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DCM Alternatives for use in Steglich Esterifications, for Green and Sustainable Liquid Crystal Syntheses

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Abstract

Dichloromethane (DCM) is a popular solvent for the synthesis of liquid crystalline materials owing to its solvating power, moderate polarity, and ease of removal. The environmental and toxicological issues surrounding DCM prompt us to explore alternatives. Here, we have screened an extensive selection of green and sustainable solvents to find the most efficacious DCM alternative for the synthesis of a conventional liquid crystal, CZP-5-N. Several factors are considered: yield, environmental impact, and health and safety concerns. The best performing solvent, dimethyl carbonate, was then used in the synthesis of common and novel liquid crystals, along with intermediates, giving excellent results, even for electron poor phenols. With esterifications prevalent in trending research areas like the ferroelectric nematic phase, this work allows a facile means for sustainability to be incorporated into synthetic pathways.

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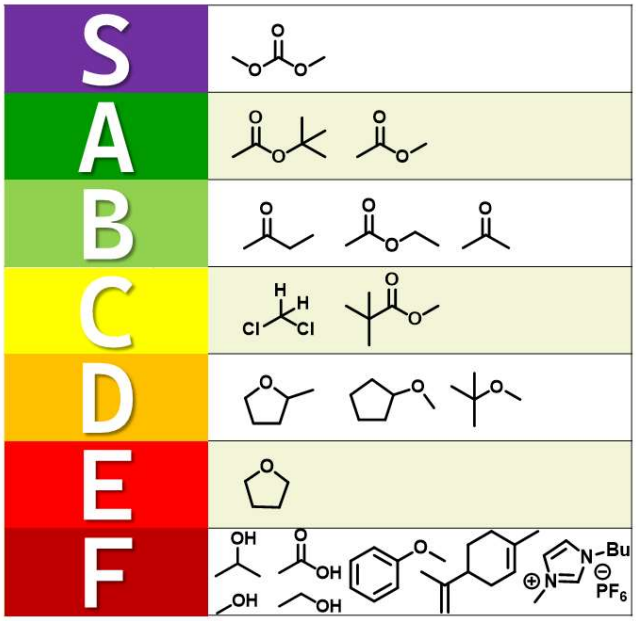
ABSTRACT

Dichloromethane (DCM) is a popular solvent for the synthesis of liquid crystalline materials owing to its solvating power, moderate polarity, and ease of removal. The environmental and toxicological issues surrounding DCM prompt us to explore alternatives. Here, we have screened an extensive selection of green and sustainable solvents to find the most efficacious DCM alternative for the synthesis of a conventional liquid crystal, CZP-5-N. Several factors are considered: yield, environmental impact, and health and safety concerns. The best performing solvent, dimethyl carbonate, was then used in the synthesis of common and novel liquid crystals, along with intermediates, giving excellent results, even for electron poor phenols. With esterifications prevalent in trending research areas like the ferroelectric nematic phase, this work allows a facile means for sustainability to be incorporated into synthetic pathways.



1 INTRODUCTION.

Sustainable chemistry has become a leading area of study in recent years,[1–3] however, one area in which it is still under studied is liquid crystals. At the international liquid crystal conference 2024, only one contribution was made to the sustainability category.[4] Liquid crystals are materials that combine fluidity with some degree of molecular organisation intermediate between crystalline solids and isotropic liquids. In the nematic (N) phase, molecules retain a degree of orientational order without positional order, thus the N phase remains fluid (Figure 1b).[5] The combination of ordering, processability and stimuli response (e.g. to temperature, or electric/ magnetic fields) underpins their widespread use in display technologies (i.e LCDs).[6] Differing degrees of positional and/or orientational ordering of the constituent molecules give rise to different phase types; for example, smectic phases possess highly diffuse layers (Figure 1b) and the molecules can be orthogonal or tilted to the layers.[7]

The Steglich esterification is widely used in the preparation of carboxylate esters across synthetic chemistry, including the synthesis of liquid-crystalline compounds,[8–12] due to their ability to connect different, readily available molecular fragments. These fragments are used to control the hydrophobicity, polarity, polarizability of the target liquid crystals. In polar liquid crystal phases, such as the ferroelectric nematic (N_F) phase, esters can be crucial to the propagation of long-range polarity in the molecule.[13]

In this reaction, a carboxylic acid reacts with a carbodiimide to form an O-acylurea intermediate which then reacts with a suitable acyl transfer catalyst (e.g. DMAP) which then reacts rapidly with the alcohol/phenol to yield the desired ester. The use of modern coupling reagents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC.HCl) ensures that the urea byproducts are trivially removed, overcoming issues with older reagents (e.g. *N*,*N*'-Dicyclohexylmethanediimine, DCC). The ambient reaction temperatures and high functional group tolerance of the Steglich Esterification make it far more attractive than Fischer-Speier Esterification, acid chlorides and so on.

The highly anisotropic shape of typical liquid crystalline materials, Figure 1a, can result in poor solubility in organic solvents; however, DCM is widely used as a solvent for Steglich esterification in these materials owing to its unique solvation properties for the reagents, products and also various intermediates in this transformation.

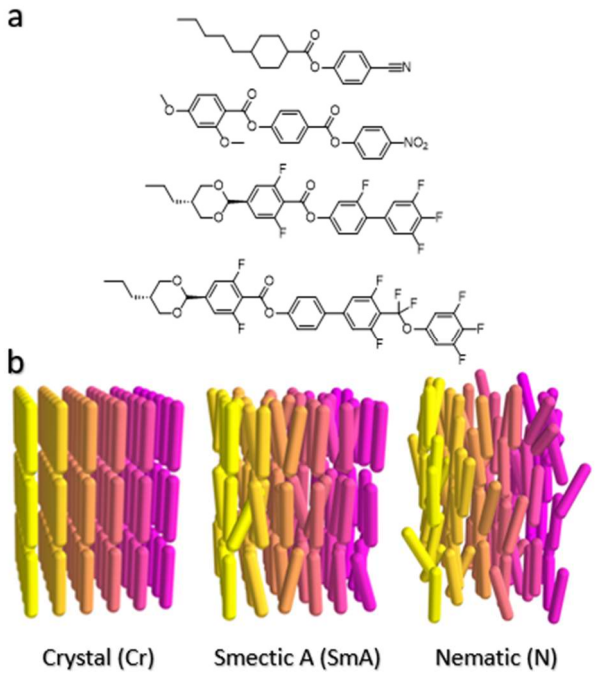


Figure 1: Figure 1a, Molecules that display liquid crystalline behaviour. From top to bottom CZP-5-N,[14] RM734,[8] DIO,[15] RM2914.[16] Figure 1b, The schematic representation of a crystal, and smectic A (SmA), and nematic (N) mesophases.

A US EPA ban has greatly limited the usage of dichloromethane (DCM), with strict workplace controls to be implemented for the limited applications in which its use remains permitted.[17,18] DCM is hepatotoxic, neurotoxic, carcinogenic, and the cause of at least 88 deaths since 1980 through acute exposure.[18–21] DCM also contributes to stratospheric ozone depletion.[21,22] However, it is difficult to replace DCM due to its solvating power, low flammability, minimal cost and high volatility. The US EPA ban aligns with the ACS Green Chemistry Institute Pharmaceutical Roundtable, who also expressed the importance of finding replacements for halogenated solvents.[21] DCM is effectively the standard solvent for the Steglich esterification of liquid-crystalline materials,[12,23,24] and identifying a greener yet equally

effective alternative for this transformation is an important challenge. This is made non-trivial as liquid-crystalline materials display somewhat poor solubility in many organic solvents.

Herein, we report a systematic approach for the replacement of DCM in the Steglich Esterification to find the optimal solvent for a synthesis of the liquid crystal CZP-5-N,[14] Figure 1a and 2a. The optimal solvent was then employed in the synthesis of a series of intermediates, other traditional and novel and polar liquid crystals.

2 METHODS

2.1 Materials

Reagents and solvents were obtained from commercial suppliers and used as received. In-house materials were synthesised as per referenced methodology. In-house phenols used in the synthesis of esters: **5**,[25], **13** and **23**,[26] **19** and **20**,[27] ; in-house carboxylic acid used in the synthesis of esters: **9**,[28] **12**,[29] **11**,[30] **14**.[31]

In-house carboxylic acids used in the synthesis of **15**, **17**, **18**, **19**, **20**, **24** were all prepared via Suzuki coupling reactions using the methodology as described in section 2.3, and S3.2.

2.2 General Steglich-Esterification Protocol

The relevant alcohol (1.0 equivalent), carboxylic acid (1.2 equivalents), EDC.HCl (1.5 equivalents) and DMAP (ca. 5 mol %) were added to a round bottomed flask or reaction vial. The relevant solvent (concentration ca. 0.3 M) was then added to the flask and left at room temperature with stirring for 24 hours (dimers 72 hours). The products were then isolated with flash chromatography. Solid compounds were then recrystalised using an appropriate solvent, typically ethanol or acetonitrile.

2.3 General Suzuki-Miyaura Protocol

A biphasic mixture of THF (~ 2 vol) and 2M aqueous K_2CO_3 (~ 1 vol) was degassed by sparging with argon for 20 minutes. Aryl bromide (1.0 mol eqv.) and boronic acid/ester (1.2 mol eqv.) were added in sequence. The reaction was stirred and heated under reflux and under an atmosphere of dry nitgrogen gas. Pd-Xphos-G3 (cat.) was added in one portion. After 16 hours, the reaction was cooled to ambient temperature, then acidified to pH 2 with 2M aqueous HCl. Ethyl acetate was added; the organic phase was separated and retained. The aqueous phase was washed three times with ethyl acetate, then discarded. The combined organic phases were washed with brine three times. The organic phase was dried over $MgSO_4$, which was subsequently removed by filtration. The volatiles were removed *in vacuo*, before recrystallisation of the crude material from isopropanol. The recrystalised material was collected by filtration, washed with cold ethanol (-18 °C), and dried under suction to yield the title compounds.

2.4 PURIFICATION

Chromatographic purification was performed using a Combiflash NextGen 300+ system (Teledyne Isco) using silica gel cartridges as the stationary phase and a hexane/ethyl acetate gradient as the mobile phase.

2.5 CHARACTORISATION

NMR was performed on a Bruker AV4 NEO 11.75 T (500 MHz 1H) NMR spectrometer (500-CP), or Bruker AV3HD 9.4 T (400 MHz 1H) NMR spectrometer (AV3HD-400).

Phase sequences of compounds were performed with polarised optical microscopy (POM) and differential scanning calorimetry (DSC). Polarised light optical microscopy (POM) was performed using a Leica DM2700P polarised light microscope (Leica Microsystems (UK) Ltd., Milton Keynes, UK), equipped with 10x magnification, and a rotatable stage. A Linkam LTS 350 heating stage (Linkam Scientific Instruments Ltd., Redhill, UK) equipped with a TMS 93 temperature controller (Linkam Scientific Instruments Ltd., Redhill, UK) was used for temperature variation. Images were recorded using a XIMEA USB3 Camera (XIMEA GmbH, Münster, Germany) using IDS uEye Camera Software (IDS Imaging Development Systems Ltd, Farnham, UK). Samples were analysed sandwiched between untreated glass substrates, unless otherwise specified. Differential scanning calorimetry (DSC) was performed using a TA instruments Q20 or TA instruments Q2000 heat flux calorimeter, both with an RCS 90 cooling system for temperature control. Transitions reported on cooling except for the initial melt recorded on the second heating cycle.

Dielectric anisotropy was measured in cells with a planar alignment layer, 5 µm LC devices (AWAT, Poland), which contained 15 Ω/ sq. ITO electrodes, SE130 planar alignment layer and were rubbed antiparallel. The quality of alignment was monitored with POM throughout. Temperatures were controlled with a THMS600 hot stage with Linkam 95-PE temperature controller. The Fréedericksz transitions were induced electrically with an out of plane electric field at 10 kHz as a function of voltage, across the nematic phase on cooling from 83 to 35 °C. An Agilent Precision LCR meter E4980A was used to measure capacitance.

Spontaneous polarisation measurements were undertaken using the current reversal technique, using an Agilent 33220A signal generator and a RIGOL DHO4204 high-resolution oscilloscope, with temperature control via an Instec HCS402 hot stage.

3 RESULTS AND DISCUSSION

3.1 Identifying Candidate Replacement Solvents

The Hansen Solubility Parameters (HSP) were used as an initial starting point to find potential suitable replacements for DCM. Within HSP there are three parameters: dispersion (δD), hydrogen bonding (δH) and polar interactions (δP), these give coordinates in 'Hansen space'.[32] Solvents with similar coordinates are more likely to dissolve similar solutes, making HSP a useful preliminary screening tool in assessing alternatives to DCM. With the use of other basic physical properties, and several solvent selection guides,[20,22,24,33,34] a short-list was created of potential DCM replacements. The GSK solvent guide is particularly insightful as it breaks SHE score into seven factors: including a LCA of the solvent from cradle to grave, heath, flammability and stability factors. The ideal replacement must have minimal toxicity, be easy to recycle, inert, and easily removed.[35] It is the solvation power of DCM that is most sought after, but this is also the aspect most difficult to replicate.

DCM occupies a rather unusual region of Hansen space (Table 2; δD: 17, δP: 7.3, δH:7.1). The high dispersion term stems from the polarisability and electronegativity of the chlorine atoms, while the moderate hydrogen bonding and polar interactions reflect a limited ability to engage in strong H-bond

or polar interactions. Few greener solvents combine these features. Solvents with comparable dispersion parameters to DCM typically contain far more carbon (and/ or oxygen) atoms but are widely different in there δP and δH for these reasons (e.g. limonene). Increasing molecular weight to reach the required δD predictably leads to increased boiling point and reduced vapour pressure, limiting ease of removal. Additionally, DCM is not flammable under typical lab conditions, distinguishing it from many classical organic solvents.

Solvent selection guides such as CHEM21, the GSK guide, and others typically recommend water, alcohols, esters, and some carboxylic acids as greener alternatives.[22,33,34] However, protic solvents are incompatible with esterification reactions. There are many high boiling point solvents that are derived from biomass,[33] such as, Cyrene, terpenoids, and esters of fatty acids, as seen in Table 2 below. Due to the energy demand on work up, these too were discounted from the study. It is likely that the environmental impact of a liquid-liquid extraction, or azeotropic removal of the solvent would negate positive effects of not using DCM to begin with, although a full life cycle assessment (beyond the scope of this work) would be required to confirm this. These solvents can potentially be removed via freeze-drying, but this is a far less flexible technique than removal under reduced pressure and is not widely used in the field. Ionic liquids were also considered but again, the product would likely be extracted into one of the solvents that is already being considered, making them a less favourable option. Solvent-less conditions are also worth considering, when possible,[36] although few liquid crystal fragments have sufficiently low melting points/ or are two costly to also facilitate the solvation role. Therefore, a selection of 'green' solvents and several classical solvents have been chosen, to assess their ability to perform the esterification.

Table 2, Showing a range of solvents along with their HSP values,[32] and physical characteristics, such as b.p., vapour pressure and flash point.

Solvent	δD	δP	δH	Boiling Point (°C)	Vapour Pressure (mbar at 20 °C)	Flash Point (°C)
Dichloromethane (DCM)	17.0	7.3	7.1	40	350	N/A
Limonene	17.2	1.8	4.3	176	2.1	48
Methyl acetate (MeOAc)	15.5	7.2	7.6	57	228	-13
Ethyl acetate (EtOAc)	15.8	5.3	7.2	77	103	-4
^{s}Butyl acetate (^{s}BuOAc)	15	3.7	7.6	112	16	25
Isobutyl acetate (Iso-BuOAc)	15.1	3.7	6.3	117	25	16
^{t}Butyl acetate (^{t}BuOAc)	15	3.7	6.0	97	56	15
Methyl pivalate (Me-Piv)	15.1	4.0	5.1	101	23	6
Methyl Laurate	15.4	3.2	3.2	261	0.0055 (at 25 °C)	139
Dimethyl carbonate (DMC)	15.5	8.6	9.7	90	53	18

Propylene Carbonate	20.0	18	4.1	240	0.04	116
Acetone	15.5	10.4	7.0	56	245.3	-17
Methyl ethyl ketone (MEK)	16.0	9.0	5.1	80	95	-1
Cyrene	18.9	12.4	7.1	227	0.28	108
Tetrahydrofuran (THF)	16.8	5.7	8	65	170	-21.2
2-Methyl tetrahydrofuran (2Me-THF)	16.9	5	4.3	78	136	-10
^{t}Butyl methyl ether (TBME)	14.8	4.3	5	55	268	-28
Cyclopentyl methyl ether (CPME)	16.7	4.3	4.3	107	42.7	< 3
Anisole	17.8	4.4	6.9	154	3.72	43

For the initial stage of the work, we focused on the synthesis of an ester-containing liquid crystal, CZP-5-N (Figure 2a),[37] using various solvents. The reaction was performed with twelve solvents, including DCM as a control, with each solvent being tested on gram scale to obtain an isolated yield, seen below Figure 2b. An isolated yield for gram scale reactions is a superior metric to HPLC conversion in this case. An in-depth characterisation and analysis of liquid crystalline materials, requires having access to >100 mg quantities of material in high purity (>99 %). A HPLC/ NMR yield in this case would not be sufficient, as isolated material is required for these analyses to fully study the applications, e.g. for display devices (LCDs).

Out of the several solvent selections guides, the numerical CHEM21 and GSK guides were the most extensive encompassing many solvents that that the others did not include.[33,38] These served to provide the safety, health, and environmental (SHE) scores for the solvents, with the CHEM21 SHE scores being normalised against the GSK SHE scores. The averaged SHE score was then combined with the yield to provide a final score to indicate the suitability of a solvent for the reaction. The final scores can be seen in Figure 2 with the score decreasing down the figure.

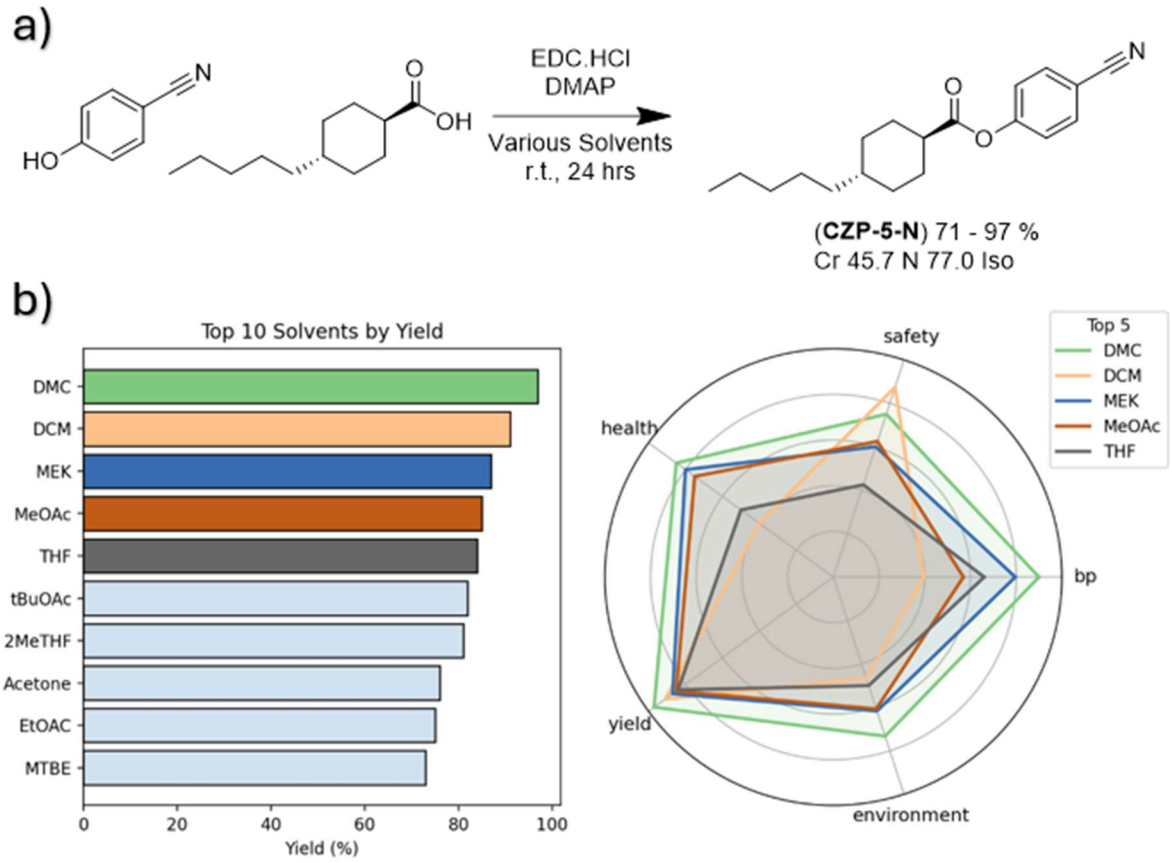


Figure 2: Figure 2a: the Steglich esterification for the liquid crystal CZP-5-N,[14] Figure 2b: Left: Bar chart of isolated yield (%) for each solvent studied in the synthesis of CZP-5-N *via* Steglich esterification of (*trans*)-4-pentylcyclohexane-1-carboxylic acid and 4-cyanophenol. Right: Radar diagram showing the differentiation of the top six solvents in terms of boiling point (bp) and average health, safety, and environmental score (see ESI for further details); [33,38] broadly speaking, higher values are better.

Dimethyl carbonate (DMC) was the only solvent that gave consistently higher yields than DCM (Figure 2b). However, all solvents shown here gave usable isolated yields. To differentiate between solvents beyond yield alone we consider the environmental, health, and safety factors described above (see ESI for details, Table S1). The radar diagram in Figure 2b shows how the top 5 solvents in terms of yield differ when SHE factors are considered. DMC is not only the most efficacious (97 % isolated yield) but also scores best across the health (85) and environmental metrics (73.3). DCM scores highly for safety (87.5) mainly due to being non-flammable, but scores lowest across the health (40) and environmental metrics (46.7). Therefore, DCM achieved a total score of 265.2, whilst DMC scored a total of 330.3, with 400 being the maximum score.

One factor not considered here, owing to its regional and temporal variation, is pricing. At time of writing DCM is vastly cheaper than DMC. For the small-scale preparations typically undertaken in academic groups, this is not a huge concern ordinarily. Sustainability can be viewed through multiple lenses and is often said to have three pillars: environmental, economic and social.[35] Perhaps then, it should be noted that the economies of scale need to shift to greener solvents for a truly sustainable solvent to emerge.

3.2 SCOPE OF DMC UTILITY IN LIQUID CRYSTAL SYNTHESIS

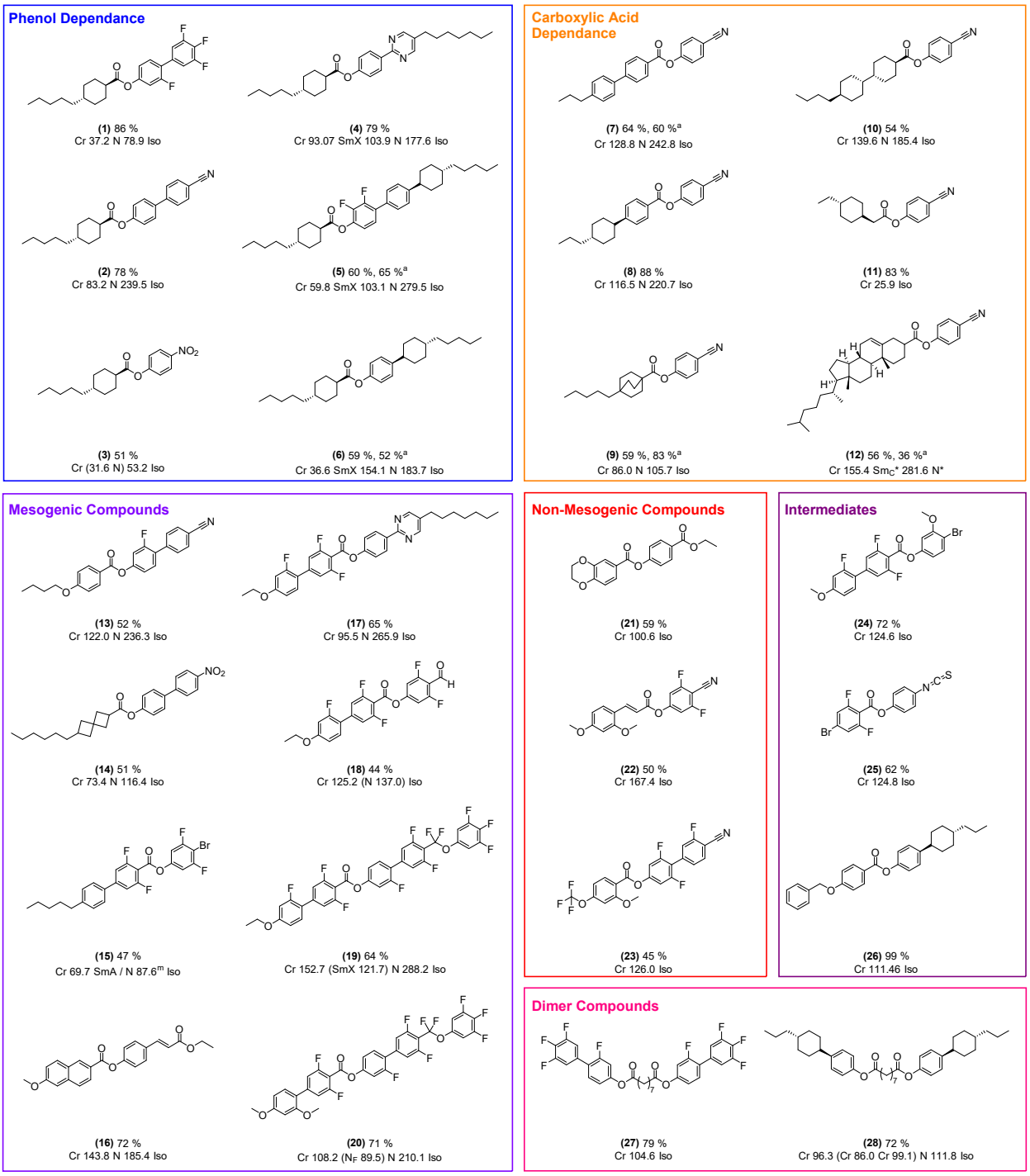


Figure 3. A series of Liquid crystals and intermediates that have been prepared using DMC the solvent. Yields refer to isolated yields of chromatographically and spectroscopically homogenous material. Transition temperatures, given in °C, at the onset. Typically, 1.0 mmol alcohol, 1.2 mmol carboxylic acid, 1.5 mmol EDC.HCl, ca. 5 % DMAP, 30 mL DMC, r.t., 24 hours. Dimers 1.0 equiv. carboxylic acid, 2.5 equiv. alcohol, 3.0 equiv EDC.HCl, 5 mol% DMAP, r.t., 72 hours. a. compounds made using a 1:1 DMC: ^{t}BuOAc solvent system. SmA and N phases were seen to occur simultaneously by POM. N = nematic, N* = chiral nematic, N_F = ferroelectric nematic, SmA = smectic A, SmC* = chiral smectic C, SmX = unknown smectic phase, Cr = melting point, Iso = isotropic liquid.

To assess the generality of DMC as a solvent for Steglich Esterification, we examined a representative series of phenols and carboxylic acids commonly used in liquid-crystal synthesis (Figure 3). These substrates cover a broad range of electronic and steric environments and include motifs used in widely studied nematic and ferroelectric nematic materials.

Esterification with electron poor 4-hydroxybiphenyls afforded **1**, and **2** (Figure 3) in excellent yield (86% and 78%, respectively). Compound **2** exhibits a nematic phase, with transition temperatures in excellent agreement with literature values.[14] Compound **1** is analogous to DIO (Figure 1a),[15] and CZGU-3-F, reported by Hobbs *et al.*[39], and displays a non-polar nematic phase close to ambient temperature. Single ringed electron poor phenols such as *4-nitrophenol* used in RM734 (Figure 1a),[8] gave a lower yield as expected (**3**, Figure 3), whereas electron rich phenols (e.g. **4**) gave a high yield. It is however, a more lipophilic starting material which lead to a slightly lower yield than might be expected, this trend was also seen in **5** and **6**.

To explore the influence of the carboxylic acid component, 4-cyanophenol (the phenol from CZP-5-N) was coupled with a variety of acids (**7-12**), including aromatic, primary, secondary, and tertiary aliphatic examples. As anticipated, electronic effects in the acid had only a minor influence on the reaction outcome. Instead, increased hydrophobicity again correlated with somewhat lower yields, suggesting that solubility in DMC is one of the main factors determining isolated yield.

To investigate the lipophilic/ hydrophilic interactions a blend of 50:50 DMC (HSP: δD 15.5, δP 8.60, δH 9.7) and ^{t}BuOAc which is far more lipophilic (HSP: δD 15.0, δP 3.7, δH 6.0) was used. As seen in Figure 3 superscript a, the yields of **5**, **6**, **7**, are near identical, with a slight decrease in the yield of **12**, but a large increase in the yield of **9**. This would suggest that the solvation is not the issue and there is another more nuanced bottleneck to higher yields.

The liquid crystalline behaviour of compounds **2**,[14] **3**,[40] **4**,[41] **7**,[42], **9**,[37] is in excellent agreement with earlier reports, with all materials displaying a non-polar nematic phase at elevated temperature.

As with the initial compounds investigated, better nucleophiles provided better yields, and as these compounds contain more polar components, lipophilic/ hydrophobic interactions playing a lesser role. Many of the compounds displayed nematic phases (**13**, **14**, **16**), slightly unusually **15** showed two phases which were indistinguishable by DSC but could be seen going from N to SmA by POM on cooling.

Compounds **19** and **20** are structurally related to the DUZPUQU-n-F materials which display polar nematic phases and spontaneously break mirror symmetry to yield heliconical polar phases.[16,27] Compound **20** exhibits a ferroelectric nematic phase, whilst compound **19** is nonpolar. **17** and **18** using the same carboxylic acid as **19**, did not show any polar phases.

Compounds **21**, **22**, and **23** are non-mesogenic and melt directly into isotropic liquids. Several intermediates for future synthesis were also produced (**24**, **25**, **26**). Interestingly, the esterification of benzyl protected hydroxybenzoic acid (**26**) gave an isolated yield of 99 %; high yielding reactions such as this are especially attractive for telescoped multi-step flow processes (e.g. esterification-hydrogenolysis-esterification).[43] Dimers were also produced **27**, **28** in high yields, although requiring longer reaction times (72 hours), possibly reflecting the reduced solubility of the mono-esterified species, but there is likely to be a significant kinetic component too. The dimer **28** displays a short-range nematic phase, whereas **27** is non-mesogenic.

Overall, our results confirm that DMC is compatible with a wide range of functional groups and structural motifs relevant to liquid-crystal chemistry, including electron-poor phenols, aliphatic acids,

and sterically hindered dimers. Importantly no transesterification was observed in the synthesis of any molecules presented in this study.

As compound **1** is a moderately close to room temperature single component nematic material; for completeness we measured the dielectric anisotropy ($\Delta\epsilon$) of this material as a function of temperature, reaching an unsaturated value of ~ 14. The magnitude is consistent with strongly polar mesogens and confirms the substitution pattern here generates the expected dielectric properties

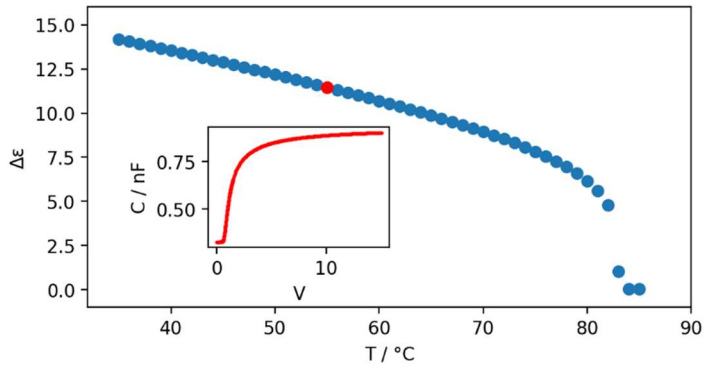


Figure 4. Dielectric anisotropy of compound **1** as a function of temperature. The inset shows the capacitance measured as a function of voltage at a temperature of 55 °C, shown with a red data point on the plot.

4 CONCLUSIONS

We have identified DMC as an effective and sustainable replacement for DCM in Steglich esterification, a transformation widely used in the synthesis of liquid-crystalline materials. Using a combination of isolated yields and composite sustainability metrics derived from the CHEM21 and GSK solvent-selection guides, DMC emerged as the top-performing solvent among more than twenty candidates.

DMC delivered excellent results across a diverse range of phenols, carboxylic acids, and more complex liquid-crystal building blocks, including sterically demanding dimers and useful synthetic intermediates. Electron-poor phenols behaved as expected, while lipophilic substrates showed slightly reduced yields due to solubility limitations; nevertheless, synthetically useful quantities of product were obtained in all cases. The method also tolerated representative mesogenic motifs without affecting their characteristic phase behaviour or dielectric properties.

DMC offers a practical, lower-toxicity alternative to DCM for the synthesis of ester-linked liquid-crystal materials. Its combination of good solvating ability, favourable environmental profile, and ease of removal makes it an attractive solvent for laboratories seeking to implement greener and more sustainable synthetic protocols.

Data Availability

The data associated with this paper are openly available from the University of Leeds Data Repository at DOI: https://doi.org/10.5518/1793

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Author Contributions

Chemical synthesis performed by WCO. Characterisation of liquid crystals performed by WCO, CJG, SRB. First draft was written by WCO and RJM, with contributions from all others.

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DCM Alternatives for use in Steglich Esterifications, for Green and Sustainable Liquid Crystal Syntheses - ESI

Contents

1. Methods

1.1 Chemical Synthesis

Chemicals were purchased from commercial suppliers (Fluorochem, Merck, ChemScene, Ambeed) and used as received. Solvents were purchased from Merck and used without further purification. Reactions were performed in standard laboratory glassware at ambient temperature and atmosphere and were monitored by TLC with an appropriate eluent and visualised with 254 nm light. Chromatographic purification was performed using a Combiflash NextGen 300+ System (Teledyne Isco) with a silica gel stationary phase and a hexane/ethyl acetate gradient as the mobile phase, with detection made in the 200-800 nm range. Chromatographed materials were filtered through 200 nm PTFE frits and then subjected to re-crystallisation from an appropriate solvent system. Yields refer to chromatographically and spectroscopically homogenous material.

1.2. Chemical Characterisation

Chemical materials were characterised by NMR spectroscopy using either a Bruker Avance III HDNMR spectrometer operating at 400 MHz, 100.5 MHz or 376.4 MHz (^{1}H, ^{13}C{^{1}H} and ^{19}F, respectively) or a Bruker AV4 NEO 11.75T spectrometer operating at 500 MHz, 125.5 MHz or 470.5 MHz (^{1}H, ^{13}C{^{1}H}). NMR were recorded in deuterated chloroform ($CDCl_3$) unless otherwise stated.

1.3. Phase characterisation

Phase transition temperatures and associated enthalpies of transition were determined by differential scanning calorimetry (DSC) using a TA instruments Q2000 heat flux calorimeter with a liquid nitrogen cooling system for temperature control. Samples were measured with 10 °C min^{-1} heating and cooling rates. The transition temperatures and enthalpy values reported are averages obtained for duplicate runs. Phase transition temperatures were measured on cooling cycles for consistency between monotropic and enantiotropic phase transitions, while crystal melts were obtained on heating. Phase identification by polarised optical microscopy (POM) was performed using a Leica DM 2700 P polarised optical microscope equipped with a Linkam TMS 92 heating stage. Samples were studied sandwiched between two untreated glass coverslips.

1.4. Dielectric Anisotropy Measurements

Dielectric anisotropy was measured in cells with a planar alignment layer, 5 μm LC devices (AWAT, Poland), which contained 15 Ω/ sq. ITO electrodes, SE130 planar alignment layer and were rubbed antiparallel. The quality of alignment was monitored with POM throughout. Temperatures were controlled with a THMS600 hot stage with Linkam 95-PE temperature controller. The Fréedericksz transitions were induced electrically with an out of plane electric field at 10 kHz as a function of voltage, across the nematic phase on cooling from 83 to 35 °C. An Agilent Precision LCR meter E4980A was used to measure capacitance.

1.5 Spontaneous Polarisation

Spontaneous polarisation (Ps) measurements were undertaken using the current reversal technique, using an Agilent 33220A signal generator and a RIGOL DHO4204 high-resolution oscilloscope, with temperature control via an Instec HCS402 hot stage.

2. Supplemental results

2.1 Liquid Crystal CharacterisationThe phase behaviour of each of the 29 materials described in the manuscript was determined by polarised optical microscopy (POM) and differential scanning calorimetry (DSC). Phase types were assigned based on characteristic POM textures, whereas transition temperatures and associated enthalpy were determined by DSC.

Nematic phases were assigned by the observation of 2 and 4-point schlieren brush singularities or marbled textures between untreated glass slides. The schlieren textures flashes under mechanical stress. The associated entropy changes are wholly consistent with this assignment. Due to the high nematic-isotropic transition temperatures (T_{N-I}), some materials decompose on repeated heating and cooling cycles to the isotropic (Iso) phase, as evidenced by the lack of reproducibility within the DSC thermograms.

The SmA phase was assigned by the observation of either a focal conic fan texture or the samples align homeotropically, and a uniformly dark texture is seen. A distinct first-order transition is observed at the SmA-N transition in the DSC thermograms with associated entropy changes consistent with the N-SmA transition.

The textures of the SmX phase are paramorphic with the preceding phase and hence differ depending on the phase sequence, however the transition is reversable on repeated heating and cooling cycles using DSC.

In the case of **12** the N* phase was characterised by the observation a typical oily streak texture. The optical flickering associated with director fluctuations in the N phase freezes upon entering the SmC* phase where a typical focal conic texture is observed.

For **20** the N_F phase was identified by its characteristic optical textures, The magnitude of the enthalpy associated with the phase transition, and by measurement of P_S *via* current reversal techniques, as seen in figure S1.

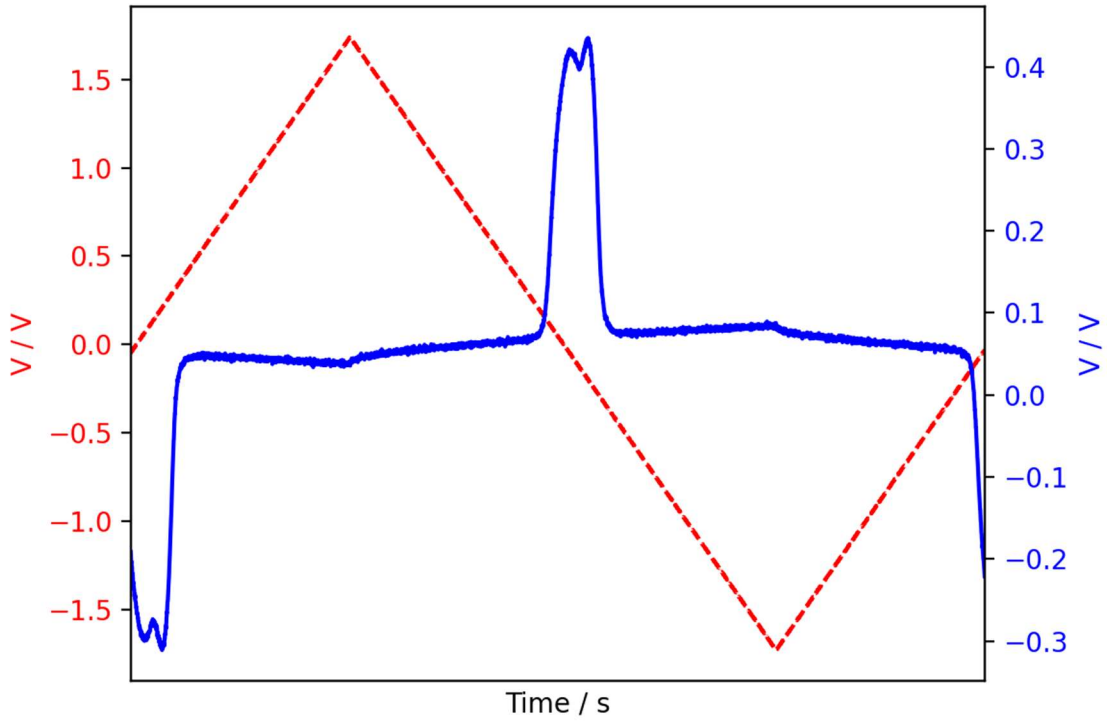


Figure S1. Ps measurement of **20** at 1 V, 20 Hz at 60 °C

2.2 Solvent Rankings

Table S1 showing the ranking of the organic solvents used. GSK Safety score and is an average of Flammability and explosion, and reactivity and stability scores. GSK Health score is used directly. GSK environmental score is the average of the waste, environmental impact and life cycle scores. CHEM21 scores are reported already reported directly as safety, health, and environmental metrics. Me-Piv not assessed by GSK at time of writing. CHEM21 score is generated for Me-Piv using autoignition of ^{t}BuOAc as it is an unreported metric for Me-Piv.

Average safety, health and environmental scores taken from CHEM21,[1] and GSK selection guides.[2] CHEM21 scores 1-10 with 1 being best. GSK from 10-1 with 10 being best. CHEM21 scores subtracted from 11 to rank them from 10-1 with 10 being best.

Average scores then multiplied by 10 to give them equal weighting to the yield scores. Yield and SHE score then summed together resulting in a final score.

Table S1. The SHE scores, yields and total score out of 400 for the solvents used in the initial screening reaction.

Solvent	Average Safety Score	Average Health Score	Average Environmental Score	Isolated Yield (%)	Sum of Scores	Rank
DMC	75	85.0	73.3	97	330.3	**S**
t-BuOAc	70	70.0	68.3	82	290.3	**A**
MEK	60	80.0	61.7	87	288.7	**A**
EtOAc	60	80.0	70.0	75	285.0	**B**
MeOAc	62.5	75.0	61.7	85	284.2	**B**
Acetone	62.5	80.0	61.7	76	280.2	**B**
DCM	87.5	40.0	46.7	91	265.2	**C**
Me-Piv	60	60.0	60.0	71	251.0	**C**
TBME	45	65.0	58.3	73	241.3	**D**
CPME	52.5	65.0	53.3	70	240.8	**D**
2Me-THF	47.5	50.0	61.7	81	240.2	**D**
THF	42.5	50.0	50.0	84	226.5	**E**

3 Organic Synthesis

3.1 Synthetic method for esterification

The relevant alcohol (1.0 equivalent), carboxylic acid (1.2 equivalents), EDC.HCl (1.5 equivalents) and DMAP (ca. 5 mol %) were added to a round bottomed flask or reaction vial. The relevant solvent (concentration ca. 0.3 M) was then added to the flask and left at room temperature with stirring for 24 hours (dimers 72 hours). The products were then isolated with flash chromatography using a Combiflash NextGen 300+ system (Teledyne Isco) using silica gel cartridges as the stationary phase and a hexane/ethyl acetate gradient as the mobile phase. Solid compounds were then recrystalised using an appropriate solvent, typically ethanol or acetonitrile.

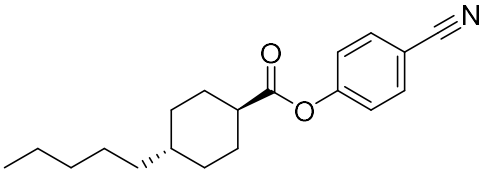
3.2 General Suzuki-Miyaura Protocol

A biphasic mixture of THF (~ 2 vol) and 2M aqueous K_2CO_3 (~ 1 vol) was degassed by sparging with argon for 20 minutes. Aryl bromide (1.0 mol eqv) and boronic acid/ester (1.2 mol eqv) were added in sequence. The reaction was stirred and heated under reflux and under an atmosphere of dry nitgrogen gas. Pd-Xphos-G3 (cat.) was added in one portion. After 16h, the reaction was cooled to ambient temperature, then acidified to pH 2 with 2M aqueous HCl. Ethyl acetate was added; the organic phase was separated and retained. The aqueous phase was washed three times with ethyl acetate, then discarded. The combined organic phases were washed with brine three times. The organic phase was dried over $MgSO_4$, which was subsequently removed by filtration. The volatiles were removed *in vacuo*, before

recrystallisation of the crude material from isopropanol. The recrystalised material was collected by filtration, washed with cold ethanol (-18 °C), and dried under suction to yield the title compounds.

3.3 Structural characterisation data for final compounds CZP-5-N and compounds 1-28

CZP-5-N | *4-cyanophenyl (1s,4r)-4-pentylcyclohexane-1-carboxylate*



Standard Steglich esterification protocol was used. See table S2 for quantities of each reactant, reagent and yields.

Table S2, values of solvent, 4-cyanophenol, trans 4-pentylcyclohexanecarboxylic acid, EDC.HCl, DMAP used, along with the isolated yield.

Solvent (12ml)	4-4-Cyanophenol (mg, mmol)	trans 4-pentylcyclohexanecarboxylic acid (mg, mmol)	EDC.HCl (mg, mmol)	DMAP	Isolated Yield (%, mg)
DCM	470, 3.946	944, 4.760	1134, 5.916	Ca. 5 mol %	91, 1070
DMC	457, 3.834	942, 4.750	1117, 5.823	Ca. 5 mol %	97, 1119
Acetone	483, 4.055	955, 4.816	1144, 5.968	Ca. 5 mol %	76, 926
MeOAc	447, 3.753	976, 4.922	1183, 6.171	Ca. 5 mol %	85, 956
EtOAc	465, 3.904	942, 4.750	1062, 5.603	Ca. 5 mol %	75, 878
MEK	465, 3.904	931, 4.695	1115, 5.816	Ca. 5 mol %	87, 1021
THF	458, 3.845	930, 4.690	1095, 5.712	Ca. 5 mol %	84, 968
2-MeTHF	455, 3.820	962, 4.851	1130, 5.895	Ca. 5 mol %	81, 924
TBME	463, 3.887	961, 4.850	1088, 5.676	Ca. 5 mol %	73, 848
CPME	472, 3.962	923, 4.654	1099, 5.733	Ca. 5 mol %	70, 0.835

^{t}BuOAc	452, 3.794	942, 4.750	1156, 6.030	Ca. 5 mol %	82, 935
Methyl Pivalate	472, 3.962	933, 4.705	1113, 5.806	Ca. 5 mol %	71, 838

Transition Temperatures (°C): Cr 45.7 N 77.0 Iso

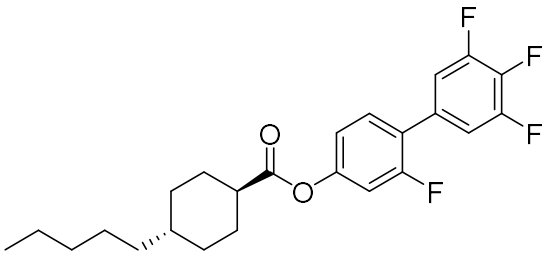
Transition Enthalpies (kJ/ mol): Cr 23.1 N 0.70 Iso

^{1}H NMR (501 MHz): 7.68 (2 H, dd, *J* = 6.6, 2.1 Hz), 7.20 (2 H, dd, *J* = 6.8, 2.1 Hz), 2.49 (1 H, tt, *J* = 12.3, 3.5 Hz), 2.17 – 2.08 (2 H, m), 1.88 (2 H, dd, *J* = 13.9, 3.2 Hz), 1.53 (2 H, qd, *J* = 13.3, 3.6 Hz), 1.37 – 1.15 (9 H, m), 0.98 (2 H, qd, *J* = 13.5, 3.5 Hz), 0.89 (3 H, t, *J* = 7.1 Hz).

^{13}C{^{1}H} NMR (126 MHz): 173.97, 154.37, 133.75, 122.87, 118.45, 109.66, 43.73, 37.21, 36.99, 32.29, 32.26, 29.04, 26.64, 22.81, 14.23.

HRMS: 301.1996 (M + H), 322.1782 (M + Na), expected 300.19

1 | *trans-[3-fluoro-4-(3,4,5-trifluorophenyl)phenyl] 4-pentylcyclohexane-1-carboxylate*



2,3',4',5'-tetrafluoro-[1,1'-biphenyl]-4-ol (230 mg, 0.950 mmol), (1r,4s)-4-pentylcyclohexane-1-carboxylic acid (236 mg, 1.190 mmol), EDC.HCl (291 mg, 1.518 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 86 %, 345 mg, 0.861 mmol

Transition Temperatures (°C): Cr 37.2 N 78.7 Iso

Transition Enthalpies (kJ/ mol): Cr 21.1 N 0.4 Iso

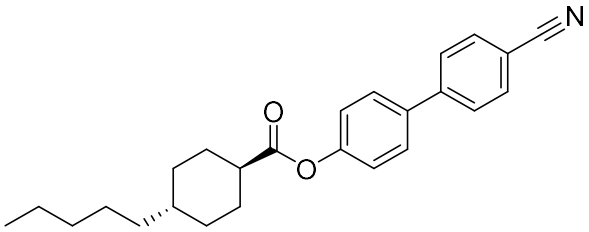
^{1}H NMR (400 MHz): 7.36 (1 H, t, *J* = 8.7 Hz), 7.15 (2 H, td, *J* = 7.5, 1.1 Hz), 6.98 (1 H, t, *J* = 2.6 Hz), 6.97 – 6.94 (1 H, m), 2.49 (1 H, tt, *J* = 12.2, 3.6 Hz), 2.14 (2 H, dd, *J* = 13.7, 3.3 Hz), 1.89 (2 H, dd, *J* = 13.7, 3.2 Hz), 1.56 (2 H, qd, *J* = 13.0, 3.5 Hz), 1.37 – 1.17 (9 H, m), 0.99 (2 H, qd, *J* = 13.3, 3.4 Hz), 0.90 (3 H, t, *J* = 7.2 Hz).

^{13}C{^{1}H} NMR (101 MHz): 174.34, 159.47 (d, *J* = 250.8 Hz), 151.88 (d, *J* = 11.0 Hz), 150.90 (ddd, *J* = 249.9, 10.1, 4.7 Hz), 139.11 (dd, *J* = 252.3, 15.1 Hz), 130.58 (d, *J* = 4.0 Hz), 123.71 (d, *J* = 14.0 Hz), 118.24 (d, *J* = 3.6 Hz), 113.29 (dd, *J* = 19.1,

3.2 Hz), 110.67 (t, *J* = 25.6 Hz), 43.74, 37.25, 37.03, 32.31 (d, *J* = 5.9 Hz), 29.10, 26.66, 22.83, 14.24.

^{19}F NMR (376 MHz): -114.88 (1 F, t, *J* = 9.7 Hz), -134.30 (1 F, dd, *J* = 20.5, 8.7 Hz), -161.40 (1 F, tt, *J* = 20.6, 6.7 Hz).

2 | *[4-(4-cyanophenyl)phenyl] 4-pentylcyclohexane-1-carboxylate*



4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile (191 mg, 0.978 mmol) (1r,4s)-4-pentylcyclohexane-1-carboxylic acid (236 mg, 1.190 mmol), EDC.HCl (301 mg, 1.570 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 78 %, 287 mg, 0.765 mmol

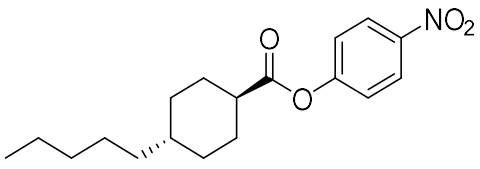
Transition Temperatures (°C): Cr 83.2 N 239.5 Iso

Transition Enthalpies (kJ/ mol): Cr 21.2 N 0.7 Iso

^{1}H NMR (400 MHz): 7.72 (2 H, d, *J* = 8.5 Hz), 7.65 (2 H, d, *J* = 8.4 Hz), 7.58 (2 H, dd, *J* = 6.4, 2.0 Hz), 7.18 (2 H, dd, *J* = 6.6, 2.0 Hz), 2.50 (1 H, tt, *J* = 12.2, 3.6 Hz), 2.15 (2 H, dd, *J* = 13.8, 3.6 Hz), 1.89 (2 H, dd, *J* = 13.6, 3.4 Hz), 1.57 (2 H, qd, *J* = 12.8, 3.5 Hz), 1.40 – 1.15 (9 H, m), 0.99 (2 H, qd, *J* = 13.5, 3.4 Hz), 0.89 (3 H, t, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (101 MHz): 174.78, 151.52, 144.99, 136.80, 132.78, 128.42, 127.82, 122.46, 119.01, 111.14, 43.81, 37.27, 37.06, 32.39, 32.29, 29.16, 26.66, 22.82, 14.24.

