UNIVERSITÉ DU QUÉBEC À CHICOUTIMI, EN EXTENSION DE

L'UNIVERSITÉ DU QUÉBEC À MONTRÉAL

SYNTHÈSE ET RELATIONS STRUCTURE-ACTIVITÉ CYTOTOXIQUE ET ANTIBACTÉRIENNE DES DIRCHROMONES

THÈSE

PRÉSENTÉE

COMME EXIGENCE PARTIELLE

DU DOCTORAT EN BIOLOGIE (MOLÉCULES BIOACTIVES)

PAR

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DÉCEMBRE 2021

REMERCIEMENTS

Mes premiers remerciements vont au professeur André Pichette, qui a dirigé cette thèse. Il a toujours eu pour moi une oreille empathique, notamment au gré des changements de thématique de recherche qui ont par la force des choses jalonné les premières années de ce programme doctoral. J'ai toujours pu compter sur sa précieuse confiance en mon jugement et mes impressions et ses perspectives traduisant sa grande expérience du domaine de la chimie des produits naturels. Il importe aussi de souligner le caractère essentiel de tout le travail de longue haleine qu'il abat depuis des années pour développer et entretenir un laboratoire de recherche de pointe en région, malgré les embûches. Sans ces infrastructures et l'expertise qui y est associée, cette thèse n'aurait jamais pu voir le jour. Enfin, je souligne qu'André a eu une grande ouverture d'esprit quant à ma situation particulière, acceptant de bonne grâce le risque (car c'en était un) de me laisser mener de front un projet entrepreneurial parallèlement à cette thèse.

Je remercie également mon codirecteur, le professeur Jean Legault, dont les perspectives sur les activités biologiques des dirchromones ont toujours été clairvoyantes et justes, offrant un recul posé et nécessaire sur les résultats obtenus. De la même manière que pour André Pichette, son investissement de longue date à maintenir un laboratoire de haute qualité au sein de l'Université du Québec à Chicoutimi a été un rouage essentiel de ce projet. Mes remerciements également au professeur Charles Gauthier de l'Institut national de la recherche scientifique pour sa contribution à l'amélioration du manuscrit du premier article de cette thèse. Enfin, cette thèse a été rendue possible grâce au soutien financier offert par des bourses doctorales du Fonds de recherche nature et technologies du Québec (FRQNT, 2014-2015) et ES

D du Conseil de recherches en sciences naturelles et en génie du Canada (CRSNG, 2015-2018).

Je tiens également à souligner l'implication du stagiaire post-doctoral (désormais professeur) Jérôme Alsarraf, arrivé au laboratoire lors de certaines des heures les plus sombres de mon parcours. Il a dès lors été très disponible pour m'apporter de nouvelles pistes, une saine perspective et de l'optimisme. Tant par le partage de bonnes techniques de travail que par ses suggestions et son humour, il aura su m'éviter le naufrage et rendre le trajet beaucoup plus agréable.

De nombreuses autres personnes du laboratoire LASEVE, chercheurs, employés, étudiants ou stagiaires, ont au fil des années contribué de diverses manières à produire les résultats de cette thèse ou à m'encourager à persévérer. S'il est probable que cette liste ne soit pas exhaustive, je remercie entre autres Catherine Dussault, François Simard, Karl Girard-Lalancette, Balla Sylla, Lydia Genthon, Mouadh Mihoub, Audrey Bélanger, Vakhtang Mshvildadze, Joanne Plourde, Pierre-Yves Fleury, Cindy Caron, Fanny Charlier, Lionel Ripoll, Serge Lavoie, Anne Ardaillou, Paul Gormand, Michael Ouellet, Rim Kboubi, Charlotte Pichard, Sophie Fortin, Simon Gandrieau, Marion Etienne, Ludivine Chaurand, Philippe Plourde, Quentin Lion, Léa Garcia, Héloïse Côté, Estelle Juere, François-Xavier Sirois, Ariane Nadeau et Valérie Bérubé. Merci également à Marie-Claude Bergeron pour son aide précieuse pour l'obtention et la gestion des bourses doctorales, à Dominique Simard du secrétariat du département des sciences fondamentales pour son efficacité et sa patience, et à Tommy Perron et Caroline Potvin pour leur appui matériel et logistique régulier tout au long du projet.

Mon inscription au doctorat en Biologie aura été un pari audacieux de la part de mes associés chez Laboratoire PhytoChemia, Laurie Caron et Hubert Marceau. Année après année, nonobstant les embûches et les défis posés par la croissance de notre entreprise, ils ont accepté de me partager avec le projet doctoral et m'ont soutenu dans les

moments de découragement. Un merci également à tous les employés de PhytoChemia qui m'ont toujours aussi supporté dans cette « double vie » singulière.

Le soutien de ma famille a également été précieux, et ils savent que ce doctorat n'a vraiment pas été un long fleuve tranquille pour moi. Je dois d'abord beaucoup à mon père, Dany St-Gelais, d'avoir entamé ces études, car déjà au début le doute m'assaillait et il a su trouver les mots pour me convaincre de me donner ma chance. Ma mère, Marie-Hélène Troestler, mon père, mon frère, Xavier St-Gelais et mes grands-mères, feu Ghislaine Jacob et Andrée Tremblay, ont tous fait preuve de beaucoup d'empathie tout au long de ce parcours régulièrement éprouvant. Quant à ma conjointe Lindsay Girard, sa patience et sa foi en ma réussite paraissent n'avoir jamais été ébranlés, alors même que je me laissais envahir par le doute. Elle est ma lumière lorsque la nuit est trop sombre.

AVANT-PROPOS

Ce document a été assemblé sur le modèle de la thèse par articles, en conformité avec les règlements applicables de l'Université du Québec à Montréal (*Règlements des études de cycles supérieurs*, règlement numéro 8, annexe 1, avril 2020), dont le doctorat en biologie est offert en extension à l'Université du Québec à Chicoutimi. À cette fin, trois publications arbitrées sont ci-après référées.

L'article « Soft-enolization Baker-Venkataraman rearrangement enabled total synthesis of dirchromones and related 2-substituted chromones » est paru en 2018 dans le journal *Organic Letters*. Le candidat au doctorat Alexis St-Gelais en est l'auteur principal. Il a pris en charge l'ensemble des manipulations qui y sont décrites, ainsi que de nombreux essais préalables infructueux dont les tout premiers remontent à 2013, avant même l'amorce du programme doctoral. Il a également procédé à la rédaction du manuscrit. Jérôme Alsarraf, second auteur, a joué un rôle important d'encadrement du candidat dans ses explorations synthétiques, a facilité leur intégration dans un tout cohérent, puis a contribué à l'amélioration du manuscrit. Jean Legault a supervisé l'ensemble des manipulations relatives aux propriétés biologiques de la dirchromone ainsi synthétisée, et révisé le manuscrit. Charles Gauthier a participé à la révision et l'amélioration du manuscrit. André Pichette a supervisé l'ensemble des travaux de ce projet.

Le second article, « On the role of the vinylsulfoxide side chain of dirchromone towards its cytotoxic and antimicrobial activities », est paru en 2020 dans le journal *Organic & Biomolecular Chemistry*. Les rôles joués par Alexis St-Gelais, Jérôme Alsarraf et André Pichette sont congrus avec ceux présentés pour le premier article. Jean Legault

et Mouadh Mihoub ont contribué à la séquence d'observations ayant mené à conclure au caractère d'accepteur de Michael de la dirchromone, en plus de superviser de nouveau l'ensemble des observations sur les activités biologiques des molécules décrites.

Le troisième manuscrit, « Effect of the Chromone Core Substitution of Dirchromone on the Resultant Biological Activities », est paru dans le *Journal of Natural Products* en 2021. Les rôles joués par les quatre auteurs précédemment cités sont respectivement semblables à ceux décrits pour les deux autres articles, alors que Joanne Plourde a contribué à l'attribution des signaux de résonnance magnétique nucléaire pour les molécules finales, suivant les demandes de correctifs soumis par les réviseurs du manuscrit avant publication.

Ces articles, sous réserve de révisions proposées par le comité d'évaluation de la présente thèse, sont conformes aux versions publiées ou soumises en date du dépôt de la thèse, à l'exception de la gestion des références. En effet, la présentation de ces dernières a été uniformisée sans égard aux styles des journaux d'origine, afin d'assurer la constance de la présentation tout au long de la thèse au format auteur-date, selon le modèle de gestion des références de la revue *Phytochemistry*.

TABLE DES MATIÈRES

LISTE DES FIGURES

LISTE DES SCHÉMAS

LISTE DES TABLEAUX

Tableau Page

LISTE DES ABRÉVIATIONS

Ac: Acétyl

ACS: American Chemical Society

APCI: Ionisation chimique à pression atmosphérique

ATR: Réflectance totale atténuée

Bu: Butyl

B-V: Baken-Venkataraman

d: Doublet (dans le contexte d'une caractérisation RMN)

DAPI: 4',6-Diaminido-2-phénylindole

DC: Dirchromone

DCM: Dichlorométhane

DEPT135: Distortionless enhancement by polarization transfer à 135°

DIPEA: Diisopropyléthylamine

DMF: Diméthylformamide

DMSO: Diméthylsulfoxide

DQF-COSY: Double quantum filtered homonuclear correlation spectroscopy

EI-MS: Spectrométrie de masse à impact électronique

Equiv: Équivalents molaires

ESI: Ionisation par électronébuliseur

Et: Éthyl

FTIR: Spectroscopie infrarouge à transformée de Fourier

GC: Chromatographie en phase gazeuse

GSH: Glutathione

Hex: Hexanes (mélange d'isomères)

HMBC: Heteronuclear multipler bond correlation

HPLC: Chromatographie liquide à haute pression

HRMS: Spectrométrie de masse de haute résolution

HSQC: Heteronuclear single quantum coherence

IC_{50}: Concentration inhibitrice à 50%

iPA: Alcool isopropylique

***i*Pr:** Isopropyl

IR: Infrarouge

***J*:** Constante de couplage (dans le contexte d'une caractérisation de RMN)

$J_{Cx\text{-}F}$: Constante de couplage entre le fluor et le xe carbone à partir de l'halogène

LC: Chromatographie liquide

m: Multiplet (dans le contexte d'une caractérisation de RMN)

***m*-CPBA:** Acide méta-chloroperbenzoïque

Me: Méthyl

MIC_{90}: Concentration minimale d'inhibition à 90%

MS: Spectrométrie de masse (ou spectromètre de masse)

MS-TOF: Spectrométrie de masse à temps de vol

NIST: National institute of standards and technology

NMR: Résonnance magnétique nucléaire

NOESY: Nuclear overhauser effect spectroscopy

PBS: Solution tampon phosphate

Ph: Phényl

q: Quadruplet (dans le contexte d'une caractérisation de RMN)

Rf: Rapport frontal

RMN: Résonnance magnétique nucléaire

rt: Température pièce

s: Singulet (dans le contexte d'une caractérisation de RMN)

SAR: Relations structures-activités

t: Triplet (dans le contexte d'une caractérisation de RMN)

TBAI: Iodure de tétrabutylammonium

***t*-Bu:** *tert*-Butyl

Tf: Triflate

THF: Tétrahydrofurane

TLC: Chromatographie sur couche mince

Tol: Toluène

tp: Température pièce

UV: Ultraviolet

Xyl: Xylène

RÉSUMÉ

L'exploration de l'espace chimique biologiquement pertinent requiert l'utilisation de règles ou de sources d'inspiration permettant de circonscrire les recherches au sein de l'immensité des assemblages possibles des atomes de carbone. Parmi ces stratégies, l'examen de substances d'origine naturelle conserve une place de choix, tant parce qu'elles fournissent des pistes qui auraient été difficilement accessibles par synthèse classique que parce qu'elles sont le résultat de coévolution de formes de vie les sécrétant précisément pour influencer d'autres organismes. Antérieurement, l'étude de l'arbuste *Dirca palustris* a permis d'y découvrir une famille de molécules soufrées, les dirchromones, présentant des activités cytotoxique et antibactérienne contre *Staphylococcus aureus*. Leur chaîne latérale comportant un vinylsulfoxyde les classe à l'écart des autres chromones végétales et leur fait donc couvrir une nouvelle niche de l'espace chimique. Cependant, leur faible abondance dans la plante ne permettait pas d'aller au-delà de leur simple catalogage. Dans le cadre de cette thèse, trois objectifs étaient donc poursuivis: développer une voie de synthèse de la dirchromone qui soit à la fois accessible, flexible et économe en étapes; déterminer la ou les caractéristiques structurales les plus critiques pour les activités biologiques; et explorer les relations entre des modifications structurales systématiques et les activités cytotoxique et antibactérienne.

Dans un premier temps, une synthèse totale des dirchromones a été développée afin de contourner les écueils rencontrés par des approches classiques, avec comme étapes clé un réarrangement de Pummerer de transfert d'oxydation inusité et le premier exemple de réarrangement de Baker-Venkataraman en conditions d'énolisation douce rapporté dans la littérature. La démarche complète comporte sept étapes ayant permis de préparer la dirchromone à l'échelle du gramme avec un rendement global de 21 % à partir de réactifs facilement accessibles. Cette même synthèse s'est avérée adaptable, permettant d'introduire des substituants à de nombreuses positions du squelette et également de préparer d'autres chromones courantes. À ce stade, la cytotoxicité de la dirchromone synthétique a été validée sur 13 lignées cellulaires cancéreuses.

En second lieu, mettant à profit cette synthèse, différentes modifications structurales ont été introduites sur le fragment moléculaire rendant la dirchromone unique, à savoir sa chaîne latérale soufrée. Il en ressort notamment que le degré d'oxydation du soufre est capital à l'expression de ses activités biologiques, le sulfoxyde étant plus

cytotoxique alors que la sulfone est plus antibactérienne et le sulfide inactif dans les deux cas. Afin de mieux comprendre l'implication de la chaîne latérale sur la réactivité de la dirchromone, cette dernière a été soumise à un test pour mesurer son caractère d'accepteur de Michael par une réaction avec de la cystéamine suivie par résonnance magnétique nucléaire. Devant le comportement surprenant observé, les produits de la réaction ont été caractérisés, mettant en évidence une séquence de réactions combinant une addition de Michael, une élimination du fragment méthylsulfinyl et des conversions oxydoréductrices. La fluorescence de certains de ces produits a également permis de mettre en évidence l'occurrence de réactions similaires au sein du cytosol de cellules traitées avec la dirchromone.

Troisièmement, 32 analogues de la dirchromone présentant différents substituants (méthylations, hétéroatomes, acylations et alkoxydations avec différentes longueurs et ramifications de chaînes alkyles, modifications du cycle) ont été préparés et criblés pour leurs activités cytotoxiques, antibactérienne gram-positive et antifongique. Les résultats ont montré une absence de corrélation entre les activités cytotoxique et antibactérienne, suggérant des mécanismes de toxicité distincts. Quelques dérivés ont montré de fortes différences d'activité, notamment par une réduction de la cytotoxicité par des groupements hydroxyle ou nitrile, alors que ce dernier augmentait le potentiel antibactérien. L'activité antifongique a émergé au fil de l'élongation des chaînes alkoxydes. Ces derniers dérivés, ainsi que la dirchromone bromée ou avec un cycle aromatique supplémentaire, sont légèrement plus cytotoxiques que le composé parent. Cependant, dans l'ensemble, le pharmacophore de la dirchromone a maintenu son activité dans la majorité des cas. Ce dernier pan du projet a donc démontré la robustesse de la dirchromone vis-à-vis la substitution de son noyau de base.

Cette thèse marque donc une avancée de l'accessibilité et de la compréhension des activités biologiques des dirchromones en fonction de leur structure. Elle a permis de jeter un peu de lumière sur une portion de l'espace chimique biologiquement pertinent qui auparavant demeurait inexplorée et hors d'atteinte, offrant ainsi des perspectives de recherche plus précises autour de ce squelette unique.

Mots clés : Dirchromone, synthèse totale, relations structure-activité, molécules cytotoxiques, activité antibactérienne

ABSTRACT

The exploration of biologically relevant chemical space requires that some rules or sources of inspiration are used so as to achieve some degree of focus while scouting the vastness of theoretically possible carbon atoms assemblies. Among such strategies, the examination of naturally occurring substances retains a place of choice, both because this approach offers insight into structures that would have been hardly accessible through classical synthesis and because natural products are the result of constant coevolution of life forms secreting them precisely to influence other organisms. Previously, a study of the shrub *Dirca palustris* had led to the discovery of a family of sulfur-bearing compounds, dirchromones. These exerted cytotoxic activity and antibacterial potential against *Staphylococcus aureus*, and they covered a new niche of the chemical space owing to their peculiar side chain featuring a vinylsulfoxide moiety. However, their low availability from the plant material did not allow for more than mere cataloguing. In the course of this thesis, three objectives were therefore pursued: developing a synthesis of dirchromone combining accessibility, flexibility and a reasonable number of steps; determining the most relevant structural characteristics towards the biological activities; and exploring the relationship between systematic structural modifications and the cytotoxic and antibacterial activities.

To begin with, a total synthesis of dirchromones was designed so as to circumvent the shortcomings of classical approaches, featuring as key steps an unusual Pummerer rearrangement allowing for an oxidation transfer, and the first reported example of a soft-enolization Baker-Venkataraman rearrangement. The whole protocol comprises seven steps which allowed to prepare dirchromone at the gram scale with an overall yield of 21 % from readily accessible reagents. The same synthesis was shown to be flexible, giving access to multiple substitutions of the core structure and also to other common chromones. At this stage, the cytotoxicity of synthetic dirchromone was confirmed on 13 malignant cell lines.

Secondly, thanks to this synthetic route, various structural modifications were incorporated to the moiety that makes dirchromone unique, i.e., its sulfur-bearing side chain. This revealed in particular that the oxidation level of the sulfur was pivotal to the expression of the biological activities, with the sulfoxide being more cytotoxic whereas the sulfone was more antibacterial and the sulfide inactive in both cases. In order to grasp a broader understanding of the implication of the lateral chain on

dirchromone's reactivity, the latter was subjected to a study of its Michael acceptor behavior by reacting it with cysteamine and following the reaction by nuclear magnetic resonance. Since a surprising outcome was observed, some reaction products were characterized, highlighting a reaction sequence comprising a Michael addition, the elimination of the methylsufinyl fragment and redox conversions. The fluorescence of some of these products also highlighted that similar reactions occurred within the cytosol of cells to which dirchromone was administered.

Furthermore, 32 analogs of dirchromone featuring various substituents (methylation, heteroatoms, acylation or alkoxidation with various chain lengths and branching, modification of the cyclic core) were prepared and screened for their cytotoxic, anti-Gram-positive bacteria and antifungal activities. The results showed a lack of correlation between antibacterial and cytotoxic activities, suggesting distinct toxicity mechanisms. A few derivatives induced strong difference in activity, especially by reducing cytotoxicity upon the introduction of hydroxyl or nitrile group, whereas the latter increased the antibacterial activity. An antifungal activity also arose as the alkoxide substituents' chain length increased. The latter as well as dirchromones featuring a bromide or an additional aromatic ring were slightly more cytotoxic than the parent compound. That being said, as a whole, the pharmacophore of dirchromone maintained its activity in the majority of cases. This last part of the project therefore outlined the robustness of dirchromone towards substitution of its core structure.

This thesis therefore furthered the accessibility and the understanding of the biological activities of dirchromone with regard to its structure. It hence shed a bit of light on a portion of the biologically relevant chemical space that previously remained unexplored and beyond reach, offering more precise research perspectives around this unique molecular entity.

Keywords : Dirchromone, total synthesis, structure-activity relationships, cytotoxic molecules, antibacterial activity

INTRODUCTION

Dans ce chapitre, les perspectives générales ayant motivé le projet seront détaillées. Les dirchromones seront ensuite présentées et mises en contexte. Les objectifs des travaux seront subséquemment décrits et justifiés, accompagnés d'un bref aperçu des approches méthodologiques retenues pour la préparation des trois articles.

L'étude des dirchromones s'inscrit dans la perspective plus large de l'exploration de l'espace chimique à la recherche de molécules bioactives. Avant de présenter plus spécifiquement le cas des dirchromones, il importe donc de replacer l'étude elle-même dans cette large quête de structures moléculaires pertinentes.

L'un des ressorts essentiels de la chimie médicinale moderne est l'exploration de l'espace chimique. Cette notion est une représentation de la somme de toutes les molécules pouvant en théorie exister notamment grâce à la saisissante diversité permise par les assemblages des atomes de carbone. L'analogie avec l'astronomie n'est pas anodine, puisque de nombreux parallèles existent entre les deux champs d'études.

Tant pour la chimie que pour l'astronomie, la taille exacte de l'espace n'est pas connue, mais est assurément immense (Larsson et al., 2007). Les estimés existants pour la chimie, basés sur des modèles mathématiques et informatiques, assignent en général un plafond de taille moléculaire ou de formule chimique avant de procéder à un dénombrement des possibilités, pour des raisons pratiques. Ainsi, pour des assemblages de 17 atomes ou moins de carbone, azote, oxygène, soufre et halogènes, en excluant certaines conformations considérées trop instables, la base de données GDB-17

présente 1,66 × 10^{11} molécules se rattachant à plus de 1,3 milliard de squelettes distincts (Ruddigkeit et al., 2012). On a avancé le nombre de 10^{60} (Rosén et al., 2009; Virshup et al., 2013) à 10^{63} (Bohacek et al., 1996) molécules organiques possibles pour un poids de moins de 500 Daltons, et estimé à 10^{180} la quantité de composés physiquement et chimiquent stables de moins de 1000 Daltons (Gorse, 2006). Notons que de tels critères excluent parfois *de facto* des molécules pourtant utiles dans un contexte médical, comme le médicament anticancéreux paclitaxel de masse moléculaire de 853,9 g/mol (Priyadarshini and Keerthi Aparajitha, 2012), les saponines cardiotoniques et cardioprotectrices pesant de 585 à 1808 Daltons (Singh and Chaudhuri, 2018), sans compter les polypeptides et polysaccharides.

À titre de comparaison, en 2020, le *Chemical Abstract Service* (CAS) répertoriait 160 millions de composés caractérisés par les chimistes, ce qui inclut toutefois des substances inorganiques et alliages (American Chemical Society, 2020). En 2018, une extraction plus ciblée de composés enregistrés au CAS, en se limitant à ceux disposant d'une structure définie comportant moins de 253 atomes appartenant à l'un des éléments tirés d'une liste pertinente à la chimie organique, en excluant les sels, et présentant au moins un cycle, regroupait plutôt 30,4 millions de composés répartis en 5,2 millions de squelettes (Lipkus et al., 2019). Dans tous les cas, ces nombres illustrent bien le caractère infinitésimal des connaissances pratiques actuelles en proportion de la taille de l'espace chimique, à l'image de l'étude astronomique.

Devant l'immensité de ces espaces, la rationalité commande d'orienter les efforts d'exploration en vue de certains objectifs précis (Rosén et al., 2009). Tout comme une large partie de l'Univers ne contient presque pas de matière ou est impropre à la vie telle qu'elle nous est familière, de vastes pans de l'espace chimique revêtent également peu d'intérêt pour, notamment, la chimie médicinale. Nombre d'assemblages abscons à base de carbone n'auront aucune action particulière sur les systèmes biologiques, puisqu'ils ne sont pas des ligands de la machinerie biochimique de la vie en raison

d'incompatibilités structurales fondamentales. L'espace chimique biologiquement pertinent est ainsi considérablement plus petit que l'espace chimique complet par suite de la coévolution des formes de vie en constantes interactions moléculaires mutuelles sur des centaines de millions d'années (Deng et al., 2013; Dobson, 2004; Larsson et al., 2007; Rosén et al., 2009). Une représentation schématique de différentes catégories de composés dans l'espace chimique est illustrée à la Figure I-1.

Ainsi, à l'image d'astronomes recherchant d'abord des exoplanètes présentant des caractéristiques rappelant celles de la Terre, les chimistes recherchant des composés bioactifs orientent prioritairement leurs efforts vers des zones de l'espace chimique où ils sont plus susceptibles de rencontrer certaines propriétés favorables à l'interaction biologique. Ces zones peuvent être repérées par le concept de similarité moléculaire: des molécules semblables présentent des propriétés semblables (Johnson and Maggiora, 1990). Cela permet ainsi de guider l'exploration sur la base de molécules bioactives déjà présentes dans la nature, ou présentant certains points communs. Si en pratique la définition et l'appréciation mathématique de ce qu'est la similarité sont complexes (Lipinski, 2004), le principe est utilisé en chimie informatique et médicinale pour anticiper des candidats potentiels pour le développement de médicaments par extrapolation des activités biologiques à partir de ressemblances structurales entre des listes de composés. Ces similitudes sont généralement évaluées sur la base de descripteurs moléculaires calculés (Aguilera-Mendoza et al., 2020; Ash and Fourches, 2017; Larsson et al., 2007; Reymond et al., 2010) ou de fragments (Koch et al., 2005; Over et al., 2013; Schuffenhauer et al., 2007; Varnek et al., 2008) (Figure I-2), qui peuvent d'ailleurs également servir de coordonnées pour établir des cartographies statistiques de l'espace chimique (Reymond et al., 2010; Virshup et al., 2013) tel qu'illustré à la Figure I-3. Les chercheurs peuvent ensuite utiliser ces descripteurs pour inférer des règles qui, bien que souffrant nombre d'exceptions, permettent de considérablement orienter la recherche de structures candidates dans le processus de découverte d'un médicament. Le groupe de telles indications le plus connu est sans

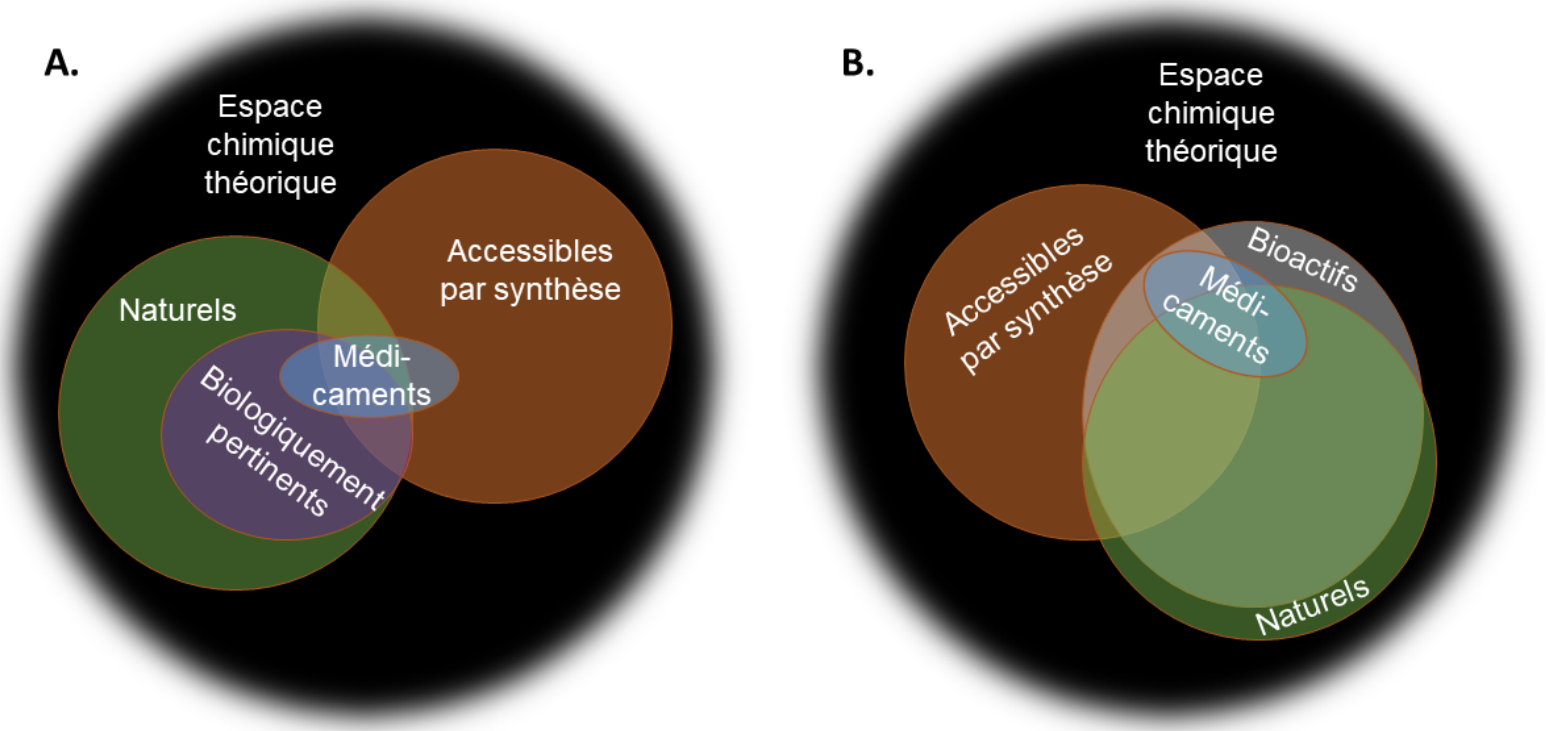

Figure I-1. Représentations schématiques de différentes parties de l'espace chimique. **A.** Modèle présenté par (Deng et al., 2013). Au sein de l'espace chimique théorique se trouvent les zones, partiellement croisées, occupées par les produits naturels et les molécules accessibles par synthèse. Leurs travaux définissent les composés biologiquement pertinents comme étant les seuls produits naturels jouant un rôle essentiel dans le métabolisme; incidemment, une bonne partie des candidats pour le développement de médicaments se situent dans cette fenêtre qui peut donc servir de guide pour la recherche. **B.** Modèle décrit par (Rosén et al., 2009). À la différence de Deng et al., leur définition de composés bioactifs est large, n'excluant pas les processus métaboliques secondaires, et recouvre presque tous les produits naturels, qui sont par pression évolutive poussés à une interaction biologique quelconque. De même, certains composés bioactifs peuvent actuellement n'être ni naturels ni accessibles par synthèse (et donc d'existence pour le moment théorique). Une partie des produits bioactifs se qualifie comme médicaments. Dans les deux modèles, il est à noter que tout candidat au titre de médicament doit forcément être accessible soit via une source naturelle, soit par synthèse.

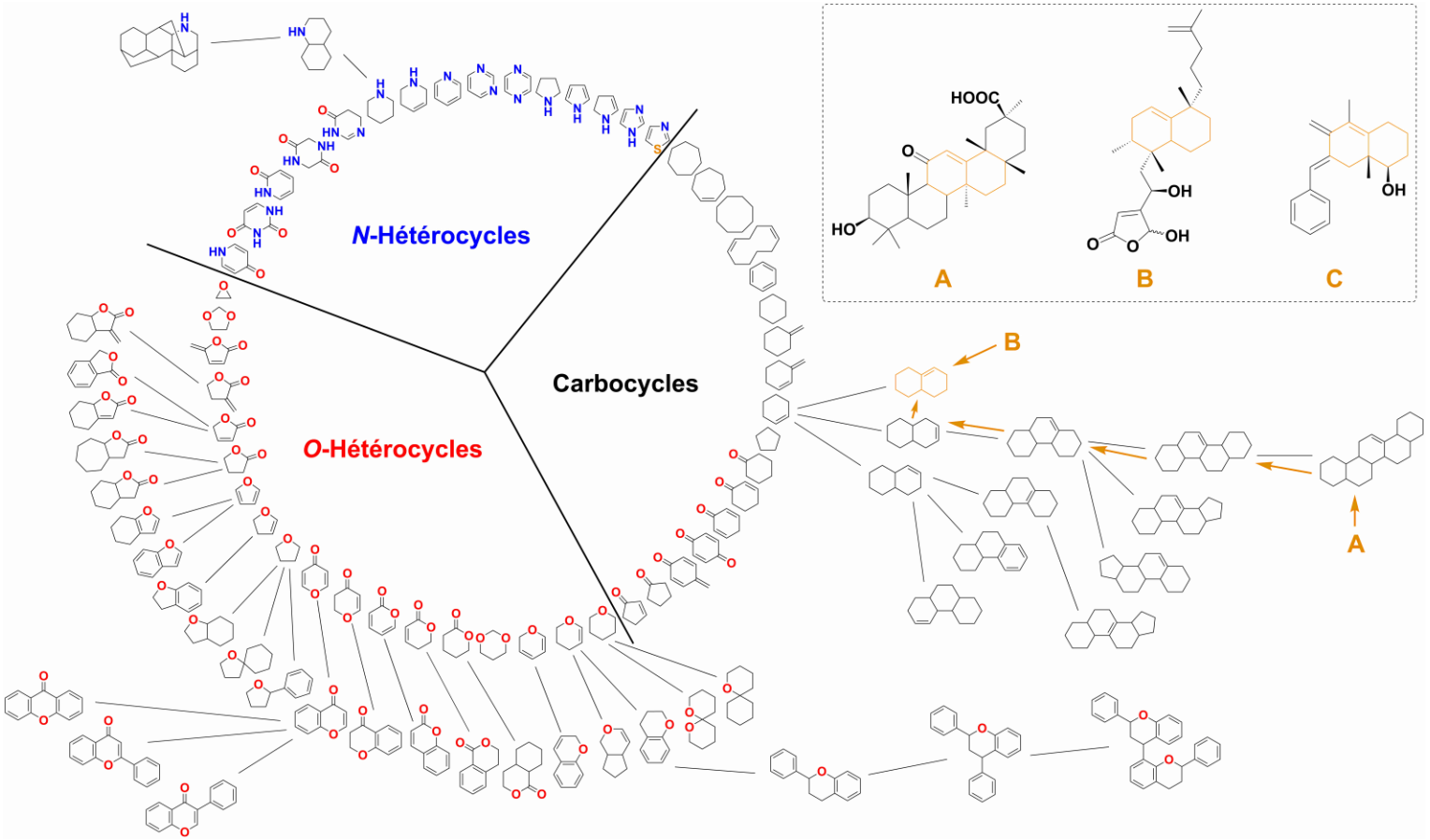

Figure I-2. Représentation partielle de l'approche *structural classification of natural products* (SCONP), préparée à partir des figures de (Koch et al., 2005) avec simplifications. Les molécules naturelles contenant au moins un cycle y sont classées au sein d'un arbre dont les couches successives ajoutent des cycles supplémentaires. Cet outil empirique a été utilisé par les auteurs pour trouver un dénominateur commun à l'acide glycyrrhétinique (**A**), un inhibiteur des 11β-hydroxystéroïde déshydrogénases, et le dysidiolide (**B**), un ligand d'une protéine structuralement proche, la Cdc25A phosphatase. Le motif cyclique commun (en orange) aux deux composés a ensuite été retracé puis utilisé pour préparer une série de dérivés simplifiés basés sur ce squelette, dont (par exemple) le composé **C** qui s'est avéré être lui aussi inhibiteur de 11β-hydroxystéroïde déshydrogénase.

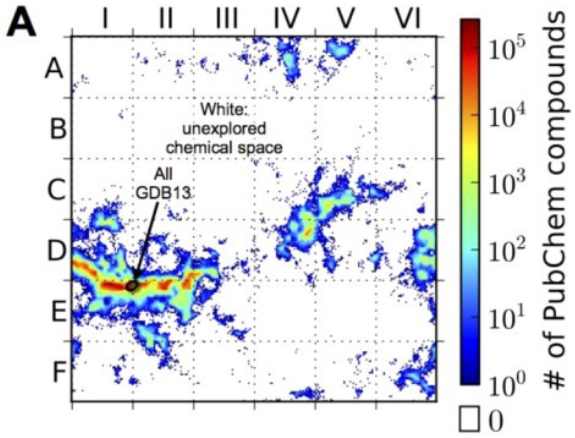

Figure I-3. Représentation statistique simulée de l'espace chimique possible pour des composés organiques de 500 Da et moins. Cette figure est assemblée en générant un sous-échantillon représentatif des 10^{60} molécules estimées comme pouvant figurer dans cet espace, puis en les regroupant. Les zones colorées indiquent celles où des molécules connues sont situées, alors que les espaces blancs représentent des zones de l'espace chimique encore inexplorées. Reproduit avec permission depuis Virshup, A.M., Contreras-García, J., Wipf, P., Yang, W., Beratan, D.N., 2013. Stochastic voyages into uncharted chemical space produce a representative library of all possible drug-like compounds. *J. Am. Chem. Soc.* 135, 7296–7303. https://doi.org/10.1021/ja401184g, en page 7300. Tous droits réservés © 2013, American Chemical Society.

conteste la « règle des cinq de Lipinski », qui constate qu'une grande partie des médicaments oraux développés ne transgressent qu'au plus un des quatre paramètres suivants: masse moléculaire de 500 Daltons ou moins, coefficient de partition octanol-eau (logP) inférieur à 5, moins de 5 donneurs de liaisons hydrogène, et moins de 10 accepteurs de telles liaisons, critères auxquels Lipinski a plus tard ajouté un maximum de 10 liaisons rotatives (Lipinski, 2004). De tels critères permettent donc de canaliser l'attention des chercheurs vers des zones plus circonscrites de l'espace chimique.

Une fois qu'une certaine idée des objectifs d'exploration est définie, le travail de découverte et de tri des molécules peut commencer. Depuis les années 1990, l'approche de la chimie combinatoire alliée au criblage à haut débit sur des cibles biologiques définies d'avance a notamment eu la faveur des chimistes médicinaux. La chimie combinatoire consiste à obtenir relativement rapidement des chimiothèques de

nombreux composés par l'assemblage de blocs moléculaires de construction, selon des méthodologies de synthèse partiellement automatisées ou pouvant aisément être réalisées en parallèle (Smith and Griebenow, 2006). Le criblage à haut débit qui s'ensuit permet de tester un très grand nombre de composés pour leur aptitude à interagir avec une cible définie (enzyme, récepteur, etc.) à l'occasion de tests réalisés dans des plaques multipuits dont la manutention peut être automatisée (Mayr and Fuerst, 2008). La chimie combinatoire permet en général d'obtenir des chimiothèques de composés de l'ordre de jusqu'à 10^6 – ce qui est énorme d'un point de vue pratique, mais qu'il convient de considérer comme restreint comparativement à la taille de l'espace chimique (Hert et al., 2009).

Jusqu'à récemment, l'attention était tournée vers la maximisation de la diversité structurale de telles chimiothèques moléculaires, mais cela n'a pas eu autant de succès qu'escompté. En effet, leur recouvrement de la partie de l'espace chimique biologiquement pertinent tend à être incomplet ou trop fragmentaire, teinté par une poignée de prérequis tenant à la nature même des molécules accessibles dans les contraintes des protocoles de synthèse (Larsson et al., 2007; Smith and Griebenow, 2006), à la recherche de certaines propriétés pharmacocinétiques et au retrait de certaines réactivités jugées nuisibles (Harvey et al., 2015), comme un caractère d'accepteur de Michael (Oprea, 2000). À titre d'exemple, les règles de Lipinski sont davantage orientées vers une bonne biodisponibilité orale, mais peu en mesure de discriminer seules un composé médicinal d'un autre qui ne l'est pas (Oprea, 2000).

Un certain nombre de raccourcis peuvent être utilisés pour orienter la construction des collections de composés, qui ne découlent pas toutes de la chimie combinatoire. Le croisement de propriétés structurales pour trouver des congénères à des molécules dont l'activité est déjà connue (Harvey et al., 2015; Koch et al., 2005; Schuffenhauer et al., 2007) ou encore la modélisation *in silico* de l'affinité à des récepteurs protéiques (Kutchukian and Shakhnovich, 2010; Vilseck et al., 2018) en font partie. L'inspiration

par les molécules naturelles est un autre de ces outils (Hert et al., 2009; Larsson et al., 2007; Rodrigues et al., 2016).

Les produits naturels ont été, pour les chimistes médicinaux, parmi les toutes premières sources d'inspiration moléculaire. De fait, le tiers des médicaments approuvés entre 1981 et 2010 aux États-Unis découlent soit directement de structures naturelles, soit par des modifications hémisynthétiques (Harvey et al., 2015). L'origine même des métabolites secondaires naturels les prédispose à figurer dans une partie biologiquement pertinente de l'espace chimique (Harvey et al., 2015; Larsson et al., 2007; Rosén et al., 2009). Résultant de la coévolution des formes de vie, l'émergence et la sélection des voies métaboliques sont en effet façonnées par la nécessité d'interagir avec les macromolécules et mécaniques biochimiques du vivant, de sorte que virtuellement tous les produits naturels devraient pouvoir exercer au moins une interaction biologique (Larsson et al., 2007; Rosén et al., 2009).

Les produits naturels peuvent par ailleurs couvrir des zones de l'espace chimique d'intérêt biologique qui ne sont pas accessibles à la chimie combinatoire (Harvey et al., 2015; Larsson et al., 2007; Rosén et al., 2009). À titre d'exemple, ils tendent à comporter plus d'atomes d'oxygène, une hydrophilie supérieure, moins d'atomes d'azote et de cycles aromatiques, et davantage de centres stéréogènes que les substances synthétiques (Larsson et al., 2007; Ortholand and Ganesan, 2004; Rodrigues et al., 2016). Les produits naturels influencent fondamentalement la manière dont la chimie combinatoire est envisagée. En effet, les connaissances acquises au fil du temps par la synthèse totale de produits naturels fourbissent l'arsenal méthodologique de la chimie médicinale. Il en va de même pour l'apport des produits naturels à la découverte des mécanismes des activités biologiques. Ces contributions induisent un biais intrinsèque dans le type de molécules incluses dans les chimothèques combinatoires. On a ainsi estimé qu'en 2009, les molécules offertes commercialement pour des criblages à haut débit dans le secteur pharmaceutique étaient 1000 fois plus

susceptibles de ressembler à un produit naturel que si elles avaient été sélectionnées au seul hasard dans l'espace chimique possible, un phénomène nommé biais biogénique. Ce dernier tend en outre à devenir plus important chez les molécules les plus complexes (Hert et al., 2009). La même étude souligne qu'à cette date, 83 % des types de squelettes cycliques rencontrés chez les produits naturels n'avaient aucun équivalent dans les collections combinatoires (Hert et al., 2009). Cette couverture plus large de l'espace chimique par les produits naturels ressort également des cartes basées sur des descripteurs moléculaires (Rosén et al., 2009; Virshup et al., 2013). Ces constatations mettent en évidence le rôle primordial des produits naturels comme source d'inspiration utile à la chimie médicinale (Harvey et al., 2015; Larsson et al., 2007; Ortholand and Ganesan, 2004; Rodrigues et al., 2016; Rosén et al., 2009).

Beaucoup de la littérature sur l'exploration de l'espace chimique biologiquement pertinent s'attarde aux stratégies de grande ampleur: construction de chimiothèques, classifications statistiques, algorithmes de tri, calculs de propriétés, etc. Toutefois, au vu de leurs propriétés indéniablement pertinentes dans un contexte de bioactivité, le rôle récemment « redécouvert » des produits naturels dans cette démarche doit également rappeler la nécessité de poursuivre les efforts de recherche vers l'identification de nouveaux métabolites secondaires végétaux et microbiens. Ces apports contribuent à leur tour à enrichir l'éventail des avenues d'exploration disponibles. Les produits naturels s'imposent en effet maintenant comme inspirations pour l'augmentation de la diversité des produits synthétisables au sein de collections moléculaires pouvant par la suite être criblées (Bajorath, 2016; Rodrigues et al., 2016).

Les dirchromones, auxquelles cette thèse s'attarde particulièrement, s'insèrent dans cette perspective, et les présents travaux ont eu pour motivation de les faire passer de curiosités phytochimiques à outils d'exploration de l'espace chimique biologiquement pertinent. Les paragraphes suivants traitent donc plus spécifiquement à la classe de composés à laquelle les travaux de cette thèse ont été consacrés, les dirchromones. Elle

situe brièvement ces dernières dans l'espace chimique des produits naturels, résume leur découverte, et expose les défis liés à leur accessibilité.

En premier lieu, les dirchromones se rattachent structuralement au squelette des chromones. Celles-ci sont des dérivés de phénylpropanoïde, largement répandus dans la nature (Sharma et al., 2011). Structuralement parlant, elles présentent un squelette bicyclique constituée d'une γ-pyrone et d'un cycle aromatique (Figure I-4). Elles peuvent présenter de nombreux substituants, et plus particulièrement un groupement aryle lié en position 2. Ce sous-groupe, d'une grande prévalence chez les végétaux, est celui des flavonoïdes.

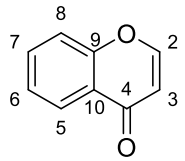

Figure I-4. Structure de la chromone.

Des dérivés de chromones peuvent présenter des propriétés biologiques variées, allant des antiviraux aux antiallergènes en passant par des hypotenseurs, des antitumoraux, des neuroprotecteurs, des relaxants musculaires, des anti-inflammatoires, etc. (Machado and Marques, 2010; Sharma et al., 2011; Silva et al., 2016). Incidemment, ce motif structural a de longue date été employé en chimie médicinale (Gaspar et al., 2014; Keri et al., 2014; Reis et al., 2017). La chromone figure d'ailleurs parmi les six squelettes hétérocycliques les plus récurrents identifiés chez les composés bioactifs en date de 2006 (Ertl et al., 2006).

Plusieurs approches de synthèse de chromones 2-substituées sont connues et couramment appliquées. Bien qu'il en existe d'autres, cinq voies d'accès sont fréquemment employées.

Une première approche régulièrement utilisée pour préparer les 2-styrylchromones consiste d'abord à coupler par crotonisation (Figure I-5A) un aldéhyde à la 2'-hydroxyacétophénone en conditions basiques (hydroxyde de sodium, de potassium ou de baryum dans un solvant alcoolique, bis(triméthylsilyl)amidure de lithium dans le tétrahydrofurane (THF)). L'intermédiaire est ensuite converti en chromone par cyclisation oxydative, avec des systèmes tels que de l'iode dans le diméthylsulfoxyde (DMSO), du peroxyde d'hydrogène en milieu basique, ou du dioxyde de sélénium dans le pentanol ou le xylène (Santos and Silva, 2017).

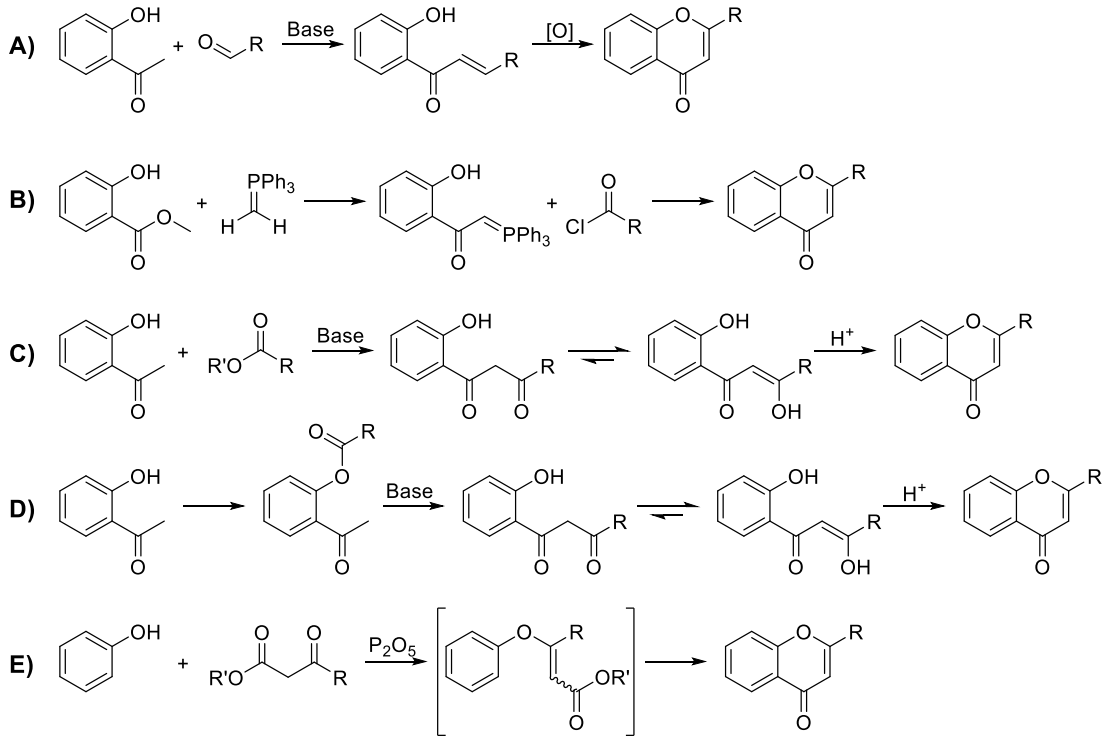

Figure I-5. Voies de synthèse communes de chromones 2-substituées. **A.** Crotonisation suivie de condensation oxydative. **B.** Couplage de Wittig intramoléculaire. **C.** Condensation de Claisen. **D.** Réarrangement de Baker-Venkataraman. **E.** Réaction de Simonis.

Un couplage de Wittig intramoléculaire peut également être employé pour former une chromone (Figure I-5B). Un ester de salicylate est mis en présence d'un ylure de phosphore. L'intermédiaire est alors estérifié avec un chlorure d'acyle à chaud dans la

pyridine, et se cyclise pendant la même étape en chromone (Santos and Silva, 2017). Des variantes sont possibles: l'ester de méthyle peut être remplacé par un trialkylsilyle, et l'estérification du phénol peut être effectuée en amont de la réaction avec l'ylure (Kumar et al., 2000), ou encore l'ylure peut être généré à partir d'une chloroacétophénone (Lee et al., 1991).

La condensation de Claisen (Figure I-5C) et certaines de ses variantes forment toutefois le groupe de stratégies les plus communément employées. (Gaspar et al., 2014; Reis et al., 2017; Santos and Silva, 2017). La réaction parente fait intervenir une base forte (un alkoxyde dans son alcool, un hydrure dans le THF, ou autrement une réduction avec du sodium métallique), la pyridine ou la triéthylamine pour obtenir l'énolate de la 2'-hydroxyacétophénone (Gaspar et al., 2014). Ce dernier réagit alors avec un ester du groupement acyle désiré. On obtient alors une dicétone (dont l'équilibre tautomérique tend vers un énol (Santos and Silva, 2017)) qui peut être cyclisée en chromone par déshydratation, généralement par catalyse avec un acide fort (acide chlorhydrique, acide *para*-toluènesulfonique, acide sulfurique) ou un agent de déshydratation (anhydride triflique, oxychlorure de phosphore), bien que des approches alternatives puissent être employées (Gaspar et al., 2014; Keri et al., 2014; Santos and Silva, 2017).

Le réarrangement de Baker-Venkataraman (Figure I-5D) est similaire, mais implique le recours à une acylation intramoléculaire à partir d'un ester de 2'-hydroxyacétophénone, typiquement en conditions basiques agressives: hydroxyde de potassium dans le DMSO ou la pyridine, hydrure de sodium ou de lithium dans le THF ou le toluène à reflux, carbonate de potassium dans différents solvants à chaud ou à reflux, alcoolate de potassium ou de sodium dans le THF, etc. (Li, 2009; Santos and Silva, 2017). D'autres réactions proches de la condensation de Claisen mais moins communes pour la préparation de 2-alkylchromones, soit la condensation d'Allan-Robinson et la réaction de Kostanecki-Robinson, peuvent également être utilisées. Dans ces variantes, l'acyle désiré, sous forme d'un mélange de son anhydride et de son

sel de sodium ou potassium, est mis en présence de 2'-hydroxyacétophénone à haute température, ce qui mène directement à la chromone sans étape distincte de cyclisation (Gaspar et al., 2014; Li, 2009; Santos and Silva, 2017).

La réaction de Simonis (Figure I-5E) prend le chemin inverse des variantes de la condensation de Claisen, pour plutôt débuter par la formation de l'éther avant l'acylation. Un phénol, typiquement appauvri en électrons par ses substituants, est d'abord condensé avec un β-cétoester en présence de pentoxyde de phosphore, d'acide sulfurique ou d'acide polyphosphorique. Dans la même séquence, l'ester peut ensuite acyler le cycle aromatique pour former une chromone (Gaspar et al., 2014).

Outre ces voies d'accès, d'autres possibilités moins communes existent. Par exemple, des alcynes terminaux peuvent, en présence d'une catalyse au palladium, convertir des esters d'iodophénols (auquel cas une carbonylation au monoxyde de carbone est également requise), ou encore de l'*ortho*-méthoxybenzaldéhyde ou le chlorure d'*ortho*-méthoxybenzoyle, en chromone 2-substituée (Gaspar et al., 2014; Oyama et al., 2011). La 2-chlorochromone peut également être préparée à partir de l'acide 3,3-dichloroacrylique et d'un phénol par une séquence impliquant un réarrangement de Fries et une cyclisation basique (Levas and Levas, 1960).

Ce bref tour d'horizon sur les chromones complété, il convient de présenter plus en détail les dirchromones et leur origine. Elles ont été isolées d'un arbuste endémique de l'est de l'Amérique du Nord, *Dirca palustris* L., de la famille des Thymelaeaceae. Leur découverte résulte de sérendipité lors d'une démarche de fractionnement bioguidé par l'activité cytotoxique. L'extrait au dichlorométhane dégraissé des parties ligneuses de *D. palustris* présentait une forte cytotoxicité sur les cellules épithéliales d'adénocarcinome pulmonaire A-549, ce qui a justifié les efforts de fractionnement. Cette cytotoxicité s'est avérée être principalement attribuable à des diterpènes hautement fonctionnalisés, des orthoesters de type daphnane, nommément la

wikstrotoxine A et la huratoxine (St-Gelais, 2014). Toutefois, en cours de route, une fraction présentant une toxicité moindre envers les cellules A-549, mais plus notable envers les cellules d'adénocarcinome colorectal DLD-1, a été observée. De cette fraction, huit composés apparentés, présentant une fluorescence caractéristique verdâtre sous irradiation UV à 365 nm, ont été purifiés et baptisés dirchromones (St-Gelais et al., 2015) (Figure I-6).

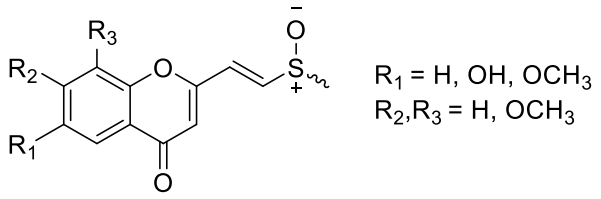

Figure I-6. Structure commune des dirchromones isolées de *Dirca palustris* L.

La singularité des dirchromones tient notamment à la présence, sur leur chaîne latérale, d'un atome de soufre. Les métabolites secondaires soufrés sont, chez les végétaux, habituellement concentrés dans quelques groupes botaniques spécifiques, notamment les Alliaceae et les Brassicales (Ariga and Seki, 2006; Cerella et al., 2011; Fahey et al., 2001; Scherer et al., 2009). L'observation de tels composés chez une espèce de Thymelaeaceae était une nouveauté, tout comme la structure de ce groupe de molécules.

Ainsi, les dirchromones se situent au croisement de deux groupes de composés naturels déjà connus. La présence d'un atome de soufre les rapproche de deux grands types de métabolites secondaires de défense, les glucosinolates et les dérivés de l'alliine. Par ailleurs, au sein des chromones, elles se rapprochent plus particulièrement des 2-alkylchromones.

Les glucosinolates se retrouvent chez les plantes de l'ordre des Brassicales. Sous leur forme native, il s'agit de thioglycosides stables d'une chaîne carbonée comportant une oxime sulfonée (Figure I-7A) (Blažević et al., 2020; Kliebenstein et al., 2005), dont environ 130 structures sont connues (Agerbirk and Olsen, 2012; Blažević et al., 2020).

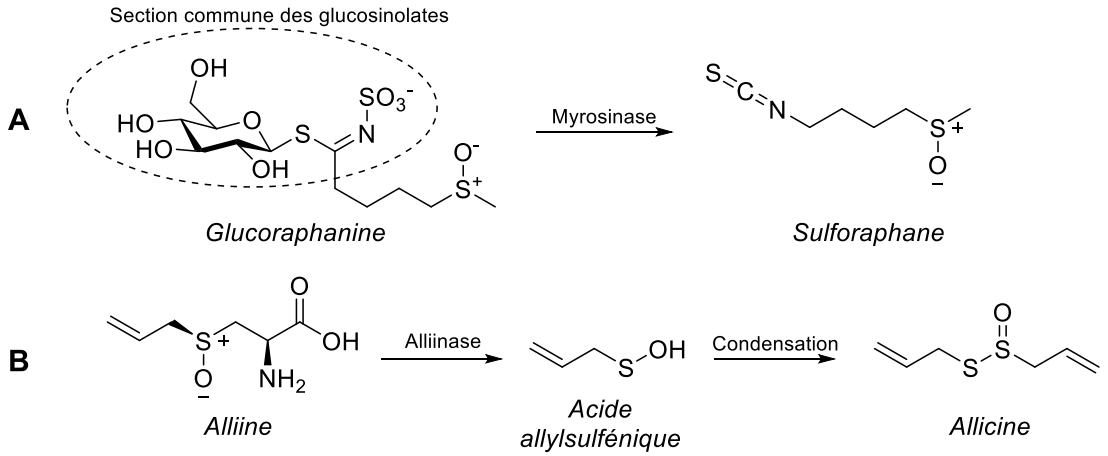

Figure I-7. A: Structure de la glucoraphanine et sa conversion en sulforaphane, illustrant la conversion typique des glucosinolates en isothiocyanates par la myrosinase chez les Brassicales. B: Structure de l'alliine et de certains composés issus de son clivage par l'alliinase. D'autres alliines présentent des *S*-alkyles variés, comportant typiquement de 1 à 4 carbones.

Dans les tissus végétaux, ils sont biosynthétisés parallèlement à des glycoprotéines, les myrosinases, dont ils sont physiquement isolés. Lorsque les cellules sont endommagées, la mise en contact de ces protéines et de leurs substrats relargue du glucose, induisant le réarrangement de Lossen des hétéroatomes par élimination d'un sulfate pour générer des isothiocyanates et dans une moindre mesure des nitriles et des thiocyanates (Fahey et al., 2001; Kliebenstein et al., 2005). Ces composés, ainsi que les glucosinolates intacts, participent à la défense des végétaux contre les agresseurs, présentant notamment des propriétés antimicrobiennes et repoussant plusieurs herbivores (Agerbirk and Olsen, 2012; Fahey et al., 2001; Kliebenstein et al., 2005), bien que certains retournent l'arme chimique à leur avantage pour se défendre eux-mêmes de leurs prédateurs (Agerbirk and Olsen, 2012).

Les dérivés d'alliines se rencontrent pour leur part chez la famille des Alliaceae, où ils jouent également un rôle de protection de la plante. Leur mécanique défensive n'est pas sans rapport avec celle des glucosinolates. Les alliines sont des sulfoxydes dérivés de la cystéine (Figure I-7B) (Burow et al., 2008). Une enzyme, l'alliinase, est également produite et stockée dans des vacuoles, dont le contenu n'est libéré que

lorsque la plante est endommagée. Les alliines sont alors clivées par ces protéines pour libérer des acides sulféniques, qui se convertissent ensuite spontanément par condensation, déshydratation, réarrangement ou hydrolyse en une grande variété de molécules aliphatiques soufrées comme l'allicine, un thiosulfinate (Benkeblia and Lanzotti, 2007; Burow et al., 2008). Cette dernière molécule, agissant possiblement en synergie avec d'autres composés soufrés, est antibactérienne et antifongique (Benkeblia and Lanzotti, 2007; Fujisawa et al., 2009).

Il n'existe qu'une poignée d'autres métabolites secondaires soufrés connus chez les végétaux (Burow et al., 2008; Nwachukwu et al., 2012), et les glucosinolates et alliines sont ceux présentant le plus souvent des sulfoxydes. Les dirchromones possèdent donc une parenté avec ce regroupement de composés, tout en l'élargissant puisqu'elles ne ressemblent pas aux autres molécules soufrées répertoriées.

Par ailleurs, dans la grande famille des chromones, les 2-alkylchromones forment un sous-groupe moins fréquemment observé que les 2-arylchromones (les flavonoïdes). Sans en faire un inventaire complet, quelques exemples permettent d'illustrer le contenu de ce groupe. L'eugénine, l'une des 2-alkylchromones les plus simples trouvée entre autres chez le giroflier *Syzygium aromaticum* (Han and Paik, 2010), est 2-méthylée (Figure I-8). Diverses espèces du genre *Aloe* produisent des 2-alkylchromones à chaîne d'un à trois carbones comportant le plus souvent un ou des alcools, une cétone, ou une insaturation (Bisrat et al., 2000; Lv et al., 2008; Okamura et al., 1998, 1996). *D. palustris* lui-même, outre les dirchromones, contient également de la 2-hydroxyéthyl-chromone (St-Gelais, 2014).

Une série de 2-alkylchromones méritant une mention particulière est celle des 2-phényléthylchromones. Il est notable que tout comme les dirchromones, ces composés soient particulièrement caractéristiques chez les Thymelaeaceae du genre *Aquillaria*. L'étude de ces composés a permis de leur attribuer des activités antimicrobiennes et

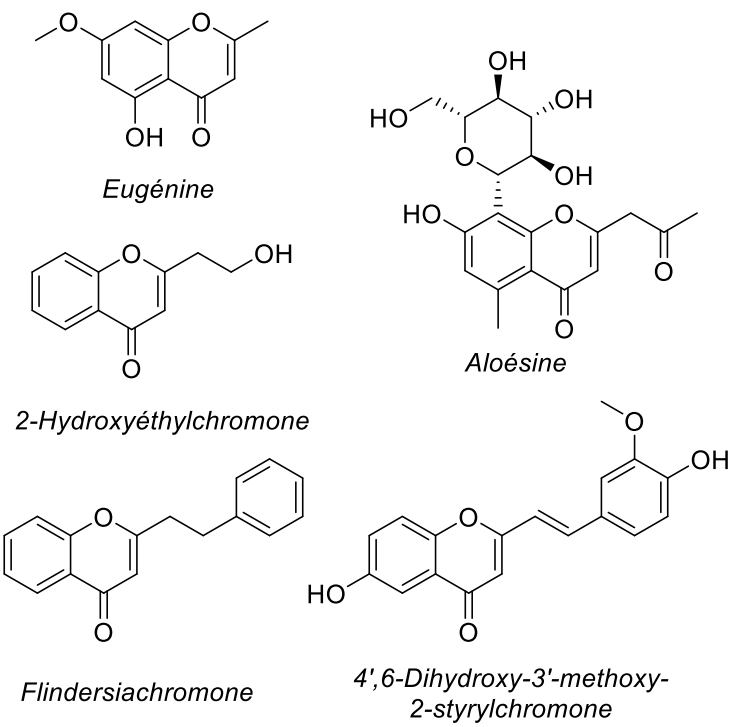

Figure I-8. Structures de quelques 2-alkylchromones n'appartenant pas à la classe des flavonoïdes.

cytotoxiques, entre autres (Ibrahim and Mohamed, 2015). De même, un dérivé des 2-styrylchromones, par ailleurs globalement rares en nature (Santos and Silva, 2017), a également été identifié chez *Aquillaria sinensis* (Yang et al., 2012). Pour ce sous-groupe, exploré en large partie par synthèse, des activités neuroprotectrices, antitumorales, antivirales et antimicrobiennes ont été répertoriées (Santos and Silva, 2017). Dans l'espace chimique, les dirchromones se rangent à proximité relative de ces 2-alkylchromones. Elles en constituent toutefois une extension particulière et sans équivalents connus, y compris du côté des composés synthétiques.

Si les dirchromones ouvrent un nouveau pan de l'espace chimique, leur faible accessibilité constitue un obstacle de taille. Les dirchromones sont des composés présents en quantités très faibles chez *D. palustris*. Pour la dirchromone elle-même, composé le plus abondant de ce groupe isolé de la plante, le rendement sec n'atteignait que 0,0003 %. Il faudrait donc plus de 3 tonnes de matière végétale pour isoler un seul

gramme de la molécule. Toute étude subséquente de la dirchromone exige donc la disponibilité d'une méthode de synthèse totale.

Certains efforts exploratoires de synthèse ont été réalisés préalablement à cette thèse. Ils se sont concentrés sur des stratégies centrées sur la formation de l'alcène latéral, partant donc de chromones construites antérieurement. Toutefois, avec ces approches, certains écueils fondamentaux ont été rencontrés. Par exemple, le couplage de Heck de la 2-chlorochromone avec le méthylvinylsulfide (Figure I-9) se bute à l'intolérance de cette chromone à des conditions basiques, menant à sa dégradation. La préparation des réactifs en présence était par ailleurs rédhibitoire (St-Gelais, 2014).

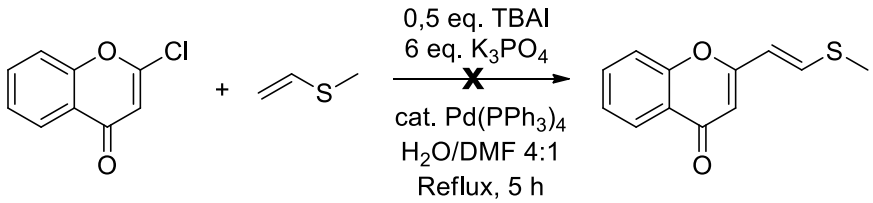

Figure I-9. Couplage de Heck (inopérant) en vue de l'obtention de la dirchromone (St-Gelais, 2014).

Similairement, les essais réalisés avec un réactif de Grignard et une chromone portant un aldéhyde (Figure I-10) n'ont fourni aucun produit caractérisable. La stabilité du réactif lui-même est incertaine et possiblement en cause. Qui plus est, même en cas de succès, la déshydratation de la chaîne latérale pour obtenir l'alcène demeurait incertaine.

De manière inattendue, le couplage de Wittig centré sur le même alcène ne fournit pas le composé voulu (Figure I-11). L'analyse du mélange réactionnel par chromatographie liquide couplée à la spectrométrie de masse semble indiquer la présence d'un intermédiaire métastable comportant à la fois la chromone et le réactif phosphoré, se dégradant lentement en une substance de masse moléculaire inférieure à la chromone de départ.

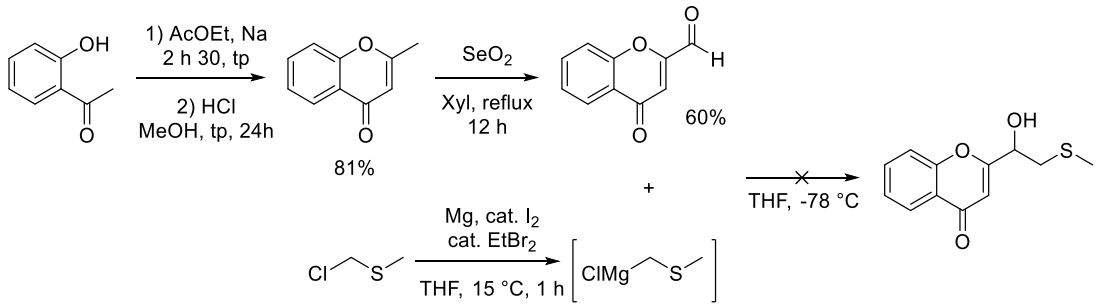

Figure I-10. Tentative de préparation d'un intermédiaire soufré en vue de la préparation de la dirchromone par recours à un réactif de Grignard.

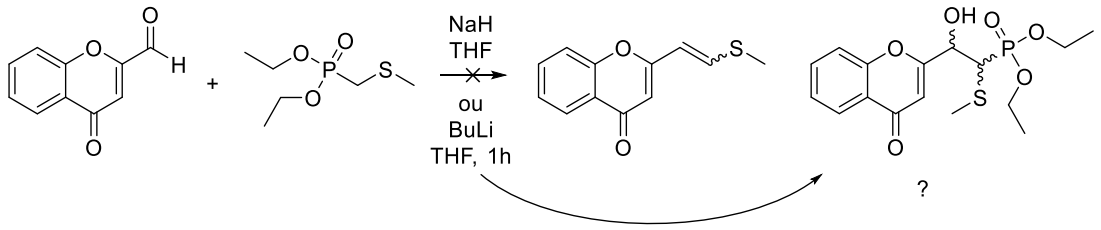

Figure I-11. Essai du couplage de Wittig pour préparer la *S*-déoxydirchromone. Plutôt que le produit désiré, un intermédiaire de masse moléculaire indiquant la rétention du réactif phosphoré a été observé. Une structure hypothétique est fournie.

L'accessibilité par synthèse à la dirchromone et ses dérivés est donc plus complexe qu'il n'y paraît au premier abord. Elle est néanmoins une condition *sine qua non* à toute compréhension subséquente du mécanisme d'action de ces molécules, ainsi qu'à toute étude de l'impact des modifications structurales sur les activités biologiques qui lui sont attribuables.

En effet, les dirchromones naturelles présentent, à des degrés variables, une cytotoxicité (avec une IC_{50} variant par exemple de 1 à >10 µM contre les cellules DLD-1, la lignée la plus sensible) et une activité antimicrobienne envers *Staphylococcus aureus* (MIC_{90} de 3,7 à 14 µg/mL) (St-Gelais et al., 2015). Il a, depuis leur découverte, été suggéré que ces composés pourraient participer au système de défense de *Dirca palustris* contre les agressions, en compensation de la faible lignification et donc de la fragilité de son bois (Mottiar et al., 2020). Le nombre restreint d'analogues isolés et les faibles quantités disponibles n'ont pas permis de détailler davantage de quelle manière

les dirchromones pouvaient exercer ces activités, ni d'explorer l'impact de différentes modifications structurales sur leur potentiel d'interaction avec le vivant.

Conséquemment, l'étude doctorale se concentre autour de la possibilité d'avoir accès par synthèse aux dirchromones afin de pouvoir étudier davantage leurs activités biologiques en relation avec leur structure. Ces travaux permettront conséquemment d'inscrire les dirchromones comme outils pertinents d'exploration d'une nouvelle fraction de l'espace chimique.

Deux hypothèses fondamentales guident les travaux de cette thèse. La première consiste à supposer la faisabilité d'une stratégie de synthèse à la fois simple à mettre en œuvre (peu d'étapes), accessible (rendement adéquat) et flexible (possibilité de modification structurale des substrats de départ). La seconde présume que l'introduction de modifications structurales simples autour du squelette de base de la dirchromone permet de moduler les activités cytotoxiques et antibactériennes, ainsi que d'améliorer la compréhension des propriétés structurales par lequel la dirchromone exerce ces activités.

La thèse comporte trois objectifs centraux:

- Développer une voie de synthèse de la dirchromone qui soit à la fois accessible, flexible et économe en étapes;

- Déterminer la ou les caractéristiques structurales les plus critiques pour les activités biologiques;

- Explorer les relations entre des modifications structurales systématiques et les activités cytotoxique et antibactérienne.

Il convient de brièvement esquisser l'approche méthodologique retenue pour atteindre ces objectifs. Dans un premier temps, une stratégie de synthèse de la dirchromone a été élaborée. Puisque les infructueuses approches préalables de synthèse s'étaient surtout attardées à la formation de l'alcène de la chaîne latérale de la dirchromone, différentes voies de synthèses se concentrant plutôt autour de l'assemblage de la chromone ont été explorées. Les réactions de condensation de Claisen et de réarrangement de Baker-Venkataraman, de mise en œuvre plus simple et d'utilisation plus générale en chimie de synthèse des chromones, ont à cet égard été favorisées. Une fois une voie de synthèse identifiée, sa robustesse aux modifications structurales a été brièvement explorée par la préparation de quelques analogues, et elle a été mise en œuvre à l'échelle du gramme.

Par la suite, plusieurs dizaines de dérivés de dirchromone ont été préparés de manière systématique en adaptant la stratégie de synthèse d'abord développée pour le composé parent. À cette occasion, l'introduction d'un même groupement fonctionnel (méthyl, méthoxyl) à différentes positions et des modifications à la structure de la chaîne latérale de la dirchromone a permis de repérer les parties de la molécule ayant le plus d'importance pour l'activité biologique. La préparation d'analogues présentant une diversité de substituants (cycles fusionnés, hétéroatomes, alkoxydes et esters) a pour sa part fourni une perspective complémentaire à ces observations sur la possibilité de moduler les activités cytotoxique et antibactérienne des dirchromones. Les composés préparés ont été caractérisés par des méthodes spectroscopiques classiques (masse à haute résolution, résonnance magnétique nucléaire), et leurs activités biologiques ont été étudiées *in vitro* en utilisant, pour la cytotoxicité, des courbes dose-réponse sur la survie de différentes lignées cellulaires obtenues en utilisant le réactif de Hoechst (Rage et al., 1990), et pour *S. aureus*, une courbe dose-réponse de la prolifération bactérienne par une méthode de microdilution (Banfi et al., 2003).

Cette thèse est présentée par cumul d'articles; chaque chapitre rapportant donc le contenu d'un article scientifique publié. Le chapitre I s'attarde à la mise en place et à la portée de la synthèse de la dirchromone. Le chapitre II décrit, à partir d'une série de dérivés ciblés, l'importance de la chaîne latérale de la dirchromone dans ses activités biologiques et fournit un aperçu du mécanisme moléculaire par lequel celles-ci pourraient s'exprimer. Le chapitre III, pour sa part, couvre les observations de l'impact de modifications structurales systématiques du squelette de base de la dirchromone sur les activités cytotoxique et antibactérienne, ainsi que des observations circonstancielles sur le potentiel antifongique de certains dérivés. Un chapitre de conclusion résumera ensuite l'ensemble des résultats obtenus, les mettra en perspective, et présentera certaines avenues pour des travaux futurs.

CHAPITRE I

SOFT-ENOLIZATION BAKER-VENKATARAMAN REARRANGEMENT ENABLED TOTAL SYNTHESIS OF DIRCHROMONES AND RELATED 2-SUBSTITUTED CHROMONES

Ce chapitre reprend le contenu d'un article de recherche publié en anglais. Il est donc présenté dans cette langue, avec un résumé en français.

Titre: Soft-enolization Baker-Venkataraman rearrangement enabled total synthesis of dirchromones and related 2-substituted chromones

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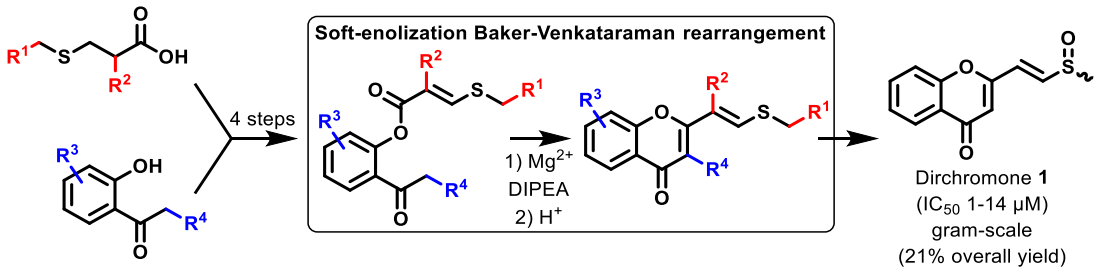
Référence complète: St-Gelais, A., Alsarraf, J., Legault, J., Gauthier, C., Pichette, A., 2018. Soft-enolization Baker-Venkataraman Rearrangement Enabled Total Synthesis of Dirchromones and Related 2-Substituted Chromones. Org. Lett. 20, 7424–7428.

1.1 Résumé en français

Une synthèse totale en sept étapes du squelette original des dirchromones cytotoxiques, impliquant un réarrangement de Baker-Venkataraman en conditions d'énolisation douce sans précédent, a été développée. La méthodologie a donné accès à la dirchromone naturelle **1** (21 % de rendement global) à l'échelle du gramme, et celle-ci a fait l'objet d'un criblage de cytotoxicité sur 13 lignées cellulaires cancéreuses. La portée du réarrangement de Baker-Venkataraman par énolisation douce englobe des chromones de substitutions diverses, incluant les flavonoïdes, les 2-styrylchromones, et les 2-phényléthylchromones.

1.2 Graphical abstract



1.3 Abstract

A seven-step total synthesis of the original scaffold of cytotoxic dirchromones involving an unprecedented soft-enolization Baker-Venkataraman rearrangement was designed. The methodology enabled access to naturally-occurring dirchromone **1** (21 % overall yield) at gram-scale, which was screened for cytotoxicity against 13 cancer cell lines. The scope of the soft-enolization Baker-Venkataraman rearrangement encompasses diversely substituted chromones, including flavonoids, 2-styrylchromones, and 2-phenylethylchromones.

1.4 Article

Dirchromones are a series of sulfur-containing compounds that were isolated from *Dirca palustris* L. bark and wood (St-Gelais et al., 2015). Some of these compounds exhibited a moderately selective cytotoxicity against human colorectal adenocarcinoma (DLD-1) cells, with dirchromone **1** (Figure 1-1) being the most active (IC_{50} 1.0 μM). However, only a limited number of derivatives were characterized and they were isolated in minute quantities. For instance, 12.5 kg of dried wood and bark of *D. palustris* were required to obtain 36 mg of dirchromone **1**, which was isolated after an extensive purification process. A synthetic route toward dirchromone **1** and analogs is thus needed for any further studies to be conducted on the mechanism of action and/or structure-activity relationships (SAR) of this peculiar class of compounds. Dirchromones are structurally similar to two other groups of biologically active molecules. The group of 2-styrylchromones **2** is uncommonly found in nature, but within a large diversity of organisms, and has been the focus of several synthetic efforts, with a variety of reported biological activities such as cytotoxic, anti-inflammatory, and neuroprotective effects (Santos and Silva, 2017). As for the second group, several of the large number of 2-phenylethylchromones **3** found in agarwood, the fungi-infected wood of several Thymelaeaceae (Kristanti et al., 2018), were reported to exhibit interesting *in vitro* anti-inflammatory properties (Chen et al., 2012; Huo et al., 2017).

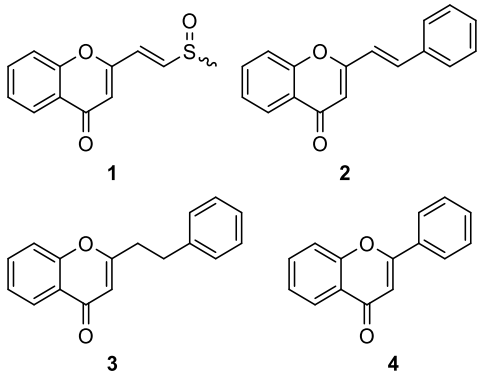
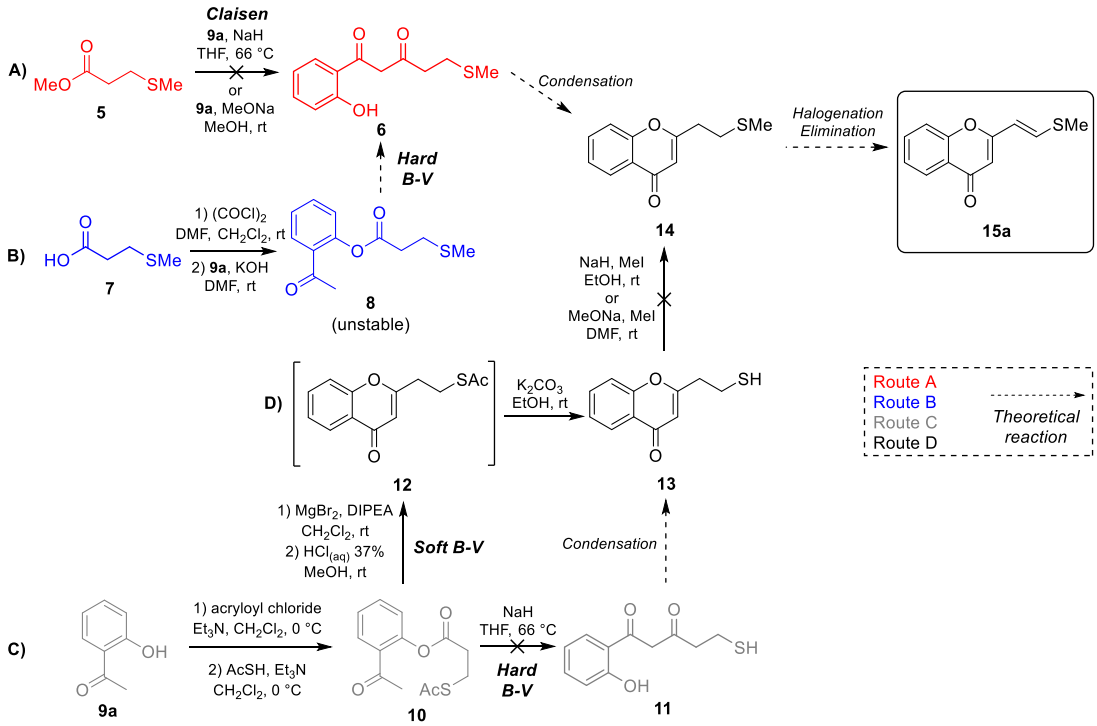


Figure 1-1. Parent structures of 2-substituted chromones: dirchromone (**1**), 2-styrylchromone (**2**), 2-phenylethylchromone (**3**) and flavone (**4**).

Among the reported synthetic approaches toward these biologically active 2-substituted chromones, including the ubiquitous flavone scaffold **4**, the Claisen condensation of activated cinnamates onto 2'-hydroxyacetophenone (Williams et al., 2013) is the most common route. More specifically, its intramolecular counterpart, *i.e.* the Baker-Venkataraman (B-V) rearrangement of cinnamoyl ester of 2'-hydroxyacetophenone (Jain et al., 1982; Santos and Silva, 2017), is widely used. This reaction requires the formation of an enolate (Evans et al., 1982) that is typically produced by deprotonation of acetophenone using a strong base (Zhao et al., 2013). The scope of the reaction is therefore restricted to substrates that tolerate strongly basic conditions, which are referred to as "hard" enolization conditions (Lim et al., 2007). On the other hand, "soft" enolization conditions, where a Lewis acid is used to enable the formation of enolates in the presence of a weak base (Lim et al., 2007; Zhou et al., 2007), have never been applied to the B-V rearrangement (Ameen and Snape, 2015). Along these lines, we demonstrate that hard enolization conditions proved inapplicable to the synthesis of dirchromones, which prompted the development of the first soft-enolization B-V rearrangement. This strategy specifically enabled a facile and scalable synthesis of diversely substituted dirchromone derivatives from readily available and affordable buildings blocks. Illustrating the utility of the proposed

Scheme 1-1. Failed synthetic routes explored for the preparation of (*S*)-deoxydirchromone (**15a**)



synthesis, it gave access to gram-scale preparation of dirchromone **1**. Its cytotoxicity was then screened against 13 cancer cell lines.

The preparation of (*S*)-deoxydirchromone **15a** was the main focus of the initial investigation, provided that it could then be readily oxidized to racemic sulfoxide **1** using 3-chloroperbenzoic acid (*m*-CPBA) (Xing et al., 2017). The first explored strategy was modelled based on classical syntheses of 2-substituted chromones through a Claisen condensation (Wang et al., 2013; Williams et al., 2013) of methyl 3-methylthiopropionate **5** and 2'-hydroxyacetophenone **9a** (Scheme 1-1, route A). This would have been followed by acidic dehydrative cyclisation to compound **14** and oxidation to generate vinylsulfide **15a**. The Claisen condensation, under classical hard conditions involving strong bases such as sodium hydride (Williams et al., 2013; Yu et

al., 2004; Zhao et al., 2013) or sodium alcoolate (Gray et al., 2003), however failed to afford the desired intermediate. A methodological change was thus required.

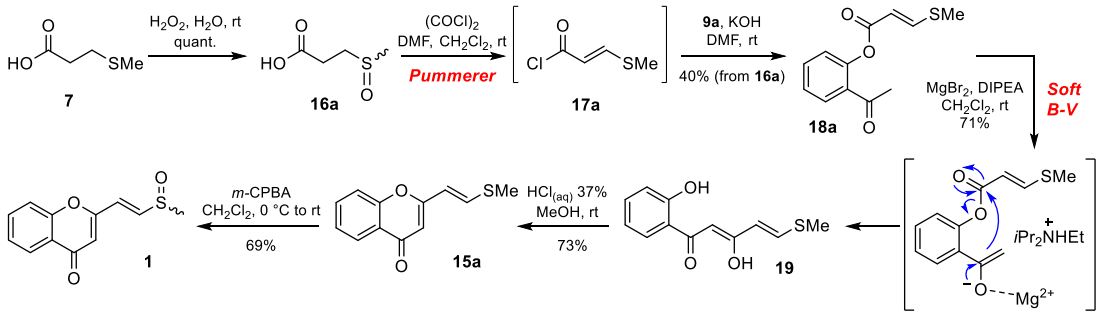
We then envisioned an intramolecular version of this transformation involving a B-V rearrangement of ester **8** followed by acidic cyclisation (Scheme 1-1, route B). However, ester **8** was found to readily degrade, preventing its isolation in sufficient amount and purity to pursue this strategy. Construction of a different sulfur-bearing chain via the easily prepared ester **10** (Scheme 1-1, route C) was found to be an acceptable workaround. The conversion of ester **10** to diketone intermediate **11** under classical B-V conditions however gave phenone **9a** and starting ester **10** as the main products.

The hard conditions involved in either the Claisen condensation or classical B-V rearrangement were suspected to interfere with the reaction. We thus envisioned applying the soft enolization Claisen reaction developed by Lim *et al.* (Lim et al., 2007) to the case of dirchromones synthesis. After screening various Lewis acids, including $ZnCl_2$, $CuOTf_2$ and NiI_2 in different solvents such as THF or toluene, the authors showed that room temperature Claisen condensations could be efficiently conducted using acetophenone and a variety of activated acylating agents. The optimized conditions were demonstrated to involve *N*-acylbenzotriazoles or pentafluorophenyl esters as acylating reagents in the presence of magnesium bromide diethyl etherate in reagent-grade CH_2Cl_2 open to air and using diisopropylethylamine (DIPEA) as a base (Lim et al., 2008). Yet, when 2'-hydroxyacetophenone (**9a**) was used as the substrate, the reported yields were significantly reduced. Furthermore, preparing activated acyl groups from sulfide bearing carboxylic acid **7** to perform a Claisen condensation would involve significant work, and our preliminary testing showed that the yields were very low (data not shown). For these reasons, the soft-enolization intermolecular Claisen condensation seemed not to be a relevant strategy for the preparation of dirchromone precursors. On the other hand, an intramolecular soft-enolization B-V rearrangement

appeared as an attractive alternative. Indeed, direct esterification of 2'-hydroxyacetophenone (**9a**) would yield a proper substrate for a B-V rearrangement, leading to chromone precursors in an atom-economical fashion. Applying Lim's conditions to ester **10** (Scheme 1-1, route D), which could be described as the first reported soft enolization B-V reaction (soft B-V), followed by acidic cyclization and cleavage of the crude thioester **12** with K_2CO_3, provided the thiol **13** in satisfactory yield. Yet, subsequent methylation of thiol **13** to afford compound **14** did not proceed under classical conditions (Rioz-Martínez et al., 2011; Roe et al., 2005).

In search of a more efficient alternative, sulfide **7** was first quantitatively oxidized to crude sulfoxide **16a** (Sato et al., 2001) (Scheme 1-2). The latter was then reacted with oxalyl chloride in anhydrous CH_2Cl_2, which had two purposes. Not only was the acyl chloride generated, but a Pummerer rearrangement followed by an elimination led to an oxidation transfer from the sulfur atom to the lateral chain, providing a vinyl sulfide with complete *E*-selectivity. The formation of a vinylsulfide in such a way is, to the best of our knowledge, quite uncommon (Bur and Padwa, 2004; Smith et al., 2010), sometimes observed as a side product in the course of other Pummerer-type reactions (Horiguchi et al., 2000). As such, our procedure proved to be a straightforward route to useful vinylsulfide building blocks (Bates et al., 2004). The overall reaction to yield derivative **17a** was completed faster when a catalytic amount of DMF was added. Once gas evolution had ceased, coupling the formed reactant with an excess of the conjugated base of 2'-hydroxyacetophenone (**9a**) yielded stable vinylsulfide ester **18a** in a convenient 40 % yield, given the relatively complex one-pot sequence. Ester **18a** was then submitted to the soft B-V conditions (2.5 equiv $MgBr_2$ etherate, 3 equiv DIPEA, CH_2Cl_2 open to air, overnight at room temperature) to afford enol **19** (71 %). Mechanistically, the reaction is likely to proceed through the coordination of Mg^{2+} to the ketone function of ester **18a** that would decrease the pK_a of the α-proton and promote deprotonation by the weak base DIPEA. The generated enolate would then undergo the B-V rearrangement to afford enol **19**. The latter was then successfully

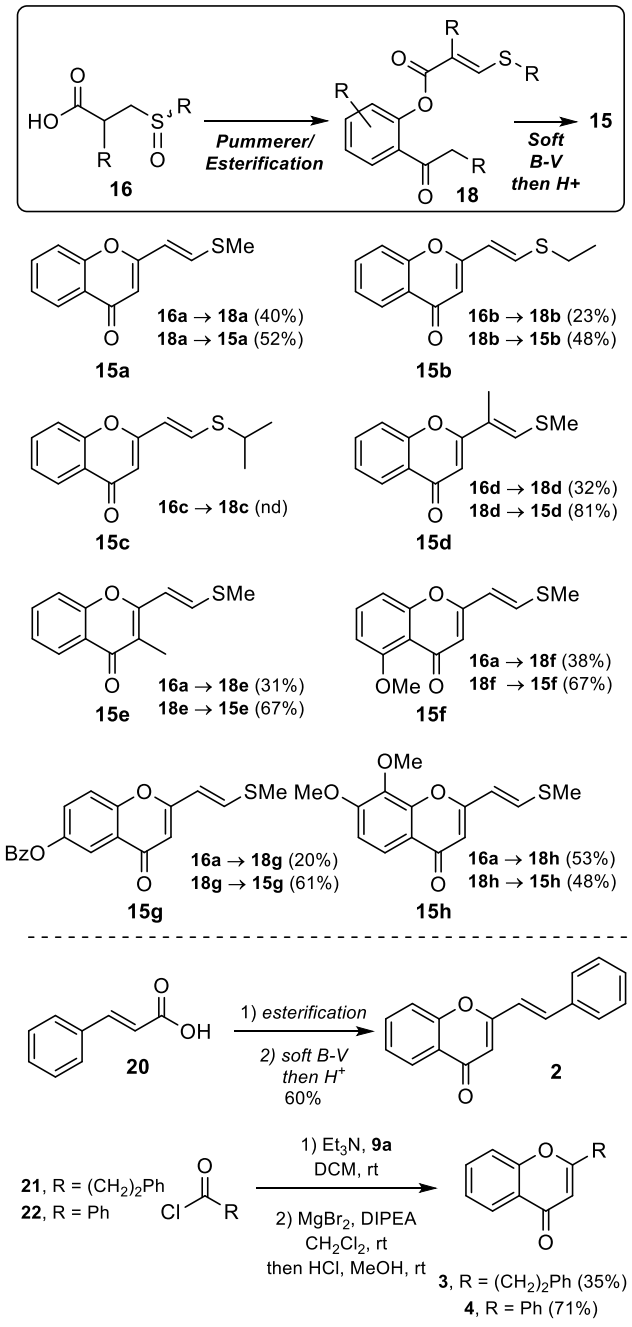
Scheme 1-2. Soft Baker-Venkataraman enabled synthesis of (*S*)-deoxydirchromone, and preparation of dirchromone (**1**)



cyclized into (*S*)-deoxydirchromone **15a** (73 %). These two steps were found to be applicable consecutively, omitting isolation of the enol, with an identical overall yield (52 % over two steps).

Since this overall strategy secured straightforward access to the dirchromone scaffold, it was applied to several substituted dirchromones to explore its scope (Scheme 1-3). The acyl chloride formation/Pummerer rearrangement/esterification step gave moderate overall yields. Pleasingly, the reaction still proceeded well with ethylsulfoxide **18b** even though the elimination step could have been expected to occur on both sides of the sulfide following the Pummerer rearrangement, which could explain the decreased yield. However, the sequence failed for isopropylsulfoxide **18c**, indicating that only unbranched alkylsulfides can be transformed by this method. When a benzoate protecting group was present (compound **18g**), generation of the phenolate had to be conducted with NaH instead of KOH, resulting in decreased esterification efficiency. For other dirchromones, at best, use of potassium phenolate of ketone **9a** in excess as both the substrate and the base was found to slightly increase the yield by 5-10 %, compared to an alternative approach using 1.5 equiv of ketone **9a** in the presence of triethylamine. It thus seems that a stronger conjugated base leads to more convenient yields. The excess phenone could be almost quantitatively retrieved by chromatography, so this procedure was preferred for preparation of compounds **18a-b**,

Scheme 1-3. Scope of the soft B-V rearrangement



18d-f and **18h**. The Pummerer rearrangement itself rather than the acyl chloride generation or esterification steps is presumed to be the most yield-limiting part of the

sequence, since transposition of the same protocol starting with *E*-cinnamic acid (**20**) toward the synthesis of chromone **3** gave a good 76 % yield of ester **21**. When commercial acyl chlorides **21** and **22** were used, a milder esterification with ketone **9a** in the presence of triethylamine was satisfactory, providing the expected ester with yields ranging from 58 to 88 %.

For the second step, it was found that the soft B-V proceeded similarly well when generating a substituted enol, starting from 2'-hydroxypropiophenone toward **15e**. Substituted vinylsulfide **18d** afforded the corresponding methylated deoxydirchromone **15d** in a very good 81 % yield, showing that steric hindrance did not interfere with the soft B-V rearrangement. Also of interest was the possibility to conduct the reaction while retaining a benzoyl group **15g**, indicating the compatibility of the soft conditions with base-sensitive functionalities. The reaction was also readily scalable. The gram-scale soft B-V, which enabled conversion of vinylsufide **18a** into chromone **15a**, proceeded even better than at the mmol scale (52 %), with a yield reaching 67 %, without changing the protocol. The conditions used for the soft B-V rearrangement represent, to the best of our knowledge, a novel approach to this classical reaction, enabling the formation of a wider scope of compounds featuring sensitive functional groups that are not compatible with classical hard conditions. Upon investigation, the reaction offered similarly useful conditions for the preparation of 2-styrylchromone (**2**), 2-phenylethylchromone (**3**) and flavone (**4**) in 79, 61, and 81 % yields, respectively. In comparison, 2-styrylchromone (**2**) was obtained in 43 % yield (from phenone **9**) when the B-V rearrangement was conducted with K_2CO_3 in refluxing acetone (Desideri et al., 2000); or in 73 % yield (from cinnamoyl chloride) following a KOH-mediated B-V rearrangement procedure (Charvin et al., 2017). These backbones of a large number of biologically relevant compounds are, as far as we are aware, always formed under strongly basic conditions (Ameen and Snape, 2015). The softer base/magnesium system was here demonstrated to be applicable to the same

reactions in high yields, foretelling that soft B-V could be usefully applied in the future to a broad variety of syntheses, especially if base-sensitive groups are present.

Oxidation of sulfide **15a** to sulfoxide **1** was completed in good yields (69-87 %) using *m*-CPBA, overall offering a straightforward and efficient synthesis of dirchromone (**1**) whose NMR data were in full agreement with the reported structure (St-Gelais et al., 2015). With no significant modification to experimental protocols, the seven-step sequence, *i.e.*, oxidation, acyl chloride generation, Pummerer rearrangement, esterification, soft B-V rearrangement, condensation, and oxidation, was consecutively and successfully applied to the synthesis of 1.5 g of dirchromone (**1**), with an overall yield of 21 %. With such quantity at hand, cytotoxic activity screening of dirchromone (**1**) was broadened to 13 cancer cell lines. As presented in Table 1-1, dirchromone **1** was found to be cytotoxic against all cancer cell lines tested, with IC_{50} ranging from 1.5 to 14.1 µM. The range of activity (µM) is similar to etoposide used as positive control. DLD-1 and PC-3 are the most sensitive cancer cell lines to dirchromones **1** with IC_{50} of 1.5 and 1.7 µM, respectively. The results confirm the previously reported activity for DLD-1 and A-549 cell lines (St-Gelais et al., 2015).

In summary, we have reported the first soft B-V rearrangement, which can be applied to base-sensitive substrates. Combined to a vinylsulfide-generating Pummerer reaction, this in turn enabled the total synthesis of biologically active dirchromone (**1**), in an amount that would have required over four tons of dried *D. palustris* wood to be isolated. Synthetic preparation of dirchromone (**1**) proceeded from two cheaply available substrates (compounds **7** and **9a**). It is expected that this work will pave the way to a detailed study of mechanism of action of dirchromone (**1**) and SAR. The vinylsulfide-generating Pummerer rearrangement described herein will also be further studied to broaden its field of application. Investigations on the mechanism of action are ongoing and will be reported in due course.

Table 1-1. Cytotoxic activity of synthesized dirchromone (**1**) against a panel of cancer cell lines

Cell line	Type	IC_{50} (µM)	
		Dirchromone (1)	**Etoposide**
DLD-1	colorectal adenocarcinoma	1.5 ± 0.2	5 ± 1
Caco-2	colorectal adenocarcinoma	6.5 ± 0.5	> 50
HT-29	colorectal adenocarcinoma	13.7 ± 0.8	10 ± 2
PC-3	prostate adenocarcinoma	1.7 ± 0.1	4.4 ± 0.7
MCF-7	mammary adenocarcinoma	3.0 ± 0.3	> 50
PA-1	ovarian teratocarcinoma	3.1 ± 0.8	< 0.4
PANC 05.04	pancreatic adenocarcinoma	3.6 ± 0.3	> 50
SK-Mel-2	skin melanoma	3.7 ± 0.5	3.5 ± 0.4
SAOS2	osteosarcoma	3.8 ± 0.2	3.5 ± 0.4
HEP-G2	hepatocarcinoma	4.1 ± 0.7	0.6 ± 0.1
U-87	brain glioblastoma	4.3 ± 0.1	> 50
A-549	lung carcinoma	11.9 ± 0.7	1.7 ± 0.3
U251	glioma	14.1 ± 0.6	3.4 ± 0.7

1.5 Author information

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1.5.2 Author contributions

All authors have given approval to the final version of the manuscript.

1.5.3 Notes

The authors declare no competing financial interest.

1.6 Acknowledgment

The authors acknowledge the Chaire de recherche sur les agents anticancéreux d'origine naturelle for funding. This work was supported by the Canadian Institutes of Health Research (CIHR, operating grants 311906 and 326083 to A. P. and J. L.) and by the Natural Sciences and Engineering Research Council of Canada (NSERC, RGPIN-2016-04950 to C. G.). A. S. G. thanks NSERC for a PhD scholarship. C. G. holds a Fonds de recherche du Québec – Santé (FRQS) Research Scholars Junior 2 Career Award. C. Dussault (UQAC) is gratefully acknowledged for cytotoxicity assays.

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1.8 Supporting information

1.8.1 General experimental procedures

All starting materials and reagents were purchased from commercial sources (Sigma-Aldrich, Toronto Research Chemicals, Alfa Aesar and Oakwood Chemicals) and used as received without further purification. Unless noted otherwise, reactions were conducted using anhydrous commercial solvents under argon atmosphere, introducing reagents with dry disposable syringes and needles. Anhydrous solvents, supplied over molecular sieves, were used as received. Reactions were monitored by thin-layer chromatography (TLC) with silica gel 60 F_{254} 0.25 mm pre-coated aluminum foil plates (Silicycle) and visualised under UV_{254} or by dipping the eluted plates into iodine-impregnated silica (*circa* 500 mg I_2 crystals shaken with *circa* 200 g SiO_2 until a uniform color was obtained, then stored in a closed glass container) for one minute. All flash chromatographic purifications were performed using a low-pressure liquid chromatographic system (Büchi) and silica gel 60 (15-40 μm) columns (Silicycle). Infrared spectra were recorded on dry compounds (a drop of liquid or a few solid particles) using an Agilent Cary 630 FTIR spectrometer equipped with an attenuated

total reflectance (ATR) module, diamond sample interface, with a resolution of 2 cm^{-1} from 4000 cm^{-1} to 650 cm^{-1}. NMR spectra were recorded with a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei, using deuterated chloroform ($CDCl_3$) as the solvent. Chemical shifts were reported in ppm relative to the solvent residual peak (δ = 7.26 ppm for ^{1}H and 77.1 ppm for ^{13}C) and coupling constants *J* in Hertz (Hz). Multiplicities were reported using the following abbreviations: s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet. HRMS were recorded on an Agilent 6224 MS-TOF mass spectrometer equipped with an electrospray source. Electron impact mass spectra (EI-MS) were recorded using an Agilent 7890 GC containing an HP5-MS 30 m × 25 mm × 0.25 µm capillary column, using helium (1 mL/min) as carrier gas with a temperature ramp of 40 °C to 300 °C in 15 minutes, coupled to an Agilent 5975C mass spectrometer. The injection port was heated at 250 °C, and the MS transfer line at 300 °C; MS mode: EI; detector voltage: 1.34 kV; mass range: 40-550 u; scan: 1458.6 u/s.

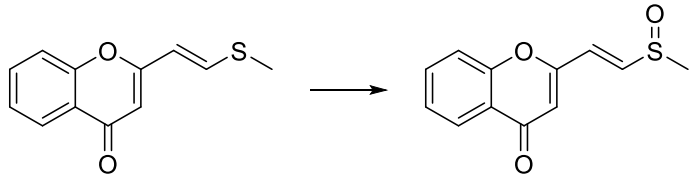
The DLD-1 human colorectal adenocarcinoma, PC-3 human prostatic adenocarcinoma, SAOS2 human osteosarcoma, HT-29 human colorectal adenocarcinoma, PANC 05.04 human pancreatic adenocarcinoma, Caco-2 human colorectal adenocarcinoma, PA-1 human metastatic ovarian teratocarcinoma, A549 human lung carcinoma, U-87 human glioblastoma, SK-Mel-2 human skin melanoma, HEP-G2 human hepatocarcinoma, U-251 human glioma and MCF-7 human mammary adenocarcinoma cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cell lines were grown in minimum essential medium containing Earle's salt (Mediatech Cellgro, Herndon, VA, USA), supplemented with 10 % fetal calf serum (Hyclone, Logan, UT, USA), 1 × solution of vitamins, 1 × sodium pyruvate, 1 × non-essential amino acids, 100 I.U. of penicillin and 100 µg/mL of streptomycin (Mediatech Cellgro). Cells were cultured at 37 °C in a humidified atmosphere containing 5 % CO_2. Exponentially growing cells were plated at a density of 5 × 10^3 cells per well in 96-well microplates (BD Falcon) in culture medium (100 µL) and were allowed to adhere

for 16 h before treatment. Then, cells were incubated for 48 h in the presence or absence of 100 µL of increasing concentrations of compounds dissolved in culture medium and DMSO. The final concentration of DMSO in the culture medium was maintained at 0.5 % (v/v) to avoid toxicity. Cytotoxicity was assessed using Hoechst (bis-benzimide) (Rage et al., 1990). It was expressed as the concentration of drug inhibiting cell growth by 50 % (IC_{50}).

1.8.2 Experimental procedures and characterization

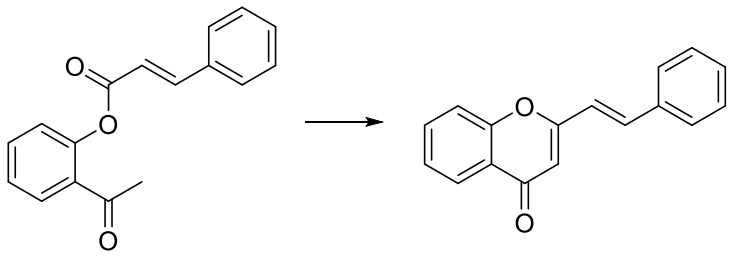
1.8.2.1 Preparation and characterization of chromones **1-4**

Dirchromone (1):



Sulfide **15a** (238 mg, 1.1 mmol) was dissolved in 15 mL of dichloromethane at 0 °C. To this stirred solution was slowly added *meta*-chloroperbenzoic acid of 75 % purity (275 mg, 1.2 mmol) in solution in 5 mL of dichloromethane, and the mixture stirred overnight at room temperature. The reaction was quenched by pouring saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 30-100 % acetone in hexanes to afford dirchromone (**1**) (177 mg, 69 %) as an off-white powder. ^{1}H and ^{13}C NMR spectra of **1** were identical to published data (St-Gelais et al., 2015).

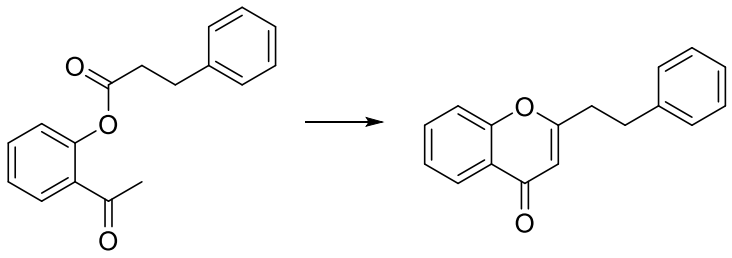
2-Styrylchromone (2):



21 **2**

2-Acetylphenyl cinnamate (**21**) (205 mg, 0.77 mmol) was dissolved in 15 mL of ACS grade dichloromethane, open to air. Magnesium bromide ethyl etherate (496 mg, 1.92 mmol) was added, and the mixture was stirred for 2 minutes. Diisopropyl ethyl amine (399 µL, 2.31 mmol) was then added, and the reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 10 mL of HCl 10 % into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The dried residue was then dissolved in 10 mL of ACS methanol, open to air. Concentrated HCl (1.5 mL) was then added, and the solution was stirred overnight. The reaction was quenched by pouring 30 mL of saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 15-30 % ethyl acetate in hexanes to afford compound **2** (151 mg, 79 %) as a light yellow powder. ^{1}H and ^{13}C NMR spectra of 2-styrylchromone **2** were identical to published data (Pinto et al., 1998).

2-Phenylethylchromone (3):

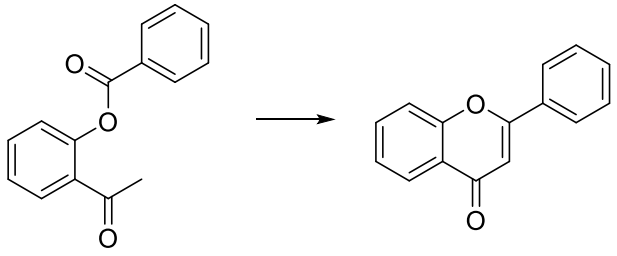


23 **3**

2-Acetylphenyl 3-phenylpropanoate (**23**) (235 mg, 0.88 mmol) was suspended in 10 mL of ACS grade dichloromethane, open to air. Magnesium bromide ethyl etherate (566 mg, 2.19 mmol) was added, and the mixture was stirred for 2 minutes. Diisopropyl ethyl amine (490 μL, 2.63 mmol) was then added, and the reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 10 mL of HCl 10 % into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The dried residue was then dissolved in 10 mL of ACS methanol, open to air. Concentrated HCl (1.5 mL) was then added, and the solution was stirred overnight. The reaction was quenched by pouring 30 mL of saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 0-50 % ethyl acetate in hexanes to afford compound **3** (135 mg, 61 1 %) as a brownish oil. R_f = 0.30 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 3062, 3027, 2922, 2851, 1644, 1603, 1574, 1497, 1464, 1379, 1246, 1220, 1160, 1151, 1119, 1076, 1024, 961, 920, 847, 778, 755, 698, 676; ^{1}H NMR (400 MHz, $CDCl_3$) δδ: 8.13 (d, *J* = 7.8, 1H), 7.58 (t, *J* = 7.1, 1H), 7.37 (d, *J* = 8.3, 1H), 7.30 (t, *J* = 7.5, 1H), 7.27 – 7.21 (m, 2H), 7.21 – 7.11 (m, 3H), 6.09 (s, 1H), 2.99 (t, *J* = 7.6, 2H), 2.86 (t, *J* = 7.6, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 168.3, 156.3, 139.6, 133.4, 128.5, 128.2, 126.4, 125.5, 124.8, 123.5, 117.7, 110.0, 35.9, 32.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ 251.1067, found 251.1077; EI-MS

m/z 251 (4), 250 (19), 131 (8), 128 (4), 92 (22), 91 (100), 77 (8), 65 (17), 64 (5), 63 (8), 51 (5).

Flavone (4):

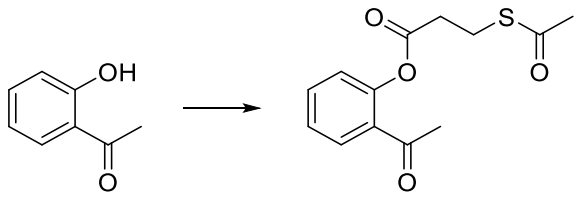


25 **4**

2-Acetylphenyl benzoate (**25**) (325 mg, 1.36 mmol) was suspended in 10 mL of ACS grade dichloromethane, open to air. Magnesium bromide ethyl etherate (875 mg, 3.39 mmol) was added, and the mixture was stirred for 2 minutes. Diisopropyl ethyl amine (706 µL, 4.08 mmol) was then added, and the reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 10 mL of HCl 10 % into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The dried residue was then dissolved in 10 mL of ACS methanol, open to air. Concentrated HCl (1.5 mL) was then added, and the solution was stirred overnight. The reaction was quenched by pouring 30 mL of saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford compound **4** (260 mg, 86 %) as an off-white solid. ^{1}H and ^{13}C NMR spectra of flavone (**4**) were identical to those of a reference commercial sample (Sigma-Aldrich).

1.8.2.2 Preparation and characterization of ester **10**

2-Acetylphenyl 3-(acetylthio)propanoate (10):

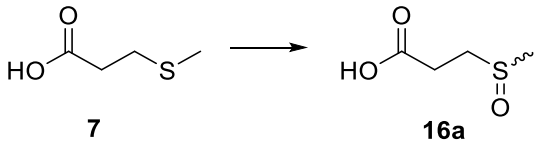


9a **10**

To a solution of 2'-hydroxyacetophenone (**9a**) (1.8 mL, 15 mmol) and triethylamine (3.1 mL, 22.5 mmol) in dry dichloromethane (20 mL) under argon atmosphere was added acryloyl chloride (1.83 mL, 15 mmol) at 0 °C. The solution was stirred at room temperature for 10 minutes. The reaction vessel was then cooled again to 0 °C and more triethylamine (1.05 mL, 7.5 mmol) was added, followed by thioacetic acid (3.22 mL, 45 mmol). The reaction was then stirred for 10 minutes at room temperature, quenched with $NaHCO_3$ and extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 10-40 % ethyl acetate in hexanes to afford compound **10** (3.14 g, 79 %) as a light yellow oil. R_f = 0.54 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 1759, 1682, 1603, 1481, 1447, 1420, 1355, 1283, 1249, 1195, 1119, 1070, 952, 926, 876, 828, 758, 707, 680; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 7.8, 1.6, 1H), 7.38 (td, *J* = 8.1, 1.6, 1H), 7.16 (td, *J* = 7.8; 0.9, 1H), 6.97 (dd, *J* = 8.1, 0.9, 1H); 3.09 (t, *J* = 7.0, 2H), 2.81 (t, *J* = 7.0, 2H), 2.37 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 194.8, 169.9, 148.5, 133.2, 130.1, 130.0, 125.8, 123.5, 34.2, 30.1, 28.9, 23.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_4NS$ $[M+NH_4]^+$ 284.0951, found 284.0958; EI-MS *m/z* 266 (t), 223 (t), 206 (5), 191 (2), 178 (2), 151 (3), 136 (53), 133 (4), 132 (5), 131 (83), 121 (100), 107 (9), 92 (15), 79 (6), 77 (14), 65 (11), 59 (7), 55 (11), 43 (70).

1.8.2.3 Preparation of precursor sulfoxides **16x**

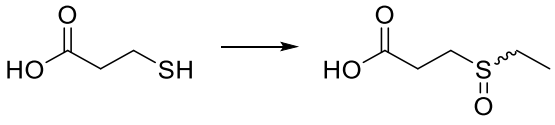
3-(Methylsulfinyl)propanoic acid (16a):



7 **16a**

To compound **7** (4.98 g, 41.5 mmol) diluted in 20 mL of distilled water was added 30 % aqueous hydrogen peroxide (4.70 mL, 45.6 mmol). The solution was stirred at room temperature for 48 h, then evaporated to afford virtually pure compound **16a** (quantitative) as a colorless oil, used for the following steps without further purification. R_f = 0.51 (n-BuOH/AcOH/H_2O, 3:1:1); IR (ATR) ν_{max}: 1708, 1597, 1418, 1295, 1235, 1187, 1149, 1125, 1004, 985, 945, 917, 812, 784, 744, 729, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.43 (s, 1H), 2.87 (dt, *J* = 13.6, 7.7, 1H), 2.76 (dt, *J* = 13.6, 6.7, 1H), 2.51 (t, *J* = 6.8, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 47.6, 37.1, 26.6; HRMS (ESI) *m/z* calcd for $C_4H_9O_3S$ $[M+H]^+$ 137.0267, found 137.0262; EI-MS: decomposes to/rearranges into several other products.

3-(Ethylsulfinyl)propanoic acid (16b)

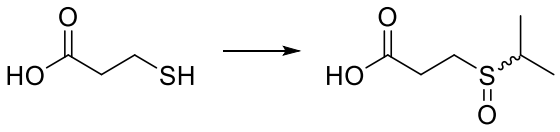


16b

The protocol was adapted from a published procedure (Vaismaa et al., 2007). To 2 mL of absolute ethanol were added 3-mercaptopropionic acid (424 µL, 4.87 mmol), ethyl bromide (397 µL, 5.4 mmol), and sodium hydroxide (390 mg, 9.7 mmol). The solution was then shaken vigorously and placed in a capped vial in an oven maintained at 80 °C for 18 h. The reaction mixture was then cooled, and 3 mL of 10 % aqueous HCl were added. The solution was diluted in water and extracted with 3 × ethyl acetate. The

organic layer was dried over Na_2SO_4, filtered, and evaporated to afford crude 3-(ethylthio)propanoic acid, which was diluted in 15 mL of distilled water containing 5 mL of methanol. To this solution was added 30 % aqueous hydrogen peroxide (491 µL, 4.8 mmol). The solution was stirred at room temperature for 48 h, then evaporated, yielding compound **16b** (659.4 mg) as a colorless oil. The crude product was used without purification for the synthesis of ester **18b**.

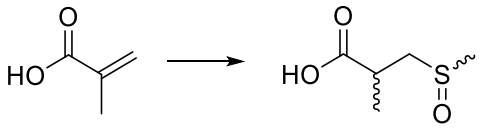
3-(Isopropylsulfinyl)propanoic acid (16c):



16c

The protocol was adapted from a published procedure (Vaismaa et al., 2007). To 2 mL of absolute ethanol were added 3-mercaptopropionic acid (522 µL, 6 mmol), isopropyl bromide (620 µL, 6.6 mmol), and sodium hydroxide (480 mg, 12 mmol). The solution was then shaken vigorously and placed in a capped vial in an oven maintained at 80 °C for 18 h. The reaction mixture was then cooled, and 3 mL of 10 % aqueous HCl were added. The solution was diluted in water and extracted with 3 × ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and evaporated to afford crude 3-(isopropylthio)propanoic acid, which was diluted in 15 mL of distilled water containing 10 mL of methanol. To this solution was added 30 % aqueous hydrogen peroxide (547 µL, 5.36 mmol). The solution was stirred at room temperature for 48 h, then evaporated, yielding compound **16c** (796.4 mg) as a colorless oil. The crude product was used without purification for the synthesis of ester **18c** (not shown here since the reaction did not proceed).

2-Methyl-3-(methylsulfinyl)propanoic acid (16d):

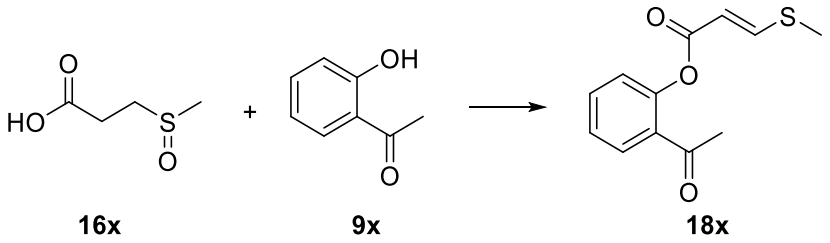


16d

Following the published procedure (Cadamuro, Silvano; Degani, Iacopo; Fochi, Rita; Regondi, 1986), to 5 mL of water were added potassium hydroxide (1.5 g, 26.7 mmol) and methacrylic acid (1.36 mL, 16 mmol), with agitation. After 3 minutes, *S*,*S*'-dimethyl dithiocarbonate (1.04 mL, 10 mmol) was added. The vigorously stirred solution was brought to reflux for 8 h then cooled down. A slight excess of HCl 37 % was added, and the resulting suspension was dried under vacuum. Several portions of hot acetone were sequentially mixed with the residue and filtered to remove the salts. The combined filtered acetone portions were dried to afford crude 2-methyl-3-(methylthio)propanoic acid. The latter (383.3 mg) was diluted in 8 mL of distilled water. To this solution was added 30 % aqueous hydrogen peroxide (321 µL, 3.15 mmol). The solution was stirred at room temperature for 48 h, then evaporated, yielding crude racemic compound **16d** (436.7 mg) as a clear oil. The crude product was used as was for the following synthesis of ester **18d**.

1.8.2.4 Preparation and characterization of vinylsulfide esters **18a-18f** and **18h**

Typical procedure:



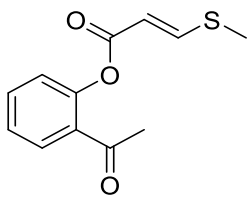
16x **9x** **18x**

A) To a solution of sulfoxide **16** (1 mmol) in dry dichloromethane (4 mL) containing a drop of dry dimethylformamide was slowly added oxalyl chloride (2 mmol) under argon atmosphere. The solution was stirred at room temperature for approximately 1h30, or until no more gas was evolving.

B) In a separate flask, phenone **9** (4 mmol) was mixed to ACS grade methanol (10 mL). To this solution was added potassium hydroxide (4 mmol), and the resulting solution was sonicated until all the base was dissolved. The solution was then thoroughly evaporated under reduced pressure and dried at 10 mbar. The resulting solid was then dissolved in 5 mL of dry dimethylformamide under argon atmosphere.

C) Solution A) was transferred dropwise to solution B) with vigorous stirring. After 10 minutes, the reaction was quenched with NH_4Cl, and extracted with ethyl acetate/toluene 1:1. The organic phase was washed with 3 × NH_4Cl, 1 × brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with a gradient of ethyl acetate in hexanes (specified below for each compound).

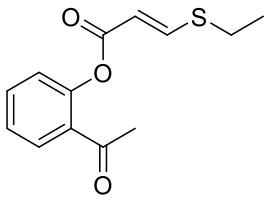
(*E*)-2-Acetylphenyl-3-(methylthio)acrylate (18a):



18a

From compound **16a** (136 mg, 1 mmol) and 2'-hydroxyacetophenone (**9a**) (489 μL, 4 mmol), purified with 0-10 % ethyl acetate in hexanes to afford compound **18a** (95 mg, 40 %) as a translucent oil. R_f = 0.53 (Hex/AcOEt, 7:3); IR (ATR) ν_{max}: 2926, 1708, 1597, 1418, 1295, 1235, 1187, 1149, 1125, 1004, 985, 946, 917, 811, 784, 744, 729, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 14.8, 1H), 7.78 (dt, *J* = 7.8, 1.7, 1H), 7.50 (td, *J* = 8.1, 1.7, 1H), 7.28 (td, *J* = 7.8, 1.0, 1H), 7.11 (dd, *J* = 8.1, 1.0, 1H), 5.86 (d, *J* = 14.8, 1H), 2.52 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.8, 163.3, 150.7, 149.1, 133.3, 131.4, 130.0, 125.9, 123.8, 111.6, 29.8, 14.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}O_3SNa$ $[M+Na]^+$ 259.0400, found 259.0407; EI-MS *m/z* 236 (2), 121 (2), 103 (4), 102 (5), 101 (100), 92 (3), 77 (3), 73 (13), 58 (5), 45 (6).

2-Acetylphenyl (*E*)-3-(ethylthio)acrylate (18b):

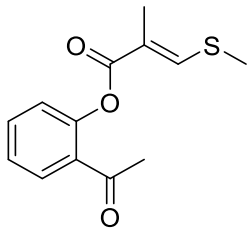


18b

From crude compound **16b** (560 mg, 3.7 mmol) and 2'-hydroxyacetophenone (**9a**) (1.82 mL, 7.5 mmol), purified with 0-10 % ethyl acetate in hexanes to afford compound **18b** (242 mg, 23 %) as an unresolved mixture with *circa* 10 % impurity (yield takes this into account) in the form of a yellow oil. R_f = 0.64 (Hex/AcOEt 7:3); IR (ATR)

ν_{max}: 2975, 2929, 1718, 1685, 1604, 1570, 1479, 1447, 1356, 1295, 1283, 1246, 1189, 1124, 1069, 1018, 947, 922, 863, 819, 745, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 15.1, 1H), 7.69 (dd, *J* = 7.9, 1.3, 1H), 7.41 (td, *J* = 7.9, 1.3, 1H), 7.19 (t, *J* = 7.5, 1H), 7.04 (d, *J* = 7.9, 1H), 5.88 (d, *J* = 15.1, 1H), 2.77 (q, *J* = 7.4, 2H), 2.43 (s, 3H), 1.26 (t, *J* = 7.4, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.4, 163.0, 150.1, 148.9, 133.0, 131.1, 129.7, 125.6, 123.5, 111.7, 29.5, 25.8, 13.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_3SNa$ $[M+Na]^+$ 273.0556, found 273.0544; EI-MS *m/z* 250 (5), 136 (3), 121 (8), 117 (10), 116 (14), 115 (100), 97 (5), 92 (7), 87 (30), 86 (5), 85 (7), 77 (6), 65 (4), 64 (3), 63 (4), 59 (18), 58 (7), 43 (7).

2-Acetylphenyl (*E*)-2-methyl-3-(methylthio)acrylate (18d):

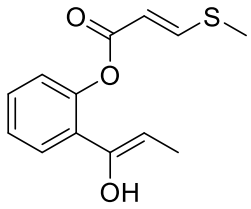


18d

From crude compound **16d** (421 mg, 2.8 mmol) and 2'-hydroxyacetophenone (**9a**) (1.4 mL, 11.2 mmol), purified with 0-10 % ethyl acetate in hexanes to afford compound **18d** (221 mg, 32 %) as a yellow solid. R_f = 0.61 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 3000, 2923, 1756, 1710, 1685, 1591, 1481, 1445, 1429, 1379, 1356, 1334, 1315, 1300, 1282, 1274, 1251, 1220, 1189, 1121, 1070, 1024, 982, 961, 951, 894, 866, 861, 832, 812, 756, 716, 676; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (dd, *J* = 7.8, 1.6, 1H); 7.75 (d, *J* = 1.1, 1H), 7.49 (td, *J* = 8.1, 0.7, 1H), 7.27 (td, *J* = 7.7, 0.6, 1H), 7.09 (dd, *J* = 8.1, 0.7, 1H), 2.50 (s, 3H), 2.45 (s, 3H), 1.96 (d, *J* = 1.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.8, 163.9, 149.5, 147.8, 133.2, 131.4, 130.0, 125.8, 123.8, 121.3, 29.7, 17.5, 13.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_4SNa$ $[M+Na]^+$ 273.0556, found 273.0548; EI-MS

m/z 250 (7), 121 (2), 117 (5), 116 (6), 115 (100), 92 (2), 87 (17), 72 (4), 71 (4), 59 (2), 53 (2), 45 (6).

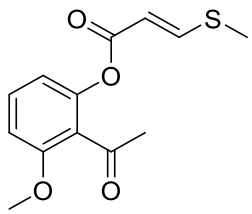
(*E*)-2-((*Z*)-1-Hydroxyprop-1-en-1-yl)phenyl 3-(methylthio)acrylate (18e):



18e

From compound **16a** (275 mg, 2 mmol) and 2'-hydroxypropiophenone (**9e**) (1.11 mL, 8.1 mmol), purified with 0-10 % ethyl acetate in hexanes to afford compound **18e** (156 mg, 31 %) as a yellow oil. R_f = 0.64 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 3049, 2985, 2934, 1731, 1632, 1610, 1540, 1485, 1445, 1371, 1276, 1239, 1205, 1154, 1102, 1061, 1045, 973, 954, 942, 896, 861, 836, 803, 751, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.12 (s, 1H), 7.84 (d, *J* = 14.6, 1H), 7.72 (d, *J* = 7.6, 1H), 7.43 (t, *J* = 7.1, 1H), 6.94 (d, *J* = 8.1, 1H), 6.85 (t, *J* = 7.1, 1H), 6.07 (d, *J* = 14.6, 1H), 4.55 (m, 1H), 2.29 (s, 3H), 1.46 (d, *J* = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.8, 191.3, 162.7, 149.8, 136.6, 130.1, 119.1, 118.8, 118.5, 118.0, 54.4, 14.5, 13.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_2S$ $[M+H]^+$-$[H_2O]$ 233.0631, found 233.0633; EI-MS *m/z* 250 (t), 203 (53), 147 (1), 130 (1), 121 (27), 115 (10), 101 (100), 93 (7), 77 (3), 73 (13), 65 (11), 58 (5), 45 (6).

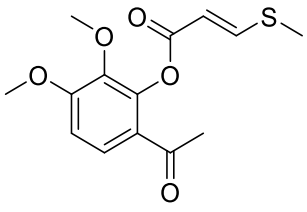
(*E*)-2-Acetyl-3-methoxyphenyl 3-(methylthio)acrylate (18f):



18f

From compound **16a** (171 mg, 1.3 mmol) and 2'-hydroxy-6'-methoxyacetophenone (**9f**) (835 mg, 5.0 mmol), purified with 0-15 % ethyl acetate in hexanes to afford compound **18f** (129 mg, 38 %) as a yellow oil. R_f = 0.53 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 2924, 2841, 1718, 1698, 1602, 1571, 1466, 1437, 1351, 1322, 1293, 1272, 1250, 1224, 1207, 1169, 1128, 1077, 1053, 1011, 942, 918, 842, 804, 766, 729, 708, 693, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 14.9, 1H), 7.29 (t, *J* = 8.30, 1H), 6.77 (d, *J* = 8.4, 1H), 6.70 (d, *J* = 8.1, 1H), 5.74 (d, *J* = 14.9, 1H), 3.79 (s, 3H), 2.45 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.6, 163.0, 157.2, 150.3, 147.5, 130.8, 124.4, 115.1, 111.3, 108.5, 55.9, 31.6, 14.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_4S$ $[M+H]^+$ 267.0686, found 267.0677; EI-MS *m/z* 266 (1), 238 (t), 219 (10), 175 (2), 166 (1), 151 (4), 107 (6), 101 (100), 91 (1), 73 (13), 58 (4), 45 (5).

(*E*)-6-Acetyl-2,3-dimethoxyphenyl 3-(methylthio)acrylate (18h):



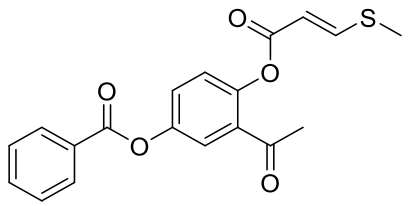
18h

From compound **16a** (172 mg, 1.3 mmol) and gallacetophenone 3',4'-dimethyl ether (**9h**) (984 mg, 5.0 mmol), purified with 25-45 % ethyl acetate in hexanes to afford

compound **18h** (201 mg, 53 %) as a sticky yellow solid. R_f = 0.23 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 2939, 2841, 1719, 1675, 1593, 1576, 1498, 1452, 1421, 1357, 1272, 1246, 1211, 1194, 1181, 1128, 1078, 1015, 969, 943, 843, 802, 740, 701, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 14.8, 1H), 7.57 (d, *J* = 8.8, 1H), 6.80 (d, *J* = 8.8, 1H), 5.90 (d, *J* = 14.8, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 2.44 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.9, 162.9, 157.1, 150.5, 144.1, 141.4, 125.8, 124.7, 111.4, 108.9, 608, 56.1, 29.7, 14.4; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_5SNa$ $[M+Na]^+$ 319.0611, found 319.0613; EI-MS *m/z* 296 (3), 196 (3), 181 (6), 137 (4), 109 (2), 101 (100), 95 (2), 73 (13), 58 (4), 43 (6).

1.8.2.5 Preparation and characterization of vinylsulfide ester **18g**

(*E*)-3-Acetyl-4-((3-(methylthio)acryloyl)oxy)phenyl benzoate (18g):



18g

A) To a solution of crude compound **16a** (138 mg, 1.0 mmol) in dry dichloromethane (4 mL) containing a drop of dry dimethylformamide was slowly added oxalyl chloride (173 µL, 2.0 mmol) under argon atmosphere. The solution was stirred at room temperature for 1 h.

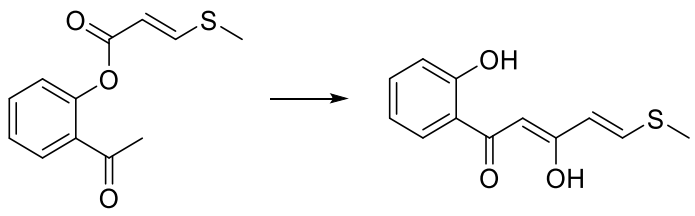
B) In a separate flask, 2'-hydroxy-5'-benzoylacetophenone (**9g**) (1.04 g, 4.0 mmol) prepared according to a published procedure (Nussbaumer et al., 2002) was dissolved in 8 mL of dry dimethylformamide. To this solution was added 60 % sodium hydride in mineral oil (162 mg, 4.0 mmol), and the resulting solution was sonicated until all the base was dissolved.

C) Solution A) was transferred dropwise to solution B) with vigorous stirring.

After 10 minutes, the reaction was quenched with NH_4Cl, and extracted with ethyl acetate/toluene 1:1. The organic phase was washed with 3 × NH_4Cl, 1 × brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 0-20 % ethyl acetate in hexanes to afford compound **18g** (73 mg, 20 %) as a white solid. R_f = 0.60 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 2920, 1730, 1723, 1691, 1584, 1480, 1451, 1425, 1362, 1317, 1293, 1274, 1265, 1240, 1213, 1177, 1128, 1081, 1063, 1024, 964, 949, 932, 910, 867, 852, 839, 814, 797, 752, 703, 685, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 7.2, 2H), 8.03 (d, *J* = 14.8, 1H), 7.70-7.61 (m, 2H), 7.51 (t, *J* = 7.7, 2H), 7.40 (dd, *J* = 8.7, 2.7, 1H), 7.20 (d, *J* = 8.7, 1H), 5.88 (d, *J* = 14.8, 1H), 2.54 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.8, 164.9, 163.3, 151.2, 148.2, 146.7, 134.0, 132.2, 130.3, 129.0, 128.7, 126.6, 125.0, 123.1, 111.4, 29.9, 14.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}O_5NS$ $[M+NH_4]^+$ 374.1057, found 374.1042; EI-MS *m/z* 256 (6), 151 (4), 106 (12), 105 (100), 78 (5), 77 (64), 53 (4), 52 (5), 51 (17), 50 (5), 43 (9).

1.8.2.6 Soft enolization Baker-Venkataraman rearrangement to afford enol **19**

(2*Z*,4*E*)-3-Hydroxy-1-(2-hydroxyphenyl)-5-(methylthio)penta-2,4-dien-1-one (19):



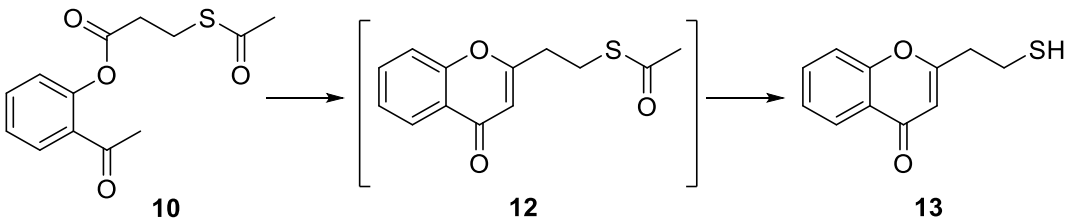
18a **19**

Compound **18a** (301 mg, 1.3 mmol) was suspended in 10 mL of ACS grade dichloromethane, open to air. Magnesium bromide ethyl etherate (822 mg, 3.2 mmol) was added, and the mixture was stirred for 2 minutes. Diisopropyl ethyl amine (659 µL,

2.8 mmol) was then added, and the reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 10 mL of HCl 10 % into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified with 0-5 % ethyl acetate in hexanes to afford compound **19** (213 mg, 71 %) as a yellow solid. R_f = 0.67 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 2920, 2116, 1731, 1575, 1534, 1481, 1425, 1341, 1294, 1255, 1237, 1163, 1129, 1037, 981, 934, 986, 956, 925, 752, 703, 676; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.87 (s, 1H), 12.26 (s, 1H), 7.70 (d, *J* = 14.7, 1H), 7.62 (d, *J* = 7.9, 1H), 7.40 (t, *J* = 7.7, 1H), 6.95 (d, *J* = 8.3, 1H), 6.85 (t, *J* = 7.5, 1H), 6.07 (s, 1H), 5.78 (d, *J* = 14.7, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.5, 173.6, 162.3, 143.0, 135.5, 128.4, 119.1, 119.0, 118.6, 117.0, 94.3, 14.6; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}O_3S$ $[M+H]^+$ 237.0580, found 237.0579; EI-MS *m/z* 236 (5), 191 (1), 190 (12), 189 (100), 121 (26), 101 (58), 93 (6), 77 (5), 73 (11), 65 (11), 58 (4), 45 (6).

1.8.2.7 Consecutive soft Baker-Venkataraman rearrangement and dehydrative cyclization toward chromones **13** and **15x**

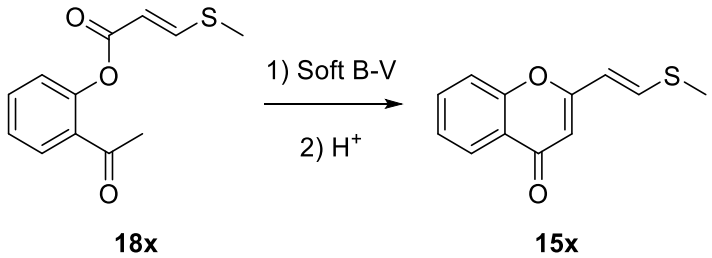
_S_-(2-(4-Oxo-4_H_-chromen-2-yl)ethyl) ethanethioate (12):



To a solution of ester **10** (2.74 g, 10.25 mmol) in ACS grade dichloromethane (100 mL), open to air, was added magnesium bromide ethyl etherate (6.62 g, 25.63 mmol) and the mixture was stirred for 2 minutes. Diisopropyl ethyl amine (5.4 mL, 31.1 mmol) was then added, and the reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 150 mL

of HCl 10 % into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The dried residue was then dissolved in 250 mL of ACS grade methanol. Concentrated HCl (15 mL) was then added, and the solution was stirred overnight. The reaction was quenched by pouring 200 mL of saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified with 30-40 % ethyl acetate in hexanes to afford a mixture of compounds **12** and **13**. This mixture (1.33 g) was dissolved in methanol/water 2:1 (25 mL) to which was added K_2CO_3 (883 mg, 6.4 mmol). The solution was vigorously stirred for 24 h at room temperature. The reaction was quenched with HCl 10 % in excess and extracted with 3 × ethyl acetate. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated to afford compound **13** (973 mg, 46 % 2-steps) as a brownish powder. R_f = 0.13 (Hex/AcOEt 1:1); IR (ATR) ν_{max}: 3056, 2029, 1633, 1607, 1571, 1466, 1419, 1388, 1332, 1275, 1252, 1221, 1162, 1118, 1029, 1019, 958, 925, 874, 846, 841, 785, 757, 680, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 7.7, 1H), 7.65 (t, *J* = 7.7, 1H), 7.51-7.31 (m, 2H), 6.22 (s, 1H), 3.14-2.74 (m, 4H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3, 166.8, 156.5, 133.8, 125.9, 125.3, 123.8, 118.0, 110.8, 34.8, 29.3; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}O_2S$ $[M+H]^+$ 207.0474, found 207.0475; EI-MS: compound **13** decomposed to 2-vinylchromone.

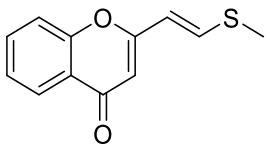
Typical procedure for 15x:



18x **15x**

To a solution of ester **18x** (1 mmol) in ACS grade dichloromethane (10 mL), open to air, magnesium bromide ethyl etherate (2.5 mmol) was added, and the mixture was stirred for 2 minutes. Diisopropyl ethyl amine (3 mmol) was then added, and the reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 15 mL of HCl 10 % into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The dried residue was then dissolved in 25 mL of ACS grade methanol. Concentrated HCl (1.5 mL) was then added, and the solution was stirred overnight. The reaction was quenched by pouring 20 mL of saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography with a gradient of ethyl acetate in hexanes (specified below for each compound).

(*E*)-2-(2-(methylthio)vinyl)-4*H*-chromen-4-one ((*S*)-deoxydirchromone, 15a):



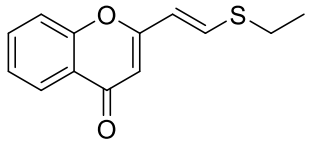
15a

From compound **18a** (244 mg, 1.0 mmol), purified with 30-40 % ethyl acetate in hexanes to afford compound **15a** (117 mg, 52 %) as a reddish solid. R_f = 0.23 (Hex/AcOEt 7:3); IR (ATR) 3062, 3042, 2997, 1639, 1616, 1601, 1571, 1463, 1427, 1380, 1329, 1292, 1245, 1236, 1219, 1178, 1124, 1026, 988, 964, 935, 853, 835, 777, 768, 754, 707, 692, 678, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 7.8, 1H), 7.58 (m, 1H), 7.53 (d, *J* = 15.1, 1H), 7.36 (d, *J* = 8.4, 1H), 7.30 (t, *J* = 7.5, 1H), 6.04 (s, 1H), 5.90 (d, *J* = 15.1, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4, 160.8, 155.8, 138.2, 133.5, 125.6, 124.8, 123.9, 117.6, 115.0, 107.7, 14.5; HRMS (ESI) *m/z* calcd for

$C_{12}H_{11}O_2S$ $[M+H]^+$ 219.0474, found 219.0465; EI-MS *m/z* 220 (2), 29 (5), 218 (33), 205 (6), 204 (13), 203 (100), 171 (3), 159 (1), 147 (6), 131 (4), 121 (7), 120 (4), 115 (4), 98 (12), 97 (13), 95 (4), 92 (13), 69 (2), 64 (7), 63 (8), 45 (4).

The same compound was obtained from enol **19** (62 mg, 0.26 mmol), applying the protocol starting at the stage of dissolution in methanol, with a yield of 73 % (38 mg).

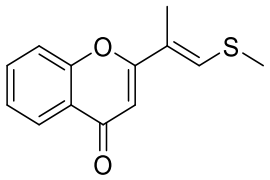
(*E*)-2-(2-(Ethylthio)vinyl)-4*H*-chromen-4-one (15b):



15b

From compound **18b** (202 mg, 0.81 mmol), purified with 10-20 % ethyl acetate in hexanes to afford compound **15b** (90 mg, 48 %) as a light orange solid. R_f = 0.44 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 3054, 2972, 2928, 2865, 1638, 1614, 1600, 1566, 1477, 1459, 1378, 1263, 1253, 1218, 1176, 1125, 1026, 970, 940, 890, 848, 832, 785, 775, 767, 753, 695, 673; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (dd, *J* = 7.9, 1.2, 1H), 7.51 (ddd, *J* = 8.4, 7.2, 1.5, 1H), 7.41 (d, *J* = 15.3, 1H), 7.30 (d, *J* = 8.4, 1H), 7.23 (t, *J* = 7.5, 1H), 5.96 (s, 1H), 5.94 (d, *J* = 15.3, 1H), 2.81 (q, *J* = 7.5, 2H), 1.30 (t, *J* = 7.5, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 160.6, 155.6, 137.8, 133.3, 125.4, 124.7, 123.8, 117.5, 115.7, 107.5, 26.1, 13.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_2S$ $[M+H]^+$ 233.0631, found 233.0627; EI-MS *m/z* 234 (1), 233 (3), 232 (15), 205 (5), 204 (13), 203 (100), 175 (3), 147 (9), 131 (6), 121 (7), 115 (4), 97 (4), 92 (12), 77 (5), 64 (6), 63 (8),45 (6).

(*E*)-2-(1-(Methylthio)prop-1-en-2-yl)-4*H*-chromen-4-one (11-Methyl-(*S*)-deoxydirchromone, 15d):



15d

From compound **18d** (220 mg, 0.88 mmol), purified with 20-30 % ethyl acetate in hexanes to afford compound **15d** (165 mg, 81 1 %) as an orange solid. R_f = 0.49 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 2921, 1624, 1595, 1570, 1464, 1392, 1370, 1327, 1247, 1225, 1129, 1067, 997, 933, 858, 836, 812, 773, 750, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (dd, *J* = 7.9, 1.4, 1H), 7.51 (ddd, *J* = 8.5, 7.3, 1.4, 1H), 7.31 (d, *J* = 8.5, 1H), 7.24 (d, *J* = 7.3, 1H), 7.21 (d, *J* = 1.1, 1H), 6.11 (s, 1H), 2.43 (s, 3H), 1.84 (d, *J* = 1.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 161.8, 155.7, 137.7, 133.4, 125.3, 124.6, 123.4, 122.2, 117.5, 105.4, 17.4, 14.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_2S$ $[M+H]^+$ 233.0631, found 233.0629; EI-MS *m/z* 234 (1), 233 (4), 232 (23), 219 (6), 218 (15), 217 (100), 185 (3), 184 (3), 128 (6), 121 (6), 115 (5), 112 (4), 111 (3), 102 (4), 97 (14), 92 (14), 77 (4), 69 (4), 65 (6), 64 (7), 63 (11), 53 (6), 45 (9).

Configuration of *E*/*Z* isomer: In a (*Z*) isomer, for two possible planar conformers, a correlation between H3 and H12 was not possible, whereas it was for one conformer of the (*E*) isomer (Figure 1-2). Such correlation was observed in 1D NOESY for proton H3.

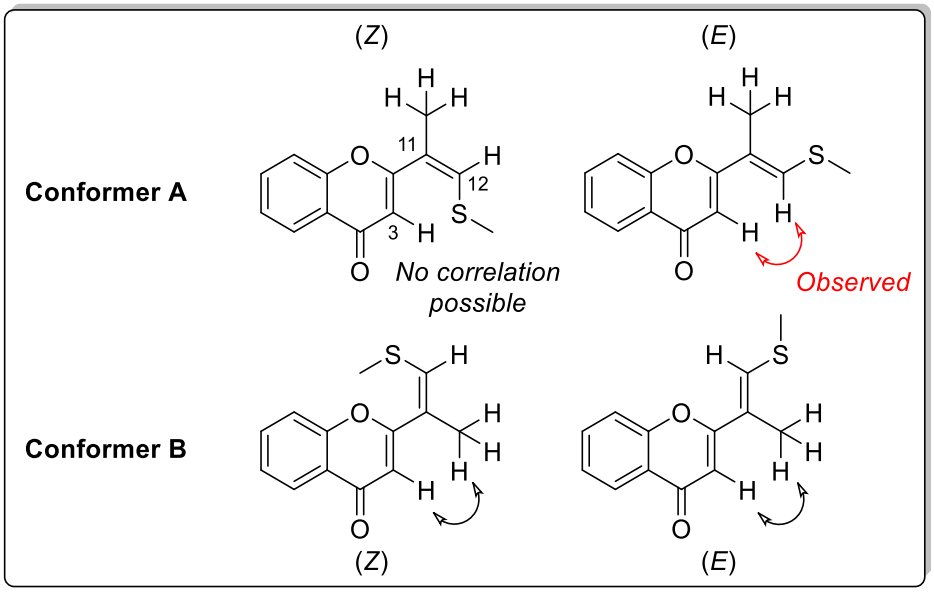
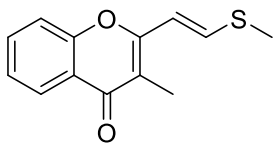


Figure 1-2. Possible planar conformers of chromone **15d** for (*Z*) and (*E*) isomers, with observed NOESY correlation confirming the (*E*) isomer shown in red.

(*E*)-3-Methyl-2-(2-(methylthio)vinyl)-4*H*-chromen-4-one (3-methyl-(*S*)-deoxydirchromone, 15e):

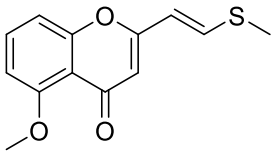


15e

From compound **18e** (101 mg, 0.43 mmol), purified with 25-35 % ethyl acetate in hexanes to afford compound **15e** (68 mg, 67 %) as an off-white solid. R_f = 0.63 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 3068, 2921, 1633, 1615, 1605, 1569, 1467, 1393, 1376, 1334, 1298, 1285, 1255, 1233, 1179, 1111, 1090, 1000, 980, 934, 909, 864, 839, 813, 789, 752, 713, 692, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (dd, *J* = 7.9, 1.4, 1H), 7.52 (m, 1H), 7.48 (d, *J* = 14.9, 1H), 7.34-7.19 (m, 2H), 6.17 (d, *J* = 14.9, 1H), 2.39 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 156.4, 155.1, 137.5, 133.0, 125.7, 124.3, 122.5, 117.2, 114.0, 113.1, 14.5, 9.3; HRMS (ESI) *m/z* calcd for

$C_{13}H_{13}O_2S$ $[M+H]^+$ 233.0631, found 233.0634; EI-MS *m/z* 234 (3), 233 (4), 232 (27), 217 (50), 185 (100), 173 (4), 155 (5), 128 (13), 121 (5), 112 (6), 102 (8), 97 (13), 92 (11), 77 (6), 65 (8), 63 (8), 53 (5), 45 (5).

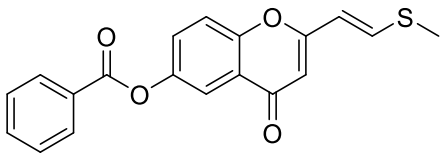
(*E*)-5-Methoxy-2-(2-(methylthio)vinyl)-4*H*-chromen-4-one (5-methoxy-(*S*)-deoxydirchromone, 15f):



15f

From compound **18f** (123 mg, 0.46 mmol), purified with 40-85 % ethyl acetate in hexanes to afford compound **15f** (76 mg, 67 %) as a pink solid. R_f = 0.23 (AcOEt); IR (ATR) ν_{max}: 3009, 2917, 2843, 1618, 1599, 1571, 1555, 1473, 1437, 1376, 1320, 1264, 1170, 1117, 1079, 1066, 990, 973, 947, 863, 841, 806, 793, 759, 714, 678, 660; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (t, *J* = 8.4, 1H); 7.41 (d, *J* = 15.1, 1H), 6.91 (d, *J* = 8.4, 1H), 6.70 (d, *J* = 8.3, 1H), 5.92 (s, 1H), 5.81 (d, *J* = 15.1, 1H), 3.89 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3, 159.6, 158.6, 157.8, 137.2, 133.4, 114.5, 114.3, 109.7, 109.1, 106.2, 56.4, 14.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_3S$ $[M+H]^+$ 249.0580, found 249.0584; EI-MS *m/z* 250 (6), 249 (17), 248 (100), 231 (12), 219 (30), 218 (9), 215 (4), 204 (210), 203 (60), 202 (60), 187 (5), 171 (7), 147 (4), 134 (4), 122 (4), 121 (5), 115 (5), 107 (17), 98 (7), 97 (8), 92 (5), 51 (3).

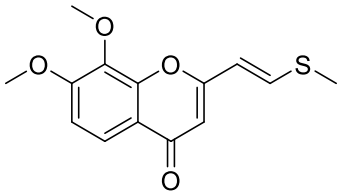
(*E*)-2-(2-(Methylthio)vinyl)-4-oxo-4*H*-chromen-6-yl benzoate (6-benzoyloxy-(*S*)-deoxydirchromone, 15g):



15g

From compound **18g** (137 mg, 0.39 mmol), purified with 10-40 % ethyl acetate in hexanes to afford compound **15g** (67 mg, 61 1 %) as a pink powder. R_f = 0.30 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 2922, 1730, 1648, 1624, 1610, 1578, 1478, 1448, 1370, 1316, 1265, 1169, 1135, 1087, 1057, 1023, 987, 968, 924, 898, 855, 830, 814, 799, 739, 739, 703, 684, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, J = 7.3, 2H), 7.98 (d, J = 1.9, 1H), 7.68 – 7.57 (m, 2H), 7.56 – 7.46 (m, 4H), 6.09 (s, 1H), 5.96 (d, J = 15.0, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 165.2, 161.1, 153.5, 147.7, 138.8, 134.0, 130.3, 129.1, 128.8, 127.8, 124.8, 119.1, 117.9, 114.9, 107.3, 14.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}O_4S$ $[M+H]^+$ 339.0686, found 339.0701; EI-MS *m/z* unavailable (compound not sufficiently volatile for GC analysis).

(*E*)-7,8-Dimethoxy-2-(2-(methylthio)vinyl)-4*H*-chromen-4-one (7,8-dimethoxy-(*S*)-deoxydirchromone, 15h):



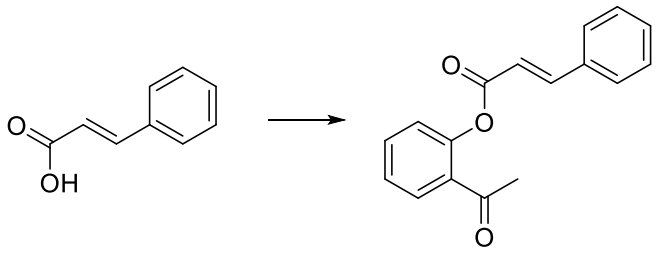
15h

From compound **18h** (144 mg, 0.49 mmol), purified with 30-55 % ethyl acetate in hexanes to afford compound **15h** (64 mg, 48 %) as a reddish powder. R_f = 0.13 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 3056, 3007, 2934, 2841, 2250, 1645, 1620, 1600,

1574, 1509, 1451, 1427, 1382, 1331, 1285, 1244, 1231, 1203, 1182, 1137, 1096, 1029, 998, 930, 867, 850, 835, 814, 796, 780, 724, 707, 662; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 9.0, 1H), 7.57 (d, *J* = 15.0, 1H), 6.94 (d, *J* = 9.0, 1H), 5.97 (s, 1H), 5.91 (d, *J* = 15.0, 1H), 3.93 (s, 6H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 160.5, 156.5, 150.1, 137.9, 136.5, 120.9, 118.6, 115.1, 109.4, 107.0, 61.5, 56.4, 14.4; HMRS (ESI) *m/z* calcd for $C_{14}H_{15}O_4S$ $[M+H]^+$ 279.0686, found 279.0692; EI-MS *m/z* 280 (4), 279 (9), 278 (57), 263 (100), 248 (10), 219 (9), 179 (6), 165 (8), 152 (20), 137 (22), 121 (12), 109 (15), 94 (11), 66 (8), 53 (8).

1.8.2.8 Preparation and characterization of intermediate esters **23**, **24** and **25**

2-Acetylphenyl cinnamate (23):



20 **23**

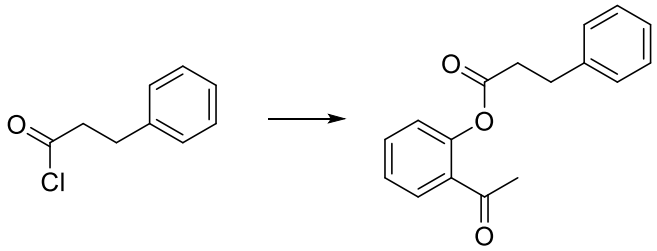
A) To a solution of (*E*)-cinnamic acid (**20**) (150 mg, 1 mmol) in dry dichloromethane (4 mL) containing a drop of dry dimethylformamide was slowly added oxalyl chloride (173 µL, 2 mmol) under argon atmosphere. The solution was stirred at room temperature for 1h30.

B) In a separate flask, 2'-hydroxyacetophenone (**9a**) (494 µL, 4 mmol) was mixed to ACS grade methanol (10 mL). To this solution was added potassium hydroxide (227 mg, 4 mmol) and the resulting solution was sonicated until all the base was dissolved. The solution was then thoroughly evaporated under reduced pressure and dried at 10 mbar. The resulting solid was then dissolved in 5 mL of dry dimethylformamide under argon atmosphere.

C) Solution A) was transferred dropwise to solution B) with vigorous stirring.

After 10 minutes, the reaction was quenched with NH_4Cl, and extracted with ethyl acetate/toluene 1:1. The organic phase was washed with 3 × NH_4Cl, 1 × brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 0-10 % ethyl acetate in hexanes to afford compound **23** (205 mg, 76 %) as a yellow solid. Identity confirmed by GC-MS with reference to NIST14 database(NIST Mass Spectrometry Data Center, 2017).

2-Acetylphenyl 3-phenylpropanoate (24):

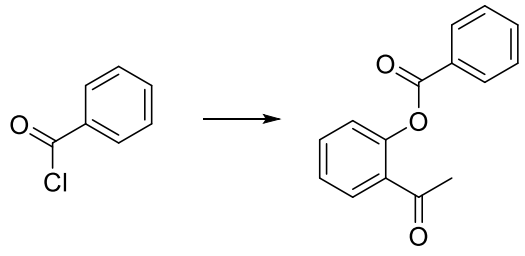


21 **24**

To a solution of 2'-hydroxyacetophenone (**9a**) (200 µL, 1.6 mmol) and triethylamine (342 µL, 2.5 mmol) in dry dichloromethane (5 mL) was added hydrocinnamyl chloride **21** (364 µL, 2.5 mmol) dropwise under argon atmosphere. The solution was stirred overnight at room temperature. The reaction was quenched with brine, and extracted with 3 × ethyl acetate. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified with 0-30 % ethyl acetate in hexanes to afford compound **24** (255 mg, 58 %) as a colorless oil. R_f = 0.71 (Hex/AcOEt 7:3); IR (ATR) ν_{max}: 3063, 3028, 2928, 1758, 1685, 1603, 1577, 1497, 1481, 1447, 1420, 1356, 1283, 1250, 1195, 1119, 1071, 1031, 955, 932, 907, 827, 745, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 7.8, 1.2, 1H), 7.54 (td, *J* = 8.0, 1.5, 1H), 7.41-7.27 (m, 6H), 7.07 (dd, *J* = 8.1, 0.7, 1H), 3.15 (t, *J* = 7.7, 2H), 3.00 (t, *J* = 7.7, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.6, 171.4, 149.0, 140.2,

133.4, 1307, 130.3, 128.6, 128.4, 126.4, 126.1, 123.8, 36.0, 30.6, 29.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}O_3$ $[M+H]^+$ 269.1172, found 269.1176; EI-MS *m/z* 268 (t), 250 (1), 222 (2), 208 (9), 136 (52), 133 (12), 121 (22), 105 (100), 91 (87), 79 (10), 77 (18), 65 (10), 51 (5), 43 (5).

2-Acetylphenyl benzoate (25):



22 **25**

To a solution of 2'-hydroxyacetophenone (**9a**) (200 µL, 1.6 mmol) and triethylamine (342 µL, 2.5 mmol) in dry dichloromethane (5 mL) was added benzoyl chloride (**22**) (286 µL, 2.5 mmol) dropwise under argon atmosphere. The solution was stirred overnight at room temperature. The reaction was quenched with brine, and extracted with 3 × ethyl acetate. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified with 0-30 % ethyl acetate in hexanes to afford compound **25** (333 mg, 84 %) as a clear oil. Identity confirmed by GC-MS with reference to NIST14 database (NIST Mass Spectrometry Data Center, 2017).

1.8.3 References

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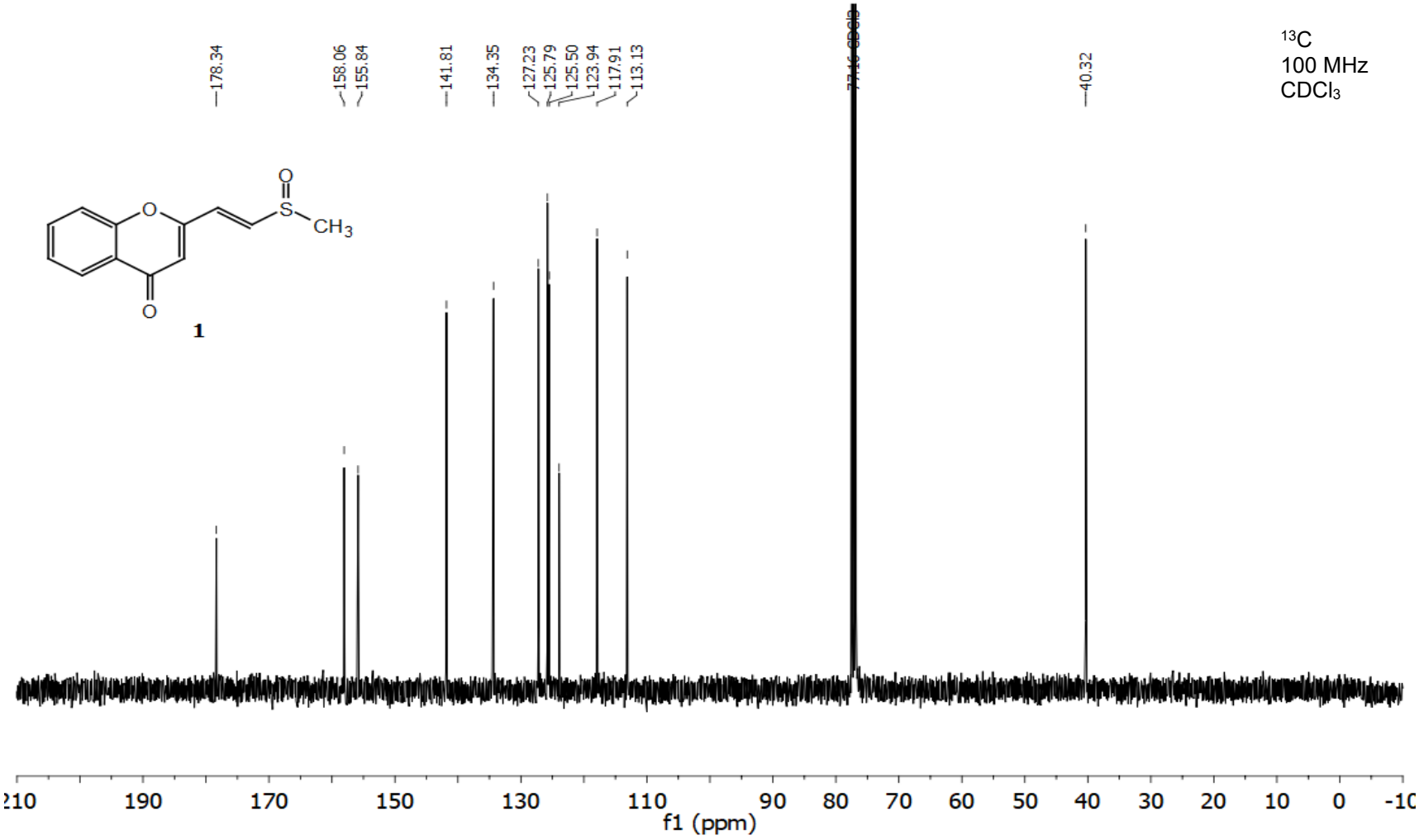
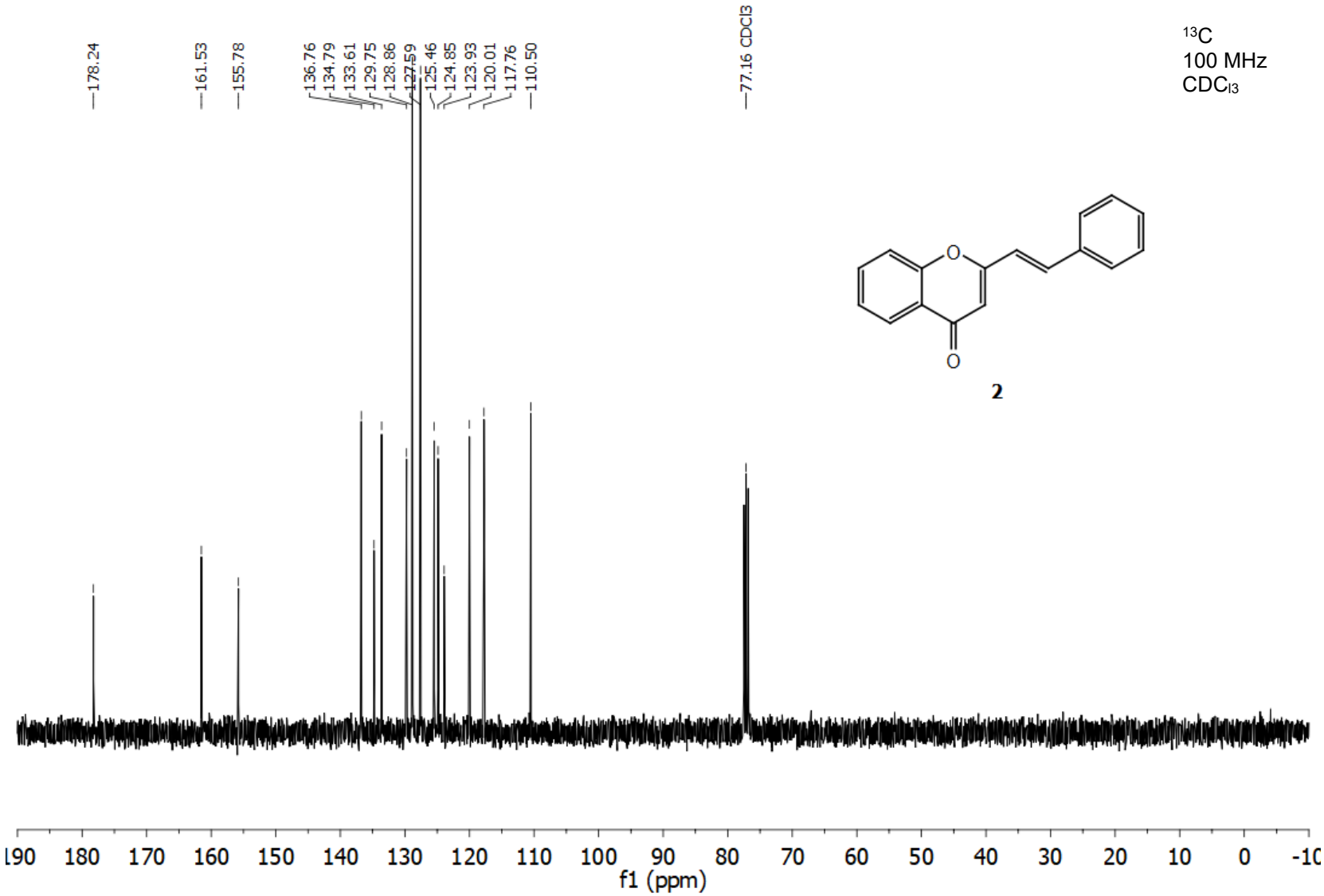
1.8.4 ^{1}H NMR, ^{13}C NMR and HRMS spectra

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127.59
125.46
124.85
123.93
120.01
117.76
110.50
77.16 CDCl3
13C
100 MHz
CDCl3
O
O
2
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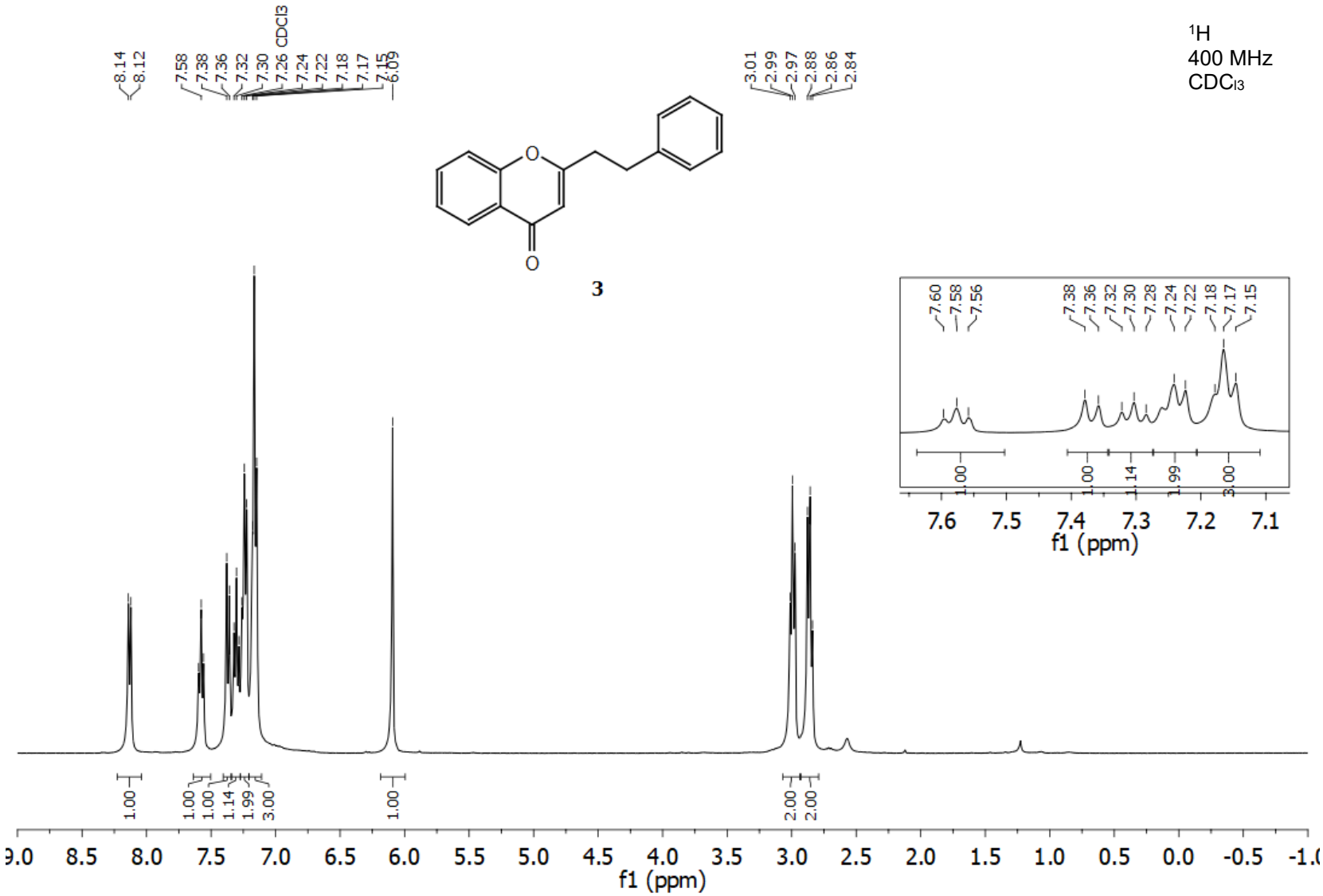
f1 (ppm)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7.30
CDCl3
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7.24
7.22
7.18
7.17
7.15
6.09
3.01
2.99
2.97
2.88
2.86
2.84
O
O
3
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7.32
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7.28
7.24
7.22
7.18
7.17
7.15
1.00
1.00
1.14
1.99
3.00
7.6
7.5
7.4
7.3
7.2
7.1
f1 (ppm)
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1.00
1.14
1.99
3.00
1.00
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
2.5
2.0
1.5
1.0
0.5
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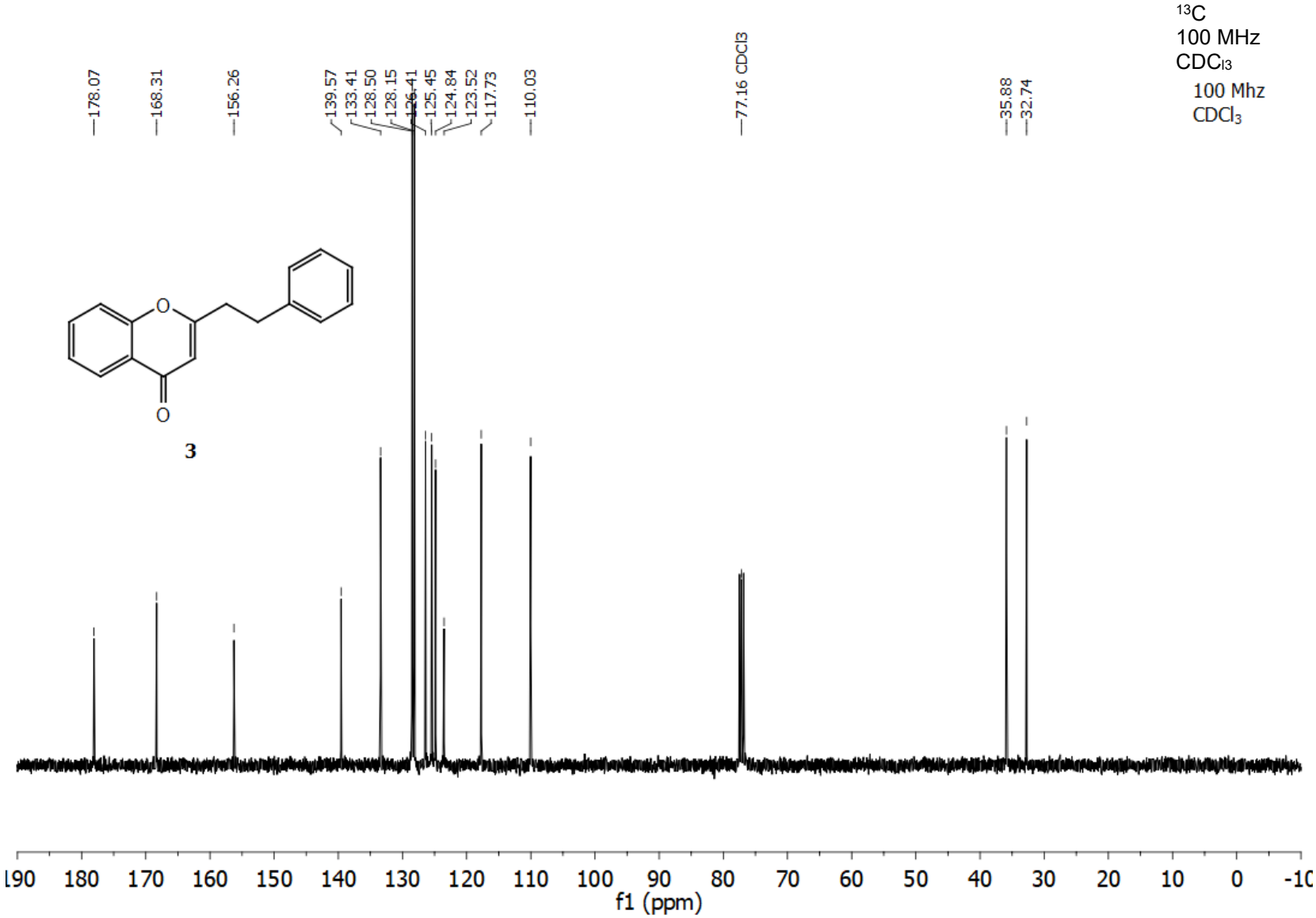
-0.5
f1 (ppm)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100 MHz
$CDCl_3$
100 Mhz
$CDCl_3$
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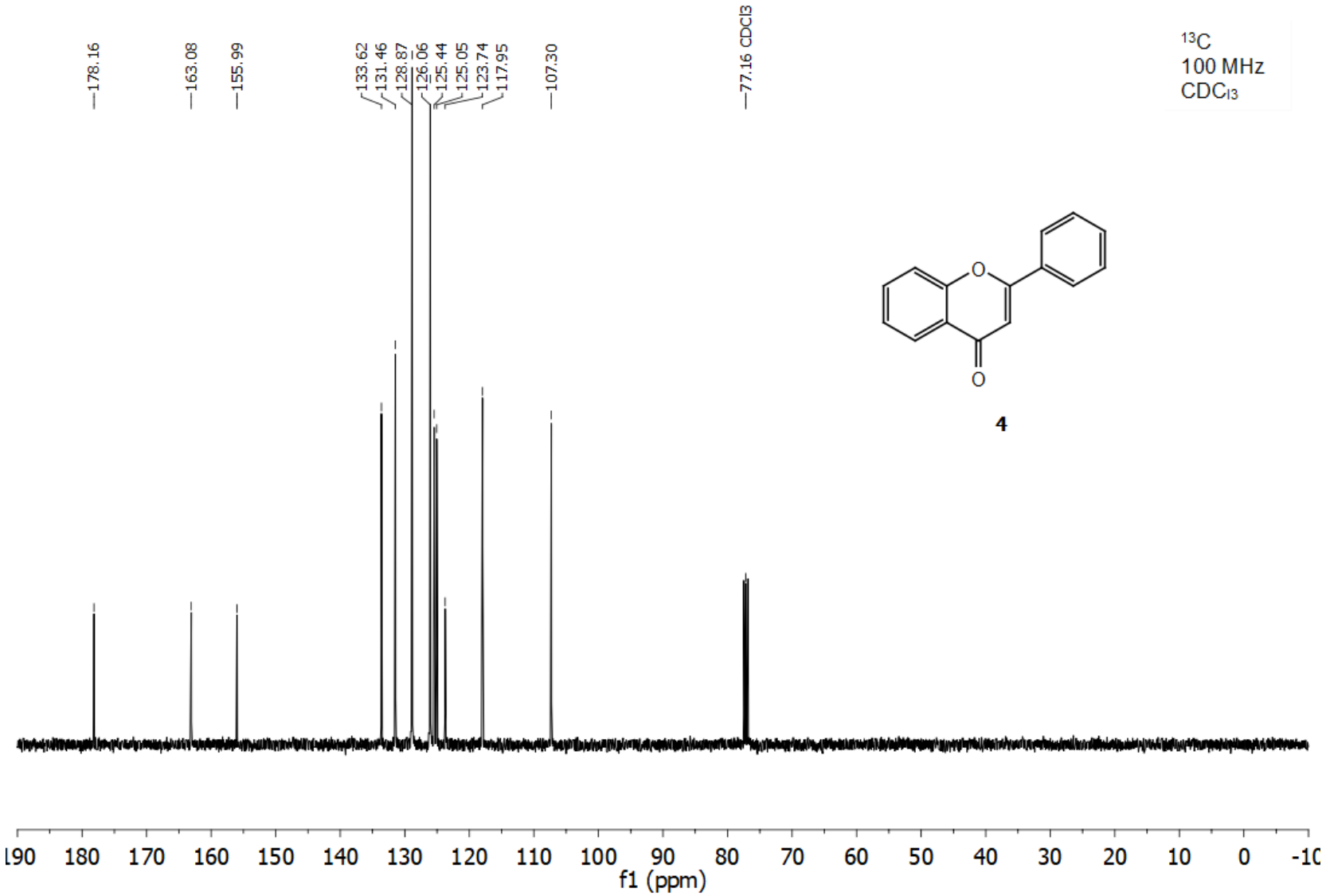
168.31
156.26
139.57
133.41
128.50
128.15
126.41
125.45
124.84
123.52
117.73
110.03
77.16 CDCl3
35.88
32.74
O
O
3
f1 (ppm)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117.95
107.30
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100 MHz
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O
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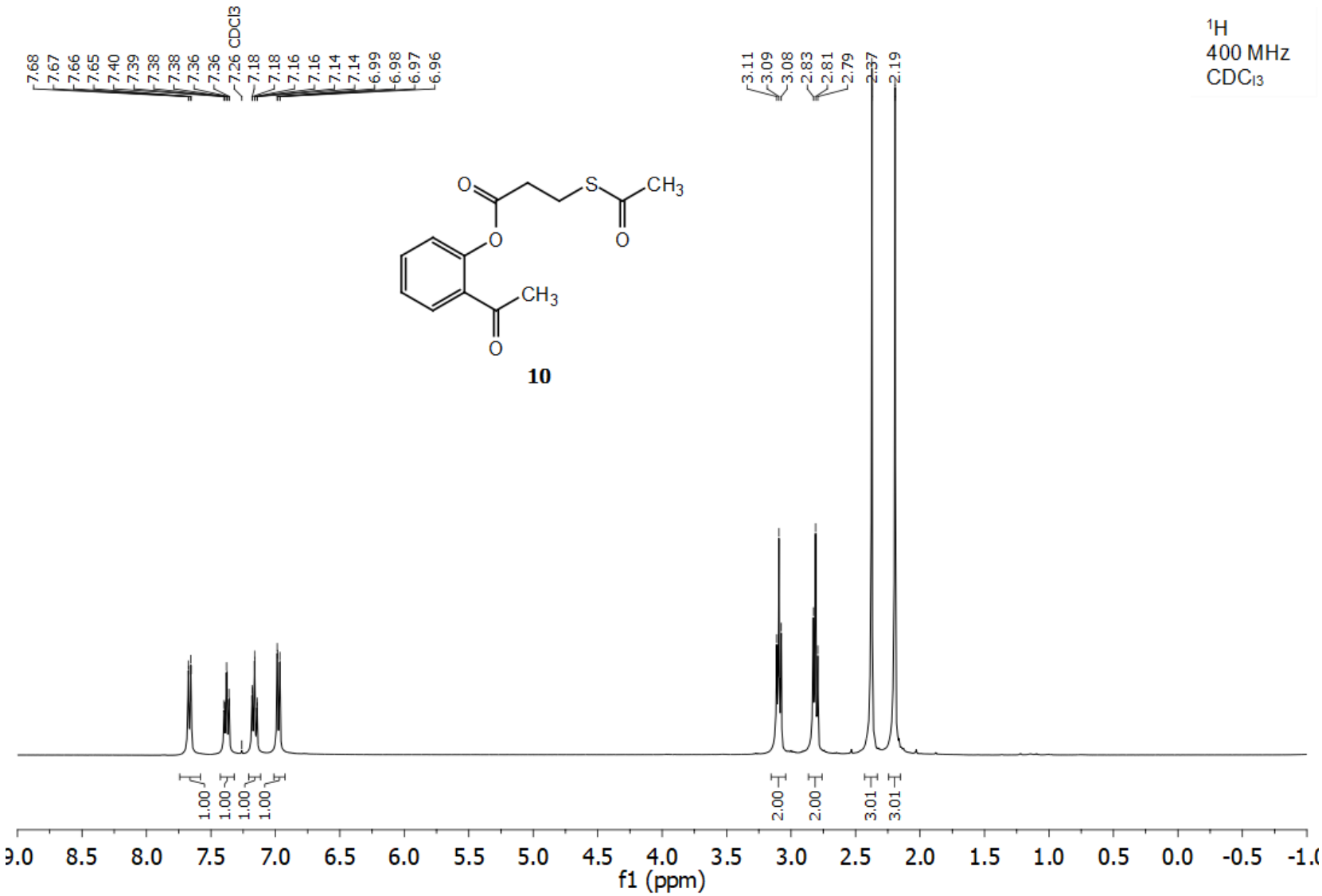
f1 (ppm)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6.98
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6.96
3.11
3.09
3.08
2.83
2.81
2.79
2.37
2.19
1H
400 MHz
CDCl3
O
S
CH3
O
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CH3
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2.00
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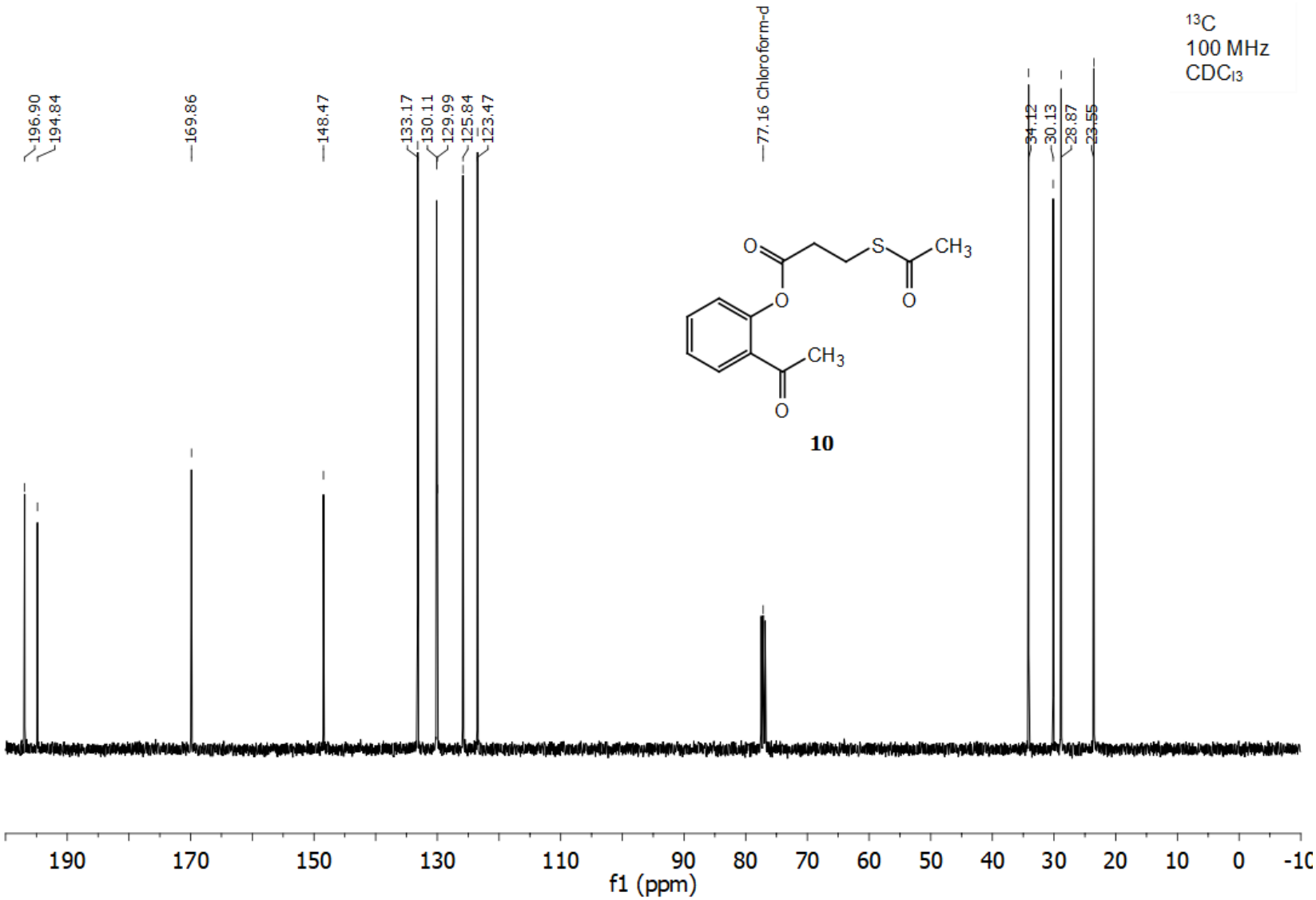
3.01
f1 (ppm)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194.84
169.86
148.47
133.17
130.11
129.99
125.84
123.47
77.16 Chloroform-d
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30.13
28.87
23.55
13C
100 MHz
CDCl3
O
S
CH3
O
O
CH3
O
10
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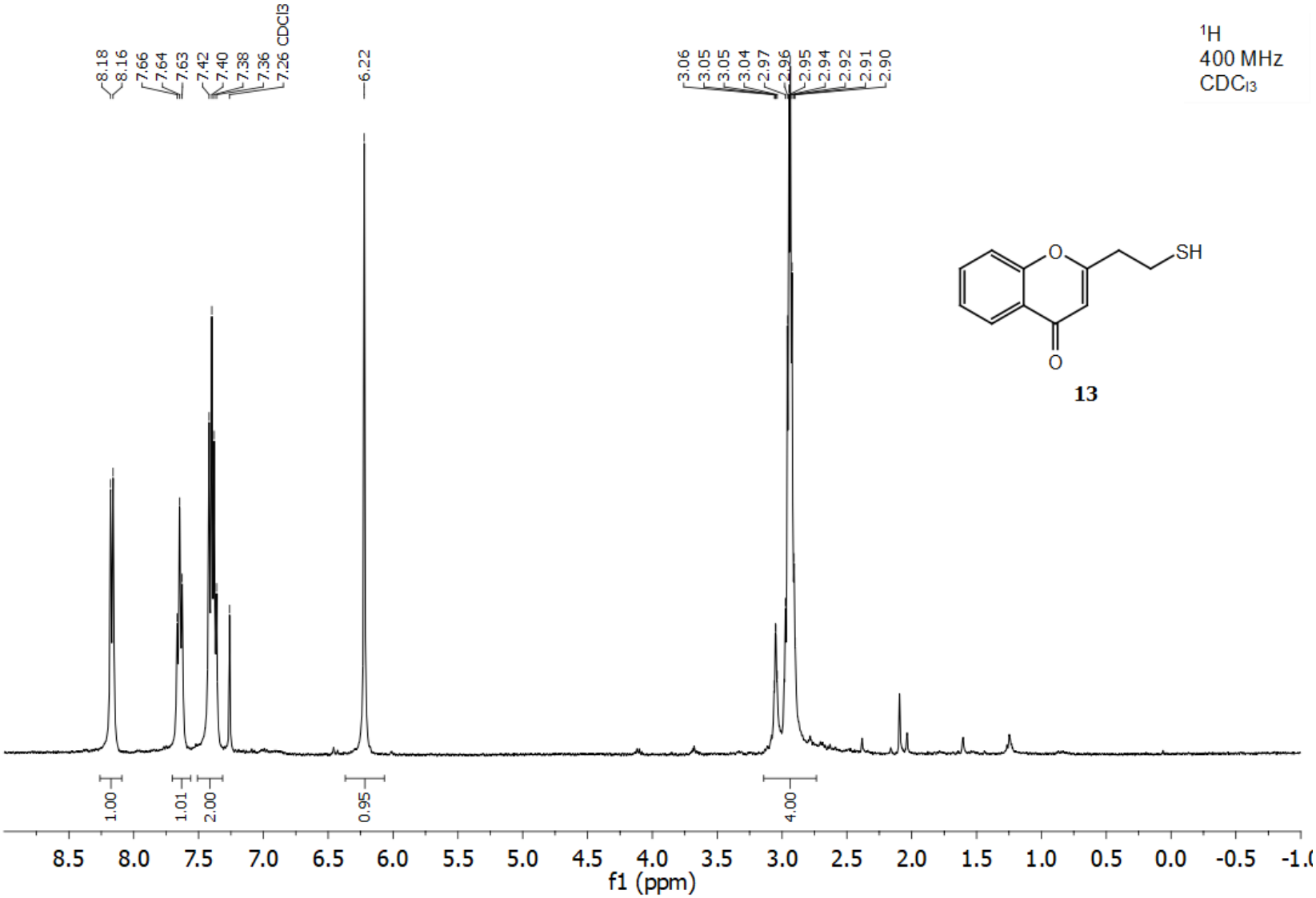
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.38
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7.26 CDCl3
6.22
3.06
3.05
3.05
3.04
2.97
2.96
2.95
2.94
2.92
2.91
2.90
1H
400 MHz
CDCl3
O
SH
O
1.00
1.01
2.00
0.95
4.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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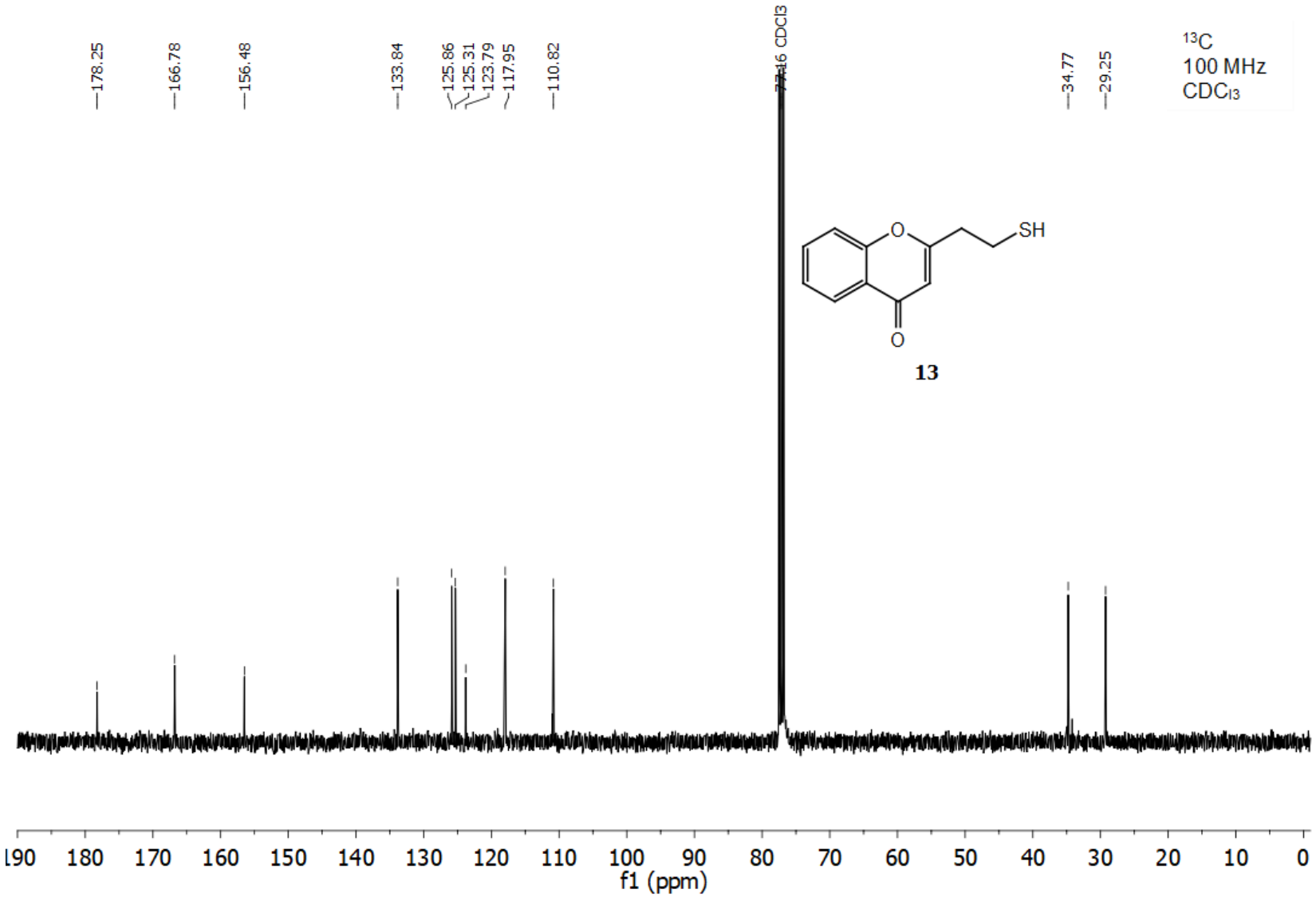
f1 (ppm)

13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100 MHz
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SH
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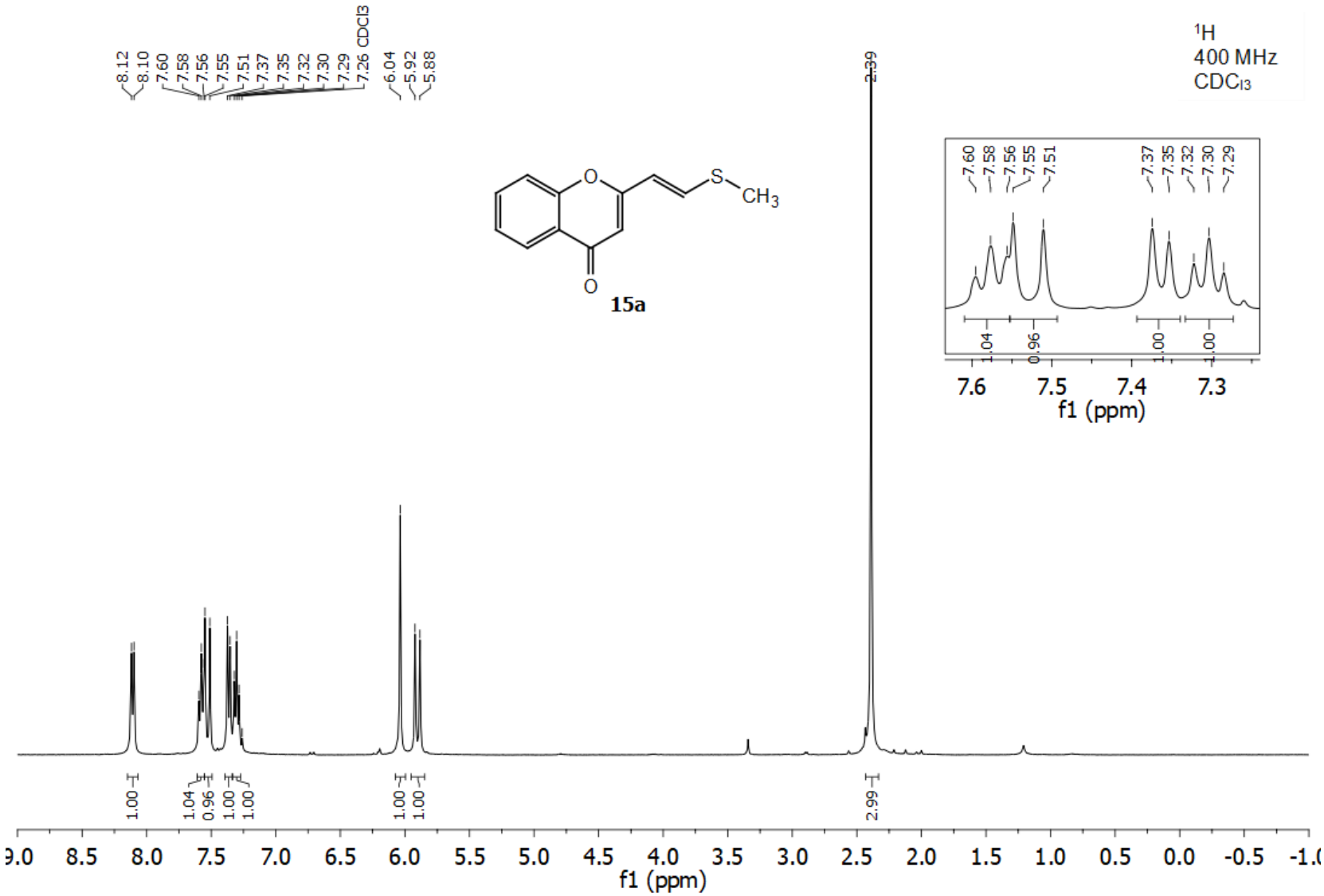
f1 (ppm)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7.32
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7.26 CDCl3
6.04
5.92
5.88
2.39
1H
400 MHz
CDCl3
O
S
CH3
O
15a
7.60
7.58
7.56
7.55
7.51
7.37
7.35
7.32
7.30
7.29
1.04
0.96
1.00
1.00
7.6
7.5
7.4
7.3
f1 (ppm)
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1.04
0.96
1.00
1.00
1.00
1.00
2.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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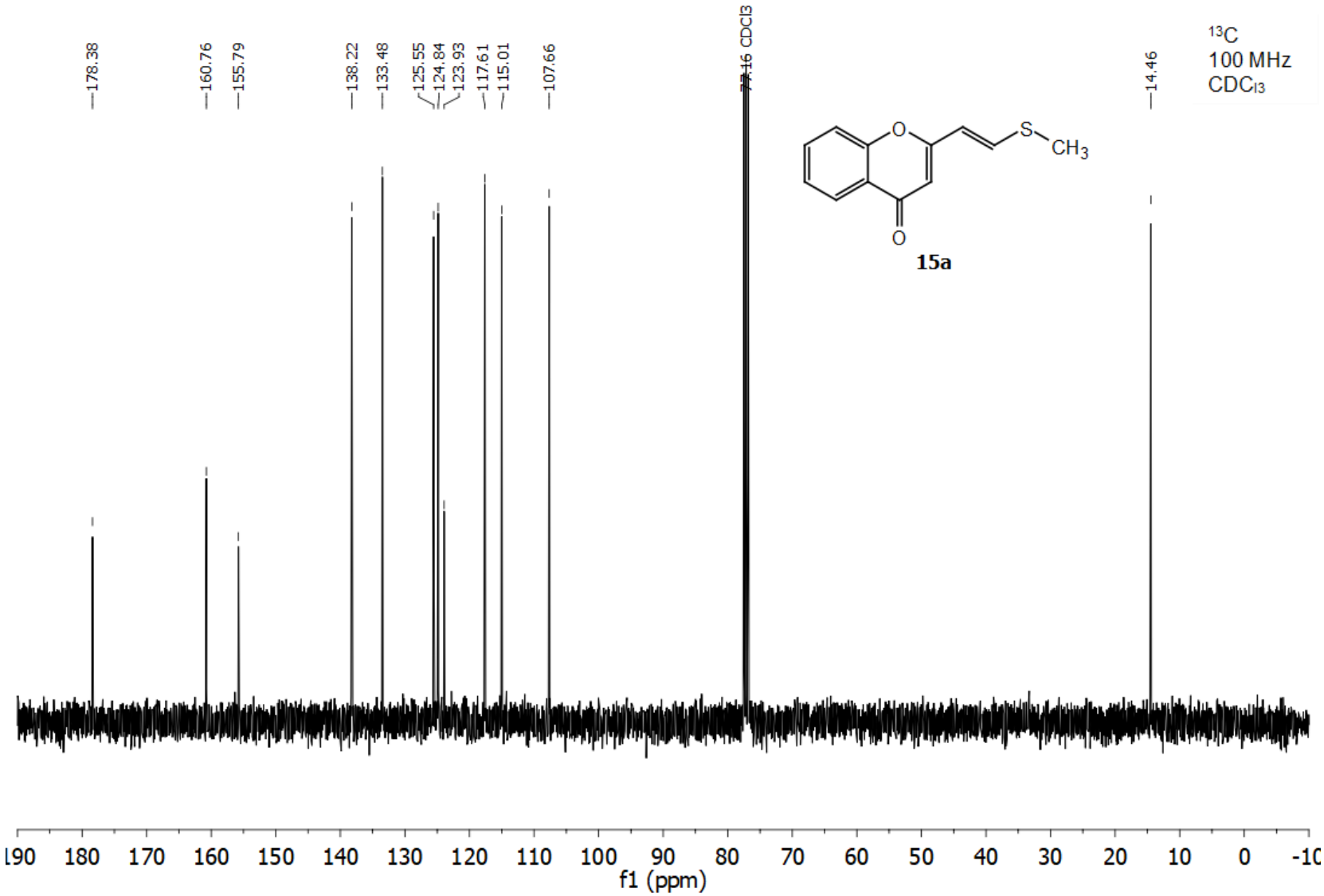
f1 (ppm)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14.46
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O
S
CH3
O
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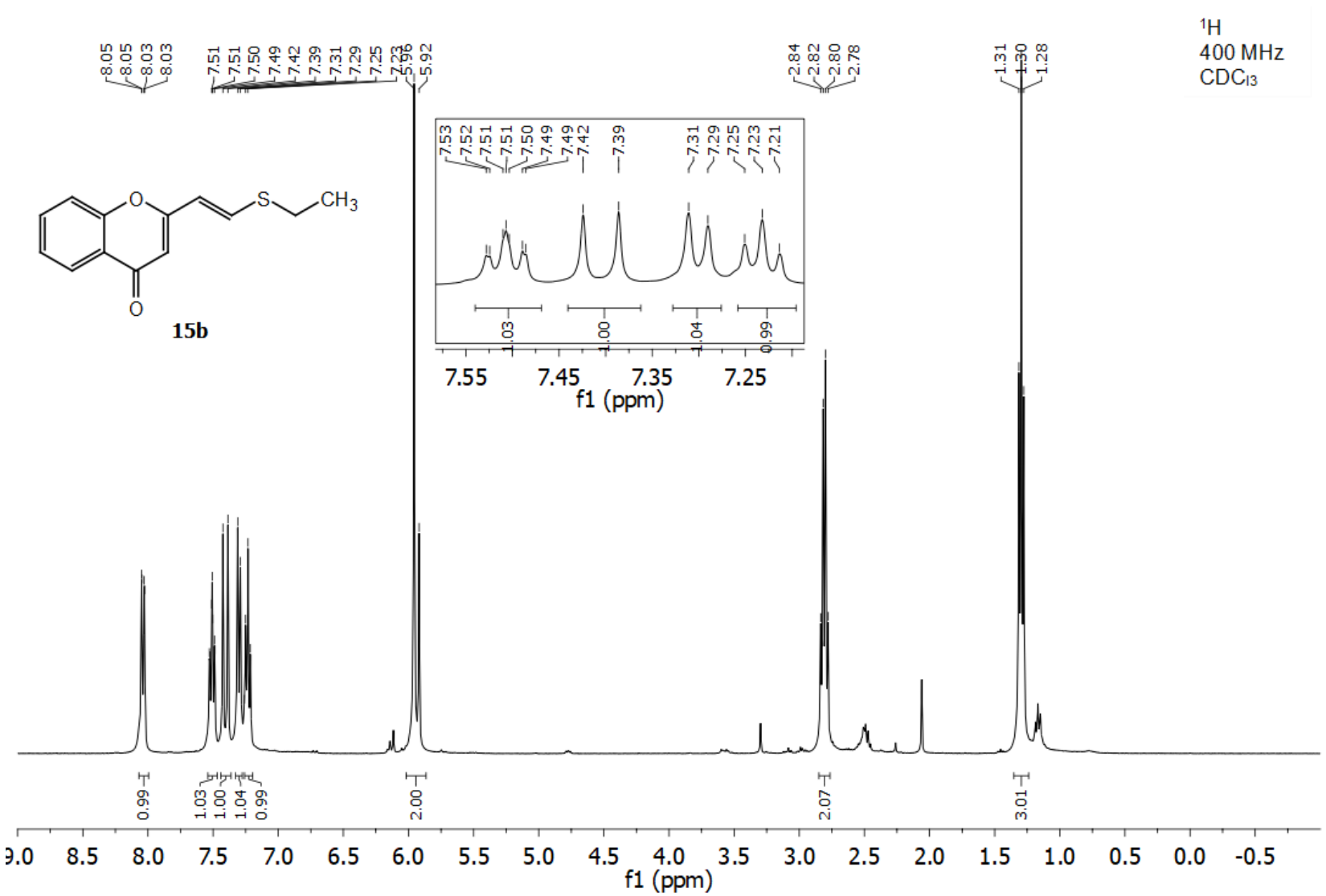
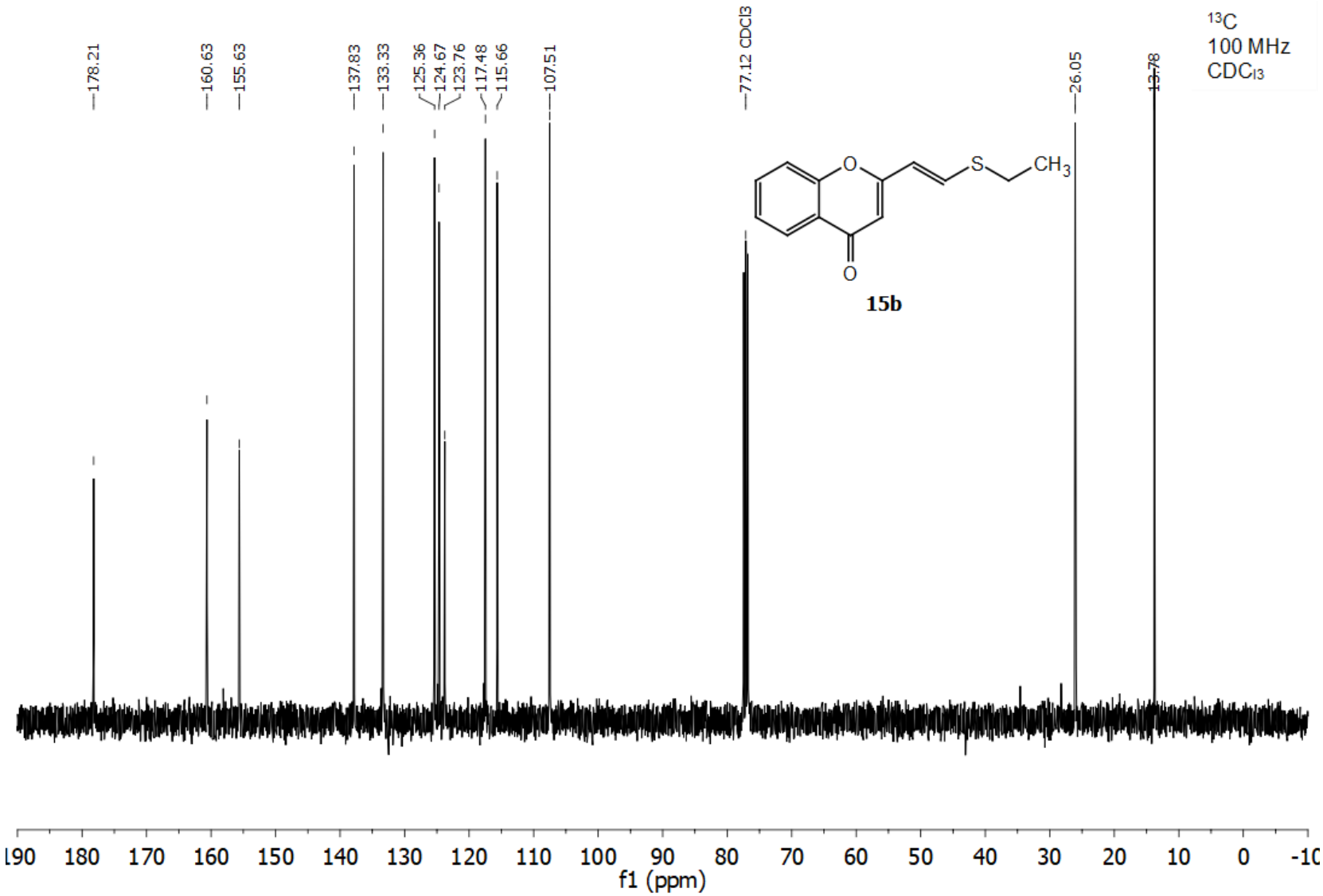
f1 (ppm)


