Introduction

2.1 Enantiomeric Discrimination

The development of quick and precise methods for determining the enantiomeric composition of scalemic mixtures has drawn increasing attention due to the development of asymmetric synthesis and the widespread availability of combinatorial techniques that can produce numerous chiral compounds in a short time. The development of effective assays based on chromatography [1], mass spectrometry [2], UV [3], fluorescence [4], IR thermography [5], circular dichroism [6], capillary electrophoresis [7], and biochemical techniques [8] has been sparked by the necessity for quick ee analysis. Our lab has prepared a number of UV [9], fluorescence [10,11] probes that can be used to measure the amount and enantiomeric excess of scalemic mixes of a variety of substances. An alternative method for determining ee quickly is NMR spectroscopy. [12] A chiral derivatizing agent (CDA), [13] a chiral solvating agent (CSA), [14] or a paramagnetic chiral shift reagent (CSR),[15] such as lanthanide chelate complexes, are typically needed for this. [16] Although CDAs are frequently used to reveal the absolute configuration of chiral compounds, CSA and CSR use is typically preferred for ee analysis since it is quicker and less error-prone.

2.1.1 CDA (Chiral Derivatising Agent)

A chiral auxiliary, sometimes referred to as a CDA or chiral resolving reagent, is used to separate a mixture of enantiomers into diastereomers so that the concentrations of each enantiomer may be determined. Both spectroscopy and chromatography can be used for such analysis.

The development of quick and effective techniques for the assignment of absolute configuration of chiral compounds has received a lot of attention as asymmetric synthesis and natural product chemistry have advanced. The NMR anisotropy method [17], which derivatizes the chiral compound determines the chemical shift difference ($\Delta\delta$) between the two resulting diastereomers, is one of the conventional approaches that is particularly helpful for non-crystalline compounds. The absolute configuration assignment of the chiral chemical can be achieved through careful study of the values based on the diastereomer conformations and the anisotropic shielding effect generated by the

CDA. Continuous attempts have been made [18] to create new CDAs with strong anisotropic effects and rigid structures that produce large (Δδ) values in order to minimise potential. [19-23]

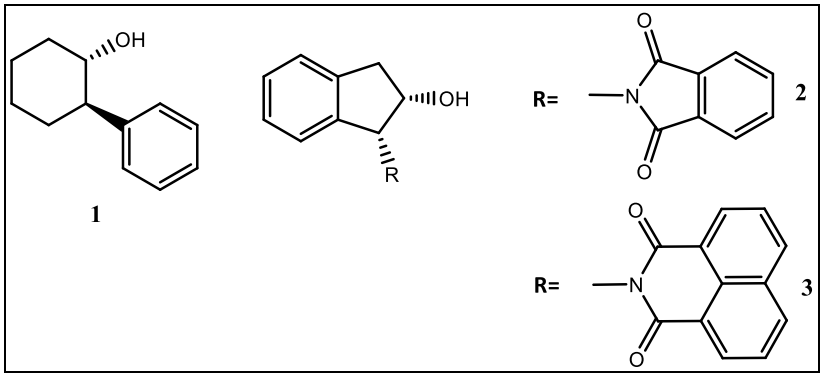


Figure 2.1: CDAs for the absolute configuration assignment of α-chiral carboxylic acids.

2.1.2 CSA (Chiral Solvating Agent)

Over the past few years, numerous CSAs have been created, including pincer-like diamines, alkaloids, BINOL derivatives, porphyrins, cyclodextrins and macrocycles. [24] Among the latter compounds, chiral perazamacrocycles [25] made from *trans*-1,2-diaminocyclohexane, which is enantiomerically pure, have been used. Tanaka and colleagues [26] described using trianglamine. Although a wide variety of chiral solvating agents have been reported, it is still difficult to conduct enantioselective NMR studies on many significant families of molecules. Amino acids, secondary alcohols, amino alcohols, carboxylic acids, hydroxy acids, and amines are some of the most well-liked substrates for NMR resolution experiments using CSAs. [27] In contrast, the discovery of tertiary alcohols with enantioselective identification and the development of efficient NMR analytical tools for substances with several functional groups near to the stereogenic centre.[28] The 3,5-dinitrobenzoyl-derived amide **7** is potent CSA for a number of protected aliphatic and aromatic amines for detection by chromatographic experiments using the Whelk-O selector and analogues. [29,30] According to Kagan et al., **7** can be utilised to tell sulfoxides' enantiomers apart. [31] According to litrature CSA is able to recognise complicated tertiary alcohols in an enantioselective manner. [32]

Using hydrogen bonds, -stacking, and CH/π interactions, crystallographic research reveals that **3** forms a chiral cleft that can only bind one enantiomer of a substrate.

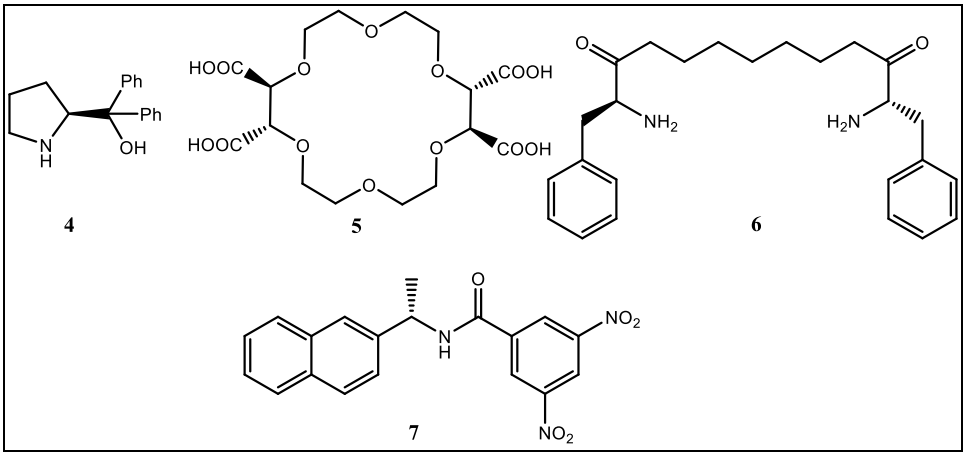


Figure 2.2: CSAs for the supramolecular interaction with α-chiral carboxylic acids.

2.2 Type of CSA (Chiral solvating Agent)

Pirkle's alcohol **9** known as [33] (S)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (TFAE, Fig. 2.3) has been one of the most well-known low-molecular-weight CSAs and has distinguished itself for adaptability and efficacy since CSA's first applications. Pirkle's CSAs have been proposed for numerous applications in the last ten years, such as the ^{13}C NMR discrimination of all eight stereoisomers of tocopherol **8**.[34]

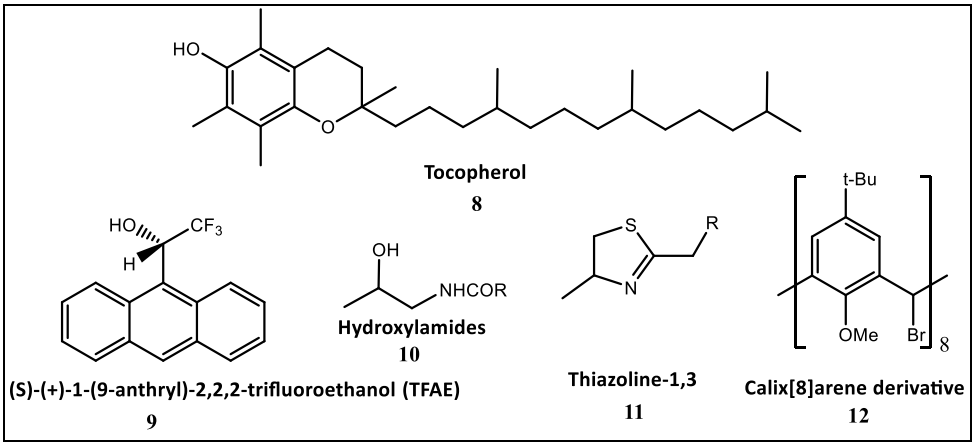


Figure 2.3: Pirkle's alcohol **9** and selected enantiodifferentiated compounds**.**

Since considerable signal splitting is frequently only seen in extremely concentrated solutions, extremely low temperatures, and nonpolar solvents, SIDA, which was first described by Uskokovic in 1969 for dihydroquinine (Fig. 2.4) [35], is both very alluring and constrained in its applicability. An alternative strategy has recently been described [36], involving the modification of the substrate by the introduction of the N-3,5-dinitrobenzoyl group, which greatly favours noncovalent self-aggregation events. This

strategy aims to increase the usefulness of SIDA in chiral analysis. Self-induced enantiodifferentiations up to 0.4 ppm in C_6D_6 were observed for 3,5-DNB-Ala-OMe (Fig. 2.4).

An alternate and elegant method to facilitate the generation of homo- and heterodimers of alcohol enantiomers for NMR discrimination entails the swift and specific cleavage of one of the nonchiral [EtAl(6-Me-2-py)3Li] reagent's pyridine sites by chiral alcohols under mild circumstances to produce heteroleptic aluminium complexes (Fig. 2.4) [37]. In toluene-d^8, the dimers may be easily separated using ^{1}H NMR spectroscopy, which enables quick evaluation of ee's. [37]

Given that diketopiperazine (S)-1-benzyl-3-[(Z)-(dimethylamino)methylidene)-6-methylpiperazine-2,5-dione **17** (DKP, Fig. 2.4) occurs concentration-dependent dimerization methods that result in self-discrimination anomalies and, consequently, Due to this, the precursor to DKP, (S)-1-benzyl-6-methylpiperazine-2,5-dione (**17**, Fig. 2.4), was used as a CSA for DKP as well as for cyclic and acylic amides. [38] This prevented the splitting of enantiomers' NMR signals in the absence of an external CSA. The inclusion of vicinal hydrogen-bond-accepting (C=O) and hydrogen-bond-donating (NH) groups is an important characteristic of this CSA. This stereoelectronic property favoured the differentiation of tryprostatin B analogues' enantiomers (Fig. 2.4a) [39].

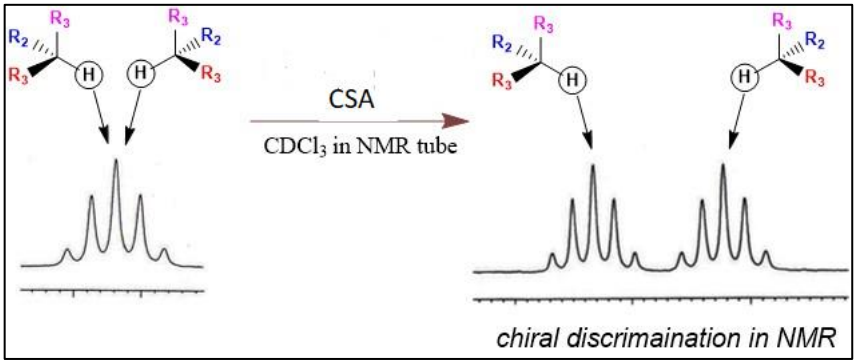


Figure 2.4: Discrimination of signal in NMR by CSA.

N-substituents Diketopiperazines's CSA properties was shown by comparing three compounds (*S*)-1-benzyl-3-methylpiperazine-2,5-dione, (*S*)-**18** and its regioisomer *(S)*-**19** *and one of their close analogue* (*S*)-1-(pentafluorobenzyl)-6-methylpiperazine-2,5-dione, (*S*)-**20** among these the strongest chiral solvating properties for racemic -amino acid derivatives were demonstrated by CSA (S)-**19** in NMR enantiodiscrimination tests of N-acylamino acid esters [40].

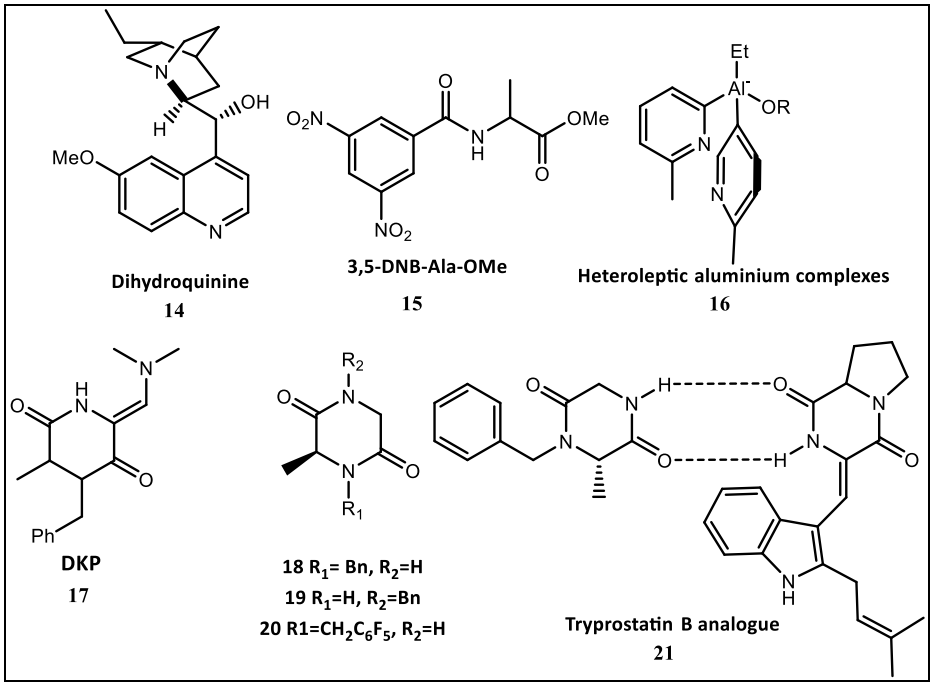


Figure 2.4a: Self-induced diastereomeric anisochronism.

2.3 Enantiomeric excess

The precise characteristics of chiral compounds frequently depend on the purity of the specific optical isomer. The different enantiomers of chiral substances may exist in the same solution, though not always in equal proportions. The most typical technique to describe the degree of enantioselectivity that was observed for a reaction is enantiomeric excess. An indicator of how much one enantiomer dominates the mixture is called enantiomeric excess. A single, absolutely pure enantiomer has an ee of 100%, compared to a racemic mixture's ee of 0%. An ee of 64% is found in a sample that has 82% of one enantiomer and 18% of the other. One metric for determining whether an asymmetric synthesis was successful is enantiomeric excess.

$$ee\% = [\,(R - S) / (R+S)\,] \times 100$$

The terms diastereomeric excess (d.e.%) and percent diastereomeric excess have equivalent meanings and applications for diastereomer combinations.

2.3.1 Analytical Methods

The desire for precise, dependable, and practical techniques of detecting enantiomeric purity has increased as a result of the recent surge in interest in enantioselective synthesis. Spectroscopy and chromatography on chiral stationary phases are the best techniques. High performance liquid chromatography, gas chromatography [41], polarimetry [42],

circular dichroism [43], electrophoresis [44], X-ray crystallography, and NMR spectroscopy are the other commonly used techniques for enantiodiscrimination. Circular dichroism and vibrational circular dichroism methods [45] do not require a separate chiral reference since they are innately chiral. Utilizing only one high-quality crystal for X-ray crystallography prevents it from being used on liquid samples and solutions. Among them, HPLC, GC, polarimetry, and NMR spectroscopy are the methods that are most frequently utilised. However, despite being an achiral technology, NMR spectroscopy is widely used in laboratories all over the world due to its accessibility and pervasiveness. This approach of chirality analysis has been enhanced by the development of stronger and more sensitive NMR instruments. To determine the ee of the chiral compounds, certain biochemical techniques have also recently been devised. [46]

2.3.2 Polarimeter, HPLC & GC method

A relatively large amount of compound is needed when using a polarimeter to detect optical activity , which is an outdated method. In HPLC, only chromatographic systems with the proper chiral selector are capable of direct enantiomeric resolutions. The latter can be deposited on the surface of the column packing material, permanently bonded to or absorbed into the stationary phase (chiral stationary phase) (chiral bonded and chiral coated stationary phases). Analytical chemistry uses gas chromatography (GC) to separate mixture components and identify individual products.

2.3.3 Limitation of HPLC & GC technique:

1. Its operation could be intricate.
2. Different types of chiral columns are needed for various types of molecules.
3. Demands work to establish a method.

2.3.4 NMR as Analytical Technique

Since the development of NMR spectrometers, the majority of chiral molecule research labs have had access to high resolution equipment for this kind of investigation. When recorded in an achiral environment, the NMR spectra of the enantiomers exhibit the identical pattern and chemical changes (solvent). However, the environment around the

nucleus of diastereomeric compounds differs significantly, and this causes a noticeable difference in the signals. As a result, enantiomers must be changed into diastereomers in order for NMR to be useful for chiral analysis. One dimensional NMR experiments and sample preparation are only two examples of how easily and simply NMR spectroscopy may be applied. In this method, one of the chiral auxiliaries, such as a chiral derivatizing agent (CDA), a chiral lanthanide shift agent (CLSR), or a chiral solvating agent (CSA), is used to convert enantiomers into diastereomers [47]. In order to transform chiral analytes into diastereomers via the derivatization technique or noncovalent interactions, one of the fundamental prerequisites of this strategy is that they contain particular functional groups, such as -COOH, -OH, -NH2, COOR, etc. When recorded in an achiral environment, the NMR spectra of the enantiomers exhibit the identical pattern and chemical changes. Diastereomeric compounds' NMR active nuclei, however, have somewhat different environments and exhibit noticeable signal changes. Therefore, it is important to quantitatively convert the analyte to the diastereomers in order to determine the ratio of enantiomers by NMR spectroscopy. By using the proper chiral additive to create diastereomeric derivatives of the analyte, this can be accomplished The three main ways that chiral additives generally change the mixture of enantiomers in a combination of diastereomeric species are as follows:

(a) In this instance, the additive is a "chiral derivatizing agent" (CDA), which forms a covalent bond with the analyte. [48]

(b) It also performs the function of a "chiral solvating agent" (CSA) by generating a labile supramolecular connection. [49]

(c) A complex that can be created between a substrate and a paramagnetic substance and utilised to distinguish enantiomers (CLSR). [50]

2.3.5 Chemical Shift

In CSA two different types of abbreviations are used.

1. **Induced Chemical shifts [Δδ]**

   The discrepancy between the signals in an acid solution and the average of the signals of the two differentiated enantiomers following the mixing of the chiral additive, which is denoted as (Δδ) and frequently expressed in ppm.

2. **Chemical shift nonequivalence [ΔΔδ]**

   After combining the chiral additive, it is the difference between two resolved peaks. The chemical shift non-equivalence symbol is in (ppm) or (ΔΔδ). This signal in (ppm) convert in Hz when this value is multiplied by the operating frequency. This value is crucial in chiral solvating agents to examine the various CSA structures that lead to signal separation. The operator will be able to precisely measure the precise composition of the non-racemic sample as the larger the separation, since it will produce higher value of

2.3.6 Experimental

Mandelic acid and 4-trifluoromandelic acid, were among the racemic functionalized acids that were purchased for usage as received. 4- Bromo mandelic acid was synthesize following the steps outlined in the literature. [51] According to a process described in the literature, other mandelic acid derivatives were synthesize in which the hydroxyl group is blocked by methyl ether. Other acids and their derivatives are made using a technique described in the literature. All Spectra were recorded 400 MHz NMR Avance Bruker spectrometer, ^{1}H NMR spectra were captured, and resonance peaks were referred to TMS (0.00 ppm) as an internal standard. All of the ^{13}C NMR spectra were recorded at 100 MHz, all of the ^{19}F spectra at 376 MHz, and all of the ^{31}P spectra at 162 MHz. The chiral solvating agent $CDCl_3$ was employed throughout the screening process and was directly obtained from Eurotopspin. Once the stock solution in $CDCl_3$ has been prepared, ^{1}H NMR spectra are recorded.

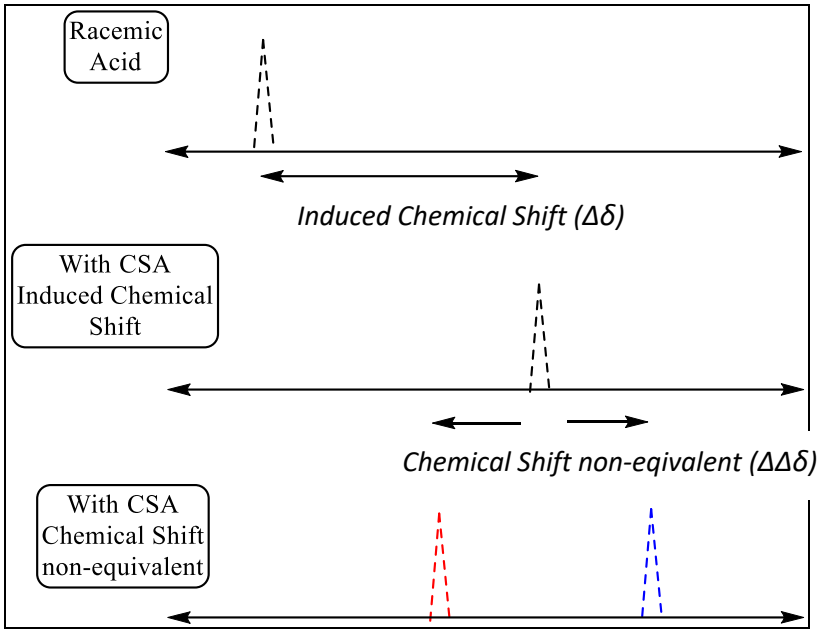


Figure 2.5: Diagrammatic representation of the appearance of H-NMR peaks for calculation of chemical shift nonequivalence (ΔΔδ). and induced chemical shift (Δδ).

2.4 Importance of α Functionalized acids

Chiral carboxylic acids are significant natural products, medicinal ingredients, and essential building blocks in the synthesis of a variety of significant chemicals.[52] Alkaloids, amino acids, and peptides all contain many types of acids and their derivatives. Because they serve as the foundation for novel pharmaceuticals and agrochemicals, chiral acids play a vital role in the chemical industry. They serve as important intermediates in synthetic chemistry as well. In the synthesis, separation, and analysis of acids, the study of chiral recognition of carboxylic acids by artificial receptors proved crucial.

2.5 Development of New Chiral Solvating Agent

The literature has a variety of chiral ligands or auxiliaries, each of which is unique to molecules that contain a particular functional group. However, ongoing research is being done to find additional compounds or ligands to add to the CSA library.

Result and Discussion

2.6 Synthesis of new chiral amide

Chiral amide **22** prepared from suitable amine and 3,5-dinitro benzoic acid was first reported by Kagan and screened for a variety of optically active analytes for the discrimination of signals in NMR.[53-56] (figure 2.5). In our previous study we have modified Kagan's amine by introducing two trifluoro methyl groups on the amide side, thereby attempting to strengthen the proposed hydrogen bonding between its N-H and the carbonyl group of the chiral analyte, by the inductive effect.[57] A considerable improvement in the recognition ability of **23a** was established as compared to **22** in a large number of neutral as well as acidic analytes. We also studied slight improvement by introduction of a para chloro group on the acid side of the amide in **23b** and tested enhanced molecular recognition in few of the examples.[58] Prior to our modifications, there are also few more derivatives of **22** reported in the literature, such as **24a**,[59] **24b**,[60] where the chiral amine is replaced by different aromatic moieties, or by **24c**,[61] where it is substituted by a bicyclic isobornyl amine. All these derivatives have been explored as efficient Chiral Solvating Agents for the successful discrimination of few selected signals of chiral analytes in the NMR analysis by focusing hydrogen as well as few other active nuclei.

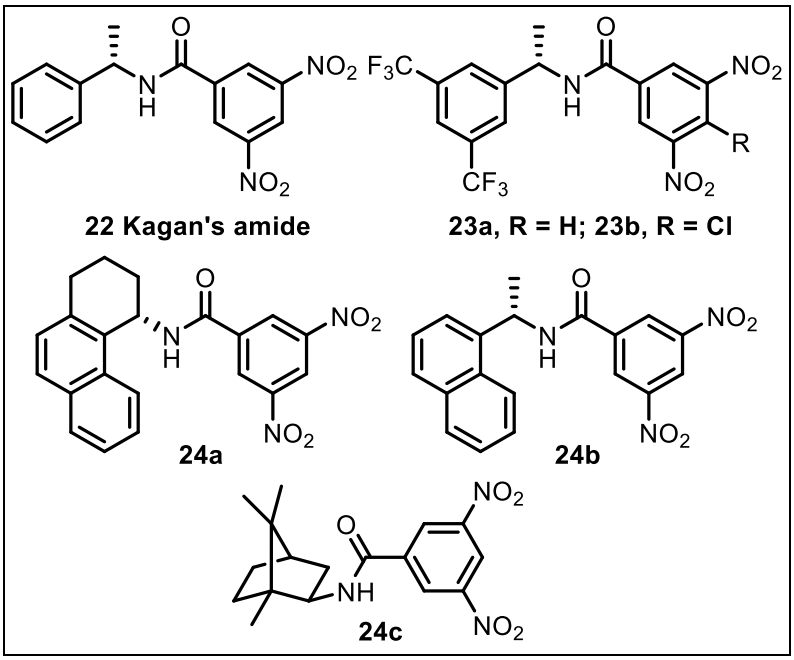


Figure 2.6: Kagan's amide and its variants

As a part of our ongoing studies to search different CSAs, we have prepared and explored aza-macrocycles,[62] amines,[63-65] aminonaphthols [66] and tested them for a range of chiral analytes. In continuation of our efforts to further search derivatives of the Kagan's amide to explore more sites of supramolecular interactions and change the nature of hydrogen bond, we propose to introduce fluorine atoms directly on the aromatic ring on the amine side of the compound (Figure 2.6). In this context we plan to prepare and study three new derivatives of **25**, where two fluorine atoms are attached at different positions of the amine ring. The effect of Ar-F can be of multiple nature, its inductive effect, CH-F interactions, hydrogen bonding with the appropriate hydrogen donor sites in the intermediate with the suitable substrates.[67-70]

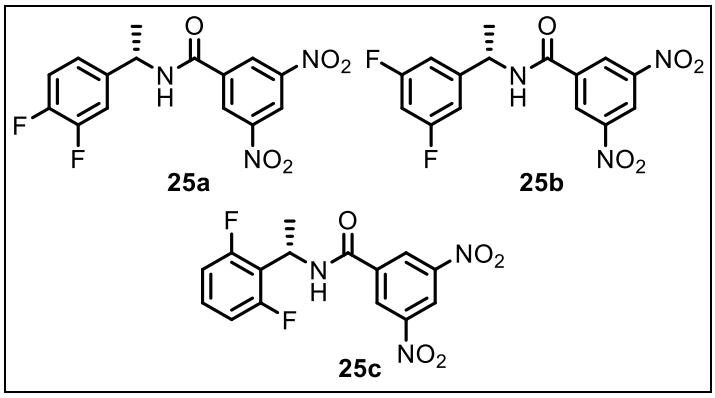


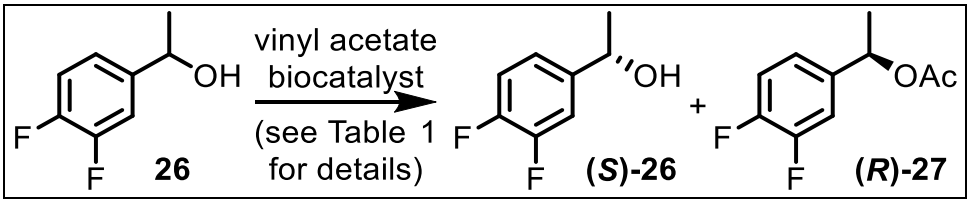
Figure 2.7 Proposed derivatives of Kagan's amide

The negative inductive effect of fluorine on the aromatic ring of amine side will influence the electro positive nature (+δ) of the amide hydrogen and hence its ability to form hydrogen bonding.

2.6.1 Enzymatic Resolution of Alcohols

The three derivatives of the Kagan's amide **25a - 25c** were designed in such a way as to explore the inductive effect of two fluorine atoms as well as the possibility for participation of Ar-F in suitable supramolecular interactions. The molecule **25a** can have the fluorine attached at C-3 position close to the functional group held by a hydrogen bond with the N-H of amide group. While in **25b** and **25c**, the similar interactions can be more controlled due to the symmetrical nature of the substitution of fluorine atoms, besides the cumulative inductive effects of fluorine atoms. The synthesis of the amides is based on the reaction of 3,5-dinitrobenzoylchloride with the corresponding optically pure 1-arylethylamines.[57] The corresponding 1-arylethylamines can be obtained from

corresponding chiral alcohols by Mitsunobu reaction.[71] Therefore, the three derivatives of difluoro Kagan's amides, **25a - 25c**, can be prepared from corresponding optically pure 1-(difluorophenyl)ethan-1-ols. For the preparation of **25a** the optically pure 1-(3,4-difluorophenyl)ethan-1-ol **26** can be obtained by separating the isomers by adopting a well-established protocol of bio-catalytic kinetic resolution of racemic alcohol. One of the more common methods of separation of isomers of alcohol include kinetic resolution involving selective esterification of one of the isomers, while the other one remains unaffected.[72] The racemic sample of **26** was subjected to enzyme mediated kinetic resolution with vinyl acetate as acyl source and immobilized lipase as the bio-catalyst **(Scheme 1)**. The results of optimization of the representative reaction conditions are presented in Table 1.



Scheme 1: Resolution of 1-(3,4-difluorophenyl)ethan-1-ol

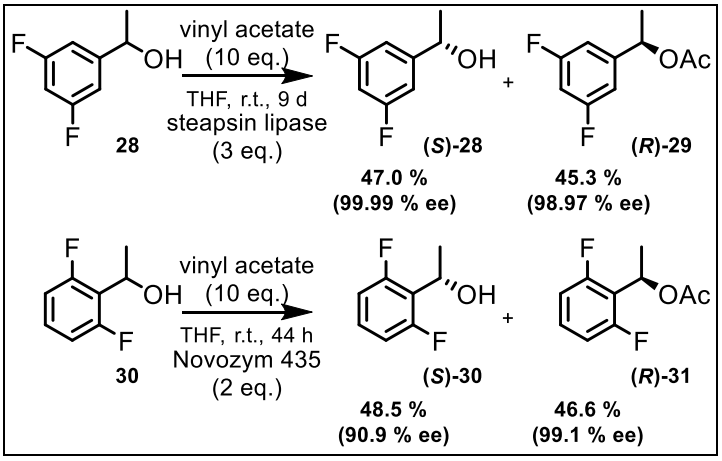
The resolution experiments gave satisfactory results with commercially available immobilized steapsin lipase, with large equivalent of vinyl acetate in dry THF at ambient conditions. The optical purity of the acetylated product **27** could be easily established by HPLC analysis on chiral phase Lux Amylose column. However, the isomers of alcohol **26** could not be separated under different conditions. The sample of the alcohol was hence converted to its acetate for the analysis. The most suitable condition was reached as described in entry 4, and the pure material was collected for further study.

Table 1 Standard conditions[a] for resolution of (±)-**26**

No	Steapsine Lipase (g)	Vinyl acetate (eq.)	Time (days)	Yield[b] of (*S*)-26 (% ee)[c]	Yield[b] of (*R*)-27 (% ee)[c]
1	0.30	2	9	58.0 (70.0)	31.8 (76.8)
2	0.60	3	9	54.6 (77.5)	33.3 (96.0)
3	0.90	5	9	45.0 (95.8)	38.1(99.4)
4	0.90	10	8	45.2 (99.2)	42.5(99.3)
5	0.90	10	9	48.7 (99.8)	46.1 (95.0)

[a]Each reaction is done with 0.30 g (±)-**26**; in dry THF, stirred at r.t.; [b]Isolated in %. [c]Determined by HPLC on Lux Amylose, alcohol was converted to acetate for the analysis.

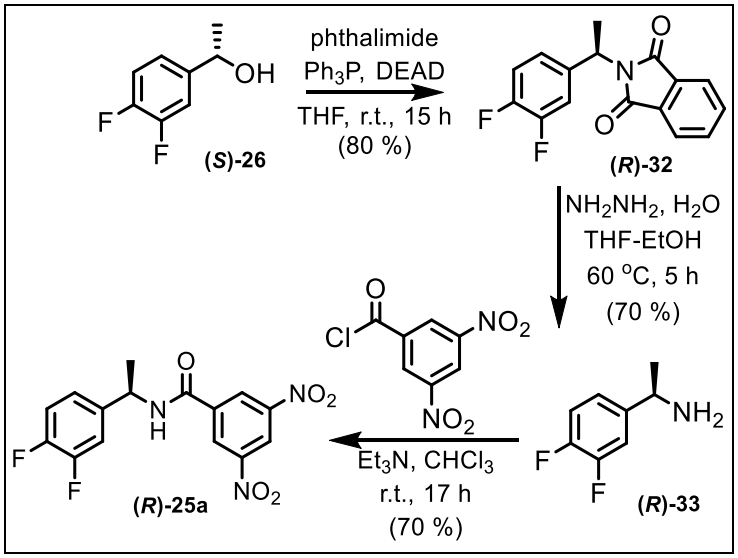
Having standardized the conditions for resolution of (±)-**26**, the focus was diverted to the other two alcohols. The racemic sample of 1-(3,5-difluorophenyl)ethan-1-ol **28** was subjected to similar conditions for kinetic resolution **(Scheme 2)**. With the same bio-catalyst, steapsin lipase, the selective esterification was achieved. The isomer of the (±)-**28** which underwent esterification had the absolute configuration (*R*), similar to the previous case. Attempts to screen the same bio-catalyst for resolution of the third isomer 1-(2,6-difluorophenyl)ethan-1-ol **30** was not successful. Another bio-catalyst Novozyme 435 was tried and the best condition is represented in **(Scheme 2)**. The absolute configuration of the products were established by comparison of the sign of the specific optical rotation with the known values.[57,74]



Scheme 2: Kinetic resolution of (±)-**28** and (±)-**30**.

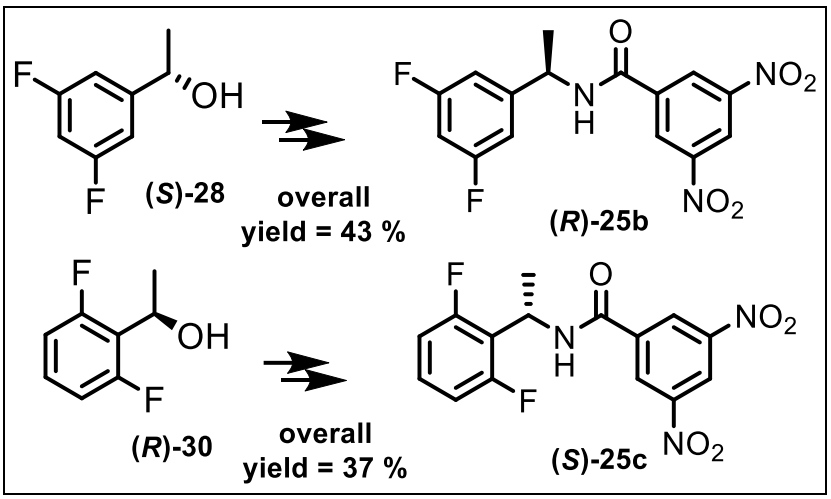
2.6.2 Synthesis of amides

The sample of optically pure alcohols were then converted to the corresponding proposed Kagan's amides by the previously reported synthetic sequence.[57] The alcohol (*S*)-**26** was treated with phthalimide under the standard Mitsunobu conditions to get (*R*)-**32** with inversion of absolute configuration **(Scheme 3)**. The optically pure amine (*R*)-1-(3,4-difluorophenyl)ethan-1-amine (*R*)-33 was obtained from the hydrazine mediated cleavage in good overall yield, which was condensed with 3,5-dinitrobenzoyl chloride to furnish the amide (*R*)-**25a**.