3 | *(4-nitrophenyl) 4-pentylcyclohexane-1-carboxylate*



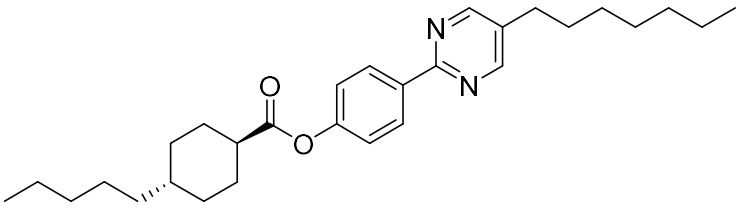
Nitrophenol (135 mg, 0.978 mmol), (1r,4s)-4-pentylcyclohexane-1-carboxylic acid (230 mg, 1.160 mmol), EDC.HCl (283 mg, 1.476 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 51 %, 159 mg, 0.498 mmol

Transition Temperatures (°C): Cr (35.12 N) 52.2 Iso

Transition Enthalpies (kJ/ mol): Cr (28.5 N) 0.2 Iso

^{1}H NMR (501 MHz):	8.26 (2 H, dd, *J* = 7.1, 2.1 Hz), 7.25 (2 H, dd, *J* = 7.3, 1.9 Hz),* 2.51 (1 H, tt, *J* = 12.2, 3.6 Hz), 2.14 (2 H, dd, *J* = 14.2, 3.7 Hz), 1.89 (2 H, dd, *J* = 13.8, 3.4 Hz), 1.55 (2 H, qd, *J* = 13.0, 3.5 Hz), 1.37 – 1.17 (9 H, m), 0.99 (2 H, qd, *J* = 13.3, 3.5 Hz), 0.89 (3 H, t, *J* = 7.1 Hz). *Solvent Overlap
^{13}C{^{1}H} NMR (126 MHz):	174.14, 156.14, 145.61, 125.57, 122.82, 44.02, 37.47, 37.26, 32.55, 32.53, 29.31, 26.91, 23.08, 14.50.
HRMS:	290.2115 (M + H)*, 321.18 (M + 2H), expected 290.21, 321.19 *Nitro group reduced to amine group in flight

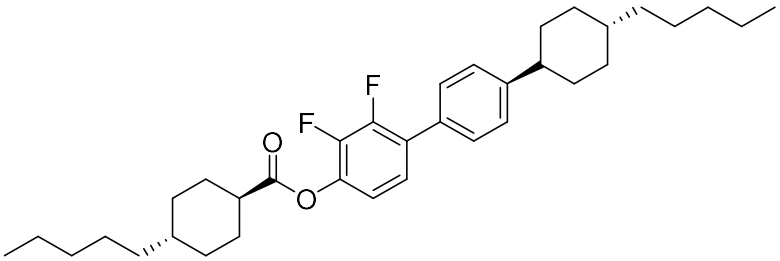
4 | *4-(5-heptylpyrimidin-2-yl)phenyl (1r,4s)-4-pentylcyclohexane-1-carboxylate*



4-(5-heptylpyrimidin-2-yl)phenol (276 mg, 1.021 mmol), (1r,4s)-4-pentylcyclohexane-1-carboxylic acid (243 mg, 1.225 mmol), EDC.HCl (273 mg, 1.424 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 79 %, 363 mg, 0.805 mmol

Transition Temperatures (°C):	Cr 93.1 SmX 103.7 N 177.6 Iso
Transition Enthalpies (kJ/ mol):	Cr 7.2 SmX 22.0 N 1.7 Iso
^{1}H NMR (400 MHz):	8.60 (2 H, s), 8.43 (2 H, dd, *J* = 6.9, 2.0 Hz), 7.18 (2 H, dd, *J* = 6.9, 2.0 Hz), 2.62 (2 H, d, *J* = 7.8 Hz), 2.49 (1 H, tt, *J* = 12.2, 3.6 Hz), 2.15 (2 H, dd, *J* = 13.9, 3.5 Hz), 1.88 (2 H, dd, *J* = 13.2, 2.7 Hz), 1.71 – 1.49 (4 H, m), 1.39 – 1.16 (17 H, m), 0.99 (2 H, qd, *J* = 13.1, 3.4 Hz), 0.92 – 0.83 (6 H, m).
^{13}C{^{1}H} NMR (101 MHz):	174.63, 162.04, 157.18, 152.92, 135.26, 133.10, 129.23, 121.78, 43.87, 37.30, 37.08, 32.43, 32.31, 31.87, 30.92, 30.33, 29.16, 26.68, 22.83, 22.76, 14.25, 14.21.
HRMS:	451.3317 (M + H), expected 451.33

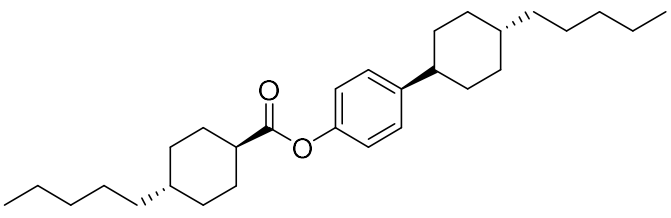
5 | *2,3-difluoro-4'-((1s,4r)-4-pentylcyclohexyl)-[1,1'-biphenyl]-4-yl (1s,4r)-4-entylcyclohexane-1-carboxylate*



2,3-difluoro-4'-((1r,4s)-4-pentylcyclohexyl)-[1,1'-biphenyl]-4-ol (349 mg, 0.974 mmol), (1r,4s)-4-pentylcyclohexane-1-carboxylic acid (231 mg, 1.165 mmol), EDC.HCl (273 mg, 1.424 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 60 %, 315 mg, 0.585 mmol

Transition Temperatures (°C):	Cr 59.8 SmX 103.1 N 279.5 Iso
Transition Enthalpies (kJ/ mol):	Cr 11.6 SmX 0.2 N 1.6 Iso
^{1}H NMR (501 MHz):	7.43 (2 H, d, *J* = 6.5 Hz), 7.29 (2 H, d, *J* = 8.0 Hz), 7.16 (1 H, td, *J* = 8.5, 2.0 Hz), 6.94 (1 H, t, *J* = 7.7 Hz), 2.61 – 2.46 (2 H, m), 2.17 (2 H, d, *J* = 10.3 Hz), 1.96 – 1.85 (6 H, m), 1.60 (2 H, qd, *J* = 12.9, 3.1 Hz), 1.49 (2 H, qd, *J* = 12.5, 2.5 Hz), 1.37 – 1.18 (18 H, m), 1.08 (2 H, d, *J* = 10.7 Hz), 0.99 (2 H, t, *J* = 13.1 Hz), 0.93 – 0.86 (6 H, m).
^{13}C{^{1}H} NMR (126 MHz):	173.68, 148.60 (dd, *J* = 250.80 Hz), 148.23, 143.76 (dd, *J* = 250.74, 15.42 Hz), 138.54 (dd, *J* = 10.69, 1.60 Hz Hz), 131.93, 128.92 (d *J* = 2.88 Hz), 128.72 (d, *J* = 10.64 Hz), 127.28, 124.02 (t, *J* = 3.55 Hz), 118.44 (d, *J* = 4.03 Hz), 44.53, 43.49, 37.53, 37.45, 37.26, 37.00, 34.41, 33.72, 32.37, 32.35, 32.29, 29.14, 26.81, 26.66, 22.88, 22.83, 14.28, 14.25
^{19}F NMR (376 MHz):	-140.56 (1 F, dd, J = 20.2, 5.9 Hz), -151.02 (1 F, dd, J = 20.1, 5.2 Hz).

6 | *4-((1s,4R)-4-pentylcyclohexyl)phenyl (1s,4R)-4-pentylcyclohexane-1-carboxylate*



4-((1r,4s)-4-pentylcyclohexyl)phenol (298 mg, 1.209 mmol), (1r,4s)-4-pentylcyclohexane-1-carboxylic acid (227 mg, 1.145 mmol), EDC.HCl (276 mg, 1.440 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 59 %, 306 mg, 0.717 mmol

Transition Temperatures (°C): Cr 36.6 SmX 154.1 N 183.7 Iso

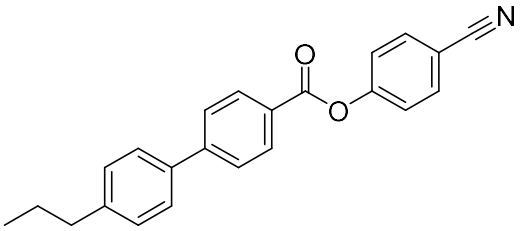
Transition Enthalpies (kJ/ mol): Cr 11.0 SmX 6.5 N 1.0 Iso

^{1}H NMR (501 MHz): 7.19 (2 H, dd, *J* = 13.1, 4.4 Hz), 6.96 (2 H, dd, *J* = 6.6, 2.1 Hz), 2.45 (2 H, tt, *J* = 12.2, 3.6 Hz), 2.12 (2 H, dd, *J* = 13.9, 3.7 Hz), 1.91 – 1.81 (6 H, m), 1.54 (2 H, qd, *J* = 13.5, 3.5 Hz), 1.41 (2 H, qd, *J* = 12.9, 3.1 Hz), 1.35 – 1.14 (18 H, m), 1.03 (2 H, qd, *J* = 12.8, 3.9), 0.96 (2 H, qd, *J* = 11.4, 3.2 Hz), 0.92 – 0.86 (6 H, m).

^{13}C{^{1}H} NMR (126 MHz): 175.09, 148.92, 145.33, 127.79, 121.27, 44.21, 43.80, 37.51, 37.42, 37.30, 37.07, 34.55, 33.72, 32.44, 32.35, 32.30, 29.18, 26.79, 26.67, 22.86, 22.83, 14.27, 14.25.

HRMS: 449.3386 (M + Na), expected 449.34

7 | *4-cyanophenyl 4'-propyl-[1,1'-biphenyl]-4-carboxylate*



4-Cyanophenol (0.111 g, 0.932 mmol), 4'-propyl-[1,1'-biphenyl]-4-carboxylic acid (295 mg, 1.228 mmol), EDC.HCl (259 mg, 1.351 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 64 %, 205 mg, 0.600 mmol

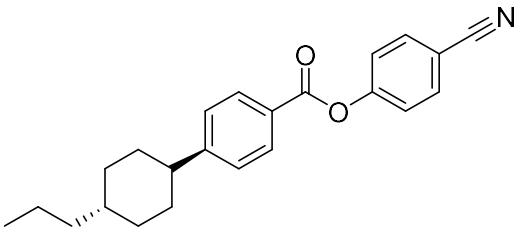
Transition Temperatures (°C): Cr 128.8 N 242.8 Iso

Transition Enthalpies (kJ/ mol): Cr 24.7 N 1.1 Iso

^{1}H NMR (501 MHz): 8.24 (2 H, d, *J* = 8.5 Hz), 7.78 – 7.72 (4 H, m), 7.59 (2 H, d, *J* = 8.2 Hz), 7.39 (2 H, d, *J* = 8.7 Hz), 7.31 (2 H, d, *J* = 8.0 Hz), 2.66 (2 H, t, *J* = 7.7 Hz), 1.70 (2 H, h, *J* = 7.3 Hz), 0.99 (3 H, t, *J* = 7.3 Hz).

^{13}C{^{1}H} NMR (126 MHz): 164.43, 154.48, 147.06, 143.55, 137.06, 133.89, 130.97, 129.34, 127.30, 127.29, 127.08, 123.11, 118.46, 109.93, 37.87, 24.66, 13.99.

8 | *4-cyanophenyl 4-((1s,4r)-4-propylcyclohexyl)benzoate*



4-Cyanophenol (110 mg, 0.923 mmol), 4-((1s,4r)-4-pentylcyclohexyl)benzoic acid (335 mg, 1.221 mmol), EDC.HCl (294 mg, 1.534 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 88 %, 282, 0.811 mmol

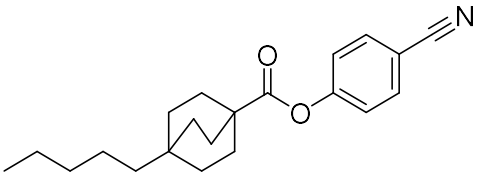
Transition Temperatures (°C): Cr 116.5 N 229.7 Iso

Transition Enthalpies (kJ/ mol): Cr 7.2 N 0.8 Iso

^{1}H NMR (400 MHz): 8.10 (2 H, dd, *J* = 6.8, 1.9 Hz), 7.74 (2 H, dd, *J* = 6.8, 2.2 Hz), 7.36 (2 H, d, *J* = 3.2 Hz), 7.35 (2 H, d, *J* = 4.0 Hz), 2.58 (1 H, tt, *J* = 12.2, 3.3 Hz), 1.91 (4 H, t, *J* = 10.8), 1.50 (2 H, qd, *J* = 12.8, 3.1 Hz), 1.40 – 1.29 (3 H, m), 1.27 – 1.18 (2 H, m), 1.08 (2 H, qd, *J* = 13.7, 4.1 Hz), 0.91 (3 H, t, *J* = 7.2 Hz).

^{13}C{^{1}H} NMR (101 MHz): 164.20, 154.76, 154.22, 133.53, 130.29, 127.14, 125.98, 122.80, 118.16, 109.52, 44.72, 39.44, 36.77, 33.84, 33.18, 19.83, 14.21.

9 | *4-cyanophenyl 4-pentylbicyclo[2.2.2]octane-1-carboxylate*



4-Cyanophenol (114 mg, 0.957 mmol), 4-pentylbicyclo[2.2.2]octane-1-carboxylic acid (268 mg, 1.195 mmol), EDC.HCl (283 mg, 1.523 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 59 %, 185 mg, 0.568 mmol

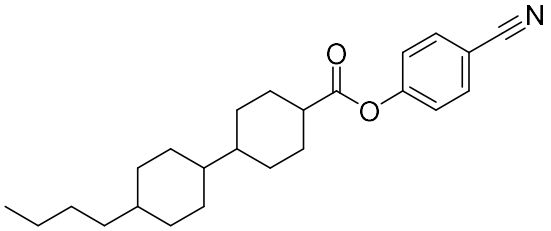
Transition Temperatures (°C): Cr 86.0 N 105.7 Iso

Transition Enthalpies (kJ/ mol): Cr 21.3 N 0.7 Iso

^{1}H NMR (400 MHz): 7.67 (2 H, dd, *J* = 6.7, 1.9 Hz), 7.17 (2 H, dd, *J* = 6.8, 2.2 Hz), 1.95 – 1.87 (6 H, m), 1.50 – 1.41 (6 H, m), 1.36 – 1.28 (2 H, m), 1.27 – 1.17 (4 H, m), 1.15 – 1.08 (2 H, m), 0.89 (3 H, t, *J* = 7.2 Hz).

$^{13}C\{^{1}H\}$ NMR (101 MHz):	176.08, 154.62, 133.72, 122.89, 118.48, 109.57, 41.37, 39.70, 32.91, 30.62, 30.39, 28.70, 23.49, 22.82, 14.22.
HRMS:	326.2116 (M + H), expected 326.21

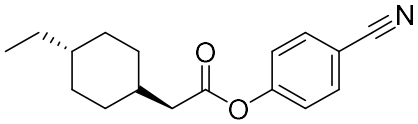
10 | *4-cyanophenyl (1s,1'r,4S,4'S)-4'-butyl-[1,1'-bi(cyclohexane)]-4-carboxylate*



4-Cyanophenol (111 mg, 0.931 mmol), (1r,1's,4R,4'R)-4'-butyl-[1,1'-bi(cyclohexane)]-4-carboxylic acid (274, 1.028 mmol), EDC.HCl (309 mg, 1.612 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 184 mg, 0.5006 mmol, 53.77 %

Transition Temperatures (°C):	Cr 79.6 N 239.4 Iso
Transition Enthalpies (kJ/ mol):	Cr 23.5 N 1.4 Iso
^{1}H NMR (501 MHz):	7.67 (2 H, dd, *J* = 6.8, 2.0 Hz), 7.21 (2 H, dd, *J* = 6.6, 2.1 Hz), 2.47 (1 H, tt, *J* = 12.2, 3.5 Hz), 2.15 (2 H, d, *J* = 13.6 Hz), 1.86 (2 H, d, *J* = 11.5 Hz), 1.77 (2 H, d, *J* = 13.7), 1.71 (2 H, d, *J* = 12.8), 1.52 (2 H, q, *J* = 12.5 Hz), 1.33 – 1.21 (4 H, m), 1.18 – 1.02 (7 H, m), 0.98 (2 H, qd, *J* = 11.7, 2.9 Hz), 0.93 – 0.79 (5 H, m).
$^{13}C\{^{1}H\}$ NMR (126 MHz):	173.98, 154.38, 133.76, 122.87, 118.46, 109.66, 43.79, 43.32, 42.59, 38.00, 37.29, 33.68, 30.14, 29.39, 29.32, 29.18, 23.17, 14.30.
HRMS:	368.2585 (M + H), 390.2403 (M + Na), expected 368.25, 390.24

11 | *4-cyanobenzyl (1r,4r)-4-ethylcyclohexane-1-carboxylate*



4-Cyanophenol (113 mg, 0.949 mmol), 2-((1r,4r)-4-ethylcyclohexyl)acetic acid (200 mg, 1.175 mmol), EDC.HCl (280 mg, 1.461 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 83 %, 213 mg, 0.785 mmol

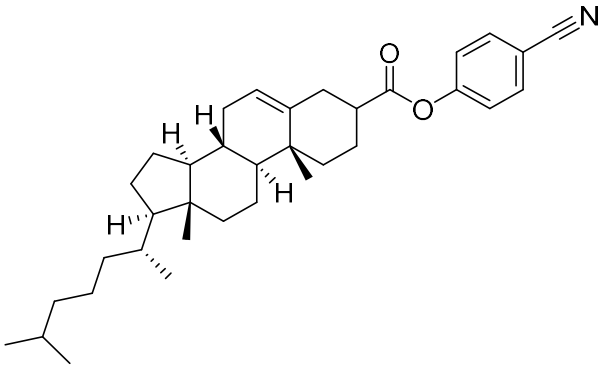
Transition Temperatures (°C): Cr 25.9 Iso

Transition Enthalpies (kJ/ mol): Cr 22.1 Iso

^{1}H NMR (400 MHz): 7.67 (2 H, dd, *J* = 7.9, 2.1 Hz), 7.21 (2 H, dd, *J* = 6.8, 2.1 Hz), 2.45 (2 H, d, *J* = 6.6 Hz), 1.92 – 1.74 (5 H, m), 1.22 (2 H, p, *J* = 7.3 Hz), 1.14 – 1.01 (3 H, m), 0.96 (2 H, t, *J* = 11.0 Hz), 0.87 (3 H, t, *J* = 7.3 Hz).

^{13}C{^{1}H} NMR (101 MHz): 170.82, 154.16, 133.76, 122.91, 118.41, 109.73, 42.11, 39.14, 35.30, 33.05, 32.53, 29.94, 11.60.

12 | *4'-cyanophenyl cholesteroate*



4-Cyanophenol (118 mg, 0.957 mmol), cholesterolic acid (495 mg, 1.193 mmol),EDC.HCl (308 mg, 1.607 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 56 %, 294 mg, 0.570 mmol

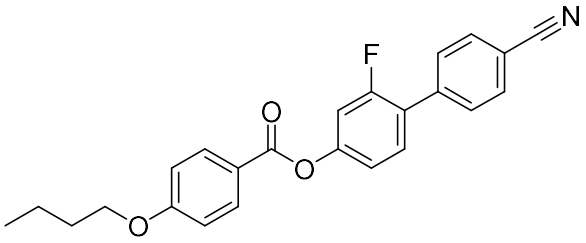
Transition Temperatures (°C): Cr 155.4 SmC* 281.6 N* – compound degrades before becoming isotropic therefore all transitions given on heating

Transition Enthalpies (kJ/ mol): Cr 24.9 SmC* 1.8 N*

^{1}H NMR (400 MHz): 7.68 (2 H, dd, *J* = 6.6, 1.9), 7.22 (2 H, dd, *J* = 6.9, 2.2), 5.42 (1 H, d, *J* = 5.1), 2.54 (2 H, d, *J* = 8.5), 2.38 (1 H, d, *J* = 8.6), 2.07 – 1.93 (5 H, m), 1.89 – 1.75 (2 H, m), 1.64 – 0.94 (24 H, m), 0.92 (3 H, d, *J* = 6.6), 0.87 (6 H, dd, *J* = 6.6, 1.7), 0.69 (3 H, s).

^{13}C{^{1}H} NMR (101 MHz): 173.50, 154.33, 140.40, 133.79, 122.88, 121.96, 118.44, 109.75, 56.92, 56.32, 50.39, 44.84, 42.46, 39.90, 39.67, 38.71, 37.09, 36.34, 35.94, 34.88, 32.05, 31.93, 28.38, 28.17, 25.32, 24.42, 23.99, 22.97, 22.72, 21.04, 19.49, 18.88, 12.02.

13 | *4'-cyano-2-fluoro-[1,1'-biphenyl]-4-yl 4-butoxybenzoate*



2'-fluoro-4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile (144 mg, 0.675 mmol), 4-butoxybenzoic acid (238 mg, 1.225 mmol), EDC.HCl (377 mg, 1.967 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 52 %, 137 mg, 0.3518 mmol

Transition Temperatures (°C): Cr 119.0 N 236.3 Iso

Transition Enthalpies (kJ/ mol): Cr 25.3 N 1.0 Iso

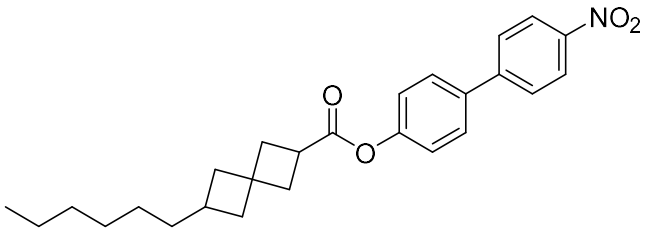
^{1}H NMR (501 MHz): 8.14 (2 H, dd, *J* = 9.0, 1.9 Hz), 7.75 (2 H, d, *J* = 8.4 Hz), 7.66 (2 H, dd, *J* = 8.1, 1.2 Hz), 7.47 (1 H, t, *J* = 8.7 Hz), 7.18 – 7.10 (2 H, m), 6.98 (2 H, dd, *J* = 9.0, 1.9 Hz), 4.07 (2 H, t, *J* = 6.5 Hz), 1.82 (2 H, p, *J* = 7.2 Hz), 1.53 (2 H, h, *J* = 7.2 Hz), 1.00 (3 H, t, *J* = 7.4 Hz).

^{13}C{^{1}H} NMR (126 MHz): 164.58, 164.03, 159.70 (d, *J* = 251.1 Hz), 152.28 (d, *J* = 11.1 Hz), 139.99 (d, *J* = 1.4 Hz), 132.51 (d, *J* = 15.3 Hz), 130.90 (d, *J* = 4.1 Hz), 129.77 (d, *J* = 3.2 Hz), 124.80 (d, *J* = 13.1 Hz), 120.89, 118.88, 118.56 (d, *J* = 3.6 Hz), 114.57, 111.62, 111.05, 110.85, 68.22, 31.24, 19.33, 13.96.

^{19}F NMR (376 MHz): -114.61 (1 F, t, *J* = 9.9 Hz).

HRMS: 390.1501 (M + H), expected 390.15

14 | *4'-nitro-[1,1'-biphenyl]-4-yl 6-hexylspiro[3.3]heptane-2-carboxylate*



4'-nitro-[1,1'-biphenyl]-4-ol (122 mg, 0.567 mmol), 6-hexylspiro[3.3]heptane-2-carboxylic acid (70 mg, 0.314 mmol), EDC.HCl (120 mg, 0.626 mmol, DMAP (cat. amount). Yield 51 %, 67 mg, 0.159 mmol

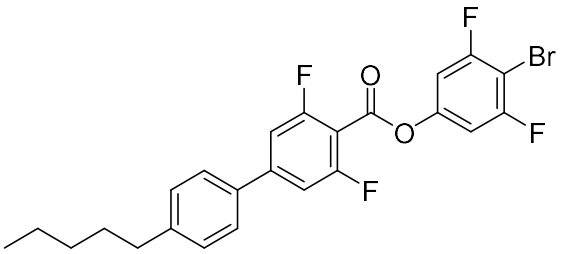
Transition Temperatures (°C): Cr 73.4 N 116.4 Iso

Transition Enthalpies (kJ/ mol): Cr 17.6 N 1.5 Iso

^{1}H NMR (501 MHz): 8.29 (2 H, d, *J* = 8.8 Hz), 7.71 (2 H, d, *J* = 8.8 Hz), 7.62 (2 H, d, *J* = 8.6 Hz), 7.20 (2 H, d, *J* = 8.6 Hz), 3.26 (1 H, p, *J* = 8.5 Hz), 2.48 – 2.39 (2 H, m), 2.36 (1 H, dd, *J* = 11.5, 8.6 Hz), 2.29 – 2.18 (2 H, m), 2.15 – 2.03 (2 H, m), 1.67 (1 H, dd, *J* = 10.9, 7.2 Hz), 1.63 – 1.57 (1 H, m), 1.37 – 1.15 (10 H, m), 0.88 (3 H, t, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (126 MHz): 174.15, 151.71, 147.22, 146.89, 136.35, 128.58, 127.86, 124.28, 122.47, 41.36, 40.82, 38.80, 38.06, 37.18, 36.85, 33.56, 32.04, 30.07, 29.42, 27.42, 22.79, 14.25.

15 | *4-bromo-3,5-difluorophenyl 3,5-difluoro-4'-pentyl-[1,1'-biphenyl]-4-carboxylate*



4-bromo-3,5-difluorophenol (312 mg, 1.025 mmol), 2,6-difluoro-4-(4-pentylphenyl)benzoic acid (227 mg, 1.086 mmol), EDC.HCl (299 mg, 1.560 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 240 mg, 0.4845 mmol, 47.26 %

Transition Temperatures (°C): Cr 71.5 SmC/ N 87.6 Iso – Nematic and smectic C phase present simultaneously

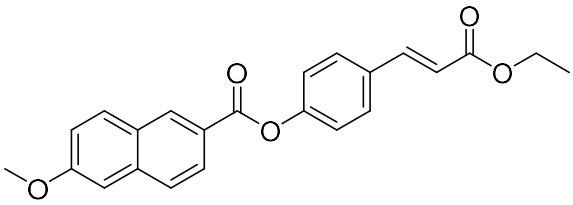
Transition Enthalpies (kJ/ mol): Cr 17.9 SmC/ N 3.1 Iso

^{1}H NMR (501 MHz, DMSO): 7.79 (2 H, d, *J* = 8.3 Hz), 7.72 (2 H, d, *J* = 10.6 Hz), 7.48 (2 H, d, *J* = 7.3 Hz), 7.34 (2 H, d, *J* = 8.5 Hz), 2.63 (2 H, t, *J* = 7.6 Hz), 1.60 (2 H, p, *J* = 7.6 Hz), 1.36 – 1.23 (4 H, m), 0.87 (3 H, t, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (126 MHz): 161.76 (dd *J* = 260.1, 7.2 Hz), 160.05 (dd, *J* = 248.6 Hz), 159.0, 149.32 (dt, *J* = 235.5, 13.0 Hz), 145.07, 134.83 (t, *J* = 2.3 Hz), 129.50, 127.03, 110.63 (dd, *J* = 22.5, 4.0 Hz), 107.20 – 106.47 (m), 95.76 (t, *J* = 24.6 Hz), 35.78, 31.62, 31.17, 22.68, 14.17.

^{19}F NMR (376 MHz): -103.20 (2 F, d, *J* = 7.9 Hz), -107.96 (2 F, d, *J* = 10.7 Hz).

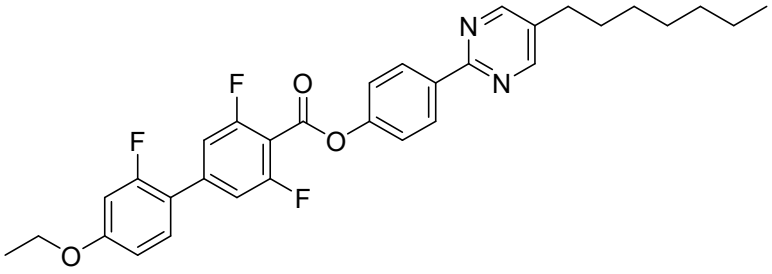
16 | *(E)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl 6-methoxy-2-naphthoate*



Ethyl (E)-3-(4-hydroxyphenyl)acrylate (198 mg, 1.030 mmol), 6-methoxy-2-naphthoic acid (268 mg, 1.325 mmol), EDC.HCl (407 mg, 2.123 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield 72 %, 280 mg, 0.744 mmol

Transition Temperatures (°C):	Cr 139.6 N 185.4 Iso
Transition Enthalpies (kJ/ mol):	Cr 33.2 N 0.4 Iso
^{1}H NMR (400 MHz):	8.70 (1 H, s), 8.15 (1 H, dd, *J* = 8.6, 1.8 Hz), 7.89 (1 H, d, *J* = 9.0 Hz), 7.83 (1 H, d, *J* = 8.7 Hz), 7.71 (1 H, d, *J* = 16.0 Hz), 7.61 (2 H, d, *J* = 8.6 Hz), 7.30 (2 H, d, *J* = 8.6 Hz), 7.24 (1 H, dd, *J* = 8.9, 2.5 Hz), 7.20 (1 H, d, *J* = 2.5 Hz), 6.43 (1 H, d, *J* = 16.0 Hz), 4.28 (2 H, q, *J* = 7.1 Hz), 3.97 (3 H, s), 1.35 (3 H, t, *J* = 7.1 Hz).
^{13}C{^{1}H} NMR (101 MHz):	167.07, 165.32, 160.12, 152.69, 143.71, 137.80, 132.33, 131.99, 131.22, 129.40, 128.04, 127.28, 126.29, 124.27, 122.52, 120.09, 118.56, 105.91, 60.71, 55.60, 14.48.
HRMS:	377.1384 (M + H), 399.1203 (M + Na), expected 377.13, 399.12

17 | *4-(5-heptylpyrimidin-2-yl)phenyl 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylate*

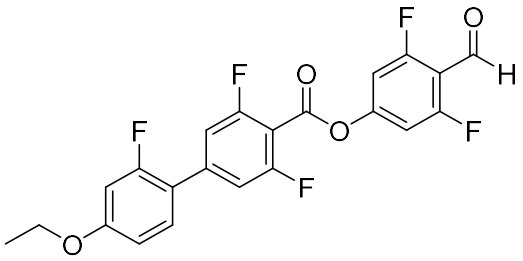


4-(5-heptylpyrimidin-2-yl)phenol (137 mg, 0.507 mmol), 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylic acid (277 mg, 0.935 mmol), EDC.HCl (289 mg, 1.508 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 180 mg, 0.3281 mmol, 64.75 %

Transition Temperatures (°C):	Cr 95.5 N 265.9 Iso
Transition Enthalpies (kJ/ mol):	Cr 30.5 N 2.9 Iso

^{1}H NMR (501 MHz):	8.63 (2 H, s), 8.51 (2 H, dd, *J* = 6.9, 1.7 Hz), 7.44 – 7.33 (3 H, m), 7.22 (2 H, d, *J* = 10.2 Hz), 6.79 (1 H, dd, *J* = 8.6, 2.5 Hz), 6.73 (1 H, dd, *J* = 12.8, 2.5 Hz), 4.08 (2 H, q, *J* = 7.0 Hz), 2.63 (2 H, t, *J* = 7.7 Hz), 1.66 (2 H, p, *J* = 7.5 Hz), 1.45 (3 H, t, *J* = 7.0 Hz), 1.41 – 1.23 (8 H, m), 0.89 (3 H, t, *J* = 6.9 Hz).
^{13}C{^{1}H} NMR (126 MHz):	161.89, 161.29 (d, *J* = 11.2 Hz), 159.78 (t, *J* = 2.0 Hz), 157.20, 152.36, 142.17 (t, *J* = 10.6 Hz), 135.88, 133.24, 130.70 (d, *J* = 4.5 Hz), 129.39, 121.81, 117.88 (d, *J* = 12.4 Hz), 112.38 (dd, *J* = 26.3, 4.1 Hz), 111.51 (d, *J* = 3.0 Hz), 108.36 (t, *J* = 17.0 Hz), 103.03, 102.82, 64.26, 31.87, 30.92, 30.34, 29.16, 22.76, 14.76, 14.21.
^{19}F NMR (376 MHz):	-109.14 (2 F, d, *J* = 10.3 Hz), -114.24 (1 F, t, *J* = 11.6 Hz).
HRMS:	549.2362 (M + H), expected 549.23

18 | *3,5-difluoro-4-formylphenyl 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylate*



2,6-difluoro-4-hydroxybenzaldehyde (110 mg, 0.696 mmol), 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylic acid (273, 0.922 mmol), EDC.HCl (303 mg, 1.581 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 134 mg, 0.3071 mmol, 44.14 %

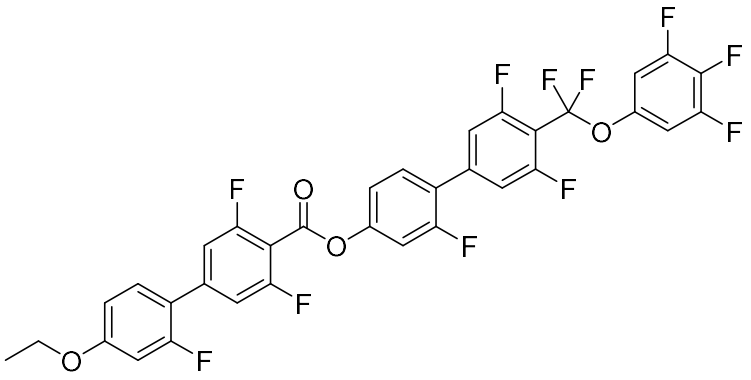
Transition Temperatures (°C):	Cr 125.2 (N 137.0) Iso
Transition Enthalpies (kJ/ mol):	Cr 30.2 N 0.2 Iso
^{1}H NMR (501 MHz):	10.32 (1 H, s), 7.37 (1 H, t, *J* = 8.8 Hz), 7.24 (3 H, d, *J* = 10.7 Hz)*, 7.04 (2 H, d, *J* = 9.1 Hz), 6.81 (1 H, dd, *J* = 8.6, 2.5 Hz), 6.73 (1 H, dd, *J* = 13.0, 2.5 Hz), 4.08 (2 H, q, *J* = 7.0 Hz), 1.46 (3 H, t, *J* = 7.0 Hz). *Solvent peak overlap
^{13}C{^{1}H} NMR (126 MHz):	183.49 (t, *J* = 4.1 Hz), 163.61 (dd, *J* = 263.6, 8.0 Hz), 161.50 (d, *J* = 5.9 Hz), 161.32 (dd, *J* = 259.1, 6.06 Hz), 160.37 (d, *J* = 233.21 Hz), 158.19 (t, *J* = 2.3 Hz), 155.57 (t, *J* = 14.9 Hz), 143.25 (t, *J* = 11.3 Hz), 130.54 (d, *J* = 4.5 Hz), 117.40 (d, *J* = 12.3 Hz), 112.66 – 112.14 (m)*,

111.51 (d, *J* = 2.9 Hz), 107.13 – 106.77 (m), 106.61 (t, *J* = 16.0 Hz), 102.85 (d, *J* = 26.1 Hz), 64.19, 14.62.

*Overlapping signals

^{19}F NMR (376 MHz): -108.15 (2 F, d, *J* = 10.8 Hz), -112.29 (2 F, d, *J* = 10.1 Hz), -114.07 (1 F, t, *J* = 10.9 Hz).

19 | *4'-(difluoro(3,4,5-trifluorophenoxy)methyl)-2,3',5'-trifluoro-[1,1'-biphenyl]-4-yl 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylate*



4'-(difluoro(3,4,5-trifluorophenoxy)methyl)-2,3',5'-trifluoro-[1,1'-biphenyl]-4-ol (189 mg, 0.450 mmol), 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylic acid (205 mg, 0.692 mmol), EDC.HCl (274 mg, 1.429 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield 64 %, 201 mg, 0.288 mmol.

Transition Temperatures (°C): Cr 152.7 (SmX 121.7) N 288.2 Iso

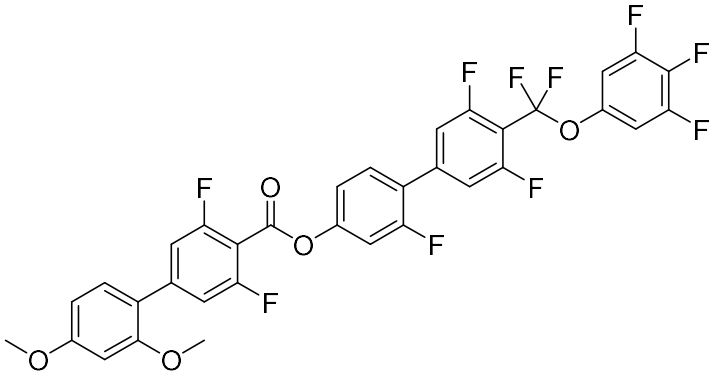
Transition Enthalpies (kJ/ mol): Cr 60.7 (SmX 6.7) N 2.1 Iso

^{1}H NMR (501 MHz): 7.51 (1 H, t, *J* = 8.5 Hz), 7.38 (1 H, t, *J* = 8.8 Hz), 7.27 – 7.19 (6 H, m), 7.05 – 6.95 (2 H, m), 6.80 (1 H, dd, *J* = 8.7, 2.6 Hz), 6.73 (1 H, dd, *J* = 12.8, 2.5 Hz), 4.09 (2 H, q, *J* = 7.0 Hz), 1.46 (3 H, t, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (126 MHz): 161.50, 161.33 (dd, *J* = 257.5, 6.52 Hz), 160.64 (d, 249.8 Hz), 160.4 (d, *J* = 250.5 Hz), 160.10 (dd, *J* = 257.5, 6.5 Hz), 159.67 (d, *J* = 252.3 Hz), 151.84 (d, *J* = 11.1 Hz), 151.16 (dq, *J* = 251.1, 5.6 Hz), 144.74 (t, *J* = 11.7 Hz), 141.95 (dt, *J* = 246.5, 10.9 Hz), 138.62 (dt, *J* = 250.6, 15.2 Hz), 130.72 (dd, *J* = 10.2, 4.1 Hz), 123.74 (d, *J* = 12.6 Hz), 122.39, 120.27, 118.52 (d, *J* = 3.7 Hz), 118.16, 117.70 (d, *J* = 12.6 Hz), 113.28 (dt, *J* = 23.7, 3.5 Hz), 112.50 (dt, *J* = 22.8, 4.0 Hz), 111.60 (d, *J* = 2.9 Hz), 111.00 (d, *J* = 25.9 Hz), 109.22 (tt, *J* = 32.5, 14.3 Hz), 107.84 – 107.44 (m), 107.42, 102.96 (d, *J* = 26.0 Hz), 64.31, 14.76.

^{19}F NMR (376 MHz): -61.78 (2 F, t, *J* = 26.3 Hz), -108.73 (2 F, d, *J* = 10.5 Hz), -110.33 (2 F, td, *J* = 26.3, 10.9 Hz), -113.61 (1 F, t, *J* = 9.7 Hz), -114.18 (1 F, t, *J* = 10.6 Hz), -132.43 (2 F, dd, *J* = 20.8, 8.5 Hz), -163.10 (1 F, tt, *J* = 20.7, 6.0 Hz).

20 | *4'-(difluoro(3,4,5-trifluorophenoxy)methyl)-2,3',5'-trifluoro-[1,1'-biphenyl]-4-yl 3,5-difluoro-2',4'-dimethoxy-[1,1'-biphenyl]-4-carboxylate*



4'-(difluoro(3,4,5-trifluorophenoxy)methyl)-2,3',5'-trifluoro-[1,1'-biphenyl]-4-ol (313 mg, 0.745 mmol), 3,5-difluoro-2',4'-dimethoxy-[1,1'-biphenyl]-4-carboxylic acid (511 mg, 1.737 mmol), EDC.HCl (527 mg, 2.749 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield 71 %, 367 mg, 0.527 mmol

Transition Temperatures (°C): Cr 108.2 (N_F 89.5) N 210.1 Iso

Transition Enthalpies (kJ/ mol): Cr 52.5 (N_F 0.7) N 1.4 Iso

^{1}H NMR (501 MHz): 7.50 (1H, t, *J* = 8.6 Hz), 7.29 (1H, d, *J* = 8.4 Hz), 7.25 – 7.19 (6H, m),* 7.05 – 6.95 (2H, m), 6.60 (1H, dd, *J* = 8.5, 2.4 Hz), 6.57 (1H, d, *J* = 2.3 Hz), 3.88 (3H, s), 3.86 (3H, s)

*Solvent Overlap, overlapping signals

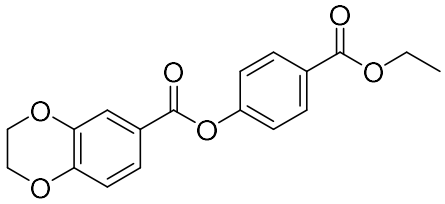
^{13}C{^{1}H} NMR (126 MHz): 162.01, 159.67, 161.1 (dd, *J* = 255.6, 6.2 Hz), 160.1 (dd, *J* = 255.9, 6.33 Hz), 159.7 (d, *J* = 252.5 Hz), 157.79, 151.94 (d, *J* = 11.1 Hz), 151.2 (ddd, *J* = 251.5, 10.7, 5.2 Hz), 145.69 (t, *J* = 11.1 Hz), 144.75 (t, *J* = 13.5 Hz), 140.88 (t, *J* = 11.1 Hz), 138.62 (dt, *J* = 250.9, 15.1 Hz), 131.25, 130.73 (d, *J* = 3.8 Hz), 123.64 (d, *J* = 12.7 Hz), 122.40, 120.28, 119.92, 118.56 (d, *J* = 3.8 Hz), 113.73 – 113.00 (m),* 111.03 (d, *J* = 25.8 Hz), 107.62 (dd, *J* = 18.1, 6.8 Hz), 106.74 (t, *J* = 16.4 Hz), 105.31, 99.26, 55.76, 55.68

* Overlapping signals

^{19}F NMR (376 MHz): -61.78 (2 F, t, *J* = 26.3 Hz), -109.85 (2 F, d, *J* = 10.9 Hz), -110.36 (2 F, td, *J* = 26.4, 11.0 Hz), -113.71 (1 F, t, *J* =

9.7 Hz), -132.43 (2 F, dd, *J* = 21.0, 8.6 Hz), -163.11 (1 F, t, *J* = 19.9 Hz)

21 | *4-(ethoxycarbonyl)phenyl 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate*



ethyl 4-hydroxybenzoate (179 mg, 1.077 mmol), 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid (246 mg, 1.365 mmol), EDC.HCl (306 mg, 1.596 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 59 %, 208 mg, 0.634 mmol

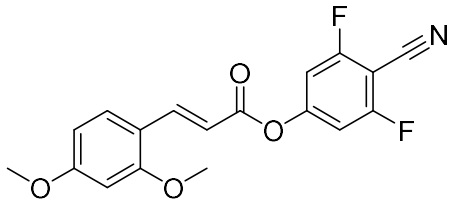
Transition Temperatures (°C): Cr 99.8 Iso

Transition Enthalpies (kJ/ mol): Cr 27.1 Iso

^{1}H NMR (400 MHz): 8.11 (2 H, dd, *J* = 6.8, 2.1 Hz), 7.75 – 7.68 (2 H, m), 7.28 (2 H, dd, *J* = 6.6, 2.0 Hz), 6.96 (1 H, d, *J* = 9.0 Hz), 4.39 (2 H, q, *J* = 7.2 Hz), 4.32 (4 H, m), 1.40 (3 H, t, *J* = 7.1 Hz).

^{13}C{^{1}H} NMR (101 MHz): 166.05, 164.25, 154.79, 148.76, 143.51, 131.26, 128.10, 124.36, 122.33, 121.85, 119.81, 117.57, 64.86, 64.22, 61.20, 14.47.

22 | *4-cyanophenyl (E)-3-(2,4-dimethoxyphenyl)acrylate*



2,6-difluoro-4-hydroxybenzonitrile (95 mg, 0.613 mmol), (E)-3-(2,4-dimethoxyphenyl)acrylic acid (216 mg, 1.037 mmol), EDC.HCl (321 mg, 1.674 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 106 mg, 0.3070 mmol, 50.12 %

Transition Temperatures (°C): Cr 164.8 Iso

Transition Enthalpies (kJ/ mol): Cr 38.6 Iso

^{1}H NMR (501 MHz): 8.09 (1 H, d, *J* = 16.0 Hz), 7.49 (1 H, d, *J* = 8.7 Hz), 7.00 (2 H, dd, *J* = 10.5, 2.8 Hz), 6.57 (1 H, d, *J* = 16.0 Hz)*, 6.55 (1 H, dd, *J* = 8.6, 2.4)*, 6.48 (1 H, d, *J* = 2.3 Hz), 3.91 (3 H, s), 3.87 (3 H, s).

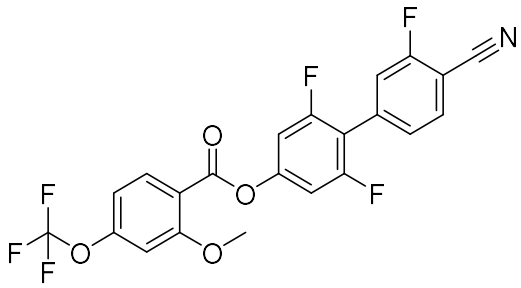
*Overlapping signals

$^{13}C\{^{1}H\}$ NMR (126 MHz): 164.61, 163.95, 163.74 (dd, *J* = 260.3, 6.3 Hz) 160.71, 156.58 (t, *J* = 13.7 Hz), 144.68, 131.70, 115.99, 112.94, 109.11, 106.89 (dd, *J* = 22.9, 3.8 Hz), 105.79, 98.62, 89.54 (t, *J* = 19.5 Hz), 55.73.

^{19}F NMR (376 MHz): -102.57 (2 F, d, *J* = 8.9 Hz).

HRMS: 346.0890 (M + H), expected 246.08

23 | *4'-cyano-2,3',6-trifluoro-[1,1'-biphenyl]-4-yl 2-methoxy-4-(trifluoromethoxy)benzoate*



2',3,6'-trifluoro-4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile (199 mg, 0.799 mmol), 2-methoxy-4-(trifluoromethoxy)benzoic acid (266 mg, 1.126 mmol), EDC.HCl (319 mg, 1.664 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 169 mg, 0.3616 mmol, 45.28 %

Transition Temperatures (°C): Cr 126.0 Iso

Transition Enthalpies (kJ/ mol): Cr 32.6 Iso

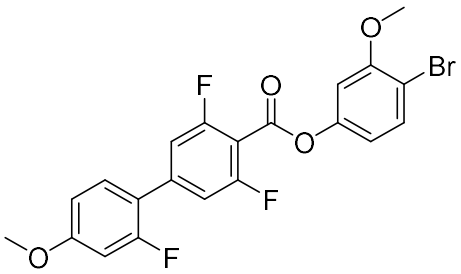
^{1}H NMR (501 MHz): 8.07 (1 H, d, *J* = 8.7 Hz), 7.72 (1 H, dd, *J* = 8.0, 6.7 Hz), 7.39 (2 H, td, *J* = 9.8, 1.2 Hz), 7.04 – 6.96 (2 H, m), 6.93 (1 H, ddt, *J* = 8.7, 2.5, 1.2 Hz), 6.87 (1 H, d, *J* = 2.2 Hz), 3.97 (3 H, s).

$^{13}C\{^{1}H\}$ NMR (126 MHz): 162.75 (d, *J* = 259.6 Hz), 162.29, 161.80, 161.23 (dd, *J* = 257.5, 7.4 Hz), 160 (d, *J* = 251.0 Hz) 159.81 (dd, *J* = 251.2, 8.6 Hz), 154.32 (d, *J* = 1.8 Hz), 152.11 (t, *J* = 14.4 Hz), 136.15 (d, *J* = 8.8 Hz), 134.28, 133.37, 127.01 (d, *J* = 2.5 Hz), 120.90 (q, *J* = 257.8 Hz) 118.63 (dt, *J* = 21.0, 1.9 Hz), 116.11, 113.86, 113.53 (td, *J* = 17.9, 1.5 Hz), 111.74 (d, *J* = 1.1 Hz), 107.40 – 106.58 (m), 105.01, 101.38 (d, *J* = 15.4 Hz), 56.57.

^{19}F (376 MHz): -57.45 (3 F, s), -106.15 (1 F, t, *J* = 8.2 Hz), -112.31 (2 F, d, *J* = 9.2 Hz).

HRMS : 468.0671 (M + H), expected 468.06

24 | *4-bromo-3-methoxyphenyl 2',3,5-trifluoro-4'-methoxy-[1,1'-biphenyl]-4-carboxylate*



4-bromo-3-methoxyphenol (194 mg, 0.955 mmol), 2',3,5-trifluoro-4'-methoxy-[1,1'-biphenyl]-4-carboxylic acid (360 mg, 1.215 mmol), EDC.HCl (491 mg, 2.561 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield 72 %, 322 mg, 0.689 mmol

Transition Temperatures (°C): Cr 124.6 Iso

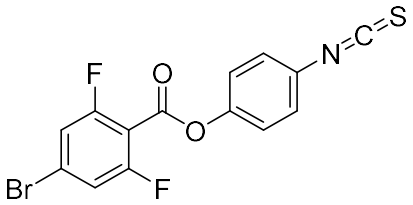
Transition Enthalpies (kJ/ mol): Cr 71.8 Iso

^{1}H NMR (501 MHz): 7.58 (1 H, d, *J* = 8.5 Hz), 7.38 (1 H, t, *J* = 8.8 Hz), 7.22 (2 H, dd, *J* = 10.9, 1.5 Hz), 6.85 (1 H, d, *J* = 2.5 Hz), 6.81 (2 H, ddd, *J* = 8.5, 6.0, 2.4 Hz), 6.74 (1 H, dd, *J* = 12.8, 2.5 Hz), 3.92 (3 H, s), 3.86 (3 H, s).

^{13}C{^{1}H} NMR (126 MHz): 161.98 (d, *J* 11.3), 161.22 (dd, *J* = 258.2 Hz), 160.61 (d, 250.5 Hz), 159.67 (t, *J* = 2.1), 156.70, 150.64, 142.32 (td, *J* 11.0, 1.5), 133.54, 130.74 (d, *J* 4.5), 117.99 (dt, *J* 12.4, 2.3), 114.91, 113.05 – 112.09 (m), 111.09 (d, *J* 3.0), 108.93, 108.08 (t, *J* 16.8), 106.30, 102.54 (d, *J* 26.2), 56.58, 55.92.

^{19}F NMR (376 MHz): -109.00 (2 F, d, *J* = 10.5 Hz), -114.14 (1 F, t, *J* = 10.1 Hz).

25 | *4-isothiocyanatophenyl 4-bromo-2,6-difluorobenzoate*



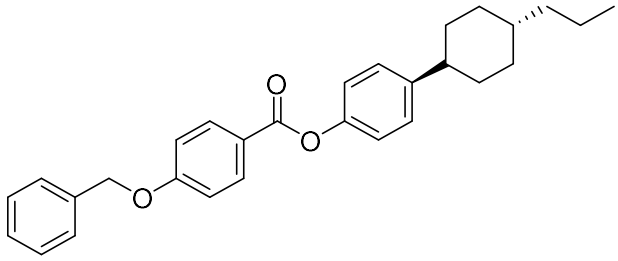
4-isothiocyanatophenol (106 mg, 0.701 mmol), 4-bromo-2,6-difluorobenzoic acid (234 mg, 0.987 mmol), EDC.HCl (399 mg, 2.081 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 161 mg, 0.4349 mmol, 62.03 %

Transition Temperatures (°C): Cr 123.6 Iso

Transition Enthalpies (kJ/ mol): Cr 33.3 Iso

^{1}H NMR (501 MHz, DMSO):	7.77 (2 H, d, *J* = 8.1 Hz), 7.56 (2 H, dd, *J* = 6.7, 2.2 Hz), 7.39 (2 H, dd, *J* = 6.7, 2.2 Hz).
^{13}C{^{1}H} NMR (126 MHz):	161.05 (dd, *J* = 262.6, 6.6 Hz), 158.97 (t, *J* = 2.0 Hz), 148.81, 136.56, 129.66, 127.07 (t, J = 12.3 Hz)*, 12.02*, 122.96, 116.63 (dd, *J* = 25.5, 3.3 Hz), 109.24 (t, *J* = 16.8 Hz). *Overlapping signals
^{19}F NMR (376 MHz):	-107.06 (2 F, d, *J* = 8.5 Hz).

