ESTUDO QUÍMICO DAS ESPÉCIES *Psychotria nuda* Cham. & Schltdl. E *Psychotria suterella* Müll. Arg. (RUBIACEAE) E AVALIAÇÃO DE ATIVIDADES BIOLÓGICAS

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CAMPOS DOS GOYTACAZES-RJ

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“Tese apresentada ao Centro de Ciência e Tecnologia da Universidade Estadual do Norte Fluminense Darcy Ribeiro, como parte das exigências para obtenção do título de Doutor em Ciências Naturais”

Orientador: Prof. Ivo Jose Curcino Vieira

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(Orientador)

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SUMÁRIO

RESUMO

CARVALHO JUNIOR, Almir Ribeiro; D.Sc. Universidade Estadual do Norte Fluminense Darcy Ribeiro. Fevereiro de 2018. Estudo Químico das Epécies *Psychotria nuda* Cham. & Schltdl. e *Psychotria suterella* Müll. Arg. (Rubiaceae) e Avaliação de Atividades Biológicas.

Espécies do gênero *Psychotria* (Rubiaceae) são reconhecidas por seus usos na medicina popular e pela produção de metabólitos com potencial biológico. Em face disto, objetivou-se com esta pesquisa realizar o estudo químico das espécies *P. nuda* e *p. suterella* e avaliar atividades biológicas de seus extratos, frações e compostos isolados. Das folhas e galhos de *P. nuda* foram isolados e identificados dezessete compostos, que são: sitosterol, estigmasterol, campesterol, fitol, β-sitosterol e β-estmasterol glucosilados, cinchonaina Ia, cinchonaina Ib, *N*,*N*,*N*-trimetiltriptamônio, lialosídeo, lawsofrutose, roseosídeo, estrictosamida, escopoletina, ácido rotungênico, estrictosidina e 5α-carboxiestrictosidina. Um novo iridoide inédito, ácido 9-*epi*-geniposídico, foi identificado das folhas de *P. suterella*, juntamente com ácido geniposídico, sacarose, ácido 3-*O*-acetiloleanólico, ácido pomólico, ácido espinósico, ácido maslínico, ácido tormêntico, metil oleanolato, ácido lialosídico e ácido estrictosidínico. Neste trabalho foram avaliadas as atividades inseticida, frente às larvas do mosquito *Aedes aegypti*, antifúngica, frente aos fungos *Fusarium oxysporum, Curvularia lunata, Colletotrichum musae, Rhizoctonia solani, and Sclerotium rolfsii*, e citotóxica frente às células cancerígenas das linhagens THP-1 e U937. Os extratos e frações testados nos dois primeiros ensaios não apresentaram resultados promissores. O alcaloide estrictosamida, dentre os compostos testados, foi o que apresentou os melhores resultados quanto a citotoxidade, com valores de EC_{50} de 120,0 ± 1 e 21,9 ± 1 μg/mL frente a células THP-1 e U937, respectivamente.

ABSTRACT

CARVALHO JUNIOR, Almir Ribeiro; D.Sc. Universidade Estadual do Norte Fluminense Darcy Ribeiro. Fevereiro de 2018. Estudo Químico das Epécies *Psychotria nuda* Cham. & Schltdl. e *Psychotria suterella* Müll. Arg. (Rubiaceae) e Avaliação de Atividades Biológicas.

Psychotria species are recognized by their use in folk medicine and by the production of biologically actives metabolites. Owing to it, the aim of this research was to perform the chemical study of *P. nuda* and *P. suterella* as well as to assess biological activities of its extracts, fractions and isolated compounds. Seventeen compounds were isolated and identified from leaves and twigs of *P. nuda*, named sitosterol, stigmasterol, campesterol, phytol, β-sitosterol-3-O-β-D-glucoside, β-stmasterol-3-O-β-D-glucoside, cinchonain Ia, cinchonain Ib, *N*,*N*,*N*-trimethyltryptamonium, lyaloside, lawsofrutose, roseoside, strictosamide, scopoletin, rotungenic acid, strictosidine, and 5α-carboxystrictosidine. The new iridoid named 9-*epi*-geniposidic acid, along with the known compounds geniposidic acid, sucrose, 3-O-acethyloleanolic acid, pomolic acid, spinosic acid, maslinic acid, tormentic acid, methyl oleanolate, lyalosidic acid, and strictosidinic acid (**11**) were isolated and identified from leaves of *P.suterella*. In this work, insecticidal, against *Aedes aegypti* larva, antifungal, against *Fusarium oxysporum, Curvularia lunata, Colletotrichum musae, Rhizoctonia solani, and Sclerotium rolfsii*, and citotoxic, THP-1 and U937 cancer cell lines, activities were assessed. Extracts and fractions tested in the first two assays did not show promising results. The alkaloid strictosamide, among the tested compounds, showed relevant citotoxicity with IC_{50} values 120 ± 1 and 21.9 ± 1 μg/mL, against THP-1 and U937 cell lines, repectively.

1. INTRODUÇÃO

A utilização de produtos naturais, principalmente da flora, com fins medicinais, nasceu com a humanidade. Registros do uso de plantas medicinais e tóxicas datam das civilizações mais antigas, sendo considerada uma das práticas mais remotas empregadas para cura, prevenção e tratamento de doenças, atuando como importante fonte de substâncias biologicamente ativas (Firmo et al. 2011).

Nos últimos anos, registrou-se um aumento expressivo no interesse em substâncias derivadas de espécies vegetais, micro-organismos, insetos e organismos marinhos. Newman & Cragg (2016) destacam que a prática da utilização de produtos naturais e seus derivados estruturais na descoberta e desenvolvimento de novos fármacos ainda está viva e progredindo. Por exemplo, na área de câncer, considerando-se o período de 1940 até o final de 2014, das 175 pequenas moléculas aprovadas, 131 ou 75% eram não sintéticas, com 85 ou 49% sendo produtos naturais ou derivados diretamente deles.

O crescente interesse em novas substâncias biologicamente ativas está diretamente relacionado à riqueza da biodiversidade. O Brasil ocupa posição privilegiada em termos de biodiversidade, em diferentes aspectos. Considerando-se apenas o restrito universo de espécies catalogadas no mundo, o país detém a maior quantidade total (13%) e a segunda maior quantidade de espécies endêmicas em valores absolutos. O território brasileiro é composto por sete biomas principais: Amazônia, Cerrado, Caatinga, Mata Atlântica, Pampa, Pantanal e Zona Costeira e Marinha. Desses, Mata Atlântica e Cerrado são exclusivos do território brasileiro (Pimentel et al. 2015). Entretanto, poucas espécies da flora nativa foram investigadas do ponto de vista químico e farmacológico.

Espécies do gênero *Psychotria*, pertencente à família Rubiaceae, se destacam por sua importância na medicina tradicional, onde são utilizadas para uma grande variedade de indicações terapêuticas como afecções do aparelho reprodutor feminino, distúrbios gastrointestinais, úlceras, “tumores”, distúrbios oculares, no tratamento de febres, dores de cabeça e ouvidos, sendo ainda empregadas em rituais religiosos devido a suas propriedades alucinógenas (Faria 2009; Lima 2011). O uso medicinal destas espécies estimulou a avaliação do potencial farmacológico de extratos, frações semi-purificadas e substâncias isoladas, destacando-se propriedades antivirais, anti-inflamatórias, antibióticas, antifúngicas, antitumorais, dentre outras (Carvalho Junior et al. 2016).

O gênero *Psychotria* é considerado de taxonomia complexa, em função das poucas características morfológicas diferenciadoras. Por esse motivo, alcaloides indólicos são considerados marcadores químicos, importantes para os estudos quimiotaxônomicos de espécies deste gênero (Porto et al. 2009; Carvalho Junior et al. 2017).

A potencialidade químico-farmacológica descrita para o gênero *Psychotria* justifica os estudos químicos e biológicos de espécies deste gênero. Neste contexto, objetivou-se com esta pesquisa realizar o estudo químico das espécies *Psychotria nuda* e *Psychotria suterella* e avaliar as atividades inseticida, antifúngica e citotóxica de extratos, frações e de algumas das substâncias isoladas.

2. REVISÃO DA LITERATURA

2.1 Informações sobre a família Rubiaceae e o gênero *Psychotria*

A família Rubiaceae é composta por mais de 600 gêneros, totalizando aproximadamente 13000 espécies, distribuídas pelo mundo (Rydin et al. 2009; Barbhuiya et al. 2014). Suas espécies são classificadas em quatro subfamílias: Cinchonoideae, Ixorideae, Antirheoideae e Rubiodeae, na qual o gênero *Psychotria* é incluído (Tomaz et al. 2008). Este gênero possuí mais de 2000 exemplares encontrados principalmente em regiões tropicais e subtropicais do globo, sendo considerado o maior da família Rubiaceae (Oliveira et al. 2013). Com base em características morfológicas e distribuição geográfica, o gênero *Psychotria* é dividido em três subgêneros: *Psychotria* (pantropical), *Heteropsychotria* (espécies neotropicais) e, *Tetramerae* (algumas encontradas na Africa e Madagascar) (Moraes et al. 2011).

Alguns relatos têm apontado que espécies deste gênero têm sido utilizadas na medicina popular como alternativa de tratamento de diversas doenças. Flores de *P. colorata*, por exemplo, são usadas por caboclos da Amazônia para tratamento de dor de ouvido, enquanto que seus frutos são empregados em casos de dores abdominais (Verotta et al. 1998). Na Malásia, folhas de *P. rostrata* são empregadas para o tratamento de constipação (Takayama et al. 2004). Infecção intestinal, tosse, distúrbios respiratórios e estomacais são outros exemplos de doenças combatidas pelo uso de outras espécies do gênero (Benevides et al. 2004). O uso etnofarmacológico de suas espécies, provavelmente, estimulou o desenvolvimento

de diversas pesquisas voltadas à investigação química e avaliação do potencial biológico de seus metabólitos.

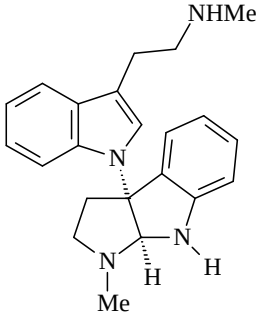
2.2 Composição química do gênero Psychotria

Em relação à composição química do gênero, vários trabalhos vêm sendo realizados, destacando-o como uma potencial fonte de alcaloides. Aproximadamente 53 % dos metabólitos isolados de suas espécies são alcaloides, dois quais 87 % são do tipo indólico. Esta classe de metabólitos secundários apresenta papel fundamental no ponto de vista quimiotaxômico. Alcaloides pirrolidinoindólicos são característicos de espécies do subgênero *Psychotria* (Lopes et al. 2004), enquanto que alcaloides indólicos monoterpênicos são marcadores quimiotaxômicos do subgênero *Heteropsychotria* (Kerber et al. 2008). Triterpenos (12 %) e flavonoides (6 %) são outras classes de metabólitos frequentemente isolados do gênero.

2.2.1 Alcaloides pirrolidinoindólicos

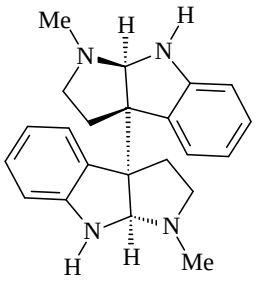
Os alcaloides pirrolidinoindólicos são caracterizados pela presença de várias unidades de *N*-metiltriptamina em suas estruturas (Lopes et al. 2004), cujas diferentes unidades apresentam, comumente, ligações do tipo C-3a/C-3a’ e C-3a/C-7’ (Takayama et al. 2004). Os alcaloides deste tipo isolados do gênero têm apresentado de dois a sete meros. Psicotridina, quadrigemina C e hodgkinsina são os alcaloides mais comumente isolados de diversas espécies (Verotta et al. 1999) (Hart et al. 1974) (Libot et al. 1987) (Roth et al. 1986) (Verotta et al. 1998) (Adjibade et al. 1992) (Zhou et al. 2010).

Além da importância no ponto de vista quimiotaxônomico, estes alcaloides despertaram interesse de pesquisadores no que tange às suas propriedades biológicas. Diversos estudos têm apontado uma série de atividades biológicas, como é o caso de quadrigemina B. Este alcaloide isolado da espécie *P. rostrata* apresentou atividade citotóxica frente a células HEp-2 e atividade antibacteriana frente a *Escherichia coli* e *Staphulococcus aureus* (Mahmud et al. 1993). Psicotridina, isolado de *P. forsteriana*, também apresentou citotoxidade contra células leucêmicas (Adjibade et al. 1989). Atividades analgésica (Amador et al. 2000) e antiparasitária são outros exemplos de atividades biológicas apresentadas por este tipo de metabólitos (Muhammad et al. 2003). A **Figura 1** apresenta alguns exemplos de alcaloides pirrolidinoindólicos isolados de espécies *Psychotria*.



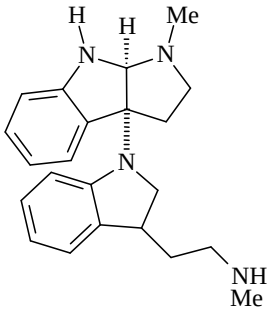
Psicotridiasina

(Zhou et al. 2010)



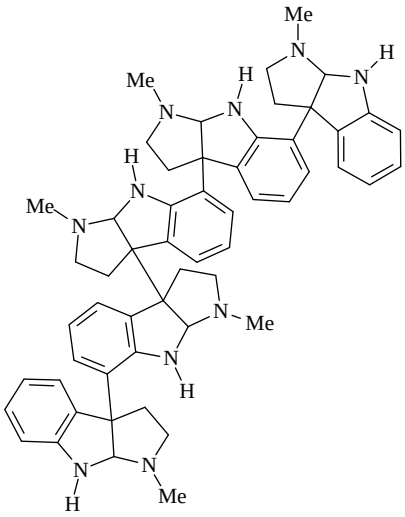
(+) Quimonantina

(Verotta et al. 1999)



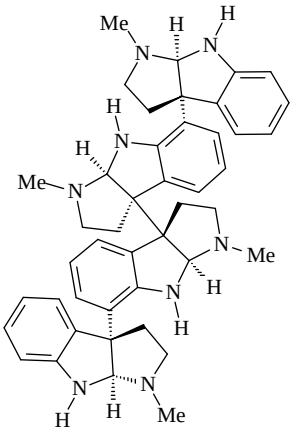
Psicohenina

(Liu et al. 2014)



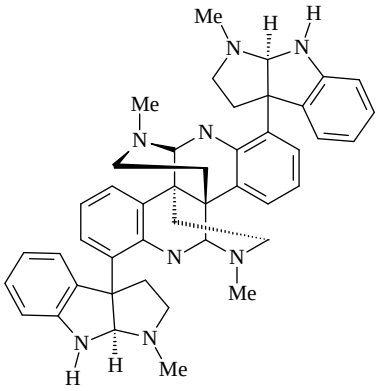
Psicotridina

(Verotta et al. 1999)



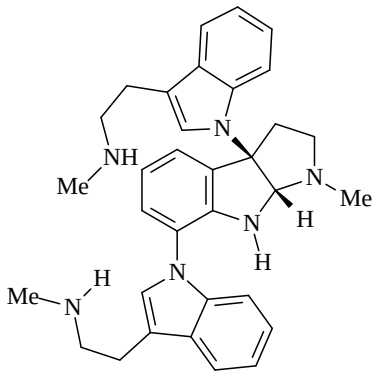
Quadrigemina C

(Verotta et al. 1998)



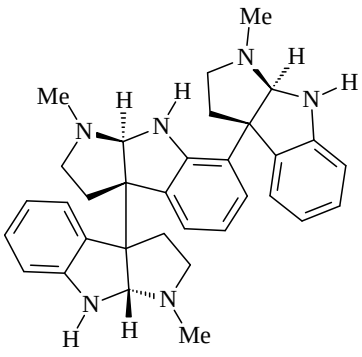
Psicoleina

(Rasolonjanahary et al. 1995)



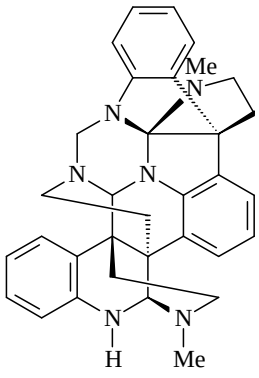
Psicotrimina

(Takayama et al. 2004)



Hodgkinsina

(Hart et al. 1974)



Psicotripina

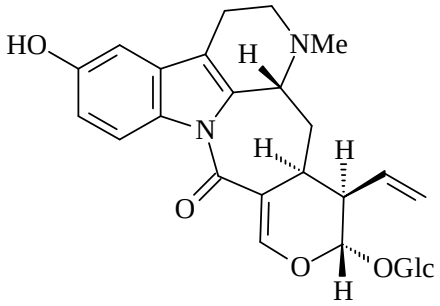
(Li et al. 2011)

Figura 1: Alcaloides pirrolidinoindólicos isolados do gênero *Psychotria*.

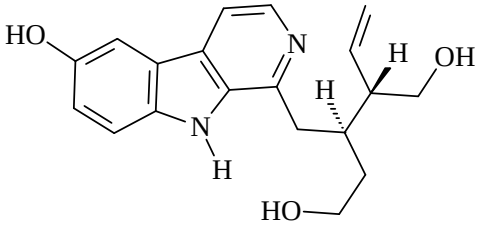
2.2.2 Alcaloides indólicos monoterpênicos (AIM)

Este tipo de alcaloide é característico de espécies encontradas no território brasileiro. Sua biossíntese envolve reação entre a triptamina (oriunda do triptofano) e o iridoide secologanina, levando a formação da estrictosidina. A diversidade estrutural destes metabólitos está relacionada, pricipalmente, a modificações envolvendo N^1 e C-22, N^4 e C-22. Os alcaloides correantinas A-C (Achenbach et al. 1995) exemplificam o primeiro caso enquanto que estrictosamida representa um caso de ciclização entre N^4 e C-22 (Faria et al. 2010). Oxidação de C-10 não é tão comum, porém, 10-hidroxi-iso-depeaninol e 10-hidroxi-antirhina, isolados de *P. prunifolia* (Kato et al. 2012) e 10-hidroxi-correantosideo (*P. Correa*) são exemplos de alcaloides com esta característica.

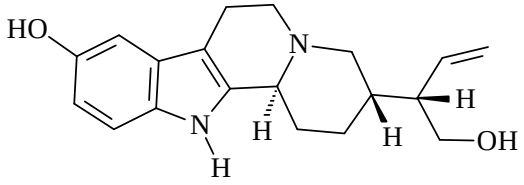
*N,*β-D-glucopiranosilvincosamida, isolado das folhas de *P. leiocarpa*, apresentou característica peculiar por ser considerado, segundo os autores, o primeiro relato de AIM *N*-glicosilado (Henriques et al. 2004). Bahienosídeos A e B, isolados de *P. bahiensis* e *P. acuminata*, são exemplos raros de alcaloides que apresentam uma porção terpênica adicional ligada ao N^4 (Berger et al. 2012) (Paul et al. 2003). A **Figura 2** apresenta exemplos de AIMs isolados do gênero.



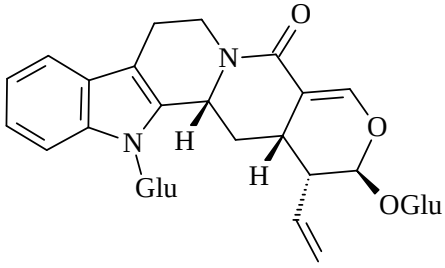
10-hidroxi-correantosídeo
(Achenbach et al. 1995)



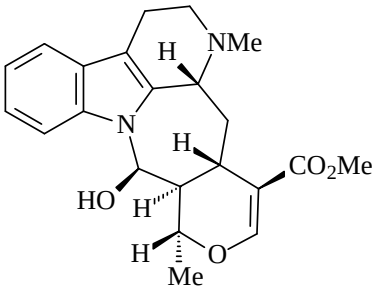
10-hidroxi-*iso*-depeaninol
(Kato et al. 2012)



10-hidroxi-antirhina
(Kato et al. 2012)

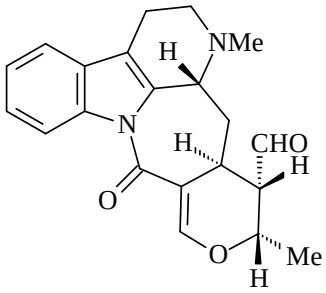


*N,*β-D-glucopiranosilvincosamida
(Henriques et al. 2004)



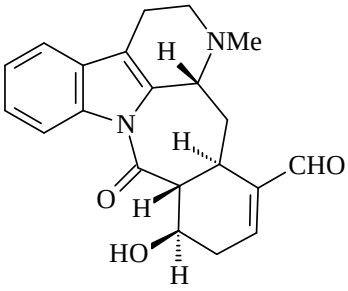
Correantina A

(Achenbach et al. 1995)



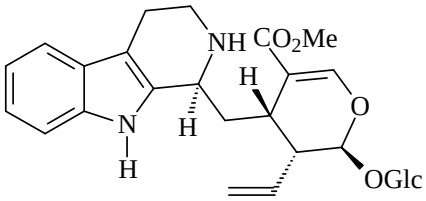
Correantina B

(Achenbach et al. 1995)



Correantina C

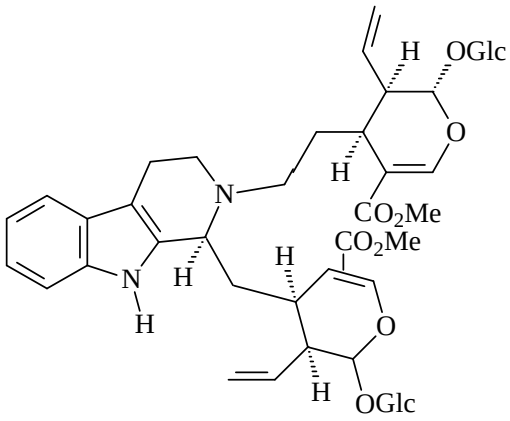
(Achenbach et al. 1995)



Estrictosidina

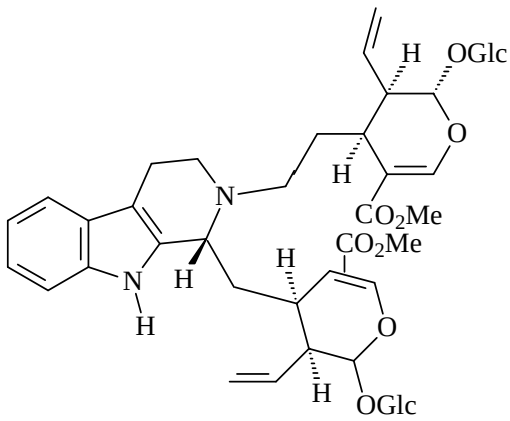
(Berger et al. 2012)

Figura 2: Acaloides indólicos monoterpênicos isolados do gênero Psychotria.



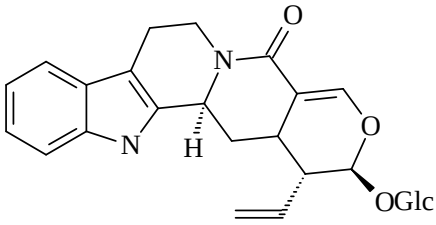
Bahienosídeo B

(Berger et al. 2012)



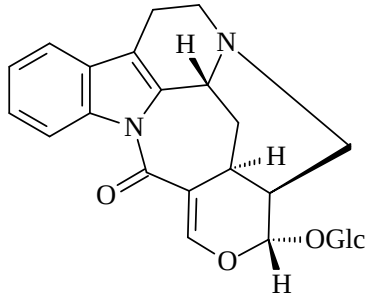
Bahienosídeo A

(Paul et al. 2003)



Estrictosamida

(Van De Santos et al. 2001)



Estaquiosídeo

(Pimenta et al. 2010)

Figura 2: Continuação.

2.3 As espécies *Psychotria nuda* e *Psychotria suterella*

A espécie *P. nuda* (**Figura 3**), conhecida popularmente como casca d' anta, é encontrada, pricipalmente, na forma de arbustos, medindo de 1 a 5 metros de altura (Miguel et al. 2009) principalmente nos estados do Rio de Janeiro, Minas Gerais, até o estado de Santa Catarina (Ferreira et al. 2014).

A espécie *P. suterella* (**Figura 4**) vulgarmente conhecida como grandiuva-de-anta cafezinho-roxo-da-mata, apresenta porte arbustivo-arbóreo, podendo alcançar até 6 m de altura (Lopes & Buzato 2005). O período de floração desta espécie ocorre de janeiro a março e frutificação de setembro a maio (Bertani 2006), períodos que facilitam a sua identificação, viabilizando sua coleta.

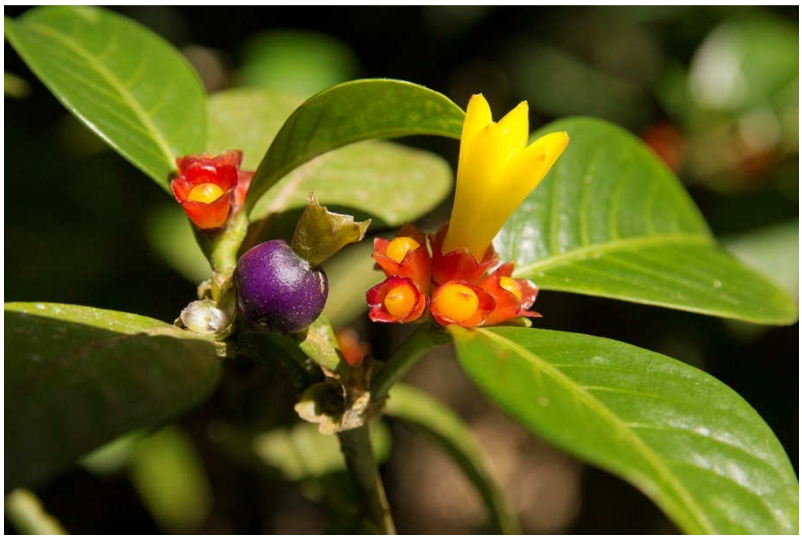


Figura 3: Fotografia da espécie *P. nuda*.

Fonte: https://www.flickr.com/photos/gustavolf/7291965490

(Acessado dia 27/01/2018)

Figura 4: Fotografia da espécie *P. suterella*.

Fonte: http://www.ufrgs.br/fitoecologia/florars/open_sp.php?img=11745

(Acessado dia 27/01/2018).

Em relação à química destas espécies, há relatos escassos a esse respeito. Referente à espécie *P. nuda* há o relato apenas de isolamento de um alcaloide indólico monoterpênico: estrictosamida (Farias et al. 2008). Já das folhas de P.suterella há o relato de identificação do alcaloide mencionado anteriormente, outros dois: lialosídeo, e naucletina (Van De Santos et al. 2001).

3. TRABALHOS

3.1 Trabalho 1:

Psychotria Genus: Chemical Constituents, Biological Activities And Synthetic Studies**

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Abstract: Natural products have been used by humankind for thousands of years in applications such as pigments, flavourings, and drugs. Since antiquity, the use of natural products has been the best or the only alternative adopted by many people worldwide, in the treatment of several diseases. In fact, plants are a potential source of bioactive compounds, but most of the world's biodiversity has not been evaluated for any biological activity. In this context, several studies have been performed regarding the chemical composition and biological properties of various species from different genera such as *Psychotria* L. (Rubiaceae). This genus is the largest of the Rubiaceae family, comprising about 2000 species, mainly found in tropical and subtropical regions of the globe. Several works have been reported concerning the chemical composition and biological activities of species of this genus. The aim of this overview is to summarise the advances in knowledge on *Psychotria* species, compiling reports related to chemical composition and biological activities of the genus.

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Introduction

Natural products have been employed in the treatment of several diseases for thousands of years [1]. Even recently, despite availability of synthetical drugs, plants remain widely used for medicinal purposes [2]. The diversity of biologically active compounds in plants has motivated chemical studies of various species. Recently, many plant-derived drugs, including semi-synthetics compounds, have either been

introduced to the market or are involved in clinical trials [3,4], highlighting the importance of medicinal plants in drug discovery.

The family Rubiaceae Juss. comprises 620 genera totaling about 13526 species, distributed worldwide [5]. *Psychotria* L. is the largest of the Rubiaceae, possessing more than 2000 species, mainly found in tropical and subtropical regions [6]. Based on its morphological features and geographical distribution, the genus was divided into three subgenera: *Psychotria* (pantropical), *Heteropsychotria* (neotropical species) and, *Tetramerae* (some African and Madagascan species) [7]. However, Nepokroeff *et al*. (1999) proposed the reorganization of the genus based on a molecular phylogenetic study [8].

Several *Psychotria* species are widely used in folk medicine around the world for the treatment of various illnesses. Flowers and fruits of *P. colorata*, for example, are used by “caboclos” from the Amazon to treat earache and abdominal pain, respectively [9]. In Malaysia, leaves of *P. rostrata* are employed for the treatment of constipation [10]. *P. viridis* is used as an ingredient in the hallucinogenic beverage called ayahuasca [11], owing to the presence of *N,N*-dimethyltriptamine, an indole alkaloid structurally related to neurotransmitter serotonin [12]. Intestinal infections, coughs, respiratory and stomach disorders are other examples of illnesses which have been treated using other *Psychotria* species [13].

Chemical Constituents

Many studies have examined the chemical composition of the species of the genus *Psychotria* (Rubiaceae). Since 1974 several works have shown that *Psychotria* is a potential source of alkaloids. Approximately 52 % of the metabolites reported were characterised as alkaloids (about 87 % belong to the subgroup of indole alkaloids), followed by triterpenes (12 %), flavonoids (6 %), along with constituents of other classes. Since *Psychotria* is taxonomically complex, alkaloids can be an important tool to distinguish its species from others which belong to genera with similar features such as *Cephaelis* Sw. and *Palicourea* Aubl. [14]. Moreover, these metabolites have shown a range of biological activities, increasing interest in the study of this genus, with the aim of discovering new natural medicines.

Dimeric and Polyindoline Alkaloids Isolated from *Psychotria* Species.

The main alkaloids found in pantropical *Psychotria* (subgenus *Psychotria*) are polyindole alkaloids, which are characterized by the presence of several *N*-methyl triptamine moieties in their structures [15], such as psychotridine (**1**). This alkaloid, derived from five *N*-methyltriptamine units, was isolated from *P. beccarioides*, *P. forsteriana*, *P*. *oleoides*, and *P.* colorota [16-19]. Quadrigemine C (**2**) is another example of a polyindole alkaloid identified in this genus having been isolated from *P. colorata* and *P*. *oleoides* [9,16,18,20–22].

Four polyindoline alkaloids, named quadrigemines A (**4**) and B (**5**), psychotridine (**1**), and isopsychotridine C (**6**), were isolated from leaves of *P. forsteriana* [19, 23]. Besides these compounds, *meso*-chimonathine (7), a dimeric indole alkaloid, was also isolated from the same species. It was the first isolation of a dimeric isomer of calycanthine, which are commonly present in the genus *Calycanthus*, from *Psychotria* [24].

The chemical study of *P. rostrata* leaves led to the isolation of two new alkaloids: psychopentamine (**8**) and psychotrimine (**9**). Compound **8** was the first example of a polymeric pyrrolidinoindoline alkaloid which contains a C-3a/C-5’ bond. This group of compounds generally display two types of common linkages: C-3a/C-3a’ bond and C-3a/C-7’ bond [10].

Other examples of polyindoline alkaloids isolated from *Psychotria*, along with the compounds mentioned above, are summarised in **Table 1** and their structures are shown in **Fig.**(**1**).

Table 1. Dimeric and polyindoline alkaloids isolated from *Psychotria* species

Compound	Species	Part	Reference
Psichotridine (**1**)	*P. forsteriana*	Leaves	[16–19]
	P. oleoides	Leaves	
	P. colorata	Leaves	
	P. beccarioides	Leaves	
Quadrigemine C (**2**)	*P. colorata*	Flowers and leaves	[9, 15, 18, 20–22]
	P. oleoides	Leaves	
Psycholeine (**3**)	*P. oleoides*	Leaves	[21]

Quadrigemine A (**4**)	*P. forsteriana*	Leaves	[19]
Quadrigemine B (**5**)	*P. forsteriana*	Leaves	[16, 19,25]
	P. colorata	Leaves	
	P. rostrata	Leaves and twigs	
Isopsychotridine C (**6**)	*P. forsteriana*	Leaves	[19]
Meso-chimonanthine (**7**)	*P. forsteriana*	Not specified	[16, 24]
	P. muscosa	Leaves	
Psichopentamine (**8**)	*P. rostrata*	Leaves	[10]
Psychotrimine (**9**)	*P. rostrata*	Leaves	[10]
Psichotriasine (**10**)	*P. calocarpa*	Leaves	[26]
Hodgkinsine (**11**)	*P. colorata*	Flowers and leaves	[9, 16, 17, 22, 25]
	P. oleoides	Leaves	
	P. lyciiflora	Leaves	
	P. muscosa;	Leaves	
	P. beccarioides	Branches and twigs	
	P. rostrata		
(+)-Chimonanthine (**12**)	*P. colorata*	Flowers	[9, 16, 25]
	P. muscosa	Leaves	
	P. rostrata	Branches and twigs	
(**13**)	*P. henryi*	Leaves and twigs	[27]
(**14**)	*P. henryi*	Leaves and twigs	[27]
N_b-demetyl-*meso*-Chimonantina (**15**)	*P. lyciiflora*	Leaves	[22]
Psychohenin (**16**)	*P. henryi*	Leaves and twigs	[28]
Quadrigemine I (**17**)	*P. oleoides*	Leaves	[22]
Isopsychotridine B (**18**)	*P. oleoides*	Leaves	[18, 22]
Oleoidine (**19**)	*P. oleoides*	Leaves	[22]
Caledonine (**20**)	*P. oleoides*	Leaves	[22]
Psychotripine (**21**)	*P. pilifera*	Leaves	[29]

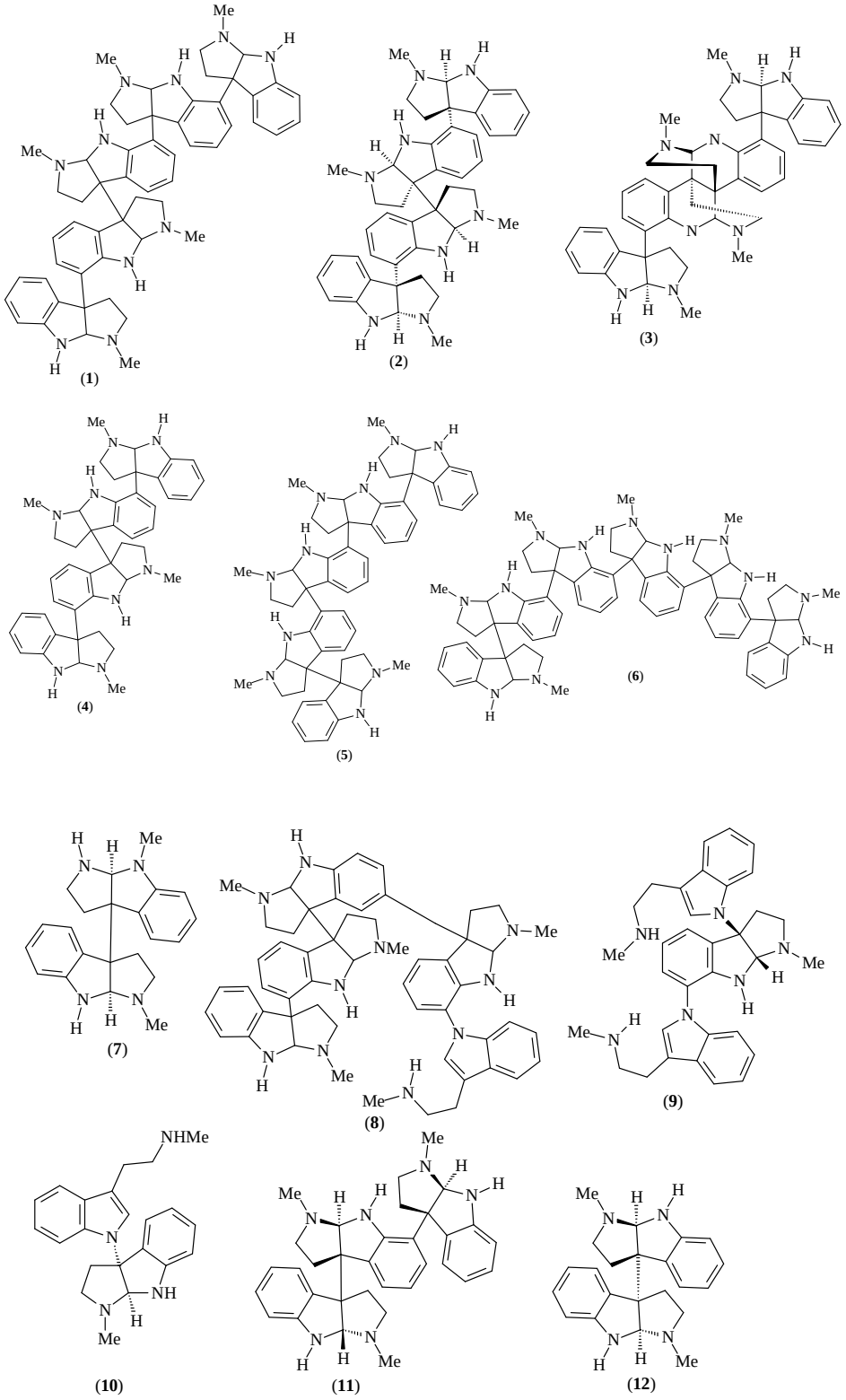


Fig. (1). Dimeric and polyindoline alkaloids isolated from *Psychotria* species

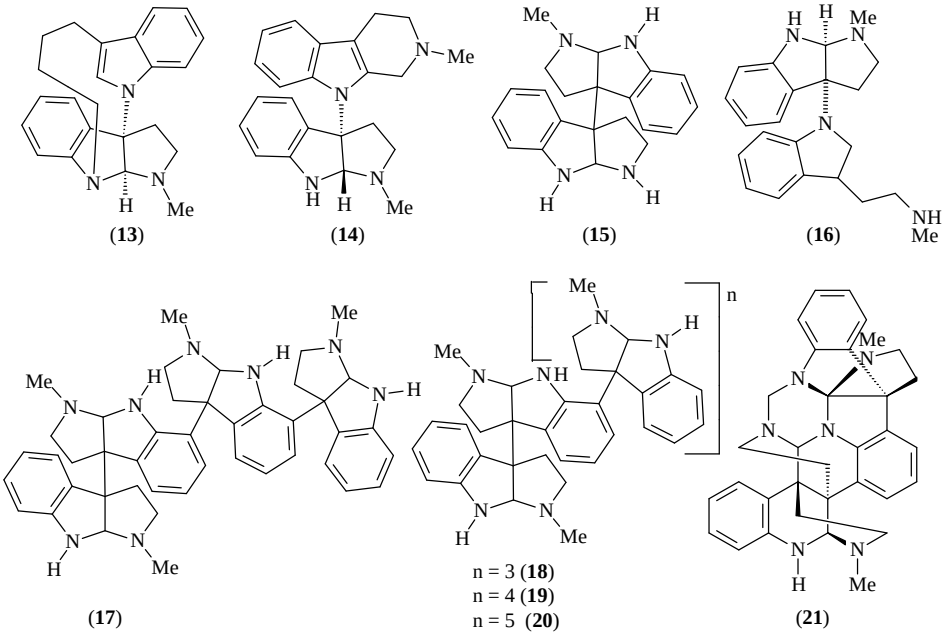


Fig. (1) continued

Monoterpene Indole Alkaloids Isolated from *Psychotria* Species.

Monoterpene indole alkaloids (MIAs) are biosynthesised by the coupling of tryptophan and the iridoid terpene secologanin. These kinds of metabolites have exhibited several biological activities, being used, for example as anti-cancer, anti-malaria and anti-arrhythmia agents [30]. MIAs are the main type of alkaloids found in the subgenus *Heteropsychotria* (neotropical species) [31], being considered chemotaxonomic markers for this subgenus [32].

The chemical investigation of *P. correae* led to the isolation of seven MIAs, along with other kinds of metabolites. Among them, six alkaloids were reported for the first time: correantoside (**22**), 10-hydroxycorreantoside (**23**), correantine A (**24**), correantine B (**25**), 20-*epi*-correantine B (**26**), and correantine C (**27**) [33].

Henriques *et al*. (2004) reported the isolation of *N*-β-D-glucopyranosyl vincosamide (**28**) from leaves of *P. leiocarpa*. It was the first report of a ***N***-glycosylated monoterpenoid indole alkaloid. The authors also concluded that the accumulation of this alkaloid depends on the age of the plant and light exposure, being restricted to the aerial parts of *P. leiocarpa* [34].

The chemical study of *P. brachyceras* led to the isolation of a new MIA named brachycerine (**29**). According to Nascimento *et al*. (2013), this alkaloid belongs to a new subclass of MIAs since its terpenoid moiety is probably derived from epiloganin rather than secologanin, as is the usual case. Subsequent studies also showed that

the concentration of brachycerine (**29**) increases on UV-B radiation exposure and osmotic/oxidative stress, suggesting that this compound may play a role in plant defence mechanisms [35,36].

From leaves of *P. umbellata*, an unusual alkaloid named psychollatine (**30**) was isolated. This compound is mainly accumulated in aerial parts of the plant but low amounts were also found in its roots [37,38]. Other studies regarding *P. umbellata*have beenmade leading to the isolation of three new MIAs: 3,4-Dehydro-18,19-β-epoxy-psychollatine (**31**), N^4-[1-((*R*)-2-hydroxypropyl)]-psychollatine (**32**), and N^4-[1-((*S*)-2-hydroxypropyl)]-psychollatine (**33**) [39].

Table 2 provides information concerning these compounds, as well as other MIAs isolated from *Psychotria* species. Their structures are displayed in **Fig.**(**2**).

Table 2. Monoterpene indole alkaloids isolated from *Psychotria* species

Compound	***Species***	**Part**	**Reference**
Correantosideo (**22**)	*P. correae*	Leaves	[33]
10-hidroxicorreantosideo (**23**)	*P. correae*	Leaves	[33]
Correantine A (**24**)	*P. correae*	Leaves	[33]
Correantine B (**25**)	*P. correae*	Leaves	[33]
20-*epi*-correantine B (**26**)	*P. correae*	Leaves	[33]
Correantine C (**27**)	*P. correae*	Root	[33]
N-β-D-glucopiranosil vincosamide (**28**)	*P. leiocarpa*	Aerial parts	[34]
Brachycerine (**29**)	*P. brachyceras*	Leaves	[40]
Psichollatine (**30**)	*P. umbellata*	Leaves	[37, 39]
3,4-Dehydro-18,19-β-epoxy-Psychollatine (**31**)	*P. umbellata*	Leaves	[39]
N^4-[1-((*R*)-2-hydroxypropyl)]-psychollatine (**32**)	*P. umbellata*	Leaves	[39]
N^4-[1-((*S*)-2-hydroxypropyl)]-Psychollatine (**33**)	*P. umbellata*	Leaves	[39]
5α-carboxystrictosidine (**34**)	*P. acuminata* *P. bahiensis*	Leaves Aerial parts	[41, 42]
Bahienoside B (**35**)	*P. acuminata* *P. bahiensis*	Leaves Aerial parts	[41, 42]
Desoxicordifoline (**36**)	*P. acuminata*	Leaves	[41]
Lagamboside (**37**)	*P. acuminata*	Leaves	[41]
(*E*/*Z*)-vallesiachotamine (**38** + **39**)	*P. acuminata* *P. bahiensis*	Leaves	[41–44]

	P. laciniata *P. suterella*	Aerial parts Leaves Leaves	
Strictosidinic acid (**40**)	*P. acuminata* *P. barbiflora* *P. myriantha* *P. myriantha*	Leaves Leaves Leaves Aerial pars	[6, 41, 45,46]
Strictosidine (**41**)	*P. acuminata*	Leaves	[41]
Palicoside (**42**)	*P. acuminata;*	Leaves	[41]
Bahienoside A (**43**)	*P. bahiensis*	Aerial parts	[42]
Angustine (**44**)	*P. bahiensis* *P. laciniata*	Aerial parts Leaves	[42, 43]
Strictosamide (**45**)	*P. bahiensis;* *P. nuda;* *P. prunifolia;* *P. suterella* *P. laciniata*	Aerial parts Leaves Leaves Leaves Leaves	[14, 42, 44, 47, 48]
Isodolichantoside (**46**)	*P. correae*	Leaves	[33]
10-hydroxy-*iso*-deppeaninol (**47**)	*P. prunifolia*	Branches	[49]
10-hydroxy-antirhine (**48**)	*P. prunifolia*	Branches	[49]
N-oxide-10-hydroxyantirhine (**49**)	*P. prunifolia*	Branches	[49]
14-oxoprunifoleine (**50**)	*P. prunifolia*	Branches	[49]
17-Vinil-19-oxa-2-azonia-12-azapentaci-clo[14.3.1.$0^{2,14}$.$0^{5,13}$.$0^{6,11}$]icosa-2(14),3,5(13),6(11),7,9-hex-aeno (**51**)	*P. prunifolia*	Leaves	[47]
17-vinil-19-oxa-2-azonia-12-azapentaci-clo[14.3.1.$0^{2,14}$.$0^{5,13}$.$0^{6,11}$]icosa-2(14),3,5(13),6(11),7,9-hex-aeno (**52**)	*P. prunifolia*	Leaves	[47]
N-demethyl-correantoside (**53**)	*P. stachyoides*	Leaves	[50]
Naucletine (**54**)	*P. suterella*	Leaves	[48]
Croceaine A (**55**)	*P. umbellata*	Leaves	[37]
Umbellatine (**56**)	*P. umbellata*	Leaves	[51]
Correantosine E (**57**)	*P. stachyoides*	Leaves	[32]
Correantosine F (**58**)	*P. stachyoides*	Stem bark	[32]
Stachyoside (**59**)	*P. stachyoides*	Aerial parts	[52]
Nor-methyl-23-oxo-correantoside (**60**)	*P. stachyoides*	Aerial parts	[52]

Lyaloside (**61**)	*P. laciniata* *P. suterella*	Leaves	[44]
Myrianthosine (**62**)	*P. myriantha*	Aerial parts	[46]

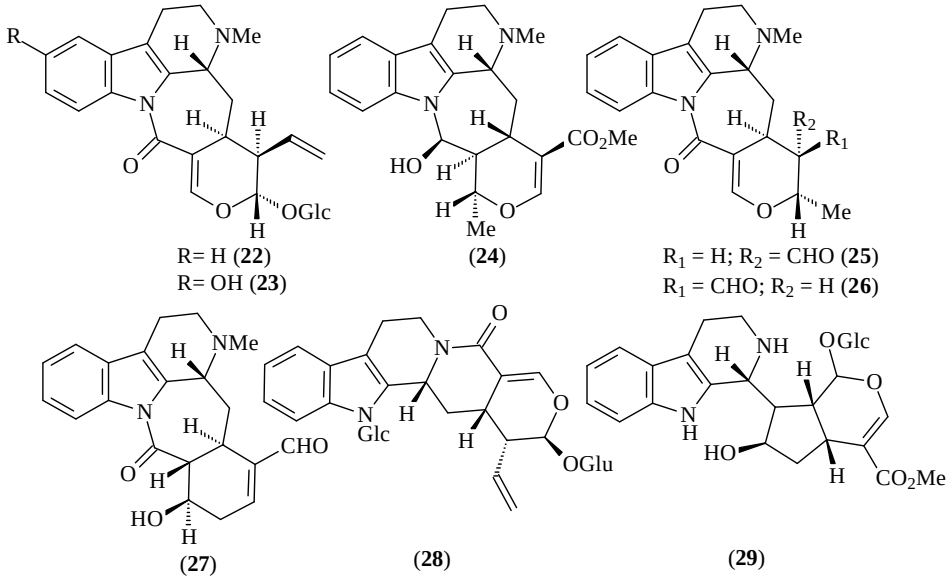


Fig.(2). Monoterpene indole alkaloids isolated from *Psychotria* species

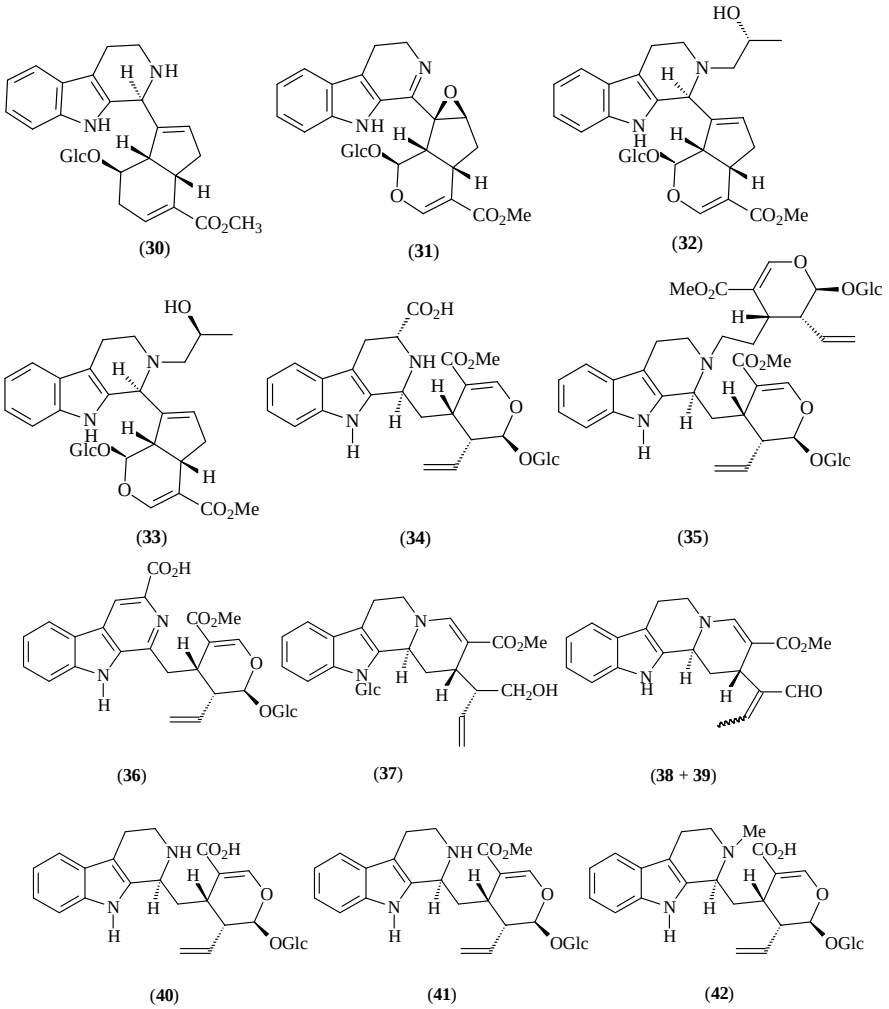
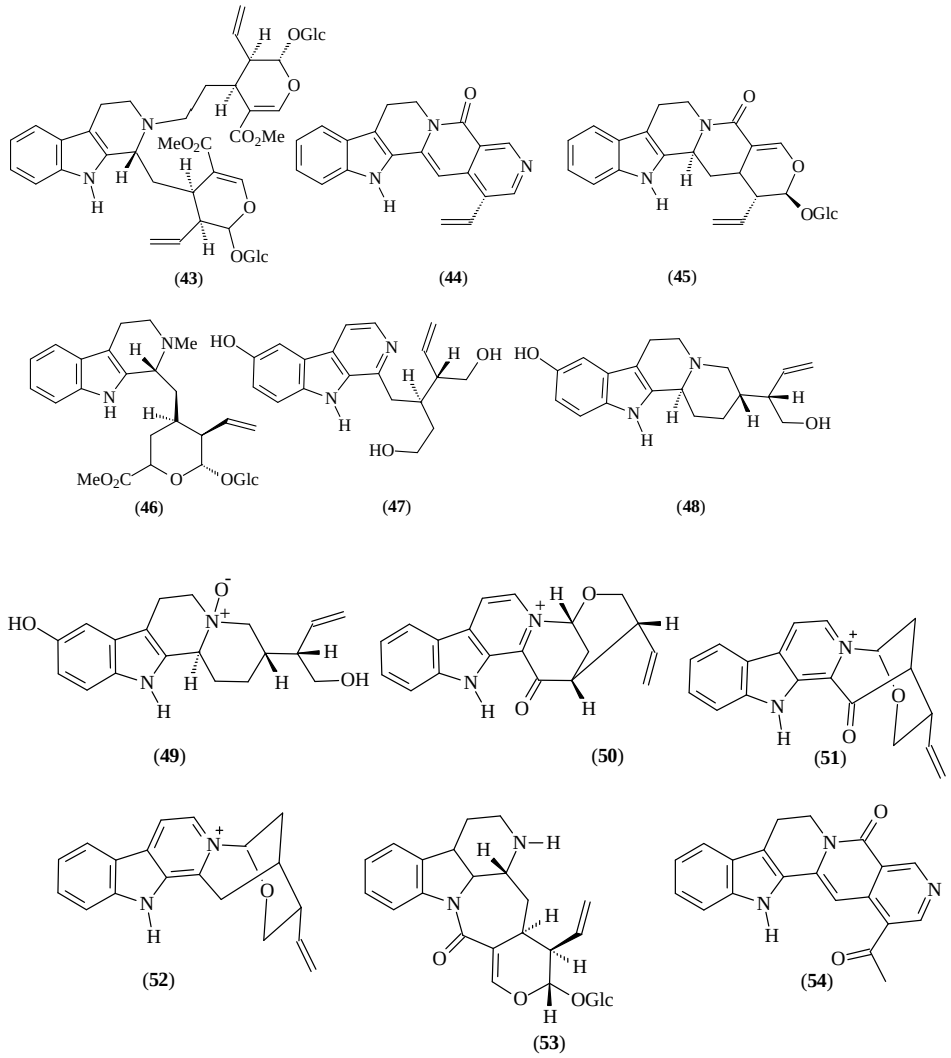


Fig.(2) continued.



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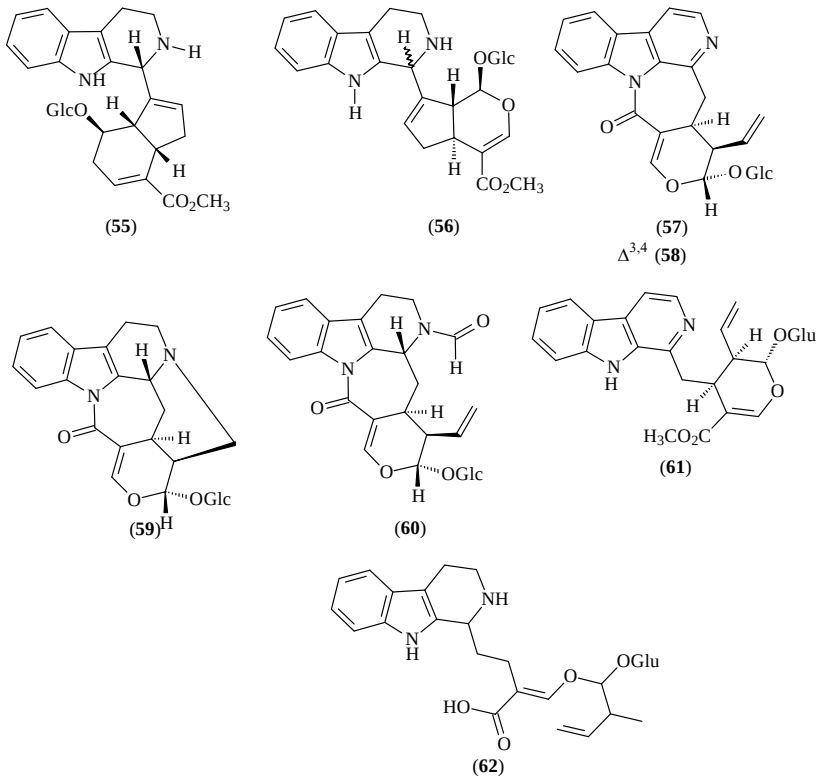


Fig.(2) continued.

Other classes of alkaloids Isolated from *Psychotria* Species

Besides the above-mentioned compounds, other kinds of alkaloids have also been reported for the genus *Psychotria*. From aerial parts of *P. glumerulla*, for example, three new quinoline alkaloids, named glomerulatine A to C (**63**–**65**, **Table 3**, **Fig. 3**) were isolated [53].

The chemical study of *P. klugii* led to the isolation of two new benzoquinolizidine alkaloids: klugine (**66**) and 7'-*O*-demethylisocepaheline (**67**). In addition, cephaeline (**68**), isocephaeline (**69**), and 7-*O*-methyllipecoside (**70**) were also isolated from stem bark of *P. klugii* [54].

Table 3. Other classes of alkaloids isolated from Psychotria species.

Compound	Species	Part	Reference
Glomerulatine A (**63**)	*P. glumerulata*	Aerial parts	[53]
Glomerulatine B (**64**)	*P. glumerulata*	Aerial parts	[53]
Glomerulatine C (**65**)	*P. glumerulata*	Aerial parts	[53]
Klugine (**66**)	*P. klugii*	Stem bark	[54]

7'-*O*-demethylisocefaeline (**67**)	*P. klugii*	Stem bark	[54]
Cephaelina (**68**)	*P. klugii*	Stem bark	[54]
Isocephaelina (**69**)	*P. klugii*	Stem bark	[54]
7-*O*-methylipecoside (**70**)	*P. klugii*	Stem bark	[54]
Harmane (**71**)	*P. barbiflora* *P. suerrensis*	Leaves	[6, 55]

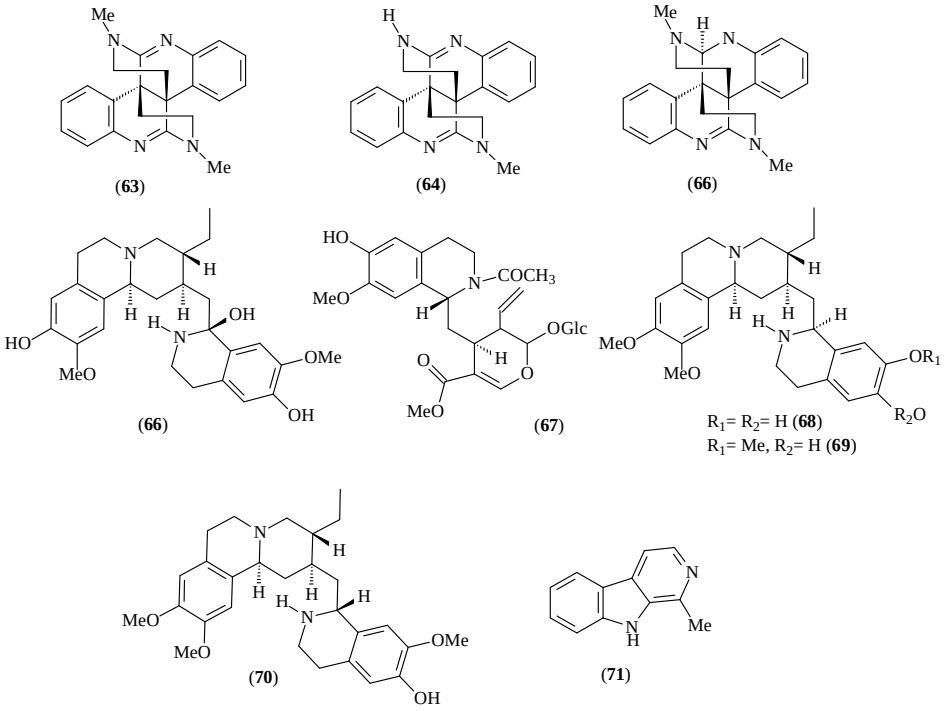


Fig. (3). Other classes of alkaloids isolated from *Psychotria* species.

Triterpenoids from *Psychotria* Species

Some studies have also reported the isolation of tritepenoids from *Psychotria* species, such as psychotrianosides A to G (**72**–**78**) and other common compounds as lupeol (**83**), betulin (**84**), friedelin (**88**), and so on. In **Table 4** we can find information regarding these and other triterpenoids and **Fig. 4** shows their structures.

Table 4. Triterpenoids isolated from *Psychotria* species.

Compound	Species	Part	Reference
Psychotrianoside A (**72**)	*P. sp*	Whole plant	[56]
Psycotrianoside B (**73**)	*P. sp*	Whole plant	[56]
Psycotrianoside C (**74**)	*P. sp*	Whole plant	[56]
Psycotrianoside D (**75**)	*P. sp*	Whole plant	[56]
Psycotrianoside E (**76**)	*P. sp*	Whole plant	[56]
Psycotrianoside F (**77**)	*P. sp*	Whole plant	[56]
Psycotrianoside G (**78**)	*P. sp*	Whole plant	[56]
Ardisianoside D (**79**)	*P. sp*	Whole plant	[56]
Barbinervic acid (**80**)	*P. stachyoides*	Leaves	[50]
α-amirin (**81**)	*P. stachyoides* *P. adenophylla*	Leaves Leavese	[50, 57]
Ursolic acid (**82**)	*P. adenophylla* *P. mariniana*	Leaves	[57, 58]
Lupeol (**83**)	*P. mariniana;* *P. vellosiana*	 Aerial parts	[58, 59]
Betulin (**84**)	*P. adenophylla* *P. mariniana*	Leaves	[57, 58]
Betulinic acid (**85**)	*P. adenophylla*	Leaves	[57]
Bauerenol (**86**)	*P. adenophylla*	Leaves	[57]
Bauerenol acetate (**87**)	*P. adenophylla*	Leaves	[57]
Friedelin (**88**)	*P. adenophylla*	Leaves	[57]

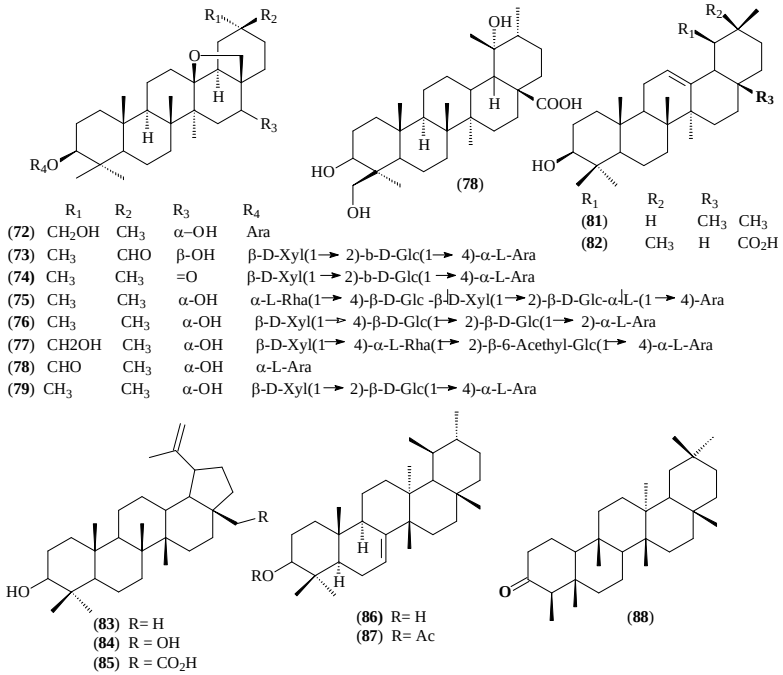


Fig. (4). Triterpenoids isolated from *Psychotria* species.

Other Classes of Metabolites from *Psychotria* Species

Other types of metabolites isolated from this genus are summarised in **Table 5** and their structures are displayed in **Fig.** (**5**).

Table 5. Other classes of metabolites isolated from *Psychotria* species.

Compound	Species	Part	Reference
Blumenol A (**89**)	*P. yunnanensis*	Aerial parts	[60]
Drummondol (**90**)	*P. yunnanensis*	Aerial parts	[60]
3*β*-hydroxy-5□, 6□-epoxi-7-megastimen-9-one (**91**)	*P. yunnanensis*	Aerial parts	[60]
Salicylic acid (**92**)	*P. yunnanensis*	Aerial parts	[60]
Resorcinol (**93**)	*P. yunnanensis*	Aerial parts	[60]
(-)-Loliolide (**94**)	*P. yunnanensis*	Aerial parts	[60]
(6*S*)-Menthiafolic acid (**95**)	*P. yunnanensis*	Aerial parts	[60]
4-hydroxybenzoic acid (**96**)	*P. yunnanensis*	Aerial parts	[60]
Vanillic acid (**97**)	*P. yunnanensis*	Aerial parts	[60]
Siringic acid (**98**)	*P. yunnanensis*	Aerial parts	[60]
Ethyl protocatechuate (**99**)	*P. yunnanensis*	Aerial parts	[60]
3β–hydroxy-1-(3,5-dimethoxy-4hydroxyphenyl)propan-1-one (**100**)	*P. yunnanensis*	Aerial parts	[60]

β-hydroxypropiovanillone (**101**)	*P. yunnanensis*	Aerial parts	[60]
(-)-Butin (**102**)	*P. yunnanensis*	Aerial parts	[60]
2-(4-hydroxy-3-metoxyphenil)-3-(2-hydroxy-5-metoxyphenyl)-3-oxo-1-propanol (**103**)	*P. yunnanensis*	Aerial parts	[60]
(+)-siringaresinol (**104**)	*P. yunnanensis*	Aerial parts	[60]
Feoforbídeo A (**105**)	*P. acuminata*	Leaves	[61]
Pirofeoforbídeo A (**106**)	*P. acuminata*	Leaves	[61]
β-sitosterol (**107**)	*P. adenophylla* *P. hainanensis* *P. mariniana; P. vellosiana*	Leaves Leaves Aerial parts	[57–60, 62]
β-sitosterol glycosylated (**108**)	*P. stachyoides*	Leaves	[50]
Stigmasterol glycosylated (**109**)	*P. stachyoides*	Leaves	[50]
Stigmasterol (**110**)	*P. vellosiana*	Aerial parts	[59]
Psicotramida A (**111**)	*P. sp.*	Stem	[63]
Psicotramida B (**112**)	*P. sp.*	Stem	[63]
Psicotramida C (**113**)	*P. sp.*	Stem	[63]
Psicotramida D (**114**)	*P. sp.*	Stem	[63]
Psicorubrina (**115**)	*P. rubra*	Stem	[64]
Stearic acid (**116**)	*P. hainanensis*	Leaves	[62]
6-hydroxy-luteolin-7-*O*-rutinoside (**117**)	*P. rubra*	Aerial parts	[65]
Luteolin-7-*O*-rutinoside (**118**)	*P. rubra*	Aerial parts	[65]
Quercetin (**119**)	*P. hainanensis;* *P. spectabilis*	Leaves Leaves	[13, 62]
Kaempferol-7-*O*-glucopyranoside (**120**)	*P. hainanensis*	Leaves	[62]
Kaempferol-3-*O*-glucopyranoside (**121**)	*P. hainanensis*	Leaves	[62]
Rutin (**122**)	*P. hainanensis*	Leaves	[62]
Psychorubrin (**123**)	*P. rubra*	Aerial parts	[65]
6α-hydroxygeniposide (**124**)	*P. rubra*	Aerial parts	[65]
Daucosterol (**125**)	*P. hainanensis*	Leaves	[62]
Psycacoraone (**126**)	*P. yunnanensis*	Aerial parts	[66]
Scopoletin (**127**)	*P. vellosiana*	Aerial parts	[59]
Squalene (**128**)	*P. vellosiana*	Aerial parts	[59]
Cyclopsychotride A (**129**)	*P. longipes*	Whole plant	[67]
Deoxysolidagenone (**130**)	*P. spectabilis*	Leaves	[13]
Solidagenone (**131**)	*P. spectabilis*	Leaves	[13]

Coumarin (**132**)	*P. spectabilis*	Leaves	[13]
Umbelliferone (**133**)	*P. spectabilis*	Leaves	[13]
Psoralene (**134**)	*P. spectabilis*	Leaves	[13]
Benz[g]isoquinoline-5,10-dione (**135**)	*P. camponutans*	Wood	[68]
1-hydroxybenzoisochromanquinone I (**136**)	*P. camponutans*	Wood	[68]

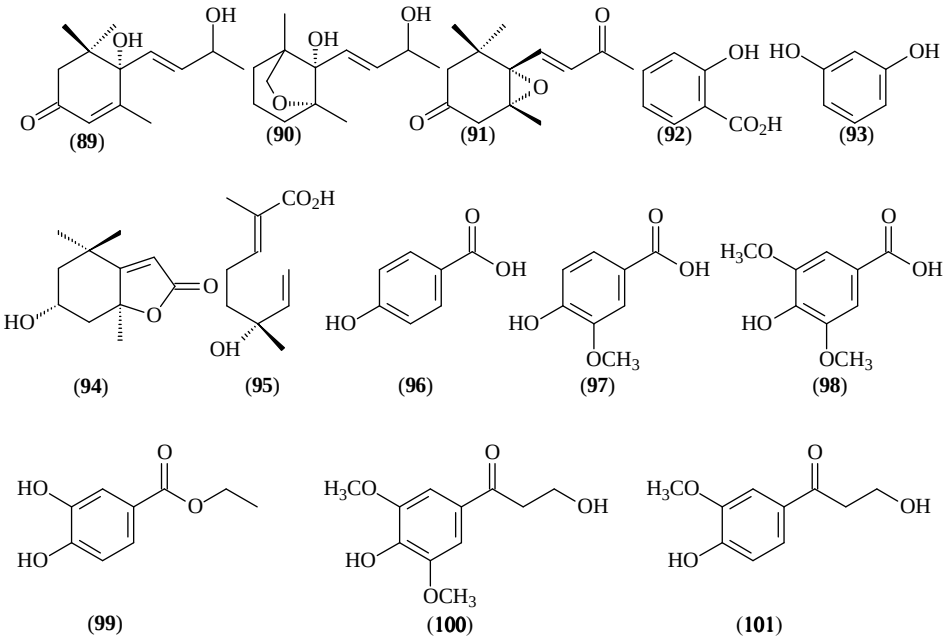


Fig. (5). Other classes of metabolites isolated from *Psychotria* species

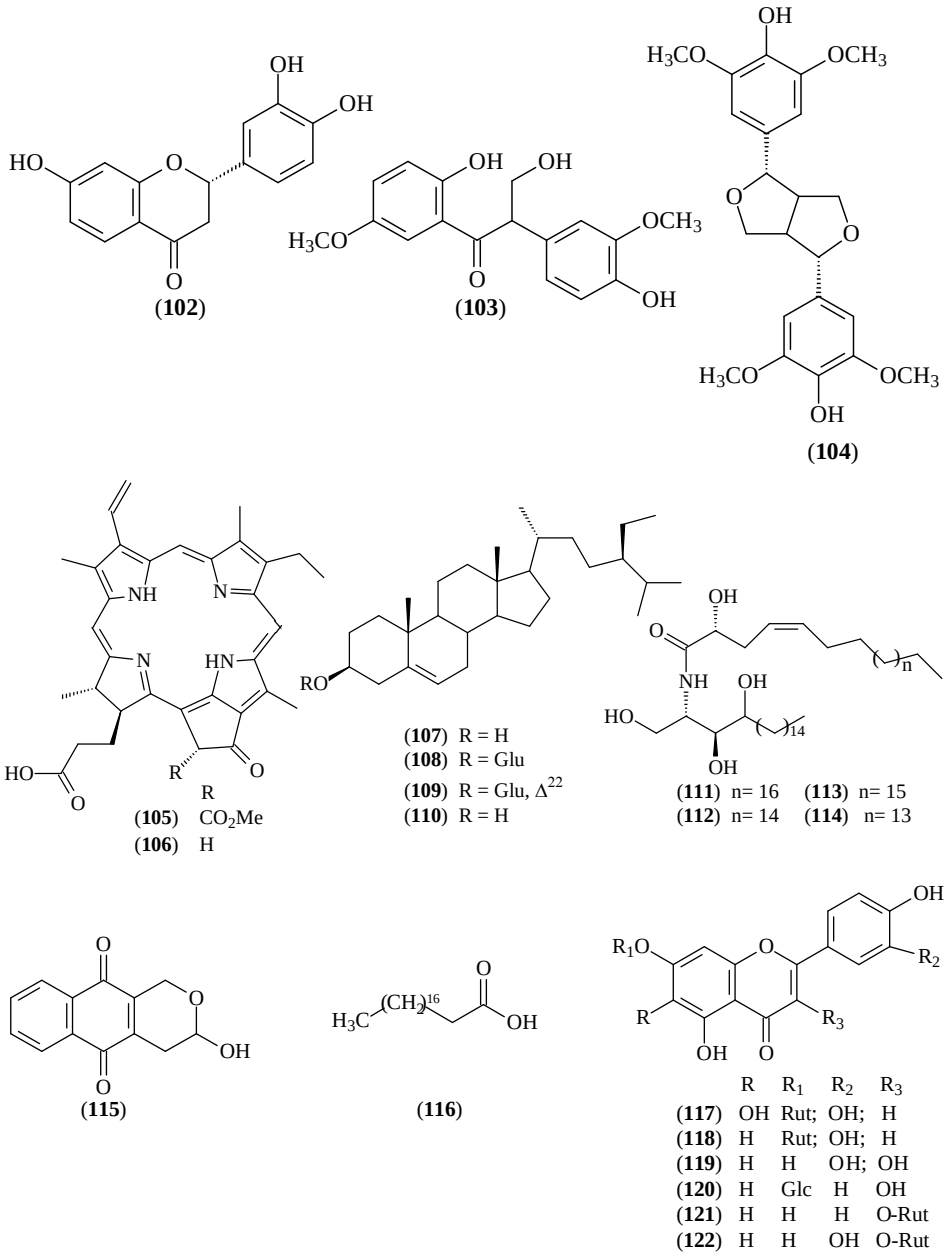


Fig. (5) continued

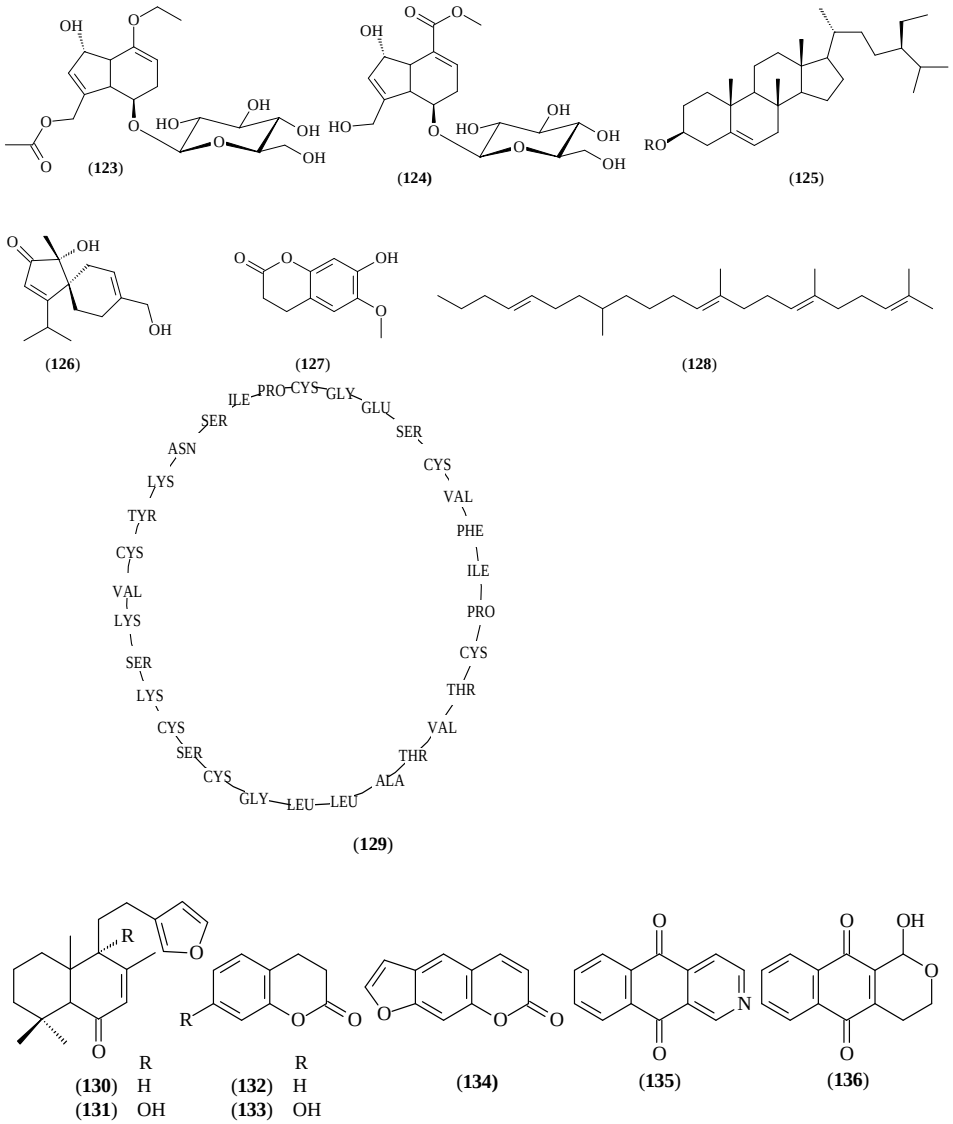


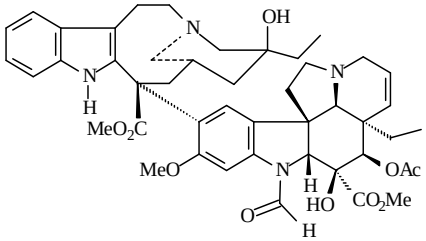
Fig. (5) continued

Biological Activities

Many studies have evaluated the biological properties of extracts, fractions, and isolated compounds from *Psychotria* species. These plants have been shown to have mostly cytotoxic, analgesic, antioxidant, and antimicrobial activities, as described in the next sections.

