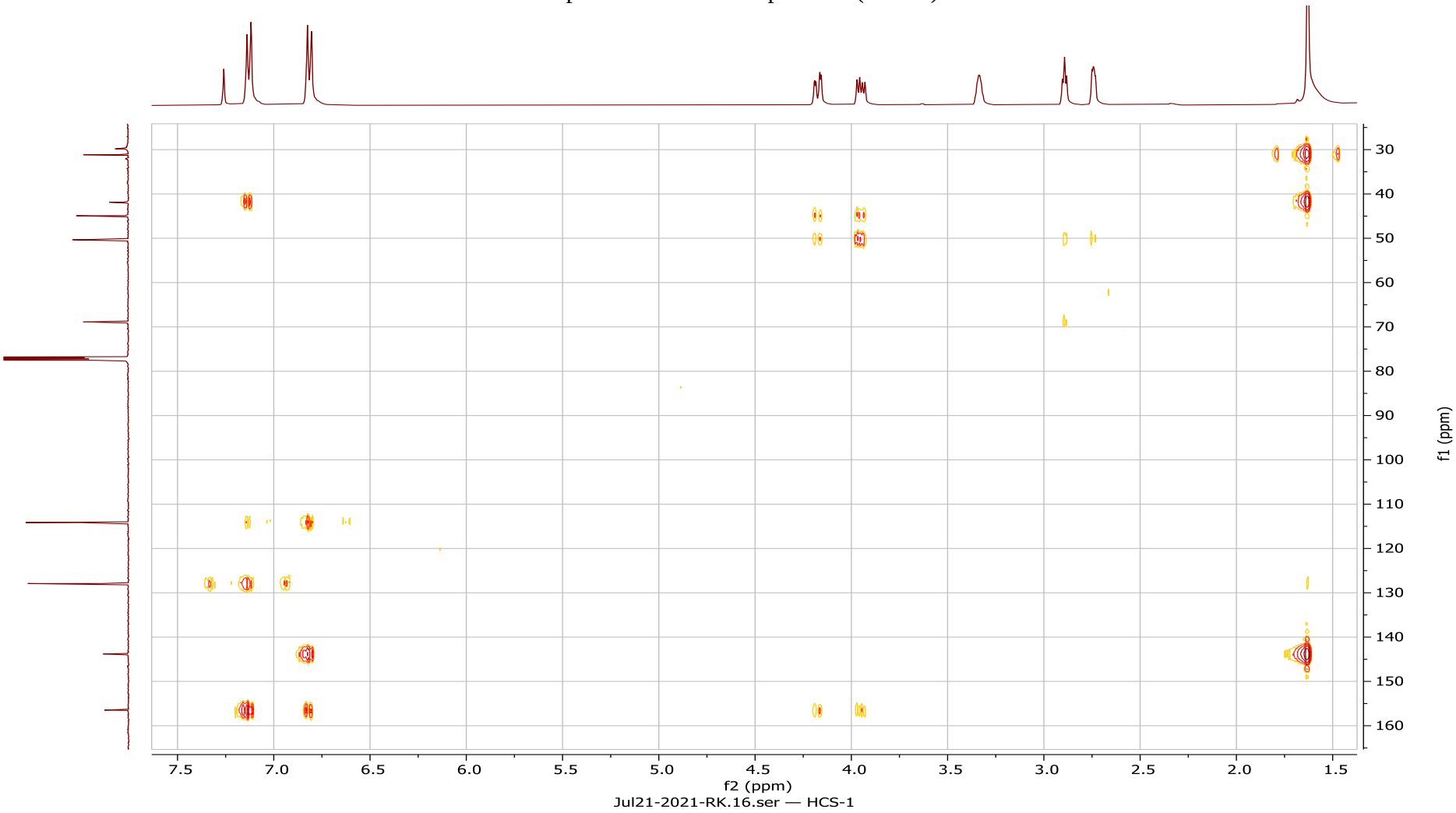
Compound **259** ^{1}H-^{1}H COSY spectrum ($CDCl_3$)



Compound **259** HSQC spectrum ($CDCl_3$)

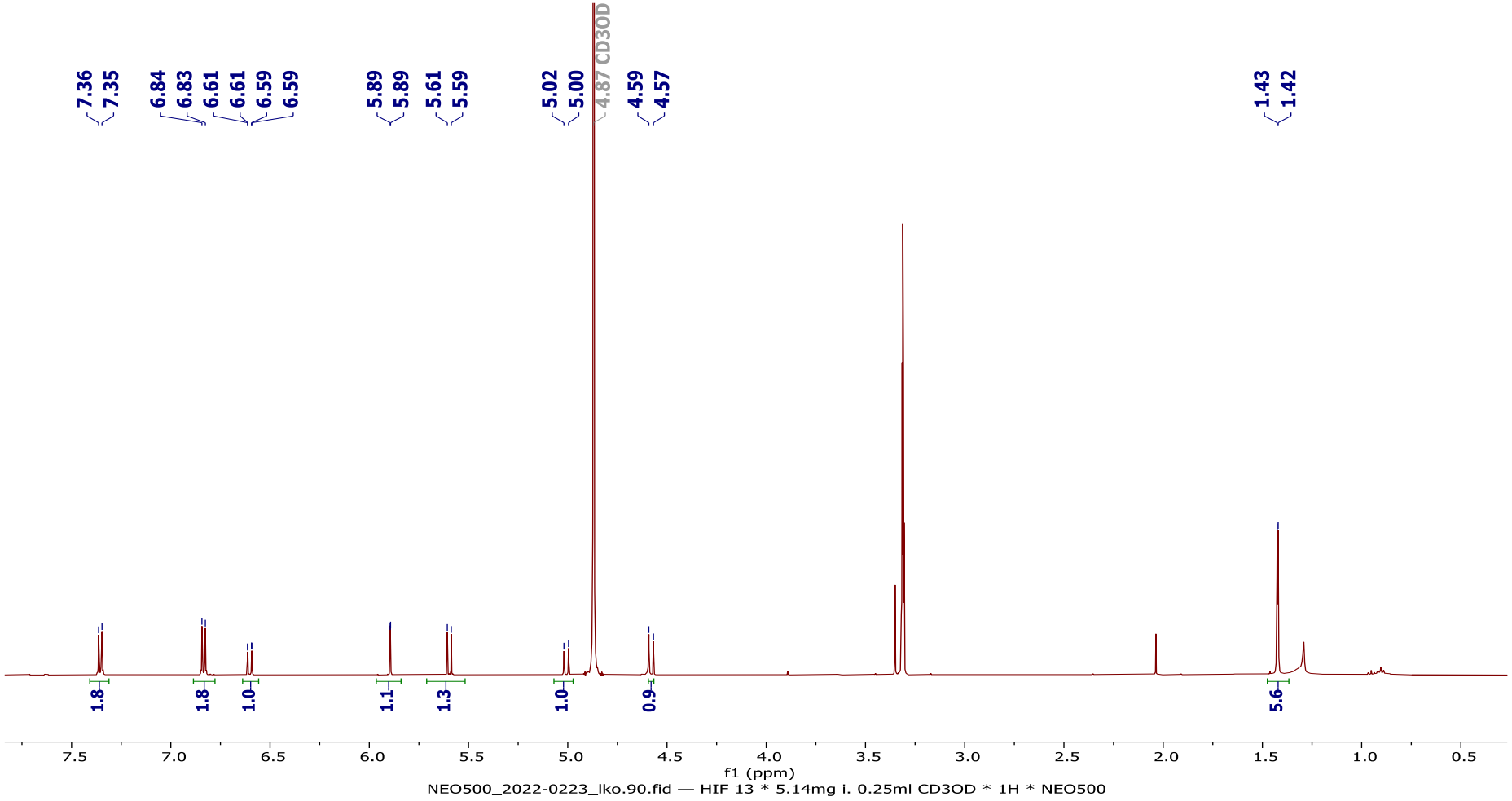


Compound **259** HMBC spectrum ($CDCl_3$)

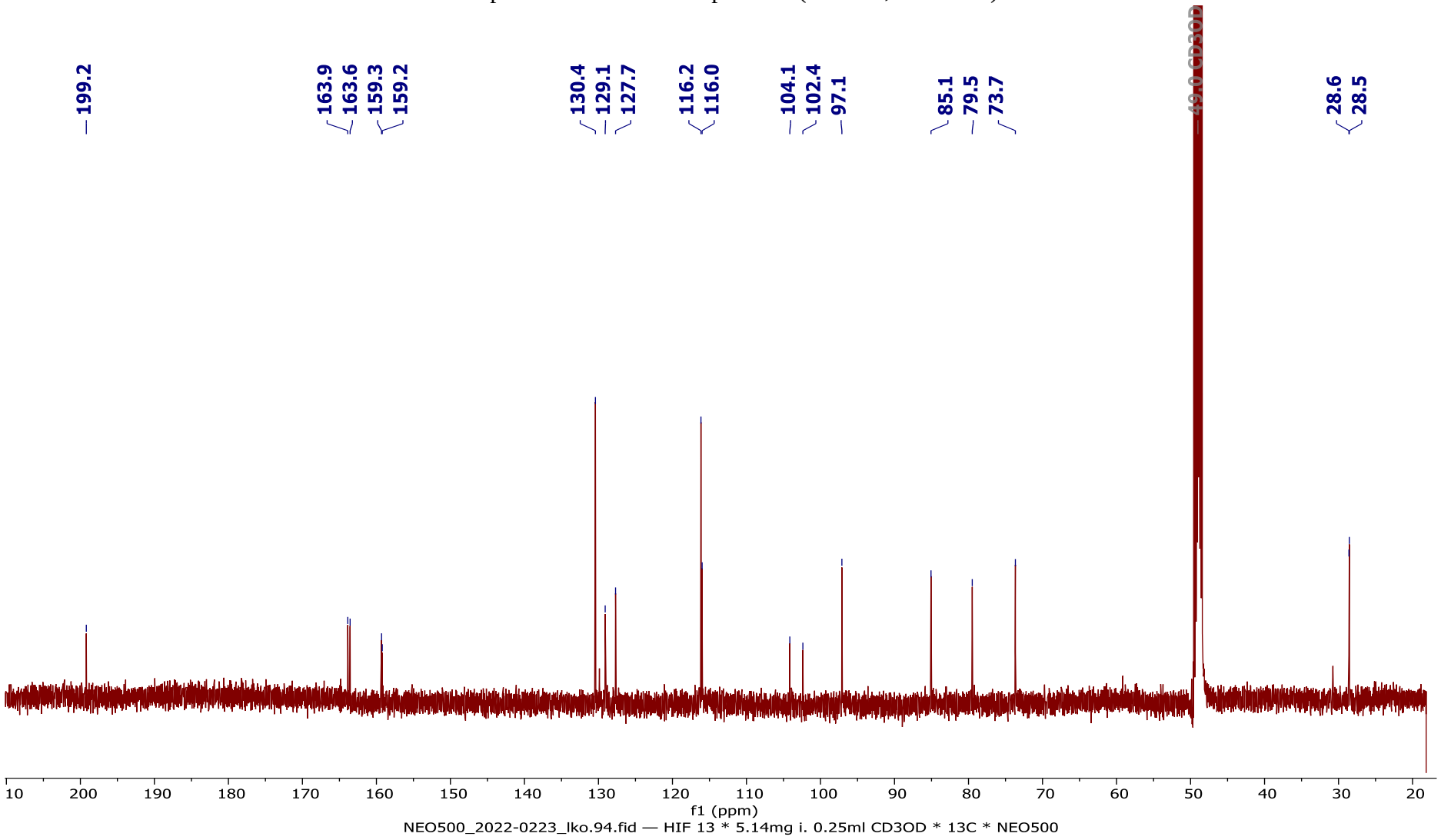


Appendix 15: Spectra of yukovanol (**260**)

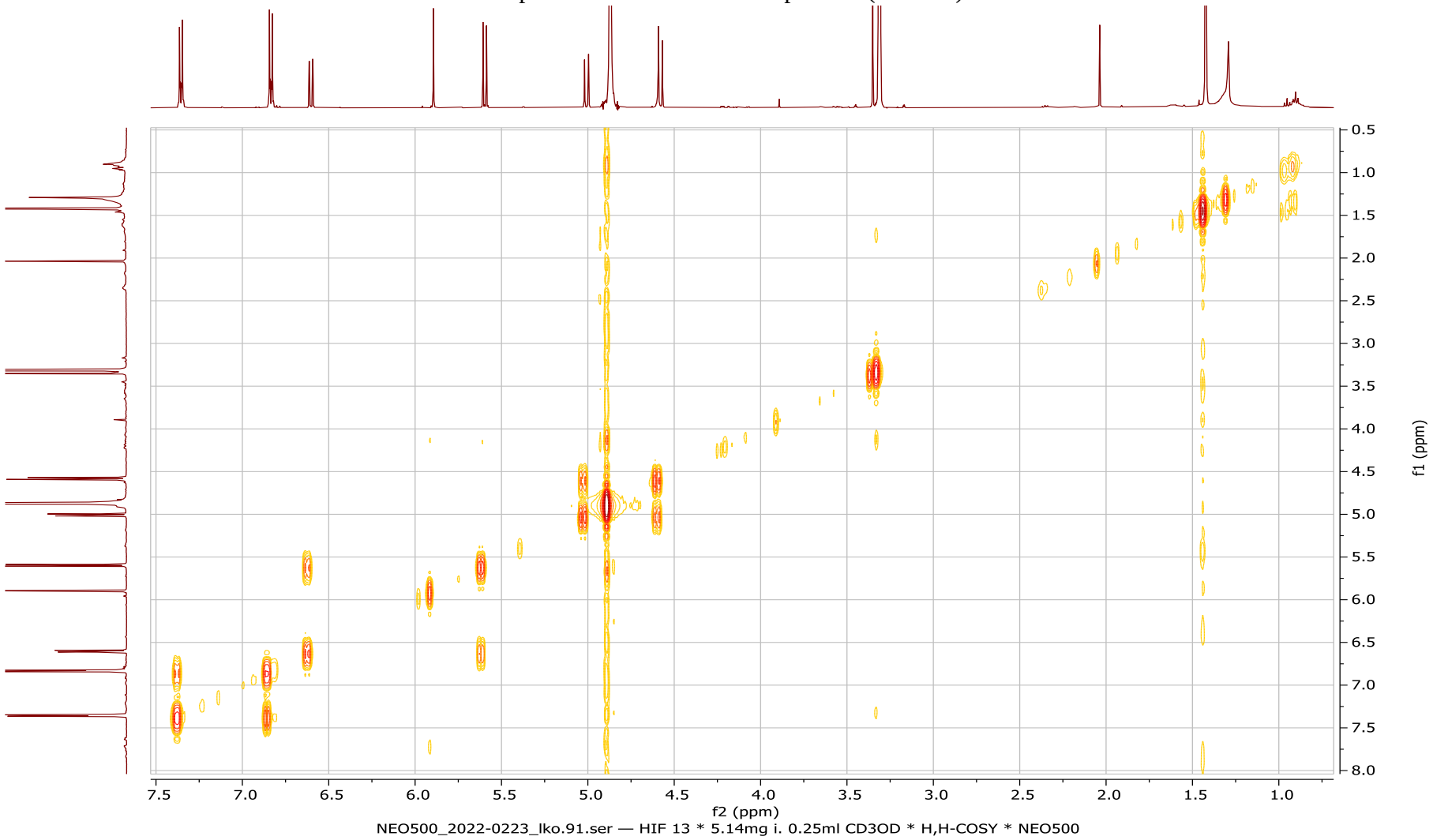
Compound **260** ^{1}H NMR spectrum (CD_3OD, 500 MHz)



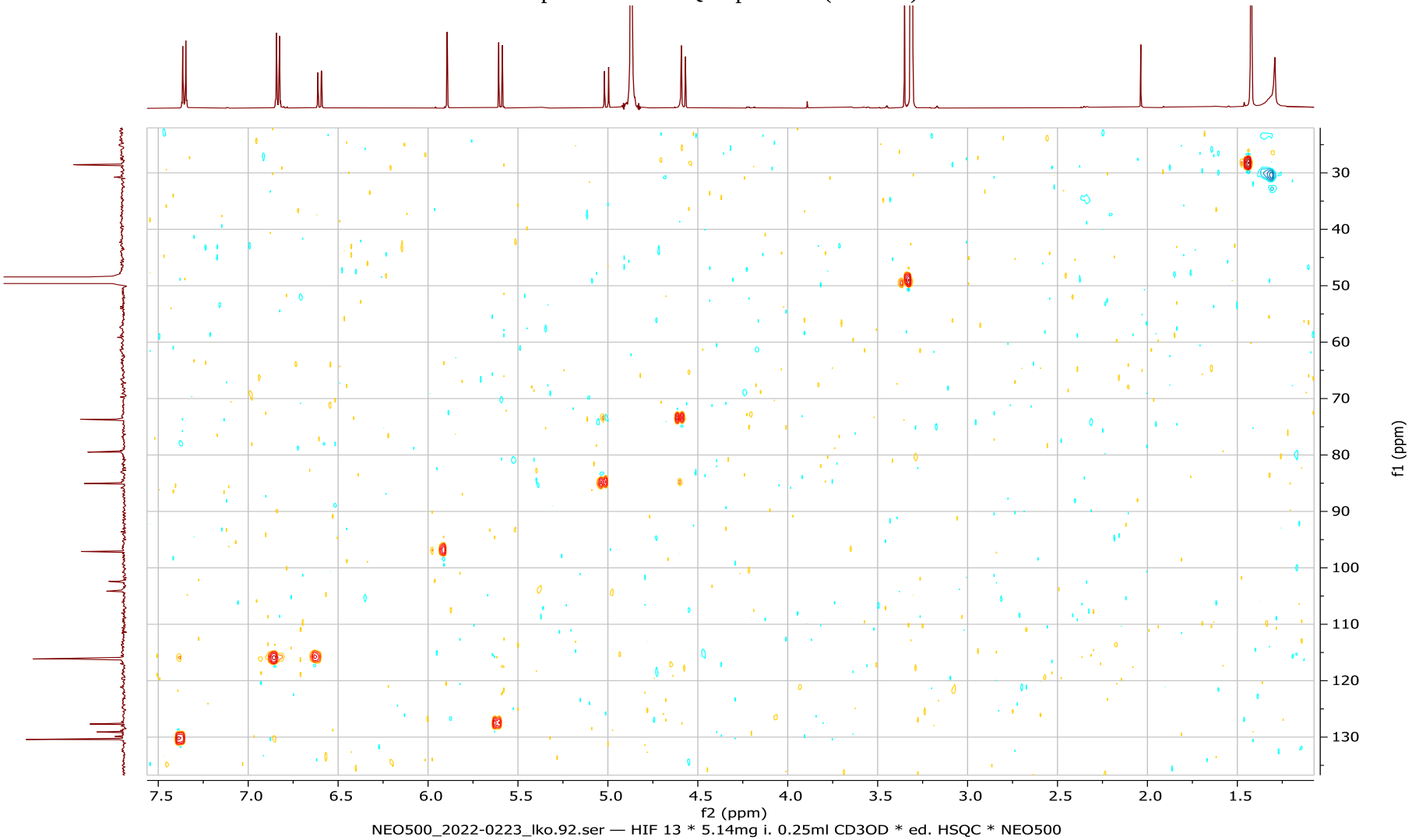
Compound **260** ^{13}C NMR spectrum (CD_3OD, 125 MHz)



