

ATROPOSELECTIVE SYNTHESIS AND REACTIONS OF AXIALLY CHIRAL THIOHYDANTOINS

by

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ABSTRACT

ATROPOSELECTIVE SYNTHESIS AND REACTIONS OF AXIALLY CHIRAL THIOHYDANTOINS

Nonracemic axially chiral thiohydantoins were synthesized atroposelectively by the reaction of *ortho*-arylisothiocyanates with amino acid ester salts in the presence of triethylamine (TEA). However, the synthesis of the nonaxially chiral derivatives gave racemic thiohydantoins. When a large substituent was present at C5, more racemization at this position was seen. The isomer compositions of the studied compounds have been determined by ^1H NMR together with HPLC analyses with chiral stationary phases. In most cases a high prevalence of the **P** isomers over the **M** ones has been obtained. The barriers to rotation determined around the $\text{N}_{(\text{sp}^2)}\text{-C}_{(\text{aryl})}$ chiral axis were found to be dependent upon the size of the *ortho*-halo aryl substituents. In addition, aldol reactions of the synthesized thiohydantoins with benzaldehyde and 4-nitrobenzaldehyde were carried out. The isomeric products were identified by ^1H NMR and it was found that the selectivity observed at the benzylic carbon was due to the preference of the phenyl group to be present at the equatorial position of the six membered ring formed as a result of an intramolecular H-bonding. In addition, it was shown that the *o*-aryl substituents at N3 had directing effects on the attachment of the electrophile to C5 of the heterocyclic ring. Lastly, the synthesized thiohydantoins were reduced to the corresponding stable hemiaminals (O, N-hemiacetals) by LiAlH_4 . The isomeric assignments were done through one or two dimensional NMR spectrometry and by HPLC analyses on chiral stationary phases. The stereoselectivity of the reactions with respect to the chiral axis was found to originate from the conformational preferences of the axially chiral hemiaminals which in turn arose from either a tendency for an intramolecular hydrogen bond formation or out of steric reasons. The stereodynamics of the axially chiral hemiaminals leading to their conformational preferences were investigated.

ÖZET

EKSENSEL KİRAL TİYOHİDANTOİNLERİN ATROPOSEÇİCİ SENTEZİ VE REAKSİYONLARI

Rasemik olmayan eksensel kiral tiyohidantoinler, *orto*-arilisotiyosiyanatın aminoasit ester tuzuyla trietilamin varlığında gerçekleştirilen reaksiyonundan sentezlenmiştir. Ancak eksensel kiral olmayan türevlerinin sentezi rasemik tiyohidantoinler vermiştir. C5 pozisyonunda büyük bir grup olduğunda, bu pozisyonda daha fazla rasemizasyon görülmüştür. Çalışılan maddelerin izomerlerinin kompozisyonu ^1H NMR ve kiral sabit fazlı HPLC ile tayin edilmiştir. Genellikle P izomerleri M izomerlerinden daha fazla elde edilmiştir. $\text{N}_{(\text{sp}^2)}\text{-C}_{(\text{aril})}$ kiral eksenini etrafındaki dönme bariyerinin *orto*-halo aril grubunun büyüklüğüne bağlı olduğu bulunmuştur. Ayrıca sentezlenen tiyohidantoinlerin benzaldehit ve 4-nitrobenzaldehitte aldol reaksiyonları yapılmıştır. İzomerik ürünler ^1H NMR ile kanıtlanmıştır ve benzilik karbondaki seçiciliğin molekül içi H-bağı sonucunda oluşan 6-üyelî halkada fenil grubunun ekvatorial pozisyonu tercih etmesinden kaynaklandığı bulunmuştur. Ayrıca, heterosiklik halkanın C5 pozisyonuna elektrofilin bağlanmasında N3'deki *o*-aril grubunun yönlendirici etkisi olduğu gösterilmiştir. Son olarak sentezlenen tiyohidantoinler ilgili hemiaminallere (O, N-hemiasetallere) LiAlH_4 ile indirgenmiştir. İzomerlerin belirlenmesi bir ya da iki boyutlu NMR spektrometresi ve kiral sabit fazlı HPLC kullanılarak yapılmıştır. Reaksiyonların kiral eksene göre stereo seçiciliğinin eksensel kiral hemiaminallerin molekül içi H-bağı oluşturma eğilimi ya da siterik etkilerden ileri gelen yapı tercihlerinden kaynaklandığı bulunmuştur. Eksensel kiral hemiaminallerin bu yapı tercihlerine neden olan sterodinamik incelenmiştir.

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LIST OF SYMBOLS

h	Planck's constant
Hz	Hertz
J	Joule
K	Equilibrium constant
k'	Capacity factor
k_b	Boltzman constant
k_f	Rate constant for forward reaction
k_r	Rate constant for reverse reaction
s	Second
t	Time
T	Temperature
RT	Retention time
δ	Chemical shift
$\Delta G^\#$	Free energy of activation

LIST OF ACRONYMS/ABBREVIATION

HPLC	High Pressure Liquid Chromatography
LiAlH ₄	Lithium aluminium hydride
S-TFAE	<i>S</i> -(+)-1-(9-antryl)-2,2,2-trifluoro ethanol

1. INTRODUCTION

1.1. Chiral Pool Approach

Enantiomerically pure compounds can be obtained in three ways (Figure 1.1).

- (i) By an asymmetric synthesis where a new chiral compound is formed from a prochiral substrate with the help of a chiral catalysis, auxiliary or an enzyme [1].
- (ii) By resolution of racemates which covers kinetic resolution, dynamic kinetic resolution, chromatography (these three methods will be explained later) and direct preferential crystallization where the racemate reacts with an optically active compound, yielding the mixture of diastereomers. The different physical and chemical properties of diastereomers are used for separation.

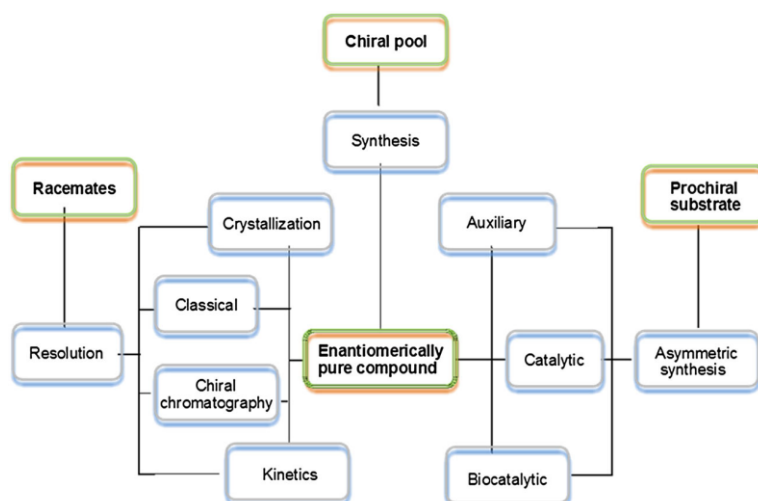


Figure 1.1. The methods for obtaining enantiomerically pure compounds [2].

- (iii) By using the “chiral pool approach”, which includes the transfer of chirality of the reactant to the product, an achiral compound is reacted with an inexpensive optically active compound and the product gains chirality coming from the starting material [3]. Aratikatla *et al.* showed chiral pool approach for the synthesis of an antiepileptic drug, (R)-lacosamide, from *N*-Boc-*N,O*-isopropylidene-L-serinol which can be obtained easily from natural L-serine (Figure 1.2) [4].

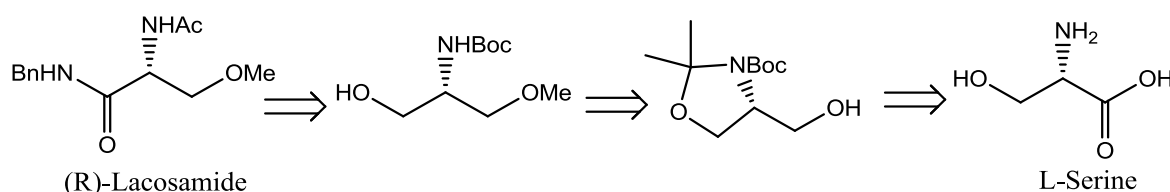


Figure 1.2. The retrosynthetic pathway for the synthesis of (R)-lacosamide from L-serine.

In addition, it was shown that optically active 4-alkoxyprolinol ethers can be obtained from chiral proline derivatives [5].

1.2. Dynamic Thermodynamic Resolution [6]

Dynamic thermodynamic resolution differs from kinetic resolution [7] and dynamic kinetic resolution [8] in that equilibration and resolution can be operative on one system in separate controllable steps. In order to convert enantiomers *A* and *epi-A* into resolved *D* and *epi-D*, *A* reacts with chiral *B*^{*} and they form diastereomers *A.B*^{*} and *epi-A.B*^{*}. Subsequent addition of *C* results in the formation of *D* and *epi-D* with the rate of *k*₂ and *k*₃, respectively. In addition to the dependence on *k*₂ and *k*₃, the resolution relies on the rates of interconversion of *A.B*^{*} and *epi-A.B*^{*} which are *k*₁ and *k*₋₁, but not the rates of the formation of complexes (Figure 1.3) [6]. This means that the enantioselectivity can be changed by changing the reaction time and/or the reaction temperature in which *k*₁, *k*₋₁, *k*₂ and *k*₃ could be changed.

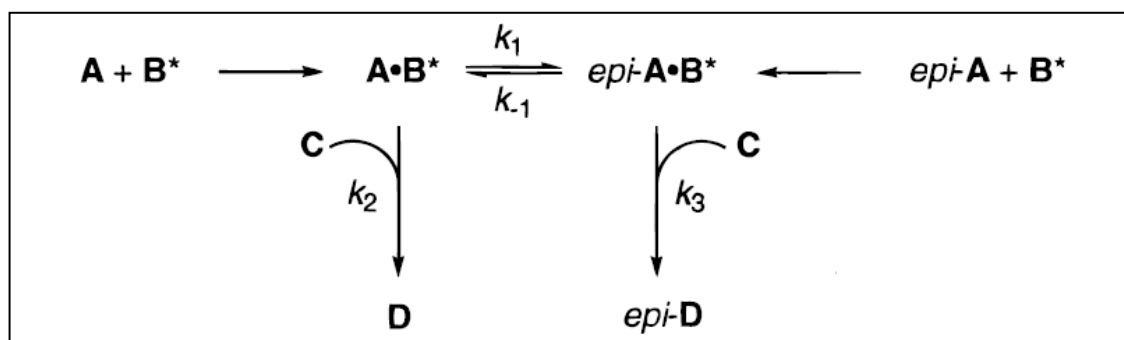


Figure 1.3. Reaction of A and *epi*-A with C mediated by chiral B^* to provide resolved D and *epi*-D [6].

There are three possible scenarios regarding the relative magnitudes of k_1 , k_{-1} , k_2 and k_3 for dynamic thermodynamic resolution. In the first possibility, the formed complexes $A \cdot B^*$ and *epi*- $A \cdot B^*$ do not interconvert each other and one of them reacts with C faster than the other one ($k_1 = k_{-1} = 0$, $k_2 \neq k_3$). In this case, a kinetic resolution is observed, in which the product ratio (D and *epi*-D) depends on the relative rates of k_2 and k_3 , the percent conversion and the populations of $A \cdot B^*$ and *epi*- $A \cdot B^*$. The energy diagram for such case is illustrated in Figure 1.4a. If the $A \cdot B^*$ and *epi*- $A \cdot B^*$ interconvert each other more rapidly than that they react with C, that is $k_1, k_{-1} \gg k_2, k_3$, a dynamic kinetic resolution is seen. In this type of resolution, the product ratio relies on the difference in energies for the two transition states, $\Delta\Delta G^{++}$ but not the conversion (Figure 1.4b). In the last scenario, the complexes interconvert each other with the rates k_1 and k_{-1} but they also react with C rapidly, that is $k_1, k_{-1} \neq 0$ and $k_2, k_3 \gg k_1, k_{-1}$. In this case, the thermodynamic ratio of $A \cdot B^*$ and *epi*- $A \cdot B^*$ determines the product ratio of D and *epi*-D when the reaction goes to completion but at lower conversions k_2 and k_3 controls the product ratios. The energy diagram for such resolution is shown in Figure 1.4c.

Therefore, it is important to modify reaction conditions in order to obtain the desired enantioselectivity for a reaction in which dynamic thermodynamic resolution is present.

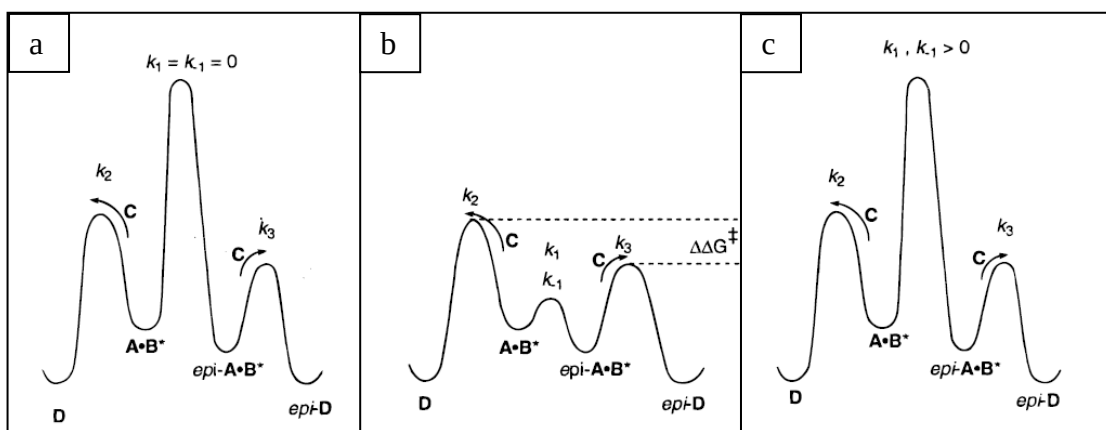


Figure 1.4. The energy diagrams for a) the kinetic resolution, b) the dynamic kinetic resolution and c) the dynamic thermodynamic resolution [6].

1.3. Separation of Enantiomers

Although enantiomers have the same properties and therefore give same signal in ordinary HPLC and ^1H NMR, separation is achieved by enantioselective HPLC and also by ^1H NMR in the presence of a chiral auxiliary. In both techniques, a chiral environment is needed.

1.3.1. By HPLC on chiral stationary phases

The resolution of enantiomers by HPLC is based on the different partitioning of the solute between mobile phase and stationary phase. This difference in partition results in different retention times.

The use of chiral stationary phases is the most common method for the enantioselective HPLC. In this way, the enantiomeric pair forms diastereomeric pairs by non-covalent interactions between the stationary phase and the solute. Based on the strength of the interactions, different retention times are obtained. If the interactions are

strong, it will retain longer resulting in longer retention times. However, if they have weak interactions, the solute comes out faster, resulting in short retention times.

In addition, chiral mobile phase additives can be used as the same principle with the chiral stationary phases. In this case, the non-covalent interactions occur between the mobile phase and the enantiomeric pair.

1.3.2. By ^1H NMR

The enantiomers give the same signal in ^1H NMR. However, if a chiral environment is created by adding chiral auxiliary or chiral solvents, the enantiomeric substrate makes diastereomeric association complexes with the chiral agent and these complexes may have different chemical shifts, enabling the separation of enantiomers.

Hydrogen bonding and π - π stacking between the aromatic rings are generally present in these diastereomeric association complexes.

The resolution of enantiomers by ^1H NMR in the presence of chiral auxiliary depends on the concentration and also temperature. High concentration and low temperature favors the formation of diastereomeric complexes whereas the non-covalent interactions between the enantiomeric substrate and the chiral auxiliary disappear at high temperatures, preventing the separation of enantiomers.

1.4. Self Association

Enantiomerically pure compounds and racemic mixtures may have different physical properties including melting point, boiling point, physical appearance and so on. Dobashi *et al.* (1986) [9] showed that when the two enantiomers undergo diastereomeric solute-solute interactions to different extents, chiral differentiation of enantiomers by self-association may be possible without the aid of any foreign chiral substances. These interactions can be homochiral or heterochiral occurring between chiral molecules having same or different chirality sense, respectively (Figure 1.5). The difference between homochiral and heterochiral dimers leads to different chemical shifts or splitting the signals, called as anisochrony. These nonbonded homochiral or heterochiral interactions can be van der Waals, electrostatic, π - π or H-bonding [9, 10].

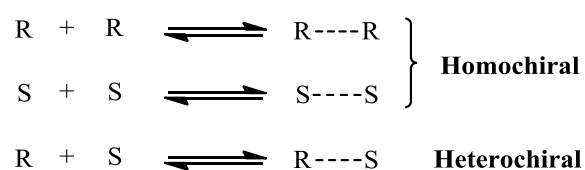


Figure 1.5. The possible interaction between R and S enantiomers

The anisochrony generally occurs under conditions of fast exchange and is favored by low temperature and high concentration whereas it is disfavored by the effects able to interfere with the self-association such as high temperature and polar solvents, like deuterated methanol instead of deuterated chloroform [11]. In addition, high dilution results in decrease in the anisochrony, leading to identical spectra of pure enantiomers and racemates [11].

1.5. Determination of Barriers to Hindered Rotation

1.5.1. By Enantioselective HPLC

The enantiomers or diastereomers can thermally interconvert each other *via* racemization or rotation around the N₃-C_{aryl} bond and it was found that they follow first-order kinetics [12]. The relative ratios obtained by considering the area under the curves of each peak in enantioselective HPLC are used for determination of the barriers.

The reversible reaction $\mathbf{M} \rightleftharpoons \mathbf{P}$ is first order in both the forward and the reverse direction so that $r_f = k_f[\mathbf{M}]$ and $r_r = k_r[\mathbf{P}]$. If $(d[\mathbf{M}]/dt)_f$ denotes the rate of change of $[\mathbf{M}]$ due to forward reaction, then $-(d[\mathbf{M}]/dt)_f = r_f = k_f[\mathbf{M}]$. The rate of formation of $[\mathbf{M}]$ by reverse reaction is $(d[\mathbf{M}]/dt)_r = r_r = k_r[\mathbf{P}]$. Then,

$$(d[\mathbf{M}]/dt) = -k_f[\mathbf{M}] + k_r[\mathbf{P}] \quad (1.1)$$

We have $\Delta[\mathbf{P}] = -\Delta[\mathbf{M}]$, so $[\mathbf{P}] - [\mathbf{P}]_0 = -([\mathbf{M}] - [\mathbf{M}]_0)$. Substitution of $[\mathbf{P}] = [\mathbf{P}]_0 + [\mathbf{M}]_0 - [\mathbf{M}]$ into Equation 1.1 gives

$$d[\mathbf{M}]/dt = k_r[\mathbf{P}]_0 + k_r[\mathbf{M}]_0 - (k_f + k_r)[\mathbf{M}] \quad (1.2)$$

At equilibrium, the rates of the forward and the reverse reactions become equal, the concentration of each species being constant, thus $d[\mathbf{M}]/dt$ is 0. Let $[\mathbf{M}]_{eq}$ be the equilibrium concentration of $\mathbf{M}$. Setting $d[\mathbf{M}]/dt = 0$ and $[\mathbf{M}] = [\mathbf{M}]_{eq}$ in Equation 1.2, we get

$$k_r[\mathbf{P}]_0 + k_r[\mathbf{M}]_0 = (k_f + k_r)[\mathbf{M}]_{eq} \quad (1.3)$$

The use of Equation 1.3 in Equation 1.2 gives $d[M]/dt = (k_f + k_r)([M]_{eq} - [M])$. Using the identity $\int (x+s)^{-1} dx = \ln(x+s)$ to integrate this equation, we get

$$\ln\{([M] - [M]_{eq})/([M]_0 - [M]_{eq})\} = -(k_f + k_r)t \quad (1.4)$$

The equilibrium constant $K = k_f/k_r$ for the conversion process can be determined from the integration of the peaks in the chromatograms given as percentages of the two isomers. By using Equation 1.4, a plot of $\ln\{([M] - [M]_{eq})/([M]_0 - [M]_{eq})\}$ versus time gives a straight line, the slope being equal to $-(k_f + k_r)$. Having determined k_f and k_r , the free energy of activation for forward ($\Delta G^\ddagger_{\text{forward}}$) and reverse reactions ($\Delta G^\ddagger_{\text{reverse}}$) can be calculated using the Eyring Equation 1.5,

$$\Delta G^\ddagger = RT \ln(k_b T / k h) \quad (1.5)$$

where $R = 8.3143 \text{ J/mol.K}$, T = temperature (Kelvin) at which the interconversion takes place, k_b (Boltzman constant) $= 1.3805 \times 10^{-23} \text{ J/K}$, h (Planck constant) $= 6.6256 \times 10^{-34} \text{ J.s}$, k is k_f = the rate constant for the forward reaction or k_r = the rate constant for the reverse reaction.

1.5.2. By Dynamic ^1H NMR

If two chemically equivalent groups in a molecule are exchanged by an intermolecular process, the NMR spectrum is a function of the difference in their resonance frequencies, $\Delta\nu$, and of the rate of the exchange, k . At low temperatures the exchange is slow and $k \ll \Delta\nu$. In this case, two signals appear for the two chemically equivalent groups. However, at high temperatures the exchange is fast because of the increase in energy and $k \gg \Delta\nu$, leading to one peak for the same groups. There is also an intermediate temperature range over which the spectrum consists of two significantly

broadened overlapping lines. This temperature refers to as the coalescence temperature, T_c , and below T_c two signals are observed whereas above T_c an overlapping is seen.

The exchange follows first-order kinetics which includes no coupling between the exchangeable groups and also the same intensity for these groups. Under these conditions, Equation 1.6 affords the rate constant, k_c , at the coalescence temperature, T_c ,

$$k_c = \pi(\nu_A - \nu_B)/\sqrt{2} = \pi\Delta\nu/\sqrt{2} \approx 2.22 \Delta\nu \quad (1.6)$$

where $\Delta\nu$ is the full width at half-maximum of the signal at the coalescence point T_c ; i.e. it corresponds to the difference in chemical shift ($\nu_A - \nu_B$) observed during slow exchange.

According to the Eyring Equation 1.5, the exchange frequency k_c decreases exponentially with the free molar activation enthalpy $\Delta G^\ddagger$;

$$k_c = [(k_b \cdot T_c)/h] e^{-\Delta G^\ddagger/RT} \quad (1.7)$$

where $R = 8.3143 \text{ J/mol.K}$, T_c coalescence temperature in Kelvin, k_b (Boltzman constant) $= 1.3805 \times 10^{-23} \text{ J/K}$ and h (Planck constant) $= 6.6256 \times 10^{-34} \text{ J.s}$. Equations 1.6 and 1.7 illustrate the value of temperature dependant NMR for the investigation of molecular dynamics: following substitution of the fundamental constants, they give Equation 1.8 for the free molar activation enthalpy $\Delta G^\ddagger$ for the first order exchange process;

$$\Delta G^\ddagger = 19.1 T_c [10.32 + \log(T_c/k_c)] \times 10^{-3} \text{ kJ/mol} \quad (1.8)$$

1.6. Aldol Reactions

Aldol reaction is a widespread method for the C-C bond formation. Particularly, stereoselective aldol reactions gained considerable attention recently [13] because it is important to obtain one isomer over the others which may have a different activity.

Our group previously showed that this type of reactions may proceed *via* the chiral lithium [14] or enolization mechanisms [15]. In the former one, LDA produces a chiral tetrahedral lithium species at C-5 of the heterocyclic ring with the retention of configuration, ie the starting isomer ratio should be obtained for the products at the end of the aldol reaction, as seen for the aldol reaction of 5-methyl-3-(*o*-aryl)-oxazolidindiones (Figure 1.6) [14].

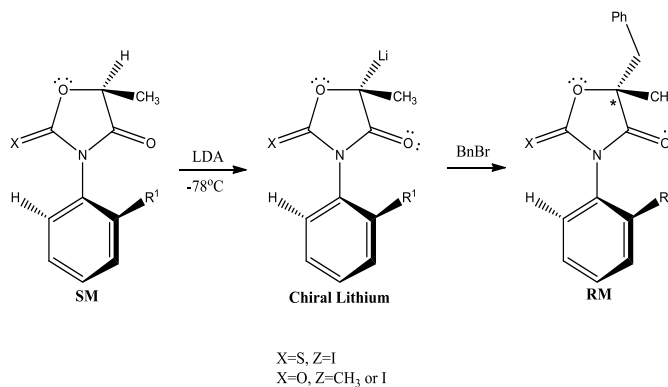


Figure 1.6. Chiral lithium mechanism

In the latter mechanism [15], LDA deprotonates the α -hydrogen at C-5 of the heterocyclic ring, leading to the formation of **P** and **M** enolates, and the coming electrophile (eg. benzaldehyde) prefers to bind from the less hindered side of the enolate which was seen for the aldol reaction of 5-methyl-2-(*o*-aryl)imino-3-(*o*-aryl)-thiazolidine-4-ones. In this mechanism, the product ratio obtained at the end of the reaction should be equal to the ratio of **P/M** isomers at the starting material.

Therefore, it is of our interest which mechanism is present for the aldol reaction of the axially chiral thiohydantoin ring.

1.7. Hemiaminals and Enamines

Hemiaminals (N,O-acetals) are known unstable intermediates because they can easily undergo elimination reaction *via* dehydration. Therefore, it is difficult to isolate these compounds. If stable on the other hand, hemiaminals are valuable compounds in organic and in medicinal chemistry because of the presence of this functionality in many catalysts, drugs and natural products [16, 17].

The presence of chirality centers in the hemiaminal structure has been proposed to be critical for the biological activity expected for these compounds [18]. In spite of this fact however asymmetric synthesis of chiral hemiaminals to date is only a few [18]. Some seminal work done for the asymmetric construction of various chiral *N,O*-aminal structures include chiral thiourea [19], phosphoric acid [20, 21] and pyrrolidine [21] catalyzed inter [19-21] or intramolecular [21] addition of alcohols to imines and Pd catalyzed C–N coupling reactions with chiral bisphosphine mono-oxides [18]. Moreover, the presence of a π -conjugation and also intramolecular H-bonding play an important role for the stabilization of hemiaminals which were obtained recently in our laboratory (Figure 1.7) [22].

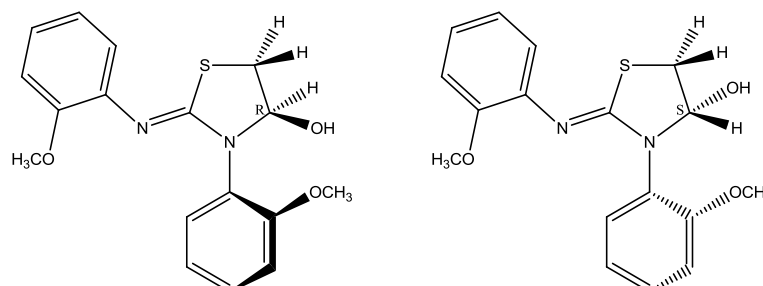


Figure 1.7. Hemiaminal stabilized by intramolecular H-bonding between the hydroxyl and methoxy groups.

1.8. Hydantoins and Thiohydantoins

Hydantoins have attracted a considerable attention since their discovery because of their antibacterial [23], anti-HIV [24] and anti tumor [25] activities. In 2004 Dort, M.E.V. and co-workers demonstrated the usage of iodinated aryl hydantoins and thiohydantoins as androgen receptor radioligands in the diagnosis of tumor sites in prostate cancer [26]. In 2008, it was shown that hydantoin derivatives were potent analogs of the (2S,3R,4S)-4-hydroxyisoleucine which stimulate insulin secretion [27]. In addition to these, phenytoin, which is a hydantoin derivative, is used as anti-epileptic drugs [28]. In 2001, enantiospecific synthesis of BIRT-377, which has anti-inflammatory properties, was achieved by Napolitano, E. and Farina, V. [29] (Figure 1.8).

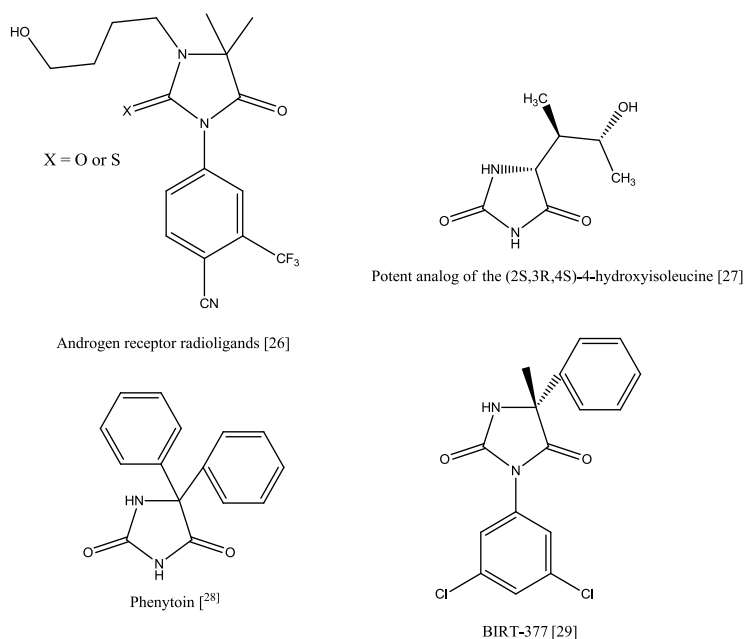


Figure 1.8. The examples of the hydantoin drugs in the literature.

Thiohydantoin derivatives, which are also important heterocyclic compounds like hydantoins, were found to be active against tumor cells (Figure 1.9) [30].

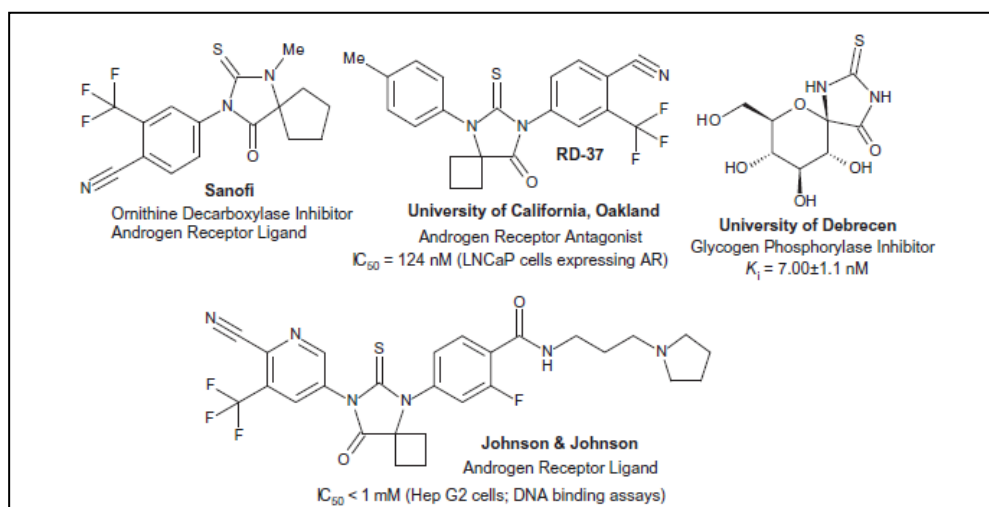


Figure 1.9. Several examples of physiologically active *spiro*-thiohydantoin [30].

Recently, novel antagonists bearing thiohydantoin ring were synthesized by modifying enzalutamide [31], a newly approved AR antagonist, which is effective for bicalutamide-resistant tumors and has been used in castration resistant prostate cancer patients (Figure 1.10 and 1.11) [32, 33].

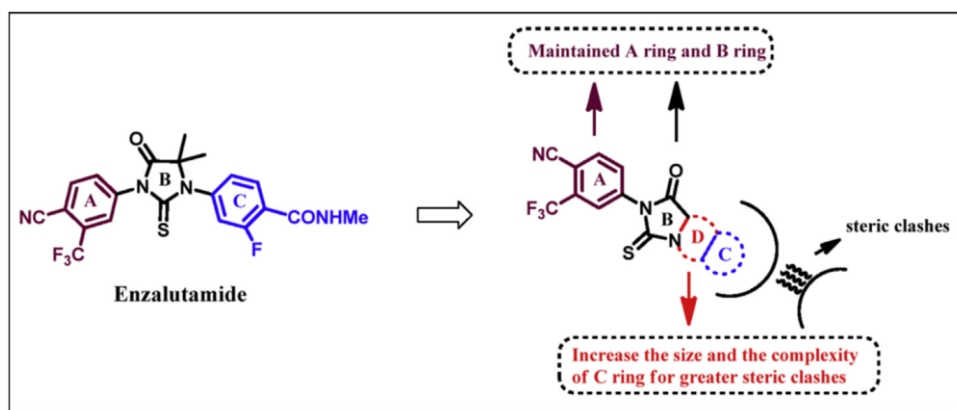


Figure 1.10. Design of a novel series of thiohydantoin derivatives as androgen receptor antagonists [31].

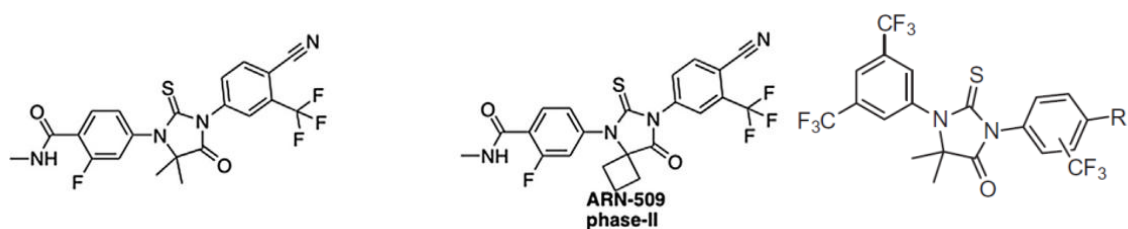


Figure 1.11. Structure of anti-androgen thiohydantoin based small molecules approved by FDA or in clinical development for the treatment of prostate cancer [32, 33].

Besides, in 2011, it was shown that thiohydantoin derivatives could be used for detecting tau, which is a primarily neuronal protein, present in the brains of patients with Alzheimer's disease (Figure.12) [34].

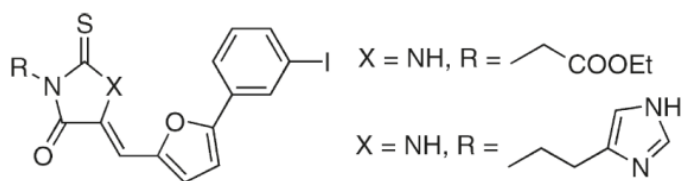


Figure 1.12. Thiohydantoin derivatives as probe for the in vivo imaging of NFT in the brain of patients with Alzheimer's disease [34].

2. AIM OF THE STUDY

The aim of this work is to synthesize axially chiral thiohydantoin derivatives asymmetrically using the chiral pool strategy and further exploitation of this scaffold in various ways to reach to other nonracemic chiral structures.

Towards this goal, firstly the axially chiral nonracemic 5-methyl- and 5-isopropyl-3-(*o*-aryl)-2-thiohydantoin derivatives were synthesized diastereoselectively and the isomers were identified based on enantioselective HPLC and NMR studies in the absence and the presence of *S*-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((*S*)-TFAE). The rotational barriers to the hindered rotation around the N_{sp2}-C_{aryl} bond were determined *via* HPLC analyses on chiral stationary phases and the **M/P** ratios were determined with the aim of doing sterically controlled enolate reactions over the synthesized axially chiral thiohydantoin derivatives.

Secondly, aldol reactions at the asymmetric carbon (C-5) of the heterocyclic ring were carried out with the synthesized axially chiral thiohydantoin derivatives with aldehydes. In this reaction, the axial chirality was expected to serve as an auxiliary in order to gain stereoselectivity. The assignments of the isomeric aldol products were done based on the enantioselective HPLC analyses together with NMR studies.

In addition, the reduction reactions of the synthesized thiohydantoin derivatives were carried out with lithium aluminium hydride (LiAlH₄) to reach to nonracemic axially chiral hemiaminals.

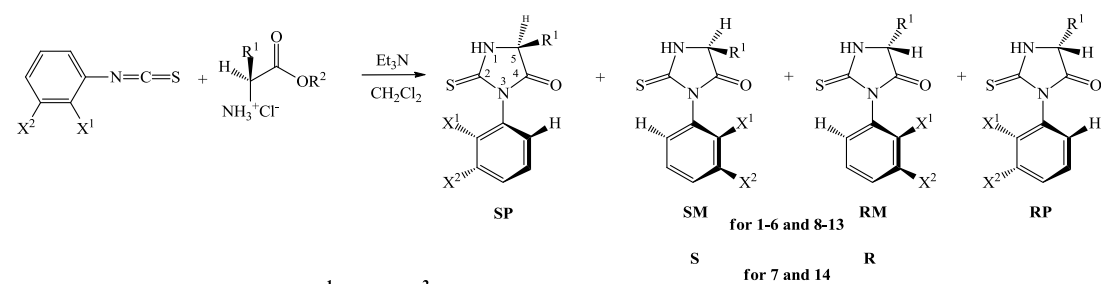
3. RESULTS AND DISCUSSION

3.1. Axially Chiral 5-Methyl- and 5-Isopropyl-3-(*o*-aryl)-2-thiohydantoins

3.1.1. Synthesis and Assignments of The Isomers [35]

Axially chiral 5-methyl- (**1-6**) and 5-isopropyl-3-(*o*-aryl)-2-thiohydantoin (**8-13**) derivatives were synthesized as nonracemic diastereomeric pairs of atropisomers from the reaction of the corresponding *o*-aryl-isothiocyanates with *L*-alanine methyl ester HCl salt (**1-6**) or *L*-valine ethyl ester HCl salt (**8-13**) in the presence of triethylamine (TEA) under reflux in CH₂Cl₂ (Figure 3.1) by a modified procedure of Burgess *et al.* [36]. The synthesis of 5-methyl-3-phenyl-2-thiohydantoin (**7**) and 5-isopropyl-3-phenyl-2-thiohydantoin (**14**) which lack chiral axes gave racemic mixtures under the same reaction conditions. The reaction times have been optimized by following the reaction progress by HPLC. For all of the compounds, except **5**, **11**, **12**, the reaction was carried out for 1 hour at 40°C whereas for the compounds **5**, **11**, **12**, it was done for 4 hours under the same conditions.

The axially chiral **1-6** and **8-13** may exist in **SP**, **RM**, **SM** and **RP** isomeric forms (Figure 3.1). **SP/RM** is *transoid* whereas **SM/RP** is *cisoid* with respect to the substituent at C-5 and the *o*-aryl substituent (Figure 3.1). For all of these compounds, except for **2** and for **9**, the isomers were resolvable to their four isomers by HPLC on chiral stationary phases (Table 3.1). Recrystallization of the products changed the *transoid/cisoid* ratios noticeably and an example is given in Figure 3.2.



Comp.	X ¹	X ²	R ¹	R ²	Rxn Time (h)	Yield (%)
1	CH ₃	H	CH ₃	CH ₃	1	66
2	F	H	CH ₃	CH ₃	1	46
3	Cl	H	CH ₃	CH ₃	1	64
4	Br	H	CH ₃	CH ₃	1	63
5	I	H	CH ₃	CH ₃	4	75
6	X ¹ =X ² =Benzo		CH ₃	CH ₃	1	55
7	H	H	CH ₃	CH ₃	1	59
8	CH ₃	H	isopropyl	C ₂ H ₅	1	58
9	F	H	isopropyl	C ₂ H ₅	1	74
10	Cl	H	isopropyl	C ₂ H ₅	1	44
11	Br	H	isopropyl	C ₂ H ₅	4	46
12	I	H	isopropyl	C ₂ H ₅	4	91
13	X ¹ =X ² =Benzo		isopropyl	C ₂ H ₅	1	69
14	H	H	isopropyl	C ₂ H ₅	1	39

Figure 3.1. The synthesis of the compounds **1-14**.Table 3.1. Chromatographic data for the resolution of compounds **1-14**.

Comp.	Stationary Phase	Mobile Phase	Flow (ml/min)
1	ChiralPak IC	95:5 Hex:EtOH	0.6
3	ChiralPak IC	95:5 Hex:EtOH	0.6
4	ChiralPak IC	95:5 Hex:EtOH	0.6
5	ChiralPak IB	95:5 Hex:EtOH	1.0
6	ChiralPak IC	95:5 Hex:EtOH	1.0
7	ChiralPak IA	95:5 Hex:EtOH	0.6
8	ChiralPak IC	95:5 Hex:EtOH	0.6
10	ChiralPak IC	95:5 Hex:EtOH	0.6
11	ChiralPak IC	95:5 Hex:EtOH	0.6
12	ChiralPak IB	95:5 Hex:EtOH	1.0
13	ChiralPak IC	95:5 Hex:EtOH	0.6
14	ChiralPak IA	95:5 Hex:EtOH	0.6

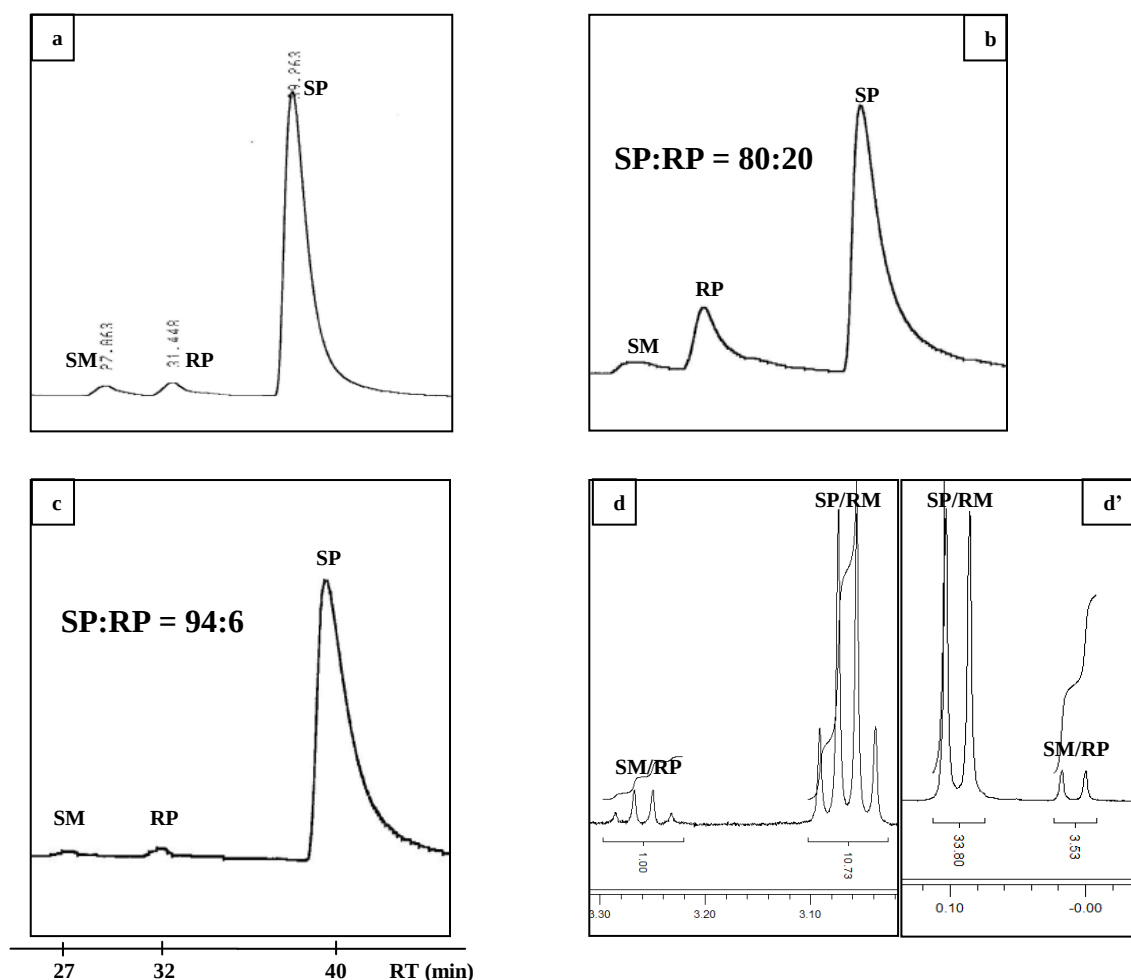


Figure 3.2. HPLC chromatogram of **4** a) of the sample taken from the reaction mixture after 15 minutes at room temperature, b) obtained after the immediate removal of the reaction solvent. c) HPLC chromatogram after recrystallization from MeOH-water of **4**; d) quartet signals in ^1H NMR, d') doublet signals in ^1H NMR.

We started with compound **4**, 5-methyl-3-(*o*-bromophenyl)-2-thiohydantoin, because X-ray for this product had been reported in literature [37]. X-ray of **4** showed a structure where the bromine atom laid *transoid* with respect to the C-5 methyl. The ^1H NMR of synthesized **4** also showed a *transoid* relationship between the *o*-Br and the C5 methyl groups as shown in Figure 3.2. ^1H NMR displays that the compound **4** is present as an unequal composition of two diastereomers. The major diastereomer has its quartet at a higher field but its doublet at a lower field than the minor isomer. This is because, when Br is *transoid* with C5 methyl, it lies on the same side with C5-H (Figure 3.1) and the anisotropy of Br will make the C5-H of this stereoisomer appear at a higher field [38].

Thus the major diastereomer is either **SP** or its enantiomer **RM**. In order to decide whether it is **SP** or **RM**, the reaction was followed by HPLC on a chiral stationary phase. In the chromatogram of the sample taken from the reaction mixture after 15 minutes from the start of the experiment at room temperature (Figure 3.2a), three peaks at 27, 31 and 39 minutes were observed, the highest intensity one having the 39 min. retention time. This peak was also the highest one in the chromatogram obtained after refluxing the reaction mixture (40°C) for 1 hour for the completion of the reaction (Figure 3.2b). Based on this, the highest intensity peak in the chromatogram has been assigned to **SP**, since it was considered unlikely for l-alanine to racemize to such an extent within 15 minutes to be able to give **RM**, based on the fact that the resolved enantiomers of **7** did not racemize even in the period of 7.5 hours at 40°C (Figure 3.3). The two major peaks on the chromatogram were found to be separable by recrystallization so they should be diastereomeric isomers. For this reason the next higher intensity peak on the chromatogram in Figure 3.2 has been assigned to **RP**, not to **SM**, based on the fact that **SP** did not interconvert to this peak during the thermal interconversion experiment, as will be explained in the determination of the rotational barrier section.

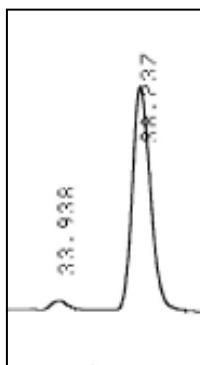


Figure 3.3. HPLC chromatogram of the resolved enantiomer of compound **7** which was subjected to thermal racemization experiment under neutral conditions.

The enantiomer assignments were done by comparing the ^1H NMR spectra in the presence of (S)-TFAE (Figure 3.4) with the HPLC chromatogram (Figure 3.2).

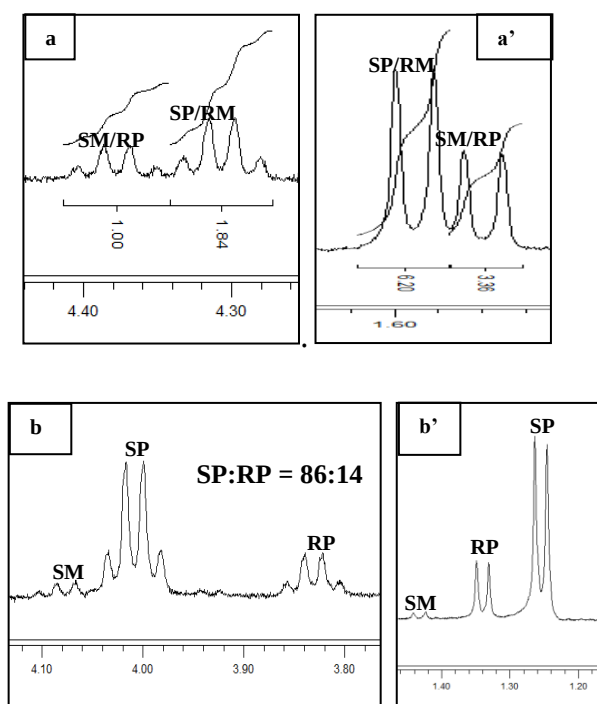


Figure 3.4. The partial ^1H NMR spectrum of compound **4** in the absence of any auxiliary; a) the quartets, a') the doublets and in the presence of six equivalents of *S*-TFAE as auxiliary; b) the quartets, b') the doublets.

^1H NMR spectrum of **4** with six equivalents of (*S*)-TFAE was taken to make the enantiomers visible. Diastereomeric complexes are expected to form through supramolecular interactions, such as H-bonding and π -stacking [39] between (*S*)-TFAE and enantiomeric stereoisomers of **4**. The ^1H NMR spectrum of **4** with (*S*)-TFAE indicated a partial racemization at C-5 of the heterocyclic ring (Figure 3.4b). By comparing the ^1H NMR of **4** taken with (*S*)-TFAE (Figure 3.4b) and the chromatogram (Figure 3.2a), the first peak on the chromatogram was assigned to **SM**. The **RM** did not form during the synthesis but it was produced to a slight extent during the thermal interconversion studies at 60°C, which will be explained in the determination of rotational barriers section.

Isomeric assignments done in this way for the axially chiral **1-6** and **8-13**, through HPLC-NMR analyses and the isomeric ratios are listed in Table 3.2. It has been shown that the isomeric compositions obtained at the end of the reaction vary depending on the type of

the *ortho* substituent and the substituent at C-5. Table 3.2 also shows the relative proportions of the isomers obtained after purification of the crude product by recrystallization. As can be inferred from the table, recrystallization for some derivatives dramatically increased the diastereomeric ratio (*transoid/cisoid* ratio) of the products. This result is important because it shows that **R** thiohydantoin can easily be separated from the **S**, by means of axial chirality, in the same way as enantiomers are separated from each other *via* formation of diastereomeric pairs [40]. Focusing on the **SP/RP** ratios, which indicate the degree of racemization at C-5, it can be seen for 5-methyl derivatives (**2-5**) that, when the *o*-halogen is changed from F to Cl, the **SP/RP** ratio increased which means that the degree of racemization at the chirality center decreased. It figures that bulkier *ortho* substituents suppress the racemization at C-5 of the thiohydantoin ring enabling the transfer of chirality of the α -amino acids to the products. Comparing the **SP/RP** ratios of **1** and **3** on the other hand, the role of the electronic effects seems to be also an important factor in determining the extent of racemization. The observed influence of the *o*-chloro substituent however is probably through space rather than being through bond as has been proposed before [41].

Table 3.2. Relative proportions of the isomers determined by enantioselective HPLC.

Comp.	SM: RP: SP: RM (Crude)	SM: RP: SP: RM (After recrystallization)
1	7 : 49 : 43 : 1	10 : 50 : 40 : 1 ^a
2^b	Not determined	10 : 36 : 34 : 19
3	4 : 7 : 89 : 0	3 : 6 : 91 : 0
4	3 : 14 : 83 : 0	3 : 6 : 91 : 0 ^c
5	4 : 12 : 84 : 0	5 : 10 : 85 : 0
6	9 : 73 : 17 : 1	10 : 74 : 17 : 0 ^d
8	7 : 32 : 51 : 11	4 : 33 : 49 : 14
9	Not determined	17 : 20 : 32 : 31
10	2 : 51 : 43 : 4	2 : 52 : 42 : 4
11	3 : 64 : 33 : 1	3 : 73 : 22 : 2
12	3 : 41 : 53 : 3	0 : 86 : 14 : 1 ^c
13	22 : 28 : 42 : 8	32 : 41 : 20 : 7

^a Compounds were recrystallized from ethyl acetate/hexane.

^b The er and dr of **2** was found by ¹H NMR in the presence of S-TFAE.

^c **4** and **12** were recrystallized from methanol/water.

^d **6** was recrystallized from ethyl acetate.

The α -naphthyl group of **6** gave rise to an interesting type of atroposelectivity where a reversal of the **SP/RP** ratio has been observed. The higher concentration of **RP+SM** is also manifested in its ^1H NMR spectrum (Figure 3.5a and 3.5a'). When the naphthyl group is *cisoid* with C-5 methyl, namely the **RP** (and **SM**), it has a shielding anisotropy effect on the ^1H NMR signal of CH_3 . When, on the other hand, the naphthyl is on C-5 H's side (**RM** and **SP**), C-5 H signal is shielded. Thus the lower intensity of the quartets and doublets in Figure 3.5a and 3.5a' belong to **RM+SP** and the higher intensity ones to **RP+SM**, as parallels with the HPLC experiment. It should be noted that for compound **5** the major isomer is **RM/ SP** appearing more shielded due to the anisotropy effect of the iodine this time (Figure 3.5b and 3.5b').

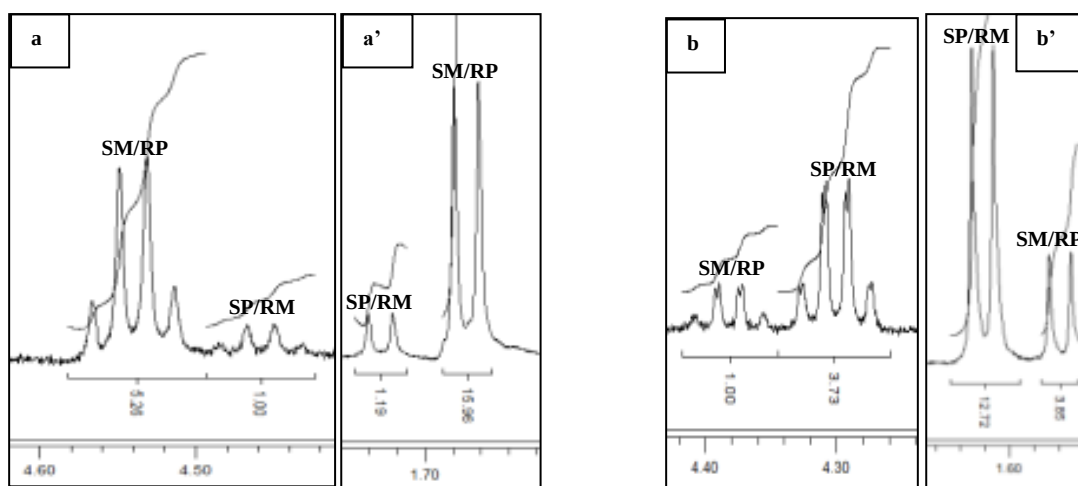


Figure 3.5. The partial ^1H NMR spectrum of compound **6** a) the quartets and a') the doublets, the partial ^1H NMR spectrum of compound **5** b) the quartets and b') the doublets.

It figures from Table 3.2 that the valine ester is more prone to racemization in forming the C-5 isopropyl substituted thiohydantoin ring. The **SP/RP** ratio of **10** is close to one, and of **11** is less than one. This result for **11** may be due to a longer reaction time required for the completion of the reaction. However compounds **8** and **10**, although subjected to the same reaction times as **3-5**, showed lower **SP/RP** ratios compared to them.

Moreover, compounds **7** and **14** are not axially chiral and were shown to be racemic through HPLC analyses on chiral columns together with NMR studies with (*S*)-TFAE (Figure 3.6).

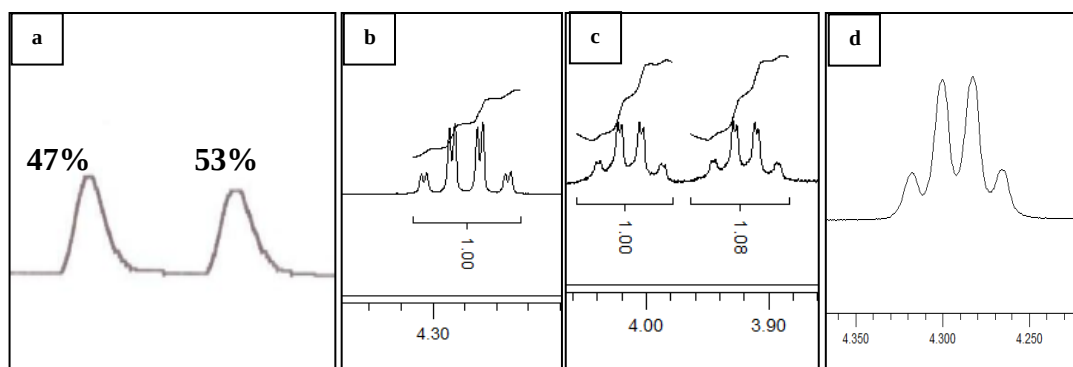


Figure 3.6. a) HPLC chromatogram of compound **7** after the reaction, partial ^1H NMR spectrum of compound **7**, b) 5 mg in 0.7 mL CDCl_3 in the absence of *S*-TFAE as the auxiliary and c) in the presence of six equivalents of *S*-TFAE as the auxiliary, d) the microreperatively resolved enantiomer of compound **7** in CDCl_3 .

As shown in Figure 3.6, the quartet corresponding to the hydrogen at C5 of compound **7** was splitted when 5 mg of compound **7** was dissolved in 0.7 mL CDCl_3 and ^1H NMR spectrum was taken. This shows the formation of the possible self-association between the enantiomers. In order to prove this association (Figure 1.5, p.7) one of the enantiomers was resolved by HPLC with ChiralPak IA column and its ^1H NMR spectrum was taken in the same amount of CDCl_3 (Figure 3.6d). The NMR of this single enantiomer showed no splitting. Therefore, it was concluded that self-association occurred between the thiohydantoin enantiomers of compound **7**, which are heterochiral (*R*-*S* and *S*-*R*). In addition to the spectrum of compound **7** taken with 5 mg in 0.7 mL CDCl_3 , 3 mg, 8 mg, 10 mg of the compound **7** was taken in the same amount of CDCl_3 , in order to see if the concentration affects the splitting or not. All of the spectrums with these amounts gave the same splitting, except the one taken with 10 mg which had a solubility problem. This exhibited that the observed splitting for compound **7** was not influenced by concentration.

3.1.2. The Mechanism of The Formation Reaction of Thiohydantoins

When the diastereomer ratios of the synthesized thiohydantoins were obtained, a high preference of **P** isomer was observed over **M** ones. In addition, it has been found that as the size of the substituent at C-5 of the heterocyclic ring increased, the formation of **RP** also increased. In order to understand the preference of **P** and the effect of the substituent of the chiral α -aminoacid, 5-benzyl-3-*o*-bromophenyl thiohydantoin (**15**), which has a bigger substituent at the chiral center, was synthesized by the same procedure used for the synthesis of 5-methyl- and 5-isopropyl- derivatives (Figure 3.7).

The preference of **P** isomer over **M** one is due to the effect of the configuration of the starting α -aminoacid. In **P** isomer, the substituents at N-3 and at C-5 are *transoid* while in **M** one, they are *cisoid*. Since in terms of the steric effect the *transoid*-isomer is more stable than *cisoid*-isomer, the former one is preferred. Therefore, the **S** configuration firstly determines the position of the chiral axis which is **P**. Then, the formed **SP*** interconverts to **RP*** with k_1 rate while **RP*** turns back to **SP*** with k_{-1} rate. And these intermediates form **SP** and **RP** products with k_2 and k_3 rates, respectively. Due to the observed interconversion between the epimers **SP*** and **RP***, the kinetic resolution, in which $k_1 = k_{-1} = 0$ [6], is eliminated. The second possibility, dynamic kinetic resolution [6] where $k_1 \& k_{-1} \gg k_2 \& k_3$, is also eliminated because the products **SP** and **RP** were found to form even after five minutes of the start of the reaction. This showed that k_2 and k_3 were high enough to yield both isomers at the reaction temperature.

Dynamic thermodynamic resolution [6], where the intermediates **SP*** and **RP*** interconvert each other with the rates of k_1 and k_{-1} , also they cyclize faster to give **SP** and **RP** with the rates of k_2 and k_3 , fits the formation reaction of thiohydantoins. Based on this type of resolution, the parameters of the reaction have been changed in order to increase the **SP:RP** ratio, which was obtained as 51:44 at 40°C for 1 hour. Firstly, the reaction was carried out at different temperatures. At 40°C, 80°C and 110°C the **SP:RP** ratio was nearly the same which was 51:44, 44:40, 41:37, respectively (Figure 3.8).

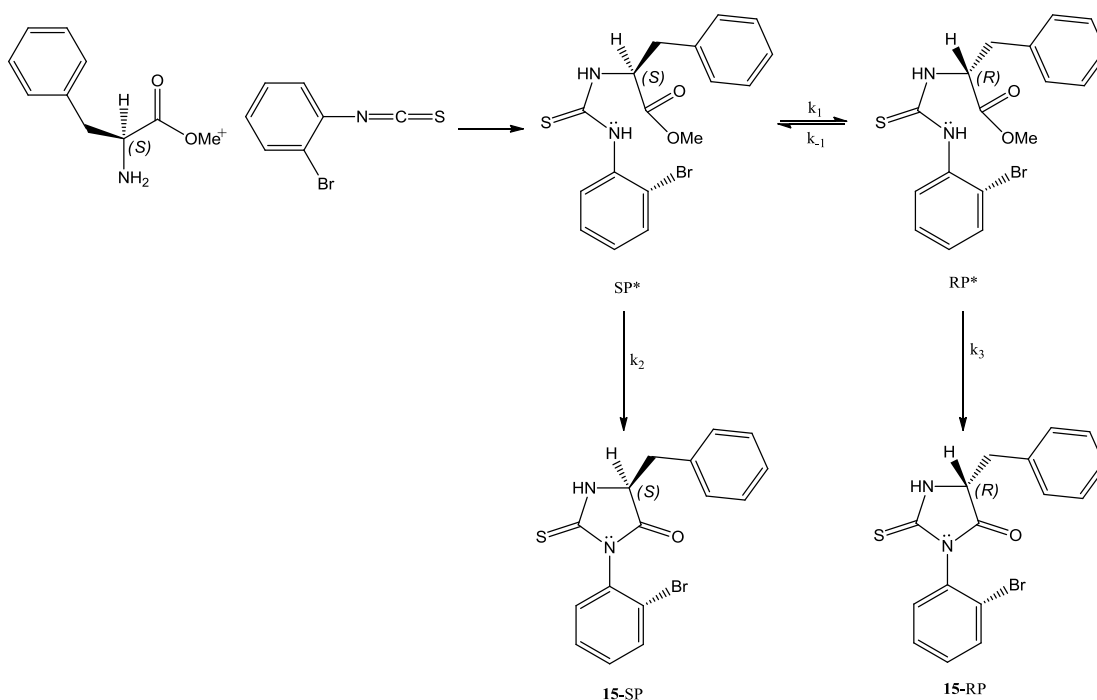


Figure 3.7. The mechanism of the formation reaction of thiohydantoin.

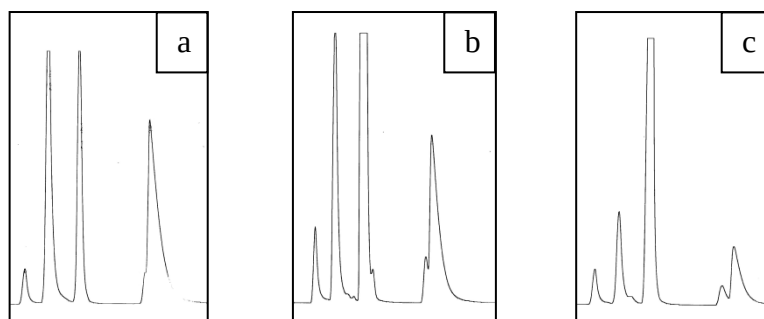


Figure 3.8. HPLC chromatogram for the synthesis of compound **15** for 1 hour a) at 40°C, b) at 80°C and c) at 110°C.

Since the temperature change did not improve the formation of epimers, SP^* and RP^* , the reaction was tried for 5 minutes at temperatures 28°C, 40°C, 60°C and 110°C. At 28°C RP was found to be present with the same amount as SP (Figure 3.9a). At 40°C, $SP:RP$ ratio was improved to 55:40 (Figure 3.9b). At 110°C, even though the reaction time is very limited, RP and SP were formed with 1:1 ratio (Figure 3.9d). However, when the reaction was carried out at 60°C for 5 minutes, $SP:RP$ ratio was increased to 75:17 (Figure

3.9c). These results can be explained by dynamic thermodynamic resolution. Since the reaction gives **SP** and **RP** products from **SP*** and **RP*** intermediates even after 5 minutes at room temperature, the cyclization rates (k_2 and k_3) have to be very high even at low temperatures. The cyclization rate k_2 at 60°C should have been higher than the racemization rate k_1 so that the **SP:RP** ratio was increased.

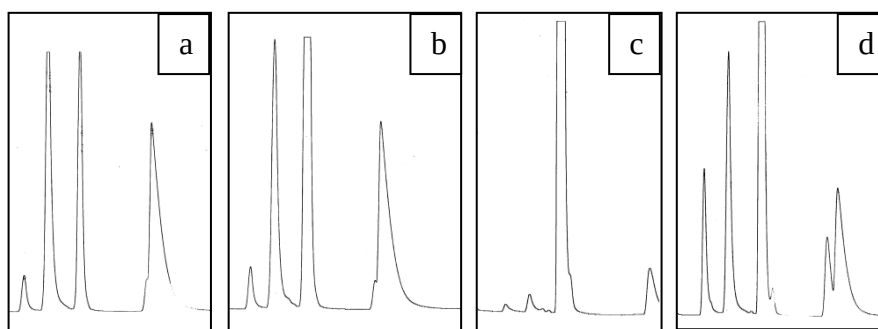


Figure 3.9. HPLC chromatogram for the synthesis of compound **15** for 5 minutes a) at 28°C, b) at 40°C, c) at 60°C and d) at 110°C.

At temperatures below 60°C, k_1 and k_{-1} are close to each other and firstly formed epimer **SP*** was converted to **RP*** with k_1 rate and then **RP*** was converted to **SP*** with k_{-1} rate. At low temperatures these intermediates equilibrate before giving cyclization reaction with k_2 and k_3 rates and this results in increase ratio of **RP**. However, at 60°C **SP*** prefers to cyclize before forming **RP*** by racemization, leading to the best **SP:RP** ratio which was 75:17. At higher temperatures, both the interconversions and the cyclizations occur very rapidly therefore **SP:RP** ratio was obtained as 1:1.

3.1.3. Determination of Rotational Barrier to Hindered Rotation [35]

It was previously reported that thiohydantoin can easily racemize in basic media [42]. Since the studied compounds have a chiral axis, it is expected to observe rotation around the chiral axis in addition to racemization (Figure 3.10).

In order to see which interconversion exists between the isomers, rotation around the chiral axis or racemization at C-5, is present (Figure 3.11), the **RP** and **SP** isomers of **4** were resolved micropreparatively by HPLC on ChiralPak IC. The resolved isomers were kept separately in toluene in a constant temperature bath at 30°C and injected to HPLC at certain time intervals for analysis. It has been observed that **RP** converted to **RM** with time and **SP** did not appear at all during the time span of the experiment (Figure 3.11a). This fact indicated that **RP** did *not* racemize at C-5, to give any **SP**. When the experiment was repeated with the resolved **SP**, it was found to convert to **SM** with time without formation of any other isomer (Figure 3.11b).