Scheme 3: Synthesis of (*R*)-**25a** from chiral alcohol

The other two alcohols (*S*)-**28** and (*R*)-**30** were similarly converted to the other two amides, (*R*)-**25b** and (*S*)-**25c** with adequately inverting the configuration in moderate overall yields (Scheme 4). The sample of (*R*)-**30** was obtained from its acetate (*R*)-**31** by acid mediated hydrolysis.[57]



Scheme 4: Similar synthesis of (*R*)-**25b** and (*S*)-**25c**

2.6.3 Single Crystal Analysis

To further understand the effect of fluorine substituents of the aromatic rings of the title amides and its effect on possible supramolecular interactions, their single crystal X-ray structural analysis was performed. The effect of angle created between the two aromatic rings, or a cleft, has a direct influence on the ability of molecular recognition in

NMR analysis.[73] The three derivatives **25a**, **25b** and **25c** show the cleft like arrangement with angle of 57.4,° 63.1° and 81.6° respectively. Moreover the angle between the plane passing through the amide -NHCO- and the difluorine containing aromatic ring was seen to be 87.14,° 80.56° and 74.13° respectively for **25a**, **25b** and **25c**. The enantiospecific recognition during the NMR analysis will depend on the effective complexation of analyte with the chiral pocket created by this orientation. The supramolecular interactions may involve π-stacking, of the phenyl rings of the guest molecules with aromatic rings of the amide, hydrogen bonding between amide proton and the carbonyl of the analyte, CH/ π interaction of the diastereotopic protons in close proximity of the aromatic ring of the analyte, Ar-F••••H interactions etc. In the crystal packing some interesting features were seen. The crystal of **4a** was in $P2_12_12_1$ space group, with four units in a single cell (Figure 1). An intermolecular short contact distance of 2.477 Å was seen between Ar-F••••H-$C_6H_2(NO_2)_2$ unit. The sample of **4b** was crystallized in P1 space group, with an intermolecular interaction of 2.519 Å between Ar-F••••H-$C_6H_2(NO_2)_2$ unit. Similarly the crystal of **25c** was grown in $I4_1$ space group, and intermolecular short contact distance of 2.492 Å was seen between Ar-F••••H-$C_6H_2(NO_2)_2$ unit. Further an intermolecular hydrogen bonding was detected in all the three amides. This bond distance of 2.208, 2.052 and 2.260 Å was measured for N-H••••O=C bond in the case of **25a**, **25b** and **25c** respectively.

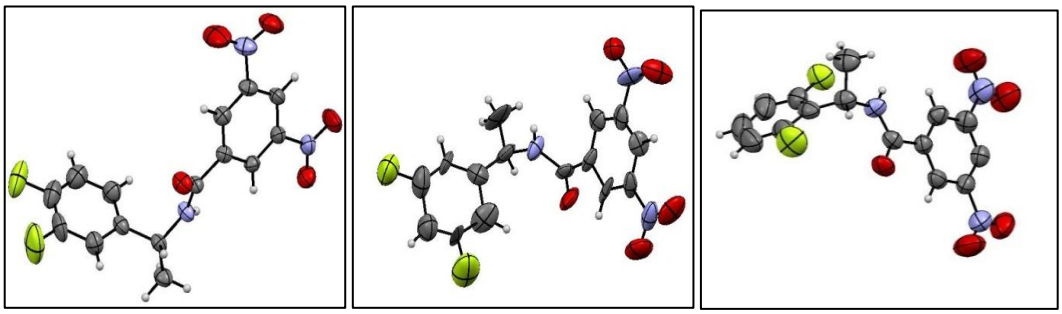


Figure 2.8: ORTEP Diagram of **25a** (CCDC-1835702), **25b** (CCDC-1835701) and **25c** (CCDC-1835751).

2.6.4 Study of Mandelic acid, their derivative and amides with Ligand 25a,25b and 25c

Having prepared and characterized the three derivatives, they were then screened to determine their ability to discriminate the signals of chiral analytes of different types. The three diverse types of analytes (Figure 2.9) were tested to compare the ability of the three derivatives of Kagan's amide. Each of these analytes were mixed with optically pure **4** (1:1 ratio) in 10 mM concentration in $CDCl_3$ and the NMR was recorded. Due to the molecular interaction the signals of analyte shift their position in NMR spectra, which is expressed as induced chemical shift (Δδ), while the gap between the separated signals of enantiomers is referred as nonequivalence (ΔΔδ), expressed in ppm (Table 2). In principal the complex formed by temporary supramolecular interactions behaves like a diastereomer and hence show two sets of signals. From the complex pattern, the distinguishable portion is located and analyzed to find out the above two parameters.

The first type of compounds, chiral amides (**A-I** - **A-IV**), are neutral in nature. For compound A-1, all the three difluoro amides show good recognition, which is seen in shifting of signals on mixing with CSA. Two different signals, the hydrogen attached at the chiral carbon, C_aH and the methyl C_aCH_3, show good separation in ^{1}H NMR spectra for **4a** and **4b**, but better recognition was seen for the latter. However, **4c** could not show any resolution for C_aH, though signals were separated slightly for C_aCH_3.

Interestingly, the amide with both aromatic rings **A-II** showed no recognition with **4a** and **4b**, but showed good discrimination with **4c**; while exactly opposite behavior was seen for the other two amides, **A-III** and **A-IV**.

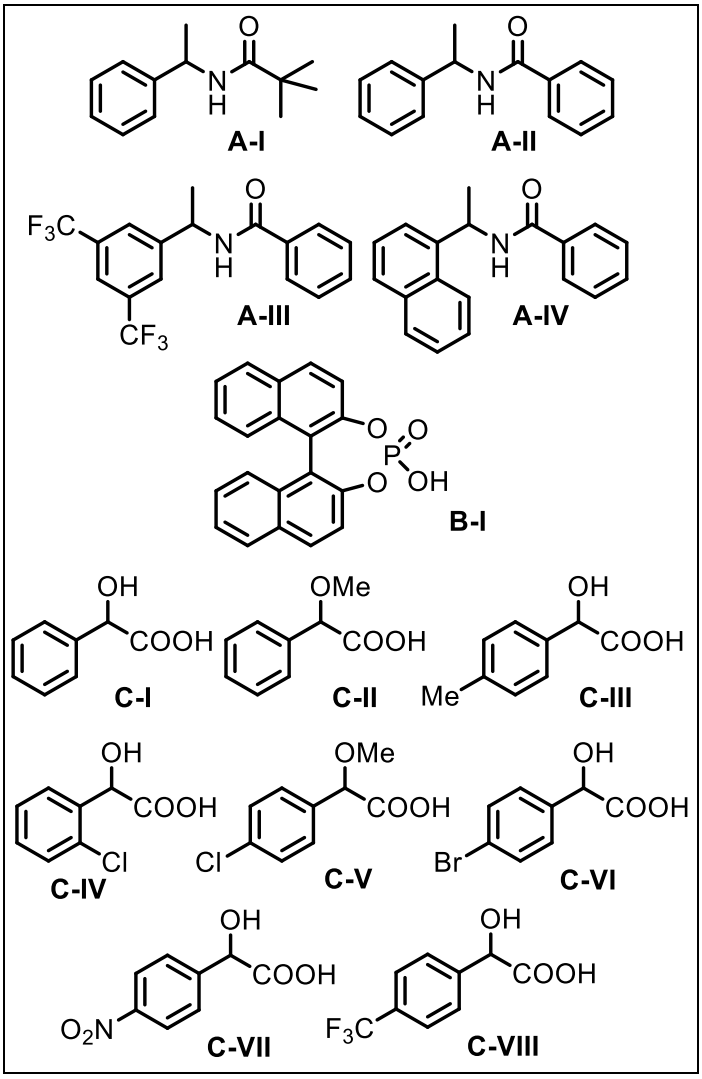


Figure 2.9: Different analytes screened for testing molecular discrimination by NMR spectroscopy

The chiral phosphoric acid such as 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**B-1**) has found much application as Brønsted acid in various asymmetric conversions.[71] The ability of discrimination of **B-1** was tested with the three CSAs, where only **25a** and **25b** were found to respond well. A very effective recognition was seen with **25b**, where the signals of phosphorous in ^{31}P NMR showed base line separation. The separation of signals to the base line is critical for quantitative determination of the ratio of enantiomers in the given sample.

The next set of examples are mandelic acid **C-I** and its derivatives, **C-II** to **C-VIII**. Racemic sample of mandelic acid **C-1** was mixed with each CSA and ^{1}H NMR spectra were recorded. With **25a** and **25b**, some degree of recognition was seen, but failed for **25c**. Interestingly, when it's methoxy derivative **C-II** was screened, better resolution was

observed for **25c**, as compared to the other two. Not only the hydrogen attached to chiral center C$_a$*H*, but the methyl group of methoxy too showed two reasonably well resolved singlets with **25c**. Rest of the derivatives of mandelic acid which were tested show more or less similar results for the three CSAs, with few exceptions. Noteworthy amongst them is the 4-methyl mandelic acid **C-III**, where the aromatic methyl group too showed nicely separated signals in case of **25a** and **25b**. In general **25b** seems to be more effective in inducing the discrimination and causing the shift as against **25c**, which may deviate from the theory of inductive effect.[57]

Table 2 ^{1}H NMR induced chemical shift (Δδ) and nonequivalence (ΔΔδ) of analytes in presence of CSAs

Analyte	**25a** Δδ (ΔΔδ)	**25b** Δδ (ΔΔδ)	**25c** Δδ (ΔΔδ)
A-I	0.073 (0.065)[a] 0.022 (0.020)[b]	0.149 (0.110)[a] 0.044 (0.041)[b]	0.030 (-)[a] 0.017 (0.017)[b]
A-II	-	-	0.214 (0.008)[a] 0.018 (0.017)[b]
A-III	0.139 (0.247)[a]	0.005 (-)[a] 0.001 (0.017)[b]	-
A-IV	0.201 (0.264)[a]	0.392 (0.464)[a]	-
B-I	1.023 (0.033)[c]	1.030 (0.179)[c]	-

C-I	-0.295 (0.006)[a]	-0.321 (0.008)[a]	-
C-II	-0.089 (0.015)[a]	-0.313 (0.017)[a] -0.076 (0.011)[d]	-0.094 (0.013)[a] -0.071 (0.025)[d]
C-III	-0.289 (0.004)[a] -0.034 (0.038)[e]	-0.317 (0.007)[a] -0.140 (0.064)[e]	-0.262 (0.011)[a] -0.078 (0.007)[e]
C-IV	-0.266 (0.004)[a]	-0.272 (0.008)[a]	-0.244 (0.012)[a]
C-V	-0.309 (0.010)[a]	-0.287 (-)[a]	-0.276 (0.011)[a]
C-VI	-0.305 (0.011)[a]	-0.316 (0.009)[a]	-0.270 (0.009)[a]
C-VII	-0.302 (0.002)[a]	-0.308 (0.004)[a]	-0.285 (-)[a]
C-VIII	-0.292 (0.006)[a]	-0.307 (0.008)[a]	-

[a]For C$_a$*H*; [b]For C$_a$C*H*$_3$; (-)= no separation/discrimination;

[c]^{31}P NMR; [d]For OC*H*$_3$; [e]For ArC*H*$_3$. All the spectra were recorded at 400 MHz in $CDCl_3$; at 10mM concentration. One equivalent of DMAP is added for all **B** and **C** analytes.

The induced chemical shift was seen to be quite substantial in the case of **C-III** to **C-VIII**. This observation probably points towards the correlation of the width of the cleft created between the two aromatic rings of the Kagan's amide and the ability of analyte to fit in it.[60,73] In the present system, two factors are influencing the mode of molecular

recognition. The hydrogen bonding between the proton of CON-*H* and the carbonyl of the substrate, while the other interaction will be within the pocket created by the cleft inducing π -π or CH- π or C-H••••F-Ar interactions.

The use of chiral solvating agents to quickly and accurately determine ratio of enantiomers by NMR spectroscopy can be a practical tool. In order to establish the ability of the present CSA to quantitatively determine the ratio of enantiomers the example of **B-I** was screened with **25b**. The study include experiments done with scalemic mixture of analyte with the CSA and plotting the observed values with the calculated ones (Figure 2.91). A similar set of experiment to determine ability for quantitative determination was carried out for analyte **A-I** with ligand **25b** (Figure 2.92)

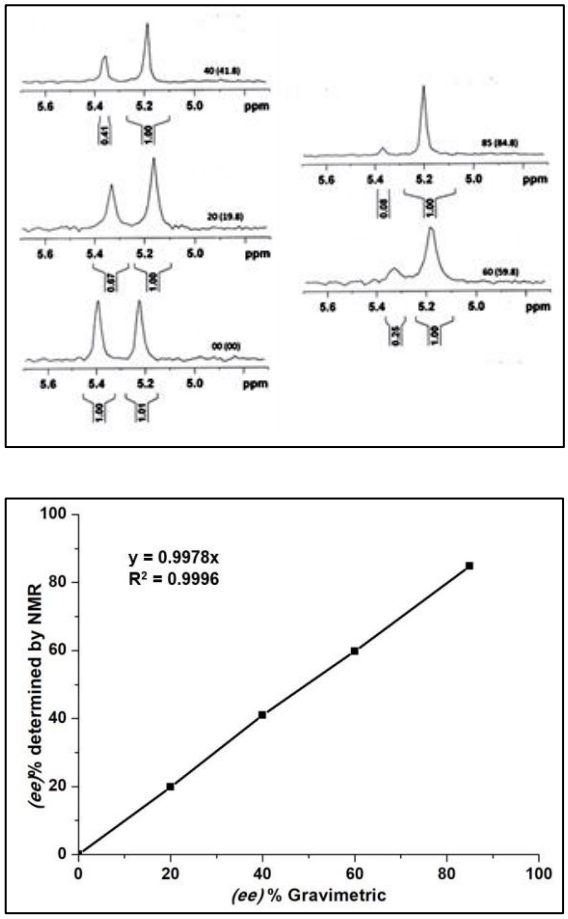


Figure 2.91 (a) Select region of ^{31}P NMR spectra of scalemic mixture of **B-I** in presence of **25b** (top); (b) correlation between theoretical and observed % *ee* values (bottom).

The results clearly indicate an acceptable level of agreement between the two values of estimated and actual enantiomeric excess, hence establishing the accuracy and consistency of the system for practical utility to extend for samples of unknown optical purity.

All the three difluoro derivatives of Kagan's amides were characterized by single crystal X-ray diffraction to understand structural features. Three different classes of analytes were screened for chiral discrimination of signals by molecular recognition with the three amide derivatives by NMR spectroscopy. To determine ability for quantitative determination was carried out for analyte **A-I** with ligand **25b** are given below

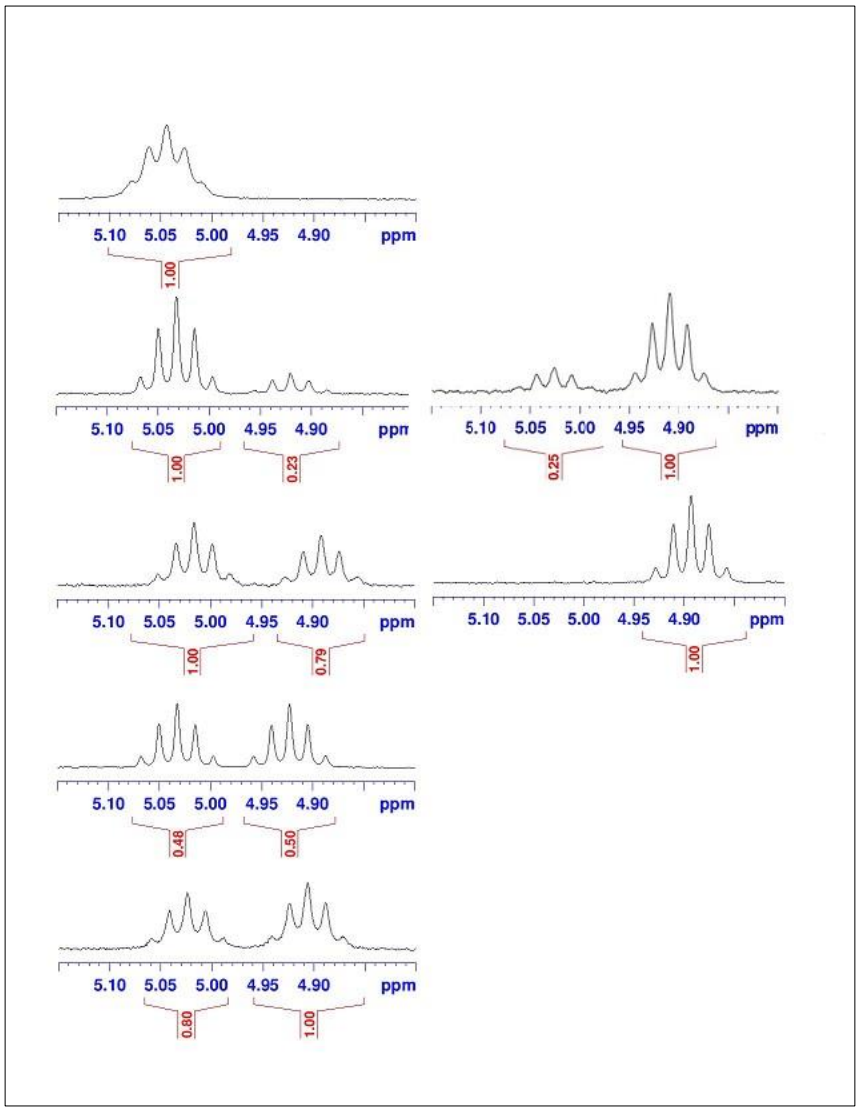


Figure 2.92: (a) Select region of ^{1}H NMR spectra of scalemic mixture of **A-I** in presence of **25b** (top

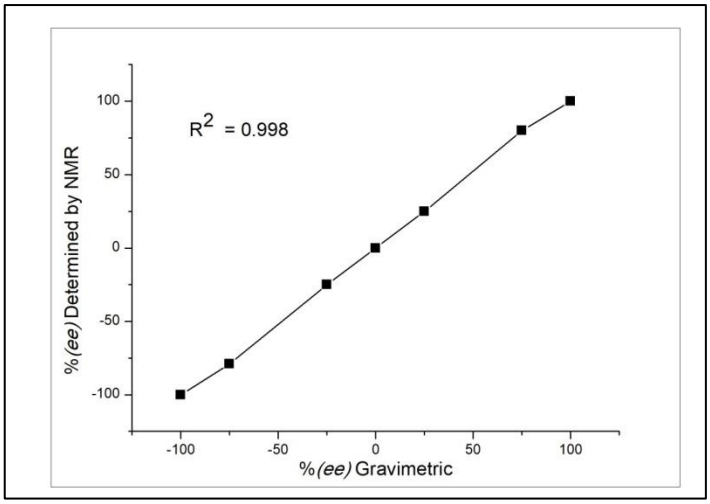


Figure 2.92 (b) correlation between theoretical and observed % *ee* values (bottom). All the spectra were recorded at 400 MHz in $CDCl_3$; at 10 mM concentration

2.7 Conclusion

we have discussed the preparation of three chiral difluorinated derivatives of Kagan's amides and screened them as chiral solvating agents for enantiodiscrimination of the signals of optically pure analytes by NMR spectroscopy. The three derivatives of the amides were in tern prepared by first accessing the optically pure samples of corresponding 1-(difluorophenyl)ethan-1-ols by bio-catalytic kinetic resolution, which were then converted to 1-(difluorophenyl)ethan-1-amine by Mitsunobu reaction, the precursor for Kagan's amides.

2.8 Experimental Section:

Thin layer chromatography was performed on silica gel plates quoted on aluminum sheets. The spots were visualized under UV light or with iodine vapor. All compounds were purified by column chromatography on silica gel (60–120 mesh). All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. NMR Spectra were recorded on a 400 MHz spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR) with $CDCl_3$ as the solvent and TMS as the internal standard. Single crystal X-ray diffraction data was collected Xcalibur, Eos, Gemini diffractometer. IR Spectra were recorded as KBr pallets and specific optical rotations were measured on JACSO P-2000 polarimeter. Melting points were recorded in Thiele's tube using paraffin oil and are uncorrected.

General procedure for resolution of alcohols:

To oven dried flask racemic alcohol **26** (0.3 g, 1.89 mmol) was dissolved in dry THF (10 mL) and steapsine lipase (0.9 g, 3eq w/w), vinyl acetate (1.75 mL, 18.9mmol) were added and stirred at room temperature. The reaction was monitored by TLC. The material was filtered and the filtrate was concentrated in vacuum. Separation was carried out by column chromatography over silica gel using petroleum ether and ethyl acetate as the eluent. The acetate was isolated with 2% ethylacetate in petroleum ether and alcohol with 5% ethylacetate in petroleum ether.

Procedure for Mitsunobu reaction:

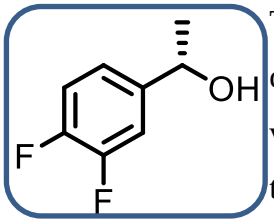
Chiral alcohol (S)-**26** (1.93 g, 1.22 mmol) was taken in a two neck round bottom flask, dissolved in dry THF (10 mL) and was kept in ice bath under nitrogen atmosphere. To this solution triphenylphosphine (3.20 g, 1.22 mmol) and pthalimide (1.79 g, 1.22 mmol) were added. A solution of diethyl diazadicarboxylate (DEAD) (3.34 mL, 1.83 mmol) in THF (5 mL) was added drop wise, and the reaction was stirred (6 h). The reaction was monitored by TLC. The product was purified by column chromatography over silica gel (10% ethyl acetate –petroleum ether) affording white solid (2.69 g, 80%).

General procedure for synthesis of amide ligand*:*

In a dry round bottom flask pthalimide (*R*)-**32** (2.69 g, 9.37 mmol) was dissolved in a mixture of THF (40 ml) & ethanol (10 mL) and treated with drop wise addition of hydrazine hydrate (4.54 ml, 93.7 mmol). The reaction mixture was stirred at $60^{0}C$ (5

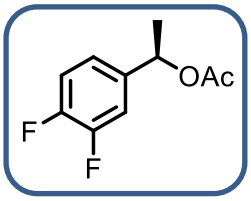
h).The white suspension formed was filtered, washed with THF (2x20 mL) and then organic solvent was evaporated under reduced pressure. To this residue water (50 mL) was added and extracted with dichloromethane (2x50 mL).The organic layer was concerted in vacuum to furnish a viscous liquid (1.02 g, 6.45 mmol). The oil was dissolved in dry chloroform (5 mL) and treated with triehyl amine (0.874 mL, 6.28 mmol).The mixture was allowed to cool (0^{o}C) and solution of 3,5 dinitrobenzoyl chloride (1.44 g, 6.28 mmol) in chloroform (5ml) slowly added (30 min). The mixture was stirred at room temperature (4 h), the solvent was evaporated and the residue was washed with sodium bicarbonate (saturated solution) and extracted with dichloromethane (2X75 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated at reduce pressure. The crude product was purified by column chromatography over silica gel (30%ethyl acetate – petroleum ether) (0.768 g, 69.50%).

(S)-1-(3,4-difluorophenyl)ethan-1-ol (S)-26



To oven dried flask racemic alcohol **26** (0.3 g, 1.89 mmol) was dissolved in dry THF (10 mL) and steapsine lipase (0.9 g, 3eq w/w), vinyl acetate (1.75 mL, 18.9mmol) were added and stirred at room temperature. The reaction was monitored by TLC. The material was filtered and the filtrate was concentrated in vacuum. Separation was carried out by column chromatography over silica gel using petroleum ether and ethyl acetate as the eluent. The acetate was isolated with 2% ethylacetate in petroleum ether and alcohol with 5% ethylacetate in petroleum ether. $[\alpha]^{28}_{D}$ -25.363 (c 2, CH_2Cl_2). {Lit.[74] +27.4 (c = 2.0, CH_2Cl_2; for *R* isomer)} **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.08 (m, 3H), 4.77 (q, *J* = 6.4 Hz, 1H), 1.35 (d, *J* = 6.4 Hz, 3H). **IR(KBr) υ**: 2978, 2929, 1615, 1519, 1433, 1374, 1283, 1151, 1118, 1085, 943, 880, 775 cm^{-1}.

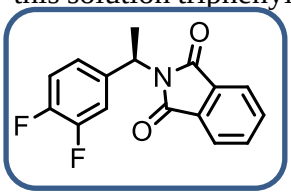
***(R)*-1-(3,4-difluorophenyl)ethyl acetate (R)-27**



$[\alpha]^{28}_{D}$ +85.40 (c 1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.14 (m, 3H), 5.83 (q, *J* = 6.4 Hz, 1H), 1.52 (d, *J* = 6.4 Hz, 3H), 2.09 (s, 3H). **IR (KBr) υ**: 3461, 2966, 1742, 1614, 1521, 1435, 1374, 1286, 1158, 1066, 953, 922, 821, 735 cm^{-1}

2-(1-(3,4-difluorophenyl)ethyl)isoindoline-1,3-dione (R)-32

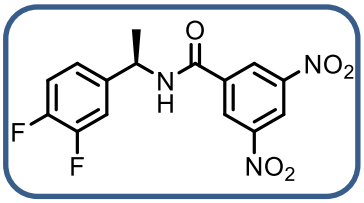
Chiral alcohol (*S*)-**26** (1.93 g, 1.22 mmol) was taken in a two neck round bottom flask, dissolved in dry THF (10 mL) and was kept in ice bath under nitrogen atmosphere. To this solution triphenylphosphine (3.20 g, 1.22 mmol) and pthalimide (1.79 g, 1.22 mmol)



were added. A solution of diethyl diazadicarboxylate (DEAD) (3.34 mL, 1.83 mmol) in THF (5 mL) was added drop wise, and the reaction was stirred (6 h). The reaction was monitored by TLC. The product was purified by column chromatography over silica gel (10% ethyl acetate –petroleum ether) affording white solid (2.69 g, 80%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.83 (m, 1H), 7.73 (m, 2H), 7.37 (m, 1H), 7.23 (m, 1H), 7.12 (m, 1H), 5.52 (q, *J* =7.2 Hz, 1H), 1.91 (d, *J* = 7.2 Hz, 3H). **IR(KBr) υ**: 3049, 2991, 2949, 1766, 1702, 1608, 1520, 1463, 1433, 1388, 1275, 1172, 1008, 960, 879, 770 cm^{-1}

N-(1-(3,4-difluorophenyl)ethyl)-3,5-dinitrobenzamide 25a

In a dry round bottom flask pthalimide (*R*)-**32** (2.69 g, 9.37 mmol) was dissolved in a mixture of THF (40 ml) & ethanol (10 mL) and treated with drop wise addition of hydrazine hydrate (4.54 ml, 93.7 mmol). The reaction mixture was stirred at 60^0C (5 h).The white suspension formed was filtered, washed with THF (2x20 mL) and then organic solvent was evaporated under reduced pressure. To this residue water (50 mL) was added and extracted with dichloromethane (2x50 mL).The organic layer was concerted in vacuum to furnish a viscous liquid (1.02 g, 6.45 mmol). The oil was dissolved in dry chloroform (5 mL) and treated with triehyl amine (0.874 mL, 6.28 mmol).The mixture was allowed to cool (0^oC) and solution of 3,5 dinitrobenzoyl chloride (1.44 g, 6.28 mmol) in chloroform (5ml) slowly added (30 min). The mixture was stirred at room temperature (4 h), the solvent was evaporated and the residue was washed with sodium bicarbonate (saturated solution) and extracted with dichloromethane (2X75 mL).

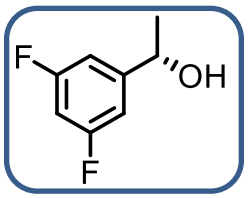


The organic layer was dried over anhydrous sodium sulfate and concentrated at reduce pressure. The crude product was purified by column chromatography over silica gel (30%ethyl acetate – petroleum ether) (0.768 g, 69.50%). $[\alpha]^{28}_D$ -12.56 (c 1, CH_2Cl_2) **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 9.20 (t, *J* = 2 Hz, 1H), 8.97 (d, *J* = 2 Hz, 1H), 7.20 (m, 3H), 5.33 (q, *J* = 6.8 Hz, 1H), 1.68 (d, *J* = 6.8 Hz, 1H), **^{19}F NMR(376 MHz, $CDCl_3$)**: δ (-136.365) - (-138.304) (d, *J* = 22 Hz, 1F), (-

138.545) - (-138.487) (d, *J* = 22 Hz, 1F).**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 22.26, 49.01, 115.78 (d, *J* =27 Hz, 1 C-F), 117.78 (d, *J* =23 Hz, 1 C-F), 121.37, 123.38 (t, *J* = 3 Hz 1 C-F), 128.18, 137.18, 142.35 (t, *J* = 4 Hz, 1 C-F), 147.60 (d, *J* =12 Hz, 1 C-F), 148.54 (d, *J* =16 Hz, 1C), 150.02 (d, *J* =13 Hz, 1 C-F), 150.96 (d, *J* =13 Hz, 1 C-F), 161.99 (s). **IR (KBr)** υ: 3281, 3098, 2924, 2854, 1643, 1708, 1645, 1596, 1540, 1455, 1345, 1284, 1163, 1079, 978, 857, 723cm^{-1} **HRMS (ESI+)** m/z calcd for $C_{15}H_{11}F_2N_3O_5Na$ $(M+Na)^+$ 374.0559, found 374.0562.

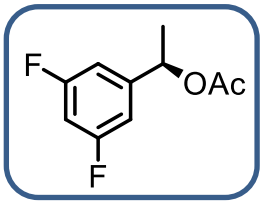
(S)-1-(3,5-difluorophenyl)ethan-1-ol (S)-28

To oven dried flask racemic alcohol **28** (0.3 g, 1.89 mmol) was dissolved in dry THF (10 mL) and steapsine lipase (0.9 g, 3eq w/w), vinyl acetate (1.75 mL, 18.9mmol) were added and stirred at room temperature. The reaction was monitored by TLC. The material was filtered and the filtrate was concentrated in vacuum. Separation was carried out by column chromatography over silica gel using petroleum ether and ethyl acetate as the eluent. The acetate was isolated with 2% ethylacetate in petroleum ether and alcohol with 5% ethylacetate in petroleum ether $[\alpha]^{28}_D$ +34.8 (c 1.3, CH_2Cl_2) {Lit. [74] +34.8 (c 1.3, CH_2Cl_2; for *R* isomer}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.91 (d, *J* = 2.4 Hz, 2H), 6.70 (t, *J* = 2.4 Hz, 1H), 4.89 (q, *J* = 6.4 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 1H).**IR (KBr)** υ: 3386, 3097, 2978, 2829, 1719, 1625, 1598, 1455, 1373, 1316, 1144, 1117, 1030, 981, 859, 692 cm^{-1}



(R)-1-(3,5-difluorophenyl)ethyl acetate (R)-29

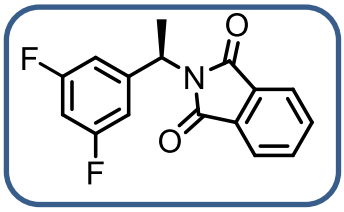
$[\alpha]^{28}_D$ +80.46 (c 1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.87 (m, *J* =2.4 Hz, 2H), 6.73 (m, *J* = 2.4 Hz, 1H), 5.83 (q, *J* = 6.4 Hz, 1H), 2.11 (s, 3H), 1.52 (d, *J* = 6.4 Hz, 1H). **IR (KBr)** υ: 3419, 2987, 2934, 1743, 1627, 1602, 1455, 1373, 1324, 1237, 1154, 1120, 1074, 981, 916, 740 cm^{-1}



2-(1-(3,5-difluorophenyl)ethyl)isoindoline-1,3-dione

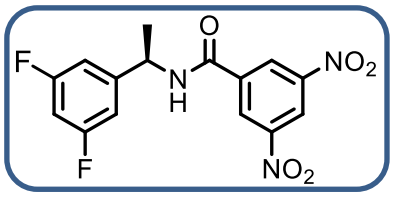
Chiral alcohol (1.80 g, 1.13 mmol) was taken in a two neck round bottom flask, dissolved in dry THF (10 mL) and was kept in ice bath under nitrogen atmosphere. To this solution triphenylphosphine (2.96 g, 1.13 mmol) and pthalimide (1.66 g, 1.13 mmol) were added.

A solution of diethyl diazadicarboxylate (DEAD) (3.11 mL, 1.68 mmol) in THF (5 mL) was added drop wise, and the reaction was stirred (6 h). The reaction was monitored by TLC. The product was purified by column chromatography over silica gel (10% ethyl acetate –petroleum ether) affording white solid (2.48 g, 73.75%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.02 (dd, *J* = 5.2, 2.4 Hz, 2H), 6.72 (tt, *J* = 4.0, 2.4 Hz, 1H), 5.52 (q, *J* = 7.6 Hz, 1H), 1.91 (d, *J* = 7.2 Hz, 3H). **IR(KBr)** υ: 3050, 2991, 2949, 2781, 2295, 2048, 1991, 1955, 1904, 1766, 1702, 1609, 1521, 1433, 1389, 1278, 1051, 937, 833, 770 cm^{-1}



N-(1-(3,5-difluorophenyl)ethyl)-3,5-dinitrobenzamide 25b

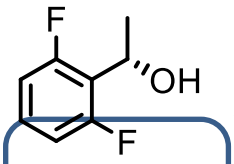
In a dry round bottom flask pthalimide (2.50 g, 8.70 mmol) was dissolved in a mixture of THF (40 ml) & ethanol (10 mL) and treated with drop wise addition of hydrazine hydrate (4.21 ml, 87 mmol). The reaction mixture was stirred at 60^0C (5 h).The white suspension formed was filtered, washed with THF (2x20 mL) and then organic solvent was evaporated under reduced pressure. To this residue water (50 mL) was added and extracted with dichloromethane (2x50 mL).The organic layer was concerted in vacuum to furnish a viscous liquid (0.90 g, 5.69 mmol). The oil was dissolved in dry chloroform (5 mL) and treated with triehyl amine (0.79 mL, 5.69 mmol).The mixture was allowed to cool (0^oC) and solution of 3,5 dinitrobenzoyl chloride (1.30 g, 5.69 mmol) in chloroform (5ml) slowly added (30 min). The mixture was stirred at room temperature (4 h), the solvent was evaporated and the residue was washed with sodium bicarbonate (saturated solution) and extracted with dichloromethane (2X75 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated at reduce pressure. The crude product was purified by column chromatography over silica gel (30%ethyl acetate – petroleum ether) (0.700, 63.34%). $[\alpha]^{28}_D$ -31.00 (c 1, CH_2Cl_2).**^{1}H NMR (400 MHz, $CDCl_3$)**: δ 9.20 (t, *J* = 2.0 Hz, 1H), 8.99 (d, *J* = 2.0 Hz, 2H), 6.92 (d, *J* = 6.4 Hz, 2H), 6.7 (t, *J* = 5.6, 2.4 Hz, 1H), 5.34 (q, *J* = 6.4 Hz, 1H), 1.65 (d, *J* = 12.8, 8 Hz 3H) **^{19}F NMR (376 MHz, $CDCl_3$)**: δ 108.37 **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 22.07, 49.36, 102.65 (t, *J* = 26 Hz, 1 C-F), 109.76 (dd, *J* =19, 7 Hz, 1 C-F), 121.30, 128.19, 137.10, 148.58, 149.35(t, *J* = 9 Hz, 1C-F), 121.39, 161.63 (d, *J* = 244, 13 Hz 1 C-F), 162.04,164.07(d, *J* = 244, 13 Hz, 1C-F). **IR (KBr)** υ: 3281, 3098, 2924, 2854,



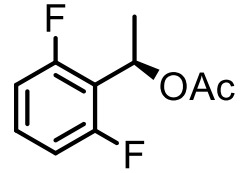
1643, 1708, 1645, 1596, 1540, 1455, 1345, 1284, 1163, 1079, 978, 857, 723 $cm.^{-1}$ **HRMS(ESI+)** m/z calcd for $C_{15}H_{12}F_2N_3O_5$ $(M+H)^+$ 352.0739, found 352.0734.