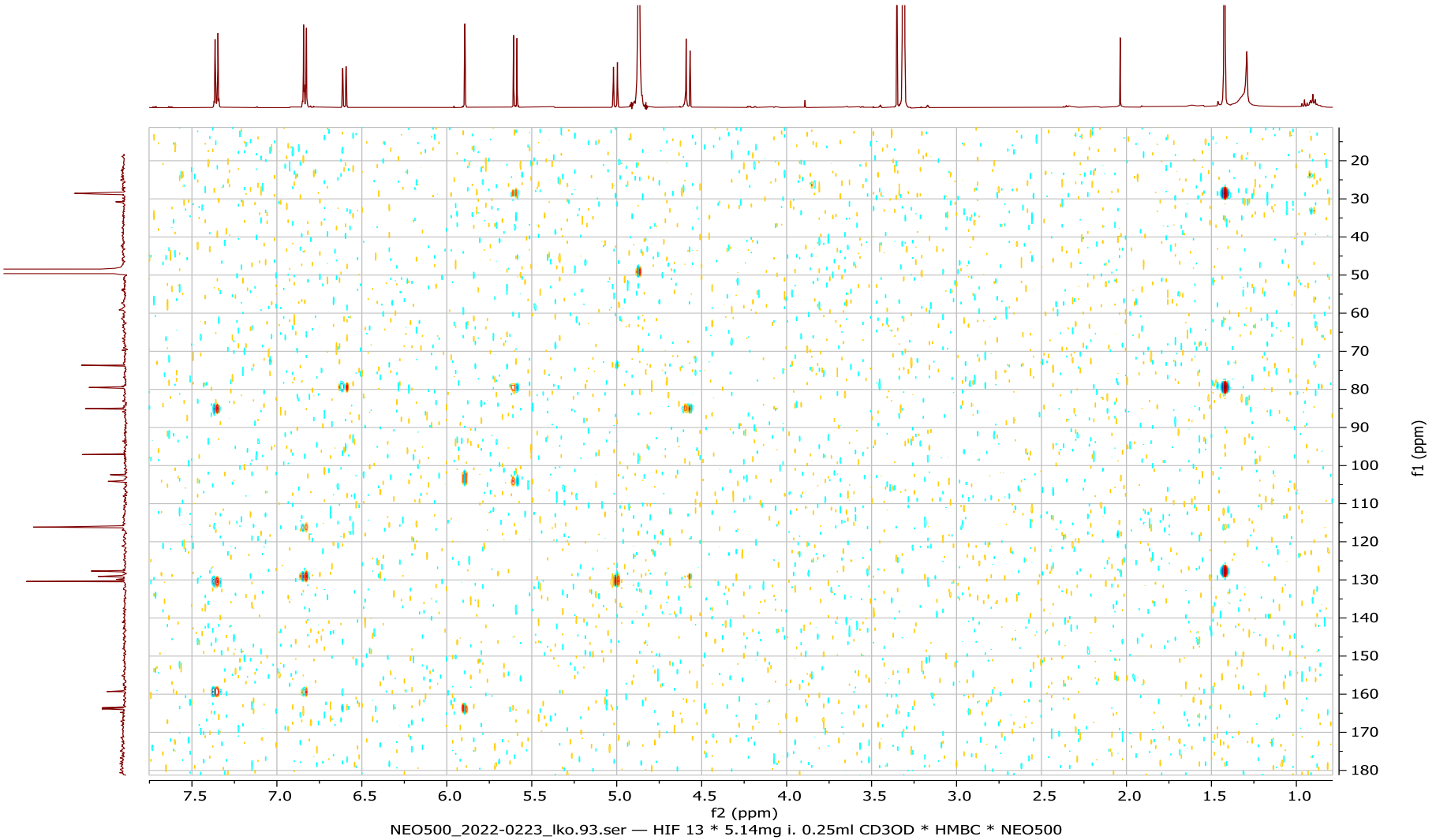
Compound **260** ^{1}H-^{1}H COSY spectrum(CD_3OD)



Compound **260** HSQC spectrum (CD_3OD)

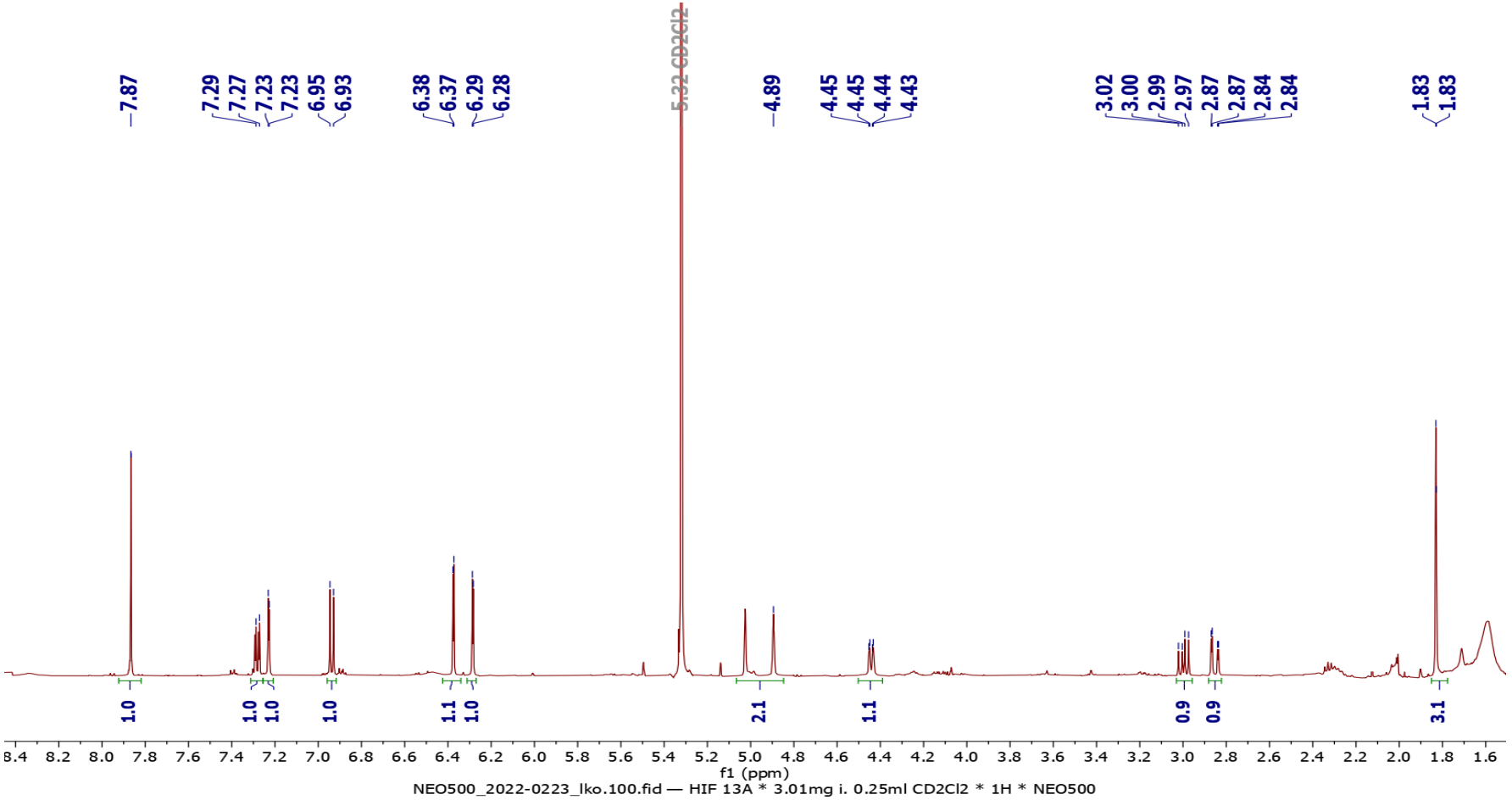


Compound **260** HMBC spectrum (CD_3OD)

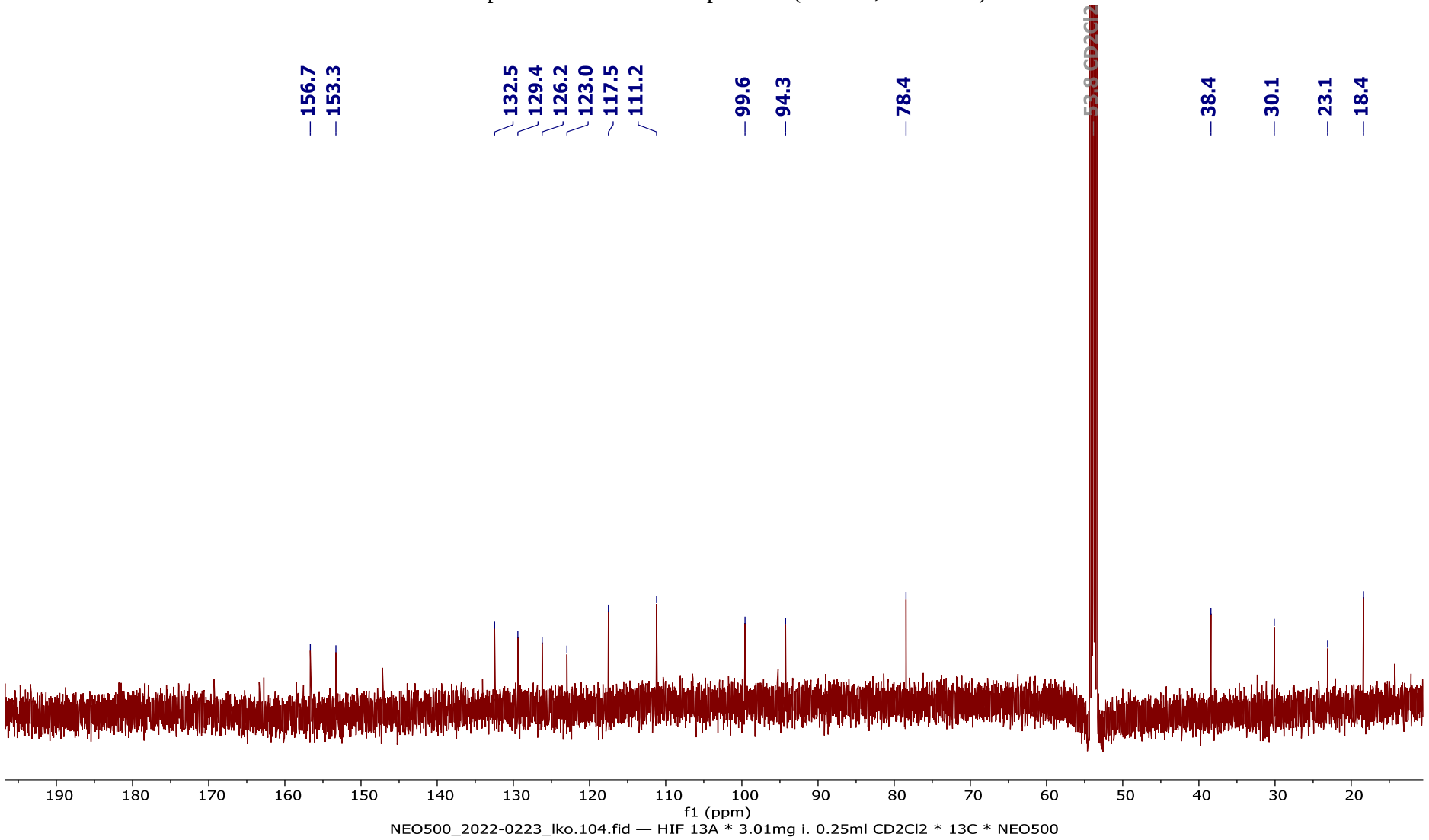


Appendix 16: Spectra of 5,7,4′-trihydroxy-3′-(2-hydroxy-3-methoxy-3butenyl)isoflavone (**261**)

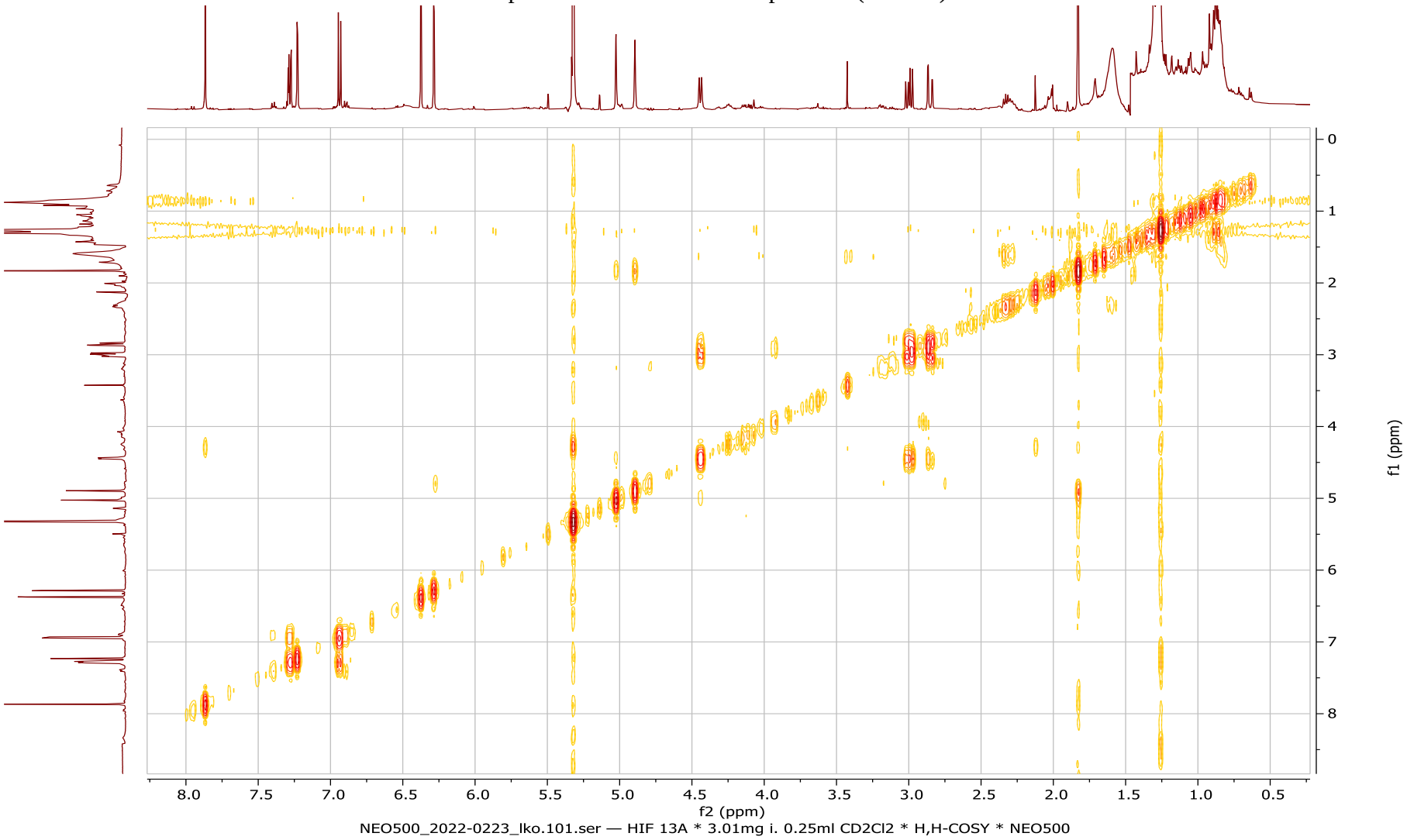
Compound **261** ^{1}H NMR spectrum (CD_2Cl_2, 500 MHz)



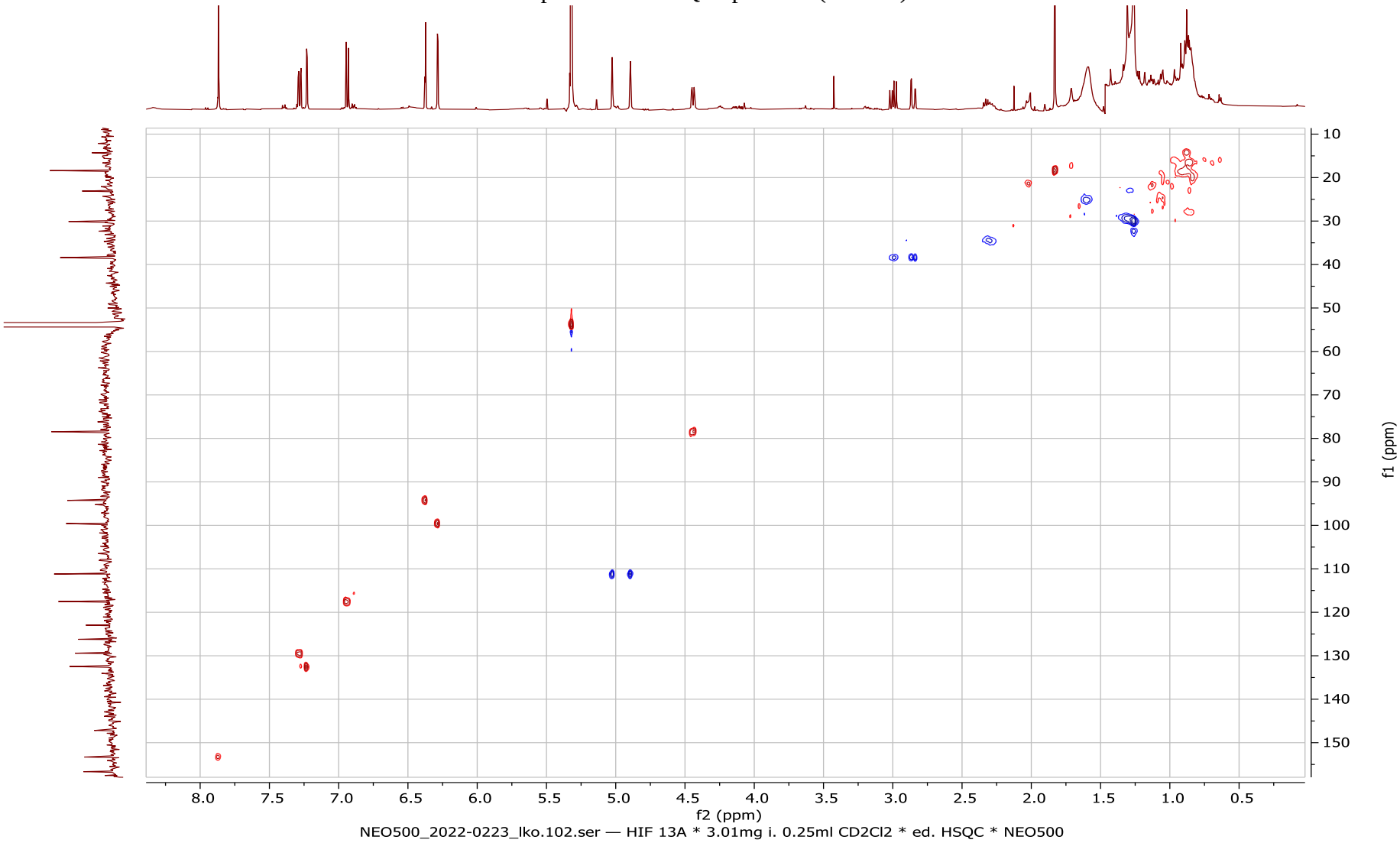
Compound **261** ^{13}C NMR spectrum (CD_2Cl_2, 125 MHz)