Cytotoxic Activity

Roth *et al.* (1986) evaluated cytotoxic activities of four polyindoline alkaloids, isolated from *P. forsteriana*on rat hepatoma cells (HTC line). Quadrigemines A (**4**) and B (**5**), psychotridine (**1**), and isopsychotridine C (**6**) exhibited higher cytotoxity than **vincristine**, used in antitumor chemotherapy.



Vincristine

In this essay, the authors concluded that the concentrations necessary to promote 100 % cellular mortality (after 24 hours of incubation) were 2.5, 5, 5, and 10 □M for compounds **1**, **4**, **6**, and **5**, respectively [14]. In a subsequent study, quadrigemine B (**5**) also showed time- and dose-dependent cytotoxic activity against HEp-2 cells [69].

Hayashi, Smith and Lee (1987) reported that psychorubrin (**123**), a new naphthoquinone isolated from *P. rubra*, showed cytotoxic activity in the KB cell assay (ED_{50} = 3.0 μg/mL). In addition, another four naphthoquinone derivatives (**137**–**140**) were prepared as a way to establish its structure-activity relationships. All derivatives exhibited higher cytotoxity than psychorubrin (ED_{50} ranging from 0.3 to 0.6 μg/mL). The authors concluded that extension of conjugation (observed for compounds **137** and **140**) is not sufficient to increase cytotoxic activity, since compound **141** (another naphthoquinone tested) was not active. Thus, other factors must be considered [64].

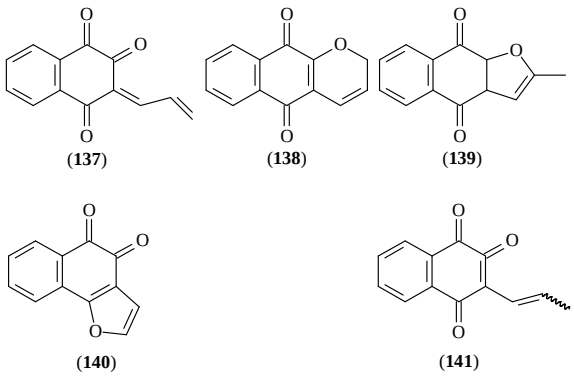
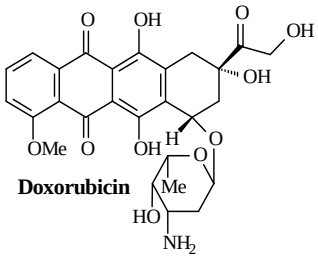
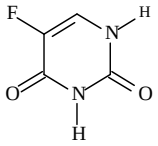


Fig. (6). Structures of compounds **137**–**141**

The *in vitro* cytotoxic activity of klugine (**66**), cephaelin (**68**), and isocephaelin (**69**), isolated from *P. klugii*, was evaluated against four human cancer cells lines, SK-MEL, KB, BT-549, and SK-OV-3. In this assay, **doxorubicin** and **5-fluorouracil** were used as positive controls, whereas DMSO was used as a negative control.



Doxorubicin



5-fluorouracil

Compound **66** was more potent against these human cancer cell lines (IC_{50} values of 0.25, 0.3, 0.86, and 0.18 μg/mL, respectively) than doxorubicin (IC_{50} values of 1.57, 1.7, 1.0, and 1.3 μg/mL, respectively). On the other hand, compounds 66 and 69 did not show cytotoxic activity against these cell lines [54].

Analgesic Activity

Aiming at discovering new painkillers, some researchers have investigated the analgesic properties of extracts and isolated compounds (mostly alkaloids) from *Psychotria* species, such as *P. colorata*, used by Amazonian Cablocos to treat earache and abdominal pain. The analgesic activity of an alkaloid extract from *P. colorata* was assessed by the formalin, writhing, and tail-flick methods, confirming the opioid-like analgesic activity of this species [70]. In a subsequent study, it was reported that the alkaloids from this plant exhibited inhibitory activity on [^{3}H]naloxone binding in rat striata membranes [71].

Other work related to *P. colorata* was carried out by Both *et al*. (2000) in order to evaluate the analgesic activity of hodgkinsine (**11**), a major alkaloid isolated from this plant. The authors concluded that this compound presented dose-dependent analgesic activity in mice, probablymediated by opioid and glutamate receptors, suggesting that it participates in the analgesia previously reported for *P.* colorata [72]. Umbellatine (**56**), an alkaloid from *P. umbellata*, is other example of a compound which showed analgesic properties [51].

Both *et al.* (2002) evaluated the analgesic activity of alkaloid extracts from three *Psychotria* species classified as *P. myriantha*, *P. nuda*, and *P. pubigera*. In this work, it was reported that only *P. myriantha* showed this property (hot plate method) [73].

Antioxidant Activity

Fragosos *et al.* (2008) evaluated antioxidant and antimutagenic potentials of psychollatine (**30**) and the crude foliar extract of *P. umbellata*. Antioxidant properties

were assessed in strains of *Saccharomyces cerevisiae* deficient in superoxide dismutase and/or catalase (exposed to H_2O_2 and paraquat) and by the hypoxanthine/xanthine oxidase assay. Psychollatine (**30**) was more efficient in protection of strains treated with paraquat, whereas the crude foliar extract showed better results for strains treated with H_2O_2. In the hypoxanthine/xanthine oxidase assay both psychollatine (**30**) and the crude extract showed a marked dose-dependent antioxidant activity, but the crude extract was more active (possibly owing to the presence of flavonoids) than the isolated compound. Both the crude extract and psychollatine (**30**) showed antimutagenic effects on strains of *S. cerevisiae* (mutagenesis was induced by H_2O_2) [74]. Brachycerine (**29**), isolated from *P. brachyceras*, is another example of an MIA which possessed antioxidant and antimutagenic activities [75].

The *in vitro* antioxidant activity of fruits, stems, and leaf extracts of *P. nilgiriensis* was investigated by DPPH, $ABTS^{\cdot+}$, and FRAP assays. An acetone extract of fruits, had the highest total phenolics (505.74 □g GAE/g extract), tannin (460.78 μg GAE/g extract), and flavonoids (67.78 μg RE/g extract). In addition, this extract presented higher values for DPPH (IC_{50} = 20.0 μg/mL), ABTS (41,343.51 μmol TE/g extract), and FRAP (4,713.33 μmol Fe (II)/mg extract) assays [76].

Antimicrobial Activity

The antimicrobial activity of methanolic extracts of leaves, roots, and stem barks of *P. microlabastra* against bacteria, protozoa, and fungi, was evaluated by the disk diffusion method. In addition, fractions obtained by partition of these extracts with petrol, dichloromethane, and ethyl acetate were also tested. In this work, the authors reported that all extracts displayed activity against all bacteria and protozoa tested, especially ethyl acetate fractions [77].

Three *Psychotria* species, along with other Rubiaceae and Meliaceae species, were studied in order to investigate their antimicrobial properties by the disc diffusion method. Extracts of leaves and bark of *P. gardineri*, *P. nigra*, and *P stenophylla* were prepared using *n*-hexane, dichloromethane, and methanol as solvents and tested against *Saccharomyces cerevisiae*, *Ustilago maydis*, *Escherichia coli*, *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *and Aspergillus niger*. *P. gardineri and P. stenophylla*showed a broad antimicrobial activity against six of the seven

microorganisms tested while *P. nigra* was active against four species [78]. The biological activities reported for *Psychotria* species are summarized in **Table 6**.

Table 6. Biological activities reported for *Psychotria* species

Species	Plant part	Extract or compound	Activity	Reference
P. rubra	Stem	Psychorubrin	Cytotoxic activity	[64]
P. rostrata	Bark and twigs	Quadrigemine B	Cytotoxic activity	[69]
P. forsteriana	Leaves	Psychotridine, auadrigemines A and B, isopsychotridine, and chimonanthine	Cytotoxic activity	[19,79]
P. camponutans	Wood	Benz[g]isoquinoline-5,10-dione	Cytotoxic activity	[68]
		1-hydroxybenzoisochromanquinone		
P. spectabilis	Leaves	Solidagenone and psoralene	Cytotoxic activity	[13]
P. colorata	Leavesand flowers	Aqueous and alkaloid extracts	Analgesic activity	[70, 71]
P. colorata	Flowers	Hodgkinsine	Analgesic activity	[72]
P. brachypoda	Leaves	ethanol extract	Analgesic activity	[80]
P. umbellata	Leaves	Umbellatine	Analgesic activity	[51]
P. myriantha	Leaves	Alkaloid extract	Analgesic activity	[73]
P. nilgiriensis	Stem and fruit	Acetone extract	Analgesic and antioxidant activities	[76]
P. sarmentosa	Leaves and stems	Aqueous extract	Analgesic activity	[81]
P. umbellata	Leaves	Methanol extract and umbellatine	Antioxidant and antimutagenic activities	[74]
P.	Leaves	Methanol extract and	Antioxidant and	[75]

brachyceras		brachycerine	antimutagenic activities	
P. leiocarpa	Leaves	*N*,β-D-glucopyranosyl vincosamide	Antioxidant activity	[82]
P. microlabastra	Leaves, stem, and roots bark	Methanol extract, petrol and ethyl acetate fractions	Antimicrobial activity	[77]
P. gardineri	Branches and leaves	Dichloromethane and methanol extracts	Antimicrobial activity	[78]
P. nigra	Branches and leaves	Dichloromethane, hexane and methanol extracts	Antimicrobial activity	[78]
P. reevesii	Aerial parts	Methanol extract	Antimicrobial activity	[83]
P. spectabilis	Leaves	Coumarin, deoxysolidagenone, psoralene, and solidagenone	Antifungal activity	[13]
P. prunifolia	Branches	Ethanol extract, strictosamide, and 14-oxoprunifoleine	Antiprotozoal activity	[49]
P. serpens	Not specified	Ethanol extract	Inhibition of herpes simplex virus (HSV-1) replication	[84]
P. klugii	Stem bark	Klugine, 7'-*O*-demethylisocephaeline, cephaeline, isocephaeline, and 7-*O*-methylipecoside	Antiparasitic activity	[54]
P. laciniata	Leaves	Alkaloid fraction, lyaloside, and strictosamide	Monoamine oxidase inhibition	[44]
P. suterella	Leaves	Alkaloid extract and (*E/Z*)-vallesiachotamine	Monoamine oxidase inhibition	[44]
P. myriantha	Leaves	Strictosidinic acid	Monoamine oxidase inhibition	[45]

P. myriantha	Aerial parts	Alkaloid extract, myrianthosine, and strictosidinic acid	Antichemotactic activity	[46]
P. leiocarpa	Leaves	Aqueous extract	Allelopathic activity	[85]
P. capitata	Leaves	Ethanol extract		
P. leiocarpa	Leaves	Ethanol extract	Antimycobacterial activity	[86]
P. glaziovii	Leaves	Ethanol extract	Antimycobacterial activitiy	[86]
P. nuda	Leaves	Ethanol extract	Antimycobacterial activitiy	[86]
P. pubigera	Leaves	Ethanol extract	Antimycobacterial activitiy	[86]
P. racemosa	Leaves	Ethanol extract	Antimycobacterial activitiy	[86]
P. ruelliifolia	Leaves	Ethanol extract	Antimycobacterial activitiy	[86]
P. suterella	Leaves	Ethanol extract	Antimycobacterial activitiy	[86]
P. vellosiana	Leaves	Ethanol extract	Antimycobacterial activitiy	[86]

Synthesis Of Some Compounds From *Psychotria* Species

Quadrigemine C (2) and Psycholeine (3)

The total synthesis of quadrigemine C (**2**) and psycholeine (**3**), isolated from *P. oleoides* [15], was performed by Lebsack *et al*. (2002) [87]. The route reported starts with *meso*-chimonanthine (**7**) which was obtained by reaction of oxindole with isatin in 13 steps, as had been reported in previous work [88]. After some steps, quadrigemine C (**2**) was obtained and acid-catalysed isomeration led to the formation of psycholeine (**3**), as described in **Fig.**(**7**).

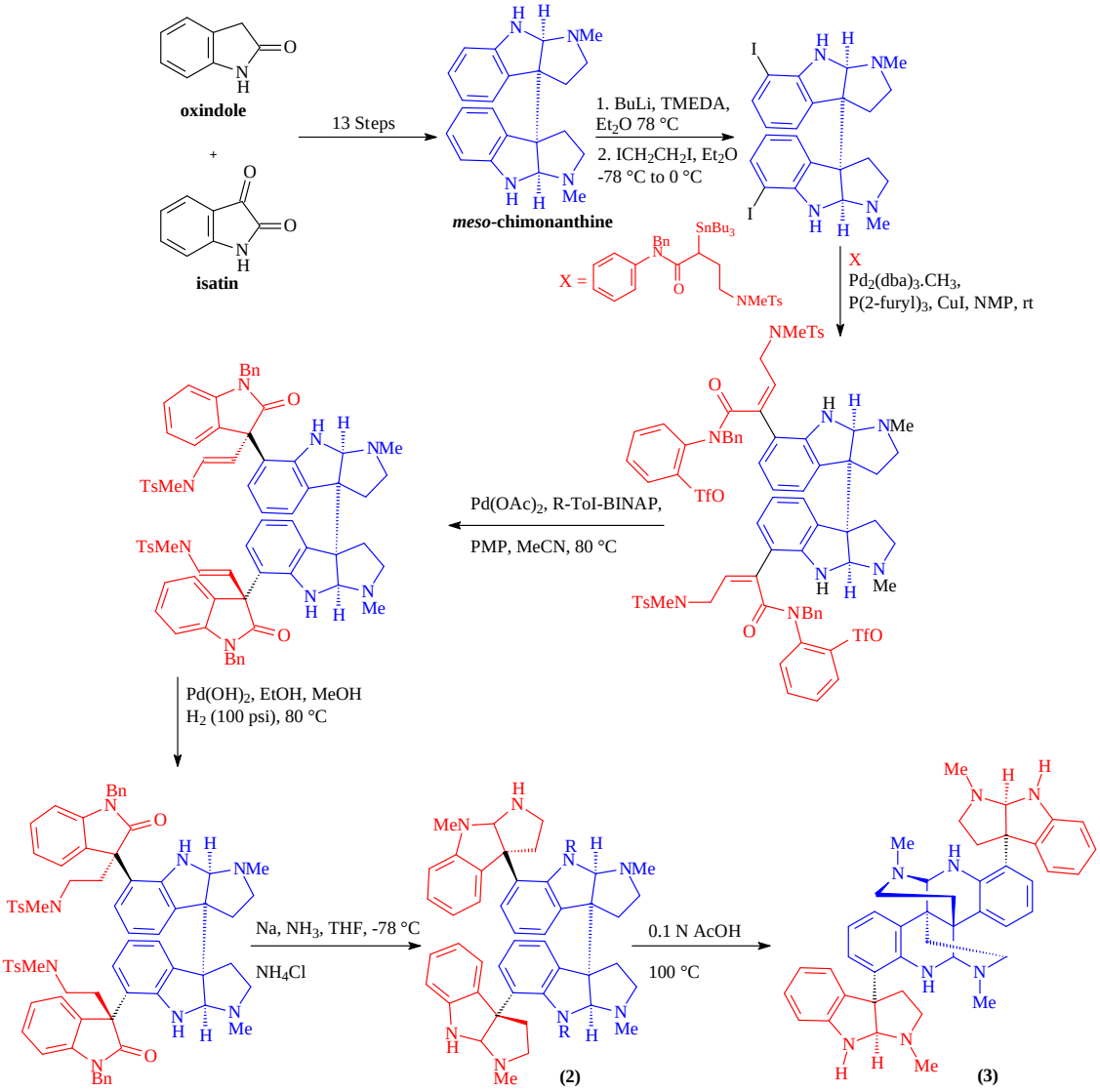


Fig.(7). Synthesis of quadrigemine C (**2**) and psycholeine (**3**) proposed by Lebsack *et al*. (2002)

Psychotrimine (9)

The first total synthesis of psychotrimine (**9**) was proposed by Matsuda, Kitagima and Takayama (2007), involving 16 steps [89]. On the other hand, Newhouse and Baran (2008) carried out the total synthesis of (±)-psycotrimine in four steps, using 7-bromotryptamine as starting material. According to them, there had been no methodology, up to that point, to construct that kind of C-N bond [90], as can be seen in **Fig.**(**8**).

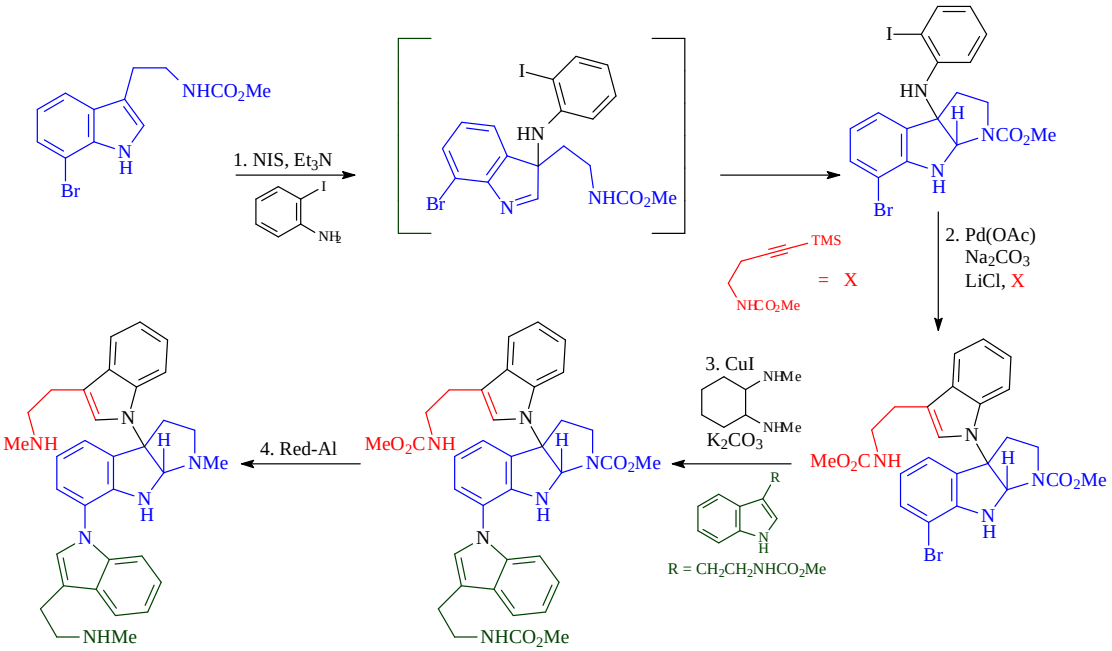


Fig.(**8).** Synthesis of psychotrimine (**9**) proposed by Newhouse and Baran (2008)

1-Hydroxybenzoisochromanquinone

This benzoquinone was isolated from the wood of *P. camponutans*. Its synthesis, performed by Jacobs, Claessens and Kimpe (2008), was achieved with a phthalide annulation reaction using 3-cyano-1(3*H*)-isobenzofuranone (**142**) and 5,6-dihydropyran-2-one (**143**), followed by reduction of the lactone moiety. This synthetic route is described in **Fig.** (9) [91]**.**

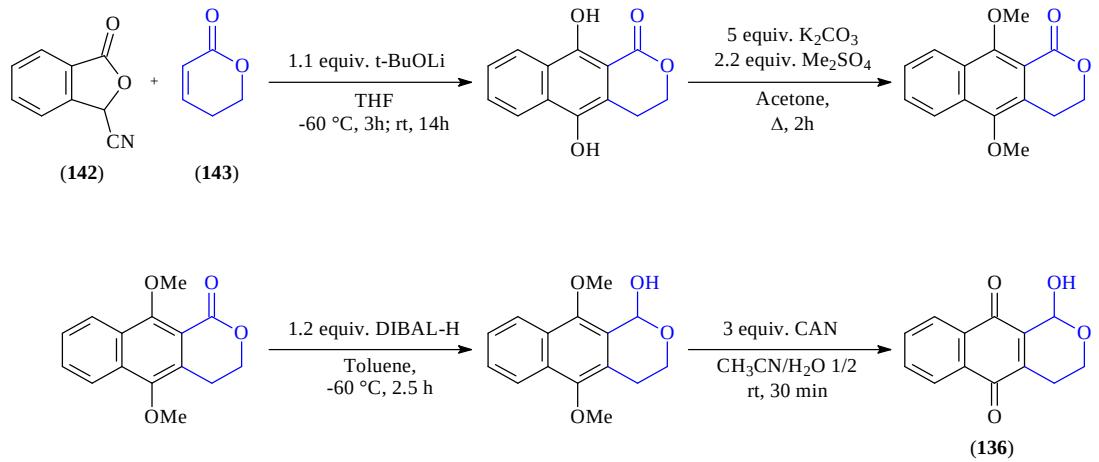


Fig.(9). Synthesis of 1-hydroxybenzoisochromanquinone proposed by Jacobs, Claessens and Kimpe (2008)

Concluding Remarks

The genus *Psychotria* presents a wide chemical diversity, comprising mainly alkaloids. The more abundant alkaloids of the subgenus *Psychotria* are polyindole alkaloids whereas MIAs are predominant in the subgenus *Heteropsychotria*. Terpenoids, flavonoids, and other compounds are well known for their biological properties and although a suite of compounds belonging to these phytochemical classes has been isolated from the *Psychotria* genus, few have been subjected to pharmacological assays. From two thousand species, only forty-seven have been examined so far. There is a perception that extensive research work has been done with some species of this genus; however, a large number of species are still chemically and/or pharmacologically unknown. While this review has attempted to unite the relevant information about *Psychotria* species, the bioactivity profiles from the genus, and its alkaloids as the main bioactive compounds, clearly suggest future research priorities. The presence of alkaloids makes the species of *Psychotria* extremely promising, considering that this class of metabolites has shown a range of biological activities. Moreover, these compounds can be used as models to obtain more potent and effective synthetic derivatives.

Abbreviations

Ac	acetyl
CAN	Cerium (IV) ammonium nitrate
Et	Ethyl
MIAs	Monoterpene indole alkaloids
NIS	N-iodosuccinimide
$Pd_2(dba)_3$	tris(dibenzylidineacetone)dipalladium (0)
PMP	1,2,2,6,6-pentamethylpiperidine
Rt	room temperature

THF Tetrahydrofuran

TMEDA Tetramethylethylenedramine

TMSOTf trimethylsilyl trifluoromethanesulfonate

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3.2 Trabalho 2:

^{13}C-NMR Spectral Data of Alkaloids Isolated from *Psychotria* Species (Rubiaceae)**

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Abstract: The genus *Psychotria* (Rubiaceae) comprises more than 2,000 species, mainly found in tropical and subtropical forests. Several studies have been conducted concerning their chemical compositions, showing that this genus is a potential source of alkaloids. At least 70 indole alkaloids have been identified from this genus so far. This review aimed to compile ^{13}C-NMR data of alkaloids isolated from the genus *Psychotria* as well as describe the main spectral features of different skeletons.

Keywords: Rubiaceae; *Psychotria*; ^{13}C-NMR Spectral Data.

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1. Introduction

In phytochemistry and related areas, structural elucidation techniques play a key role because precise knowledge of the chemistry of plants requires unequivocal structural characterization of its metabolites to obtain information related to the taxonomy of plant groups. Moreover, correct identification of biologically active

compounds is important, both to understand their possible mechanisms of action and propose chemical modifications aimed at enhancing their activity.

The characterization of natural products requires, apart from patience and dedication, knowledge about spectroscopic techniques (interpretation of these data) and the biosynthesis of different types of metabolites. Comparison with literature data is another important auxiliary tool that aids the structural characterization of a given compound. In this context, finding a material that provides as much information as possible about the spectral data of metabolites isolated from a genus (such as *Psychotria*) may enable saving time.

The genus *Psychotria* (Rubiaceae) comprises more than 2,000 species, which occur mostly in tropical and subtropical regions[1], with many of these species being employed in folk medicine to treat several diseases [2,3]. The biological potential of the chemical constituents of the species of this genus has possibly motivated several studies regarding the chemical composition of such species. Most of these have focused on investigating alkaloid fractions obtained by acid–base extraction, probably owing to the biological importance of this type of metabolite. Such efforts have led to the isolation and/or identification of various alkaloids, primarily indole-type. Some of them exhibit some biological properties such as analgesic [4,5], antioxidant [6], antiparasitic [7], and cytotoxic[8,9] activities.

This review aimed to compile ^{13}C NMR spectral data of alkaloids isolated from *Psychotria* species as well as to discuss the main spectral features observed for the different types of skeletons.

2. Discussion

2.1. ^{13}C Chemical Shifts of Monoterpene Indole Alkaloids Isolated from Psychotria Species.

Monoterpene indole alkaloids (MIAs) comprise a wide group of secondary metabolites, found mainly in the Apocynaceae, Loganiaceae, and Rubiaceae families [10]. Their biosynthesis involves a reaction between tryptamine (derived from

tryptophan) and the iridoid secologanin, catalyzed by strictosidine synthase [11]. This initial step leads to the formation of strictosidine (**1**) (**Table 1**, **Figure 1**), the key precursor of other MIAs.

Strictosidine (**1**) was isolated from *P. elata* [12] and *P*. *nuda* (data not reported), and presents an *ortho*-substituted ring system (as do most of the MIAs isolated from this genus), characterized by the presence of four methine carbon signals at δ_C 118.8 (CH-9), 120.1 (CH-10), 122.7 (CH-11), and 112.0 (CH-12), and two quaternary carbon signals at δ_C 127.9 (C-8) and 137.9 (C-13). The signals of two quaternary carbons at δ_C 133.2 (C-2) and 107.7 (C-7), along with a methine carbon at δ_C 52.4 (CH-3) and two methylene carbons at δ_C 42.9 (CH_2-5) and 21.0 (CH_2-6) complete the tetrahydro-β-carboline system. The secologanin moiety is confirmed by the presence of signals resonating at δ_C170.6 (C-22), δ_C 109.9 (C-16), and 156.1 (C-17), relative to an α,β-unsaturated carboxyl group, a terminal vinyl at δ_C135.7 (CH-19) and 119.5 (CH_2-18), besides signals at δ_C97.5 (CH-21), 45.6 (CH-20), 35.9 (CH_2-14), and 32.5 (CH-15). The carbon signals of the glucose unit are observed at δ_C100.3 (CH-1'), with four mono-oxygenated methines in the interval from δ_C78.6 to 71.7 and one oxygenated methylene at δ_C 62.9 [13].

Strictosidine (**1**) may function as a precursor of other biosynthetic pathways, leading to different skeletons and consequently changes in spectral properties. Carbonylation at C-5 (δ_C = 176.5 ppm), as observed for 5□-carboxystrictosidine (**4**), for example, promotes a chemical shift displacement of CH_2-6 ($\Delta\delta$ = 4.2 ppm, *β* effect) when compared with **1**, as can be seen in **Table 2.** A similar pattern was observed for methylation of *N*-4 on correantoside (**7**) isolated from *P. correa* [14], where $\Delta\delta$variations of 5.4 and 3.5 ppm are observed for CH-3 and CH_2-5, respectively (*β* effect). For 10-hydroxycorreantoside (**8**), it is possible to observe the electronic influence of a hydroxyl by the inductive effect at the *ipso* carbon (C-10) and an increase in the electron densities at the *ortho* (CH-9 and CH-11) and *para* (C-13) positions by the mesomeric effect. On the basis of this mesomeric effect, the signals corresponding to carbon atoms at the *ortho,* CH-9 [δ_C118.8 (**1**) and 104.4 (**8**), $\Delta\delta_C$= −14.8 ppm] and

CH-11 [δ_C 122.7 (**1**) and 114.2 (**8**), $\Delta\delta_C$= −8.5 ppm], and *para* positions, C-13 [δ_C 137.9 (**1**) and 131.4 (**8**), $\Delta\delta_C$= −6.5 ppm], are displaced upfield.

Other metabolic pathways of this class of alkaloid revealed cyclization reactions involving *N*-1(**5** and **6**) or *N*-4 (**7**–**14**) with C-22, or *N*-1 with C-18 and *N*-4 with C-22, as particularly observed for stachyoside (**30**) isolated from *P.* stachyoides [15] (**Figure 2**). Strictosamide (**5**), isolated from four different species,[16-19] is an example of lactam formation between *N*-4 and C-22. By examining **Table 2**,it is possible to notice, apart from the absence of a methoxyl group (carbomethoxy function) signal at δ_C 52.4, a slight difference in the chemical shift of C-22 (δ_C 167.1 ppm), when compared with compound **1** (δ_C 170.6 ppm), as well as a $\Delta\delta_C$ variation of 6.9 ppm for C-17. In contrast, correantoside (**7**) exemplified the first possibility involving cyclization between *N*-1 and C-22. It is possible, in this case, to observe the variation in the chemical shifts of the *ortho* CH-12 ($\Delta\delta$ = 4.0 ppm) and *para* CH-10 ($\Delta\delta$ = 4.1 ppm) atoms, promoted by the inductive and mesomeric effects of the carboxyl group at C-22. These effects were also observed for compounds **8** [$\Delta\delta_C$ = 4.8 (CH-12) ppm], **13** [$\Delta\delta_C$ = 4.4 (CH-12) and 4.1 (CH-10) ppm], **14** [$\Delta\delta_C$ = 4.4 (CH-12) and 4.5 (CH-10) ppm], **18** [$\Delta\delta_C$ = 7.8 (CH-12) and 6.2 (CH-10) ppm], and **19** [$\Delta\delta_C$ = 7.3 (CH-12) and 5.4 (CH-10) ppm], showing that the downfield displacements of the CH-12 and CH-10 signals may be used to suggest that *N*-1 is attached to C-22.

There are some examples of alkaloids isolated from this genus, whose biosynthesis involves hydrolysis of a glycoside moiety such as (*E*/*Z*)-vallesiachotamines, **23** and **24,** isolated from *P. bahiensis* [17], and10-hydroxy-*iso*-deppeaninol (**27**) and *N*-oxide-10-hydroxyantirhine (**29**) isolated from *P. prunifolia* [20]. These types of skeletons may be suggested by analysis of the region of the ^{13}C spectrum that is typical of sugar, revealing the absence of the typical signal of the anomeric carbon around δ_C 100.0, apart from additional signals of the oxy-carbons characteristic of this unit.

Kerber et al. (2001) reported the isolation of a new MIA from *P. brachyceras* leaves [21], named brachycerine (**33**), which showed a new alkaloid skeleton. Its biosynthesis

involved the coupling of tryptamine to a 1-*epi*-loganin derivative. Psychollatine (**34**), a new MIA from *P. umbellate* [22], presented a terpenoid derivative from geniposide. Both alkaloids as well as compounds **21**, **22**, and **35** revealed an important characteristic in their ^{13}C spectra: the absence of typical signals of a terminal vinyl group (~δ_C 119 ppm). In contrast, bahienosides A (**38**) and B (**37**), isolated from *P. bahiensis*[17], showed duplicate signals relative to two secologanin moieties. **Figure 2** shows typical carbon assignments, which may indicate some different structural possibilities in comparison with those values observed for strictosidine (**1**).

Table 1. Monoterpene indole alkaloids from *Psychotria* species.

Compounds	**Species**	**References**	**^{13}C NMR Data**
Strictosidine (**1**)	*P.elata*	[12]	[13]
Strictosidinic acid (**2**)	*P. acuminata* *P. barbiflora* *P. myriantha*	[1, 23-25]	[25]
Palicoside (**3**)	*P. racemosa*	[12]	[26]
5α-carboxystrictosidine (**4**)	*P. acuminata* *P. bahiensis*	[17, 23]	[27]
Strictosamide (**5**)	*P. bahiensis* *P. nuda* *P. prunifolia* *P. suterella*	[16-19]	[18]
N,*β*-D-glucopyranosilvincosamide (**6**)	*P. leiocarpa*	[28]	[28]
Correantoside (**7**)	*P. correae*	[14]	[14]
10-hydroxycorreantoside (**8**)	*P. correae*	[14]	[14]
Correantine B (**9**)	*P. correae*	[14]	[14]
20-*epi*-correantine B (**10**)	*P. correae*	[14]	[14]
Correantine A (**11**)	*P. correae*	[14]	[14]
Correantine C (**12**)	*P. correae*	[14]	[14]
N-desmethyl-correantoside (**13**)	*P. stachyoides*	[29]	[29]
Nor-methyl-23-oxo-correantoside (**14**)	*P stachyoides*	[15]	[15]
14-oxoprunifoleine (**15**)	*P. prunifolia*	[18, 20]	[18]
17-vinyl-19-oxa-2-azonia-12-azapentacy-clo [14.3.1.$0^{2,14}$.$0^{5,13}$.$0^{6,11}$]icosa-2(14),3,5(13),6(11),7,9-hex-aene (**16**)	*P. prunifolia*	[18]	[18]
Naucletine (**17**)	*P. suterella*	[19]	[30]
Correantosine E (**18**)	*P stachyoides*	[31]	[31]
Correantosine F (**19**)	*P stachyoides*	[31]	[31]

Lagamboside (**20**)	*P. acuminata*	[23]	[23]
N^4-[1-((*R*)-2-hydroxypropyl)]-psychollatine (**21**)	*P. umbellata*	[32]	[32]
N^4-[1-((*S*)-2-hydroxypropyl)]-psychollatine (**22**)	*P. umbellata*	[32]	[32]
(*E/Z*)-vallesiachotamine (**23** + **24**)	*P. bahiensis* *P laciniata*	[17, 33]	[34]
Isodolichantoside (**25**)	*P. correae*	[14]	[14]
Angustine (**26**)	*P. bahiensis* *P laciniata*	[17, 33]	[35]
10-hydroxy-*iso*-deppeaninol (**27**)	*P. prunifolia*	[20]	[20]
10-hydroxy-antirhine (**28**)	*P. prunifolia*	[20]	[20]
N-oxide-10-hydroxyantirhine (**29**)	*P. prunifolia*	[20]	[20]
Stachyoside (**30**)	*P stachyoides*	[15]	[15]
Lyaloside (**31**)	*P. laciniata* *P. suterella*	[19, 36]	[37]
Myrianthosine (**32**)	*P. myriantha*	[25]	[25]
Brachycerine (**33**)	*P. brachyceras*	[21]	[21]
Psychollatine (**34**)	*P. umbellata* *P umbellata*	[5, 22, 38]	[22]
3,4-Dehydro-18,19-β-epoxy-psychollatine (**35**)	*P. umbellata*	[32]	[32]
Desoxycordifoline (**36**)	*P. acuminata*	[23]	[39]
Bahienoside B (**37**)	*P. acuminata* *P. bahiensis*	[17, 23]	[17]
Bahienoside A (**38**)	*P. bahiensis*	[17]	[17]

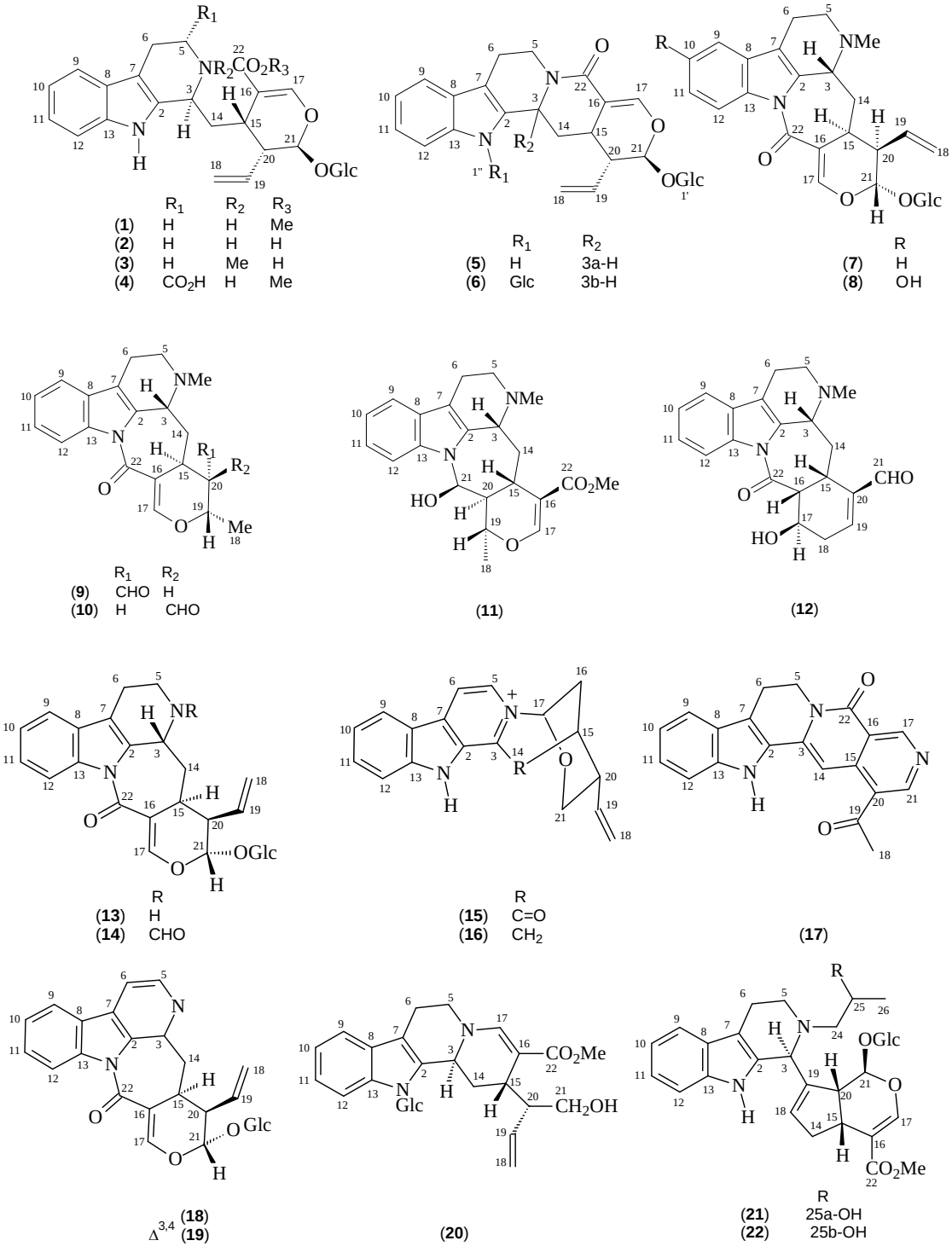
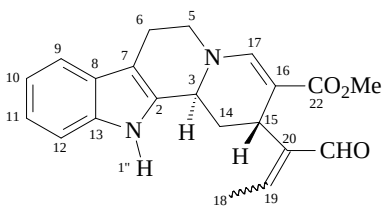
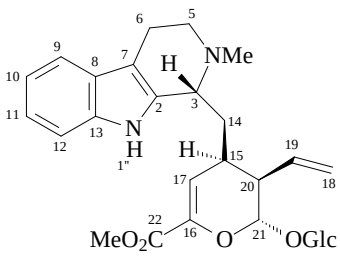


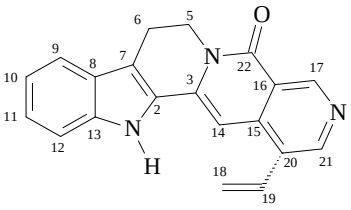
Figure 1. Structures of monoterpene indole alkaloids from *Psychotria* species



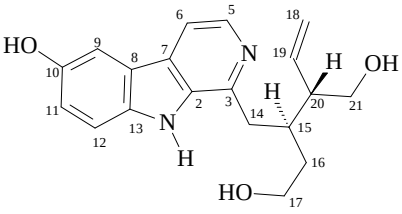
(**23** + **24**)



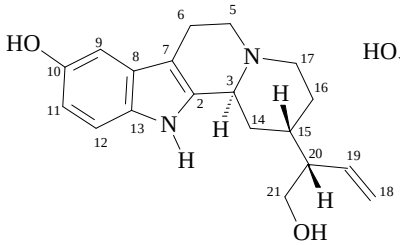
(**25**)



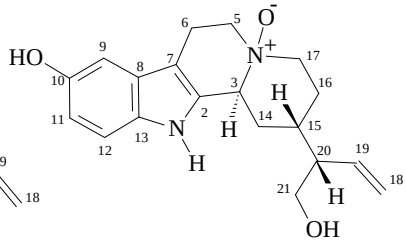
(**26**)



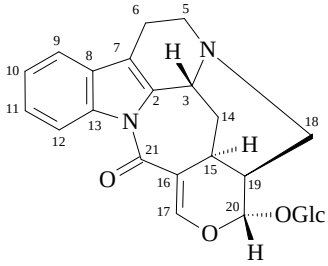
(**27**)



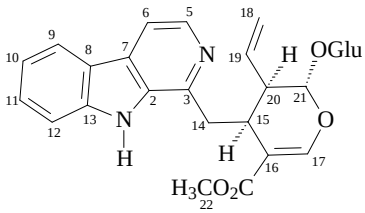
(**28**)



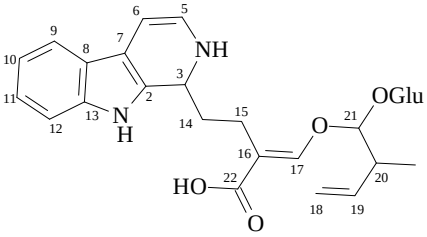
(**29**)



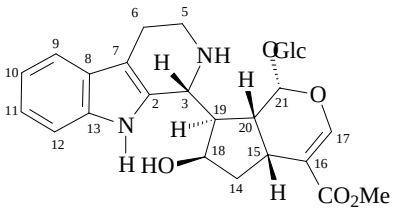
(**30**)



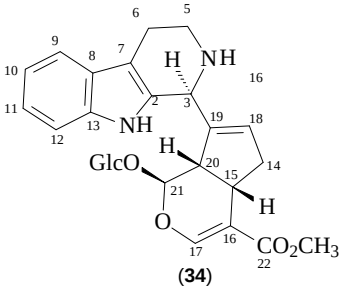
(**31**)



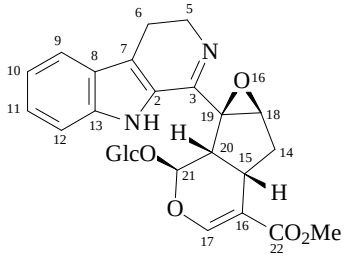
(**32**)



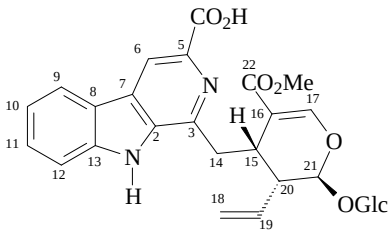
(**33**)



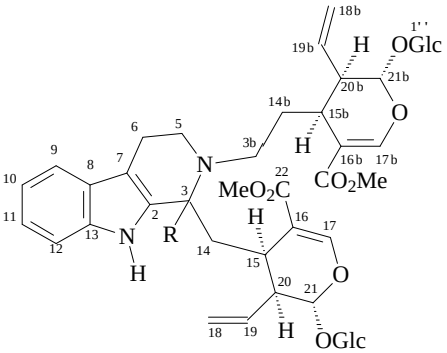
(**34**)



(**35**)



(**36**)



(**37**) 3α-OH
(**38**) 3β-OH

Figure 1. Continued

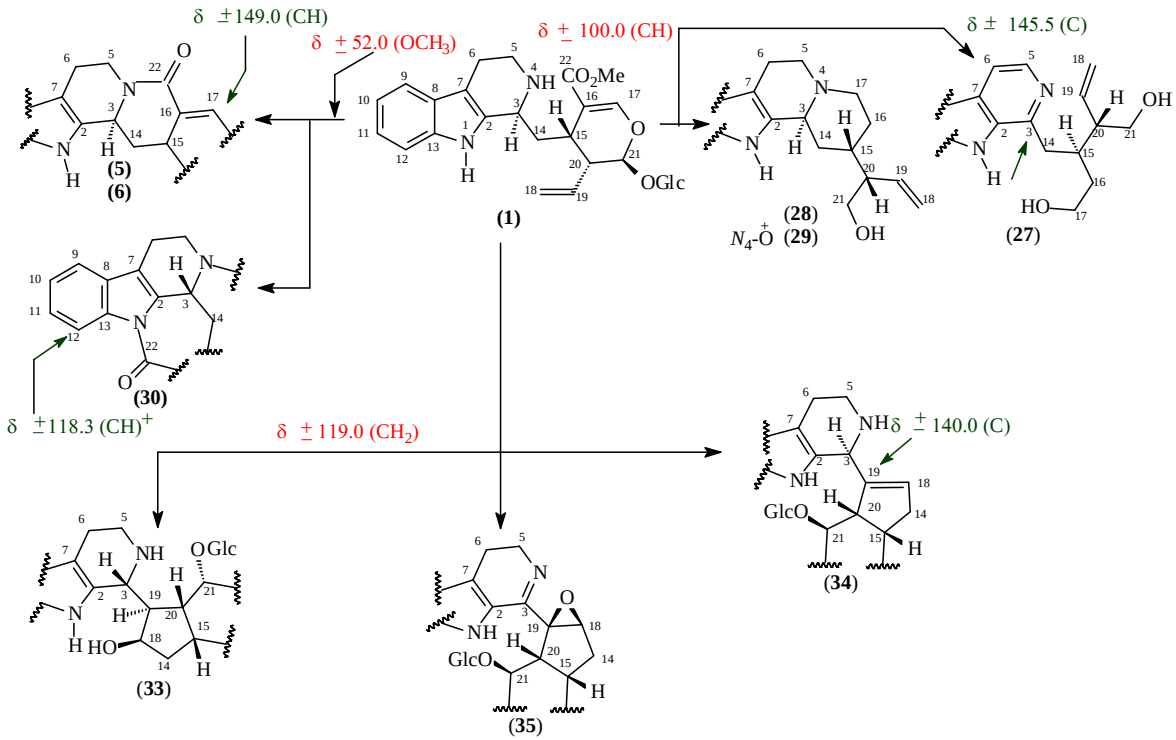


Figure 2. Structural signaling based on specific signals compared with values for strictosidine (**1**): absence of a given signal in red and presence in green.

Table 2. ^{13}C NMR data of MIAs from *Psychotria* species.

Carbons	Compounds/δ_C (ppm)									
	1^{I}	**2^{III}**	**3^{III}**	**4^{I}**	**5^{I}**	**6^{I}**	**7^{I}**	**8^{I}**	**9^{II}**	**10^{II}**
C										
2	133.2	132.3	134.7	133.2	134.8	136.1	134.3	133.8	132.9	133.0
7	107.7	106.0	105.2	109.0	110.3	111.5	115.7	115.3	114.8	114.8
8	127.9	126.1	126.6	128.0	128.7	129.5	130.4	131.3	129.1	129.1
13	137.9	135.8	135.8	138.4	137.8	137.7	137.3	131.4	136.0	136.0
22	170.6	170.0	168.4	170.9	167.1	166.3	168.2	167.8	166.2	166.2
16	109.9	113.4	112.5	109.9	109.2	109.1	112.2	112.0	108.6	109.6
CH										
3	52.4	49.6	56.1	53.2	55.1	54.5	57.8	58.2	56.4	56.7
5	-	-	-	60.1	-	-	-	-	-	-
9	118.8	117.8	117.4	118.8	118.7	119.3	119.2	104.4	118.1	118.0
10	120.1	118.7	118.1	120.1	120.2	121.3	124.2	155.1	123.2	123.2

11	122.7	121.2	120.3	122.6	122.6	122.9	125.5	114.2	124.6	124.6
12	112.0	111.5	110.8	112.1	112.3	114.8	116.0	116.8	115.4	115.2
15	32.5	31.8	30.6	32.4	24.9	27.9	35.7	35.6	29.7	29.2
17	156.1	150.0	151.8	156.1	149.2	149.2	155.7	155.5	158.0	156.4
19	135.7	135.6	135.6	135.2	134.4	133.4	135.1	135.0	70.2	69.4
20	45.6	44.3	44.0	45.7	44.7	44.1	45.4	45.4	51.8	53.9
21	97.5	95.1	95.9	97.6	98.1	97.5	97.4	97.3	-	-
CH_2										
5	42.9	40.0	45.2	60.1	44.8	41.6	46.4	46.7	45.5	45.5
6	21.0	19.2	15.9	25.2	22.1	22.3	18.8	18.8	17.6	17.7
14	35.9	33.7	35.3	35.6	27.3	35.6	34.4	34.1	39.1	35.3
18	119.5	117.8	117.8	119.6	120.6	120.7	119.2	119.3	-	-
CH_3										
MeN-	-	-	39.8	-	-	-	41.4	41.2	-	41.5
Me	-	-	-	-	-	-	-	-	18.3	19.3
Glucose										
1'	100.3	98.9	98.7	100.5	100.5	99.6	100.5	100.5	-	-
2'	78.6	69.8	73.0	74.7	74.3	74.9	74.7	74.7	-	-
3'	78.0	73.1	77.2	78.0	77.9	77.9	78.6	78.6	-	-
4'	74.6	77.2	70.0	71.9	71.3	71.6[a]	71.6	71.7	-	-
5'	71.7	76.5	76.6	78.6	78.2	78.3	78.0	78.0	-	-
6'	62.9	61.0	61.0	63.1	62.6	62.7	62.9	62.9	-	-
1''	-	-	-	-	-	87.6	-	-	-	-
2''	-	-	-	-	-	71.9	-	-	-	-
3''	-	-	-	-	-	75.1	-	-	-	-
4''	-	-	-	-	-	71.6[a]	-	-	-	-
5''	-	-	-	-	-	81.2	-	-	-	-

6''	-	-	-	-	-	62.9	-	-	-	-
CHO	-	-	-	-	-	-	-	-	199.5	199.2
CO_2 Me	52.4	-	-	52.6	-	-	-	-	-	-
CO_2H	-	-	-	176.5	-	-	-	-	-	-

[I] CD_3OD, [II] $CDCl_3$ e [III] DMSO-d_6, letters (a–e) indicate signals that may be interchanged.

Table 2. Continued.

Carbons	**Compounds/δ_C (ppm)**									
	11[II]	**12[I]**	**13[I]**	**14[I]**	**15[I]**	**16[I]**	**17[II]**	**18[I]**	**19[I]**	**20[I]**
C										
2	136.2	134.6	136.0	132.4	134.4	132.2	127.4	145.7	134.4	136.0
3	-	-	-	-	139.7	139.5	140.8	-	148.1	-
7	108.0	117.4	117.0	116.2	124.6	132.9	116.9	138.0	134.0	111.3
8	126.8	130.6	131.0	130.1	118.9	119.7	125.7	123.9	125.2	129.7
13	137.1	137.7	137.3	137.7	146.9	144.6	139.0	140.0	142.3	136.0
14	-	-	-	-	191.6	-	-	-	-	-
15	-	-	-	-	-	-	141.1	-	-	-
16	111.2	-	112.7	111.8	-	-	117.1	113.5	114.5	95.3
19	-	-	-	-	-	-	199.6	-	-	-
20	-	-	-	-	-	-	138.8	-	-	-
21	-	194.3	-	-	-	-	-	-	-	-
22	167.5	174.8	168.6	168.1	-	-	161.6	167.9	168.8	171.8
CH										
3	61.4	58.5	50.6	47.9	-	-	-	50.0	-	50.2
5	-	-	-	-	134.1	132.5	-	137.0	142.6	-
6	-	-	-	-	120.6	116.0	-	116.2	114.5	-
9	118.5	117.8	119.2	119.5	123.6	122.8	119.3	123.9	122.3	119.0
10	119.8	119.0	124.4	124.6	123.4	122.4	119.9	126.3	125.5	121.0
11	121.5	125.0	125.5	126.0	137.2	132.3	120.9	133.5	131.3	122.7

12	109.2	126.0	116.4	116.4	113.7	113.2	112.0	119.8	119.3	114.6
14	-	-	-	-	-	-	95.6	-	-	-
15	30.8	34.5	35.7	35.6	42.8	25.6	-	30.5	21.2	33.7
16	-	52.0	-	-	-	-	-	-	-	-
17	155.2	67.5	155.6	156.5	87.9	86.7	154.0	157.2	155.9	149.3
19	74.8	149.7	135.2	134.9	132.8	134.9	-	133.6	134.1	140.8
20	52.0	-	45.6	45.3	42.0	41.2	-	46.4	46.7	55.2
21	75.5	-	97.5	97.6	-	-	155.4	97.9	97.9	-
CH_2										
5	52.0	48.0	40.0	41.6	-	-	40.7	-	-	53.0
6	20.9	19.6	23.2	23.2	-	-	19.8	-	-	23.4
14	36.7	35.9	36.7	34.8	-	24.8	-	36.7	39.8	35.1
16	-	-	-	-	42.8	25.6	-	-	-	-
18	-	33.8	119.3	119.5	118.9	117.9	-	121.8	121.3	116.9
21	-	-	-	-	63.4	61.9	-	-	-	65.4
CH_3										
18	18.6	-	-	-	-	-	29.3	-	-	-
MeN-	43.0	41.9	-	-	-	-	-	-	-	-
Glucose										
1'	-	-	100.7	100.8	-	-	-	100.1	100.1	87.6
2'	-	-	74.9	74.9	-	-	-	74.8	74.7	72.4
3'	-	-	78.7	78.2	-	-	-	78.0	77.9	79.4
4'	-	-	71.8	71.7	-	-	-	71.7	71.7	71.8
5'	-	-	78.2	78.7	-	-	-	78.0	78.6	81.2
6'	-	-	63.1	63.0	-	-	-	62.9	62.9	63.0
CHO	-	-	-	163.9	-	-	-	-	-	-
CO_2Me	51.1	-	-	-	-	-	-	-	-	51.2

[I] CD_3OD, [II] $CDCl_3$ e [III] DMSO-d_6, letters (a–e) indicate signals that may be interchanged.

Table 2. Continued.

Carbons	Compounds/δ_C (ppm)								
	21[I]	**22[I]**	**23[III]**	**24[III]**	**25[I]**	**26[III]**	**27[I]**	**28[I]**	**29[I]**
C									
2	134.0	133.4	133.1	133.6	134.0	126.8	136.9	130.5	131.0
3	-	-	-	-	-	136.9	145.5	-	-
7	108.4	108.4	106.6	107.4	106.5	114.8	130.6	106.0	105.7
8	138.6	138.1	126.2	127.0	128.1	125.5	123.1	128.6	128.3
10	-	-	-	-	-	-	152.6	151.8	152.0
13	128.4	128.0	136.1	136.8	137.8	138.5	137.5	133.1	133.6
15	-	-	-	-	-	139.0	-	-	-
19	141.0	142.1	-	-	-	-	-	-	-
16	112.2	112.0	93.2	93.4	112.0	119.8	-	-	-
20	-	-	146.1	143.9	-	127.8	-	-	-
22	169.7	169.0	166.9	167.6	169.8	161.1	-	-	-
CH									
3	61.7	59.3	48.6	47.9	58.8	-	-	57.0	71.6
5	-	-	-	-	-	-	135.7	-	-
6	-	-	-	-	-	-	114.6	-	-
9	118.6	118.0	117.4	118.4	118.7	119.9	106.6	103.2	103.3
10	119.5	120.0	118.3	119.2	119.9	119.9	-	-	-
11	121.9	122.0	120.7	121.6	122.3	124.6	120.4	112.9	113.2
12	112.0	112.0	110.8	111.8	111.8	112.0	113.7	112.8	113.0
14	-	-	-	-	-	93.8	-	-	-
15	33.0	35.3	27.4	30.5	30.5	-	36.4	31.1	30.6
17	153.3	153.0	147.2	148.5	154.0	149.7	-	-	-
18	132.6	131.0	-	-	-	-	-	-	-
19	-	-	152.0	146.3	135.8	130.2	138.1	138.7	138.2
20	49.0	48.4	-	-	45.5	-	51.0	50.8	52.3
21	95.6	97.0	-	-	97.8	147.7	-	-	-
25	65.1	66.3	-	-	-	-	-	-	-
CH_2									
5	49.0	49.6	49.8	50.7	47.9	40.4	-	52.4	69.0
6	21.4	19.7	21.3	22.2	17.9	19.2	-	18.1	20.6

14	39.4	39.5	32.9	32.9	34.5	-	37.0	31.6	28.5
17	-	-	-	-	-	-	61.4	48.0	59.1
18	-	-	-	-	119.8	119.8	118.7	118.5	118.5
21	-	-	-	-	-	-	64.4	64.0	63.8
24	62.4	61.6	-	-	-	-	-	-	-
CH_3									
18	-	-	14.3	13.8	-	-	-	-	-
26	20.7	21.2	-	-	-	-	-	-	-
MeN-	-	-	-	-	40.6	-	-	-	-
Gluc									
ose									
1'	100.1	100.1	-	-	100.5	-	-	-	-
2'	74.6	74.8	-	-	74.7	-	-	-	-
3'	78.0	78.0	-	-	78.6	-	-	-	-
4'	78.2	71.6	-	-	71.6	-	-	-	-
5'	76.2	78.5	-	-	78.0	-	-	-	-
6'	62.7	62.5	-	-	62.9	-	-	-	-
CHO	-	-	195.5	191.5	-	-		-	-
CO_2	51.6	51.7	49.7	50.8	51.9	-	-	-	-
Me									

[I] CD_3OD, [II] $CDCl_3$ e [III] DMSO-d_6, letters (a–e) indicate signals that may be interchanged.

Table 2. Continued.

Carbons	**Compounds/δ_C (ppm)**								
	30[I]	**31**	**32[III]**	**33[I]**	**34[I]**	**35[I]**	**36[I]**	**37[I]**	**38[I]**
C									
2	137.1	140.3	134.8	130.7	131.1	128.8	135.6	135.0	138.0
3	-	143.8	-	-	-	158.9	142.9	-	-
5	-	-	-	-	-	-	135.6	-	-
7	118.4	121.0	121.0	108.3	107.9	118.8	128.4	107.3	106.6
8	129.2	126.9	121.5	127.7	127.6	139.9	121.7	128.4	128.0
13	139.1	134.6	140.2	112.3	138.1	126.1	141.6	137.8	138.0
15									
19	-	-	-	-	140.0	67.3	-	-	-

16	114.8	109.9	112.0	111.8	112.2	110.2	108.7	112.1	111.5
21	169.0	-	-	-	-	-	-	-	-
22	-	166.6	170.0	169.1	169.1	168.9	171.3	169.7	170.0
22 b	-	-		-	-	-	-	169.5	169.4
C H									
3	51.7	-	48.5	54.7	53.7	-	-	58.8	59.6
5	-	137.3	137.0	-	-	-	-	-	-
6	-	112.6	118.0	-	-	-	114.2	-	-
9	119.7	121.4	126.6	118.9	119.0	121.2	121.4	120.6	118.7
10	125.2	119.0	118.9	120.2	120.3	121.1	119.9	119.7	120.0
11	126.8	127.6	127.5	123.2	123.6	126.2	128.4	122.0	122.5
12	118.3	111.8	112.5	112.3	112.3	113.6	111.6	112.0	112.0
15	32.9	30.1	-	35.5	37.5	31.7	34.5	31.5	31.6
17	148.7	151.6	151.0	153.5	153.4	153.1	153.2	154.0	154.7
18	-	-	-	74.3	138.5	62.5	-	-	-
19	53.3	134.0	134.5	49.0	-	-	133.8	136.2	136.1
20	95.5	42.9	45.5	41.9	49.0	43.8	44.4	45.5	45.4
21	-	95.9	95.4	99.0	99.4	95.2	96.1	98.2	97.9
15 b	-	-		-	-	-	-	30.3	30.5
17 b	-	-		-	-	-	-	153.2	153.5
19 b	-	-		-	-	-	-	135.7	135.5
20 b	-	-		-	-	-	-	44.8	44.8
21 b	-	-		-	-	-	-	98.5	98.3
C H_2									
5	48.0	-	-	41.8	42.1	48.2	-	44.8	44.8
6	21.2	-	-	24.4	20.5	20.1	-	17.6	17.4
14	43.7	32.1	45.6	43.5	40.5	34.7	34.0	36.9	36.7

15	-	-	30.0	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-	-
18	72.4	118.6	118.9	-	-	-	117.6	119.8	119.8
3b	-	-		-	-	-	-	52.0	51.9
14b	-	-	-	-	-	-	-	28.0	27.4
18b	-	-	-	-	-	-	-	120.1	120.1
CH_3									
Me	-	-	10.4	-	-	-	-	-	-
Glucose									
1'	100.3	98.79	98.6	100.6	101.5	99.4	99.0	100.4	100.4
2'	74.9	73.1	73.0	74.0	71.0	74.7	73.2	74.6	74.8[c]
3'	78.5	77.3	69.9	71.1	78.6	78.1	76.6	78.0	78.6[a]
4'	71.9	71.10	77.3	78.3	74.6	72.1	70.4	71.6	71.7[d]
5'	78.5	77.8	76.8	77.7	77.6	78.8	76.6	78.4	78.2[b]
6'	63.0	61.2	61.0	62.1	61.8	63.3	61.8	62.9	62.9[e]
1''	-	-	-	-	-	-	-	100.3	100.4
2''	-	-	-	-	-	-	-	74.8	74.6[c]
3''	-	-	-	-	-	-	-	78.1	78.4[a]
4''	-	-	-	-	-	-	-	71.6	71.6[d]
5''	-	-	-	-	-	-	-	78.3	78.0[b]
6''	-	-	-	-	-	-	-	62.8	62.8[e]
CO_2 Me	-	50.7	-	51.8	51.9	51.9	50.6	52.1	52.1

[I] CD_3OD, [II] $CDCl_3$ e [III] DMSO-d_6, letters (a–e) indicate signals that may be interchanged.

2.2. ^{13}C Chemical Shifts of Pyrrolidinoindoline Alkaloids Isolated from Psychotria Species.

Some studies have also reported that the isolation of pyrrolidinoindoline alkaloids seems to be specific to the *Psychotria* species (**Table 3**). As shown in **Figure 3**, its chemical structures present the condensation of some *N*-methyl-tryptamine units with different connection patterns, mainly involving C-3a-C3'a, C-3a-C-7, and *N*-C-3 bonds or containing N-methyl-tryptamine units linked to a bis-quinoline part. The compound (+)-chimonanthine (**40**) was isolated from several *Psychotria* species[40-42] and is an example of a dimer that presents a C-3a-C-3'a-type linkage between its two units. Its ^{13}C spectrum exhibited 11 carbon-signal equivalents for both units. The signals at δ_C 52.4 (CH_2-2) and 84.6 (C-8a) are typical of carbons bearing one and two nitrogen atoms, respectively. The signals at δ_C 33.2 and 63.6 were attributed to C-3 and C-3a, respectively, whereas the signal at δ_C 33.8 is consistent with a methyl carbon attached to a nitrogen atom. The *ortho*-substituted aromatic rings are characterized by signals at δ_C 124.9 (CH-4/CH-4'), 128.3 (C-4a/C-4a'), 122.3 (CH-5), 119.8 (CH-5'), 129.9 (CH-6/CH-6'), 110.5 (CH-7/CH-7'), and 150.5 (C-7a/C-7a') [40] (**Table 4**).

Since some compounds with more than two units present a chimonanthine portion in their structures, the monitoring of C-3a and C-7 (main binding sites) and their neighborhood may be a good alternative, in order to determine the positions of the other monomeric units. Hodgkinsine (**52**) occurs frequently in the genus [41-46] and presents a third unit with a C-3''a-C-7' linkage. In this case, besides replacement of a methine aromatic carbon by a quaternary carbon (C-7'), observing the upfield displacements of C-6' and C-4' ($\Delta\delta$ around 3.0 ppm) is possible probably because of the presence of a group that increases the electron densities of these positions (comparison with compound **40**). Takayama *et al*. (2004), however, reported the isolation of psychopentamine (**60**) from *P. rostrata*[2], which showed a new type of linkage between C-3'''a and C-5'' [2].

The chemical study of *P. calocarpa* leaves [43] led to the isolation of a new alkaloid named psychotriasine (**45**), which presents a tryptamine unit linked to a pyrroloindole unit by an *N*-C3'a linkage. This type of junction was also observed for psychohenin (**46**) and compound **48** isolated from *P. henryi* [47, 48] and may be indicated by the

presence of a quaternary carbon (C-3'a) that resonates at δ_C 79.4, 77.8, and 76.7 ppm, in the three compounds, respectively. In contrast, psychotrimine (**53**), isolated from *P. rostrata* [2] shows, besides the *N*-C-3'a bond, an *N*-C-7' linkage indicated by the signal of a quaternary aromatic carbon C-7' at δ_C 121.5 ppm.

Alkaloids with more complex structures, containing from four to seven units, such as quadrigemines A–C (**55**–**57**), psychotridine (**61**), oleoidine (**64**), and caledonine (**65**), have also been isolated from this genus; however, the structural elucidation of these compounds becomes more difficult as the number of units increases. Probably owing to this, some studies did not provide detailed attributions of their carbon signals. In such cases, mass spectrometry plays an important role in establishing the number of units present in their structures as well as the pattern of the junctions.

Table 3. Pyrrolidinoindoline alkaloids from *Psychotria* species.