(S)-1-(2,6-difluorophenyl)ethan-1-ol (S)-30

To oven dried flask racemic alcohol **30** (0.3 g, 1.89 mmol) was dissolved in dry THF (10 mL) and Novozyme lipase (0.6 g, 2eq w/w), vinyl acetate (1.75 mL, 18.9mmol) were added and stirred at room temperature. The reaction was monitored by TLC. The material was filtered and the filtrate was concentrated in vacuum. Separation was carried out by column chromatography over silica gel using petroleum ether and ethyl acetate as the eluent. The acetate was isolated with 2% ethylacetate in petroleum ether and alcohol with 5% ethylacetate in petroleum ether



$[\alpha]^{28}_D$ -20.20 (c 1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.21 (m, 1H), 6.75 (m, 1H), 5.27 (q, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.8 Hz, 3H). **IR (KBr)** υ: 3609, 3416, 2982, 2937, 1713, 1624, 1593, 1470, 1406, 1373, 1265, 1198, 1064, 972,899,788 cm^{-1}.



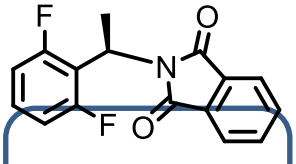
(R)-1-(2,6-difluorophenyl)ethyl acetate (R)-31

$[\alpha]^{28}_D$ +84.26 (c 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (m, 1H), 6.87 (m, 2H), 6.21 (q, *J* = 6.8 Hz, 1H), 2.06 (s, 3H), 1.65 (d, *J* = 6.8 Hz, 3H). IR (KBr) υ: 3466, 2987, 2940, 1744, 1626, 1593, 1472, 1373, 1287, 1289, 1237, 1077, 944, 857 cm^{-1}.

(*R*)-**31** Acetate was converted to (*R*)-**30** alcohol by conc. HCl in MeOH.[75]

2-(1-(2,6-difluorophenyl)ethyl)-1H-indene-1,3(2H)-dione

Chiral alcohol (*R*)-**30** (1.90 g, 1.21 mmol) was taken in a two neck round bottom flask, dissolved in dry THF (10 mL) and was kept in ice bath under nitrogen atmosphere. To this solution triphenylphosphine (3.14 g, 1.21 mmol) and pthalimide (1.75 g, 1.21 mmol) were added. A solution of diethyl diazadicarboxylate (DEAD) (3.31 mL, 1.80 mmol) in



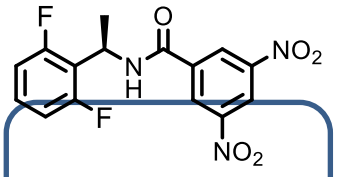
THF (5 mL) was added drop wise, and the reaction was stirred (6 h). The reaction was monitored by TLC. The product was purified by column chromatography over silica gel (10% ethyl

acetate –petroleum ether) affording white solid (2.65 g, 78%).**^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.81 (m, 2H), 7.70 (m, 2H), 7.25 (m, 1H), 6.87 (m, 2H), 5.83 (q, *J* = 7.2 Hz, 1H), 1.95 (tt, *J* = 2.0 Hz, 3H). **IR (KBr)** υ: 3446, 3317, 3050, 2992, 2949, 1766, 1702, 1608, 1521, 1464, 1359, 1275, 1114, 1050, 960, 937, 833, 738 cm^{-1}

N-(1-(2,6-difluorophenyl)ethyl)-3,5-dinitrobenzamide 25c

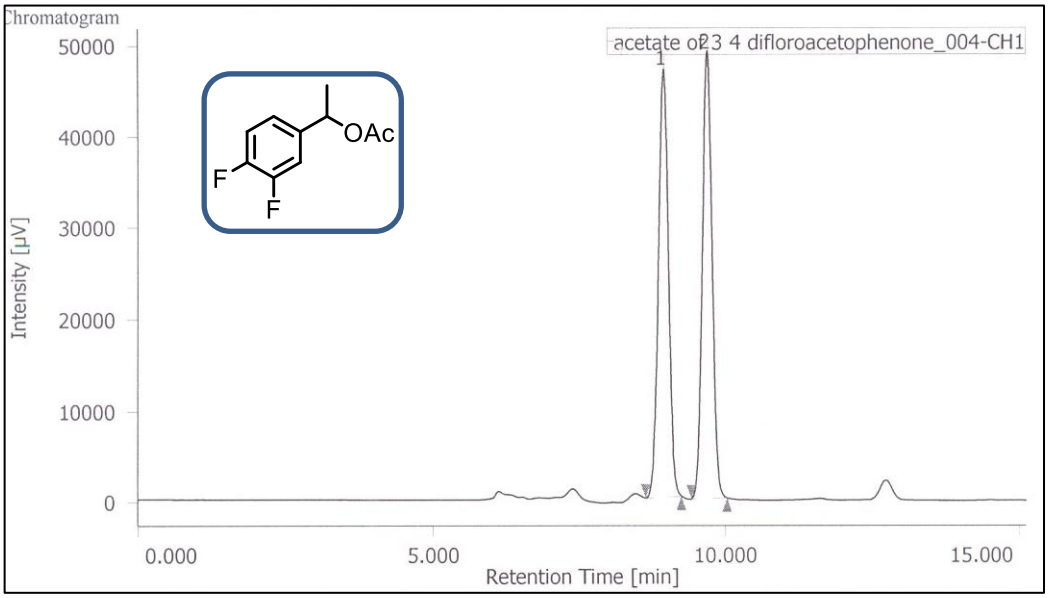
$[\alpha]^{28}_D$ +28.50 (c 1, CH_2Cl_2). [The absolute configuration was confirmed by comparison of optical rotation of the intermediate amine][76].

In a dry round bottom flask pthalimide (2.60 g, 9.05 mmol) was dissolved in a mixture of THF (40 ml) & ethanol (10 mL) and treated with drop wise addition of hydrazine hydrate (4.38 ml, 90.5 mmol). The reaction mixture was stirred at 60^0C (5 h). the white suspension formed was filtered, washed with THF (2x20 mL) and then organic solvent was evaporated under reduced pressure. To this residue water (50 mL) was added and extracted with dichloromethane (2x50 mL).The organic layer was concerted in vacuum to furnish a viscous liquid (0.98 g, 6.19 mmol). The oil was dissolved in dry chloroform (5 mL) and treated with triehyl amine (0.862 mL, 6.19 mmol).The mixture was allowed to cool (0^oC) and solution of 3,5 dinitrobenzoyl chloride (1.41 g, 6.19 mmol) in chloroform (5ml) slowly added (30 min). The mixture was stirred at room temperature (4 h), the solvent was evaporated and the residue was washed with sodium bicarbonate (saturated solution) and extracted with dichloromethane (2X75 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated at reduce pressure. The crude product was purified by column chromatography over silica gel (30%ethyl acetate –

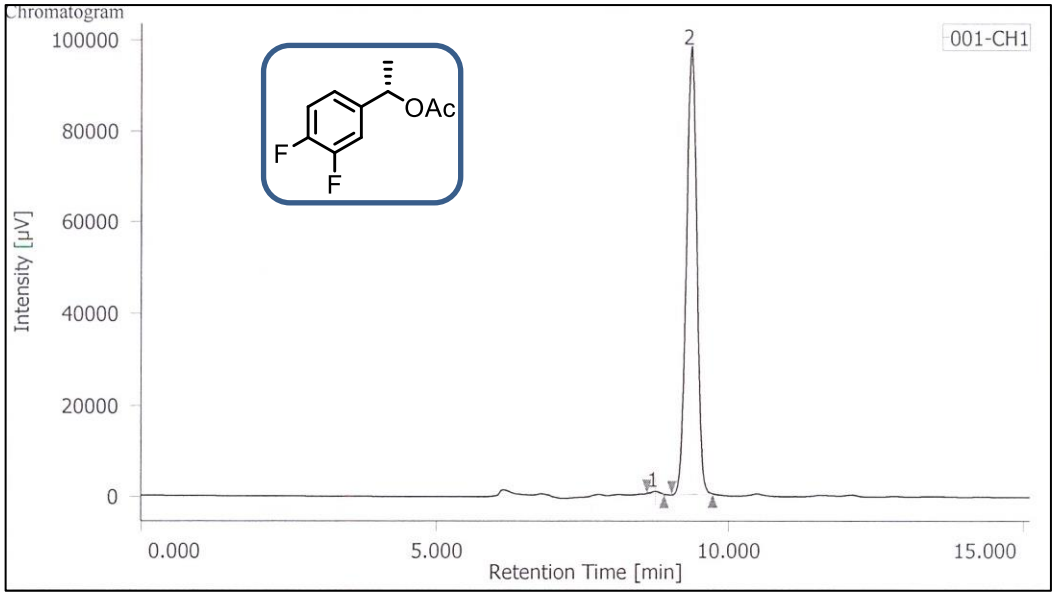


petroleum ether) (0.750 g, 67.87%).**^{1}H NMR (400 MHz, $CDCl_3$)**: δ 9.20 (t, *J* = 2.0 Hz 1H), 8.96 (d, *J* = 2.0 Hz, 2H), 5.83 (q, *J* = 7.6 Hz, 1H), 1.71 (d, *J* = 7.6 Hz, 3H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -115.07. **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 19.76, 41.79, 112.32 (d, *J* = 26 Hz, 1 C-F), 119.50, 121.39, 128.24, 129.80 (t, *J* = 21 Hz, 1 C-F), 136.92, 148.60, 159.63 (d, *J* =18 Hz, 1 C-F), 162.20. **IR (KBr)** υ: 3344, 3069, 2923, 1648, 1544, 1460, 1349, 1310, 1280, 1173, 1128, 924, 897, 869, 773, 680 cm^{-1}. **HRMS(ESI+)** m/z calcd for $C_{15}H_{11}F_2N_3O_5Na$ $(M+Na)^+$ 374.0559, found 374.0567.

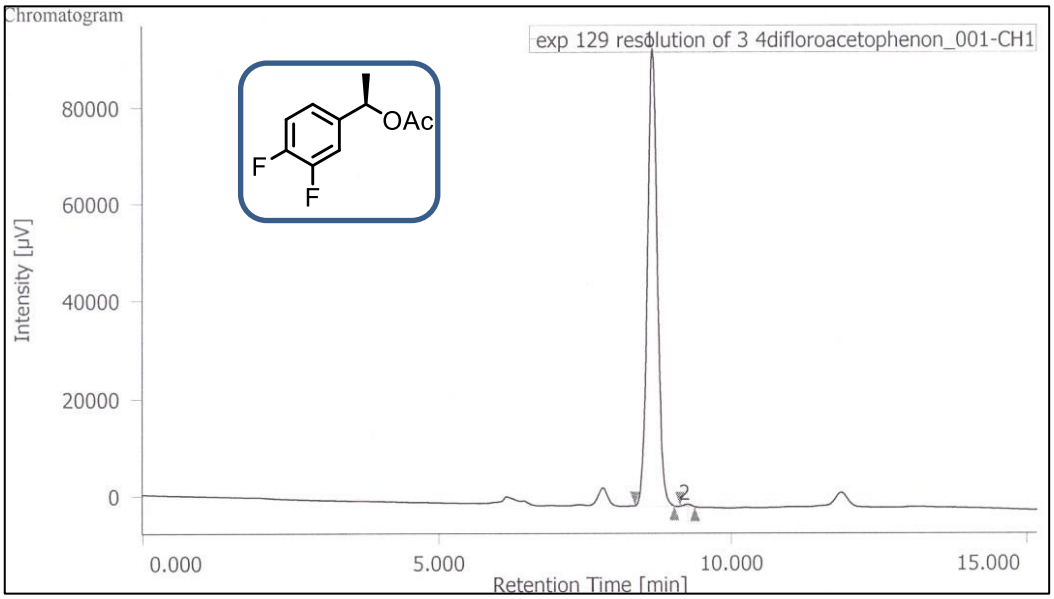
2.81 Spectral Data



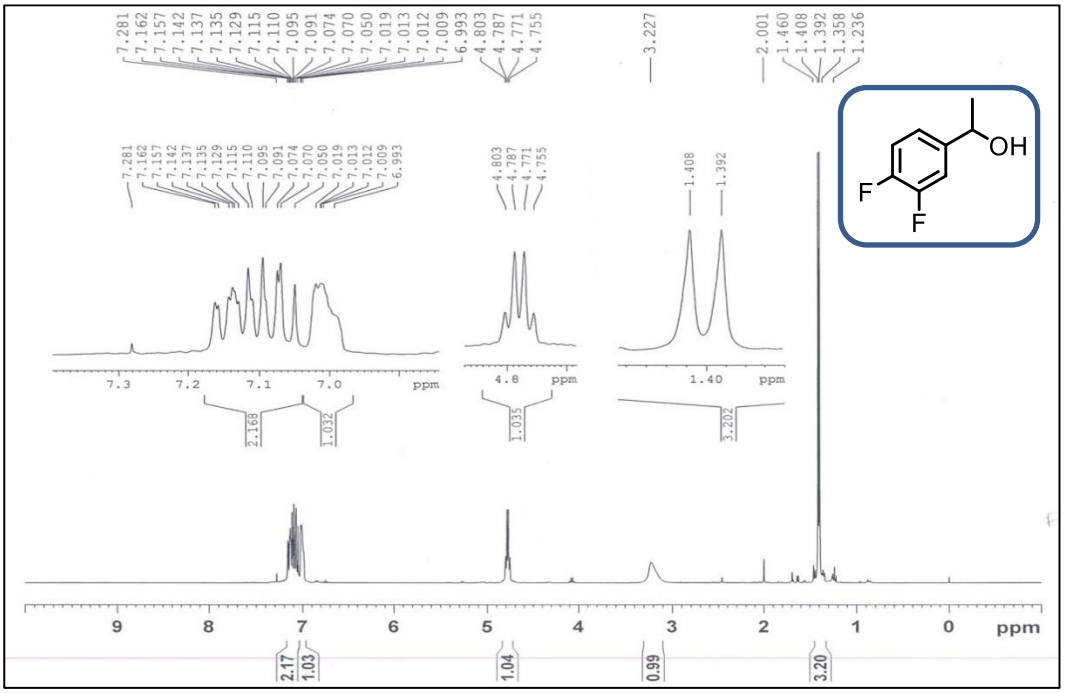
HPLC Fig: 1-(3,4-difluorophenyl)ethyl acetate **27**



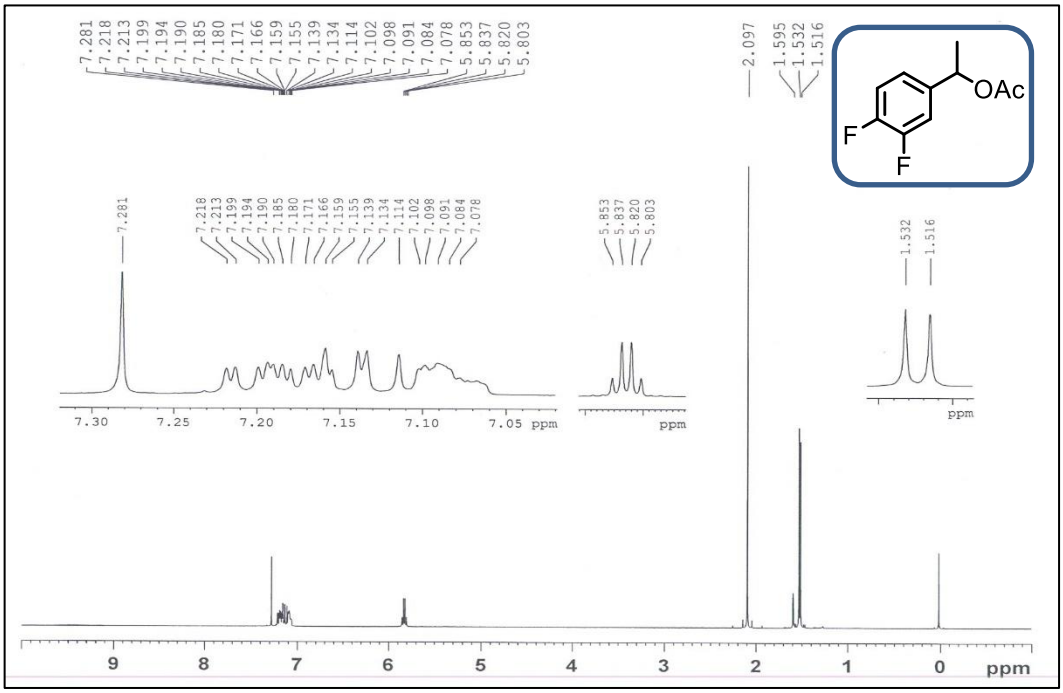
HPLC of *(S)* 1-(3,4-difluorophenyl)ethyl acetate (S)-**27**



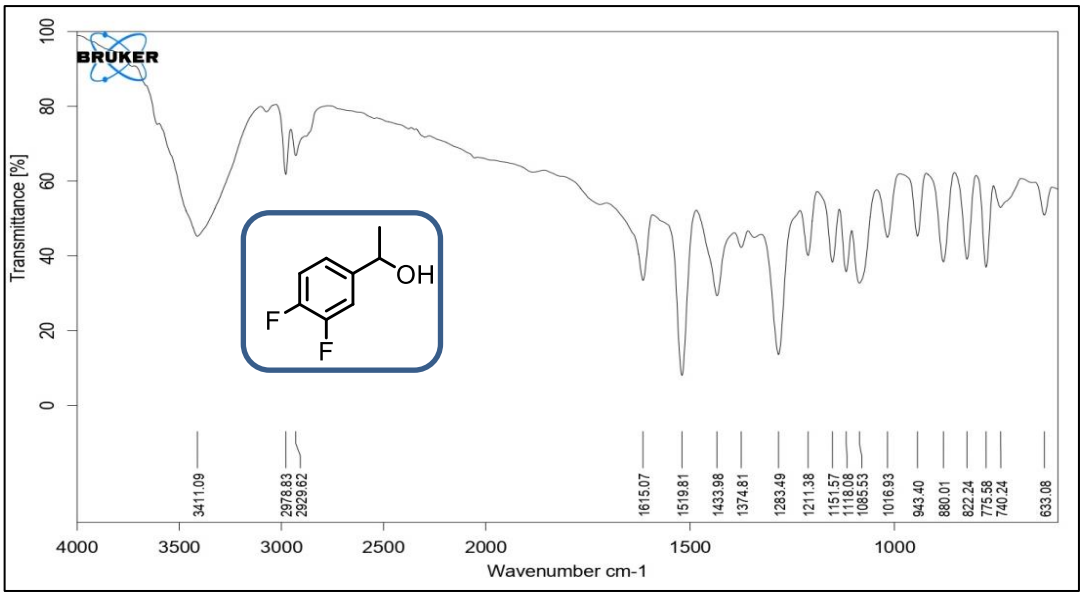
HPLC of *(R)* 1-(3,4-difluorophenyl)ethyl acetate (R)-**27**



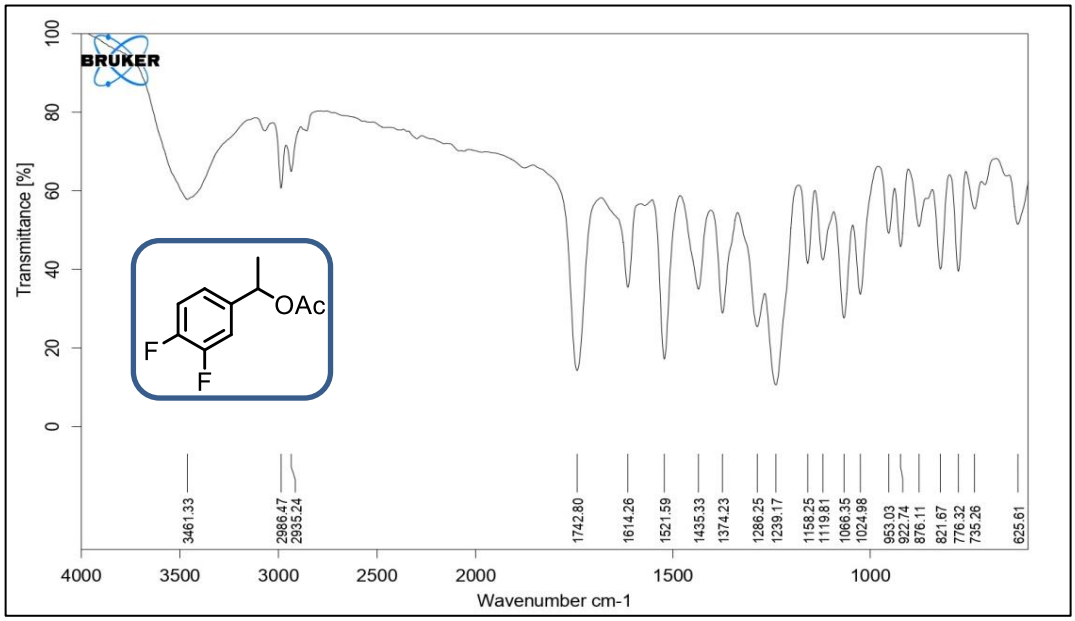
^{1}H NMR spectrum of (*S*)-1-(3,4-difluorophenyl)ethan-1-ol **26**



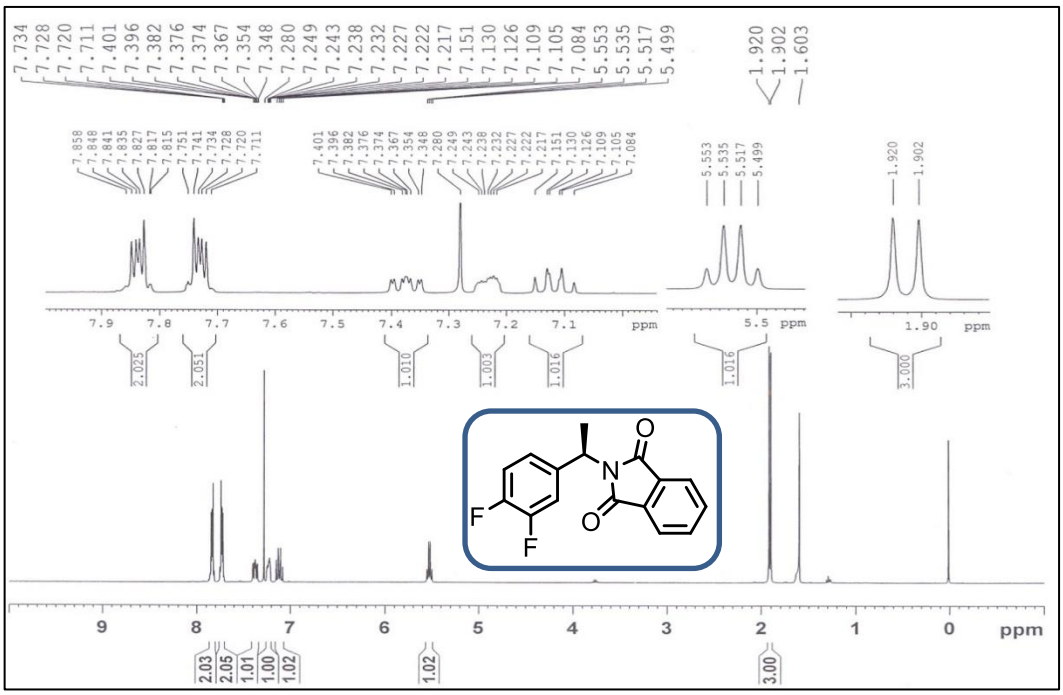
^{1}H NMR spectrum of 1-(3,4-difluorophenyl)ethyl acetate **27**



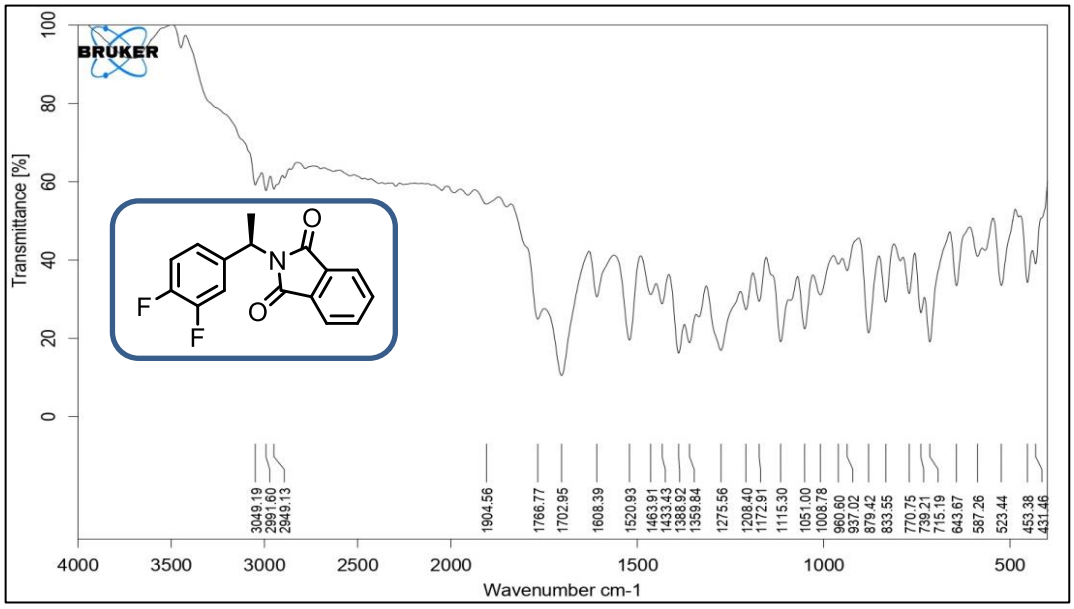
IR spectrum of (*S*)-1-(3,4-difluorophenyl)ethan-1-ol **26**



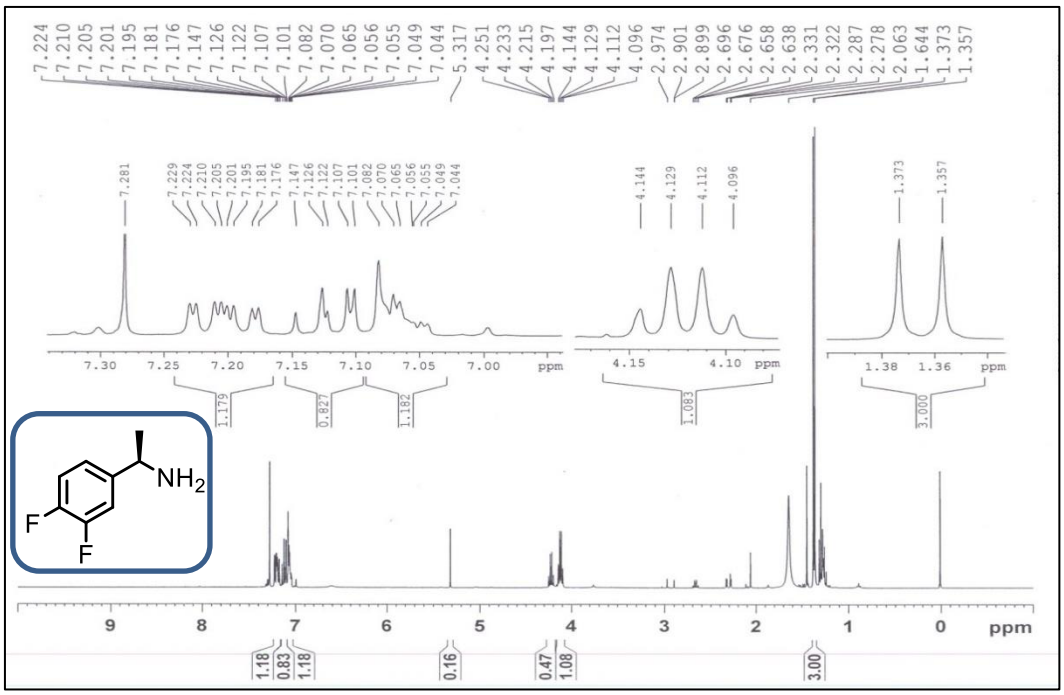
IR spectrum of 1-(3,4-difluorophenyl)ethyl acetate **27**



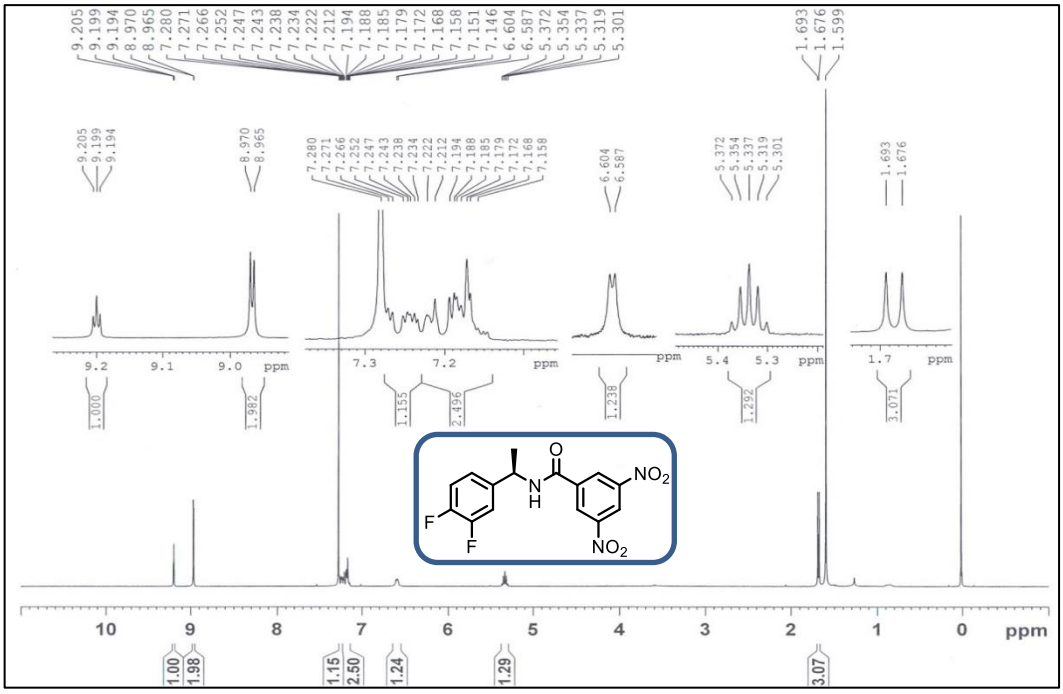
^{1}H NMR spectrum of 2-(1-(3,4-difluorophenyl)ethyl)isoindoline-1,3-dione (R)-**32**



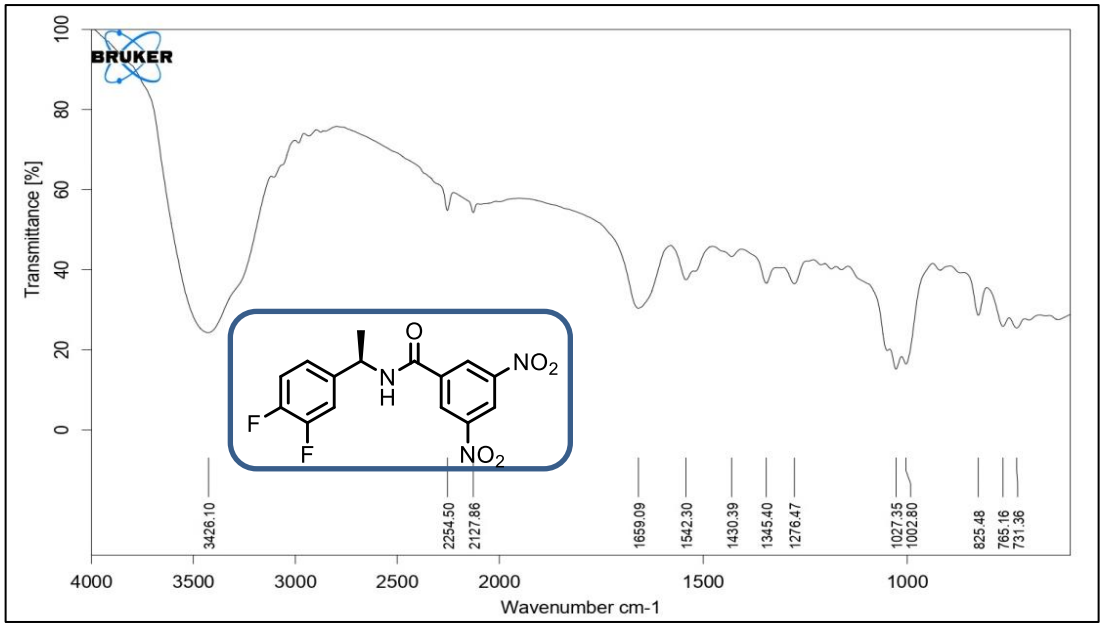
IR spectrum of 2-(1-(3,4-difluorophenyl)ethyl)isoindoline-1,3-dione (R)-**32**



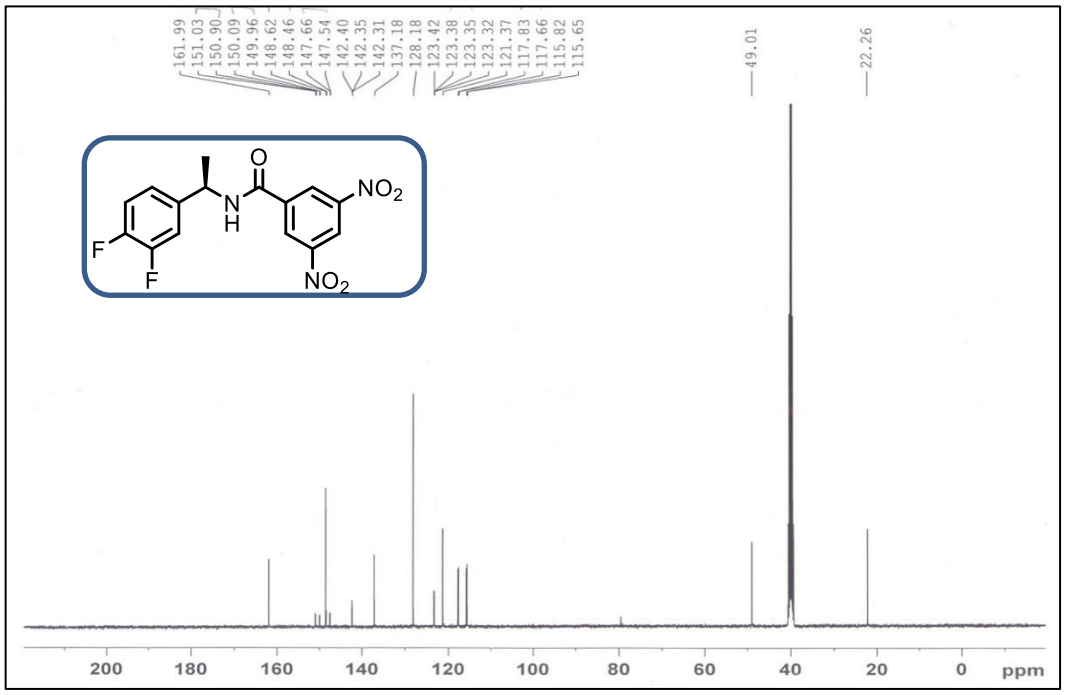
^{1}H NMR spectrum of 1-(3,4-difluorophenyl)ethan-1-amine