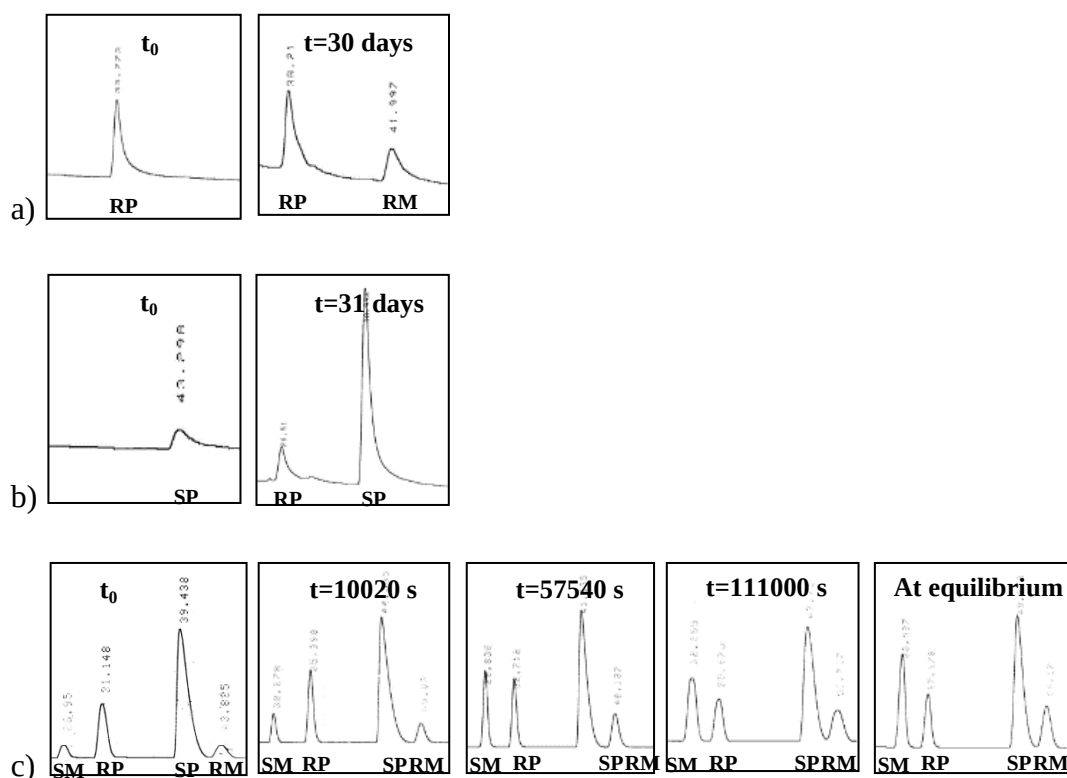


Figure 3.11. a) Thermal interconversion of micropreparatively resolved **RP** to **RM** of **4** through rotation, in toluene at 30°C by HPLC on ChiralPak IC, b) Thermal interconversion of micropreparatively resolved **SP** to **SM** of **4** through rotation, in toluene at 30°C by HPLC on ChiralPak IC, c) The thermal interconversion experiment was done in toluene at 60°C starting with the initial mixture of isomers of **4** by HPLC on ChiralPak IC.

Next, isomers of compound **1** were resolved micropreparatively and the resolved **SP** and **RP** were subjected to thermal interconversion experiments. Chromatograms (Figure 3.12) indicate that the conversions occurred only between **SP** and **SM** and between **RP** and **RM**. **SP** did not convert to **RP**. This result, similar to that of **4**, points to the fact that **RP** was produced during the formation of the heterocycle and not by a racemization of the ring *via* enolization followed by reprotonation. To further prove that enolization is not taking place, deuteration experiments were done on **1** in methanol- d_4 using ^1H NMR where there was a possibility to follow the deuteration by comparing the *o*-methyl signals with the C-5 hydrogen signal. This experiment did not show any sign of deuteration, also in the presence of a few drops of D_2O .

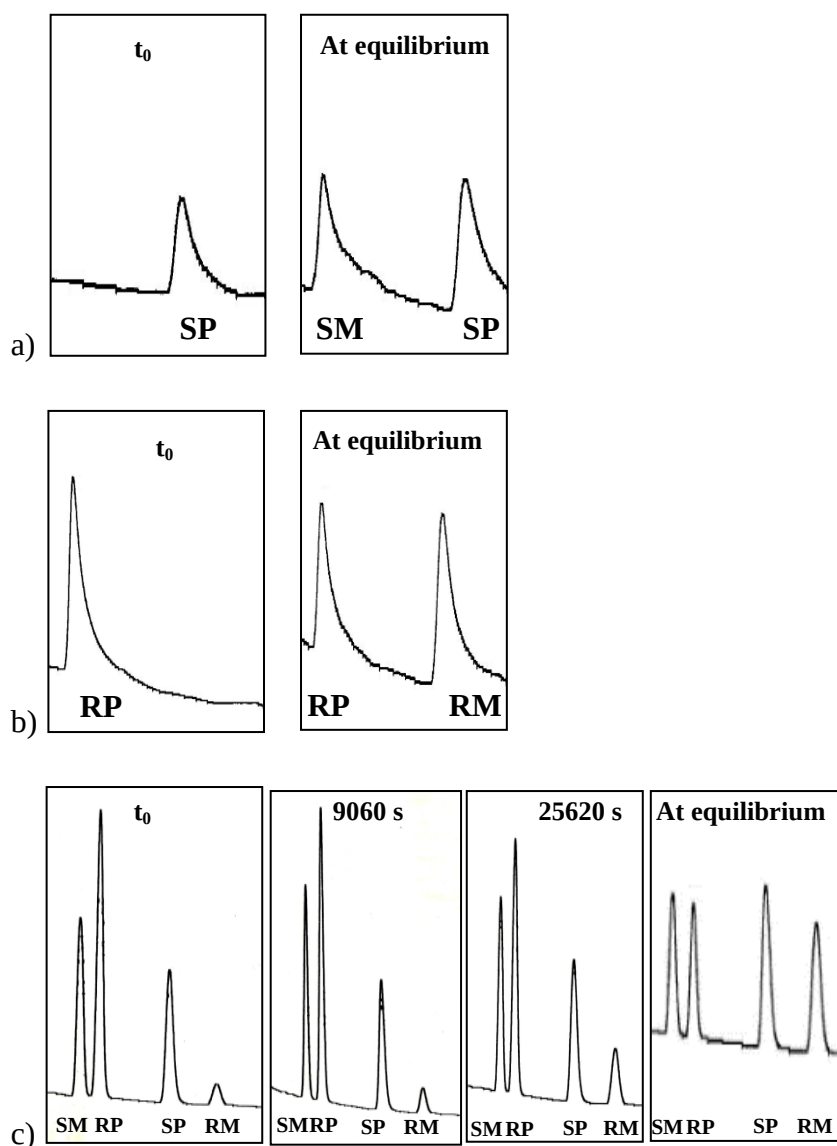


Figure 3.12. HPLC chromatograms for a) rotation of microreperatively resolved **SP** of **1** in toluene at 30°C, b) rotation of microreperatively resolved **RP** of **1** in toluene at 30°C, c) rotation of all isomers of **1** in toluene at 30°C.

Having found out that the only occurring dynamic process was between the rotational isomers, the barrier to hindered rotation around the $N_{(sp^2)}-C_{(aryl)}$ chiral axis has been determined. A nonequilibrium mixture of isomers of **4** was kept in toluene at 60°C and analyzed by HPLC on Chiralpak IC within the certain time intervals. During this thermal process the peaks of **SM** and **RM** increased while those of the other two decreased (Figure 3.11c). A plot of $\ln \left[\frac{M_0 - Meq}{M_t - Meq} \right]$ versus time [12] (Figure 3.13a and 3.13b), where M_0

is the initial concentration of the isomer, M_{eq} is the equilibrium concentration and M_t is the concentration at time t , gave the first order rate constants for the hindered rotation around the $N_{(sp^2)}-C_{(aryl)}$ chiral axis. The substitution of the obtained rate constant in Eyring Equation 1.8, $\Delta G^\ddagger = RT \ln(k_b \cdot T / k \cdot h)$ [43], gave the rotational barrier summarized in Table 3.3.

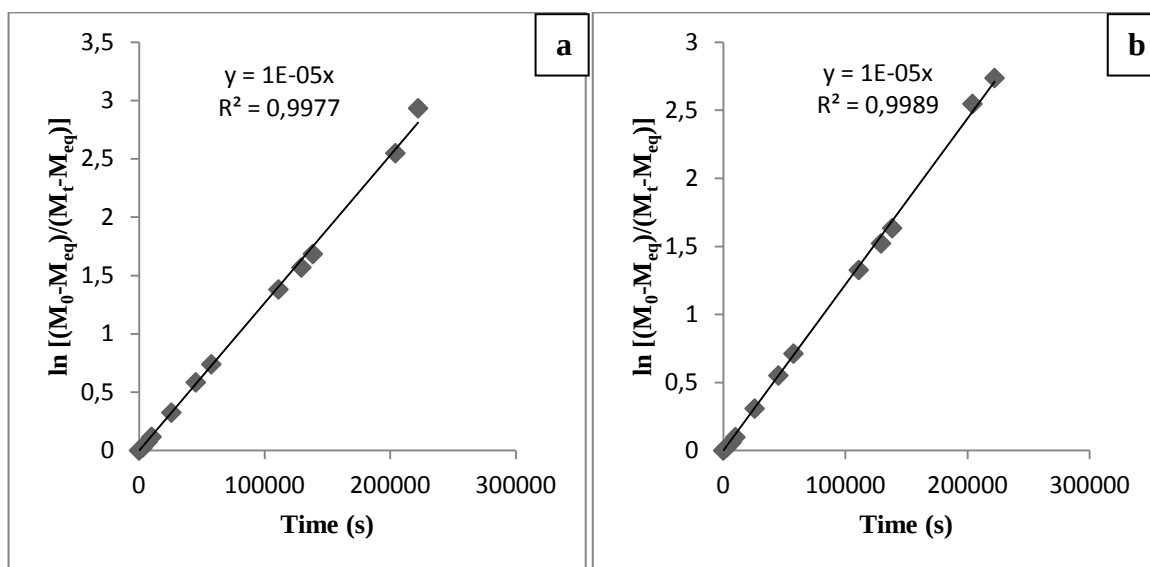


Figure 3.13. $\ln[\frac{M_0 - M_{eq}}{M_t - M_{eq}}]$ vs time graph a) for the conversion of **RP** to **RM** from the mixture of all isomers of **4**, b) for the conversion of **SP** to **SM** from the mixture of all isomers of **4**.

Figure 3.12c shows the thermal interconversion experiment for **1** carried out with the isomeric mixture from which the data for the conversion of **SP** to **SM** and that of **RP** to **RM** have been obtained. The rate constants for the intramolecular rotation of **1** are obtained by the same way followed for that of **4**, from the slopes of the lines shown in Figure 3.14a and 3.14b and the corresponding barriers from the Eyring Equation 1.8, $\Delta G^\ddagger = RT \ln(k_b \cdot T / k \cdot h)$ were calculated [35].

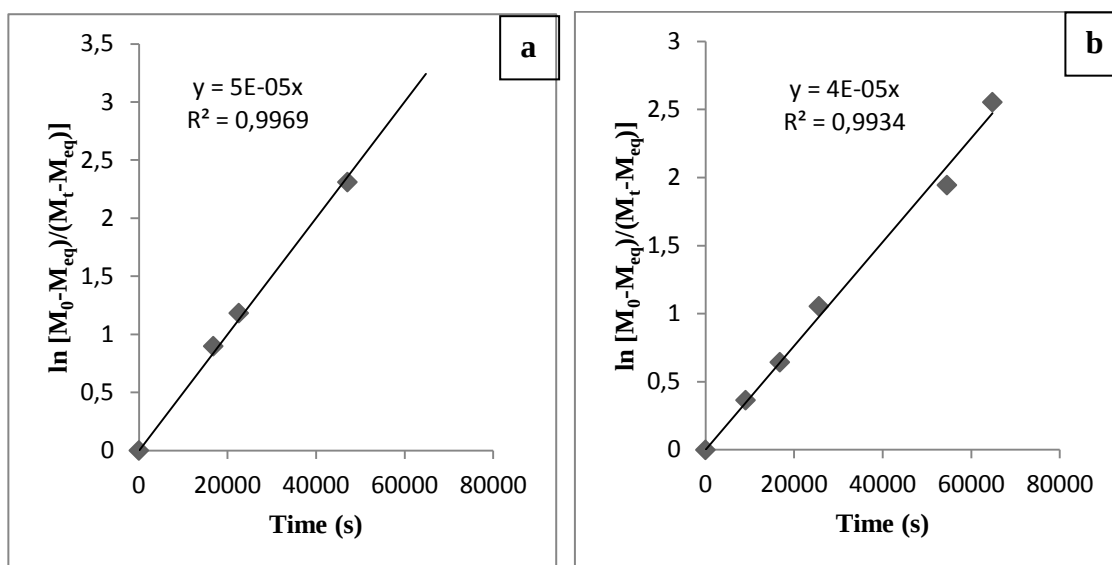


Figure 3.14. a) $\ln \left[\frac{M_0 - M_{eq}}{M_t - M_{eq}} \right]$ vs time graph for the conversion of **SP** to **SM** of **1**, b)

$\ln \left[\frac{M_0 - M_{eq}}{M_t - M_{eq}} \right]$ vs time graph for the conversion of **RP** to **RM** of **1**.

The rotational barriers for the forward and the reverse directions are listed in Table 3.3. The $\Delta G^\ddagger$ value we found for the **SP** to **SM** conversion of **4** at 60°C, 116.2 kJ/mol (27.8 kcal/mol), is larger than the $\Delta G^\ddagger$ reported by Colebrook *et al.* (25.2 kcal/mol) for the rotational barrier of the same compound for hindered rotation [44]. The difference, in addition to the different methods used may also be due to the different temperatures and solvents used (toluene vs pyridine, 60°C vs 25°C). The barriers for **2-5** and **9-12** indicate that $\Delta G^\ddagger$ values increase with the size of the the *ortho*- substituent on the aryl ring. Comparing the barriers to rotation of **1&3** and **8&10** however, chlorine was found to exert a greater steric effect than methyl as has been observed before [44]. The barrier determined in an earlier work for the 3-*o*-chlorophenyl-5-methylthiohydantoin (25.7 kcal/mole) was found to be slightly higher than that of the corresponding *o*-bromo derivative (25.2 kcal/mole) [44]. This unexpected result may be due to different temperatures used in the two experiments.

Table 3.3. Rotational barriers of the compounds **1-6** and **8-13**.

Comp	Temp (K)	SP $\longleftrightarrow$ SM					RP $\longleftrightarrow$ RM				
		K	k_f (s^{-1})	ΔG_f (kJ/mol)	k_r (s^{-1})	ΔG_r (kJ/mol)	K	k_f (s^{-1})	ΔG_f (kJ/mol)	k_r (s^{-1})	ΔG_r (kJ/mol)
1	303	0.7	3.0×10^{-5}	100.5 ± 0.7	2.0×10^{-5}	101.5 ± 0.7	1.3	1.7×10^{-5}	101.9 ± 0.7	2.3×10^{-5}	101.3 ± 0.7
2[44]	359	1.1	7.6	82.4	-	-	-	-	-	-	-
3	333	0.7	4.2×10^{-5}	109.8 ± 0.7	5.8×10^{-5}	108.9 ± 0.7	1.3	5.6×10^{-5}	109.0 ± 0.7	4.4×10^{-5}	109.7 ± 0.7
4	333	0.7	4.1×10^{-6}	116.2 ± 0.7	6.0×10^{-6}	115.2 ± 0.7	1.5	5.9×10^{-6}	115.2 ± 0.7	4.1×10^{-6}	116.2 ± 0.7
5	333	0.9	1.9×10^{-6}	118.4 ± 0.7	2.1×10^{-6}	118.0 ± 0.7	N.D.				
	383	0.8	1.7×10^{-4}	122.2 ± 0.7	2.3×10^{-4}	121.3 ± 0.7	N.D.				
6	303	N.D.					1.0	1.5×10^{-6}	108.0 ± 0.7	1.5×10^{-6}	108.0 ± 0.7
	333	1.2	1.1×10^{-4}	107.1 ± 0.7	9.1×10^{-5}	107.6 ± 0.7	1.1	1.1×10^{-4}	107.2 ± 0.7	9.4×10^{-5}	107.5 ± 0.7
8	303	1.0	1.0×10^{-5}	103.3 ± 0.7	1.0×10^{-5}	103.2 ± 0.7	1.0	9.9×10^{-6}	103.3 ± 0.7	1.0×10^{-5}	103.2 ± 0.7
9	358 ^a	-	5.3	83.2	-	-	-	-	-	-	-
	378 ^b	-	8.0	86.8	-	-	-	-	-	-	-
10	333	0.9	9.3×10^{-5}	107.6 ± 0.7	1.1×10^{-4}	107.2 ± 0.7	1.1	1.1×10^{-4}	107.2 ± 0.7	9.4×10^{-5}	107.5 ± 0.7
11	333	1.0	5.1×10^{-6}	115.6 ± 0.7	4.9×10^{-6}	115.7 ± 0.7	1.0	5.0×10^{-6}	115.7 ± 0.7	5.1×10^{-6}	115.6 ± 0.7
12	333	1.3	2.3×10^{-6}	117.8 ± 0.7	1.7×10^{-6}	118.6 ± 0.7	0.7	1.7×10^{-6}	118.7 ± 0.7	2.3×10^{-6}	117.8 ± 0.7
13	333	N.D.					0.9	9.6×10^{-5}	107.5 ± 0.7	1.0×10^{-4}	107.3 ± 0.7

^a The rotational barrier of **9** was determined by dynamic NMR. Coalescence temperature and coalescence rate constant was calculated from the coalescence of two methyl signals which are doublets.

^b The rotational barrier of **9** was determined by dynamic NMR. Coalescence temperature and coalescence rate constant was calculated from the coalescence of α -hydrogen at C-5 which is a doublet.

Since the isomeric separation of compounds **2** and **9** by HPLC on chiral columns could not be achieved, the rotational barrier of compound **2** was considered as the same with the one found by Colebrook [44] which is 82.4 kJ/mol but it was determined for compound **9** by dynamic NMR (Figure 3.15 and 3.16). The coalescence temperature (T_c) was determined as 85°C from the coalescence of two methyl groups which are doublets and 105°C from the coalescence of α -hydrogen at C-5 which is a doublet. The difference in chemical shifts $\Delta\nu$ was used for the calculation of the coalescence rate constants, 5.3 s^{-1} and 8.0 s^{-1} respectively, and substitution these rate constants in Eyring Equation 1.8 gives the free energy of activation of compound **9** as 83.2 and 86.8 kJ/mol, respectively.

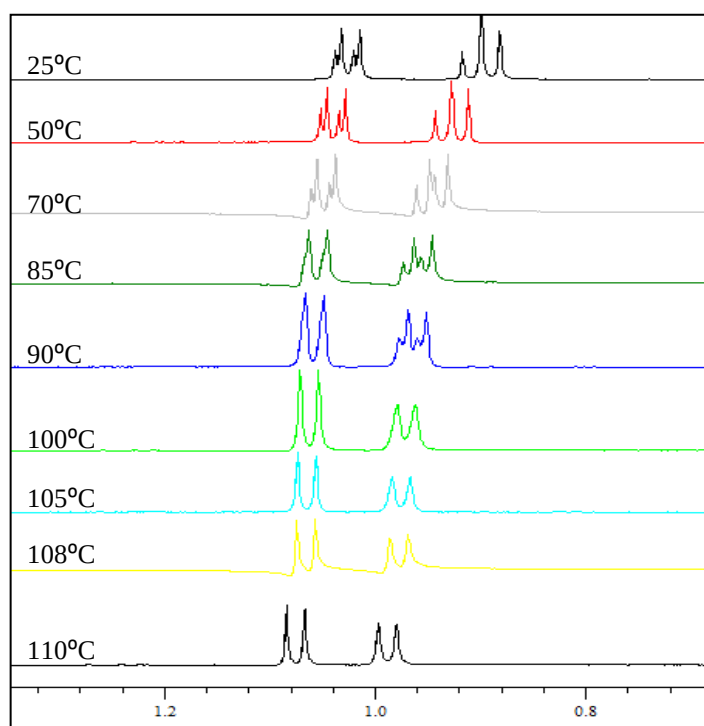


Figure 3.15. The coalescence of two methyl groups in partial dynamic ^1H NMR spectrum of **9** in DMSO.

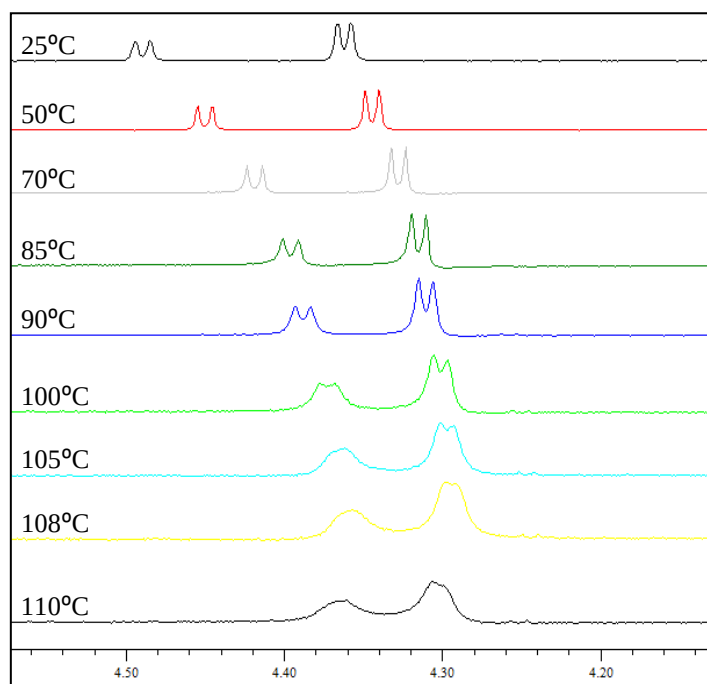


Figure 3.16. The coalescence of α -hydrogen at C-5 in partial dynamic ^1H NMR spectrum of **9** in DMSO.

Figure 3.17 shows the increase of $\Delta G^\ddagger$ in the *o*-halogen substituted derivatives **2-5** and **9-12**. It was observed that there is a linear relationship between the size of the *o*-halogen substituent and the rotational barrier around the chiral axis, the bigger the atomic radius, the larger the rotational barrier.

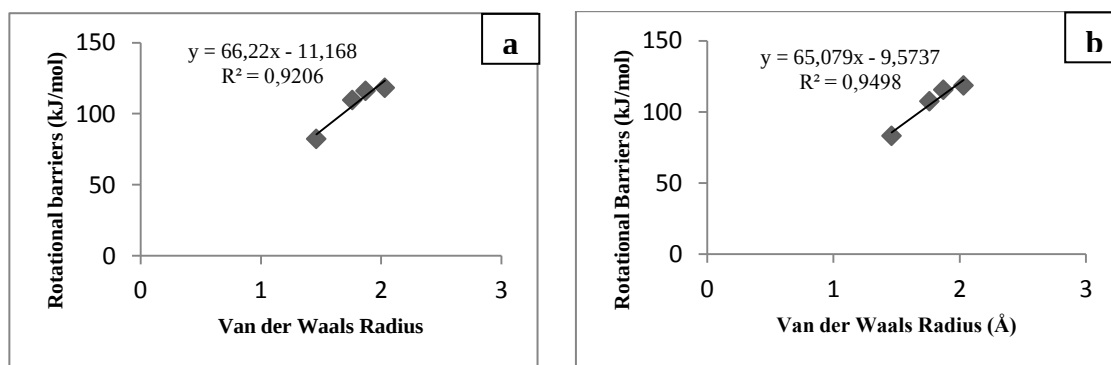


Figure 3.17. Van der Waals radius vs rotational barriers of a) compounds **2-5**, b) compounds **9-12**.

The chromatograms and the graphs obtained from the rotation around the chiral axis for all compounds are below.

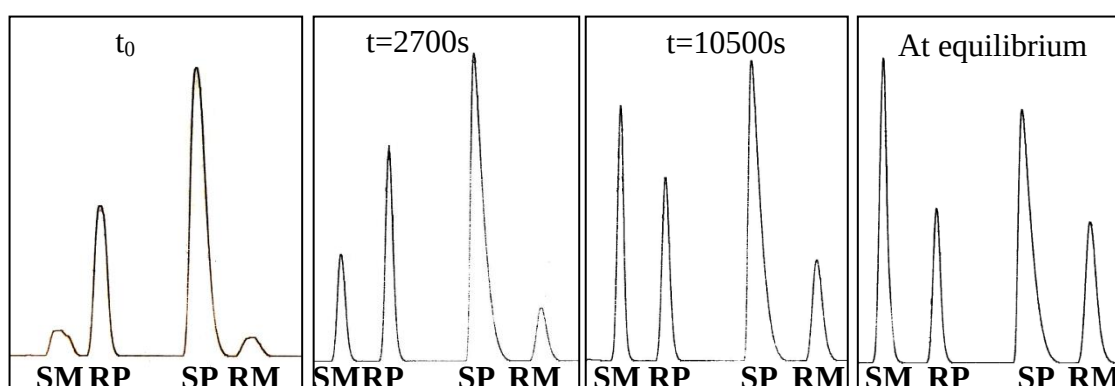


Figure 3.18. Interconversion of the isomers of **3** with time *via* rotation in toluene at 60°C by HPLC on ChiralPak IC.

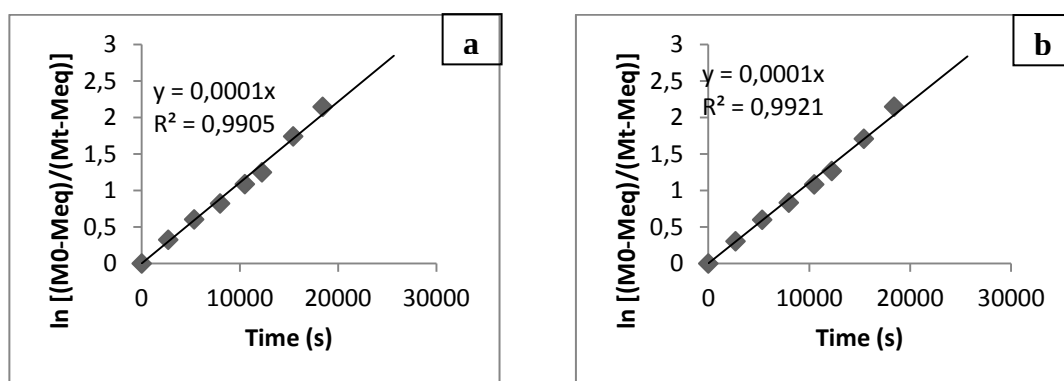


Figure 3.19. $\ln\left[\frac{M_0-M_{eq}}{M_t-M_{eq}}\right]$ vs time graphs, a) for the conversion of **SP** to **SM** of **3** without resolving at 60°C, b) for the conversion of **RP** to **RM** of **3** without resolving at 60°C.

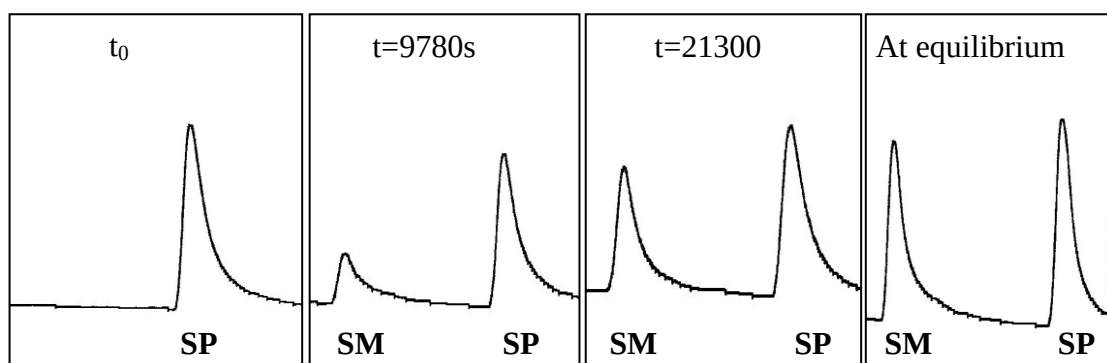


Figure 3.20. Interconversion *via* rotation of the micropreperatively resolved **SP** of **3** with time in toluene at 30°C by HPLC on ChiralPak IC.

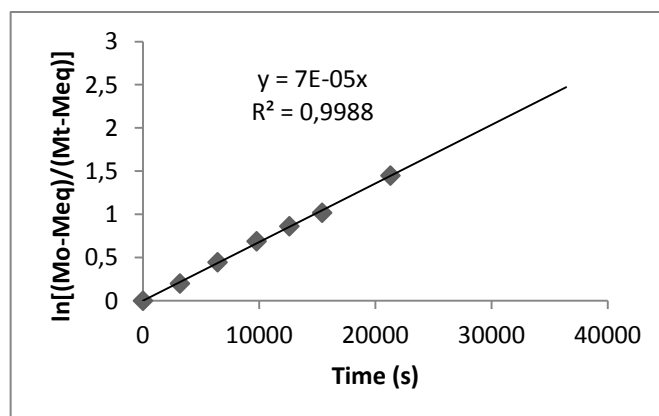


Figure 3.21. $\ln\left[\frac{M_0-M_{eq}}{M_t-M_{eq}}\right]$ vs time graph for the conversion of **SP** to **SM** of **3** after resolving **SP** at 60°C.

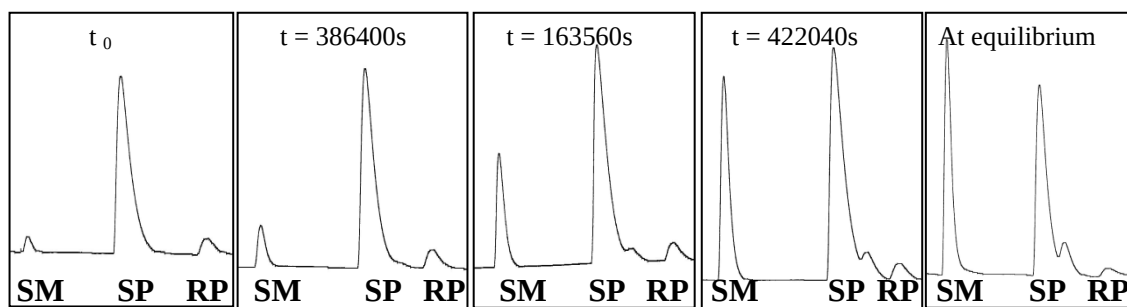


Figure 3.22. Interconversion of the isomers of **5** with time *via* rotation in toluene at 60°C by HPLC on ChiralPak IB.

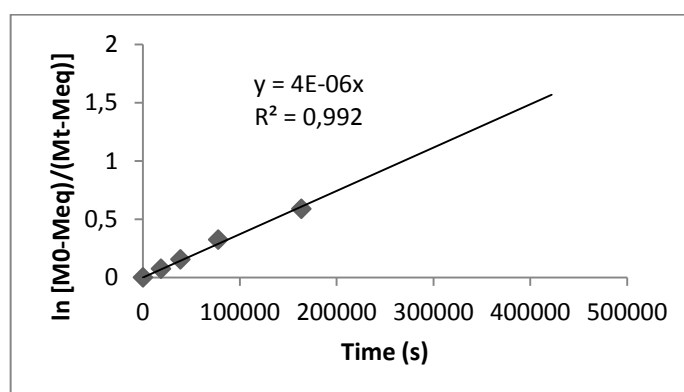


Figure 3.23. $\ln\left[\frac{M0-Meq}{Mt-Meq}\right]$ vs time graph for the conversion of **SP** to **SM** from the mixture of all isomers of **5** at 60°C.

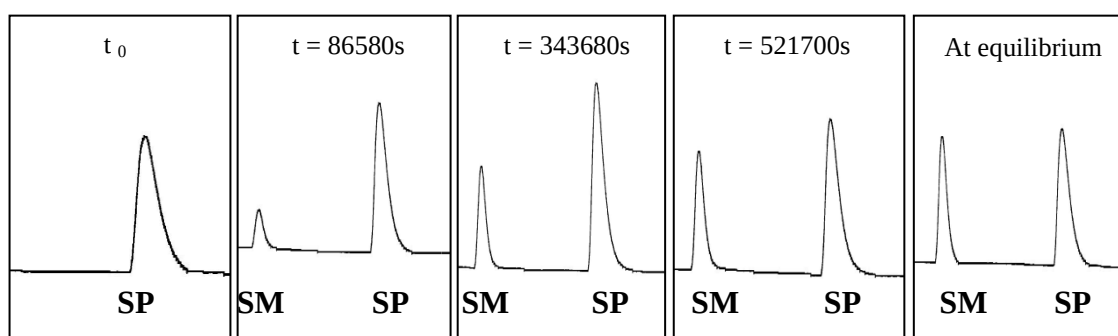


Figure 3.24. Interconversion *via* rotation of the microreperatively resolved **SP** of **5** with time in toluene at 60°C by HPLC on ChiralPak IB.

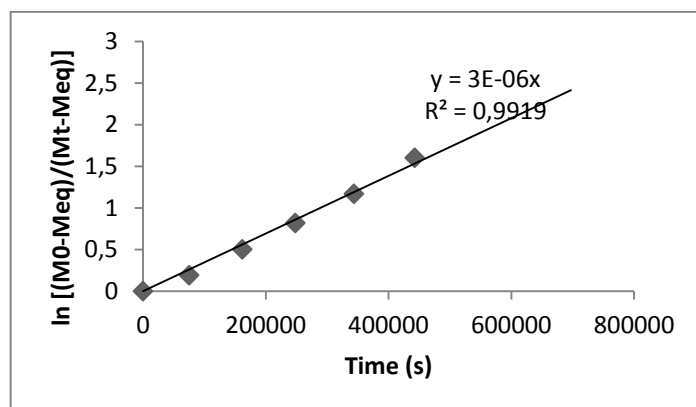


Figure 3.25. $\ln\left[\frac{M_0 - M_{eq}}{M_t - M_{eq}}\right]$ vs time graph for the conversion of **SP** to **SM** from the micropreperatively resolved **SP** of **5** at 60°C.

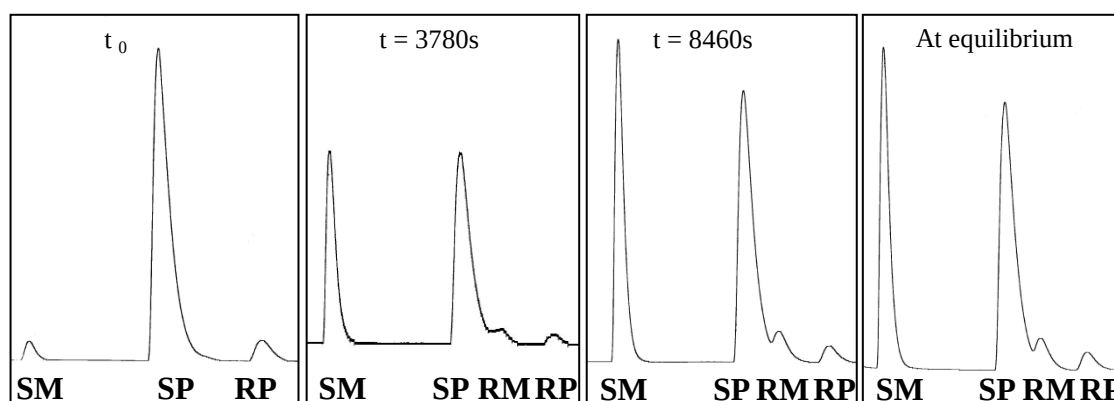


Figure 3.26. Interconversion of the isomers of **5** with time *via* rotation in toluene at 110°C by HPLC on ChiralPak IB.

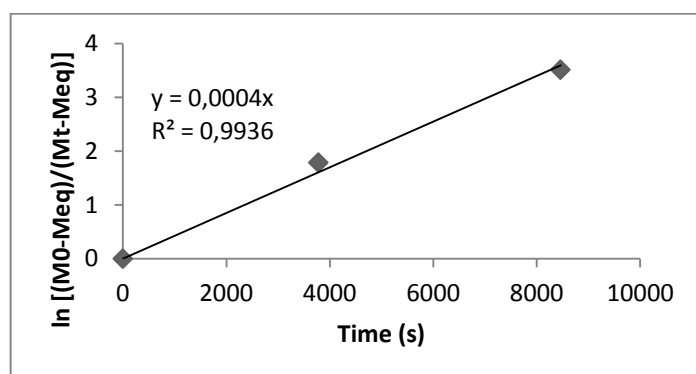


Figure 3.27. $\ln\left[\frac{M_0 - M_{eq}}{M_t - M_{eq}}\right]$ vs time graph for the conversion of **SP** to **SM** from the mixture of all isomers of **5** at 110°C.

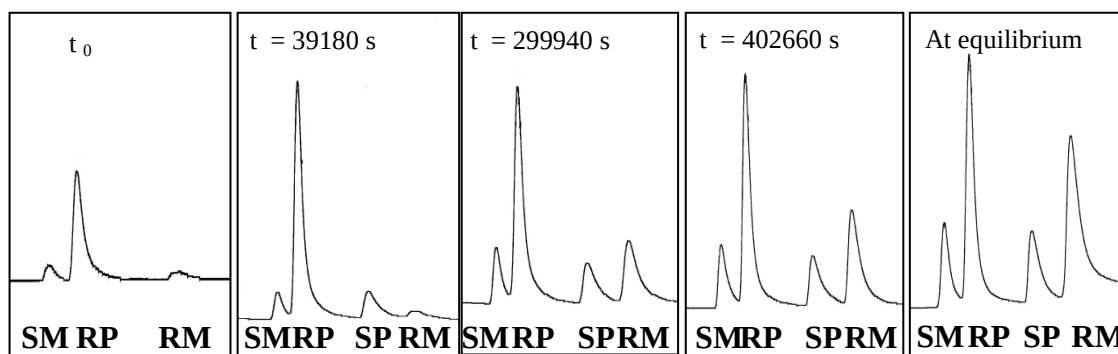


Figure 3.28. Interconversion of the isomers of **6** with time *via* rotation in toluene at 30°C by HPLC on ChiralPak IC.

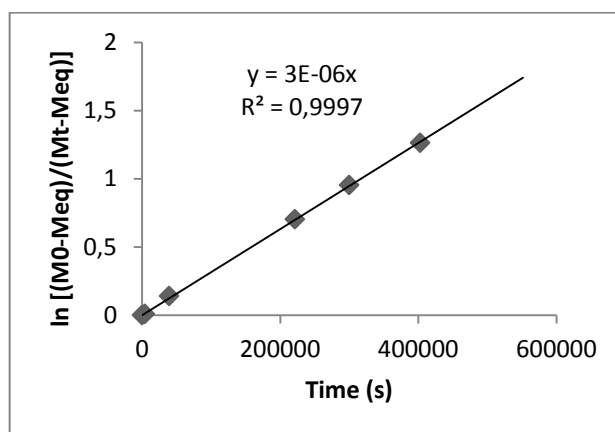


Figure 3.29. $\ln \left[\frac{M_0 - M_{eq}}{M_t - M_{eq}} \right]$ vs time graph for the conversion of **RP** to **RM** from the mixture of all isomers of **6** at 30°C.

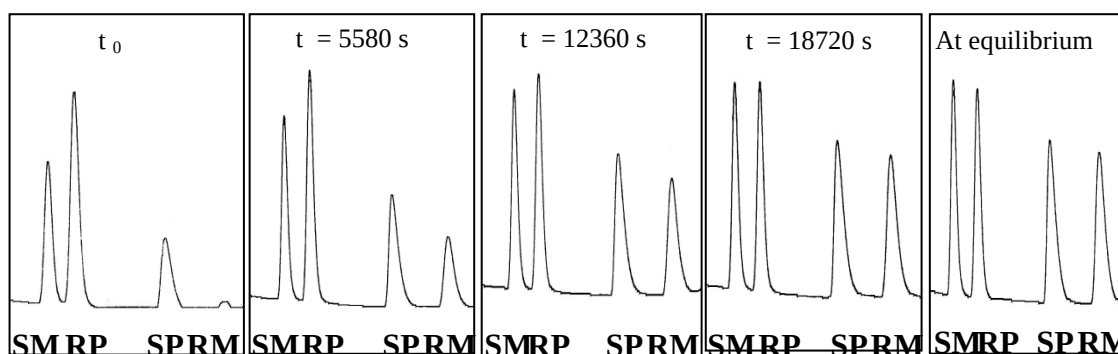


Figure 3.30. Interconversion of the isomers of **6** with time *via* rotation in toluene at 60°C by HPLC on ChiralPak IC.

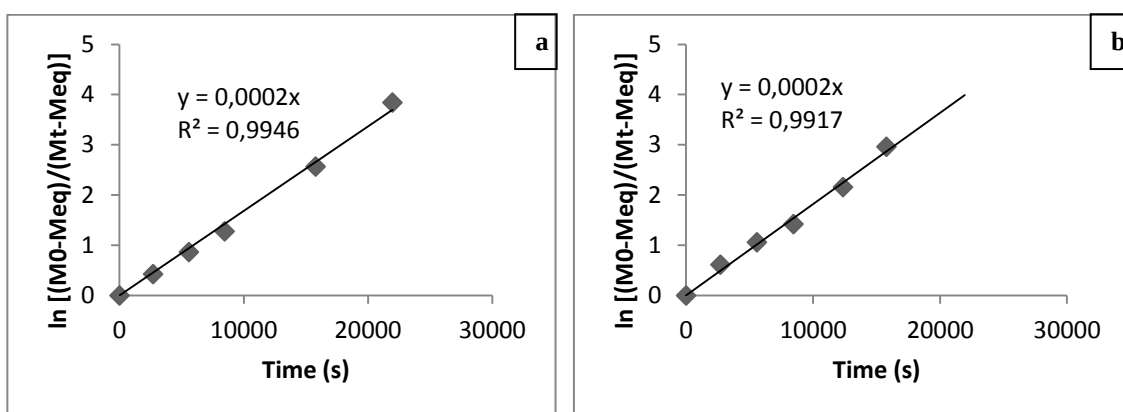


Figure 3.31. $\ln\left[\frac{M_0 - M_{eq}}{M_t - M_{eq}}\right]$ vs time graph, a) for the conversion of **RP** to **RM** from the mixture of all isomers of **6** at 60°C, b) for the conversion of **SP** to **SM** from the mixture of all isomers of **6** at 60°C.

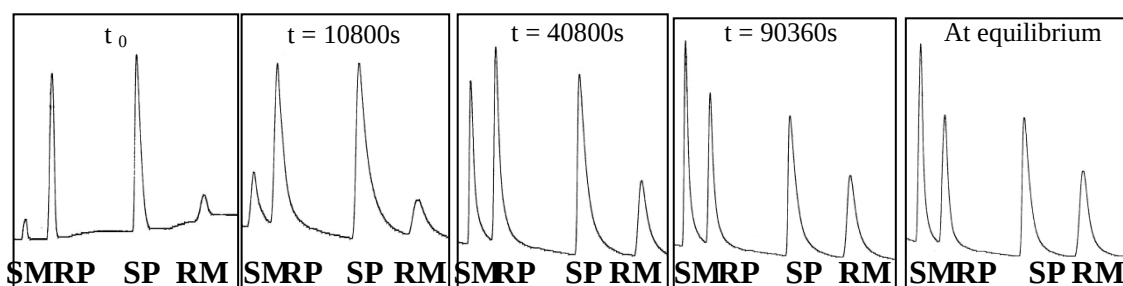


Figure 3.32. Interconversion of the isomers of **8** with time *via* rotation in toluene at 30°C by HPLC on ChiralPak IC.

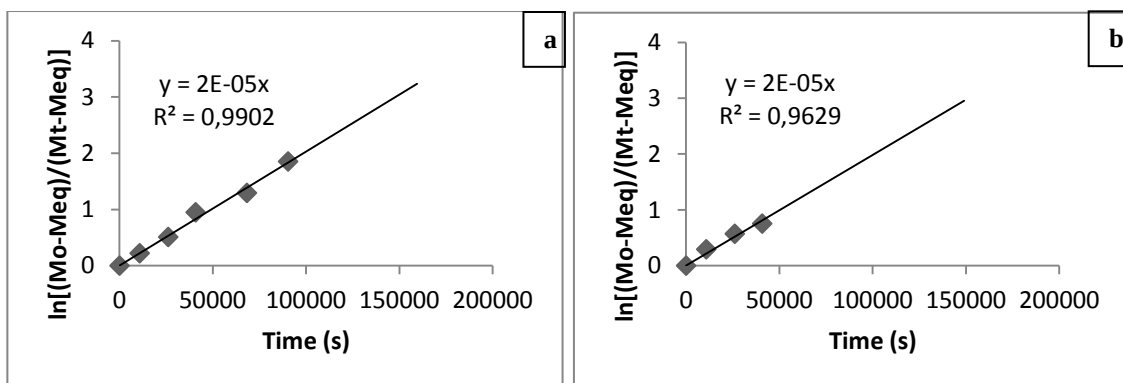


Figure 3.33. $\ln\left[\frac{M_0 - M_{eq}}{M_t - M_{eq}}\right]$ vs time graph, a) for the conversion of **SP** to **SM** of **8** without resolving at 30°C, b) for the conversion of **RP** to **RM** of **8** without resolving at 30°C.

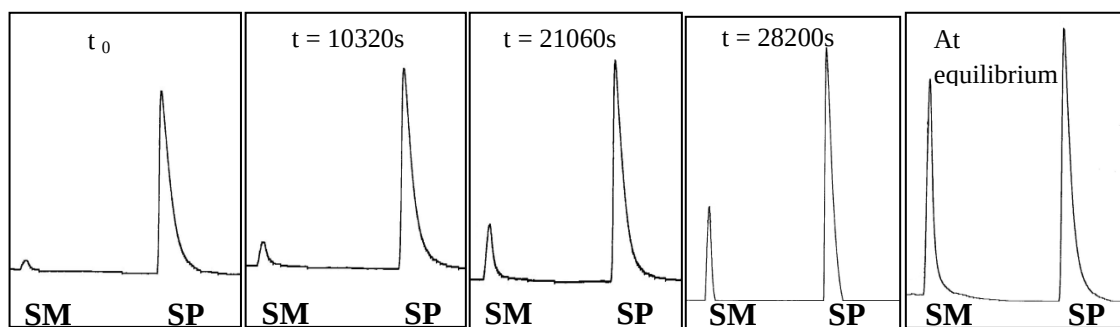


Figure 3.34. Interconversion *via* rotation of the microreperatively resolved **SP** of **8** with time in toluene at 30°C by HPLC on ChiralPak IC.

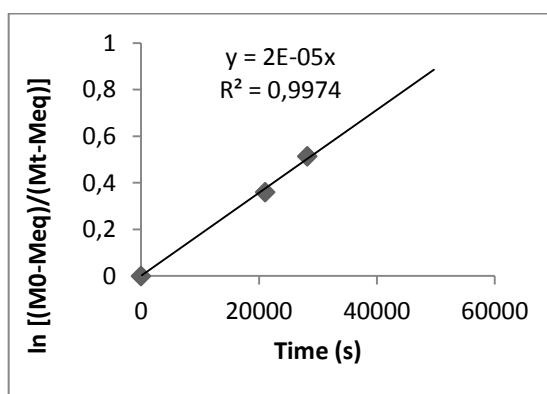


Figure 3.35. $\ln\left[\frac{M_0-M_{eq}}{M_t-M_{eq}}\right]$ vs time graph for the conversion of **SP** to **SM** from the microreperatively resolved **SP** of **8** at 30°C.

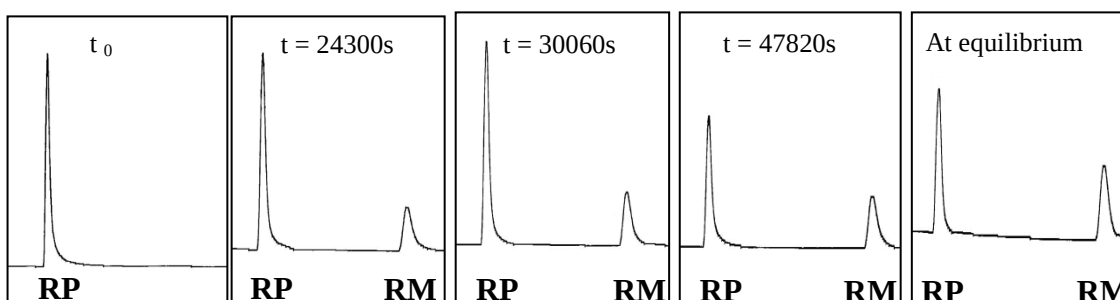


Figure 3.36. Interconversion *via* rotation of the microreperatively resolved **RP** of **8** with time in toluene at 30°C by HPLC on ChiralPak IC.

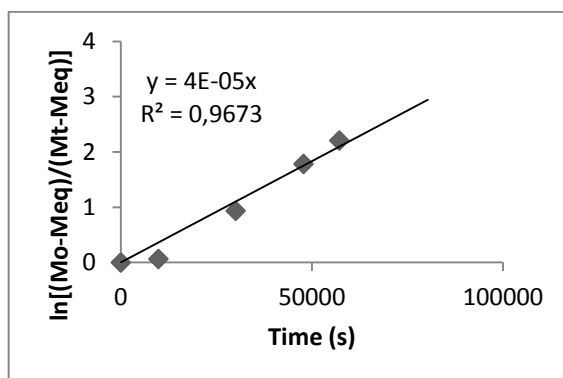


Figure 3.37. $\ln[\frac{M0-Meq}{Mt-Meq}]$ vs time graph for the conversion of **RP** to **RM** from the micropreperatively resolved **RP** of **8** at 30°C.

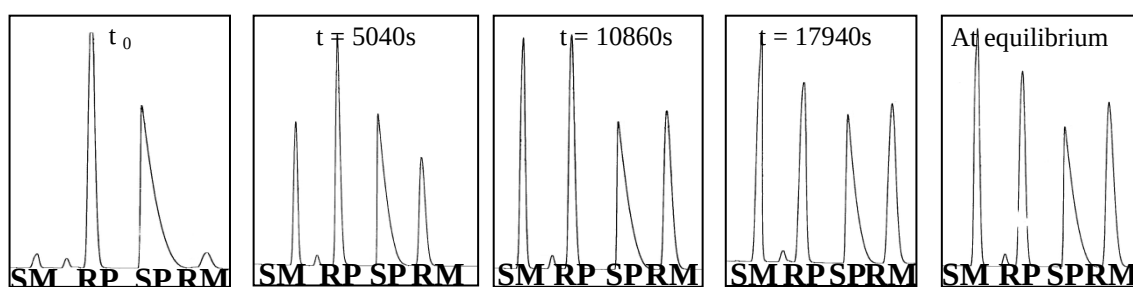


Figure 3.38. Interconversion of the isomers of **10** with time *via* rotation in toluene at 60°C by HPLC on ChiralPak IC.

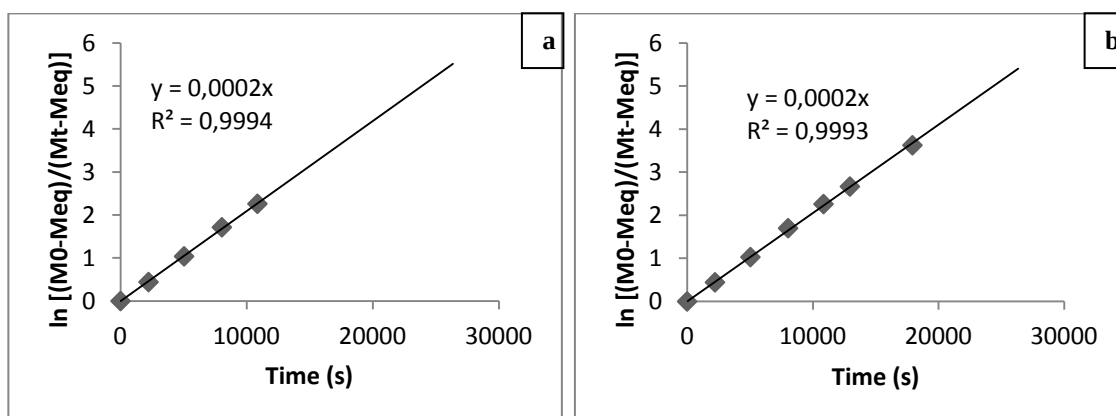


Figure 3.39. $\ln[\frac{M0-Meq}{Mt-Meq}]$ vs time graph, a) for the conversion of **SP** to **SM** from the mixture of all isomers of **10** at 60°C, b) for the conversion of **RP** to **RM** from the mixture of all isomers of **10** at 60°C.

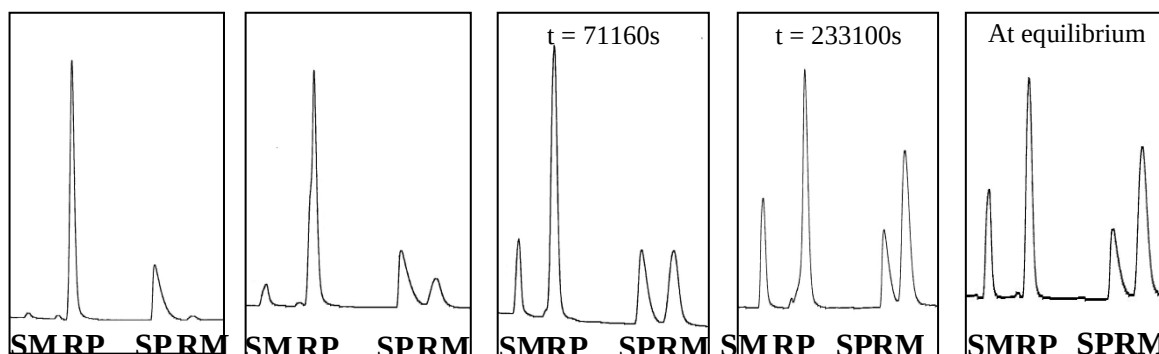


Figure 3.40. Interconversion of the isomers of **11** with time *via* rotation in toluene at 60°C by HPLC on ChiralPak IC.

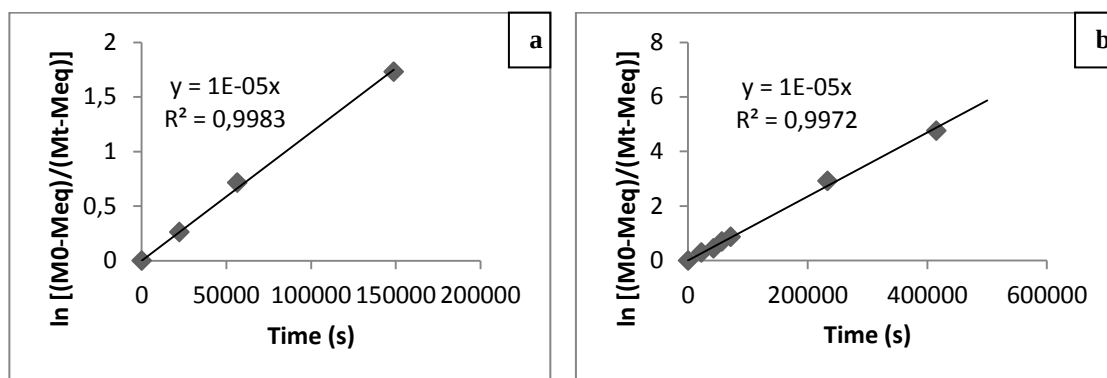


Figure 3.41. $\ln\left[\frac{M_0-M_{eq}}{M_t-M_{eq}}\right]$ vs time graph, a) for the conversion of **SP** to **SM** from the mixture of all isomers of **11** at 60°C, b) for the conversion of **RP** to **RM** from the mixture of all isomers of **11** at 60°C.

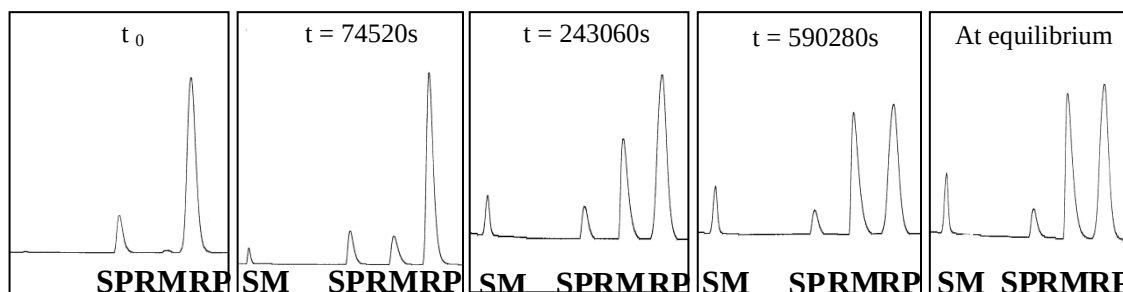


Figure 3.42. Interconversion of the isomers of **12** with time *via* rotation in toluene at 60°C by HPLC on ChiralPak IB.

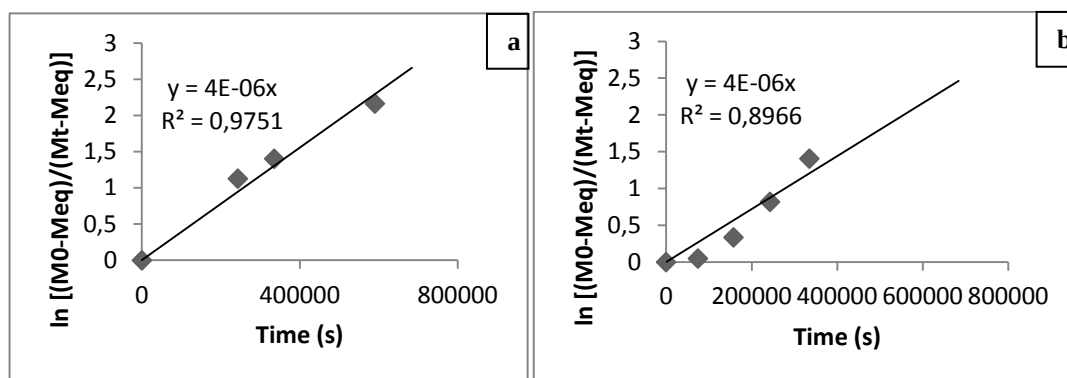


Figure 3.43. $\ln\left[\frac{M_0 - M_{eq}}{M_t - M_{eq}}\right]$ vs time graph, for the conversion **SP** to **SM** from the mixture of all isomers of **12** at 60°C, b) for the conversion from **RP** to **RM** from the mixture of all isomers of **12** at 60°C.

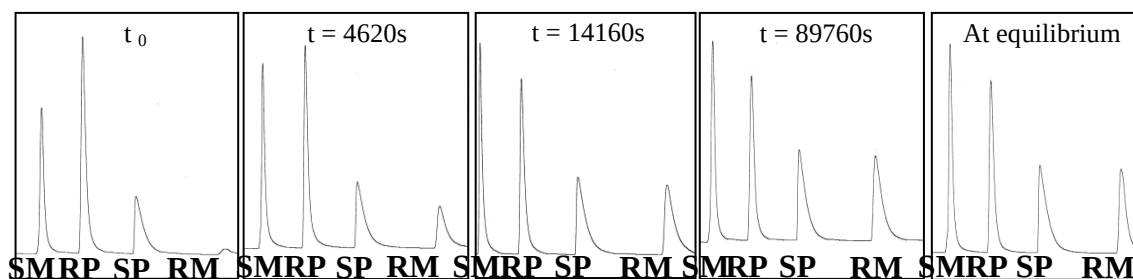


Figure 3.44. Interconversion of the isomers of **13** with time *via* rotation in toluene at 60°C by HPLC on ChiralPak IC.

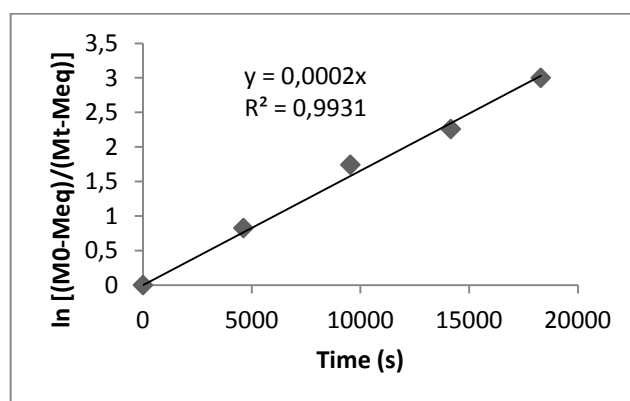


Figure 3.45. $\ln\left[\frac{M_0 - M_{eq}}{M_t - M_{eq}}\right]$ vs time graph, for the conversion **RP** to **RM** from the mixture of all isomers of **13** at 60°C.

3.2. Atroposelective Aldol Reactions of 5-Methyl and 5-Isopropyl-3-(*o*-aryl)-2-thiohydantoins

3.2.1. Reactions with Benzaldehyde

The aldol reactions were carried out *via* the reaction of some of the synthesized thiohydantoin derivatives (**2-7** and **9-14**) with benzaldehyde at -78°C (2 hours for **16-21** and 6 hours for **22-27**) after the abstraction of hydrogen at C-5 of the heterocyclic ring by LDA (lithium diisopropylamide) at -78°C for 1 hour (Figure 3.46) by a modified procedure previously used in our laboratory [12], [14].

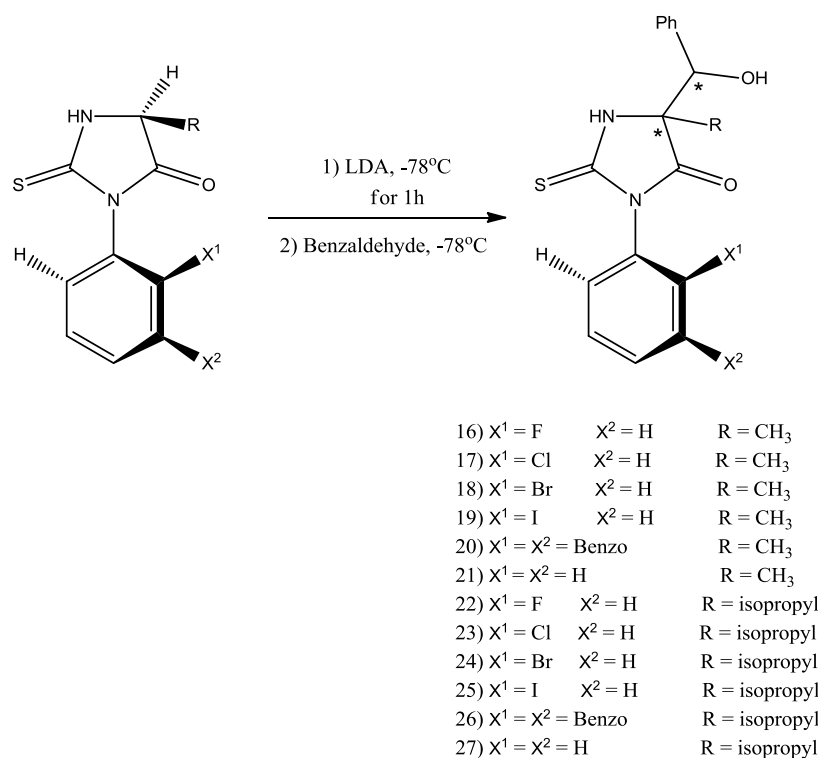


Figure 3.46. The synthesis of the aldol products (**16-27**).

Since there are three chiral elements in the aldol adducts, the chiral center at C-5 of the heterocyclic ring, the chiral axis ($\text{N}_{\text{sp}^2}\text{-C}_{\text{aryl}}$ bond) and the newly formed chiral center

which is denoted by *, eight isomers (**RPR***, **RPS***, **SPR***, **SPS***, **SMS***, **SMR***, **RMS***, **RMR***), as four diastereomeric pairs are expected in ^1H NMR (Figure 3.47).

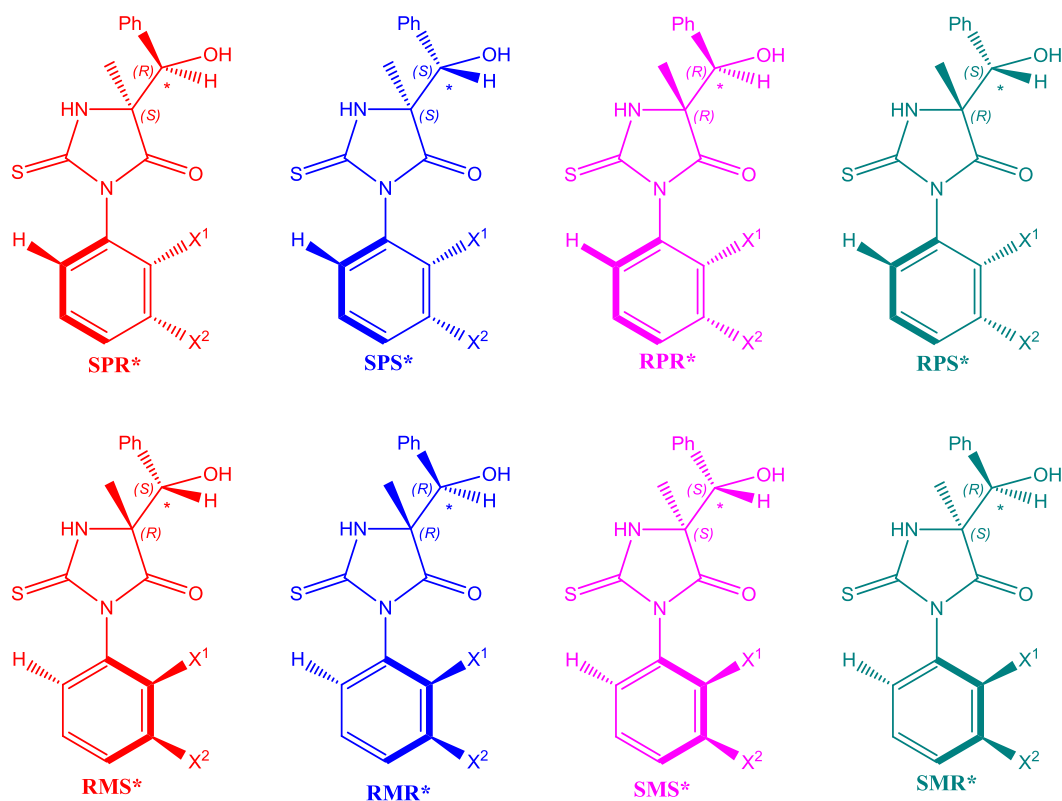


Figure 3.47. The possible isomers of the aldol adduct.

In order to assign isomers more easily, aldol reaction was tried firstly with compound **7**, which has no axial chirality. In this way, the absence of one chiral element, namely chiral axis, the number of isomers of the aldol adducts are reduced to four (**SS*&RR*** and **SR*&RS***), which means that two sets of peaks are expected to appear in ^1H NMR. In Figure 3.48 these two singlets at 4.94 ppm and 4.88 ppm, which correspond to the signal of the hydrogen at the newly formed chiral center for one major isomer and one minor one, were seen in ^1H NMR of compound **21** taken in CDCl_3 without any purification. The obtained diastereomer ratio, 21:79 by per cent, exhibits that even the reaction started with a racemic mixture, it showed a selectivity at the newly formed chiral center.

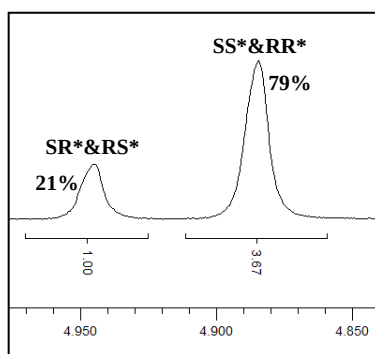


Figure 3.48. Partial ^1H NMR spectrum of crude compound **21** in CDCl_3 .

It was thought that the formation of a six membered ring resulting from the presence of an intramolecular hydrogen bonding between the hydroxyl and the carbonyl groups (Figure 3.49) may help for the observed selective attachment of the benzaldehyde. In **SS*&RR***, the phenyl ring at the newly formed chiral center is present in the equatorial position, leading to a stable structure. Therefore this pair, **SS*&RR*** is more stable than the other enantiomeric pair, **SR*&RS***, whose phenyl substituent is in the axial position. Due to being on the axial position of the aromatic ring at the newly formed chiral center, this latter pair was formed less than the previous one, making **SS*&RR*** the major product.

Based on the results obtained for compound **21** in which the phenyl ring at the newly formed chiral center prefers to be on equatorial position, isomers of the axially chiral aldol products were assigned by examining their ^1H NMR spectra. The four diastereomeric pairs were identified by ^1H NMR for **16-20**, except for **19**. The hydrogen attached to the newly formed chiral center gave a singlet around 5 ppm. When the ^1H NMR spectrum of the crude compounds was taken in CDCl_3 , four singlets were seen in the corresponding region for **16**, **17**, **18**, indicating the formation of all isomers (Figure 3.50). Table 3.4 shows the **P:M** per cent ratios of the starting thiohydantoin (**2-7** and **9-14**) and the diastereomeric ratios of the products determined from the integrations of the singlets around 5 ppm, which are 13:23:22:42 for compound **16** (Figure 3.50a), 2:8:21:69 for compound **17** (Figure 3.50b) and 2:7:23:68 for compound **18** (Figure 3.50c) by per cent.