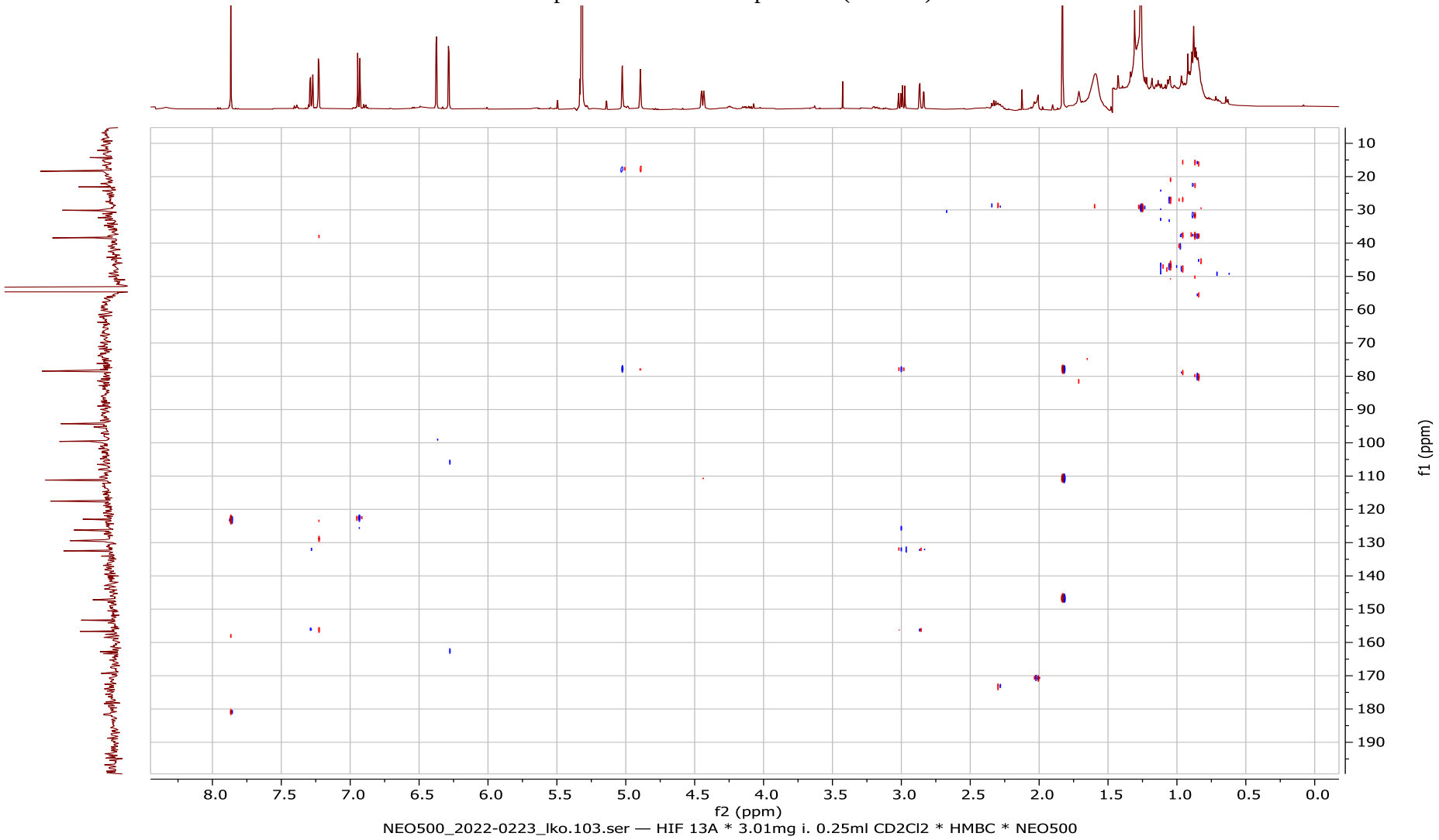
Compound **261** ^{1}H-^{1}H COSY spectrum (CD_2Cl_2)



Compound **261** HSQC spectrum (CD_2Cl_2)

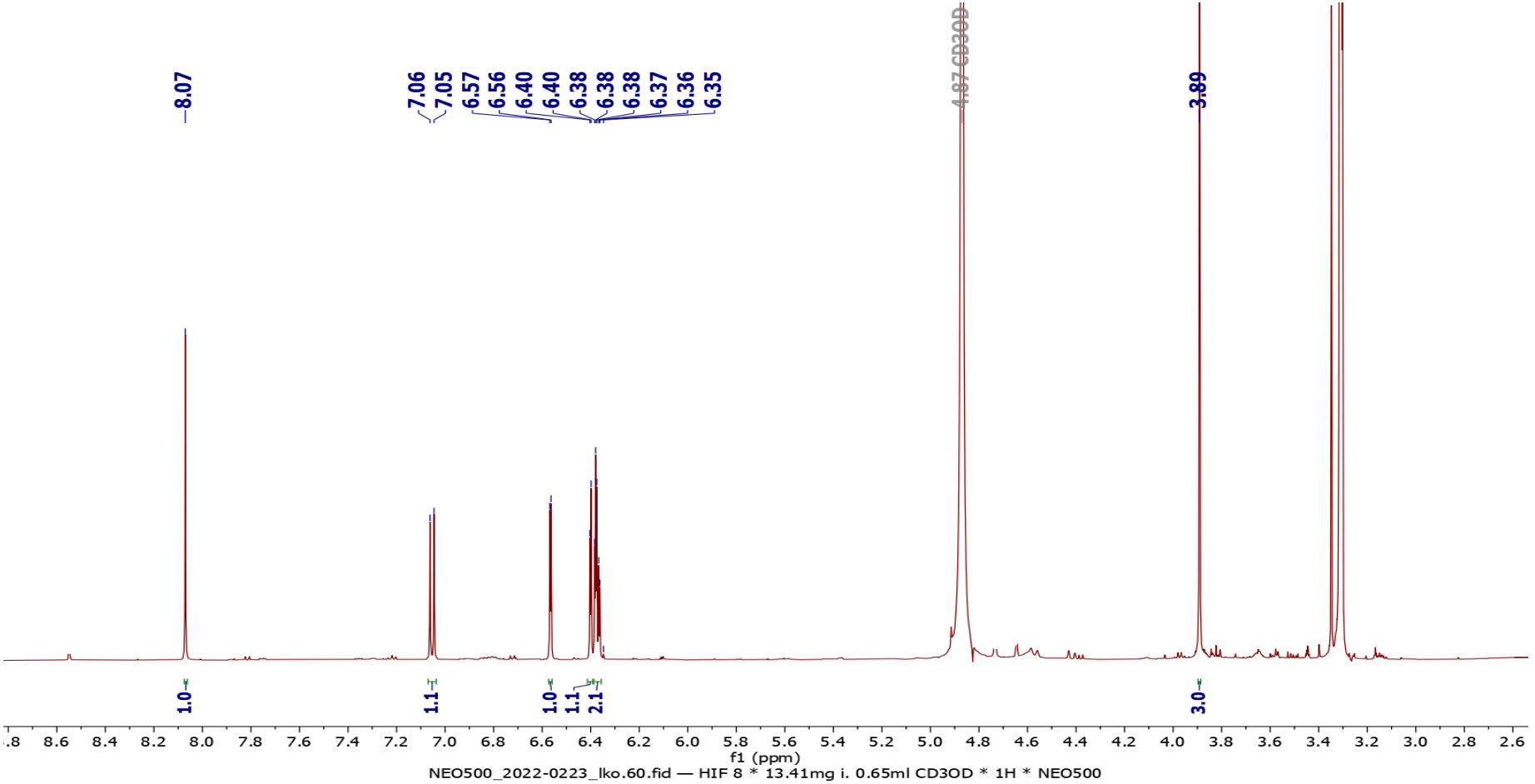


Compound **261** HMBC spectrum (CD_2Cl_2)

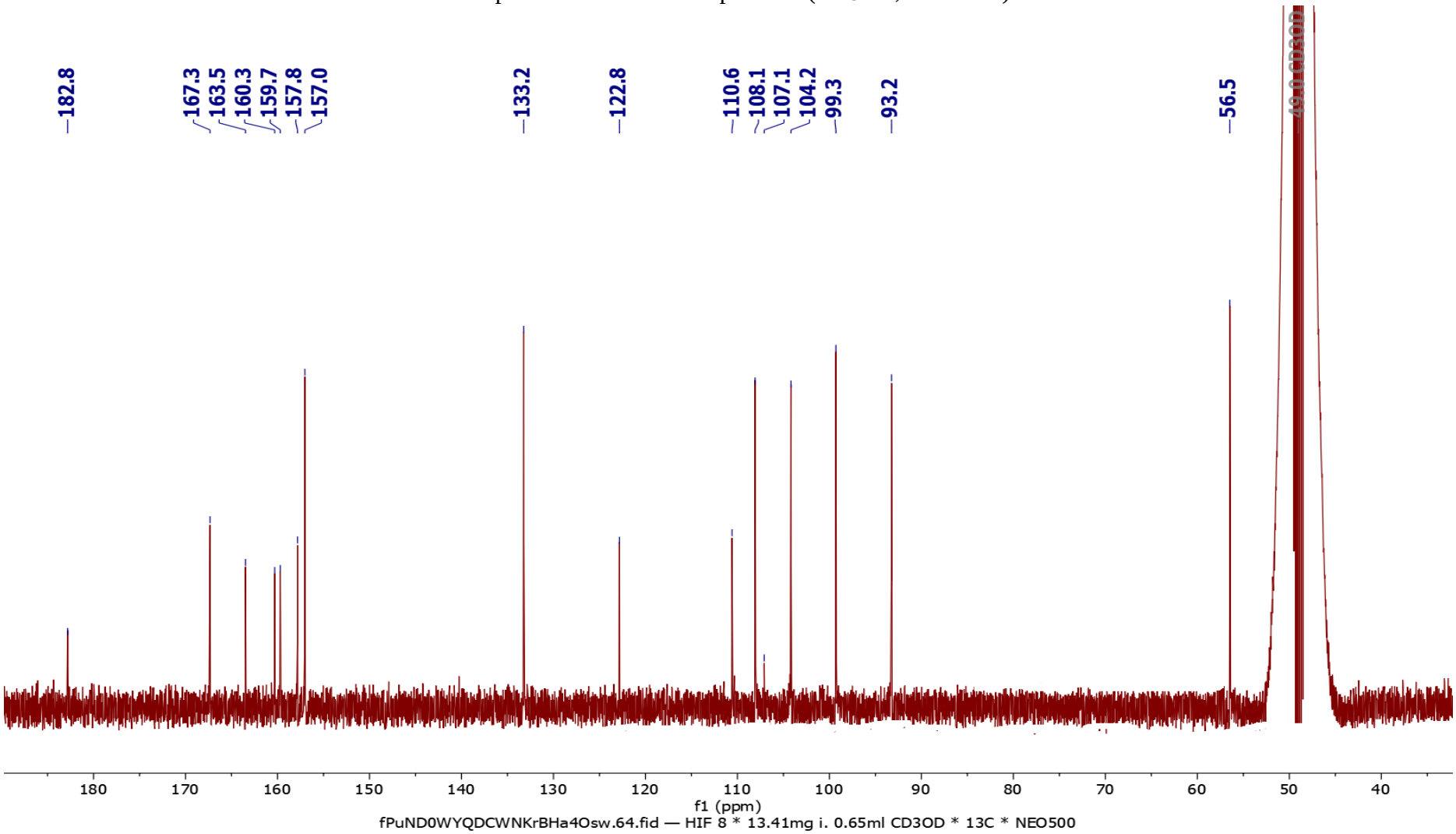


Appendix 17: Spectra of cajanin (**262**)

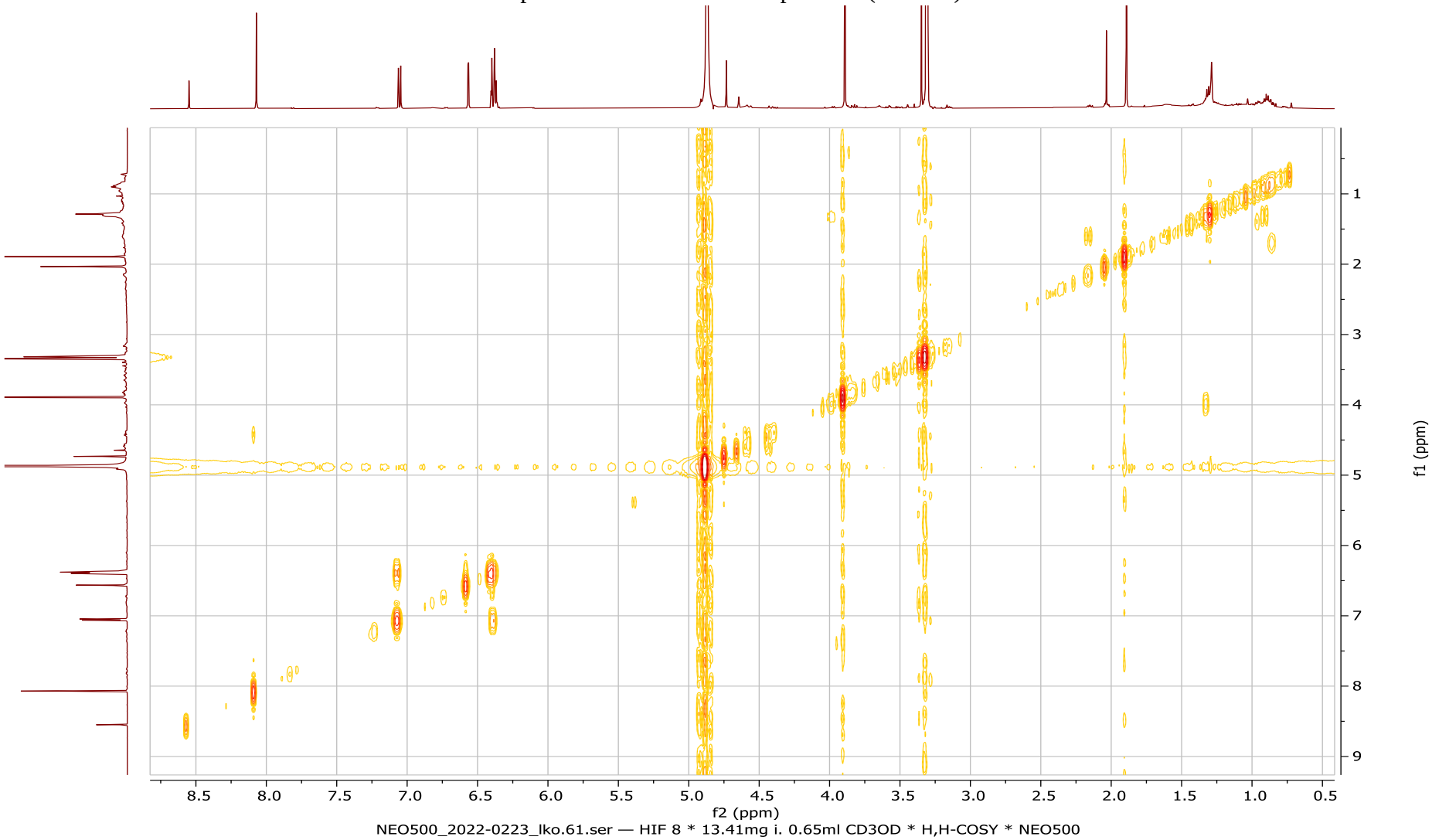
Compound **262** ^{1}H NMR spectrum (CD_3OD, 500 MHz)