1H
400 MHz
CDCl3
15b
f1 (ppm)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115.66
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26.05
13.78
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S
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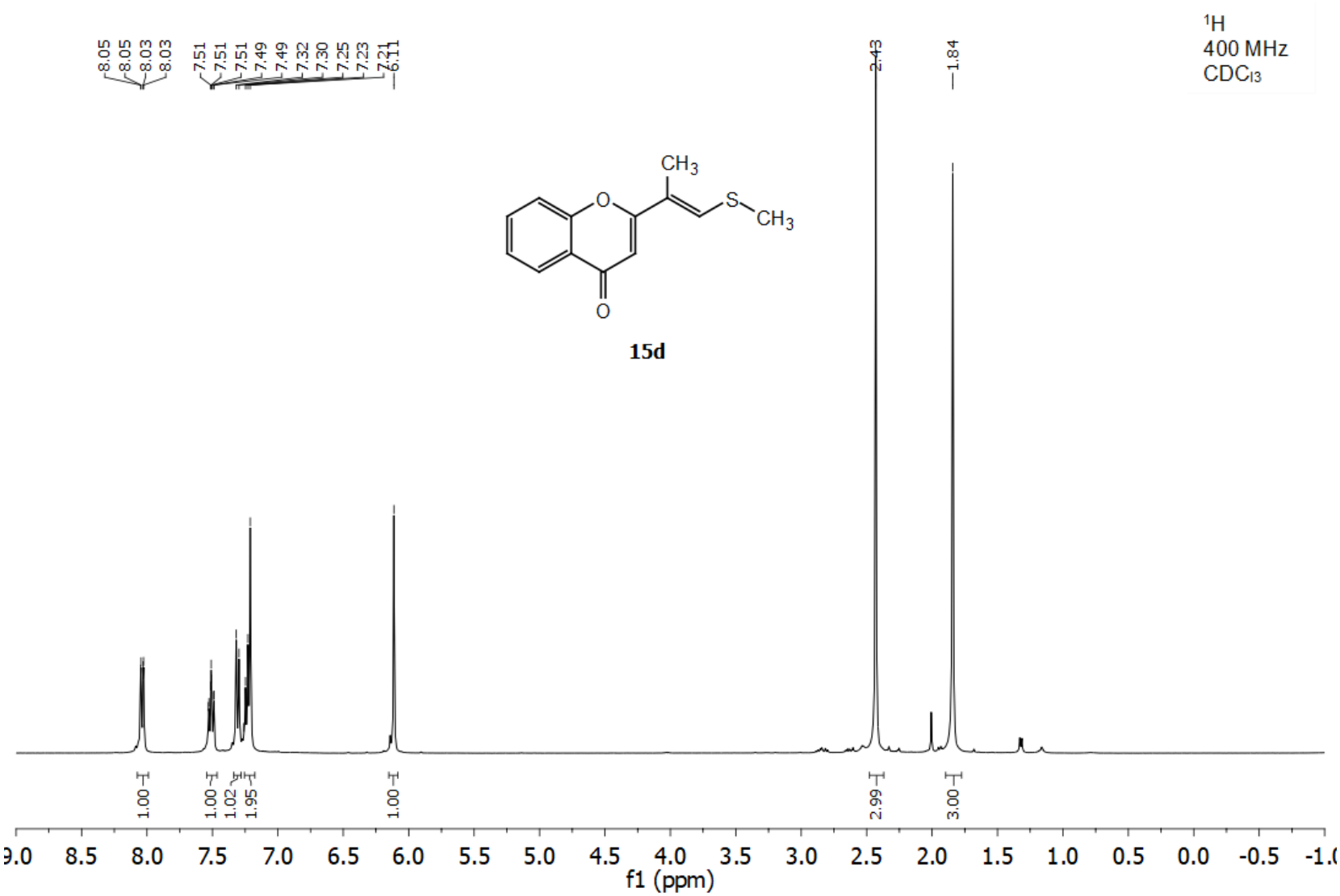
f1 (ppm)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7.51
7.51
7.49
7.49
7.32
7.30
7.25
7.23
7.21
6.11
2.43
1.84
^{1}H
400 MHz
CDCl3
CH3
O
S
CH3
O
15d
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1.00
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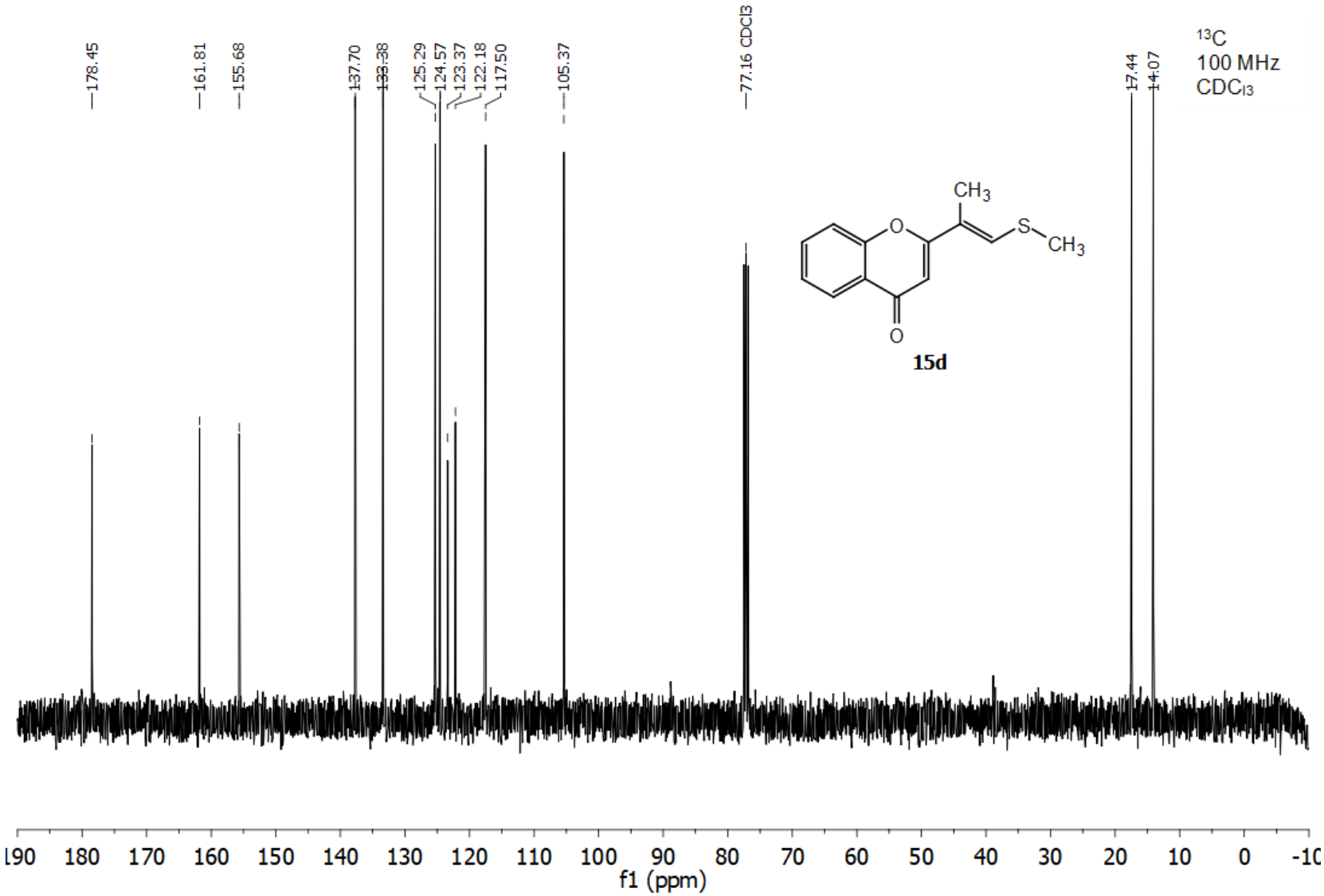
1.00
2.99
3.00
f1 (ppm)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105.37
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17.44
14.07
13C
100 MHz
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S
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O
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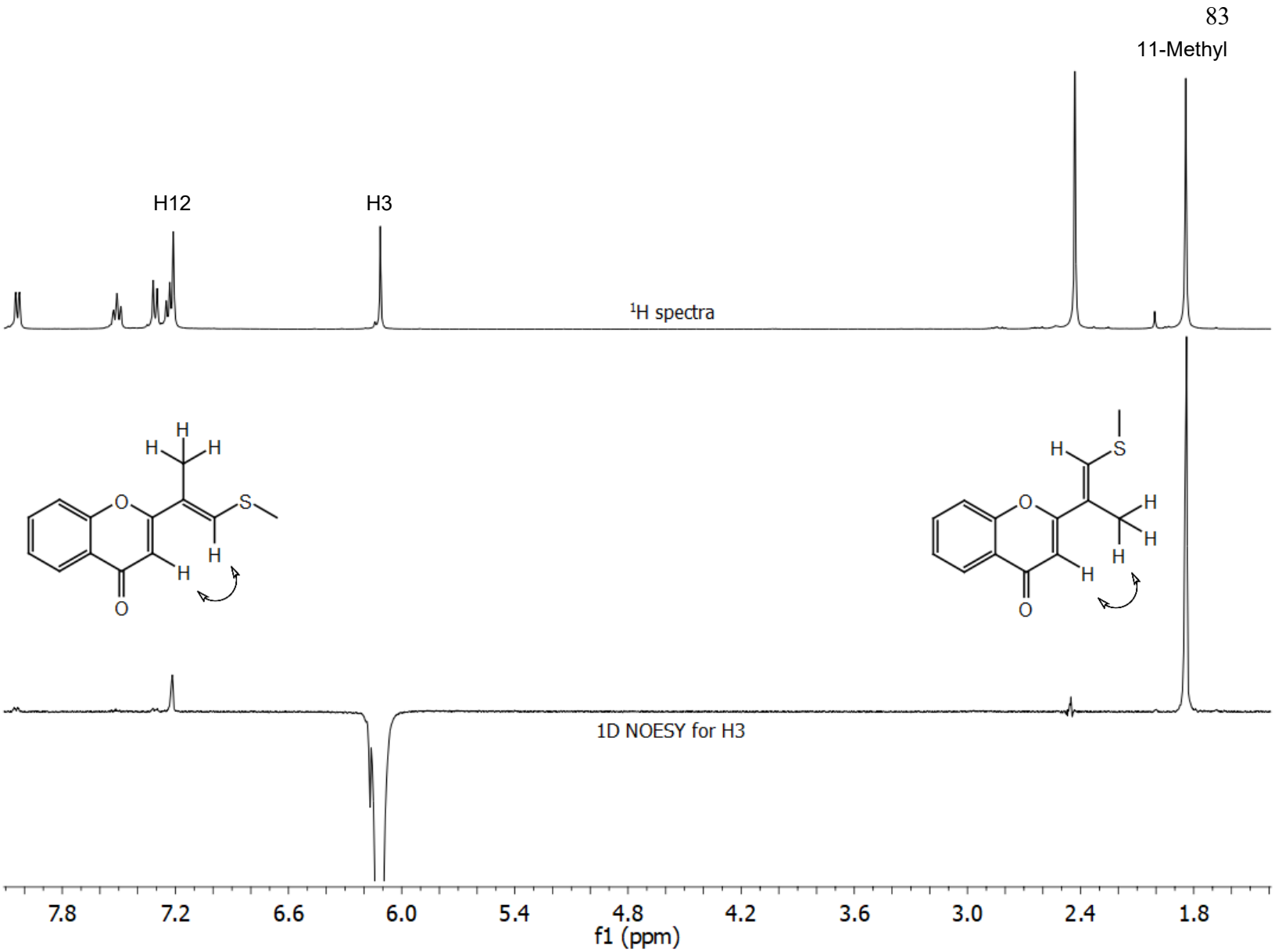
f1 (ppm)


11-Methyl
H12
H3
¹H spectra
1D NOESY for H3
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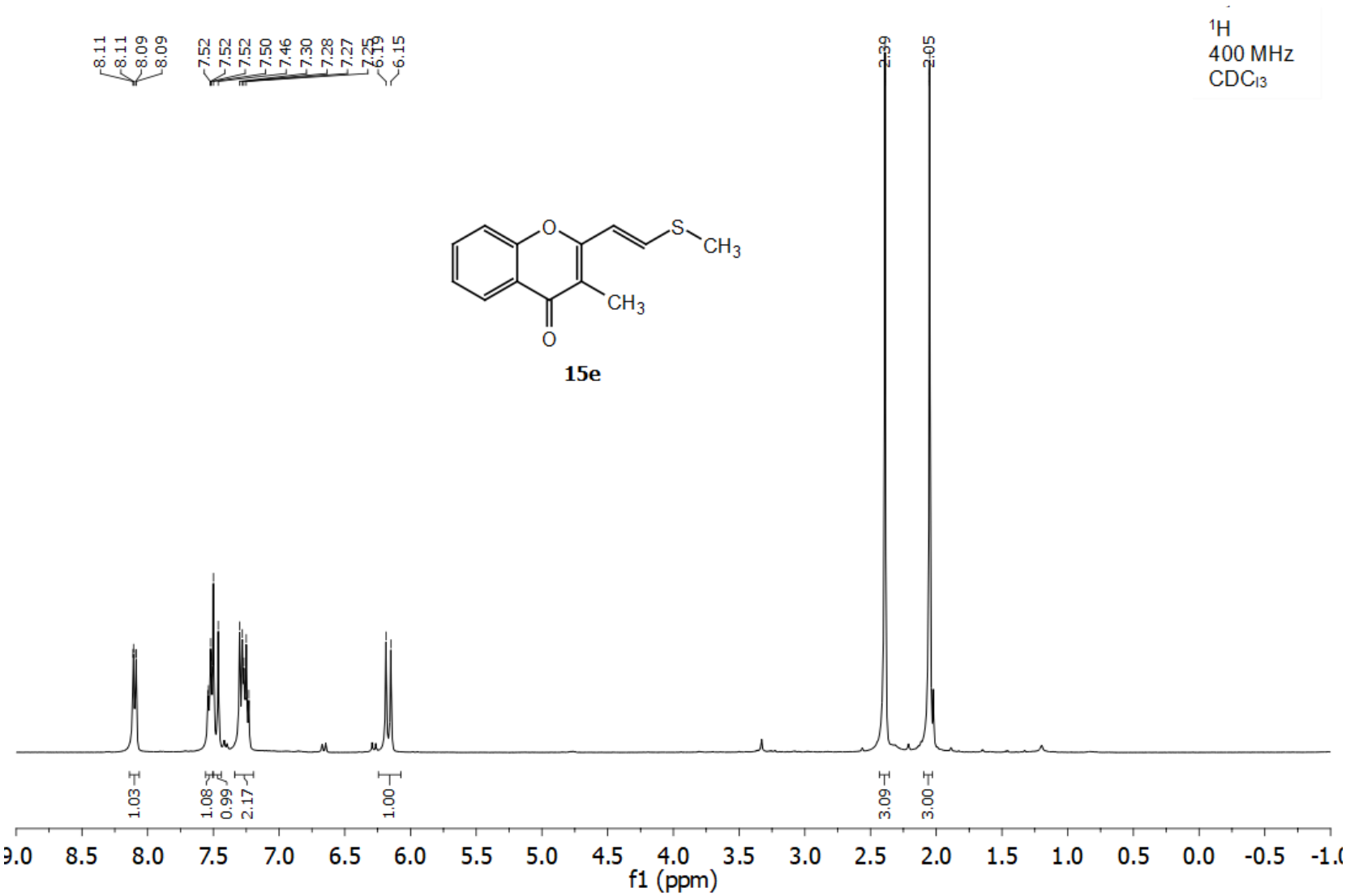
1.8
f1 (ppm)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7.52
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7.28
7.27
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6.19
6.15
2.39
2.05
1H
400 MHz
CDCl3
O
S
CH3
CH3
O
15e
1.03
1.08
0.99
2.17
1.00
3.09
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.0
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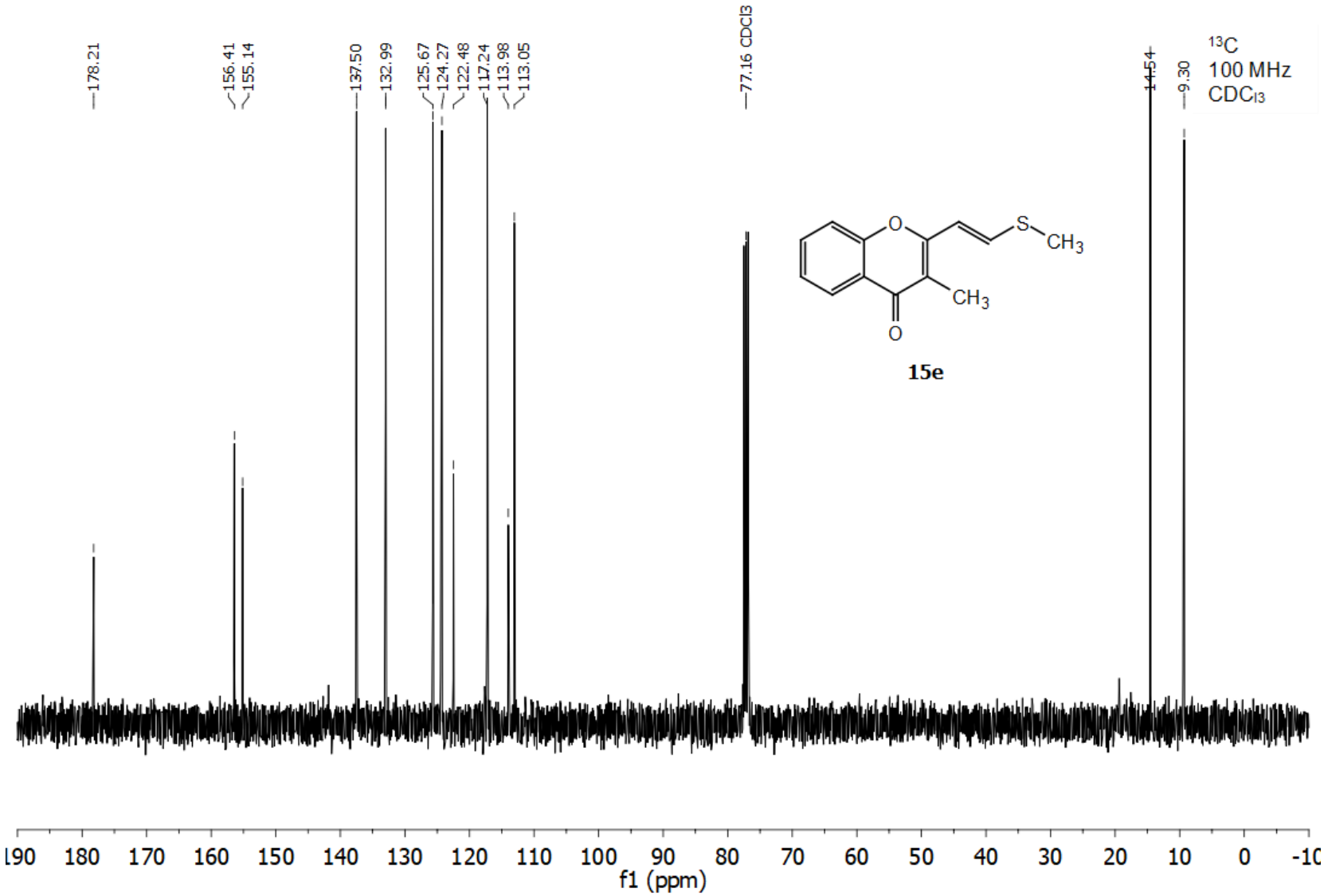
f1 (ppm)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113.98
113.05
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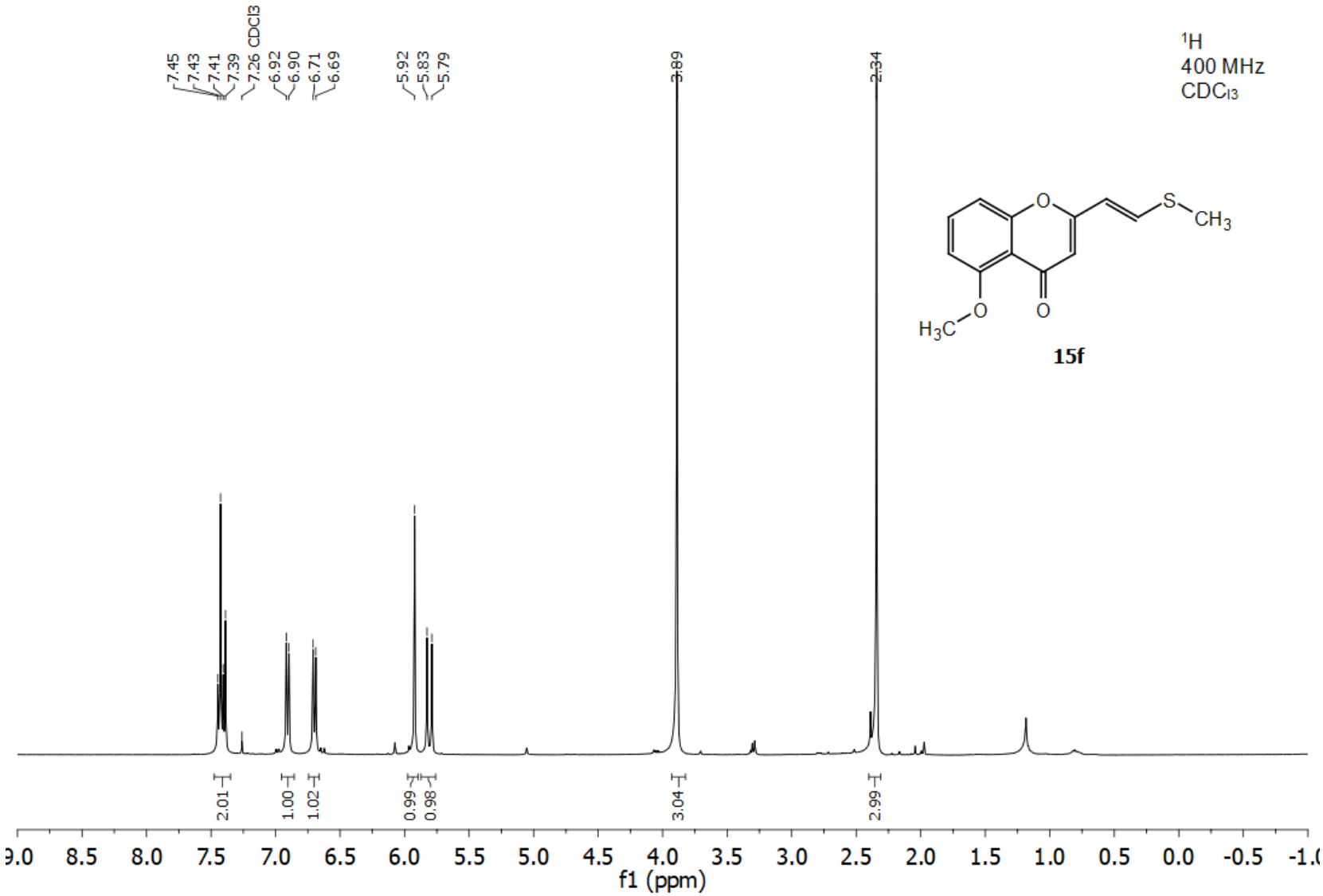
14.54
9.30
13C
100 MHz
CDCl3
O
S
CH3
CH3
O
15e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.43
7.41
7.39
7.26 CDCl3
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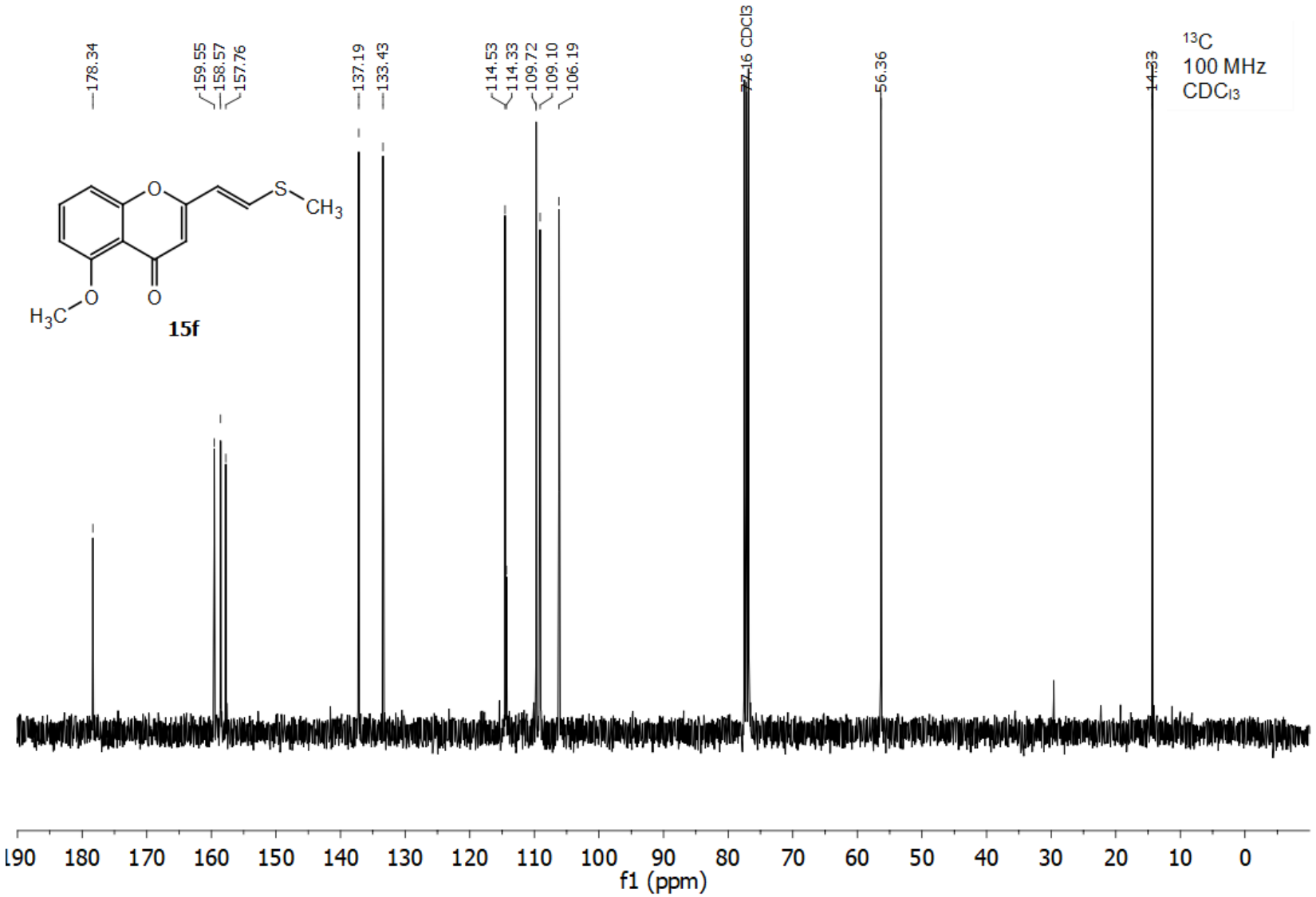
6.71
6.69
5.92
5.83
5.79
3.89
2.34
1H
400 MHz
CDCl3
O
S
CH3
H3C
O
O
O
15f
2.01
1.00
1.02
0.99
0.98
3.04
2.99
f1 (ppm)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106.19
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56.36
14.33
13C
100 MHz
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O
S
CH3
H3C
O
O
15f
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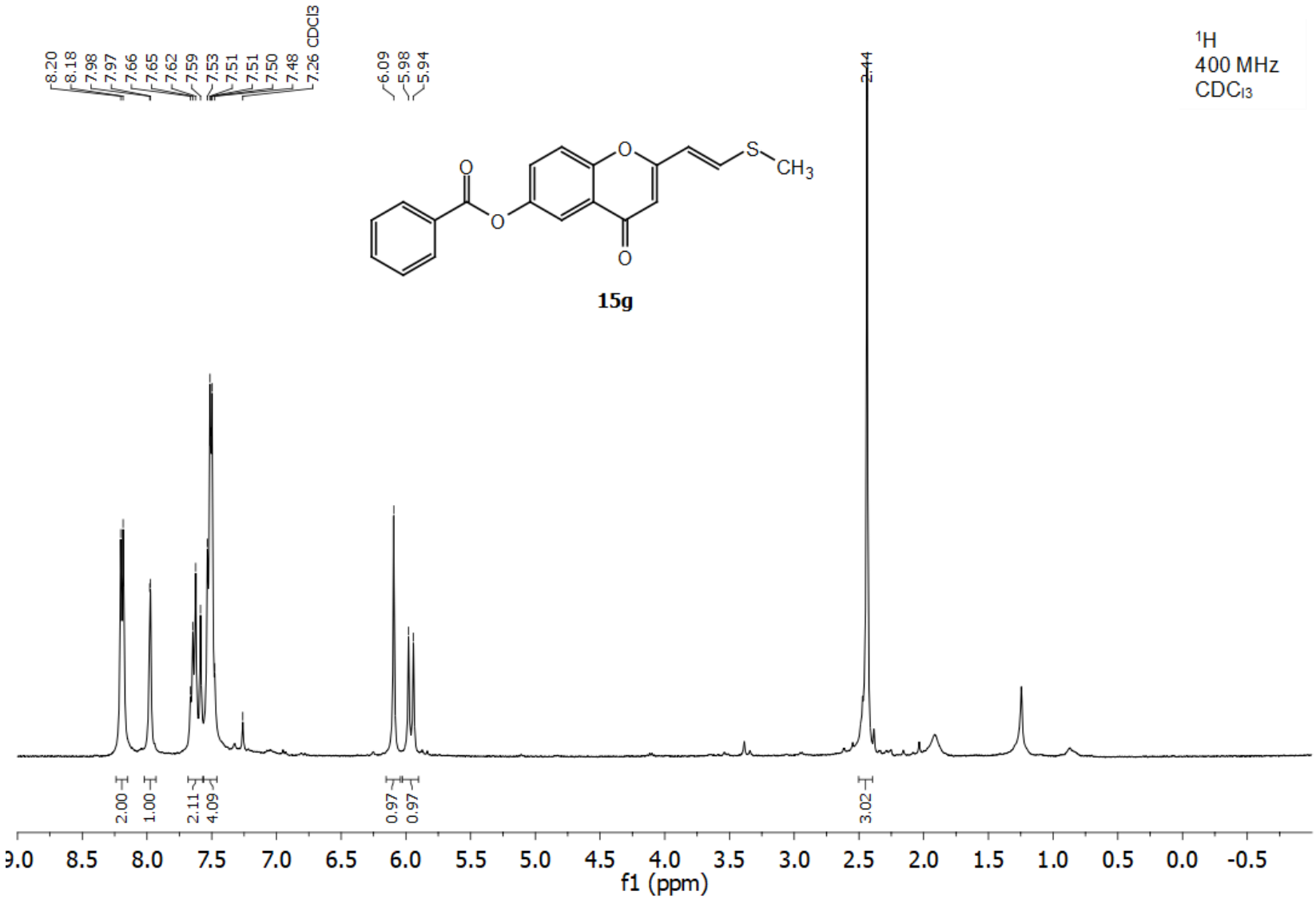
f1 (ppm)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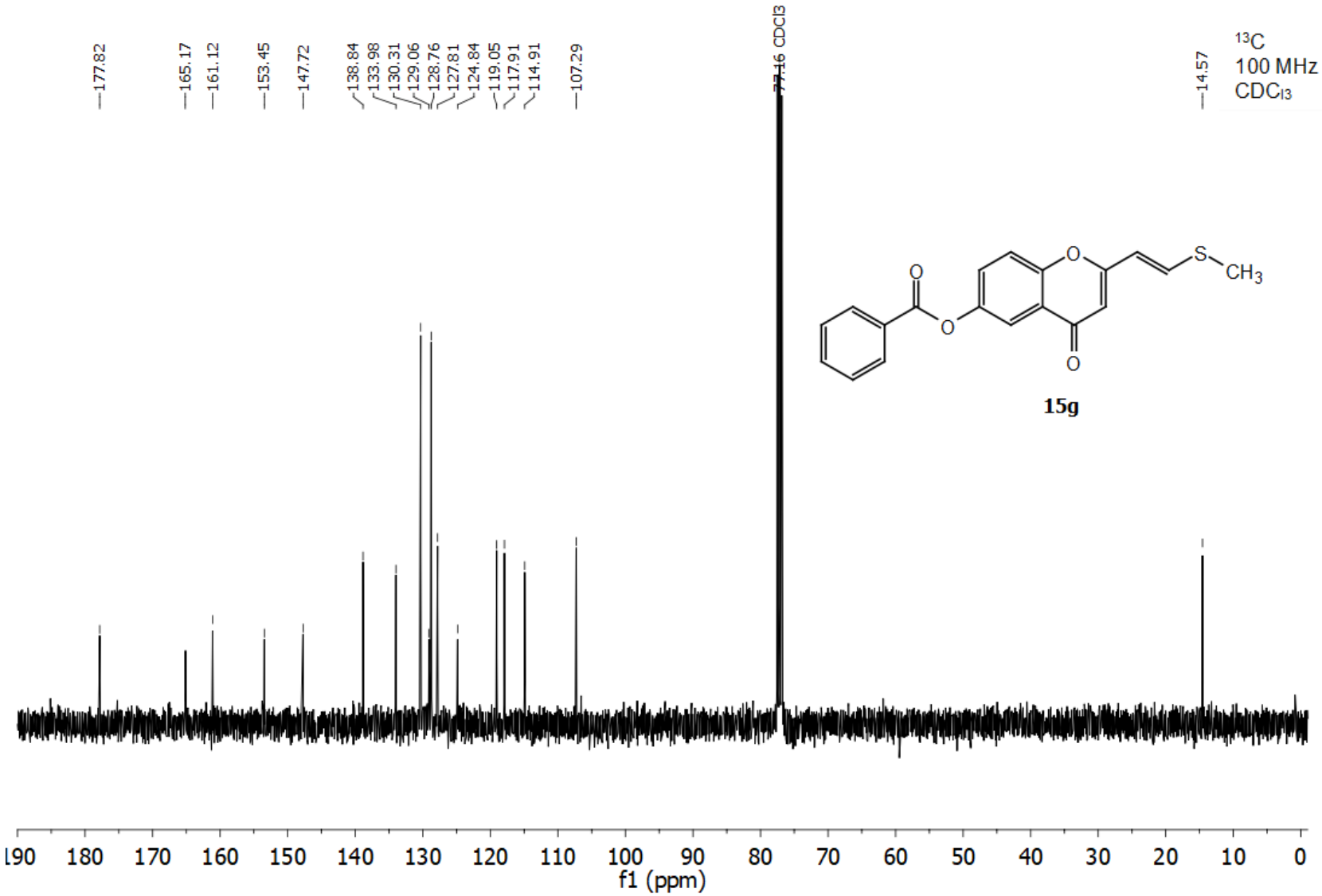
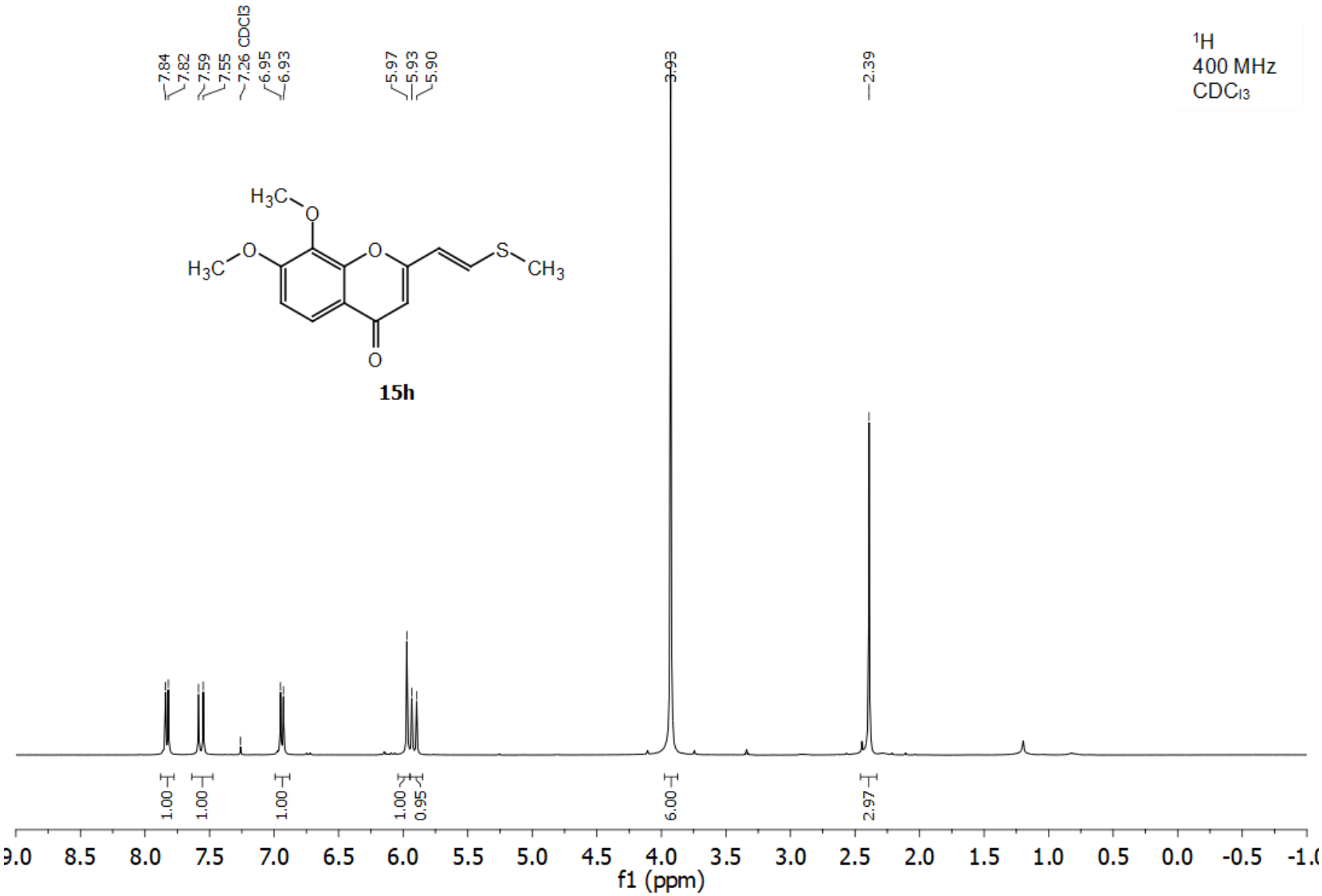
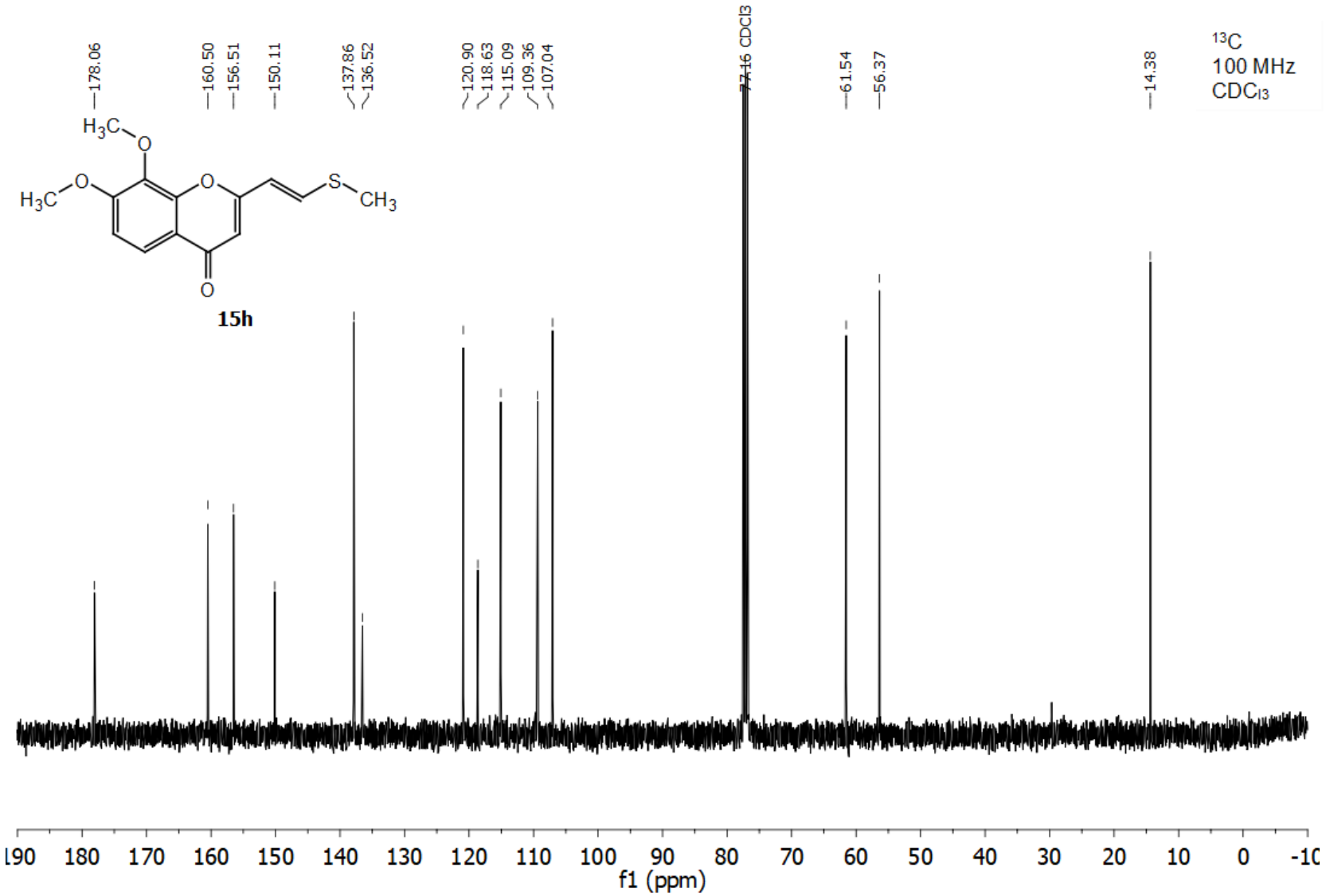
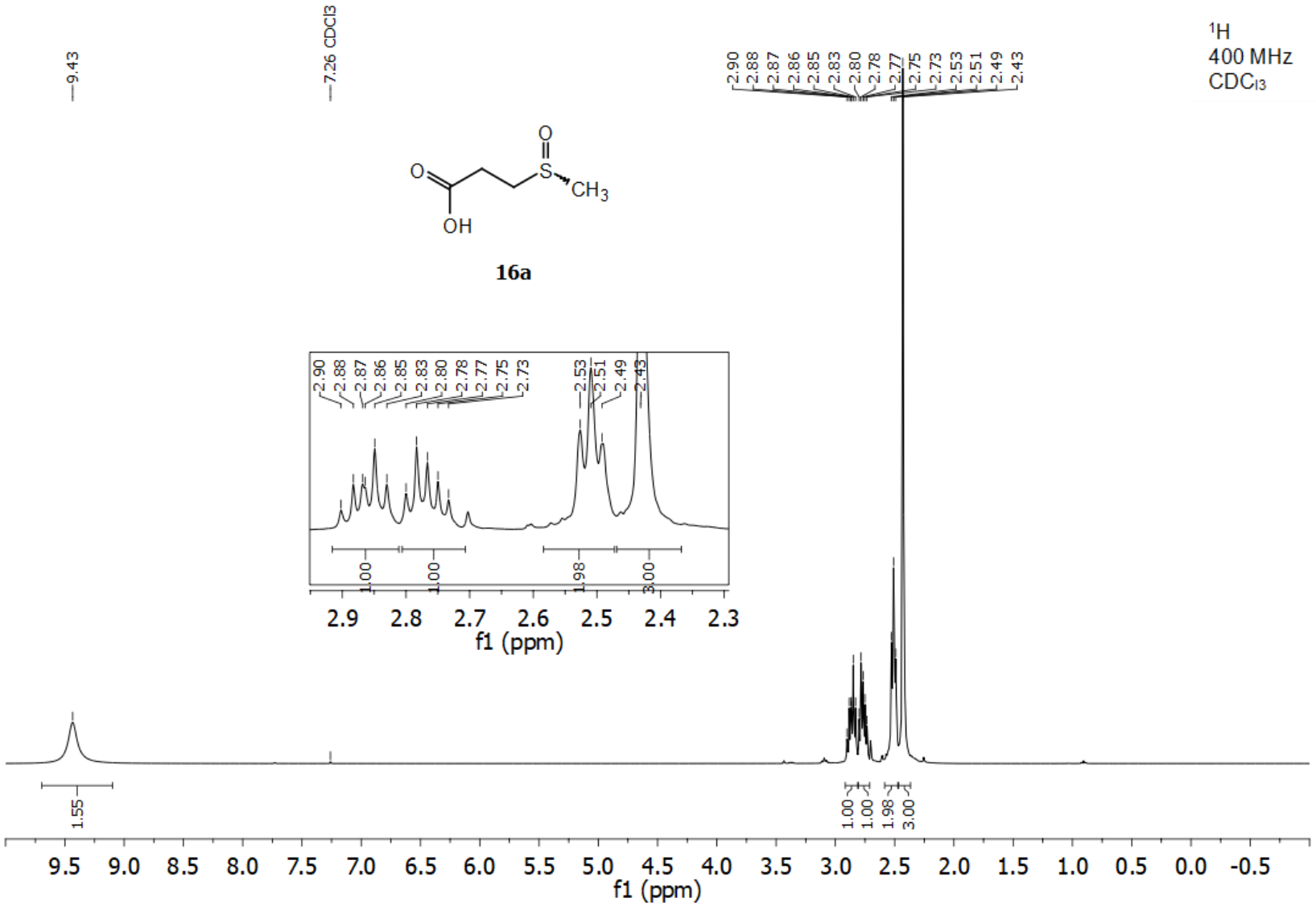
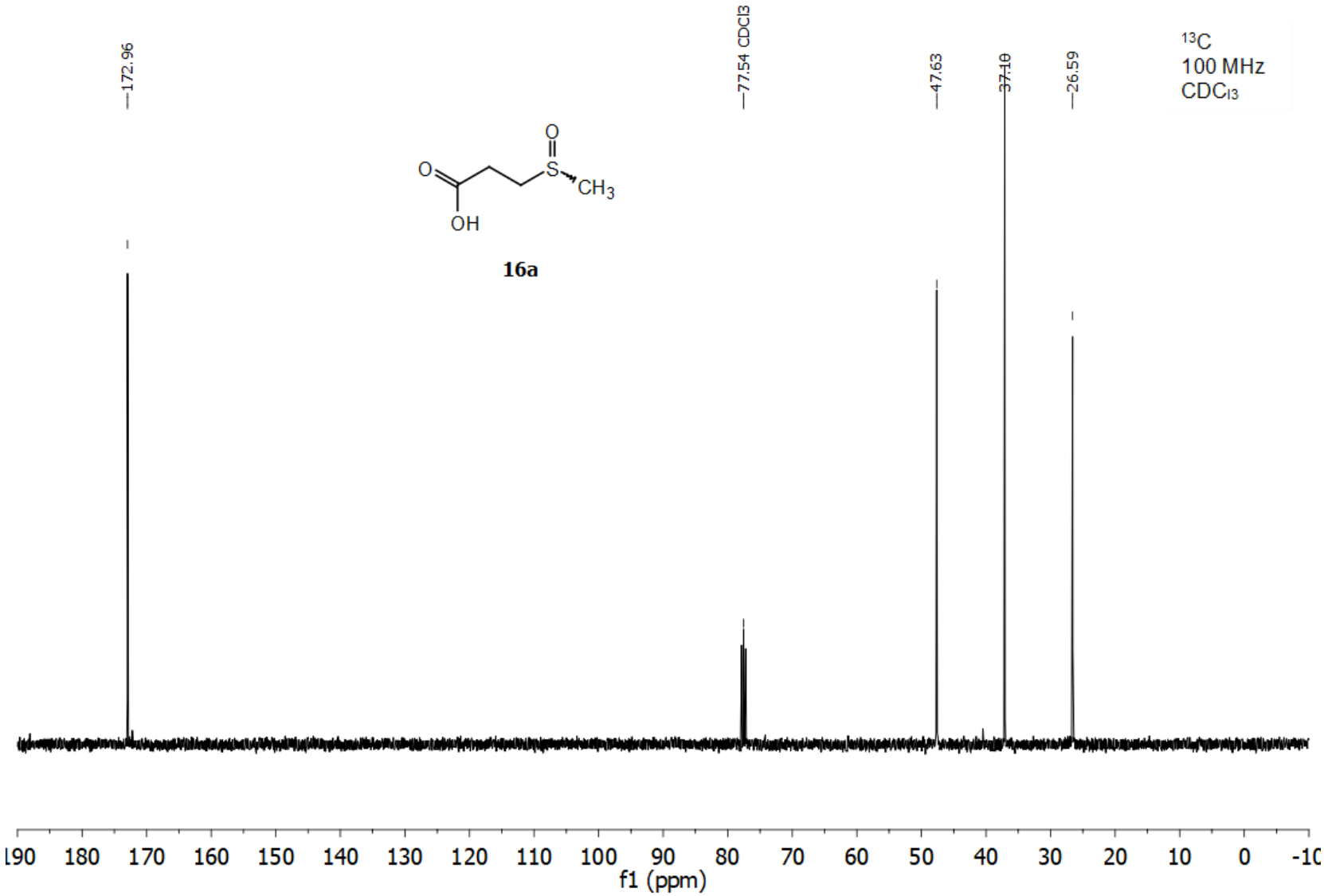
7.48
7.26 CDCl3
6.09
5.98
5.94
2.44
1H
400 MHz
CDCl3
O
O
O
S
CH3
O
15g
2.00
1.00
2.11
4.09
0.97
0.97
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

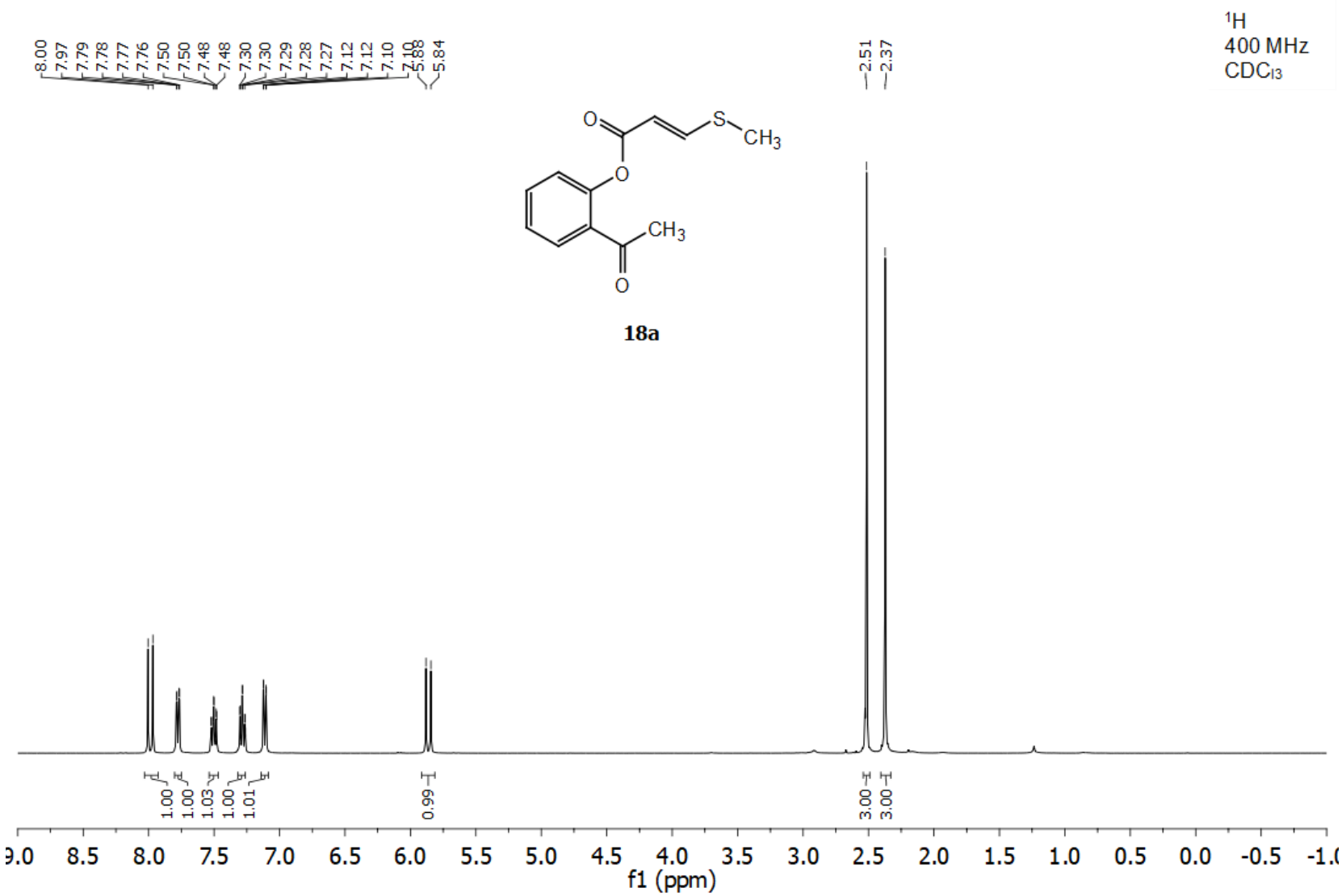

177.82
165.17
161.12
153.45
147.72
138.84
133.98
130.31
129.06
128.76
127.81
124.84
119.05
117.91
114.91
107.29
77.16 CDCl3
14.57
13C
100 MHz
CDCl3
O
O
O
O
S
CH3
15g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

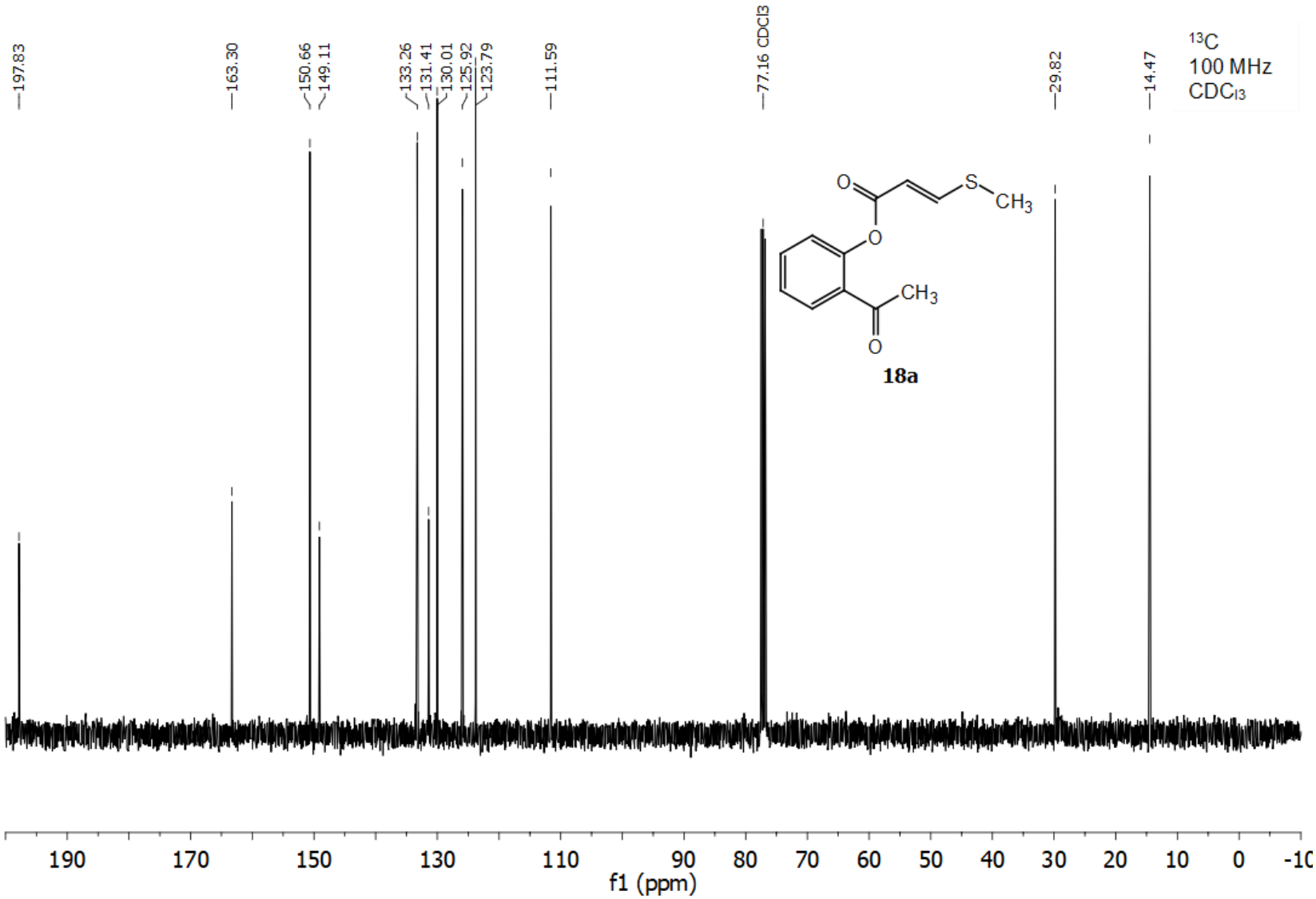

7.84
7.82
7.59
7.55
7.26 CDCl3
6.95
6.93
5.97
5.93
5.90
3.93
2.39
1H
400 MHz
CDCl3
H3C
O
H3C
O
O
S
CH3
O
15h
1.00
1.00
1.00
1.00
0.95
6.00
2.97
f1 (ppm)

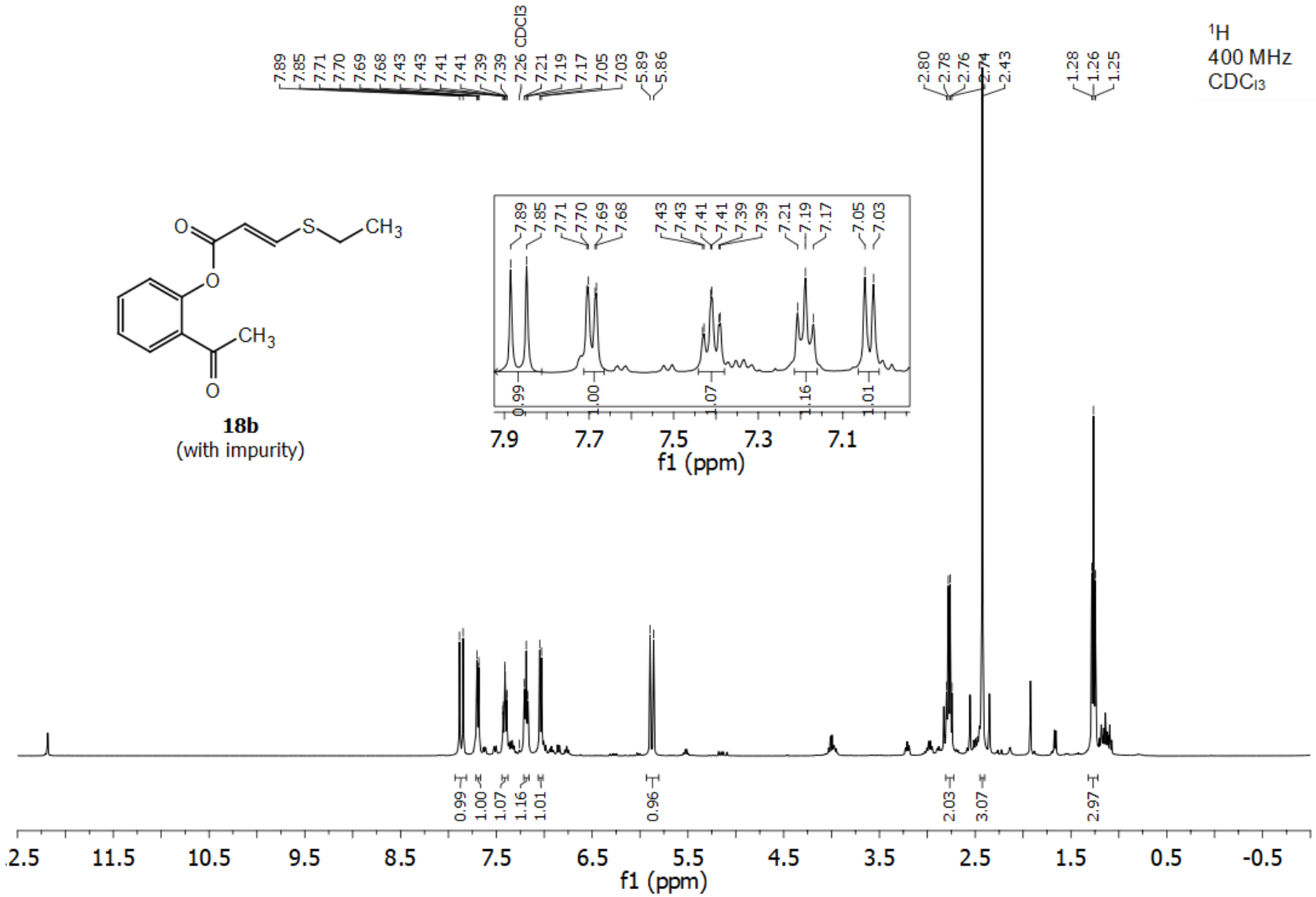

178.06
160.50
156.51
150.11
137.86
136.52
120.90
118.63
115.09
109.36
107.04
77.16 CDCl3
61.54
56.37
14.38
13C
100 MHz
CDCl3
H3C
O
O
O
S
CH3
O
15h
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

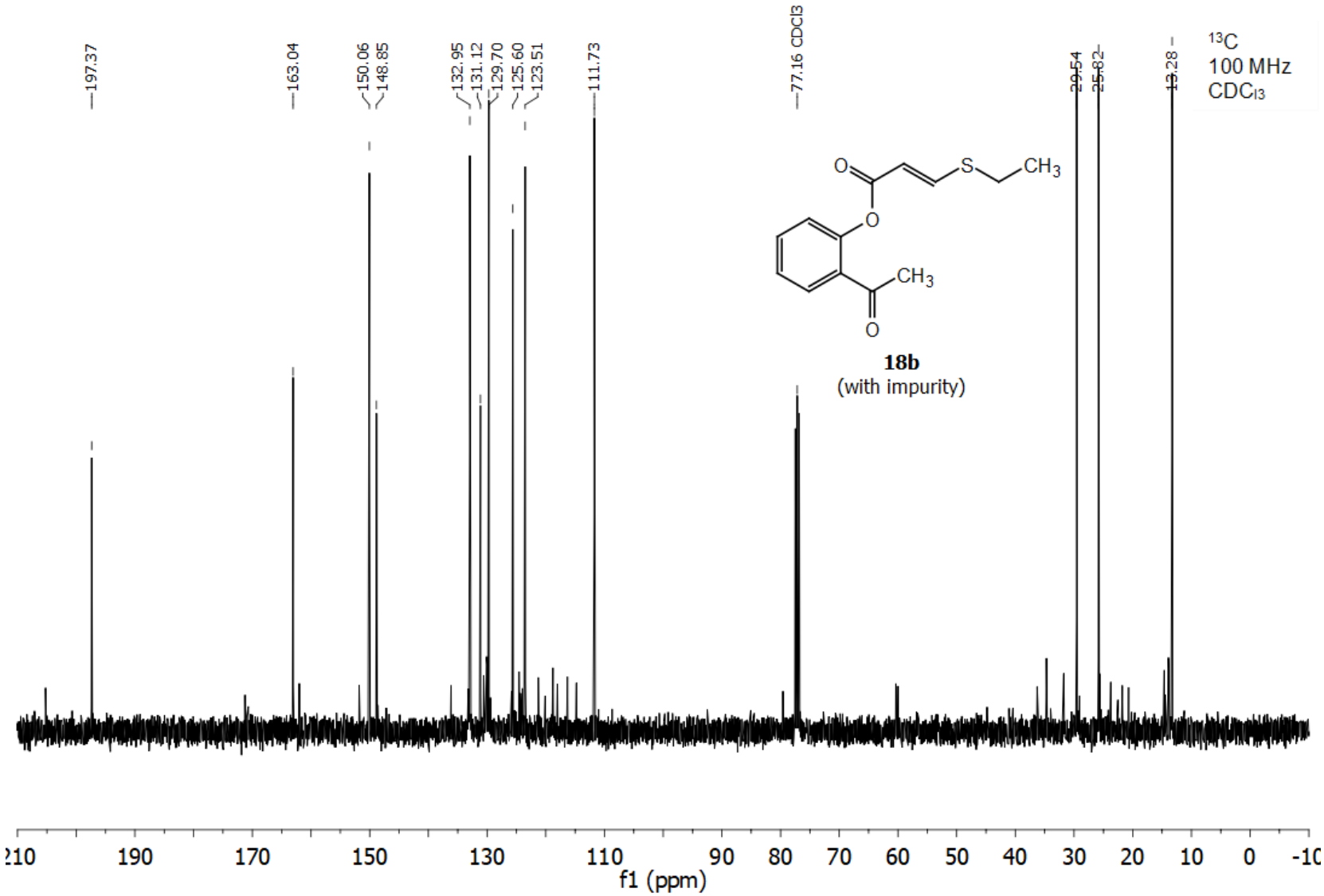

9.43
7.26 CDCl3
2.90
2.88
2.87
2.86
2.85
2.83
2.80
2.78
2.77
2.75
2.73
2.53
2.51
2.49
2.43
1H
400 MHz
CDCl3
O
O
S
CH3
OH
16a
1.55
1.00
1.00
1.98
3.00
f1 (ppm)

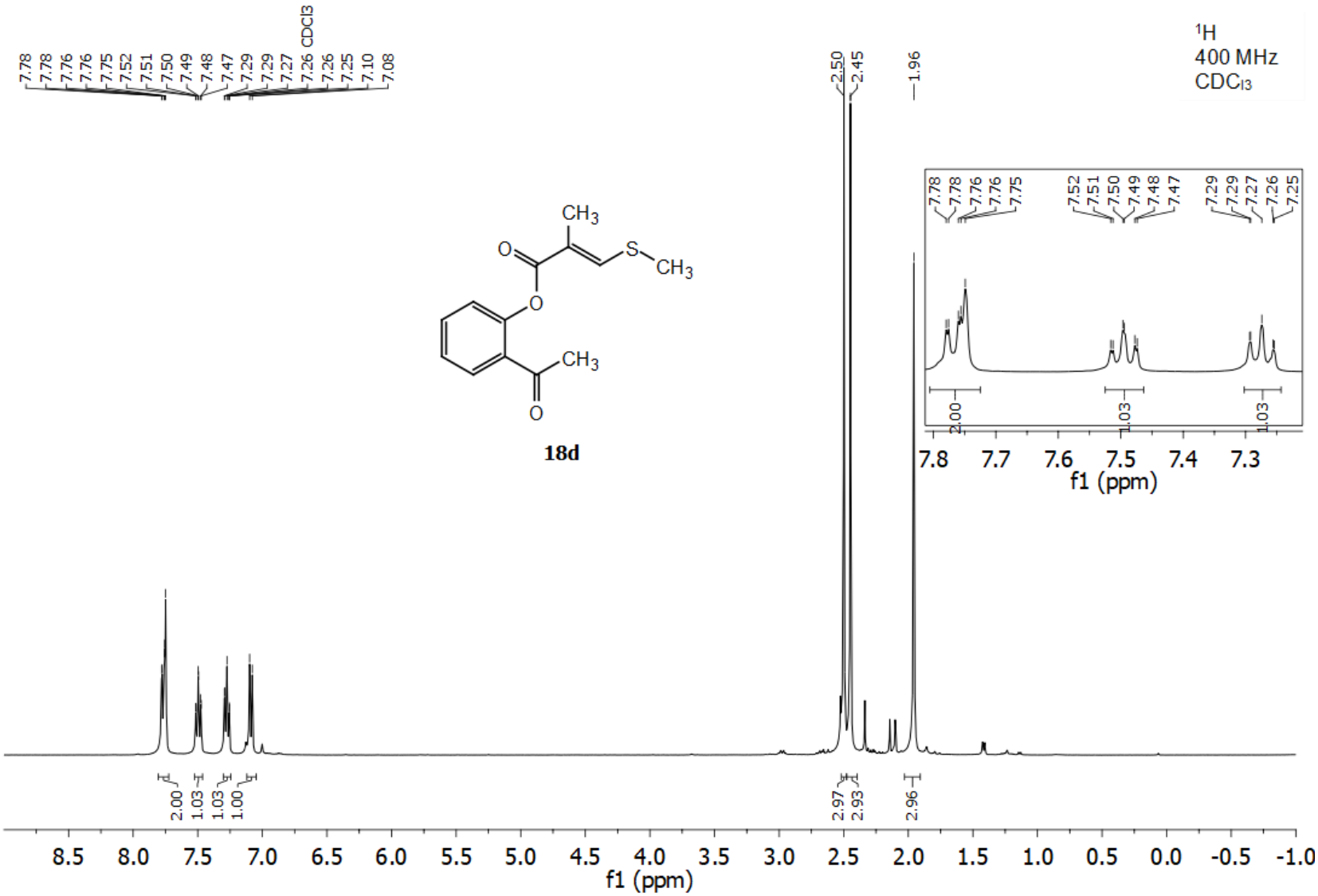

172.96
77.54 CDCl3
47.63
37.10
26.59
13C
100 MHz
CDCl3
O
O
S
CH3
OH
16a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

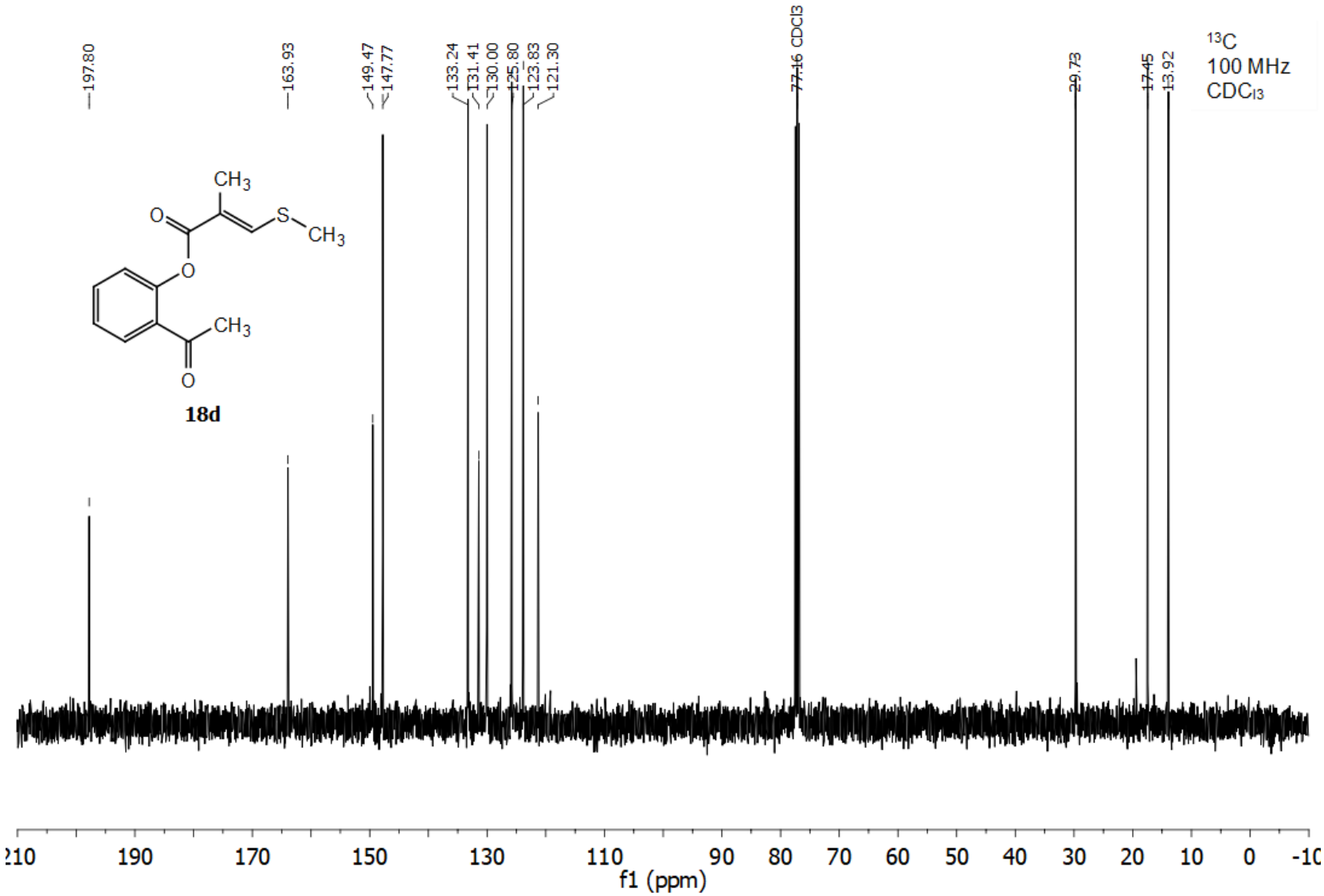

8.00
7.97
7.79
7.78
7.77
7.76
7.50
7.50
7.48
7.48
7.30
7.30
7.29
7.28
7.27
7.12
7.12
7.10
5.88
5.84
2.51
2.37
1H
400 MHz
CDCl3
O
O
S
CH3
O
CH3
O
18a
1.00
1.00
1.03
1.00
1.01
0.99
3.00
3.00
f1 (ppm)

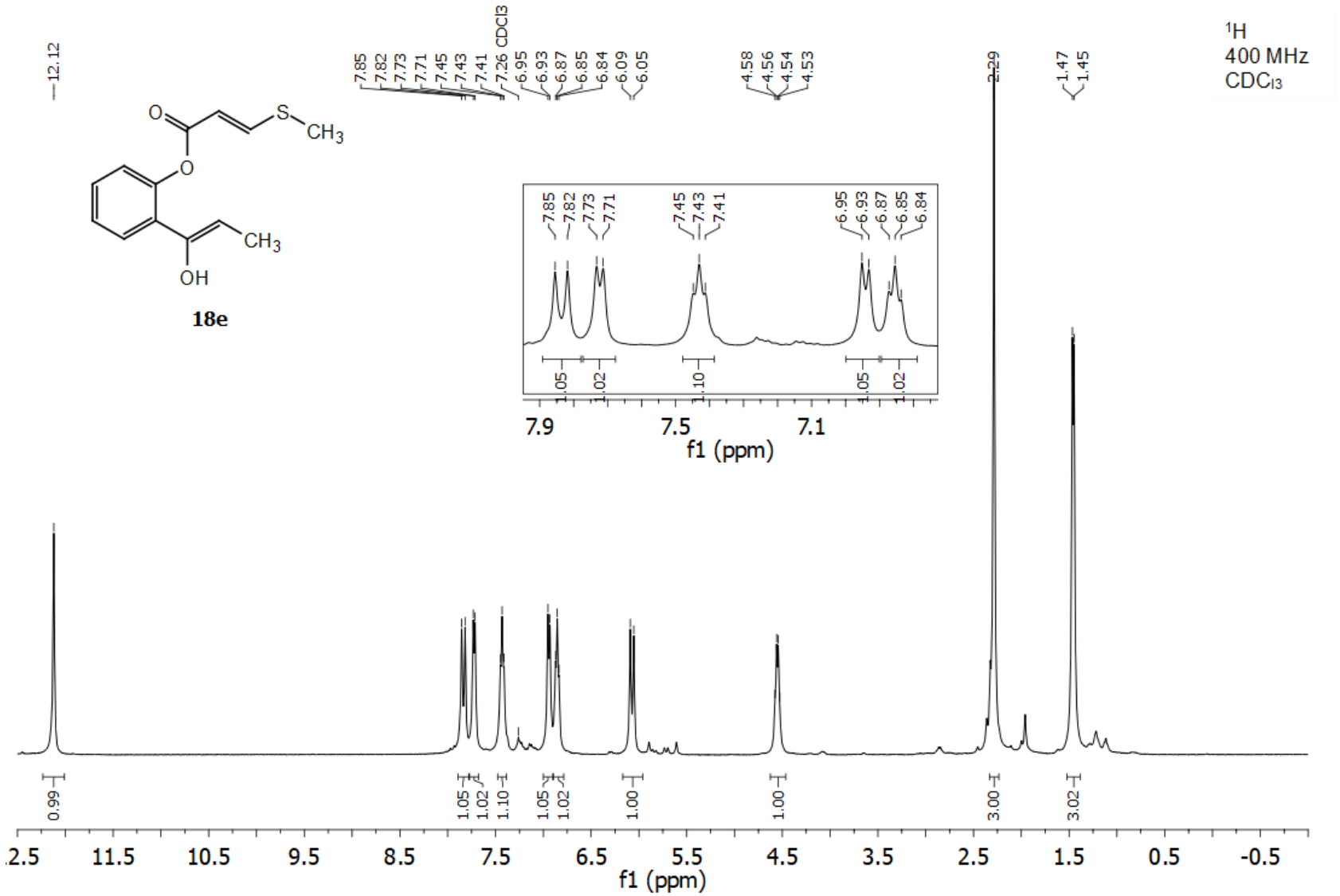

197.83
163.30
150.66
149.11
133.26
131.41
130.01
125.92
123.79
111.59
77.16 CDCl3
29.82
14.47
13C
100 MHz
CDCl3
O
O
S
CH3
O
CH3
O
18a
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

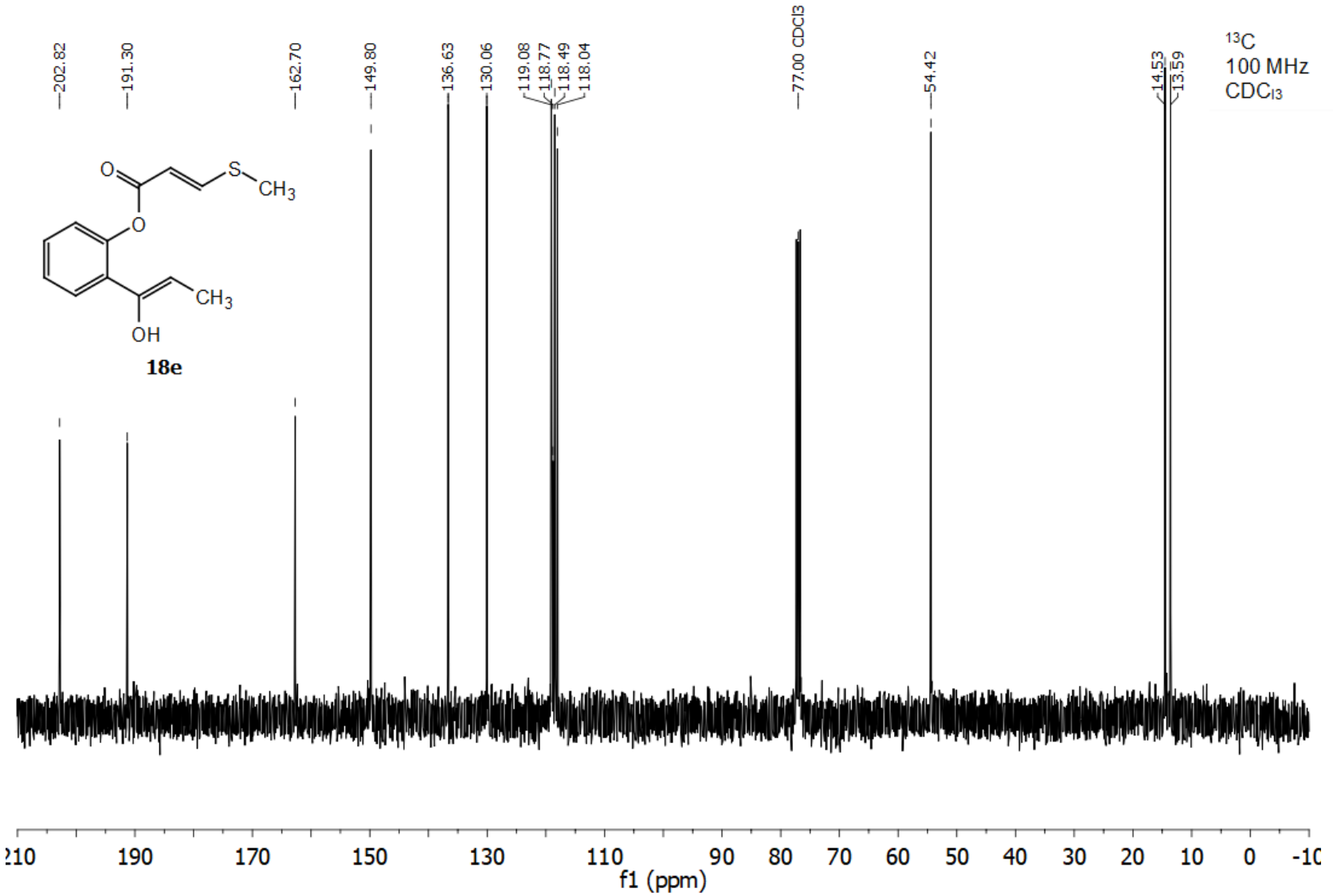

1H
400 MHz
CDCl3
7.89
7.85
7.71
7.70
7.69
7.68
7.43
7.43
7.41
7.41
7.39
7.39
7.26 CDCl3
7.21
7.19
7.17
7.05
7.03
5.89
5.86
2.80
2.78
2.76
2.74
2.43
1.28
1.26
1.25
0.99
1.00
1.07
1.16
1.01
0.96
2.03
3.07
2.97
f1 (ppm)
18b
(with impurity)

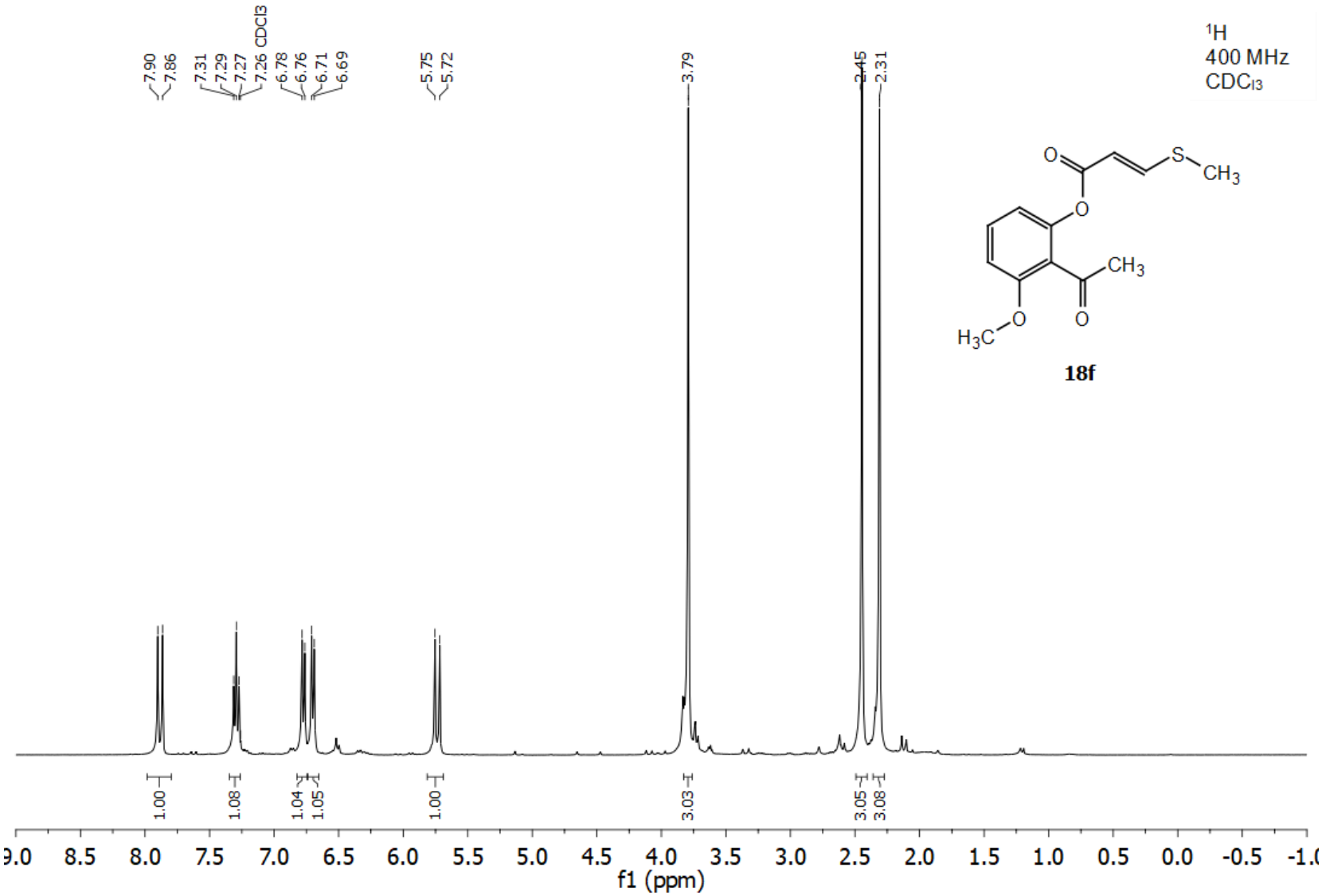

197.37
163.04
150.06
148.85
132.95
131.12
129.70
125.60
123.51
111.73
77.16 CDCl3
29.54
25.82
13.28
13C
100 MHz
CDCl3
O
S
CH3
O
CH3
O
18b
(with impurity)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

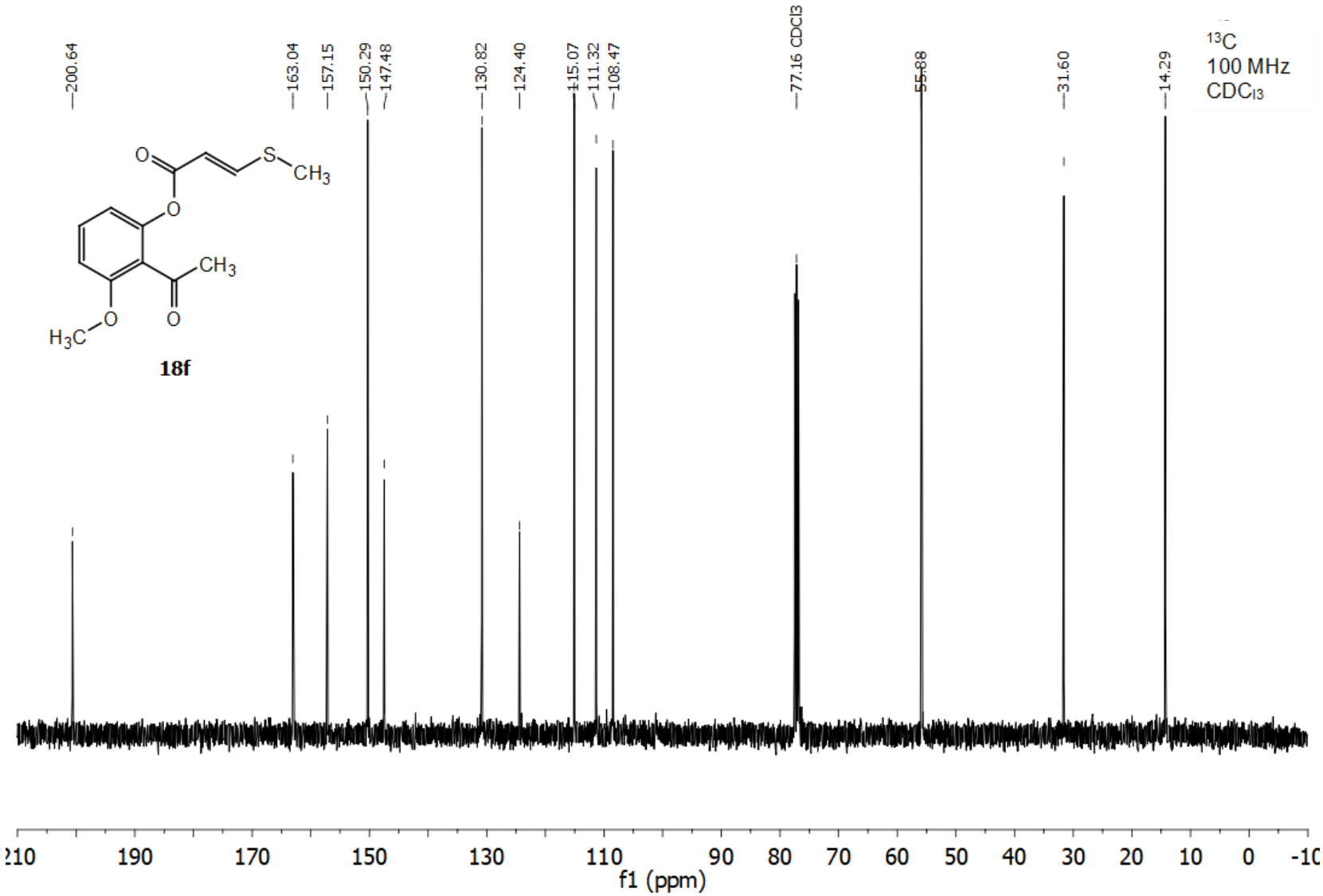

7.78
7.78
7.76
7.76
7.75
7.52
7.51
7.50
7.49
7.48
7.47
7.29
7.29
7.27
CDCl3
7.26
7.25
7.10
7.08
2.50
2.45
1.96
1H
400 MHz
CDCl3
CH3
O
S
CH3
O
CH3
O
18d
2.00
1.03
1.03
1.00
2.97
2.93
2.96
f1 (ppm)

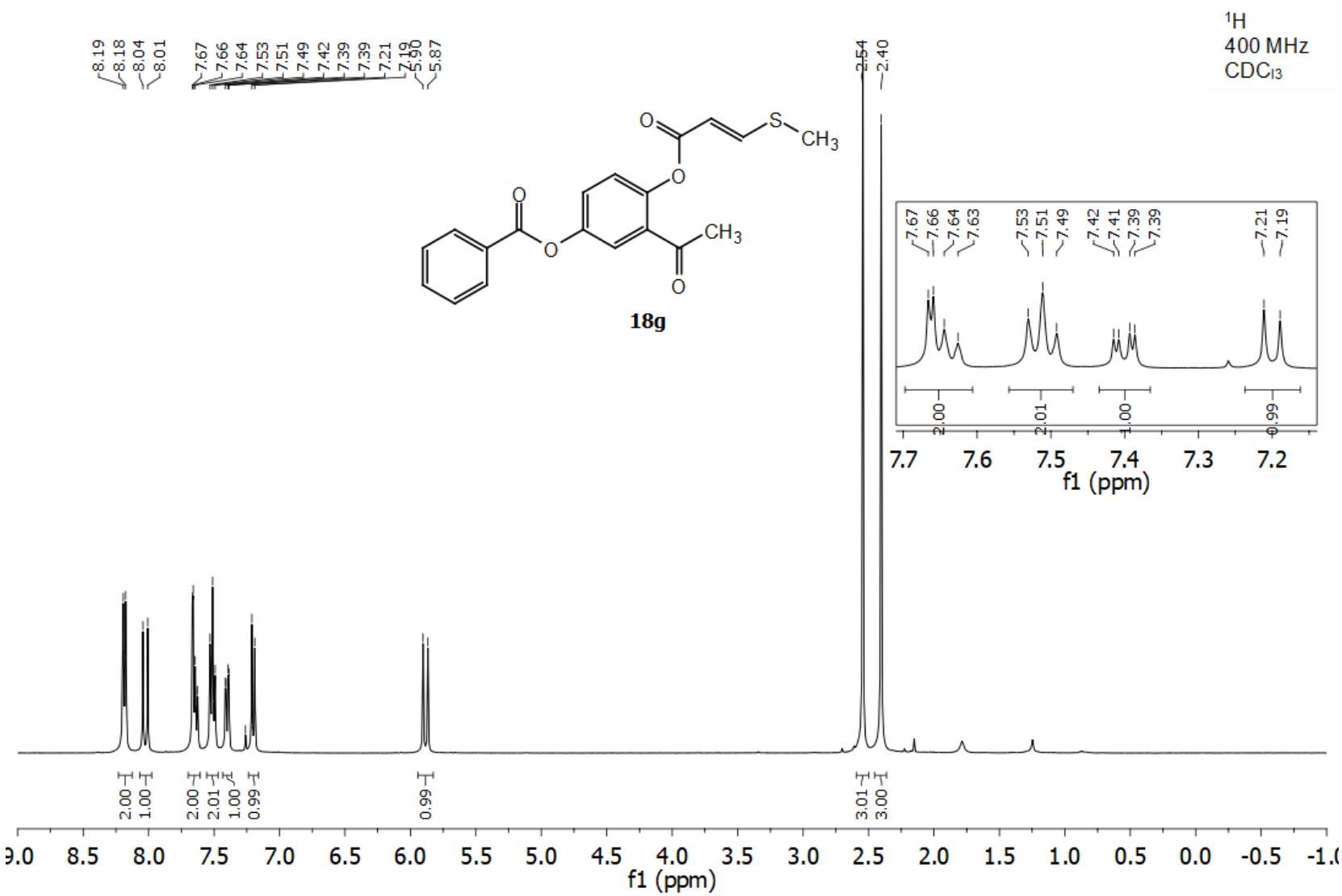

197.80
163.93
149.47
147.77
133.24
131.41
130.00
125.80
123.83
121.30
77.16 CDCl3
29.73
17.45
13.92
13C
100 MHz
CDCl3
CH3
O
S
CH3
O
CH3
O
18d
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

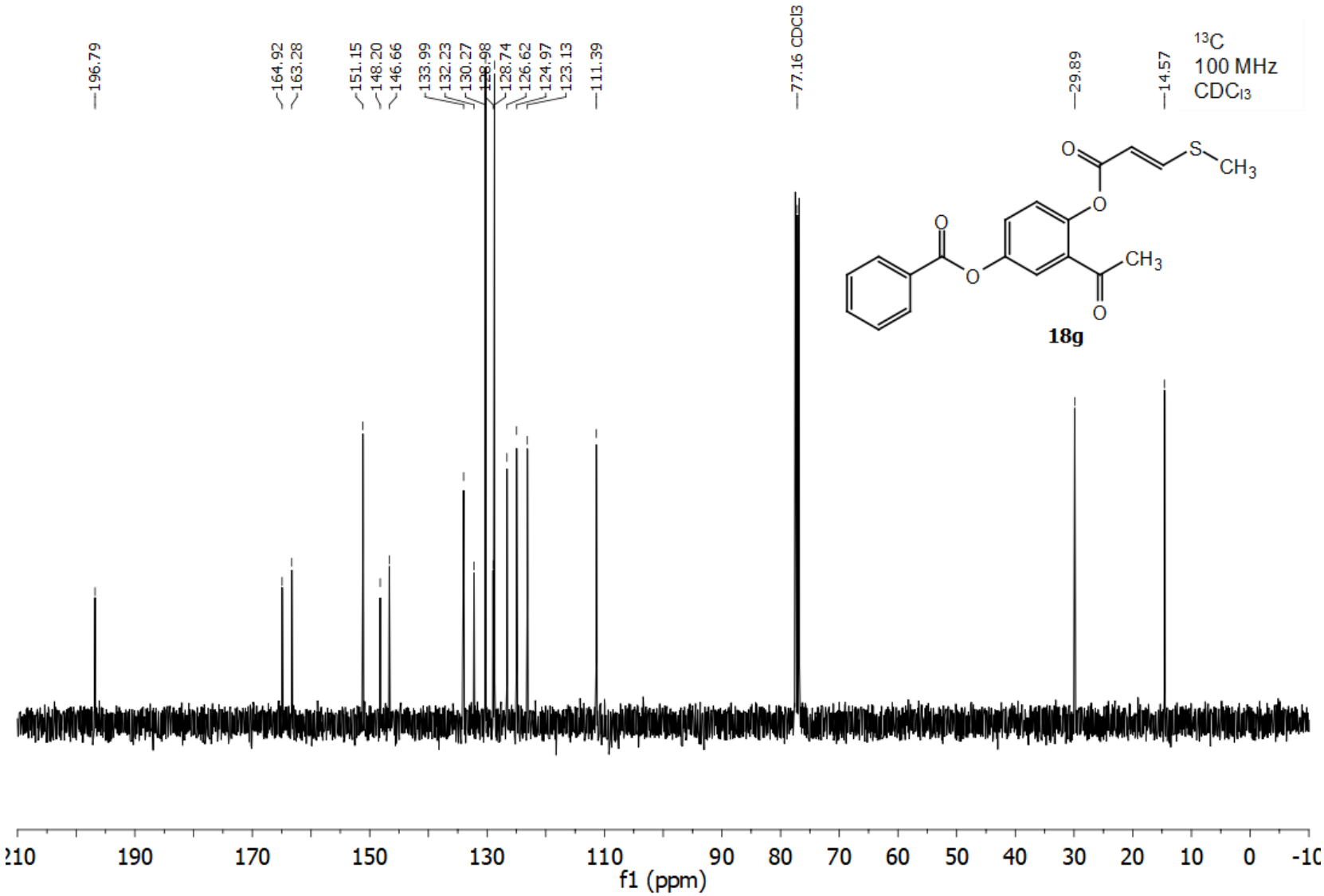

12.12
7.85
7.82
7.73
7.71
7.45
7.43
7.41
7.26 CDCl3
6.95
6.93
6.87
6.85
6.84
6.09
6.05
4.58
4.56
4.54
4.53
2.29
1.47
1.45
1H
400 MHz
CDCl3
O
O
S
CH3
CH3
OH
18e
0.99
1.05
1.02
1.10
1.05
1.02
1.00
1.00
3.00
3.02
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)
1.05
1.02
1.10
1.05
1.02
7.9
7.5
7.1
f1 (ppm)

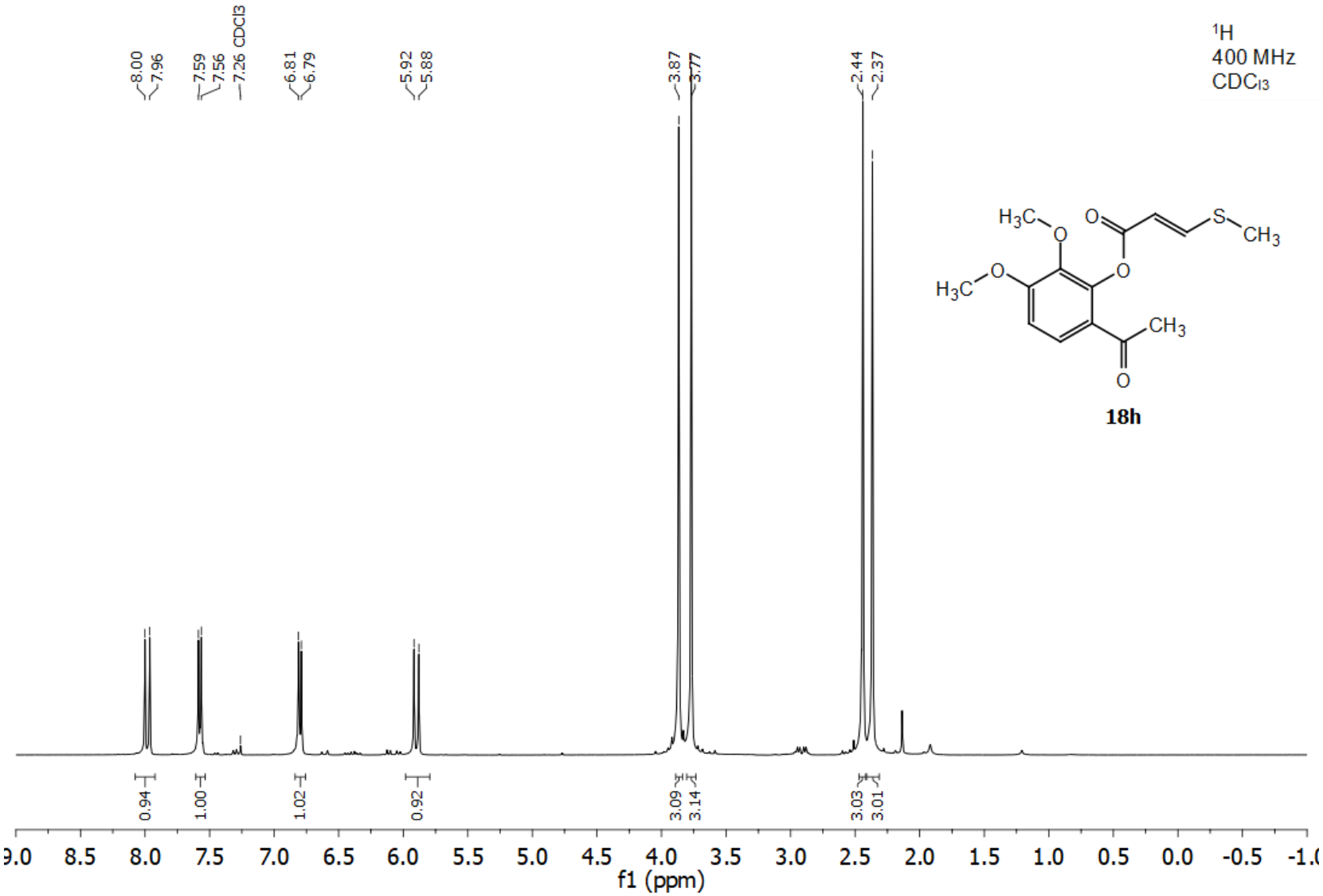

202.82
191.30
162.70
149.80
136.63
130.06
119.08
118.77
118.49
118.04
77.00 CDCl3
54.42
14.53
13.59
13C
100 MHz
CDCl3
O
S
CH3
O
CH3
OH
18e
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

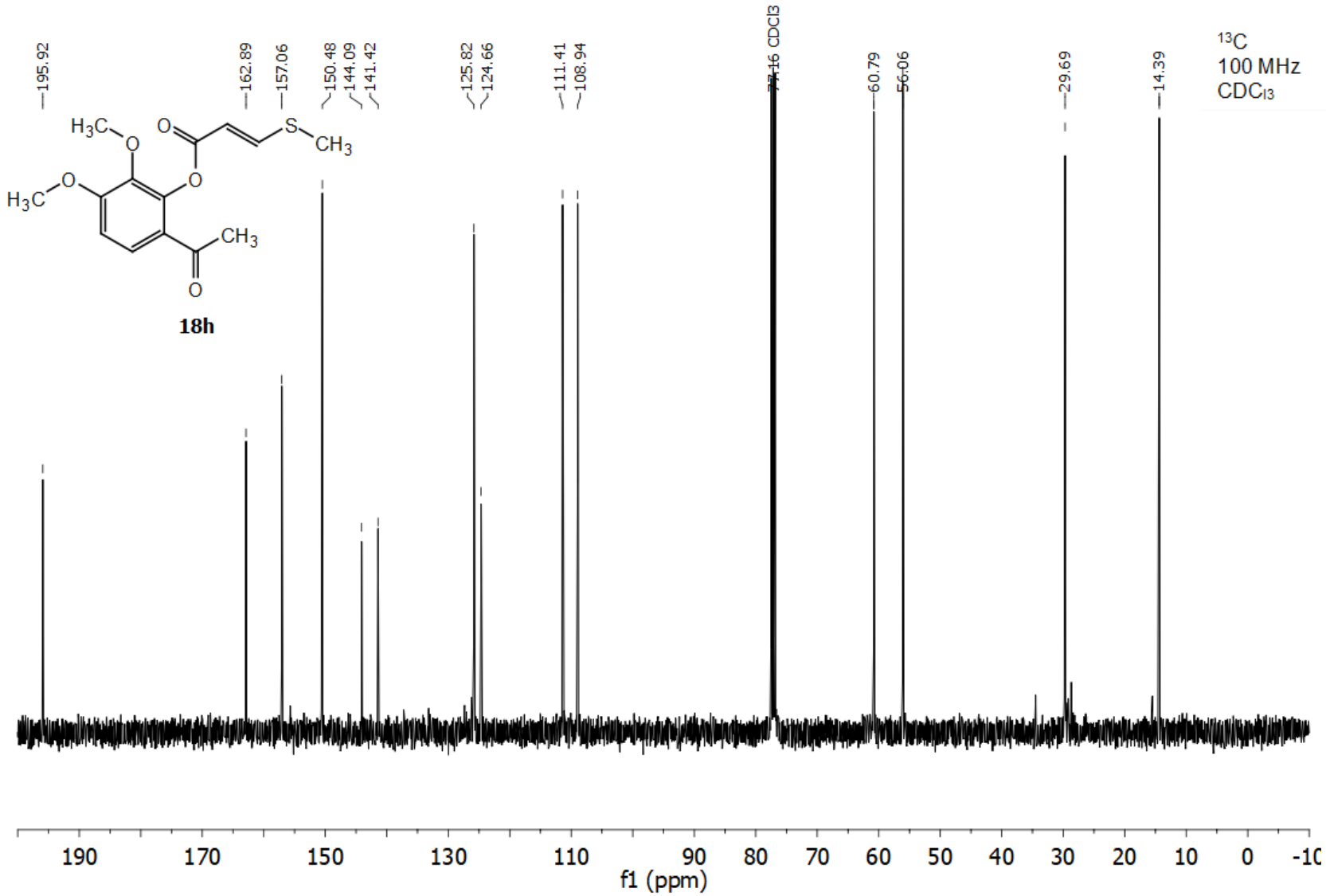

7.90
7.86
7.31
7.29
7.27
7.26 CDCl3
6.78
6.76
6.71
6.69
5.75
5.72
3.79
2.45
2.31
1H
400 MHz
CDCl3
O
S
CH3
O
CH3
O
O
H3C
18f
1.00
1.08
1.04
1.05
1.00
3.03
3.05
3.08
f1 (ppm)

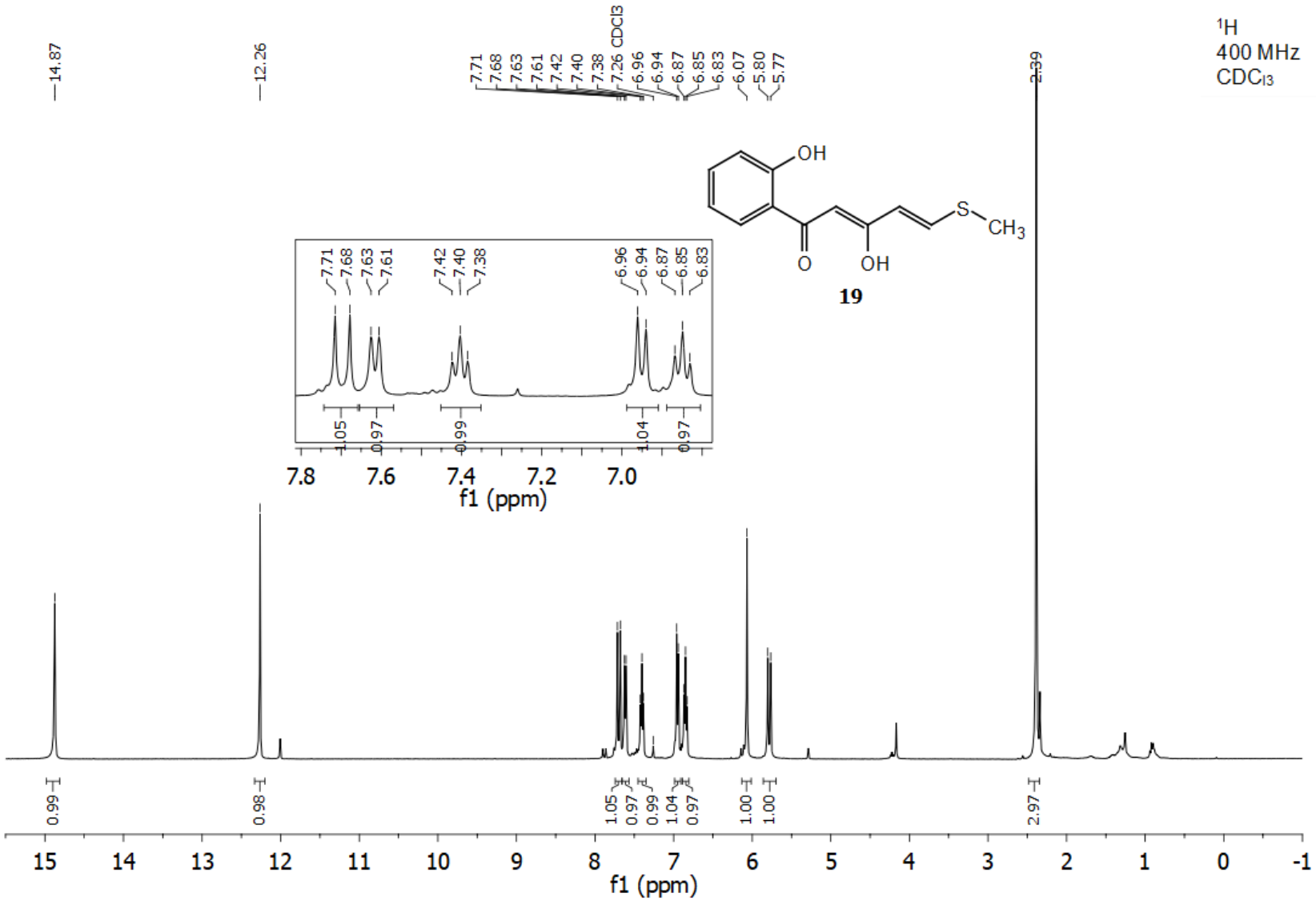

200.64
163.04
157.15
150.29
147.48
130.82
124.40
115.07
111.32
108.47
77.16 CDCl3
55.88
31.60
14.29
13C
100 MHz
CDCl3
O
S
CH3
O
CH3
O
O
H3C
18f
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

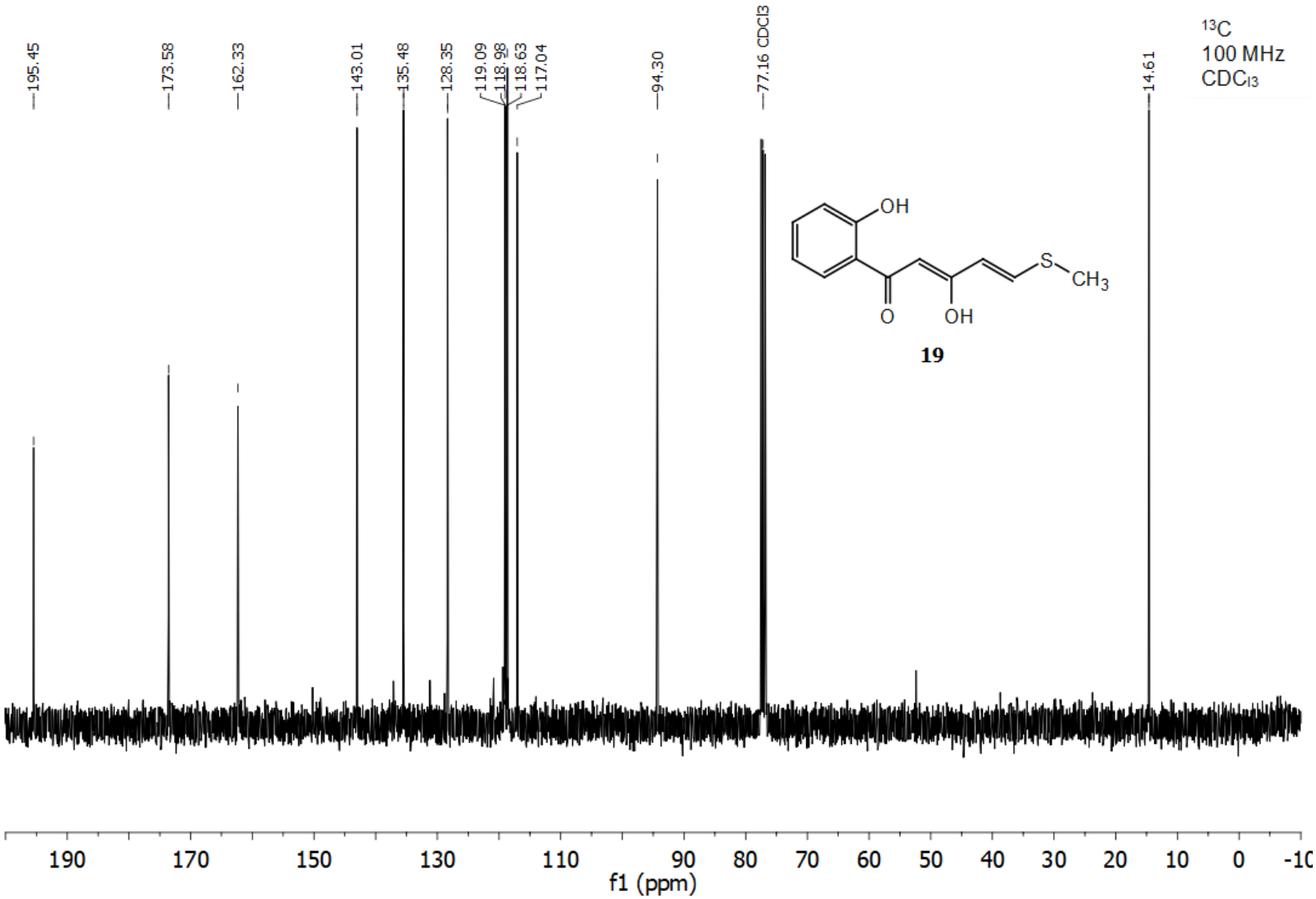

1H
400 MHz
CDCl3
8.19
8.18
8.04
8.01
7.67
7.66
7.64
7.53
7.51
7.49
7.42
7.39
7.39
7.21
7.19
5.90
5.87
2.54
2.40
O
O
S
CH3
O
O
CH3
O
18g
7.67
7.66
7.64
7.63
7.53
7.51
7.49
7.42
7.41
7.39
7.39
7.21
7.19
2.00
2.01
1.00
0.99
7.7
7.6
7.5
7.4
7.3
7.2
f1 (ppm)
2.00
1.00
2.00
2.01
1.00
0.99
0.99
3.01
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

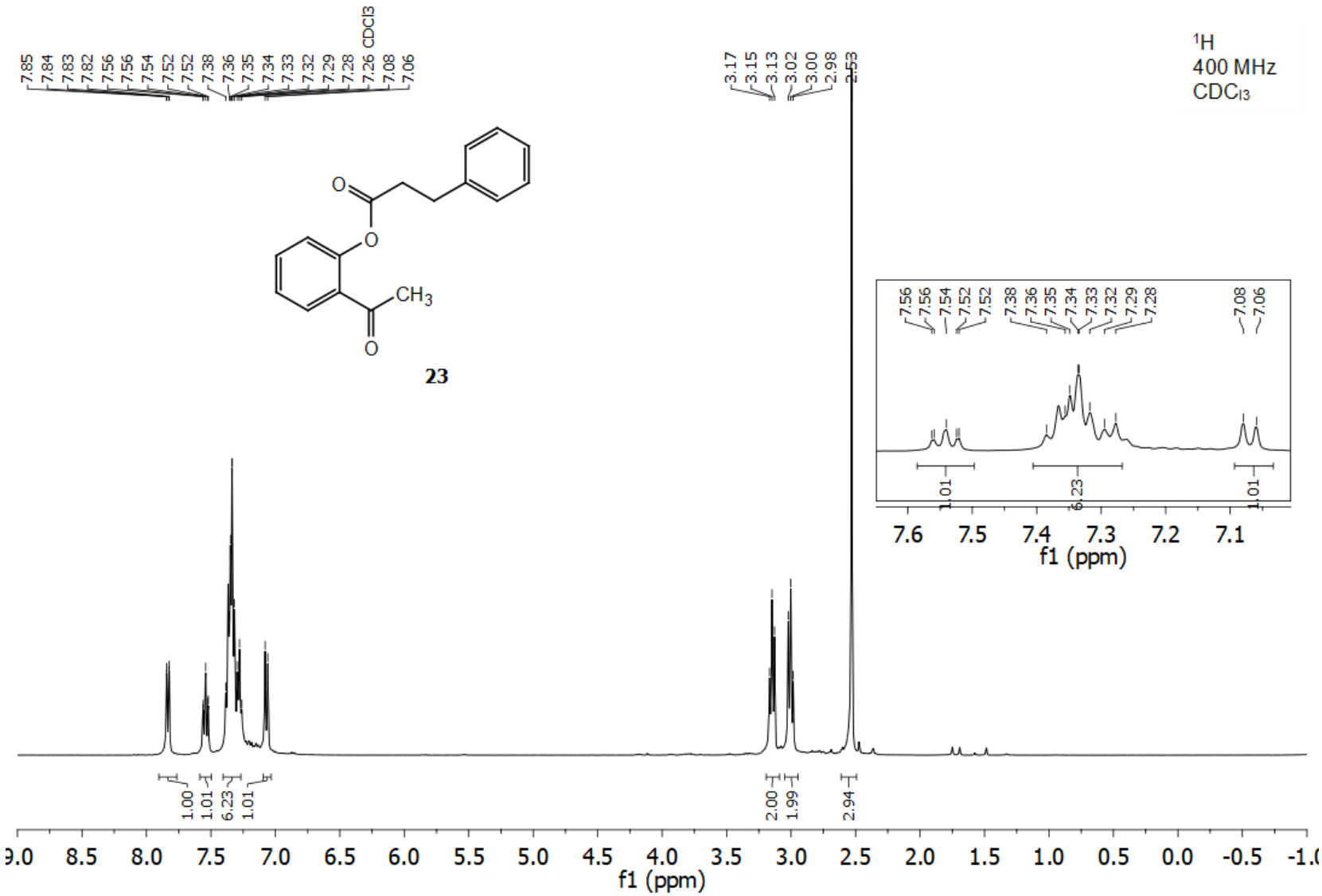

196.79
164.92
163.28
151.15
148.20
146.66
133.99
132.23
130.27
128.98
128.74
126.62
124.97
123.13
111.39
77.16 CDCl3
29.89
14.57
13C
100 MHz
CDCl3
O
O
S
CH3
O
O
O
CH3
O
18g
f1 (ppm)

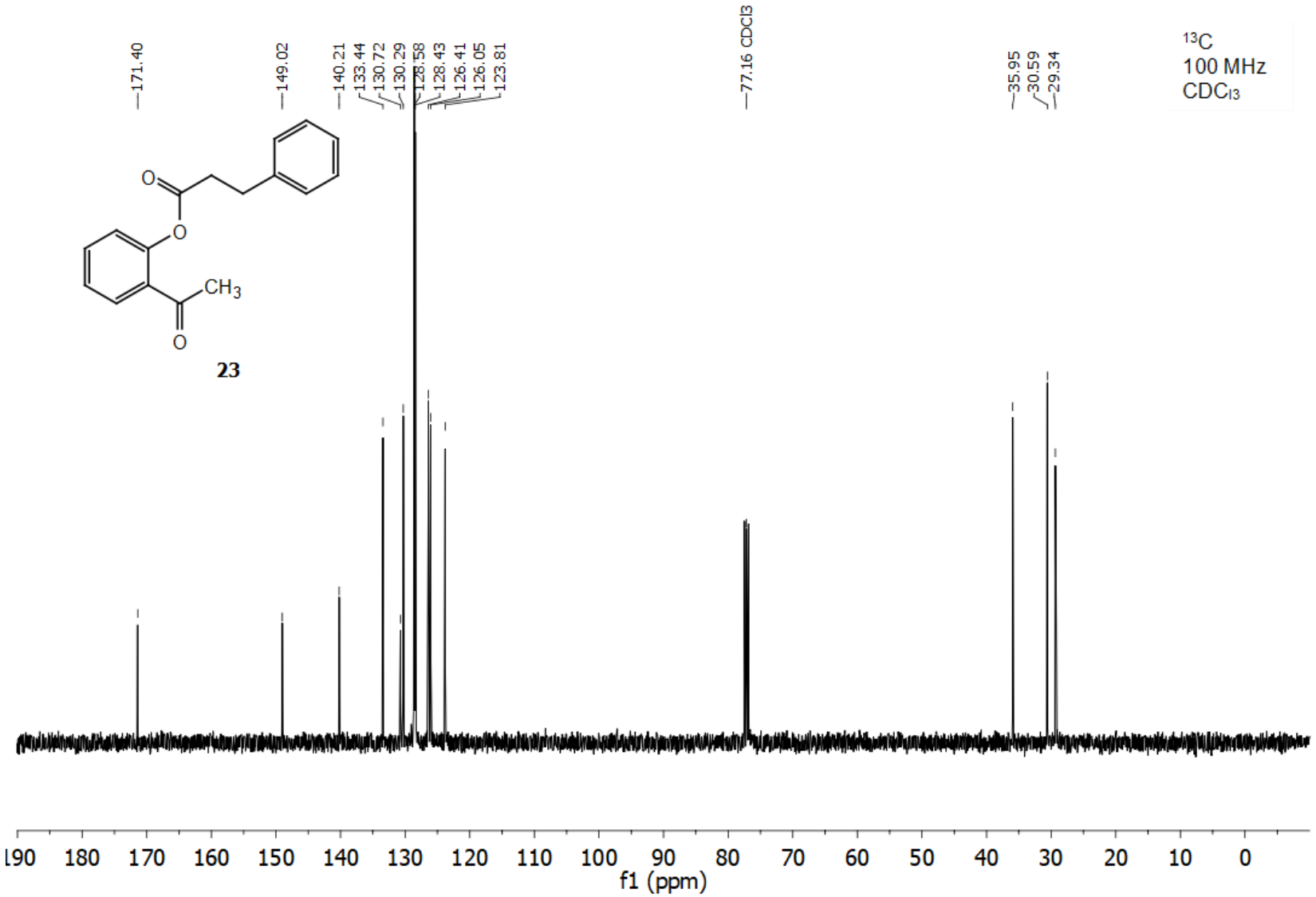

8.00
7.96
7.59
7.56
7.26 CDCl3
6.81
6.79
5.92
5.88
3.87
3.77
2.44
2.37
1H
400 MHz
CDCl3
H3C
O
O
S
CH3
H3C
O
O
CH3
O
18h
0.94
1.00
1.02
0.92
3.09
3.14
3.03
3.01
f1 (ppm)

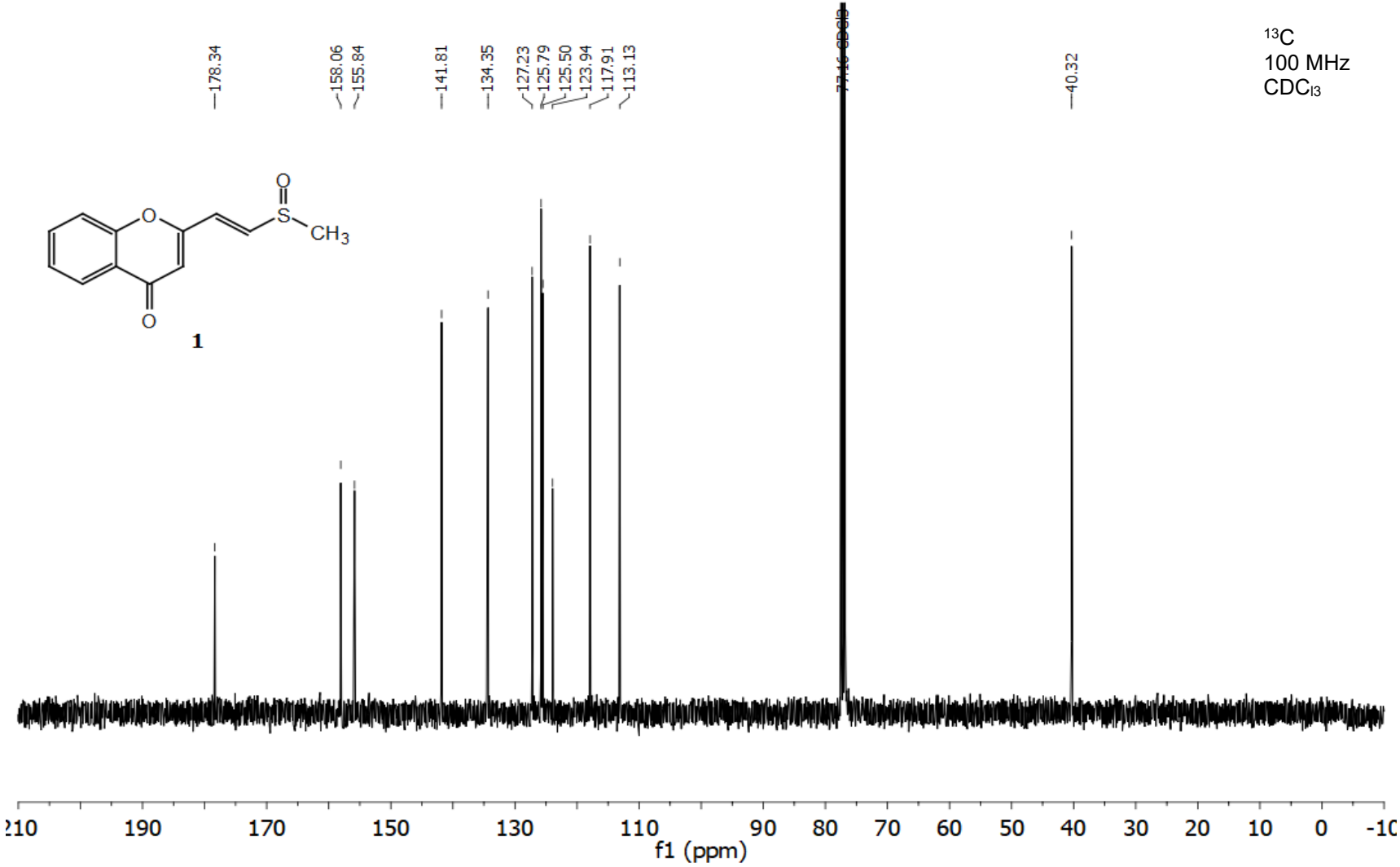

195.92
162.89
157.06
150.48
144.09
141.42
125.82
124.66
111.41
108.94
77.16 CDCl3
60.79
56.06
29.69
14.39
13C
100 MHz
CDCl3
H3C
O
O
S
CH3
H3C
O
O
CH3
O
18h
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

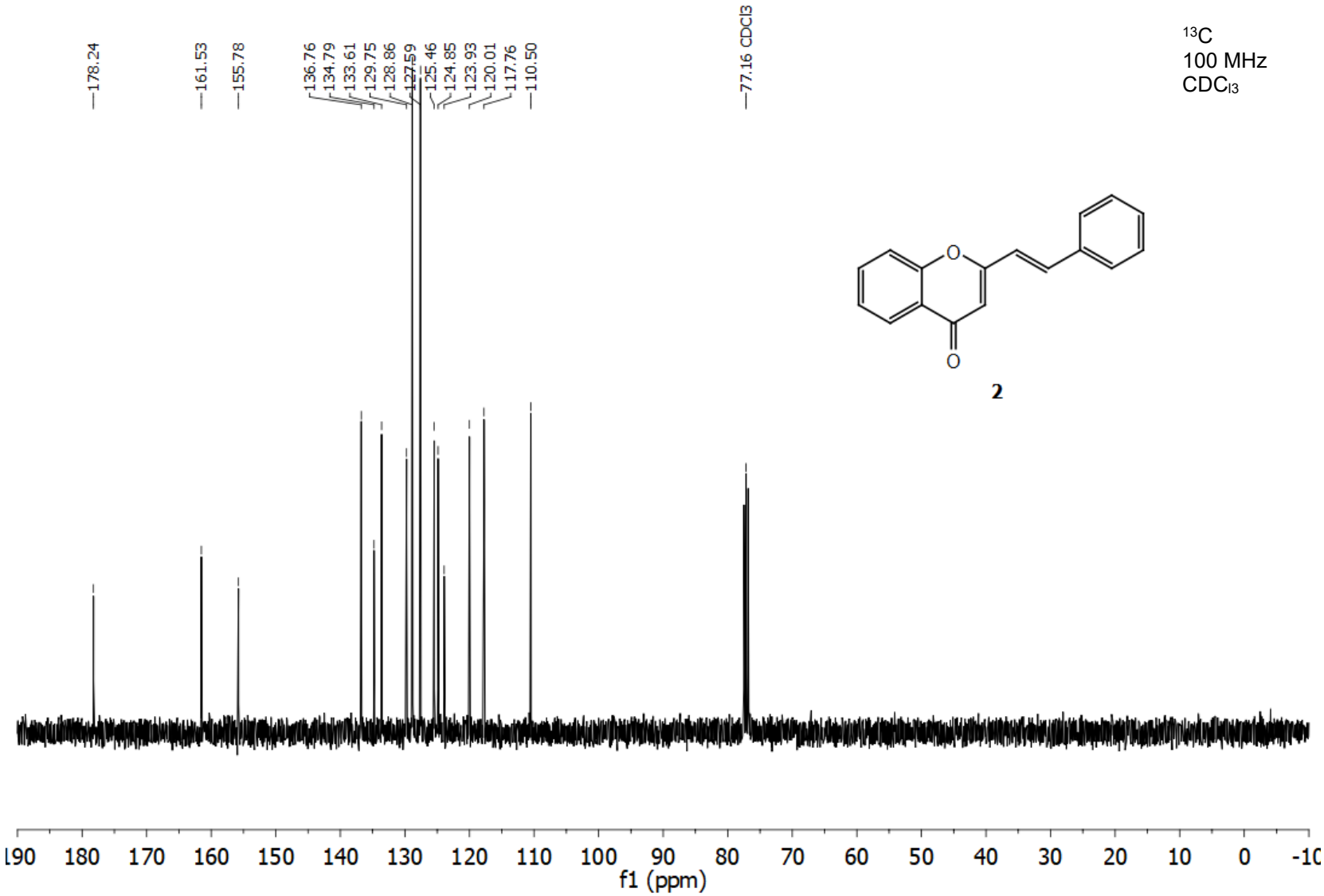

14.87
12.26
7.71
7.68
7.63
7.61
7.42
7.40
7.38
7.26 CDCl3
6.96
6.94
6.87
6.85
6.83
6.07
5.80
5.77
2.39
1H
400 MHz
CDCl3
OH
S
CH3
O
OH
19
1.05
0.97
0.99
1.04
0.97
7.8
7.6
7.4
7.2
7.0
f1 (ppm)
0.99
0.98
1.05
0.97
0.99
1.04
0.97
1.00
1.00
2.97
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

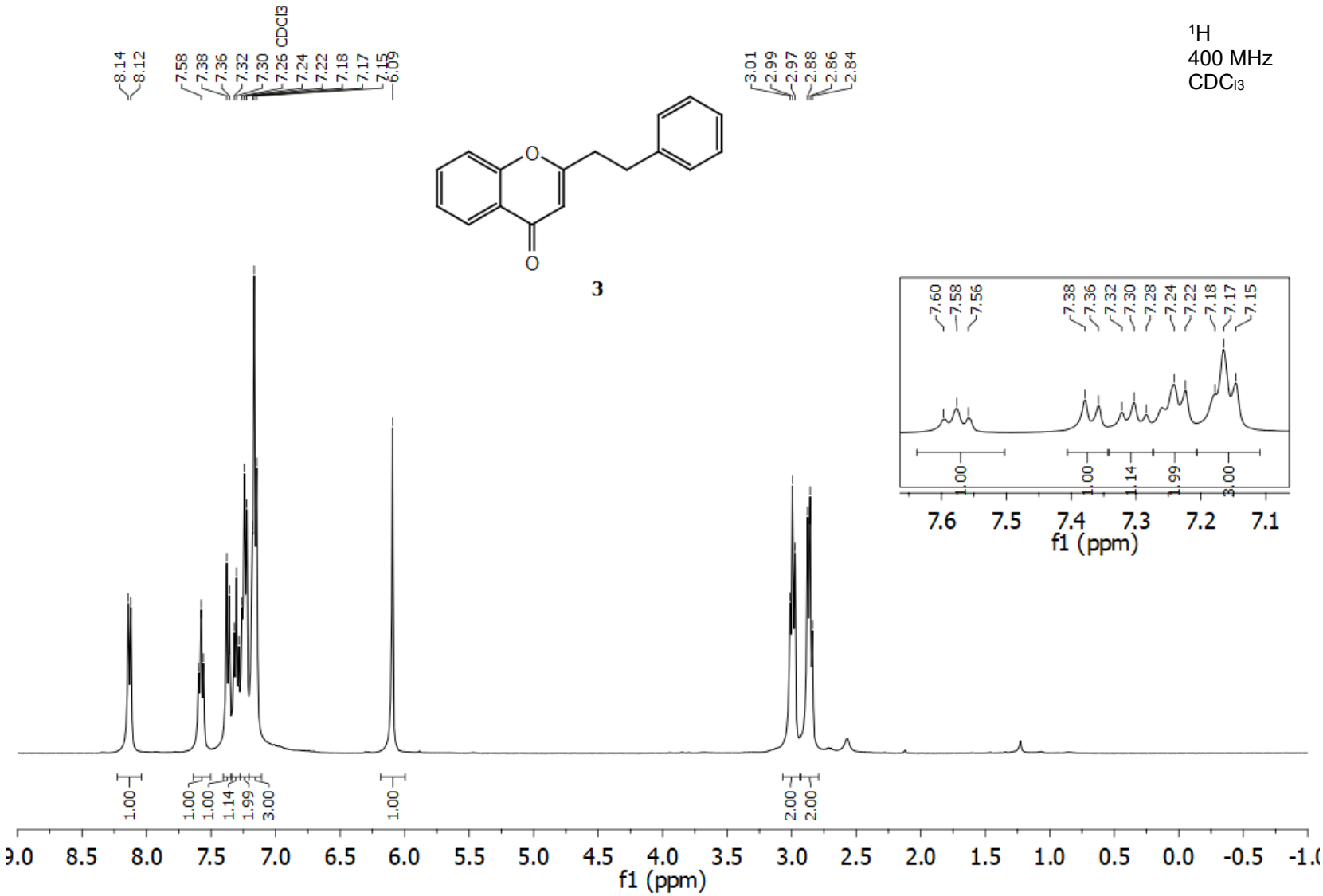

195.45
173.58
162.33
143.01
135.48
128.35
119.09
118.98
118.63
117.04
94.30
77.16 CDCl3
14.61
13C
100 MHz
CDCl3
OH
O
OH
S
CH3
19
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

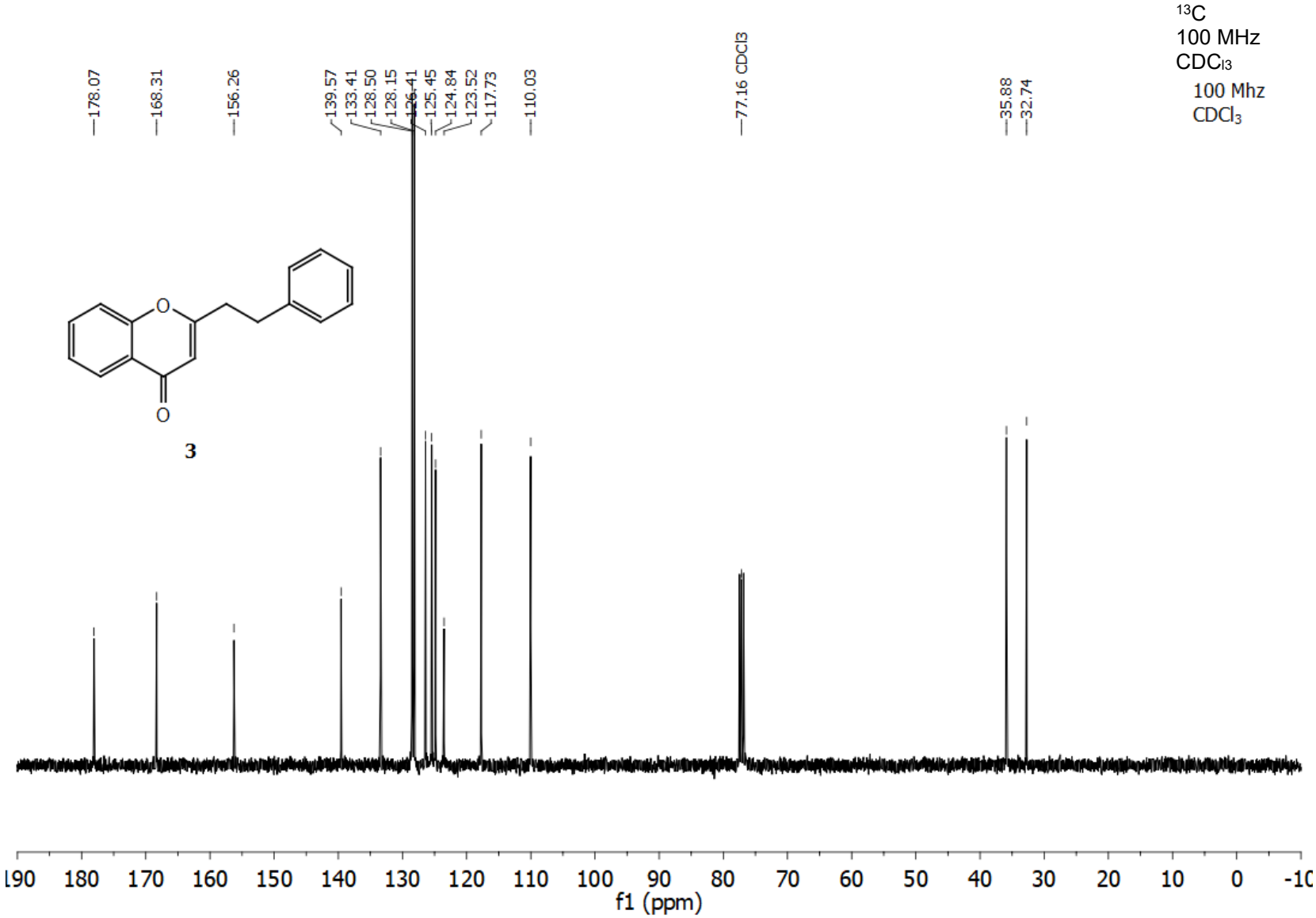

1H
400 MHz
CDCl3
7.85
7.84
7.83
7.82
7.56
7.56
7.54
7.52
7.52
7.38
7.36
7.35
7.34
7.33
7.32
7.29
7.28
7.26 CDCl3
7.08
7.06
3.17
3.15
3.13
3.02
3.00
2.98
2.53
O
O
CH3
O
23
1.00
1.01
6.23
1.01
2.00
1.99
2.94
f1 (ppm)
7.6
7.5
7.4
7.3
7.2
7.1

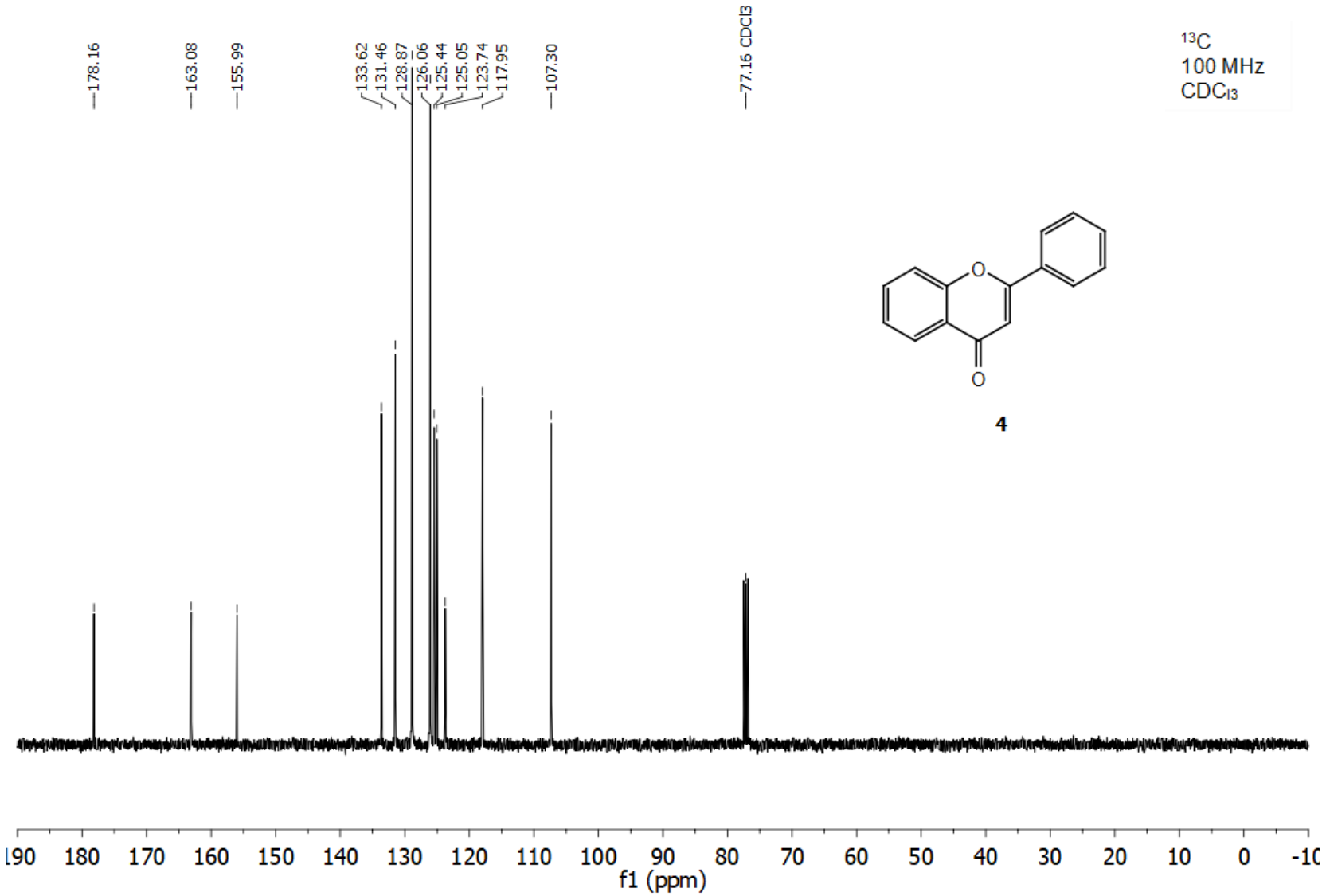

171.40
149.02
140.21
133.44
130.72
130.29
128.58
128.43
126.41
126.05
123.81
77.16 CDCl3
35.95
30.59
29.34
13C
100 MHz
CDCl3
O
O
O
CH3
23
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

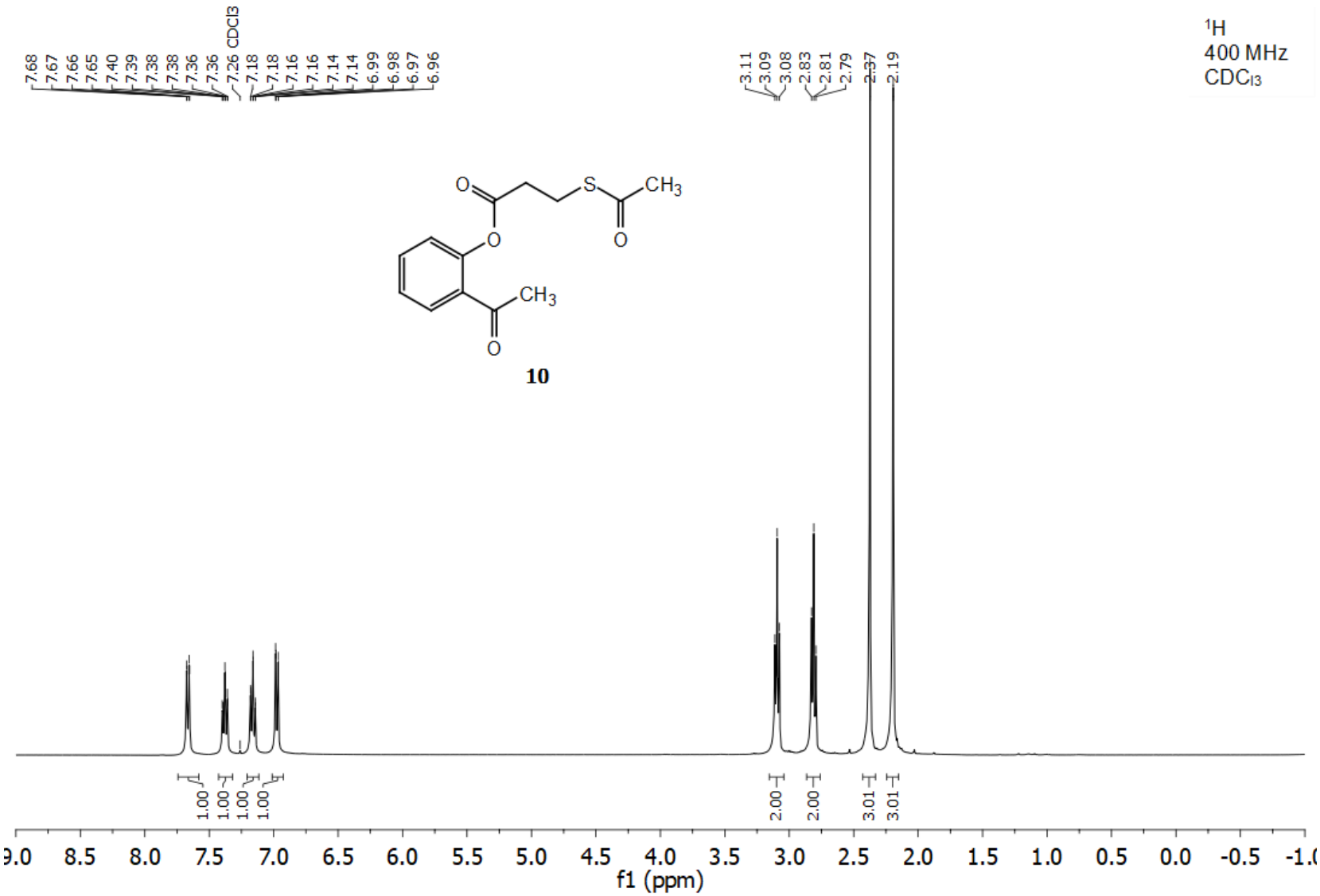

178.34
158.06
155.84
141.81
134.35
127.23
125.79
125.50
123.94
117.91
113.13
77.16 CDCl3
40.32
^{13}C
100 MHz
CDCl3
O
S
CH3
O
O
1
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

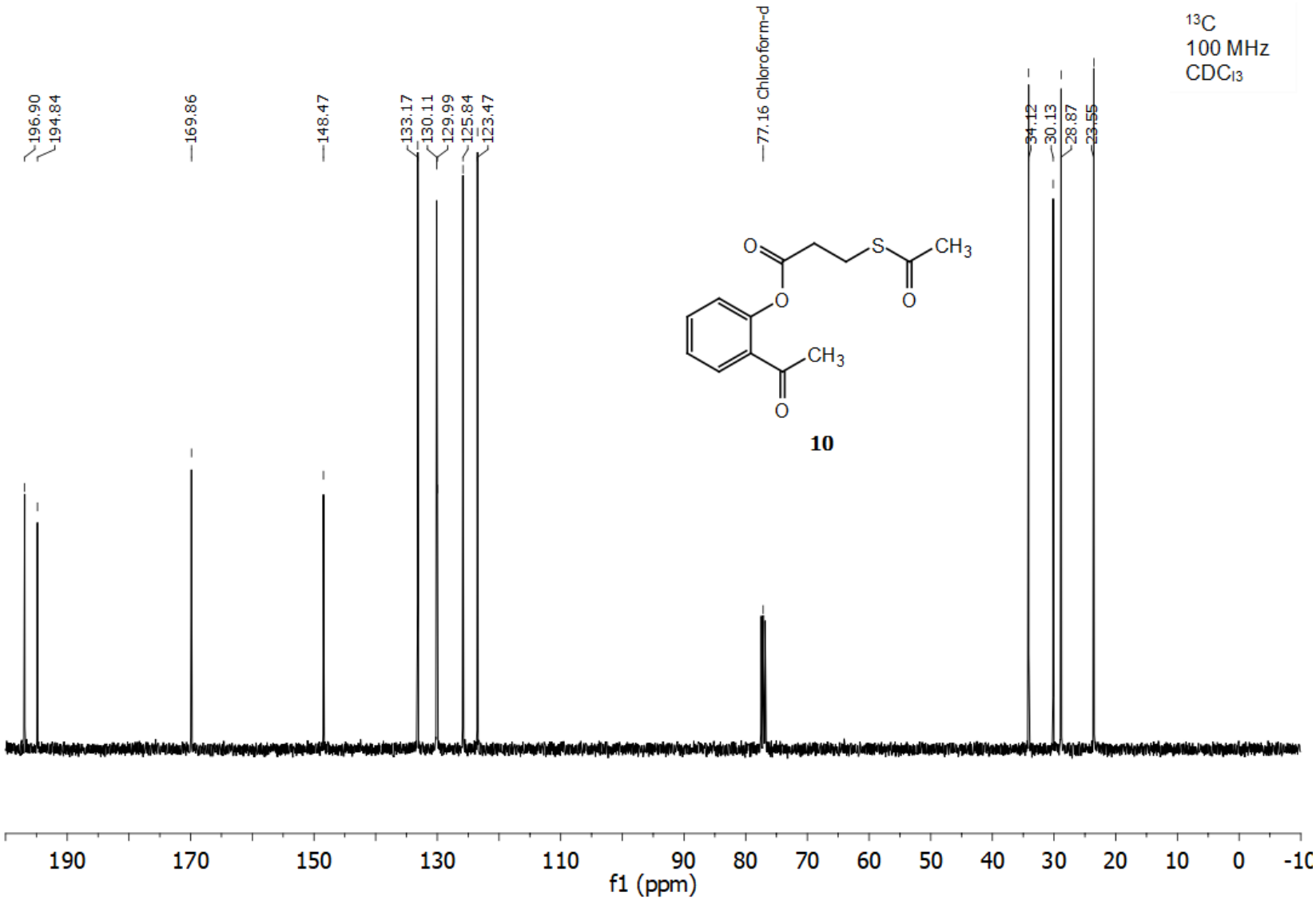

178.24
161.53
155.78
136.76
134.79
133.61
129.75
128.86
127.59
125.46
124.85
123.93
120.01
117.76
110.50
77.16 CDCl3
13C
100 MHz
CDCl3
O
O
2
f1 (ppm)

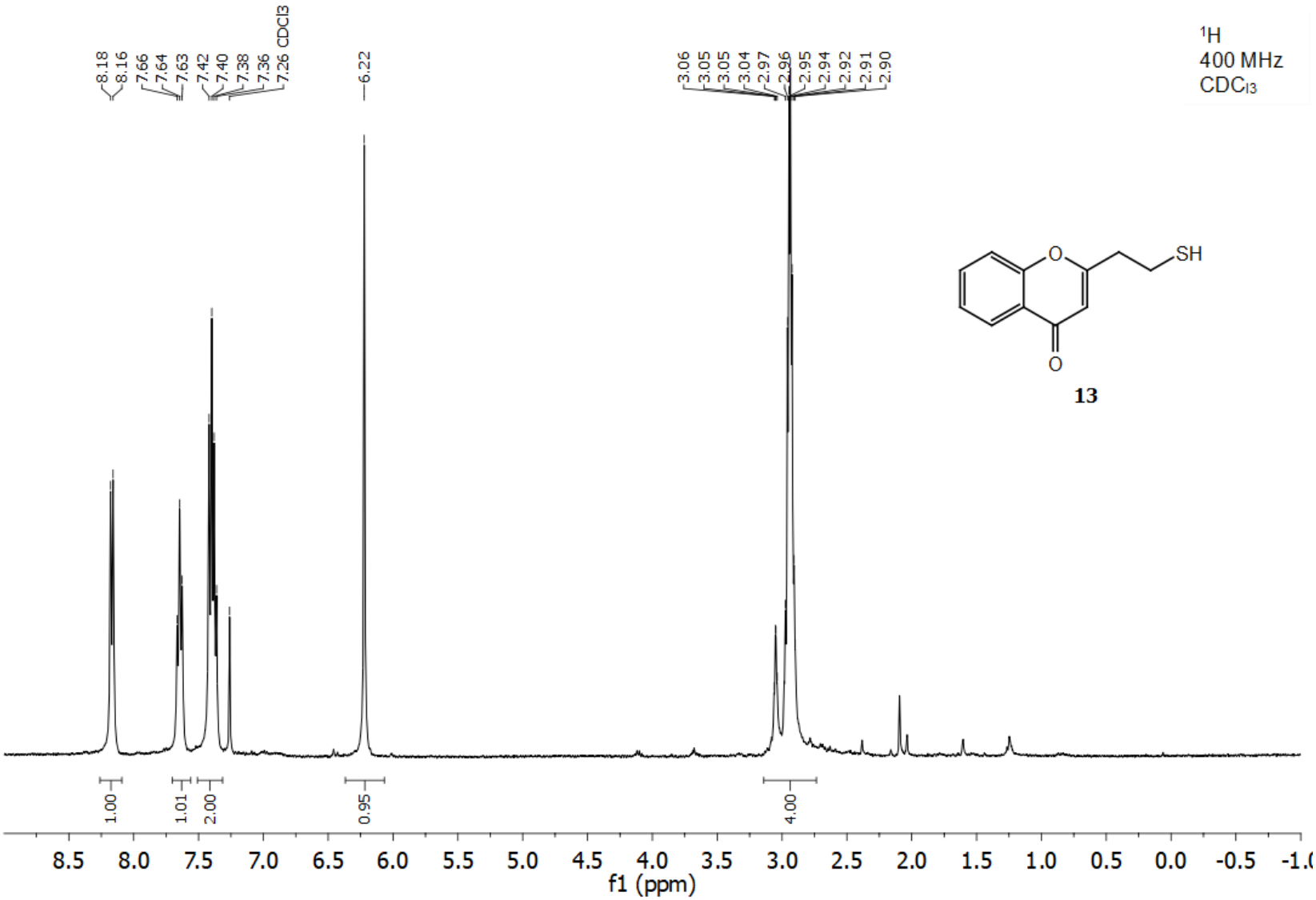

^{1}H
400 MHz
$CDCl_3$
8.14
8.12
7.58
7.38
7.36
7.32
7.30
CDCl3
7.26
7.24
7.22
7.18
7.17
7.15
6.09
3.01
2.99
2.97
2.88
2.86
2.84
O
O
3
7.60
7.58
7.56
7.38
7.36
7.32
7.30
7.28
7.24
7.22
7.18
7.17
7.15
1.00
1.00
1.14
1.99
3.00
7.6
7.5
7.4
7.3
7.2
7.1
f1 (ppm)
1.00
1.00
1.14
1.99
3.00
1.00
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


^{13}C
100 MHz
CDC_{l3}
100 Mhz
$CDCl_3$
178.07
168.31
156.26
139.57
133.41
128.50
128.15
126.41
125.45
124.84
123.52
117.73
110.03
77.16 CDCl3
35.88
32.74
O
O
3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

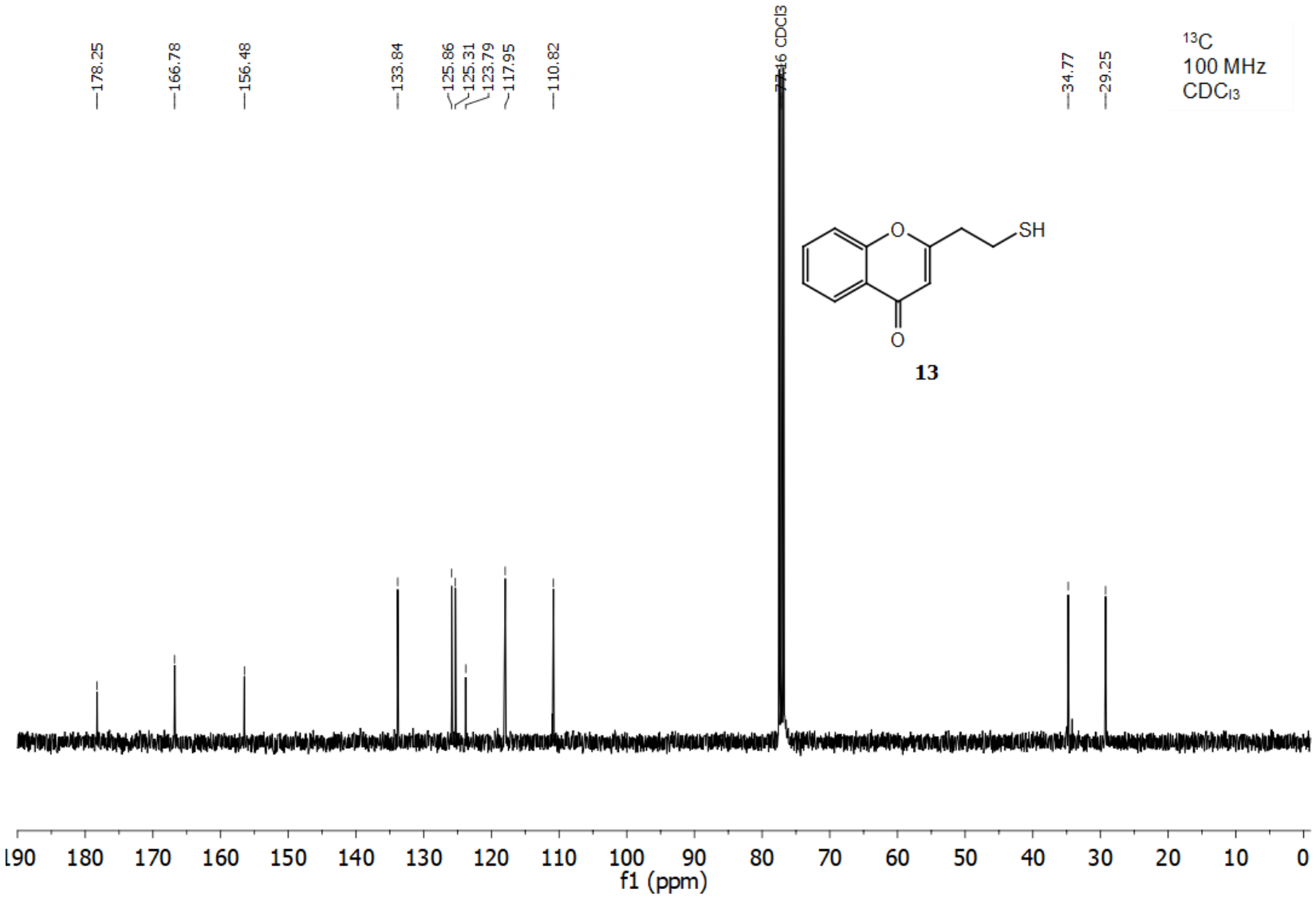

178.16
163.08
155.99
133.62
131.46
128.87
126.06
125.44
125.05
123.74
117.95
107.30
77.16 CDCl3
13C
100 MHz
CDCl3
O
O
4
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

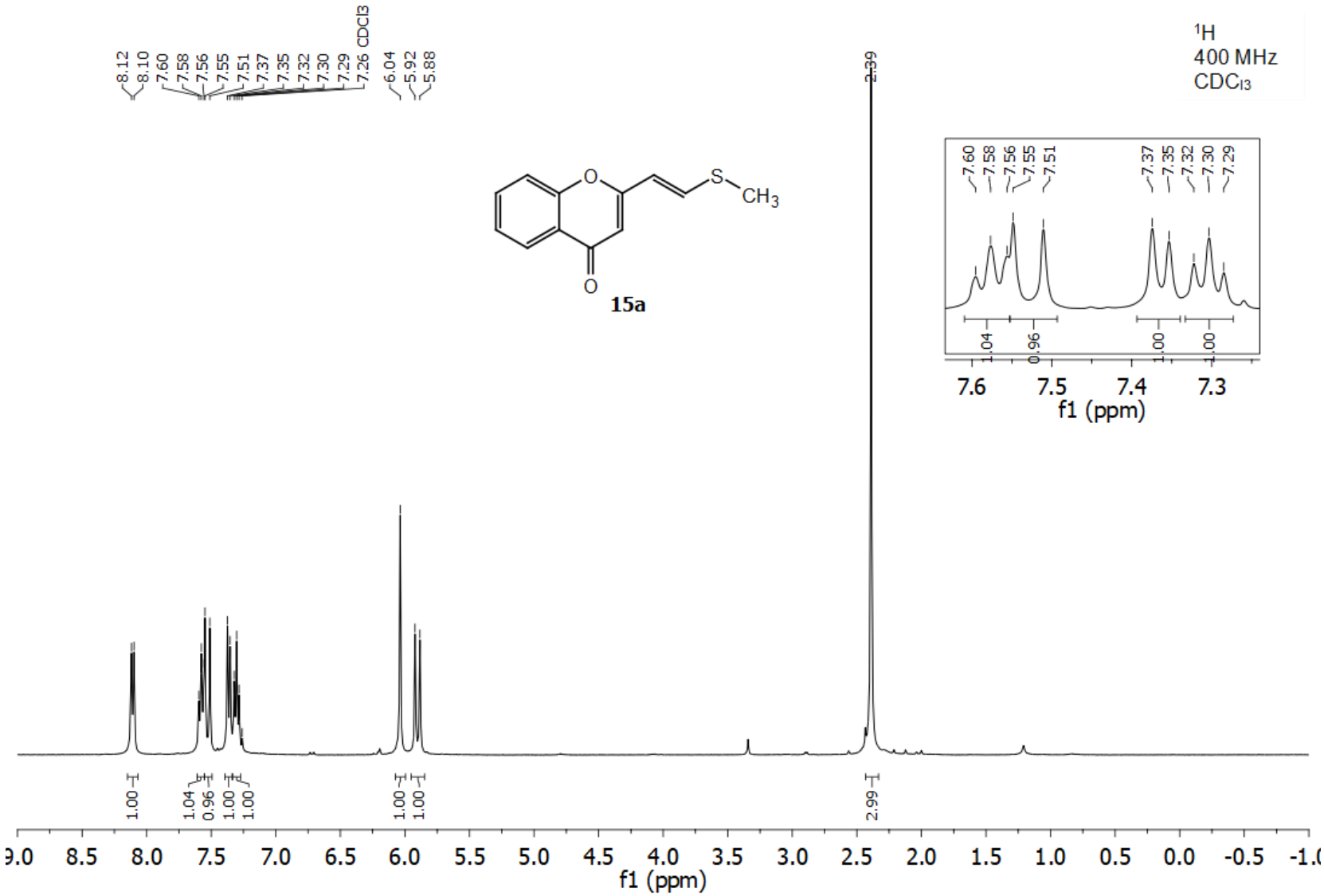

7.68
7.67
7.66
7.65
7.40
7.39
7.38
7.38
7.36
7.36
7.26 CDCl3
7.18
7.18
7.16
7.16
7.14
7.14
6.99
6.98
6.97
6.96
3.11
3.09
3.08
2.83
2.81
2.79
2.37
2.19
1H
400 MHz
CDCl3
O
S
CH3
O
O
CH3
O
10
1.00
1.00
1.00
1.00
2.00
2.00
3.01
3.01
f1 (ppm)

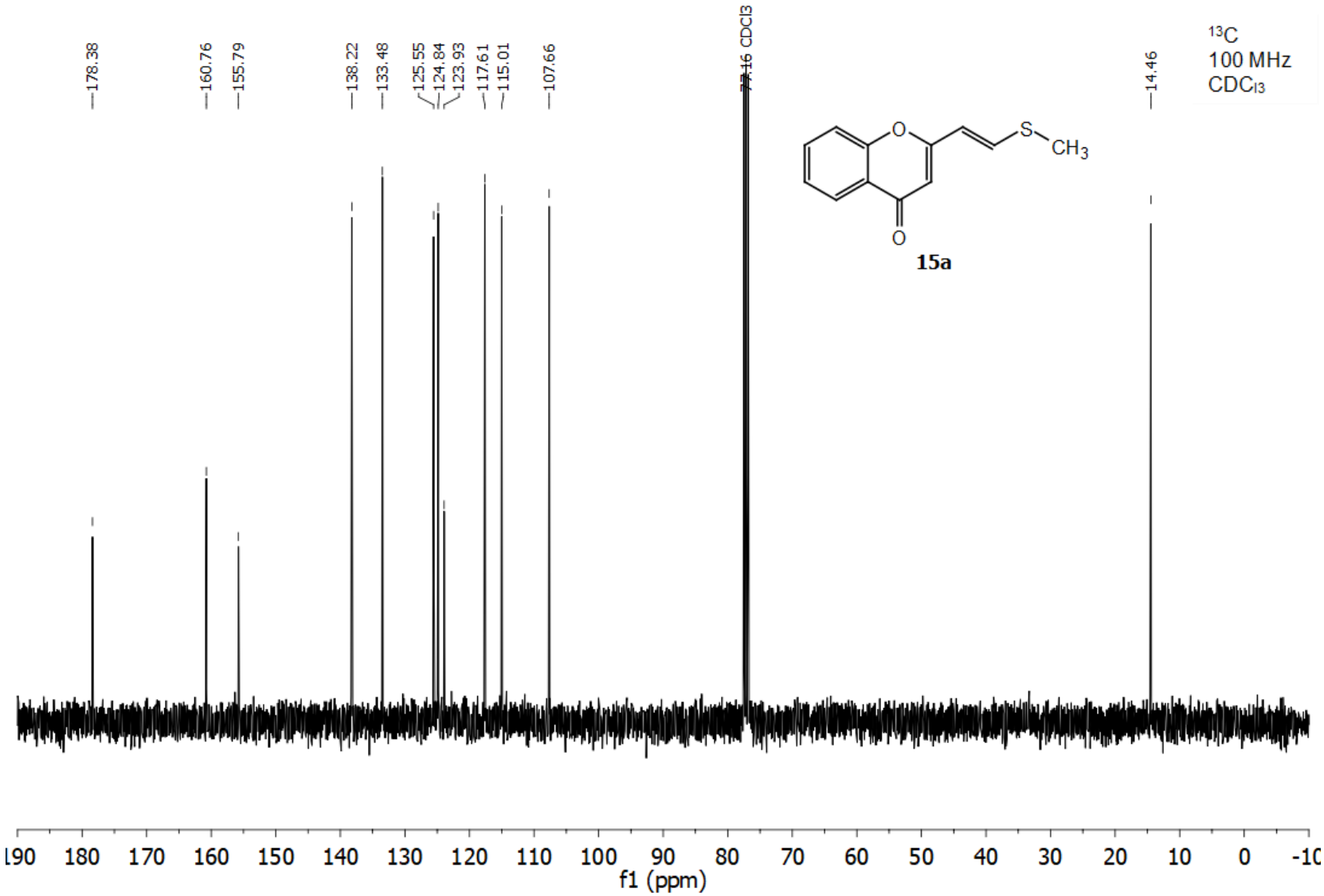

196.90
194.84
169.86
148.47
133.17
130.11
129.99
125.84
123.47
77.16 Chloroform-d
34.12
30.13
28.87
23.55
13C
100 MHz
CDCl3
O
S
CH3
O
O
CH3
O
10
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

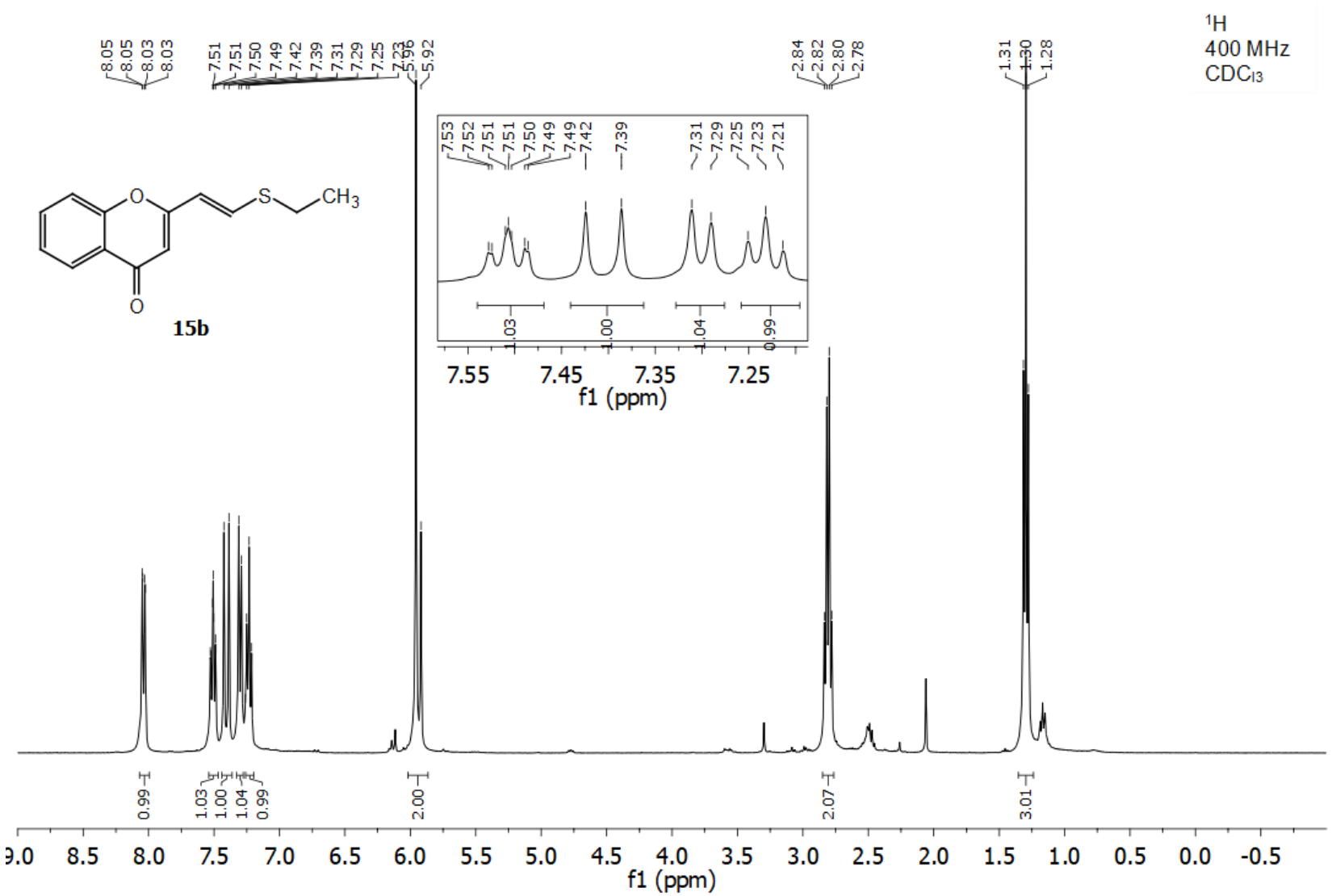

8.18
8.16
7.66
7.64
7.63
7.42
7.40
7.38
7.36
7.26 CDCl3
6.22
3.06
3.05
3.05
3.04
2.97
2.96
2.95
2.94
2.92
2.91
2.90
1H
400 MHz
CDCl3
O
SH
O
1.00
1.01
2.00
0.95
4.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

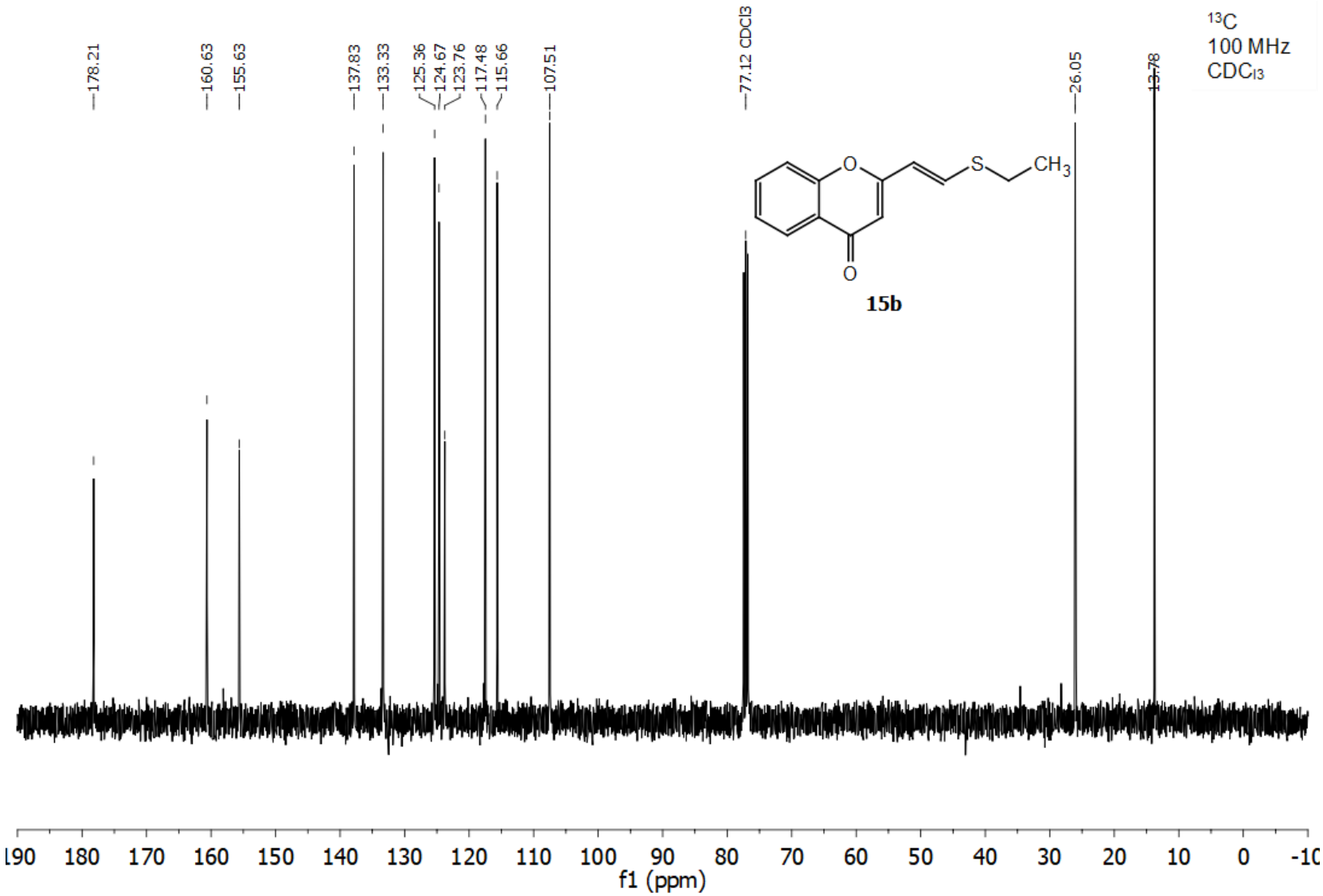
13

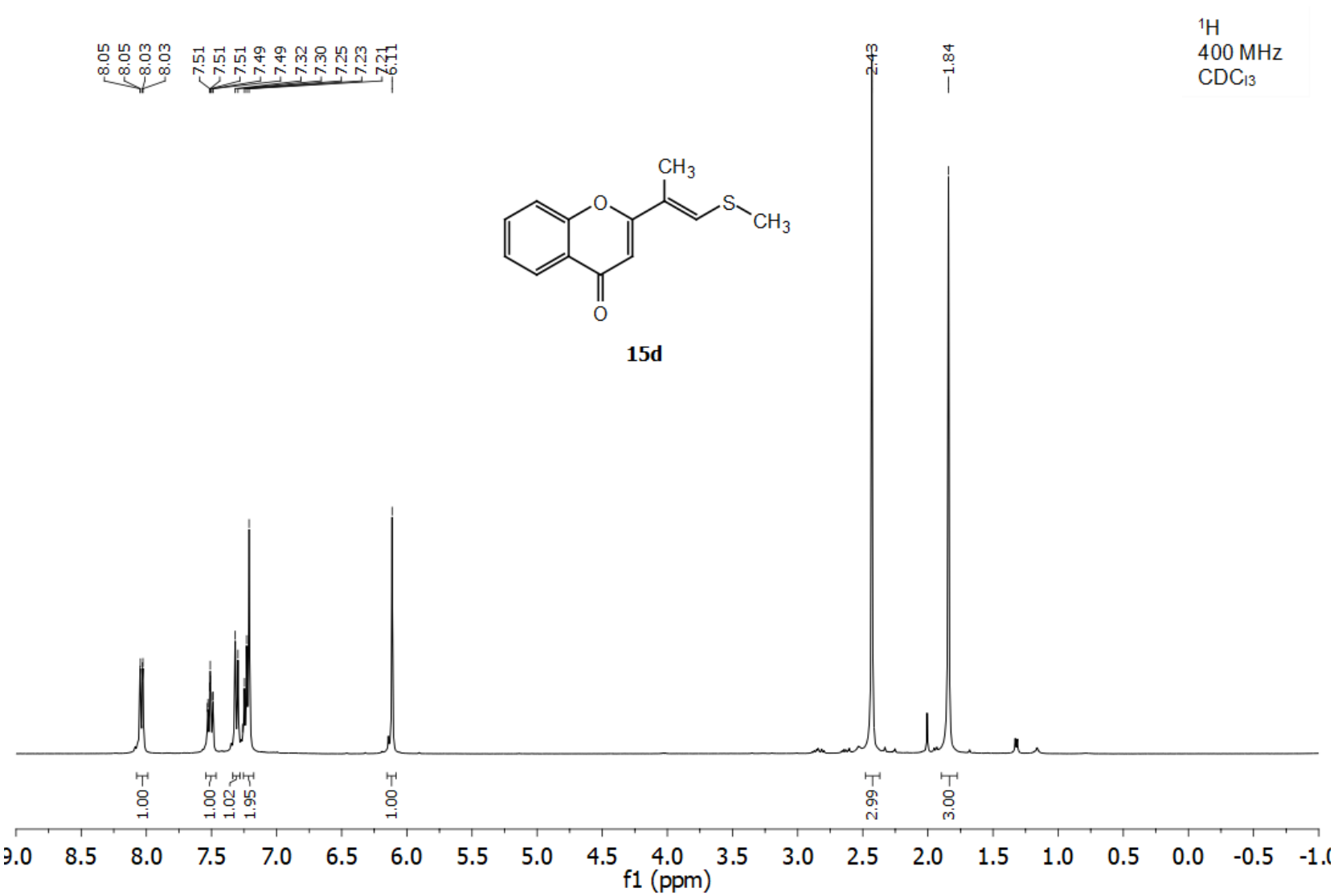

178.25
166.78
156.48
133.84
125.86
125.31
123.79
117.95
110.82
77.16 CDCl3
34.77
29.25
13C
100 MHz
CDCl3
O
SH
O
13
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

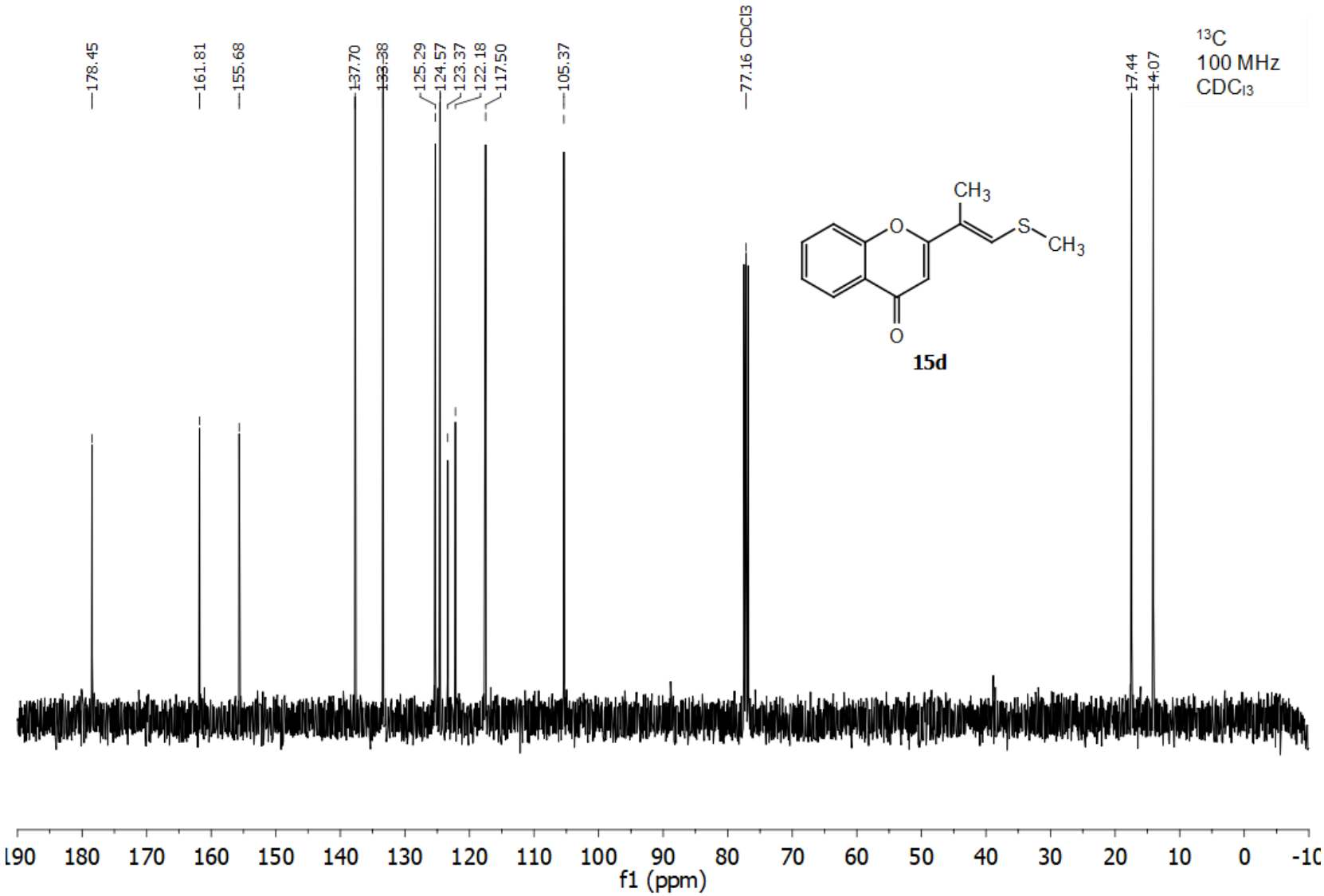

8.12
8.10
7.60
7.58
7.56
7.55
7.51
7.37
7.35
7.32
7.30
7.29
7.26 CDCl3
6.04
5.92
5.88
2.39
1H
400 MHz
CDCl3
O
S
CH3
O
15a
1.00
1.04
0.96
1.00
1.00
1.00
1.00
2.99
f1 (ppm)

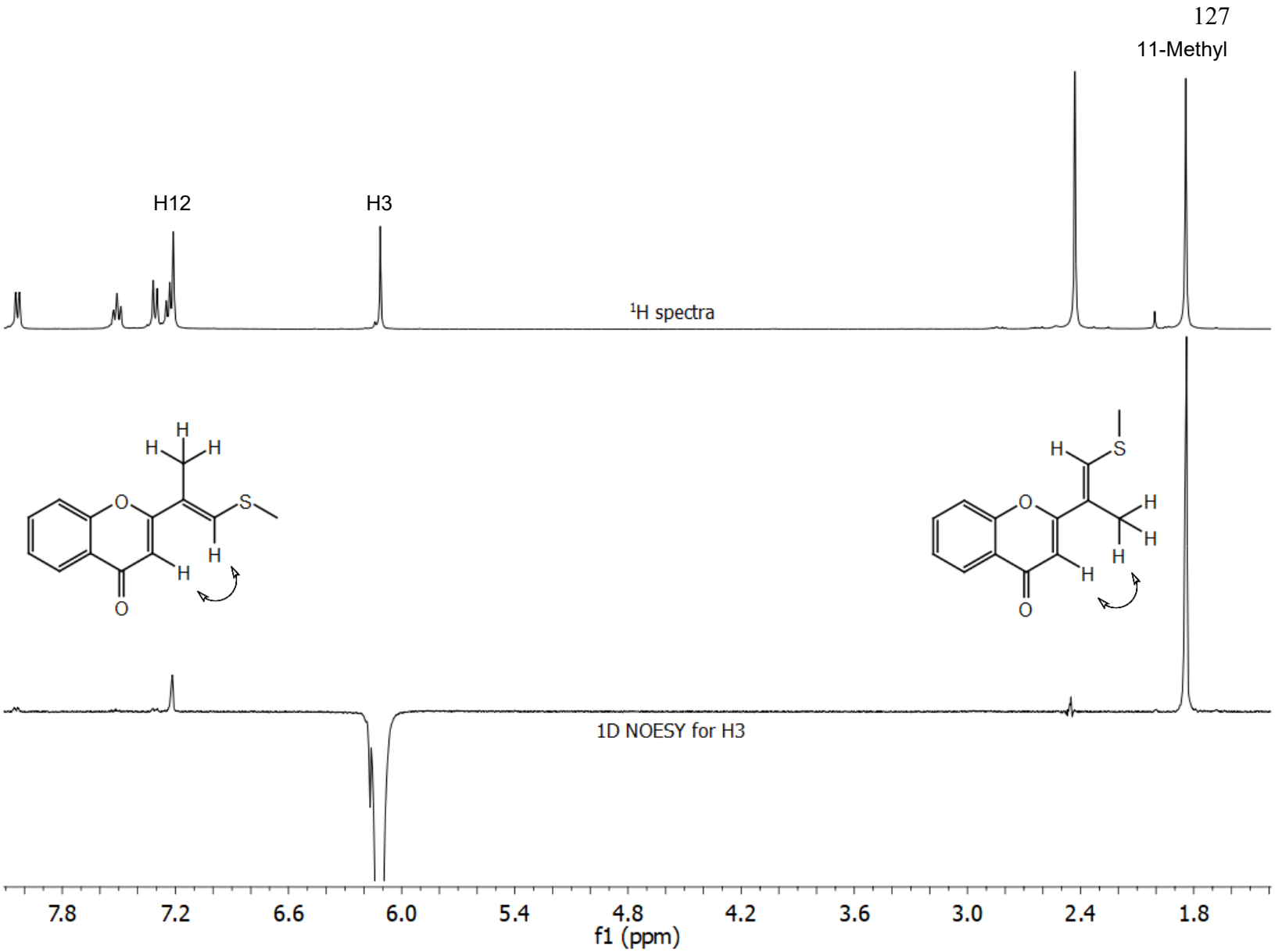

178.38
160.76
155.79
138.22
133.48
125.55
124.84
123.93
117.61
115.01
107.66
77.16 CDCl3
14.46
13C
100 MHz
CDCl3
O
S
CH3
O
15a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

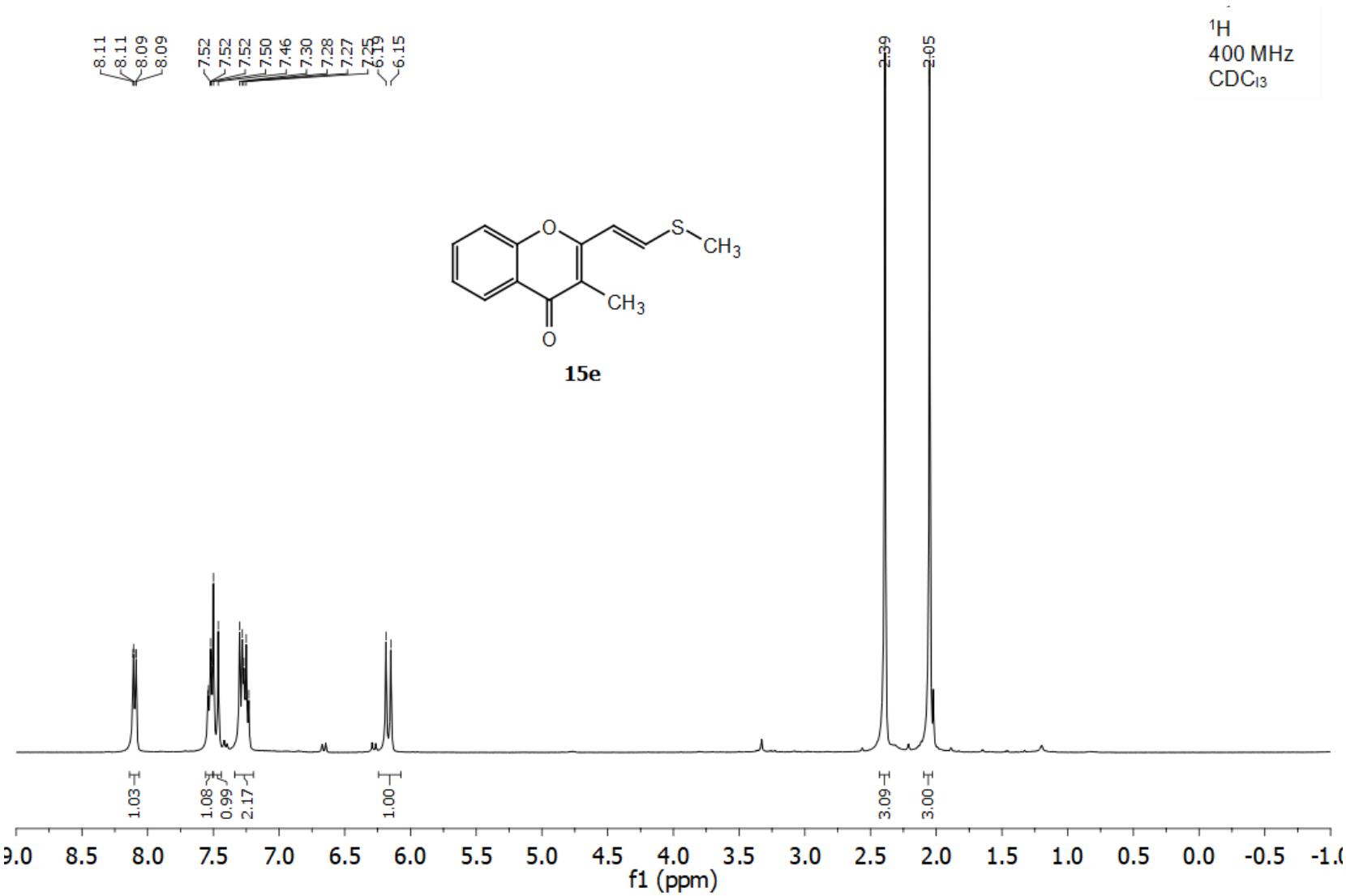

1H
400 MHz
CDCl3
15b
f1 (ppm)

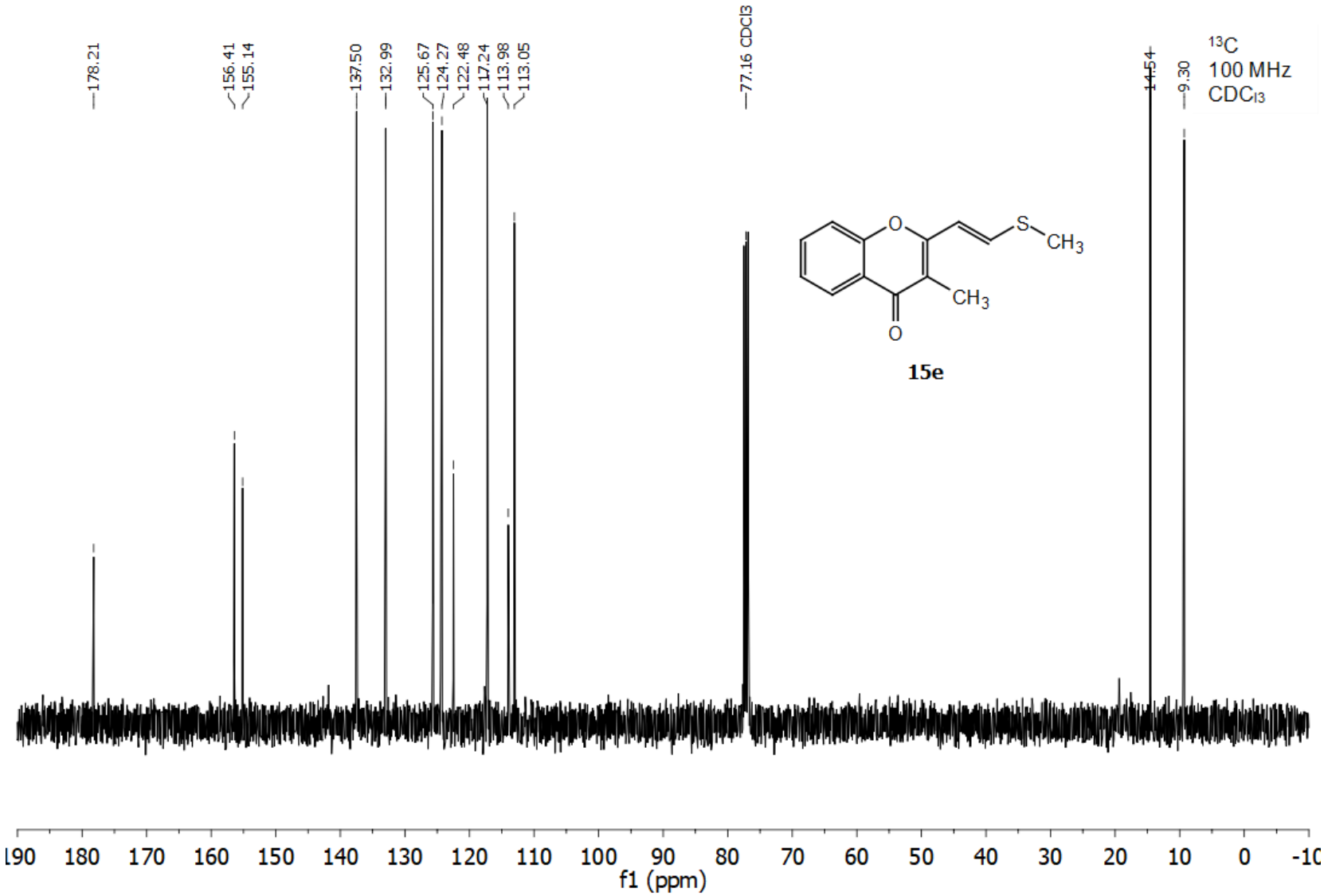

178.21
160.63
155.63
137.83
133.33
125.36
124.67
123.76
117.48
115.66
107.51
77.12 CDCl3
26.05
13.78
13C
100 MHz
CDCl3
O
S
CH3
O
15b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

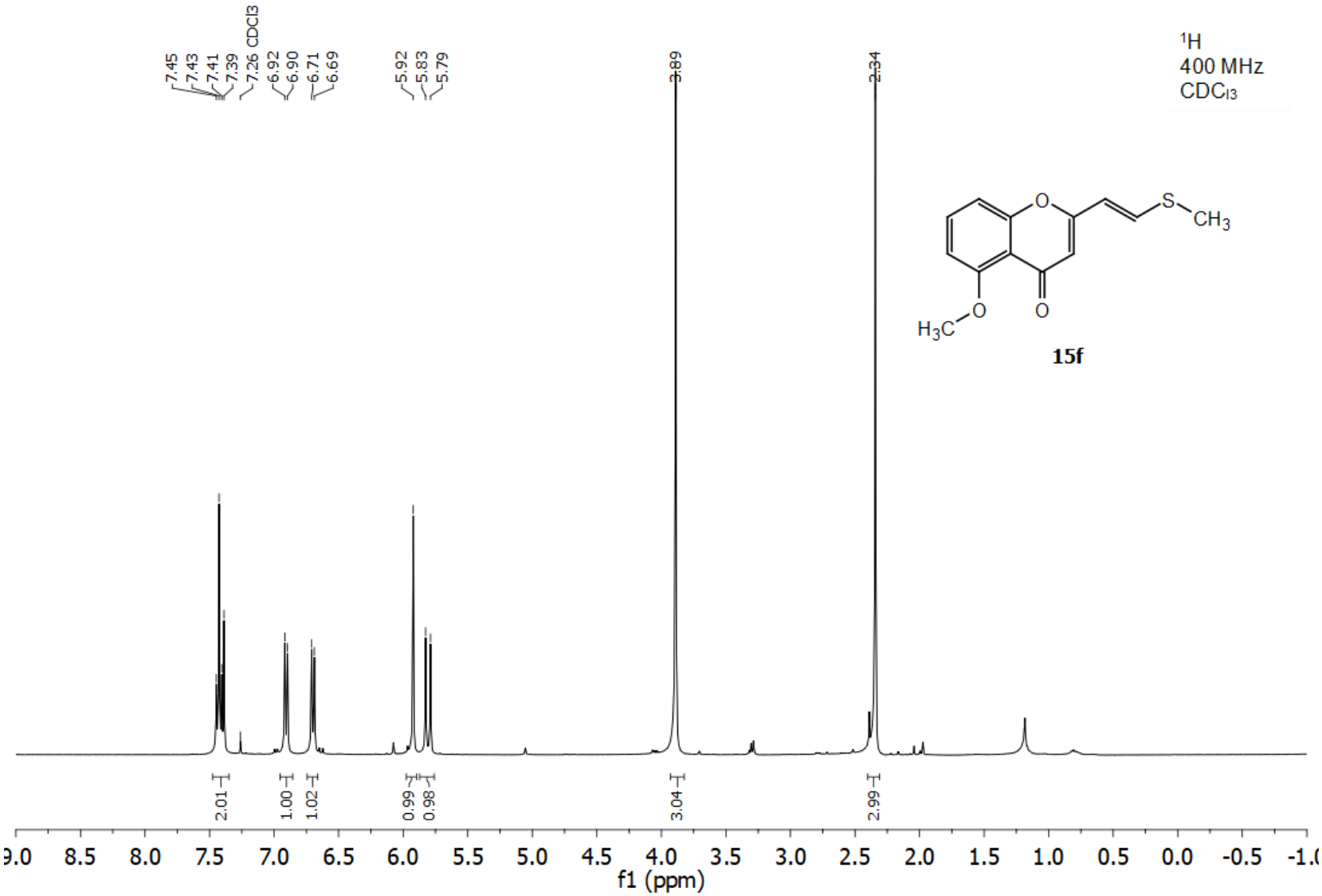

8.05
8.05
8.03
8.03
7.51
7.51
7.51
7.49
7.49
7.32
7.30
7.25
7.23
7.21
6.11
2.43
1.84
1H
400 MHz
CDCl3
CH3
O
S
CH3
O
15d
1.00
1.00
1.02
1.95
1.00
2.99
3.00
f1 (ppm)


178.45
161.81
155.68
137.70
133.38
125.29
124.57
123.37
122.18
117.50
105.37
77.16 CDCl3
17.44
14.07
13C
100 MHz
CDCl3
CH3
O
S
CH3
O
15d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

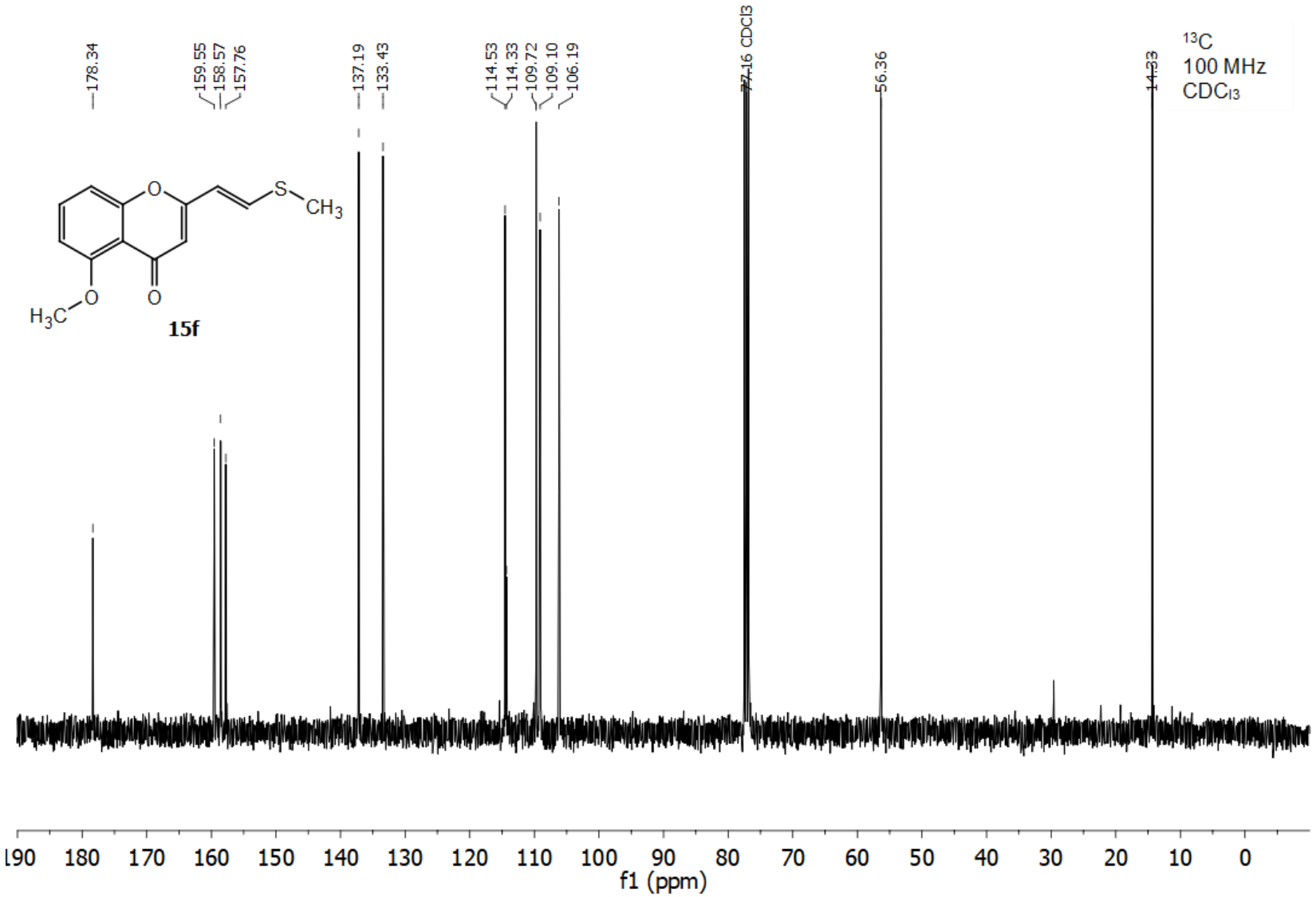

11-Methyl
H12
H3
¹H spectra
1D NOESY for H3
7.8
7.2
6.6
6.0
5.4
4.8
4.2
3.6
3.0
2.4
1.8
f1 (ppm)

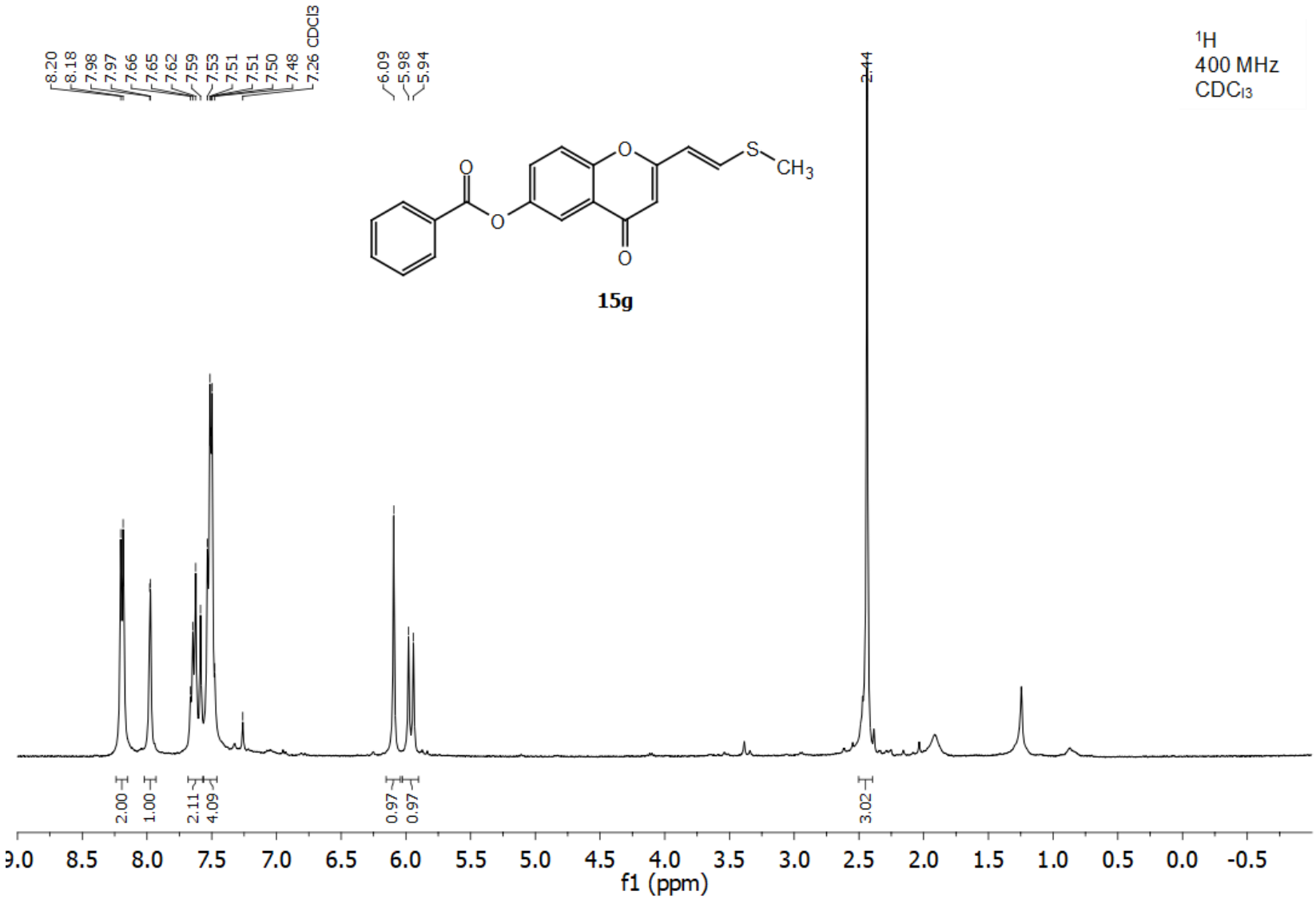

8.11
8.11
8.09
8.09
7.52
7.52
7.52
7.50
7.46
7.30
7.28
7.27
7.25
6.19
6.15
2.39
2.05
1H
400 MHz
CDCl3
O
S
CH3
CH3
O
15e
1.03
1.08
0.99
2.17
1.00
3.09
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

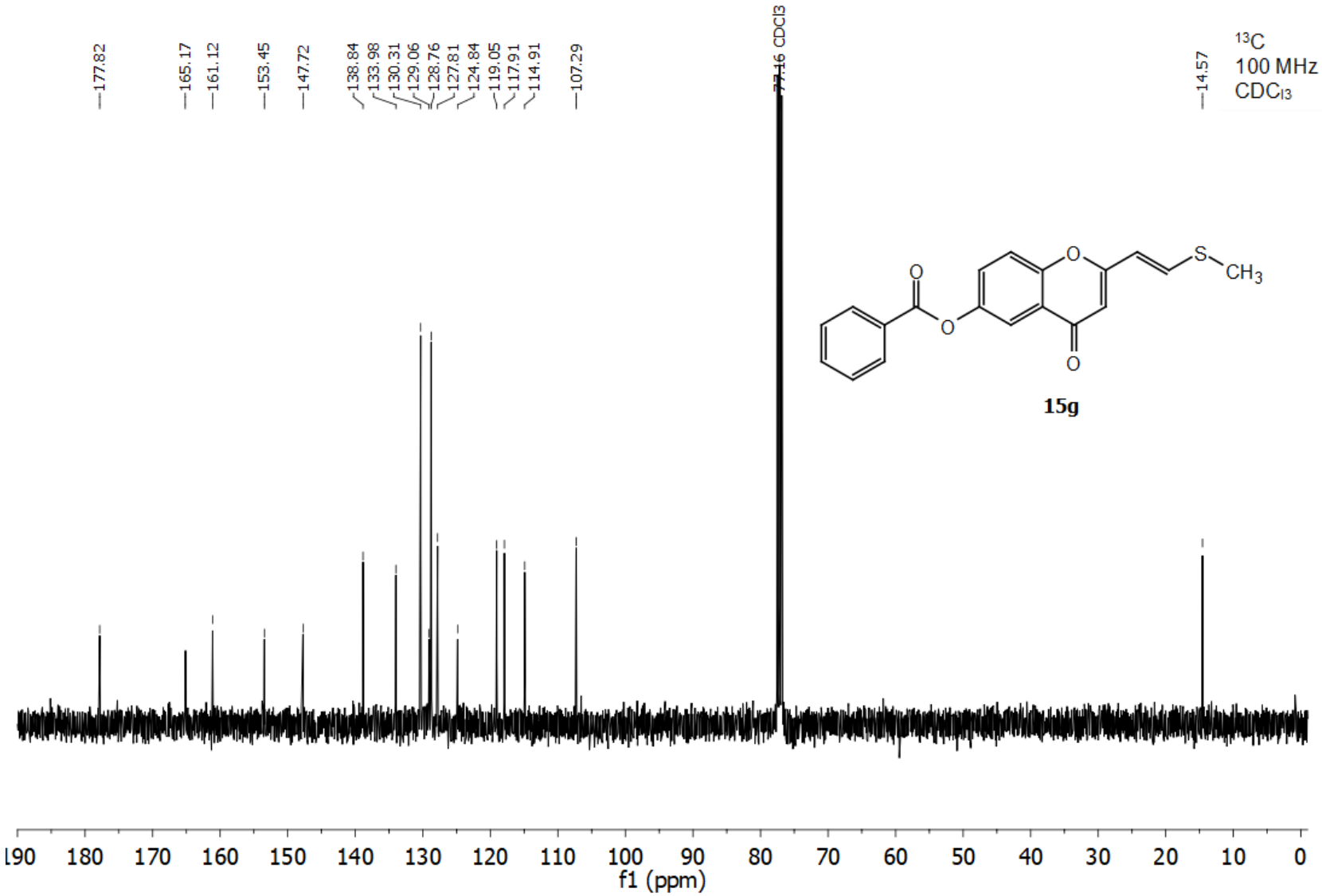

178.21
156.41
155.14
137.50
132.99
125.67
124.27
122.48
117.24
113.98
113.05
77.16 CDCl3
14.54
9.30
13C
100 MHz
CDCl3
O
S
CH3
CH3
O
15e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