Compounds	Species	References	^{13}C NMR Data
Meso-chimonanthine (**39**)	*P. forsteriana*	[41, 49, 50]	[50]
	P. muscosa		
(+)-Chimonanthine (**40**)	*P. colorata*	[40-42]	[40]
	P. muscosa		
	P. rostrata		
	P. hoffmannseggiana		
Iso-calycanthine (**41**)	*P. forsteriana*	[50]	[50]
Calycanthine (**42**)	*P. forsteriana*	[50]	[50]
(8-8a),(8'-8'a)-tetradehydroisocalycanthine 3a(*R*), 3'a(*R*) (**43**)	*P. colorata*	[42]	[42]
N_b-desmethyl-*meso*-chimonanthine (**44**)	*P. lyciiflora*	[49]	[49]
Psychotriasine (**45**)	*P. calocarpa*	[43]	[43]
Psychohenin (**46**)	*P. henryi*	[47]	[47]
Compound (**47**)	*P. henryi*	[48]	[48]
Compound (**48**)	*P. henryi*	[48]	[48]
Glomerulatine A (**49**)	*P. glumerulata*	[51]	[51]
Glomerulatine B (**50**)	*P. glumerulata*	[51]	[51]

Glomerulatine C (**51**)	*P. glumerulata*	[51]	[51]
Hodgkinsine (**52**)	*P. colorata* *P. oleoides* *P. lyciiflora* *P. muscosa* *P. beccarioides* *P. rostrata*	[41-46]	[42]
Psychotrimine (**53**)	*P. rostrata*	[2]	[2]
Psychotripine (**54**)	*P. pilífera*	[52]	[52]
Quadrigemine A (**55**)	*P. forsteriana*	[53]	[53]
Quadrigemine B (**56**)	*P. forsteriana* *P. colorata* *P. rostrata*	[41, 53]	[53]
Quadrigemine C (**57**)	*P. colorata* *P. oleoides*	[41-43, 45, 46, 50, 54]	[45]
Quadrigemine I (**58**)	*P. oleoides*	[49]	[49]
Psycholeine (**59**)	*P. oleoides*	[46, 54]	[46]
Psychopentamine (**60**)	*P. rostrata*	[2]	[2]
Psychotridine (6**1**)	*P. forsteriana* *P. oleoides* *P. colorata* *P. beccarioides*	[41, 44, 45, 53]	[45]
Isopsychotridine C (**62**)	*P. forsteriana*	[53, 55]	[55]
Isopsychotridine B (**63**)	*P. oleoides*	[49, 50]	[45]
Oleoidine (**64**)	*P. oleoides*	[49]	[49]
Caledonine (**65**)	*P. oleoides*	[49]	[49]

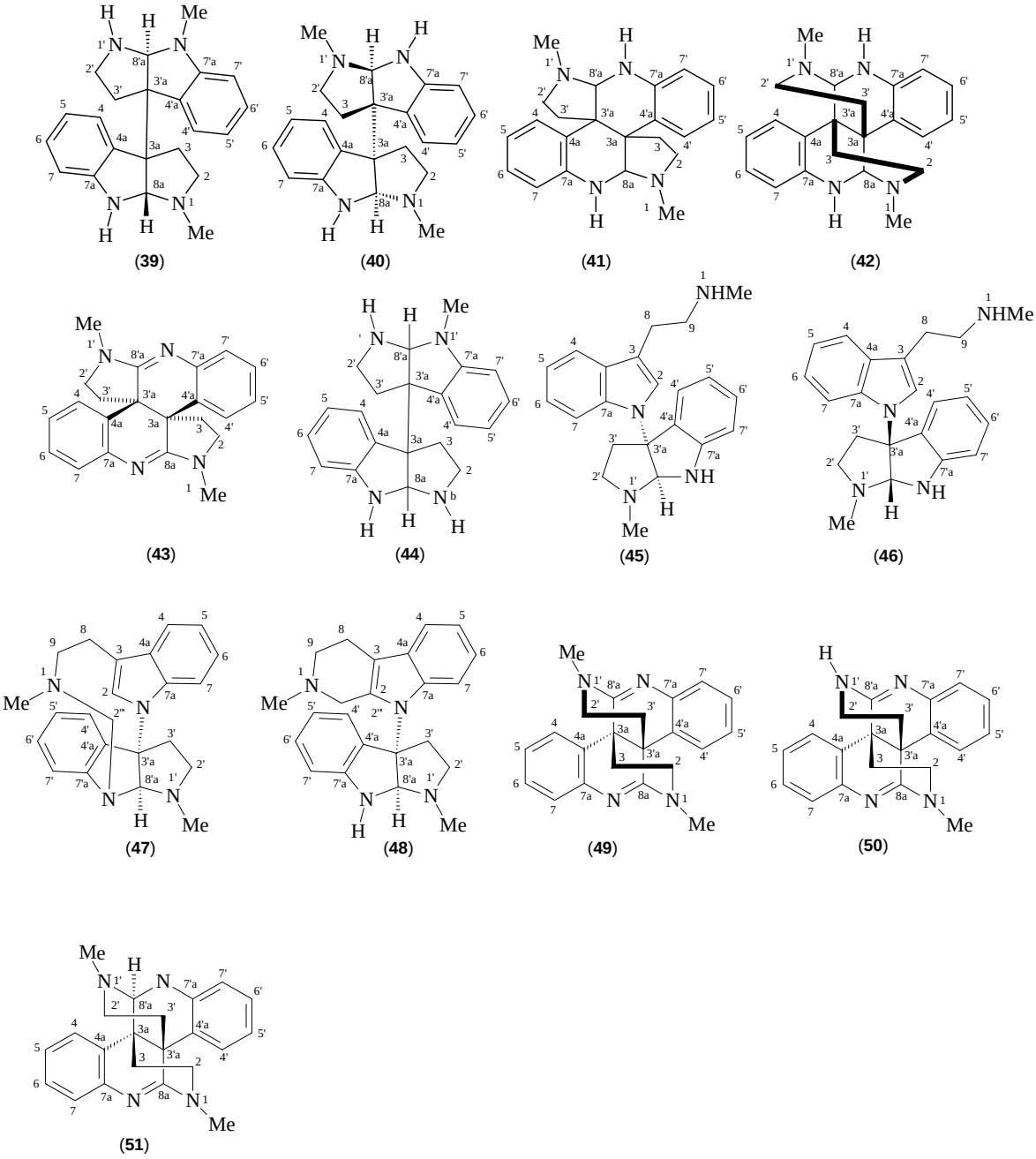
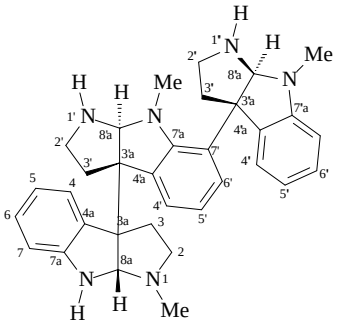
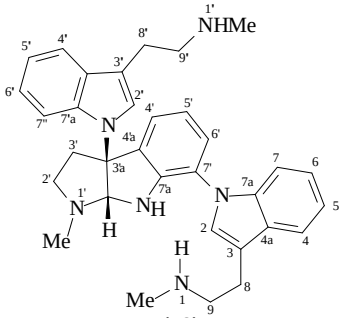


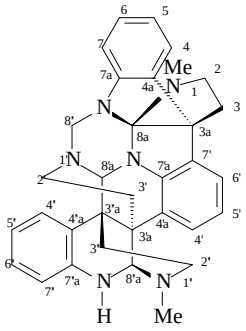
Figure 3. Structures of pyrrolidinoindoline alkaloids from *Psychotria* species.



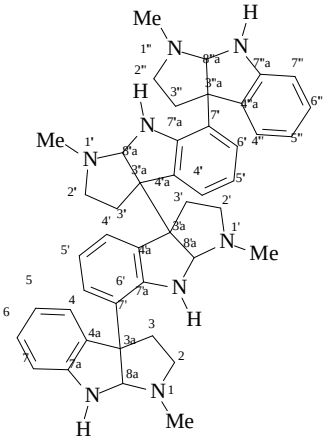
(**52**)



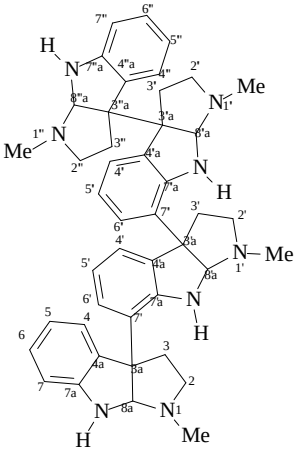
(**53**)



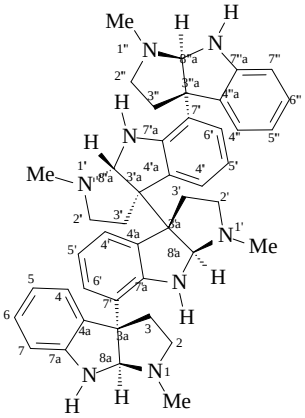
(**54**)



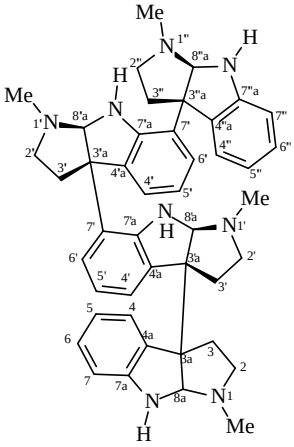
(**55**)



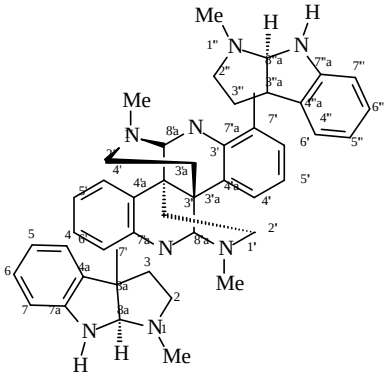
(**56**)



(**57**)

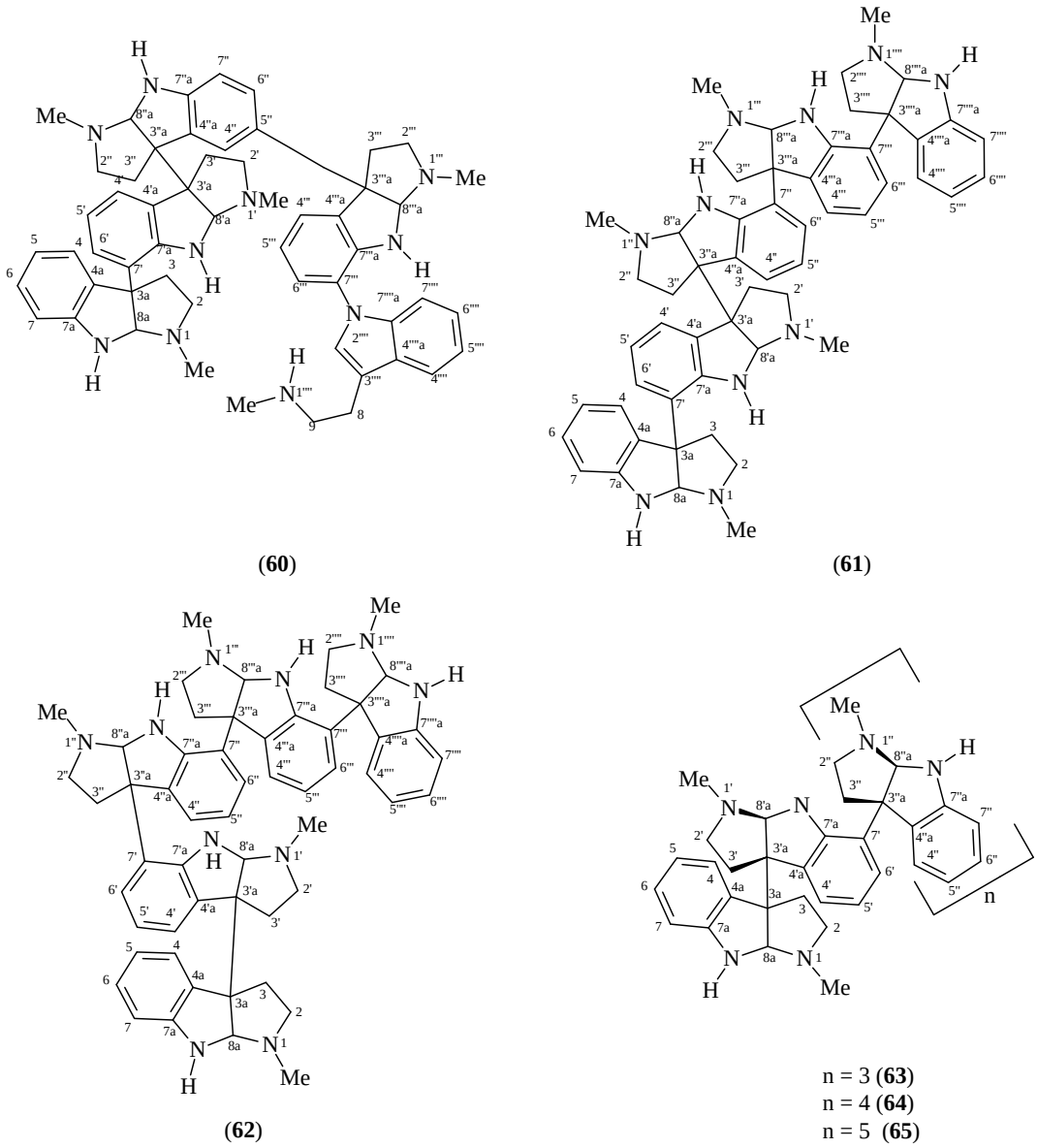


(**58**)



(**59**)

Figure 3. Continued



(**60**) (**61**)

(**62**)

n = 3 (**63**)
n = 4 (**64**)
n = 5 (**65**)

Figure 3. Continued

Table 4.^{13}C NMR data of pyrrolidinoindoline alkaloids from *Psychotria* species.

Carbons	Compounds/ δ_C (ppm)								
	39^{II}	**40**^{II}	**41**^{ns}	**42**^{II}	**43**^{II}	**44**^{II}	**45**^{I}	**46**^{I}	**47**^{II}
C									
3	-	-	-	-	-	-	112.7	110.0	112.3
3a	64.7	63.6	37.8	36.8	48.9	62.8	-	-	-
4a	133.7	128.3	127.0	125.9	125.6	132.2	130.4	130.5	130.0
7a	152.5	150.5	145.3	146.2	145.8	151.7	137.7	138.0	135.0
8a	-	-	-	-	165.0	-	-	-	-
3'a	64.7	63.6	37.8	36.8	48.9	63.9	79.4	77.8	75.3
4'a	133.7	128.3	127.0	125.9	125.6	130.0	131.3	131.3	128.9

7'a	152.5	150.5	145.3	146.2	145.8	150.3	152.5	152.7	152.4
8'a	-	-	-	-	165.0	-	-	-	-
CH									
2	-	-	-	-	-	-	125.0	126.1	123.4
4	125.2	124.9	118.3	117.1	123.0	123.9	124.7	119.5	119.0
5	119.2	122.3	122.2[b]	122.1	118.5	119.9	119.3	118.8[e]	119.1[f]
6	128.9	129.9	127.7	127.3	128.2	128.2	130.7	123.0	121.4
7	109.5	110.5	112.9	112.8	123.9	109.1	120.1	117.4	112.8
8a	83.9	84.6	71.7	71.82	-	79.3	-	-	-
4'	125.2	124.9	118.3	117.1	123.0	124.4	112.2	124.9	126.4
5'	119.2	119.8	125.2	125.2	121.9	117.9	122.4	119.8	118.7
6'	128.9	129.9	127.7	127.3	128.2	128.4	119.6	130.9	130.2
7'	109.5	110.5	112.9	112.8	123.9	108.2	110.0	110.4	108.8
8'a	83.9	84.6	71.7	71.82	-	82.4	87.0	87.3	86.6
CH_2									
2	53.1	52.4	46.9	47.3	48.5	44.9	-	-	-
3	36.4	33.2	34.9	32.5	29.9	35.3	-	-	-
2'	53.1	52.4	46.9	47.4	48.5	51.8	52.0	52.3	53.6
3'	36.4	33.2	34.9	32.5	29.9	38.1	39.9	40.0	37.7
2''	-	-	-	-	-	-	-	-	69.1
CH_3									
Me-N^1-	nd	33.8	46.9	43.4	31.1	-	36.3	33.9	40.6
MeN$^{1'}$-	nd	33.8	46.9	43.4	31.1	35.12	35.7	36.4	37.1

[I] CD_3OD, [II] $CDCl_3$ e [III] benzene-d_6, letters indicate signals that may be interchanged.

Table 4.Continued.

Carbons	**Compounds/ δ_C (ppm)**								
	48[II]	**49[III]**	**50[III]**	**51[III]**	**52[II]**	**53[II]**	**54[I + II]**	**55[II*]**	**56[II*]**
C									
2	129.6	-	-	-	-	-	-	-	-
3	109.4	-	-	-	-	114.9	-	-	-
3a	-	49.1	48.6	49.2	62.8	-	69.1	60.9[c]	60.1[c]
4a	128.0	126.4	126.1[a]	129.5	131.7	128.3	133.8	132.3[d]	133.2[e]
7a	137.4	177.3	147.1	148.6	150.8	136.1	152.2	150.9[h]	150.6[h]

8a	-	165.1	164.7	166.5	-	-	106.9	-	-
3'a	76.7	49.1	48.6	45.3	63.0	76.7	37.0	63.2[j]	63.9[i]
4'a	130.5	126.4	125.4[a]	122.3	132.3	132.0	122.0	132.4[d]	132.9[e]
7'	-	-	-	-	-	121.5	130.9	108.9[g]	-
8'a	-	165.1	164.7	-	-	-	-	-	-
3''	-	-	-	-	-	112.5	-	-	-
3''a	-	-	-	-	60.0	-	38.4	62.9[j]	63.3[i]
8''	-	-	-	-	-	25.7[b]	68.0	-	-
9''	-	-	-	-	-	52.0	-	-	-
4''a	-	-	-	-	131.7	129.8	122.3	132.6[d]	-
7''a	-	-	-	-	151.1	136.1	144.4	-	-
3'''a	-	-	-	-	-	-	-	60.8[c]	60.9[c]
CH									
2	-	-	-	-	-	126.0	-	-	-
4	117.9	123.7	120.9	123.0	126.4	119.4[a]	122.9	-	125.9[d]
5	119.2	122.3	122.2[b]	122.1	118.5	119.9	119.3	118.8[e]	119.1[f]
6	121.3	128.9	129.0[c]	128.8	127.9	122.4	128.2	127.9[f]	128.0[g]
7	112.1	125.0	125.2[d]	125.2	109.0	111.2	107.7	109.0[g]	108.9
8a	-	-	-	-	86.4	-	-	86.9[i]	85.9[i]
4'	124.5	123.7	124.0[d]	117.5	121.9	123.7	123.7	122.5	125.1[d]
5'	119.0	122.3	122.6[b]	124.9	116.8	119.3[a]	122.0	116.3[k]	118.3[f]
6'	129.6	128.9	128.8[c]	127.1	126.0	127.3	121.1	125.4	127.8[g]
7'	108.9	125.0	124.4[d]	114.4	-	-	-	-	-
8'a	86.5	-	-	76.5	81.7	86.1	69.7	86.1[i]	83.3[j]
2''	-	-	-	-	-	124.3	-	-	-
4''	-	-	-	-	124.2	119.3[a]	125.4	-	-
5''	-	-	-	-	117.5	119.3[a]	117.8	118.7[e]	117.2[f]
6''	-	-	-	-	127.4	121.7	127.6	-	-
7''	-	-	-	-	108.1	112.2	112.5	-	-
8''a	-	-	-	-	82.3	-	69.4	-	82.3[j]
8'''a	-	-	-	-	-	-	-	-	87.1[i]
5'''	-	-	-	-	-	-	-	116.2[k]	116.8[f]
6'''	-	-	-	-	-	-	-	126.4[f]	-

CH_2									
2	-	48.2	48.1	48.5	51.7	-	54.9	52.6[a]	52.3[a]
3	-	30.3	30.3	31.7	37.6	-	36.3	38.8[b]	38.5[b]
2'	51.2	48.2	48.1	50.5	51.9	51.7	42.3	52.5[a]	52.2[a]
3'	40.6	30.3	30.3	34.0	36.7	39.1	33.1	38.7[b]	36.6[b]
2''	-	-	-	-	51.9	-	45.9	52.2[a]	-
3''	-	-	-	-	38.0	-	33.7	38.5[b]	-
3'''	-	-	-	-	-	-	-	36.6[b]	-
CH_3									
Me-N[1]-	44.8	30.9	30.8	30.7	35.2	36.3	36.4	35.7[l]	35.8[k]
MeN[1']-	36.1	30.9	-	36.6	35.0	36.4	-	35.5[l]	35.7[k]
Me-N[1'']-	-	-	-	-	35.1	36.4	41.8	35.0[l]	35.6[k]
Me-N[1''']-	-	-	-	-	-	-	-	-	35.2[k]

[I] CD_3OD, [II] $CDCl_3$ e [III] benzene-d_6, letters indicate signals that may be interchanged, * indicates cases for which there was no complete detailed attribution of carbon signals.

Table 4.Continued.

Carbons	**Compounds/ δ_C (ppm)**								
	57[II*]	**58[II*]**	**59[II*]**	**60[II]**	**61[II*]**	**62[II*]**	**63[II*]**	**64[II**]**	**65[II*]**
C									
3a	60.6	60.0	59.6[b]	61.1	60.1[a]	60.9[c]	63.0[a]	60.4[c]	60.0[c]
4a	-	132.0	132.4[c]	132.9[b]	-	132.7[d]	-	132.8	132.1[e]
7a	-	-	-	152.8	-	150.6[f]	-	150.7[e]	150.5[f]
3'a	62.6	63.0	37.5[f]	63.1	62.9	63.7[h]	63.3[a]	63.3[c]	63.0
4'a	-	-	-	132.8[b]	-	132.0[d]	-	-	132.4[e]
7'	-	110.0[c]	-	123.8	-	-	-	-	108.8
7'a	-	-	-	151.0	-	148.9[f]	-	150.3[e]	148.9[f]
5''	-	-	-	136.2	-	117.1	-	-	-
3''a	62.6	-	38.0[f]	64.2	62.9	63.2[h]	59.8[c]	60.9[c]	-

4’’a	-	-	-	132.6	-	-	-	-	-
7’’a	-	-	-	149.8	-	-	-	-	148.6
3’’’a	60.6	-	60.6[b]	62.3	60.6[a]	60.1[c]	59.8[c]	-	60.5[c]
4’’’a	-	-	133.8[c]	138.6	-	-	-	-	-
7’’’	-	-	-	120.4	-	-	-	-	-
7’’’a	-	-	-	144.7	-	-	-	-	-
3’’’’	-	-	-	114.5	-	-	-	-	-
3’’’’a	-	-	-	128.3	60.8[a]	-	60.7[c]	-	-
4’’’’a	-	-	-		-	-	-	-	-
CH									
4	-	126.0	-	126.9	-	123.6	-	126.1[d]	125.3[d]
4’	-	124.0	-	122.1	-	122.2	-	124.1	125.2[d]
5	-	117.0[b]	-	118.8	-	119.1[e]	-	116.3	118.9
6	-	129.5	-	128.0	-	128.2	-	128.7	128.1
7	-	109.0[c]	-	110.5	-	109.0	-	109.3	107.7
8a	85.8[a]	88.0[d]	88.5[d]	87.3	86.0[b]	87.2[g]	81.8[b]	86.6	86.9
5’	-	118.5[b]	-	116.2	-	118.4[e]	-	119.4	117.3
6’	-	127.5	-	126.5	-	126.1	-	126.2	125.3
8’a	82.3	83.0[d]	74.0[g]	82.4	82.6[c]	85.8[g]	86.8[b]	82.8	86.0
4’’	-	-	-	121.4	-	-	-	125.7[d]	124.1
5’’	-	119.0[b]	-	-	-	117.1	-	-	-
6’’	-	-	-	126.1	-	125.4	-	128.4	-
7’’	-	-	-	108.5	-	-	-	-	-
8’’a	82.3	-	72.0[g]	83.4	82.3[c]	83.1	86.8[d]	83.0	-
4’’’	-	-	-	123.3	-	-	-	122.7	123.6
5’’’	-	119.5[b]	-	118.8	-	-	-	-	-
6’’’	-	128.5	-	125.1	-	-	-	-	-
7’’’	-	-	-	120.4	-	-	-	-	-
8’’’a	86.7[a]	-	87.5[d]	88.4	86.9[b]	82.1	85.5[d]	-	-
2’’’’	-	-	-	126.1	-	-	-	-	-
4’’’’	-	-	-	119.3	-	-	-	125.7	123.2
5’’’’	-	-	-	111.2	-	-	-	-	-
6’’’’	-	-	-	122.3	-	-	-	-	-

7’’’’	-	-	-	119.7	-	-	-	-	-
8’’’’a	-	-	-	-	85.1[b]	-	84.8[d]	-	-
CH2	-	-	-	-	-	-	-	-	-
2	-	53.0	47.17[a]	52.7[a]	-	52.5[a]	-	52[a]	52.1[a]
3	-	38.0[a]	-	37.8	-	38.8[b]	-	38.7[b]	38.3[d]
8		-	-	-	-	-	-	-	-
9		-	-	-	-	-	-	-	-
2’		-	-	52.7[a]	-	52.0[a]	-	52.8[a]	52.4[a]
3’		39.0[a]	32.8[e]	35.8	-	38.5[b]	-	38.7[b]	38.6[b]
2’’		-	-	52.6[a]	-	-	-	52.9[a]	-
3’’		-	32.4[e]	37.2	-	-	-	-	-
2’’’		-	48.0[a]	52.5[a]	-	-	-	-	-
3’’’		-	-	39.2	-	-	-	-	-
3’’’’		-	-	114.5	-	-	-	-	-
CH_3		-	-	-	-	-	-	-	-
Me-N 1-		36.0	36.1[h]	34.8	-	35.6[i]	-	35.7	35.4[g]
Me-N 1’-		-	42.6[i]	35.3	-	35.1[i]	-	-	35.6[g]
Me-N 1’’-		-	42.6[i]	35.8	-	-	-	-	-
Me-N 1’’’-		-	36.1[h]	35.7	-	-	-	-	-
Me-N 1’’’’-		-	-	36.5	-	-	-	-	-

[I] CD_3OD, [II] $CDCl_3$ e [III] benzene-d_6, letters indicate signals that may be interchanged, * indicates cases for which there was no complete detailed attribution of carbon signals.

2.3. ^{13}C Chemical Shifts of Benzoquinolizidine Alkaloids Isolated from Psychotria Species.

Muhammad et al. (2003) reported the isolation of five benzoquinolizidine alkaloids from *Psychotria klugii* [7] (**Table 5**). Among them, klugine (**66**) and 7’-O-demethylisocephaeline (**67**) were reported for the first time, whereas cephaeline

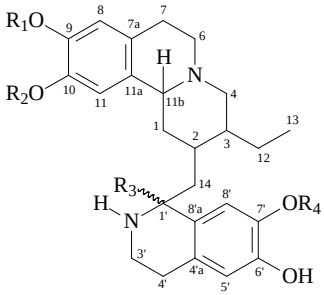
(**68**), isocephaeline (**69**), and 7-O-methylipecoside (**70**) were previously isolated from *Cephaelis* species [56, 57].

Compound **68** (ipecac alkaloid) as along with compounds **66**, **67**, and **69** possesses an unusual skeleton with two tetrahydroisoquinoline ring systems [10] characterized by the presence of four quaternary carbon signs at δ_C 147.2, 147.5 (C-9 and C-10, oxygenated *ortho*-substituted carbons), 126.8 (C-7a), and 130.1 (C-11a), two methine carbons at δ_C 108.6 (CH-11) and 111.5 (C-8), and signals at δ_C 62.4 (CH-11b), 52.3 (CH_2-6), and 29.2 (CH_2-7). A similar system is observed for the lower unit, with the exception of the absence of a methoxyl group attaching C-6' (a hydroxyl group in this position). The remarkable difference between compounds **68** and **69** (isomers) is associated with the chemical shift of carbon C-1' at δ_C 51.9 and 55.3 respectively, whereas compounds **66** and **67** differ from **68** and **69** in the number and positions of the methoxyl groups. Interestingly, compound **70** exhibits carbon assignments relative to a tetrahydroisoquinoline ring attached to a secologanin moiety at C-1.

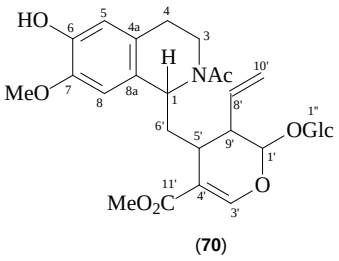
The chemical structures of compounds **68**–**70** are shown in **Figure 4**, and their ^{13}C NMR data are listed in **Table 6**.

Table 5.Benzoquinolizidine Alkaloids from *P. kluggi*.

Compound	Species	Reference	^{13}C NMR Data
klugine (**66**)	*P. klugii*	[7]	[7]
7'-*O*-demethylisocephaeline (**67**)	*P. klugii*	[7]	[7]
cephaeline (**68**)	*P. klugii*	[7]	[56]
isocephaeline (**69**)	*P. klugii*	[7]	[56]
7-*O*-methylipecoside (**70**)	*P. klugii*	[7]	[57]



	R_1	R_2	R_3	R_4
(**66**)	H	Me	OH	Me
(**67**)	Me	Me	H	H
(**68**)	Me	Me	1'β-H	Me
(**69**)	Me	Me	1'α-H	Me



(**70**)

Figure 4. Structures of Benzoquinolizidine Alkaloids from *P. klugii*

Table 6.^{13}C NMR Data ofBenzoquinolizidine Alkaloids from *P. kluggi*.

Carbons	**Compound/δ_C (ppm)**				
	66[ns]	**67[ns]**	**68[II]**	**69[II]**	**70[I]**
C					
6	-	-	-	-	146.5[a]
7	-	-	-	-	147.8[a]
9	146.5[a]	146.8	147.2[a]	147.2[a]	-
10	147.8[b]	148.0	147.5[a]	147.4[a]	-
4a	-	-	-	-	126.9
7a	127.8	126.9	126.8	126.5	-
8a	-	-	-	-	130.2
11a	129.7	127.9	130.1	129.9	-
1'	79.5	-	-	-	-
4'	-	-	-	-	111.7
4'a	127.7	123.2	127.6	127.9	-
6'	146.4[a]	145.6	143.9[b]	144.0	-
7'					
11'	-	-	-	-	169.2
8'a	129.7	126.0	131.1	131.0	-
CH					

1	-	-	-	-	50.6
2					
3	42.5	41.3	41.7	61.5	-
5	-	-	-	-	116.2
8	116.2	112.1	111.5	111.4	111.1
11	109.7	109.0	108.6	108.2	-
11b	63.8	62.7	62.4	62.8	-
1'	-	53.6	51.9	55.3	98.7
3'	-	-	-	-	153.1
4'	28.5	27.6	29.0	29.3	-
5'	116.4	115.2	114.7	114.8	27.5
8'	110.0	113.2	108.4	108.6	136.3
9'	-	-	-	-	45.1
CH_2					
1	40.6	36.9	36.9	39.3	-
3	-	-	-	-	36.1
4	62.2	61.6	61.3	52.6	29.1
6	53.3	51.9	52.3	52.6	-
7	29.3	25.3	29.2	29.1	-
12	24.4	23.3	23.6	24.0	-
14	37.0	38.0	40.9	40.4	-
3'	41.0	39.5	40.1	41.4	-
4'	28.5	27.6	29.0	29.3	-
6'	-	-	-	-	41.1
10'	-	-	-	-	120.1
CH_3	11.5	10.1	11.2	11.3	-
13	11.5	10.1	11.2	11.3	-
Me^7-O-	-	-	-		56.5

Me[9]-O-	-	55.4[d]	55.8[e]	55.8[f]	-
Me[10]-O-	56.8[c]	55.8[d]	56.0[e]	56.0[f]	-
Me[7']-O-	56.6[c]	-	56.3[e]	56.0[f]	-
Glucose					
1''	-	-	-	-	100.5
2''	-	-	-	-	74.8
3''	-	-	-	-	78.2[b]
4''	-	-	-	-	71.5
5''	-	-	-	-	78.3[b]
6''	-	-	-	-	62.7
CO_2Me					51.7

[I] CD_3OD, [II] $CDCl_3$ e [ns]not specified, letters indicate signals that may be interchanged.

3. Conclusions

In this work, we attempted to compile ^{13}C data of alkaloids isolated from the *Psychotria* genus and provide information that may be useful in order to distinguish different types of skeletons. For monoterpene indole alkaloids (MIAs), mainly found in tropical species, a good strategy for their structural elucidation is to compare their spectral data with those observed for strictosidine (**1**). The monitoring of differences in specific parts of the spectrum, such as the signals of C-22, CH-17, CH-12, CH_2-5, and CH-1', may suggest alternative structural possibilities. Note that all comparisons performed in this work are restricted preferably to compounds whose ^{13}C NMR experiments were run in the same solvent.

The main pyrrolidinoindoline alkaloids found in this genus are chimonanthine derivatives, with units linked mostly by C3a-C3'a or C-3a-C7a bonds. Some examples have shown different patterns of linkages between *N* (from tryptamine terminal units)

and C-3a. For compounds with more than three units, such as quadrigemines A–C and psychotridine and its isomer, obtaining detailed assignments of these carbons is not possible owing to structural complexity.

The occurrence of benzoquinolizidine alkaloids in *Psychotria* species is less common, comprising some compounds isolated from *Psychotria klugii*.

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3.3 Trabalho 3:

Metabolites from *Psychotria suterella* Müll. Arg. and *Psychotria nuda* Cham. & Schltdl. Wawra (Rubiaceae) and Evaluation of Cytotoxic Activity

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The chemical study of *P. suterell*a leaves led to the identification of a new iridoid named 9-*epi*-geniposidic acid (**1**), along with the known compounds geniposidic acid (**2**), sucrose (**3**), 3-O-acethyloleanolic acid (**4**), pomolic acid (**5**), spinosic acid (**6**), maslinic acid (**7**),tormentic acid (**8**), methyl oleanolate (**9**), lyalosidic acid (**10**), and strictosidinic acid (**11**). From twigs and leaves of *P. nuda* sitosterol (**12**), stigmasterol (**13**), campesterol (**14**), phytol (**15**), β-sitosterol-3-O-β-D-glucoside (**16**), β-stmasterol-3-O-β-D-glucoside (**17**), cinchonain Ia (**18**), cinchonain Ib (**19**), *N*,*N*,*N*-trimethyltryptamonium (**20**), lyaloside (**21**), lawsofrutose (**22**), roseoside (**23**), strictosamide (**24**), scopoletin (**25**), rotungenic acid (**26**), strictosidine (**27**), and 5α-carboxystrictosidine (**28**) were identified. These structures were elucidated based on NMR, HR-MS, IR spectrum as well as comparison with literature data. Furthermore, the cytotoxic activity of compounds 20, 23, and 24 was evaluated against two cancer cell lines (THP-1 and U937). Only compound 24 showed significant cytotoxic activity against the U937 cell line (IC_{50} = 29.1 ± 1 μg/L).

Keywords: *Psychotria*; iridoid; 9-*epi*-geniposidic acid; alkaloids; MTT

**** Este trabalho será submetido ao periódico Natural Product Research.**

1. Introduction

The genus *Psychotria* comprises about 2000 species, occurring mostly in tropical and subtropical regions of the world (Marques de Oliveira et al. 2013). Some of its species are widely used in folk medicine for several purposes such as earache (Verotta et al. 1998), abdominal pain (Amador et al. 1996), constipation (Zhou et al. 2010), coughs (Benevides et al. 2004), etc. Several biological activities have been reported for this genus, such as cytotoxic (Zhang et al. 2013), analgesic (Both et al. 2002), and antimicrobial (Jayasinghe et al. 2002) activities, highlighting the biological potential of

its species.

Chemical studies related to these species have been shown that this genus is a potential source of monoterpene indole alkaloids whose the biosynthesis involves the coupling between tryptamine and the iridoid secologanin (Runguphan et al. 2009). The chemical diversity of this genus also includes flavonoids (Lu et al. 2014), triterpenes (Zhang et al. 2013), coumarins (Benevides et al. 2004), iridoids (Lu et al. 2014), etc.

In order to contribute to the expansion of the knowledge about the chemistry of this genus, in this paper we describe the isolation and identification of metabolites from *P. suterella* and *P. nuda* (Rubiaceae). In addition, it also shows the cytotoxic activity of some of these compounds against THP-1 and U937 cancer cell lines.

2. Results and discussion

2.1 Metabolites from *P. suterella*

Compound **1** (Figure 1) was obtained in mixture with compounds **2** and **3** as a brown oil. The molecular formula $C_{16}H_{22}NaO_{10}$ was determined based on HR-ESI-MS (m/z 397.1064, $[M + Na]^+$, calculated for 397.1111). Its NMR data (Table S1, **Supplemental online material**) showed a doublet at δ_H 5.15 (H-1, J = 3.4 Hz) attached to a carbon at δ_C 92.5 (CH-1), typical of methinedioxy group. The doublet at δ_H 4.51 (*d*, 7.7, H-1') was attributed to the anomeric proton of the glucose moiety. The signal at δ_H 7.50 (H-3), attached to the carbon at δ_C151.5 (CH-3) suggested a α,β-unsatured carboxyl group (δ_C170.4, C-11). Moreover, it was also possible to verify signals of another double bound (H-7, δ_H 5.82) and a terminal hydroxyl group (CH_2-10, δ_C 60.1). Its relative stereochemistry was proposed based on the coupling constant value of H-1 (3.4 Hz), typical of an axial-equatorial coupling and the shielding effect on C-1' (δ_C 96.6, suggesting H-9 in equatorial position). All correlations observed by 2D NMR experiments are summarized in Table S1.

The known compounds were identified as geniposidic acid (**2**, Güvenalp et al. 2006), sucrose (3), 3-*O*-acethyloleanolic acid (**4**, Itokawa et al. 1989), pomolic acid (**5**, Chama et al. 2015), spinosic acid (**6**, Wang et al. 2011), maslinic acid (**7**, Pnou et al. 2011), tormentic acid (**8**, Taniguchi et al. 2002), methyl oleanolate (**9**, Mahato &

Kundu), lyalosidic acid (**10**, Lin et al. 2011), and strictosidinic acid (**11**, Berger et al. 2015).

2.2. Metabolites from P. nuda

The metabolites isolated from twigs and leaves of *P. nuda* were identified as pomolic acid (**5**, Chama et al. 2015), spinosic acid (**6**, Wang et al. 2011), sitosterol (**12**), stigmasterol (**13**), campesterol (**14**), phytol (**15**, Miranda et al. 2012), β-sitosterol-3-O-β-D-glucoside (**16**), β-stmasterol-3-O-β-D-glucoside (**17**, Kojima et al. 1990), cinchonain Ia (**18**), cinchonain Ib (**19**, Nonaka & Nishioka 1982), *N*,*N*,*N*-trimethyltryptamonium (**20**, Martins et al. 2009), lyaloside (**21**, Berger et al. 2015), lawsofrutose (**22**, Uddin et al. 2013), roseoside (**23**, Otsuka et al. 1995), strictosamide (**24**, Zhang et al. 2001), scopoletin (**25**, Darmawan et al. 2012), , rotungenic acid (**26**) (Nakatani et al. 1989), strictosidine (**27**, Patthy-luka et al. 1997), and 5α-carboxystrictosidine (**28**, Ferrari et al. 1986).

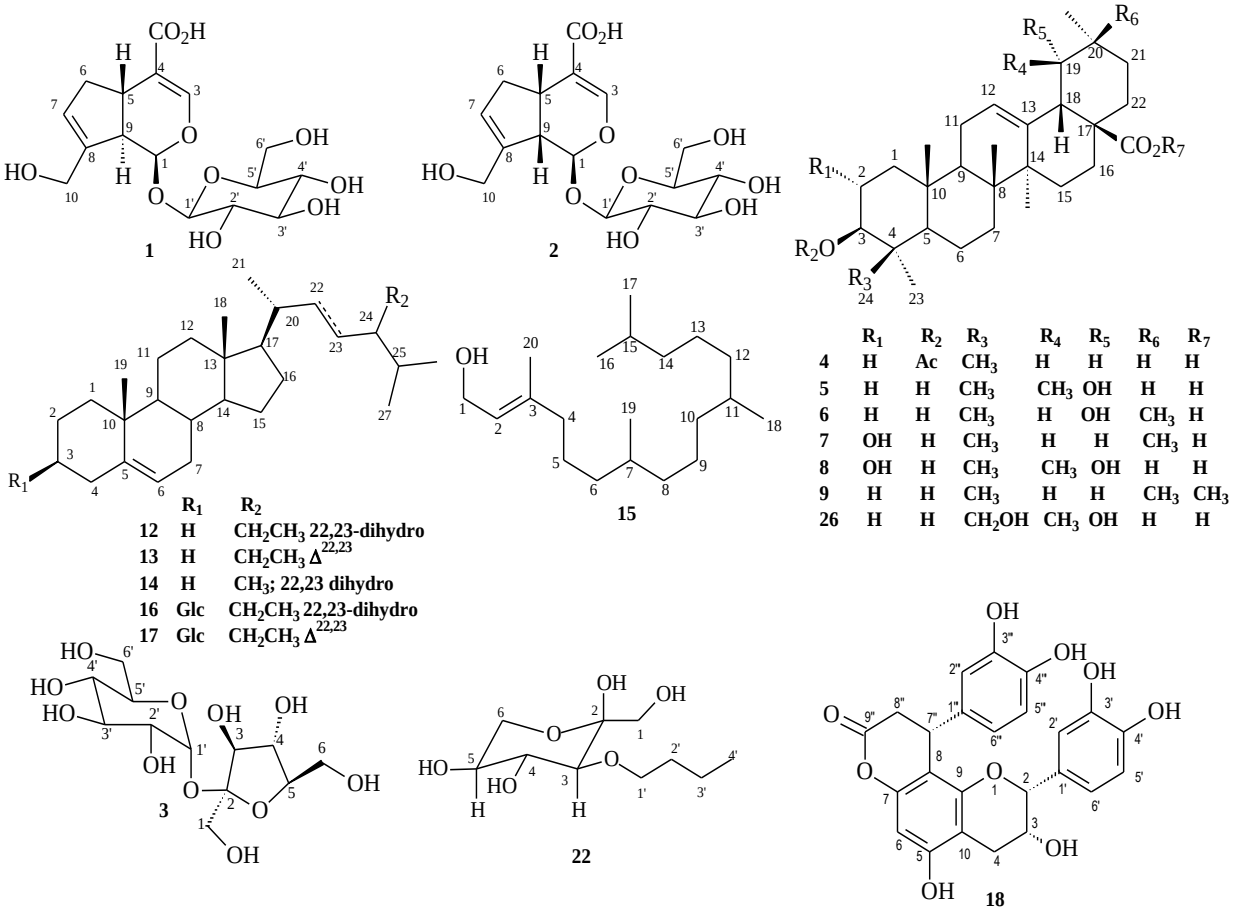

Figure 1. Chemical structures of compounds **1**-**28**.

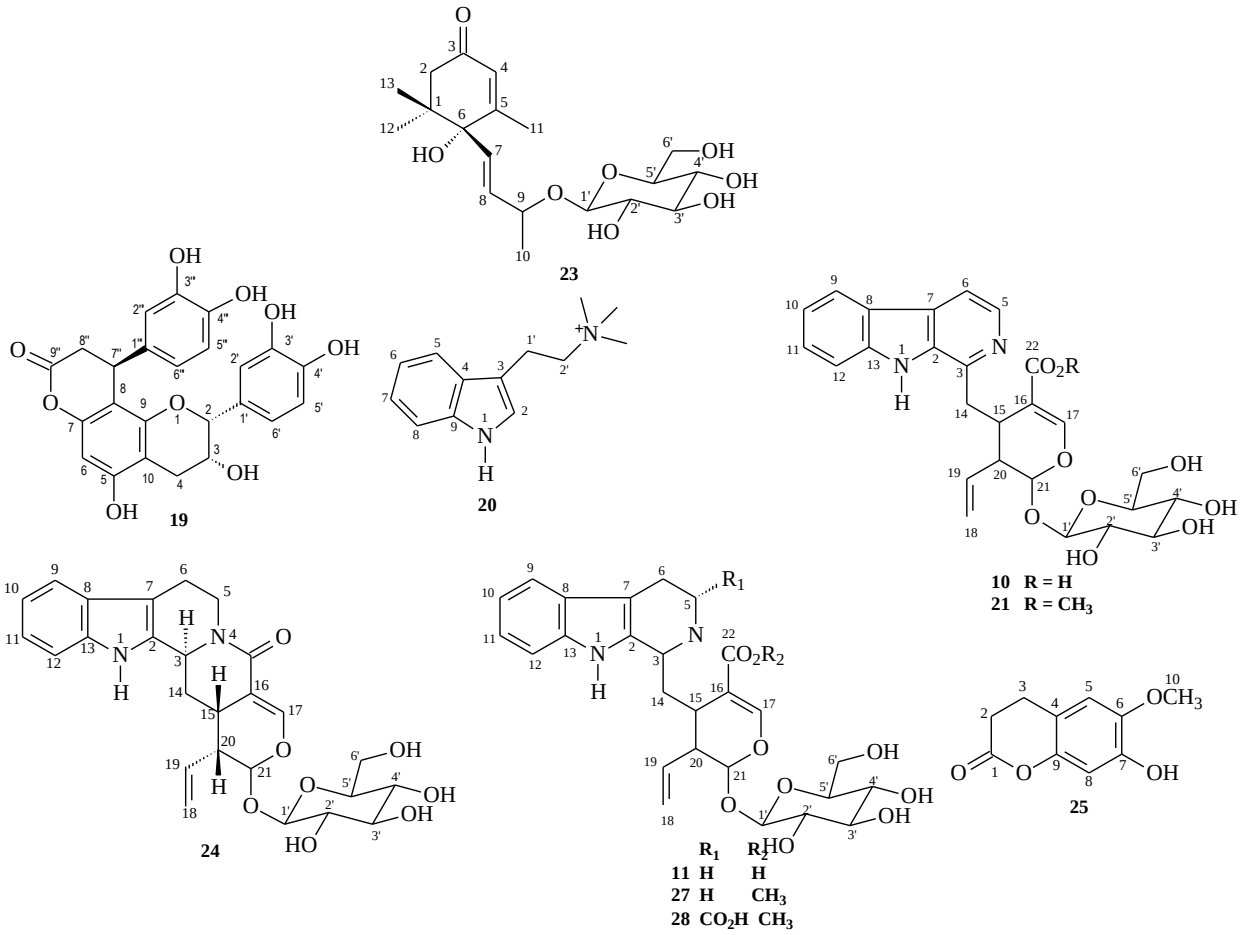

Figure 1. Continued.

2.3. Assessment of cell viability by MTT assay

The cytotoxic potential of compounds **20**, **23**, and **24** was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The results of cell viability of THP-1 and U937 cell lines, treated with these compounds, after 48 h of incubation, are shown in Figures S89 and S90 show the. In both cases, compounds **20** and **23** did not promoted significant cell death and the IC_{50} values were higher than 200 μg/mL. Compound **24** did not display promising result against THP-1 cell line (IC_{50} = 120 ± 1 μg/mL). However, this compound showed significant cytotoxicity against U937 cell line (IC_{50} = 21.9 ± 1). This result is in accordance with previous reports in literature, since indole alkaloids have been recognized by their cytotoxicity against different cancer cell lines (Chaturvedula et al. 2003; Figueiredo et al. 2010; Shao et al. 2015; Zhang et al. 2015; Wang et al. 2015).

3. Experimental

3.1. Apparatus and instruments

Fourier transform infrared (FTIR) spectra were recorded on an IRAffinity-1 Shimadzu spectrometer using KBr disk. The NMR analysis were carried out on a Bruker Ascend 500 in pyridine-d_5, $CDCl_3$ or methanol-d_4 at 500 MHz for ^{1}H and 125 MHz for ^{13}C, using TMS as internal reference. Chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hz. HR-ESI-MS mass spectra were obtained on a micrOTOF-Q II Bruker Daltonics mass spectrometer, using positive and negative ion mode of analysis. Gas chromatography coupled to Mass Spectrometry (GC/MS) of low resolution experiments were carried out on a GCMS-QP5050A Shimadzu, operating with an ionization energy of 70 eV. Silica gel 60 and silica gel 60 silanized (0.063-0.200 mm, MERCK) were used for column chromatography (CC) and silica gel 60 F_{254} for thin layer chromatography (TLC, MERK).

3.2. Plant material

Leaves of *P. suterella* and leaves and twigs of *P. nuda* were collected at the Reserva Biológica de Poço das Antas, Nova Iguaçu-RJ, Brazil, and identified by the botanist Sebastião José da Silva Neto. Both voucher specimens (H9724 and H9726, respectively) are deposited at the herbarium of UENF.

3.3. Extraction and isolation

3.3.1.1. P. suterella

The powdered air-dried leaves of *P. suterella* (345.4 g) were exhaustively extracted with methanol, at room temperature, affording 50.1 g of crude extract. After suspended in a MeOH-H_2O (1:3) solution, part of this extract (40.0 g) was partitioned with dichloromethane, ethyl acetate and n-butane, affording, respectively, 19.7 g, 5.1 g, and 8.4 g of each fraction. The dichloromethane fraction was suspended in a hexane:MeOH (1:1) solution, obtaining a hexane fraction (11.0 g) and a methanol fraction (7.8 g).

The methanolic fraction (7.0 g) was subjected to CC on silica gel and eluted with CH_2Cl_2 and CH_2Cl_2:MeOH solutions, increasing polarity till 15% of MeOH, affording 10

subfractions. Subfraction 4 (700 mg) was similarly chromatographed, affording compound **9** (25.3 mg). Subfraction 5 (840.0 mg) was analogously chromatographed affording compound **4** (27.0 mg) and a mixture of **5** and **6** (246.0 mg). From fraction 8 (660 mg), by analogous chromatographic procedure, a mixture of compounds **7** and **8** (88.0 mg) was obtained. Fraction 9 (457.3 mg) was also similarly chromatographed, yielding a mixture of compounds **1**, **2**, and **3** (67.2 mg). The n-butanol fraction was subjected to CC on silica silanized, eluted with isocratic mixture of MeOH:H_2O (1:1), yielding six fractions. Fraction 3 (300 mg) was chromatographed on Sephadex LH-20 and eluted with MeOH, affording compounds **10** (27.0 mg) and **11** (34.2 mg).

3.3.1.2. 9-epi-geniposidic acid

Brown oil. IR (KBr) ν_{max} cm^{-1}: 3418, 2928, 2860, 1686, 1639, 1275. ^{1}H NMR (500 MHz, CD_3OD): 5.15 (1H, *d*, 3.4, H-1), 7.50 (1H, *d*, 0.9, H-3), 3.10 (1H, *m*, H-5), 2.85 (1H, *dd*, 16.4, 6.2, 1H-6), 2.14-2.04 (1H, *m*, 1H-6), 5.82 (1H, *br s*, H-7), 2.76 (1H, *t*, 7.5, H-9), 4.33 (1H, *br d*, 13.3, 1H-10), 4.21 (1H, *br d*, 13.3, 1H-10), 4.51 (1H, *d*, 7.7, H-1'), 3.15 (1H, *m*, H-2'), 3.45 (1H, *m*, H-3'), 3.55 (1H, *m*, 1H-4'), 3.54 (1H, *m*, 1H-5'), 3.80 (1H, *m*, 1H-6'), 3.70 (1H, *m*, 1H-6'). ^{13}C NMR (125 MHz, CD_3OD): 96.8 (CH-1), 151.5 (CH-3), 112.1 (C-4), 35.4 (CH-5), 38.4 (CH_2-6), 127.2 (CH-7), 143.3 (C-8), 45.6 (CH-9), 60.1 (CH_2-10), 98.7 (CH-1'), 73.4 (CH-2'), 76.3 (CH-3'), 70.1 (CH-4'), 76.9 (CH-5'), 61.3 (CH_2-6').

3.3.2. P. nuda

The methanolic extract of twigs (1.45 Kg) and leaves (426.0 g) of *P. nuda* were obtained as previously mentioned (section 3.3.1.1), affording, respectively, 36.7g and 46.5 g of each crude extract. Both extracts were also partitioned as previously.

Part of the dichloromethane fraction of the twigs (1.2 g) was successively chromatographed on silica gel and eluted with CH_2Cl_2 and CH_2Cl_2:MeOH solutions, leading to the identification of a mixture of compounds **12**-**14** (153.0 mg), **15** (23.2 mg), and a mixture of **16** and **17** (53.0 mg). The ethyl acetate fraction of leaves (790.0 mg) was similarly chromatographed (except for the use of CH_2Cl_2:AcOET as eluent), allowing the identification of compounds **18** and **19** (35.0 mg) whereas n-butanol fraction yielded compound **20** (26.0 mg).

The n-butanol fraction of leaves (1.85 g) was successively chromatographed, leading to the identification compounds **21** and **22** (in mixture, 64.2 mg). Besides, another fraction (88.0 mg), obtained from this procedure, was purified on Sephadex LH-20 and compounds **23** (13.0 mg) and **24** (11.0 mg) were identified. The ethyl acetate fraction (920 mg) was similarly chromatographed, affording 18 fractions. Fraction 5 (28.3 mg) was purified by preparative TLC and compound **25** (4.0 mg) was obtained. Fraction 12 (114.5 mg) was rechromatographed leading to the identification of a mixture of compounds **5** and **6** (21.0 mg). Fraction 16 (121.3 mg) was rechromatographed leading to the isolation of compound **26** (26.0 mg).

The metanolic fraction o leaves (1.7 g) was fractionated by CC on silica gel and eluted with CH_2Cl_2 and CH_2Cl_2:MeOH solutions (till 20 % of MeOH), affording 12 fractions. Fraction 5 (200 mg) was similarly chromatographed and, after purification by CC on Sephadex LH-20 (eluted with MeOH), compound **27** (22.0 mg) was identified. From fraction 10 (210 mg), compound **28** (32 mg) was, analogously, obtained.

3.3. Culture of cells

Human leukemia cell lines U937 (histiocytic lymphoma cell line) and THP-1 (acute monocytic leukemia cell line were cultured in DMEM-F12 medium (Gibco, BRL), supplemented with 20 mg/mL gentamycin (Gibco, BRL) and 10 % fetal bovine serum (Gibco, BRL). The cultures were replicated every 2 days and incubated at 37 °C, with 5 % of CO_2 and humidity control.

3.4. MTT assay

Cell lines were plated into a 100 μL/well ($1x10^6$ cells/mL) in 96-well plates and treated with compounds **20**, **23**, and **24** at concentrations of 0, 6.25, 12.5, 25.0, 50.0, 100.0 and 200 μg/mL. The cells were kept at 37 °C, with 5 % of CO_2 and humidity control. Cell viability was measured by MTT assay after 48 h of incubation (Terra et al. 2013). The assays were analyzed by ANOVA, followed by Tukey test using Graph Pad Software 5.0 program.

4. Conclusion

This study led to the isolation and identification of 28 compounds from these two species. To the best of our knowledge, besides the novel iridoid (compound **1**), compounds **2**-**10**, **18**-**19**, **20**, and **23** are reported for the first time in this genus. This work, then, may add relevant information related to the chemotaxonomy of this complex genus. With respect to the MTT assay, only compound **24** showed significant cytotoxicity.

Disclosure statement

No potential conflict of interest.

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Supplemental online material

Compound 1

Table S1. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **1**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	HSQC		HMBC	
	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$
C				-
2	112.1	-	H-3	
4	143,3	-	H-7; H-9; 2H-10	H-1
8	170.4	-		H-3; H-5
11				
CH				H-3; H-1’
1	92.5	5.15 (*d*, 3.4)		H-1; H-5
3	151.5	7.50 (*d*, 0.9)	-	-
4	-	-		H-1; H-3; H-7
5	35.4	3.22-3.15 (m)		H-5; 2H-10
7	127.2	5.82 (*brs*)	H-1	H-7
9	45.6	2.73 (*t*, 7.5)		H-1
1’	96.6	4.51 (*d*, 7.7)		
2’	73.4	3.22-3.15 (m)		
3’	76.3	3.45 (*m*)		
4’	70.1	3.55 (*m*)		
5’	76.9	3.54 (*m*)		
CH_2				
6	38.4	2.85 (*dd*, 16.4, 6.2) 2.14 – 2.04 (*m*)	H-5; H-7	
10	60.1	4.33 (*d*, 13,3) 4.21 (*d*, 13.3)		H-7
6’	61.3	3.80 (*m*), 3.70 (*m*)		

Compound 2

Table S2. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **2**, including results of HSQC and HMBC experiments. Chemical δ shifts are given in ppm and coupling constants in Hz

	HSQC		HMBC	
	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$
C				
2	112.1	-	H-3	
4	143,3	-	H-7; H-9; 2H-10	H-1
8	170.4	-		H-3; H-5
11				
CH				H-3; H-1’
1	96.8	5.16 (*d*, 7.5)		H-1; H-5
3	151.5	7.50 (*d*, 0.9)	-	-
4	-	-		H-1; H-3; H-7
5	35.4	3.10 (*m*)		H-5; 2H-10
7	127.2	5.82 (*brs*)	H-1	H-7
9	45.6	2.73 (*t*, 7.5)		H-1
1’	98.7	4.74 (*d*, 7.9)		
2’	73.4	3.15 (*m*)		
3’	76.3	3.45 (*m*)		
4’	70.1	3.55 (*m*)		
5’	76.9	3.54 (*m*)		
CH_2				
6	38.4	2.85 (*dd*, 16.4, 6.2) 2.14 – 2.04 (*m*)	H-5; H-7	
10	60.1	4.33 (*d*, 13,3) 4.21 (*d*, 13.3)		H-7
6’	61.3	3.80 (*m*), 3.70 (*m*)		

Compound 3

Table S3. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **3**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	HSQC		HMBC	
	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$
C				
2	103.9	-	2H-1	H-1’
CH				
3	77.9	4.13 (*d*, 8.3)		
4	74.3	4.05 (*t*, 8.3)	H-4; 1H-3	
5	82.2	3.80 (*m*)	H-4	
1’	92.5	5.42 (*d*, 3.8)		H-3’
2’	71.7	3.40 (*m*)	H-1’	
3’	73.2	3.75 (*m*)		
4’	70.0	3.40 (*m*)		
5’	72.9	3.86 (*m*)		
CH_2				
1	62.6	3.80 (*m*); 3.69 (*m*)		H-3
6	62.0	3.80 (*m*); 3.70 (*m*)		
6’	60.9	3.82 (*m*); 3.75 (*m*)		

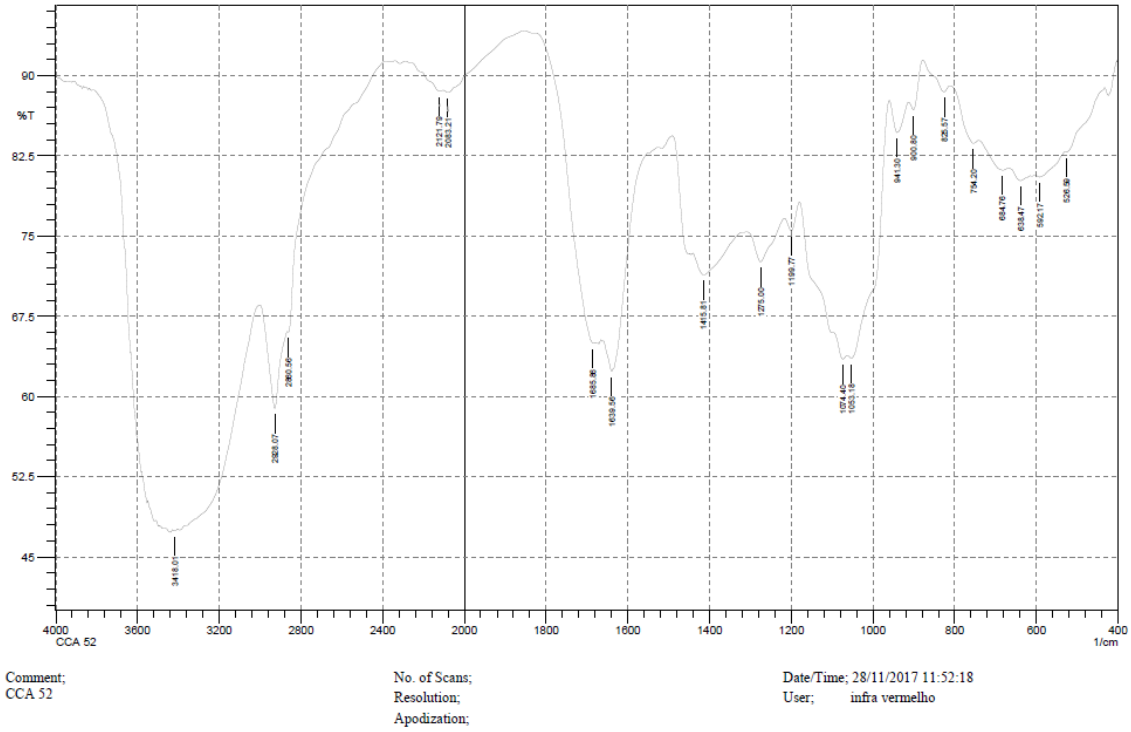


Figure S1. Infrared spectrum of compounds **1**-**3**.

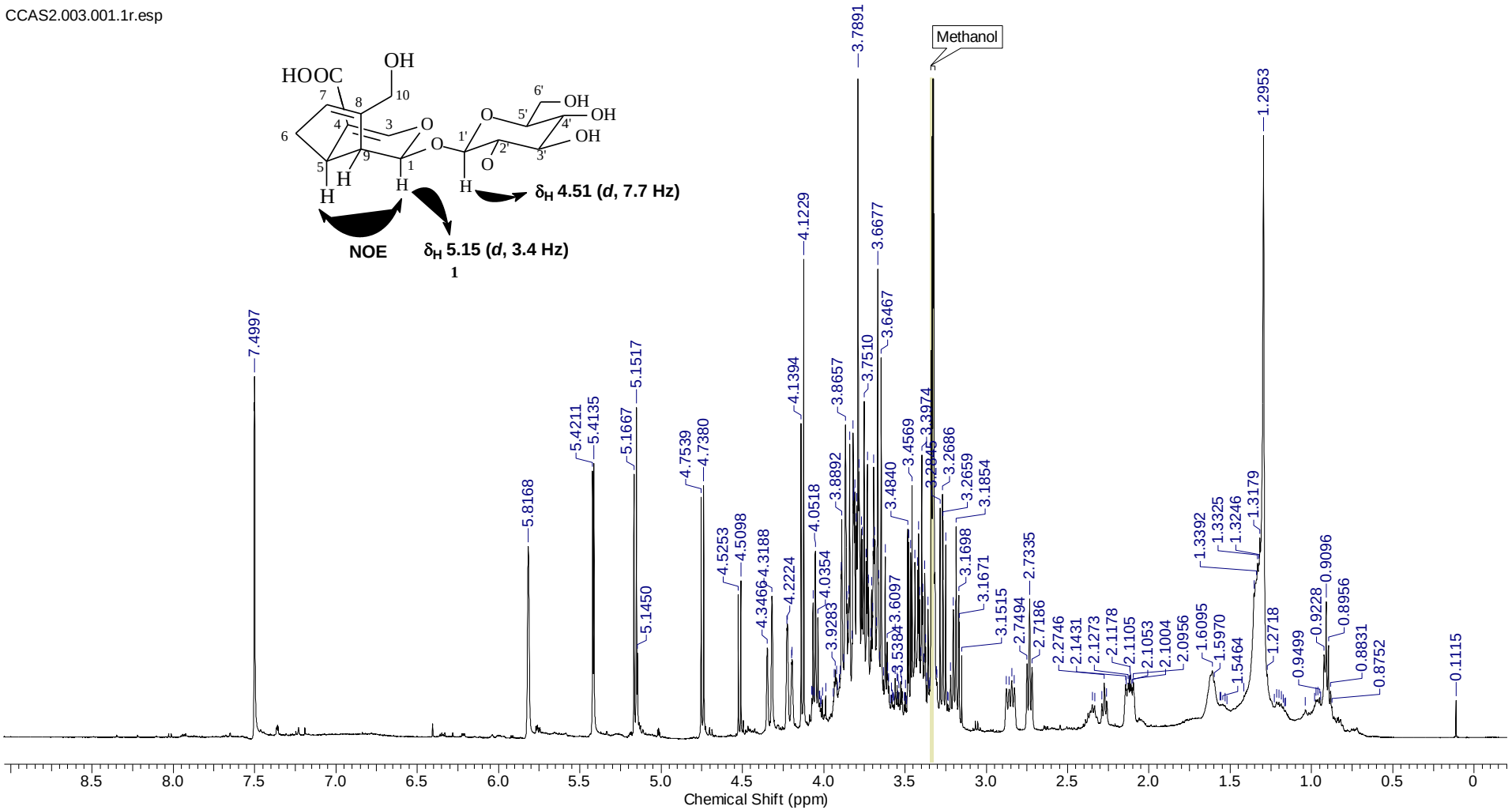


Figure S2. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compounds **1**-**3**.

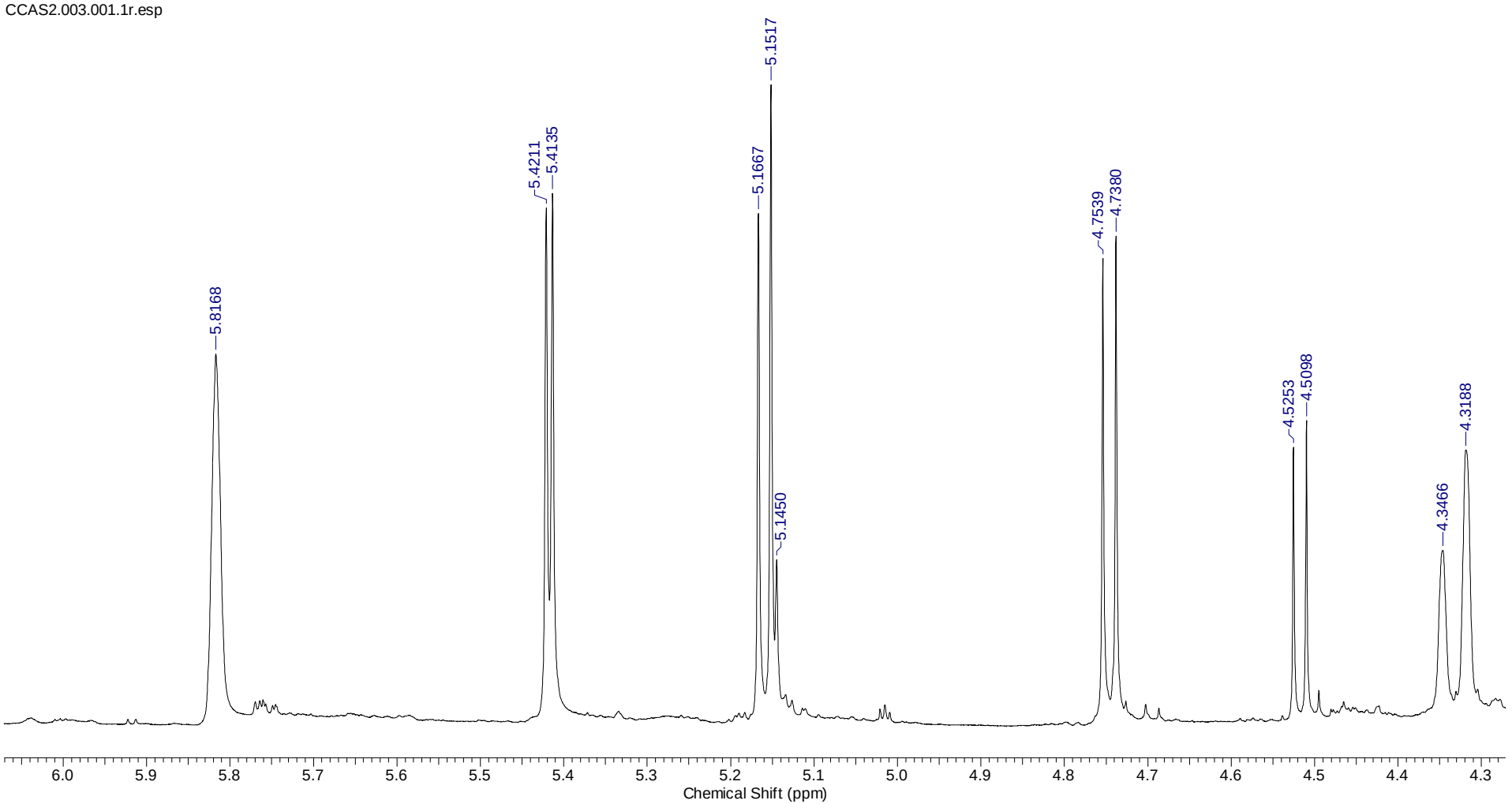


Figure S3. Expansion of ^{1}H NMR spectrum (500 MHz, CD_3OD) of compounds **1**-**3**.

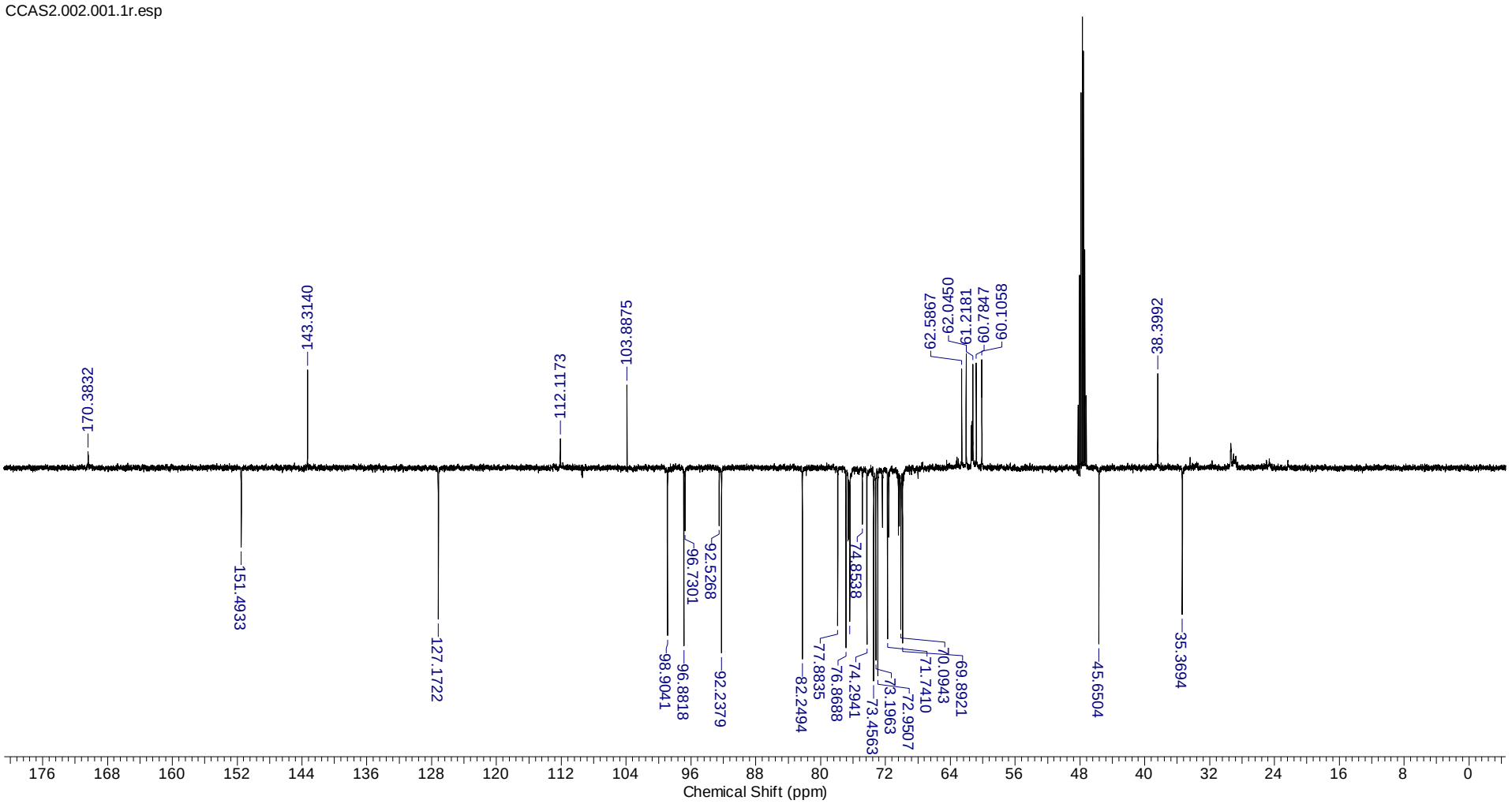


Figure S4. DEPTQ spectrum (125 MHz, CD_3OD) of compounds **1**-**3**.

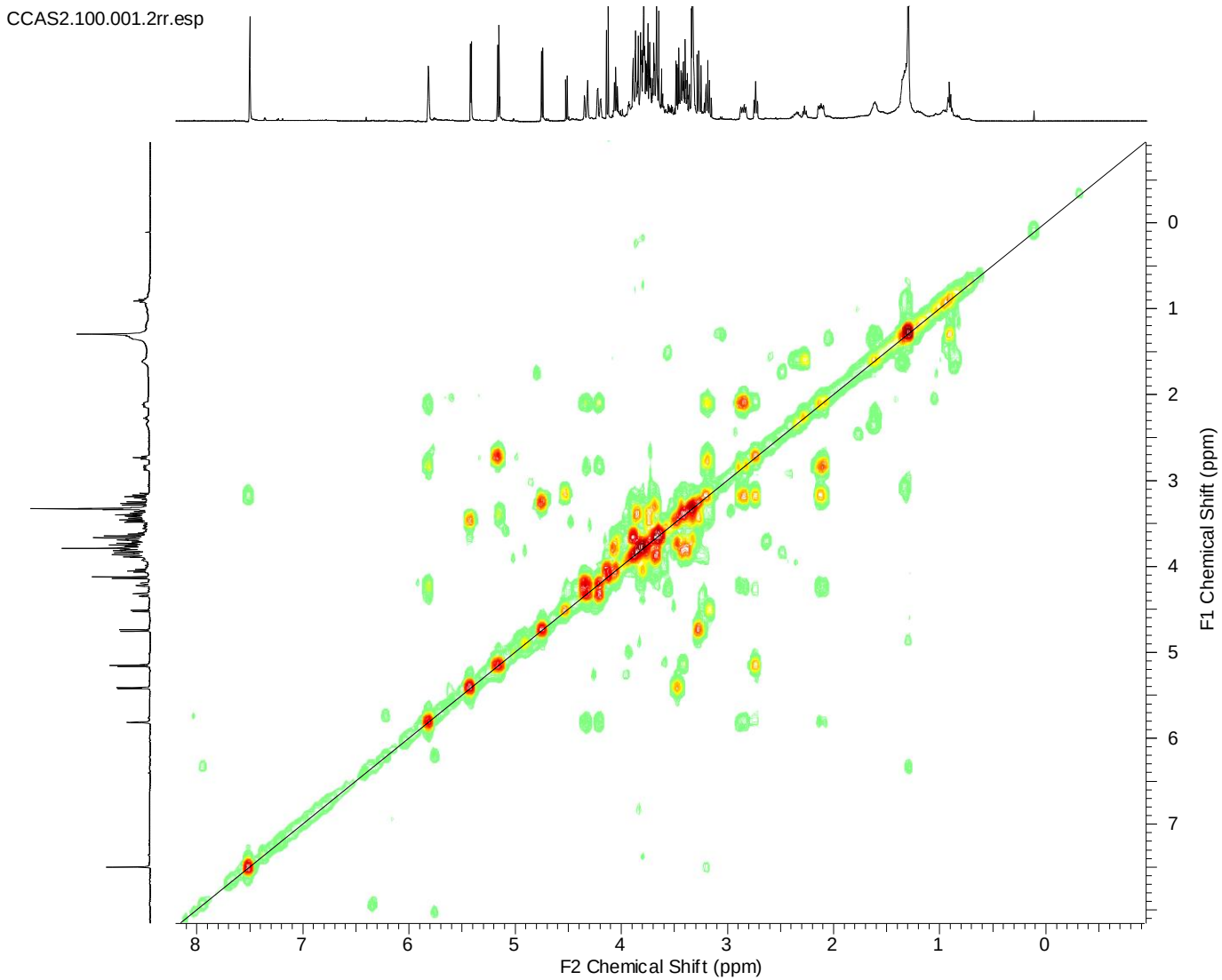


Figure S5. ^{1}H-^{1}H-COSY spectrum of compounds **1**-**3**.