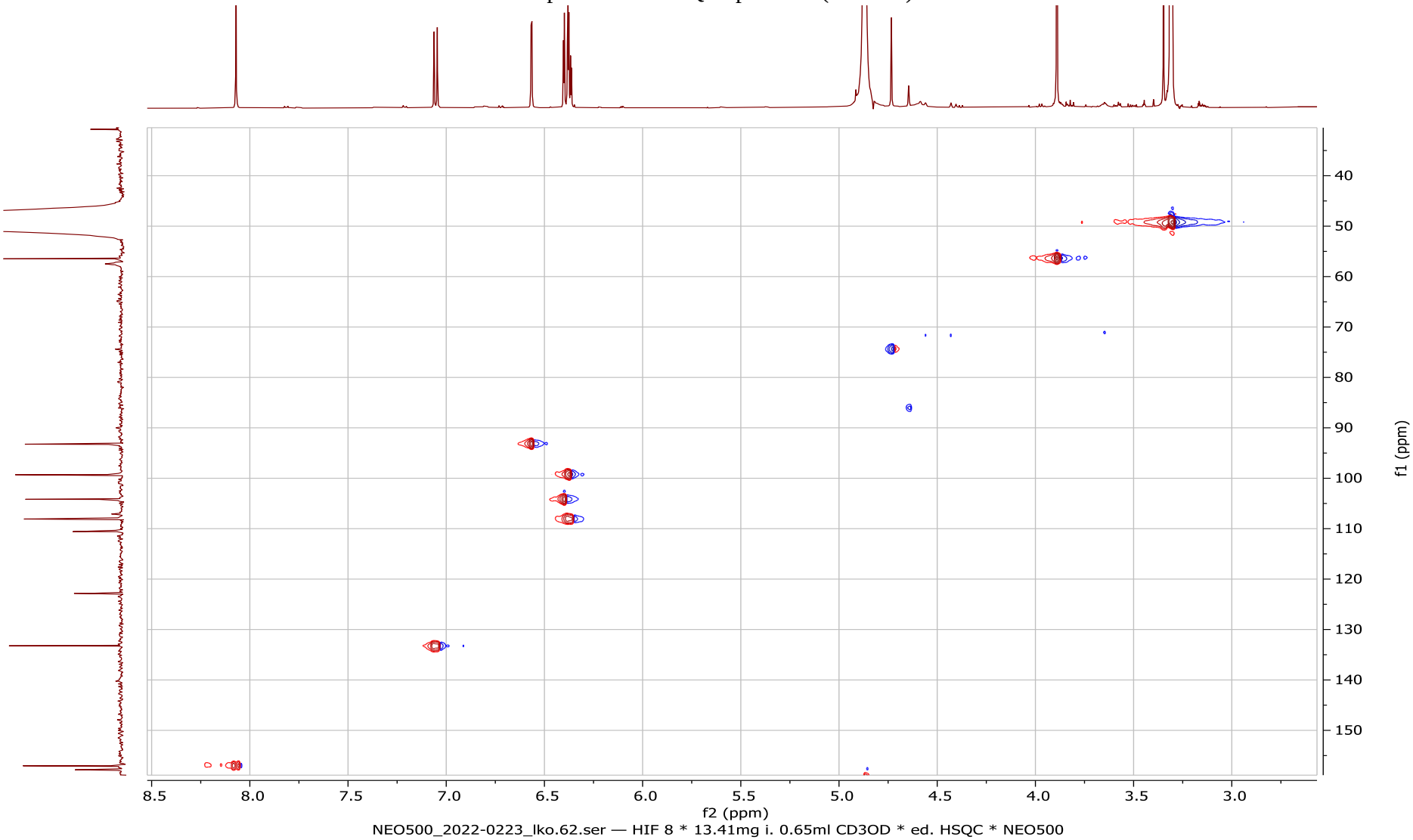
Compound **262** ^{13}C NMR spectrum (CD_3OD, 125 MHz)



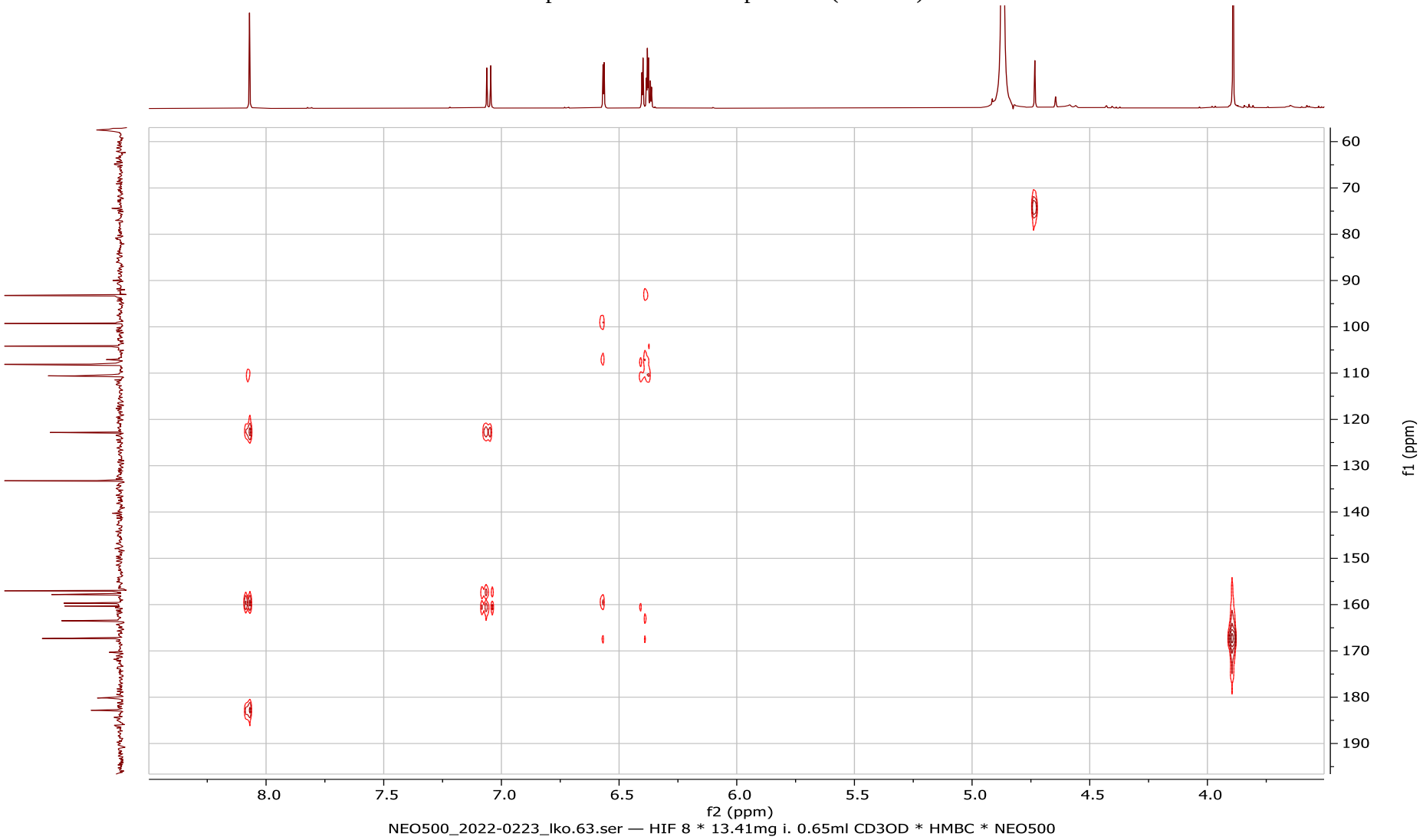
Compound **262** ^{1}H-^{1}H COSY spectrum (CD_3OD)



Compound **262** HSQC spectrum (CD_3OD)

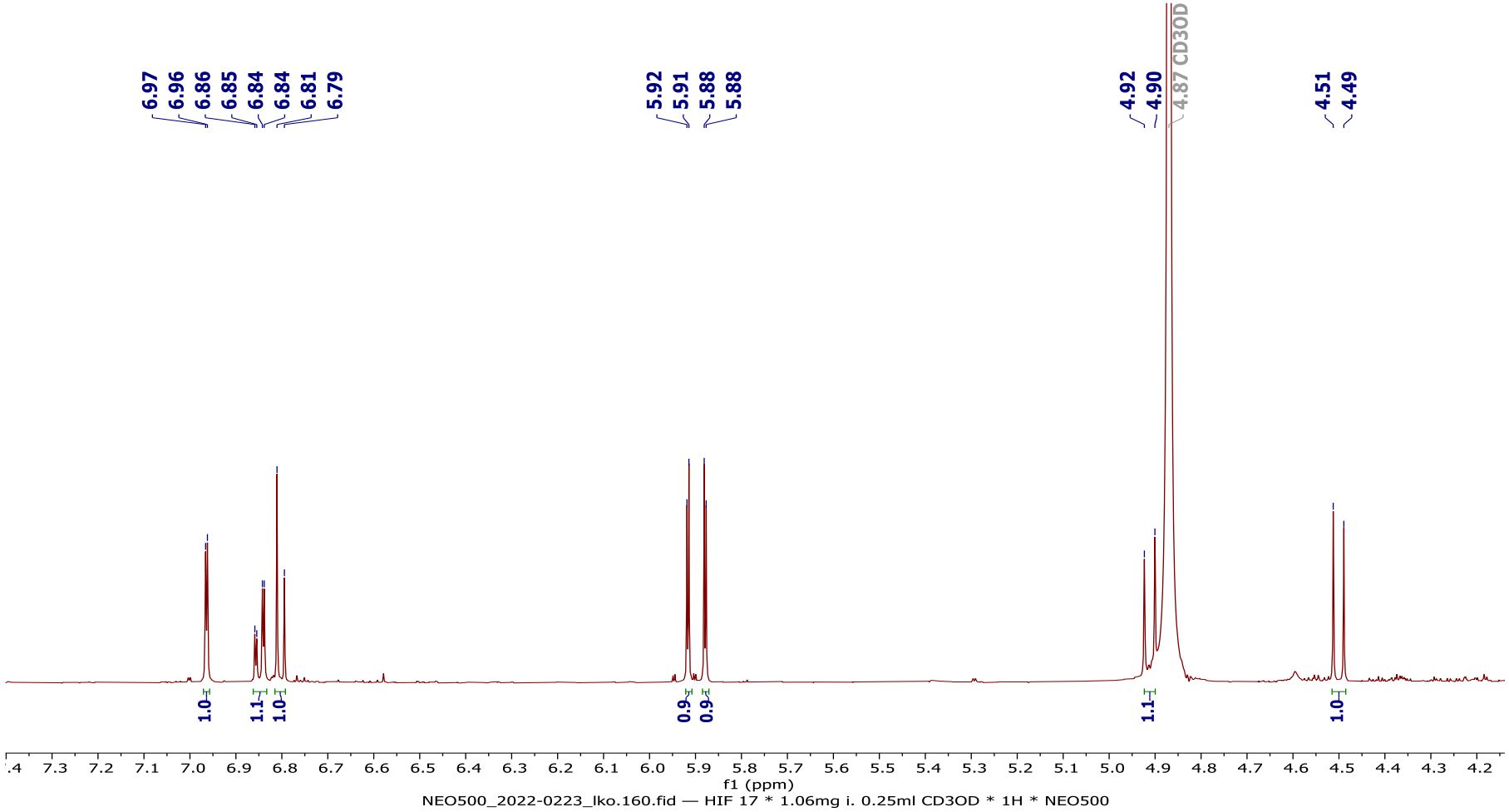


Compound **262** HMBC spectrum (CD_3OD)

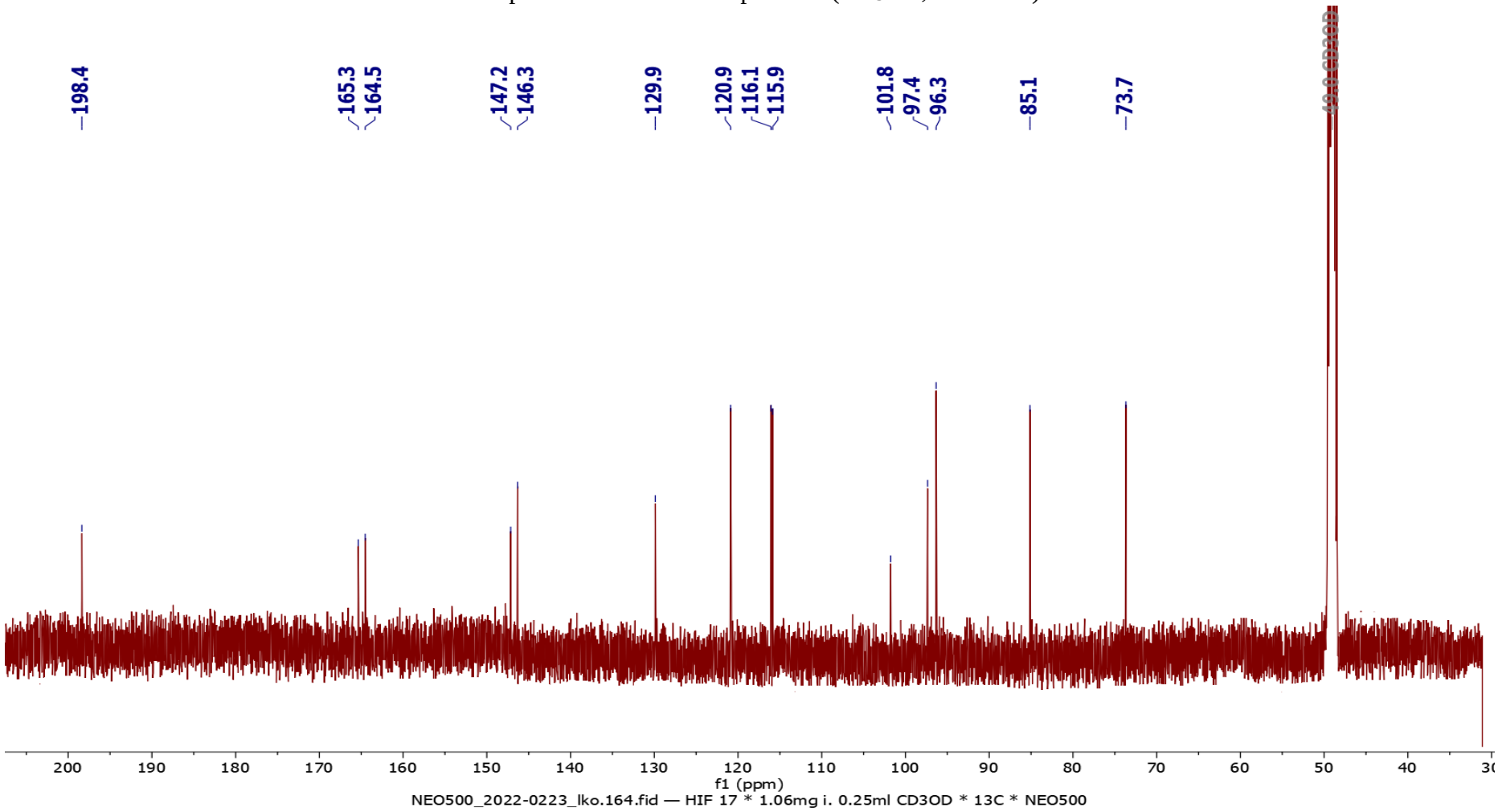


Appendix 18: Spectra of taxifolin (**263**)

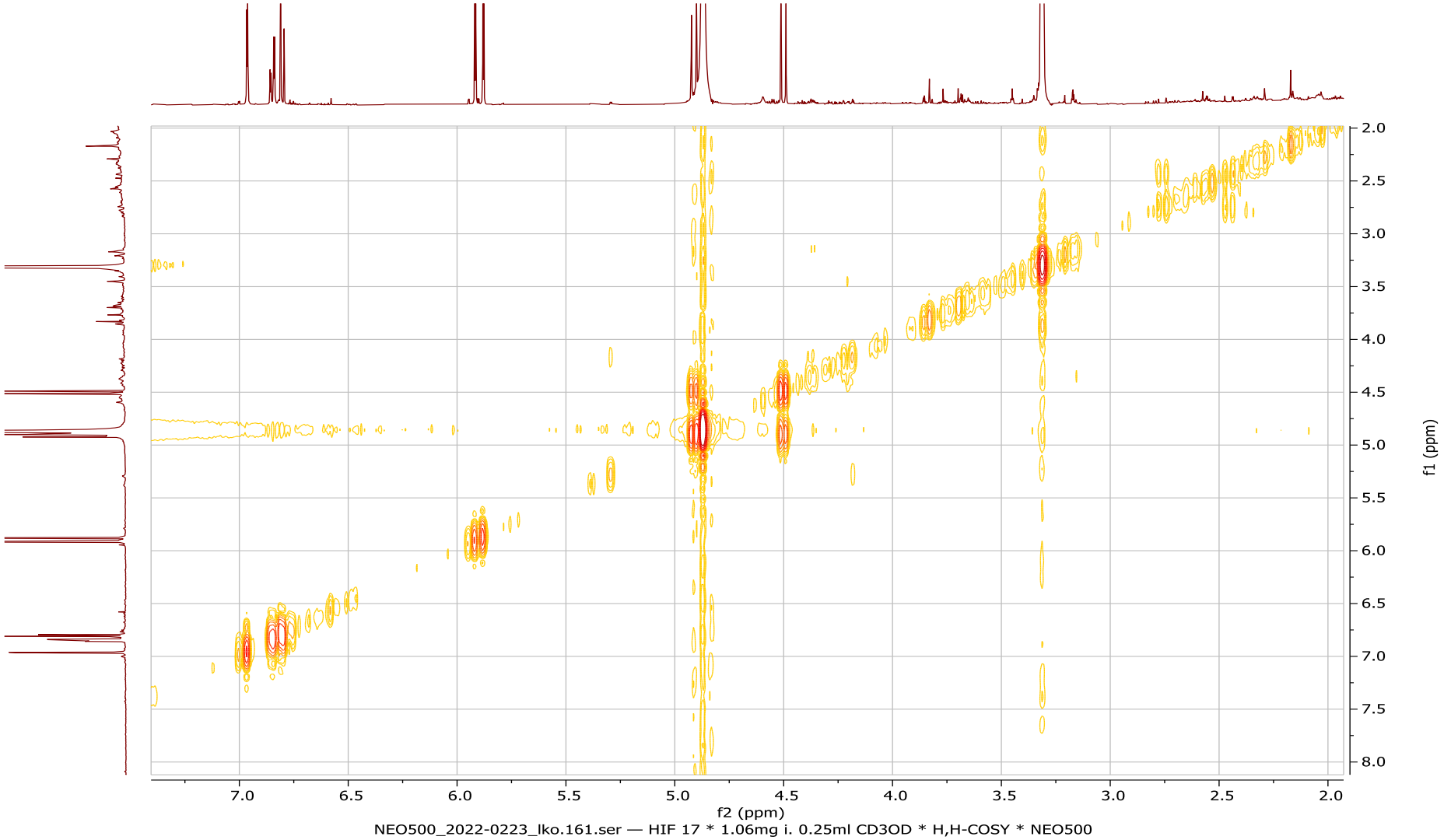
Compound **263** ^{1}H NMR spectrum (CD_3OD, 500 MHz)