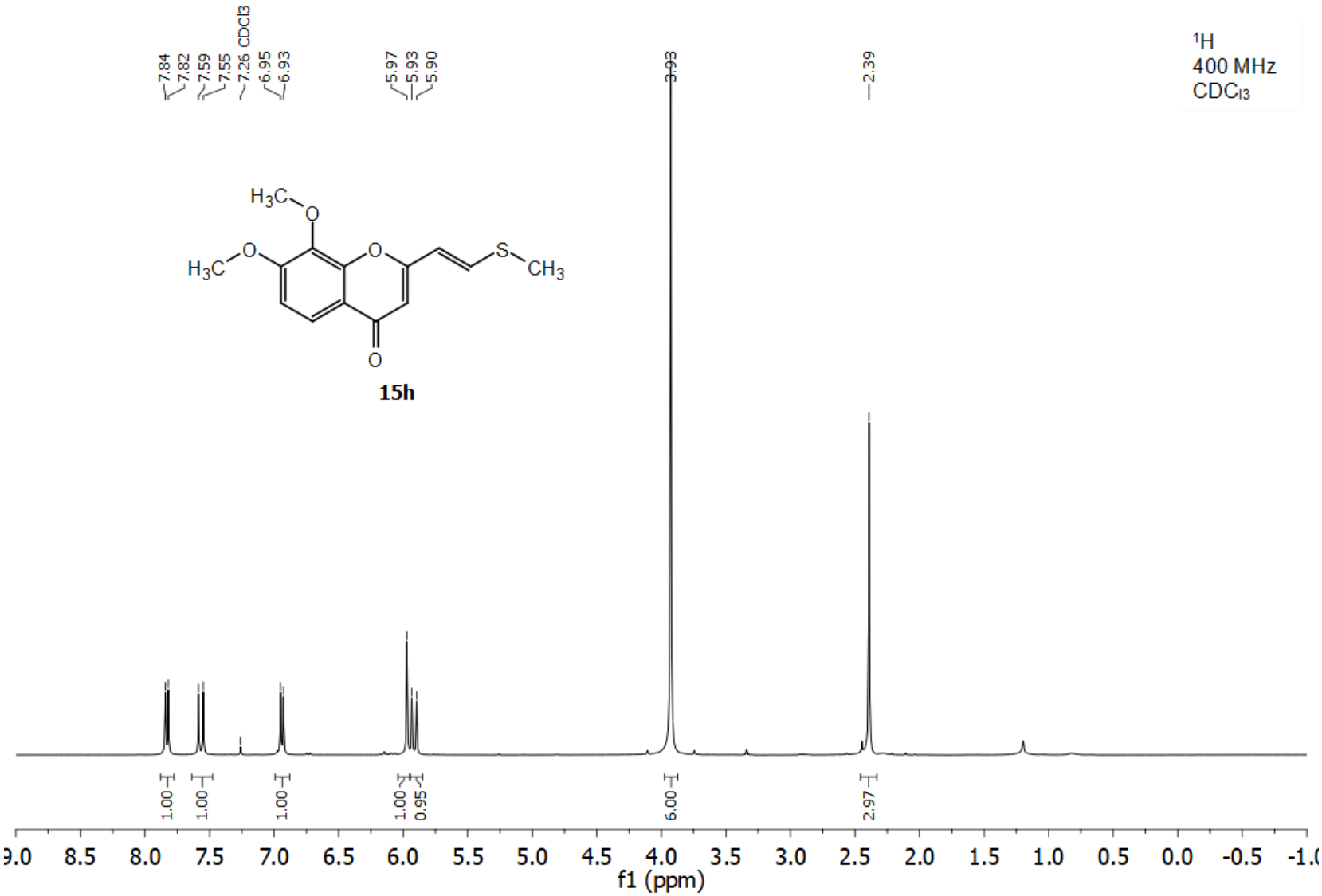

7.45
7.43
7.41
7.39
7.26 CDCl3
6.92
6.90
6.71
6.69
5.92
5.83
5.79
3.89
2.34
1H
400 MHz
CDCl3
O
S
CH3
H3C
O
O
2.01
1.00
1.02
0.99
0.98
3.04
2.99
f1 (ppm)

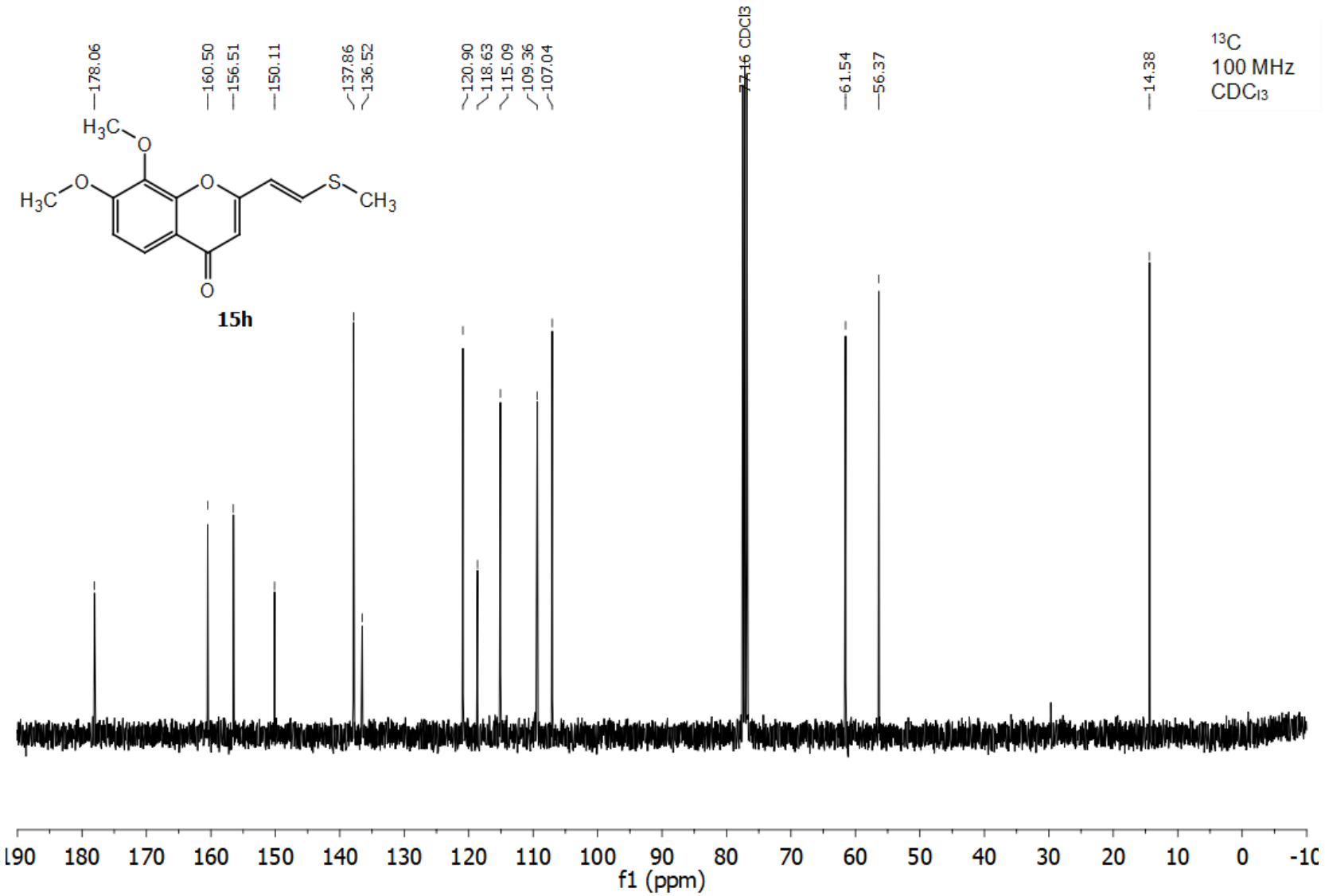
15f

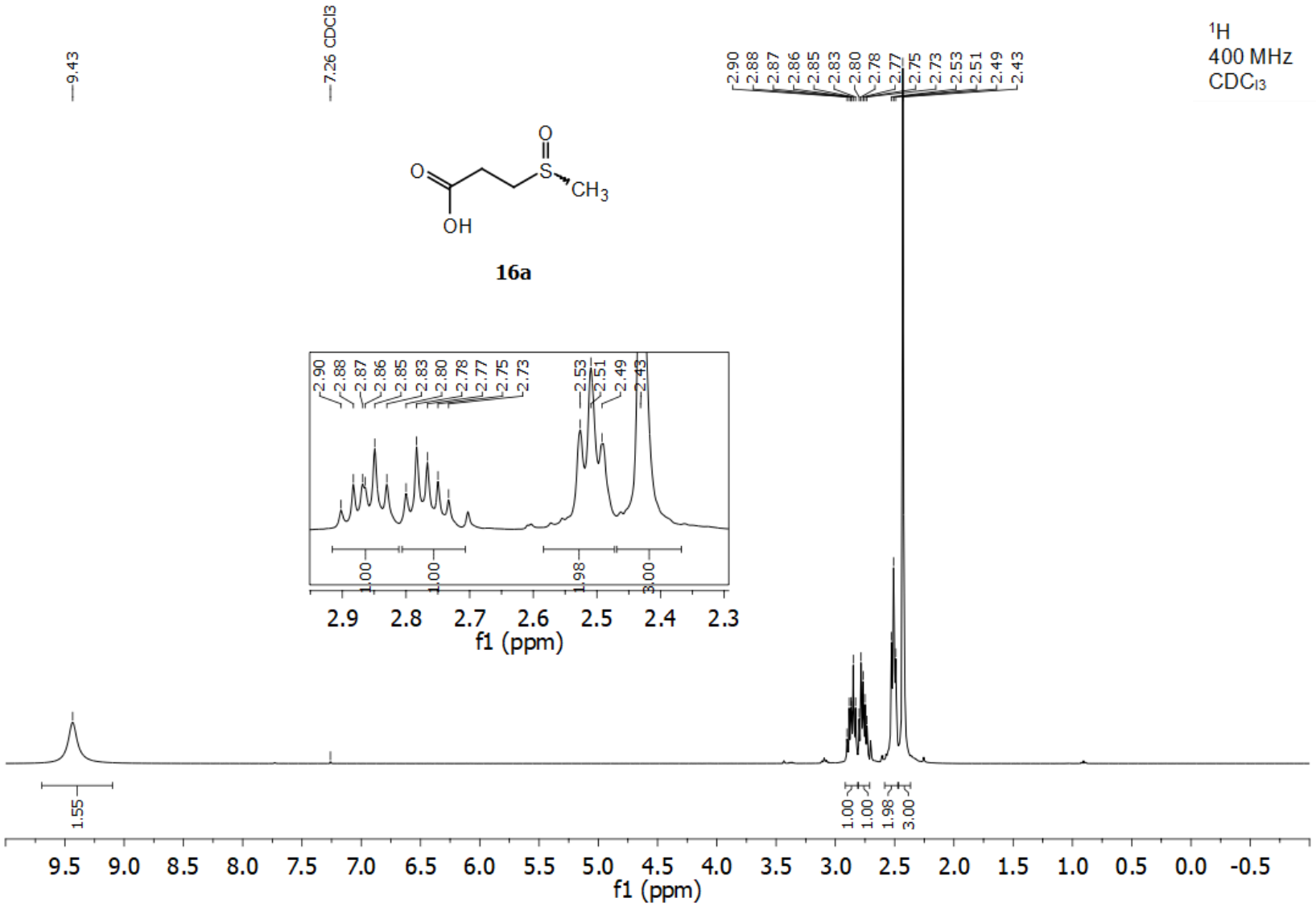

178.34
159.55
158.57
157.76
137.19
133.43
114.53
114.33
109.72
109.10
106.19
77.16 CDCl3
56.36
14.33
13C
100 MHz
CDCl3
O
S
CH3
O
O
H3C
15f
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

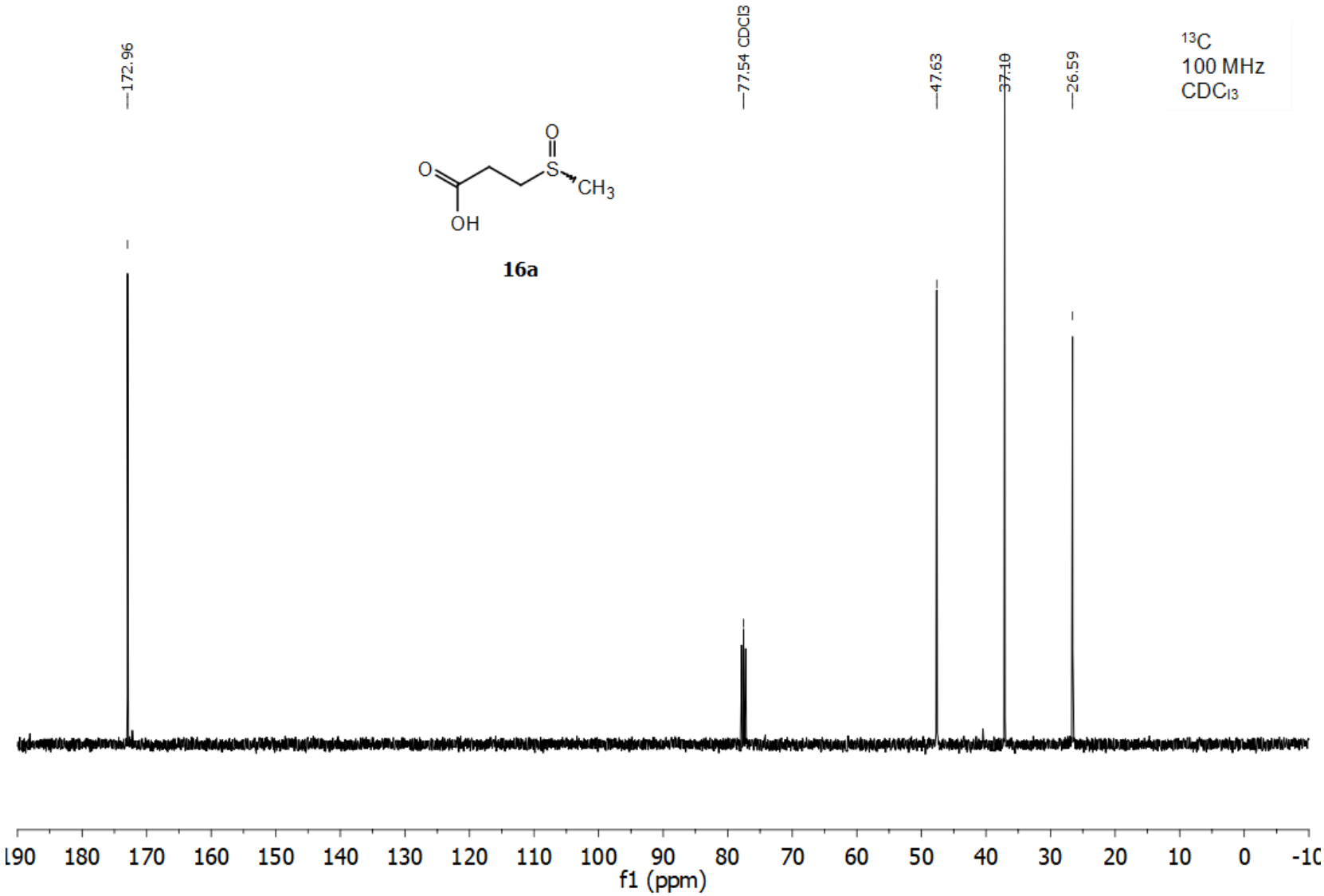

8.20
8.18
7.98
7.97
7.66
7.65
7.62
7.59
7.53
7.51
7.51
7.50
7.48
7.26 CDCl3
6.09
5.98
5.94
2.44
1H
400 MHz
CDCl3
O
O
O
S
CH3
O
15g
2.00
1.00
2.11
4.09
0.97
0.97
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


177.82
165.17
161.12
153.45
147.72
138.84
133.98
130.31
129.06
128.76
127.81
124.84
119.05
117.91
114.91
107.29
77.16 CDCl3
14.57
13C
100 MHz
CDCl3
O
O
O
O
S
CH3
15g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.84
7.82
7.59
7.55
7.26 CDCl3
6.95
6.93
5.97
5.93
5.90
3.93
2.39
1H
400 MHz
CDCl3
H3C
O
H3C
O
O
S
CH3
O
15h
1.00
1.00
1.00
1.00
0.95
6.00
2.97
f1 (ppm)


178.06
160.50
156.51
150.11
137.86
136.52
120.90
118.63
115.09
109.36
107.04
77.16 CDCl3
61.54
56.37
14.38
13C
100 MHz
CDCl3
H3C
O
O
O
S
CH3
O
15h
f1 (ppm)


9.43
7.26 CDCl3
2.90
2.88
2.87
2.86
2.85
2.83
2.80
2.78
2.77
2.75
2.73
2.53
2.51
2.49
2.43
1H
400 MHz
CDCl3
O
O
S
CH3
OH
16a
1.00
1.00
1.98
3.00
2.9 2.8 2.7 2.6 2.5 2.4 2.3
f1 (ppm)
1.55
1.00
1.00
1.98
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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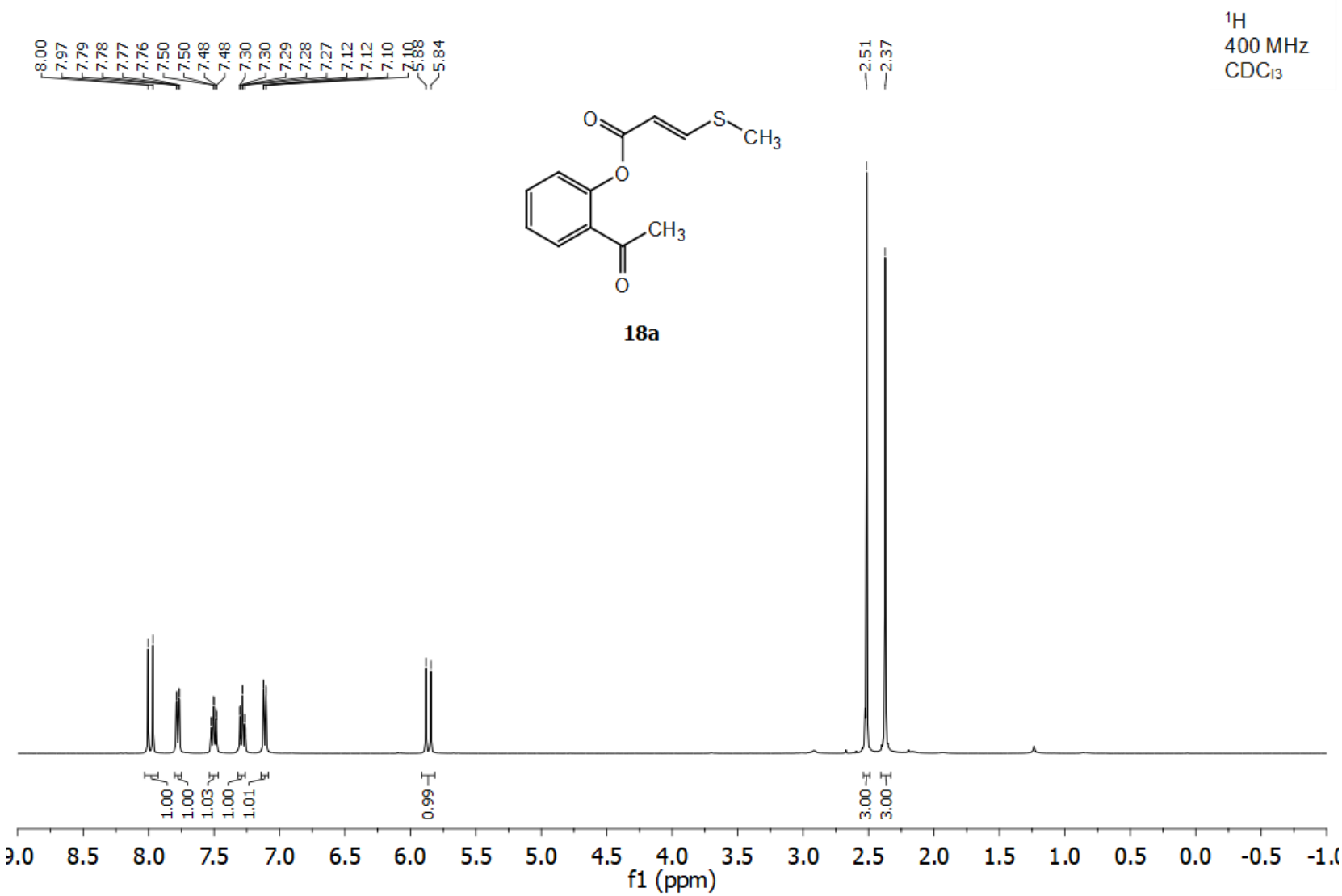
77.54 CDCl3
47.63
37.10
26.59
13C
100 MHz
CDCl3
O
O
S
CH3
OH
16a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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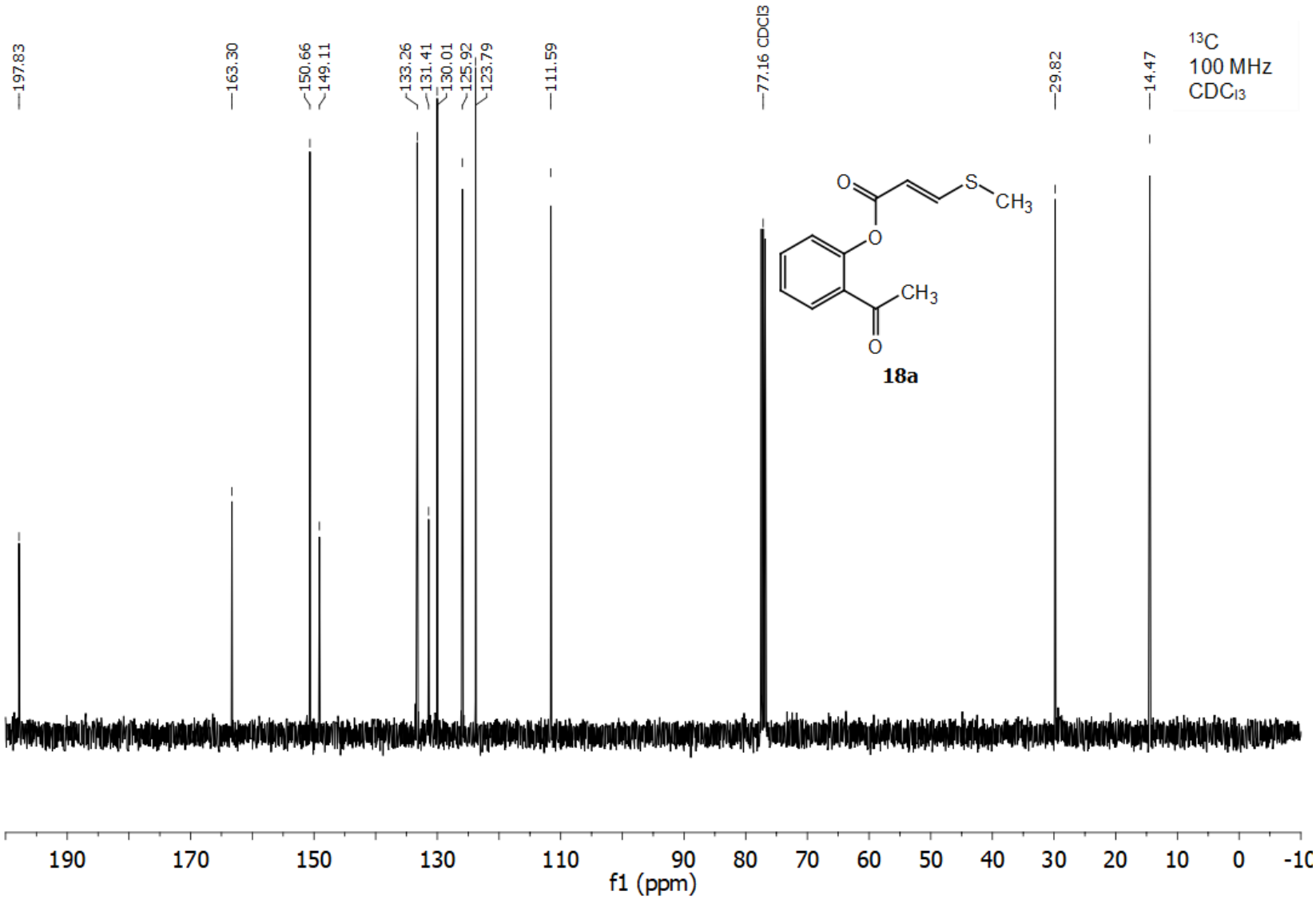
7.97
7.79
7.78
7.77
7.76
7.50
7.50
7.48
7.48
7.30
7.30
7.29
7.28
7.27
7.12
7.12
7.10
5.88
5.84
2.51
2.37
1H
400 MHz
CDCl3
O
S
CH3
O
CH3
O
18a
1.00
1.00
1.03
1.00
1.01
0.99
3.00
3.00
f1 (ppm)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149.11
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131.41
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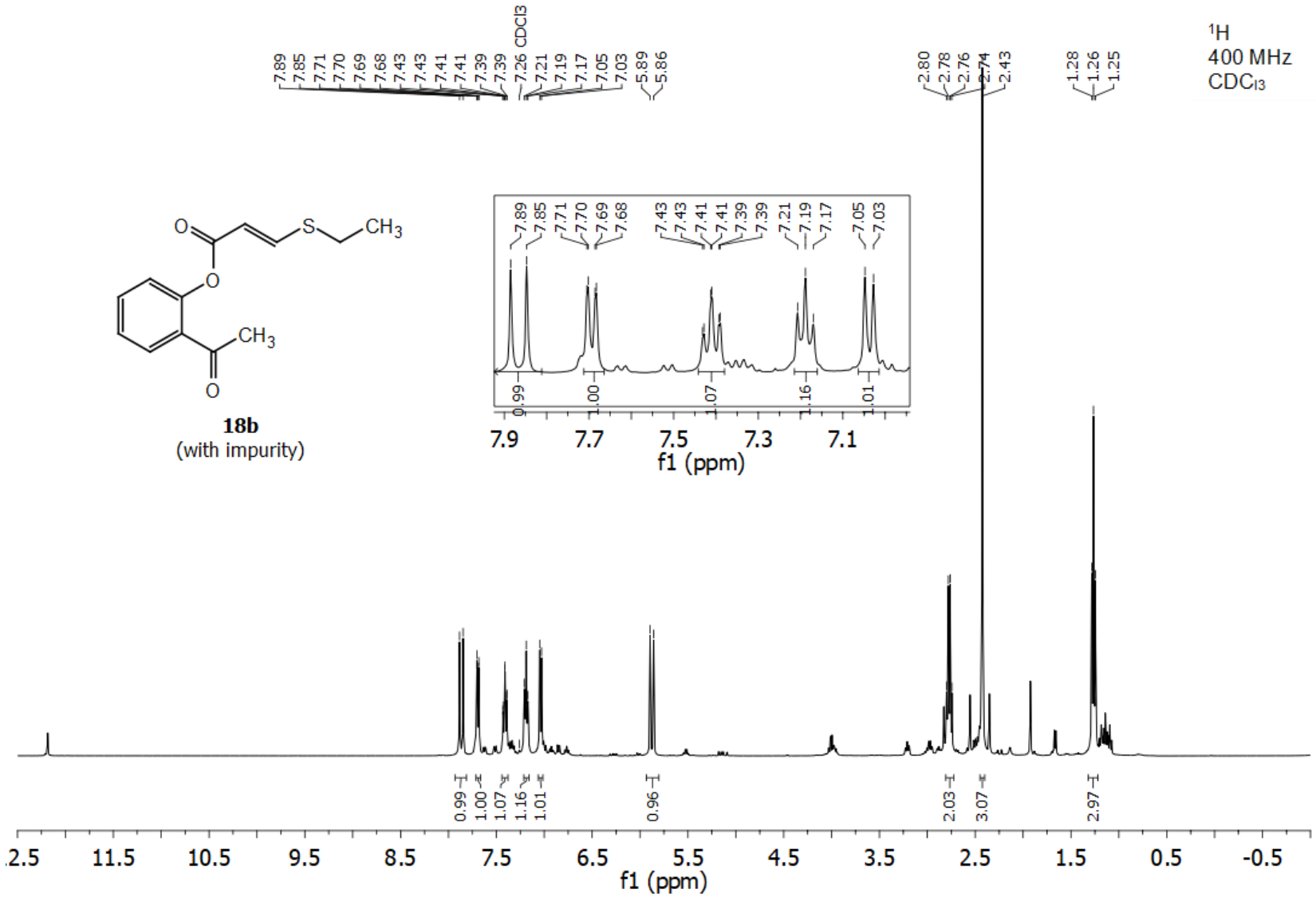
125.92
123.79
111.59
77.16 CDCl3
29.82
14.47
13C
100 MHz
CDCl3
O
S
CH3
O
CH3
O
18a
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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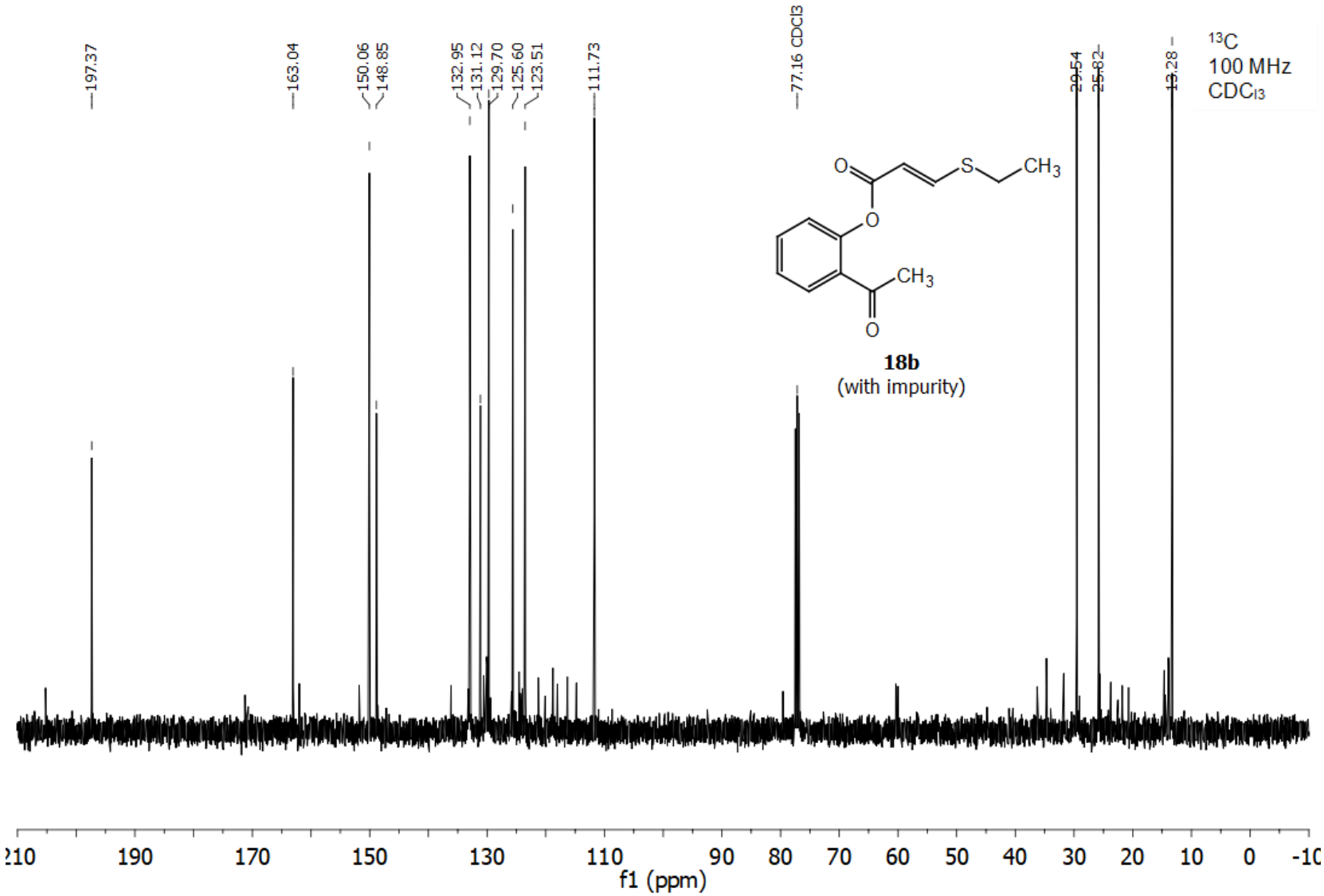
7.43
7.41
7.41
7.39
7.39
7.26 CDCl3
7.21
7.19
7.17
7.05
7.03
5.89
5.86
2.80
2.78
2.76
2.74
2.43
1.28
1.26
1.25
1H
400 MHz
CDCl3
O
O
S
CH3
O
CH3
O
18b
(with impurity)
0.99
1.00
1.07
1.16
1.01
7.9
7.7
7.5
7.3
7.1
f1 (ppm)
0.99
1.00
1.07
1.16
1.01
0.96
2.03
3.07
2.97
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)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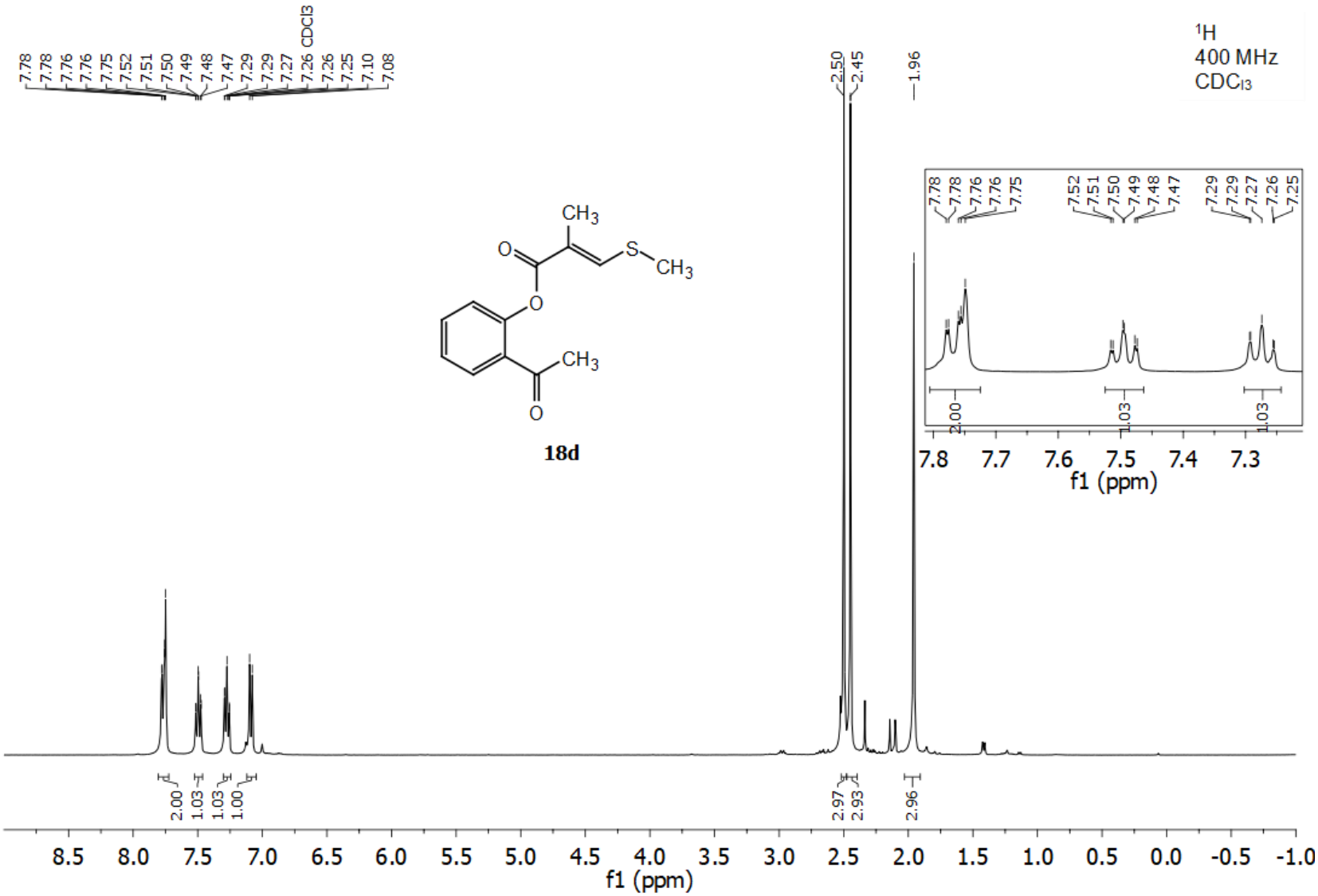
111.73
77.16 CDCl3
29.54
25.82
13.28
13C
100 MHz
CDCl3
O
S
CH3
O
CH3
O
18b
(with impurity)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.78
7.76
7.76
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7.50
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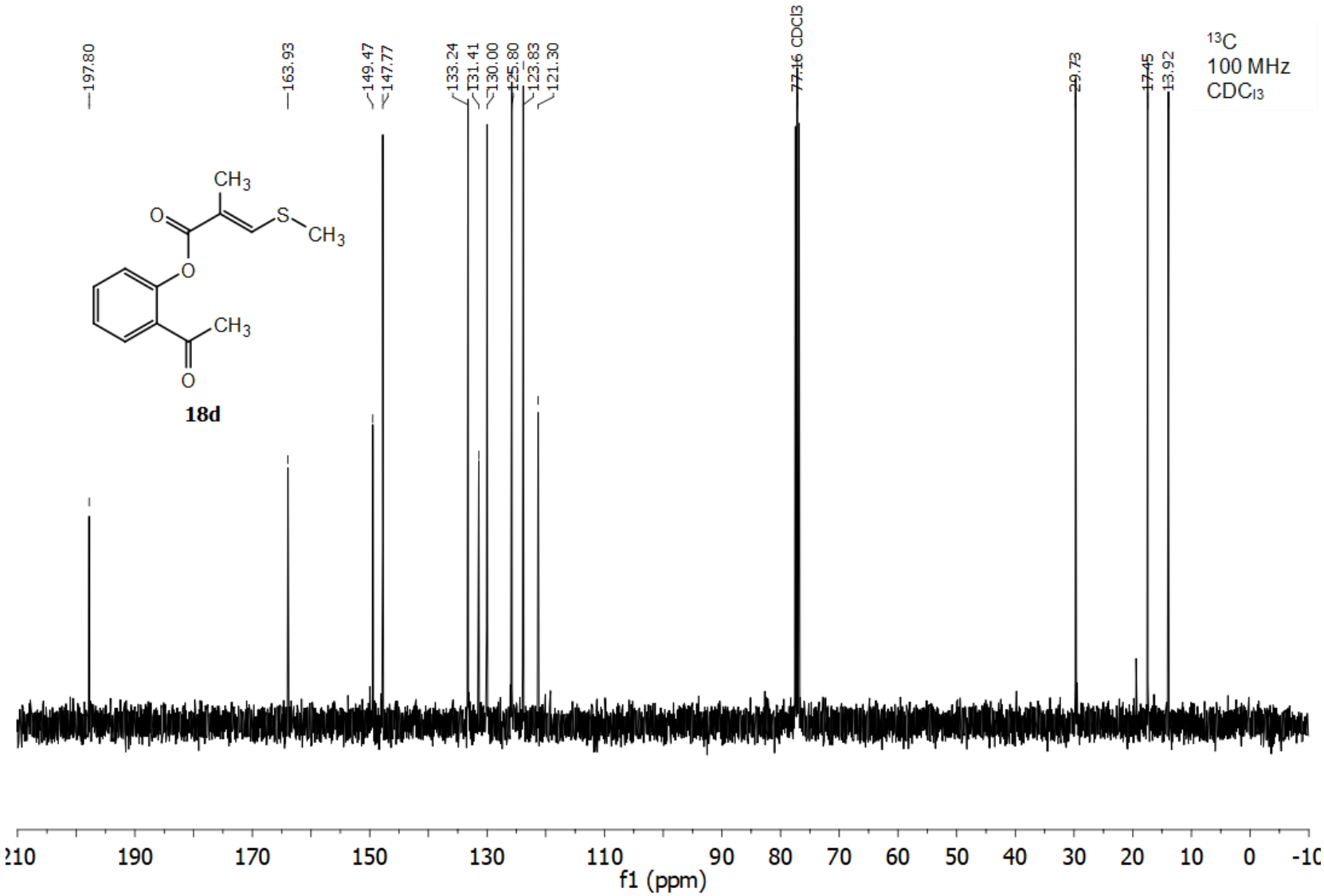
7.48
7.47
7.29
7.29
7.27
CDCl3
7.26
7.25
7.10
7.08
2.50
2.45
1.96
1H
400 MHz
CDCl3
CH3
O
S
CH3
O
CH3
O
18d
2.00
1.03
1.03
1.00
2.97
2.93
2.96
f1 (ppm)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149.47
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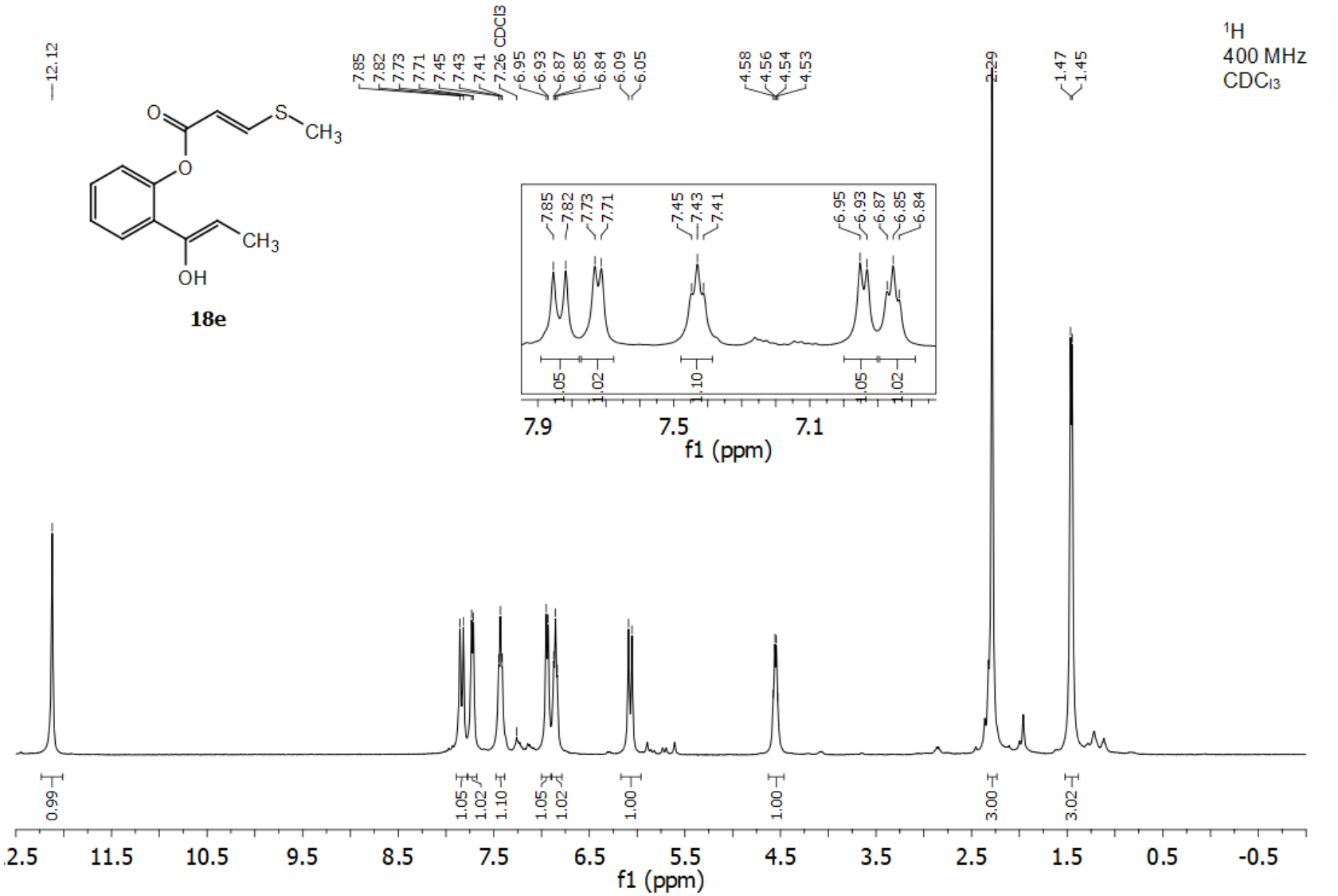
125.80
123.83
121.30
77.16 CDCl3
29.73
17.45
13.92
13C
100 MHz
CDCl3
CH3
O
S
CH3
O
CH3
O
18d
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.45
7.43
7.41
7.26 CDCl3
6.95
6.93
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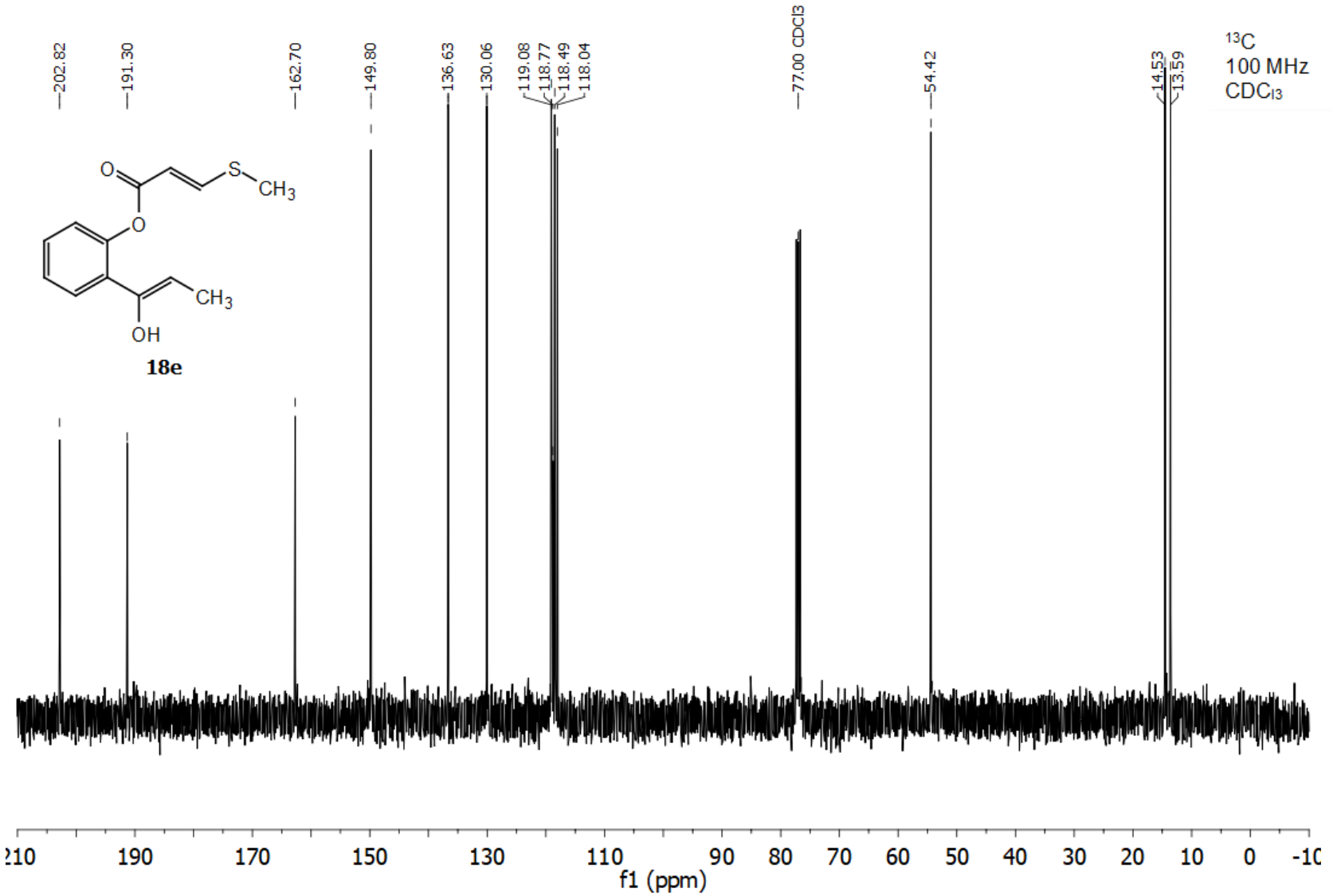
6.85
6.84
6.09
6.05
4.58
4.56
4.54
4.53
2.29
1.47
1.45
1H
400 MHz
CDCl3
O
O
S
CH3
CH3
OH
18e
0.99
1.05
1.02
1.10
1.05
1.02
1.00
1.00
3.00
3.02
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)
1.05
1.02
1.10
1.05
1.02
7.9
7.5
7.1
f1 (ppm)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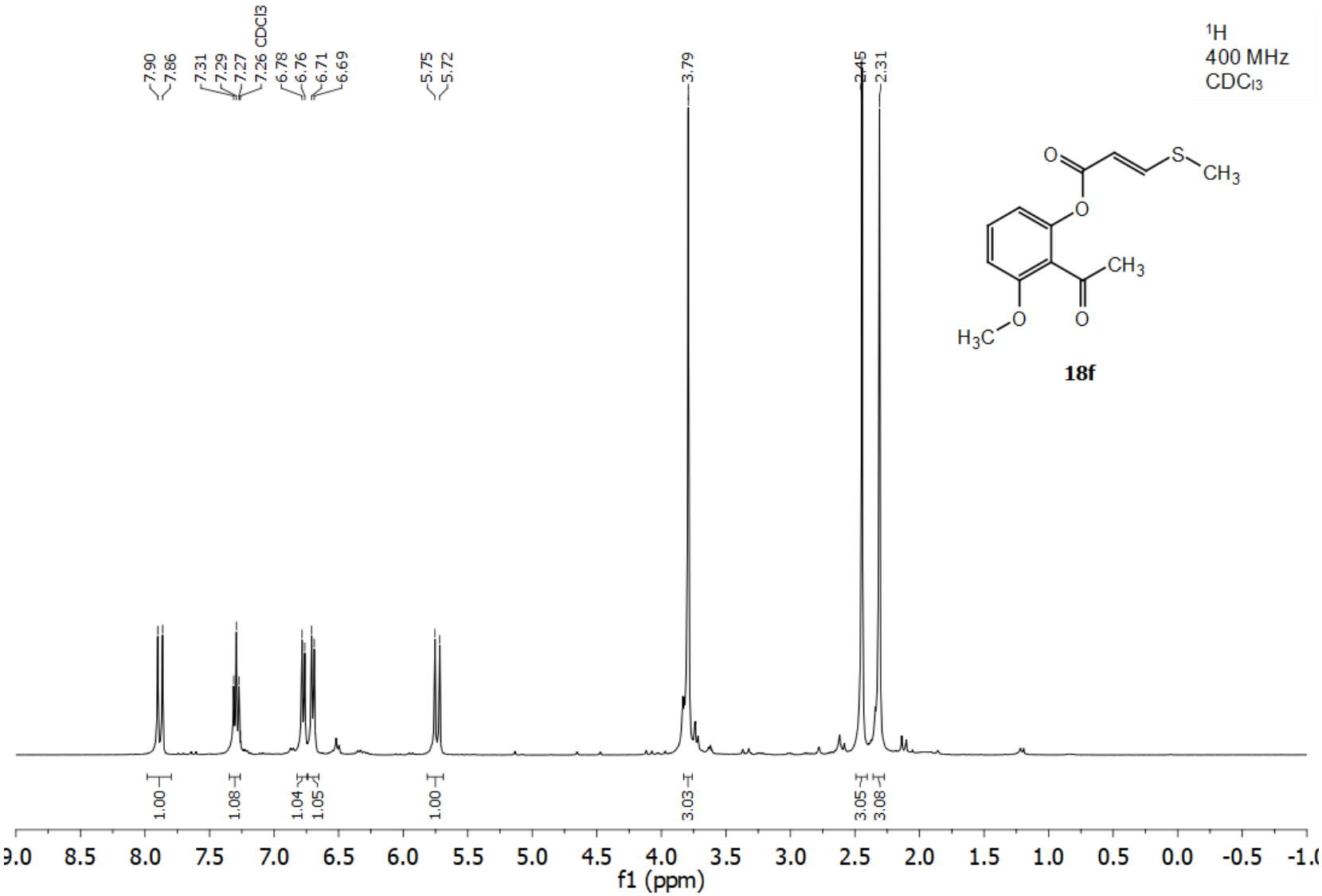
191.30
162.70
149.80
136.63
130.06
119.08
118.77
118.49
118.04
77.00 CDCl3
54.42
14.53
13.59
13C
100 MHz
CDCl3
O
S
CH3
O
CH3
OH
18e
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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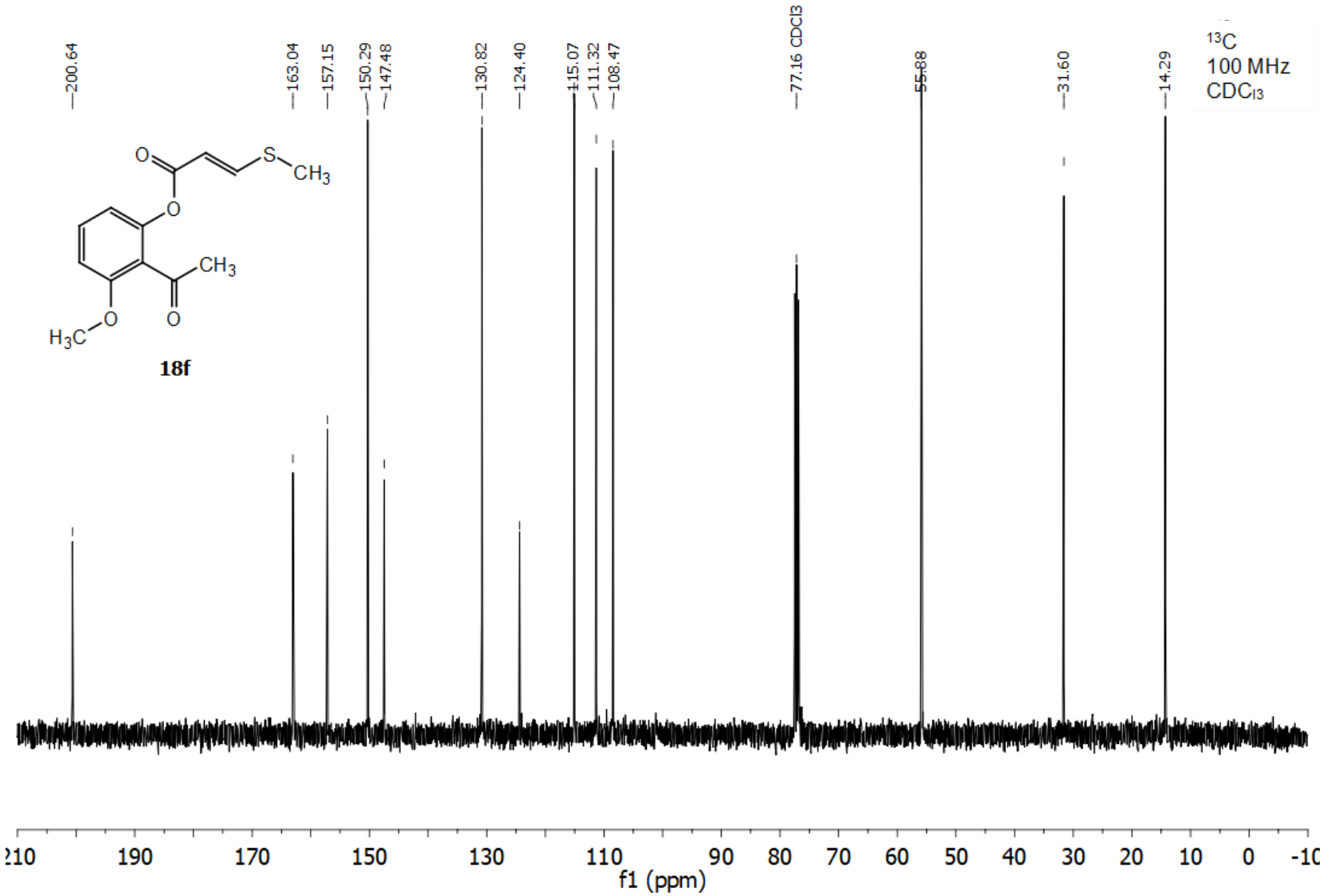
7.86
7.31
7.29
7.27
7.26 CDCl3
6.78
6.76
6.71
6.69
5.75
5.72
3.79
2.45
2.31
1H
400 MHz
CDCl3
O
S
CH3
O
CH3
O
O
H3C
18f
1.00
1.08
1.04
1.05
1.00
3.03
3.05
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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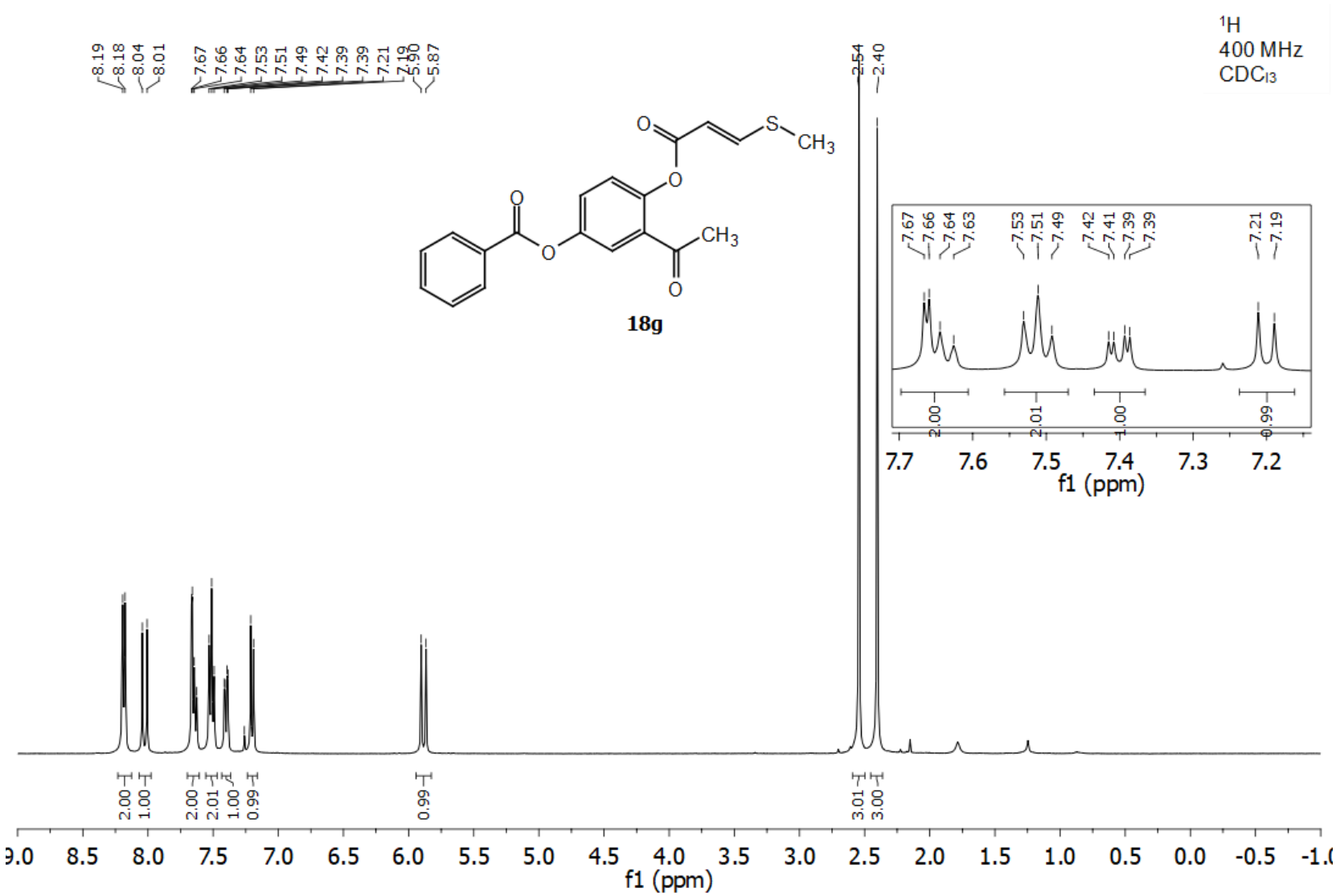
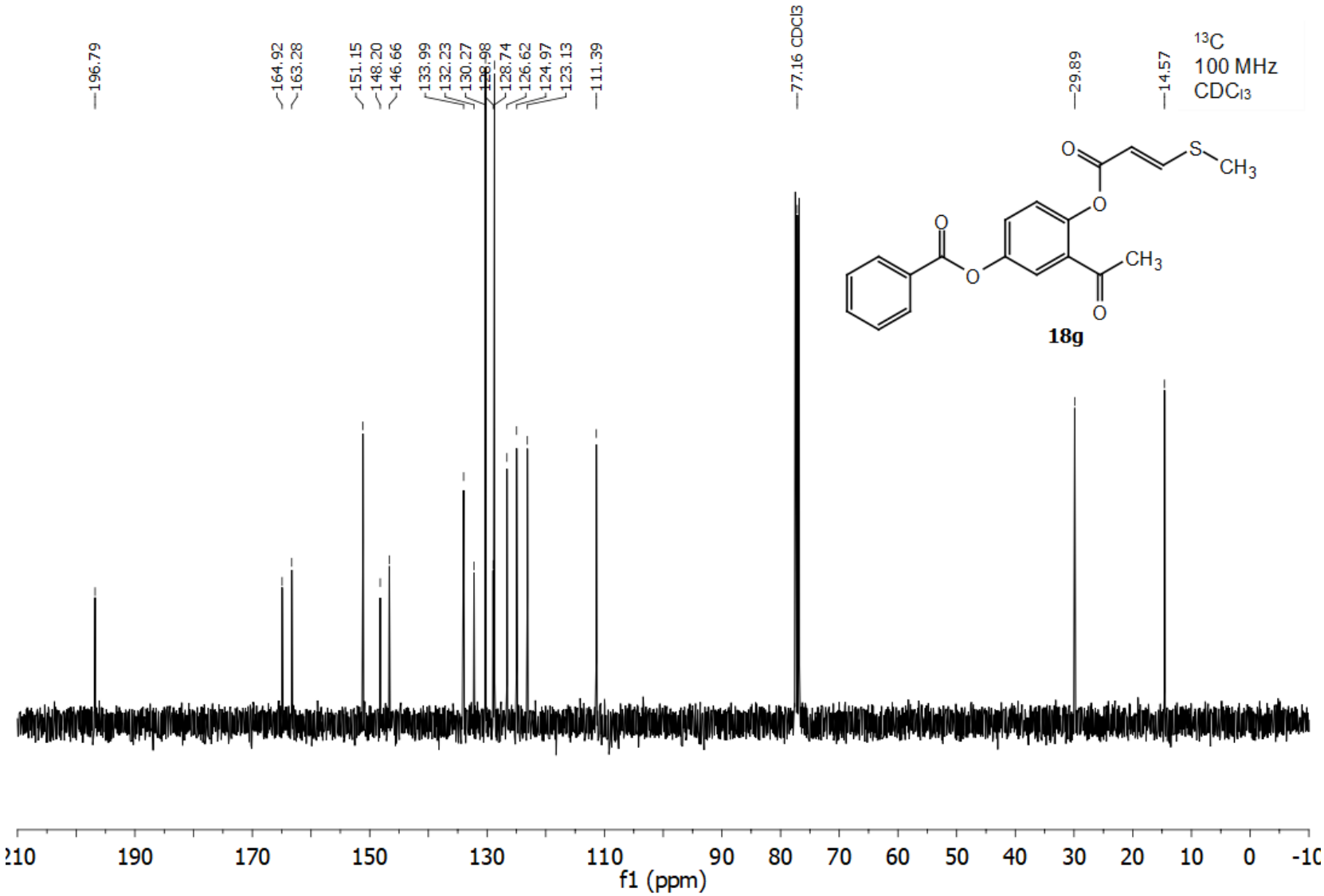
157.15
150.29
147.48
130.82
124.40
115.07
111.32
108.47
77.16 CDCl3
55.88
31.60
14.29
13C
100 MHz
CDCl3
O
S
CH3
O
CH3
O
O
H3C
18f
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


1H
400 MHz
CDCl3
18g
f1 (ppm)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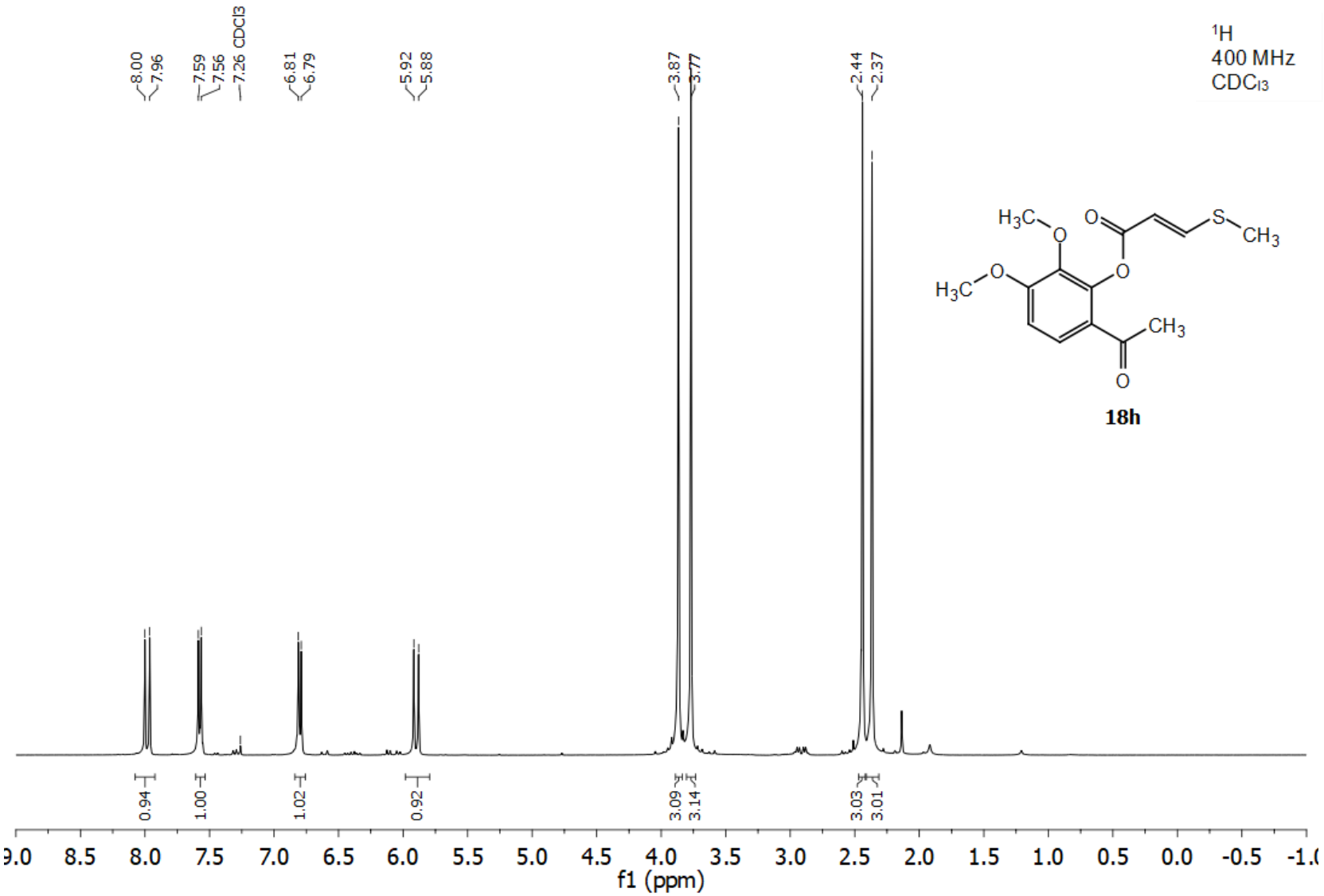
132.23
130.27
128.98
128.74
126.62
124.97
123.13
111.39
77.16 CDCl3
29.89
14.57
13C
100 MHz
CDCl3
O
O
S
CH3
O
O
O
CH3
O
18g
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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5.88
3.87
3.77
2.44
2.37
1H
400 MHz
CDCl3
H3C
O
O
S
CH3
H3C
O
O
CH3
O
18h
0.94
1.00
1.02
0.92
3.09
3.14
3.03
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
2.5
2.0
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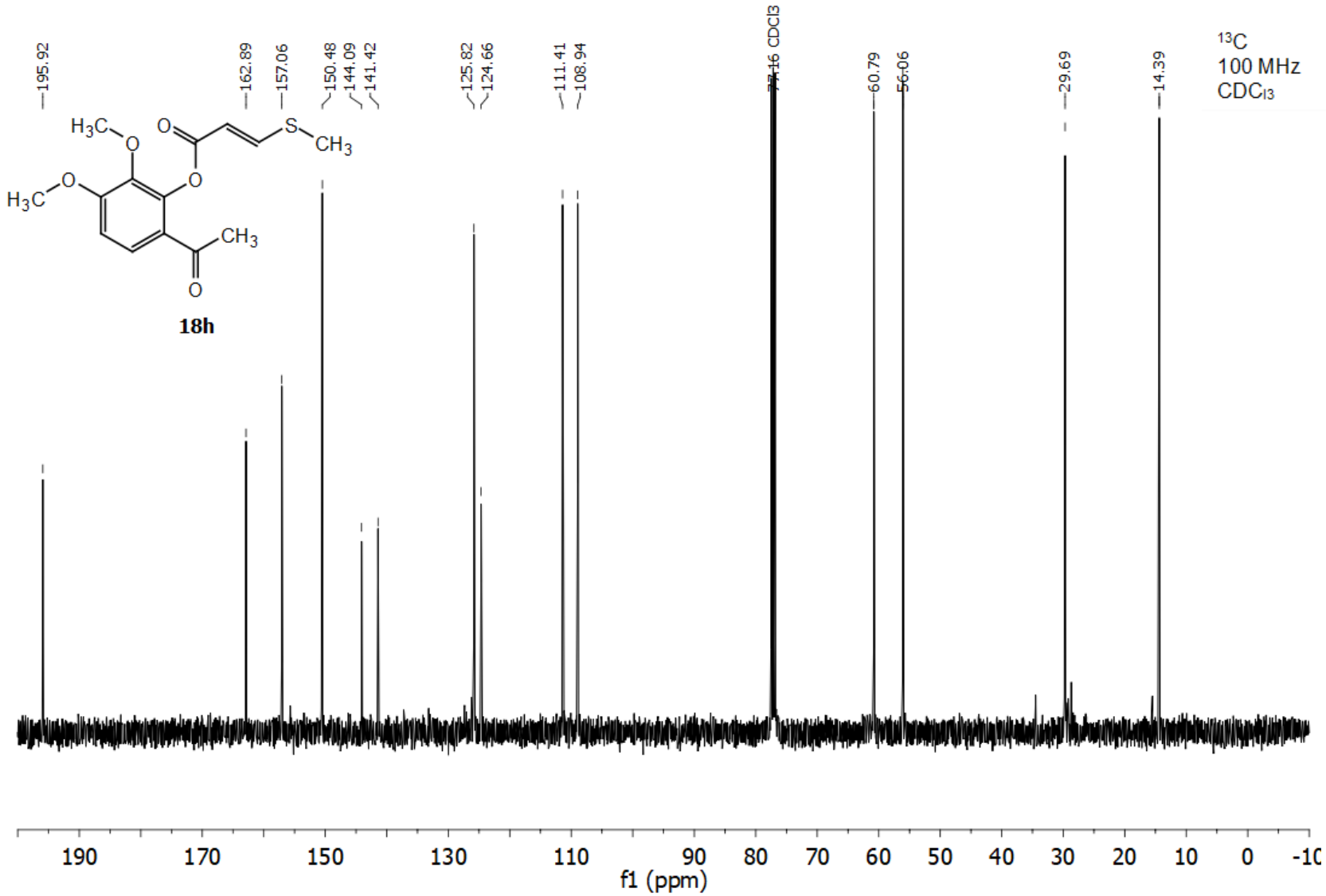
1.0
0.5
0.0
-0.5
f1 (ppm)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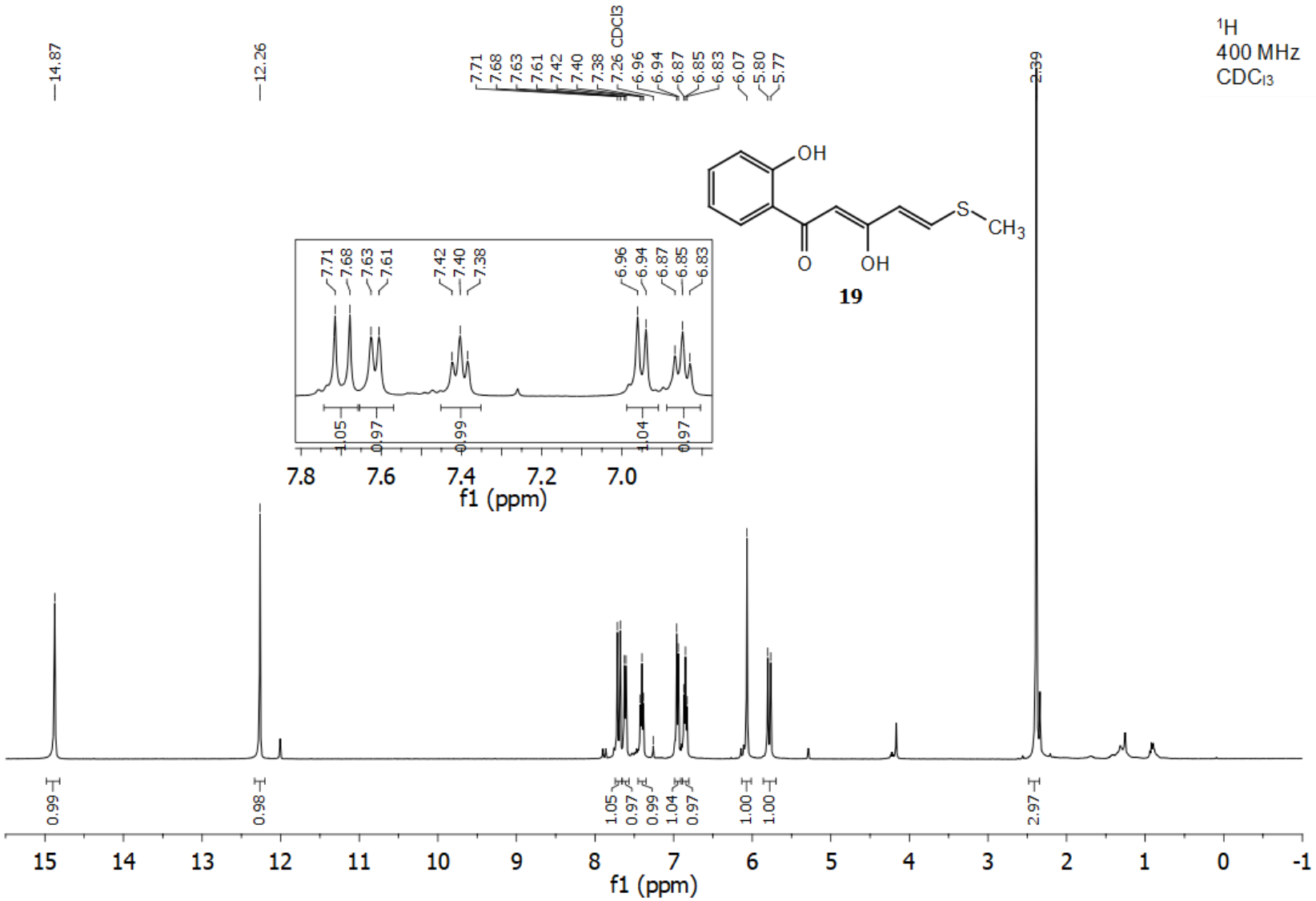
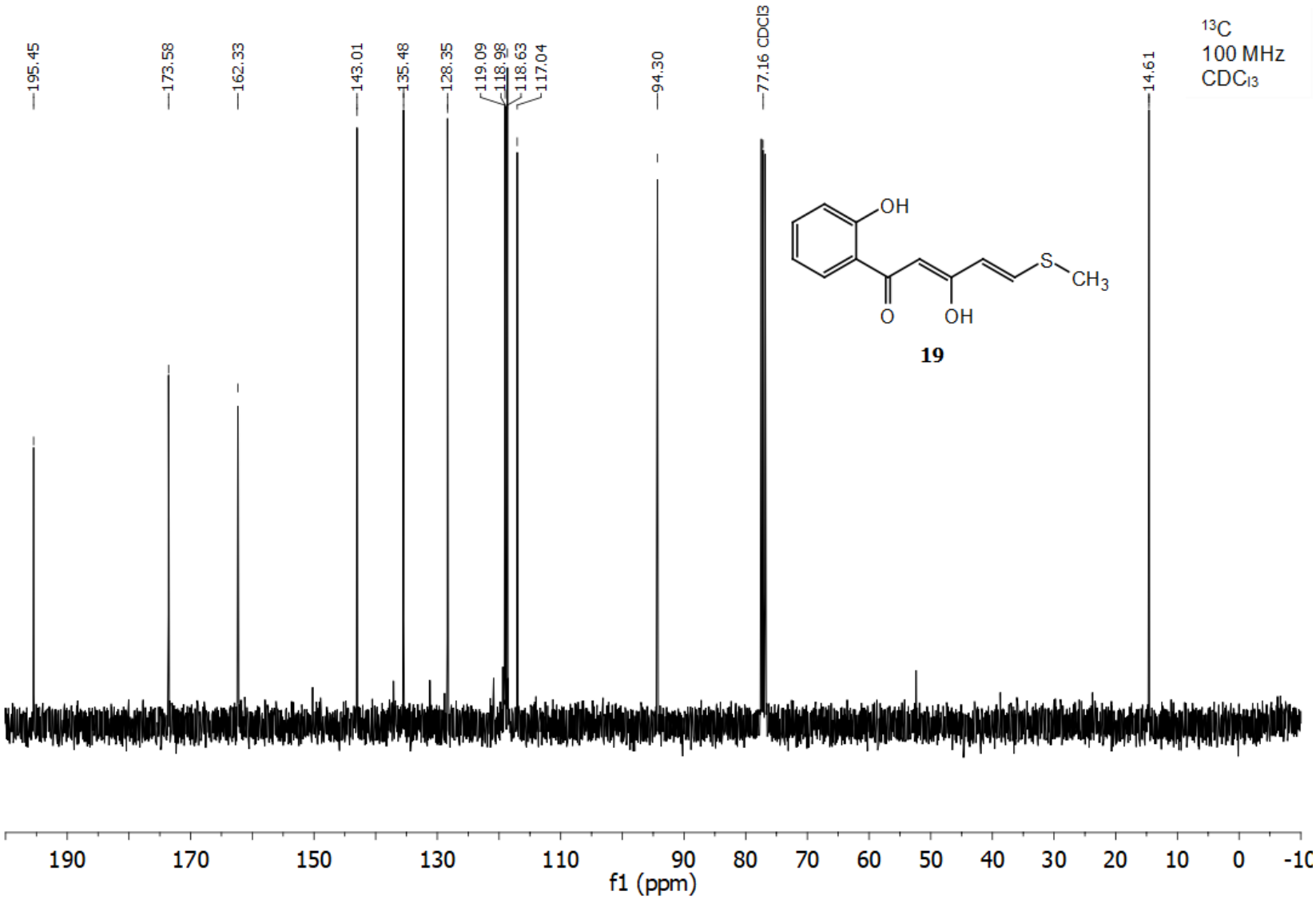
150.48
144.09
141.42
125.82
124.66
111.41
108.94
77.16 CDCl3
60.79
56.06
29.69
14.39
13C
100 MHz
CDCl3
H3C
O
O
S
CH3
H3C
O
O
CH3
O
18h
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


1H
400 MHz
CDCl3
14.87
12.26
7.71
7.68
7.63
7.61
7.42
7.40
7.38
7.26 CDCl3
6.96
6.94
6.87
6.85
6.83
6.07
5.80
5.77
2.39
OH
S
CH3
O
OH
19
0.99
0.98
1.05
0.97
0.99
1.04
0.97
1.00
1.00
2.97
f1 (ppm)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118.98
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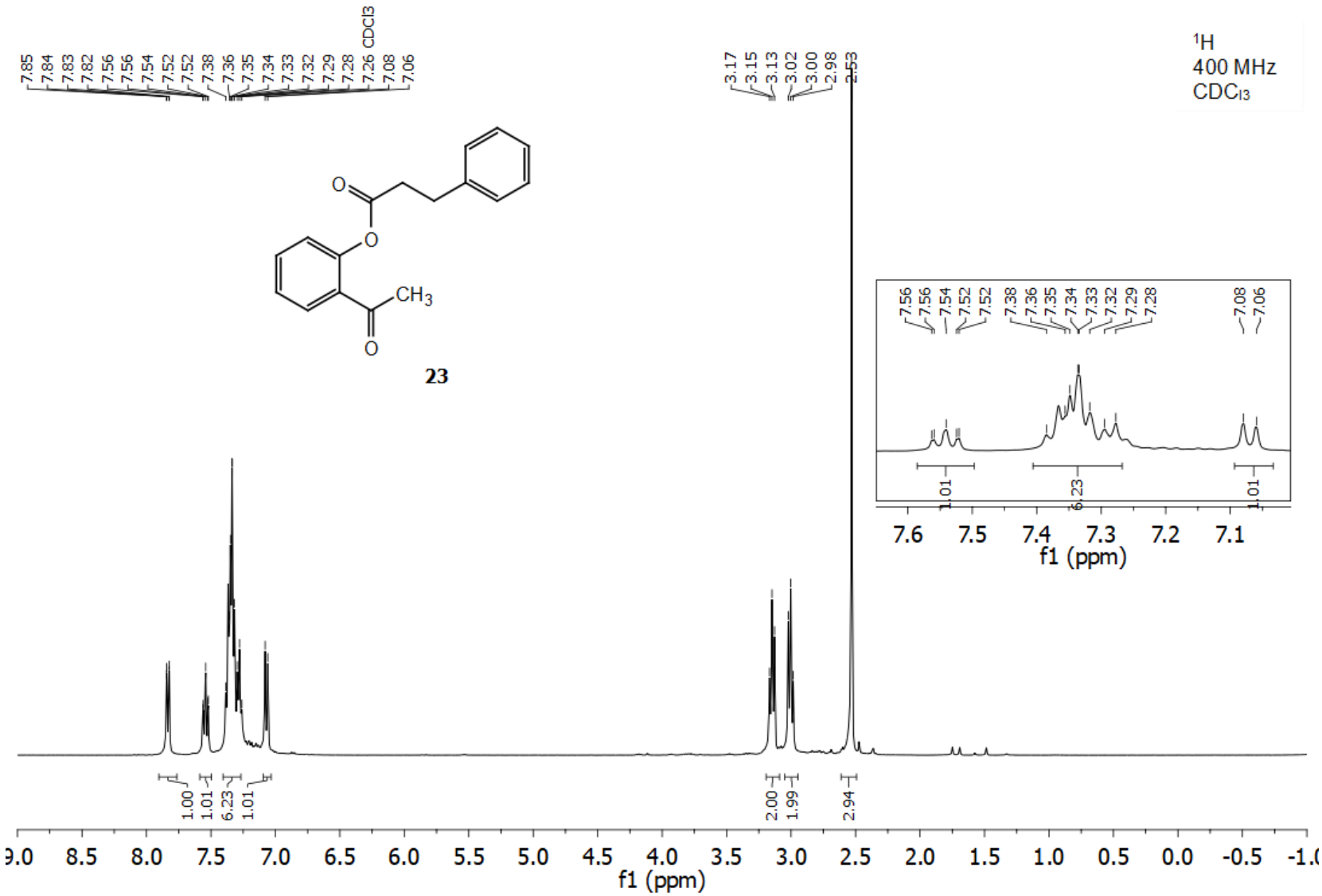
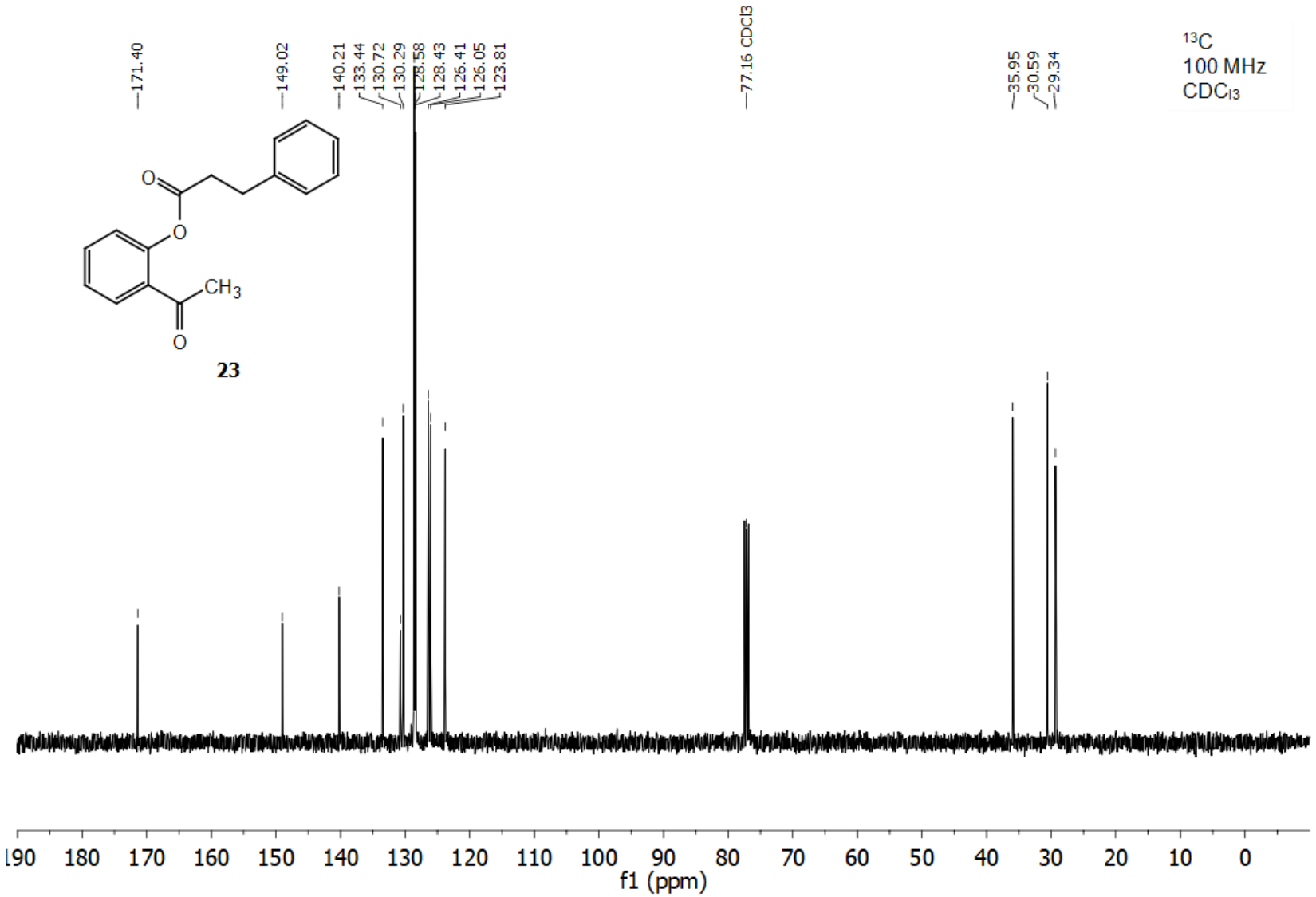
117.04
94.30
77.16 CDCl3
14.61
13C
100 MHz
CDCl3
OH
S
CH3
O
OH
19
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


1H
400 MHz
CDCl3
7.85
7.84
7.83
7.82
7.56
7.56
7.54
7.52
7.52
7.38
7.36
7.35
7.34
7.33
7.32
7.29
7.28
7.26 CDCl3
7.08
7.06
3.17
3.15
3.13
3.02
3.00
2.98
2.53
O
O
CH3
O
23
1.00
1.01
6.23
1.01
2.00
1.99
2.94
f1 (ppm)
1.01
6.23
1.01
f1 (ppm)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128.43
126.41
126.05
123.81
77.16 CDCl3
35.95
30.59
29.34
13C
100 MHz
CDCl3
O
O
O
CH3
23
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

CHAPITRE II

ON THE ROLE OF THE VINYLSULFOXIDE SIDE CHAIN OF DIRCHROMONE TOWARDS ITS BIOACTIVITIES

Ce chapitre reprend le contenu d'un article de recherche publié en anglais. Il est donc présenté dans cette langue, avec un résumé en français.

Titre: On the role of the vinylsulfoxide side chain of dirchromone towards its bioactivities

Auteurs: Alexis St-Gelais†, Jérôme Alsarraf†*, Jean Legault†, Mouadh Mihoub†, André Pichette†*

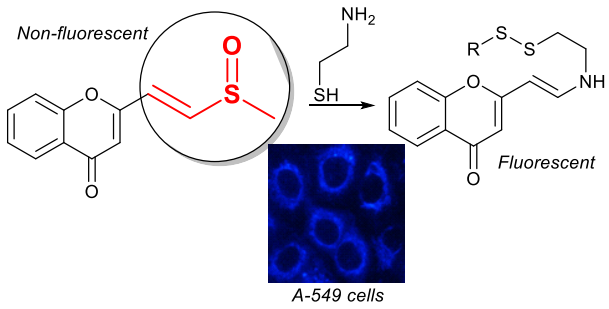
Affiliation: †Chaire de recherche sur les agents anticancéreux d'origine naturelle, Laboratoire d'analyse et de séparation des essences végétales (LASEVE), Département des Sciences Fondamentales, Université du Québec à Chicoutimi, 555, boulevard de l'Université, Chicoutimi (Québec), Canada, G7H 2B1

Référence complète: St-Gelais, A., Alsarraf, J., Legault, J., Mihoub, M., Pichette, A., 2020. On the role of the vinylsulfoxide side chain of dirchromone towards its bioactivities. Org. Biomol. Chem. **18** (*47*), 9700–9705.

2.1 Résumé en français

Des analogues de la dirchromone ont été préparés pour mettre en lumière le rôle central de sa chaîne latérale vinylsulfoxyde particulière en regard de ses propriétés cytotoxiques et antimicrobiennes, notamment en ce qui concerne la présence et le degré d'oxydation du soufre. La réaction de la dirchromone avec de la cystéamine a révélé un comportement surprenant d'accepteur de Michael couplé à une élimination du radical méthylsulfinyl et à une transformation oxydo-réductrice de l'atome de soufre, qui pourrait être impliqué dans le mode d'action de la dirchromone au sein des cellules.

2.2 Graphical abstract



2.3 Abstract

Analogs of dirchromone were prepared to shed light on the pivotal role of its peculiar vinylsulfoxide side chain towards its cytotoxic and antimicrobial properties, especially dependant upon the presence and oxidation state of sulfur. The reaction of dirchromone with cysteamine revealed a surprising Michael acceptor behavior with elimination of the methylsulfinyl moiety and redox transformation of the sulfur atom that could be involved in the mode of action of dirchromone within cells.

2.4 Article

2.4.1 Introduction

Dirchromones are a group of unique sulfur-bearing compounds found in minute amounts in the stem, bark and roots of the North American shrub *Dirca palustris* L. (Thymelaeaceae). Depending on their aromatic substitution pattern, they exhibited various degrees of cytotoxic and Gram-positive antimicrobial activities *in vitro* (St-Gelais et al., 2015). Their scarcity in the plant, however, initially prevented any rational structure-activity relationship studies. A synthetic route to gram-scale preparation of dirchromone (**1**) was therefore specifically devised (St-Gelais et al., 2018) as the inclusion of the vinylsulfoxide moiety as the side chain of a chromone proved to be a challenging task. The incorporation of the peculiar conjugated sulfur function relied on an original Pummerer reaction where an alkyl sulfoxide was converted into a vinyl sulfide. A novel soft-enolization Baker-Venkataraman rearrangement, inspired by the conditions developed by Lim *et al.* for mixed Claisen condensations (Lim et al., 2007), then enabled the construction of the chromone framework which bore this sensitive function. With this fruitful strategy available, the ensuing step naturally was to define the relevant features of the parent scaffold towards its cytotoxic and antimicrobial activities.

The lateral chain of dirchromone (**1**) features a conjugated stereogenic sulfoxide. This moiety naturally draws attention as the salient structural originality of dirchromone, which is one of the relatively rare examples of sulfur-bearing secondary metabolites in terrestrial plants outside the Alliaceae and Brassicaceae families (Nwachukwu et al., 2012), and the first within the Thymelaeaceae (St-Gelais et al., 2015). It lends itself to several potential structural modifications in order to define its role in the biological activity of dirchromone (Figure 2-1).

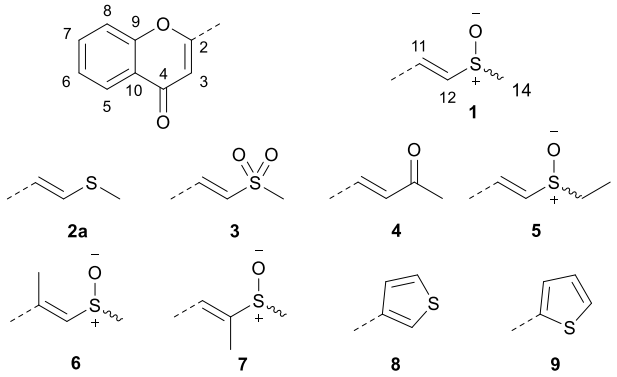


Figure 2-1. Structural modifications introduced to the lateral chain of dirchromone (**1**) in order to study their influence on bioactivity.

Firstly, the chiral nature of the sulfoxide must be addressed. The natural dirchromone (**1**) and its derivatives were isolated as racemates. However, sulfoxide chirality regularly features a key impact on bioactivity: a relevant example is the affinity of the sulfoxide (*R*)-modafinil for dopamine D2 receptors in rat brain tissues, whereas its (*S*) counterpart is virtually inactive (Seeman et al., 2009). Various pharmaceutically relevant sulfoxides are preferably prepared as enantiomerically pure drugs (Wojaczyńska and Wojaczyński, 2010). In other instances, chirality is not as directly critical. Sulindac, a non-steroidal anti-inflammatory drug, is produced as a racemic methylsulfoxide. The active compound in fact being its sulfide metabolite, both enantiomers can elicit activity; it is, however, worth noting that the metabolization profiles of these enantiomers differ (Brunell et al., 2011). In addition to chirality, the example of sulindac also points out the importance of verifying this impact of the oxidation state of the sulfur atom in dirchromone. To complete this study of the sulfur moiety, the recurring bioisosteric replacement between carbonyl, sulfoxide, and sulfone in medicinal chemistry has to be considered (Patani and LaVoie, 1996). Broadening this exploration, thiophene analogs, which were prepared previously (Wu et al., 2012), but apparently never tested for their cytotoxicity, have been included in the structural study herein reported.

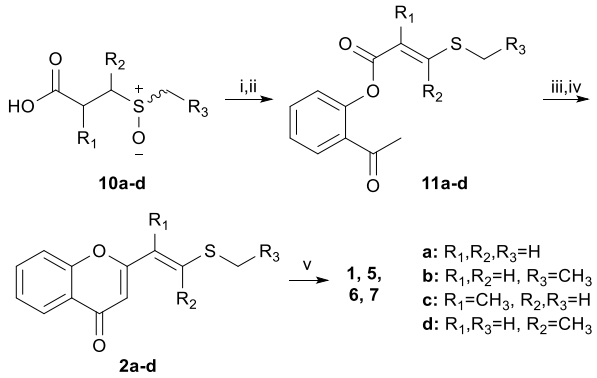
In addition of the side chain heteroatoms, its carbon backbone must also be considered. On the one hand, the homologation of the alkyl chain of the sulfoxide could have an impact. On the other hand, the role of the alkene should be clarified, as it induces extended conjugation of the chromone and sulfoxide. This could in turn, among others, produce a relevant Michael acceptor. For instance, vinylsulfones were developed to irreversibly bind to cysteine proteases by such a mechanism (Palmer et al., 1995). Michael acceptor properties are relevant both for desired biological effects and toxicity of drugs, for example inducing binding to macromolecules (often via free cysteine thiols) or depleting glutathione (GSH) stocks in target cells to increase susceptibility to other treatments. Modulation of this reactivity can be a helpful approach in tuning the activity of drug candidates (H. Johansson, 2012). Therefore, the Michael acceptor nature of dirchromone was studied, and the products of this reaction were in part characterized.

2.4.2 Results and discussion

2.4.2.1 Preparation of dirchromone analogs

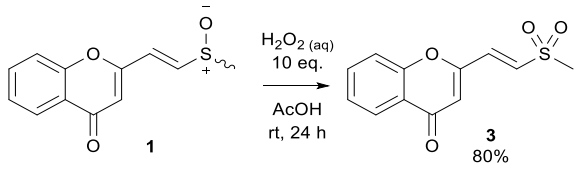
Dirchromone (**1**) and its deoxy counterpart **2a** were obtained from the dirchromone preparation described earlier (St-Gelais et al., 2018) (Scheme 2-1). Briefly, commercial 3-methylthiopropionic acid was quantitatively oxidized into the corresponding sulfoxide **10a**, which then underwent an uncommon Pummerer rearrangement transferring the oxidation to the carbon chain while simultaneously generating a suitable acyl chloride to obtain a phenone ester **11a**. This intermediate was in turn submitted to a soft-enolization Baker-Venkataraman rearrangement enabled by the addition of magnesium bromide diethyl etherate, and further dehydrated to the chromone to yield sulfide **2a**. Racemic dirchromone (**1**) was produced by oxidation with *meta*-chloroperbenzoic acid (*m*-CPBA). Attempts at preparing enantiopure sulfoxides from sulfide **2a** using classical Kagan oxidation conditions (Kagan, 1986) afforded equivocal results with unpredictable enantiomeric excesses. Therefore, direct

Scheme 2-1. Synthetic route to dirchromone analogs. i: Oxalyl chloride (2 equiv), cat. DMF, DCM, 1h, rt; ii: 2'-hydroxyacetophenone (4 equiv), KOH (4 equiv), DMF, 5 min, rt; iii: $MgBr_2 \cdot Et_2O$ (2.5 equiv), diisopropylethylamine (3 equiv), DCM, 24 h, rt; iv: HCl 37 %, MeOH, 24h, rt; v: *m*-CPBA (1 equiv), DCM, 24 h, rt.



separation of the enantiomers of dirchromone (**(−)-1** and **(+)-1**) by chiral preparative HPLC was achieved at milligram scale. Sulfone **3** was prepared in good yield by oxidation of dirchromone (**1**) with an excess of hydrogen peroxide in acetic acid (Scheme 2-2).

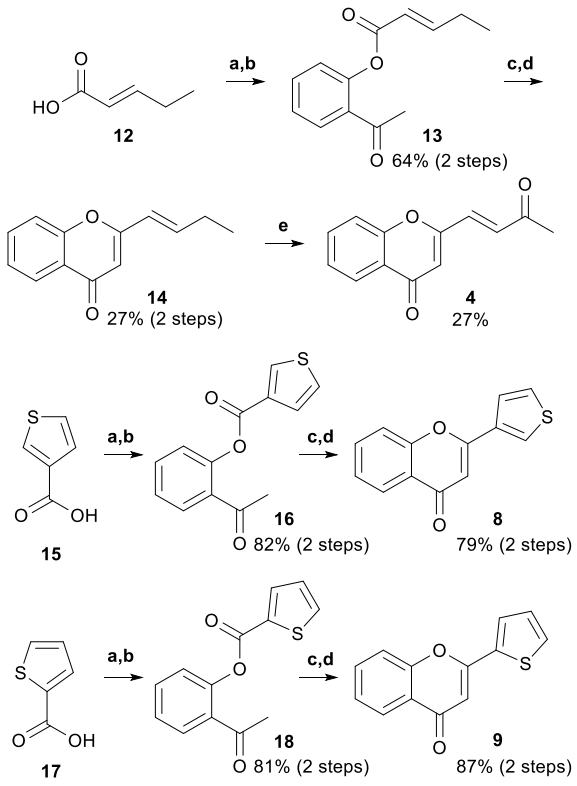
Scheme 2-2. Oxidation of dirchromone (**1**) to sulfone **3**.



The same synthetic route was successfully applied to the preparation of substituted compounds **5**, **6**, and **7** (see the supporting information). 3-(Ethylsulfinyl)propanoic acid (**10b**) was obtained by first reacting 3-mercaptopropionic acid with ethyl bromide (Vaismaa et al., 2007) to obtain crude *S*-ethyl-3-mercaptopropionic acid and oxidizing the latter to sulfoxide. Compound **2b** was obtained from 3-mercaptopropionic acid in 11 % yield over 6 steps following a published procedure (St-Gelais et al., 2018); compound **5** was then prepared by oxidation in a yield of 67 %. Methacrylic acid was

used as the starting material towards compound **6** by reacting with *S*,*S*'-dimethyl dithiocarbonate in presence of aqueous potassium hydroxide (Cadamuro, Silvano; Degani, Iacopo; Fochi, Rita; Regondi, 1986) followed by oxidation to sulfoxide **10c.** The 11-methylated product **6** was subsequently prepared in an overall 18 % yield (7 steps from methacrylic acid). 12-methyl-dirchromone **7** was prepared by first performing a Michael addition on methyl crotonate using *S*-methyl-isothiourea (Zhao et al., 2007), hydrolyzing the ester and oxidizing the obtained sulfide-bearing acid to prepare crude 3-(methylsulfinyl)-butanoic acid **10d**. The presence of a methyl group α to the sulfoxide apparently interfered with the ensuing Pummerer rearrangement, with roughly equivalent quantities of the sulfur-bearing ester and of the crotonate ester of 2'-hydroxy-acetophenone being obtained as an inseparable mixture. These were thus submitted as is, without further purification, to the soft-enolization Baker-Venkataraman rearrangement and acidic methanolic dehydration providing a mixture of the expected chromone and 2-(2-methoxypropyl)-chromone. Nevertheless, with the oxidation of the sulfide, the desired product **7** could be obtained separately albeit in low overall yield (6 % from methyl crotonate, over 5 steps). The bioisosteric replacement of the sulfoxide by a ketone to obtain compound **4** was carried through the synthesis of (*E*)-2-but-1- en-1-ylchromone **14** (Scheme 2-3). Esterification of (2*E*)-pentenoic acid (**12**) via its acyl chloride and 2'-hydroxyacetophenone afforded ester **13** in 64 % yield. Chromone **14** was then prepared in 27 % yield over two steps by the soft-enolization Baker-Venkataraman rearrangement and cyclization sequence used for other derivatives. The moderate yield could be explained by partial loss of **14** via the acid-catalyzed methoxylation of the 11,12-alkene during chromone cyclization in methanol. Classical Riley oxidation conditions (Kürti and Czakó, 2005) using SeO_2 failed to oxidize the allylic methylene of chromone **14**, but a $Pd(OH)_2/K_2CO_3$/*tert*-butyl hydroperoxide system (Yu and Corey, 2003) afforded ketone **4** albeit in a modest 27 % oxidation yield.

Scheme 2-3. Synthesis of compounds **4**, **8** and **9**. (a) $(COCl)_2$ (1.5 equiv), cat. DMF, DCM, rt, 1 h; (b) 2'-hydroxyacetophenone (4 equiv), KOH (4 equiv), DMF, rt, 5 min; (c) $MgBr_2$•Et_2O (2.5 equiv), diisopropylethylamine (3 equiv), rt, 24 h; (d) HCl 37 %, MeOH, rt, 24 h; (e) $Pd(OH)_2$ (0.05 equiv), K_2CO_3 (0.25 equiv), *t*-BuOOH (10 equiv), DCM, rt, 48 h.



The soft-enolization Baker-Venkataraman rearrangement was also efficiently extended to the preparation of thiophenes **8** and **9** from commercial thiophenecarboxylic acids **15** and **17** (Scheme 3). Preparation of their sulfone analogs was attempted, but the molecules either resisted oxidation or entirely degraded, depending on the amount of *m*-CPBA used. To complete this study, the preparation of the deconjugated sulfoxide 2-(2-(methylsulfinyl)ethyl)chromone was attempted by successive treatment of 2-(2-mercaptoethy)chromone (St-Gelais et al., 2018) with aqueous dimethylsulfate in the presence of a base and immediate oxidation to the sulfoxide, but the prevalence of byproducts (notably 2-vinylchromone) prevented isolation of a sufficient amount to proceed to testing.

2.4.2.2 Effect of structural modifications on bioactivities

Synthesized compounds were screened for their cytotoxicity using two malignant (DLD-1 colorectal adenocarcinoma and A-549 pulmonary adenocarcinoma) and one healthy (WS1 skin fibroblasts) human cell lines (Table 2-1). The results are expressed as half-maximal inhibitory concentration (IC_{50}) using etoposide as a positive control. Overall, it is of interest to note that DLD-1 cells appeared to be more affected than the other cell lines by dirchromone and its analogs. It could be of interest to pursue experiments towards other colorectal malignant cells.

No relevant difference in cytotoxic activities was recorded between the two enantiomers of dirchromone (**(−)-1** and **(+)-1**). Although this structural feature could have relevance for other aspects of the biological interactions of dirchromone *in vivo*, such as systemic toxicity and metabolization, this result established that further *in vitro*

Table 2-1. Cytotoxicity and anti-Gram-positive activities of compounds **1-9**

Compound	IC_{50} (µM)[a]			MIC_{90} (µM)[a]
	DLD-1	**A-549**	**WS1**	***S. aureus***
1	2.8 ± 0.2	13 ± 1	3.1 ± 0.1	12 ± 1
(−)-1	2.5 ± 0.3	14 ± 1	2.8 ± 0.2	22 ± 2
(+)-1	2.8 ± 0.4	17 ± 1	3.8 ± 0.5	16 ± 2
2a	36 ± 7	62 ± 7	>100	>100
3	6.2 ± 0.3	28 ± 2	6.1 ± 0.1	2.9 ± 0.4
4	13 ± 2	22 ± 1	12 ± 1	>100
5	1.4 ± 0.1	7.2 ± 0.9	3.3 ± 0.1	37 ± 3
6	1.7 ± 0.2	6.7 ± 0.5	1.5 ± 0.1	83 ± 4
7	2.8 ± 0.2	5 ± 1	3.1 ± 0.4	>100
8	53 ± 2	84 ± 10	>100	>100
9	>100	93 ± 8	>100	>100
Etoposide	3.0 ± 0.4	2.0 ± 0.3	46 ± 12	-
Gentamycin	-	-	-	0.072 ± 0.006

[a]Values ± SD (n = 3) are representative of three different experiments

screening efforts could proceed with racemic sulfoxides like those initially isolated from *D. palustris*. Other sulfoxide analogs **5-7** were therefore tested as racemates.

Modifications to the sulfur heteroatom generally reduced cytotoxicity. The sulfide **2a** is much less active, even exerting no effect (IC_{50} >100 μM) on healthy WS1 cells. Thiophenes **8-9** also feature greatly diminished potency. Bioisosteric replacement of the sulfoxide by a carbonyl in compound **4** had a detrimental effect on activity, especially for DLD-1 and WS1 cells. Sulfone **3** was slightly less active than dirchromone (**1**) on these lines, but not as clearly affected as the sulfide **2a** and carbonyl **4**. This demonstrates that the sulfur atom is an advantageous feature to exert the biological response, and that the S-O bond is pivotal in that regard at least for DLD-1 and WS1 cell lines. Methylation in compound **7** only slightly increased activity on A-549, while in compounds **5** and **6**, the increment affected both DLD-1 and A-549. Although the effects are modest, this suggests that alkylation with longer carbon chains could be explored to obtain more active analogs.

Antimicrobial activity is reported on Gram-positive *Staphylococcus aureus* whereas the analogs were not active on Gram-negative bacteria, as found with natural dirchromones (St-Gelais et al., 2015). Here again, chirality of the sulfoxide had a limited effect. Several of the structural modifications abolish activity: thiophenes **8-9**, sulfide **2a**, carbonyl **4** and methylated dirchromones **6** and **7** were inactive (>100 μM), or nearly so. Homologation of the sulfoxide in compound **5** did not affect the antimicrobial effect much. The most interesting observation is, however, that sulfone **3** is consistently more active than dirchromone (**1**). Since this modification also decreased cytotoxicity, it provides perspective to design analogs that would be less toxic and more potent against Gram-positive bacteria. Finally, there does not appear to be a relationship between cytotoxicity and antibacterial potential, implying that the mechanisms underlying both activities are possibly distinct and not merely arising from

generic toxicity. Future investigations should thus not only seek increased cytotoxicity, but also identification of less toxic analogs expressing antibacterial potential.

2.4.2.3 Dirchromone as a peculiar Michael acceptor

As these results highlighted the importance of the vinylsulfoxide side chain of dirchromone (**1**) towards its cytotoxicity, the possibility that dirchromone might act as a thia-Michael acceptor was then examined. Vinyl sulfoxides, to the best of our awareness, have not been commonly considered as useful Michael acceptors; Nicponski and Marchi also noted scarcity of reports of Michael additions to unsaturated sulfoxides even though they could be suitable substrates (Nicponski and Marchi, 2014). Conversely, one could envision that the 2-vinylchromone motif, independently of the sulfoxide, could be a thia-Michael acceptor. This type of structure has seemingly not been studied extensively in that regard as only two studies reporting Michael addition of amines and nitrilimines to 2-styrylchromone derivatives could be retrieved (Bouchama et al., 2018; Hassaneen et al., 2002), nevertheless showing some potential for this hypothesis. Since thia-Michael addition mechanisms are known to be involved in several biological trapping agents, dirchromone was submitted to the cysteamine adduct NMR test proposed by Avonto *et al* (Avonto et al., 2011). Addition of 2 equiv of cysteamine to a solution of dirchromone (**1**) in deuterated dimethylsulfoxide clearly led, within minutes, to disappearance of the original alkene signals (Amslinger, 2010; H. Johansson, 2012) (Figure 2-2, zones A and B) in an irreversible fashion (based on the $CDCl_3$ dilution reversibility test, data not shown). However, this transformation led to the formation of several products with the ^1H NMR spectrum of the mixture progressively evolving over the course of 45 minutes (zones C and D) with loss of the methylsulfinyl signal (zone E). When the experiment was repeated with 4 equiv of cysteamine, the process immediately proceeded towards a cleaner mixture, but in no cases did a single compound form. Under the same conditions, *S*-oxodirchromone (**3**) featured a similar behavior, with loss of the alkene and *S*-methyl signals and emergence

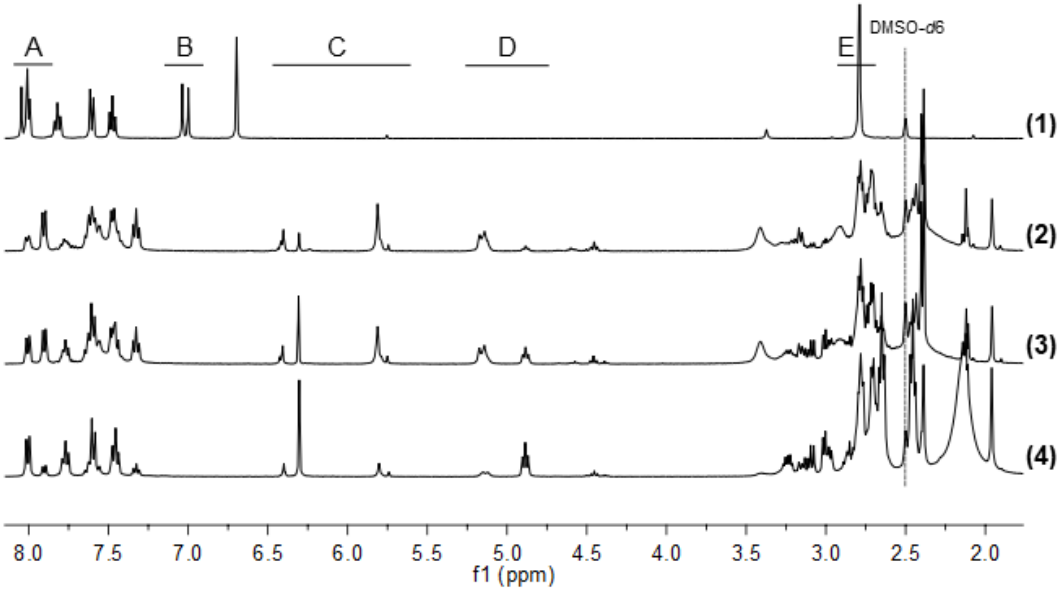


Figure 2-2. ^{1}H NMR experiments of the cysteamine adduct test of Avonto et al. for dirchromone, with all spectra locked on DMSO-d_6 residual peak. Spectrum (1) shows pure dirchromone, spectrum (2) its reaction with 2 equiv cysteamine after 10 min, spectrum (3) its reaction with 2 equiv cysteamine after 45 min, and spectrum (4) its reaction with 4 equiv cysteamine (which was stable over time). Zones A and B indicate the original side chain olefinic signals; zone C the C-3 signals; zone D evolving side chain signals; zone E the methylsulfoxide singlet.

of new NMR peaks (see Supporting information). The bioisosteric ketone **4** also reacted as an irreversible Michael acceptor, but the terminal methyl signal remained as a more shielded signal, setting it apart from sulfur-bearing compounds.

Some reaction products of 0.5 mmol dirchromone and 4 equiv cysteamine in DMSO were isolated by flash chromatography. This allowed identification of part of the products as compounds **19-21** (Figure 2-3). Since Michael addition occurred at position 12, 2-vinylchromone could be the driving Michael acceptor moiety. The methylsulfinyl moiety was then effectively locking the adduct in place. Interestingly, a similar elimination of methylsulfoxide (as methanesulfenic acid) was already reported for the reaction of GSH with aromatic *S*-oxides of agrochemicals derivatives such as terbutryn sulfoxide (Huwe et al., 1991). Furthermore, the presence of disulfide bridges in compounds **19** and **21** and the incorporation (after reduction) of at least some of the

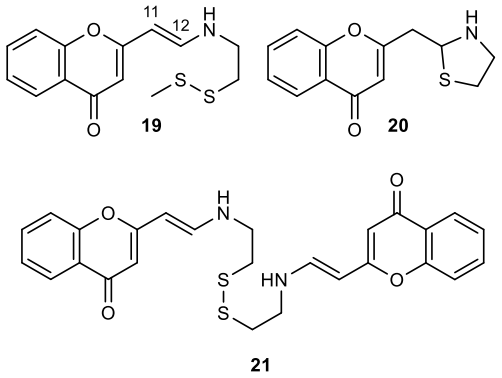


Figure 2-3. Characterized products **19-21** from the reaction of dirchromone (**1**) with an excess of cysteamine in DMSO.

methylsulfur released by dirchromone in structure **19** further indicated redox transformations driven by the sulfur atom. Such a phenomenon may be relevant in biological activities, since many natural sulfur-bearing molecules exert part of their action via redox reactions: for example, the thiosulfinate generated enzymatically from alliin in *Allium* sp., allicin, can in turn mobilize four equiv of thiol to yield disulfides, which may effectively disrupt microbial biochemical integrity and could depress GSH stocks in mammalian cells (Jacob, 2006).

In perspective, these findings could rationalize why sulfoxides and the sulfone were more efficient than the other derivatives in the cytotoxic assays: carbonyl **4**, for which the terminal methyl remains, would not undergo the elimination step. Acknowledging that cysteamine is not the only biologically relevant substrate that could react with dirchromone, reaction of the latter with excess cysteine or GSH in aqueous media was tested. All attempts similarly led to quick and complete transformation of compound **1** into polar products, which could not be isolated but illustrated that this sequence of events was reasonably not limited to cysteamine and could take place with other biomolecules. It is noteworthy that in pure acetonitrile, no reaction between dirchromone and cysteamine took place in over 48 h, at which point addition of water

triggered the conversion within seconds. The presence of either water or DMSO appears to be necessary to the reaction.

This offers an intriguing overall picture, where dirchromone combines three distinct reactivity mechanisms (Michael addition, concomitant elimination of the methylsuflinyl moiety, and redox capabilities) to generate a structurally original series of reaction products. How this sequence of reactions takes place and precisely contribute to bioactivity is currently unknown, but the contribution is plausible: it could for example deplete the GSH stocks of the cells, generate toxic amounts of small sulfur-bearing compounds, disable enzymes or proteins, or generate metabolites related to **19-21** that in turn exert the activity. Further research is warranted to describe the reactivity of dirchromone and its sulfone analog in more detail, with a variety of thiols or amines and in different reaction conditions.

Notwithstanding, empirical observations suggest that this reaction was likely to take place within cells cytosol. None of the synthesized dirchromone derivatives exhibited fluorescence when exposed to 365 nm UV light, to the exception of sulfide **2a** which emitted a blue color. Compounds **19** and **21** (but not **20**) shared this property with the sulfide. Treatment of A549 cells with dirchromone (**1**) at the IC_{50} concentration gave rise to a clear blue fluorescence in the cytoplasm upon exposure to 377 nm UV light (Figure 2-4). Dirchromone could therefore serve as its own fluorescent probe to confirm that the Michael addition/sulfur elimination/redox sequence took place within the cells.

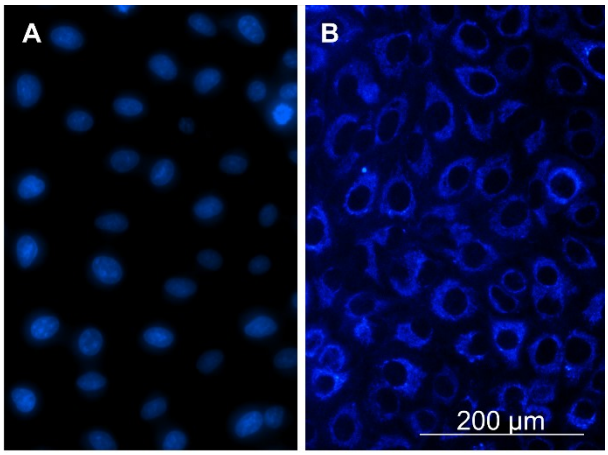


Figure 2-4. A-549 cells monolayer incubated with A) 4',6-diaminido-2-phenylindole (DAPI) nucleus stain and B) 10 µM dirchromone (**1**) for 4 h, both excited at 377 nm and monitored at 447 nm.

2.4.3 Conclusions

The versatile strategy established for the total synthesis of dirchromone (**1**) granted a straightforward access to various analogs, thus enabling the exploration of the relevant features of the side chain of dirchromone towards its biological properties. This study showed that its peculiar vinylsulfoxide function played a pivotal role to exert cytotoxicity. Chirality of the sulfoxide did not influence these activities, but the S-O bond presence was critical to induce them. Homologation of the alkylsulfoxide slightly increased cytotoxicity. Methylation of the olefin also had a mild increasing effect on this activity, but these modifications disabled antibacterial potential. On the other hand, sulfone **3** displayed reduced cytotoxicity and improved activity against *S. aureus*, making sulfone analogs of dirchromones a relevant class of compounds to be explored for antimicrobial properties. In presence of cysteamine, dirchromone acted as a Michael acceptor, followed by elimination of the sulfoxide moiety and redox reactions to generate a series of structurally original compounds, some of which exhibiting fluorescence. Therefore, dirchromone could probe such transformations within cells. These initial findings not only stress the uniqueness of reactivity of dirchromone, but also calls for future detailed investigation of the Michael acceptor properties and mechanism of action of dirchromone within cells.

2.5 Conflicts of interest

There are no conflicts to declare.

2.6 Acknowledgment

The authors acknowledge the Chaire de recherche sur les agents anticancéreux d'origine naturelle for funding. This work was supported by the Canadian Institutes of Health Research (CIHR, operating grants 311906 and 326083 to A. P. and J. L.). A. S. G. thanks NSERC for a PhD scholarship. C. Dussault (UQAC) is gratefully acknowledged for biological assays, and A. Ardaillou for additional NMR experiments over the course of manuscript revision.

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2.8 Supporting information

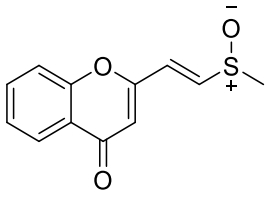
2.8.1 General experimental procedures

All starting materials and reagents were purchased from commercial sources (Sigma-Aldrich, Toronto Research Chemicals, TCI America, Alfa Aesar and Oakwood Chemicals) and used as received without further purification. Unless noted otherwise, reactions were conducted using anhydrous commercial solvents under argon atmosphere, introducing reagents with dry disposable syringes and needles. Anhydrous solvents, supplied over molecular sieves, were used as received. Reactions were monitored by thin-layer chromatography (TLC) with silica gel 60 F_{254} 0.25 mm pre-coated aluminum foil plates (MilliPore) and visualised under UV_{254}. All flash chromatographic purifications were performed using a low-pressure liquid chromatographic system (Büchi) and silica gel 60 (15-40 μm) columns packed on-site. NMR spectra were recorded with a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei, using deuterated chloroform ($CDCl_3$) or pyridine (C_6D_5N) as the solvent. Chemical shifts were reported in ppm relative to the solvent residual peak (δ = 7.26 ppm for ^{1}H and 77.1 ppm for ^{13}C) in chloroform, and to TMS in pyridine, and coupling constants *J* were expressed in Hertz (Hz). Multiplicities were reported using the following abbreviations: s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet. HRMS were recorded on an Agilent 6210 TOF-MS mass spectrometer equipped with an electrospray source. Purities were measured by injecting the compounds dissolved at about 1 mg/mL in acetonitrile on an Agilent 1100 HPLC system equipped with a DAD detector, and monitoring the chromatogram at 250 nm with a 100 nm bw (reference 375 nm, 5 nm bw), except where noted otherwise; a blank run was substracted. The column used was a Kinetex C_{18} 250 x 4.6 mm column (5 μm particle size, Phenomenex), maintained at 25 °C, with a gradient from 10 to 100 % acetonitrile (0.1 % formic acid) in water (0.1 % formic acid) in 12 minutes, with pure acetonitrile maintained for 3 further minutes, at 1 mL/min.

The DLD-1 human colorectal adenocarcinoma, A549 human lung carcinoma and WS1 human skin fibroblast cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cell lines were grown in minimum essential medium containing Earle's salt (Mediatech Cellgro, Herndon, VA, USA), supplemented with 10 % fetal calf serum (Hyclone, Logan, UT, USA), 1 × solution of vitamins, 1 × sodium pyruvate, 1 × non-essential amino acids, 100 I.U. of penicillin and 100 µg/mL of streptomycin (Mediatech Cellgro). Cells were cultured at 37 °C in a humidified atmosphere containing 5 % CO_2. Exponentially growing cells were plated at a density of 5 × 10^3 cells per well in 96-well microplates (BD Falcon) in culture medium (100 µL) and were allowed to adhere for 16 h before treatment. Then, cells were were incubated for 48 h in the presence or absence of 100 µL of increasing concentrations of compounds dissolved in culture medium and DMSO. The final concentration of DMSO in the culture medium was maintained at 0.5 % (v/v) to avoid toxicity. Cytotoxicity was assessed using Hoechst (bis-benzimide) (Rage et al., 1990). It was expressed as the concentration of drug inhibiting cell growth by 50 % (IC_{50}). For fluorescent visualization, a A-549 cells monolayer was incubated with 10 µM dirchromone (**1**) in phosphate buffer (PBS) for 4 h. The PBS was then removed, replaced with fresh PBS, and the cells were observed using a Cytation 3 imaging system (BioTek, Winooski, VT, USA) using a DAPI filter (exc. 377 nm, em. 447 nm).

2.8.2 Experimental procedures and characterization

Dirchromone (1):



1

This compound was prepared according to the published procedure (St-Gelais et al., 2018). Its HPLC purity was 99.7 %.

Enantiomeric separation

rac-Dirchromone was suspended in denatured reagent alcohol, HPLC grade, at a concentration of 33 mg/mL (almost saturated). This solution was injected by preparative HPLC (Shimadzu) in 250 µL portions onto a Lux® 5µm *i*-Amylose 1 semi-preparative column, 250 x 10.0 mm (Phenomenex, CA), eluting isocratically with 15 % denatured reagent alcohol (HPLC) in hexanes (HPLC) at a rate of 12 mL/min. The (−) enantiomer eluted first and collected separately; the (+) enantiomer was partly contaminated with tailing (−), and had to be repurified. The process was repeated until enough (+)-dirchromone was obtained. Enantiomeric excesses (Figure 2-5) were measured at 251 nm (100 nm bw) onto the same column, eluting isocratically with 20 % denatured reagent alcohol in hexanes, by injecting 10 µL of each enantiomer at a concentration of 5 mg/mL

(−)-Dirchromone (**(−)-1**). $[\alpha]_D^{20}$: -164.1 (c = 0.2, Acetone); *ee* (HPLC-UV) 92 %; HPLC purity 99.2 %.

(+)-Dirchromone (**(+)-1**). $[\alpha]_D^{20}$: +161.8 (c = 0.6, Acetone); *ee* (HPLC-UV) 98 %; HPLC purity 99.7 %.

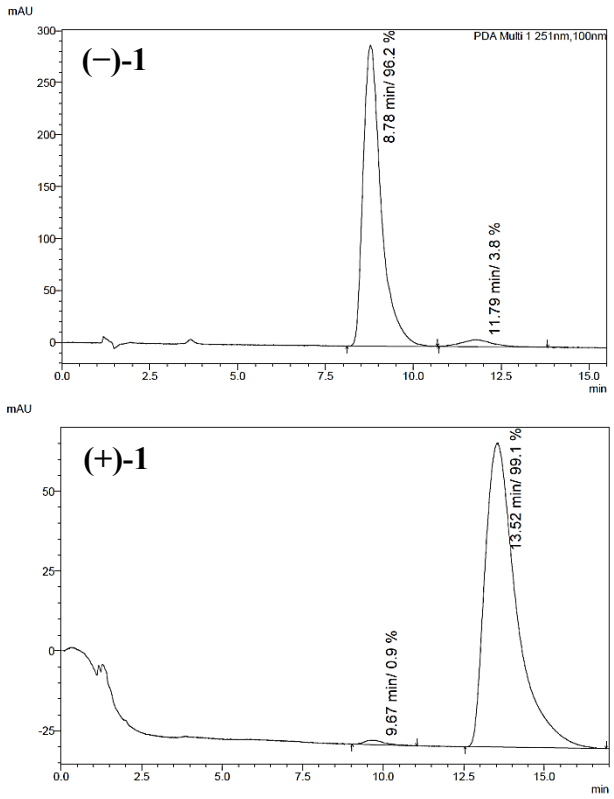
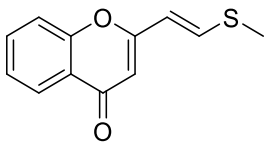


Figure 2-5. Enantiomeric excesses measured by chiral HPLC-UV for enantiomers of compound **1**.

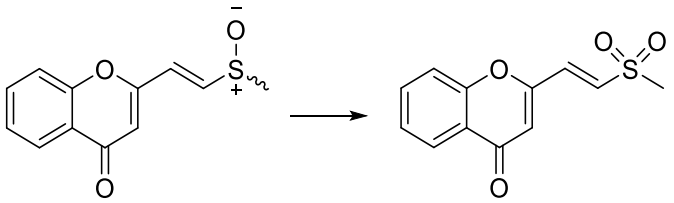
(*S*)-Deoxydirchromone (2a)



2a

(*S*)-Deoxydirchromone (**2a**) was prepared according to the published procedure (St-Gelais et al., 2018) as a red solid. The latter was repeatedly recrystallized from methanol to afford straw-coloured needles. Its HPLC purity was 99.8 %; contrarily to the other compounds, purity was evaluated at 275 nm (150 nm bw) from a solution at 2 mg/mL, owing to a significantly different UV absorption spectrum of **2** compared to the other analogs.

(*S*)-Oxodirchromone (3)

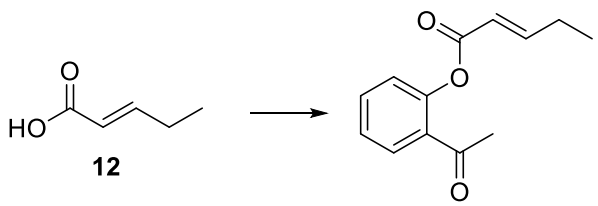


1 **3**

Dirchromone (**1**) (234 mg, 1.0 mmol) was stirred at room temperature in 2 mL acetic acid. Hydrogen peroxide 30 % (1.02 mL, 10 mmol) was added. After 18 h, saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with 3 × ethyl acetate. The combined organic phases were dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography with 10-50 % acetone in hexanes to afford compound **3** (201 mg, 80 % yield) as a white solid.

R_f = 0.46 (Hex/Act 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, *J* = 7.9, 1.6, 1H), 7.72 (ddd, *J* = 8.6, 7.3, 1.6, 1H), 7.47 (d, *J* = 8.4, 1H), 7.42 (ddd, *J* = 8.0, 7.2, 0,7, 1H), 7.41 (d, *J* = 15.1, 1H), 7.30 (d, *J* = 15.1 , 1H), 6.49 (s, 1H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9, 156.7, 155.8, 135.3, 134.9, 133.8, 126.0, 125.9, 124.1, 118.1, 116.1, 43.0; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}O_4S$ $[M+H]^+$ 251.0373, found 251.0374; HPLC purity 99.8 %.

2-Acetylphenyl (*E*)-pent-2-enoate (13)



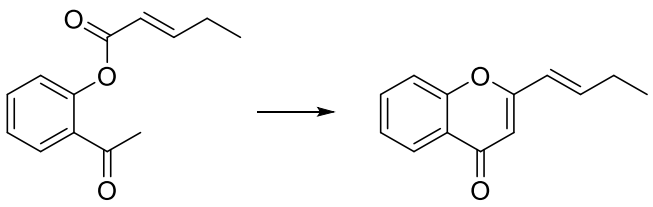
12 **13**

(2*E*)-Pentenoic acid **12** (2.65 g, 26.4 mmol) was dissolved in 10 mL anhydrous dichloromethane under argon atmosphere. After addition of 5 drops of dimethylformamide, oxalyl chloride (3.40 mL, 39.7 mmol) was added slowly, and the resulting mixture was stirred until no more gas evolved.

In a separate flask, 2'-hydroxyacetophenone (6.46 mL, 52.8 mmol) was suspended in 25 mL methanol and potassium hydroxide (2.96 g, 52.8 mmol) was added. When all of the base had dissolved, the solution was dried under reduced vacuum, and resuspended in 30 mL anhydrous dimethylformamide. The (2*E*)-pentenoyl chloride solution was then poured slowly into this solution, stirring vigorously. After 5 minutes stirring, saturated aqueous NH_4Cl was added, alongside 50 mL of ethyl acetate/toluene 1:1. The organic layer was decanted, washed with a further portion of NH_4Cl then brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography with 0-15 % ethyl acetate in hexanes to afford compound **13** (3.70 g, 64 % yield) as a yellow oil.

R_f = 0.59 (Hex/AcOEt 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (dd, *J* = 7.7, 1.3, 1H), 7.49 (td, *J* = 8.1, 1.5, 1H), 7.30 – 7.19 (m, 2H), 7.10 (d, *J* = 8.1, 1H), 6.04 (dt, *J* = 15.8, 1.6, 1H), 2.50 (s, 3H), 2.34 – 2.25 (m, 2H), 1.10 (t, *J* = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7, 164.8, 154.0, 149.1, 133.3, 131.3, 130.0, 125.9, 123.7, 119.3, 29.7, 25.5, 11.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_3Na$ $[M+Na]^+$ 241.0835, found 241.0836.

(*E*)-2-(but-1-en-1-yl)-4*H*-chromen-4-one (14)

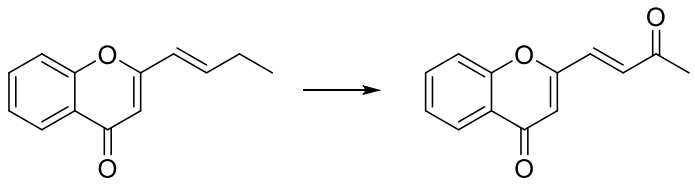


13 **14**

Ester **13** (3.7 g, 17.0 mmol) was stirred into 25 mL dichloromethane open to air. Magnesium bromide diethyl etherate (5.47 g, 21.2 mmol) was added, then diisopropylethylamine (4.4 mL, 25.4 mmol) was added slowly. The reaction was stirred overnight, then quenched by pouring 50 mL of 10 % HCl into the reaction vessel. Ethyl acetate (50 mL) was added, and the organic phase was decanted. The aqueous phase was extracted twice more with 10 mL ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was redissolved in 25 mL methanol, to which was added 6 mL of HCl 37 %. The reaction was stirred overnight, then quenched by pouring 50 mL of saturated $NaHCO_3$. The reaction mixture was then extracted with 3 × ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography with 0-50 % ethyl acetate in hexanes to afford compound **14** (930 mg, 27 %) as a yellow oil. It was noticed that another portion of the product has undergone addition of a methoxy residue to the double bond, lowering overall yield, and this byproduct was discarded.

R_f = 0.42 (Hex/AcOEt 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, J = 7.9, 1H), 7.30 (ddd, J = 8.4, 7.2, 1.4, 1H), 7.08 (d, J = 8.4, 1H), 7.02 (t, J = 7.5, 1H), 6.53 (dt, J = 15.7, 6.4, 1H), 5.83 (s, 1H), 5.78 (d, J = 15.7, 1H), 2.03 – 1.91 (m, 2H), 0.82 (t, J = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7, 161.2, 155.3, 142.2, 133.0, 124.8, 124.2, 123.3, 121.3, 117.3, 108.5, 25.4, 12.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_2$ $[M+H]^+$ 201.0910, found 201.0908.

(*E*)-2-(3-oxobut-1-en-1-yl)-4*H*-chromen-4-one (4)

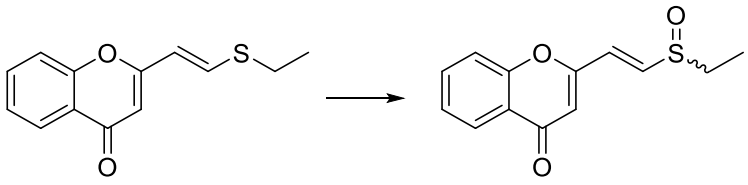


14 **4**

Inspired by a published procedure (Yu and Corey, 2003), compound **14** (479 mg, 2.4 mmol) was mixed with 169 mg 10 % coal-supported palladium hydroxide (0.12 mmol) and 83 mg (0.6 mmol) potassium carbonate, and vigorously stirred at room temperature in 7.5 mL dichloromethane, open to air. *Tert*-butyl hydrogen peroxide 70 % (1.65 mL, 12.0 mmol) was added. After 48 h, a further portion of 1.65 mL of *tert*-butyl hydrogen peroxide 70 % (12.0 mmol) was again added. After 72 h, the reaction mixture was filtered over celite and dried. The residue was purified by flash chromatography with 20-55 % ethyl acetate in hexanes to afford compound **4** (137 mg, 27 % yield) as a white solid.

R_f = 0.19 (Hex/AcOEt 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J = 7.9, 1H), 7.63 (t, J = 7.7, 1H), 7.41 (d, J = 8.4, 1H), 7.33 (t, J = 7.5, 1H), 7.03 (q, J = 15.9, 2H), 6.39 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.0, 178.0, 158.9, 155.8, 134.4, 133.8, 132.5, 125.6, 125.5, 123.9, 118.0, 114.8, 28.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{11}O_3$ $[M+H]^+$ 215.0703, found 215.0699; HPLC purity 93.7 %.

Homodirchromone (5)

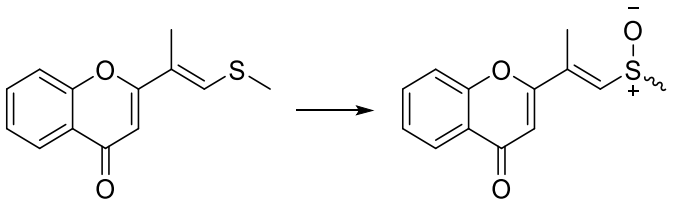


2b **5**

To (*E*)-2-(2-(ethylthio)vinyl)-4H-chromen-4-one (**2b**) (90 mg, 0.39 mmol) prepared according to the published procedure (St-Gelais et al., 2018) and dissolved in 5 mL dichloromethane open to air was added *meta*-chloroperbenzoic acid 75 % (89 mg, 0.39 mmol). The reaction was stirred overnight. The dried residue was purified by flash chromatography with 0-35 % acetone in dichloromethane to afford compound **5** (64 mg, 67 %) as an off-white solid.

R_f = 0.34 (Hex/Act 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 7.9, 1H), 7.64 (t, *J* = 7.8, 1H), 7.48 – 7.39 (m, 2H), 7.35 (t, *J* = 7.5, 1H), 6.94 (d, *J* = 14.9, 1H), 6.32 (s, 1H), 3.01 (dq, *J* = 14.6, 7.4 Hz, 1H), 2.76 (dq, *J* = 14.3, 7.4, 1H), 1.32 (t, *J* = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3, 158.1, 155.8, 139.7, 134.3, 128.1, 125.7, 125.4, 123.9, 117.9, 112.9, 46.4, 5.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_3S$ $[M+H]^+$ 249.0580, found 249.0575; HPLC purity 99.7 %.

11-Methyldirchromone (6)

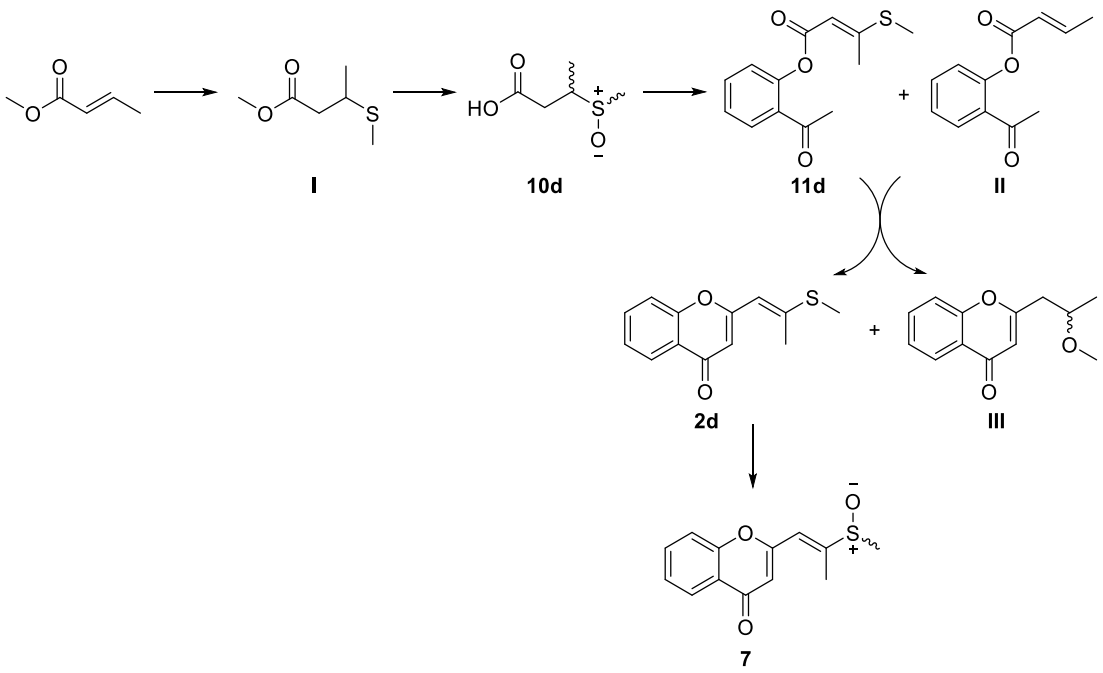


2c **6**

11-methyldeoxydirchromone (**2c**) (165 mg, 0.71 mmol), prepared as described previously (St-Gelais et al., 2018), was dissolved in 10 mL dichloromethane open to air. To this solution was added *meta*-chloroperbenzoic acid 75 % (163 mg, 0.71 mmol), and the resulting solution was stirred overnight. The dried residue was purified by flash chromatography with 5-50 % acetone in dichloromethane to afford compound **6** (124 mg, 70 %) as a beige solid.

R_f = 0.18 (Hex/Act 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (dd, *J* = 7.9, 1.3, 1H), 7.60 (ddd, *J* = 8.6, 7.3, 1.3, 1H), 7.37 (d, *J* = 8.6, 1H), 7.30 (t, *J* = 7.5, 1H), 7.24 (s, 1H), 6.41 (s, 1H), 2.71 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 159.8, 155.6, 139.2, 137.0, 134.4, 125.5, 125.4, 123.4, 117.9, 110.3, 40.2, 14.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_3S$ $[M+H]^+$ 249.0580, found 249.0575; HPLC purity 98.1 %.

12-Methyldirchromone (7)



To a solution of methyl crotonate (479 µL, 4.5 mmol) in 50 mL water was added *S*-methylthiourea (1.26 g, 4.5 mmol) and sodium hydroxide (452 mg, 11.3 mmol). The reaction was stirred 30 min, then more sodium hydroxide (542 mg, 13.5 mmol) was added and the reaction was heated at 60 °C for 30 min. The reaction was quenched with an excess of 37 % aqueous HCl, and the reaction was extracted with 2 × ethyl acetate. The combined organic phases were dried over Na_2SO_4 and evaporated to dryness to afford 623 mg of a yellow oil of the intermediate sulfide **I**, which was used as is (without further purification) for the next step.

A) The residue was resuspended in 20 mL water + 5 mL methanol, and 508 µL 30 % aqueous hydrogen peroxide (5.0 mmol) was added. The reaction was stirred overnight and evaporated to dryness to afford intermediate sulfoxide **10d** (626 mg) as a colorless oil, which was used as is (without further purification) for the ensuing steps.

B) To a solution of sulfoxide **10d** (626 mg, 4.2 mmol) in dry dichloromethane (15 mL) containing a drop of dry dimethylformamide was slowly added oxalyl chloride (714 µL, 8.3 mmol) under argon atmosphere. The solution was stirred at room temperature for approximately 1h30, or until no more gas was evolving.

C) In a separate flask, 2'-hydroxyacetophenone (2.1 mL, 16.7 mmol) was mixed to ACS grade methanol (15 mL). To this solution was added potassium hydroxide (934 mg, 16.7 mmol), and the resulting solution was sonicated until all the base was dissolved. This solution was then thoroughly evaporated under reduced pressure and dried at 10 mbar. The resulting solid was then dissolved in 5 mL of dry dimethylformamide under argon atmosphere.

D) Solution A) was transferred dropwise to solution B) with vigorous stirring. After 10 minutes, the reaction was quenched with NH_4Cl, and extracted with ethyl acetate/toluene 1:1. The organic phase was washed with 3 × NH_4Cl, 1 × brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford 401 mg of a mixture of two intermediate esters **11d** and **II** in an approximate 6:4 proportion which could not be readily separated. These were thus engaged together in the ensuing step.

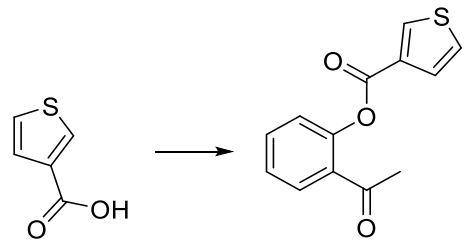
E) Esters **11d** and **II** were suspended in 15 mL ACS grade dichloromethane open to air, and 1.03 g (4.0 mmol) magnesium bromide diethyl etherate was added.

The resulting suspension was stirred for 2 minutes, and diisopropylethylamine (832 μL, 4.8 mmol) was added. The reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 15 mL of HCl 10 % into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The dried residue was then dissolved in 25 mL of ACS grade methanol. Concentrated HCl (3.0 mL) was then added, and the solution was stirred overnight. The reaction was quenched by pouring 30 mL of saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography with 15-25 % ethyl acetate in hexanes to 147 mg of an unresolved mixture of chromones **2d** and **III** in an approximate 4:6 ratio which could not be readily separated. These were thus engaged together in the ensuing step.

F) Chromones **2d** and **III** were suspended in 10 mL ACS grade dichloromethane open to air, and 64 mg of *meta*-chloroperbenzoic acid 75 % (0.28 mmol) was added. The reaction was stirred overnight and evaporated to dryness. The residue was purified by flash chromatography with 0-65 % acetonitrile in dichloromethane to afford 12-methyldirchromone **7** (71 mg, 6.3 % overall yield from methyl crotonate) as an off-white solid.

R_f = 0.21 (Hex/Act 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, J = 7.9, 1.5, 1H), 7.68 (ddd, J = 8.4, 7.1, 1.5, 1H), 7.44 (d, J = 8.4, 1H), 7.40 (t, J = 7.6, 1H), 6.84 (s, 1H), 6.38 (s, 1H), 2.67 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3, 160.5, 156.0, 152.3, 134.2, 125.9, 125.6, 124.0, 120.9, 118.0, 113.7, 39.1, 13.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}O_3S$ $[M+H]^+$ 249.0580, found 249.0580; HPLC purity 98.8 %.

2-Acetylphenyl thiophene-3-carboxylate (16)



15 **16**

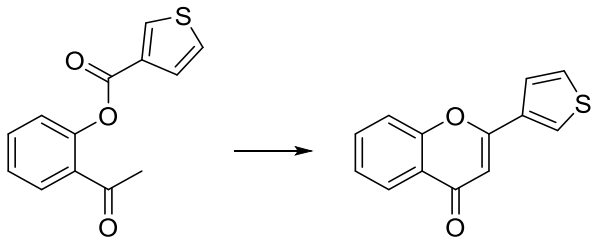
Thiophene-3-carboxylic acid (**15**) (254 mg, 2.0 mmol) was dissolved in 8 mL anhydrous dichloromethane under argon atmosphere. After addition of 2 drops of dimethylformamide, oxalyl chloride (340 µL, 4.0 mmol) was added slowly, and the resulting mixture was stirred until no more gas evolved.

In a separate flask, 2'-hydroxyacetophenone (969 µL, 7.9 mmol) was suspended in 5 mL methanol and potassium hydroxide (444 mg, 7.9 mmol) was added. When all the base had dissolved, the solution was dried under reduced vacuum, and resuspended in 8 mL anhydrous dimethylformamide. The thiophene-3-carboxyloyl chloride solution was then poured slowly into this solution, stirring vigorously. After 5 minutes stirring, saturated aqueous NH_4Cl was added, alongside 20 mL of ethyl acetate/toluene 1:1. The organic layer was decanted, washed with a further portion of NH_4Cl then brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography with 0-15 % ethyl acetate in hexanes to afford compound **16** (402 mg, 82 % yield) as a white solid.

R_f = 0.71 (Hex/AcOEt 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (dd, *J* = 2.9, 1.0, 1H), 7.85 (dd, *J* = 7.8, 1.3, 1H), 7.67 (dd, *J* = 5.1, 0.9, 1H), 7.57 (td, *J* = 7.9, 1.5, 1H), 7.39 (dd, *J* = 5.0, 3.1, 1H), 7.35 (t, *J* = 7.6, 1H), 7.23 (d, *J* = 8.1, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7, 160.9, 149.1, 134.6, 133.5, 132.5, 131.4, 130.3, 128.3,

126.7, 126.3, 124.0, 29.9; HRMS (ESI) *m/z* calcd for $C_{26}H_{20}NaO_6S_2$ $[2M+Na]^+$ 515.0594, found 515.0595.

2-(Thiophen-3-yl)-4H-chromen-4-one (8)

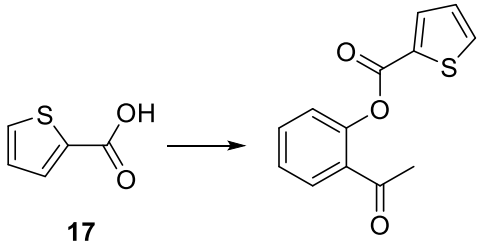


Ester **16** (390 mg, 1.6 mmol) was stirred into 10 mL dichloromethane open to air. Magnesium bromide diethyl etherate (1020 mg, 4.0 mmol) was added, then diisopropylethylamine (822 µL, 4.8 mmol) was added slowly. The reaction was stirred overnight, then quenched by pouring 20 mL of 10 % HCl into the reaction vessel. Ethyl acetate (20 mL) was added, and the organic phase was decanted. The aqueous phase was extracted twice more with 10 mL ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was redissolved in 10 mL methanol, to which was added 2 mL of HCl 37 %. The reaction was stirred overnight, then quenched by pouring 30 mL of saturated $NaHCO_3$. The reaction mixture was then extracted with 3 × ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography with 10-30 % ethyl acetate in hexanes to afford compound **8** (286 mg, 79 %) as an off-white solid.

R_f = 0.45 (Hex/AcOEt 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, J = 7.9, 1.5, 1H), 7.97 (dd, J = 2.8, 1.2, 1H), 7.63 (ddd, J = 8.6, 7.4, 1.6, 1H), 7.47 (d, J = 8.3, 1H), 7.44 – 7.38 (m, 2H), 7.35 (t, J = 7.5, 1H), 6.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:

178.4, 159.5, 156.0, 134.1, 133.7, 127.4, 126.9, 125.6, 125.2, 125.0, 123.9, 118.0, 107.1; HRMS (ESI) *m/z* calcd for $C_{13}H_9O_2S$ $[M+H]^+$ 229.0318, found 229.0316.

2-Acetylphenyl thiophene-2-carboxylate (18)



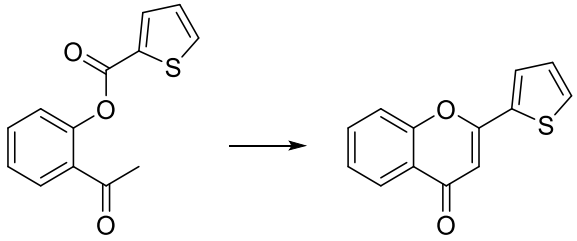
Thiophene-2-carboxylic acid (**17**) (263 mg, 2.1 mmol) was dissolved in 8 mL anhydrous dichloromethane under argon atmosphere. After addition of 2 drops of dimethylformamide, oxalyl chloride (352 µL, 4.1 mmol) was added slowly, and the resulting mixture was stirred until no more gas evolved.

In a separate flask, 2'-hydroxyacetophenone (1005 µL, 8.2 mmol) was suspended in 5 mL methanol and potassium hydroxide (461 mg, 8.2 mmol) was added. When all the base had dissolved, the solution was dried under reduced vacuum, and resuspended in 8 mL anhydrous dimethylformamide. The thiophene-2-carboxyloyl chloride solution was then poured slowly into this solution, stirring vigorously. After 5 minutes stirring, saturated aqueous NH_4Cl was added, alongside 20 mL of ethyl acetate/toluene 1:1. The organic layer was decanted, washed with a further portion of NH_4Cl then brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography with 0-15 % ethyl acetate in hexanes to afford compound **18** (407 mg, 81 % yield) as a white solid.

R_f = 0.41 (Hex/Act 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (dd, *J* = 3.7, 1.1, 1H), 7.85 (dd, *J* = 7.8, 1.3, 1H), 7.69 (dd, *J* = 5.0, 1.0, 1H), 7.57 (td, *J* = 8.1, 1.5, 1H), 7.36

(td, J = 7.7, 0.9, 1H), 7.25 (d, J = 7.4, 1H), 7.19 (dd, J = 4.9, 3.9, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7, 160.5, 149.0, 135.3, 134.1, 133.5, 132.5, 131.4, 130.4, 128.3, 126.4, 124.0, 30.1; HRMS (ESI) *m/z* calcd for $C_{26}H_{20}NaO_6S_2$ $[2M+Na]^+$ 515.0594, found 515.0597.

2-(Thiophen-2-yl)-4H-chromen-4-one (9)



18 **9**

Ester **18** (387 mg, 1.6 mmol) was stirred into 10 mL dichloromethane open to air. Magnesium bromide diethyl etherate (1015 mg, 3.9 mmol) was added, then diisopropylethylamine (816 µL, 4.7 mmol) was added slowly. The reaction was stirred overnight, then quenched by pouring 20 mL of 10 % HCl into the reaction vessel. Ethyl acetate (20 mL) was added, and the organic phase was decanted. The aqueous phase was extracted twice more with 10 mL ethyl acetate. The combined organic phases were dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was redissolved in 10 mL methanol, to which was added 2 mL of HCl 37 %. The reaction was stirred overnight, then quenched by pouring 30 mL of saturated $NaHCO_3$. The reaction mixture was then extracted with 3 × ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography with 10-30 % ethyl acetate in hexanes to afford compound **9** (311 mg, 87 %) as a yellow solid.

R_f = 0.40 (Hex/Act 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (dd, J = 7.9, 1.3, 1H), 7.69 – 7.58 (m, 2H), 7.51 (d, J = 5.0, 1H), 7.45 (d, J = 8.4, 1H), 7.35 (t, J = 7.5, 1H),

7.12 (dd, J = 4.9, 3.9, 1H), 6.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 159.0, 155.8, 135.0, 133.7, 130.3, 128.50, 128.46, 125.6, 125.2, 123.9, 117.9, 106.1; HRMS (ESI) *m/z* calcd for $C_{13}H_9O_2S$ $[M+H]^+$ 229.0318, found 229.0318.

Reaction products of dirchromone and cysteamine

A chromatographic profile (Figure 2-6) was established by dissolving 5 mg of dirchromone in 1 mL dimethylsulfoxide and adding 7 mg of cysteamine. After a few minutes, the reaction mixture was directly injected on the HPLC system described in the general experimental procedures for purity determinations, using the same column and gradient.

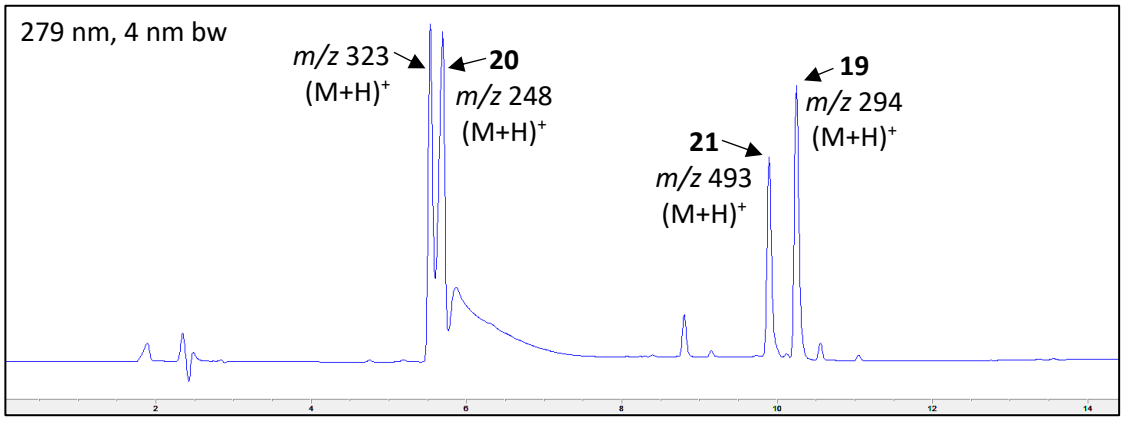
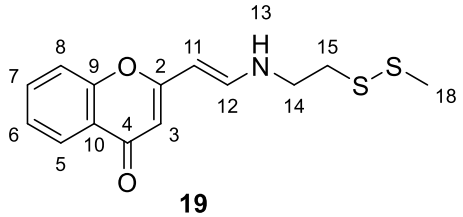


Figure 2-6. Chromatographic profile of the fresh reaction of dirchromone with 4 equiv cysteamine in dimethylsulfoxide.

To dirchromone (150 mg, 0.64 mmol) suspended in dimethylsulfoxide (2 mL) was added cysteamine (198 mg, 2.6 mmol). The solution was sonicated until all cysteamine was dissolved, which was accompanied by evolution of a mercaptan-like odour and a brownish colour. The reaction mixture was diluted with 25 mL ethyl acetate and washed with 2 × brine and evaporated to dryness. The residue was purified by column chromatography with 15-100 % isopropanol in toluene to afford compounds **19-21**. Given partial peak overlaps and tailing of some compounds, the peaks were not fully

recovered, and efforts were chiefly made to characterize compounds rather than to establish yields.

(*E*)-2-(2-((2-(Methyldisulfaneyl)ethyl)amino)vinyl)-4H-chromen-4-one (19)



19

R_f = 0.54 (Tol/iPA 4:1; blue fluorescence under 365 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (dd, *J* = 7.9, 1.5, H-5), 7.55 (ddd, *J* = 8.6, 7.2, 1.7, H-7), 7.48 (dd, *J* = 13.4, 8.0, H-12), 7.33 (d, *J* = 8.3, H-8), 7.30 (ddd, *J* = 8.0, 7.1, 0.9, H-6), 5.92 (s, H-3), 5.14 (d, *J* = 13.5, H-11), 3.52 (dd, *J* = 12.3, 6.1, H-14), 2.91 (t, *J* = 6.3, H-15), 2.43 (s, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7 (C-4), 166.0 (C-2), 155.8 (C-9), 142.5 (C-12), 132.7 (C-7), 125.6 (C-5), 124.4 (C-6), 124.2 (C-10), 117.2 (C-8), 103.7 (C-3), 90.2 (C-11), 42.6 (C-14), 36.0 (C-15), 23.2 (C-18); HRMS (ESI) *m/z* calcd for $C_{14}H_{16}NO_2S_2$ $[M+H]^+$ 294.0617, found 294.0621.

Compound **19** was isolated as a yellow film, and found to correspond to the formula $C_{14}H_{15}NO_2S_2$ based on the LC-MS-APCI peak $[M+H]^+$ pseudomolecular ion peak at *m/z* = 294. The 2-substituted chromone moiety could readily be assigned on the basis of the analogous structures, with the characteristic olefinic H-3 methine being more shielded than in dirchromone analogs. The latter predictably correlated in HMBC with C-4, C-2, C-10 and C-11, which was also quite upfield compared to dirchromones. H-11 and H-12 were part of a spin system, with H-12 showing as a doubled doublet whose coupling constants indicated a (*E*) olefin and further interaction with another proton (concluded to be from the amine). Additionally, H-12 featured a HMBC correlation with the shielded signals of methylene C-14 (showing as a weak peak in 1D

experiments, but clearly legible from 2D cross-couplings). H-14 and H-15 are part of a separate spin system. At this point, a strongly shielded methyl (C-18) was left, with no correlation to any other signal of the NMR experiments, alongside the two sulfur atoms: it was therefore concluded that this likely arose from a disulfide bridge, which was consistent with observed chemical shifts. The key correlations are depicted in Figure 2-7.

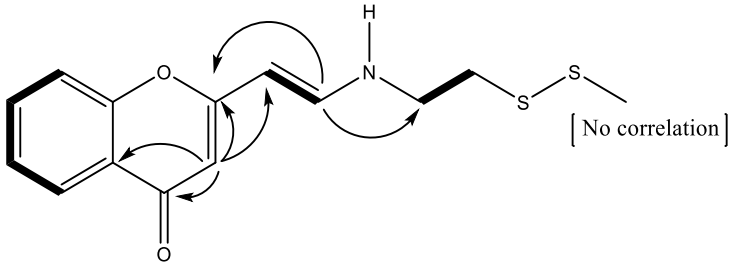
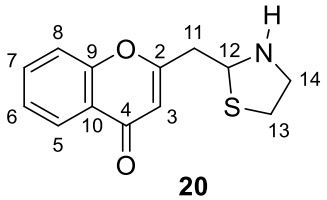


Figure 2-7. DQF-COSY correlations (in bold) and key HMBC correlations (arrows, H→C) used to elucidate the structure of compound **19**.

2-(Thiazolidin-2-ylmethyl)-4*H*-chromen-4-one (20)



20

R_f = 0.37 (Tol/iPA 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, *J* = 8.0, 1.4, H-5), 7.65 (ddd, *J* = 8.6, 7.2, 1.7, H-7), 7.43 (d, *J* = 8.5, H-8), 7.39 (ddd, *J* = 8.0, 7.2, 0.9, H-6), 6.28 (s, H-3), 4.95 (t, *J* = 6.9 Hz, H-12), 3.41 (dt, *J* = 12.4, 5.8, H-14a), 3.16 (dd, *J* = 12.7, 6.5, H-14b), 3.08 (d, *J* = 7.4, H-11a), 3.04 (d, *J* = 6.4, H-11b), 3.02 – 2.97 (m, H-13); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3 (C-4), 165.7 (C-2), 156.6 (C-9), 133.7 (C-7), 125.9 (C-5), 125.3 (C-6), 124.0 (C-10), 118.1 (C-8), 111.5 (C-3), 67.8 (C-12), 51.9 (C-14), 41.9 (C-11), 36.1 (C-13); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}NO_2S$ $[M+H]^+$ 248.0740, found 248.0736.

Compound **20** was isolated as a white solid and found to correspond to the formula $C_{13}H_{13}NO_2S$ based on the LC-MS-APCI peak $[M+H]^+$ pseudomolecular ion peak at *m/z* = 248. As for compound **19**, the chromone moiety was easily assigned by analogy with other derivatives. Olefinic H-3 showed HMBC correlations with C-4, C-10, C-2 and C-11, the latter corresponding to a methylene and therefore saturated compared to the parent structure. H-11 was part of a spin system with the methine H-12, and the latter was likely chiral given the differentiation in signals associated to the two protons H-11. Two other vicinal methylenes, H-13 and H-14, both exhibited HMBC correlation with C-11. Based on the structure of compound **19**, it was envisioned that compound **20** could arise from the Michael addition of the terminal thiol of cysteamine on the lateral chain alkene instead of its reduction with another thiol in the reaction media, suggesting a structure that was consistent with observed correlations. Methylenes H-13 and H-14 were respectively assigned based on their shielding, with the proximity of the amine leading to downfield signals for position 14. The key correlations are depicted in Figure 2-8.

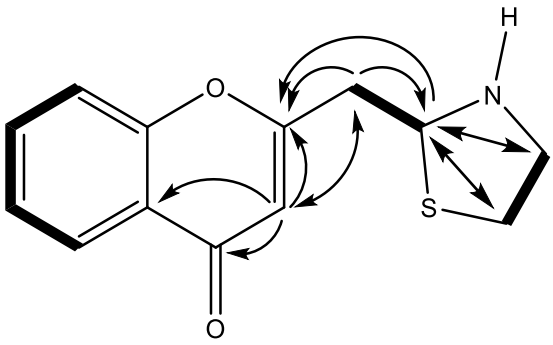
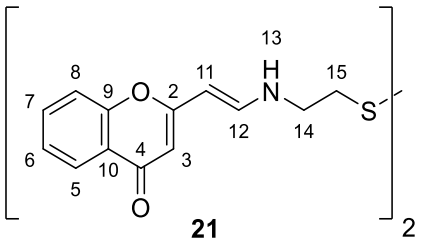


Figure 2-8. DQF-COSY correlations (in bold) and key HMBC correlations (arrows, H→C) used to elucidate the structure of compound **20**.

2,2'-((1*E*,1'*E*)-((disulfanediylbis(ethane-2,1-diyl))bis(azanediyl))bis(ethene-2,1-diyl))bis(4*H*-chromen-4-one) (21)



R_f = 0.28 (Tol/iPA 4:1; blue fluorescence under 365 nm); ^{1}H NMR (400 MHz, C_6D_5N) δ: 8.48 (dd, *J* = 8.0, 2.0, H-5), 7.88 (dd, *J* = 13.5, 8.0, H-12), 7.51 (ddd, *J* = 8.3, 7.1, 1.9, H-7), 7.35 (dd, *J* = 8.2, 1.9, H-8), 7.29 (ddd, *J* = 8.0, 7.1, 1.4, H-6), 6.30 (s, H-3), 5.39 (d, *J* = 13.5, H-11), 3.52 (m, H-14), 3.07 (t, *J* = 6.5, H-15); ^{13}C NMR (100 MHz, C_6D_5N) δ: 176.7 (C-4), 167.1 (C-2), 156.1 (C-9), 144.1* (C-12), 132.7 (C-7), 125.6 (C-5), 124.9 (C-10), 124.5 (C-6), 117.6 (C-8), 102.7 (C-3), 88.3 (C-11), 43.0* (C-14), 37.2* (C-15); HRMS (ESI) *m/z* calcd for $C_{26}H_{25}N_2O_4S_2$ $[M+H]^+$ 493.1250, found 493.1262.

**Not visible in DEPT135 owing to peak broadening; visible in 2D experiments*

Compound **21** was isolated as a yellow solid and found to correspond to the formula $C_{26}H_{24}N_2O_4S_2$ based on the LC-MS-APCI peak $[M+H]^+$ pseudomolecular ion peak at *m/z* = 493. As for compounds **19-20**, the chromone moiety was easily assigned by analogy with other derivatives. The compound was only poorly soluble in both deuterated DMSO and pyridine, and the side-chain carbon signals did not relax well. Nevertheless, 2D NMR experiments cross peaks allowed to situate them satisfactorily. Examination of the correlations pointed toward a similar structure to **19**, without the lone methyl group at the end of the sidechain. Based on the molecular mass, it was concluded that **21** was a symmetrical dimer assembled by a central disulfide bridge,

which was consistent with the other structures. The key correlations are depicted in Figure 2-9.

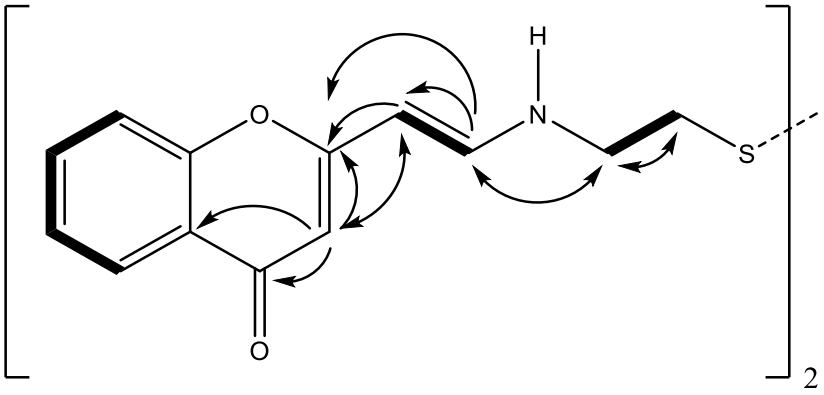


Figure 2-9. DQF-COSY correlations (in bold) and key HMBC correlations (arrows, H→C) used to elucidate the structure of compound **21**.

2.8.3 References

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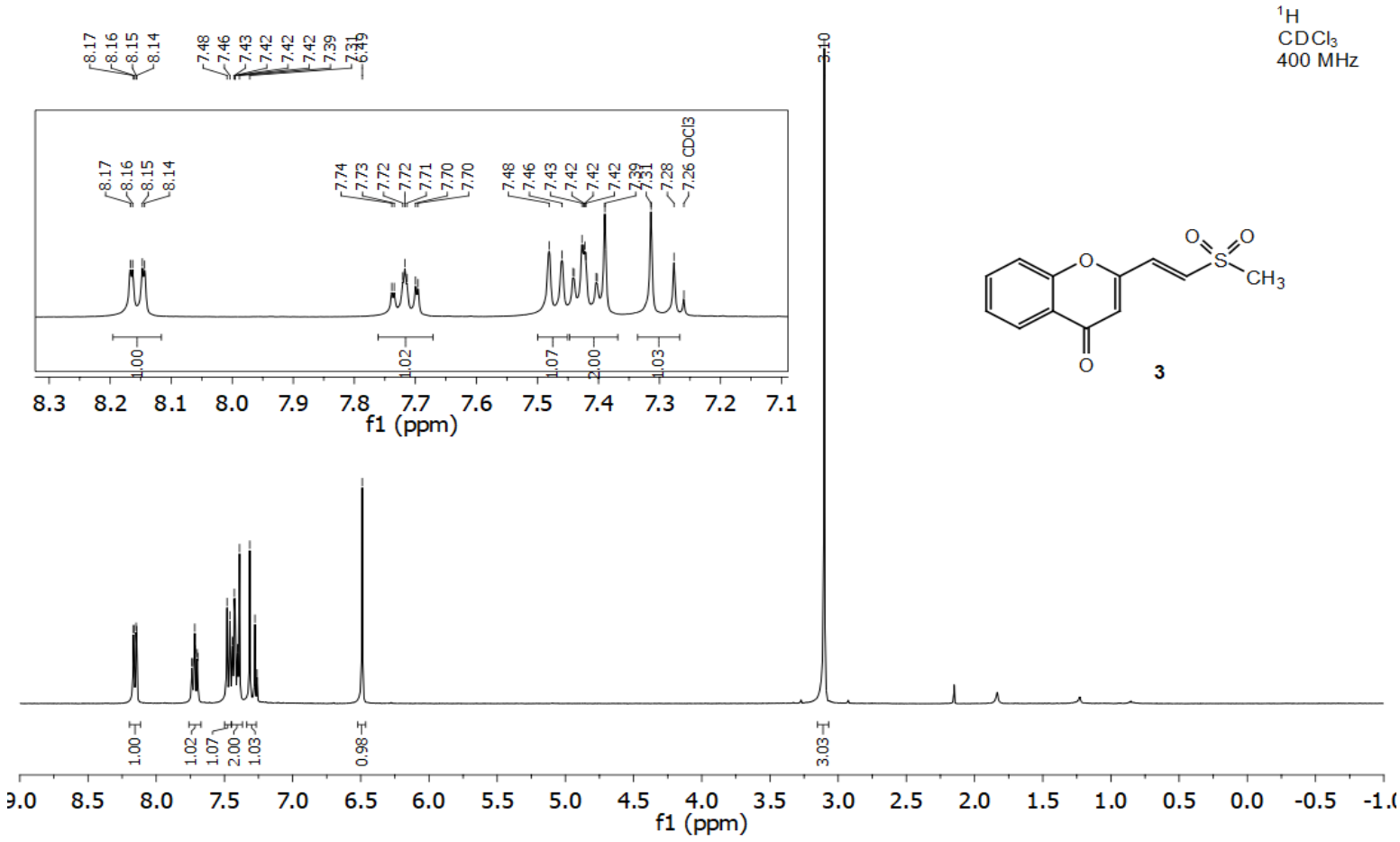
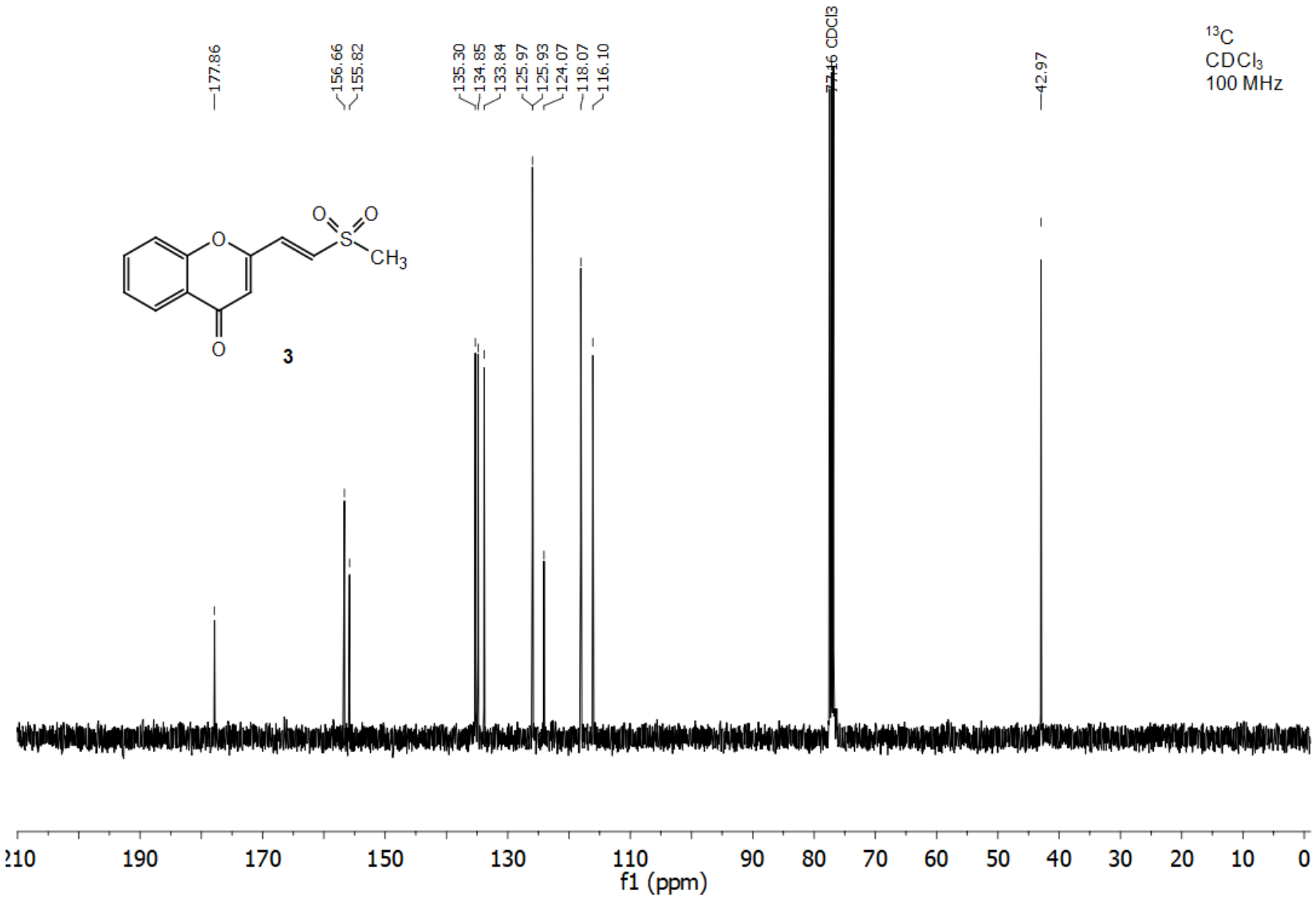
Yu, J.-Q., Corey, E.J., 2003. A mild, catalytic, and highly selective method for the oxidation of α,β-enones to 1,4-enediones. J. Am. Chem. Soc. 125, 3232–3233. https://doi.org/10.1021/ja0340735

2.8.4 NMR spectra

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116.10
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13C
CDCl3
100 MHz
O
O
O
S
CH3
O
3
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170
150
130
110
90
80
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50
40
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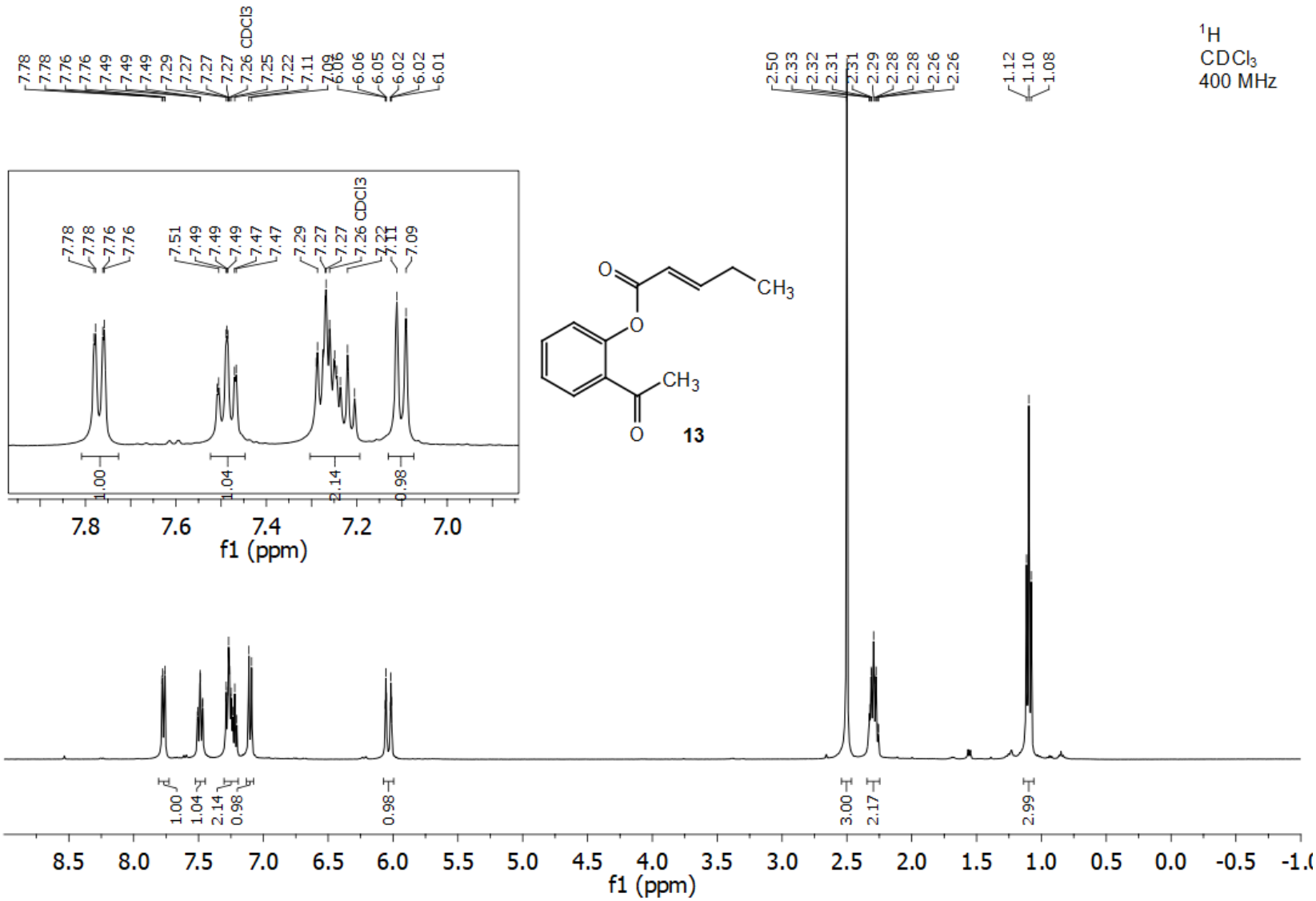
0
f1 (ppm)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$CDCl_3$
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CDCl3
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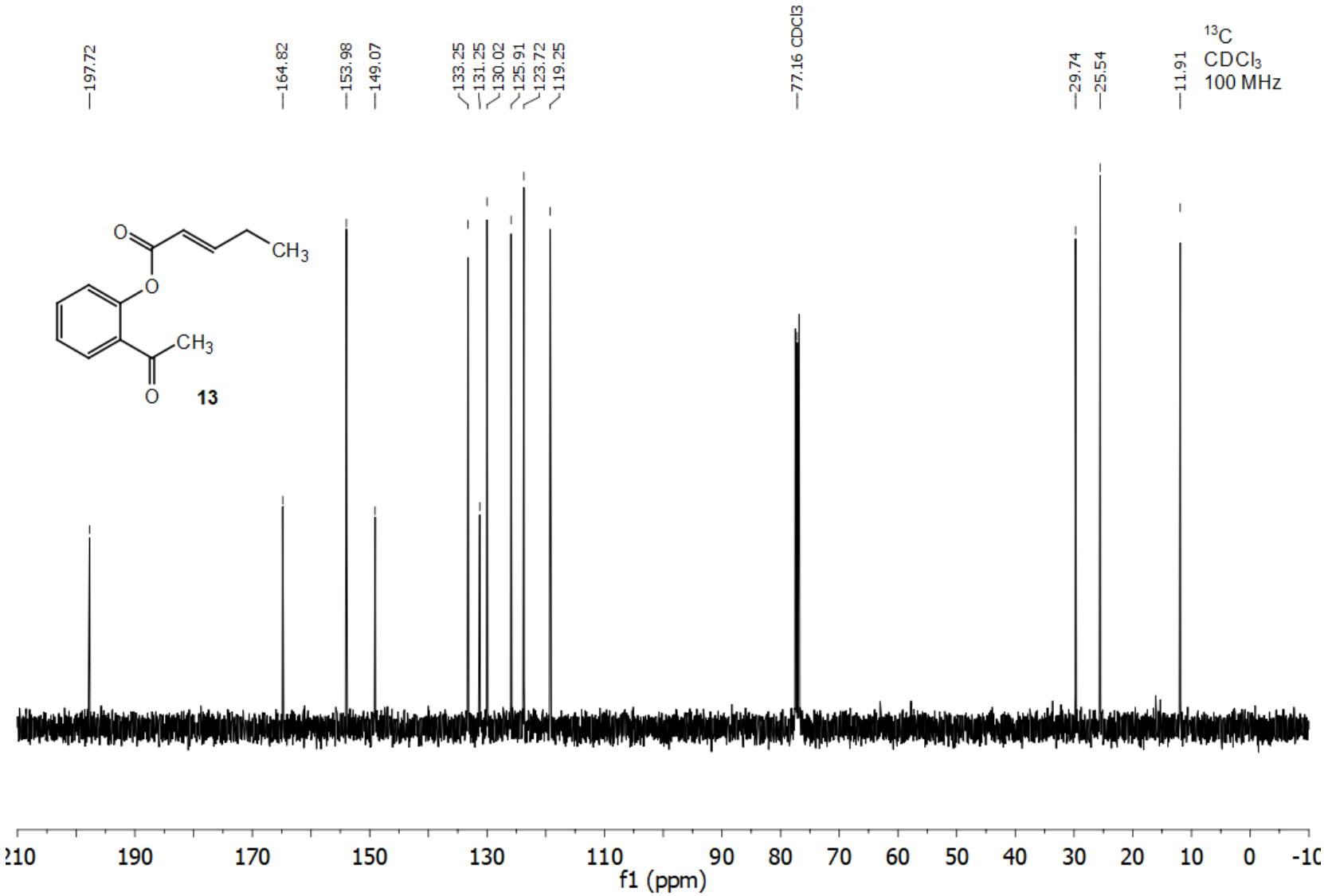
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100 MHz
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O
CH3
O
CH3
O
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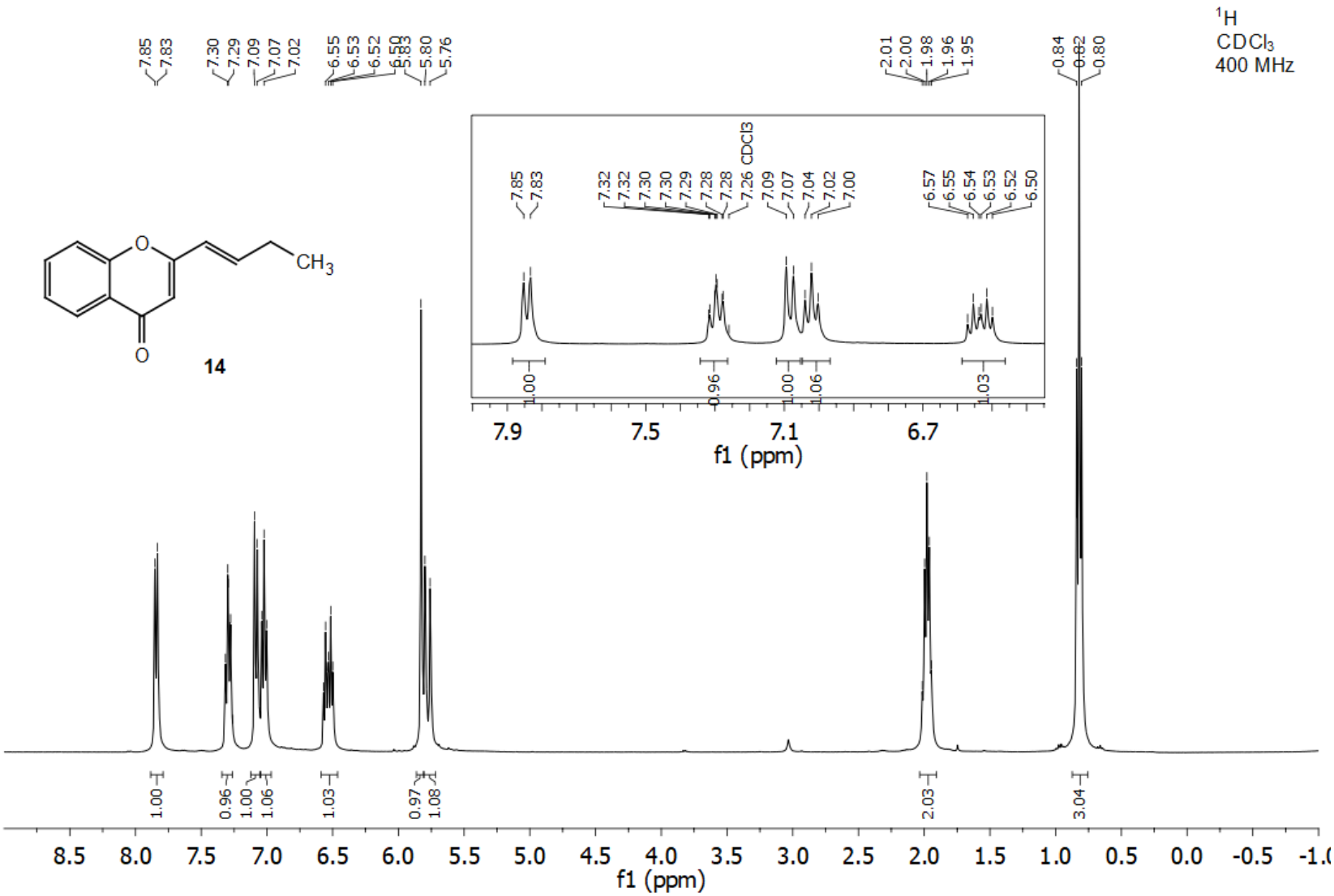
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6.50
6.83
5.80
5.76
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2.00
1.98
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1.95
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0.80
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7.32
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7.29
7.28
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4.0
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3.0
2.5
2.0
1.5
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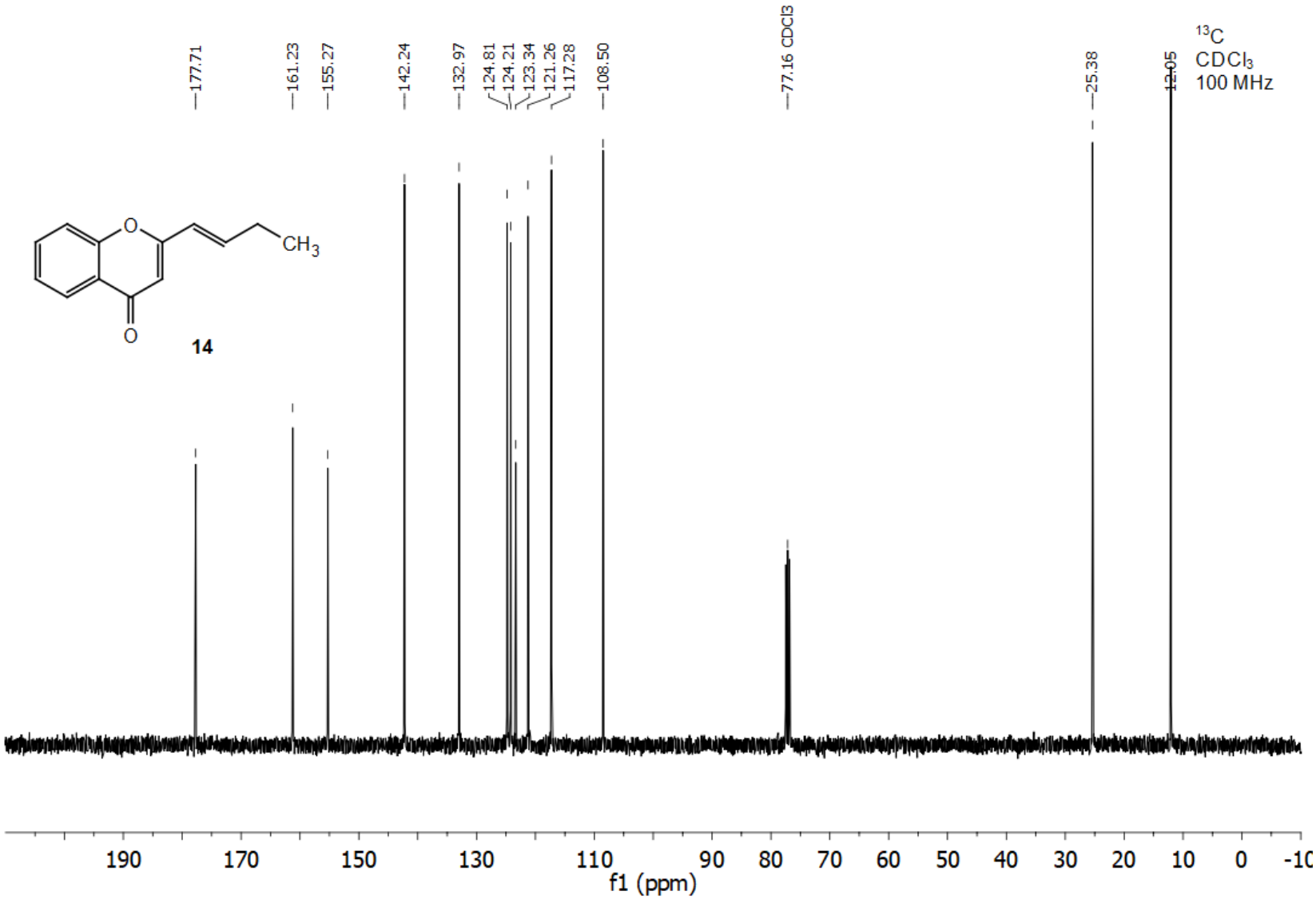
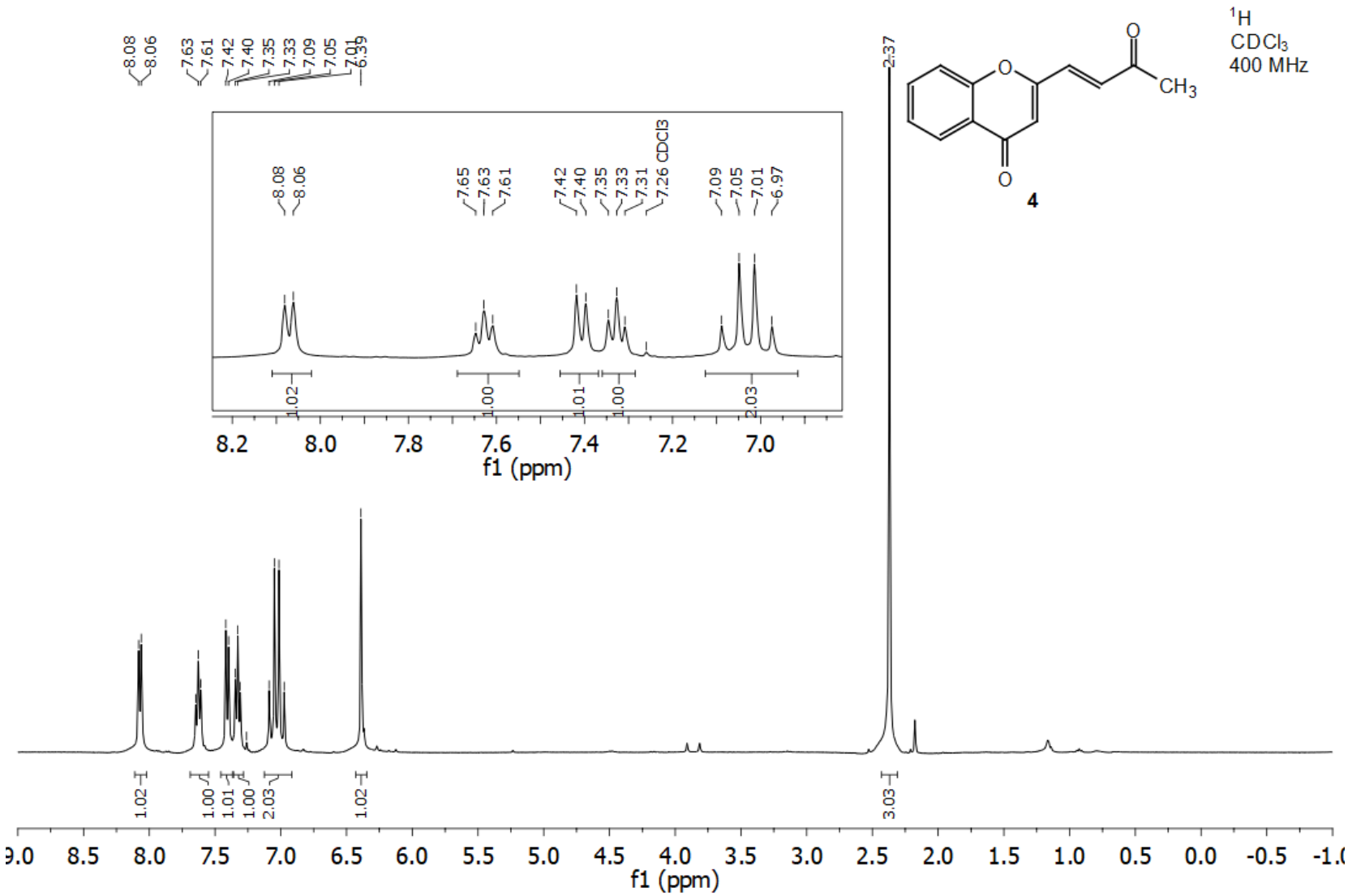
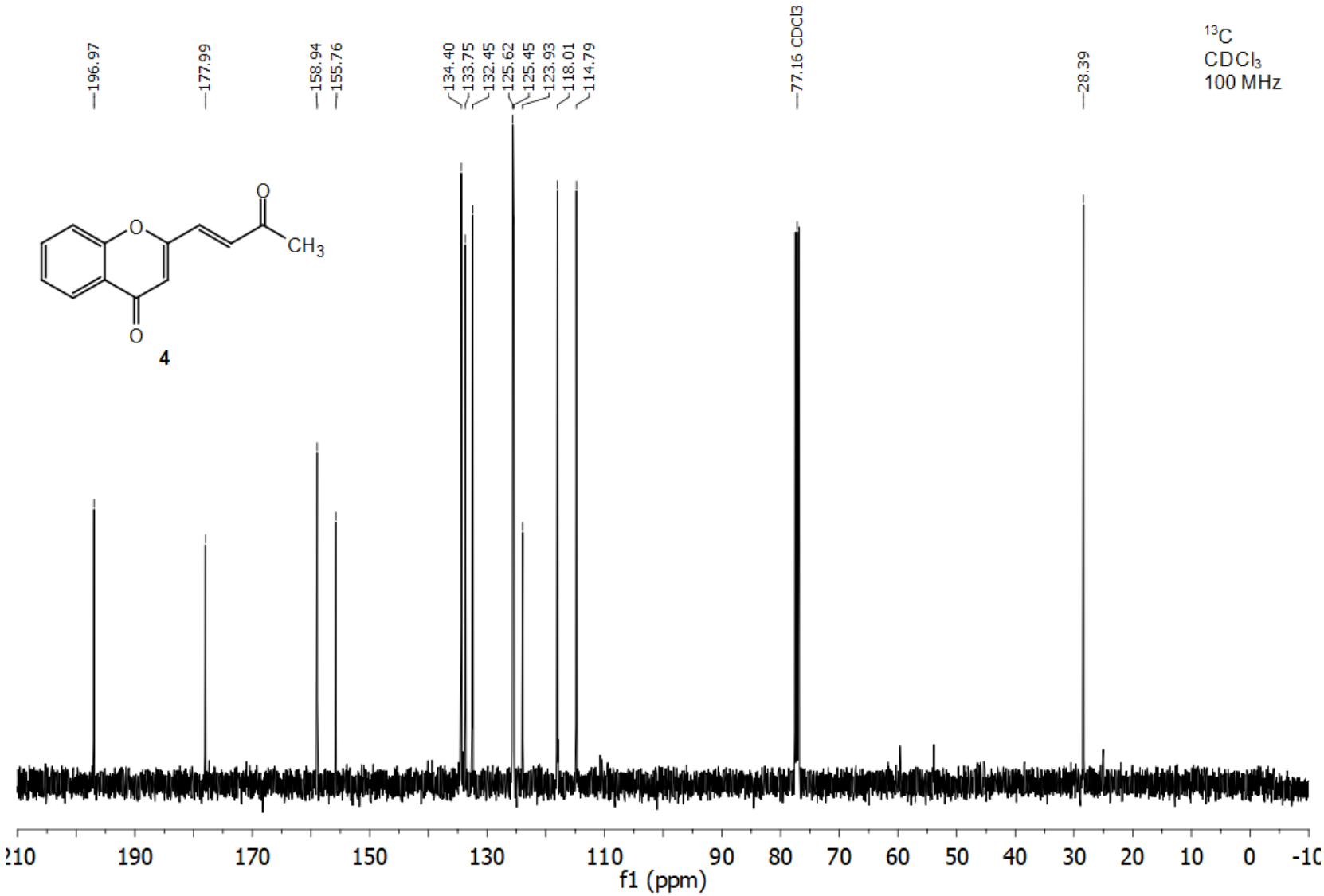
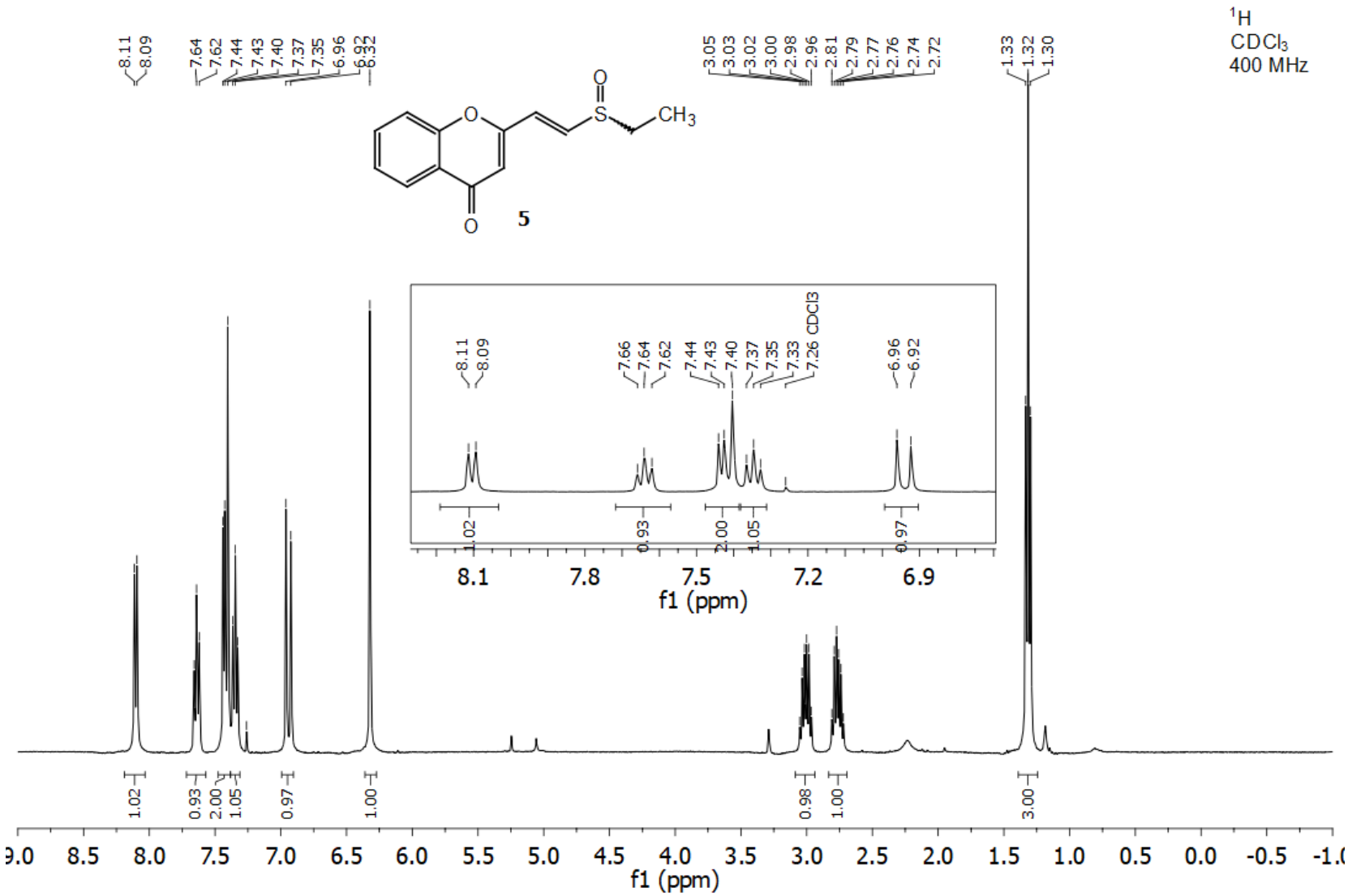
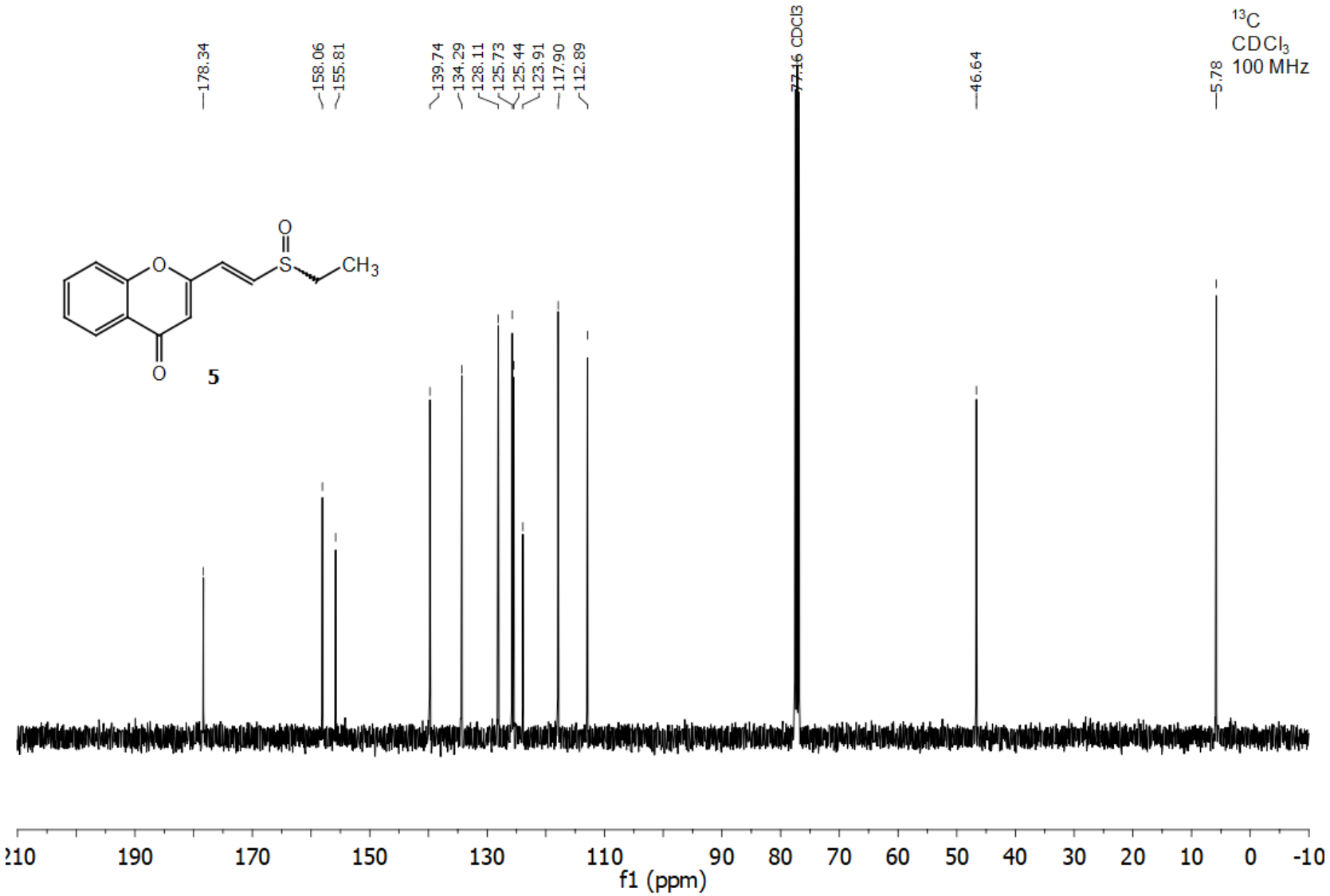
0.5
0.0
-0.5
f1 (ppm)