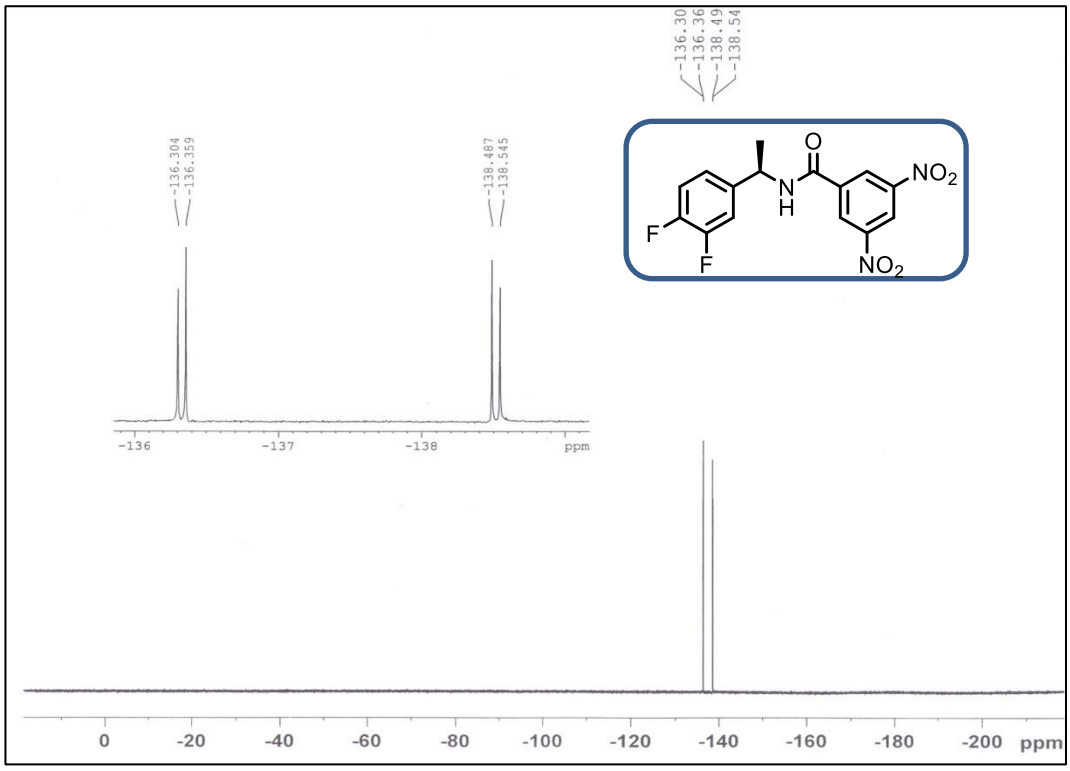
^{1}H NMR spectrum of N-(1-(3,4-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25a**



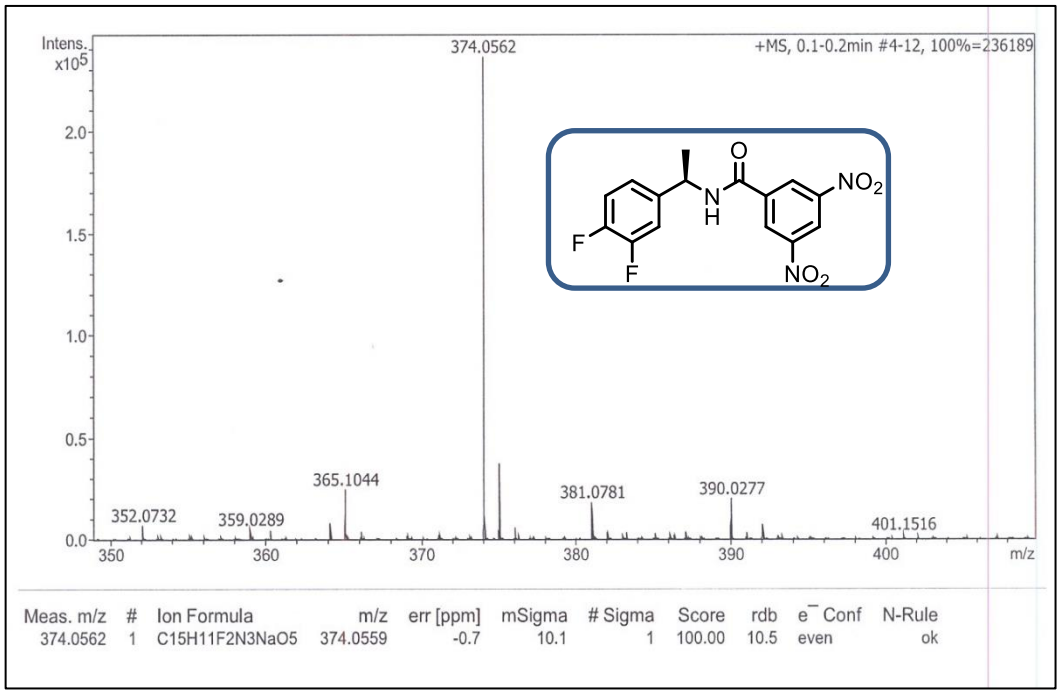
^{1}H NMR spectrum of N-(1-(3,4-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25a**



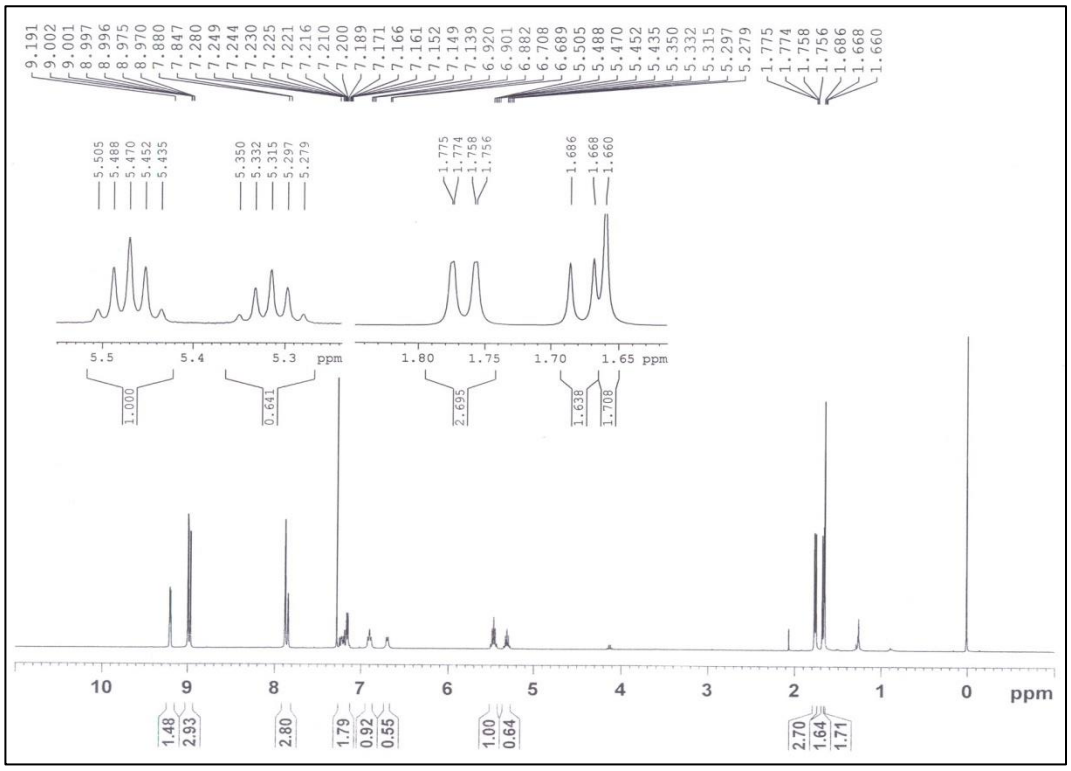
^{13}C NMR spectrum of N-(1-(3,4-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25a**



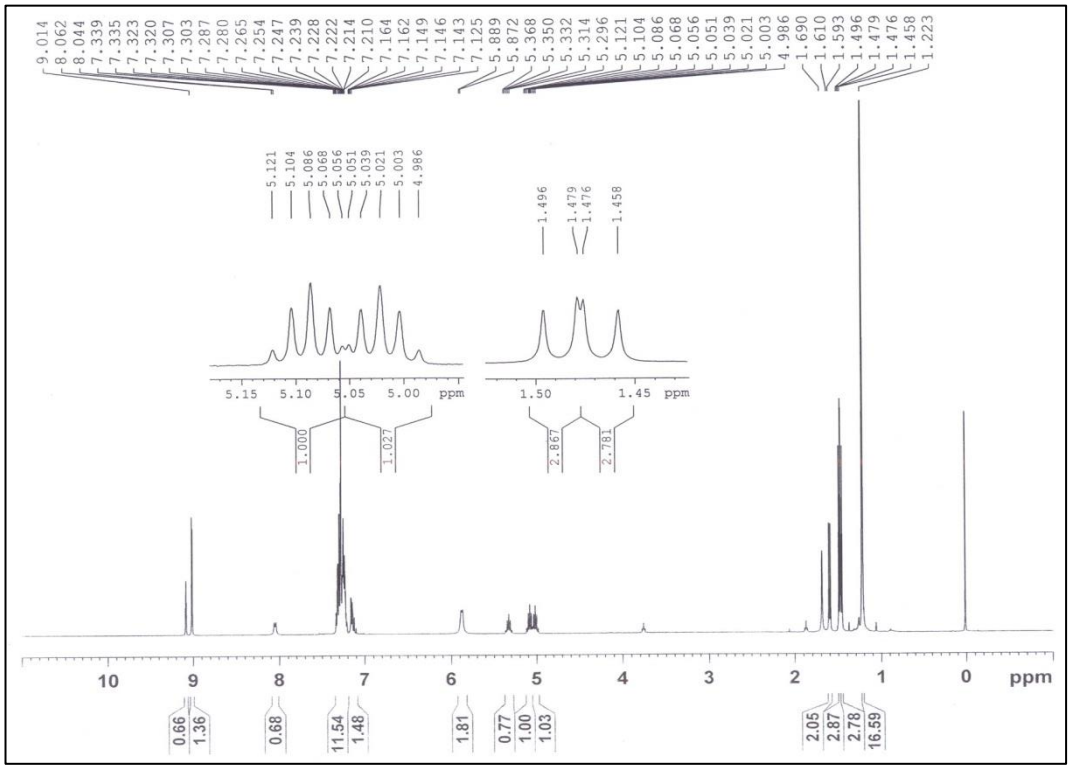
^{19}F NMR spectrum of N-(1-(3,4-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25**



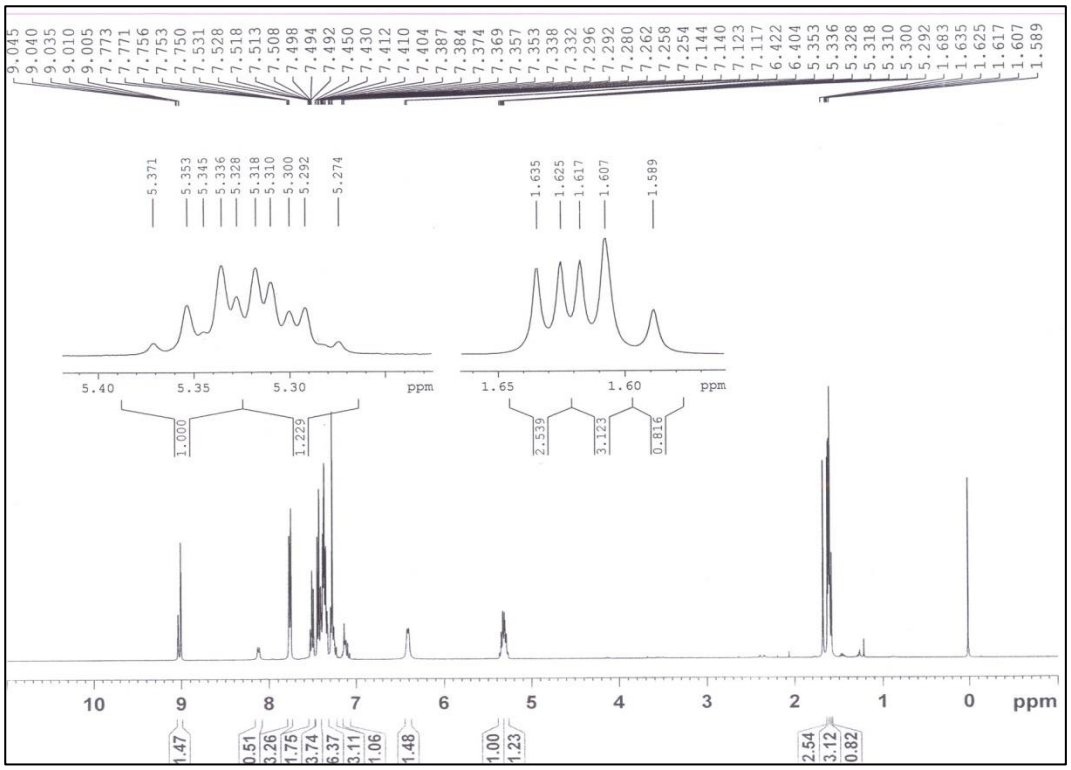
HRMS spectrum of N-(1-(3,4-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25a**



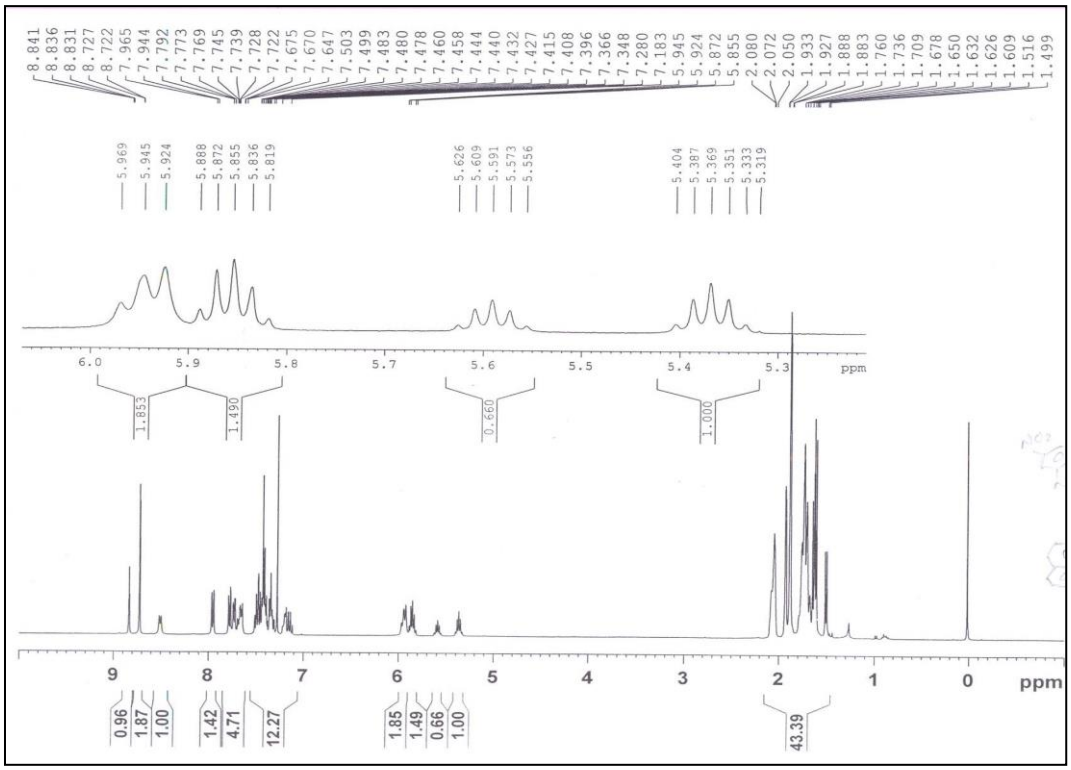
^{1}H NMR spectrum of **25a**+A1



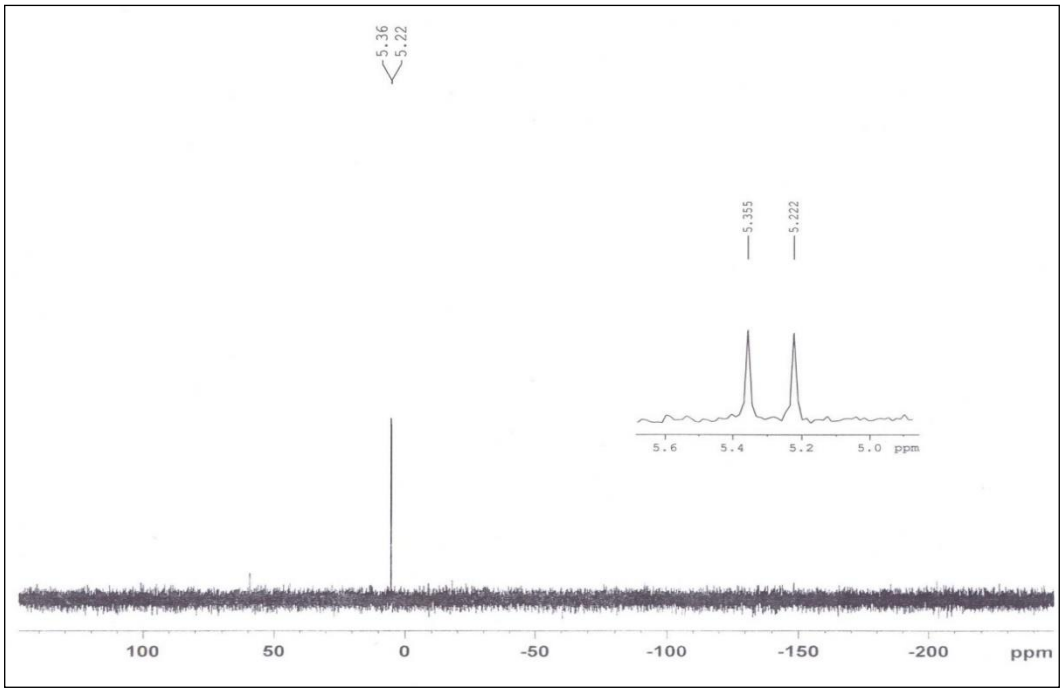
^{1}H NMR spectrum of ^{1}H NMR spectrum of **25a**+A2