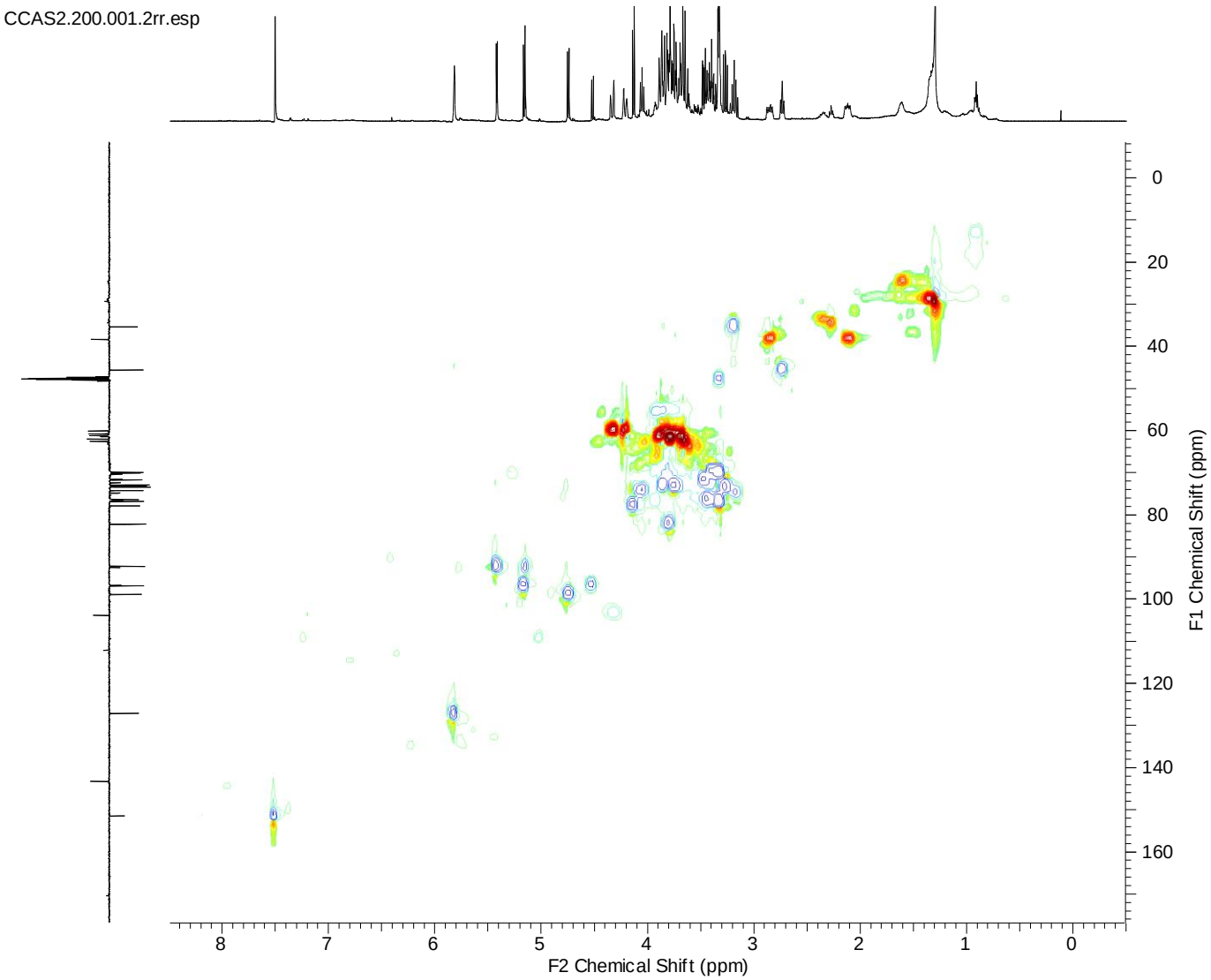


Figure S6. HSQC spectrum of compounds **1**-**3**.

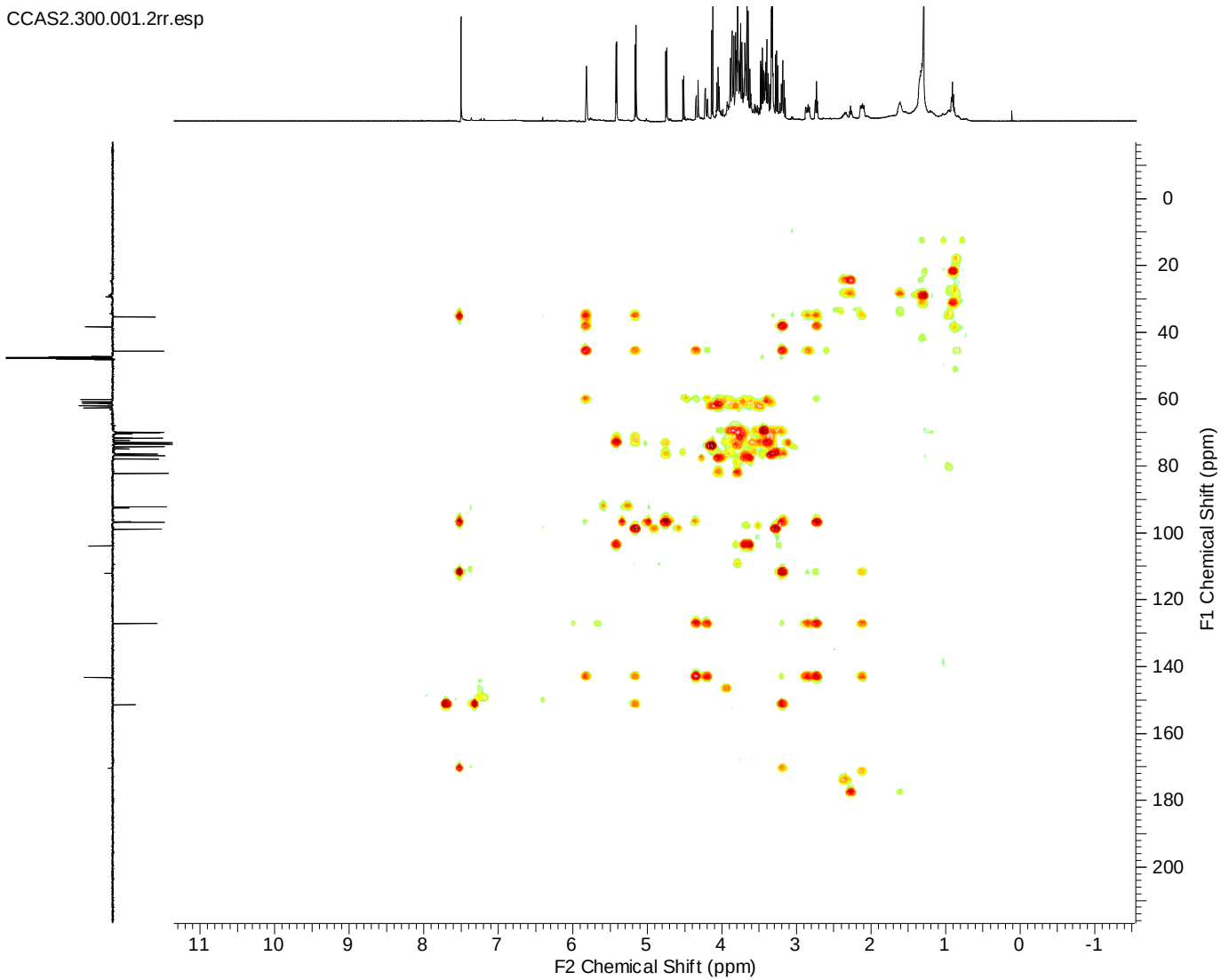


Figure S7. HMBC spectrum of compounds **1**-**3**.

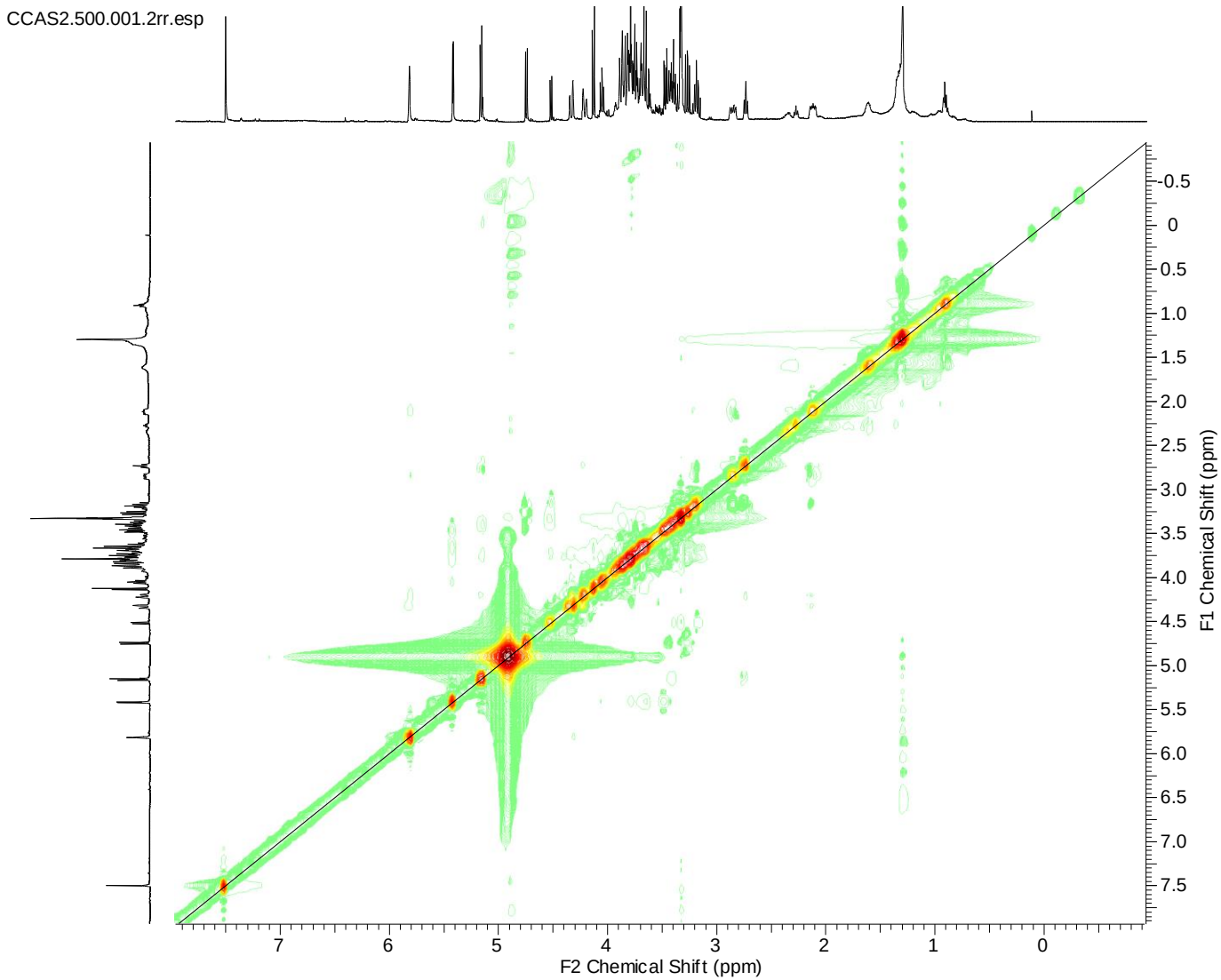


Figure S8. NOESY spectrum of compounds **1**-**3**.

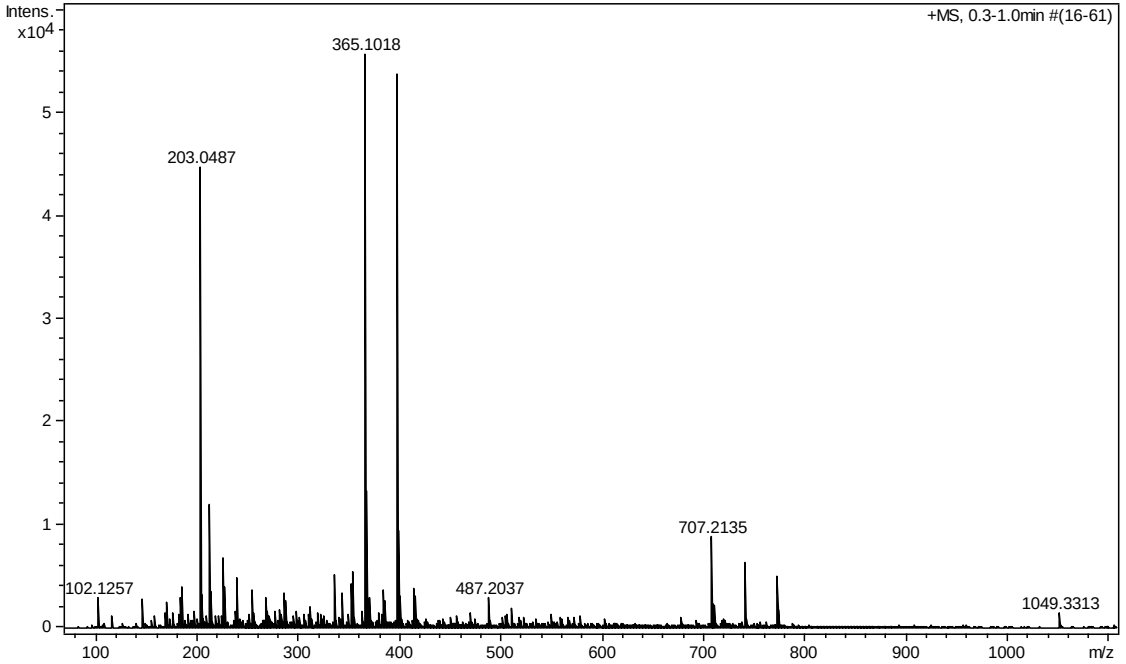


Figure S9. ESI-MS spectrum of compounds **1**-**3** (positive mode).

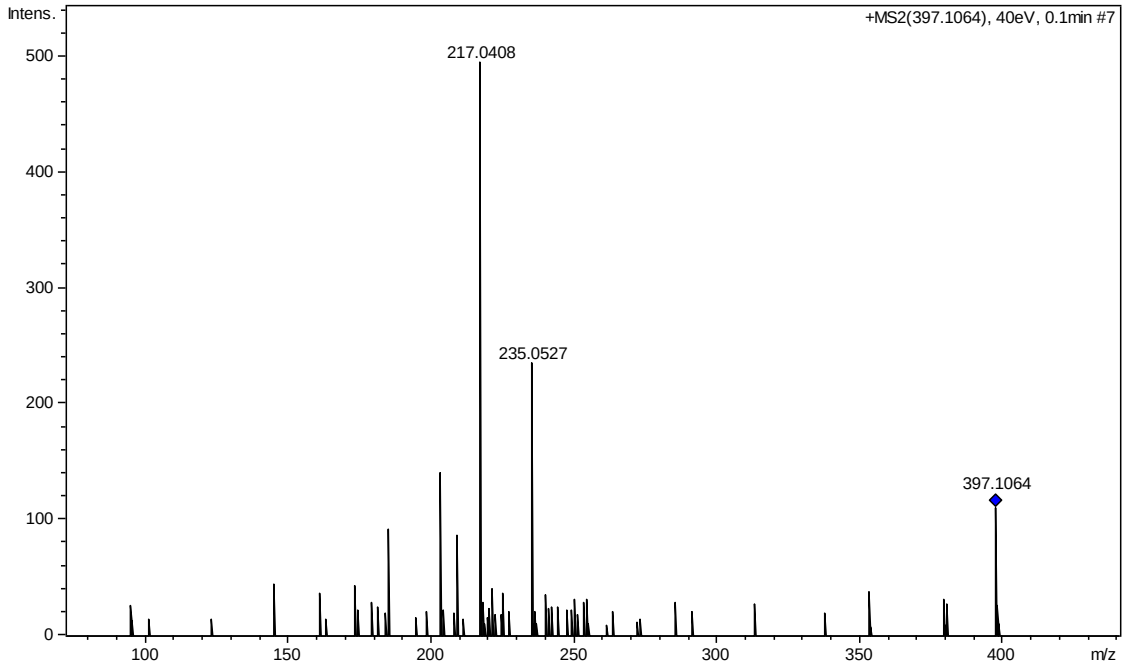


Figure S10. ESI-MS2 (*m/z* 397.1064) spectrum of compound **1** (positive mode).

Compound 4

Table S4. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **4**, including results of HSQC and HMBC experiments. Chemical shifts δ are given inppm and coupling constants in Hz

	4				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_{C**}
4	37.8		3H-23; 3H-24		37.9
8	39.6	-	H-9; 3H-26	2H-11; 3H-27	40.0
10	37.1	-	H-7b; 3H-25	2H-11	37.3
13	142.6	-	H-18	2H-11; H-19	144.9
14	41.2	-	3H-27	H-9; H-18; 3H-26	42.2
17	45.3	-	H-18	H-19	46.1
20	34.6				35.7
28	184.8	-		H-16a; H-18; H-22a	180.9
O-Ac	171.0	-		H-3	170.6
CH					
3	80.9	4.50 (*dd*, 10.2, 6.2)		3H-23; 3H-24	80.8
5	55.3	0.90 (*m*)		H-7b; 3H-23; 3H-24; 3H-25	55.6
9	47.8	1.70 (*m*)	2H-11	3H-25; 3H-26	48.2
12	125.18	5.43 (*brs*)	2H-11	H-18	123.2
18	43.4	3.09 (*brs*)	H-19	2H-16; H-22b	44.8
19	81.5	3.34 (*d*, 3.6)	H-18	H-21; 3H-29; 3H-30	81.3
CH_2					
1	37.8	1.62 (*m*); 1.08 (*m*)		3H-25	38.1
2	23.7	1.70-1.60 (*m*)			24.1
6	18.3	1.58 (*m*); 1.42 (*m*)	H-7b		18.6
7	32.3	1.70 (*m*); 1.30 (*m*)		3H-26	33.7
11	23.4	1.96 (*dd*, 8.5, 2.4)			23.9
15	28.0	1.60 (*m*); 1.05 (*m*)	2H-16	3H-27	28.4
16	27.3	2.28 (*td*, 13.3, 3.2), 1.68 (*m*)		H-18	29.2
21	28.0	1.80 (*m*)		H-19; 3H-29; 3H-30	29.1
22	32.5	1.85 (*m*); 1.48 (*m*)		H-16b	33.2
CH_3					
23	28.0	0.87 (*s*)		3H-24	28.2
24	16.6	0.87 (*s*)		3H-23	16.9
25	15.2	0.93 (*s*)		H-9	15.3
26	17.3	0.71 (*s*)		H-9	17.4
27	25.0	1.25 (*s*)			24.9
29	28.0	0.98 (*s*)		H-19; 3H-30	28.9
30	24.3	0.97 (*s*)		H-19; 3H-29	24.9
O-Ac	21.3	2.05 (*s*)			21.1

* Itokawa et al. 1989 **Pyridine-d_5

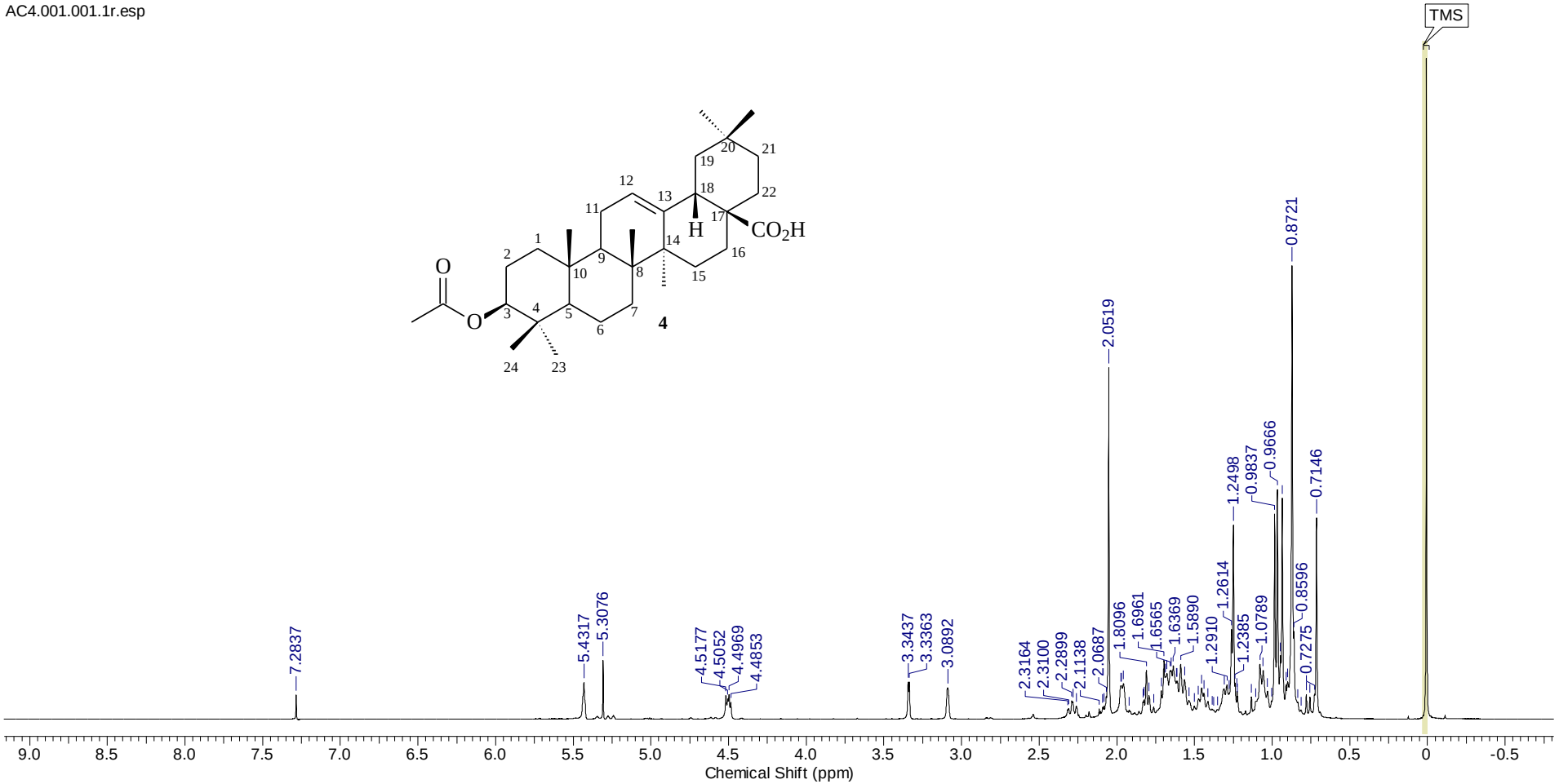


Figure S11. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **4**.

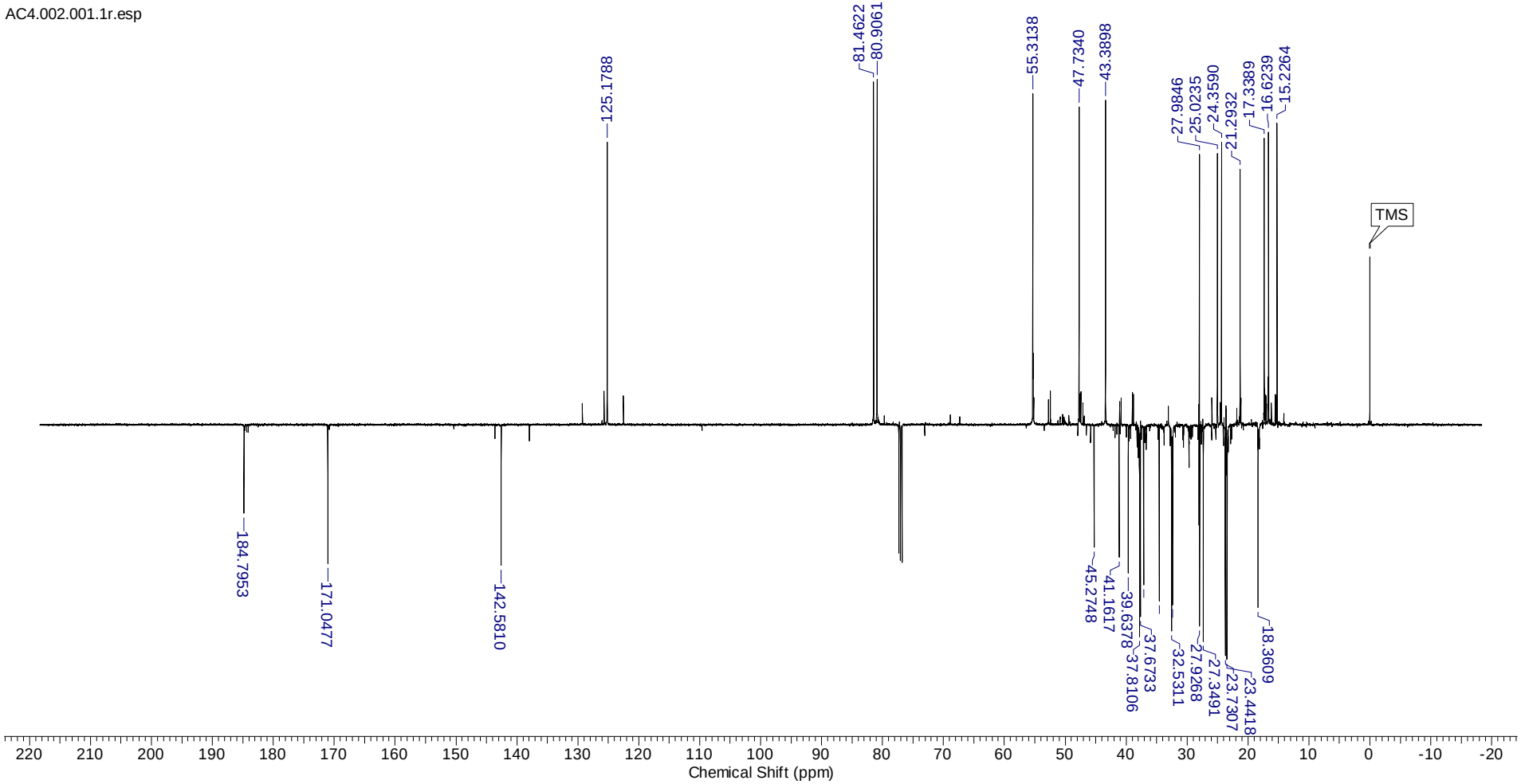


Figure S12. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **4**.

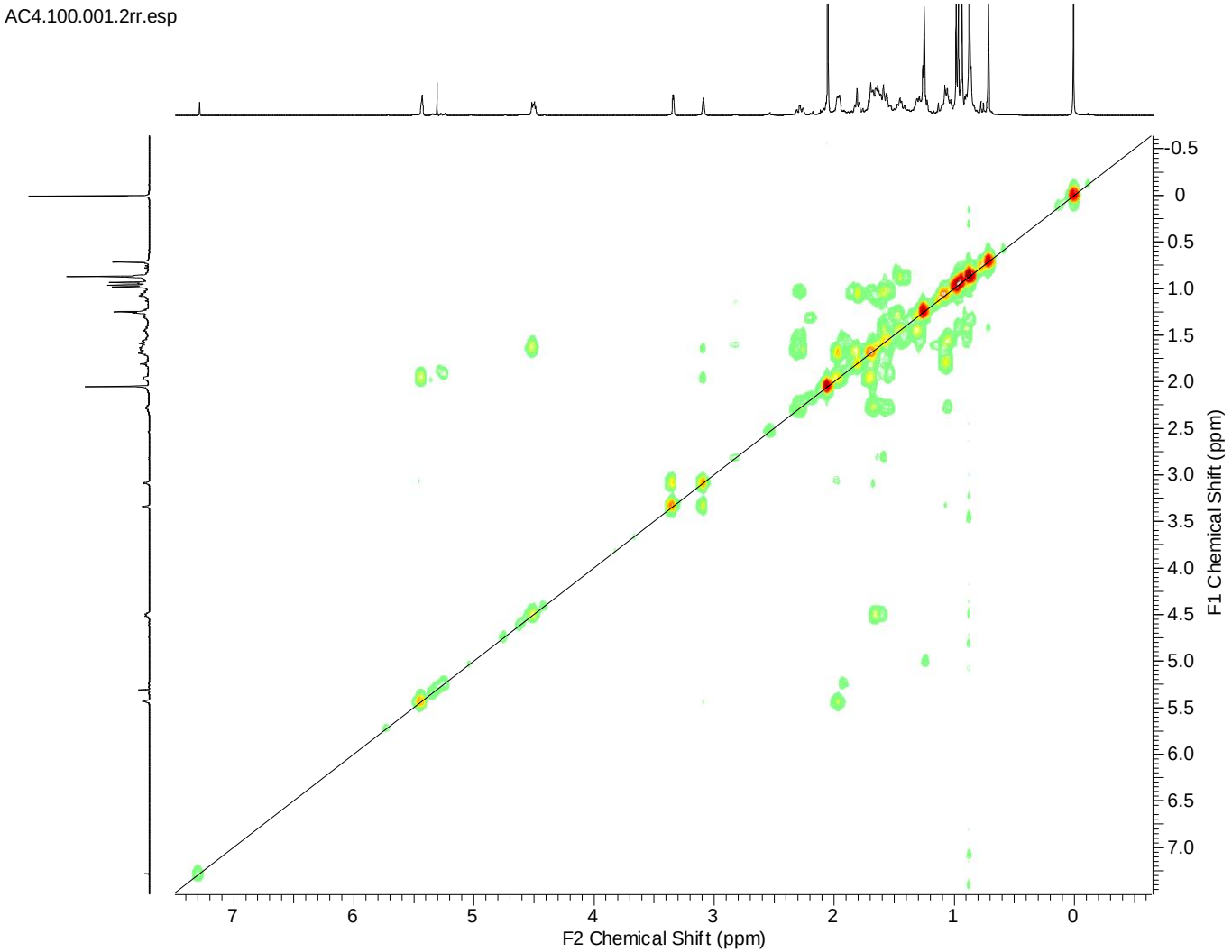


Figure S13. ^{1}H-^{1}H-COSY spectrum of compound **4**.

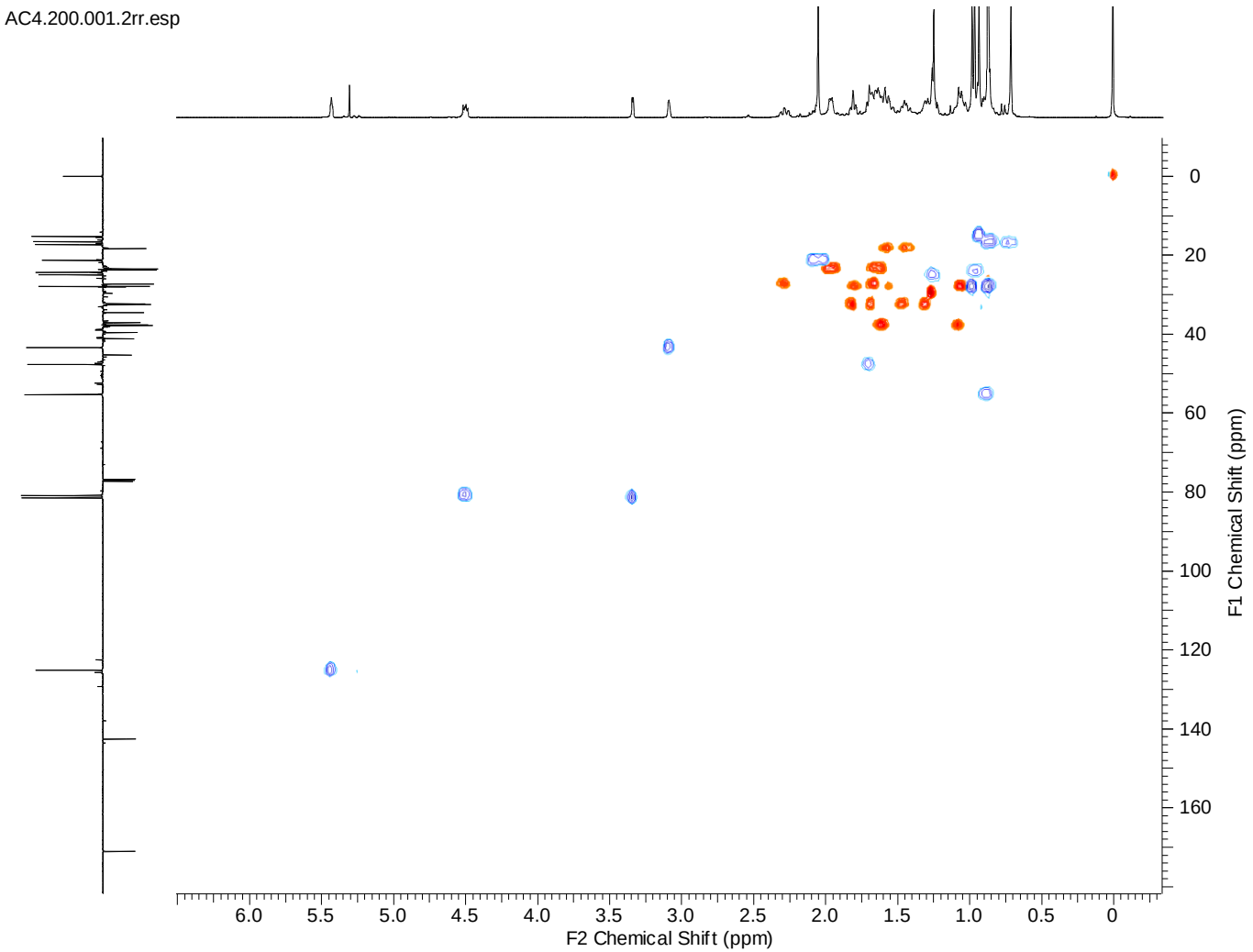


Figure S14. HSQC spectrum of compound **4**.

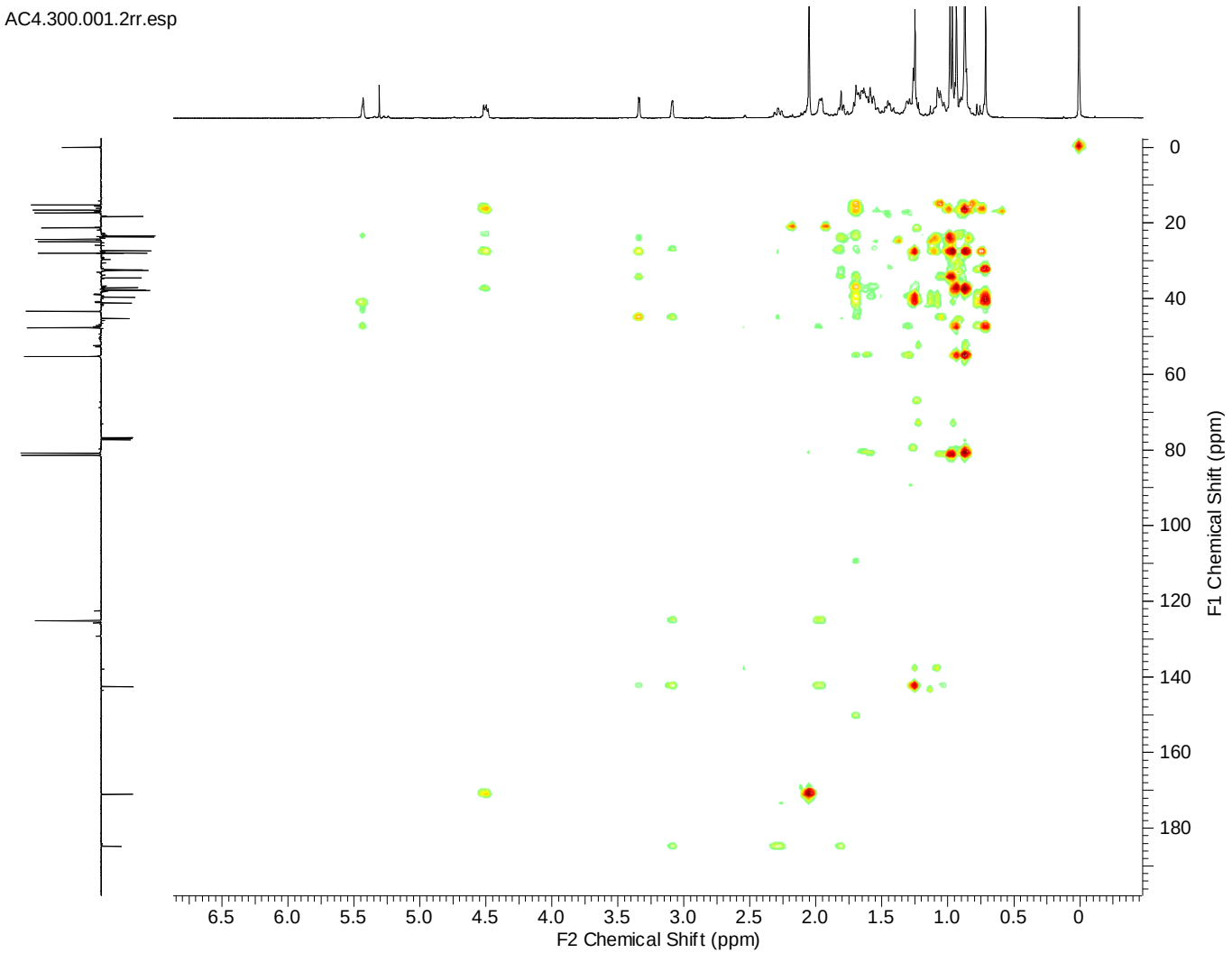


Figure S15. HMBC spectrum of compound **4**.

Compounds 5 and 6

Table S5. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **5**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	5				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
4	40.1	-			40.4
8	39.7	-			39.0
10	37,3	-			37.4
13	138.7	-	H-18	3H-27	137.9
14	41.9	-	3H-27	H-12	42.4
17	48.0	-	2H-16; H-18		47.8
19	72.5	-	H-18; 3H-29		72.7
28	180.4	-		H-18; 3H-27	180.7
CH					
3	78.0	3.43 (*dd*, 10.7, 5.2)			78.2
5	55.6	0.89 (*m*)		3H-25	55.9
9	47.9	1.85 (*m*)		H-12; 3H-25	48.3
12	127.6	5.60 (*t*, 3.4)		H-18	128.1
18	54.3	3.06 (*sl*)		H-12; 3H-29	54.7
20	41.9	1.50 (*m*)		H-18; 3H-29	42.2
CH_2					
1	39.8	2.15 (*m*) e 2.06 (*m*)		H-3	39.4
2	28.2	1.28 (*m*)			28.2
6	18.7	1.58 (*m*) e 1.41 (*m*)			19.0
7	33.4	1.64 (*m*); 1.40 (*m*)			33.6
11	23.8	2.03 (*m*)			24.1
15	28.9	1.28 (*m*)	2H-16	3H-27	29.4
16	26.6	3.12 (*dt*, 13.0, 4.5)			26.4
21	26.7	1.39 (*m*)		H-18	27.0
22	38.6	1.58 (*m*) e 0.98 (*m*)			38.5
CH_3					
23	28.5	1.19 (*s*)		H-3	28.8
24	16.1	0.99 (*s*)		H-3	16.8
25	15.3	0.96 (*s*)			15.6
26	16.8	1.06 (*s*)			17.3
27	24.4	1.73 (*s*)			24.7
29	26.9	1.45 (*s*)		1H-18	27.2
30	16.8	1.06 (*m*)			16.5

* Chama et al. 2015.

Table S6. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **6**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	6				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
4	40.1	-			38.5
8	39.7	-			39.6
10	37,3	-	3H-25		37.2
13	144.6	-	H-18	3H-27; H-19	143.4
14	41.9	-	3H-27	H-12	41.4
17	45.9	-	2H-16; 1H-18		45.5
28	180.7	-		H-18; 3H-27	181.1
CH					
3	77.9	3.43 (*dd*, 10.7, 5.2)			78.6
5	55.6	0.89 (*m*)		3H-25	55.7
9	47.9	1.85 (*m*)		H-12; 3H-25	47.7
12	123.6	5.60 (*t*, 3.4)		H-18	123.7
18	54.3	3.06 (*sl*)		H-12; 3H-29	44.0
19	81.0	3.62 (*m*)	H-18; 3H-29		81.3
20	41.9	1.50 (*m*)		H-18; 3H-29	34.9
CH_2					
1	39.8	2.15 (*m*) e 2.06 (*m*)		H-3	38.7
2	28.2	1.28 (*m*)			26.8
6	18.7	1.58 (*m*) e 1.41 (*m*)			18.5
7	33.4	1.64 (*m*) e 1.40 (*m*)			32.8
11	23.8	2.03 (*m*)			23.9
15	28.9	1.28 (*m*)	2H-16	3H-27	28.3
16	26.6	3.12 (*td*, 13.0, 4.5)			27.5
21	26.7	1.39 (*m*)		H-18	28.4
22	38.6	1.58 (*m*) e 0.98 (*m*)			32.8
CH_3					
23	28.5	1.19 (*s*)		H-3	27.6
24	15.1	0.88 (*s*)		H-3	15.1
25	15.3	0.96 (*s*)			14.6
26	16.8	1.06 (*s*)			16.6
27	24.4	1.73 (*s*)			24.0
29	26.9	1.45 (*s*)		H-18; 1H-19	27.5
30	24.2	1.14 (s)		H-19	24.0

*Wang et al. 2011.

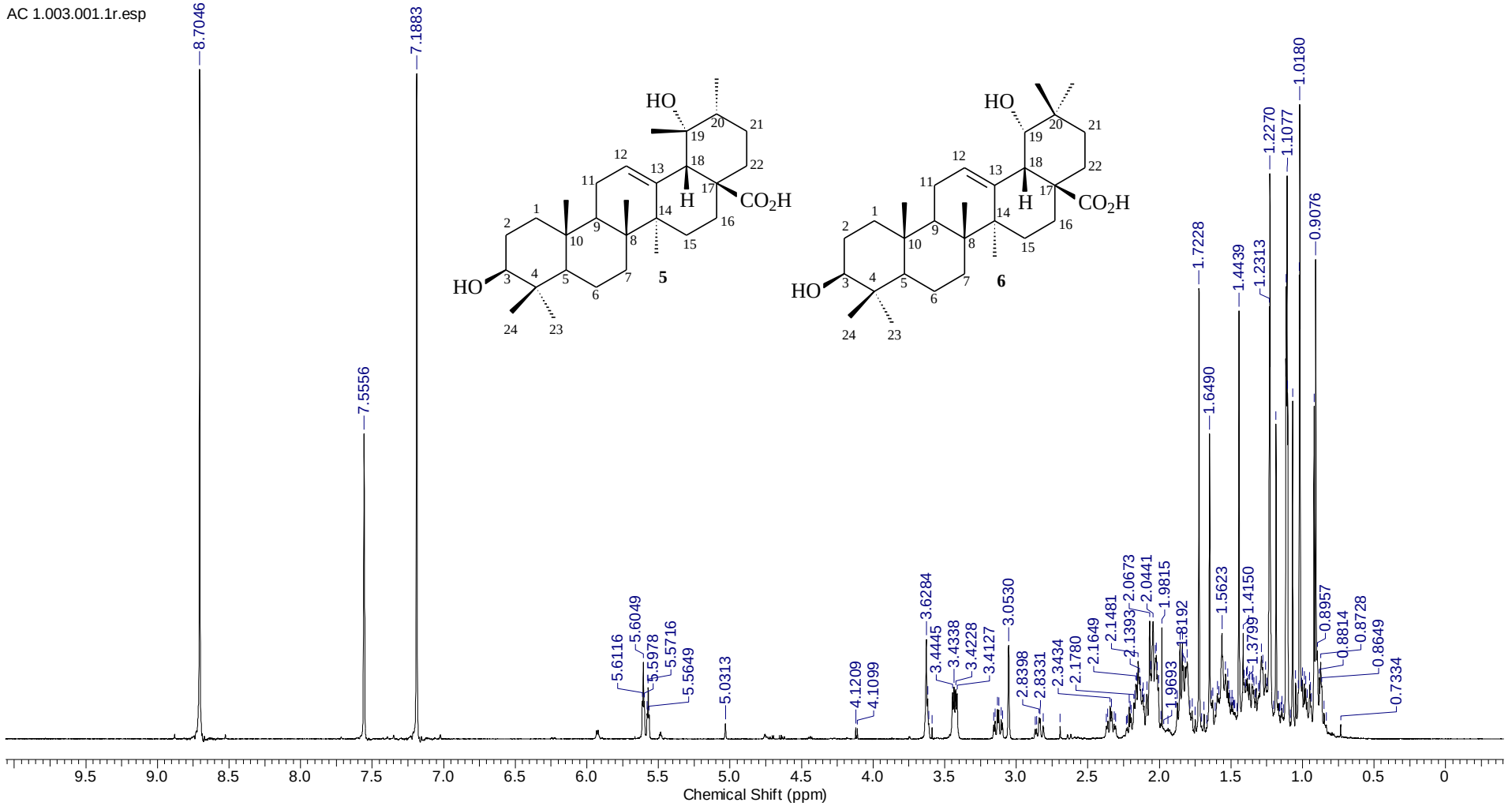


Figure S15. ^{1}H NMR spectrum (500 MHz, Pyridine-d_5) of compounds **5** and **6**.

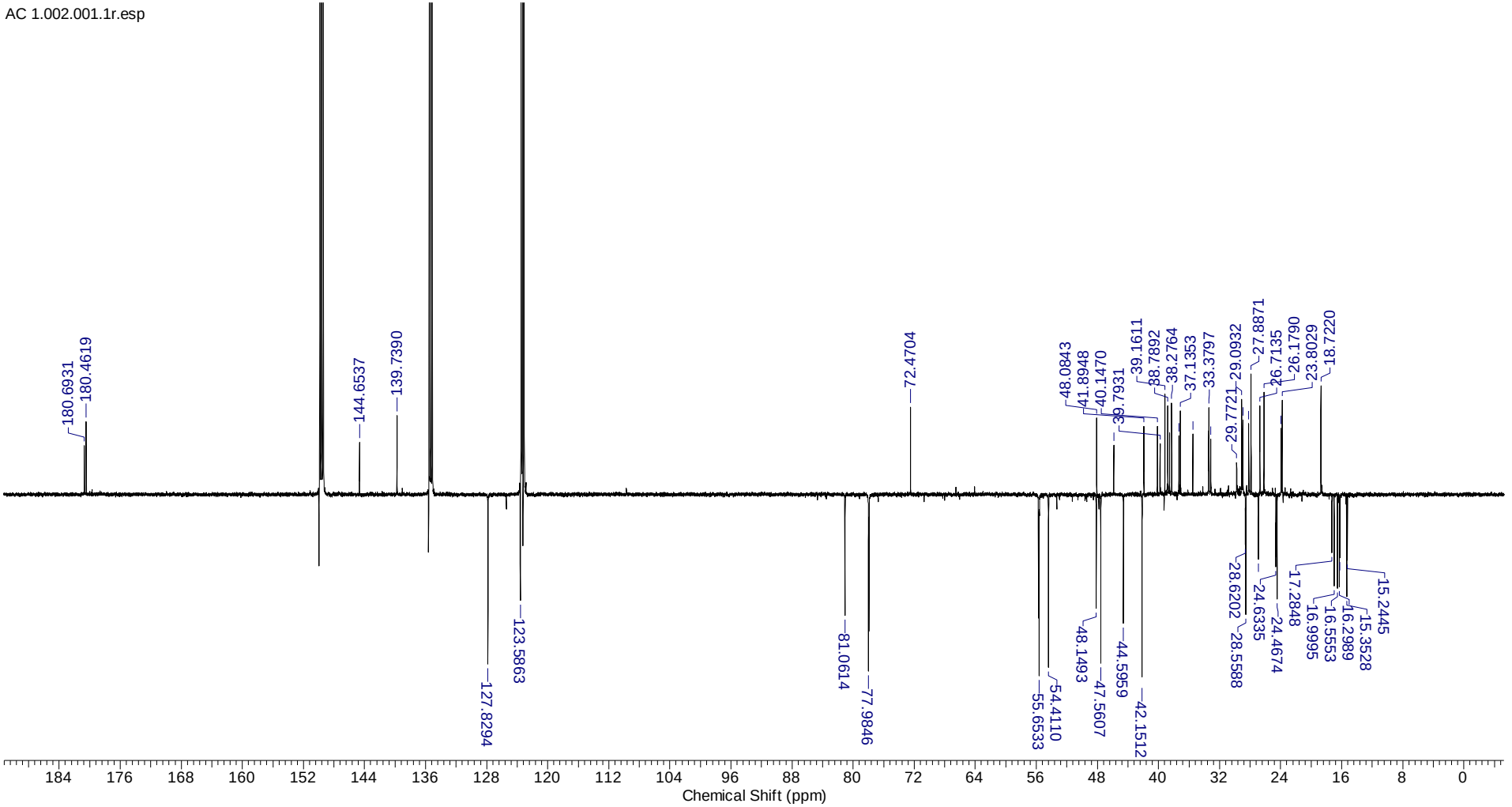


Figure S16. DEPTQ spectrum (125 MHz, Pyridine-d_5) of compounds **5** and **6**.

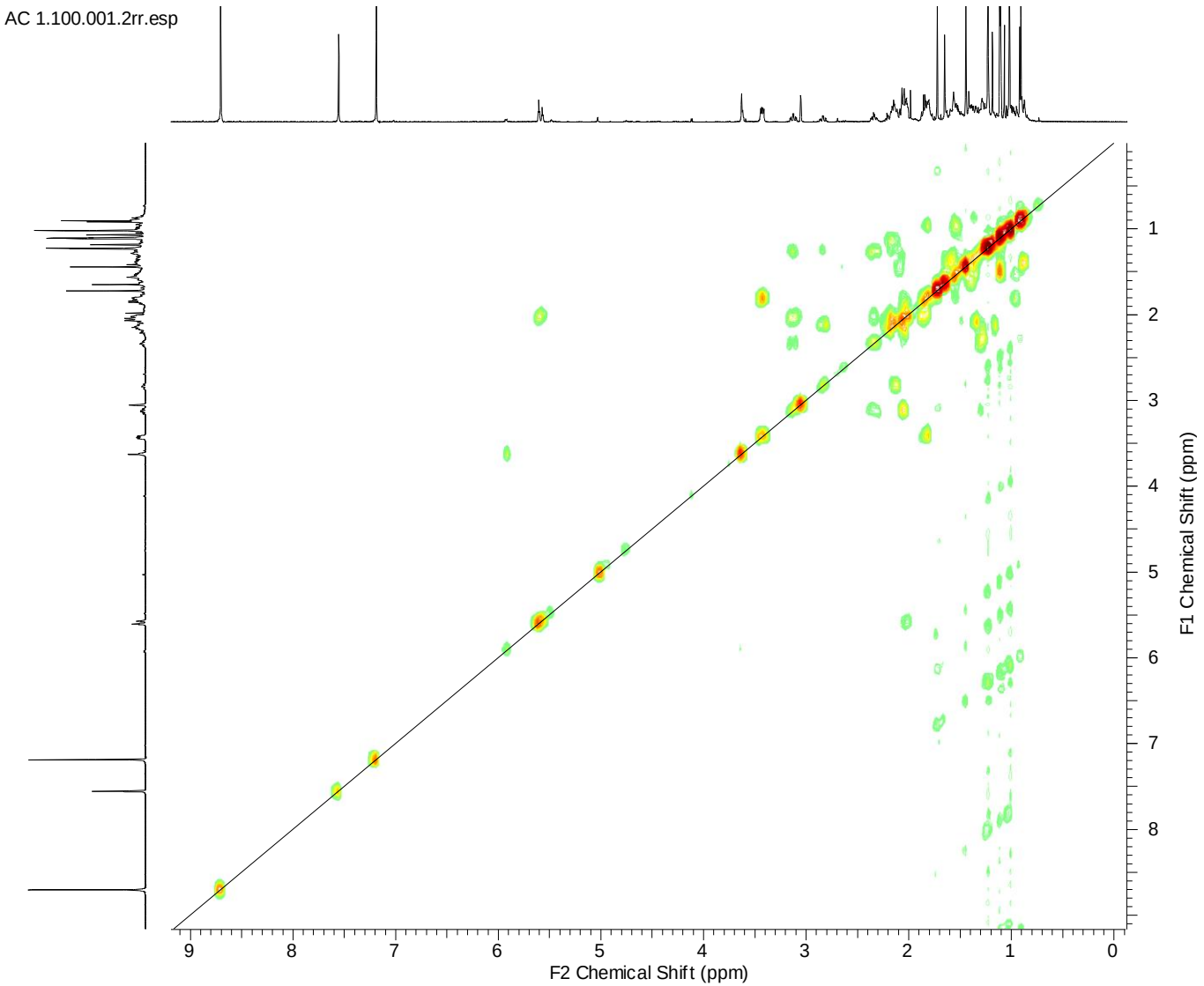


Figure S17. ^{1}H-^{1}H spectrum of compounds **5** and **6**.

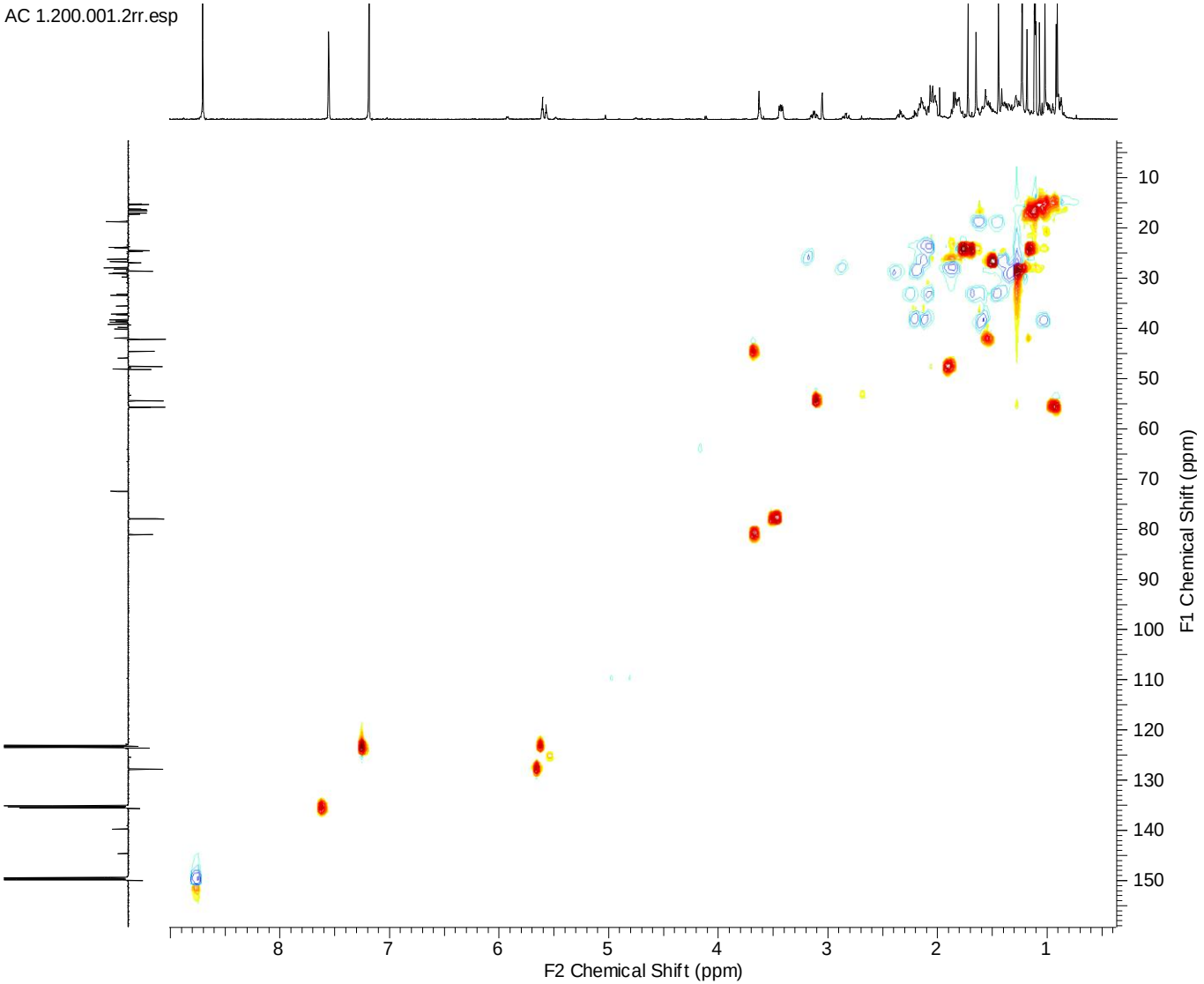


Figure S18. HHSQC spectrum of compounds **5** and **6**.

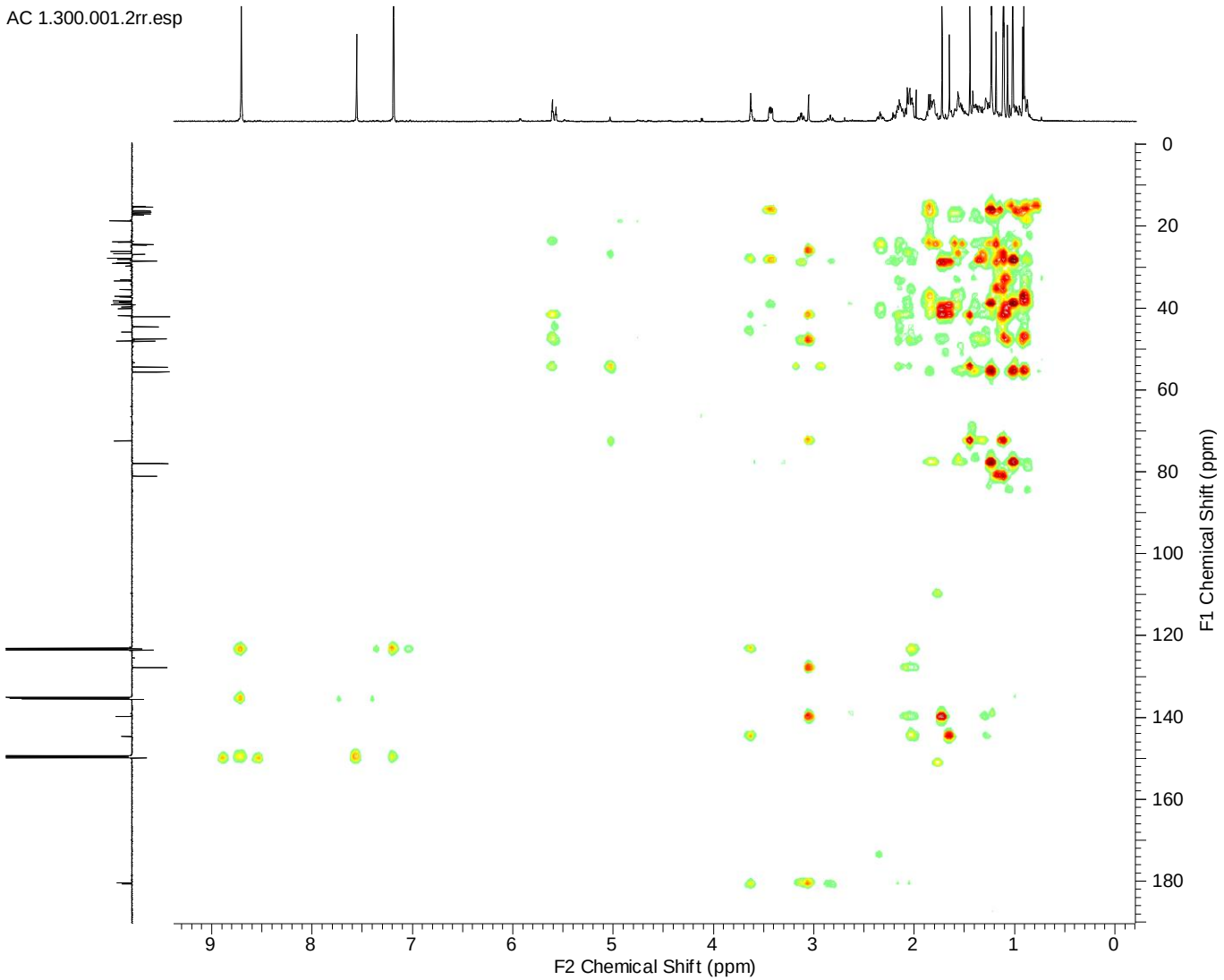


Figure S19. HMBC spectrum of compounds **5** and **6**.

Compounds 7 and 8

Table S7. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **7**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	7				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_{C**}
4	39.8	-	H-3		40.7
8	40.2	-			40.9
10	39.6	-	3H-25		39.5
13	144.6	-	H-18	3H-27; H-19	144.9
14	41.9	-	3H-27	H-12	42.8
17	45.8	-	2H-16; H-18		46.8
20	35.1	-		H-18; 3H-29	36.2
28	180.7	-		H-18; 3H27	182.5
CH					
2	68.5	4.08 (*m*)	H-3; 2H-1		69.6
3	83.7	3.37 (*dd*, 9.4, 2.4)		2H-1; H-5	84.7
5	55.8	1.05 (*m*)		3H-25	57.0
9	48.0	1.94 (*m*)		H-12; 3H-25	49.4
12	123.1	5.54 (*m*)		H-18	124.9
18	54.4	3.03 (*brs*)		H-12; 3H-29	54.3
19	81.2	3.59 (*brs*)	H-18; 3H-29		82.6
CH_2					
1	47.3	2.2 (*m*);1.48 (*m*)		H-3	48.1
6	18.7	1.42 (*m*)			19.8
7	33.4	1.64 (m)/1.39 (*m*)			34.0
11	24.1	2.10 (*m*)			25.0
15	28.9	1.57 (*m*)	2H-16	3H-27	29.6
16	28.6	1.43 (*m*)			28.7
21	29.0	1.08 (*m*)		H-18	29.6
22	33.4	1.58 (*m*)			34.2
CH_3					
23	28.6	1.18 (*s*)		H-3	29.4
24	17.0	1.06 (*s*)		H-3	17.5
25	17.3	1.00 (*s*)			17.1
26	17.4	0.90 (*s*)			17.9
27	24.5	1.62 (*s*)			25.2
29	28.6	1.18 (*s*)		H-18; 1H-19	28.8
30	24.6	1.10 (*s*)		H-19	25.3

*Ponou et al. 2011. ** CD_3OD.

Table S8. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **8**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	8				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_{C**}
4	39.8	-	1H-3		39.9
8	40.2	-			40.5
10	39.6	-	3H-25		38.5
13	139.7	-	H-18	3H-27; H-19	140.0
14	41.9	-	3H-27	H-12	42.2
17	48.0	-	2H-16; H-18		48.3
19	72.5	-	H-18; 3H-29		72.7
20	41.9	-		H-18; 3H-29	42.4
28	180.4	-		H-18; 3H27	180.6
CH					
2	68.5	4.08 (*m*)	H-3; 2H-1		68.6
3	83.7	3.37 (*dd*, 9.4, 2.4)		2H-1; H-5	83.9
5	55.8	1.05 (*m*)		3H-25	56.0
9	48.0	1.94 (*m*)		H-12; 3H-25	47.9
12	127.7	5.54 (*m*)		H-18	128.0
18	54.4	3.03 (*brs*)		H-12; 3H-29	54.6
20	41.9	-		H-18; 3H-29	42.4
CH_2					
1	47.3	2.2 (*m*)/1.48 (*m*)		H-3	48.0
6	18.7	1.42 (*m*)			19.0
7	33.4	1.64 (*m*)/1.39 (*m*)			33.5
11	24.1	2.10 (*m*)			24.1
15	28.9	1.57 (*m*)	2H-16	3H-27	29.3
16	26.2	1.43 (*m*)			26.4
21	26.7	1.08 (*m*)		H-18	27.1
22	38.5	1.58 (*m*)			38.5
CH_3					
23	28.6	1.18 (*s*)		H-3	29.3
24	17.4	1.06 (*s*)		H-3	17.7
25	17.3	1.00 (*s*)			16.9
26	17.4	0.90 (*s*)			17.2
27	24.5	1.62 (*s*)			24.7
29	26.7	1.18 (*s*)		H-18; H-19	27.1
30	16.5	1.10 (*d*, 5.8)		H-19	16.9

*Taniguchi et al. 2002. **Pyridine-d_5.

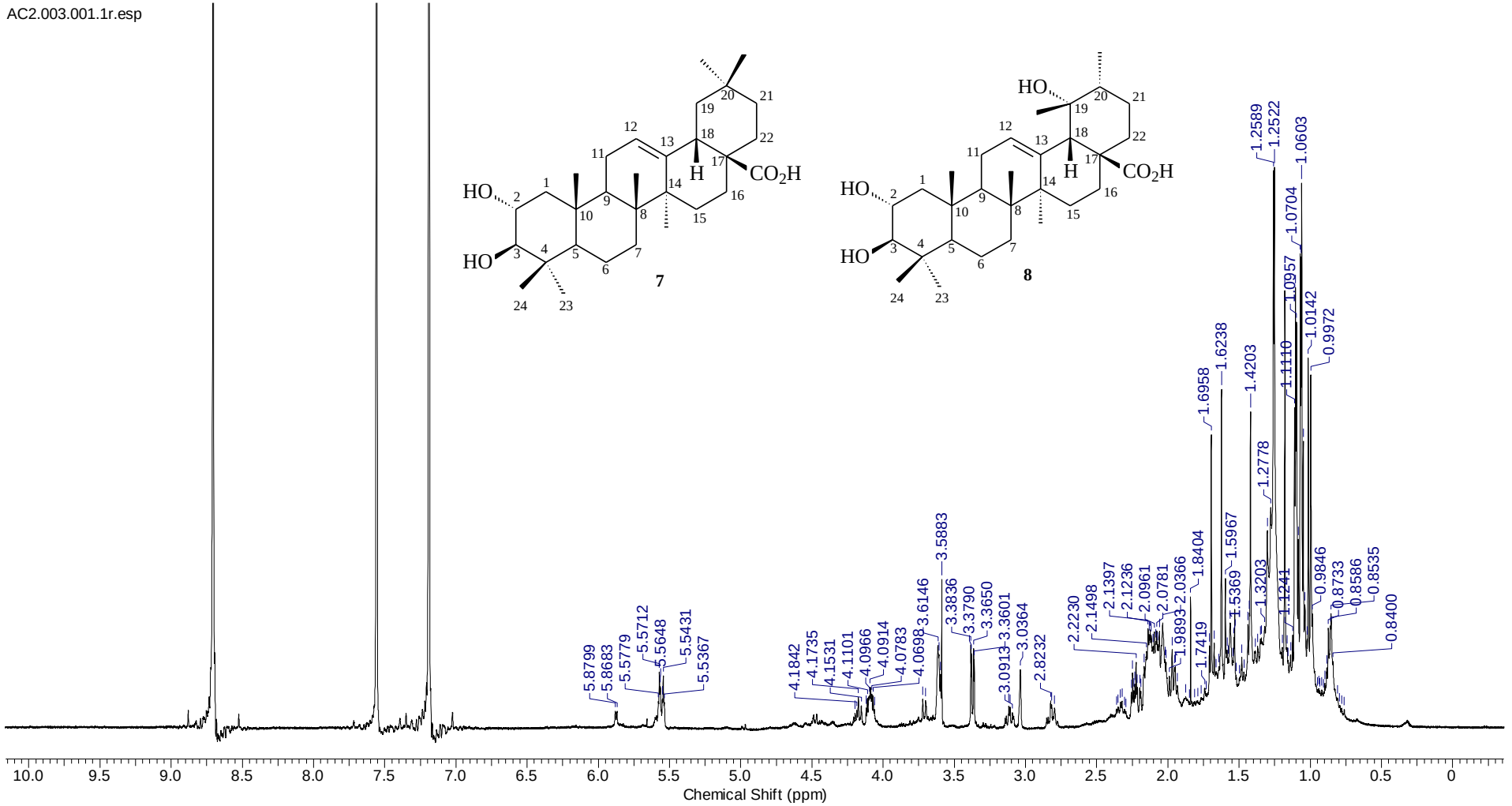


Figure S20. ^{1}H NMR spectrum (500 MHz, Pyridine-d5) of compounds **7** and **8**.

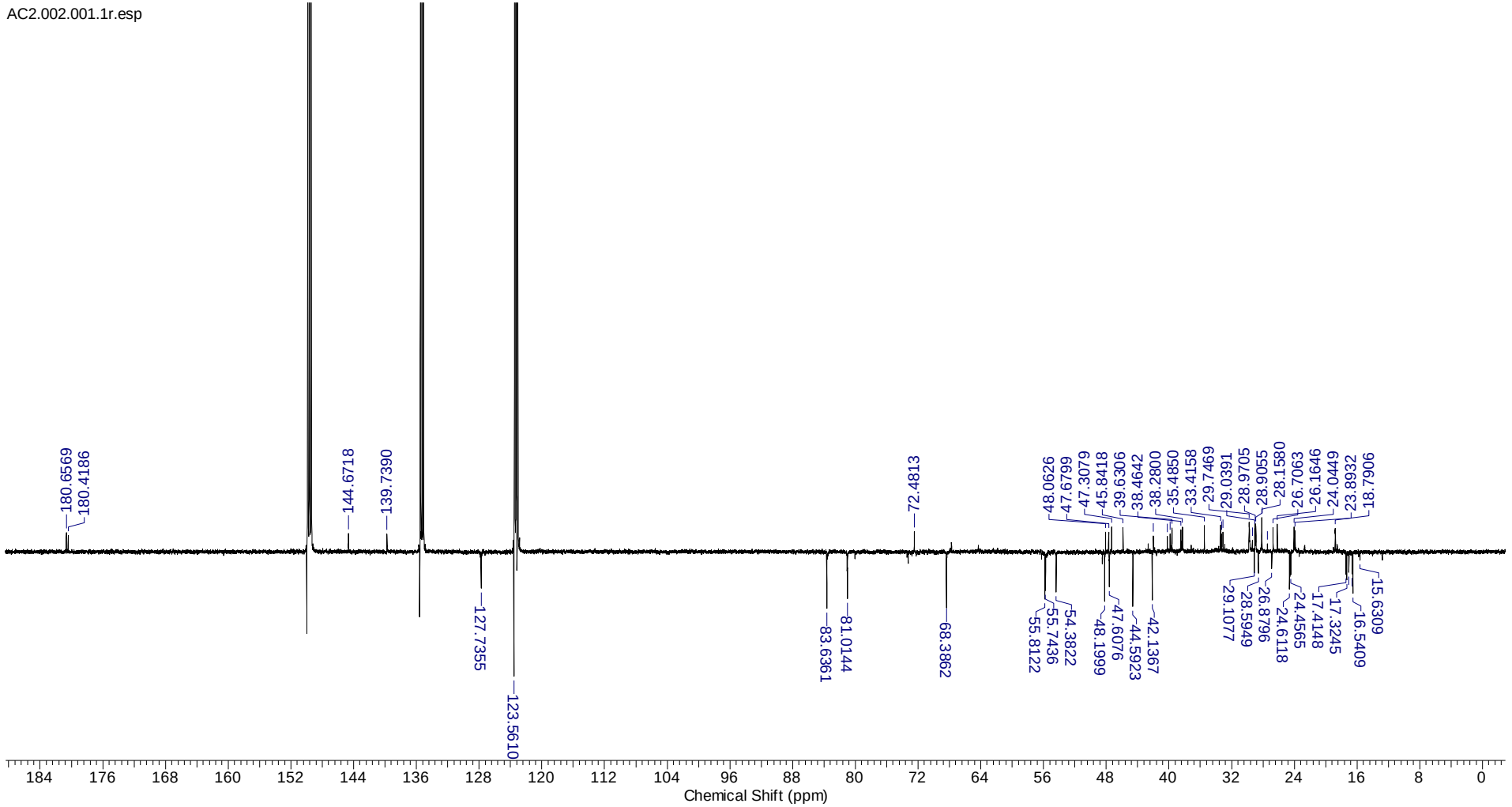


Figure S21. DEPTQ NMR spectrum (125 MHz, Pyridine-d_5) of compounds **7** and **8**.