For compound **19**, however, two singlets were observed with 29:71 diastereomeric ratio (Figure 3.50d).

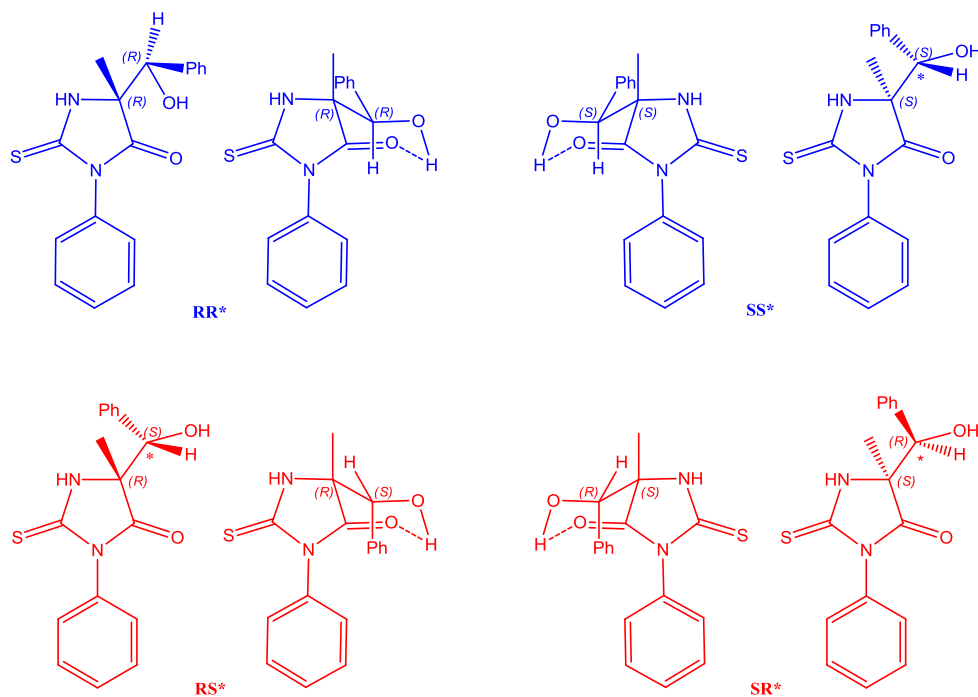


Figure 3.49. The formation of a six-membered ring between the hydroxyl and carbonyl groups.

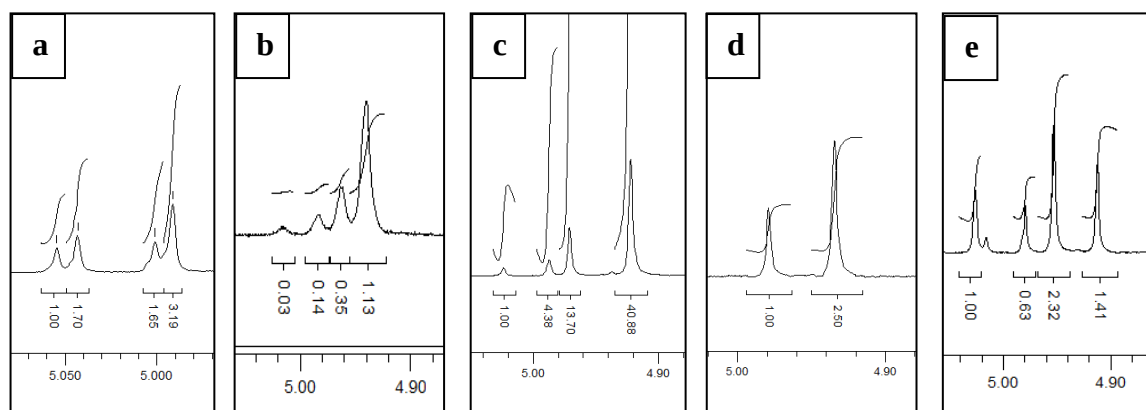


Figure 3.50. Partial ^1H NMR spectrum of crude compounds a) **16**, b) **17**, c) **18**, d) **19**, e) **20** in CDCl_3 .

Table 3.4. Enantiomeric ratios (er) and diastereomeric ratios (dr) of the aldol reaction of the compounds **16-27**

Compounds	Er (P:M) ^a	dr ^b RPS*:SPR*:RPR*:SPS*	dr ^c RPS*:SPR*:RPR*:SPS*
16	70 : 30	13:23:22:42	39 ^e :61 ^f
17	97 : 3	2:8:21:69	0:0:40:60
18	97 : 3	2:7:23:68	3:7:31:59
19	95:5	0:29:0:71	0:7:0:93
20	90: 10	19:12:43:26	25:16:33:26
21	racemic	21:79 ^d	Not determined
22	52:48	25 ^e :24:51	20 ^e :18:62
23	94:6	4:64:3:29	2:45:6:47
24	95:5	6:43:1:50	15:26:0:59
25	94:6	11:37:13:39	11:27:0:62
26	61:39	41:28:18:13	Not determined
27	racemic	24:76 ^d	20:80

^a **P:M** ratio was the ratio of the (**SP+RP**):(**SM+RM**) of the starting thiohydantoin. Since this ratio did not change during the aldol reaction and the enantiomers of **P** isomers were formed from the **M** ones, it gave the enantiomer ratio of the aldol reaction.

^b dr was obtained from the integrations of the singlets observed for the hydrogen at the benzylic carbon around 5 ppm in ¹H NMR spectrum taken in CDCl₃ after the reaction without any purification.

^c dr was obtained from the integrations of the singlets observed for the hydrogen at the benzylic carbon around 5 ppm in ¹H NMR spectrum taken in CDCl₃ after the precipitation.

^d Since the product has no axial chirality, the diastereomers are **SS*&RR*** as the major isomer and **SR*&RS*** as the minor one .

^e **RPS*** and **SPR*** could not be separated by ¹H NMR in CDCl₃.

^f **RPR*** and **SPS*** could not be separated by ¹H NMR in CDCl₃.

Since these isomer ratios are different from the **S:R** ratios of the starting thiohydantoin ring (44:56 for **2**, 94:6 for **3** and 94:6 for **4**) the first mechanism, which includes the formation of the chiral lithium species where the product ratio should be the same with the reactant ratio (Figure 1.6), was eliminated and it was concluded that the aldol reaction follows the enolization mechanism (Figure 3.51).

In the enolization mechanism (Figure 3.51), the major isomers formed due to the attack from the less hindered side of the **P** and **M** enolates are **SPS*&SPR*** and their enantiomers **RMR*&RMS***. The minor ones, which are formed because of the attack

from the more hindered side, are **RPS*** & **RPR*** and their mirror images **SMR*** & **SMS***. If the formed enolate is protected from the side where the *o*-aryl substituent is present by 100% towards the electrophilic attack of benzaldehyde, only the isomers **SPR*** & **SPS*** from the **P** and their enantiomers, **RMS*** & **RMR*** from the **M** are expected to form. However if the protection is less than 100%, all of the isomers should be seen in the ^1H NMR spectrum of the crude products.

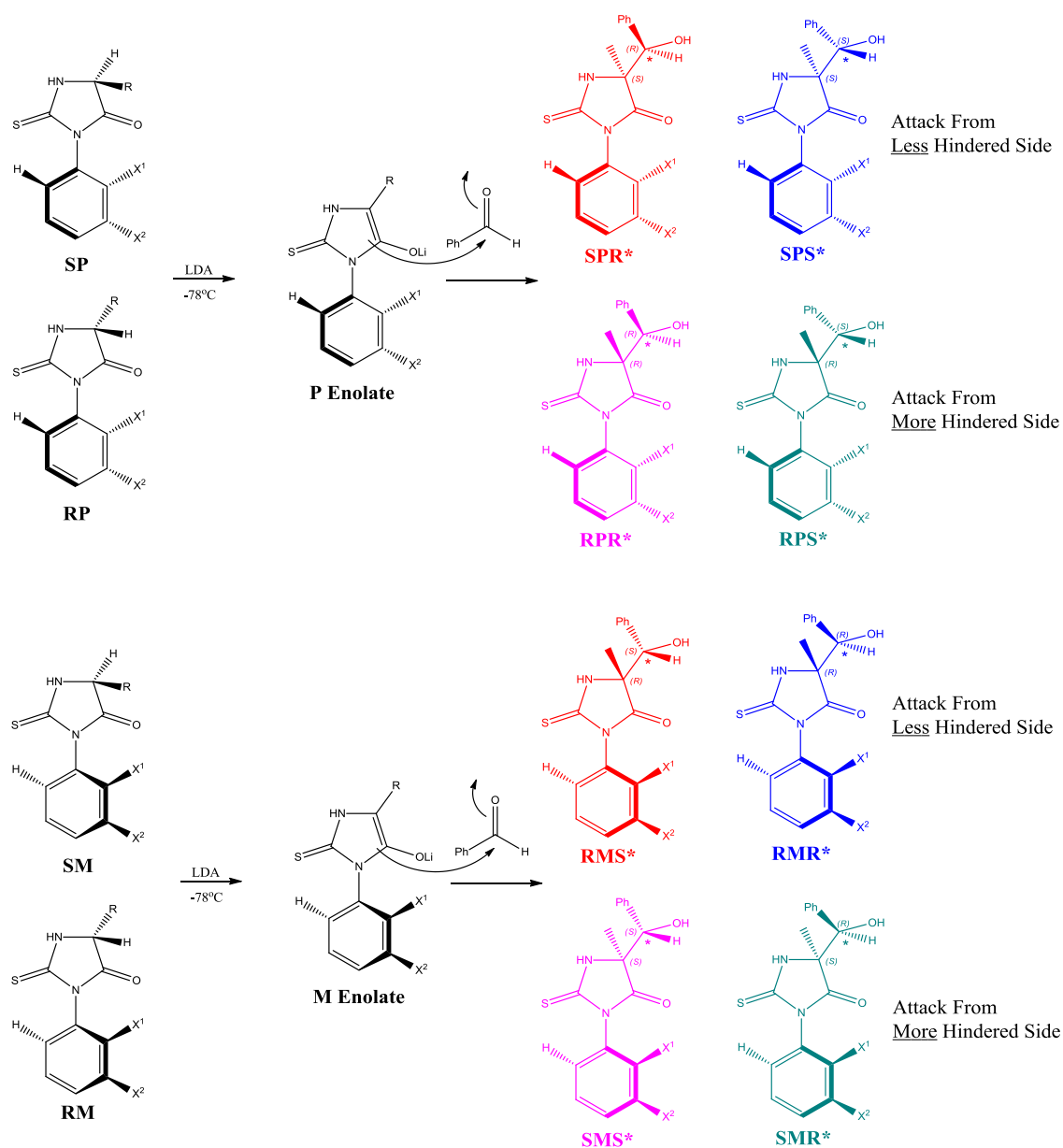


Figure 3.51. The possible stereoisomers of aldol products.

The ratio of **SPS*:****SPR*** should be the same with the one of **RPS*:****RPR*** because if benzaldehyde is attached selectively while forming **SPS*** and **SPR***, it has to have the same selectivity for producing **RPS*** and **RPR***. Based on this idea and the results obtained for compound **21** where the large phenyl ring is preferentially in equatorial position, the assignments were done for the axially chiral aldol isomers observed by ¹H NMR. The singlet in the most upfield should belong to **SPS*** while the one next to it should be **RPR***. The singlet which appears most downfield belongs to **RPS*** and the other belongs to **SPR***. When the ratios between **SPS*:****SPR*** and **RPR*:****RPS*** were compared, similar ratios between these two pairs, 65:35 and 63:37 for **16**, 90:10 and 91:9 for **17**, 91:9 and 92:8 for **18**, 71:29 (**SPS*:****SPR***) for **19** (no **RPR*:****RPS*** were produced) were found. That means the isomers from the most upfield to the most downfield is **SPS***, **RPR***, **SPR*** and **RPS*** (and also their enantiomers), respectively. The observed diastereomer ratio (79:21) for **21**, which is due to the selective attachment of benzaldehyde resulting from preferred equatorial position, forming **SS*:****RR*** more than **SR*:****RS***, is obtained higher for most of the axially chiral derivatives which is given by the ratio of the sum of **SPS*** and **RPR*** to that of **SPR*** and **RPS*** determined as 64:36 for **16**, 90:10 for **17**, 91:9 for **18** and 71:29 for **19**. When an *o*-substituent is present, it may cause a larger steric hindrance for the axial position and this favors the formation of the **SPS*:****RPR*** in which the aromatic ring is in equatorial position.

The diastereomer ratio of **20**, however, was observed opposite to what expected from the mechanism, ie **RPR*** was produced as the major product formed due to the attack from the more hindered side (Figure 3.50e). The reason for that may be attributed to the attraction between the phenyl group of the benzaldehyde and the naphthyl group at N-3 of the thiohydantoin ring. When the electrophile is attached to the C5 from the same side of the naphthyl group at N3, forming **R** chiral center at C5, they are closer to each other, leading to more π - π attraction between the two aromatic rings (Figure 3.52). This is thought to be the dominant effect on the formation of **R** configuration at C5 of the heterocyclic ring. The per cent ratio for forming **R** chirality over the **S** one is 62%.

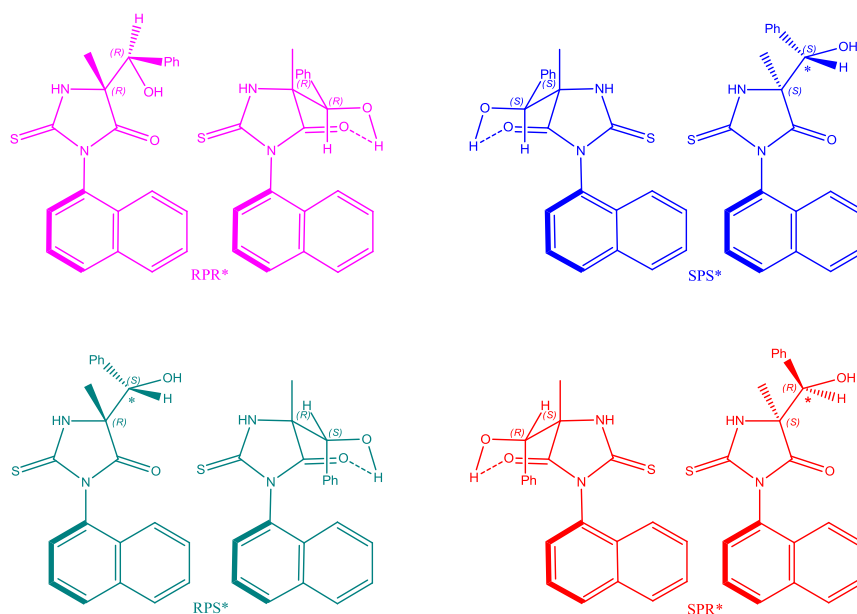


Figure 3.52. The proposed attraction between the phenyl and naphthyl ring *via* π - π stacking when the six-membered ring *via* H-bonding between –OH group and the carbonyl oxygen is formed.

The degree of protection by the *o*-substituent was determined by the per cent ratio of the sum of **SPS*** and **SPR***, formed due to the attack from the less hindered side, over the sum of **RPR*** and **RPS***, produced by the attack from the more hindered side. 65:35 for **16**, 77:23 for **17**, 75:25 for **18** and 100% for **19** were found from the integrations of the singlets around 5 ppm in ^1H NMR spectra of each crude compounds (Figure 3.50 and Table 3.4) in CDCl_3 . These ratios show that the smallest halogen, fluoro, protects the least towards the electrophilic attack while the bigger substituents hinder their side more than their fluoro analogues and there is no difference between chloro and bromo derivatives in terms of face selectivity of the electrophilic attack. However, the protection of the halogen reaches to a maximum for the biggest halogen, *iodo*, in which full protection was seen.

The enantiomer ratios of the aldol products were determined by the **P:M** ratio of the starting thiohydantoins because the formation of the enantiomers of the **P** products is due to the presence of the **M** enolate. It was assumed that between **P** and **M** isomers there is no rotation around the chiral axis at -78°C , ie the starting **P:M** ratio should not change

during the reaction at this temperature. For **3-6** **P:M** ratio ranges from 89:11 to 97:3 and hence, er of the aldol reaction varies from 89:11 to 97:3 (Table 3.4).

It was concluded that at the end of the aldol reaction of 5-methyl derivatives (**16-21**) face selectivity for the benzaldehyde addition was observed due to the preferred position (equatorial position in the six membered ring formed *via* an intramolecular H-bond between the hydroxyl and the carbonyl) of the phenyl ring at the newly formed chiral center. In addition to this selectivity, the expected protection of the *o*-substituent towards the electrophilic attack was proved and the best result, in which 100% protection was obtained, was seen for the iodo derivative **5**, could be used for a stereoselective aldol reaction. Apart from this, the π - π interaction between phenyl and naphthyl rings is responsible for the reverse selectivity at C5 of the heterocycle observed for the compound **20**. In terms of enantioselectivity, it was found that the high presence of **P** isomer of the starting thiohydantoin is very important because **P:M** ratio determines the er for the aldol reaction.

The aldol reactions of 5-isopropyl-3-(*o*-aryl)-2-thiohydantoin derivatives (**22-27**) were carried out from the modified procedure done for the 5-methyl derivatives (Figure 3.46). Here, the reaction times which are 1 hour for the abstraction of α -hydrogen and 2 hours for the addition of the benzaldehyde were changed. The reaction was firstly tried with axially chiral compound **10** which has a moderate size chloro substituent on the aryl ring and high **P:M** ratio.

The aldol reaction of 5-isopropyl-3-*o*-chloro-2-thiohydantoin (**23**) was carried out under different conditions summarized in Table 3.5. The first trial is the same procedure used for the 5-methyl derivatives in which benzaldehyde reacted with the formed enolate for 2 hours at -78°C after deprotonation of the α -hydrogen by LDA for 1 hour at -78°C (Table 3.5, Trial 1). When the ^1H NMR spectrum of this reaction was taken without any purification, it was observed that the ratio of the singlets around 5 ppm, which belong to the hydrogen at the newly formed chiral center of the aldol products, with the doublets

around 4 ppm, which belong to the hydrogen at C-5 of the starting material, is the 50:50 (Table 3.5 and Figure 3.53). This means that the reaction is not completed under these conditions. Firstly, the reaction time for binding benzaldehyde was increased because the bulkier isopropyl group at C-5 was expected to make the approach of the electrophile more difficult compared to the methyl group. In the second trial, LDA was made to react with compound **10** for 1 hour at -78°C and then benzaldehyde was reacted for 7 hour at -78°C (Table 3.5, Trial 2). When the sample taken from the reaction mixture was analyzed by HPLC with a chiral stationary phase, the peaks at 26 and 39 minutes belonging to the starting thiohydantoin were seen (Figure 3.54a), ie there was still reactant in the reaction medium. In this case, the reaction temperature was raised and the reaction was carried out for another 2 hours from -40°C to -11°C. ¹H NMR spectrum (Figure 3.55) and HPLC chromatogram (Figure 3.54b) showed that the starting thiohydantoin still remained at the end of the reaction. The increase in the reaction time and temperature for the addition of the electrophile raised the yield from 50% to 72% but the selectivity was not changed. (Table 3.5).

Table 3.5. The reaction conditions for the synthesis of compound **23**.

Trials	Rxn with LDA	Rxn with benzaldehyde	% product Distribution	Remaining (RP+SM):(SP+RM) reactant after rxn	Product:Reactant
1	1h, -78°C	2h, -78°C	10:60:1:29	33: 67	50:50
2	1h, -78°C	7h, -78°C and 70 min, -40°C to -11°C	4:64:3:29	15:85	72:28
3	2h, -78°C	6.5h, -78°C	4:86:trace:9	22: 78	52:48
4	1h, -40°C	4h, -40°C and 4h, -25°C to 0°C	No desired product		
5	1h, -78°C	6h, -78°C	10:65:1:24	32:68	56:44

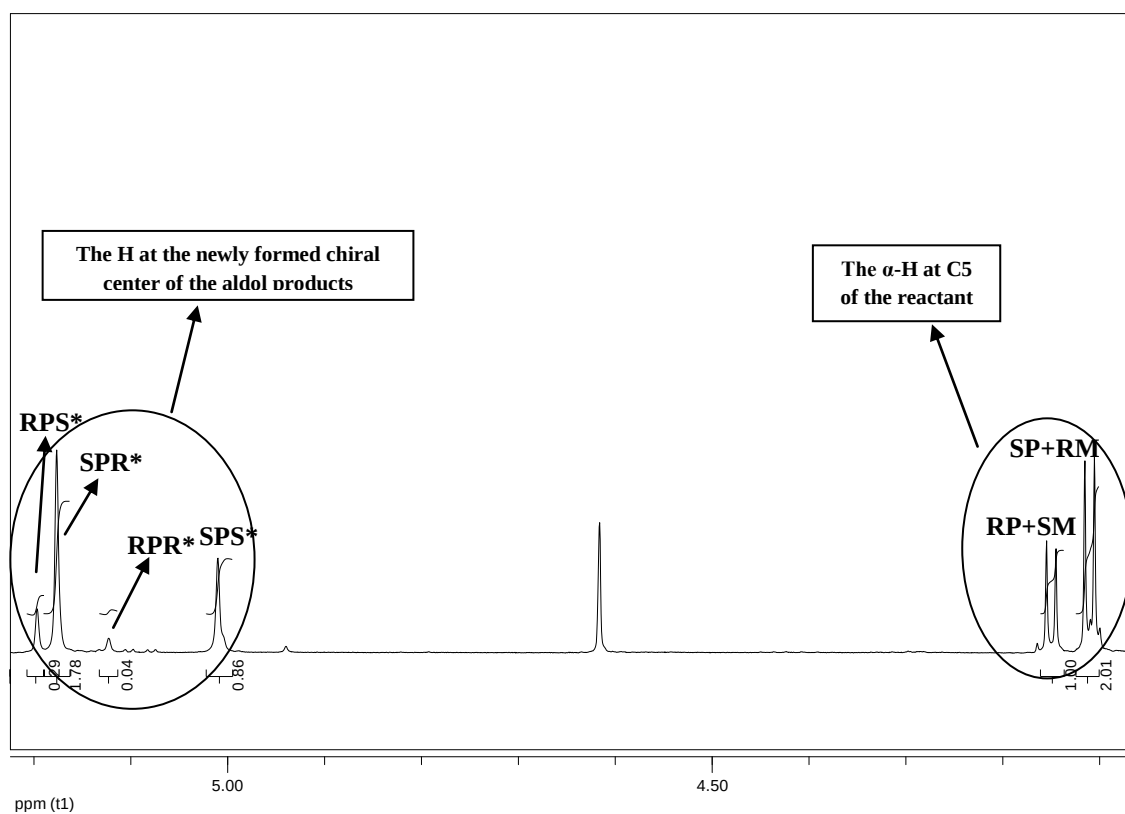


Figure 3.53. Partial ^1H NMR spectrum of trail 1 for compound **23**.

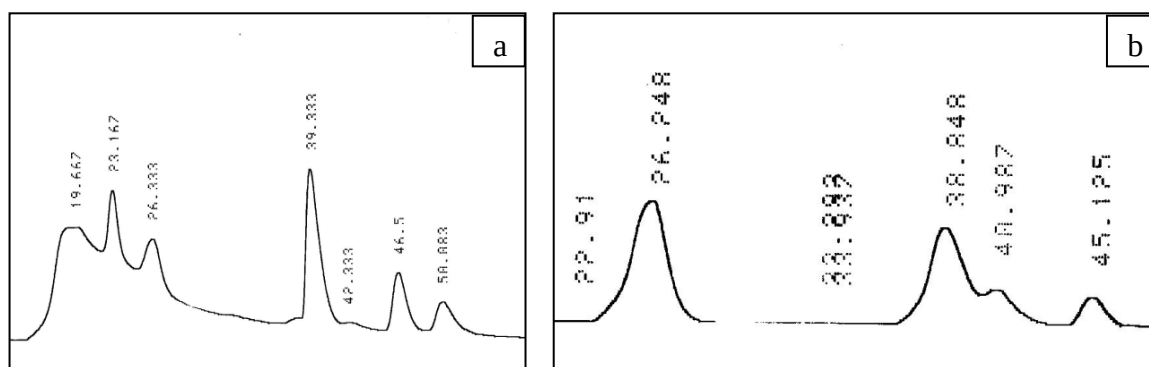


Figure 3.54. HPLC chromatogram for following the synthesis of compound **23**, benzaldehyde addition a) after 4 hours at -78°C , b) after 2 hours from -40°C to -11°C (at the end of the reaction).

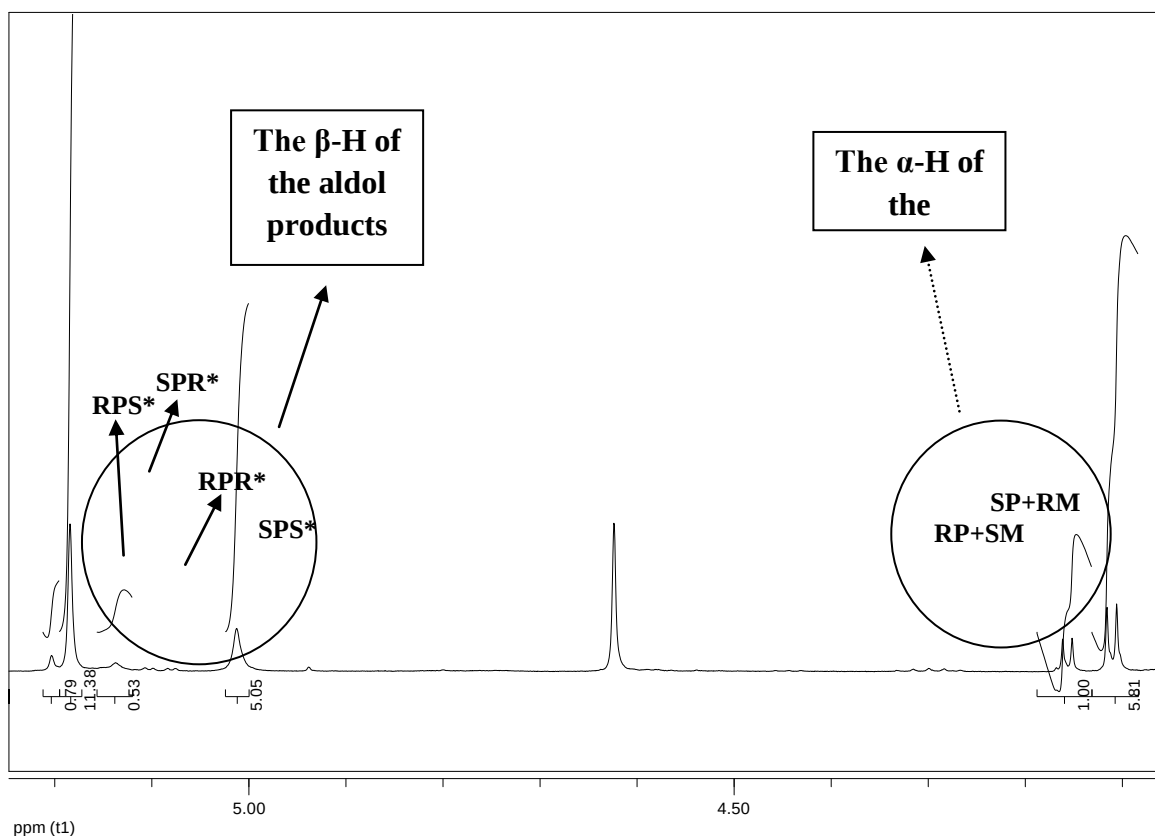


Figure 3.55. Partial ^1H NMR spectrum of trail 2 for compound **23**.

In order to gain better selectivity and yield for aldol products, the reaction temperature was not raised but the reaction time for LDA was extended to 2 hours and that for benzaldehyde to 6.5 hours at -78°C (Table 3.5, trial 3). At the end of the reaction the selectivity was improved while the yield remained almost the same-as that of trial 1. One of minor isomers did form in trace amount and the isomer ratio was obtained as 4:86:trace:9 by per cent (Figure 3.56 and Table 3.5). Although the selectivity was improved, the reaction was still not completed because in HPLC and ^1H NMR there were still peaks belonging to the reactant. The starting thiohydantoin could be removed by precipitation from diethyl ether&petroleum ether mixture.

The reason for incomplete reaction was thought to be the low temperature. Therefore, trail 4 in which LDA was treated for 1 hour with 5-isopropyl-3-*o*-chloro thiohydantoin (**10**) at -40°C and benzaldehyde for 4 hours without raise in temperature was

tried. When the reaction was followed by HPLC with a chiral stationary phase, it was seen that the starting thiohydantoin was still present in the reaction medium (Figure 3.57a). With the aim of finishing starting material, the reaction temperature was raised from -25°C to 0°C and the reaction continued for another 4 hours between this temperature range (Figure 3.57b). However, the ^1H NMR spectrum of this product taken at the end of the reaction without any purification showed no singlets between 5-5.2 ppm belonging to the aldol product but there was doublets corresponding the starting thiohydantoin which was still present. This means that the reaction was not completed and the desired products did not form under these conditions because at such a high temperature the formed enolates would not survive and not give aldol products.

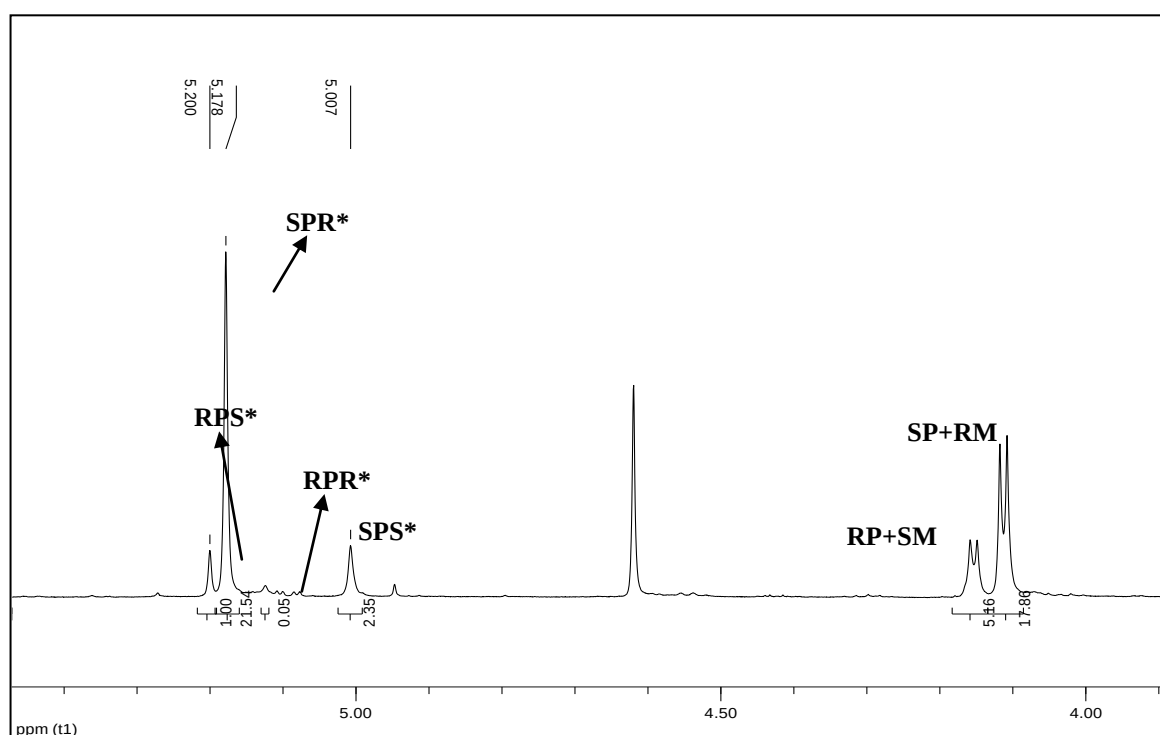


Figure 3.56. Partial ^1H NMR spectrum of trail 3 for compound **23**.

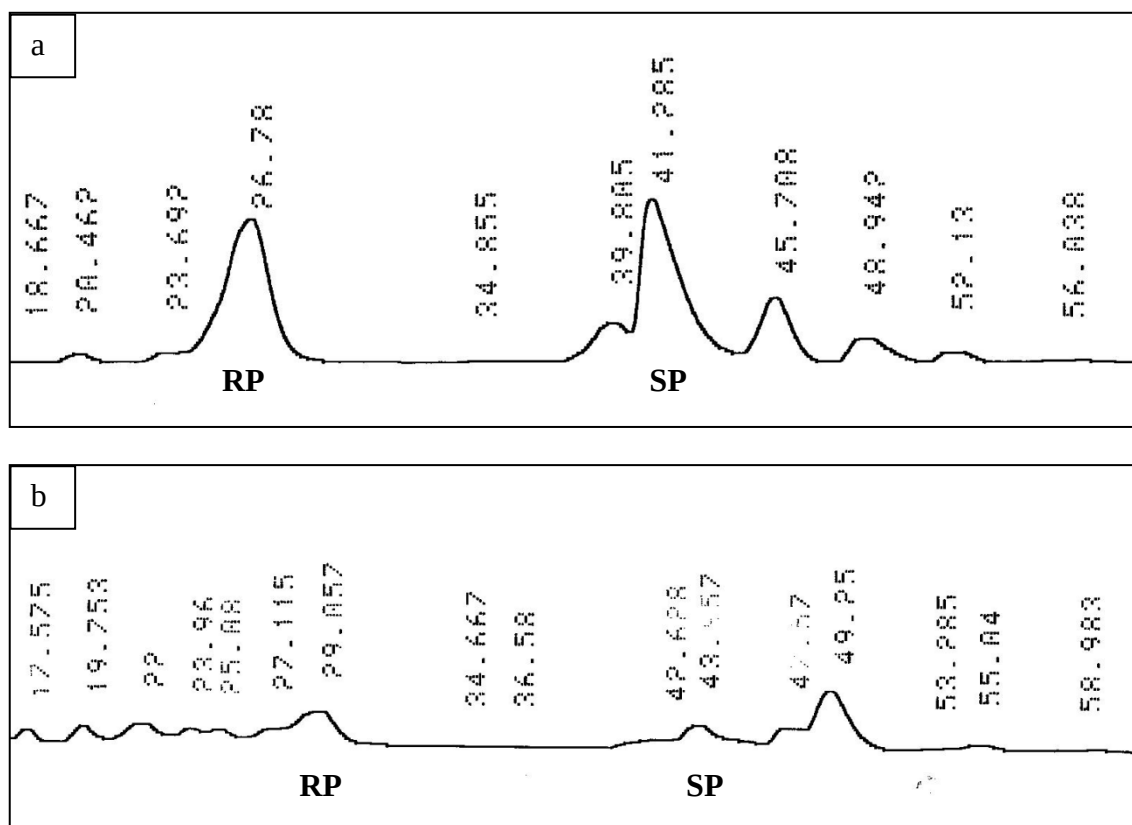


Figure 3.57. HPLC chromatogram for following the synthesis of compound **23** in trial 4, benzaldehyde addition a) after 4 hours at -40°C , b) after 4 hours from -25°C to 0°C (at the end of the reaction).

The isomeric products of **23** were assigned with the help of the results obtained for its methyl analogues (compound **17**) (Figure 3.46) in which **SPS*** was the major product. Here, the major product is **SPR***, in which the isopropyl group at C5 and the phenyl ring at the newly formed chiral center are *transoid* with each other. Both large groups prefer to be on different sides because of the steric reasons although they are present in axial position (Figure 3.58).

In addition, it was found that the ratio of **(RP+SM)/(SP+RM)** of 5-isopropyl-3-*o*-chloro thiohydantoin (**10**) remained at the end of the reaction was found to be 15:85 (Table 3.5) which was different from the starting ratio of 54:46 (Table 3.2). **(RP+SM)** was present less than **(SP+RM)**, ie the former reacts more than the latter. In **(RP+SM)**, the

hydrogen at C-5 is *transoid* with *o*-chloro group at N-3 while in (**SP+RM**) it is *cisoid* and this can make the abstraction of hydrogen of **RP** easier than that of **SP**. However, if this was the reason, the similar results should have been obtained with the same reaction of 5-methyl-3-*o*-chloro thiohydantoin (**3**) in which there was no starting material after the addition of benzaldehyde for 2 hours at -78°C followed by the abstraction of α -hydrogen for 1 hour at -78°C . Therefore, the reason for such a different ratio between the remained starting isomers at the end of the reaction should be related with the group at C-5. Either the large isopropyl group hinders the abstraction of hydrogen at C-5 by LDA or it may hinder the approach to benzaldehyde so that it cannot bind to the formed enolate.

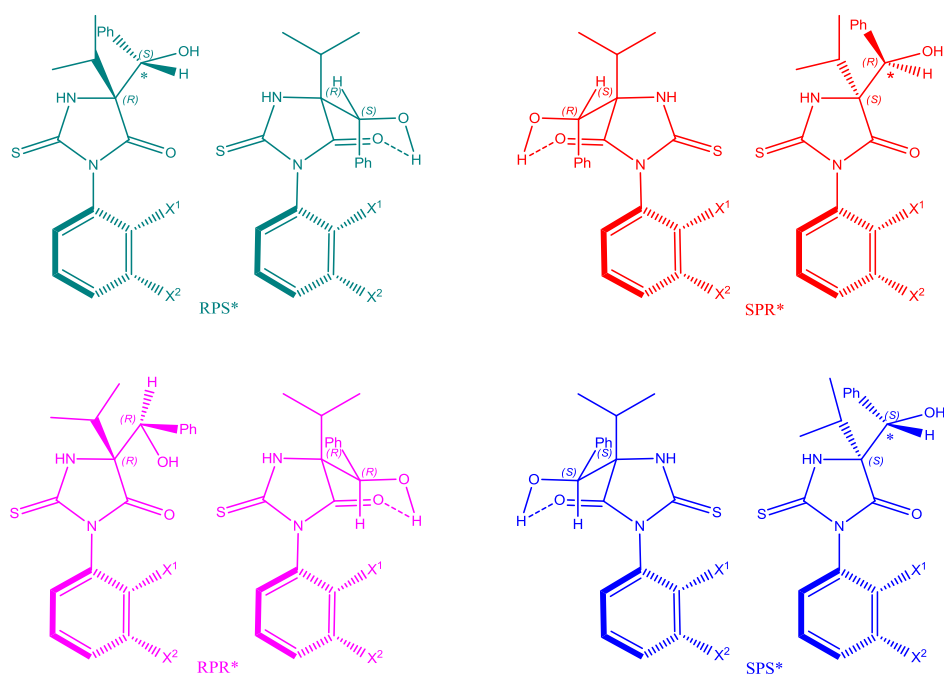


Figure 3.58. The possible aldol isomers of the 5-isopropyl derivatives (**22-27**).

With the findings obtained from these experiments, it was concluded that the aldol reaction of 5-isopropyl derivatives (**22-27**) should be carried out for longer reaction times than that of 5-methyl ones (**16-21**) and at -78°C . The best selectivity was obtained with a moderate yield. However, the yield can be enhanced if selectivity is sacrificed (Table 3.5). The isomer assignments were done in similar way used for compounds **16-21**.

After modifying the reaction conditions for axially chiral 5-isopropyl-3-*o*-chloro thiohydantoin (**10**), the aldol reaction of racemic compound **14**, in which there is no chiral axis, was carried out in order to compare the results with the ones obtained for the reaction of compound **7**. LDA was allowed to react for one hour and benzaldehyde for six hours without any increase in temperature. Figure 3.59 shows the ^1H NMR signals of the hydrogen at the benzylic carbon of the aldol product **27** (Figure 3.46). **SS* & RR*** isomers are the major product and **SR* & RS*** are the minor ones with the ratio of 76:24 by per cent. This result is similar to the one obtained for the methyl derivative **21**, where the diastereomeric ratio was 79:21. In addition, the yield of the synthesis of compound **27** was found as 89% from the ratio of the sum of the integrations of the singlets at 5.27 ppm and 5.11 ppm, corresponding to the product isomers, to the integration of the doublet at 4.18 ppm, belonging to the starting thiohydantoin (**14**). These results indicate that the selectivity for the attachment of benzaldehyde forming new chiral center for **7** and **14** is not affected by the substituent at C5. However, it has an influence on the yield because the reaction of compound **7** was completed within two hours while that of compound **14** was finished with only 89% yield although the reaction time, in this case, was increased to six hours. This yield is larger than that obtained for the synthesis of **23** which has axial chirality. Therefore, the reason for incomplete reaction of the axially chiral isopropyl derivatives (**9-13**) to such an extent (yields for **10** between 50%-72%) was thought to be the steric hindrance brought by the *o*-substituent of the axially chiral derivatives.

The aldol reaction of compounds **9**, **11**, **12** and **13** (Figure 3.1) were carried out by the reaction of LDA at -78°C for 1 hour and the addition of benzaldehyde at -78°C for 6 hours. The ^1H NMR spectrum of the crude compound **22** (Figure 3.46) taken in CDCl_3 (Figure 3.60) showed that three singlets were formed while four was expected and the major one at 5.02 ppm is **SPS*** as obtained for its methyl derivative, **16**. Due to the results found for **16** and the expectation that if **SPS*** is formed, **SPR*** should also be produced, it was reasoned that the broad singlet seen in most downfield at 5.19 ppm (Figure 3.60) corresponds to coincided signals of **RPS*** and **SPR*** and the singlet in the middle of two signals at 5.11 ppm belongs to **RPR***. In this way, the ratio of the sum of the singlets of **SPS*** at 5.02 ppm and **RPR*** at 5.11 ppm, in which the phenyl ring is present in the equatorial position, to the singlet in most downfield at 5.19 ppm corresponding to

RPS*&SPR* is 75:25 by per cent. This is the ratio obtained for racemic **27**. The yields of the reactions for **27** and **22** are also similar, which are 89% and 84%, respectively. Therefore, it was concluded that in the aldol reaction compound **9** reacts similarly to compound **14**.

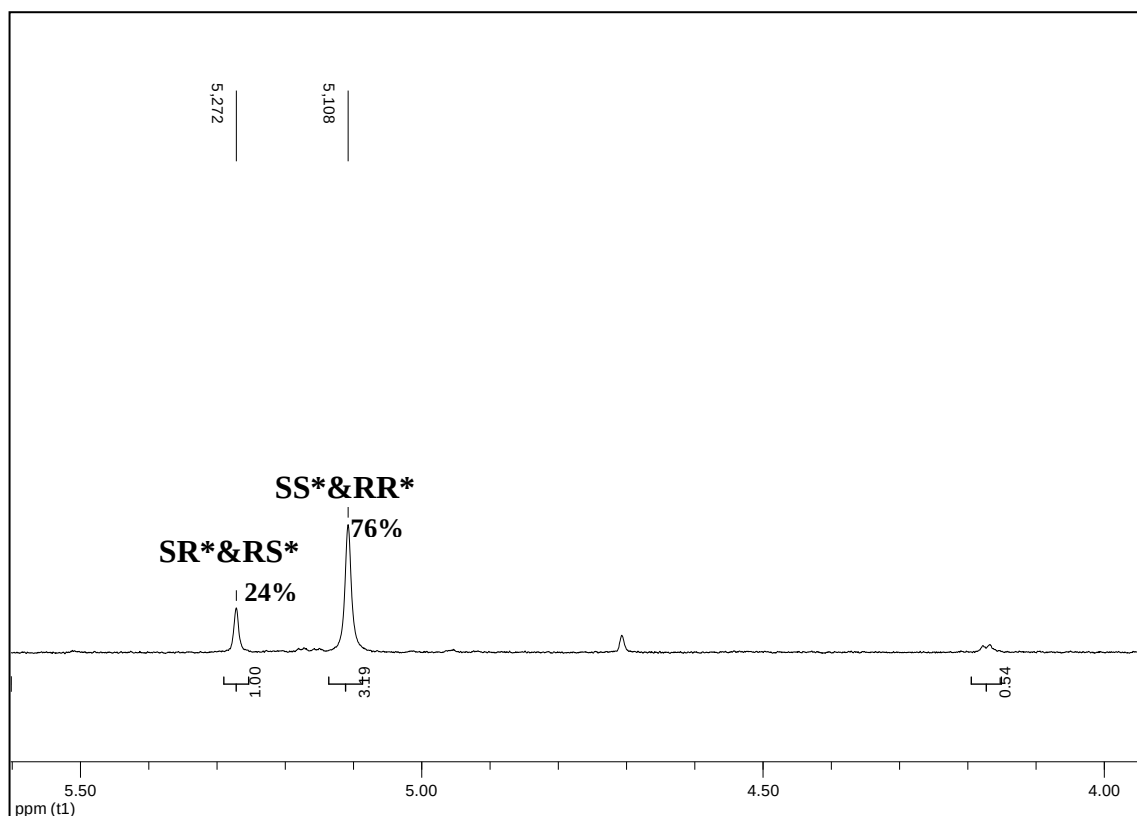


Figure 3.59. Partial ^1H NMR spectrum of compound **27**.

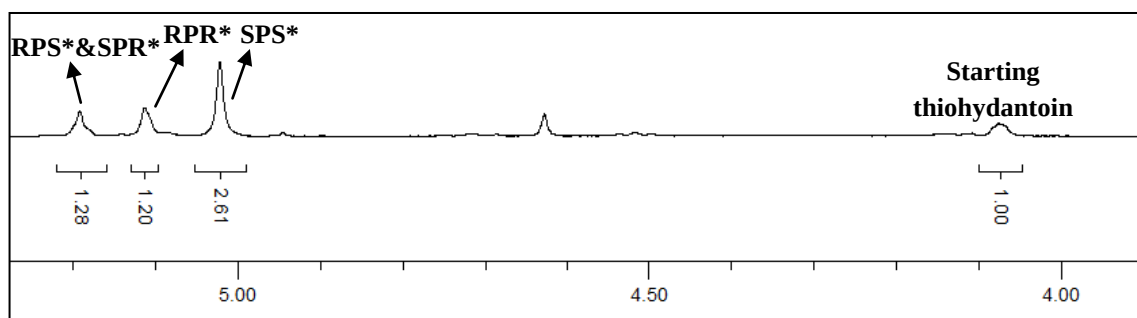


Figure 3.60. Partial ^1H NMR of compound **22** in CDCl_3 .

The partial ^1H NMR spectrum of compound **24** in CDCl_3 obtained after the reaction without any purification (Figure 3.61) shows four singlets at 5.20, 5.17, 5.16 and 5.02 ppm with the per cent ratio of 6:43:1:50, respectively, showing the formation of the aldol isomers. When the assignments were done with the help of the ones for **18** (the methyl analogue), it was seen that **RPS***, **SPR***, **RPR*** and **SPS*** (from the most downfield to the most upfield) were formed. Here, the selectivity observed for the attachment of benzaldehyde was lost but the selective electrophilic attack from the less hindered side was enhanced from 75% to 93%. In addition, the yield was calculated as 56%.

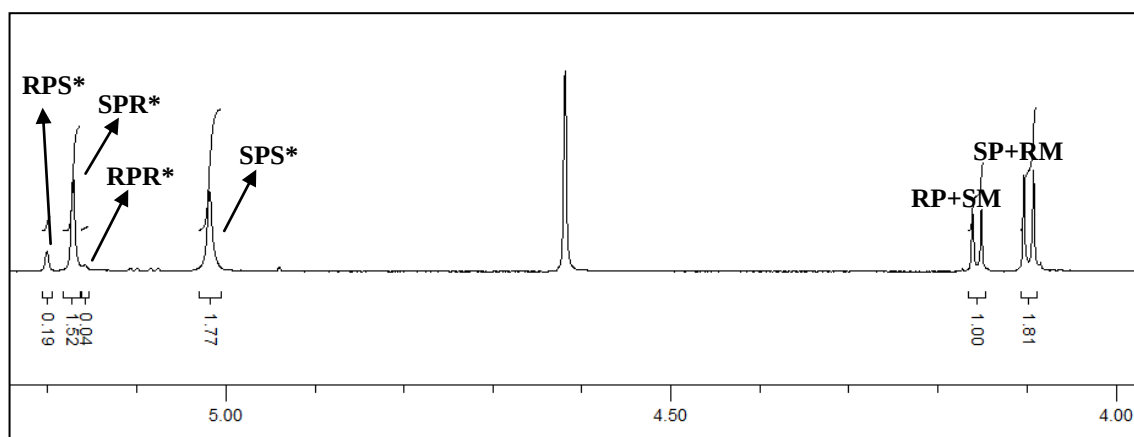


Figure 3.61. Partial ^1H NMR of compound **24** in CDCl_3 .

The aldol reaction of compound **12** (Figure 3.1) yielded four isomers, **SPS***, **RPR***, **SPR*** and **RPS***, with the ratio of 39:13:37:11 (Figure 3.62). Here, the protection of the *o*-iodo towards the electrophilic attack is less than that observed for its methyl analogue (compound **19**) in which only the formation of **S** chiral center at C5 was seen (100% protection). This difference might be because of the larger isopropyl group. When the electrophilic attack occurs from the opposite side where *o*-iodo is present, the **S** chiral center at C5 is produced, leading to 100% protection, and the isopropyl and the *o*-iodo becomes *cisoid*. However, when the attack takes place from the same side, **R** chirality at C5 is formed and these groups are *transoid*. Therefore, in addition to the attack from the less hindered side by 76% (the sum of **SPS*** and **SPR***), the one from the more hindered side was observed for compound **25** by 24% (the sum of **RPR*** and **RPS***) due to a less

steric hindrance between the isopropyl and *o*-iodo substituents when the attached electrophile produced **R** chirality at C5.

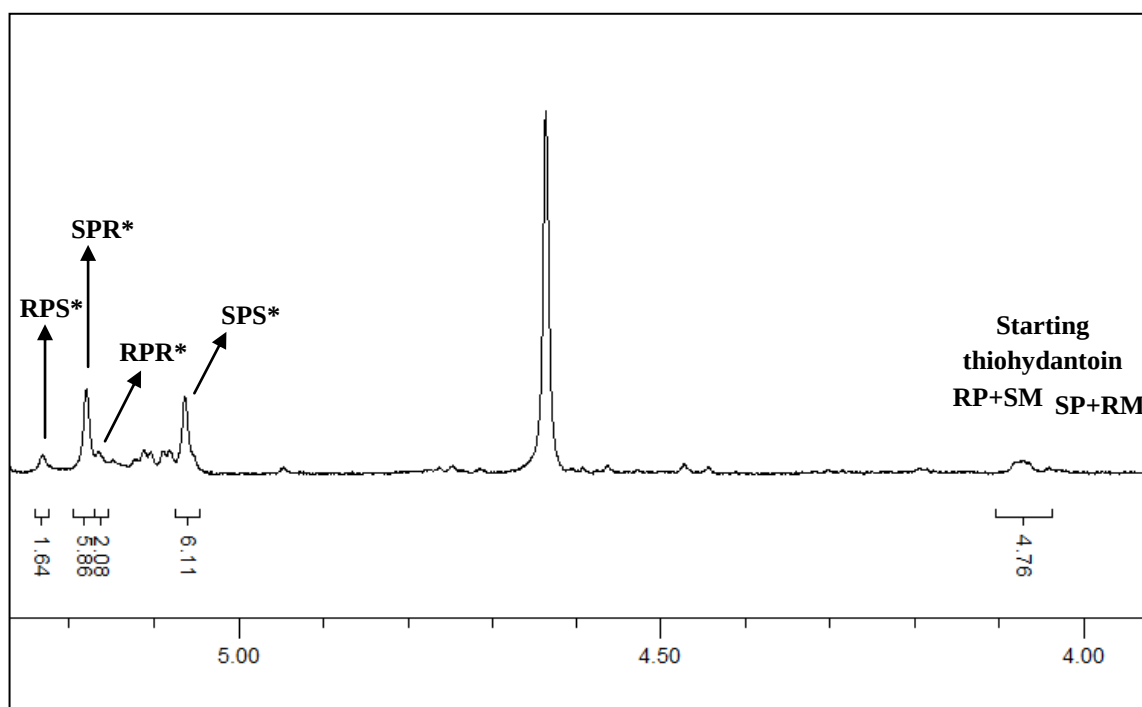


Figure 3.62. Partial ^1H NMR of compound **25** in CDCl_3 .

For compound **26**, by ^1H NMR (Figure 3.63) it was found that **RPS*** and **SPR*** were the major isomers together with their enantiomers in which the phenyl ring of the benzylic carbon prefers to be on the axial position. In this way, the naphthyl ring at N3 of the heterocyclic ring is closer to the phenyl ring and has more π - π interaction between the aromatic rings.

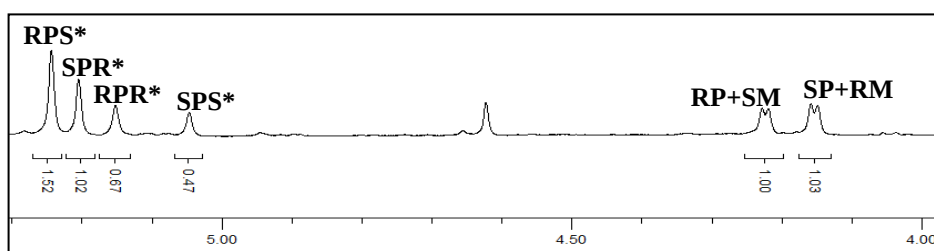


Figure 3.63. Partial ^1H NMR of compound **26** in CDCl_3 .

With all of the results obtained for the aldol reaction of the studied thiohydantoins, it was concluded that the best yield was obtained for the C5 methyl derivatives when benzaldehyde was reacted for two hours with the enolates. The reactions were complete with an 21:79 *syn-anti* selectivity. For the C5 *iso*-propyl compounds where the reactions were incomplete, the aldol products were easily purified by precipitation from ether or from a mixture of diethyl ether&petroleum ether.

When these results were compared, it was concluded that at the same reaction conditions the size of the *o*-substituent and the group at C5 affect both the yield and the isomer distribution of the aldol products. The racemic (**7** and **14**) and *o*-fluoro thiohydantoin derivatives (**2** and **9**) gave similar selectivity for the attachment of benzaldehyde, resulting in that the absence of the substituent and the presence of the small fluoro group on the aryl ring at N3 had no influence on the selectivity of the aldol reaction. For the larger groups (the *o*-chloro and *o*-bromo derivatives), as the size of the group at C5 increased, the less **RPR*&RPS*** was formed by the electrophilic attack from the hindered side. In addition the protection of the *o*-substituent at N3 towards the electrophilic attack, the large isopropyl group at C5 contributed to the selectivity of the aldol reaction. However, this effect was observed oppositely for the *o*-iodo derivatives, in which only **S** chirality was produced for the methyl analogue (**19**) while **R** chiral center was formed by 24% for the isopropyl one (**25**). This is because of the isopropyl group does not prefer to be on the same side with the large *o*-iodo group and the electrophilic attack occurred from the same side of the N3 substituent. For naphthyl derivatives, **R** chirality was preferred at C5 of the heterocyclic ring due to the more π - π interaction between the aromatic rings.

The aldol reaction of the studied thiohydantoins with 4-nitrobenzaldehyde was also carried out in order to investigate the effect of the electrophile.

3.2.2. Reactions with 4-Nitrobenzaldehyde

The procedure for the aldol reaction with 4-nitrobenzaldehyde (Figure 3.64) was the same with the one used for the benzaldehyde in which electrophile was added at -78°C (2 hours for **16-21** and 6 hours for **22-27**) and LDA was mixed with the thiohydantoin at the same temperature for 1 hour.

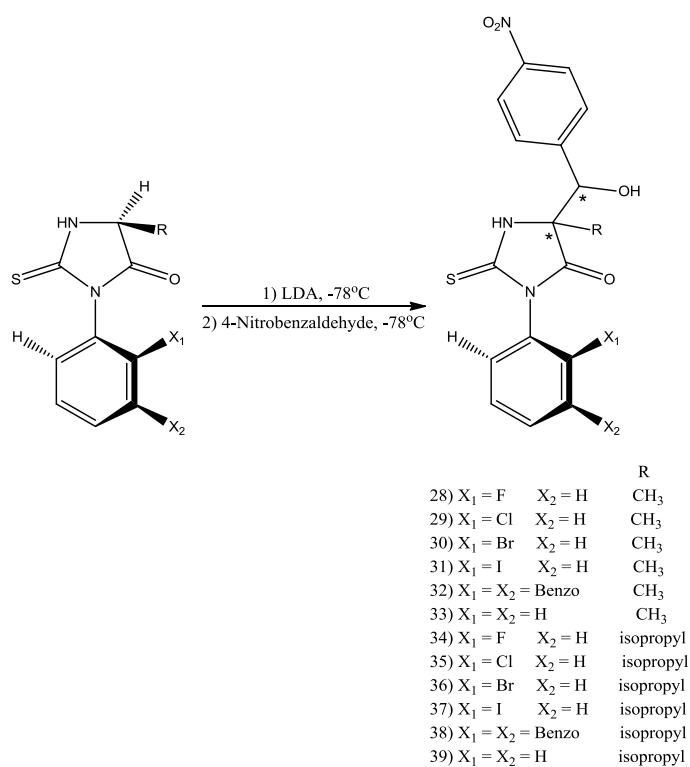


Figure 3.64. The synthesis of the aldol products (**28-39**).

The reaction firstly tried with the racemic thiohydantoin (**7** and **14**) in order to simplify the spectrum because when the reaction is completed, the product will have two chiral centers, one at C5 and one at the newly formed chiral center denoted by *, that is, two sets of peaks are expected in the ^1H NMR spectrum for **SS*&RR*** and **SR*&RS***.

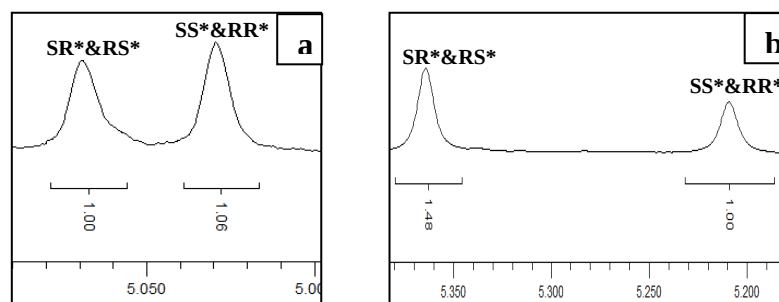


Figure 3.65. Partial ^1H NMR spectrum of compounds a) **33** and b) **39** in CDCl_3 .

Figure 3.65 shows the the partial ^1H NMR spectra in taken in CDCl_3 indicating the formation of racemic aldol products **33** and **39**. The isomer assignments were done in the same way as the benzaldehyde derivatives. The singlet in the most upfield region of the NMR spectrum belongs to **SS*&RR*** and the most downfield corresponds to **SR*&RS***. The selectivity for binding benzaldehyde (*syn-anti* selectivity) was obtained as 21:79 for **21** and 24:76 for **27** and **SS*&RR*** was the major product while **SR*&RS*** the minor one. Here, the selectivity was found as 49:51 for compound **33** and 60:40 for compound **39** which were obtained from the ratios of the two singlets around 5 ppm corresponding to the isomers of the aldol product. Since 4-nitrobenzaldehyde is a stronger electrophile, it did not show any selectivity.

The products were identified by ^1H NMR at the end of the aldol reaction of the axially chiral thiohydantoin with 4-nitrobenzaldehyde without any purification (Figure 3.66). The ^1H NMR spectrum of compound **28** taken in CDCl_3 showed the formation of **RPS*** and **SPR*** as minor products with the ratio of 13% and 12% (Figure 3.66a). The major product which was formed by 75% was assigned as **SPS*&RPR*** because if **RPS*** and **SPR*** were produced, **SPS*** and **RPR*** should also been formed. Figure 3.66b exhibits the formation of all aldol isomers of **29** and in this case **RPS*** and **SPR*** were coincided. The singlets corresponding to **RPR*** and **SPS*** were barely seen separately. The isomer ratio was determined as 50% for **RPS*&SPR***, 18% for **RPR*** and 32% for **SPS***. The partial ^1H NMR spectrum of compound **30** (Figure 3.66c) shows four singlets belonging to **RPS***, **SPR***, **RPR*** and **SPS*** from the most downfield to the most upfield with the per cent ratio of 12, 35, 15 and 38, resepectively. The selectivity for the aldehyde attachment

can be determined from the proton NMR spectrum of this derivative because this is the only spectrum in which all isomers of crude product were seen separately. The ratio of **SPS*:****SPR*** is 52:48 and that of **RPR*:****RPS*** is 56:44 by per cent, ie the selectivity for the attachment of aldehyde has been lost because 4-nitrobenzaldehyde is a strong electrophile. In Figure 3.66d **RPS*** and **SPR*** were seen separately with the per cent ratios of 7 and 33, respectively, whereas **SPS*** and **RPR*** were coincided and their ratio was determined as 60%. This coincided singlet was assigned as **SPS*** and **RPR*** since all isomers were separated after purification by precipitation from diethyl ether&petroleum ether mixture, in which the sum of the integrations of two singlets in the most upfield (14%+45%) was the same with the one seen in the most shielded region of the spectrum taken without precipitation from the mixture of diethyl ether&petroleum ether (58%). The ^1H NMR spectrum of compound **32** exhibited two separate singlets and one coincided singlet (Figure 3.66e). With the results obtained from its benzaldehyde derivative (**20**) **RPS*** and **RPR*** should be major isomers and **SPR* & SPS*** the minor ones. In addition, their ratios (**RPR*:****RPS*** and **SPS*:****SPR***) may be expected to be the same. From the NMR spectrum shown in Figure 3.66e these ratios were determined as 56:44 and 59:41, respectively. Therefore, in this case the coincided singlet should be **SPR*** and **RPR***.

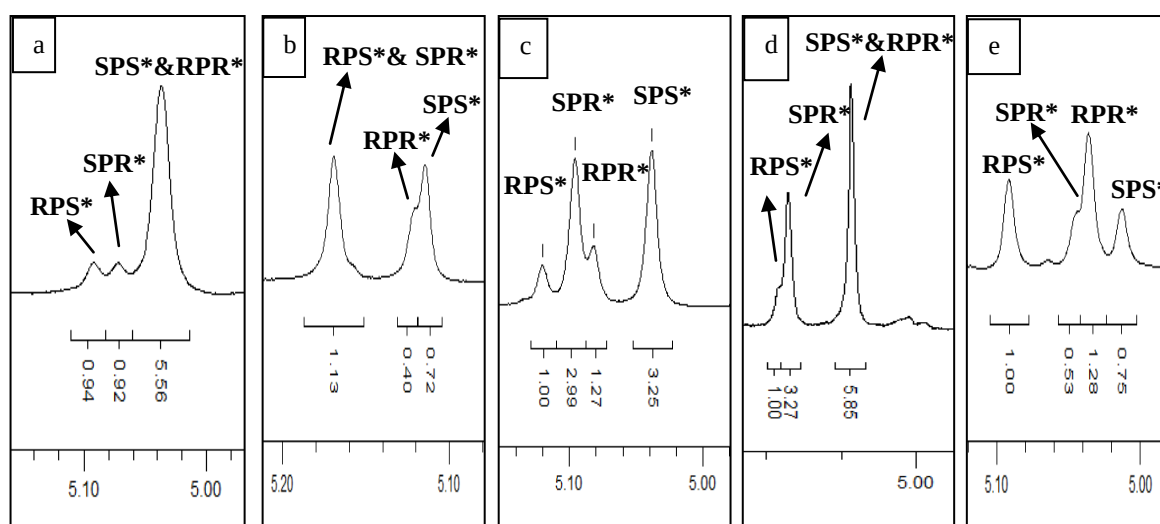


Figure 3.66. Partial ^1H NMR of crude compounds in CDCl_3 a) **28**, b) **29**, c) **30** and d) **31**, e)

32.

In Figure 3.67, the per cent ratio of the singlets of compound **34** (5-isopropyl-3-*o*-fluoro derivative) was found as 67:22:11 is shown. Since the isomer ratio of compound **39** (5-isopropyl-3-phenyl derivative) was 60:40, in which the singlet at the most downfield was **RS*&SR*** as the major isomer and **RR*&SS*** as the minor one, the singlet at 5.31 ppm was assigned as the sum of **RPS*&SPR*** having 67% and the others were **RPR*** (22%), **SPS*** (11%).

Table 3.6. Enantiomeric ratios (er) and diastereomeric ratios (dr) of the aldol reaction of the compounds **28-39**

Compounds	er (P:M) ^a	dr ^b	
		RPS*:SPR*:RPR*:SPS*	RPS*:SPR*:RPR*:SPS*
28	70:30	13:12:75 ^d	29:25:45 ^d
29	97:3	50 ^e :18:32	67 ^e :33 ^d
30	97:3	12:35:15:38	18:55 ^g :27
31	95:5	7:33:60 ^d	8:28:10:54
32	90:10	29:16:36:19	Not determined
33	Racemic	49:51 ^f	50:50
34	52:48	67:22:11	Not determined
35	94:6	22:39:14:25	22:45:8:25
36	95:5	11:23:41:25	10:26:42:23
37	94:6	7:23:21:48	14:22:34:30
38	61:39	19:27:23:31	19:30:19:32
39	Racemic	60:40	Not determined

^a **P:M** ratio was the ratio of the (**SP+RP**):(**SM+RM**) of the starting thiohydantoin. Since this ratio did not change during the aldol reaction and the enantiomers of **P** isomers were formed from the **M** ones, it gave the enantiomer ratio of the aldol reaction.

^b dr was obtained from the integrations of the singlets observed for the hydrogen at the benzylic carbon around 5 ppm in ¹H NMR spectrum taken in CDCl₃ after the reaction without any purification.

^c dr was obtained from the integrations of the singlets observed for the hydrogen at the benzylic carbon around 5 ppm in ¹H NMR spectrum taken in CDCl₃ after the precipitation.

^d **RPR*** and **SPS*** were not separated in ¹H NMR spectrum taken in CDCl₃.

^e **RPS*** and **SPR*** were not separated in ¹H NMR spectrum taken in CDCl₃.

^f Since the product has no axial chirality, the diastereomers are **SS*&RR*** as the major isomer and **SR*&RS*** as the minor one.

^g **SPR*** and **RPR*** were not separated in ¹H NMR spectrum taken in CDCl₃.

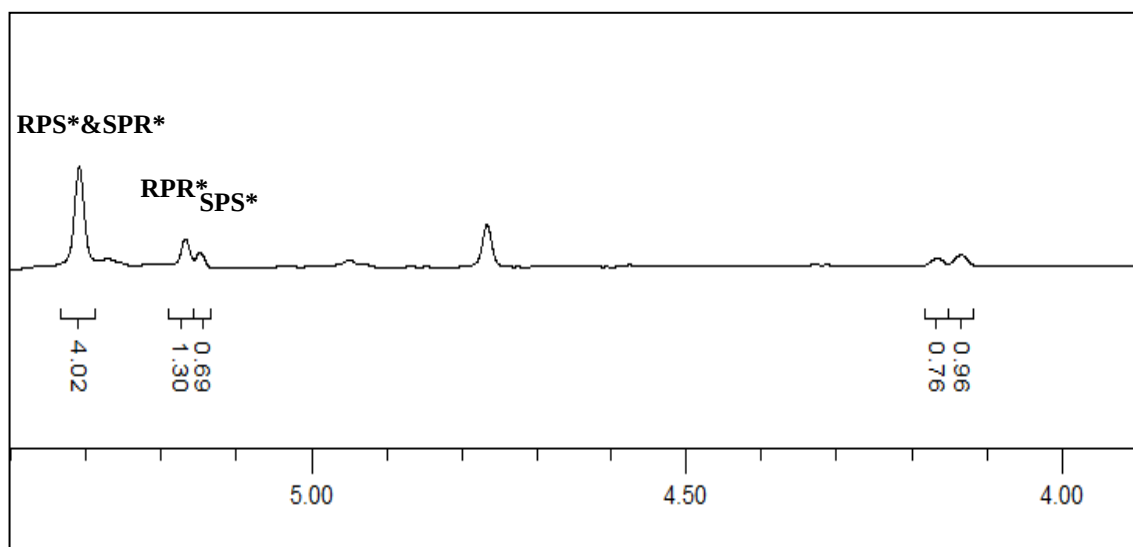


Figure 3.67. Partial ^1H NMR of compound **34** in CDCl_3 .