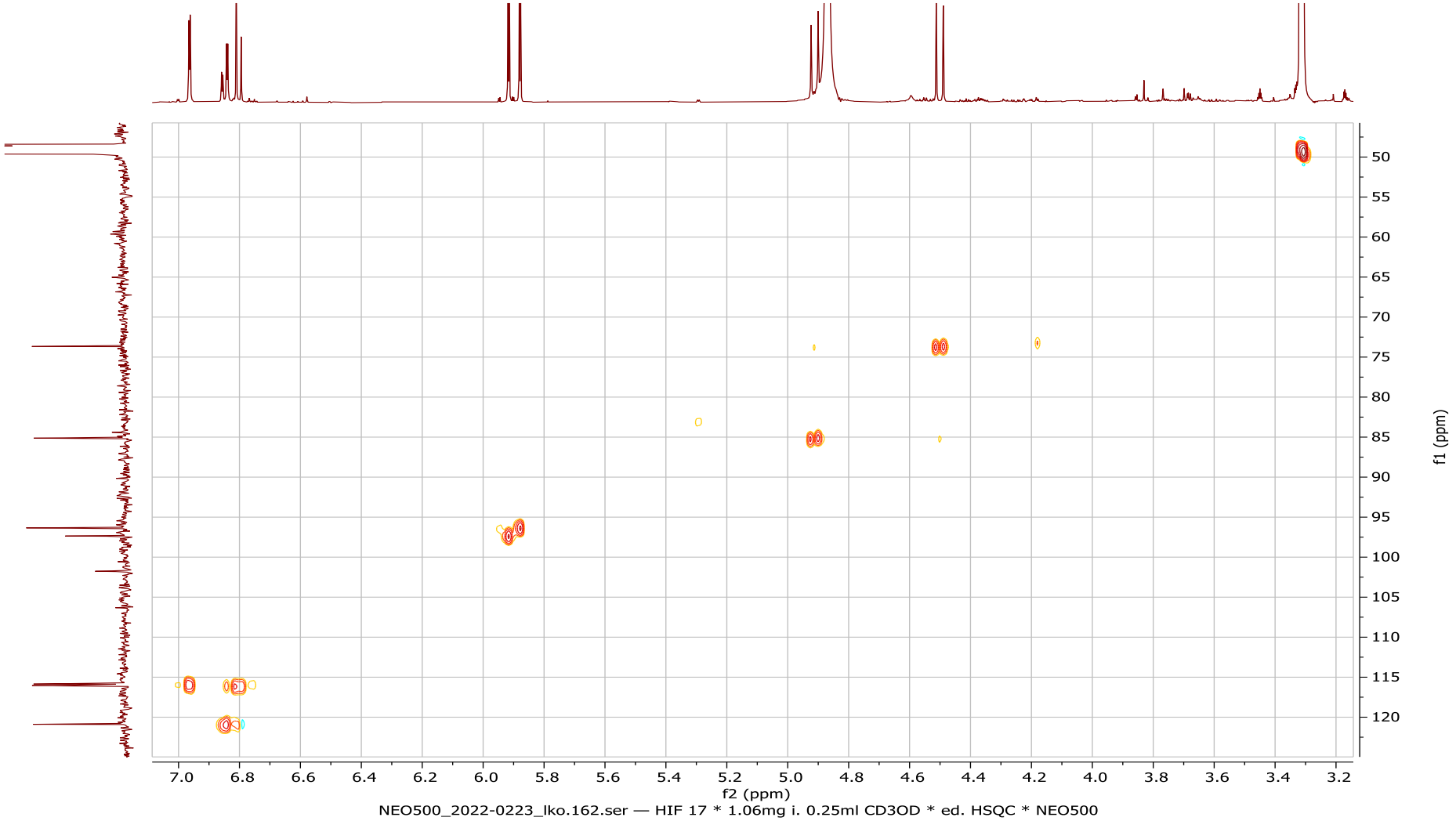
Compound **263** ^{13}C NMR spectrum (CD_3OD, 125 MHz)



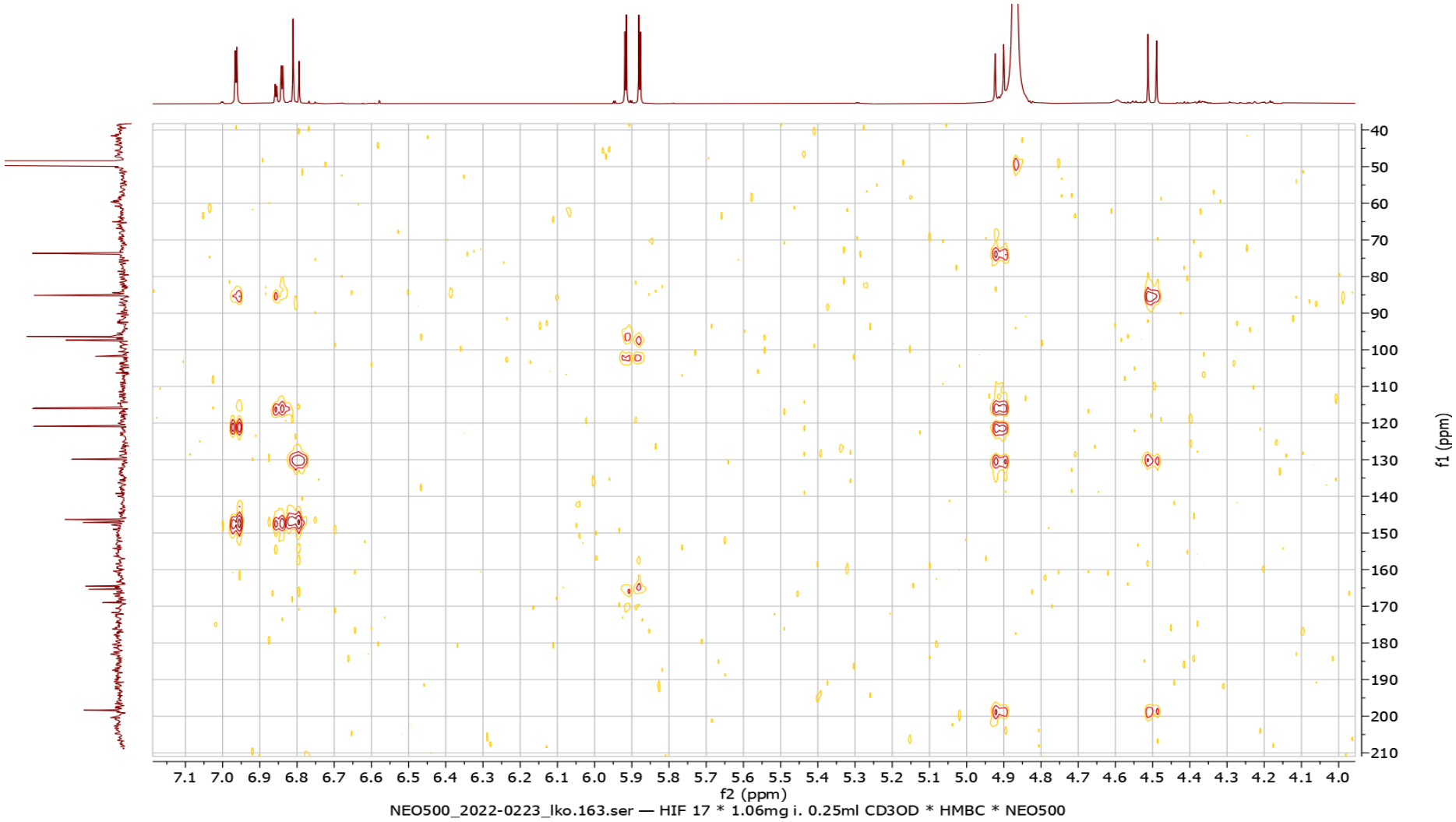
Compound **263** ^{1}H-^{1}H COSY spectrum (CD_3OD)



Compound **263** HSQC spectrum (CD_3OD)

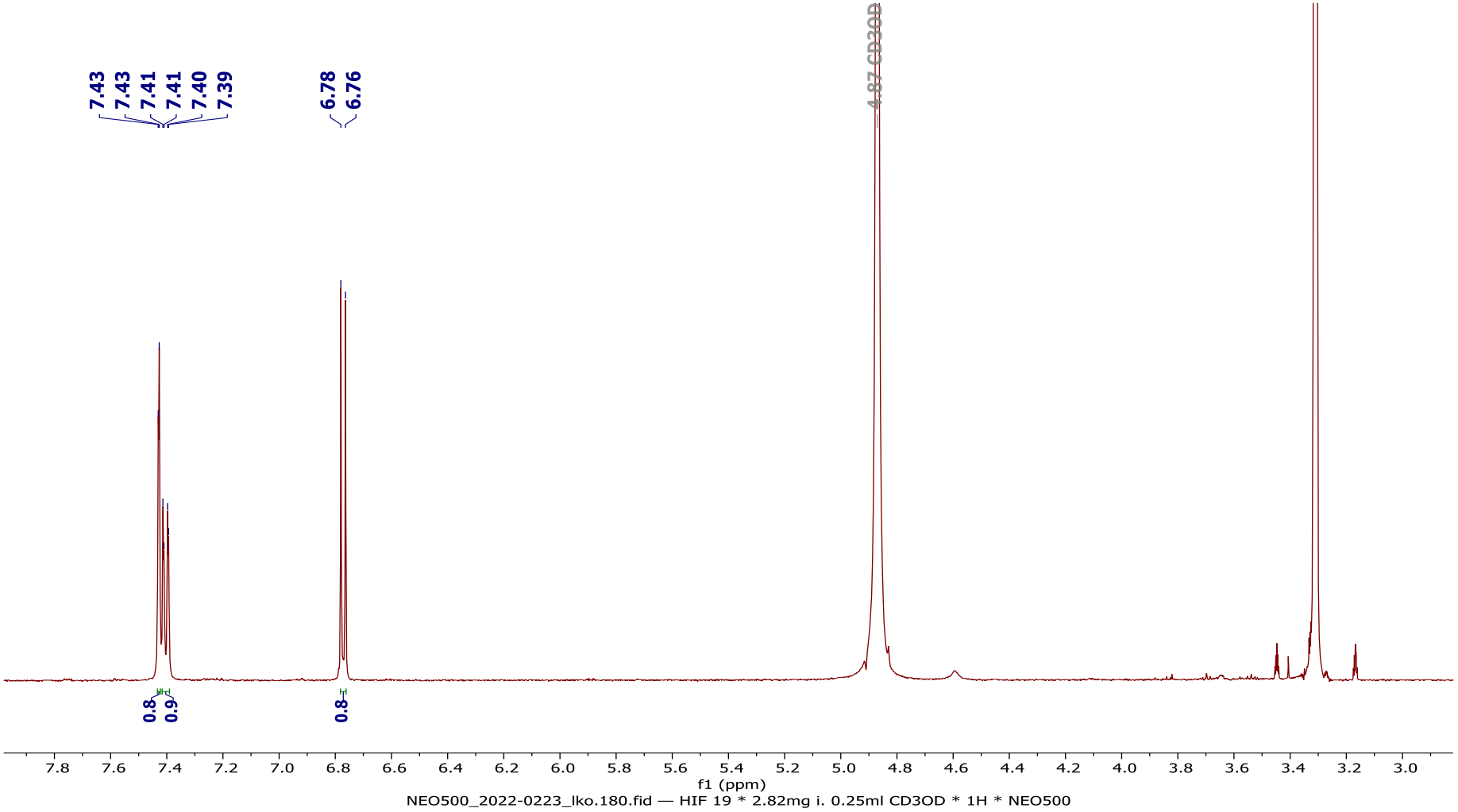


Compound **263** HMBC spectrum (CD_3OD)

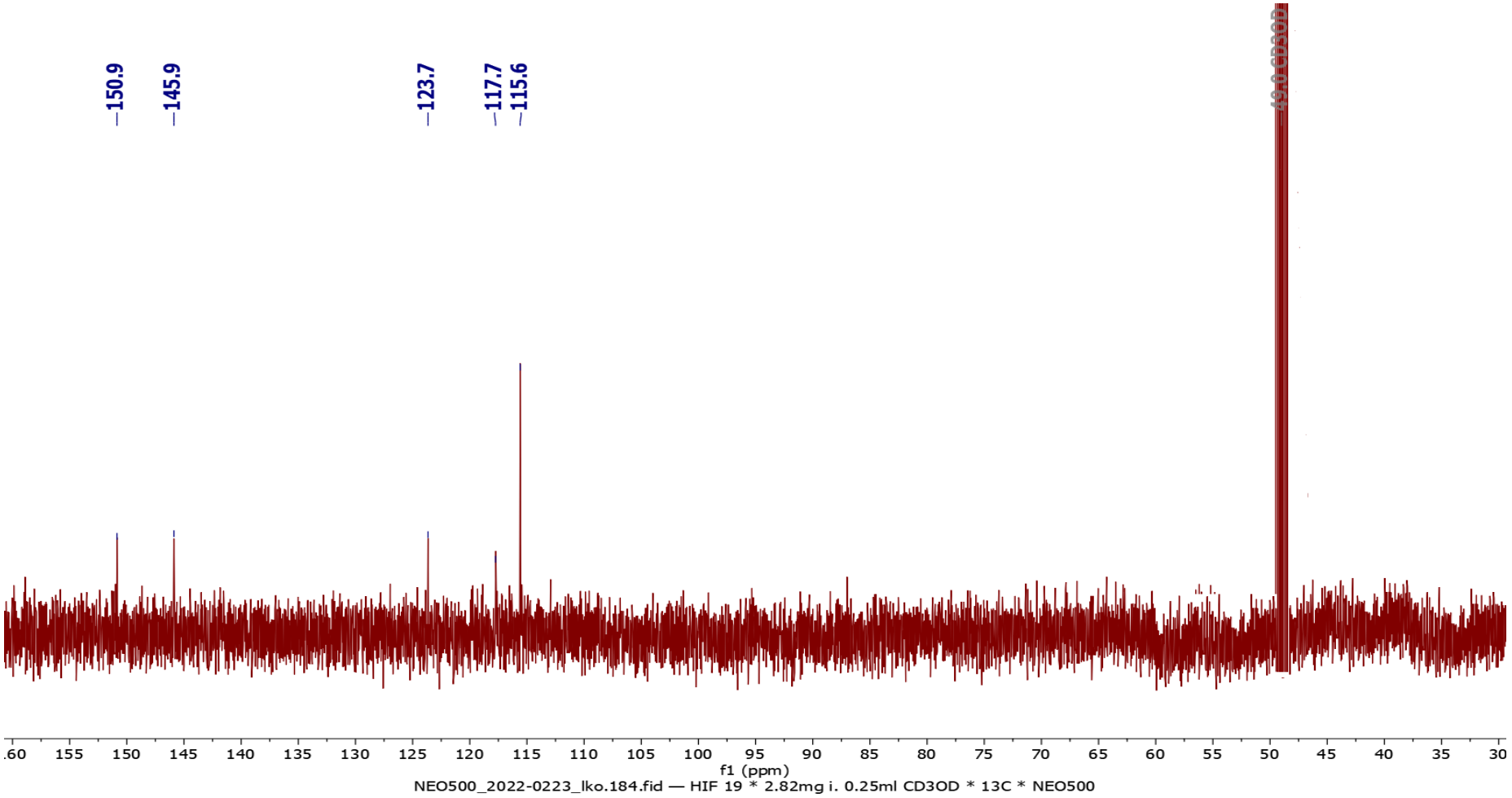


Appendix 19: Spectra of protocateuchuic acid (**264**)

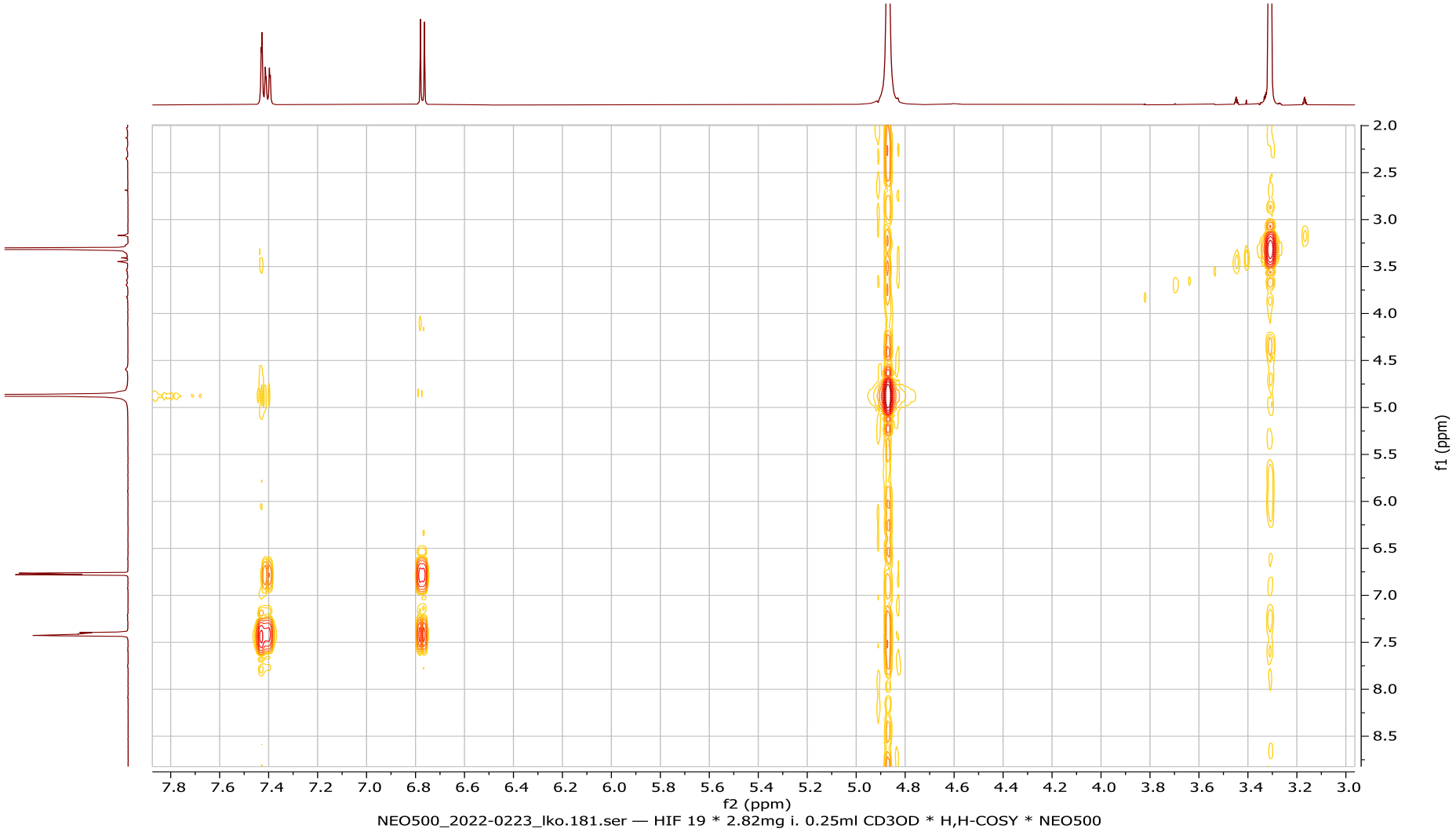
Compound **264** ^{1}H NMR spectrum (CD_3OD, 500 MHz)