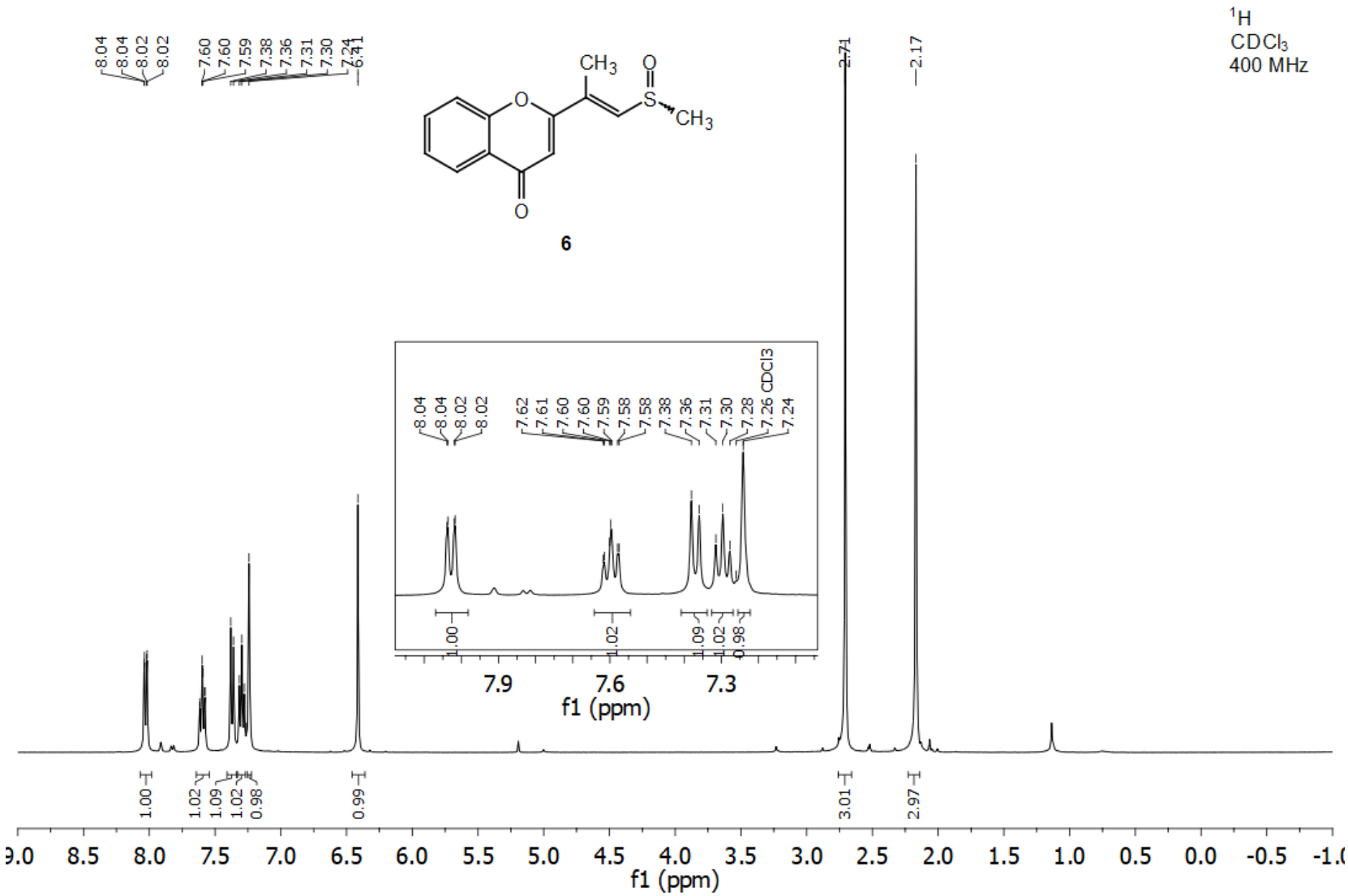

177.71
161.23
155.27
142.24
132.97
124.81
124.21
123.34
121.26
117.28
108.50
77.16 CDCl3
25.38
12.05
13C
CDCl3
100 MHz
O
O
CH3
14
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

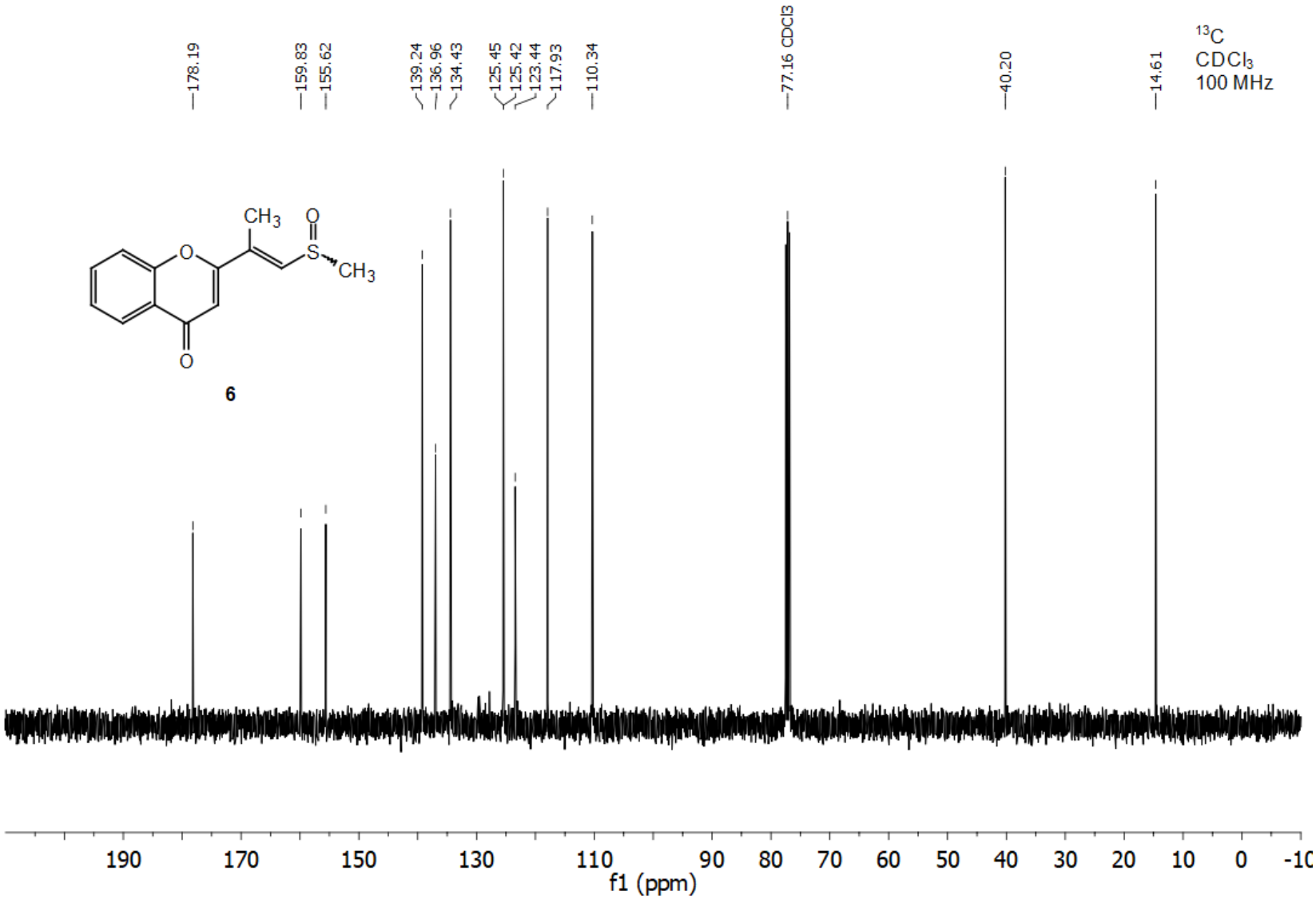

8.08
8.06
7.63
7.61
7.42
7.40
7.35
7.33
7.09
7.05
7.01
6.39
2.37
1.02
1.00
1.01
1.00
2.03
1.02
3.03
f1 (ppm)
7.65
7.31
7.26 CDCl3
6.97
4
^{1}H
CDCl$_3$
400 MHz
CH$_3$

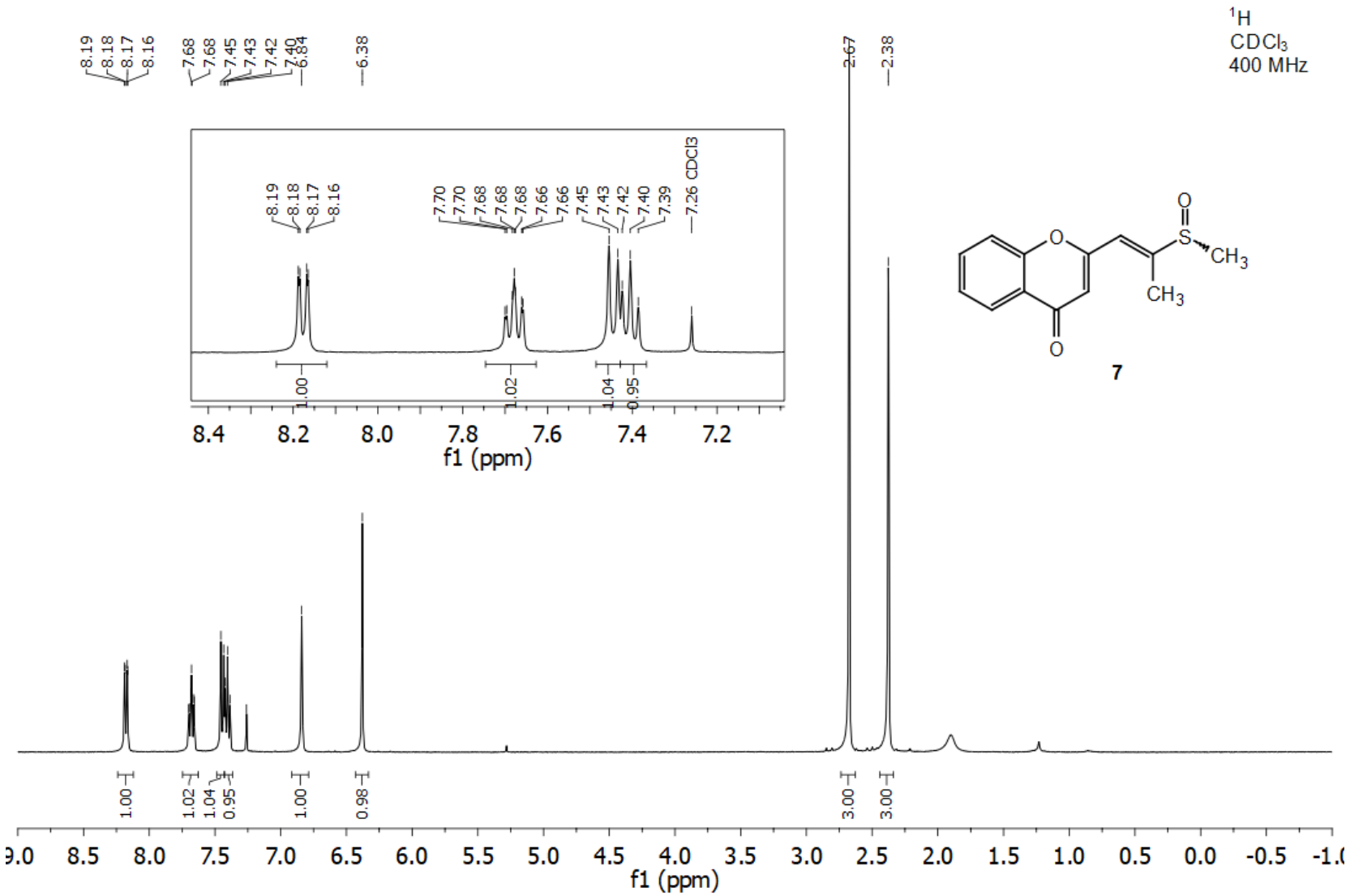

196.97
177.99
158.94
155.76
134.40
133.75
132.45
125.62
125.45
123.93
118.01
114.79
77.16 CDCl3
28.39
13C
CDCl3
100 MHz
O
O
CH3
O
4
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

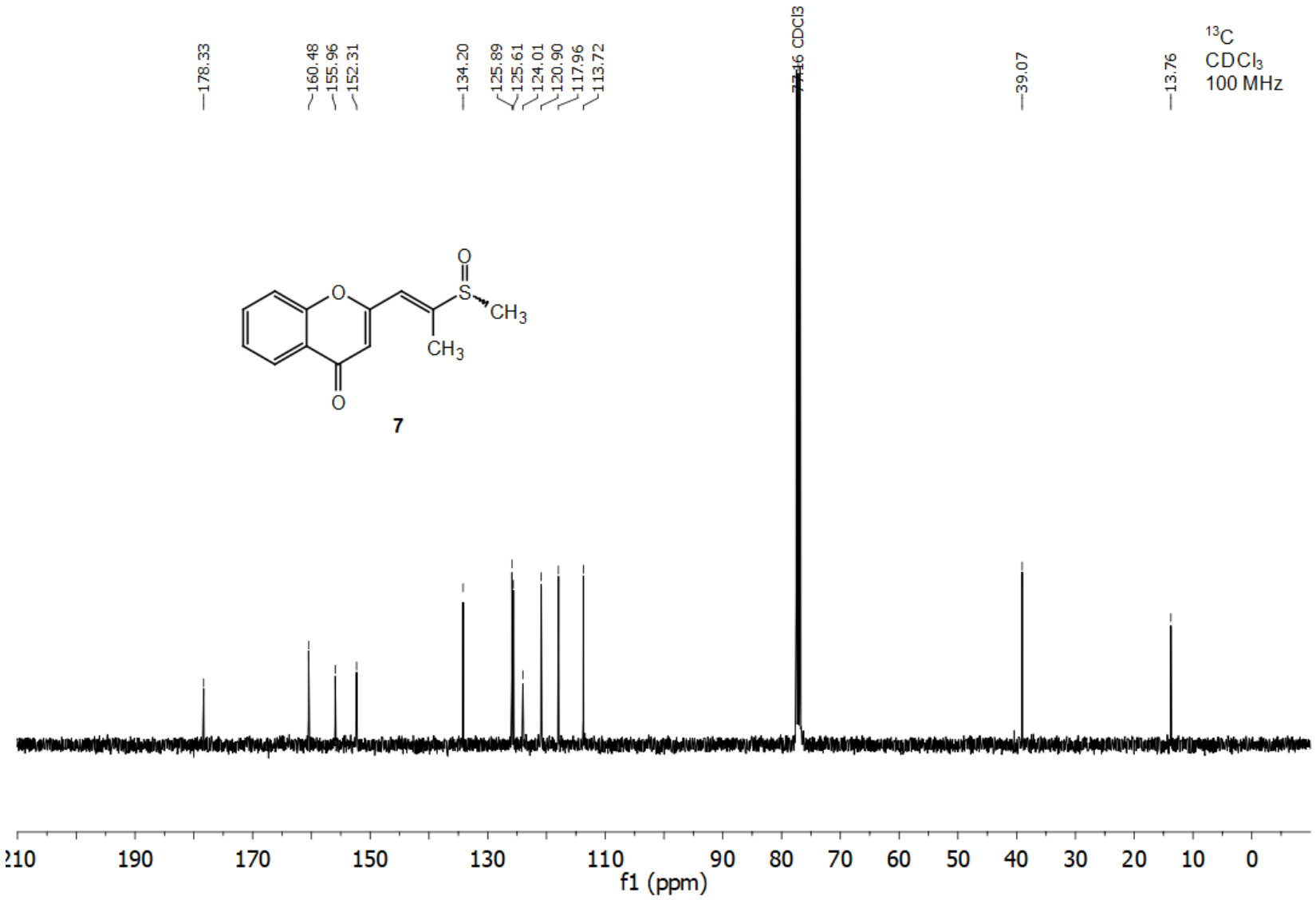

^{1}H
$CDCl_3$
400 MHz
8.11
8.09
7.64
7.62
7.44
7.43
7.40
7.37
7.35
6.96
6.92
6.32
3.05
3.03
3.02
3.00
2.98
2.96
2.81
2.79
2.77
2.76
2.74
2.72
1.33
1.32
1.30
O
S
CH_3
O
O
5
7.66
7.33
7.26 CDCl3
1.02
0.93
2.00
1.05
0.97
8.1
7.8
7.5
7.2
6.9
f1 (ppm)
0.98
1.00
3.00
f1 (ppm)

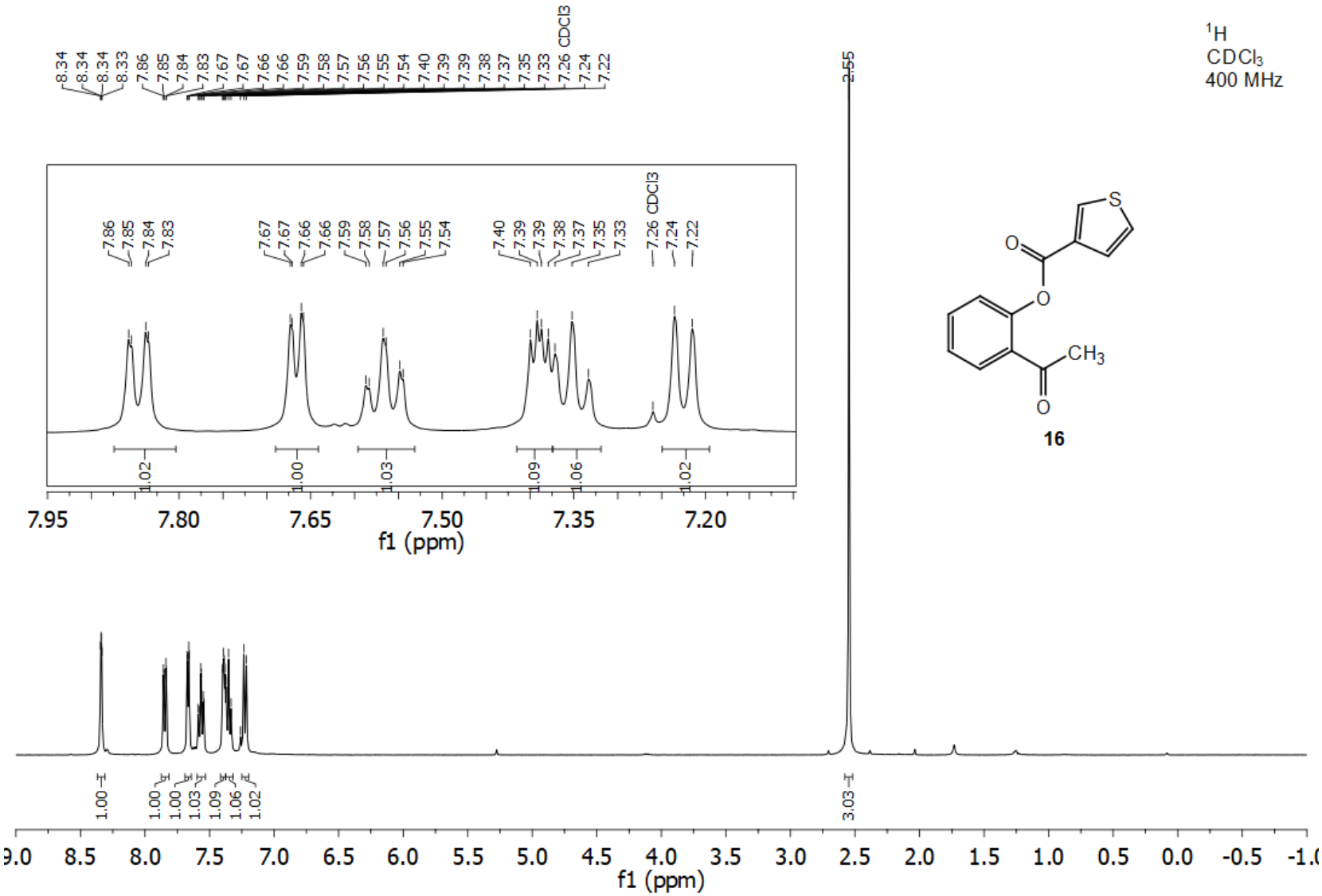

178.34
158.06
155.81
139.74
134.29
128.11
125.73
125.44
123.91
117.90
112.89
77.16 CDCl3
46.64
5.78
13C
CDCl3
100 MHz
O
S
CH3
O
O
5
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

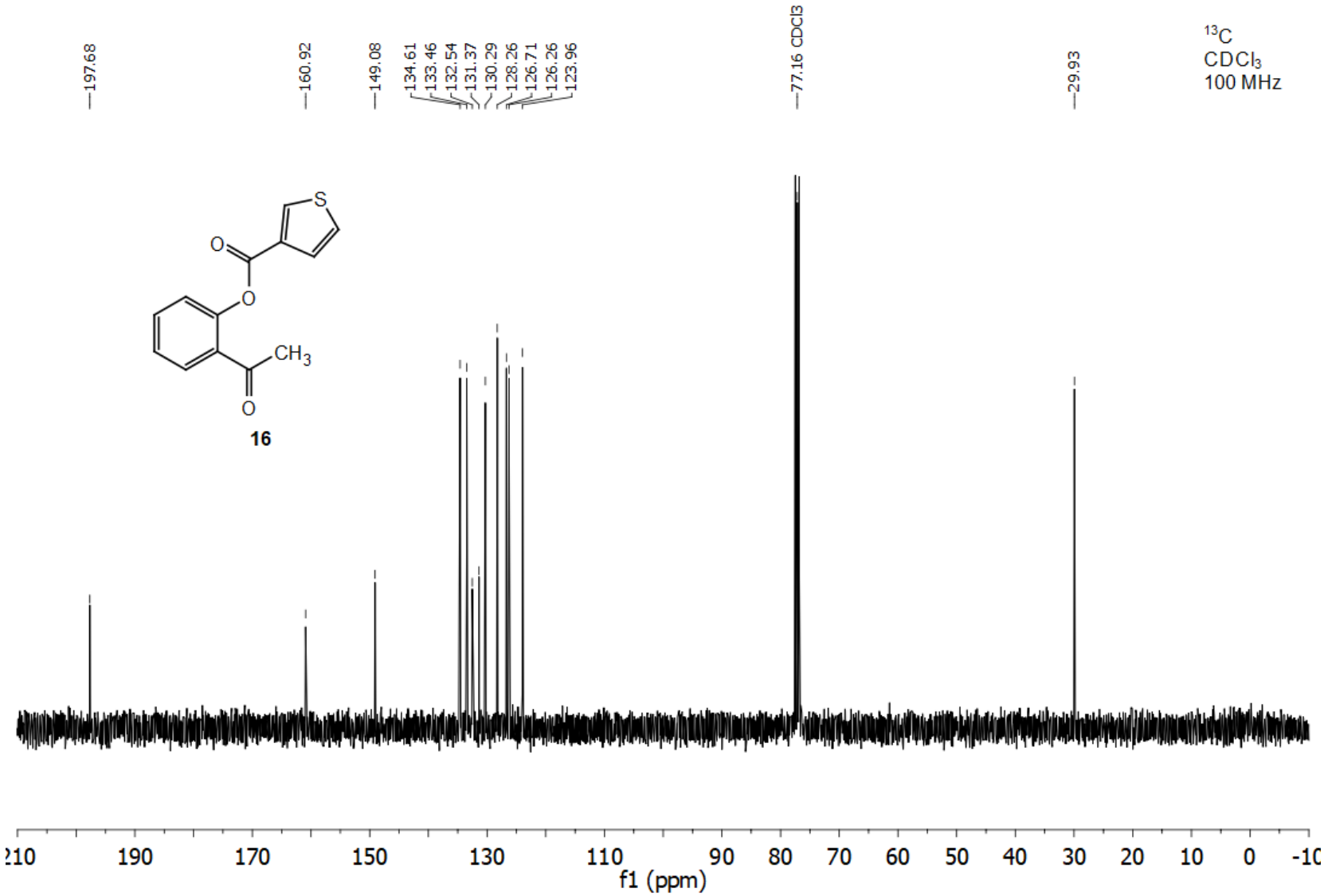

^{1}H
$CDCl_3$
400 MHz
8.04
8.04
8.02
8.02
7.60
7.60
7.59
7.38
7.36
7.31
7.30
7.24
7.41
2.71
2.17
CH_3
O
S
CH_3
O
O
6
7.62
7.61
7.60
7.60
7.59
7.58
7.58
7.38
7.36
7.31
7.30
7.28
7.26 CDCl3
7.24
1.00
1.02
1.09
1.02
0.98
7.9
7.6
7.3
f1 (ppm)
1.00
1.02
1.09
1.02
0.98
0.99
3.01
2.97
f1 (ppm)

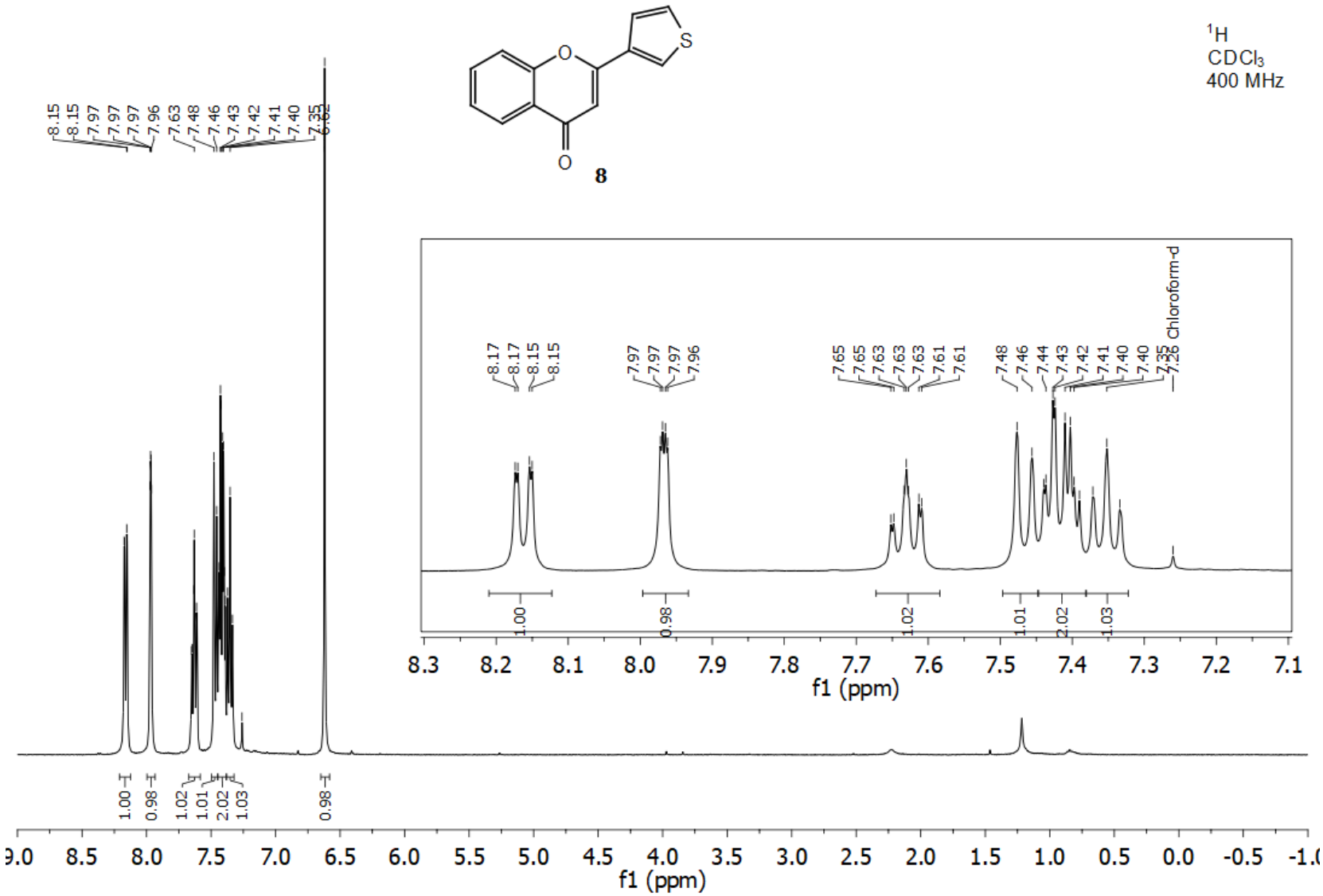

178.19
159.83
155.62
139.24
136.96
134.43
125.45
125.42
123.44
117.93
110.34
77.16 CDCl3
40.20
14.61
13C
CDCl3
100 MHz
CH3
O
S
CH3
O
O
6
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

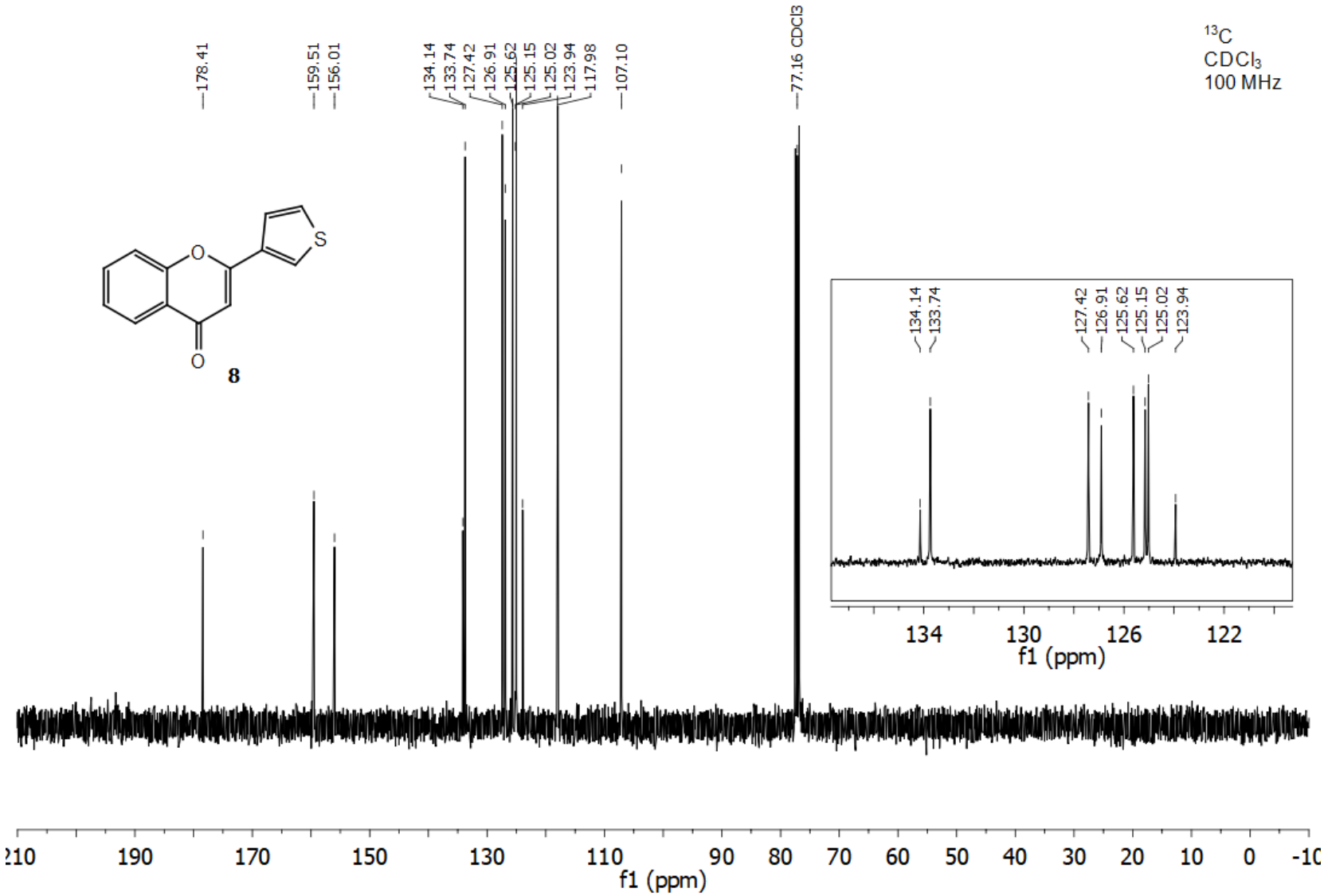

^{1}H
$CDCl_3$
400 MHz
8.19
8.18
8.17
8.16
7.68
7.68
7.45
7.43
7.42
7.40
6.84
6.38
2.67
2.38
7.70
7.70
7.68
7.68
7.68
7.66
7.66
7.45
7.43
7.42
7.40
7.39
7.26 CDCl3
1.00
1.02
1.04
0.95
0.98
3.00
3.00
f1 (ppm)
O
S
CH_3
CH_3
O
O
7

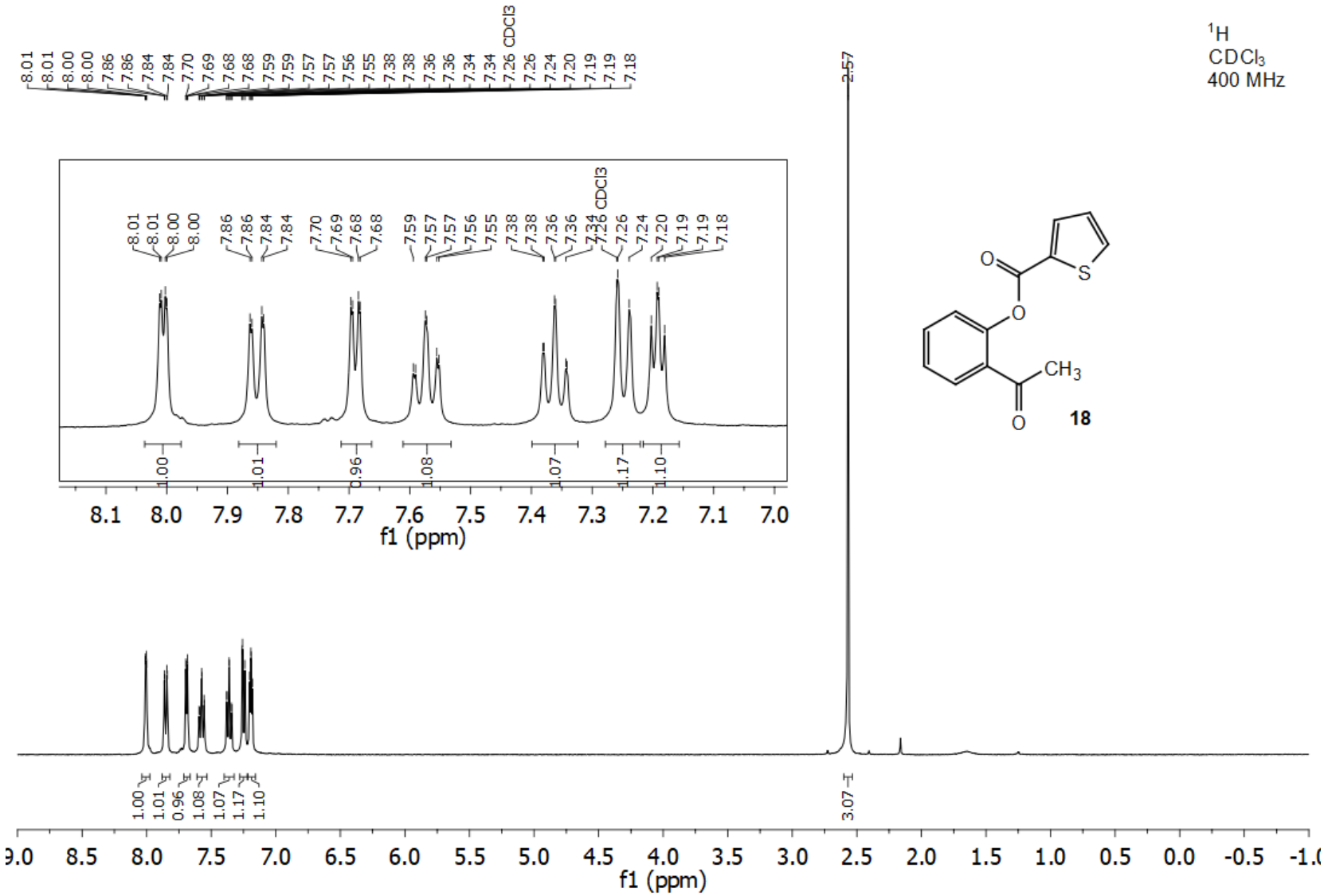

178.33
160.48
155.96
152.31
134.20
125.89
125.61
124.01
120.90
117.96
113.72
77.46 CDCl3
39.07
13.76
13C
CDCl3
100 MHz
O
S
CH3
CH3
O
O
7
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

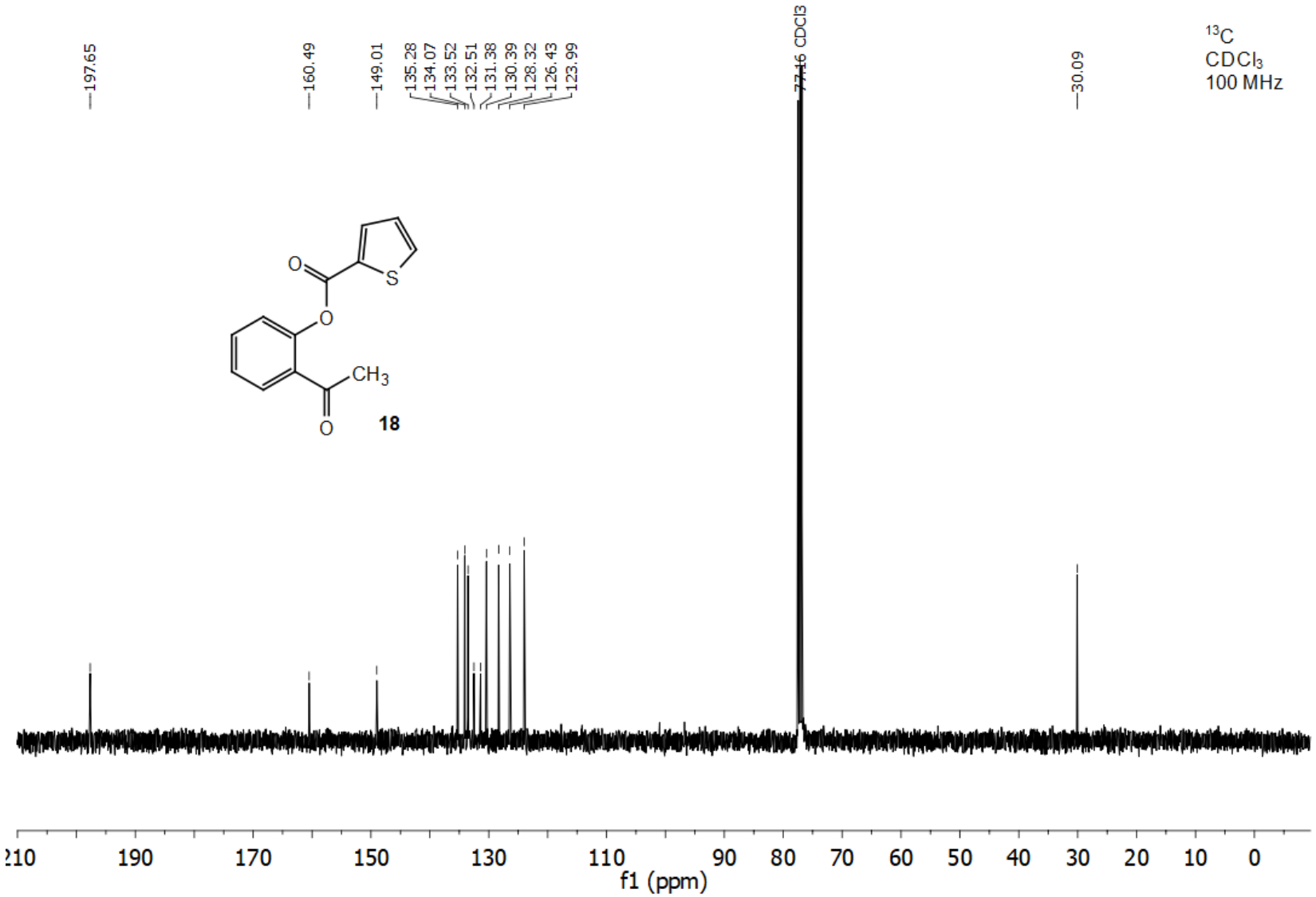

^{1}H
$CDCl_3$
400 MHz
16
f1 (ppm)

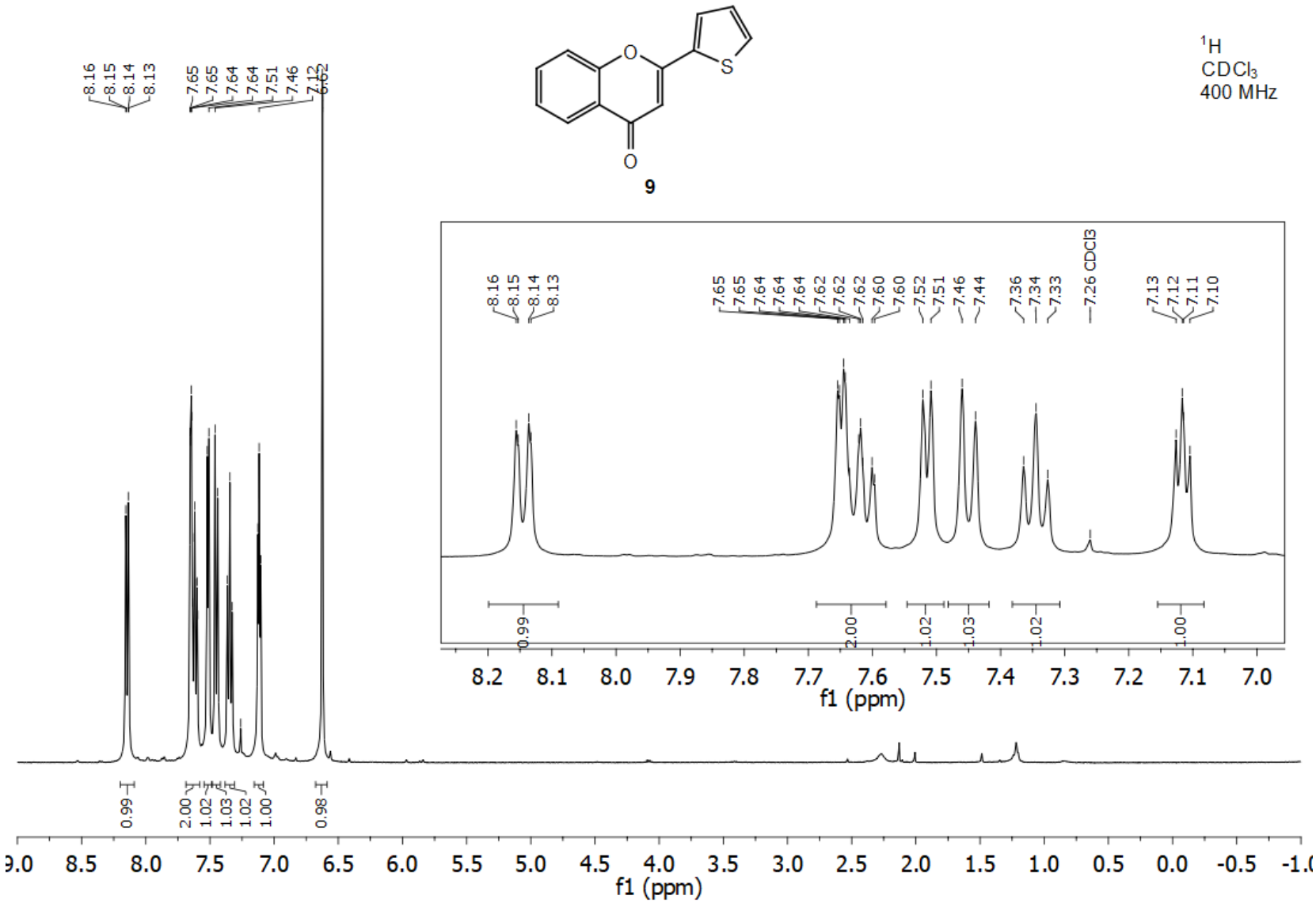

197.68
160.92
149.08
134.61
133.46
132.54
131.37
130.29
128.26
126.71
126.26
123.96
77.16 CDCl3
29.93
13C
CDCl3
100 MHz
S
O
O
CH3
O
16
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

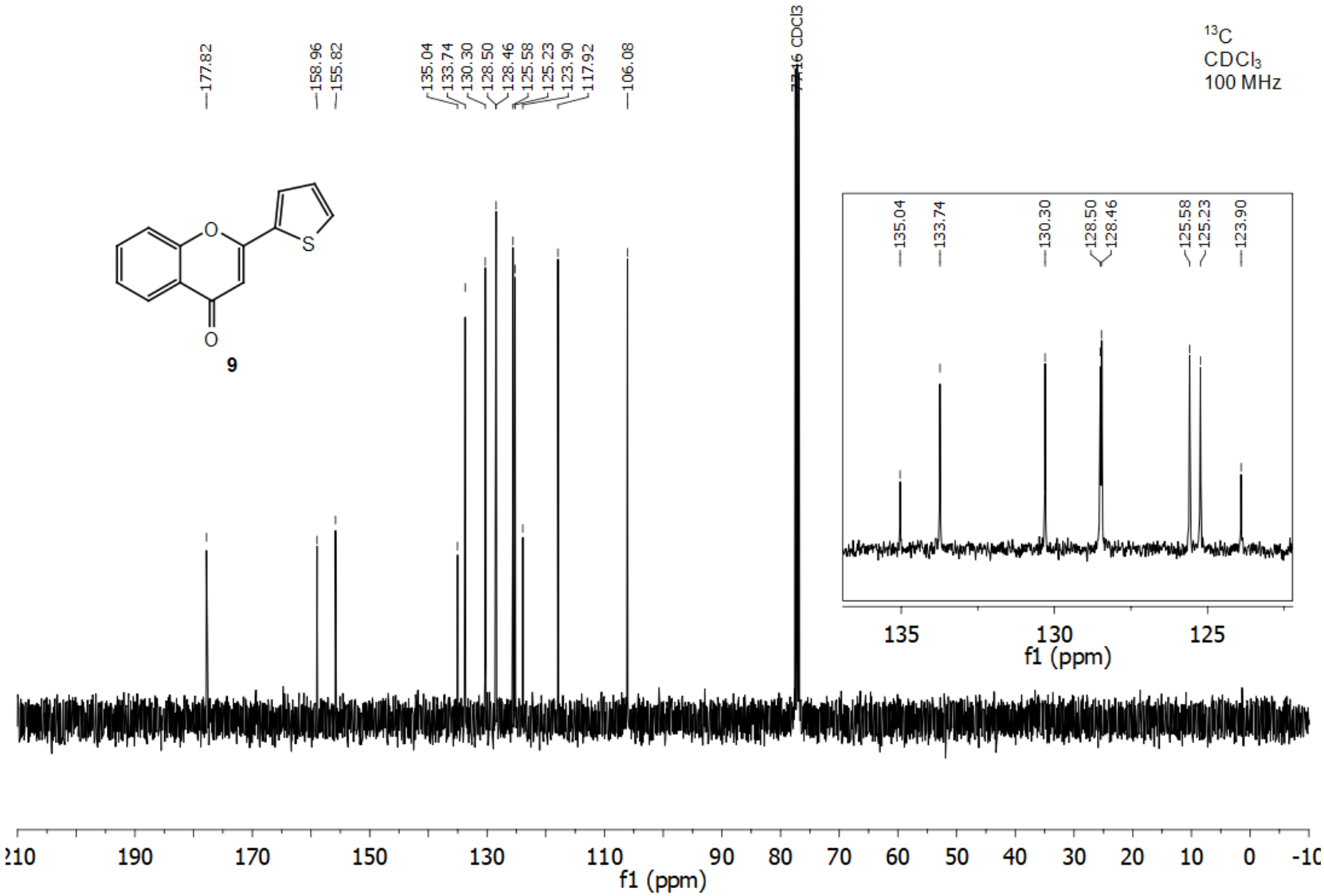

8
^{1}H
$CDCl_3$
400 MHz
Chloroform-d
f1 (ppm)

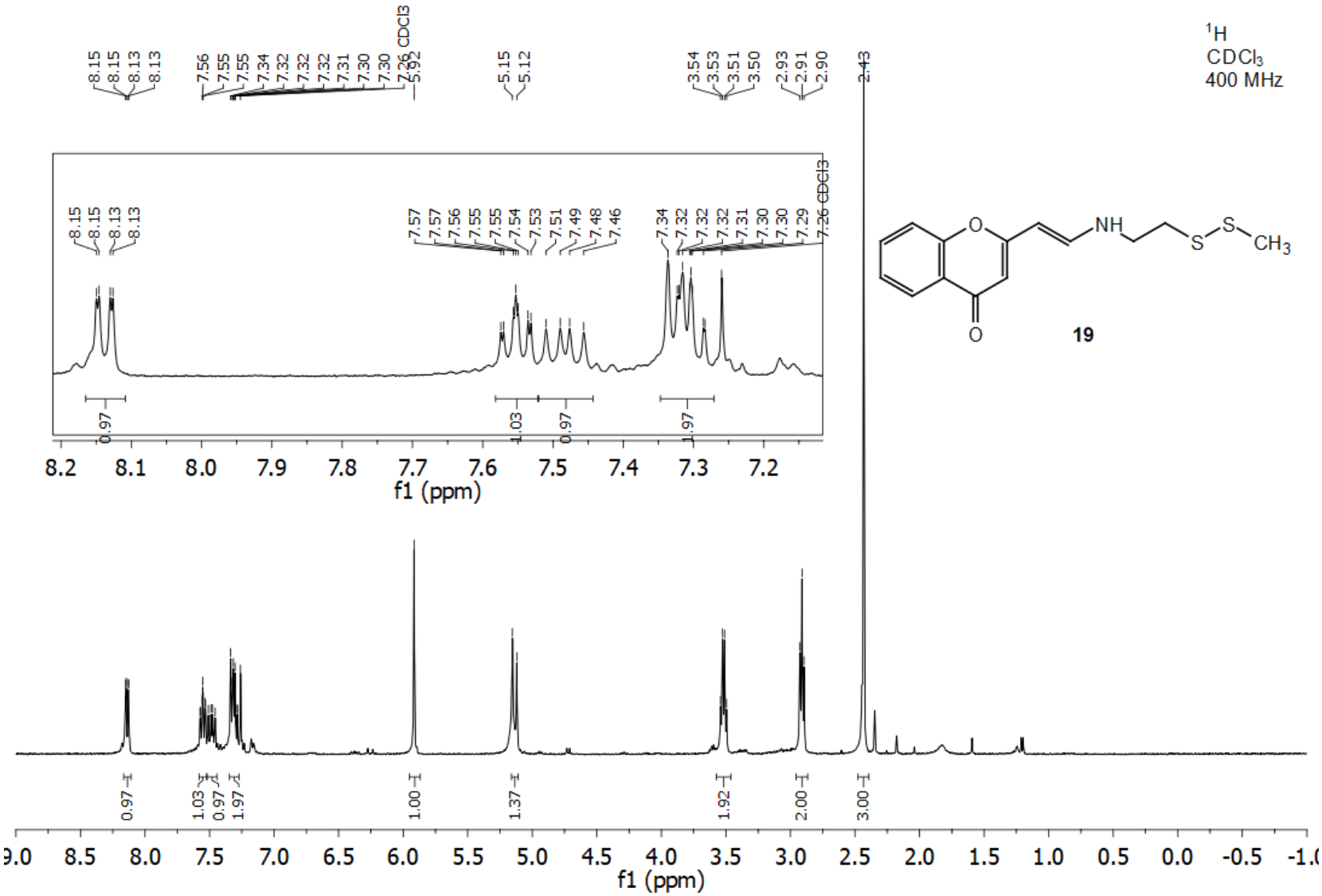

178.41
159.51
156.01
134.14
133.74
127.42
126.91
125.62
125.15
125.02
123.94
117.98
107.10
77.16 CDCl3
^{13}C
CDCl$_3$
100 MHz
O
S
O
8
134.14
133.74
127.42
126.91
125.62
125.15
125.02
123.94
134
130
126
122
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

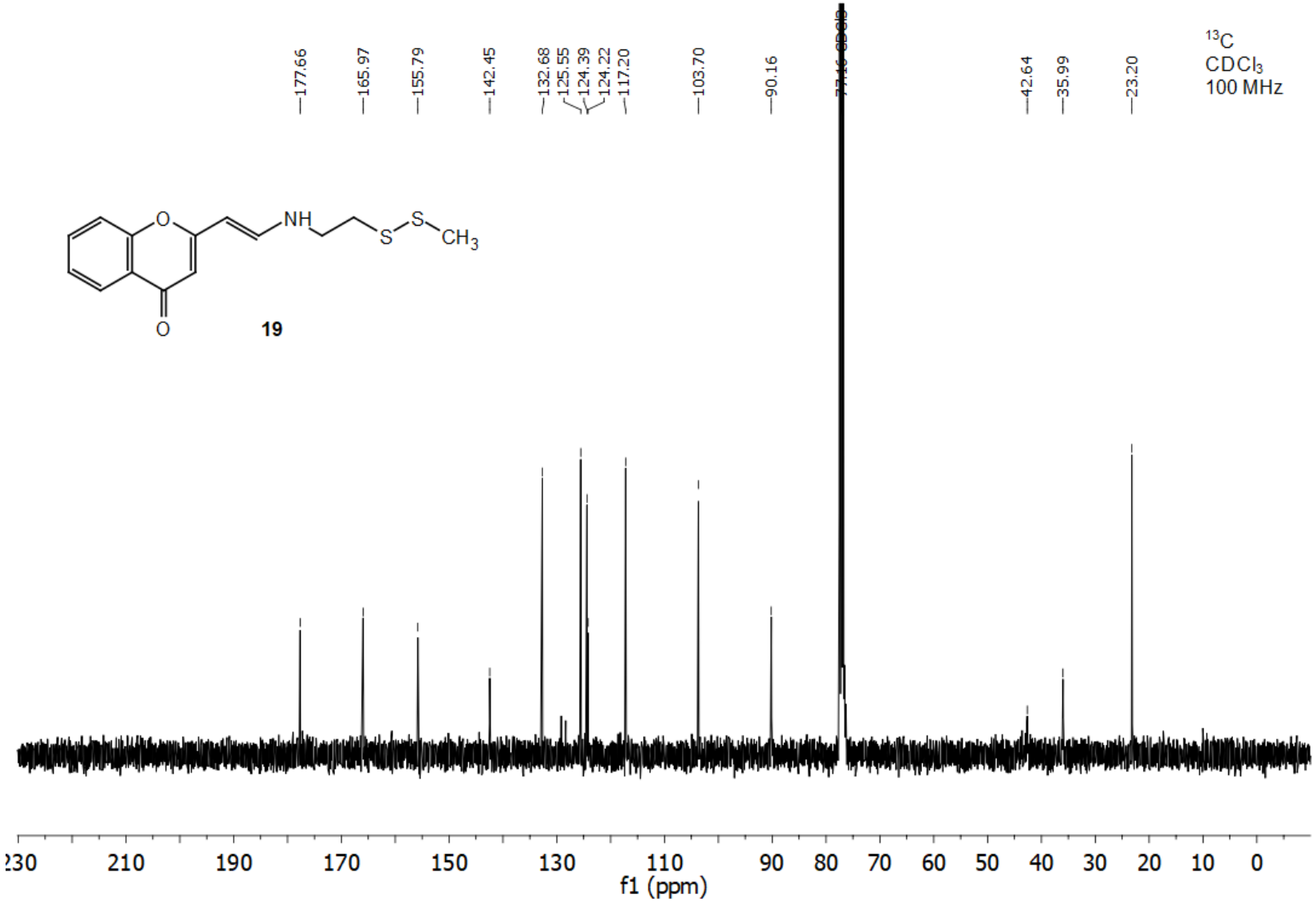

^{1}H
$CDCl_3$
400 MHz
18
f1 (ppm)

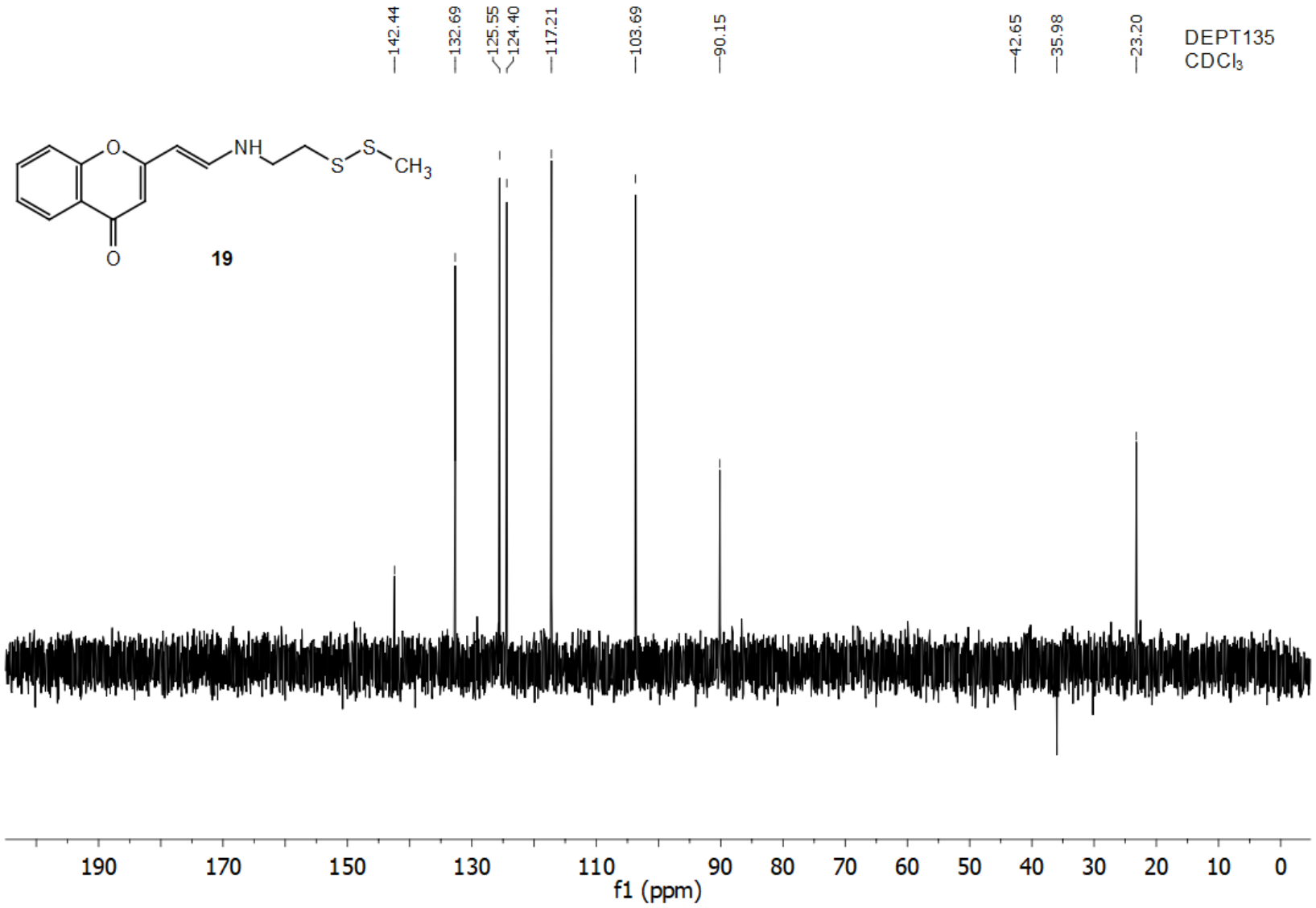

197.65
160.49
149.01
135.28
134.07
133.52
132.51
131.38
130.39
128.32
126.43
123.99
77.16 CDCl3
30.09
13C
CDCl3
100 MHz
O
S
O
CH3
O
18
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

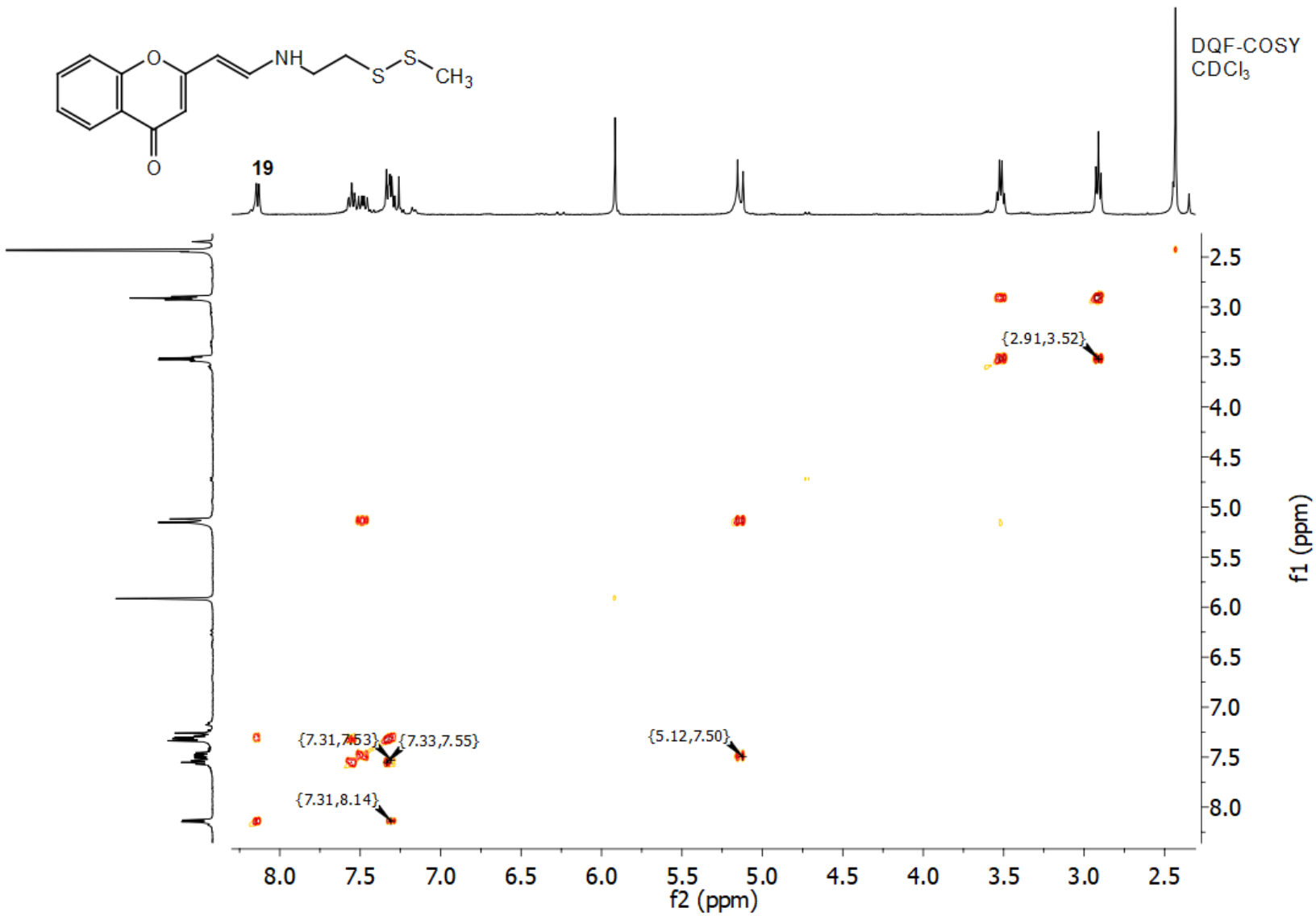

9
^{1}H
CDCl$_3$
400 MHz
8.16
8.15
8.14
8.13
7.65
7.65
7.64
7.64
7.51
7.46
7.12
6.62
7.62
7.60
7.60
7.52
7.44
7.36
7.34
7.33
7.26 CDCl3
7.13
7.11
7.10
0.99
2.00
1.02
1.03
1.02
1.00
0.98
f1 (ppm)

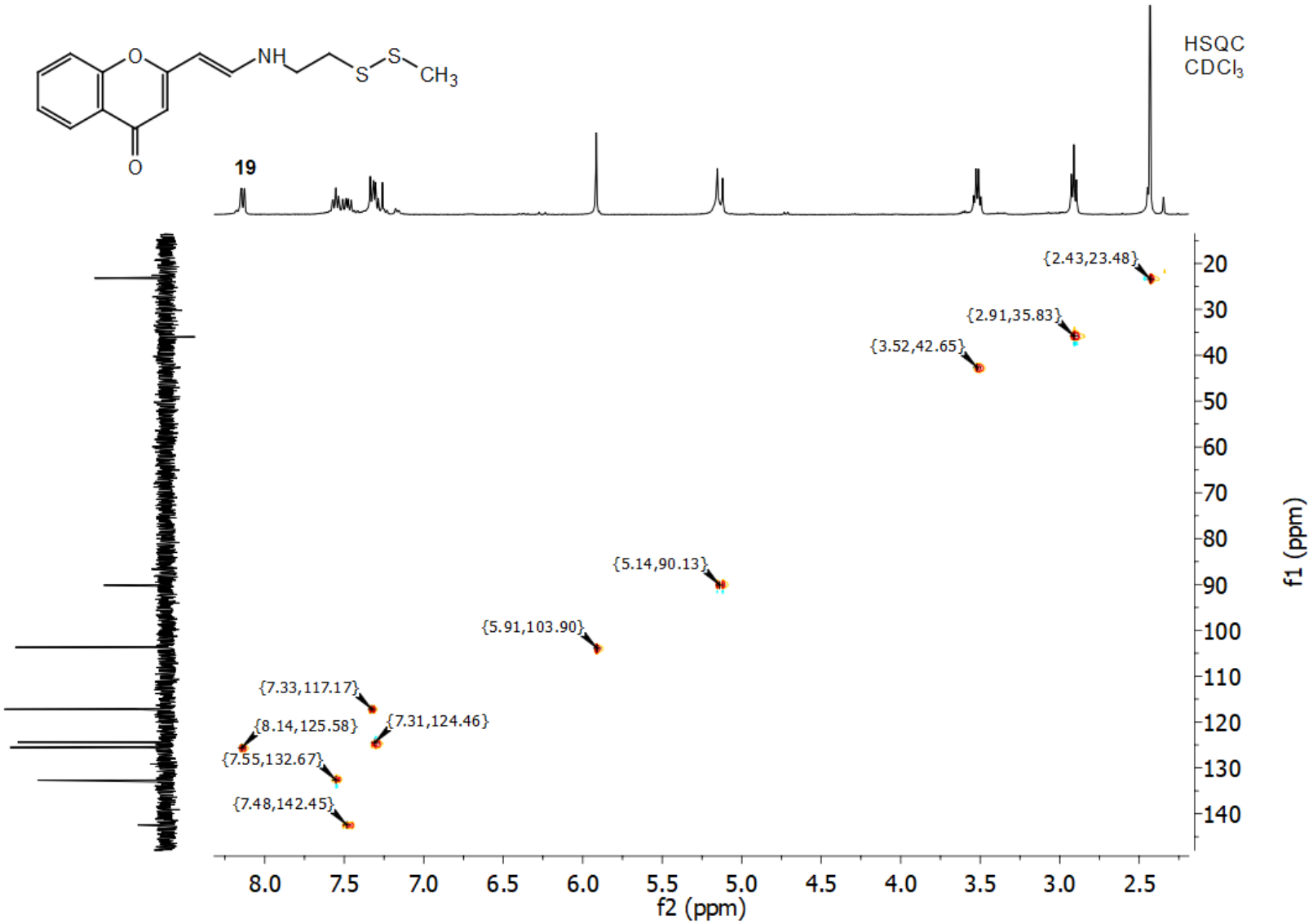

177.82
158.96
155.82
135.04
133.74
130.30
128.50
128.46
125.58
125.23
123.90
117.92
106.08
77.16 CDCl3
13C
CDCl3
100 MHz
O
S
O
9
135.04
133.74
130.30
128.50
128.46
125.58
125.23
123.90
135
130
125
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

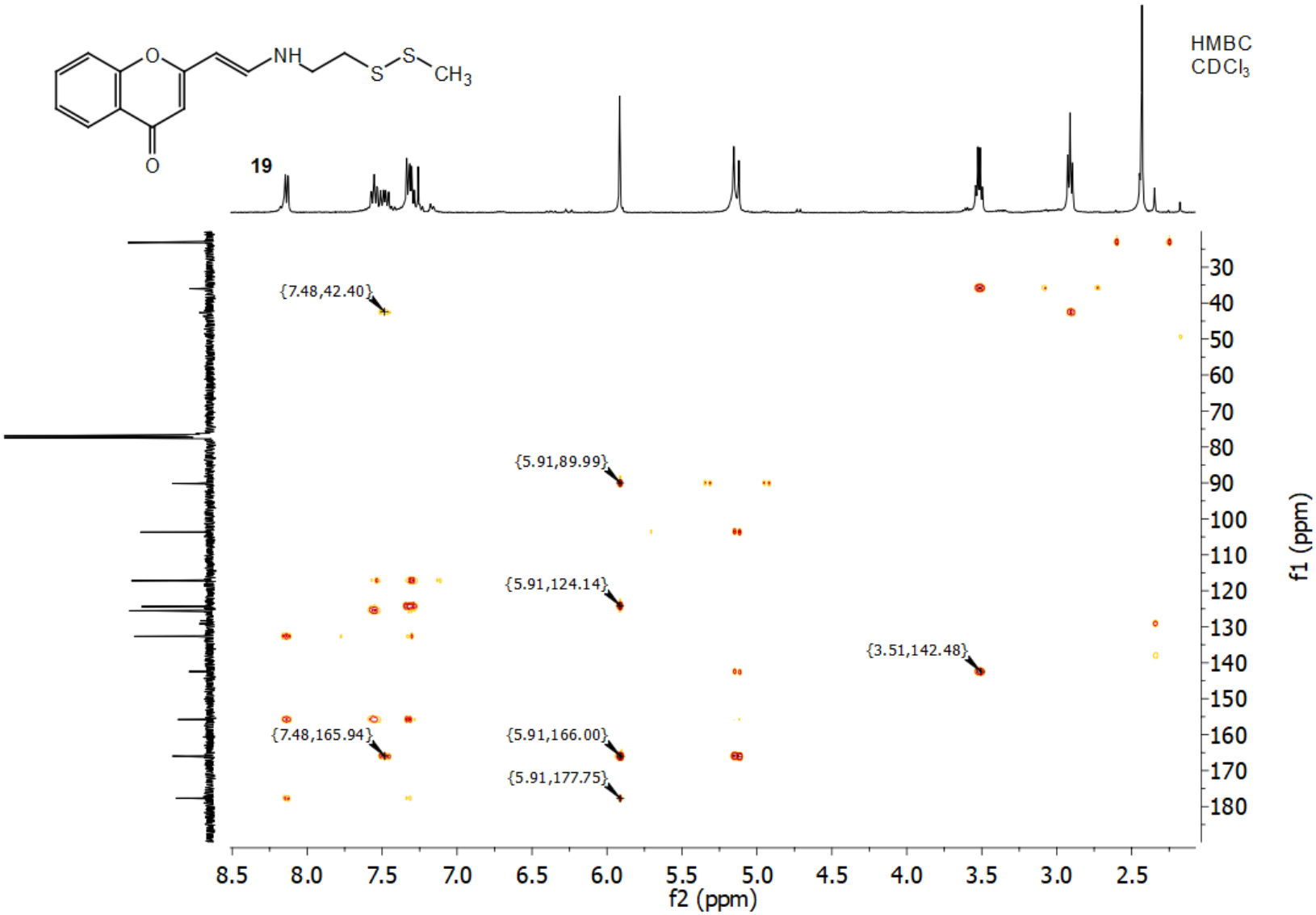

1H
CDCl3
400 MHz
8.15
8.15
8.13
8.13
7.56
7.55
7.55
7.34
7.32
7.32
7.32
7.31
7.30
7.30
7.26 CDCl3
5.92
5.15
5.12
3.54
3.53
3.51
3.50
2.93
2.91
2.90
2.43
7.57
7.57
7.56
7.55
7.55
7.54
7.53
7.51
7.49
7.48
7.46
7.34
7.32
7.32
7.32
7.31
7.30
7.30
7.29
7.26 CDCl3
0.97
1.03
0.97
1.97
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
f1 (ppm)
O
NH
S
S
CH3
O
19
0.97
1.03
0.97
1.97
1.00
1.37
1.92
2.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

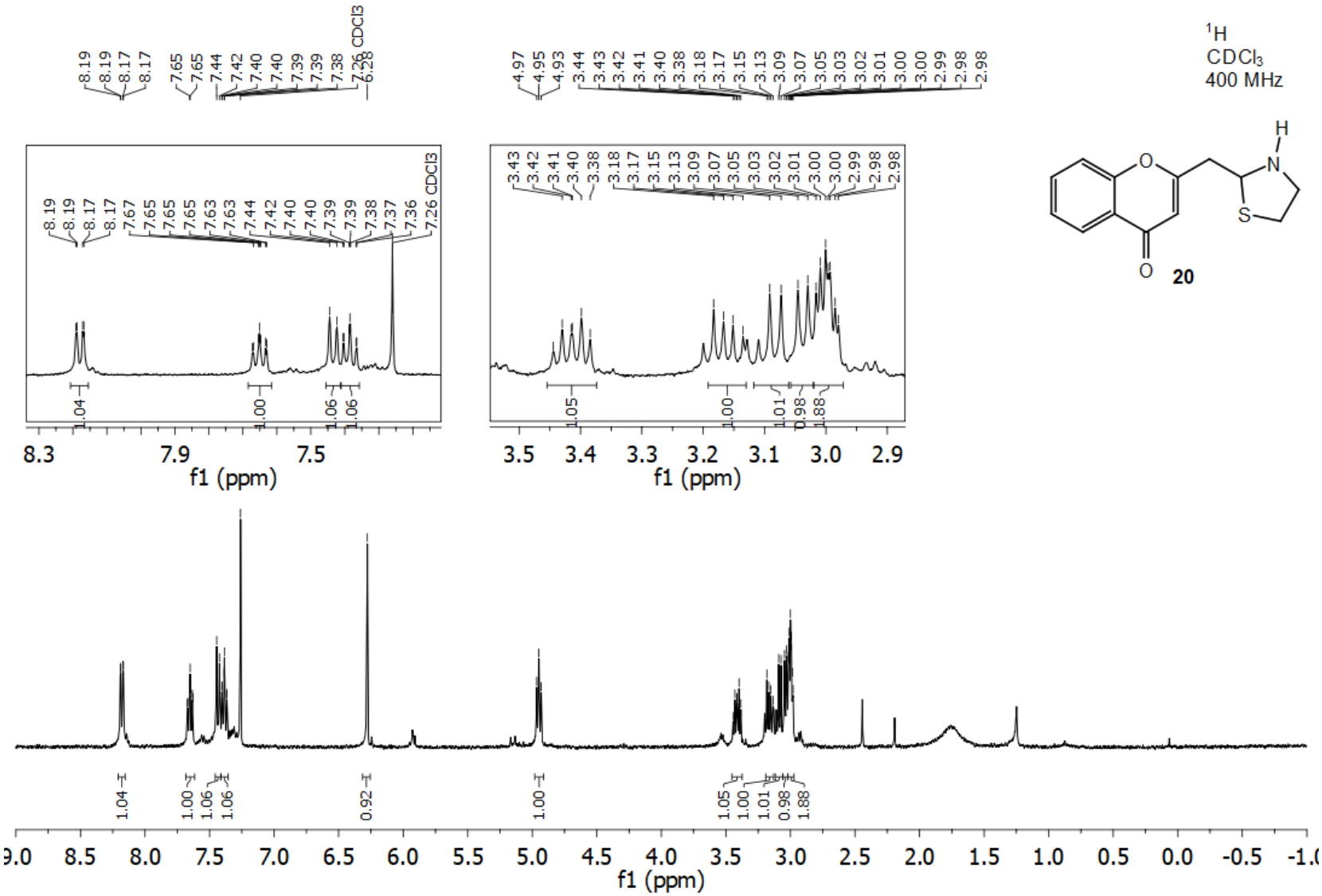

177.66
165.97
155.79
142.45
132.68
125.55
124.39
124.22
117.20
103.70
90.16
77.16 CDCl3
42.64
35.99
23.20
13C
CDCl3
100 MHz
O
NH
S
S
CH3
O
19
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

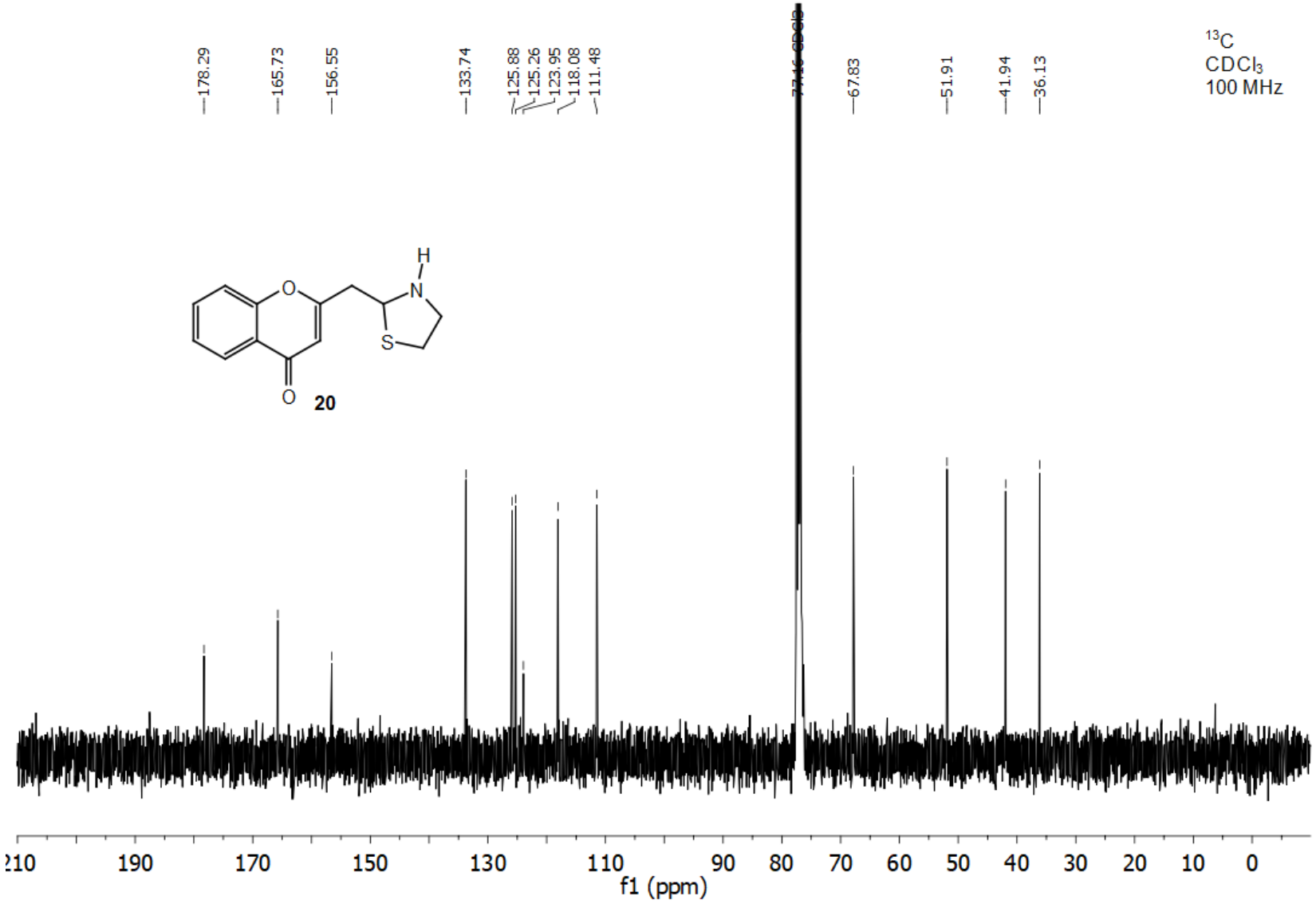

142.44
132.69
125.55
124.40
117.21
103.69
90.15
42.65
35.98
23.20
DEPT135
CDCl3
O
NH
S
S
CH3
O
19
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

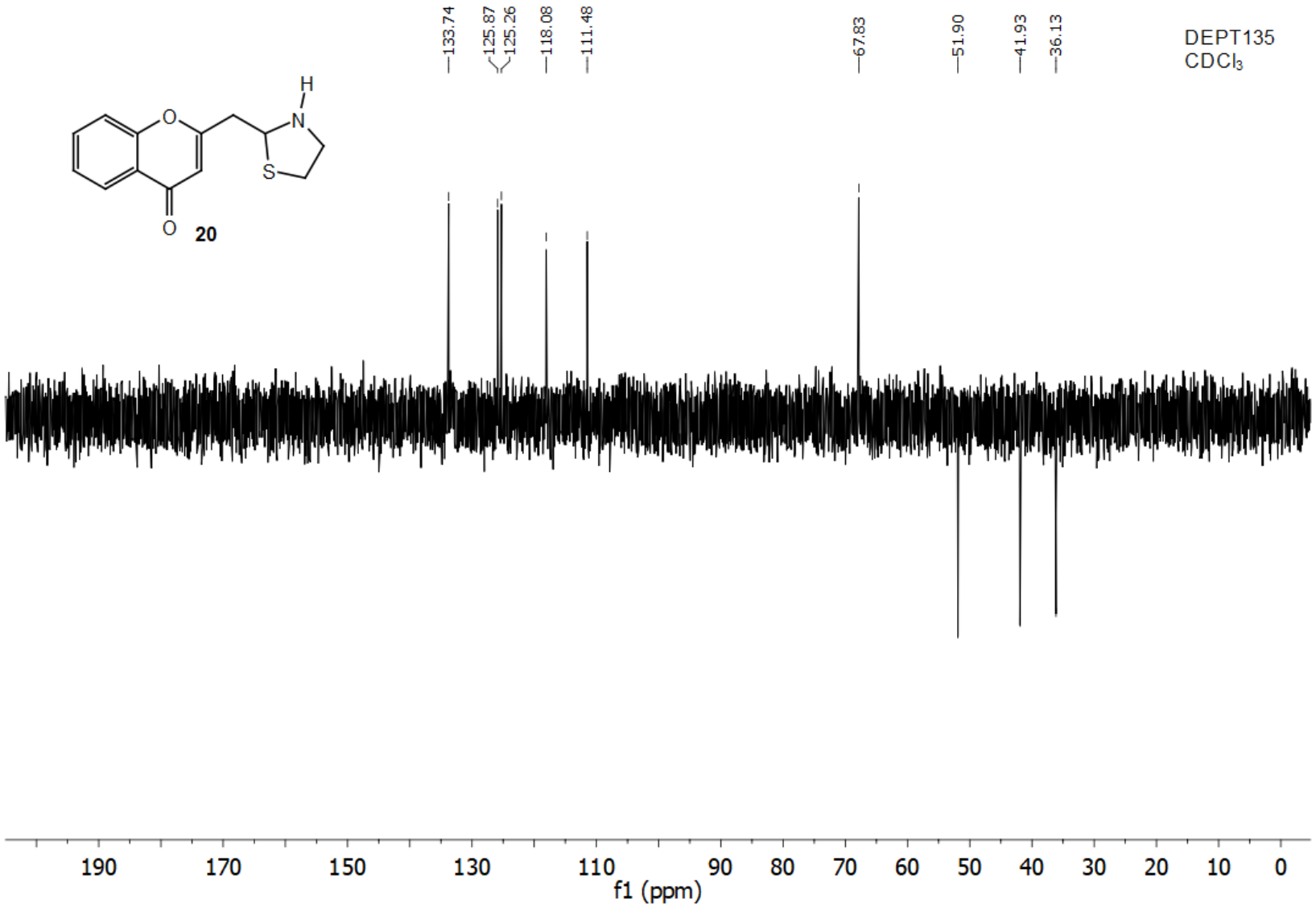

DQF-COSY
CDCl3
19
{2.91,3.52}
{7.31,7.53}
{7.33,7.55}
{5.12,7.50}
{7.31,8.14}
f2 (ppm)
f1 (ppm)


HSQC
CDCl3
19
{2.43,23.48}
{2.91,35.83}
{3.52,42.65}
{5.14,90.13}
{5.91,103.90}
{7.33,117.17}
{7.31,124.46}
{8.14,125.58}
{7.55,132.67}
{7.48,142.45}
f2 (ppm)
f1 (ppm)


HMBC
CDCl3
19
{7.48,42.40}
{5.91,89.99}
{5.91,124.14}
{3.51,142.48}
{7.48,165.94}
{5.91,166.00}
{5.91,177.75}
f2 (ppm)
f1 (ppm)


^{1}H
$CDCl_3$
400 MHz
20
f1 (ppm)


178.29
165.73
156.55
133.74
125.88
125.26
123.95
118.08
111.48
67.83
51.91
41.94
36.13
13C
CDCl3
100 MHz
H
N
O
S
O
20
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


133.74
125.87
125.26
118.08
111.48
67.83
51.90
41.93
36.13
DEPT135
CDCl3
H
N
O
S
O
20
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150
130
110
90
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70
60
50
40
30
20
10
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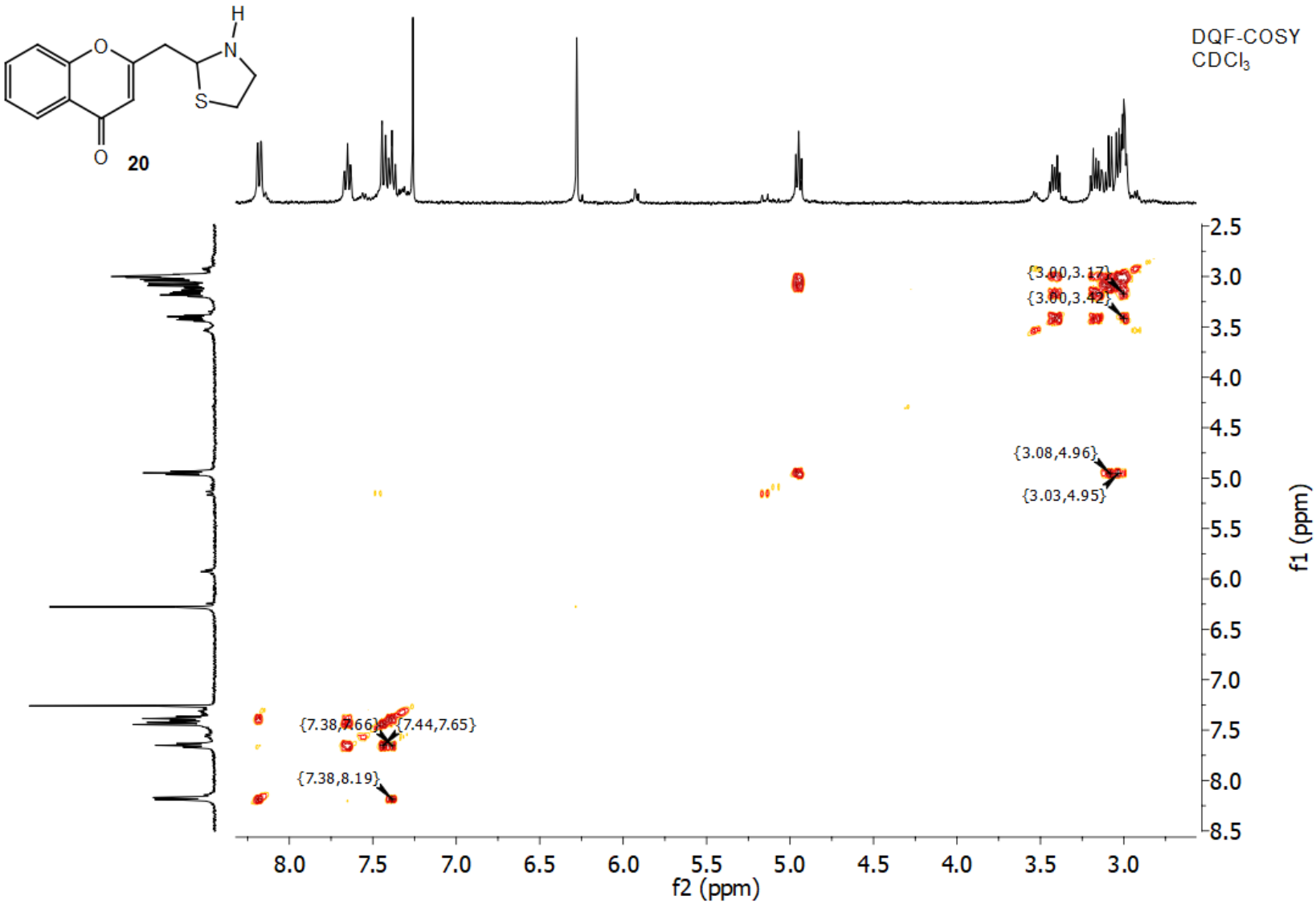
f1 (ppm)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S
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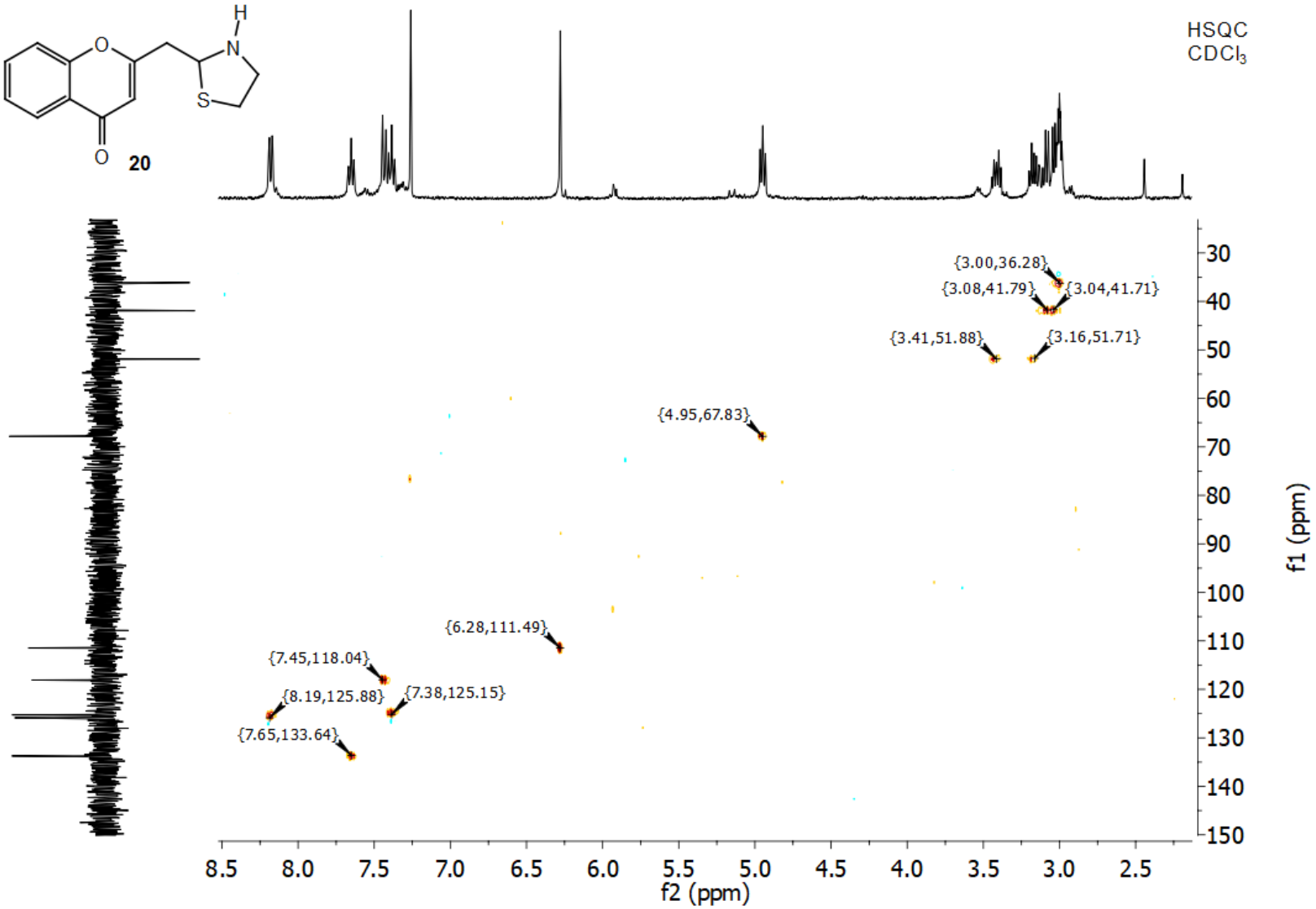
f1 (ppm)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6.5
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4.5
4.0
3.5
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100
110
120
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140
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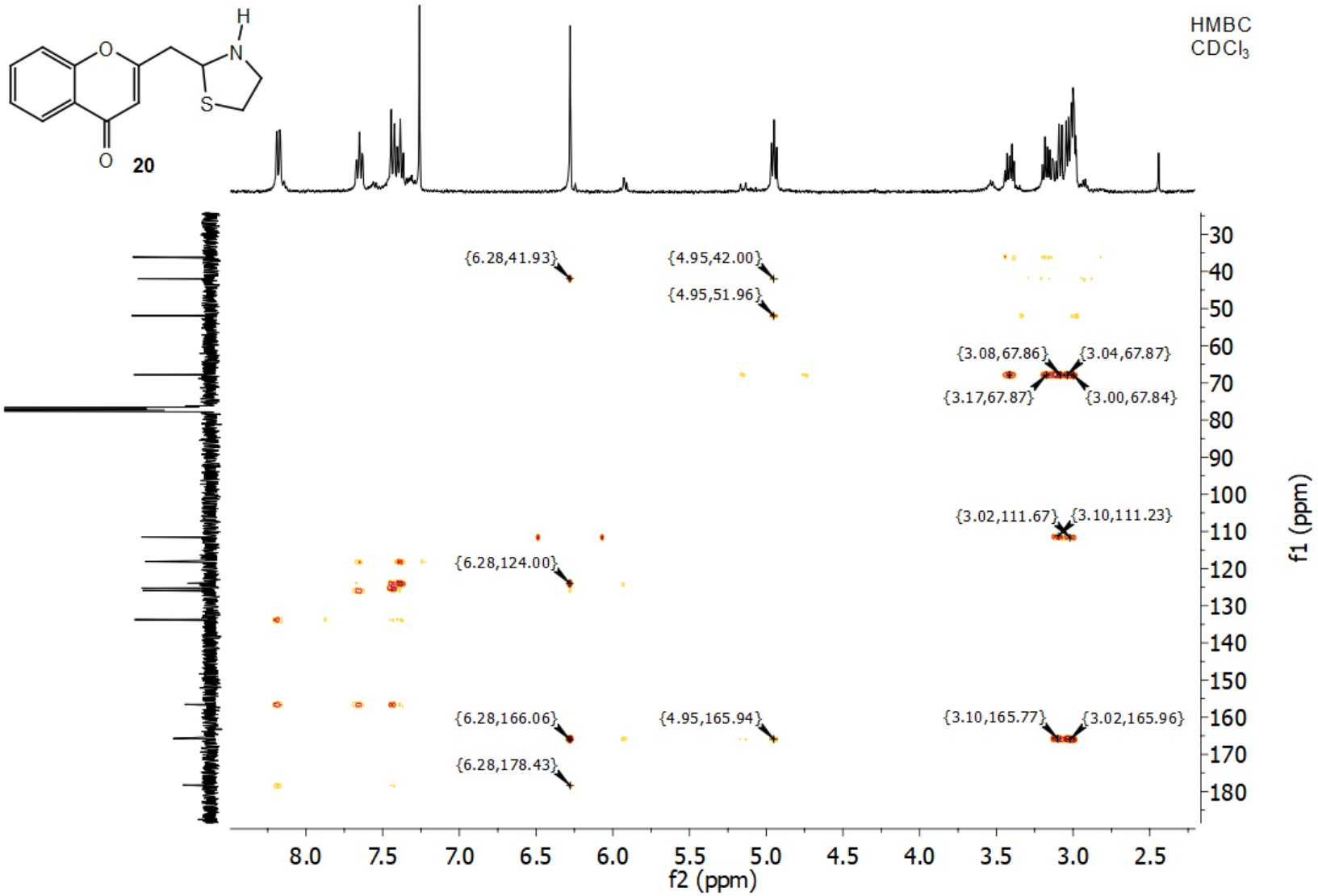
f1 (ppm)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S
O
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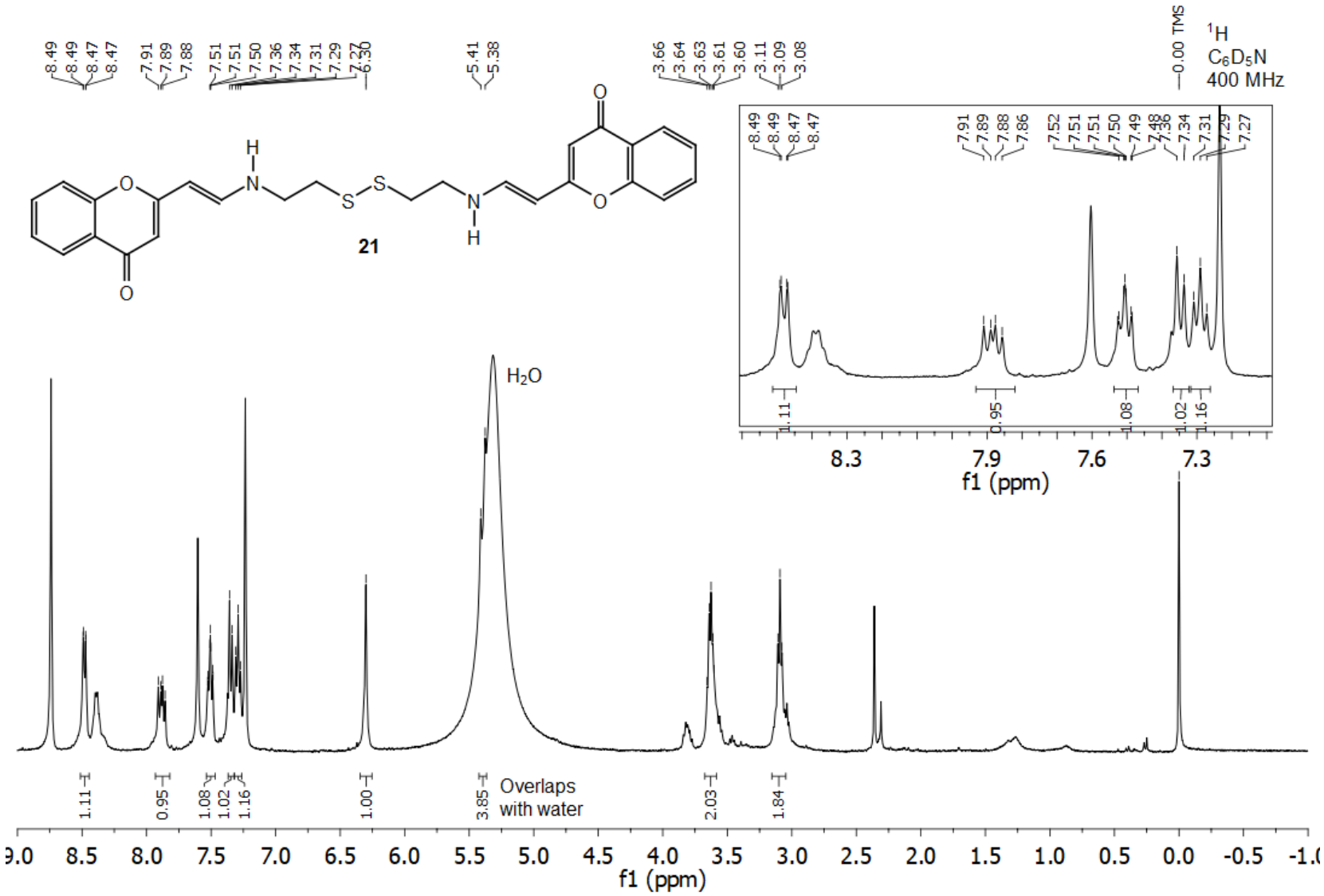
f2 (ppm)
f1 (ppm)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8.49
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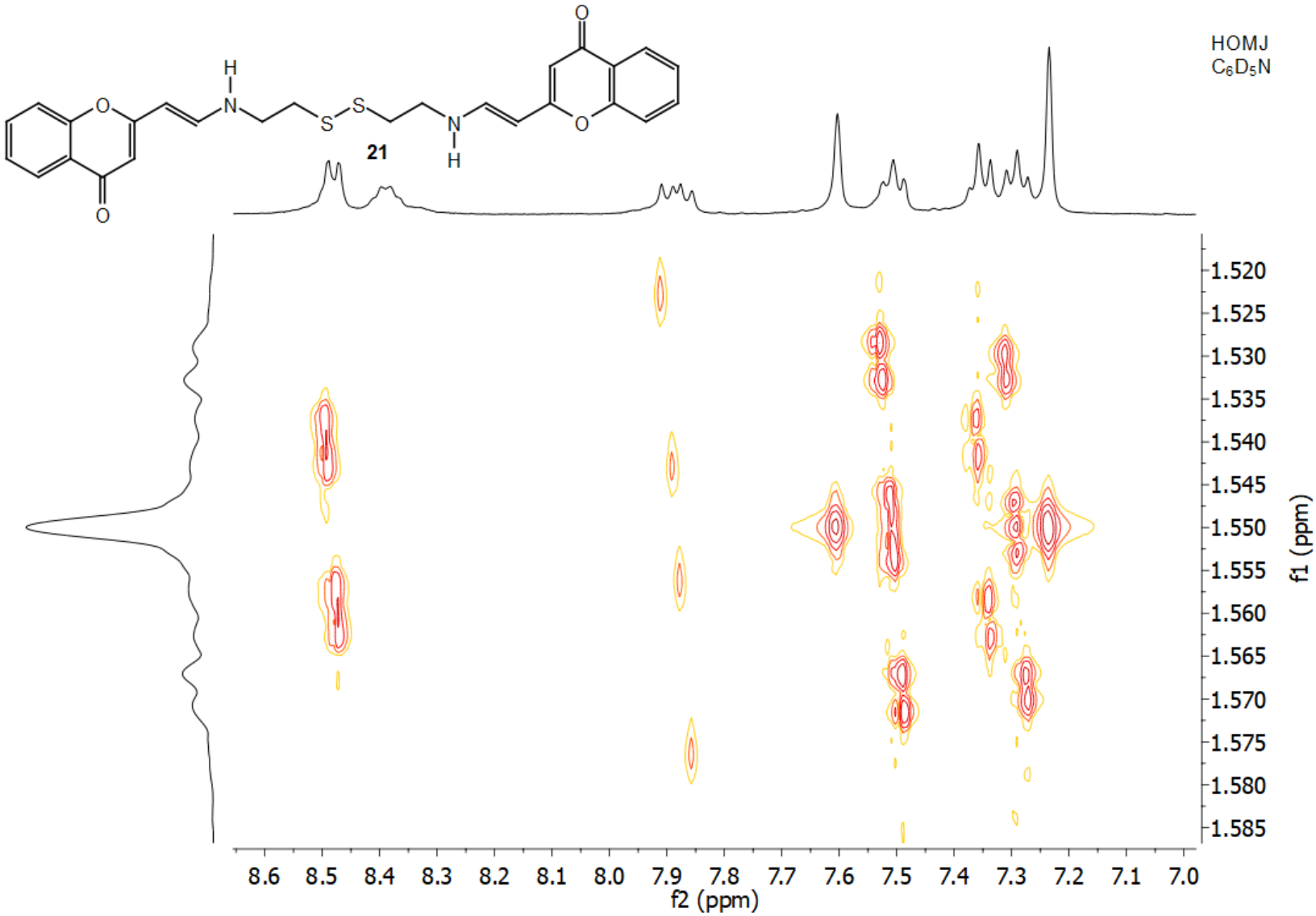
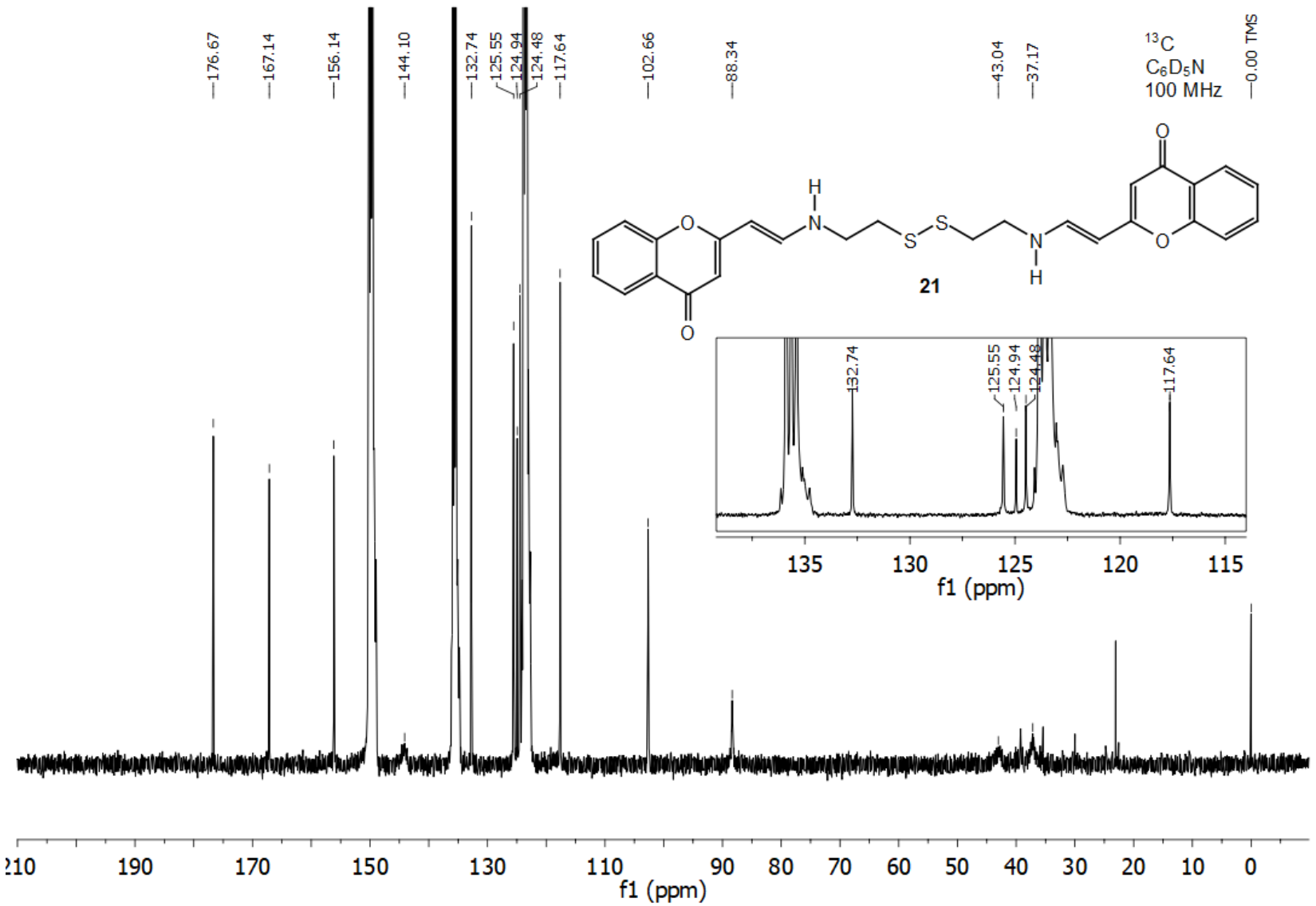
8.47
7.91
7.89
7.88
7.51
7.51
7.50
7.36
7.34
7.31
7.29
7.27
6.30
5.41
5.38
3.66
3.64
3.63
3.61
3.60
3.11
3.09
3.08
0.00 TMS
1H
C6D5N
400 MHz
21
H2O
Overlaps
with water
f1 (ppm)
1.11
0.95
1.08
1.02
1.16
1.00
3.85
2.03
1.84


21
HOMJ
C6D5N
f2 (ppm)
f1 (ppm)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156.14
144.10
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124.48
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43.04
37.17
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13C
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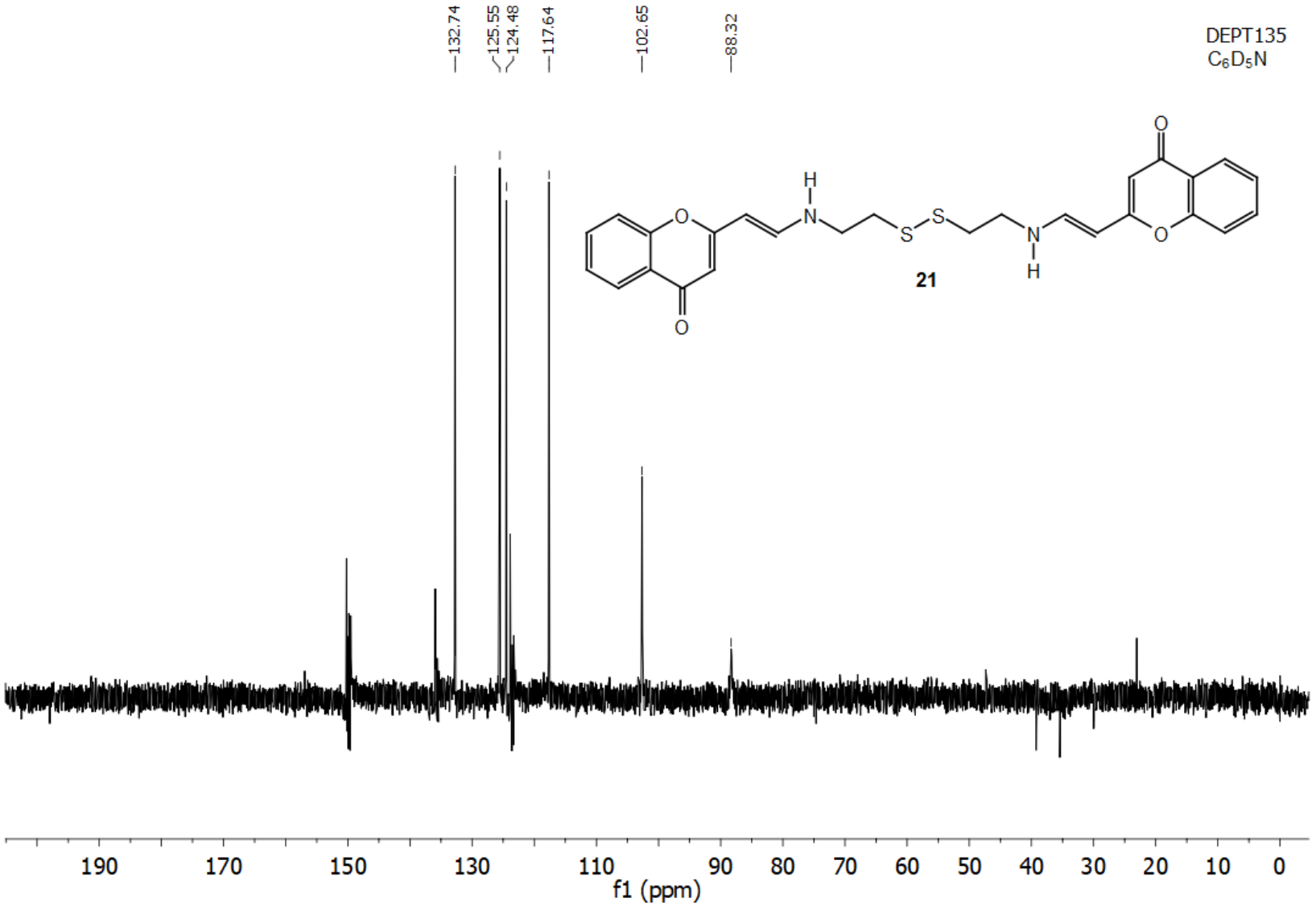
100 MHz
21
f1 (ppm)
f1 (ppm)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88.32
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C6D5N
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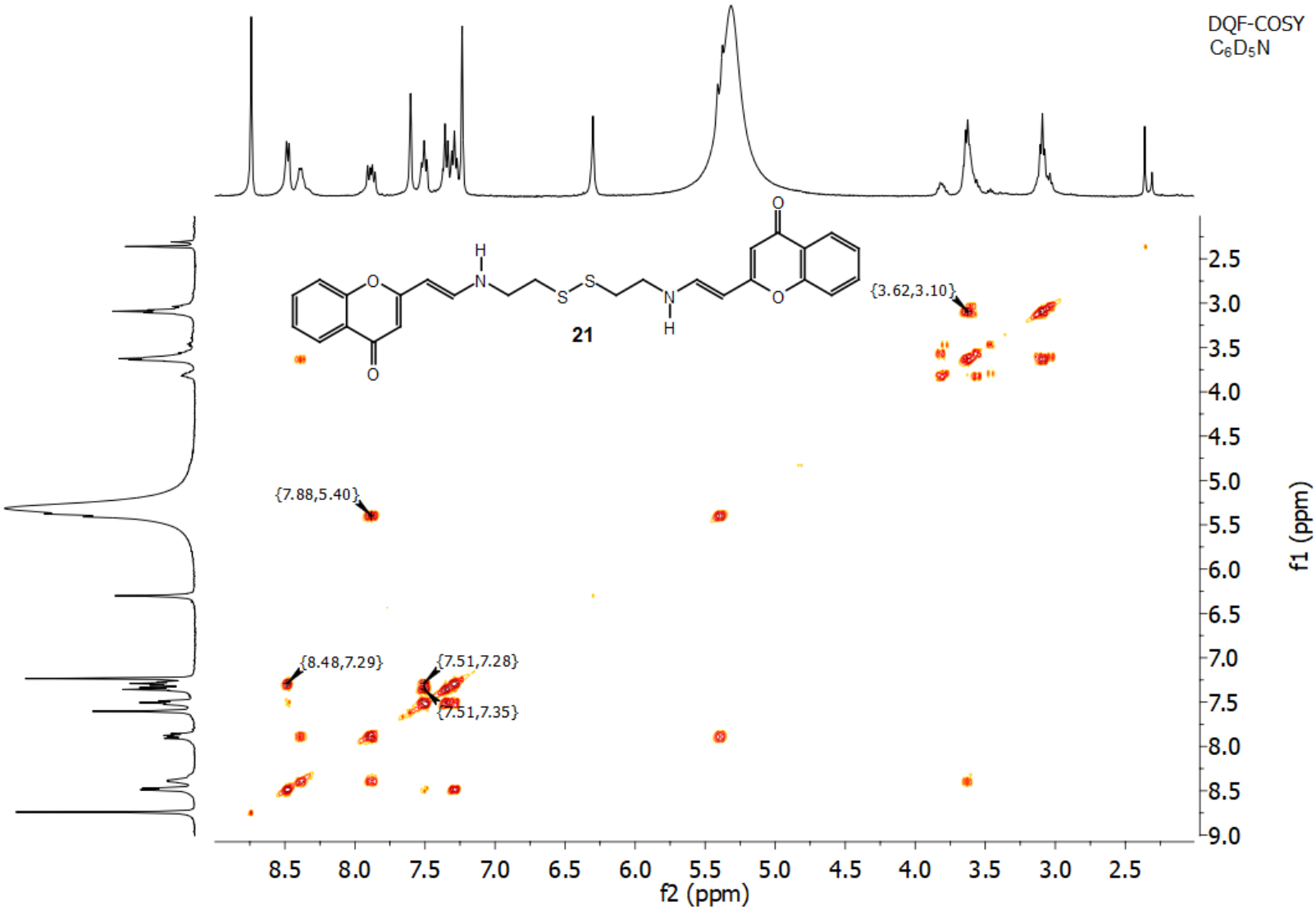
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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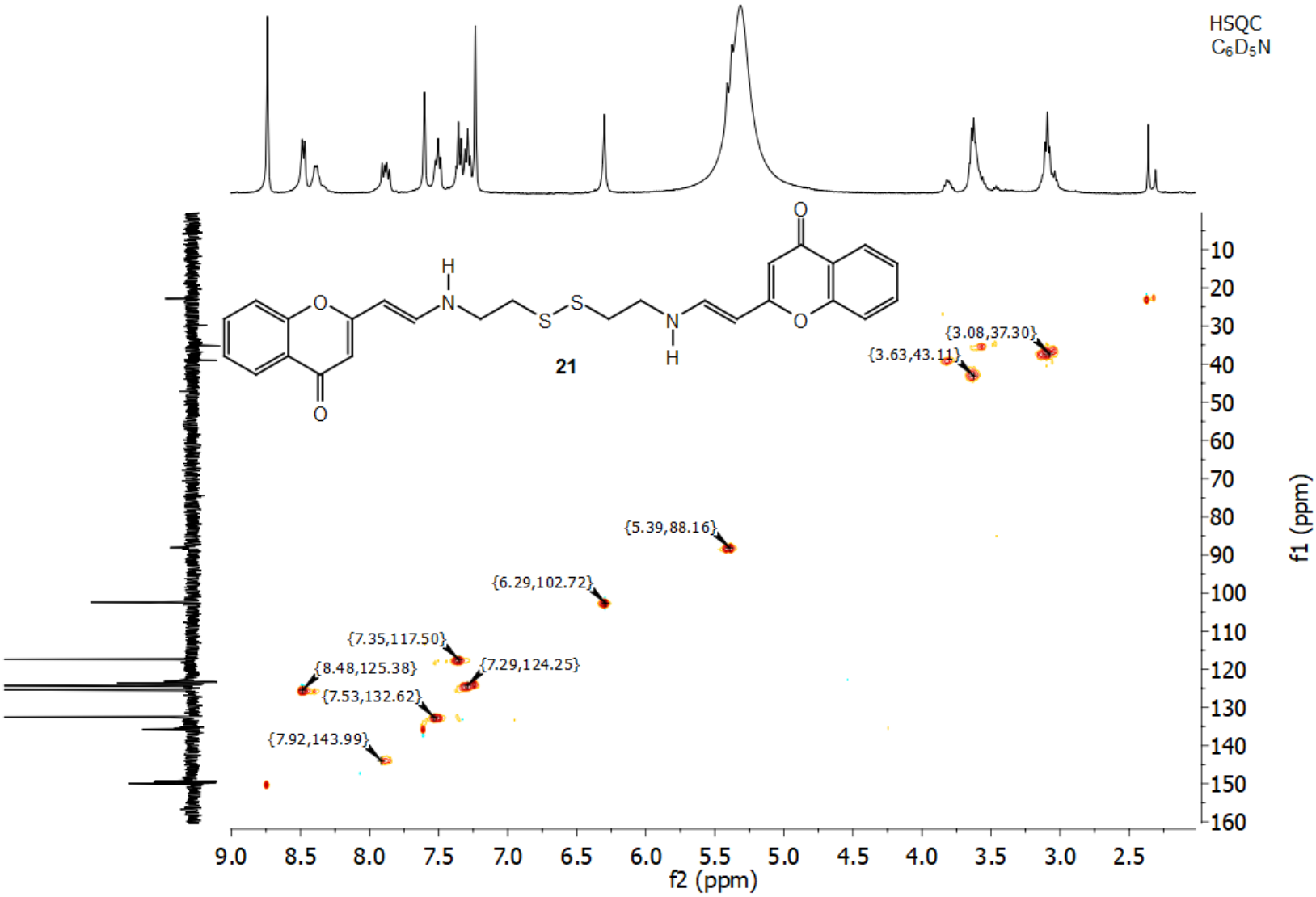
{7.51,7.35}
f2 (ppm)
f1 (ppm)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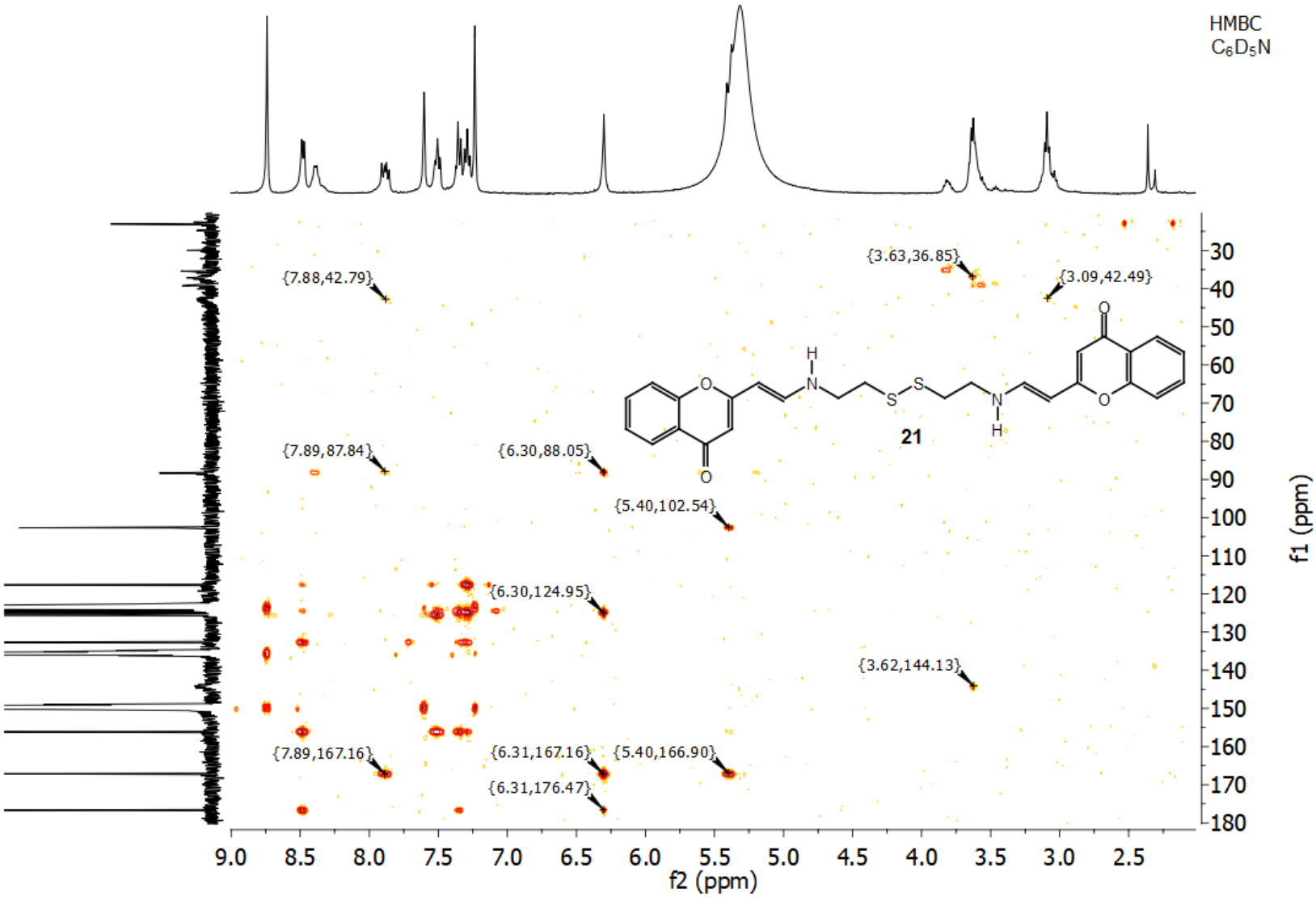
{7.53,132.62}
{7.92,143.99}
f2 (ppm)
f1 (ppm)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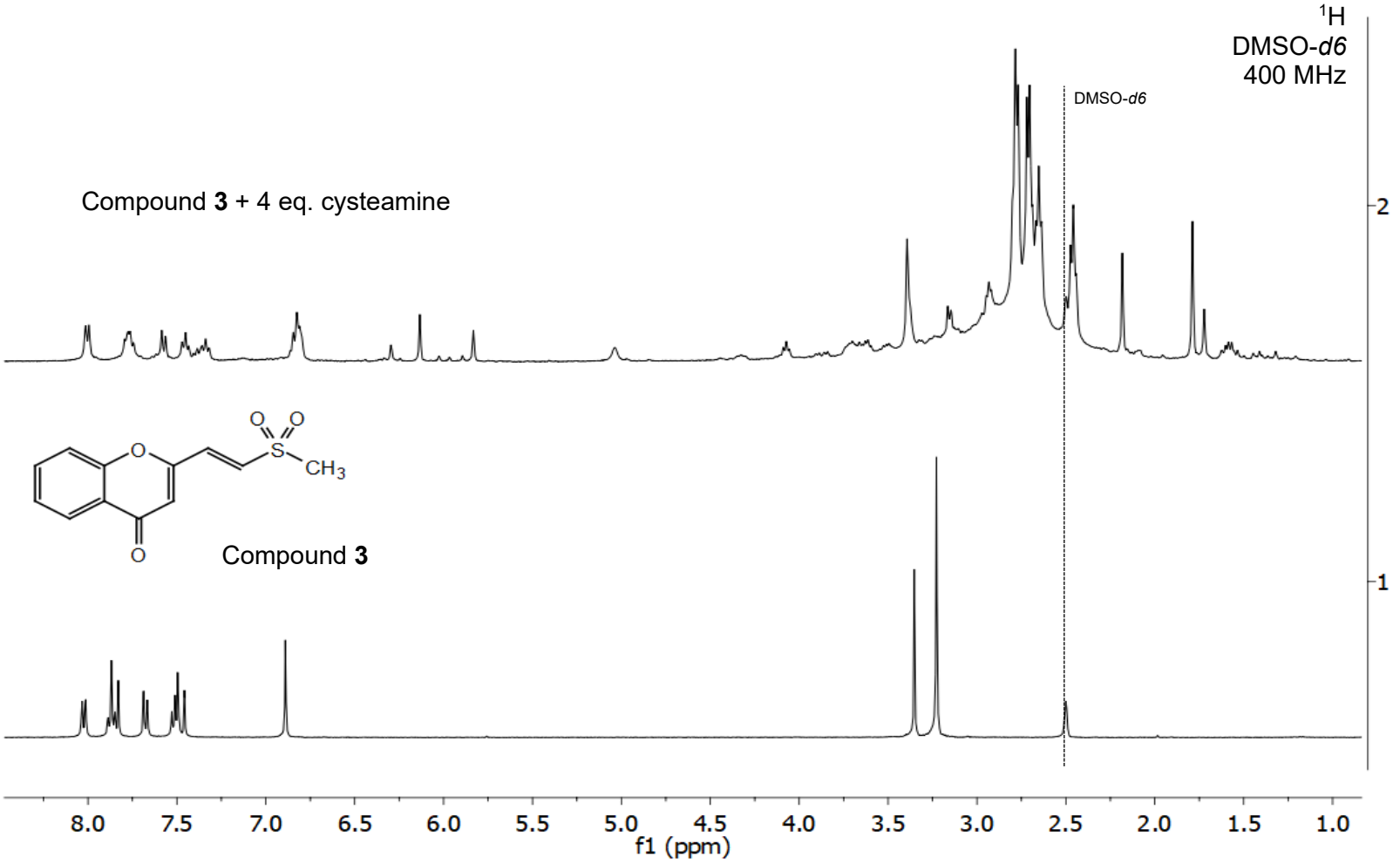
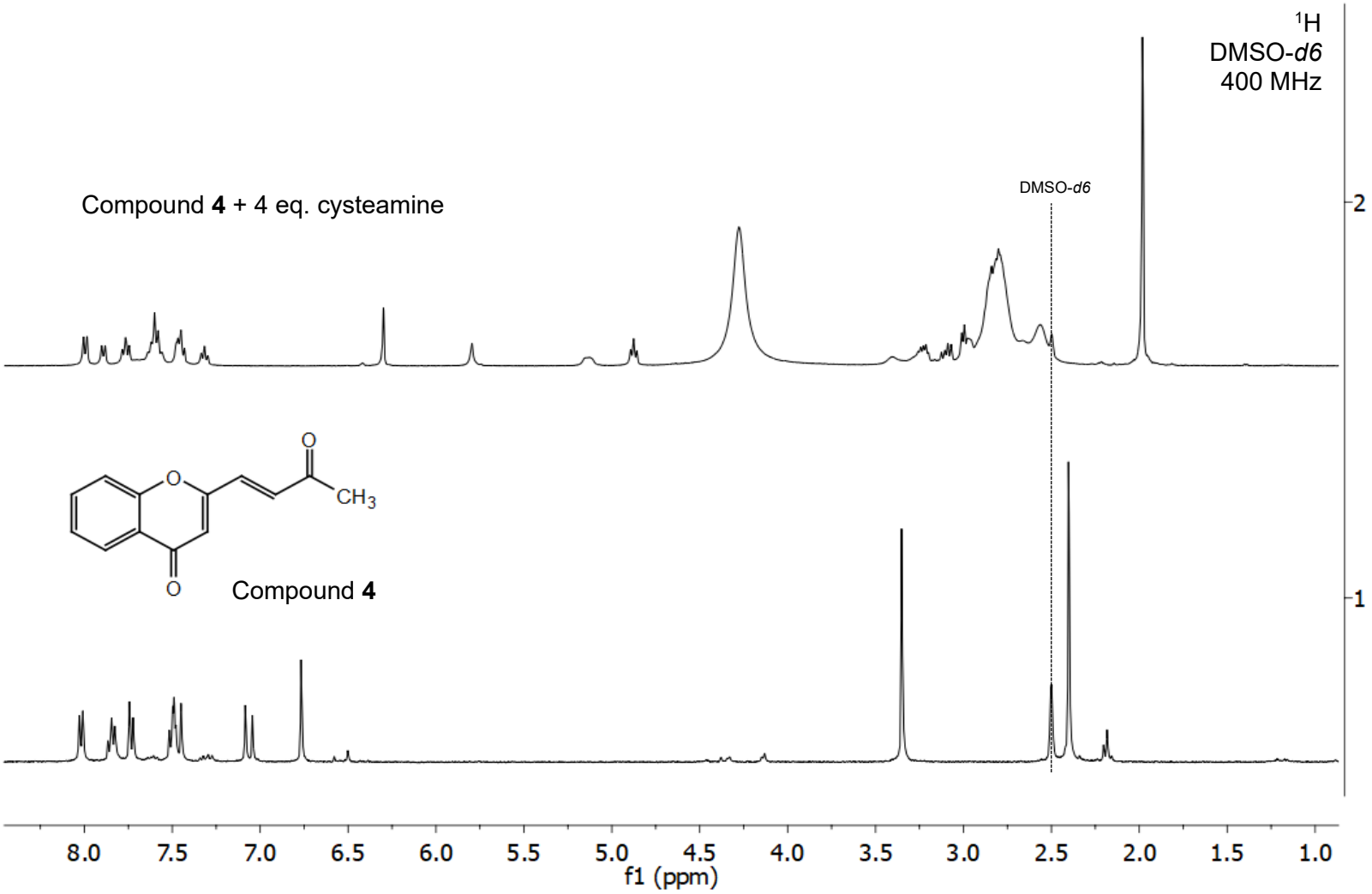
21
f2 (ppm)
f1 (ppm)

2.8.5 NMR spectra of Michael addition NMR assays




^{1}H
DMSO-*d6*
400 MHz
DMSO-*d6*
Compound **4** + 4 eq. cysteamine
Compound **4**
2
1
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

CHAPITRE III

EFFECT OF THE CHROMONE CORE SUBSTITUTION OF DIRCHROMONE ON THE RESULTANT BIOLOGICAL ACTIVITIES

Ce chapitre reprend le contenu d'un article de recherche publié en anglais. Il est donc présenté dans cette langue, avec un résumé en français.

Titre: Effect of the chromone core substitution of dirchromone on the resultant biological activities

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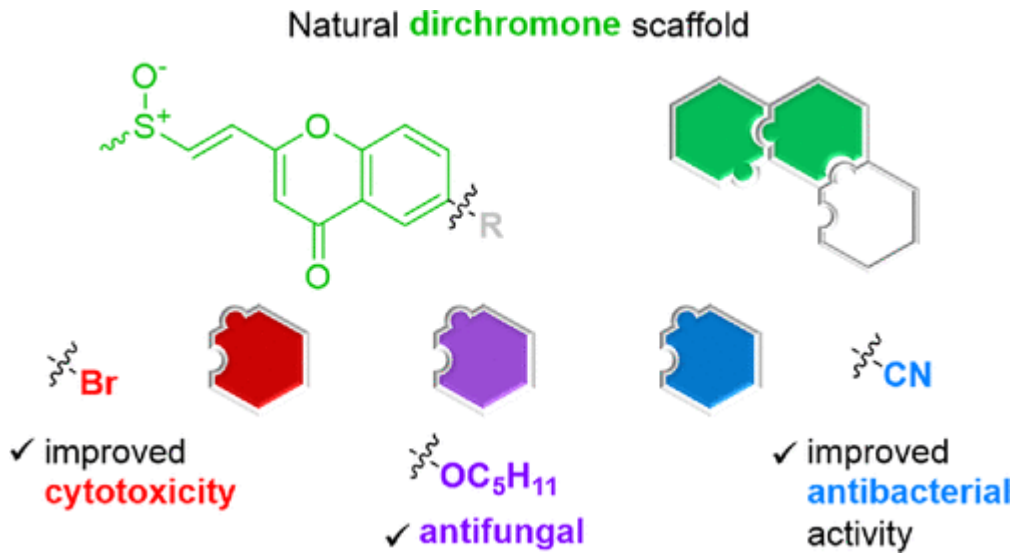
Référence complète: St-Gelais, A., Alsarraf, J., Legault, J., Mihoub, M., Pichette, A., 2021. Effect of the chromone core substitution of dirchromone on the resultant biological activities. J. Nat. Prod. **84** (*11*), 2786–2794.

3.1 Résumé en français

La dirchromone est une chromone bioactive porteuse d'une chaîne vinylsulfoxyde d'abord isolée à partir de l'arbuste *Dirca palustris*. Au total, 32 de ses dérivés ont été préparés pour évaluer l'effet de la substitution de son motif chromone sur les activités contre les lignées cellulaires cancéreuses du poumon et du côlon, les bactéries Gram-positive *Staphylococcus aureus*, et les champignons *Candida albicans*. Tous les composés ont été synthétisés suivant une stratégie de synthèse unifiée impliquant des réarrangements de Pummerer et de Baker-Vekataraman en conditions d'énolisation douce. La position des substituants a induit peu de variabilité pour les activités biologiques testées. Il n'existait pas de corrélation entre les activités cytotoxique et antibactérienne, suggérant des mécanismes d'action sous-jacents distincts. Tout particulièrement, les groupements hydroxyl et cyanure ont abaissé la cytotoxicité, alors que ce dernier a augmenté l'activité antibactérienne. Les homologues supérieurs de la série des 6-alkoxydirchromones ont également montré une activité antifongique émergeant progressivement. D'autres modifications ont eu un effet modéré sur la cytotoxicité avec certains analogues augmentant l'activité. Ce comportement a mis en lumière la robustesse du pharmacophore de la dirchromone vis-à-vis de la substitution, pavant la route vers l'ajout de groupements complexes conçus pour augmenter la sélectivité ou la capacité de ciblage de dérivés.

3.2 Graphical abstract



3.3 Abstract

Dirchromone is a bioactive vinyl sulfoxide-bearing chromone first isolated from the shrub *Dirca palustris*. Altogether, 32 of its derivatives were prepared to assess the effect of substitution of its chromone core upon activities against cancer cell lines, Gram-positive bacteria, and fungi (such as *Candida albicans*). All compounds were synthesized following a synthetic strategy involving Pummerer and soft-enolization Baker–Venkataraman rearrangements. Substituent position changes induced little variability on the activities tested. There was no correlation between cytotoxic and antibacterial effects, suggesting different underlying mechanisms of action. In particular, hydroxy group and cyanide substituents diminished cytotoxicity, with the latter featuring enhanced antibacterial activity. Higher homologues of 6-alkoxydirchromones also exhibited progressively emerging antifungal activity. Other modifications had moderate effects on cytotoxicity with some derivatives leading to

increased potency. This behavior highlights the robustness of the natural dirchromone pharmacophore toward decoration, thus paving the way for more elaborate drug design.

3.4 Article

3.4.1 Introduction

Chromone is a widely distributed molecular scaffold among natural products. Even discounting the numerous derivatives pertaining to the flavonoid and isoflavonoid families, the diversity of substitution groups and patterns found in plant secondary metabolites assembled around a chromone moiety is striking (Sharma et al., 2011). Chromones are also recurring synthetic molecular targets as many of their derivatives interact in pharmacologically relevant fashion with biochemical processes covering, among others, cancer, inflammation, microbial infections, coagulation, diabetes, neurological disorders and cardiovascular diseases, aptly qualifying them as a relevant motif in medicinal chemistry (Gaspar et al., 2014; Keri et al., 2014; Reis et al., 2017; Silva et al., 2016). Modulation and improvement of these activities is frequently approached through modification of their substituents nature and/or position (e.g., Feng et al., 2014; Fridén-Saxin et al., 2012; Gautam et al., 2011; Venkateswararao et al., 2014; Winter et al., 2013).

Eight sulfur-bearing chromones were previously isolated from *Dirca palustris* L. (Thymelaeaceae). These compounds, named dirchromones, share a distinctive vinylsulfoxide sidechain and differ by their aromatic substitution pattern with methoxy and hydroxy groups. Some of them exhibited encouraging activities in vitro against cancer cell lines and Gram-positive bacteria (St-Gelais et al., 2015). Consequently, a synthesis strategy comprising an uncommon Pummerer rearrangement and an unprecedented soft-enolization Baker-Venkataraman rearrangement as pivotal features was devised, allowing preparation of structurally diversified dirchromones in amenable

yields (St-Gelais et al., 2018). It was more recently demonstrated that the peculiar vinylsulfoxide sidechain has a high relevance for the aforementioned bioactivities, with the sulfone analogue having additional interest for antimicrobial properties (St-Gelais et al., 2020). Results obtained from the original set of eight natural derivatives further suggested that substitution of the chromone moiety also had relevance to modulate the activities: for example, when compared to the parent compound dirchromone (**1**) (Figure 3-1), 6-hydroxydirchromone (**11**) was not cytotoxic against human cell lines but retained some antibacterial activity. This triggered the investigation herein reported of the effects of position, nature, and bulkiness of substituents on bioactivity, taking advantage of the straightforward synthetic preparation of dirchromones. In addition to cytotoxic and antibacterial properties, antifungal activity on *Candida albicans* was also assessed despite the original eight natural dirchromones being inactive in that regard.

3.4.2 Results and discussion

Altogether, 33 dirchromones were prepared (Figure 3-1), including dirchromone (DC) itself (compound **1**). All compounds were obtained and tested as racemates of the sulfoxide since chirality was shown to have no impact on cytotoxic or antibacterial activities (St-Gelais et al., 2020). The effect of the position of substituents was studied by synthesizing DC methylated at positions 3, 5, 6, 7 and 8 (compounds **2-6**), as well as four methoxy-substituted DCs (compounds **7-10**, of which **8** and **9** were also observed in *D. palustris*). The importance of the nature of the substituent groups was screened at reference position 6, based on the previous isolation of the methoxy- and hydroxy- analogues (compounds **8** and **11**, respectively) of this series in the plant. Other introduced substituents were halogens (6-fluoro, 6-chloro and 6-bromoDCs, **12-14**), DC nitrile **15**, as well as DC esters **16a-g** and DC ethers **17a-g** of various chain lengths. The latter were prepared with the objective of assessing the effects of bulkiness and polarity on activity, with chains varying from two to five carbons and branching. Finally, additional rings were added to the DC scaffold by preparing 3-benzylDC (**18**),

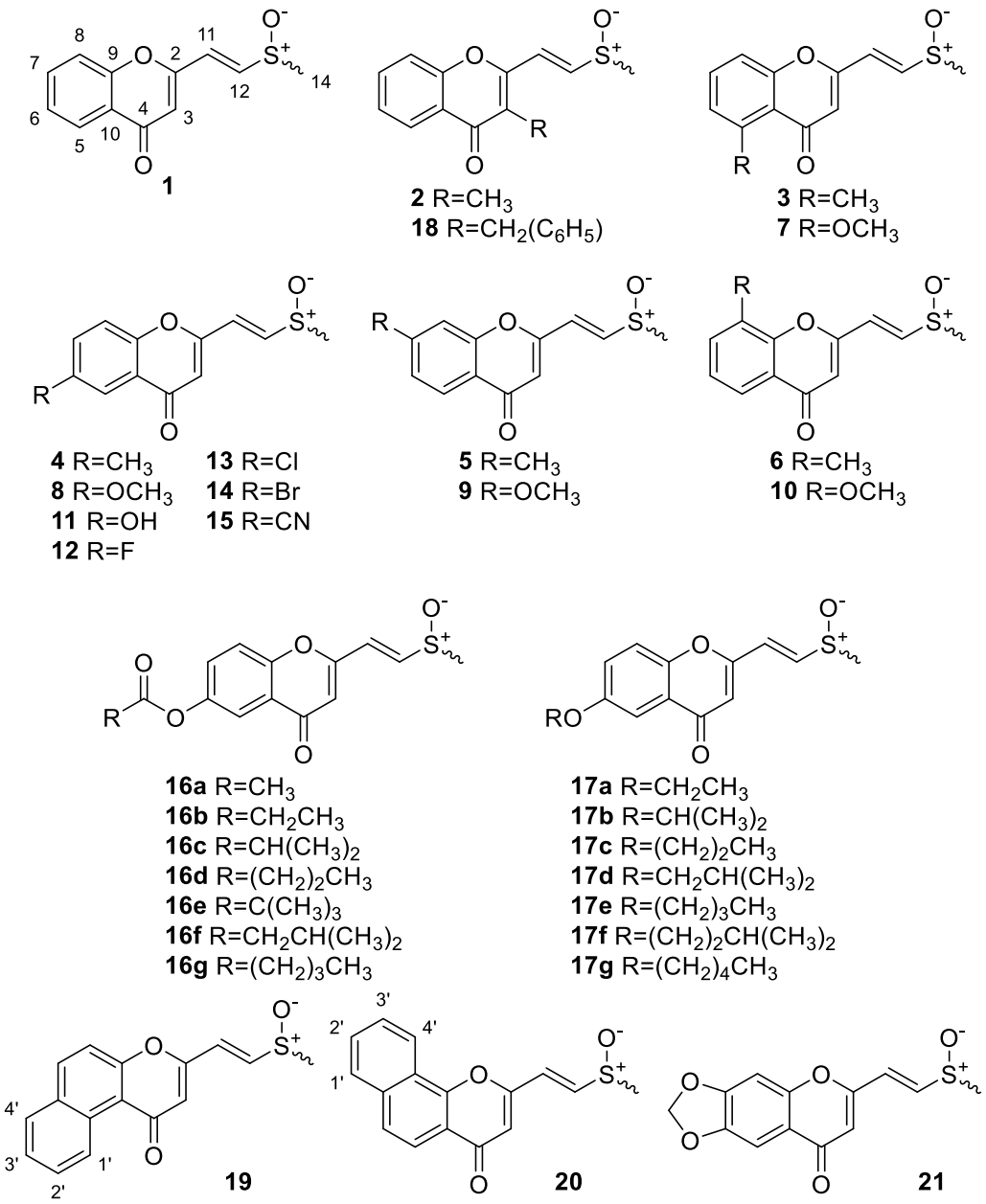
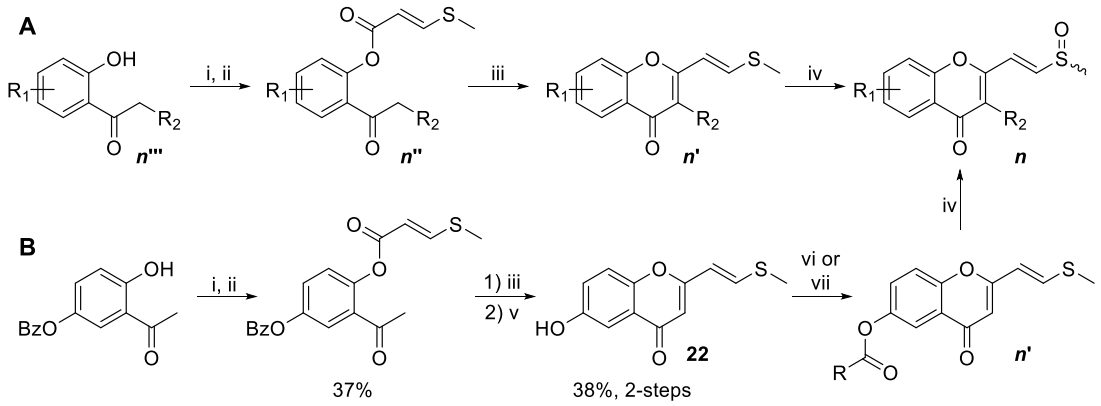


Figure 3-1. Structures of dirchromone (**1**) and its prepared and tested substituted analogs (**2-21**).

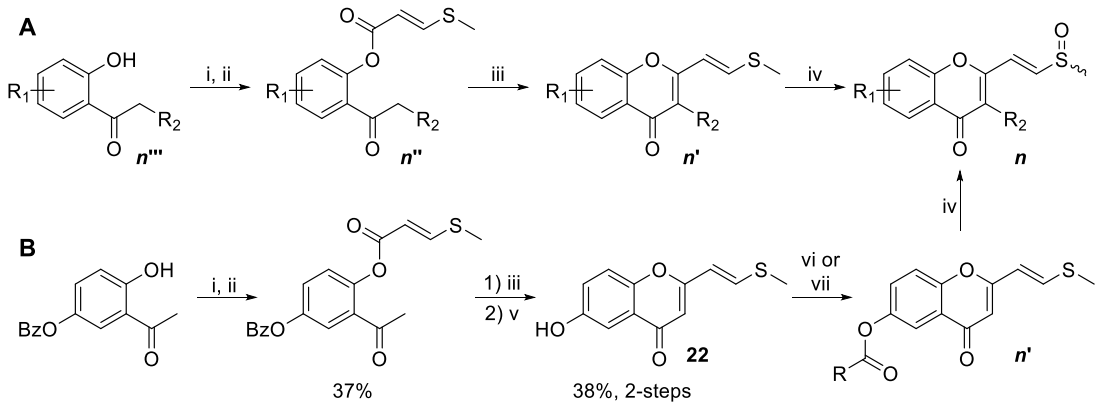
fused aromatics (compounds **19-20**), and a dioxolane derivative **21** to explore the influence of bulkiness.

Scheme 3-1. Synthetic routes for the preparation of compounds **2-15**, **17a-g**, and **18-21**. Reagents and conditions: *i)* KOH, CH_3OH, 5 min, rt then dried and dissolved in DMF; *ii)* 3-methylsulfinylpropionic acid, $(COCl)_2$ DMF, CH_2Cl_2, rt, 30 min then added slowly to *i*; *iii)* $MgBr_2 \cdot Et_2O$, diisopropylethylamine, CH_2Cl_2, 24 h, rt; *iv) meta*-chloroperbenzoic acid, CH_2Cl_2, 12-24 h, rt. Overall yields from the starting phenones: **2** (16 %), **3** (30 %), **4** (19 %), **5** (23 %), **6** (20 %), **7** (20 %), **8** (20 %), **9** (20 %), **10** (14 %), **12** (12 %), **13** (10 %), **14** (26 %), **15** (12 %), **17a** (12 %), **17b** (14 %), **17c** (11 %), **17d** (7 %), **17e** (18 %), **17f** (9 %), **17g** (10 %), **18** (16 %), **19** (28 %), **20** (13 %), **21** (8 %).



Whenever possible, compounds were prepared starting from commercially available, suitable 2′-hydroxyacetophenones, following the previously described synthetic strategy involving successive Pummerer and soft-enolization Baker-Venkataraman rearrangements (Scheme 3-1) (St-Gelais et al., 2018). 1-(2-Hydroxy-6-methylphenyl)-ethan-1-one (**3‴**) was prepared from ethyl 6-methylsalicylate and methylmagnesium bromide according to a previously described procedure (Fosso et al., 2015); a similar approach was used to convert methyl 3-methoxysalicylate to 1-(2-hydroxy-3-methoxyphenyl)ethan-1-one (**10‴**). 2′-Hydroxy-4′,5′-(methylenedioxy)-acetophenone (**21‴**), required to prepare compound **21**, was prepared from sesamol by heating the latter at 90 °C in acetic anhydride and boron trifluoride etherate (Vasquez-Martinez et al., 2007). The starting phenones **17a-g‴** were all obtained by Williamson alkylation, refluxing 2′,5′-dihydroxyacetophenone with the appropriate alkyl iodide or bromide in acetone with excess K_2CO_3 following a procedure described elsewhere (Roma et al., 2003); it should be mentioned that synthesis of the *tert*-butoxy derivative was attempted but that no alkylation occurred. Overall yields from the starting phenones to

Scheme 3-2. Synthesis of dirchromone esters **16a-g**. Reagents and conditions: i) acyl chloride, triethylamine, THF, rt, 24 h or ii) aliphatic acid, N-ethyl-N′-(3-dimethylaminopropyl)carbodiimide; iii) meta-chloroperbenzoic acid, CH_2Cl_2, 12-24 h, rt. Overall yields from compound **22**: **16a** (80 %), **16b** (41 %), **16c** (37 %), **16d** (39 %), **16e** (39 %), **16f** (45 %), **16g** (33 %).



the final DCs are summarized in Scheme 3-1. Finally, 6-hydroxyDC (**11**) and the corresponding esters (compounds **16a-g**) were prepared from 6-hydroxy-*S*-deoxyDC (**22**) (St-Gelais et al., 2018), which was esterified using either acyl chlorides and triethylamine or Steglich esterification conditions with the corresponding acids, then proceeding with sulfide to sulfoxide oxidation (Scheme 3-2).

Over the course of this study, only two exceptions to the generalization of DCs synthesis were observed. Preparation of 6-nitro-DC failed at the soft-enolization Baker-Venkataraman rearrangement step, with all products degrading. An attempt at replacing the aromatic ring with a pyridine analog, starting from 1-(3-hydroxypyridin-2-yl)ethan-1-one, failed at the same step, precluding isosteric replacement of the aromatic ring. Otherwise, the synthesis proceeded smoothly, illustrating the versatility of the strategy in the perspective of an ongoing investigation of DCs. In all cases, the most yield-limiting step was the dual esterification/Pummerer rearrangement step, which typically proceeded below 40 % yield.

The 33 DC analogues were screened for cytotoxic, antibacterial, and antifungal activities (Table 3-1). The cytotoxicity of the 33 DC analogs was evaluated against two cancer (A-549 and DLD-1) cell lines and one non-tumorigenic (WS1) cell line. The impact of the position of substituents was evaluated with a series of methylations and methoxylations. Overall, these modifications did not notably affect cytotoxicity (methylated compounds **2-6** and methoxy-bearing compound **8-10**), with the main exception being 5-methoxylation (compound **7**) that decreased activity about two-fold for all cell lines. This overall suggested that the substituent position was not critical for the observed biological activity. Observations on the impact of the type of substituent at position C-6 would therefore be expected to transpose reasonably to other positions. The nature of substituents in position 6 had, generally, moderate effects on cytotoxicity levels. A few exceptions stand out, and 6-hydroxyDC (**11**) and 6-cyanoDC (**15**) were less active than DC (**1**). Among the 6-halides, fluorine and chlorine derivatives **12** and **13** did not affect cytotoxicity, but bromine derivative **14** sensibly decreased the resultant IC_{50} values. The 6-alkoxydes **17d-f** reached similar activities to 6-bromo-DC (**14**). Within the series of esters **16a-g**, 6-acetyl-DC (**16a**) stood out as being less active than its homologues. This presumably arose from the lability of this function, with potential partial in situ hydrolysis of the molecule into the less cytotoxic 6-hydroxy-DC (**11**); otherwise, the esters prepared did not modulate cytotoxicity. Finally, the addition of aromatic substituents at position 3 (compound **18**) or fused to the ring (compound **19,** in particular) also yielded about a two-fold increase in cytotoxicity levels. In a more general perspective, most synthesized constituents were active with IC_{50} values well below 10 µM against the DLD-1 cell line. This is an interesting property of DCs, because it shows the tolerance to modification of the pharmacophore, previously shown to rely primarily on the vinylsulfoxide side chain (St-Gelais et al., 2020). Addition of lipophilic and/or bulkier substituents to the chromone core, such as bromide, isoamyloxyl or aryls, potentiated the activity somewhat. Since the DCs did not exhibit much selectivity between normal and cancer cell lines, future design efforts will need to include vectorization strategies. The fact that one can introduce a variety

Table 3-1. Biological activities of compounds **1-21**.

Compound *n*	MIC_{90} ± SD (*n* = 3), µM		IC_{50} ± SD (*n* = 3), µM		
	S. aureus	***C. albicans***	**A-549**	**DLD-1**[b]	**WS1**[c]
1	9 ± 1	>100	8 ± 1	1.9 ± 0.1	2.0 ± 0.2
2	20 ± 3	>100	7.2 ± 0.5	1.5 ± 0.1	2.1 ± 0.2
3	23 ± 2	>100	5.5 ± 0.5	1.3 ± 0.1	1.9 ± 0.2
4	10 ± 3	>100	7.0 ± 0.6	1.7 ± 0.2	1.8 ± 0.1
5	10 ± 3	>100	7 ± 1	2.0 ± 0.2	1.9 ± 0.1
6	10 ± 2	>100	6.8 ± 0.3	1.7 ± 0.2	2.2 ± 0.1
7	43 ± 4	>100	>10	3.8 ± 0.4	3.8 ± 0.5
8	6.1 ± 0.4	>100	5.7 ± 0.4	1.6 ± 0.2	1.3 ± 0.1
9	20 ± 2	>100	7.8 ± 0.2	2.2 ± 0.1	1.8 ± 0.1
10	11 ± 1	>100	9 ± 1	2.2 ± 0.2	1.9 ± 0.2
11	24 ± 3	>100	>10	10.5 ± 0.7	7.5 ± 0.6
12	5.3 ± 0.8	>100	7.0 ± 0.8	2.1 ± 0.2	1.7 ± 0.1
13	2.7 ± 0.7	>100	6.5 ± 0.2	1.7 ± 0.2	1.6 ± 0.1
14	2.5 ± 0.7	47 ± 5	4.5 ± 0.3	1.1 ± 0.1	1.0 ± 0.1
15	5.6 ± 0.6	>100	>10	>10	>10
16a	11 ± 3	>100	>10	4.1 ± 0.2	2.5 ± 0.2
16b	10 ± 2	>100	9.0 ± 0.8	2.4 ± 0.2	2.1 ± 0.2
16c	9 ± 2	>100	9.1 ± 0.9	2.4 ± 0.2	1.9 ± 0.1
16d	7.2 ± 0.9	>100	8.7 ± 0.5	2.2 ± 0.2	1.5 ± 0.1
16e	10 ± 1	71 ± 5	8 ± 1	1.6 ± 0.1	1.0 ± 0.1
16f	5.1 ± 0.3	72 ± 2	6.1 ± 0.7	2.3 ± 0.2	1.7 ± 0.1
16g	5.1 ± 0.3	47 ± 1	6.7 ± 0.4	2.4 ± 0.1	1.8 ± 0.1
17a	11.4 ± 0.9	67 ± 3	4.9 ± 0.7	1.5 ± 0.1	2.0 ± 0.3
17b	11.1 ± 0.7	84 ± 5	8 ± 1	1.5 ± 0.1	1.4 ± 0.2
17c	11 ± 1	39 ± 3	6.2 ± 0.9	1.1 ± 0.1	1.9 ± 0.2
17d	5.7 ± 0.4	13.4 ± 0.6	5 ± 1	1.1 ± 0.1	1.2 ± 0.1
17e	5.4 ± 0.9	14.1 ± 0.6	4.8 ± 0.7	1.4 ± 0.1	1.1 ± 0.1
17f	2.8 ± 0.1	8.4 ± 0.4	4.1 ± 0.9	1.0 ± 0.1	0.85 ± 0.03
17g	4.3 ± 0.6	7 ± 1	6.6 ± 0.3	1.6 ± 0.1	1.7 ± 0.1

18	2.9 ± 0.3	>100	5.1 ± 0.1	1.3 ± 0.1	1.2 ± 0.1
19	18 ± 2	>100	4.3 ± 0.3	0.94 ± 0.10	0.88 ± 0.03
20	4.8 ± 0.6	>100	7.0 ±0.8	1.4 ± 0.1	1.9 ± 0.1
21	39 ± 3	>100	6.0 ± 0.2	2.1 ± 0.2	2.0 ± 0.2
gentamicin[d]	0.09 ± 0.01	-	-	-	-
amphotericin B[e]	-	1.4 ± 0.1	-	-	-
etoposide[f]	-	-	0.57 ± 0.09	4.8 ± 0.8	47 ± 16

[a] A-549: human lung carcinoma cell line. [b] DLD-1: human colorectal adenocarcinoma cell line. [c] WS1: human skin fibroblast cell line. [d] Gentamicin was used as a positive control for antibacterial assays. [e] Amphotericin B was used as a positive control for antifungal assays. [f] Etoposide was used as a positive control for cytotoxicity assays.

of substituents, even adding in bulkiness, while retaining the core activity is therefore an incentive to pursue investigations of elaborate molecular constructs that include advanced drug delivery and targeting designs. One could then take advantage of the fluorescence generated by DC to probe its delivery to target cells or tissues (St-Gelais et al., 2020).

The antibacterial activity of the 33 DC analogues was measured against the Gram-positive *Staphylococcus aureus* (Table 3-1). As far as the substituent positions were concerned, methylation of positions C-3 and C-5 (compounds **2** and **3**), and methoxylation of positions C-5 and C-7 (compounds **7** and **9**) decreased antibacterial activity, whereas this remained unchanged at other positions. Most other derivatives at least matched the activity of DC (**1**). Exceptions included compounds **19** and **21** along with 6-hydroxyDC (**11**). It should be noted that the loss in activity for compound **11** was less important for antibacterial activity than it was for cytotoxicity, thereby leading to increased selectivity of the antibacterial activity. On the other hand, halides of DC, in particular, 6-chloroDC (**13**) and 6-bromoDC (**14**), displayed increased antibacterial potential, as did compound **18**. This was also observed for higher homologues of the esters **16a-g** and ethers **17a-g** series. That being said, of all prepared derivatives, 6-

cyano-DC (**15**) possibly is the most interesting candidate for further examination. Although it was not the most active derivative against *S. aureus*, it combined an increase in antibacterial potential with a lack of cytotoxicity on human cell lines (the IC_{50} concentration was not yet reached at 100 μM). This was the most telling example of a more generic observation: for all prepared compounds, there was no correlation at all between cytotoxicity and MIC_{90} values (e.g., Pearson's r of -0.07, p = 0.69 for DLD-1 vs. *S. aureus*). This was a strong argument that the fundamental mechanism of toxicity is different in bacteria in comparison to human cells. Therefore, a future search for non-toxic antibacterial derivatives of dirchromone could include combining oxidation of the side chain to the sulfone[13] to either hydroxy or nitrile substituents of the aromatic ring, with all these modifications taking advantage of this differentiation between toxicity mechanisms against human cells and Gram-positive bacteria.

Although the originally reported natural DCs lacked antifungal activity, the compounds prepared herein were nevertheless screened for *C. albicans* inhibiting activity. While most derivatives were inactive, as expected, this led to the serendipitous observation that C-5 esters **16e-16g** (marginally), 6-bromo-DC (**14**) and the 6-alkoxides **17a-g** did exhibit some antifungal response. The alkoxide series was particularly interesting, since there was a definite trend seen for progressively longer carbon chains to induce more potent activity, with 6-amyloxy-DC (**17g**) being the most active. This trend was more pronounced than for the slight increase in cytotoxicity observed for the same series. Therefore, it would be interesting to explore in the future the potential of long-chain alkoxides of DCs to exert antifungal activity at levels sensibly lower than their cytotoxic threshold.

The preparation of 33 diversely substituted dirchromone derivatives illustrates the robustness of the combined Pummerer rearrangement/soft-enolization Baker-Venkataraman synthetic route towards this particular class of compounds. Cytotoxic assays showed that several analogues including 6-bromo-DC (**14**), 6-isoamyloxy-DC

(**16f**), as well as addition of aromatic rings in compounds **18** and **19** slightly improved the potency. The natural pharmacophore, however, generally appeared robust regardless of most substituents, opening some perspectives for more refined designs and eventually vectorization of dirchromone. Antibacterial activity was also increased for some derivatives, with the most interesting compound likely being 6-cyano-DC (**15**) with improvement of the antibacterial potential coupled to inhibition of the cytotoxicity on human cell lines. Absence of correlation between cytotoxic and antibacterial activities suggested that the underlying mechanism of activity differed in both cases, further prompting research toward non-toxic, antibacterial analogues. Higher homologs of 6-alkoxydirchromone also exhibited an emerging antifungal activity against *C. albicans*. These findings offer interesting perspectives toward future exploration of the dirchromone pharmacophore.

3.4.3 Experimental section

General Experimental Procedures. All starting materials and reagents were purchased from commercial sources (Sigma-Aldrich, Toronto Research Chemicals, TCI America, Alfa Aesar, and Oakwood Chemicals) and were used as received without further purification. Unless noted otherwise, reactions were conducted using anhydrous commercial solvents under argon atmosphere, introducing reagents with dry disposable syringes and needles. Anhydrous solvents, supplied over molecular sieves, were used as received. Reactions were monitored by thin-layer chromatography (TLC) with silica gel 60 F_{254} 0.25 mm pre-coated aluminum foil plates (MilliPore) and visualized under UV_{254} light. All flash chromatographic purifications were performed using a low-pressure liquid chromatographic system (Büchi) and silica gel 60 (15-40 µm) columns (Silicycle). NMR spectra were recorded with a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei, using deuterated chloroform ($CDCl_3$) or dimethylsulfoxide ($(CD_3)_2SO$) as the solvent. Chemical shifts were reported in ppm relative to the solvent residual peak (δ = 7.26 ppm for ^{1}H and 77.1 ppm for ^{13}C in

chloroform; δ = 2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C in DMSO (Fulmer et al., 2010)) and coupling constants *J* in Hertz (Hz). Multiplicities were reported using the following abbreviations: s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet. HRMS were recorded on an Agilent 6224 MS-TOF mass spectrometer equipped with an electrospray source. Purities were measured by injecting the compounds dissolved at about 1 mg/mL in acetonitrile on an Agilent 1100 HPLC system equipped with a DAD detector, and monitoring the chromatogram at 254 nm with a 100 nm bw (reference 375 nm, 5 nm bw), except where noted otherwise; a blank run was substracted. The column used was a Kinetex C_{18} 250 x 4.6 mm column (5 µm particle size, Phenomenex), maintained at 25 °C, with a gradient from 10 to 100 % acetonitrile (0.1 % formic acid) in water (0.1 % formic acid) in 12 min, with pure acetonitrile maintained for 3 further min, at 1 mL/min.

The DLD-1 human colorectal adenocarcinoma, A549 human lung carcinoma, and WS1 human skin fibroblast cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cell lines were grown in minimum essential medium containing Earle's salt (Mediatech Cellgro, Herndon, VA, USA), supplemented with 10 % fetal calf serum (Hyclone, Logan, UT, USA), 1 × solution of vitamins, 1 × sodium pyruvate, 1 × non-essential amino acids, 100 I.U. of penicillin and 100 µg/mL of streptomycin (Mediatech Cellgro). Cells were cultured at 37 °C in a humidified atmosphere containing 5 % CO_2. Exponentially growing cells were plated at a density of 5×10^3 cells per well in 96-well microplates (BD Falcon) in culture medium (100 µL) and were allowed to adhere for 16 h before treatment. Then, cells were were incubated for 48 h in the presence or absence of 100 µL of increasing concentrations of compounds dissolved in culture medium and DMSO. The final concentration of DMSO in the culture medium was maintained at 0.5 % (v/v) to avoid toxicity. Cytotoxicity was assessed using Hoechst (bis-benzimide) (Rage et al., 1990). It was expressed as the concentration of drug inhibiting cell growth by 50 % (IC_{50}).

Antibacterial and antifungal activities were evaluated using a modified microdilution method (Banfi et al., 2003). Exponentially growing microorganisms were plated in 96-well round-bottomed microplates (Costar, Corning Inc.) at a density of 3.5×10^4 Gram-positive *Staphylococcus aureus* (ATCC 25923) per well in 100 µL of nutrient broth (Difco) or 2×10^3 *Candida albicans* (ATCC 10231) per well in 100 µL of Sabouraud dextrose (Difco). Increasing concentrations of compounds (solubilized in Biotech DMSO, then diluted in nutrient broth or Sabouraud dextrose) were then added (100 µL per well). The final concentration of DMSO in the culture medium was maintained at 0.1 % (volume/volume) to avoid solvent toxicity. The plates were incubated for 24 h at 37 °C. Absorbance was read using a Varioskan Ascent plate reader (Thermo Electron) at 600 nm for bacteria and 540 nm for yeasts.

General Procedure for the Preparation of Phenolates (*i*). Phenone **n‴** (generally of commercial origin) was mixed to ACS grade methanol. To this solution was added potassium hydroxide (1 equiv.), and the resulting solution was sonicated until all the base was dissolved. This solution was then thoroughly evaporated under reduced pressure. The resulting solid was then dissolved in 5 mL of dry dimethylformamide and used immediately in the Pummerer rearrangement/esterification sequence (*ii*).

General procedure for the Pummerer rearrangement/esterification sequence (*ii*). To a solution of 3-methylsulfinylpropionic acid in dry dichloromethane containing a drop of dry dimethylformamide was slowly added oxalyl chloride (2 equiv.) under an argon atmosphere. The solution was stirred at room temperature for approximately 1 h, or until no more gas was evolving.

At this point, the solution was transferred into solution *i*. containing 2-4 equiv. of phenone **n‴** with vigorous stirring. After 10 min, the reaction was quenched with NH_4Cl, and extracted with ethyl acetate/toluene (1:1). The organic phase was washed

with 3 × NH_4Cl, 1 × brine, dried with Na_2SO_4, and evaporated prior to chromatographic purification.

General Procedure for the Soft-enolization Baker-Venkataraman Rearrangement Followed by Dehydrative Cyclization (*iii*). Ester **n″** was suspended in ACS grade dichloromethane open to air, and magnesium bromide diethyl etherate (2.5 equiv.) was added. The resulting suspension was stirred for 2 min, and diisopropylethylamine (3 equiv.) was added. The reaction was stirred overnight with a stopper to prevent excessive evaporation of the solvent. The reaction was quenched by pouring 10 % aqueous hydrochloric acid into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, and evaporated. The dried residue was then dissolved in ACS grade methanol. Concentrated (37 %) hydrochloric acid was then added, and the solution was stirred overnight. The reaction was quenched by pouring 30 mL of saturated $NaHCO_3$ into the reaction vessel and was extracted with 3 × dichloromethane. The combined organic phases were washed with brine, dried with Na_2SO_4, and evaporated prior to chromatographic purification.

General Procedure for the Oxidation of Sulfides (*iv*). Sulfide **n'** was suspended in ACS grade dichloromethane open to air, and *meta*-chloroperbenzoic acid 75 % (1 equiv.) dissolved in a small amount of dichloromethane was added. The reaction was stirred overnight and evaporated to dryness prior to chromatographic purification.

3-Methyldirchromone (2). The compound was prepared from 3-methyldeoxydirchromone (St-Gelais et al., 2018) (**2′**, 89 mg, 0.38 mmol). The dried residue was purified by flash chromatography with 5-25 % acetone in dichloromethane to afford compound **2** (71 mg, 75 %) as an off-white solid; R_f = 0.50 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, dd, *J* = 8.0, 1.1 Hz, H-5), 7.60 (1H, ddd, *J* = 8.5, 7.1, 1.4 Hz, H-7), 7.49 (1H, d, *J* = 14.8 Hz, H-12), 7.35 (1H, d, *J* = 8.5 Hz, H-

8), 7.32 (1H, d, *J* = 14.8 Hz, H-11), 7.30 (1H, t, *J* = 7.5 Hz, H-6), 2.75 (3H, s, H-14), 2.16 (3H, s, 3-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (C, C-4), 155.2 (C, C-9), 153.7 (C, C-2), 141.1 (CH, C-12), 133.9 (CH, C-7), 125.9 (CH, C-5), 124.93 (CH, C-11), 124.89 (CH, C-6), 122.4 (C, C-10), 120.2 (C, C-3), 117.5 (CH, C-8), 40.4 (CH_3, C-14), 9.6 (CH_3, 3-CH_3); HRESIMS *m/z* 249.0573 $[M+H]^+$, calcd for $C_{13}H_{13}O_3S$, 249.0580; HPLC purity 99.5 %.

5-Methyldirchromone (3). The compound was prepared from 5-methyldeoxydirchromone (**3′**, 157 mg, 0.68 mmol). The dried residue was purified by flash chromatography with 10-70 % ethyl acetate in hexanes to afford compound **3** (137 mg, 81 %) as a white solid; R_f = 0.28 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 14.9 Hz, H-12), 7.45 (1H, t, *J* = 7.9 Hz, H-7), 7.23 (1H, d, *J* = 8.3 Hz, H-8), 7.06 (1H, d, *J* = 7.3 Hz, H-6), 6.93 (1H, d, *J* = 14.9 Hz, H-11), 6.23 (1H, s, H-3), 2.77 (3H, s, 5-CH_3), 2.74 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3 (C, C-4), 157.3 (C, C-9), 156.4 (C, C-2), 141.2 (CH, C-12), 141.1 (C, C-5), 133.1 (CH, C-7), 128.0 (CH, C-6), 127.1 (CH, C-11), 122.3 (C, C-10), 115.8 (CH, C-8), 114.3 (CH, C-3), 40.3 (CH_3, C-14), 22.7 (CH_3, 5-CH_3); HRESIMS *m/z* 249.0576 $[M+H]^+$, calcd for $C_{13}H_{13}O_3S$, 249.0580; HPLC purity 98.6 %.

6-Methyldirchromone (4). The compound was prepared from 6-methyldeoxydirchromone (**4′**, 101 mg, 0.43 mmol). The dried residue was purified by flash chromatography with 30-70 % ethyl acetate in hexanes to afford compound **4** (98.1 mg, 92 %) as a white solid; R_f = 0.26 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, s, H-5), 7.48 (1H, d, *J* = 14.9 Hz, H-12), 7.38 (1H, d, *J* = 8.3 Hz, H-7), 7.24 (1H, d, *J* = 8.3,H-8), 6.89 (1H, d, *J* = 14.9, H-11), 6.24 (1H, s, H-3), 2.70 (3H, s, H-14), 2.31 (3H, s, 6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C, C-4), 157.8 (C, C-2), 153.9 (C, C-9), 141.6 (CH, C-12), 135.4 (C, C-6), 135.3 (CH, C-7), 127.0 (CH, C-11), 124.8 (CH, C-5), 123.4 (C, C-10), 117.5 (CH, C-8), 112.7 (CH, C-3), 40.2 (CH3, C-14), 20.8 (CH_3, 6-CH_3); HPLC purity 99.6 %.

7-Methyldirchromone (5). The compound was prepared from 7-methyldeoxydirchromone (**5′**, 135 mg, 0.58 mmol). The dried residue was purified by flash chromatography with 0-35 % acetone in dichloromethane to afford compound **5** (111 mg, 77 %) as a beige solid; R_f = 0.30 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* = 8.1 Hz, H-5), 7.48 (1H, d, *J* = 14.9 Hz, H-12), 7.17 (1H, s, H-8), 7.13 (1H, d, *J* = 8.1 Hz, H-6), 6.93 (1H, d, *J* = 14.9 Hz, H-11), 6.26 (1H, s, H-3), 2.72 (3H, s, H-14), 2.40 (3H, s, 7-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C, C-4), 157.7 (C, C-2), 155.9 (C, C-9), 145.7 (C, C-7), 141.5 (CH, C-12), 127.2 (CH, C-11), 126.9 (CH, C-6), 125.4 (CH, C-5), 121.6 (C, C-10), 117.6 (CH, C-8), 113.0 (CH, C-3), 40.3 (CH_3, C-14) 21.8 (CH_3, 7-CH3); HRESIMS *m/z* 249.0573 $[M+H]^+$, calcd for $C_{13}H_{13}O_3S$, 249.0580; HPLC purity 99.8 %.

8-Methyldirchromone (6). The compound was prepared from 8-methyldeoxydirchromone (**6′**, 117 mg, 0.51 mmol). The dried residue was purified by flash chromatography with 30-70 % ethyl acetate in hexanes to afford compound **6** (107 mg, 85 %) as an off-white solid; R_f = 0.21 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 7.9 Hz, H-5), 7.46 (1H, d, *J* = 14.9 Hz, H-12), 7.43 (1H, d, *J* = 7.0 Hz, H-7) 7.19 (1H, t, *J* = 7.6 Hz, H-6), 6.96 (1H, d, *J* = 14.9 Hz, H-11), 6.29 (1H, s, H-3), 2.75 (3H, s, H-14), 2.42 (3H, s, 8-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 (C, C-4), 157.6 (C, C-2), 154.1 (C, C-9), 141.4 (CH, C-12), 135.2 (CH, C-7), 127.4 (CH, C-11), 127.2 (C, C-8), 124.9 (CH, C-6), 123.6 (C, C-10), 123.2 (CH, C-5), 112.7 (CH, C-3), 40.2 (CH_3, C-14), 15.6 (CH_3, 8-CH_3); HRESIMS *m/z* 249.0573 [M+H]+, calcd for $C_{13}H_{13}O_3S$, 249.0580; HPLC purity 97.5 %.

5-Methoxydirchromone (7). The compound was prepared from 5-methoxydeoxydirchromone (St-Gelais et al., 2018) (**7′**, 134 mg, 0.54 mmol). The dried residue was purified by flash chromatography with 40-80 % acetone in hexanes to afford compound **7** (115 mg, 80 %) as an off-white solid; R_f = 0.22 (hexane-acetone

1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, t, *J* = 8.4 Hz, H-7), 7.43 (1H, d, *J* = 14.9 Hz, H-12), 6.93 (1H, d, *J* = 8.4 Hz, H-8), 6.86 (1H, d, *J* = 14.9 Hz, H-11), 6.74 (1H, d, *J* = 8.3 Hz, H-6), 6.19 (1H, s, H-3), 3.88 (3H, s, 5-OCH_3), 2.70 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C, C-4), 159.7 (C, C-5), 157.7 (C, C-9), 156.0 (C, C-2), 141.2 (CH, C-12), 134.3 (CH, C-7), 126.7 (CH, C-11), 114.43 (CH, C-3), 114.40 (C, C-10), 109.8 (CH, C-8), 106.6 (CH, C-6), 56.4 (CH_3, 5-OCH_3), 40.2 (CH_3, C-14); HRESIMS *m/z* 265.0519 $[M+H]^+$, calcd for $C_{13}H_{13}O_4S$, 265.0529 ; HPLC purity 98.7 %.

6-Methoxydirchromone (8). The compound was prepared from 6-methoxydeoxydirchromone (**8′** , 138 mg, 0.56 mmol). The dried residue was purified by flash chromatography with 10-100 % acetonitrile in dichloromethane to afford compound **8** (120 mg, 81 %) as an off-white solid; R_f = 0.15 (hexane-acetone 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 15.1 Hz, H-12), 7.46 (1H, d, *J* = 3.0 Hz, H-5), 7.34 (1H, d, *J* = 9.1 Hz, H-8), 7.22 (1H, dd, *J* = 9.1, 3.0 Hz, H-7), 6.96 (1H, d, *J* = 15.1 Hz, H-11), 6.31 (1H, s, H-3), 3.82 (3H, s, 6-OCH_3), 2.73 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C, C-4), 157.8 (C, C-2), 157.1 (C, C-6), 150.6 (C, C-9), 141.5 (CH, C-12), 127.3 (CH, C-11), 124.6 (C, C-10), 124.2 (CH, C-7), 119.3 (CH, C-8), 112.3 (CH, C-3), 104.9 (CH, C-5), 55.9 (CH_3, 6-OCH_3), 40.3 (CH_3, C-14); HRESIMS *m/z* 265.0518 $[M+H]^+$, calcd for $C_{13}H_{13}O_4S$, 265.0529; HPLC purity 99.4 %.

7-Methoxydirchromone (9). The compound was prepared from 7-methoxydeoxydirchromone (**9′** , 60 mg, 0.24 mmol). The dried residue was purified by flash chromatography with 30-70 % acetone in hexanes to afford compound **9** (53 mg, 84 %) as an off-white solid; R_f = 0.35 (hexane-acetone 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 8.9 Hz, H-5), 7.46 (1H, d, *J* = 14.9 Hz, H-12), 6.94 (1H, d, *J* = 14.9 Hz, H-11), 6.91 (1H, dd, *J* = 8.9, 2.3 Hz, H-6), 6.80 (1H, d, *J* = 2.3 Hz, H-8), 6.26 (1H, s, H-3), 3.86 (3H, s, 7-OCH_3), 2.74 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C, C-4), 164.5 (C, C-7), 157.7 (C, C-2), 157.6 (C, C-9), 141.2 (CH,

C-12), 127.2 (CH, C-5 or C-11), 127.1 (CH, C-5 or C-11), 117.8 (C, C-10), 114.5 (CH, C-6), 113.1 (CH, C-3), 100.3 (CH, C-8), 55.9 (CH_3, 7-OCH_3), 40.3 (CH_3, C-14); HRESIMS *m/z* 265.0519 $[M+H]^+$, calcd for $C_{13}H_{13}O_4S$, 265.0529; HPLC purity 99.9 %.

8-Methoxydirchromone (10). The compound was prepared from 8-methoxydeoxydirchromone (**10′**, 116 mg, 0.47 mmol). The dried residue was purified by flash chromatography with 20-85 % acetonitrile in dichloromethane to afford compound **10** (74 mg, 60 %) as an off-white solid; R_f = 0.29 (hexane-acetone 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, dd, *J* = 8.0, 1.0 Hz, H-5), 7.57 (1H, d, *J* = 14.9 Hz, H-12), 7.26 (1H, dd, *J* = 9.0, 7.1 Hz, H-6), 7.13 (1H, dd, *J* = 8.1, 1.0 Hz, H-7), 6.98 (1H, d, *J* = 14.9 Hz, H-11), 6.33 (1H, s, H-3), 3.94 (3H, s, 8-OCH_3), 2.75 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (C, C-2), 157.8 (C, C-2), 148.8 (C, C-8), 146.1 (C, C-9), 142.0 (CH, C-12), 127.2 (CH, C-11), 125.1 (CH, C-6), 124.9 (C, C-10), 116.4 (CH, C-5), 114.8 (CH, C-7), 112.9 (CH, C-3), 56.3 (CH_3, 8-OCH_3), 40.3 (CH_3, C-14); HRESIMS *m/z* 265.0527 $[M+H]^+$, calcd for $C_{13}H_{13}O_4S$, 265.0529; HPLC purity 99.4 %.

6-Hydroxydirchromone (11). The compound was prepared from 6-hydroxydeoxydirchromone (**22**, 122 mg, 0.52 mmol). The dried residue was purified by flash chromatography with 0-10 % methanol in dichloromethane to afford compound **11** (75 mg, 57 %) as an off-white solid which corresponded to natural 6-hydroxydirchromone;[11] R_f = 0.10 (dichloromethane-acetone 3:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (1H, d, *J* = 15.1 Hz, H-12), 7.48 (1H, d, *J* = 8.9 Hz, H-8), 7.28 (1H, d, *J* = 3.0 Hz, H-5), 7.25 (1H, dd, *J* = 8.9, 3.0 Hz, H-7), 6.98 (1H, d, *J* = 15.1 Hz, H-11), 6.60 (1H, s, H-3), 2.77 (3H, s, H-14); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 177.2 (C, C-4), 158.2 (C, C-2), 154.9 (C, C-6), 149.1 (C, C-9), 144.0 (CH, C-12), 125.7 (CH, C-11), 124.3 (C, C-10), 123.5 (CH, C-7), 119.6 (CH, C-8), 111.1 (CH, C-3), 107.6 (CH, C-5), 39.6 (CH_3, C-14); HPLC purity 97.8 %.

6-Fluorodirchromone (12). The compound was prepared from 6-fluorodeoxydirchromone (**12′**, 94 mg, 0.40 mmol). The dried residue was purified by flash chromatography with 0-60 % acetonitrile in dichloromethane to afford compound **12** (72 mg, 71 %) as a straw-coloured solid; R_f = 0.26 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, dd, *J* = 8.0, 3.0 Hz, H-5), 7.54 (1H, d, *J* = 14.9 Hz, H-12), 7.45 (1H, dd, *J* = 9.2, 4.2 Hz, H-8), 7.38 (1H, ddd, *J* = 9.2, 7.5, 3.0 Hz, H-7), 7.00 (1H, d, *J* = 14.9 Hz, H-11), 6.34 (1H, s, H-3), 2.76 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C, C-4), 159.7 (d, $J_{C\text{-}1,F}$ = 247.7 Hz, C, C-6), 158.3 (C, C-2), 152.1 (d, $J_{C\text{-}4,F}$ = 1.3 Hz, C, C-9), 142.3 (CH, C-12), 127.0 (CH, C-11), 125.2 (d, $J_{C\text{-}3,F}$ = 7.4 Hz, C, C-10), 122.5 (d, $J_{C\text{-}2,F}$ = 25.5 Hz, CH, C-7), 120.1 (d, $J_{C\text{-}3,F}$ = 8.1 Hz, CH, C-8), 112.3 (CH, C-3), 110.8 (d, $J_{C\text{-}2,F}$ = 23.8 Hz, CH, C-5), 40.3 (CH_3, C-14); HRESIMS *m/z* 253.0330 $[M+H]^+$, calcd for $C_{12}H_{10}FO_3S$, 253.0329; HPLC purity 99.1 %.

6-Chlorodirchromone (13). The compound was prepared from 6-chlorodeoxydirchromone (**13′**, 87 mg, 0.34 mmol). The dried residue was purified by flash chromatography with 0-65 % acetonitrile in dichloromethane to afford compound **13** (64 mg, 69 %) as a pink solid; R_f = 0.21 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, d, *J* = 1.7 Hz, H-5), 7.59 (1H, dd, *J* = 8.8, 1.7 Hz, H-7), 7.54 (1H, d, *J* = 15.0 Hz, H-12), 7.40 (1H, d, *J* = 8.8 Hz, H-8), 7.00 (1H, d, *J* = 15.0 Hz, H-11), 6.36 (1H, s, H-3), 2.76 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C, C-4), 158.3 (C, C-2), 154.2 (C, C-9), 142.4 (CH, C-12), 134.5 (CH, C-7), 131.5 (C, C-6), 127.0 (CH, C-11), 125.3 (C, C-5), 125.0 (C, C-10), 119.7 (CH, C-8), 113.0 (CH, C-3), 40.4 (CH_3, C-14); HRESIMS *m/z* 269.0024 $[M+H]^+$, calcd for $C_{12}H_{10}ClO_3S$, 269.0034; HPLC purity 99.7 %.

6-Bromodirchromone (14). The compound was prepared from 6-bromodeoxydirchromone (**14′**, 213 mg, 0.72 mmol). The dried residue was purified by flash chromatography with 0-65 % acetonitrile in dichloromethane to afford

compound **14** (180 mg, 80 %) as a white solid; R_f = 0.17 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, s, H-5), 7.72 (1H, d, *J* = 8.8 Hz, H-7), 7.54 (1H, d, *J* = 14.8 Hz, H-12), 7.32 (1H, d, *J* = 8.8, H-8), 6.99 (1H, d, *J* = 14.8 Hz, H-11), 6.35 (1H, s, H-3), 2.76 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (C, C-4), 158.3 (C, C-2), 154.6 (C, C-9), 142.5 (CH, C-12), 137.3 (CH, C-7), 128.5 (CH, C-5), 126.9 (CH, C-11), 125.3 (C, C-10), 119.9 (CH, C-8), 119.0 (C, C-6), 113.0 (CH, C-3), 40.4 (CH_3, C-14); HRESIMS *m/z* 312.9516 $[M+H]^+$, calcd for $C_{12}H_{10}{}^{79}BrO_3S$, 312.9529; HPLC purity 99.8 %.

6-Cyanodirchromone (15). The compound was prepared from 6-cyanodeoxydirchromone (**15′**, 79 mg, 0.32 mmol). The dried residue was purified by flash chromatography with 0-55 % acetonitrile in dichloromethane to afford compound **15** (79 mg, 95 %) as an off-white solid; R_f = 0.57 (hexane-acetone 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, d, *J* = 1.9 Hz, H-5), 7.92 (1H, dd, *J* = 8.6, 1.9 Hz, H-7), 7.60 (1H, d, *J* = 14.9 Hz, H-12), 7.59 (1H, d, *J* = 8.6 Hz, H-8), 7.06 (1H, d, *J* = 14.9 Hz, H-11), 6.45 (1H, s, H-3), 2.79 (3H, s, H14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C, C-4), 158.7 (C, C-2), 157.7 (C, C-9), 143.4 (CH, C-12), 136.7 (CH, C-7), 131.6 (CH, C-5), 126.6 (CH, C-11), 124.5 (C, C-10), 119.7 (CH, C-8), 117.4 (C, 6-CN), 113.6 (CH, C-3), 109.9 (C, C-6), 40.4 (CH_3, C-14); HRESIMS *m/z* 260.0375 $[M+H]^+$, calcd for $C_{13}H_{10}NO_3S$, 260.0376; HPLC purity 99.8 %.

6-Acetyloxydirchromone (16a). The compound was prepared from 6-acetyldeoxydirchromone (**16a′**, 33 mg, 0.12 mmol). The dried residue was purified by flash chromatography with 20-100 % acetonitrile in dichloromethane to afford compound **16** (33 mg, 94 %) as an off-white solid; R_f = 0.31 (hexane-acetone 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 2.4 Hz, H-5), 7.53 (1H, d, *J* = 14.9 Hz, H-12), 7.47 (1H, d, *J* = 9.0 Hz, H-8), 7.42 (1H, dd, *J* = 9.0 Hz, 2.4, H-7), 7.02 (1H, d, *J* = 14.9 Hz, H-11), 6.36 (1H, s, H-3), 2.77 (3H, s, H-14), 2.31 (3H, s, 6-OC(O)C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C, C-4), 169.3 (C, 6-O$\underline{C}$(O)CH_3), 158.3 (C, C-2),

153.4 (C, C-9), 147.8 (C, C-6), 142.2 (CH, C-12), 128.5 (CH, C-7), 127.2 (CH, C-11), 124.8 (C, C-10), 119.3 (CH, C-8), 118.0 (CH, C-5), 112.7 (CH, C-3), 40.4 (CH_3, C-14), 21.1 (CH_3, 6-OC(O)$\underline{C}H_3$); HRESIMS *m/z* 293.0470 $[M+H]^+$, calcd for $C_{14}H_{13}O_5S$, 293.0478; HPLC purity 98.8 %.

6-Propionyloxydirchromone (16b). The compound was prepared from 6-propionyldeoxydirchromone (**16b′**, 28 mg, 0.10 mmol). The dried residue was purified by flash chromatography with 15-100 % acetonitrile in dichloromethane to afford compound **16b** (22 mg, 74 %) as an off-white solid; R_f = 16 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 2.3 Hz, H-5), 7.53 (1H, d, *J* = 14.9 Hz, H-12), 7.48 (1H, d, *J* = 9.0 Hz, H-8), 7.44 (1H dd, *J* = 9.1, 2.3 Hz, H-7), 7.03 (1H, d, *J* = 14.9 Hz, H-11), 6.38 (1H, s, H-3), 2.78 (3H, s, H-14), 2.62 (2H, q, *J* = 7.5 Hz, 6-OC(O)C$\underline{H}_2$CH$_3$), 1.27 (3H, t, *J* = 7.5 Hz, 6-OC(O)CH$_2$C$\underline{H}_3$)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C, C-4), 172.9 (C, 6-O$\underline{C}$(O)CH$_2$CH$_3$), 158.3 (C, C-2), 153.4 (C, C-9), 148.0 (C, C-6), 142.1 (CH, C-12), 128.6 (CH, C-7), 127.3 (CH, C-11), 124.8 (C, C-10), 119.2 (CH, C-8), 118.0 (CH, C-5), 112.7 (CH, C-3), 40.4 (CH_3, C-14), 27.7 (CH_2, 6-OC(O)$\underline{C}$H$_2$CH$_3$), 9.1 (CH_3, 6-OC(O)CH$_2$$\underline{C}H_3$); HRESIMS *m/z* 307.0635 $[M+H]^+$, calcd for $C_{15}H_{15}O_5S$, 307.0635; HPLC purity 98.5 %.

6-Isobutyryloxydirchromone (16c). The compound was prepared from 6-isobutyryldeoxydirchromone (**16c′**, 41 mg, 0.14 mmol). The dried residue was purified by flash chromatography with 10-85 % acetonitrile in dichloromethane to afford compound **16c** (25 mg, 59 %) as an off-white solid; R_f = 0.21 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 2.8 Hz, H-5), 7.53 (1H, d, *J* = 14.9 Hz, H-12), 7.48 (1H, d, *J* = 9.0 Hz, H-8), 7.42 (1H, dd, *J* = 9.0, 2.8 Hz, H-7), 7.03 (1H, d, *J* = 14.9 Hz, H-11), 6.38 (1H, s, H-3), 2.82 (1H, m, 6-OC(O)C$\underline{H}$(CH$_3$)), 2.78 (3H, s, H-14), 1.32 (6H, d, *J* = 7.1 Hz, 6-OC(O)CH(C$\underline{H}_3$)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C, C-4), 175.5 (C, 6-O$\underline{C}$(O)CH(CH$_3$), 158.3 (C, C-2), 153.3 (C, C-9), 148.1 (C, C-6), 142.2 (CH, C-12), 128.6 (CH, C-7), 127.2 (CH, C-11), 124.8 (C, C-10), 119.2

(CH, C-8), 117.9 (CH, C-5), 112.7 (CH, C-3), 40.4 (CH_3, C-14), 34.2 (CH, 6-OC(O)$\underline{C}$H(CH_3), 19.0 (CH_3, 6-OC(O)CH($\underline{C}H_3$); HRESIMS *m/z* 321.0784 $[M+H]^+$, calcd for $C_{16}H_{17}O_5S$, 321.0791; HPLC purity 98.4 %.

6-Butyryloxydirchromone (16d). The compound was prepared from 6-butyryldeoxydirchromone (**16d′**, 40 mg, 0.13 mmol). The dried residue was purified by flash chromatography with 10-90 % acetonitrile in dichloromethane to afford compound **16d** (27 mg, 64 %) as an off-white solid; R_f = 0.32 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 2.7 Hz, H-5), 7.54 (1H, d, *J* = 14.9 Hz, H-12), 7.47 (1H, d, *J* = 9.0 Hz, H-8), 7.42 (1H, dd, *J* = 9.0, 2.7 Hz, H-7), 7.02 (1H, d, *J* = 14.9 Hz, H-11), 6.37 (1H, s, H-3), 2.78 (3H, s, H-14), 2.56 (2H, t, *J* = 7.4 Hz, 6-OC(O)C$\underline{H}_2$$CH_2CH_3$), 1.78 (2H, tq, *J* = 7.4, 7.4 Hz, 6-OC(O)CH_2C$\underline{H}_2$$CH_3$), 1.04 (3H, t, *J* = 7.4 Hz, 6-OC(O)CH_2CH_2C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C, C-4), 172.0 (C, 6-O$\underline{C}$(O)$CH_2CH_2CH_3$), 158.3 (C, C-2), 153.3 (C, C-9), 147.9 (C, C-6), 142.1 (CH, C-12), 128.6 (CH, C-7), 127.2 (CH, C-11), 124.8 (C, C-10), 119.2 (CH, C-8), 118.0 (CH, C-5), 112.7 (CH, C-3), 40.4 (CH_3, C-14), 36.1 (CH_2, 6-OC(O)$\underline{C}H_2CH_2CH_3$), 18.5 (CH_2, 6-OC(O)$CH_2\underline{C}H_2CH_3$), 13.7 (CH_3, 6-OC(O)$CH_2CH_2\underline{C}H_3$); HRESIMS *m/z* 321.0783 $[M+H]^+$, calcd for $C_{16}H_{17}O_5S$, 321.0791; HPLC purity 96.0 %.

6-Pivaloyloxydirchromone (16e). The compound was prepared from 6-isobutyryldeoxydirchromone (**16e′**, 36 mg, 0.11 mmol). The dried residue was purified by flash chromatography with 0-85 % acetonitrile in dichloromethane to afford compound **16e** (20 mg, 52 %) as a light orange solid; R_f = 0.32 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 2.6 Hz, H-5), 7.54 (1H, d, *J* = 14.9 Hz, H-12), 7.49 (1H, d, *J* = 9.0 Hz, H-8), 7.41 (1H, dd, *J* = 9.0, 2.6 Hz, H-7), 7.04 (1H, d, *J* = 14.9 Hz, H-11), 6.39 (1H, s, H-3), 2.78 (3H, s, H-14), 1.36 (9H, s, 6-OC(O)C(C$\underline{H}$3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C, C-4), 177.0 (C, 6-O$\underline{C}$(O)C(CH3)$_3$), 158.3 (C, C-2), 153.4 (C, C-9), 148.4 (C, C-6), 142.1 (CH, C-12),

128.6 (CH, C-7), 127.3 (CH, C-11), 124.8 (C, C-10), 119.2 (CH, C-8), 117.9 (CH, C-5), 112.8 (CH, C-3), 40.4 (CH_3, C-14), 39.3 (C, 6-OC(O)C(CH3)$_3$), 27.2 (CH_3, 6-OC(O)C(CH3)$_3$); HRESIMS *m/z* 335.0937 $[M+H]^+$, calcd for $C_{17}H_{19}O_5S$, 335.0948; HPLC purity 93.8 %.

6-Isovaleryloxydirchromone (16f). The compound was prepared from 6-isovaleryldeoxydirchromone (**16f′**, 43 mg, 0.14 mmol). The dried residue was purified by flash chromatography with 10-90 % acetonitrile in dichloromethane to afford compound **16f** (34 mg, 75 %) as an off-white solid; R_f = 0.29 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 2.2 Hz, H-5), 7.53 (1H, d, *J* = 14.9 Hz, H-12), 7.47 (1H, d, *J* = 9.0 Hz, H-8), 7.42 (1H, dd, *J* = 9.0, 2.2 Hz, H-7), 7.02 (1H d, *J* = 14.9 Hz, H-11), 6.37 (1H, s, H-3), 2.77 (3H, s, H-14), 2.45 (2H, d, *J* = 7.1 Hz, 2H, 6-OC(O)CH_2CH(CH_3)$_2$), 2.29 – 2.17 (1H, m, 6-OC(O)CH_2CH(CH_3)$_2$), 1.05 (6H, d, *J* = 6.6 Hz, 6-OC(O)CH_2CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C, C-4), 171.5 (C, 6-OC(O)CH_2CH(CH_3)$_2$), 158.3 (C, C-2), 153.4 (C, C-9), 147.9 (C, C-6), 142.1 (CH, C-12), 128.6 (CH, C-7), 127.2 (CH, C-11), 124.8 (C, C-10), 119.2 (CH, C-8), 118.0 (CH, C-5), 112.7 (CH, C-3), 43.2 (CH_3, C-14), 40.4 (CH_2, 6-OC(O)CH_2CH(CH_3)$_2$), 25.9 (CH, 6-OC(O)CH_2CH(CH_3)$_2$), 22.5 (CH_3, 6-OC(O)CH_2CH(CH_3)$_2$); HRESIMS *m/z* 335.0948 $[M+H]^+$, calcd for $C_{17}H_{19}O_5S$, 335.0948; HPLC purity 98.3 %.

6-Valeryloxydirchromone (16g). The compound was prepared from 6-isobutyryldeoxydirchromone (**16g′**, 52 mg, 0.16 mmol). The dried residue was purified by flash chromatography with 0-90 % acetonitrile in dichloromethane to afford compound **16g** (50 mg, 92 %) as a white solid; R_f = 0.30 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 2.0 Hz, H-5), 7.53 (1H, d, *J* = 14.9 Hz, H-12), 7.45 (1H, d, *J* = 9.0 Hz, H-8), 7.40 (1H, dd, *J* = 9.0, 2.0 Hz, H-7), 7.00 (1H, d, *J* = 14.9 Hz, H-11), 6.35 (1H, s, H-3), 2.76 (3H, s, H-14), 2.56 (2H, t, *J* = 7.4 Hz, 6-OC(O)C$H_2$$CH_2$$CH_2$$CH_3$), 1.77 – 1.66 (2H, m, 6-OC(O)CH_2C$H_2$$CH_2$$CH_3$), 1.48 – 1.37

(2H, m, 6-OC(O)$CH_2CH_2C\underline{H}_2CH_3$), 0.95 (3H, t, J = 7.3 Hz, 6-OC(O)$CH_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C, C-4), 172.2 (C, 6-O$\underline{C}$(O)$CH_2CH_2CH_2CH_3$), 158.3 (C, C-2), 153.3 (C, C-9), 147.9 (C, C-6), 142.2 (CH, C-12), 128.6 (CH, C-7), 127.1 (CH, C-11), 124.7 (C, C-10), 119.2 (CH, C-8), 117.9 (CH, C-5), 112.6 (CH, C-3), 40.3 (CH_3, C-14), 34.0 (CH_2, 6-OC(O)$\underline{C}H_2CH_2CH_2CH_3$), 27.0 ($CH_2$, 6-OC(O)$CH_2\underline{C}H_2CH_2CH_3$), 22.3 ($CH_2$, 6-OC(O)$CH_2CH_2\underline{C}H_2CH_3$), 13.8 ($CH_3$, 6-OC(O)$CH_2CH_2CH_2\underline{C}H_3$); HRESIMS *m/z* 335.0941 $[M+H]^+$, calcd for $C_{17}H_{19}O_5S$, 335.0948; HPLC purity 98.6 %.

6-Ethoxydirchromone (17a). The compound was prepared from 6-ethoxydeoxydirchromone (**17a′**, 76 mg, 0.29 mmol). The dried residue was purified by flash chromatography with 0-90 % acetonitrile in dichloromethane to afford compound **17a** (64 mg, 79 %) as an off-white solid; R_f = 0.40 (hexane-acetone 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, J = 14.9 Hz, H-12), 7.45 (1H, d, J = 3.0 Hz, H-5), 7.34 (1H, d, J = 9.1 Hz, H-8), 7.21 (1H, dd, J = 9.1, 3.0 Hz, H-7), 6.97 (1H, d, J = 14.9 Hz, H-11), 6.31 (1H, s, H-3), 4.06 (2H, q, J = 7.0 Hz, 6-OC$\underline{H}_2CH_3$), 2.74 (3H, s, H-14), 1.39 (3H, t, J = 7.0 Hz, 6-$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C, C-4), 157.8 (C, C-2), 156.5 (C, C-6), 150.5 (C, C-9), 141.4 (CH, C-12), 127.3 (CH, C-11), 124.57 (C, C-10), 124.55 (CH, C-7), 119.3 (CH, C-8), 112.3 (CH, C-3), 105.5 (CH, C-5), 64.2 (CH_2, 6-O$\underline{C}H_2CH_3$), 40.4 (CH_3, C-14), 14.7 (CH_3, 6-$OCH_2\underline{C}H_3$); HRESIMS *m/z* 279.0675 $[M+H]^+$, calcd for $C_{14}H_{15}O_4S$, 279.0686; HPLC purity 99.0 %.

6-Isopropoxydirchromone (17b). The compound was prepared from 6-isopropoxydeoxydirchromone (**17b′**, 62 mg, 0.22 mmol). The dried residue was purified by flash chromatography with 0-90 % acetonitrile in dichloromethane to afford compound **17b** (59 mg, 92 %) as an off-white solid; R_f = 0.46 (hexane-acetone 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 3.0 Hz, H-5), 7.49 (1H, d, J = 14.9 Hz, H-12), 7.36 (1H, d, J = 9.1 Hz, H-8), 7.22 (1H, dd, J = 9.1, 3.0 Hz, H-7), 7.00 (1H, d, J = 14.9 Hz, H-11), 6.35 (1H, s, H-3), 4.64 (1H, hept, J = 6.0 Hz, 6-OC$\underline{H}(CH_3)_2$), 2.76 (3H,

s, H-14), 1.34 (6H, d, J = 6.0 Hz, 6-OCH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C, C-4), 157.8 (C, C-2), 155.5 (C, C-6), 150.4 (C, C-9), 141.4 (CH, C-12), 127.5 (CH, C-11), 125.6 (C, C-10), 124.7 (CH, C-7), 119.4 (CH, C-8), 112.4 (CH, C-3), 107.0 (CH, C-5), 70.7 (CH, 6-O<u>C</u>H(CH$_3$)$_2$), 40.4 (CH$_3$, C-14), 21.9 (CH$_3$, 6-OCH(<u>C</u>H$_3$)$_2$); HRESIMS *m/z* 293.0836 $[M+H]^+$, calcd for $C_{15}H_{17}O_4S$, 293.0842; HPLC purity 97.9 %.

6-Propoxydirchromone (17c). The compound was prepared from 6-propoxydeoxydirchromone (**17c′**, 98 mg, 0.35 mmol). The dried residue was purified by flash chromatography with 10-100 % acetonitrile in dichloromethane to afford compound **17c** (76 mg, 74 %) as an off-white solid; R_f = 0.37 (hexane-acetone 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, d, J = 14.9 Hz, H-12), 7.48 (1H, d, J = 2.7 Hz, H-5), 7.36 (1H, d, J = 9.1 Hz, H-8), 7.24 (1H, dd, J = 9.1, 2.7 Hz, H-7), 6.99 (1H, d, J = 14.9, H-11), 6.33 (1H, s, H-3), 3.96 (2H, t, J = 6.5 Hz, 6-OC<u>H</u>$_2$CH$_2$CH$_3$), 2.75 (3H, s, H-14), 1.85 – 1.75 (2H, m, 6-OCH$_2$C<u>H</u>$_2$CH$_3$), 1.01 (3H, t, J = 7.4 Hz, 6-OCH$_2$CH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C, C-4), 157.8 (C, C-2), 156.7 (C, C-6), 150.5 (C, C-9), 141.4 (CH, C-12), 127.4 (CH, C-11), 124.63 (C, C-10), 124.60 (CH, C-7), 119.3 (CH, C-8), 112.4 (CH, C-3), 105.6 (CH, C-5), 70.3 (CH$_2$, 6-O<u>C</u>H$_2$CH$_2$CH$_3$), 40.4 (CH$_3$, C-14), 22.5 (CH$_2$, 6-OCH$_2$<u>C</u>H$_2$CH$_3$), 10.5 (CH$_3$, 6-OCH$_2$CH$_2$<u>C</u>H$_3$); HRESIMS *m/z* 293.0834 $[M+H]^+$, calcd for $C_{15}H_{17}O_4S$, 293.0842; HPLC purity 99.2 %.

6-Isobutoxydirchromone (17d). The compound was prepared from 6-isobutoxydeoxydirchromone (**17d′**, 38 mg, 0.13 mmol). The dried residue was purified by flash chromatography with 10-90 % acetonitrile in dichloromethane to afford compound **17d** (33 mg, 82 %) as an off-white solid; R_f = 0.40 (hexane-acetone 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 14.9 Hz, H-12), 7.50 (1H, d, J = 3.0 Hz, H-5), 7.38 (1H, d, J = 9.1 Hz, H-8), 7.27 (1H, dd, J = 8.9, 2.7 Hz, H-7), 7.02 (1H, d, J = 14.9 Hz, H-11), 6.37 (1H, s, H-3), 3.79 (2H, d, J = 6.6 Hz, 6-OC<u>H</u>$_2$CH(CH$_3$)$_2$), 2.77 (3H, s, H-14), 2.14 – 2.03 (1H, m, 6-OCH$_2$C<u>H</u>(CH$_3$)$_2$), 1.02

(6H, d, J = 6.7 Hz, 6-$OCH_2CH(C\underline{H}_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C, C-4), 157.8 (C, C-2), 156.9 (C, C-6), 150.6 (C, C-9), 141.4 (CH, C-12), 127.6 (CH, C-11), 124.7 (C, C-10 and CH, C-7), 119.3 (CH, C-8), 112.5 (CH, C-3), 105.7 (CH, C-5), 75.2 (CH_2, 6-$O\underline{C}H_2CH(CH_3)_2$), 40.5 ($CH_3$, C-14), 28.3 (CH, 6-$OCH_2\underline{C}H(CH_3)_2$), 19.3 ($CH_3$, 6-$OCH_2CH(\underline{C}H_3)_2$); HRESIMS *m/z* 307.0989 $[M+H]^+$, calcd for $C_{16}H_{19}O_4S$, 307.0999; HPLC purity 96.5 %.

6-Butoxydirchromone (17e). The compound was prepared from 6-butoxydeoxydirchromone (**17e′**, 197 mg, 0.68 mmol). The dried residue was purified by flash chromatography with 0-90 % acetonitrile in dichloromethane to afford compound **17e** (163 mg, 78 %) as a pinkish solid; R_f = 0.49 (hexane-acetone 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, J = 14.9 Hz, H-12), 7.43 (1H, d, J = 3.0 Hz, H-5), 7.32 (1H, d, J = 9.1 Hz, H-8), 7.20 (1H, dd, J = 9.1, 3.0 Hz, H-7), 6.95 (1H, d, J = 14.9 Hz, H-11), 6.30 (1H, s, H-3), 3.96 (2H, t, J = 6.5 Hz, 6-$OC\underline{H}_2CH_2CH_2CH_3$), 2.72 (3H, s, H-14), 1.76 – 1.67 (2H, m, 6-$OCH_2C\underline{H}_2CH_2CH_3$), 1.48 – 1.37 (2H, m, 6-$OCH_2CH_2C\underline{H}_2CH_3$), 0.91 (3H, t, J = 7.4 Hz, 6-$OCH_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C, C-4), 157.7 (C, C-2), 156.6 (C, C-6), 150.4 (C, C-9), 141.5 (CH, C-12), 127.3 (CH, C-11), 124.52 (C, C-10), 124.49 (CH, C-7), 119.2 (CH, C-8), 112.2 (CH, C-3), 105.5 (CH, C-5), 68.4 (CH_2, 6-$O\underline{C}H_2CH_2CH_2CH_3$), 40.3 ($CH_3$, C-14), 31.1 ($CH_2$, 6-$OCH_2\underline{C}H_2CH_2CH_3$), 19.1 ($CH_2$, 6-$OCH_2CH_2\underline{C}H_2CH_3$), 13.8 ($CH_3$, 6-$OCH_2CH_2CH_2C\underline{H}_3$); HRESIMS *m/z* 307.0990 $[M+H]^+$, calcd for $C_{16}H_{19}O_4S$, 307.0999; HPLC purity 98.5 %.

6-Isoamyloxydirchromone (17f). The compound was prepared from 6-isoamyloxydeoxydirchromone (**17f′**, 67 mg, 0.22 mmol). The dried residue was purified by flash chromatography with 0-60 % acetonitrile in dichloromethane to afford compound **17f** (56 mg, 80 %) as a white solid; R_f = 0.18 (hexane-acetone 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, d, J = 2.9 Hz, H-5), 7.49 (1H, d, J = 14.9 Hz, H-12), 7.37 (1H, d, J = 9.0 Hz, H-8), 7.25 (1H, dd, J = 9.0, 2.9 Hz, H-7), 7.01 (1H, d, J = 14.9

Hz, H-11), 6.35 (1H, s, H-3), 4.05 (2H, t, J = 6.4 Hz, 6-OC<u>H</u>$_2$CH$_2$CH(CH$_3$)$_2$), 2.76 (3H, s, H-14), 1.87 – 1.76 (1H, m, 6-OCH$_2$CH$_2$C<u>H</u>(CH$_3$)$_2$), 1.73 – 1.64 (2H, m, 6-OCH$_2$C<u>H</u>$_2$CH(CH$_3$)$_2$), 0.95 (6H, d, J = 6.3 Hz, 6-OCH$_2$CH$_2$CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.3 (C, C-4), 157.8 (C, C-2), 156.7 (C, C-6), 150.6 (C, C-9), 141.4 (CH, C-12), 127.4 (CH, C-11), 124.7 (C, C-10 and CH, C-7), 119.3 (CH, C-8), 112.4 (CH, C-3), 105.6 (CH, C-5), 67.2 (CH$_2$, 6-O<u>C</u>H$_2$CH$_2$CH(CH$_3$)$_2$), 40.4 (CH$_3$, C-14), 37.8 (CH$_2$, 6-OCH$_2$<u>C</u>H$_2$CH(CH$_3$)$_2$), 25.1 (CH, 6-OCH$_2$CH$_2$<u>C</u>H(CH$_3$)$_2$), 22.6 (CH$_3$, 6-OCH$_2$CH$_2$CH(<u>C</u>H$_3$)$_2$); HRESIMS *m/z* 321.1158 [M+H]$^+$, calcd for C$_{17}$H$_{21}$O$_4$S, 321.1155; HPLC purity 98.8 %.