The aldol reaction of compound **10** (5-isopropyl-(3-*o*-chlorophenyl) thiohydantoin) with 4-nitrobenzaldehyde gave all of the aldol isomers (compound **35**) shown in ^1H NMR in Figure 3.68, with the ratio of 22:39:14:25 from the most downfield to the most upfield. With the results obtained for the benzaldehyde derivative (compound **23**), the singlets were assigned as **RPS*:****SPR*:****RPR*:****SPS***, respectively. By this assignment, the same ratio was found for that of **SPR*** to **SPS*** and that of **RPS*** to **RPR***, which is 64:36 by per cent. This supports the result obtained for the compound **39** (5-isopropyl-3-phenyl derivative) in which the selectivity for the attachment of the electrophile was found as 60:40 when a strong electrophile has been used. Also, in this case, *o*-chloro substituent at N3 has less protection against the electrophilic attack from the more hindered side forming **R** chiral center at C5 more because the ratio of the sum of **R** isomers increased to 36%, which was 7% for benzaldehyde derivative (compound **23**). This points to the fact that the use of strong electrophile reduces the protection of the chloro substituent since the electrophilic attack occurs from both sides. Therefore the selectivity for the approach from the more hindered side was increased. However, the yield was enhanced to 77%, which was 52% for compound **23**.

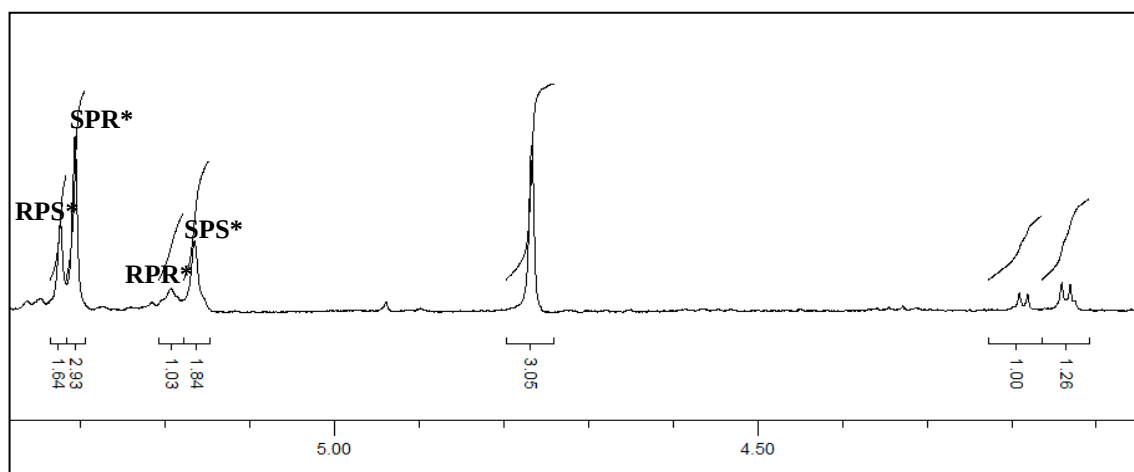


Figure 3.68. Partial ^1H NMR of compound **35** in CDCl_3 .

When the reaction was tried with compound **11** (5-isopropyl-3-(*o*-bromophenyl)thiohydantoin), the isomer ratio of the aldol product (compound **36**) was obtained as 11:23:41:25 (Figure 3.69) and they were assigned as **RPS*:SPR*:RPR*:SPS*** from the most downfield to the most upfield with the help of the results obtained for the benzaldehyde derivatives. In addition, the yield was enhanced to 68%, which means when a strong electrophile was used, the yield can be increased if the selectivity is sacrificed. By the use of the strong electrophile, the rate of the attachment of the electrophile from the more hindered side increased and **R** chiral center at C5 was formed with the same ratio of **S** one, 52%.

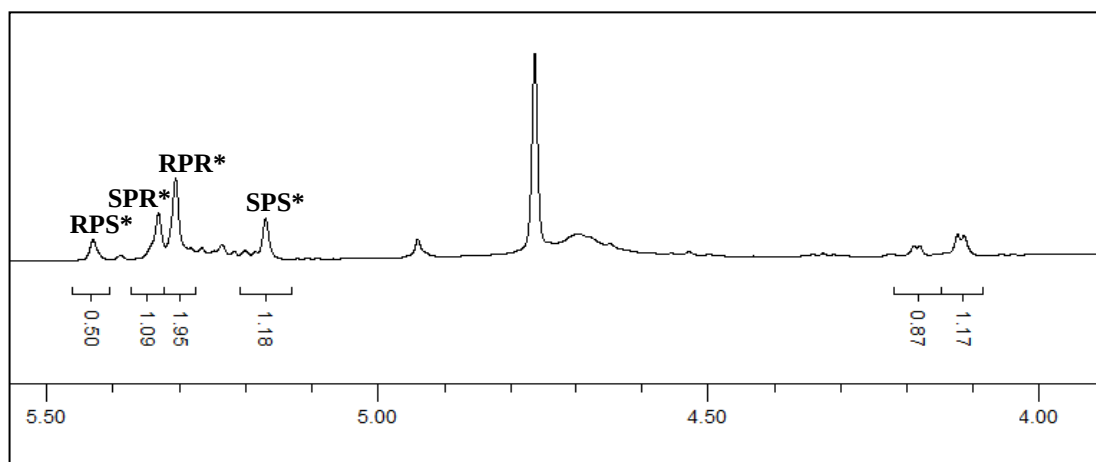


Figure 3.69. Partial ^1H NMR of compound **36** in CDCl_3 .

Figure 3.70 exhibits the formation of all isomers of the 5-isopropyl-3-*o*-iodophenyl derivative (**37**), **RPS*:****SPR*:****RPR*SPS*** with the per cent ratio as **7:23:21:48**, respectively. This shows that **R** chirality at C5 was produced by 28%, as seen for compound **25** in which **R** at C5 was formed by 24%.

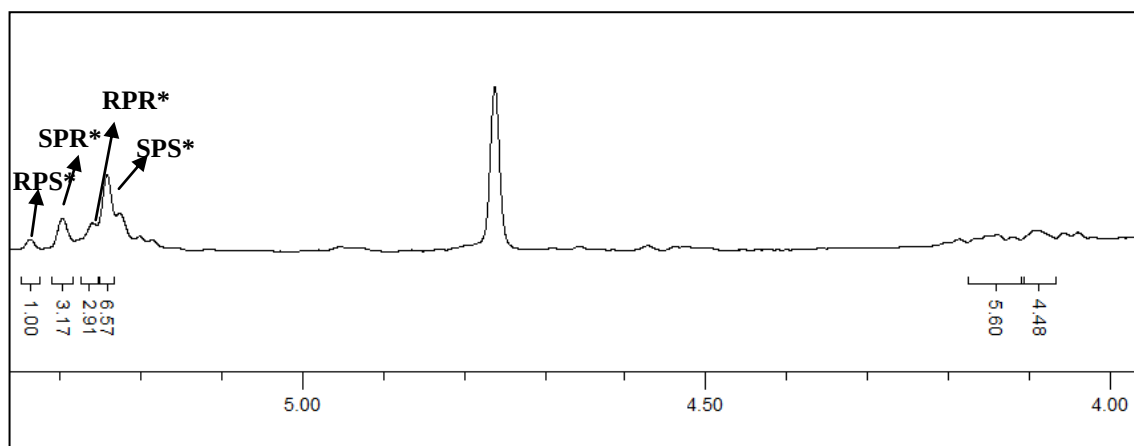


Figure 3.70. Partial ^1H NMR of compound **37** in CDCl_3 .

Figure 3.71 shows the formation of all isomers of the compound **38**, where **SPS*** and **SPR*** were formed more than **RPR*** and **RPS***, which is opposite to the findings for the previously synthesized naphthyl derivatives (**20**, **26** and **32**). The per cent ratio was determined as 19:27:23:31 for **RPS*:****SPR*:****RPR*:****SPS***.

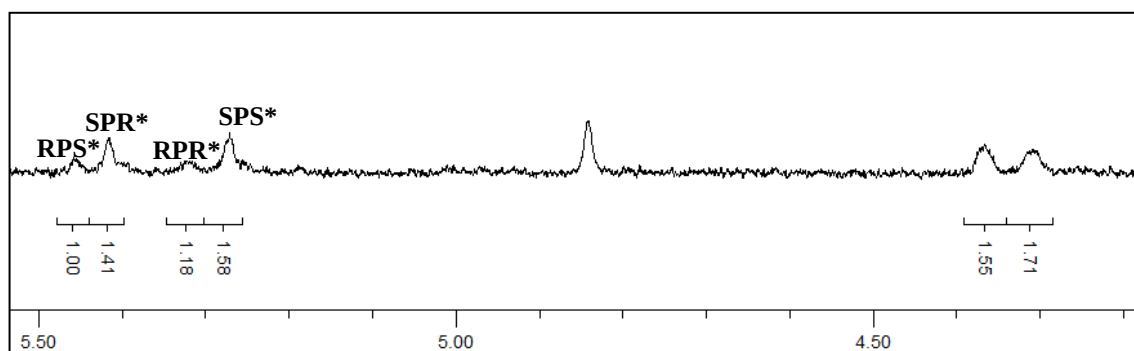


Figure 3.71. Partial ^1H NMR of compound **38** in CDCl_3 .

The use of a strong electrophile decreases the selective attachment of the aldehyde from the less hindered site and in this way increases the formation of **R** chiral center at C5. Therefore it was concluded that for the aldol reaction of the studied thiohydantoins, for high enantioselectivity in addition to the high starting ratio of **P** to **M** isomer ratio, an electrophile with a moderate power should be used.

3.3. Reduction Reactions of 5-Methyl-3-(*o*-aryl)-2-thiohydantoins and 5-Isopropyl-3-(*o*-aryl)-2-thiohydantoins

3.3.1. The Synthesis

5-Methyl-(**1-6**) and 5-isopropyl-3-(*o*-aryl)-2-thiohydantoins (**8-13**) were reduced to the corresponding hemiaminals **40-53** by the reaction of lithium aluminum hydride (LiAlH_4) in THF at room temperature for 10 minutes and subsequent addition of water for quenching (Figure 3.72). The diastereomeric ratios of the isomeric products ranged from 99:1 to 46:54 and enantiomeric ratios from 94:6 to 56:44, by per cent. The hemiaminals were stable in the solid state for at least three months.

The compounds **40-45** and **47-52** were expected to be present as eight isomers due to the chiral center at C-5, the $\text{N}_{\text{sp}^2}\text{-C}_{(\text{aryl})}$ chiral axis and the newly formed chiral center at C-4 (Figure 3.73). The eight isomers should give four sets of peaks in ^1H NMR. The assignment of the configurations to the chiral carbons, the conformational preferences with respect to the $\text{N}_3\text{-C}_{(\text{aryl})}$ chiral axis (Figure 3.73) and isomeric assignments were done through one or two dimensional NMR spectrometry and by HPLC analyses on chiral stationary phases. One dimensional NMR analyses relied mainly on two factors; (i) *cis* and *trans* hydrogens of the imidazolidine ring have different coupling constants. Larger *J* values for the coupling of the hydrogen at C4 with the H at C5 are expected for the *cis*-isomer (Figure 3.74), while smaller ones for hydrogens of the *trans*- one (Figure 3.74) [45]. (ii) long range anisotropic effects of the C-5 and of the *o*-aryl substituents have an

influence on the C-4 hydrogen resonance when these groups are on the same side with the C-4H as in **SMS*&RPR*** (Figure 3.73). The anisotropic effects of these groups make the signal for C4-H to appear relatively upfield [46]. 2D-NOESY experiments were performed to be able to determine the conformational preferences of the axially chiral hemiaminals, based on which the presence or absence of hydrogen bonding between the OH at position 4 of the heterocyclic ring and the halogen on the aryl ring were deduced.

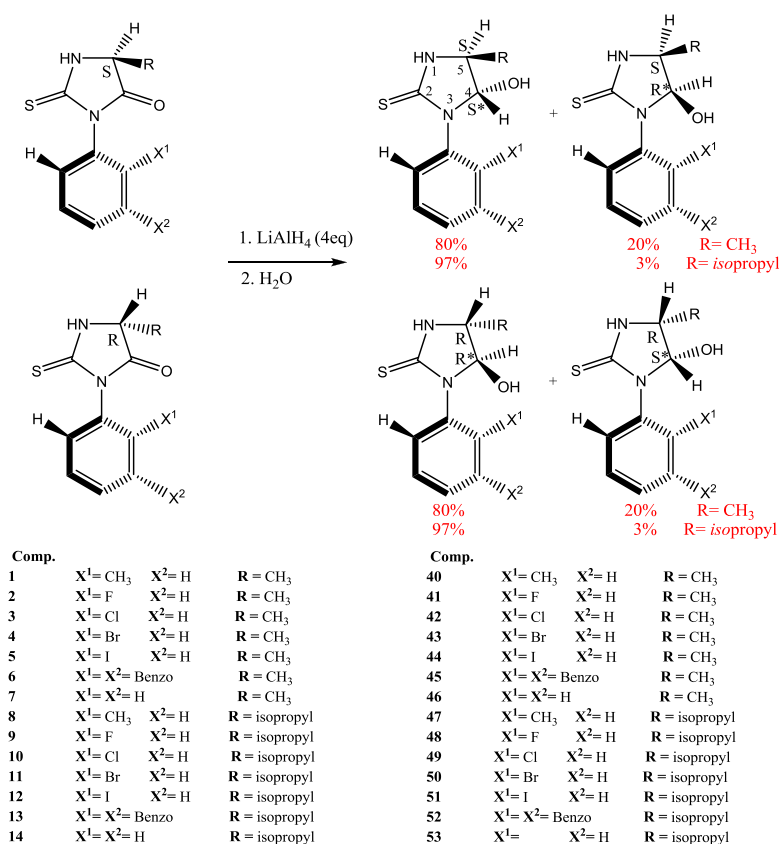


Figure 3.72. The reduction reaction of 5-methyl- and 5-isopropyl-3-(*o*-aryl)-thiohydantoin.

In order to assign the isomers more easily, the reduction reaction was firstly tried with the racemic compound **7** which has no axial chirality. The absence of one chiral element (the chiral axis) reduces the number of hemiaminal isomers to four (Figure 3.74), thus two sets of the product peaks are expected to appear in ^1H NMR.

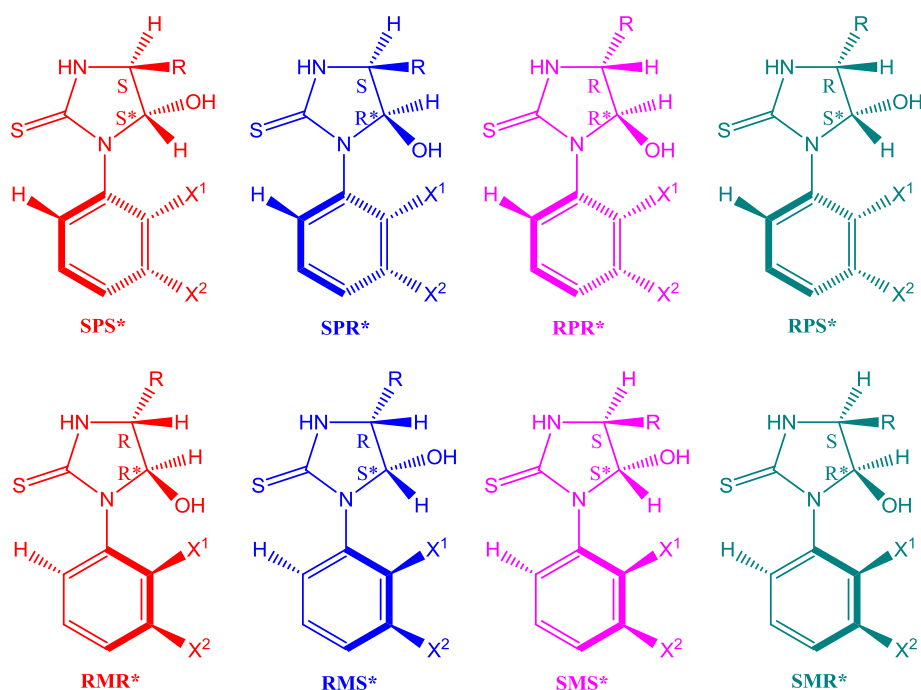


Figure 3.73. Possible eight isomers of the reduced axially chiral thiohydantoin.

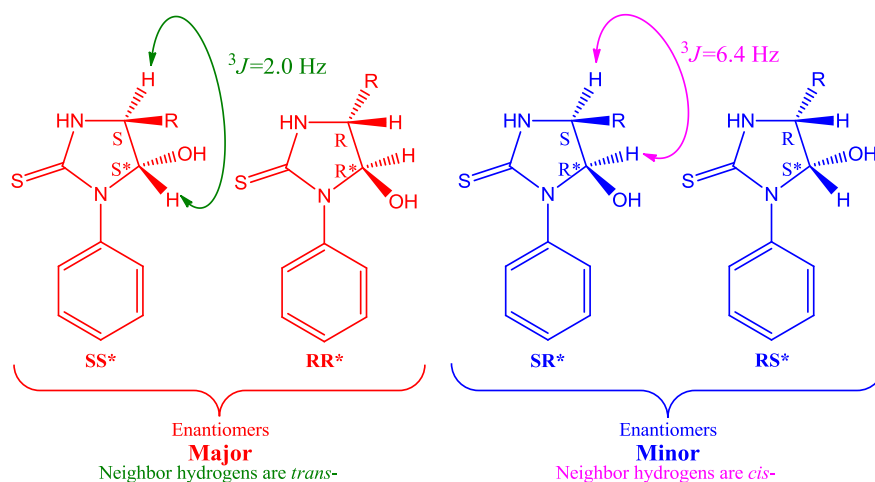


Figure 3.74. The possible isomers of compound **46**.

When the racemic **7** was reduced to the corresponding hemiaminal **46** by $LiAlH_4$, the ^1H NMR spectrum of **46** showed the disappearance of the peaks of the starting thiohydantoin and appearance of new peaks including the doublets at 5.35 and 5.08 ppm (Figure 3.75). In this region of the spectrum the signal of the hydrogen at C-4 of the

hemiaminal **46** is expected. In addition, two sets of the hemiaminal peaks, one major and one minor, were seen which indicated the formation of the two diastereomeric isomers. The diastereomer ratio was found as 20:80 from the integrations of the doublets in the NMR spectrum. This indicated that the starting racemic thiohydantoin yielded one diastereomeric pair in excess of the other.

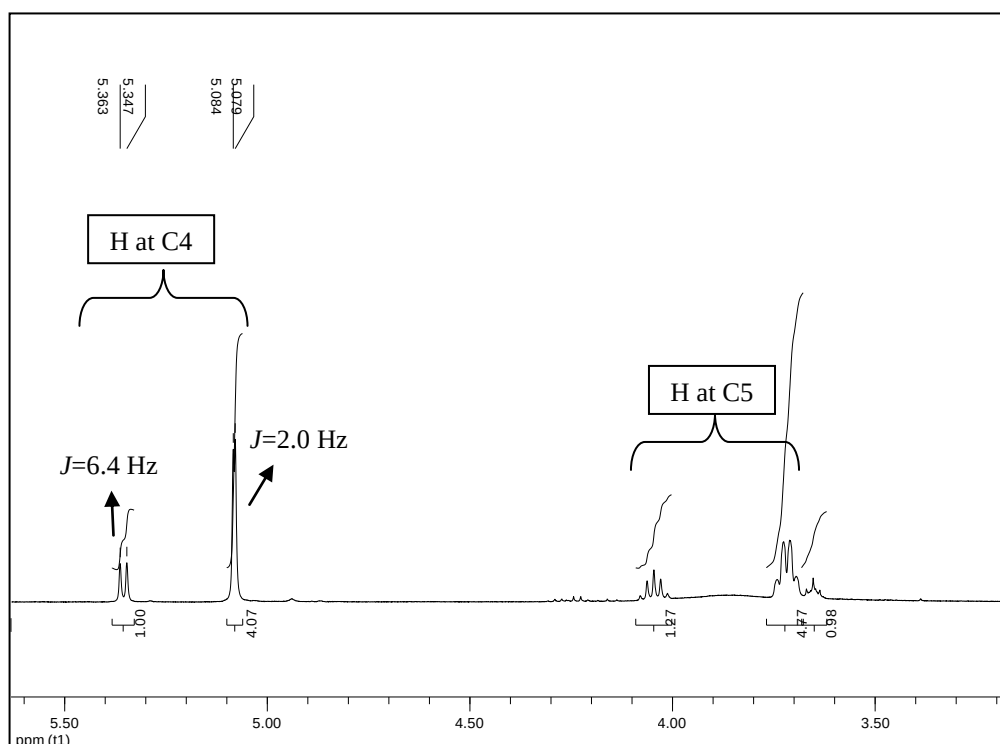


Figure 3.75. Partial ^1H NMR spectrum of crude compound **46** in CDCl_3 .

As can be seen from Figure 3.75, the C-4 hydrogen of the major isomer has a very small coupling constant (2.0 Hz), as expected for the *trans*- isomer, whereas the minor one of the same proton couples with a larger J (6.4 Hz), pointing to a *cis*- isomer. Thus the major isomer of **46** should be the SS^*/RR^* enantiomeric pair and the minor one SR^*/RS^* (Figure 3.74 and 3.75). This shows that the hydride prefers to get attached from the same side of the methyl group, leading to the two substituents (methyl at C-5 and OH at C-4) to be *trans* to each other in the major isomer. Therefore, S^* chiral center at C-4 is preferred from the S starting thiohydantoin and R^* from the R isomer which points to a stereospecific reaction.

With these findings for compound **46** we could determine which hemiaminal isomers (**40-45** and **47-52**) were produced when the reduction reaction was carried out with the nonracemic axially chiral compounds (**1-6** and **8-13**). All of the hemiaminal derivatives were proved by ^1H NMR and the results were summarized in Table 3.7.

Table 3.7. The chemical shifts and coupling constants (J) of *cis*- and *trans*- isomers of crude products **40-53** in CDCl_3 .

Comp.	H at C-4 and H at C-5 are <i>cis</i>		H at C-4 and H at C-5 are <i>trans</i>		<i>cis:trans</i> (%)
	Chemical shift (ppm)	J (Hz)	Chemical shift (ppm)	J (Hz)	
40	5.26	N.C. ^a	5.02 & 4.79	N.C. ^a	(26):(22:51)
41	5.37	6.8	5.08	1.6	(24):(76)
42	5.53	6.4	5.25	0.8	(23):(77)
43	5.52 & 5.48	5.2 & 6.4	5.26 & 5.22	N.C. ^a & 0.8	(19:trace):(72:9)
44	5.34 & 5.31	6.8 & N.C. ^a	5.09 & 5.07	N.C. ^a & 1.2	(20:3):(21:56)
45	5.61 & 5.40	7.2 & 6.4	5.30 & 5.15	2.8 & N.C. ^a	(3:10):(24:63)
46	5.35	6.4	5.08	2.0	(20):(80)
47	5.29	N.C. ^a	5.11	N.C. ^a	(40):(60)
48	5.45	6.0	5.29	2.0	(1):(99)
49	5.42	5.6	5.29	2.4	(9):(91)
50	5.48	6.4	5.36 & 5.26	N.C. ^a & 1.2	(1):(89:10)
51	5.48	6.2	5.41 & 5.29	N.C. ^a & N.C. ^a	(11):(33:56)
52	5.44 & 5.42	2.0 & N.C. ^a	5.29	N.C. ^a	(31:1):(68)
53	5.39	8.4	5.18	5.6	(3):(97)

^a N.C. represents "No Coupling".

The ^1H NMR spectrum of compound **41** (Figure 3.72) showed the presence of only two sets of doublets, one minor and one major with the ratio of 24 to 76 (Figure 3.76a) which showed the *cis:trans* ratio of the isomers. Apparently for this compound NMR could not distinguish the **M** isomers from the **P** ones due to a fast interconversion. For compound **42** on the other hand, although the **M** and **P** isomers were distinguishable (only barely) for the *cis* isomers, the signals of the *trans* ones coincided (Figure 3.76b). In the HPLC chromatogram of compound **42** on ChiralPak IC as the stationary phase (Table 3.8), six peaks were observed at 7°C with the per cent ratios of 5, 1, 65, 2, 11 and 16 (Figure

3.77). Together with the NMR results, these peaks in the chromatogram were assigned as **SPR***, **RMS***, **SPS*&SMS***, **RPS***, **SMR*** and **RMR*&RPR***, respectively. **SMS*** and **RPR*** could not be separated; neither by NMR nor by HPLC. The synthesis of this compound started with compound **3** with an isomeric composition of **SP**, **SM** and **RP** 83, 5 and 12 per cent, respectively. HPLC results show that the sum of the **S** products (**SPS*&SMS***+ **SMR***+ **SPR***) matches with the **S** population of the starting thiohydantoin. It was therefore deduced that no racemization at C5 took place upon LiAlH_4 addition.

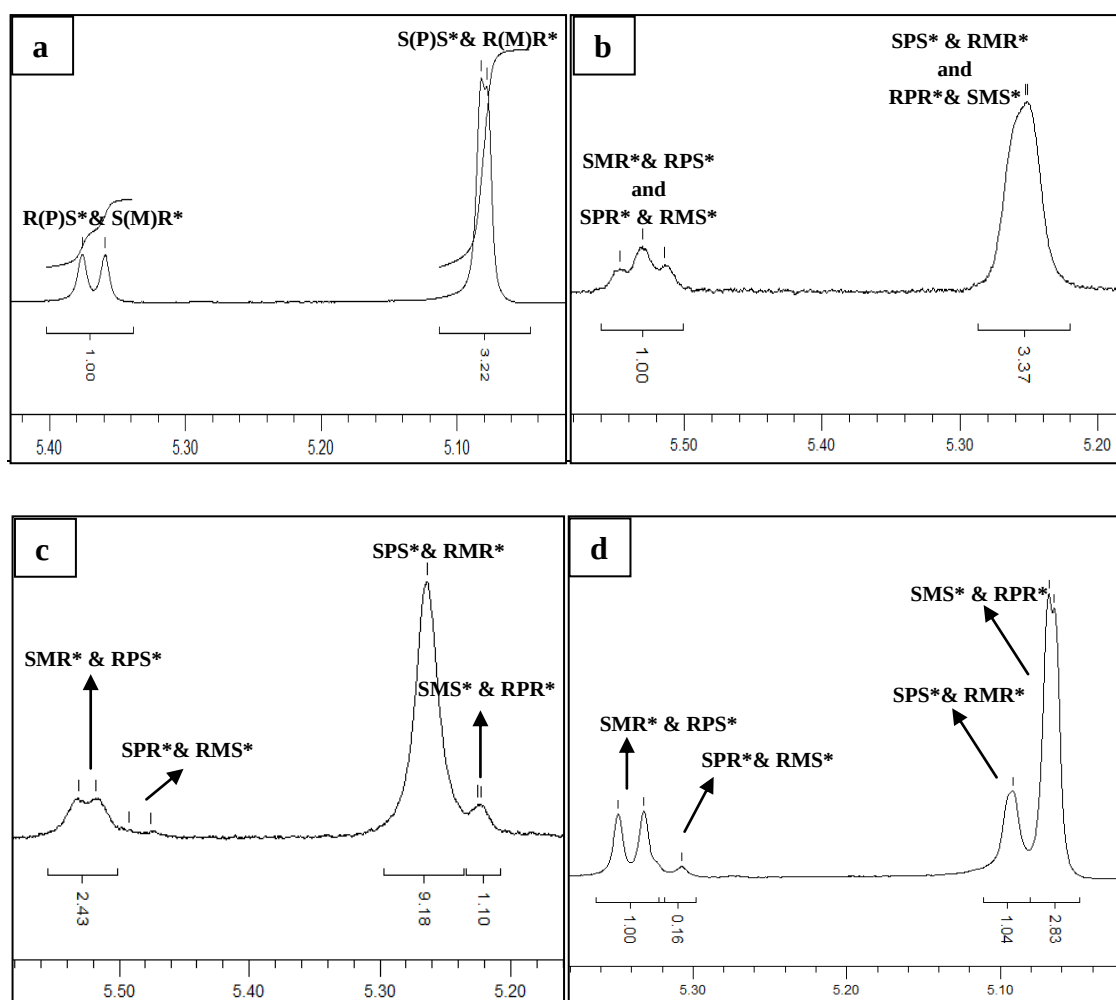


Figure 3.76. Partial ^1H NMR spectrum of crude compounds a) **41**, b) **42**, c) **43** and d) **44** in CDCl_3 .

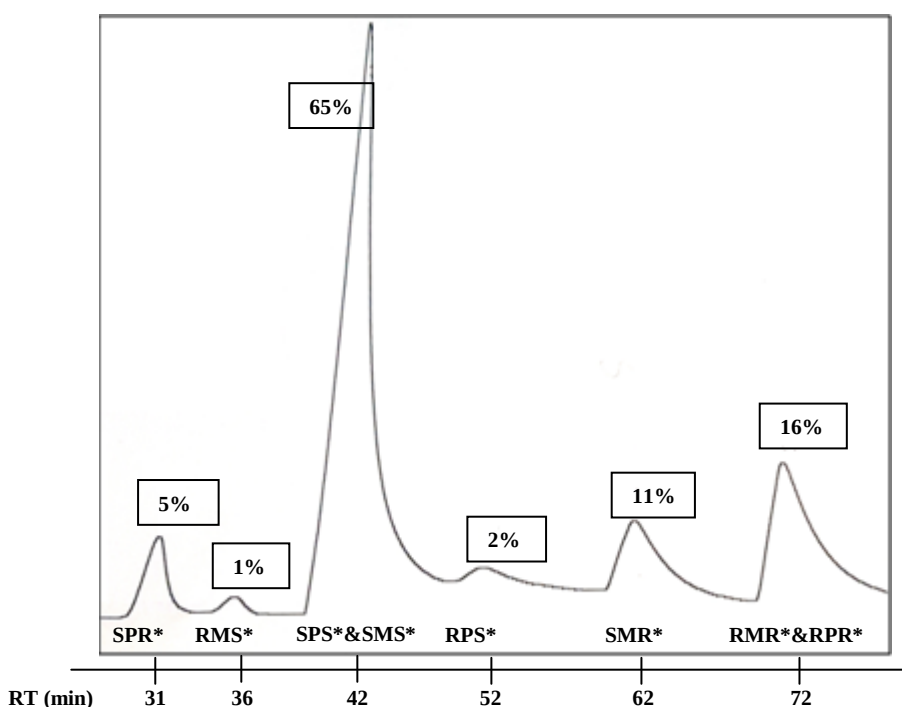


Figure 3.77. HPLC chromatogram of compound **42**.

For the *o*-bromophenyl hemiaminal, **43**, all the **M** and the **P** isomers were resolvable on the NMR time scale (Figure 3.76c). The synthesis of this compound started with compound **4** that had an isomeric composition of **SP**, **SM** and **RP** 68, 23 and 9 per cent, respectively. In the ^1H NMR of compound **43** (Figure 3.76c), the ratio of the isomers was found as 19:trace:72:9. With the observed different coupling constants and the presumed possibility of hydrogen bonding, the signal at 5.52 ppm (19%) has been assigned to **RPS*** and its enantiomer **SMR*** and the doublet at 5.48 ppm (trace amount) was assigned to the other *cis*- enantiomeric pair, **SPR*&RMS***, where there is not a hydrogen bonding possibility between *o*-Br and OH. In addition, two other peaks, the one at 5.26 (72%) which did not have a coupling constant while the other one at 5.22 (9%) ppm coupling with 0.8 Hz, were present. This indicated that the two neighboring hydrogens are *trans*- with respect to each other ie they are **SPS*&RMR*** and **SMS*&RPR***. Between these two isomers, the minor one should be **SMS*&RPR*** because the OH at C-4 of this isomer is on the opposite side with the *o*-Br substituent.

When the Br and the methyl group are on the same side with C4-H (**SMS*&RPR***), the combined anisotropic effects of these two groups led the C4-H signal to appear relatively upfield (5.22 ppm). In **SPS*&RMR***, although methyl at C-5 is on the same side with the hydrogen at C-4 and makes its signal to appear more upfield bromine has no effect due to being on different sides with this hydrogen and hence its signal was seen at relatively more downfield (5.26 ppm). Thus the ratio of the diastereomeric pairs **SMR*&RPS***, **SMS*&RPR*** and **SPS*&RMR*** was found as 19%, 9% and 72%, respectively (**SPR*&RMS*** was formed in trace amount).

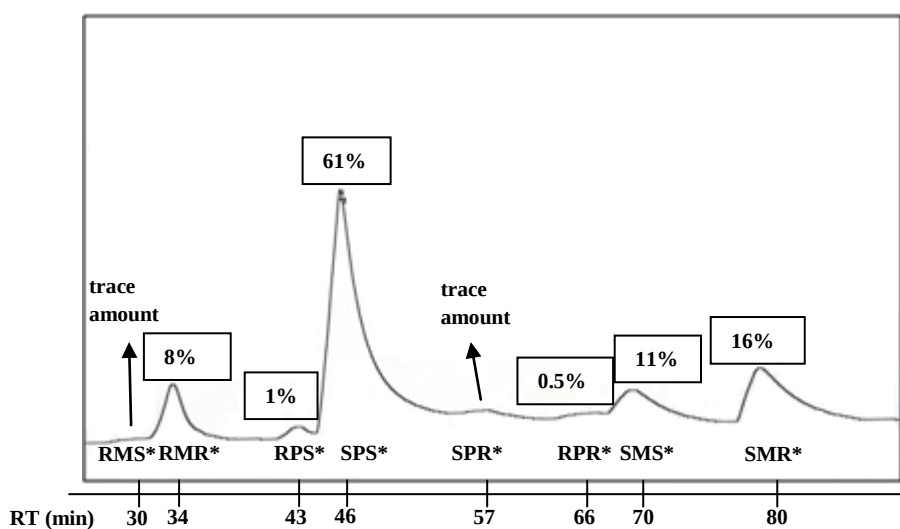


Figure 3.78. HPLC chromatogram of crude compound 43.

When **43** was resolved analytically into its enantiomers by HPLC (Table 3.8 and Figure 3.78), the per cent ratios of the peaks were found as 8, 1, 61, 0.5, 11 and 16 and together with the ratios obtained in ^1H NMR, these are assigned as **RMR***, **RPS***, **SPS***, **RPR***, **SMS***, and **SMR***, respectively (**RMS*** and **SPR*** were formed in trace amounts). The ratios of the corresponding enantiomers **SPS*:RMR***, **SMS*:RPR*** and **SMR*:RPS*** from the HPLC analysis on ChiralPak IC column were determined as 88:12, 96:4 and 94:6, respectively (Figure 3.78 and Table 3.8).

For the hemiaminals whose isomers were resolved by HPLC with chiral stationary phases, the chromatographic conditions and the enantiomeric ratios are summarized in Table 3.8.

Table 3.8. HPLC conditions for the resolution of **40-53** and their enantiomer ratios^a

Comp	Stationary Phase	Mobile Phase (Hex:EtOH)	Flow (mL/min)	Enantiomer ratios obtained in enantioselective HPLC			
				SPS*:RMR*	SMS*:RPR*	SMR*:RPS*	SPR*:RMS*
41^b	ChiralPak IB	95:5	0.6	Racemic			
42^c	ChiralPak IC	95:5	0.6	80:20	-	86:14	78:22
43^c	ChiralPak IC	95:5	0.6	88:12	96:4	94:6	trace amount
44	ChiralPak IA	97:3	1.0	80:20	42:58	18:82	41:59
46^b	ChiralPak AD-H	95:5	0.6	Racemic			
48^b	ChiralPak IC	95:5	0.8	Racemic			
51	ChiralPak IC	98:2	1.0	8:92	40:60		94:6
53^b	ChiralPak AD-H	90:10	0.6	Racemic			

^a Compounds **40**, **45**, **47**, **49**, **50** and **52** could not be resolved on HPLC with a chiral stationary phase.

^b Compounds **46**, **48** and **53** were obtained as racemic mixture because starting thiohydantoins was a mixture of racemates.

^c **RPS*&SMR*:SPR*&RMS*** could not be separated by ¹H NMR at room temperature.

In the reduction reaction of compound **5** (**SP:SM:RP** 80:9:11) to **44** all four isomeric pairs, **SMR*&RPS***, **SPR*&RMS***, **SPS*&RMR*** and **SMS*&RPR*** of **44** were observed in NMR with the ratio of 20%, 3%, 21% and 56% (Figure 3.76d). Among the isomers whose hydrogens are *trans*- with respect to each other, the major one (a in Figure 3.79), whose C4H appeared the most upfield, was assigned as **SMS*&RPR*** based on the fact that in this conformation the proton is under the anisotropic shielding effect of both the methyl group and the *o*-iodo substituent. In order to validate this assignment a 2D NOESY experiment was carried out for compound **44** (Figure 3.79). In **SPS*&RMR*** (b in Figure 3.79), a crosspeak should be observed between the H at C4 and the *ortho* aromatic proton because of being on the same side, whereas in **SMS*&RPR*** no crosspeak should be seen between these hydrogens. In the 2D NOESY experiment of **44** carried out in CDCl₃, there was an interaction between the hydrogen at C4 of the minor *trans*- isomer (b in Figure 3.79) and the aromatic region (Figure 3.79). This minor isomer was therefore assigned as **SPS*&RMR***. Besides, no crosspeak was seen between the H at C4 of the major isomer and the aromatic region, whereas a crosspeak between the hydroxyl and aromatic protons was observed. These results prove the **SMS*&RPR***

stereochemistry of the major isomers. Thus the large iodine atom of **44** was found to prefer to be *transoid* with the OH bonded to C4.

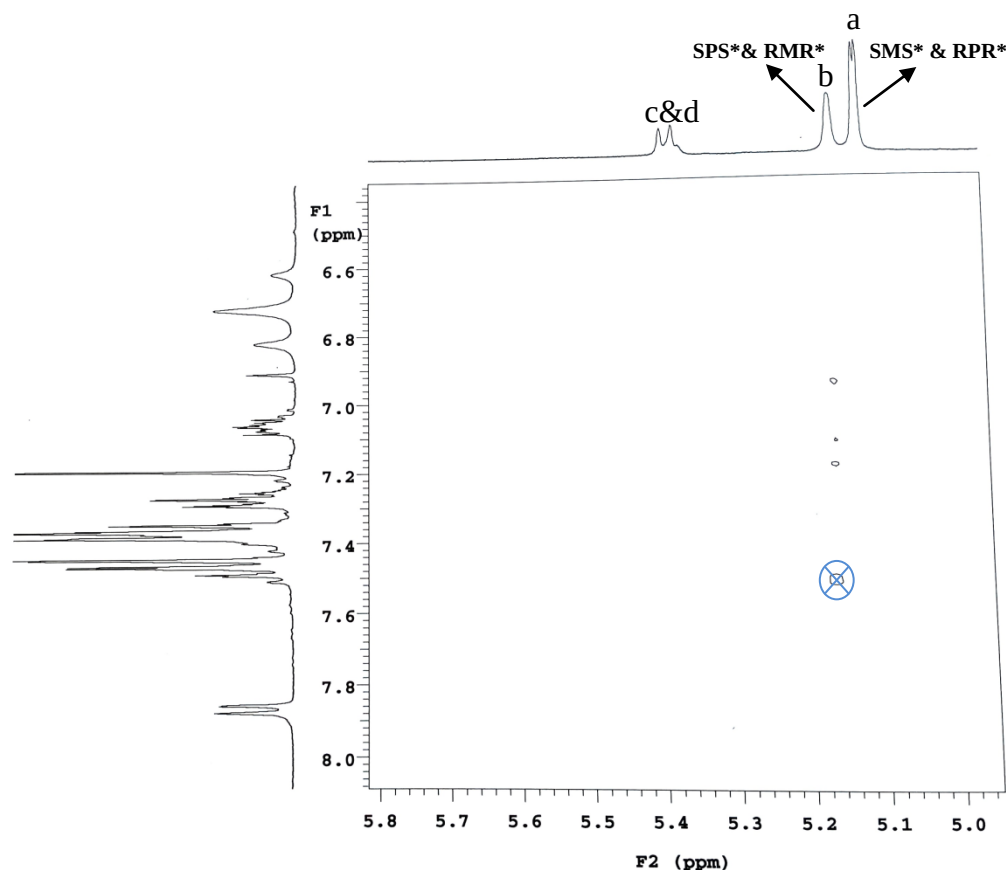


Figure 3.79. 2D-NOESY spectrum of compound **44** in CDCl_3 , the crosspeak between the signal corresponding to the hydrogen at C4 of the minor *trans*- isomer and the aromatic region.

For the 5-isopropyl derivatives (**47-53**), the assignments of the isomers were done in a similar way as for the 5-methyl derivatives (**40-46**). The ratio between major and minor peaks (*cis-trans* isomers) was found to be higher in the isopropyl derivatives (**47-53**) (Figure 3.80) than that observed for the methyl derivatives (**40-46**) (Table 3.7). This result is understandable considering the bulkiness of the isopropyl group at C5 causing a larger steric effect.

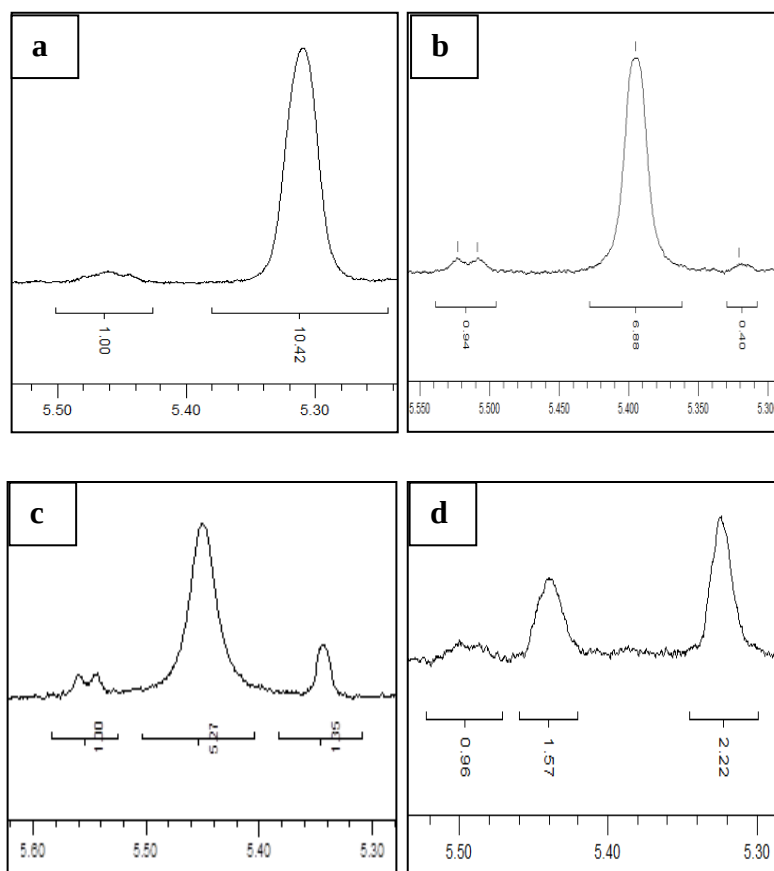


Figure 3.80. Partial ^1H NMR spectrum of crude compounds a) **48**, b) **49**, c) **50** and d) **51** in CDCl_3 .

In order to show that the major isomer of **50** (5-isopropyl-3-(*o*-bromophenyl)) derivative) is **SPS*&RMR*** where an H-bond between the *ortho* substituent Br and the OH at C4 is possible, a 2D-NOESY experiment for this compound was carried out (Figure 3.81). The 2D-NOESY spectrum of compound **50** taken in CDCl_3 did show a crosspeak between the signal of the major isomer at 5.40 ppm and the aromatic region (Figure 3.81). No crosspeak was detected between the hydroxyl group at C-4 and aromatic proton. These results indicate that hydrogen at C-4 and one aromatic proton are on the same side in the major isomer, making the bromo substituent *cisoid* with the hydroxyl group. Therefore, it was concluded that **SPS*&RMR*** pair was the major isomer.

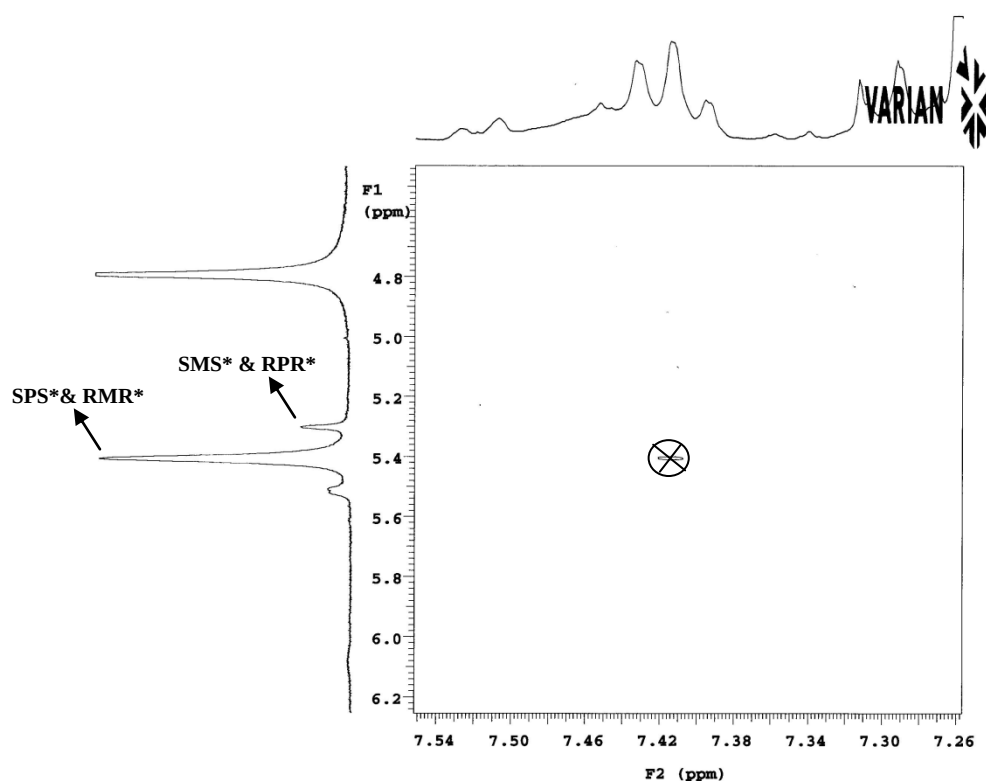


Figure 3.81. 2D-NOESY spectrum of compound **50** in CDCl_3 showing the crosspeak between the signal corresponding to the hydrogen at C4 of the major isomer and the aromatic region.

For compound **51** (5-isopropyl-3-(*o*-iodophenyl) derivative), ^1H NMR exhibited that isomers, **SMR*&RPS***, **SPR*&RMS***, **SPS*&RMR*** and **SMS*&RPR***, were formed (Figure 3.80d). In this case the *cis*- isomers, **SMR*&RPS*** and **SPR*&RMS***, could not be differentiated by NMR and the per cent ratios were determined as 11% for **SMR*&RPS*** and **SPR*&RMS***, 33% for **SPS*&RMR*** and 56% for **SMS*&RPR***. It figures that for the bulky *o*-iodo containing derivative **51** analogous to **44** (5-methyl-3-(*o*-iodophenyl) derivative), the conformational preference of the axially chiral hemiaminal is determined by steric considerations. The larger iodine atom does not prefer to be on the same side with the OH group, whereas for the more electronegative and smaller substituents, Cl and Br, the intramolecular H-bonding between the OH and the halogen determines the conformational preference as shown by the NOESY experiments

For the naphthyl (**45**) and the *o*-tolyl (**40**) derivatives (Figure 3.82), the reactions yielded the **SMS*&RPR*** isomers as the major product while **SMR*&RPS*** was the minor one. The reason for this is the lack of a possibility for an intramolecular hydrogen bond formation for these compounds. Hence, because of the steric reasons, the naphthyl and the *o*-methyl groups prefer to be on opposite sides with the hydroxyl group, which supports the results obtained for **44** and **51**.

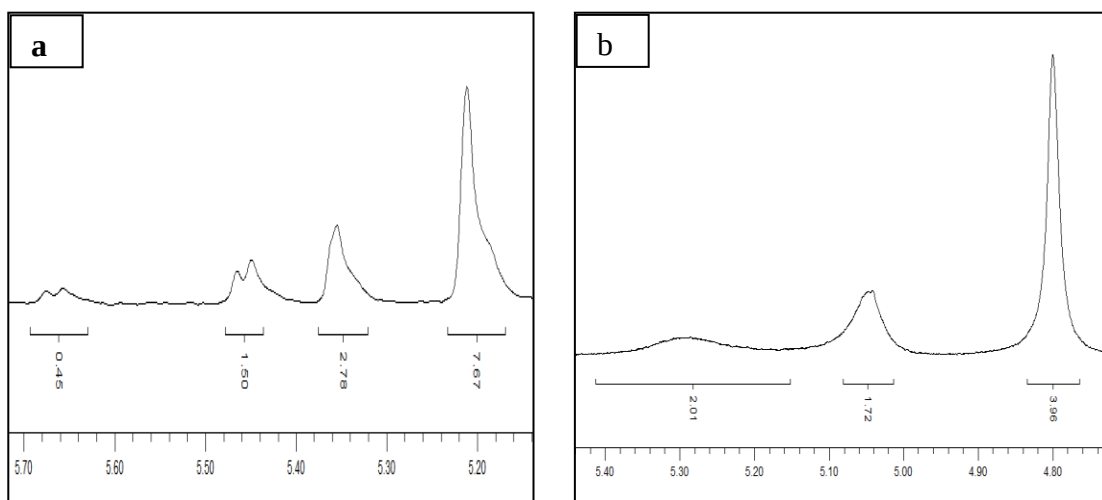


Figure 3.82. Partial ^1H NMR spectrum of crude compounds a) **45**, b) **40** in CDCl_3 .

3.3.2. Stereodynamics

The reduction reaction of **4** started with the absence of the **RM** isomer, however as shown in Figure 3.78, among the other isomers **RMR*** and **RMS*** were also formed. This can only be possible *via* a fast interconversion between **RPR*/RPS*** and **RMR*/RMS*** upon hemiaminal formation. The hydride ion can attack to **4** from both faces of the carbonyl (Figure 3.83). When **RPR*** was produced by the attack from the *re*-face, it interconverts immediately, to form **RMR*** which is the enantiomer of **SPS*** (Figure 3.83). The driving force for the interconversion to give **RMR*** should be the formation of a hydrogen bond between the bromine atom with the OH hydrogen. **SPS***, **SMS*** and **RPS*** were formed by the hydride attack from the *si*-face and **SPR***, **SMR*** and **RPR*** by the

attack from the *re*-face. Since there is an equilibrium for the interconversion, **RMS*** was also formed in trace amount from **RPS*** (Figure 3.83).

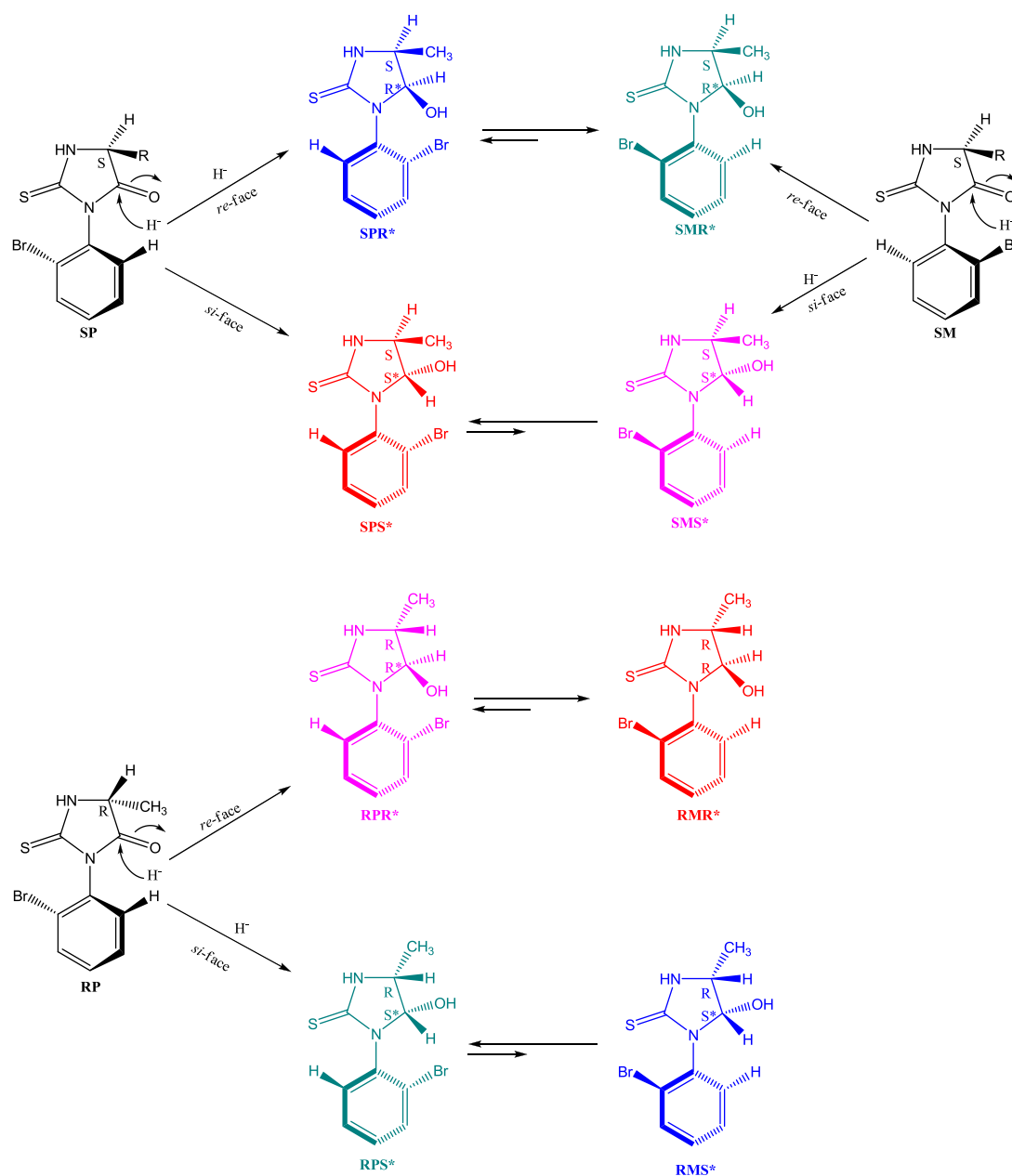


Figure 3.83. The stereodynamics of the **43** isomers. The reduction started with 68% **SP**, 23% **SM**, 9% **RP** and 0% **RM** isomeric composition of the thiohydantoin **4**.

The barrier for the interconversion between the *cis* isomers of **43** was determined by dynamic NMR in $CDCl_3$ by observing the coalescence of the signals at 5.50 and 5.47

ppm corresponding to **SMR*/RPS*** and **SPR*/RMS*** isomers. The coalescence was seen at 35°C (Figure 3.84). The rate constant for interconversion was calculated as 32.9 s^{-1} from $k_c = \pi(\nu_A - \nu_B)/\sqrt{2} = \pi\Delta\nu/\sqrt{2} \approx 2.22 \Delta\nu$, using the difference in chemical shift ($\Delta\nu = \nu_A - \nu_B$) at 21°C. The corresponding activation barrier, $\Delta G^\ddagger$, was determined as 66.4 kJ/mol from the Eyring Equation [47], $\Delta G^\ddagger = RT \ln[(k_b T_c)/(k_c h)]$, where T_c is the coalescence temperature in Kelvin and k_c is the rate constant. The **SPS*** isomer did not convert to the **SMS*** under these conditions, indicating a higher barrier for the interconversion between the *trans* isomers.

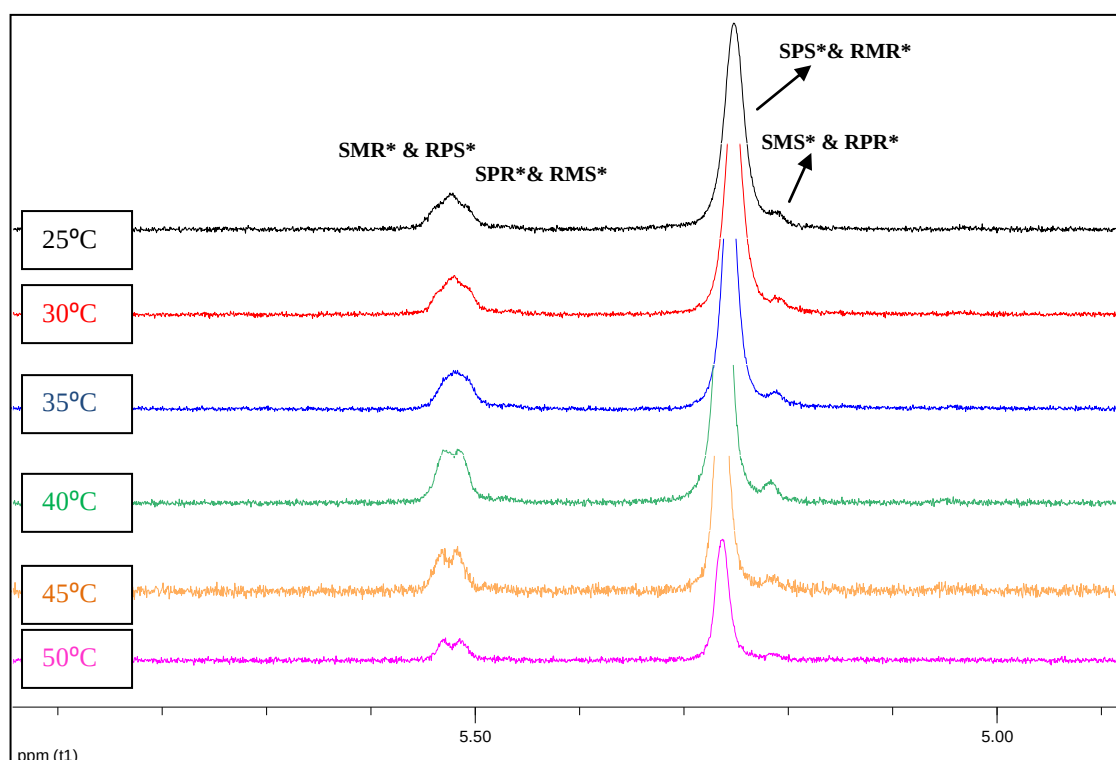


Figure 3.84. Dynamic NMR of **43** in CDCl_3 showing the coalescence of **SPR*&RMS*** and **SMR*&RPS*** at 35°C.

The interconversion of hemiaminal isomers can take place by either rotation around the $\text{N}_3\text{-C}_{(\text{aryl})}$ chiral axis or *via* an aldehyde intermediate formed from a ring opening, as previously observed for oxazolidinone derivatives [46]. Throughout the ring chain tautomerization, it had been shown by Fülöp group that, the *trans* isomers were more stable than the *cis* isomers [48, 49].

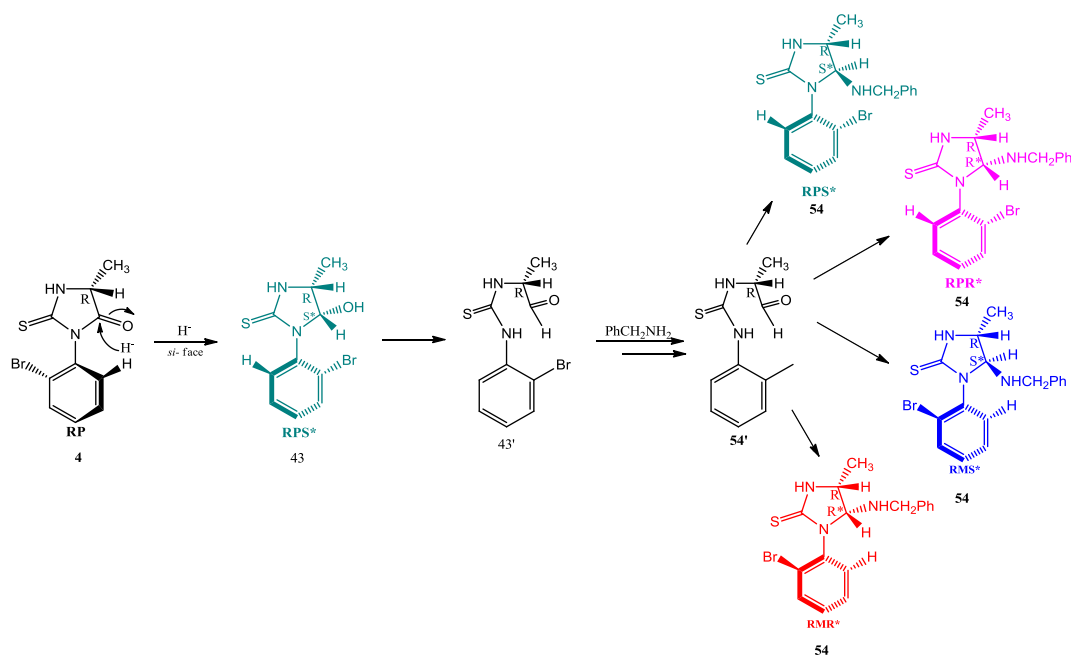


Figure 3.85. The ring opening and reclosure mechanism *via* ring chain tautomerization in the presence of bezyl amine. The open chain imine (**54'**) could not be observed. However its existence is inferred based on the formation of the aminal product (**54**).

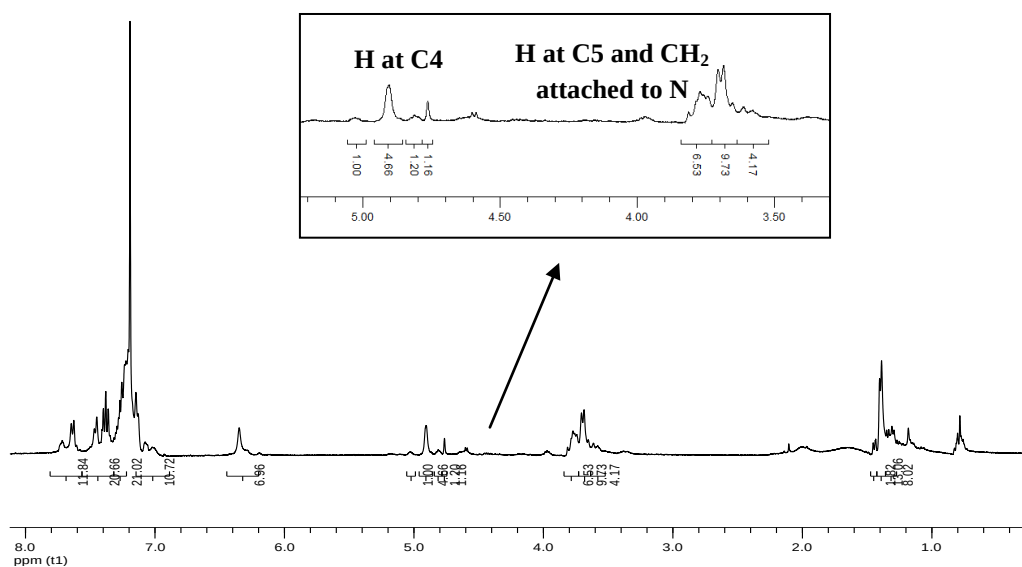


Figure 3.86. ^1H NMR spectrum of aminal (**54**) in $CDCl_3$.

With the aim of testing the ring-chain mechanism, hemiaminal **43** was refluxed with benzyl amine in benzene for one day (Figure 3.85). If the heterocyclic ring would

open to form the corresponding aldehyde and re-closed after the imine formation as shown in Figure 3.84, the **S*** or **R*** configurations at C4 and **M** and **P** conformations of the chiral axis could be produced. The ^1H NMR spectrum of this reaction product (**54**) (Figure 3.86) showed no signs of the starting hemiaminal. The appearance of the new singlets between 4.8-5.0 ppm belonging to the H at C4 of the newly formed aminal product (**54**) and the multiplet at 3.5-3.8 ppm which was assigned to the overlapped signals of H at C5 and CH_2 group attached to the aminal N, (the ratio of the singlets to this multiplet was found as 1:3) were in accordance with the formation of **54**. Therefore, although the open chain imine (**54'**) could not be observed, its existence was inferred based on the formation of the aminal product (**54**) and it was reasoned that a ring opening and reclosure took place for the interconversion of the isomers of the hemiaminal. With the aim of determining the energy barrier between the *trans* isomers of **43** by a thermal interconversion process, the **SPS*** isomer was resolved micropreparatively by HPLC on a chiral stationary phase and kept in toluene at a constant temperature. Immediately after resolution, the chromatogram taken showed a ratio of **SPS*:****SMS*** 89:11, showing that **SMS*** was formed from **SPS*** during its resolution process (Figure 3.87a). The chromatogram of the sample taken after 90 minutes showed no change of the isomeric ratio, pointing to an equilibrium ratio of the **SPS*:****SMS*** isomers (Figure 3.87b). This experimental finding on the other hand pointed to an interconversion *via* a rotation mechanism but the barrier height could not be determined. It looks like that for the *trans* isomer, at lower temperatures the interconversion is *via* rotation, however upon prolonged heating at the reflux temperature of benzene (80°C) interconversion of isomers *via* a ring opening and reclosure mechanism took place.

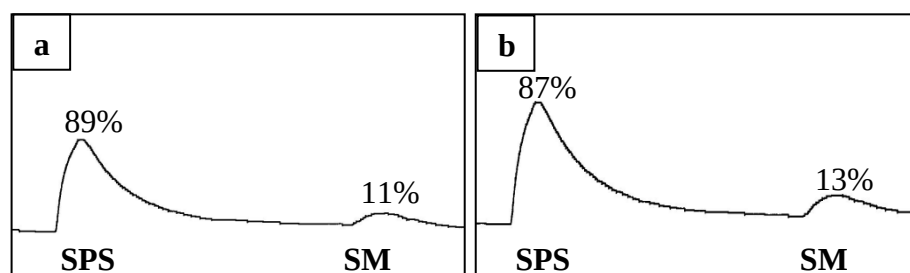


Figure 3.87. Partial HPLC chromatogram of resolved **SPS*** which is kept in toluene at room temperature a) t_0 and b) after 90 minutes.

The rate constant and the barrier for the interconversion the *cis* isomers of **44** in toluene- d_8 were determined in the same way as for **43**. The coalescence of the signals at 4.63 and 4.62 ppm corresponding to **SMR*/RPS*** and **SPR*/RMS*** isomers was seen at 40°C, and the rate constant and the barrier to interconversion were found as 15.1 s⁻¹ and 69.6 kJ/mol respectively (Figure 3.88). A barrier for the interconversion of the *trans* isomers could not be determined.