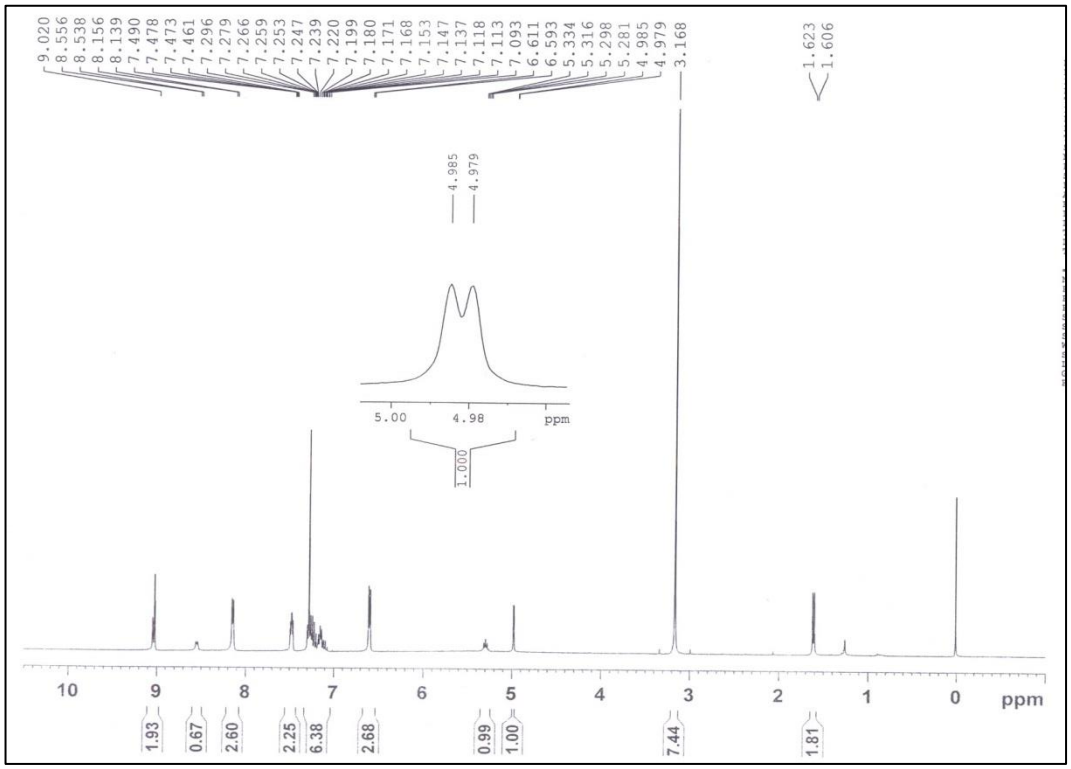
^{1}H NMR spectrum of 25a+A3



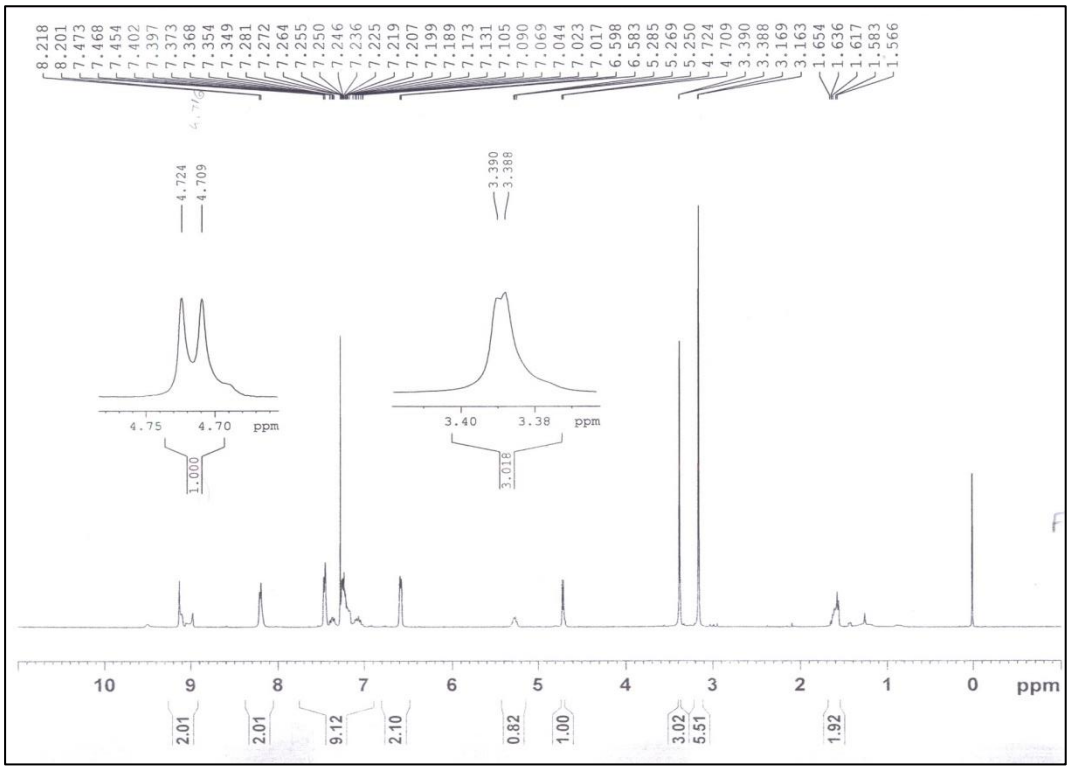
^{1}H NMR spectrum of **25a**+A4



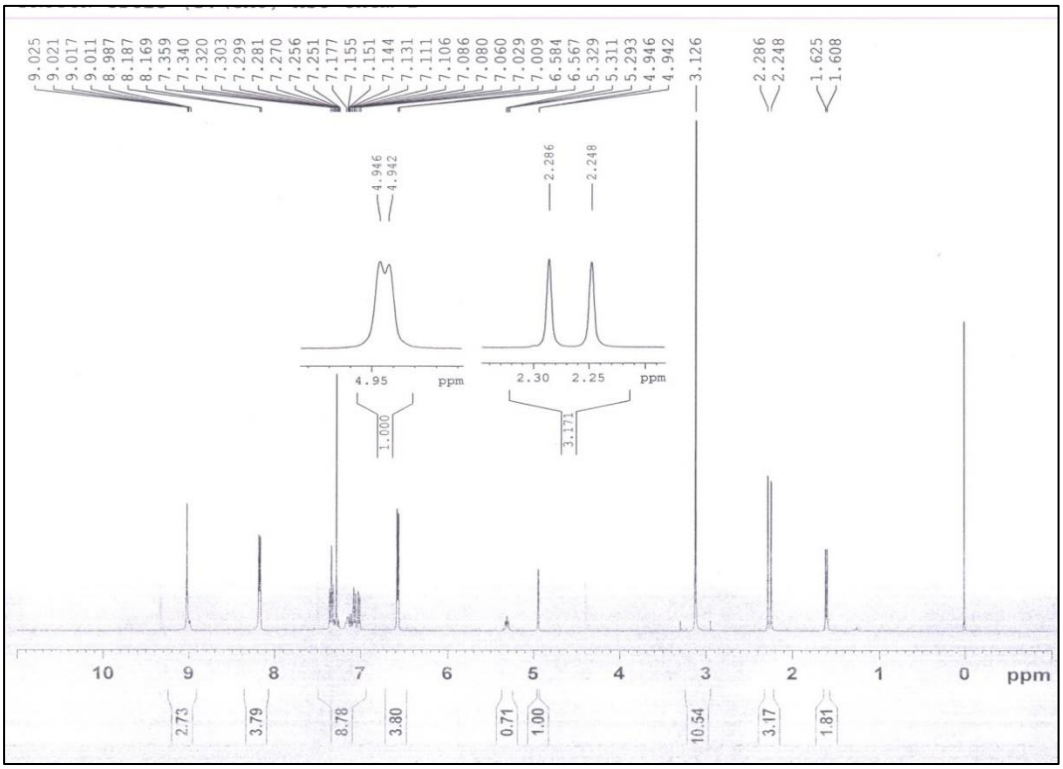
^{31}P NMR spectrum of **25a**+B1



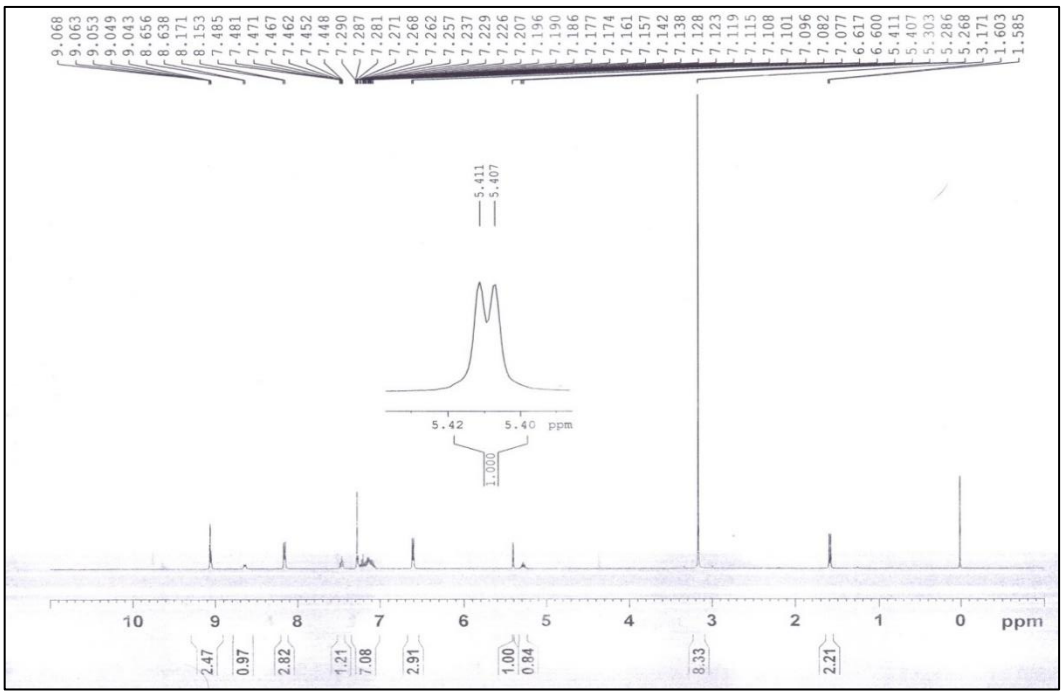
^{1}H NMR spectrum of **25a**+C1



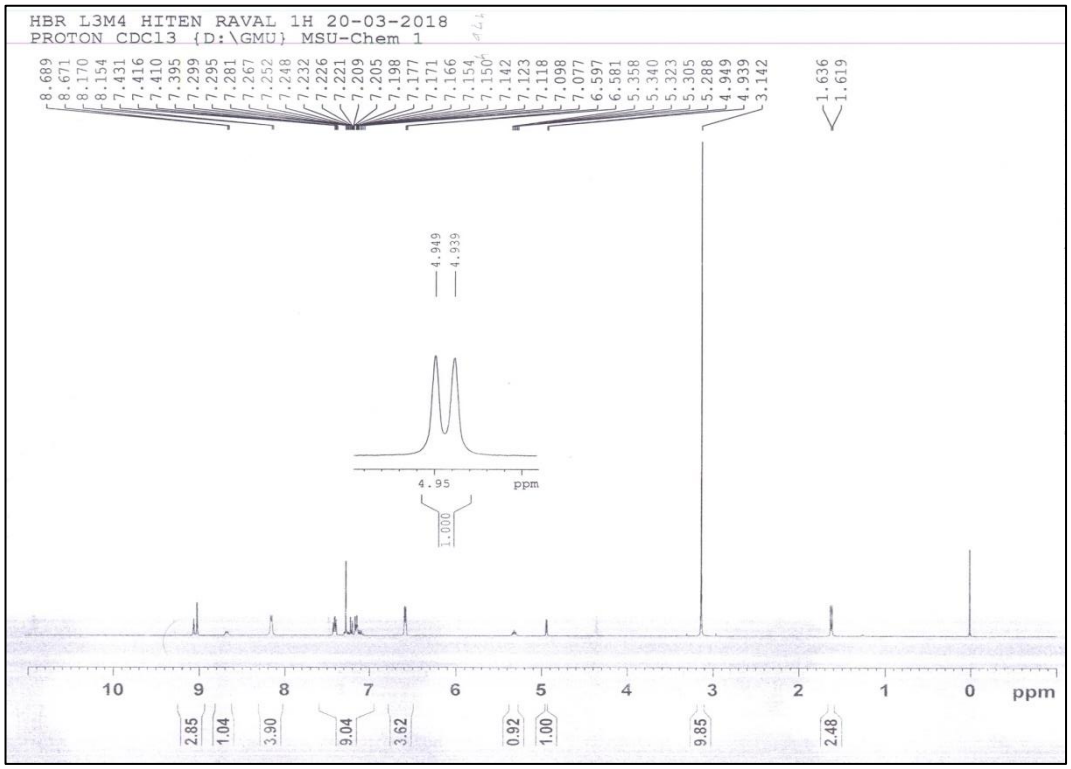
^{1}H NMR spectrum of **25a**+C2



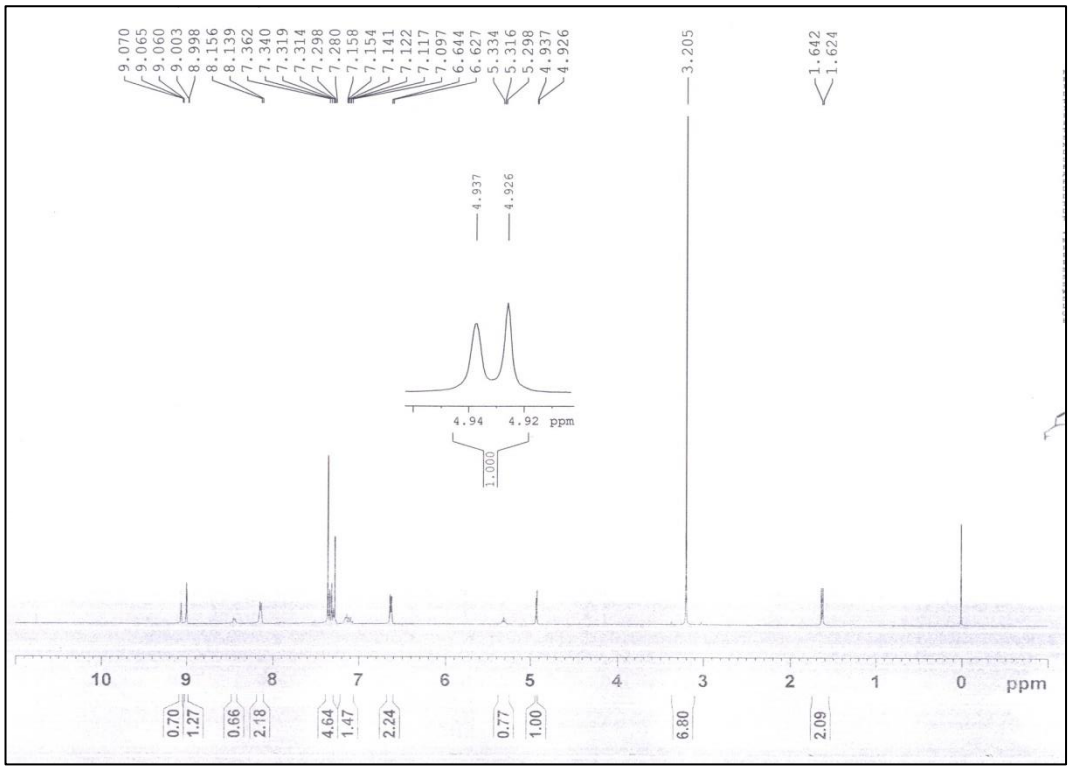
^{1}H NMR spectrum of **25a**+C3



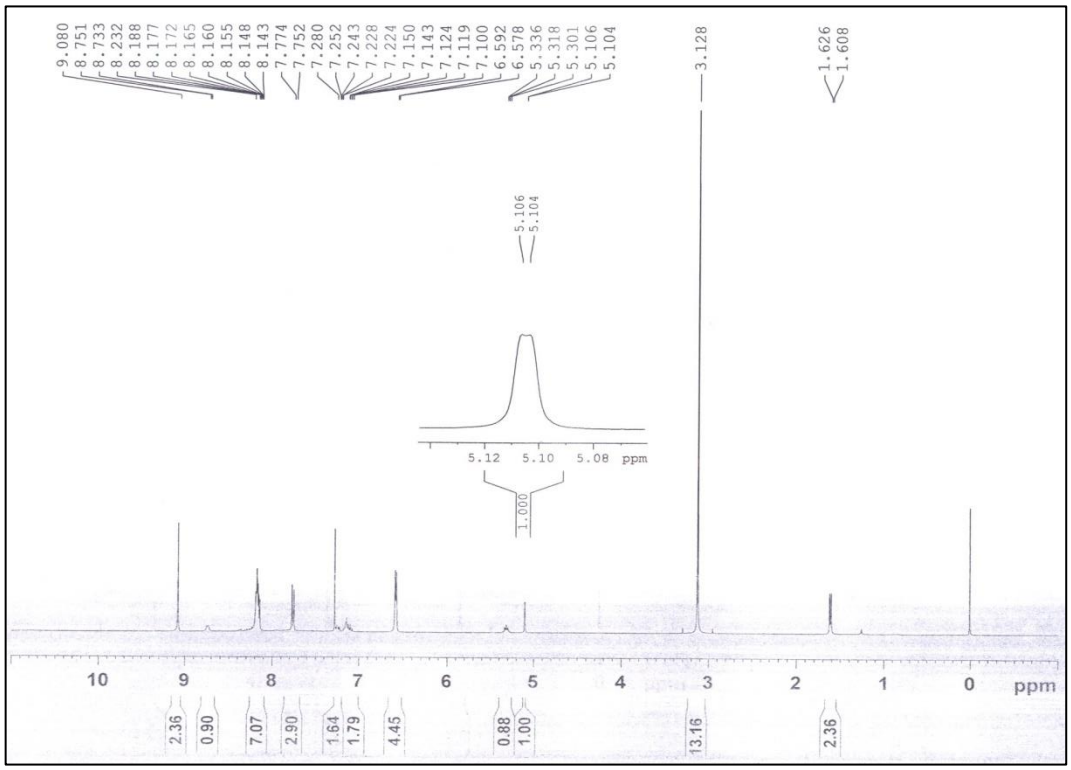
^{1}H NMR spectrum of **25a**+C4



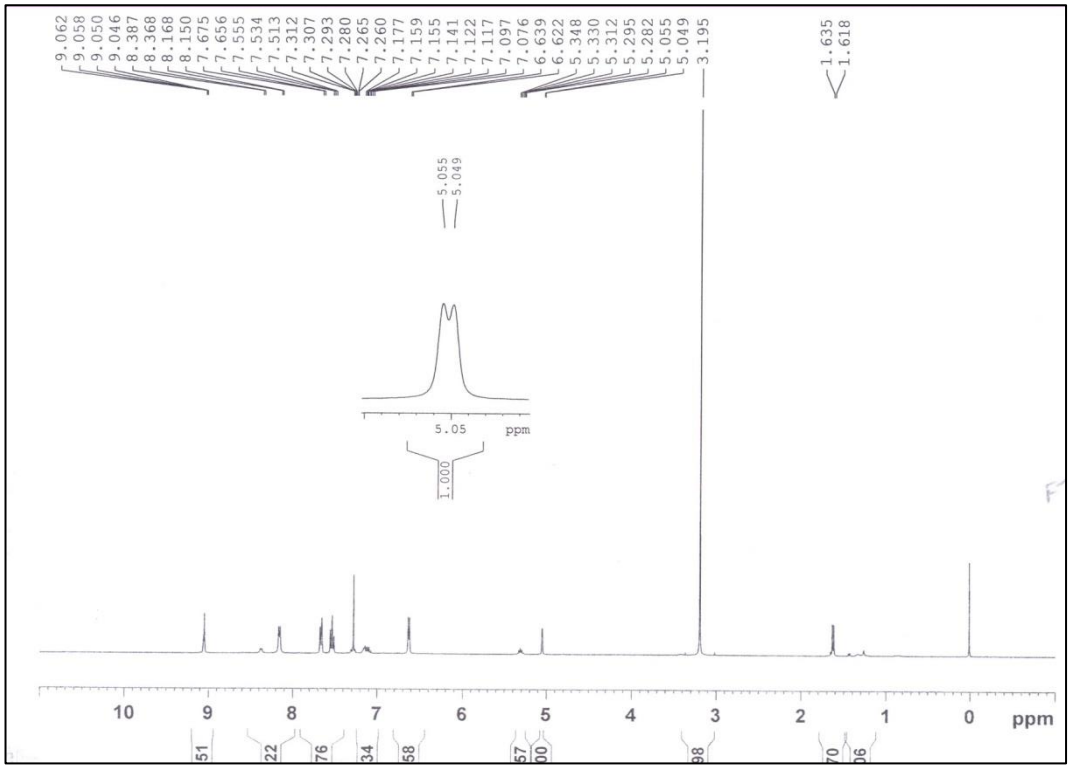
^{1}H NMR spectrum of **25a**+C5



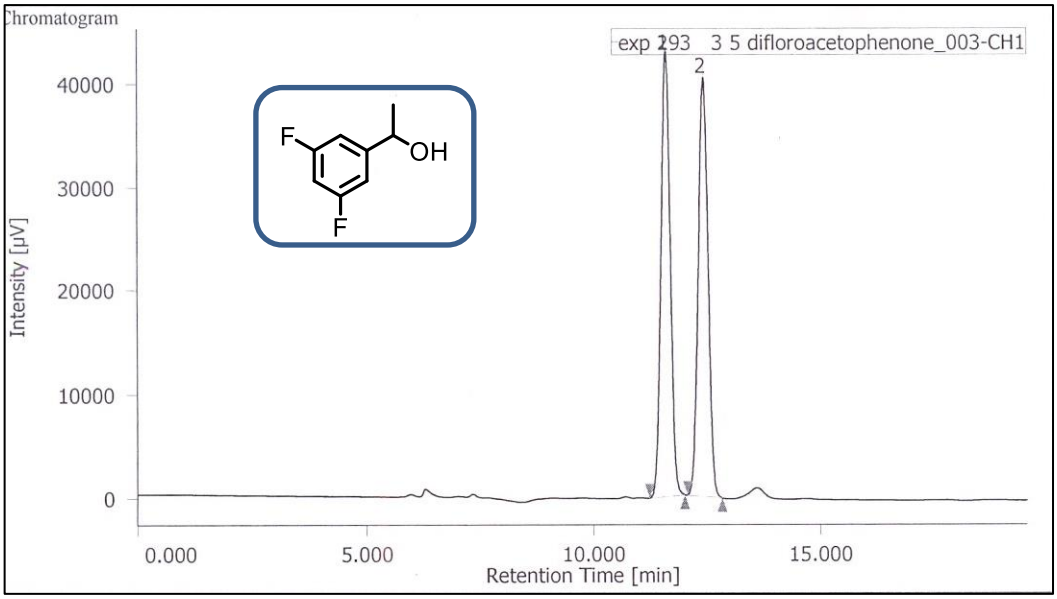
^{1}H NMR spectrum of **25a**+C6



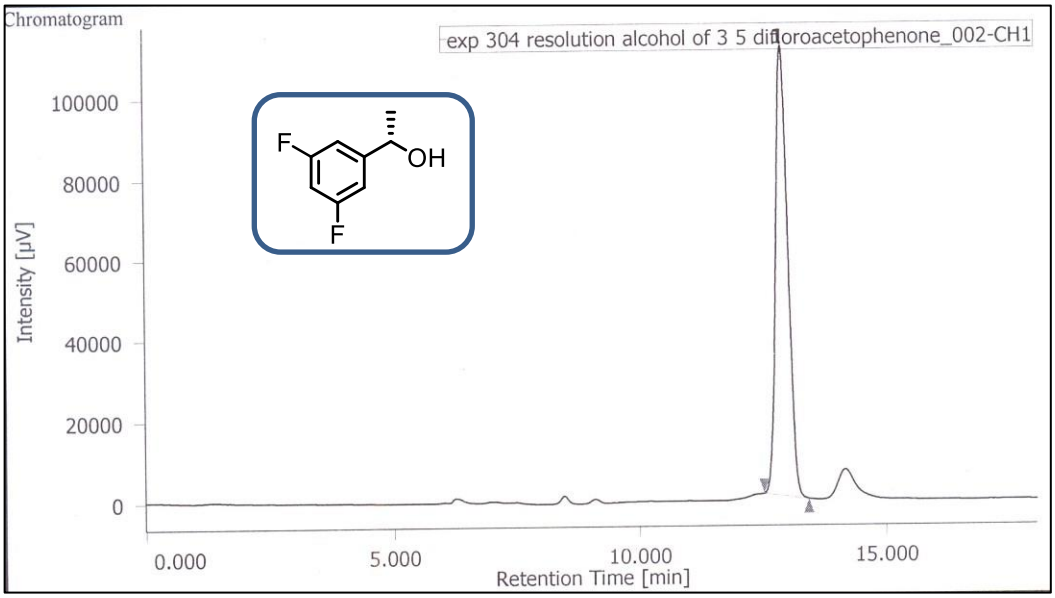
^{1}H NMR spectrum of **25a**+C7



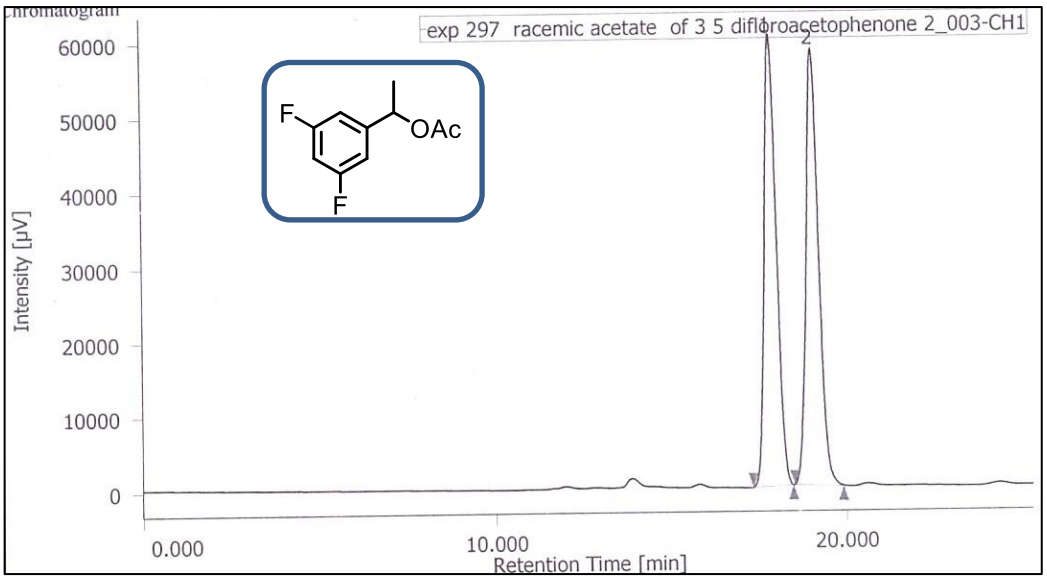
^{1}H NMR spectrum of **25a**+C8



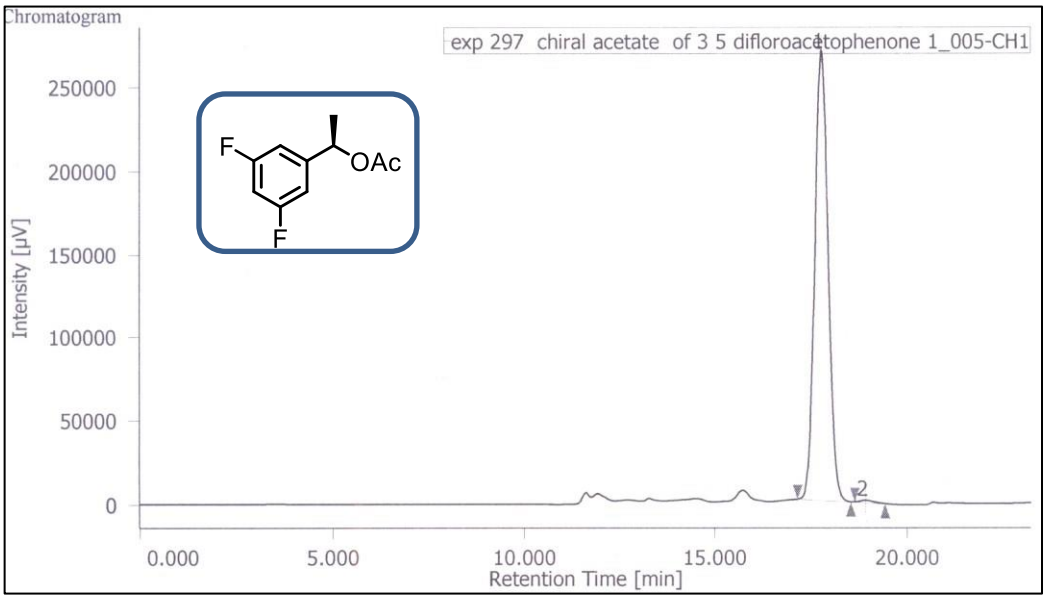
HPLC of 1-(3,5-difluorophenyl)ethan-1-ol **28**



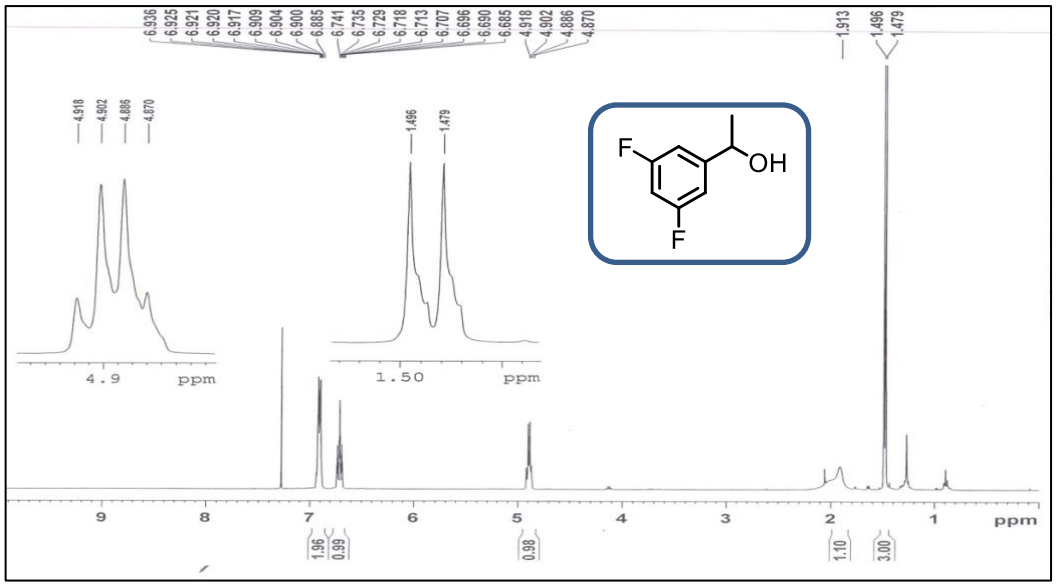
HPLC of 1-(3,5-difluorophenyl)ethan-1-ol (*S*)-**28**



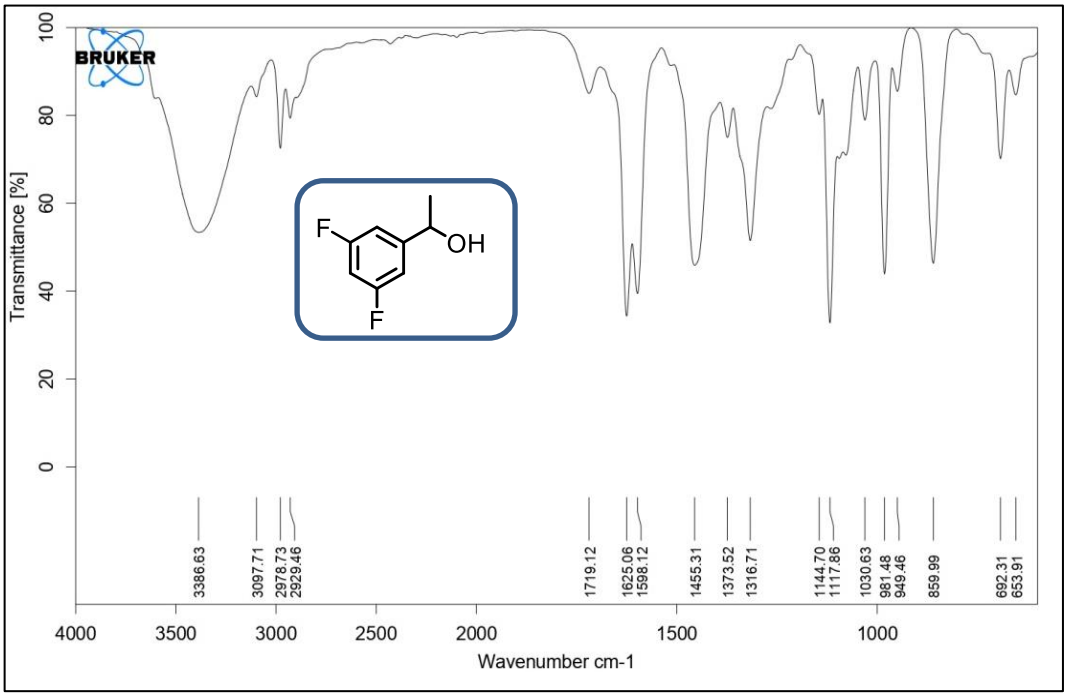
HPLC of 1-(3,5-difluorophenyl)ethyl acetate **29**



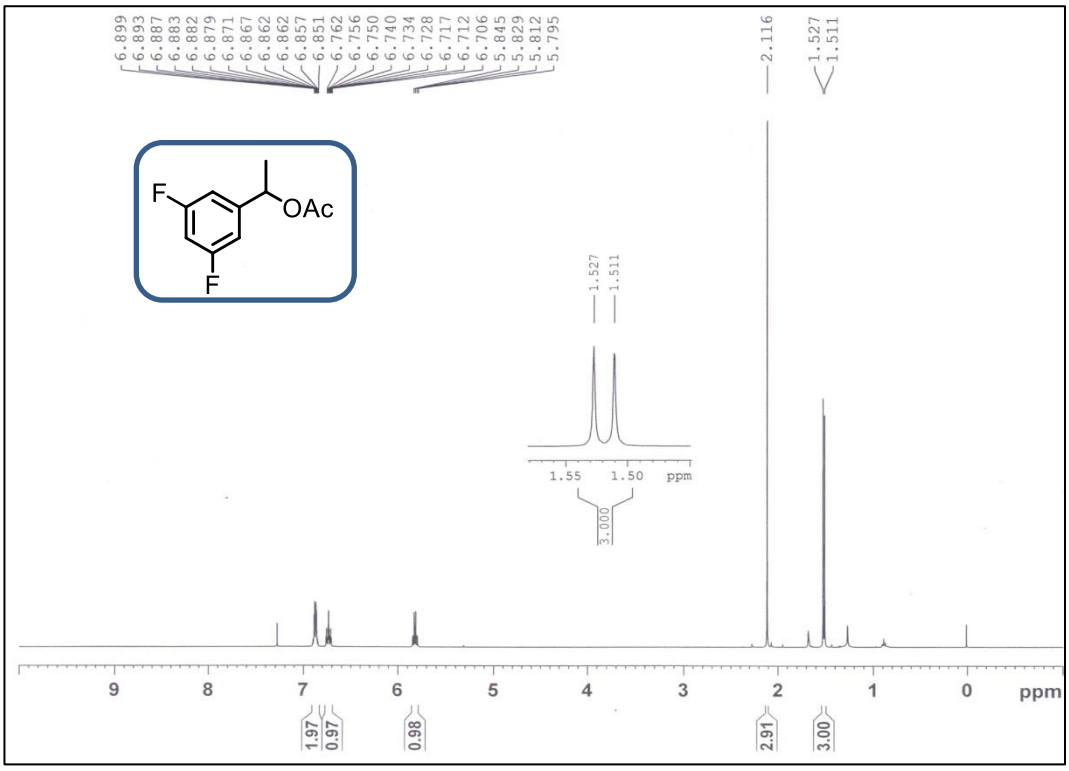
HPLC of 1-(3,5-difluorophenyl)ethyl acetate (*R*)-**29**



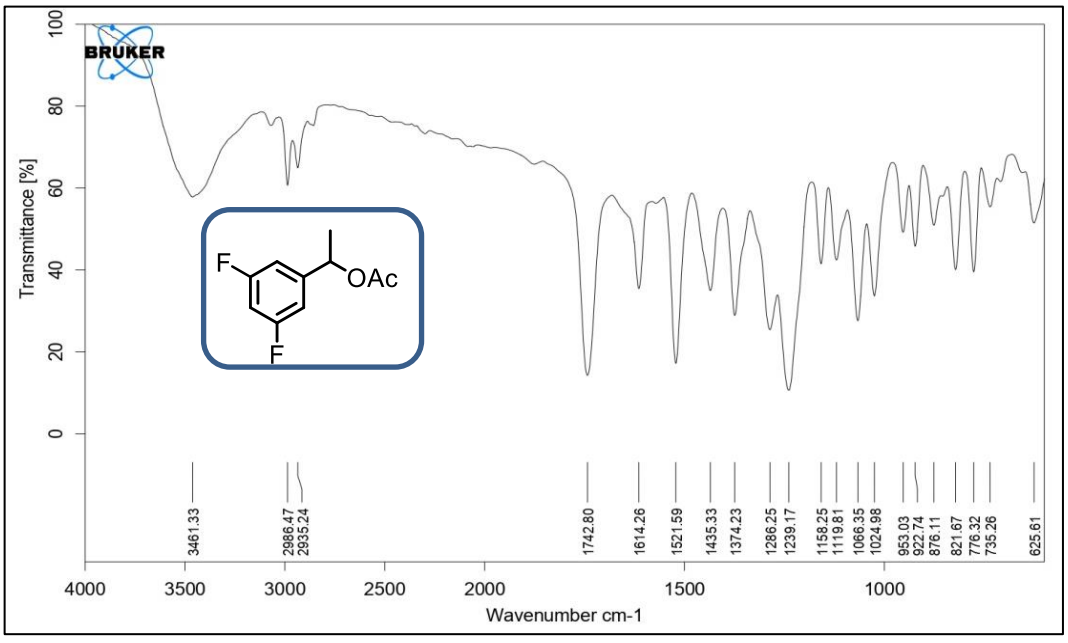
^{1}H NMR spectrum of 1-(3,5-difluorophenyl)ethan-1-ol **28**



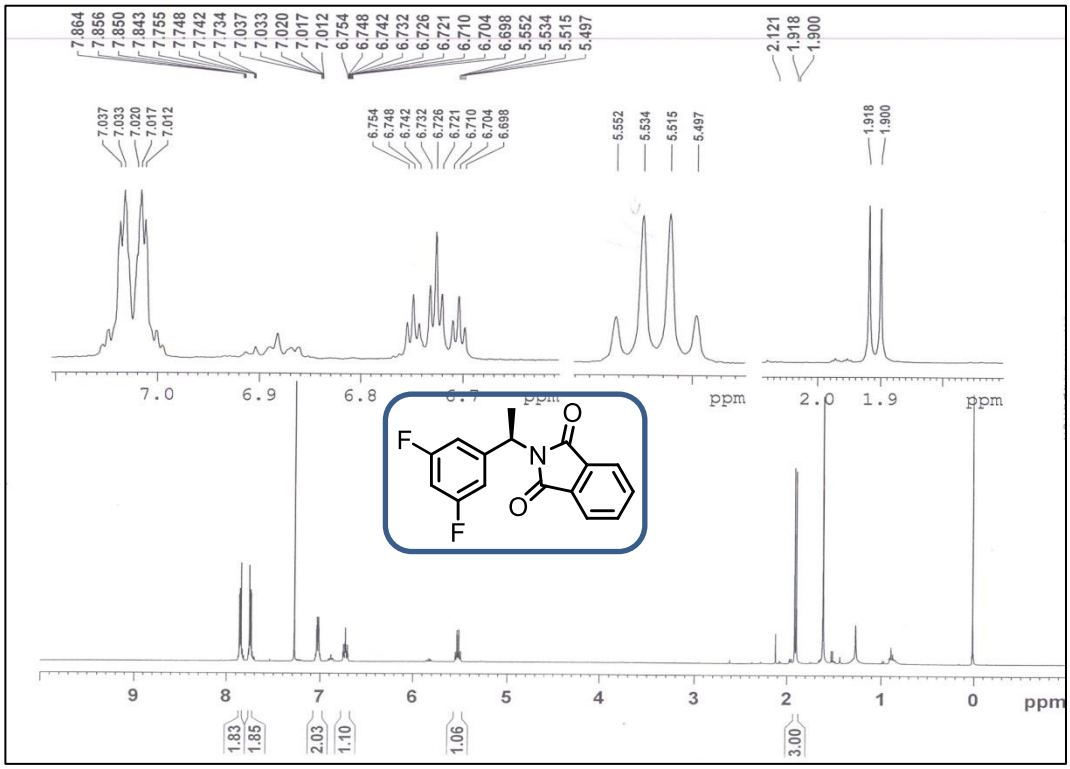
IR spectrum of 1-(3,5-difluorophenyl)ethan-1-ol **28**



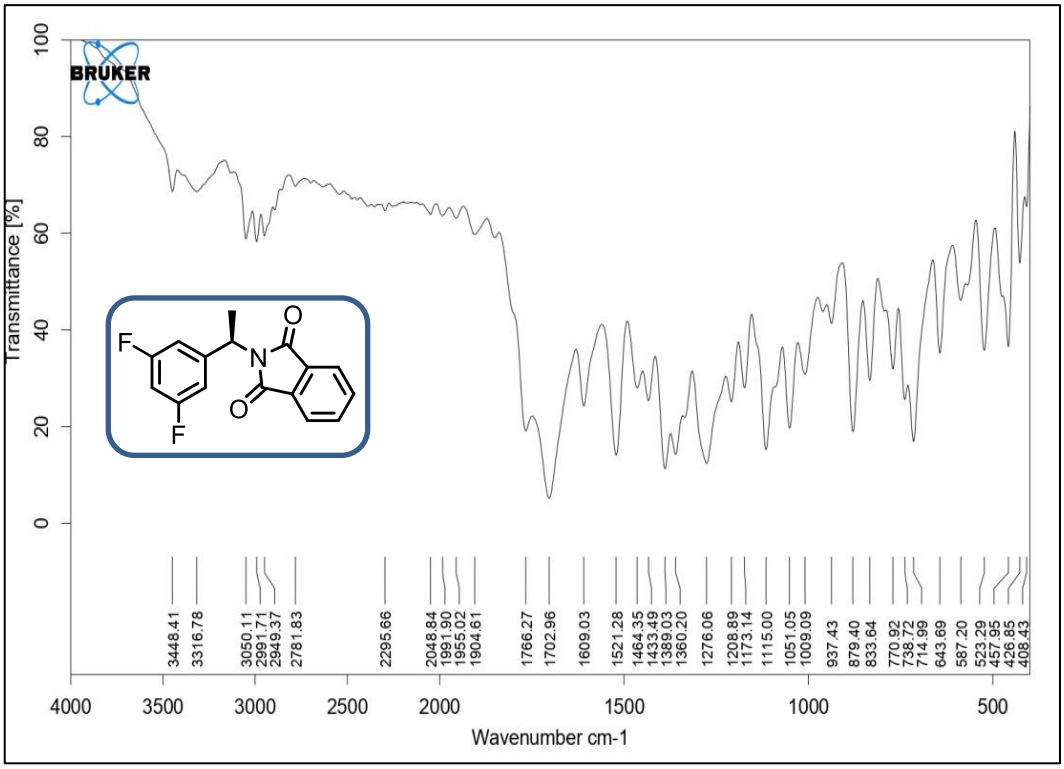
^{1}H NMR spectrum of 1-(3,5-difluorophenyl)ethyl acetate **29**



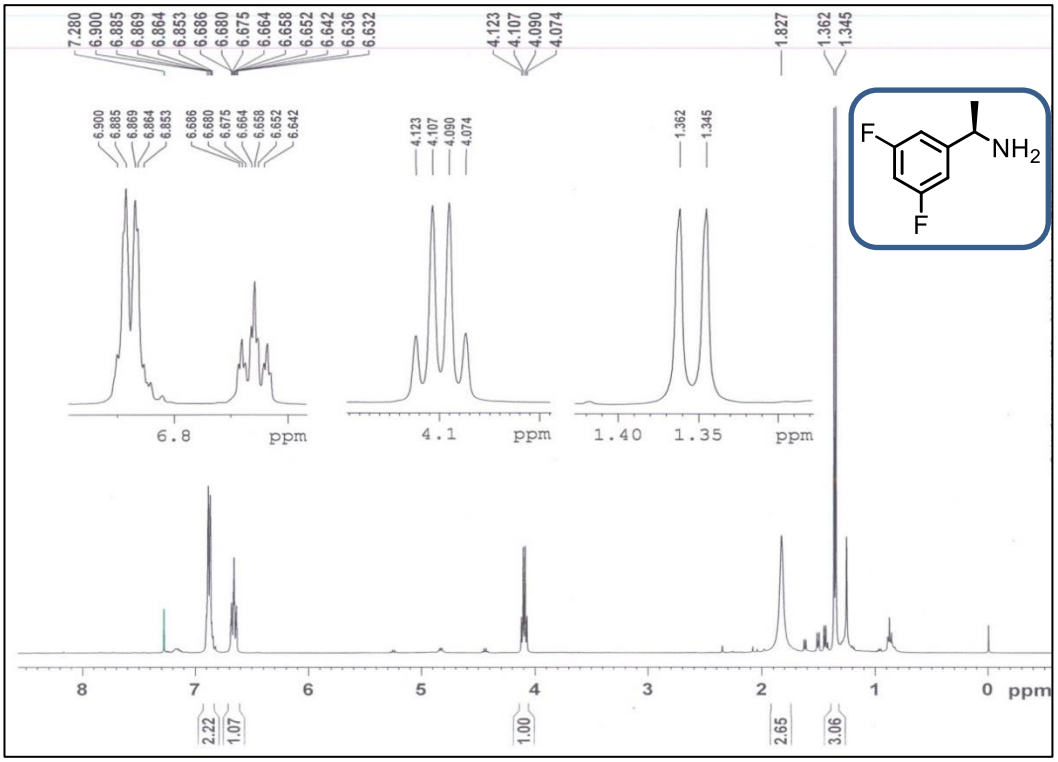
IR spectrum of 1-(3,5-difluorophenyl))ethyl acetate **29**



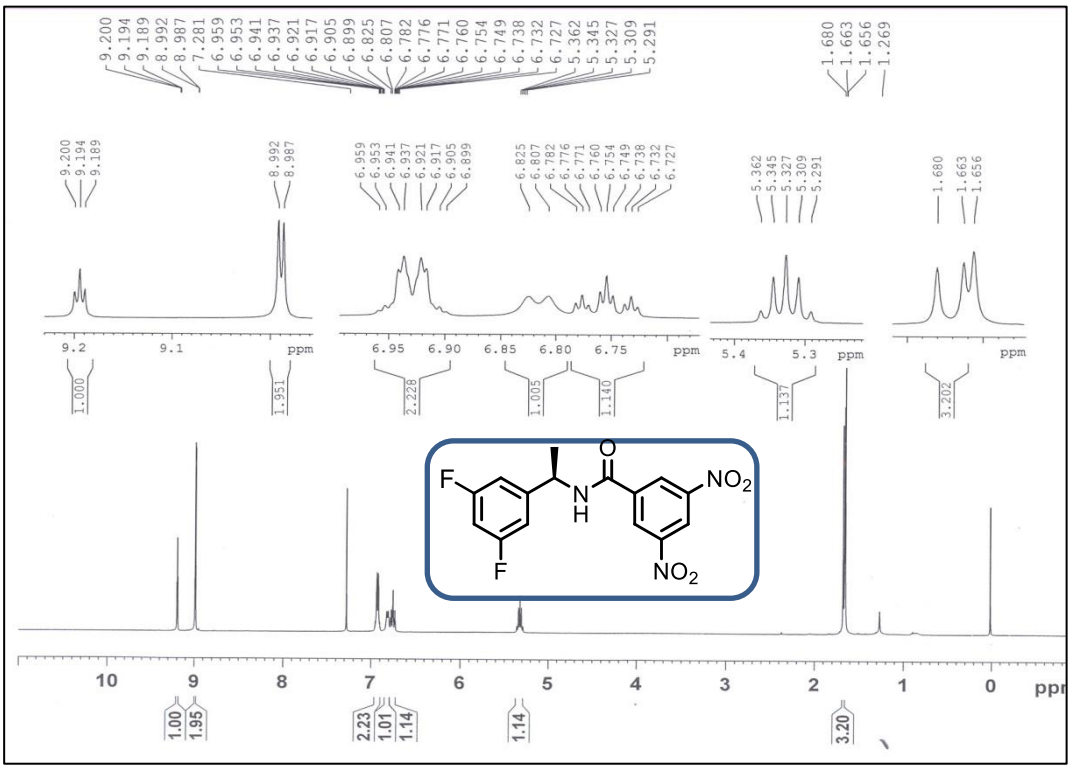
^{1}H NMR spectrum of 2-(1-(3,5-difluorophenyl)ethyl)isoindoline-1,3-dione



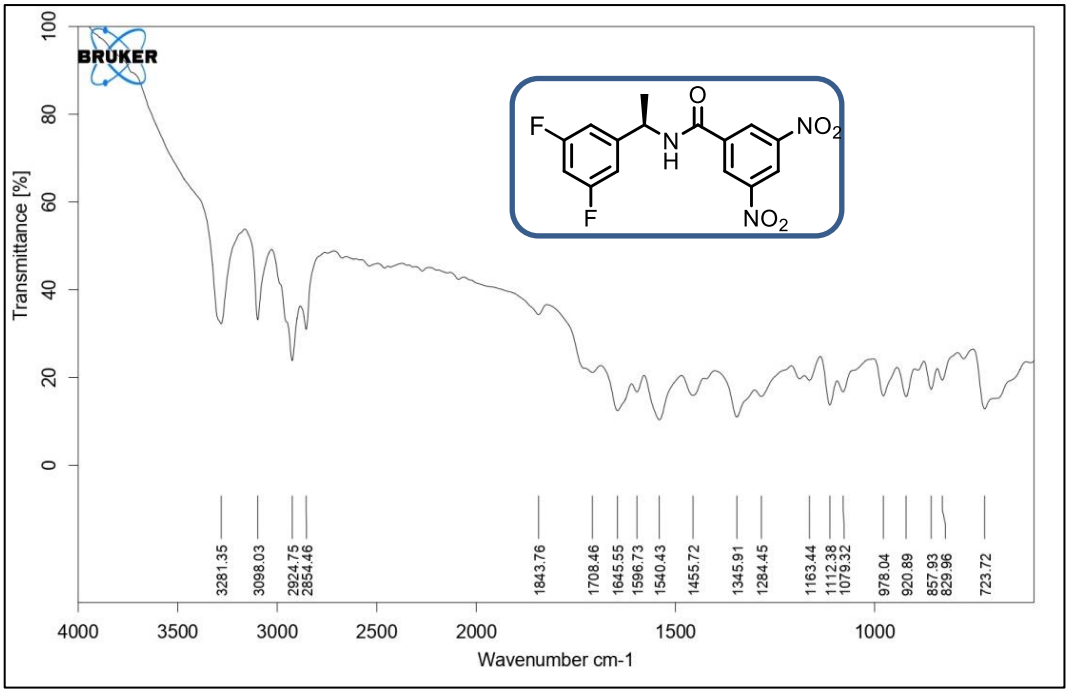
IR spectrum of 2-(1-(3,5-difluorophenyl)ethyl)isoindoline-1,3-dion