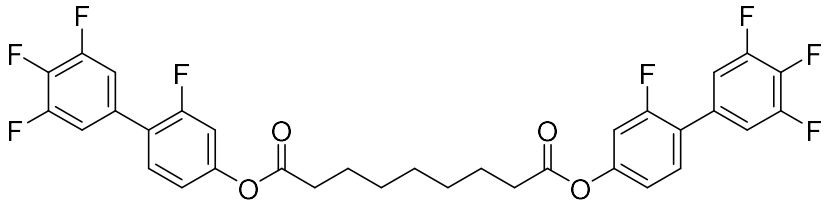
26 | *4-((1r,4s)-4-propylcyclohexyl)phenyl 4-(benzyloxy)benzoate*



4-((1s,4r)-4-propylcyclohexyl)phenol (115 mg, 0.527 mmol), 4-(benzyloxy)benzoic acid (255 mg, 1.117 mmol), EDC.HCl (399 mg, 2.081 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 223 mg, 0.5203 mmol, 98.79 %

Transition Temperatures (°C):	Cr 106.4 Iso
Transition Enthalpies (kJ/ mol):	Cr 30.7 Iso
^{1}H NMR (501 MHz, DMSO):	7.71 (1 H, dt, *J* = 7.7, 1.2 Hz), 7.69 – 7.67 (1 H, m), 7.52 (1 H, t, *J* = 8.0 Hz), 7.48 (2 H, d, *J* = 7.0 Hz), 7.40 (3 H, t, *J* = 7.9 Hz), 7.34 (1 H, tt, *J* = 7.3, 1.8 Hz), 7.30 (2 H, d, *J* = 8.6 Hz), 7.16 (2 H, dd, *J* = 6.6, 2.0 Hz), 5.21 (2 H, s), 2.54 – 2.46 (1 H, m)*, 1.82 (4 H, d, *J* = 11.6 Hz), 1.45 (2 H, qd, *J* = 12.6, 2.8 Hz), 1.38 – 1.27 (3 H, m), 1.24 – 1.15 (2 H, m), 1.03 (2 H, qd, *J* = 12.4, 2.5 Hz), 0.88 (3 H, t, *J* = 7.3 Hz). *Solvent Overlap
^{13}C{^{1}H} NMR (101 MHz):	165.30, 158.96, 148.99, 145.65, 136.62, 131.18, 129.76, 128.80, 128.29, 127.93, 127.73, 122.96, 121.40, 120.89, 115.78, 70.39, 44.25, 39.85, 37.15, 34.56, 33.69, 20.18, 14.56.
HRMS:	429.2420 (M + H), 451.2241 (M + Na), expected 429.24

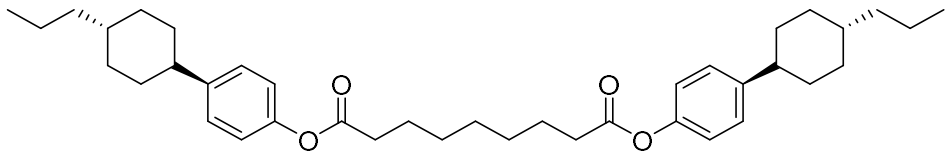
27 | *bis(2,3',4',5'-tetrafluoro-[1,1'-biphenyl]-4-yl) nonanedioate*



2,3',4',5'-tetrafluoro-[1,1'-biphenyl]-4-ol (885 mg, 3.654 mmol), heptanedioic acid (199 mg, 1.057 mmol), EDC.HCl (730 mg, 3.801 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 532 mg, 0.8358 mmol %, 79.05 %

Transition Temperatures (°C):	Cr 104.6 Iso
Transition Enthalpies (kJ/ mol):	Cr 49.1 Iso
^{1}H NMR (501 MHz, acetone):	7.65 (2 H, dd, *J* = 11.5, 2.2 Hz), 7.61 – 7.54 (6 H, m), 7.36 (2 H, t, *J* = 8.2 Hz), 2.69 (4 H, t, *J* = 7.4 Hz), 1.79 (4 H, p, *J* = 7.4 Hz), 1.56 – 1.42 (6 H, m).
^{13}C{^{1}H} NMR (126 MHz):	171.22, 154.42 (d, *J* = 250.4 Hz), 151.62 (ddd, *J* = 250.4, 10.1, 4.3 Hz), 139.76 (dt, *J* = 253.1, 15.4 Hz), 138.43 (d, *J* = 13.1 Hz), 137.61 (dd, *J* = 7.1, 1.9 Hz), 135.54 (dtd, *J* = 7.9, 5.2, 2.5 Hz), 124.57 (d, *J* = 1.6 Hz), 122.99 (d, *J* = 3.4 Hz), 115.42 (d, *J* = 20.0 Hz), 111.28 (dd, *J* = 16.5, 5.3 Hz), 33.96, 28.94, 28.89, 24.90.
^{19}F NMR (376 MHz):	-126.73 (1 F, t, *J* = 9.0 Hz), -133.40 (2 F, dd, *J* = 20.5, 8.6 Hz), -161.37 (1 F, tt, *J* = 20.7, 6.5 Hz).
HRMS:	637.13 (M + H), 660.14 (M + H + Na), expected 637.16, 660.15

28 | *bis(4-((1s,4r)-4-propylcyclohexyl)phenyl) nonanedioate*



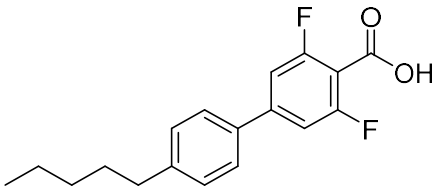
4-((1s,4r)-4-propylcyclohexyl)phenol (660 mg, 3.023 mmol), heptanedioic acid (200 mg, 1.062 mmol), EDC.HCl (625 mg, 3.260 mmol), DMAP (cat. amount). Standard Steglich esterification protocol was used. Yield: 452 mg, 0.7676 mmol, 72.24 %

Transition Temperatures (°C):	Cr (Cr 86.0 Cr 99.1) N 111.8 Iso
Transition Enthalpies (kJ/ mol):	Cr 36.0 (12.3 Cr 23.1) N 2.2 Iso

^{1}H NMR (501 MHz):	7.19 (4 H, dd, *J* = 6.5, 2.1 Hz), 6.98 (4 H, dd, *J* = 6.6, 2.0 Hz), 2.55 (4 H, t, *J* = 7.5 Hz), 2.46 (2 H, tt, *J* = 12.2, 3.3 Hz), 1.87 (8 H, t, *J* = 12.4 Hz), 1.76 (4 H, p, *J* = 7.5 Hz), 1.48 – 1.24 (16 H, m), 1.24 – 1.17 (4 H, m), 1.04 (4 H, qd, *J* = 13.8, 4.4 Hz), 0.90 (6 H, t, *J* = 7.3 Hz).
^{13}C{^{1}H} NMR (126 MHz):	172.58, 148.78, 145.43, 127.83, 121.29, 44.20, 39.84, 37.13, 34.51 (d, *J* = 4.5 Hz), 33.67, 29.02, 25.03, 20.17, 14.55
HRMS:	589.4250 (M + H), 611.4068 (M + Na), expected 589.42, 611.41

3.4 Novel biphenyl carboxylic acid intermediates

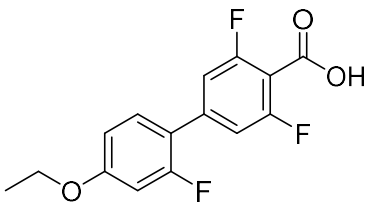
CA1 | *2,6-difluoro-4-(4-pentylphenyl)benzoic acid*



THF (100 ml), potassium carbonate 2 M aqueous (50 ml), *4-bromo-2,6-difluorobenzoic acid* (3.550 g, 14.98 mmol), *(4-pentylphenyl)boronic* acid (2.660 g, 13.85 mmol) and PdXPhos G3 (cat. amount). The general Suzuki-Miyaura protocol afforded the title compound with a yield of 61.47 %, 2.591 g, 8.514 mmol.

^{1}H NMR (501 MHz, DMSO):	13.84 (1 H, s), 7.70 (2 H, d, *J* = 8.2 Hz), 7.54 (2 H, d, *J* = 10.1 Hz), 7.31 (2 H, d, *J* = 8.0 Hz), 2.61 (2 H, t, *J* = 7.7 Hz), 1.59 (2 H, p, *J* = 7.4 Hz), 1.37 – 1.22 (4 H, m), 0.86 (3 H, t, *J* = 6.9 Hz).
^{13}C{^{1}H} NMR (126 MHz, DMSO):	162.14, 160.91 (d, *J* = 7.9 Hz), 158.91 (d, *J* = 7.9 Hz), 144.93 (t, *J* = 10.3 Hz), 143.81, 134.10 (t, *J* = 2.3 Hz), 129.05, 126.89, 110.07 – 109.71 (m), 34.72, 30.86, 30.47, 21.95, 13.91.
^{19}F NMR (376 MHz, DMSO):	-111.34 (2 F, d, *J* = 10.3 Hz).

CA2 | *4-(4-Ethoxy-2-fluorophenyl)-2,6-difluorobenzoic acid*



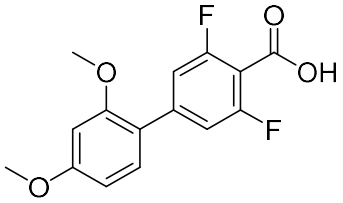
THF (ca. 100 ml), potassium carbonate 2 M aqueous (ca. 50 ml), *4-bromo-2,6-difluorobenzoic acid* (7.787 g, 32.85 mmol), *(4-ethoxy-2,fluorophenyl)boronic acid* (5.045 g, 27.42 mmol) and PdXPhos G3 (cat. amount). The general Suzuki-Miyaura protocol afforded the title compound with a yield of (77.90 %, 6.362 g, 21.36 mmol).

^{1}H NMR (501 MHz, DMSO): 13.92 (1 H, s), 7.58 (1 H, t, *J* = 9.0 Hz), 7.36 (2 H, d, *J* = 9.1 Hz), 6.97 (1 H, dd, *J* = 13.3, 2.5 Hz), 6.89 (1 H, dd, *J* = 8.6, 2.5 Hz), 4.10 (2 H, q, *J* = 7.0 Hz), 1.34 (3 H, t, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (126 MHz, DMSO): 162.01, 160.63 (d, *J* = 11.5 Hz), 159.83 (d, *J* = 247.8 Hz), 159.4 (dd, *J* = 251.9, 7.81 Hz) 139.78 (t, *J* = 10.2 Hz), 131.25 (d, *J* = 4.4 Hz), 117.09 (d, *J* = 12.6 Hz), 112.08 (dt, *J* = 21.3, 4.2 Hz), 111.62 (d, *J* = 2.8 Hz), 102.59 (d, *J* = 26.1 Hz), 63.94, 14.44.

^{19}F NMR (376 MHz, DMSO): -111.83 (2 F, d, *J* = 10.1 Hz), -114.90 (1 F, t, *J* = 11.5 Hz).

CA3 | *4-(2,4-Dimethoxyphenyl)-2,6-difluorobenzoic acid*



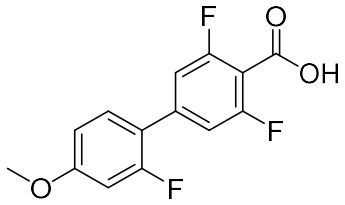
THF (ca. 100 ml), potassium carbonate 2 M aqueous (50 ml), *4-bromo-2,6-difluorobenzoic acid* (3.644 g, 15.38 mmol), *(2,4-methoxyphenyl)boronic acid* (2.420 g, 13.30 mmol) and PdXPhos G3 (cat. amount). The general Suzuki-Miyaura protocol afforded the title compound with a yield of (62.44 %, 2.442 g, 8.302 mmol).

^{1}H NMR (501 MHz, DMSO): 13.78 (1 H, s), 7.37 (1 H, d, *J* = 8.5 Hz), 7.29 (2 H, d, *J* = 9.7 Hz), 6.69 (1 H, d, *J* = 2.4 Hz), 6.64 (1 H, dd, *J* = 8.5, 2.4 Hz), 3.81 (6 H, d, *J* = 3.2 Hz).

^{13}C{^{1}H} NMR (126 MHz, DMSO): 162.20, 161.33, 159.07 (dd, *J* = 250.6, 8.1 Hz), 157.34, 142.96 (t, *J* = 10.8 Hz), 131.16, 118.92 (t, *J* = 2.2 Hz), 112.44 (dd, *J* = 20.7, 4.6 Hz), 109.40 (t, *J* = 19.9 Hz), 105.73, 98.99, 55.74, 55.43.

^{19}F NMR (376 MHz, DMSO): -112.78 (2 F, d, *J* = 10.5 Hz).

CA4 | *4-(4-Methoxy-2-fluorophenyl)-2,6-difluorobenzoic acid*



THF (120 ml), potassium carbonate 2 M aqueous (40 ml), *4-bromo-2,6-difluorobenzoic acid* (3.508 g, 14.80 mmol), *(2-fluoro-4-methoxyphenyl)boronic acid* (2.289 g, 13.47 mmol), and PdXPhos G3 (cat. amount). The general Suzuki-Miyaura protocol afforded the title compound with a yield of (71.10 %, 2.703 g, 9.577 mmol).

^{1}H NMR (501 MHz, DMSO): 13.92 (1 H, s), 7.59 (1 H, t, *J* = 9.0 Hz), 7.38 (2 H, dd, *J* = 9.5, 1.2 Hz), 7.00 (1 H, dd, *J* = 13.3, 2.5 Hz), 6.92 (1 H, dd, *J* = 8.7, 2.6 Hz), 3.83 (3 H, s).

^{13}C{^{1}H} NMR (126 MHz, DMSO): 162.01, 161.39 (d, *J* = 11.5 Hz), 159.89 (d, *J* = 247.7 Hz), 159.85 (dd, *J* = 251.6, 7.7 Hz), 139.79 (t, *J* = 11.0 Hz), 131.27 (d, *J* = 4.5 Hz), 117.23 (d, *J* = 12.3 Hz), 112.47 – 111.87 (m), 111.26 (d, *J* = 2.8 Hz), 110.39 (t, *J* = 19.8 Hz), 102.23 (d, *J* = 26.3 Hz), 55.91.

^{19}F NMR (376 MHz, DMSO): -111.82 (2 F, d, *J* = 10.1 Hz), -114.88 (1 F, t, *J* = 11.1 Hz).

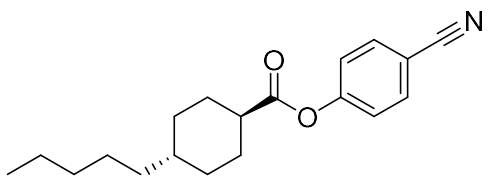
4 Supplemental References

1 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chemistry*, 2015, **18**, 288–296.

2 R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, *Green Chemistry*, 2011, **13**, 854–862.

5 Compound Spectra, Plots and Thermograms

CZP-5-N | *4-cyanophenyl (1s,4r)-4-pentylcyclohexane-1-carboxylate*



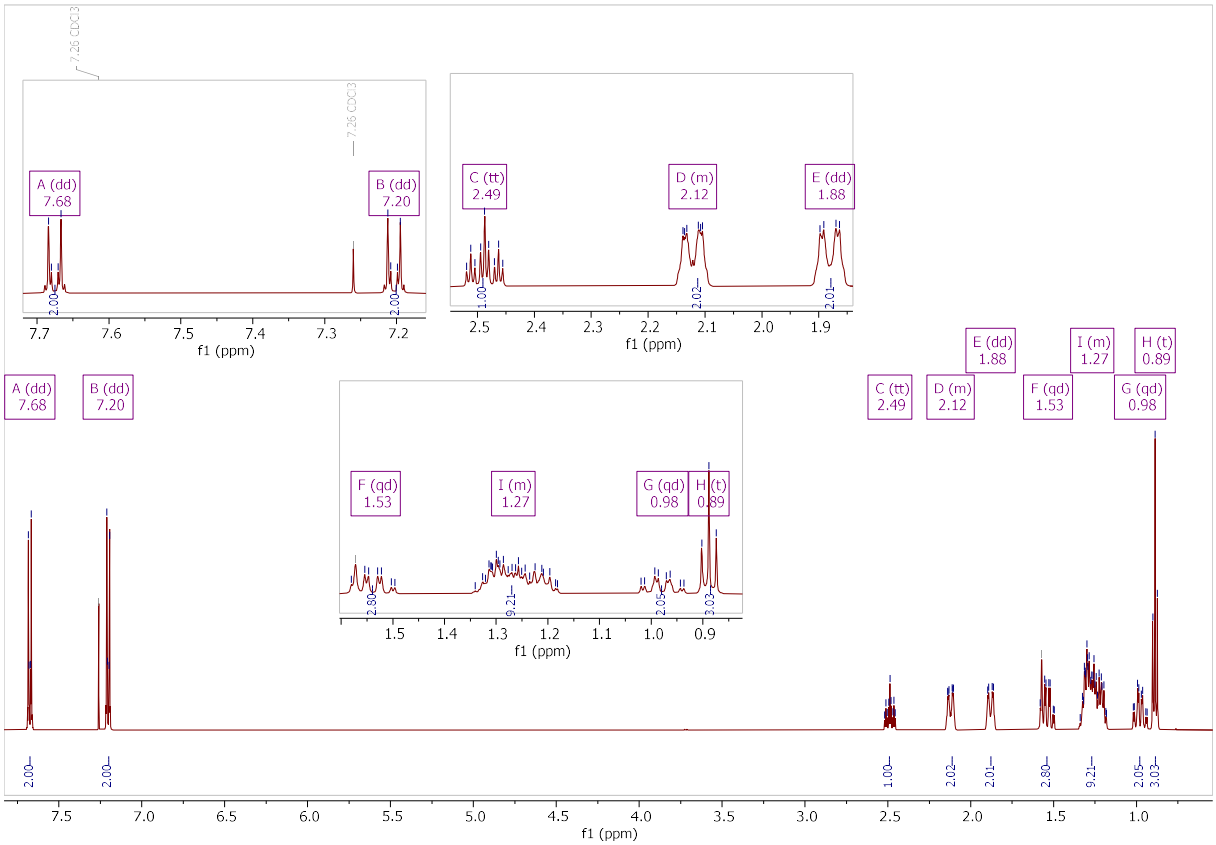


Figure S2 proton NMR spectrum of **CZP-5-N**

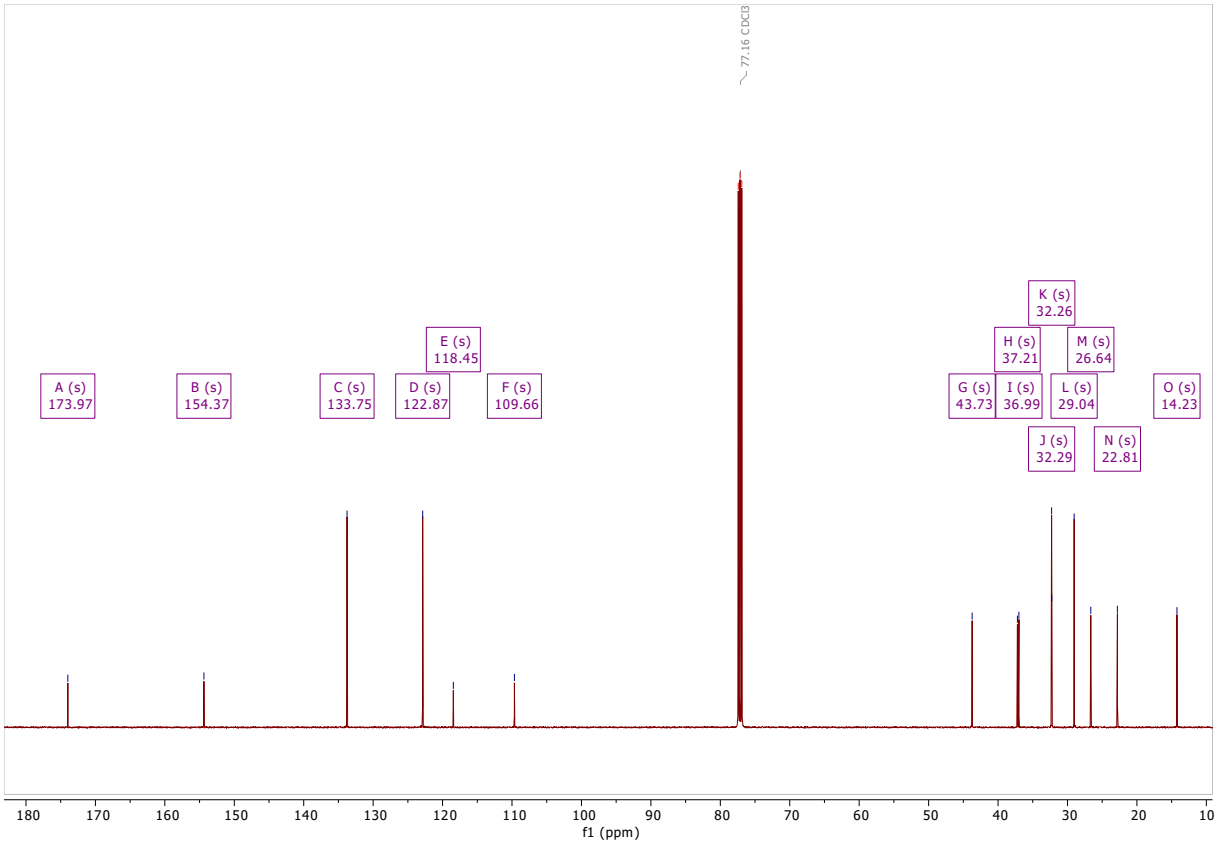


Figure S3 carbon NMR Spectrum of **CZP-5-N**

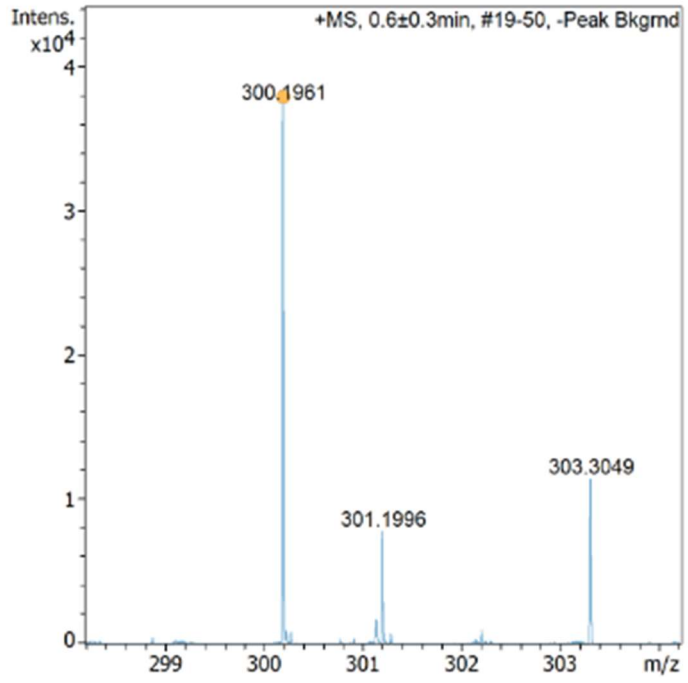


Figure S4 HRMS of **CZP-5-N**

1 | *trans-[3-fluoro-4-(3,4,5-trifluorophenyl)phenyl] 4-pentylcyclohexane-1-carboxylate*

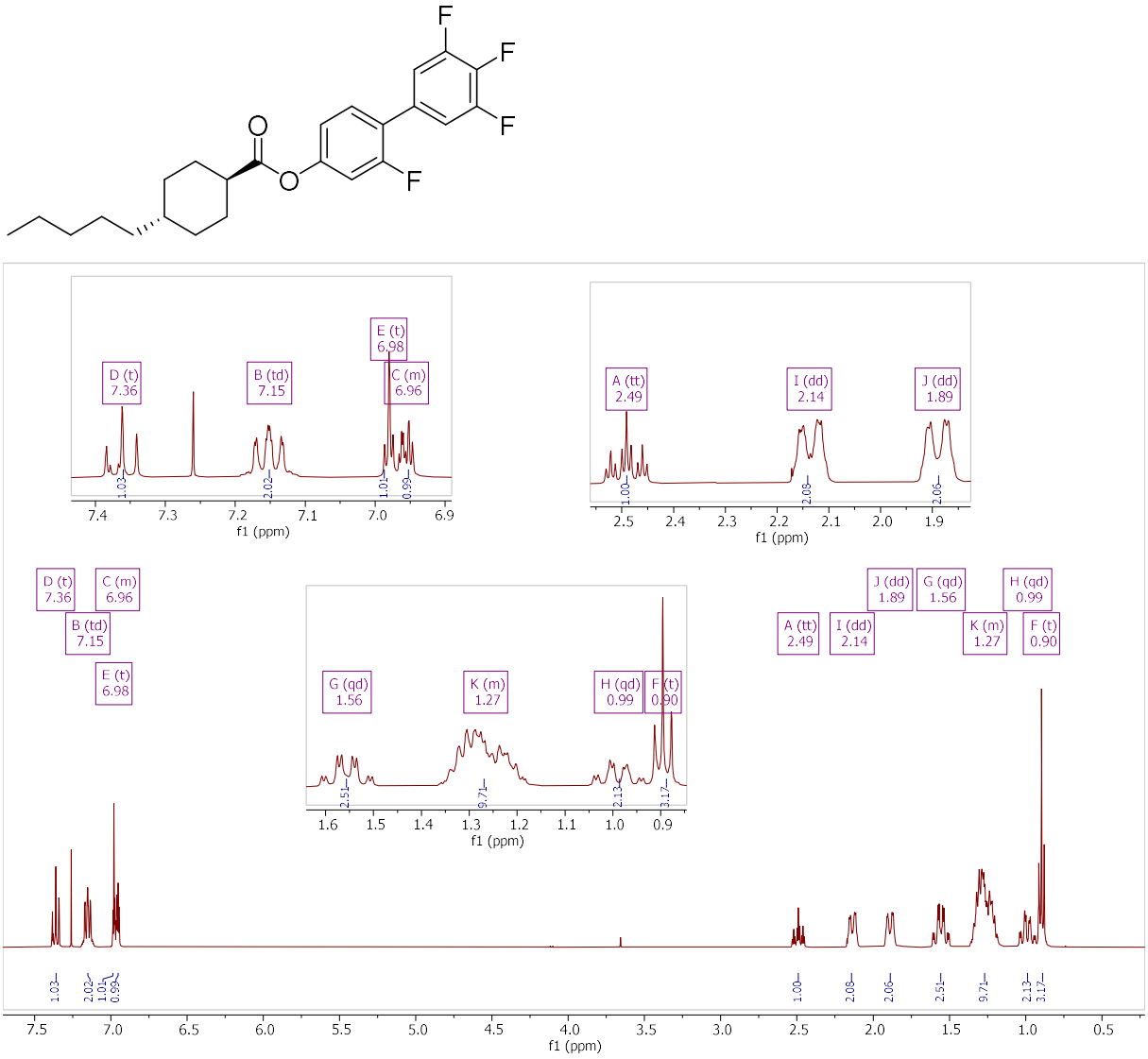


Figure S4 proton NMR spectrum of **1**

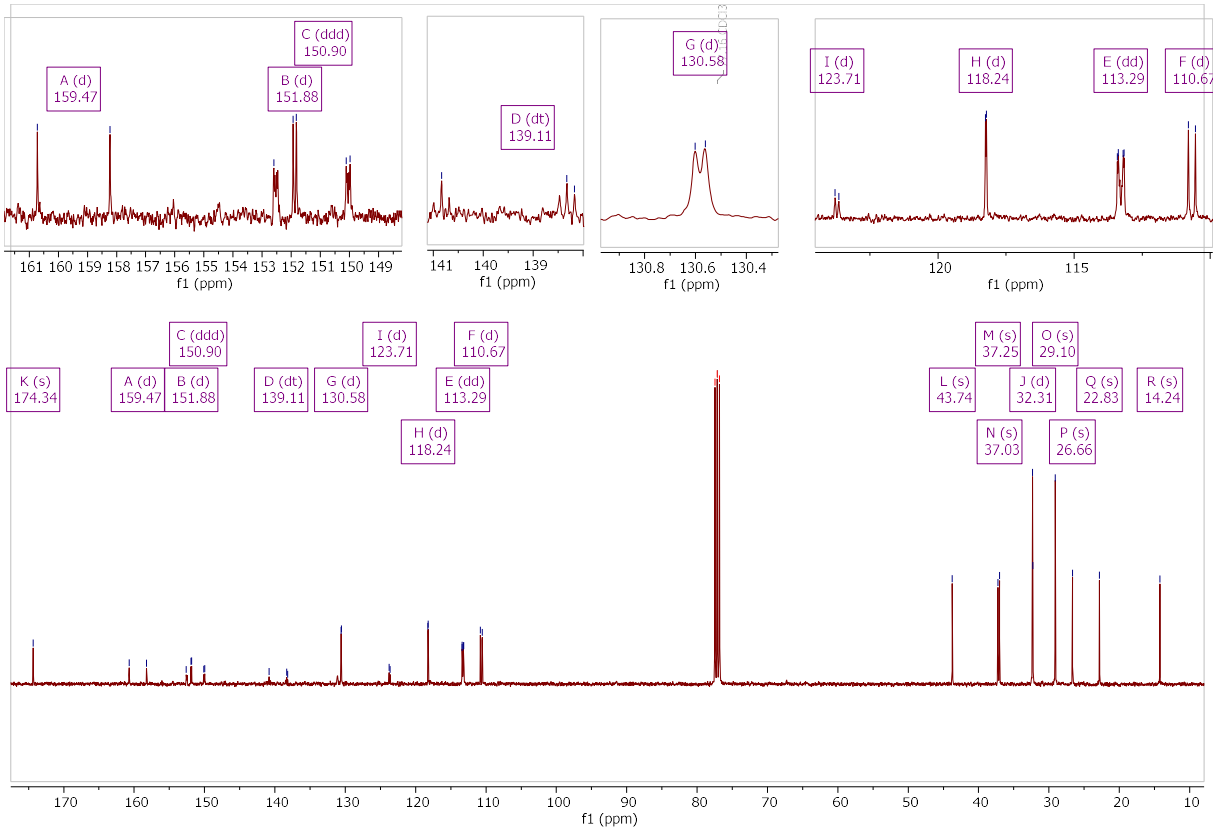


Figure S5 carbon NMR spectrum of **1**

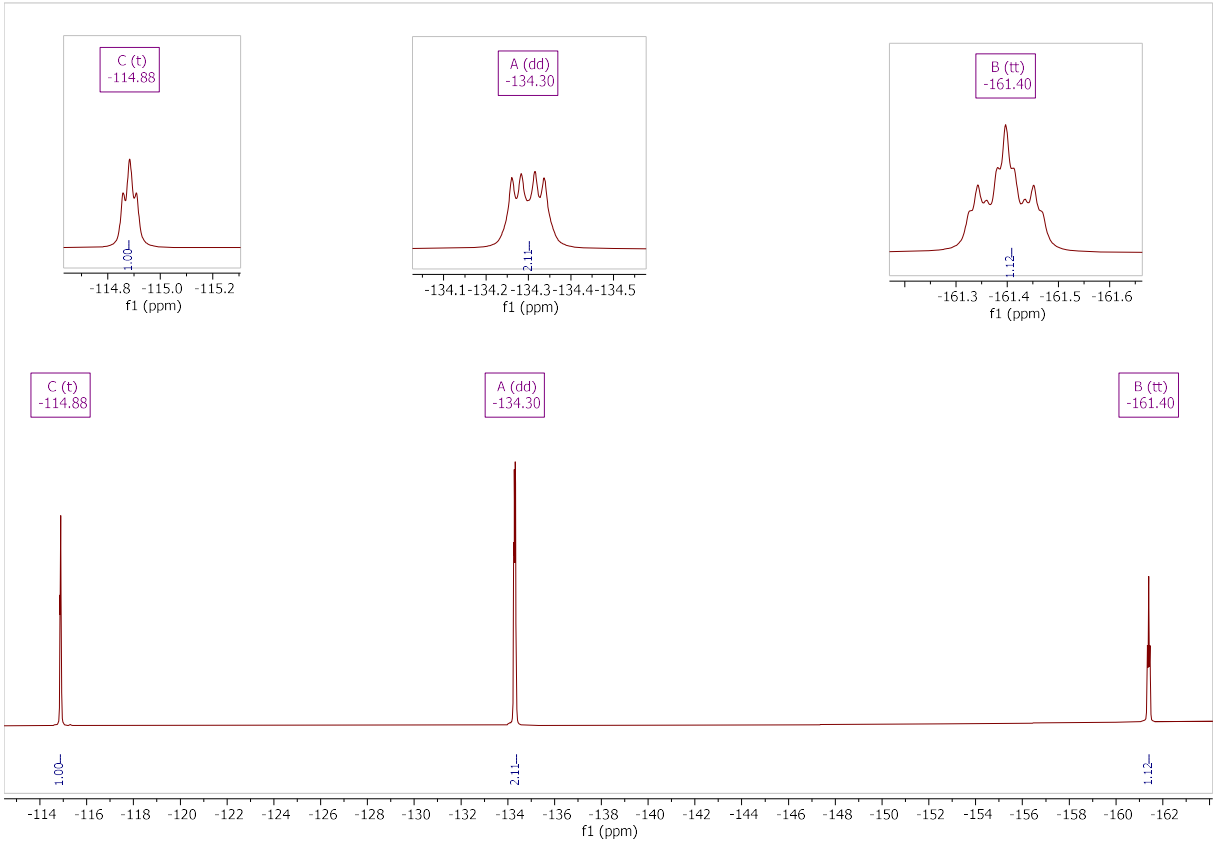
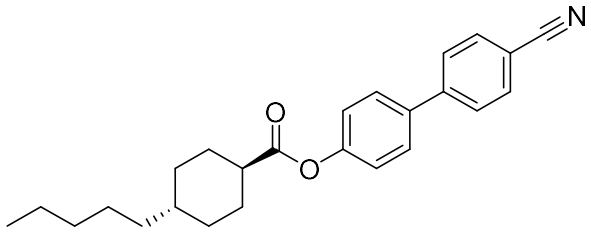


Figure S6 fluorine NMR spectrum of **1**

2 | *[4-(4-cyanophenyl)phenyl] 4-pentylcyclohexane-1-carboxylate*



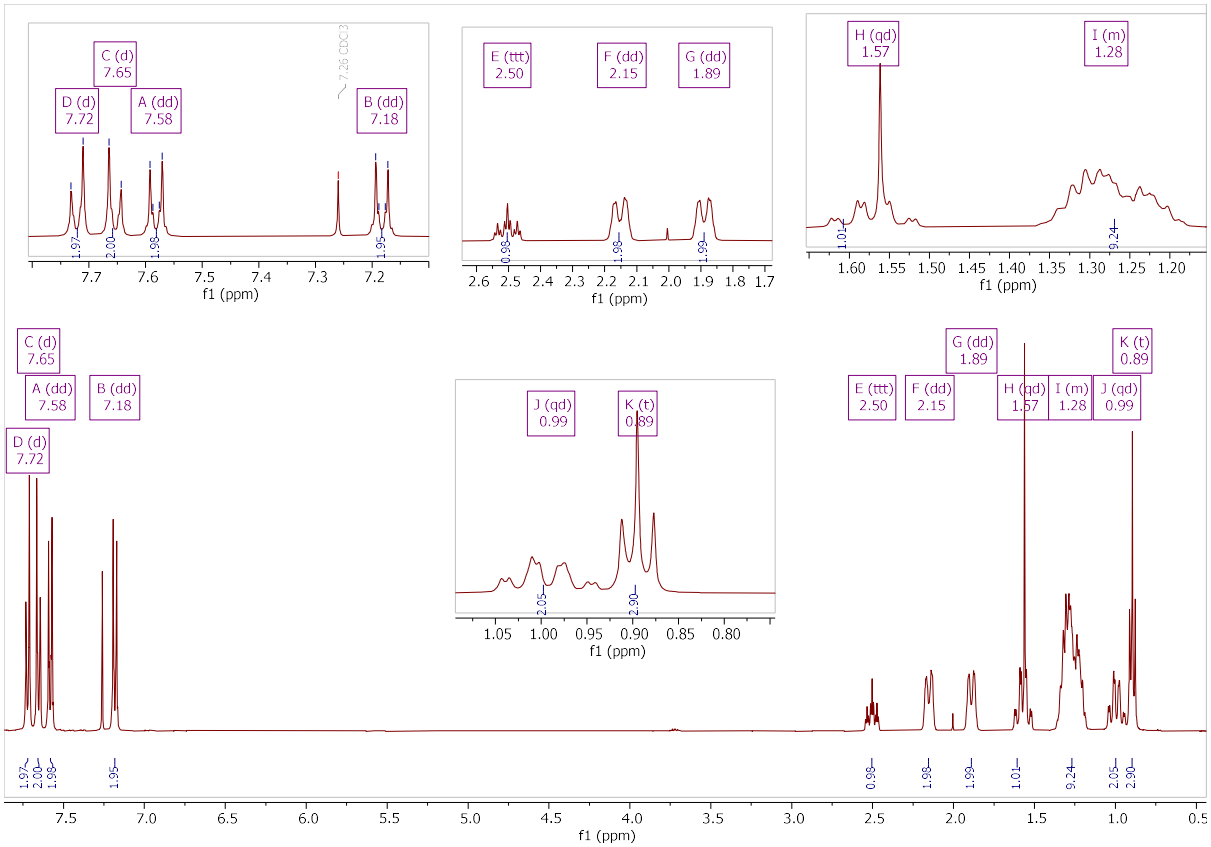


Figure S proton NMR spectrum of **2**

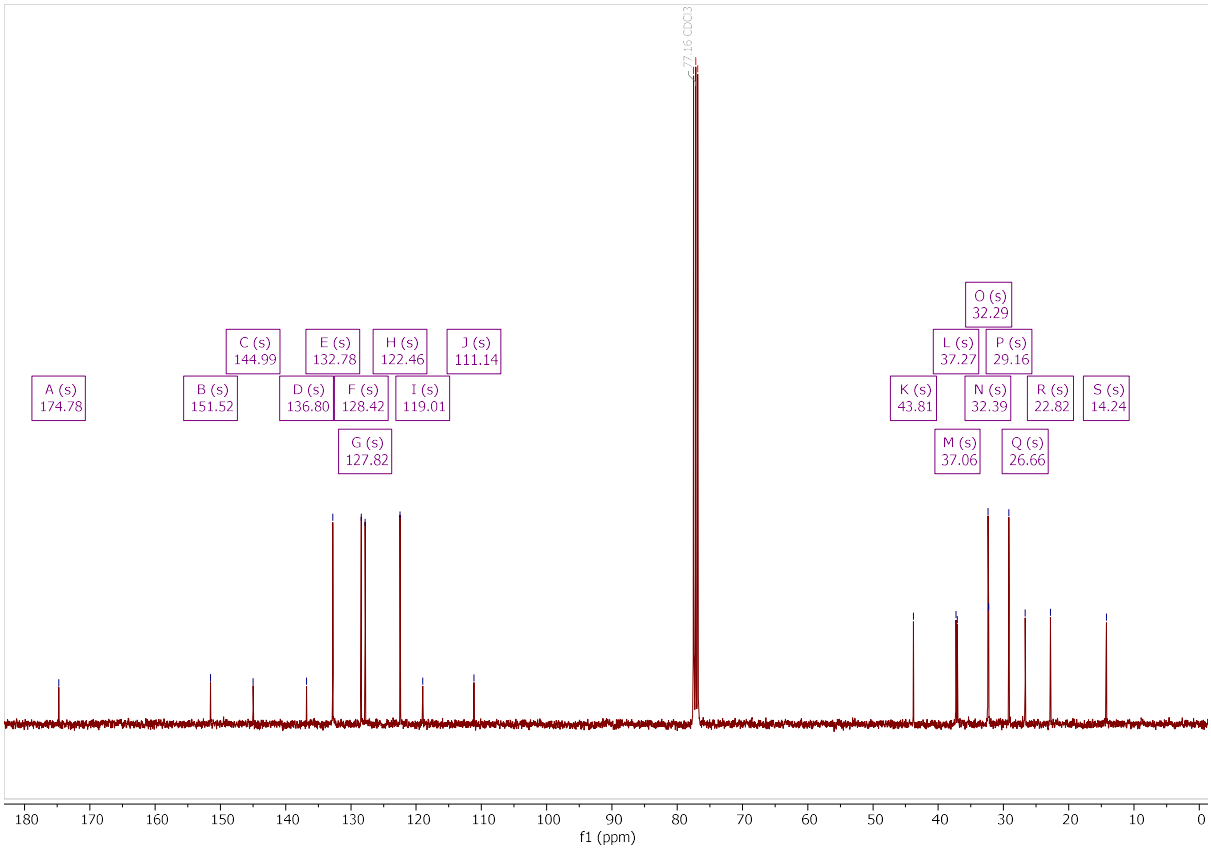
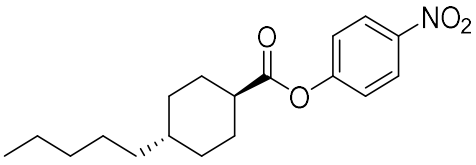


Figure S carbon NMR spectrum of **2**

3 | *(4-nitrophenyl) 4-pentylcyclohexane-1-carboxylate*



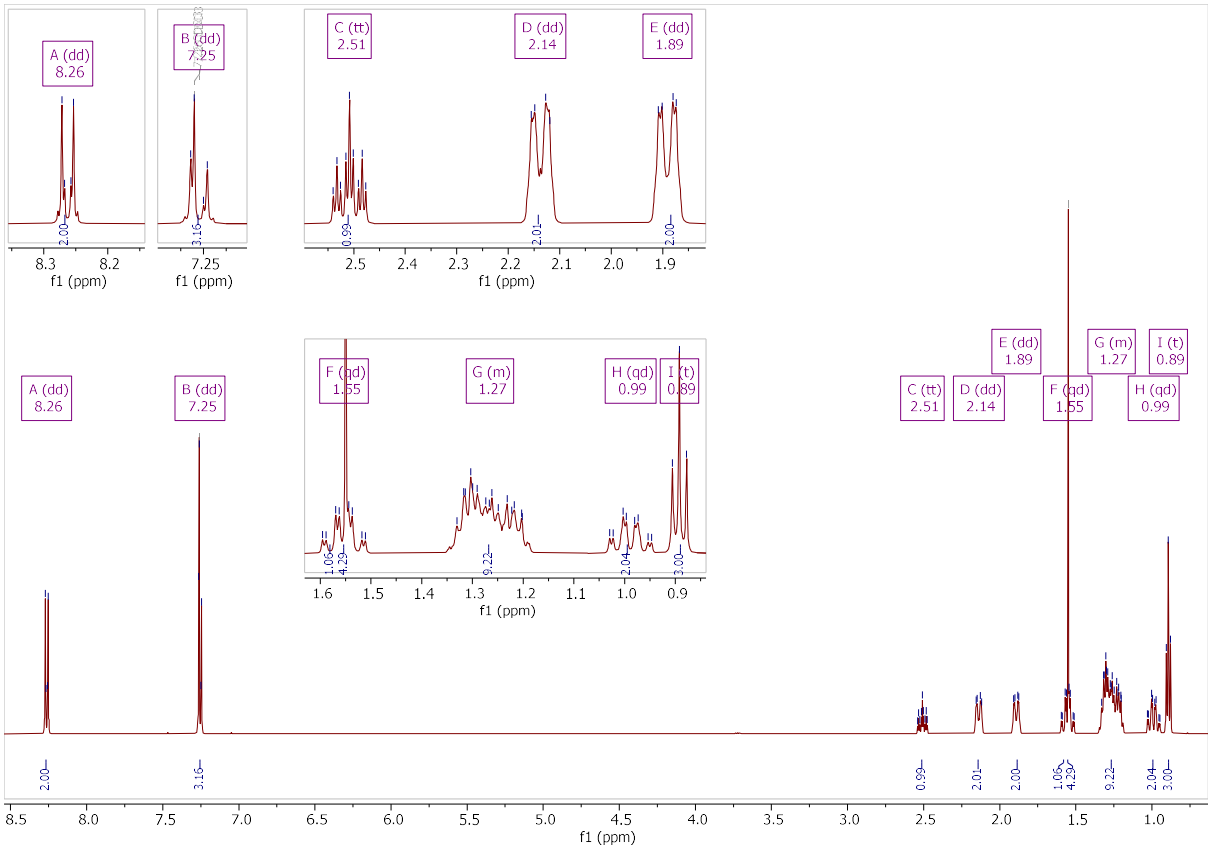


Figure S proton NMR spectrum of **3**

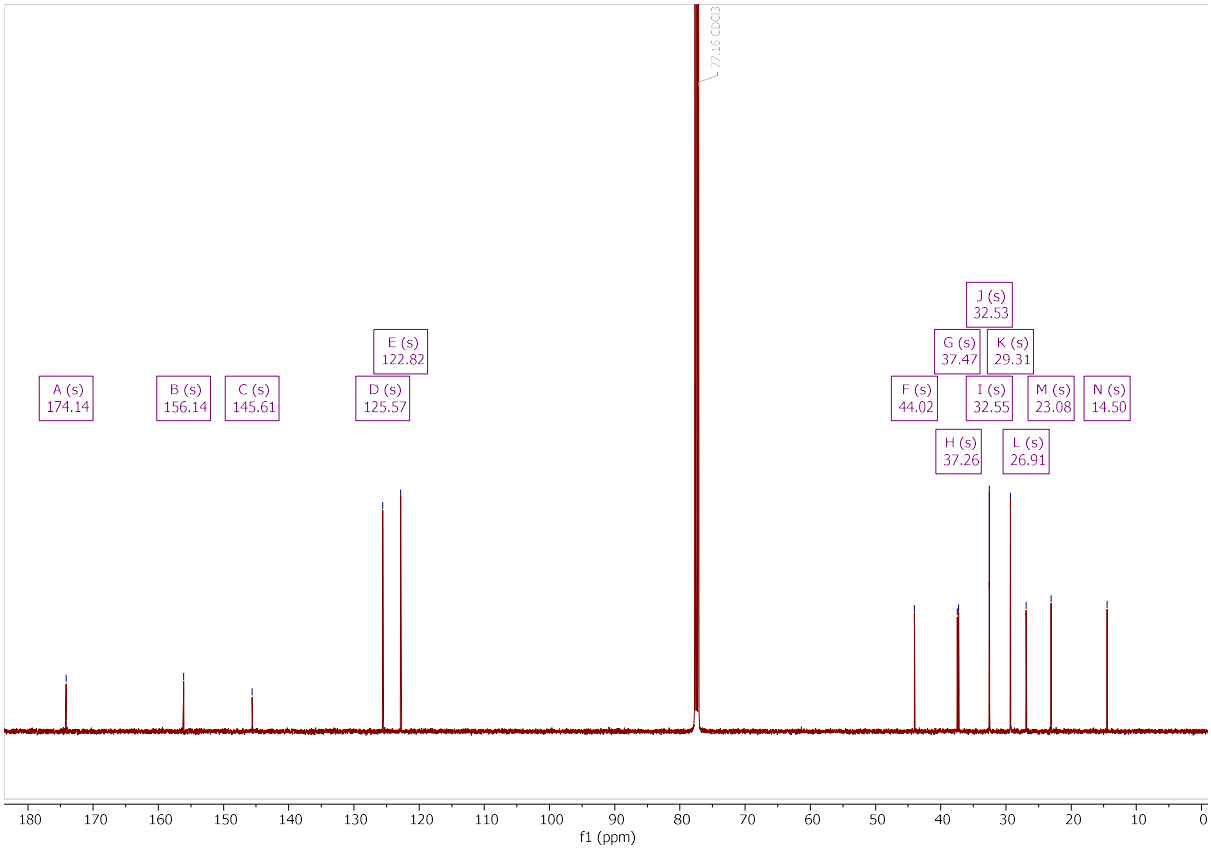


Figure S carbon NMR spectrum of **3**

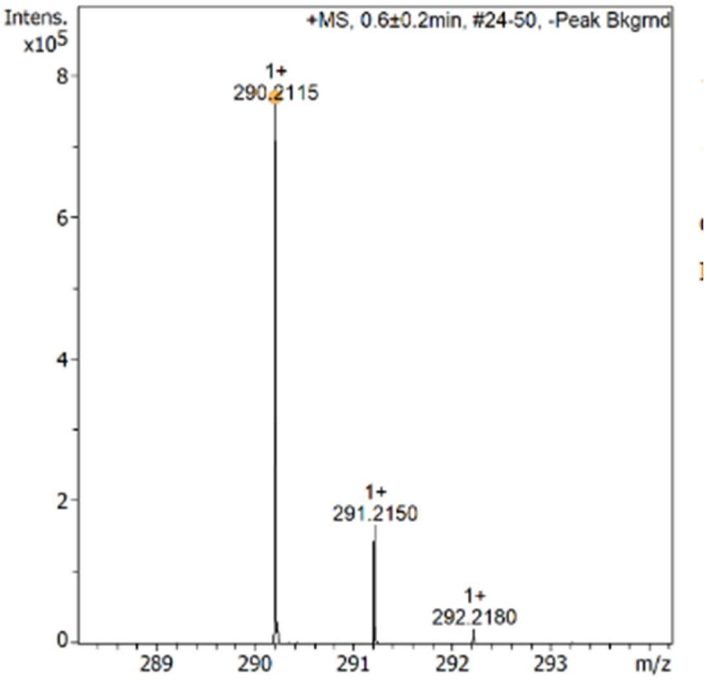
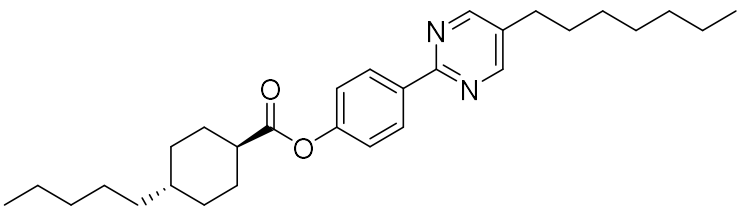


Figure S HRMS of **3.** Nitro group reduced to amine group in flight.