6-Amyloxydirchromone (17g). The compound was prepared from 6-amyloxydeoxydirchromone (**17g′**, 84 mg, 0.28 mmol). The dried residue was purified by flash chromatography with 10-90 % acetonitrile in dichloromethane to afford compound **17g** (71 mg, 79 %) as an off-white solid; R_f = 0.42 (hexane-acetone 2:3); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (1H, dd, J = 14.9 Hz, H-12), 7.47 (1H, d, J = 3.0 Hz, H-5), 7.35 (1H, d, J = 9.1 Hz, H-8), 7.23 (1H, dd, J = 9.1, 3.0 Hz, H-7), 6.98 (1H, d, J = 14.9 Hz, H-11), 6.33 (1H, s, H-3), 3.98 (2H, t, J = 6.6 Hz, 6-OC<u>H</u>$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.75 (3H, s, H-14), 1.82 – 1.72 (2H, m, 6-OCH$_2$C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.45 – 1.29 (4H, m, 6-OCH$_2$CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.89 (3H, t, J = 7.1 Hz, 6-OCH$_2$CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.2 (C, C-4), 157.8 (C, C-2), 156.7 (C, C-6), 150.5 (C, C-9), 141.4 (CH, C-12), 127.4 (CH, C-11), 124.61 (C, C-10), 124.59 (CH, C-7), 119.2 (CH, C-8), 112.3 (CH, C-3), 105.6 (CH, C-5), 68.8 (CH$_2$, 6-O<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 40.4 (CH$_3$, C-14), 28.8 (CH2, 6-OCH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 28.1 (CH$_2$, 6-OCH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$), 22.4 (CH$_2$, 6-OCH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 14.0 (CH$_3$, 6-OCH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$); HRESIMS *m/z* 321.1149 [M+H]$^+$, calcd for C$_{17}$H$_{21}$O$_4$S, 321.1155; HPLC purity 98.7 %.

3-Benzyldirchromone (18). The compound was prepared from 3-benzyldeoxydirchromone (**18′**, 173 mg, 0.56 mmol). The dried residue was purified

by flash chromatography with 0-35 % acetonitrile in dichloromethane to afford compound **18** (103 mg, 57 %) as a white solid; R_f = 0.33 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, dd, *J* = 7.9, 1.2 Hz, H-5), 7.64 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, H-7), 7.53 (2H, m, H-11 and H-12), 7.40 (1H, d, *J* = 8.4 Hz, H-8), 7.35 (1H, t, *J* = 7.6 Hz, H-6), 7.30 (2H, d, *J* = 7.5 Hz, H-2' and H-6'), 7.23 (2H, t, *J* = 7.5 Hz, H-3' and H-5'), 7.14 (1H, t, *J* = 7.2 Hz, H-4'), 4.08 (2H, ABq, $\Delta\nu_{AB}$ = 14.9 Hz, J_{AB} = 14.9 Hz, C$\underline{H}_2$Ar), 2.73 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C, C-4), 155.4 (C, C-9), 155.0 (C, C-2), 142.0 (CH, C-12), 139.3 (C, C-1'), 134.1 (CH, C-7), 128.6 (CH, C-3' and C-5'), 128.5 (CH, C-2' and C-6'), 126.4 (CH, C-4'), 126.2 (CH, C-5), 125.2 (CH, C-6 or C-11), 125.1 (CH, C-6 or C-11), 123.6 (C, C-3), 123.0 (C, C-10), 117.6 (CH, C-8), 40.4 (CH_3, C-14), 29.5 (CH_2, $\underline{C}H_2$Ar); HRESIMS *m/z* 325.0883 [M+H]+, calcd for $C_{19}H_{18}O_3S$, 325.0983; HPLC purity 96.8 %.

(*E*)-3-(2-(methylsulfinyl)vinyl)-1*H*-benzo[*f*]chromen-1-one (19). The compound was prepared from (*E*)-3-(2-(methylthio)vinyl)-1*H*-benzo[*f*]chromen-1-one (**19′** , 237 mg, 0.88 mmol). The dried residue was purified by flash chromatography with 0-90 % acetonitrile in dichloromethane to afford compound **19** (184 mg, 73 %) as an off-white solid; R_f = 0.32 (hexane-acetone 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (1H, d, *J* = 8.5 Hz, H-1'), 8.07 (1H, d, *J* = 9.0 Hz, H-7), 7.87 (1H, d, *J* = 8.0 Hz, H-4'), 7.73 (1H, t, *J* = 7.7 Hz, H-2'), 7.60 (1H, t, *J* = 7.4 Hz, H-3'), 7.51 (1H, d, *J* = 14.9 Hz, H-12), 7.46 (1H, d, *J* = 9.0 Hz, H-8), 7.03 (1H, d, *J* = 14.9 Hz, H-11), 6.50 (1H, s, H-3), 2.78 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 (C, C-4), 157.2 (C, C-9), 155.8 (C, C-2), 141.1 (CH, C-12), 136.1 (CH, C-7), 130.7 (C, C-6), 130.4 (C, C-5), 129.6 (CH, C-2'), 128.3 (CH, C-4'), 127.1 (CH, C-1'), 126.94 (CH, C-11 or C-3'), 126.92 (CH, C-11 or C-3'), 117.5 (C, C-10), 117.3 (CH, C-8), 116.0 (CH, C-3), 40.5 (CH_3, C-14); HRESIMS *m/z* 285.0572 $[M+H]^+$, calcd for $C_{16}H_{13}O_3S$, 285.0580; HPLC purity 98.9 %.

(*E*)-2-(2-(methylsulfinyl)vinyl)-4*H*-benzo[*h*]chromen-4-one (20). The compound was prepared from (*E*)-2-(2-(methylthio)vinyl)-4*H*-benzo[*h*]chromen-4-one (**20′** , 96

mg, 0.34 mmol). The dried residue was purified by flash chromatography with 0-85 % acetonitrile in dichloromethane to afford compound **20** (83 mg, 86 %) as a white solid; R_f = 0.44 (hexane-acetone 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, d, *J* = 8.0 Hz, H-4'), 8.08 (1H, d, *J* = 8.7 Hz, H-5), 7.92 (1H, d, *J* = 7.7 Hz, H-1'), 7.76 – 7.64 (3H, m, H-6, H-2' and H-3'), 7.64 (1H, d, *J* = 15.0 Hz, H-12), 7.12 (1H, d, *J* = 15.0 Hz, H-11), 6.53 (1H, s, H-3), 2.85 (3H, s, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C, C-4), 157.5 (C, C-2), 153.3 (C, C-9), 141.3 (CH, C-12), 136.3 (C, C-7), 129.7 (CH, C-2'), 128.5 (CH, C-1'), 127.6 (CH, C-11), 127.4 (CH, C-3'), 125.8 (CH, C-6), 123.8 (C, C-8), 122.2, 120.7 (CH, C-5), 120.5 (C, C-10), 114.4 (CH, C-3), 40.6 (CH_3, C-14); HRESIMS *m/z* 285.0579 [M+H]+, calcd for $C_{16}H_{13}O_3S$, 285.0580; HPLC purity 99.3 %.

6,7-Methylenedioxydirchromone (21). The compound was prepared from 6,7-methylenedioxydeoxydirchromone (**21′**, 60 mg, 0.23 mmol). The dried residue was purified by flash chromatography with 15-80 % acetone in hexanes to afford compound **21** (54 mg, 84 %) as an off-white solid; R_f = 0.17 (hexane-acetone 1:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (1H, d, *J* = 15.1 Hz, H-12), 7.29 (1H, s, H-5), 7.17 (1H, s, H-8), 6.97 (1H, d, *J* = 15.1 Hz, H-11), 6.61 (1H, s, H-3), 6.22 (2H, s, O$C\underline{H}_2$O), 2.77 (3H, s, H-14); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.1 (C, C-4), 158.0 (C, C-2), 152.9 (C, C-7), 152.7 (C, C-9), 146.2 (C, C-6), 143.7 (CH, C-12), 125.4 (CH, C-11), 118.3 (C, C-10), 111.5 (CH, C-3), 103.0 (CH_2, O$\underline{C}H_2$O), 101.0 (CH, C-5), 98.1 (CH, C-8), 39.7 (CH_3, C-14); HRESIMS *m/z* 279.0320 $[M+H]^+$, calcd for $C_{13}H_{11}O_5S$, 279.0322; HPLC purity 98.0 %.

3.5 Associated content

Supporting Information. The following files are available free of charge. Preparation and characterization of intermediate compounds **n′**, **n″**, **n‴** and **22**, ^{1}H and ^{13}C NMR spectra of new compounds, HPLC chromatograms of compounds **2-21**

(https://pubs.acs.org/doi/suppl/10.1021/acs.jnatprod.1c00385/suppl_file/np1c00385_si_001.pdf).

3.6 Author information

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

This work was supported by the Canadian Institutes of Health Research (CIHR, operating grants 311906 and 326083 to A. P. and J. L.). A. S. G. thanks NSERC for a PhD scholarship.

3.7 Acknowledgements

The authors acknowledge funding from the Chaire de recherche sur les agents anticancéreux d'origine naturelle. This work was supported by the Canadian Institutes of Health Research (CIHR, operating grants 311906 and 326083 to A. P. and J. L.). A. S. G. thanks NSERC for a Ph.D. scholarship. The authors gratefully acknowledge C. Dussault (UQAC) for the biological assays.

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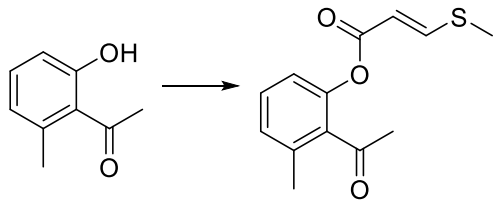
3.9 Supporting information

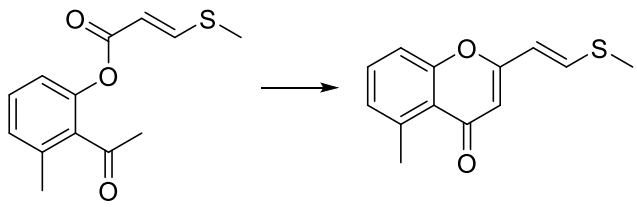
3.9.1 Preparation and characterization of intermediate compounds

2-Acetyl-3-methylphenyl (*E*)-3-(methylthio)acrylate (3″)



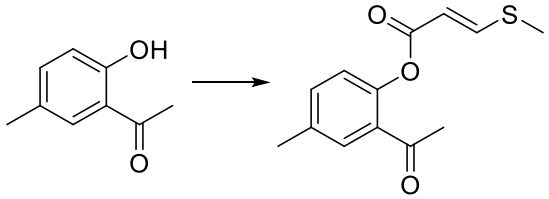
The compound was prepared from 1-(2-hydroxy-6-methylphenyl)ethan-1-one (***3‴***) which in turn was prepared according to a published procedure (Fosso et al., 2015) (1.12 g, 7.4 mmol), and 3-methylsulfinylpropionic acid (254 mg, 1.9 mmol). The dried residue was purified by flash chromatography with 0-10 % ethyl acetate in hexanes to afford compound **3″** (206 mg, 44 %) as a yellow solid; R_f = 0.73 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 14.8 Hz), 7.57 (1H, s), 7.30 (1H, d, *J* = 7.8 Hz), 6.99 (1H, d, *J* = 8.2 Hz), 5.86 (1H, d, *J* = 14.8 Hz), 2.50 (3H, s), 2.38 (3H, s), 2.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 163.5, 150.5, 147.0, 135.7, 133.9, 131.0, 130.4, 123.5, 111.7, 29.9, 20.8, 14.5.

5-Methyldeoxydirchromone (3′)



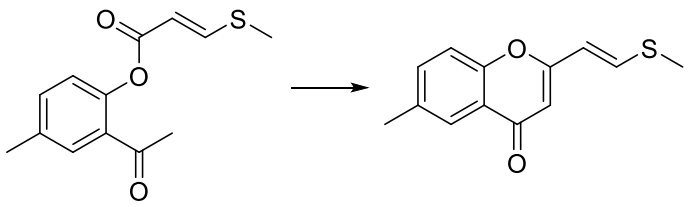
The compound was prepared from 2-acetyl-3-methylphenyl (*E*)-3-(methylthio)acrylate (**3″**, 205 mg, 0.82 mmol). The dried residue was purified by flash chromatography with 10-20 % ethyl acetate in hexanes to afford compound **3′** (53 mg, 83 %) as an off-white solid; R_f = 0.39 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 15.0 Hz), 7.34 (1H, t, *J* = 7.9 Hz), 7.13 (1H, d, *J* = 8.3 Hz), 6.97 (1H, d, *J* = 7.3 Hz), 5.91 (1H, s), 5.81 (1H, d, *J* = 15.0 Hz), 2.76 (3H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 158.9, 157.1, 140.6, 137.2, 132.2, 127.3, 122.1, 115.5, 114.7, 108.8, 22.6, 14.3.

2-Acetyl-4-methylphenyl (*E*)-3-(methylthio)acrylate (4″)



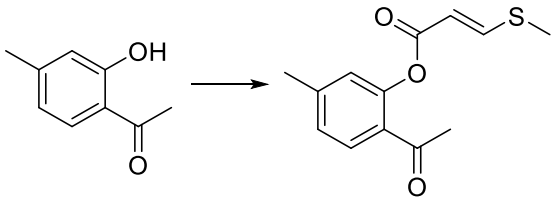
The compound was prepared from 1-(2-hydroxy-6-methylphenyl)ethan-1-one (**4‴**, 601 mg, 4.0 mmol) and 3-methylsulfinyl-propionic acid (136 mg, 1.0 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **4″** (85 mg, 34 %) as a yellow oil; R_f = 0.66 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 14.8 Hz), 7.22 (1H, t, *J* = 7.9 Hz), 7.01 (1H, d, *J* = 7.6 Hz), 6.94 (1H, d, *J* = 8.1 Hz), 5.74 (1H, d, *J* = 14.8 Hz), 2.38 (3H, s), 2.30 (3H, s), 2.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 163.5, 150.5, 147.0, 135.7, 133.9, 131.0, 130.4, 123.5, 111.7, 29.9, 20.8, 14.5.

6-Methyldeoxydirchromone (4′)



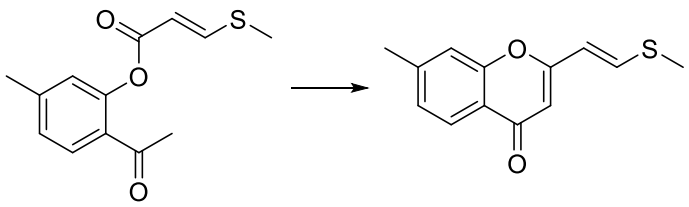
The compound was prepared from 2-acetyl-4-methylphenyl (*E*)-3-(methylthio)acrylate (**4″**, 108 mg, 0.43 mmol). The dried residue was purified by flash chromatography with 25-40 % ethyl acetate in hexanes to afford compound **4′** (61 mg, 60 %) as a reddish solid; R_f = 0.22 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, s), 7.52 (1H, d, *J* = 15.0 Hz), 7.40 (1H, dd, *J* = 8.2, 1.3 Hz), 7.28 (1H, d, *J* = 8.5 Hz), 6.03 (1H, s), 5.91 (1H, d, *J* = 15.0 Hz), 2.40 (3H, s), 2.39 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 160.7, 154.1, 138.0, 134.8, 134.7, 125.0, 123.6, 117.4, 115.2, 107.6, 20.9, 14.5.

2-Acetyl-5-methylphenyl (*E*)-3-(methylthio)acrylate (5″)



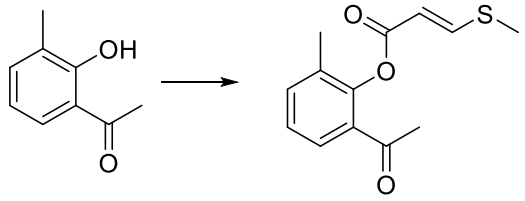
The compound was prepared from 1-(2-hydroxy-4-methylphenyl)ethan-1-one (**5‴**, 1.12 mL, 8.1 mmol) and 3-methylsulfinyl-propionic acid (275 mg, 2.0 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **5″** (197 mg, 39 %) as a yellow oil; R_f = 0.61 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 14.8 Hz), 7.22 (1H, t, *J* = 7.9 Hz), 7.01 (1H, d, *J* = 7.6 Hz), 6.94 (1H, d, *J* = 8.1 Hz), 5.74 (1H, d, *J* = 14.8 Hz), 2.38 (3H, s), 2.30 (3H, s), 2.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 163.3, 150.3, 149.2, 144.5, 130.1, 128.3, 126.6, 124.2, 111.6, 29.6, 21.2, 14.3.

7-Methyldeoxydirchromone (5′)



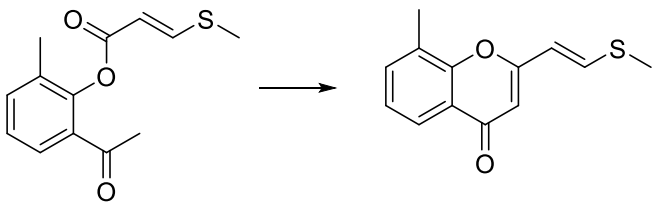
The compound was prepared from 2-acetyl-5-methylphenyl (*E*)-3-(methylthio)acrylate (**5″**, 196 mg, 0.78 mmol). The dried residue was purified by flash chromatography with 0-15 % acetone in dichloromethane to afford compound **5′** (135 mg, 75 %) as a red solid; R_f = 0.19 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 8.1 Hz), 7.43 (1H, d, *J* = 15.0 Hz), 7.08 (1H, s), 7.05 (1H, d, *J* = 8.1 Hz), 5.95 (1H, s), 5.83 (1H, d, *J* = 15.0 Hz), 2.35 (3H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 160.4, 155.7, 144.6, 137.7, 126.1, 125.1, 121.5, 117.3, 115.0, 107.4, 21.7, 14.3.

2-Acetyl-6-methylphenyl (*E*)-3-(methylthio)acrylate (6″)



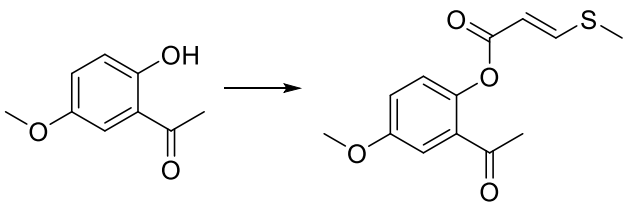
The compound was prepared from 1-(2-hydroxy-3-methylphenyl)ethan-1-one (**6‴**, 1.12 g, 7.5 mmol) and 3-methylsulfinyl-propionic acid (296 mg, 2.2 mmol). The dried residue was purified by flash chromatography to afford compound **6″** (225 mg, 41 %) as a yellow oil; R_f = 0.60 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 14.9 Hz), 7.58 (1H, d, *J* = 7.7 Hz), 7.36 (1H, d, *J* = 7.3 Hz), 7.17 (1H, t, *J* = 7.6 Hz), 5.88 (1H, d, *J* = 14.9 Hz), 2.48 (3H, s), 2.36 (3H, s), 2.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 162.9, 150.4, 147.4, 134.8, 132.2, 131.5, 127.6, 125.6, 111.4, 29.6, 16.2, 14.4.

8-Methyldeoxydirchromone (6′)



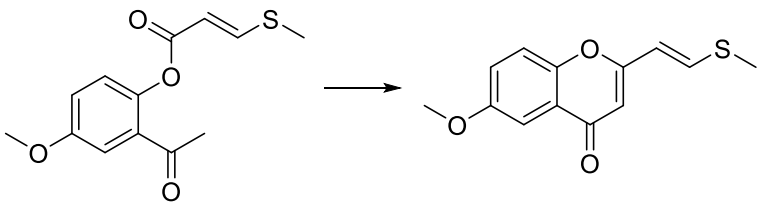
The compound was prepared from 2-acetyl-6-methylphenyl (*E*)-3-(methylthio)acrylate (**6″**, 224 mg, 0.89 mmol). The dried residue was purified by flash chromatography with 20-40 % ethyl acetate in hexanes to afford compound **6′** (117 mg, 57 %) as a pink solid; R_f = 0.15 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 7.7 Hz), 7.41 (1H, d, *J* = 15.0 Hz), 7.32 (1H, d, *J* = 6.9 Hz), 7.11 (1H, t, *J* = 7.5 Hz), 5.95 (1H, s), 5.83 (1H, d, *J* = 15.0 Hz), 2.35 (3H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 160.1, 153.9, 137.5, 134.3, 126.8, 124.1, 123.5, 123.0, 115.0, 107.3, 15.5, 14.2.

2-Acetyl-4-methoxyphenyl (*E*)-3-(methylthio)acrylate (8″)



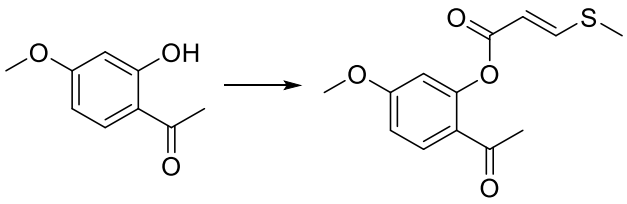
The compound was prepared from 1-(2-hydroxy-5-methoxyphenyl)ethan-1-one (**8‴**, 1.5 g, 9.3 mmol) and 3-methylsulfinyl-propionic acid (315 mg, 2.3 mmol). The dried residue was purified by flash chromatography with 5-20 % ethyl acetate in hexanes to afford compound **8″** (302 mg, 49 %) as a yellow oil; R_f = 0.45 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 14.9 Hz), 7.21 (1H, s), 6.96 (2H, s), 5.79 (1H, d, *J* = 14.9 Hz), 3.72 (3H, s), 2.43 (3H, s), 2.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 163.4, 156.8, 150.3, 142.5, 131.7, 124.5, 118.8, 113.8, 111.4, 55.5, 29.7, 14.2.

6-Methoxydeoxydirchromone (8′)



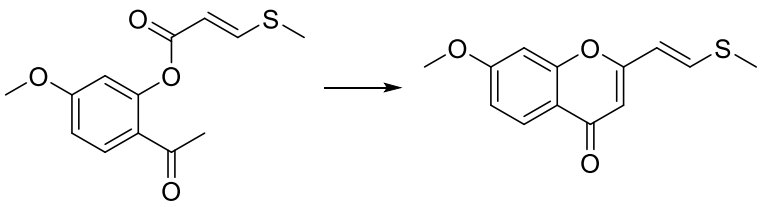
The compound was prepared from 2-acetyl-5-methoxyphenyl (*E*)-3-(methylthio)acrylate (**8″**, 300 mg, 1.1 mmol). The dried residue was purified by flash chromatography with 15-45 % ethyl acetate in hexanes to afford compound **8′** (139 mg, 50 %) as a red solid; R_f = 0.15 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 15.0 Hz), 7.42 (1H, d, *J* = 2.6 Hz), 7.24 (1H, d, *J* = 9.0 Hz), 7.11 (1H, dd, *J* = 9.0, 2.6 Hz), 5.97 (1H, s), 5.84 (1H, d, *J* = 15.0 Hz), 3.78 (3H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 160.5, 156.6, 150.4, 137.8, 124.4, 123.1, 118.9, 115.0, 106.9, 104.8, 55.8, 14.4.

2-Acetyl-5-methoxyphenyl (*E*)-3-(methylthio)acrylate (9″)



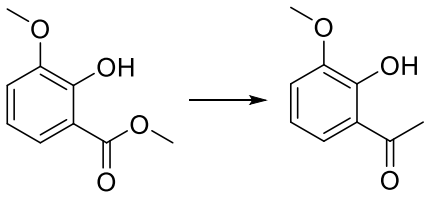
The compound was prepared from 1-(2-hydroxy-4-methoxyphenyl)ethan-1-one (**9‴**, 671 mg, 4.0 mmol) and 3-methylsulfinyl-propionic acid (138 mg, 1.0 mmol). The dried residue was purified by flash chromatography with 2-20 % ethyl acetate in hexanes to afford compound **9″** (116 mg, 43 %) as a clear oil; R_f = 0.60 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 14.8 Hz), 7.80 (1H, d, *J* = 8.8 Hz), 6.78 (1H, dd, *J* = 8.8, 2.3 Hz), 6.59 (1H, d, *J* = 2.3 Hz), 5.85 (1H, d, *J* = 14.8 Hz), 3.79 (3H, s), 2.45 (3H, s), 2.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 163.6, 163.2, 151.4, 150.5, 132.2, 123.6, 111.67, 111.65, 109.1, 55.7, 29.5, 14.4.

7-Methoxydeoxydirchromone (9′)



The compound was prepared from 2-acetyl-5-methoxyphenyl (*E*)-3-(methylthio)acrylate (**9″**, 116 mg, 0.44 mmol). The dried residue was purified by flash chromatography with 25-40 % ethyl acetate in hexanes to afford compound **9′** (61 mg, 56 %) as a purple solid; R_f = 0.12 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 8.8 Hz), 7.46 (1H, d, *J* = 15.0 Hz), 6.85 (1H, dd, *J* = 8.8, 2.0 Hz), 6.75 (1H, d, *J* = 2.0 Hz), 5.95 (1H, s), 5.86 (1H, d, *J* = 15.0 Hz), 3.83 (3H, s), 2.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 163.9, 160.5, 157.5, 137.5, 126.8, 117.7, 115.1, 113.8, 107.5, 100.2, 55.8, 14.4.

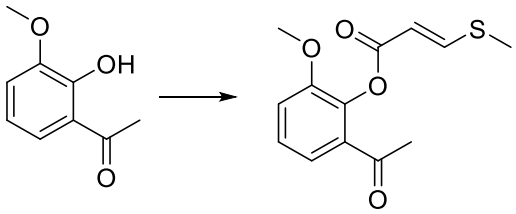
1-(2-Hydroxy-3-methoxyphenyl)ethan-1-one (10‴)



A commercial solution of methylmagnesium bromide at 3.0 M in diethyl ether (18.4 mL, 55.1 mmol) was mixed with triethylamine (7.7 mL, 55.1 mmol) in anhydrous toluene (40 mL) at 0 °C under argon. Methyl 3-methoxysalicylate (2.51 g, 13.8 mmol), dissolved in 10 mL anhydrous toluene, was then slowly added. The stirred reaction was left to temperate overnight. The reaction was quenched by adding saturated aqueous NH_4Cl and filtered on a Whatman 4 filter paper. The filtrate was extracted with 3 × ethyl acetate, and the organic phases were combined. The solid portion left on the filter was for its part triturated three times with acetone, which was then filtered and

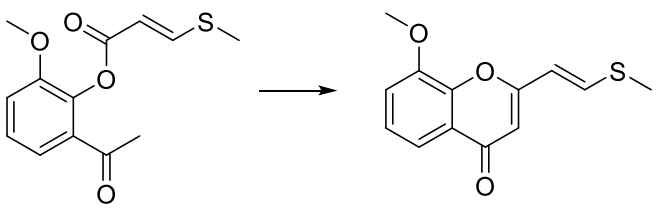
combined with the organic phases. The collected phases were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford 1-(2-hydroxy-3-methoxyphenyl)ethan-1-one (**10‴**, 312 mg, 14 %) as a yellow solid; R_f = 0.55 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (1H, s), 7.21 (1H, d, J = 8.1 Hz), 6.93 (1H, d, J = 7.9 Hz), 6.72 (1H, t, J = 8.0 Hz), 3.78 (3H, s), 2.51 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 152.5, 148.6, 121.7, 119.4, 118.1, 116.7, 55.9, 26.8.

2-Acetyl-6-methoxyphenyl (*E*)-3-(methylthio)acrylate (10″)



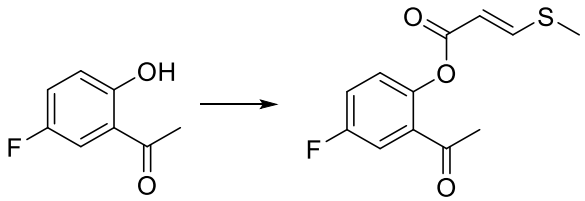
The compound was prepared from 1-(2-hydroxy-3-methoxyphenyl)ethan-1-one (**10‴**, 669 mg, 4.0 mmol) and 3-methylsulfinyl-propionic acid (274 mg, 2.0 mmol). The dried residue was purified by flash chromatography with 3-30 % ethyl acetate in hexanes to afford compound **10″** (196 mg, 37 %) as a colorless oil; R_f = 0.33 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, dd, J = 14.8, 0.6 Hz), 7.28 (1H, t, J = 7.2 Hz), 7.18 (1H, td, J = 8.0, 0.6 Hz), 7.05 (1H, d, J = 8.1 Hz), 5.85 (1H, d, J = 14.8 Hz), 3.75 (3H, s), 2.45 (3H, s), 2.32 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 162.5, 151.7, 150.4, 138.5, 132.5, 126.2, 120.8, 115.7, 111.2, 56.1, 30.1, 14.2.

8-Methoxydeoxydirchromone (10′)



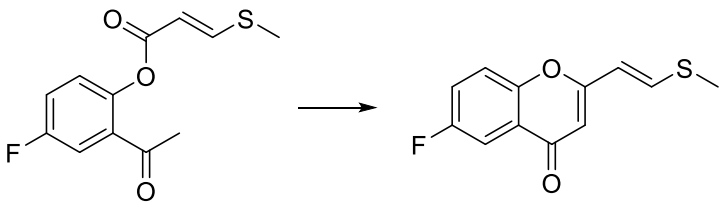
The compound was prepared from 2-acetyl-6-methoxyphenyl (*E*)-3-(methylthio)acrylate (**10″**, 195 mg, 0.73 mmol). The dried residue was purified by flash chromatography with 20-40 % ethyl acetate in hexanes to afford compound **10′** (117 mg, 64 %) as a red solid; R_f = 0.18 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 8.0 Hz), 7.55 (1H, d, *J* = 15.0 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 7.02 (1H, d, *J* = 7.9 Hz), 6.00 (1H, s), 5.87 (1H, d, *J* = 15.0 Hz), 3.86 (3H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 160.5, 148.5, 146.0, 138.4, 124.7, 124.3, 116.1, 114.8, 114.1, 107.2, 56.1, 14.3.

2-Acetyl-4-fluorophenyl (*E*)-3-(methylthio)acrylate (12″)



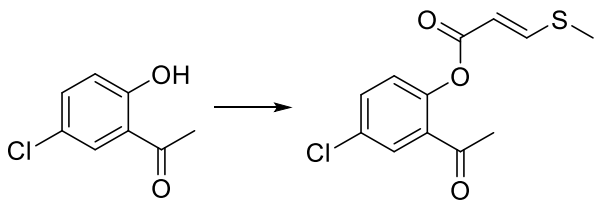
The compound was prepared from 2-acetyl-4-fluorophenol (**12‴**, 720 mg, 4.7 mmol) and 3-methylsulfinylpropionic acid (318 mg, 2.3 mmol). The dried residue was purified by flash chromatography with 0-20 % ethyl acetate in hexanes to afford compound **12″** (156 mg, 26 %) as a translucent oil; R_f = 0.63 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 14.8 Hz), 7.44 (1H, dd, *J* = 8.7, 3.0 Hz), 7.18 (1H, ddd, *J* = 8.9, 7.4, 3.1 Hz), 7.07 (1H, dd, *J* = 8.9, 4.6 Hz), 5.83 (1H, d, *J* = 14.8 Hz), 2.48 (3H, s), 2.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 163.3, 159.7 (d, $J_{C\text{-}1,F}$ = 246 Hz), 151.2, 145.0 (d, $J_{C\text{-}4,F}$ = 2.9 Hz), 132.6 (d, $J_{C\text{-}3,F}$ = 6.2 Hz), 125.5 (d, $J_{C\text{-}3,F}$ = 8.0 Hz), 120.0 (d, $J_{C\text{-}2,F}$ = 23.4 Hz), 116.3 (d, $J_{C\text{-}2,F}$ = 23.3 Hz), 111.2, 29.8, 14.4.

6-Fluorodeoxydirchromone (12′)



The compound was prepared from 2-acetyl-4-fluorophenyl (*E*)-3-(methylthio)acrylate (**12″**, 155 mg, 0.61 mmol). The dried residue was purified by flash chromatography with 0-35 % ethyl acetate in hexanes to afford compound **12′** (94 mg, 65 %) as a red solid; R_f = 0.34 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* = 8.2, 3.0 Hz), 7.58 (1H, d, *J* = 15.0 Hz), 7.42 (1H, dd, *J* = 9.1, 4.2 Hz), 7.34 (1H, ddd, *J* = 9.1, 7.7, 3.1 Hz), 6.06 (1H, s), 5.94 (1H, d, *J* = 15.0 Hz), 2.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 161.1, 159.5 (d, $J_{C\text{-}1,F}$ = 246.2 Hz), 152.1 (d, $J_{C\text{-}4,F}$ = 1.4 Hz), 138.9, 125.3 (d, $J_{C\text{-}3,F}$ = 7.3 Hz), 121.6 (d, $J_{C\text{-}2,F}$ = 25.4 Hz), 119.7 (d, $J_{C\text{-}3,F}$ = 8.0 Hz), 114.9, 110.7 (d, $J_{C\text{-}2,F}$ = 23.7 Hz), 107.1, 14.6.

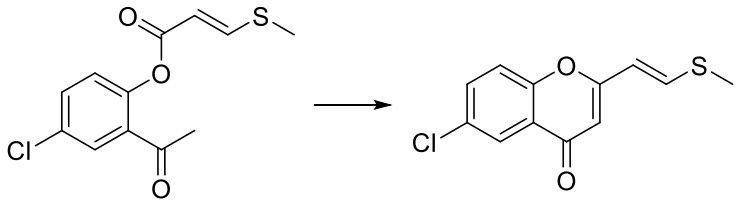
2-Acetyl-4-chlorophenyl (*E*)-3-(methylthio)acrylate (13″)



The compound was prepared from 2-acetyl-4-chlorophenol (**13‴**, 786 mg, 4.6 mmol) and 3-methylsulfinylpropionic acid (314 mg, 2.3 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **13″** (152 mg, 24 %) as a colorless solid; R_f = 0.56 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 14.8 Hz), 7.73 (1H, d, *J* = 2.6 Hz), 7.45 (1H, dd, *J* = 8.6, 2.6 Hz), 7.07 (1H, d, *J* = 8.6 Hz), 5.84 (1H, d, *J* = 14.8 Hz), 2.50 (3H, s), 2.38 (3H, s); ^{13}C

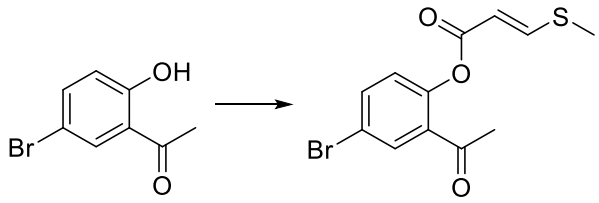
NMR (100 MHz, $CDCl_3$) δ 196.6, 163.0, 151.4, 147.6, 133.0, 132.7, 131.4, 129.8, 125.3, 111.1, 29.8, 14.6.

6-Chlorodeoxydirchromone (13′)



The compound was prepared from 2-acetyl-4-chlorophenyl (*E*)-3-(methylthio)acrylate (**13″**, 152 mg, 0.56 mmol). The dried residue was purified by flash chromatography with 0-38 % ethyl acetate in hexanes to afford compound **13′** (88 mg, 62 %) as a red solid; R_f = 0.38 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, d, *J* = 2.7 Hz), 7.59 (1H, d, *J* = 15.0 Hz), 7.56 (1H, dd, *J* = 8.9, 2.7 Hz), 7.38 (1H, d, *J* = 8.9 Hz), 6.08 (1H, s), 5.94 (1H, d, *J* = 15.0 Hz), 2.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 161.1, 154.3, 139.1, 133.7, 130.9, 125.3, 125.1, 119.4, 114.8, 107.6, 14.6.

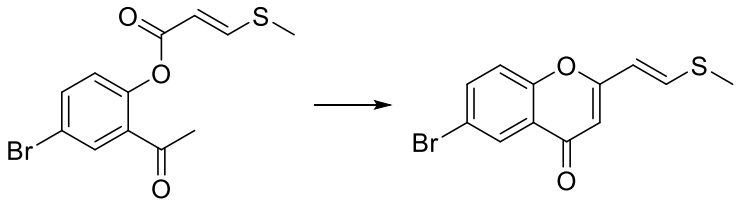
2-Acetyl-4-bromophenyl (*E*)-3-(methylthio)acrylate (14″)



The compound was prepared from 2-acetyl-4-bromophenol (**14‴**, 1.93 g, 9.0 mmol) and 3-methylsulfinylpropionic acid (306 mg, 2.3 mmol). The dried residue was purified by flash chromatography with 0-10 % ethyl acetate in hexanes to afford compound **14″** (331 mg, 47 %) as an off-white solid; R_f = 0.56 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 14.8 Hz), 7.88 (1H, d, *J* = 2.4 Hz), 7.61 (1H, dd, *J* = 8.6, 2.4 Hz), 7.02 (1H, d, *J* = 8.6 Hz), 5.84 (1H, d, *J* = 14.8 Hz), 2.51 (3H, s), 2.40 (3H,

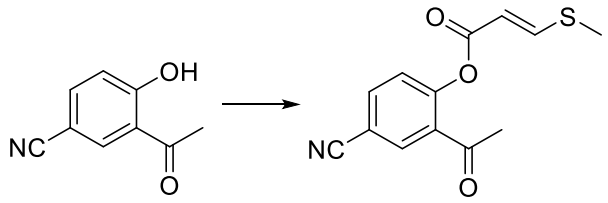
s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 163.0, 151.5, 148.2, 136.0, 133.1, 132.8, 125.7, 119.1, 111.2, 29.9, 14.6.

6-Bromodeoxydirchromone (14′)



The compound was prepared from 2-acetyl-4-bromophenyl (*E*)-3-(methylthio)acrylate (**14″**, 331 mg, 1.1 mmol). The dried residue was purified by flash chromatography with 0-38 % ethyl acetate in hexanes to afford compound **14′** (214 mg, 68 %) as a red solid; R_f = 0.30 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, d, *J* = 2.5 Hz), 7.70 (1H, dd, *J* = 8.8, 2.5 Hz), 7.59 (1H, d, *J* = 15.0 Hz), 7.31 (1H, d, *J* = 8.8 Hz), 6.08 (1H, s), 5.94 (1H, d, *J* = 15.0 Hz), 2.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 161.1, 154.7, 139.1, 136.5, 128.4, 125.4, 119.7, 118.4, 114.8, 107.7, 14.6.

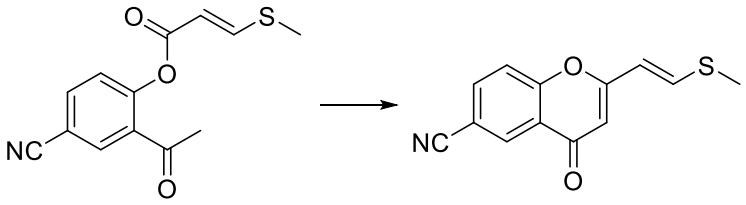
2-Acetyl-4-cyanophenyl (*E*)-3-(methylthio)acrylate (15″)



The compound was prepared from 2-acetyl-4-cyanophenol (**15‴**, 859 mg, 5.3 mmol) and 3-methylsulfinylpropionic acid (363 mg, 2.7 mmol). The dried residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford compound **15″** (215 mg, 31 %) as a white solid; R_f = 0.44 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, d, J = 14.8 Hz), 8.04 (1H, d, *J* = 1.9 Hz), 7.76 (1H, dd, *J* = 8.4, 1.9 Hz), 7.27 (1H, d, *J* = 8.4 Hz), 5.83 (1H, d, *J* = 14.8 Hz), 2.52 (3H, s), 2.39 (3H, s); ^{13}C

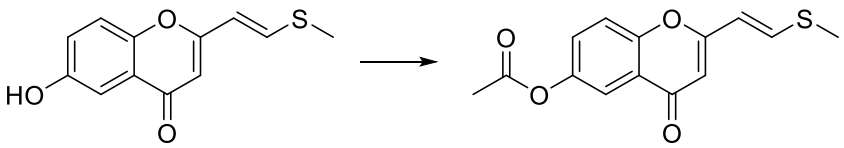
NMR (100 MHz, $CDCl_3$) δ 195.9, 162.3, 152.6, 152.2, 136.2, 134.0, 132.6, 125.2, 117.5, 110.5, 110.0, 29.9, 14.6.

6-Cyanodeoxydirchromone (15′)



The compound was prepared from 2-acetyl-4-cyanophenyl (*E*)-3-(methylthio)acrylate (**15″**, 215 mg, 0.82 mmol). The dried residue was purified by flash chromatography with 15-40 % ethyl acetate in hexanes to afford compound **15′** (79 mg, 40 %) as a yellow solid; R_f = 0.25 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (1H, d, *J* = 1.3 Hz), 7.83 (1H, dd, *J* = 8.7, 1.3 Hz), 7.63 (1H, d, *J* = 15.0 Hz), 7.51 (1H, d, *J* = 8.7 Hz), 6.08 (1H, s), 5.94 (1H, d, *J* = 15.0 Hz), 2.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 161.3, 157.6, 140.4, 135.9, 131.2, 124.4, 119.3, 117.7, 114.2, 109.0, 107.8, 14.6.

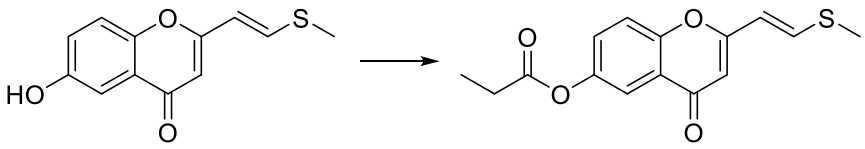
6-Acetyloxydeoxydirchromone (16a′)



To a solution of 6-hydroxydeoxydirchromone (**22**, 47 mg, 0.20 mmol) in 10 mL anhydrous THF was added triethylamine (84 µL, 0.60 mmol) and acetyl chloride (36 µL, 0.50 mmol). The reaction was stirred overnight, and ethyl acetate was added. The organic phase was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The dried residue was purified by flash chromatography with 0-20 % acetone in dichloromethane to afford compound **16a′** (48

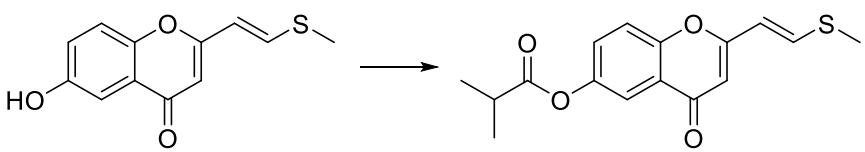
mg, 85 %) as a pink solid; R_f = 0.71 (dichloromethane-acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 2.7 Hz), 7.55 (1H, d, *J* = 15.0 Hz), 7.40 (1H, d, *J* = 9.0 Hz), 7.33 (1H, dd, *J* = 9.0, 2.7 Hz), 6.04 (1H, s), 5.91 (1H, d, *J* = 15.0 Hz), 2.40 (3H, s), 2.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 169.4, 161.0, 153.3, 147.3, 138.7, 127.6, 124.7, 118.9, 117.7, 114.8, 107.2, 21.0, 14.4.

6-Propionyloxydeoxydirchromone (16b′)



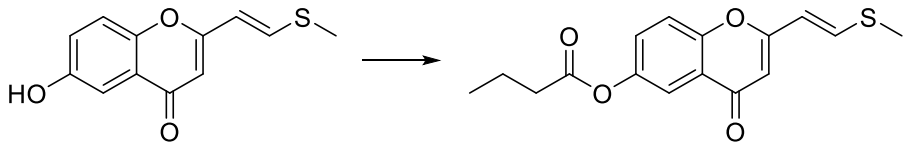
To a solution of 6-hydroxydeoxydirchromone (**22**, 40 mg, 0.17 mmol) in 2 mL anhydrous DMF was added propionic acid (16 µL, 0.21 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (49 mg, 0.26 mmol) and dimethyl aminopyridine (63 mg, 0.52 mmol). The reaction was stirred overnight then evaporated under reduced pressure. The dried residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford compound **16b′** (28 mg, 56 %) as an off-white solid; R_f = 0.8 (dichloromethane-acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 2.8 Hz), 7.57 (1H, d, *J* = 15.0 Hz), 7.43 (1H, d, *J* = 9.0 Hz), 7.36 (1H, dd, *J* = 9.0, 2.8 Hz), 6.06 (1H, s), 5.94 (1H, d, *J* = 15.0 Hz), 2.60 (2H, q, *J* = 7.5 Hz), 2.43 (3H, s), 1.26 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 172.9, 161.0, 153.3, 147.5, 138.7, 127.7, 124.8, 118.9, 117.8, 114.9, 107.3, 27.7, 14.6, 9.1.

6-Isobutyryloxydeoxydirchromone (16c′)



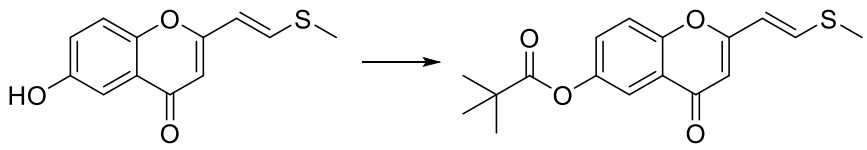
To a solution of 6-hydroxydeoxydirchromone (**22**, 52 mg, 0.22 mmol) in 2 mL anhydrous DMF was added isobutyric acid (41 µL, 0.44 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (101 mg, 0.53 mmol) and dimethyl aminopyridine (129 mg, 1.1 mmol). The reaction was stirred overnight then evaporated under reduced pressure. The dried residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford compound **16c′** (41 mg, 63 %) as an off-white solid; R_f = 0.33 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 2.8 Hz), 7.57 (1H, d, *J* = 15.0 Hz), 7.42 (1H, d, *J* = 9.0 Hz), 7.34 (1H, dd, *J* = 9.0, 2.8 Hz), 6.06 (1H, s), 5.93 (1H, d, *J* = 15.0 Hz), 2.81 (1H, m), 2.42 (3H, s), 1.31 (6H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 175.6, 161.1, 153.3, 147.6, 138.7, 127.7, 124.8, 118.9, 117.7, 114.9, 107.3, 34.2, 19.0, 14.6.

6-Butyryloxydeoxydirchromone (16d′)



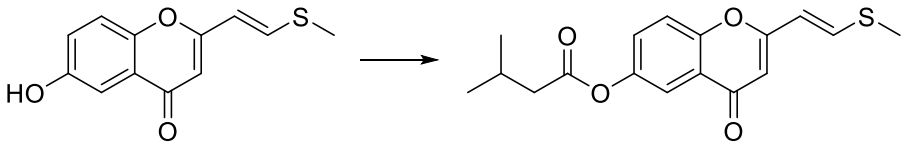
To a solution of 6-hydroxydeoxydirchromone (**22**, 51 mg, 0.22 mmol) in 2 mL anhydrous DMF was added isobutyric acid (40 µL, 0.44 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (100 mg, 0.52 mmol) and dimethyl aminopyridine (128 mg, 1.1 mmol). The reaction was stirred overnight then evaporated under reduced pressure. The dried residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford compound **16d′** (41 mg, 61 %) as an off-white solid; R_f = 0.27 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 2.8 Hz), 7.56 (1H, d, *J* = 15.0 Hz), 7.41 (1H, d, *J* = 9.0 Hz), 7.34 (1H, dd, *J* = 9.0, 2.8 Hz), 6.05 (1H, s), 5.92 (1H, d, *J* = 15.0 Hz), 2.54 (2H, t, *J* = 7.4 Hz), 2.41 (3H, s), 1.77 (2H, h, *J* = 7.4 Hz), 1.03 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 172.1, 161.0, 153.3, 147.5, 138.7, 127.7, 124.7, 118.9, 117.7, 114.9, 107.2, 36.1, 18.5, 14.5, 13.7.

6-Pivaloyloxydeoxydirchromone (16e′)



To a solution of 6-hydroxydeoxydirchromone (**22**, 37 mg, 0.16 mmol) in 8 mL anhydrous THF was added triethylamine (66 µL, 0.47 mmol) and pivaloyl chloride (49 µL, 0.39 mmol). The reaction was stirred overnight, then ethyl acetate was added. The organic phase was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The dried residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford compound **16e′** (36 mg, 75 %) as an orange solid; R_f = 0.21 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 2.4 Hz), 7.58 (1H, d, *J* = 15.0 Hz), 7.44 (1H, d, *J* = 8.9 Hz), 7.34 (1H, dd, *J* = 8.9, 2.4 Hz), 6.07 (1H, s), 5.95 (1H, d, *J* = 15.0 Hz), 2.43 (3H, s), 1.35 (9 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 177.1, 161.1, 153.3, 147.9, 138.8, 127.7, 124.8, 118.9, 117.7, 115.0, 107.3, 39.2, 27.2, 14.6.

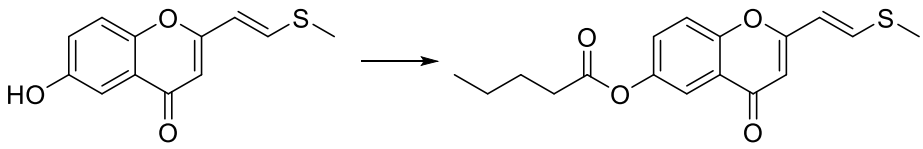
6-Isovaleryloxydeoxydirchromone (16f′)



To a solution of 6-hydroxydeoxydirchromone (**22**, 53 mg, 0.23 mmol) in 2 mL anhydrous DMF was added isovaleric acid (50 µL, 0.45 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (104 mg, 0.55 mmol) and dimethyl aminopyridine (133 mg, 1.1 mmol). The reaction was stirred overnight then evaporated under reduced pressure. The dried residue was purified by flash chromatography with 0-30 % ethyl acetate in hexanes to afford compound **16f′** (43 mg, 60 %) as an orange solid; R_f = 0.24 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* =

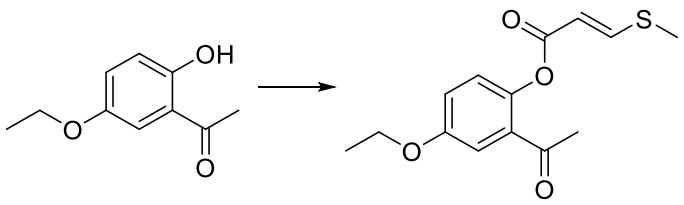
2.8 Hz), 7.55 (1H, d, *J* = 15.0 Hz), 7.41 (1H, d, *J* = 9.0 Hz), 7.33 (1H, dd, *J* = 9.0, 2.8 Hz), 6.05 (1H, s), 5.92 (1H, d, *J* = 15.0 Hz), 2.43 (2H, d, *J* = 7.2 Hz), 2.41 (3H, s), 2.28 – 2.16 (1H, m), 1.04 (6H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 171.5, 161.0, 153.3, 147.4, 138.8, 127.7, 124.7, 118.9, 117.7, 114.9, 107.2, 43.2, 25.9, 22.5, 14.5.

6-Valeryloxydeoxydirchromone (16g′)



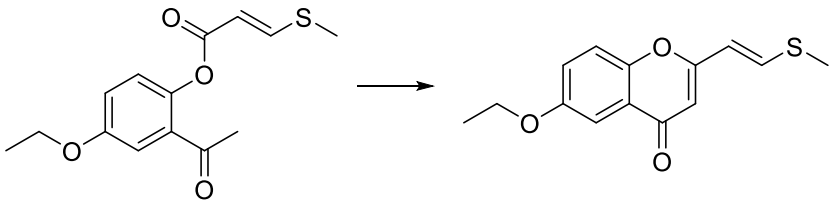
To a solution of 6-hydroxydeoxydirchromone (**22**, 107 mg, 0.46 mmol) in 5 mL anhydrous DMF was added valeric acid (99 µL, 0.91 mmol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (209 mg, 1.1 mmol) and dimethyl aminopyridine (267 mg, 2.2 mmol). The reaction was stirred overnight then evaporated under reduced pressure. The dried residue was purified by flash chromatography with 0-40 % ethyl acetate in hexanes to afford compound **16g′** (53 mg, 36 %) as a white solid; R_f = 0.29 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 2.8 Hz), 7.54 (1H, d, *J* = 15.0 Hz), 7.40 (1H, d, *J* = 9.0 Hz), 7.33 (1H, dd, *J* = 9.0, 2.8 Hz), 6.03 (1H, s), 5.91 (1H, d, *J* = 15.0 Hz), 2.55 (2H,t, *J* = 7.5 Hz), 2.40 (3H, s), 1.76 – 1.67 (2H, m), 1.48 – 1.37 (2H, m), 0.94 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 172.2, 161.0, 153.3, 147.4, 138.7, 127.6, 124.7, 118.9, 117.7, 114.8, 107.2, 34.0, 27.0, 22.3, 14.5, 13.8.

2-Acetyl-4-ethoxyphenyl (*E*)-3-(methylthio)acrylate (17a″)



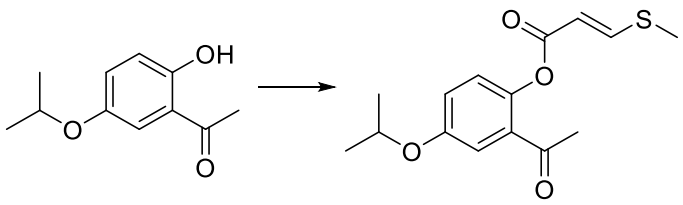
The compound was prepared from 1-(5-ethoxy-2-hydroxyphenyl)ethan-1-one (**17a‴**, 691 mg, 3.8 mmol) and 3-methylsulfinylpropionic acid (261 mg, 1.9 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **17a″** (170 mg, 31 %) as a yellow oil; R_f = 0.56 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 14.8 Hz), 7.21 (1H, s), 6.95 (2H, s), 5.79 (1H, d, *J* = 14.8 Hz), 3.95 (2H, q, *J* = 6.8 Hz), 2.43 (3H, s), 2.30 (3H, s), 1.33 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 163.5, 156.2, 150.2, 142.4, 131.6, 124.5, 119.2, 114.5, 111.4, 63.8, 29.7, 14.5, 14.2.

6-Ethoxydeoxydirchromone (17a′)



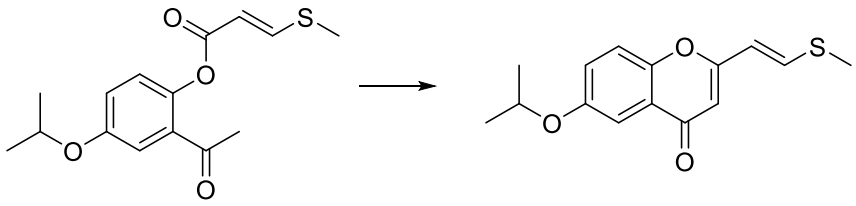
The compound was prepared from 2-acetyl-4-ethoxyphenyl (*E*)-3-(methylthio)acrylate (**17a″**, 169 mg, 0.60 mmol). The dried residue was purified by flash chromatography with 20-50 % ethyl acetate in hexanes to afford compound **17a′** (77 mg, 49 %) as a red solid; R_f = 0.09 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 15.0 Hz), 7.43 (1H, d, *J* = 3.0 Hz), 7.27 (1H, d, *J* = 9.1 Hz), 7.13 (1H, dd, *J* = 9.1, 3.0 Hz), 5.99 (1H, s), 5.86 (1H, d, *J* = 15.0 Hz), 4.03 (2H, q, *J* = 7.0 Hz), 2.36 (3H, s), 1.37 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 160.5, 156.0, 150.4, 137.8, 124.4, 123.5, 118.9, 115.0, 106.9, 105.5, 64.1, 14.7, 14.4.

2-Acetyl-4-isopropoxyphenyl (*E*)-3-(methylthio)acrylate (17b″)



The compound was prepared from 1-(5-isopropoxy-2-hydroxyphenyl)ethan-1-one (**17b‴**, 599 mg, 3.1 mmol) and 3-methylsulfinylpropionic acid (210 mg, 1.5 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **17b″** (131 mg, 29 %) as a yellow oil; R_f = 0.60 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 14.9 Hz), 7.26 – 7.23 (1H, m), 7.00 – 6.97 (2H, m), 5.84 (1H, d, *J* = 14.9 Hz), 4.52 (1H, hept, *J* = 6.1 Hz), 2.48 (3H, s), 2.36 (3H, s), 1.30 (6H, d, *J* = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 163.7, 155.4, 150.4, 142.4, 131.9, 124.7, 120.6, 116.3, 111.7, 70.6, 29.9, 21.9, 14.5.

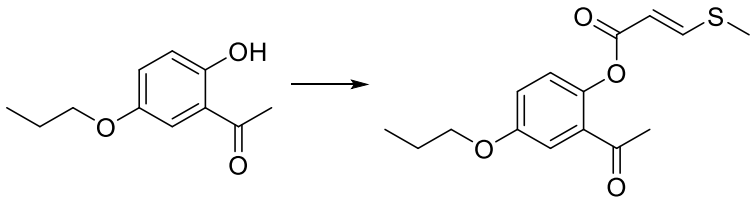
6-Isopropoxydeoxydirchromone (17b′)



The compound was prepared from 2-acetyl-4-isopropoxyphenyl (*E*)-3-(methylthio)acrylate (**17b″**, 131 mg, 0.45 mmol). The dried residue was purified by flash chromatography with 10-50 % ethyl acetate in hexanes to afford compound **17b′** (63 mg, 51 %) as a red solid; R_f = 0.17 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 15.0 Hz), 7.50 (1H, d, *J* = 3.0 Hz), 7.31 (1H, d, *J* = 9.1 Hz), 7.15 (1H, dd, *J* = 9.1, 3.0 Hz), 6.04 (1H, s), 5.91 (1H, d, *J* = 15.0 Hz), 4.63 (1H, hept, *J* = 6.0 Hz), 2.40 (3H, s), 1.33 (6H, d, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ

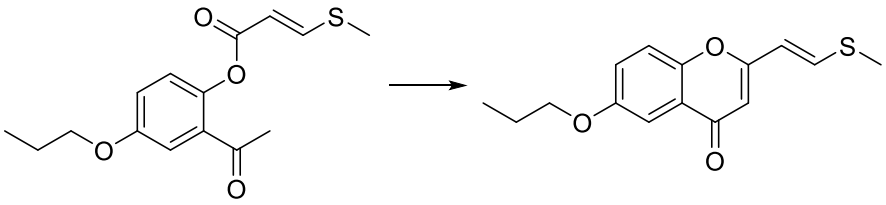
178.4, 160.6, 155.0, 150.4, 137.8, 124.7, 124.6, 119.1, 115.2, 107.2, 107.1, 70.6, 21.9, 14.5.

2-Acetyl-4-propoxyphenyl (*E*)-3-(methylthio)acrylate (17c″)



The compound was prepared from 1-(5-propoxy-2-hydroxyphenyl)ethan-1-one (**17c‴**, 1.01 g, 5.2 mmol) and 3-methylsulfinyl-propionic acid (355 mg, 2.6 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **17c″** (179 mg, 23 %) as a yellow oil; R_f = 0.66 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* = 14.9 Hz), 7.25 (1H, dd, *J* = 2.2, 0.9 Hz), 6.99 (1H, d, *J* = 2.2 Hz), 6.99 (1H, s), 5.82 (1H, d, *J* = 14.9 Hz), 3.88 (2H, t, *J* = 6.5 Hz), 2.47 (3H, s), 2.34 (3H, s), 1.81 – 1.71 (2H, m), 0.99 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 163.6, 156.5, 150.3, 142.4, 131.7, 124.6, 119.4, 114.6, 111.6, 69.9, 29.8, 22.4, 14.4, 10.4.

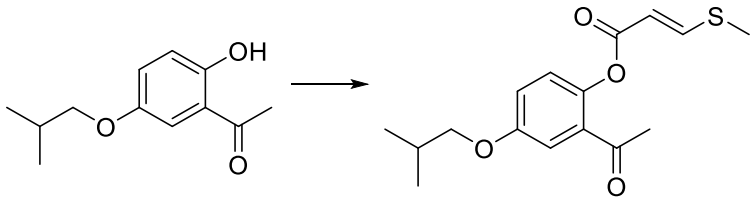
6-Propoxydeoxydirchromone (17c′)



The compound was prepared from 2-acetyl-4-propoxyphenyl (*E*)-3-(methylthio)acrylate (**17c″**, 178 mg, 0.61 mmol). The dried residue was purified by flash chromatography with 10-50 % ethyl acetate in hexanes to afford compound **17c′** (99 mg, 59 %) as a red solid; R_f = 0.2 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$)

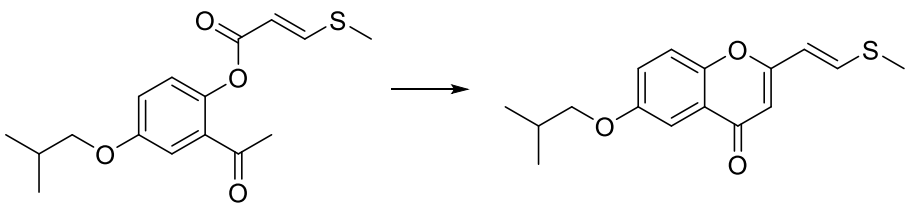
δ 7.47 (1H, d, *J* = 15.1 Hz), 7.45 (1H, d, *J* = 2.8 Hz), 7.28 (1H, d, *J* = 9.1 Hz), 7.15 (1H, dd, *J* = 9.1, 2.8 Hz), 6.00 (1H, s), 5.88 (1H, d, *J* = 15.1 Hz), 3.93 (2H, t, *J* = 6.6 Hz), 2.37 (3H, s), 1.82 – 1.72 (2H, m), 0.99 (3H, t, *J* = 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 160.6, 156.2, 150.4, 137.8, 124.5, 123.5, 118.9, 115.1, 107.0, 105.7, 70.2, 22.5, 14.4, 10.5.

2-Acetyl-4-isobutoxyphenyl (*E*)-3-(methylthio)acrylate (17d″)



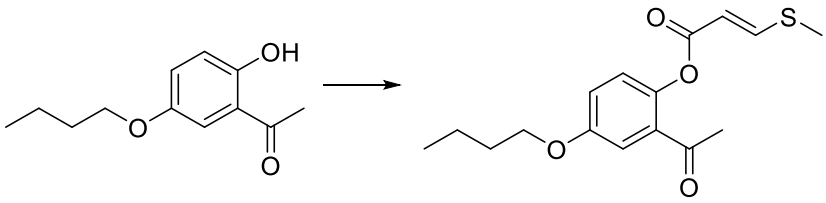
The compound was prepared from 1-(5-isobutoxy-2-hydroxyphenyl)ethan-1-one (**17d‴**, 613 mg, 3.0 mmol) and 3-methylsulfinylpropionic acid (201 mg, 1.5 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **17d″** (81 mg, 18 %) as a slightly yellow oil; R_f = 0.65 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 14.8 Hz), 7.28 (1H, s), 7.02 (2H, m), 5.86 (1H, d, *J* = 14.8 Hz), 3.72 (2H, d, *J* = 6.2 Hz), 2.51 (3H, s), 2.39 (3H, s), 2.13 – 2.01 (1H, m), 1.01 (6H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 163.8, 156.9, 150.5, 142.6, 132.0, 124.7, 119.6, 114.8, 111.8, 75.0, 30.0, 28.3, 19.3, 14.6.

6-Isobutoxydeoxydirchromone (17d′)



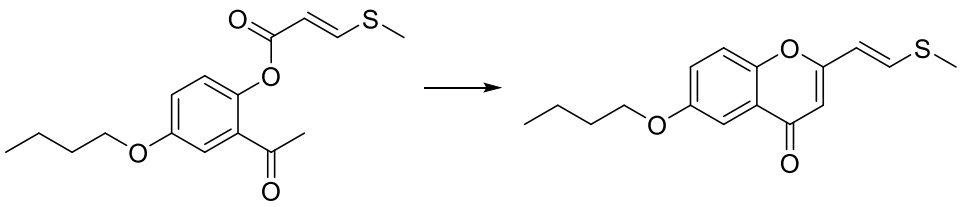
The compound was prepared from 2-acetyl-4-isbutoxyphenyl (*E*)-3-(methylthio)acrylate (**17d″**, 80 mg, 0.26 mmol). The dried residue was purified by flash chromatography with 10-40 % ethyl acetate in hexanes to afford compound **17d′** (38mg, 50 %) as a pink solid; R_f = 0.18 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 15.1 Hz), 7.50 (1H, d, *J* = 2.8 Hz), 7.34 (1H, d, *J* = 9.1 Hz), 7.21 (1H, dd, *J* = 9.1, 2.8 Hz), 6.06 (1H, s), 5.94 (1H, d, *J* = 15.1 Hz), 3.79 (2H, d, *J* = 6.5 Hz), 2.42 (3H, s), 2.15 – 2.03 (1H, m), 1.02 (6H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 160.7, 156.5, 150.6, 137.9, 124.6, 123.7, 119.0, 115.3, 107.1, 105.8, 75.2, 28.3, 19.3, 14.6.

2-Acetyl-4-butoxyphenyl (*E*)-3-(methylthio)acrylate (17e″)



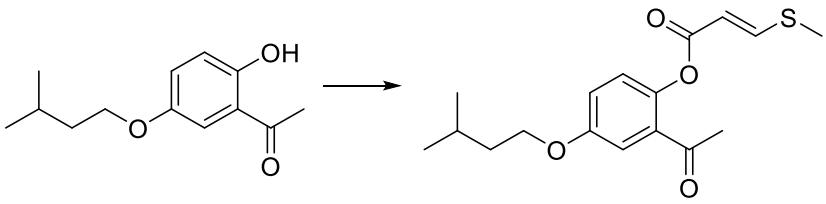
The compound was prepared from 1-(5-butoxy-2-hydroxyphenyl)ethan-1-one (**17e‴**, 1.24 g, 6.0 mmol) and 3-methylsulfinyl-propionic acid (406 mg, 3.0 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **17e″** (344 mg, 37 %) as a yellow oil; R_f = 0.64 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* = 14.9 Hz), 7.25 (1H, d, *J* = 1.4 Hz), 6.99 (2H, m, *J* = 2.1 Hz), 5.83 (1H, d, *J* = 14.9 Hz), 3.93 (2H, t, *J* = 6.5 Hz), 2.48 (3H, s), 2.35 (3H, s), 1.72 (2H, dq, *J* = 7.9, 6.5 Hz), 1.50 – 1.40 (2H, m), 0.93 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 163.6, 156.6, 150.4, 142.5, 131.8, 124.6, 119.4, 114.7, 111.6, 68.2, 31.1, 29.9, 19.1, 14.4, 13.8.

6-Butoxydeoxydirchromone (17e′)



The compound was prepared from 2-acetyl-4-butoxyphenyl (*E*)-3-(methylthio)acrylate (**17e″**, 343 mg, 1.1 mmol). The dried residue was purified by flash chromatography with 10-50 % ethyl acetate in hexanes to afford compound **17e′** (197 mg, 61 %) as a red solid; R_f = 0.22 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 14.9 Hz), 7.46 (1H, d, *J* = 3.0 Hz), 7.28 (1H, d, *J* = 9.1 Hz), 7.15 (1H, dd, *J* = 9.1, 3.0 Hz), 6.01 (1H, s), 5.88 (1H, d, *J* = 14.9 Hz), 3.98 (2H, t, *J* = 6.5 Hz), 2.37 (3H, s), 1.78 – 1.69 (2H, m), 1.50 – 1.39 (2H, m), 0.93 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 160.6, 156.2, 150.4, 137.8, 124.5, 123.6, 118.9, 115.1, 107.0, 105.6, 68.4, 31.2, 19.2, 14.4, 13.9.

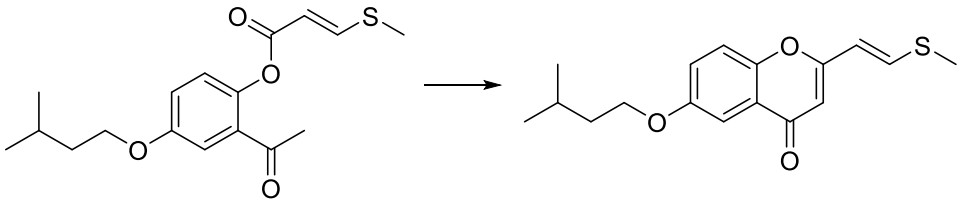
2-Acetyl-4-isoamyloxyphenyl (*E*)-3-(methylthio)acrylate (17f″)



The compound was prepared from 1-(5-isoamyloxy-2-hydroxyphenyl)ethan-1-one (**17f‴**, 913 mg, 4.1 mmol) and 3-methyl-sulfinylpropionic acid (279 mg, 2.1 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **17f″** (104 mg, 16 %) as a colorless oil; R_f = 0.61 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 14.9 Hz), 7.28 (1H, d, *J* = 1.5 Hz), 7.06 – 6.99 (2H, m), 5.86 (1H, d, *J* = 14.9 Hz), 3.99 (2H, t, *J* = 6.6 Hz), 2.51 (3H, s), 2.40 (3H, s), 1.89 – 1.77 (1H, m), 1.67 (2H, q, *J* = 6.6 Hz), 0.95 (6H, d, *J* = 6.6

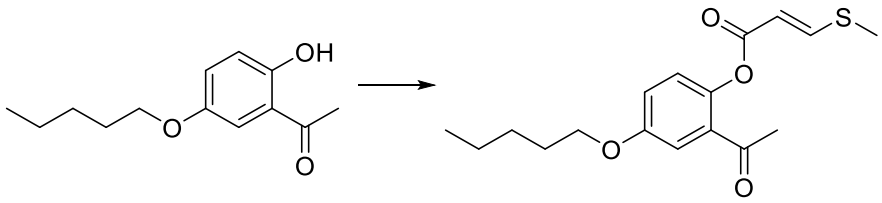
Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 163.8, 156.7, 150.6, 142.6, 131.9, 124.7, 119.6, 114.8, 111.8, 67.0, 37.9, 30.1, 25.1, 22.6, 14.6.

6-Isoamyloxydeoxydirchromone (17f′)



The compound was prepared from 2-acetyl-4-isoamyloxyphenyl (*E*)-3-(methylthio)acrylate (**17f″**, 103 mg, 0.32 mmol). The dried residue was purified by flash chromatography with 15-30 % ethyl acetate in hexanes to afford compound **17f′** (67 mg, 69 %) as a red solid; R_f = 0.33 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 15.1 Hz), 7.52 (1H, d, *J* = 3.1 Hz), 7.34 (1H, d, *J* = 9.1 Hz), 7.20 (1H, dd, *J* = 9.1, 3.1 Hz), 6.07 (1H, s), 5.94 (1H, d, *J* = 15.0 Hz), 4.05 (2H, t, *J* = 6.7 Hz), 2.43 (3H, s), 1.88 – 1.77 (1H, m), 1.70 (2H, t, *J* = 6.7 Hz), 0.96 (6H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 160.7, 156.4, 150.6, 137.9, 124.6, 123.8, 119.0, 115.3, 107.2, 105.7, 67.2, 38.0, 25.2, 22.7, 14.6.

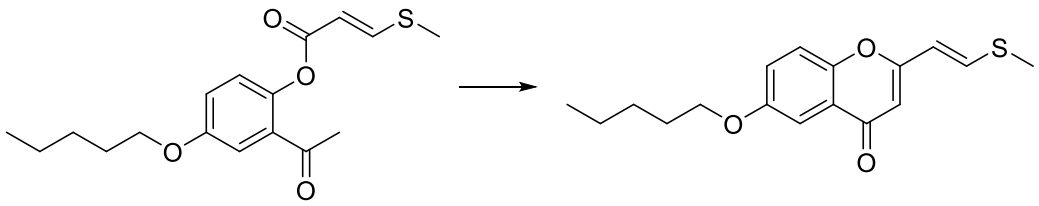
2-Acetyl-4-amyloxyphenyl (*E*)-3-(methylthio)acrylate (17g″)



The compound was prepared from 1-(5-amyloxy-2-hydroxyphenyl)ethan-1-one (**17g‴**, 1.02 g, 4.6 mmol) and 3-methylsulfinyl-propionic acid (314 mg, 2.3 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **17g″** (182 mg, 25 %) as a slightly yellow oil; R_f = 0.65 (hexane-

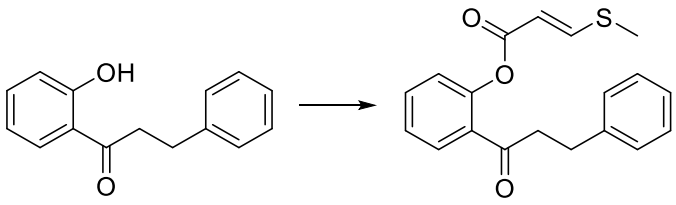
EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 14.9 Hz), 7.26 (1H, d, *J* = 2.4 Hz), 7.02 – 7.00 (2H, m), 5.85 (1H, d, *J* = 14.9 Hz), 3.94 (2H, t, *J* = 6.5 Hz), 2.49 (3H, s), 2.38 (3H, s), 1.80 – 1.72 (2H, m), 1.46 – 1.31 (4H, m), 0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 163.7, 156.66, 150.5, 142.6, 131.9, 124.7, 119.5, 114.8, 111.7, 68.6, 30.0, 28.9, 28.2, 22.4, 14.5, 14.0.

6-Amyloxydeoxydirchromone (17g′)



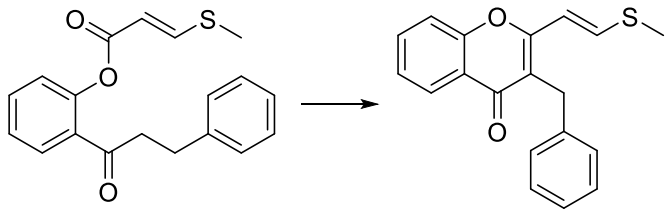
The compound was prepared from 2-acetyl-4-amyloxyphenyl (*E*)-3-(methylthio)acrylate (**17g″**, 182 mg, 0.56 mmol). The dried residue was purified by flash chromatography with 10-40 % ethyl acetate in hexanes to afford compound **17g′** (84 mg, 49 %) as a red solid; R_f = 0.20 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 15.0 Hz), 7.46 (1H, d, *J* = 2.1 Hz), 7.29 (1H, d, *J* = 9.0 Hz), 7.16 (1H, dd, *J* = 9.0, 2.1 Hz), 6.02 (1H, s), 5.89 (1H, d, *J* = 15.0 Hz), 3.97 (2H, t, *J* = 6.4 Hz), 2.38 (3H, s), 1.80 – 1.71 (2H, m), 1.44 – 1.29 (4H, m), 0.89 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 160.6, 156.3, 150.4, 137.8, 124.5, 123.6, 118.9, 115.2, 107.0, 105.6, 68.7, 28.8, 28.1, 22.5, 14.5, 14.0.

2-(3-Phenylpropanoyl)phenyl (*E*)-3-(methylthio)acrylate (18″)



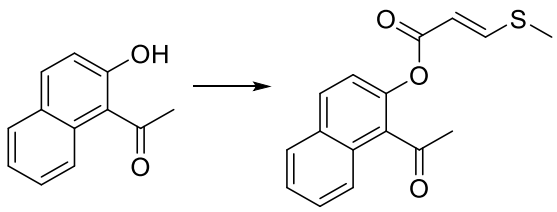
The compound was prepared from 1-(2-hydroxyphenyl)-3-phenylpropan-1-one (**18‴**, 930 mg, 4.1 mmol) and 3-methylsulfinyl-propionic acid (280 mg, 2.1 mmol). The dried residue was purified by flash chromatography with 0-10 % ethyl acetate in hexanes to afford compound **18″** (232 mg, 34 %) as a yellow oil; R_f = 0.64 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 14.8 Hz), 7.76 (1H, d, *J* = 7.7 Hz), 7.52 (1H, td, *J* = 7.8, 1.4 Hz), 7.33 – 7.28 (3H, m), 7.23 (3H, m), 7.17 (1H, d, *J* = 8.1 Hz), 5.86 (1H, d, *J* = 14.8 Hz), 3.24 (2H, t, *J* = 7.6 Hz), 3.04 (2H, t, *J* = 7.6 Hz), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 163.1, 150.5, 148.7, 140.9, 132.9, 131.3, 129.5, 128.3, 128.2, 125.9, 125.8, 123.7, 111.4, 43.3, 29.8, 14.2.

3-Benzyldeoxydirchromone (18′)



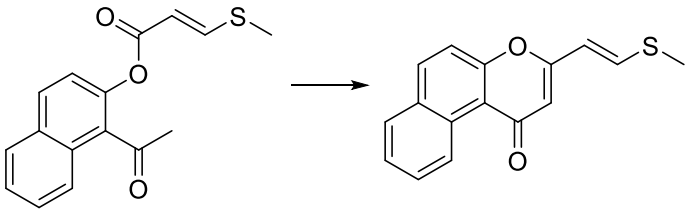
The compound was prepared from 2-(3-phenylpropanoyl)phenyl (*E*)-3-(methylthio)acrylate (**18″**, 231 mg, 0.71 mmol). The dried residue was purified by flash chromatography with 0-15 % ethyl acetate in hexanes to afford compound **18′** (174 mg, 80 %) as an orange solid; R_f = 0.79 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, d, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 14.8 Hz), 7.57 (1H, d, *J* = 8.7 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 7.3 (1H, t, *J* = 7.6 Hz), 7.29 – 7.22 (4H, m), 7.19 – 7.13 (1H, m), 6.25 (1H, d, *J* = 14.8 Hz), 4.03 (2H, s), 2.32 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 157.7, 155.3, 140.2, 138.4, 133.2, 128.5, 128.3, 126.1, 126.0, 124.5, 122.9, 117.6, 117.4, 113.1, 29.3, 14.5.

1-Acetylnaphthalen-2-yl (*E*)-3-(methylthio)acrylate (19″)



The compound was prepared from 1-acetyl-2-naphthol (**19‴**, 1.70 g, 9.1 mmol) and 3-methylsulfinylpropionic acid (310 mg, 2.3 mmol). The dried residue was purified by flash chromatography with 0-13 % ethyl acetate in hexanes to afford impure compound **19″** (361 mg, 55 %) as a slightly yellow oil, which was used as is for the ensuing step. R_f = 0.64 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 14.9 Hz), 7.84 (1H, d, *J* = 8.9 Hz), 7.79 (2H, t, *J* = 7.9 Hz), 7.51 – 7.42 (2H, m), 7.26 (1H, d, *J* = 8.9 Hz), 5.84 (1H, d, *J* = 14.9 Hz), 2.59 (3H, s), 2.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 163.0, 151.1, 144.7, 131.3, 130.7, 130.2, 129.6, 128.2, 127.5, 125.9, 124.3, 121.4, 110.9, 32.4, 32.3, 14.3.

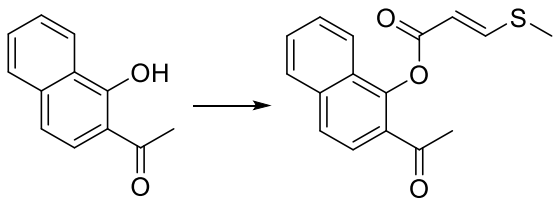
(*E*)-3-(2-(methylthio)vinyl)-1*H*-benzo[*f*]chromen-1-one (19′)



The compound was prepared from 1-acetylnaphthalen-2-yl (*E*)-3-(methylthio)acrylate (**19″**, 360 mg, 1.3 mmol). The dried residue was purified by flash chromatography with 0-40 % ethyl acetate in hexanes to afford compound **19′** (237 mg, 70 %) as a pink solid; R_f = 0.31 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (1H, d, *J* = 8.6 Hz), 8.02 (1H, d, *J* = 9.0 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.72 (1H, t, *J* = 7.7 Hz), 7.57 (1H, t, *J* = 7.2 Hz), 7.53 (1H, d, *J* = 15.1 Hz), 7.45 (1H, d, *J* = 9.0 Hz), 6.22 (1H, s),

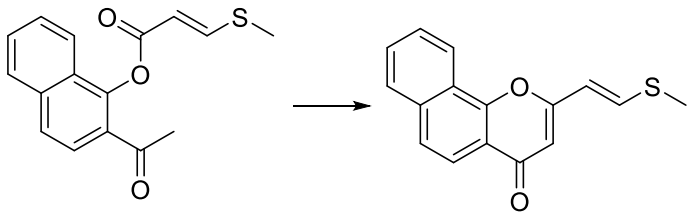
5.95 (1H, d, *J* = 15.1 Hz), 2.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 158.6, 157.0, 137.2, 135.3, 130.6, 130.6, 129.2, 128.2, 127.2, 126.5, 117.5, 117.1, 114.6, 110.6, 14.5.

2-Acetylnaphthalen-1-yl (*E*)-3-(methylthio)acrylate (20″)



The compound was prepared from 1′-hydroxy-2′-acetonaphthone (**20‴**, 817 mg, 4.4 mmol) and 3-methylsulfinylpropionic acid (299 mg, 2.2 mmol). The dried residue was purified by flash chromatography with 0-13 % ethyl acetate in hexanes to afford impure compound **20″** (215 mg, 34 %) as a colorless oil, which was used as is (without further purification) for the ensuing step. R_f = 0.60 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, d, *J* = 14.8 Hz), 7.95 (1H, d, *J* = 8.1 Hz), 7.83 (2H, d, *J* = 8.4 Hz), 7.73 (1H, d, *J* = 8.7 Hz), 7.58 – 7.50 (2H, m), 6.05 (1H, d, *J* = 14.8 Hz), 2.62 (3H, s), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 163.3, 151.4, 146.5, 136.2, 128.5, 127.8, 127.3, 127.2, 127.2, 125.9, 125.0, 123.0, 111.2, 30.2, 14.5.

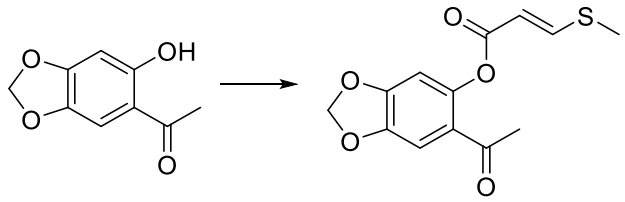
(*E*)-2-(2-(methylthio)vinyl)-4*H*-benzo[*h*]chromen-4-one (20′)



The compound was prepared from 2-acetylnaphthalen-1-yl (*E*)-3-(methylthio)acrylate (**20″**, 215 mg, 0.75 mmol). The dried residue was purified by flash chromatography with 15-50 % ethyl acetate in hexanes to afford compound **20′** (97 mg, 45 %) as a

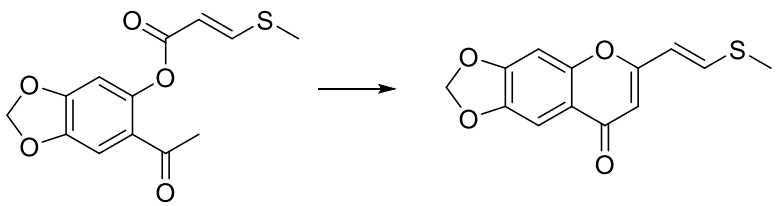
purple solid; R_f = 0.29 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, d, *J* = 8.0 Hz), 8.02 (1H, d, *J* = 8.7 Hz), 7.80 (1H, d, *J* = 7.8 Hz), 7.65 – 7.51 (4H, m), 6.14 (1H, s), 5.94 (1H, d, *J* = 15.0 Hz), 2.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 160.0, 152.8, 137.5, 135.8, 129.0, 128.1, 126.9, 124.9, 123.8, 122.0, 120.7, 120.0, 115.0, 108.7, 14.5.

6-Acetylbenzo[*d*][1,3]dioxol-5-yl (*E*)-3-(methylthio)acrylate (21″)



The compound was prepared from 1-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)ethan-1-one (Vasquez-Martinez et al., 2007) (**21‴**, 827 mg, 4.6 mmol) and 3-methylsulfinylpropionic acid (312 mg, 2.3 mmol). The dried residue was purified by flash chromatography with 5-20 % ethyl acetate in hexanes to afford compound **21″** (221 mg, 34 %) as a yellow solid; R_f = 0.45 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 14.8 Hz), 7.28 (1H, s), 6.57 (1H, s), 6.03 (2H, s), 5.85 (1H, d, *J* = 14.8 Hz), 2.46 (3H, s), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 163.5, 151.5, 151.0, 146.1, 145.7, 124.5, 111.4, 108.6, 104.8, 102.6, 30.2, 14.6.

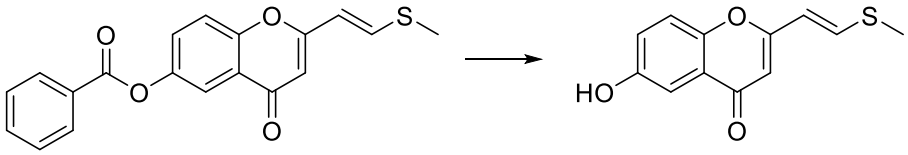
6,7-Methylenedioxydeoxydirchromone (21′)



The compound was prepared from 6-acetylbenzo[*d*][1,3]dioxol-5-yl (*E*)-3-(methylthio)acrylate (**21″**, 221 mg, 0.79 mmol). The dried residue was purified by flash

chromatography with 25-65 % ethyl acetate in hexanes to afford compound **21′** (61 mg, 29 %) as a pink solid; R_f = 0.12 (hexane-EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 15.1 Hz), 7.47 (1H, s), 6.82 (1H, s), 6.08 (2H, s), 6.02 (1H, s), 5.91 (1H, d, *J* = 15.1 Hz), 2.42 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 160.4, 153.1, 152.6, 146.0, 137.3, 119.0, 115.1, 107.2, 102.5, 102.5, 97.9, 14.6.

6-Hydroxydeoxydirchromone (22)



To a solution of 6-benzoyloxydeoxydirchromone (St-Gelais et al., 2018) (1.45 g, 4.3 mmol) in 25 mL methanol was added KOH (1.2 g, 21 mmol). The solution was brought to reflux for 10 min, cooled, and quenched with 10 % HCl. The solution was extracted with 3 × ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The dried residue was purified by flash chromatography with 20-30 % acetone in dichloromethane to afford compound **22** (633 mg, 63 %) as a yellow solid; R_f = 0.54 (dichloromethane-acetone 3:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, OH), 7.74 (1H, d, *J* = 15.1 Hz), 7.46 (1H, d, *J* = 9.0 Hz), 7.26 (1H, d, *J* = 3.0 Hz), 7.18 (1H, dd, *J* = 9.0, 3.0 Hz), 6.23 (1H, d, *J* = 15.1 Hz), 6.16 (1H, s Hz), 2.43 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9, 160.6, 154.6, 149.0, 138.2, 124.3, 122.6, 119.3, 115.2, 107.7, 106.0, 13.9.

3.9.2 References

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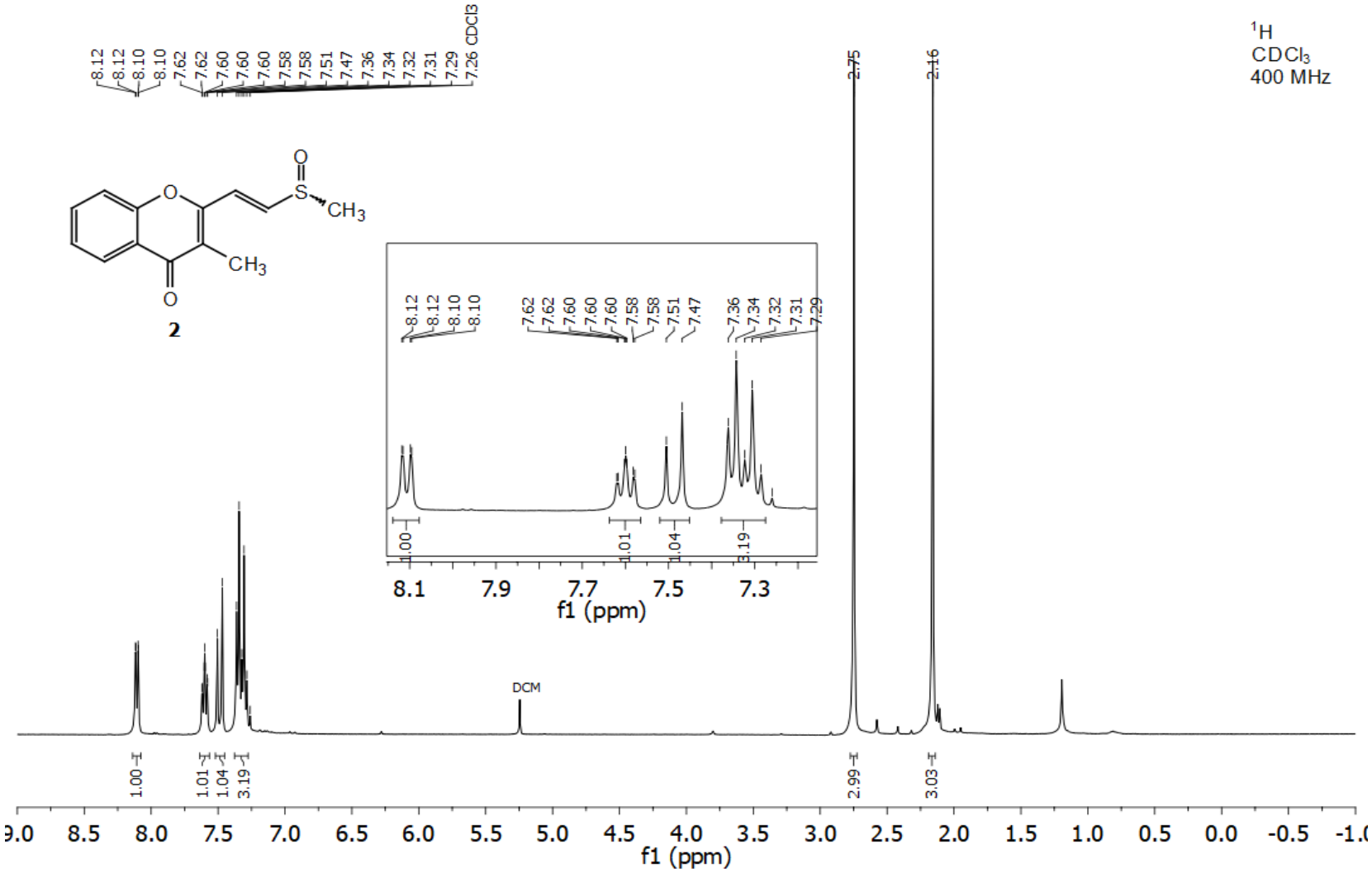
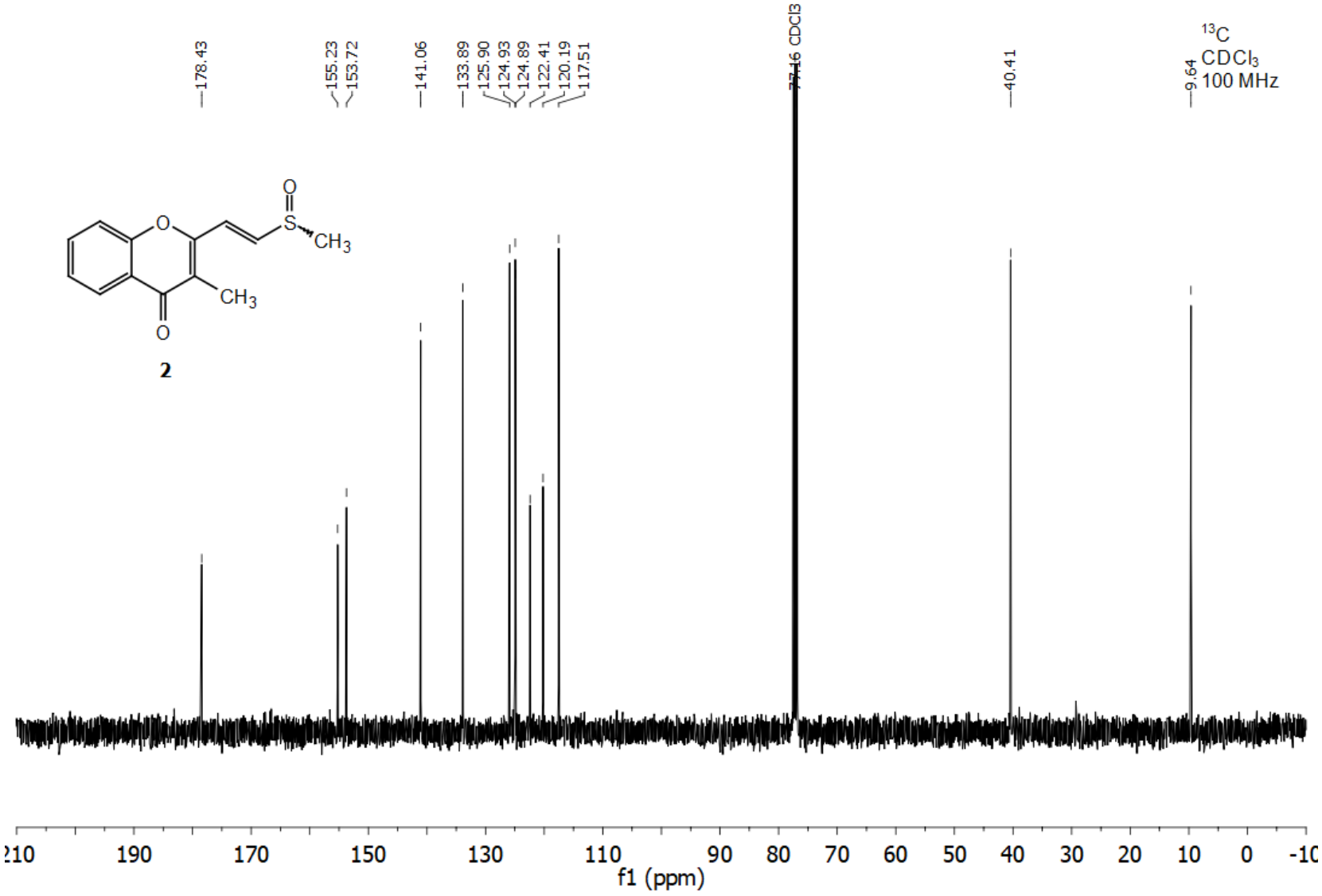
3.9.3 NMR spectra

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40.41
9.64
13C
CDCl3
100 MHz
O
S
CH3
CH3
O
O
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150
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80
70
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40
30
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0
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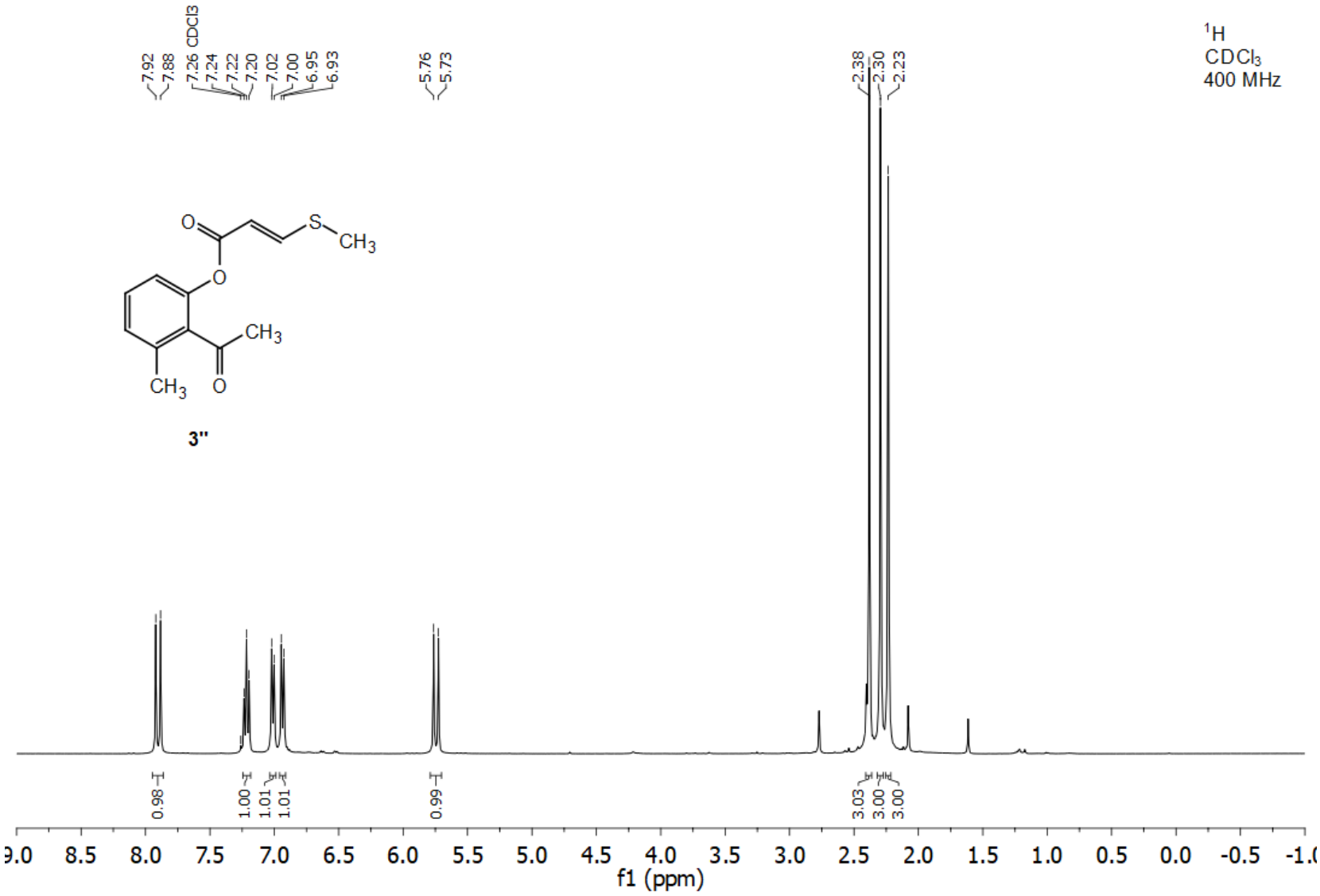
f1 (ppm)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2.38
2.30
2.23
1H
CDCl3
400 MHz
O
S
CH3
O
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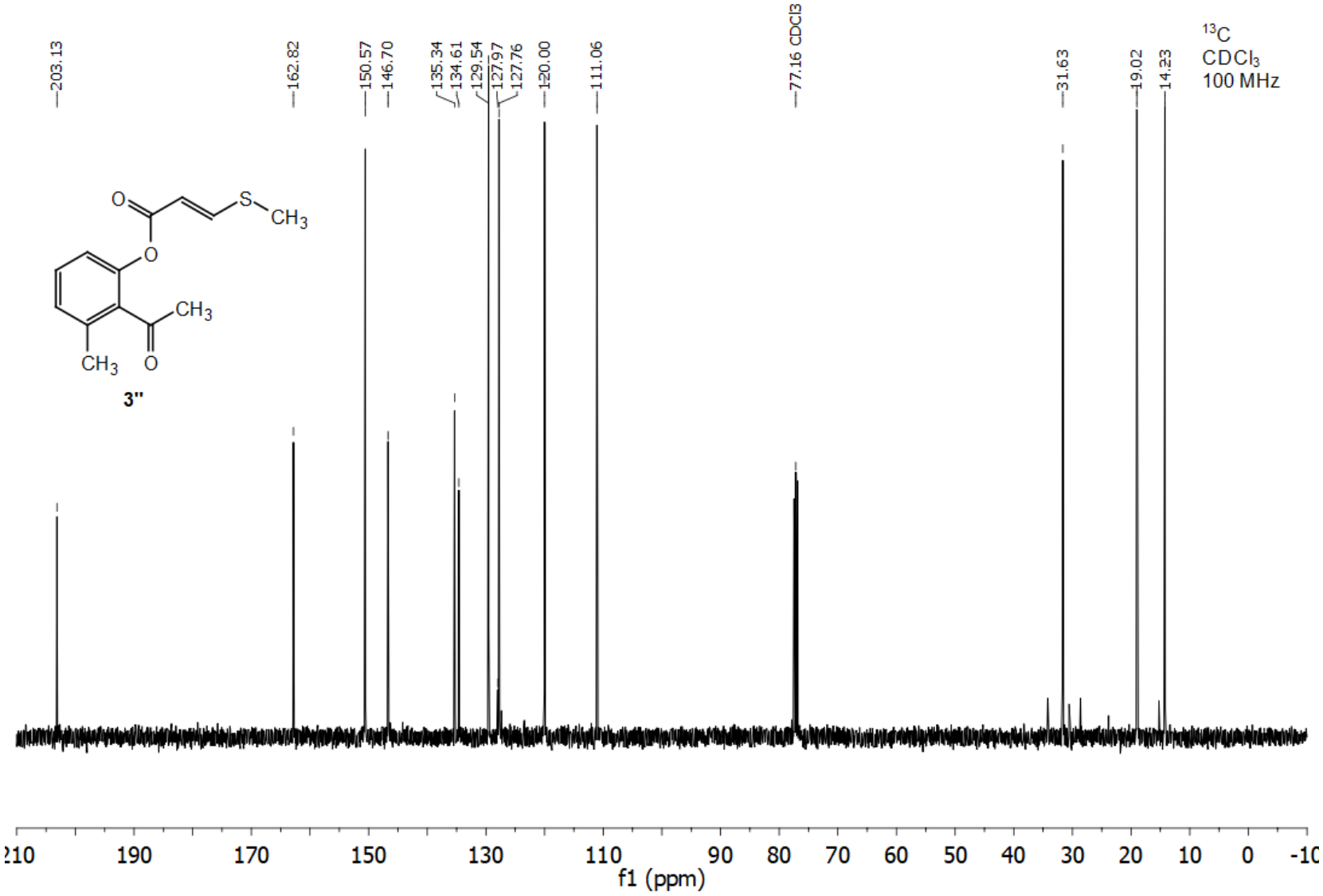
f1 (ppm)

3''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O
S
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CH3
CH3
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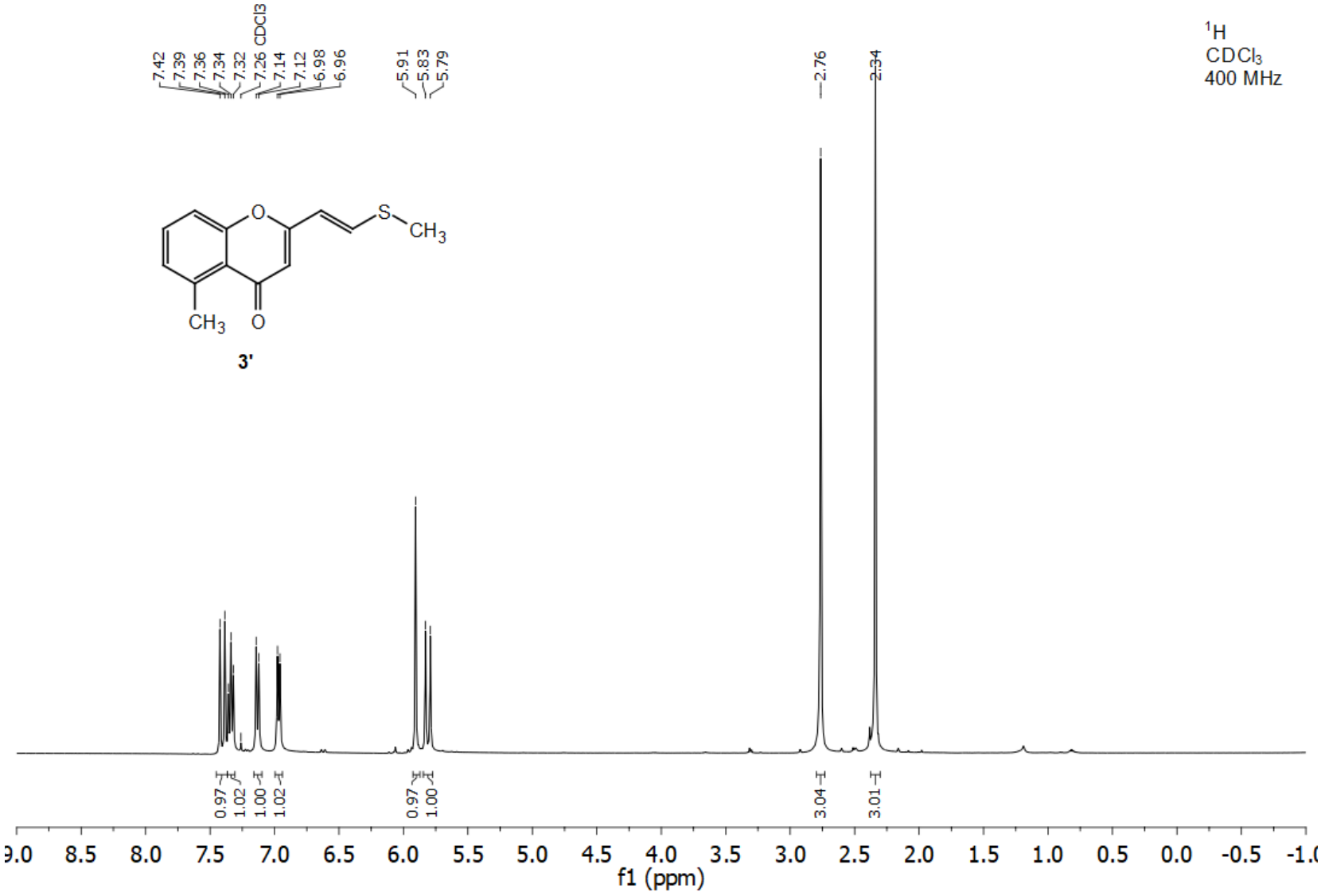
f1 (ppm)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5.79
2.76
2.34
1H
CDCl3
400 MHz
O
S
CH3
CH3
O
3'
0.97
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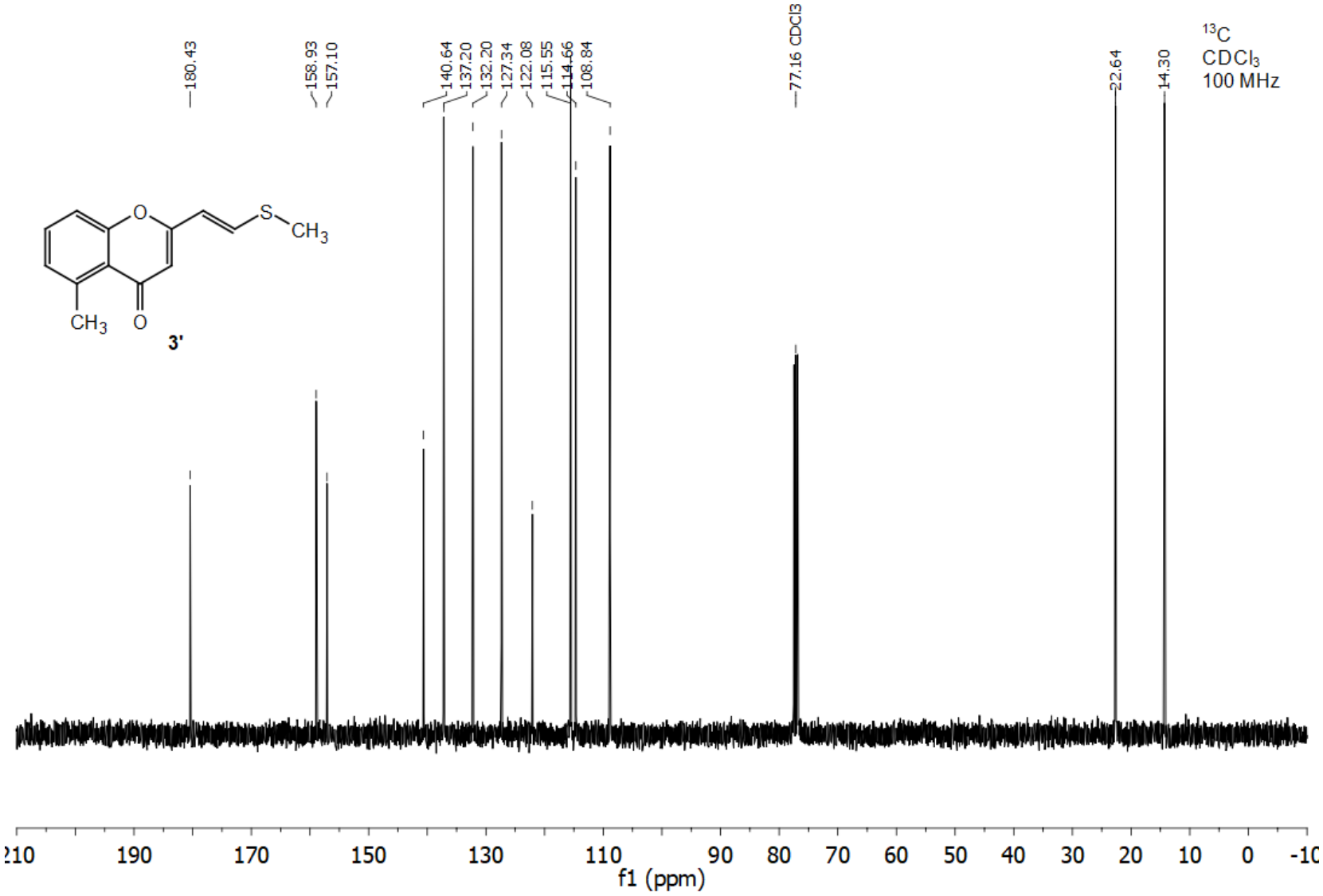
1.00
1.02
0.97
1.00
3.04
3.01
f1 (ppm)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22.64
14.30
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O
S
CH3
CH3
O
3'
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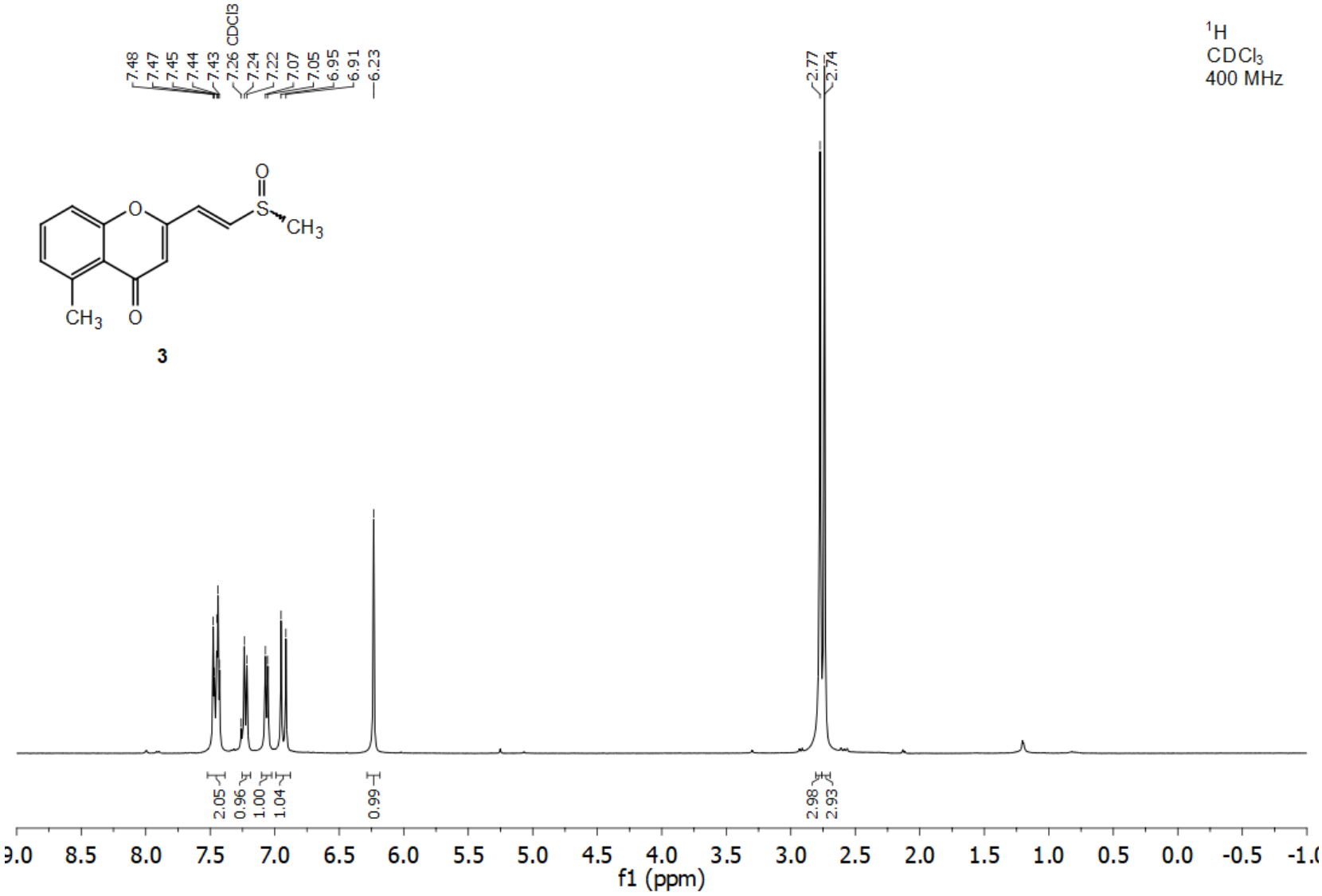
f1 (ppm)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CDCl3
400 MHz
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1.00
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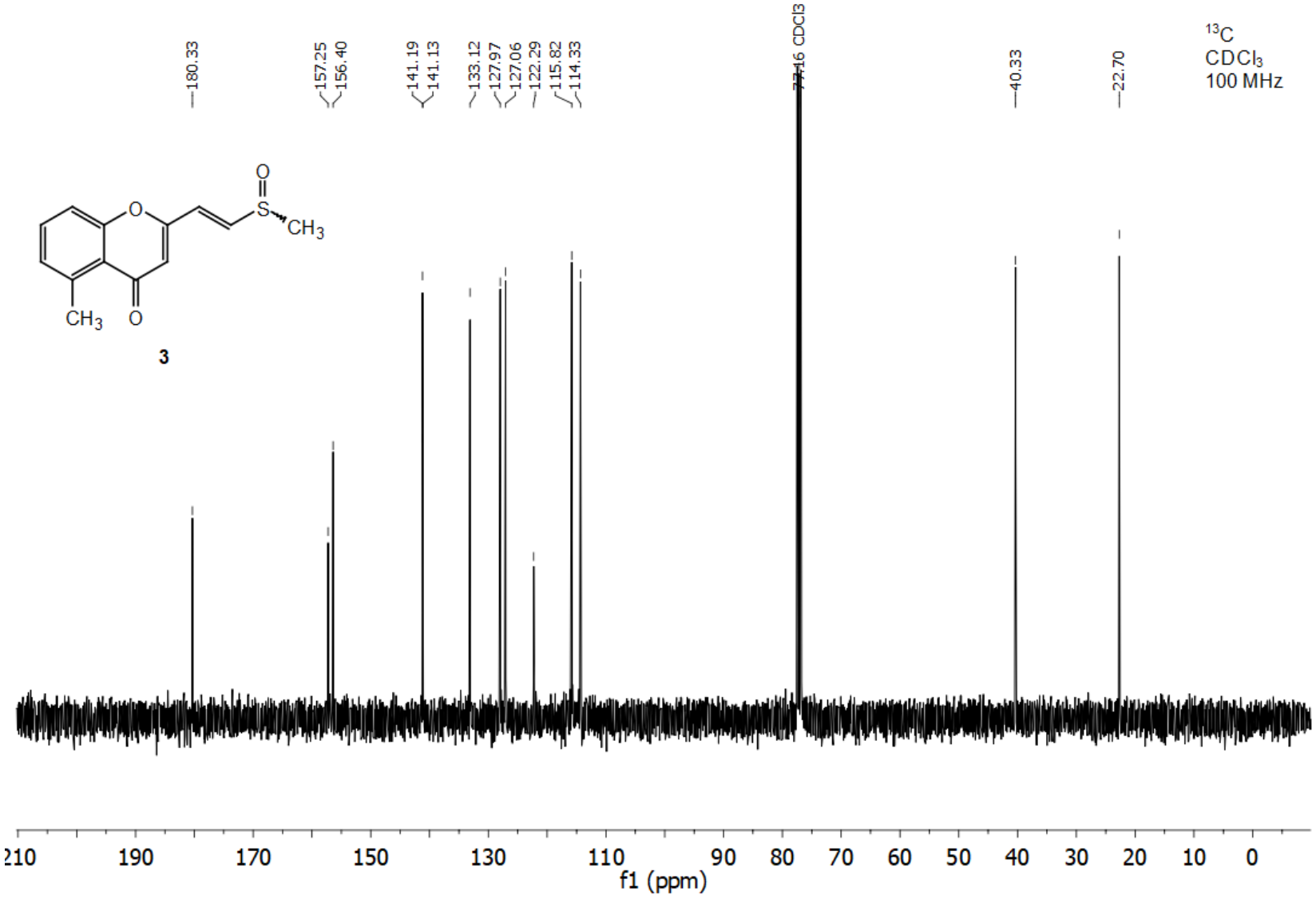
2.93
f1 (ppm)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22.70
13C
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S
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CH3
O
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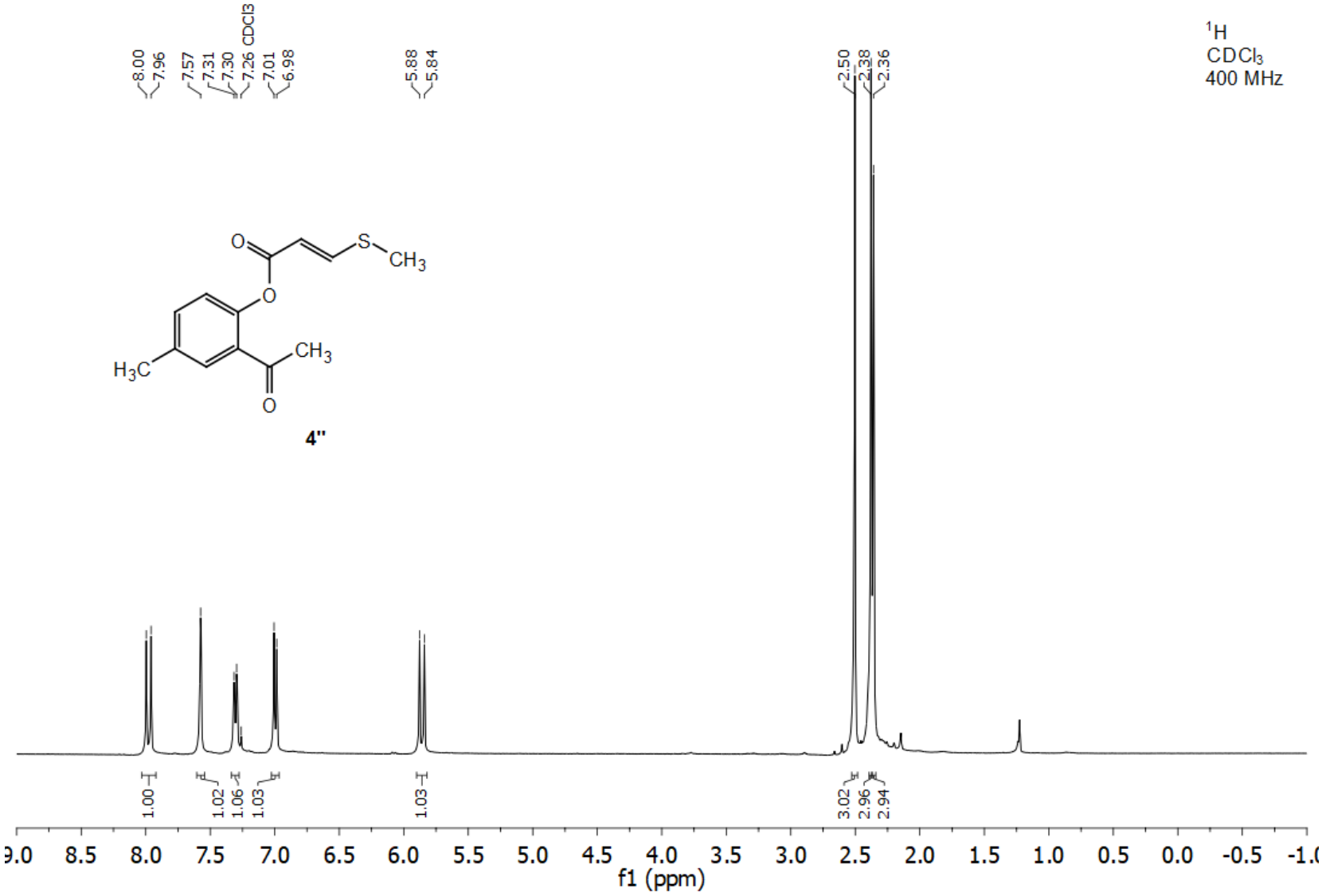
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7.30
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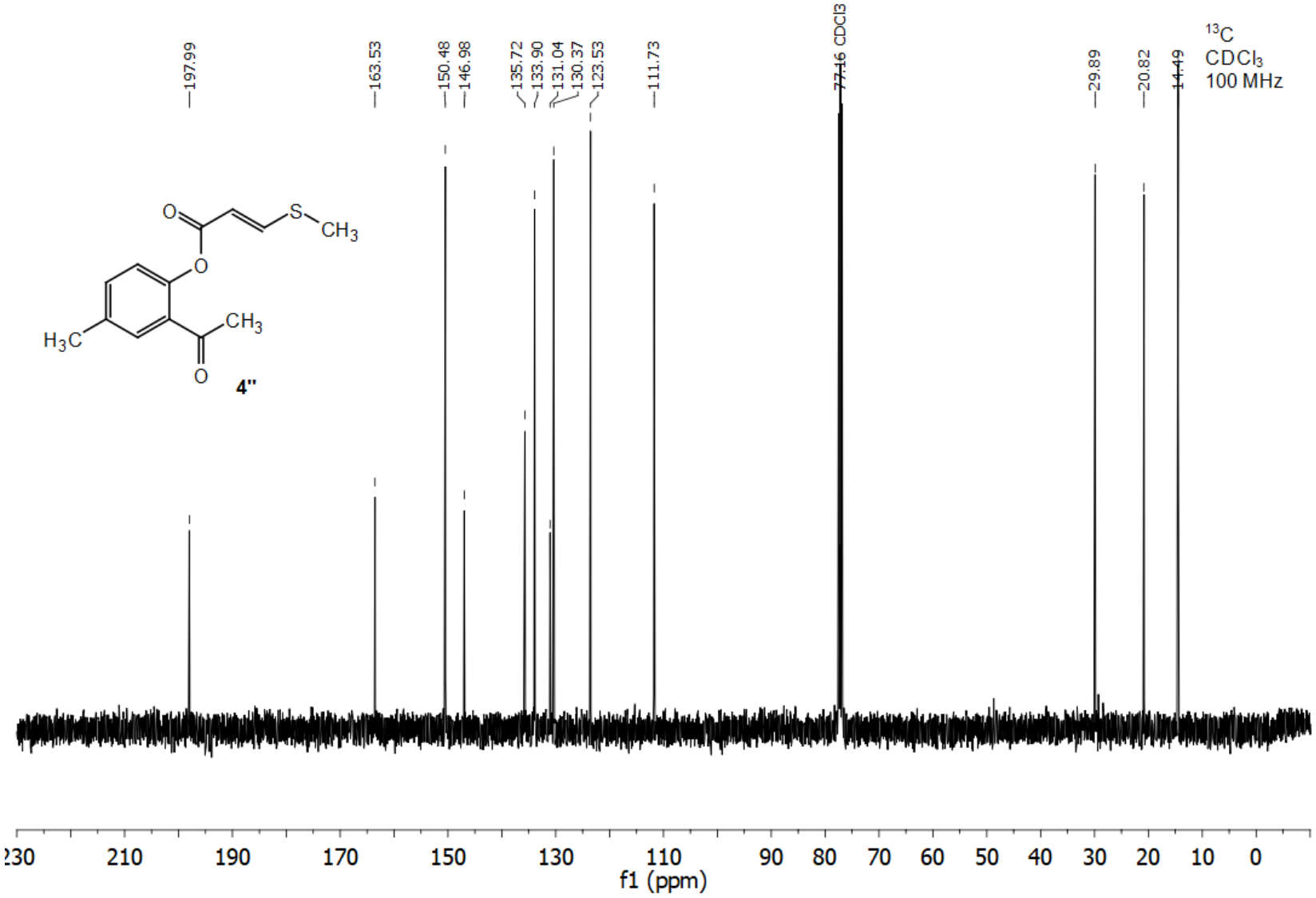
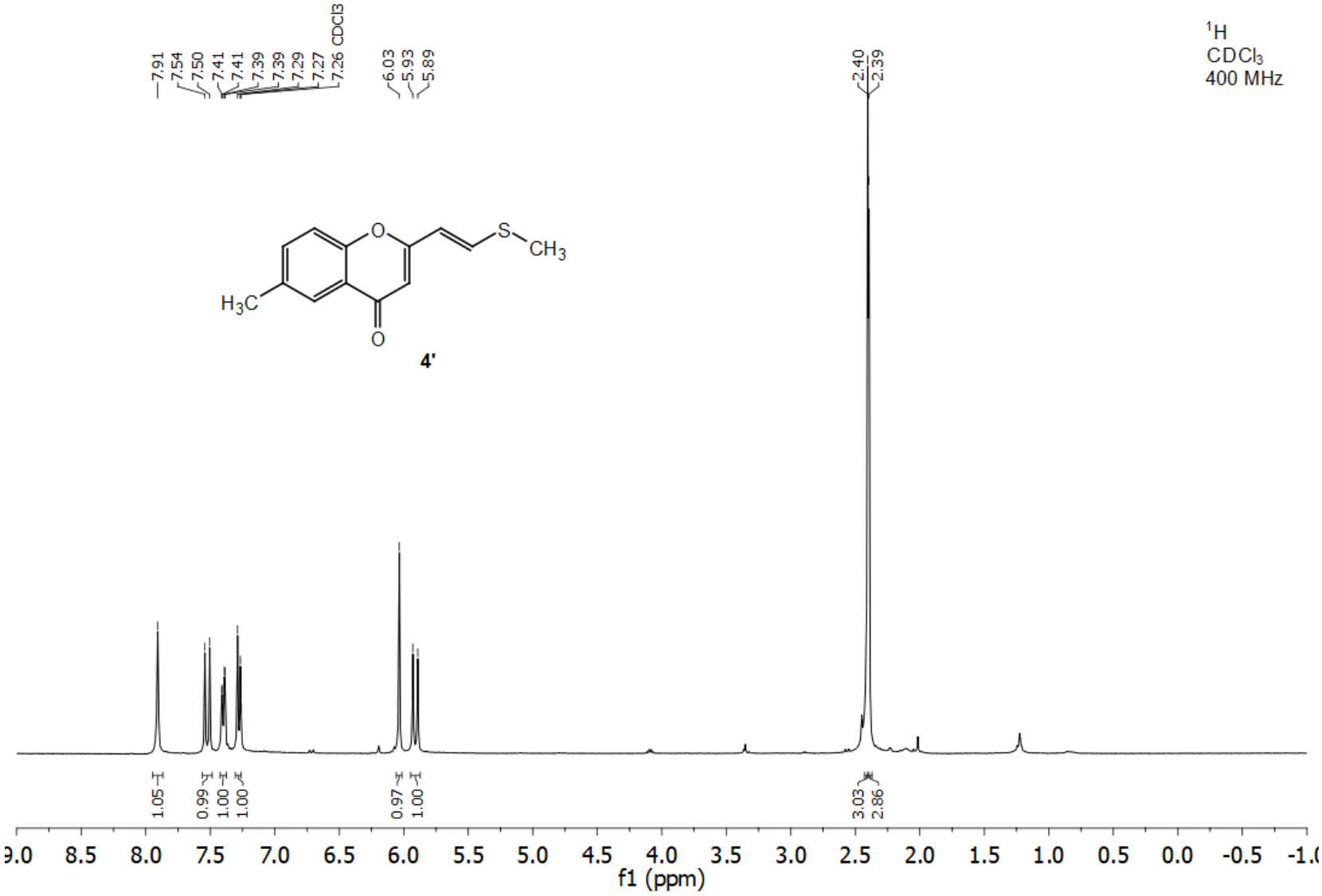
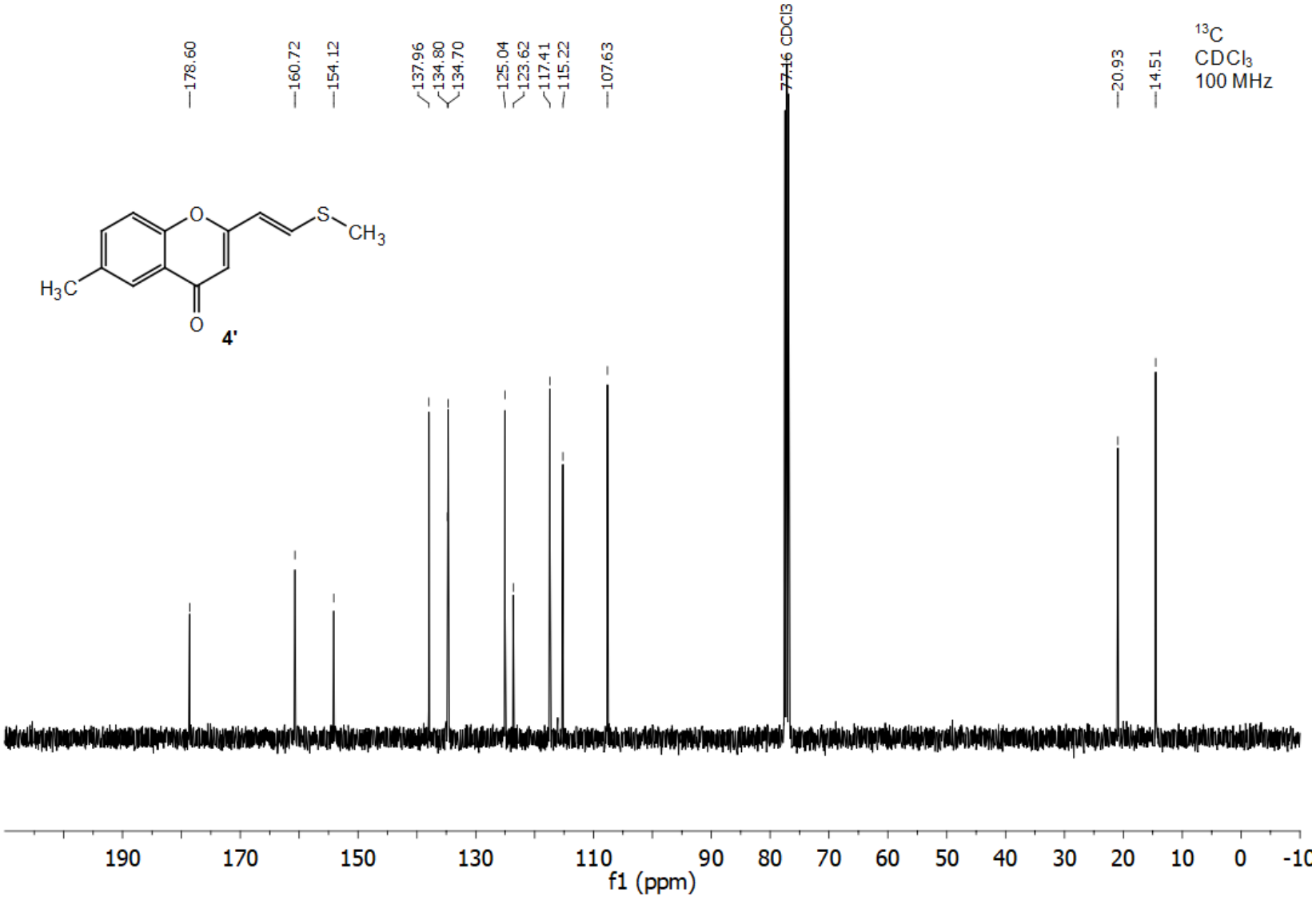
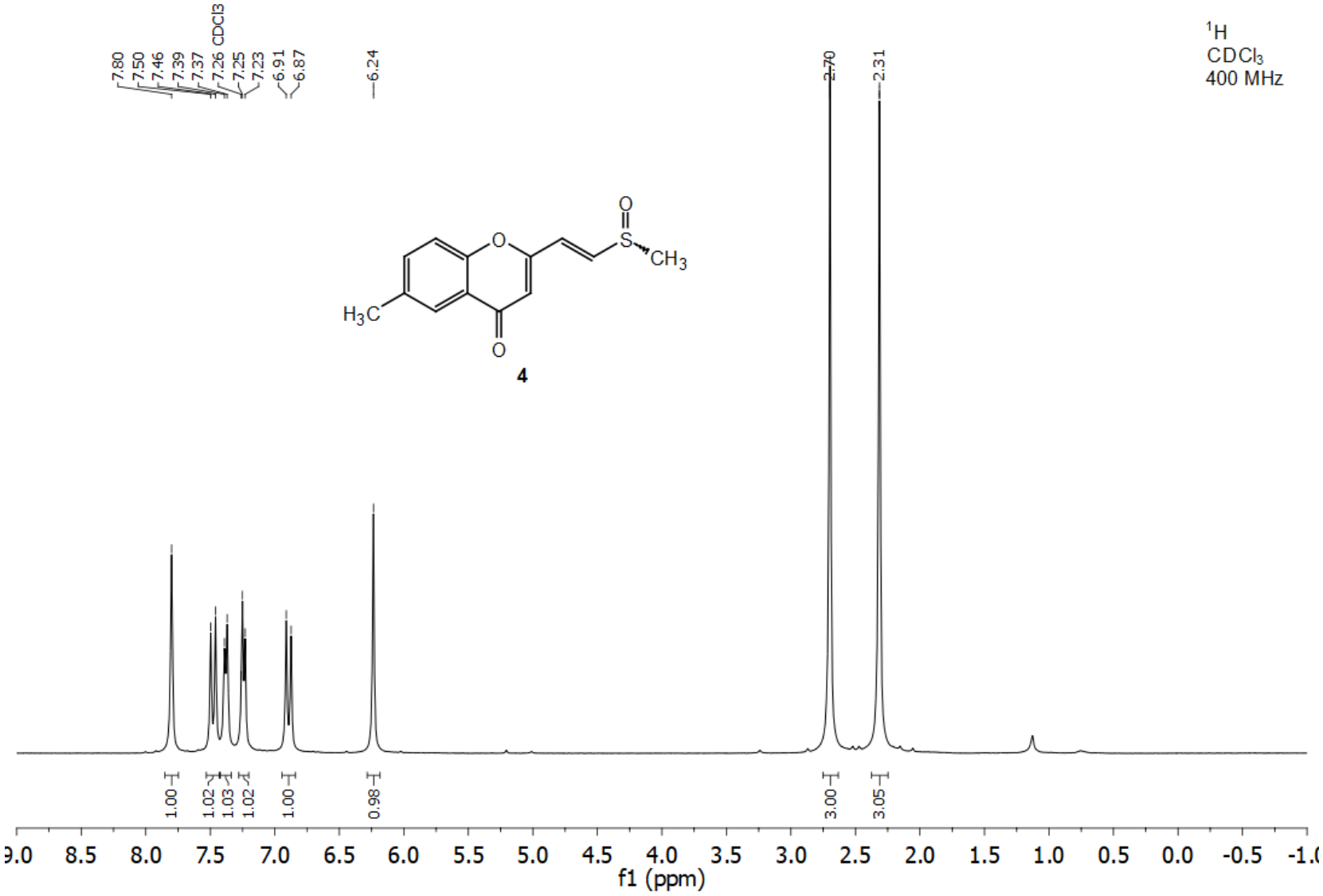
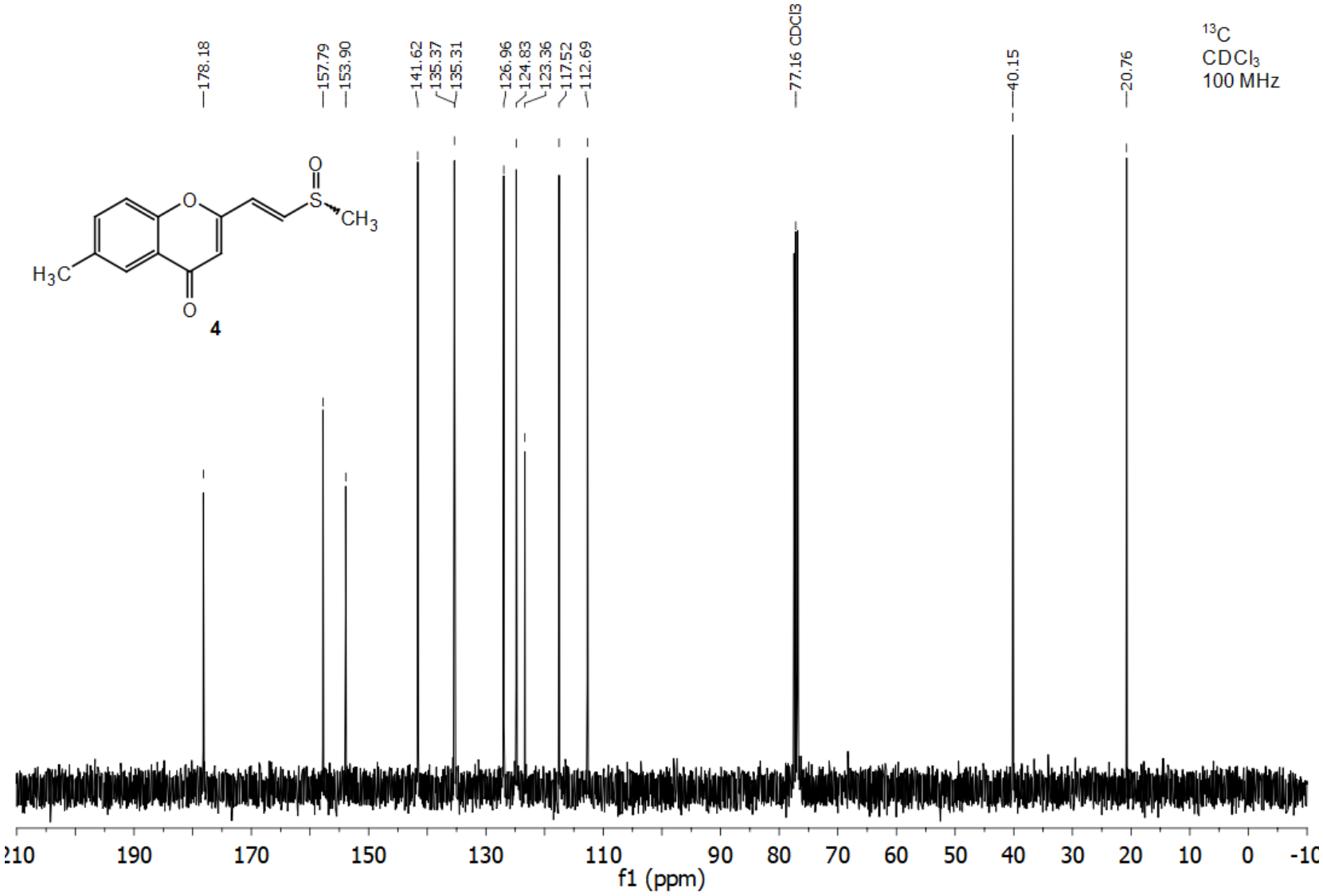
2.38
2.36
1H
CDCl3
400 MHz
O
S
CH3
O
CH3
H3C
O
4"
1.00
1.02
1.06
1.03
1.03
3.02
2.96
2.94
f1 (ppm)

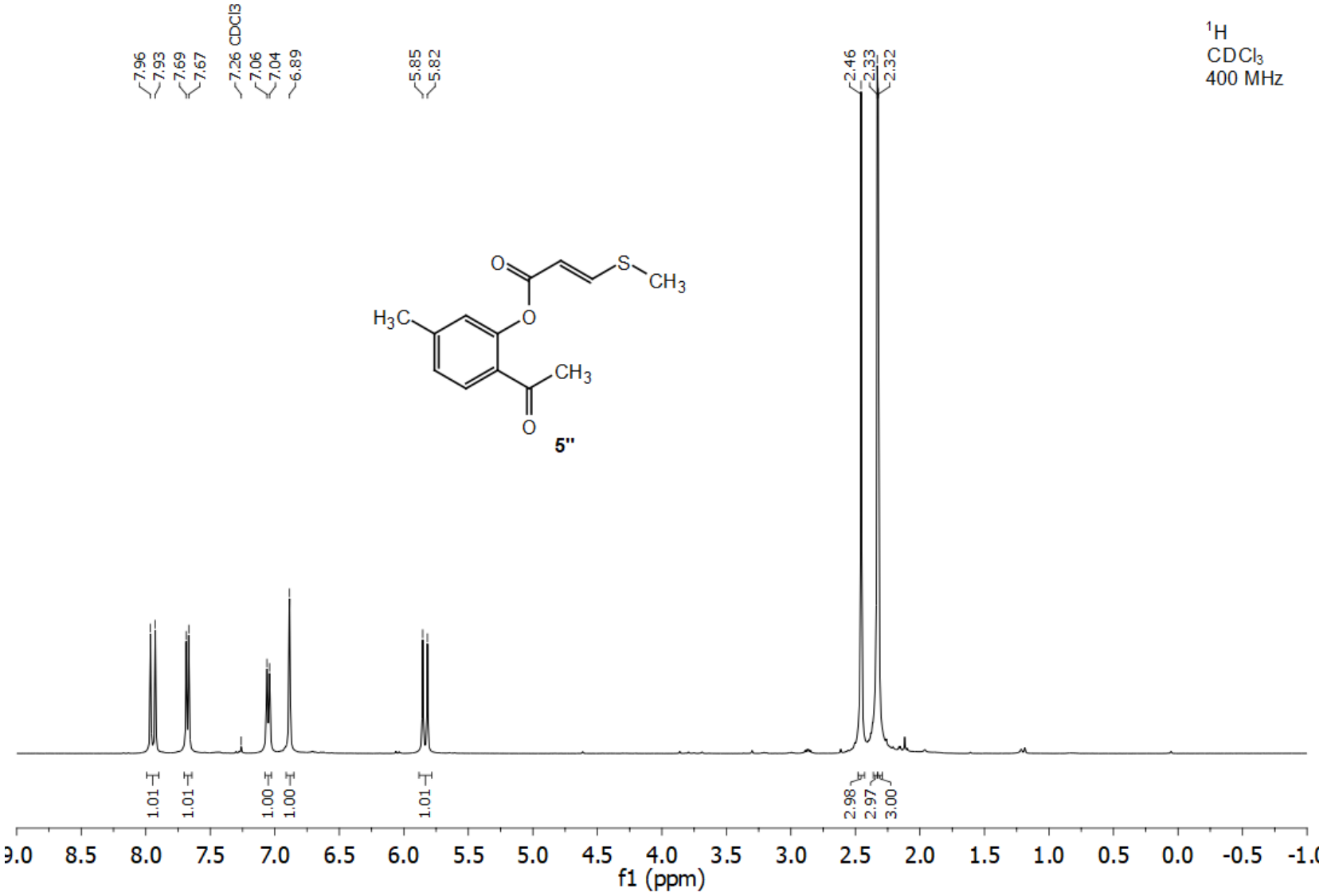

197.99
163.53
150.48
146.98
135.72
133.90
131.04
130.37
123.53
111.73
77.16 CDCl3
29.89
20.82
14.49
13C
CDCl3
100 MHz
O
O
S
CH3
O
CH3
H3C
O
4''
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

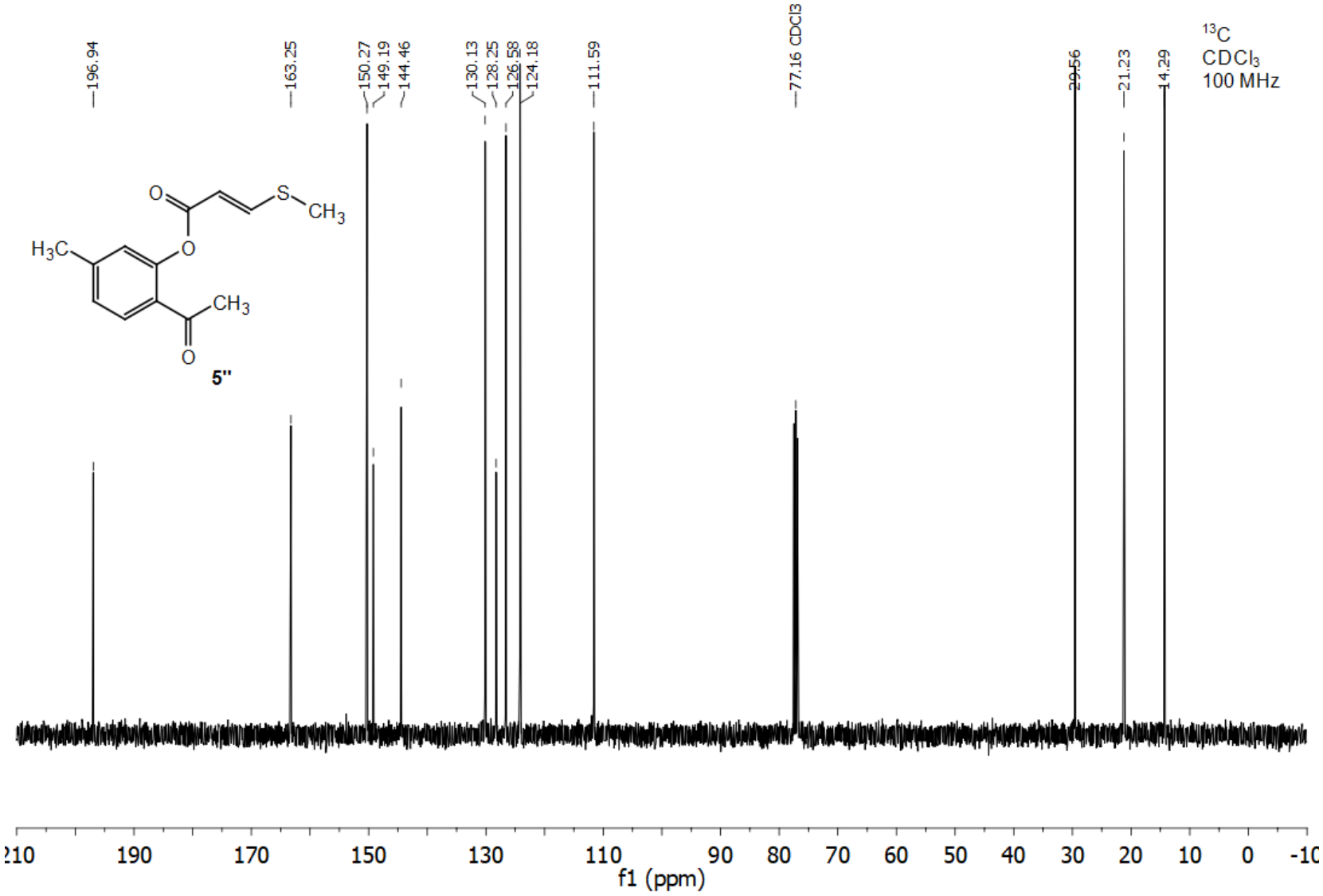

7.91
7.54
7.50
7.41
7.41
7.39
7.39
7.29
7.27
7.26 CDCl3
6.03
5.93
5.89
2.40
2.39
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
4'
1.05
0.99
1.00
1.00
0.97
1.00
3.03
2.86
f1 (ppm)

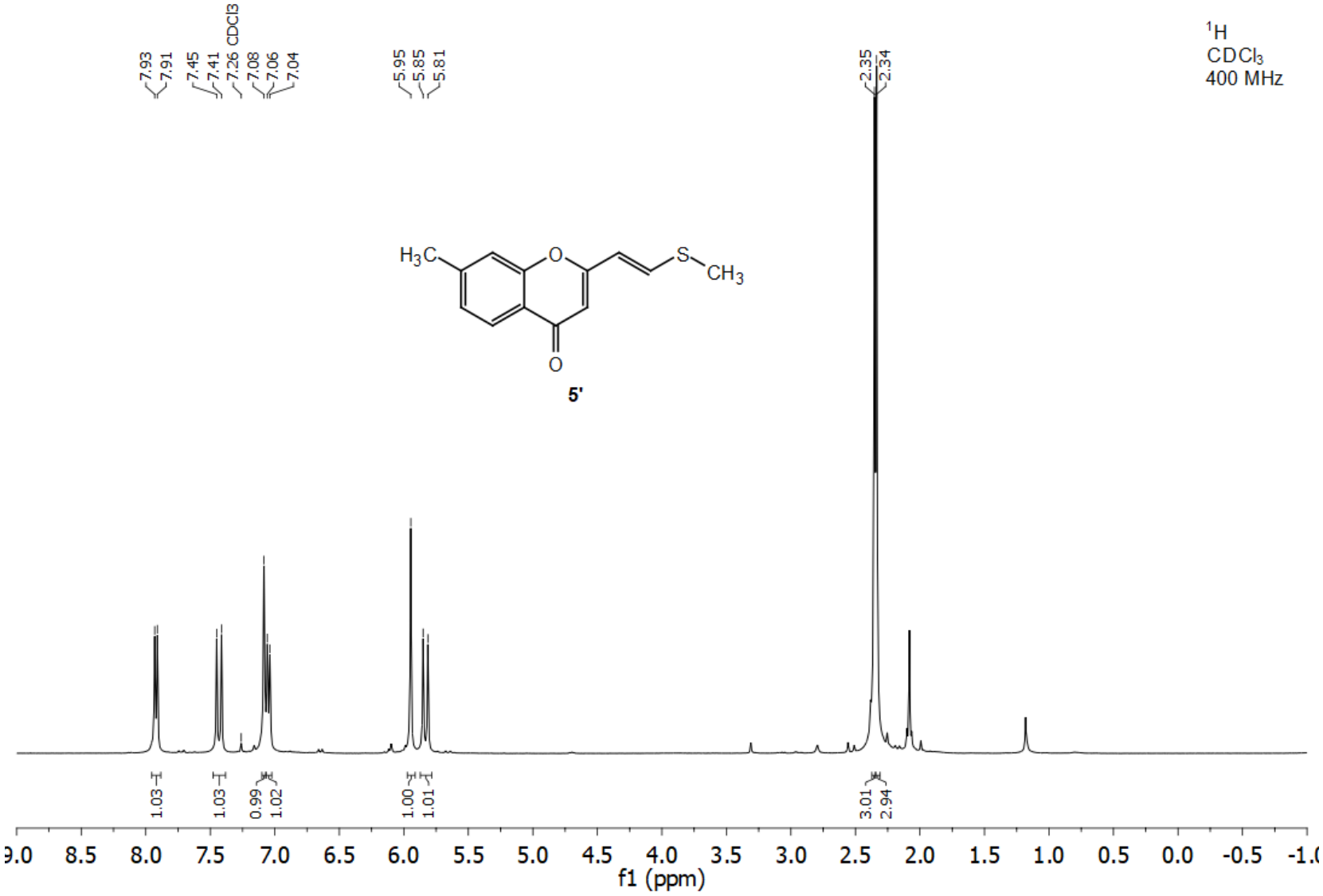

178.60
160.72
154.12
137.96
134.80
134.70
125.04
123.62
117.41
115.22
107.63
77.16 CDCl3
20.93
14.51
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
4'
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

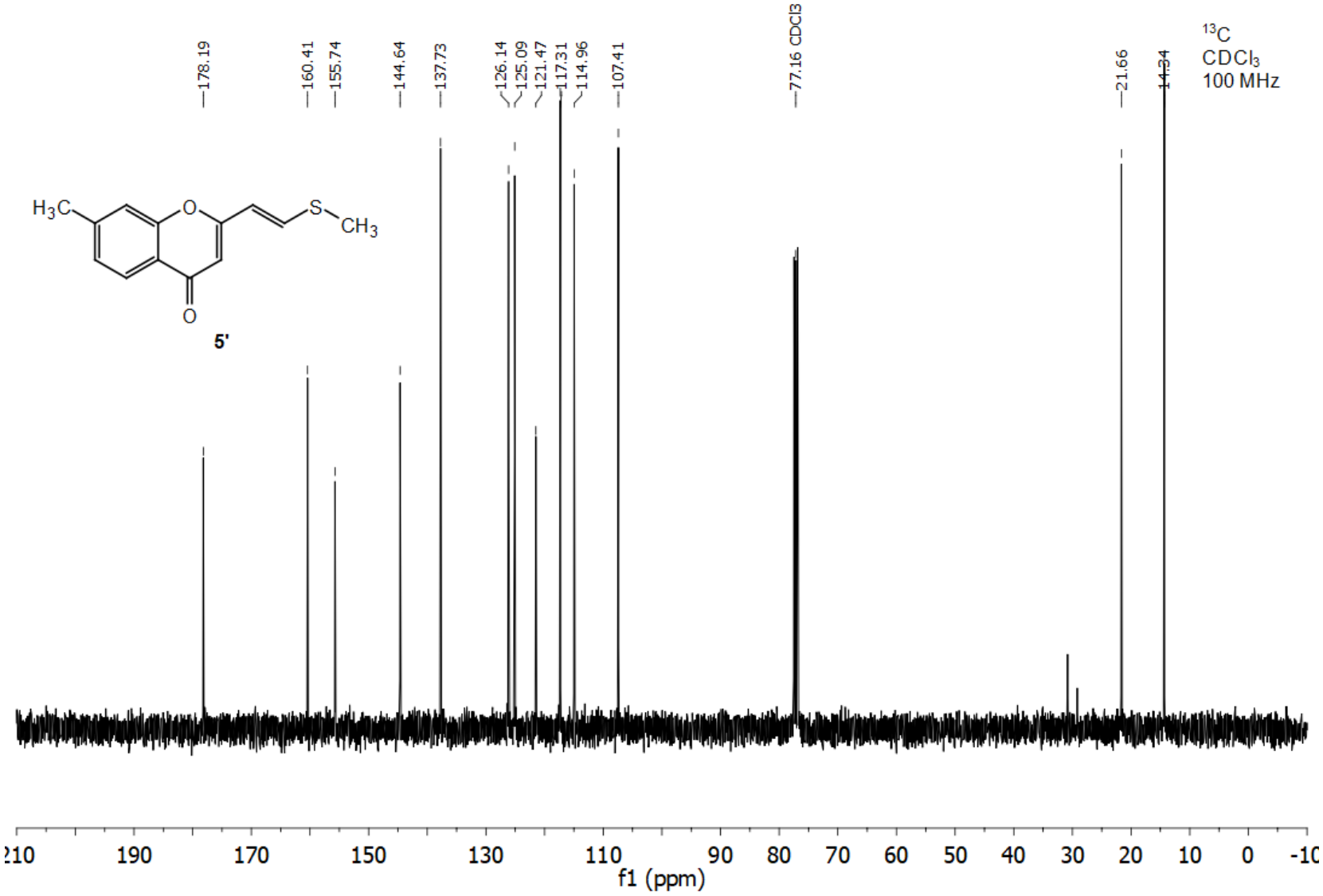

7.80
7.50
7.46
7.39
7.37
7.26 CDCl3
7.25
7.23
6.91
6.87
6.24
2.70
2.31
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
O
4
1.00
1.02
1.03
1.02
1.00
0.98
3.00
3.05
f1 (ppm)

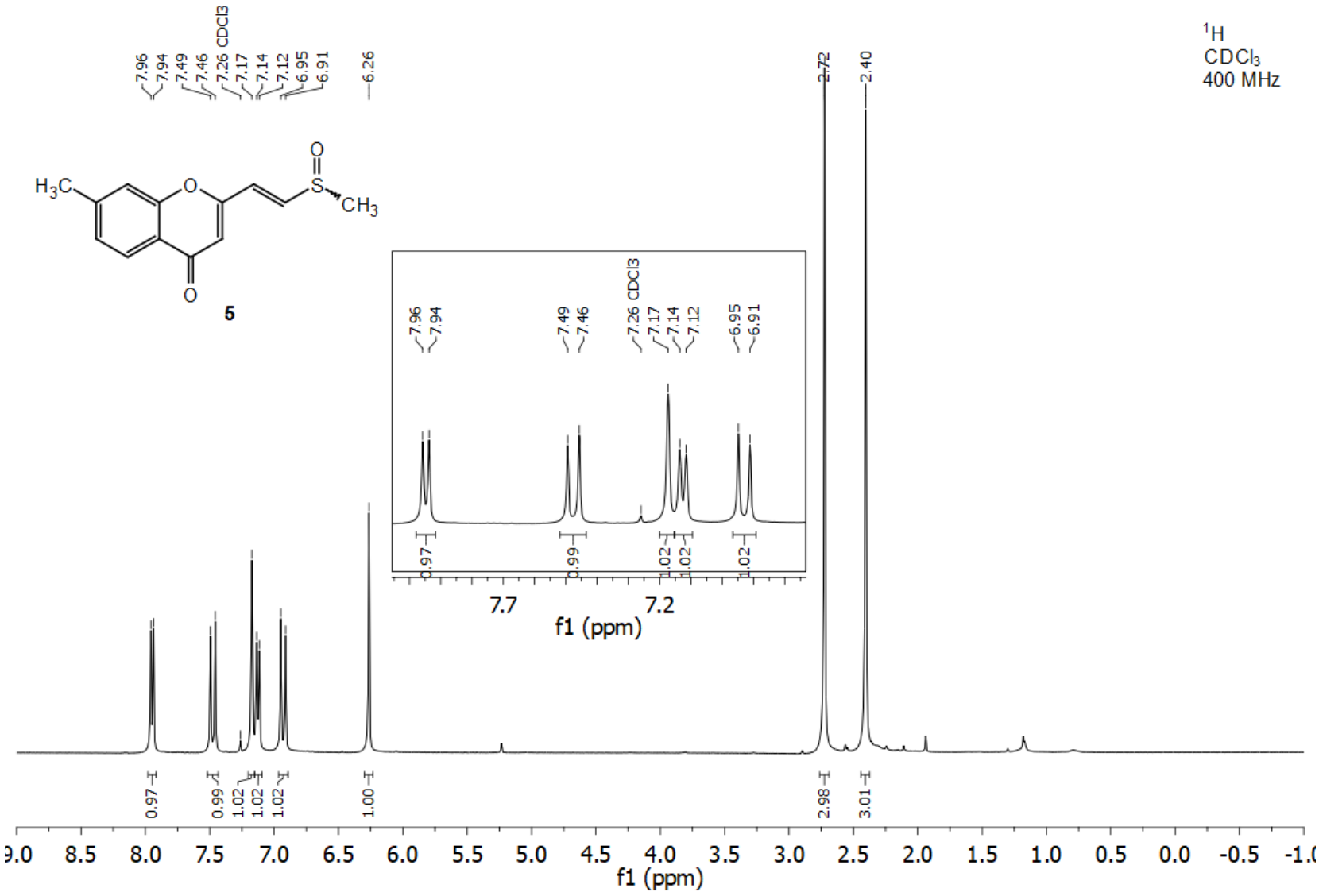

178.18
157.79
153.90
141.62
135.37
135.31
126.96
124.83
123.36
117.52
112.69
77.16 CDCl3
40.15
20.76
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
4
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

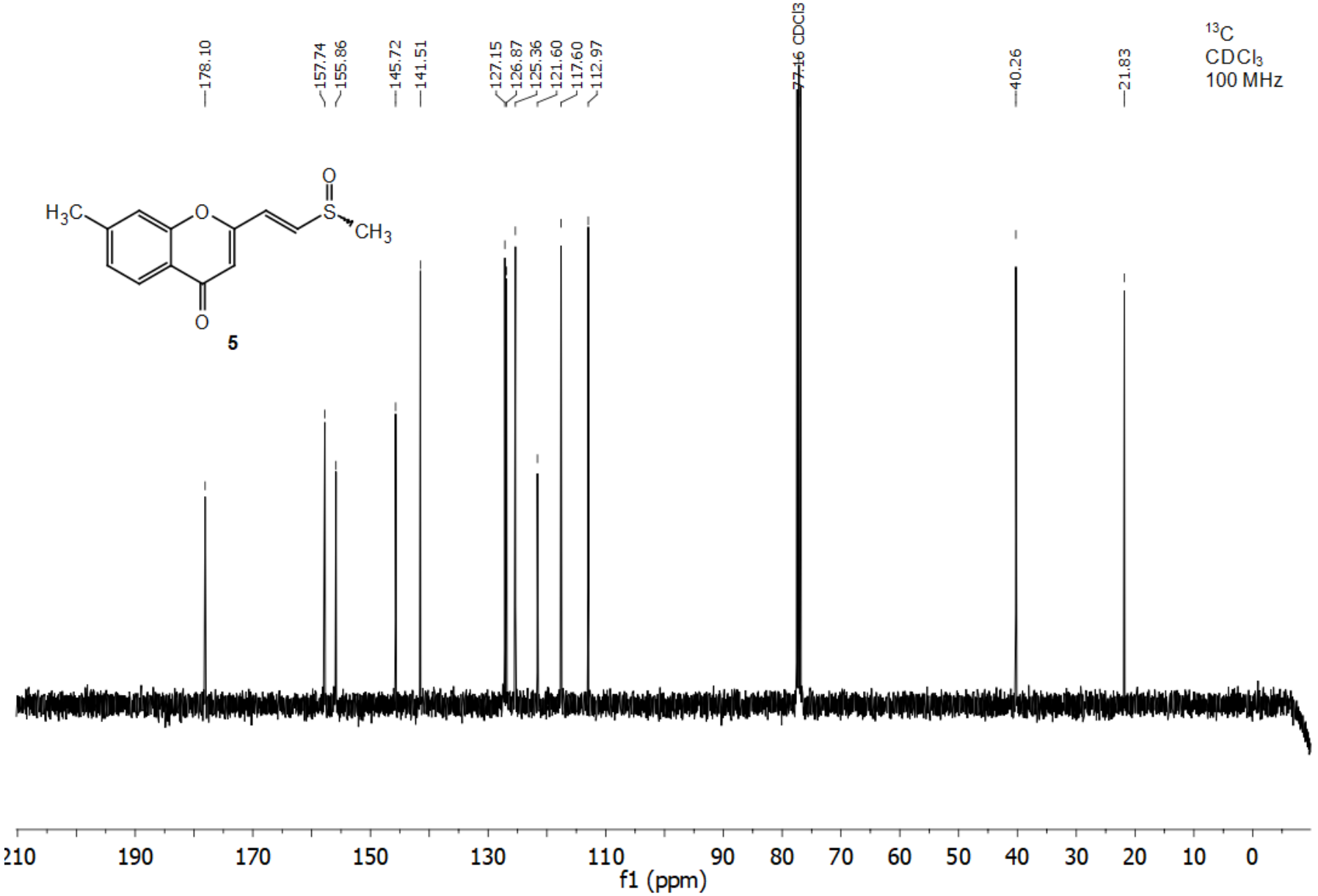

7.96
7.93
7.69
7.67
7.26 CDCl3
7.06
7.04
6.89
5.85
5.82
2.46
2.33
2.32
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
CH3
O
5''
1.01
1.01
1.00
1.00
1.01
2.98
2.97
3.00
f1 (ppm)

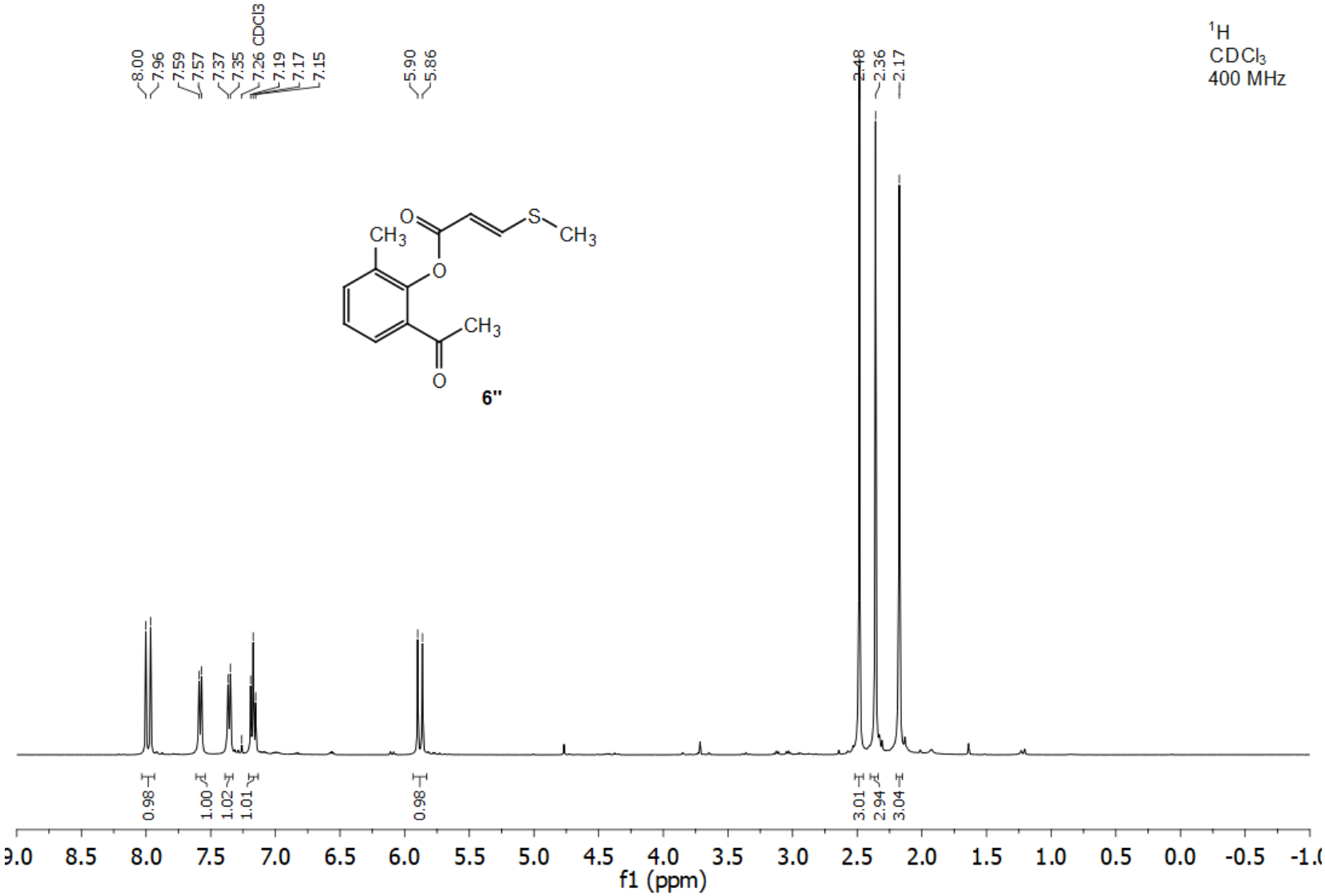

196.94
163.25
150.27
149.19
144.46
130.13
128.25
126.58
124.18
111.59
77.16 CDCl3
29.56
21.23
14.29
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
CH3
O
5''
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

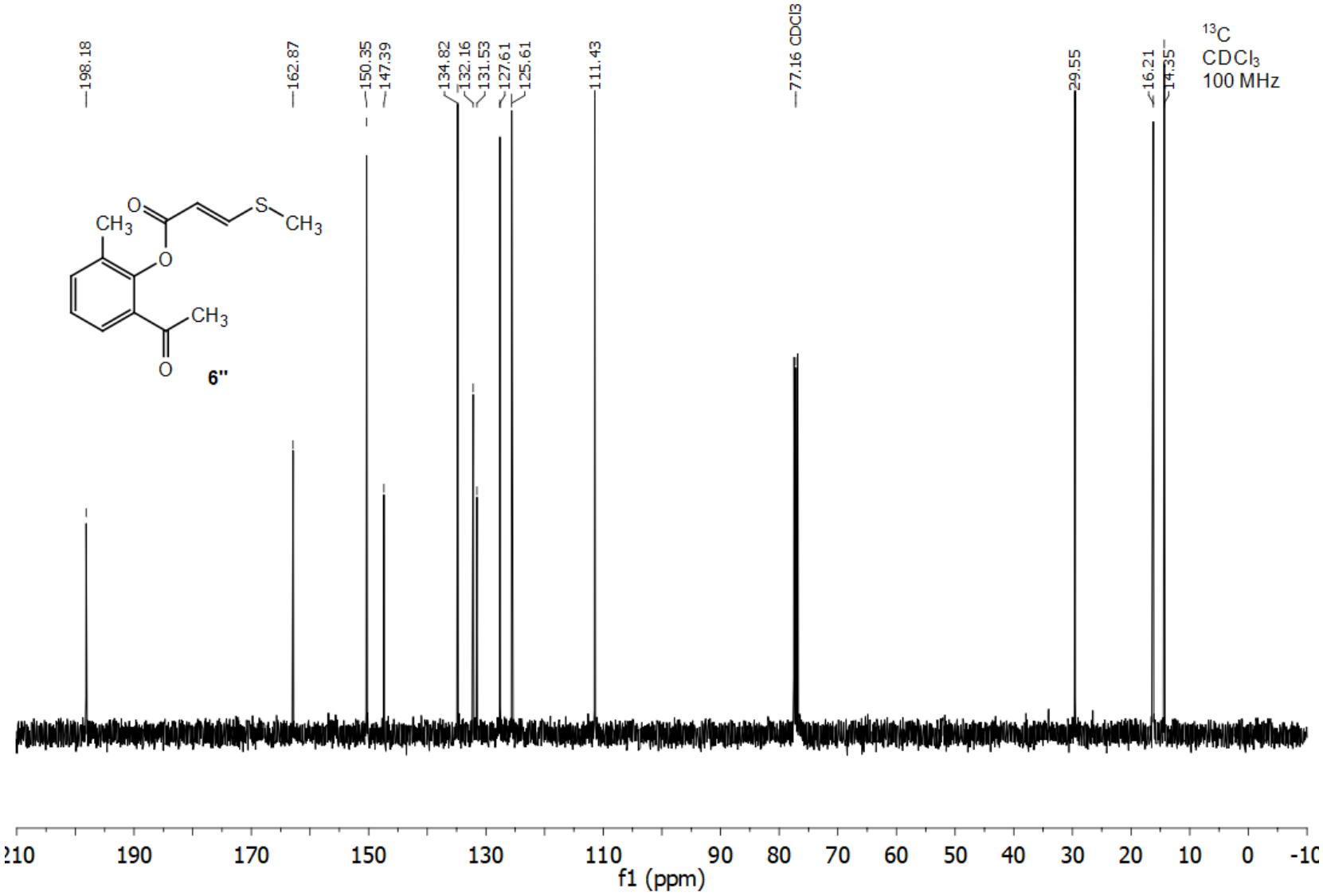

7.93
7.91
7.45
7.41
7.26 CDCl3
7.08
7.06
7.04
5.95
5.85
5.81
2.35
2.34
1H
CDCl3
400 MHz
H3C
O
S
CH3
O
5'
1.03
1.03
0.99
1.02
1.00
1.01
3.01
2.94
f1 (ppm)

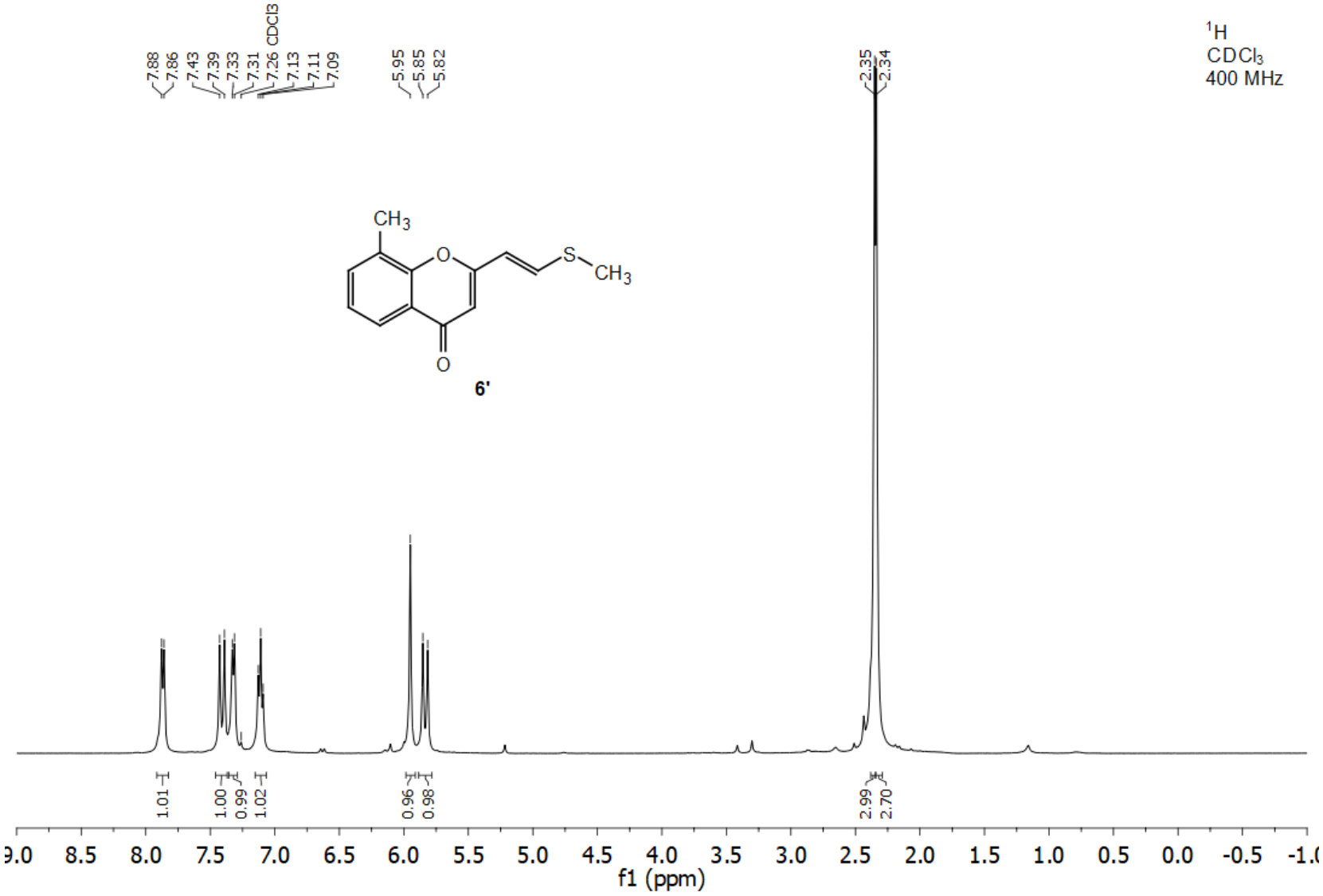

178.19
160.41
155.74
144.64
137.73
126.14
125.09
121.47
117.31
114.96
107.41
77.16 CDCl3
21.66
14.34
13C
CDCl3
100 MHz
H3C
O
S
CH3
O
5'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

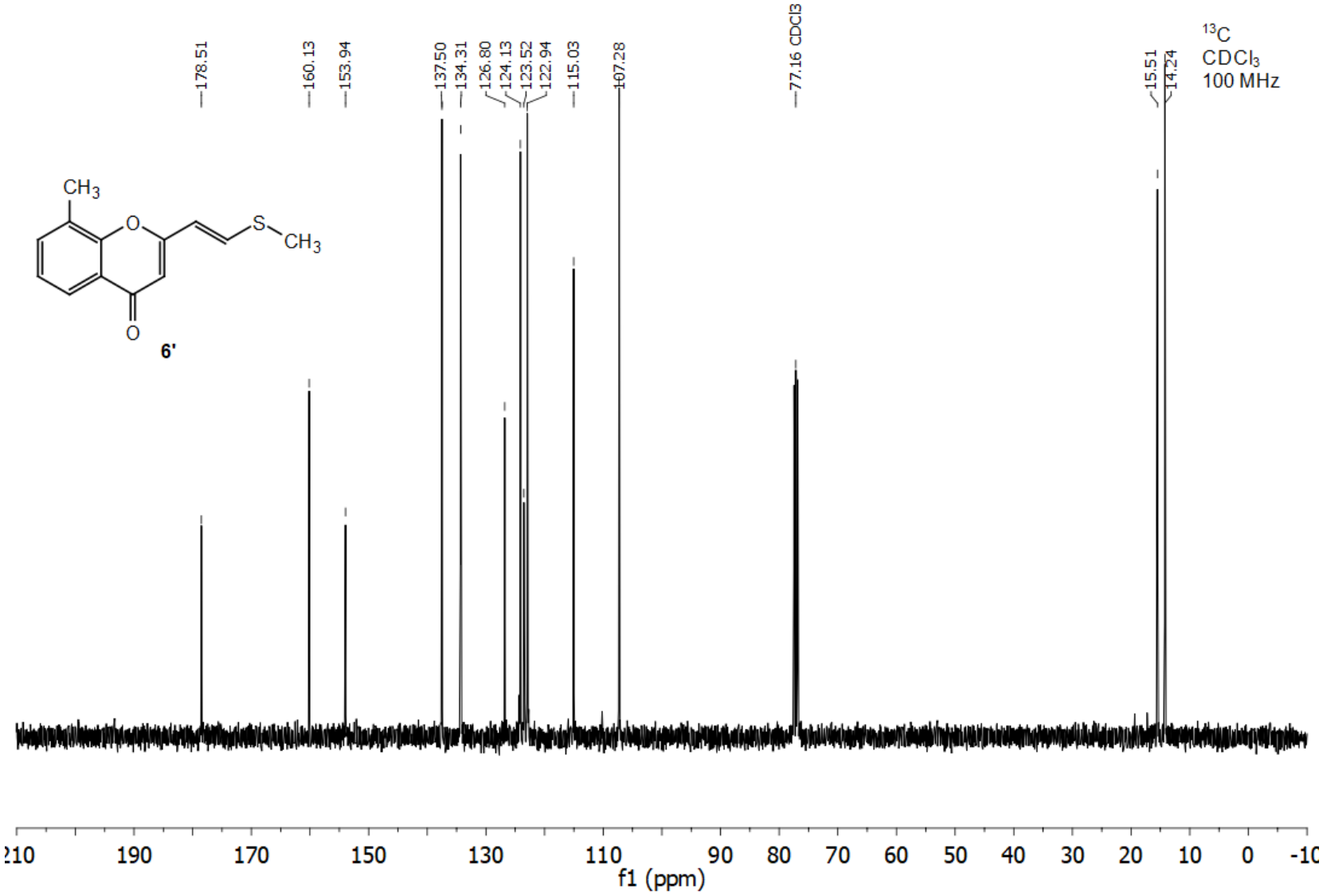

7.96
7.94
7.49
7.46
7.26 CDCl3
7.17
7.14
7.12
6.95
6.91
6.26
2.72
2.40
1H
CDCl3
400 MHz
H3C
O
S
CH3
O
O
5
0.97
0.99
1.02
1.02
1.02
1.00
2.98
3.01
7.7
7.2
f1 (ppm)
f1 (ppm)

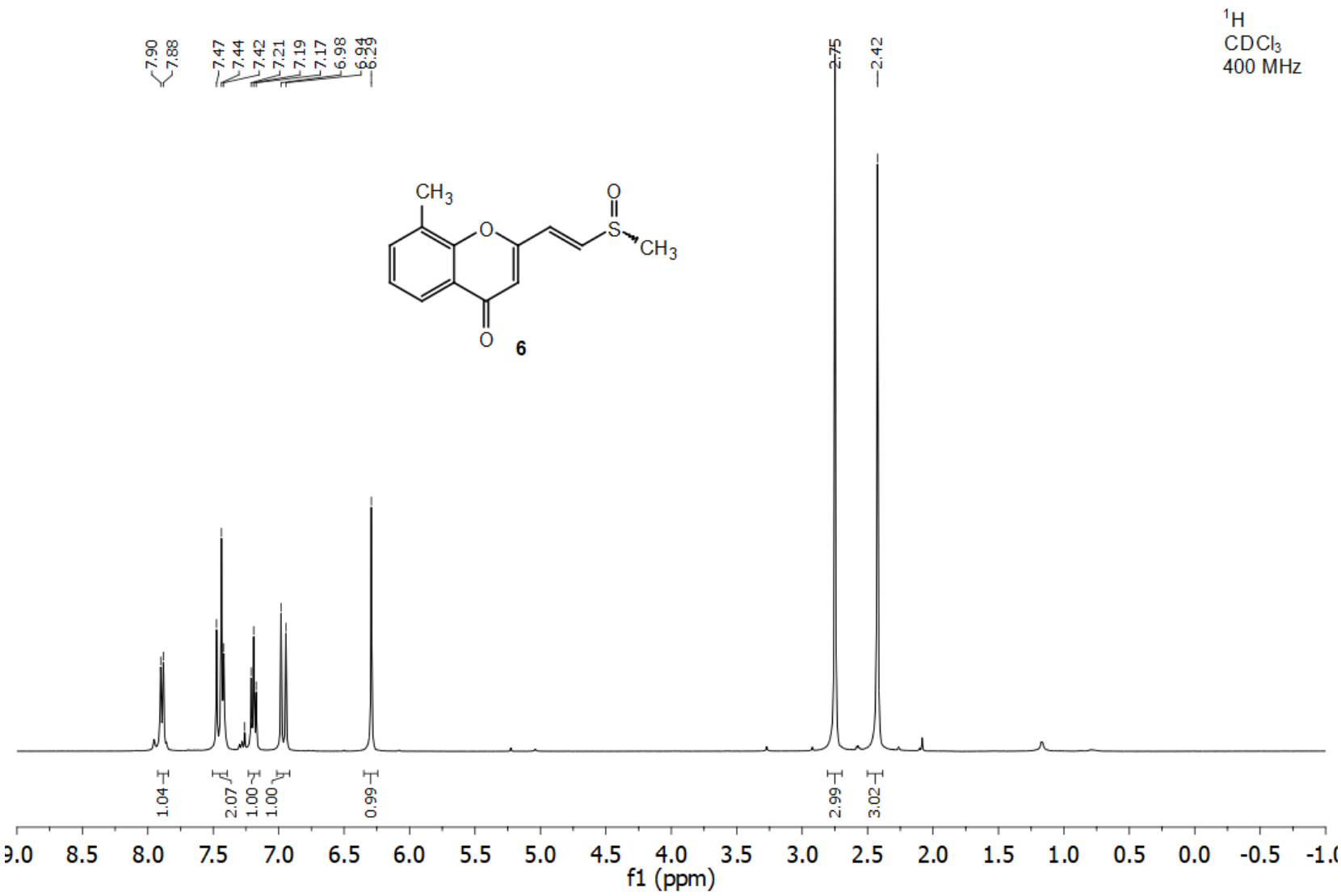

178.10
157.74
155.86
145.72
141.51
127.15
126.87
125.36
121.60
117.60
112.97
77.46 CDCl3
40.26
21.83
13C
CDCl3
100 MHz
H3C
O
S
CH3
O
O
5
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

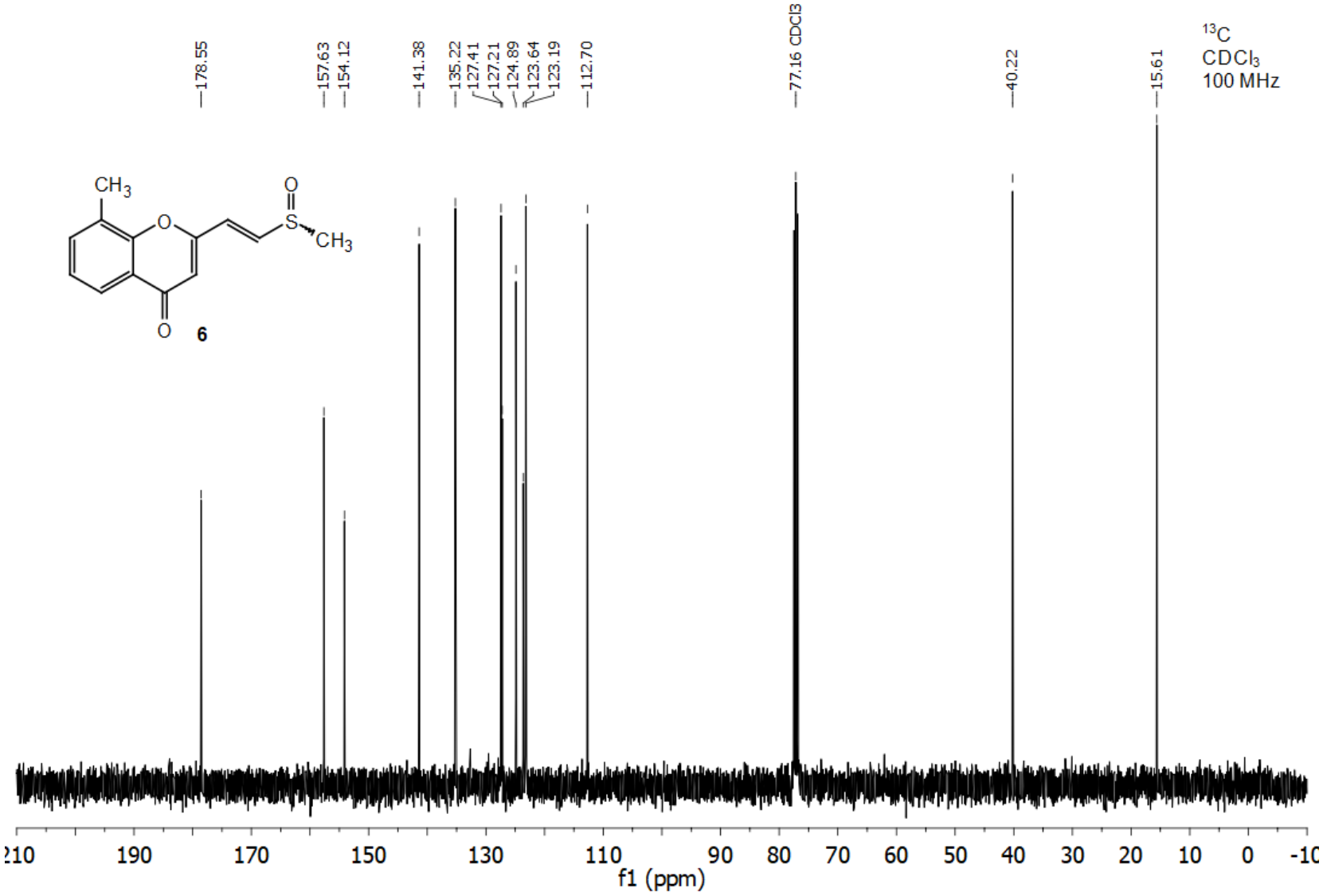

8.00
7.96
7.59
7.57
7.37
7.35
7.26 CDCl3
7.19
7.17
7.15
5.90
5.86
2.48
2.36
2.17
1H
CDCl3
400 MHz
O
S
CH3
CH3
O
CH3
O
6''
0.98
1.00
1.02
1.01
0.98
3.01
2.94
3.04
f1 (ppm)

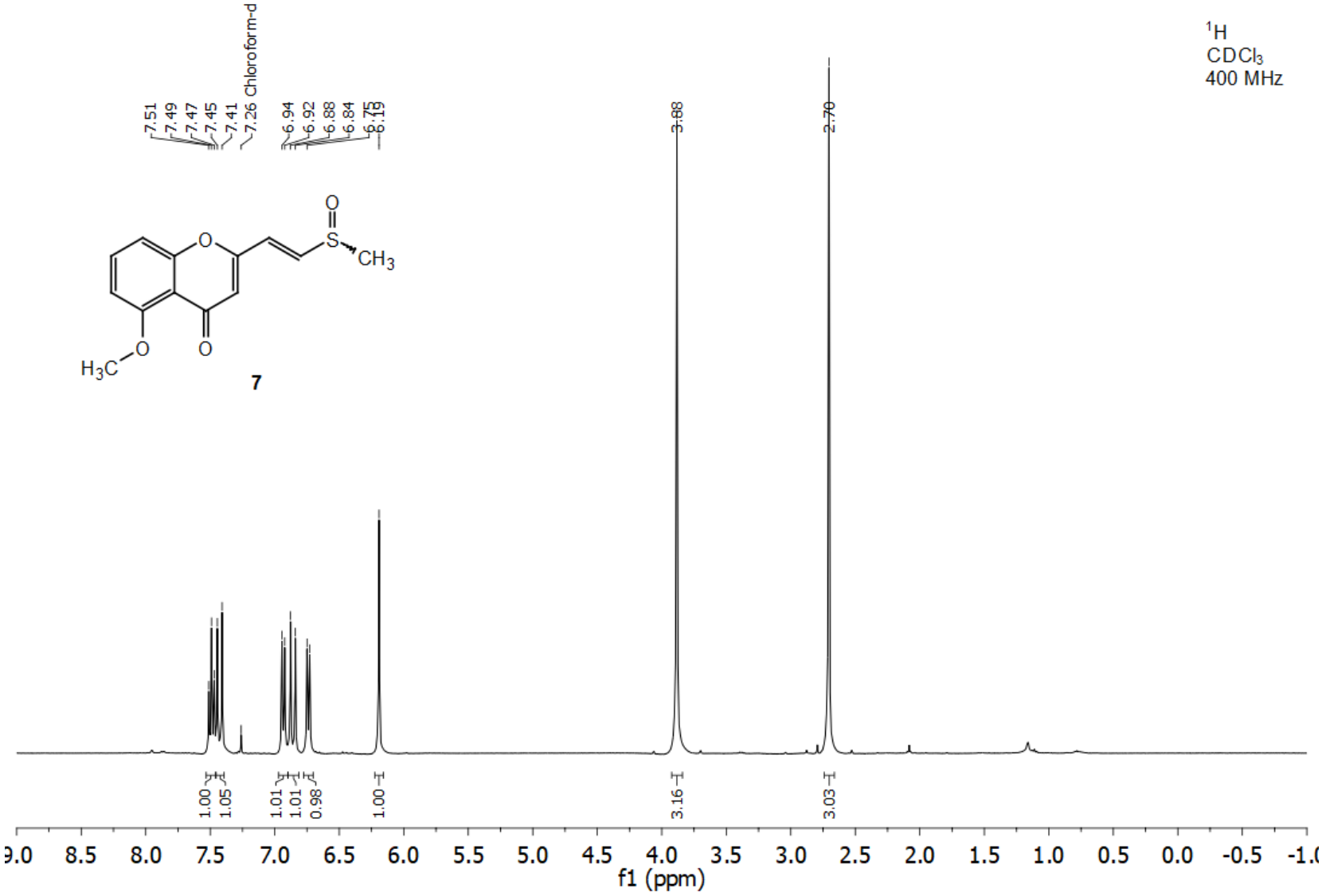

198.18
162.87
150.35
147.39
134.82
132.16
131.53
127.61
125.61
111.43
77.16 CDCl3
29.55
16.21
14.35
13C
CDCl3
100 MHz
O
S
CH3
CH3
O
CH3
O
6''
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

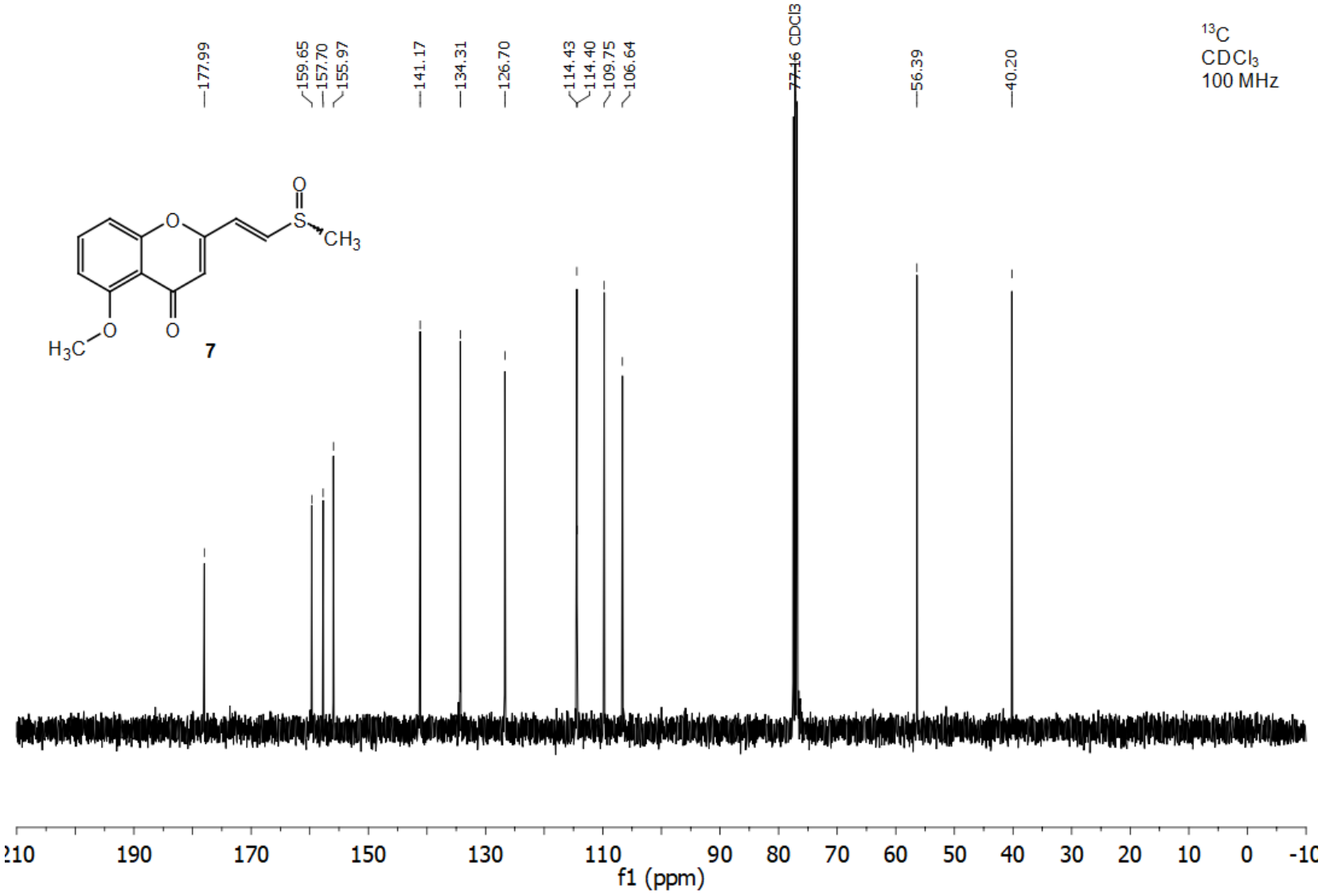

7.88
7.86
7.43
7.39
7.33
7.31
7.26 CDCl3
7.13
7.11
7.09
5.95
5.85
5.82
2.35
2.34
1H
CDCl3
400 MHz
CH3
O
S
CH3
O
6'
1.01
1.00
0.99
1.02
0.96
0.98
2.99
2.70
f1 (ppm)

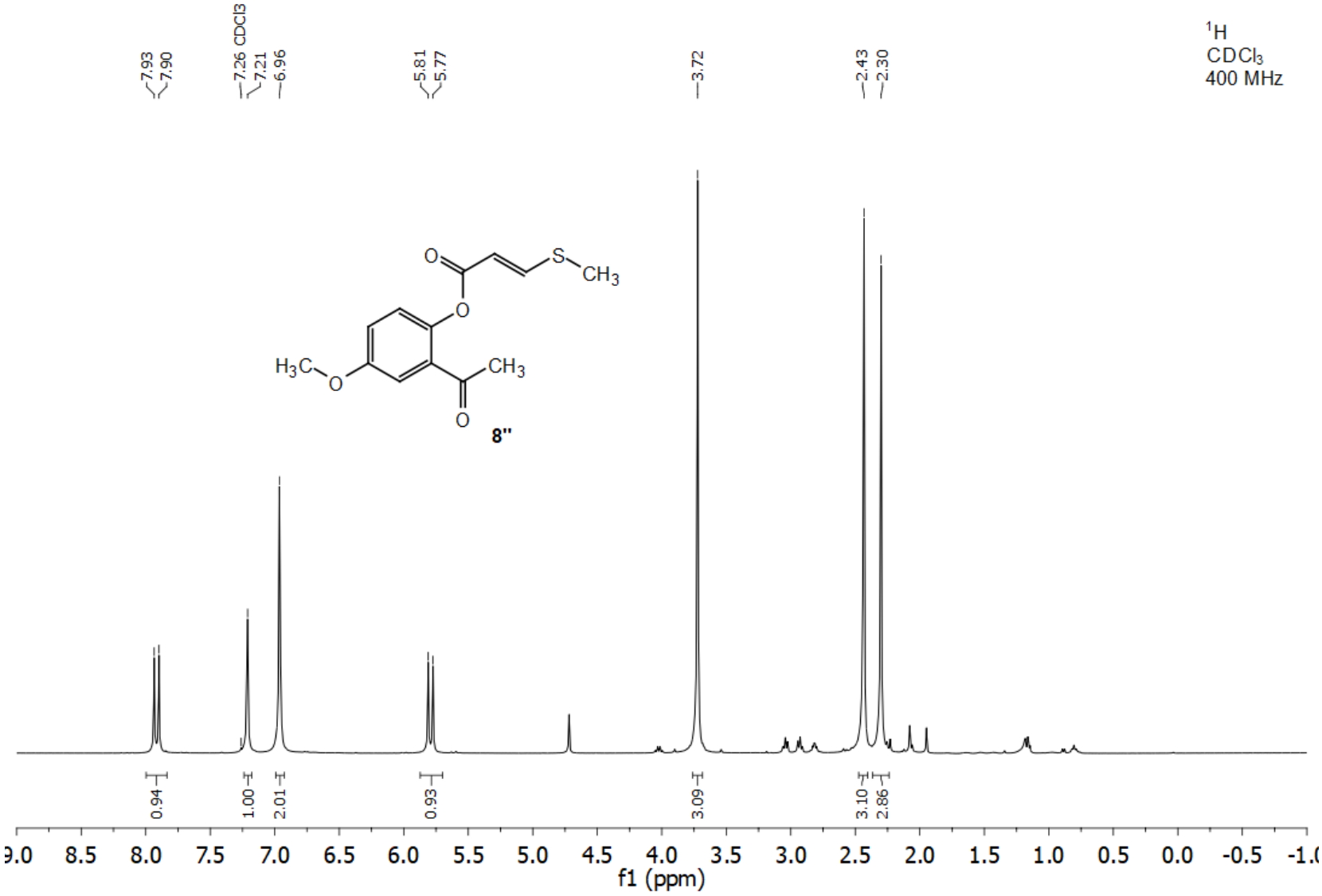

178.51
160.13
153.94
137.50
134.31
126.80
124.13
123.52
122.94
115.03
107.28
77.16 CDCl3
15.51
14.24
13C
CDCl3
100 MHz
CH3
O
S
CH3
O
6'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

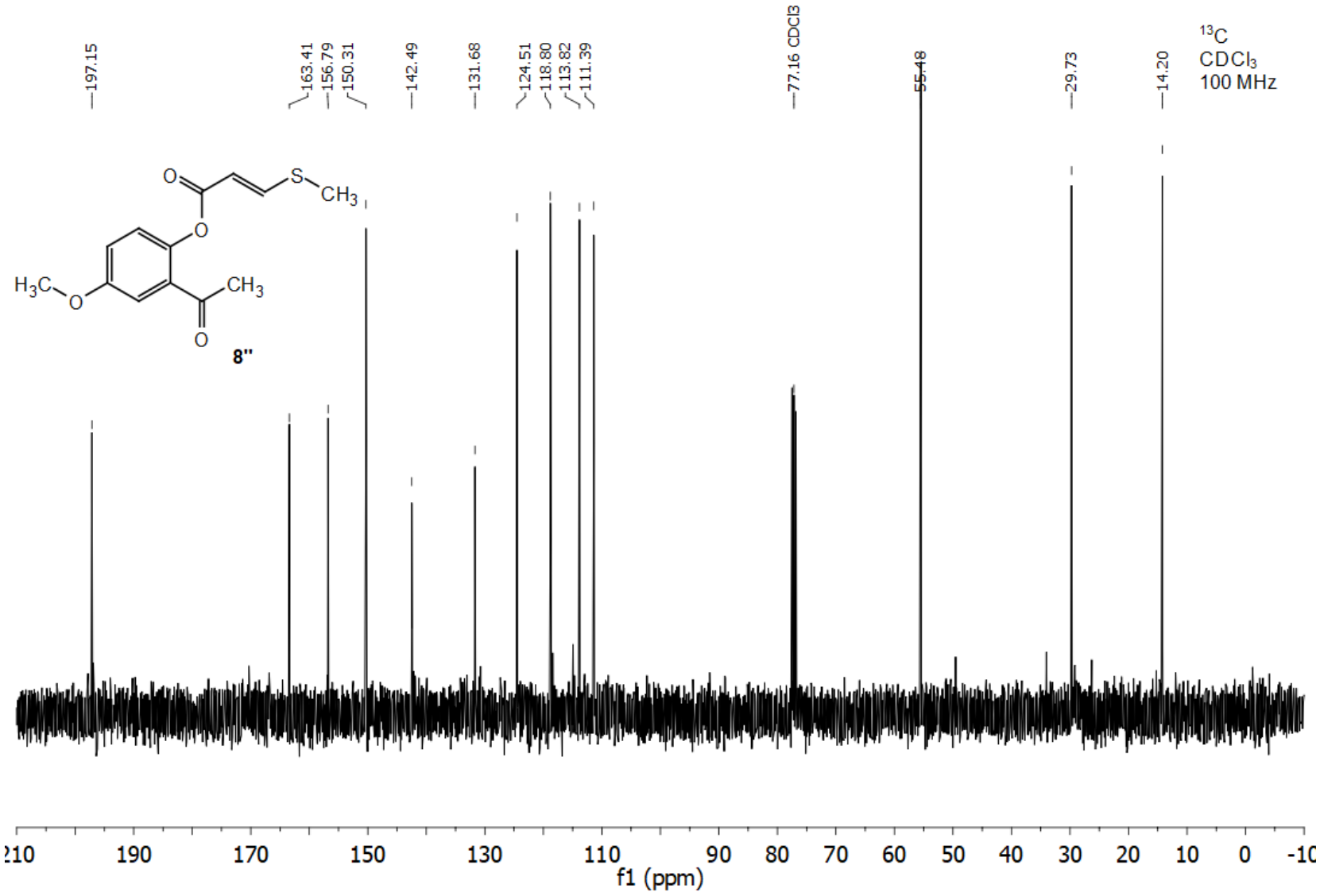

^{1}H
$CDCl_3$
400 MHz
7.90
7.88
7.47
7.44
7.42
7.21
7.19
7.17
6.98
6.94
6.29
2.75
2.42
CH_3
O
S
CH_3
O
O
6
1.04
2.07
1.00
1.00
0.99
2.99
3.02
f1 (ppm)

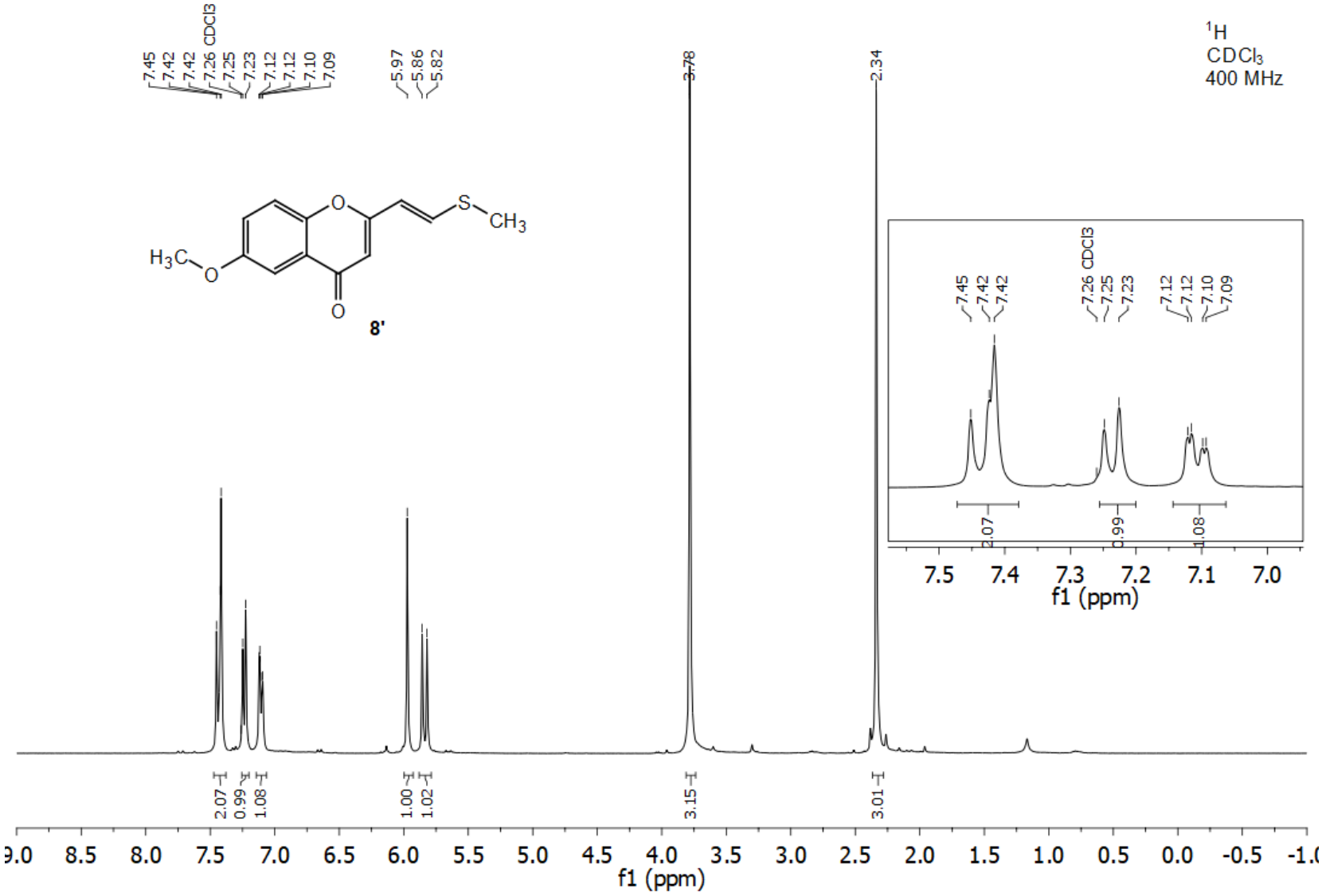

178.55
157.63
154.12
141.38
135.22
127.41
127.21
124.89
123.64
123.19
112.70
77.16 CDCl3
40.22
15.61
13C
CDCl3
100 MHz
CH3
O
S
CH3
O
O
6
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