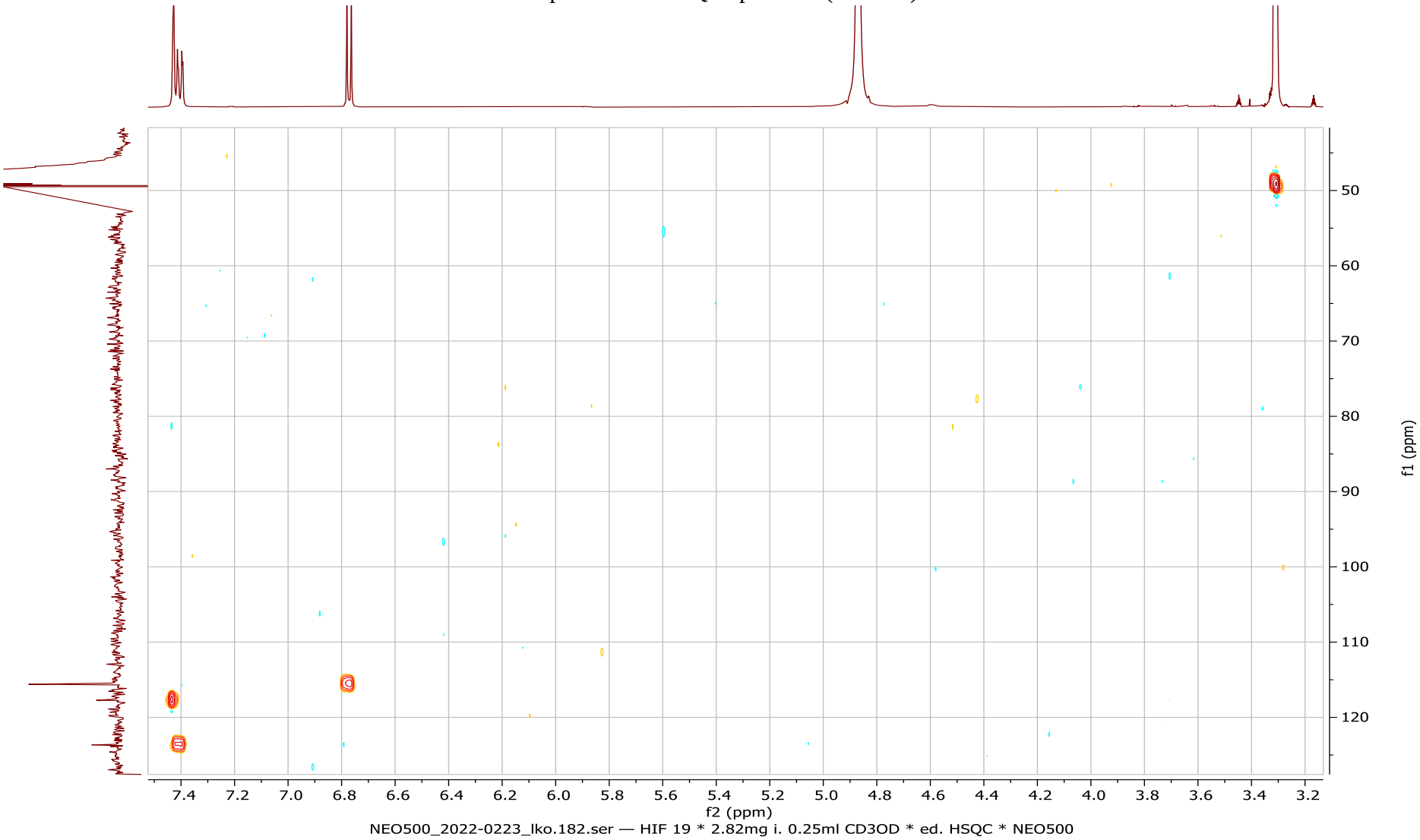
Compound **264** ^{13}C NMR spectrum (CD_3OD, 125 MHz)



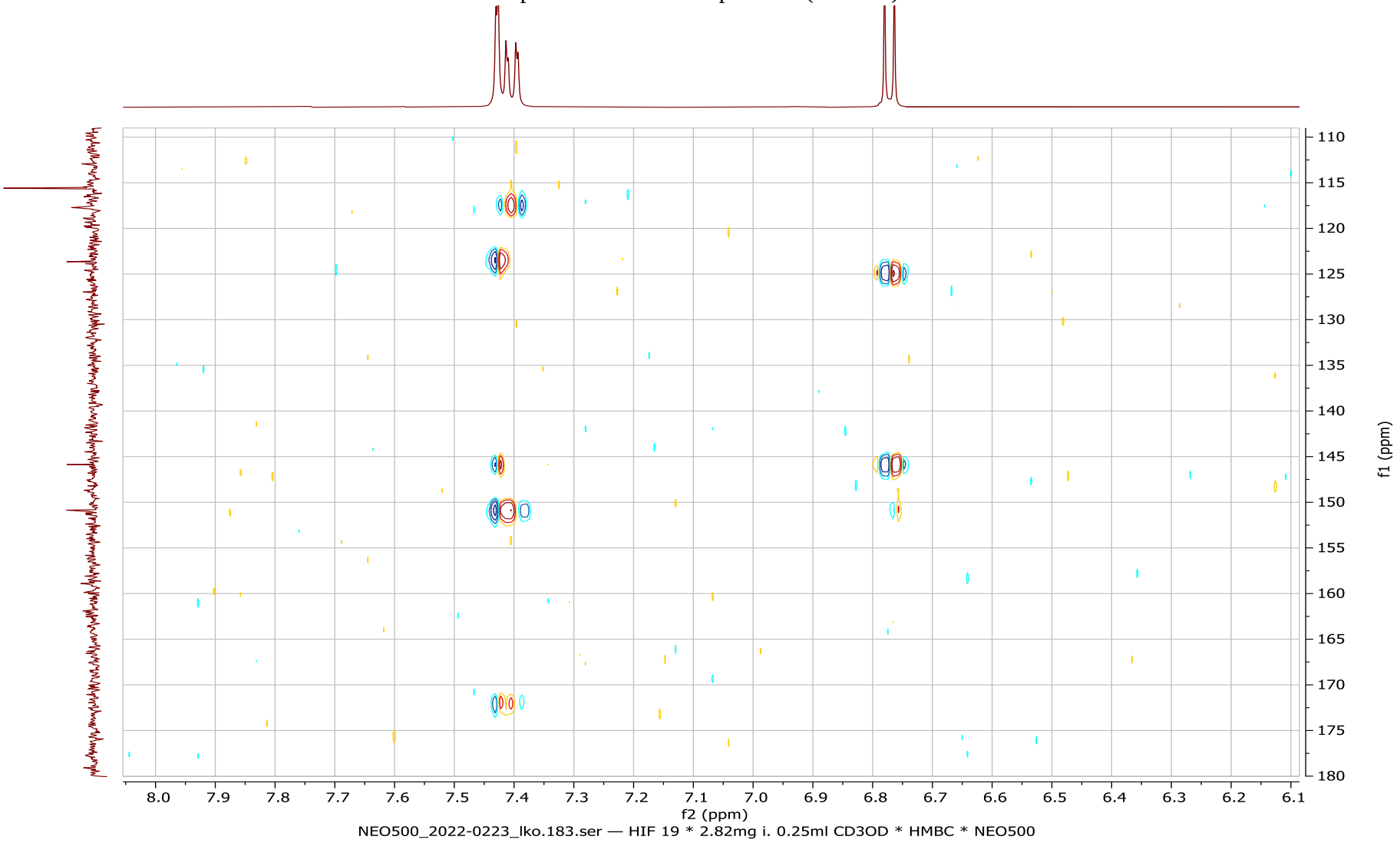
Compound **264** ^{1}H-^{1}H COSY spectrum (CD_3OD)



Compound **264** HSQC spectrum (CD_3OD)

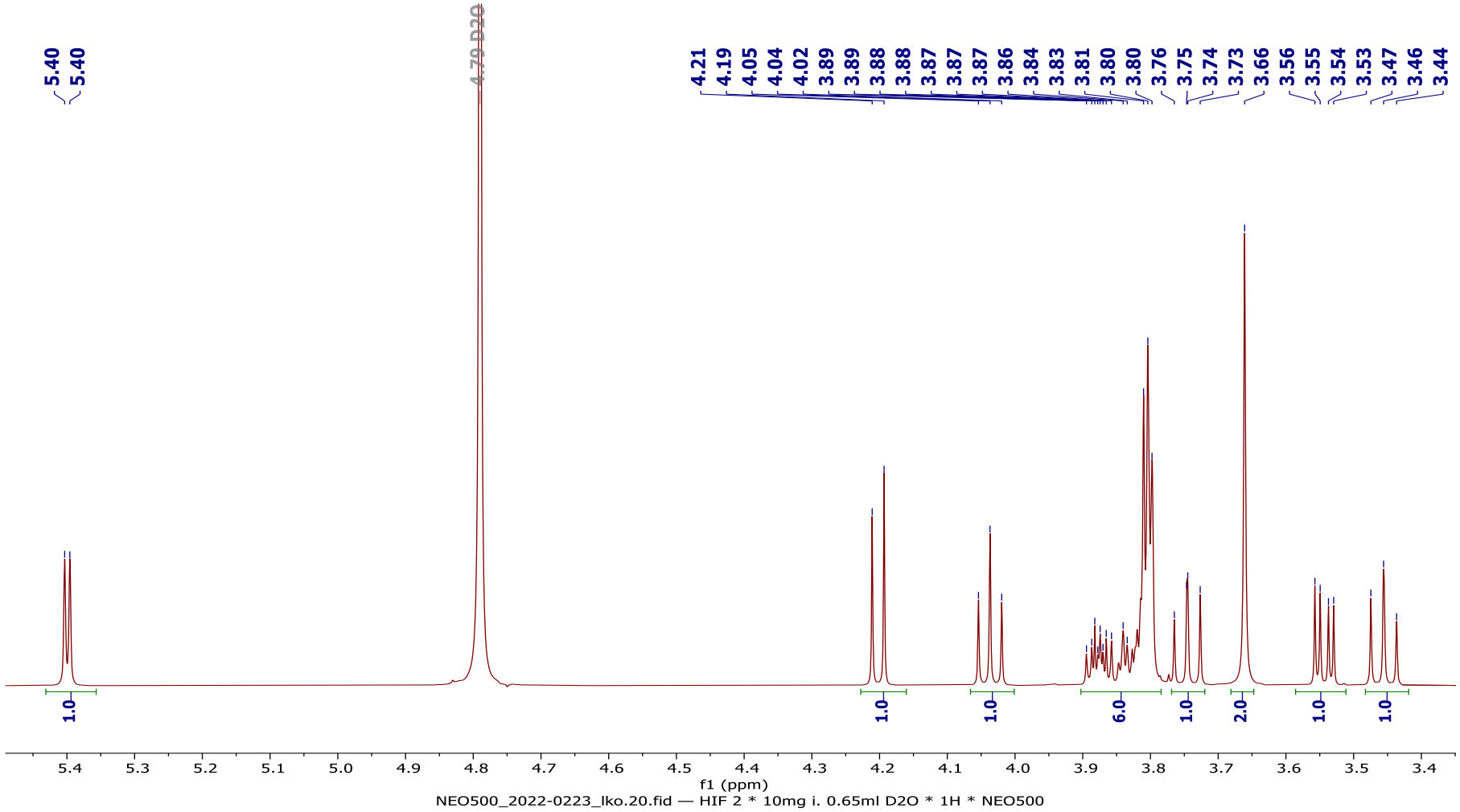


Compound **264** HMBC spectrum (CD_3OD)

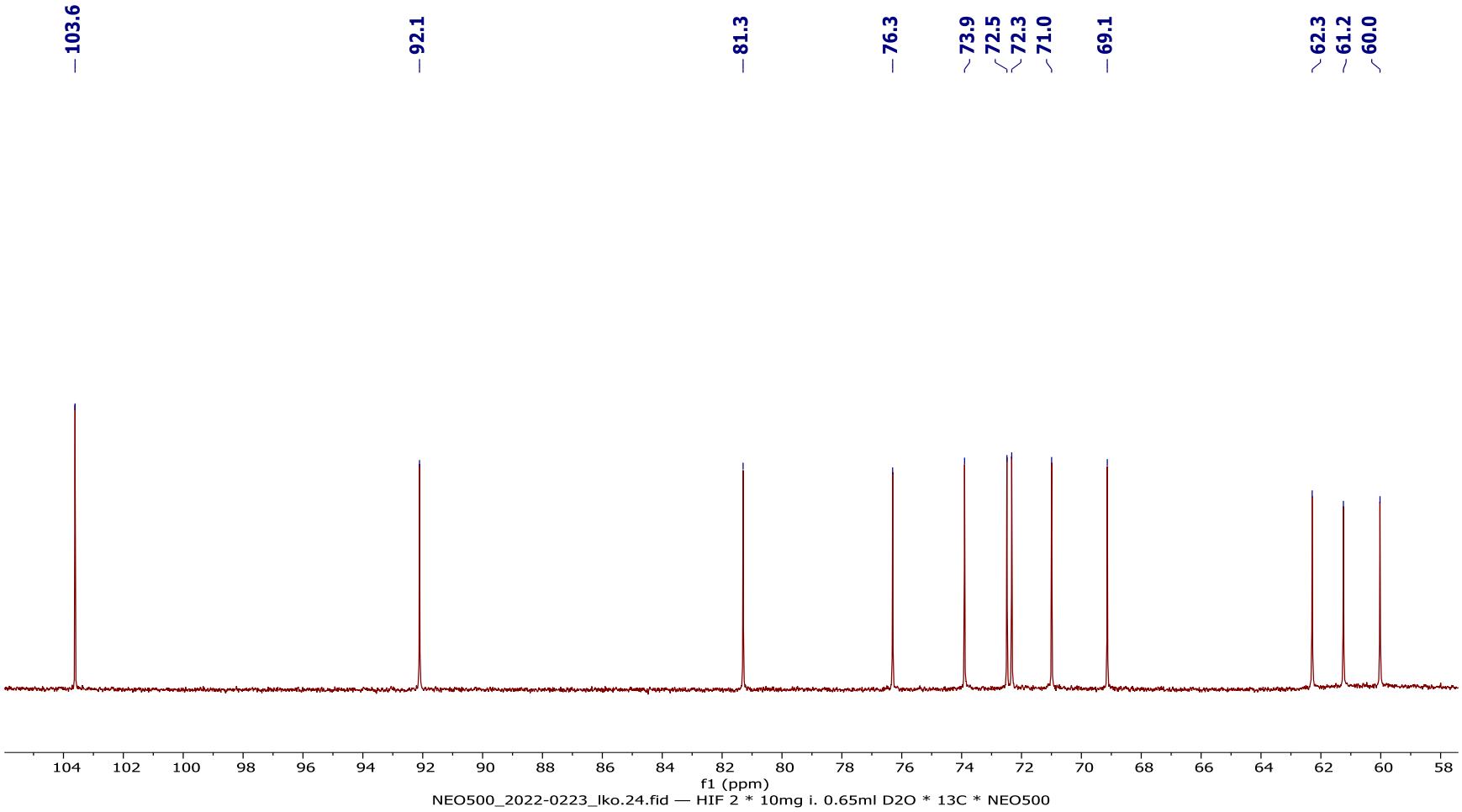


Appendix 20: Spectra of saccharose (**265**)

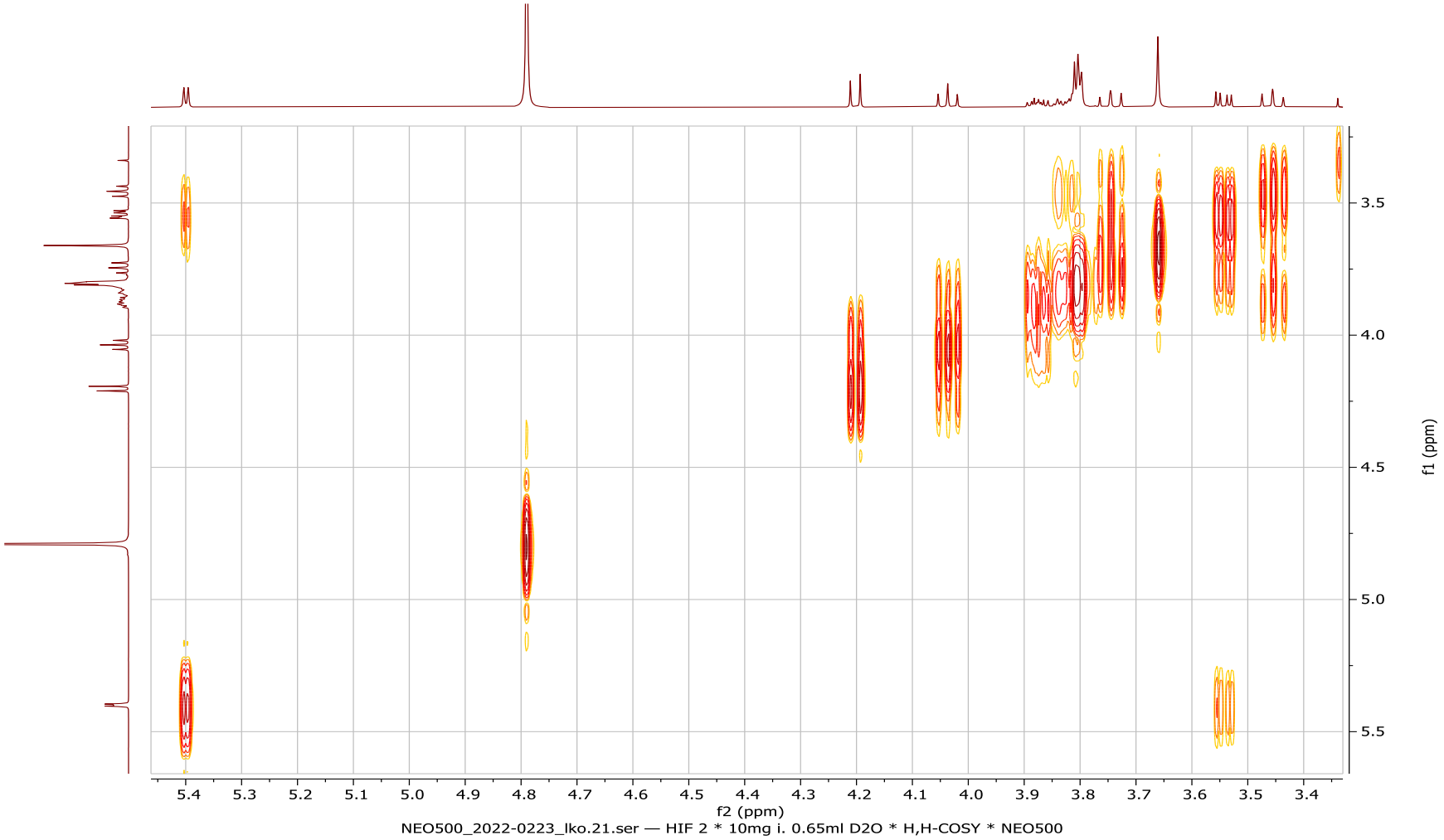
Compound **265** ^{1}H NMR spectrum (D_2O, 500 MHz)