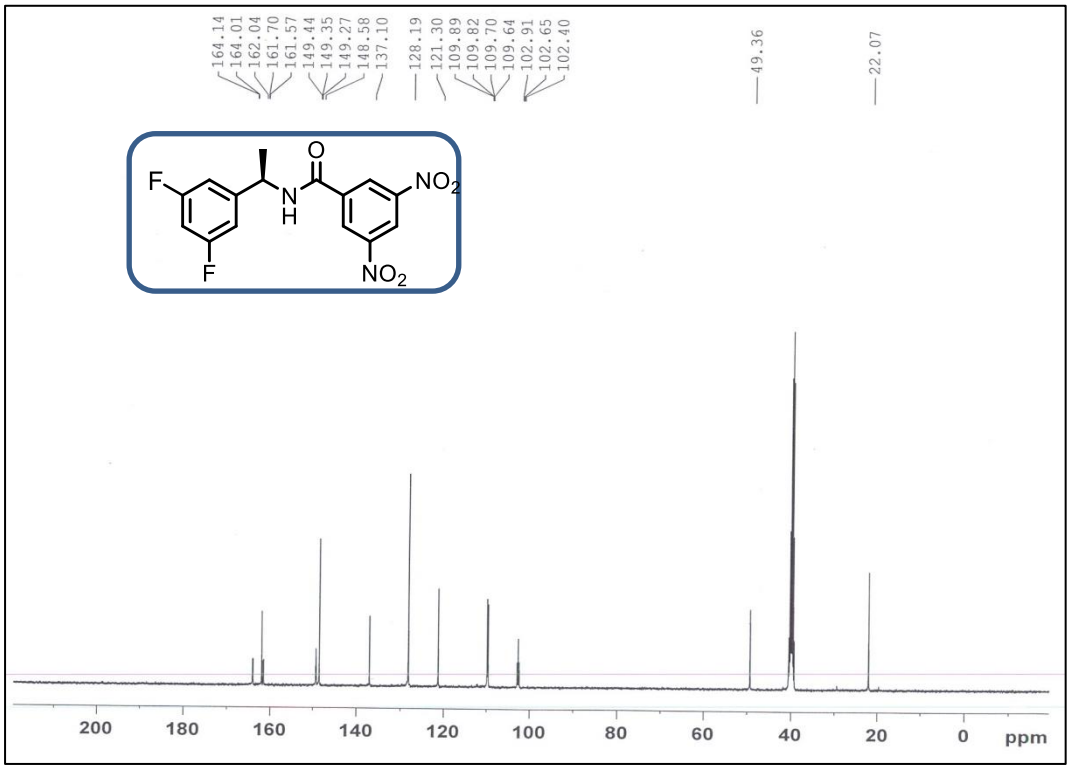
^{1}H NMR spectrum of 1-(3,5-difluorophenyl)ethan-1-amine



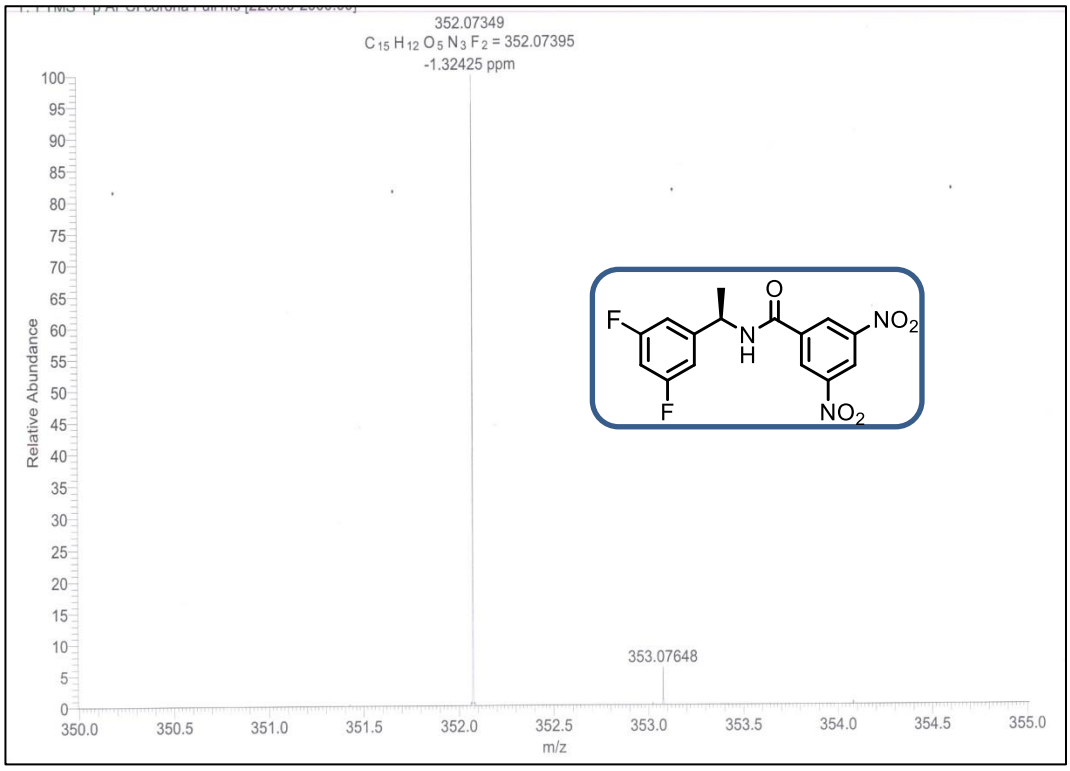
^{1}H NMR spectrum of N-(1-(3,5-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25b**



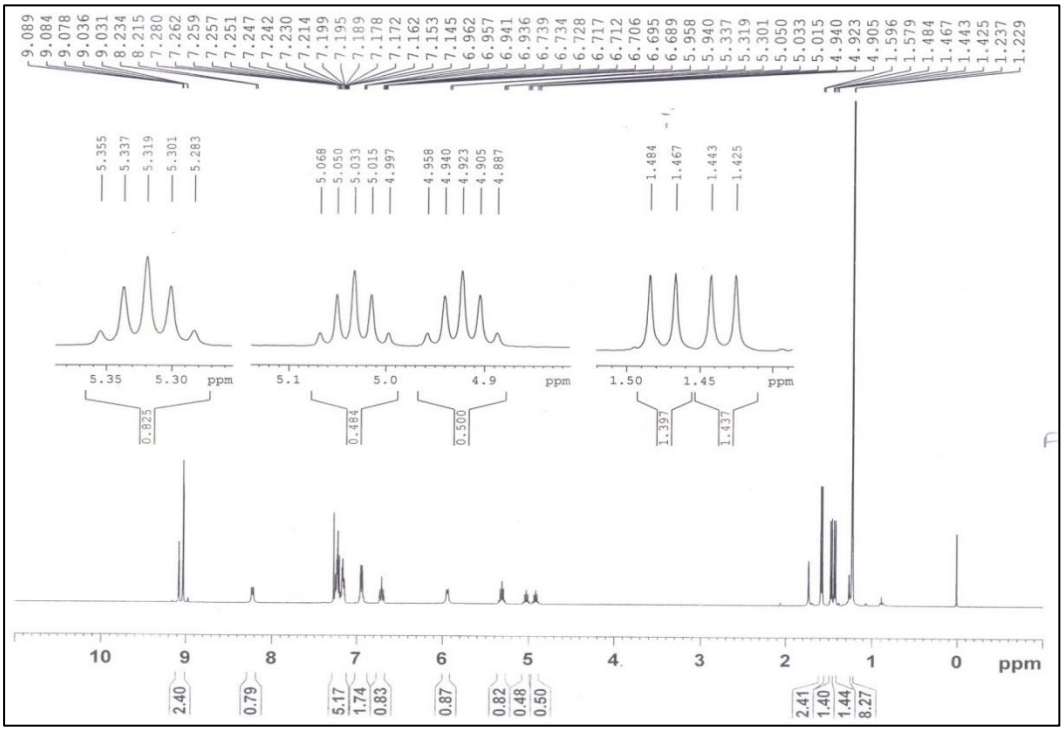
IR spectrum of N-(1-(3,5-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25b**



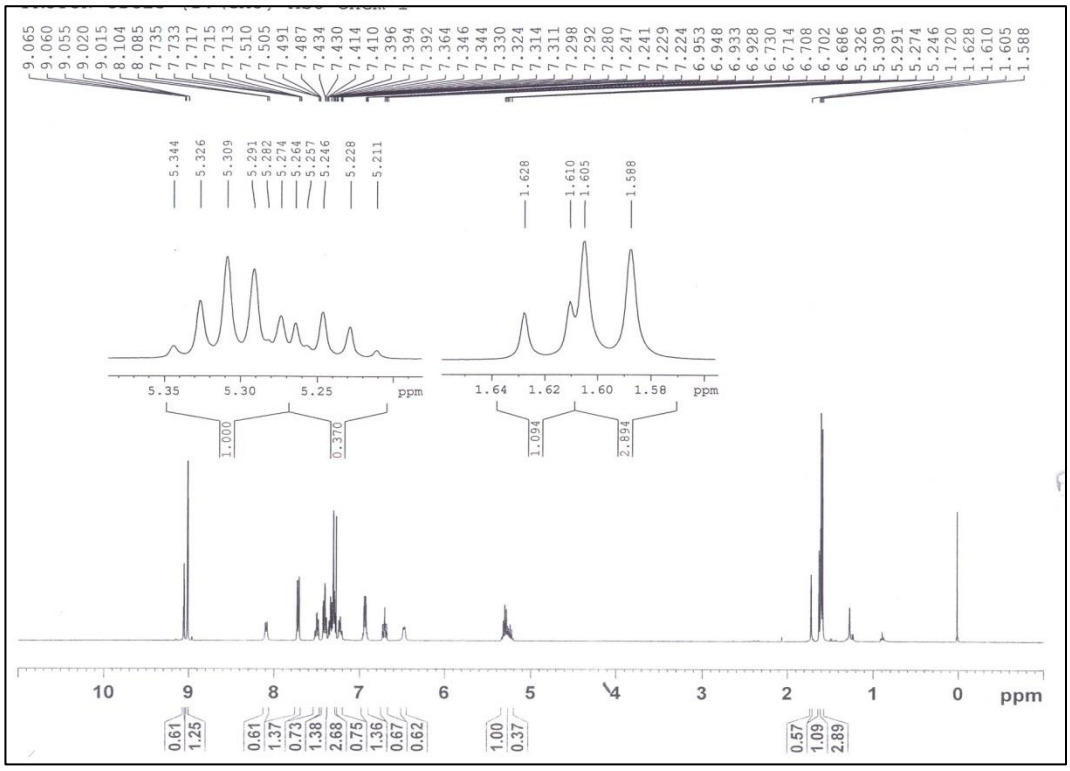
^{13}C NMR spectrum of N-(1-(3,5-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25b**



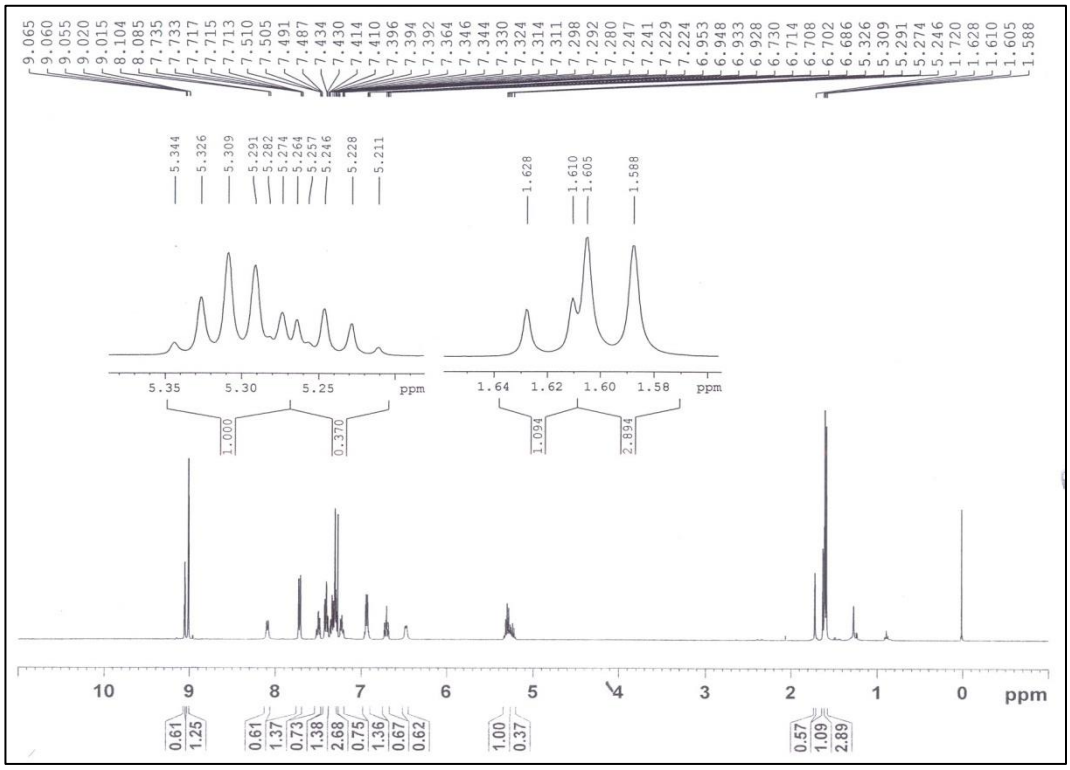
HRMS spectrum of N-(1-(3,5-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25b**