4 | *4-(5-heptylpyrimidin-2-yl)phenyl (1r,4s)-4-pentylcyclohexane-1-carboxylate*



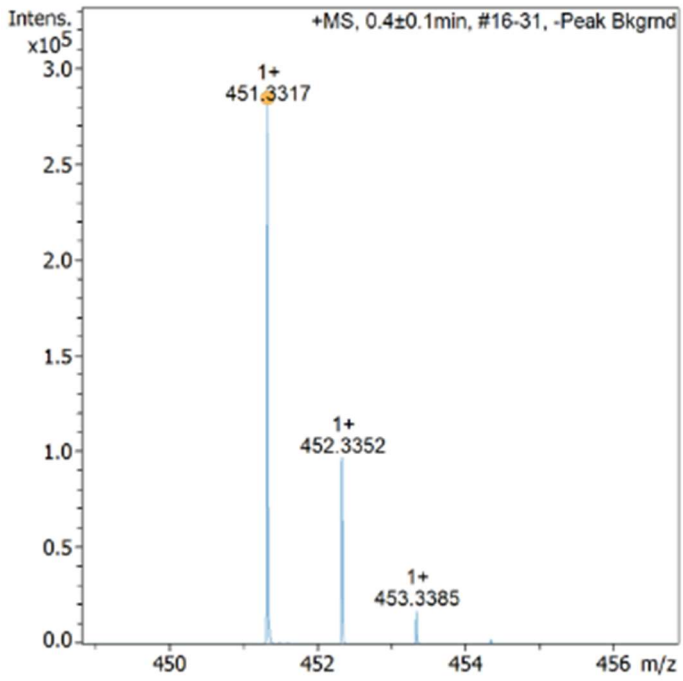
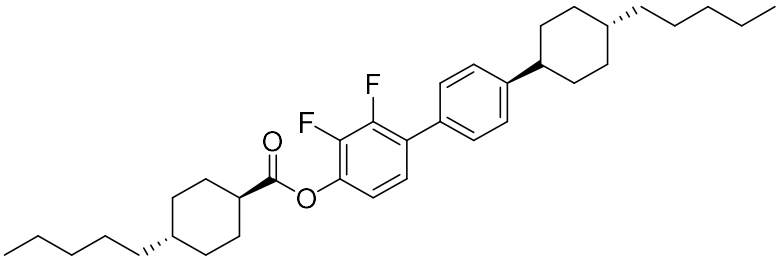


Figure S HRMS of **9**

5 | *2,3-difluoro-4'-((1s,4r)-4-pentylcyclohexyl)-[1,1'-biphenyl]-4-yl (1s,4r)-4-entylcyclohexane-1-carboxylate*



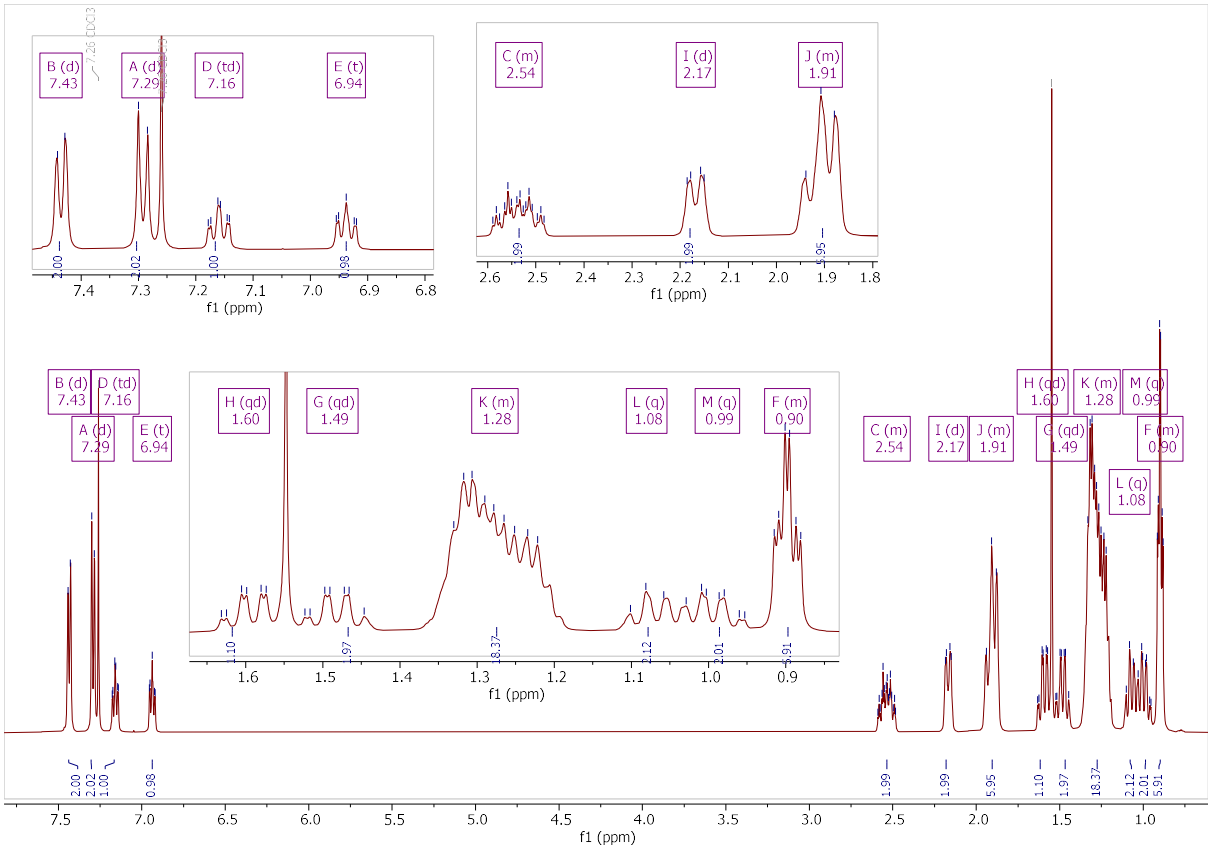


Figure S proton NMR spectrum of **5**

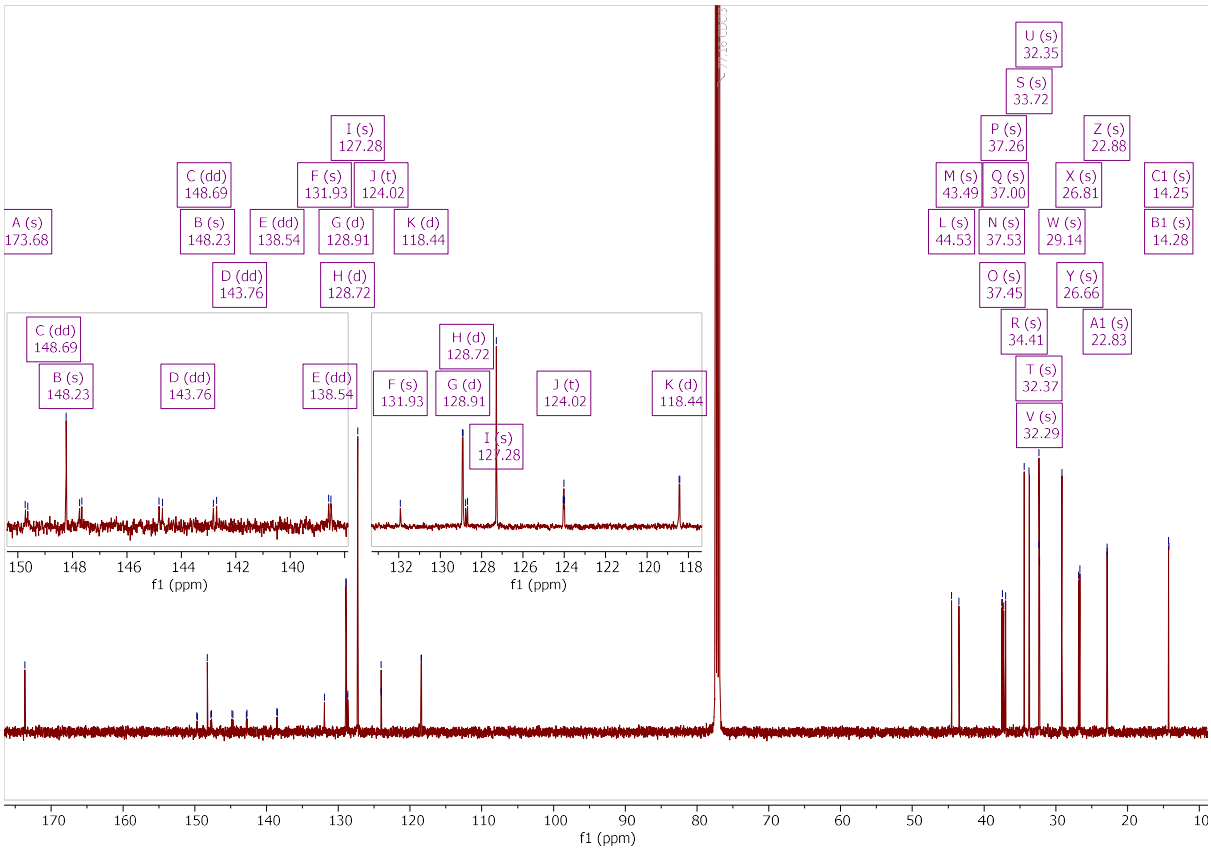


Figure S carbon NMR spectrum of **5**

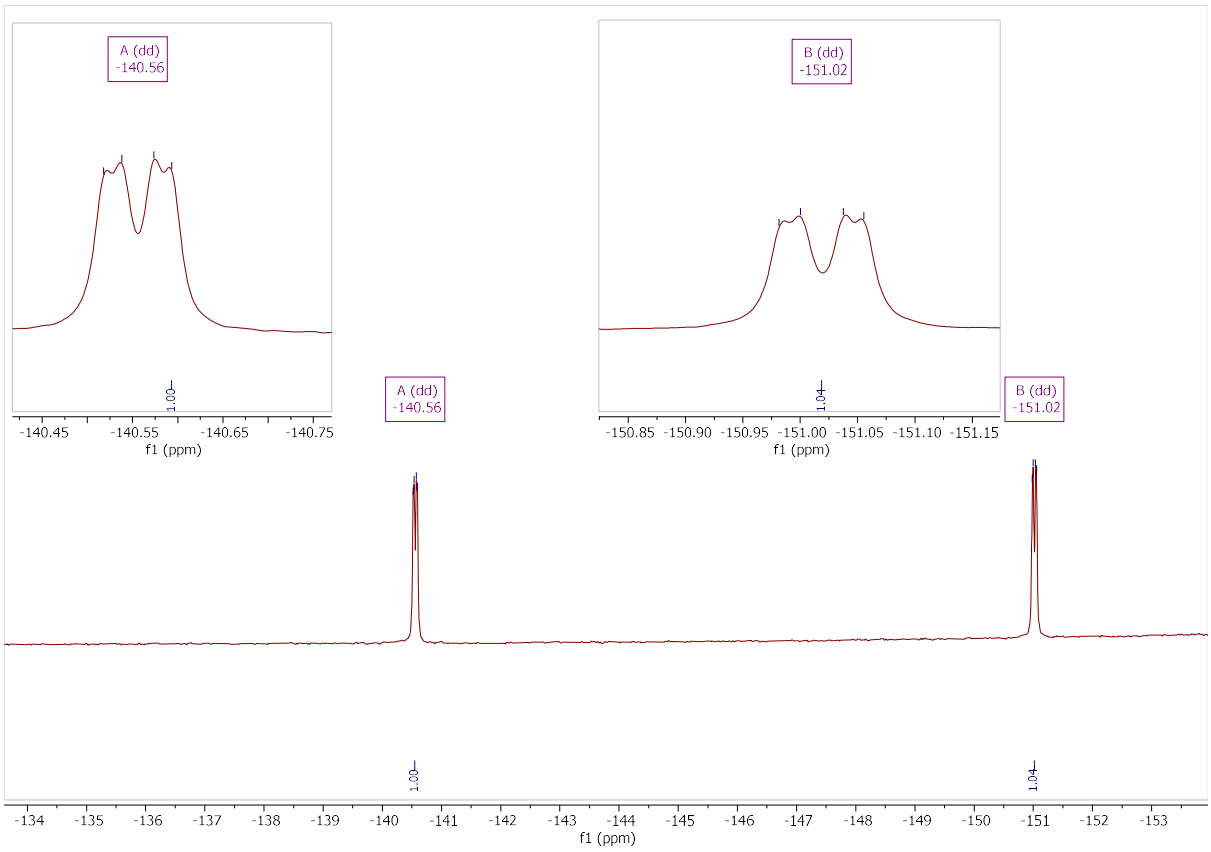
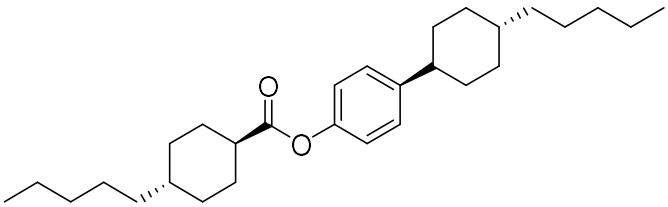


Figure S fluorine NMR spectrum of **5**

6 | *4-((1s,4R)-4-pentylcyclohexyl)phenyl (1s,4R)-4-pentylcyclohexane-1-carboxylate*



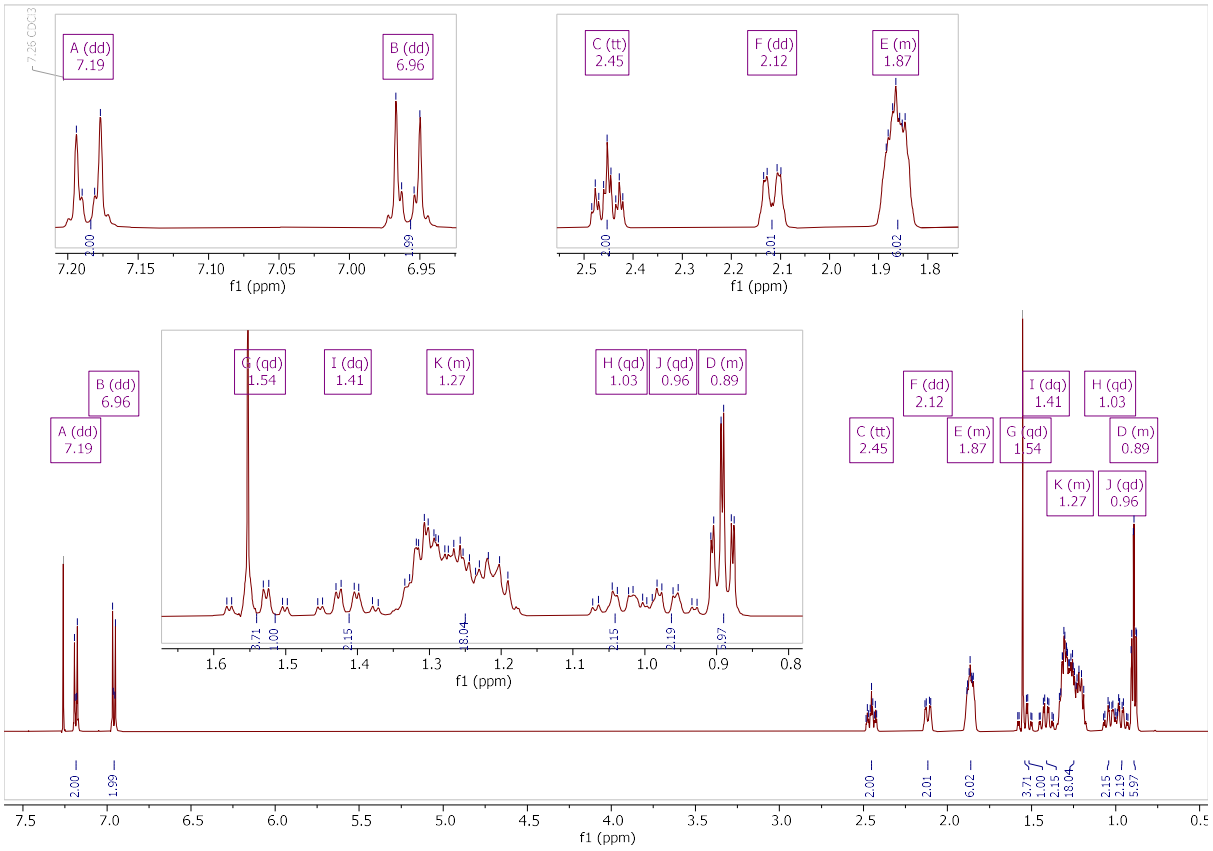


Figure S proton NMR spectrum of **6**

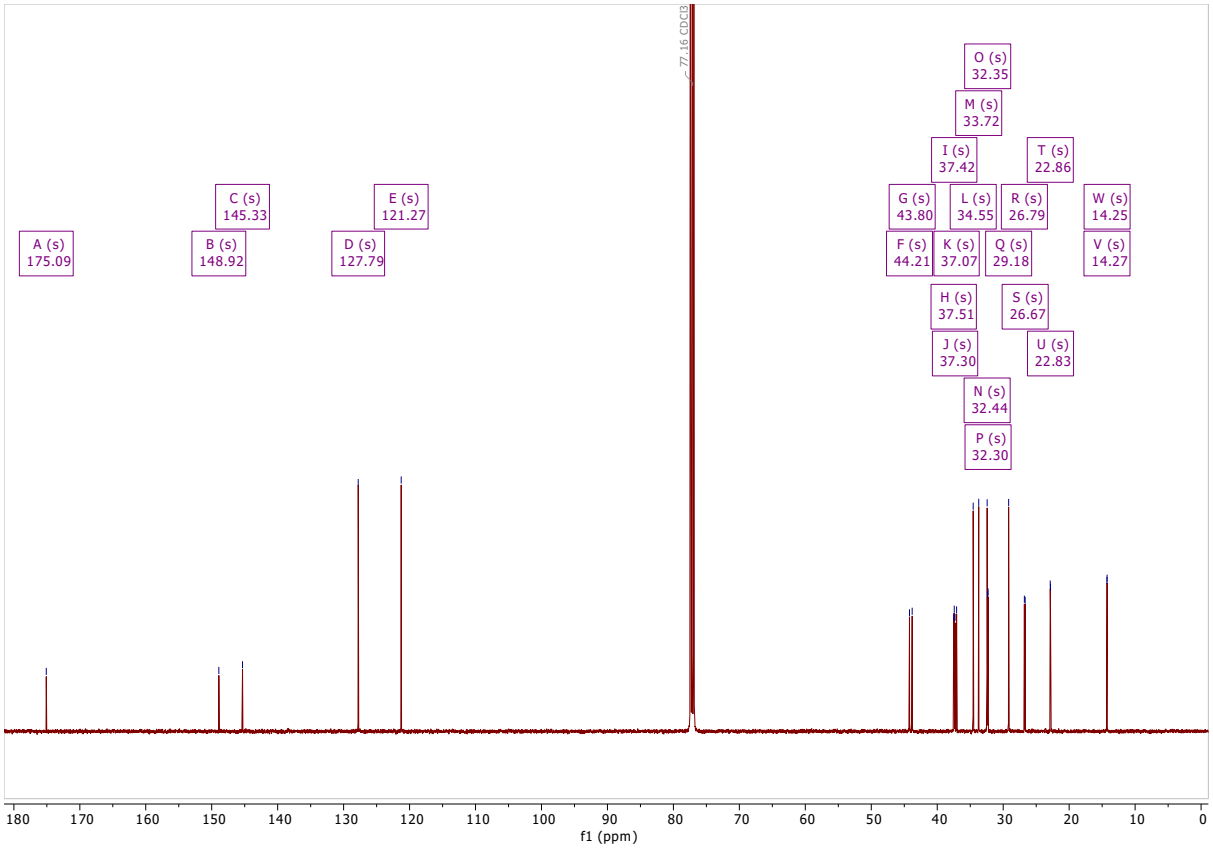


Figure S carbon NMR spectrum of **6**

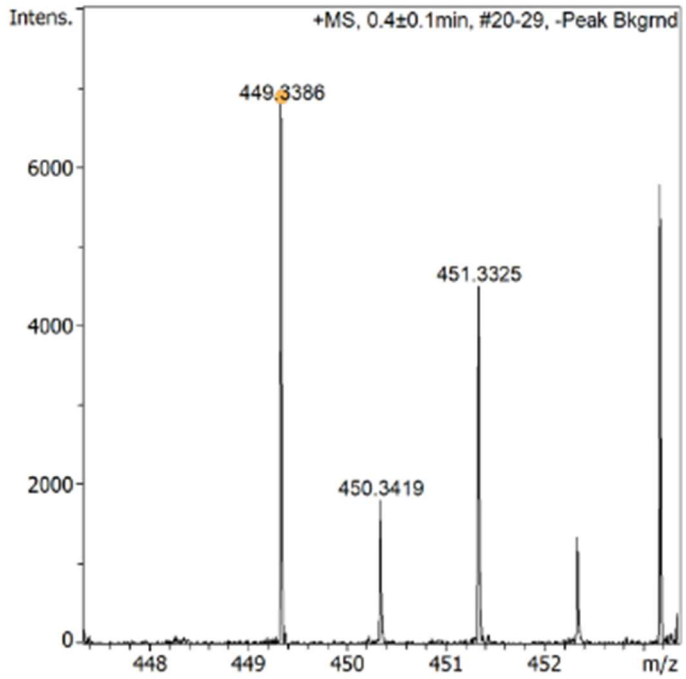


Figure S HRMS of **6**

7 | *4-cyanophenyl 4'-propyl-[1,1'-biphenyl]-4-carboxylate*

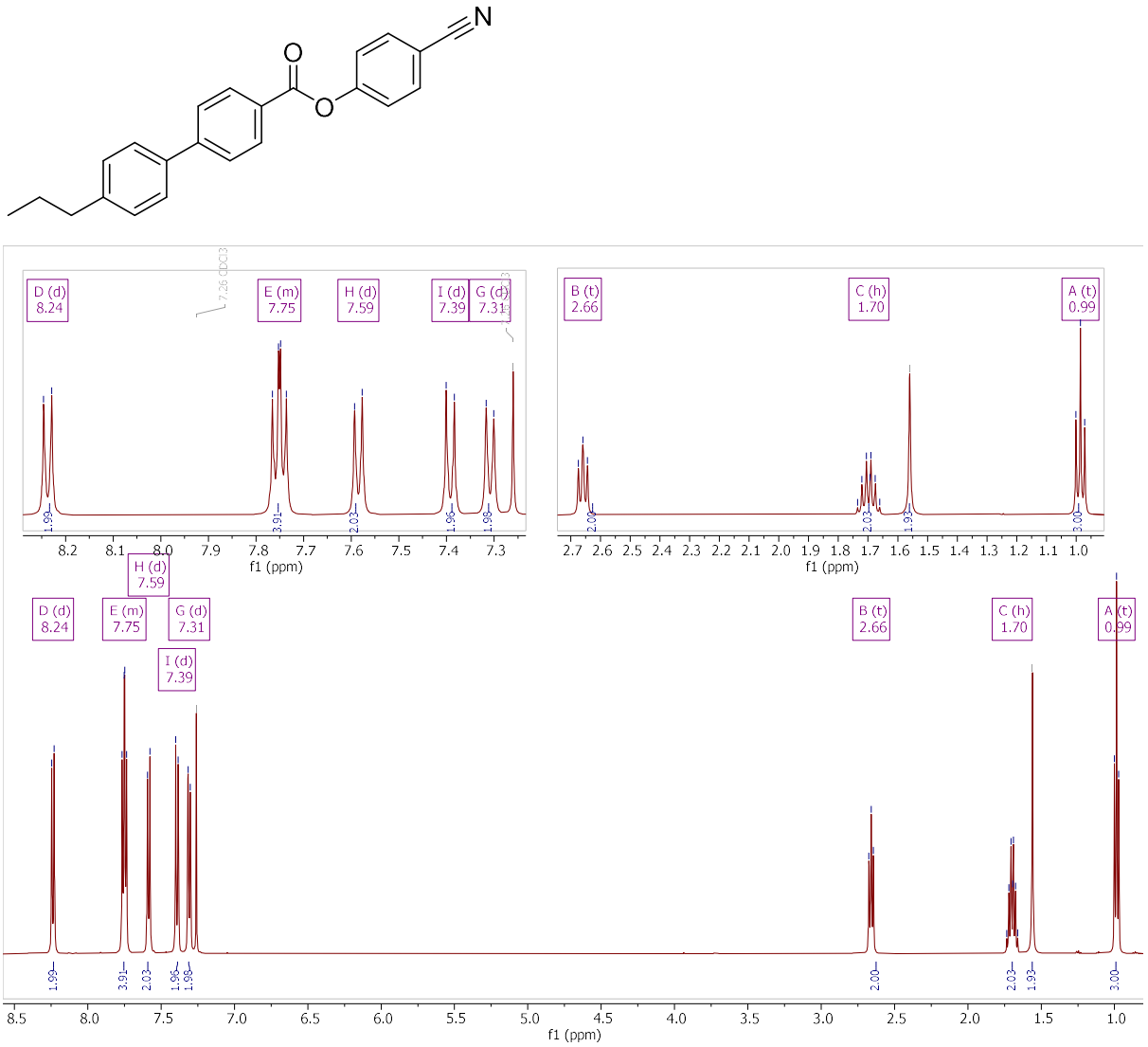


Figure S proton NMR spectrum of **7**

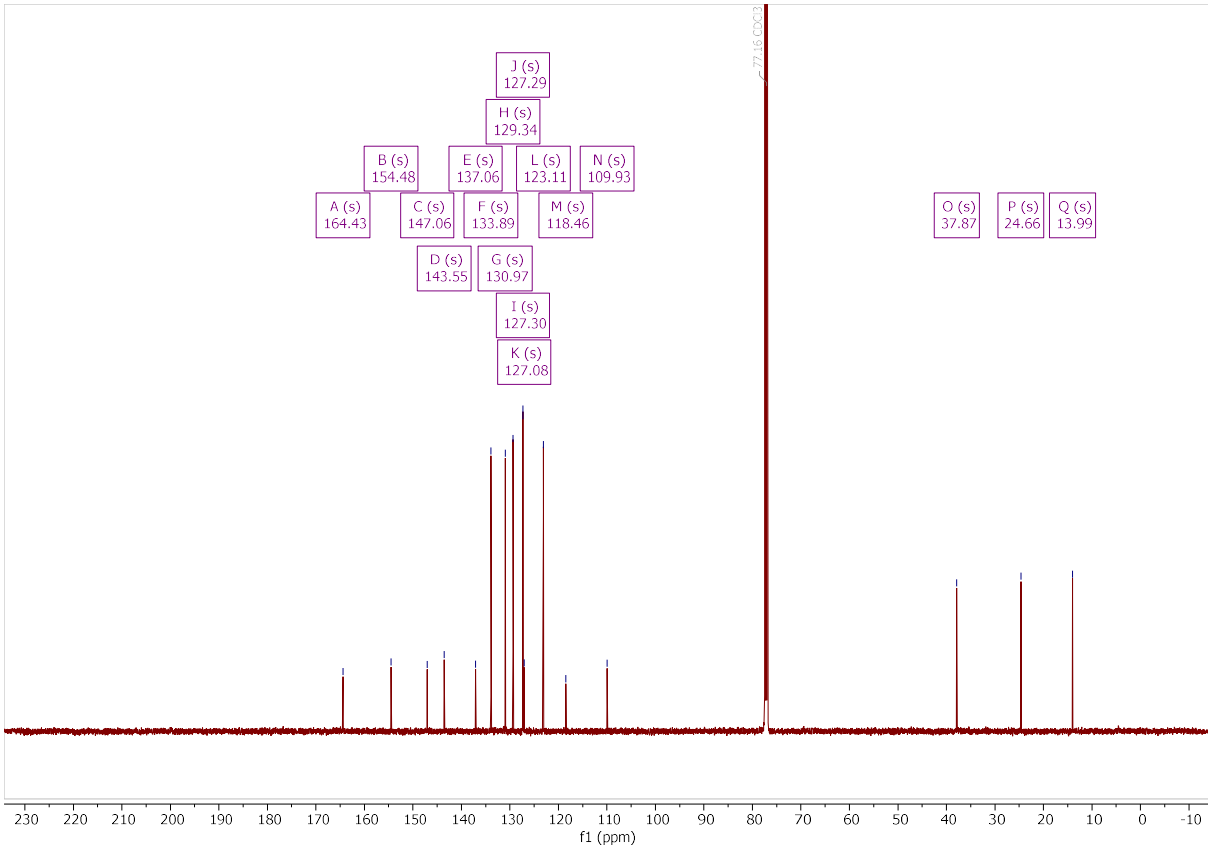
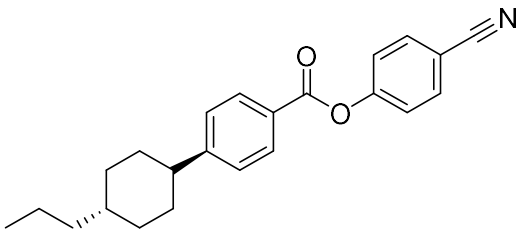


Figure S carbon NMR spectrum of **7**

8 | *4-cyanophenyl 4-((1s,4r)-4-propylcyclohexyl)benzoate*



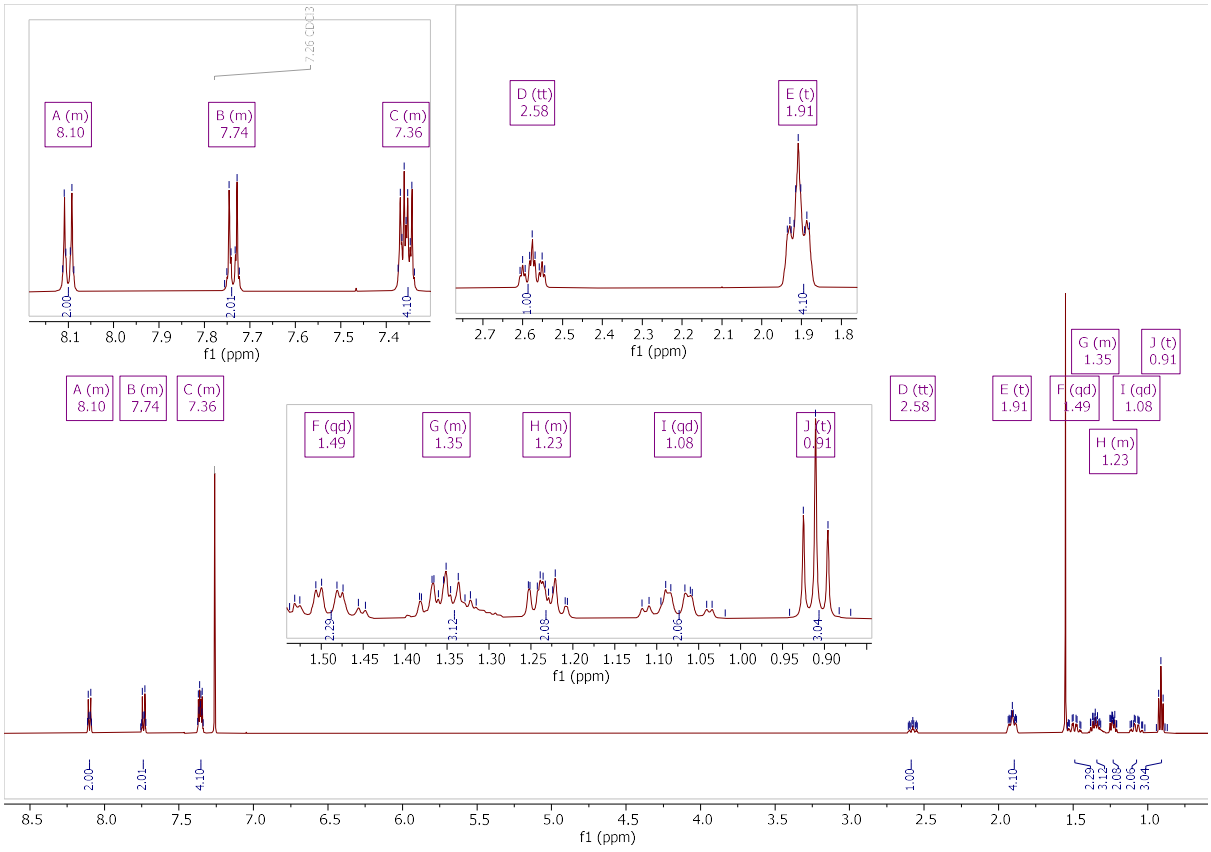


Figure S proton NMR spectrum of **8**

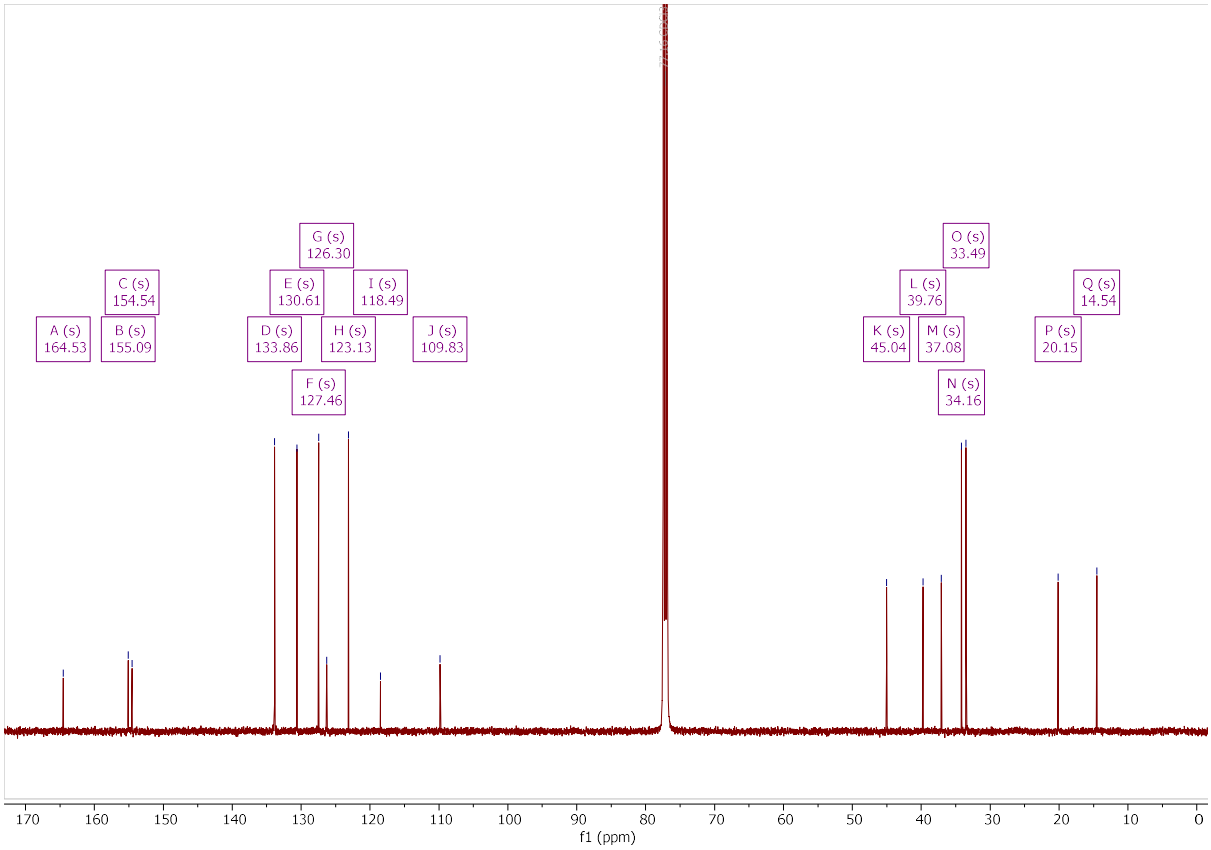
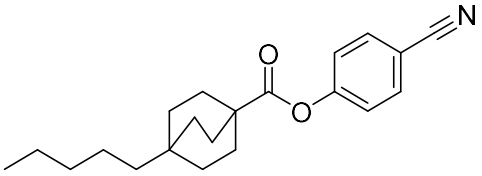


Figure S carbon NMR spectrum of **8**

9 | *4-cyanophenyl 4-pentylbicyclo[2.2.2]octane-1-carboxylate*



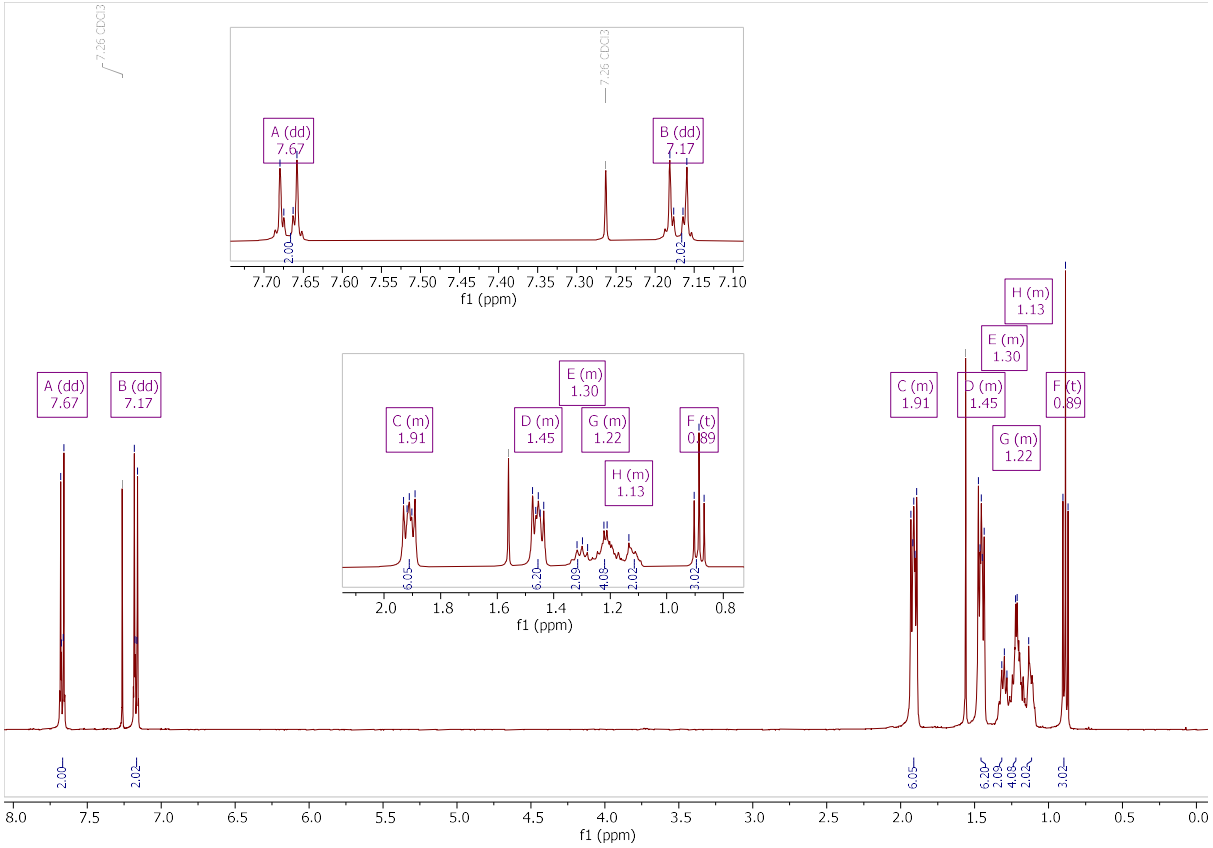


Figure S proton NMR spectrum of **9**

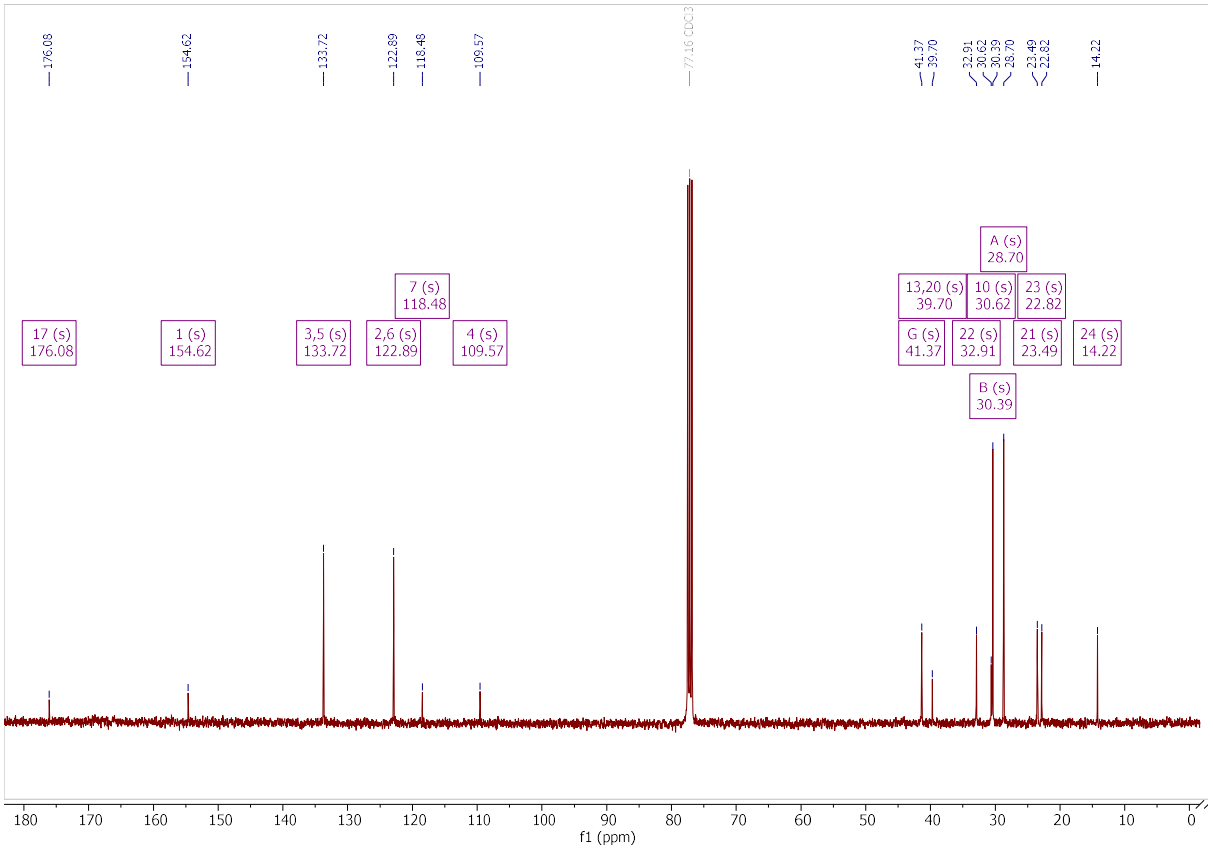


Figure S carbon NMR spectrum of **9**

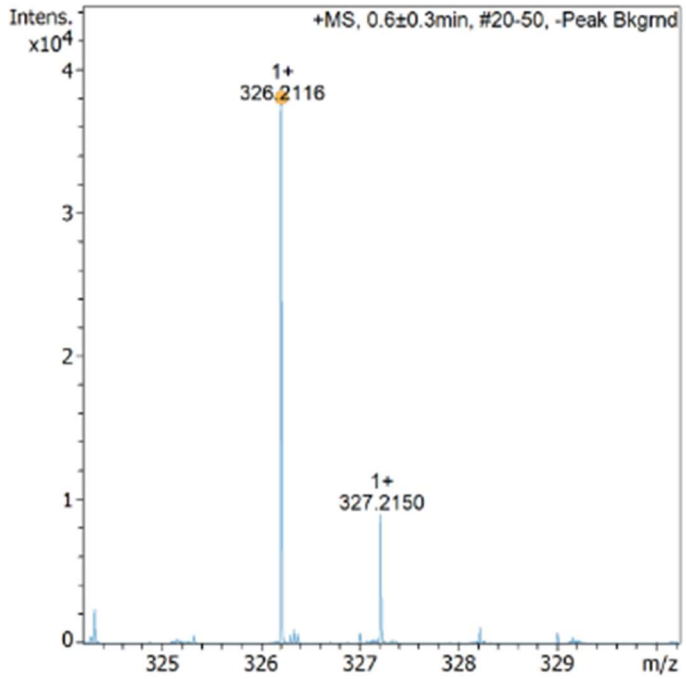
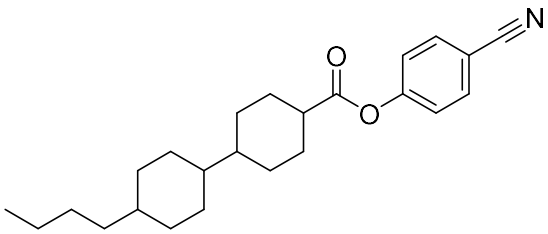


Figure S, HRMS of 9

10 | *4-cyanophenyl (1s,1'r,4S,4'S)-4'-butyl-[1,1'-bi(cyclohexane)]-4-carboxylate*



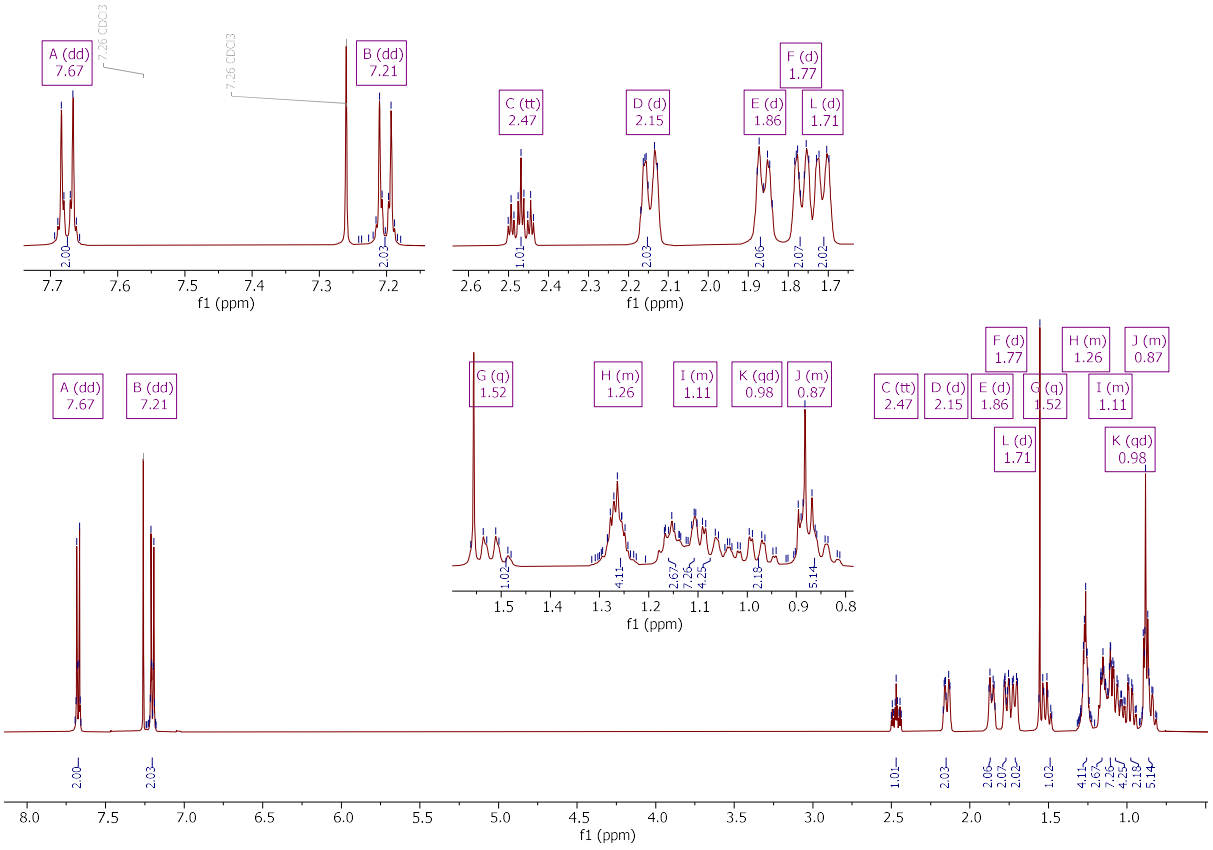


Figure S proton NMR spectrum of **10**

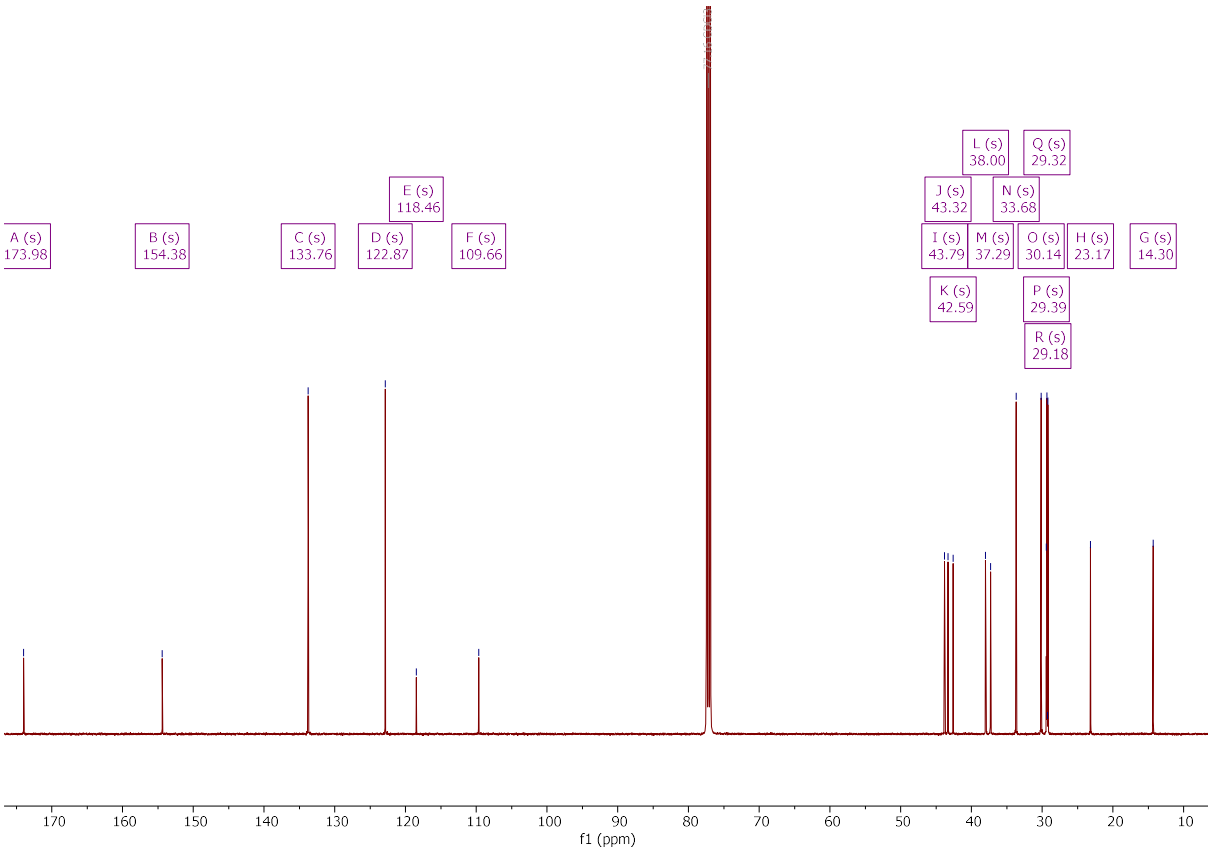


Figure S carbon NMR spectrum of **10**

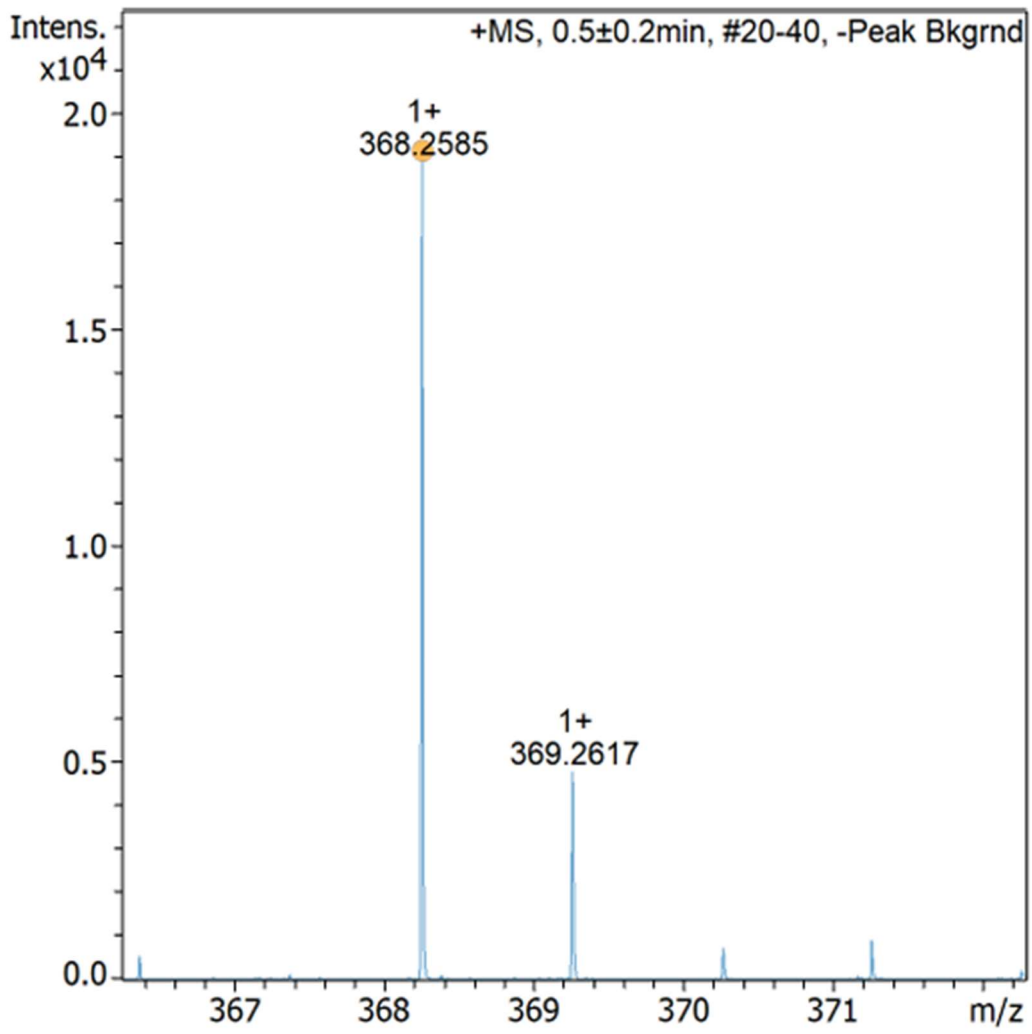
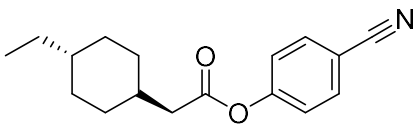


Figure S HRMS of **10**

11 | *4-cyanobenzyl (1r,4r)-4-ethylcyclohexane-1-carboxylate*



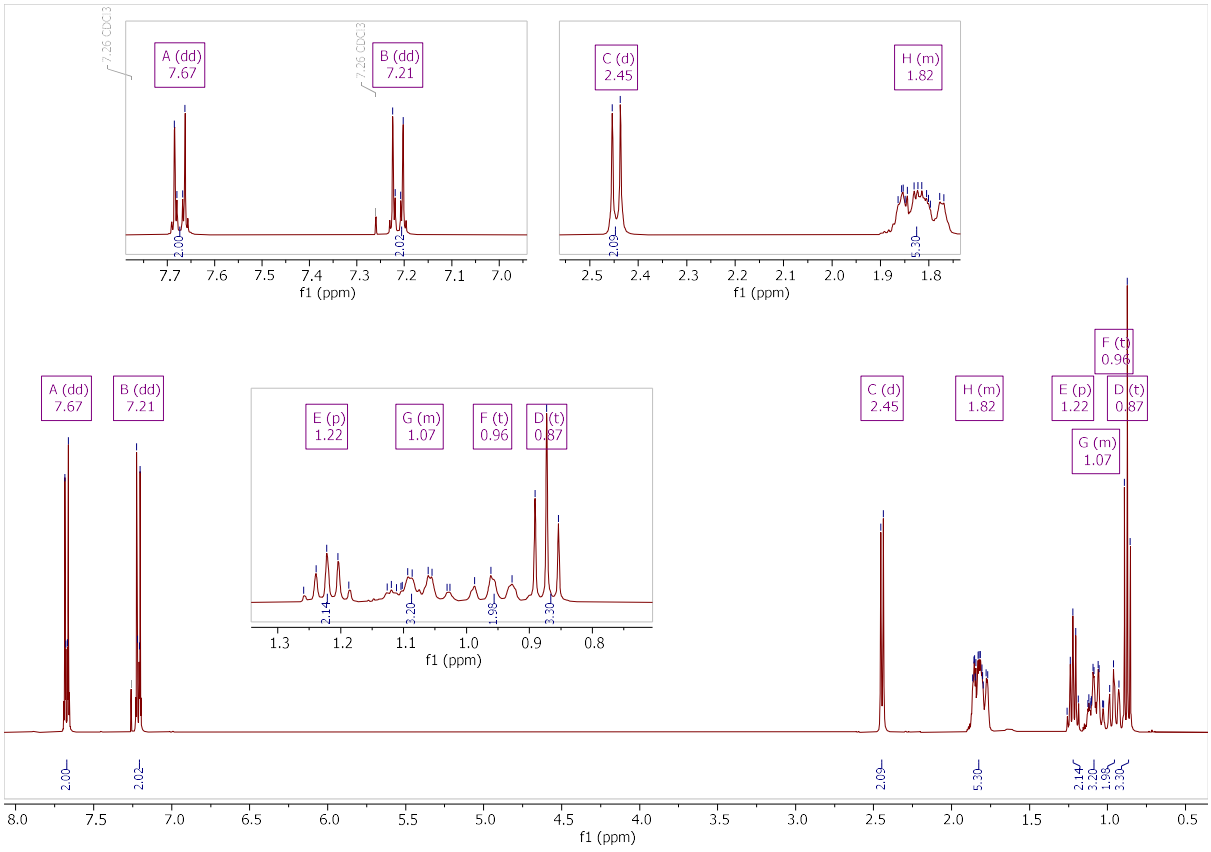


Figure S proton NMR spectrum of **11**

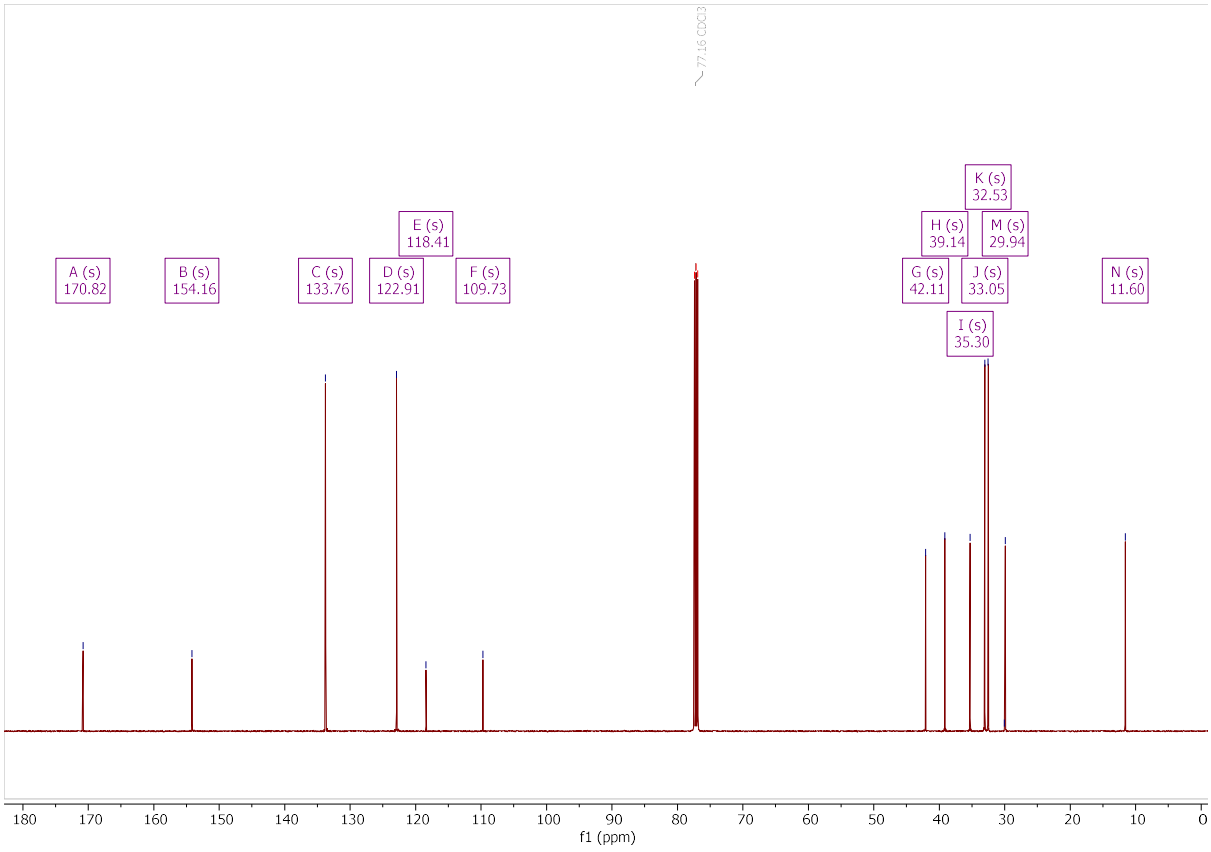
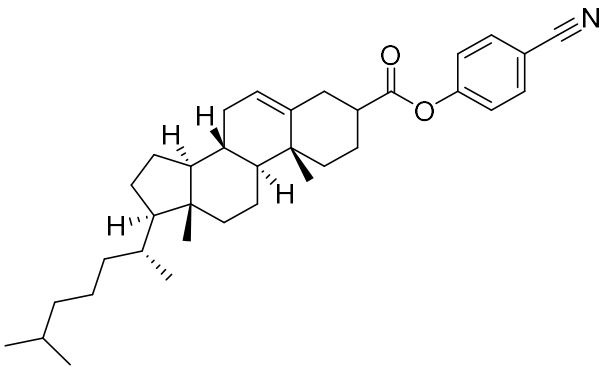