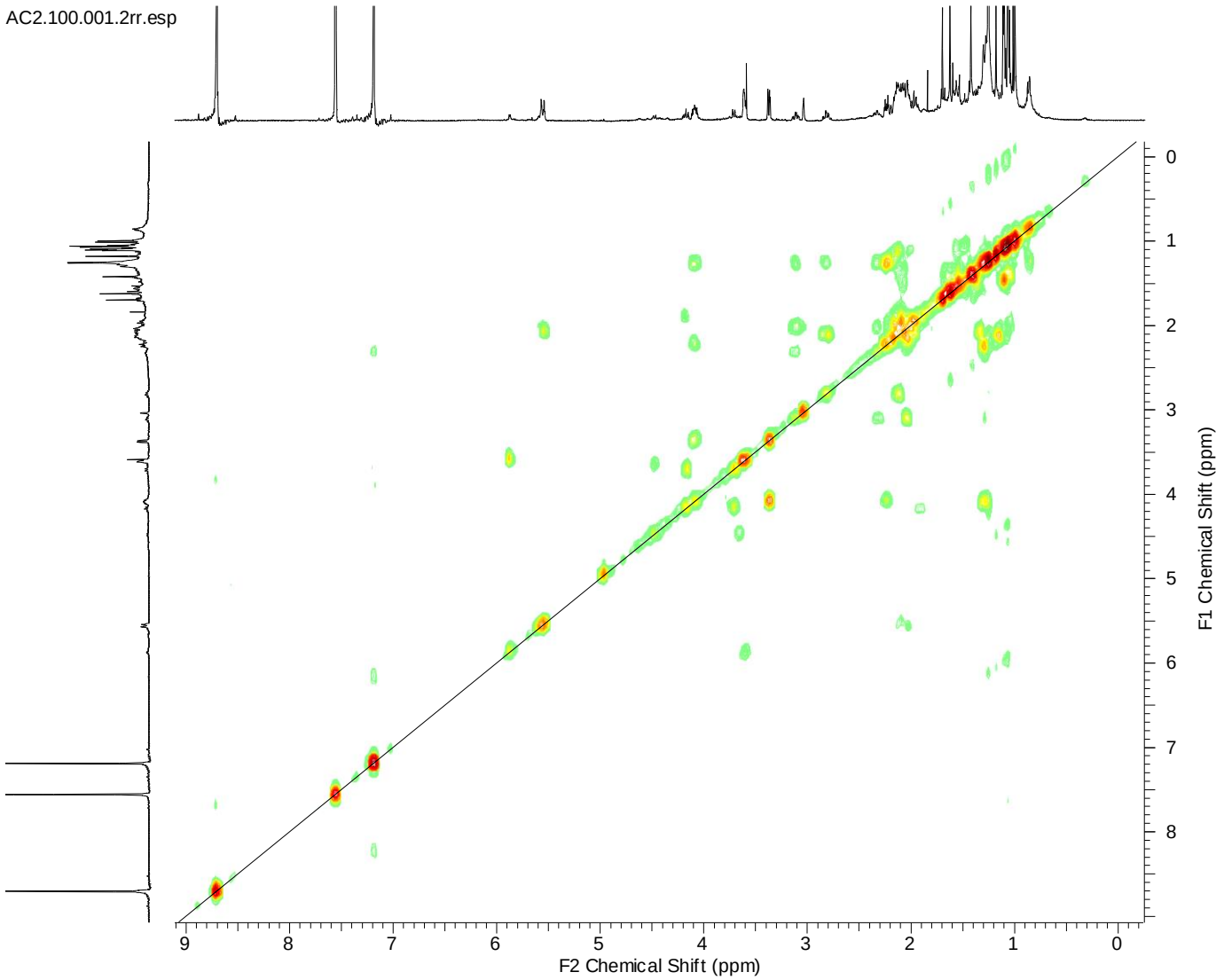


Figure S22. ^{1}H-^{1}H-COSY spectrum of compounds **7** and **8**.

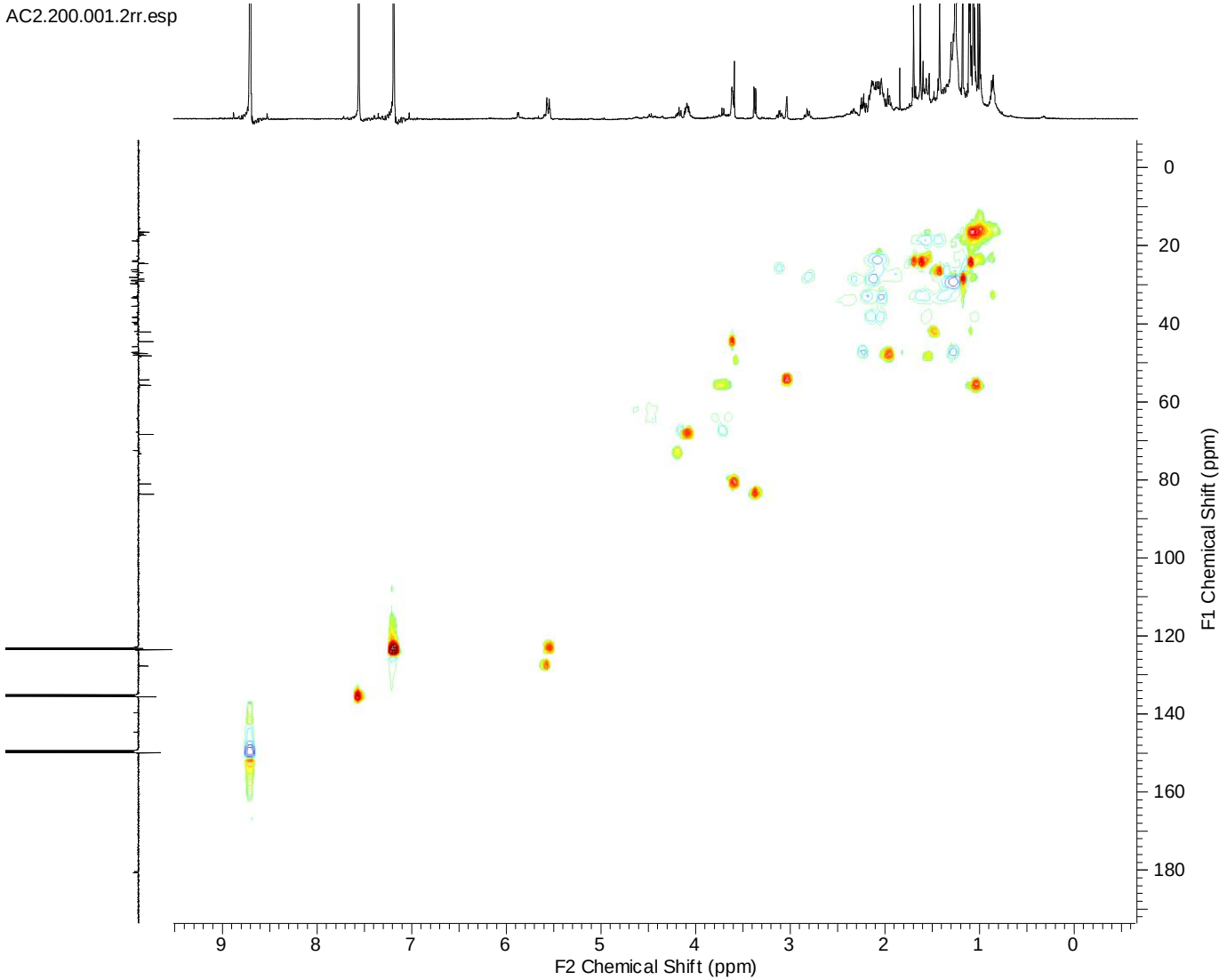


Figure S23. HSQC spectrum of compounds **7** and **8**.

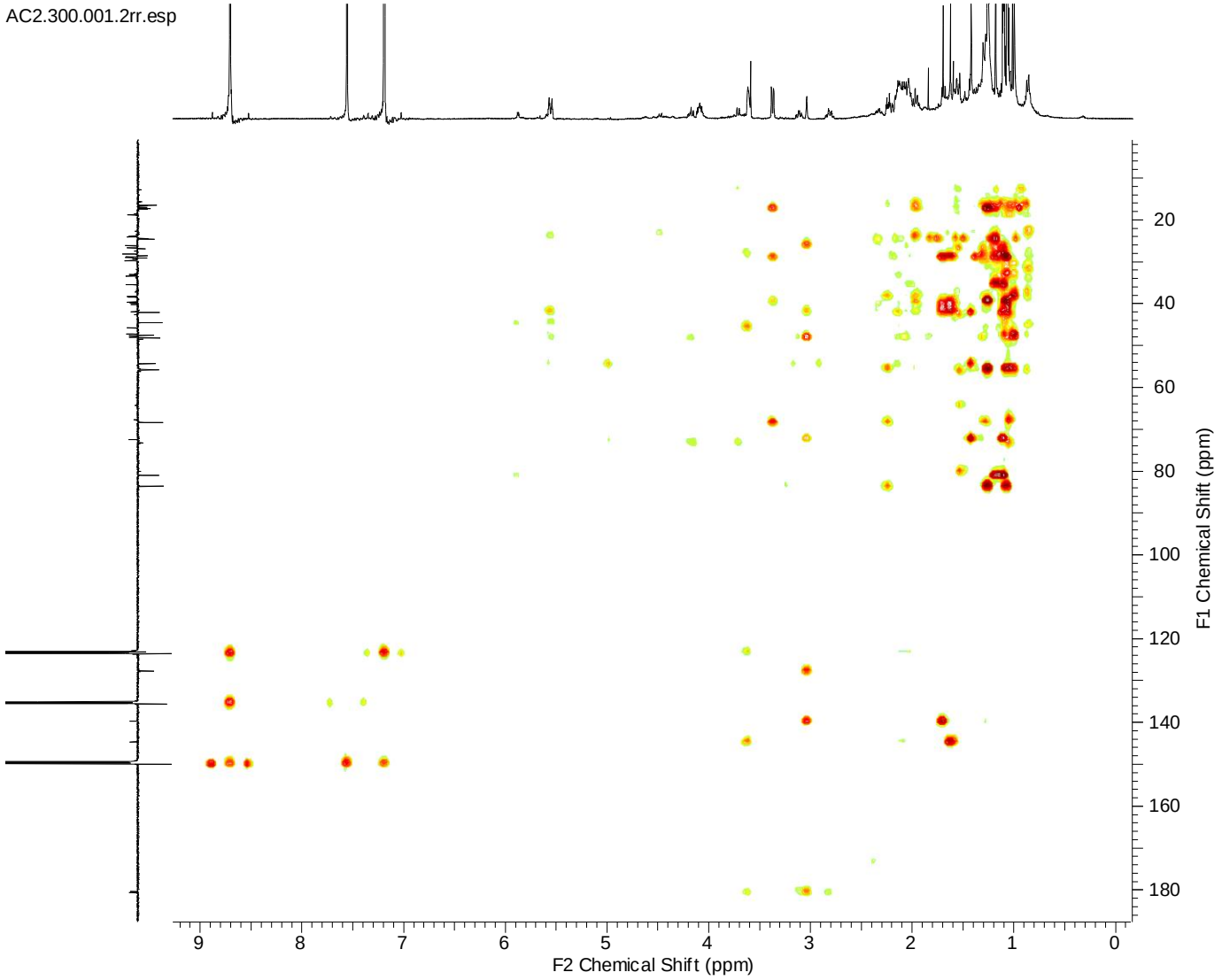


Figure S24. HMBC spectrum of compounds **7** and **8**.

Compound 9

Table S9. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **9**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	9				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
4	39.1	-	3H-23; 3H-24		38.9
8	39.5	-	3H-26; H-9	3H-27	39.8
10	37.2	-	3H-25	2H-2	37.1
13	144.6	-	H-18	3H-27; 2H-11	143.4
14	41.9	-	3H-27	3H-26	41.6
17	46.4	-	H-18		46.6
20	30.7	-	3H-29; 3H-30		30.6
28	180.1	-			181.0
CH					
3	78.1	3.45 (*m*)	2H-2	3H-23;3H24	78.7
5	55.6	0.85 (*m*)		3H-23; 3H-25	55.2
9	48.1	1.65 (*m*)		3H-25; 3H-26	47.6
12	122.9	5.60 (*m*)	2H-11	H-18	122.1
18	41.9	3.30 (*m*)			41.3
CH_2					
1	38.7	1.61 (*m*); 1.02 (*m*)		3H-25	38.5
2	27.8	1.95 (*m*); 1.05 (*m*)			27.4
6	18.5	1.65 (*m*); 1.40 (*m*)			18.3
7	33.0	1.65 (*m*); 1.35 (*m*)			32.6
11	23.0	1.95 (*m*)			23.1
15	28.1	2.19 (*m*); 1.99 (*m*)		3H-27	27.7
16	23.4	2.20 (*m*); 2.00 (*m*)			23.4
19	46.2	1.85 (*m*), 1.30 (*m*)		3H-29; 3H-30	45.8
21	34.0	1.45 (*m*), 1.25 (*m*)		3H-29; 3H-30	33.8
22	33.0	2.00 (*m*), 1.78 (*m*)			32.3
CH_3					
23	28.8	1.12 (*s*)		3H-24; H-3	28.1
24	16.2	1.03 (*s*)			15.6
25	15.1	0.87 (*s*)			15.3
26	17.3	1.01 (*s*)		H-9	16.8

27	25.9	1.18 (*s*)		26.0
29	33.0	.094 (*s*)		33.1
30	23.6	0.99 (*s*)	3H-29	23.6
Me-O-28		3.58 (*s*)		-

*Mahato & Kundo, 1994.

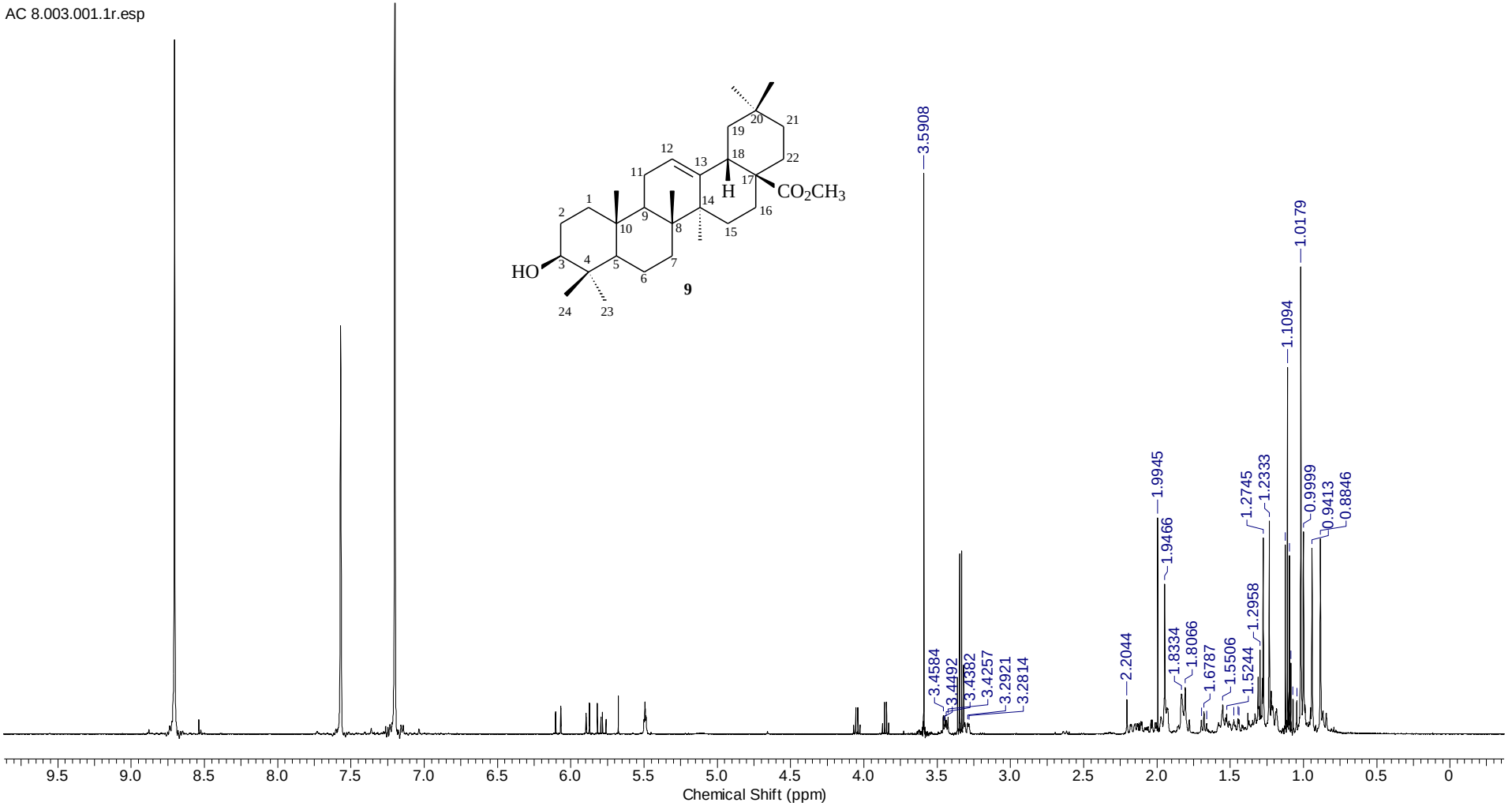


Figure S25. ^{1}H NMR spectrum (500 MHz, Pyridine-d_5) of compound **9**.

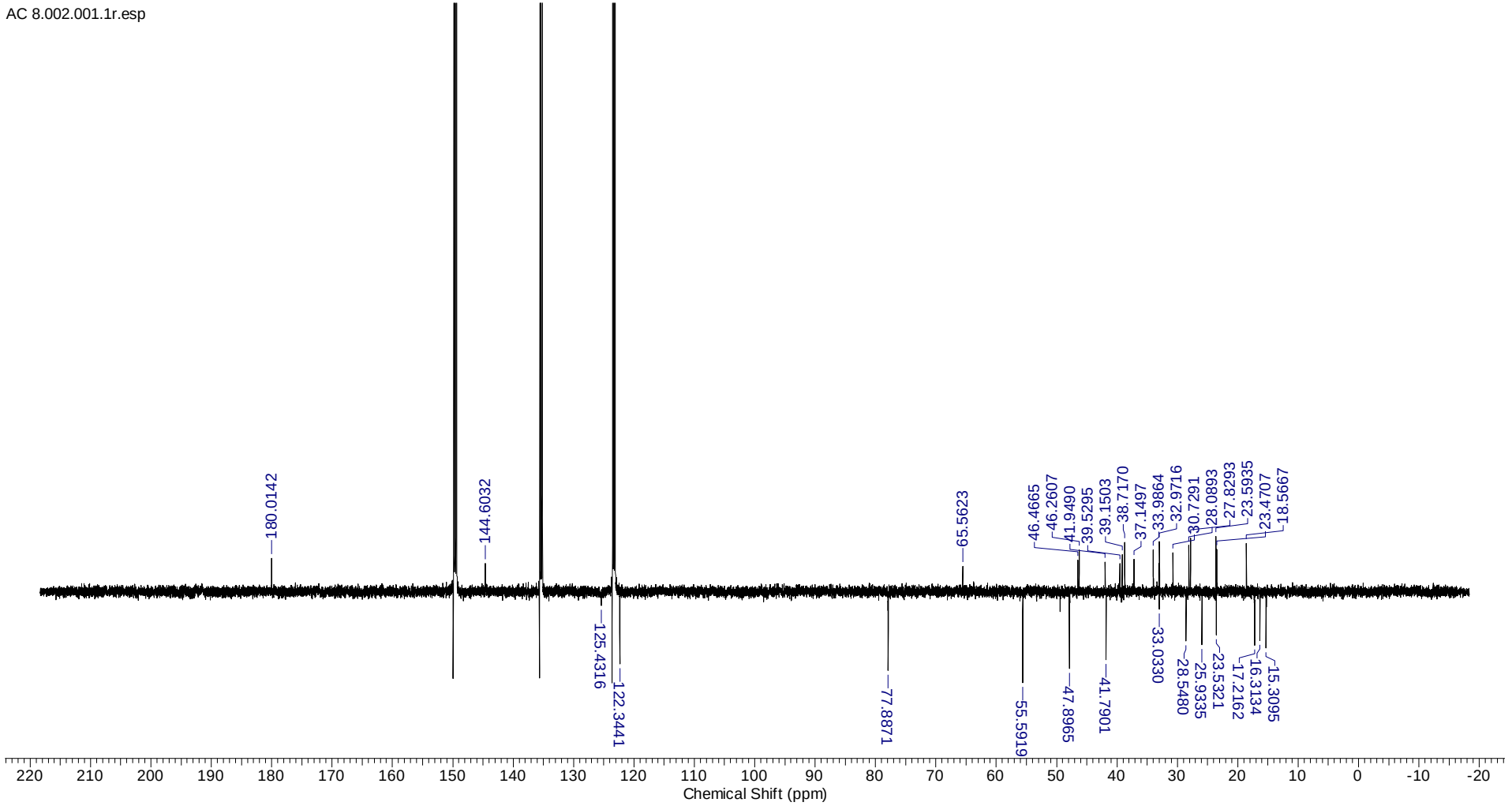


Figure S26. ^{13}C NMR spectrum (125 MHz, Pyridine-d_5) of compound **9**.

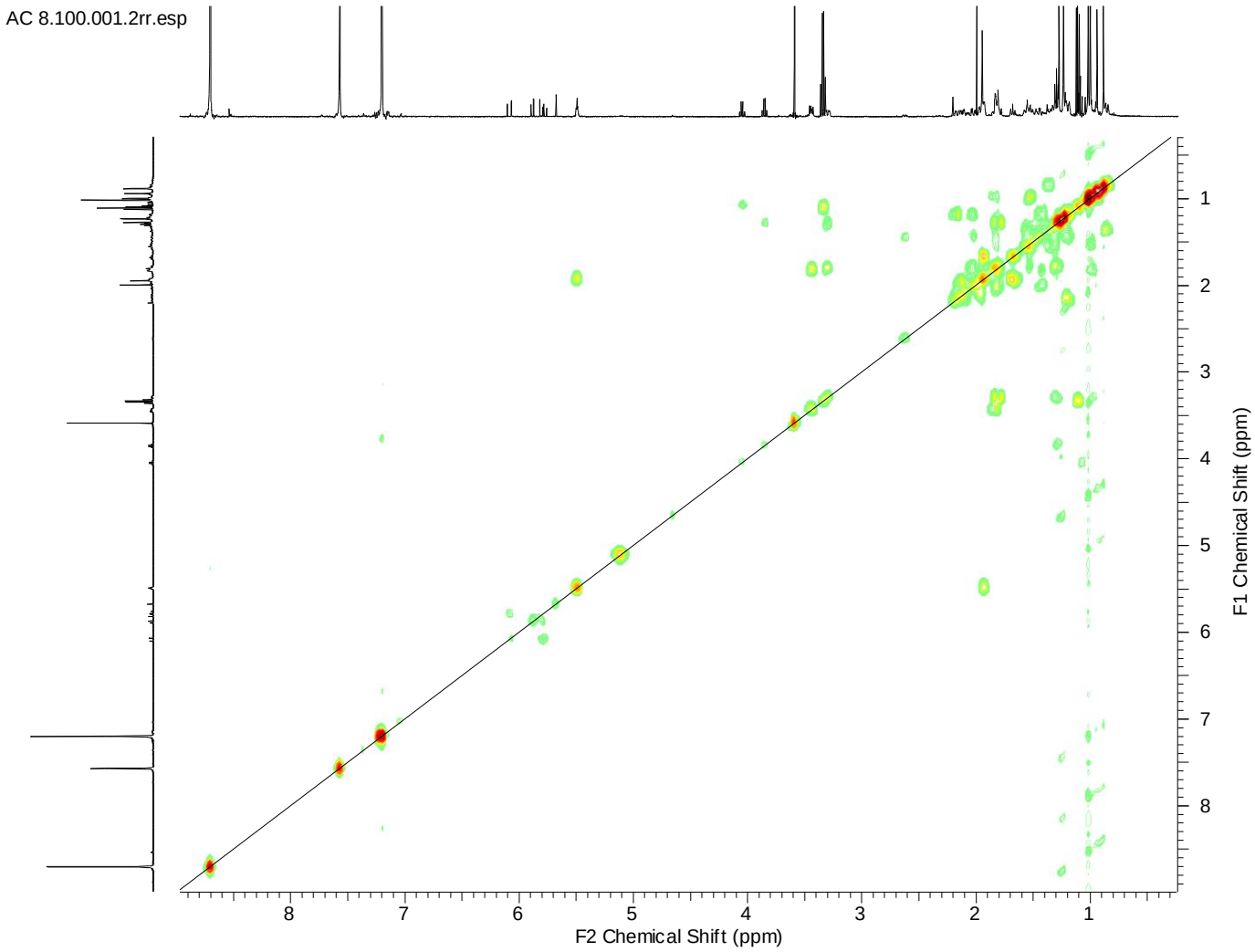


Figure S27. ^{1}H-^{1}H-COSY spectrum of compound **9**.

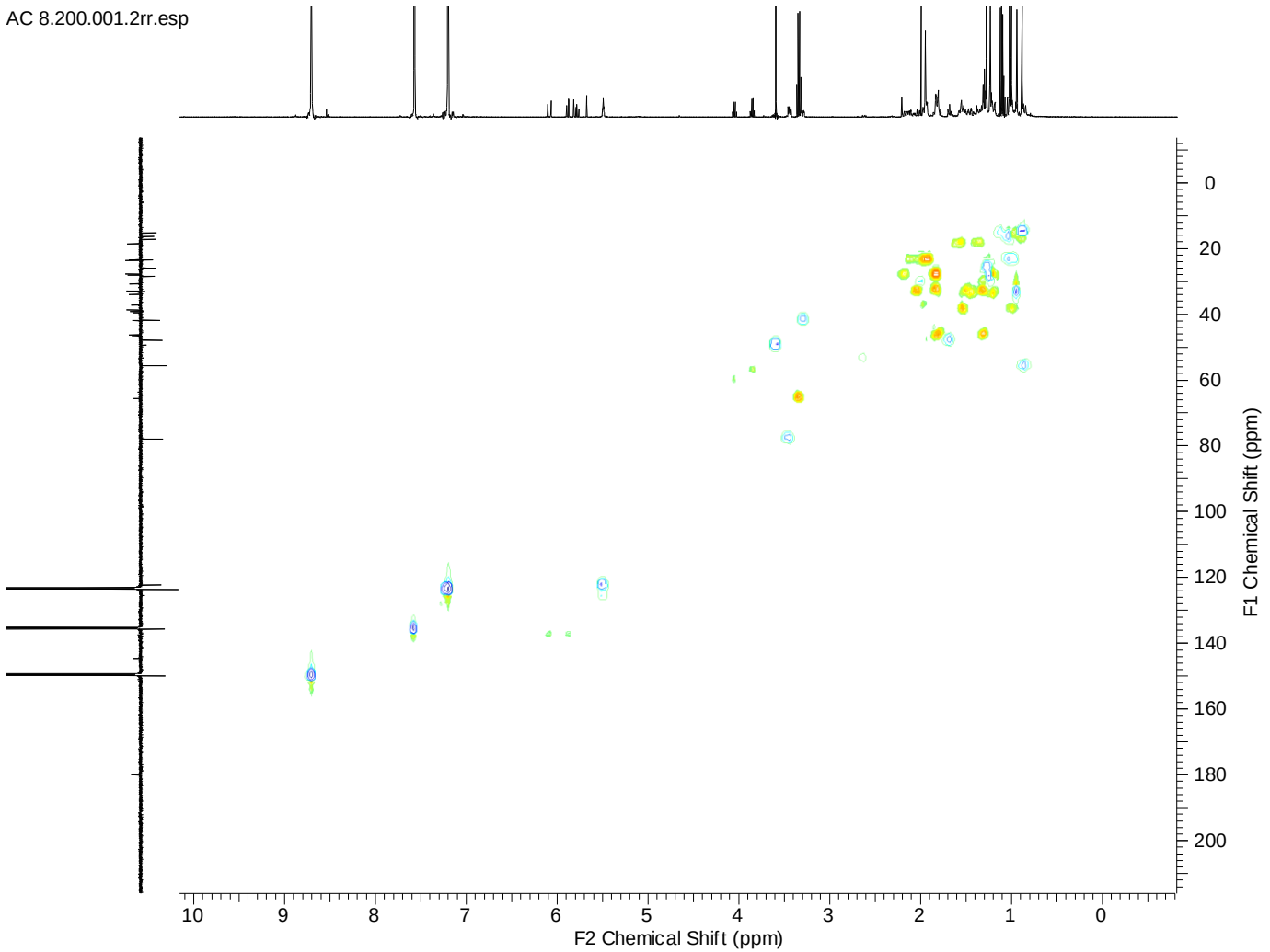


Figure S28. ^{1}H-^{1}H-COSY spectrum of compound **9**.

Compound 10

Table S10. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **10**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	10				**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
2	136.7	-		H-14b	138.2
3	145.2		H-14b	H-5	144.8
7	129.7	-		H-5; H-9	130.8
8	120.8	-		H-6; H-12	122.1
13	141.7	-		H-9; H-11	135.8
16	113.5	-	H-17		114.8
22	171.8	-		H-17	174.7
CH					
5	134.57	8.22 (*d*, 5.6)	H-6		136.7
6	113.52	8.10 (*d*, 5.6)	H-5		114.9
9	121.54	8.11 (*d,* 8.1)			
10	119.80	7.31 (*t*, 8.1)	H-10	H-11	122.7
11	128.90	7.62 (*t*, 8.1)		H-12	121.2
12	111.89	7.70(*d*, 8.1)		H-9	130.3
15	34.02	3.57 (*m*)		H-10	113.4
17	150.70	7.50 (*s*)		H-17; H-21	36.0
19	133.75	5.87 (*dd*, 17.1, 9.5)		H-21	151.2
20	44.67	2.61 (*m*)	2H-18; H-20		134.6
21	95.79	5.67 (*d*, 6.8)		2H-18	46.4
CH_2	95.8	2.61 (*m*)	H-20	H-17; H-1'A	97.6
14	34.5	3.70 (*m*)			36.6
		3.23 (*m*)			
18	117.6	4.95-4.80 (*m*)		H-20	118.8
Glucose					
1'	98.9	4.76 (*d*, 8.4)	H-2'A	H-21	100.4
2'	73.2	3.21 (*dd*)			74.6
3'	76.5	3.45 (*m*)			78.4
4'	70.2	3.30 (*m*)			71.7
5'	77.1	3.35 (*m*)			78.1
6'	61.5	3.94 (*dd*, 12.1, 1.9)			63.2
		3.70 (*m*)			

*Lin et al. 2011.

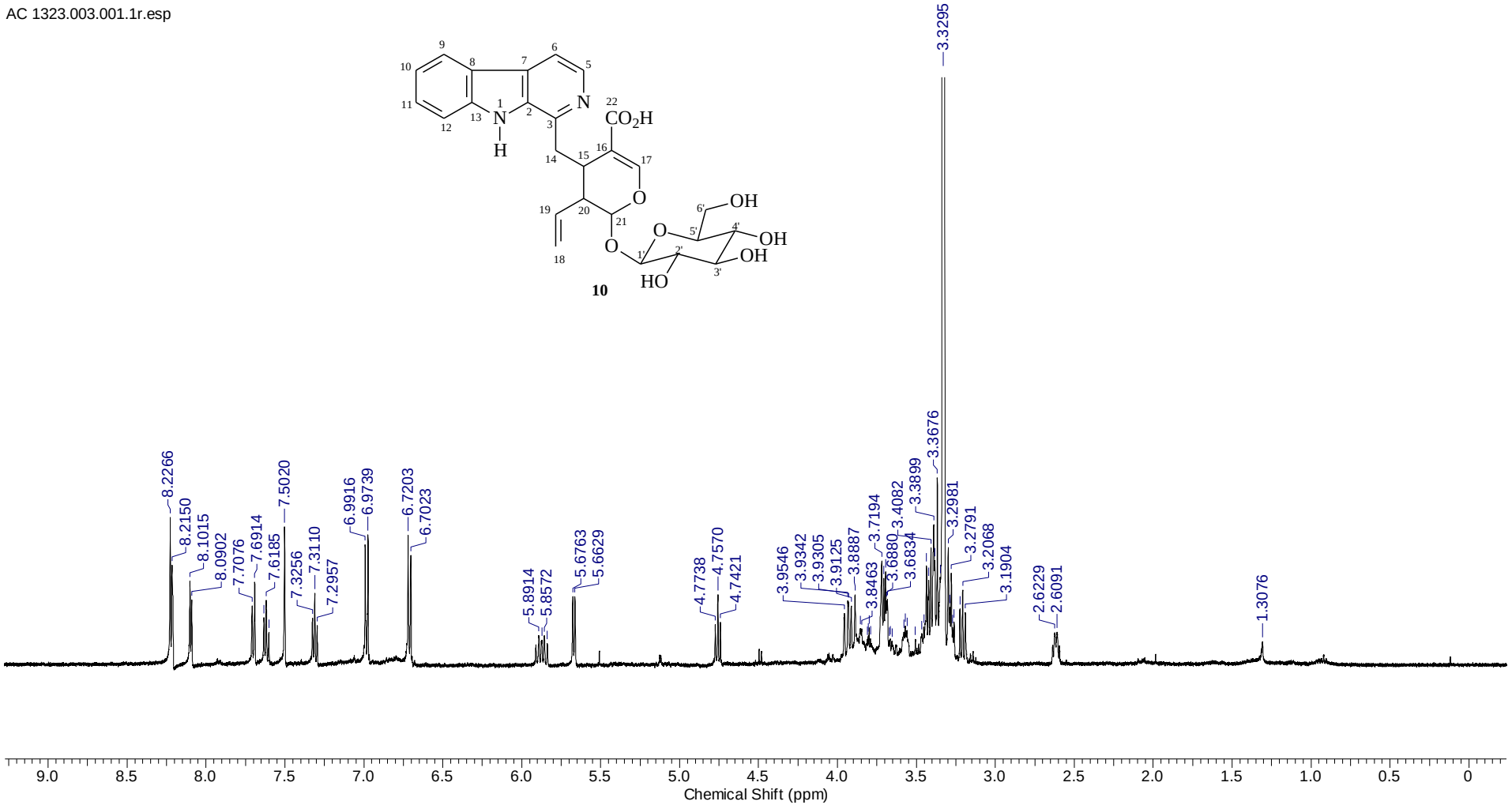


Figure S29. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **10**.

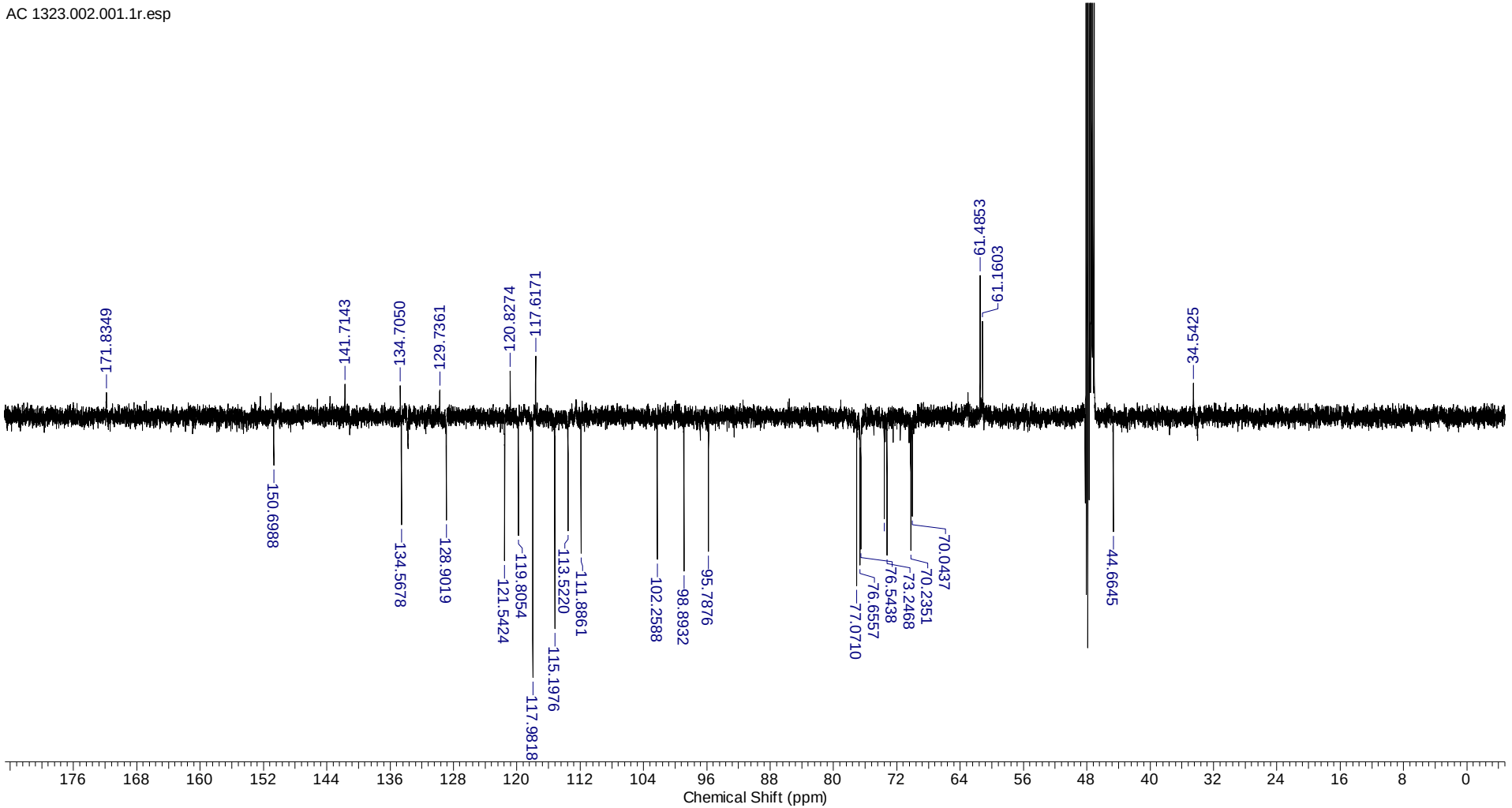


Figure S30. ^{13}C NMR spectrum (125 MHz, CD_3OD) of compound **10**.

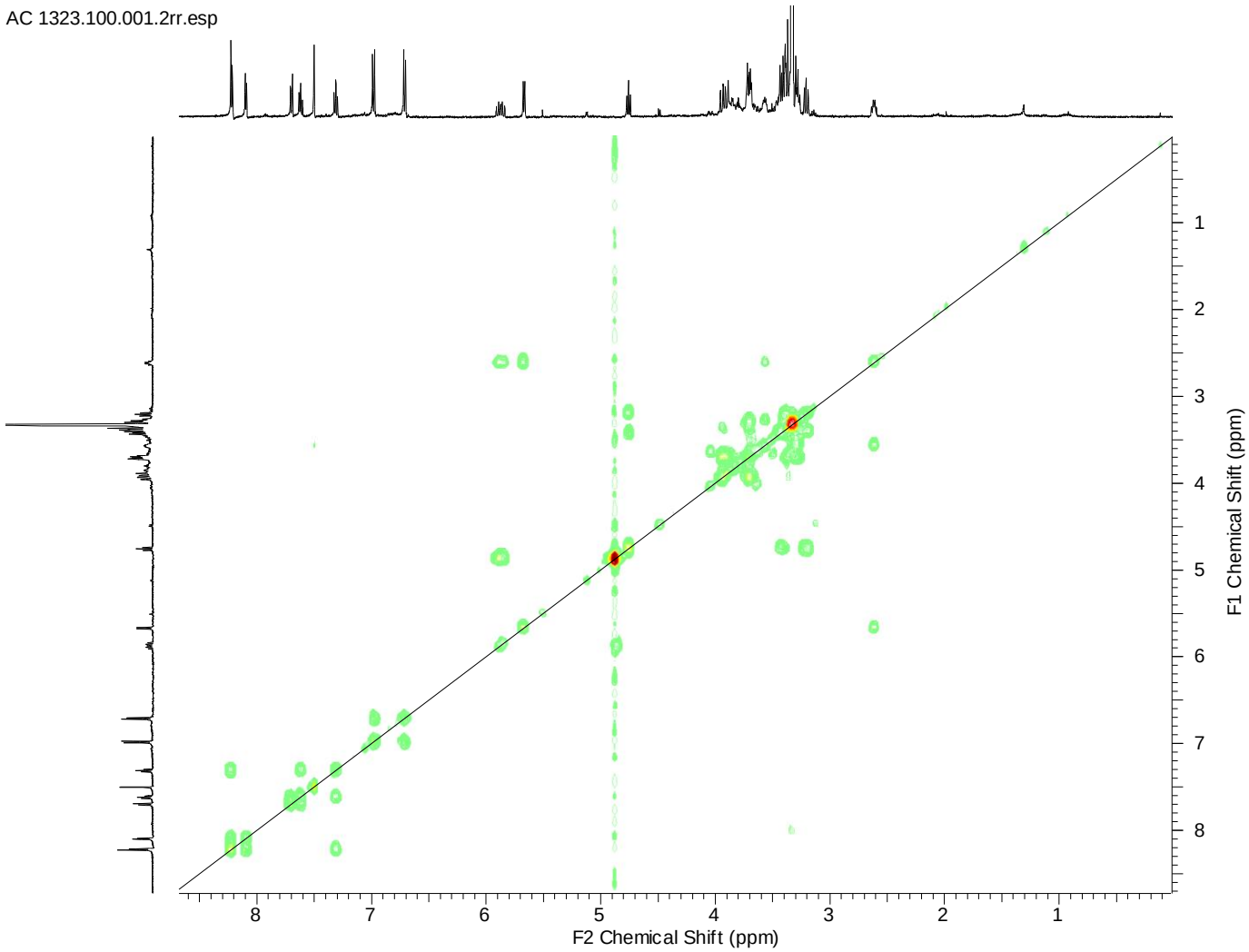


Figure S31. ^{1}H-^{1}H-COSY spectrum of compound **10**.

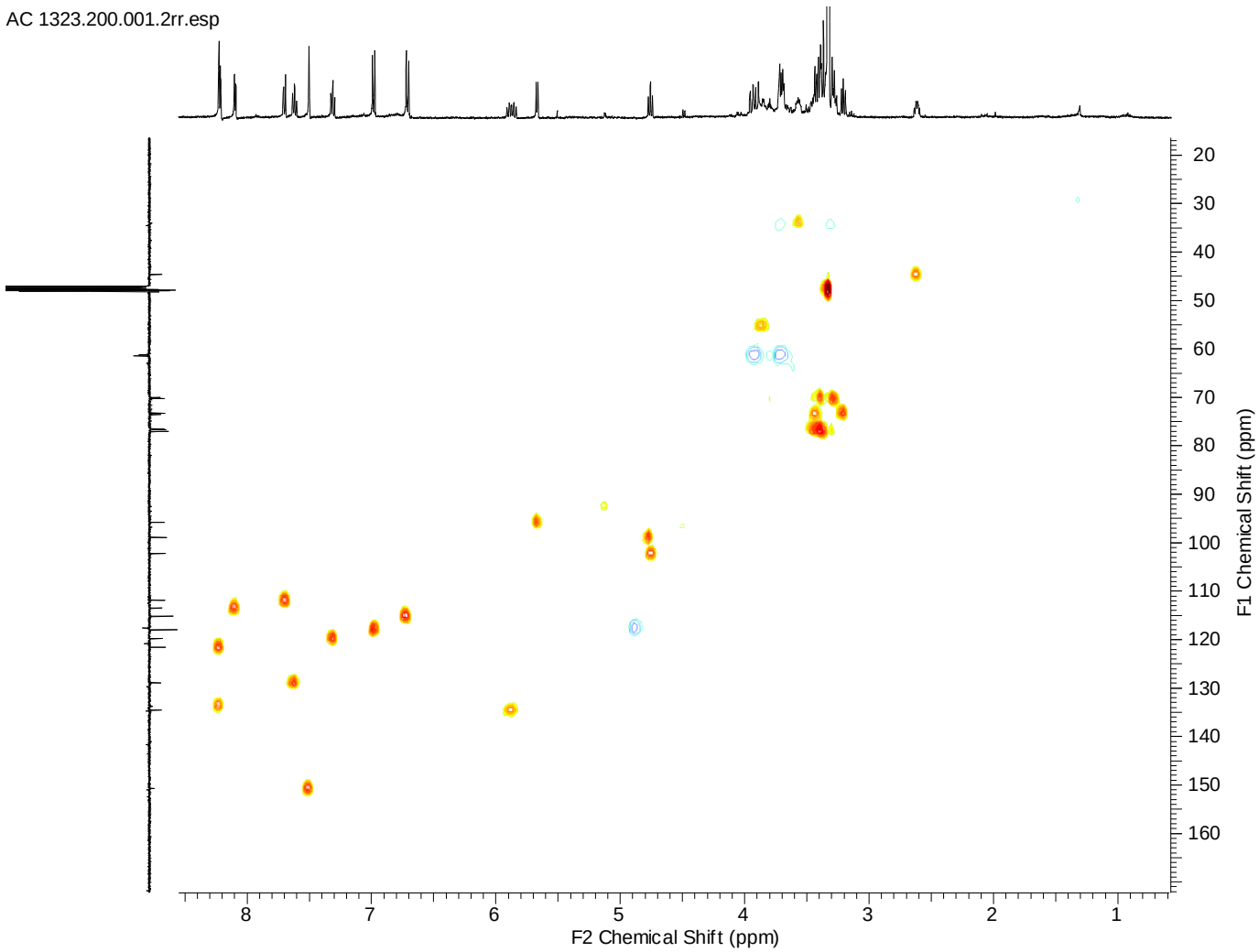


Figure S32. HSQC spectrum of compound **10**.

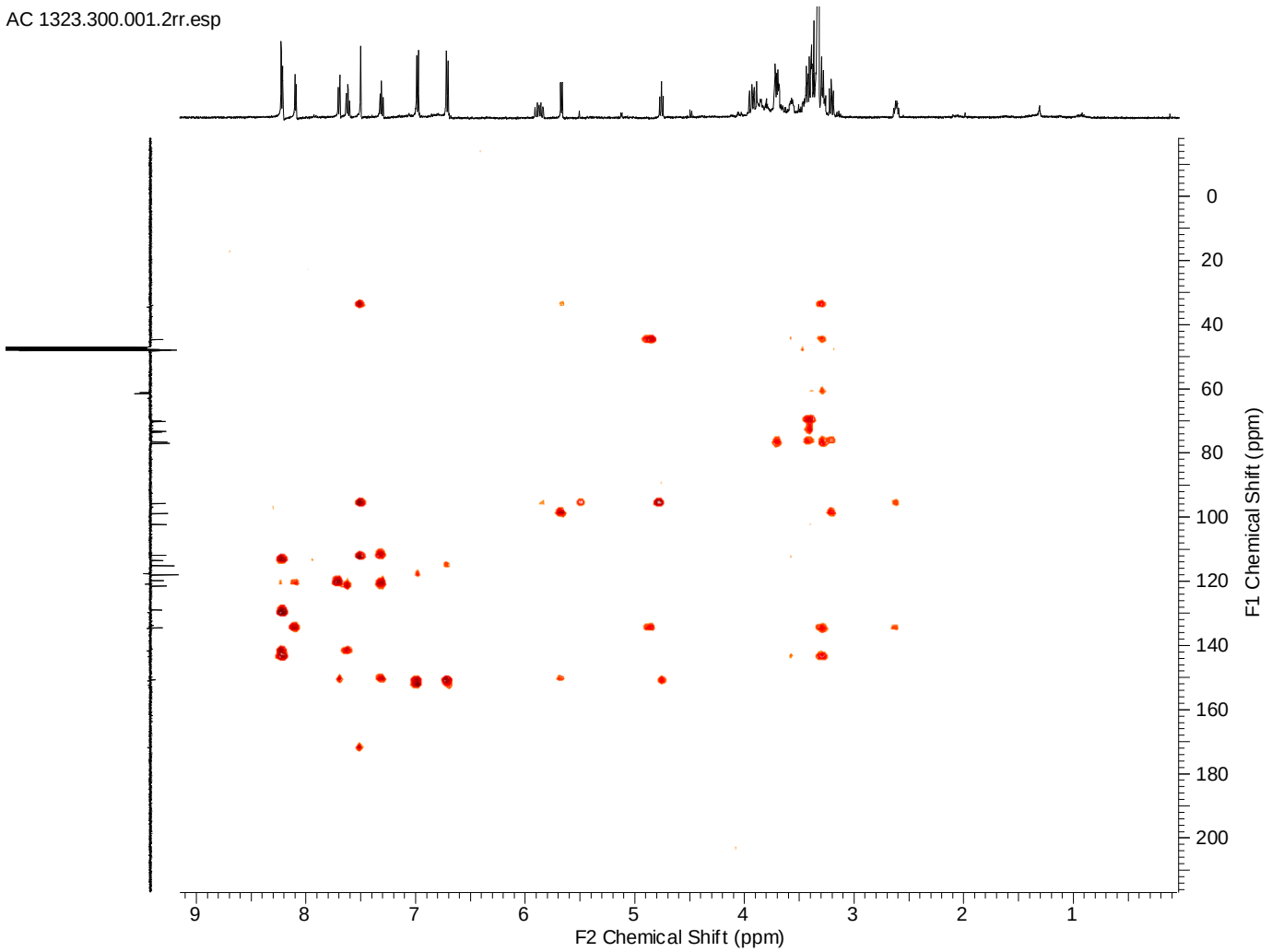


Figure S33. HMBC spectrum of compound **10**.

Compound 11

Table S11. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **11**, including results of HSQC and HMBC 2D experiments. Chemical shifts δ in ppm and coupling constants in Hz

	11				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
2	129.6	--			130.4
7	105.9	--			105.3
8	126.1	--		H-10	127.5
13	136.8	--		H-9; H-11	138.2
16	111.0		H-17		109.3
22	175.0	--		H-17	175.4
CH					
3	50.9	4.47 (*d*, 11.4)			52.5
9	117.7	7.47 (*d*, 7.8)		H-11	119.1
10	119.1	7.05 (*t*, 7.8)		H-12	120.6
11	121.9	7.15 (*dd*, 7.8, 7.3)		H-9	123.4
12	110.5	7.33 (*d*, 7.3)		H-10	112.3
15	32.6	3.01 (*m*)			33.8
17	150.5	7.59 (*s*)			151.2
19	134.8	5.87 (*m*)			136.2
20	44.3	2.72 (*m*)		2H-18	45.6
21	95.2	5.84 (*d*, 9.3)		H-17; H-1’	96.7
CH_2					
5	41.6	3.35 (*m*)			43.0
6	18.2	3.10-2.90 (*m*)			19.6
14	33.7	2.39 (*m*)			35.1
		2.14 (*m*)			
18	118.0	5.83 (*d*, 17.4)			119.1
		5.22 (*d*, 10.7)			
Glucose					
1’	100.0	4.76 (*d*, 7.9)	H-2’	H-21	100.3
2’	73.3	3.21 (*m*)	H-3’		74.6
3’	76.6	3.42 (*m*)	H-4’		77.9
4’	70.4	3.29 (*m*)	H-3’		72.0
5’	77.3	3.35 (*m*)	H-4’		78.1
6’	61.7	3.94 (*dd*, 12.3, 2.0)		H-4’	52.9
		3.70 (*m*)			

Berger et al. 2015.

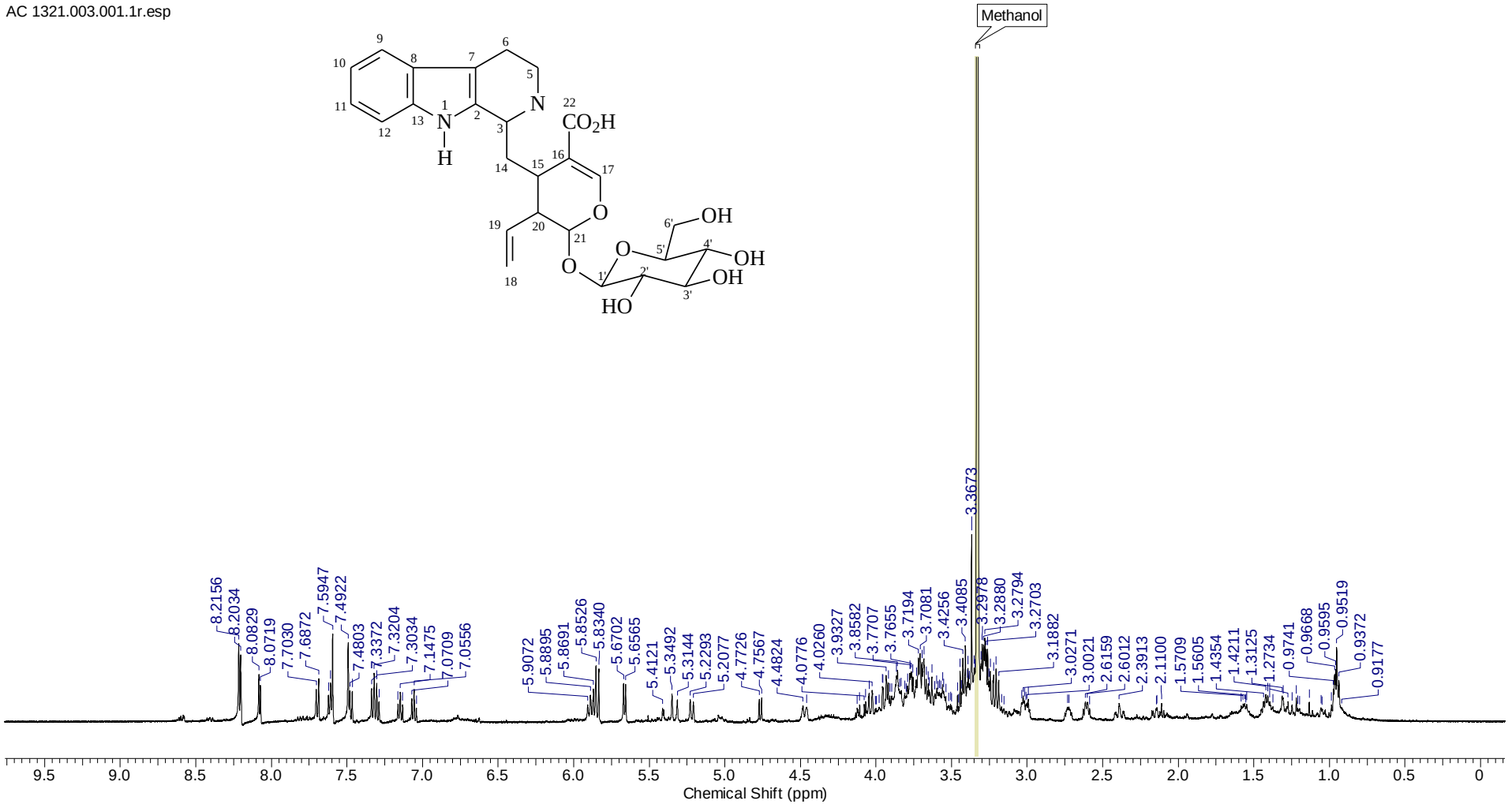


Figure S34. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **11**.

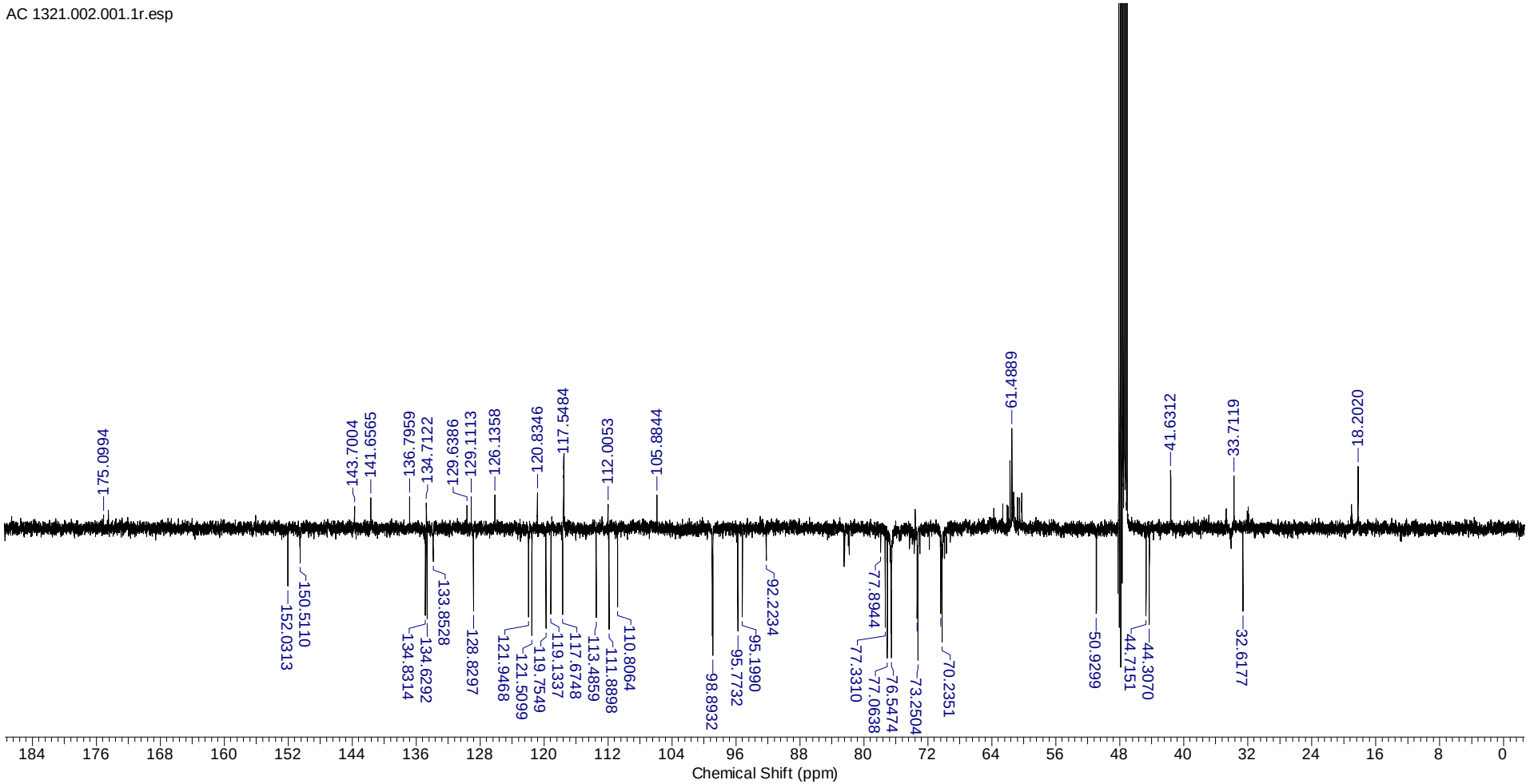


Figure S35. ^{13}C NMR spectrum (125 MHz, CD_3OD) of compound **11**.

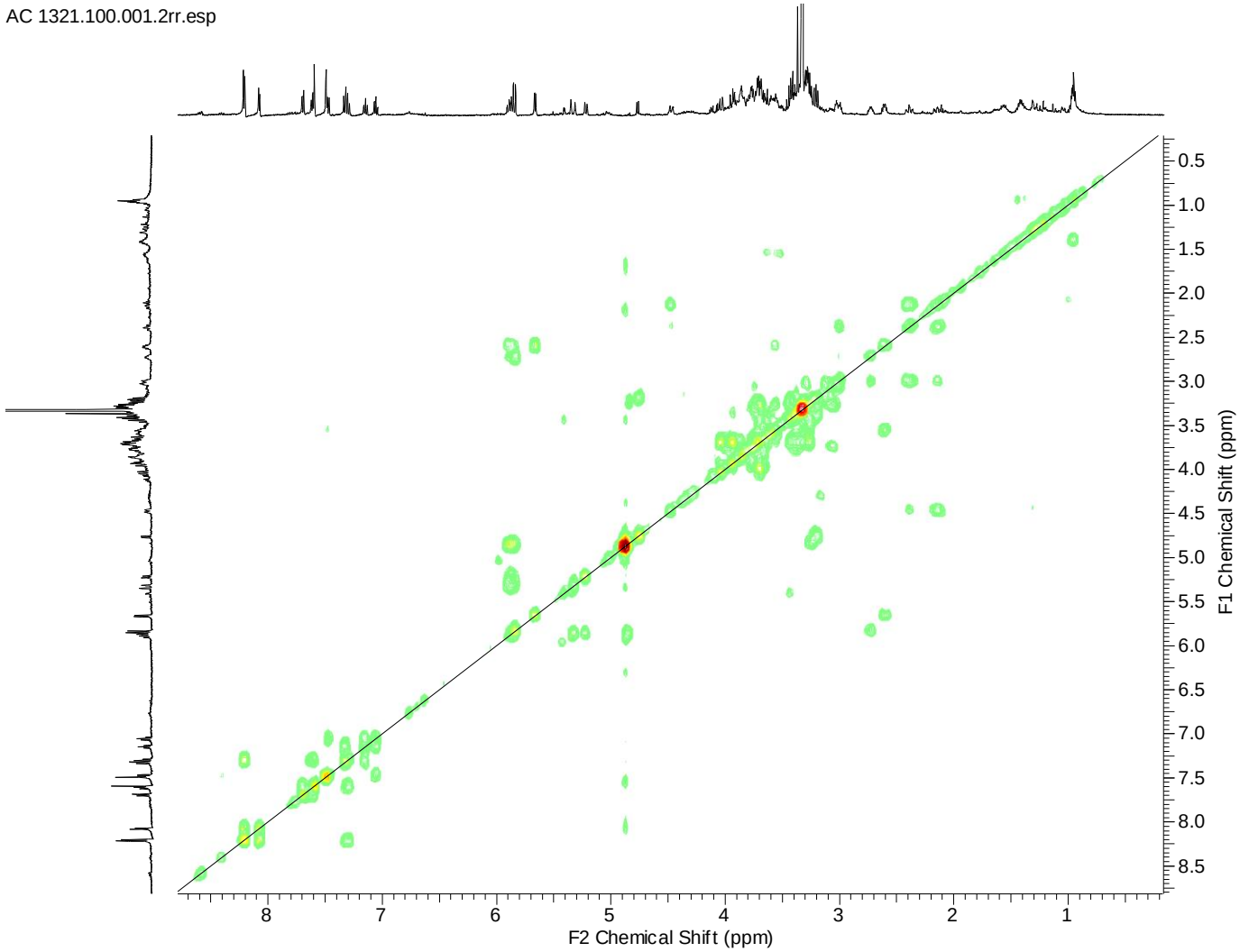


Figure S36. ^{1}H-^{1}H-COSY spectrum of compound **11**.

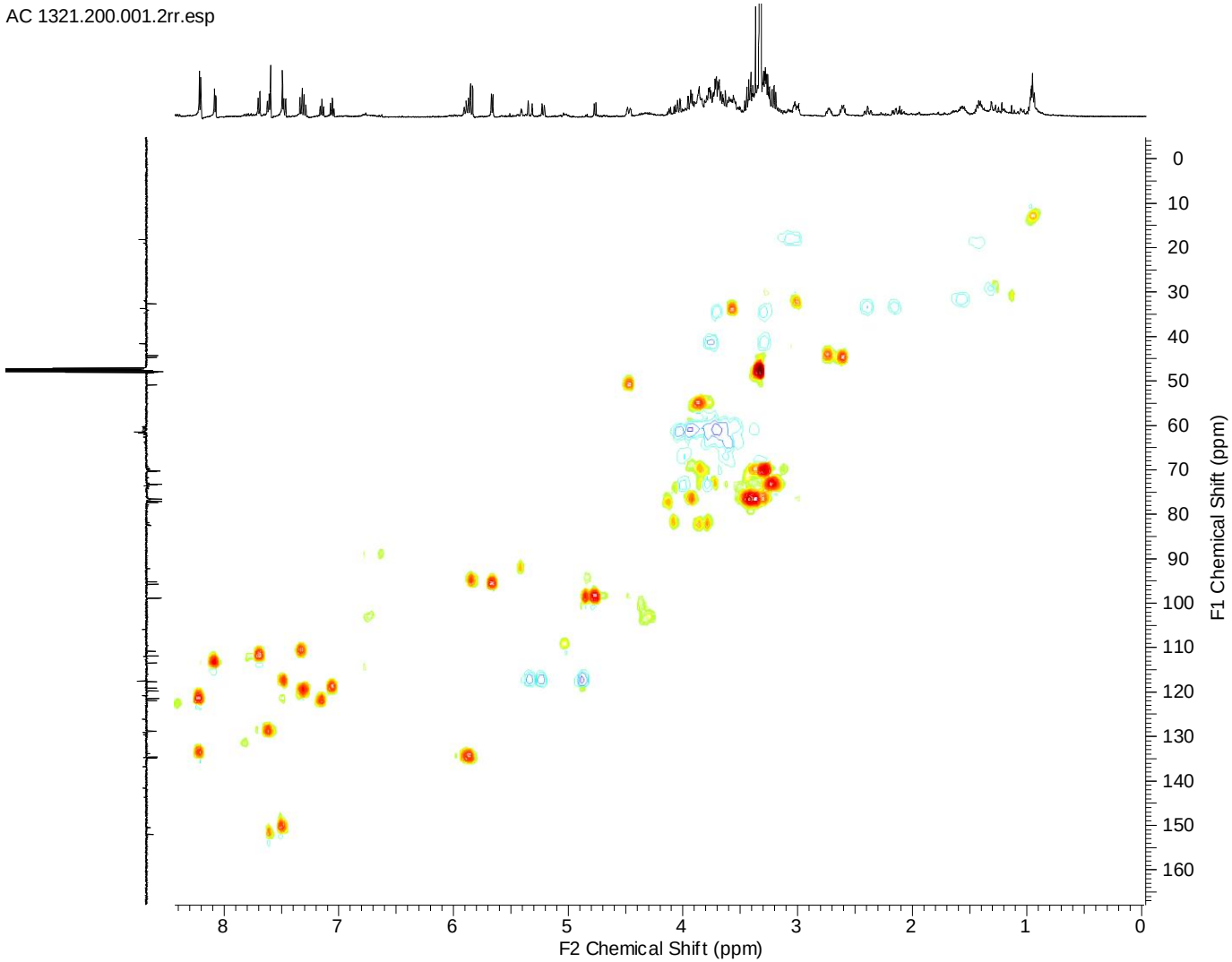


Figure S37. HSQC spectrum of compound **11**.

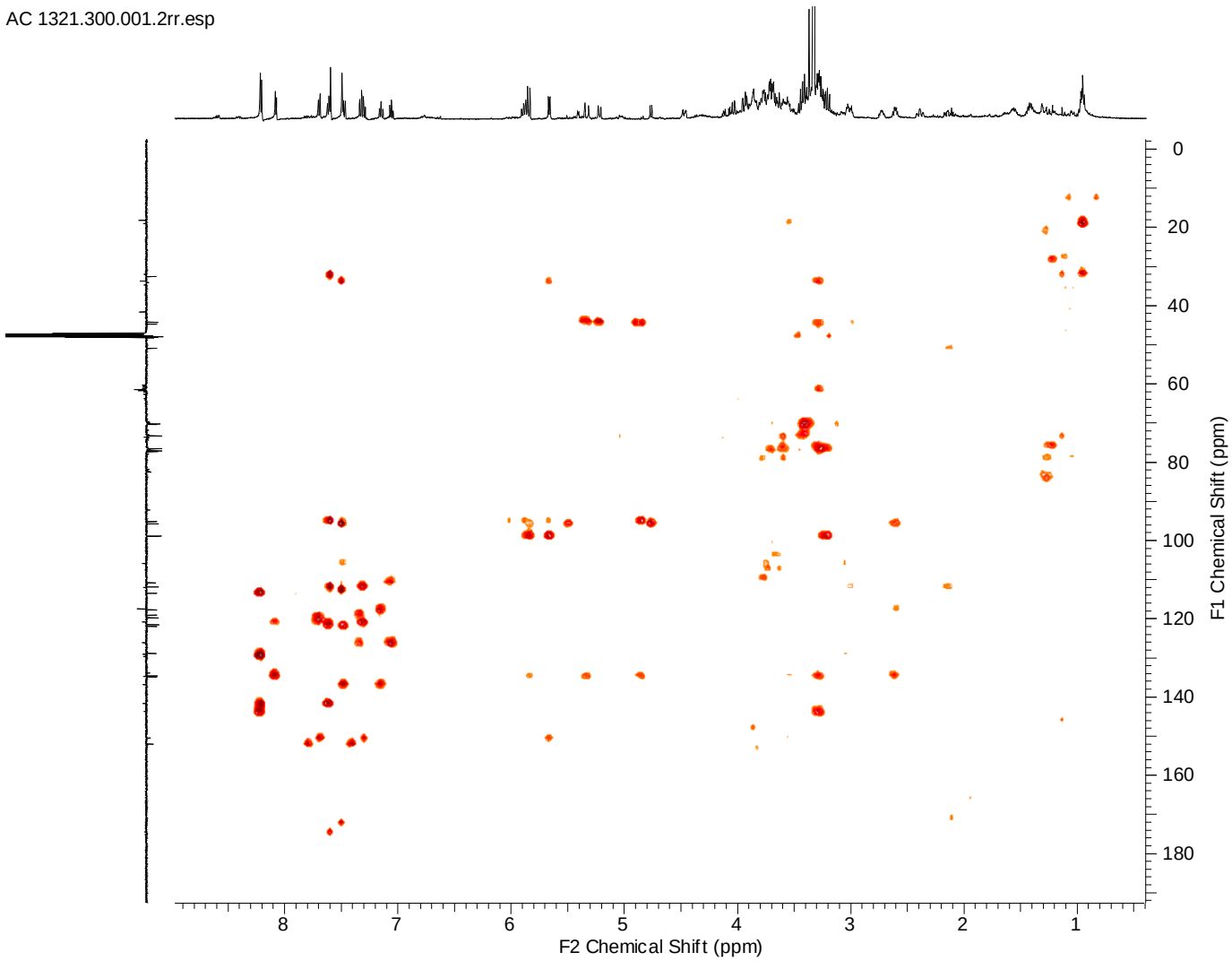


Figure S38. HMBC spectrum of compound **11**.

Compounds 12-14

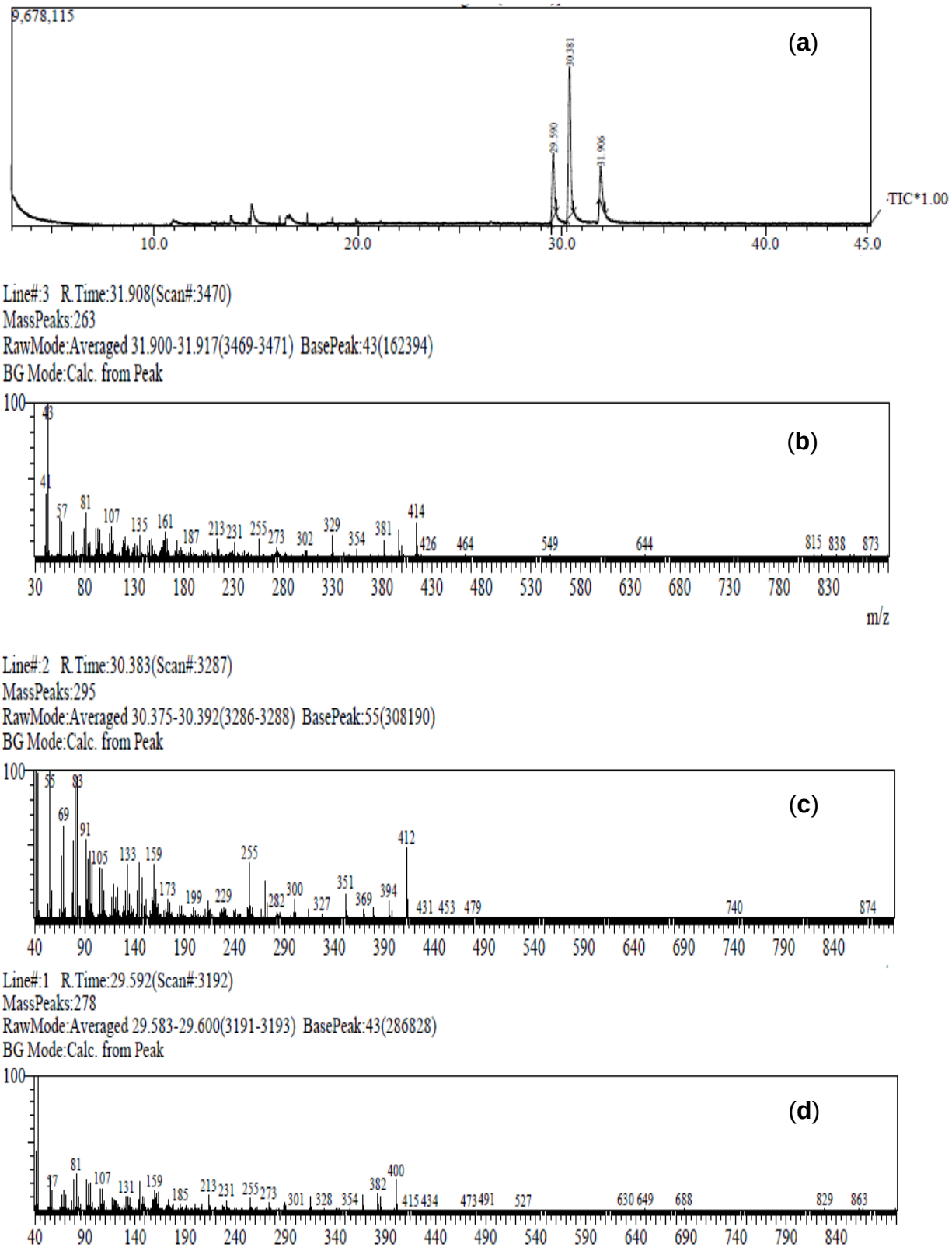


Figure S39. GC/MS chromatogram (**a**) and LRMS of compounds **12** (**b**), **13** (**c**), and **14** (**d**).