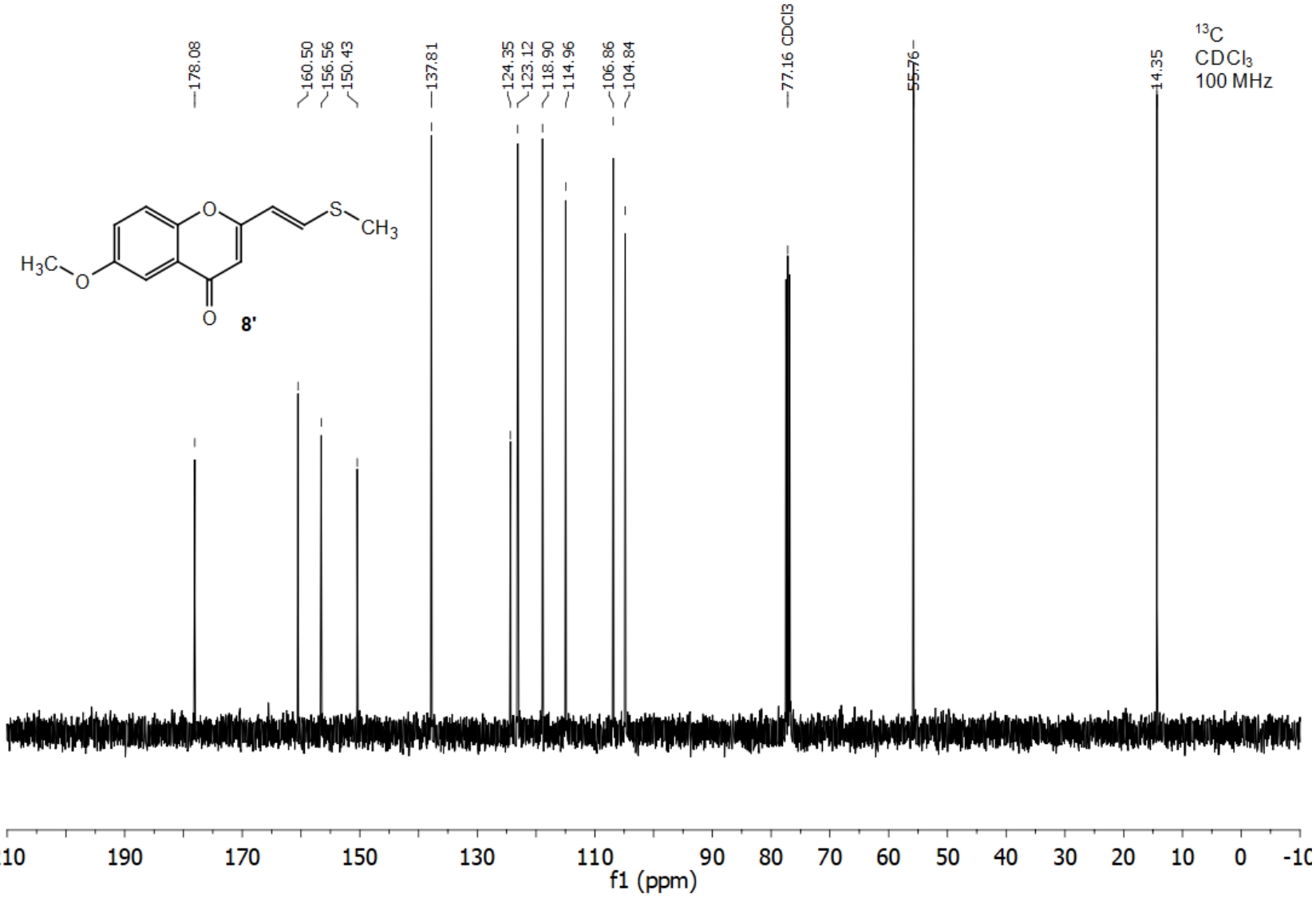

^{1}H
$CDCl_3$
400 MHz
7.51
7.49
7.47
7.45
7.41
7.26 Chloroform-d
6.94
6.92
6.88
6.84
6.75
6.19
3.88
2.70
O
S
CH_3
O
O
H_3C
O
7
1.00
1.05
1.01
1.01
0.98
1.00
3.16
3.03
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.(
f1 (ppm)

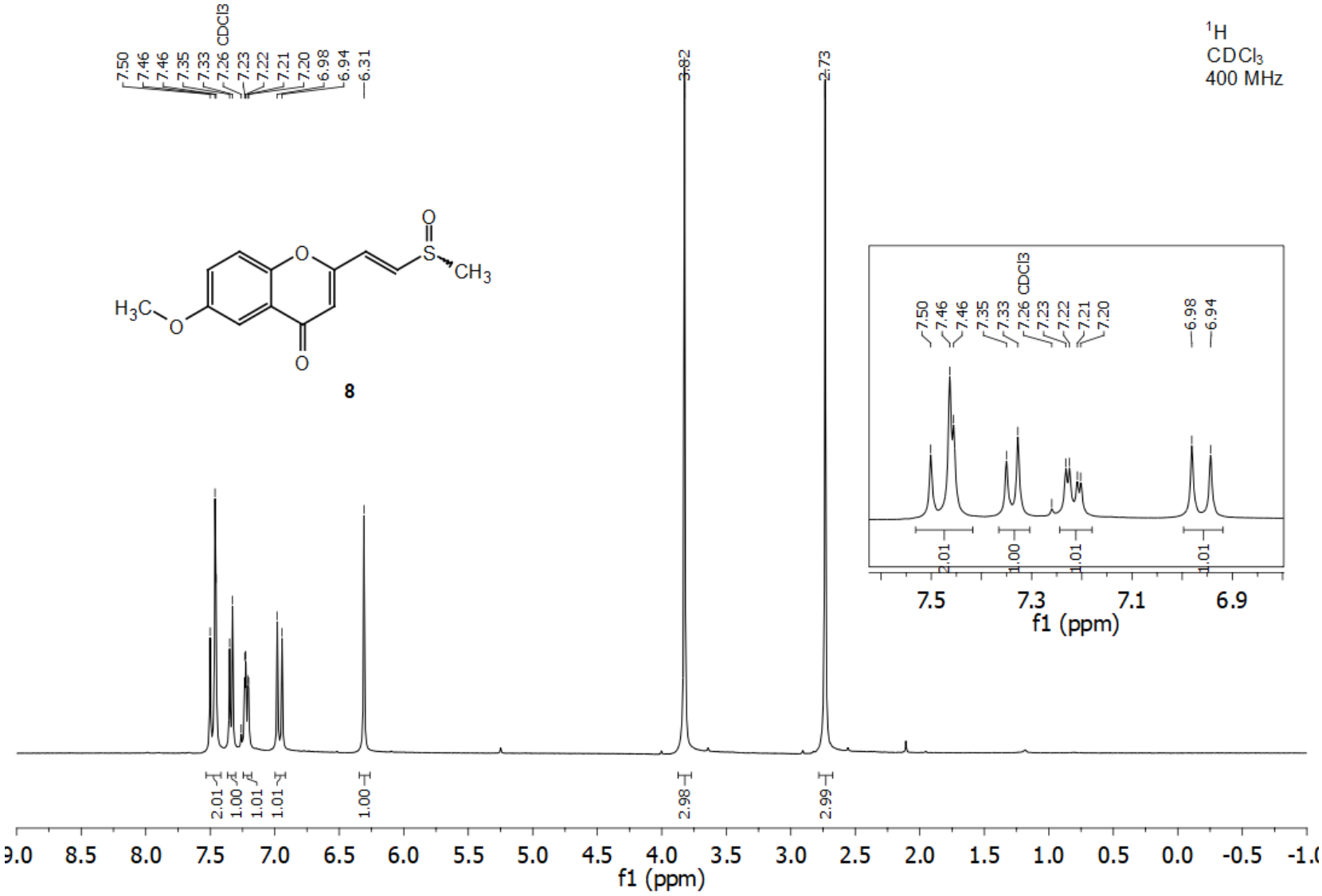

177.99
159.65
157.70
155.97
141.17
134.31
126.70
114.43
114.40
109.75
106.64
77.16 CDCl3
56.39
40.20
13C
CDCl3
100 MHz
O
S
CH3
O
O
H3C
O
7
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

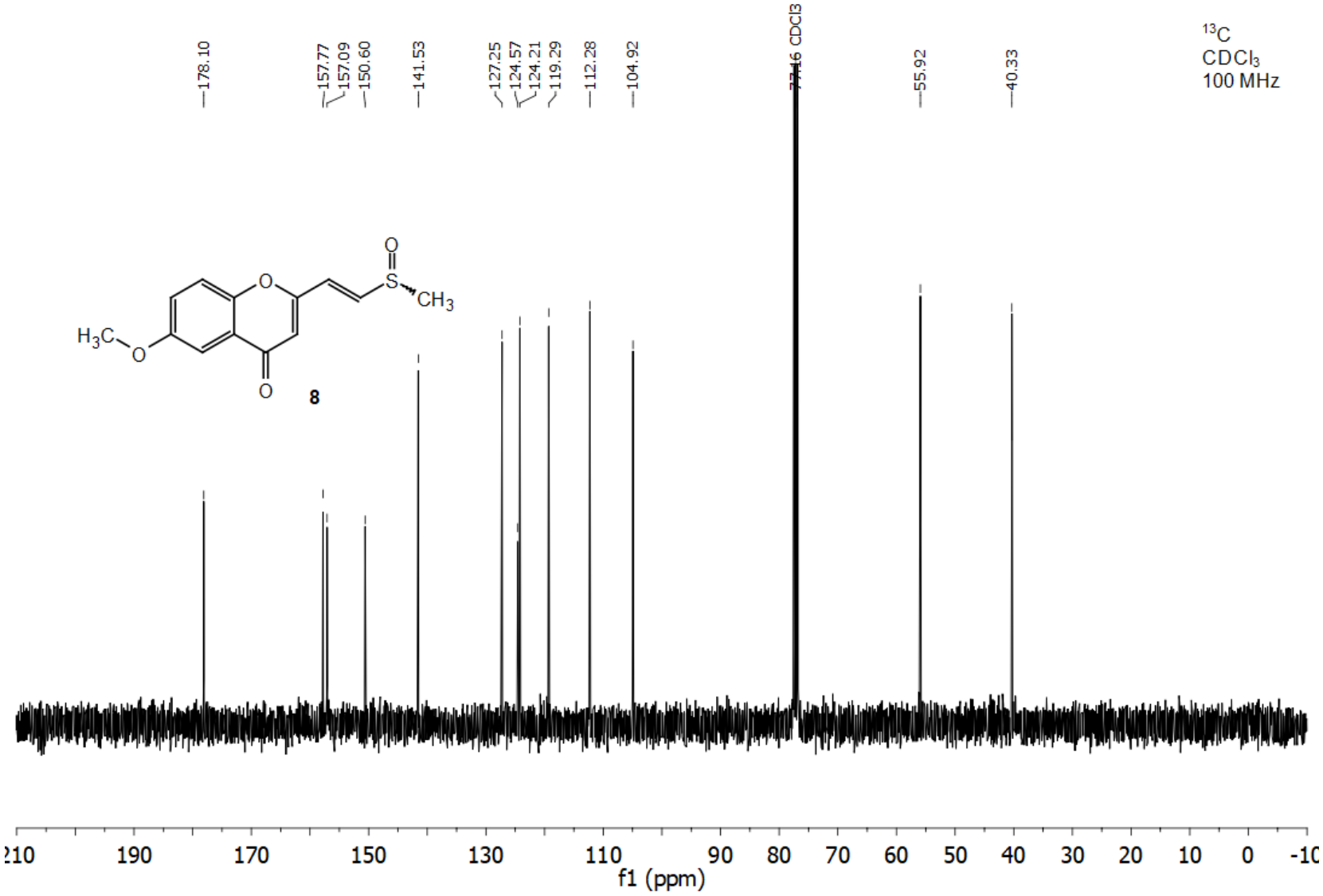

7.93
7.90
7.26 CDCl3
7.21
6.96
5.81
5.77
3.72
2.43
2.30
1H
CDCl3
400 MHz
O
O
S
CH3
O
H3C
O
CH3
O
8''
0.94
1.00
2.01
0.93
3.09
3.10
2.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

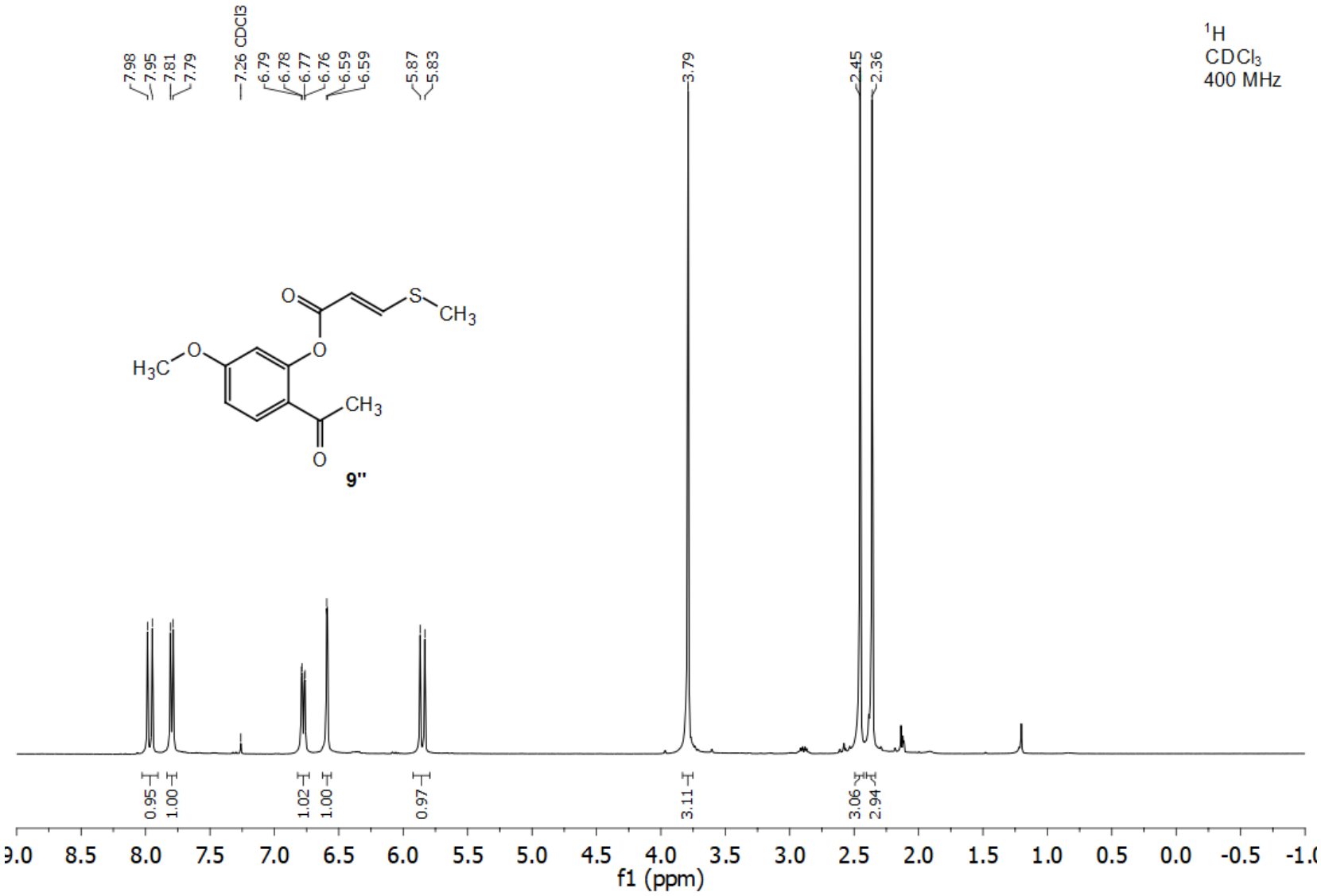

197.15
163.41
156.79
150.31
142.49
131.68
124.51
118.80
113.82
111.39
77.16 CDCl3
55.48
29.73
14.20
13C
CDCl3
100 MHz
O
S
CH3
O
H3C
O
CH3
O
8''
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

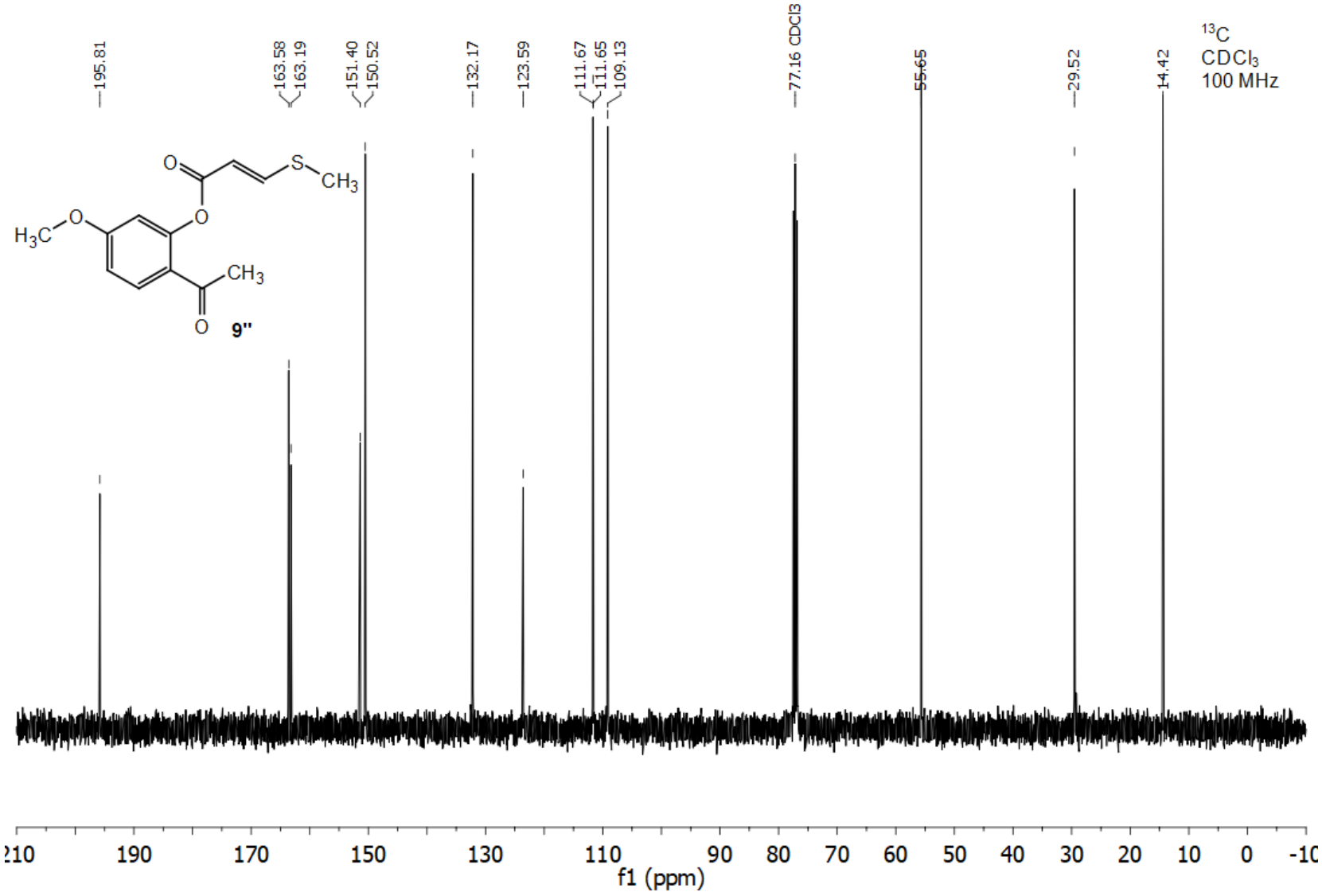

7.45
7.42
7.42
7.26 CDCl3
7.25
7.23
7.12
7.12
7.10
7.09
5.97
5.86
5.82
3.78
2.34
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
O
8'
2.07
0.99
1.08
1.00
1.02
3.15
3.01
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
7.45
7.42
7.42
7.26 CDCl3
7.25
7.23
7.12
7.12
7.10
7.09
2.07
0.99
1.08
7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)

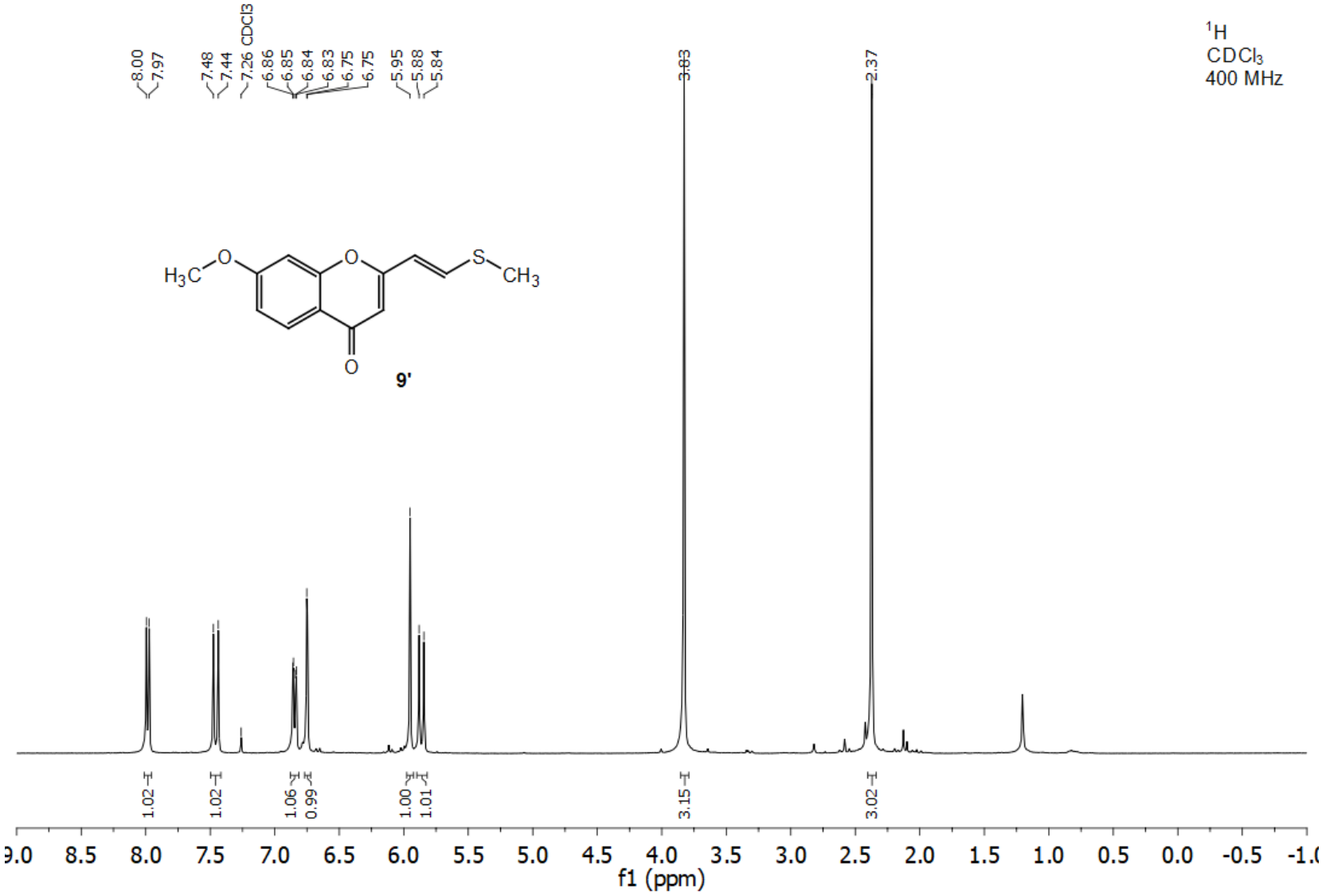

178.08
160.50
156.56
150.43
137.81
124.35
123.12
118.90
114.96
106.86
104.84
77.16 CDCl3
55.76
14.35
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
8'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

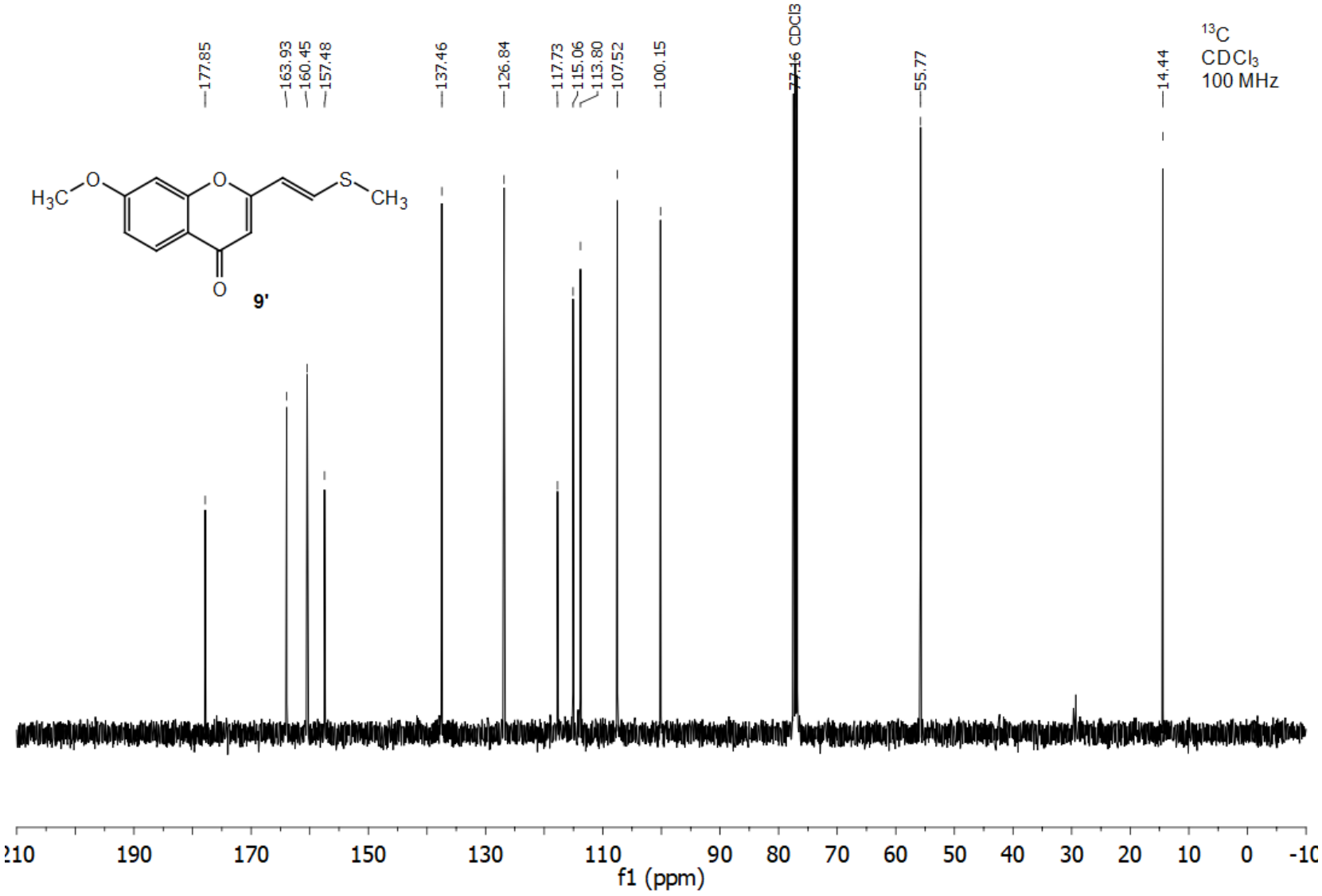

7.50
7.46
7.46
7.35
7.33
7.26 CDCl3
7.23
7.22
7.21
7.20
6.98
6.94
6.31
3.82
2.73
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
O
O
8
2.01
1.00
1.01
1.01
1.00
2.98
2.99
f1 (ppm)
7.5
7.3
7.1
6.9

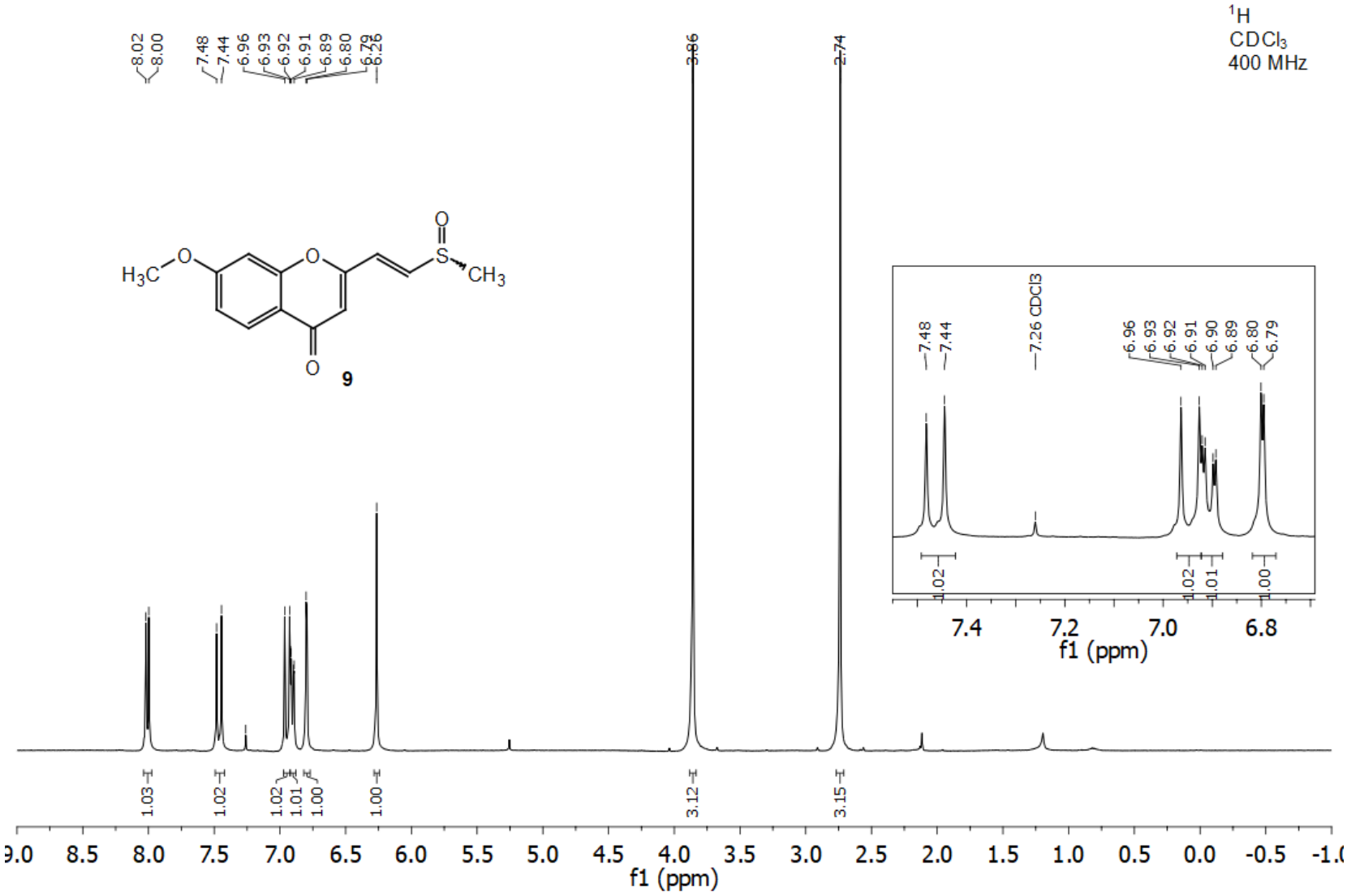

178.10
157.77
157.09
150.60
141.53
127.25
124.57
124.21
119.29
112.28
104.92
77.16 CDCl3
55.92
40.33
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
O
8
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

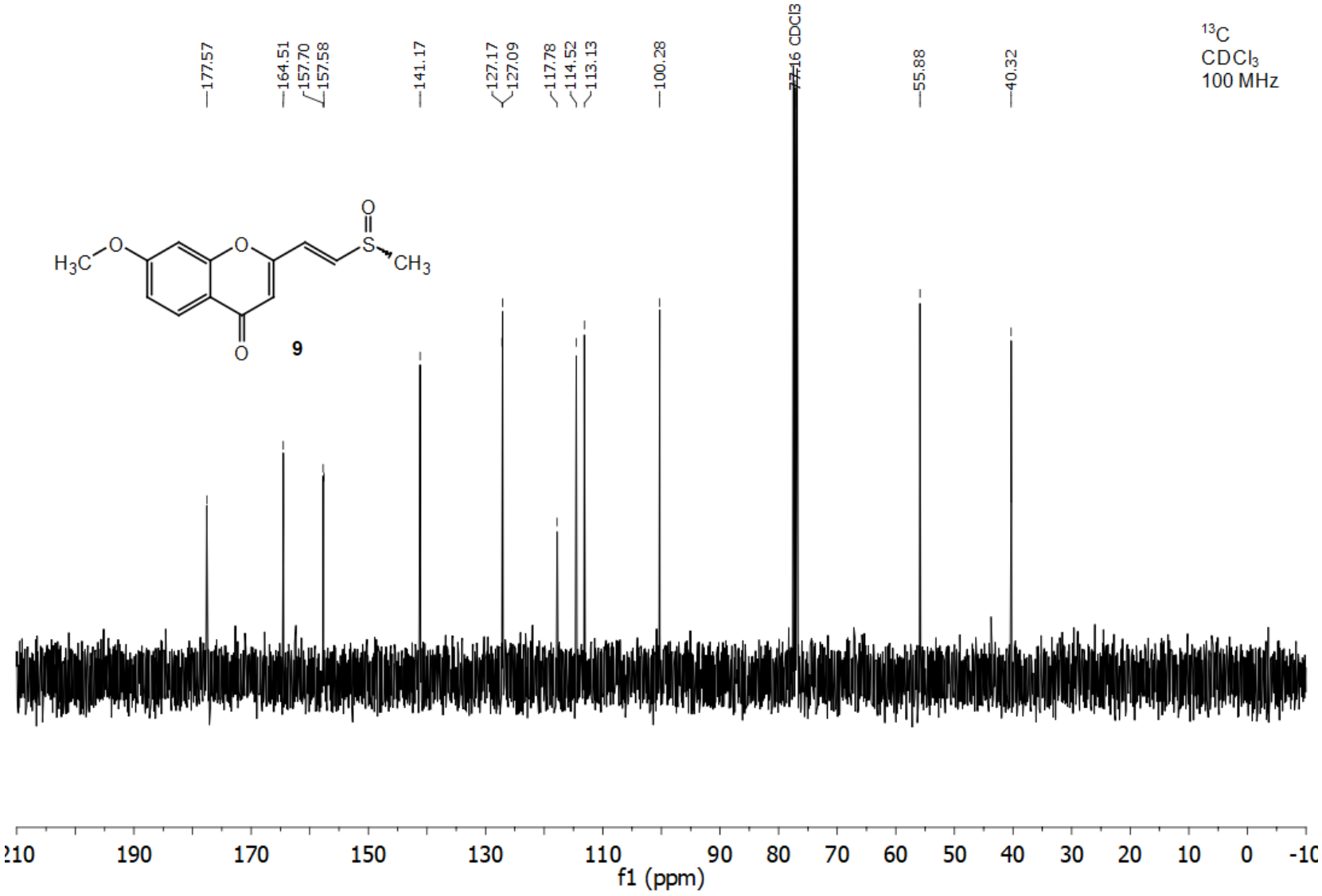

7.98
7.95
7.81
7.79
7.26 CDCl3
6.79
6.78
6.77
6.76
6.59
6.59
5.87
5.83
3.79
2.45
2.36
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
O
CH3
O
9''
0.95
1.00
1.02
1.00
0.97
3.11
3.06
2.94
f1 (ppm)

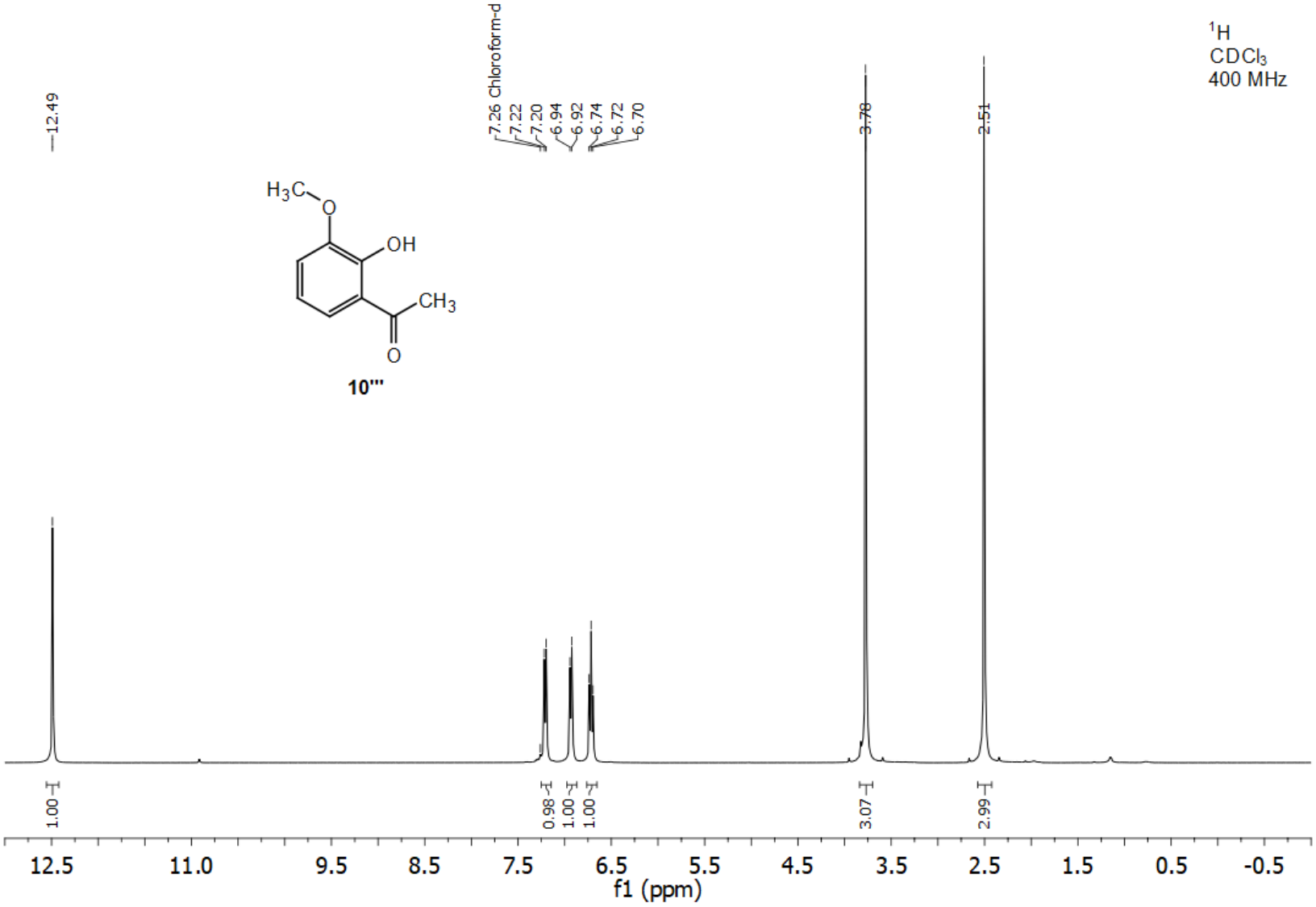

195.81
163.58
163.19
151.40
150.52
132.17
123.59
111.67
111.65
109.13
77.16 CDCl3
55.65
29.52
14.42
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
CH3
O
9''
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

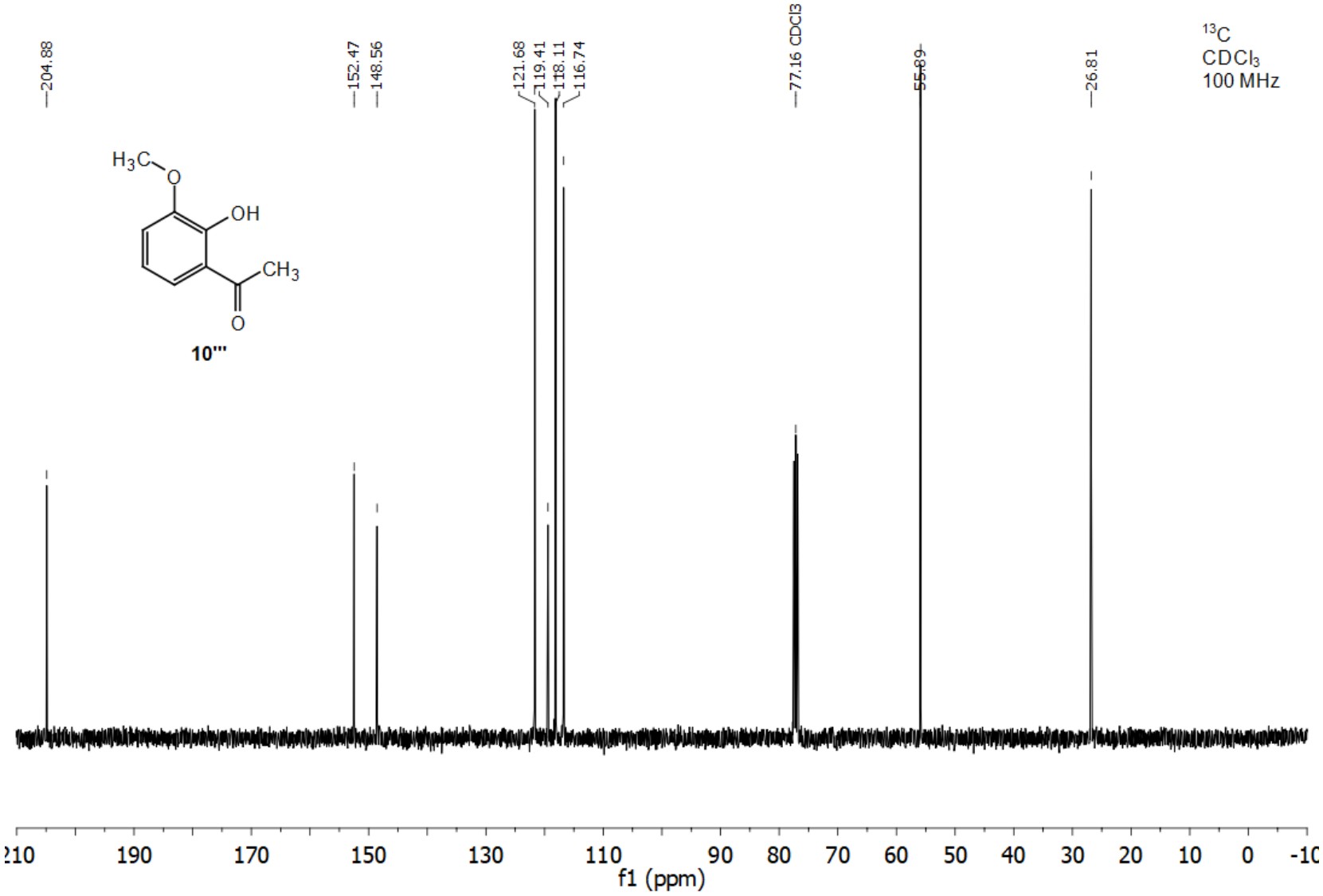

8.00
7.97
7.48
7.44
7.26 CDCl3
6.86
6.85
6.84
6.83
6.75
6.75
5.95
5.88
5.84
3.83
2.37
1H
CDCl3
400 MHz
H3C
O
O
S
CH3
O
9'
1.02
1.02
1.06
0.99
1.00
1.01
3.15
3.02
f1 (ppm)

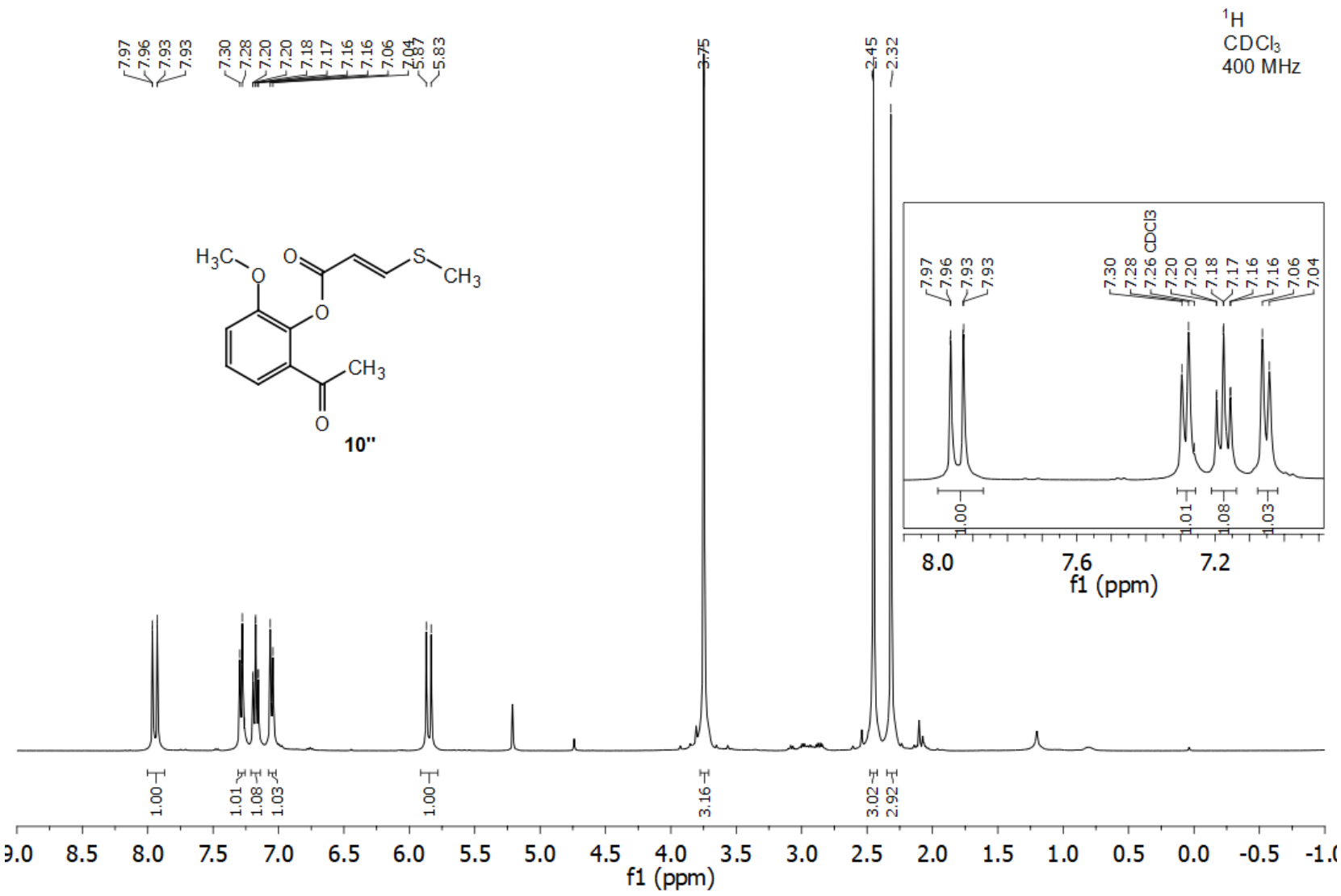

177.85
163.93
160.45
157.48
137.46
126.84
117.73
115.06
113.80
107.52
100.15
77.16 CDCl3
55.77
14.44
13C
CDCl3
100 MHz
H3C
O
O
S
CH3
O
9'
f1 (ppm)

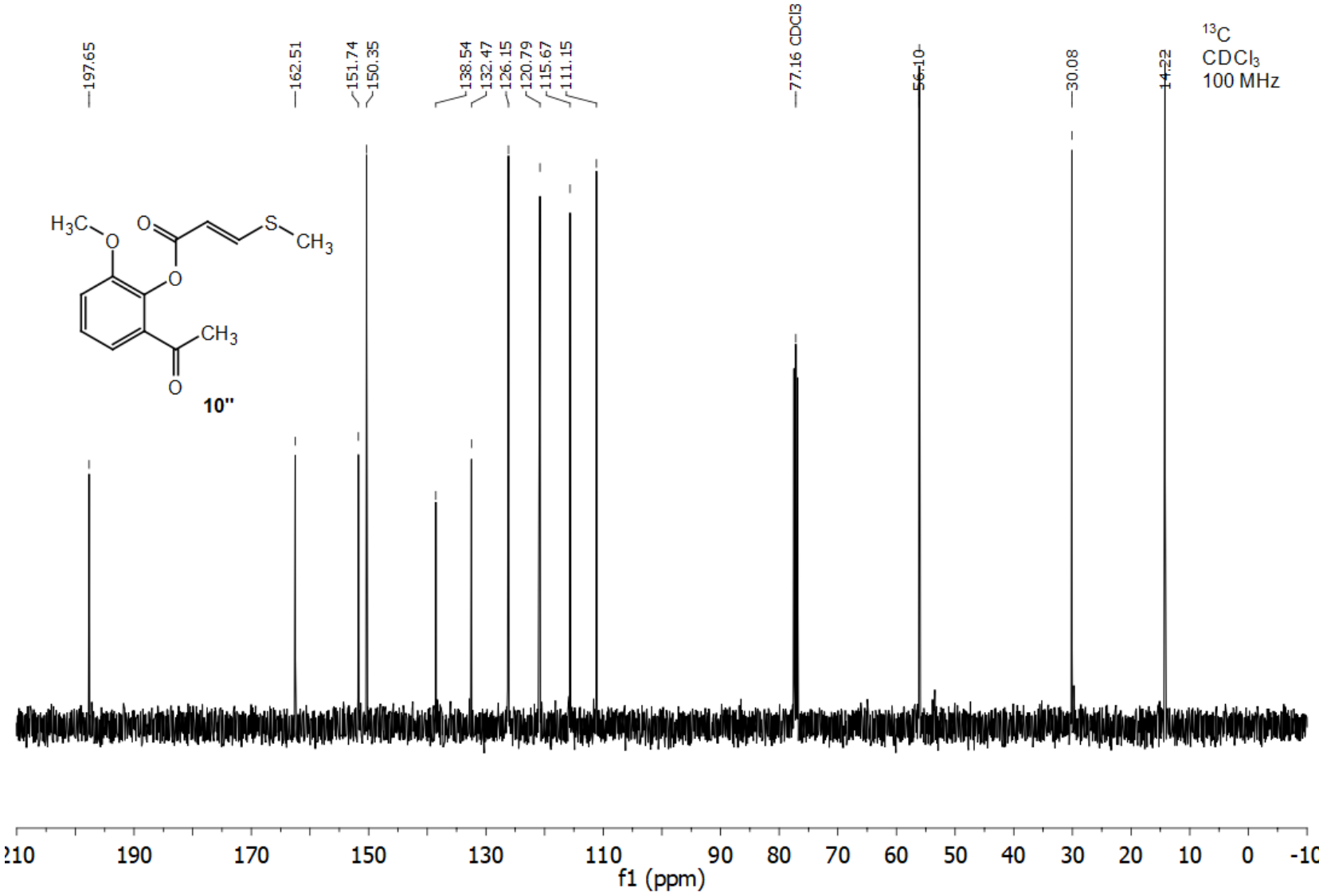

1H
CDCl3
400 MHz
8.02
8.00
7.48
7.44
6.96
6.93
6.92
6.91
6.89
6.80
6.79
6.26
3.86
2.74
H3C
O
O
S
CH3
O
O
9
7.26 CDCl3
1.03
1.02
1.02
1.01
1.00
1.00
3.12
3.15
f1 (ppm)

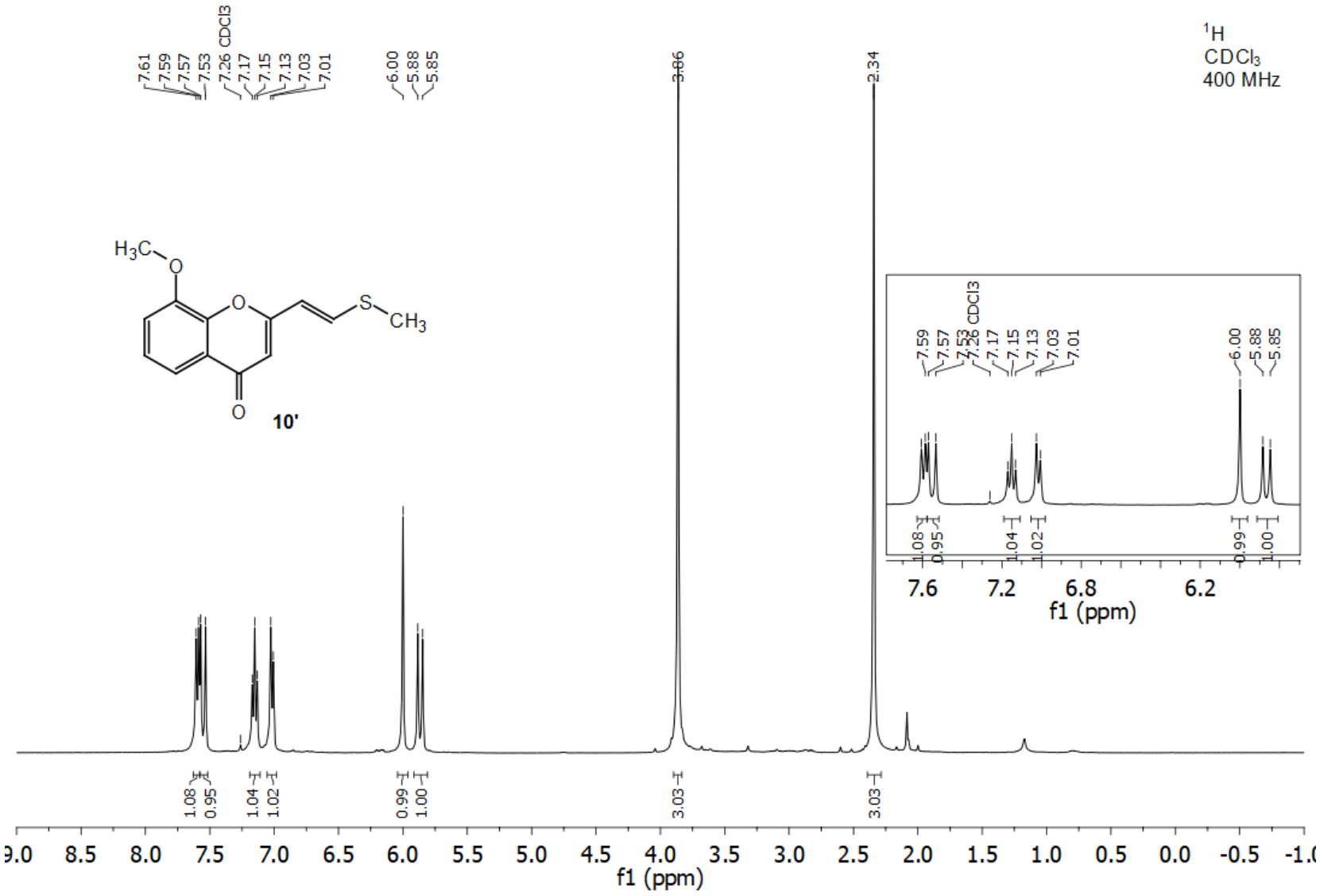

177.57
164.51
157.70
157.58
141.17
127.17
127.09
117.78
114.52
113.13
100.28
77.16 CDCl3
55.88
40.32
13C
CDCl3
100 MHz
H3C
O
O
O
S
CH3
O
9
f1 (ppm)

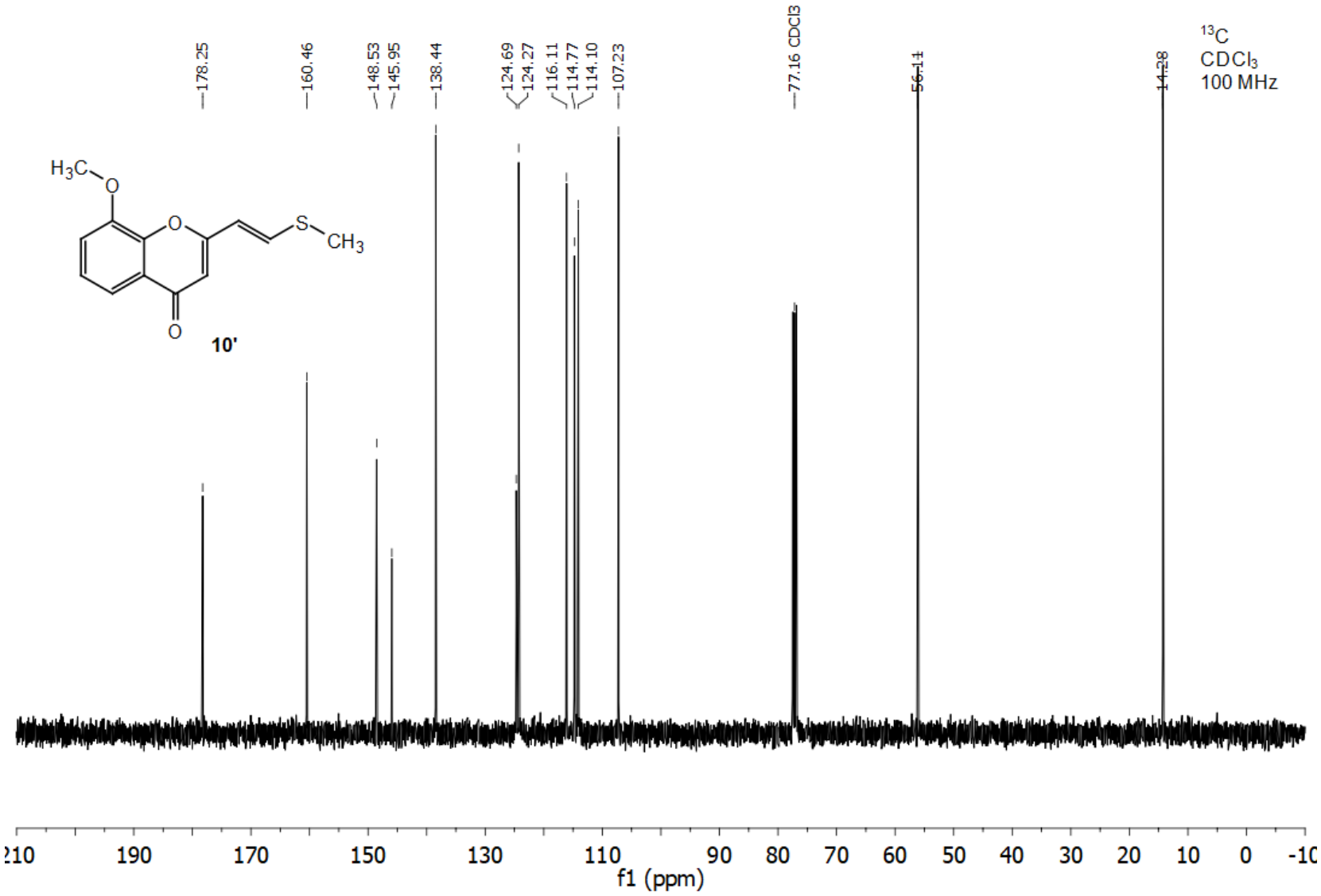

12.49
7.26 Chloroform-d
7.22
7.20
6.94
6.92
6.74
6.72
6.70
3.78
2.51
^{1}H
$CDCl_3$
400 MHz
H_3C
O
OH
CH_3
O
10'''
1.00
0.98
1.00
1.00
3.07
2.99
12.5
11.0
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

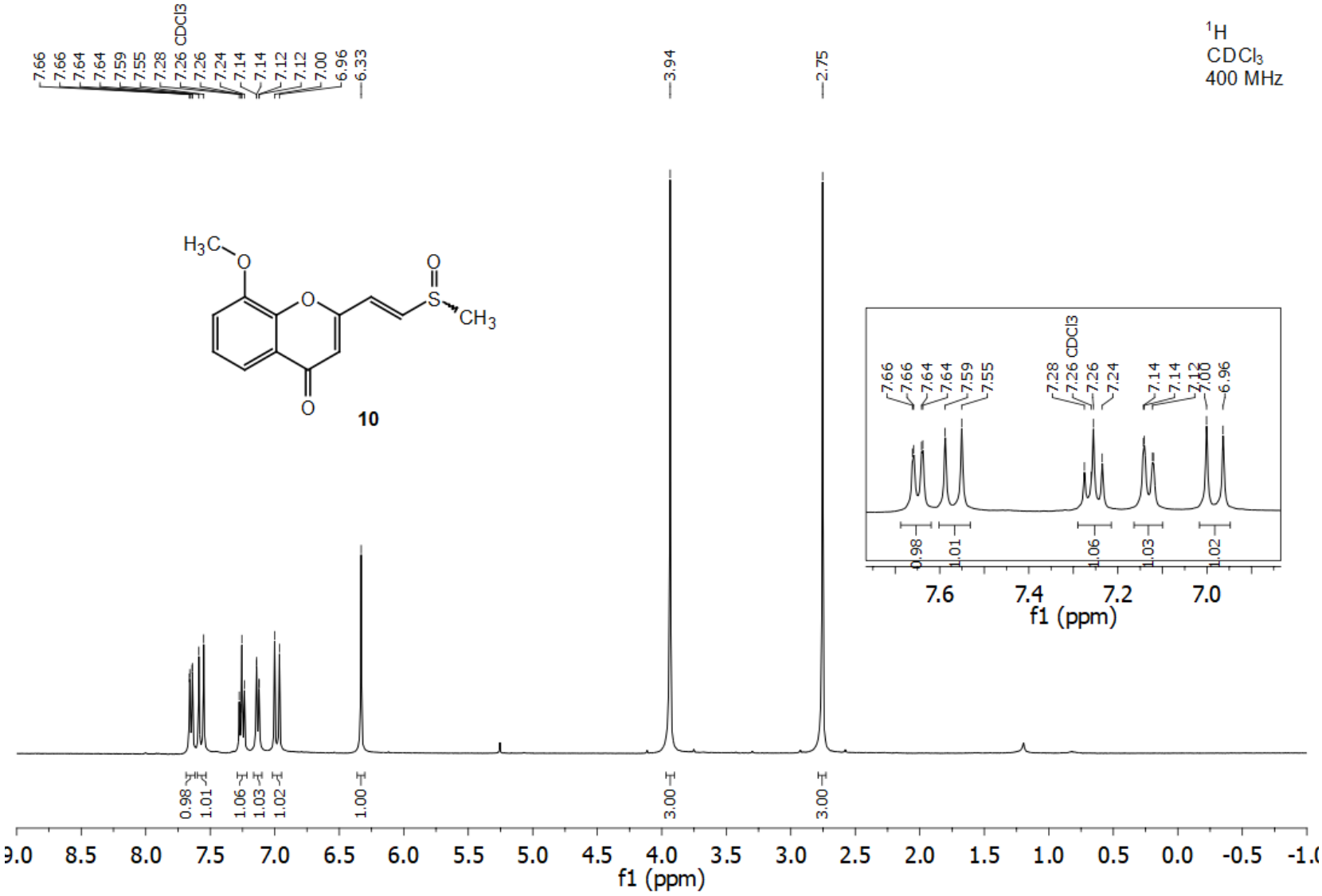

204.88
152.47
148.56
121.68
119.41
118.11
116.74
77.16 CDCl3
55.89
26.81
13C
CDCl3
100 MHz
H3C
O
OH
CH3
O
10'''
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

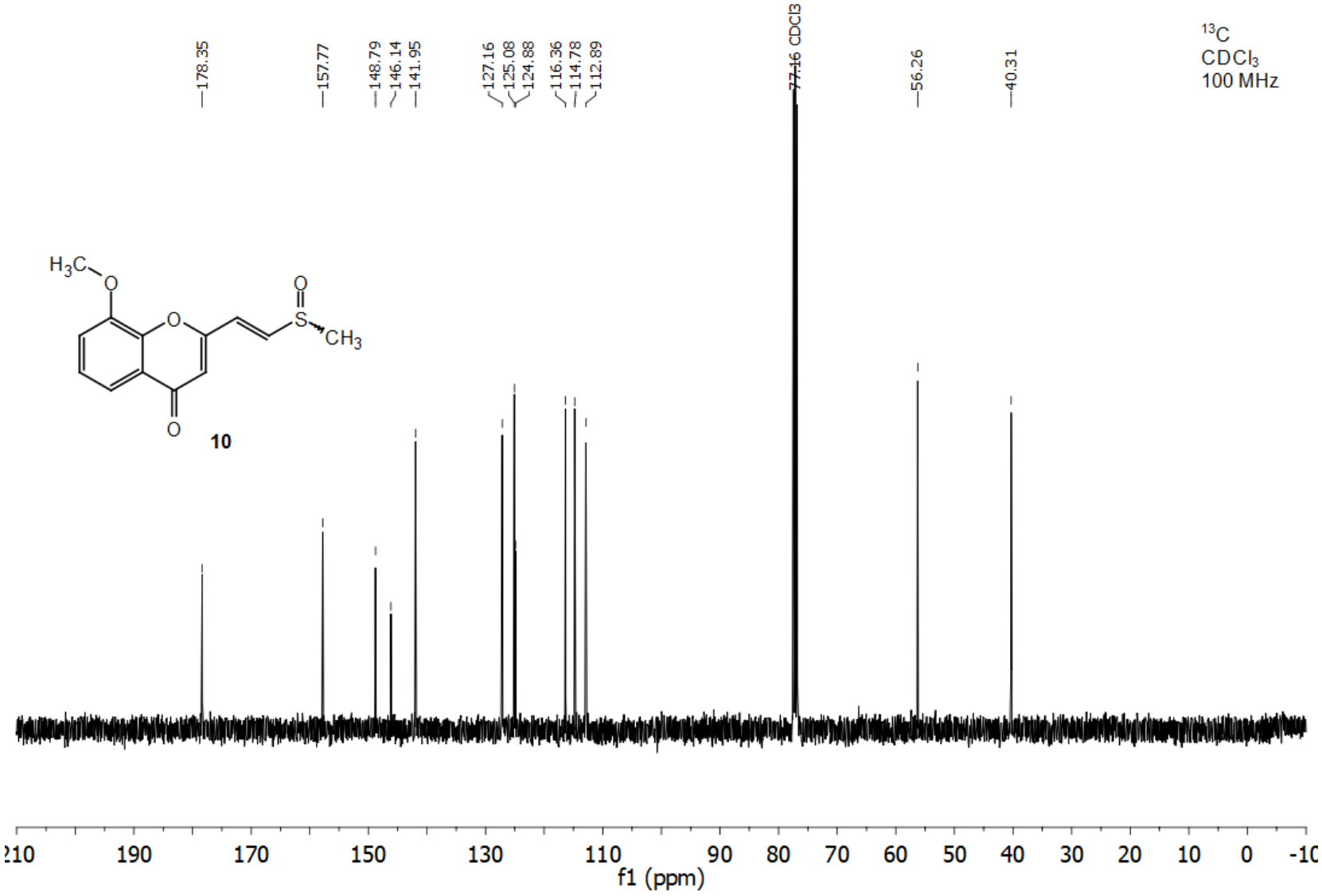

1H
CDCl3
400 MHz
7.97
7.96
7.93
7.93
7.30
7.28
7.20
7.20
7.18
7.17
7.16
7.16
7.06
7.04
5.87
5.83
3.75
2.45
2.32
CDCl3
1.00
1.01
1.08
1.03
1.00
3.16
3.02
2.92
f1 (ppm)
10''

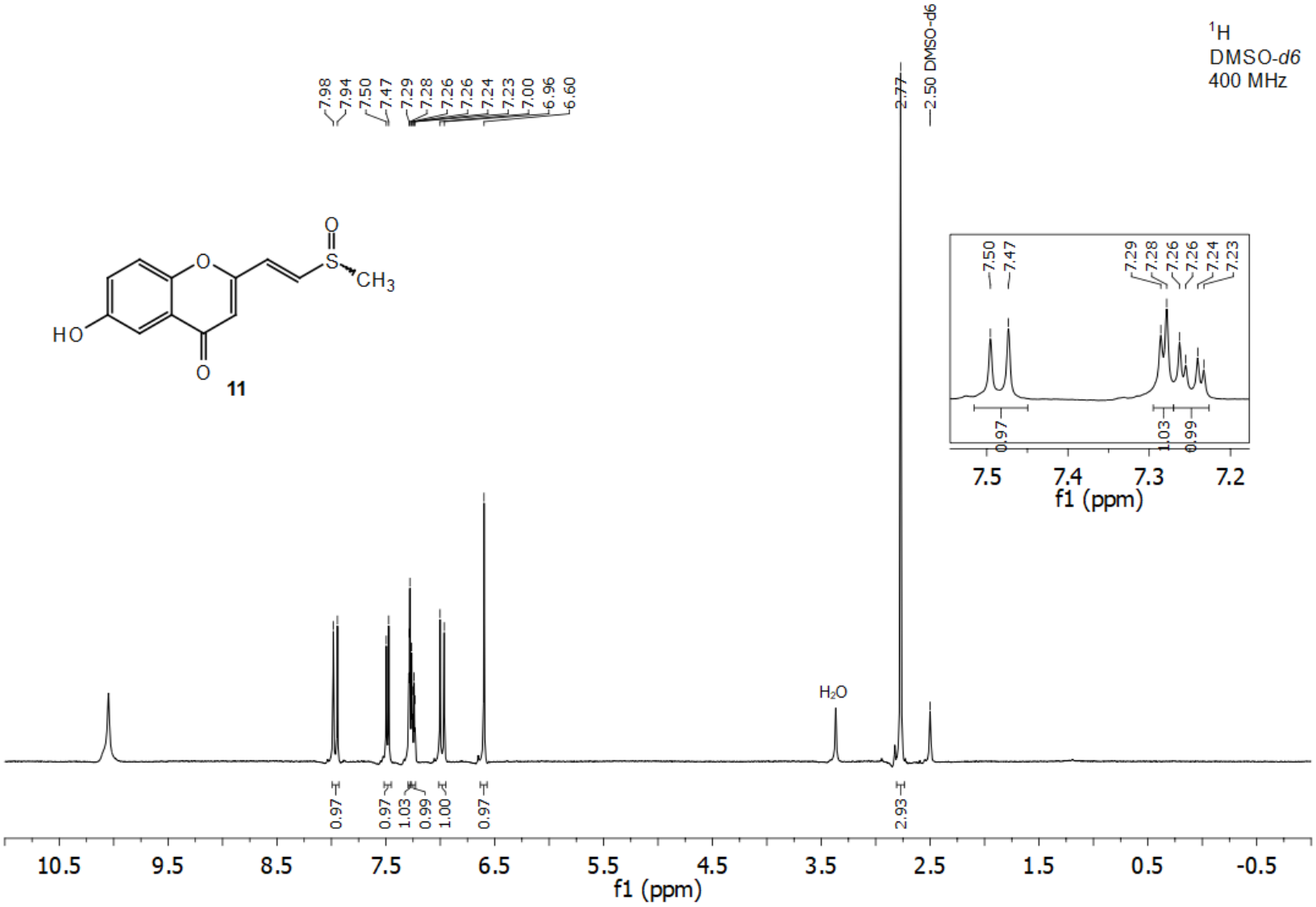

197.65
162.51
151.74
150.35
138.54
132.47
126.15
120.79
115.67
111.15
77.16 CDCl3
56.10
30.08
14.22
13C
CDCl3
100 MHz
H3C
O
O
O
S
CH3
CH3
O
10"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

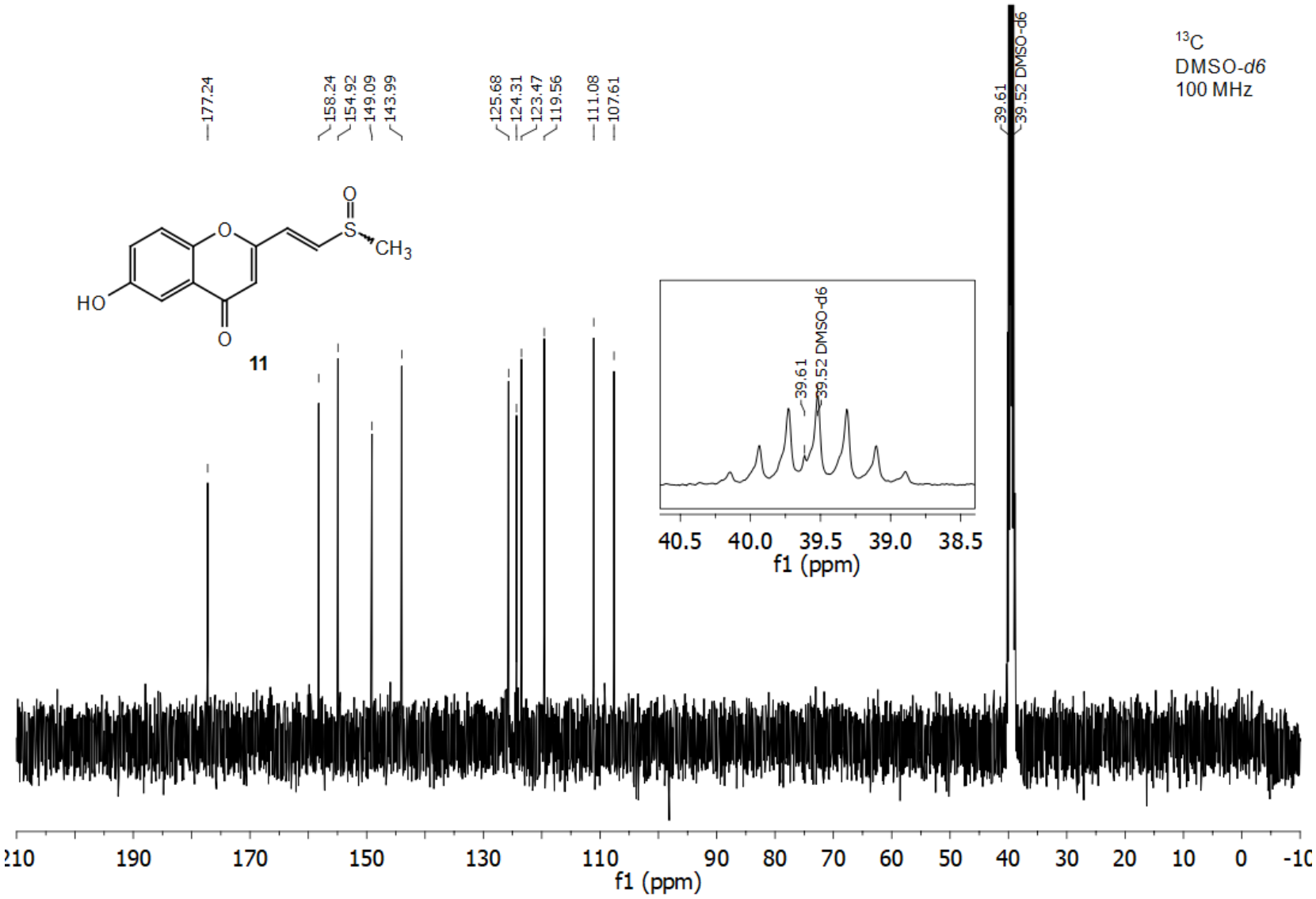

^{1}H
$CDCl_3$
400 MHz
7.61
7.59
7.57
7.53
7.26 CDCl3
7.17
7.15
7.13
7.03
7.01
6.00
5.88
5.85
3.86
2.34
H_3C
O
O
S
CH_3
O
10'
1.08
0.95
1.04
1.02
0.99
1.00
3.03
3.03
f1 (ppm)
7.6
7.2
6.8
6.2

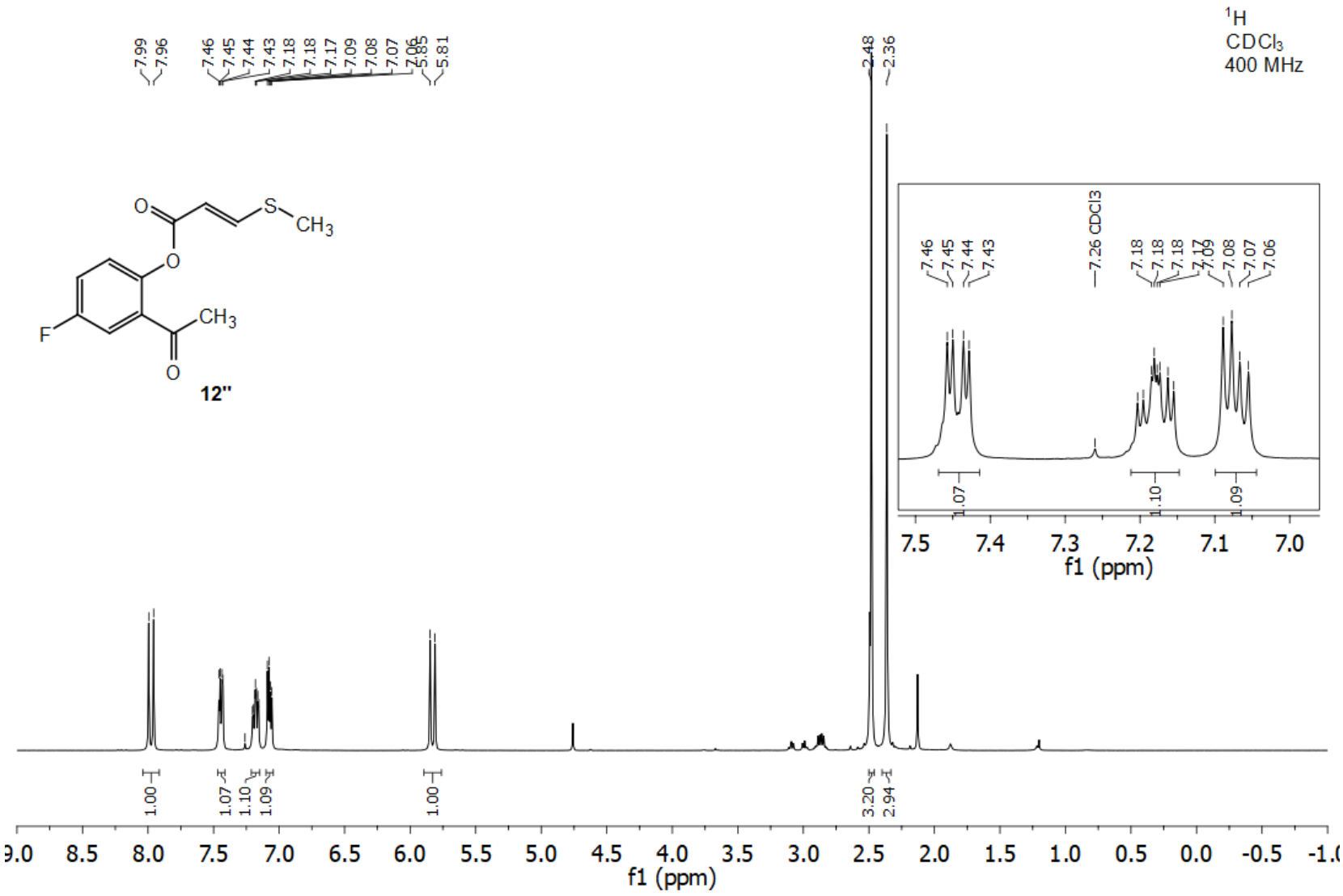

178.25
160.46
148.53
145.95
138.44
124.69
124.27
116.11
114.77
114.10
107.23
77.16 CDCl3
56.11
14.28
13C
CDCl3
100 MHz
H3C
O
O
S
CH3
O
10'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

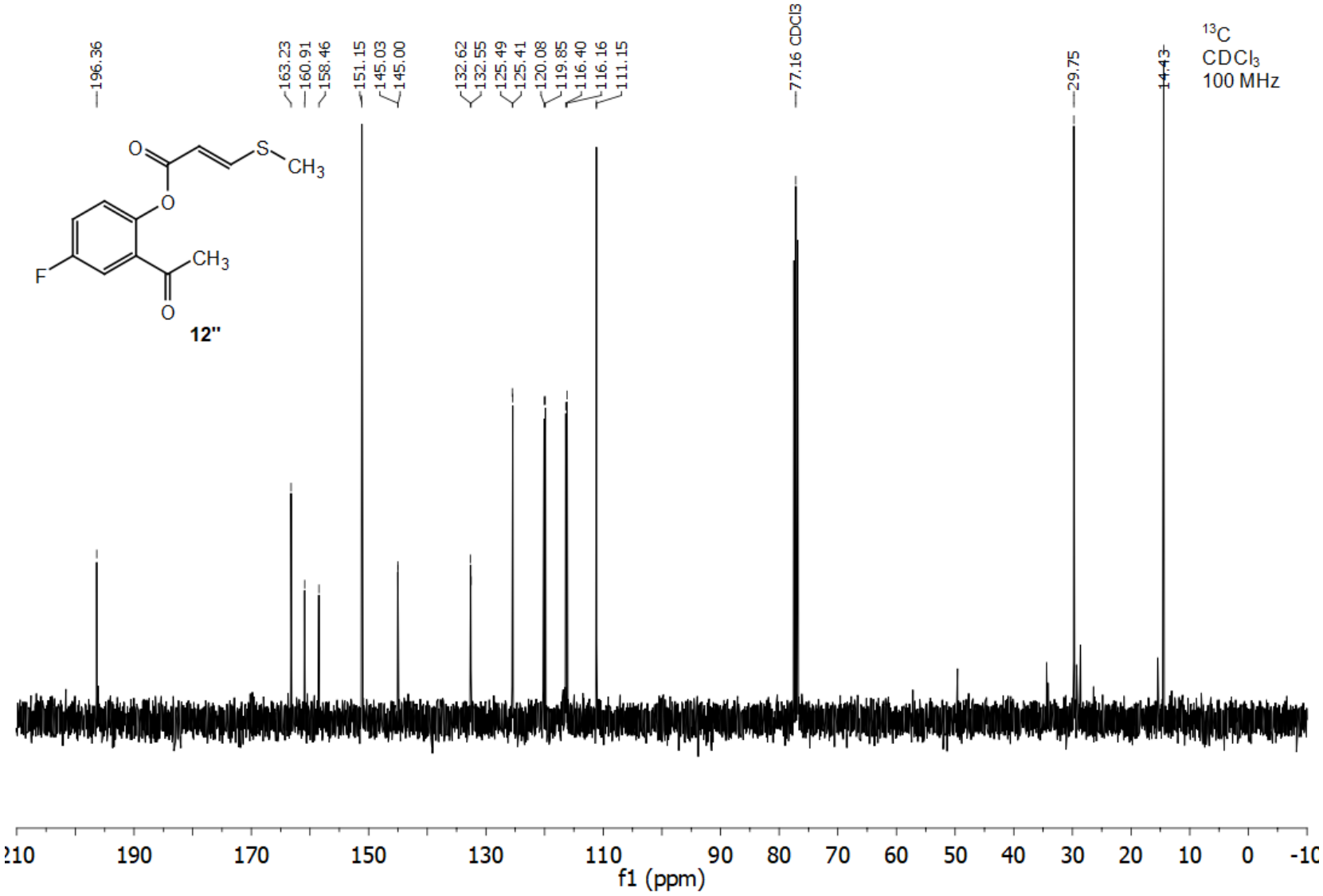

7.66
7.66
7.64
7.64
7.59
7.55
7.28
7.26 CDCl3
7.26
7.24
7.14
7.14
7.12
7.12
7.00
6.96
6.33
3.94
2.75
1H
CDCl3
400 MHz
H3C
O
O
O
S
CH3
O
10
0.98
1.01
1.06
1.03
1.02
1.00
3.00
3.00
f1 (ppm)

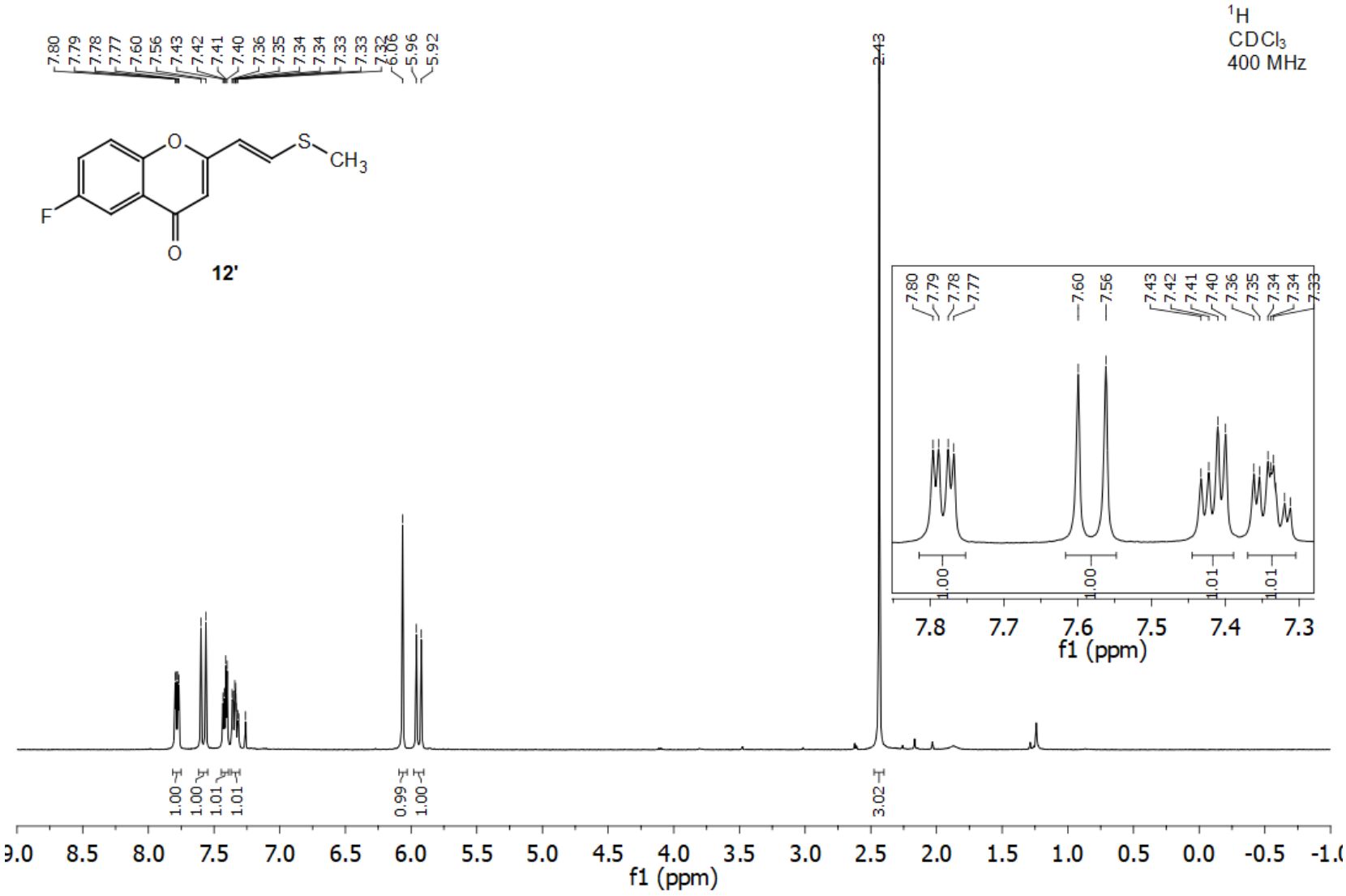

178.35
157.77
148.79
146.14
141.95
127.16
125.08
124.88
116.36
114.78
112.89
77.16 CDCl3
56.26
40.31
13C
CDCl3
100 MHz
H3C
O
O
O
S
CH3
O
10
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

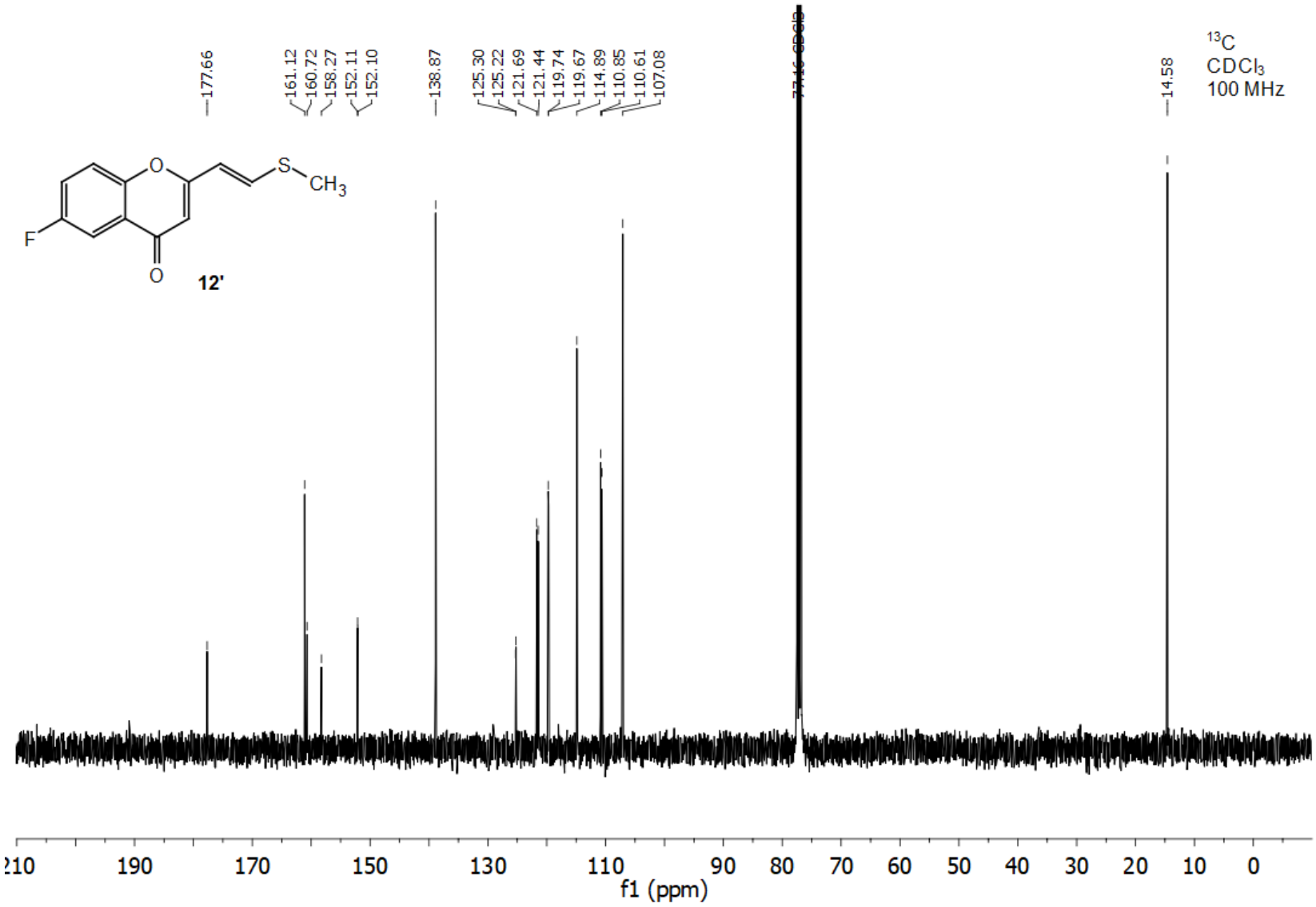

^{1}H
DMSO-*d6*
400 MHz
2.50 DMSO-d6
2.77
7.98
7.94
7.50
7.47
7.29
7.28
7.26
7.26
7.24
7.23
7.00
6.96
6.60
HO
O
O
S
CH3
11
H2O
0.97
0.97
1.03
0.99
1.00
0.97
2.93
f1 (ppm)
0.97
1.03
0.99
f1 (ppm)

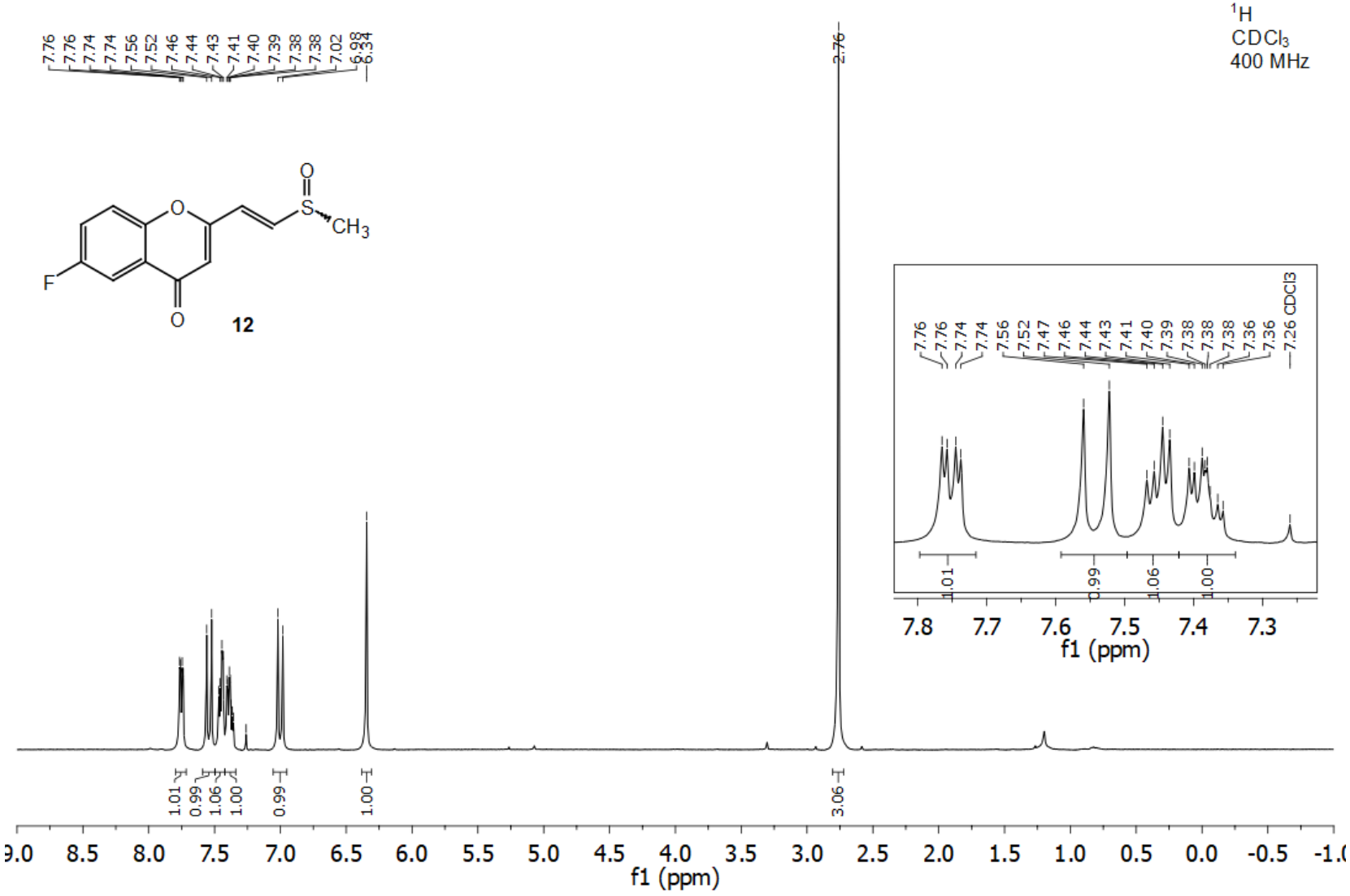

177.24
158.24
154.92
149.09
143.99
125.68
124.31
123.47
119.56
111.08
107.61
39.61
39.52 DMSO-d6
13C
DMSO-d6
100 MHz
HO
O
S
CH3
11
39.61
39.52 DMSO-d6
40.5
40.0
39.5
39.0
38.5
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

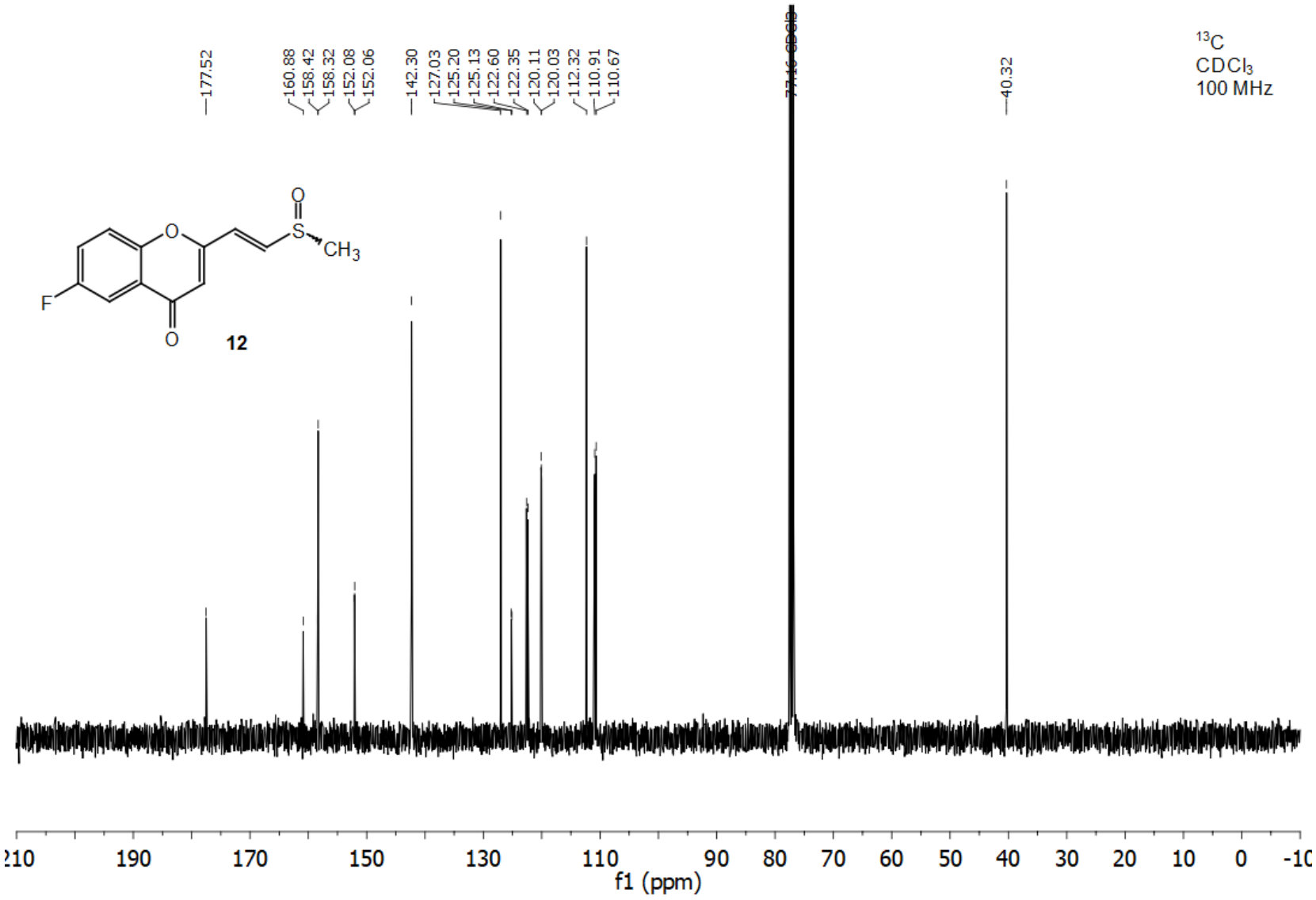

1H
CDCl3
400 MHz
12"
7.26 CDCl3
f1 (ppm)

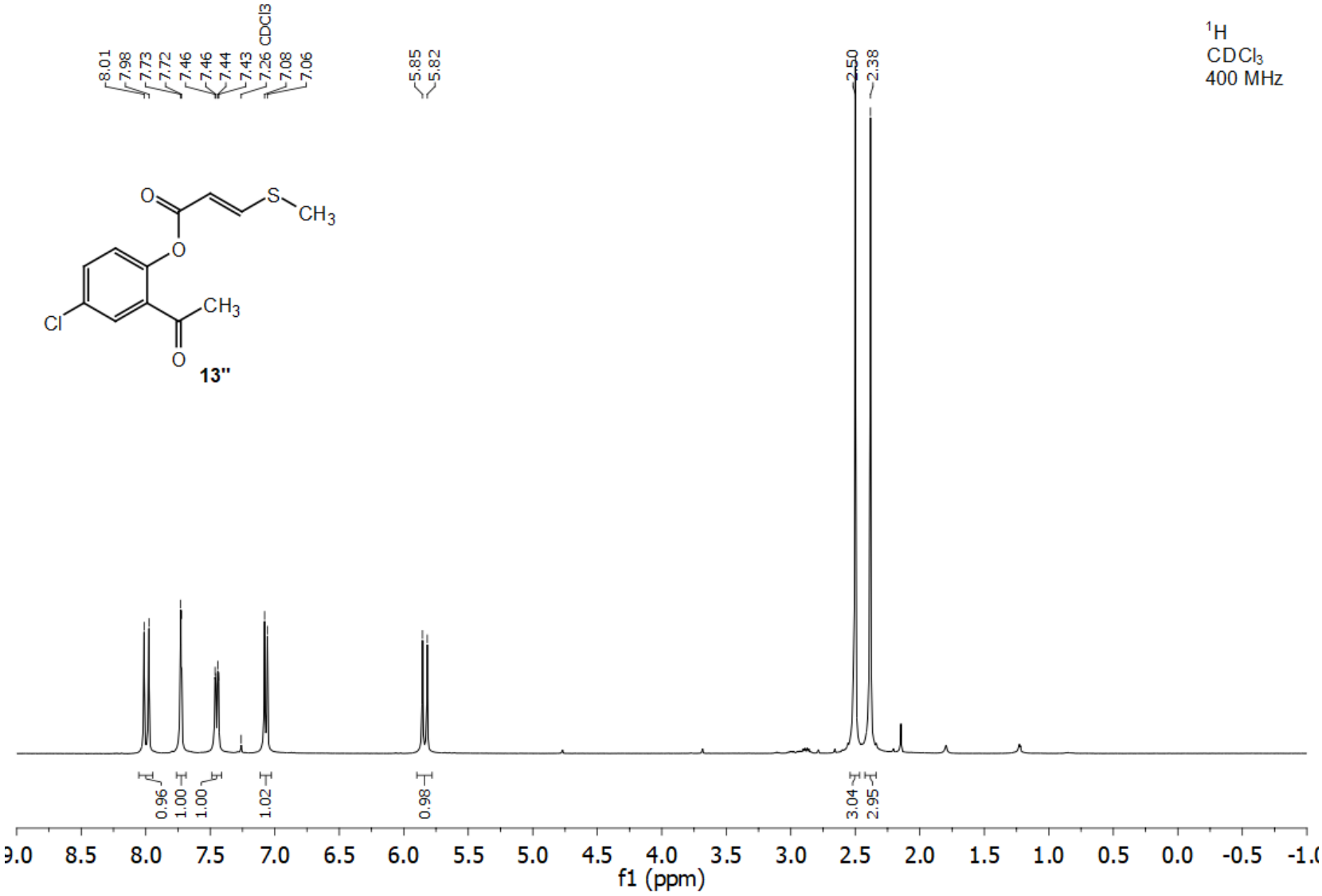

196.36
163.23
160.91
158.46
151.15
145.03
145.00
132.62
132.55
125.49
125.41
120.08
119.85
116.40
116.16
111.15
77.16 CDCl3
29.75
14.43
13C
CDCl3
100 MHz
O
S
CH3
O
CH3
F
O
12''
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

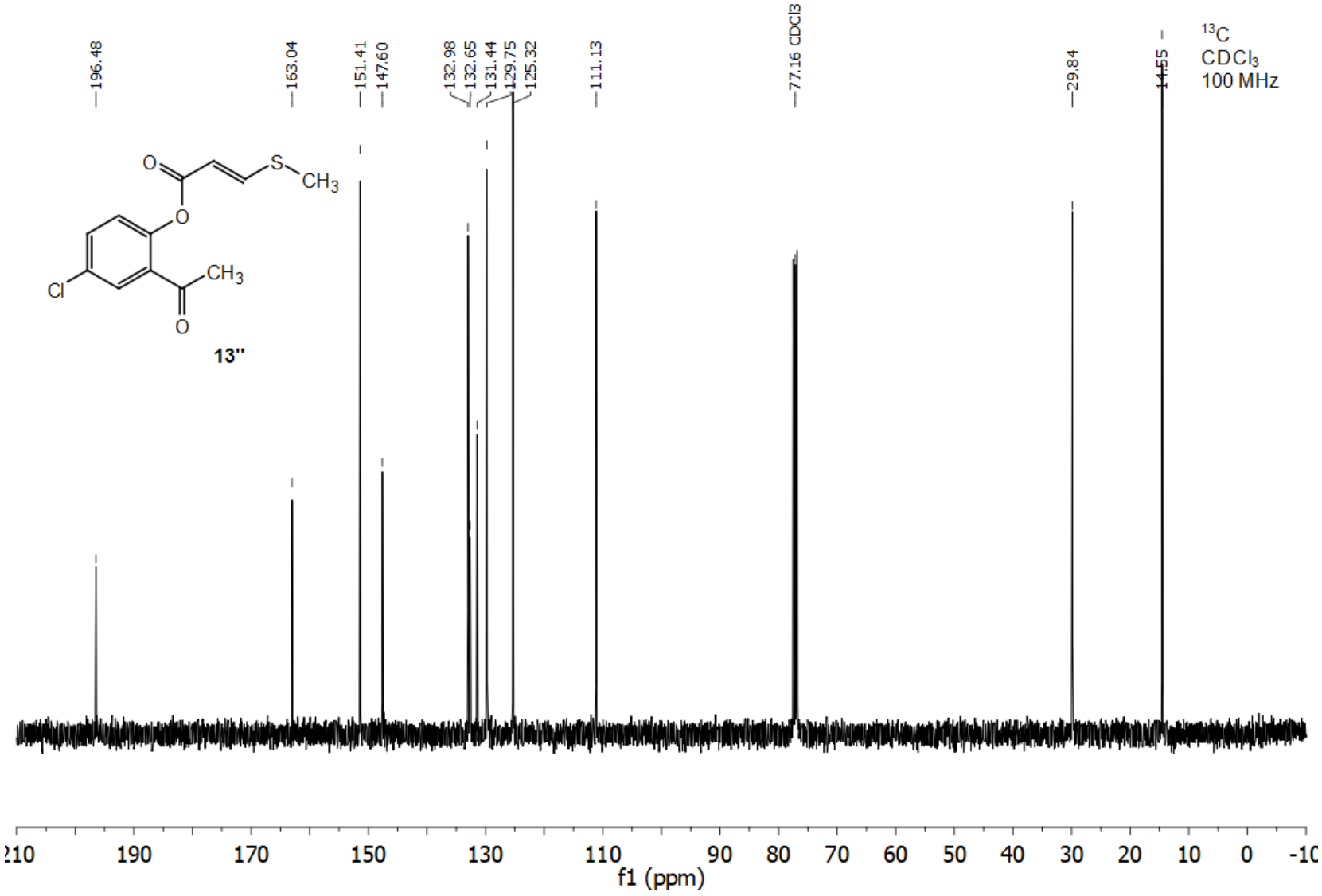

7.80
7.79
7.78
7.77
7.60
7.56
7.43
7.42
7.41
7.40
7.36
7.35
7.34
7.34
7.33
7.33
7.32
6.06
5.96
5.92
2.43
1H
CDCl3
400 MHz
O
S
CH3
F
O
12'
1.00
1.00
1.01
1.01
0.99
1.00
3.02
f1 (ppm)
f1 (ppm)

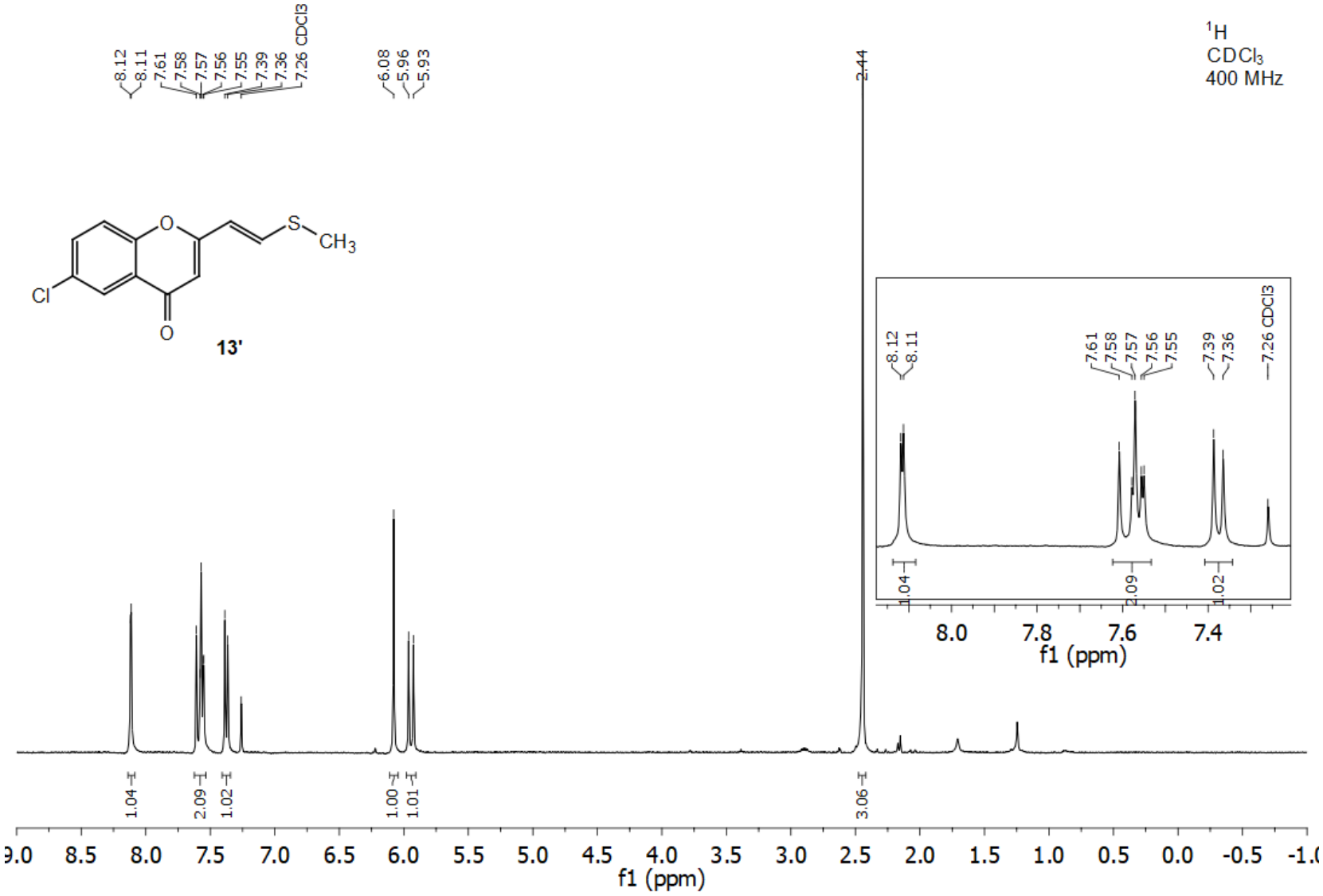

177.66
161.12
160.72
158.27
152.11
152.10
138.87
125.30
125.22
121.69
121.44
119.74
119.67
114.89
110.85
110.61
107.08
77.16 CDCl3
14.58
13C
CDCl3
100 MHz
O
S
CH3
F
O
12'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

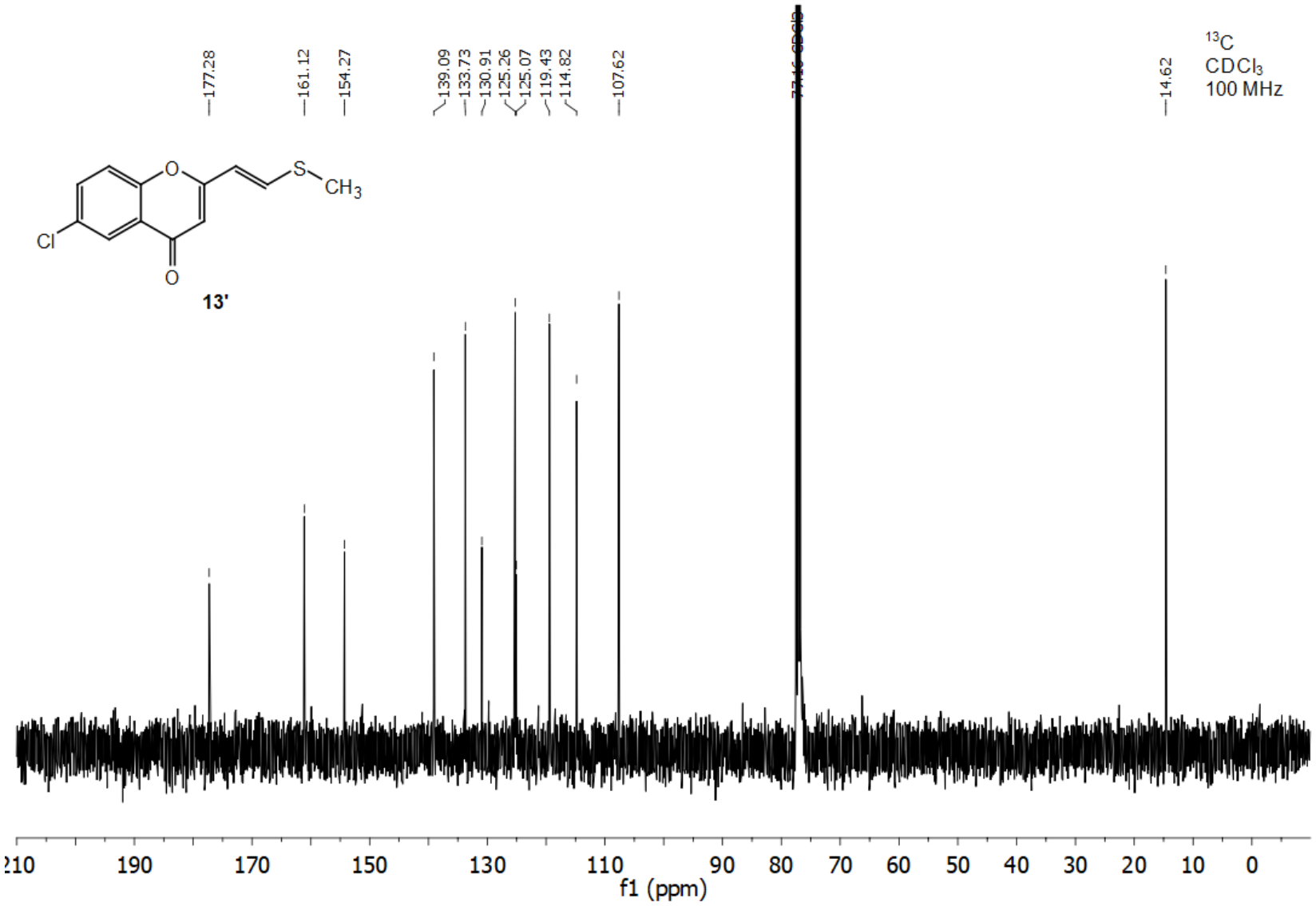

1H
CDCl3
400 MHz
7.76
7.76
7.74
7.74
7.56
7.52
7.46
7.44
7.43
7.41
7.40
7.39
7.38
7.38
7.02
6.98
6.34
2.76
O
S
CH3
O
F
O
12
7.26 CDCl3
1.01
0.99
1.06
1.00
0.99
1.00
3.06
f1 (ppm)

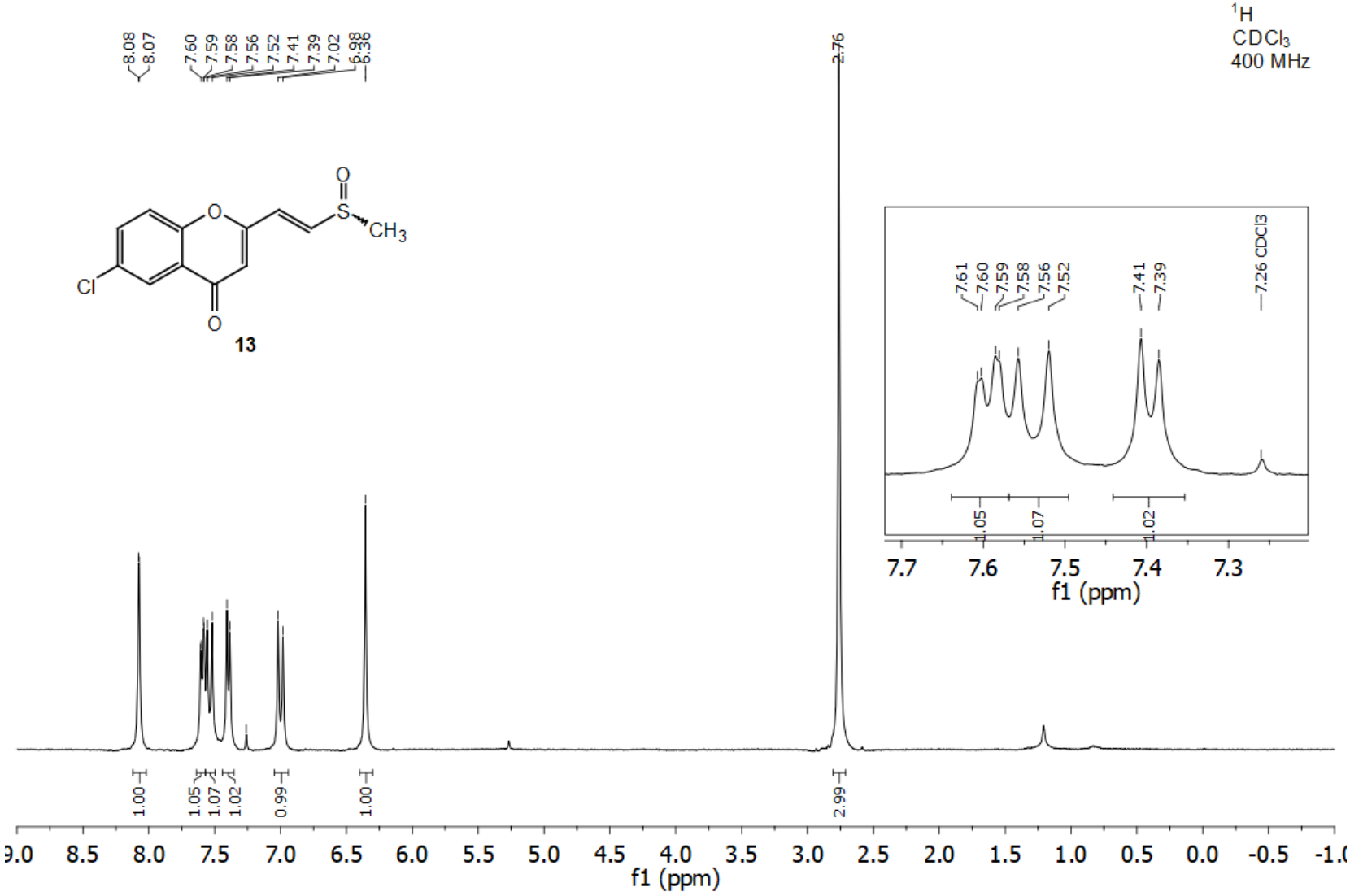

177.52
160.88
158.42
158.32
152.08
152.06
142.30
127.03
125.20
125.13
122.60
122.35
120.11
120.03
112.32
110.91
110.67
77.16 CDCl3
40.32
13C
CDCl3
100 MHz
O
S
CH3
F
O
O
12
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

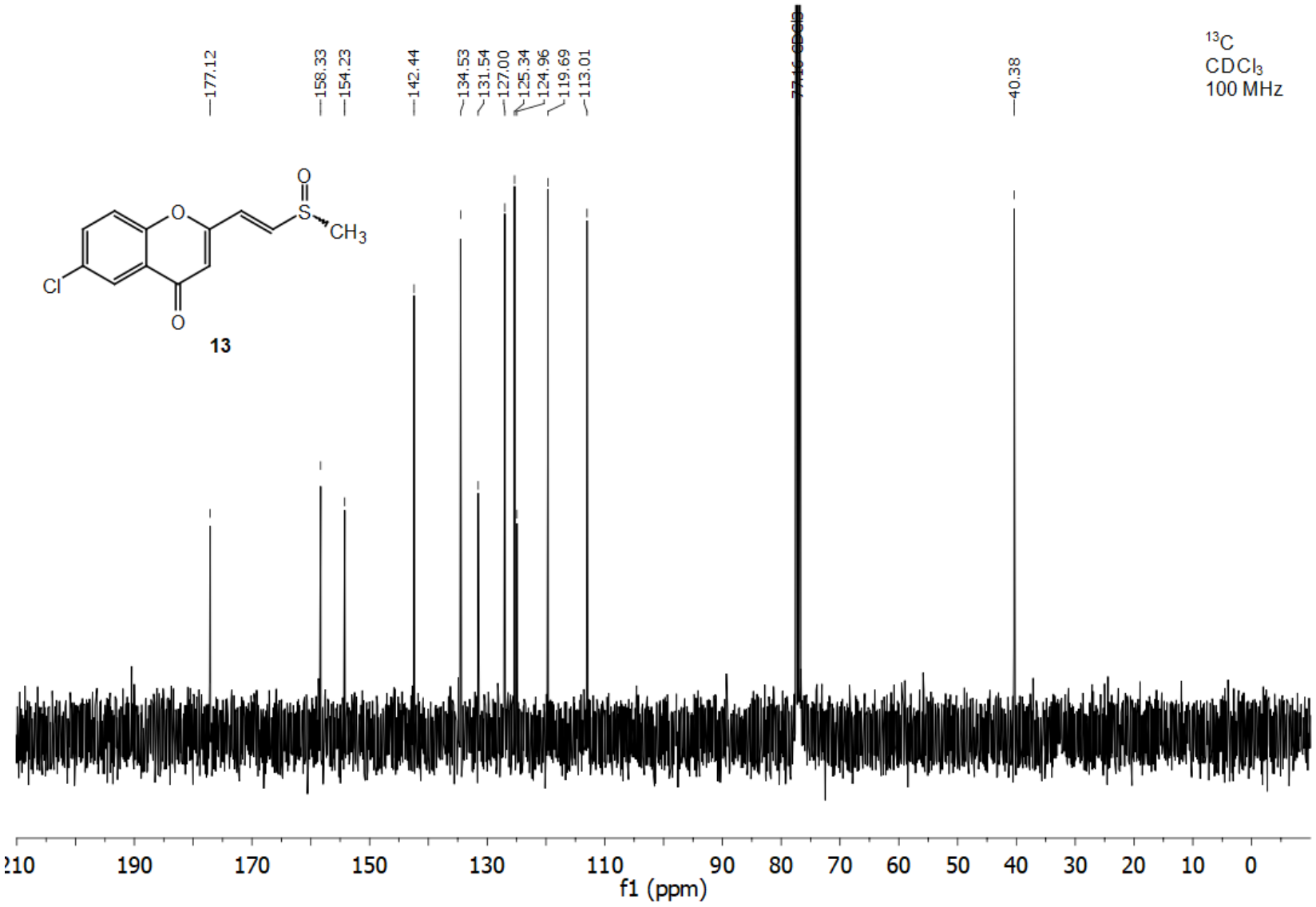

8.01
7.98
7.73
7.72
7.46
7.46
7.44
7.43
7.26 CDCl3
7.08
7.06
5.85
5.82
2.50
2.38
1H
CDCl3
400 MHz
O
S
CH3
O
CH3
Cl
O
13''
0.96
1.00
1.00
1.02
0.98
3.04
2.95
f1 (ppm)

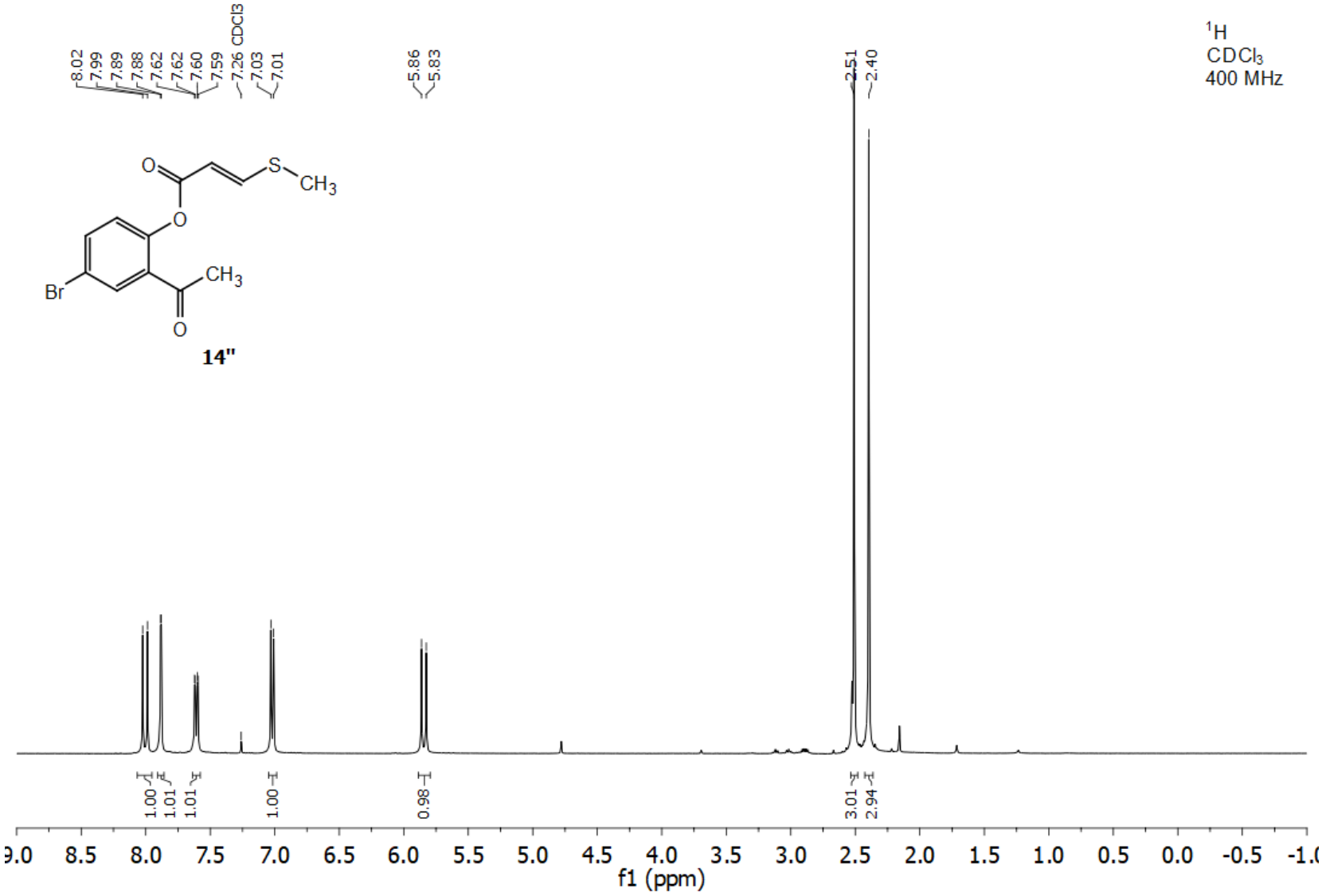

196.48
163.04
151.41
147.60
132.98
132.65
131.44
129.75
125.32
111.13
77.16 CDCl3
29.84
14.55
13C
CDCl3
100 MHz
O
S
CH3
O
Cl
CH3
O
13"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

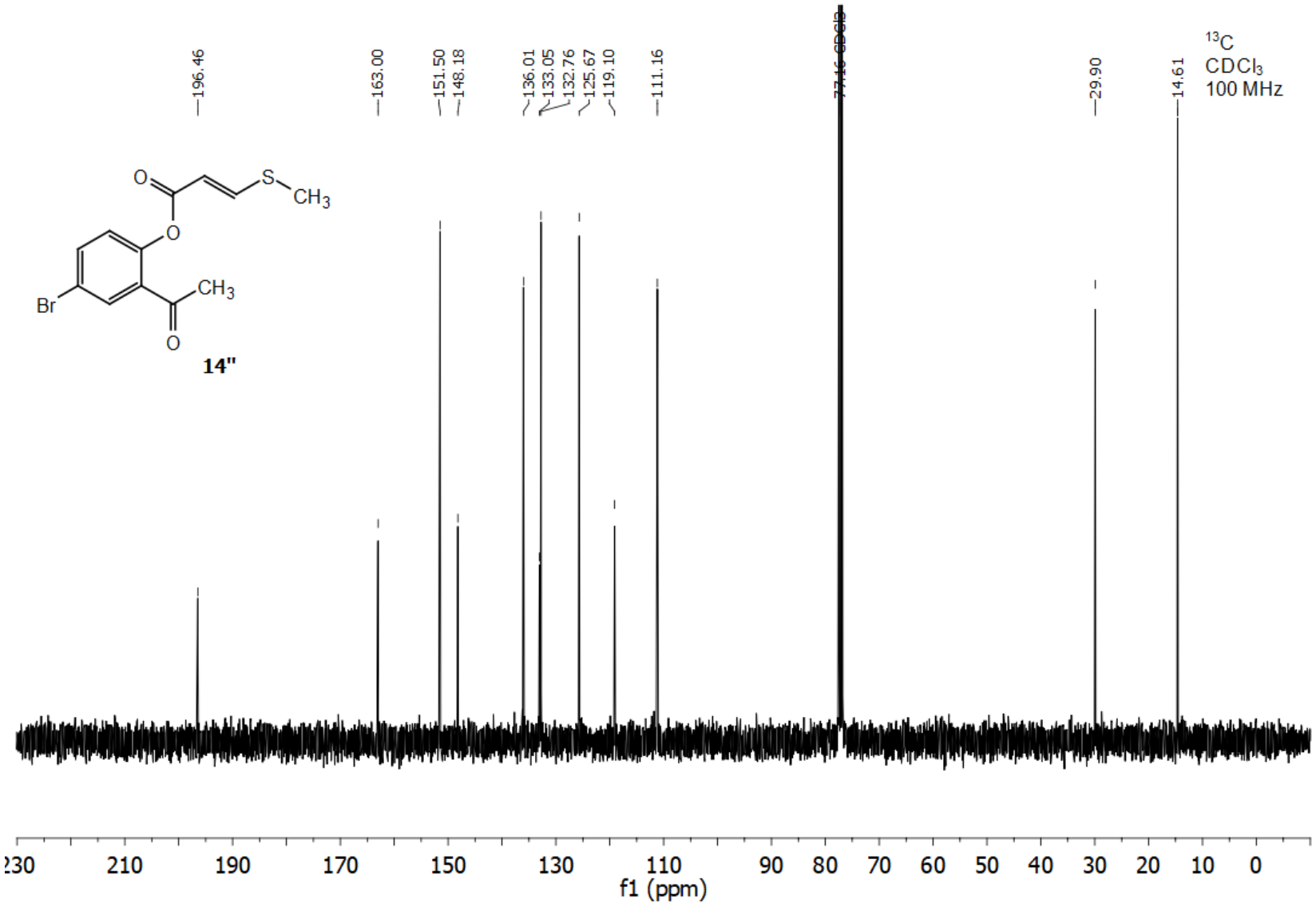

8.12
8.11
7.61
7.58
7.57
7.56
7.55
7.39
7.36
7.26 CDCl3
6.08
5.96
5.93
2.44
1H
CDCl3
400 MHz
O
S
CH3
Cl
O
13'
1.04
2.09
1.02
1.00
1.01
3.06
f1 (ppm)

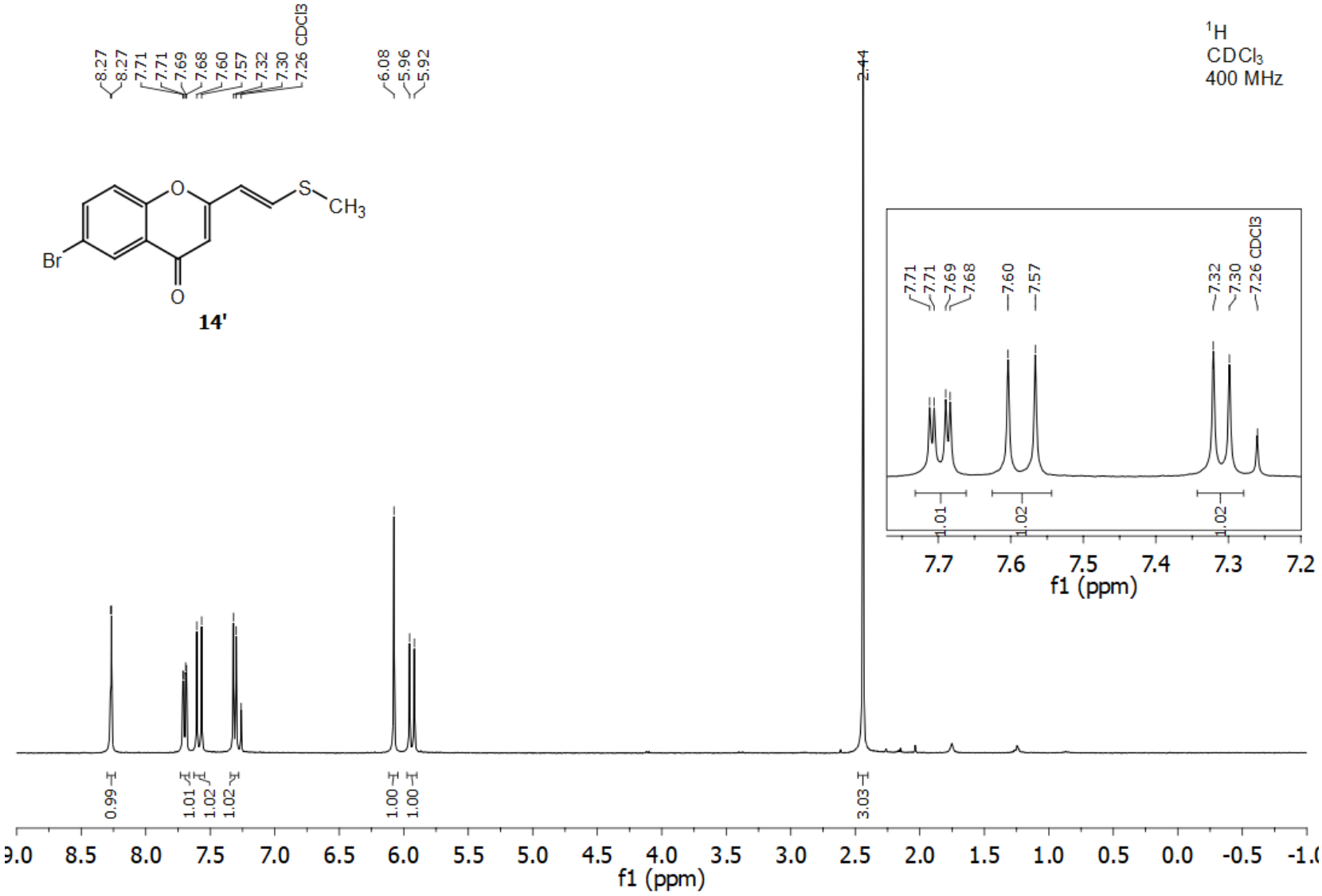

177.28
161.12
154.27
139.09
133.73
130.91
125.26
125.07
119.43
114.82
107.62
14.62
13C
CDCl3
100 MHz
O
S
CH3
Cl
O
13'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

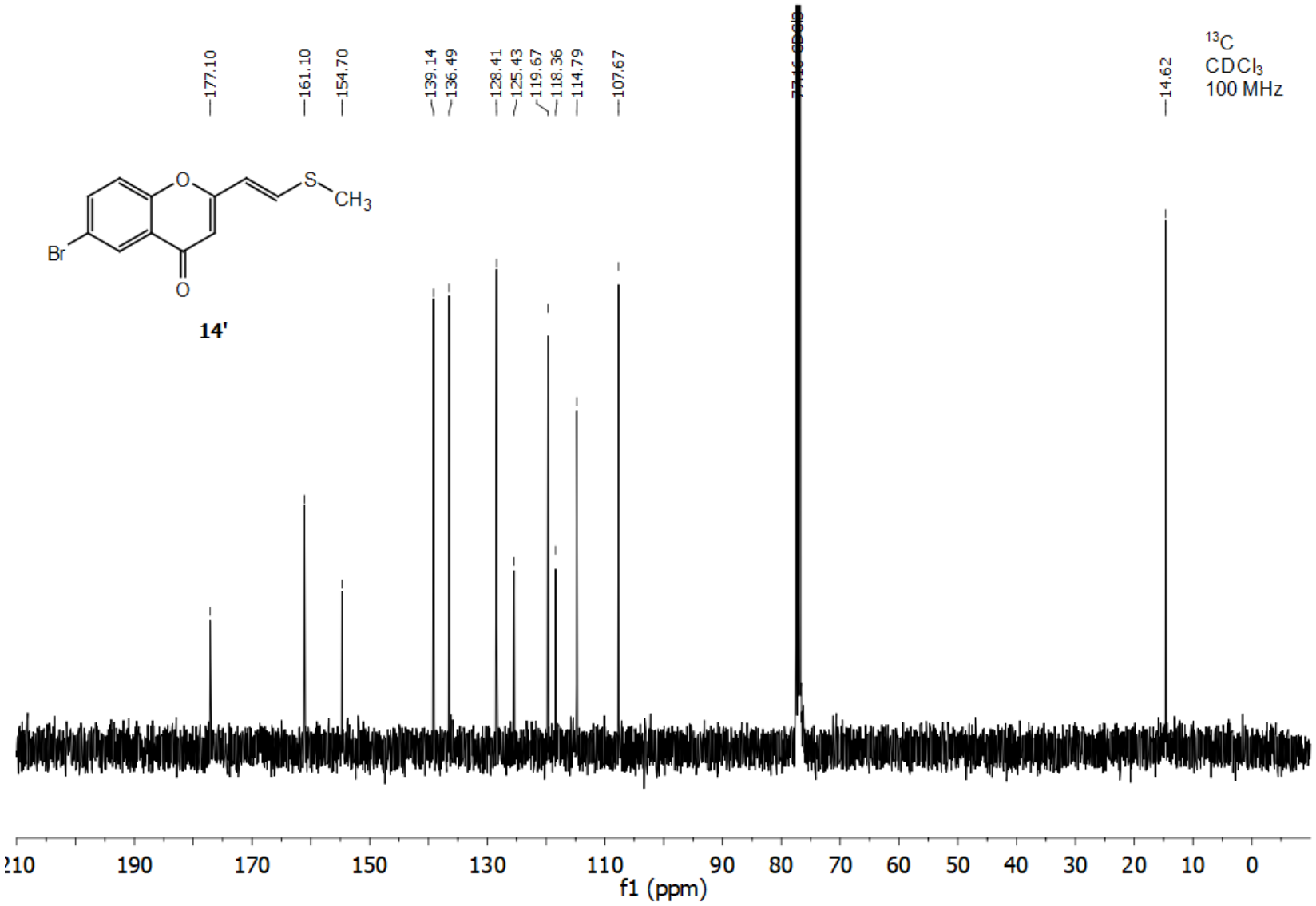

^{1}H
$CDCl_3$
400 MHz
8.08
8.07
7.60
7.59
7.58
7.56
7.52
7.41
7.39
7.02
6.98
6.96
2.76
O
S
CH_3
Cl
O
O
13
7.61
7.60
7.59
7.58
7.56
7.52
7.41
7.39
7.26 CDCl3
1.05
1.07
1.02
7.7
7.6
7.5
7.4
7.3
f1 (ppm)
1.00
1.05
1.07
1.02
0.99
1.00
2.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

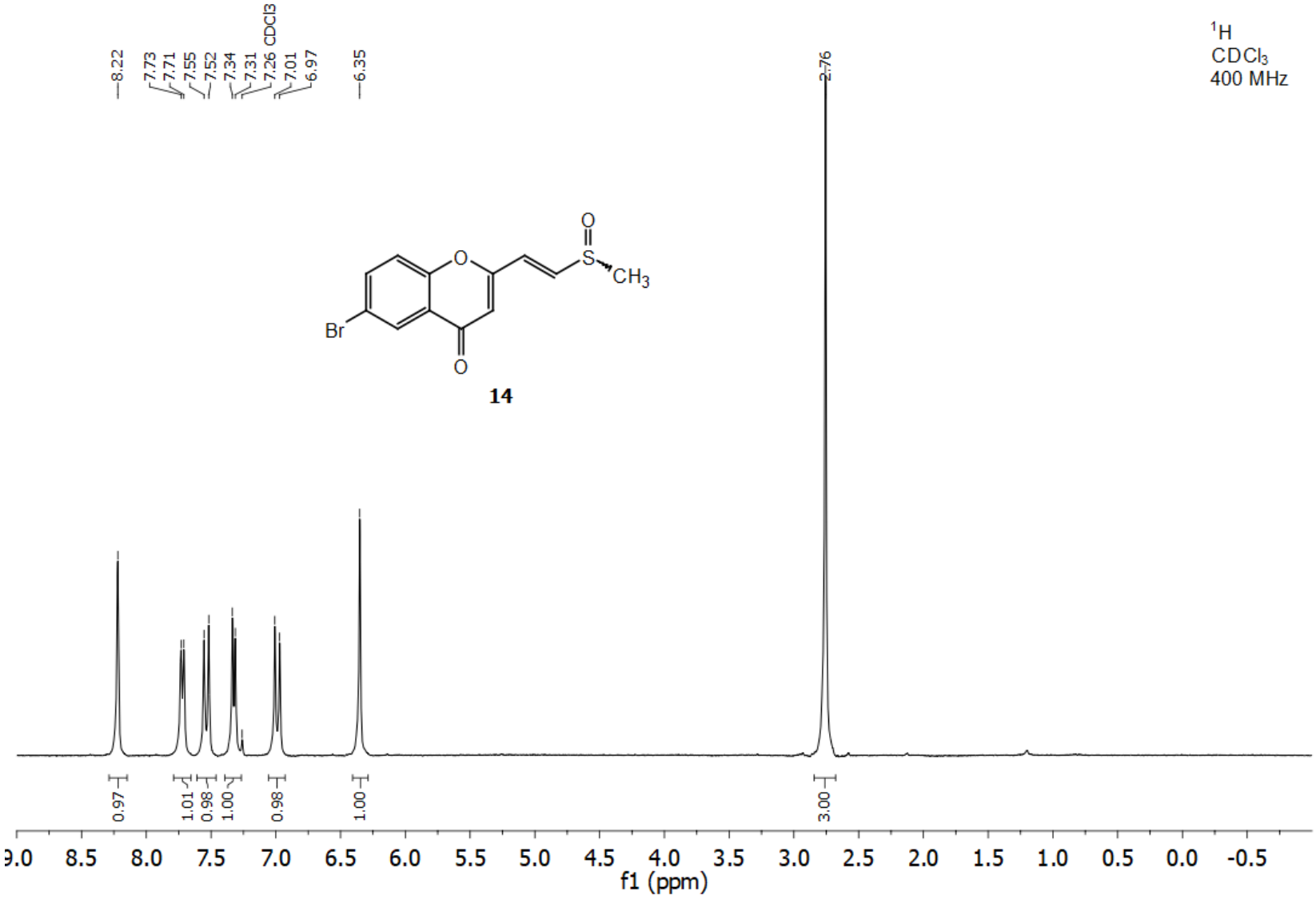

177.12
158.33
154.23
142.44
134.53
131.54
127.00
125.34
124.96
119.69
113.01
77.16 CDCl3
40.38
13C
CDCl3
100 MHz
O
S
CH3
Cl
O
O
13
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

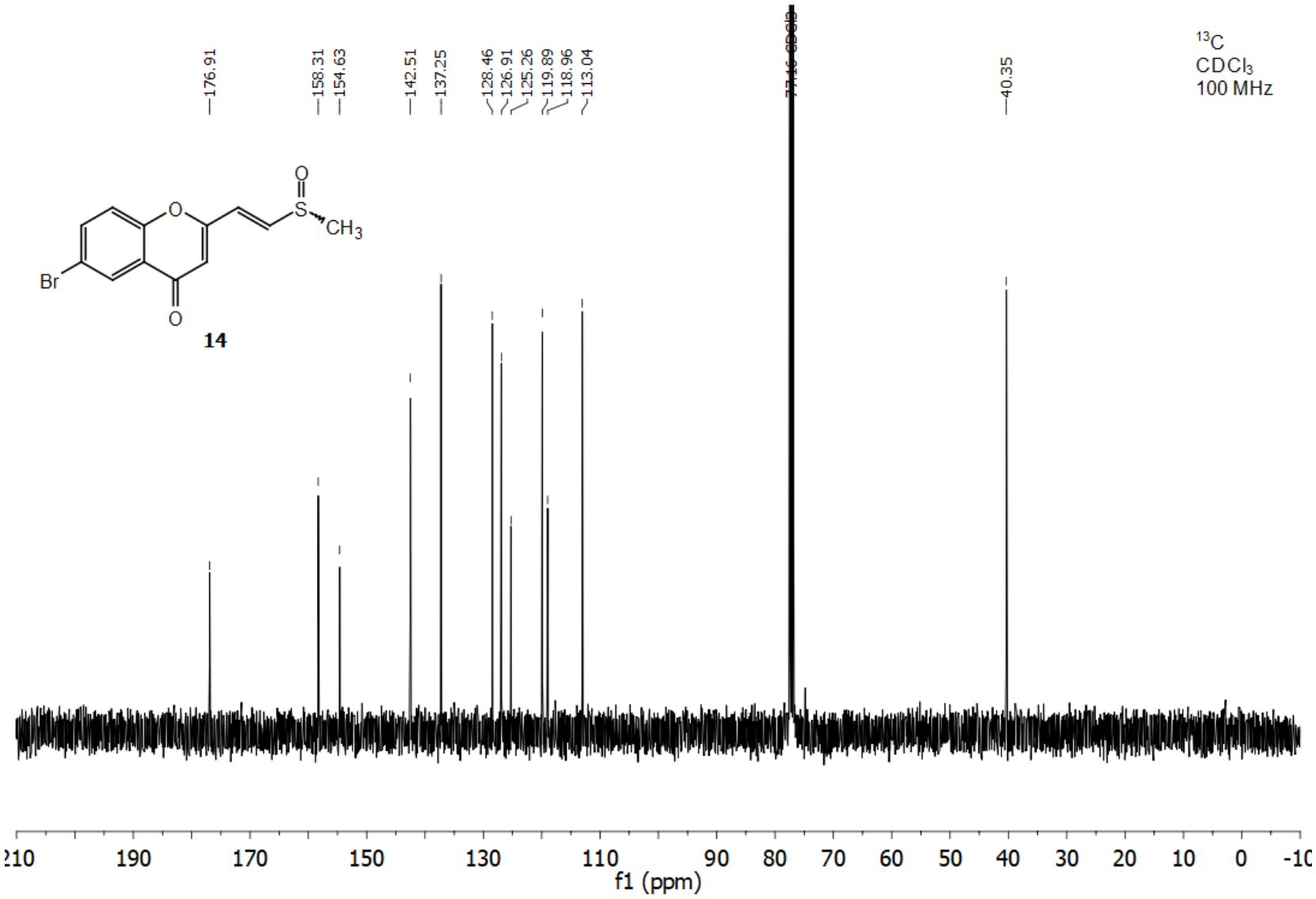

8.02
7.99
7.89
7.88
7.62
7.62
7.60
7.59
7.26 CDCl3
7.03
7.01
5.86
5.83
2.51
2.40
1H
CDCl3
400 MHz
O
O
S
CH3
Br
CH3
O
14"
1.00
1.01
1.01
1.00
0.98
3.01
2.94
f1 (ppm)

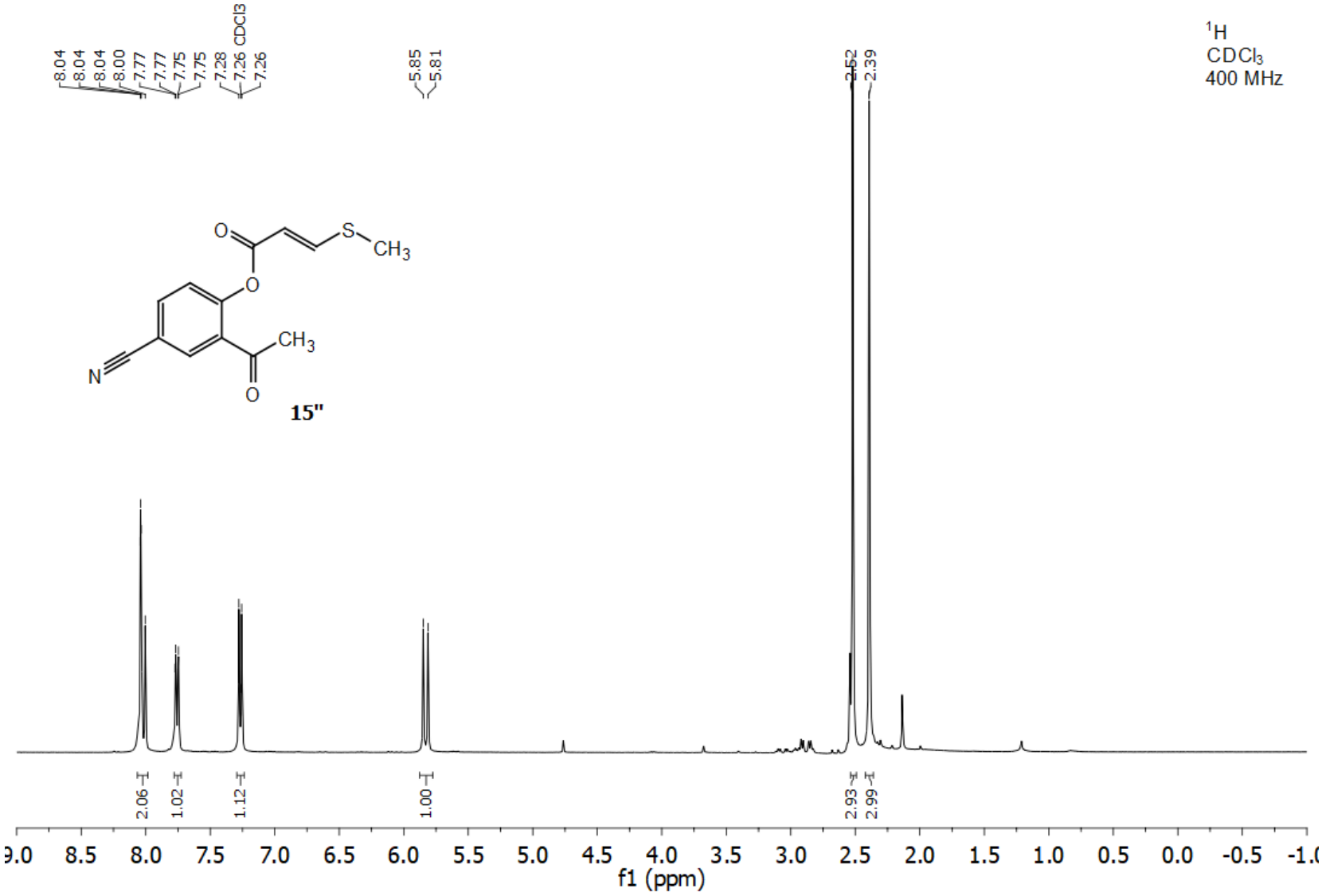

196.46
163.00
151.50
148.18
136.01
133.05
132.76
125.67
119.10
111.16
77.16 CDCl3
29.90
14.61
13C
CDCl3
100 MHz
O
S
CH3
O
Br
CH3
O
14"
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

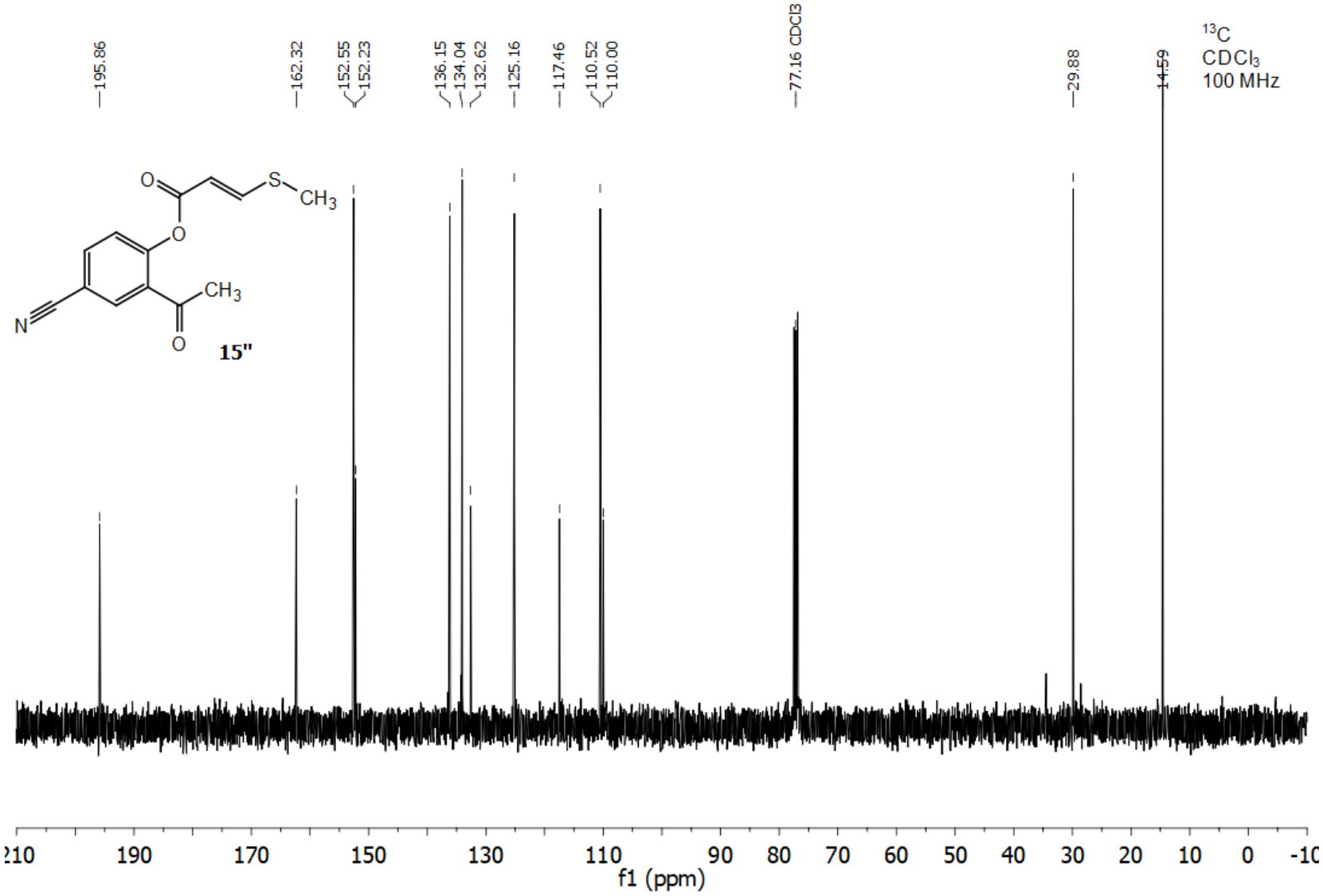

8.27
8.27
7.71
7.71
7.69
7.68
7.60
7.57
7.32
7.30
7.26 CDCl3
6.08
5.96
5.92
2.44
1H
CDCl3
400 MHz
O
S
CH3
Br
O
14'
7.71
7.71
7.69
7.68
7.60
7.57
7.32
7.30
7.26 CDCl3
1.01
1.02
1.02
7.7
7.6
7.5
7.4
7.3
7.2
f1 (ppm)
0.99
1.01
1.02
1.02
1.00
1.00
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

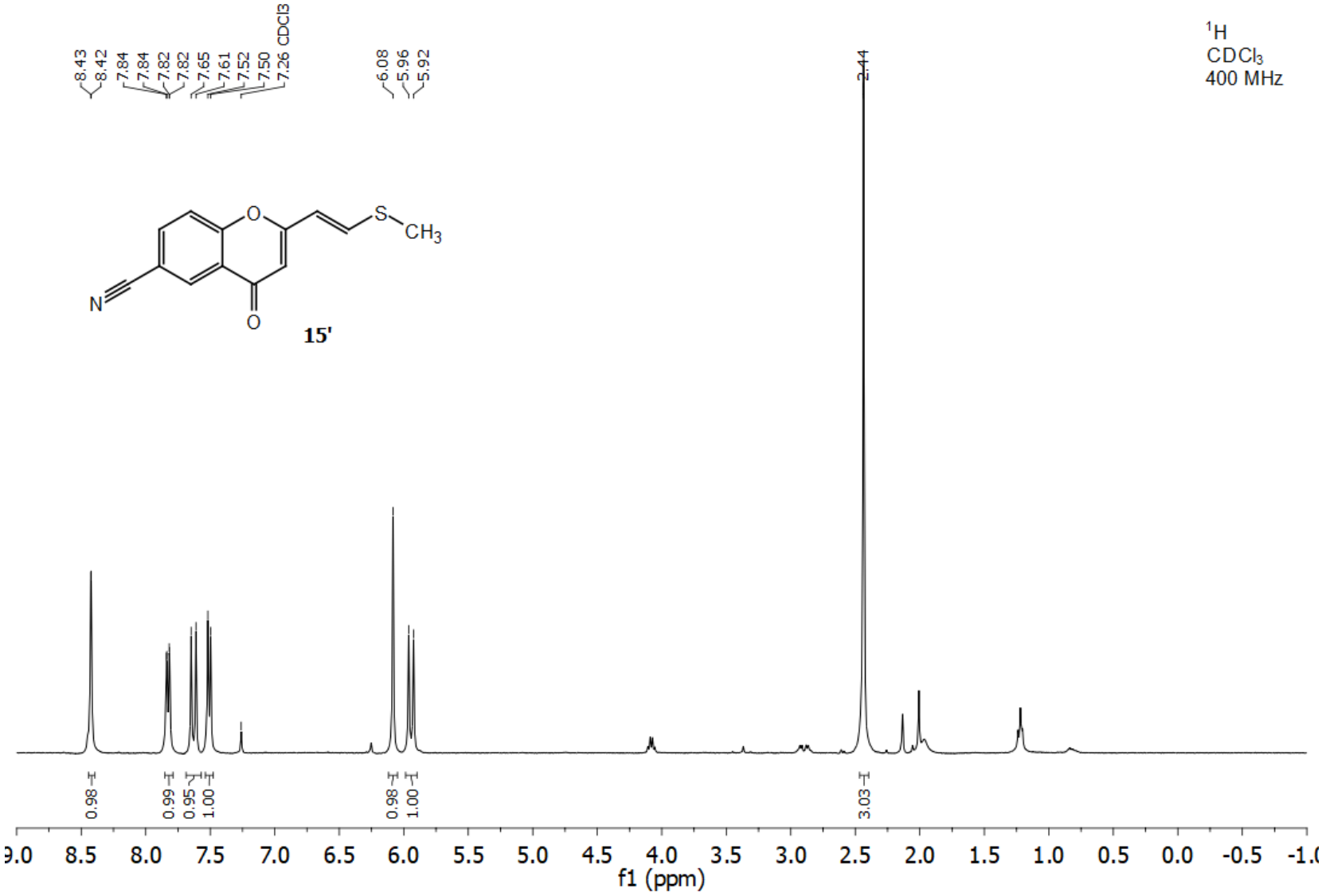

177.10
161.10
154.70
139.14
136.49
128.41
125.43
119.67
118.36
114.79
107.67
14.62
13C
CDCl3
100 MHz
O
S
CH3
Br
O
14'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

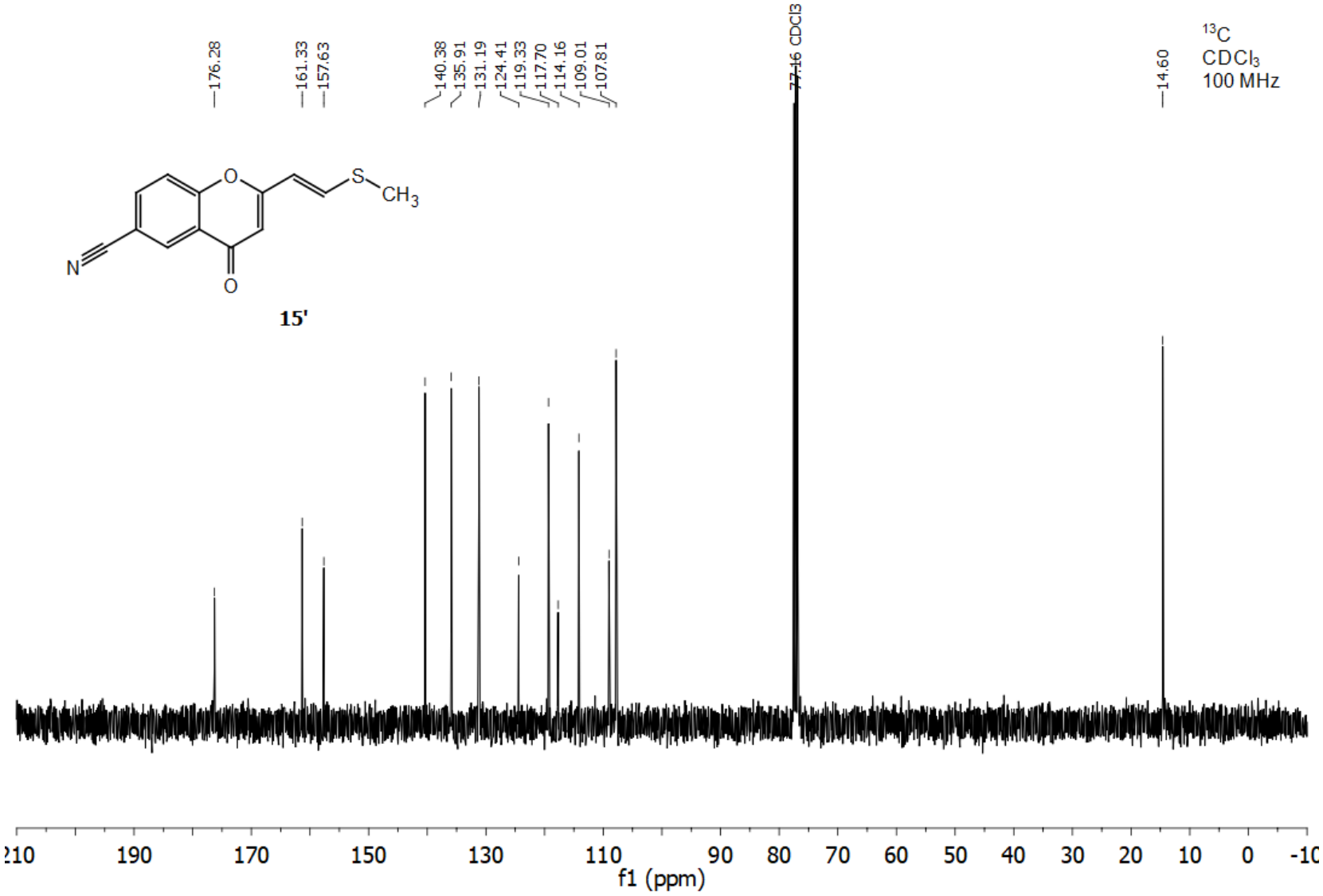

8.22
7.73
7.71
7.55
7.52
7.34
7.31
7.26 CDCl3
7.01
6.97
6.35
2.76
1H
CDCl3
400 MHz
O
S
CH3
Br
O
O
14
0.97
1.01
0.98
1.00
0.98
1.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

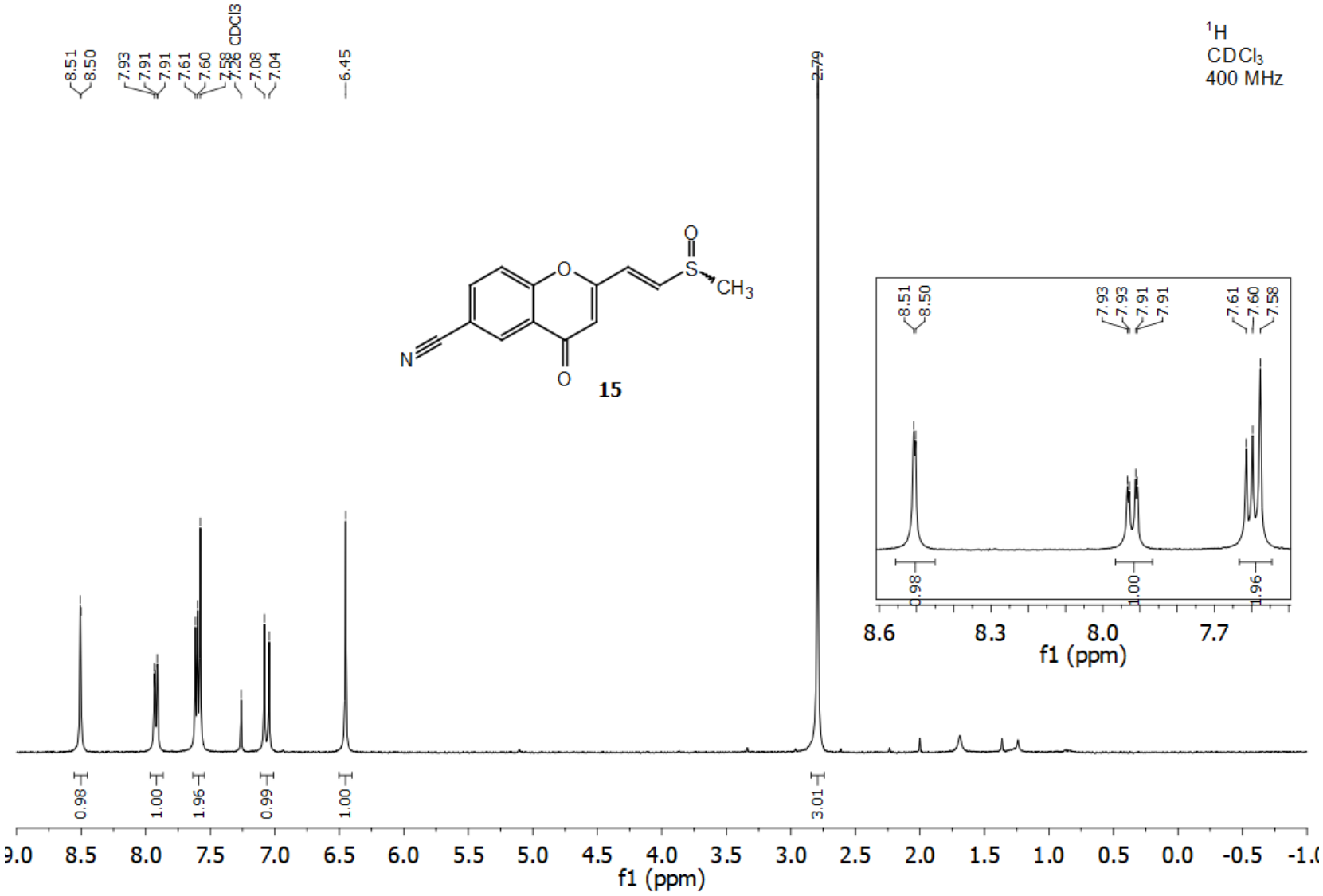

176.91
158.31
154.63
142.51
137.25
128.46
126.91
125.26
119.89
118.96
113.04
77.16 CDCl3
40.35
13C
CDCl3
100 MHz
O
S
CH3
Br
O
O
14
f1 (ppm)

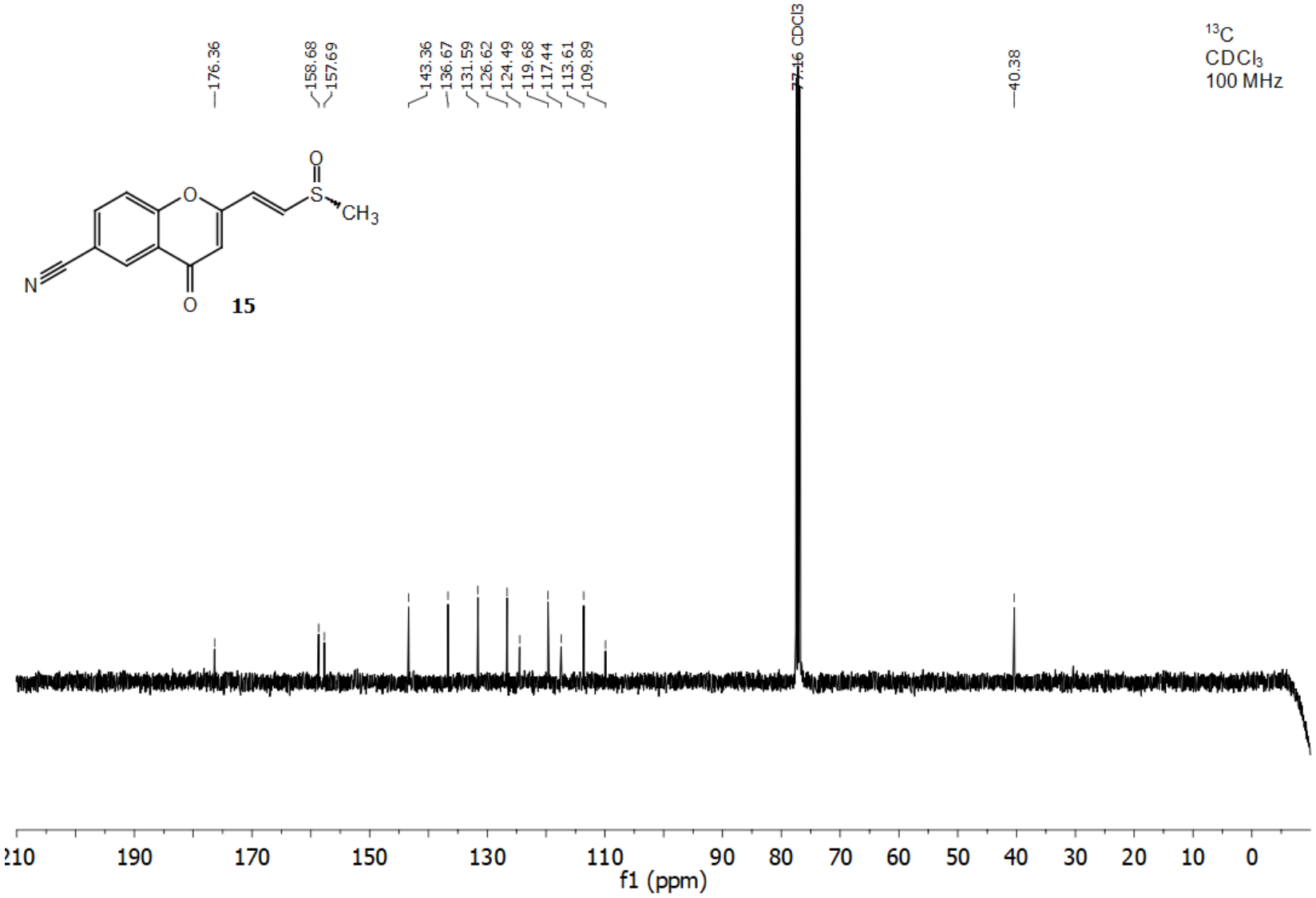

8.04
8.04
8.04
8.00
7.77
7.77
7.75
7.75
7.28
7.26 CDCl3
7.26
5.85
5.81
2.52
2.39
1H
CDCl3
400 MHz
O
S
CH3
O
CH3
N
O
15"
2.06
1.02
1.12
1.00
2.93
2.99
f1 (ppm)

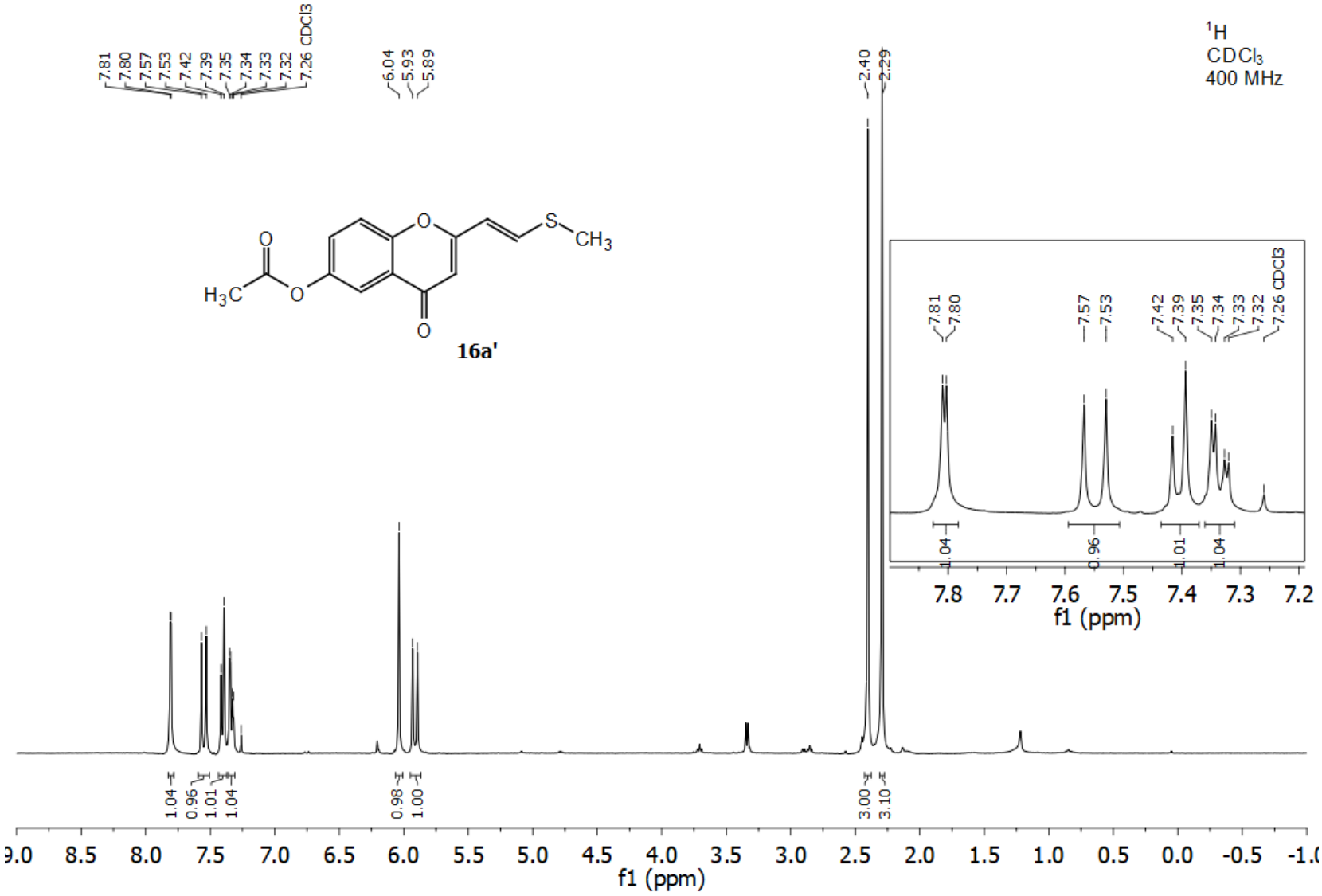

195.86
162.32
152.55
152.23
136.15
134.04
132.62
125.16
117.46
110.52
110.00
77.16 CDCl3
29.88
14.59
13C
CDCl3
100 MHz
O
S
CH3
O
CH3
N
O
15"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

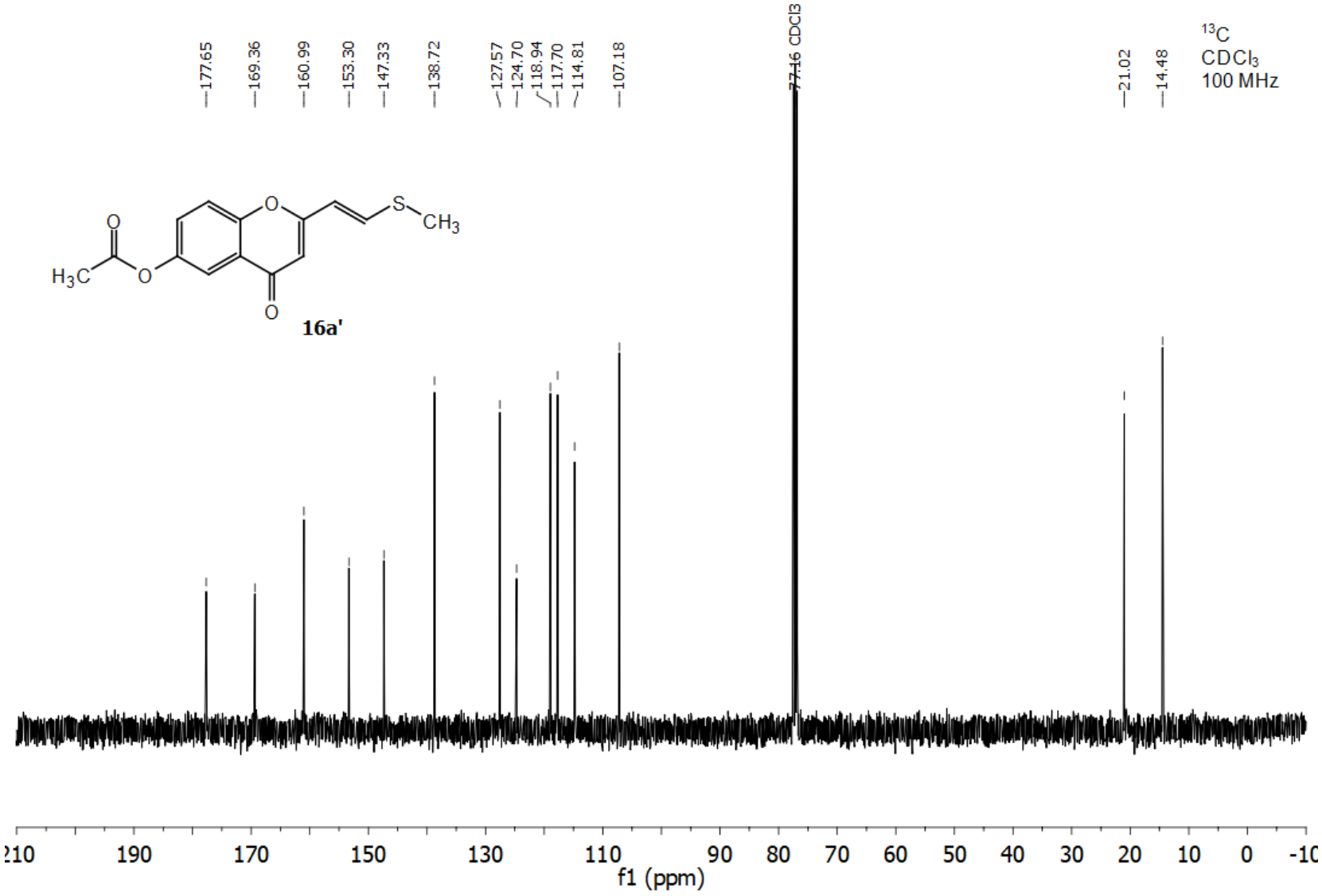

8.43
8.42
7.84
7.84
7.82
7.82
7.65
7.61
7.52
7.50
7.26 CDCl3
6.08
5.96
5.92
2.44
1H
CDCl3
400 MHz
O
S
CH3
N
O
15'
0.98
0.99
0.95
1.00
0.98
1.00
3.03
f1 (ppm)

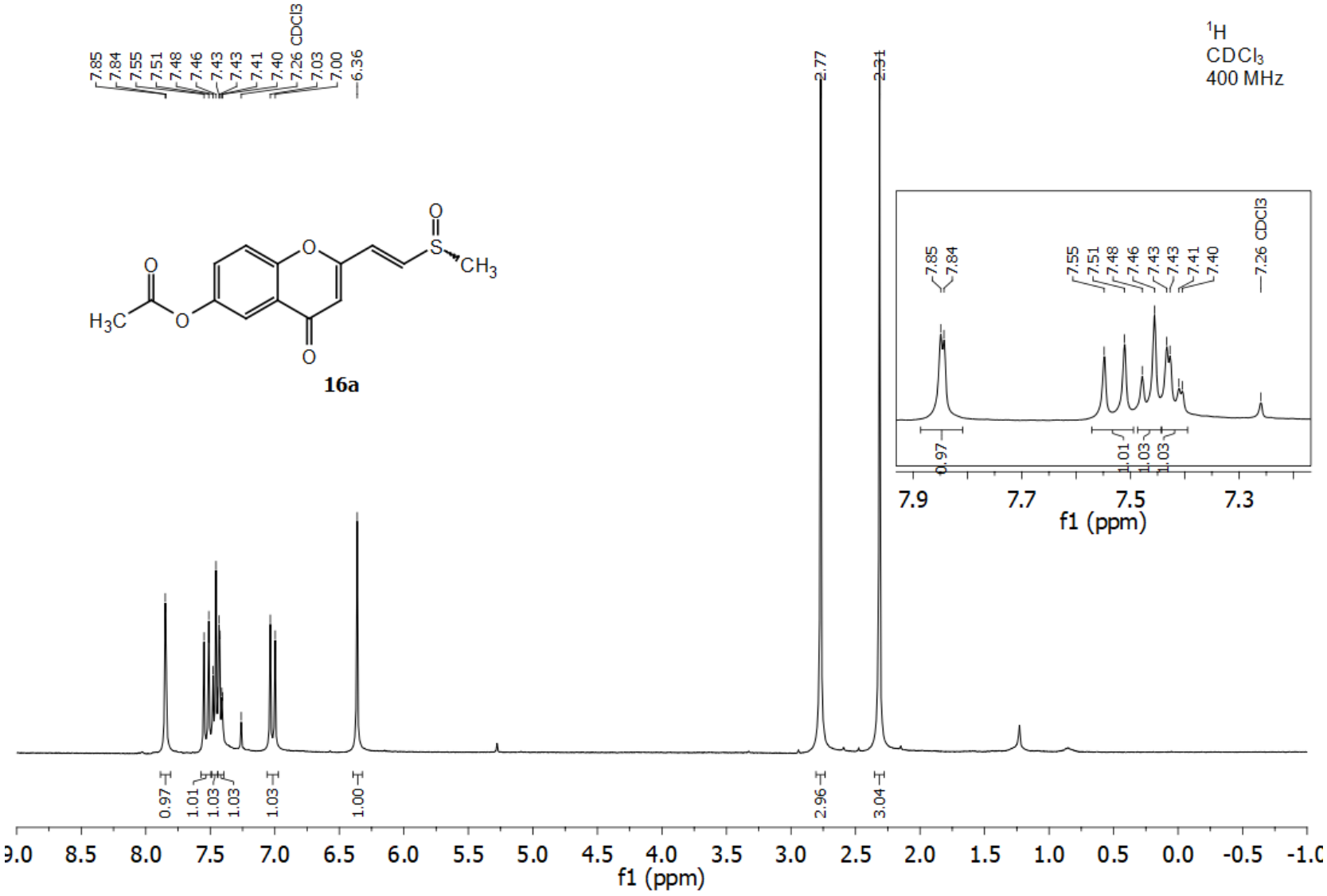

176.28
161.33
157.63
140.38
135.91
131.19
124.41
119.33
117.70
114.16
109.01
107.81
77.16 CDCl3
14.60
13C
CDCl3
100 MHz
O
S
CH3
N
O
15'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

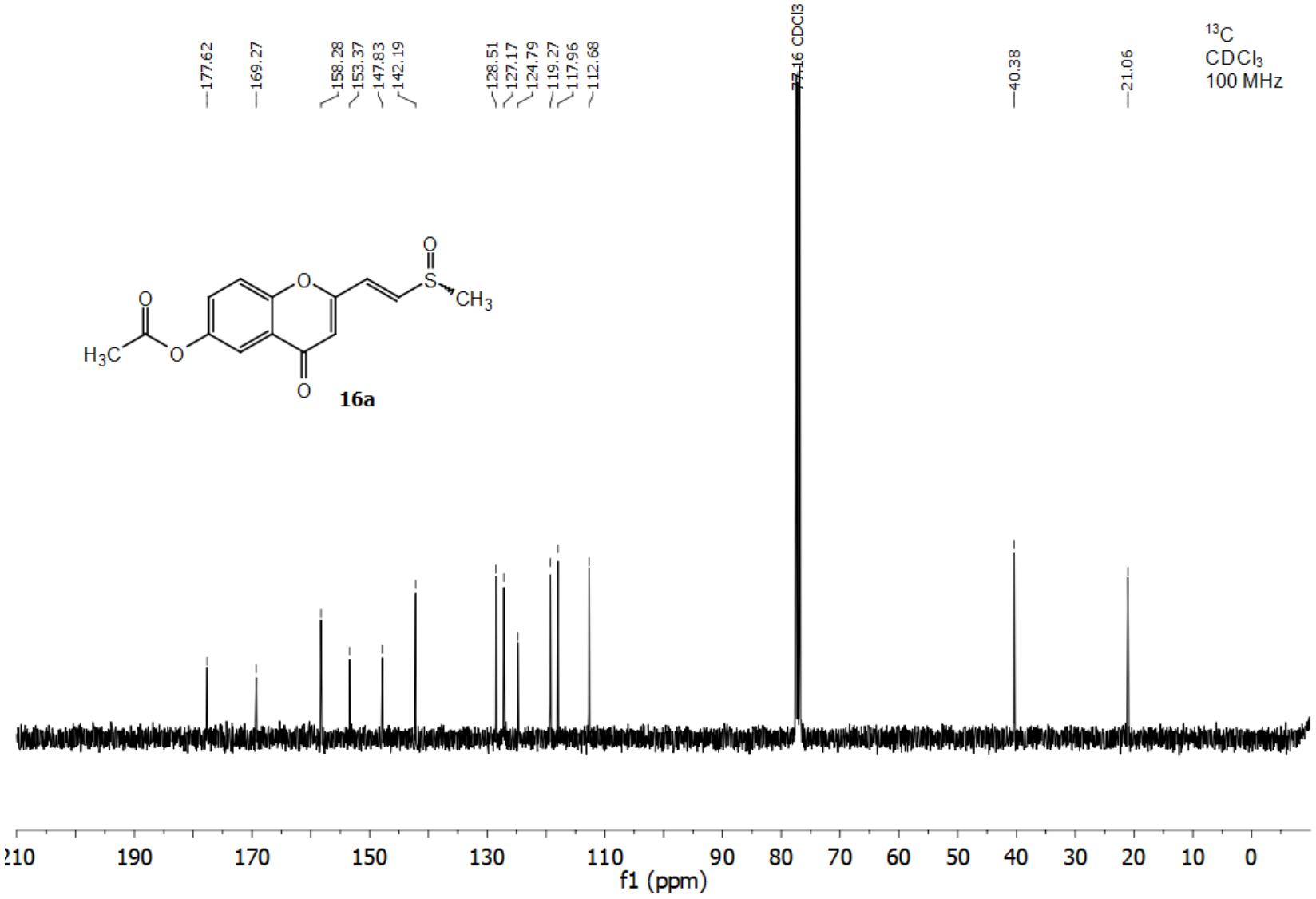

8.51
8.50
7.93
7.91
7.91
7.61
7.60
7.58
CDCl3
7.08
7.04
6.45
2.79
1H
CDCl3
400 MHz
O
S
CH3
N
O
O
15
0.98
1.00
1.96
0.99
1.00
3.01
f1 (ppm)
8.6
8.3
8.0
7.7

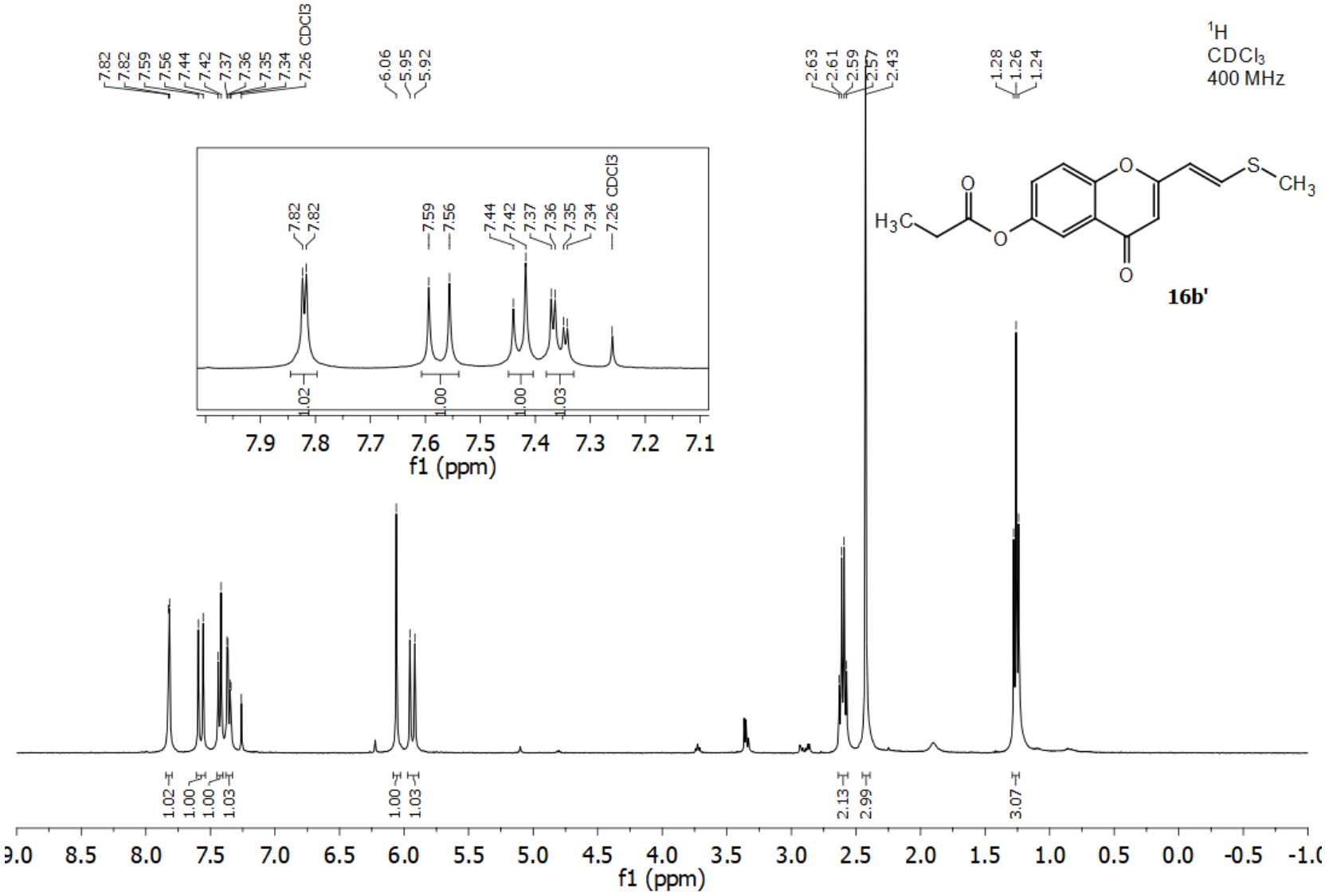

176.36
158.68
157.69
143.36
136.67
131.59
126.62
124.49
119.68
117.44
113.61
109.89
77.16 CDCl3
40.38
13C
CDCl3
100 MHz
O
S
CH3
N
O
O
15
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

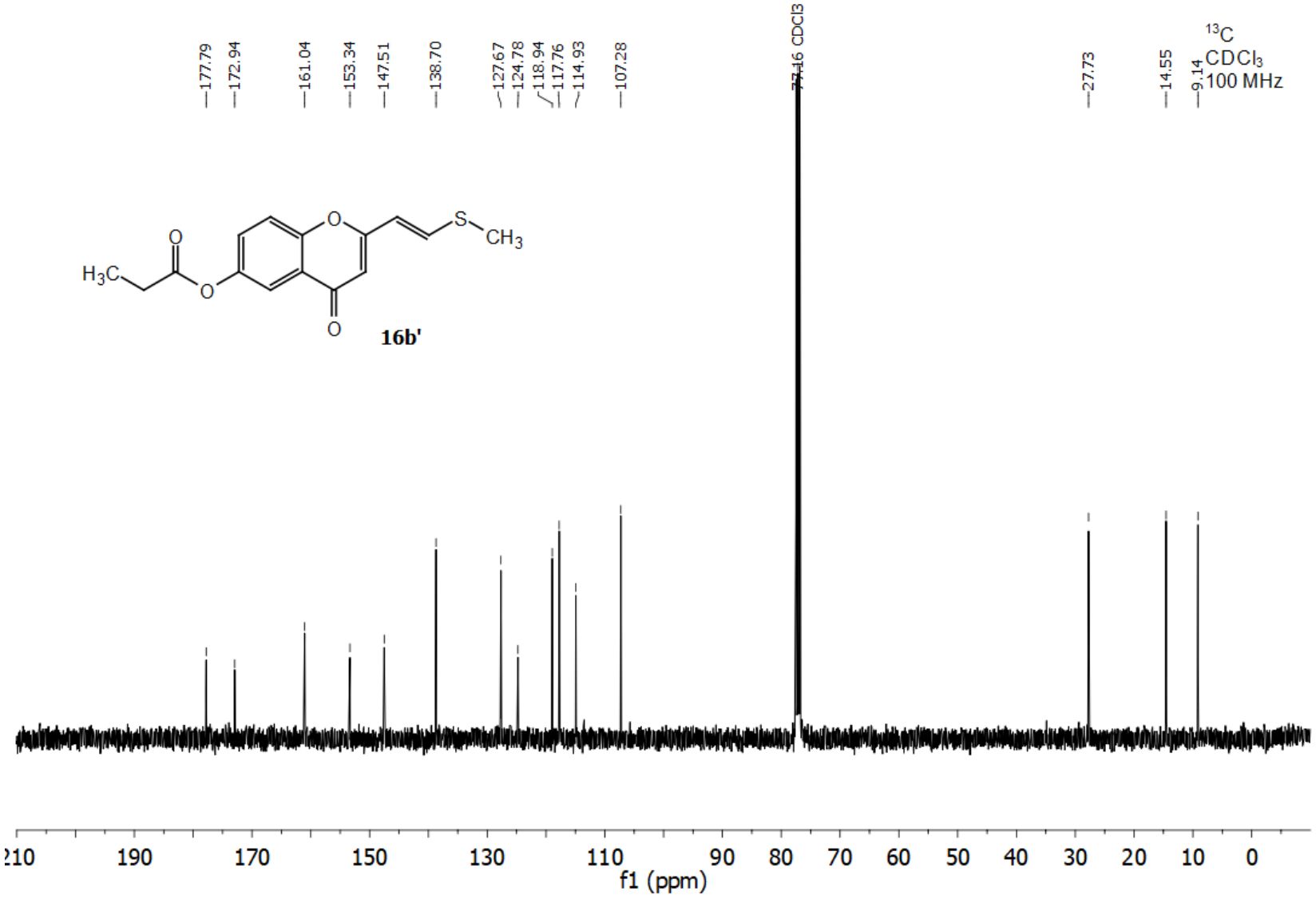

7.81
7.80
7.57
7.53
7.42
7.39
7.35
7.34
7.33
7.32
7.26 CDCl3
6.04
5.93
5.89
2.40
2.29
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
O
O
16a'
1.04
0.96
1.01
1.04
0.98
1.00
3.00
3.10
f1 (ppm)

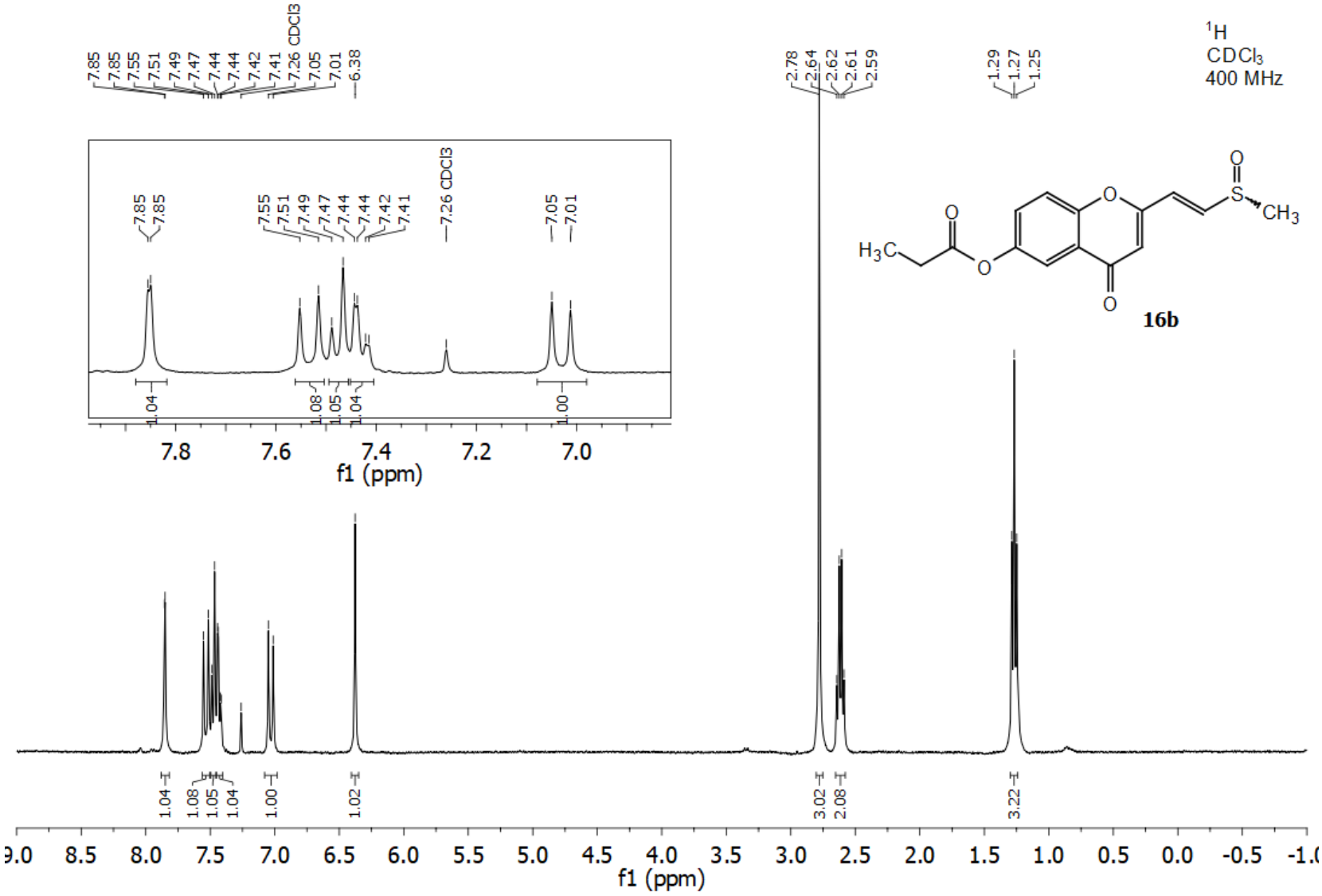

177.65
169.36
160.99
153.30
147.33
138.72
127.57
124.70
118.94
117.70
114.81
107.18
77.16 CDCl3
21.02
14.48
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
16a'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

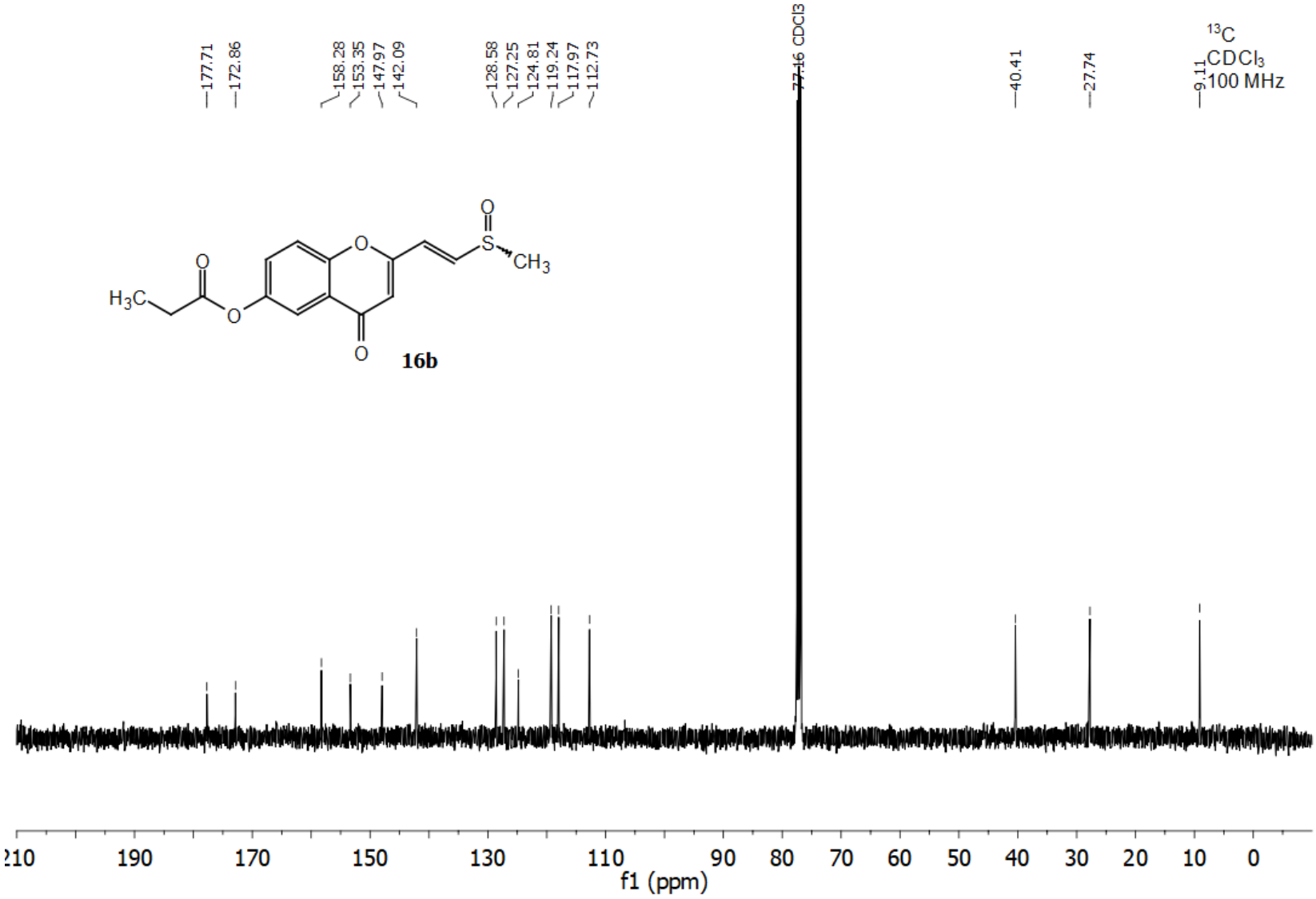

7.85
7.84
7.55
7.51
7.48
7.46
7.43
7.43
7.41
7.40
7.26 CDCl3
7.03
7.00
6.36
2.77
2.31
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
O
O
O
16a
0.97
1.01
1.03
1.03
1.03
1.00
2.96
3.04
f1 (ppm)

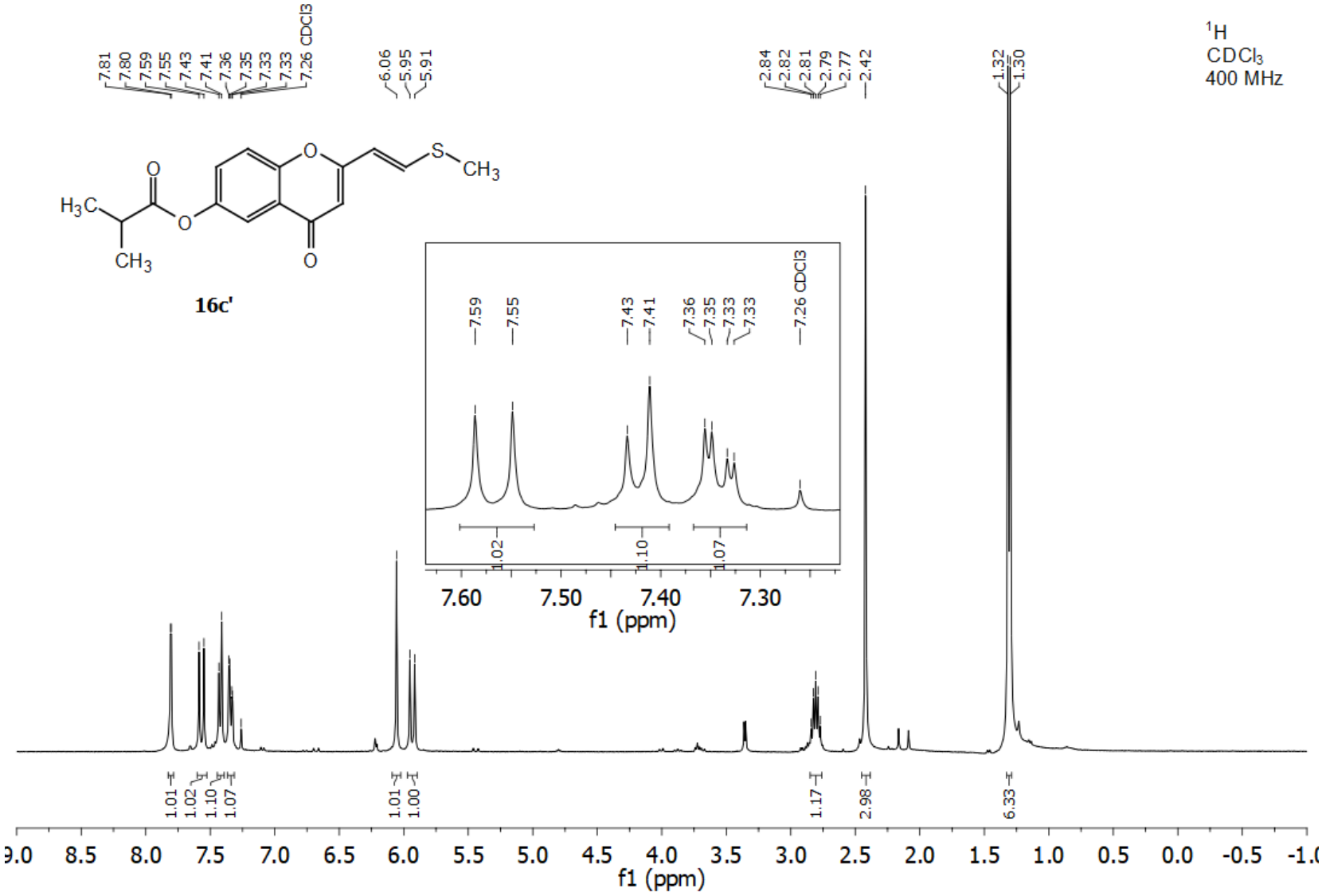

177.62
169.27
158.28
153.37
147.83
142.19
128.51
127.17
124.79
119.27
117.96
112.68
77.16 CDCl3
40.38
21.06
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
O
16a
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