Figure S carbon NMR spectrum of **11**

12 | *4'-cyanophenyl cholesteroate*



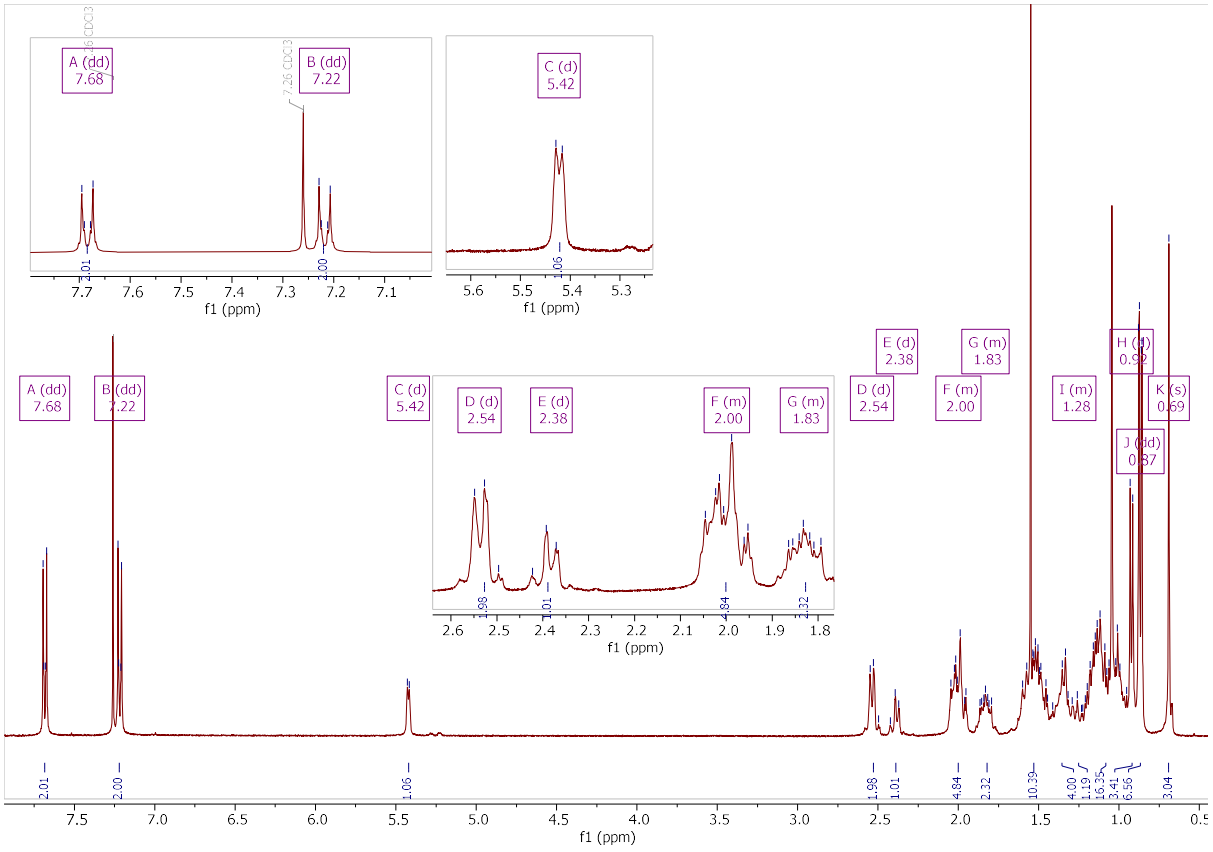


Figure S proton NMR spectrum of **12**

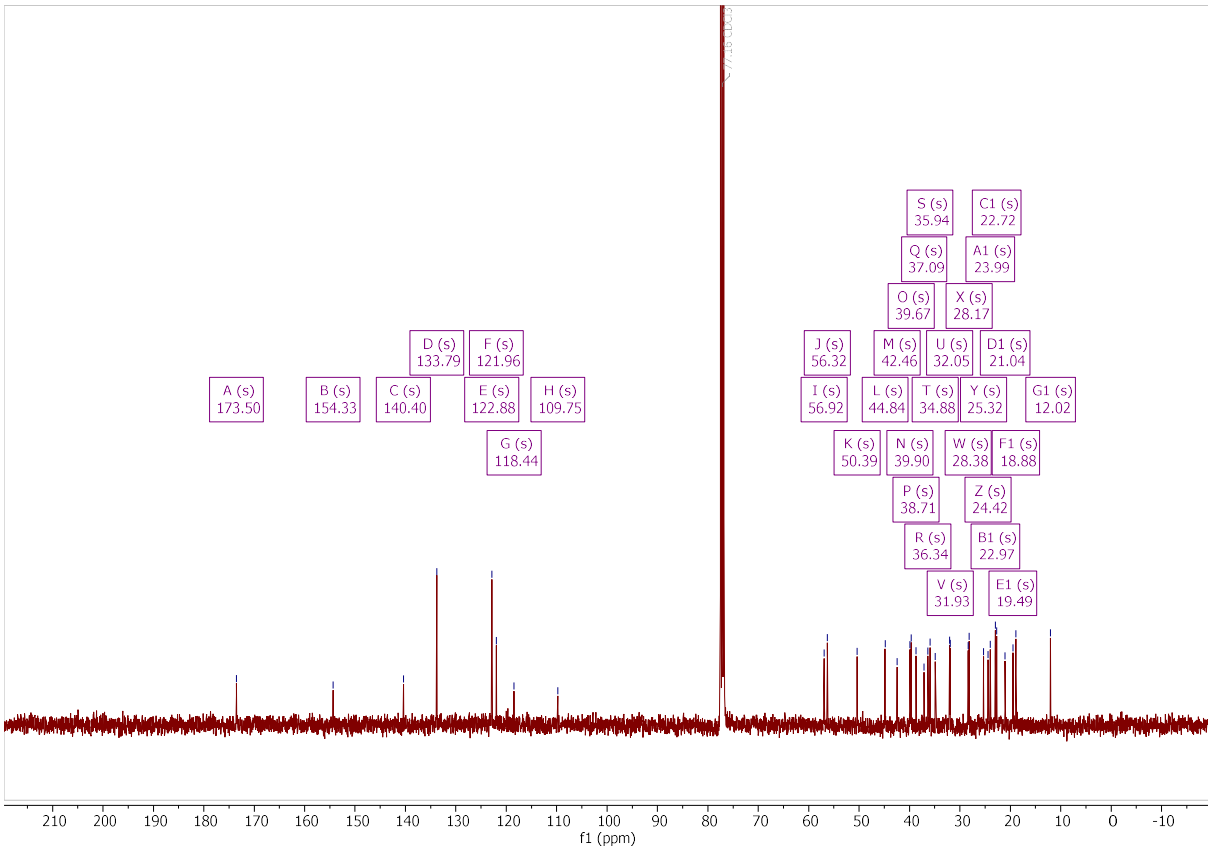


Figure S carbon NMR spectrum of **12**

13 | *4'-cyano-2-fluoro-[1,1'-biphenyl]-4-yl 4-butoxybenzoate*

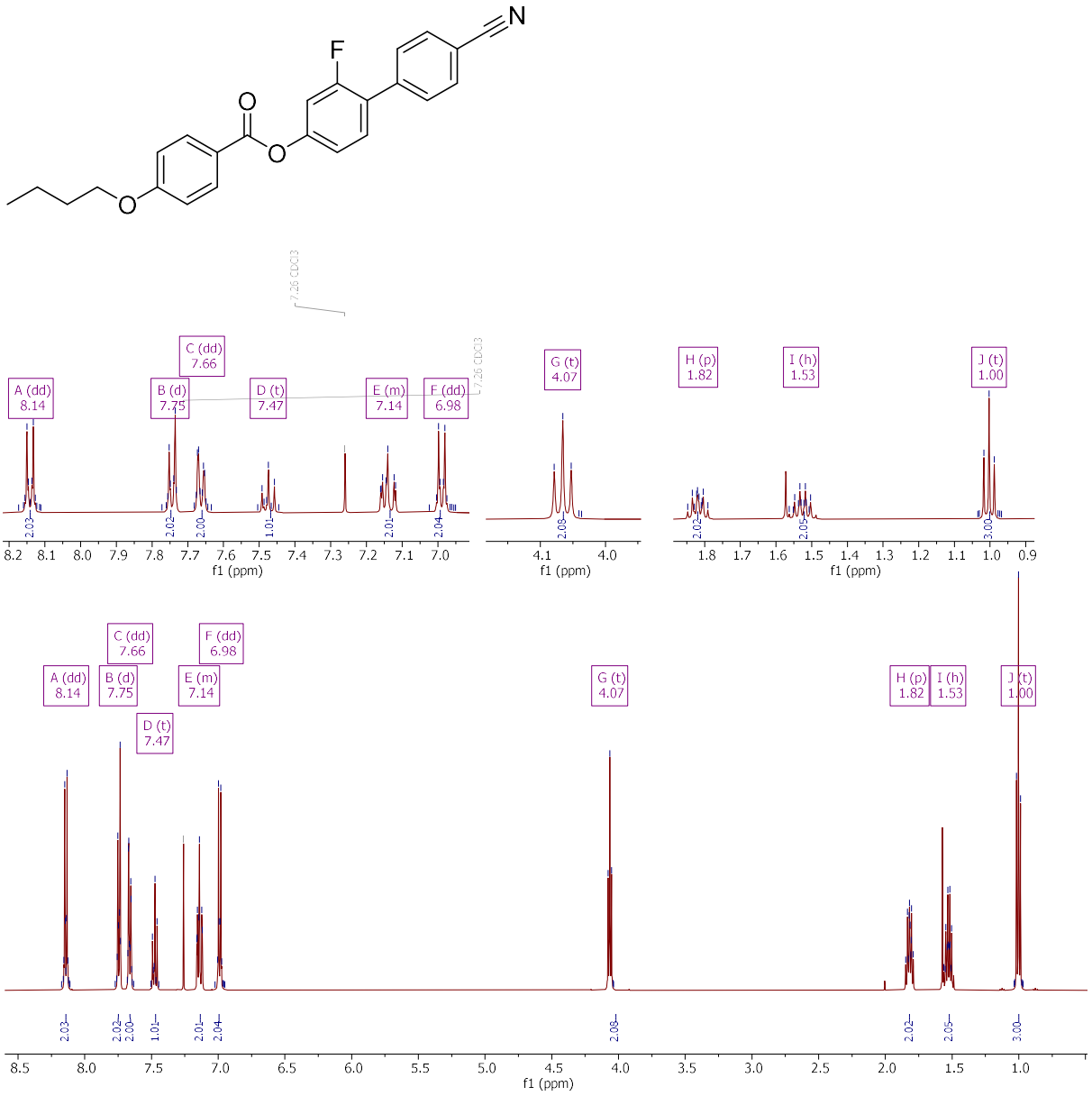


Figure S proton NMR spectrum of **13**

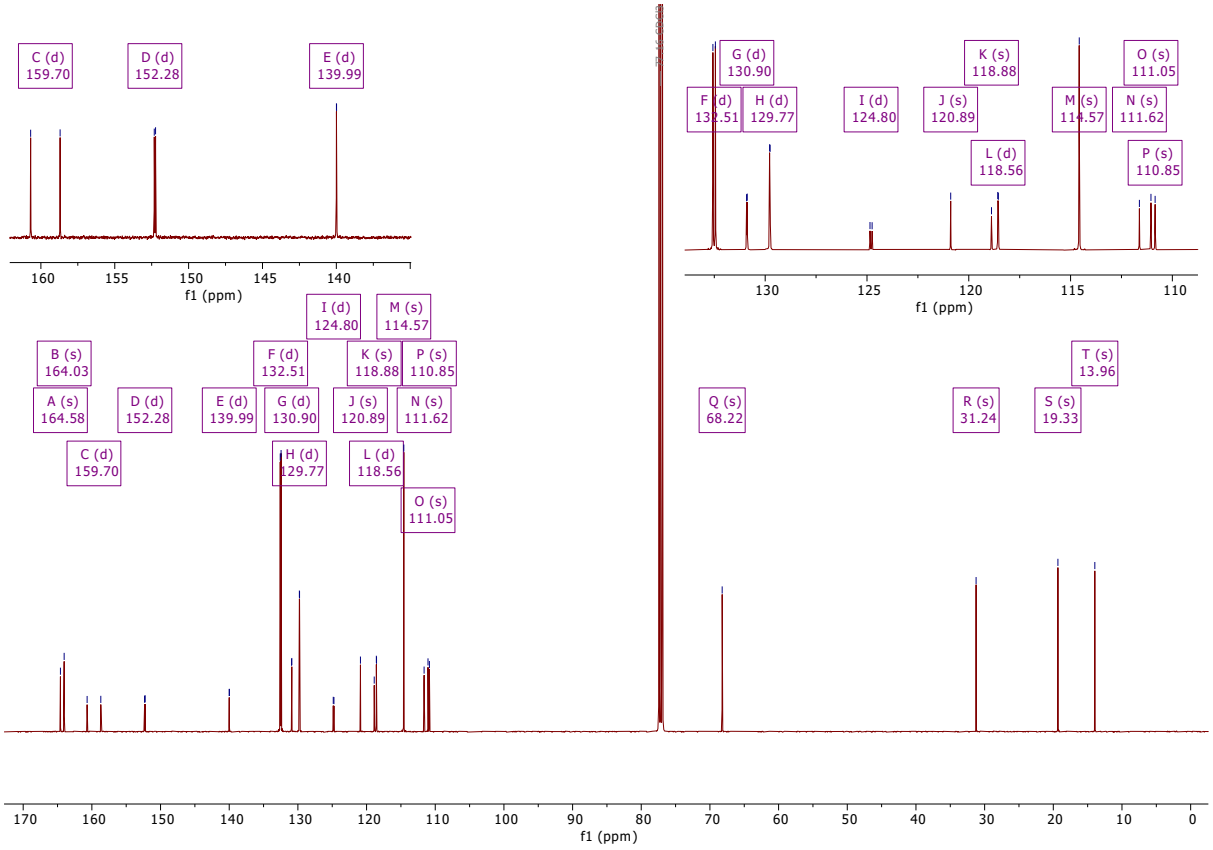


Figure S carbon NMR spectrum of **13**

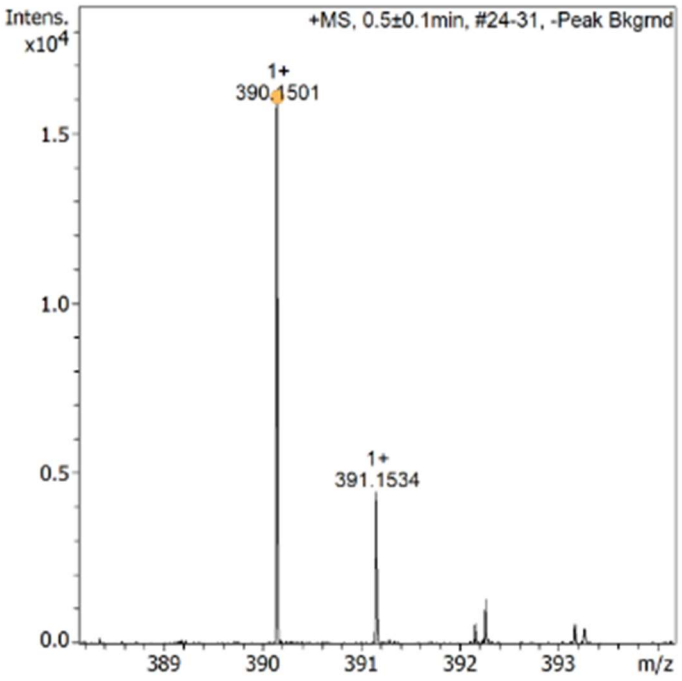


Figure S HRMS of **13**

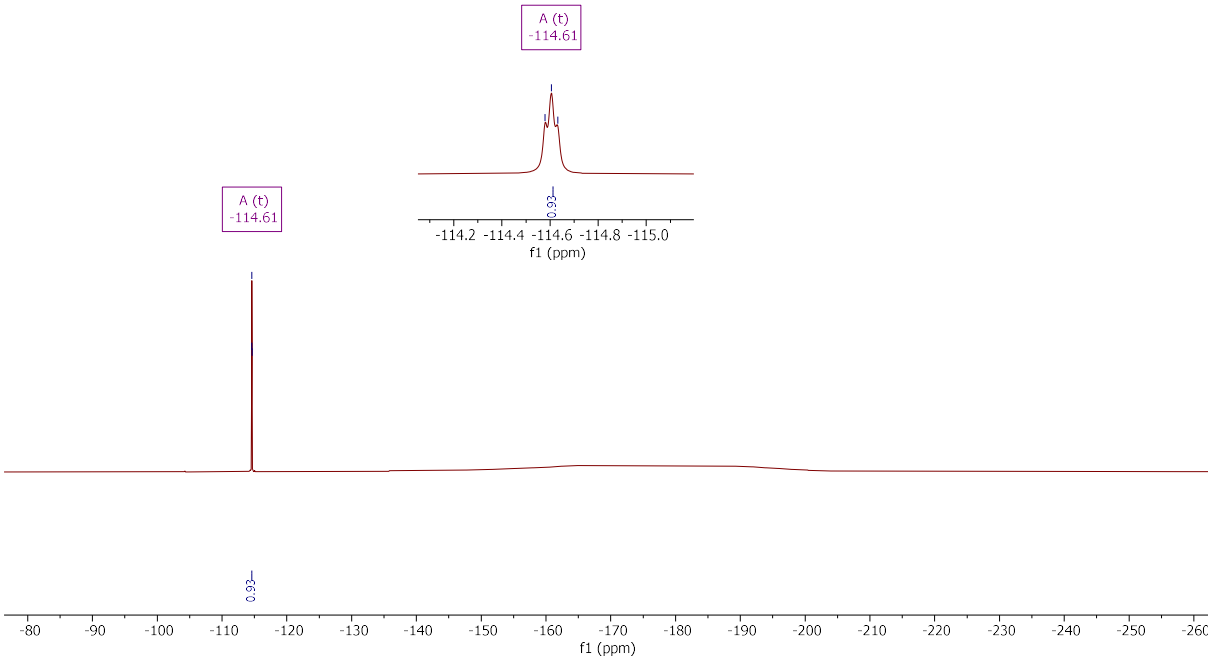
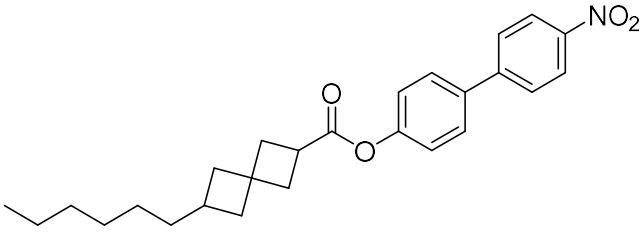


Figure S32 fluorine NMR spectrum of **13**

14 | *4'-nitro-[1,1'-biphenyl]-4-yl 6-hexylspiro[3.3]heptane-2-carboxylate*



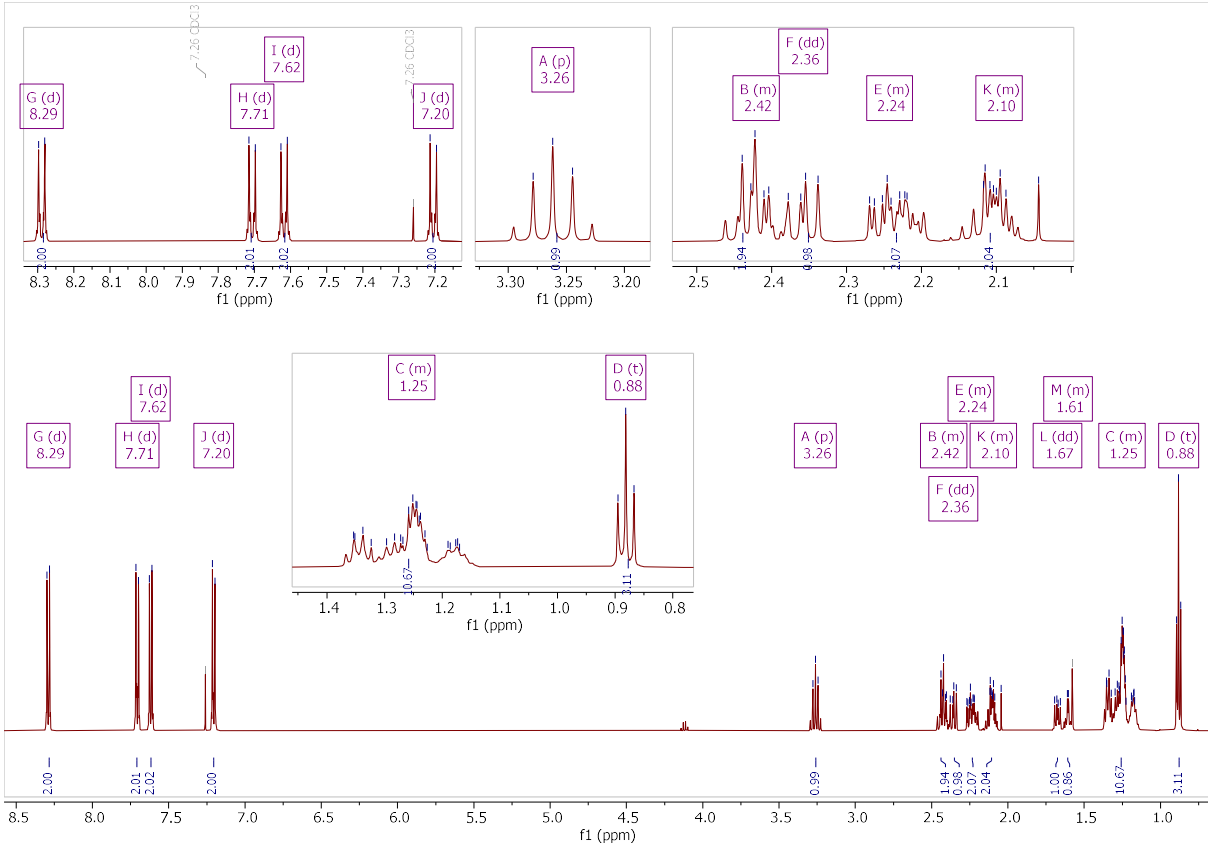


Figure S proton NMR spectrum of **14**

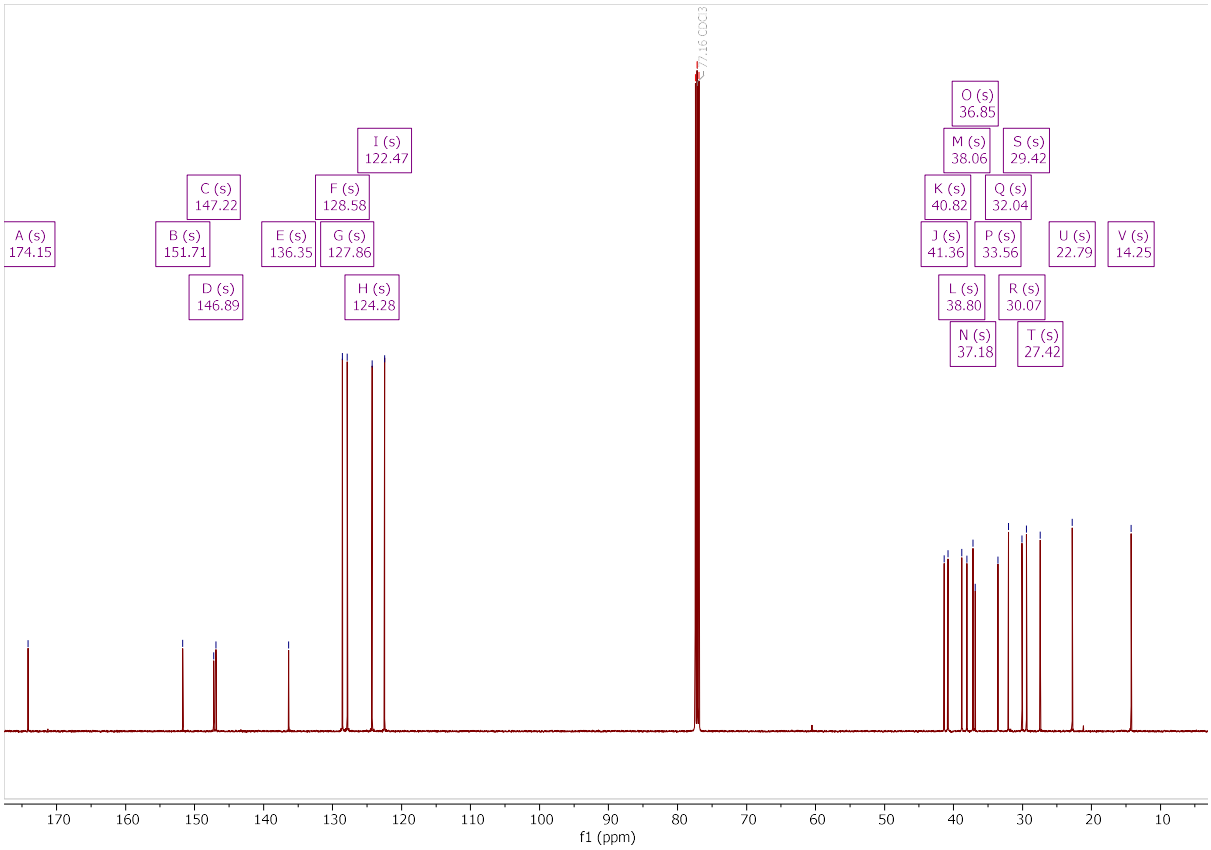
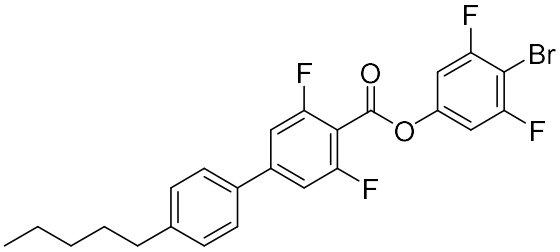


Figure S carbon NMR spectrum of **14**

15 | *4-bromo-3,5-difluorophenyl 3,5-difluoro-4'-pentyl-[1,1'-biphenyl]-4-carboxylate*



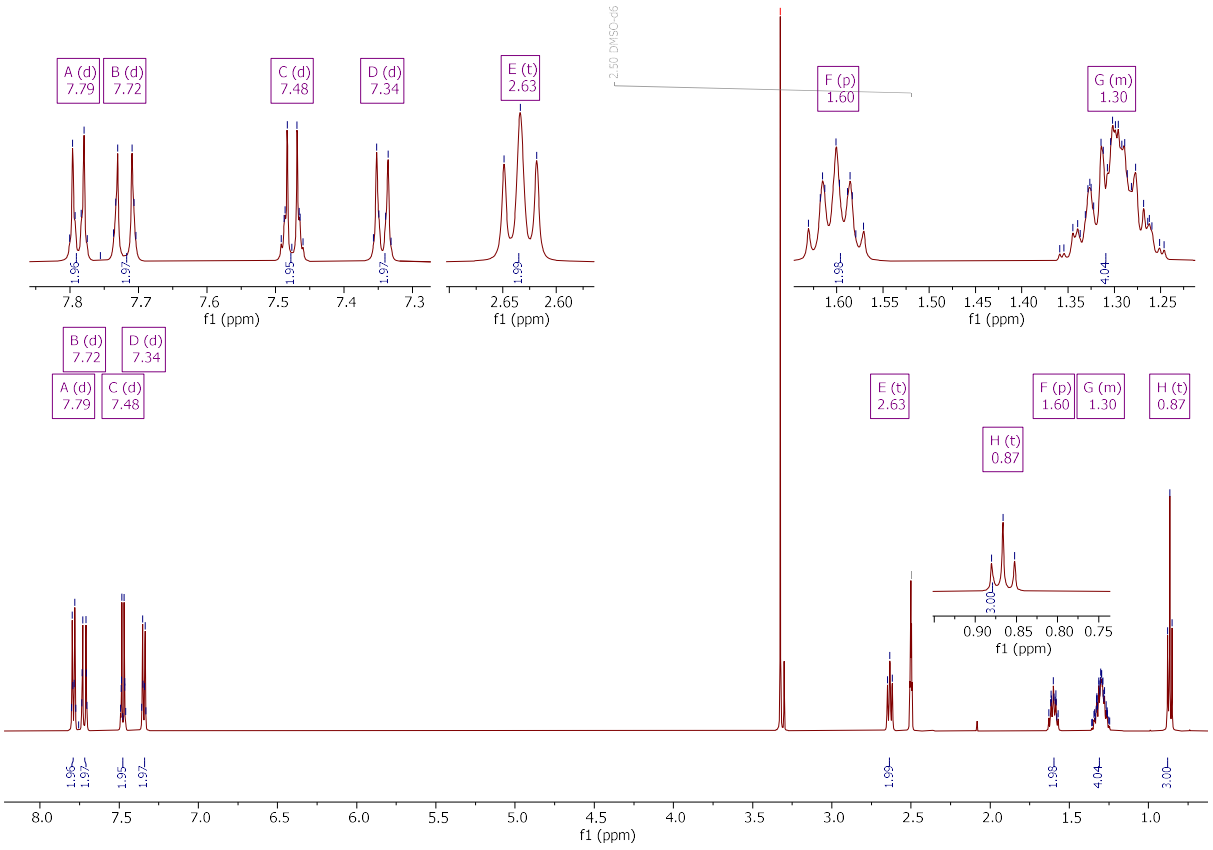


Figure S proton NMR spectrum of **15**

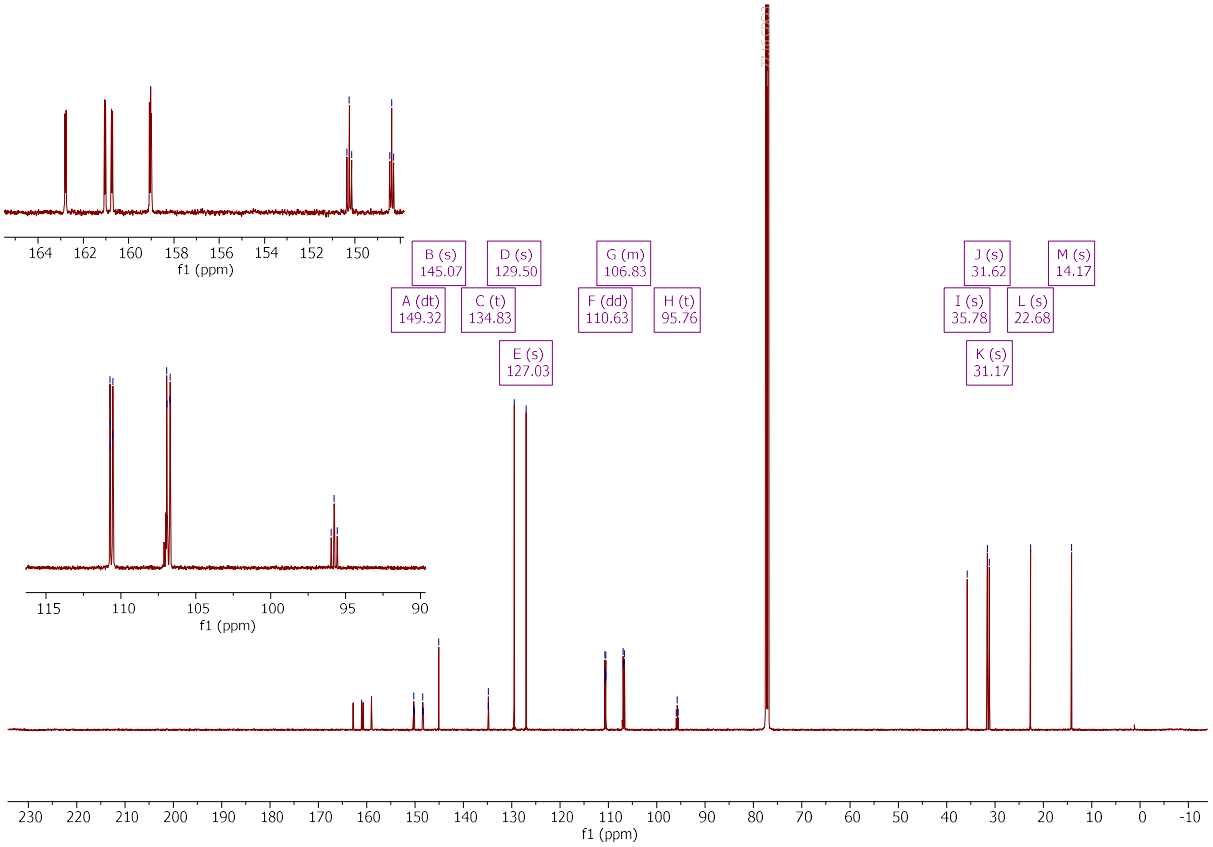


Figure S carbon NMR spectrum of **15.** Overlapping C=O, and Ar-F bonds do not have multiple labels but are recorded in data set in section 3.

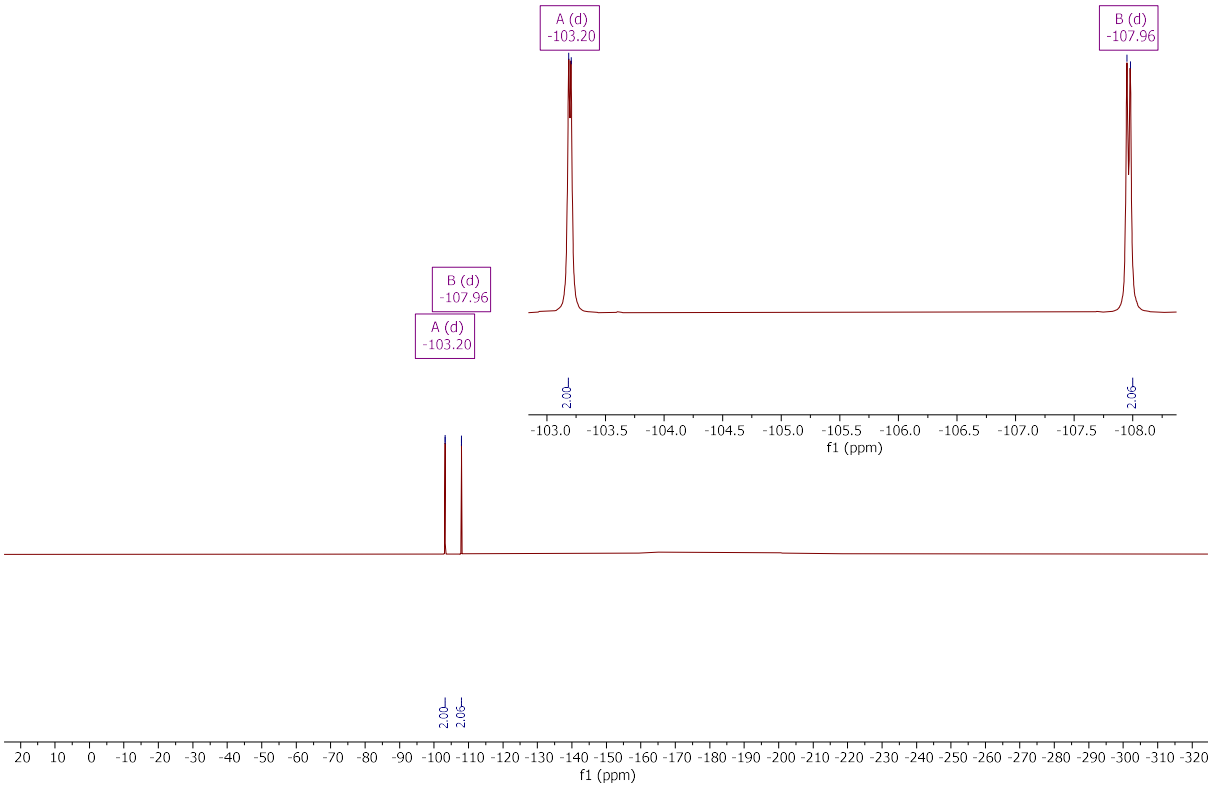


Figure S fluorine NMR spectrum of **15**

16 | *(E)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl 6-methoxy-2-naphthoate*

Figure S proton NMR spectrum of **16**

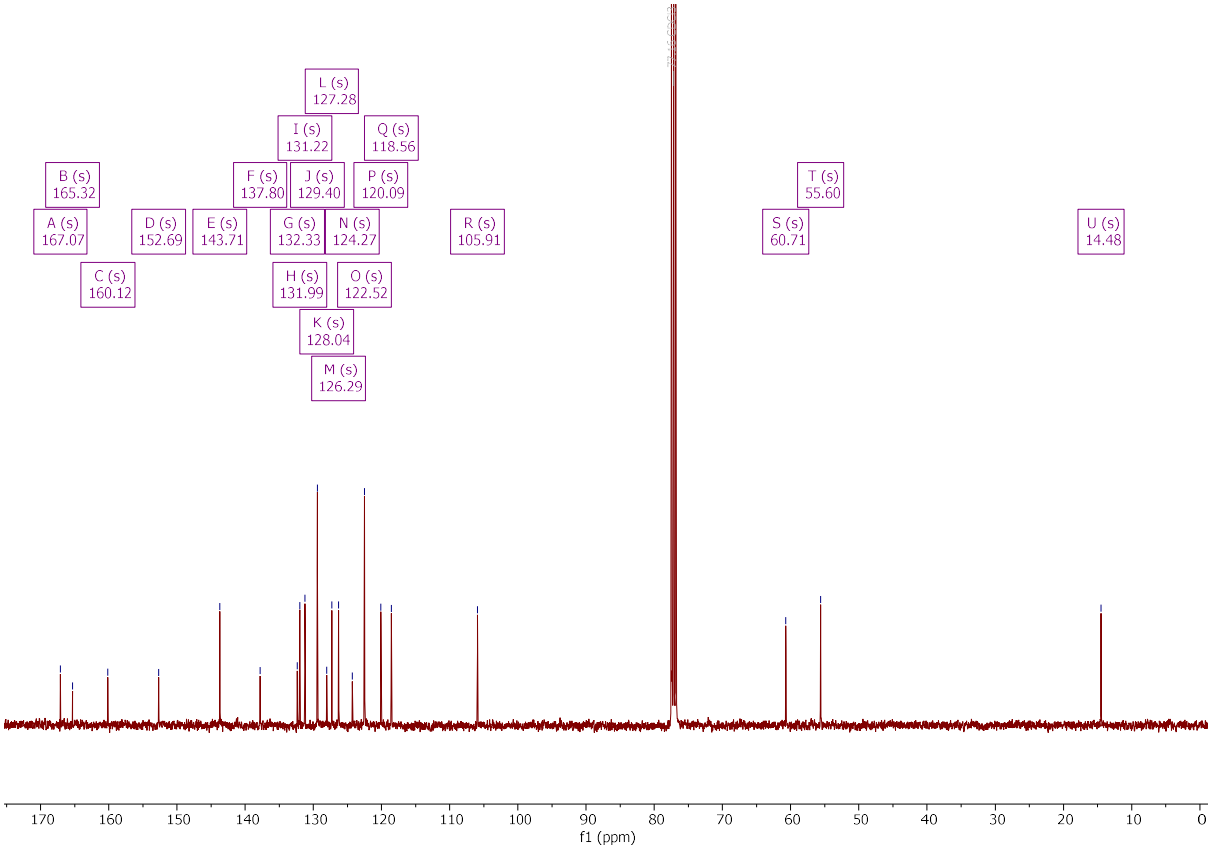


Figure S carbon NMR spectrum of **16**

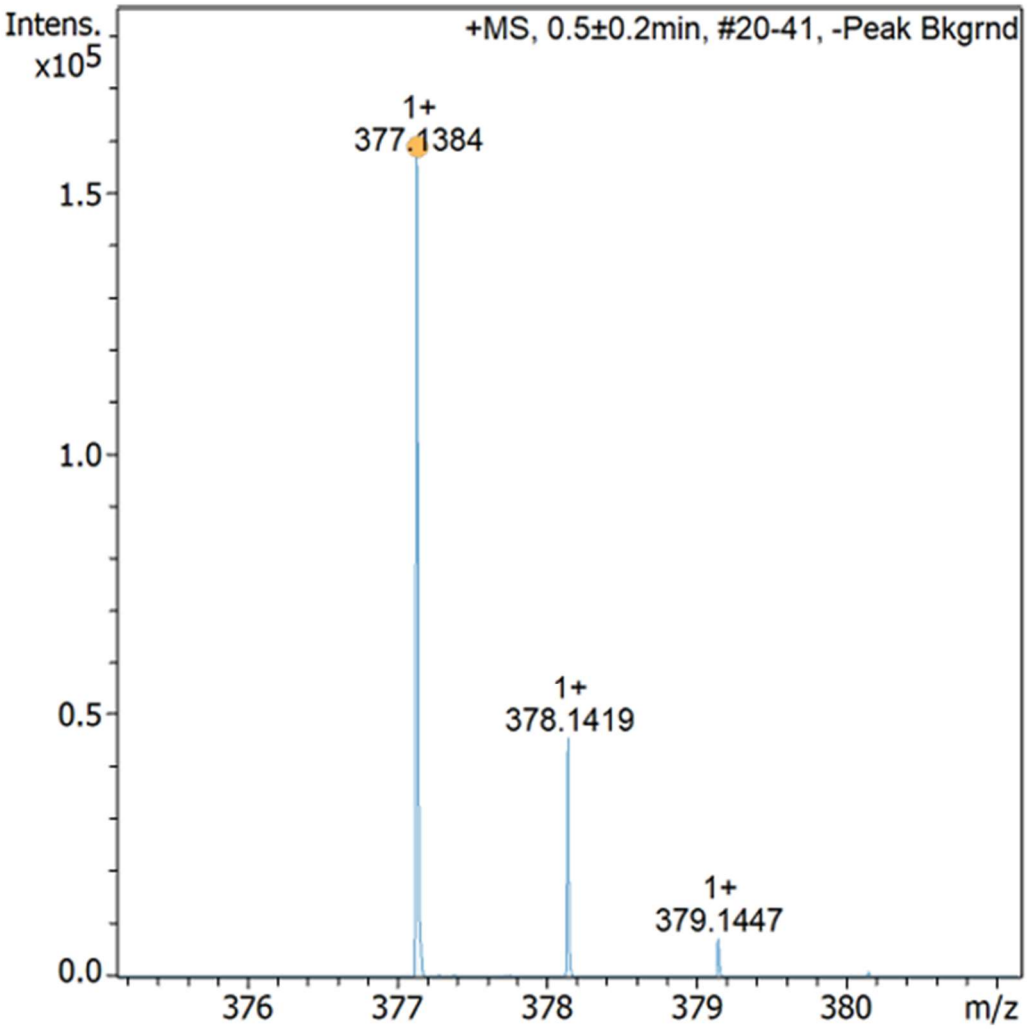
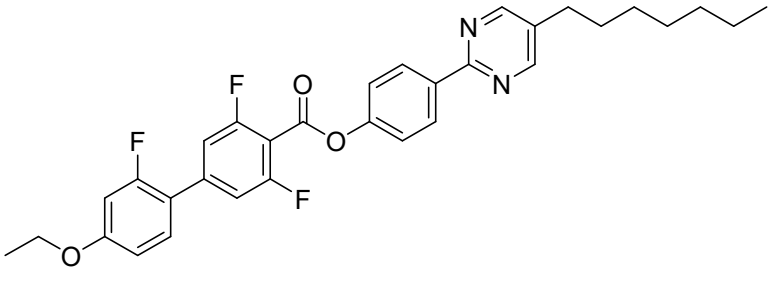


Figure S HRMS of **16**

17 | *4-(5-heptylpyrimidin-2-yl)phenyl 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylate*



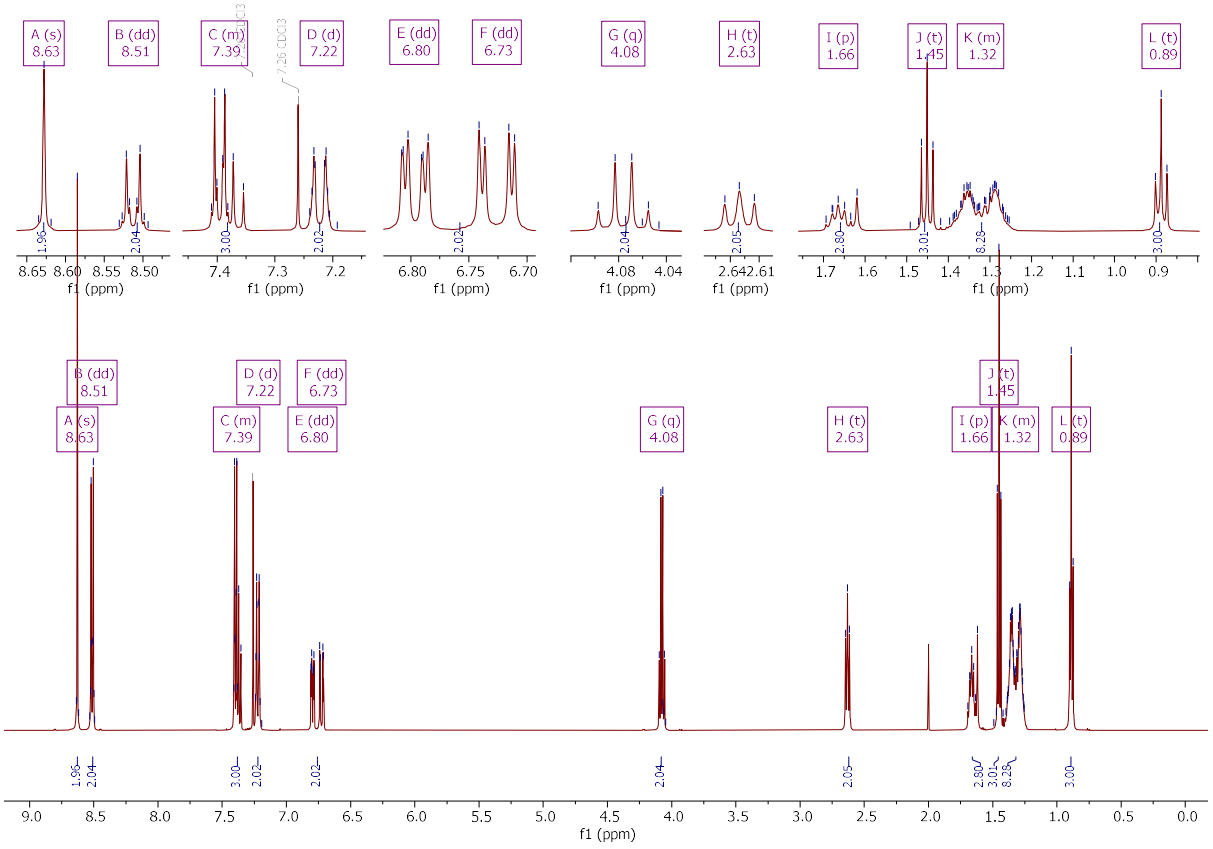


Figure S proton NMR spectrum of **17**

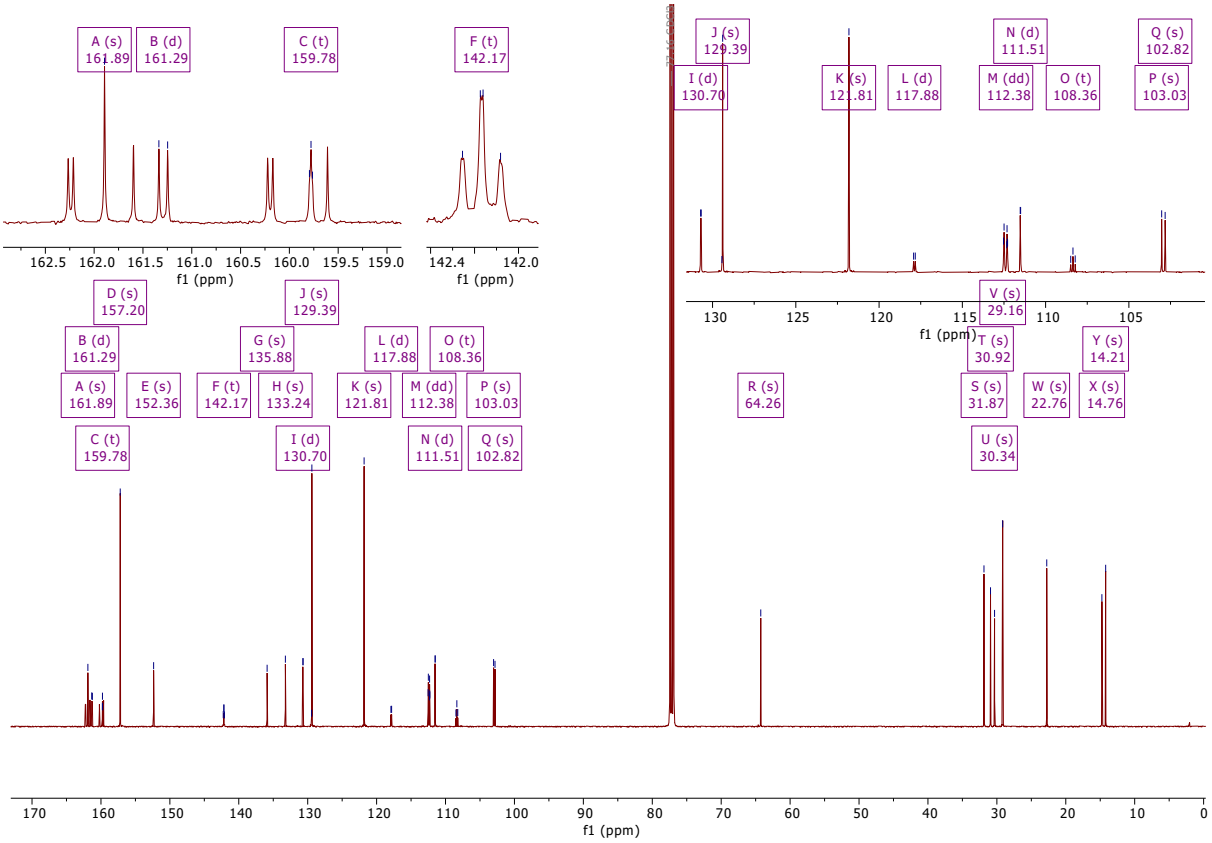


Figure S carbon NMR spectrum of **17.** Overlapping C=O, and Ar-F bonds do not have multiple labels but are recorded in data set in section 3.