Compound 15

Table S12. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **15**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

15					**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
3	140.3	-	3H-20	2H-1; 2H-4	140.3
CH					
2	123.1	5.40 (td, 7.0, 1.3)	2H-1	3H-20	123.0
7	32.7	1.39 (m)	3H-19		32.7
11	32.8				32.7
15	28.0	1.54 (m)	3H-17		27.9
CH_2					
1	59.4	4.17 (d, 6.9)			59.4
4	39.9	2.01 (m)		3H-20	39.8
5	25.1	1.48 (m)			25.2
6	36.6				36.6
8	37.3	1.08 (*m*)			37.4
9	24.5	1.27 (*m*)			24.4
10	37.4	1.28 (*m*)			37.4
12	24.5	1.37 (*m*)			39.3
13	39.4	1.16 (*m*)			24.4
14	39.4	1.16 (m)		3H-17	39.3
CH_3					
16	22.7	0.86 (*d*, 6.5)			22.7
17	22.6	0.87 (*d*, 6.5)			22.6
18	19.7	0.88 (*d*, 6.5)			19.7
19	19.7	0.92 (*s*)			19.7
20	16.1	1.70 (*s*)			16.1

*Miranda et al. 2012.

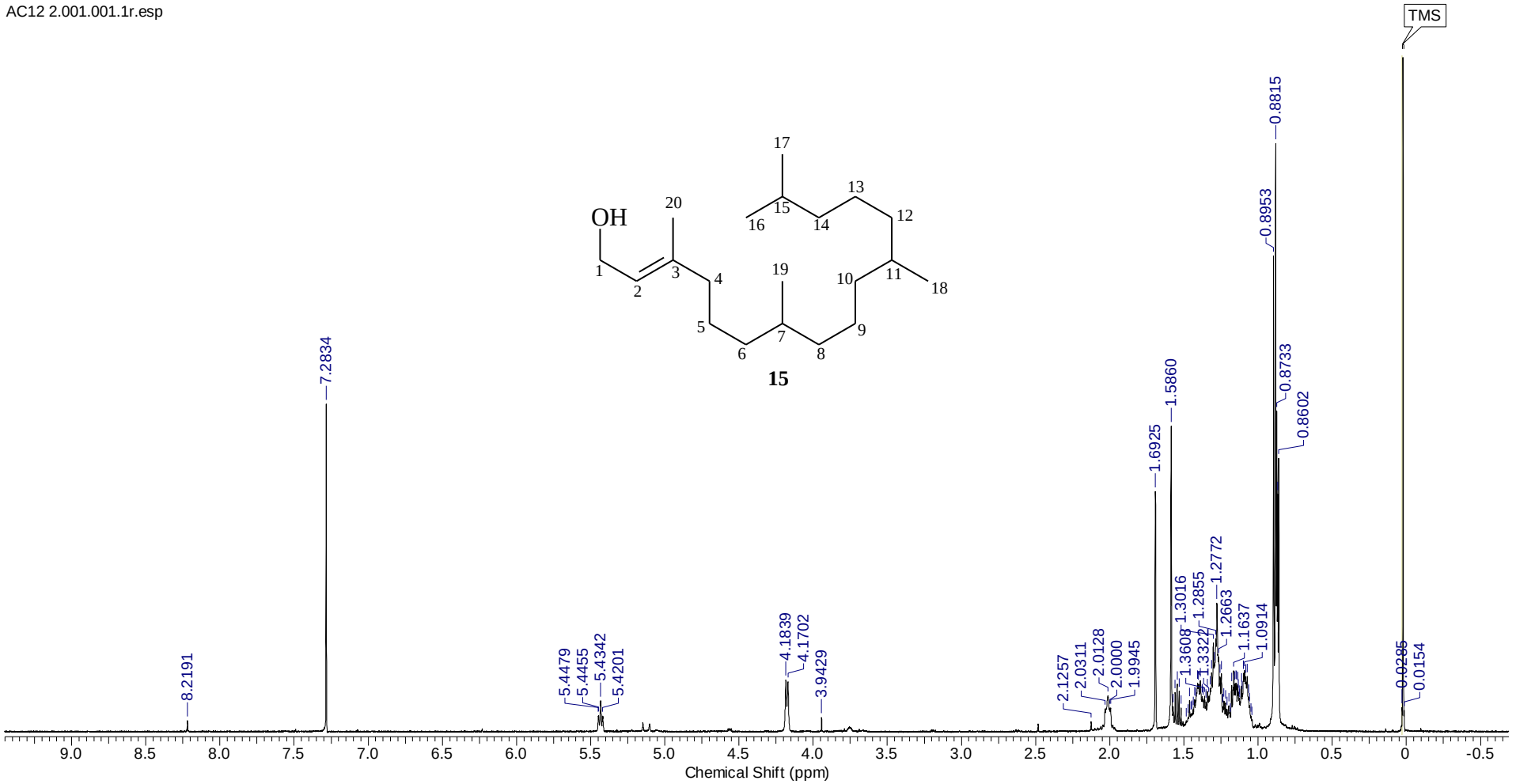


Figure S40. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **15**.

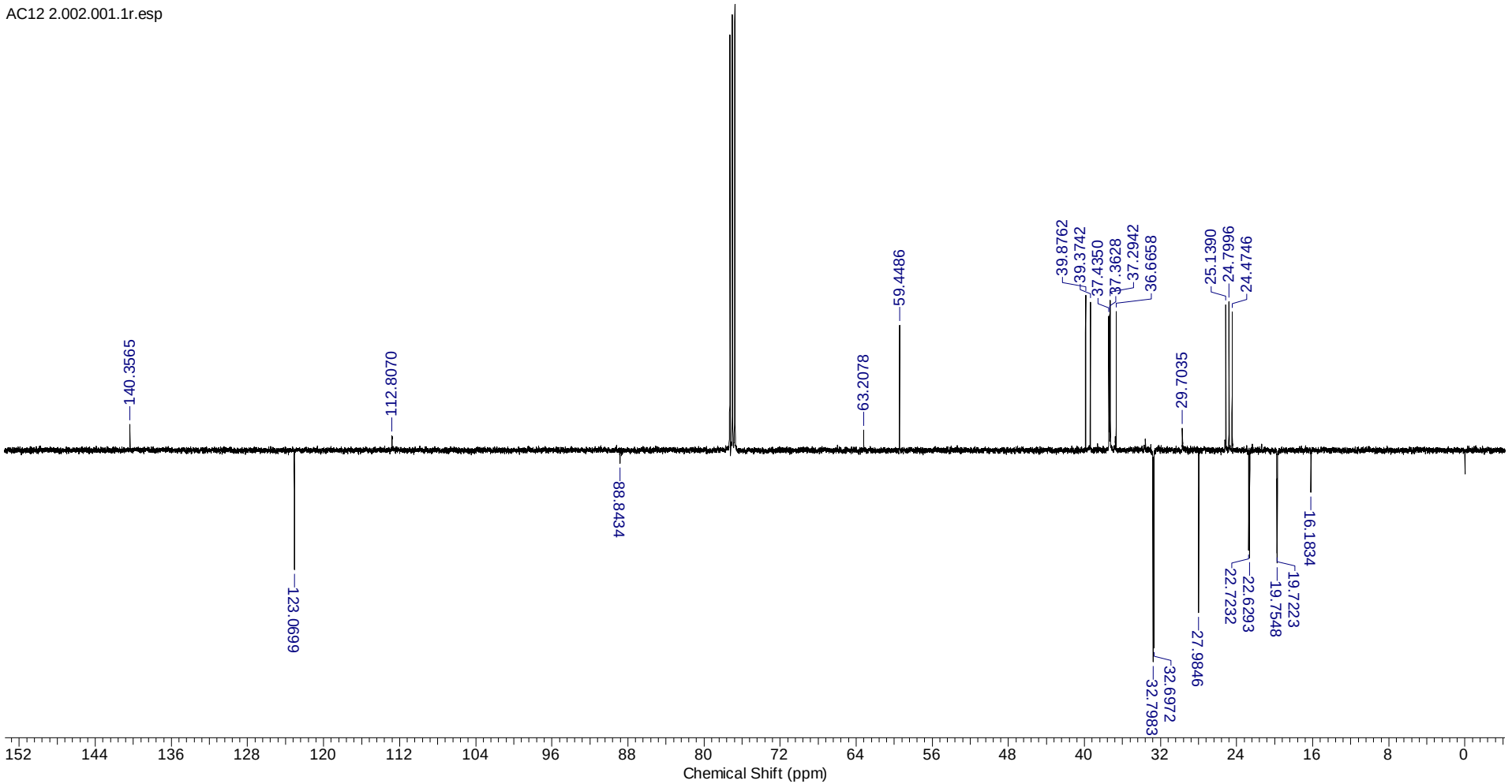


Figure S41. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **15**.

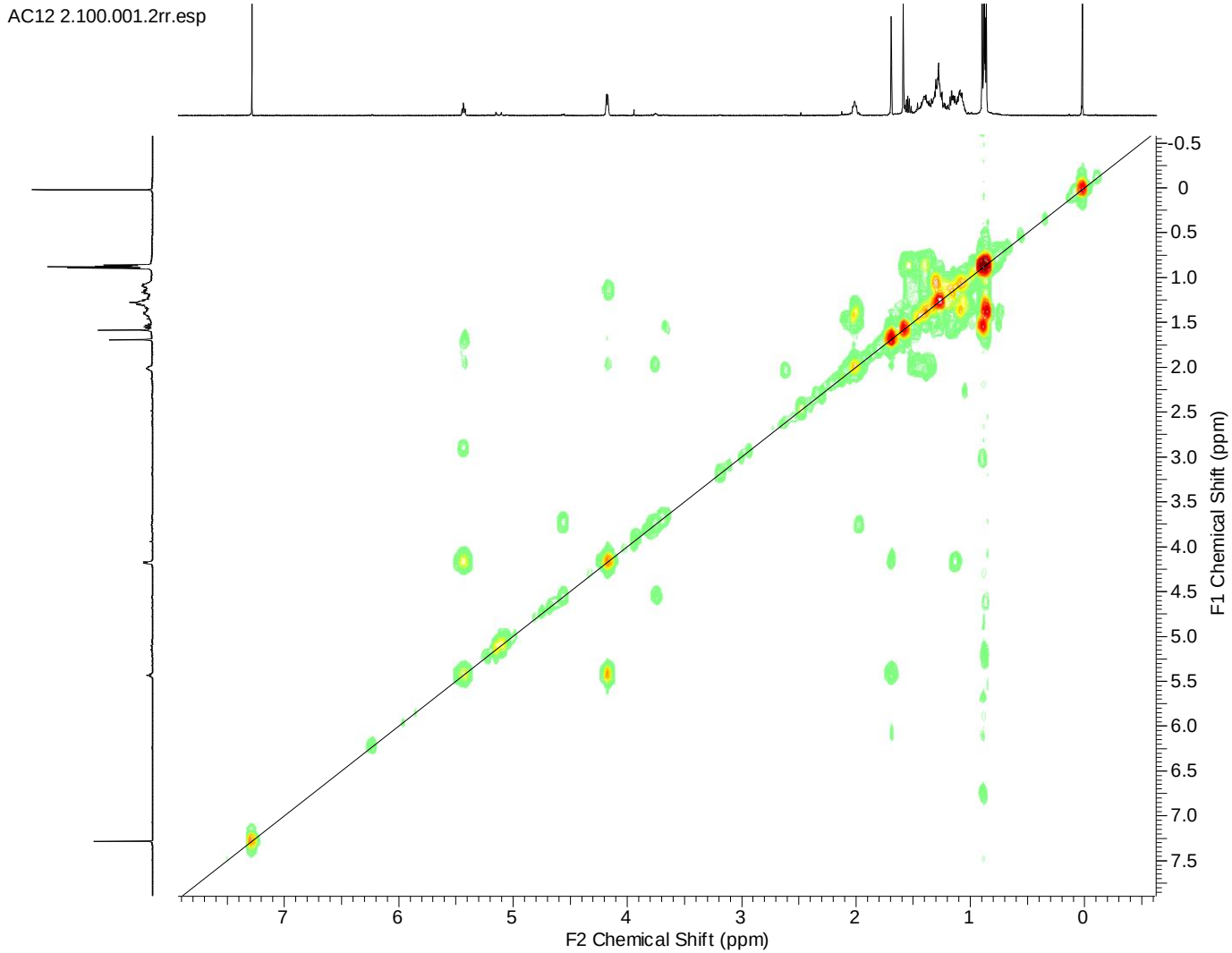


Figure S42. ^{1}H-^{1}H-COSY spectrum of compound **15**.

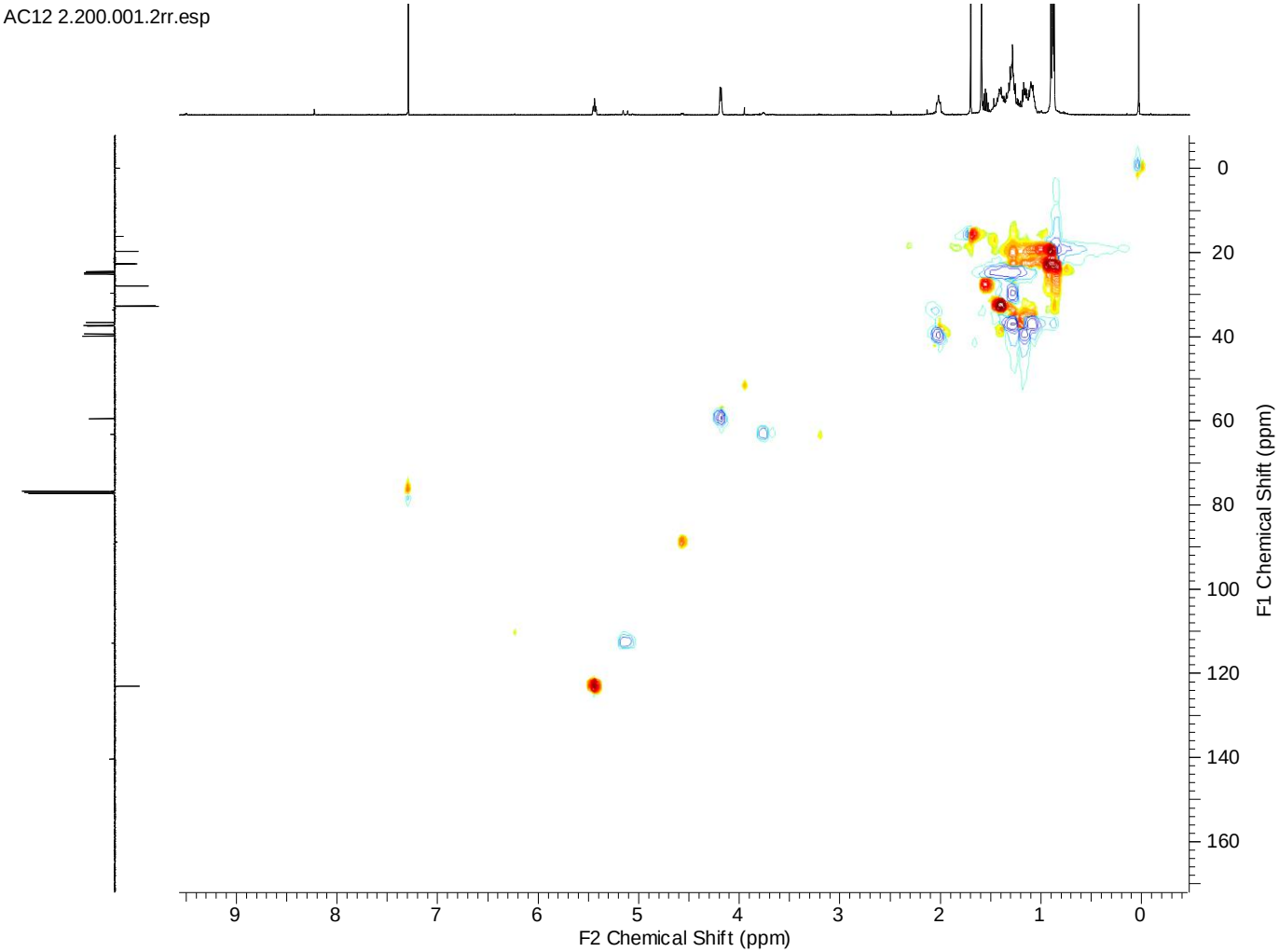


Figure S43. HSQC spectrum of compound **15**.

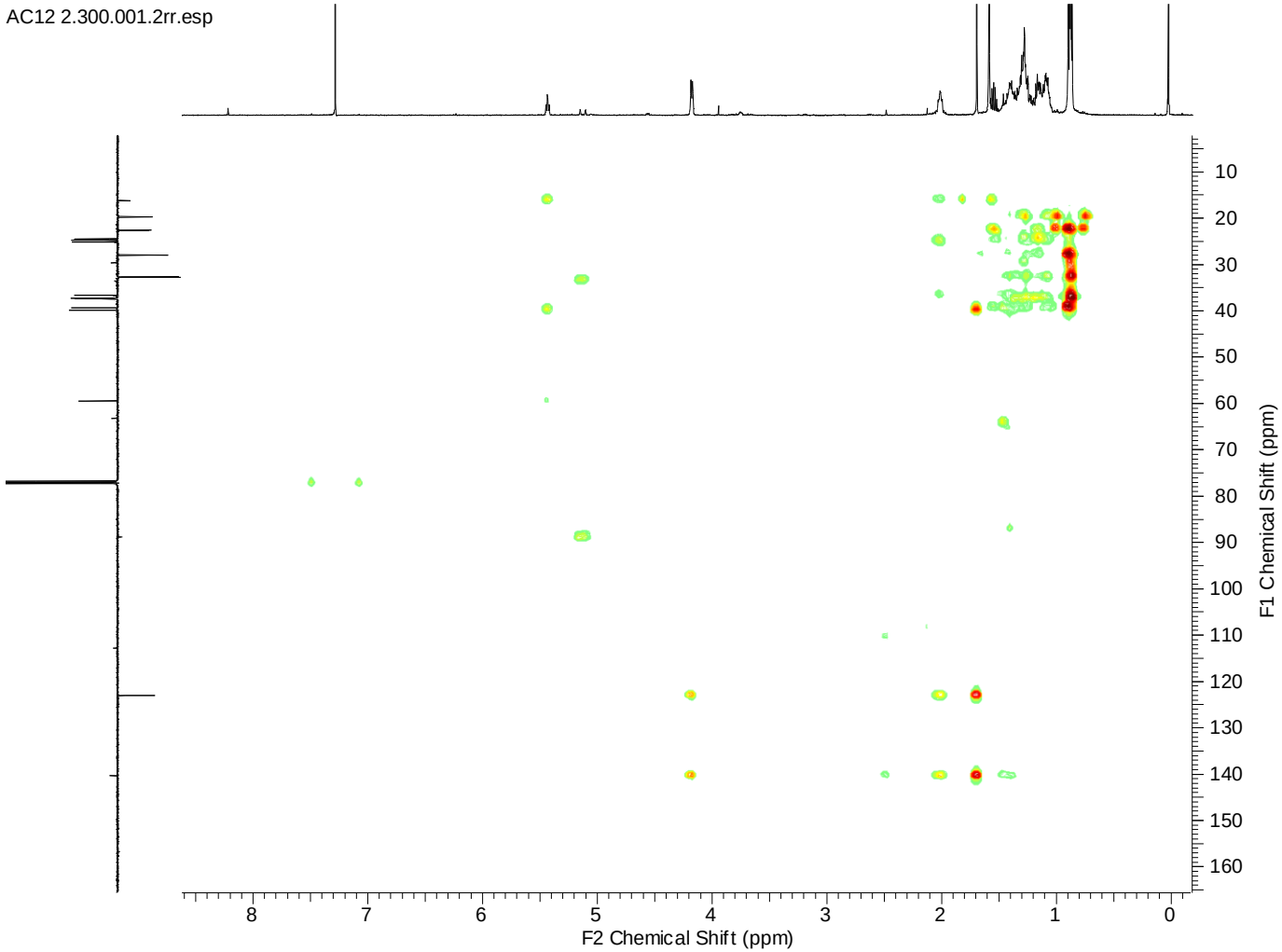


Figure S44. HMBC spectrum of compound **15**.

Compounds 16 and 17

Table S13. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **16** and **17**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

		16	**Literature**		**17**	**Literature***
C	δ_C	δ_H	δ_C	δ_C	δ_H	δ_C
5	140,7	-	141,0	140,7	-	141,0
10	36,7	-	37,0	36,7	-	37,0
13	42,3	-	42,4	42,1	-	42,4
CH						
3	78,4	3,98 (*m*)	78,2	78,4	3,98 (*m*)	78,2
6	121,7	5,34 (*d*, 2,9)	122,0	121,7	5,34 (*d*, 2,9)	122,0
8	31,8		32,1	31,8		32,1
9	50,1		50,4	50,1		50,4
14	56,7		56,9	56,7		57,0
17	57,6		56,3	56,7		56,2
20	36,7		36,5	36,6		36,5
22			-	138,6	5,21 (*dd*, 15,1, 8,9)	138,3
23			-	129,2	5,05 (*m*)	129,5
24	46,6		46,1	51,2		51,5
25	30,8		29,6	31,9		32,7
CH_2						
2	30,0		30,3	30,0		30,3
4	39,1	2,72 (*dd*, 13.3, 2.7); 2,47 (*m*)	39,4	39,1	2,72 (*dd*, 13.3, 2.7); 2,47 (*m*)	39,4
7	31,9		32,2	31,9		32,2
11	21,1		21,4	21,3		21,5
12	39,7		40,0	39,6		39,9
15	24,2		24,6	24,3		24,7
16	29,1		28,6	29,2		29,4
22	34,5		34,3	-		-
23	26,2		26,5	-		-
28	23,9		23,5	25,5		25,7
CH_3	-					
18	12,3	0,65 (*s*)	12,0	11,9	0,67 (*s*)	12,0
19	19,4	0,92 (*s*)	19,3	19,7	0.93 (*s*)	19,3
21	19,2	0,98 (*d*, 6.6)	19,1	21,3	1,07 (*d*, 6,6)	21,5
26	19,3	0,88 (*d*, 1.5)	19,5	21,1	0,88 (*d*, 1.5)	21,4
27	19,6	0,87 (*d*, 2.4)	20,0	19,8	0,87 (*d*, 2.4)	20,0
29	12,7	0,86 (*m*)	12,2	19,9	0,86 (*m*)	12,6
Glucose						
1’	102,4	5,05 (*m*)	102,6	102,4	5,05 (*m*)	102,6
2’	78,3	4,27 (*m*)	75,4	78,3	4,27 (*m*)	75,4
3’	75,8	4,05 (*t*, 8,2)	78,6	75,8	4,05 (*t*, 8,2)	78,6
4’	72,2	4,27 (*m*)	71,7	72,2	4,27 (*m*)	71,7
5’	79,1	4,27 (*m*)	78,5	79,1	4,27 (*m*)	78,5
6’	63,3	4,41 (*dd*, 11.7, 2,4; 4,54 (*dd*, 11,7, 2,4)	62,9	63,3	4,41 (*dd*, 11.7, 2,4); 4,54 (*dd*, 11,7, 2,4)	62,9

Kojima et al. 1990.

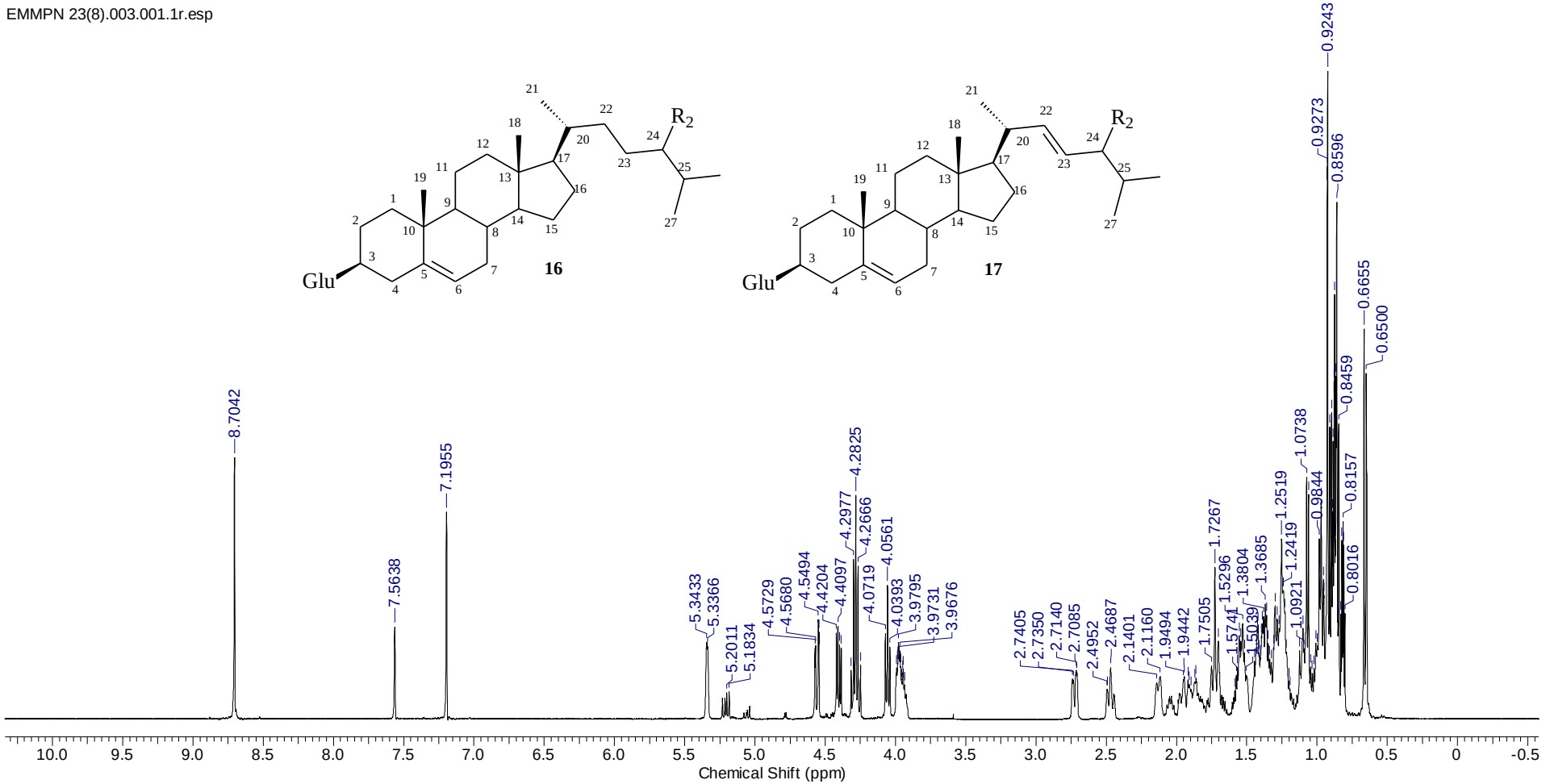


Figure S45. ^{1}H NMR spectrum (500 MHz, Py-d_5) of compounds **16** and **17**.

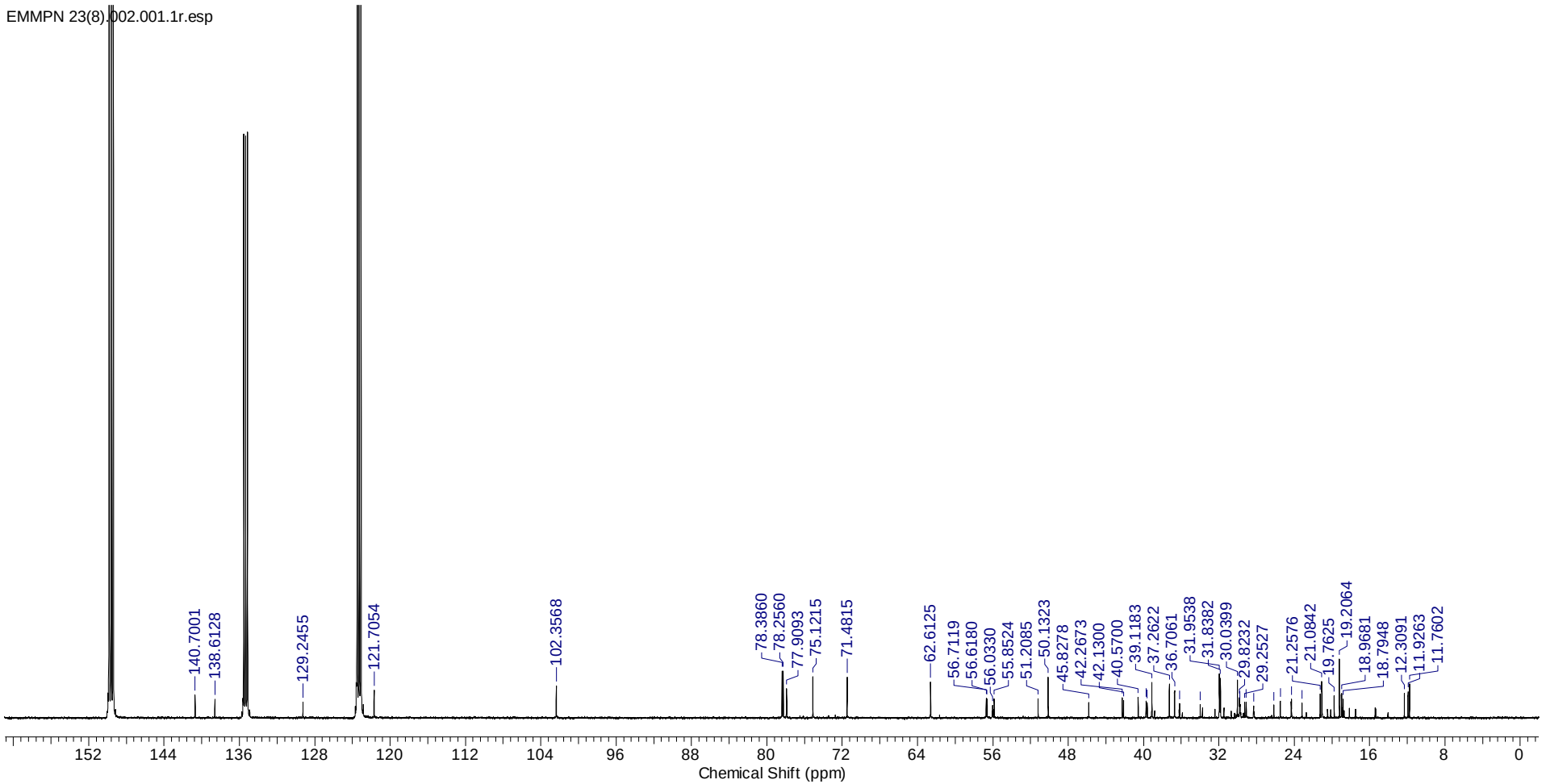


Figure S46. ^{13}C NMR spectrum (125 MHz, Py-d_5) of compounds **16** and **17**.

Compounds 18 and 19

Table S14. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **18**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

	18				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
5	155.9	-	H-6	2H-4	156.2
7	150.6	-	H-6	H-7''	151.2
8	104.6	-	H-7''	H-6	105.2
9	152.1	-		H-7''	152.5
10	103.8	-	2H-4	H-6	104.5
1'	130.5	-	H-2	H-5'	131.2
3'	144.6	-		H-5'	144.1[a]
4'	144.4	-		H-2'	144.7[b]
1''	133.9	-	H-7''	H-5''; 2H-8''	134.5
3''	144.9	-		H-5	145.0[b]
4''	143.8	-		H-6''	145.4[b]
9''	169.4	-	2H-8''	H-7''	168.9
CH					
2	78.3	4.90		H-2'; H-4; H-6'	79.0
3	65.2	4.27 (*m*)	2H-4		65.8
6	94.9	6.23 (*s*)			95.8
2'	113.7	6.99 (*d*, 1.8)		H-2; H-6'	114.4[a]
5'	114.5	6.77 (*d*, 8.1)			144.1[b]
6'	117.8	6.80 (*dd*, 1.8, 8.1)		H-2; H-2'	118.4
2''	113.6	6.55 (*d*, 2.1)		H-6''; H-7''	115.4[a]
5''	115.5	6.62 (*d*, 8.2)			115.8[a]
6''	117.8	6.46 (*dd*, 2.1, 8.2)		H-2''; H-7''	118.4
7''	33.9	4.56 (*d*, 5.6)	2H-8''	H-2''; H-6''	34.5
CH2					
4	28.1	3.05-2.95 (*m*)			28.9
8''	37.2	3.07 (*dd*, 15.7, 7.0) 2.90 (*m*)			38.0

*Nonaka & Nishioka, 1982. **Acetone-d_6 + D_2O. Letters a and b indicate signals that may be interchanged.

Table S15. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **19**, including results of HSQC and HMBC 2D experiments. Chemical shifts in ppm and coupling constants in Hz

	19				**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_{C**}
5	155.85	-	H-6	2H-4	156.2
7	150.67	-	H-6	H-7''	151.2
8	104.78		H-7''	H-6	105.4
9	152.02	-		H-7''	152.6
10	103.86	-	2H-4	H-6	104.7
1'	130.30	-	H-2	H-5'	131.0
3'	144.51	-		H-5'	144.3[b]
4'	144.35	-		H-2'	144.8[b]
1''	133.85	-	H-7''	H-5''; 2H-8''	134.4
3''	144.90	-		H-5''	144.9[b]
4''	143.71			H-2''; H-6''	145.5[b]
9''	169.37	-	2H-8''	H-7''	168.9
CH					
2	78.80	4.96		H-2'; H-4; H-6'	79.4
3	65.61	4.22 (*m*)	2H-4		66.0
6	95.00	6.22 (*s*)			96.0
2'	113.60	6.85 (*d*, 1.8)		H-2; H-6'	114.5[a]
5'	114.59	6.70 (*d*, 8.1)			114.8[a]
6'	117.91	6.63 (*dd*, 1.8, 8.1)		H-2; H-2'	118.7[c]
2''	113.94	6.65 (*d*, 2.1)		H-6''; H-7''	115.3[a]
5''	115.09	6.71 (*d*, 8.2)			115.9[a]
6''	117.9	6.56 (*dd*, 2.1, 8.2)		H-2''; H-7''	118.5[c]
7''	33.70	4.56 (*d*, 5.6)	2H-8''	H-2''; H-6''	34.2
CH2					
4	27.89	2.90-2.85 (*m*)			28.8
8''	36.94	3.02 (*dd*, 15.7, 6.9) 2.92(*m*)			37.6

*Nonaka & Nishioka, 1982. **Acetone-d_6 + D_2O. Letters a-c indicate signals that may be interchanged.

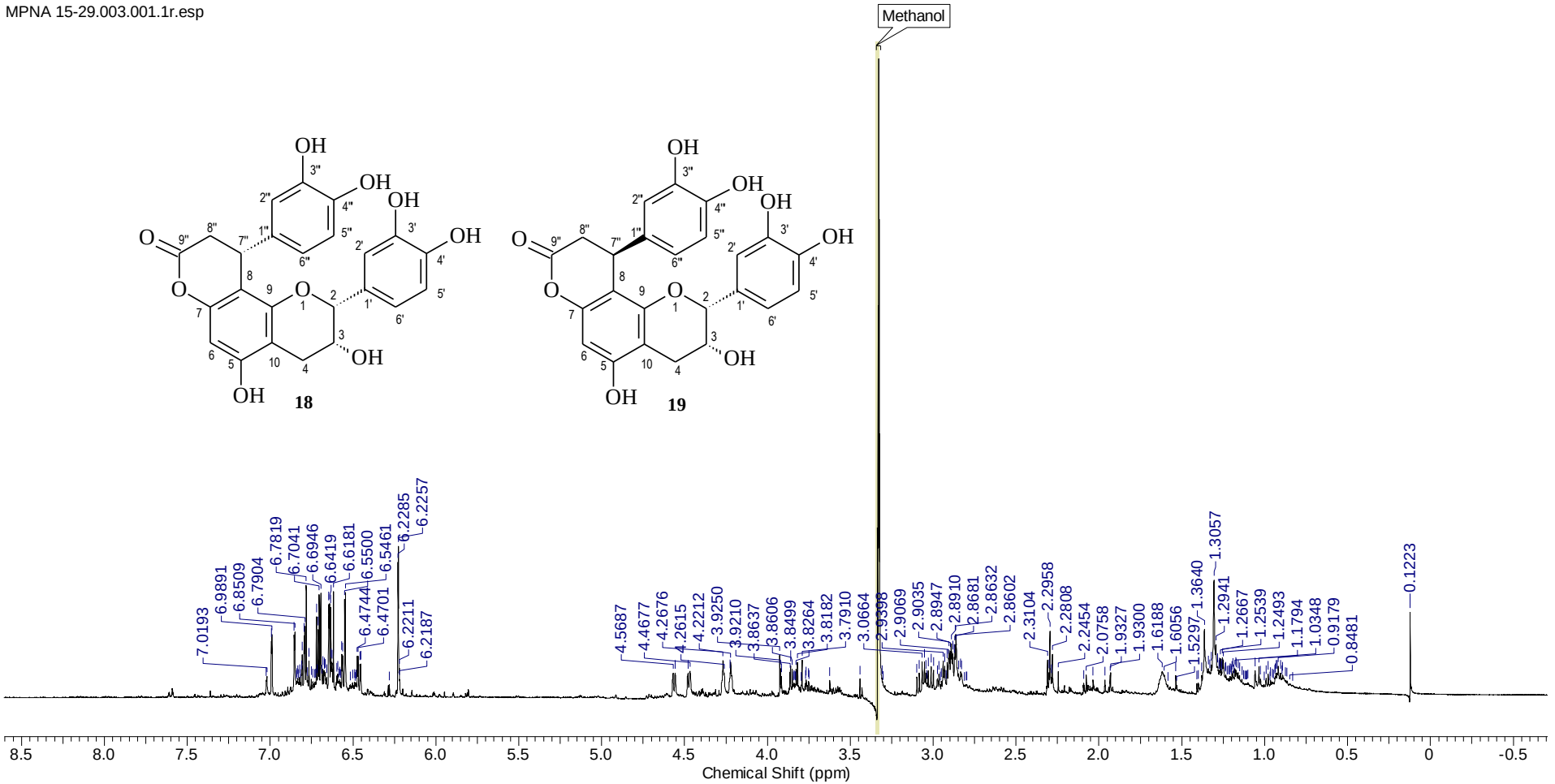


Figure S47. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compounds **18** and **19**.

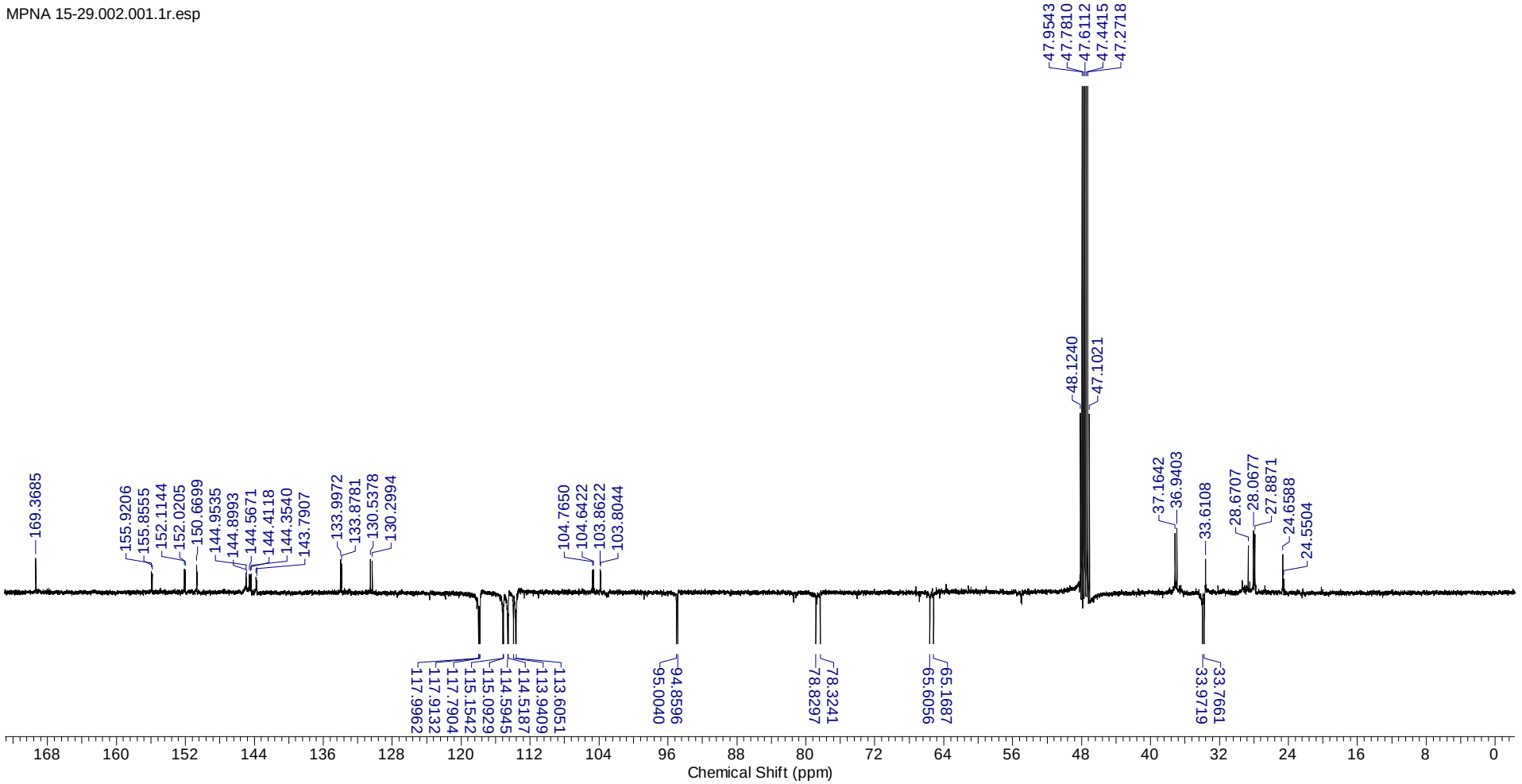


Figure S48. ^{1}H NMR spectrum (125 MHz, CD_3OD) of compounds **18** and **19**.

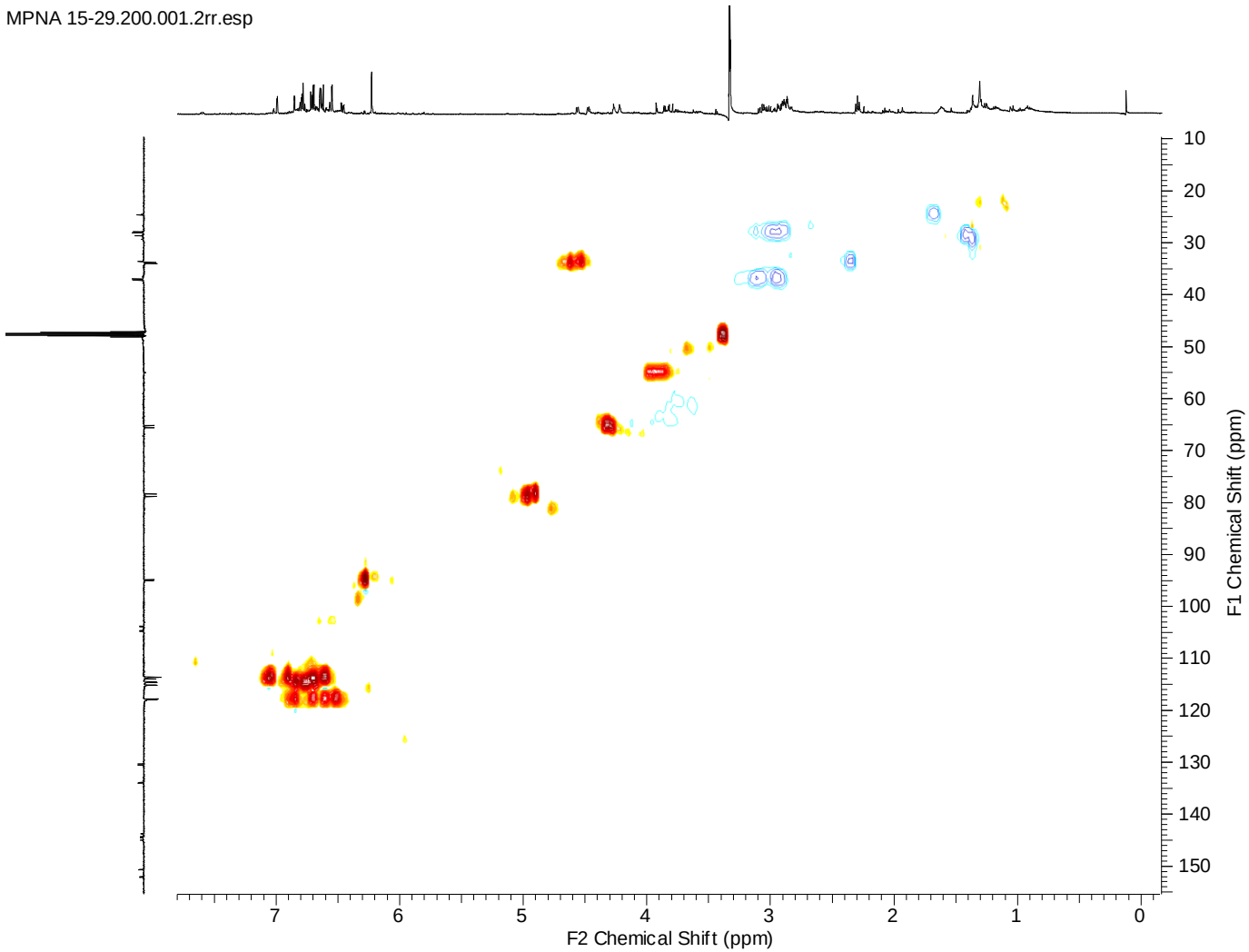


Figure S49. HSQC spectrum of compounds **18** and **19**.

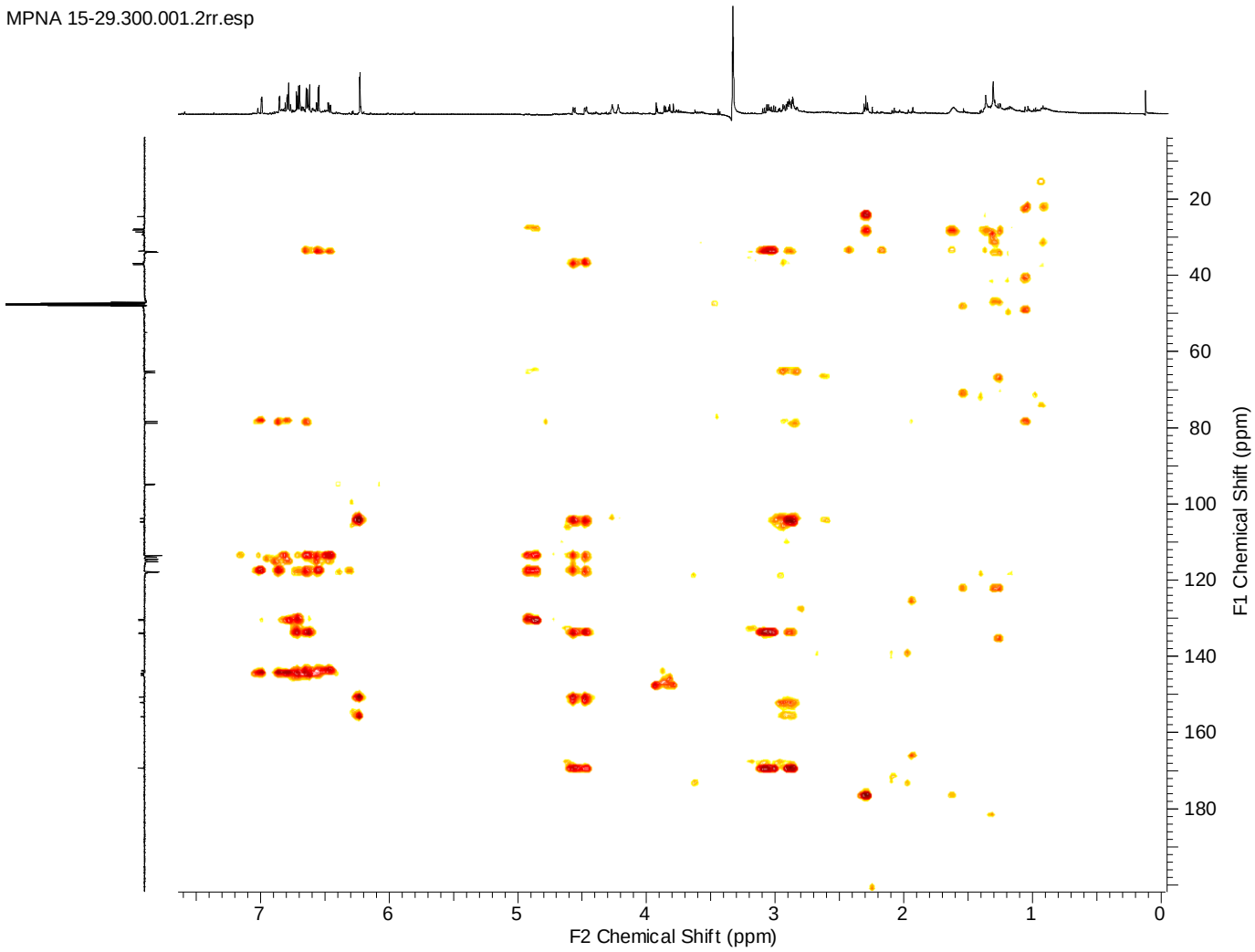


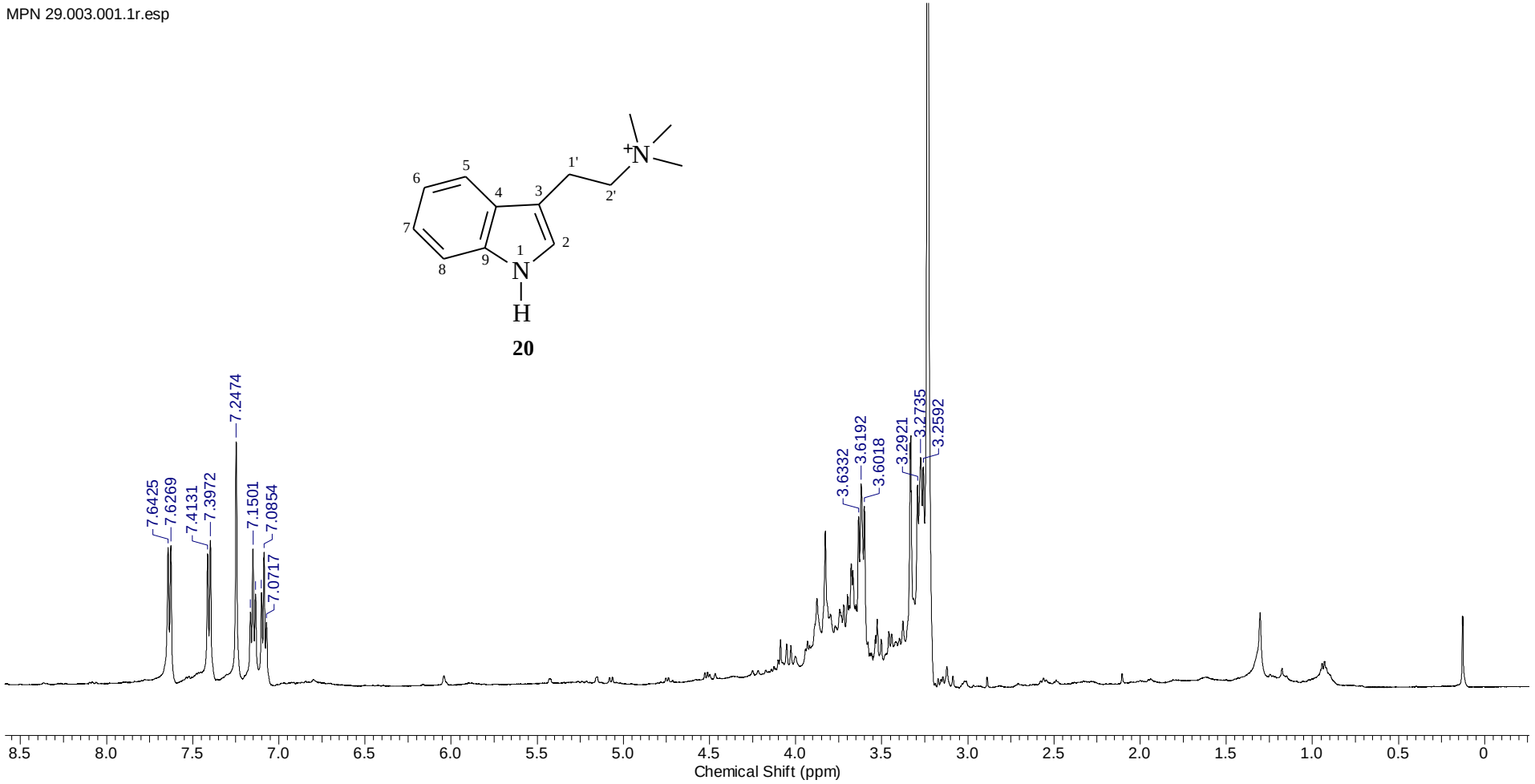
Figure S50. HMBC spectrum of compounds **18** and **19**.

Compounds 20

Table S16. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **20**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

	20				**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C**
3	107.97	-	2H-1'; H-2	2H-2'; H-5	110.8
4	126.65	-		2H-1'; H-2; H-6; H-8	127.0
9	136.78	-		H-2; H-5; H-7	136.5
CH					
2	122.95	7.25 (*s*)		2H-1'	123.8
5	118.77	7.64 (*d*, 8,0 Hz)		H-7	118.9
6	117.53	7.09 (*t*, 7,5 Hz)		H-8	118.7
7	121.44	7.15 (*t*, 7,5 Hz)		H-5	121.7
8	111.20	7.41 (*d*, 8,0 Hz)		H-6	111.9
CH_2					
1'	18.95	3.27 (*m*)	2H-2'		19.0
2'	66.47	3.62 (*m*)	2H-1'	NMe_3	65.5
CH_3					-
N-$\underline{M_3}$	52.27	3.23 (*s*)			52.5

*Martins et al. 2009. **DMSO-d_6.



20

Figure S51. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **20**.

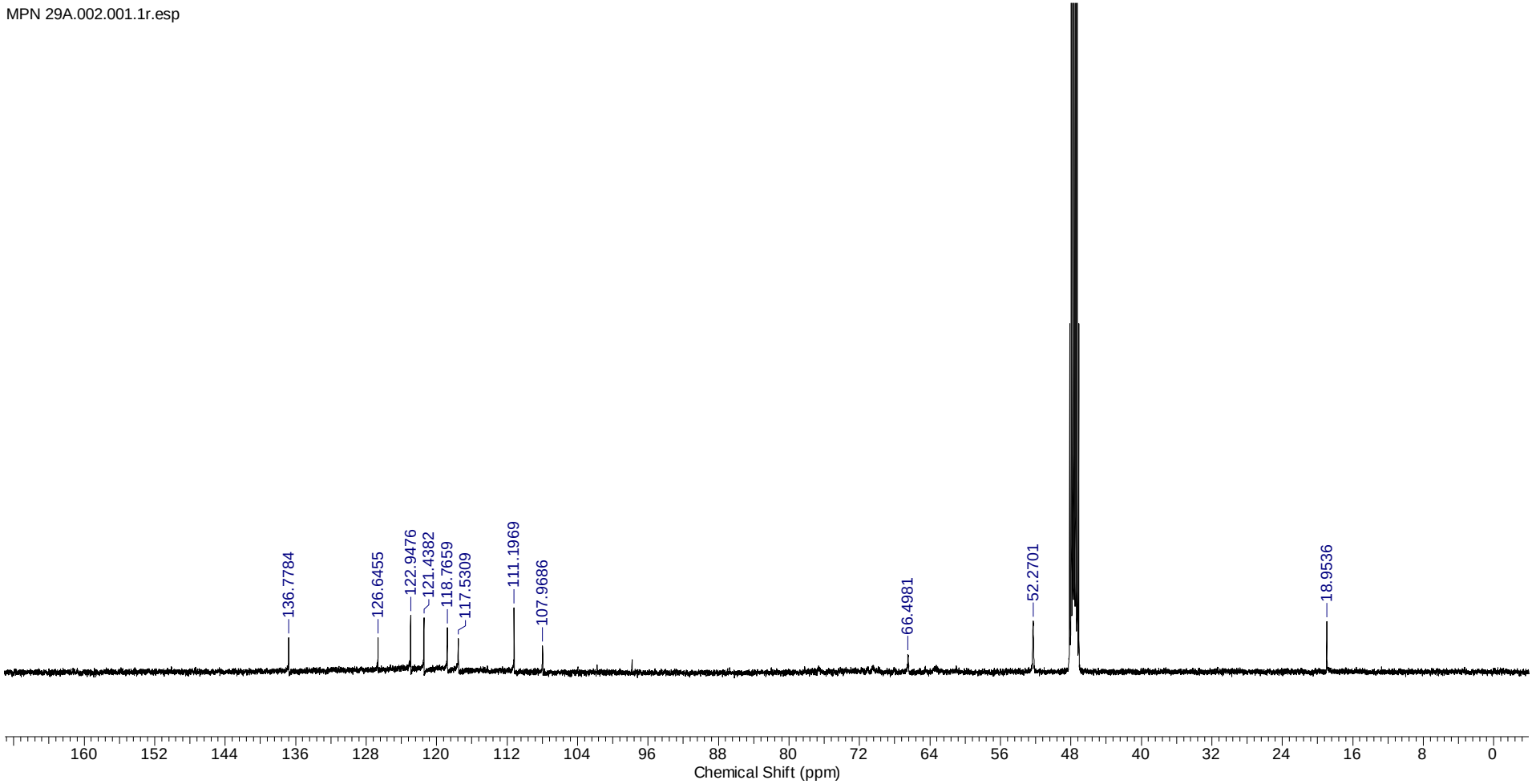


Figure S52. ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **20**.

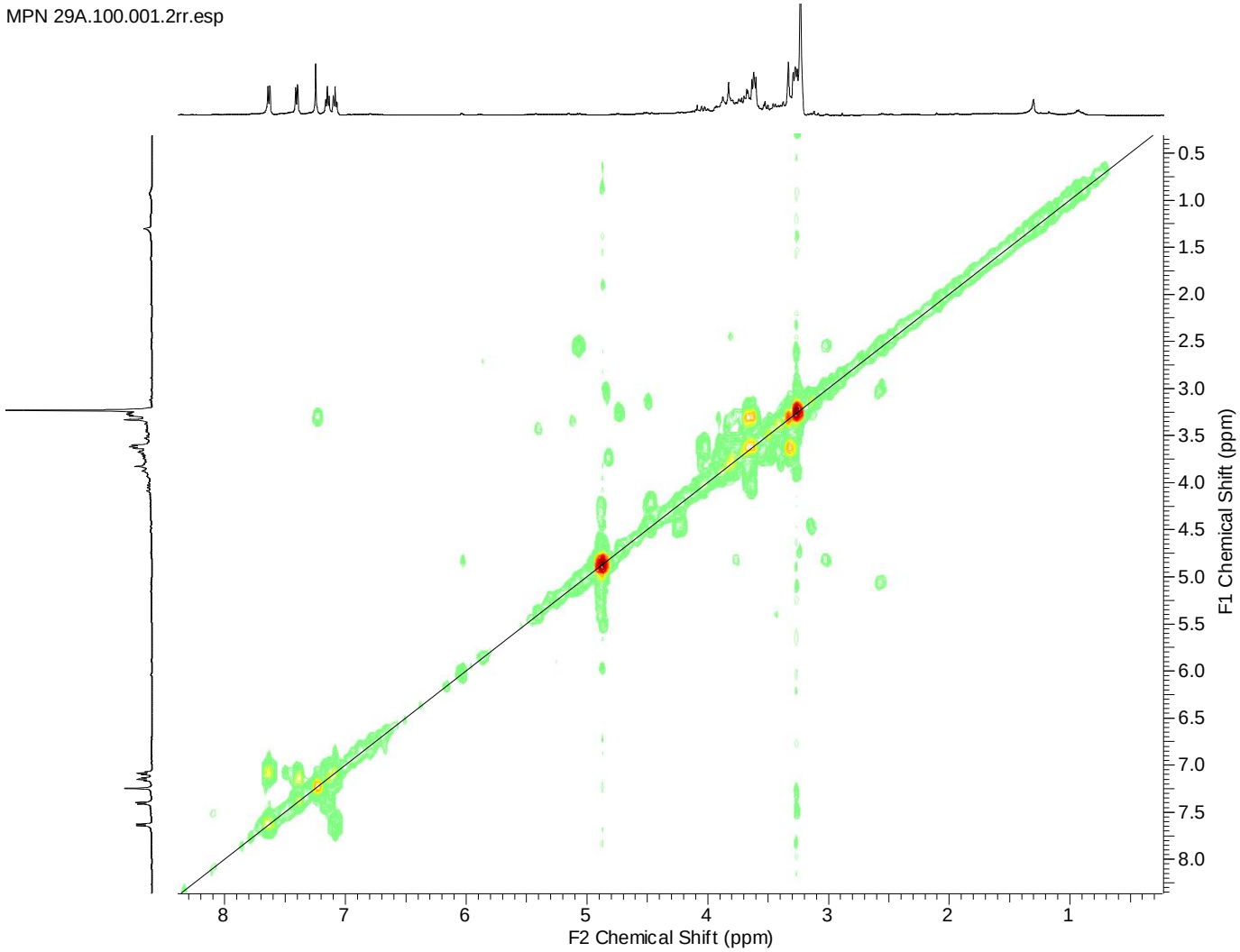


Figure S53. ^{1}H-^{1}H-COSY spectrum of compound **20**.

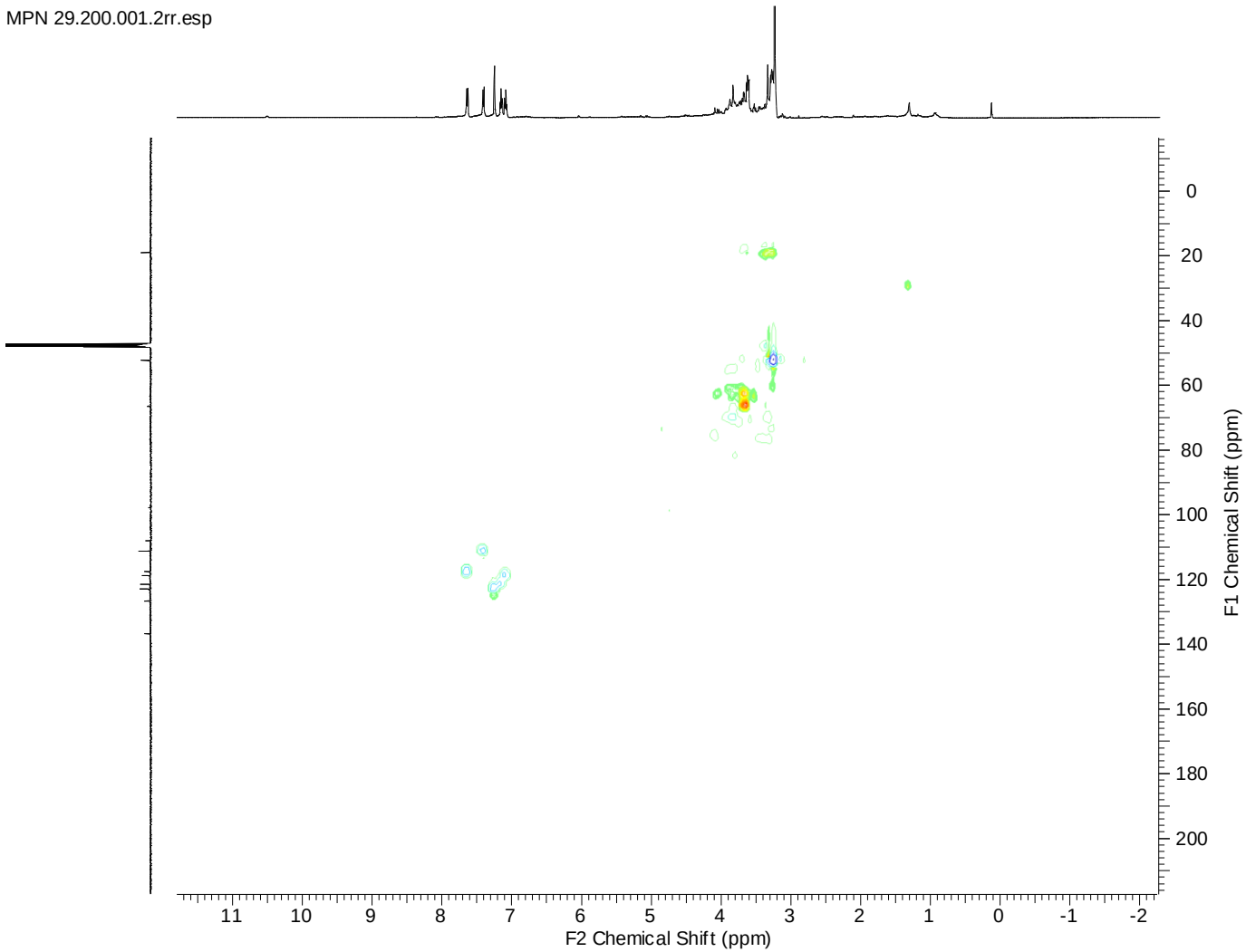


Figure S54. HSQC spectrum of compound **20**.

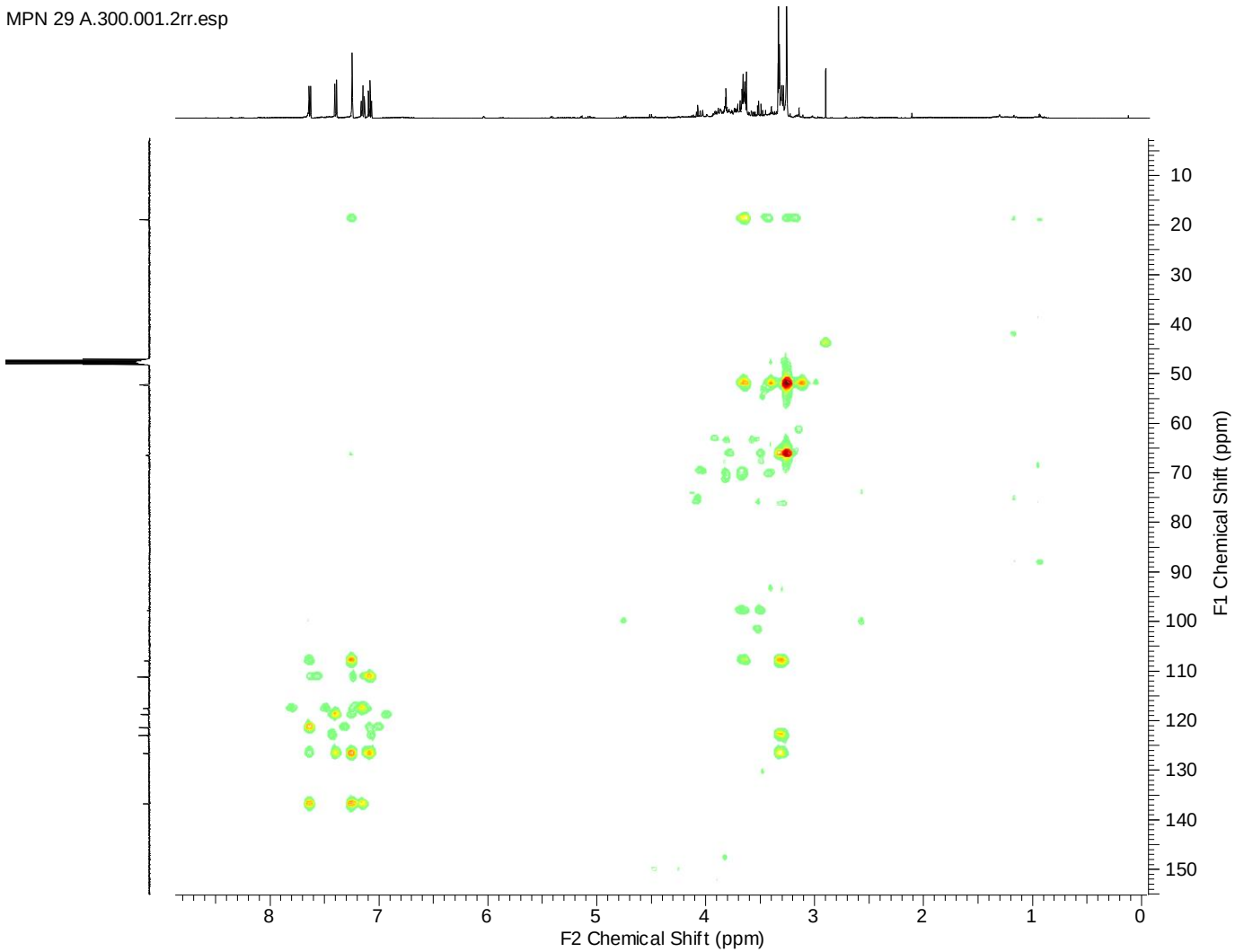


Figure S55. HMBC spectrum of compound **20**.

Compounds 21 and 22

Table S17. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **21**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

21					**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
2	135.1	--		H-6; 2H-14	135.5
3	143.5	--	2H-14	H-5	142.9
7	128.9	--		H-5	128.4
8	121.1	--		H-6; H-12	121.5
13	141.1	--		H-9; H-11	141.2
16	109.5	-	H-15; H-17	H-14b	110.8
22	167.9	--		H-17; CO_2-Me	167.3
CH					
5	136.1	8.23 (*d*, 5.4)	H-6		136.4
6	112.9	7.98 (*d*, 5.4)	H-5		112.6
9	121.3	8.17 (*d*, 7.9)		H-11	121.2
10	119.4	7.27 (*dd*, 7.9, 1.1)		H-12	119.1
11	128.2	7.57 (*m*)	H-10; H-12	H-9	127.8
12	111.5	7.60 (*brd*, 8.0)		H-10	111.3
15	32.9	3.61 (*m*)	2H-14	H-17; H-21	34.9
17	152.8	7.55 (*d*, 0.9)		H-21	152.2
19	134.0	5.58 (*ddd*, 16.5, 10.6, 8.9)	H-18b; H-20		134.4
20	44.11	2.62 (*m*)	H-15	2H-14; 2H-18	44.2
21	96.04	5.75 (*d*, 6.7)	H-20	H-15; H-17; H-1'	96.4
CH_2					
14	33.80	3.60 (*m*); 3.35 (*m*)	H-15	H-20	35.8
18	118.09	5.05 (*dd*, 10.6, 1.1) 4.94 (*brs*, 16.5)		H-20	117.9
CH_3					
CO2-Me	50.2	3.38 (*s*)			49.9
Glucose					
1'	96.78	4.77 (*d*, 7.9)	H-2'	H-21	99.7
2'	73.22	3.25(dd, 7.9, 9.2)	H-3'		73.0
3'	76.56	3.41 (*t*, 9.2)			76.4
4'	70.21	3.30 (*m*)			70.8
5'	77.15	3.32 (*m*)			74.4
6'	61.44	3.93, 3.87 (*m*)			62.9

*Berger et al. 2015.