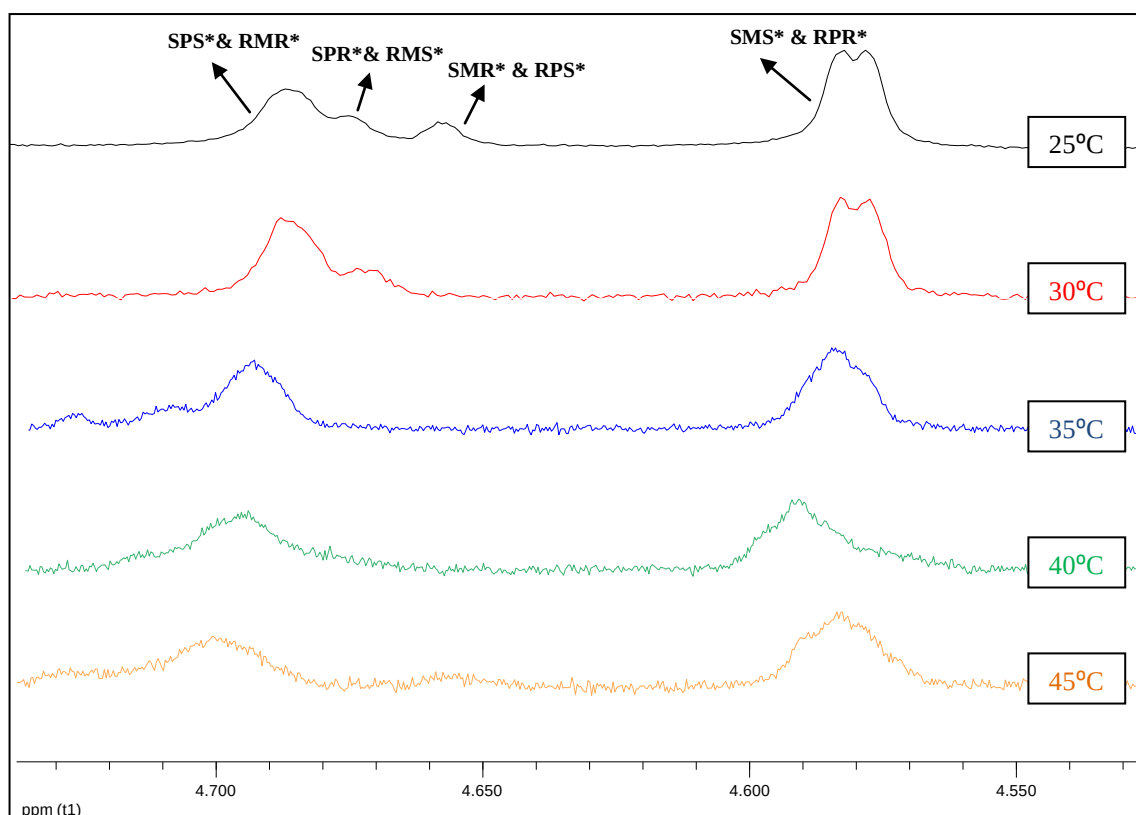


Figure 3.88. Dynamic NMR of **44** in toluene- d_8 showing the coalescence of **SPR*&RMS*** and **SMR*&RPS*** at 40°C.

The barrier of the interconversion for the *cis* isomers of **40** (Figure 3.72) has been found 73.8 kJ/mol using the rate constant, k_c , determined as 89.7 s⁻¹ from the coalescence of the peaks at 5.49 and 5.39 ppm corresponding to the *cis*- isomers (Figure 3.89). This value is larger than the electron withdrawing *ortho* halogen bearing hemiaminals **43** and **44** (Figure 3.84 and Figure 3.88).

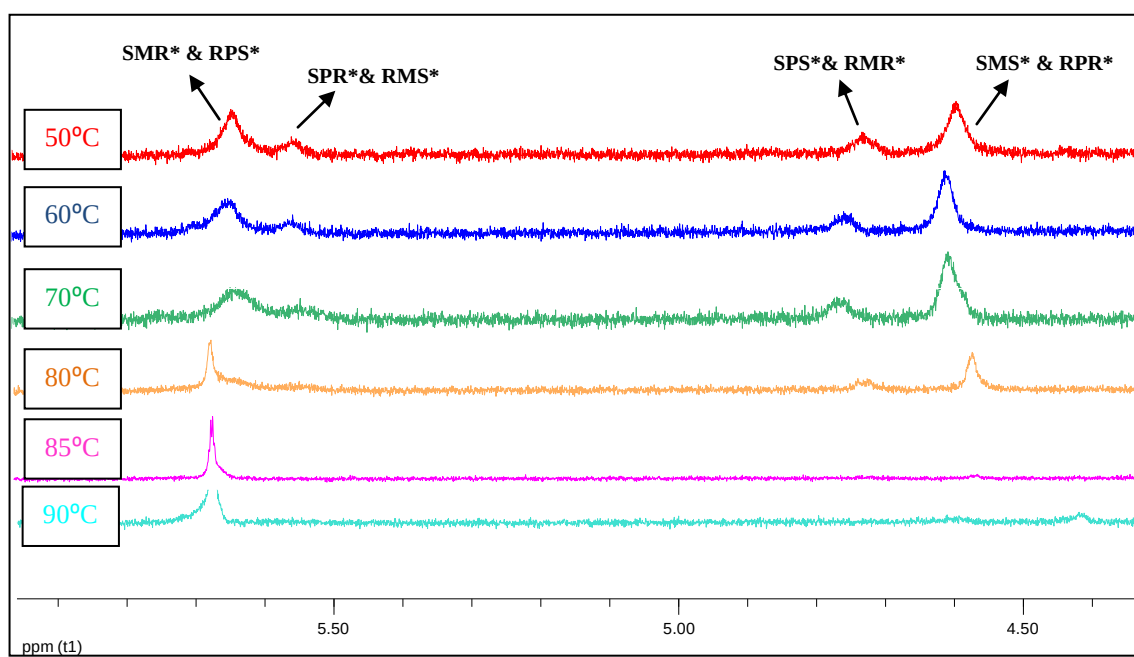


Figure 3.89. Dynamic NMR of **40** in toluene-*d*₈ showing no coalescence of **SPR*&RMS*** and **SMR*&RPS*** at the studied temperature range, 50°C-90°C.

4. EXPERIMENTAL

4.1. Synthesis of 5-methyl- and 5-isopropyl-3-o-aryl thiohydantoins

4.1.1. General Procedure

The compounds, **1-7**, were synthesized by the reaction of the corresponding isothiocyanate and *L*-alanine methyl ester HCl salt in the presence of triethylamine (Et₃N) and CH₂Cl₂ under reflux for one hour. For the compounds **8-14**, *L*-valine ethyl ester HCl salt was used under the same conditions. At the end of the reaction, the crude product was extracted with distilled water and saturated brine solution. Finally the solution was dried over MgSO₄, filtered and the solvent removed immediately. The crude products were recrystallized from ethyl acetate/hexane, ethyl acetate or methanol/water.

4.1.1.1. 5-Methyl-3-*o*-tolyl thiohydantoin (1). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.43 ml (3.58 mmole) of *o*-tolyl isothiocyanate was added to the solution of 0.5 g (3.58 mmole) of *L*-alanine methyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.52g (66%). Mp: 215-218 °C ¹H NMR (400MHz, CDCl₃): δ 7.67 (bs, 1H, NH), 7.41-7.12 (m, 8H, aromatic ring), 4.37 and 4.35 (two quartets, *J* = 7.2 Hz and *J* = 6.8 Hz, 2H, α-H), 2.20 and 2.17 (two singlets, 6H, methyl attached to the aromatic ring), 1.61-1.59 (two doublets, *J* = 7.2 Hz, 6H, methyl signals at C-5 coincided). ¹³C NMR (100 MHz, CDCl₃): δ 183.77, 183.72, 174.14, 174.10, 136.83, 136.63, 132.01, 131.94, 131.39, 131.34, 130.23, 129.37, 129.17, 127.26, 127.19, 55.82, 55.74, 17.96, 17.74, 17.63, 17.35 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.2. 5-Methyl-3-*o*-fluorophenyl thiohydantoin (2). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.44 ml (3.58 mmole) of *o*-

fluorophenyl isothiocyanate was added to the solution of 0.5 g (3.58 mmole) of L-alanine methyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.37g (46%). Mp: 174-176 °C ¹H NMR (400MHz, CDCl₃): δ 7.67 (bs, 1H, NH), 7.50-7.22 (m, 8H, aromatic ring), 4.41 and 4.36 (two quartets, *J* = 7.2 Hz and *J* = 6.4 Hz, 2H, α-H at C-5 coincided), 1.61 and 1.60 (two doublets, *J* = 6.8 Hz, 6H, methyl signals at C-5). ¹³C NMR (100 MHz, CDCl₃): δ 182.98, 182.88, 173.55, 173.36, 159.24, 159.16, 156.72, 156.64, 131.64, 131.56, 130.82, 130.65, 124.66, 124.62, 124.61, 124.57, 120.58, 120.48, 120.45, 120.35, 116.85, 116.79, 116.66, 116.60, 55.76, 55.65, 17.20, 16.93 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.3. 5-Methyl-3-*o*-chlorophenyl thiohydantoin (3). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.47 ml (3.58 mmole) of *o*-chlorophenyl isothiocyanate was added to the solution of 0.5 g (3.58 mmole) of L-alanine methyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10ml CH₂Cl₂. Yield: 0.55 g (64%). Mp: 198-200 °C ¹H NMR (400MHz, CDCl₃): δ 7.58-7.30 (m, 10H, aromatic ring and NH), 4.43 and 4.36 (two quartets, *J* = 6.8 Hz and *J* = 7.2 Hz, 2H, α-H at C-5), 1.64-1.59 (two methyl signals coincided with the solvent signal, 6H, methyls at C-5). ¹³C NMR (100 MHz, CDCl₃): δ 182.91, 182.82, 173.37, 173.24, 133.29, 133.23, 131.20, 131.15, 131.00, 130.66, 130.59, 130.41, 130.35, 127.78, 127.70, 55.82, 55.69, 17.38, 16.87 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.4. 5-Methyl-3-*o*-bromophenyl thiohydantoin (4). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.48 ml (3.58 mmole) of *o*-bromophenyl isothiocyanate was added to the solution of 0.5 g (3.58 mmole) of L-alanine methyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10ml CH₂Cl₂. Yield: 0.65 g (63%). Mp: 224-225 °C ¹H NMR (400MHz, CDCl₃): δ 7.67-7.14 (m, 10H, aromatic ring and NH), 4.38 and 4.31 (two quartets, *J* = 7.2 Hz and *J* = 6.8 Hz, 2H, α-H at C-), 1.59 and 1.56 (d, *J* = 7.2 Hz and *J* = 6.8 Hz, 6H, methyl signals at C-5). ¹³C NMR (100 MHz, CDCl₃): δ 182.76, 173.21, 133.58, 133.54, 132.19, 131.36, 131.24, 131.06, 128.53, 128.45, 123.42, 123.39, 55.88, 55.75, 17.44, 16.89 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.5. 5-Methyl-3-*o*-iodophenyl thiohydantoin (5). The compound was synthesized according to the general procedure, the reflux time being 4 h. 1.00 g (3.83 mmole) of *o*-iodophenyl isothiocyanate was added to the solution of 0.53 g (3.83 mmole) of L-alanine methyl ester HCl salt and 0.53 ml (3.83 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.95 g (75%). Mp: 222-224 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.91-7.12 (m, 10H, aromatic ring and NH), 4.38 and 4.30 (two quartets, *J* = 7.2 Hz, 2H, α-H at C-5), 1.62 and 1.56 (two doublets, *J* = 7.2 Hz, 3H, methyl signals at C-5). ¹³C NMR (100 MHz, CDCl₃): δ 182.54, 173.06, 139.85, 135.61, 131.33, 130.57, 129.50, 99.04, 55.99, 17.43 ppm.

4.1.1.6. 5-Methyl-3-α-naphthyl thiohydantoin (6). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.66 g (3.58 mmole) of 1-naphthyl isothiocyanate was added to the solution of 0.5 g (3.58 mmole) of L-alanine methyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.51 g (55%). Mp: 238-240 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.94-7.33 (m, 16H, NH and aromatic ring), 4.46 and 4.38 (two quartets, *J* = 7.2 Hz, 2H, α-H at C-5), 1.65-1.59 (two doublets, *J* = 7.2 Hz, 6H, methyl signals at C-5). ¹³C NMR (100 MHz, CDCl₃): δ 184.10, 184.04, 174.35, 174.32, 134.38, 134.36, 130.49, 130.42, 129.96, 129.86, 129.30, 128.77, 128.71, 127.69, 127.47, 127.40, 127.30, 126.64, 125.37, 125.31, 122.03, 121.58, 55.81, 55.71, 17.76, 17.21 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.7. 5-Methyl-3-phenyl thiohydantoin (7). The compound was synthesized according to the general procedure, reflux time being 1 h. 0.43 g (3.58 mmole) of phenyl isothiocyanate was added to the solution of 0.50 g (3.58 mmole) of L-alanine methyl ester HCl salt and 0.50 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.43 g (59%). Mp: 184-186 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.48-7.24 (m, 5H, aromatic ring and NH), 4.28 (one quartet, *J* = 7.2 Hz, 1H, α-H at C-5), 1.53 (one doublet, *J* = 7.2 Hz, 3H, methyl signal at C-5). ¹³C NMR (100 MHz, CDCl₃): δ 183.62, 174.06, 132.61, 129.30, 129.18, 128.244, 55.47, 17.03 ppm.

4.1.1.8. 5-Isopropyl-3-*o*-tolyl thiohydantoin (8). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.48 ml (3.58 mmole) of *o*-tolylphenyl isothiocyanate was added to the solution of 0.65 g (3.58 mmole) of L-valine ethyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.51g (58%). Mp: 162-164 °C ¹H NMR (400MHz, CDCl₃): δ 7.66 (bs, 1H, NH), 7.40-7.05 (m, 8H, aromatic ring), 4.22-4.19 (m, 2H, α-H's at C-5 coincided), 2.43-2.35 (m, 2H, β-H's coincided), 2.20 (s, two *o*-methyl signals coincided), 1.15 and 1.14 (two doublets, *J* = 7.2 Hz, 6H, methyls at β-C), 1.07 (two doublets, *J* = 6.8 Hz, 6H, two methyl signals coincided at β-C). ¹³C NMR (100 MHz, CDCl₃): δ 184.40, 172.99, 172.97, 136.96, 136.76, 132.12, 131.39, 130.21, 130.17, 129.36, 129.06, 127.26, 127.21, 65.57, 65.22, 31.38, 30.90, 19.23, 18.96, 18.28, 17.96, 16.86, 16.39 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.9. 5-Isopropyl-3-*o*-fluorophenyl thiohydantoin (9). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.44 ml (3.58 mmole) of *o*-fluorophenyl isothiocyanate was added to the solution of 0.65 g (3.58 mmole) of L-valine ethyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.67g (74%). Mp: 158-160 °C ¹H NMR (400MHz, CDCl₃): δ 7.49-7.21 (m, 10H, aromatic ring and NH), 4.23 and 4.19 (two doublets, *J* = 4.0 Hz, 2H, α-H at C-5), 2.42-2.34 (m, 2H, β-H), 1.14 (d, *J* = 7.2 Hz, 6H, one of the diastereotopic methyl signals at β-C), 1.05 (two methyl signals coincided, *J* = 6.8 Hz, 6H, other diastereotopic methyl signals at β-C). ¹³C NMR (100 MHz, CDCl₃): δ 183.85, 183.75, 172.61, 172.45, 159.53, 159.39, 156.88, 131.84, 131.79, 131.76, 131.70, 131.09, 130.78, 124.83, 124.80, 120.69, 120.56, 117.10, 116.96, 116.90, 116.77, 65.62, 65.41, 31.37, 31.29, 18.99, 18.95, 16.47, 16.20 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.10. 5-Isopropyl-3-*o*-chlorophenyl thiohydantoin (10). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.43 ml (3.58 mmole) of *o*-chlorophenyl isothiocyanate was added to the solution of 0.65 g (3.58 mmole) of L-valine ethyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.42g (44%). Mp: 176-178 °C ¹H NMR (400MHz, CDCl₃): δ 7.79 (bs, 1H, NH), 7.58-7.23 (m, 8H, aromatic ring), 4.26 and 4.20 (two doublets, *J* = 4.0 Hz, 2H, α-H at C-5),

2.45-2.35 (m, 2H, β -H's coincided), 1.16 (two doublets, $J = 7.2$, 6H, two methyl signals at β -C coincided), 1.11 and 1.06 (d, $J = 6.8$, 6H, methyl signals at β -C). ^{13}C NMR (100 MHz, CDCl_3): δ 183.61, 183.60, 172.45, 172.34, 133.58, 133.43, 131.38, 131.33, 131.10, 130.85, 130.82, 130.66, 128.00, 127.97, 65.84, 65.46, 31.25, 31.11, 19.36, 18.99, 17.03, 16.50 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.11. 5-Isopropyl-3-*o*-bromophenyl thiohydantoin (11). The compound was synthesized according to the general procedure, the reflux time being 4 h. 0.48 ml (3.58 mmole) of *o*-bromophenyl isothiocyanate was added to the solution of 0.65 g (3.58 mmole) of L-valine ethyl ester HCl salt and 0.5 ml (3.58 mmole) of Et_3N in 10 ml CH_2Cl_2 . Yield: 0.51g (46%). Mp: 170-172 °C ^1H NMR (400MHz, CDCl_3): δ 7.67 (bs, 1H, NH), 7.74-7.23 (m, 8H, aromatic ring), 4.26 and 4.19 (two doublets, $J = 4.0$ Hz and $J = 4.4$, 2H, α -H at C-5), 2.41-2.37 (m, 2H, β -H), 1.18 and 1.14 (d, $J = 7.2$ Hz, 6H, two methyl signals at β -C), 1.15 and 1.07 (d, $J = 6.8$ Hz, 6H, two methyl signals at β -C) ^{13}C NMR (100 MHz, CDCl_3): δ 183.30, 183.24, 172.07, 172.01, 133.66, 133.60, 132.37, 131.32, 131.26, 131.19, 130.95, 128.50, 128.46, 123.50, 123.24, 65.62, 65.25, 31.01, 30.86, 19.22, 18.73, 17.31, 16.31 ppm (Diastereomeric isomers gave different carbon signals).

4.1.1.12. 5-Isopropyl-3-*o*-iodophenyl thiohydantoin (12). The compound was synthesized according to the general procedure, the reflux time being 4 h. 1.00 g (3.83 mmole) of *o*-iodophenyl isothiocyanate was added to the solution of 0.70 g (3.83 mmole) of L-valine ethyl ester HCl salt and 0.53 ml (3.83 mmole) of Et_3N in 10ml CH_2Cl_2 . Yield: 1.25 g (91%). Mp: 177-180 °C ^1H NMR (400MHz, CDCl_3): δ 7.97-7.17 (m, 5H, NH and aromatic ring), 4.26 and 4.14 (d, $J = 4.0$ Hz and $J = 4.8$ Hz, 2H, α -H at C-5), 2.43-2.36 (m, 2H, β -H), 1.20 (two doublets, $J = 7.2$ and $J = 6.8$ Hz, 6H, two methyl signals at β -C), 1.15 and 1.06 (two doublets, $J = 7.2$ Hz and $J = 6.8$ Hz, 6H, two methyl signals at β -C). ^{13}C NMR (100 MHz, CDCl_3): δ 183.06, 172.01, 139.87, 135.92, 131.32, 130.28, 129.45, 99.27, 65.52, 30.99, 18.83, 16.33 ppm.

4.1.1.13. 5-Isopropyl- α -naphthyl thiohydantoin (13). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.66 g (3.58 mmole) of 1-naphthyl isothiocyanate was added to the solution of 0.65 g (3.58 mmole) of L-valine ethyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.70g (69%). Mp: 199-201 °C ¹H NMR (400MHz, CDCl₃): δ 8.25 (bs, 1H, NH), 8.00-7.33 (m, 14H, aromatic ring), 4.32 and 4.25 (two doublets, J = 3.6 Hz, 2H, α -H at C-5), 2.49-2.36 (m, 2H, β -H), 1.18 and 1.17 (d, J = 7.2 Hz and J = 6.8 Hz, 6H, methyl signals at β -C), 1.14 and 1.09 (d, J = 6.8 Hz, 6H, methyl signals at β -C). ¹³C NMR (100 MHz, CDCl₃): δ 184.72, 173.67, 134.54, 130.53, 130.30, 129.71, 128.86, 127.89, 127.50, 126.84, 125.54, 122.41, 65.48, 46.02, 31.47, 18.92, 16.48 ppm.

4.1.1.14. 5-Isopropyl-3-phenyl thiohydantoin (14). The compound was synthesized according to the general procedure, the reflux time being 1 h. 0.43 ml (3.58 mmole) of phenyl isothiocyanate was added to the solution of 0.65 g (3.58 mmole) of L-valine ethyl ester HCl salt and 0.5 ml (3.58 mmole) of Et₃N in 10 ml CH₂Cl₂. Yield: 0.33g (39%). Mp: 210-212 °C ¹H NMR (400MHz, CDCl₃): δ 7.64 (bs, 1H, NH), 7.47-7.21 (m, 5H, aromatic ring), 4.11 (d, J = 1.2 Hz, 1H, α -H), 2.37-2.28 (m, 1H, β -H), 1.08 (d, J = 7.2 Hz, 3H, methyl signal at β -C), 0.98 (d, J = 6.8 Hz, 3H, methyl signals at β -C). ¹³C NMR (100 MHz, CDCl₃): δ 184.48, 173.18, 132.82, 129.52, 129.41, 128.46, 65.21, 31.38, 19.02, 16.41 ppm.

4.1.1.15. 5-Benzyl-3-*o*-bromophenyl thiohydantoin (15). The compound was synthesized according to the general procedure, using 0.5 g (2.32 mmol) of *L*-phenyl alanine methyl ester salt, 0.32 ml (2.32 mmol) of Et₃N and 0.31 ml (2.32 mmol) of *o*-bromophenyl isothiocyanate in 10 ml CH₂Cl₂. Yield: 0.63g (76%). Mp: 150 °C ¹H NMR (400MHz, CDCl₃): δ 7.8-6.8 (m, 9H, aromatic ring), 7.2 (bs, 1H, NH), 4.5-4.7 (dd, J_{H-Ha} = 4 Hz for both **SM&RP** and **RM&SP**, J_{H-Hb} = 8 Hz for **SM&RP** and 10 Hz for **RM&SP**, 1H, α -H), 3.6-3.0 (dd, J_{Ha-H} = 4 Hz for both **SM&RP** and **RM&SP**, J_{Hb-H} = 8 Hz for **SM&RP** and 10 Hz for **RM&SP**, J_{Ha-Hb} = 14 Hz for both **SM&RP** and **RM&SP**, 2H, CH₂).

4.2. Aldol Reactions of 5-Methyl- and 5-Isopropyl-3-o-aryl Thiohydantoins

4.2.1. General Procedure for Aldol Reactions with Benzaldehyde

The aldol reactions were carried out under nitrogen. To the solution of 5-methyl- or 5-isopropyl-3-o-aryl thiohydantoins (0.16M) in THF at -78°C was added lithium diisopropylamide (2M, 2.4 equivalents). The mixture was stirred for 1h for enolate formation and then benzaldehyde (2 equivalents) was added. The reaction mixture was stirred for 2h for **16-21** and for 6h for **22-27** at -78°C and quenched with saturated NH_4Cl solution (2 equivalents). The solution was extracted with diethyl ether for three times and dried over anhydrous CaCl_2 . The ether was evaporated and the crude product was precipitated from diethyl ether/petroleum ether.

4.2.1.1. 5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-florophenyl thiohydantoin (16). The compound was synthesized according to the general procedure using 0.27 g (1.20 mmol) of compound **2** in 7.52 mL THF, 1.45 mL (2.89 mmol) of LDA and 0.24 mL (2.41 mmol) of benzaldehyde. Yield: 0.16 g (42%), mp: 69-72 $^{\circ}\text{C}$. ^1H NMR (400MHz, CDCl_3): δ 7.50-7.00 (m, 8H, aromatic ring), 6.92 and 6.88 (bs, 1H, NH), 6.11 (dd, $J = 7.6$ Hz, 1H, aromatic proton), 5.05 and 5.01 (s, 1H, benzylic H), 2.7 and 2.3 (bs, 1H, -OH), 1.82, 1.75, 1.42 and 1.40 (s, 3H, CH_3 at α -C). ^{13}C NMR (100MHz, CDCl_3): δ 182.7, 182.6, 179.9, 171.8, 171.73, 171.70, 135.4, 134.8, 134.4, 134.1, 134.0, 133.9, 133.5, 133.4, 132.19, 132.16, 131.34, 131.26, 131.2, 130.8, 129.54, 129.51, 129.31, 129.27, 129.2, 129.0, 128.7, 128.6, 128.5, 128.4, 127.83, 127.76, 127.2, 127.0, 123.40, 123.38, 120.2, 61.4, 61.1, 58.4, 52.5, 46.0, 37.9, 37.4, 29.7 ppm (Diastereomeric isomers gave different carbon signals).

4.2.1.2. 5-(Hydroxy(phenyl)methyl)-5-methyl-3-o-chlorophenyl thiohydantoin (17). The compound was synthesized according to the general procedure using 0.50 g (2.08 mmol) of compound **3** in 13 mL THF, 2.5 mL (4.99 mmol) of LDA and 0.42 mL (4.16 mmol) of benzaldehyde. Yield: 0.34 g (47%), mp: 165-166 $^{\circ}\text{C}$. ^1H NMR (400MHz, CDCl_3): δ 7.61

(bs, 1H, NH), 7.46-7.16 (m, 9H, aromatic ring), 6.07 (dd, 1H, aromatic proton), 5.04 and 5.02 (s, 1H, benzylic H), 2.86 and 2.58 (bs, 1H, -OH), 1.83 and 1.73 (s, 3H, CH₃ at α -C). ¹³C NMR (100MHz, CDCl₃): δ 181.8, 173.4, 137.2, 136.9, 133.4, 133.2, 131.1, 130.9, 130.8, 130.5, 130.3, 130.2, 130.0, 129.29, 129.26, 128.9, 128.6, 127.6, 127.5, 127.2, 69.3, 68.0, 20.1, 19.9 ppm (Diastereomeric isomers gave different carbon signals).

4.2.1.3. 5-(Hydroxy(phenyl)methyl)-5-methyl-3-*o*-bromophenyl thiohydantoin (18). The compound was synthesized according to the general procedure using 0.25 g (0.88 mmol) of compound **4** in 5.5 mL THF, 1.05 mL (2.10 mmol) of LDA and 0.18 mL (1.75 mmol) of benzaldehyde. Yield: 0.14 g (41%), mp: 158-160 °C. ¹H NMR (400MHz, CDCl₃): δ 7.76 (bs, 1H, NH), 7.74-7.00 (m, 9H, aromatic ring), 6.05 (m, 1H, aromatic proton), 5.11, 5.08, 5.06 and 5.01 (s, 1H, benzylic H), 1.91, 1.83 and 1.70 (s, 3H, CH₃ at α -C). ¹³C NMR (100MHz, CDCl₃): δ 181.6, 173.3, 137.3, 137.2, 133.5, 133.4, 133.2, 131.8, 131.3, 131.2, 131.1, 130.5, 129.3, 129.23, 129.19, 129.17, 128.99, 128.93, 128.6, 128.5, 128.3, 127.7, 127.24, 127.21, 127.0, 123.5, 123.3, 69.5, 68.6, 20.3, 20.1 ppm (Diastereomeric isomers gave different carbon signals).

4.2.1.4. 5-(Hydroxy(phenyl)methyl)-5-methyl-3-*o*-iodophenyl thiohydantoin (19). The compound was synthesized according to the general procedure using 0.25 g (0.75 mmol) of compound **5** in 4.7 mL THF, 0.9 mL (1.81 mmol) of LDA and 0.15 mL (1.51 mmol) of benzaldehyde. Yield: 0.084 g (25%), mp: 176-179 °C. ¹H NMR (400MHz, CDCl₃): δ 7.00-8.00 (m, 10H, NH and aromatic ring), 5.98 (d, 1H, aromatic proton), 5.05 and 5.01 (s, 1H, benzylic H), 2.68 (bs, 1H, -OH), 1.86 (s, 3H, CH₃ at α -C). ¹³C NMR (100MHz, CDCl₃): δ 181.5, 173.1, 139.7, 139.5, 137.2, 135.3, 131.3, 130.5, 129.8, 129.5, 129.4, 129.2, 129.0, 128.6, 127.3, 127.0, 99.2, 98.9, 69.5, 68.6, 20.3, 20.2 ppm (Diastereomeric isomers gave different carbon signals).

4.2.1.5. 5-(Hydroxy(phenyl)methyl)-5-methyl-3- α -naphthyl thiohydantoin (20). The compound was synthesized according to the general procedure using 0.25 g (0.98 mmol) of compound **6** in 6.1 mL THF, 1.2 mL (2.34 mmol) of LDA and 0.2 mL (1.95 mmol) of

benzaldehyde. Yield: 0.19 g (54%). ^1H NMR (400MHz, CDCl_3): δ 7.00-8.00 (m, 12H, NH and aromatic ring), 5.99 and 5.61 (d, $J = 7.2$ Hz and $J = 8.0$ Hz, 1H, aromatic proton), 5.07, 5.03, 5.01 and 4.97 (s, 1H, benzylic H), 3.2-2.4 (bs, 1H, -OH), 1.85, 1.82, 1.46 and 1.38 (s, 3H, CH_3 at α -C). ^{13}C NMR (100MHz, CDCl_3): δ 184.1, 183.1, 183.0, 175.9, 174.7, 137.8, 137.4, 137.34, 137.29, 134.4, 134.3, 134.09, 134.07, 130.44, 130.35, 130.3, 130.2, 130.1, 129.97, 129.91, 129.7, 129.38, 129.36, 129.32, 129.29, 129.12, 129.08, 129.0, 128.9, 128.7, 128.5, 128.4, 128.1, 127.7, 127.52, 127.46, 127.33, 127.29, 127.25, 127.17, 127.1, 127.04, 126.96, 126.6, 126.54, 126.47, 126.3, 125.4, 125.20, 125.18, 125.1, 123.1, 122.0, 121.8, 121.7, 69.5, 69.4, 68.5, 68.4, 21.6, 20.6, 20.5 ppm (Diastereomeric isomers gave different carbon signals).

4.2.1.6. 5-(Hydroxy(phenyl)methyl)-5-methyl-3-phenyl thiohydantoin (21). The compound was synthesized according to the general procedure using 0.23 g (1.12 mmol) of compound **7** in 7.0 mL THF, 1.3 mL (2.68 mmol) of LDA and 0.23 mL (2.23 mmol) of benzaldehyde. Yield: 0.23 g (66%). ^1H NMR (400MHz, CDCl_3): δ 8.22 (bs, 1H, NH); 7.81-7.00 (m, 9H, aromatic rings); 6.52 (d, $J = 5.2$ Hz, 1H, aromatic proton); 4.95 and 4.88 (s, 1H, benzylic H); 3.66 and 3.24 (bs, 1H, -OH), 1.96 and 1.72 (s, 3H, CH_3 at α -C).

4.2.1.7. 5-(Hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-florophenyl thiohydantoin (22). The compound was synthesized according to the general procedure using 0.19 g (0.75 mmol) of compound **9** in 4.7 mL THF, 0.9 mL (1.81 mmol) of LDA and 0.15 mL (1.51 mmol) of benzaldehyde. Yield: 0.12 g (44%). ^1H NMR (400MHz, CDCl_3): δ 8.4-6.0 (m, 10H, NH and aromatic rings); 5.31, 5.25 and 5.15 (s, 1H, benzylic H); 4.56, 4.20 and 3.38 (bs, 1H, -OH); 2.50, 2.38 and 2.23 (m, 1H, β -H); 1.46-1.00 (m, 6H, diastereotopic methyl signals).

4.2.1.8. 5-(Hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-chlorophenyl thiohydantoin (23). The compound was synthesized according to the general procedure using 0.20 g (0.74 mmol) of compound **10** in 4.7 mL THF, 0.89 mL (1.79 mmol) of LDA and 0.15 mL (1.49 mmol) of benzaldehyde. Yield: 0.10 g (36%). ^1H NMR (400MHz, CDCl_3): δ 7.60-7.08 (m, 10H, NH and aromatic rings); 6.43, 6.41, 5.71, 5.69 (d, $J = 1.6$ Hz, 1H, aromatic H of major

isomers); 5.28, 5.27, 5.25 and 5.10 (s, 1H, benzylic H); 2.60-2.30 (m, 1H, β -H); 1.45-1.06 (d, J = 6.8 Hz, 6H, diastereotopic methyl signals).

4.2.1.9. 5-(Hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-bromophenyl thiohydantoin (24). The compound was synthesized according to the general procedure using 0.10 g (0.32 mmol) of compound **11** in 2.0 mL THF, 0.38 mL (0.77 mmol) of LDA and 0.065 mL (0.64 mmol) of benzaldehyde. Yield: 0.036 g (28%). ^1H NMR (400MHz, CDCl_3): δ 8.83, (bs, 1H, NH); 7.54-7.00 (m, 9H, aromatic rings); 6.31, 6.30, 5.54, 5.25 (d, J = 3.6 Hz and J = 1.6 Hz, 1H, aromatic H of major isomers); 5.23, 5.21 and 5.06 (s, 1H, benzylic H); 3.32, 2.86 (bs, 1H, OH); 2.60-2.40 (m, 1H, β -H); 1.40-1.00 (d, J = 6.8 Hz, 6H, diastereotopic methyl signals).

4.2.1.10. 5-(Hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-iodophenyl thiohydantoin (25). The compound was synthesized according to the general procedure using 0.021 g (0.058 mmol) of compound **12** in 0.36 mL THF, 0.07 mL (0.14 mmol) of LDA and 0.012 mL (0.12 mmol) of benzaldehyde. Yield: 0.011 g (41%). ^1H NMR (400MHz, CDCl_3): δ 8.4-6.8 (m, 9H, aromatic rings); 6.20 (d, J = 7.6 Hz, 1H, aromatic H of major isomers); 6.11, 5.96 (bs, 1H, NH); 5.25, 5.20 and 5.07 (s, 1H, benzylic H); 2.80-1.60 (m, 2H, OH and β -H); 1.50-0.80 (m, 6H, diastereotopic methyl signals).

4.2.1.11. 5-(Hydroxy(phenyl)methyl)-5-isopropyl-3- α -naphthyl thiohydantoin (26). The compound was synthesized according to the general procedure using 0.13 g (0.46 mmol) of compound **13** in 2.9 mL THF, 0.55 mL (1.10 mmol) of LDA and 0.093 mL (0.92 mmol) of benzaldehyde. Yield: 0.12 g (47%). ^1H NMR (400MHz, CDCl_3): δ 8.03-6.80 (m, 10H, NH and aromatic rings); 5.80, 5.61 (d, J = 7.6 Hz and J = 9.2 Hz, 1H, aromatic H of major isomers); 5.39, 5.35, 5.31 and 5.20 (s, 1H, benzylic H); 2.78-2.38 (m, 2H, OH and β -H); 1.48-1.12 (m, 6H, diastereotopic methyl signals).

4.2.1.12. 5-(Hydroxy(phenyl)methyl)-5-isopropyl-3-phenyl thiohydantoin (27). The compound was synthesized according to the general procedure using 0.10 g (0.43 mmol) of

compound **14** in 2.7 mL THF, 0.51 mL (1.03 mmol) of LDA and 0.087 mL (0.85 mmol) of benzaldehyde. Yield: 0.10 g (67%). ^1H NMR (400MHz, CDCl_3): δ 8.56, (bs, 1H, NH); 7.90-7.20 (m, 8H, aromatic rings); 6.88, 6.53, (d, $J = 6.8$ Hz and $J = 7.2$ Hz, 1H, one aromatic H); 5.27 and 5.11 (s, 1H, benzylic H); 3.34 and 3.02 (bs, 1H, OH); 2.61-2.47 (m, 1H, β -H); 2.81, 1.35 (d, $J = 6.4$ Hz, 3H, one of the diastereotopic methyl signals of the isomers), 1.13 (two doublets were coincided, 3H, the other diastereotopic methyl signals of the isomers).

4.2.2. General Procedure for Aldol Reactions with 4-Nitrobenzaldehyde

The aldol reactions were carried out under nitrogen. To the solution of 5-methyl-(**2-7**) or 5-isopropyl-3-*o*-aryl thiohydantoin (**9-14**) (0.16M) in THF at -78°C was added lithium diisopropylamide (2M, 2.4 equivalents). The mixture was stirred for 1h for enolate formation and then benzaldehyde (2 equivalents) was added. The reaction mixture was stirred for 2h for **28-33** and for 6h for **34-39** at -78°C and quenched with saturated NH_4Cl solution (2 equivalents). The solution was extracted with diethyl ether for three times and dried over anhydrous CaCl_2 . The ether was evaporated and the crude product was precipitated from diethyl ether/petroleum ether.

4.2.2.1. 5-(Hydroxy(4-nitrophenyl)methyl)-5-methyl-3-*o*-fluorophenyl thiohydantoin (28).

The compound was synthesized according to the general procedure using 0.17 g (0.76 mmol) of compound **2** in 4.7 mL THF, 0.91 mL (1.82 mmol) of LDA and 0.23 g (1.52 mmol) of 4-nitrobenzaldehyde. Yield: 0.17 g (60%). ^1H NMR (400MHz, CDCl_3): δ 8.6-7.0 (m, 9H, aromatic rings); 6.28 (bs, 1H, NH); 5.20, 5.19 and 5.15 (s, 1H, benzylic H); 3.51 and 3.42 (bs, 1H, -OH); 2.00-1.00 (m, 3H, methyl signals at C5 were coincided).

4.2.2.2. 5-(Hydroxy(4-nitrophenyl)methyl)-5-methyl-3-*o*-chlorophenyl thiohydantoin (29).

The compound was synthesized according to the general procedure using 0.33 g (1.37 mmol) of compound **3** in 8.6 mL THF, 1.65 mL (3.29 mmol) of LDA and 0.41 g (2.74

mmol) of 4-nitrobenzaldehyde. Yield: 0.37 g (63%). ^1H NMR (400MHz, CDCl_3): δ 8.37-7.34 (m, 9H, NH and aromatic rings); 6.20 (d, $J = 8.0$ Hz, 1H, one aromatic H); 5.15 and 5.11 (s, 1H, benzylic H); 3.34 and 2.83 (bs, 1H, -OH); 1.8-1.2 (m, 3H, methyl signals at C5 were coincided with the solvent peak).

4.2.2.3. 5-(Hydroxy(4-nitrophenyl)methyl)-5-methyl-3-*o*-bromophenyl thiohydantoin (30).

The compound was synthesized according to the general procedure using 0.35 g (1.23 mmol) of compound **4** in 7.7 mL THF, 1.47 mL (2.95 mmol) of LDA and 0.37 g (2.46 mmol) of 4-nitrobenzaldehyde. Yield: 0.43 g (80%). ^1H NMR (400MHz, CDCl_3): δ 8.50-7.40 (m, 9H, NH and aromatic rings); 6.23 (bs, 1H, one aromatic H could not be splitted); 5.26, 5.21 and 5.17 (s, 1H, benzylic H); 3.50 and 3.40 (bs, 1H, -OH); 1.89, 1.52 and 1.48 (s, 3H, methyl signals at C5).

4.2.2.4. 5-(Hydroxy(4-nitrophenyl)methyl)-5-methyl-3-*o*-iodophenyl thiohydantoin (31).

The compound was synthesized according to the general procedure using 0.20 g (0.60 mmol) of compound **5** in 3.8 mL THF, 0.72 mL (1.45 mmol) of LDA and 0.18 g (1.20 mmol) of 4-nitrobenzaldehyde. Yield: 0.21 g (74%). ^1H NMR (400MHz, CDCl_3): δ 8.60-7.00 (m, 9H, NH and aromatic rings); 6.27, 6.14 (bs, 1H, one aromatic H of one minor and one major isomers); 5.25, 5.21, 5.16 and 5.13 (s, 1H, benzylic H); 3.50 and 3.42 (m, 1H, -OH); 1.95, 1.58 and 1.45 (s, 3H, methyl signals at C5).

4.2.2.5. 5-(Hydroxy(4-nitrophenyl)methyl)-5-methyl-3- α -naphthyl thiohydantoin (32).

The compound was synthesized according to the general procedure using 0.27 g (1.05 mmol) of compound **6** in 6.6 mL THF, 1.26 mL (2.53 mmol) of LDA and 0.32 g (2.11 mmol) of 4-nitrobenzaldehyde. Yield: 0.29 g (67%). ^1H NMR (400MHz, CDCl_3): δ 8.60-7.00 (m, 11H, NH and aromatic rings); 6.27, 6.14 (bs, 1H, one aromatic H of one minor and one major isomers); 5.25, 5.21, 5.16 and 5.13 (s, 1H, benzylic H); 3.50 and 3.42 (m, 1H, -OH); 1.95, 1.58 and 1.45 (s, 3H, methyl signals at C5).

4.2.2.6. 5-(Hydroxy(4-nitrophenyl)methyl)-5-methyl-3-phenyl thiohydantoin (33). The compound was synthesized according to the general procedure using 0.15 g (0.70 mmol) of compound **7** in 4.4 mL THF, 0.84 mL (1.69 mmol) of LDA and 0.21 g (1.41 mmol) of 4-nitrobenzaldehyde. Yield: 0.23 g (93%). ^1H NMR (400MHz, CDCl_3): δ 8.50-7.30 (m, 9H, NH and aromatic rings); 6.71 (d, $J = 2.8$ Hz, 1H, one aromatic H); 5.18 and 5.14 (s, 1H, benzylic H); 3.50 and 3.40 (m, 1H, -OH); 2.07 and 1.29 (s, 3H, one of the methyl signals at C5 was coincided with the solvent peak).

4.2.2.7. 5-(Hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-*o*-fluorophenyl thiohydantoin (34). The compound was synthesized according to the general procedure using 0.2 g (0.79 mmol) of compound **9** in 5.0 mL THF, 0.95 mL (1.90 mmol) of LDA and 0.24 g (1.59 mmol) of 4-nitrobenzaldehyde. Yield: 0.13 g (41%). ^1H NMR (400MHz, CDCl_3): δ 8.4-7.0 (m, 8H, NH and aromatic rings); 6.06 (dd, $J = 7.2$ Hz, 1H, one aromatic H); 5.31, 5.17 and 5.15 (s, 1H, benzylic H); 3.55 and 3.20 (bs, 1H, -OH); 2.80-2.00 (m, 1H, β -H); 1.4-0.8 (m, 6H, coincided diastereotopic methyl signals).

4.2.2.8. 5-(Hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-*o*-chlorophenyl thiohydantoin (35). The compound was synthesized according to the general procedure using 0.1 g (0.37 mmol) of compound **10** in 2.3 mL THF, 0.45 mL (0.89 mmol) of LDA and 0.11 g (0.74 mmol) of 4-nitrobenzaldehyde. Yield: 0.085 g (54%). ^1H NMR (400MHz, CDCl_3): δ 8.4-7.0 (m, 8H, NH and aromatic rings); 6.33, 5.80 (d, $J = 7.6$ Hz, 1H, one aromatic H); 5.42, 5.40, 5.28 and 5.23 (s, 1H, benzylic H); 3.50-3.20 (bs, 1H, -OH); 2.70-2.30 (m, 1H, β -H); 1.50-1.00 (m, 6H, coincided diastereotopic methyl signals).

4.2.2.9. 5-(Hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-*o*-bromophenyl thiohydantoin (36). The compound was synthesized according to the general procedure using 0.17 g (0.54 mmol) of compound **11** in 3.4 mL THF, 0.65 mL (1.30 mmol) of LDA and 0.16 g (1.09 mmol) of 4-nitrobenzaldehyde. Yield: 0.057 g (23%). ^1H NMR (400MHz, CDCl_3): δ 8.40-6.80 (m, 8H, NH and aromatic rings); 6.20, 5.97 and 5.70 (d, $J = 4.4$ Hz, $J = 8.4$ Hz and $J = 7.6$ Hz, 1H, one aromatic H); 5.47, 5.39, 5.37 and 5.23 (s, 1H, benzylic H); 3.40-3.30 (m,

1H, -OH); 2.98-2.31 (m, 1H, β -H); 1.41-1.02 (m, 6H, coincided diastereotopic methyl signals).

4.2.2.10. 5-(Hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-*o*-iodophenyl thiohydantoin (37). The compound was synthesized according to the general procedure using 0.1 g (0.28 mmol) of compound **12** in 1.7 mL THF, 0.33 mL (0.67 mmol) of LDA and 0.084 g (0.56 mmol) of 4-nitrobenzaldehyde. Yield: 0.053 g (38%). ^1H NMR (400MHz, CDCl_3): δ 8.80-6.90 (m, 7H, aromatic rings); 5.92 and 5.88 (d, $J = 7.6$ Hz and $J = 8.4$ Hz, 1H, one aromatic H); 5.59 and 5.57 (bs, 1H, NH); 5.32, 5.28, 5.25 and 5.22 (s, 1H, benzylic H); 5.0, 3.48-3.20 (bs, 1H, -OH); 2.96-2.46 (m, 1H, β -H); 1.30-1.00 (m, 6H, coincided diastereotopic methyl signals).

4.2.2.11. 5-(Hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3- α -naphthylthiohydantoin(38). The compound was synthesized according to the general procedure using 0.053 g (0.19 mmol) of compound **13** in 1.2 mL THF, 0.2 mL (0.45 mmol) of LDA and 0.056 g (0.37 mmol) of 4-nitrobenzaldehyde. Yield: 0.013 g (16%). ^1H NMR (400MHz, CDCl_3): δ 8.56-7.27 (m, 11H, NH and aromatic rings); 6.24, 5.89 and 5.75 (d, $J = 5.6$, $J = 6.8$ Hz and $J = 8.0$ Hz, 1H, one aromatic H); 5.33, 5.29, 5.27 and 5.22 (s, 1H, benzylic H); 3.27 (bs, 1H, -OH); 2.79-2.16 (m, 1H, β -H); 1.33-1.03 (m, 6H, coincided diastereotopic methyl signals).

4.2.2.12. 5-(Hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-phenyl thiohydantoin (39). The compound was synthesized according to the general procedure using 0.1 g (0.43 mmol) of compound **14** in 2.7 mL THF, 0.51 mL (1.03 mmol) of LDA and 0.13 g (0.85 mmol) of 4-nitrobenzaldehyde. Yield: 0.054 g (57%). ^1H NMR (400MHz, CDCl_3): δ 8.91 (bs, 1H, NH); 8.34-7.00 (m, 8H, aromatic rings); 6.74 and 6.55 (d, $J = 2.4$ Hz and $J = 4.0$ Hz, 1H, one aromatic H); 5.30 and 5.14 (s, 1H, benzylic H); 3.67 and 3.32 (m, 1H, -OH); 2.61-2.48 and 2.32-2.27 (m, 1H, β -H); 1.33, 1.29, 1.09 and 1.05 (d, , $J = 6.4$ Hz, , $J = 6.8$ Hz, $J = 7.6$ Hz and $J = 6.8$ Hz, 6H, diastereotopic methyl signals).

4.3. Reduction Reactions of 5-Methyl- and 5-Isopropyl-3-o-aryl Thiohydantoins

4.3.1. General Procedure

To a solution of compounds **1-14** in THF was added 4 equivalents LiAlH_4 . The reaction mixture was stirred for 10 minutes at room temperature, quenched with water and extracted with ethyl acetate (If the reaction was quenched with HCl, the reaction gave elimination product resulting from the dehydration which is favored in acidic conditions). After the combined organic layers were dried over anhydrous CaCl_2 , it was filtered and the solvent was evaporated. The crude product was recrystallized from diethyl ether or diethyl ether-petroleum ether.

4.3.1.1. 4-Hydroxy-5-methyl-3-o-tolyl-2-imidazolidinethione (40). It was synthesized according to the general procedure using 0.2 g of compound **1** (0.91 mmol) and 0.14 g of LiAlH_4 (3.6 mmol) in 10 mL THF. Yield: 0.17g (84%), white solid, mp: 208-210 °C ^1H NMR (400MHz, CDCl_3): δ 7.40-7.28 (m, 4H, aromatic ring); 6.80-6.60 (bs, 1H, NH); 5.26, 5.02 and 4.79 (three singlets, 1H, H at C4); 4.20 and 3.87 (two multiplets, 1H, H at C5); 3.42 and 3.05-3.2 (three bs, OH), 2.44-2.20 (bs, 3H, *o*- CH_3); 1.42-1.36 (methyl signals coincided, 3H, CH_3 at C5). ^{13}C NMR (100 MHz, CDCl_3): δ 181.7, 135.6-127.1, 91.2, 58.9, 55.1, 19.8, 17.9 ppm (the C5 and methyl signals for diastereomers gave different carbon signals).

4.3.1.2. 4-Hydroxy-5-methyl-3-o-fluorophenyl-2-imidazolidinethione (41). It was synthesized according to the general procedure using 0.1 g of compound **2** (0.45 mmol) and 0.068 g LiAlH_4 (1.8 mmol) in 10 mL THF. Yield: 0.098g (98%), light-beige solid, mp: 94-98 °C ^1H NMR (400MHz, CDCl_3): δ 7.6-7.2 (m, 4H, aromatic ring); 6.89 and 6.79 (bs, 1H, NH); 5.46 and 5.18 (d and s, $J=6.0$ Hz, 1H, H at C4); 4.23 and 3.89 (m and q, $J=6.0$ Hz, 1H, H at C5); 3.43 and 2.98 (bs, 1H, OH); 1.44-1.36 (d, $J = 6.8$ Hz, 3H, CH_3 at C5). ^{13}C NMR (100 MHz, CDCl_3): δ 182.5, 181.7, 158.6 ($^1J_{\text{C-F}} = 249$ Hz), 131.9, 131.7, 130.3,

130.2, 125.1, 125.0, 124.6, 124.5, 116.7, 116.5, 91.7, 86.5, 59.1, 54.9, 19.2, 13.1 ppm (Diastereomeric isomers gave different carbon signals).

4.3.1.3. 4-Hydroxy-5-methyl-3-*o*-chlorophenyl-2-imidazolidinethione (42). It was synthesized according to the general procedure using compound **3** (0.049g, 0.20 mmol), LiAlH₄ (0.031g, 0.81 mmol) and 10 mL THF. Yield: 0.087g (87%), white solid, mp: 233-236 °C. ¹H NMR (400MHz, CDCl₃): δ 7.56-7.34 (m, 4H, aromatic ring); 6.49 and 6.38 (bs, 1H, NH); 5.53 and 5.26 (bs, 1H, H at C4); 4.28 and 3.89 (m and q, 1H, H at C5); 3.00 and 2.74 (bs, 1H, OH); 1.46 and 1.40 (d, *J* = 6.8 Hz, 3H, CH₃ at C5). ¹³C NMR (100 MHz, CDCl₃): δ 182.01, 134.52, 133.31, 130.58, 130.50, 130.39, 130.26, 127.88, 91.12, 59.45, 55.19, 19.67, 13.42 ppm (aromatic, C5 and methyl groups of diastereomers gave different carbon signals).

4.3.1.4. 4-Hydroxy-5-methyl-3-*o*-bromophenyl-2-imidazolidinethione (43). It was synthesized according to the general procedure using compound **4** (0.25g, 0.88 mmol), LiAlH₄ (0.13g, 3.51 mmol) and 10 mL THF. Yield: 0.22g (85%), light yellow solid, mp: 129-132 °C ¹H NMR (400MHz, CDCl₃): δ 7.72-7.28 (m, 4H, aromatic ring); 6.68 and 6.56 (bs, 1H, NH); 5.53, 5.27 and 5.22 (t, d and d, 1H, H at C4); 4.29 and 3.89 (m and q, 1H, H at C5); 3.22 and 2.92 (bs, 1H, OH); 1.47 and 1.39 (d, 3H, CH₃ at C5) ¹³C NMR (100 MHz, CDCl₃): δ 181.6, 133.5, 130.4, 130.3, 129.2, 128.3, 127.4, 126.5, 126.4, 90.5, 59.2, 55.0, 19.6, 11.8 ppm (aromatic, C5 and methyl groups of diastereomers gave different carbon signals).

4.3.1.5. 4-Hydroxy-5-methyl-3-*o*-iodophenyl-2-imidazolidinethione (44). It was synthesized according to the general procedure using compound **5** (0.1g, 0.30 mmol), LiAlH₄ (0.046g, 1.20 mmol) and 10 mL THF. Yield: 0.091g (90%), light-beige solid, mp: 68-71 °C. ¹H NMR (400MHz, CDCl₃): δ 7.90-7.00 (m, 4H, aromatic ring); 6.52, 6.45 and 6.29 (bs, 1H, NH); 5.42, 5.20 and 5.15 (d *J* = 6.8 Hz, s, s, 1H, H at C4); 4.50-3.50 (m, 2H, H at C5 and OH at C4); 1.44 and 1.31 (d, *J* = 6.8 Hz and *J* = 6.4 Hz, 3H, CH₃ at C5). ¹³C NMR (100 MHz, CDCl₃): δ 181.1, 139.7, 137.8, 129.09, 129.07, 129.0, 128.2, 127.75,

127.66, 127.4, 125.7, 115.8, 92.3, 87.2, 58.4, 54.6, 30.3, 19.2 ppm (Diastereomeric isomers gave different carbon signals).

4.3.1.6. 4-Hydroxy-5-methyl-3- α -naphtyl-2-imidazolidinethione (45). It was synthesized according to the general procedure using compound **6** (0.1g, 0.39 mmol), LiAlH₄ (0.059g, 1.56 mmol) and 10 mL THF. Yield: 0.095g (94%), beige solid. ¹H NMR (400MHz, CDCl₃): δ 8.2-7.4 (m, 7H, aromatic ring); 6.61, 6.52 and 6.43 (bs, 1H, NH); 5.68, 5.47, 5.37 and 5.22 (bs, t J =6.0, d J =1.2 and d J =0.4 1H, H at C4); 4.42, 3.99 and 3.47 (t J =6.0 Hz, m, q J =6.8, 1H, H at C5); 3.06, 2.90, 2.80 and 2.68 (bs, 1H, OH); 1.54, 1.48, 1.44 and 1.21 (d, 3H J =6.4, CH₃ at C5). ¹³C NMR (100 MHz, CDCl₃): δ 134.6, 132.6, 129.5, 129.4, 128.9, 127.3, 126.5, 125.7, 125.6, 121.9, 91.3, 58.7, 19.9 ppm

4.3.1.7. 4-Hydroxy-5-methyl-3-phenyl-2-imidazolidinethione (46). It was synthesized according to the general procedure using compound **7** (0.3g, 1.45 mmol), LiAlH₄ (0.22g, 5.80 mmol) and 10 mL THF. Yield: 0.26g (86%). ¹H NMR (400MHz, CDCl₃): δ 7.49-7.15 (m, 4H, aromatic ring); 6.92 and 6.82 (bs, 1H, NH); 5.36 and 5.08 (d, 1H, H at C4); 4.05 and 3.72 (m and q, 1H, H at C5); 3.65 (bs, OH); 1.253 and 1.246 (d, 3H, CH₃ at C5). ¹³C NMR (100 MHz, CDCl₃): δ 181.7, 180.8, 138.0, 137.8, 130.2, 129.05, 128.98, 128.3, 128.2, 127.7, 127.6, 127.3, 125.7, 125.1, 92.3, 87.2, 58.5, 54.6, 19.2, 12.9 ppm (Diastereomeric isomers gave different carbon signals).

4.3.1.8. 4-Hydroxy-5-isopropyl-3-*o*-tolyl-2-imidazolidinethione (47). It was synthesized according to the general procedure using compound **8** (0.1g, 0.40 mmol), LiAlH₄ (0.061g, 1.61 mmol) and 10 mL THF. Yield: 0.092g (91%), white solid, mp: 116-118 °C ¹H NMR (400MHz, CDCl₃): δ 7.31-7.26 (m, 4H, aromatic ring); 6.39 (bs, 1H, NH); 5.38 and 5.21 (bs, 1H, H at C4); 3.55 (bs, 1H, H at C5); 2.94, 2.84, 2.50-1.80 (m, OH and H of isopropyl group); 1.09, 1.05 and 0.97 (d, J = 6.4 Hz, J = 6.8 Hz and J = 6.8 Hz, 6H, methyl signals). ¹³C NMR (100 MHz, CDCl₃): δ 136.8, 131.2, 129.4, 129.1, 127.8, 126.8, 120.7, 88.0, 69.0, 31.3, 21.4, 18.1 ppm.

4.3.1.9. 4-Hydroxy-5-isopropyl-3-o-fluorophenyl-2-imidazolidinethione (48). It was synthesized according to the general procedure using compound **9** (0.2g, 0.79 mmol), LiAlH₄ (0.12g, 3.2 mmol) and 10 mL THF. Yield: 0.19g (93%), white solid, mp: 133-135 °C ¹H NMR (400MHz, CDCl₃): δ 7.6-7.1 (m, 4H, aromatic ring); 6.90 and 6.63 (bs, 1H, NH); 5.46 and 5.31 (bs, 1H, H at C4); 4.12 and 3.59 (m and d, *J*=5.6 Hz, 1H, H at C5); 3.26 and 2.84 (bs, 1H, OH at C4); 1.98-1.88 (m, 1H, H of isopropyl group); 1.08, 1.03 and 0.96 (d, *J*=6.8 Hz, 6H, methyl groups). ¹³C NMR (100 MHz, CDCl₃): δ 181.77, 181.73, 158.59 (¹*J*_{C-F} = 249.1 Hz), 131.92, 130.28, 130.26, 130.20, 130.18, 125.00, 124.88, 124.58, 124.57, 124.55, 116.69, 116.49, 88.62, 88.60, 69.05, 31.26, 17.88, 17.38 ppm (Diastereomeric isomers gave different carbon signals).

4.3.1.10. 4-Hydroxy-5-isopropyl-3-o-chlorophenyl-2-imidazolidinethione (49). It was synthesized according to the general procedure using compound **10** (0.28g, 1.04 mmol), LiAlH₄ (0.16g, 4.2 mmol) and 20 mL THF. Yield: 0.26g (91%), white solid, mp: 170-173 °C ¹H NMR (400MHz, CDCl₃): δ 7.58-7.34 (m, 4H, aromatic ring); 6.68 and 6.48 (bs, 1H, NH); 5.52, 5.40 and 5.32 (d, bs and bs, 1H, H at C4); 3.98-3.46 (m, 2H, OH of two isomers and H at C5); 3.02 (bs, 1H, OH at C4 of one isomer); 2.00-1.90 (m, 1H, H of isopropyl group); 1.10-1.00 (m, 6H, methyl groups). ¹³C NMR (100 MHz, CDCl₃): δ 181.9, 134.4, 133.5, 130.4, 130.1, 127.6, 88.2, 69.5, 31.1, 18.1 ppm.

4.3.1.11. 4-Hydroxy-5-isopropyl-3-o-bromophenyl-2-imidazolidinethione (50). It was synthesized according to the general procedure using compound **11** (0.1g, 0.32 mmol), LiAlH₄ (0.049g, 1.3 mmol) and 10 mL THF. Yield: 0.081g (81%), white solid, mp: 142-144 °C ¹H NMR (400MHz, CDCl₃): δ 7.76-7.10 (m, 4H, aromatic ring); 6.74 and 6.70 (bs, 1H, NH); 5.55, 5.45 and 5.34 (d, bs and bs, 1H, H at C4); 3.92-3.48 (m, 2H, OH of two isomers and H at C5); 3.11 (bs, 1H, OH at C4 of one isomer); 2.10-1.88 (m, 1H, H of isopropyl group); 1.26-1.02 (m, 6H, methyl groups). ¹³C NMR (100 MHz, CDCl₃): δ 181.80, 133.72, 130.59, 130.47, 129.34, 128.49, 127.93, 127.43, 127.39, 126.33, 122.10, 121.02, 118.79, 89.63, 87.99, 69.97, 68.63, 66.50, 63.94, 31.51, 31.38, 30.06, 29.60, 20.17, 19.86, 19.65, 19.21, 19.16, 18.50, 18.13, 17.64 ppm (aromatic, C5 and isopropyl signals of diastereomers gave different carbon signals).

4.3.1.12. 4-Hydroxy-5-isopropyl-3-*o*-iodophenyl-2-imidazolidinethione (51). It was synthesized according to the general procedure using compound **12** (0.085g, 0.24 mmol), LiAlH₄ (0.036g, 0.94 mmol) and 10 mL THF. Yield: 0.059g (69%), light yellow solid, mp: 68-70 °C ¹H NMR (400MHz, CDCl₃): δ 7.95-7.10 (m, 4H, aromatic ring); 6.58 and 6.50 (bs, 1H, NH); 5.49, 5.44 and 5.32 (m, bs and bs, 1H, H at C4); 3.42-3.90 (m, 2H, OH at C4 and H at C5), 2.06 and 1.90 (m, 1H, H of isopropyl group); 1.10-0.96 (m, 6H, methyl groups).

4.3.1.13. 4-Hydroxy-5-isopropyl-3- α -naphthyl-2-imidazolidinethione (52). It was synthesized according to the general procedure using compound **13** (0.1g, 0.35 mmol), LiAlH₄ (0.053g, 1.41 mmol) and 10 mL THF. Yield: 0.091g (91%), beige solid, mp: 240-242 °C ¹H NMR (400MHz, CDCl₃): δ 8.11-7.36 (m, 7H, aromatic ring); 7.10 and 6.98 (bs, 1H, NH); 5.44, 5.42 and 5.29 (bs, 1H, H at C4); 3.65 and 3.58 (d, 1H, H at C5); 3.44, 3.18 (bs, 1H, OH at C4); 2.02-1.92 (m, 1H, H of isopropyl group); 1.11 and 1.07 (d, *J* = 6.4 Hz, 6H, methyl groups).

4.3.1.14. 4-Hydroxy-5-isopropyl-3-phenyl-2-imidazolidinethione (53). It was synthesized according to the general procedure using compound **14** (0.1g, 0.43 mmol), LiAlH₄ (0.065g, 1.7 mmol) and 10 mL THF. Yield: 0.096g (95%), white solid, mp: 133-136 °C ¹H NMR (400MHz, CDCl₃): δ 7.77-7.32 (m, 5H, aromatic ring), 6.86 and 6.61 (bs, 1H, NH); 5.50 and 5.31 (d and s, *J* = 3.2 Hz, 1H, H at C4); 3.57 and 3.12 (bs, 1H, OH); 3.52 (d *J* = 5.2 Hz, 1H, H at C5); 1.90 (m, 1H, H of the isopropyl group); 1.16, 1.08, 1.02 (d, *J* = 6.8 Hz, *J* = 7.6 Hz, *J* = 6.4 Hz, 6H, methyl groups). ¹³C NMR (100 MHz, CDCl₃): δ 180.9, 137.9, 129.1, 129.0, 128.8, 127.7, 127.2, 124.4, 89.4, 68.4, 31.3, 17.9, 17.4 ppm.

4.3.1.15. 4-Benzylamine-5-methyl-3-*o*-bromophenyl-2-imidazolidinethione (54). It was synthesized by the reaction of 0.05g (0.17 mmol) compound **43** with 0.019 mL benzylamine in 2 mL benzene at reflux temperature of benzene for 24 hours.

5. CONCLUSION

Atroposelective synthesis of 5-methyl- and 5-isopropyl-3-(*o*-aryl)-2-thiohydantoins was achieved easily [35]. Diastereomeric ratios were found to increase by recrystallization up to 93% in favor of **SP**. The reaction yielded a high prevalence of the **P** isomers for **3-6** and **10-13** and the syntheses of **3-5** proceeded with almost complete enantioselectivities with respect to the formation of **SP**. The stereoselectivities depended on the substituents at N3 and at C5 of the heterocyclic ring. It was found that the chirality of the α -amino acid derivative firstly determined the conformation of the chiral axis as **P**, then **SP** and **RP** were produced depending on the rate of conversion between the intermediates **SP*** and **RP***, their cyclization rates and also on the reaction temperature.

In addition, it was found that the thiohydantoin isomers converted to one another *via* rotation around the chiral axis, N_{sp2}-C_{aryl}, without racemization at C5 in toluene and the rotational barriers, determined by HPLC with chiral stationary phases, were found to increase with the size of the *o*-substituents in the halogen series [35].

The studied compounds (**2-7** and **9-14**) were used for atroposelective aldol reactions at C-5 of the heteroring. It was found that the reaction followed an enolization mechanism where the benzaldehyde reacted with a 4:1 selectivity to give the *anti* aldol products. The selectivity at C5 largely depended on the substituent at N3, resulting from the electrophilic attack occurring predominantly from the opposite side of the *ortho* substituent. It has been observed that the selective attachment of benzaldehyde was lost when a stronger electrophile, 4-nitrobenzaldehyde, was used. When the isopropyl group was present at C5 (**9-14**), the aldol reactions of the thiohydantoins did not go to a completion because of the hindrance caused by the large group to the approach of the electrophile. The enantioselectivities of the aldol syntheses depended on the ratio of **P:M** of the starting thiohydantoins. Thus, a high **P:M** ratio of the thiohydantoin should be used

to achieve a good enantioselectivity in the aldol reactions. The best diastereomer and enantiomer ratios were obtained with the 5-methyl-*o*-iodophenyl derivative, **5**.

Finally, the thiohydantoins (**1-14**) were reduced to stable hemiaminals (**40-53**) by the reduction reaction with LiAlH_4 . The **S** configuration at C-5 of the thiohydantoin ring was found to direct the reduction to produce predominantly **S** configured hemiaminals at C-4 of the heterocyclic ring. The isomer assignments were done based on the differences in the coupling constants of *cis*- and *trans*- hydrogens at C4 and C5 of the heterocyclic ring and also the anisotropic shielding effects of the substituents at C5 together with the *ortho* aryl group on the signal of the hydrogen at C4. The diastereomeric ratios of the isomeric products ranged from 99:1 to 46:54 and enantiomeric ratios from 94:6 to 56:44, by per cent. The observed diastereomer selectivity was attributed to the formation of an intramolecular H-bond between the hydroxyl group and the *o*-substituent. Besides, it was found that the isomers interconverted to each other and the barriers determined for the *cis* isomers of **40**, **43** and **44** by dynamic NMR were as low as 66.4 to 73.8 kJ/mol, which pointed to a ring-chain tautomerization process and supported by the amination reaction of **43** with benzyl amine. In terms of enantiomer and diastereomer ratios, the best results were obtained for **43**.

6. FUTURE WORK

As future work, other thiohydantoins can be synthesized from the different amino acids. Here, the **S** amino acid resulted in **P** conformation of the chiral axis. If the synthesis starts with an **R** amino acid, it can be expected to form predominantly **M** isomers over the **P** ones and their atroposelective reactions over the corresponding enolates may be done.

The aldol reactions of the studied thiohydantoins can be carried out with other aromatic aldehydes having different substituent and different positions at the aryl ring. In addition, the synthesized aldol products can be reduced to hemiaminals which will be also 1,3-diols and they can be used in the asymmetric synthesis.

The synthesized stable hemiaminals can be exploited for their catalytic activities in asymmetric reactions and compound **43** is a good candidate for these type of reactions due to its relatively high stereoisomeric purity.

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APPENDIX A: SPECTROSCOPY DATA

^1H NMR and ^{13}C NMR data for the synthesized compounds are given.

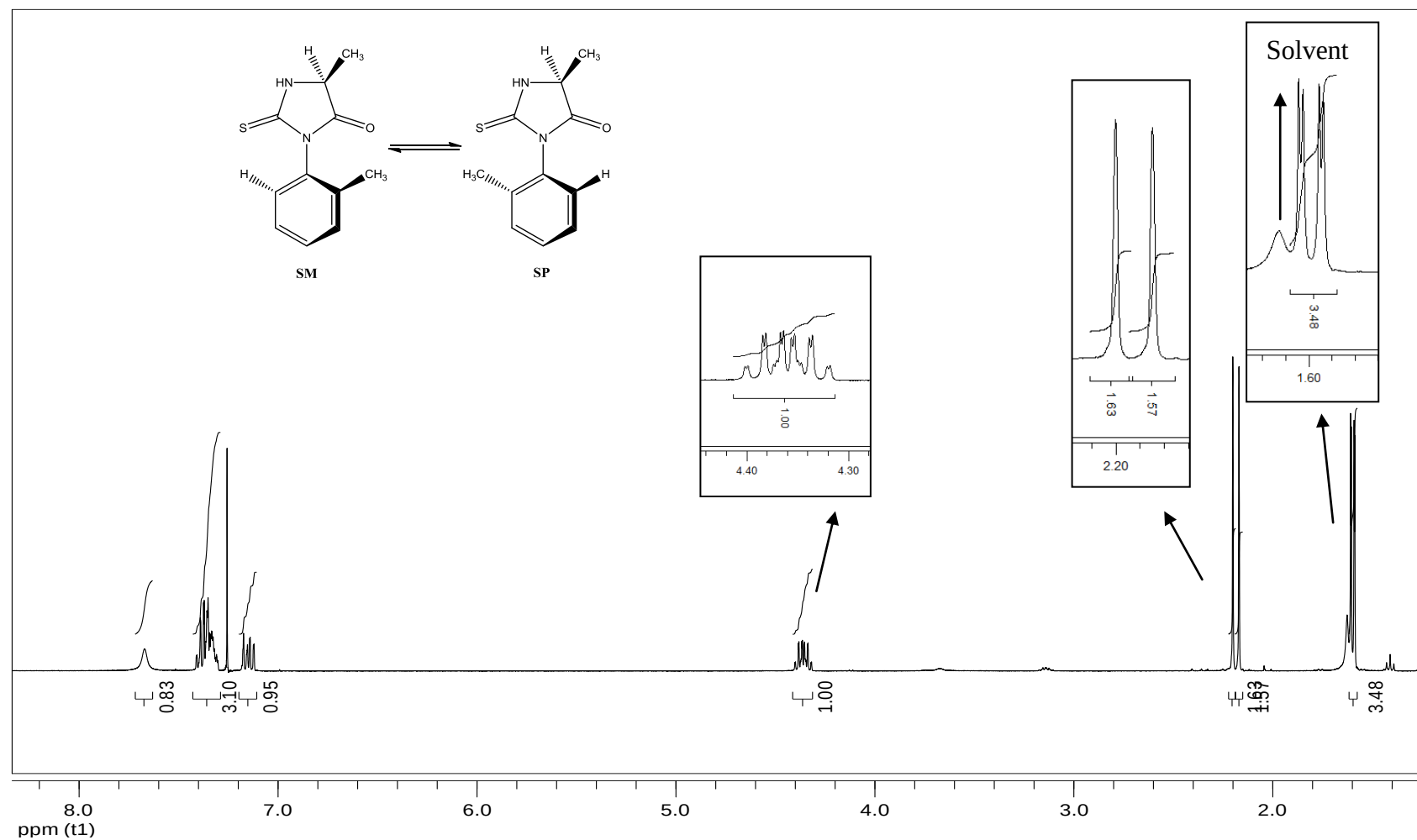


Figure A.1. 400 MHz ^1H NMR spectrum of 5-methyl-3-*o*-tolyl thiohydantoin (**1**) in CDCl_3 .