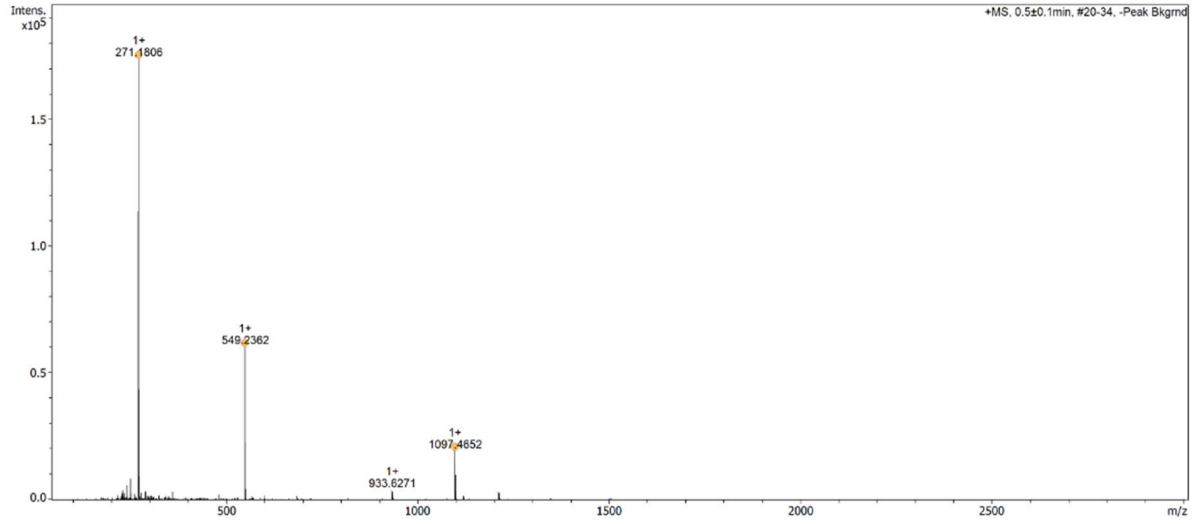


Figure S HRMS of **17**

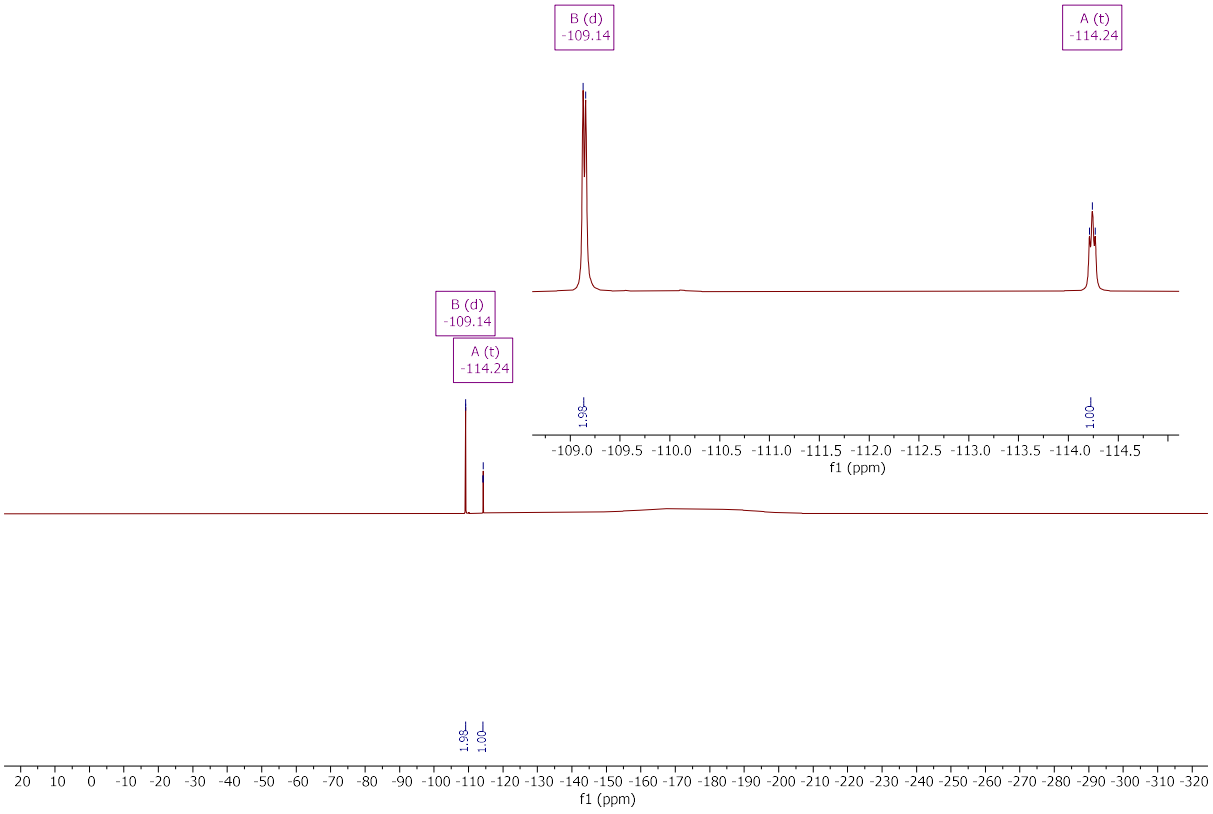
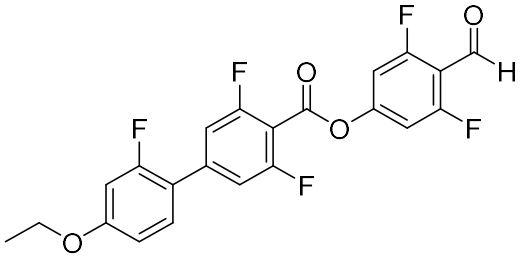


Figure S fluorine NMR spectrum of **17**

18 | *3,5-difluoro-4-formylphenyl 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylate*



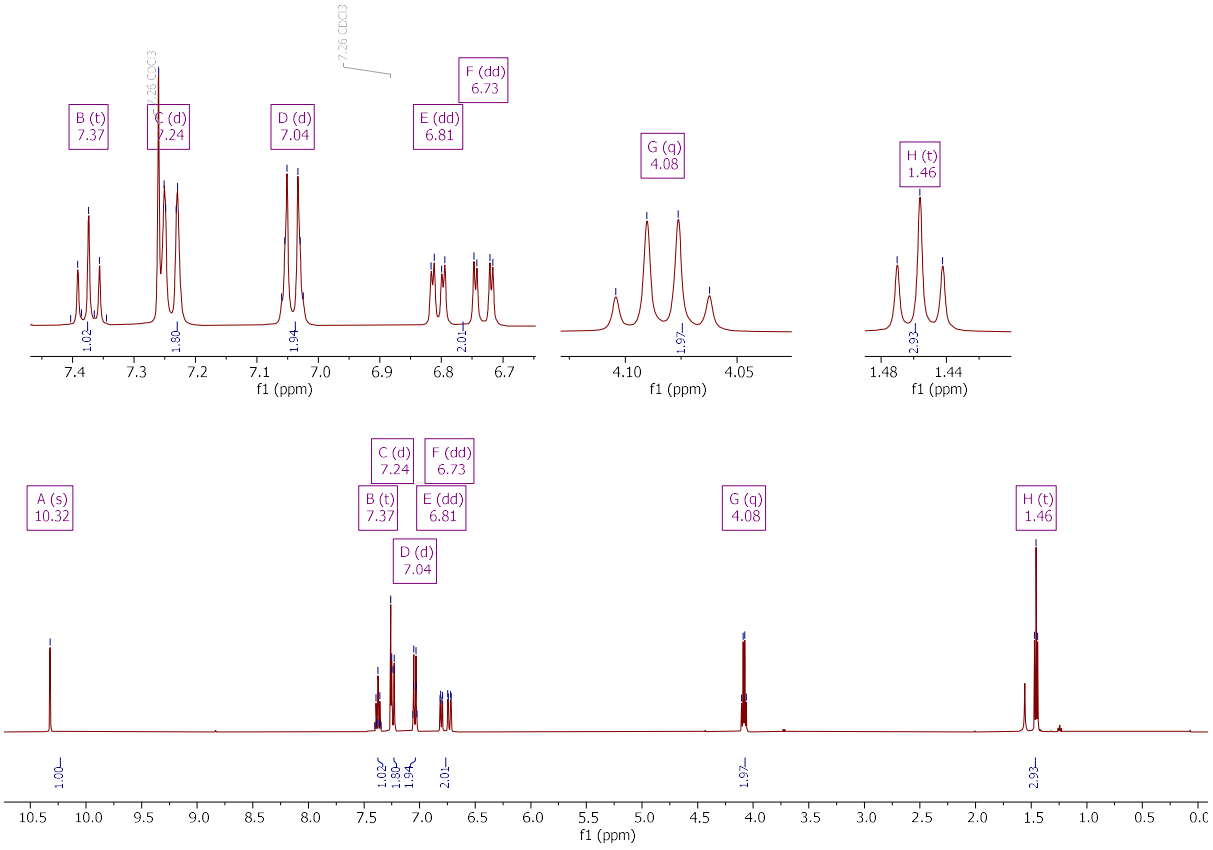


Figure S proton NMR spectrum of **18**

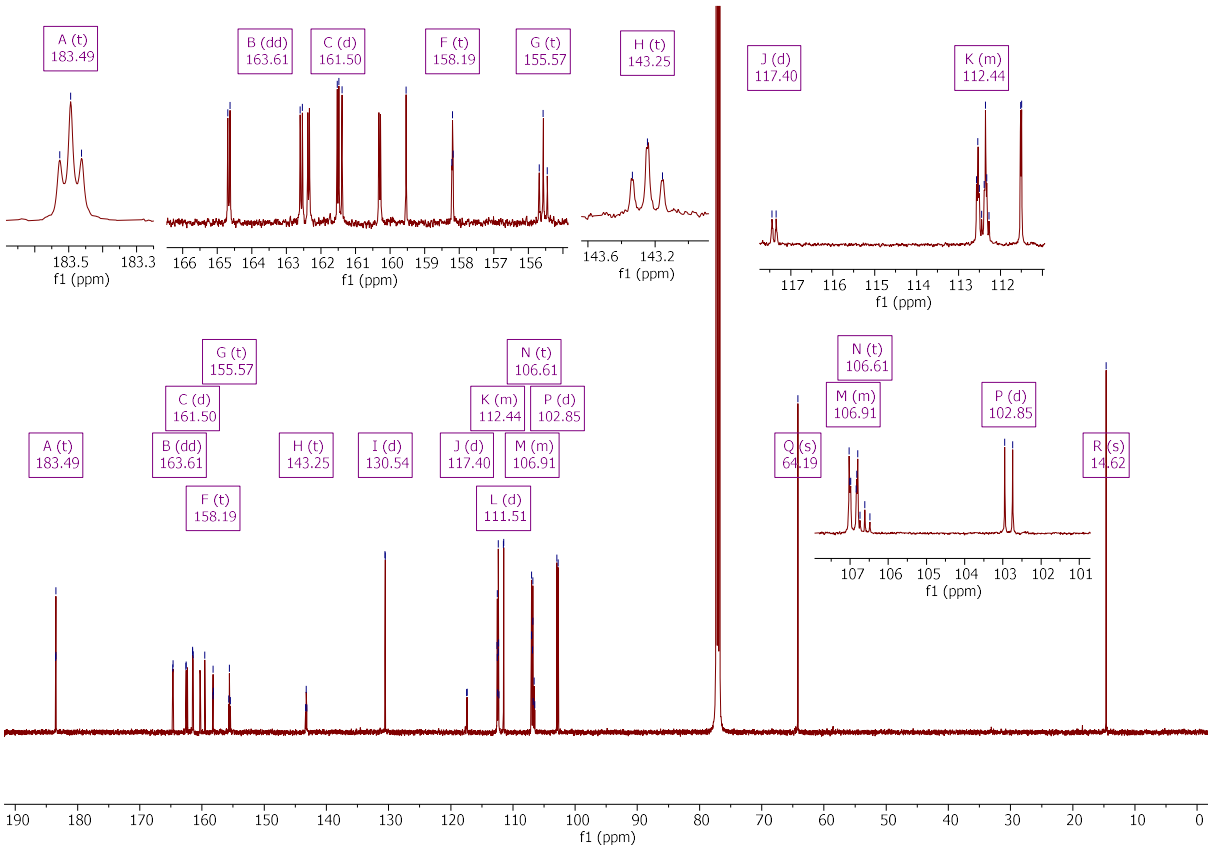


Figure S carbon NMR spectrum of **18.** Overlapping C=O, and Ar-F bonds do not have multiple labels but are recorded in data set in section 3.

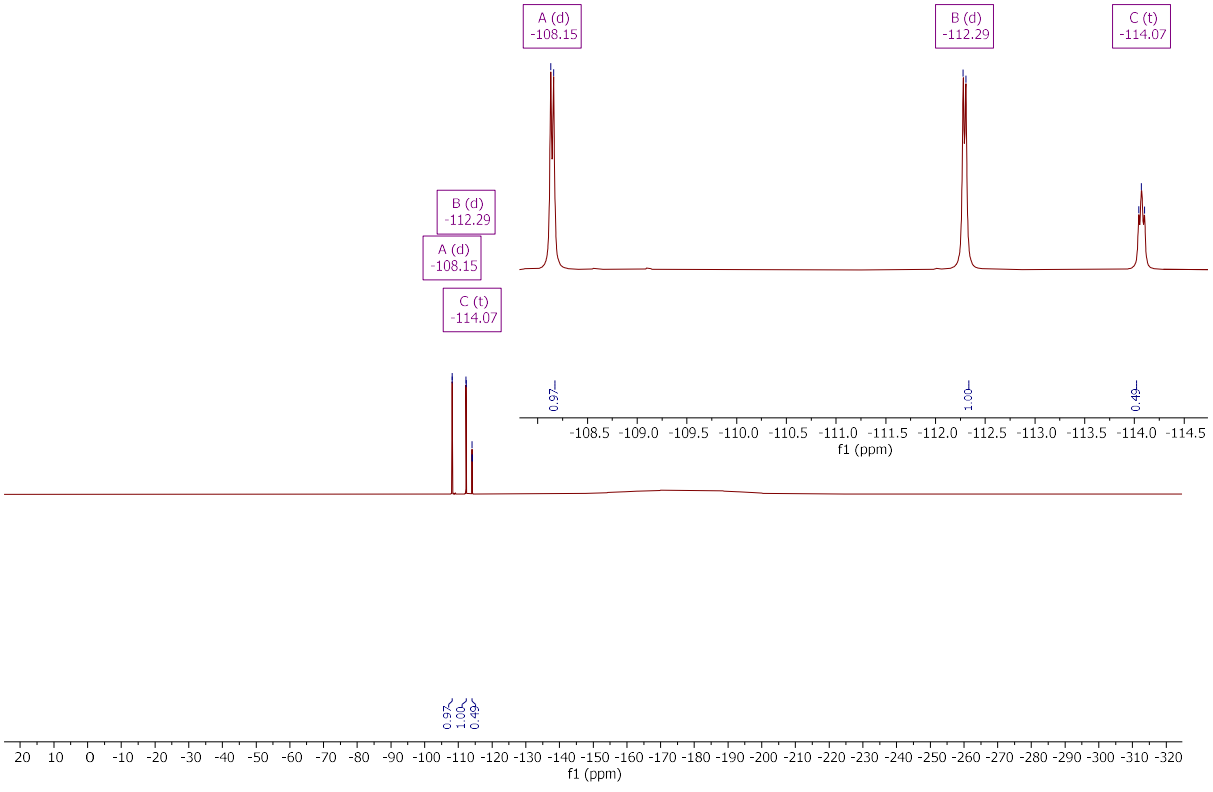


Figure S fluorine NMR spectrum of **18**

19 | *4'-(difluoro(3,4,5-trifluorophenoxy)methyl)-2,3',5'-trifluoro-[1,1'-biphenyl]-4-yl 4'-ethoxy-2',3,5-trifluoro-[1,1'-biphenyl]-4-carboxylate*

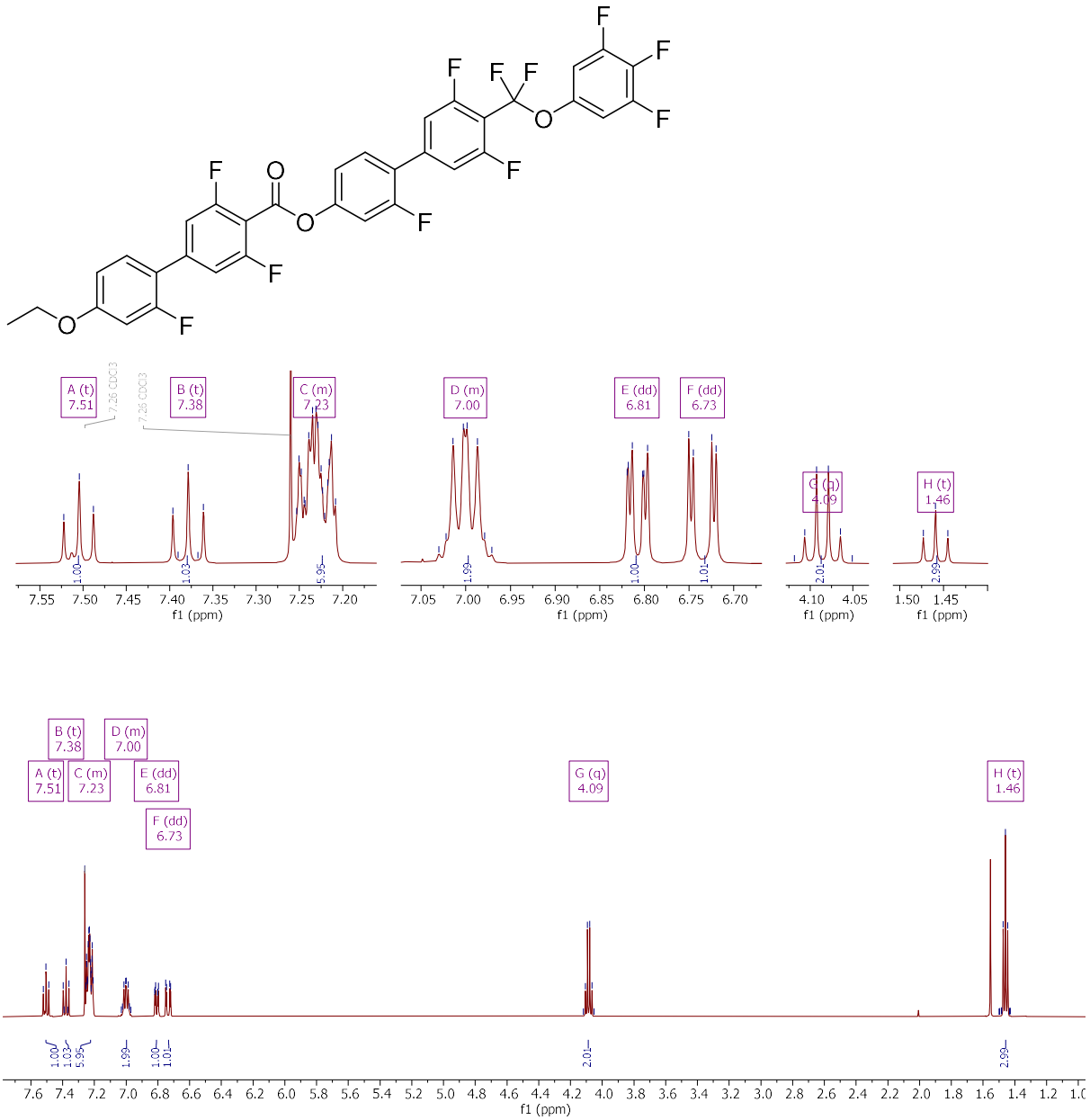


Figure S proton NMR spectrum of **19**

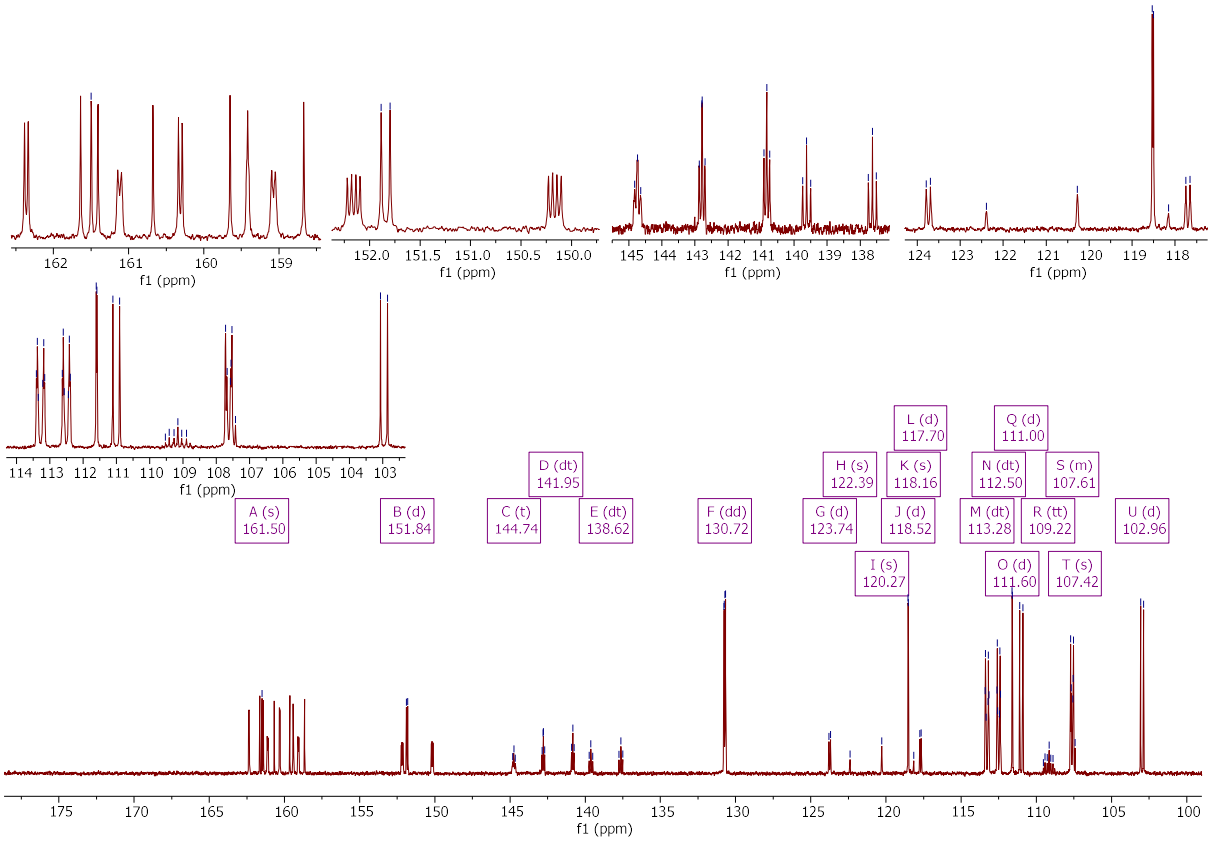


Figure S carbon NMR spectrum of **19.** Overlapping C=O, and Ar-F bonds do not have multiple labels but are recorded in data set in section 3.

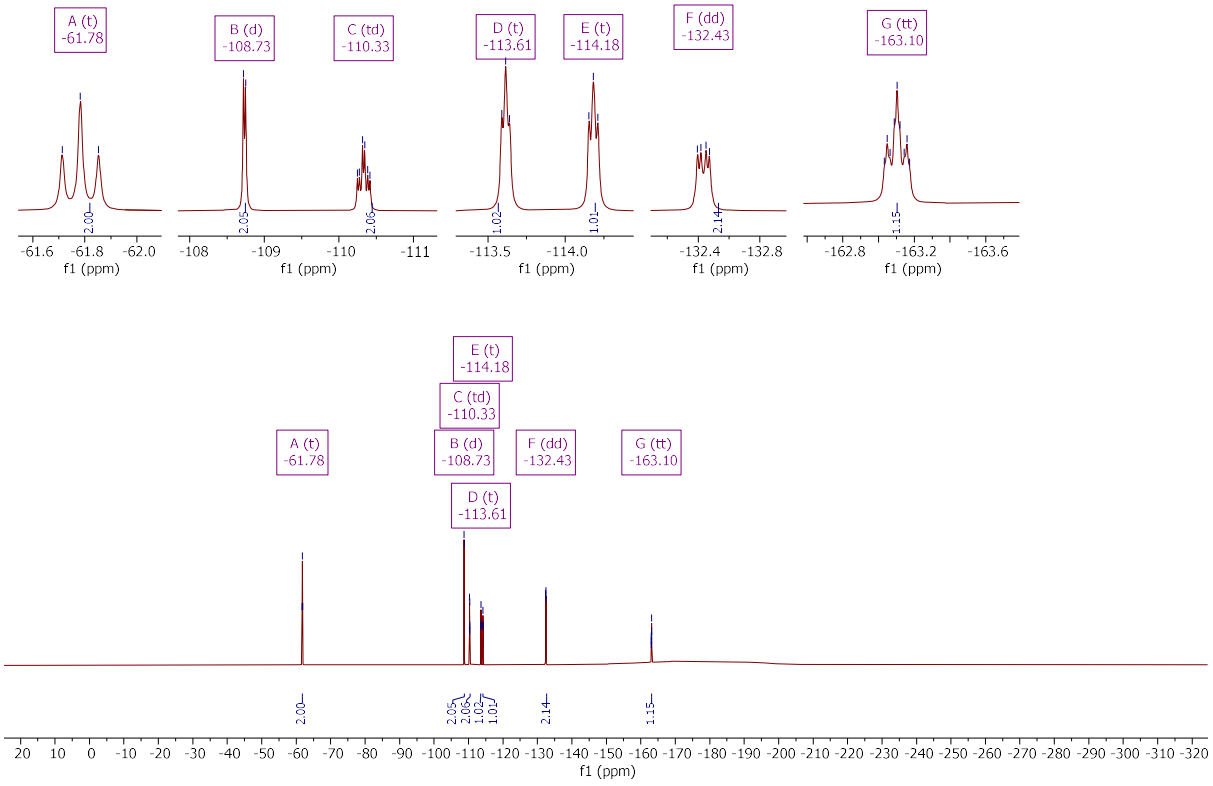
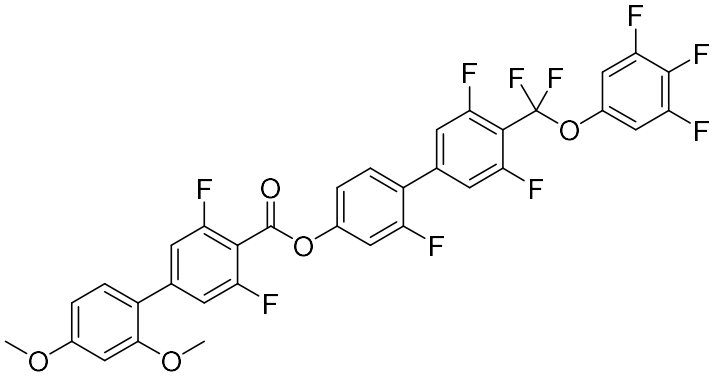


Figure S fluorine NMR spectrum of **19**

20 | *4'-(difluoro(3,4,5-trifluorophenoxy)methyl)-2,3',5'-trifluoro-[1,1'-biphenyl]-4-yl 3,5-difluoro-2',4'-dimethoxy-[1,1'-biphenyl]-4-carboxylate*



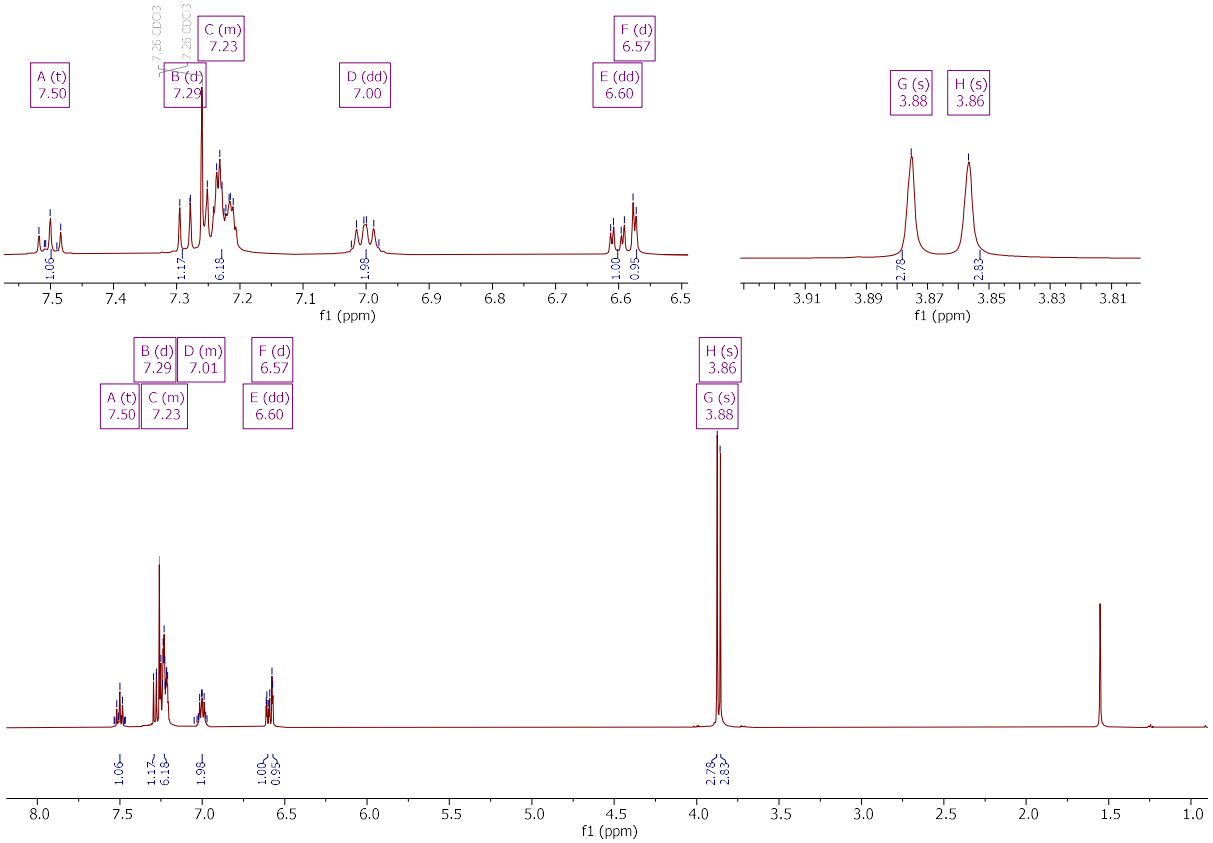


Figure S proton NMR spectrum of **20**

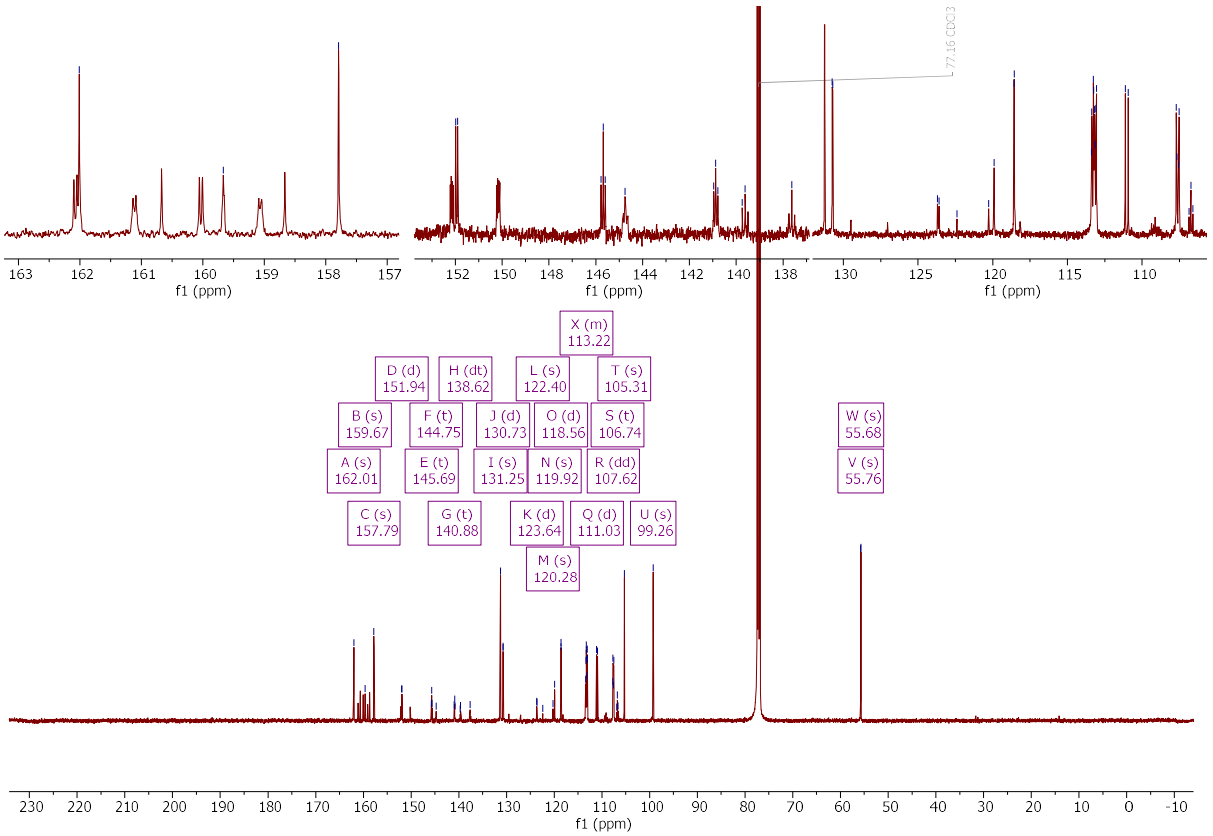


Figure S carbon NMR spectrum of **20.** Overlapping C=O, and Ar-F bonds do not have multiple labels but are recorded in data set in section 3.

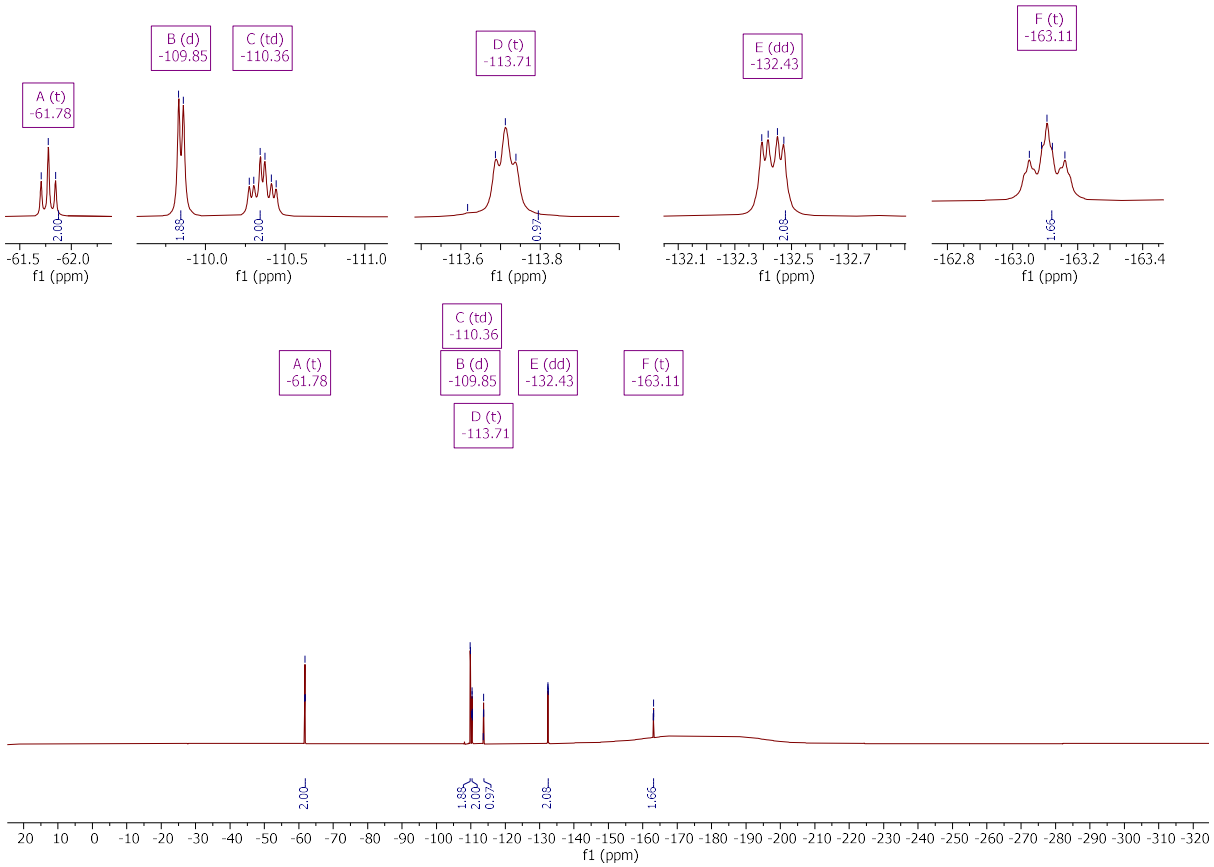
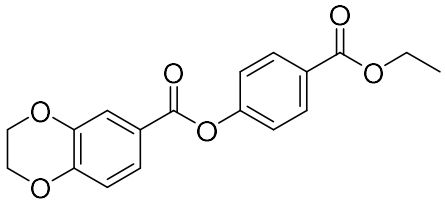


Figure S fluorine NMR spectrum of **20**

21 | *4-(ethoxycarbonyl)phenyl 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate*



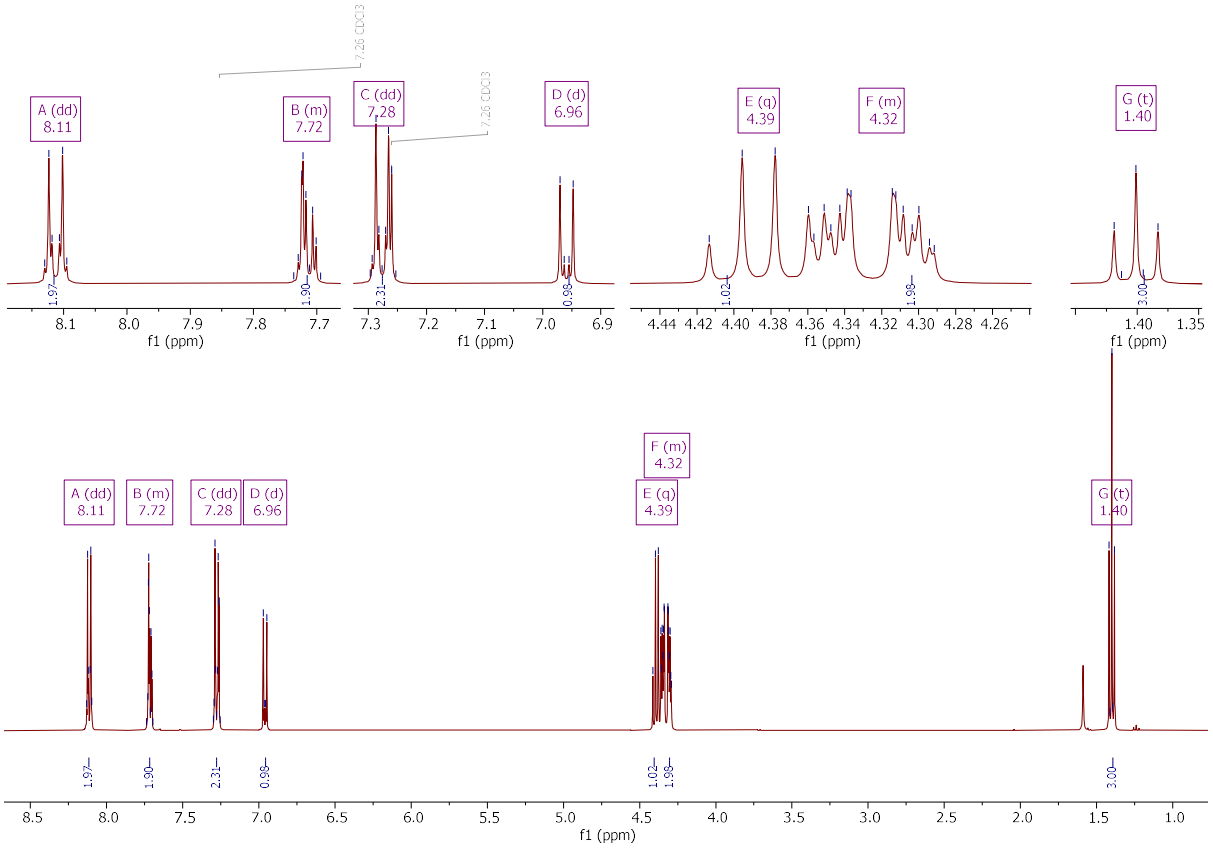


Figure S proton NMR spectrum of **21**

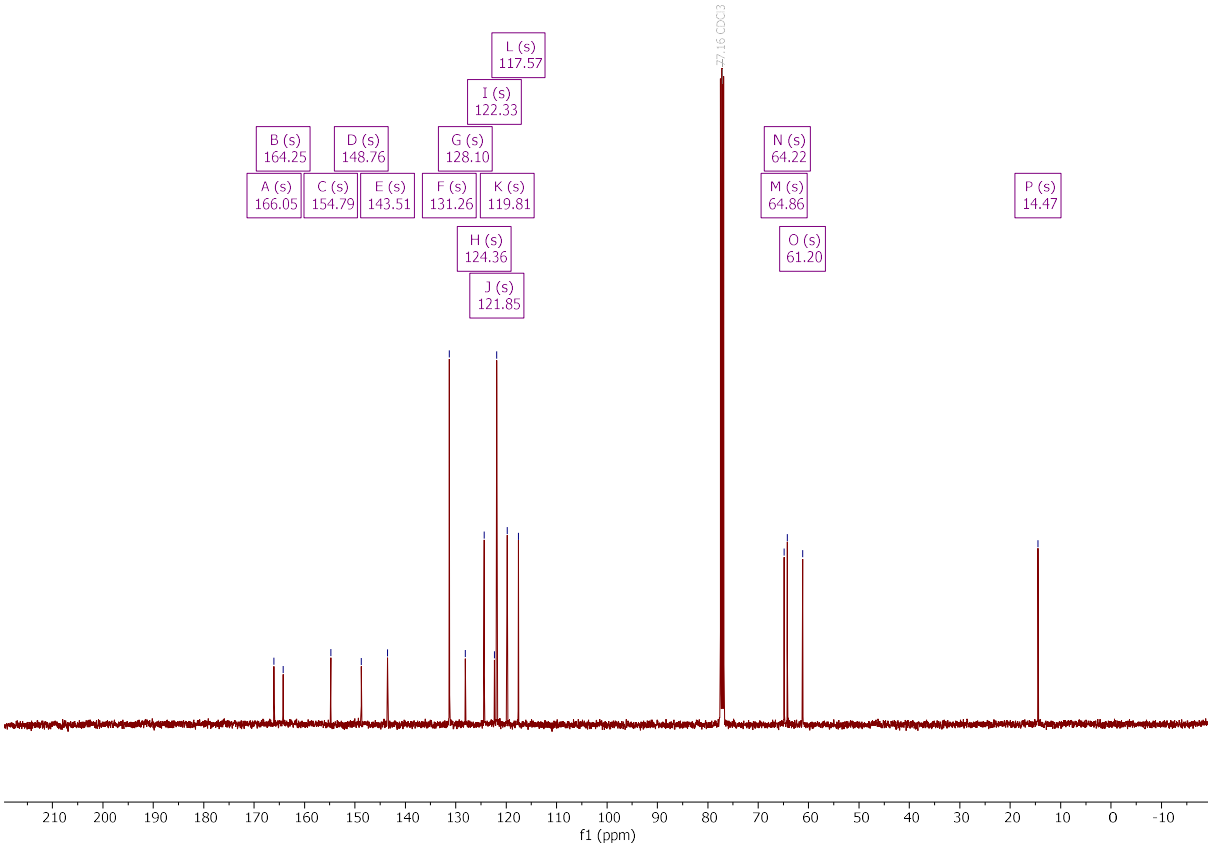
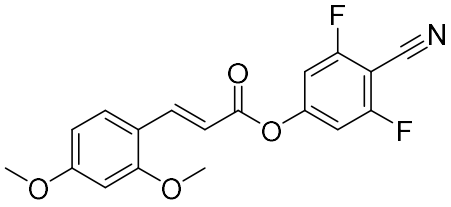


Figure S carbon NMR spectrum of **21**

22 | *4-cyanophenyl (E)-3-(2,4-dimethoxyphenyl)acrylate*



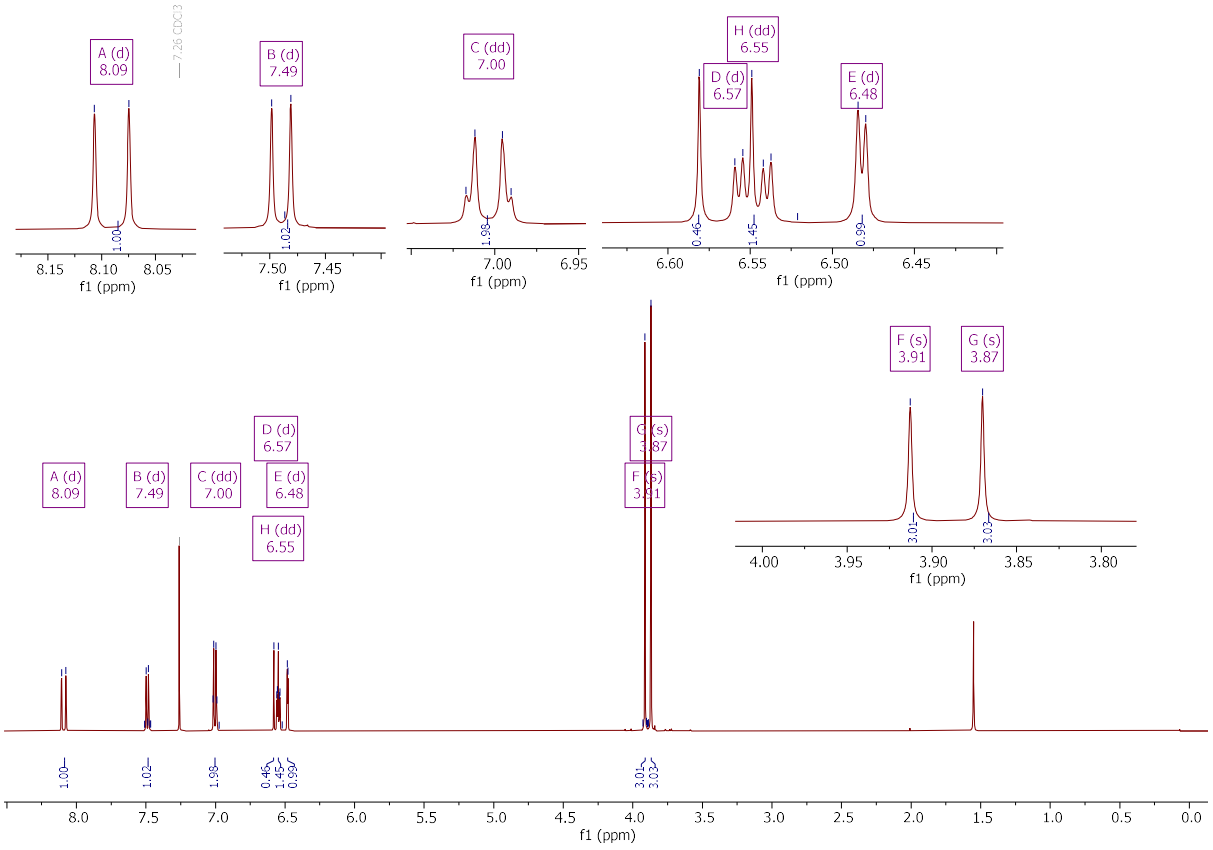


Figure S proton NMR spectrum of **22**

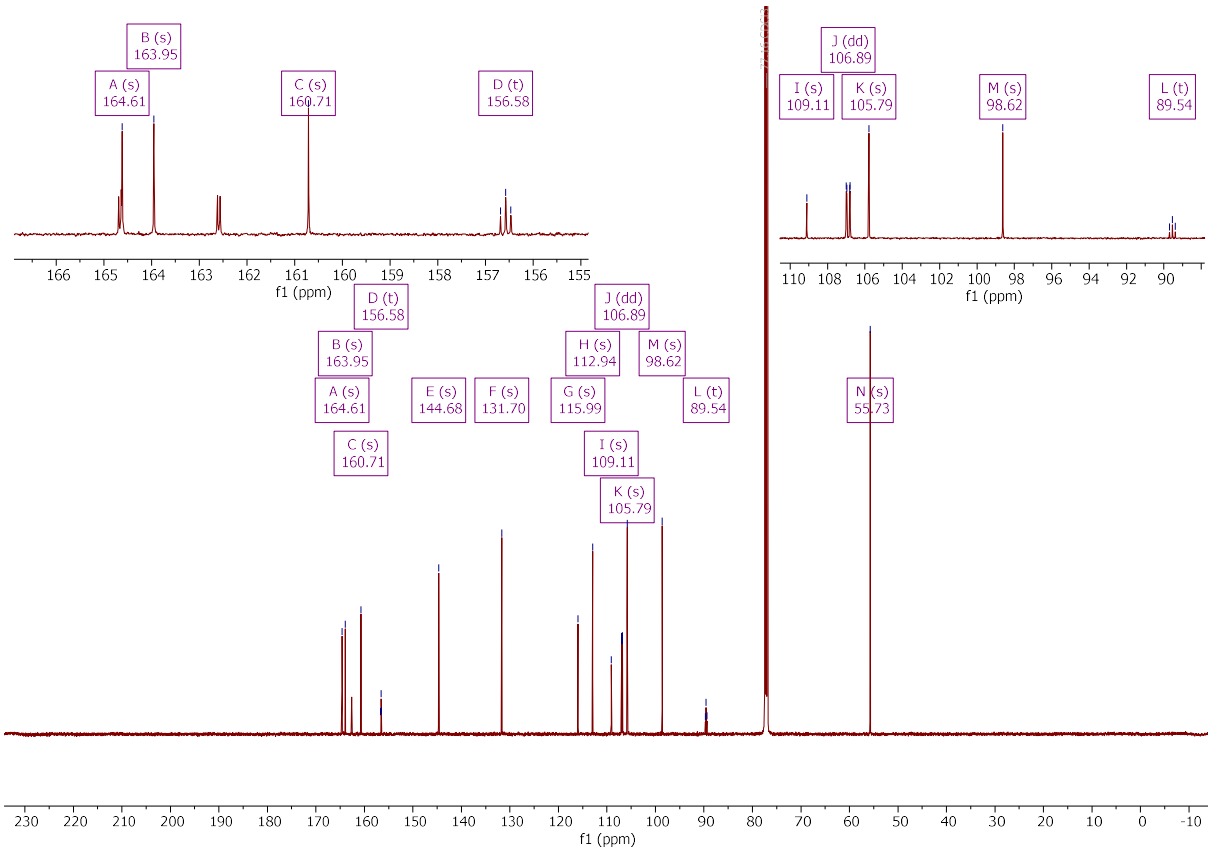


Figure S carbon NMR spectrum of **22**

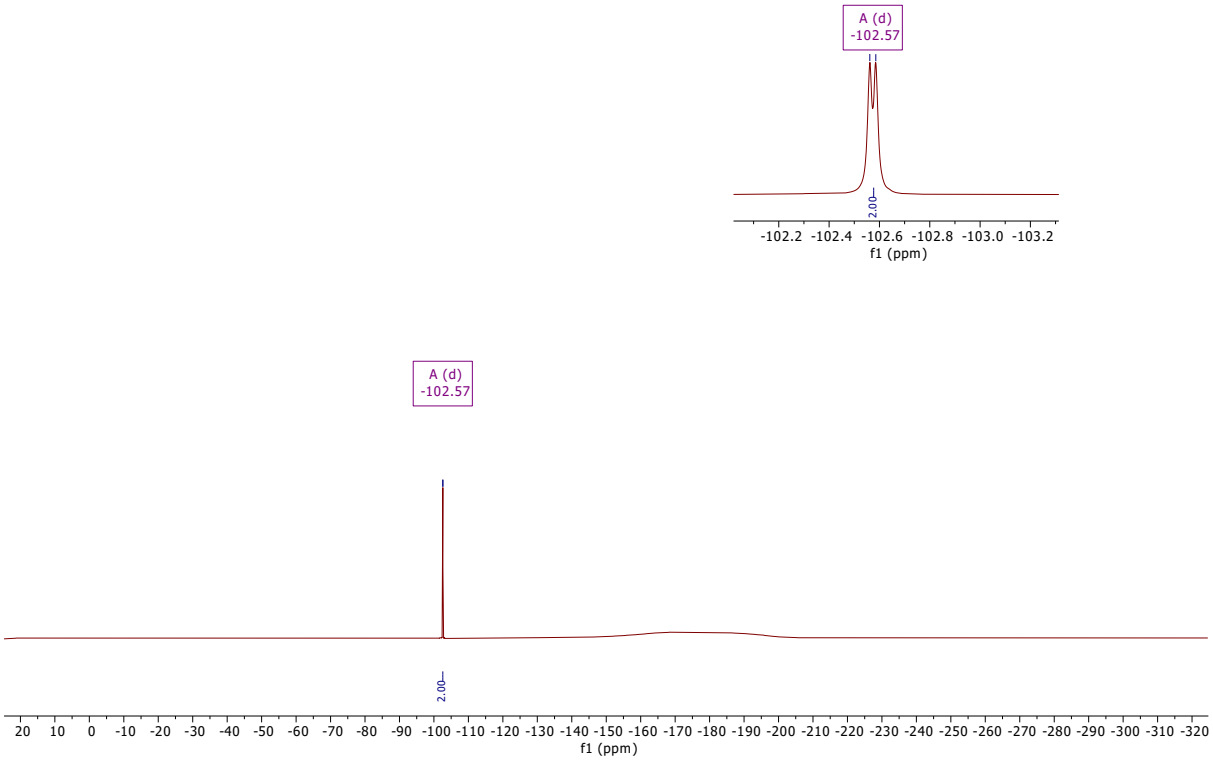


Figure S fluorine NMR spectrum of **22**

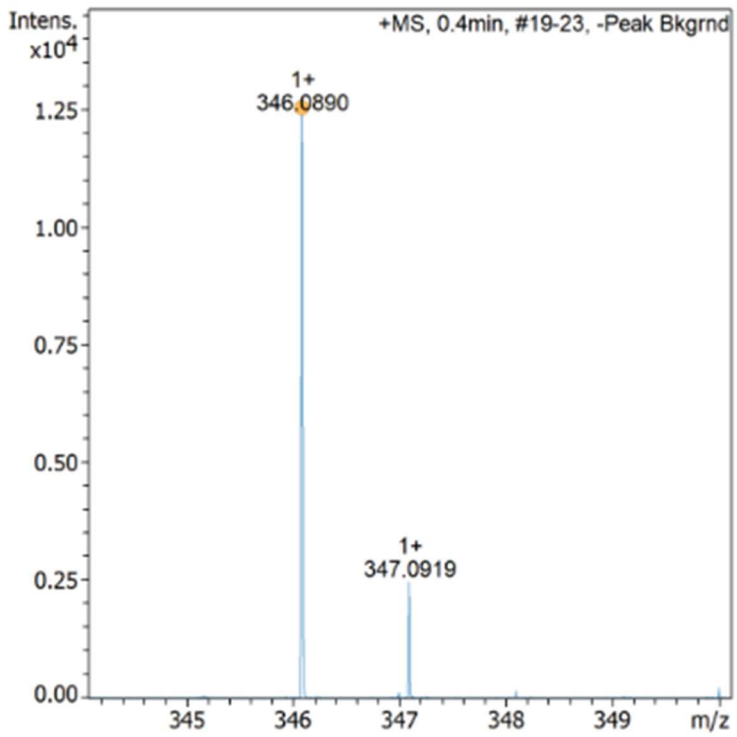


Figure S HRMS of **22**

23 | *4'-cyano-2,3',6-trifluoro-[1,1'-biphenyl]-4-yl 2-methoxy-4-(trifluoromethoxy)benzoate*