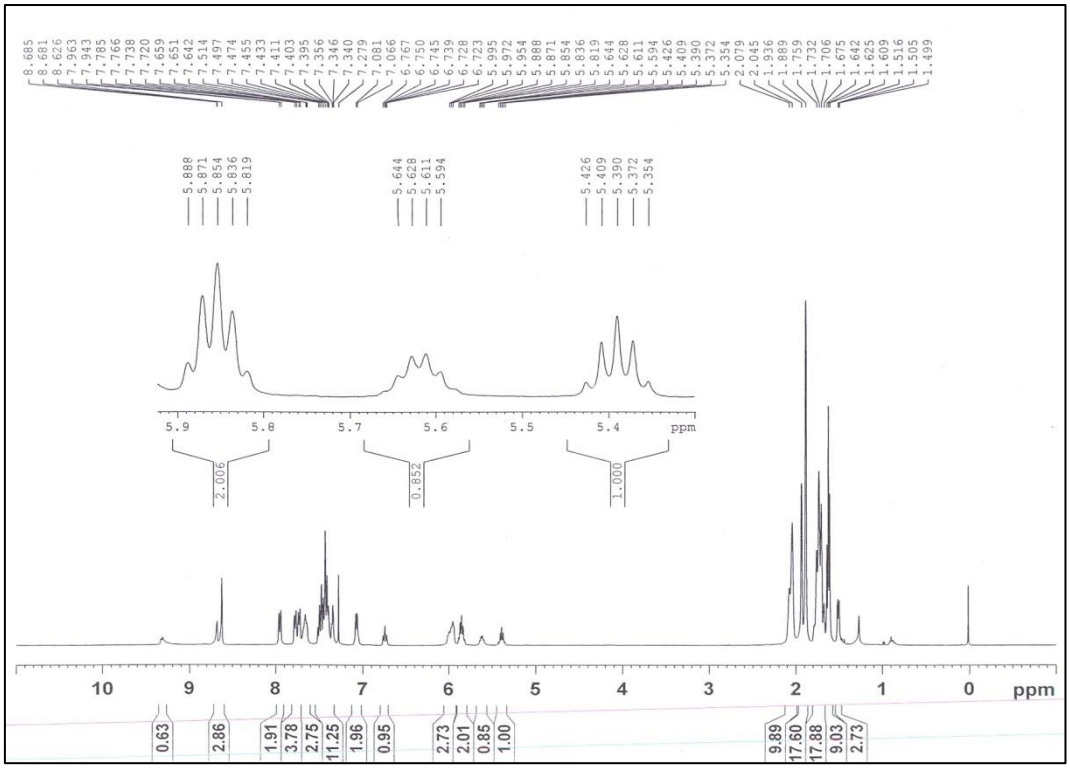
^{1}H NMR spectrum of **25b**+A1



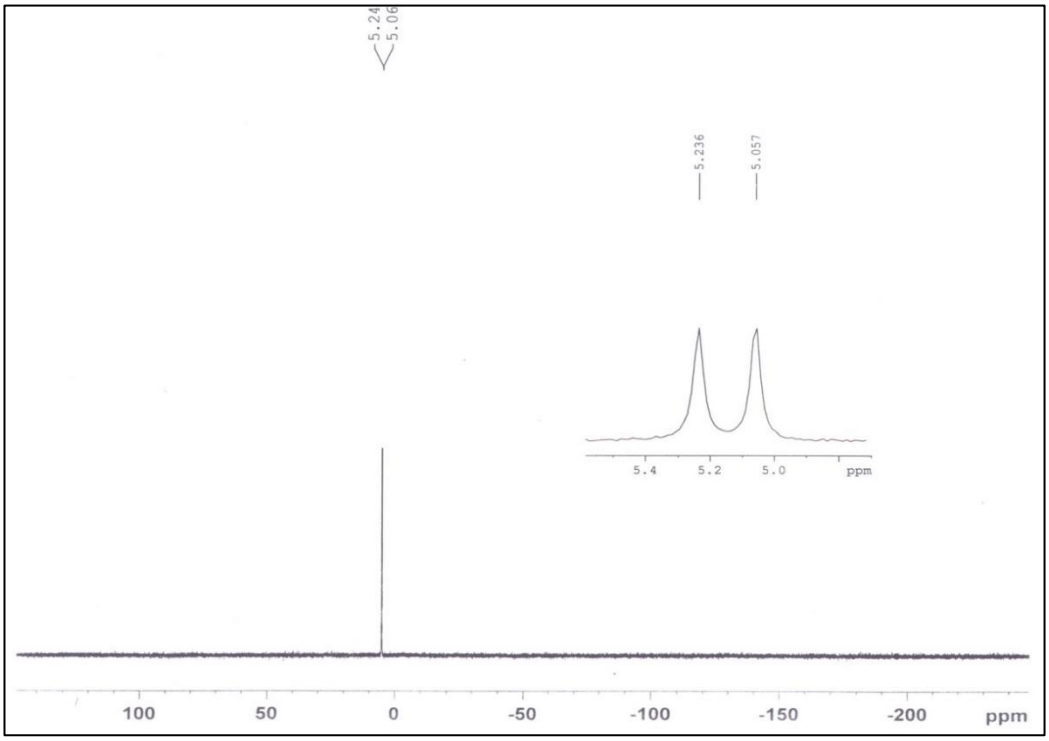
^{1}H NMR spectrum of **25b**+A2



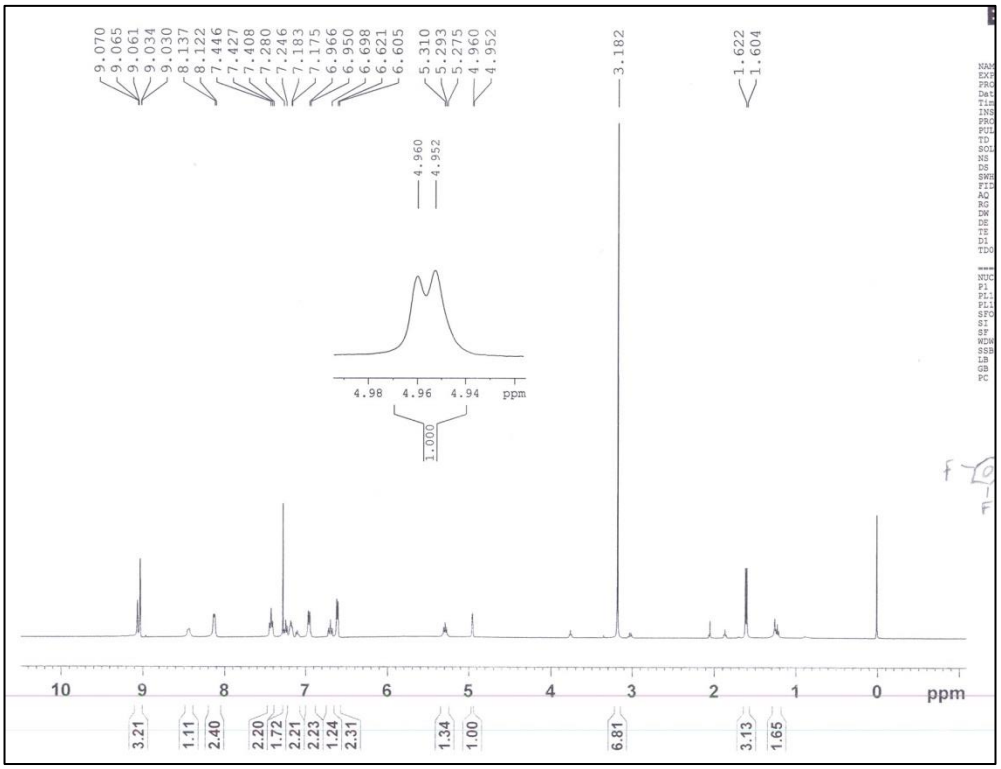
^{1}H NMR spectrum of **25b**+A3



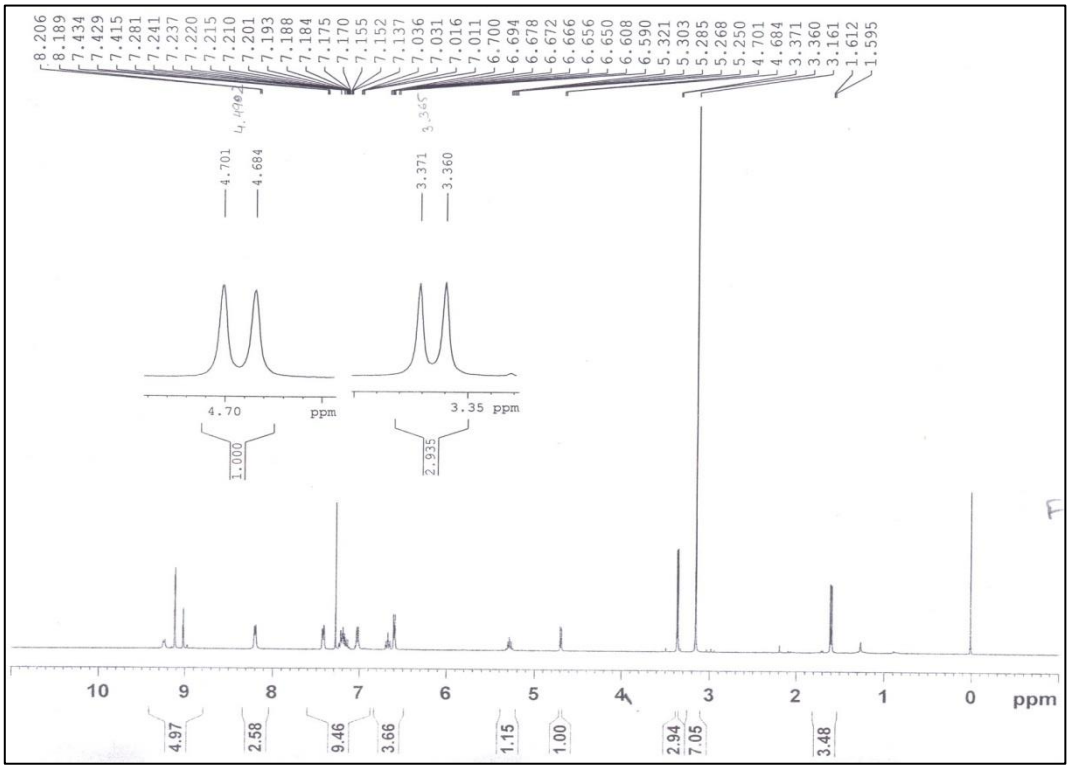
^{1}H NMR spectrum of **25b**+A4



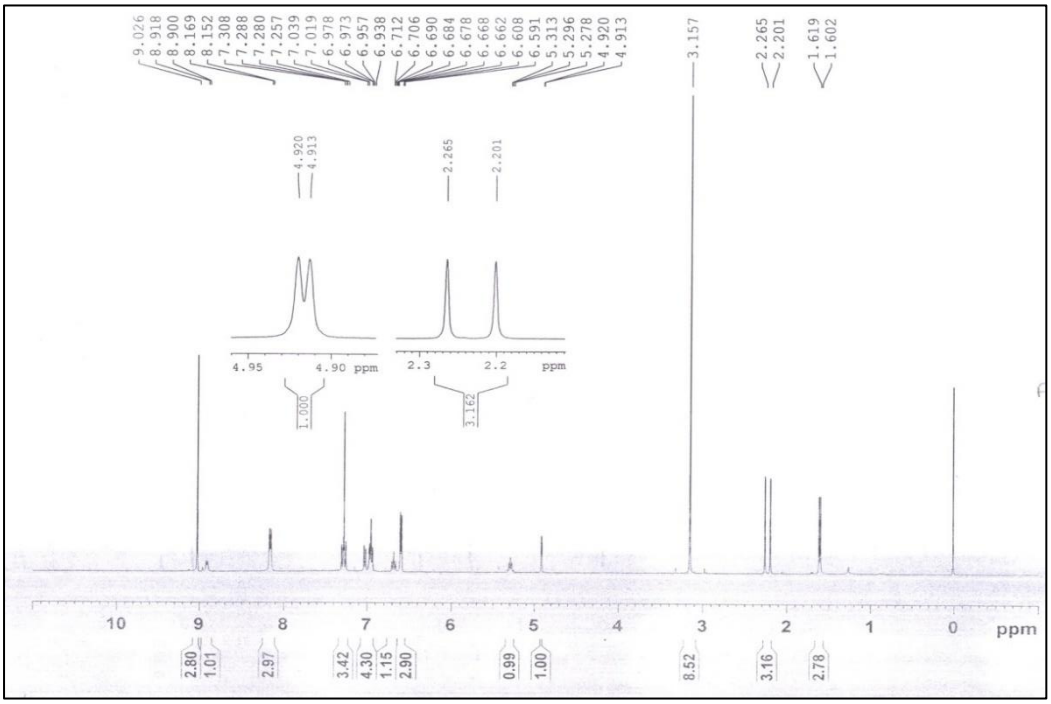
^{31}P NMR spectrum of **25b**+B1



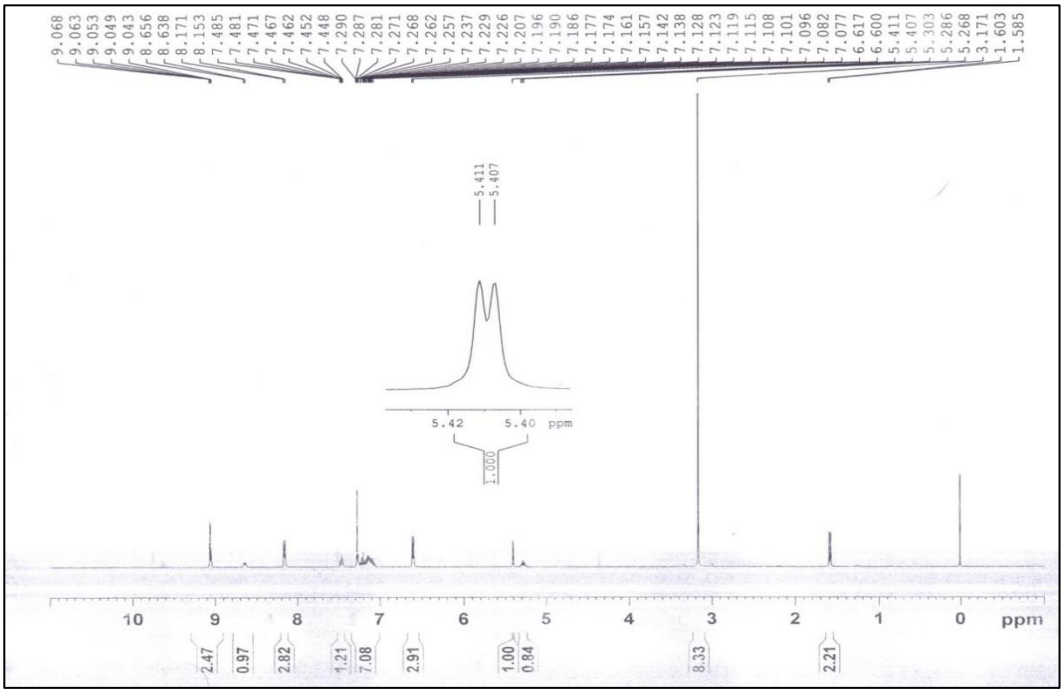
^{1}H NMR spectrum of **25b**+C1



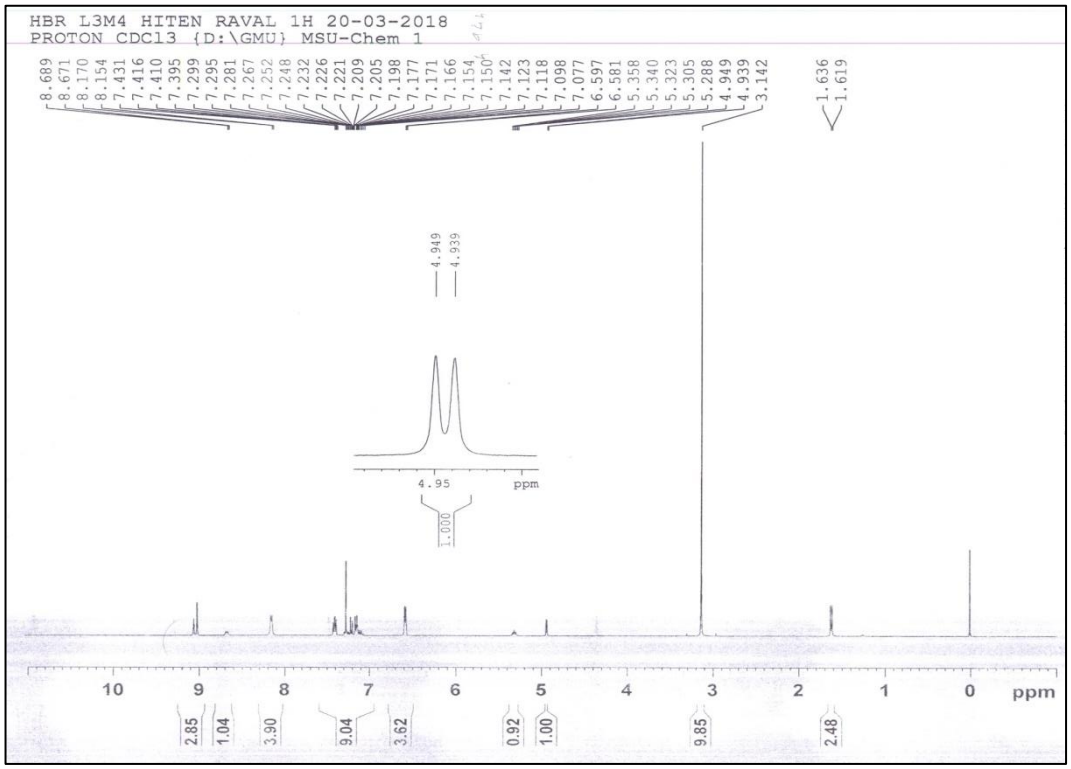
^{1}H NMR spectrum of **25b**+C2



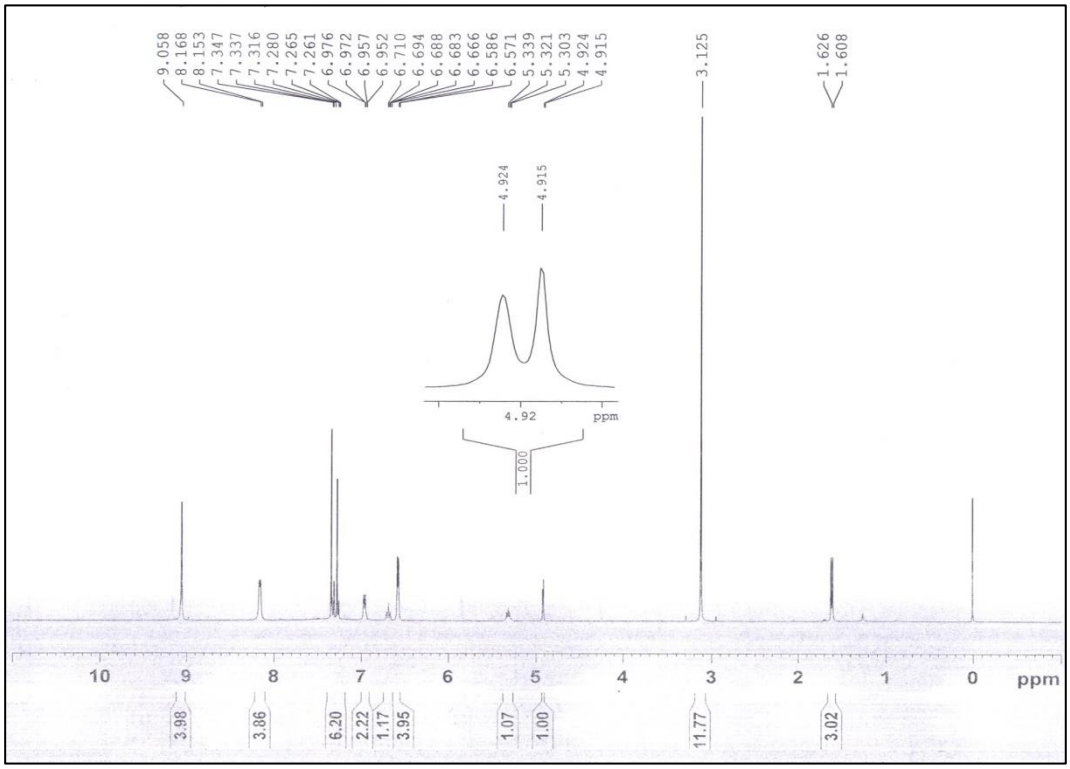
^{1}H NMR spectrum of **25b**+C3



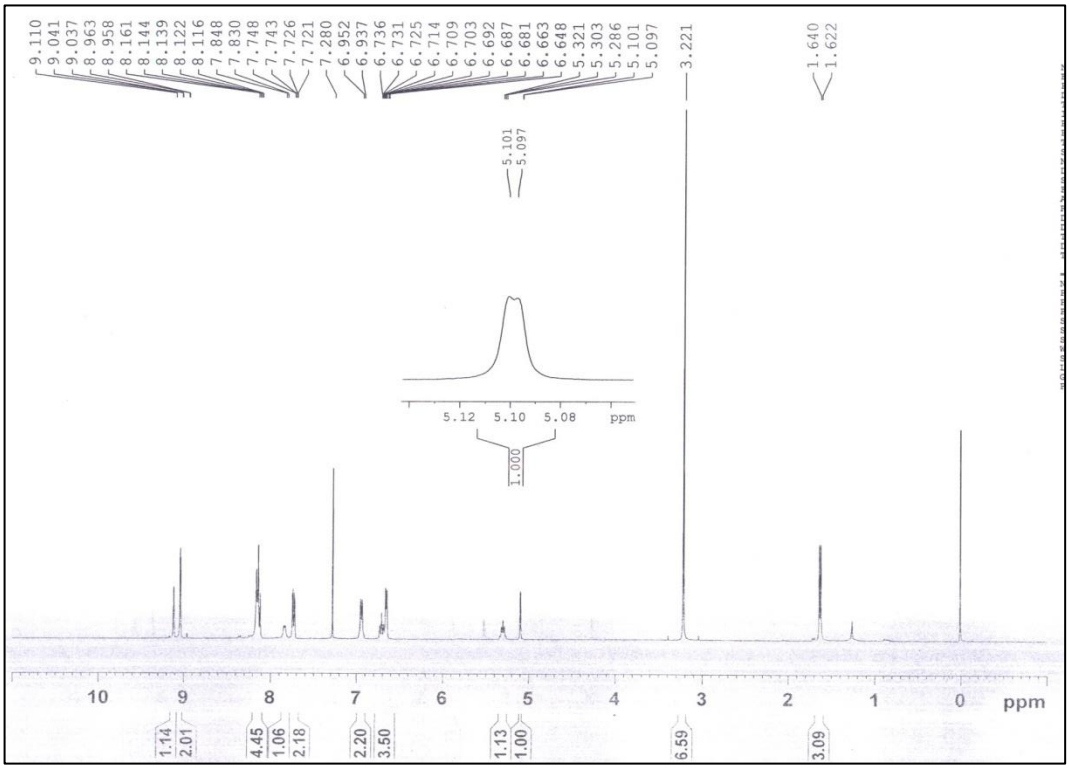
^{1}H NMR spectrum of **25b**+C4



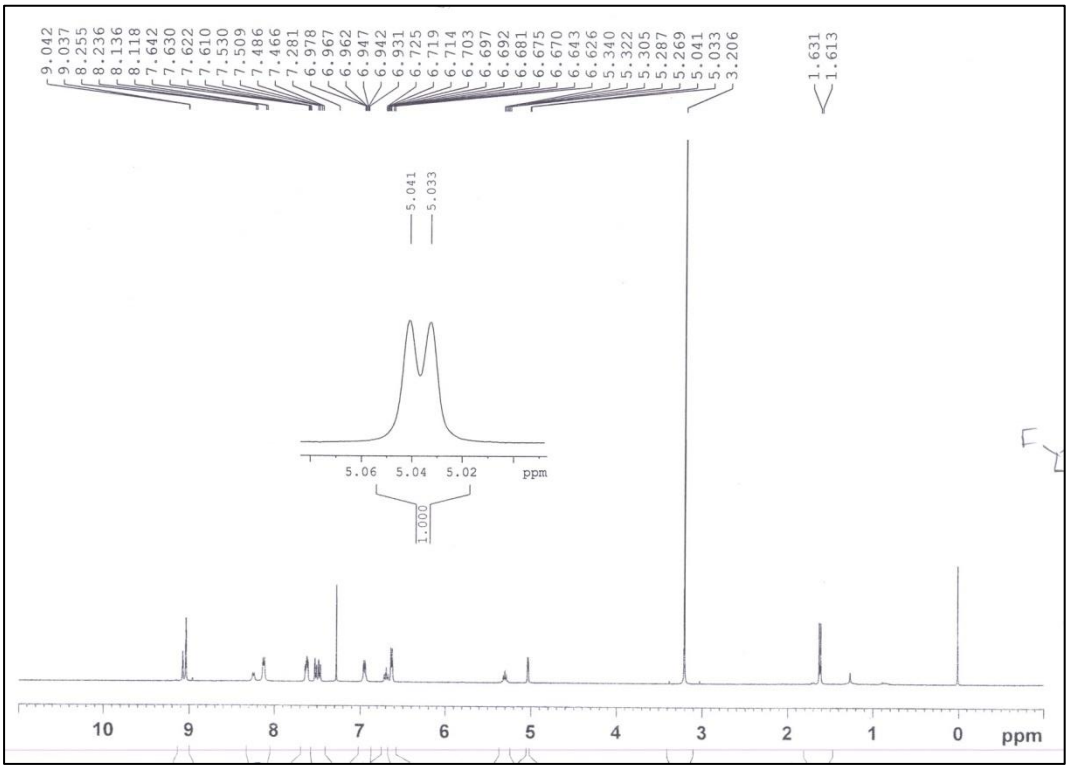
^{1}H NMR spectrum of **25b**+C5



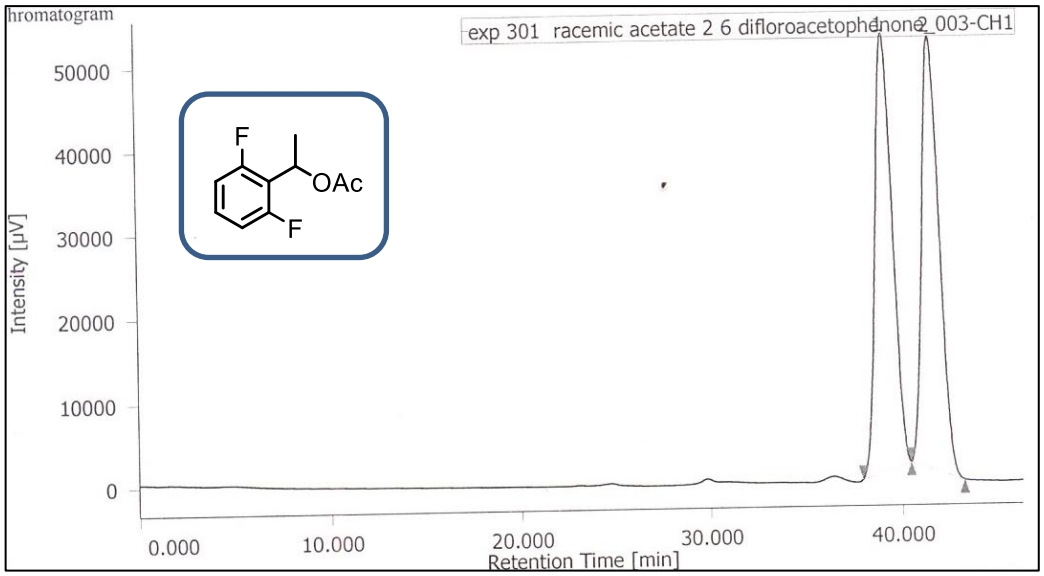
^{1}H NMR spectrum of **25b**+C6



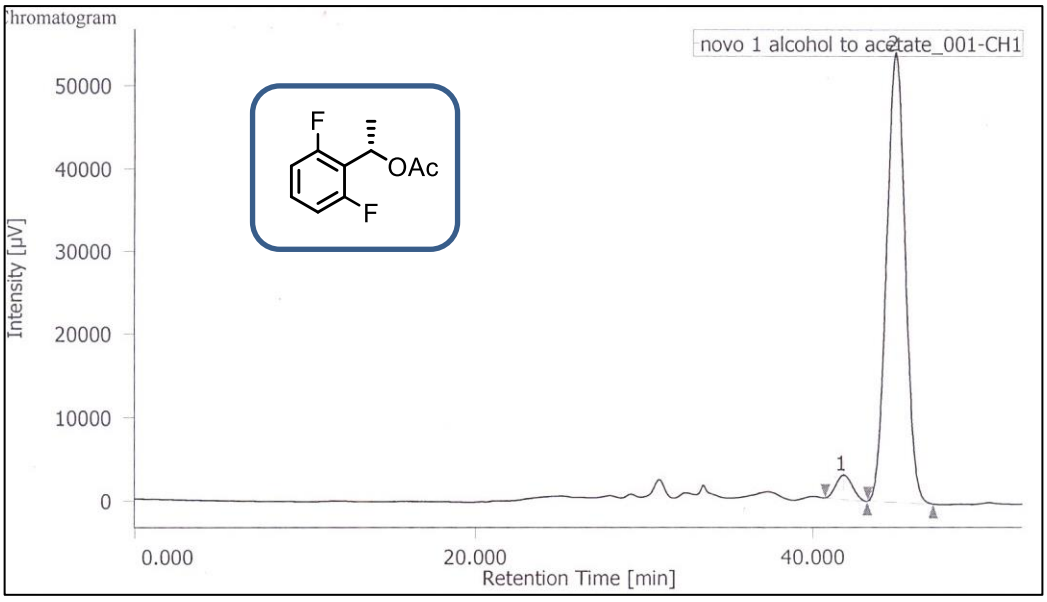
^{1}H NMR spectrum of **25b**+C7



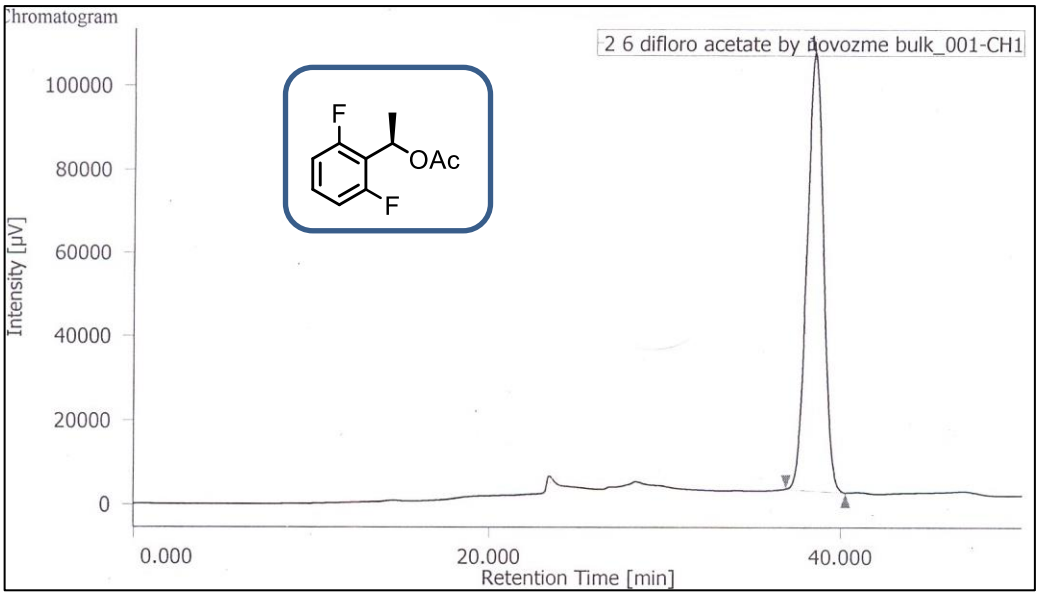
^{1}H NMR spectrum of **25b**+C8



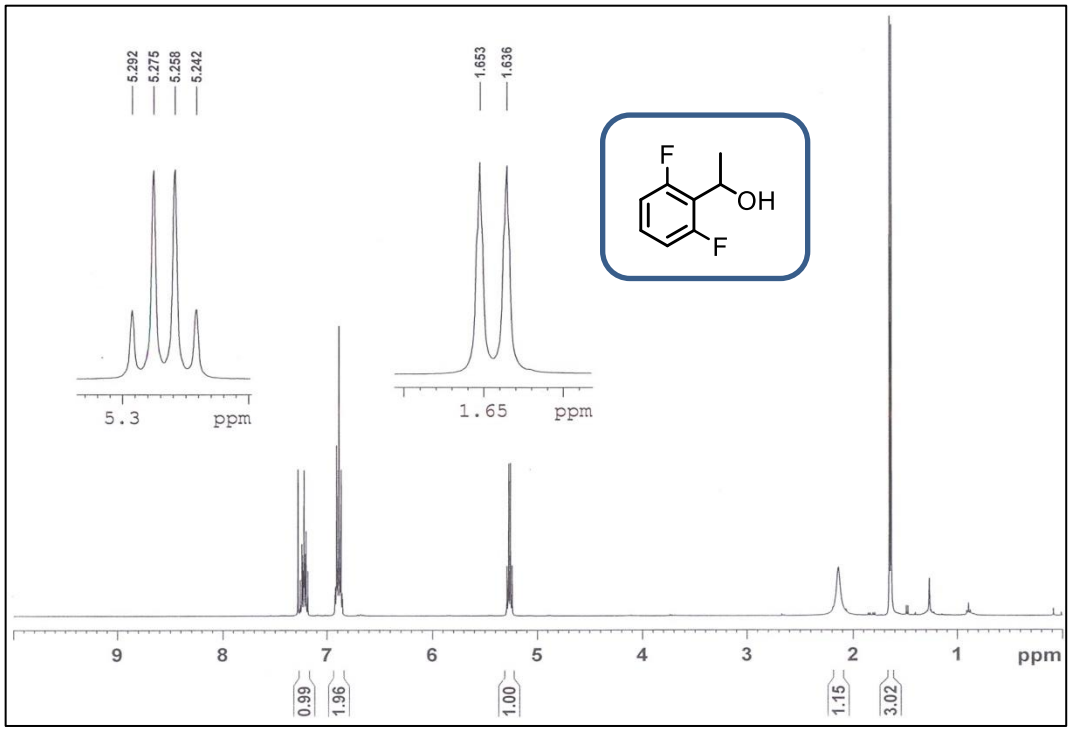
HPLC of 1-(2,6-difluorophenyl)ethyl acetate **31**



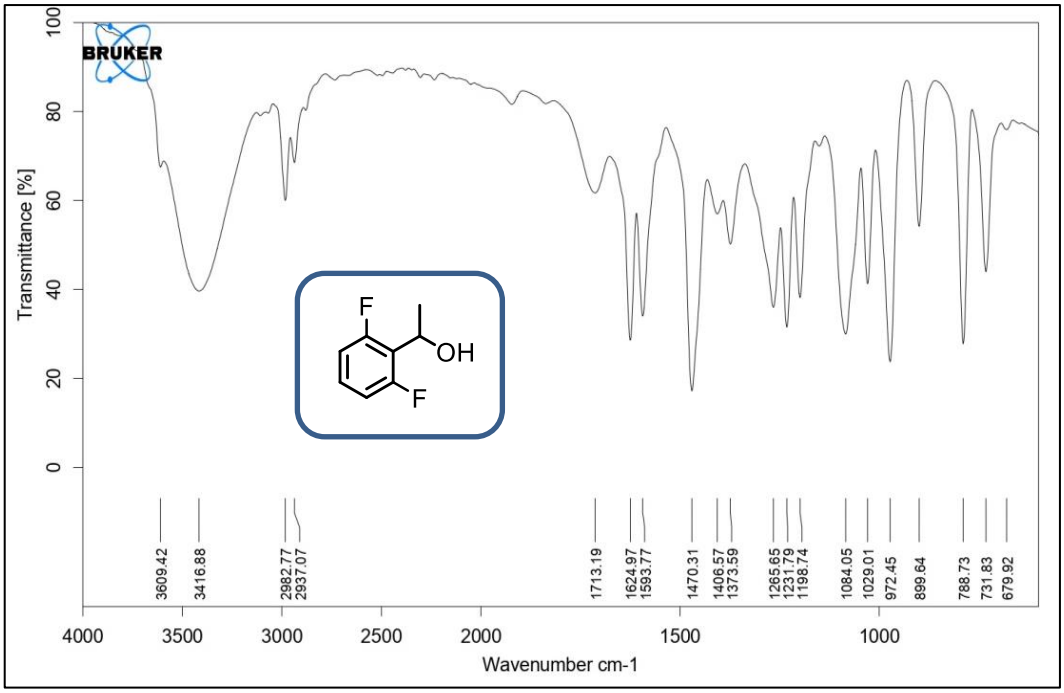
HPLC of 1-(2,6-difluorophenyl)ethyl acetate (*S*)-**31**



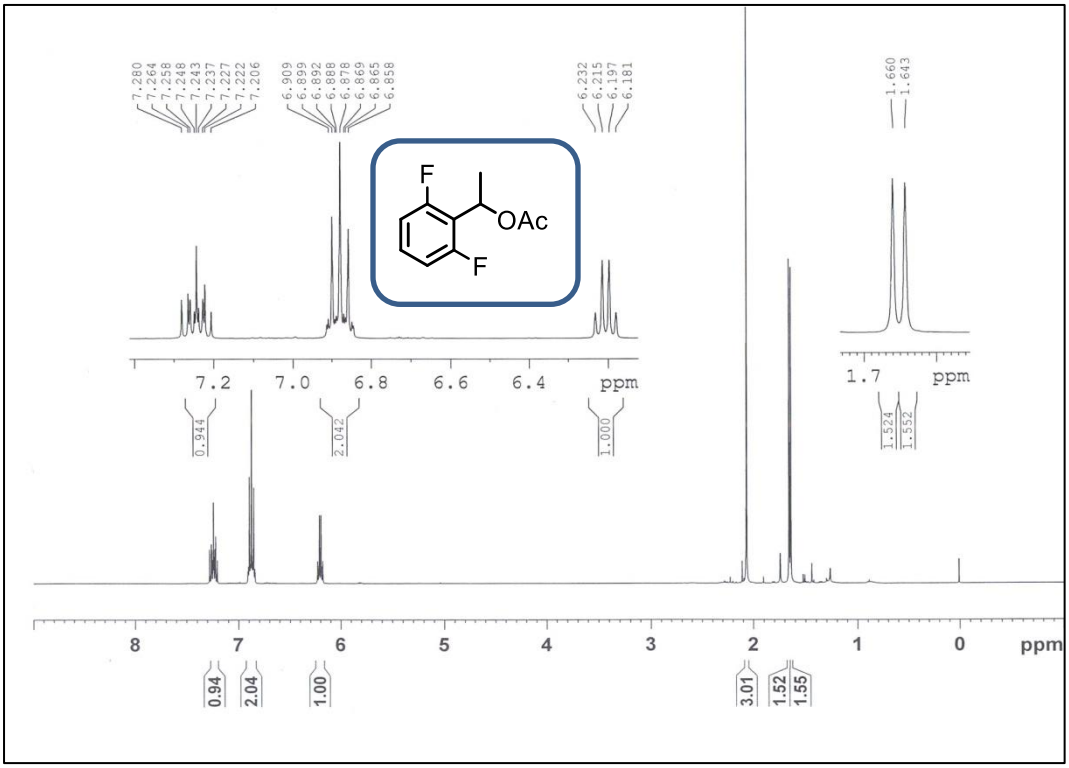
HPLC of 1-(2,6-difluorophenyl)ethyl acetate (*R*)-**31**



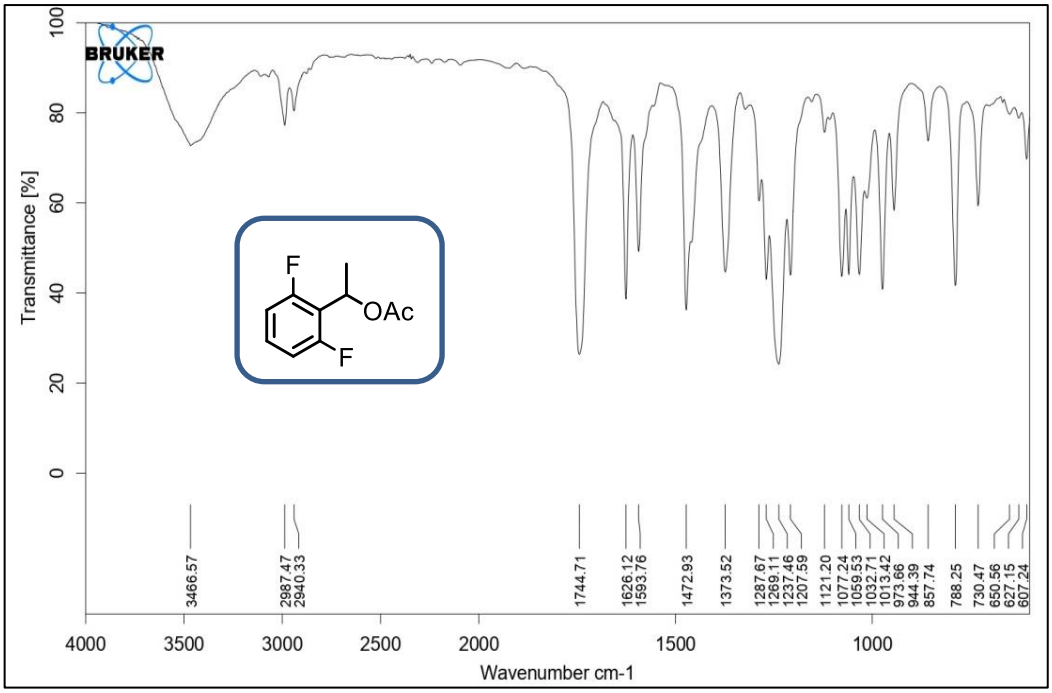
^{1}H NMR spectrum of 1-(2,6-difluorophenyl)ethan-1-ol **30**



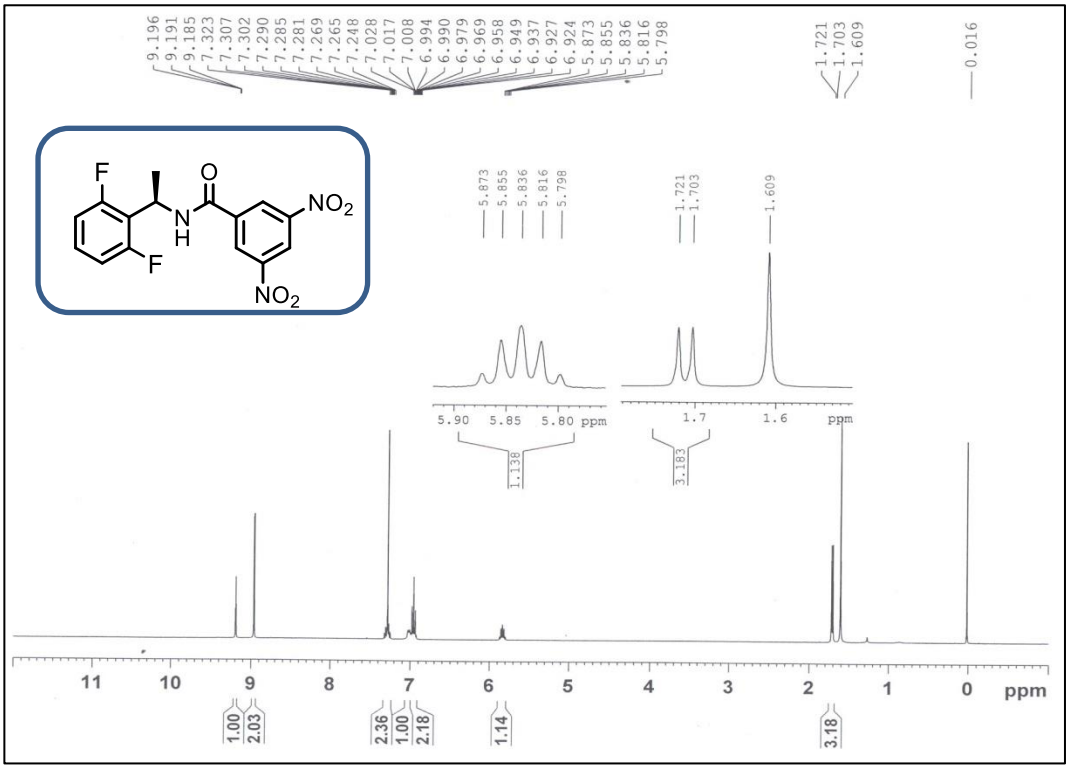
IR spectrum of 1-(2,6-difluorophenyl)ethan-1-ol **30**



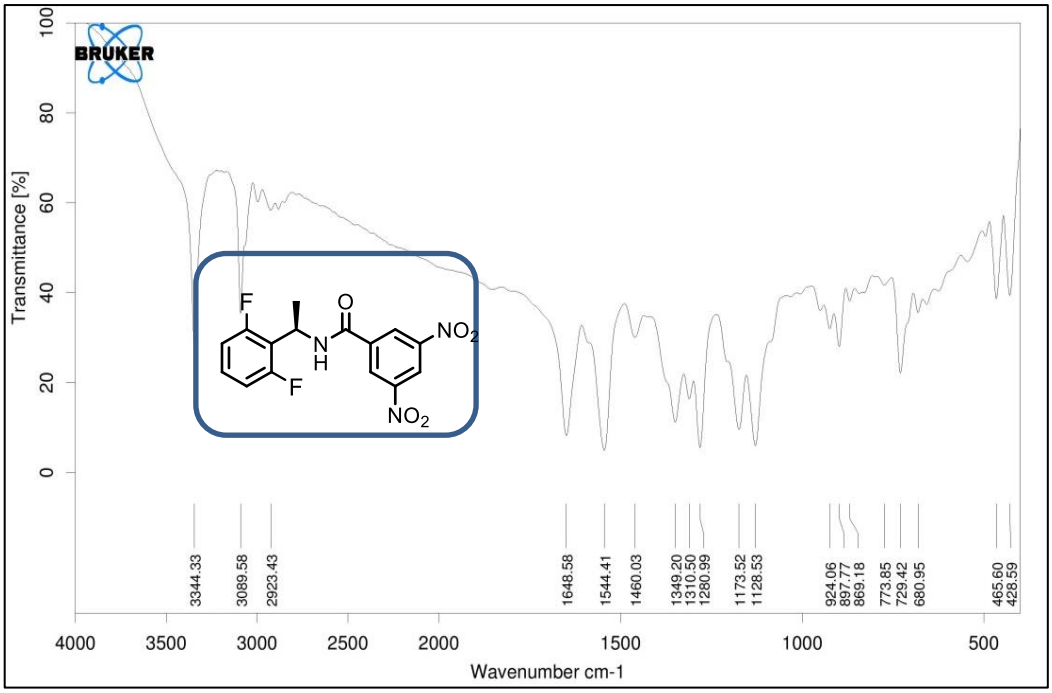
^{1}H NMR spectrum of 1-(2,6-difluorophenyl) ethyl acetate **31**



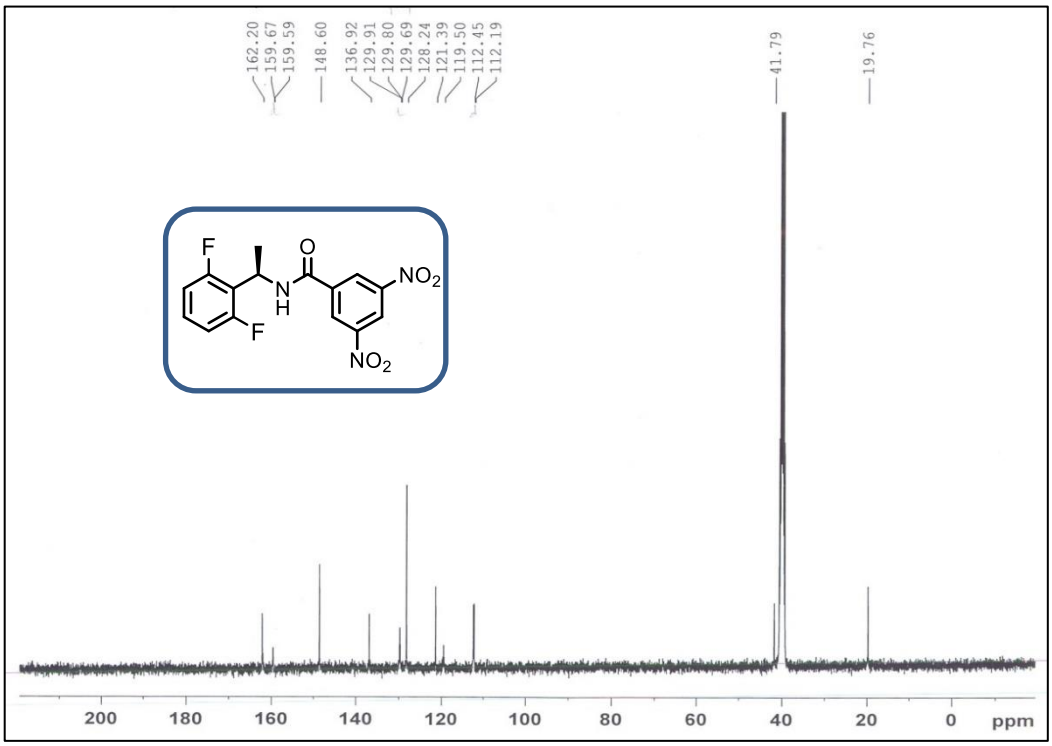
IR spectrum of 1-(2,6-difluorophenyl) ethyl acetate **31**



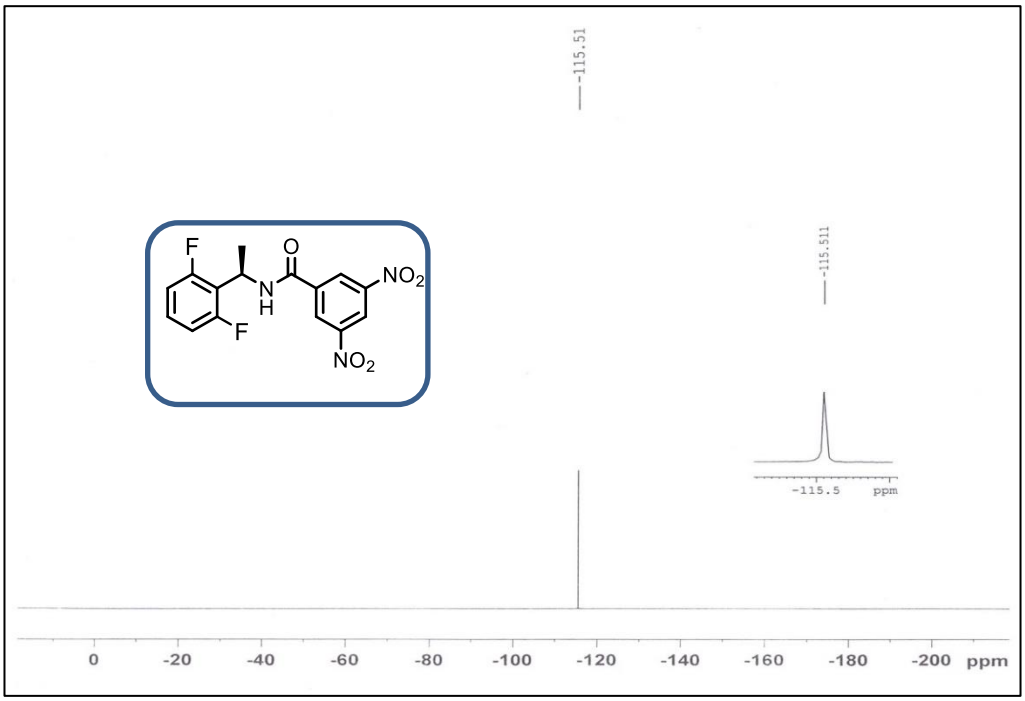
^{1}H NMR spectrum of N-(1-(2,6-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25c**



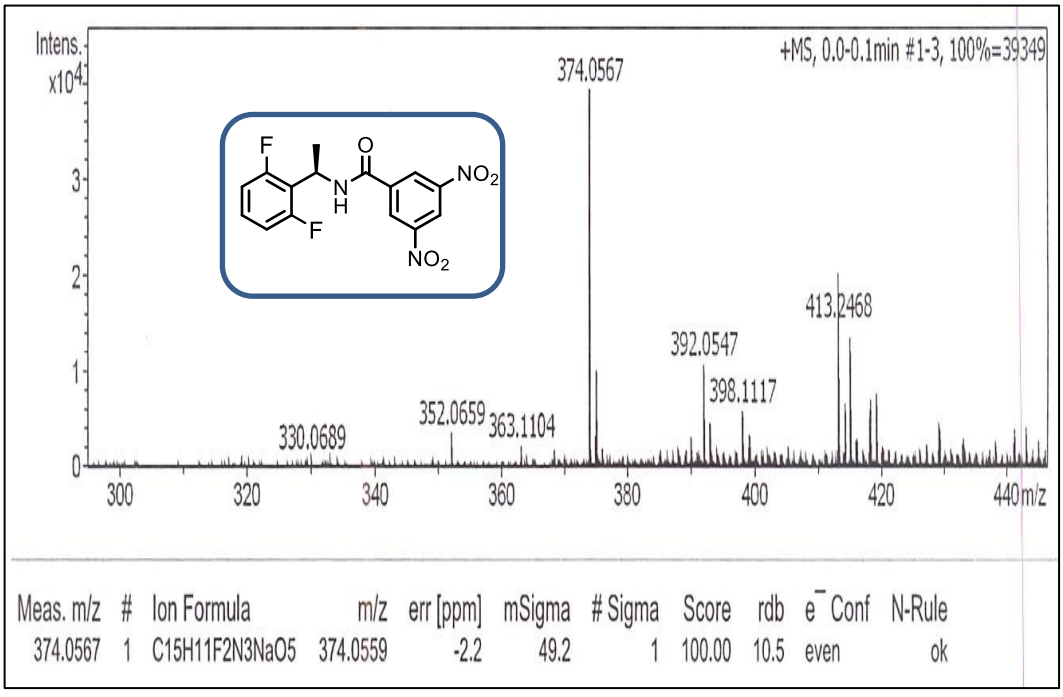
IR spectrum of N-(1-(2,6-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25c**



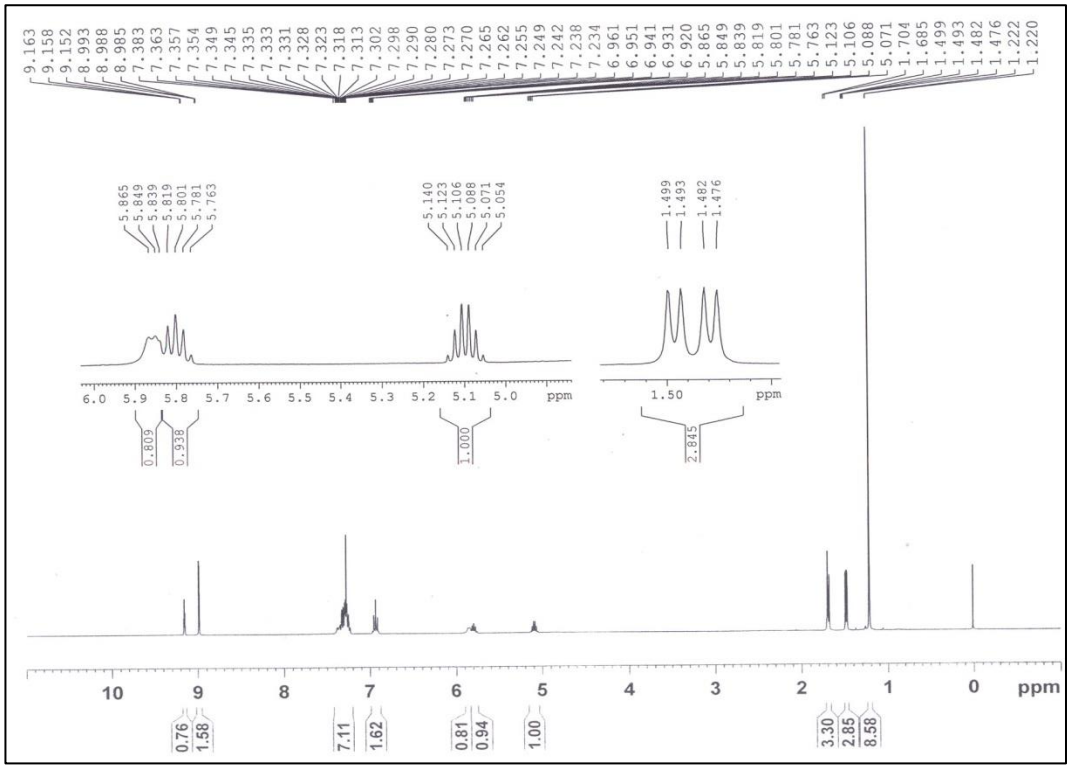
^{1}H NMR spectrum of N-(1-(2,6-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25c**