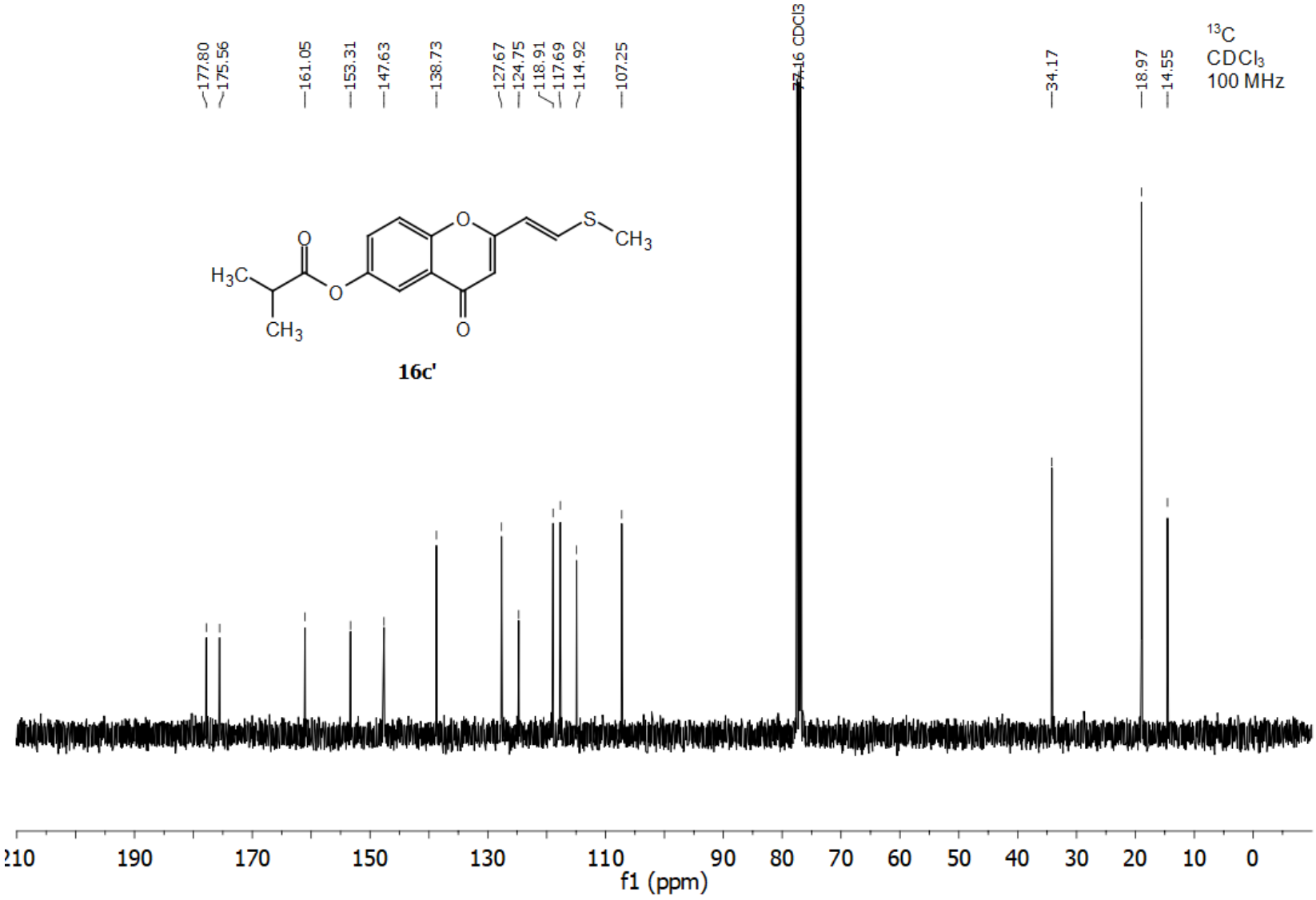

1H
CDCl3
400 MHz
16b'
f1 (ppm)

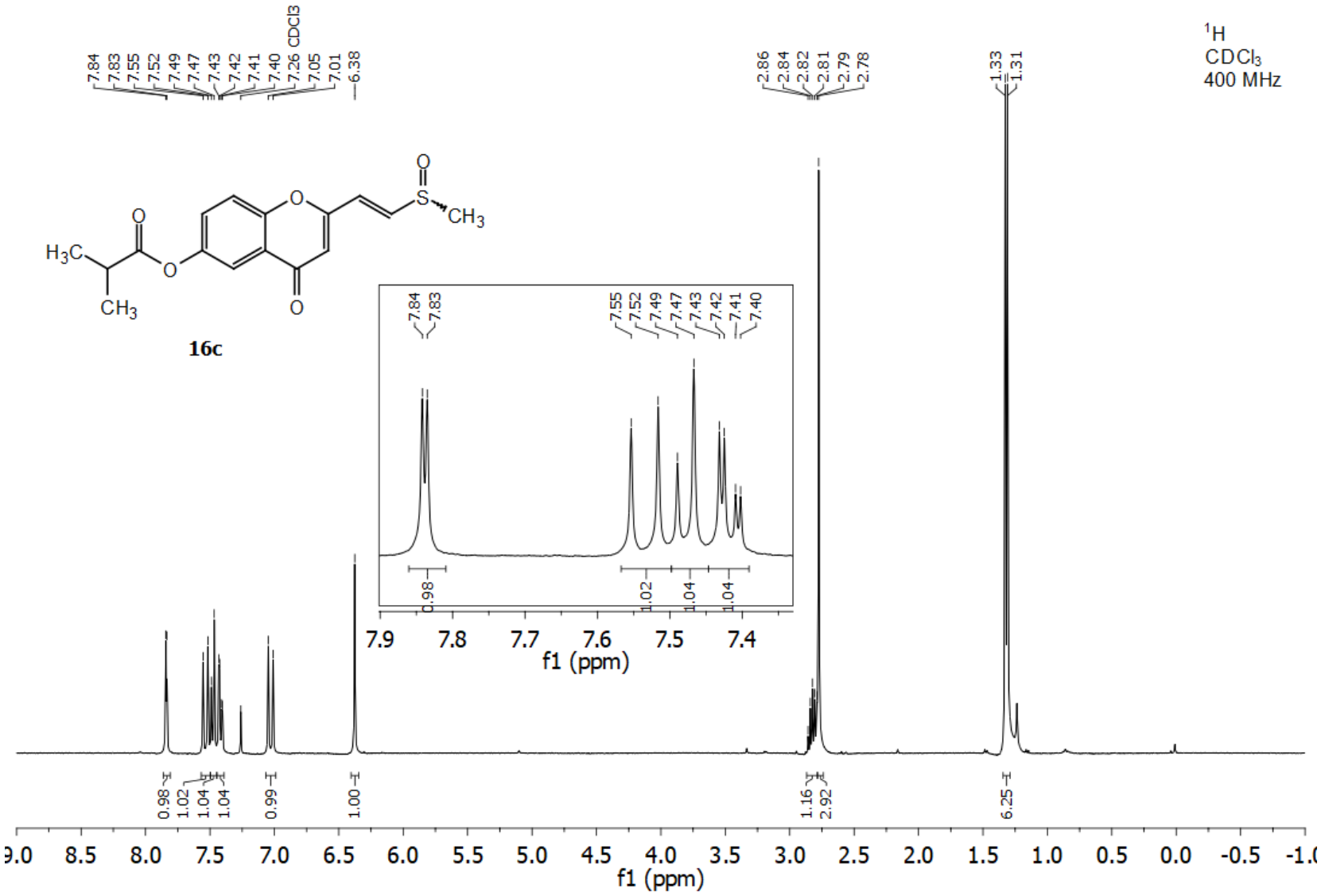

177.79
172.94
161.04
153.34
147.51
138.70
127.67
124.78
118.94
117.76
114.93
107.28
77.16 CDCl3
27.73
14.55
9.14
13C
CDCl3
100 MHz
O
H3C
O
O
O
S
CH3
16b'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

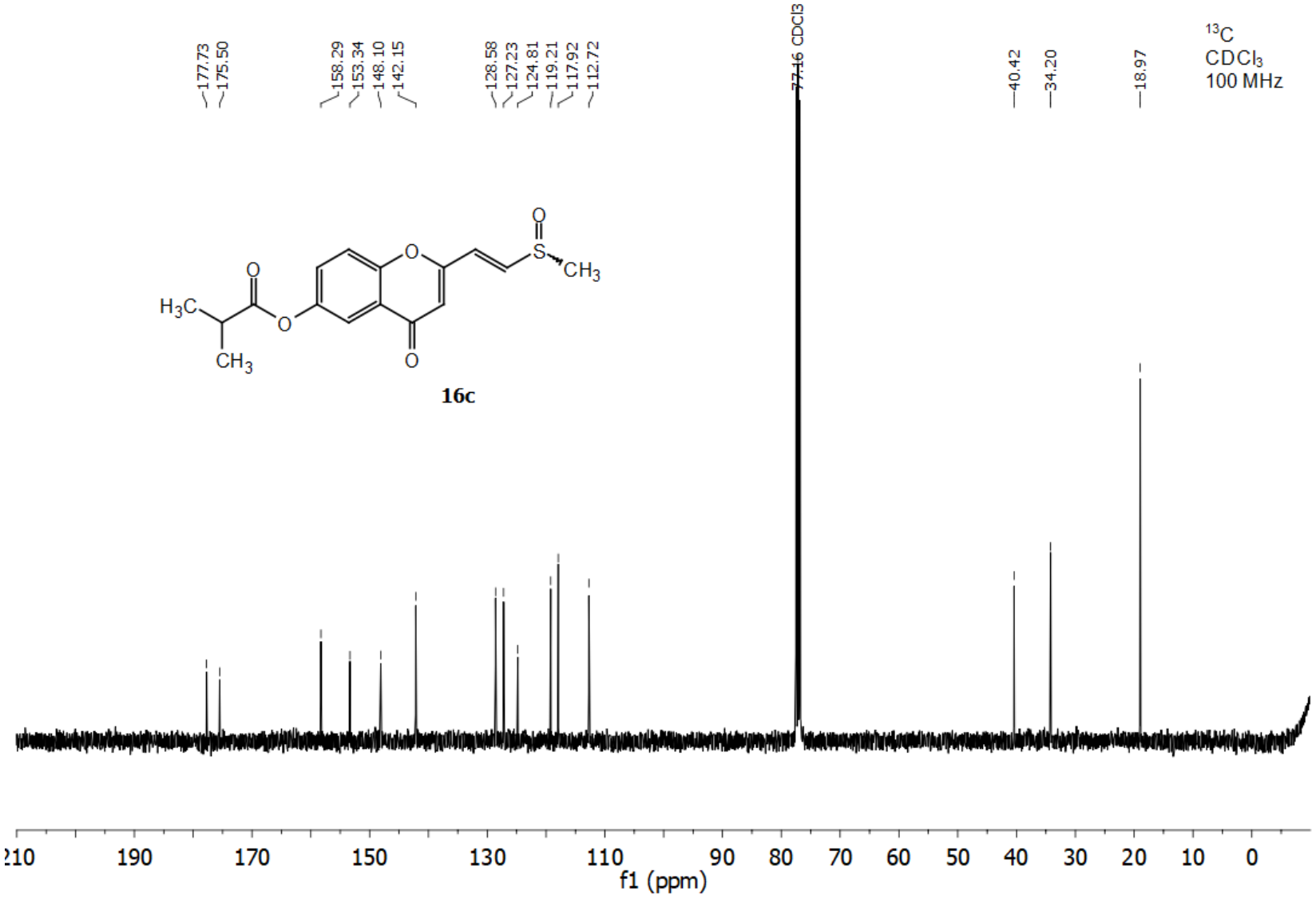

^{1}H
$CDCl_3$
400 MHz
16b
f1 (ppm)


177.71
172.86
158.28
153.35
147.97
142.09
128.58
127.25
124.81
119.24
117.97
112.73
77.16 CDCl3
40.41
27.74
9.11
13C
CDCl3
100 MHz
H3C
O
O
O
O
O
S
CH3
16b
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.81
7.80
7.59
7.55
7.43
7.41
7.36
7.35
7.33
7.33
7.26 CDCl3
6.06
5.95
5.91
2.84
2.82
2.81
2.79
2.77
2.42
1.32
1.30
1H
CDCl3
400 MHz
O
O
O
O
S
CH3
H3C
CH3
16c'
7.59
7.55
7.43
7.41
7.36
7.35
7.33
7.33
7.26 CDCl3
1.02
1.10
1.07
7.60
7.50
7.40
7.30
f1 (ppm)
1.01
1.02
1.10
1.07
1.01
1.00
1.17
2.98
6.33
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


177.80
175.56
161.05
153.31
147.63
138.73
127.67
124.75
118.91
117.69
114.92
107.25
77.16 CDCl3
34.17
18.97
14.55
13C
CDCl3
100 MHz
O
O
H3C
CH3
O
O
S
CH3
16c'
f1 (ppm)


7.84
7.83
7.55
7.52
7.49
7.47
7.43
7.42
7.41
7.40
7.26 CDCl3
7.05
7.01
6.38
2.86
2.84
2.82
2.81
2.79
2.78
1.33
1.31
1H
CDCl3
400 MHz
H3C
CH3
O
O
O
O
S
CH3
16c
0.98
1.02
1.04
1.04
0.99
1.00
1.16
2.92
6.25
f1 (ppm)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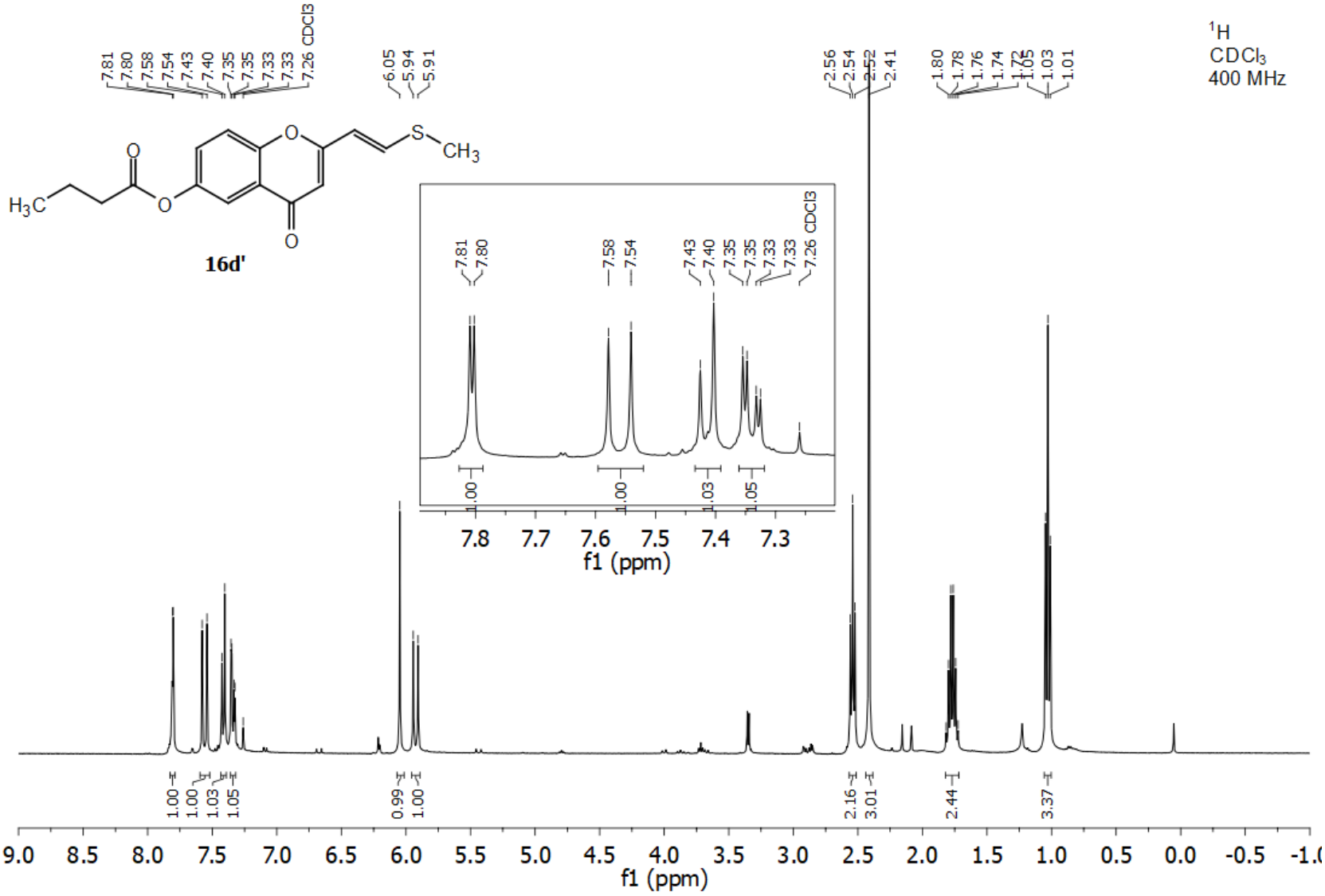
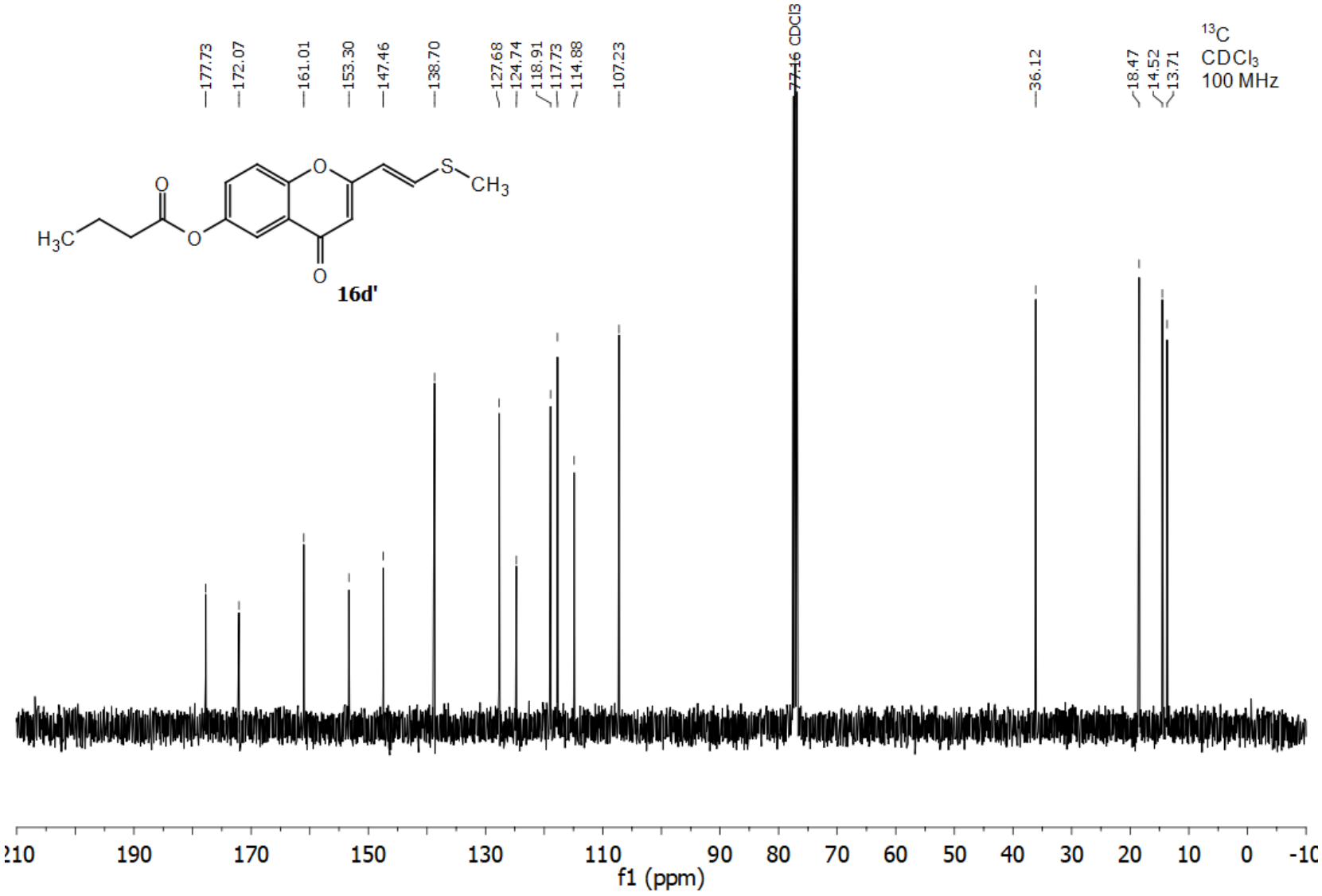
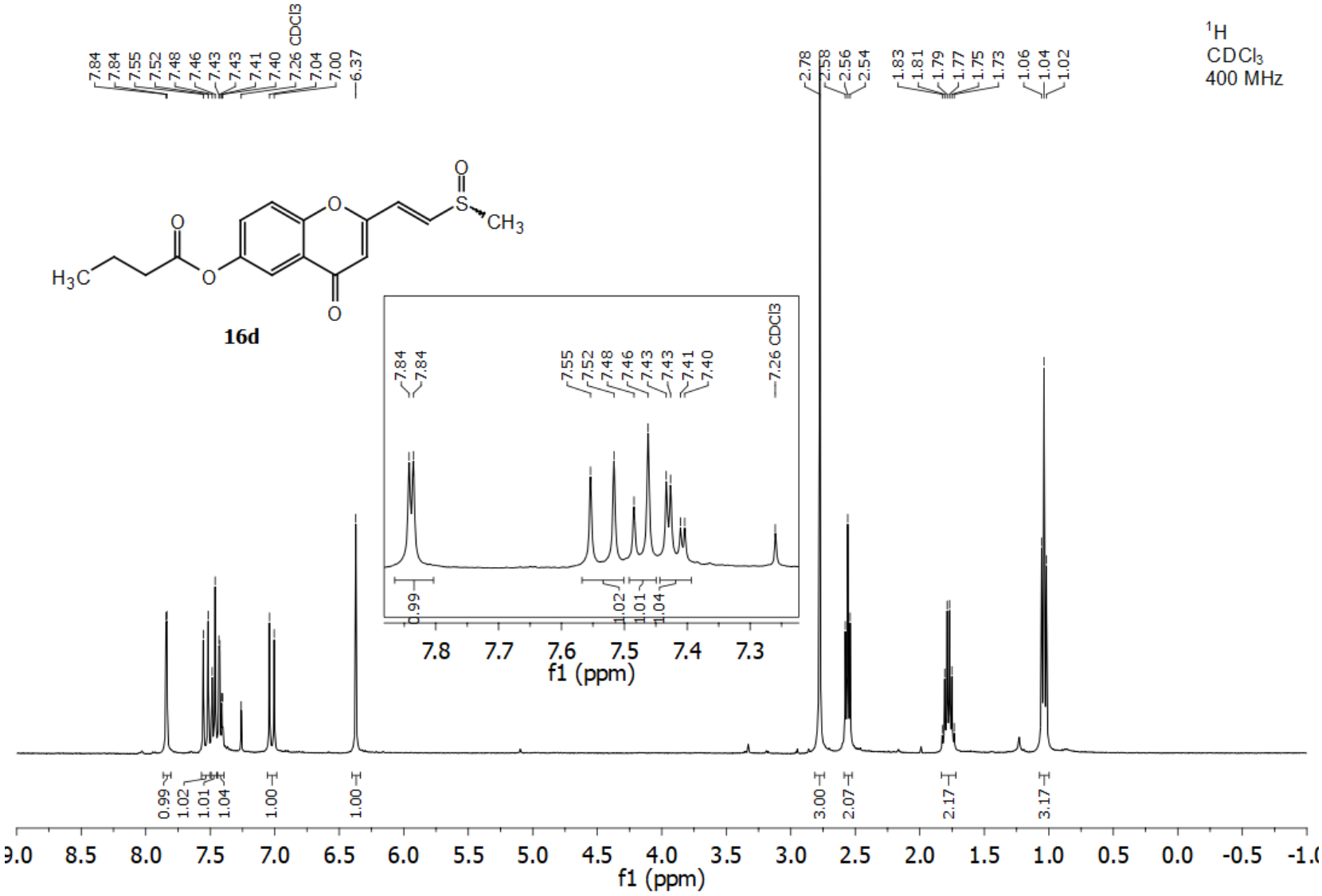
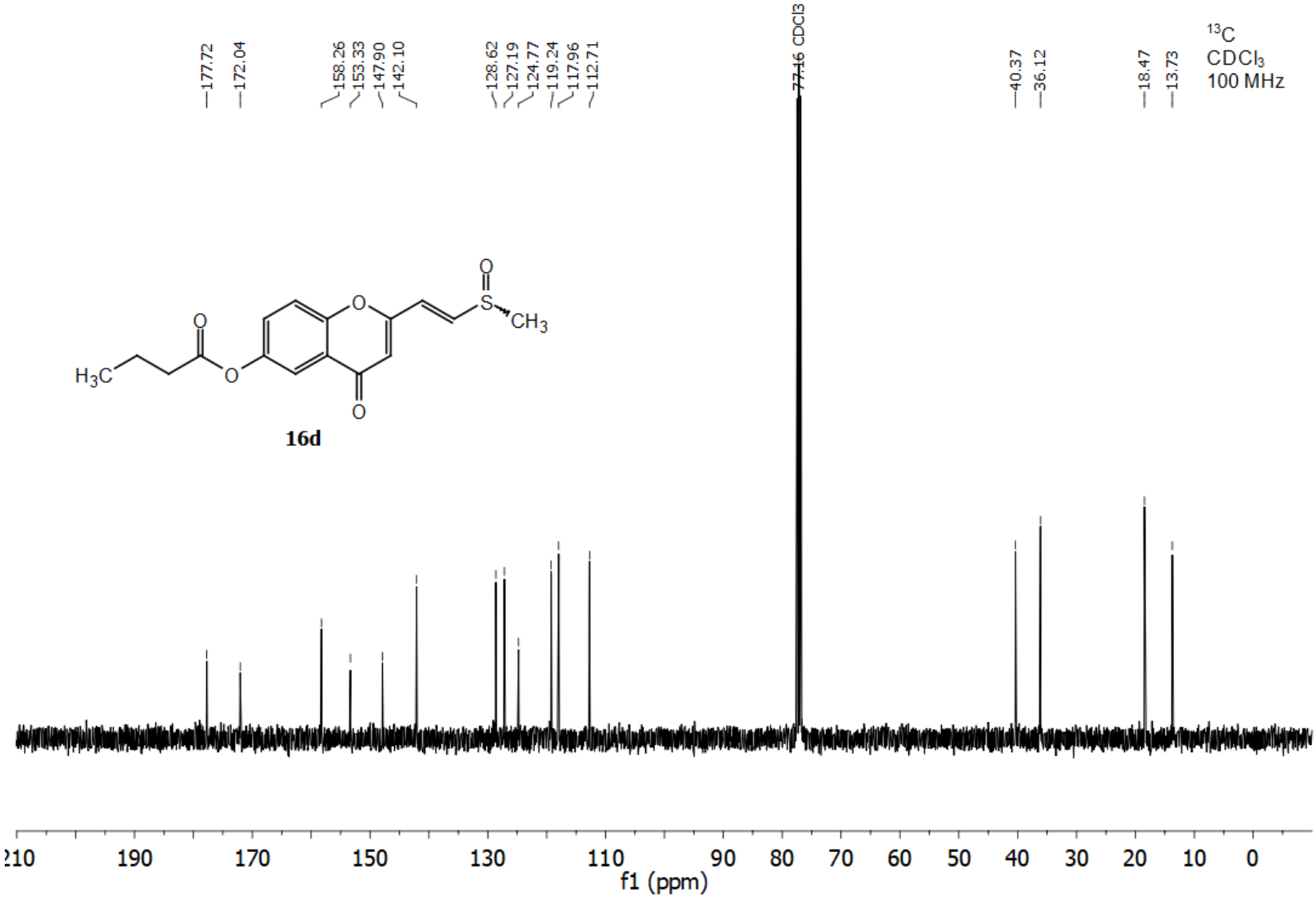
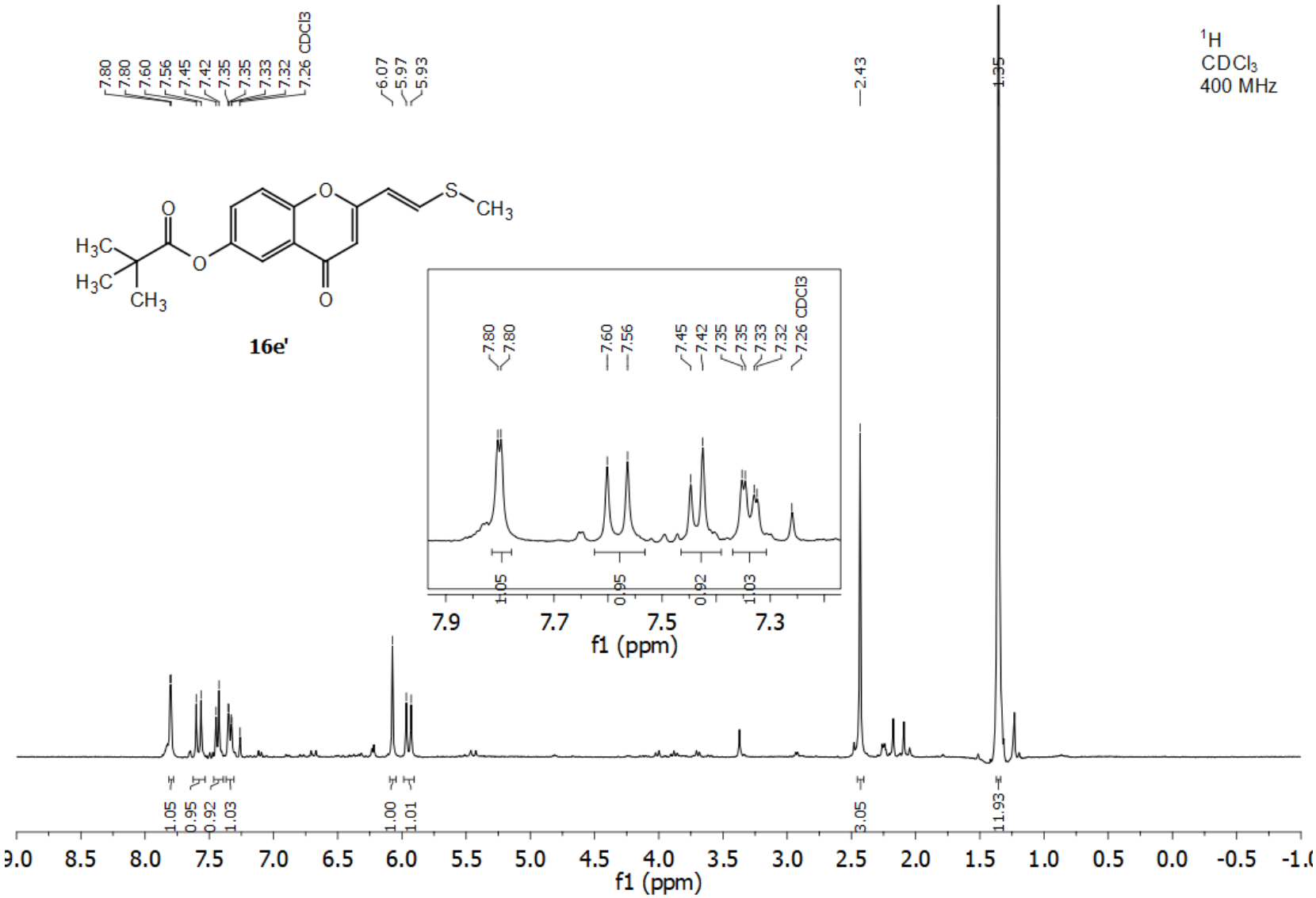
175.50
158.29
153.34
148.10
142.15
128.58
127.23
124.81
119.21
117.92
112.72
77.16 CDCl3
40.42
34.20
18.97
13C
CDCl3
100 MHz
O
S
CH3
H3C
CH3
O
O
O
O
16c
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

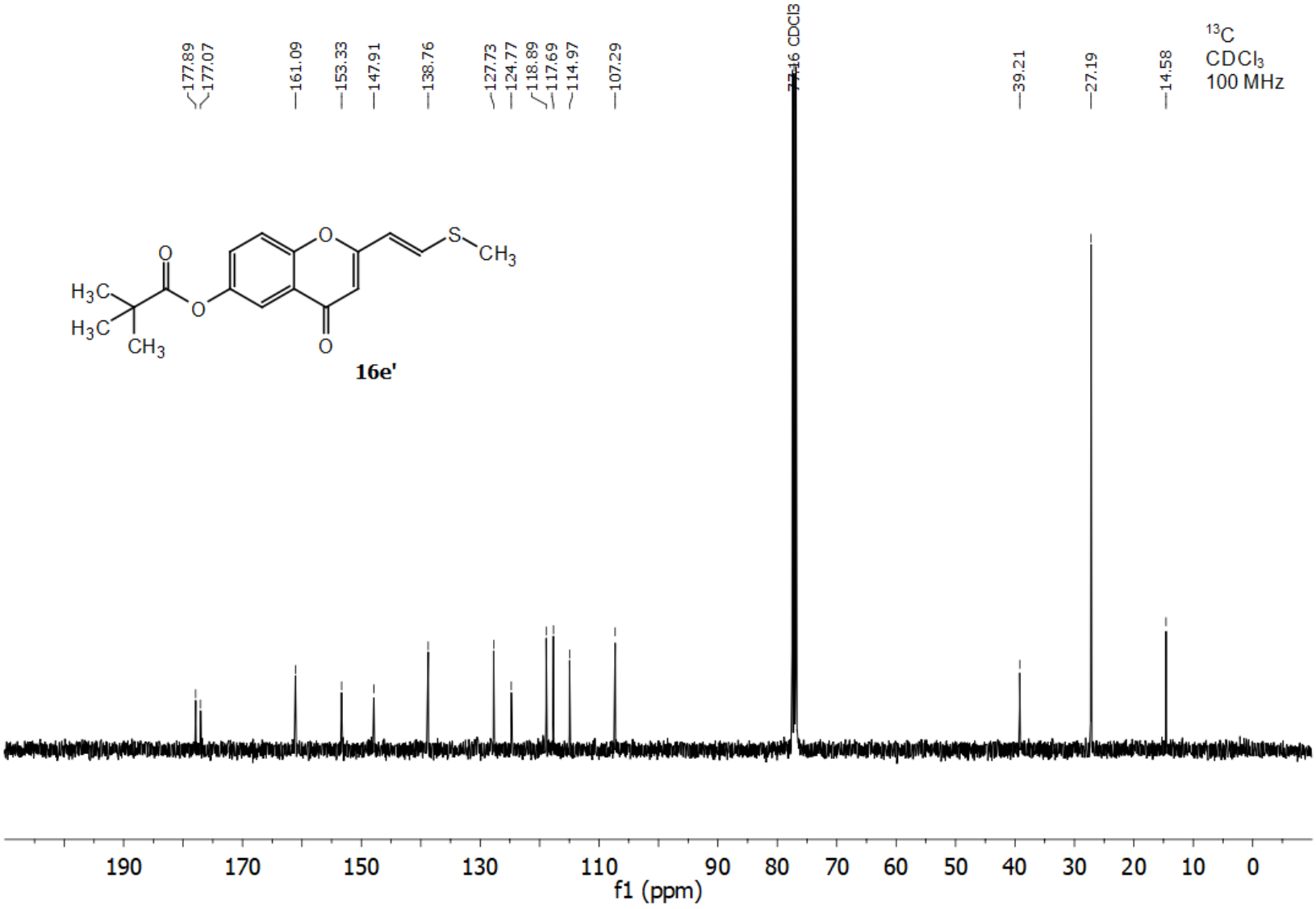

16d'
^{1}H
CDCl$_3$
400 MHz
f1 (ppm)

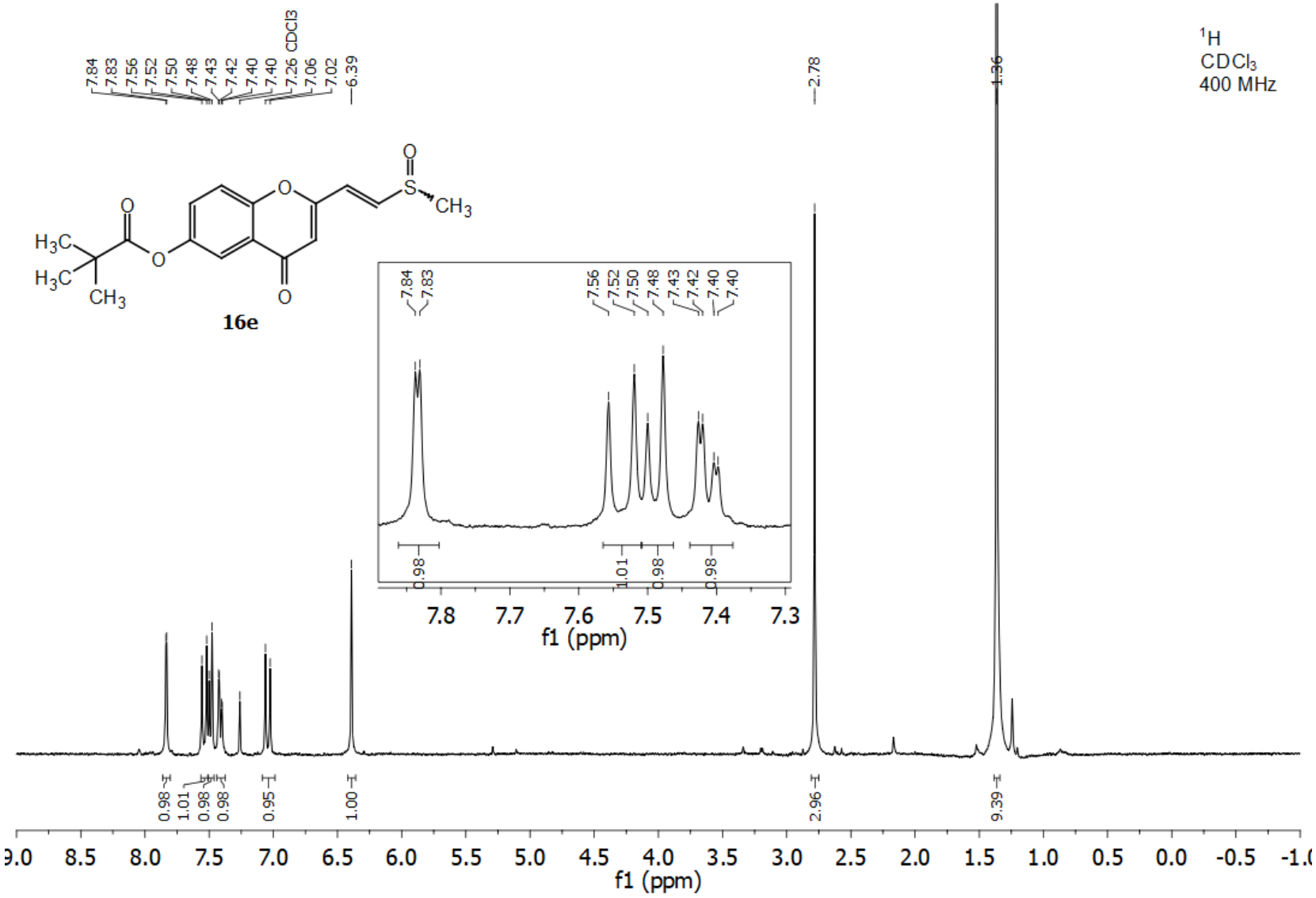

177.73
172.07
161.01
153.30
147.46
138.70
127.68
124.74
118.91
117.73
114.88
107.23
77.16 CDCl3
36.12
18.47
14.52
13.71
13C
CDCl3
100 MHz
O
O
O
O
S
CH3
H3C
16d'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

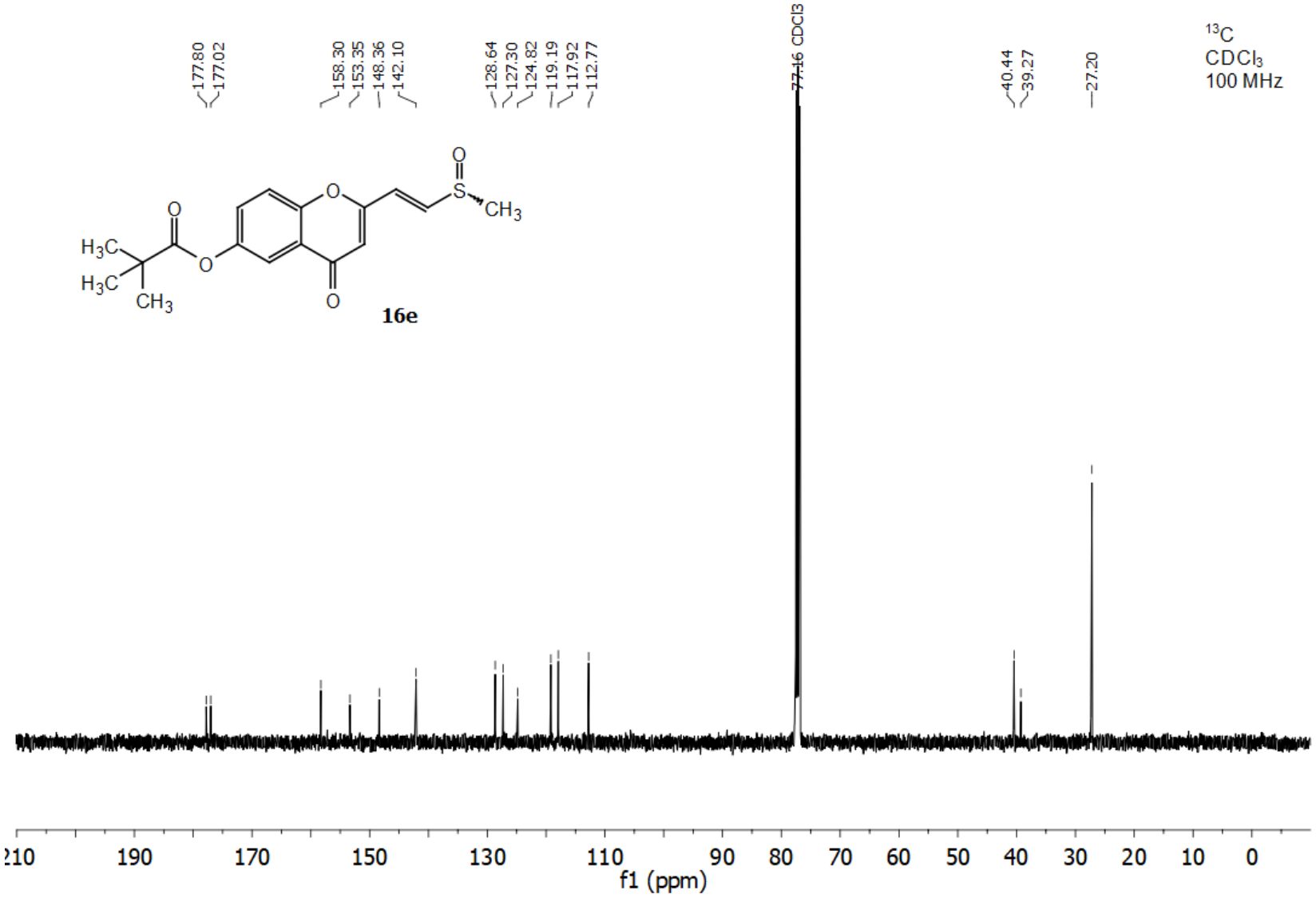

1H
CDCl3
400 MHz
7.84
7.84
7.55
7.52
7.48
7.46
7.43
7.43
7.41
7.40
7.26 CDCl3
7.04
7.00
6.37
2.78
2.58
2.56
2.54
1.83
1.81
1.79
1.77
1.75
1.73
1.06
1.04
1.02
O
O
S
CH3
H3C
O
O
O
16d
0.99
1.02
1.01
1.04
1.00
1.00
3.00
2.07
2.17
3.17
f1 (ppm)

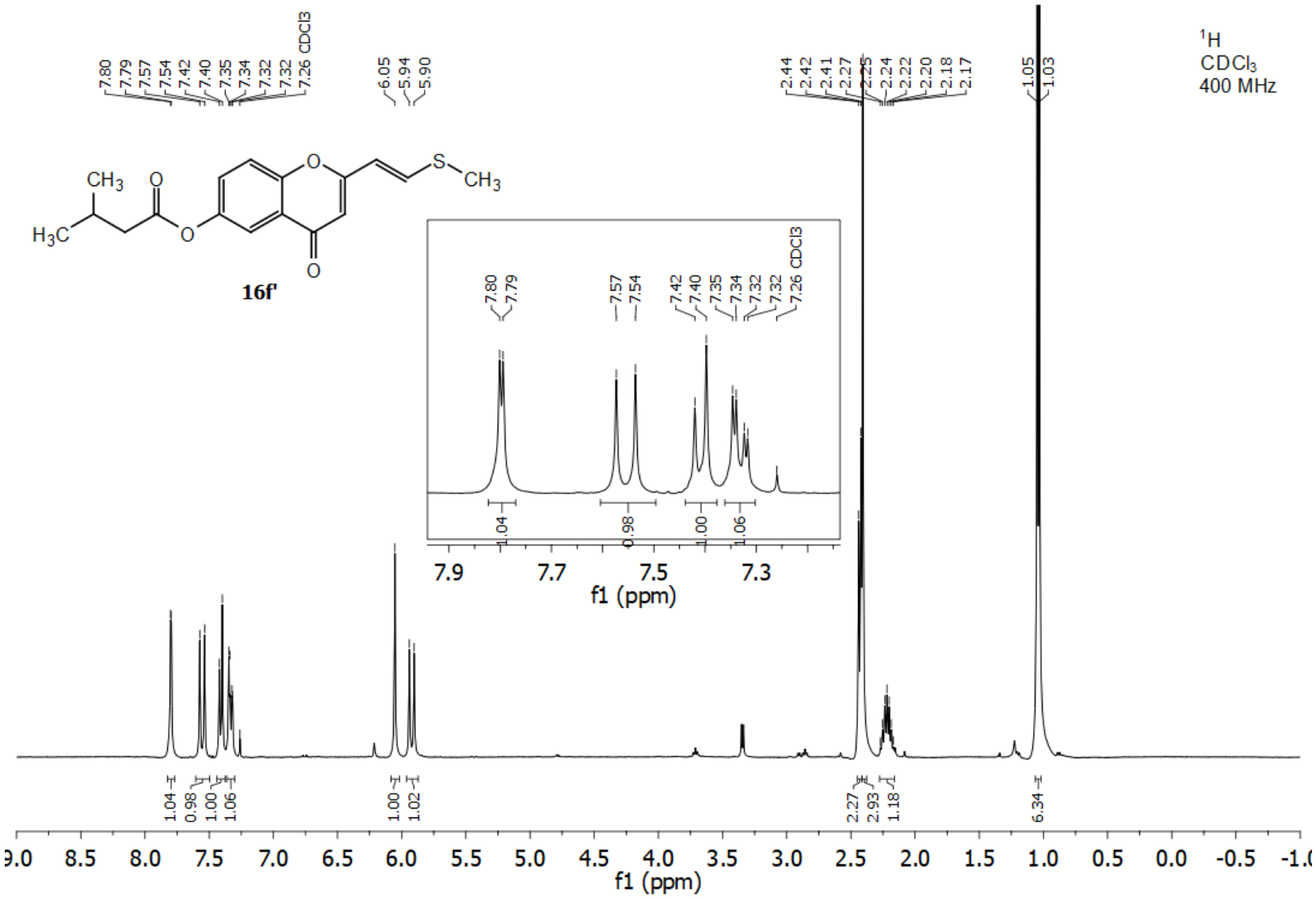

177.72
172.04
158.26
153.33
147.90
142.10
128.62
127.19
124.77
119.24
117.96
112.71
77.16 CDCl3
40.37
36.12
18.47
13.73
13C
CDCl3
100 MHz
O
O
O
S
CH3
H3C
O
O
16d
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

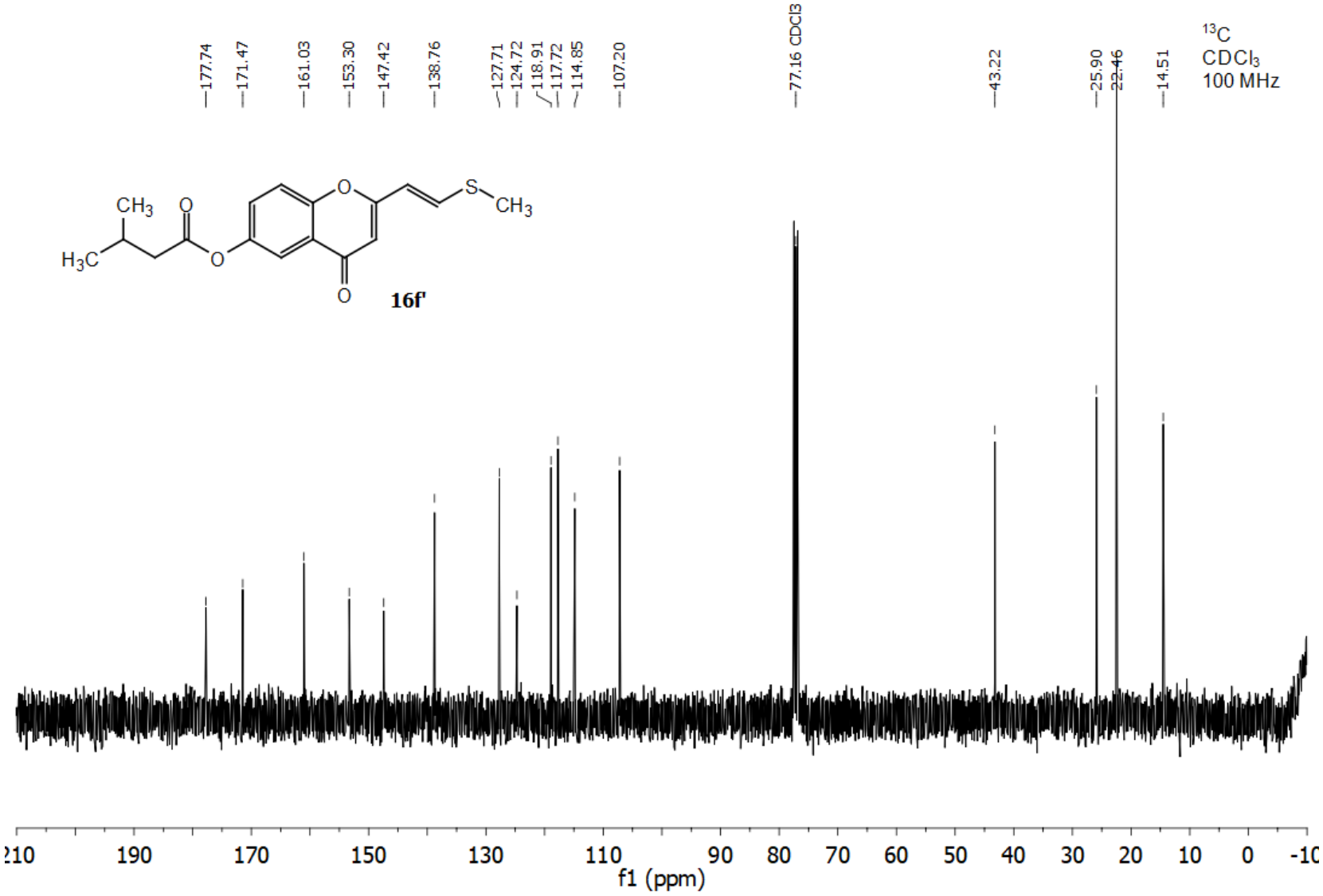

7.80
7.80
7.60
7.56
7.45
7.42
7.35
7.35
7.33
7.32
7.26 CDCl3
6.07
5.97
5.93
2.43
1.35
1H
CDCl3
400 MHz
16e'
f1 (ppm)
1.05
0.95
0.92
1.03
1.00
1.01
3.05
11.93


177.89
177.07
161.09
153.33
147.91
138.76
127.73
124.77
118.89
117.69
114.97
107.29
77.16 CDCl3
39.21
27.19
14.58
13C
CDCl3
100 MHz
O
O
O
O
S
CH3
H3C
H3C
CH3
16e'
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.84
7.83
7.56
7.52
7.50
7.48
7.43
7.42
7.40
7.40
7.26 CDCl3
7.06
7.02
6.39
2.78
1.36
1H
CDCl3
400 MHz
16e
f1 (ppm)
f1 (ppm)


177.80
177.02
158.30
153.35
148.36
142.10
128.64
127.30
124.82
119.19
117.92
112.77
77.16 CDCl3
40.44
39.27
27.20
13C
CDCl3
100 MHz
O
S
CH3
H3C
H3C
CH3
O
O
O
16e
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.80
7.79
7.57
7.54
7.42
7.40
7.35
7.34
7.32
7.32
7.26 CDCl3
6.05
5.94
5.90
2.44
2.42
2.41
2.27
2.25
2.24
2.22
2.20
2.18
2.17
1.05
1.03
1H
CDCl3
400 MHz
CH3
O
H3C
O
O
O
S
CH3
16f'
1.04
0.98
1.00
1.06
1.00
1.02
2.27
2.93
1.18
6.34
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
7.9 7.7 7.5 7.3
f1 (ppm)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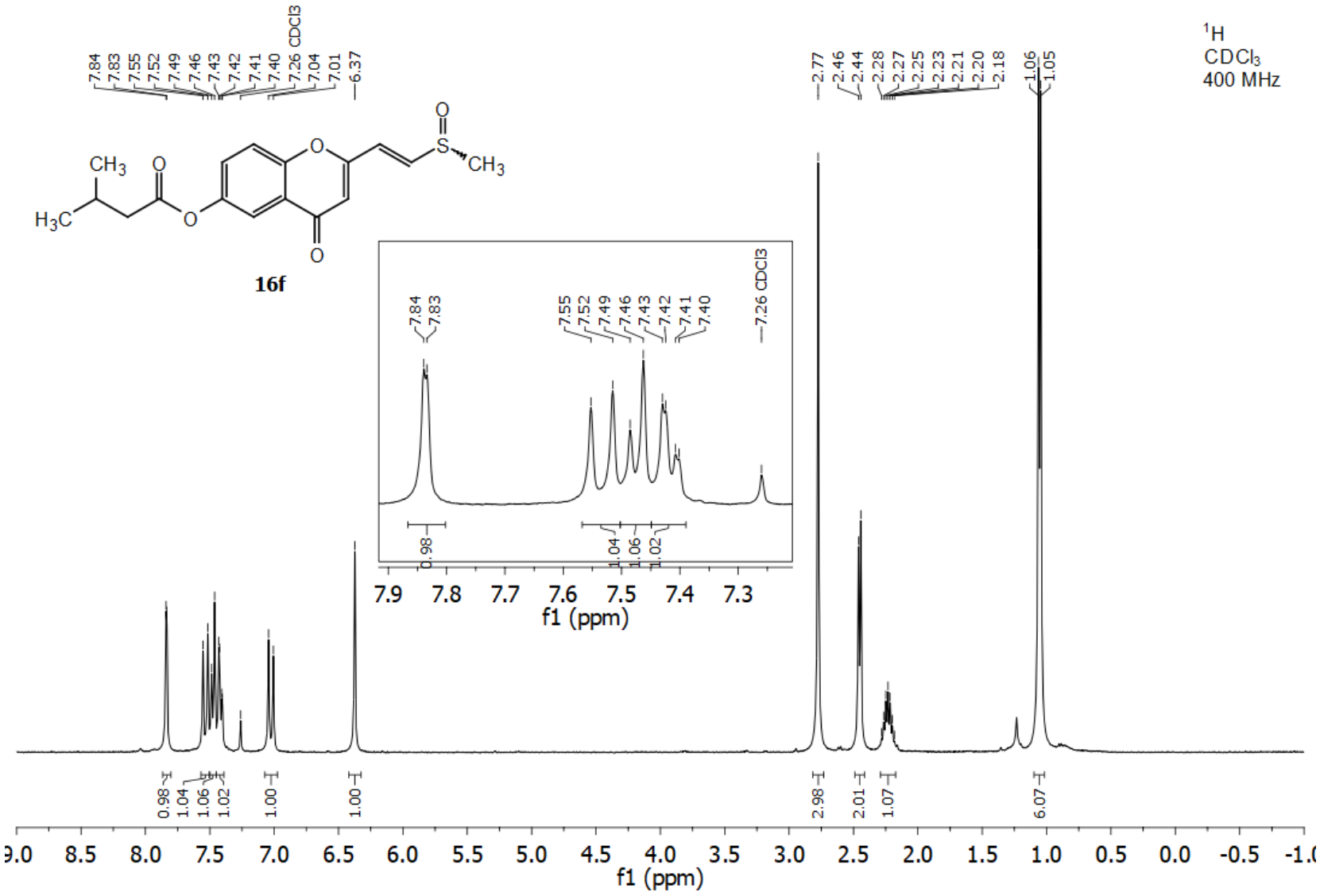
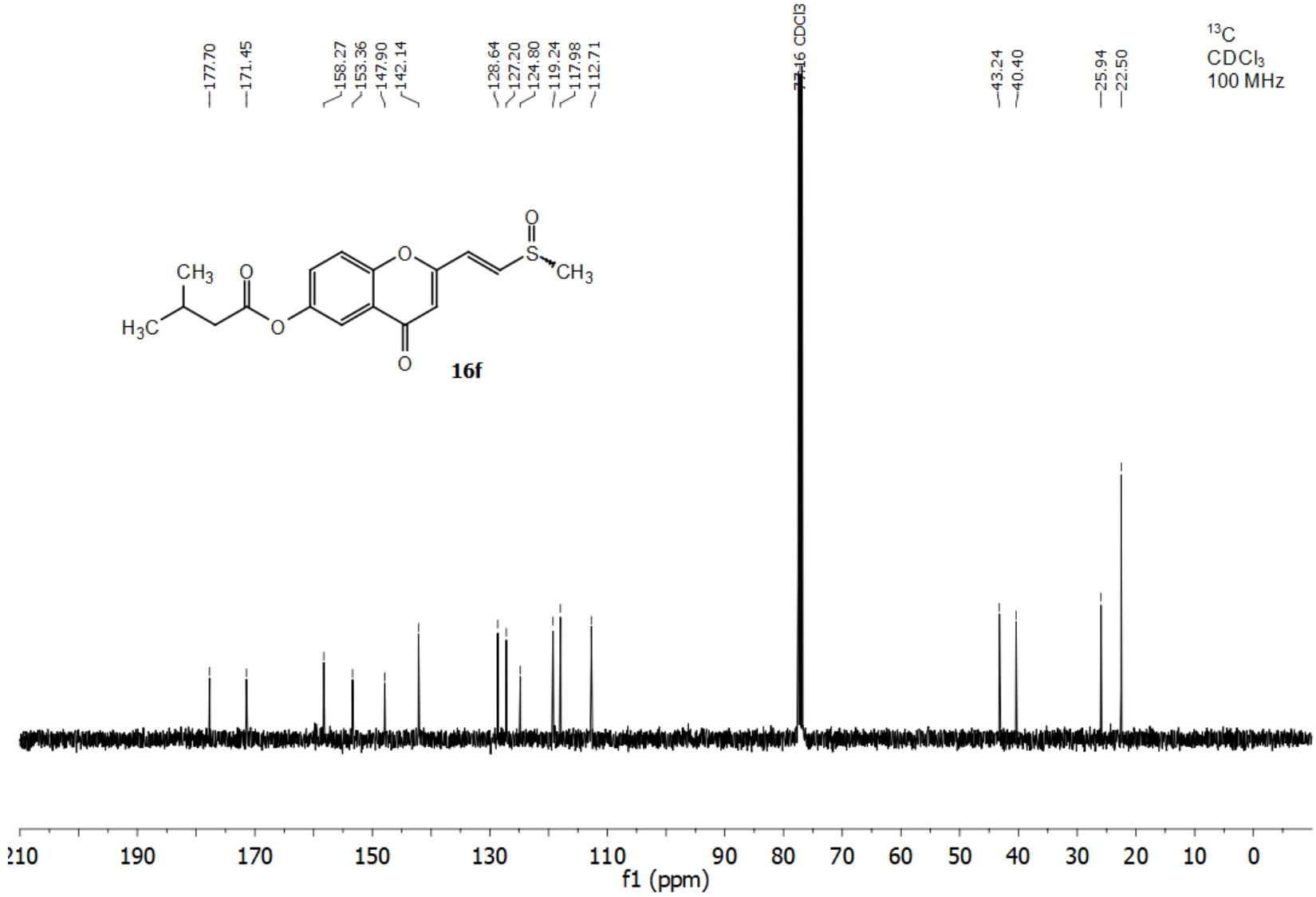
171.47
161.03
153.30
147.42
138.76
127.71
124.72
118.91
117.72
114.85
107.20
77.16 CDCl3
43.22
25.90
22.46
14.51
13C
CDCl3
100 MHz
CH3
O
H3C
O
O
O
S
CH3
16f'
f1 (ppm)


7.84
7.83
7.55
7.52
7.49
7.46
7.43
7.42
7.41
7.40
7.26 CDCl3
7.04
7.01
6.37
2.77
2.46
2.44
2.28
2.27
2.25
2.23
2.21
2.20
2.18
1.06
1.05
1H
CDCl3
400 MHz
CH3
O
O
O
H3C
O
S
CH3
O
16f
0.98
1.04
1.06
1.02
1.00
1.00
2.98
2.01
1.07
6.07
f1 (ppm)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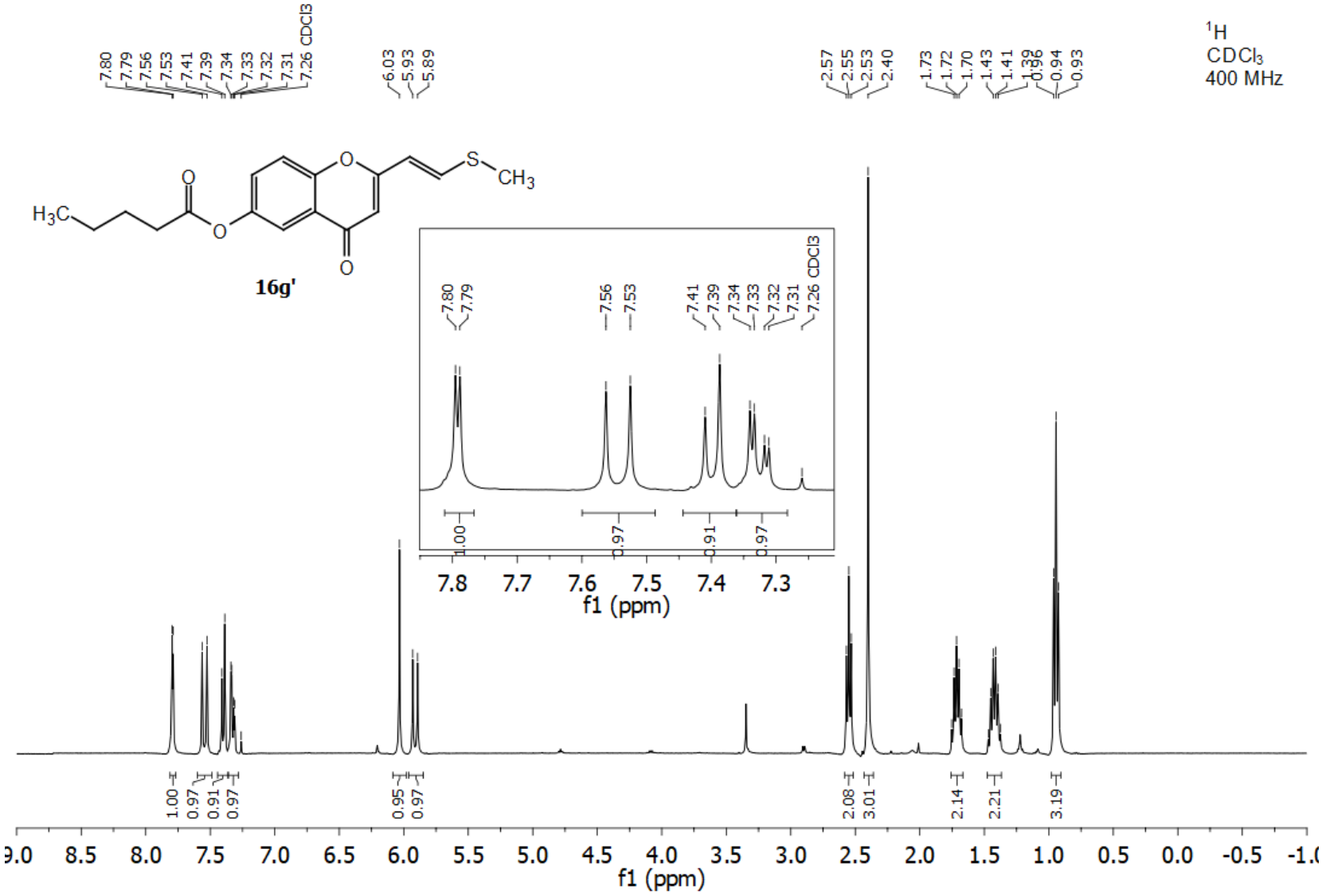
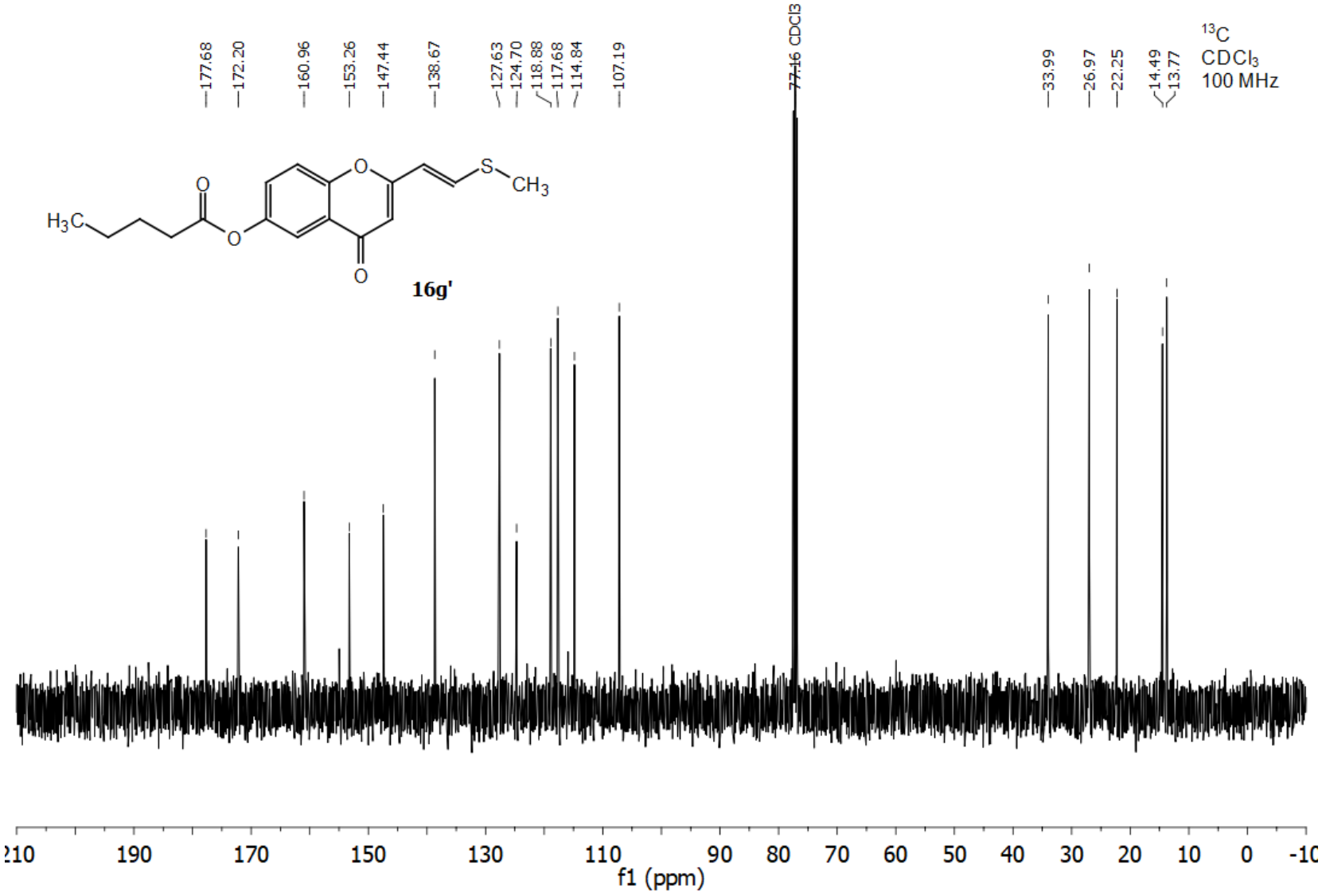
171.45
158.27
153.36
147.90
142.14
128.64
127.20
124.80
119.24
117.98
112.71
77.16 CDCl3
43.24
40.40
25.94
22.50
13C
CDCl3
100 MHz
CH3
O
H3C
O
O
O
O
S
CH3
16f
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.80
7.79
7.56
7.53
7.41
7.39
7.34
7.33
7.32
7.31
7.26 CDCl3
6.03
5.93
5.89
2.57
2.55
2.53
2.40
1.73
1.72
1.70
1.43
1.41
1.39
0.96
0.94
0.93
1H
CDCl3
400 MHz
H3C
O
O
O
O
S
CH3
16g'
1.00
0.97
0.91
0.97
0.95
0.97
2.08
3.01
2.14
2.21
3.19
f1 (ppm)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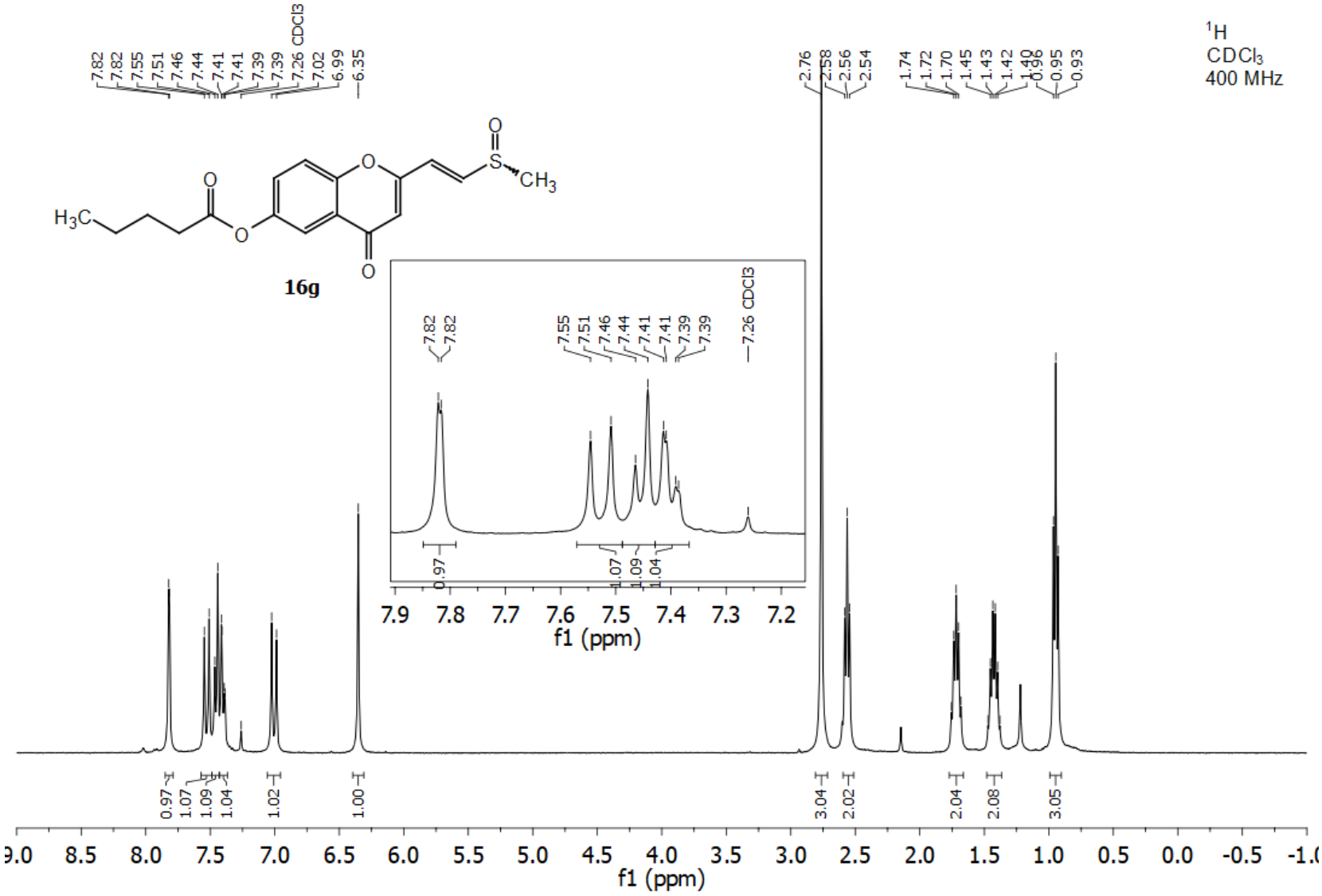
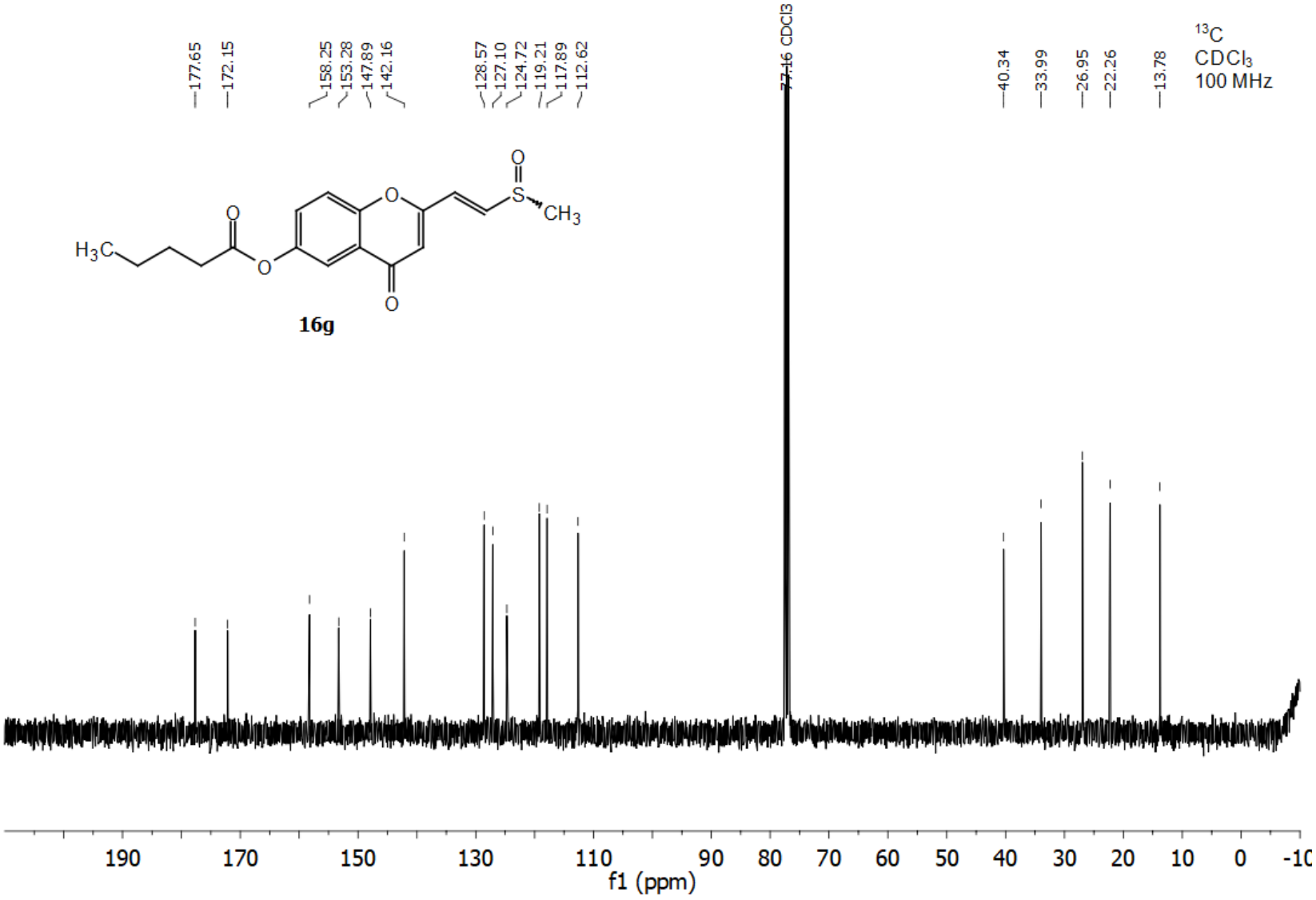
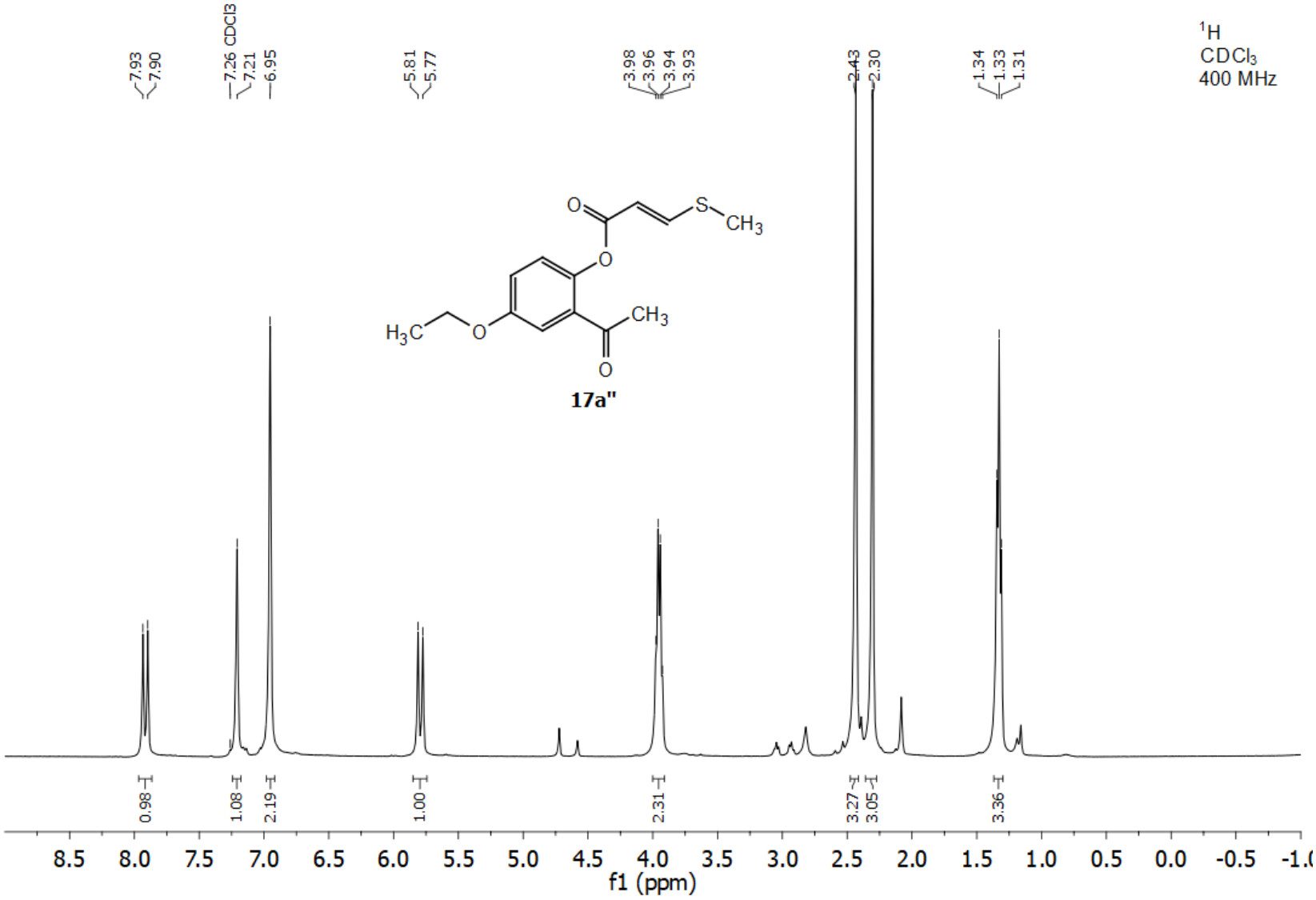
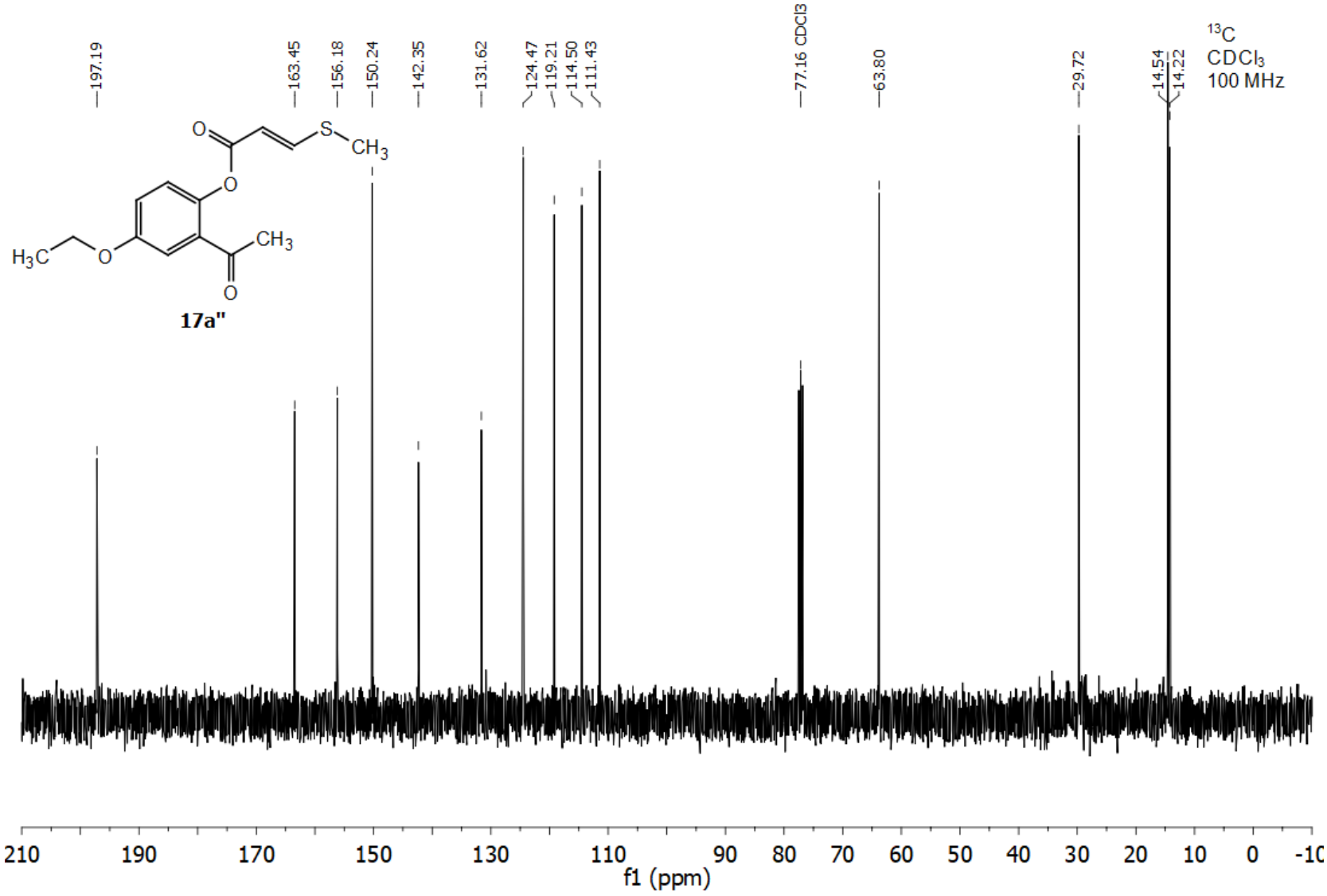
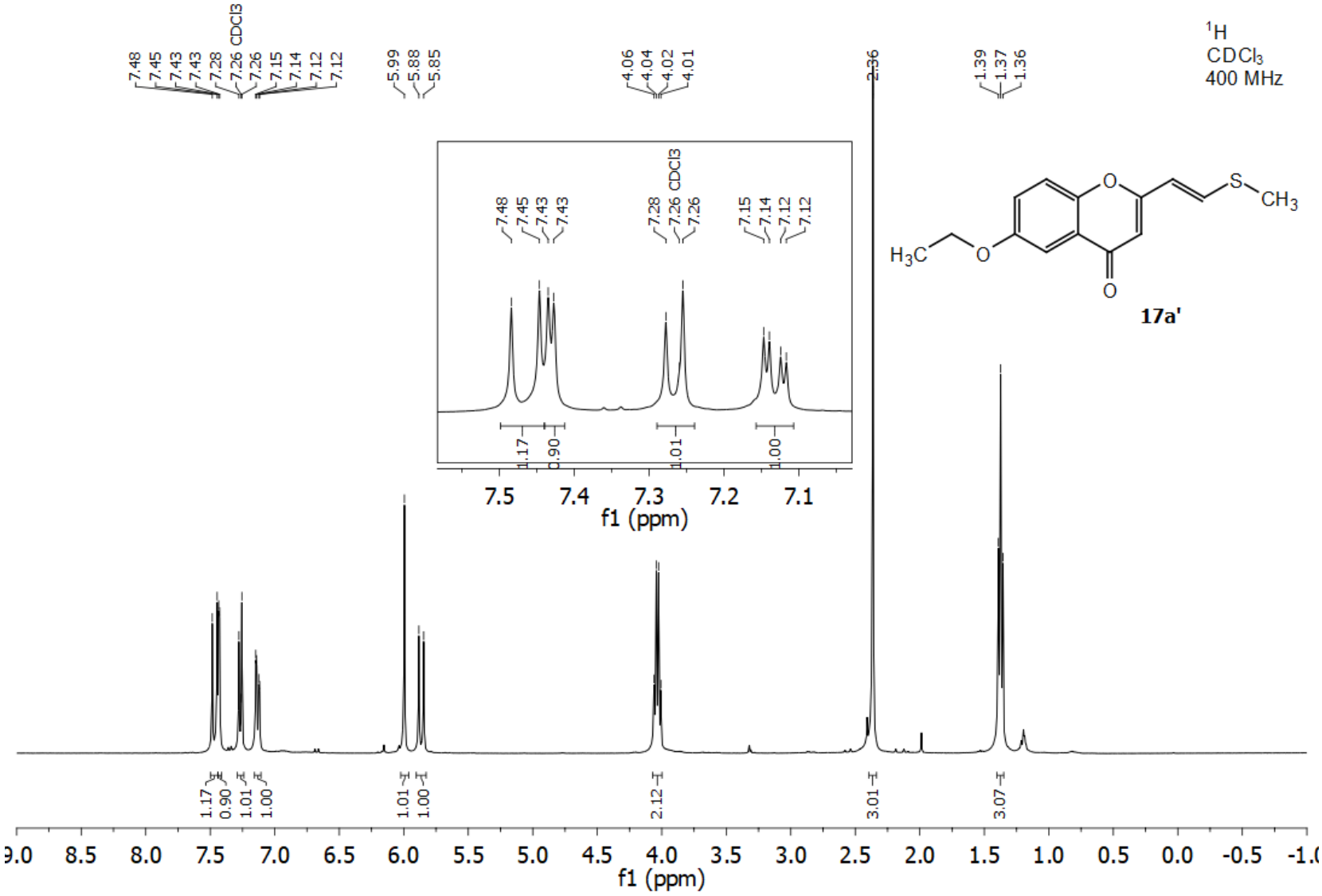
172.20
160.96
153.26
147.44
138.67
127.63
124.70
118.88
117.68
114.84
107.19
77.16 CDCl3
33.99
26.97
22.25
14.49
13.77
13C
CDCl3
100 MHz
H3C
O
O
O
O
S
CH3
16g'
f1 (ppm)

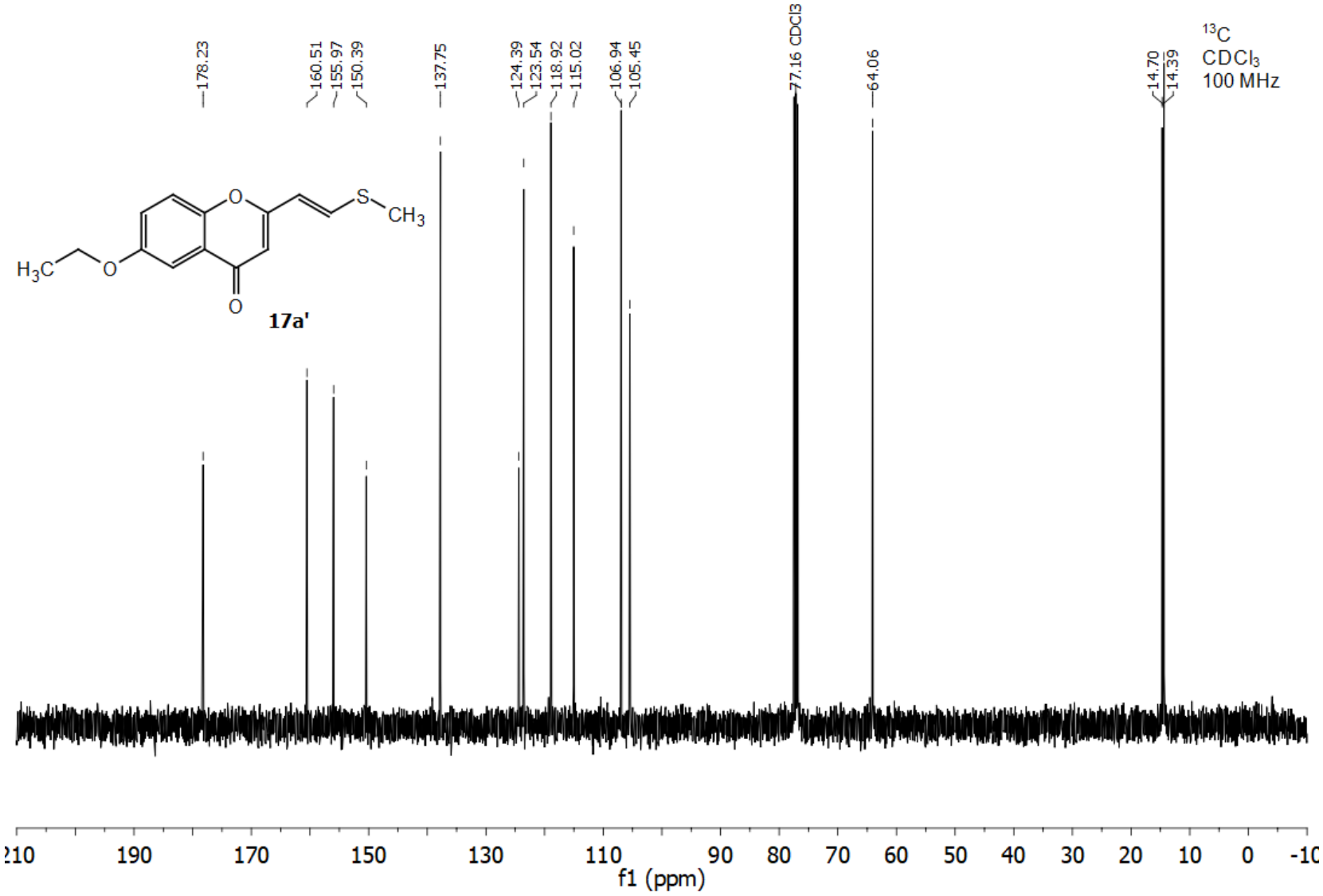

7.82
7.82
7.55
7.51
7.46
7.44
7.41
7.41
7.39
7.39
7.26 CDCl3
7.02
6.99
6.35
2.76
2.58
2.56
2.54
1.74
1.72
1.70
1.45
1.43
1.42
1.40
0.98
0.95
0.93
1H
CDCl3
400 MHz
16g
f1 (ppm)
0.97
1.07
1.09
1.04
1.02
1.00
3.04
2.02
2.04
2.08
3.05

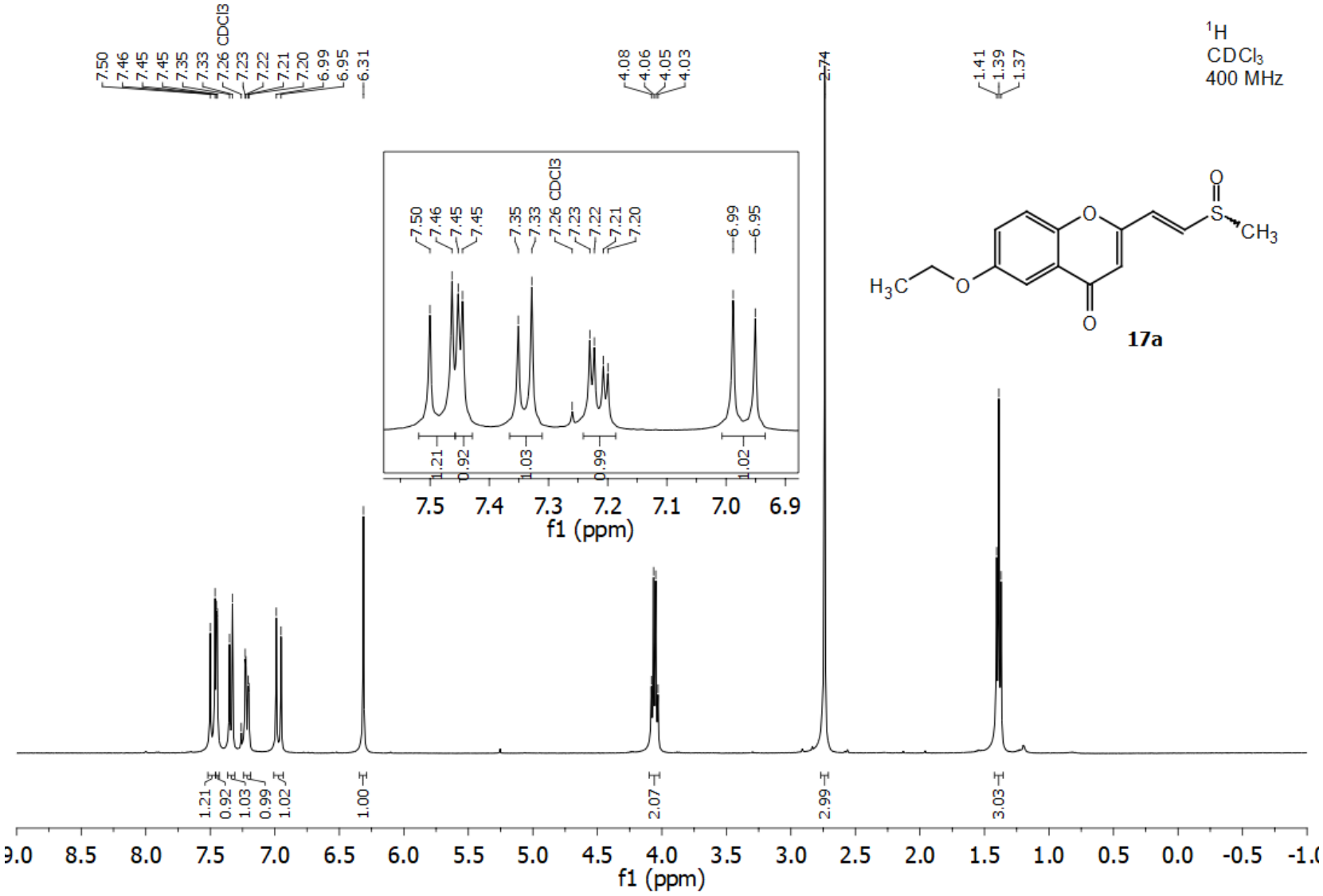

177.65
172.15
158.25
153.28
147.89
142.16
128.57
127.10
124.72
119.21
117.89
112.62
77.16 CDCl3
40.34
33.99
26.95
22.26
13.78
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
O
16g
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

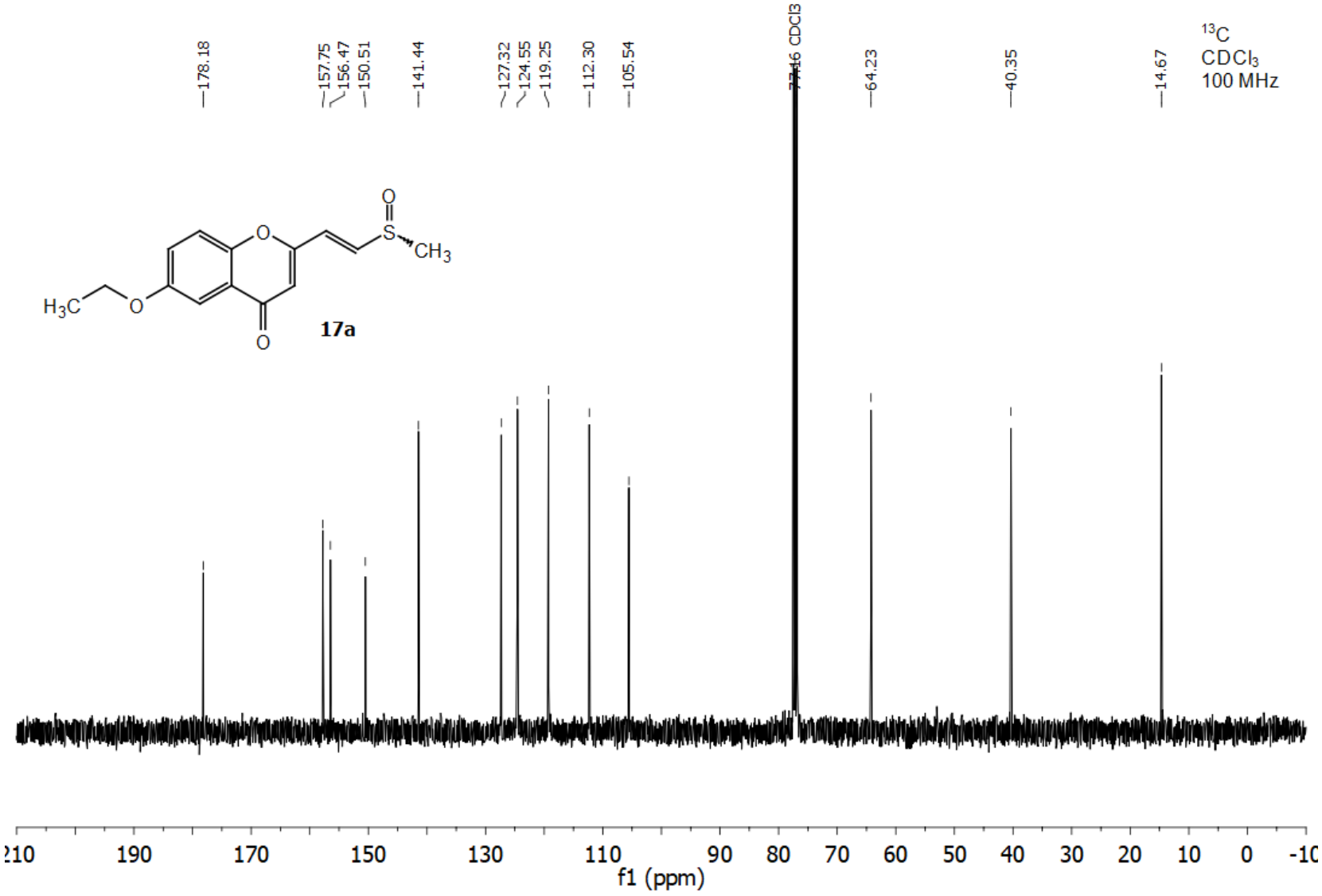

7.93
7.90
7.26 CDCl3
7.21
6.95
5.81
5.77
3.98
3.96
3.94
3.93
2.43
2.30
1.34
1.33
1.31
1H
CDCl3
400 MHz
O
S
CH3
O
H3C
O
CH3
O
17a"
0.98
1.08
2.19
1.00
2.31
3.27
3.05
3.36
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

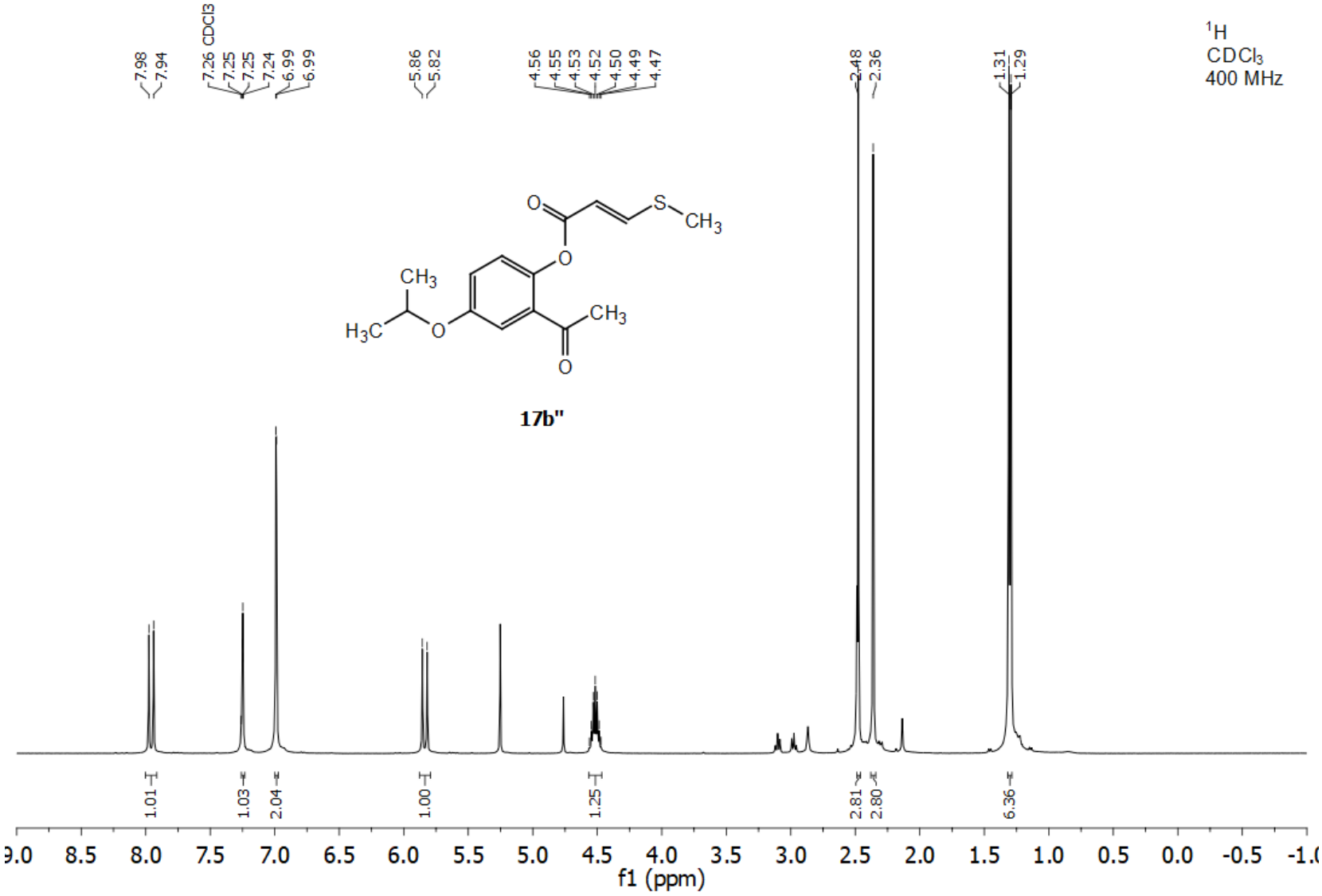

197.19
163.45
156.18
150.24
142.35
131.62
124.47
119.21
114.50
111.43
77.16 CDCl3
63.80
29.72
14.54
14.22
13C
CDCl3
100 MHz
O
S
CH3
O
H3C
O
CH3
O
17a"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

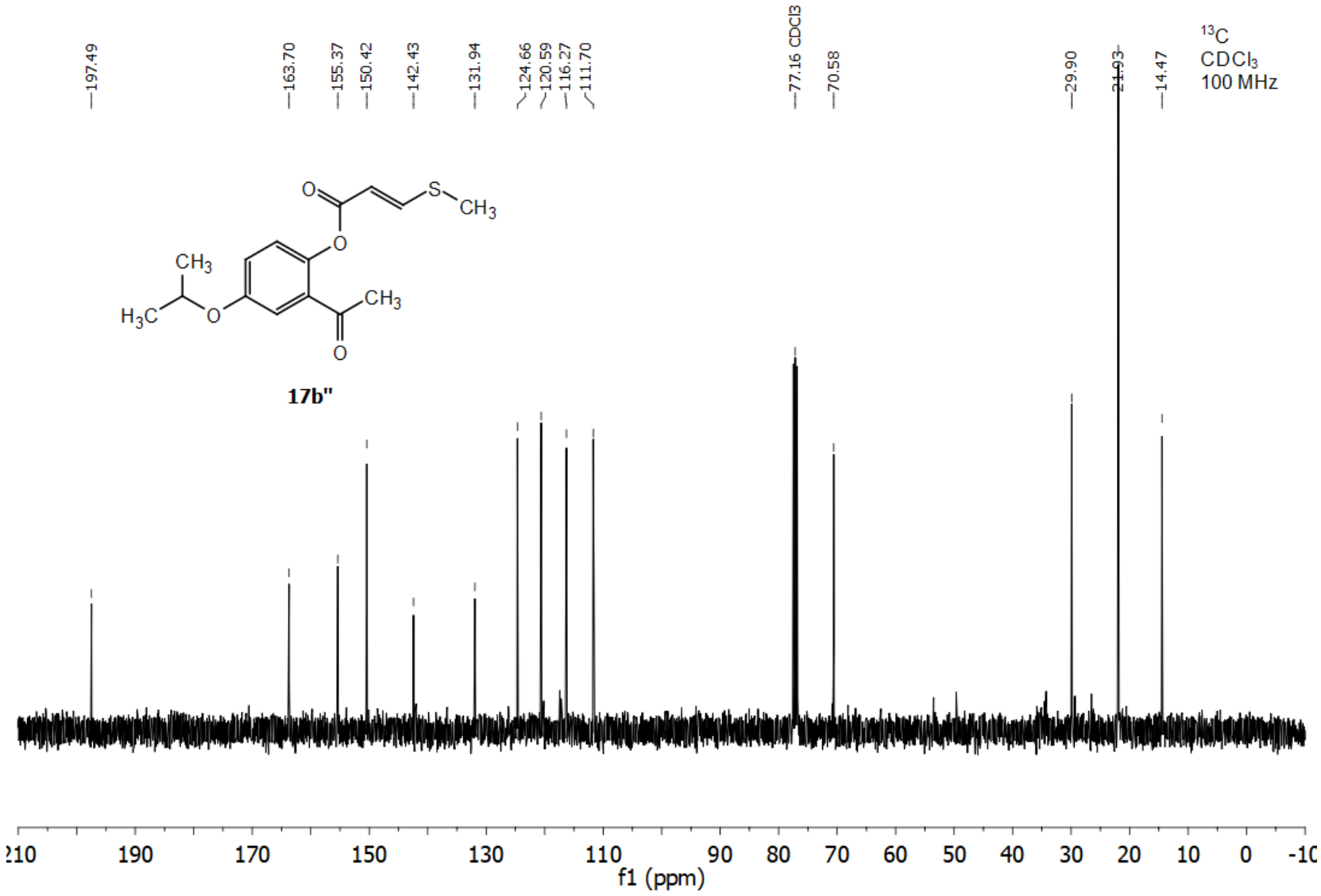

^{1}H
$CDCl_3$
400 MHz
17a'
f1 (ppm)


178.23
160.51
155.97
150.39
137.75
124.39
123.54
118.92
115.02
106.94
105.45
77.16 CDCl3
64.06
14.70
14.39
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
17a'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

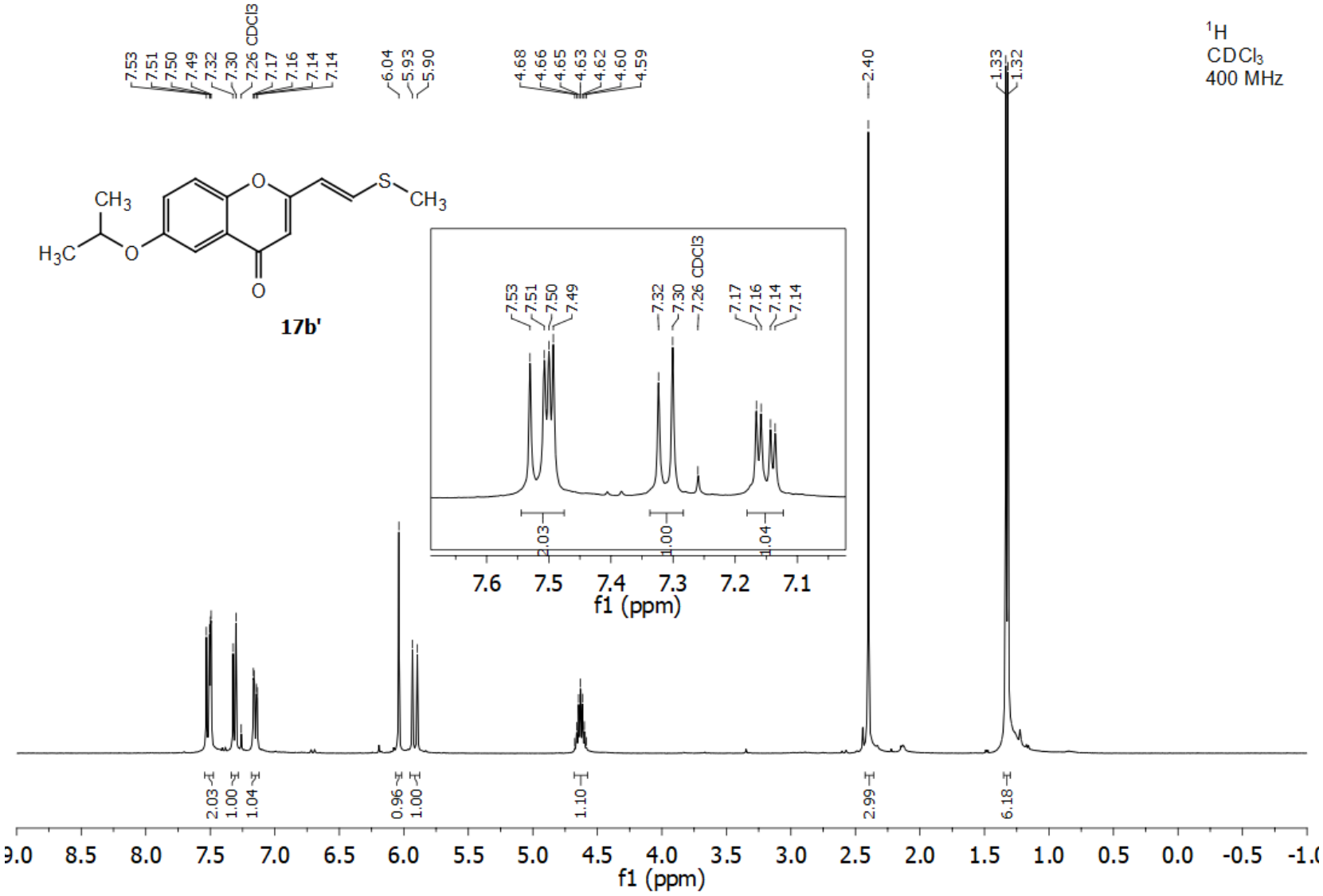

1H
CDCl3
400 MHz
17a
f1 (ppm)

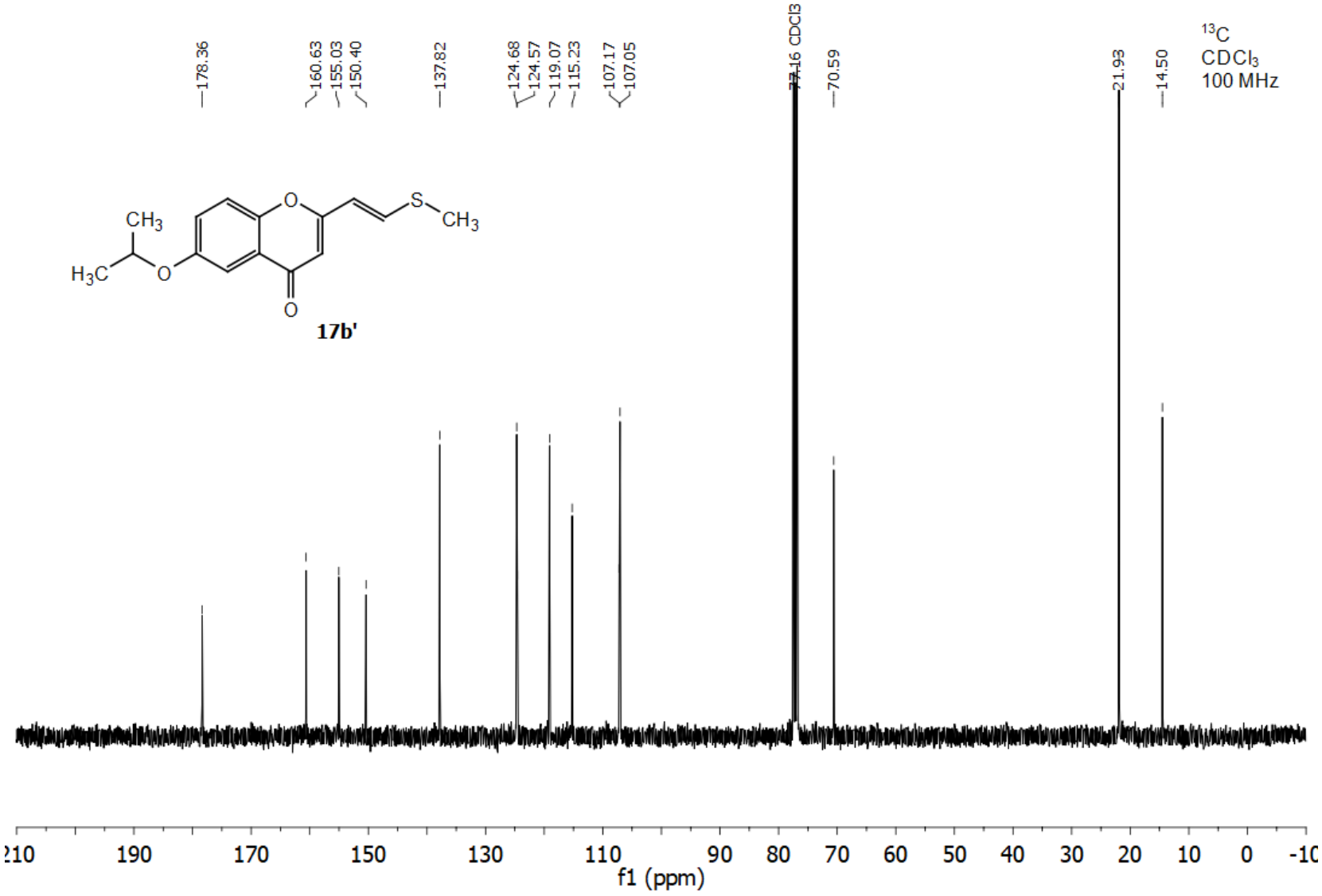

178.18
157.75
156.47
150.51
141.44
127.32
124.55
119.25
112.30
105.54
77.16 CDCl3
64.23
40.35
14.67
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
17a
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

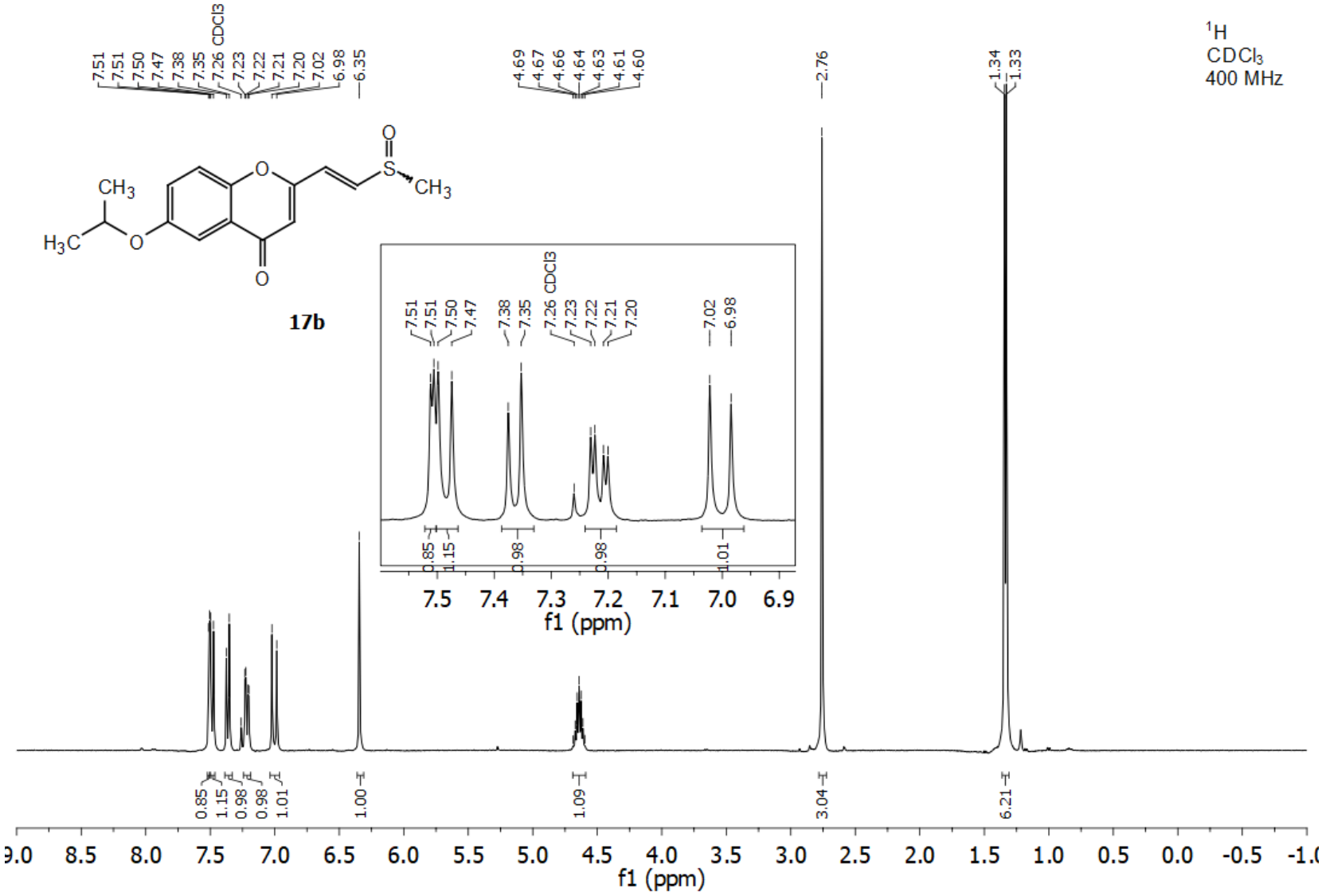

7.98
7.94
7.26 CDCl3
7.25
7.25
7.24
6.99
6.99
5.86
5.82
4.56
4.55
4.53
4.52
4.50
4.49
4.47
2.48
2.36
1.31
1.29
1H
CDCl3
400 MHz
O
S
CH3
O
CH3
H3C
O
CH3
O
17b"
1.01
1.03
2.04
1.00
1.25
2.81
2.80
6.36
f1 (ppm)

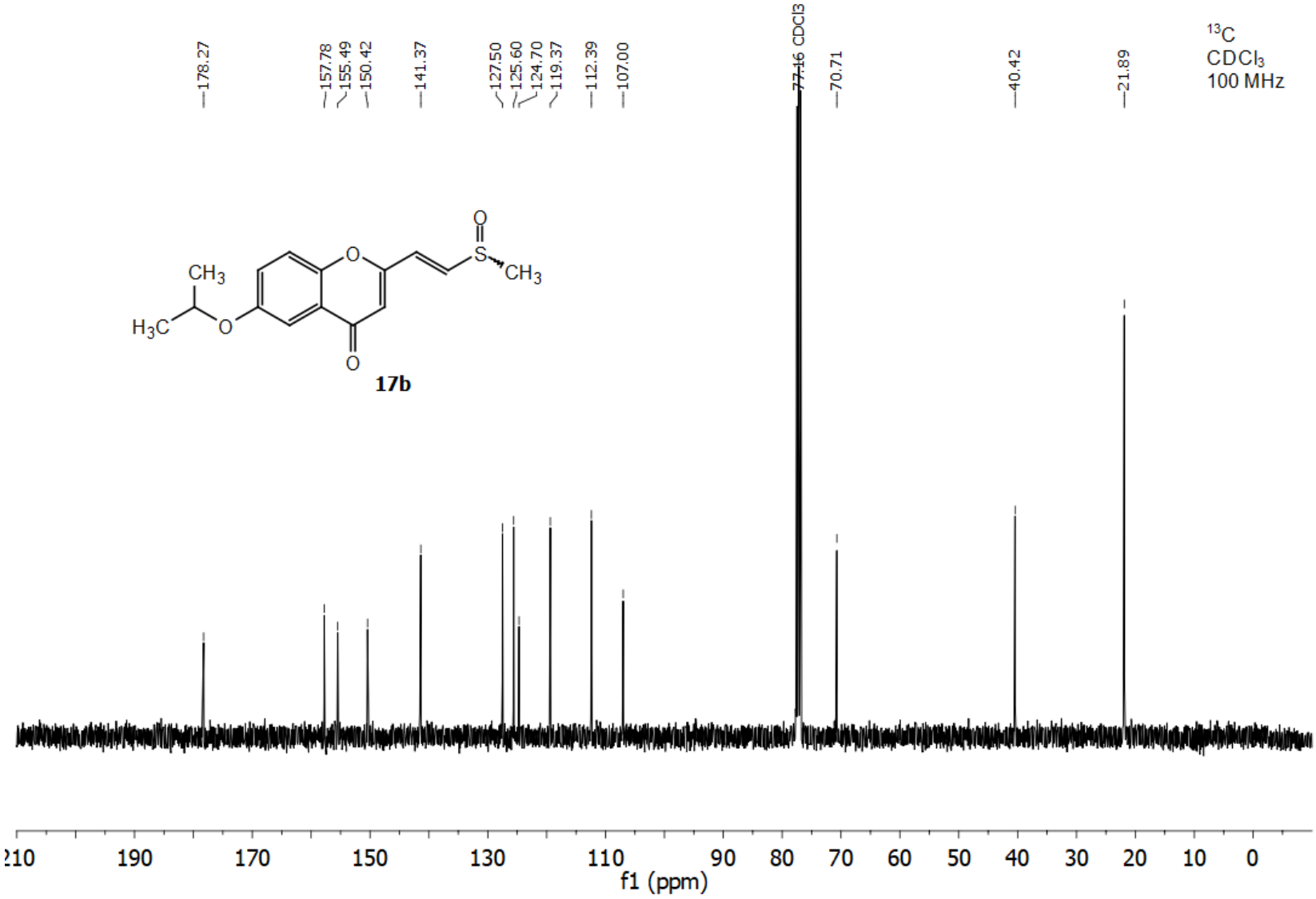

197.49
163.70
155.37
150.42
142.43
131.94
124.66
120.59
116.27
111.70
77.16 CDCl3
70.58
29.90
21.93
14.47
13C
CDCl3
100 MHz
O
O
S
CH3
CH3
H3C
O
CH3
O
f1 (ppm)

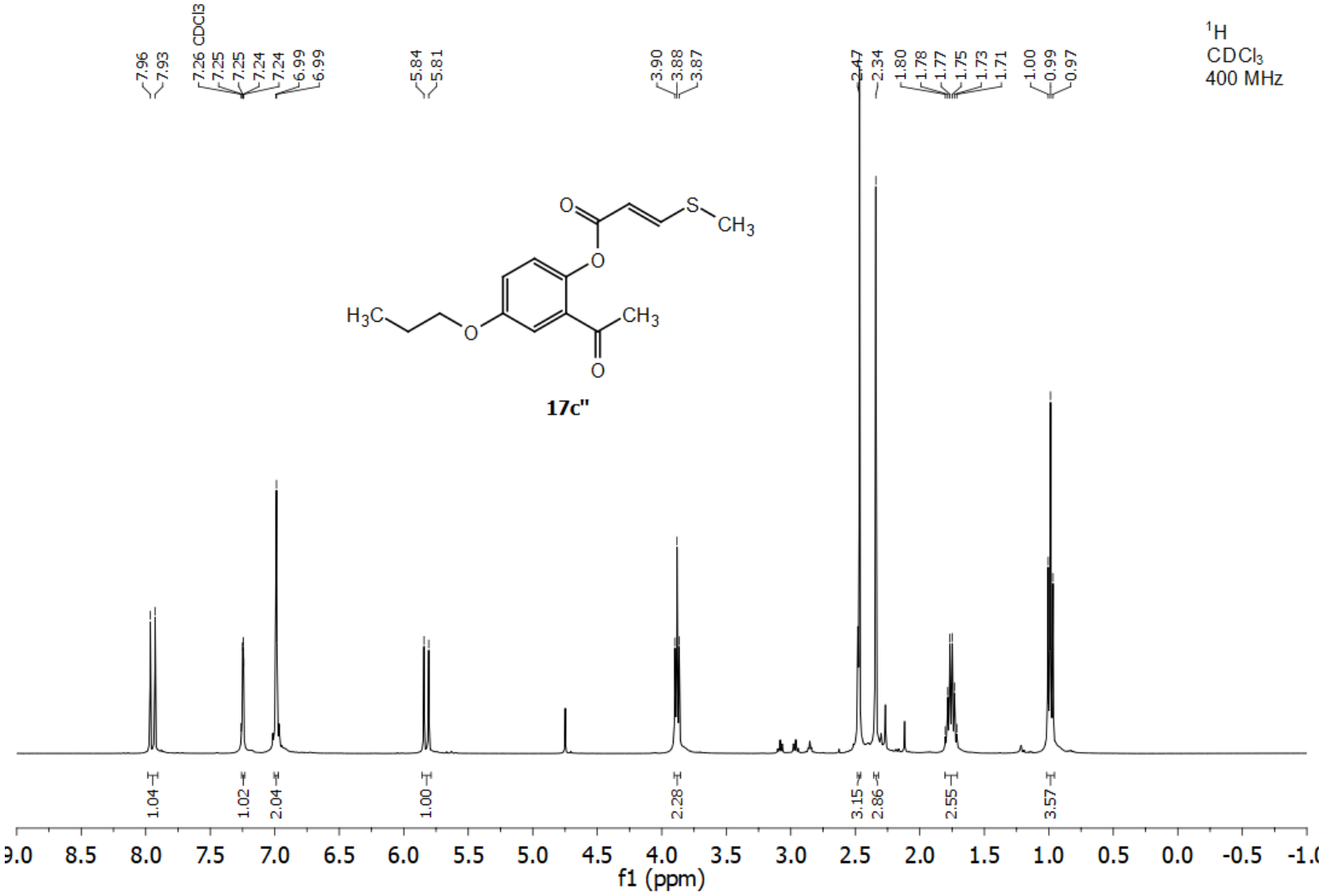
17b"


1H
CDCl3
400 MHz
7.53
7.51
7.50
7.49
7.32
7.30
7.26 CDCl3
7.17
7.16
7.14
7.14
6.04
5.93
5.90
4.68
4.66
4.65
4.63
4.62
4.60
4.59
2.40
1.33
1.32
CH3
H3C
O
O
O
S
CH3
17b'
2.03
1.00
1.04
7.6
7.5
7.4
7.3
7.2
7.1
f1 (ppm)
2.03
1.00
1.04
0.96
1.00
1.10
2.99
6.18
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

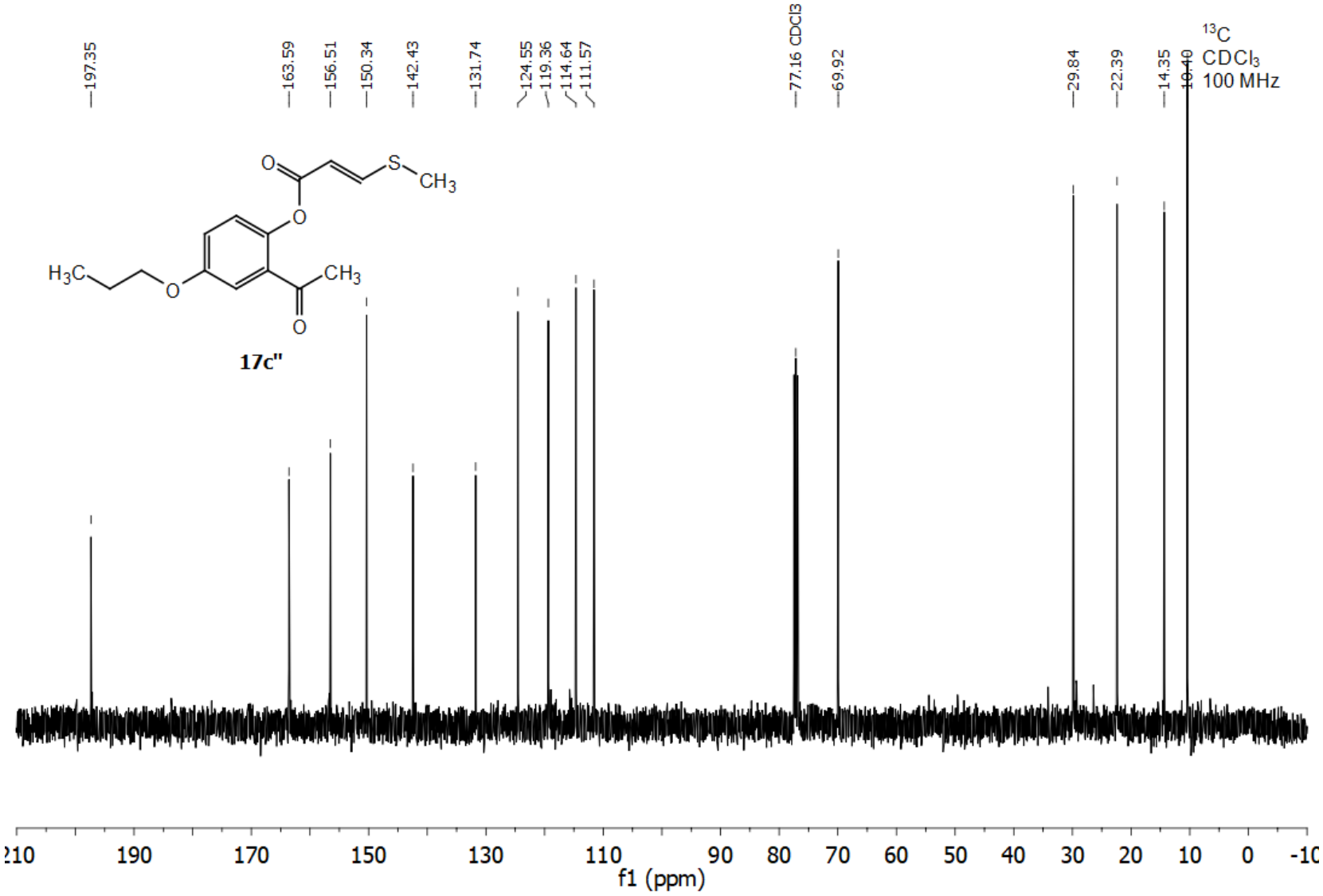

178.36
160.63
155.03
150.40
137.82
124.68
124.57
119.07
115.23
107.17
107.05
77.16 CDCl3
70.59
21.93
14.50
13C
CDCl3
100 MHz
CH3
H3C
O
O
O
S
CH3
17b'
f1 (ppm)

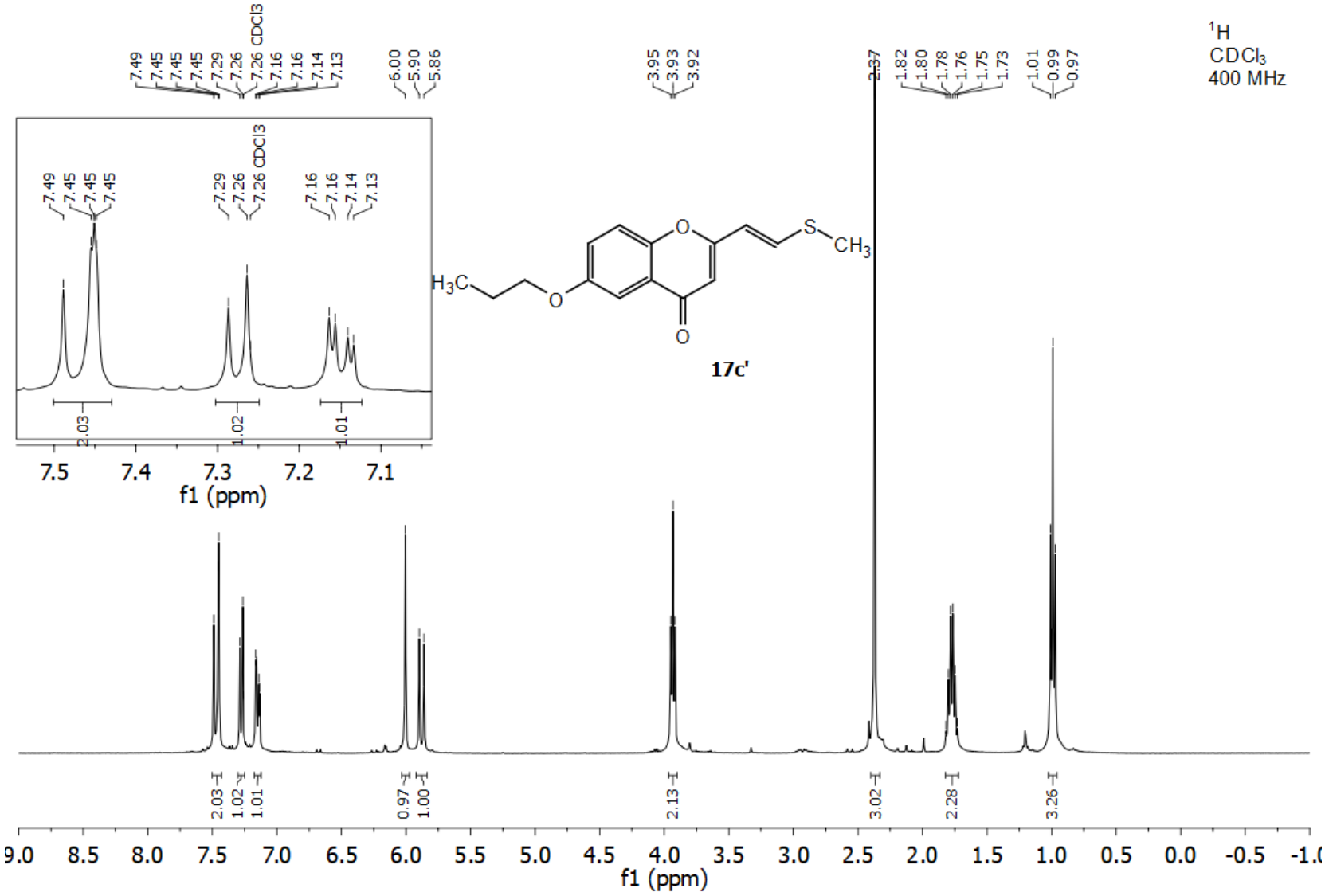

7.51
7.51
7.50
7.47
7.38
7.35
7.26 CDCl3
7.23
7.22
7.21
7.20
7.02
6.98
6.35
4.69
4.67
4.66
4.64
4.63
4.61
4.60
2.76
1.34
1.33
1H
CDCl3
400 MHz
CH3
H3C
O
O
S
CH3
O
O
17b
0.85
1.15
0.98
0.98
1.01
1.00
1.09
3.04
6.21
7.5
7.4
7.3
7.2
7.1
7.0
6.9
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

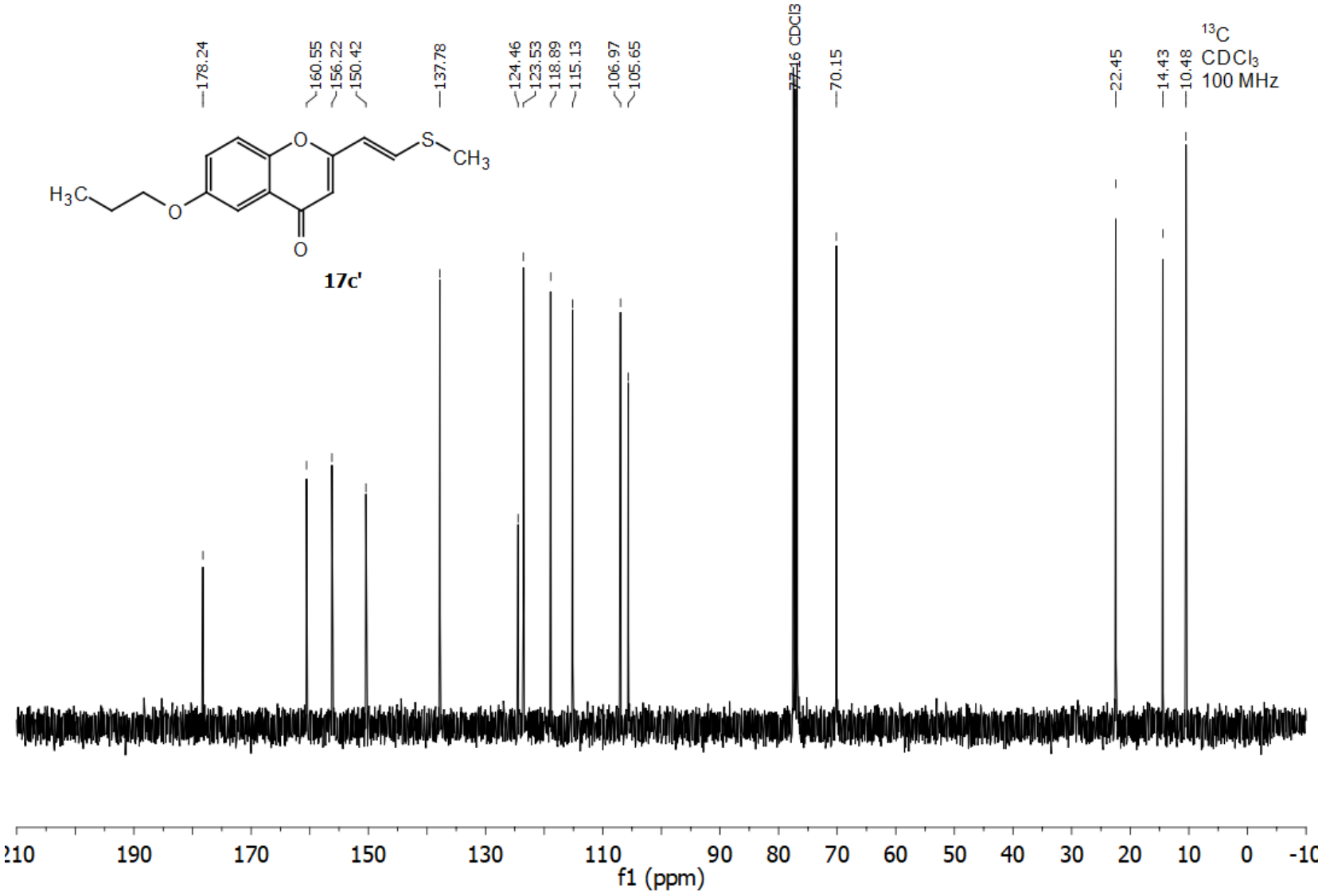

178.27
157.78
155.49
150.42
141.37
127.50
125.60
124.70
119.37
112.39
107.00
77.16 CDCl3
70.71
40.42
21.89
13C
CDCl3
100 MHz
CH3
H3C
O
O
O
S
CH3
O
17b
f1 (ppm)

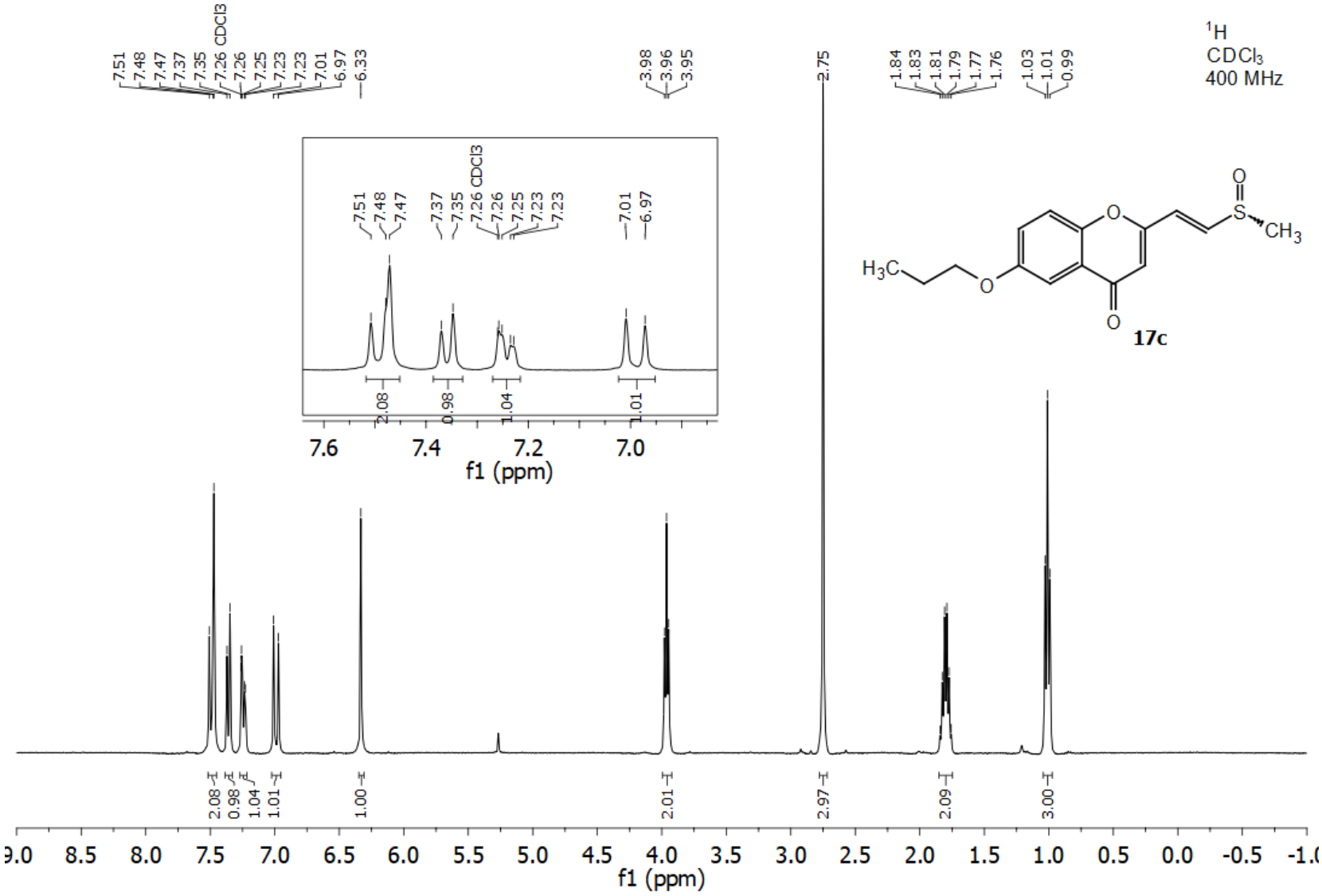

7.96
7.93
7.26 CDCl3
7.25
7.25
7.24
7.24
6.99
6.99
5.84
5.81
3.90
3.88
3.87
2.47
2.34
1.80
1.78
1.77
1.75
1.73
1.71
1.00
0.99
0.97
1H
CDCl3
400 MHz
O
O
S
CH3
H3C
O
CH3
O
1.04
1.02
2.04
1.00
2.28
3.15
2.86
2.55
3.57
f1 (ppm)

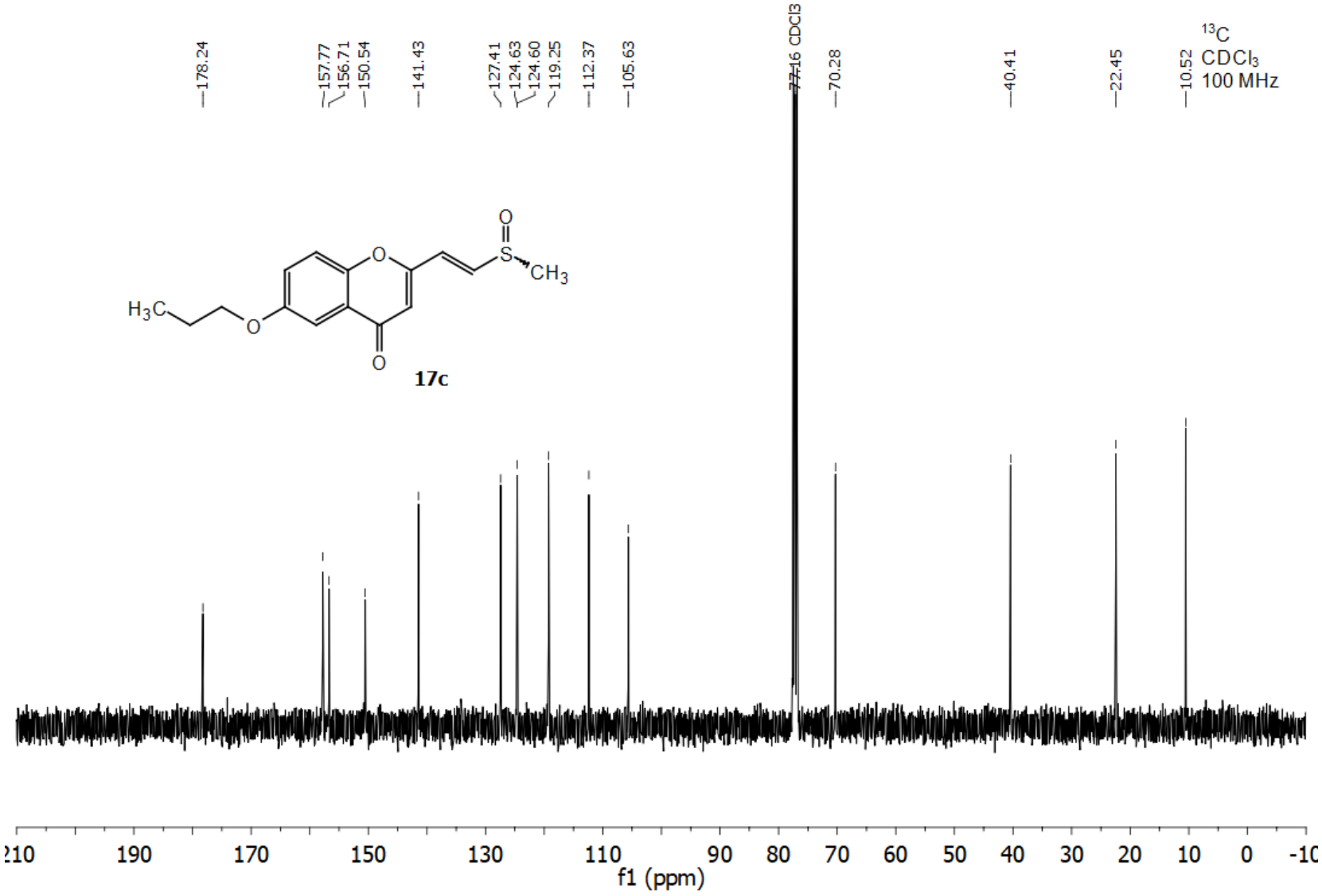
17c"

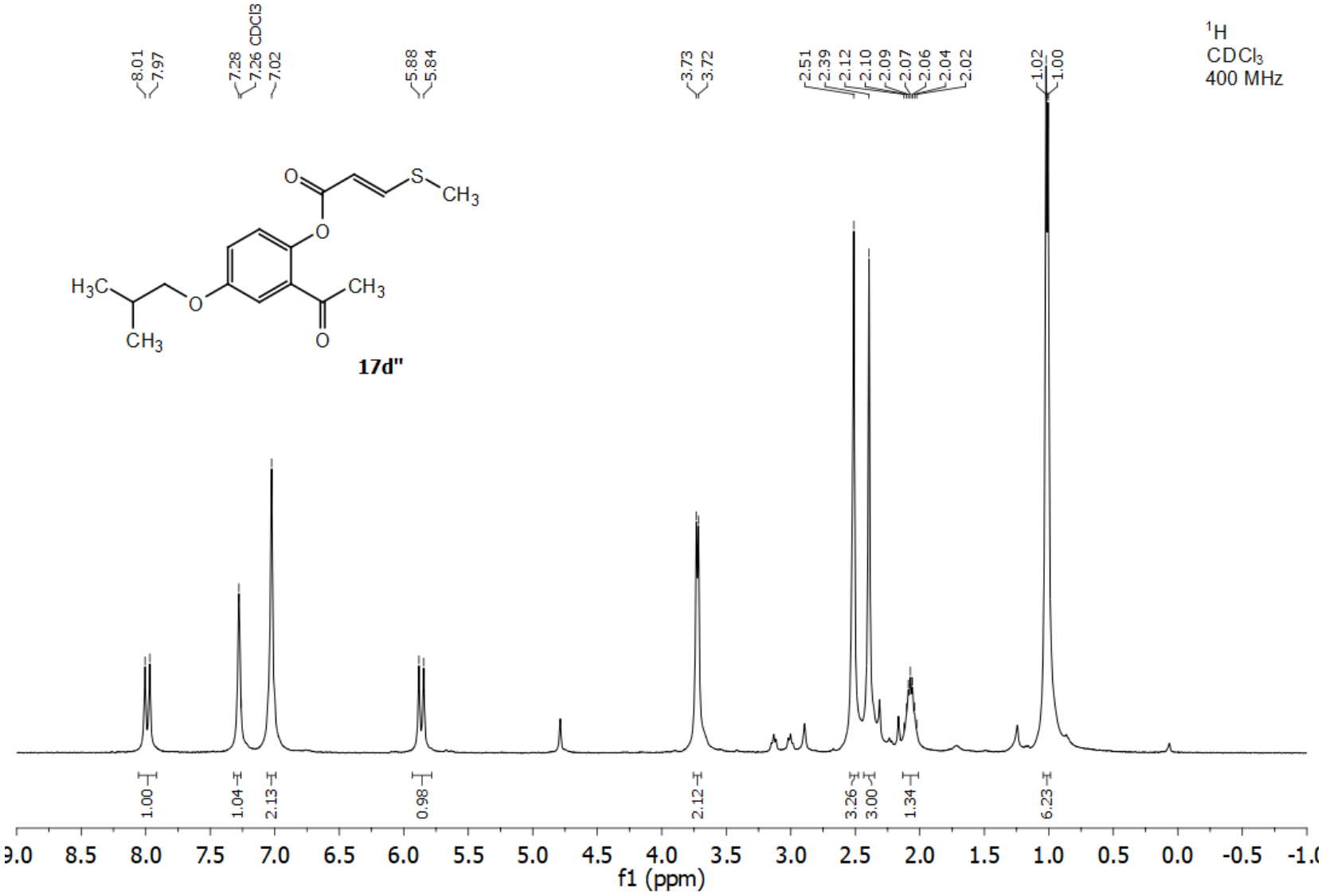

197.35
163.59
156.51
150.34
142.43
131.74
124.55
119.36
114.64
111.57
77.16 CDCl3
69.92
29.84
22.39
14.35
10.40
13C
CDCl3
100 MHz
O
S
CH3
O
H3C
O
CH3
O
17c"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


1H
CDCl3
400 MHz
7.49
7.45
7.45
7.45
7.29
7.26
7.26 CDCl3
7.16
7.16
7.14
7.13
6.00
5.90
5.86
3.95
3.93
3.92
2.37
1.82
1.80
1.78
1.76
1.75
1.73
1.01
0.99
0.97
H3C
O
O
O
S
CH3
17c'
2.03
1.02
1.01
0.97
1.00
2.13
3.02
2.28
3.26
f1 (ppm)

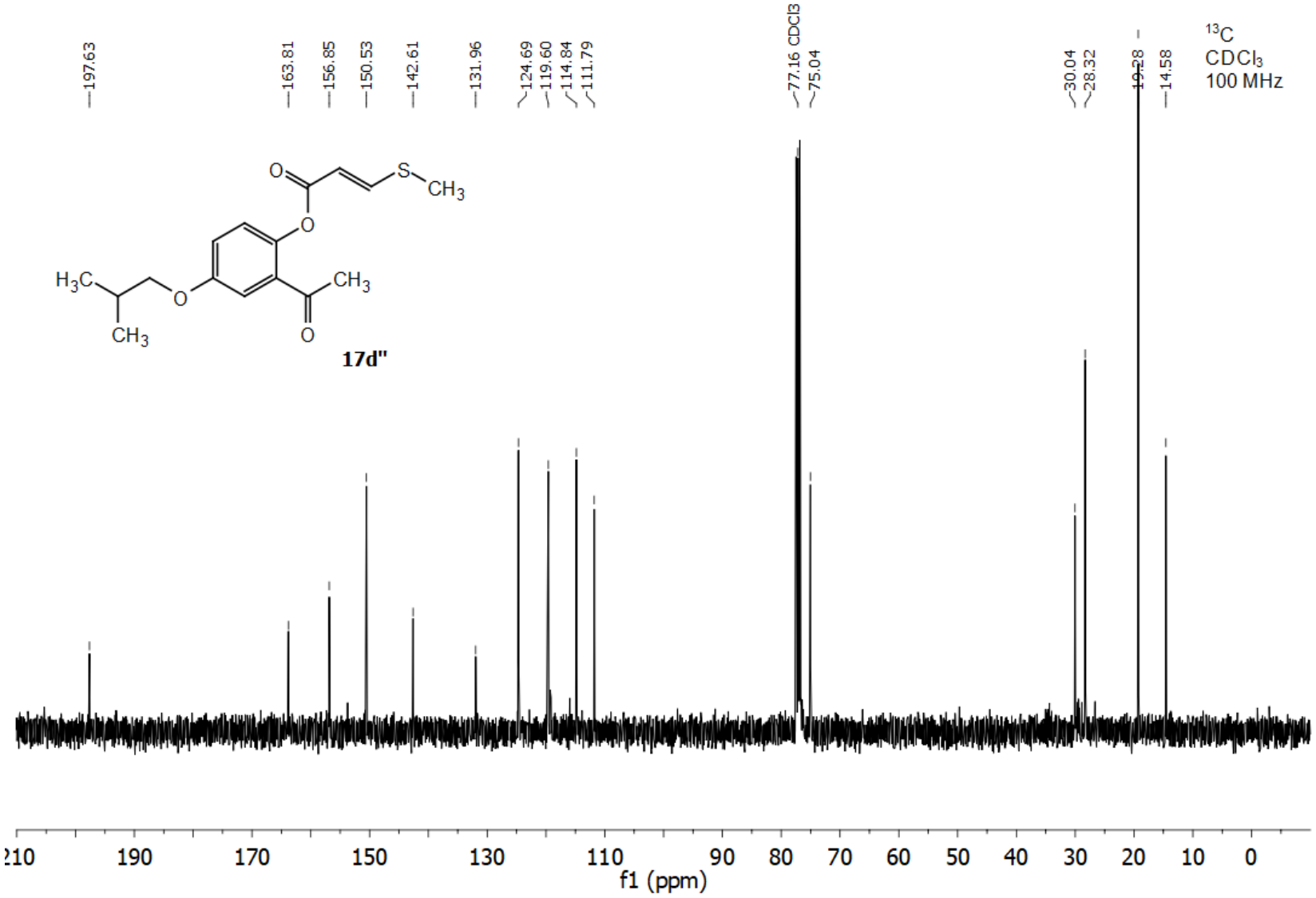

178.24
160.55
156.22
150.42
137.78
124.46
123.53
118.89
115.13
106.97
105.65
77.16 CDCl3
70.15
22.45
14.43
10.48
13C
CDCl3
100 MHz
H3C
O
O
O
S
CH3
17c'
f1 (ppm)

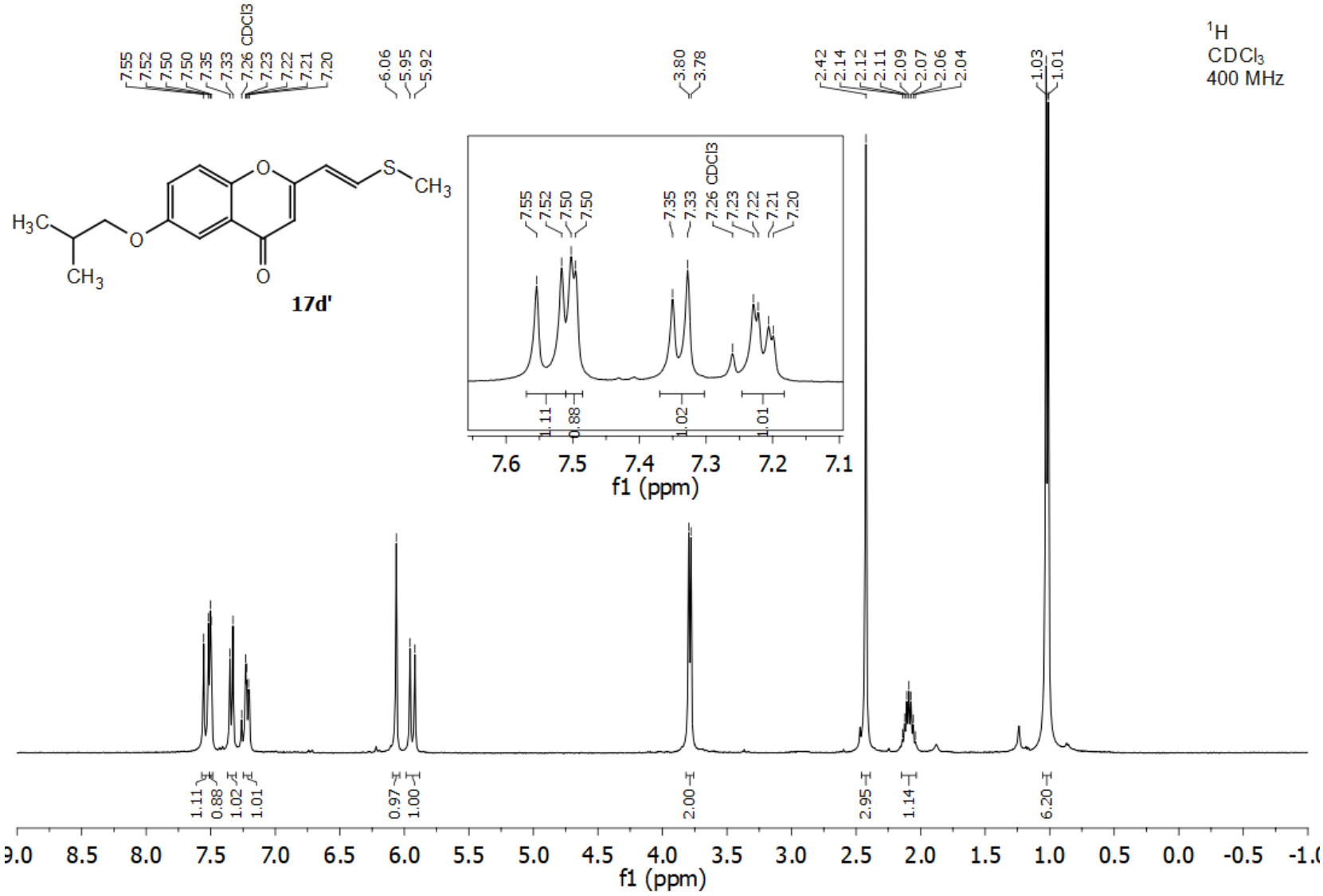

1H
CDCl3
400 MHz
17c
f1 (ppm)

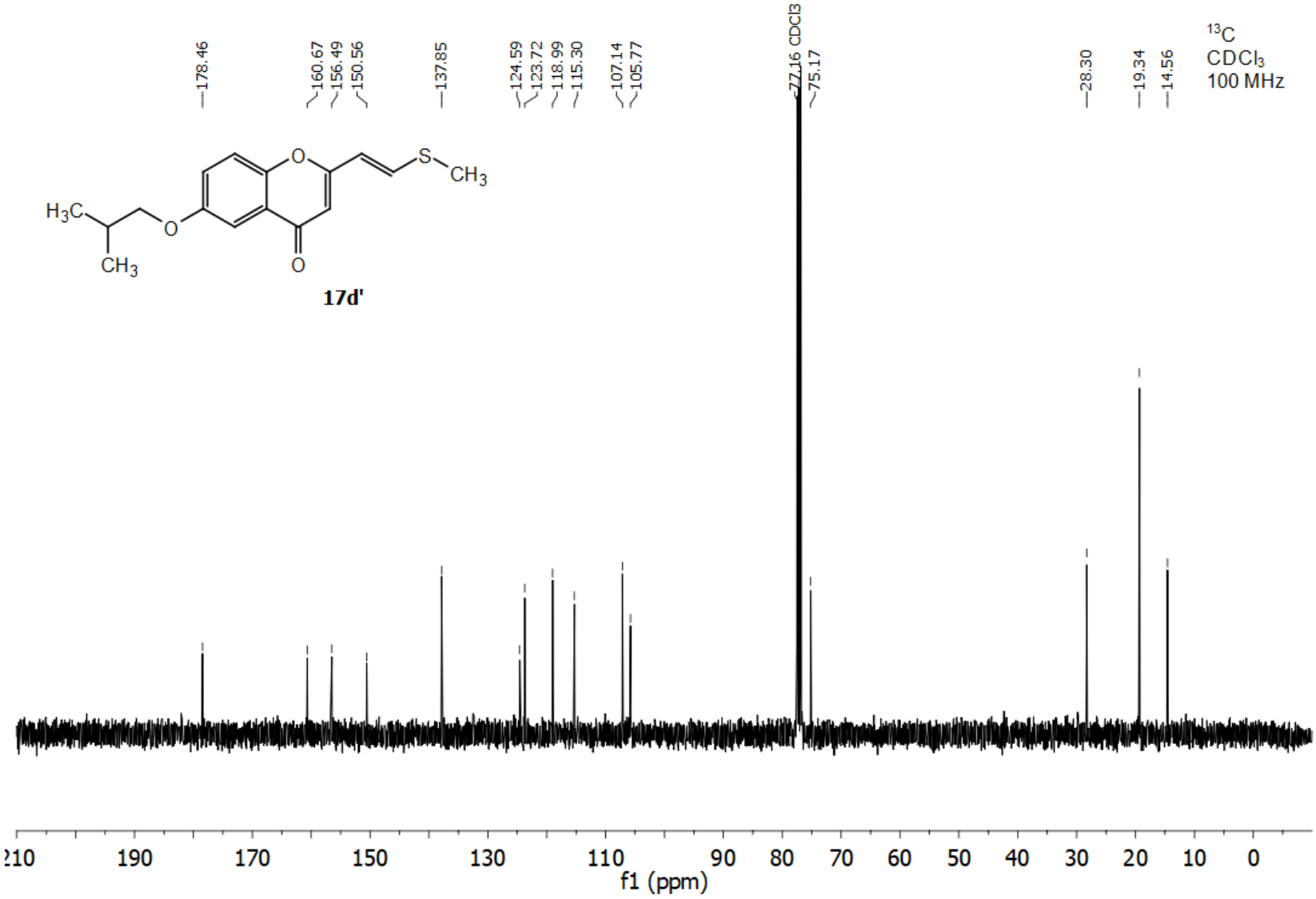

178.24
157.77
156.71
150.54
141.43
127.41
124.63
124.60
119.25
112.37
105.63
77.16 CDCl3
70.28
40.41
22.45
10.52
13C
CDCl3
100 MHz
H3C
O
O
O
S
CH3
O
17c
f1 (ppm)

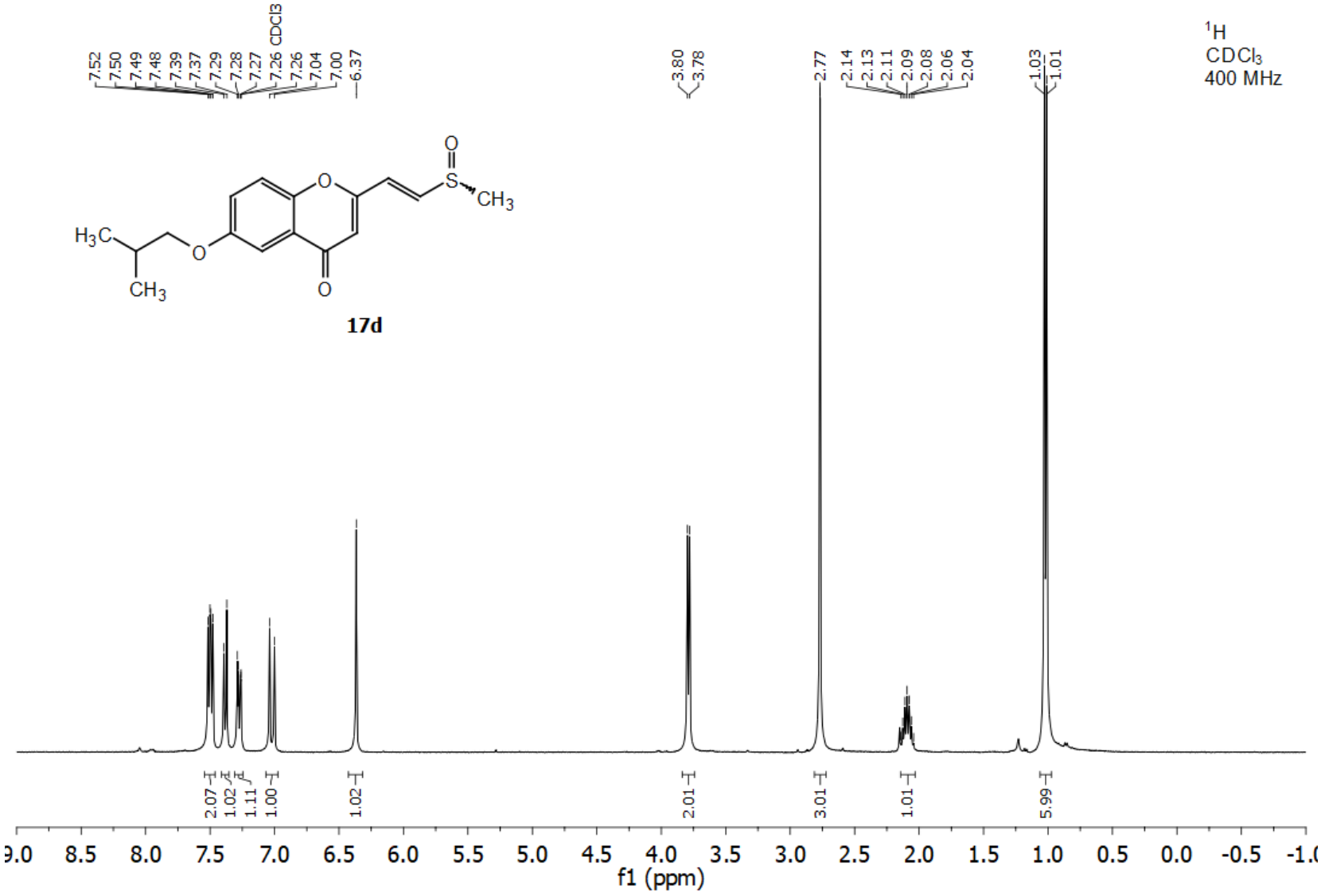

8.01
7.97
7.28
7.26 CDCl3
7.02
5.88
5.84
3.73
3.72
2.51
2.39
2.12
2.10
2.09
2.07
2.06
2.04
2.02
1.02
1.00
1H
CDCl3
400 MHz
O
S
CH3
O
H3C
O
CH3
CH3
O
1.00
1.04
2.13
0.98
2.12
3.26
3.00
1.34
6.23
f1 (ppm)

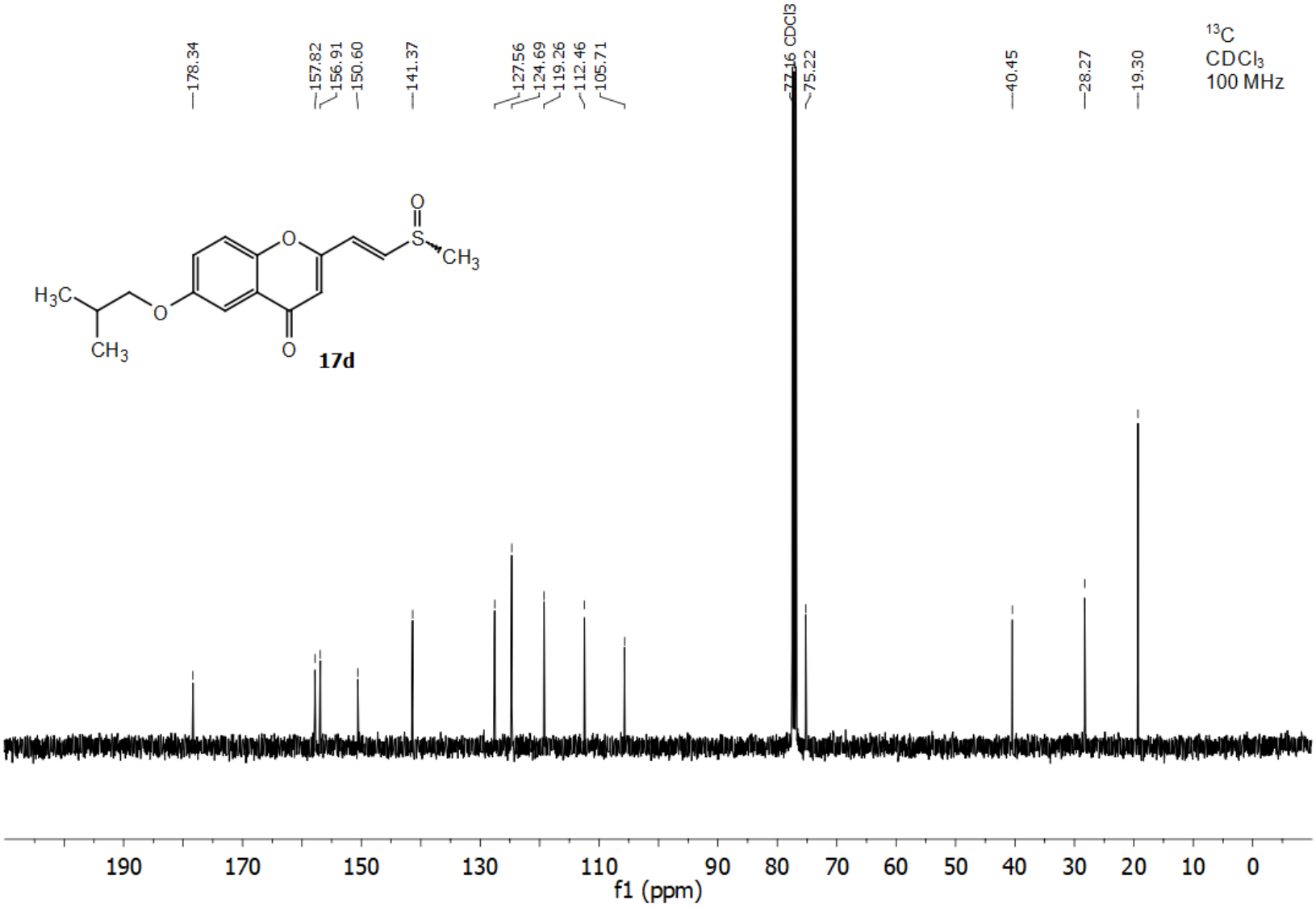
17d"

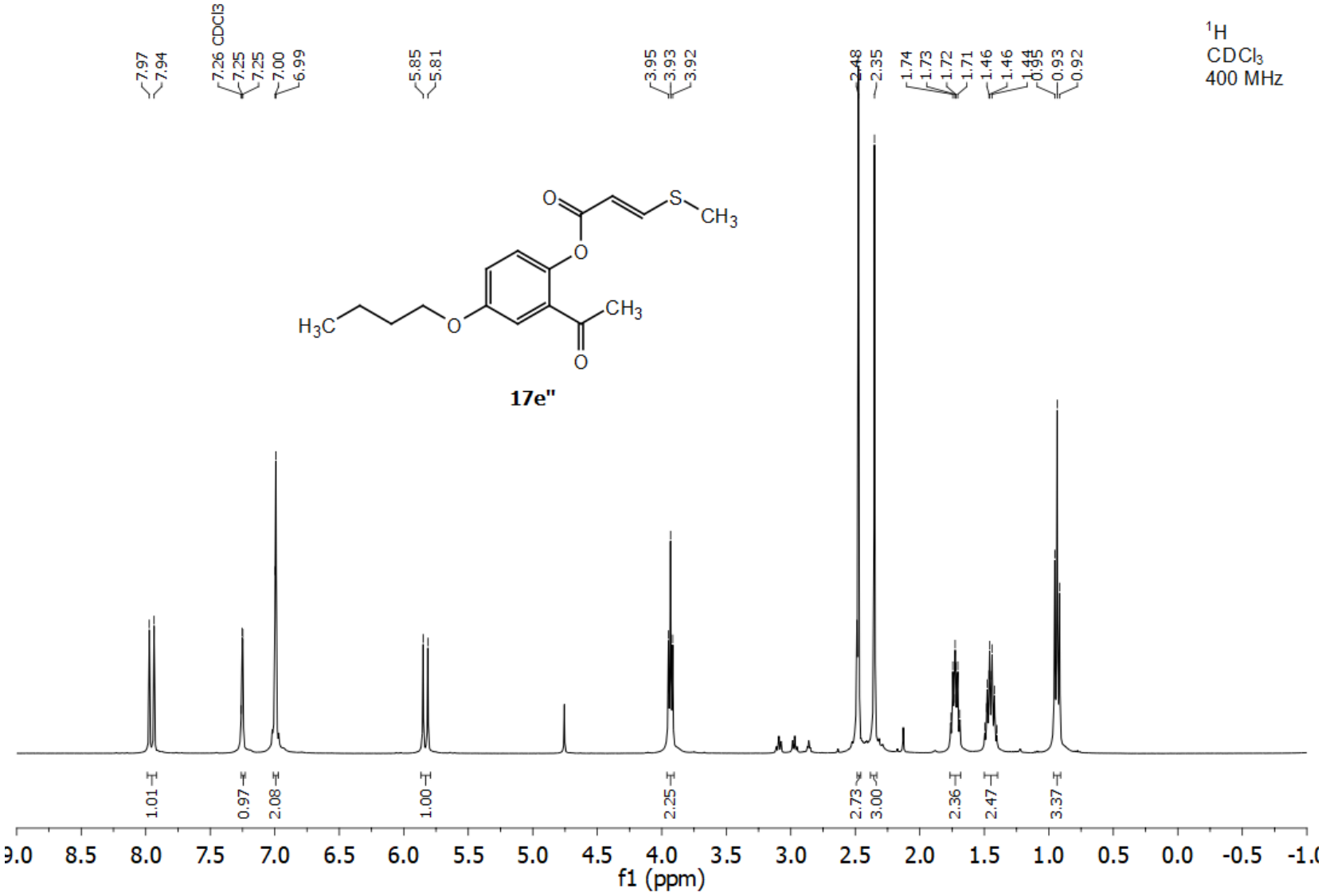

197.63
163.81
156.85
150.53
142.61
131.96
124.69
119.60
114.84
111.79
77.16 CDCl3
75.04
30.04
28.32
19.28
14.58
13C
CDCl3
100 MHz
O
O
S
CH3
H3C
O
CH3
CH3
O
17d"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

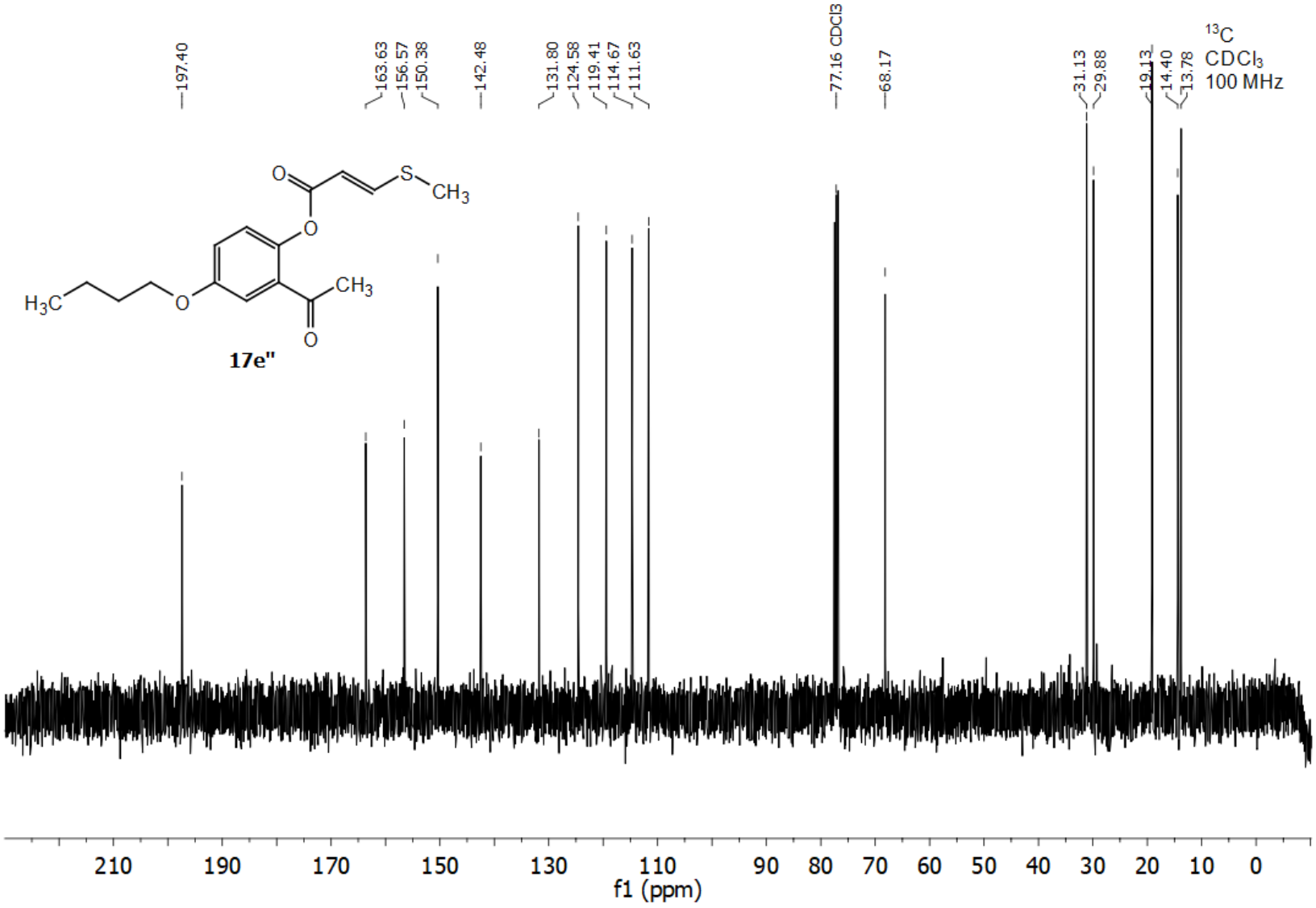

^{1}H
$CDCl_3$
400 MHz
7.55
7.52
7.50
7.50
7.35
7.33
7.26 CDCl3
7.23
7.22
7.21
7.20
6.06
5.95
5.92
3.80
3.78
2.42
2.14
2.12
2.11
2.09
2.07
2.06
2.04
1.03
1.01
O
S
CH_3
H_3C
O
CH_3
O
17d'
1.11
0.88
1.02
1.01
0.97
1.00
2.00
2.95
1.14
6.20
f1 (ppm)

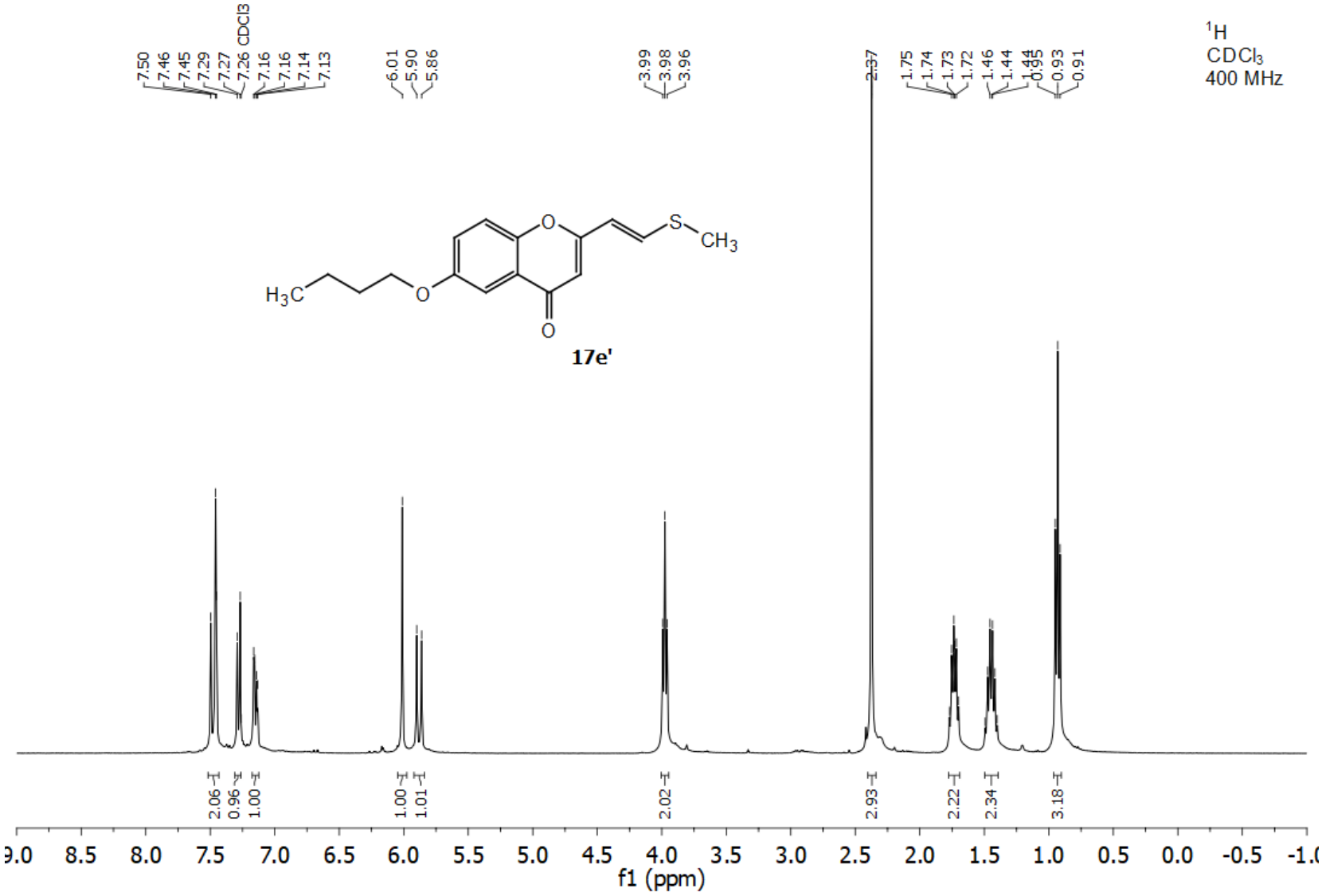

178.46
160.67
156.49
150.56
137.85
124.59
123.72
118.99
115.30
107.14
105.77
77.16 CDCl3
75.17
28.30
19.34
14.56
13C
CDCl3
100 MHz
H3C
CH3
O
O
O
S
CH3
17d'
f1 (ppm)

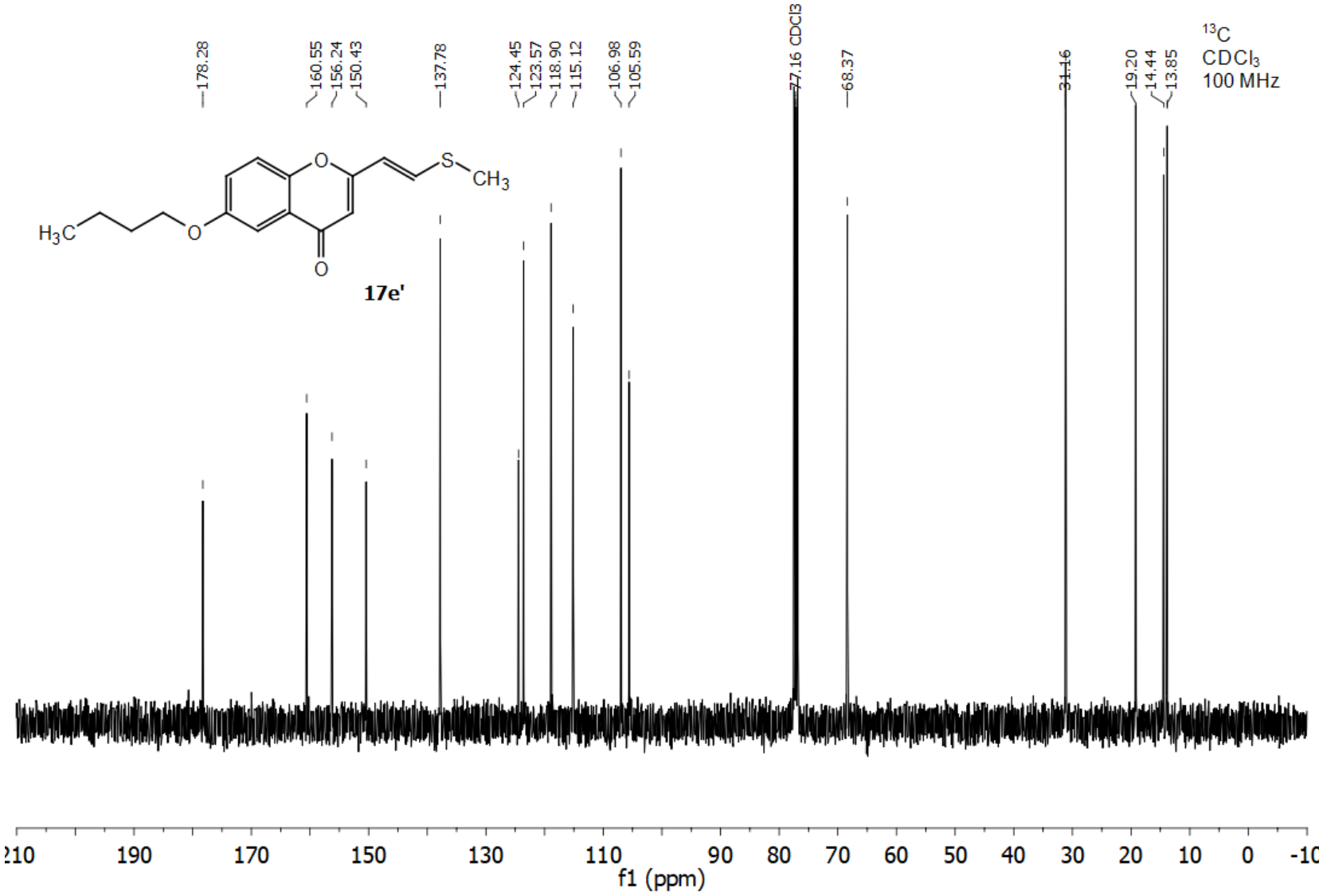

7.52
7.50
7.49
7.48
7.39
7.37
7.29
7.28
7.27
CDCl3
7.26
7.26
7.04
7.00
6.37
3.80
3.78
2.77
2.14
2.13
2.11
2.09
2.08
2.06
2.04
1.03
1.01
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
CH3
O
O
17d
2.07
1.02
1.11
1.00
1.02
2.01
3.01
1.01
5.99
f1 (ppm)

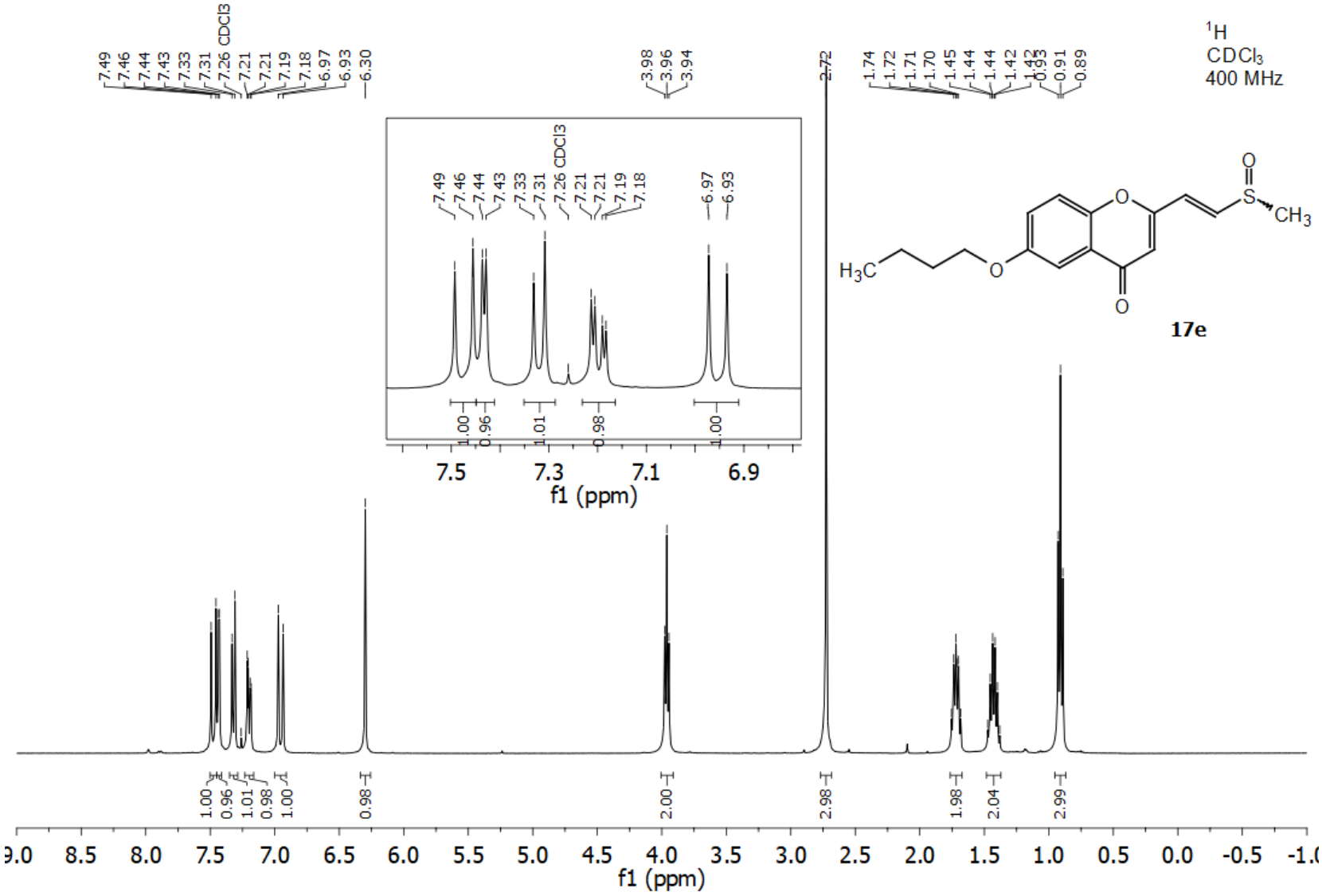

178.34
157.82
156.91
150.60
141.37
127.56
124.69
119.26
112.46
105.71
77.16 CDCl3
75.22
40.45
28.27
19.30
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
CH3
O
O
17d
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

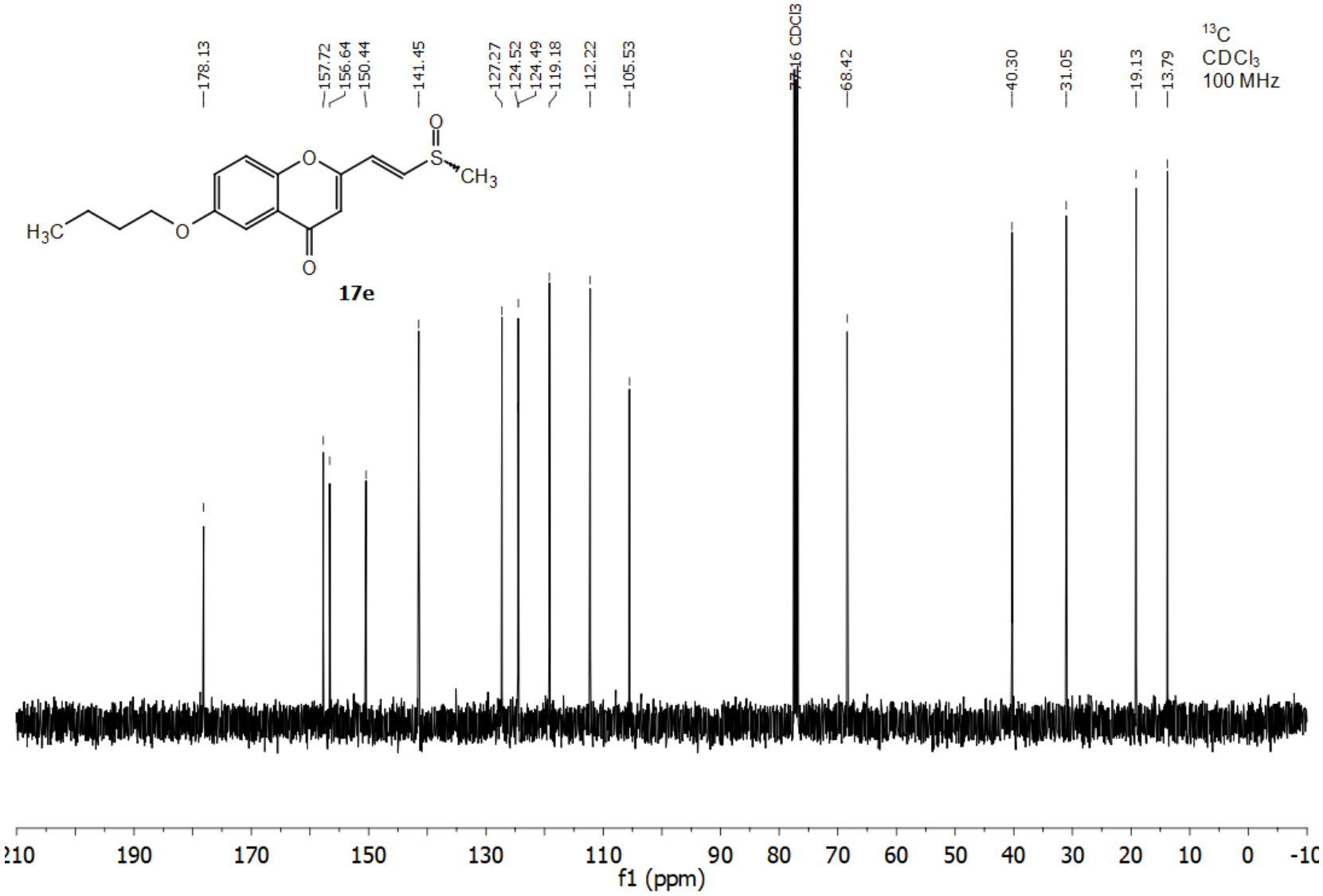

7.97
7.94
7.26 CDCl3
7.25
7.25
7.00
6.99
5.85
5.81
3.95
3.93
3.92
2.48
2.35
1.74
1.73
1.72
1.71
1.46
1.46
1.44
0.95
0.93
0.92
1H
CDCl3
400 MHz
O
O
S
CH3
O
H3C
O
CH3
O
17e"
1.01
0.97
2.08
1.00
2.25
2.73
3.00
2.36
2.47
3.37
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

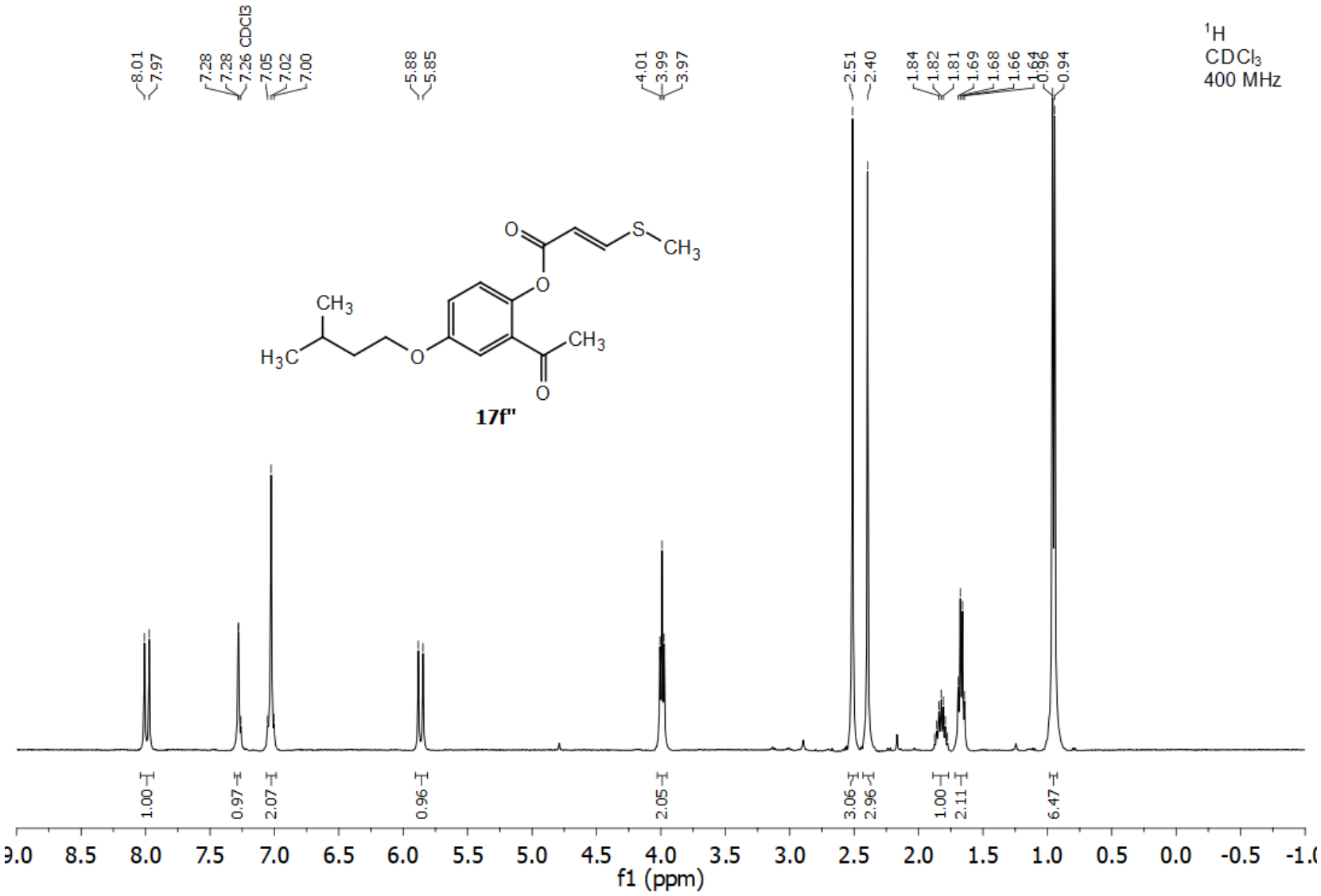

197.40
163.63
156.57
150.38
142.48
131.80
124.58
119.41
114.67
111.63
77.16 CDCl3
68.17
31.13
29.88
19.13
14.40
13.78
13C
CDCl3
100 MHz
17e"
f1 (ppm)

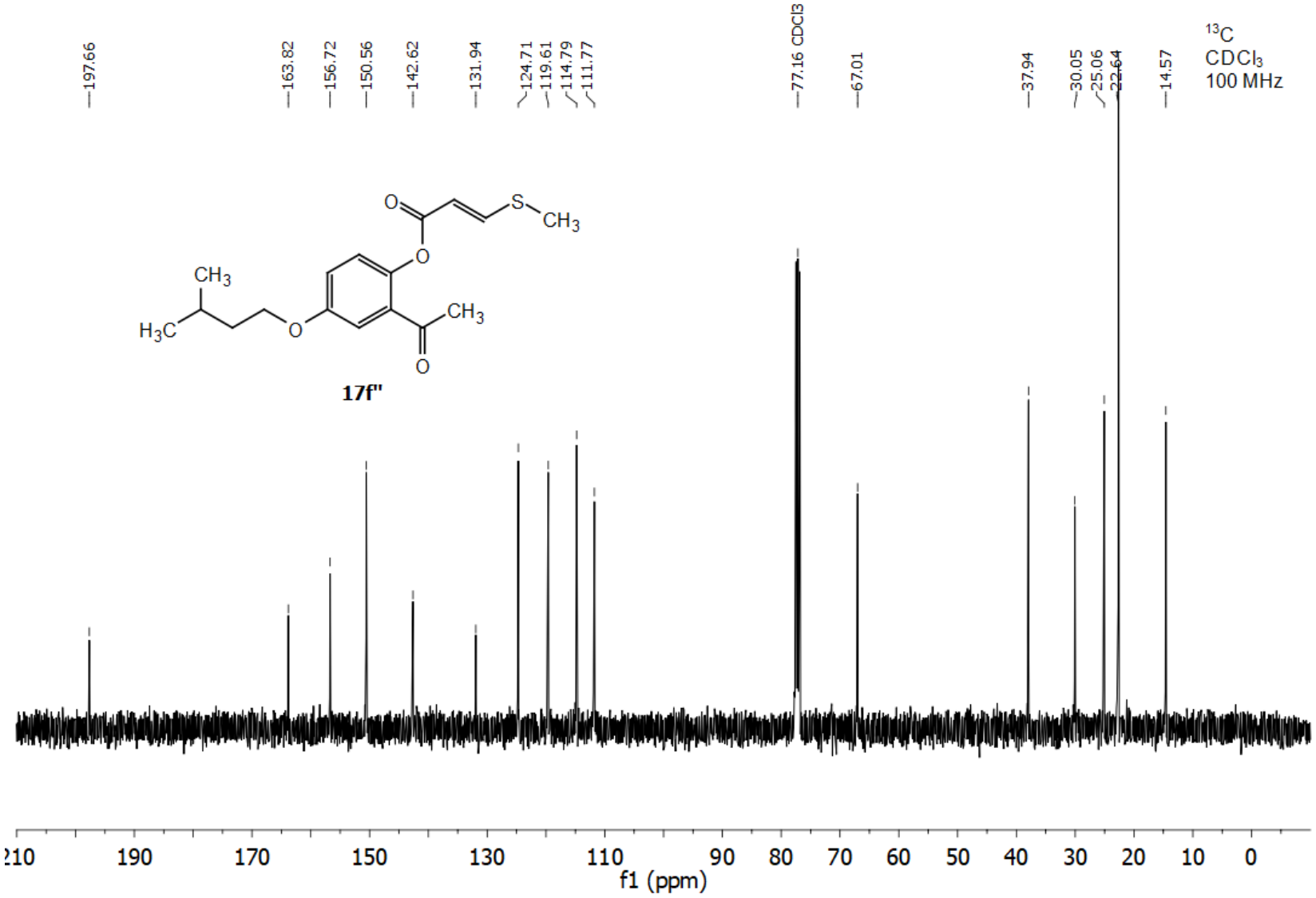

7.50
7.46
7.45
7.29
7.27
7.26 CDCl3
7.16
7.16
7.14
7.13
6.01
5.90
5.86
3.99
3.98
3.96
2.37
1.75
1.74
1.73
1.72
1.46
1.44
1.44
0.95
0.93
0.91
1H
CDCl3
400 MHz
O
S
CH3
H3C
O
O
17e'
2.06
0.96
1.00
1.00
1.01
2.02
2.93
2.22
2.34
3.18
f1 (ppm)

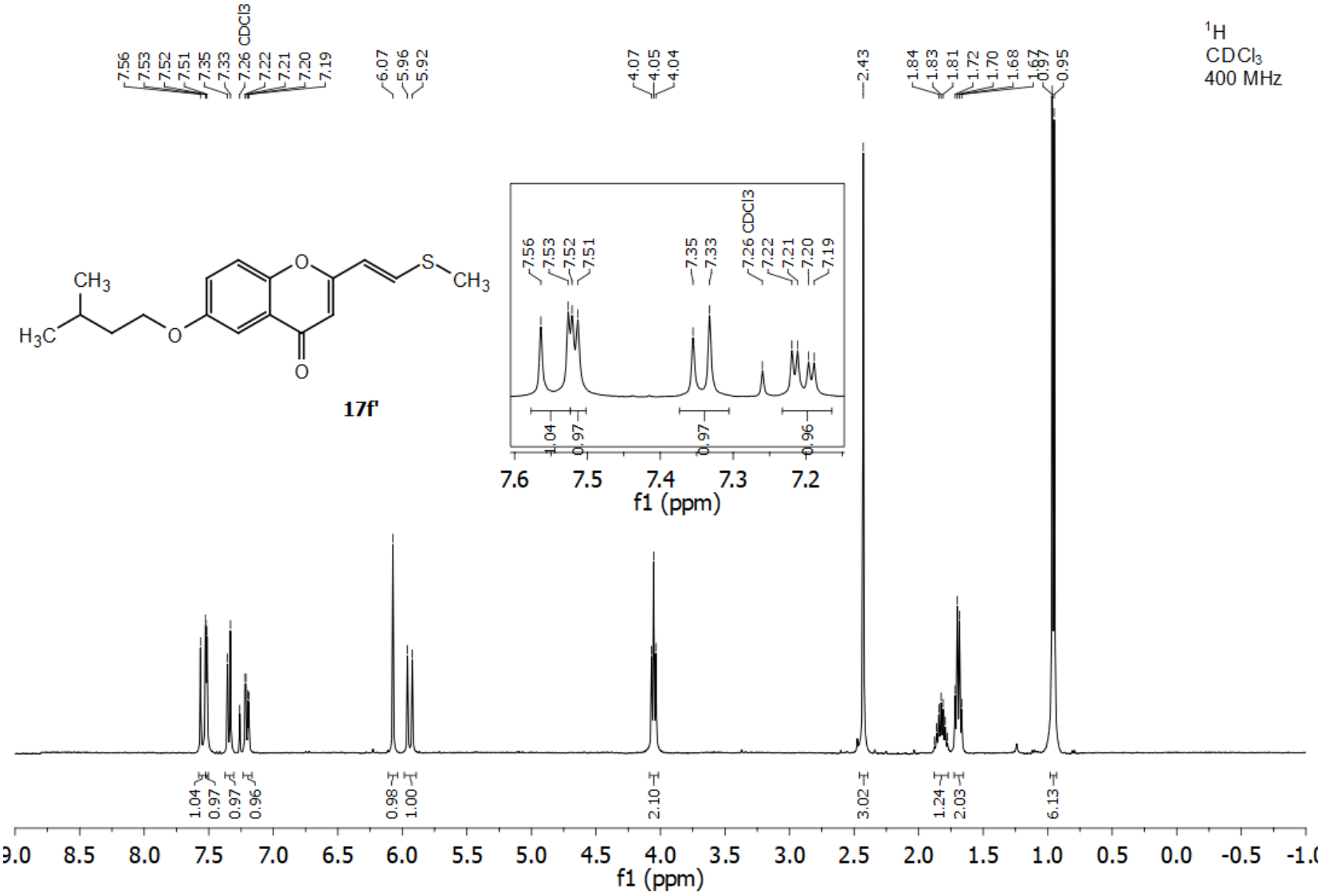

178.28
160.55
156.24
150.43
137.78
124.45
123.57
118.90
115.12
106.98
105.59
77.16 CDCl3
68.37
31.16
19.20
14.44
13.85
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
17e'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