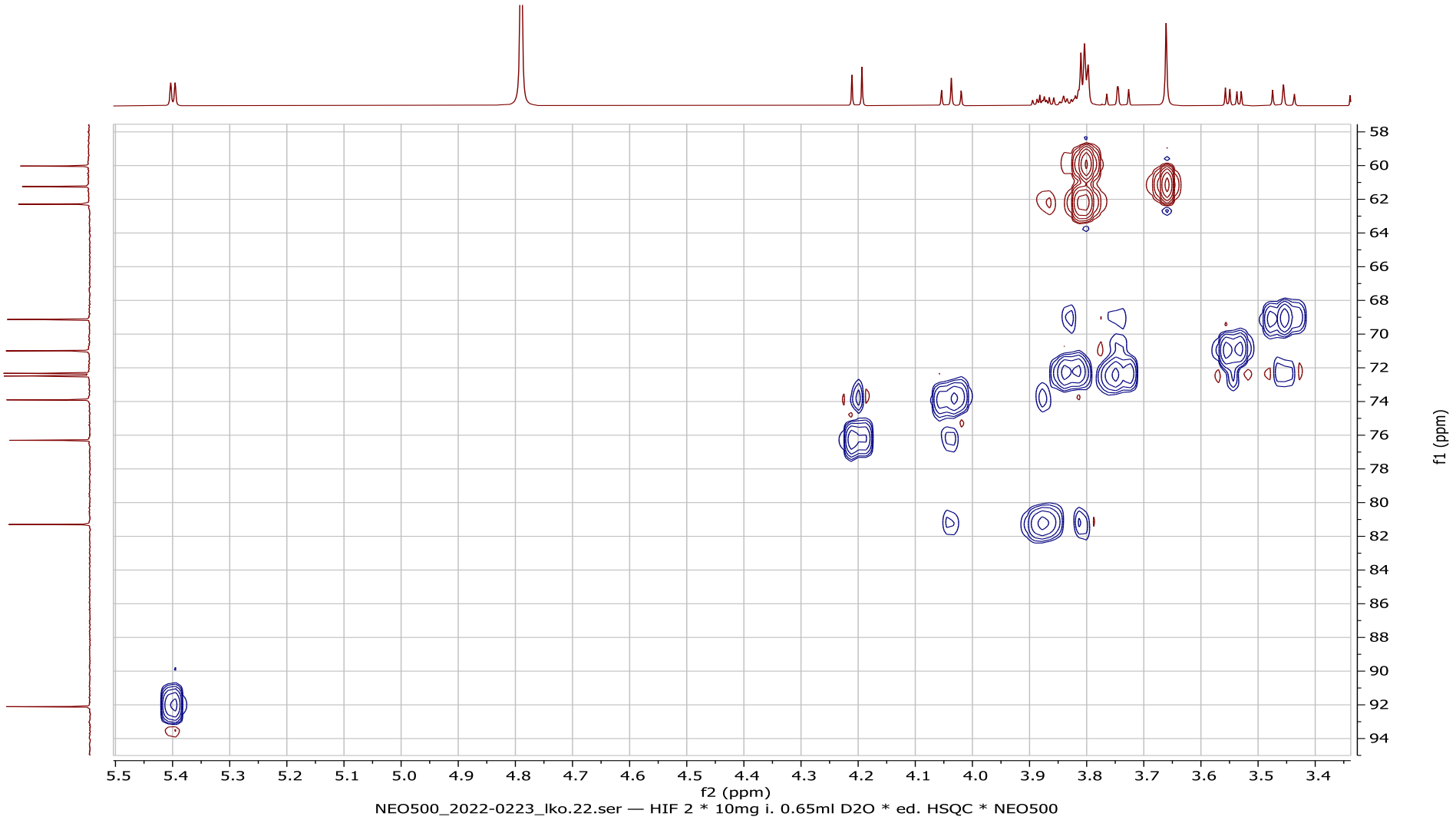
Compound **265** ^{13}C NMR spectrum (D_2O, 125 MHz)



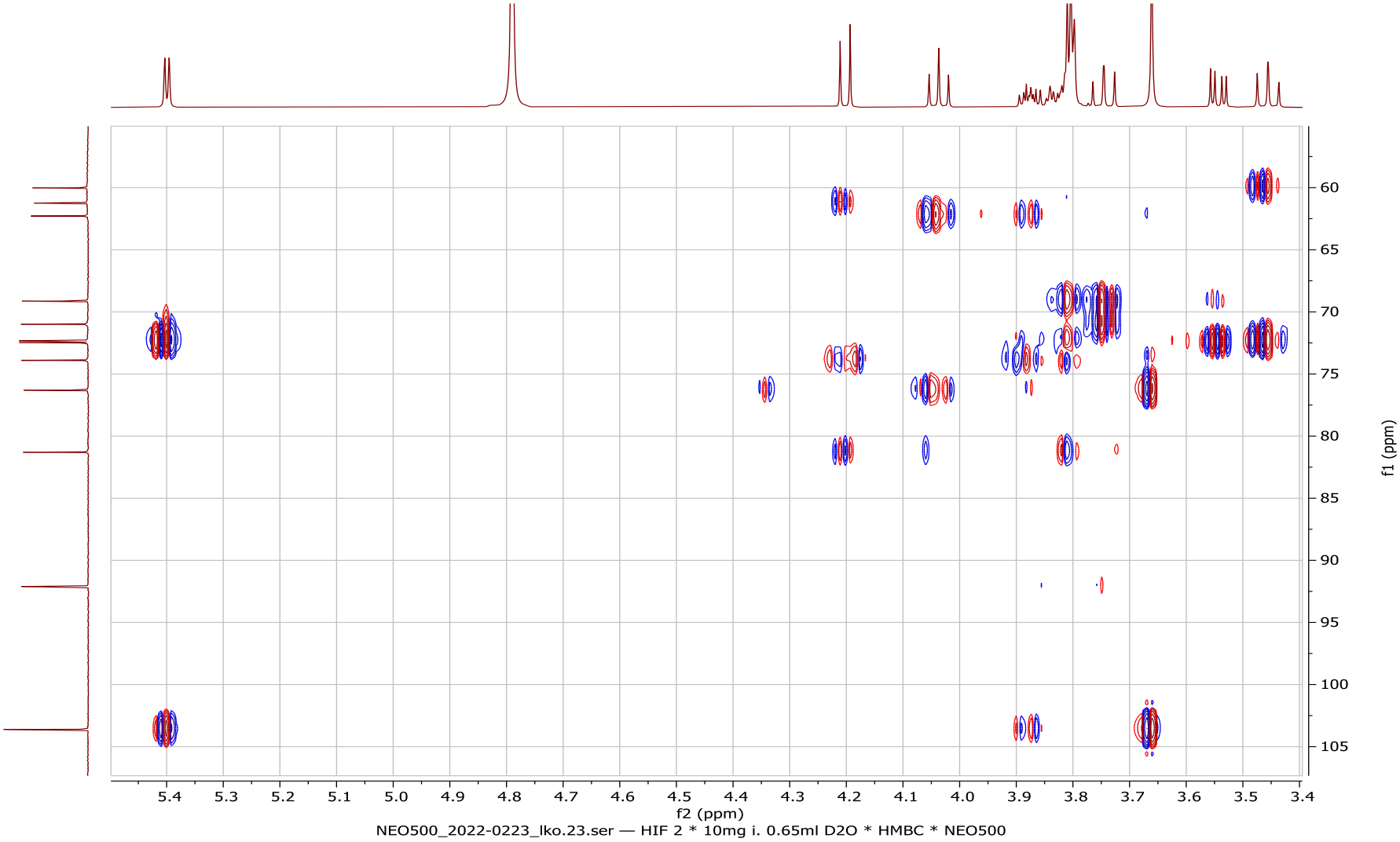
Compound **265** ^{1}H-^{1}H COSY spectrum (D_2O)



Compound **265** HSQC spectrum (D_2O)

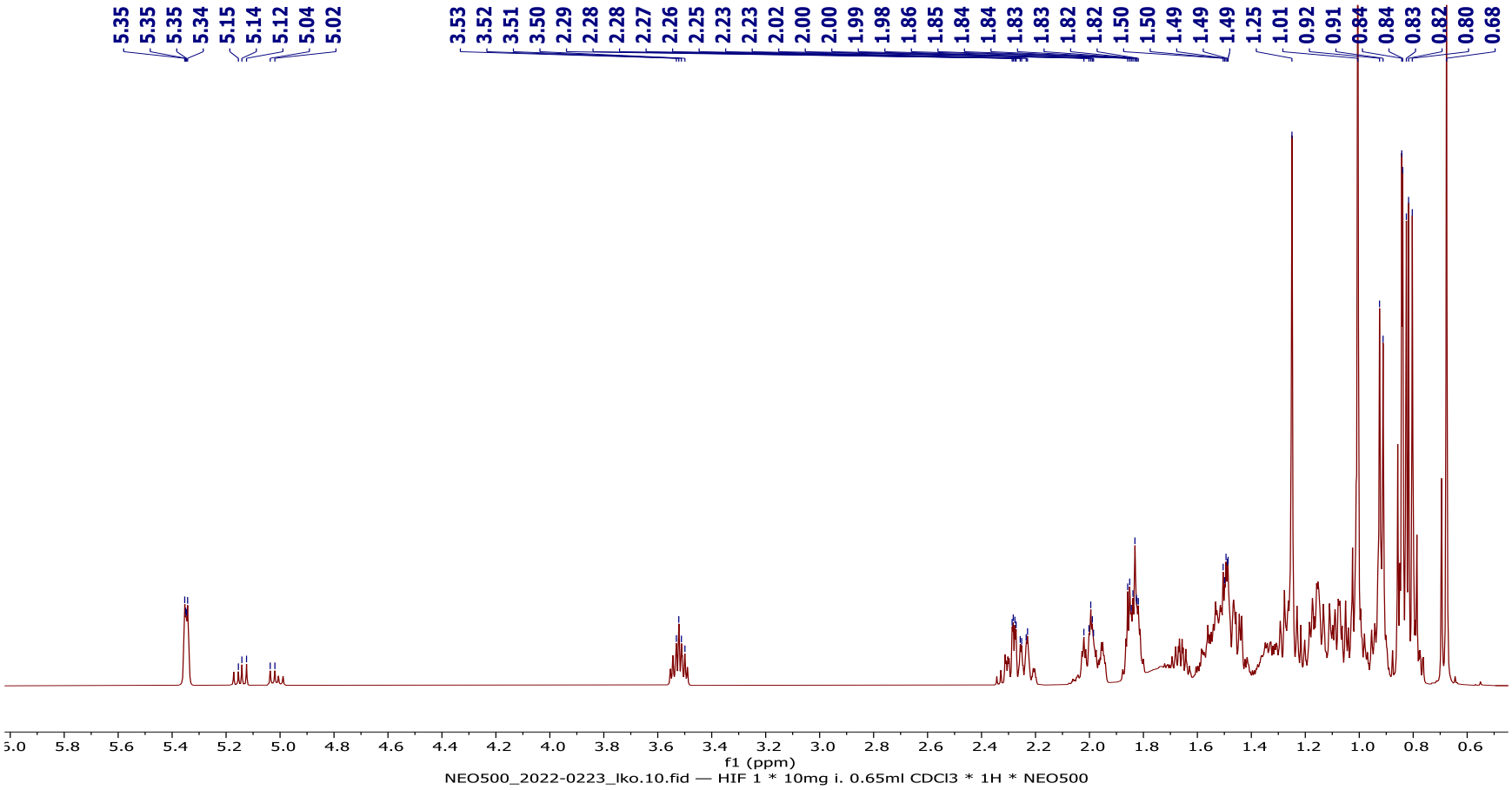


Compound **265** HMBC spectrum (D_2O)

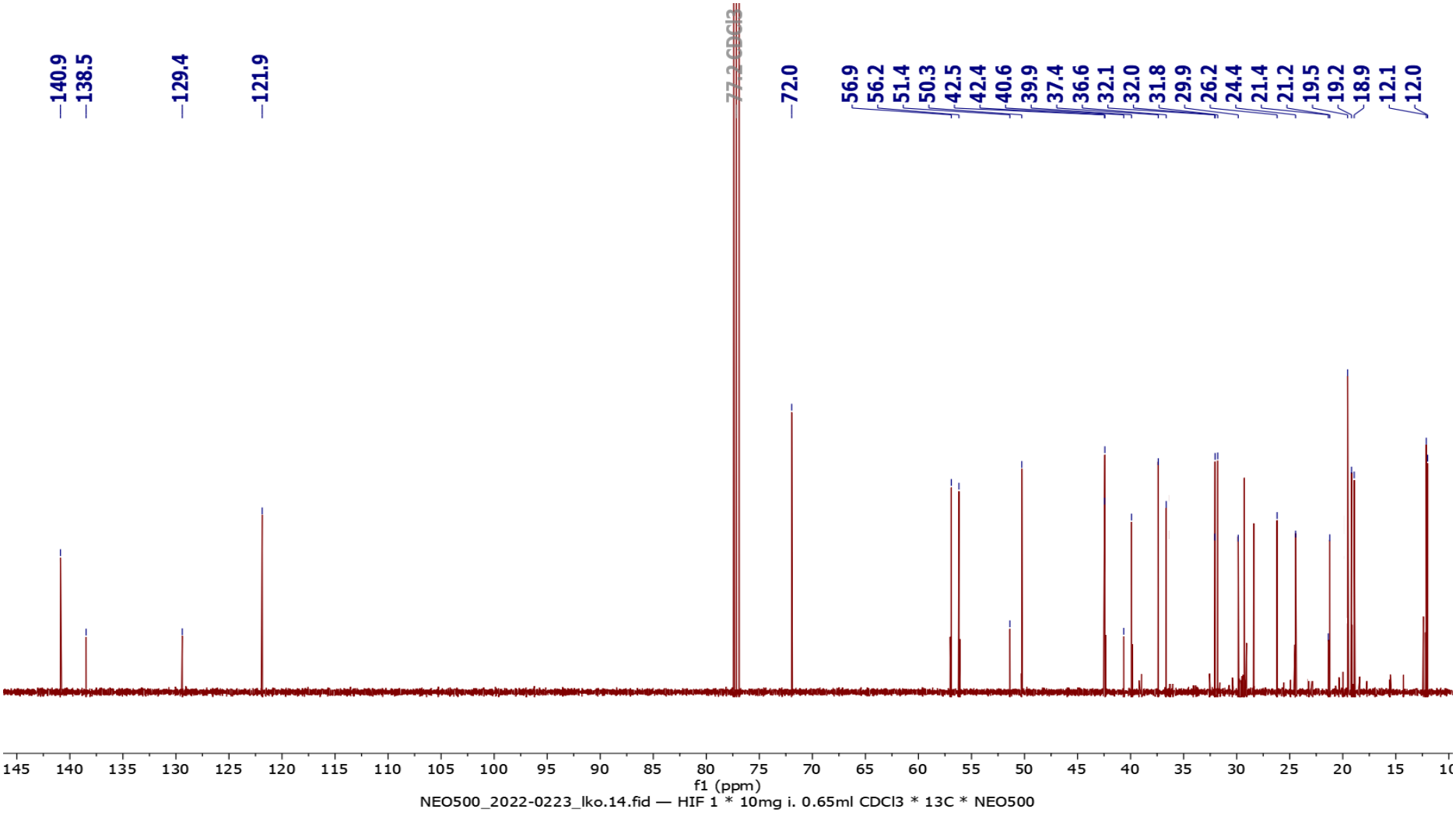


Appendix 21: Spectra of stigmasterol (**266**)