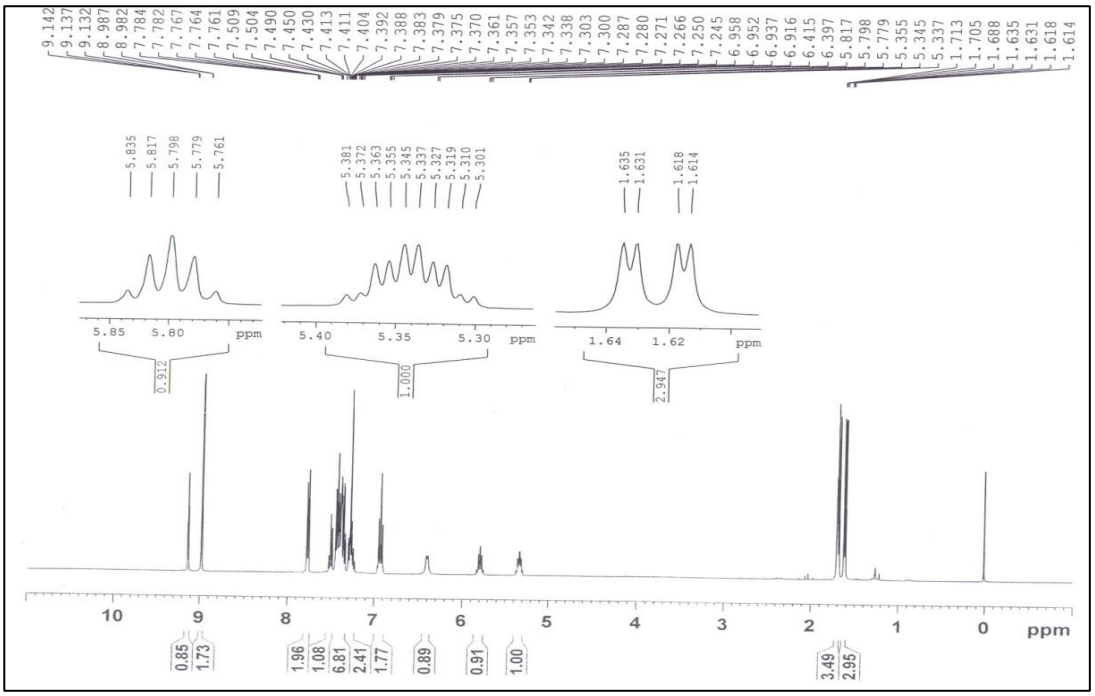
^{19}F spectrum of N-(1-(2,6-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25c**



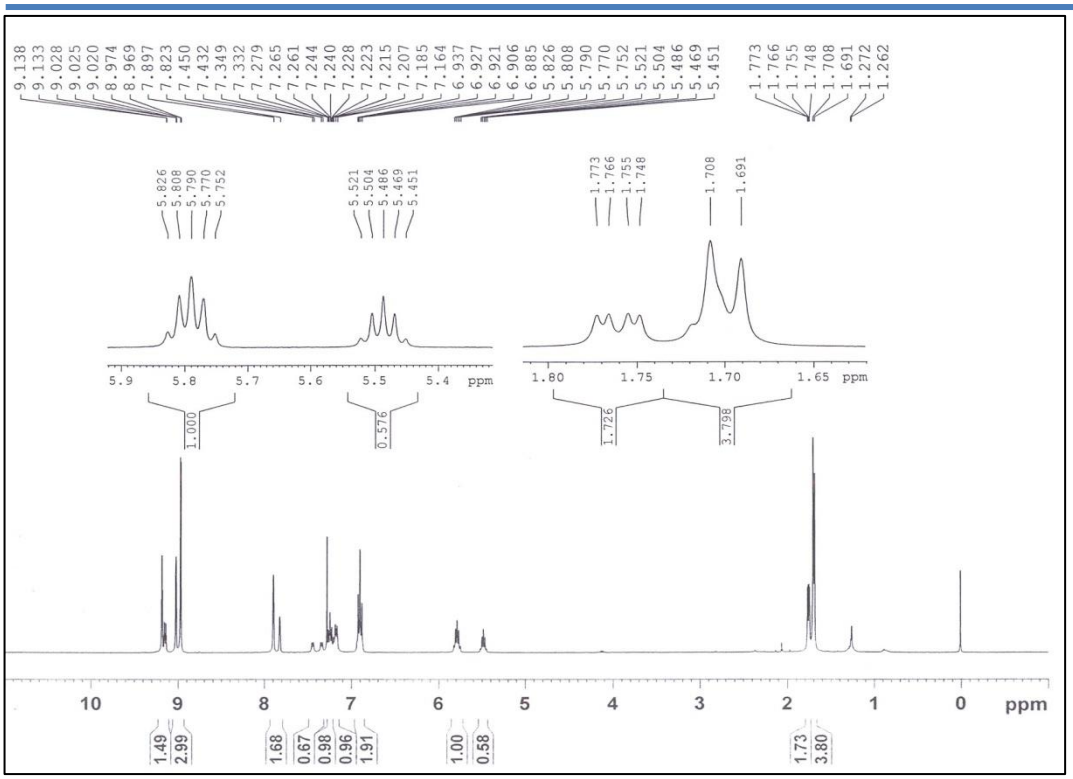
HRMS spectrum of N-(1-(2,6-difluorophenyl)ethyl)-3,5-dinitrobenzamide **25c**



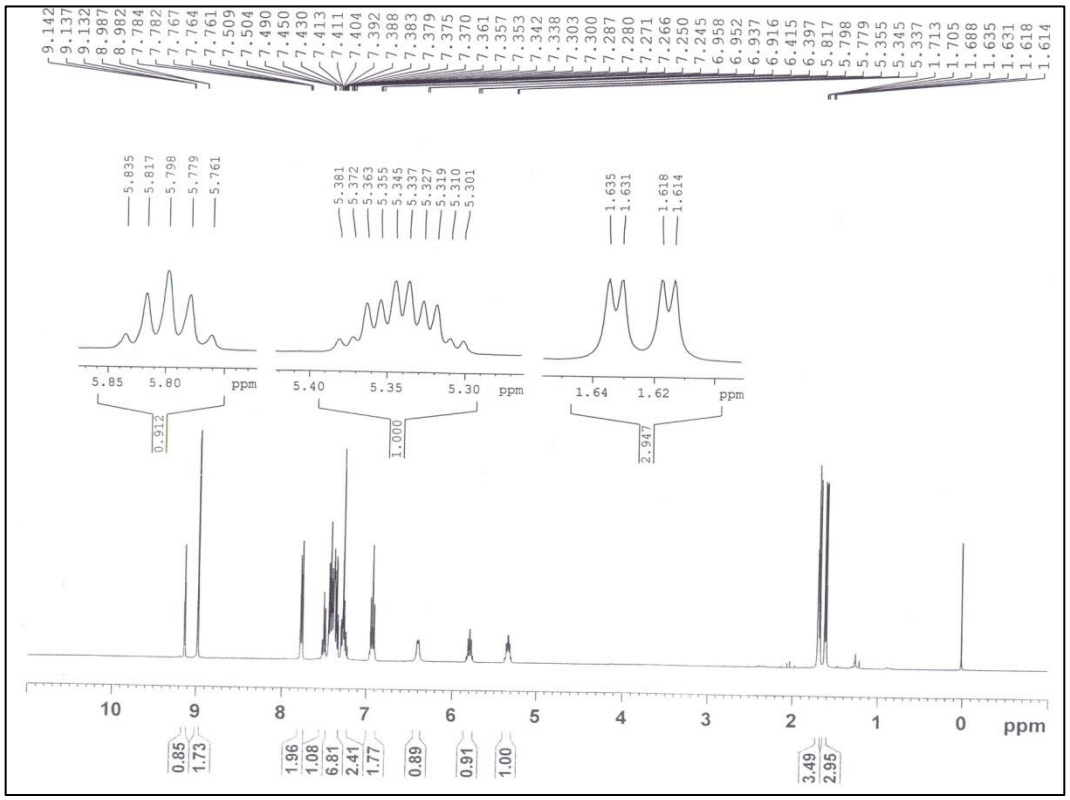
^{1}H NMR spectrum of **25c**+A1



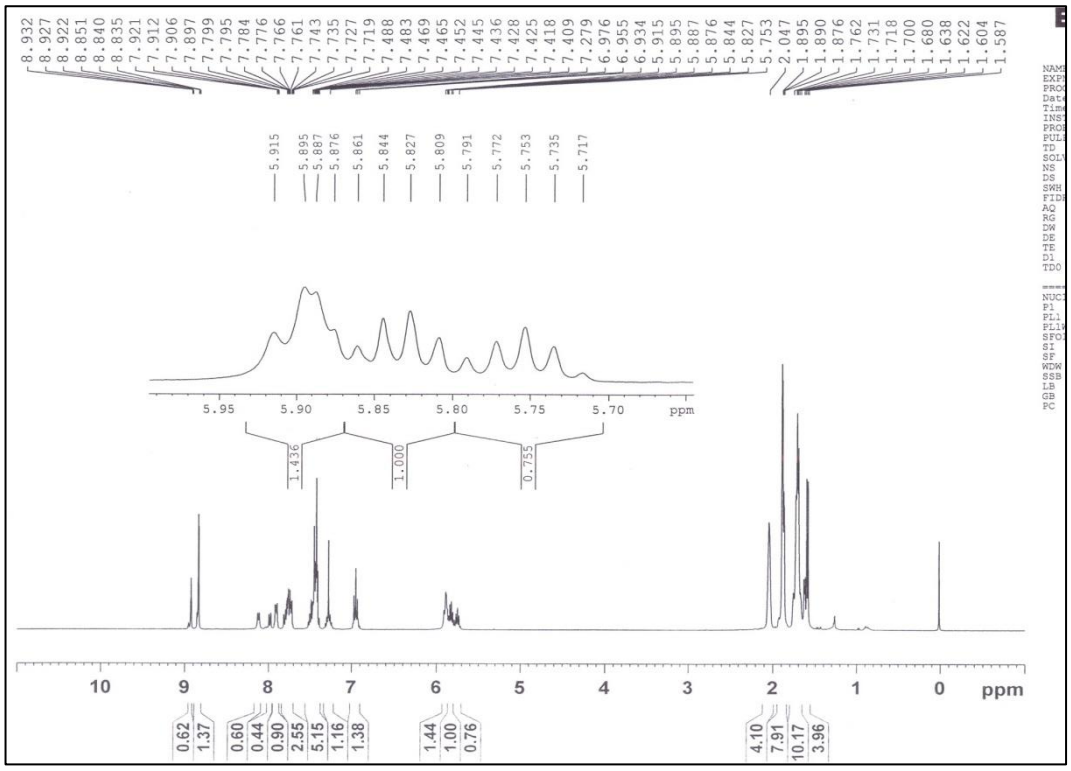
^{1}H NMR spectrum of **25c**+A2



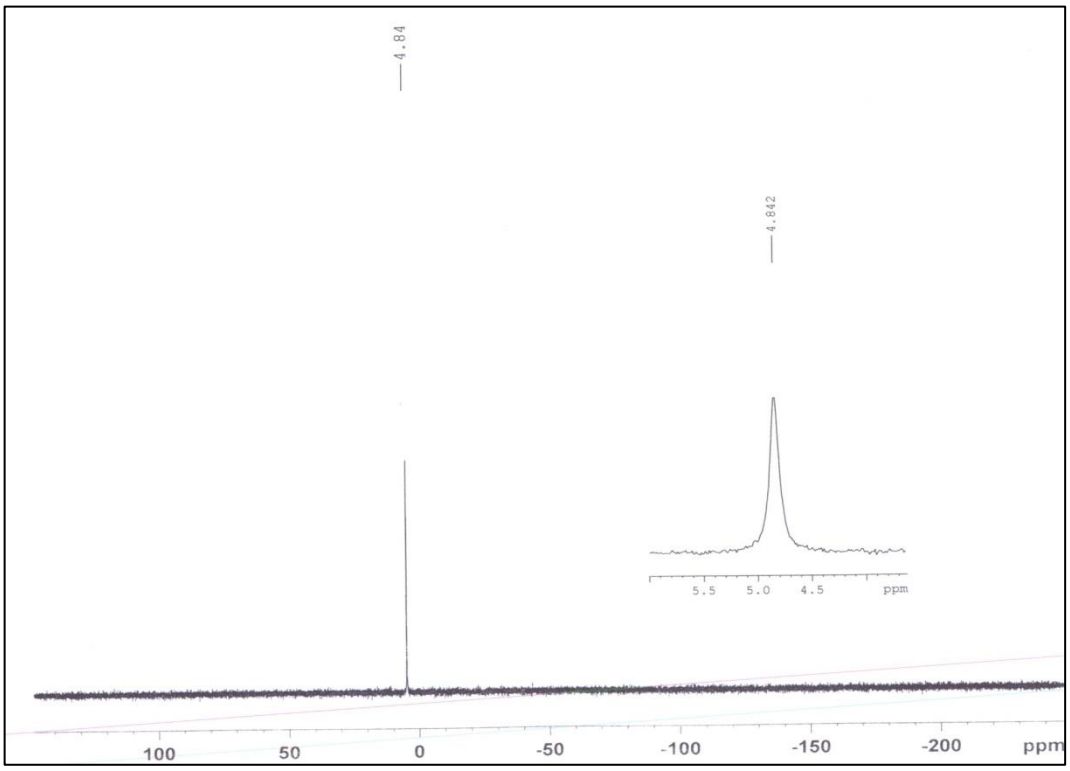
^{1}H NMR spectrum of **25c**+A2



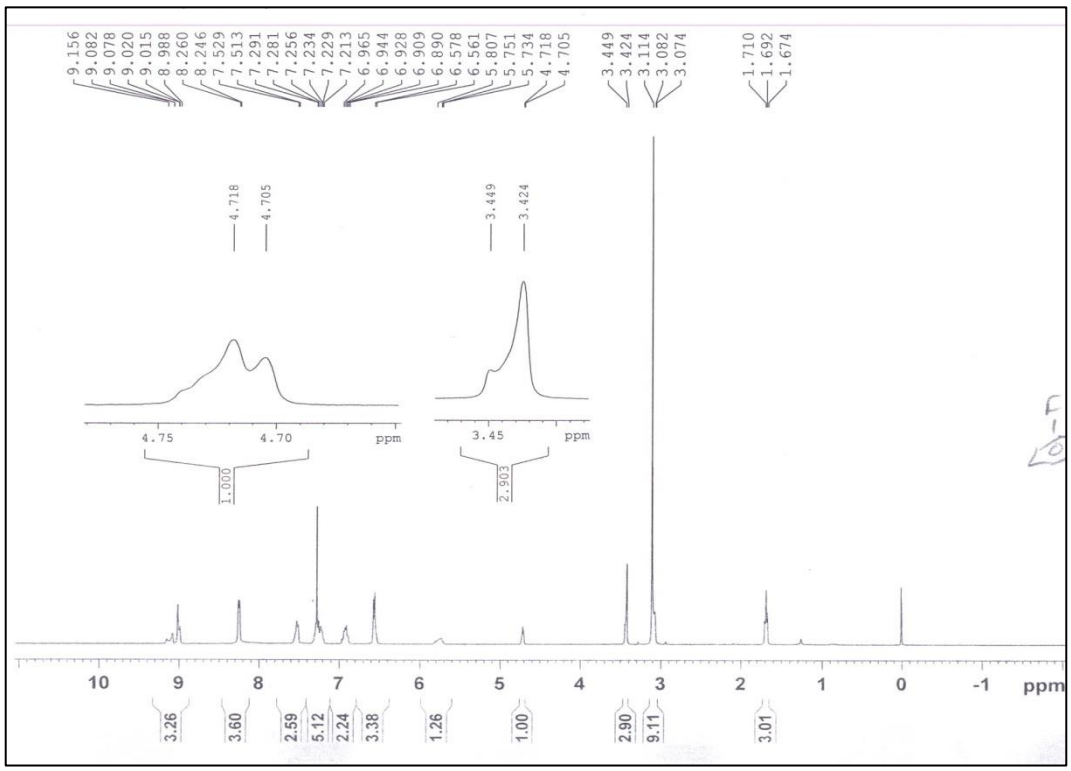
^{1}H NMR spectrum of **25c**+A3



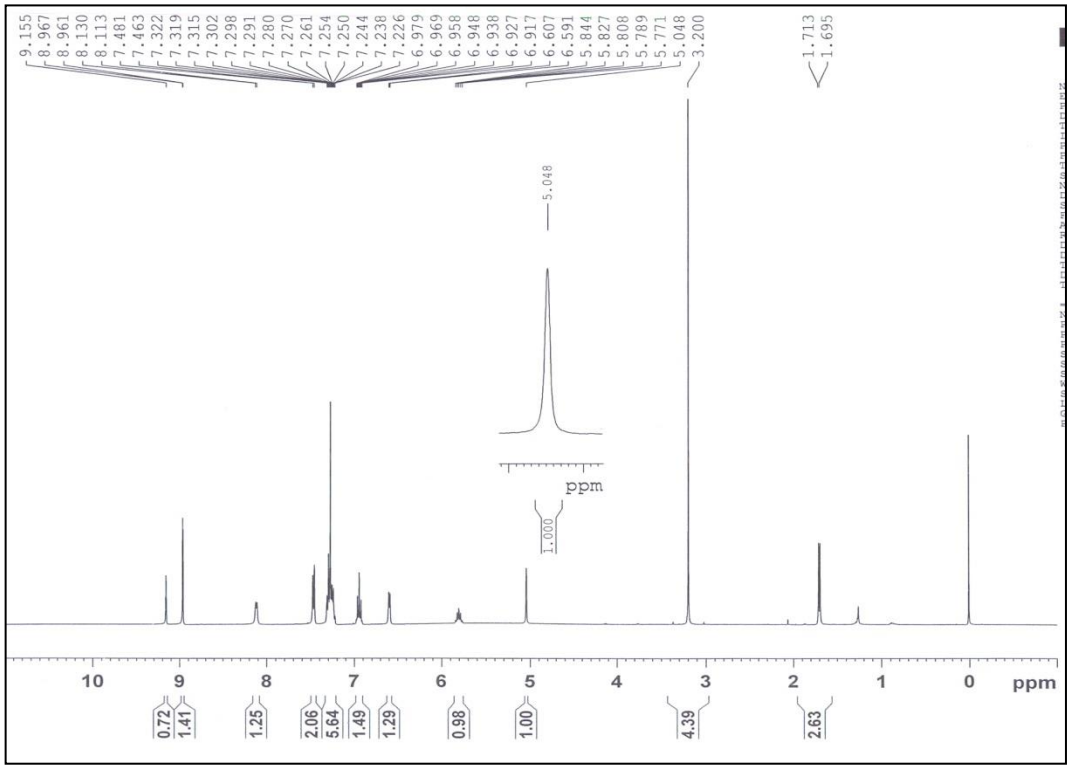
^{1}H NMR spectrum of **25c**+A4



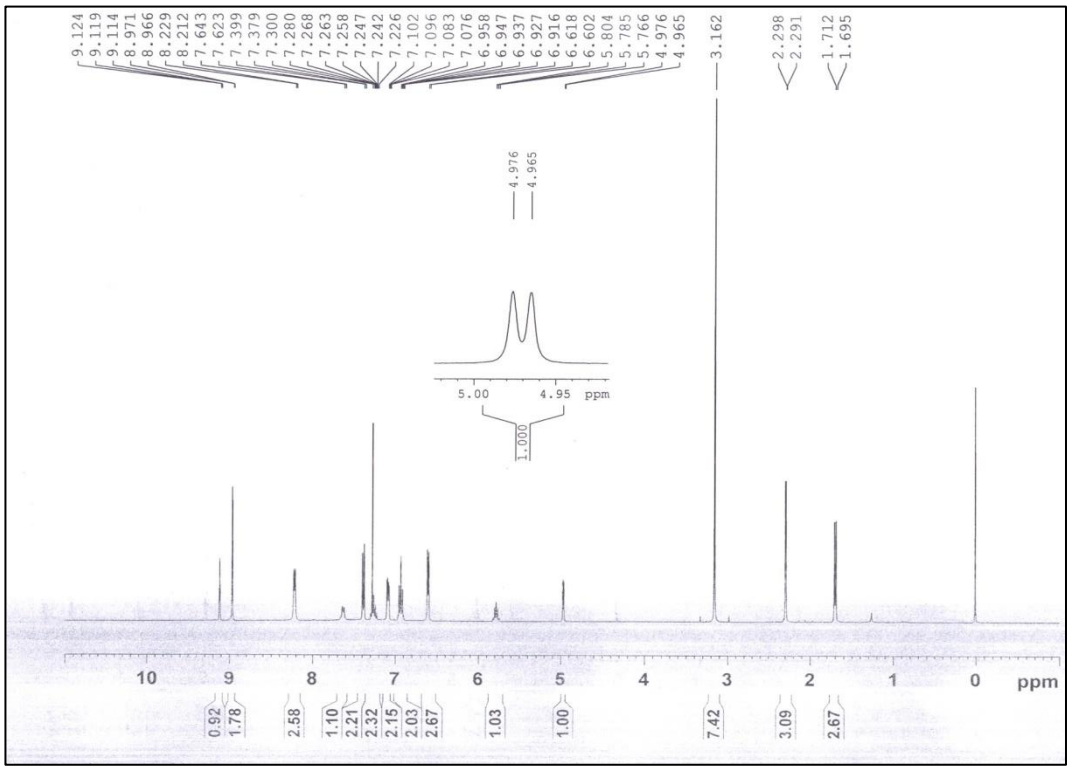
^{31}P NMR spectrum of **25c**+B1



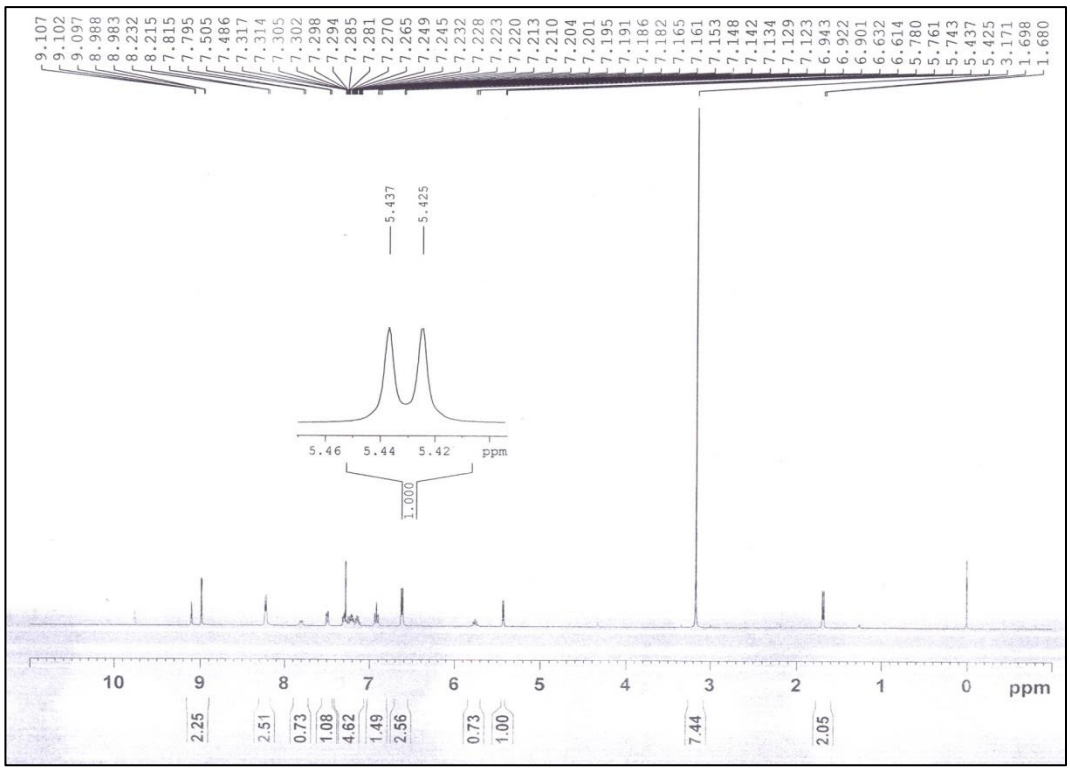
^{1}H NMR spectrum of **25c**+C1



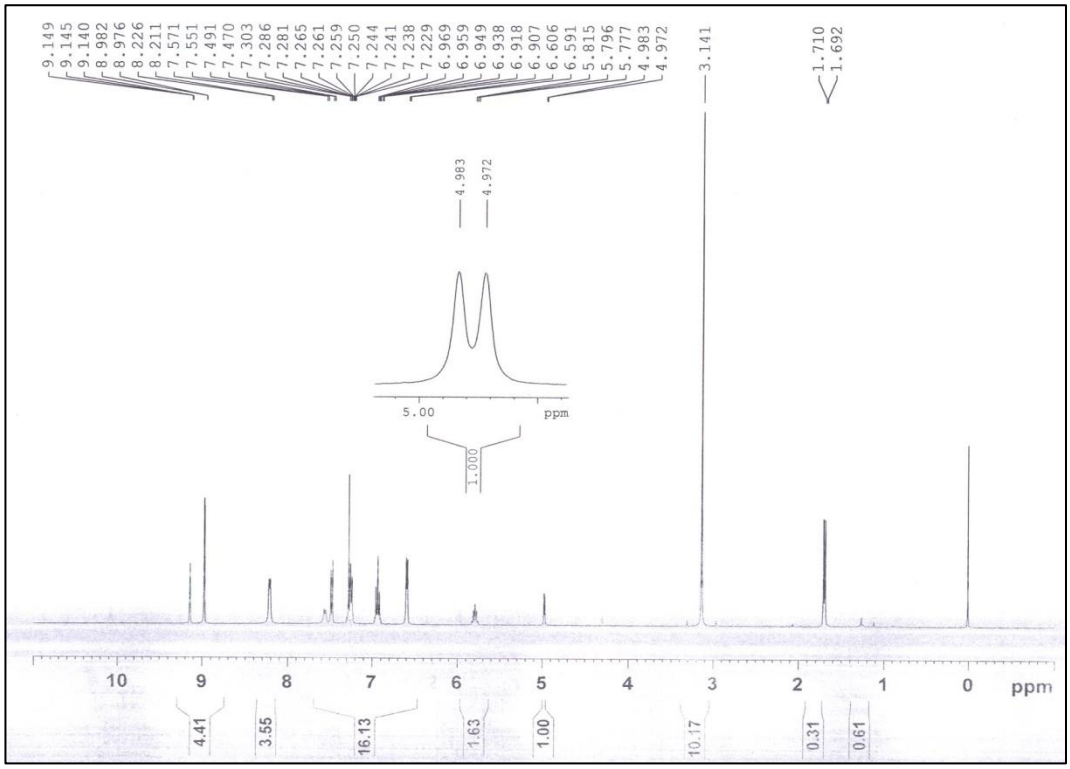
^{1}H NMR spectrum of **25c**+C2



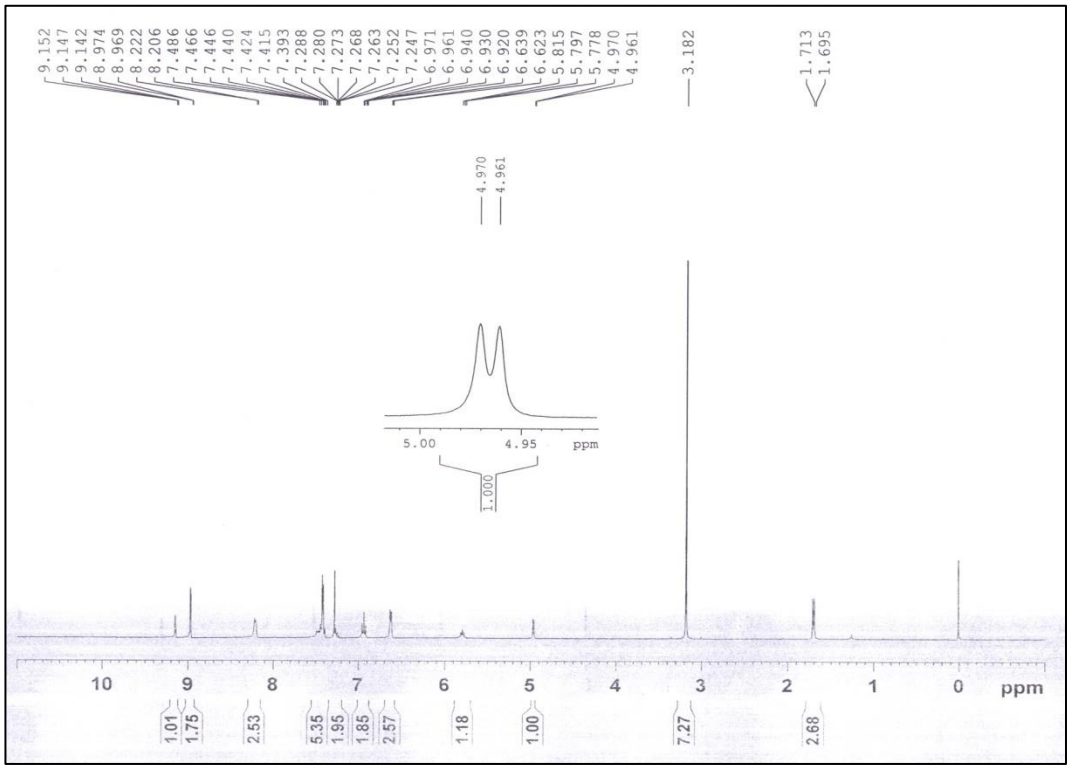
^{1}H NMR spectrum of **25c**+C3



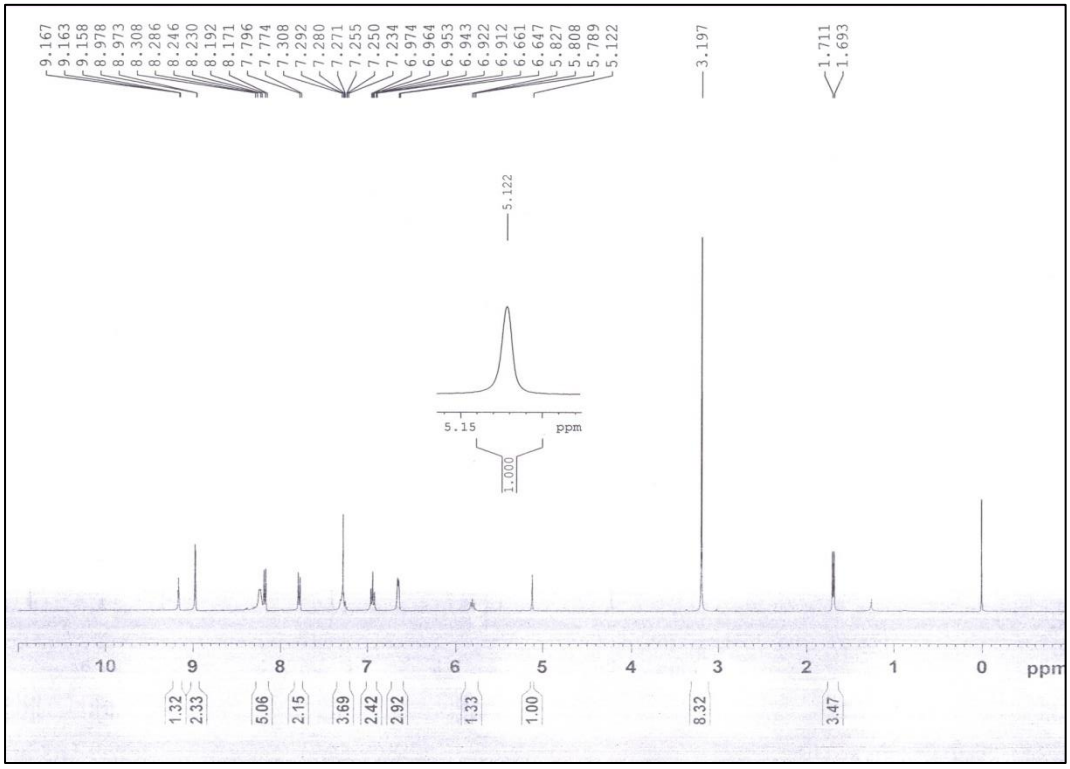
^{1}H NMR spectrum of **25c**+C4



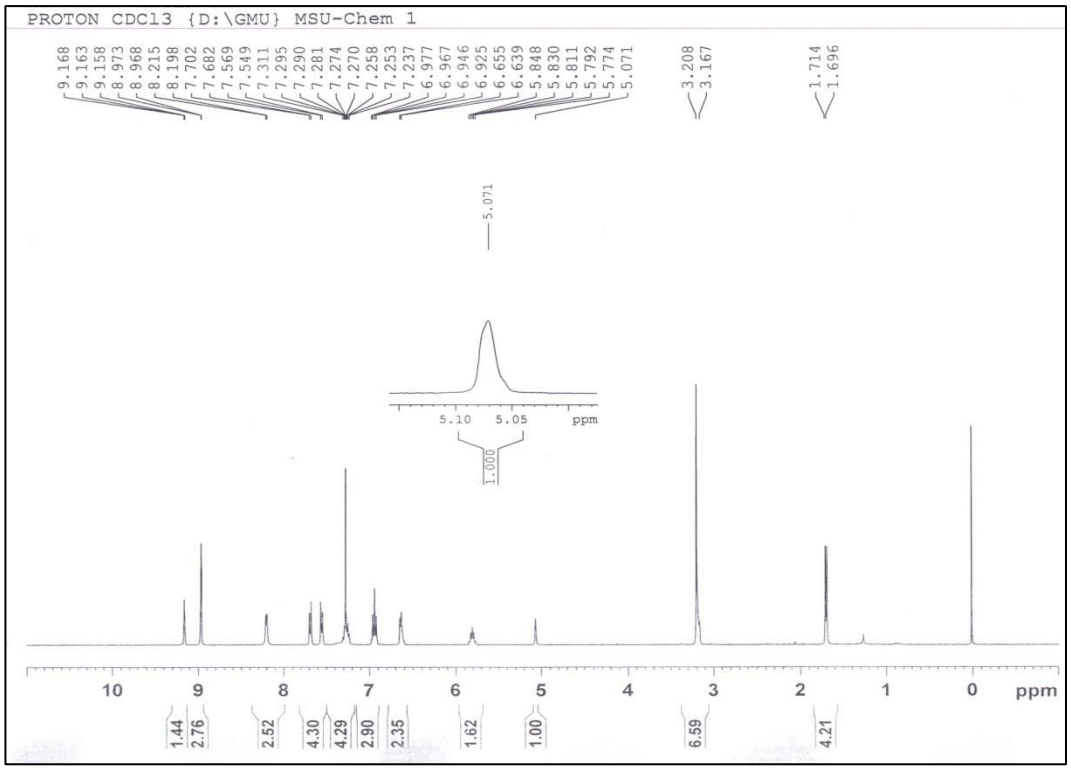
^{1}H NMR spectrum of **25c**+C5



^{1}H NMR spectrum of **25c**+C6



^{1}H NMR spectrum of **25c**+C7



^{1}H NMR spectrum of **25c**+C8

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