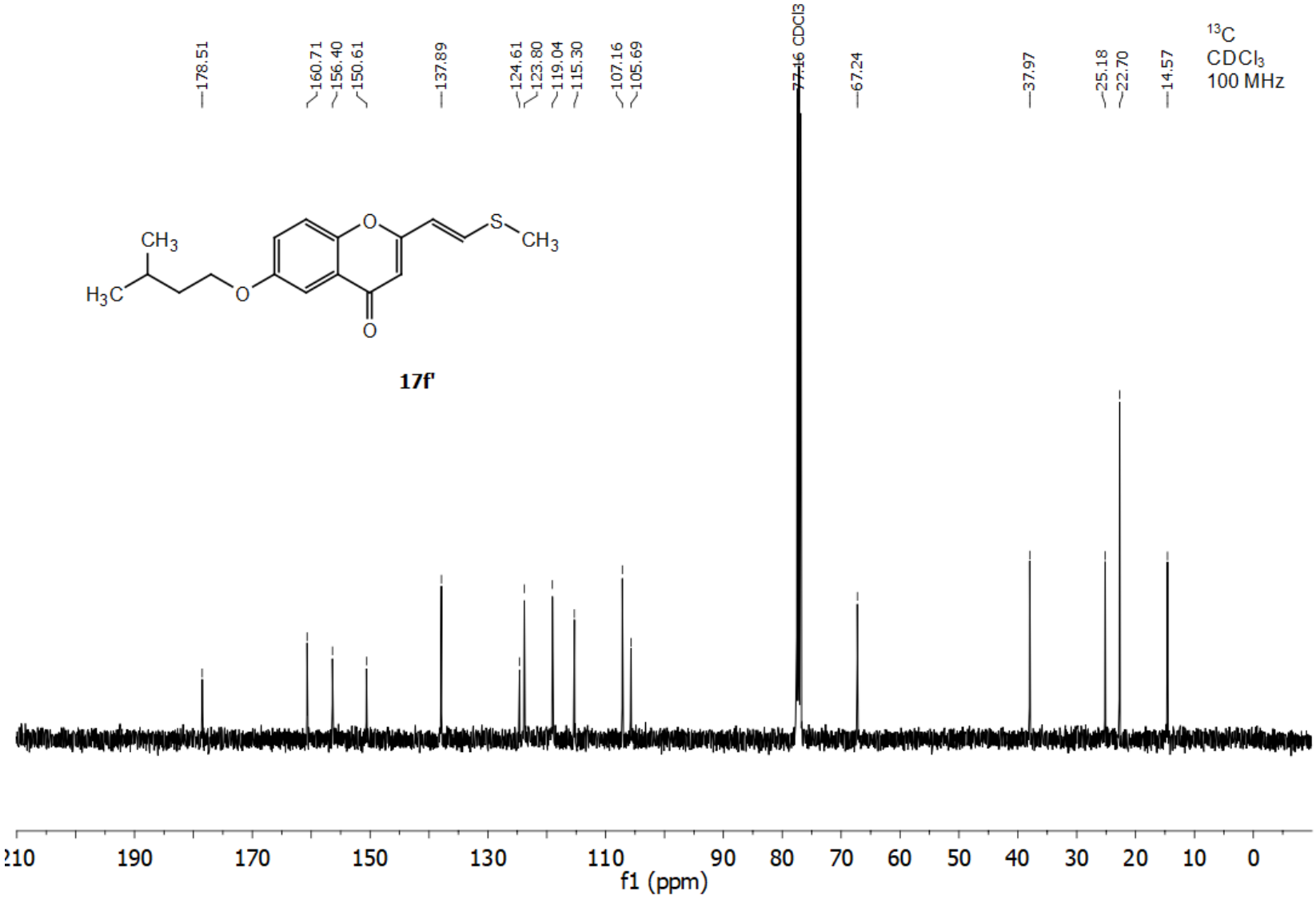

1H
CDCl3
400 MHz
17e
f1 (ppm)


178.13
157.72
156.64
150.44
141.45
127.27
124.52
124.49
119.18
112.22
105.53
77.16 CDCl3
68.42
40.30
31.05
19.13
13.79
13C
CDCl3
100 MHz
O
S
CH3
H3C
O
O
O
17e
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

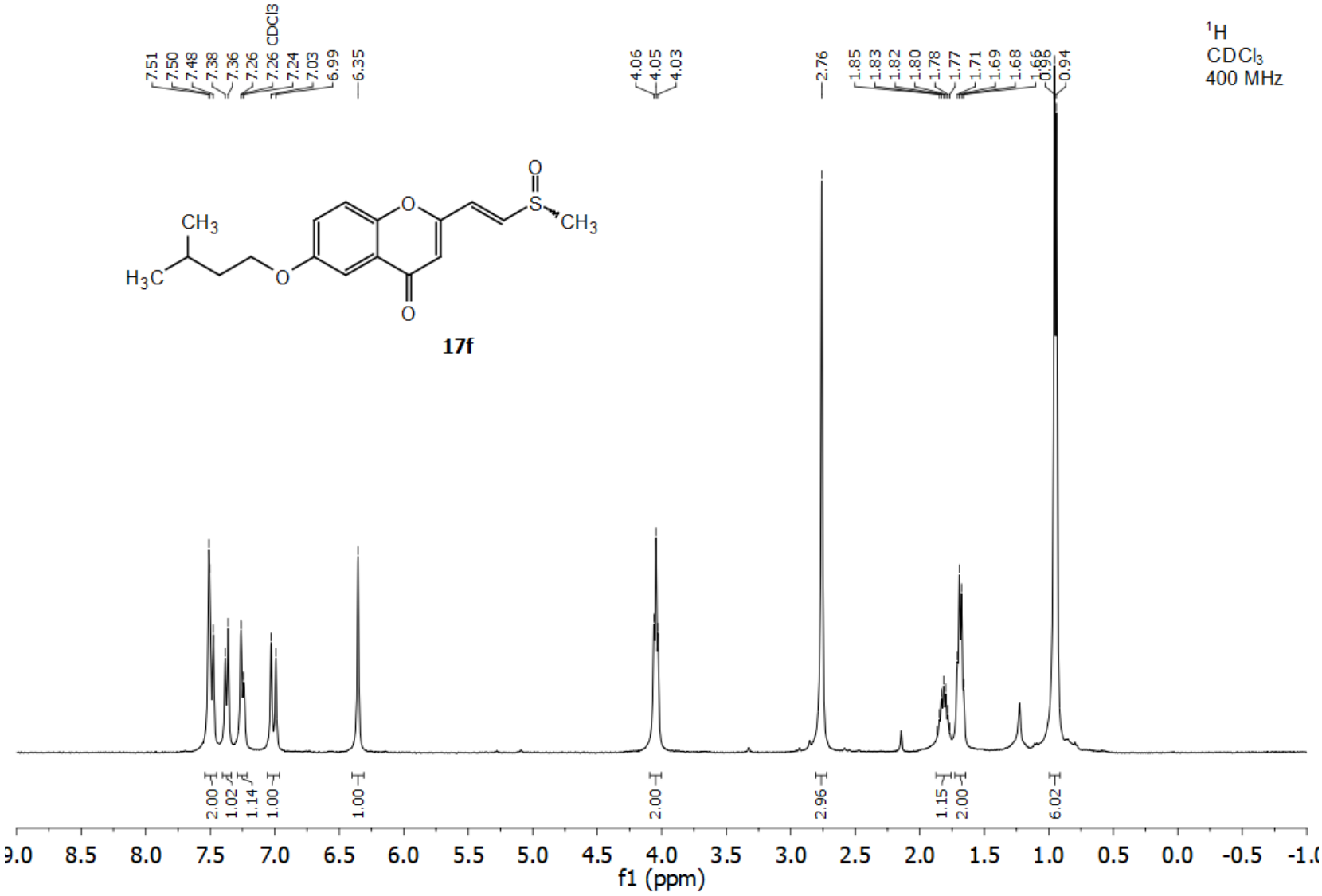

8.01
7.97
7.28
7.28
7.26 CDCl3
7.05
7.02
7.00
5.88
5.85
4.01
3.99
3.97
2.51
2.40
1.84
1.82
1.81
1.69
1.68
1.66
1.64
0.96
0.94
1H
CDCl3
400 MHz
O
S
CH3
O
CH3
H3C
O
CH3
O
17f"
1.00
0.97
2.07
0.96
2.05
3.06
2.96
1.00
2.11
6.47
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

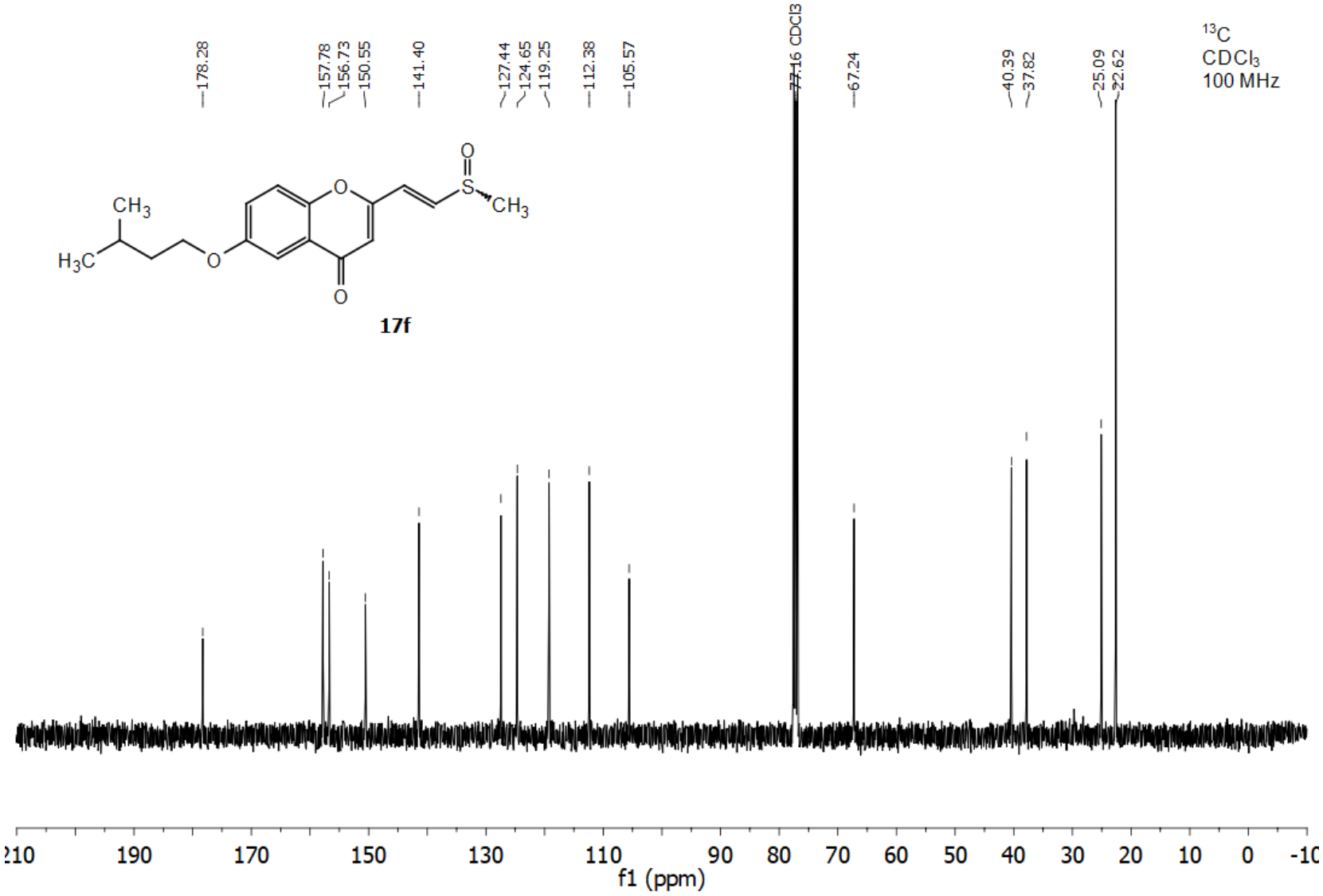

197.66
163.82
156.72
150.56
142.62
131.94
124.71
119.61
114.79
111.77
77.16 CDCl3
67.01
37.94
30.05
25.06
22.64
14.57
13C
CDCl3
100 MHz
O
S
CH3
O
CH3
H3C
O
CH3
O
17f''
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

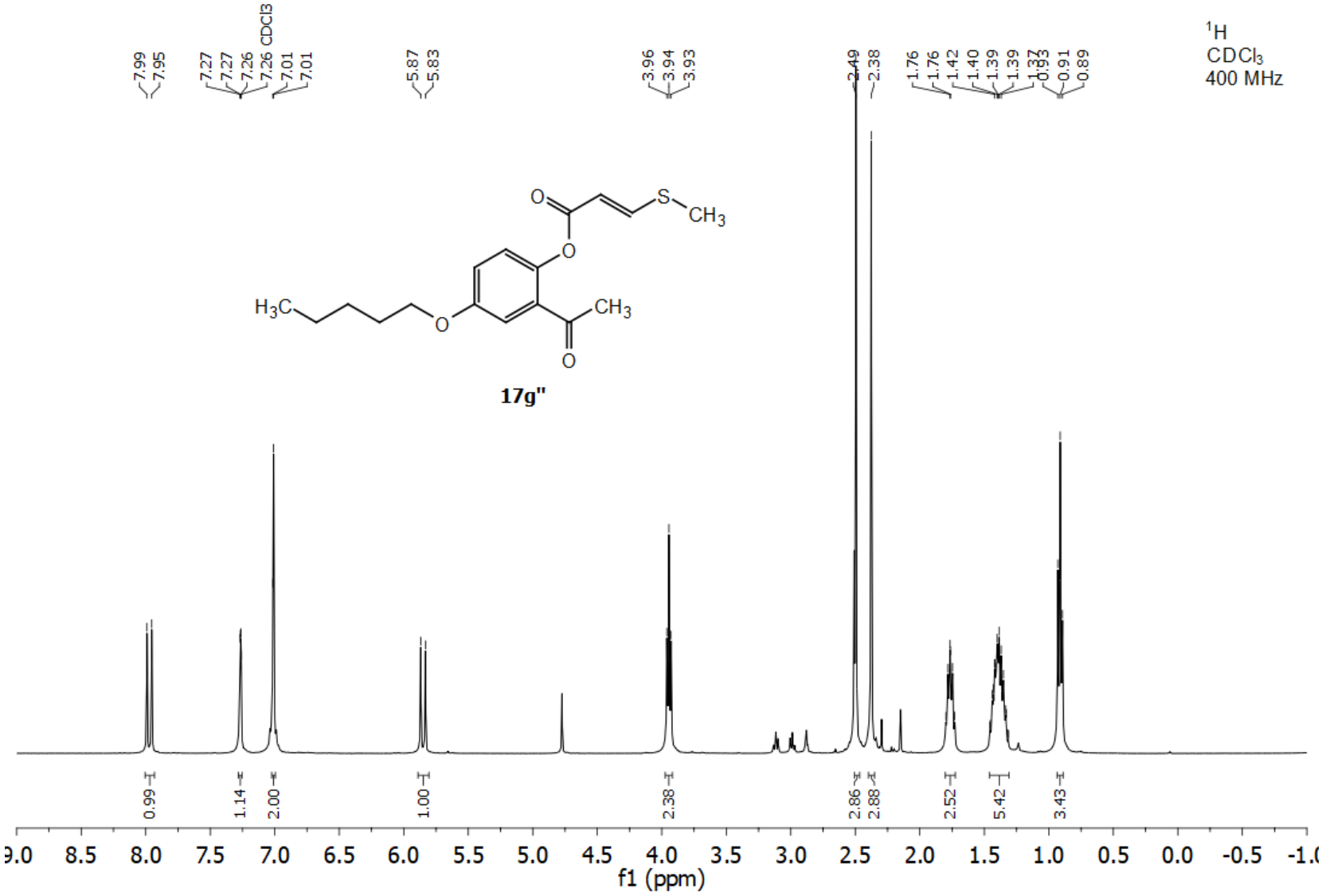

1H
CDCl3
400 MHz
7.56
7.53
7.52
7.51
7.35
7.33
7.26 CDCl3
7.22
7.21
7.20
7.19
6.07
5.96
5.92
4.07
4.05
4.04
2.43
1.84
1.83
1.81
1.72
1.70
1.68
1.67
0.97
0.95
CH3
H3C
O
O
O
S
CH3
17f'
1.04
0.97
0.97
0.96
0.98
1.00
2.10
3.02
1.24
2.03
6.13
f1 (ppm)

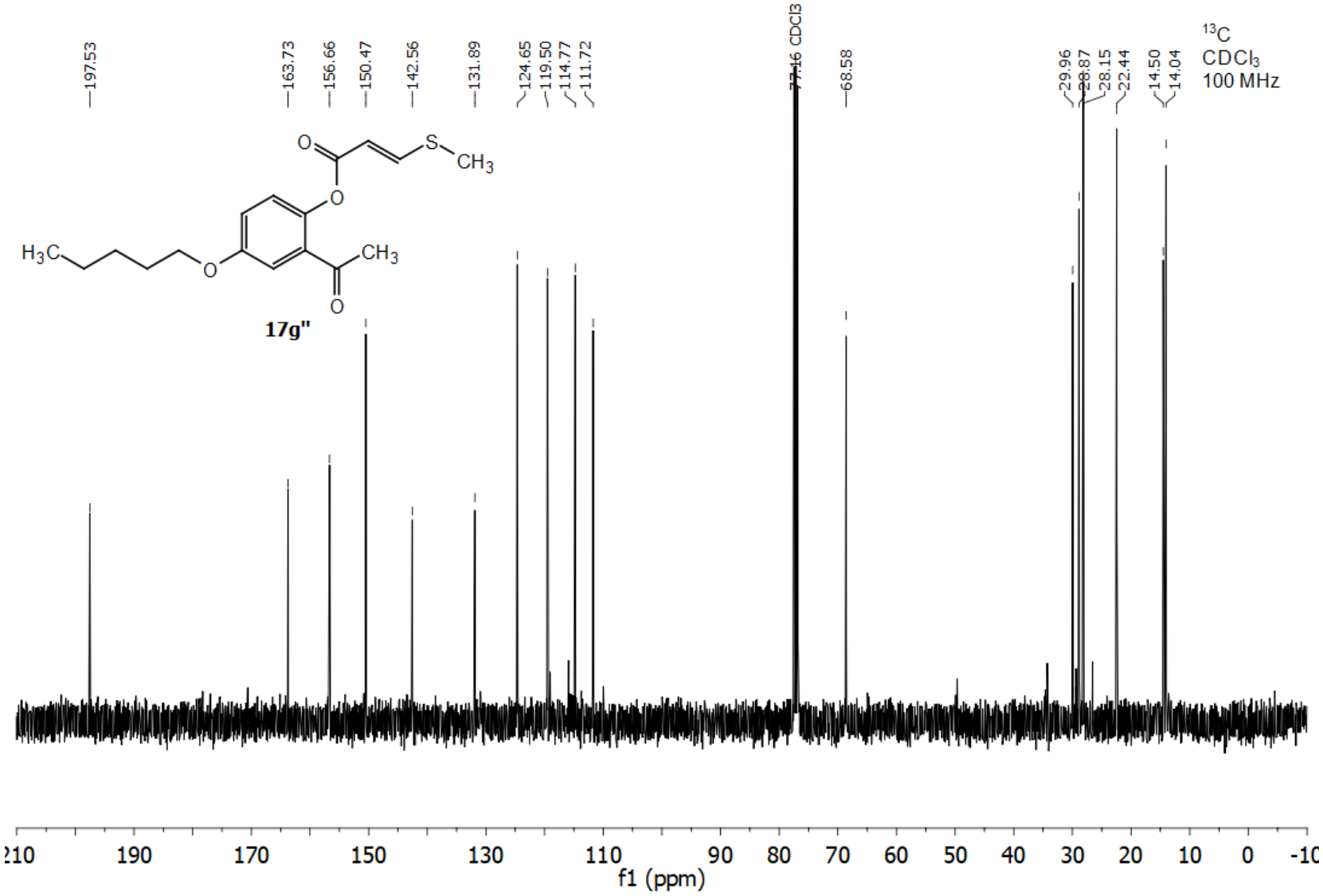

178.51
160.71
156.40
150.61
137.89
124.61
123.80
119.04
115.30
107.16
105.69
77.16 CDCl3
67.24
37.97
25.18
22.70
14.57
13C
CDCl3
100 MHz
CH3
H3C
O
O
O
S
CH3
f1 (ppm)

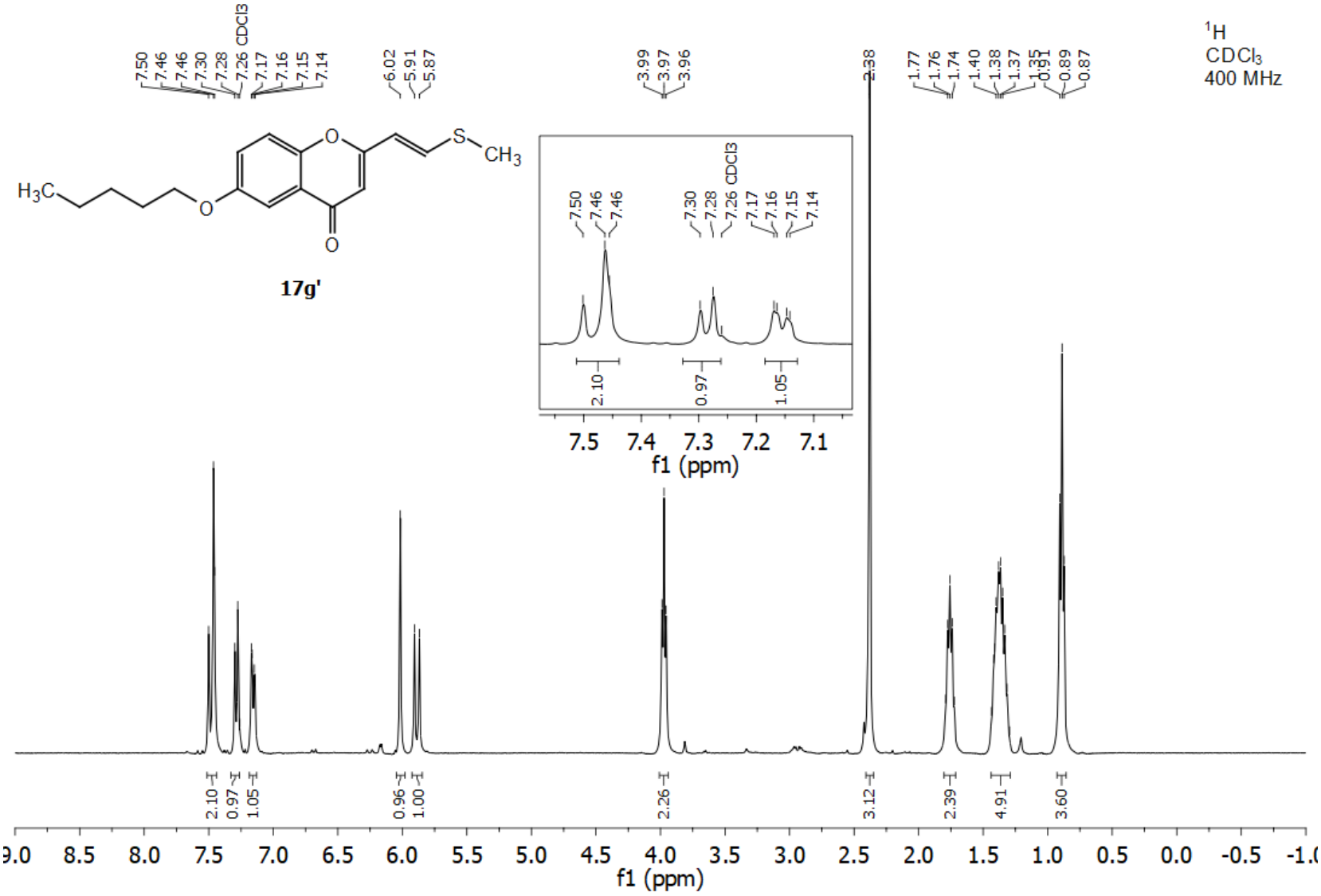
17f'

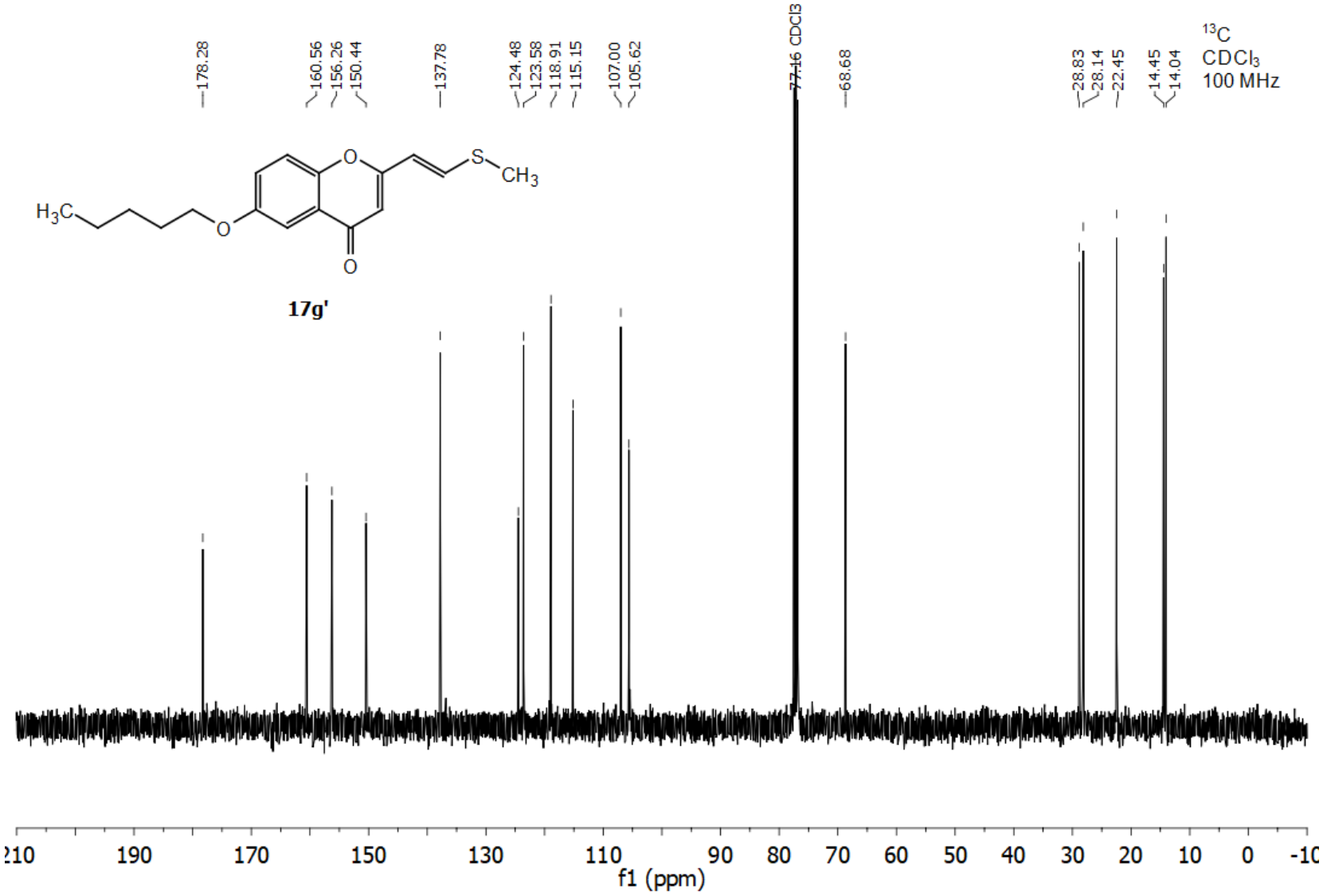

7.51
7.50
7.48
7.38
7.36
7.26
7.26 CDCl3
7.24
7.03
6.99
6.35
4.06
4.05
4.03
2.76
1.85
1.83
1.82
1.80
1.78
1.77
1.71
1.69
1.68
1.66
0.96
0.94
1H
CDCl3
400 MHz
CH3
H3C
O
O
O
S
CH3
O
17f
2.00
1.02
1.14
1.00
1.00
2.00
2.96
1.15
2.00
6.02
f1 (ppm)

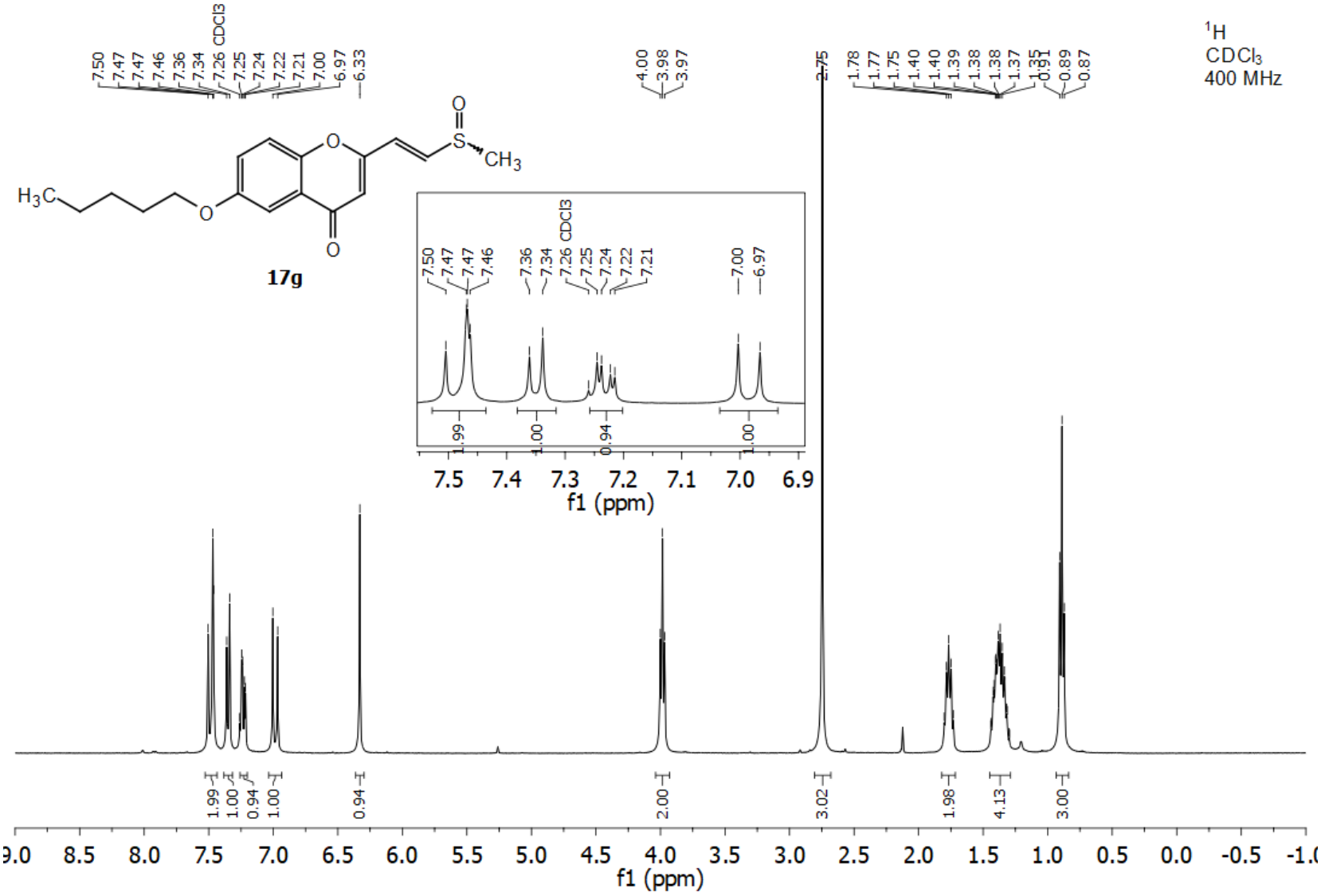

178.28
157.78
156.73
150.55
141.40
127.44
124.65
119.25
112.38
105.57
77.16 CDCl3
67.24
40.39
37.82
25.09
22.62
13C
CDCl3
100 MHz
CH3
H3C
O
O
O
S
CH3
O
17f
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

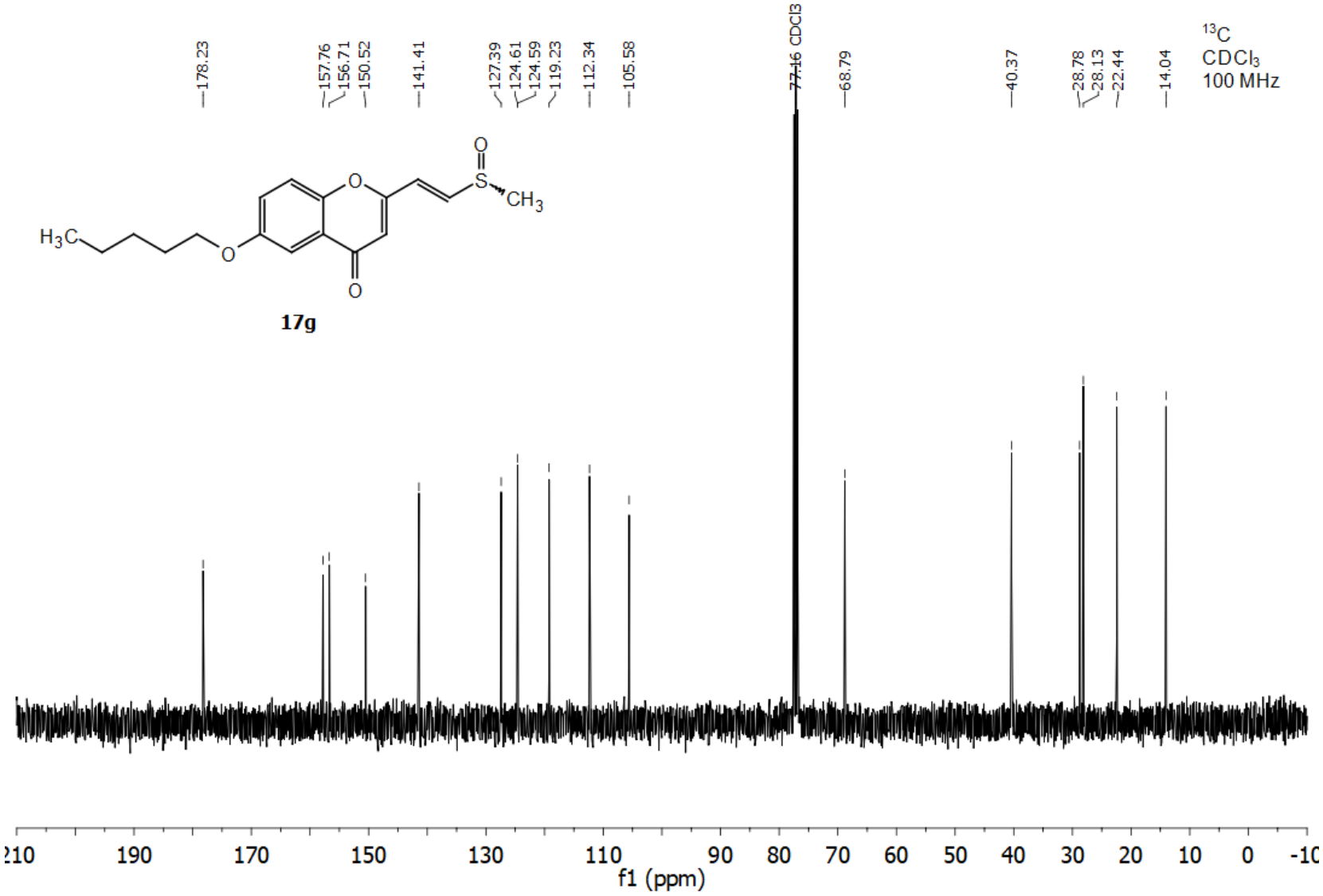

7.99
7.95
7.27
7.27
7.26
CDCl3
7.26
7.01
7.01
5.87
5.83
3.96
3.94
3.93
2.49
2.38
1.76
1.76
1.42
1.40
1.39
1.39
1.37
0.93
0.91
0.89
1H
CDCl3
400 MHz
O
O
S
CH3
O
H3C
O
CH3
O
17g"
0.99
1.14
2.00
1.00
2.38
2.86
2.88
2.52
5.42
3.43
f1 (ppm)

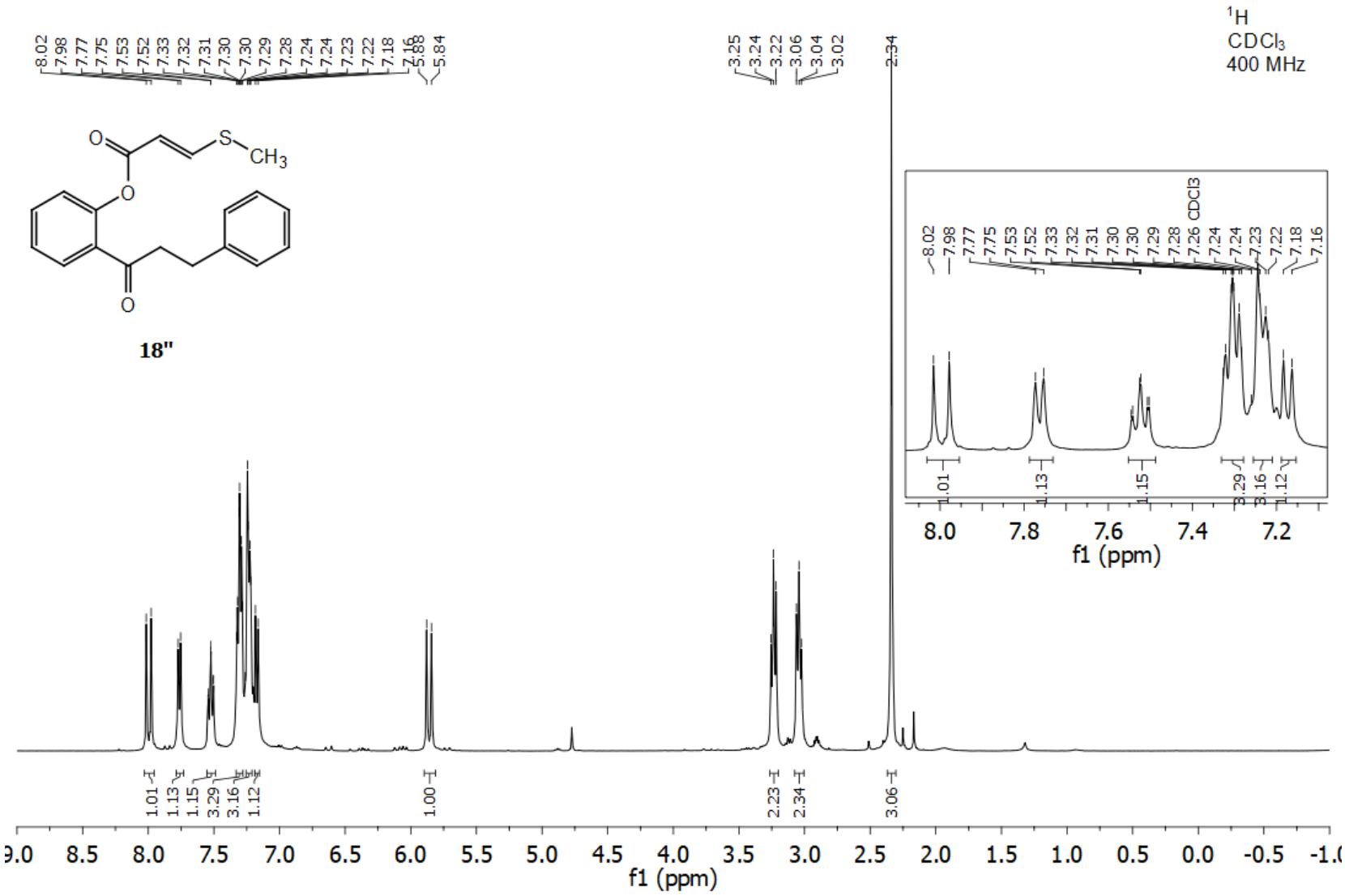

197.53
163.73
156.66
150.47
142.56
131.89
124.65
119.50
114.77
111.72
77.16 CDCl3
68.58
29.96
28.87
28.15
22.44
14.50
14.04
13C
CDCl3
100 MHz
O
O
S
CH3
H3C
O
CH3
O
17g"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

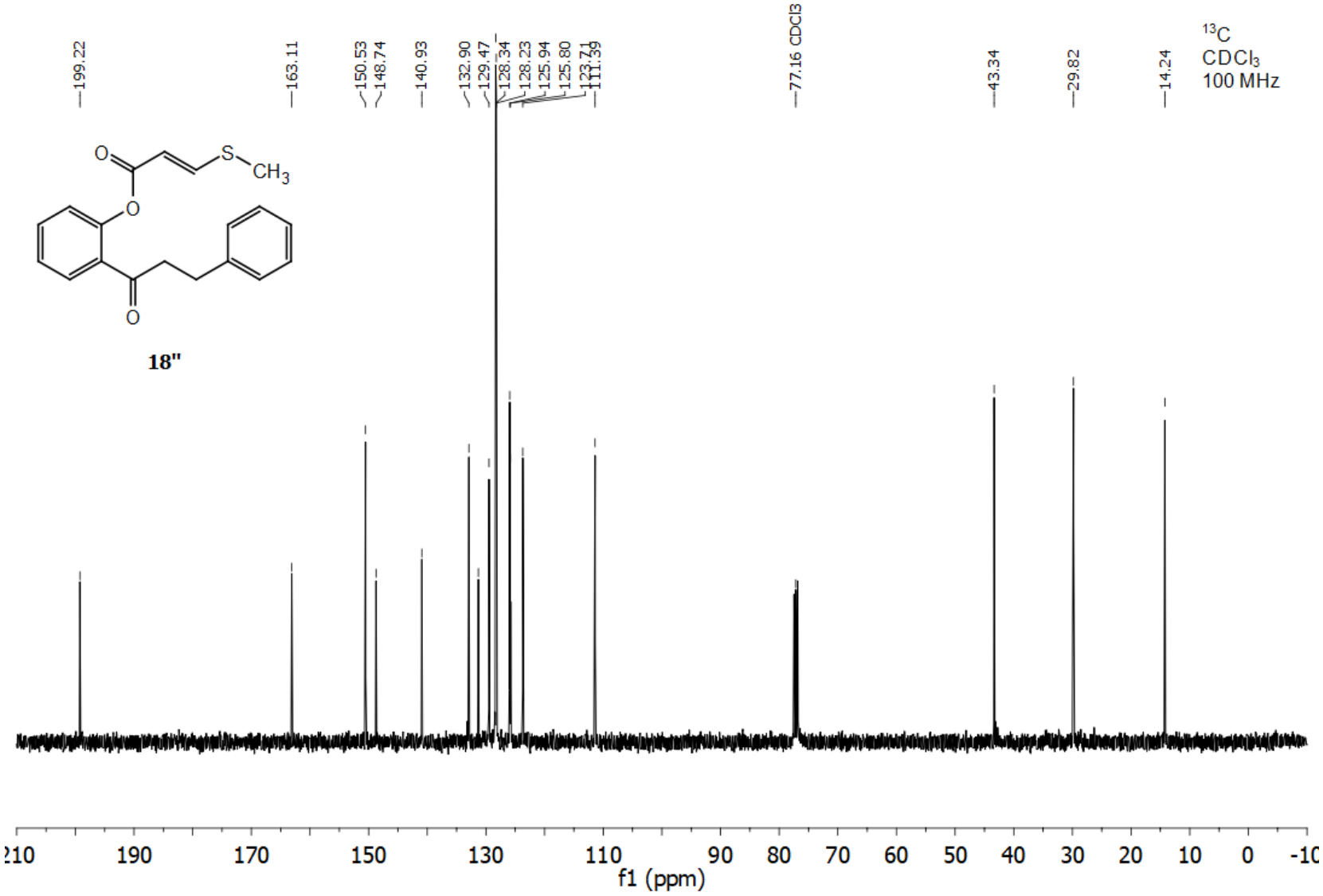

7.50
7.46
7.46
7.30
7.28
7.26 CDCl3
7.17
7.16
7.15
7.14
6.02
5.91
5.87
3.99
3.97
3.96
2.38
1.77
1.76
1.74
1.40
1.38
1.37
1.35
0.91
0.89
0.87
1H
CDCl3
400 MHz
H3C
O
O
O
S
CH3
17g'
2.10
0.97
1.05
0.96
1.00
2.26
3.12
2.39
4.91
3.60
f1 (ppm)

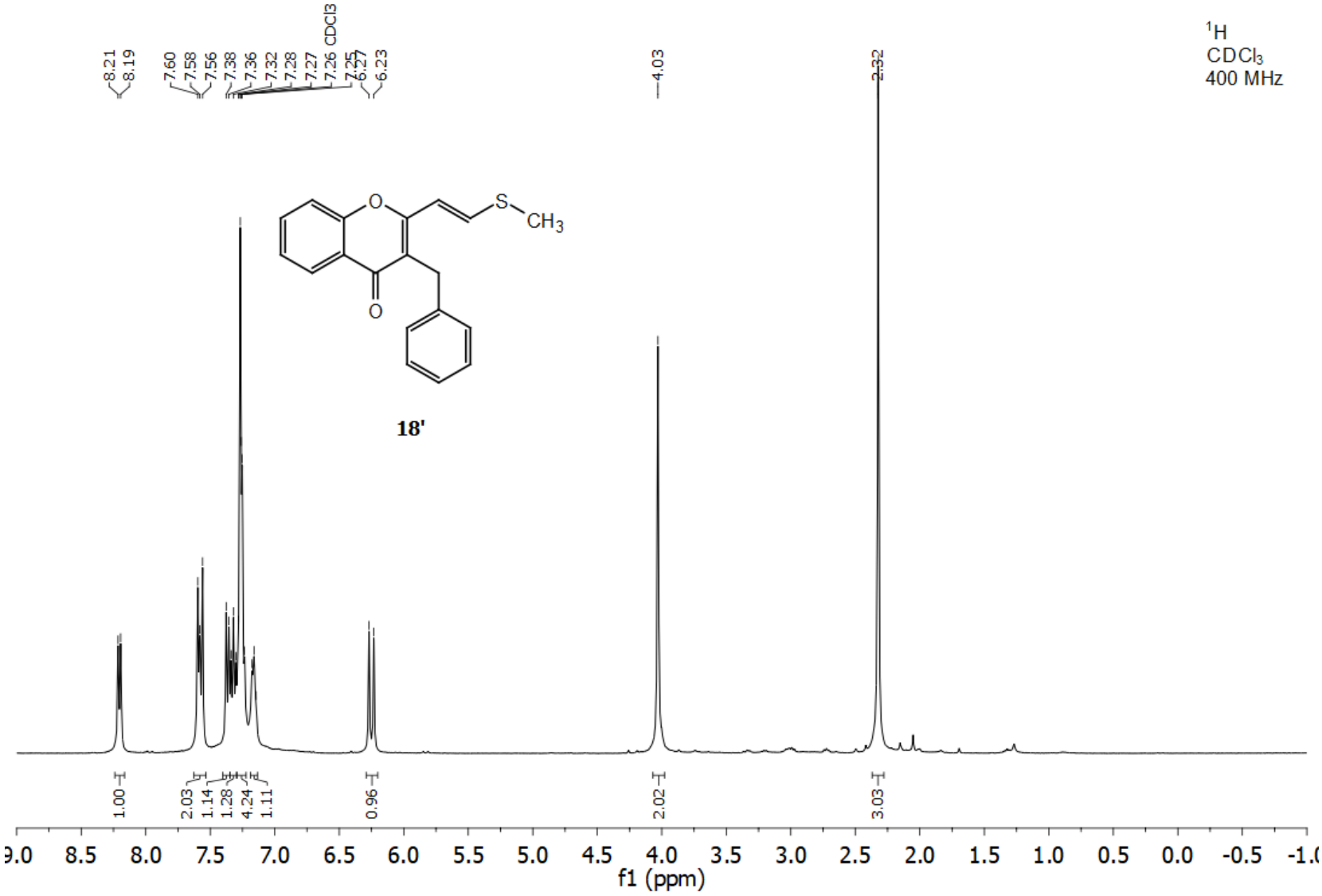

178.28
160.56
156.26
150.44
137.78
124.48
123.58
118.91
115.15
107.00
105.62
77.16 CDCl3
68.68
28.83
28.14
22.45
14.45
14.04
13C
CDCl3
100 MHz
H3C
O
O
O
S
CH3
17g'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

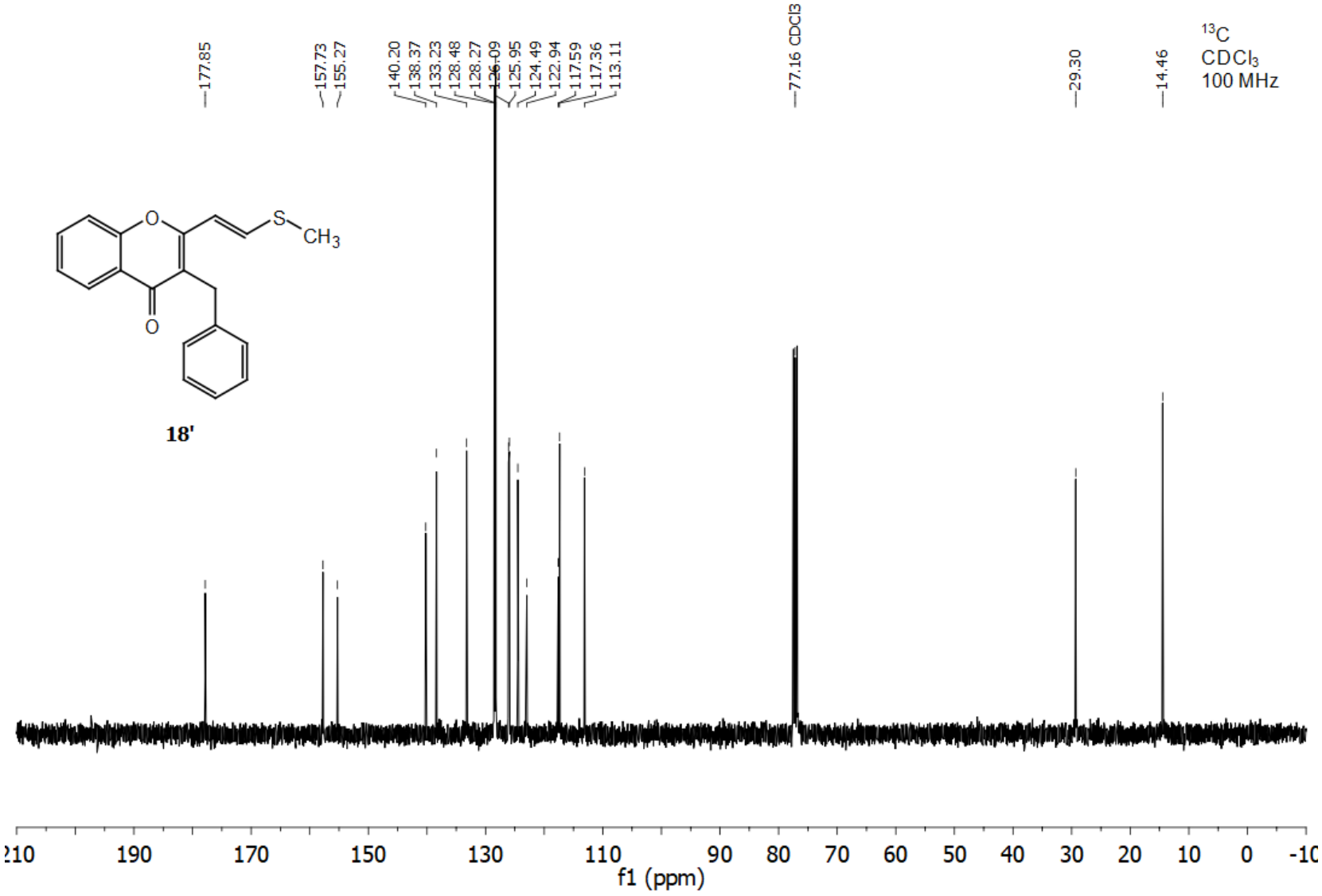

17g
^{1}H
CDCl$_3$
400 MHz
f1 (ppm)

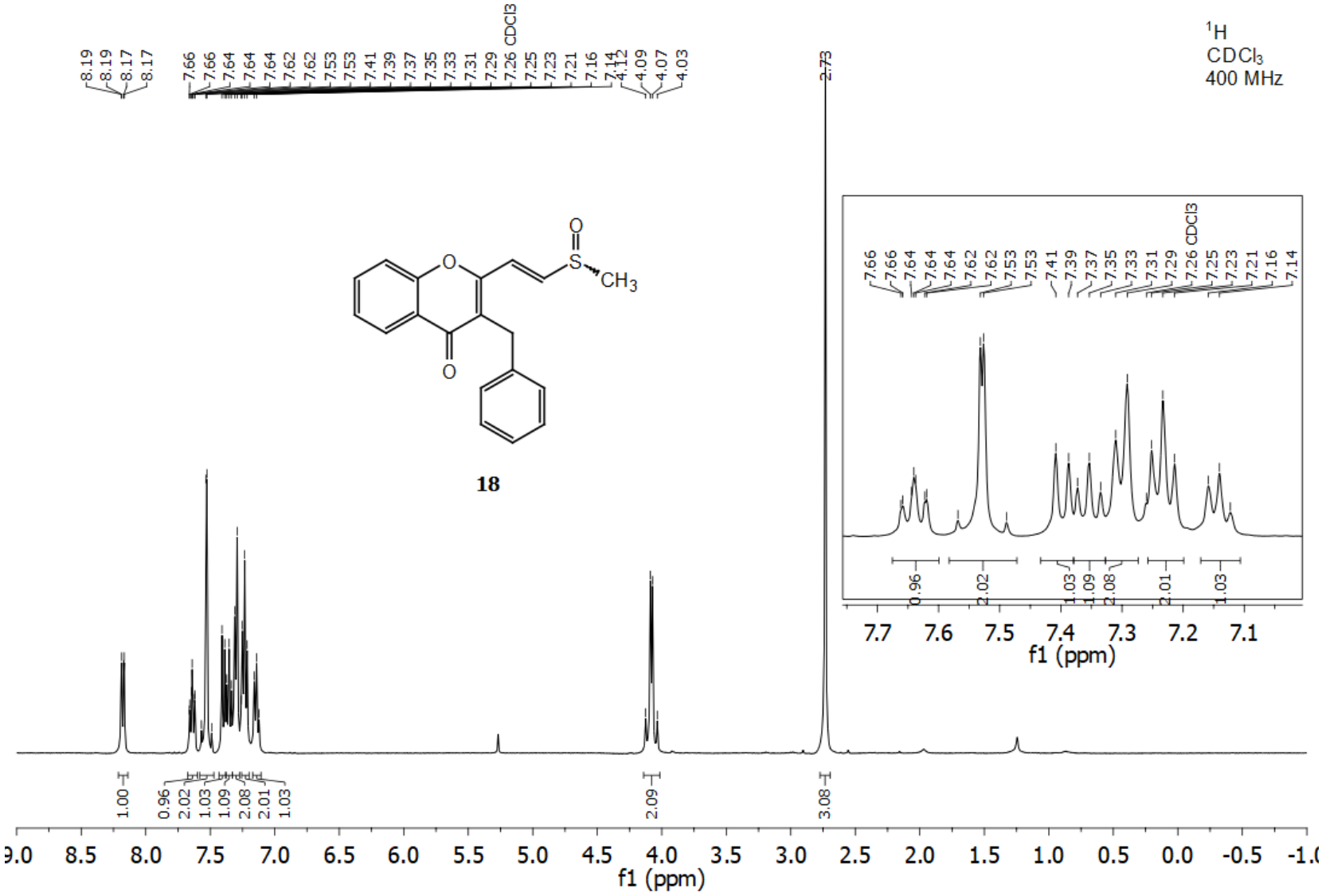

178.23
157.76
156.71
150.52
141.41
127.39
124.61
124.59
119.23
112.34
105.58
77.16 CDCl3
68.79
40.37
28.78
28.13
22.44
14.04
13C
CDCl3
100 MHz
H3C
O
O
O
S
CH3
O
17g
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


^{1}H
$CDCl_3$
400 MHz
8.02 7.98 7.77 7.75 7.53 7.52 7.33 7.32 7.31 7.30 7.30 7.29 7.28 7.24 7.24 7.23 7.22 7.18 7.16 5.88 5.84
3.25 3.24 3.22 3.06 3.04 3.02 2.34
O
S
CH_3
O
O
18"
1.01 1.13 1.15 3.29 3.16 1.12 1.00 2.23 2.34 3.06
f1 (ppm)
8.02 7.98 7.77 7.75 7.53 7.52 7.33 7.32 7.31 7.30 7.30 7.29 7.28 7.26 CDCl3 7.24 7.24 7.23 7.22 7.18 7.16
1.01 1.13 1.15 3.29 3.16 1.12
f1 (ppm)

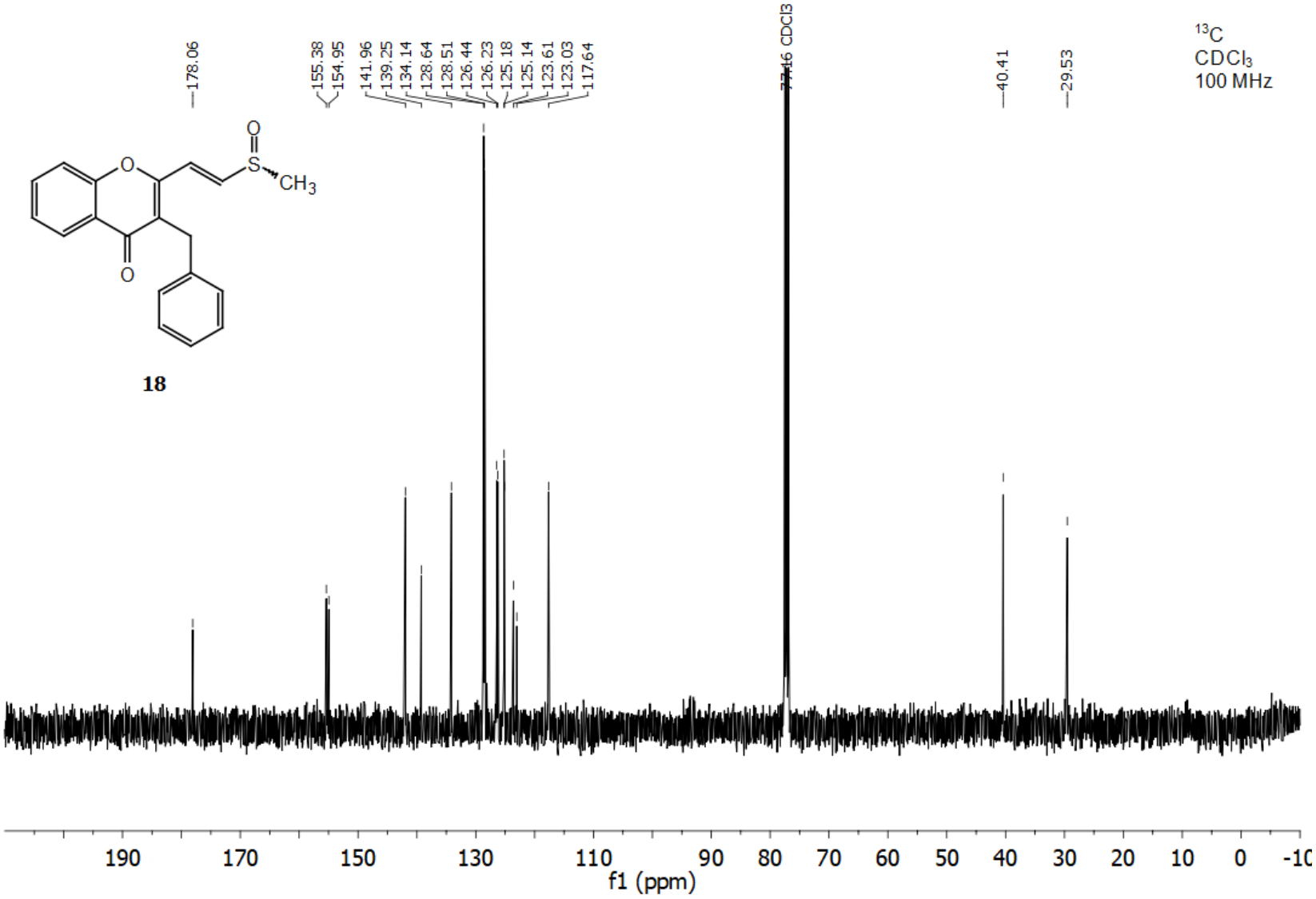

199.22
163.11
150.53
148.74
140.93
132.90
129.47
128.34
128.23
125.94
125.80
123.71
111.39
77.16 CDCl3
43.34
29.82
14.24
13C
CDCl3
100 MHz
O
S
CH3
O
O
18"
f1 (ppm)

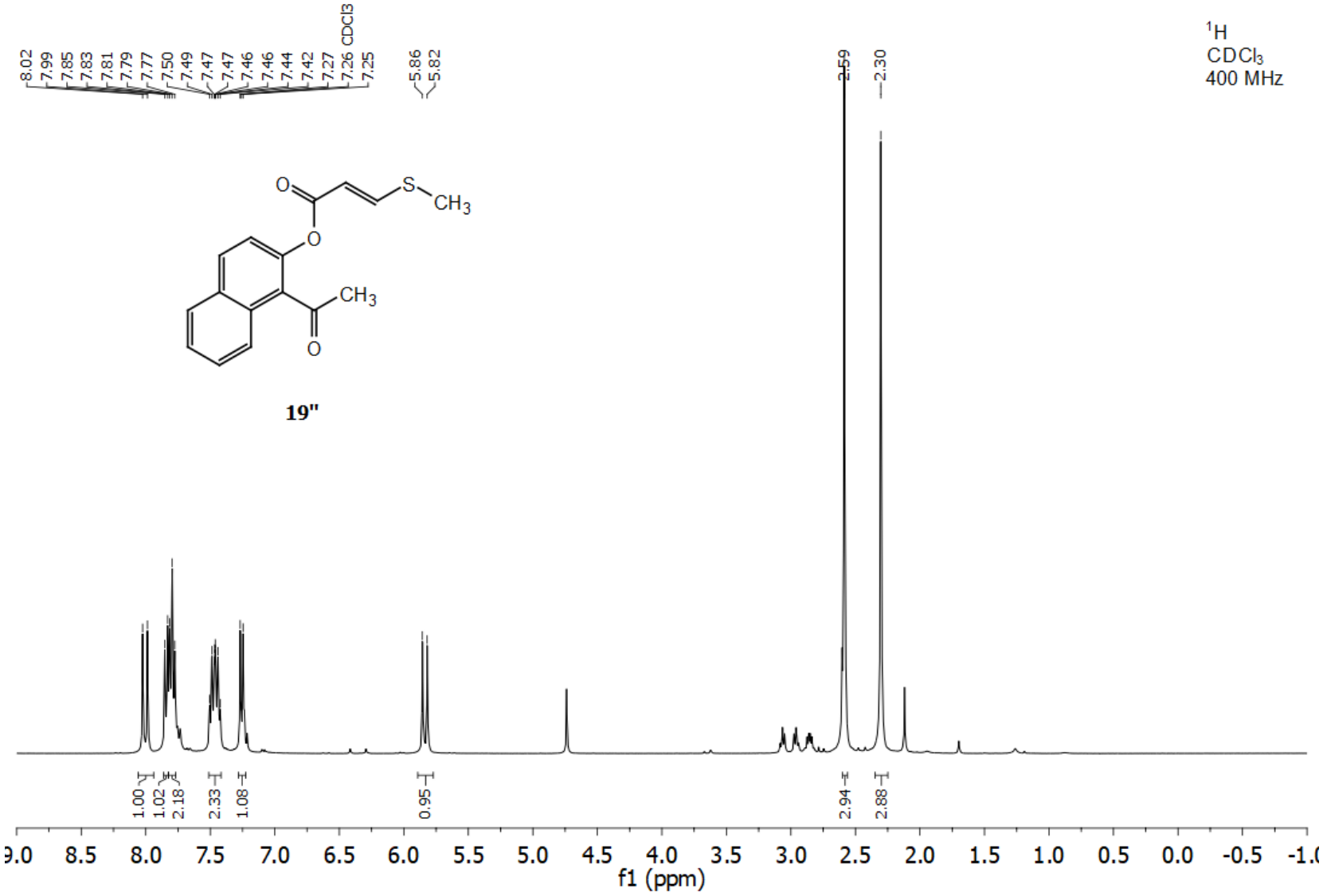

8.21
8.19
7.60
7.58
7.56
7.38
7.36
7.32
7.28
7.27
7.26 CDCl3
7.25
6.27
6.23
4.03
2.32
1H
CDCl3
400 MHz
O
S
CH3
O
18'
1.00
2.03
1.14
1.28
4.24
1.11
0.96
2.02
3.03
f1 (ppm)


177.85
157.73
155.27
140.20
138.37
133.23
128.48
128.27
126.09
125.95
124.49
122.94
117.59
117.36
113.11
77.16 CDCl3
29.30
14.46
13C
CDCl3
100 MHz
O
S
CH3
O
18'
f1 (ppm)

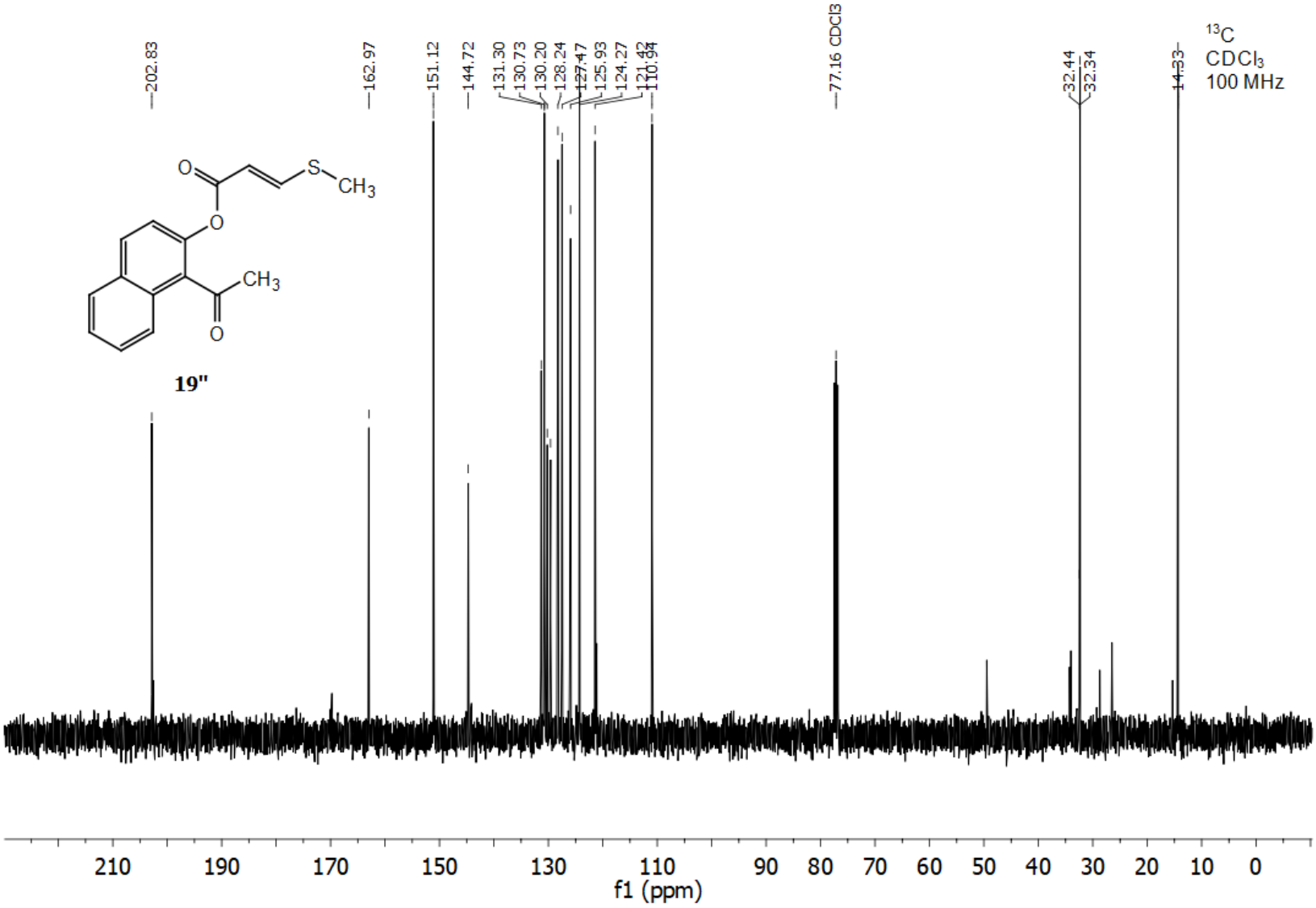


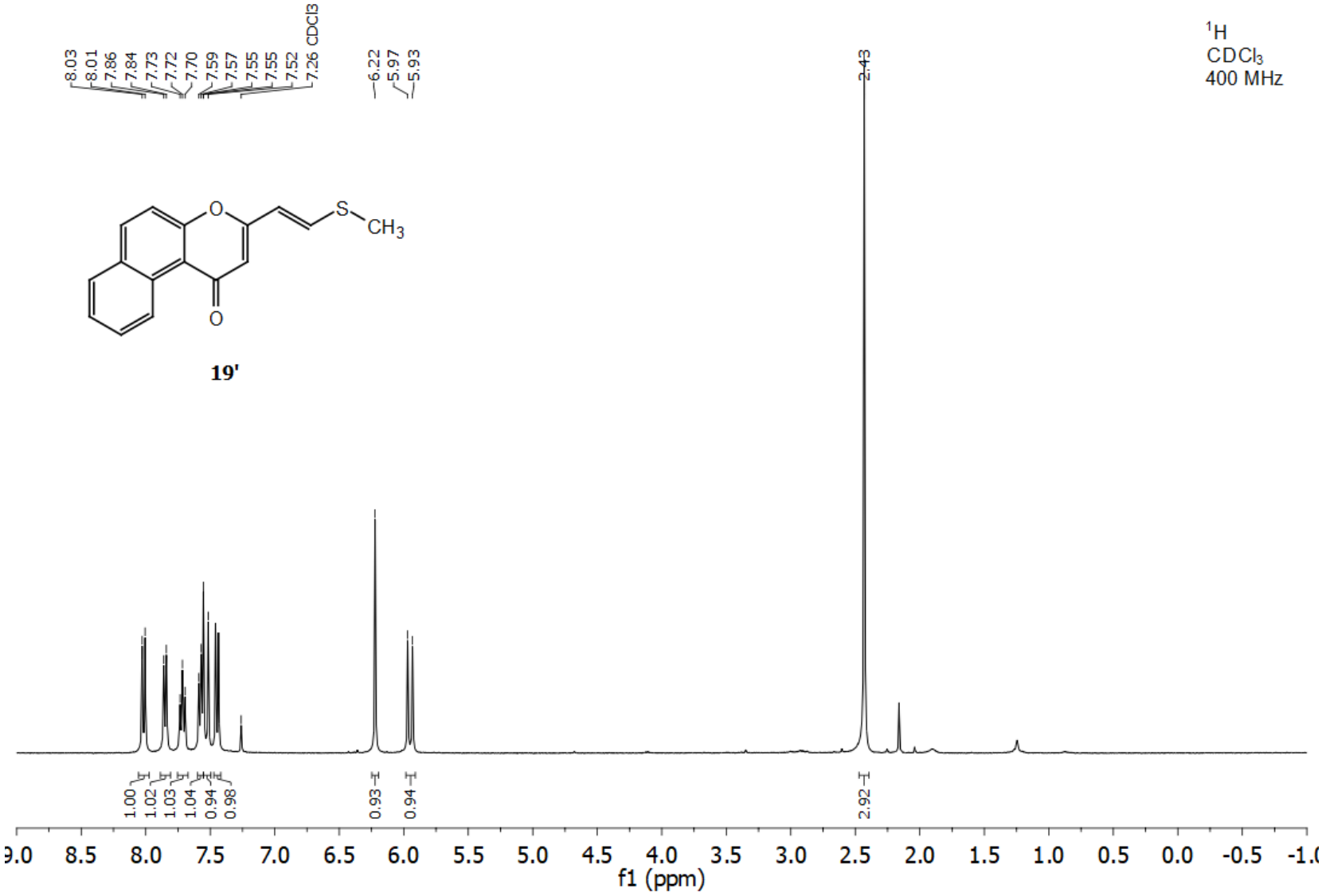
18

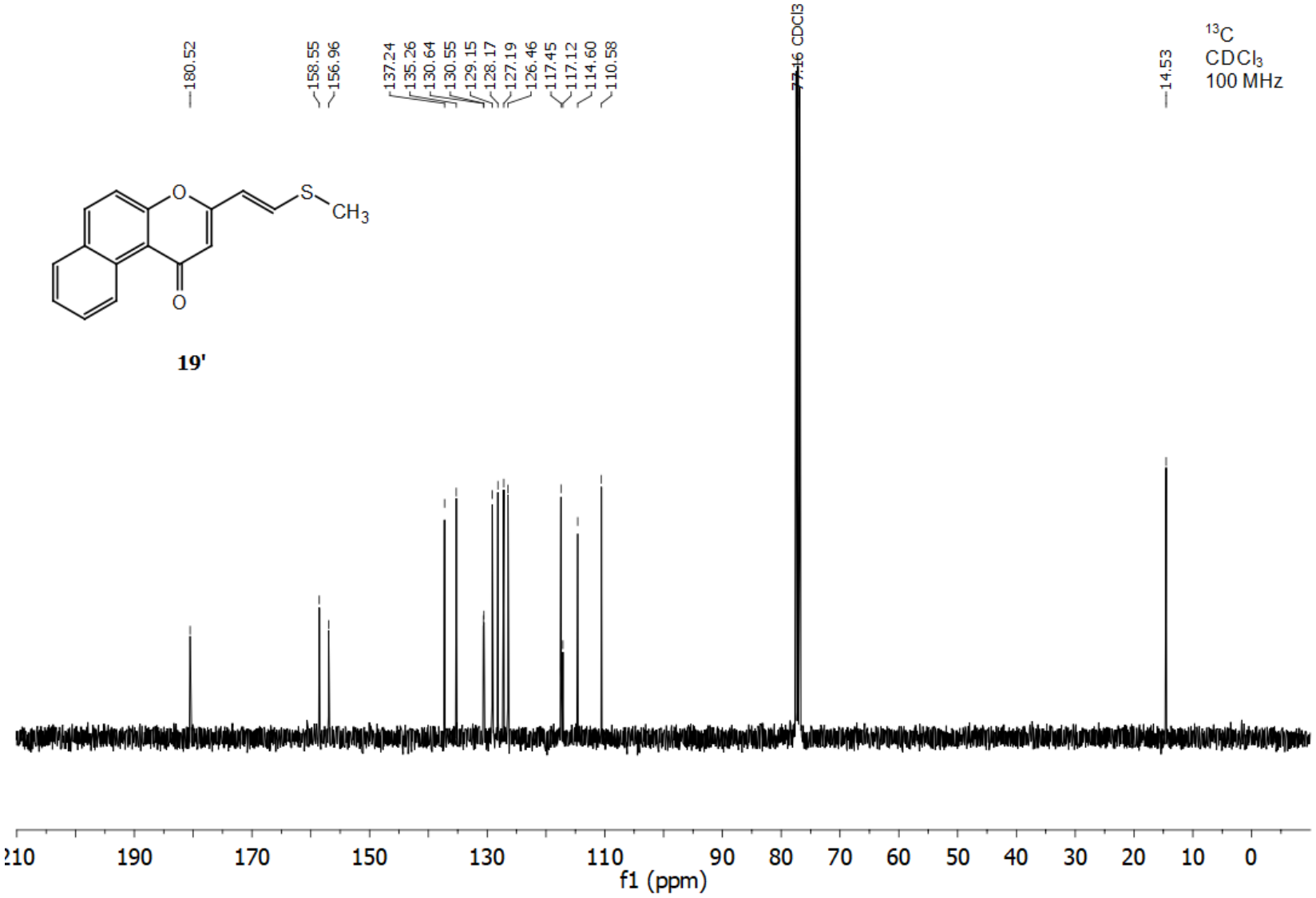

178.06
155.38
154.95
141.96
139.25
134.14
128.64
128.51
126.44
126.23
125.18
125.14
123.61
123.03
117.64
77.16 CDCl3
40.41
29.53
13C
CDCl3
100 MHz
O
S
CH3
O
O
18
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.02
7.99
7.85
7.83
7.81
7.79
7.77
7.50
7.49
7.47
7.47
7.46
7.46
7.44
7.42
7.27
7.26 CDCl3
7.25
5.86
5.82
2.59
2.30
1H
CDCl3
400 MHz
O
S
CH3
O
CH3
O
1.00
1.02
2.18
2.33
1.08
0.95
2.94
2.88
f1 (ppm)

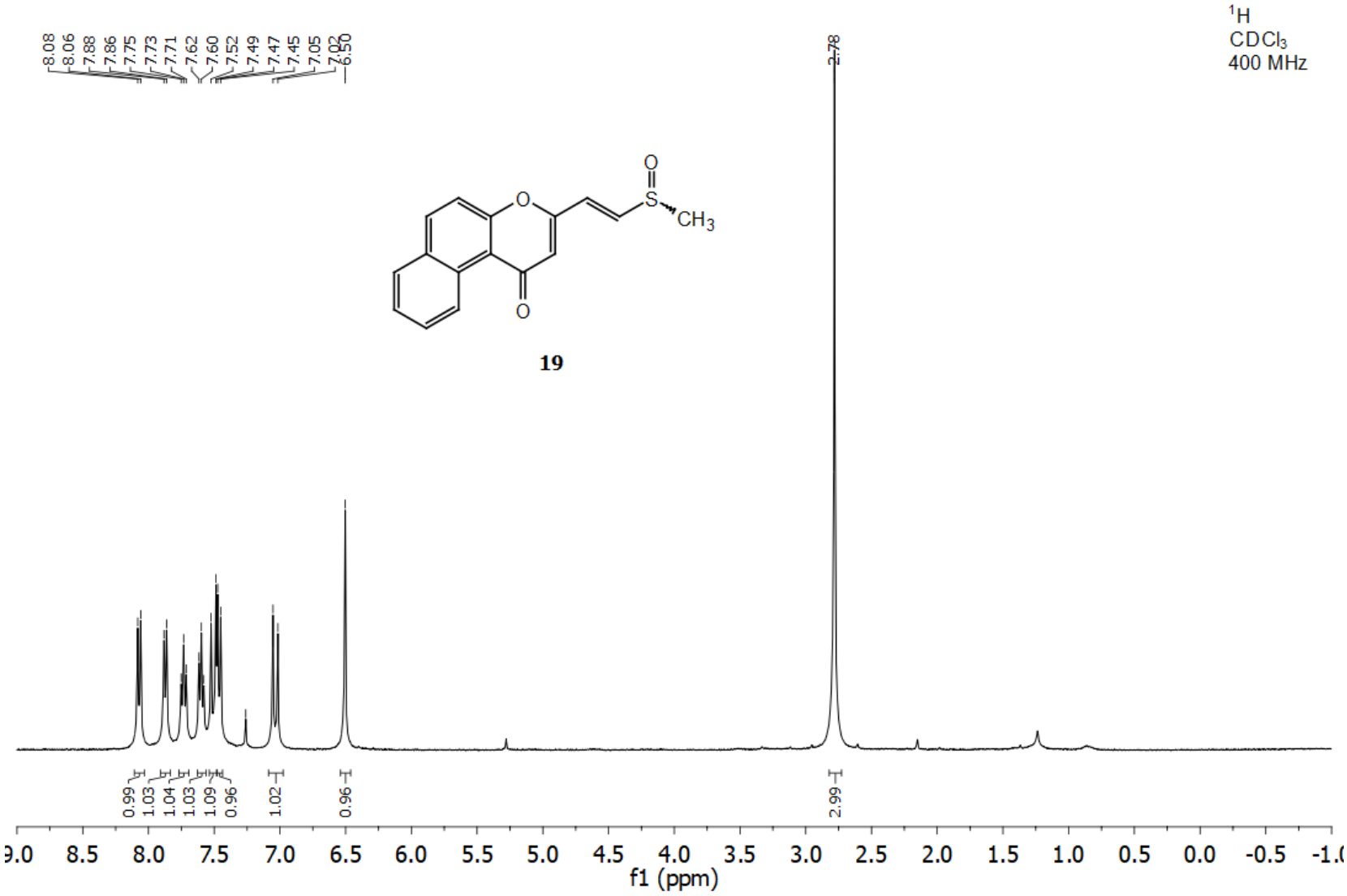
19"


202.83
162.97
151.12
144.72
131.30
130.73
130.20
128.24
127.47
125.93
124.27
121.42
110.94
77.16 CDCl3
32.44
32.34
14.33
13C
CDCl3
100 MHz
O
O
S
CH3
O
CH3
O
19"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

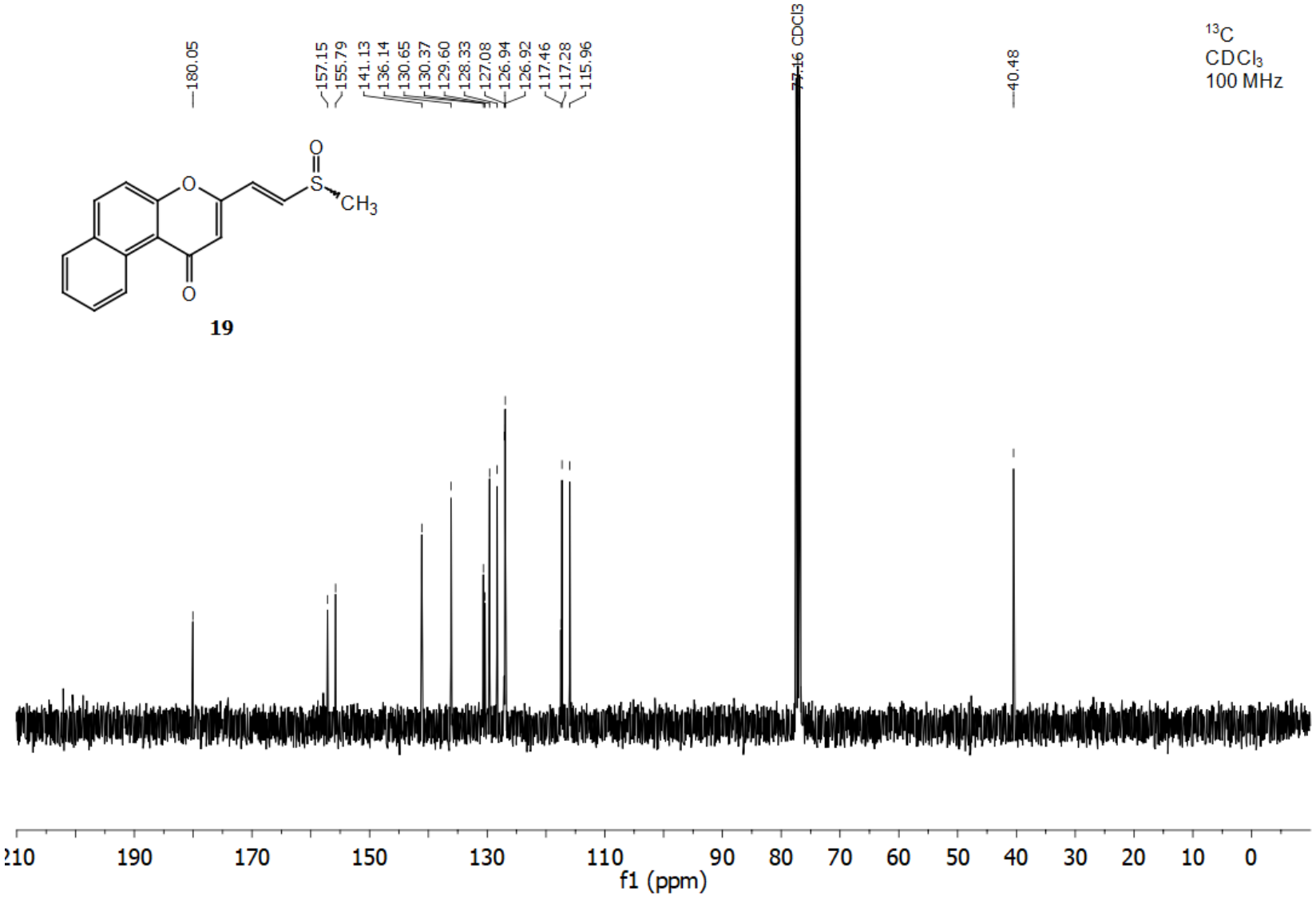

8.03
8.01
7.86
7.84
7.73
7.72
7.70
7.59
7.57
7.55
7.55
7.52
7.26 CDCl3
6.22
5.97
5.93
2.43
1H
CDCl3
400 MHz
O
S
CH3
O
19'
1.00
1.02
1.03
1.04
0.94
0.98
0.93
0.94
2.92
f1 (ppm)

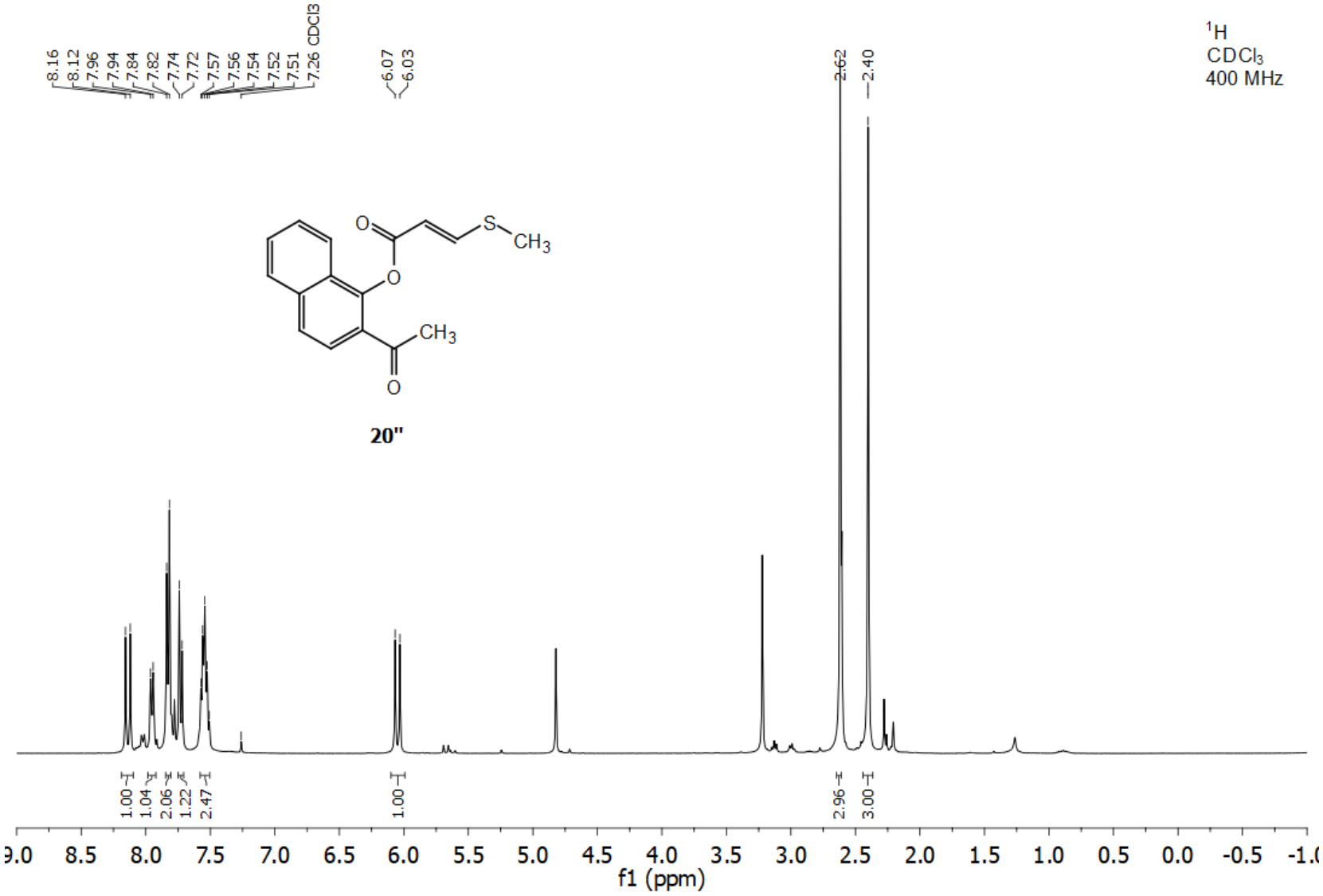

180.52
158.55
156.96
137.24
135.26
130.64
130.55
129.15
128.17
127.19
126.46
117.45
117.12
114.60
110.58
77.16 CDCl3
14.53
13C
CDCl3
100 MHz
O
S
CH3
O
f1 (ppm)

19'

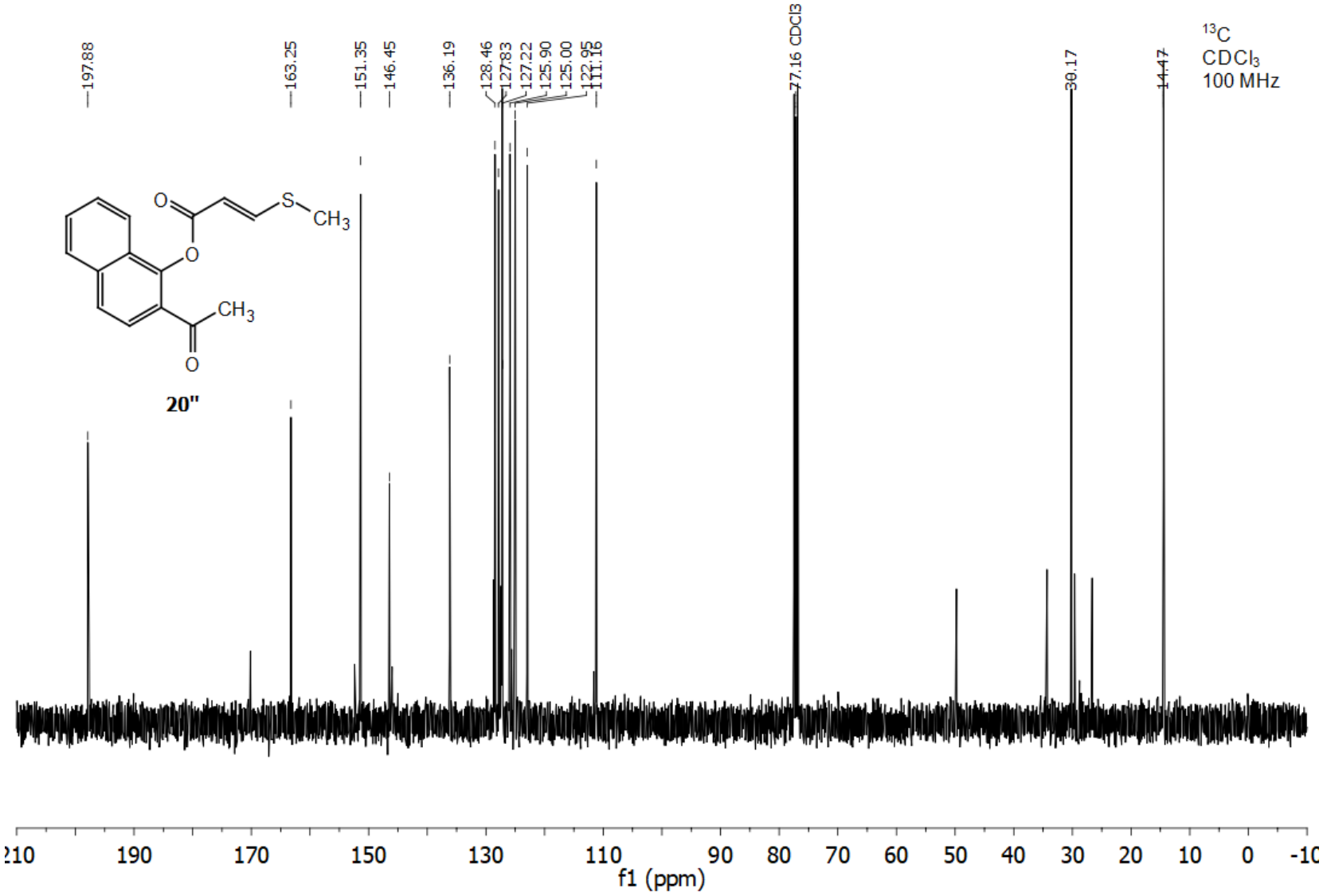

8.08
8.06
7.88
7.86
7.75
7.73
7.71
7.62
7.60
7.52
7.49
7.47
7.45
7.05
7.02
6.50
2.78
^{1}H
$CDCl_3$
400 MHz
O
S
CH_3
O
O
0.99
1.03
1.04
1.03
1.09
0.96
1.02
0.96
2.99
f1 (ppm)

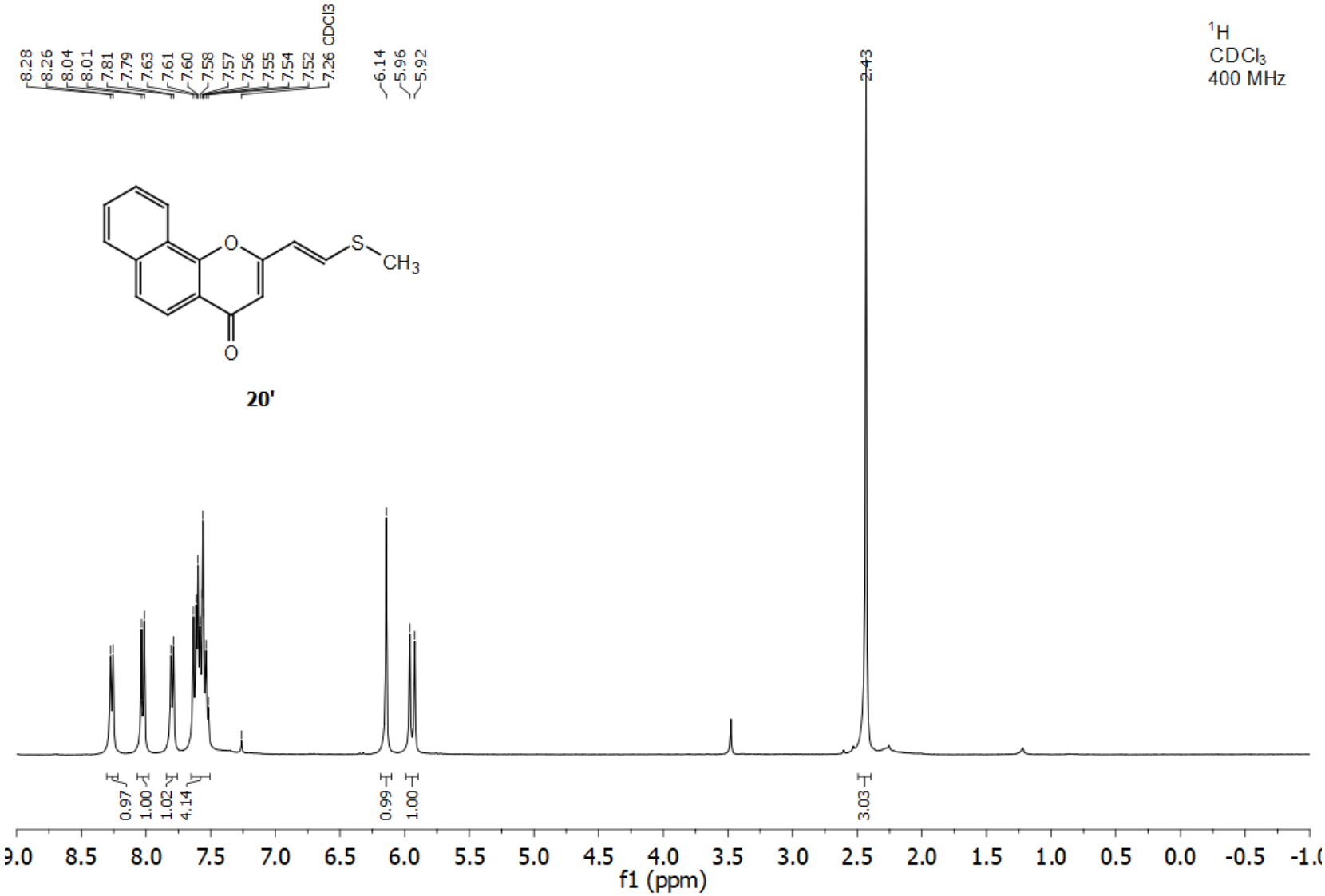
19


180.05
157.15
155.79
141.13
136.14
130.65
130.37
129.60
128.33
127.08
126.94
126.92
117.46
117.28
115.96
77.16 CDCl3
40.48
13C
CDCl3
100 MHz
O
S
CH3
O
O
19
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

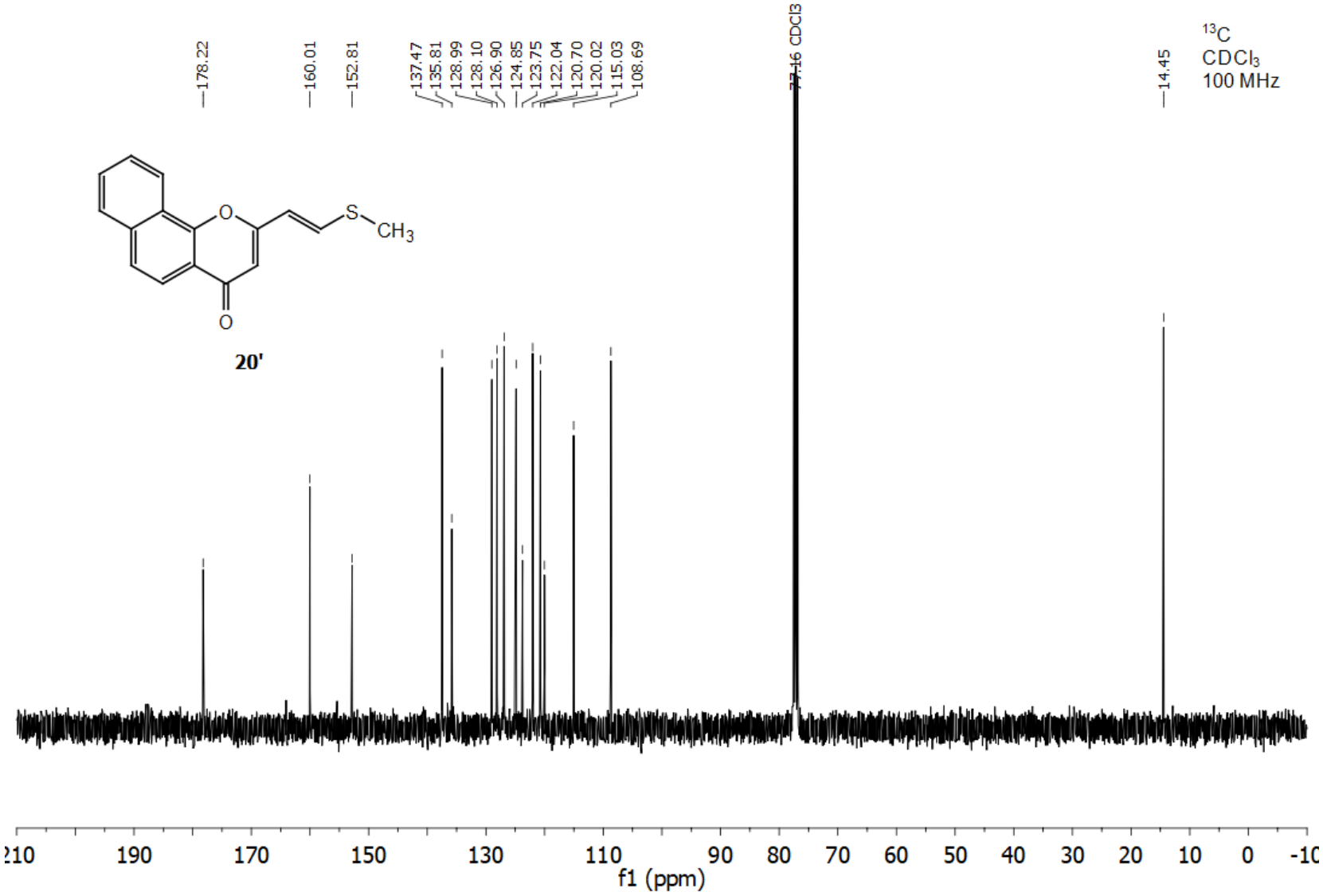

8.16
8.12
7.96
7.94
7.84
7.82
7.74
7.72
7.57
7.56
7.54
7.52
7.51
7.26 CDCl3
6.07
6.03
2.62
2.40
1H
CDCl3
400 MHz
O
S
CH3
O
CH3
O
1.00
1.04
2.06
1.22
2.47
1.00
2.96
3.00
f1 (ppm)

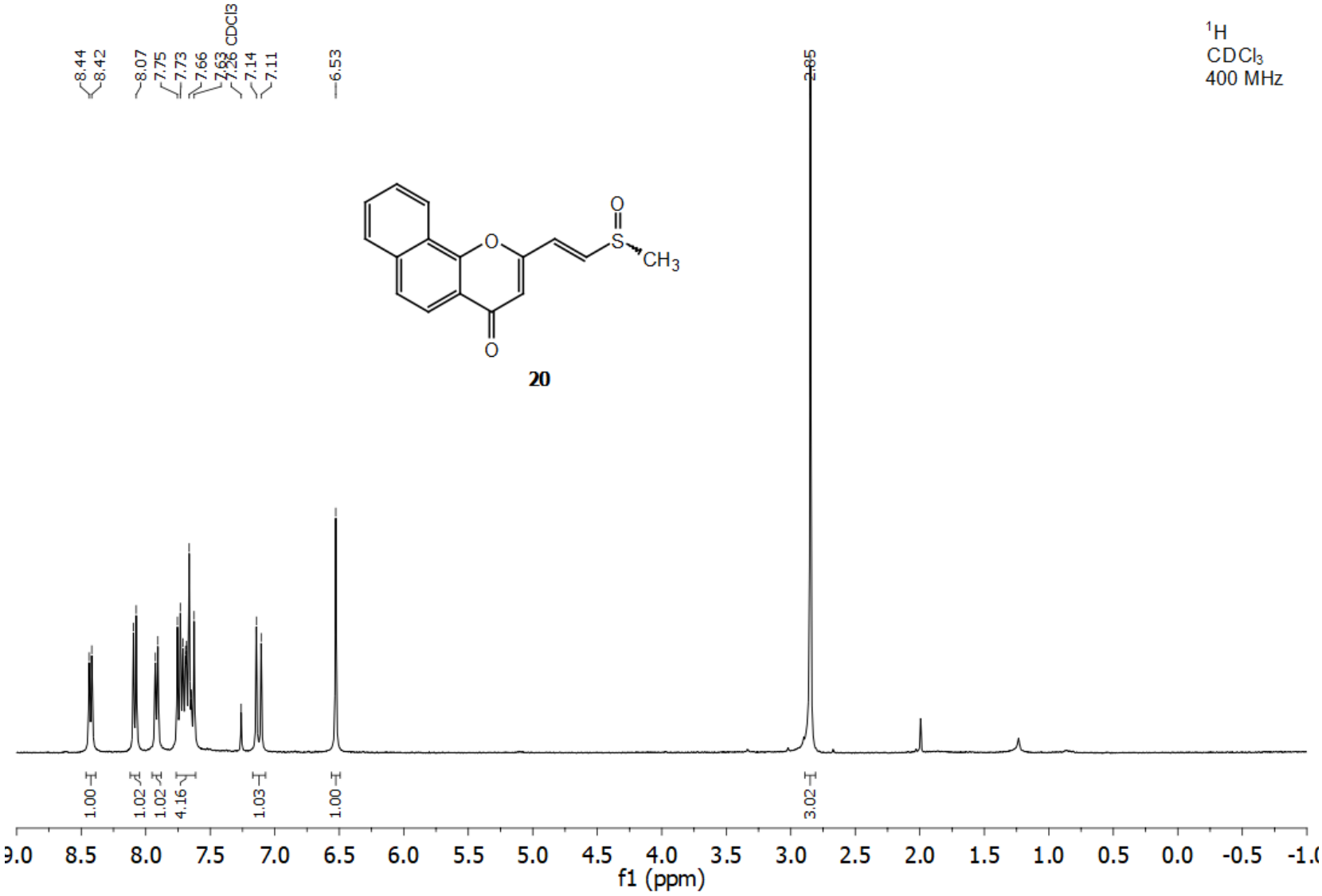
20"

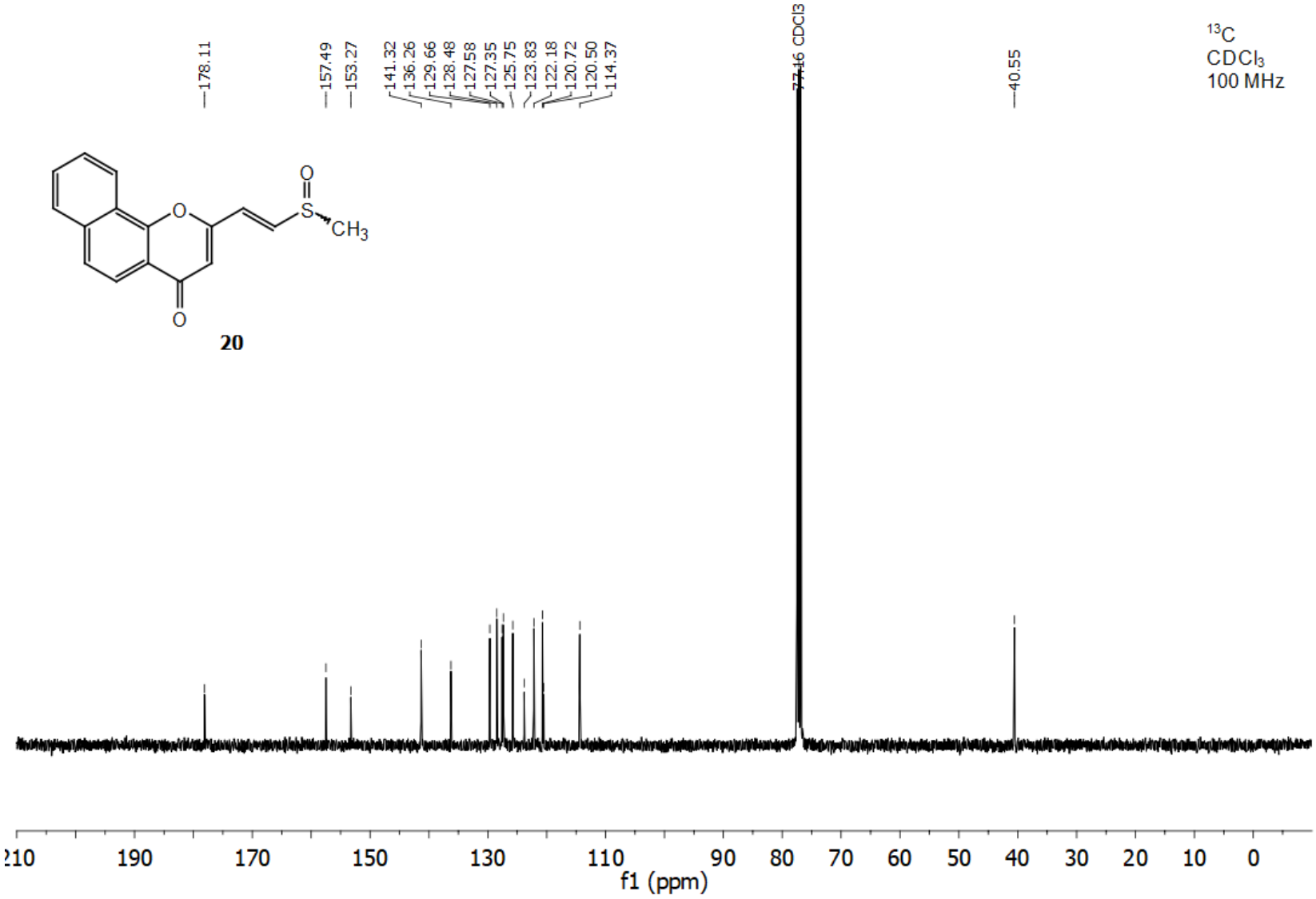

197.88
163.25
151.35
146.45
136.19
128.46
127.83
127.22
125.90
125.00
122.95
111.16
77.16 CDCl3
30.17
14.47
13C
CDCl3
100 MHz
O
O
S
CH3
CH3
O
20"
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

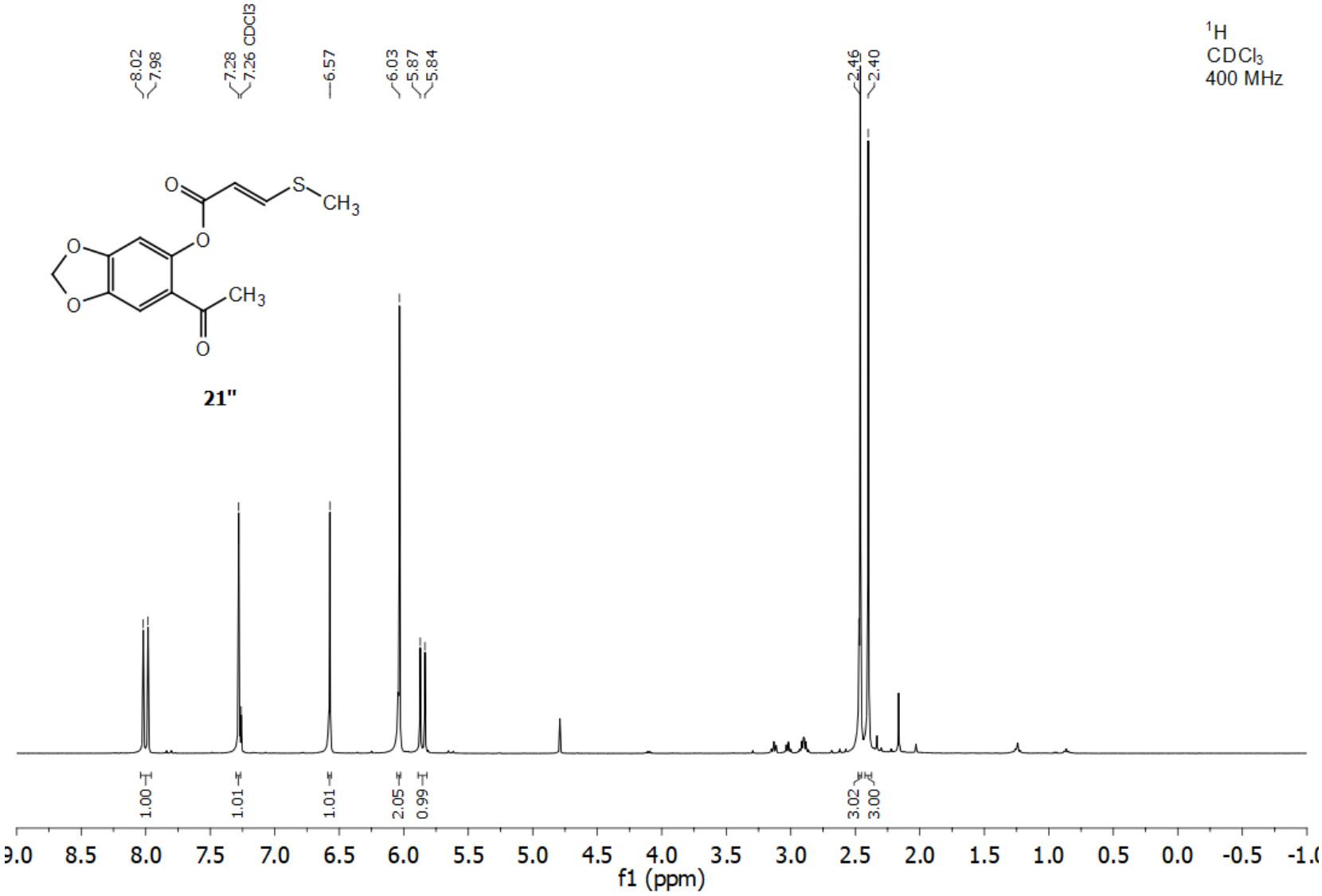

8.28
8.26
8.04
8.01
7.81
7.79
7.63
7.61
7.60
7.58
7.57
7.56
7.55
7.54
7.52
7.26 CDCl3
6.14
5.96
5.92
2.43
^{1}H
CDCl$_3$
400 MHz
O
S
CH$_3$
O
0.97
1.00
1.02
4.14
0.99
1.00
3.03
f1 (ppm)

20'

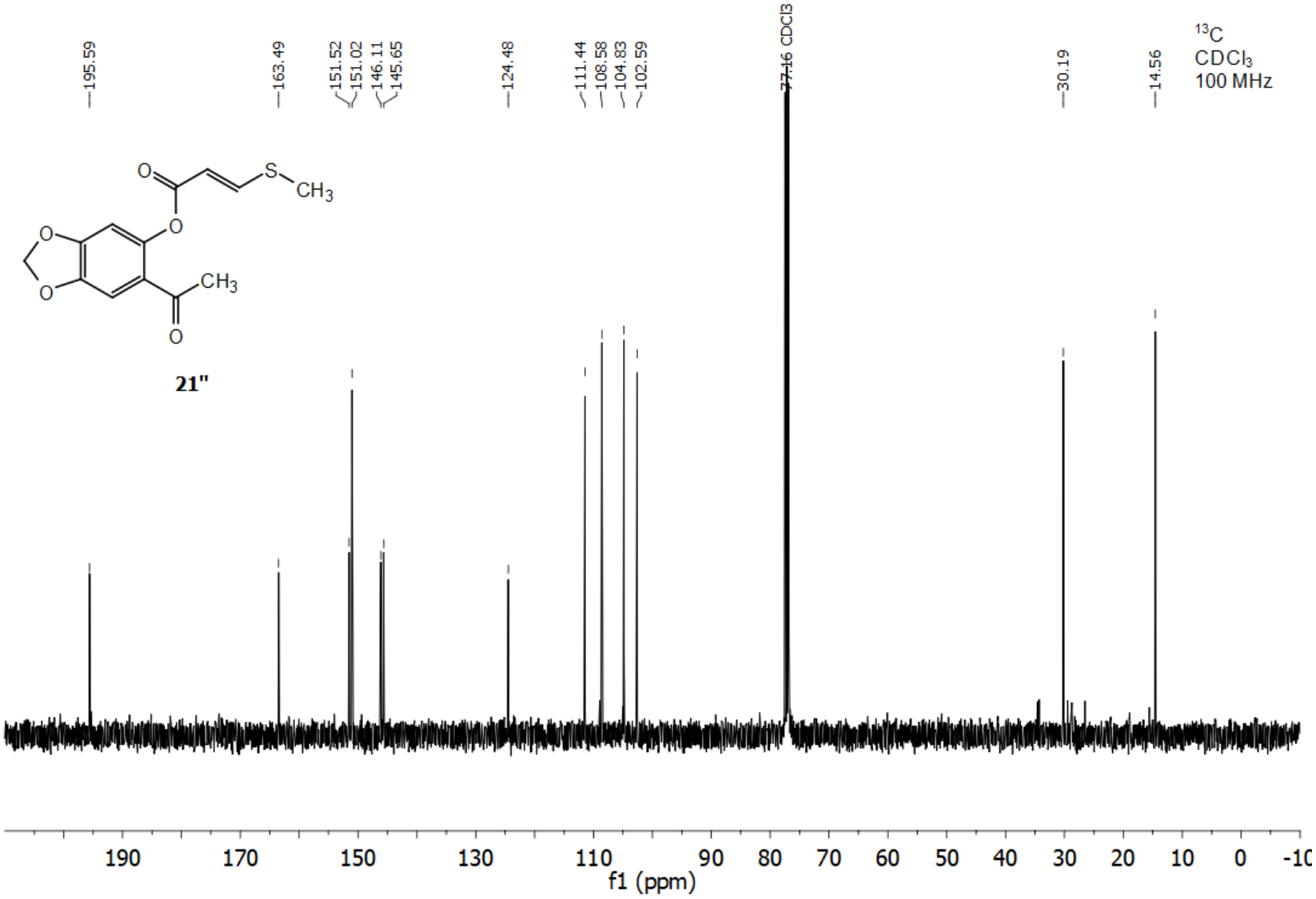

178.22
160.01
152.81
137.47
135.81
128.99
128.10
126.90
124.85
123.75
122.04
120.70
120.02
115.03
108.69
77.16 CDCl3
14.45
13C
CDCl3
100 MHz
O
S
CH3
O
20'
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

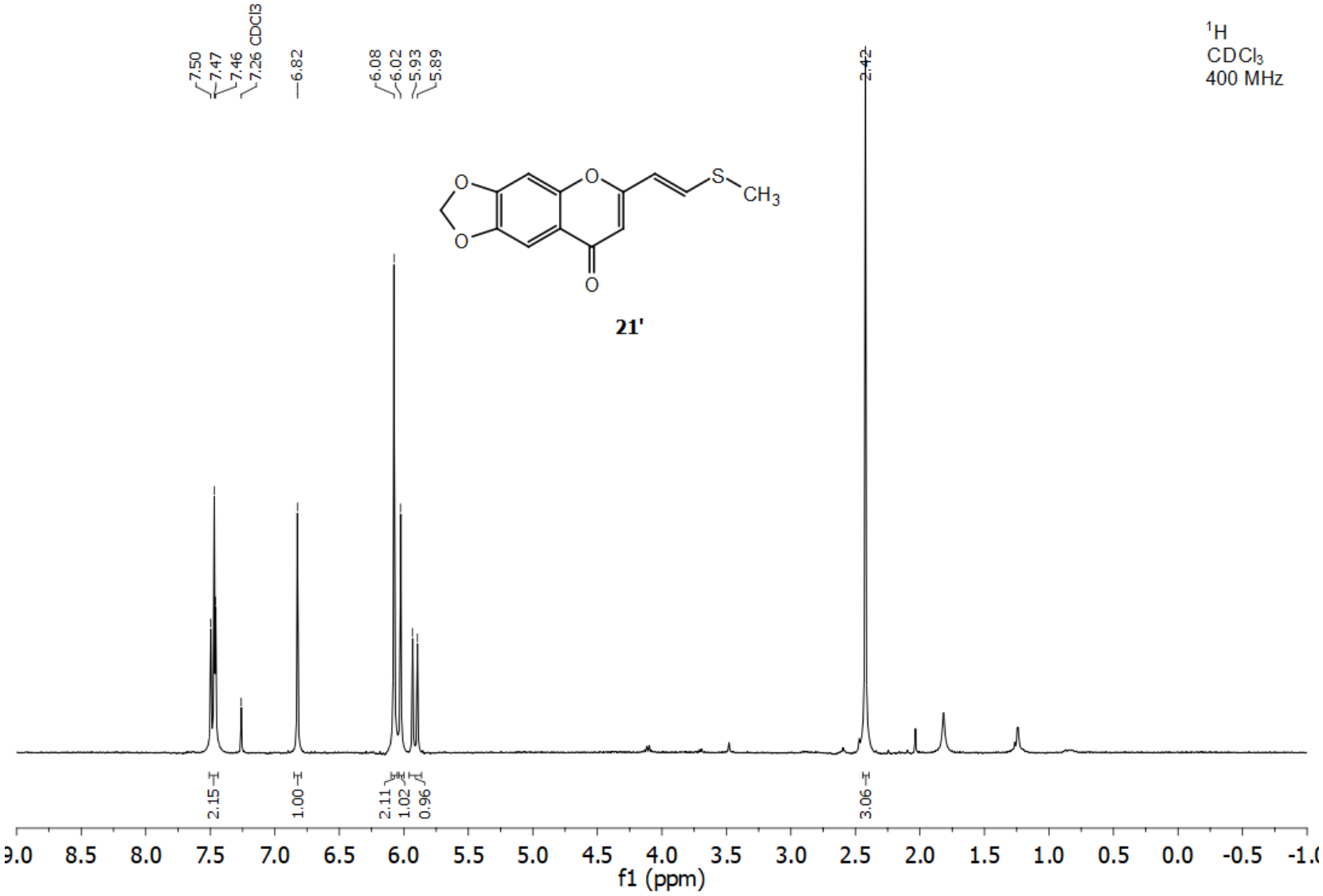

8.44
8.42
8.07
7.75
7.73
7.66
7.63
7.26 CDCl3
7.14
7.11
6.53
2.85
1H
CDCl3
400 MHz
O
S
CH3
O
O
20
1.00
1.02
1.02
4.16
1.03
1.00
3.02
f1 (ppm)


178.11
157.49
153.27
141.32
136.26
129.66
128.48
127.58
127.35
125.75
123.83
122.18
120.72
120.50
114.37
77.16 CDCl3
40.55
13C
CDCl3
100 MHz
O
S
CH3
O
O
20
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

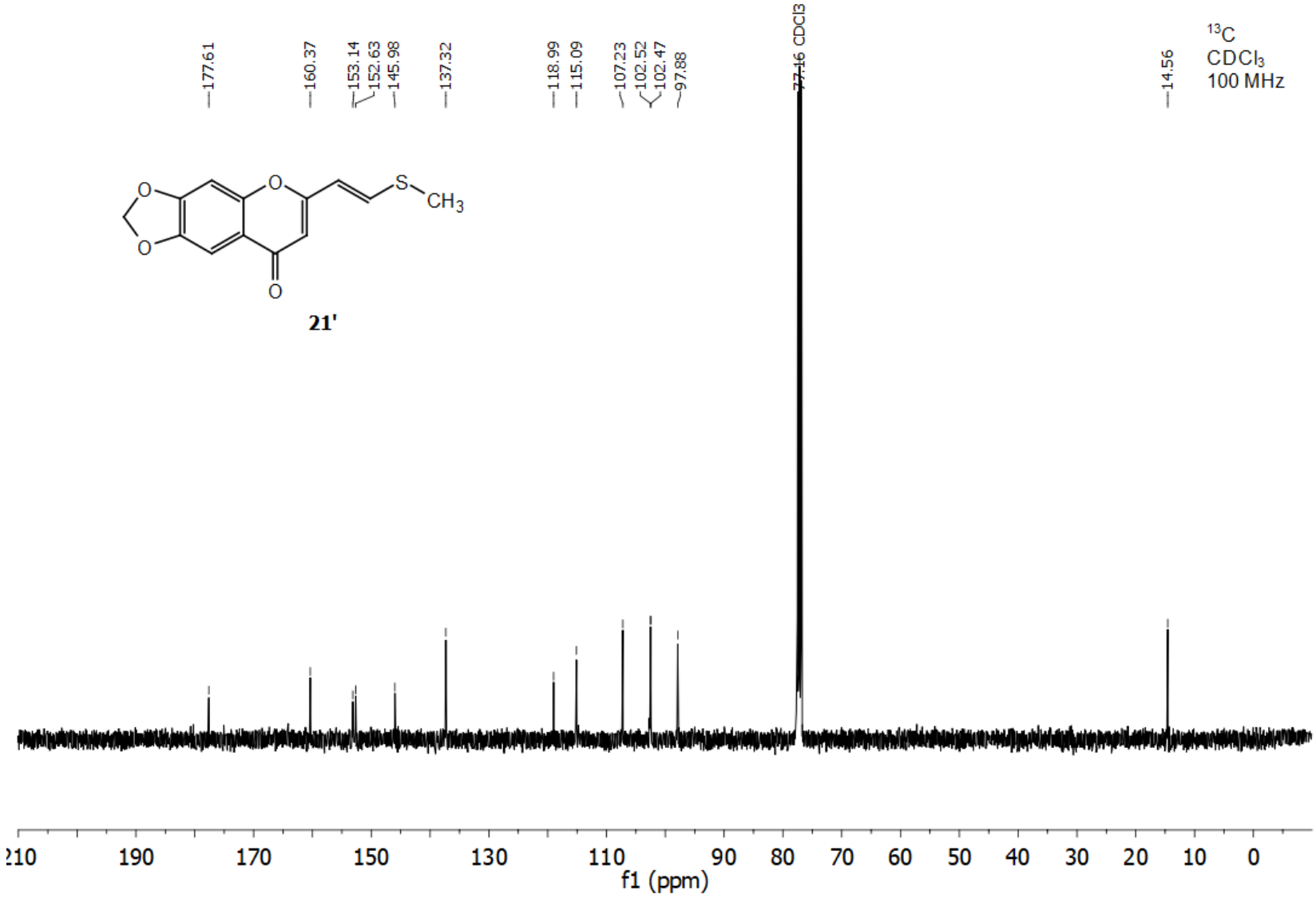

8.02
7.98
7.28
7.26 CDCl3
6.57
6.03
5.87
5.84
2.46
2.40
1H
CDCl3
400 MHz
O
S
CH3
O
O
O
CH3
O
1.00
1.01
1.01
2.05
0.99
3.02
3.00
f1 (ppm)

21"

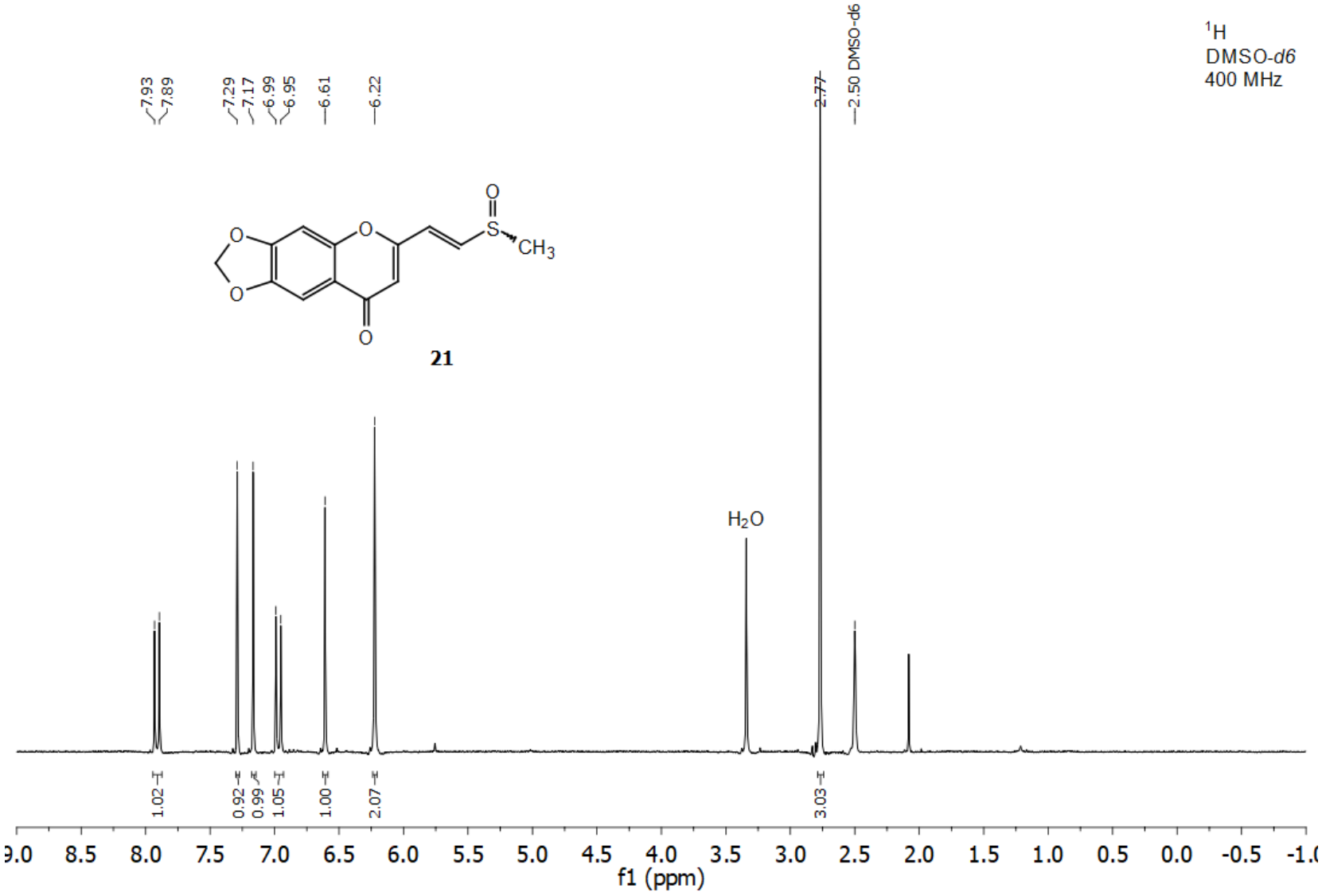

195.59
163.49
151.52
151.02
146.11
145.65
124.48
111.44
108.58
104.83
102.59
77.16 CDCl3
30.19
14.56
13C
CDCl3
100 MHz
O
S
CH3
O
O
O
CH3
O
21"
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

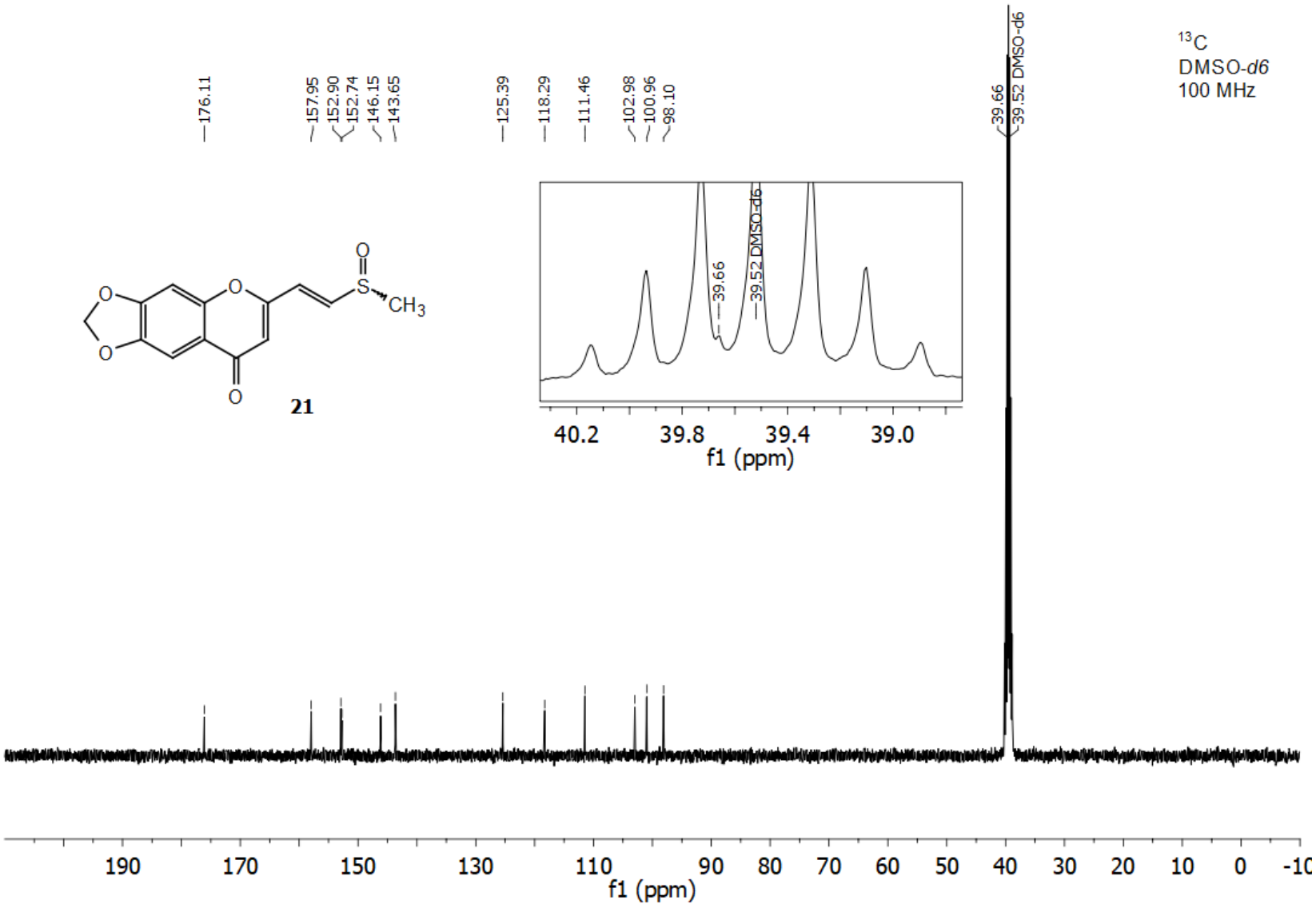

7.50
7.47
7.46
7.26 CDCl3
6.82
6.08
6.02
5.93
5.89
2.42
1H
CDCl3
400 MHz
O
O
O
O
S
CH3
2.15
1.00
2.11
1.02
0.96
3.06
f1 (ppm)

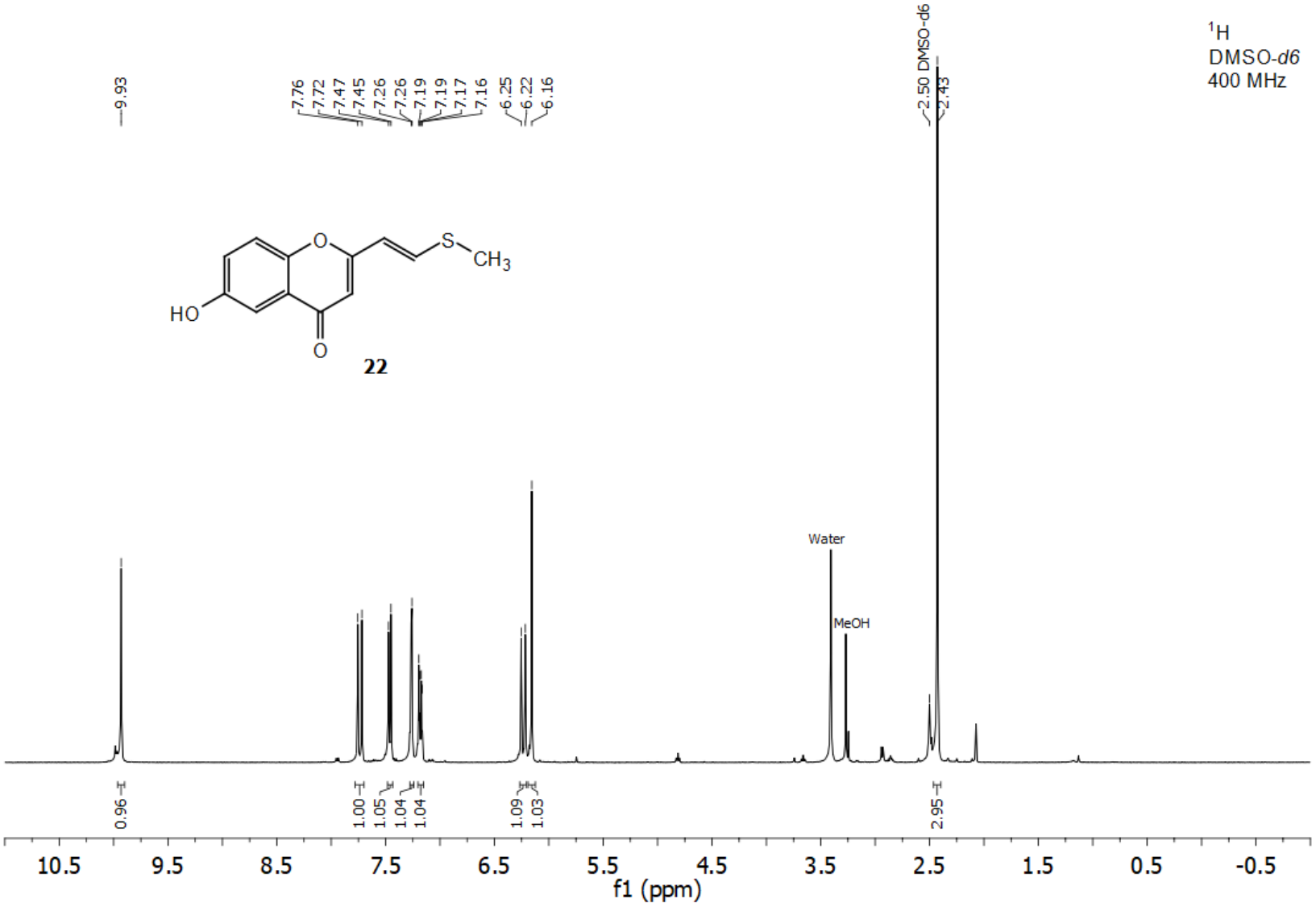
21'

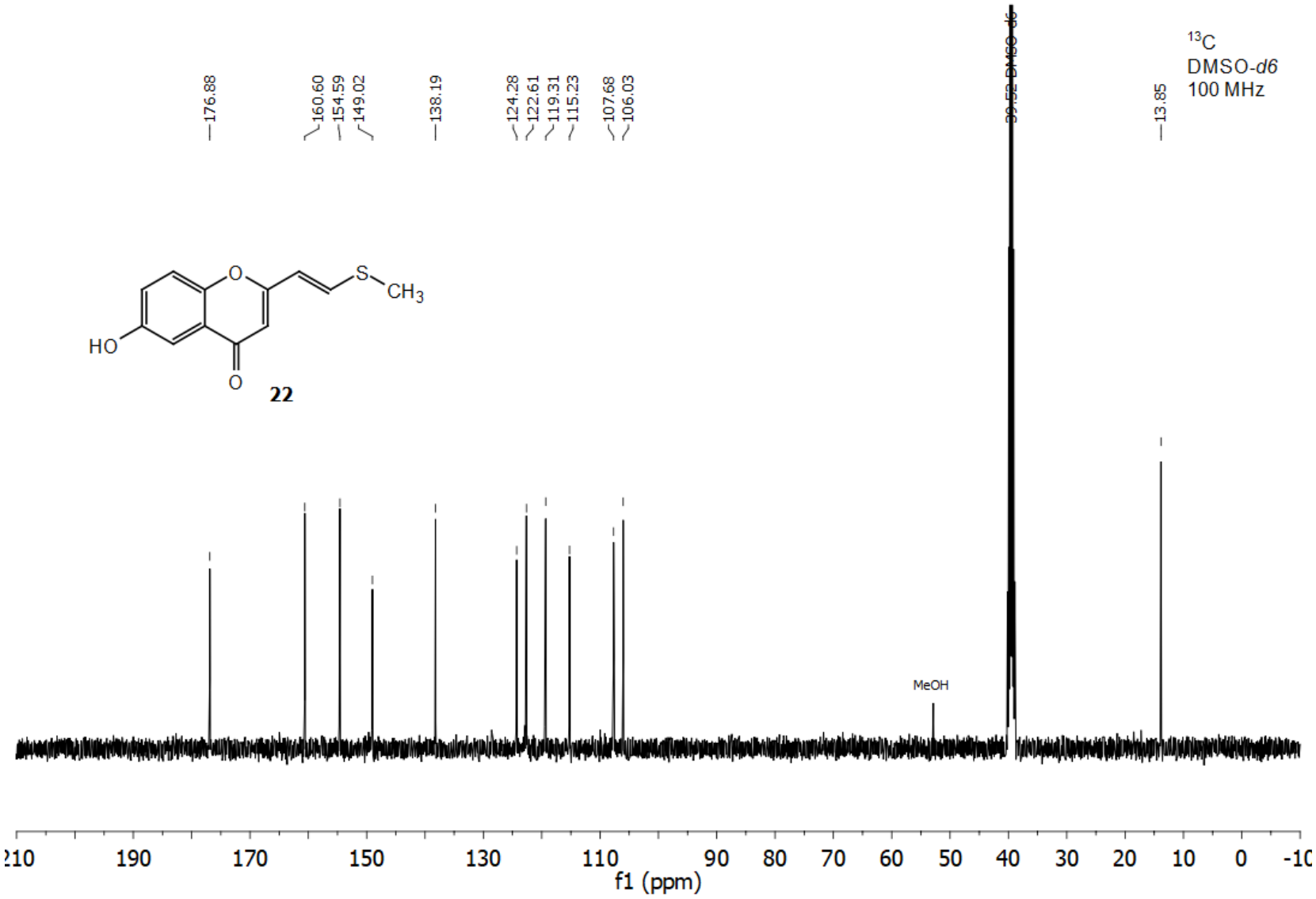

177.61
160.37
153.14
152.63
145.98
137.32
118.99
115.09
107.23
102.52
102.47
97.88
77.16 CDCl3
14.56
13C
CDCl3
100 MHz
O
O
O
O
S
CH3
f1 (ppm)

21'

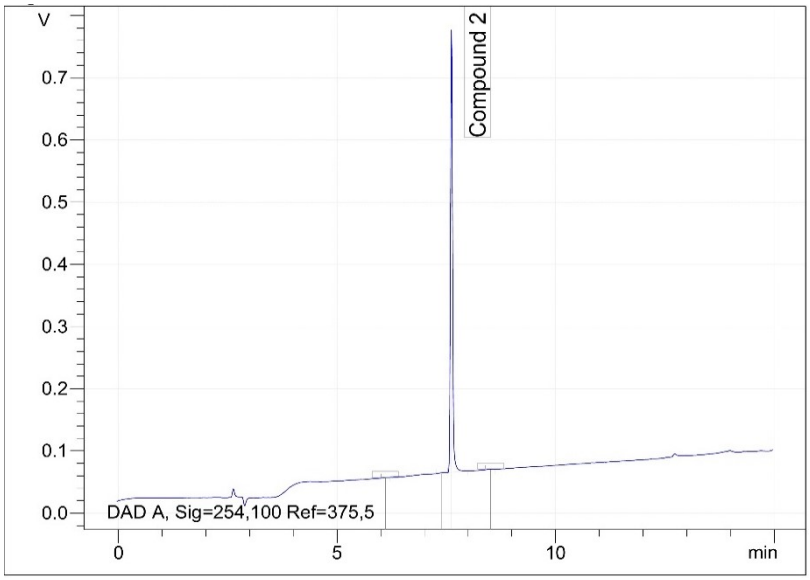

^{1}H
DMSO-*d6*
400 MHz
7.93
7.89
7.29
7.17
6.99
6.95
6.61
6.22
2.77
2.50 DMSO-d6
O
S
CH$_3$
O
O
O
O
21
H$_2$O
1.02
0.92
0.99
1.05
1.00
2.07
3.03
f1 (ppm)

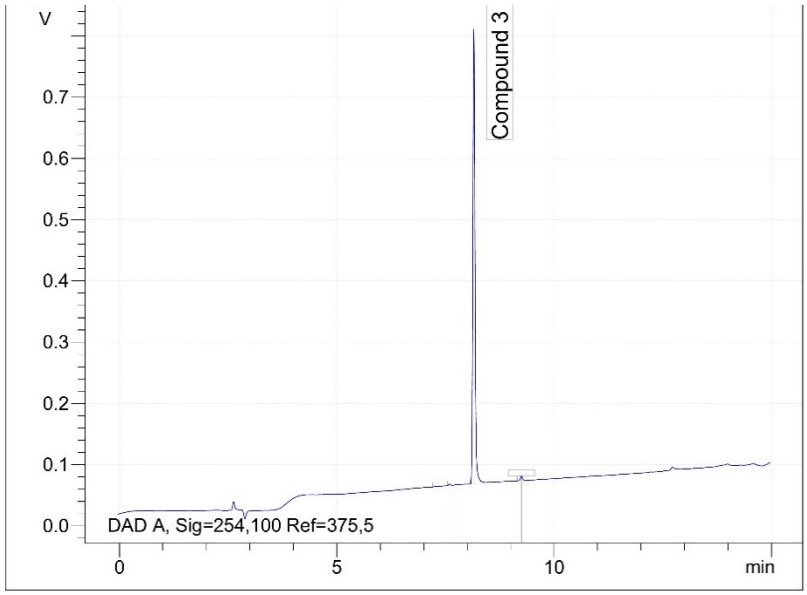

176.11
157.95
152.90
152.74
146.15
143.65
125.39
118.29
111.46
102.98
100.96
98.10
39.66
39.52 DMSO-d6
13C
DMSO-d6
100 MHz
O
O
O
O
S
CH3
21
39.66
39.52 DMSO-d6
40.2
39.8
39.4
39.0
f1 (ppm)
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

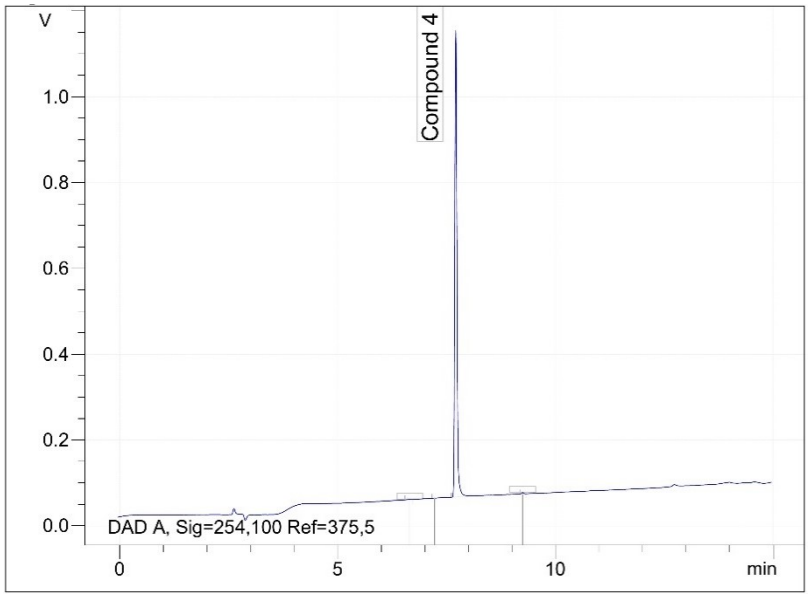

9.93
7.76
7.72
7.47
7.45
7.26
7.26
7.19
7.19
7.17
7.16
6.25
6.22
6.16
2.50 DMSO-d6
2.43
1H
DMSO-d6
400 MHz
HO
O
O
S
CH3
22
Water
MeOH
0.96
1.00
1.05
1.04
1.04
1.09
1.03
2.95
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

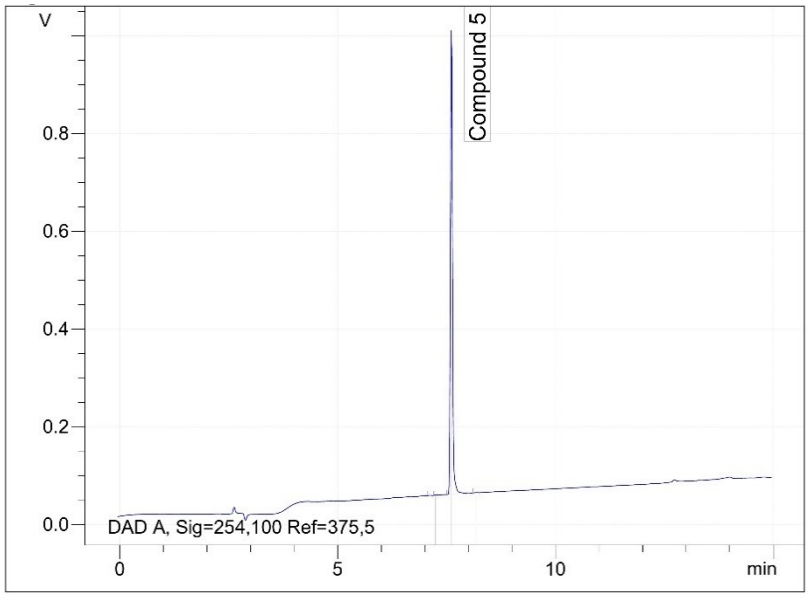

176.88
160.60
154.59
149.02
138.19
124.28
122.61
119.31
115.23
107.68
106.03
39.52 DMSO-d6
13.85
13C
DMSO-d6
100 MHz
MeOH
HO
O
O
S
CH3
22
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

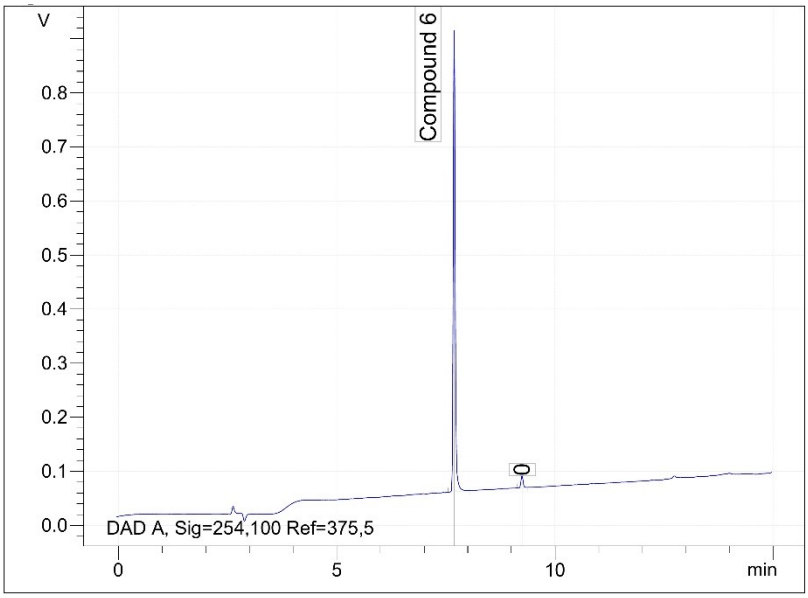
3.9.4 HPLC purities of compounds **2-21**

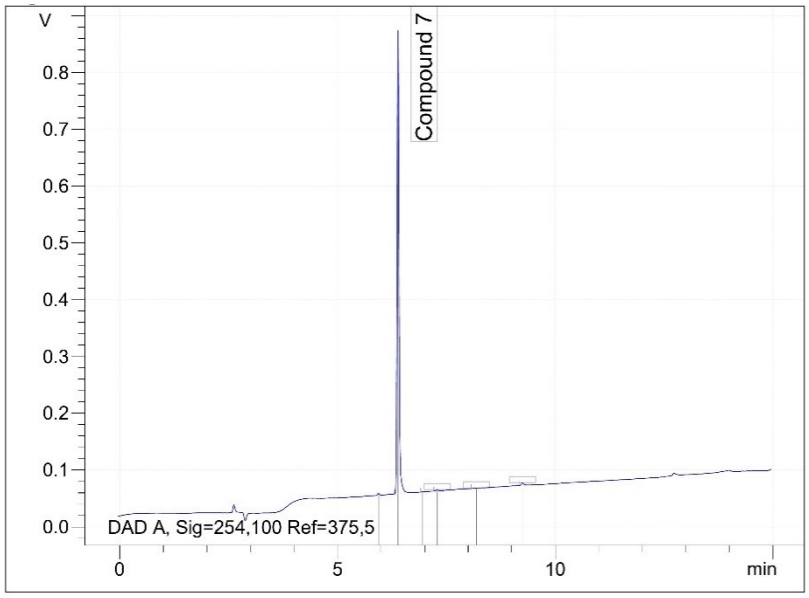


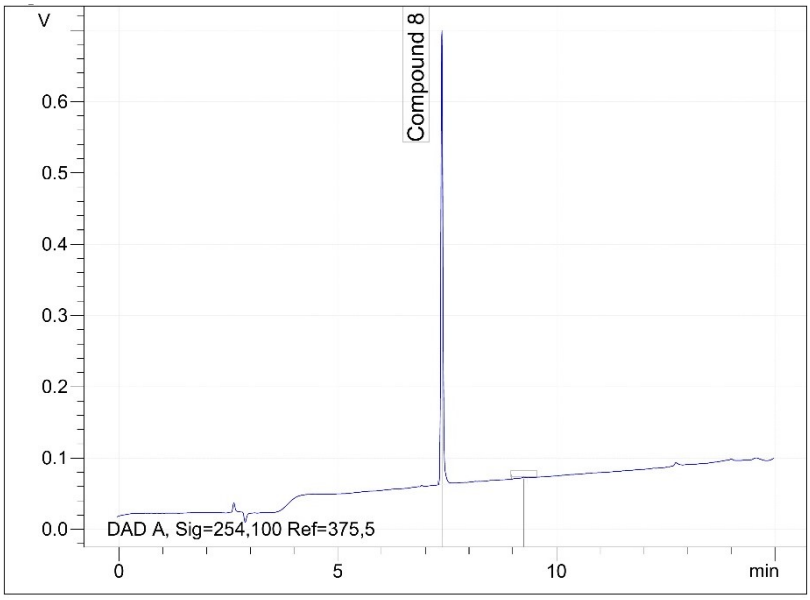


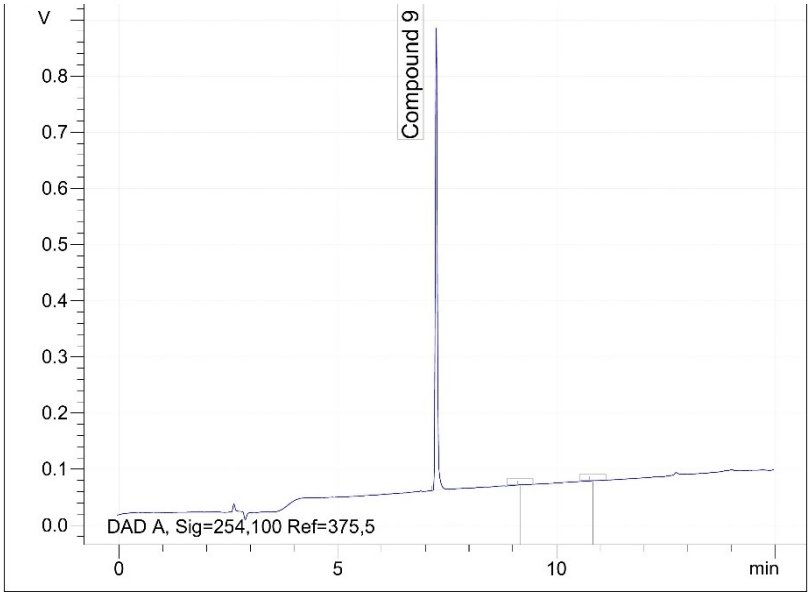

V
1.0
0.8
0.6
0.4
0.2
0.0
Compound 4
DAD A, Sig=254,100 Ref=375,5
0
5
10
min

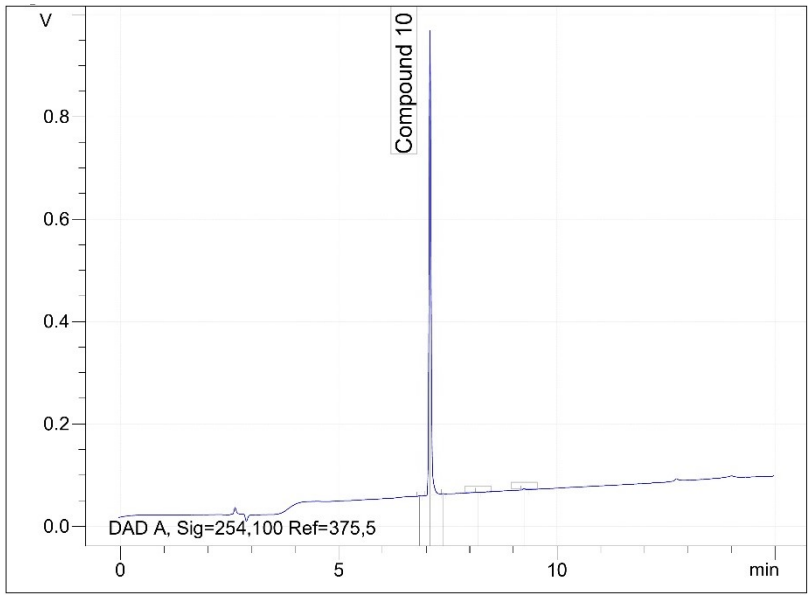

V
0.8
0.6
0.4
0.2
0.0
Compound 5
DAD A, Sig=254,100 Ref=375,5
0
5
10
min

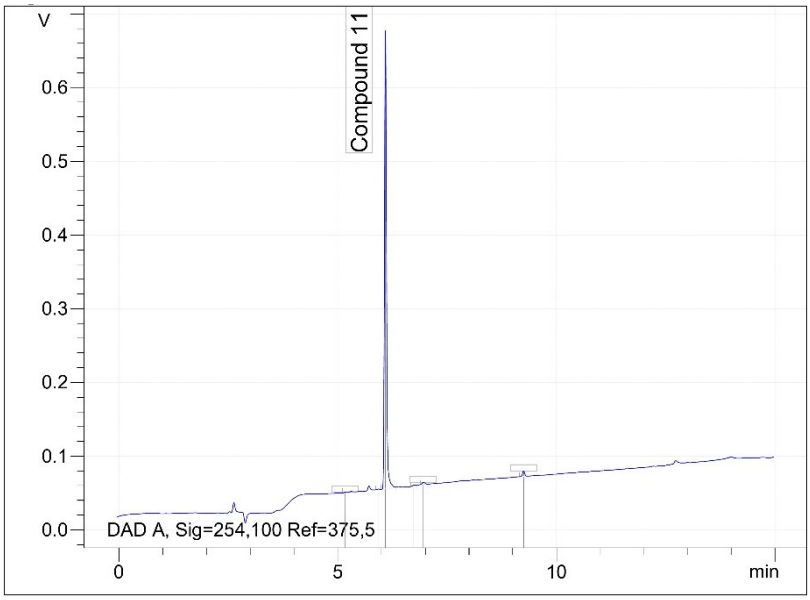

V
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Compound 6
0
DAD A, Sig=254,100 Ref=375,5
0
5
10
min

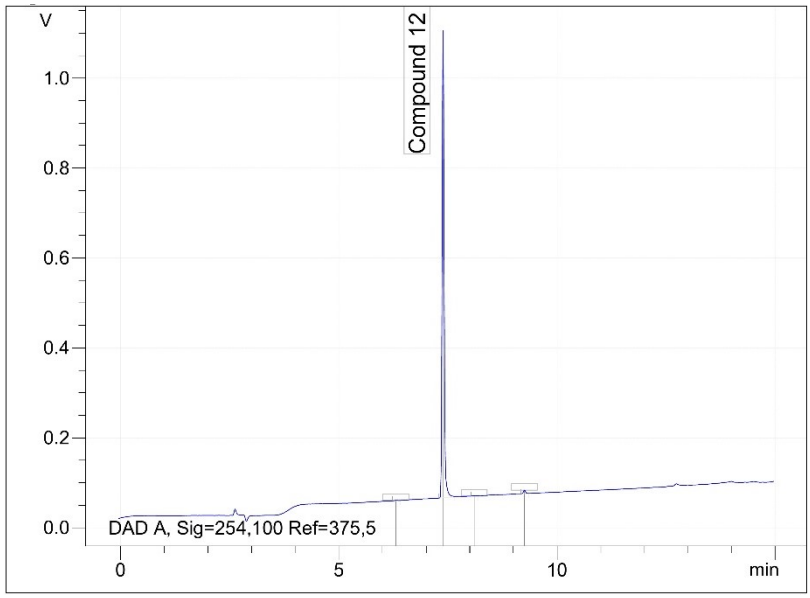

V
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Compound 7
DAD A, Sig=254,100 Ref=375,5
0
5
10
min

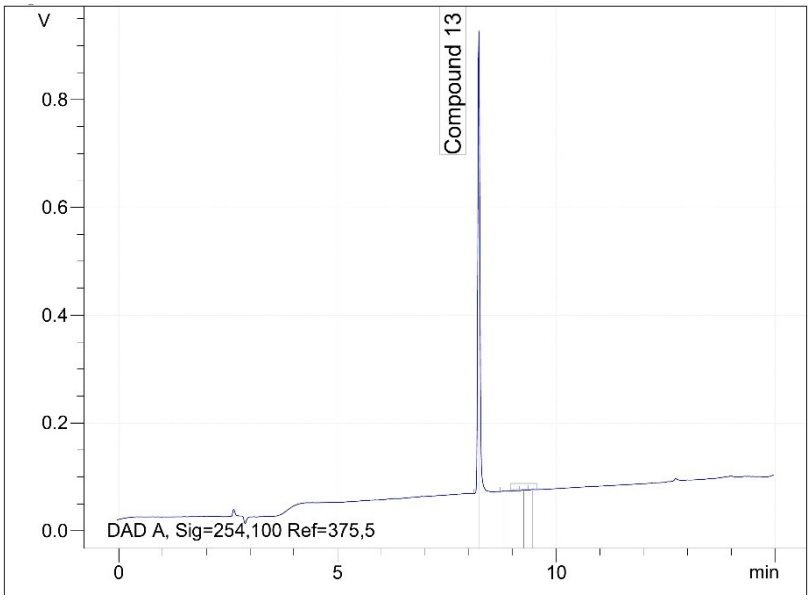

V
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Compound 8
DAD A, Sig=254,100 Ref=375,5
0
5
10
min

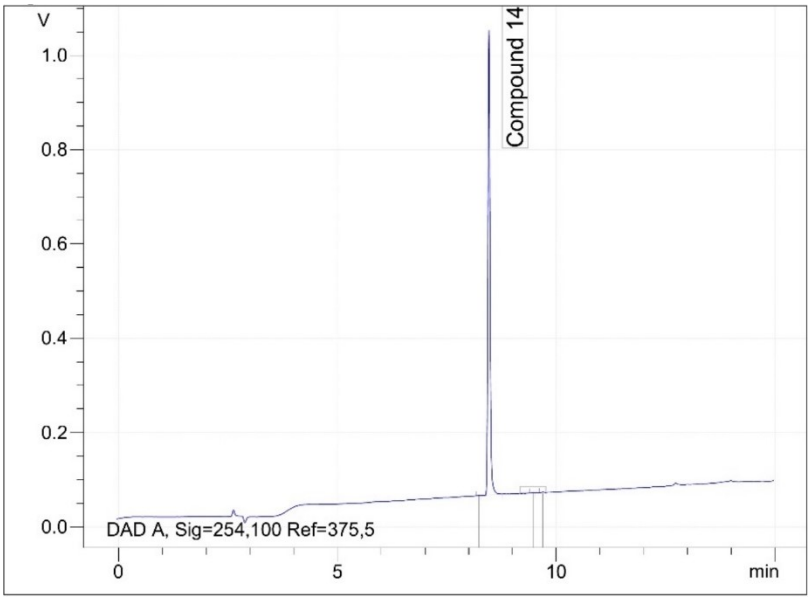

V
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Compound 9
DAD A, Sig=254,100 Ref=375,5
0
5
10
min

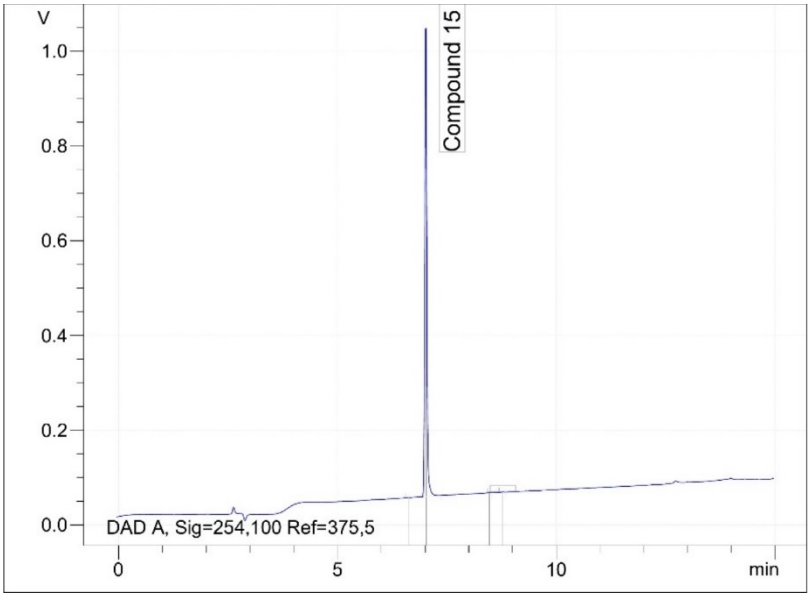

V
0.8
0.6
0.4
0.2
0.0
Compound 10
DAD A, Sig=254,100 Ref=375,5
0
5
10
min

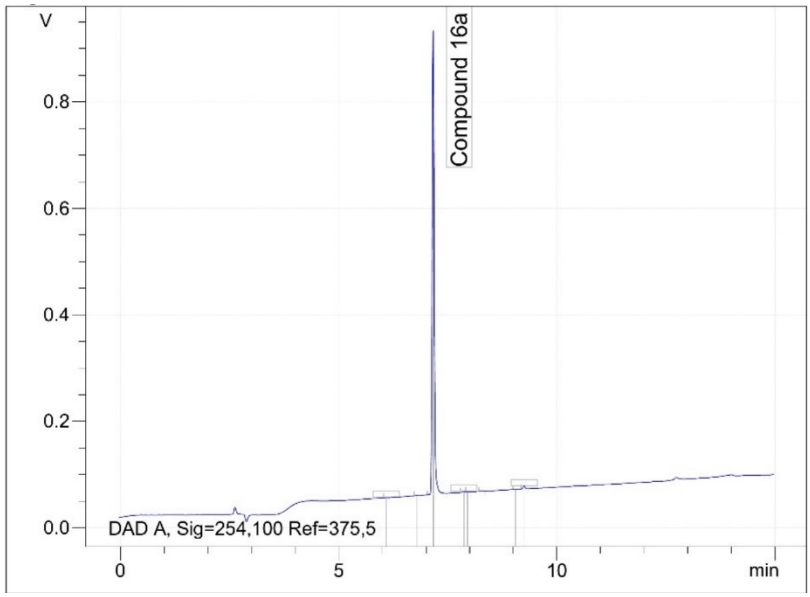

V
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Compound 11
DAD A, Sig=254,100 Ref=375,5
0
5
10
min


V
1.0
0.8
0.6
0.4
0.2
0.0
Compound 12
DAD A, Sig=254,100 Ref=375,5
0
5
10
min


V
0.8
0.6
0.4
0.2
0.0
Compound 13
DAD A, Sig=254,100 Ref=375,5
0
5
10
min


V
1.0
0.8
0.6
0.4
0.2
0.0
Compound 14
DAD A, Sig=254,100 Ref=375,5
0
5
10
min


V
1.0
0.8
0.6
0.4
0.2
0.0
Compound 15
DAD A, Sig=254,100 Ref=375,5
0
5
10
min


V
0.8
0.6
0.4
0.2
0.0
Compound 16a
DAD A, Sig=254,100 Ref=375,5
0
5
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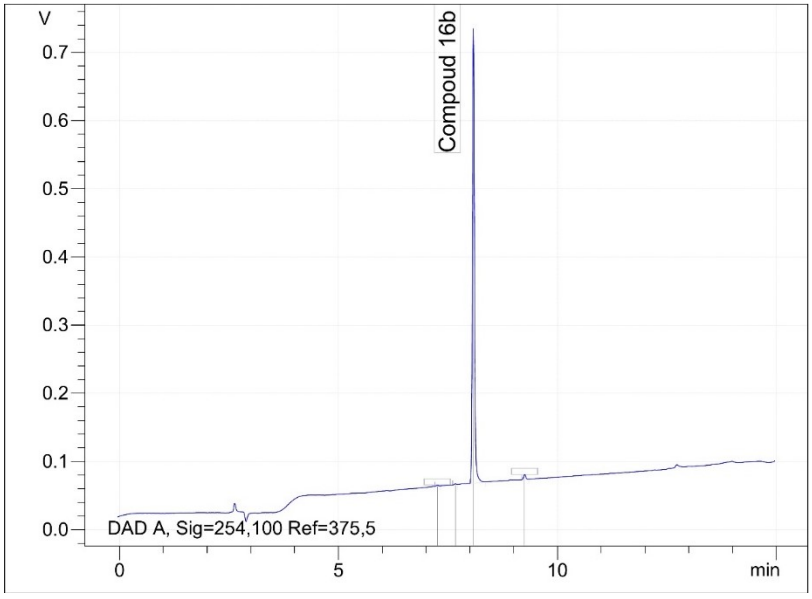
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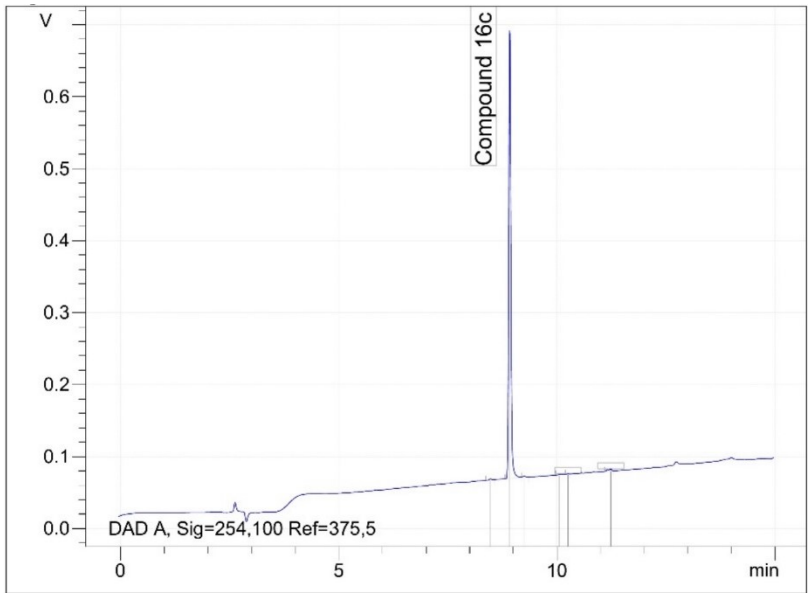
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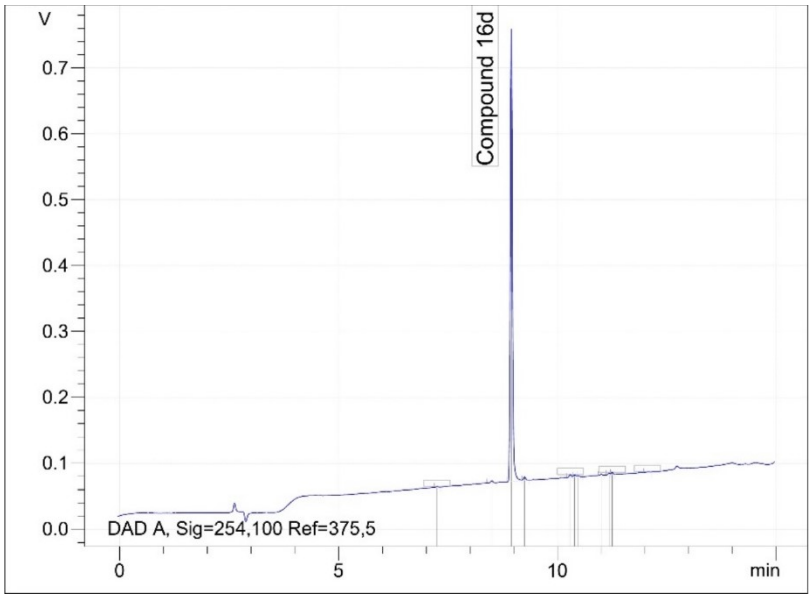
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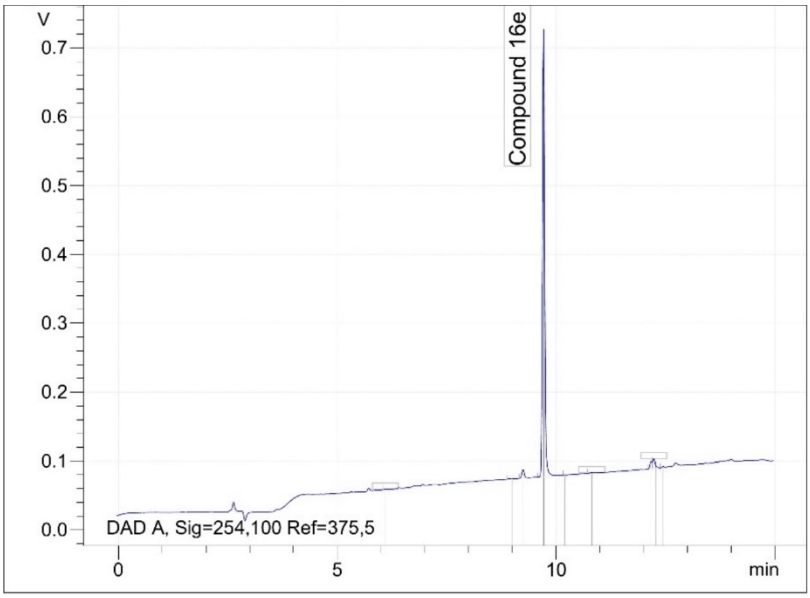
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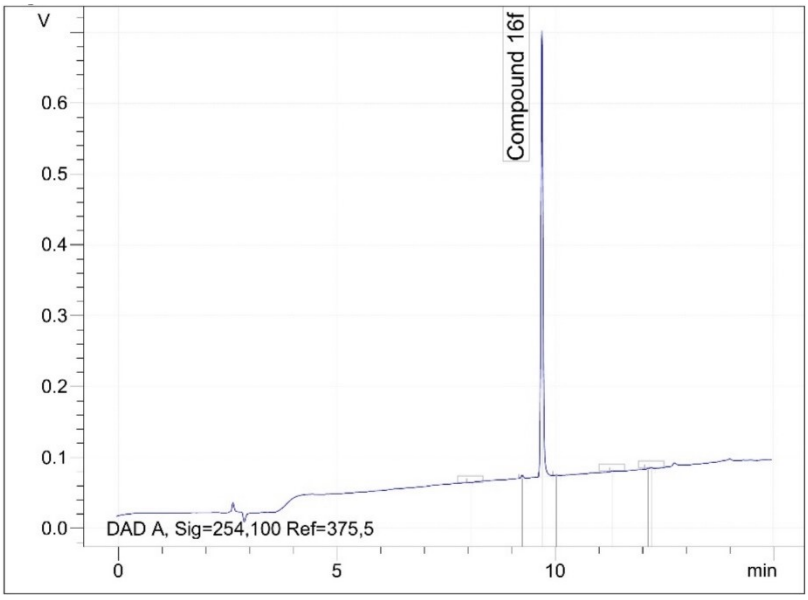
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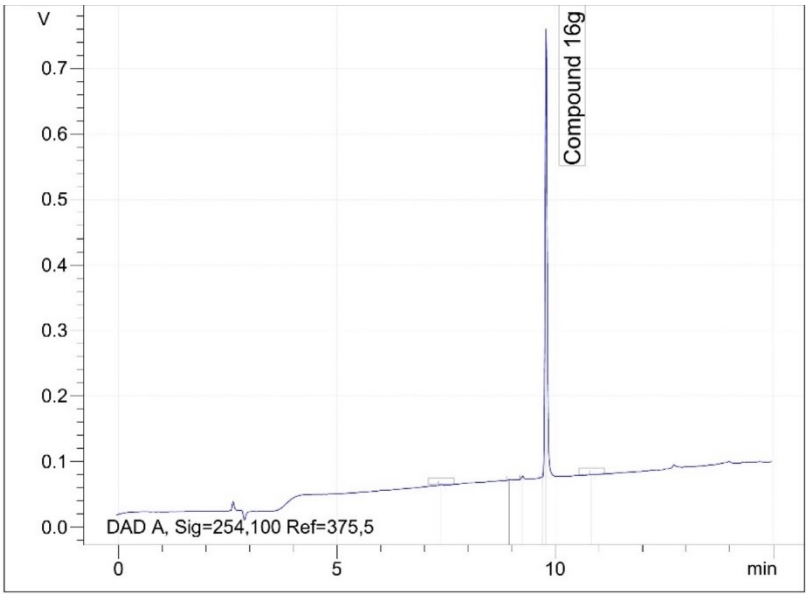
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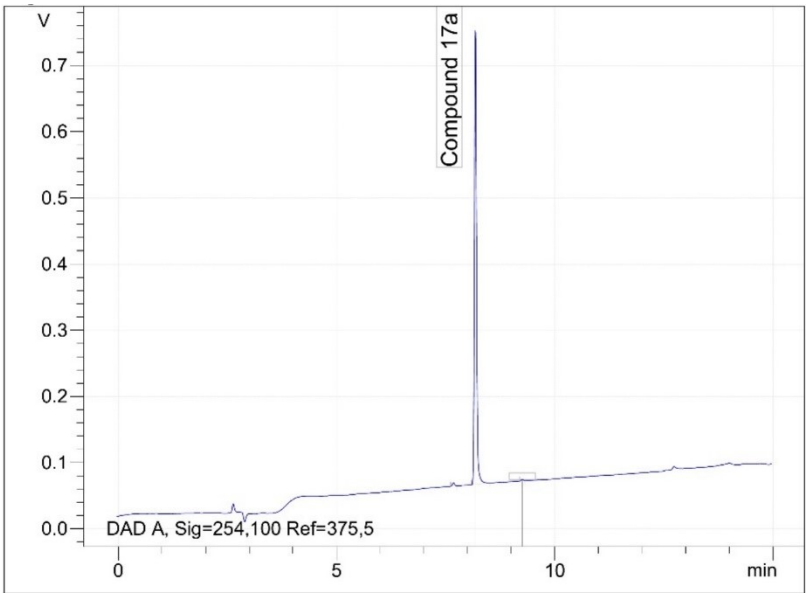
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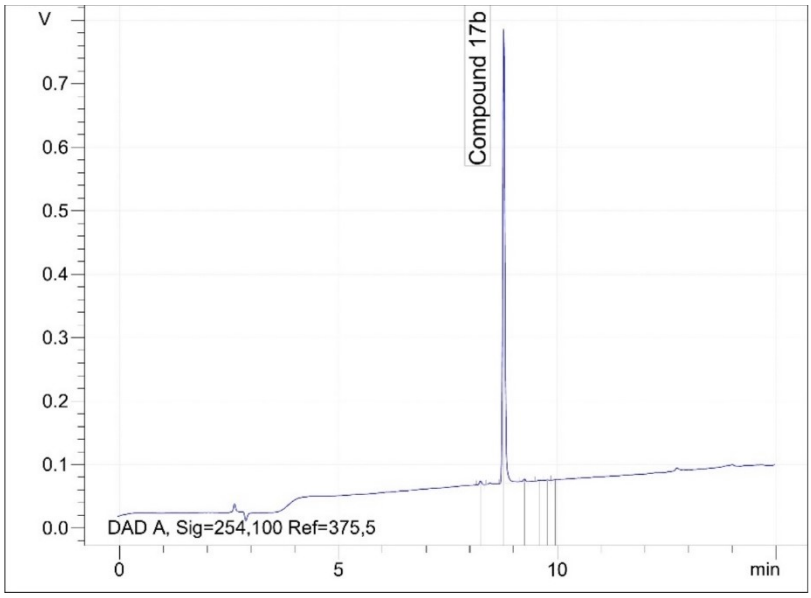
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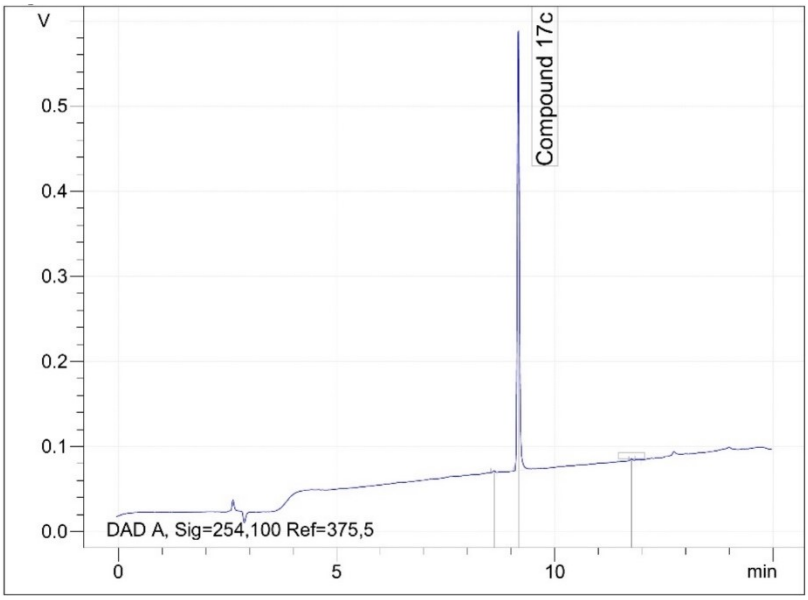
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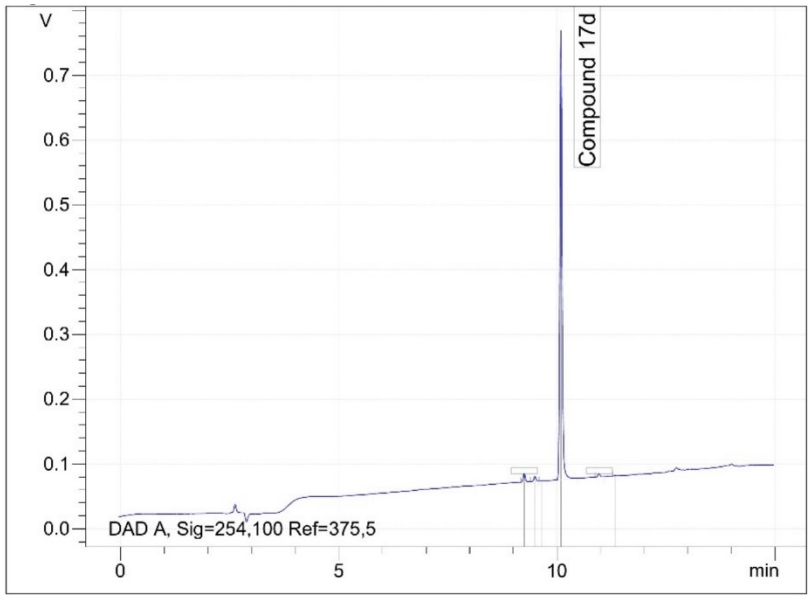
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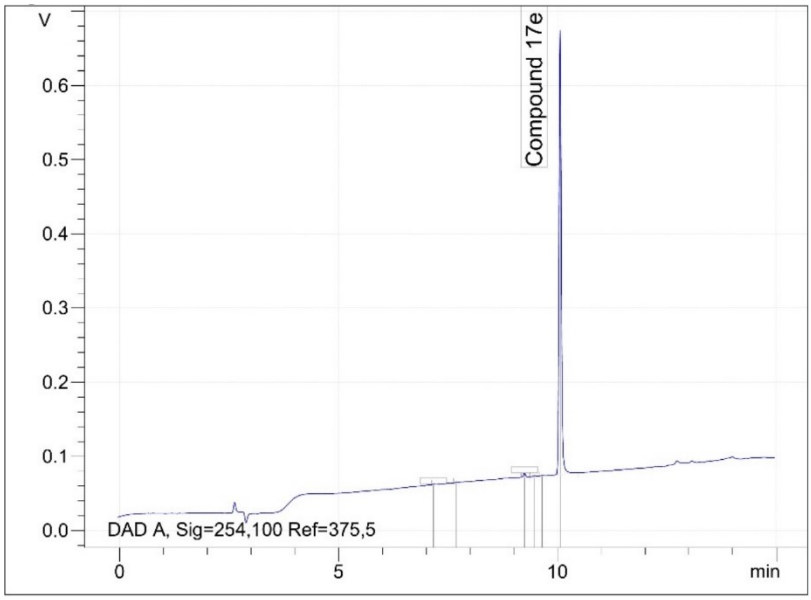
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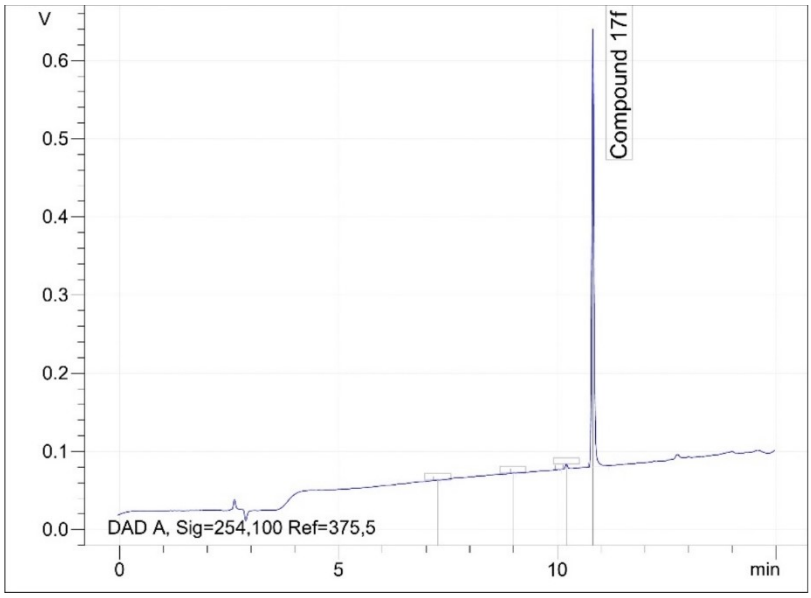
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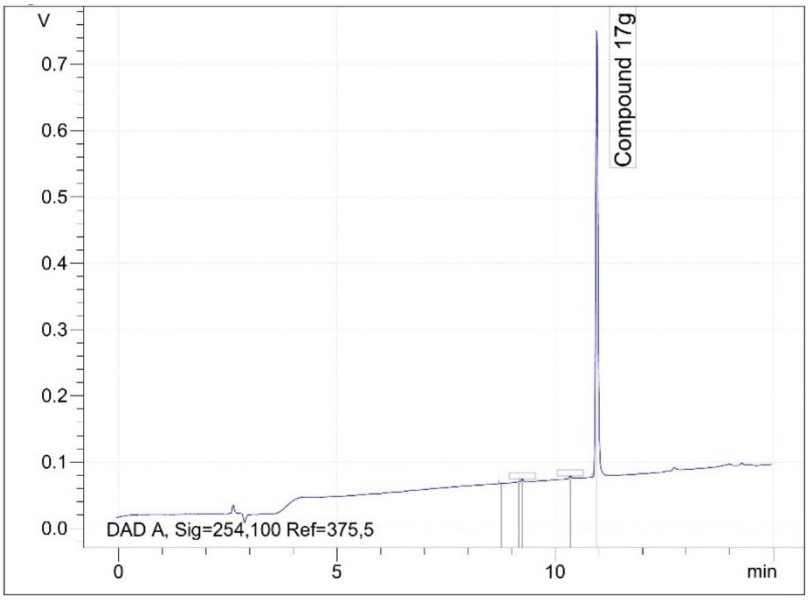
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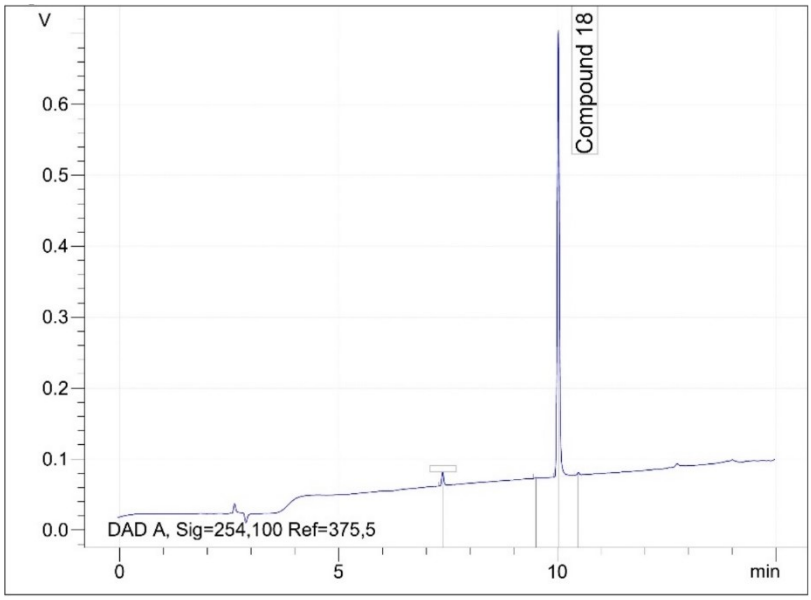
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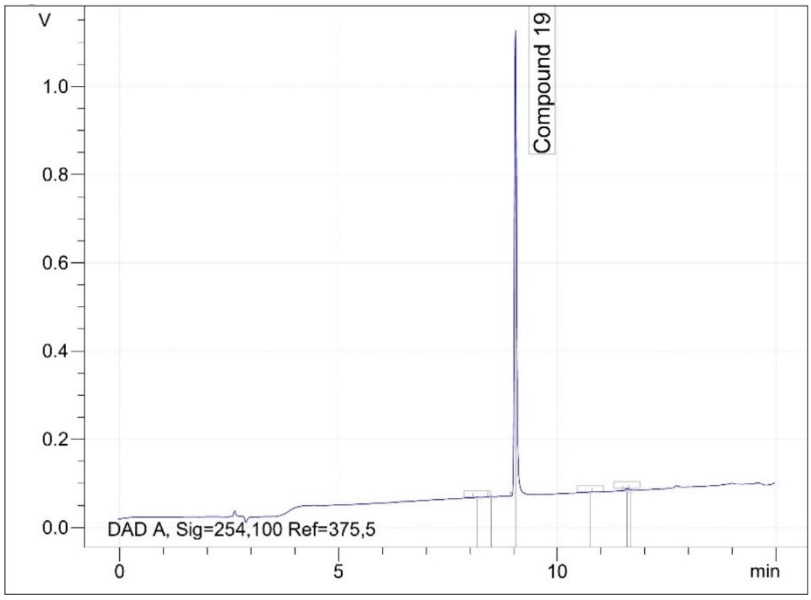
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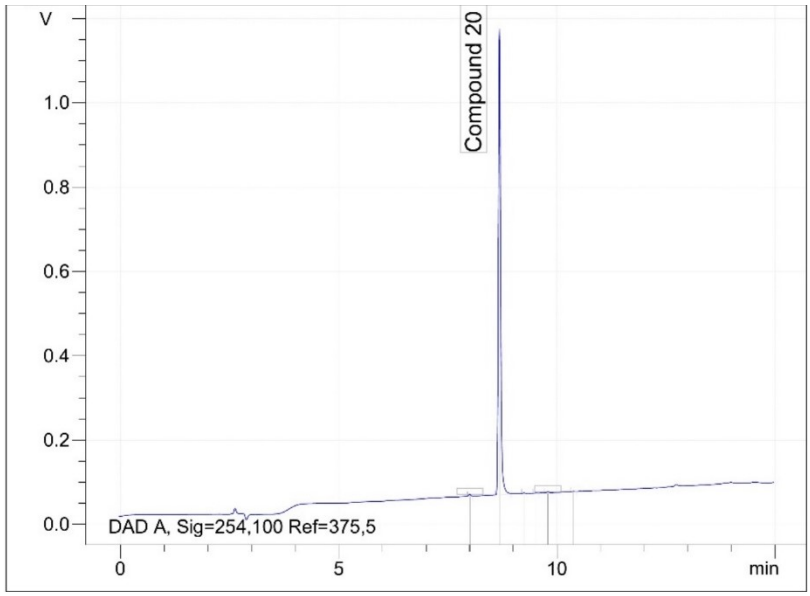
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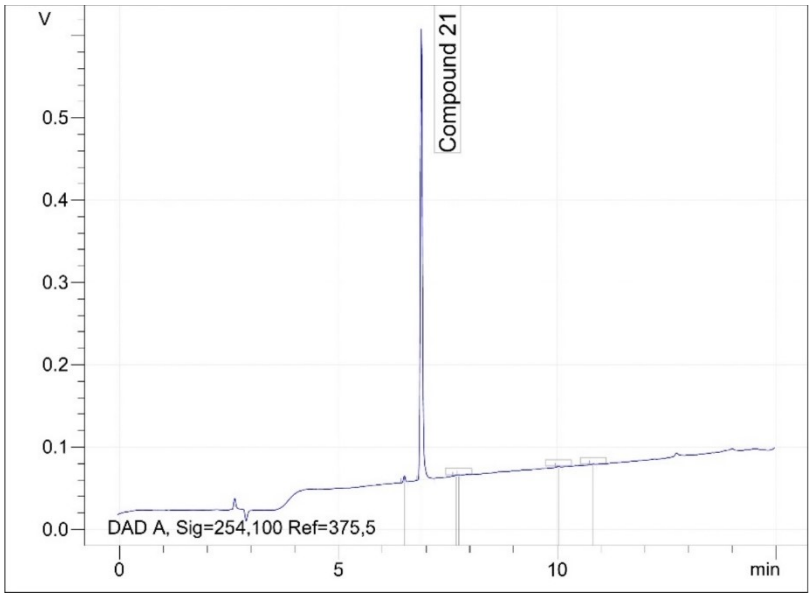
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CONCLUSIONS GÉNÉRALES ET PERSPECTIVES

L'exploration de l'espace chimique en quête de substances bioactives est, à l'échelle humaine, une tâche colossale reposant sur une myriade de contributions individuelles. Malgré l'existence de certaines tendances, comme la règle des cinq de Lipinski (Lipinski, 2004), qui permettent d'orienter les travaux de chimie combinatoire, de chimie classique et de synthèses *de novo*, le vaste réservoir de molécules produites par les êtres vivants au fil de leurs interactions avec leur environnement et leurs congénères utiles ou hostiles demeure une source d'inspiration d'importance capitale. À leur humble échelle, les dirchromones issues de *Dirca palustris* pouvaient constituer une telle parcelle de nouvelles structures bioactives pertinentes dans l'immensité de l'espace chimique, mais leur seule constatation dans la plante les aurait probablement confinées au rôle de curiosités phytochimiques sans autre perspective. Les trois objectifs centraux de cette thèse auront permis de creuser davantage le filon mis au jour par la découverte antérieure des dirchromones.

D'abord, une voie de synthèse de la dirchromone et de nombreux analogues a été mise au point (Chapitre I), répondant au premier objectif de cette thèse. Après de nombreux essais infructueux, l'approche retenue combine un réarrangement de Pummerer peu courant, permettant d'effectuer un transfert d'oxydation du soufre vers sa chaîne latérale pour introduire la fonction vinylique de la dirchromone, et le premier réarrangement de Baker-Venkataraman en conditions d'énolisation douce, prolongeant les travaux initiaux de Lim *et al*. (Lim et al., 2007). Cette stratégie de synthèse répond aux critères initialement fixés pour atteindre cet objectif fondateur. L'approche retenue est accessible. Les blocs de construction moléculaires requis (2'-hydroxyacétophénone et acide 3-méthylthiopropionique) sont abordables et accessibles en grandes quantités,

et les réactifs employés lors des étapes subséquentes sont facilement disponibles. La méthode est également flexible, puisque de nombreuses modifications structurales au produit final peuvent être introduites grâce à un choix diversifié de substrats de départ tout en étant compatibles avec les conditions réactionnelles mises en œuvre, à de rares exceptions près. Le nombre d'étapes impliquées est également raisonnable, permettant l'obtention d'une grande quantité (à l'échelle du gramme) d'une dirchromone en environ une semaine de manipulations. La préparation de plusieurs dizaines d'analogues tout au long de cette thèse illustre cette flexibilité et cette mise en œuvre efficace. Le principal défi synthétique se posant à l'avenir se rapporte à l'optimisation du rendement. En effet, tout particulièrement lors de la séquence conjointe d'estérification/réarrangement de Pummerer, les rendements obtenus oscillent fréquemment autour de 20 à 30 %, ce qui était suffisant aux fins de ce projet, mais certainement pas optimal. Si la phénone de départ non convertie peut être récupérée aisément lors de la purification, une bonne partie du réactif soufré est perdue, générant par ailleurs des impuretés qui contaminent fréquemment (bien que sans conséquences sur l'efficacité des étapes subséquentes) l'ester désiré même après la purification chromatographique. Un réexamen du réarrangement de Pummerer, peut-être assisté par certains catalyseurs comme hypothétiquement le triazabicyclodécène ou la triéthylamine pour faciliter l'abduction d'un proton, pourrait permettre non seulement d'améliorer le taux de conversion utile du réactif soufré, mais aussi d'établir la portée de cette réaction pour préparer une certaine diversité de chaînes latérales potentielles pour d'autres analogues de dirchromones.

Fort d'une voie de synthèse, le projet a ensuite permis de s'attarder au second objectif de la thèse, soit de déterminer ce qui, structuralement, rendait la dirchromone active (Chapitre II). Des modifications structurales choisies sur la chaîne latérale ont mis en lumière des variations parfois majeures de l'activité. Notamment, le degré d'oxydation du soufre joue un rôle crucial: si la sulfone conserve une activité (moins cytotoxique, davantage antibactérienne), le sulfide est en revanche inactif ; l'homologation du

sulfoxyde augmente également légèrement la cytotoxicité sur les lignées malignes. Il est également intéressant de rappeler que si la méthylation de l'alcène latéral et le remplacement du sulfoxyde par un carbonyle ont respectivement légèrement augmenté et sensiblement réduit la cytotoxicité, ces modifications ont toutefois anéanti le potentiel antibactérien, soulignant un découplage entre l'expression de la cytotoxicité et de l'activité antibactérienne Gram-positif des dirchromones. Cette constatation suggère un mécanisme d'action toxique distinct dans les deux cas de figure. Dans le même chapitre, un examen plus attentif des propriétés d'accepteur de Michael de la dirchromone a permis de caractériser certains produits de la réaction spontanée de la dirchromone avec la cystéamine, révélant une réactivité étonnante. Cette dernière combine le caractère d'accepteur de Michael de la 2-vinylchromone, une élimination du radical terminal soufré, et des réactions oxydoréductrices périphériques, menant à une diversité de produits de réaction. Qui plus est, le caractère fluorescent de certains de ces dérivés a permis d'observer que ce phénomène se déroulait dans le cytosol cellulaire. Tout ceci souligne le caractère fondamental du rôle de la chaîne latérale soufrée dans l'expression de ses activités biologiques et précise en quoi la dirchromone ouvre un petit pan inexploré de l'espace chimique biologiquement pertinent: l'interaction unique de la chromone conjuguée et du soufre mène à une réactivité surprenante. Bien évidemment, ces constatations préliminaires ne sont qu'une première étape. L'identification de la cible moléculaire cellulaire exacte de la dirchromone, ainsi que la manière dont la molécule et son substrat réagissent précisément, devrait logiquement être un des prochains objectifs. Cette connaissance permettrait d'une part de comprendre quelle(s) partie(s) de la séquence réactionnelle induit la toxicité, par exemple par interférence irréversible avec un site actif par addition de thia-Michael, par consommation rapide du glutathion via l'oxydoréduction, ou encore par génération *in situ* de fragments moléculaires soufrés eux-mêmes toxiques grâce à l'élimination du soufre. La faculté de la dirchromone d'être son propre marqueur fluorescent pourrait à cet égard se révéler un atout précieux. En ce sens, la dirchromone pourrait être vue comme un outil moléculaire, tel que défini par Lipinski: une molécule bioactive, même

si elle n'a pas intrinsèquement des propriétés la destinant à devenir directement une substance médicamenteuse, peut servir d'outil permettant d'identifier des cibles biologiques pertinentes et de comprendre des mécanismes ayant à leur tour une pertinence pharmacologique (Lipinski and Hopkins, 2004).[1]

Enfin, la flexibilité de la voie de synthèse mise en œuvre dans cette thèse a permis l'atteinte du troisième objectif, consistant à préparer une série de 32 analogues diversement substitués de la dirchromone pour examiner les relations entre la structure de la chromone et les activités cytotoxiques et antibactériennes (Chapitre III). Le portrait d'ensemble suggère, une fois de plus, une absence de corrélation entre les activités cytotoxique et antibactérienne, et par le fait même une toxicité différenciée. En outre, cette étude permet de constater que la position des substituants semble n'avoir qu'un impact faible, leur nature ayant plus d'influence. Deux substituants, l'hydroxyle et le nitrile, réduisent respectivement modérément (d'un facteur cinq) et fortement (plus d'un ordre de grandeur) la cytotoxicité, alors que le second groupe augmente le potentiel antibactérien. D'autres substituants augmentent à l'inverse légèrement (d'environ un facteur deux) la cytotoxicité, comme le bromure, l'isoamyloxyde ou

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[1] Il faut noter que Lipinski ne considérait pas les composés établissant des liaisons covalentes comme de bons candidats pour de tels outils (Lipinski, 2004), puisqu'ils perturbent fondamentalement la fonctionnalité des protéines. Si la prudence à l'égard des interactions covalentes irréversibles était la norme à l'époque, la discussion autour de ce thème a beaucoup évolué depuis. Les composés présentant une telle réactivité ne sont plus forcément balayés du revers de la main dès le départ, malgré les écueils associés à ce type de mécanisme d'action, et peuvent jouer un rôle constructif dans l'évolution de la chimie médicinale (Vita, 2020). Il serait donc prématuré de disqualifier l'étude de la dirchromone sur ce seul critère sans acquérir une meilleure compréhension du mécanisme à l'œuvre.

l'ajout de cycles aromatiques. L'alkoxydation de la chromone avec des chaînes de longueur croissante mène également à l'émergence progressive d'une activité inhibitrice de la levure *Candida albicans*, initialement insoupçonnée et se potentialisant plus rapidement que la cytotoxicité. Il semble donc possible de moduler l'activité de la dirchromone afin d'en faire un pharmacophore moins toxique et utilisable comme antibactérien ou antifongique. Notablement, la combinaison d'une sulfone sur la chaîne latérale et d'un substituant nitrile sur la chromone devrait fournir un dérivé sensiblement plus antibactérien tout en réduisant fortement la toxicité cellulaire et pourrait servir de point de départ à un examen séparé de dérivés de dirchromone ciblant en tout premier lieu les bactéries.

En perspective, la revue des résultats obtenus pour ce troisième objectif montre que le pharmacophore de la dirchromone est assez tolérant à la substitution, puisque la plupart des analogues préparés conservent une activité ne variant que légèrement par rapport à la dirchromone elle-même et de manière assez congrue entre les différentes lignées cellulaires. D'un côté, cela met en lumière une limitation qui paraît en rétrospective inhérente aux dirchromones en tant que pharmacophore, à tout le moins du point de vue de la cytotoxicité. En effet, malgré le grand nombre d'analogues préparés dans le cadre de cette thèse, la sélectivité entre les cellules malignes et saines n'a jamais profondément été modulée. Quant à la la toxicité elle-même, elle a été modérément augmentée, mais un gain d'un ordre de grandeur est demeuré hors d'atteinte. Ainsi, la de modulation de l'activité à l'aide des modifications structurales variées effectuées dans le cadre de cette thèse a exposé les éléments structuraux critiques au maintien de la cytotoxicité comme le degré d'oxydation du soufre, mais n'a pas permis de mettre en lumière une orientation précise à suivre pour la préparation d'une seconde génération de dérivés plus cytotoxiques et/ou sélectifs. Il serait donc peu avisé de poursuivre la même approche méthodologique d'introduction de modifications structurales classiques pour donner suite au projet. D'un autre côté, en renversant la perspective des résultats obtenus, la dirchromone fait montre d'une robustesse

remarquable de son activité en dépit de modifications structurales variées. Il devient donc raisonnable de poser l'hypothèse qu'un grand nombre de substituants complexes pourraient également être adjoints au squelette moléculaire principal sans pour autant entraver son activité. Cette constatation ouvre la porte à des assemblages moléculaires plus raffinés qui pourraient permettre de contourner le manque de sélectivité de la dirchromone, et peut-être de réduire la dose requise pour obtenir une réponse biologique. Par exemple, des glycosylations peuvent dans certains cas permettre d'améliorer la spécificité de substances cytotoxiques pour des tissus malins (Alsarraf and Legault, 2018; Chang et al., 1998; Ma et al., 2018; Pastuch-Gawołek et al., 2016; Sylla et al., 2019). Les études ayant déjà cours au LASEVE en ce sens pourraient être étendues à la dirchromone, et ce, à la recherche d'un effet similaire. De manière plus ambitieuse, une stratégie qui permettrait d'administrer un sulfide inactif et de le convertir en sulfoxyde aux abords ou au sein d'un tissu cancéreux pourrait permettre de contourner l'absence de sélectivité. Une telle approche constituerait un vaste défi en soi, et sa mise en œuvre dépasse toutefois largement le cadre de la présente discussion.

Plus largement, la dirchromone inspire également un rappel méthodologique dont la portée dépasse celle de cette thèse. Beaucoup de littérature sur l'exploration de l'espace chimique repose lourdement sur la classification des structures cycliques (Ertl et al., 2006; Hert et al., 2009; Koch et al., 2005; Taylor et al., 2014), semblant de manière générale accorder une importance de second ordre (au sens d'étape secondaire) aux substituants. Ce type d'inférence est bien sûr très utile pour organiser, trier, disséquer et prioriser des chimiothèques de composés. Toutefois, la mise en évidence de l'importance de la chaîne latérale soufrée dans l'activité de la dirchromone (chapitre II) montre que certaines propriétés critiques peuvent émerger de l'interaction des cycles et de leurs substituants. Il apparaît au vu des résultats de ce chapitre que la chromone seule, ni plus d'ailleurs qu'un vinylsulfoxide isolé, ne pourrait mener à la cascade réactionnelle observée. En d'autres termes, il est peu probable qu'une approche classique de chimie combinatoire aurait mené dans un avenir prévisible à la préparation

d’une structure telle que la dirchromone, à plus forte raison considérant l’exotisme du motif vinylsufloxyde et son inaccessibilité initiale. Sans évidemment exagérer l’importance de ce composé dans la vaste entreprise de l’exploration de l’espace chimique biologiquement pertinent, la dirchromone nous rappelle toutefois que l’examen « classique » des produits naturels, incluant une partie de sérendipité, a encore un rôle à jouer pour inspirer la chimie médicinale.

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