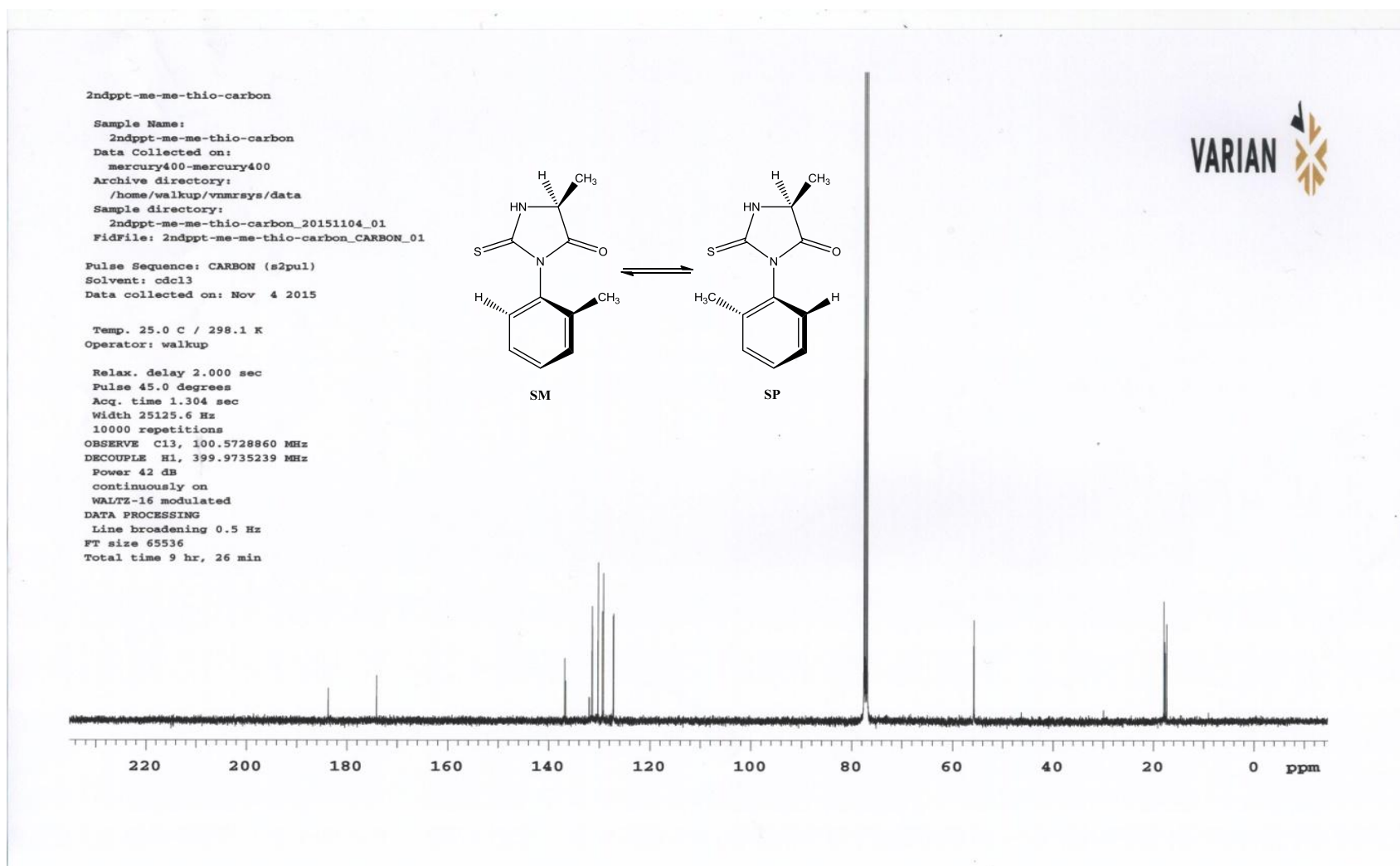


Figure A.2. 100 MHz ^{13}C NMR spectrum of 5-methyl-3-*o*-tolyl thiohydantoin (**1**) in CDCl_3 .

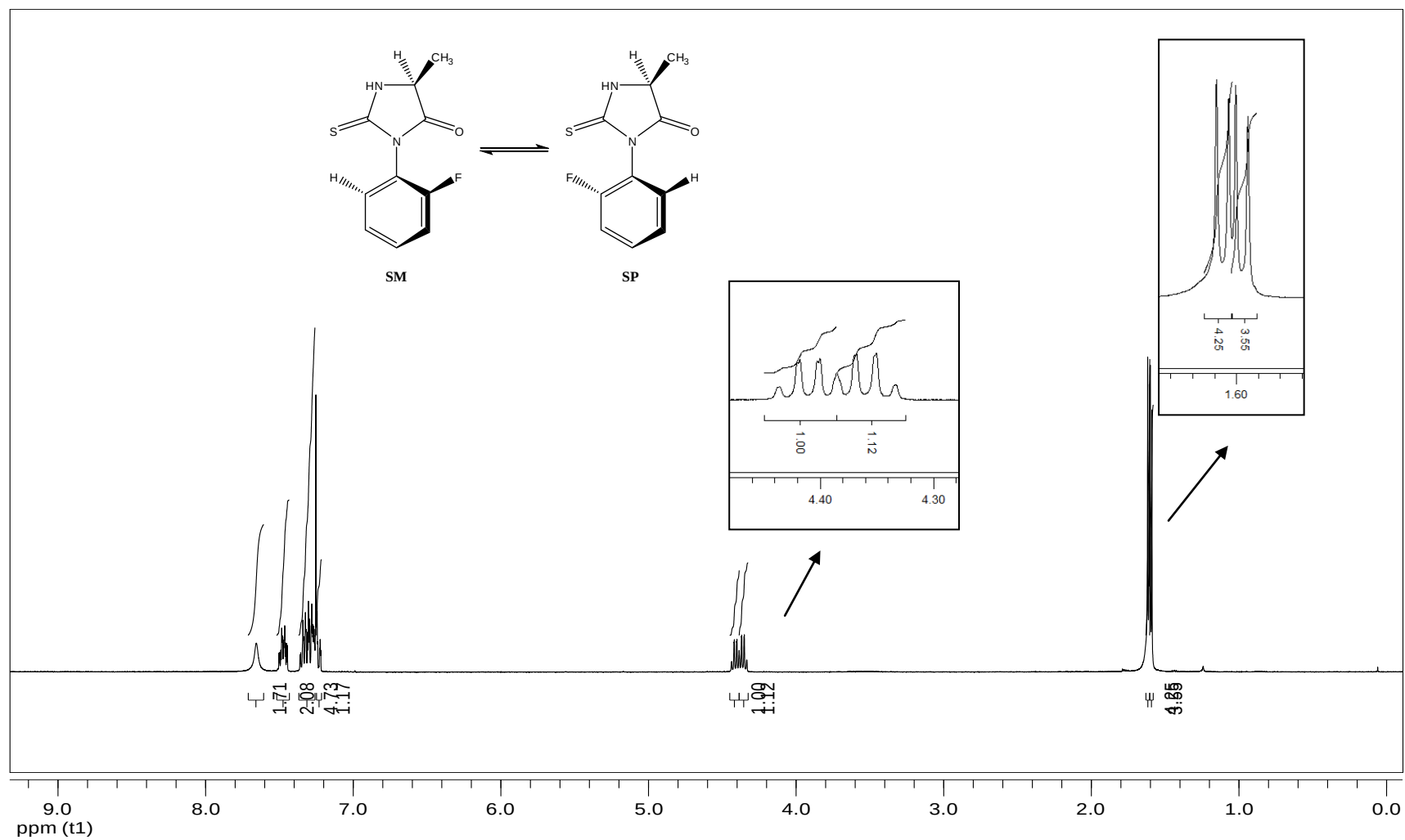


Figure A.3. 400 MHz ^1H NMR spectrum of 5-methyl-3-o-fluorophenyl thiohydantoin (2) in CDCl_3 .

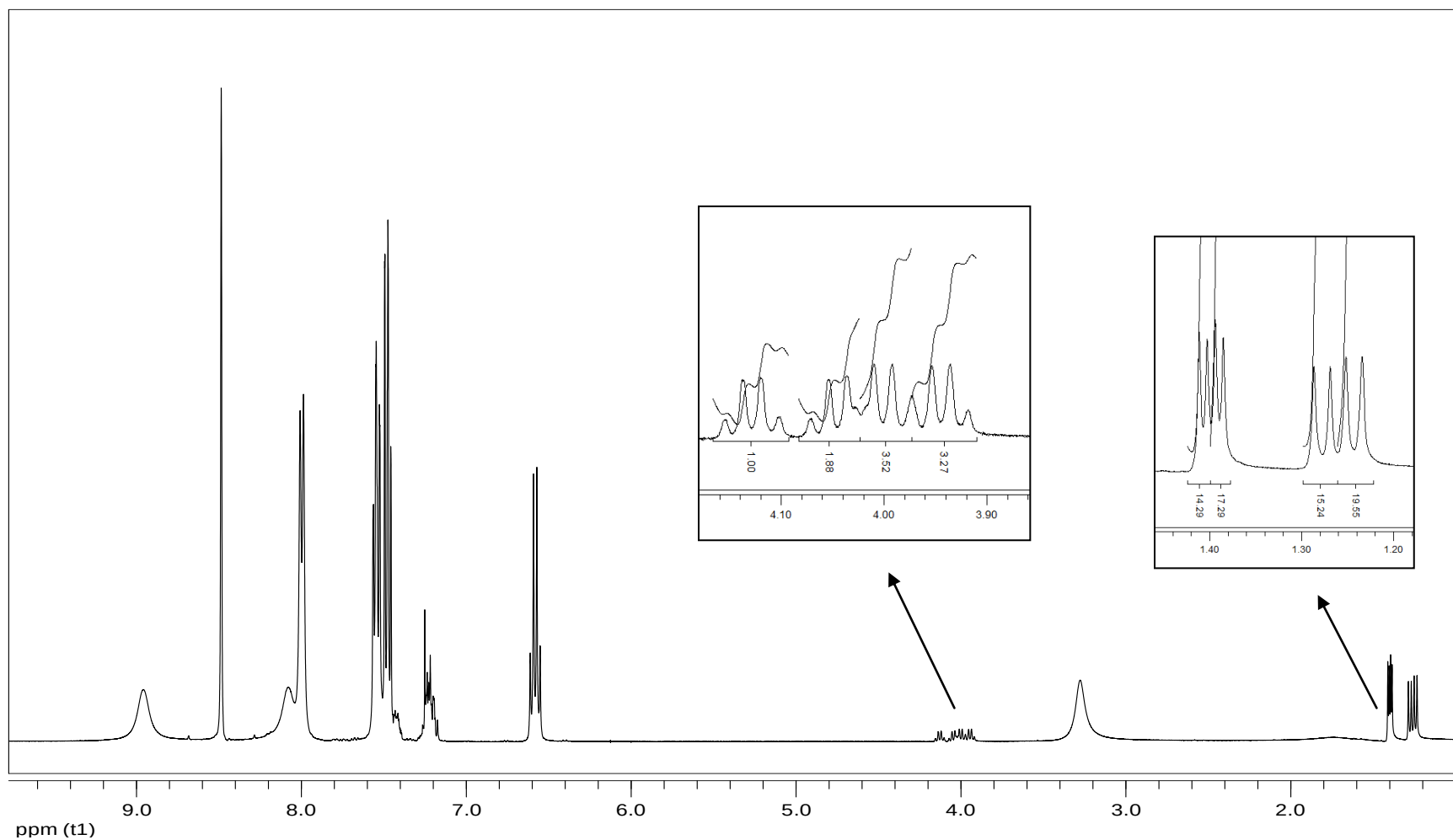


Figure A.4. 400 MHz ^1H NMR spectrum of 5-methyl-3-*o*-fluorophenyl thiohydantoin (**2**) in the presence of six equivalents of *S*-TFAE in CDCl_3 .

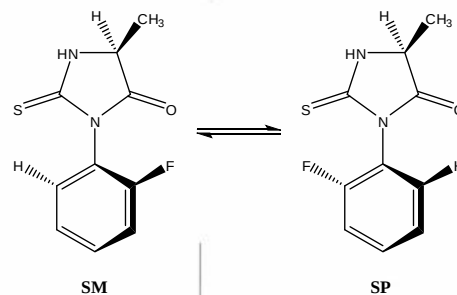
methyl-f-thio-1h-ppt

Sample Name:
methyl-f-thio-1h-ppt
Data Collected on:
mercury400-mercury400
Archive directory:
/home/walkup/vnmrsys/data
Sample directory:
methyl-f-thio-1h-ppt_20140903_01
FidFile: methyl-f-thio-1h-ppt_CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 3 2014

Temp. 24.0 C / 297.1 K
Operator: walkup

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
5000 repetitions
OBSERVE C13, 100.5729084 MHz
DECOUPLE H1, 399.9735239 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 4 hr, 43 min



VARIAN

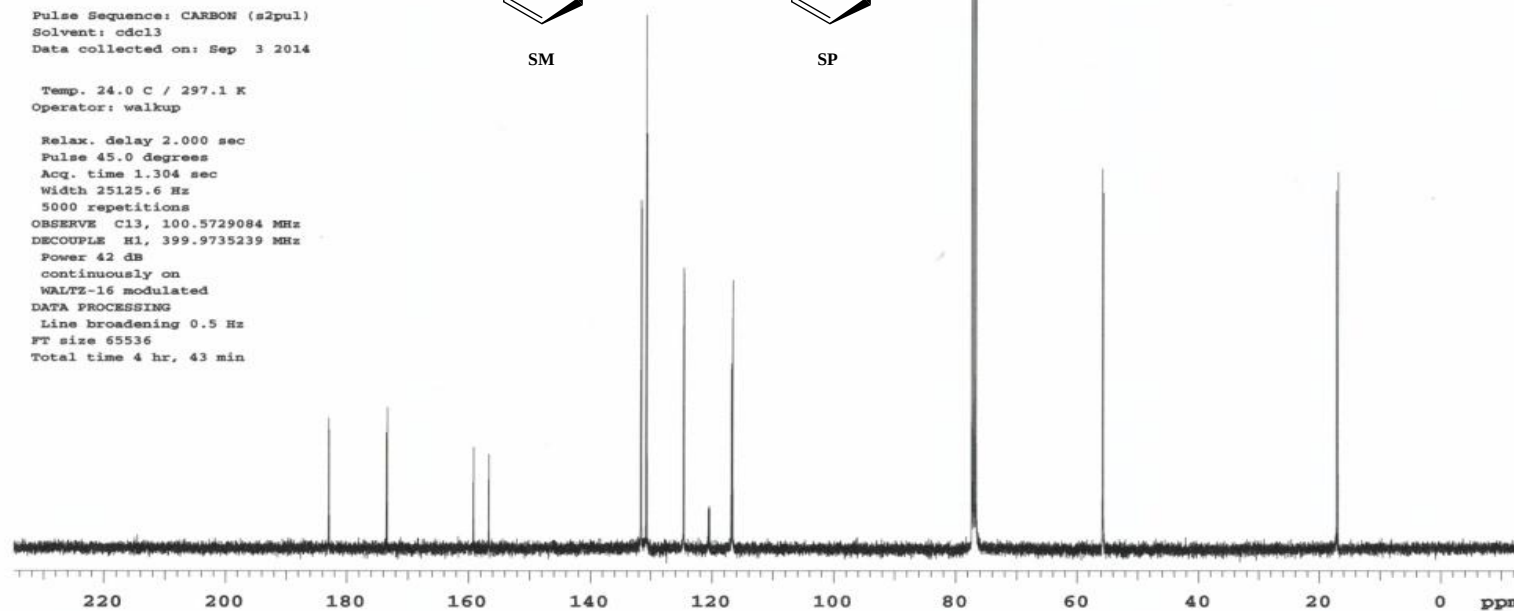


Figure A.5. 100 MHz ^{13}C NMR spectrum of 5-methyl-3-o-fluorophenyl thiohydantoin (**2**) in CDCl_3 .

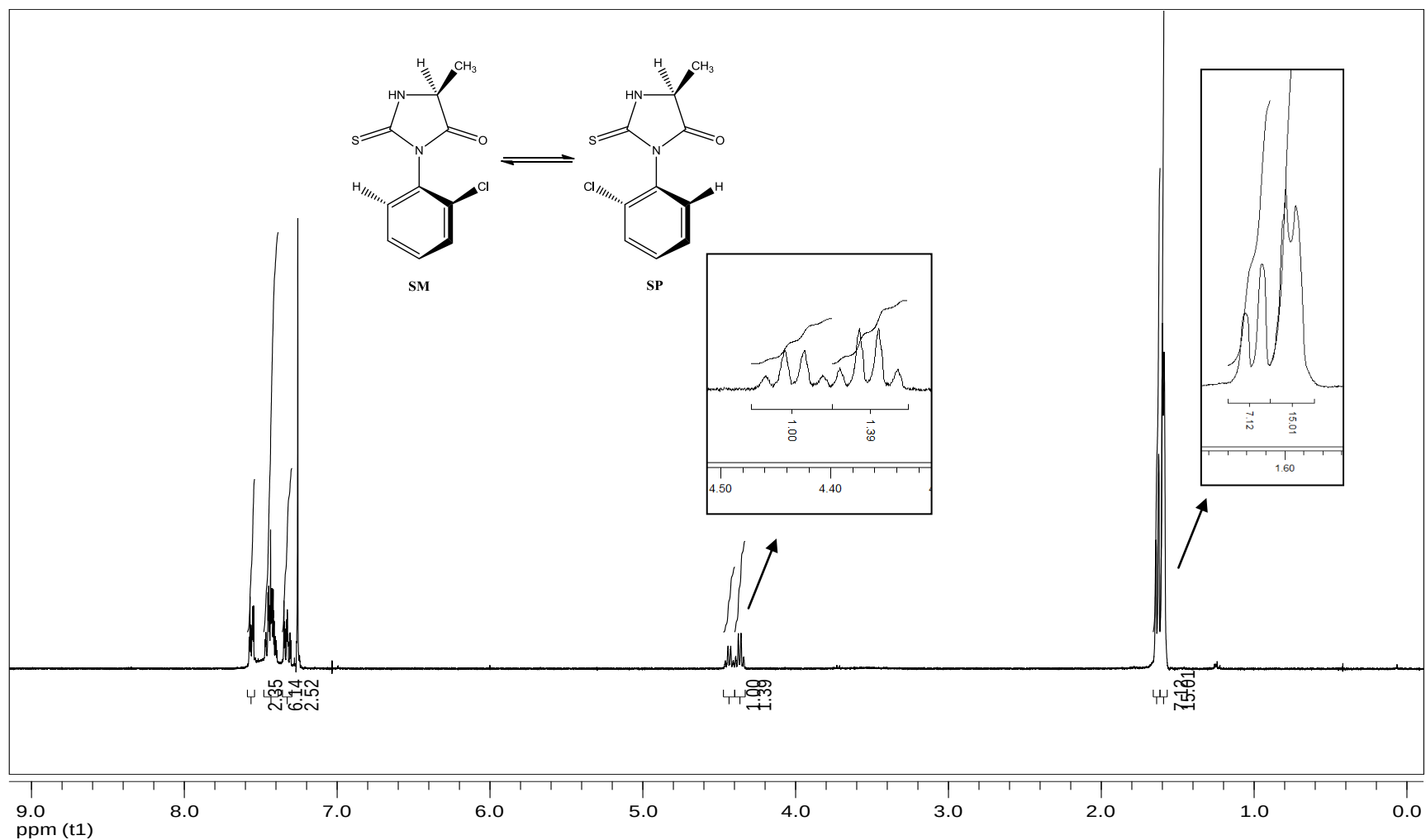


Figure A.6. 400 MHz ^1H NMR spectrum of 5-Methyl-3-*o*-chlorophenyl thiohydantoin (**3**) in CDCl_3 .

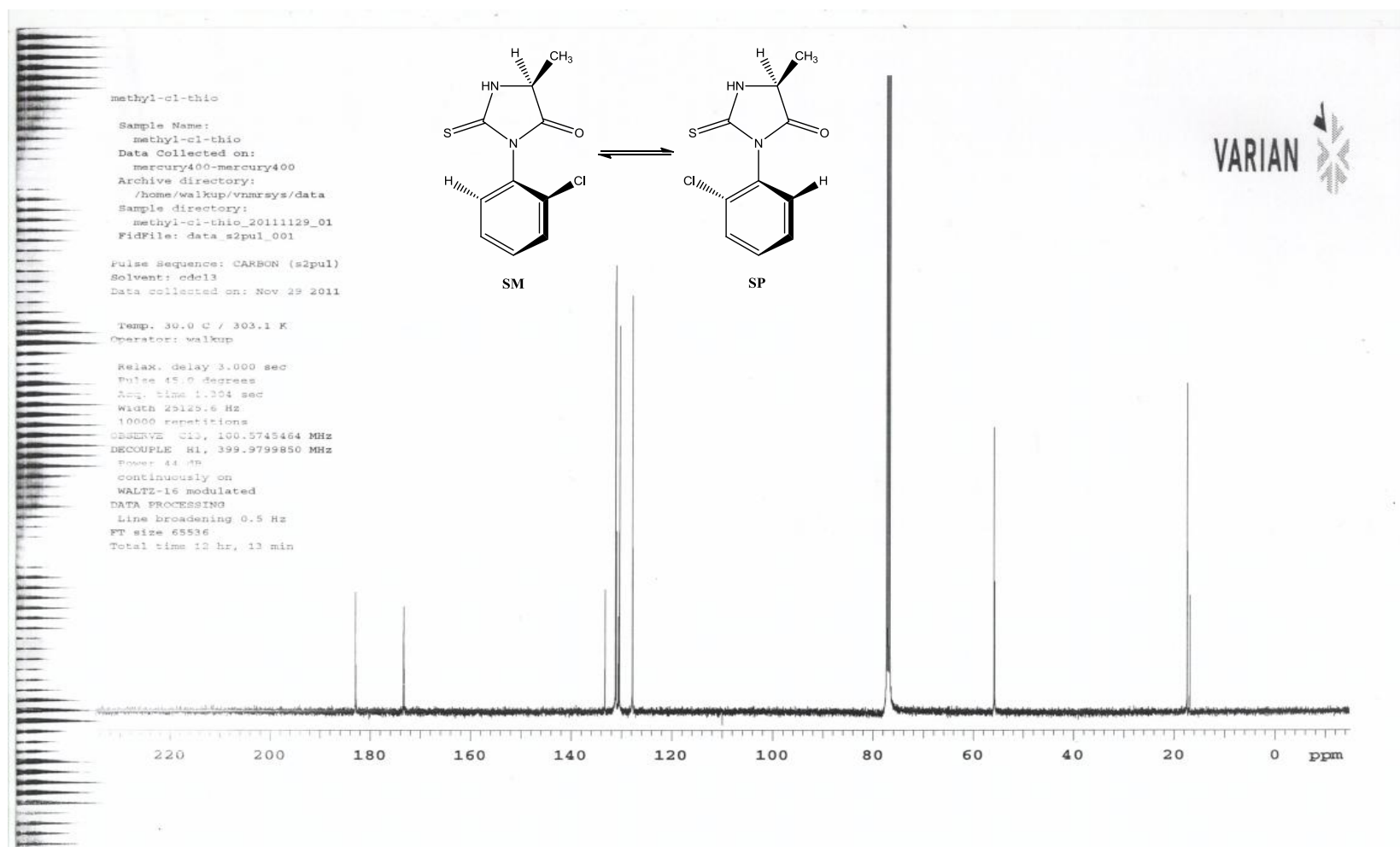


Figure A.7. 100 MHz ^{13}C NMR spectrum of 5-Methyl-3-*o*-chlorophenyl thiohydantoin (**3**) in CDCl_3 .

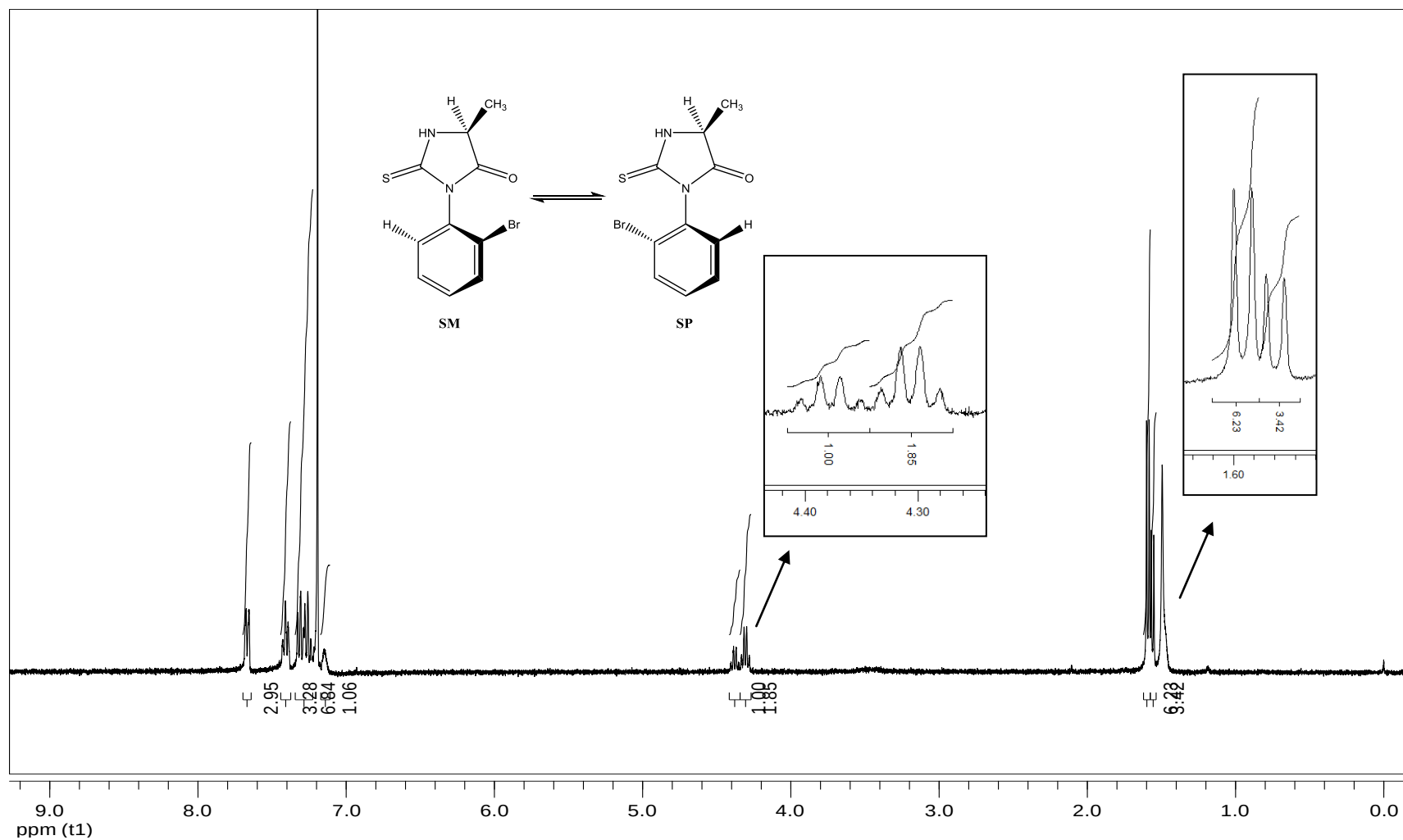


Figure A.8. 400 MHz ^1H NMR spectrum of 5-methyl-3-*o*-bromophenyl thiohydantoin (4) in CDCl_3 .

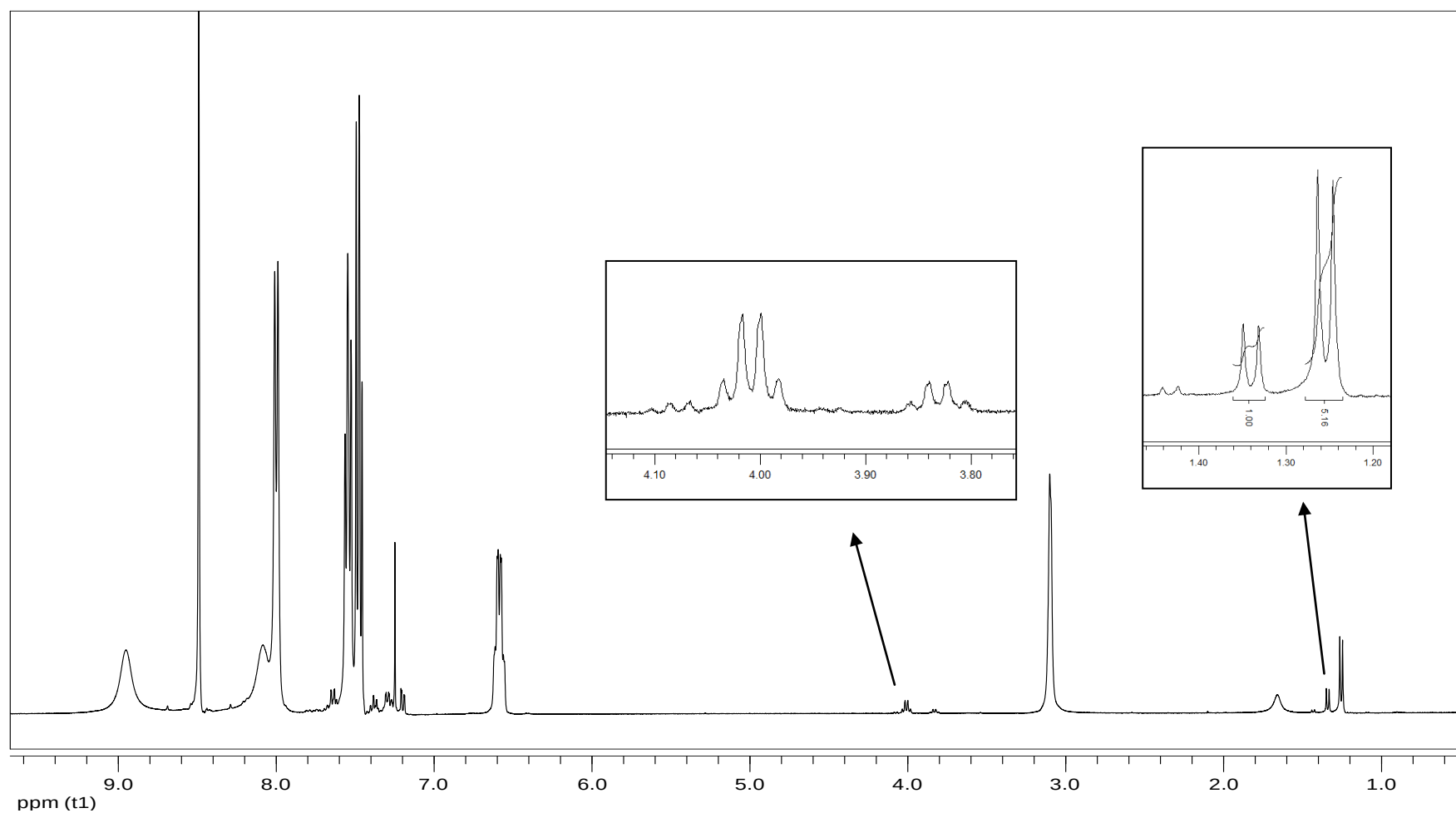


Figure A.9. 400 MHz ^1H NMR spectrum of 5-methyl-3-*o*-bromophenyl thiohydantoin (**4**) in the presence of six equivalents of S-TFAE in CDCl_3 .

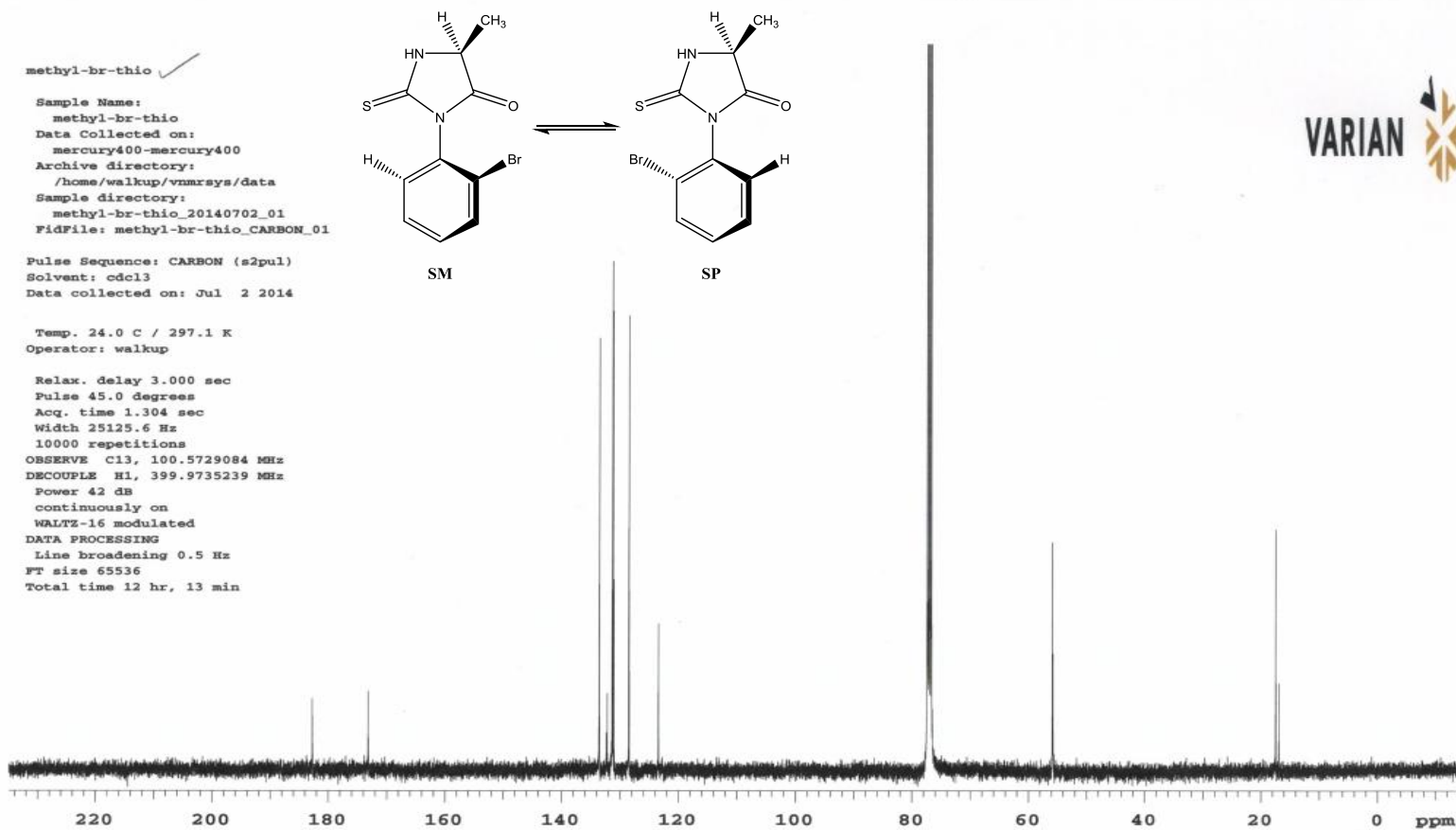


Figure A.10. 100 MHz ^{13}C NMR spectrum of 5-methyl-3-o-bromophenyl thiohydantoin (**4**) in CDCl_3 .

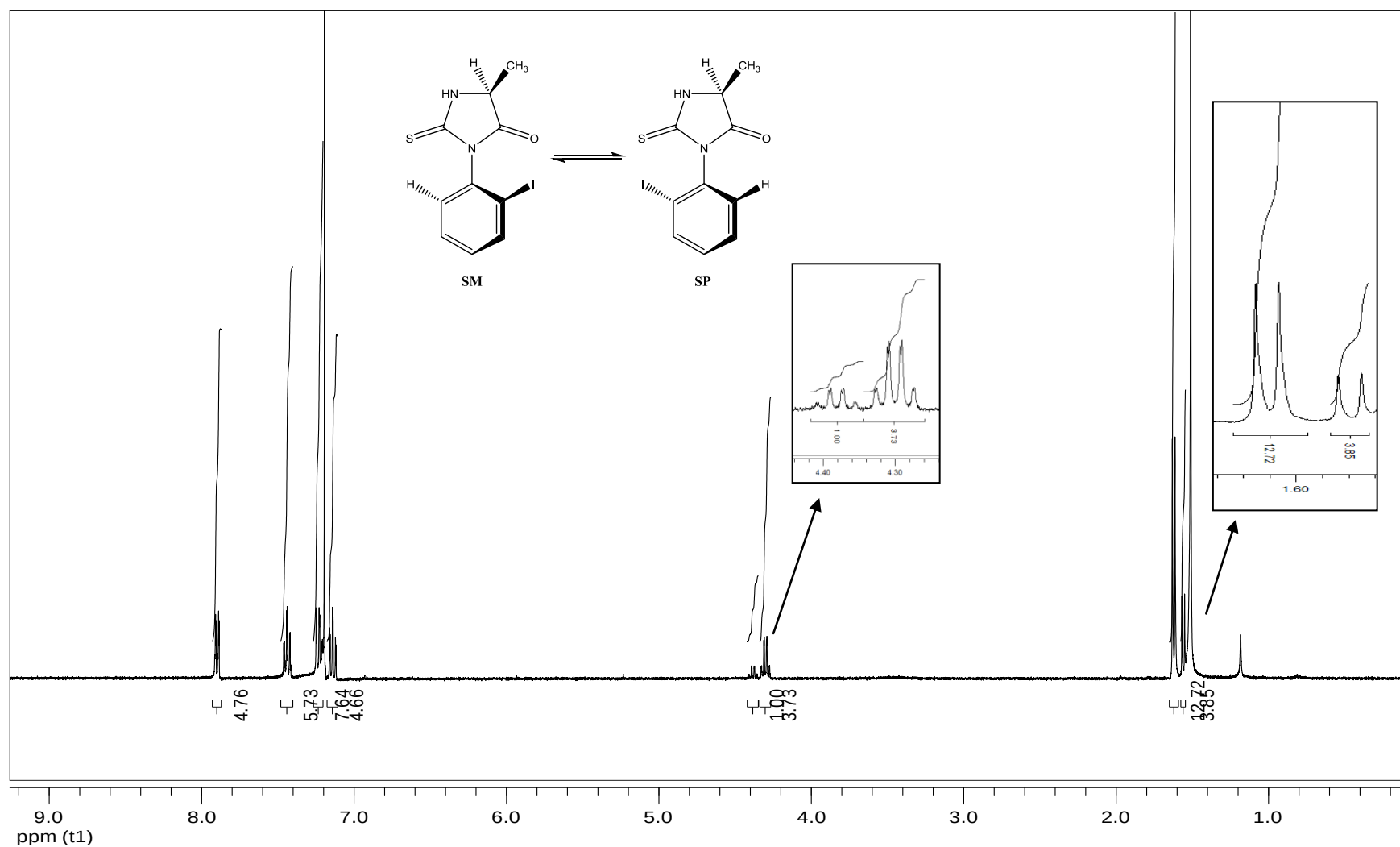


Figure A.11. 400 MHz ^1H NMR spectrum of 5-methyl-3-*o*-iodophenyl thiohydantoin (5) in CDCl_3 .

methyl-I-thio

Sample Name:
methyl-I-thio
Data Collected on:
mercury400-mercury400
Archive directory:
/home/walkup/vnmrsys/data
Sample directory:
methyl-I-thio_20130916_01
FidFile: methyl-I-thio_CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 16 2013

Temp. 24.0 C / 297.1 K
Operator: walkup

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
1000 repetitions
OBSERVE C13, 100.5729084 MHz
DECOUPLE H1, 399.9735239 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 56 min

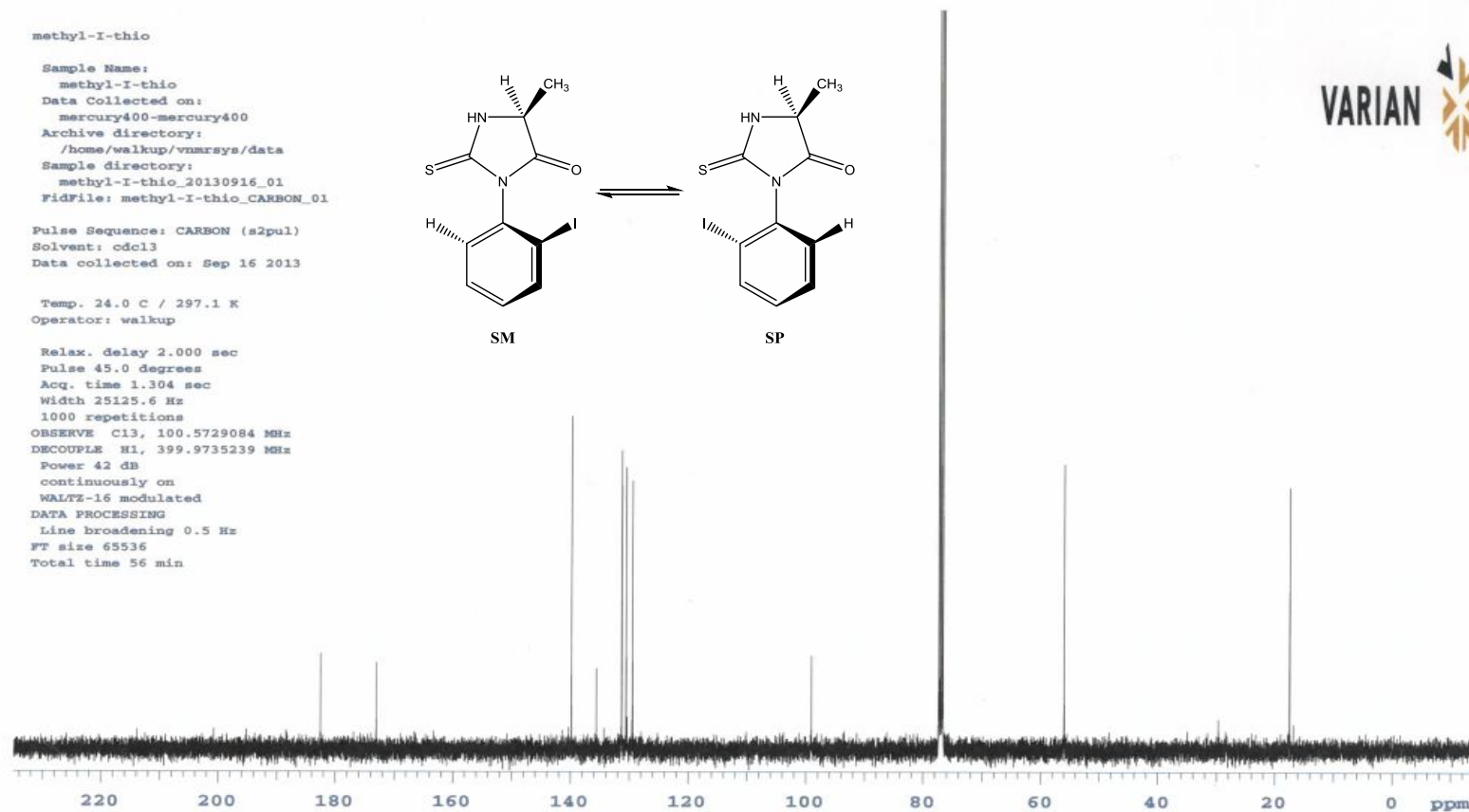
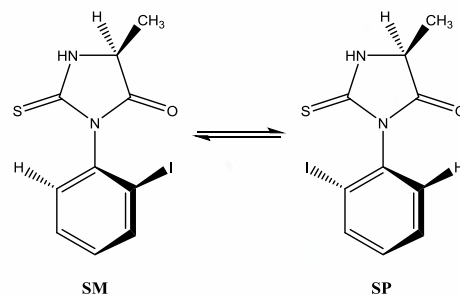


Figure A.12. 100 MHz ^{13}C NMR spectrum of 5-methyl-3-o-iodophenyl thiohydantoin (5) in CDCl_3 .

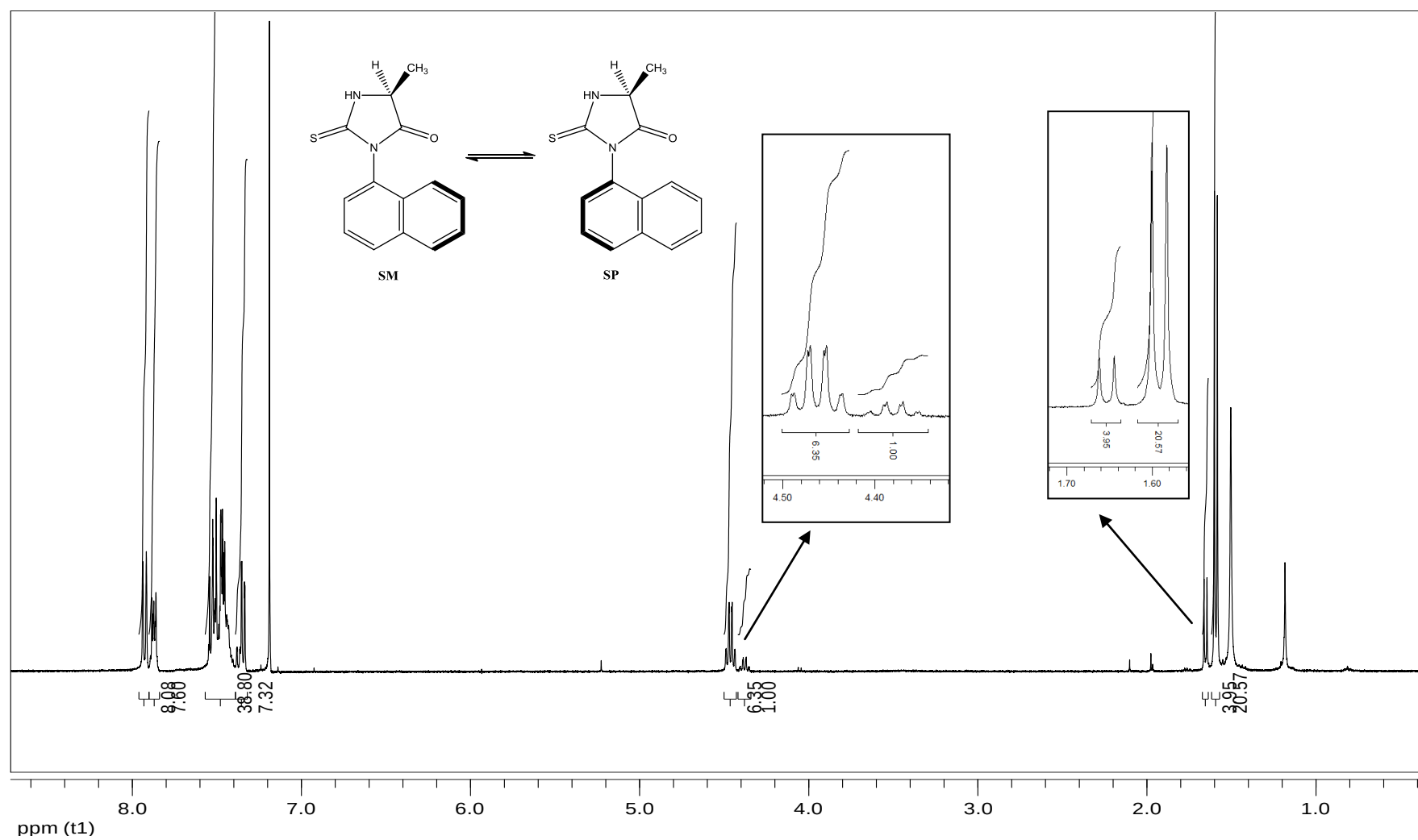


Figure A.13. 400 MHz ^1H NMR spectrum of 5-methyl-3- α -naphthyl thiohydantoin (6) in CDCl_3 .

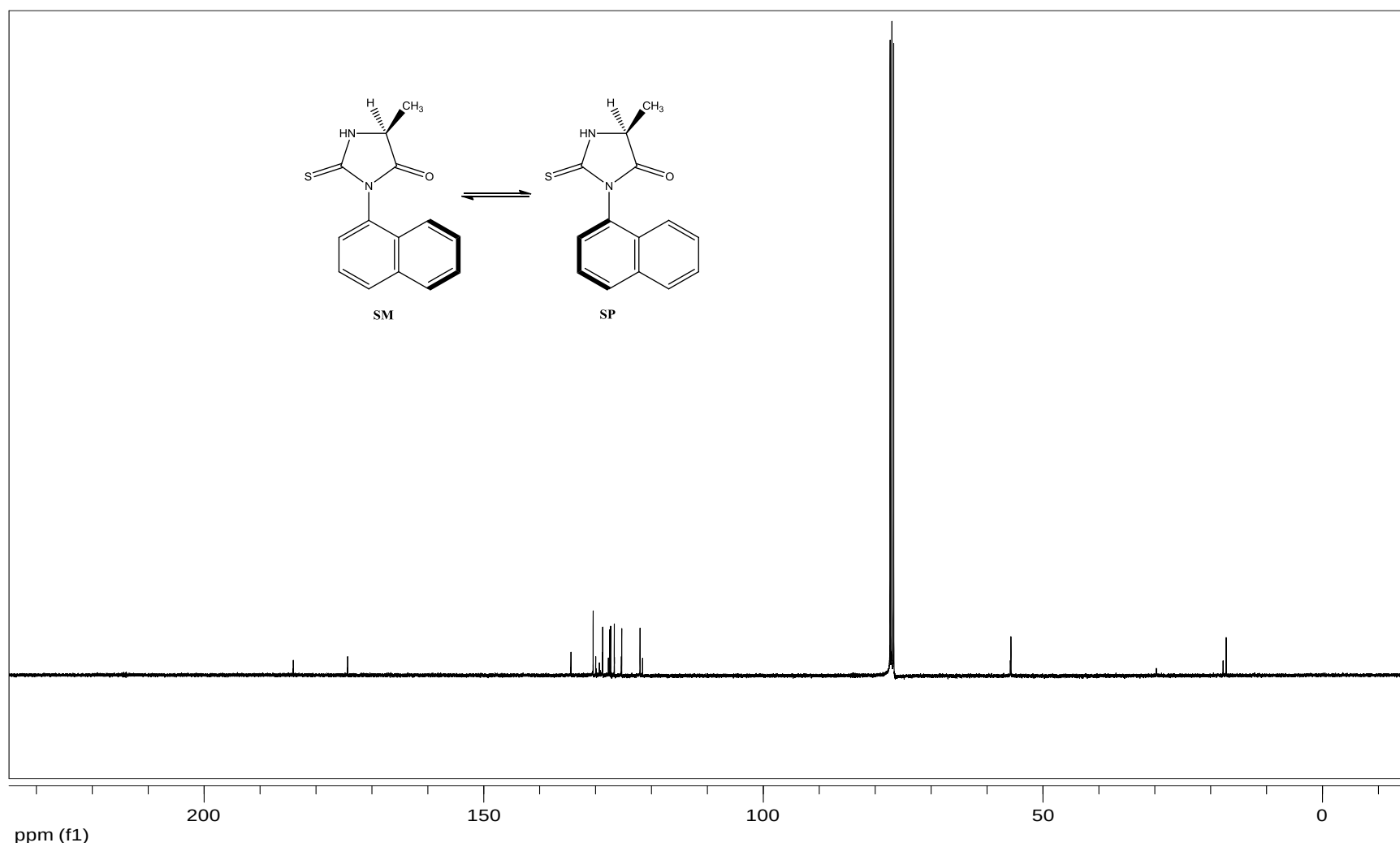


Figure A.14. 100 MHz ^{13}C NMR spectrum of 5-methyl-3- α -naphthyl thiohydantoin (**6**) in CDCl_3 .

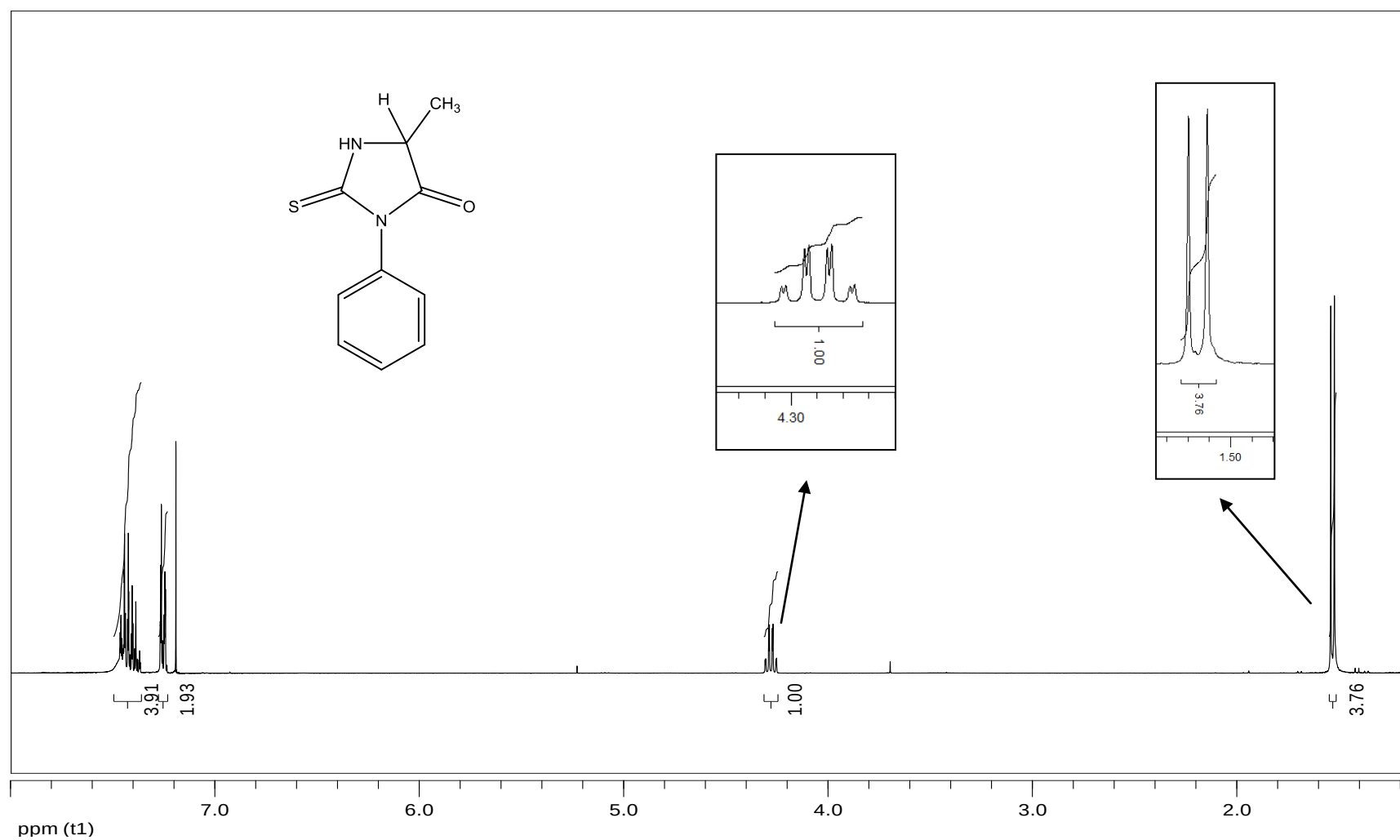


Figure A.15. 400 MHz ^1H NMR spectrum of 5-methyl-3-phenyl thiohydantoin (7) in CDCl_3 .

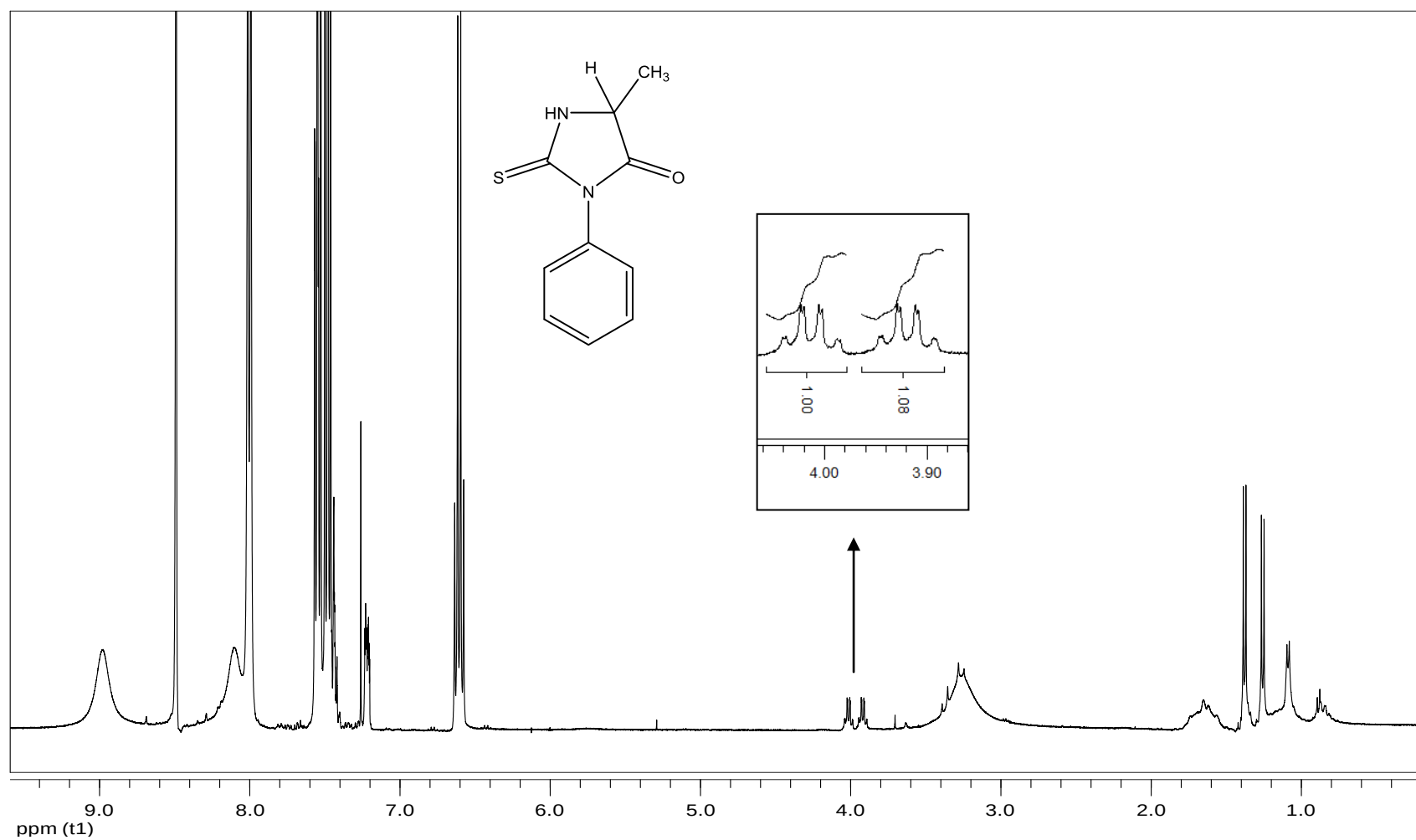


Figure A. 16. 400 MHz ^1H NMR spectrum of 5-methyl-3-phenyl thiohydantoin (7) in the presence of six equivalents of S-TFAE in CDCl_3 .

ppt-methyl-ph-thio

Sample Name:
ppt-methyl-ph-thio
Data Collected on:
mercury400-mercury400
Archive directory:
/home/walkup/vnmrsys/data
Sample directory:
ppt-methyl-ph-thio_20140320_01
FidFile: ppt-methyl-ph-thio_CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 20 2014

Temp. 25.0 C / 298.1 K
Operator: walkup

Relax. delay 3.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
10000 repetitions
OBSERVE C13, 100.5729084 MHz
DECOUPLE H1, 399.9735239 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 12 hr, 13 min

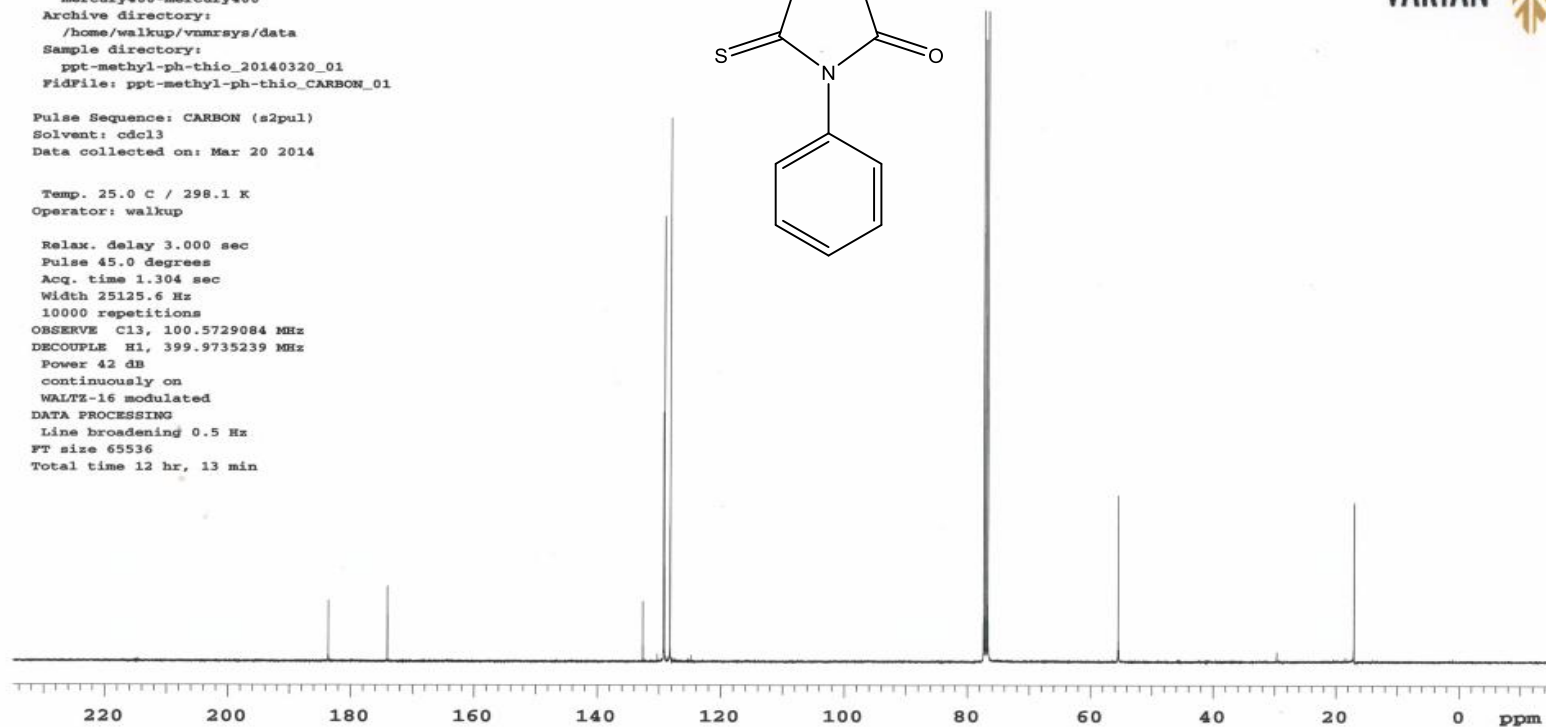
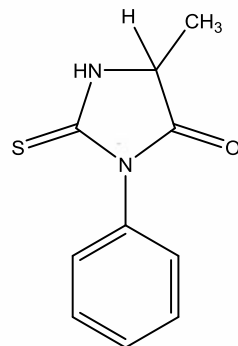


Figure A.17. 100 MHz ^{13}C NMR spectrum of 5-methyl-3-phenyl thiohydantoin (7) in CDCl_3 .

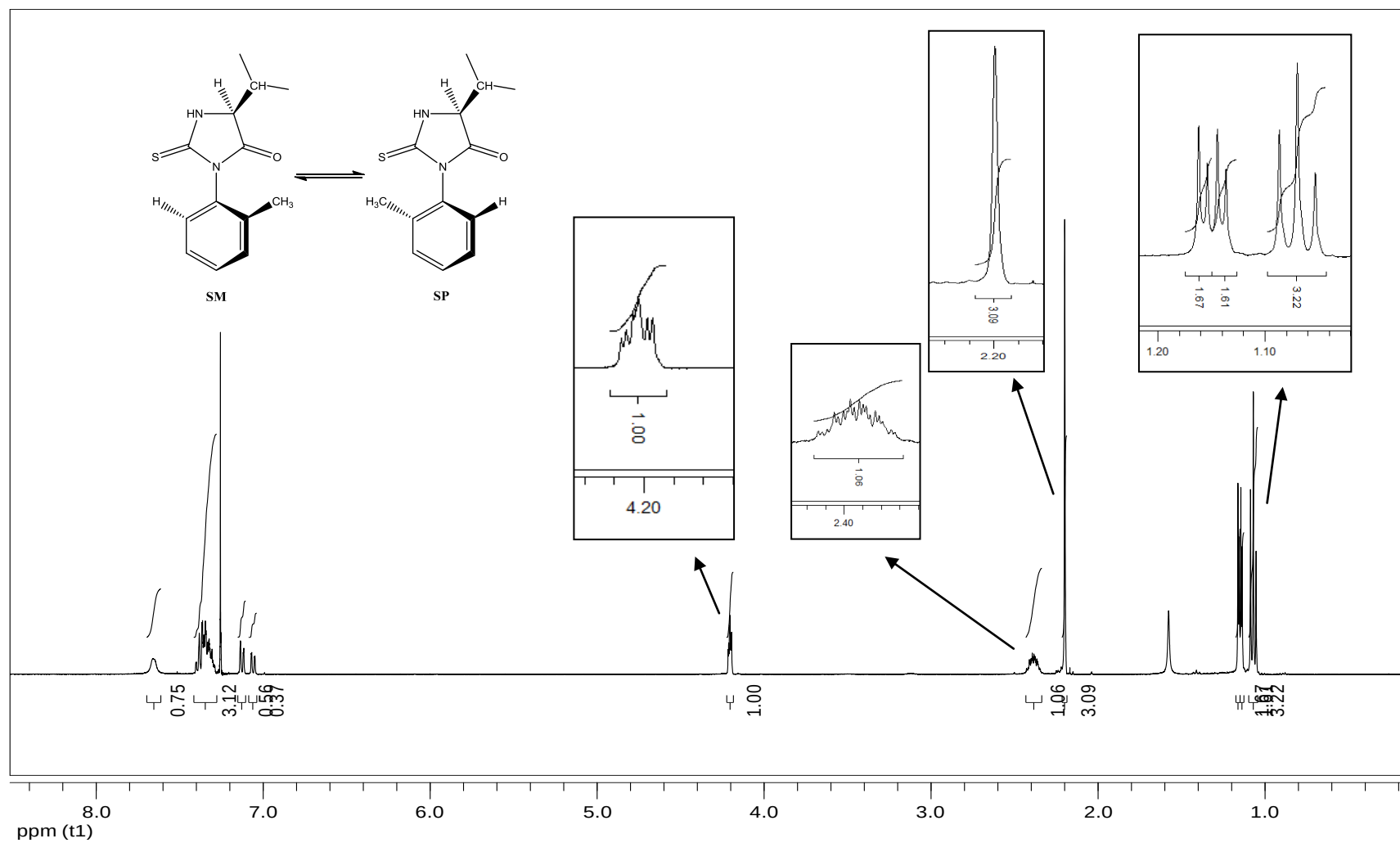


Figure A.18. 400 MHz ¹H NMR spectrum 5-isopropyl-3-o-tolyl thiohydantoin (**8**) in CDCl₃.