Figure S proton NMR spectrum of **23**

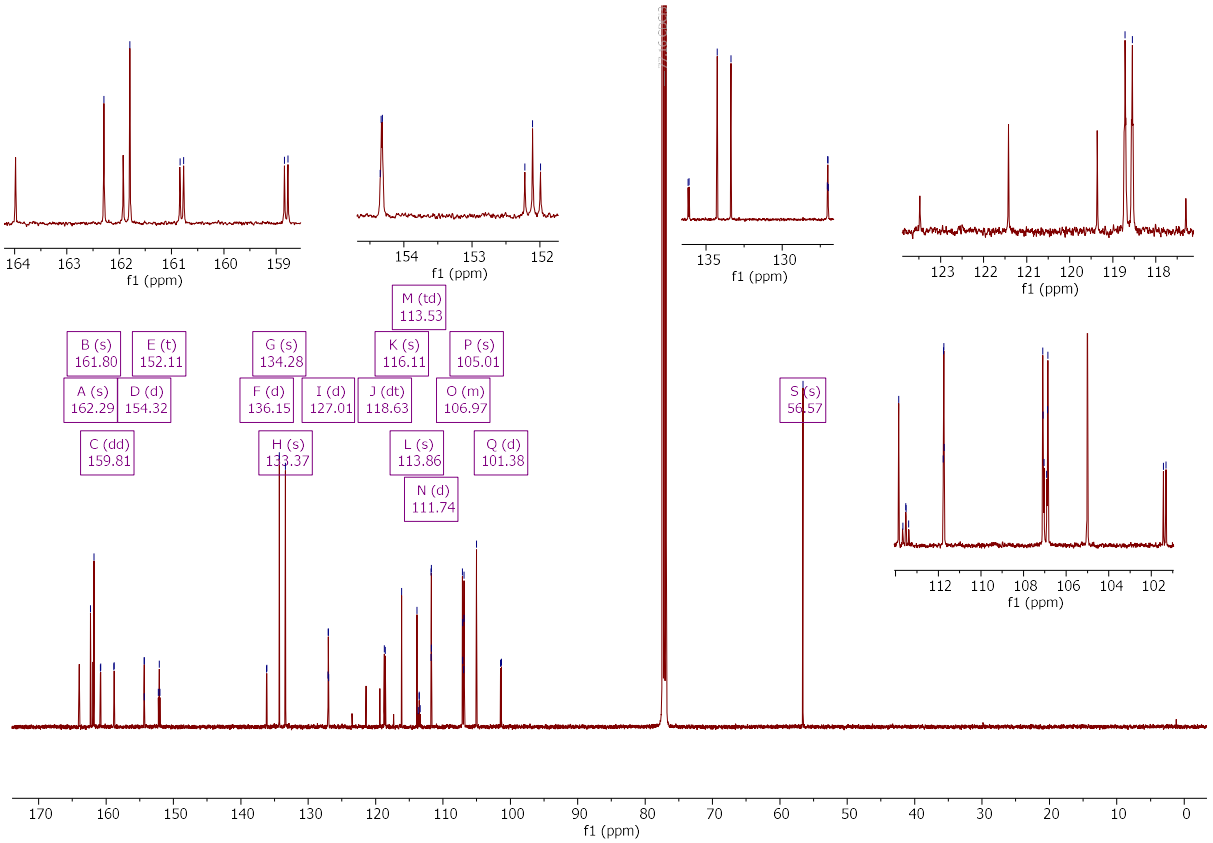


Figure S carbon NMR spectrum of **23**

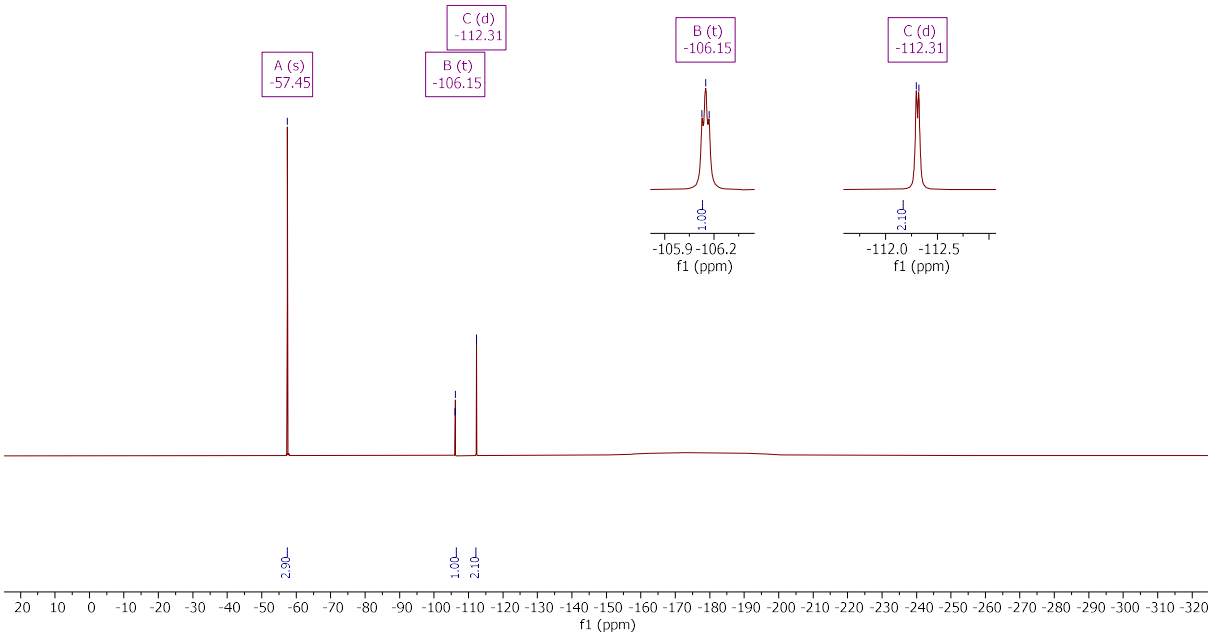


Figure S fluorine NMR spectrum of **23**

24 | *4-bromo-3-methoxyphenyl 2',3,5-trifluoro-4'-methoxy-[1,1'-biphenyl]-4-carboxylate*

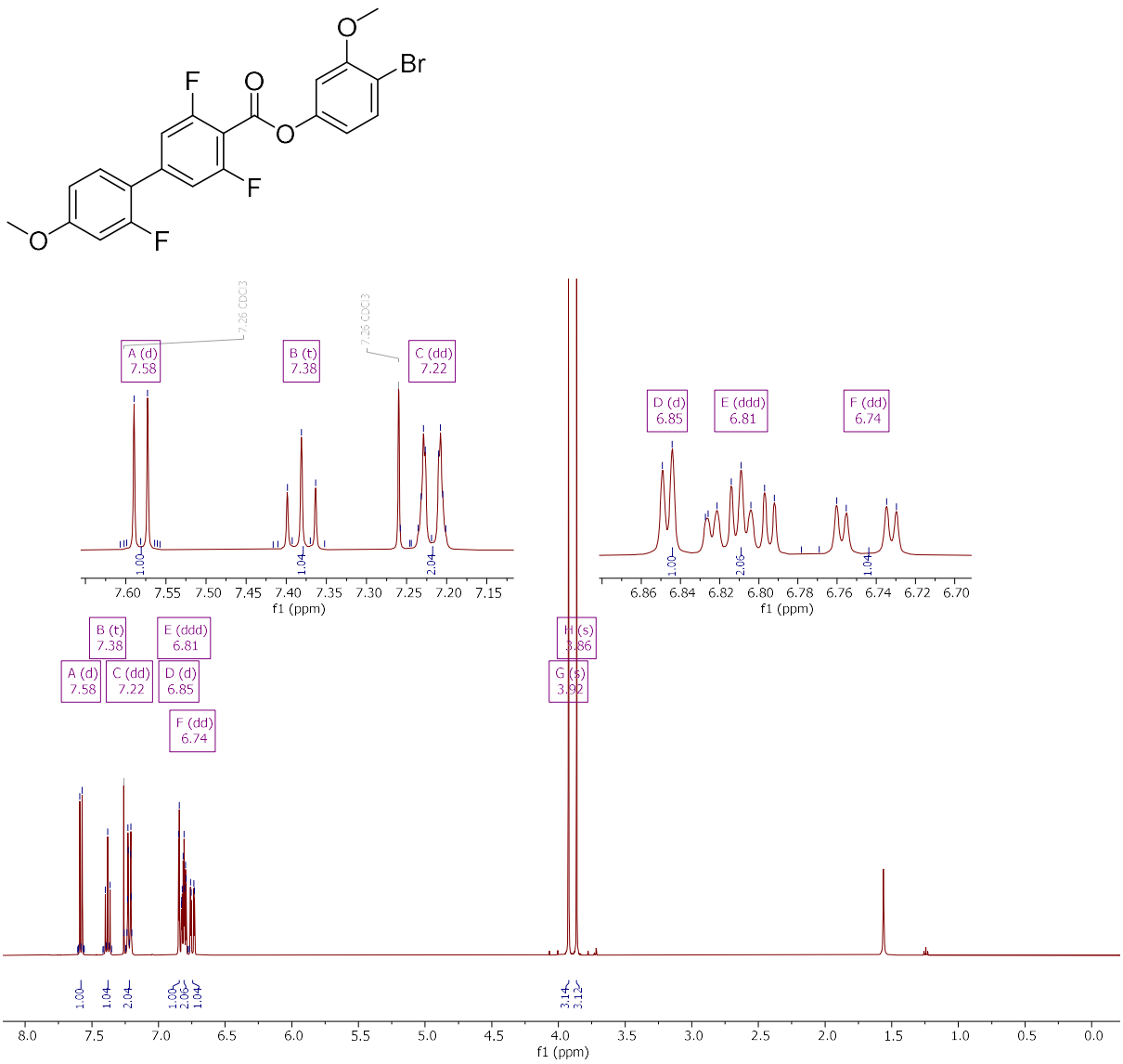


Figure S proton NMR spectrum of **24**

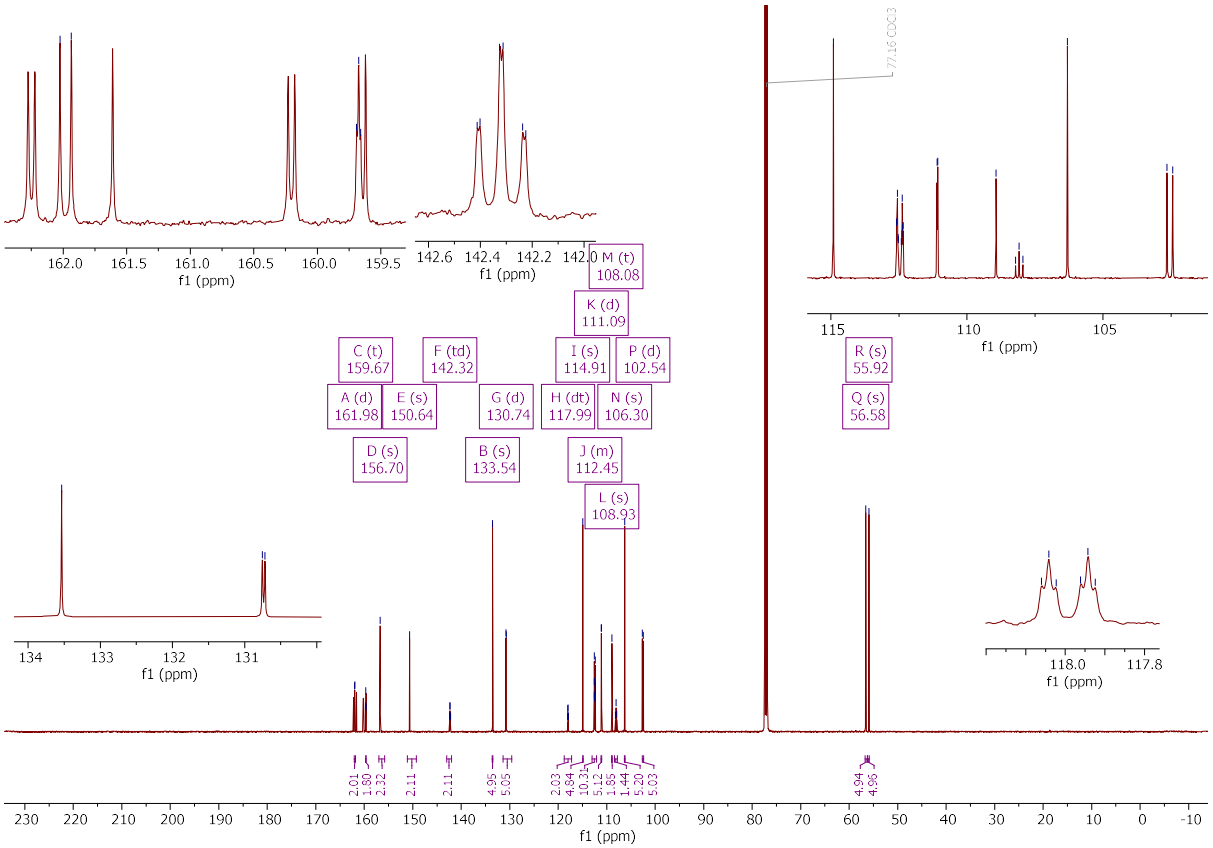


Figure S carbon NMR spectrum of **24**

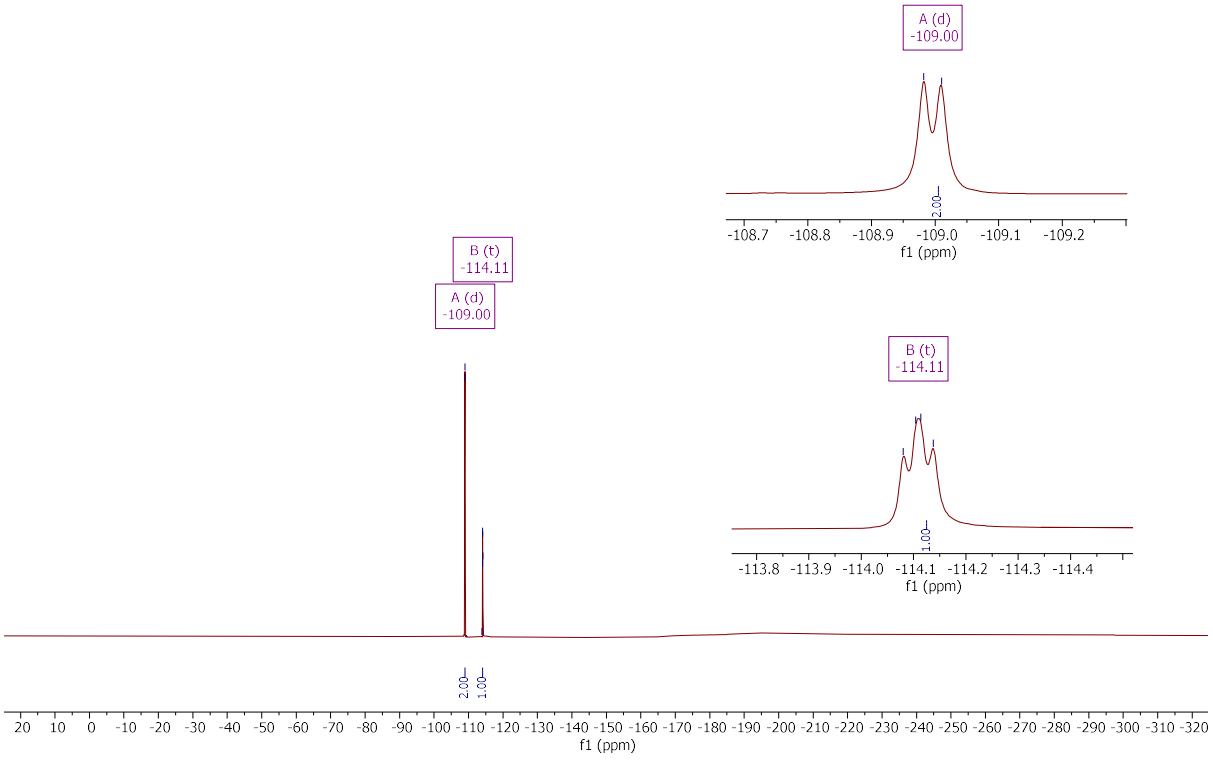
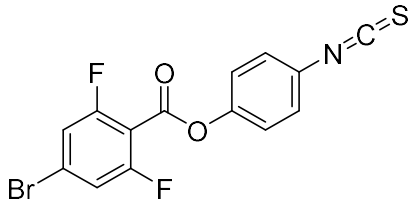


Figure S fluorine NMR spectrum of **24**

25 | *4-isothiocyanatophenyl 4-bromo-2,6-difluorobenzoate*



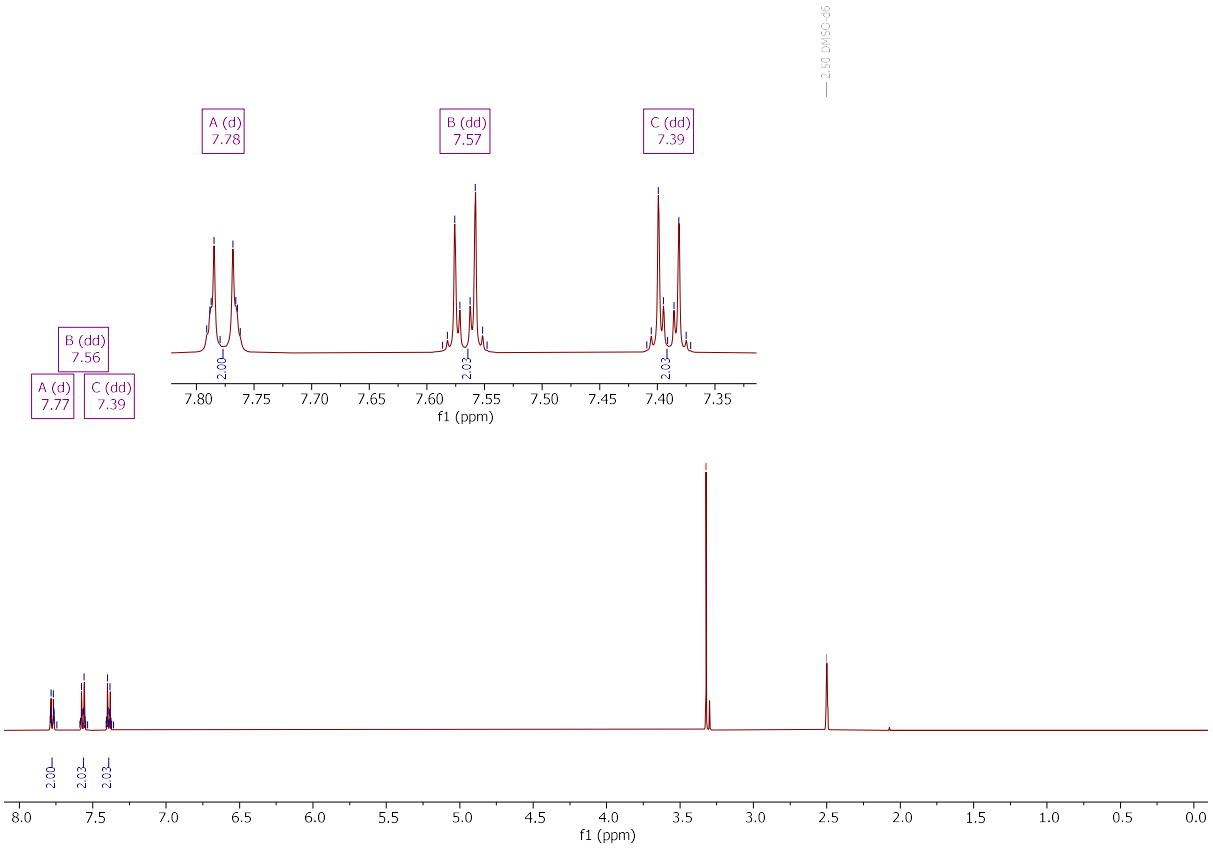


Figure S proton NMR spectrum of **25**

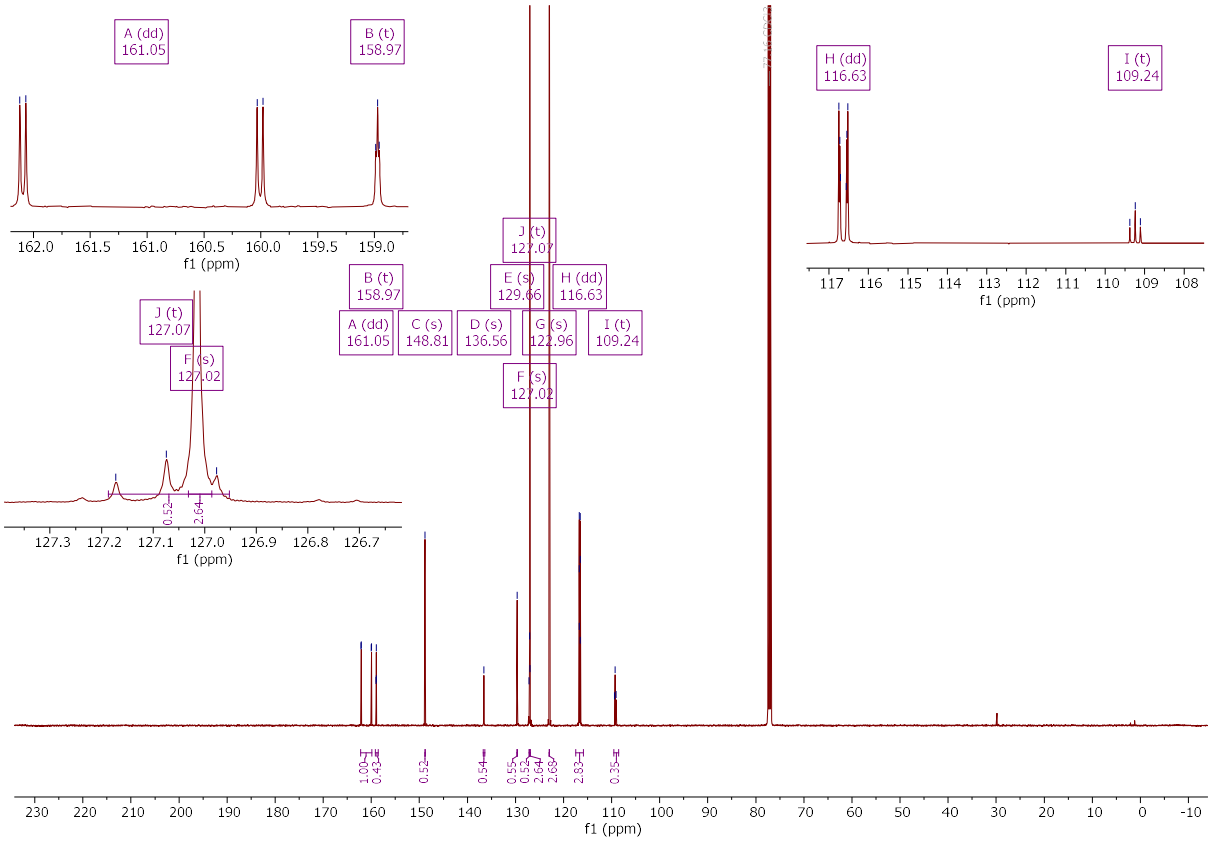


Figure S carbon NMR spectrum of **25**

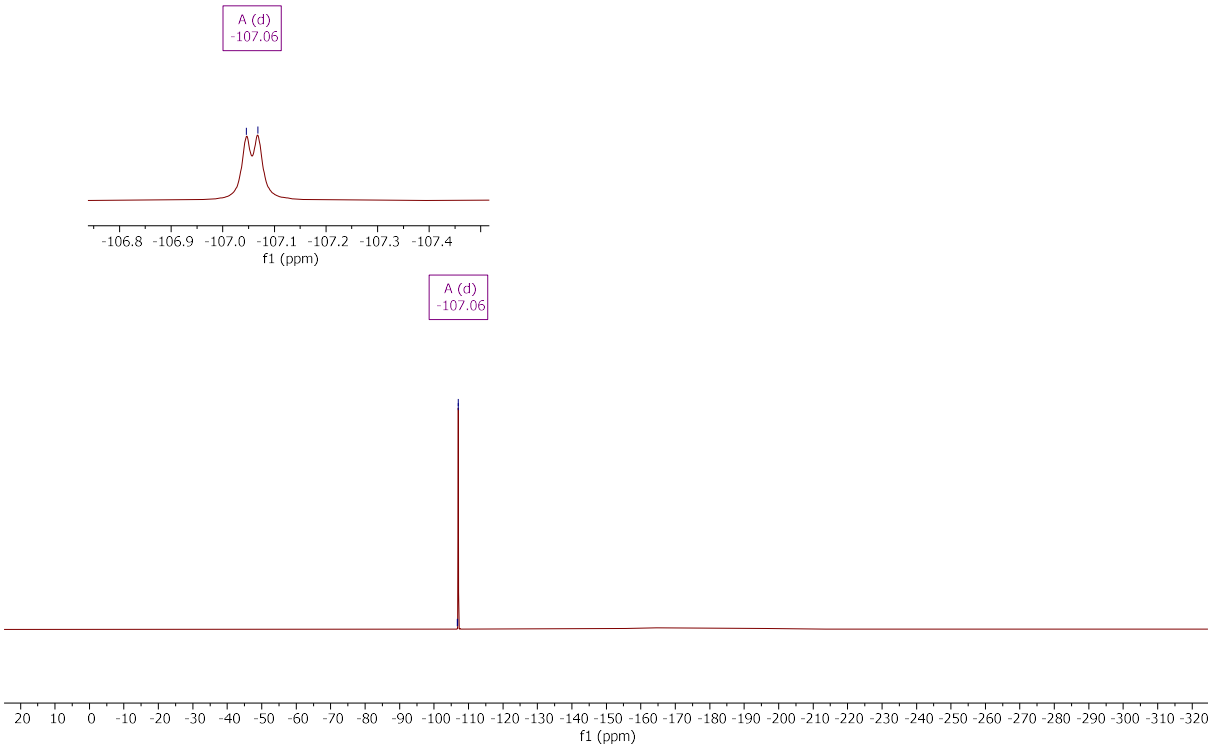
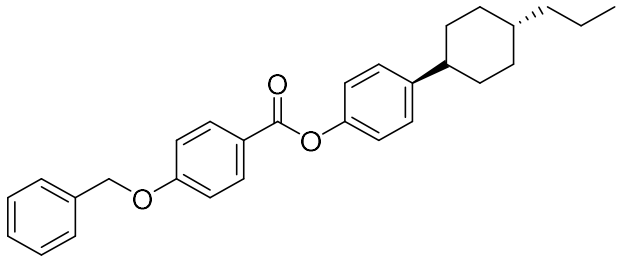


Figure S fluorine NMR spectrum of **25**

26 | *4-((1r,4s)-4-propylcyclohexyl)phenyl 4-(benzyloxy)benzoate*



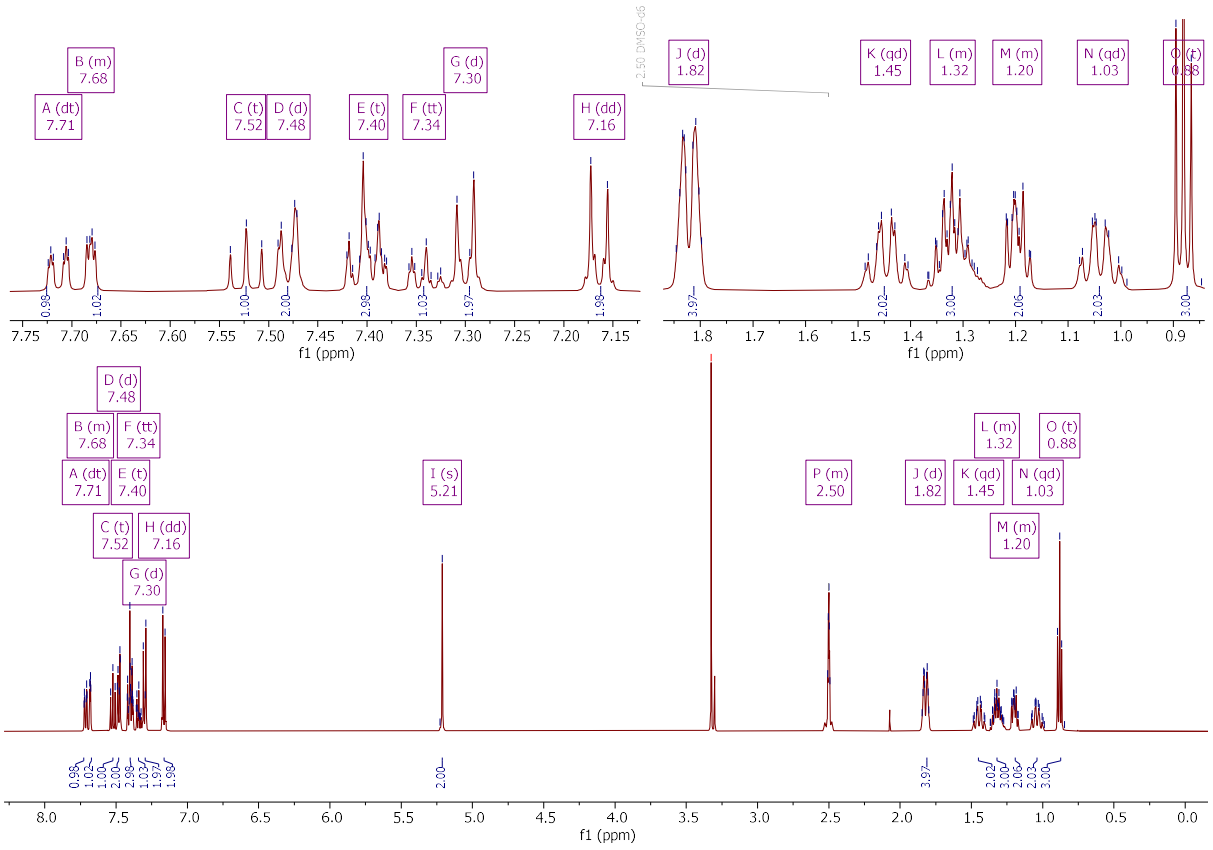


Figure S proton NMR spectrum of **26**

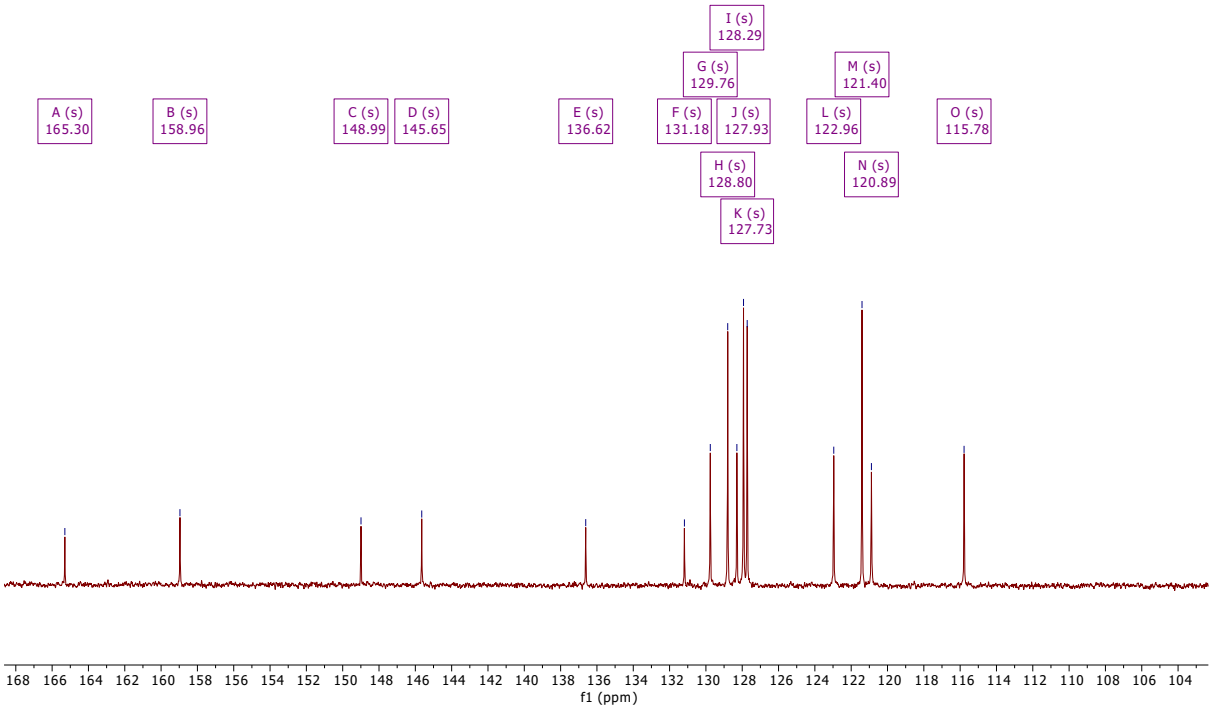


Figure S carbon NMR spectrum of **26**

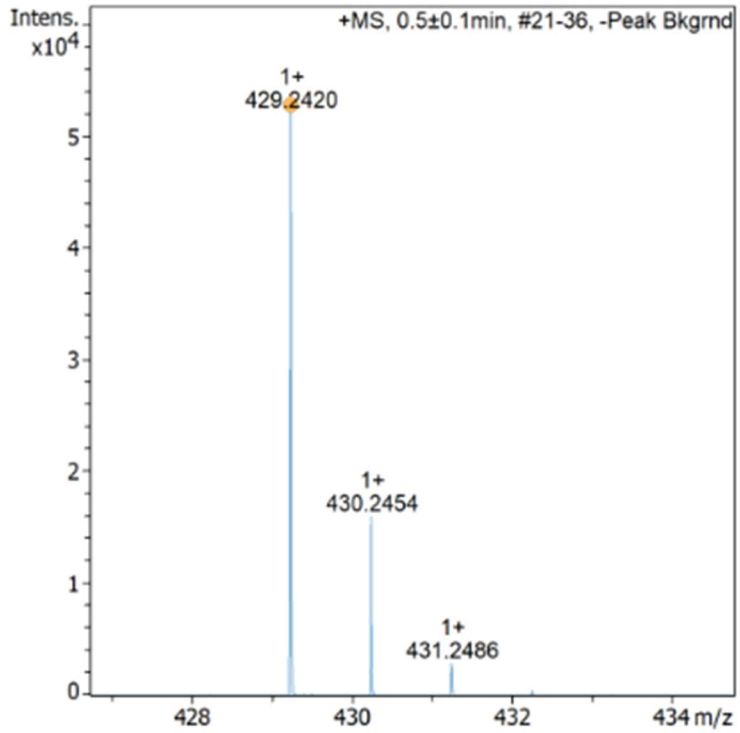


Figure S HRMS of **26**

27 | *bis(2,3',4',5'-tetrafluoro-[1,1'-biphenyl]-4-yl) nonanedioate*

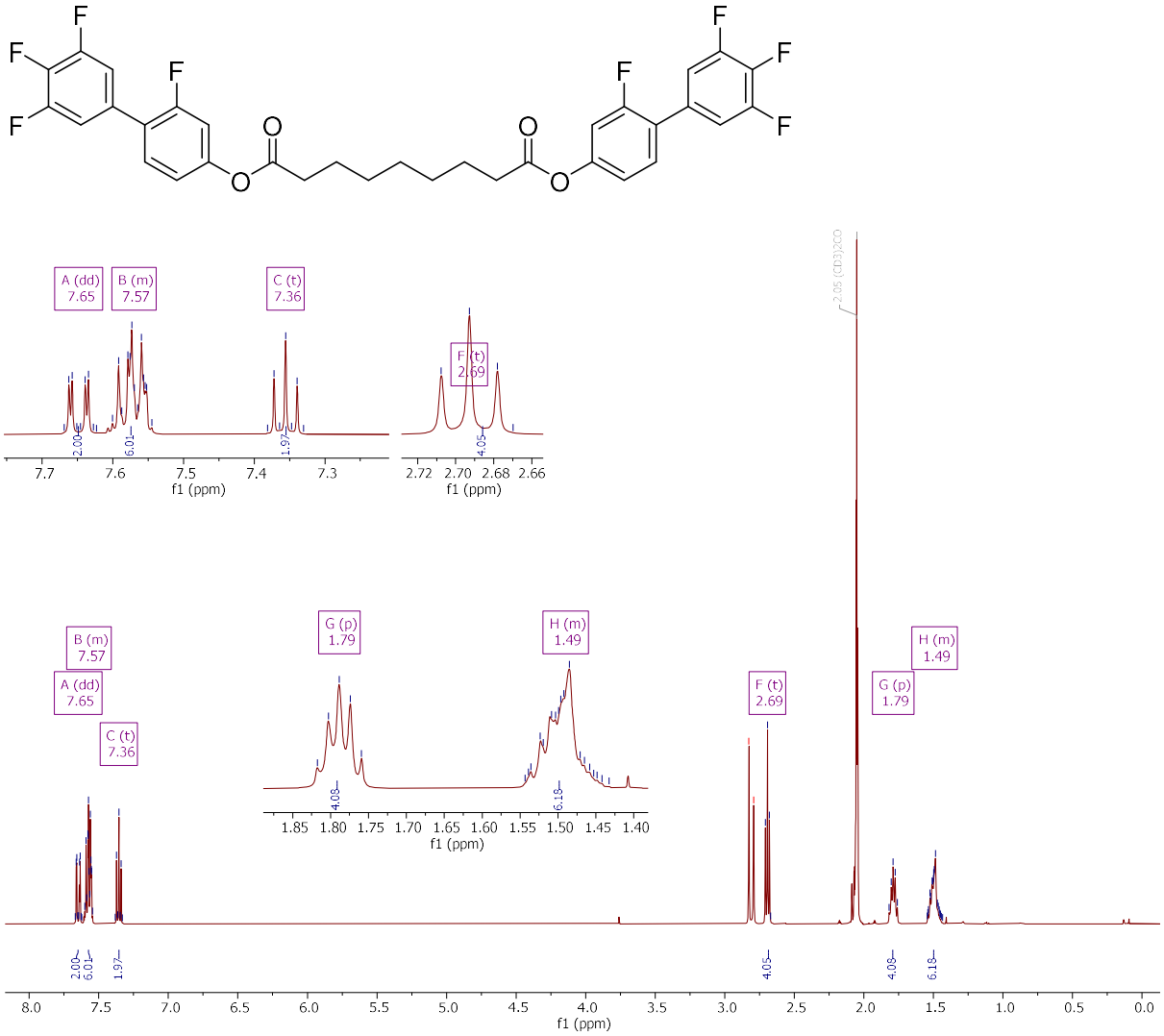


Figure S proton NMR spectrum of **27**

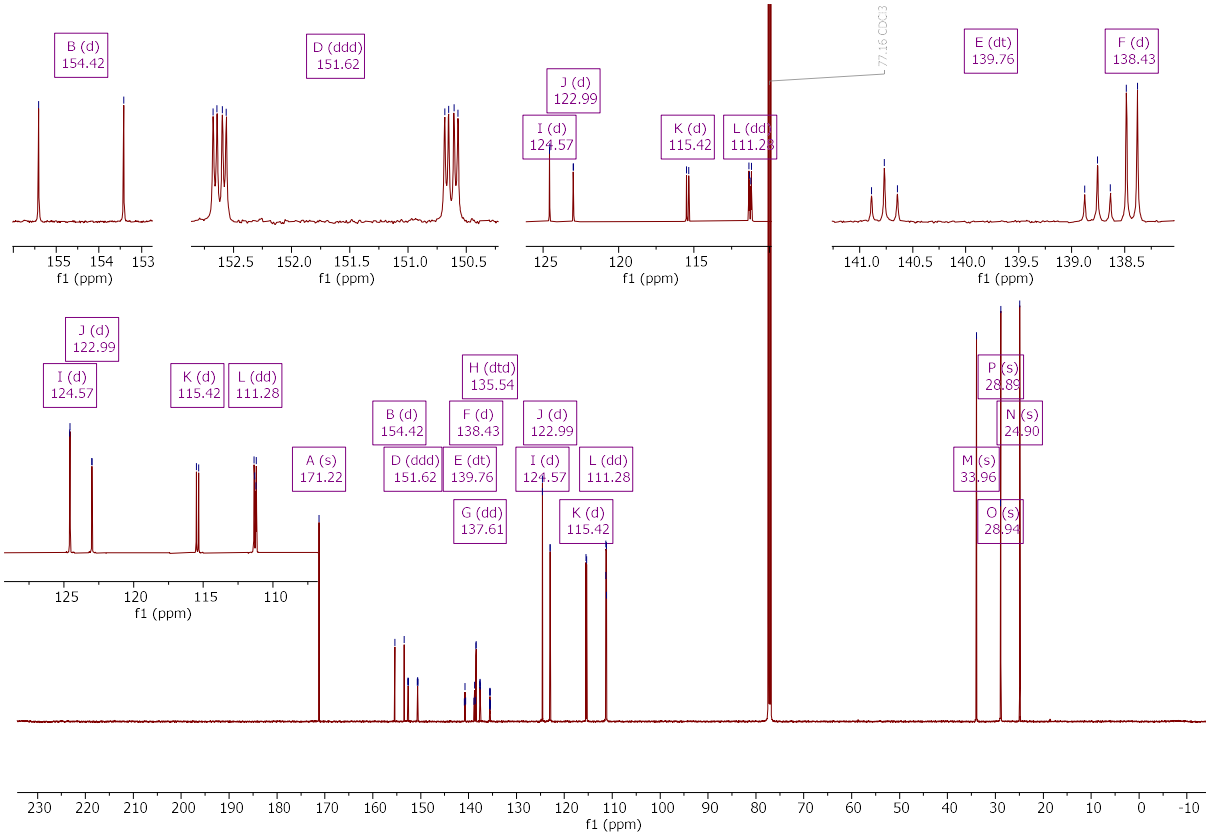


Figure S carbon NMR spectrum of **27**

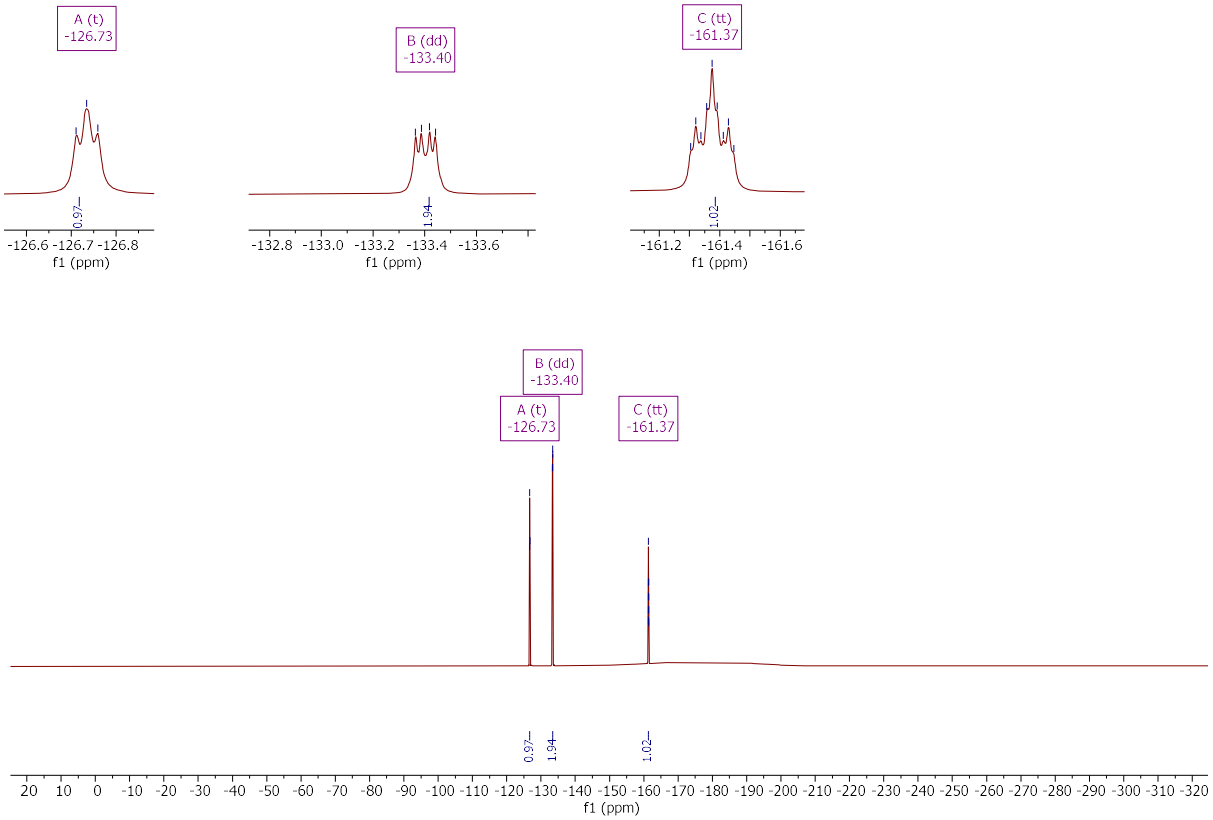


Figure S fluorine NMR spectrum of **27**

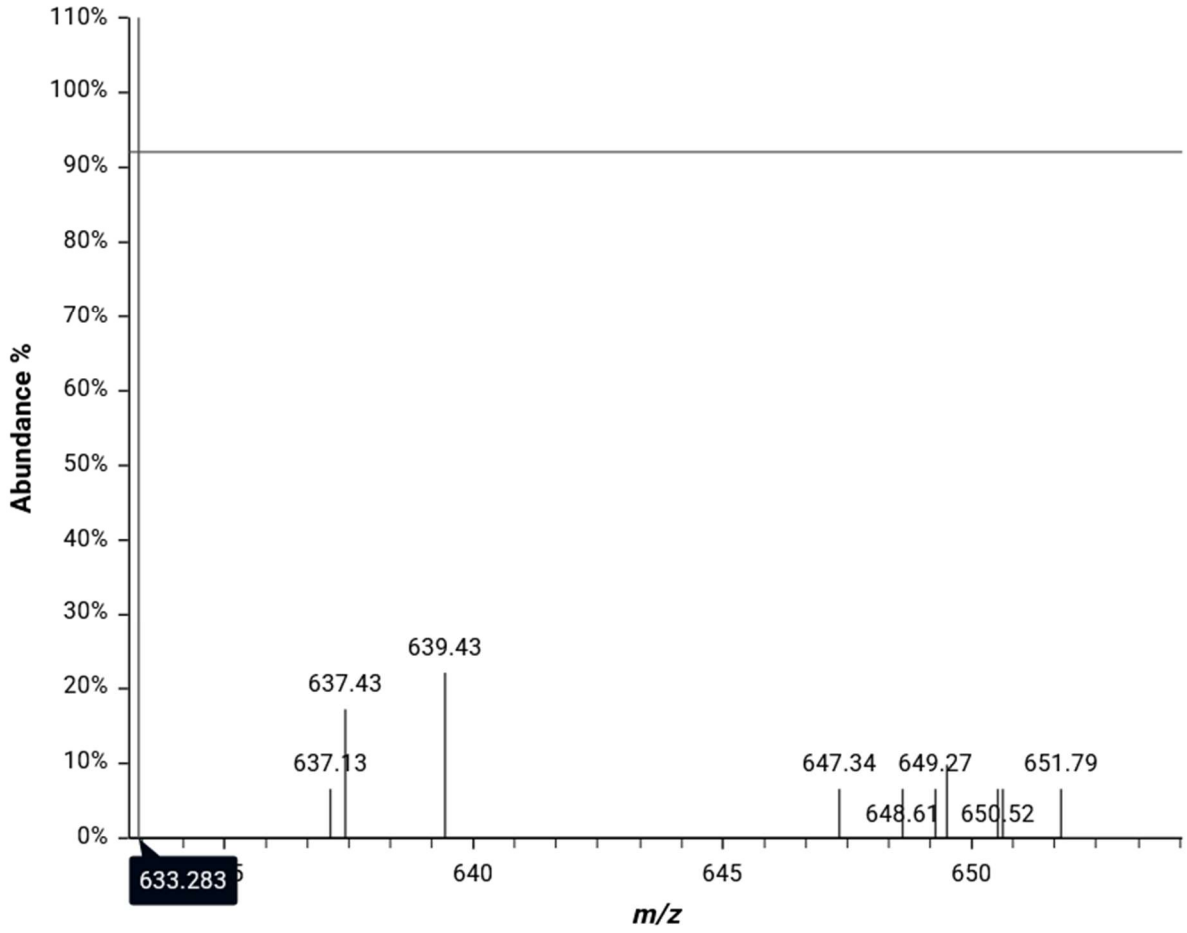


Figure S HRMS of **27**

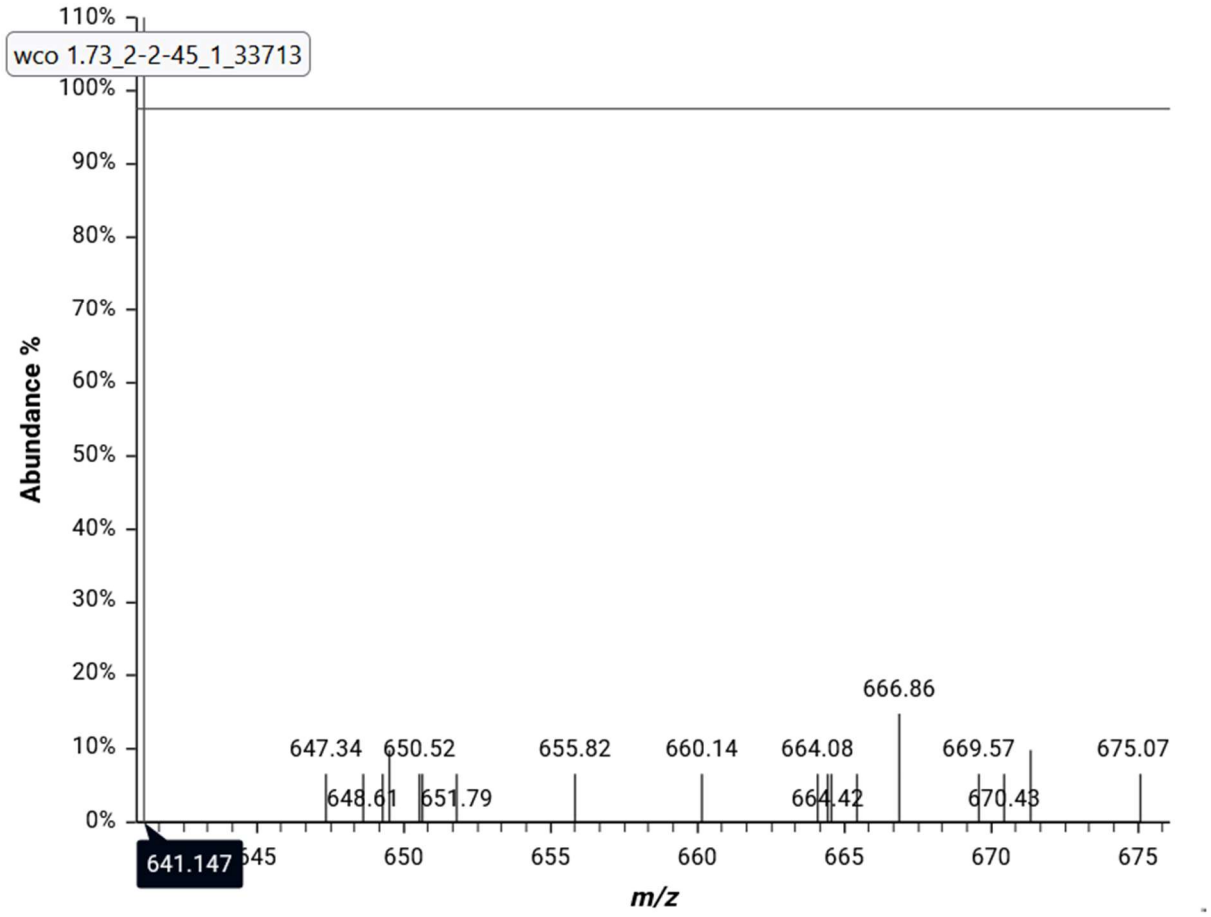
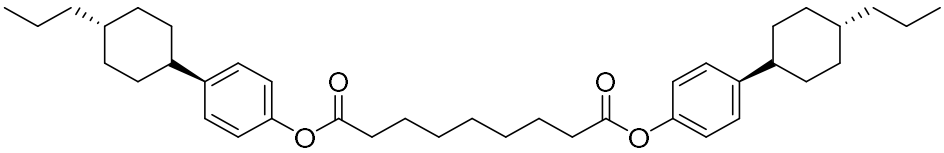