Table S18. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **22**, including results of HSQC and HMBC 2D experiments. Chemical shifts δ in ppm and coupling constants in Hz

	22				**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
2	103.78	-	2H-1		108.7
CH					
3	77.00	4.16 (*d*, 8.1)	H-4	2H-1’	83.2
4	75.90	3.94 (*dd*, 8.1, 7.2)	H-3		78.4
5	81.96	3.77 (*dd*, 7.2, 3.2)	H-4; 2H-6		83.8
CH_2					
1	60.54	3.67 (*d*, 11.7) 3.54 (*d*, 11.7)			61.6
6	63.70	3.74 (*d*, 9.4) 3.60 (*m*)		H-4	62.6
1’	60.78	3.71 (*m*), 3.51 (*m*)	2H-2’	2H-3’	61.9
2’	32.05	1.55 (*m*)	2H-3’	3H-4’	33.4
3’	18.96	1.40 (*m*)	2H-2’; 3H-4’	2H-1’	20.4
CH_3					
4	12.96	0.95 (*t*, 7.2)	2H-3	2H-2’	14.2

*Uddin et al. 2013.

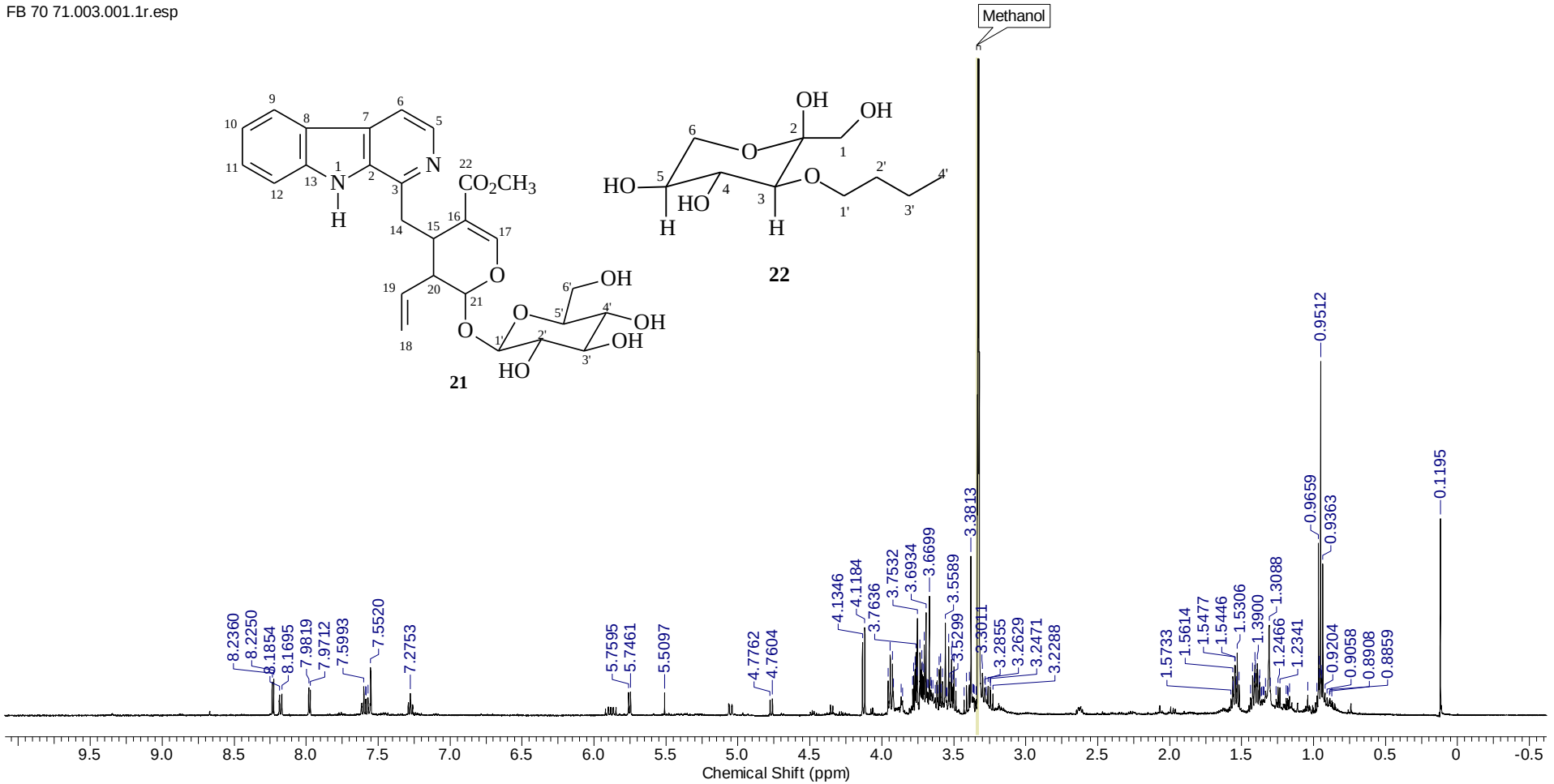


Figure S56. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compounds **21** and **22**.

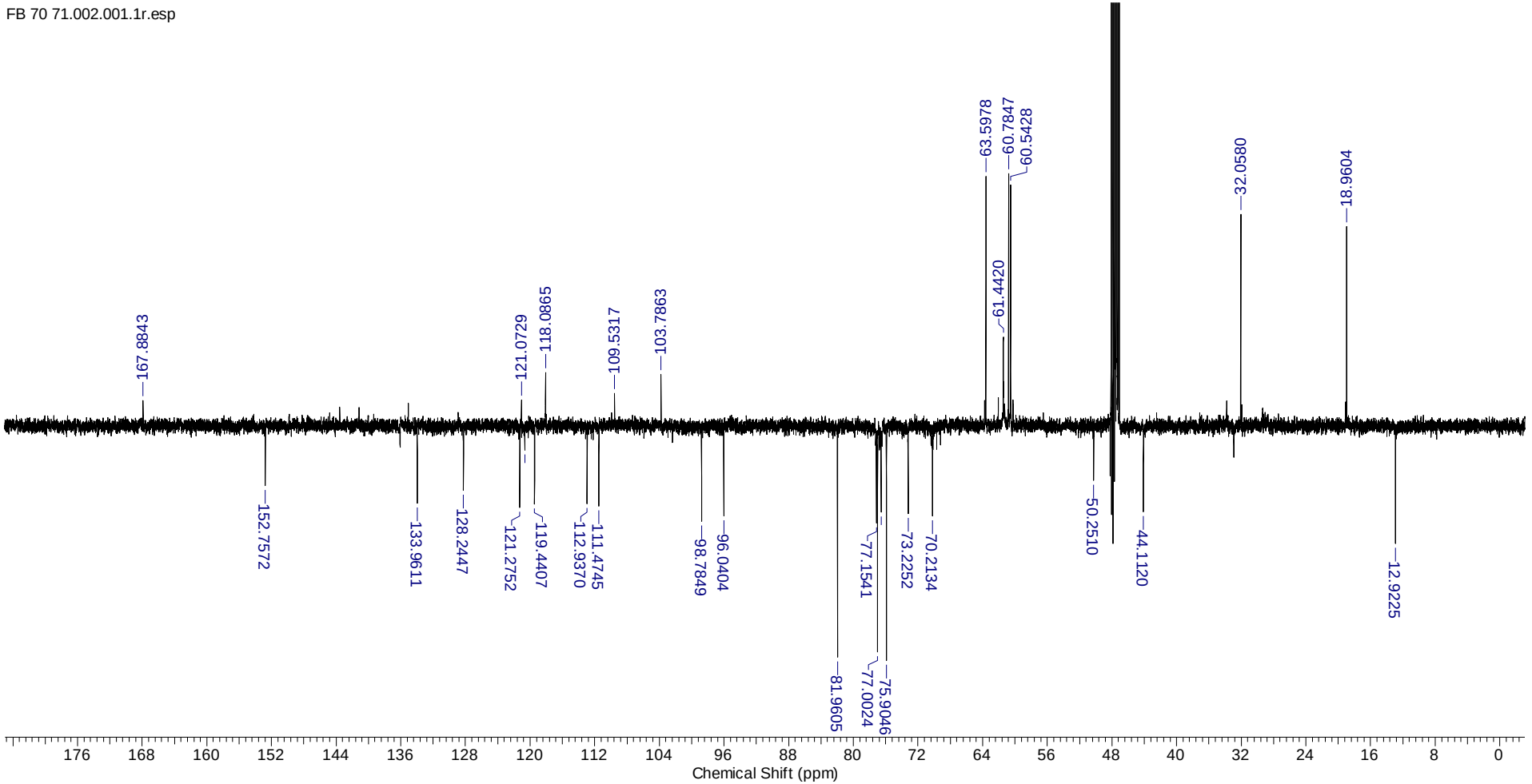


Figure S57. ^{13}C NMR spectrum (125 MHz, CD_3OD) of compounds **21** and **22**.

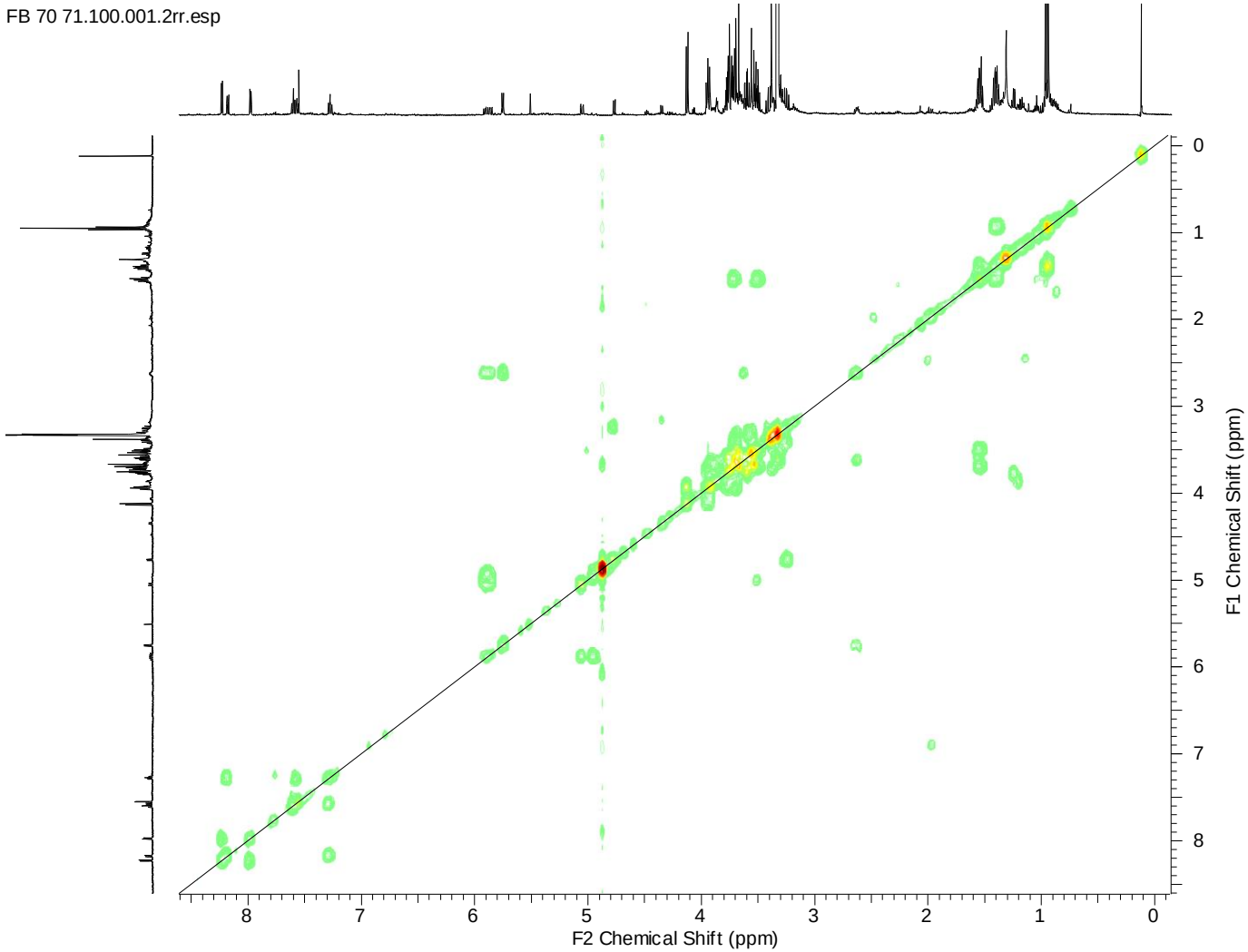


Figure S58. ^{1}H-^{1}H-COSY spectrum of compounds **21** and **22**.

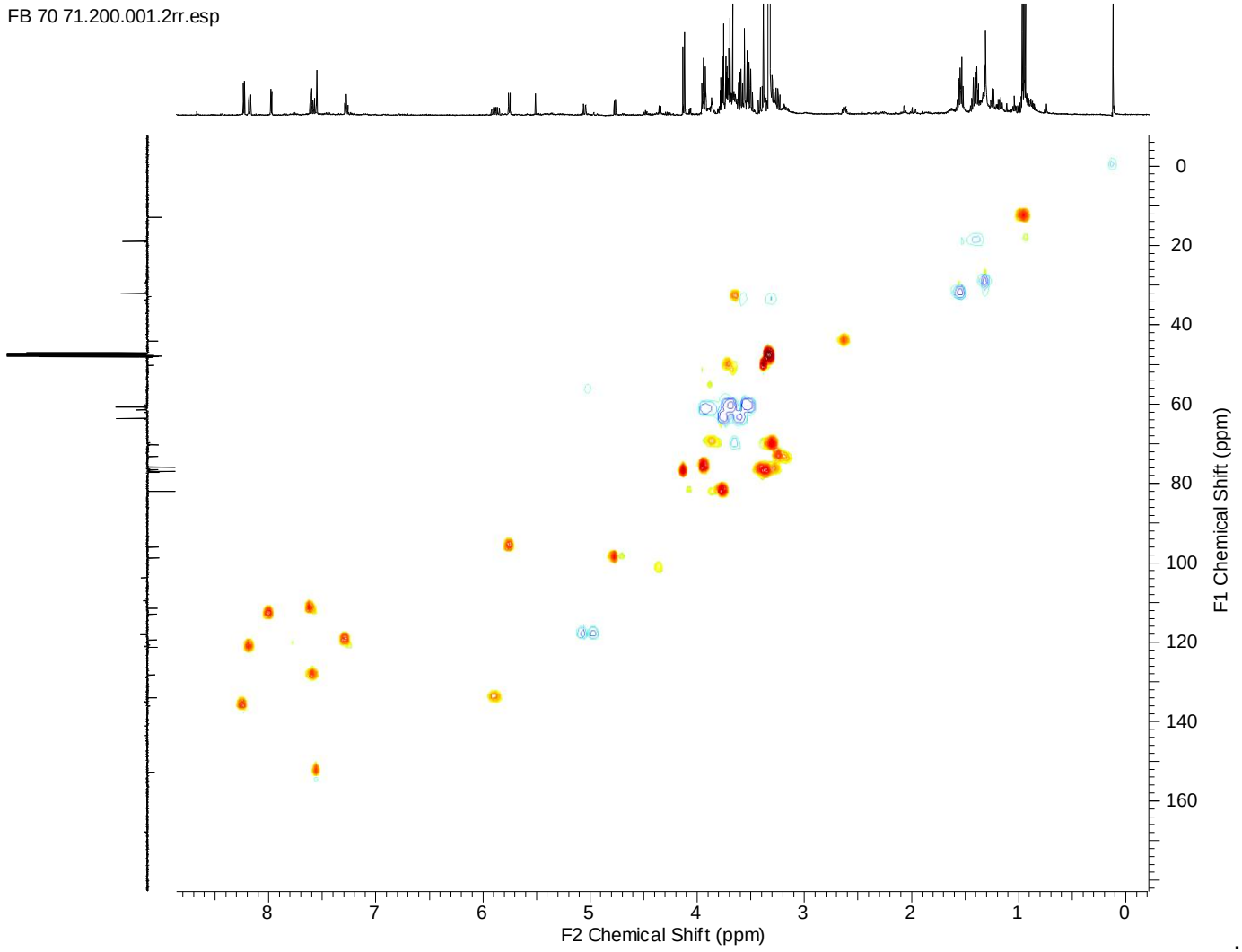


Figure S59. HSQC spectrum of compounds **21** and **22**.

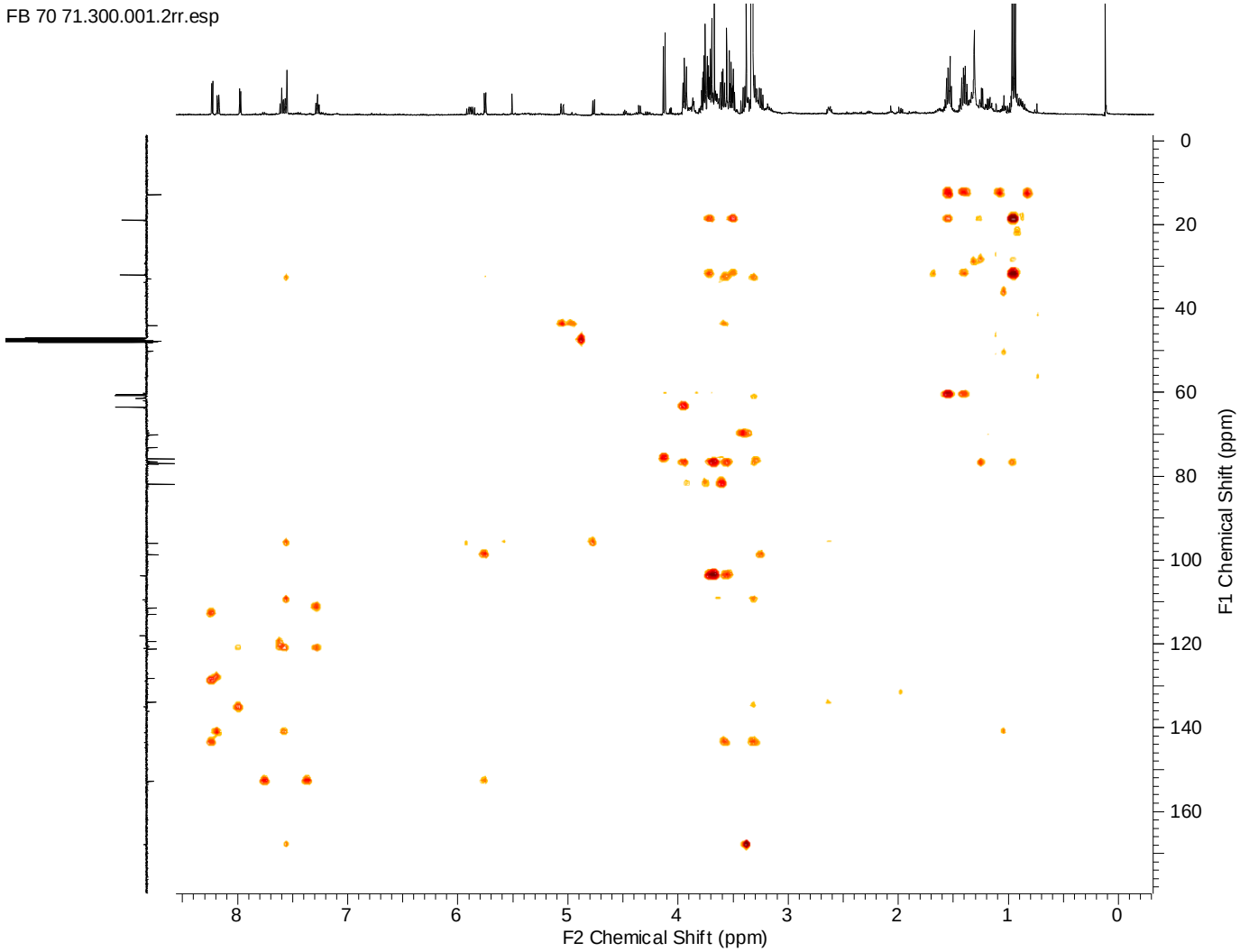


Figure S60. HMBC spectrum of compounds **21** and **22**.

Compound 23

Table S19. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of **23**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

	23				**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
1	41.03	-	2H-2; 3H-12; 3H-13		42,5
3	199.82	-	2H-2		201,3
5	165.87	-	3H-11	H-8	167,4
6	78.61	-	H-7	2H-2; H-8; 3H-11; 3H-12; 3H-13	80,0
CH					
4	125.78	5.89 (*s*)		3H-11	127,2
7	130.14	5.87 (*m*)	H-8	H-9	131,8
8	133.88	5.88 (*m*)	H-7; H-9	3H-1-0	135,2
9	75.89	4.45 (m)	3H-10	H-1'; H-7	77,0
CH_2					
2	49.29	2.52 (*d*, 16.9 2.17 (*d*, 16.9)		3H-12; 3H-13	50,9
CH_3					
10	19.79	1.31 (*d*, 6.3)			21,2
11	18.16	1.94 (*s*)		H-4	19,8
12	23.29	1.06 (*s*)		2H-2	24,7
13	22.03	1.05 (*s*)		2H-2	23,5
Glucose					
1'	101.33	4.36 (*d*, 7.7)	H-2'		102,7
2'	73.84	3.19 (*dd*, 9.9, 7.7)	H-1'; H-3'		75,3
3'	76.70	3.35 (*m*)	H-2'; H-4'	H-5'	75,1
4'	70.24	4,27 (*t*, 9.6)	H-3'; H-5'	H-6'a	71,6
5'	76.63	3.25 (*m*)	H-6'b		78,0
6'	61.42	3.86 (*dd*,13.5, 2.0) 3.64 (*dd*, 13.5, 5.4)	H-5'		62,7

*Otsuka et al. 1995.

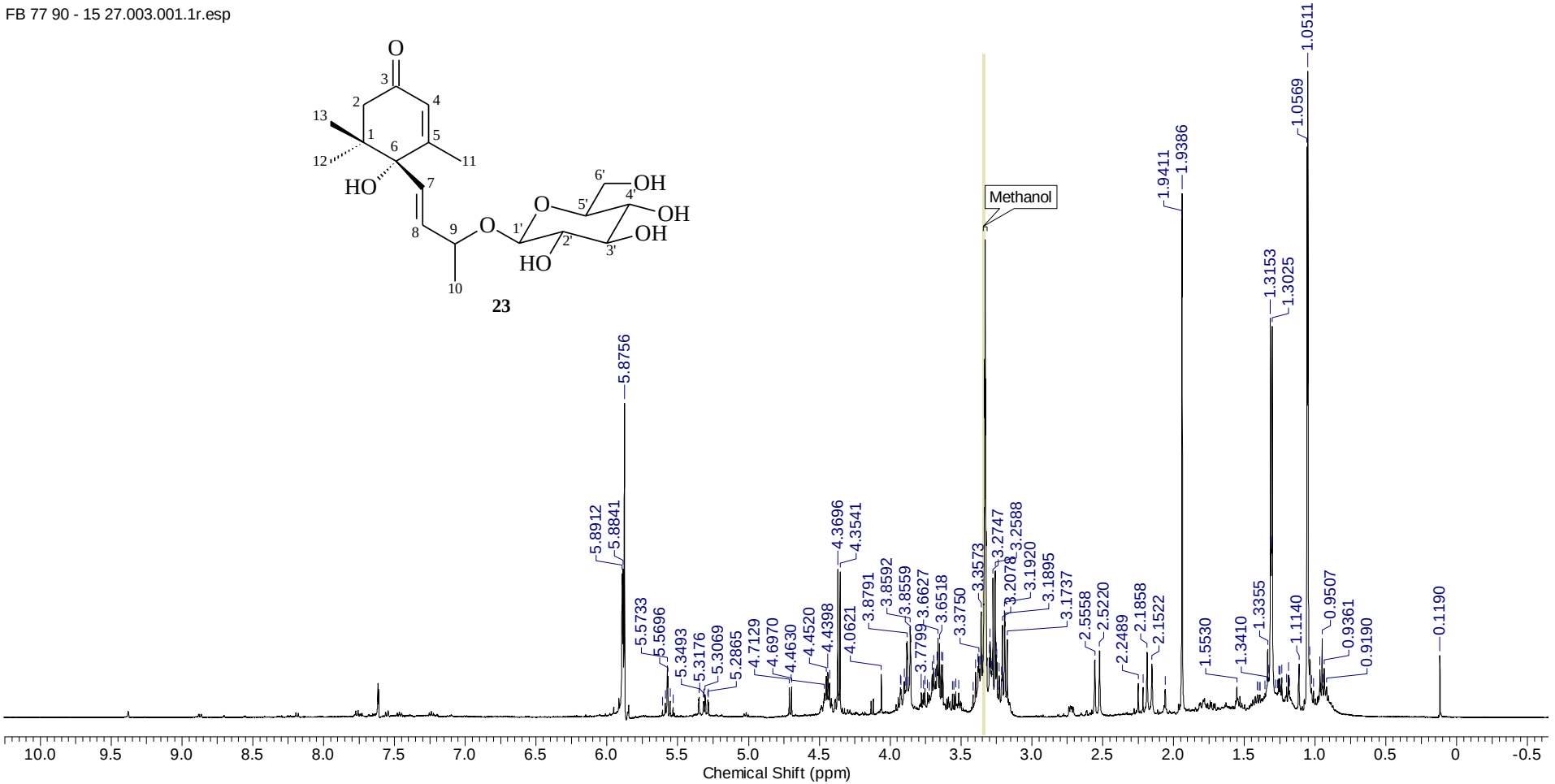


Figure S61. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **23**.

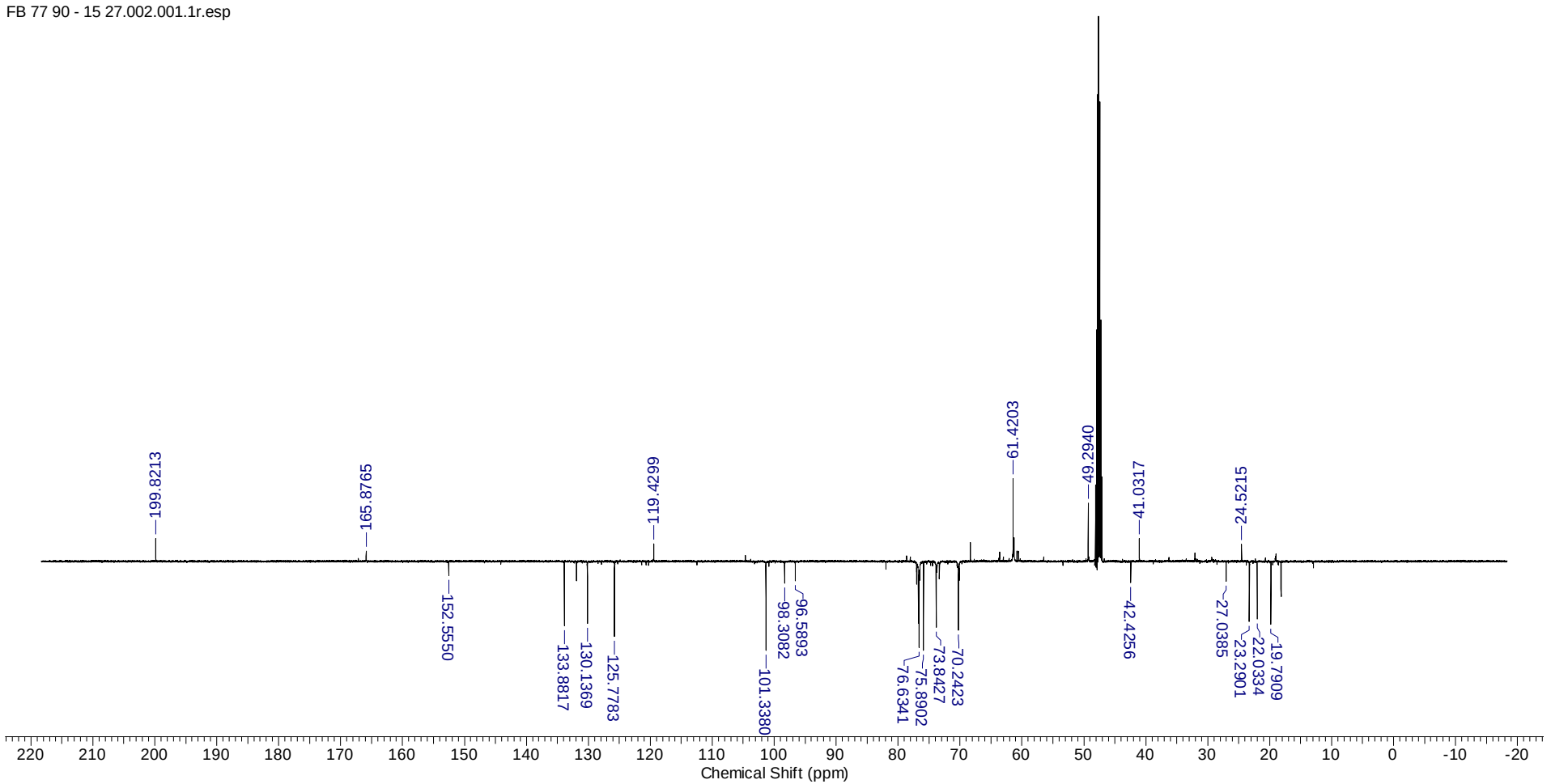


Figure S62. ^{13}C NMR spectrum (125 MHz, CD_3OD) of compound **23**.

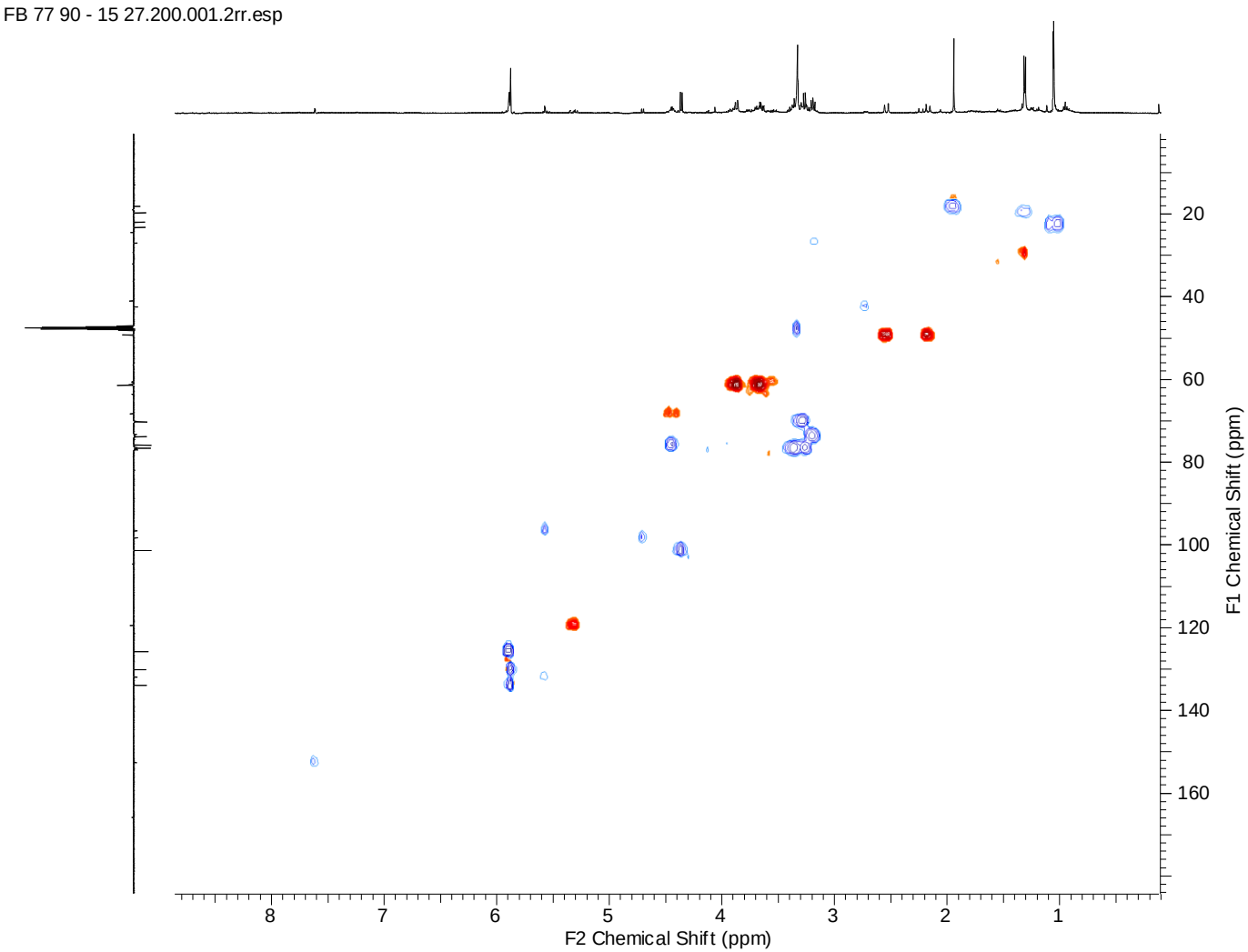


Figure S63. HSQC spectrum of compound **23**.

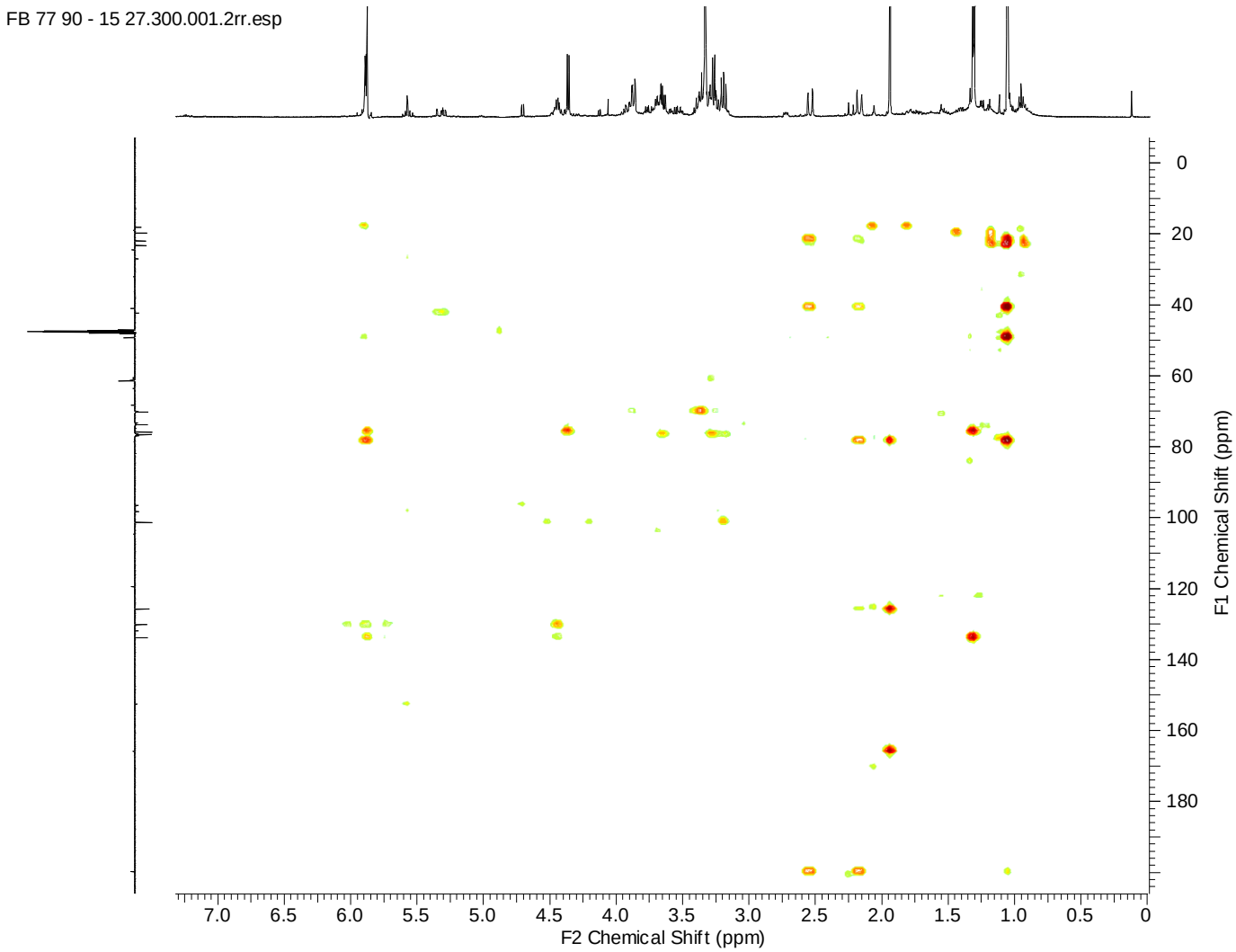


Figure S64. HMBC spectrum of compound **23**.

Compound 24

Table S20. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of **24**, including result 2D experiments (HSQC and HMBC). Chemical shifts δ in ppm and coupling constants in Hz

	24				**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
2	133.37	-	H-3	H-6b; 2H-14	134.9
7	108.96	-	2H-6	H-9	110.4
8	127.31	-		H-10; H-12	128.8
13	136.37	-		H-9; H-11	137.8
16	107.84	-	H-17	2H-14; H-20	109.3
22	165.70	-		H-3; 2H-5; H-17	167.2
CH					
3	53.72	5.09 (*d*, 4.6)	H-14b	2H-5	55.2
9	117.28	7.40 (*d*, 7.7)		H-11	118.8
10	118.78	7.01 (*ddd*, 7.9, 7.7, 0.9)		H-12	120.3
11	121.09	7.10 (*ddd*, 7.7, 8.1, 1.0)		H-9	122.6
12	110.86	7.34 (*d*, 8.1)		H-10	112.4
15	23.54	2.48 (*ddd*, 14.1, 4.4, 2.3)	2H-14; H-20	H-3; H-17; H-21	25.0
17	147.77	7.39 (*d*, 2.3)		H-21	149.3
19	132.97	5.67 (*dt*, 17.1, 10.1)	2H-18; H-20		134.4
20	43.36	2.98 (*dd*, 9.1, 8.8)	H-15; H-19	H-14b; 2H-18	44.8
21	96.67	5.43 (*d*, 1.8)		H-1'; H-17	98.2
CH_2					
5	43.39	4.97 (*dd*, 12.8, 5.5) 3.12 td, 12.8, 4.6)			44.9
6	20.70	2.99 (*t*, 5.5) 2.95 (*m*)			22.2
14	25.93	2.81 (*m*) 2.06 (*td*, 13.9, 6.0)			27.4
18	119.13	5.38 (*dd*, 17.1, 1.6) 5.34 (*dd*, 10.1, 1.9)		H-20	120.8
Glucose					
1'	99.11	4.59 (*d*, 7.9)	H-2'	H-21	100.6
2'	72.92	2.71 (*m*)	H-3'		74.3
3'	76.56	3.27 (*t*, 9.1)	H-2'; H-4'		78.2
4'	69.95	3.20 (*t*, 9.1)	H-5'	H-6'a	71.4
5'	76.83	3.28 (*m*)	H-6'b		78.0
6'	61.20	3.87 (*dd*, 11.8, 2.1) 3.65 (*dd*, 11.8, 5.2)		H-4'	62.7

*Zhang et al. 2001

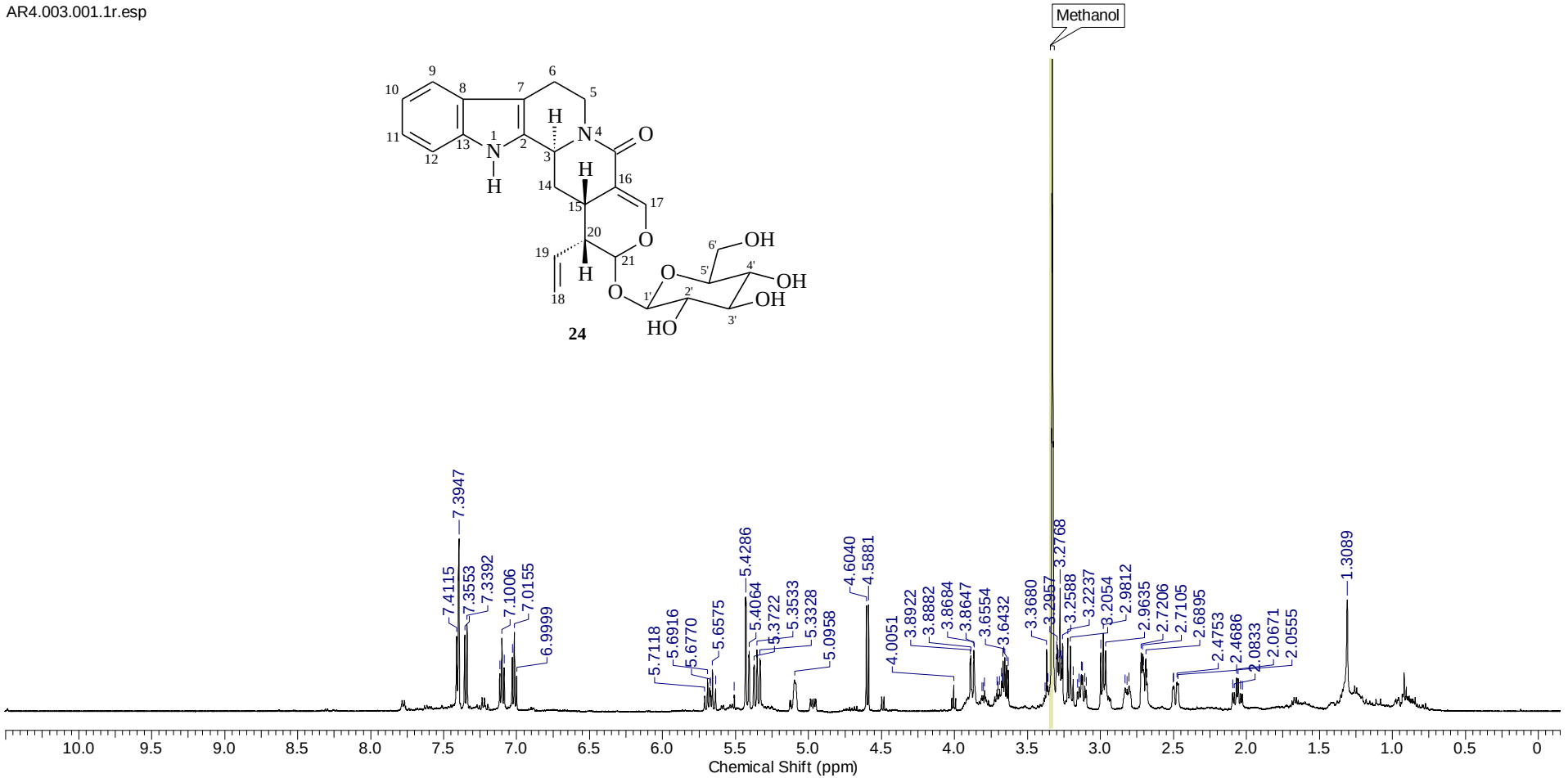


Figure S65. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **24**.

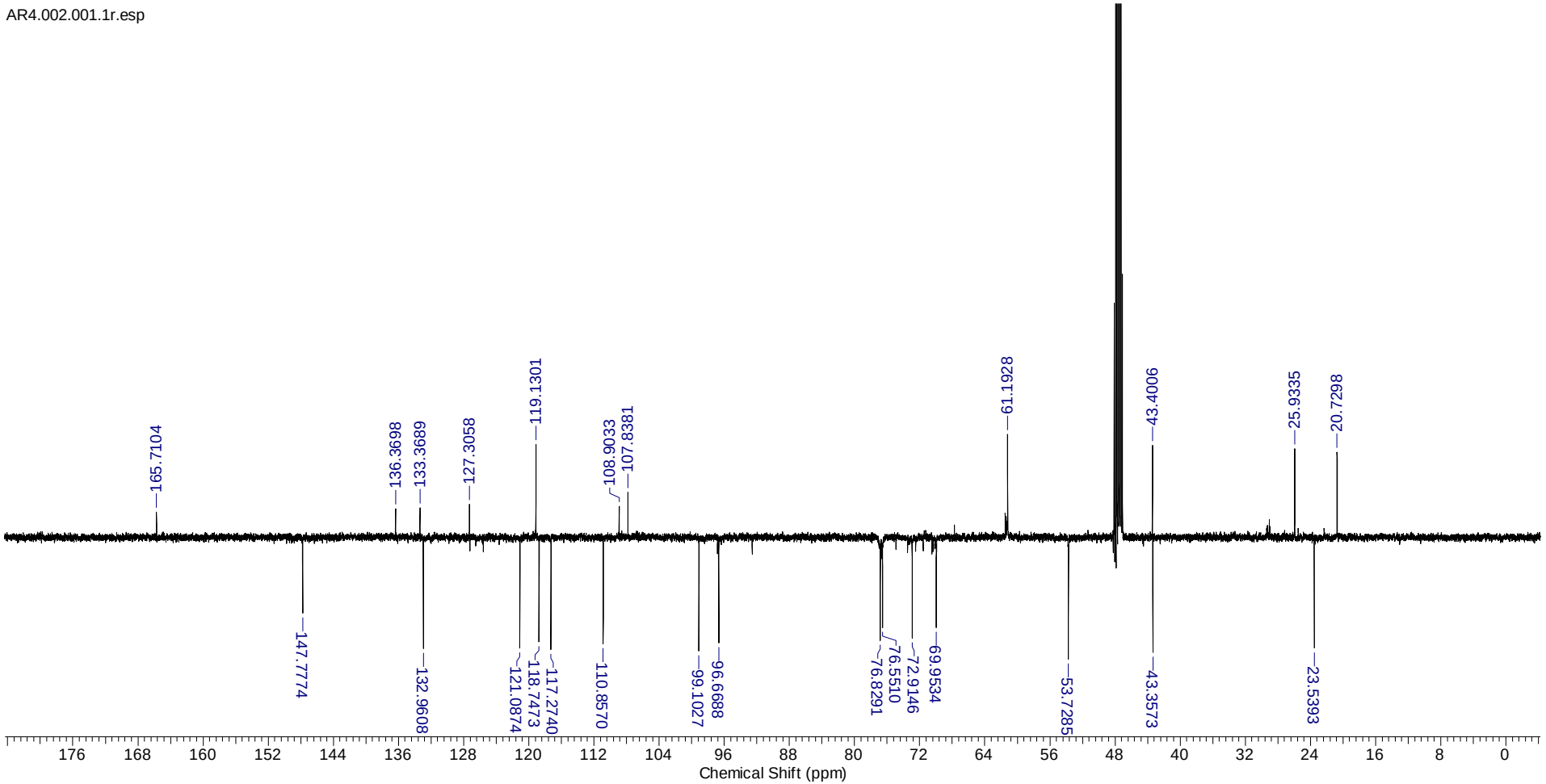


Figure S66. ^{13}C NMR spectrum (125 MHz, CD_3OD) of compound **24**.

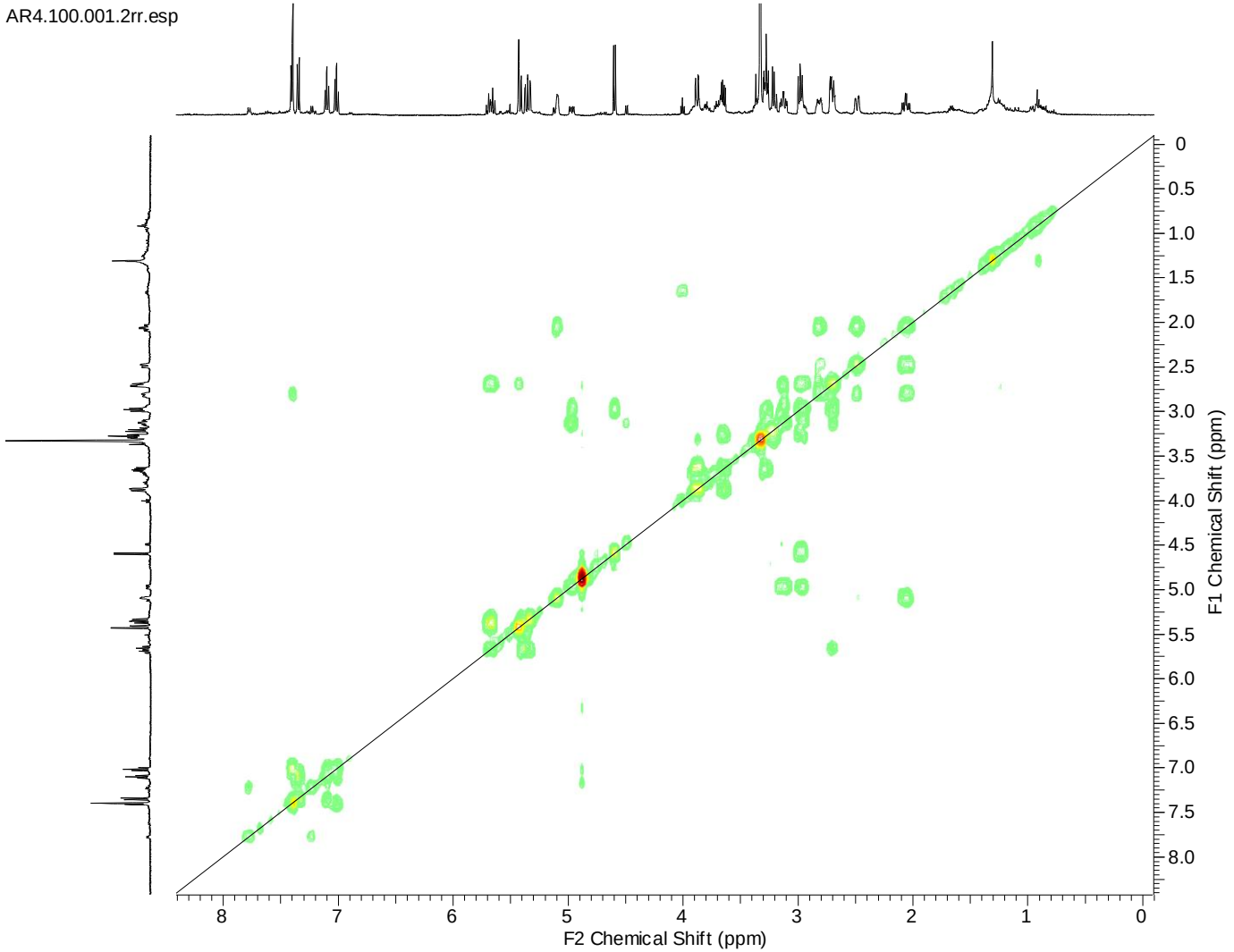


Figure S67. ^{1}H-^{1}H-COSY spectrum of compound **24**.

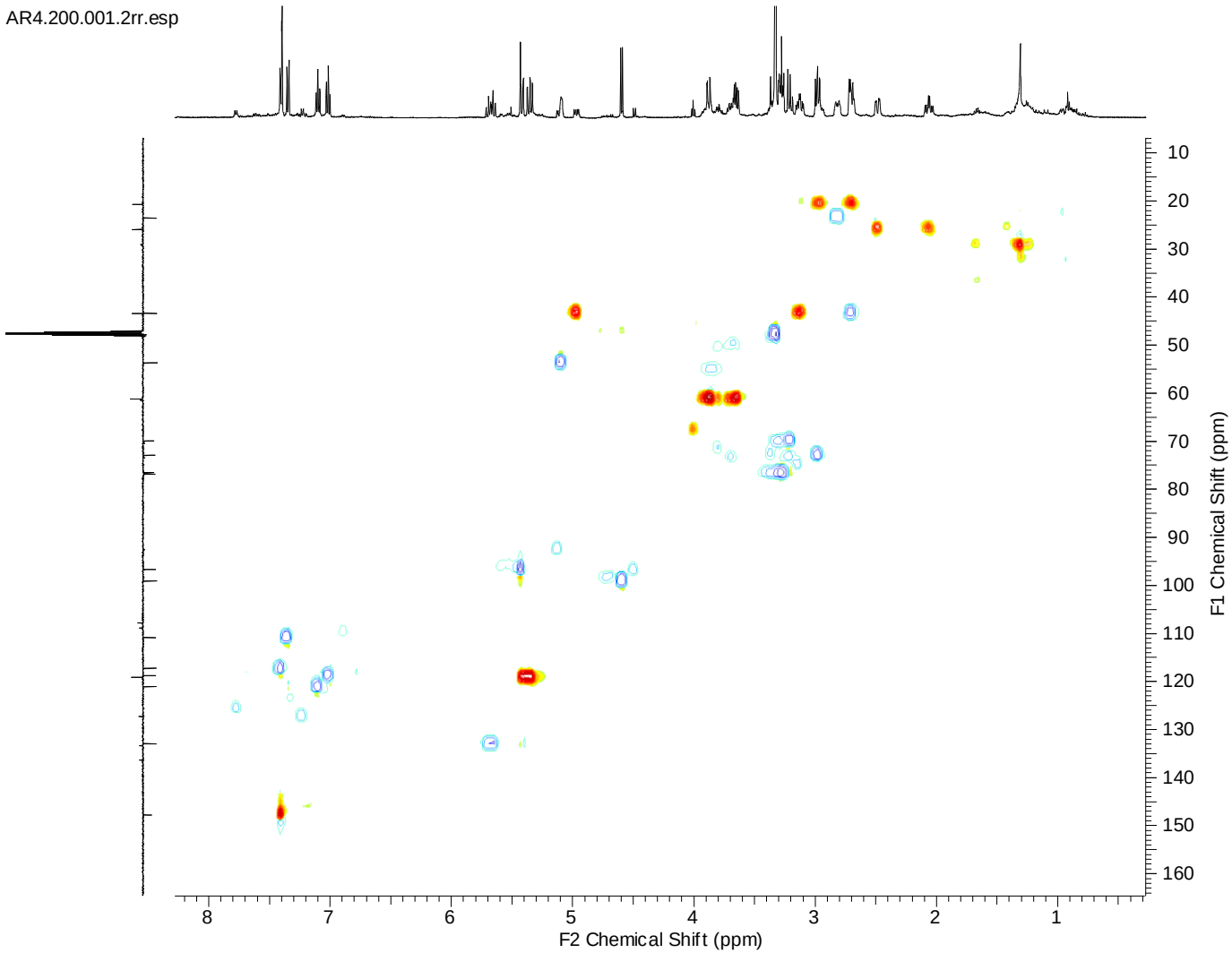


Figure S68. HSQC spectrum of compound **24**.

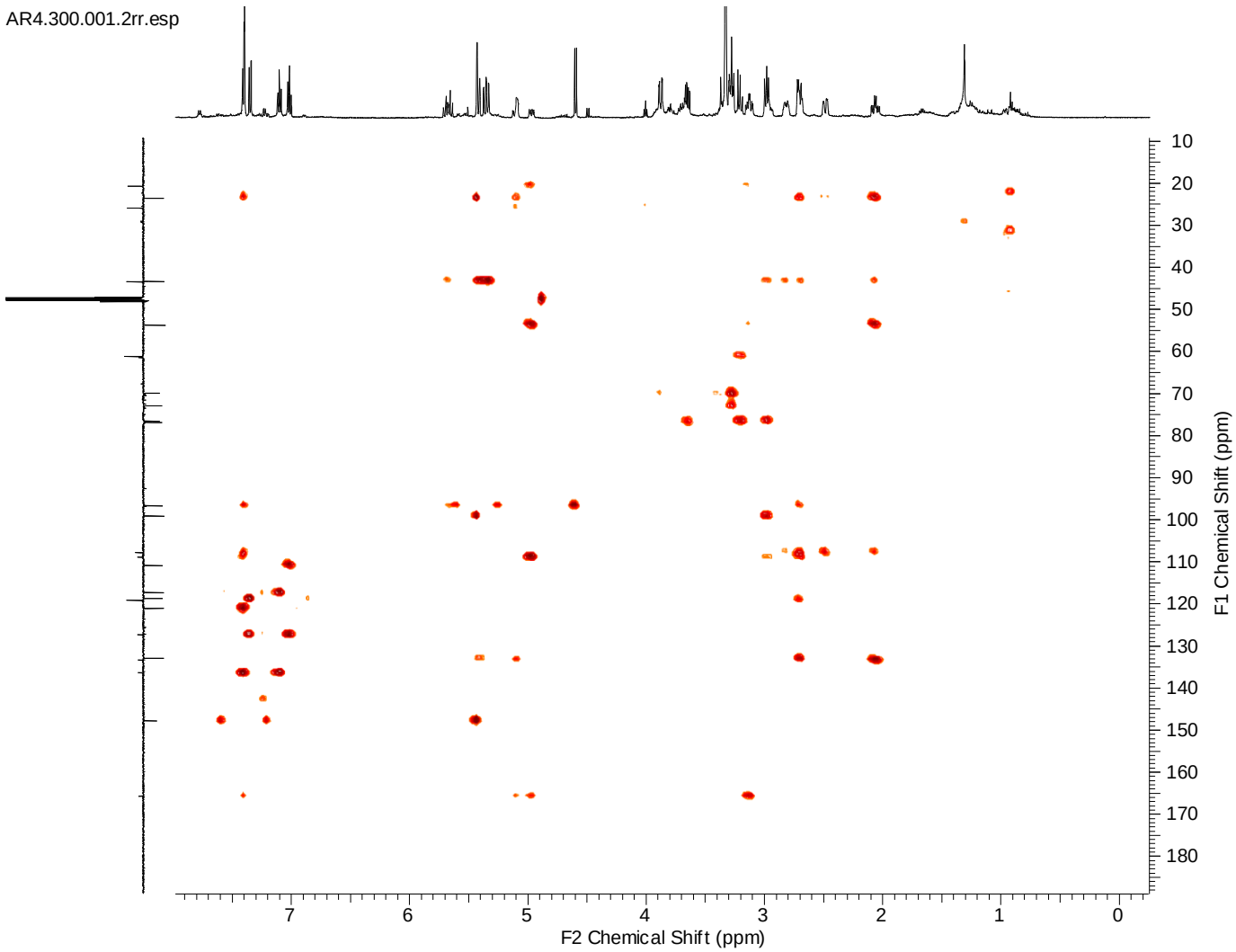


Figure S69. HMBC spectrum of compound **24**.

Compound 25

Table S21. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of **26**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

25					**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
1	161.0	-		1H-3	160.8
4	111.6	-		1H-2	112.1
6	143.3	-		3H-10/1H-8	146.0
7	150.2	-			151.9
9	149.9	-	1H-8	1H-3	151.2
CH					
2	113.6	6.24 (*d*, 9.4)			113.3
3	143.3	7.62 (*dd*, 9.5, 1.8)			144.7
5	107.7	6.84 (*s*)		1H-3	109.9
8	103.3	6.87 (*s*)			103.7
CH_2					
10	56.5	3.92 (*s*)			56.5

*Darmawan et al. 2012.

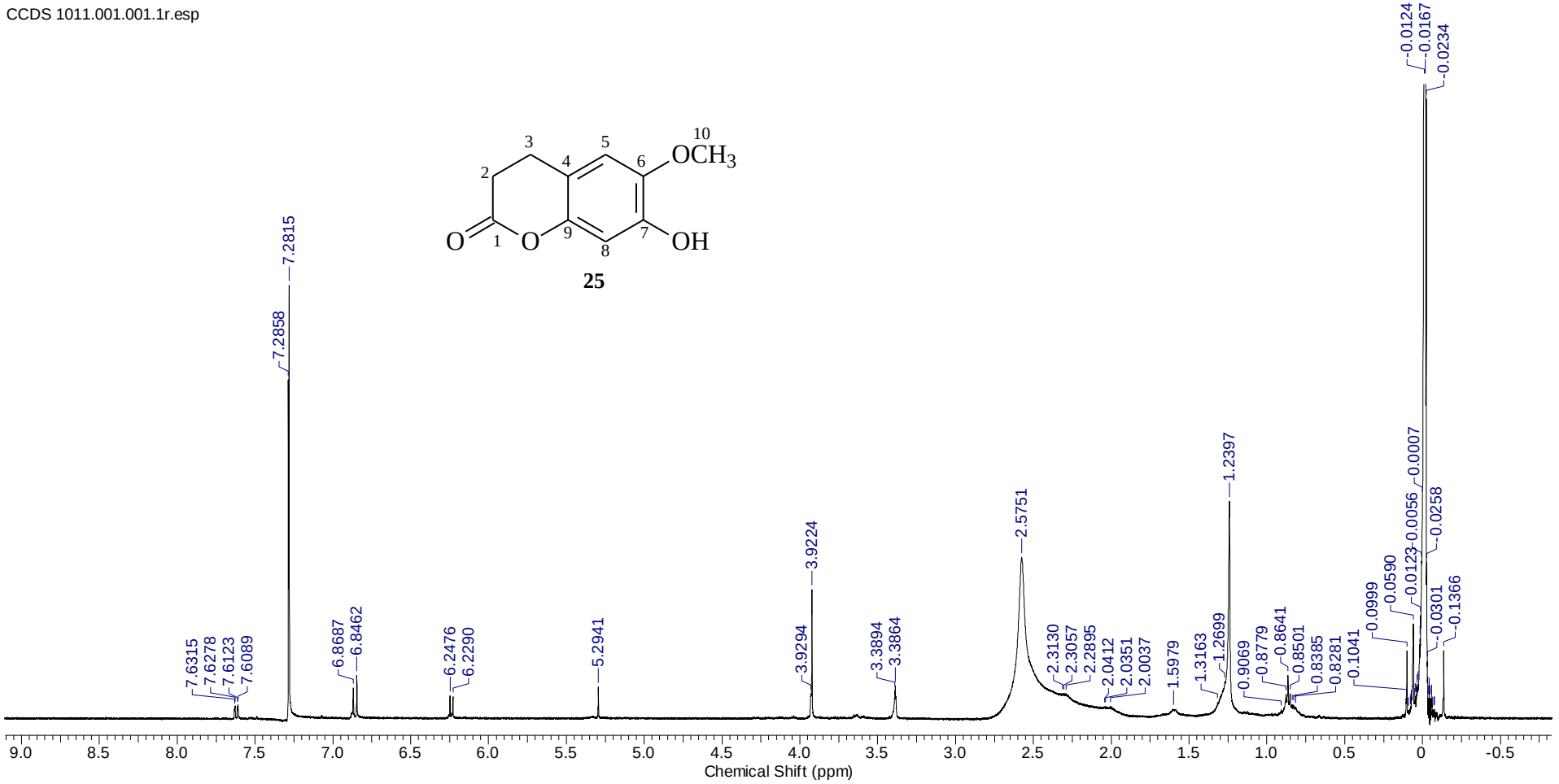


Figure S70. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **25**.

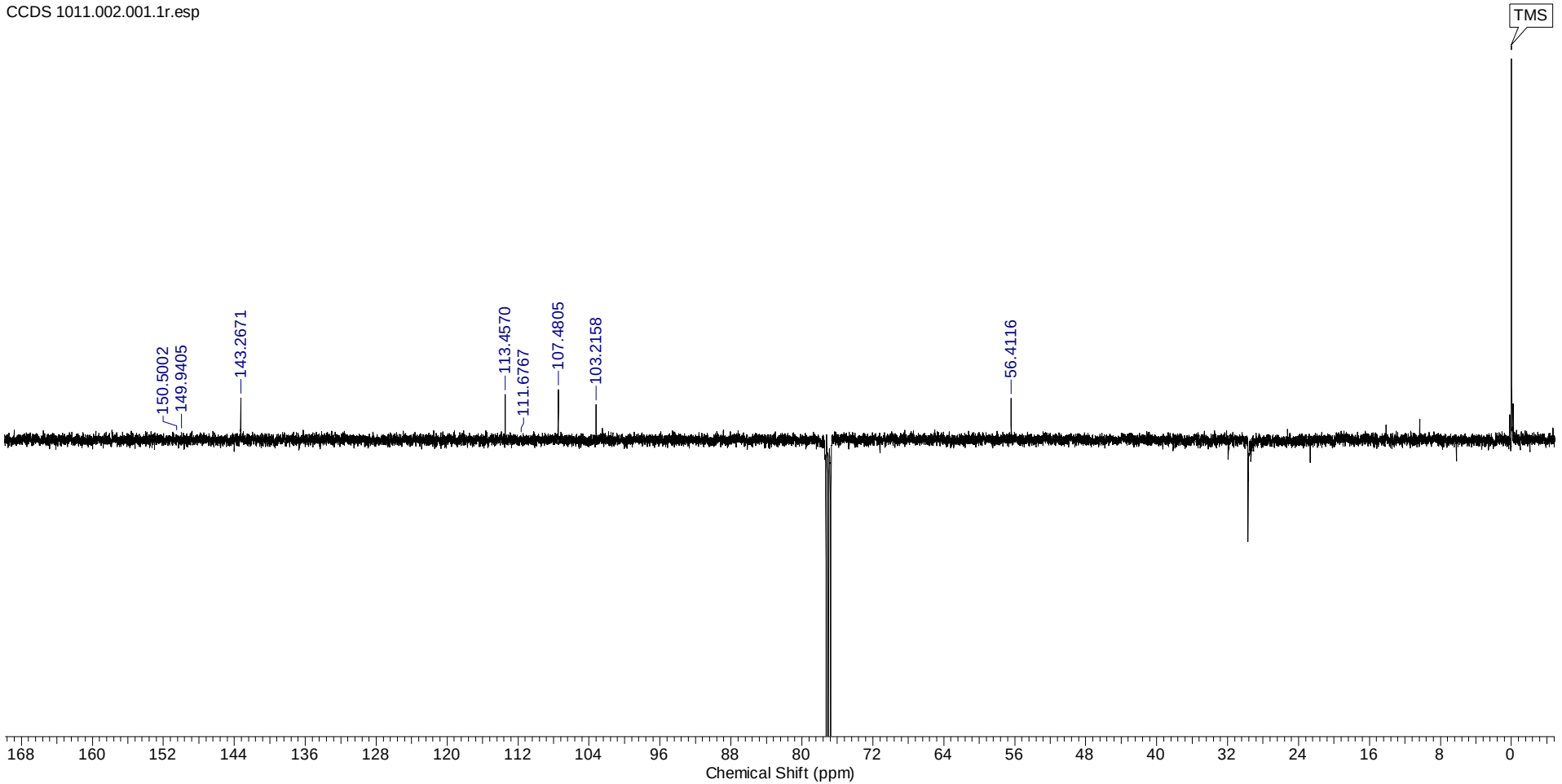


Figure S71. ^{1}H NMR spectrum (125 MHz, $CDCl_3$) of compound **25**.

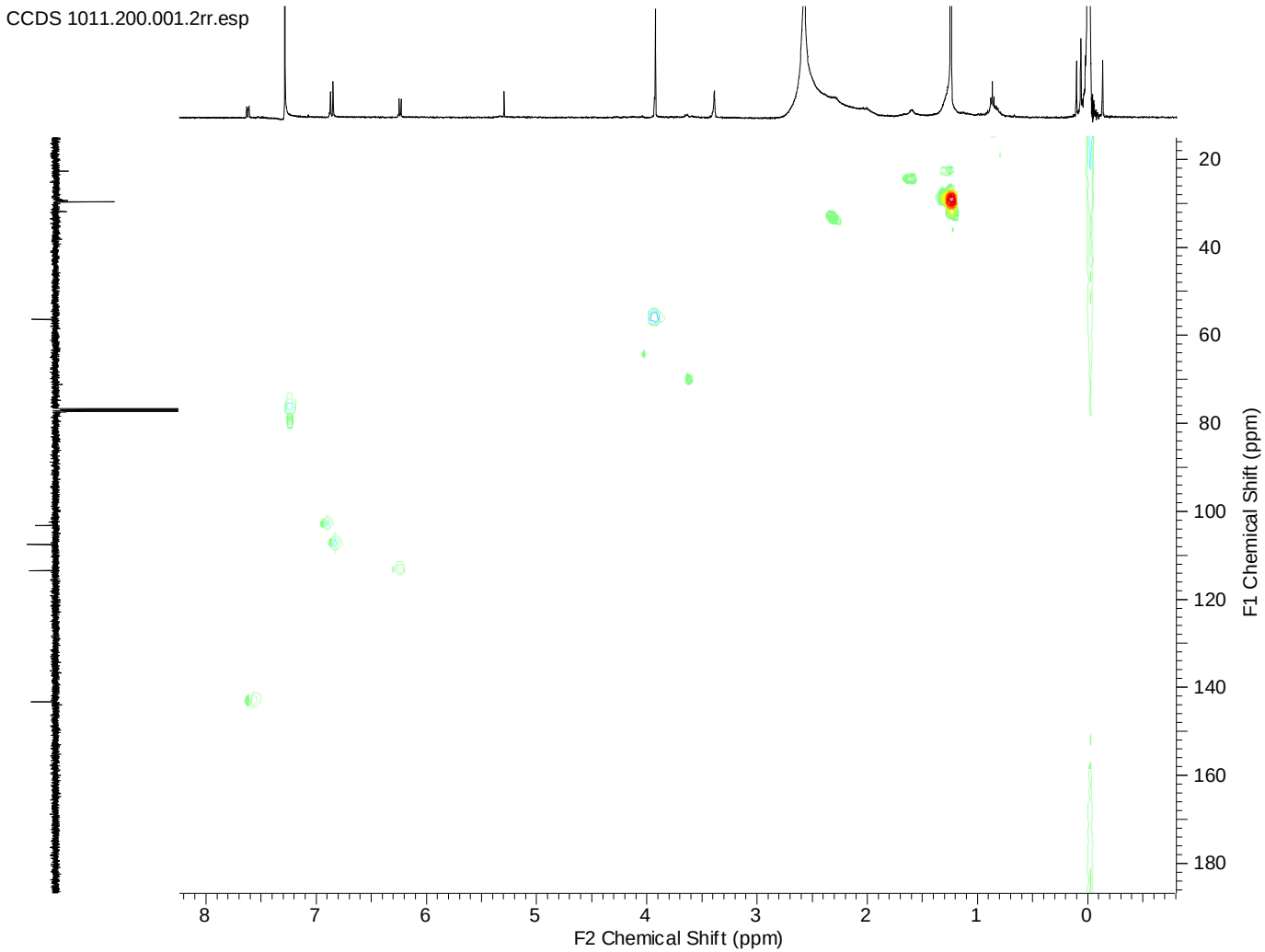


Figure S72. HSQC spectrum of compound **25**.

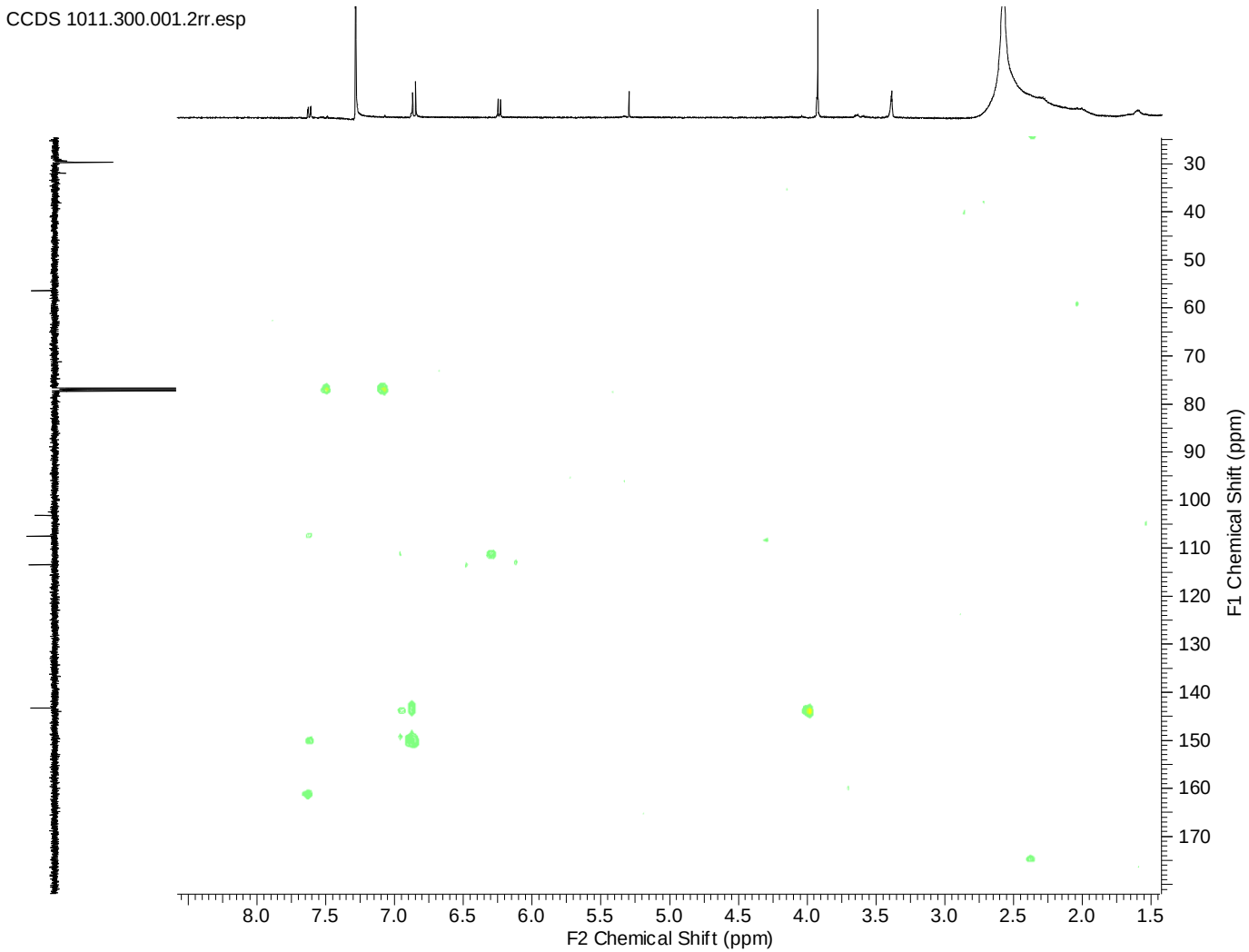


Figure S73. HMBC spectrum of compound **25**.