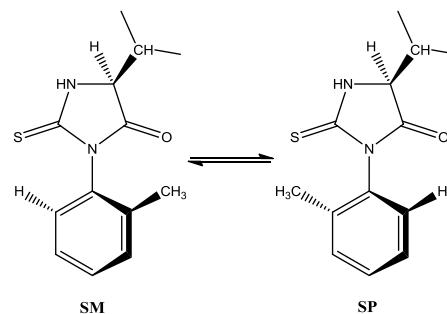
ppt-5-isop-me-thio-EtAc-Hex-carbon

Sample Name:
ppt-5-isop-me-thio-EtAc-Hex-carbon
Data Collected on:
mercury400-mercury400
Archive directory:
/home/walkup/vnmrsys/data
Sample directory:
ppt-5-isop-me-thio-EtAc-Hex-carbon_20150910_01
FidFile: ppt-5-isop-me-thio-EtAc-Hex-carbon_CARBON_01

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Sep 10 2015

Temp. 25.0 C / 298.1 K
Operator: walkup

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Width 25125.6 Hz
10000 repetitions
OBSERVE C13, 100.5728851 MHz
DECOUPLE H1, 399.9735239 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 hr, 26 min



VARIAN

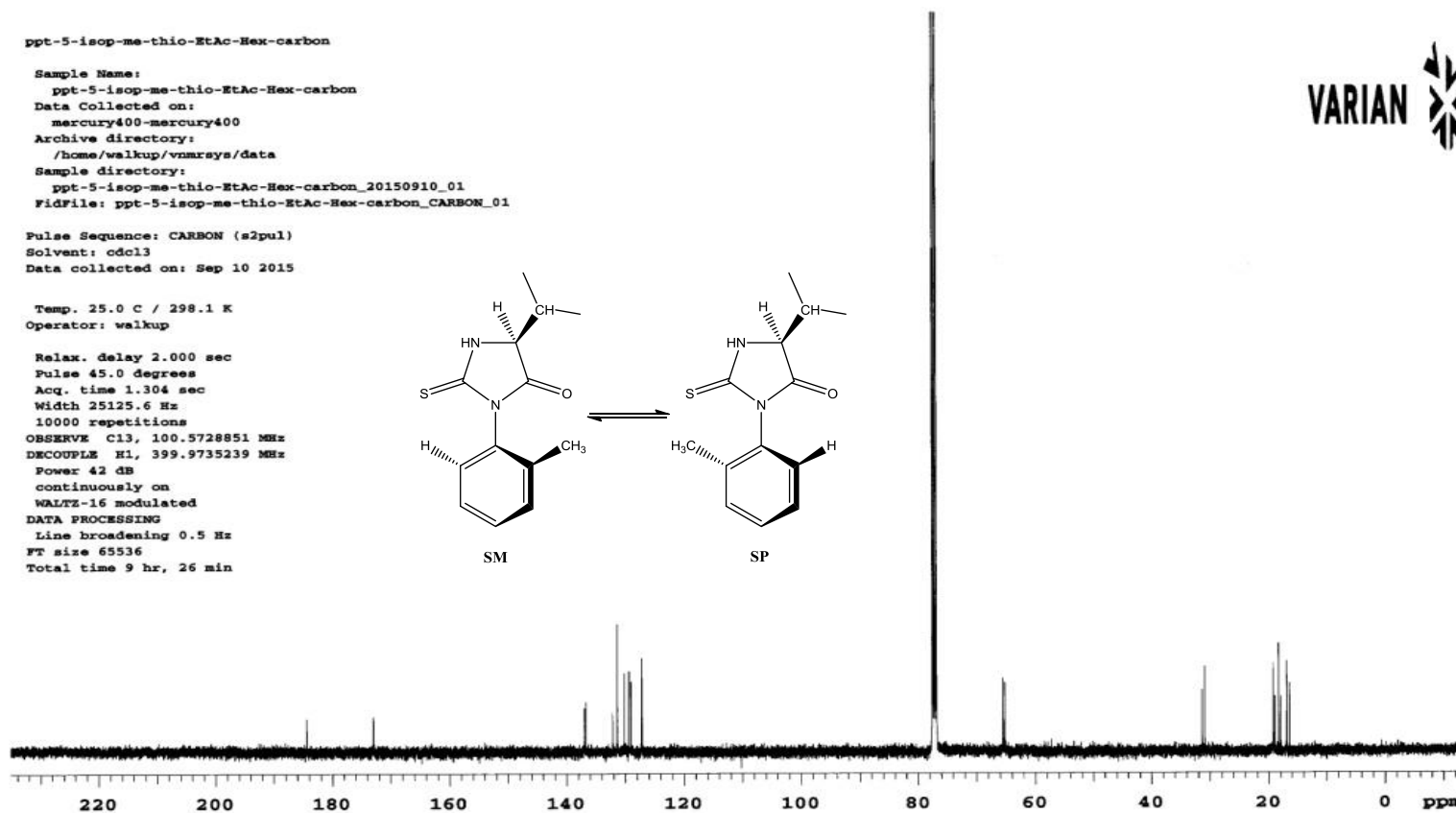


Figure A.19. 100 MHz ^{13}C NMR spectrum 5-isopropyl-3-o-tolyl thiohydantoin (**8**) in CDCl_3 .

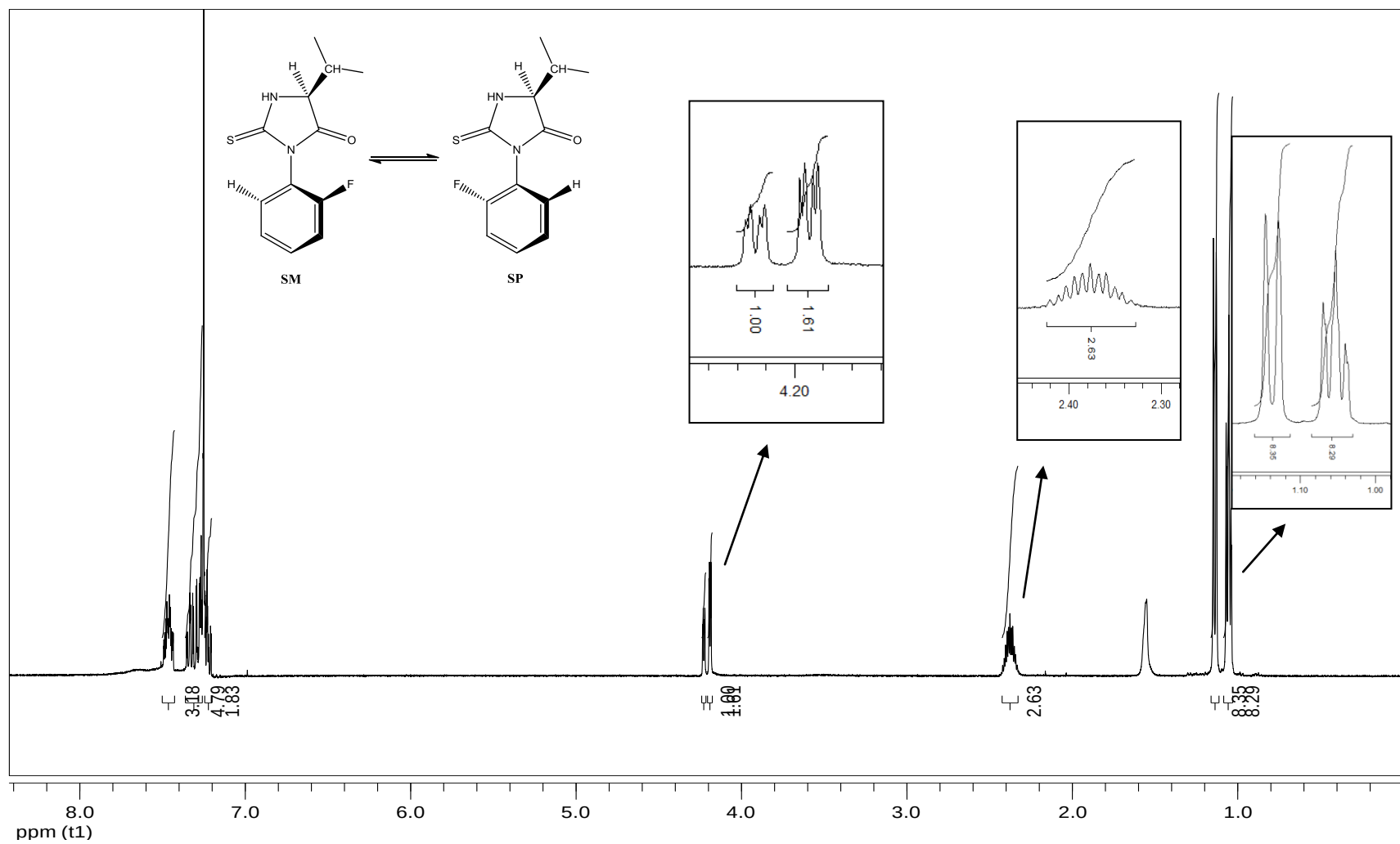


Figure A.20. 400 MHz ^1H NMR spectrum 5-isopropyl-3-o-fluorophenyl thiohydantoin (**9**) in CDCl_3 .

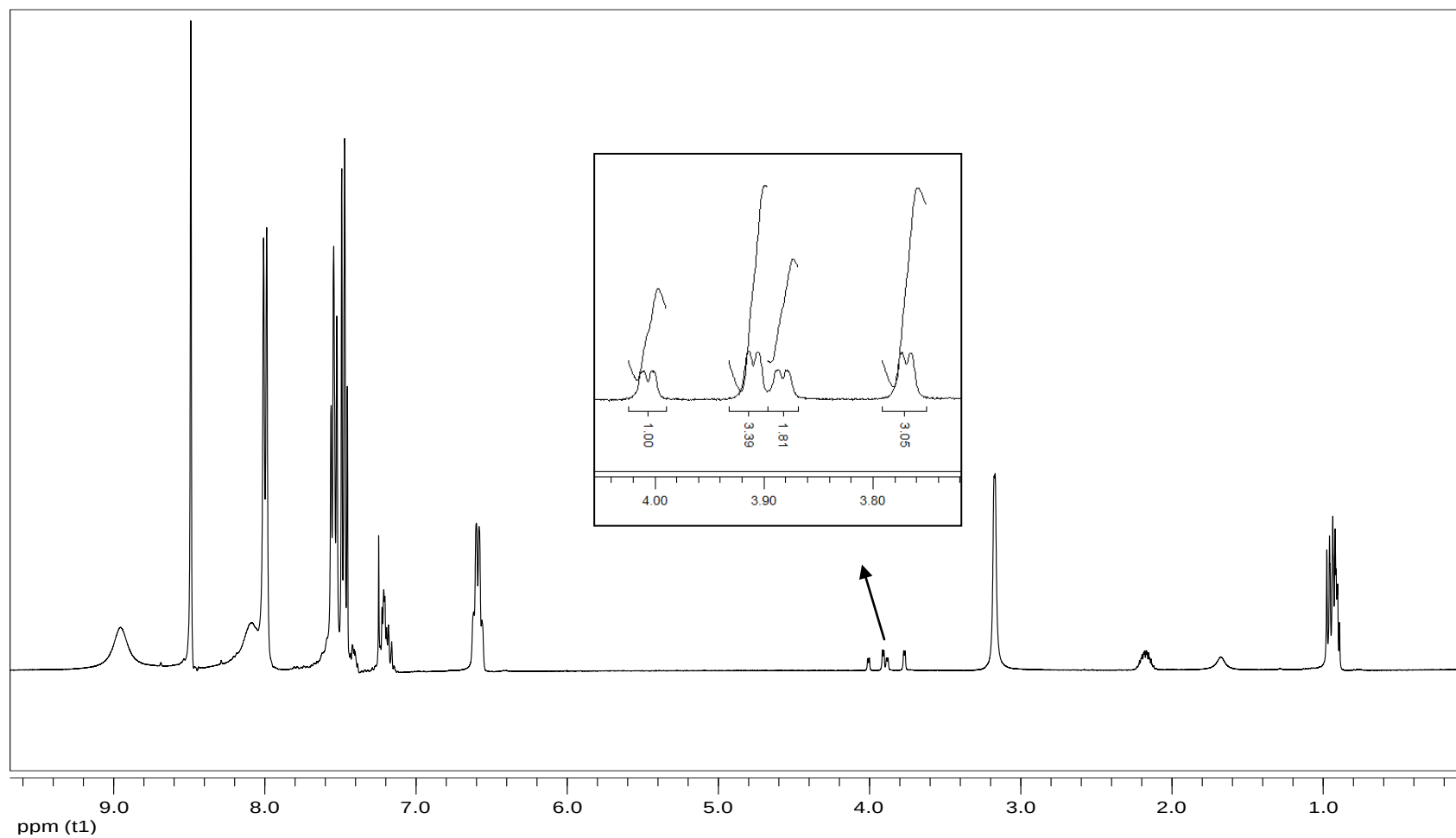


Figure A.21. 400 MHz ^1H NMR spectrum 5-isopropyl-3-*o*-fluorophenyl thiohydantoin (**9**) in the presence of six equivalents of *S*-TFAE in CDCl_3 .

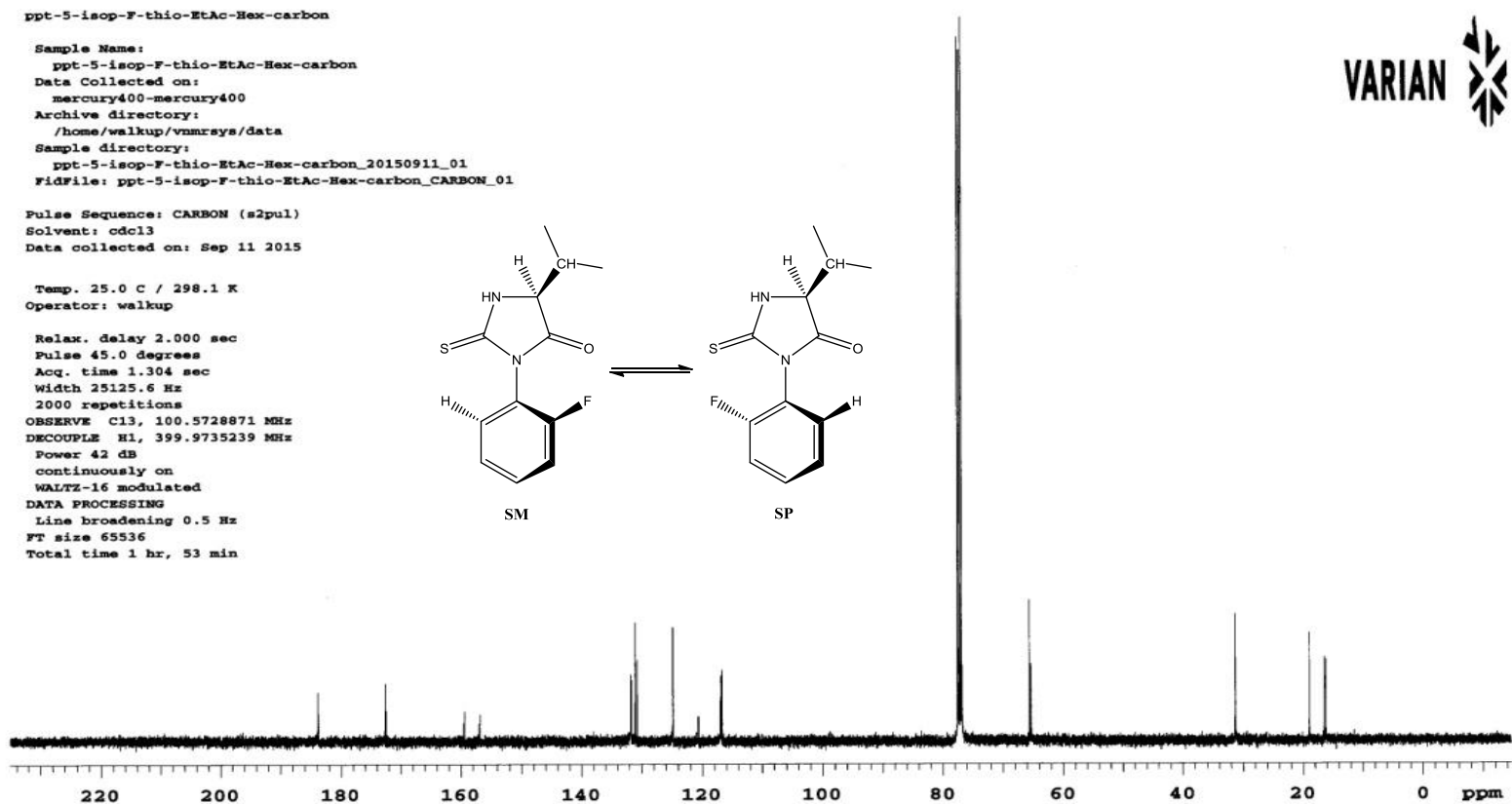


Figure A.22. 100 MHz ^{13}C NMR spectrum 5-isopropyl-3-o-fluorophenyl thiohydantoin (**9**) in CDCl_3 .

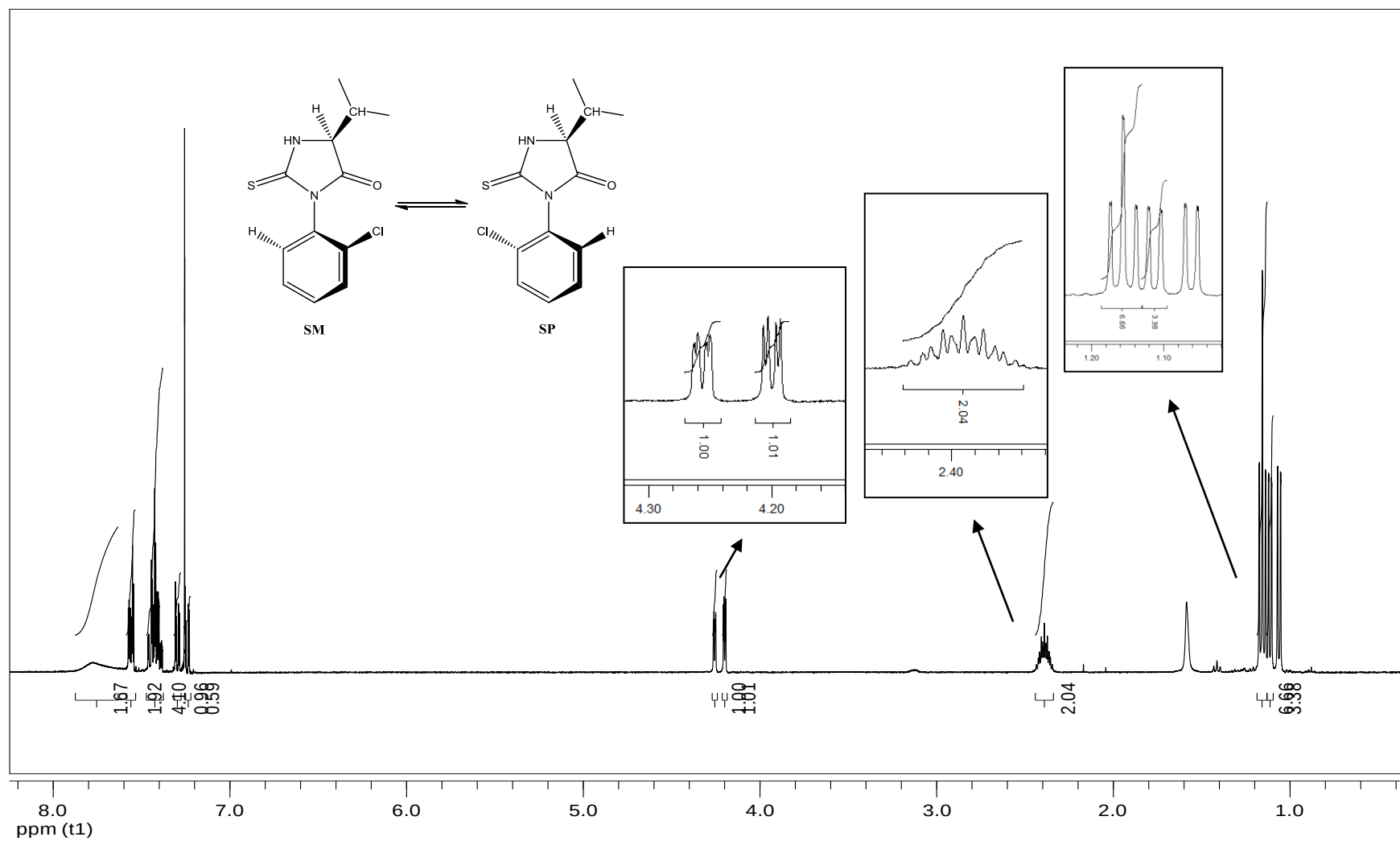


Figure A.23. 400 MHz ^1H NMR spectrum 5-isopropyl-3-o-chlorophenyl thiohydantoin (**10**) in CDCl_3 .

ppt-5-isop-cl-thio-tof1000-5000scan

Sample Name:

ppt-5-isop-cl-thio-tof1000-5000scan

Data Collected on:

mercury400-mercury400

Archive directory:

/home/walkup1/vnmrsva/data

Sample directory:

ppt-5-isop-cl-thio-tof1000-5000scan_20160128_01

FidFile: data_s2pul_001

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jan 28 2016

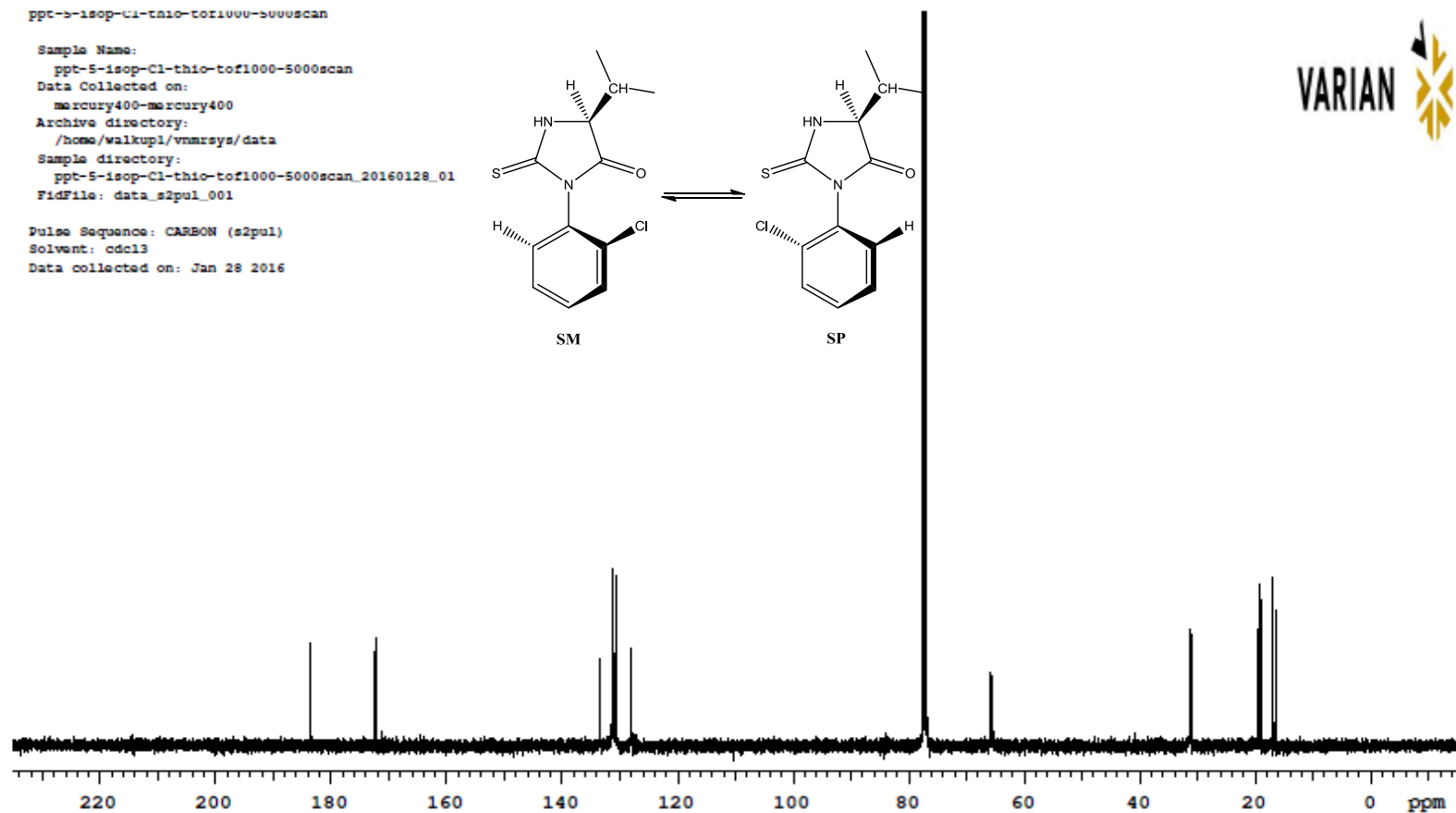


Figure A.24. 100 MHz ^{13}C NMR spectrum 5-isopropyl-3-o-chlorophenyl thiohydantoin (**10**) in CDCl_3 .

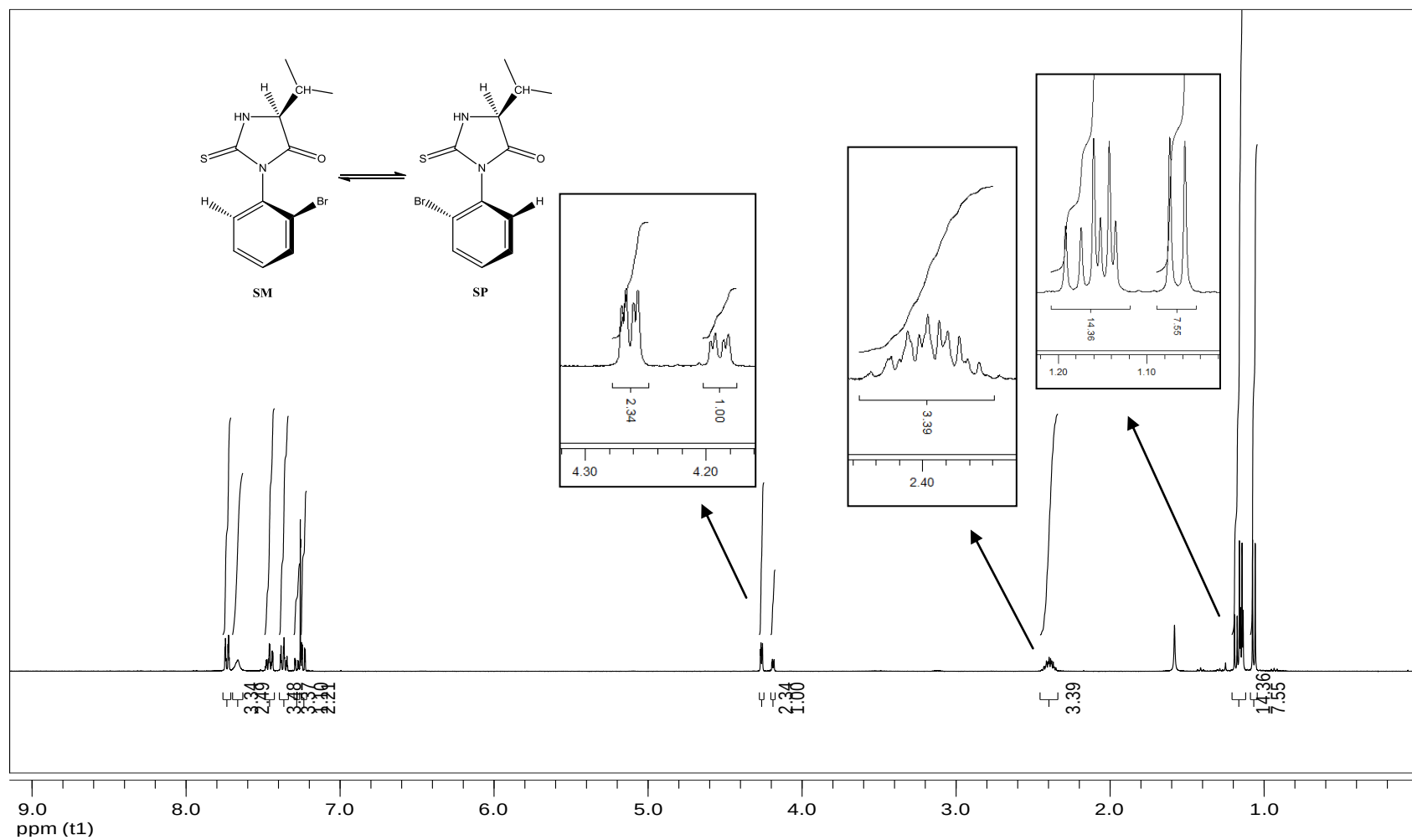


Figure A.25. 400 MHz ^1H NMR spectrum 5-isopropyl-3-o-bromophenyl thiohydantoin (**11**) in CDCl_3 .

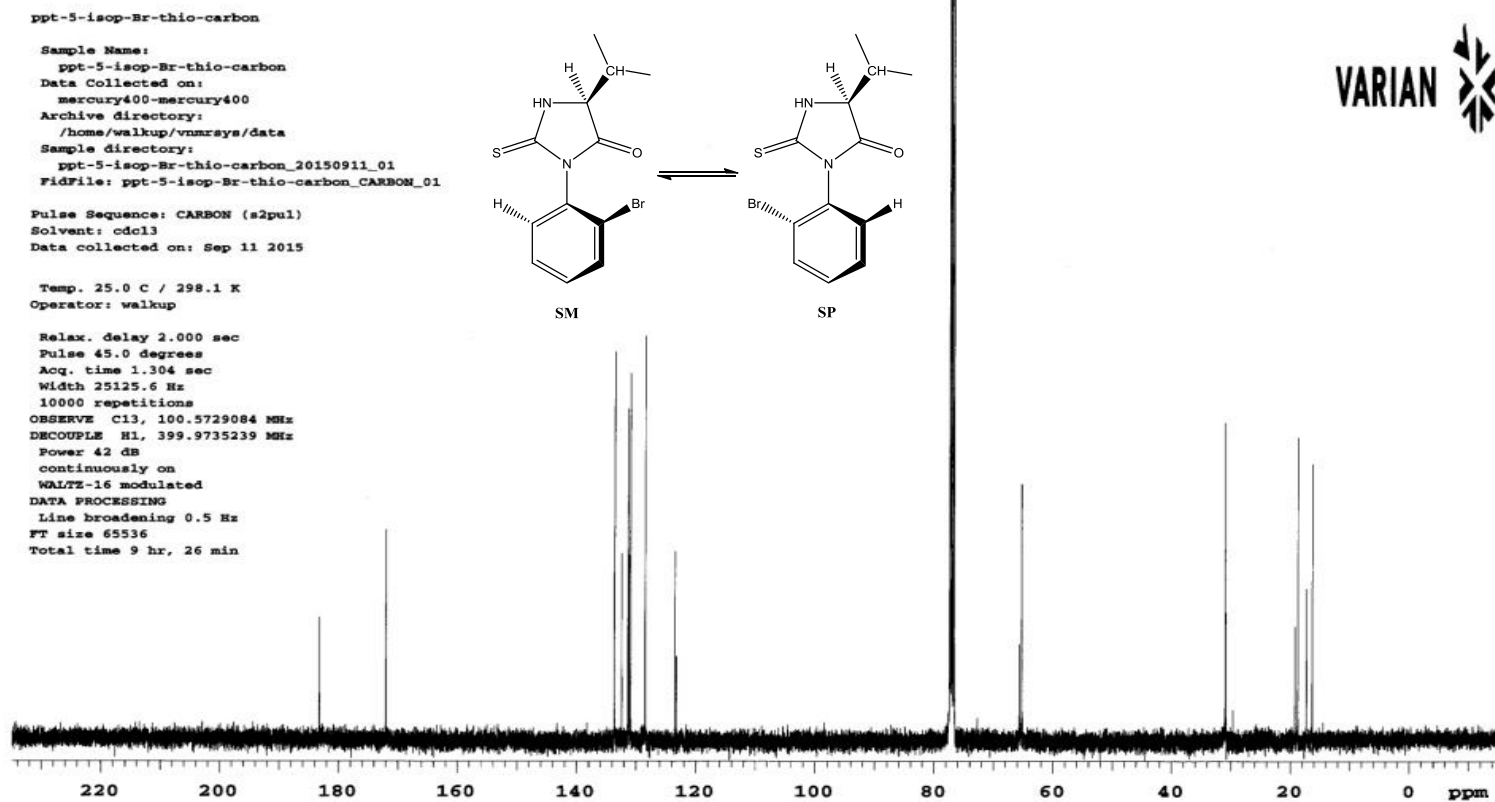


Figure A.26. 100 MHz ^{13}C NMR spectrum 5-isopropyl-3-o-bromophenyl thiohydantoin (**11**) in CDCl_3 .

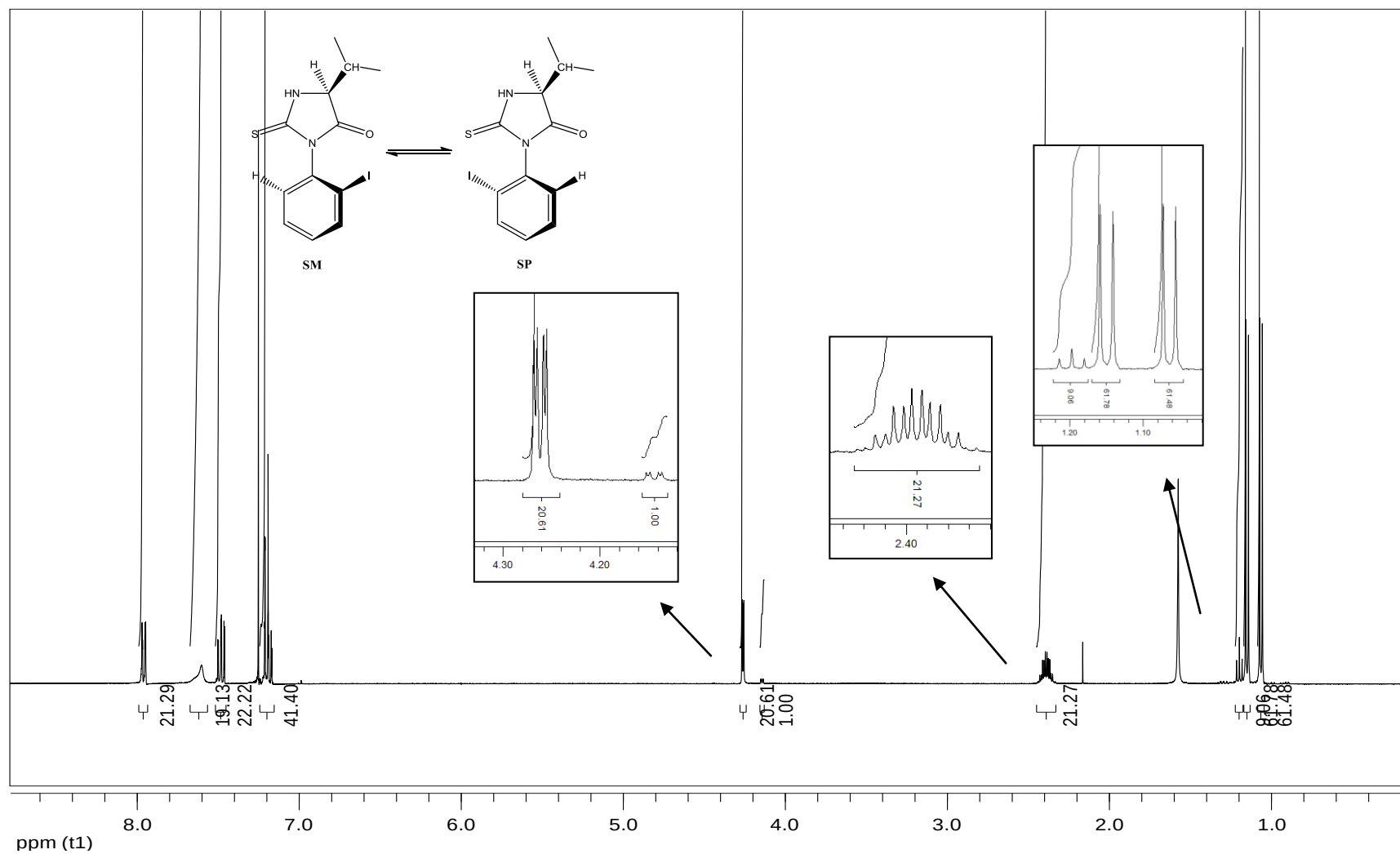


Figure A.27. 400 MHz ^1H NMR spectrum 5-isopropyl-3-o-iodophenyl thiohydantoin (**12**) in CDCl_3 .

ppt-5-isop-i-thio
 Sample name:
 ppt-5-isop-i-thio
 Data Collected on:
 Mercury400-Mercury400
 Archive directory:
 /home/walkup1/vnmrsys/data
 Sample directory:
 ppt-5-isop-i-thio_20160121_01
 FID file: data_s2pul_001
 Pulse Sequence: CAMEX (s2pul)
 Solvent: cdcl3
 Data collected on: Jan 21 2016

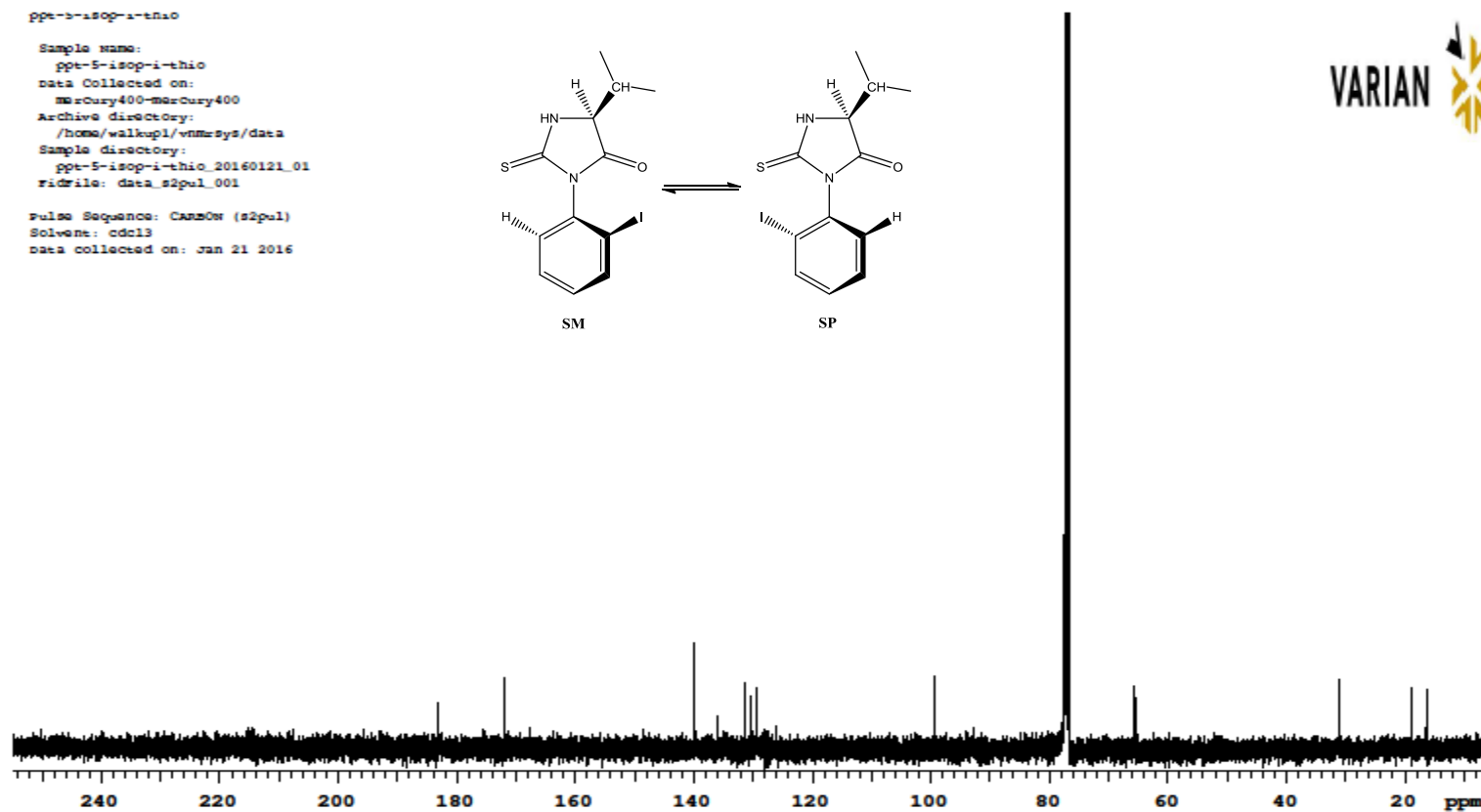
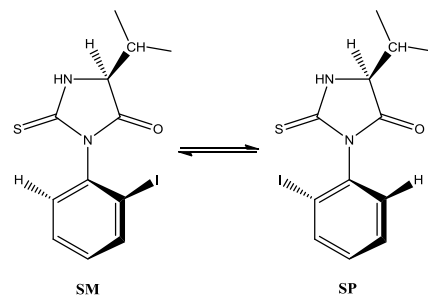


Figure A.28. 100 MHz ^{13}C NMR spectrum 5-isopropyl-3-o-iodophenyl thiohydantoin (**12**) in CDCl_3 .

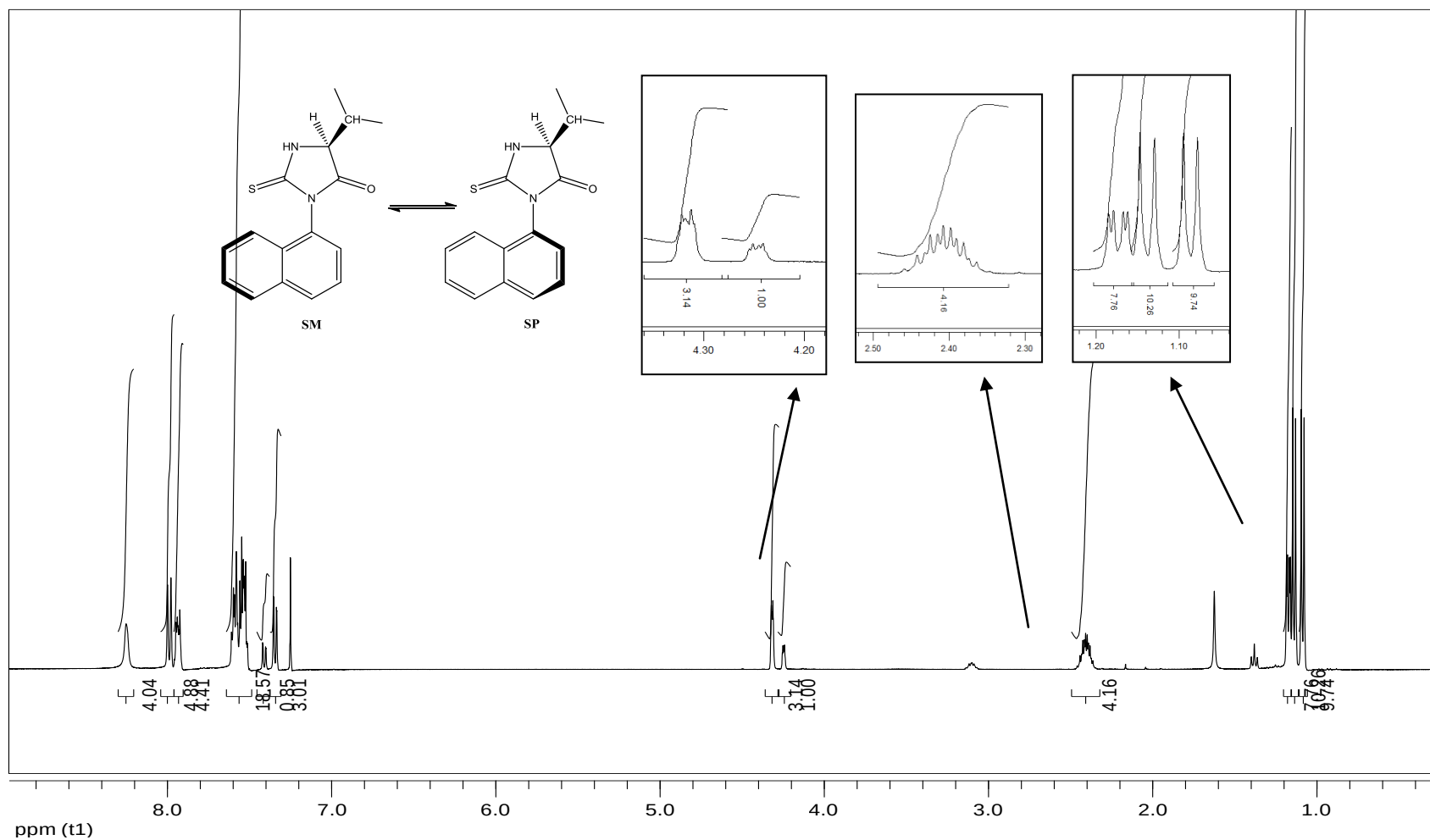


Figure A.29. 400 MHz ^1H NMR spectrum 5-isopropyl- α -naphthyl thiohydantoin (**13**) in CDCl_3 .

ppt-5-isop-np-thio-carbon

Sample Name:

ppt-5-isop-np-thio-carbon

Data Collected on:

mercury400-mercury400

Archive directory:

/home/walkup1/vnmrsys/data

Sample directory:

ppt-5-isop-np-thio-carbon_20160127_01

FidFile: data_s2pul_001

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Jan 27 2016

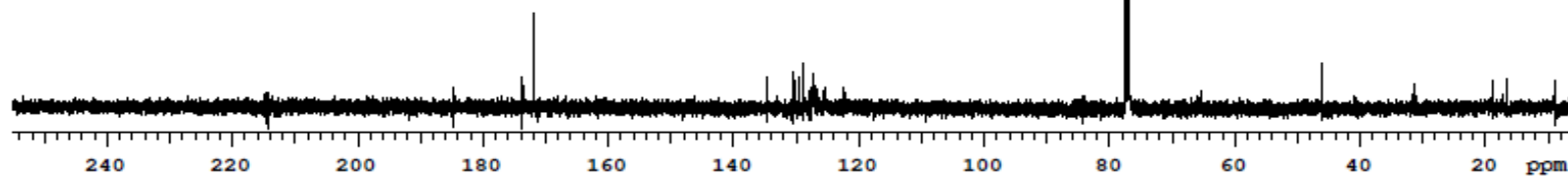
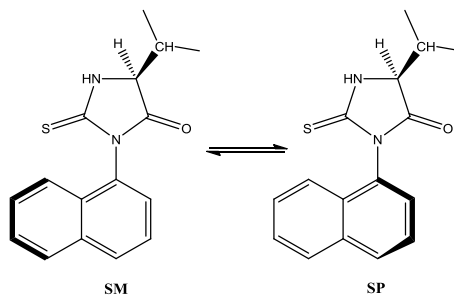


Figure A.30. 100 MHz ¹³C NMR spectrum 5-isopropyl-α-naphthyl thiohydantoin (**13**) in CDCl₃.

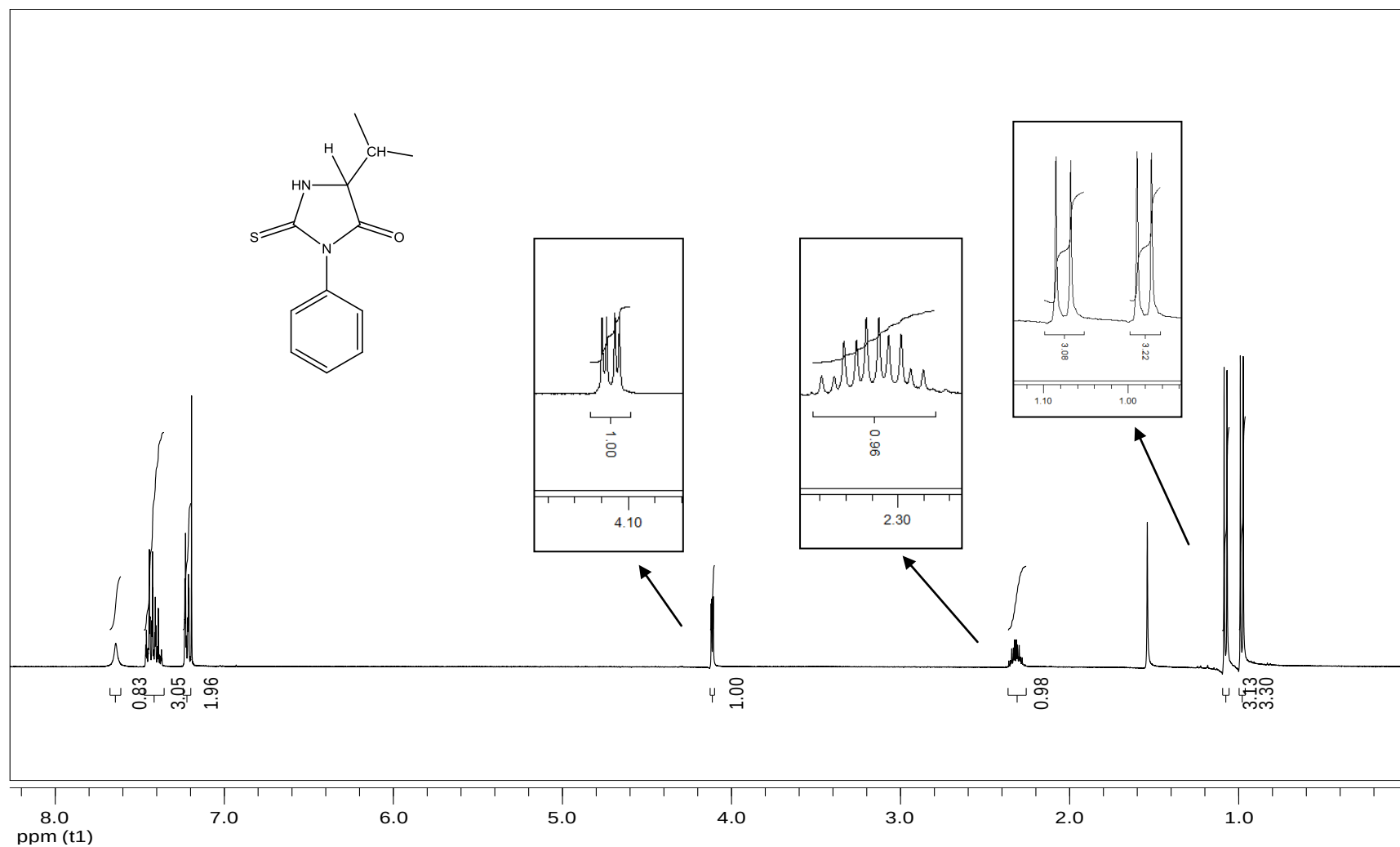


Figure A.31. 400 MHz ^1H NMR spectrum 5-isopropyl-phenyl thiohydantoin (**14**) in CDCl_3 .

ppt-5-isop-ph-thio-EtAc-Hex-carbon

Sample Name:
ppt-5-isop-ph-thio-EtAc-Hex-carbon

Data Collected on:
mercury400-mercury400

Archive directory:
/home/walkup/vnmrsys/data

Sample directory:
ppt-5-isop-ph-thio-EtAc-Hex-carbon_20150909_01

FidFile: ppt-5-isop-ph-thio-EtAc-Hex-carbon_CARBON_01

Pulse Sequence: CARBON (s2pul)

Solvent: cdcl3

Data collected on: Sep 9 2015

Temp. 25.0 C / 298.1 K

Operator: walkup

Relax. delay 2.000 sec

Pulse 45.0 degrees

Acq. time 1.304 sec

Width 25125.6 Hz

10000 repetitions

OBSERVE C13, 100.5728673 MHz

DECOUPLE H1, 399.9735239 MHz

Power 42 dB

continuously on

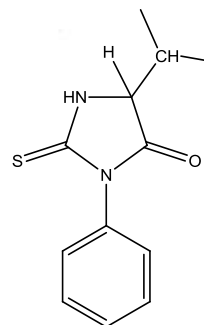
WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 9 hr, 26 min



VARIAN

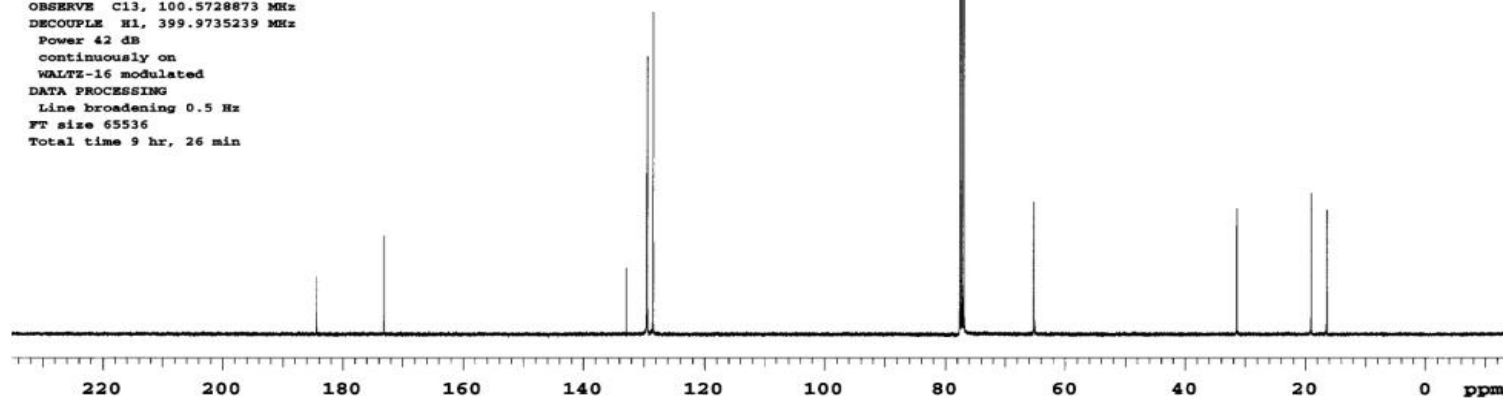


Figure A.32. 100 MHz ^{13}C NMR spectrum 5-isopropyl-phenyl thiohydantoin (**14**) in CDCl_3 .

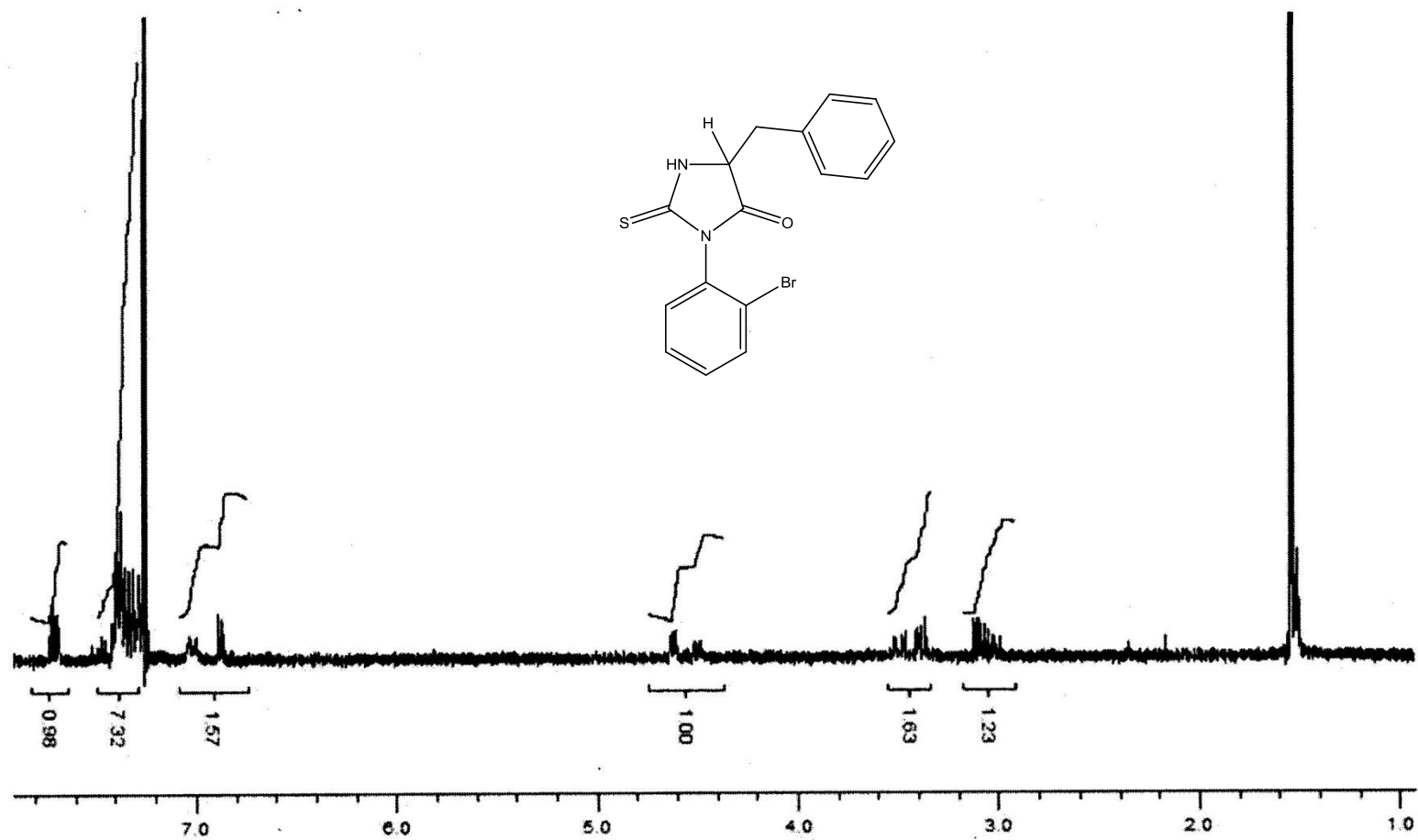


Figure A.33. 400 MHz ^1H NMR spectrum 5-benzyl-3-o-bromophenyl thiohydantoin (15) in CDCl_3 .

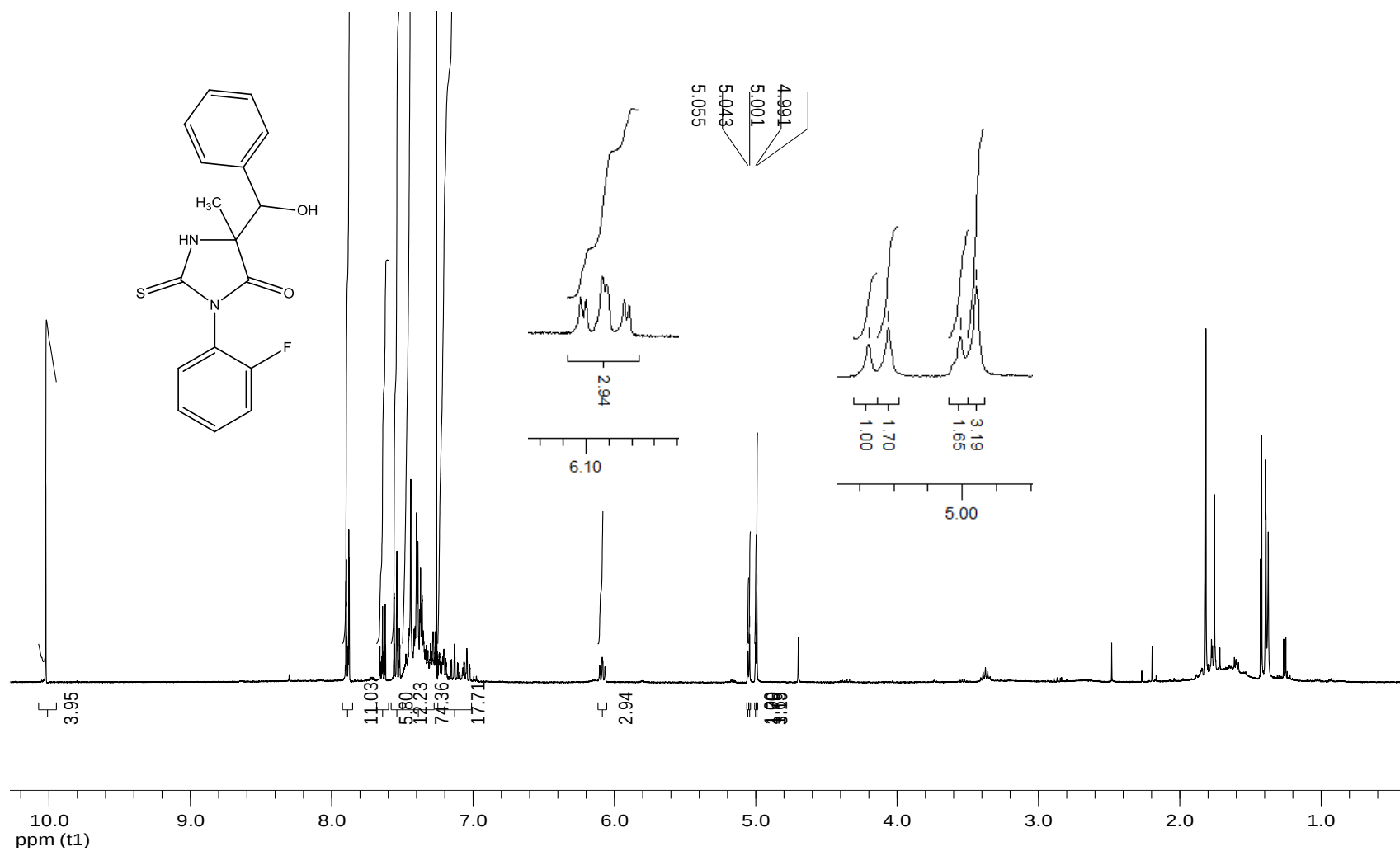


Figure A.34. 400 MHz ¹H NMR of crude 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-florophenyl thiohydantoin (**16**) in CDCl₃.

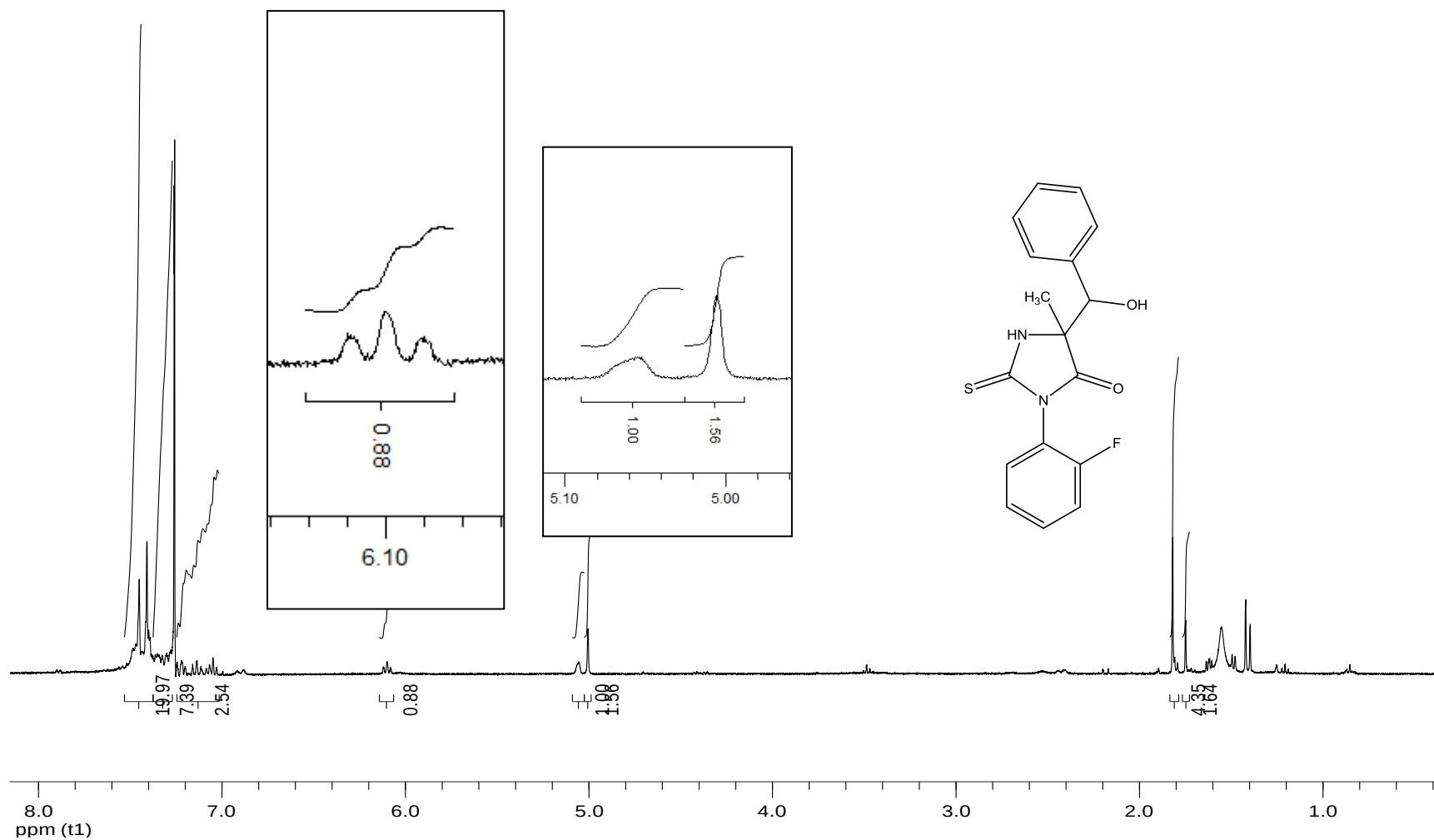


Figure A.35. 400 MHz ¹H NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-florophenyl thiohydantoin (**16**) in CDCl₃ after purification.