Figure S HRMS of **27**

28 | *bis(4-((1s,4r)-4-propylcyclohexyl)phenyl) nonanedioate*



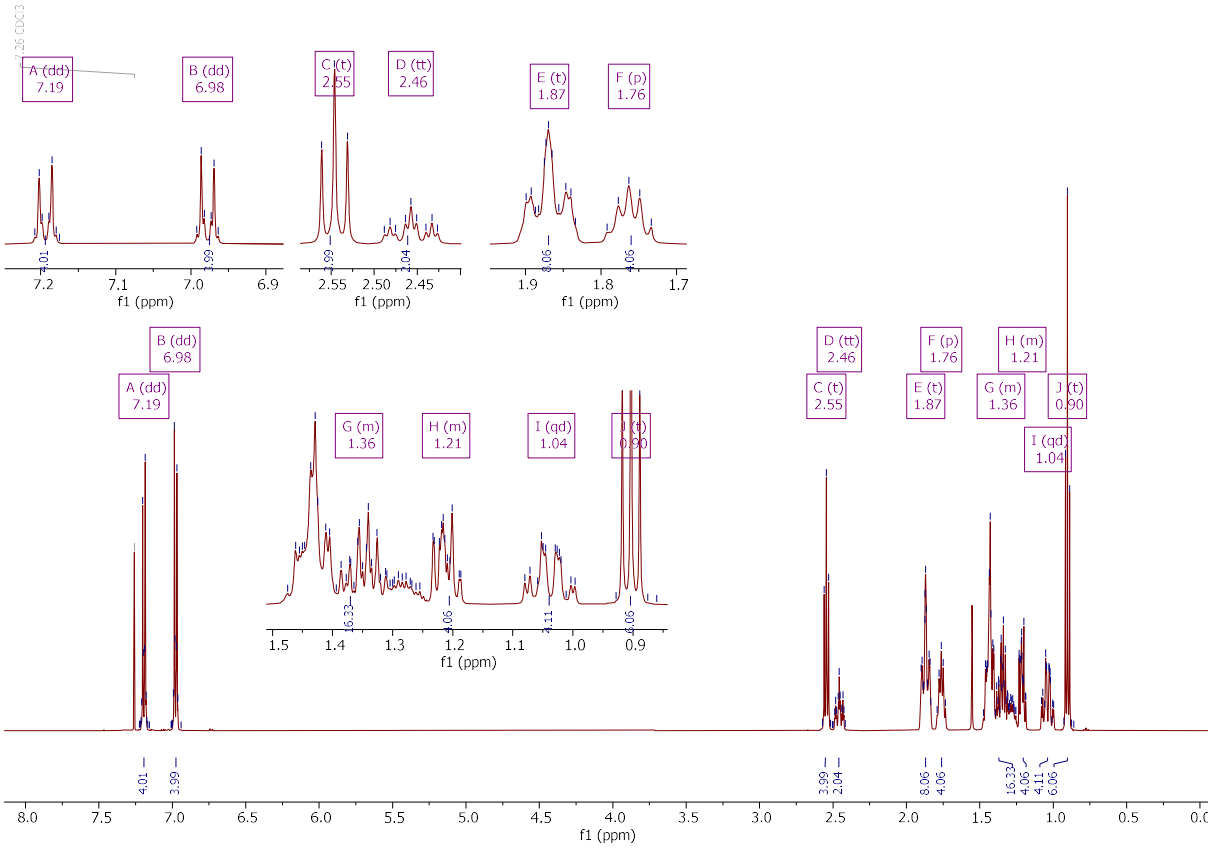


Figure S proton NMR spectrum of **28**

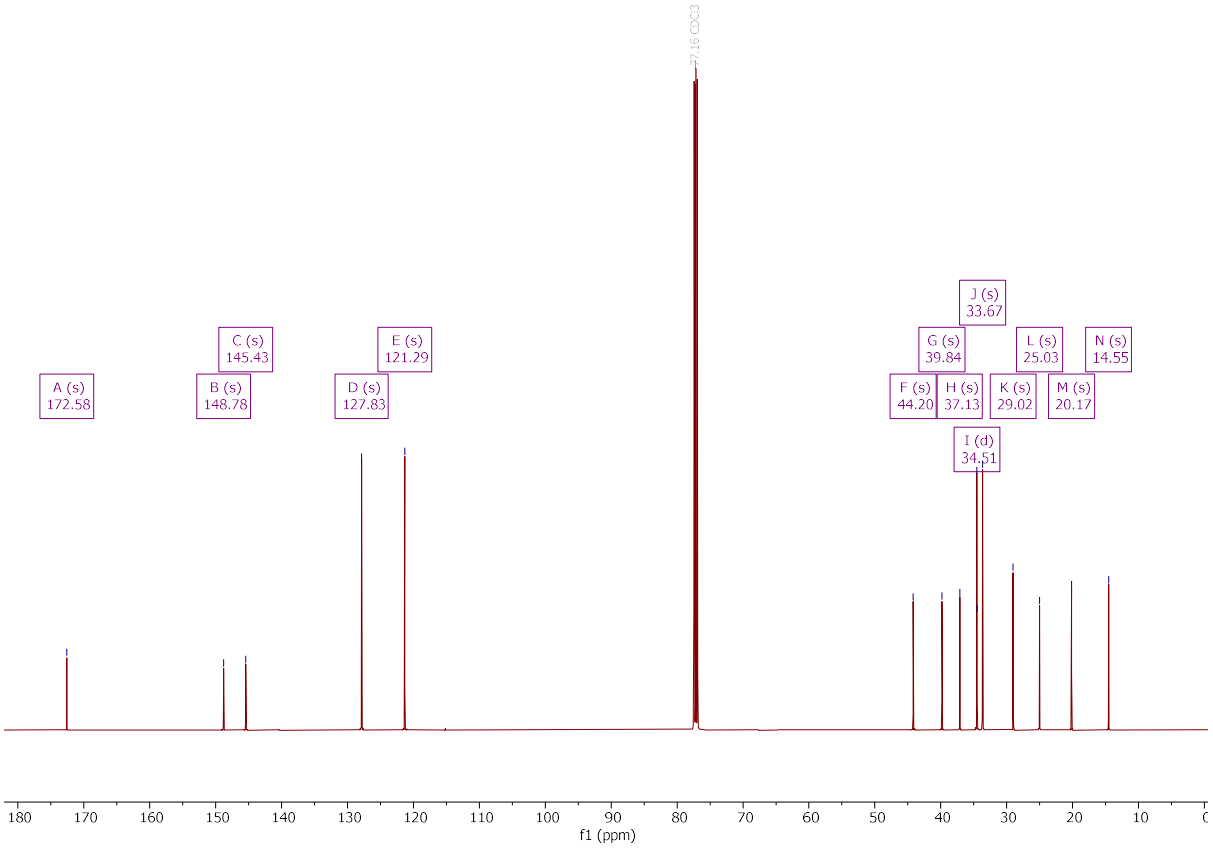


Figure S carbon NMR spectrum of **28**

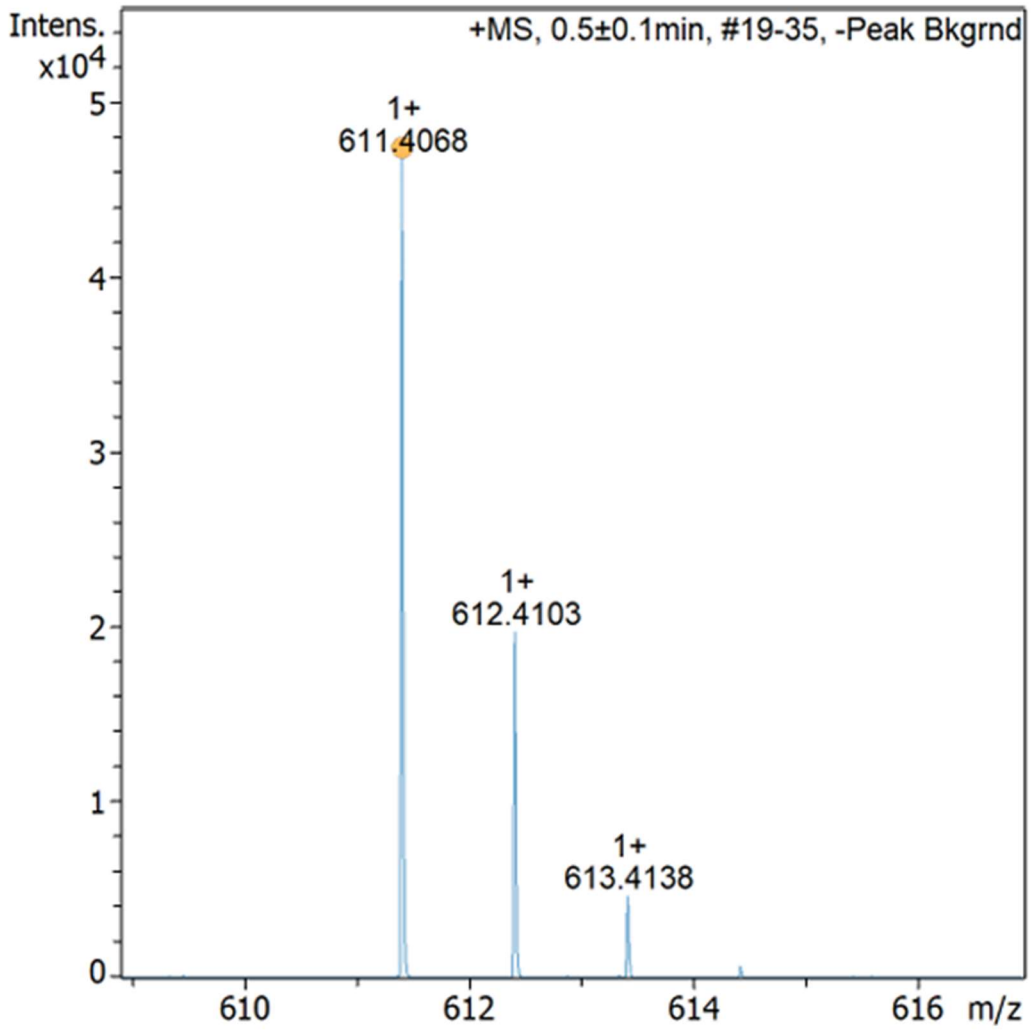
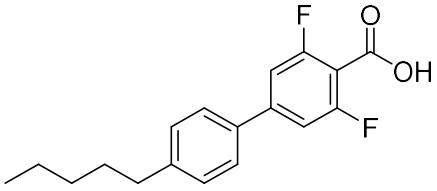


Figure S HRMS of **28**

CA1 | *2,6-difluoro-4-(4-pentylphenyl)benzoic acid*



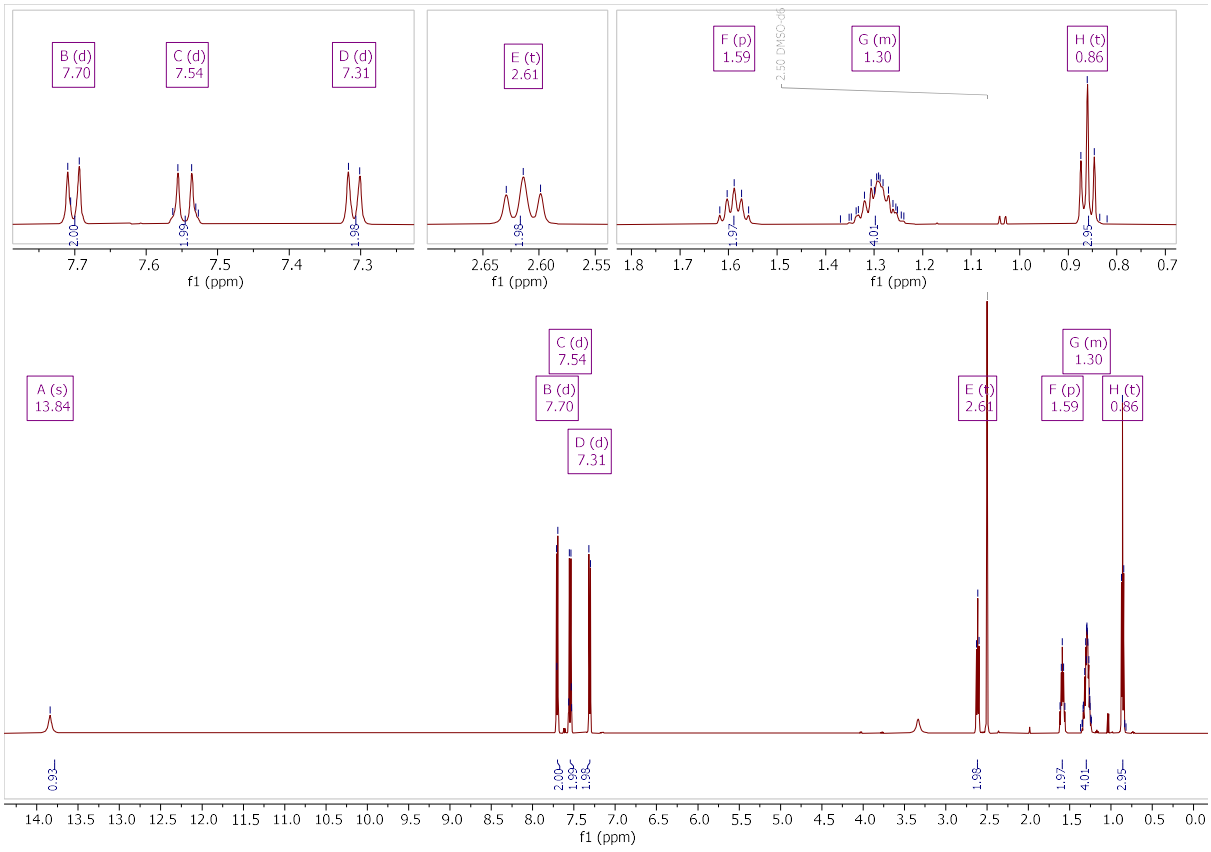


Figure S proton NMR spectrum of **CA1**

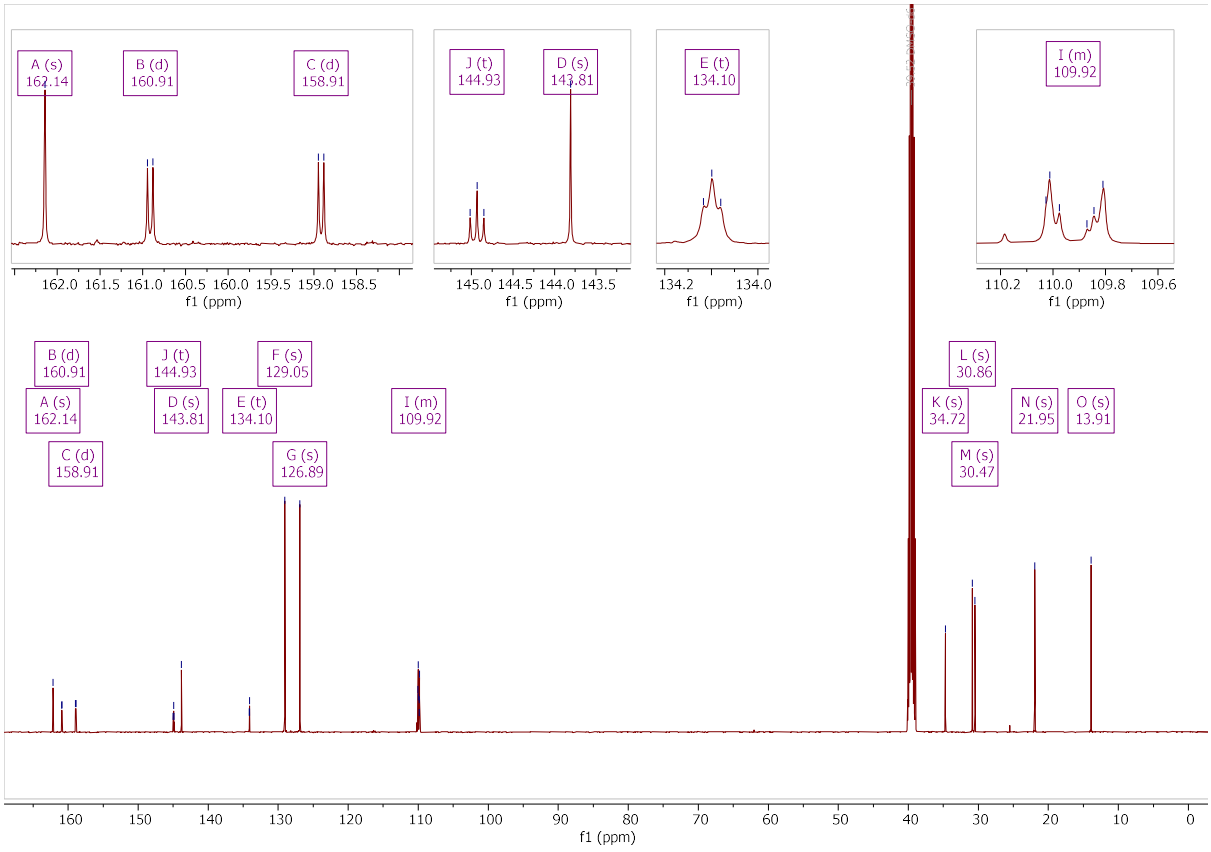


Figure S carbon NMR spectrum of **CA1**

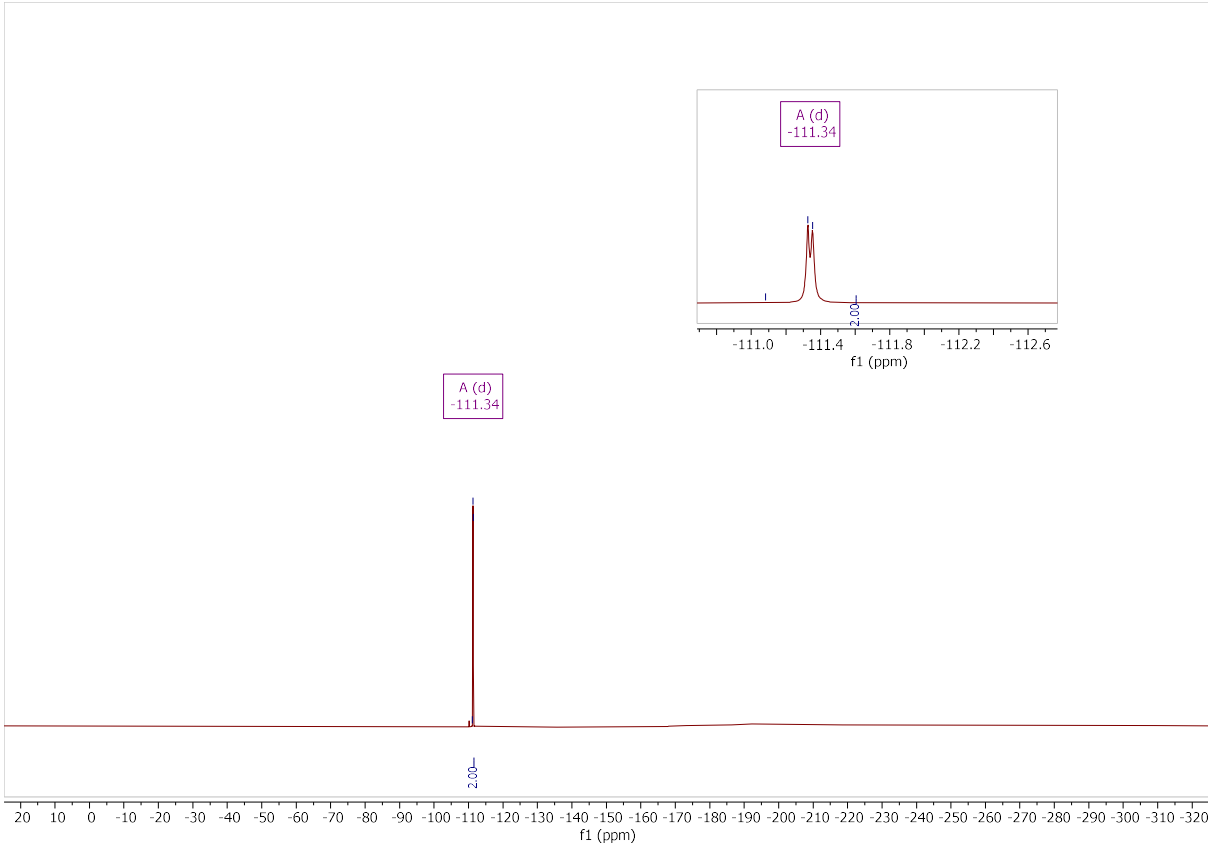
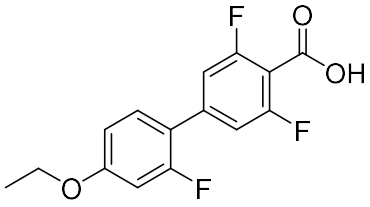


Figure S fluorine NMR spectrum of **CA1**

CA2 | *4-(4-Ethoxy-2-fluorophenyl)-2,6-difluorobenzoic acid*



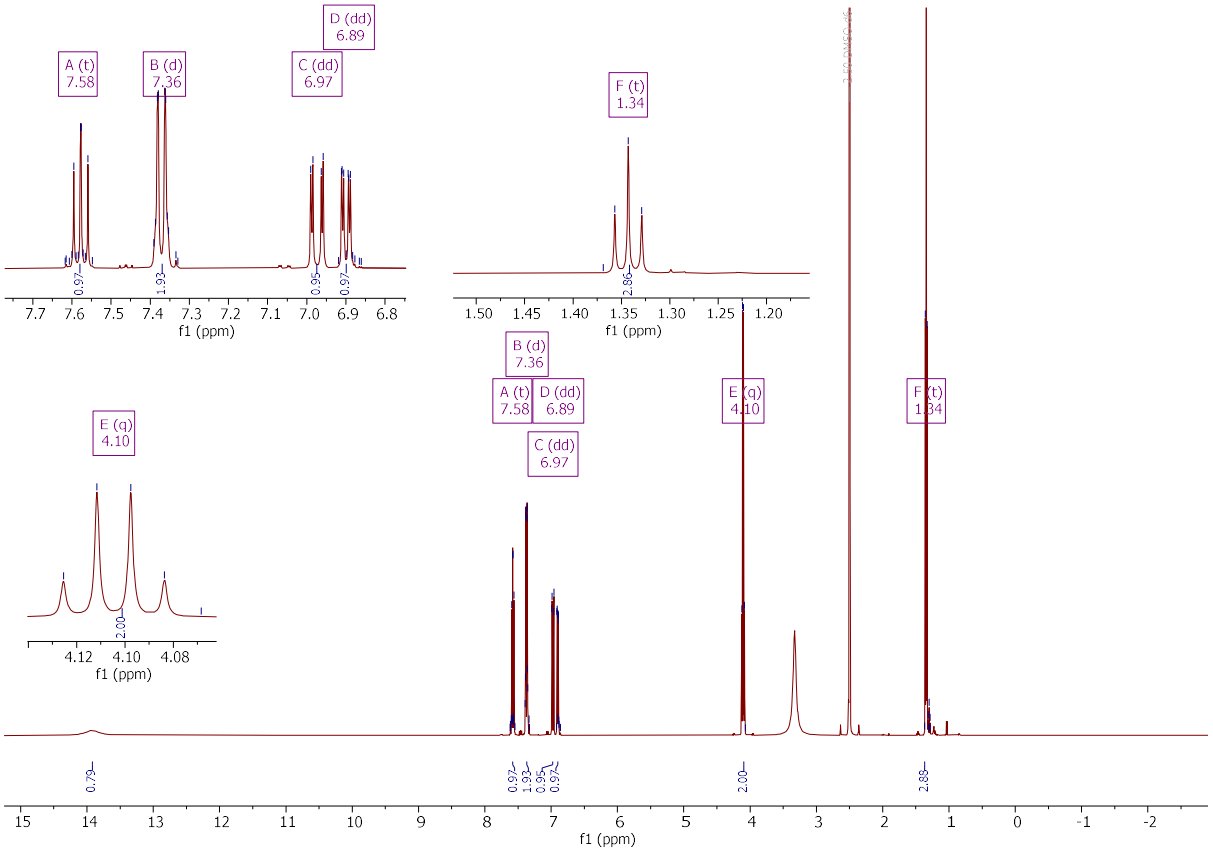


Figure S proton NMR spectrum of **CA2**

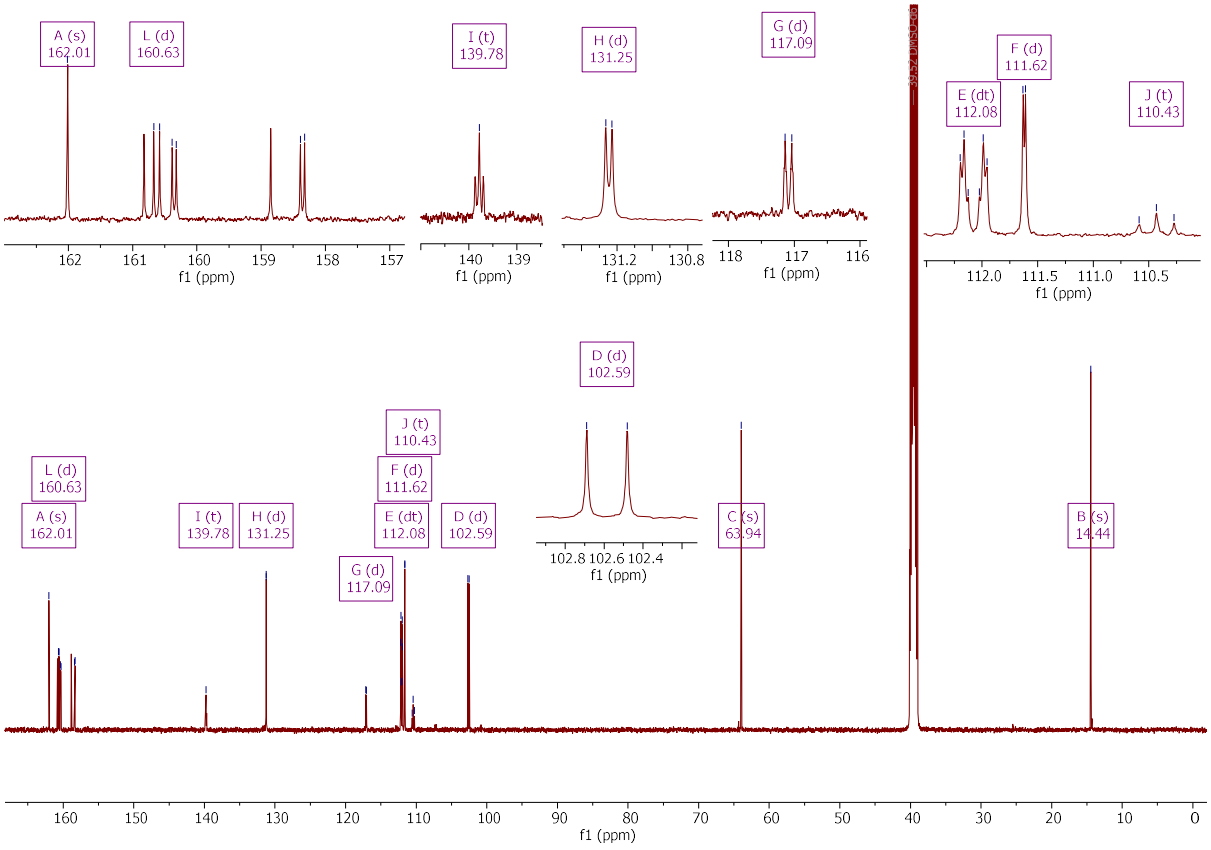


Figure S carbon NMR spectrum of **CA2**

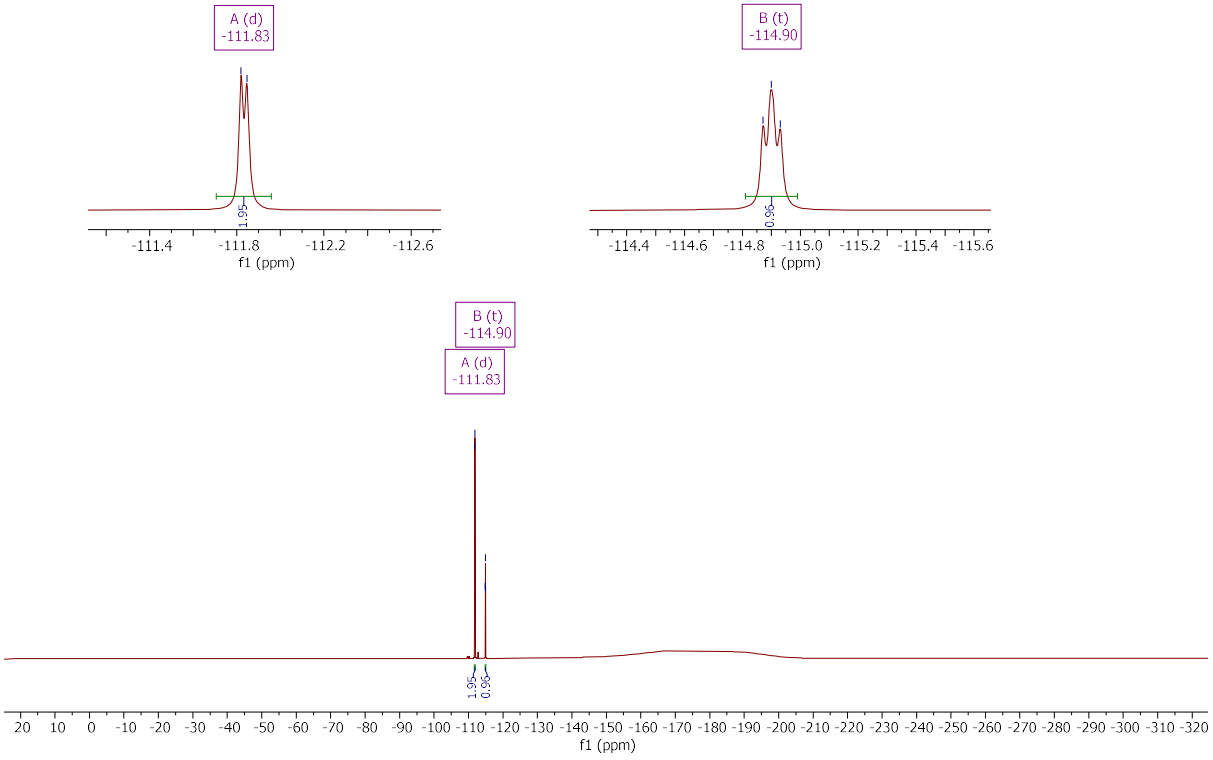
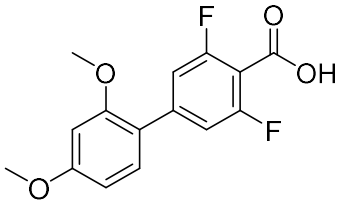


Figure S fluorine NMR spectrum of **CA2**

CA3 | *4-(2,4-Dimethoxyphenyl)-2,6-difluorobenzoic acid*



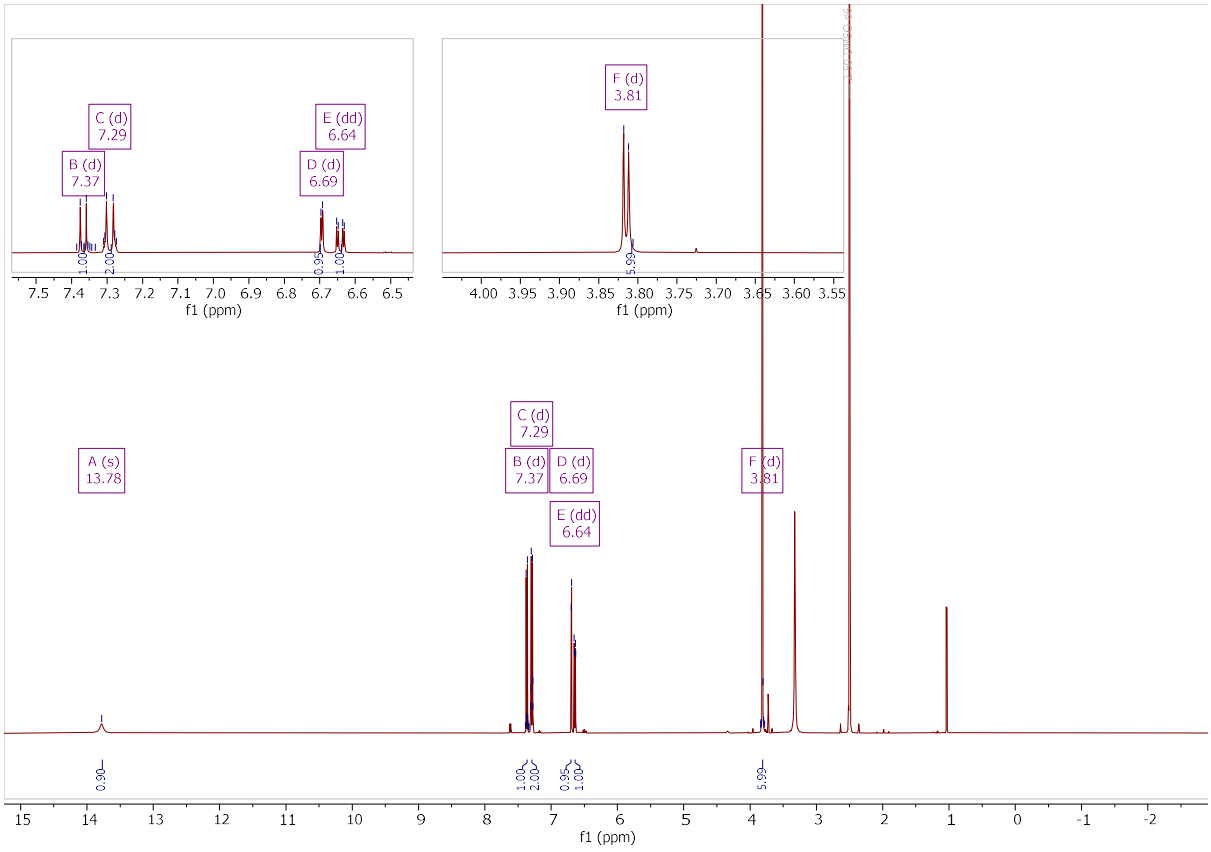


Figure S proton NMR spectrum of **CA3**

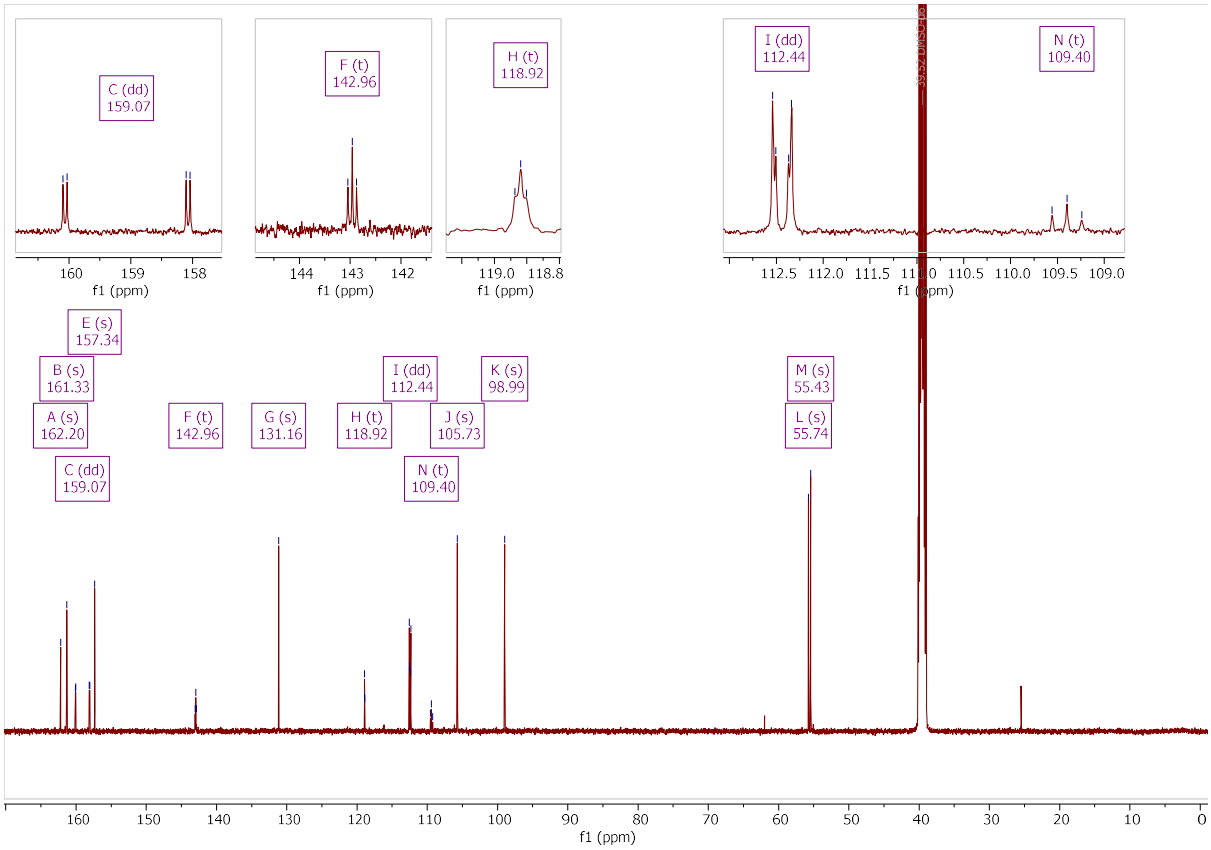


Figure S carbon NMR spectrum of **CA3.** Overlapping C=O, and Ar-F bonds do not have multiple labels but are recorded in data set in section 3.

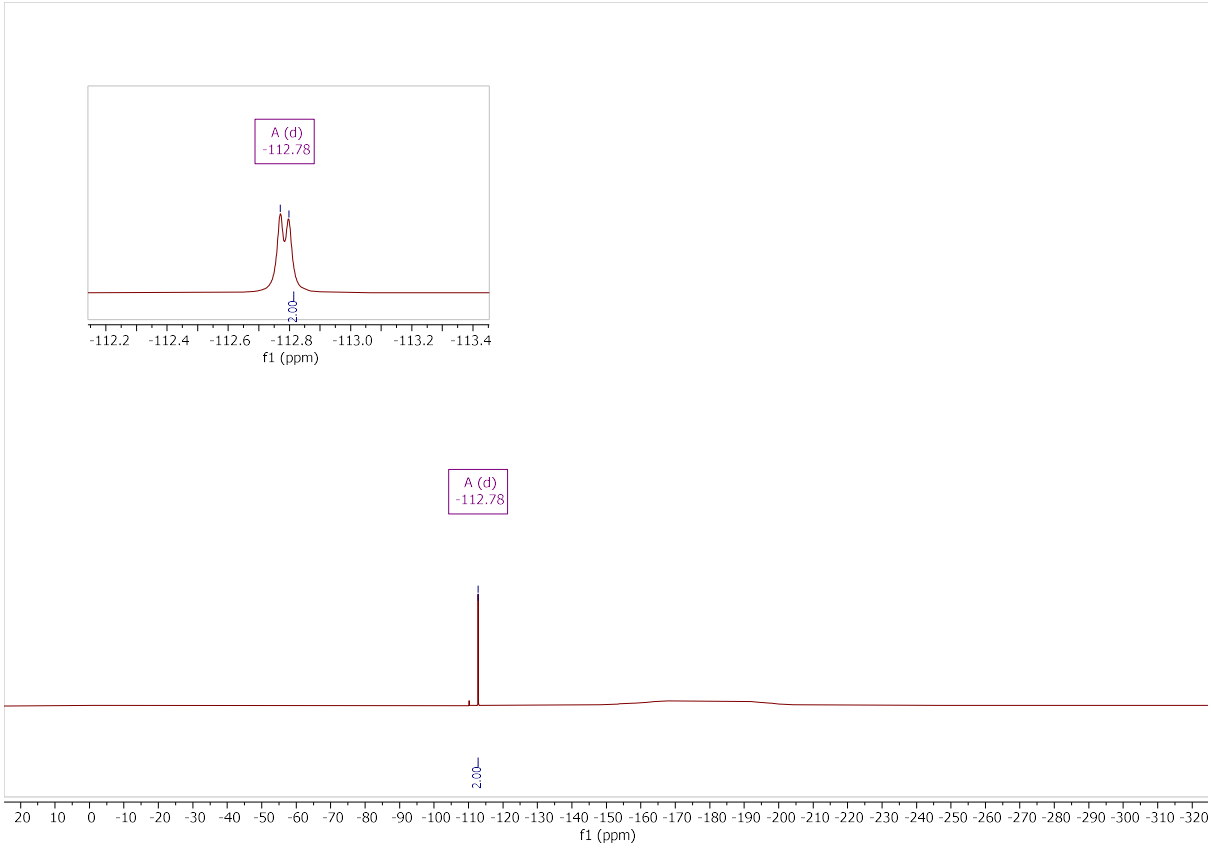
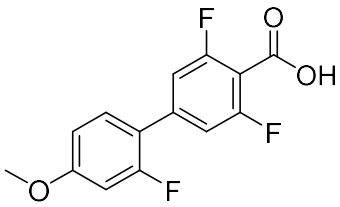


Figure S fluorine NMR spectrum of **CA3**

CA4 | *4-(4-Methoxy-2-fluorophenyl)-2,6-difluorobenzoic acid*



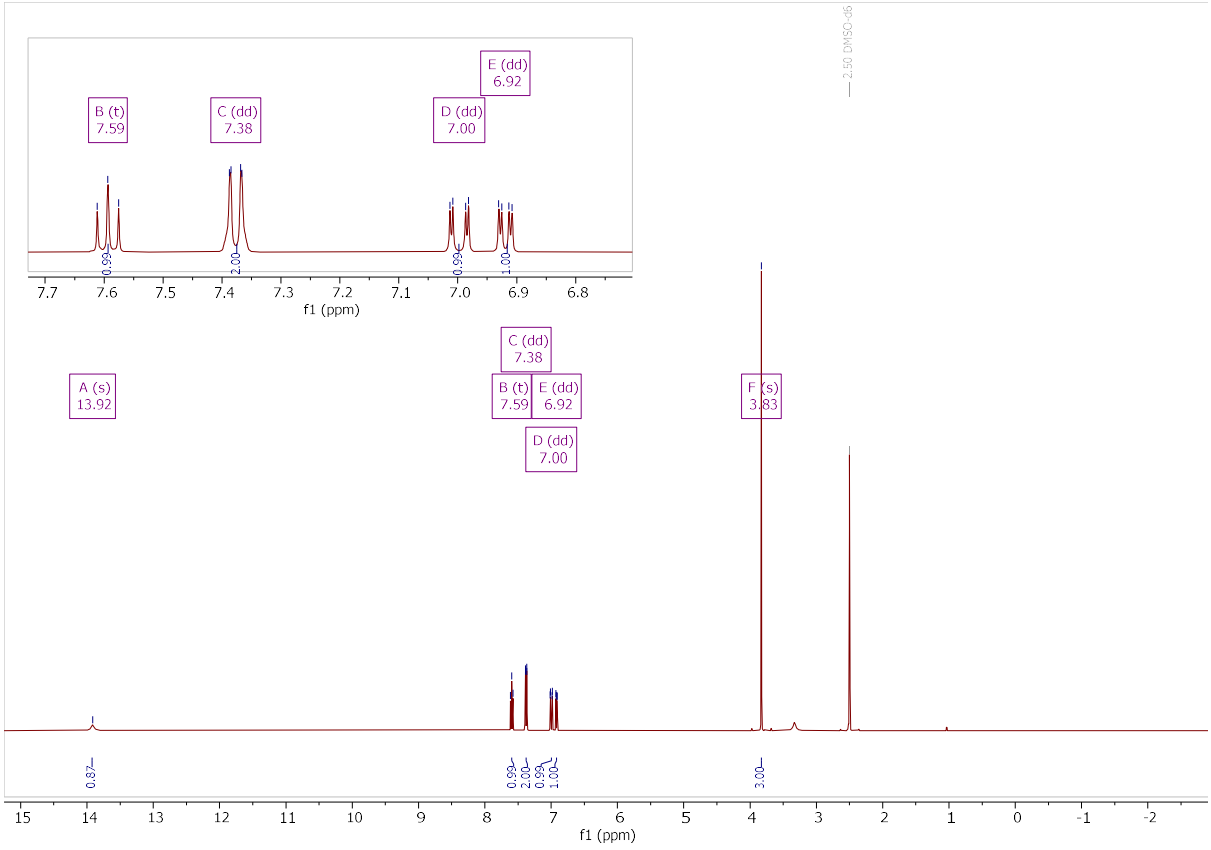


Figure S proton NMR spectrum of **CA4**

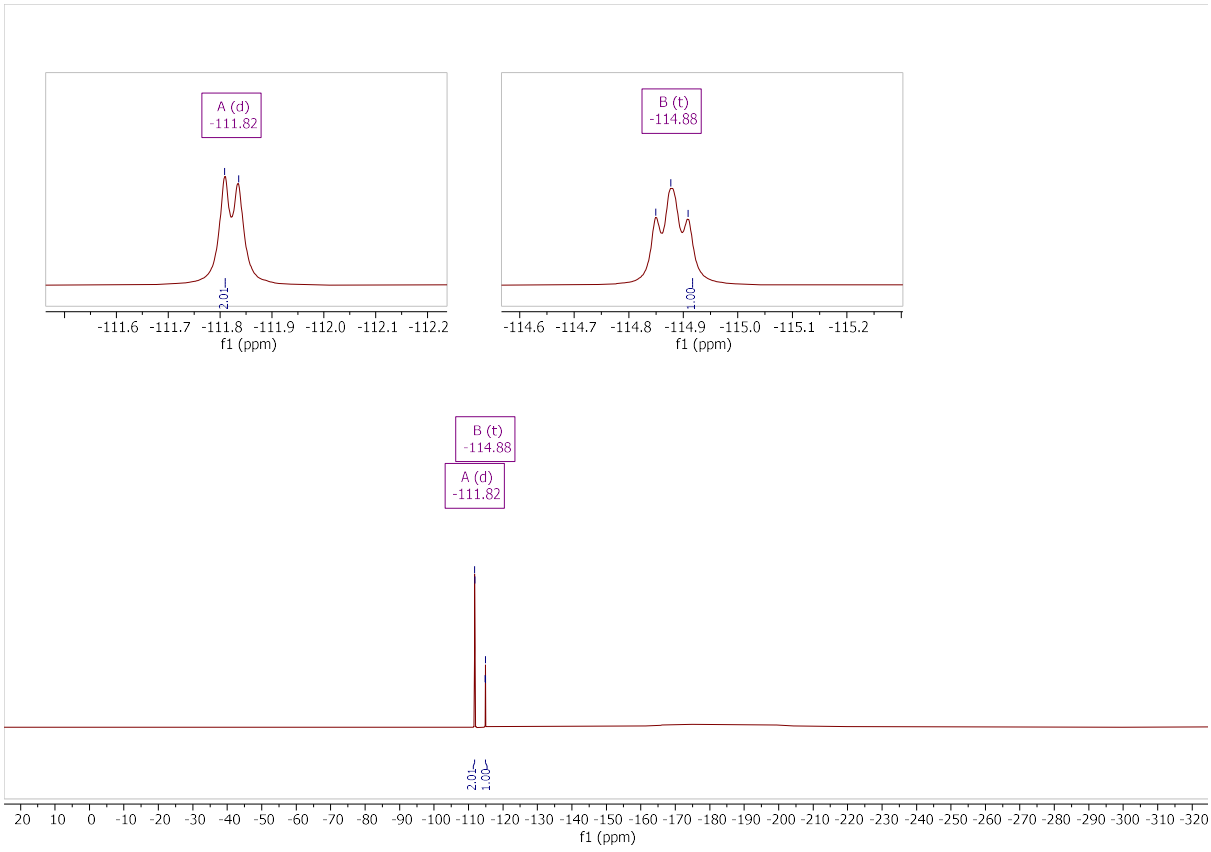


Figure S carbon NMR spectrum of **CA4**

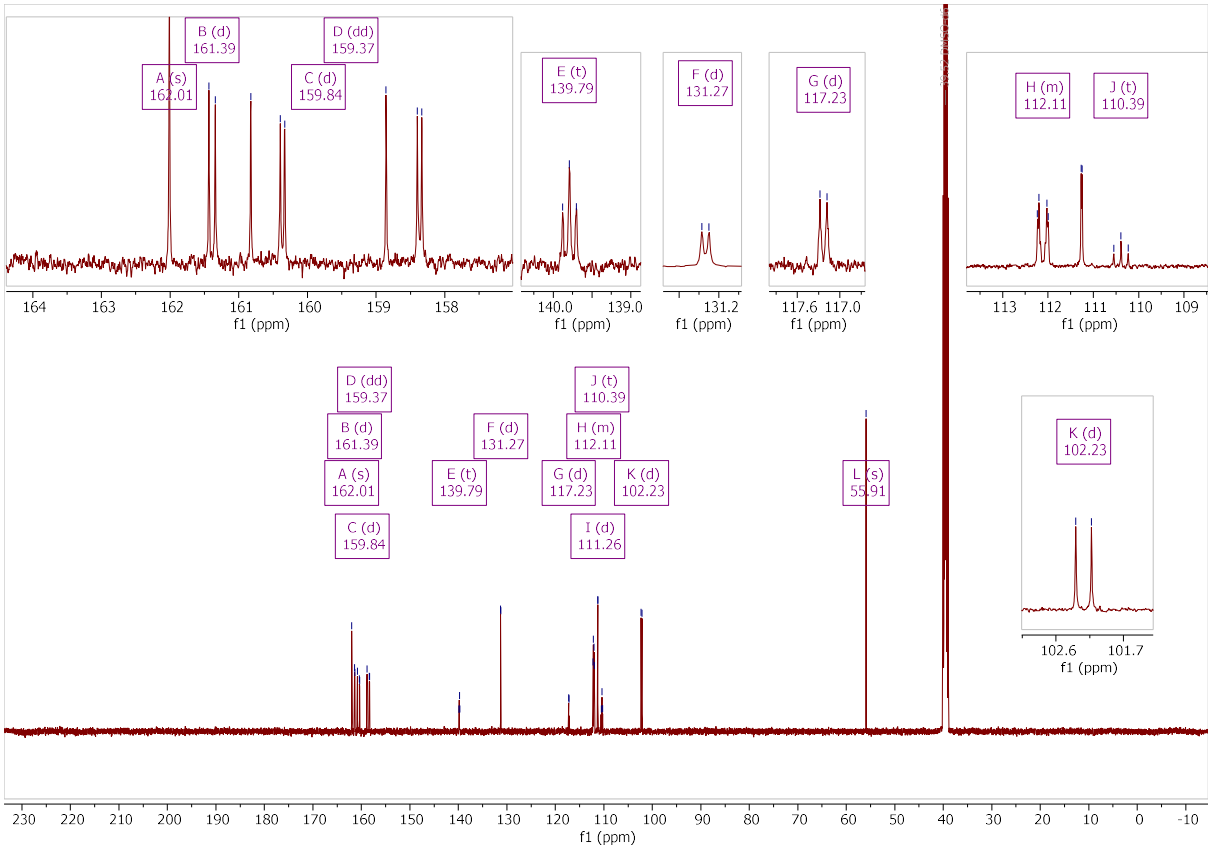


Figure S fluorine NMR spectrum of **CA4**