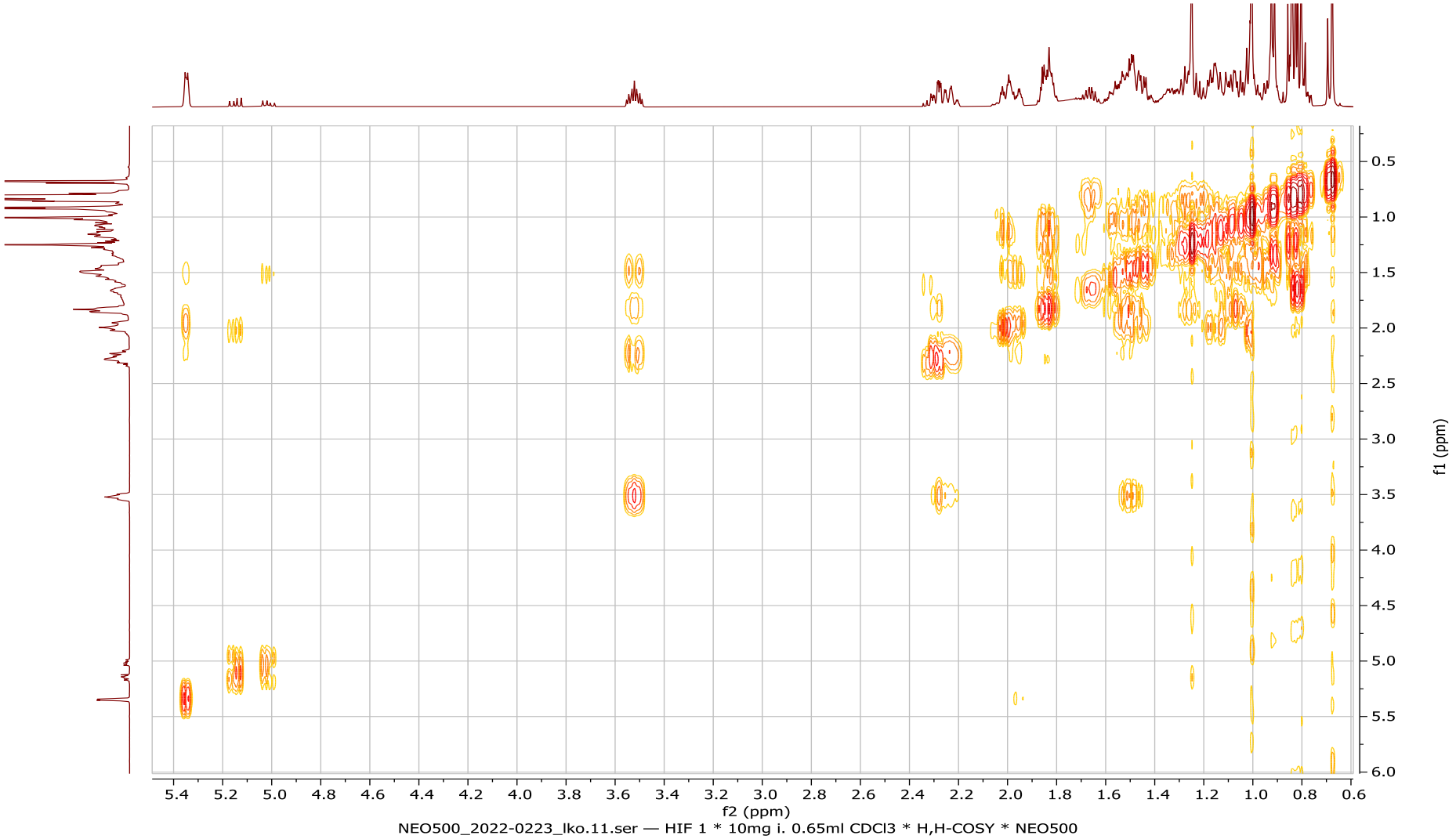
Compound **266** ^{1}H NMR spectrum ($CDCl_3$, 500 MHz)



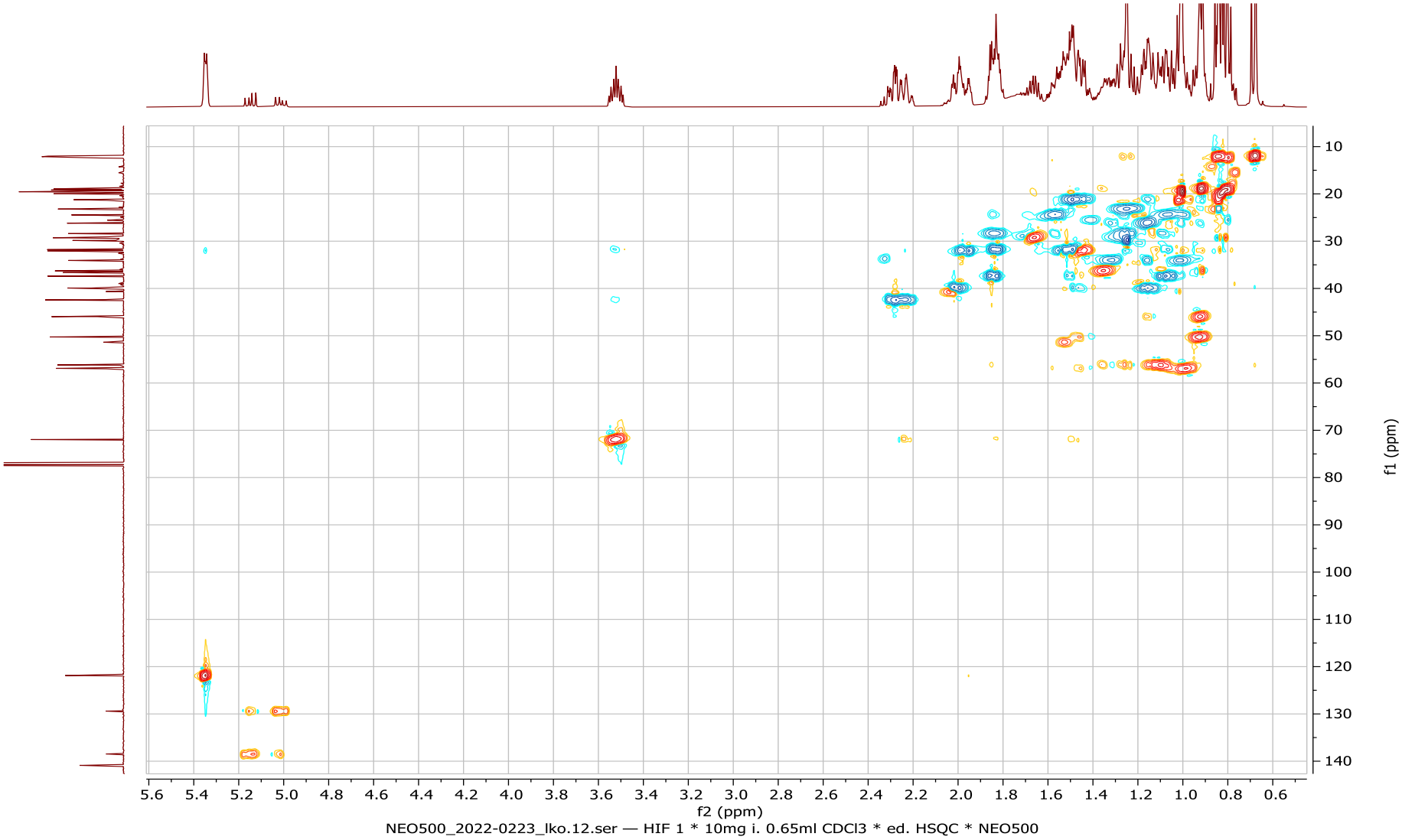
Compound **266** ^{13}C NMR spectrum ($CDCl_3$, 125 MHz)



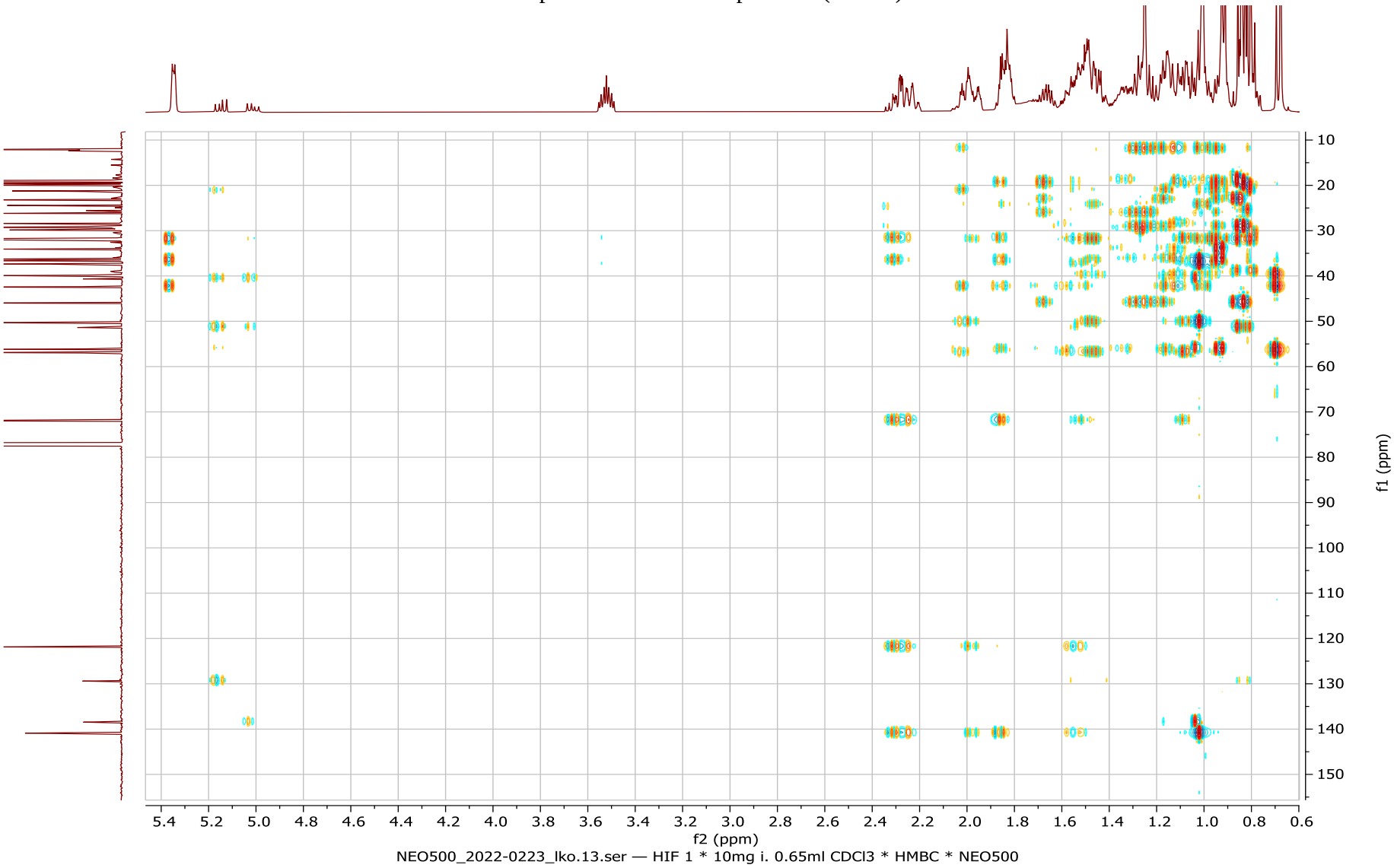
Compound **266** ^{1}H-^{1}H COSY spectrum ($CDCl_3$)



Compound **266** HSQC spectrum ($CDCl_3$)



Compound **266** HMBC spectrum ($CDCl_3$)



Appendix 22: Excerpt from the first page of publications from this thesis

Pharmacogn. Commn. 2021;11(2):119-126.
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
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Original Article

Antibacterial Activities and Phytochemical Screening of Crude Extracts from Kenyan *Macaranga* Species Towards MDR Phenotypes Expressing Efflux Pumps

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ABSTRACT

Introduction: *Macaranga* species are traditionally used for the treatment and management of coughing, fungal infection, and wounds. In this study, the phytochemical screening and antibacterial activities of nine crude extracts from *Macaranga conglomerata*, *Macaranga kilimandscharica* and *Macaranga capensis* were determined against 13 bacterial strains expressing multi-drug resistance (MDR) phenotypes. **Methods:** Phytochemical screening of the extracts were carried out according to the standard methods, while the iodonitrotetrazolium chloride (INT) colorimetric assay was used to determine the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of the plants extracts. **Results:** Flavonoids, terpenoids, saponins and coumarins were the major secondary metabolites found in all the plant extracts. The results of antibacterial studies revealed that all the plant extracts displayed good activities with MIC values ranging from 4 – 128 µg/mL against the tested micro-organisms. Most of the extracts exhibited a bactericidal effect against *E. coli*, *E. aerogenes*, *K. pneumoniae*, *P. stuartii*, *P. aeruginosa*, and *S. aureus* with MBC/MIC ratio ≤ 4. In the presence of efflux pump inhibitor (PaβN), the inhibition potency of all the crude extracts against the tested bacterial strains were substantially enhanced. It is worth noting that the activities of MKL, MCL, and MCR towards *P. stuartii* (NEA16), *E. aerogenes* (ATCC13048), and *K. pneumoniae* (KP55), respectively were improved by more than 8-fold in the presence of PAβN. **Conclusion:** The findings of this study indicated the possibility of using all the tested plant extracts as a source of therapeutic agents in the fight against multi-drug resistant bacteria.

Key words: *Macaranga capensis*, *Macaranga kilimandscharica*, *Macaranga conglomerata*, Euphorbiaceae, Pathogenic microbes, Multidrug resistance.

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INTRODUCTION

The emergence and spread of multi-drug resistant (MDR) micro-organisms (bacteria, fungi, viruses and protozoans) have compromised the management and/or treatment of common infections such as malaria, pneumonia, tuberculosis, measles and HIV/AIDS.[1,2] As a result, the costs of treatment, hospitalization time, morbidity and mortality rate are all in the rise. A high poverty index, limited access to modern health care facilities, clean water and affordable medicines as well as the gross misuse and overuse of antimicrobials, particularly in developing nations, are the contributing factors accelerating the development and spread of multi-drug resistant micro-organisms.[3]

The prevalence of multi-drug resistant bacteria constitutes a very big burden to both the developed and developing nations with respect to public health. These bacteria cause different classes of antibiotics to lose their effectiveness in the treatment of infectious diseases.[4-8] thereby, resulting in high morbidity and mortality rate, in addition to the negative impact on the World's economy.[9,10]

Due to the presence of diverse phytochemicals with multiple pharmacological potentials, medicinal plant extracts present a very good prospect in combating effectively the multi-drug resistant bacteria and potentially restore the efficacy in the management of infectious diseases using antibiotics.[11] There is an urgent need therefore, to continue to search for better antimicrobial agents especially of natural origin, which are not only available, but also affordable.

Macaranga genus consist of over 300 species mainly found in tropical Asia and New Guinea.[12] It belongs to the Euphorbiaceae family and it's a soft-wooded tree that rapidly grows to about 15 – 20 m tall.[13,14] Seven species of *Macaranga* were reported to be native of East African forest of which *M. kilimandscharica*, *M. capensis*, *M. schweinfurthii* and *Macaranga conglomerata* are found in Kenya.[12-14]

The species in this genus are used traditionally in the treatments of several ailments in different parts of the world. For instance, the roots and leaves decoction of *M. kilimandscharica* are used, in Kenya for the treatment of bilharzia and cough, as well as stomach problems.[15] *M. tanarius* root decoctions are used for fever relief and to suppress coughing;[16] leaf extract is used for healing of wounds and relieve inflammation;[17] dried root is used as an emetic agent.[18] Stem and leaf decoctions of *M. denticulate* are used in the prevention of infections after childbirth.[19] Red gum of *M. indica*, leaves of *M. deheiculata*, and young shoot of *M. gigantean* are used for healing wounds,[20] treating jaundice,[21] and treating fungal infection.[22] Besides the traditional uses, crude extracts obtained from *Macaranga* species have been reported for diverse biological activities including anticancer,[23] antibacterial,[16] antiplasmodial,[24] antifungal,[25] and anti-inflammatory activity.[26] Phytochemical studies indicated prenylated flavonoids and stilbenes as the main secondary metabolites found in the genus.[14,27] Other phytochemicals including diterpenes and tannins were also reported from the genus, although few (< 10%) of the 300 species in the genus have been investigated phytochemically.[14]

Despite the wide-range of ethnomedicinal applications and potential pharmacological activities of *Macaranga* species reported in the

NATURAL PRODUCT RESEARCH
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Conglomeratin: a new antibacterial flavonol derivative from *Macaranga conglomerata* Brenan (Euphorbiaceae)

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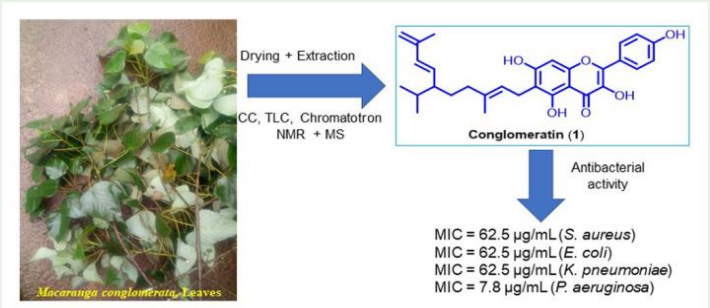
ABSTRACT

A new prenylated kaempferol, conglomeratin (**1**), alongside **7** known compounds including flavonoids (**2** and **3**), ellagic acid derivatives (**4** and **5**), triterpenoids (**6** and **7**), and a coumarin (**8**) were isolated from the leaves (**1 − 5**) and stem bark (**6 − 8**) of *Macaranga conglomerata*. Their structures were elucidated using spectroscopic and spectrometric techniques. The antibacterial assay was performed using disc diffusion method against Gram-positive and Gram-negative microorganisms. Compound **1** was significantly active against *Pseudomonas aeruginosa* ATCC 27853 (MIC = 7.8 µg/mL) and moderately active towards *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 31488 (MIC = 62.5 µg/mL). Compound **2** showed potency against *P. aeruginosa* ATCC 27853 (MIC = 1.0 µg/mL) while **4** and **7** were selective towards *K. pneumoniae* ATCC 31488 (MIC = 7.8 and 1.0 µg/mL, respectively). These findings suggest that prenylation of flavonoids may contribute to improving their broad-spectrum antimicrobial activities.



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KEYWORDS
Macaranga conglomerata; Euphorbiaceae; flavonol; antibacterial

1. Introduction

The World Health Organization has identified the rising prevalence of microbial infections, combined with increased antibiotic drug resistance, as one of the most serious

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Chemical Constituents from the Stem Bark of *Ficus thonningii* and their Chemotaxonomic Significance

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Authors' contributions

This work was carried out in collaboration among all authors. Author IH collected samples and wrote the original draft of the manuscript. Authors IH and JM carried out the experiment. Authors IH and JM performed the structure elucidation. Authors LKO, JMO and SMM managed experimental design and supervised the study. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background of the Study: Tropical plants of the *Ficus* genus (Moraceae) are among the earliest fruit trees that humans have cultivated. Since ancient times, many folk medicines have used species of this genus to treat a variety of ailments. Evidence from earlier investigations has shown these plants contain abundant secondary metabolites with a variety of structural properties and biological functions.
Place and Duration of Study: The research was carried out at the University of Nairobi (Faculty of Science and Technology, Department of Chemistry) from January to June 2022.
Aim: The study focuses on isolating and identifying secondary metabolites from the stem bark of *Ficus thonningii* Blume found in Kenya and their chemotaxonomic significance.
Methodology: Dried powdered stem bark of *Ficus thonningii* was extracted by maceration at room temperature using CH_2Cl_2/CH_3OH (1:1) to yield a crude extract which was fractionated in a chromatographic column (CC) using silica gel (60 – 120 mesh) as an adsorbent eluting with

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