Compound 26

Table S22. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for **26**, including results of HSQC and HMBC experiments. Chemical shifts δ in ppm and coupling constants in Hz

26					**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
4	43.7	-	2H-24		43.2
8	40.8	-	3H-26		40.4
10	37.6	-	3H-25		37.2
13	139.7	-	H-18		140.0
14	42.6	-	3H-27		42.1
17	48.8	-	H-18		48.4
19	72.5	-	H-18	2H-21; 3H-30	54.7
28	180.4	-		H-18	180.0
CH					
3	80.8	3.61 (*m*)		2H-24	80.3
5	56.1	0.96 (*m*)			56.5
9	48.4	1.80 (*m*)			47.9
12	126.7	5.59 (*m*)		1H-18	127.9
18	54.4	3.04 (*brs*)			54.7
20	42.9	1.49 (*m*)	3H-30		42.4
CH_2					
1	38.2	2.15 (*m*); 2.04 (*m*)			38.8
2	28.2	1.26 (*m*)			28.5
6	19.7	1.65 (*m*); 1.35 (*m*)			19.3
7	34.4	1.58 (*m*); 1.35 (*m*)			34.0
11	27.8	1.97 (*m*)			24.3
15	29.8	1.26 (*m*)			29.1
16	26.9	1.89 (*m*)			26.5
21	27.4	1.52 (*m*); 0.93 (*m*)			27.0
22	39.3	1.32 (*m*)			38.6
24	65.1	4.48 (*d*, 11.0); 3.65 (*m*)			64.6
CH_3					
23	23.3	1.53 (*s*)		2H-24	23.7
25	17.6	0.82 (*s*)			17.2
26	16.6	1.02 (*s*)			16.8
27	24.4	1,71 (*s*)			24.7
29	26.6	1.43 (*s*)			27.2
30	16.5	1.11 (*d*, 6.5)			16.1

*Nakatani et al. 1989.

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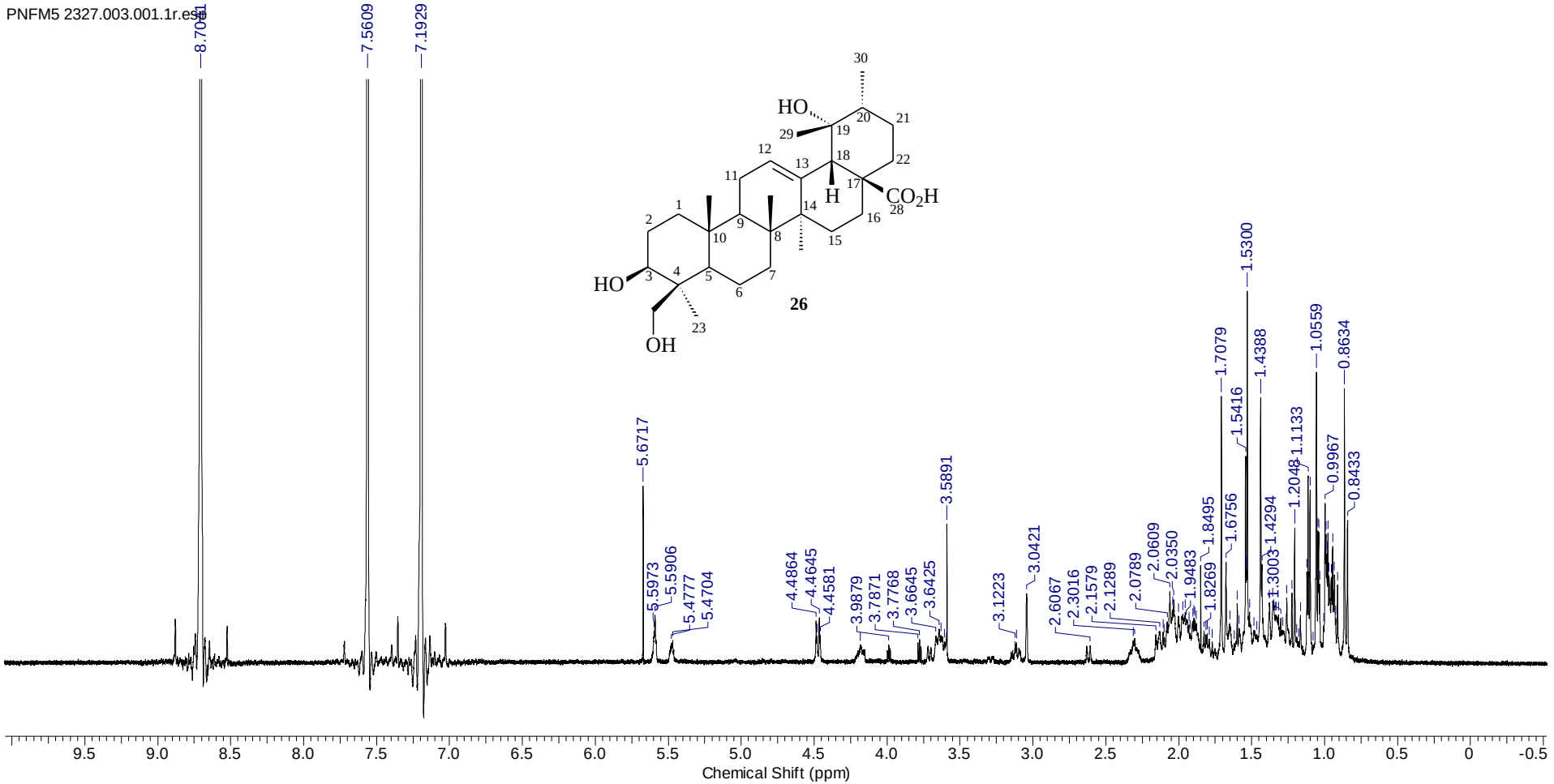

Figure S74. ^{1}H NMR spectrum (500 MHz, Pyridine-d_5) of compound **26**.

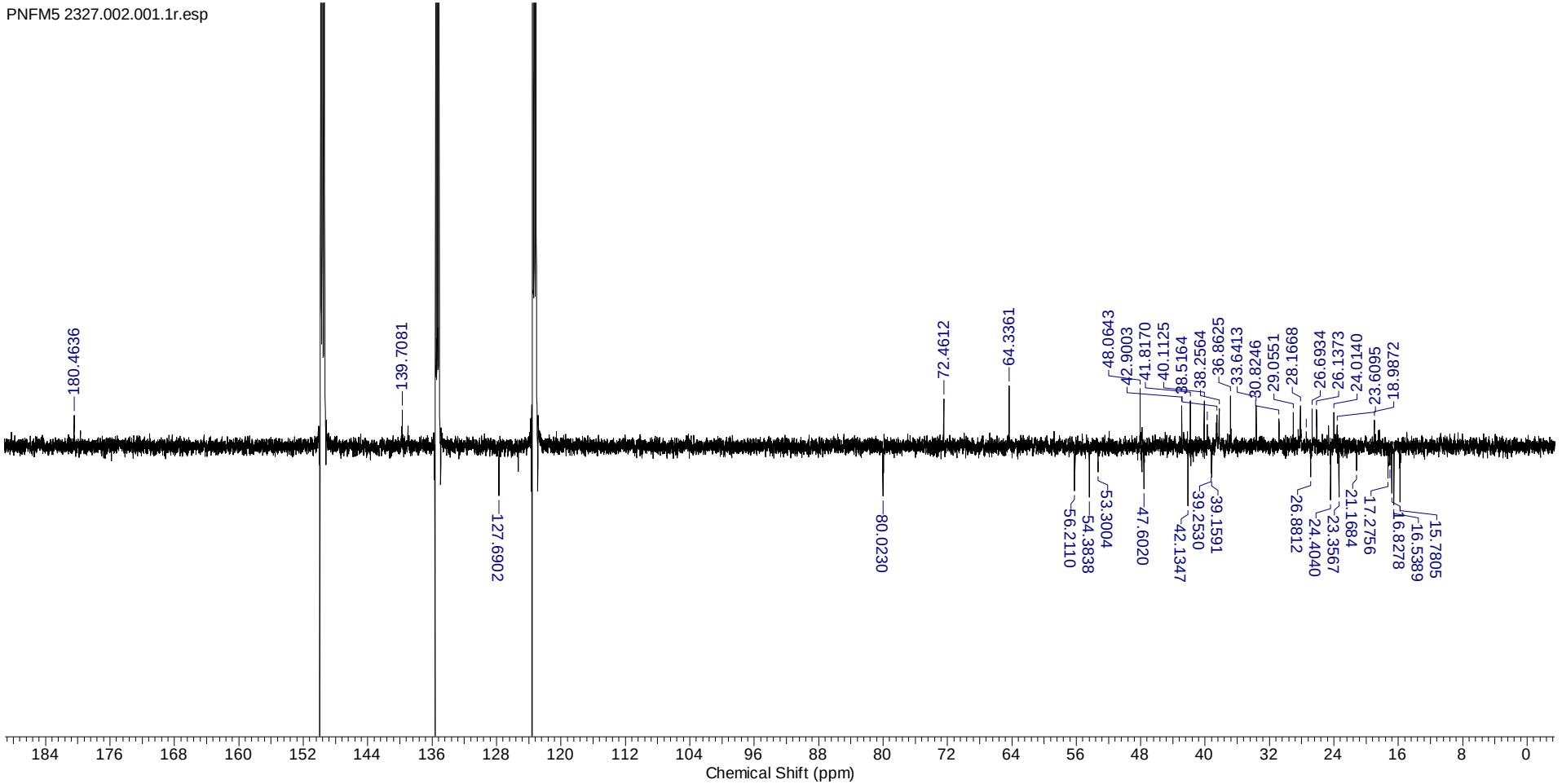

Figure S75. ^{13}C NMR spectrum (125 MHz, Pyridine-d_5) of compound **26**.

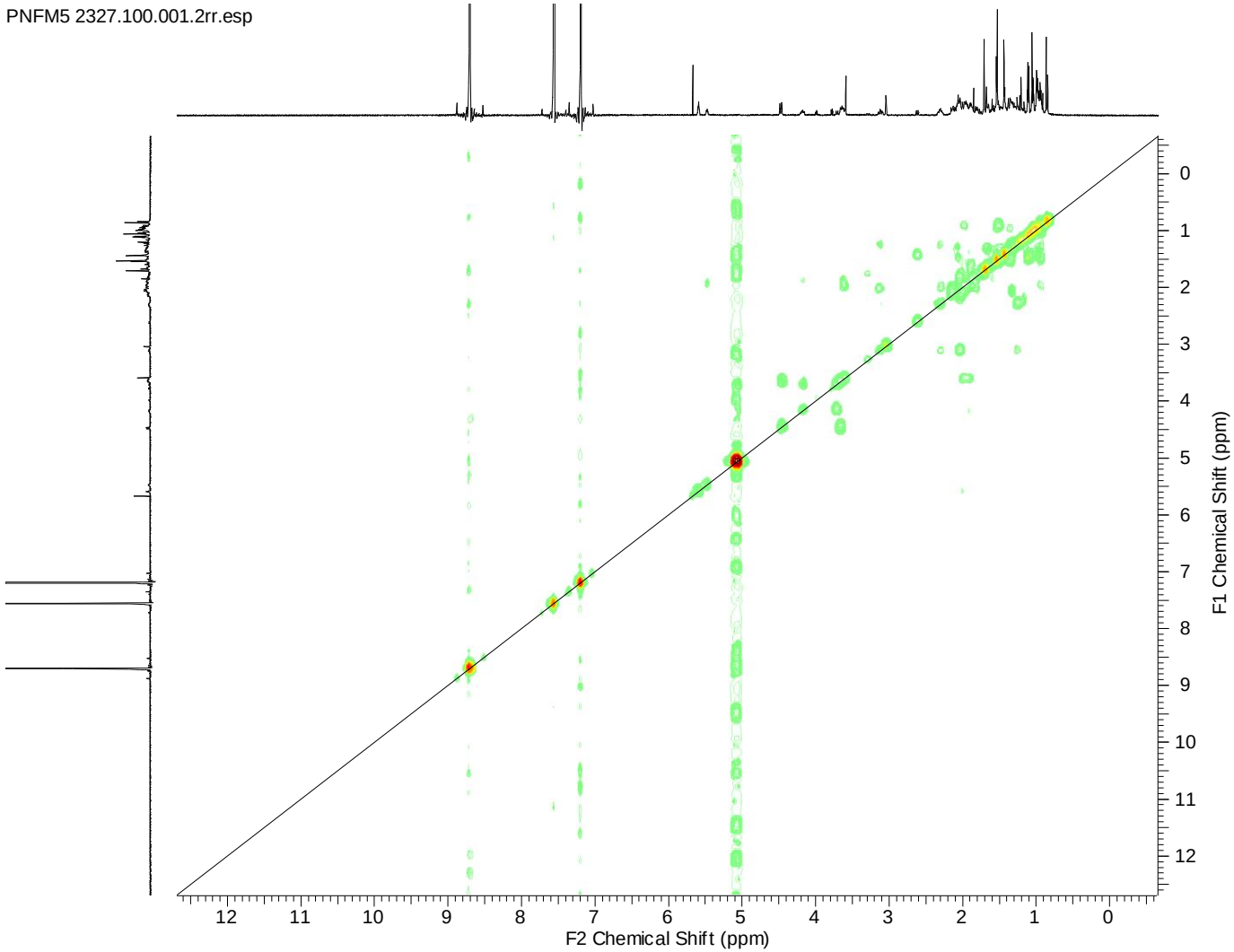

Figure S76. ^{1}H-^{1}H-COSY spectrum of compound **26**.

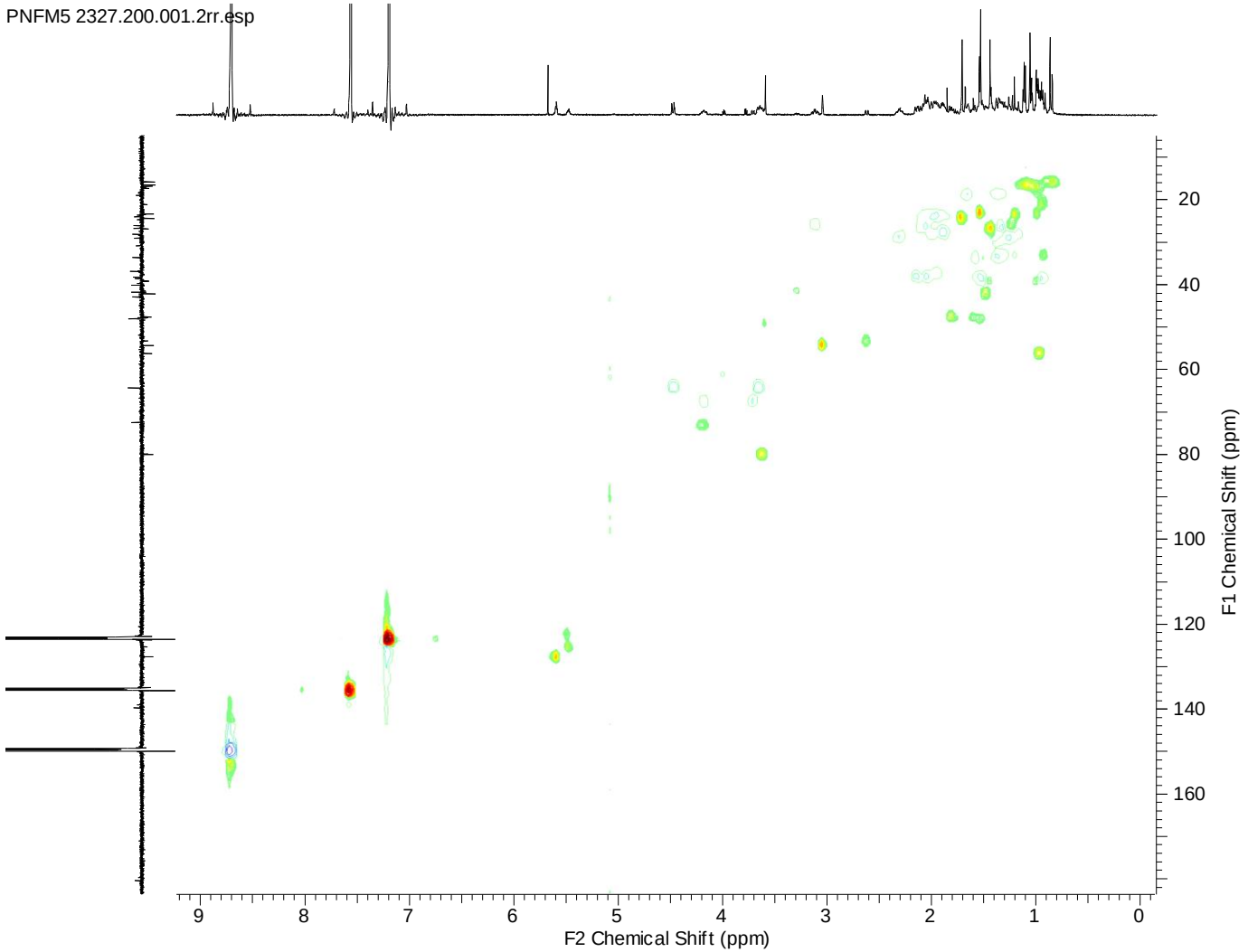

Figure S77. HSQC spectrum of compound **26**.

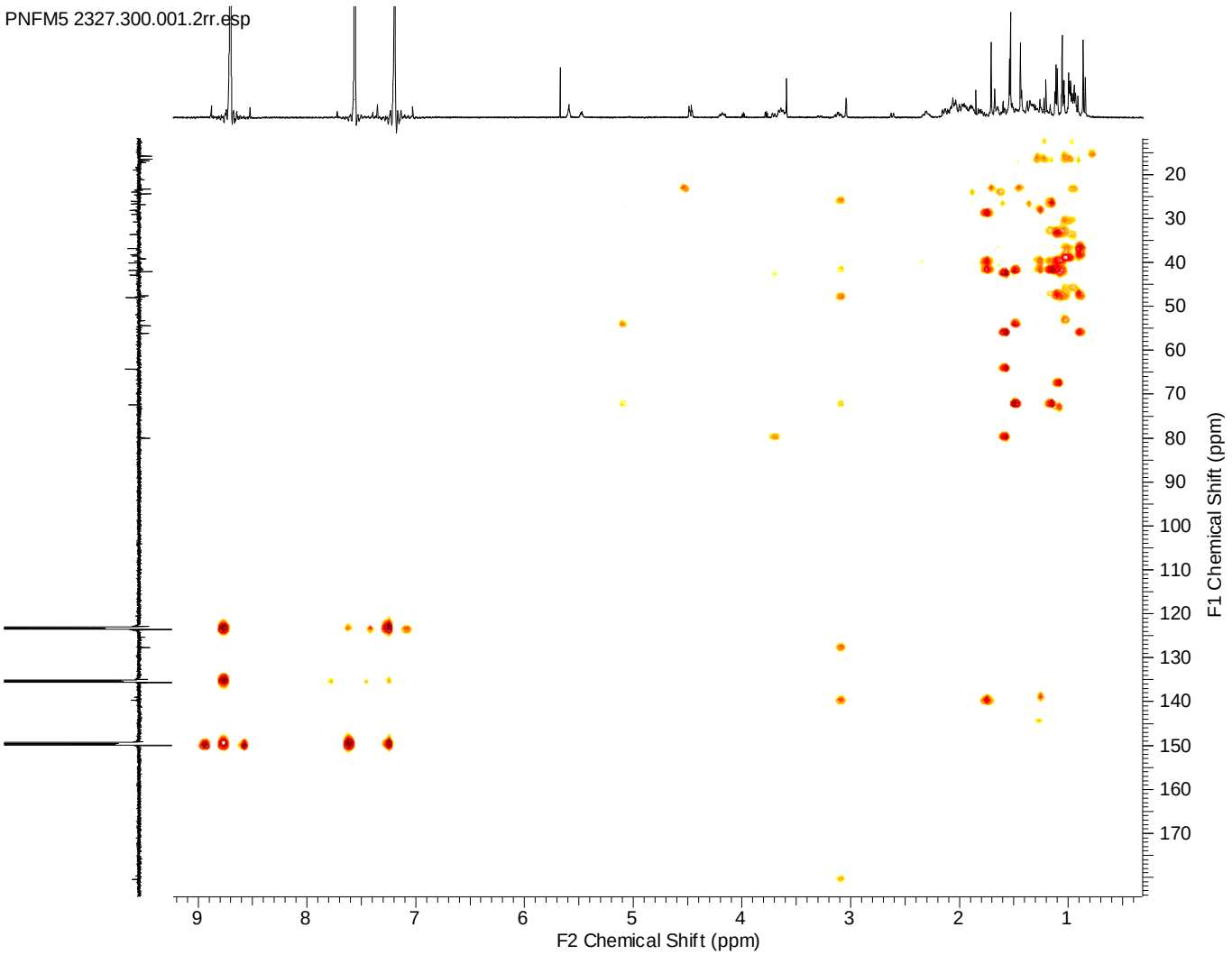

Figure S78. HMBC spectrum of compound **26**.

Compound 27

Table S23. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **27**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

27					**Literature***
	HSQC		HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
2	128.8	-	H-3	2H-14	133.2
7	105.7	-		H-9	107.7
8	126.0	-			127.9
13	136.8	-	H-12	H-9	137.9
16	107.6	-	H-17		109.9
22	170.0	-		H-17;Me-O-22	170.6
CH					
3	51.6	3.81 (*s*)			52.4
9	117.7	7.48 (*d*, 7.9)			118.8
10	119.7	7.08 (*t*, 7.6)			120.1
11	122.1	7.16 (*d*, 7.7)			122.7
12	110.9	7.34 (*d*, 8.0)			112.0
15	31.0	3.10 (*m*)	2H-14	H-17;1H-19	32.5
17	155,5	7.83 (*s*)			165.1
19	134,0	5.86 (*m*)	H-20	H-21	135.7
20	44.0	2.77 (*m*)			45.6
21	95.9	5.86 (*m*)		H-17;1H-19	97.5
CH_2					
5	41.3	3.75 (*m*); 3.48 (*m*)			42.9
6	18.1	3.10 (*m*)	1H-5		21.0
14	33.4	2.37 (*m*)			35.9
18	118,4	2.25 (*m*)			119.5
CH_3					
Me-O-22	51.2	3.82 (*s*)			52.4
Glucose					
1’	99,0	4.82 (*d*, 8.2)	H-2	H-3	100.3
2’	77,4	3.39 (*m*)	H-3		78.6
3’	76,6	3.42 (*m*)	H-4		78.0
4’	73,2	3.23 (*m*)			74.6
5’	70,3	3.25 (*m*)	2H-6		71.7
6’	61,6	4.0 (*dd*, 11.8, 1.9); 3.66 (*dd*, 11.8, 7.1)	H-5		62.9

*Patthy-Lukáts et al. 1997.

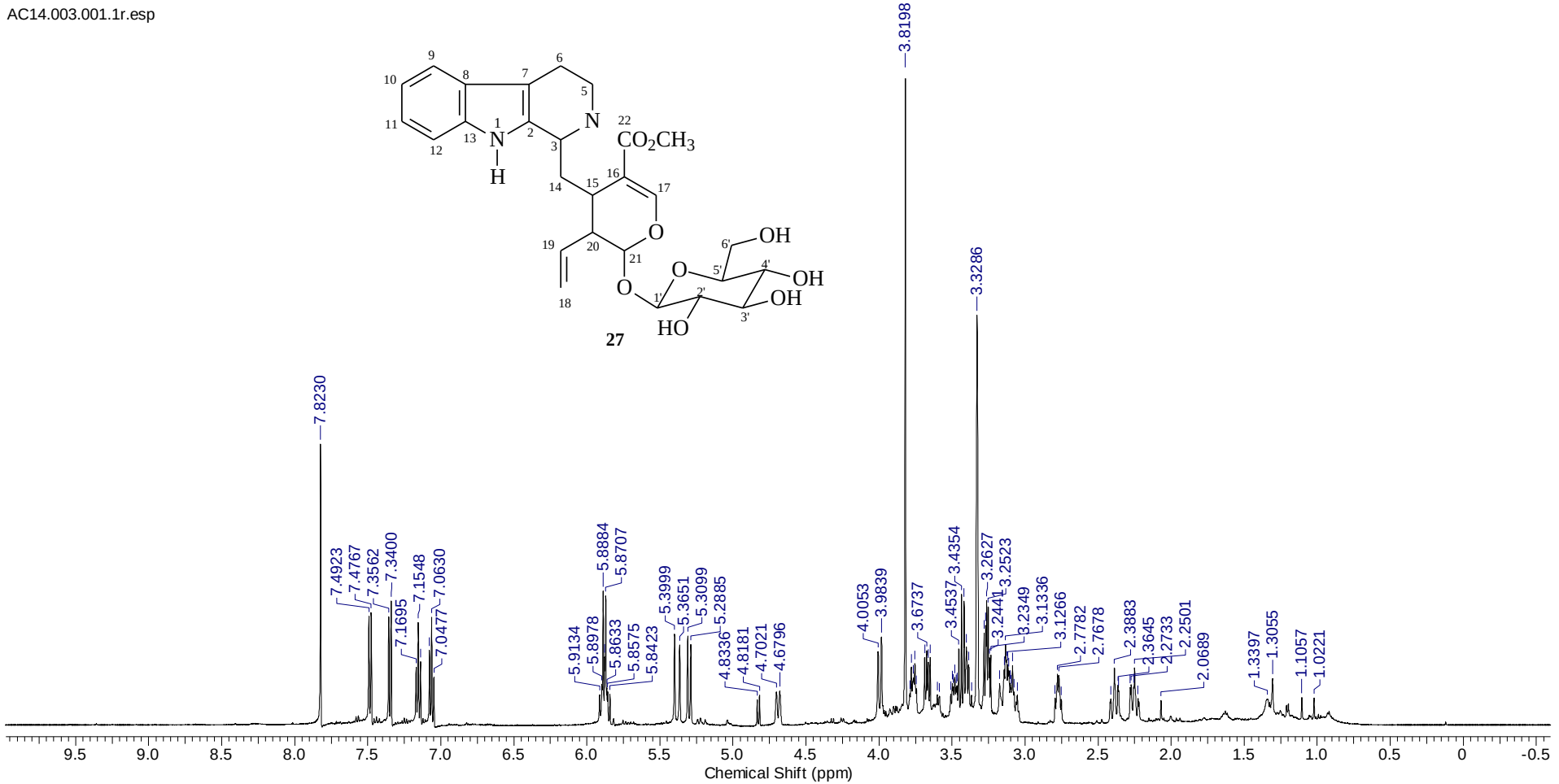

Figure S79. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **27**.

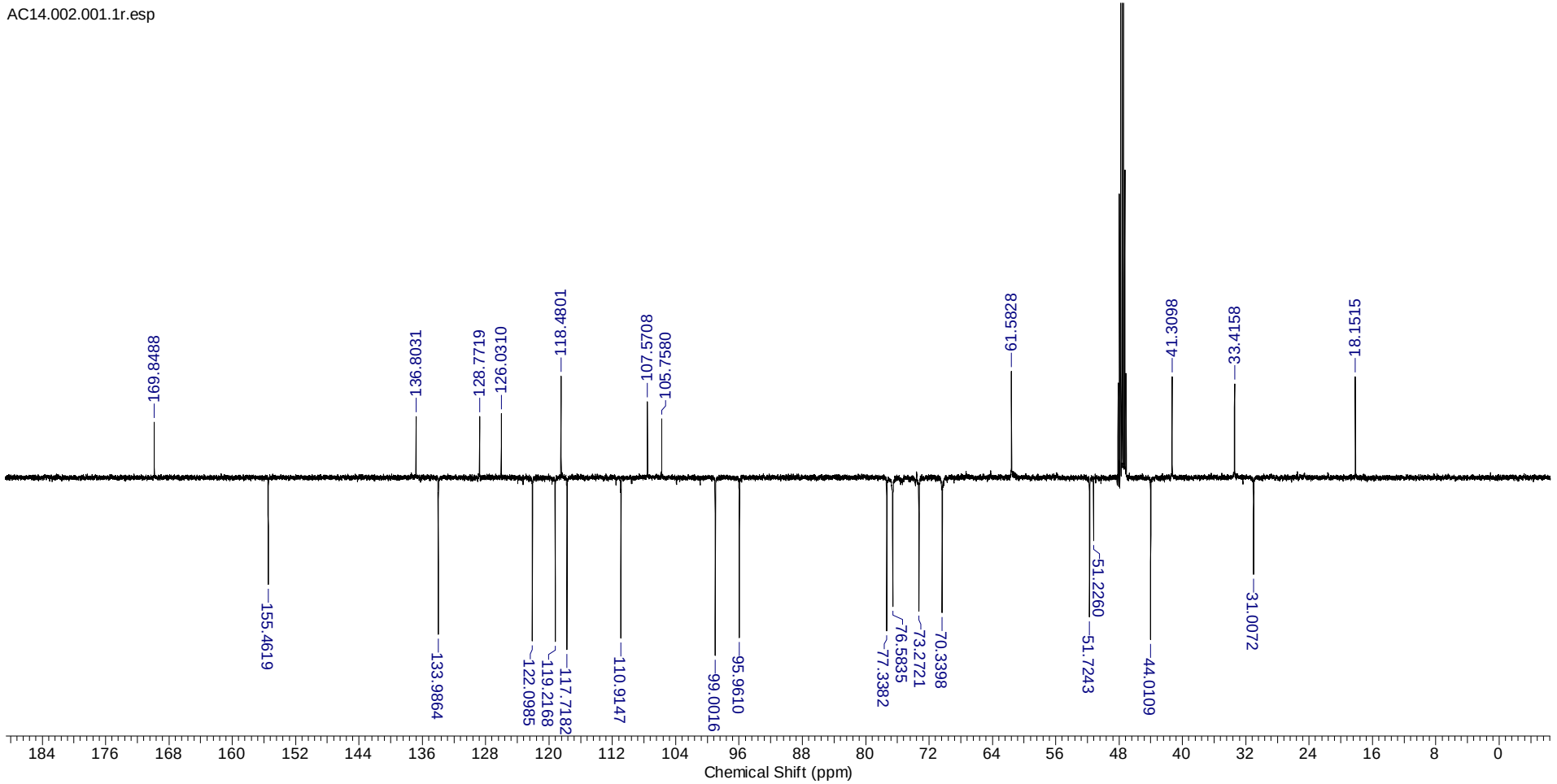

Figure S80. ^{13}C NMR spectrum (125 MHz, CD_3OD) of compound **27**.

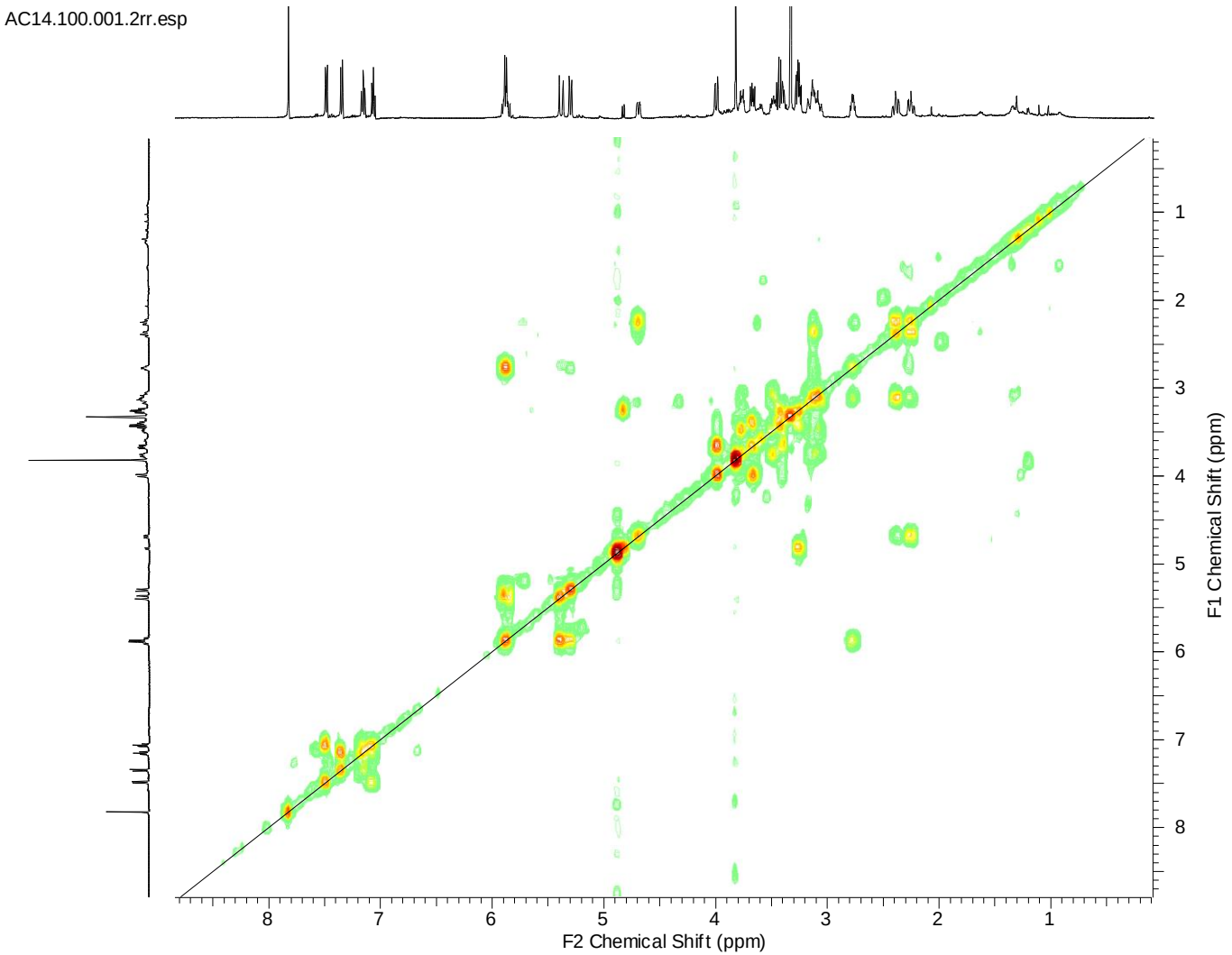

Figure S81. ^{1}H-^{1}H-COSY spectrum of compound **27**.

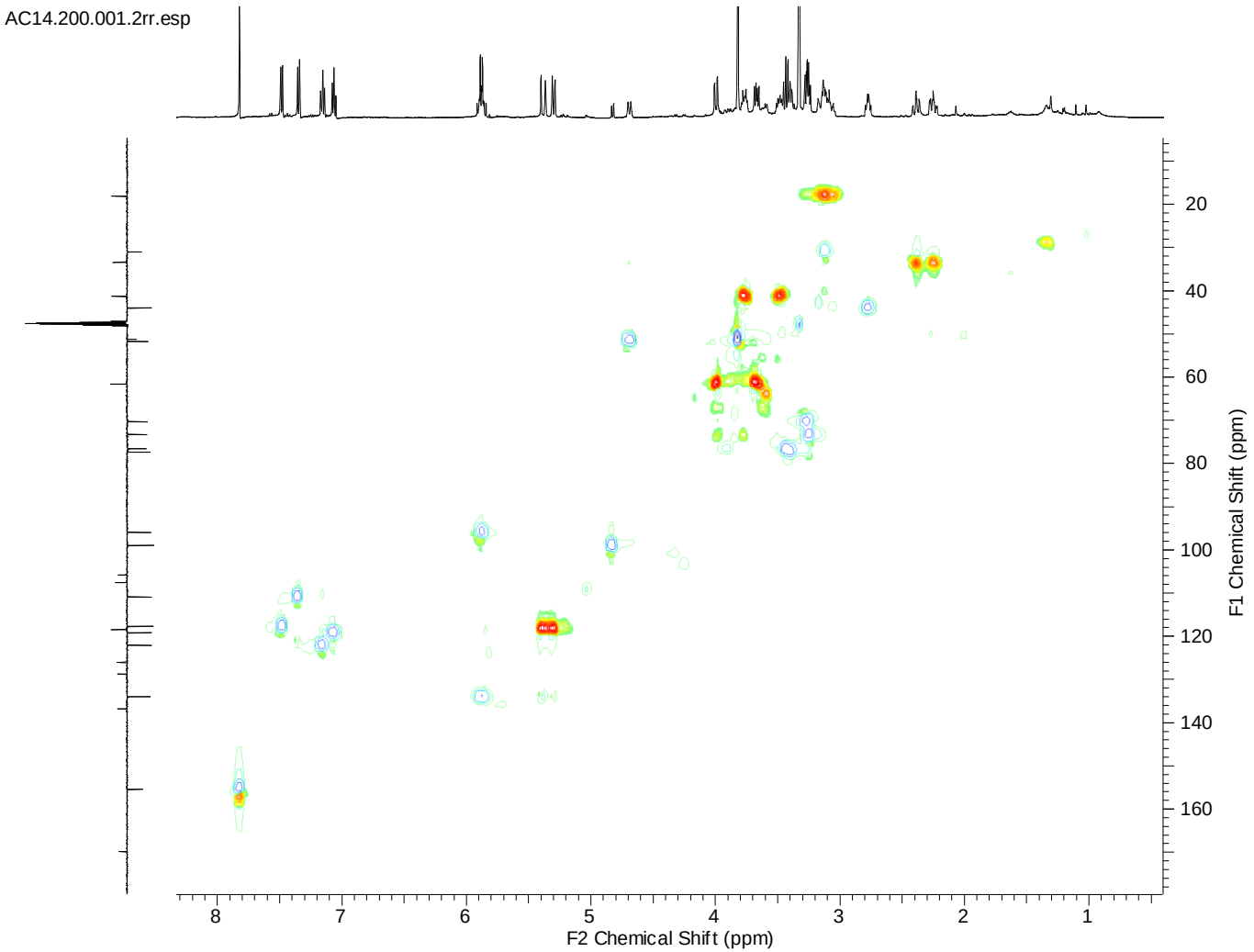

Figure S82. HSQC spectrum of compound **27**.

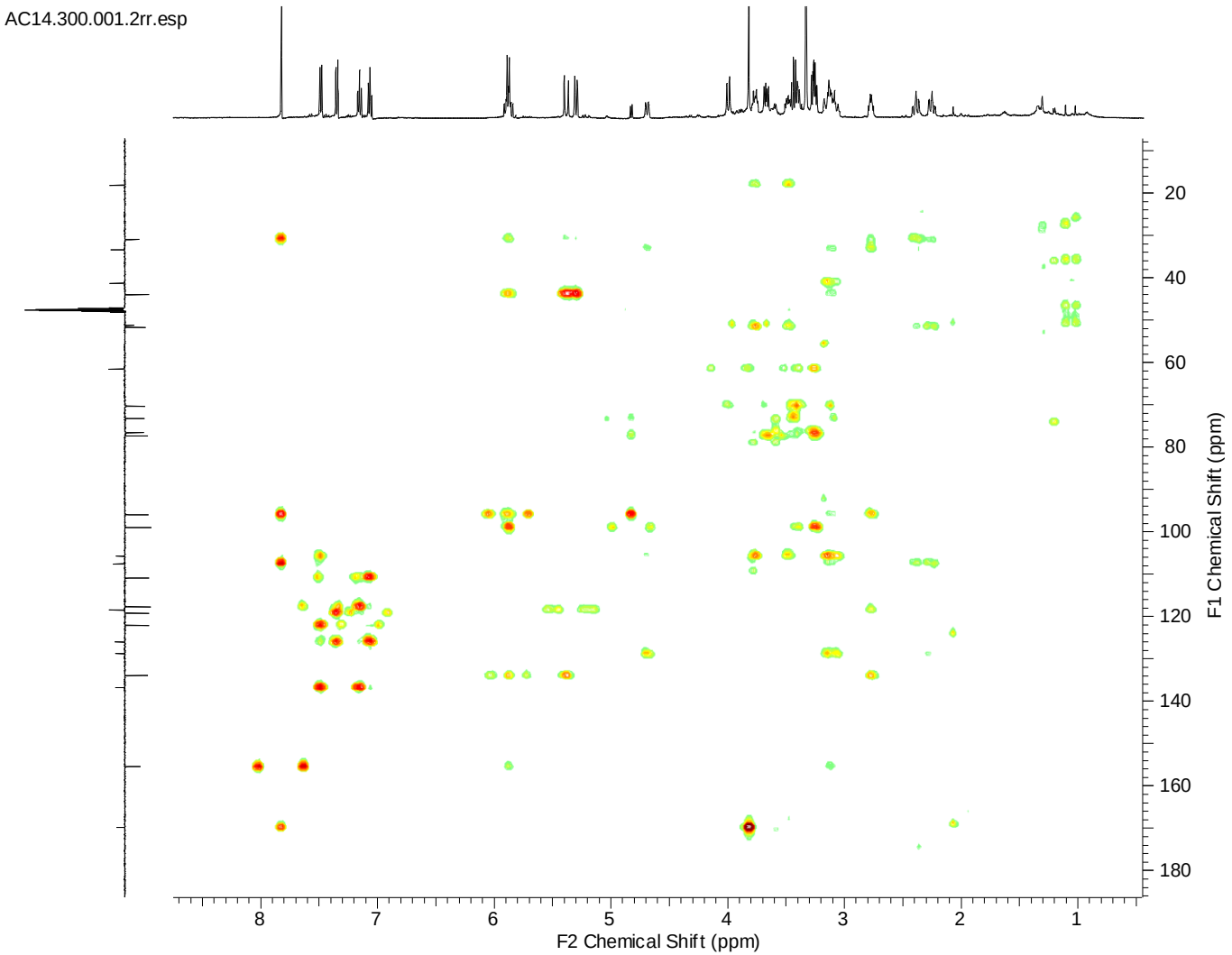

Figure S83. HMBC spectrum of compound **27**.

Compound 28

Table S24. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compound **28**, including results of HSQC and HMBC experiments. Chemical shifts δ are given in ppm and coupling constants in Hz

	28				**Literature***
		HSQC	HMBC		
C	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	δ_C
2	129.0	-	H-3	2H-6	133.2
7	106.9	-	2H-6	HN-1; H-9	109.0
8	126.1	-		HN-1; H-10; H-12	128.0
13	137.1	-		H-9; H-11	138.4
16	107.2	-	H-17	2H-14	109.9
22	170.4	-		H-17; MeO-22	170.9
23	172.2	-		H-5	176.5
CH					
3	51.7	4.62 (*d*, 11.7)	2H-14	H-5	53.2
5	58.3	3.94 (*dd*, 12.0, 5.0)	2H-6		60.1
9	117.7	7.48 (*d*, 7.0)		H-11	118.8
10	119.2	7.05 (*t*, 7.0)		H-12	120.1
11	122.0	7.14 (*t*, 7.0)		H-9	122.6
12	110.9	7.33 (*d*, 7.0)	H-11	H-10	112.1
15	31.6	3.11 (*m*)	2H-14; H-20	H-17; H-19; H-21	32.4
17	155.8	7.84 (*s*)		H-21	156.1
19	133.8	5.87 (*ddd*, 17.4, 10.7, 7.5)	H-18; H-20	H-21	135.2
20	43.8	2.79 (*m*)	H-19; H-21	H-18	45.7
21	96.0	5.94 (*d*, 9.2)	H-20	H-15; H-17; H-1’	97.6
CH_2					
6	22.7	3.45 (*m*), 3.05 (*m*)	H-5		25.2
14	33.3	2.46 (*m*), 2.25 (*m*)	H-3		35.6
18	118.4	5.39 (*d*, 17.7); 5.27 (d, 10.7)		H-20	119.6
CH_3					
Me-O-22	51.4	3.85 (*s*)			
Glucose					
1’	99.0	4.85 (*d*, 8.0)	H-2’	H-21	100.5
2’	73.2	3.27 (*dd*, 9.1, 8.0)	H-3’		74.7
3’	77.4	3.43 (*t*, 9.1)	H-2’; H-4’		78.0
4’	70.4	3.28 (*t*, 9.1)	H-3’; H-5’		71.9
5’	76.5	3.38 (*m*)	H-6’b		78.6
6’	61.7	4.04 (*dd*, 11.8, 1.8) 3.70 (*dd*, 11.8, 7.0)	H-5’	H-4’	63.1

Ferrari et al. 1986.

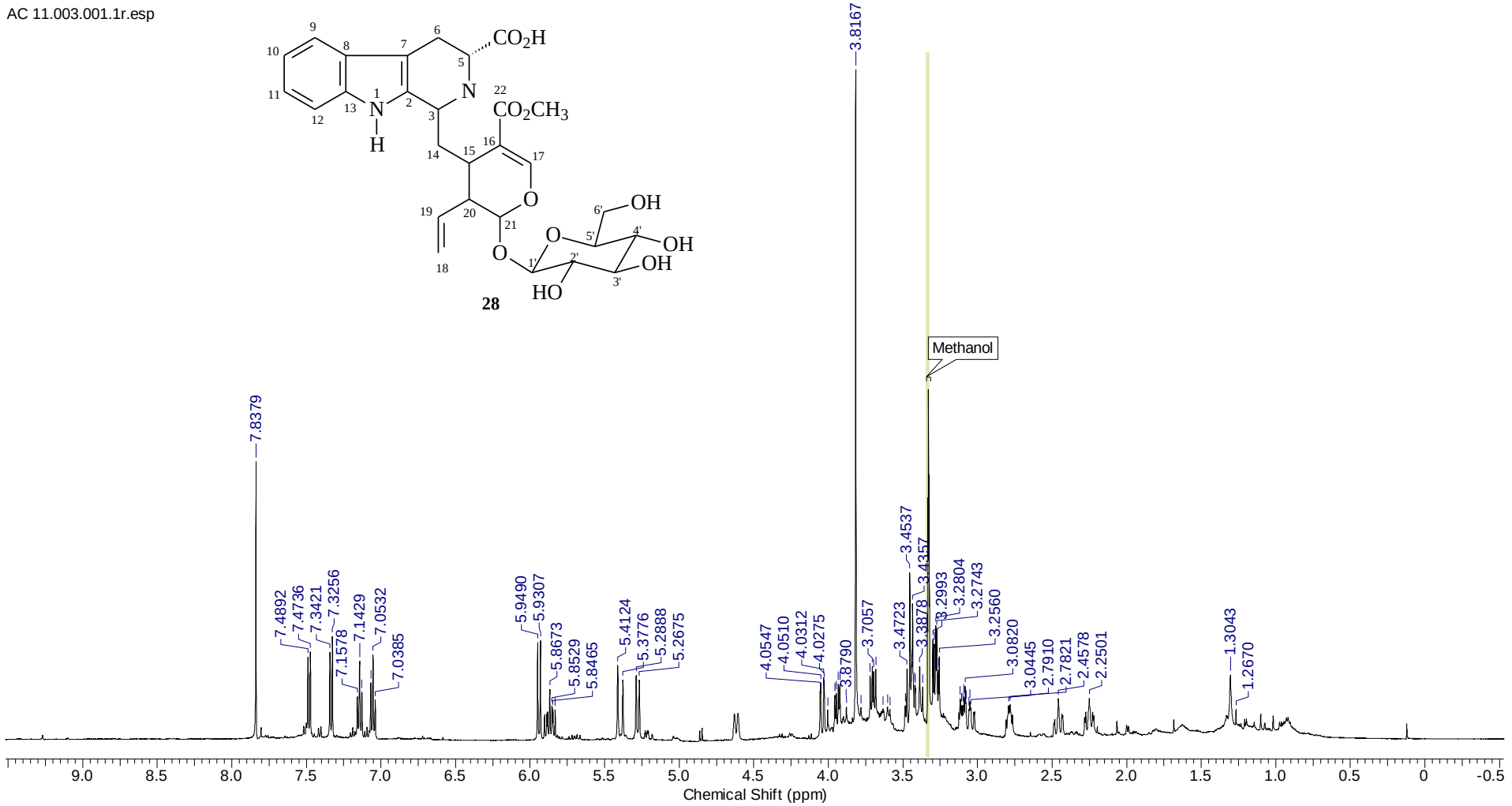

Figure S84. ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **28**.

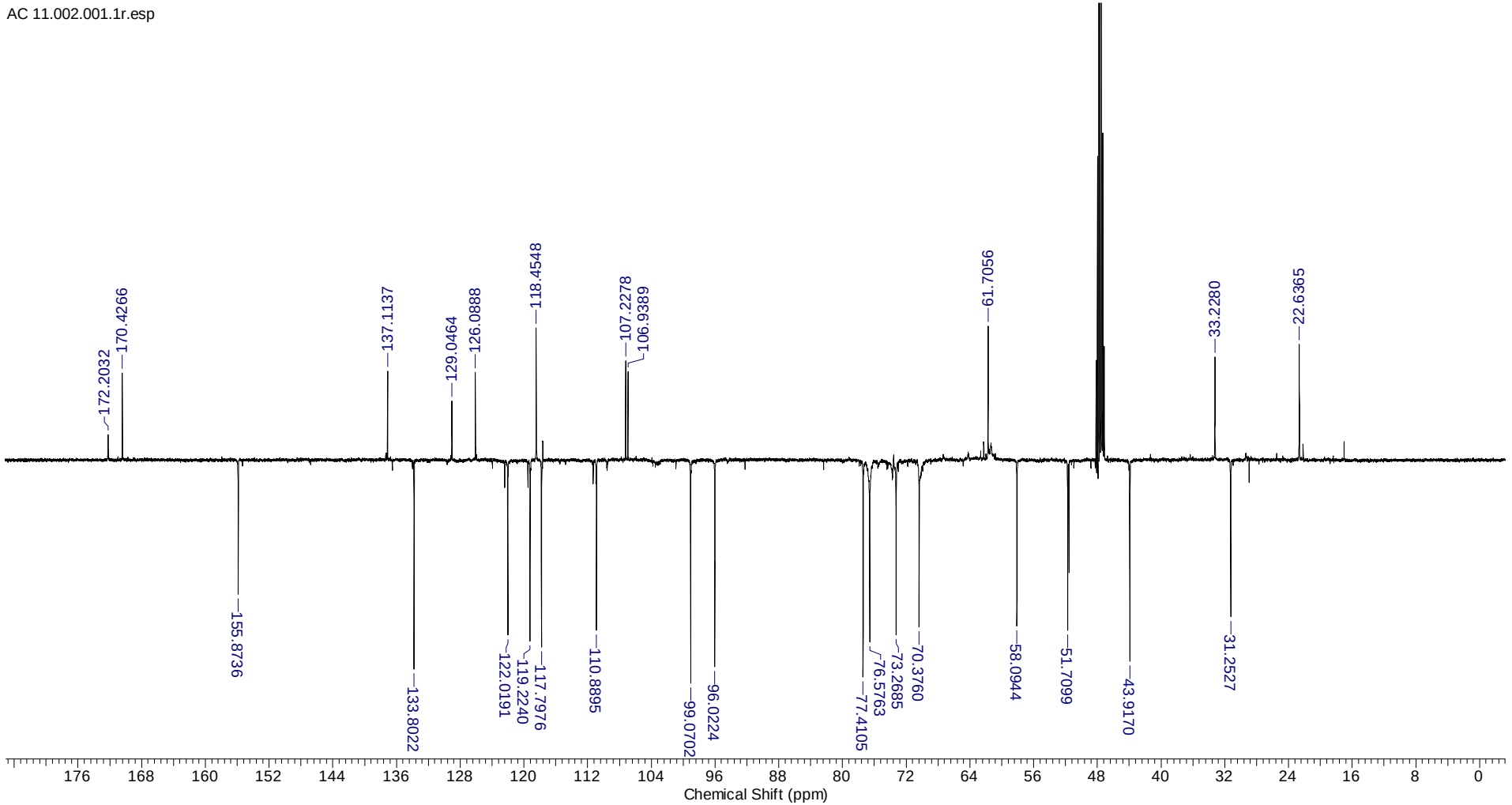

Figure S85. ^{13}C NMR spectrum (125 MHz, CD_3OD) of compound **28**.

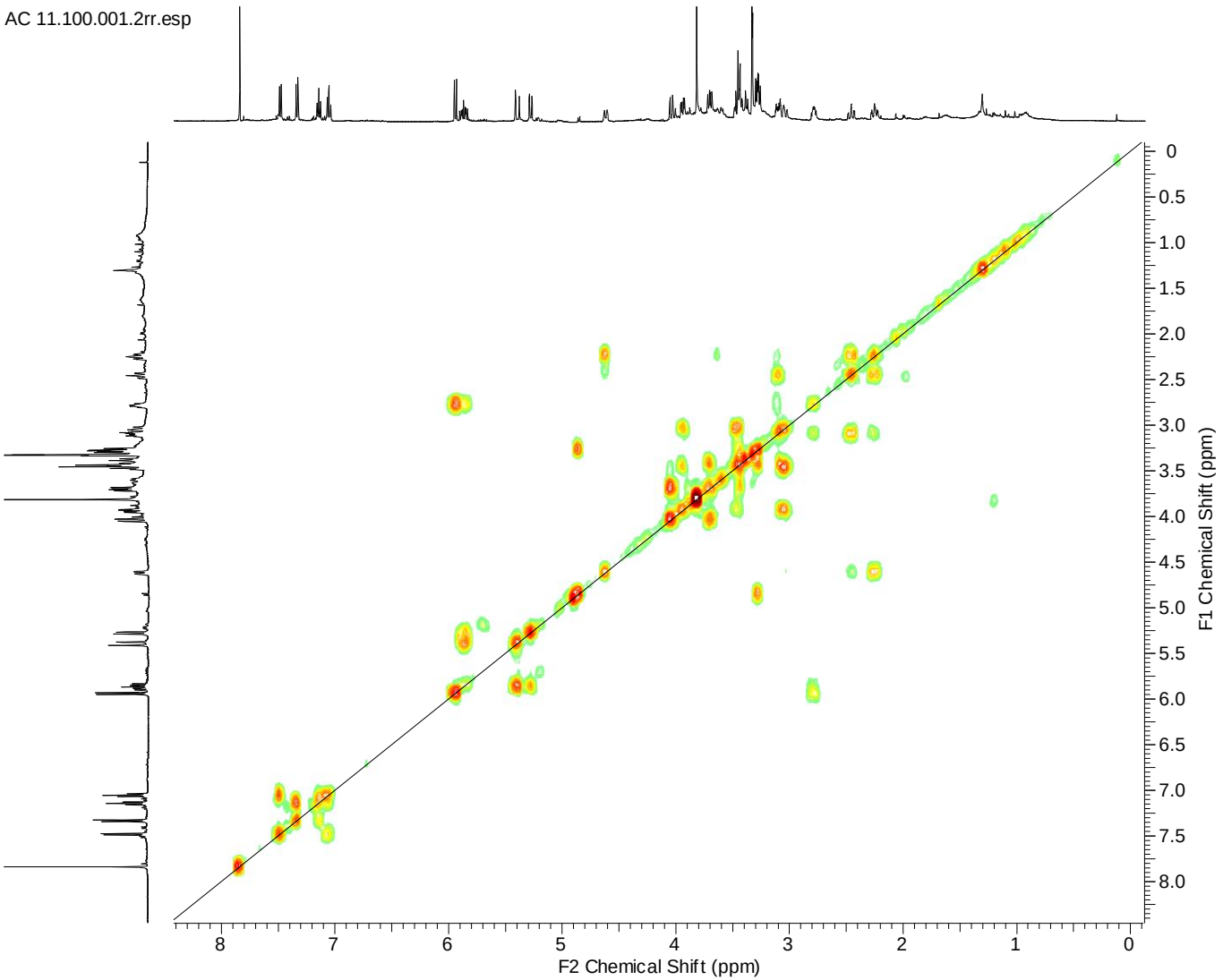

Figure S86. ^{1}H-^{1}H-COSY spectrum of compound **28**.

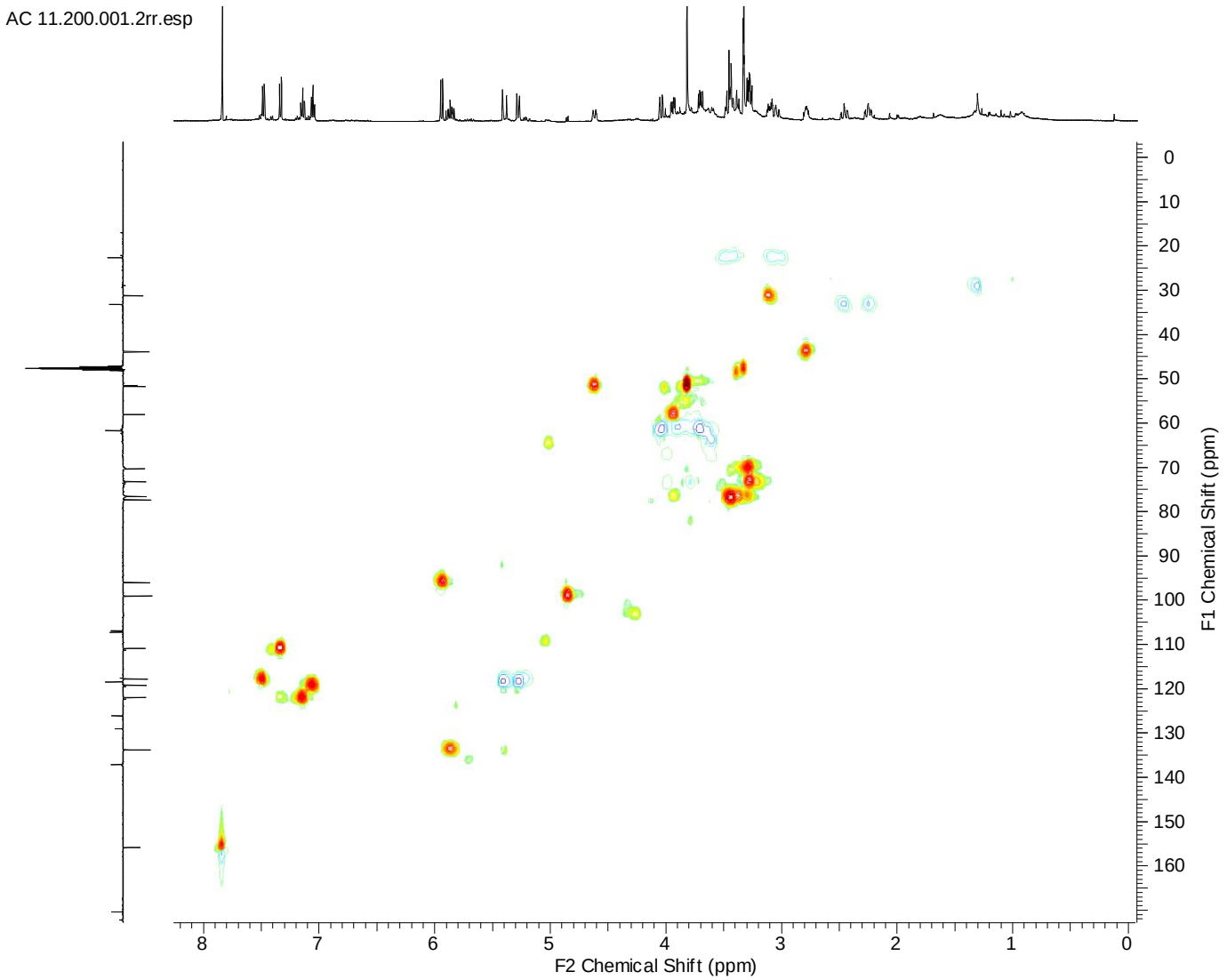

Figure S87. HSQC spectrum of compound **28**.

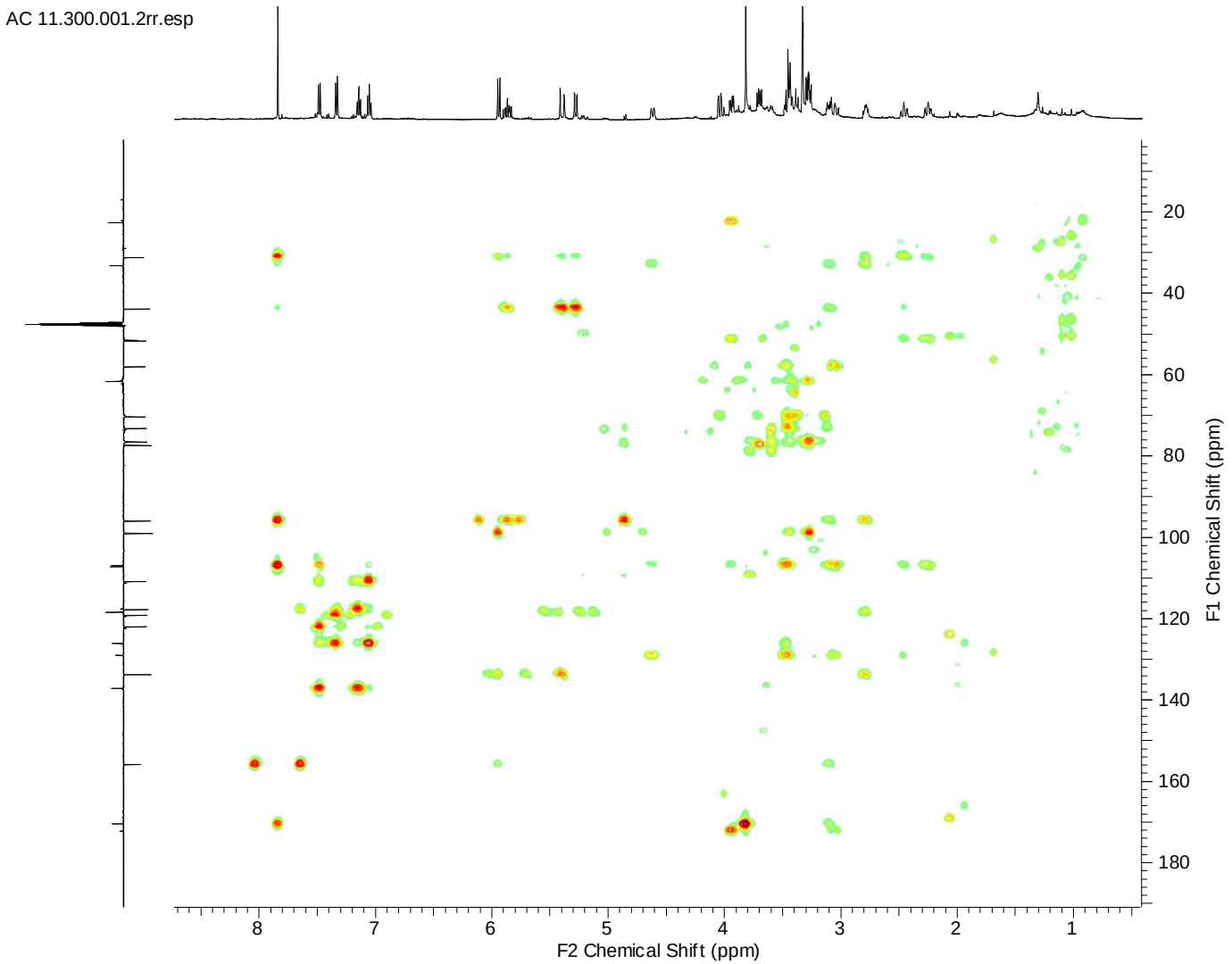

Figure S88. HMBC spectrum of compound **28**.

MTT assay

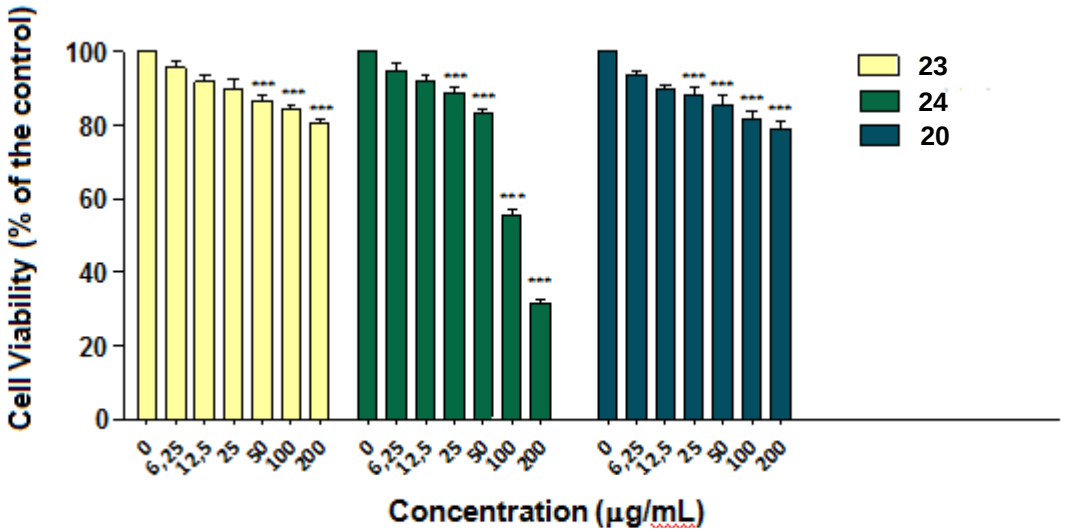

Figure S89. Evaluation of cell viability of U937 leukemic cell lines by MTT assay (n = 3), after 48 h of incubation with compounds **20**, **23**, and **24**. The concentration 0 is the negative control test (cells and culture medium). The concentration of DMSO was 0.2 %.

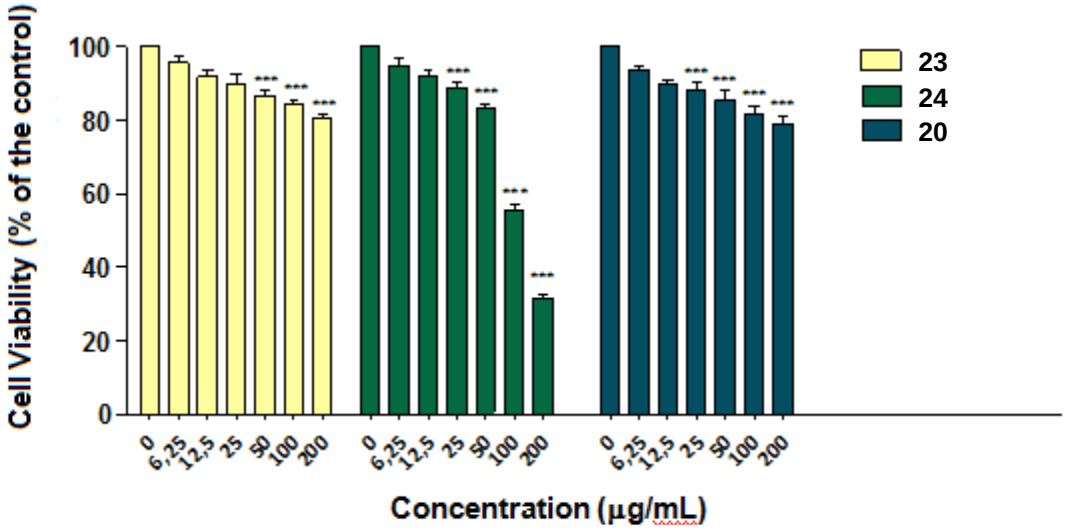

Figure S90. Evaluation of cell viability of THP-1 leukemic cell lines by MTT assay (n = 3), after 48 h of incubation with compounds **20**, **23**, and **24**. The concentration 0 is the negative control test (cells and culture medium). The concentration of DMSO was 0.2 %.

4. CONCLUSÕES

Com o desenvolvimento desta pesquisa foi possível, além de compreender a química do gênero Psychotria, contribuir com mais informações que poderão ser úteis no ponto de vista quimiotaxonômico. Neste trabalho, descrevemos os dados espectrais de um novo iridoide (ácido 9-*epi*-geniposídico), além de outros dez metabólitos isolados de *P. suterella*. Da espécie *P. nuda* outros dezessete metabólitos foram isolados. Através de uma busca na literatura foi possível constatar que, além do composto inédito, os ácidos geniposídico, 3-*O*-acetiloleanólico, pomólico, espinólico, maslínico, tormêntico e lyalosídico, metil oleleanato, cinchonainas Ia e Ib, roseosídeo e o alcaloide raro *N,N,N*-trimetiltriptamônio estão sendo, provavelmente, relatados pela primeira vez no gênero.

Além do estudo químico das espécies mencionadas, este estudo também consistiu na avaliação de atividades inseticida, antifúngica e citotóxica de extratos, frações e compostos isolados. As amostras testadas não promoveram, de forma considerável, a morte das larvas do mosquito *A. aegypti*, que é o vetor de doenças como a dengue e febre amarela. Os extratos e frações testadas nos ensaios para avaliação de atividade antifúngica não inibiram, consideravelmente, o crescimento dos fungos fitopatogênicos *Fusarium oxysporum, Curvularia lunata, Colletotrichum musae, Rhizoctonia solani, and Sclerotium rolfsii*, que causam prejuízos ao agronegócio. Em relação ao ensaio de atividade citotóxica, o alcaloide estrictosamida apresentou os melhores resultados frente às duas linhagens de células cancerígenas THP-1 e U937, com valores de EC_{50} de 120 ± 1 e 21.9 ± 1 μg/mL, respectivamente. Este resultado aponta para a possibilidade de testar outros alcaloides e outras linhagens de células cancerígenas em pesquisas futuras.

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6. ANEXOS

6.1 Metodologia do Ensaio para Avaliação de Atividade Inseticida

Os extratos e frações das espécies *P. nuda* e *P. suterella*, obtidos como mencionados na seção **3.3.1.1** (páginas 82-83), foram solubilizados em DMSO / H2O ou DMSO puro. Quinze larvas de terceiro instar (*Aedes aegypti*) foram adicionadas aos potes contendo água destilada e adicionadas às soluções de teste à temperatura ambiente, 27 ° C. Os testes foram realizados em triplicado e em duas repetições. O controle negativo foi a água pura, DMSO puro e uma solução DMSO / H2O (2,5%). Para o controle positivo foi utilizado o composto Imidacloprid, com concentrações entre 0,01 µg / mL e 1,0 µg / mL. A avaliação da mortalidade foi feita 24 horas após a exposição das larvas às soluções. Todas as amostras testadas não apresentaram atividade larvicida numa escala considerável.

6.2 Metodologia do Ensaio para Avaliação de Atividade Antifúngica

Os bioensaios foram conduzidos por adição ao meio de cultura PDA (Sigma-Aldrich®), às soluções aquosas de extratos e frações das duas plantas testadas, utilizando-se volumes apropriados para obter uma concentração de 3500 μg mL^{-1}, igualmente para cada microrganismo. Com o meio já vertido em placas de Petri, foram inoculados discos de micélio-ágar de 5 mm de diâmetro feitos de culturas puras de fungos na superfície de cada cultura com seus respectivos tratamentos. Posteriormente, as placas foram seladas com película de plástico e incubadas em uma câmara de crescimento (25 ± 1 ° C) e expostas a um fotoperíodo de 12 horas. Para estimar a eficiência dos tratamentos, o diâmetro de cada uma das colônias foi medido durante o crescimento micelial e comparado ao controle. O crescimento radial foi medido com paquímetro, em dois eixos ortogonais um ao outro calculando uma média para cada placa. As amostras testadas não apresentaram resultados satisfatórios.