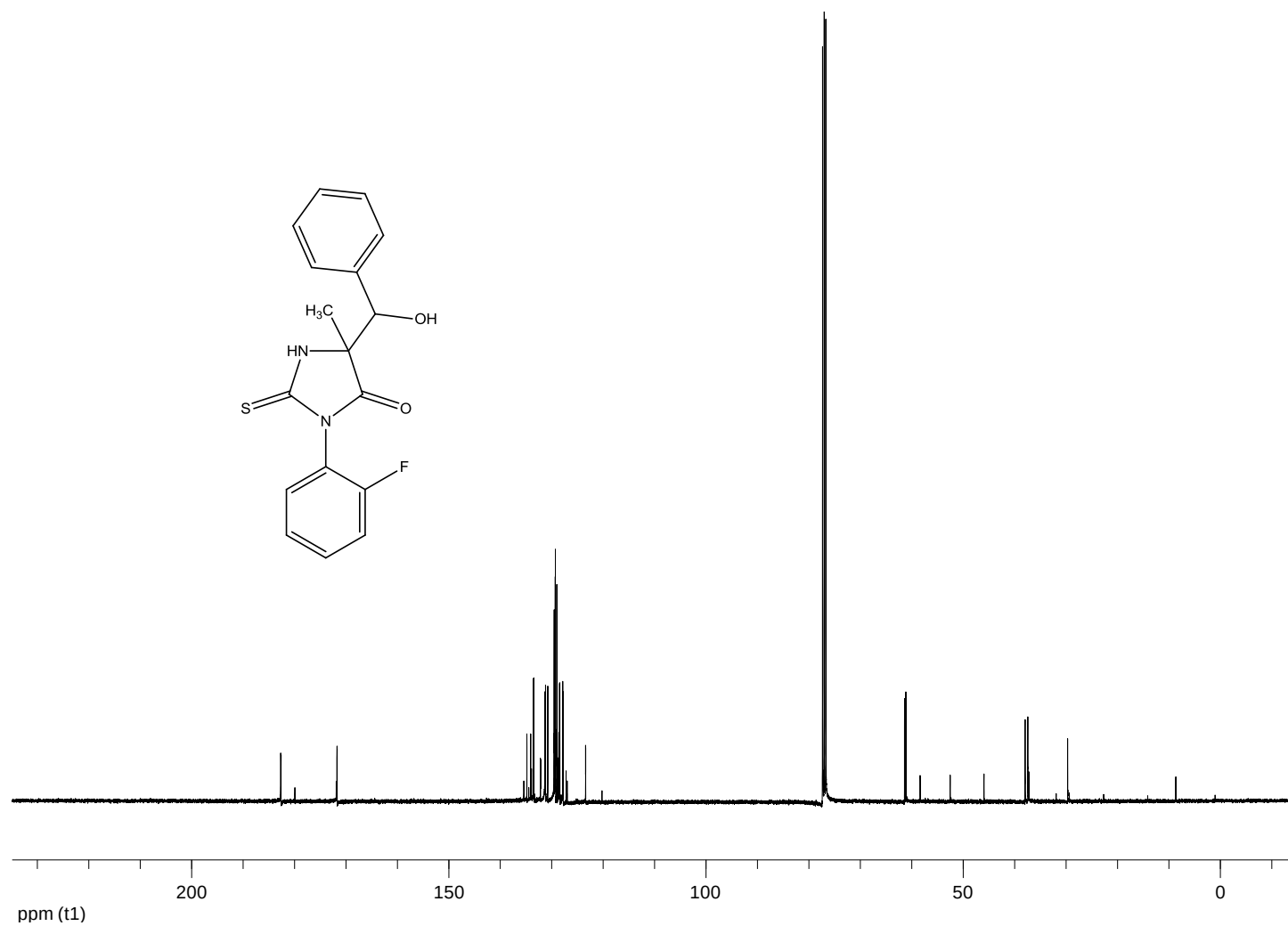


Figure A.36. 100 MHz ^{13}C NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-*o*-fluorophenyl thiohydantoin (**16**) in CDCl_3 .

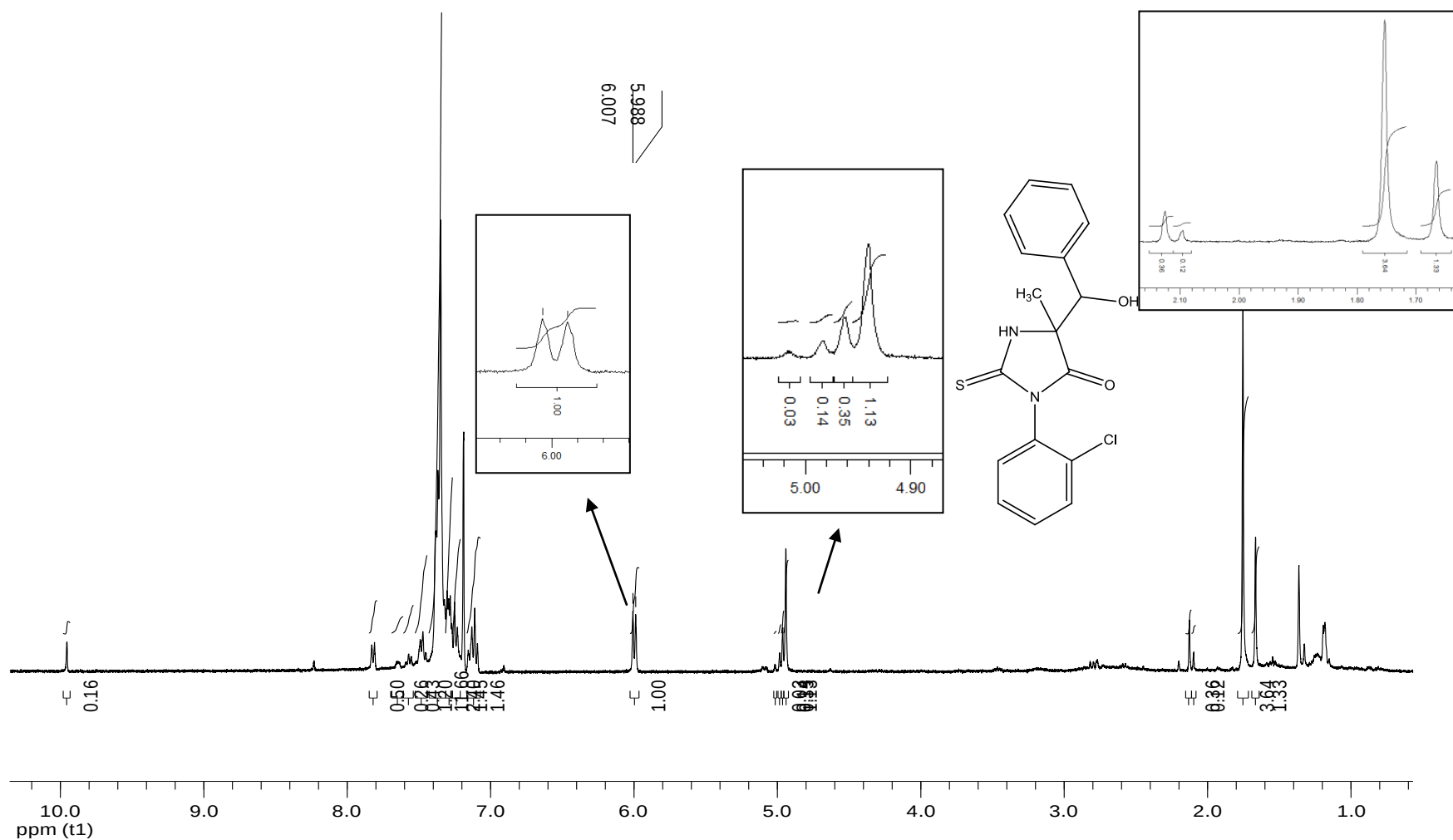


Figure A.37. 400 MHz ¹H NMR of crude 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-chlorophenyl thiohydantoin (**17**) in CDCl₃.

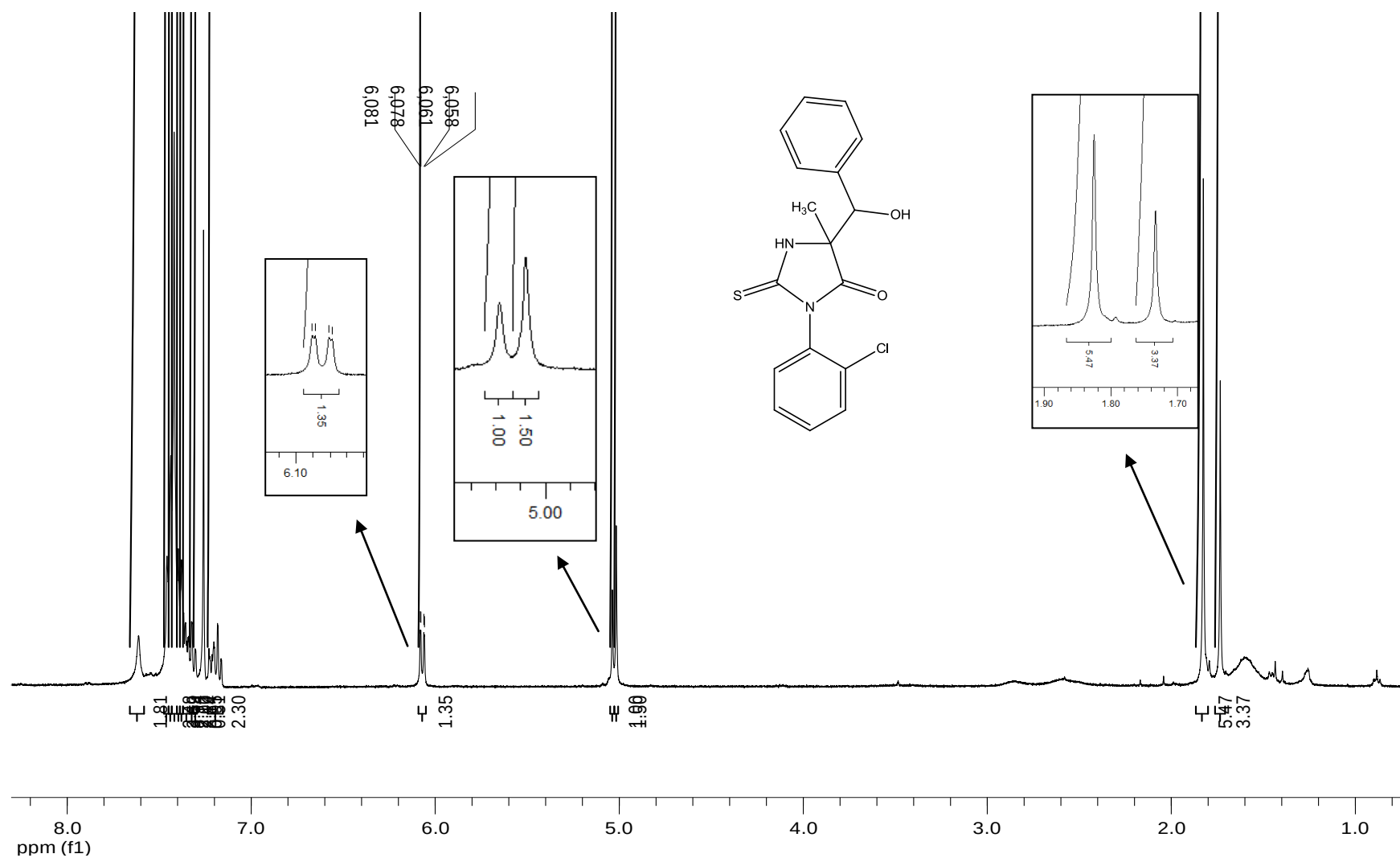


Figure A.38. 400 MHz ¹H NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-chlorophenyl thiohydantoin (**17**) in CDCl₃ after purification.

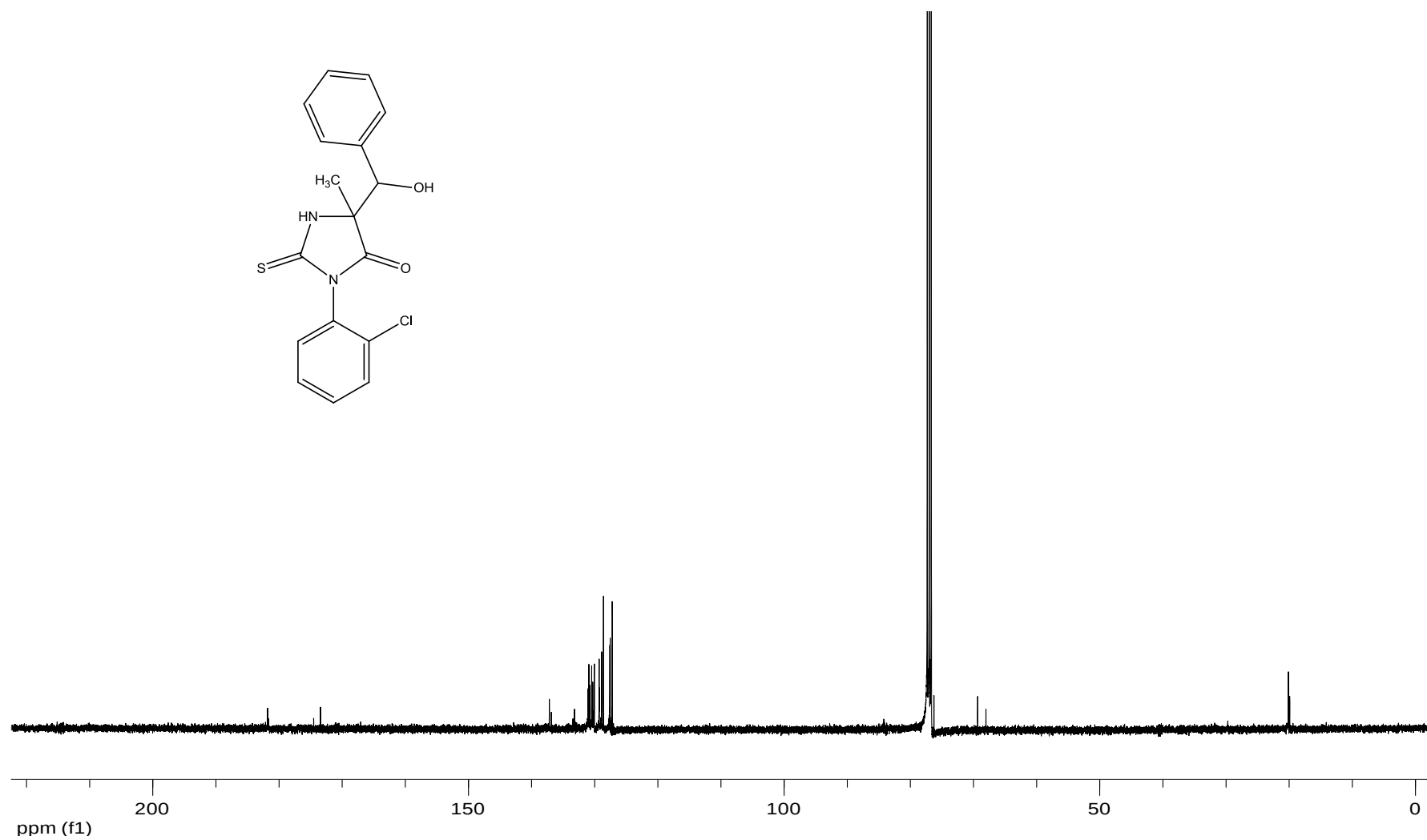


Figure A.39. 100 MHz ^{13}C NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-chlorophenyl thiohydantoin (**17**) in CDCl_3 .

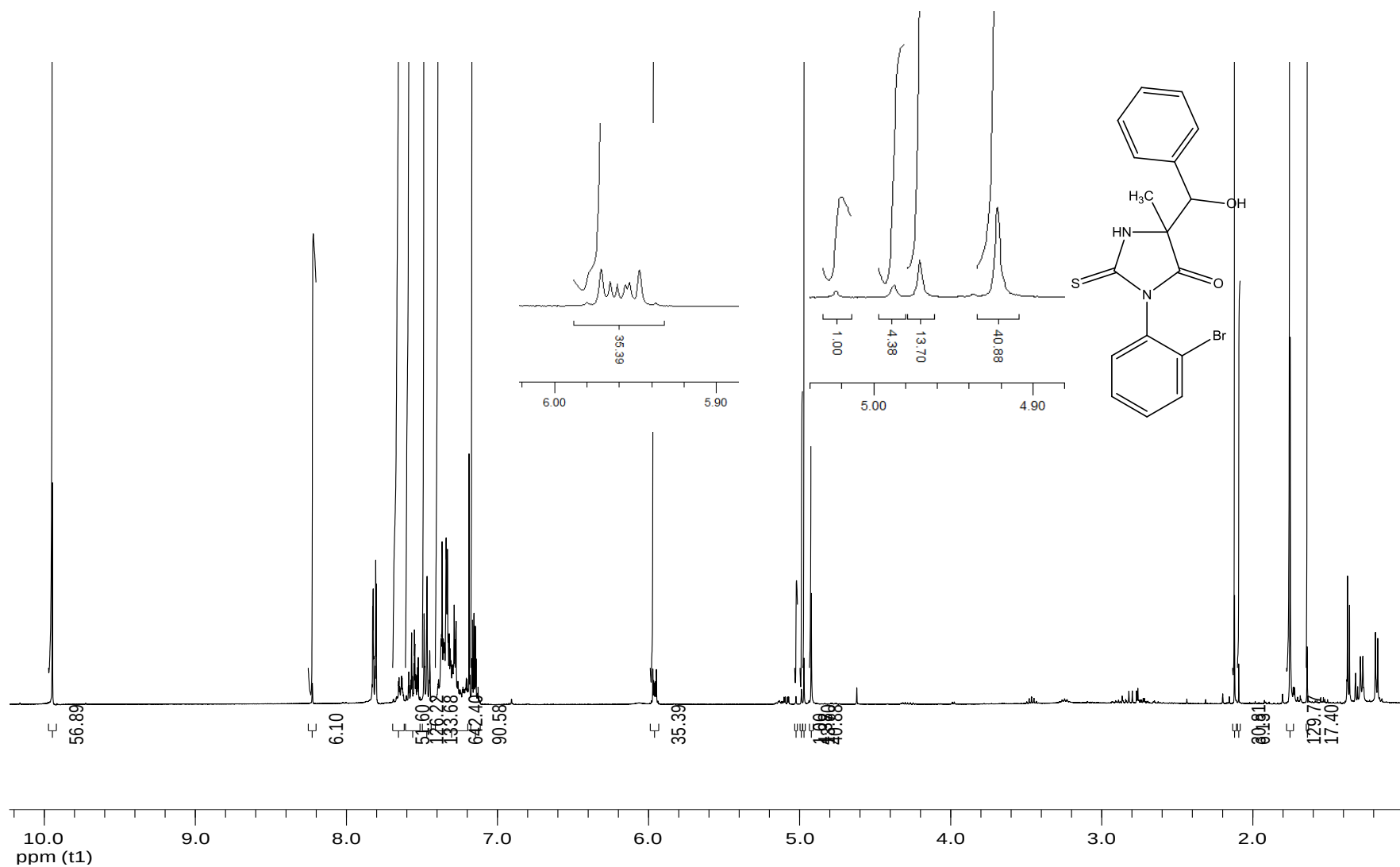


Figure A.40. 400 MHz ^1H NMR of crude 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-bromophenyl thiohydantoin (**18**) in CDCl_3 .

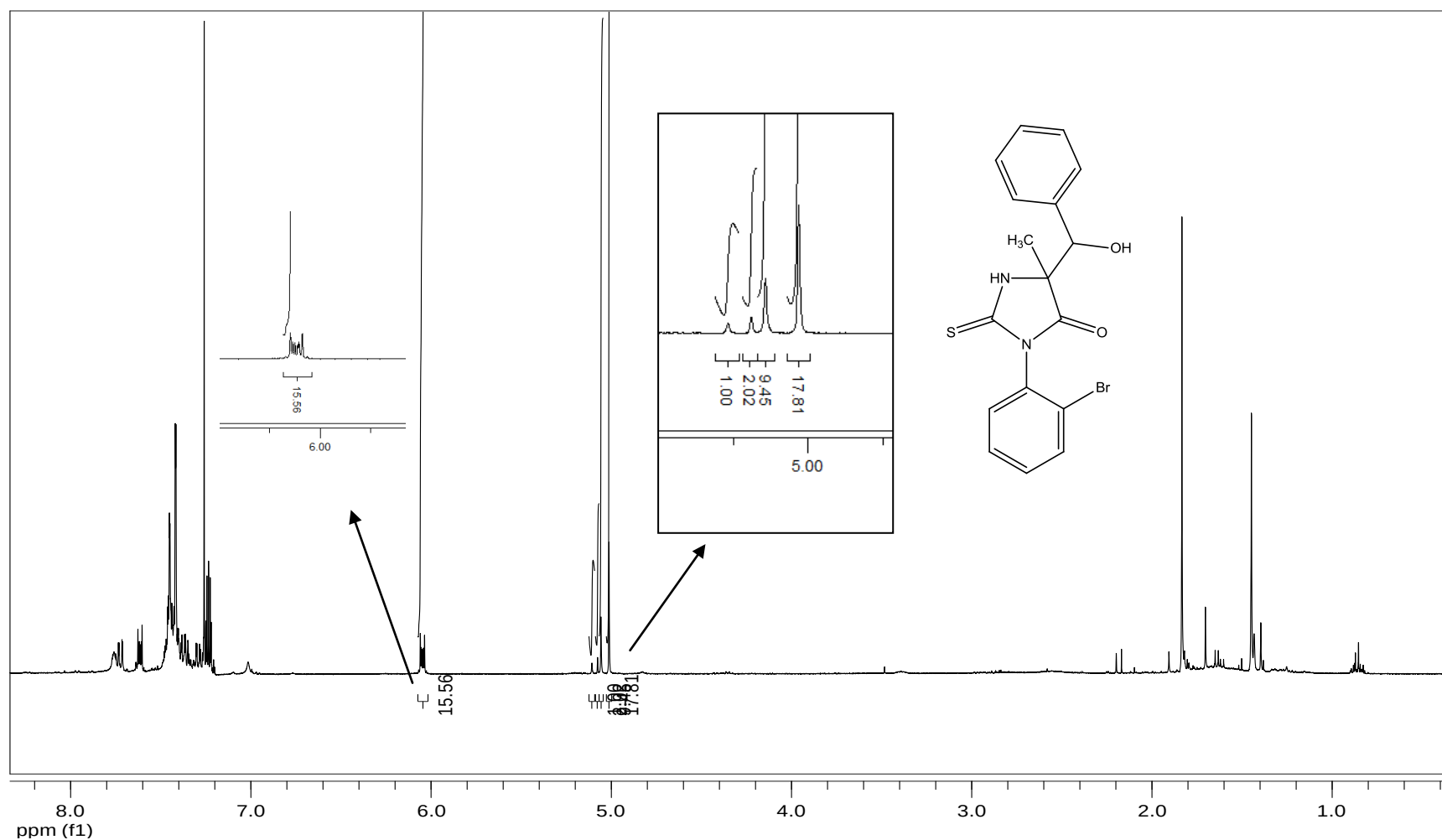


Figure A.41. 400 MHz ¹H NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-bromophenyl thiohydantoin (**18**) in CDCl₃ after purification.

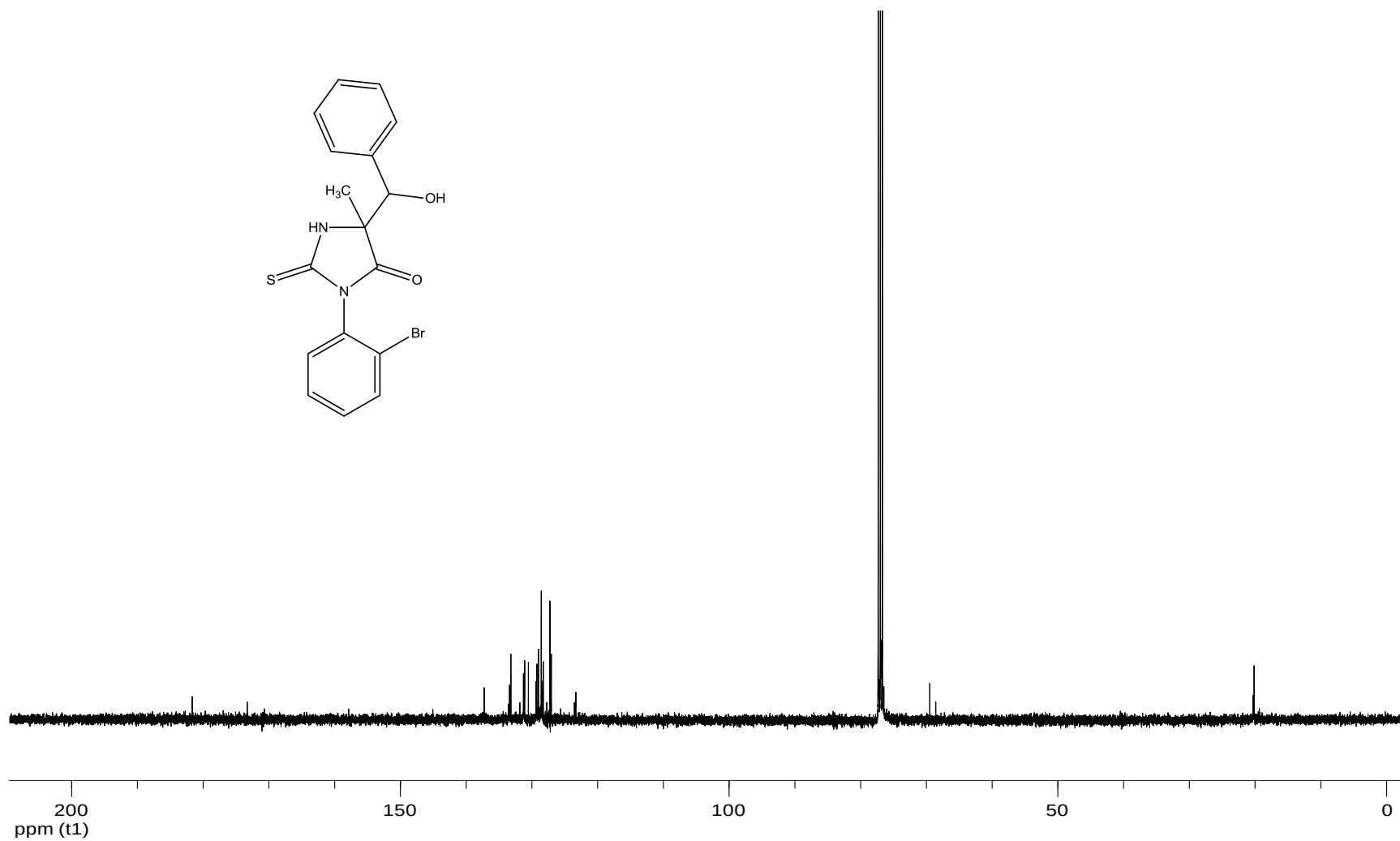


Figure A.42. 100 MHz ^{13}C NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-bromophenyl thiohydantoin (**18**) in CDCl_3 .

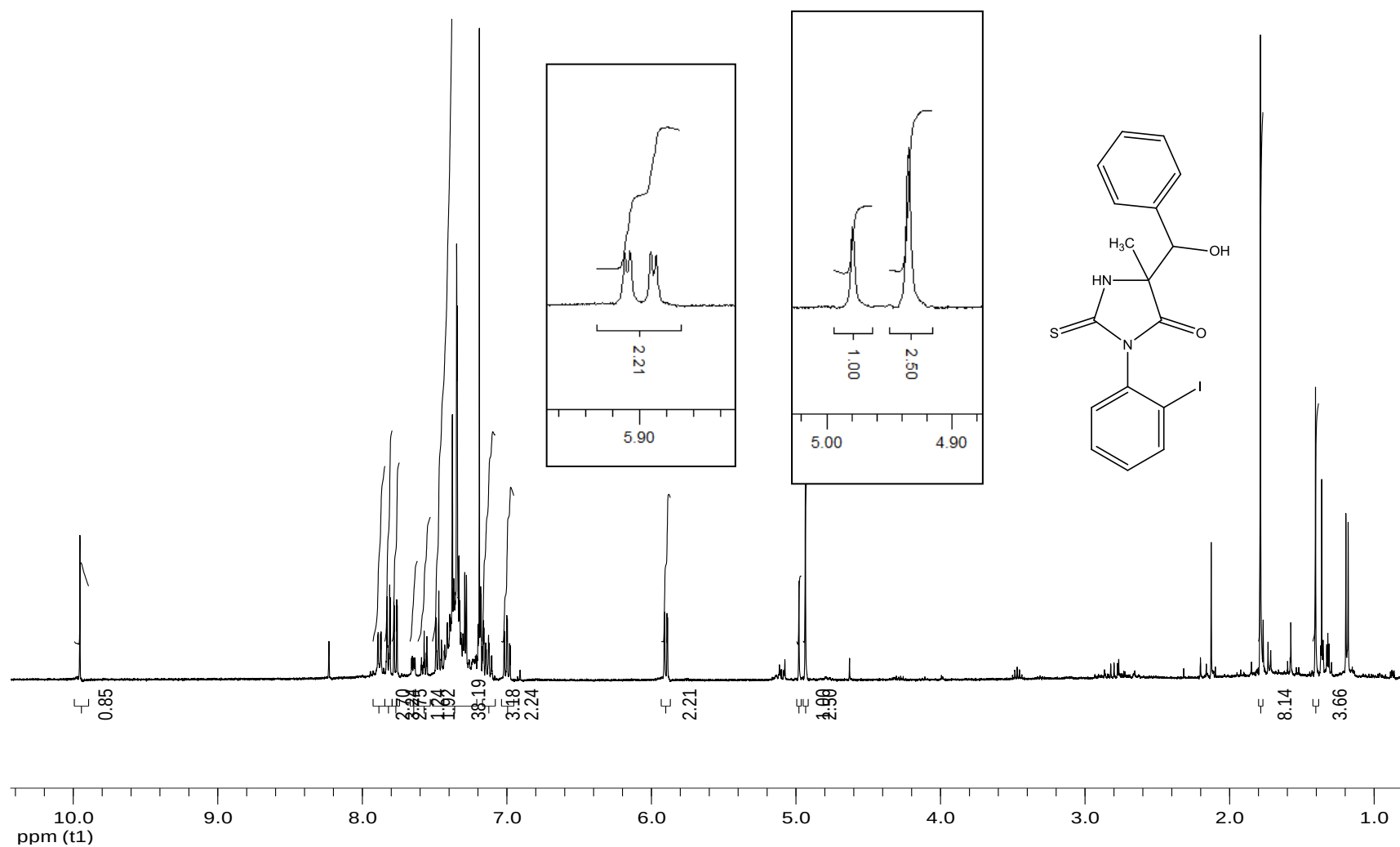


Figure A.43. 400 MHz ^1H NMR of crude 5-(hydroxy(phenyl)methyl)-5-methyl-3-*o*-iodophenyl thiohydantoin (**19**) in CDCl_3 .

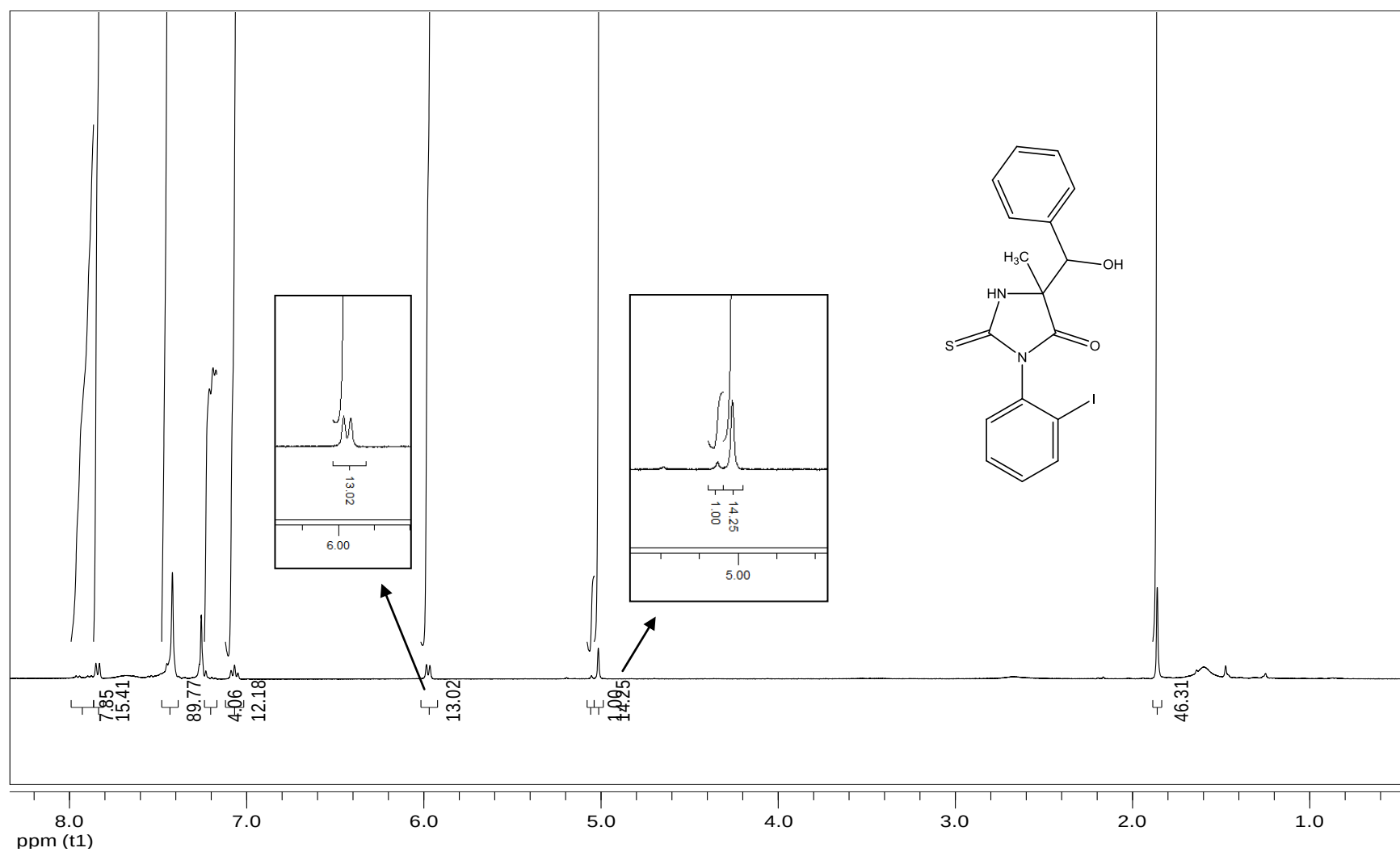


Figure A.44. 400 MHz ¹H NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-o-iodophenyl thiohydantoin (**19**) in CDCl₃.

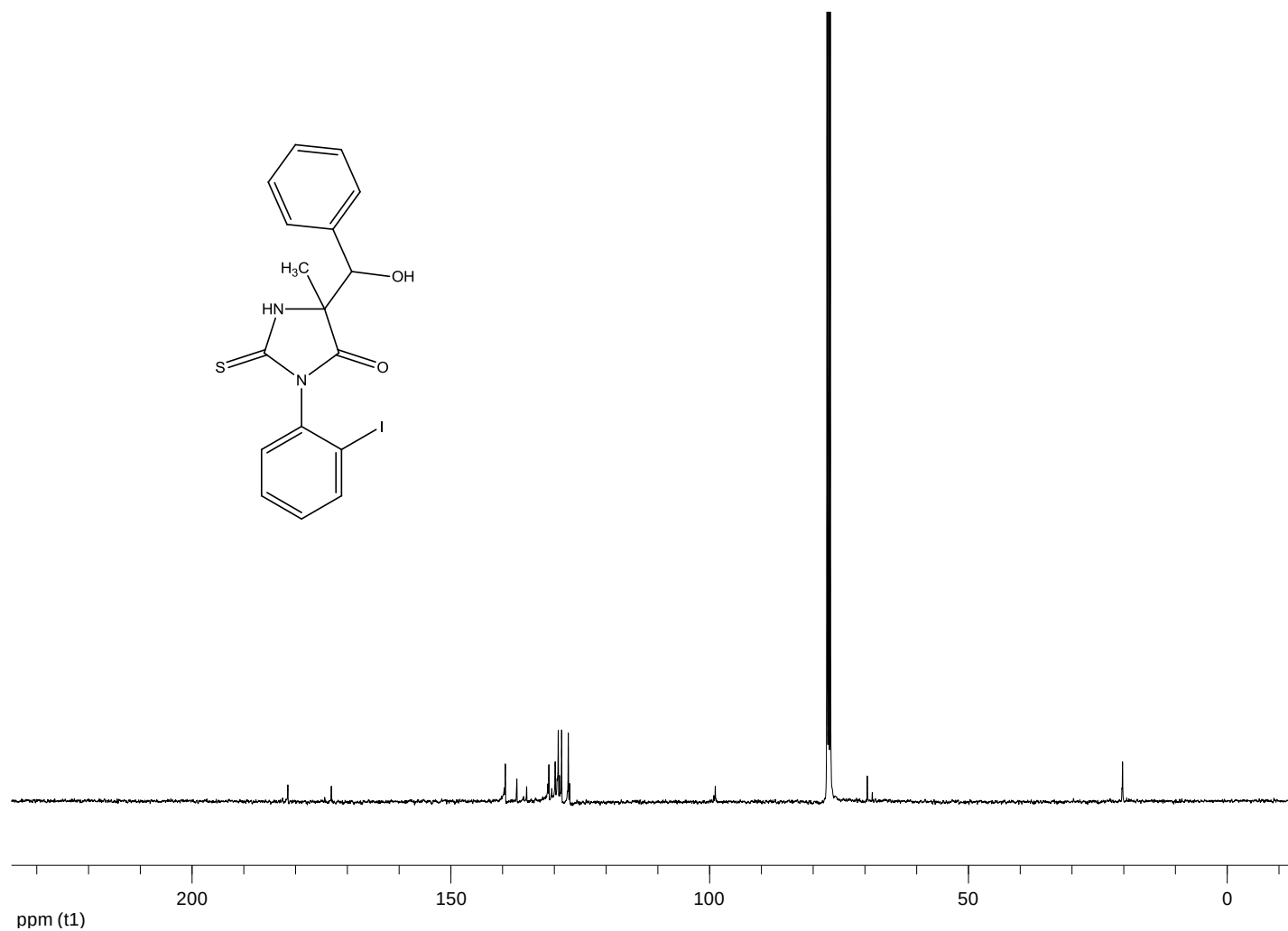


Figure A.45. 100 MHz ^{13}C NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3-*o*-iodophenyl thiohydantoin (**19**) in CDCl_3 .

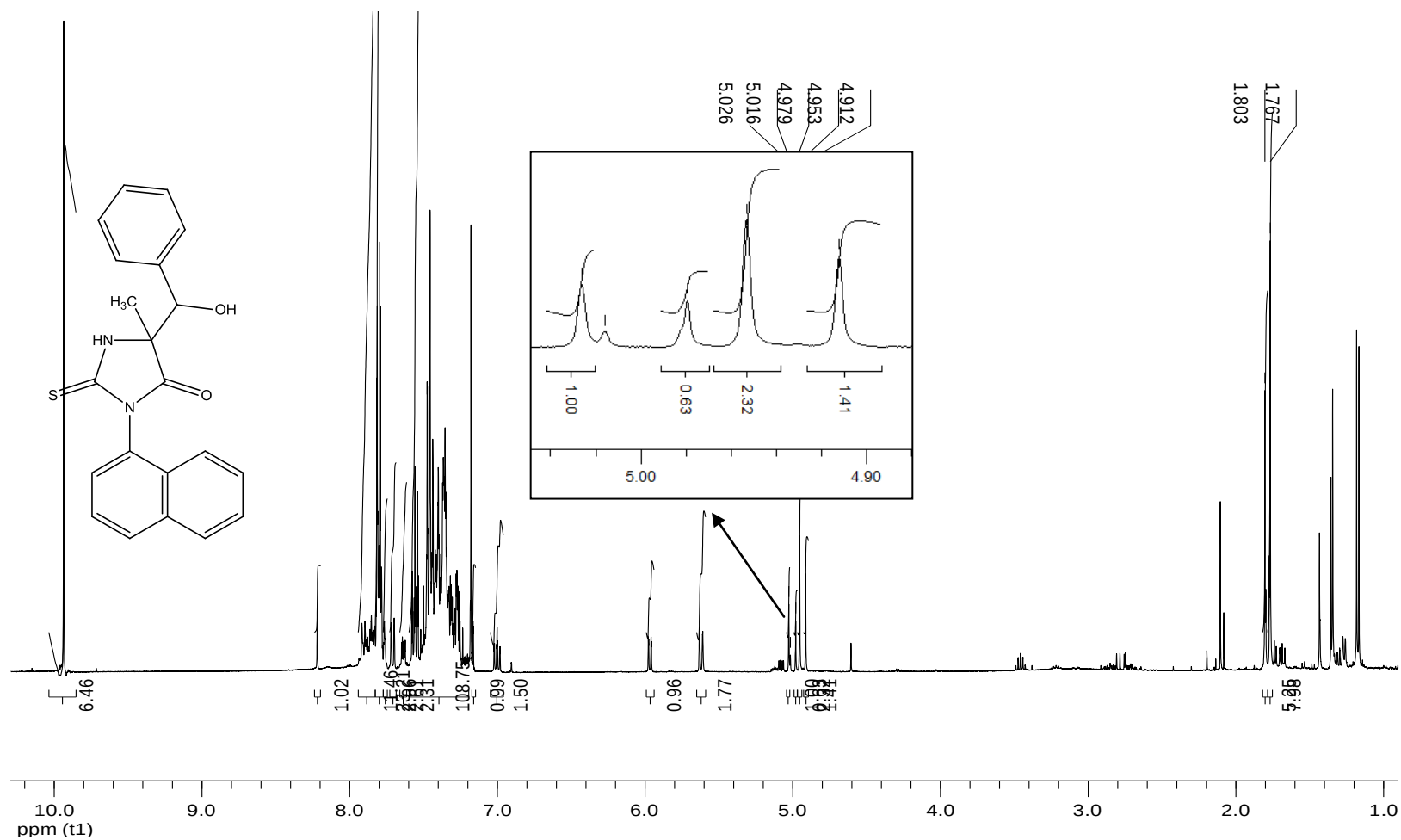


Figure A.46. 400 MHz ¹H NMR of crude 5-(hydroxy(phenyl)methyl)-5-methyl-3- α -naphthyl thiohydantoin (**20**) in CDCl₃.

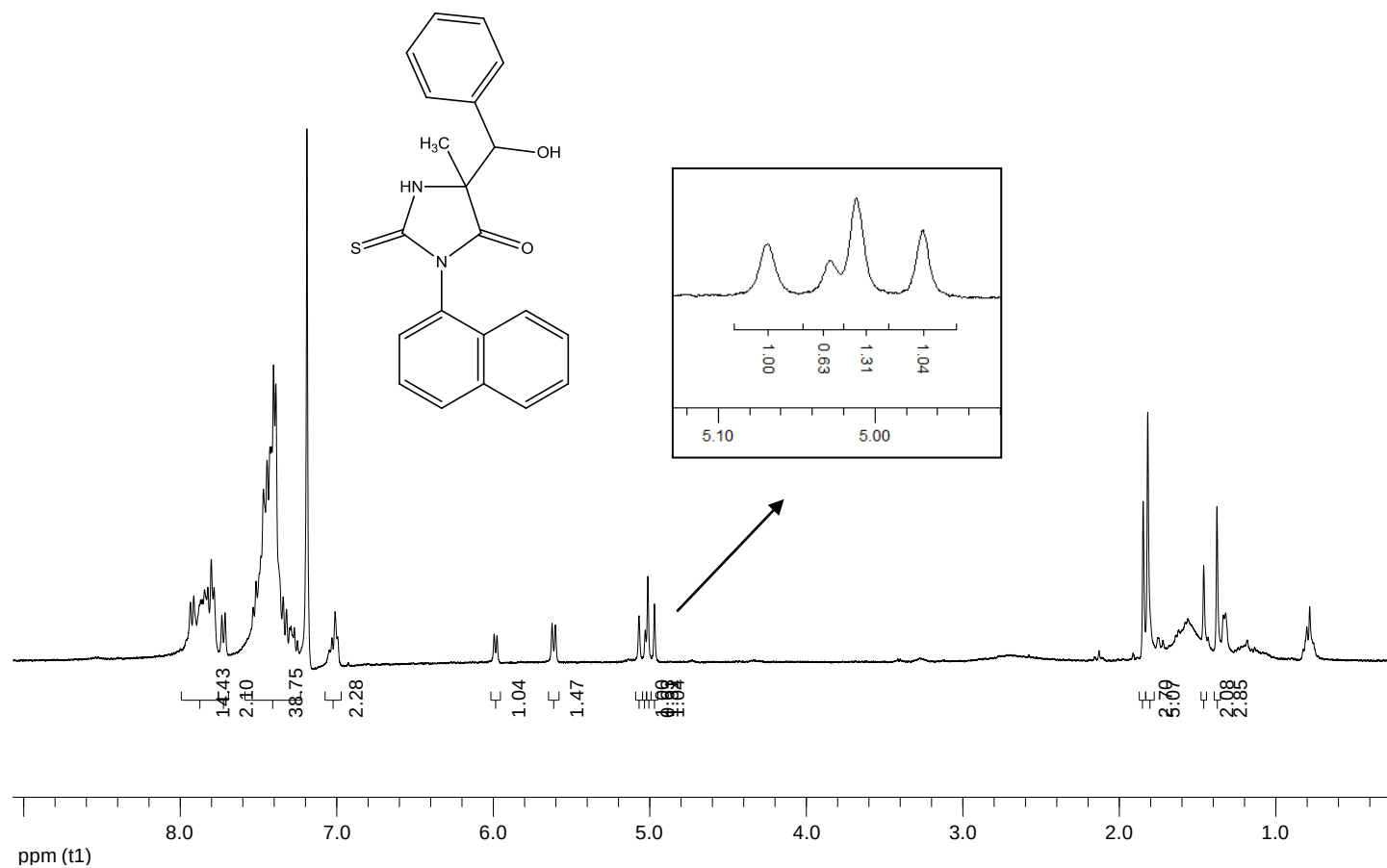


Figure A.47. 400 MHz ¹H NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3- α -naphthyl thiohydantoin (**20**) in CDCl₃ after purification.

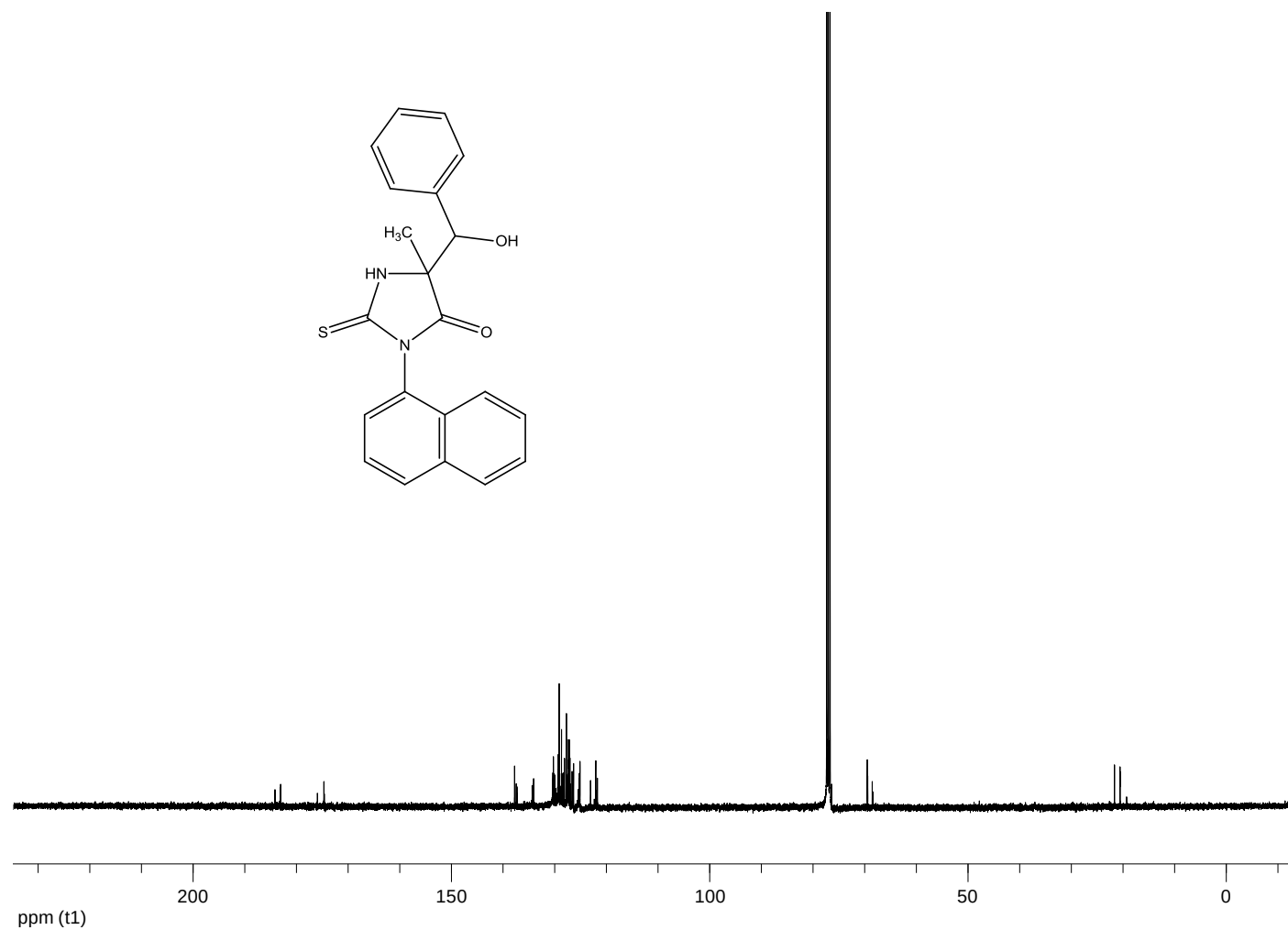


Figure A.48. 100 MHz ^{13}C NMR of 5-(hydroxy(phenyl)methyl)-5-methyl-3- α -naphthyl thiohydantoin (**20**) in CDCl_3 .

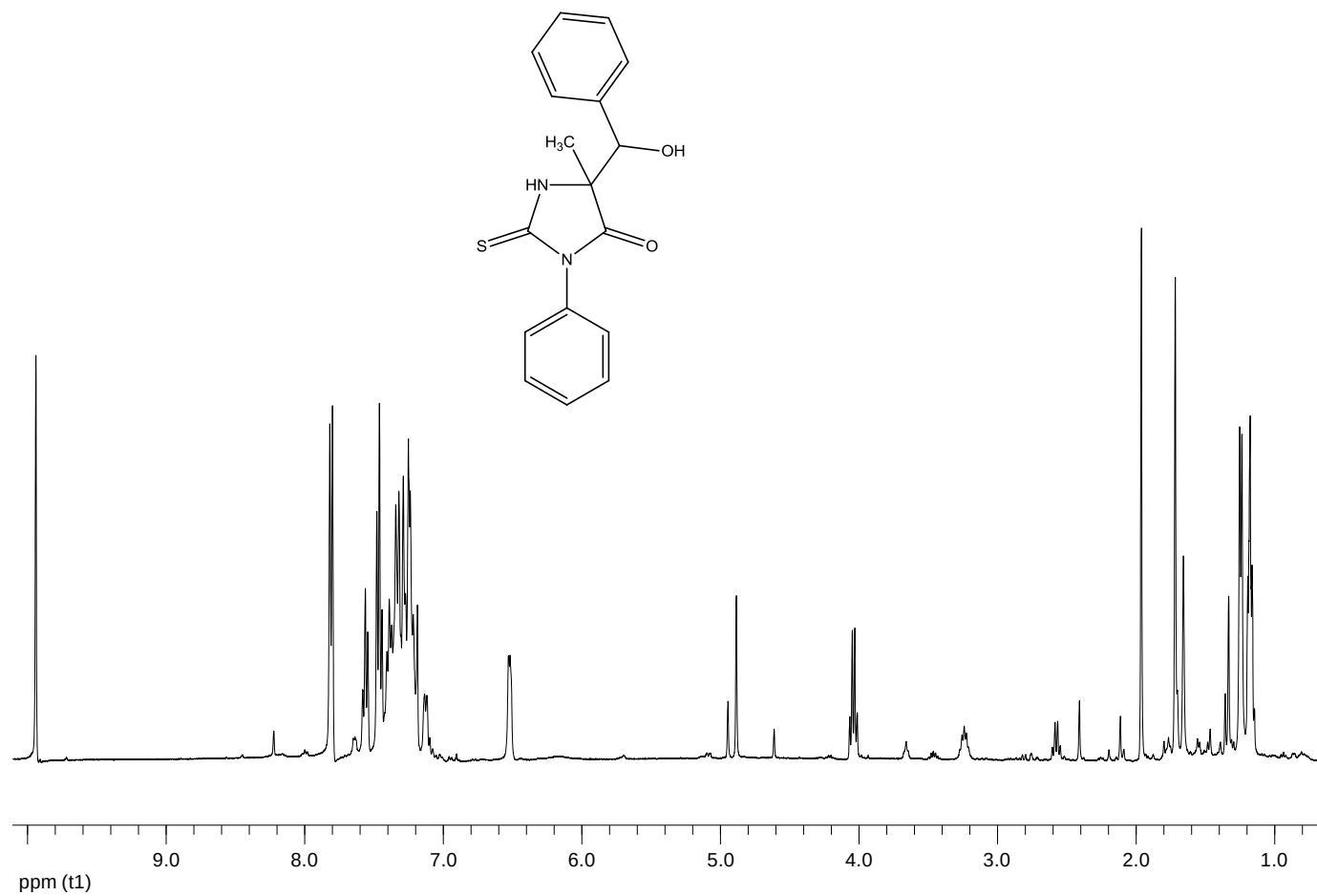


Figure A.49. 400 MHz ¹H NMR of crude 5-(hydroxy(phenyl)methyl)-5-methyl-3-phenyl thiohydantoin (**21**) in CDCl₃.

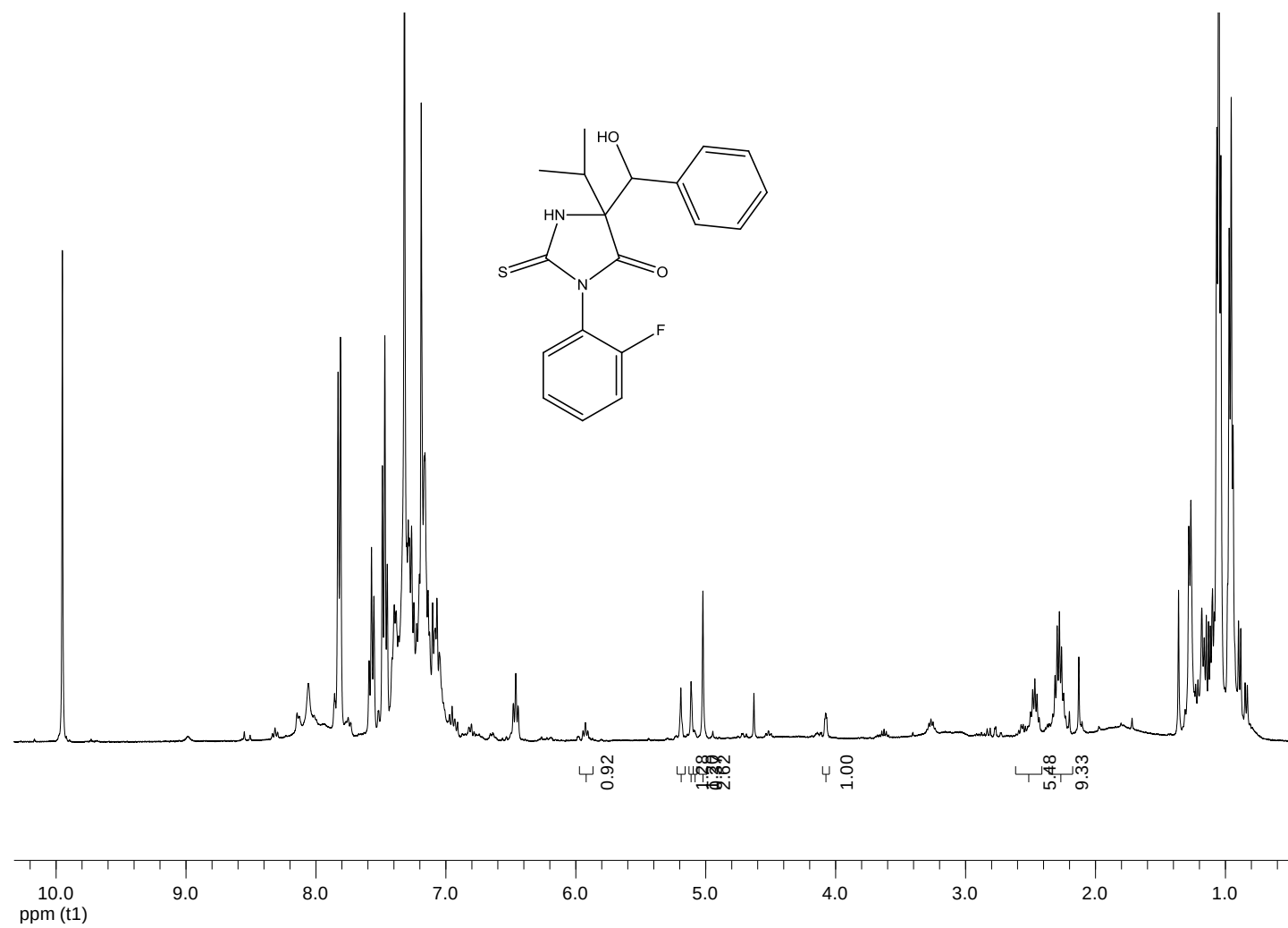


Figure A.50. 400 MHz ^1H NMR of crude 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-florophenyl thiohydantoin (**22**) in CDCl_3 .

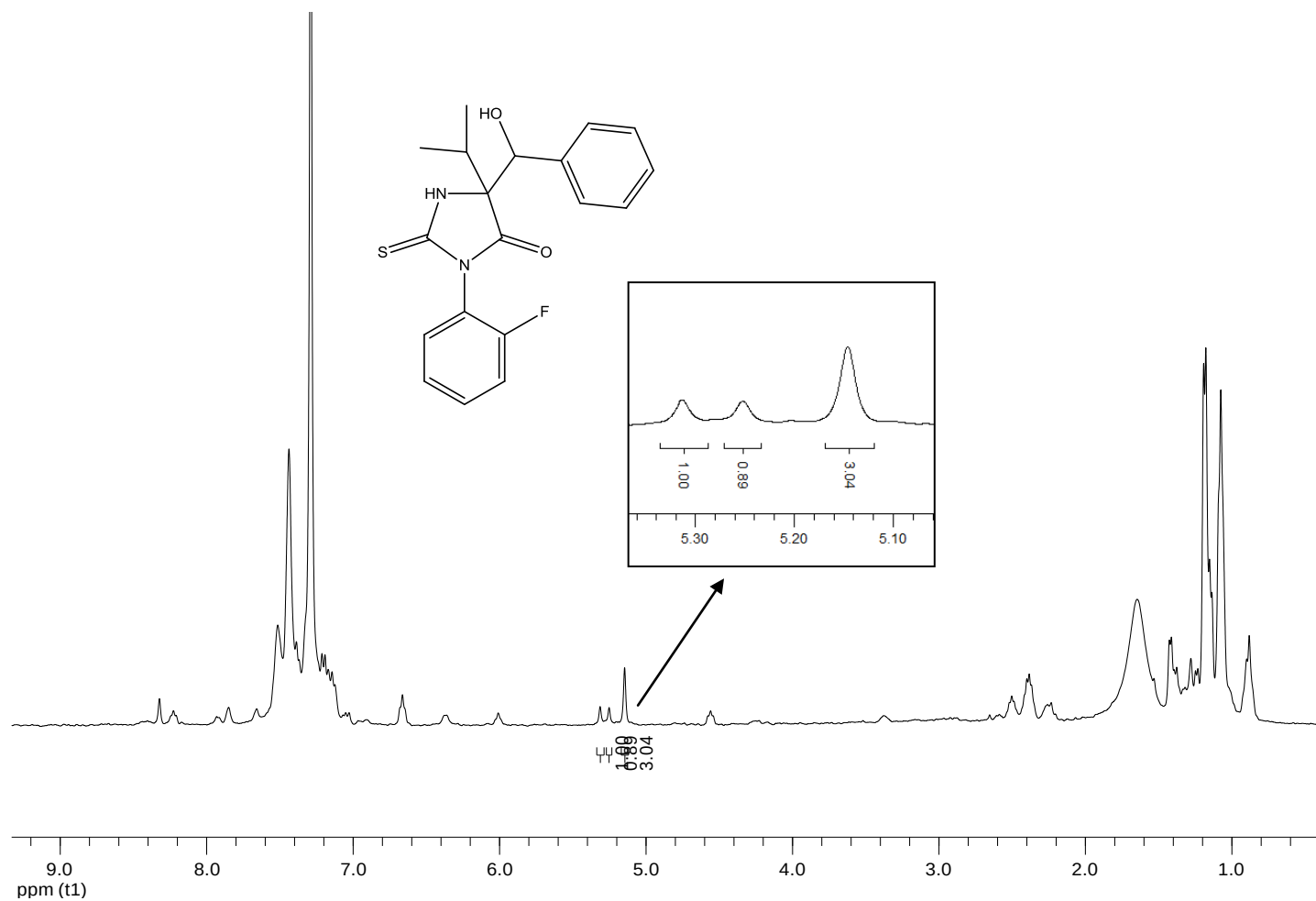


Figure A.51. 400 MHz ^1H NMR of 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-fluorophenyl thiohydantoin (**22**) in CDCl_3 after precipitation from diethyl ether&petroleum ether.

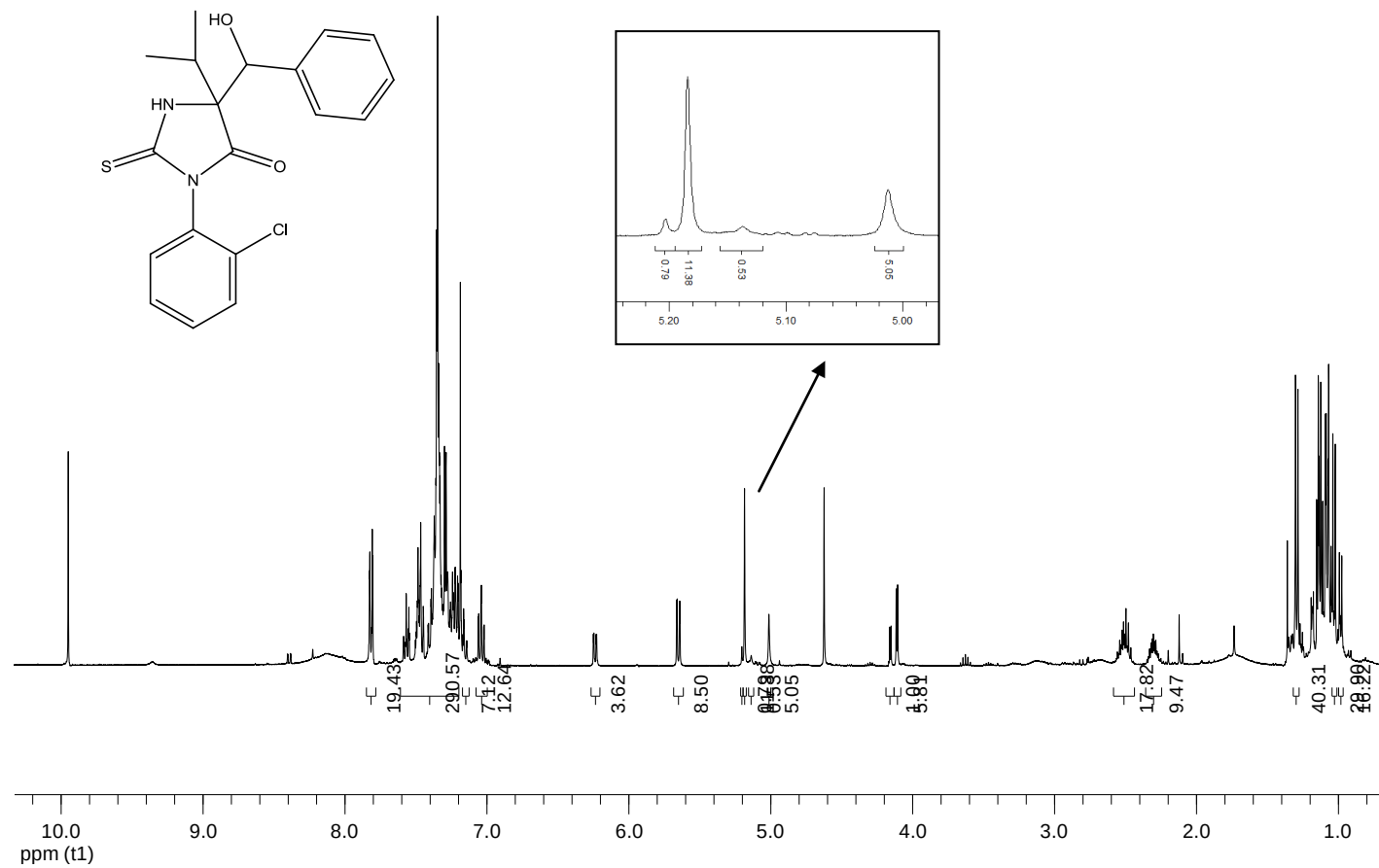


Figure A.52. 400 MHz ¹H NMR of crude 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-o-chlorophenyl thiohydantoin (23) in CDCl₃.

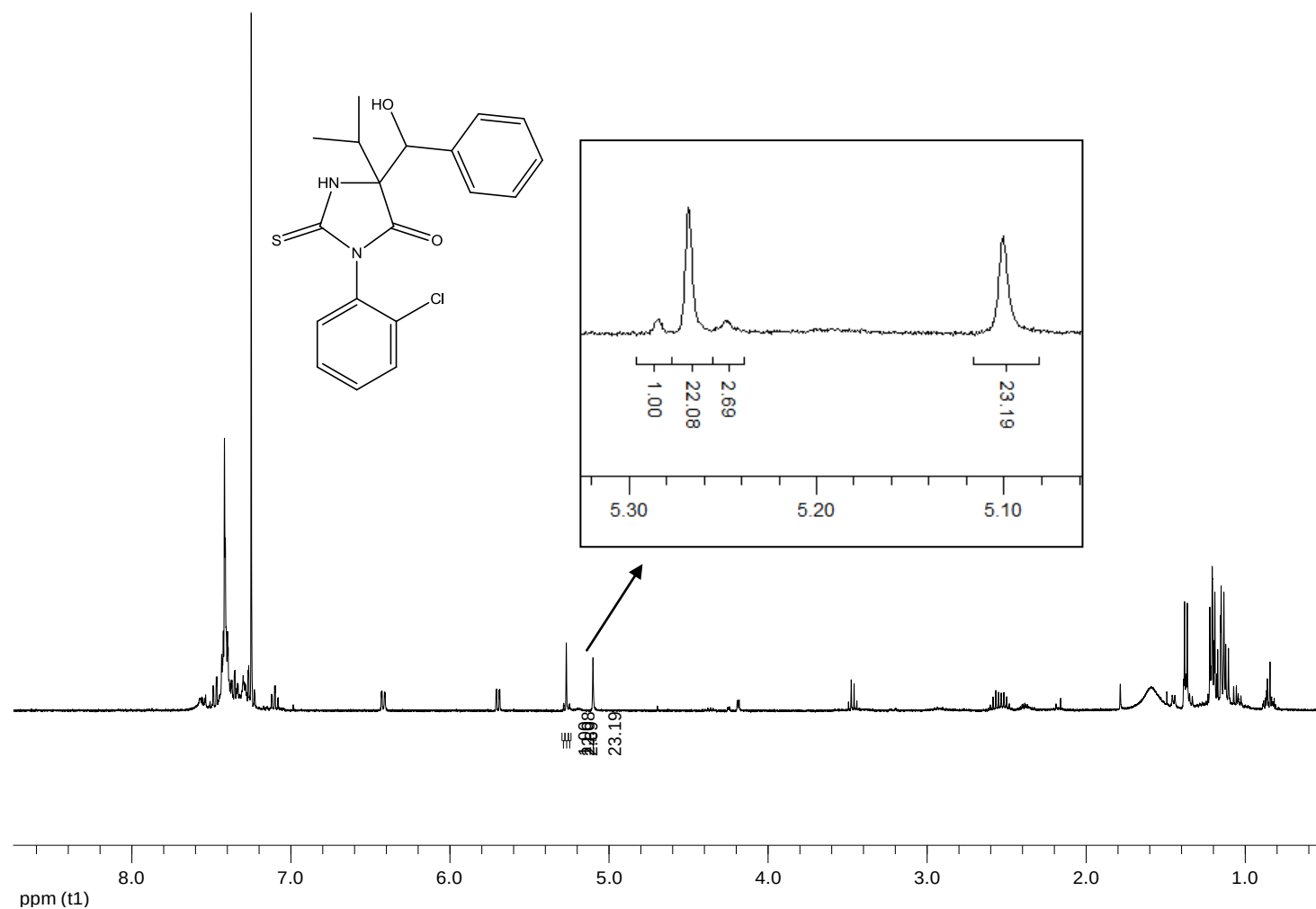


Figure A.53. 400 MHz ¹H NMR of 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-o-chlorophenyl thiohydantoin (**23**) in CDCl₃ after precipitation from diethyl ether&petroleum ether.

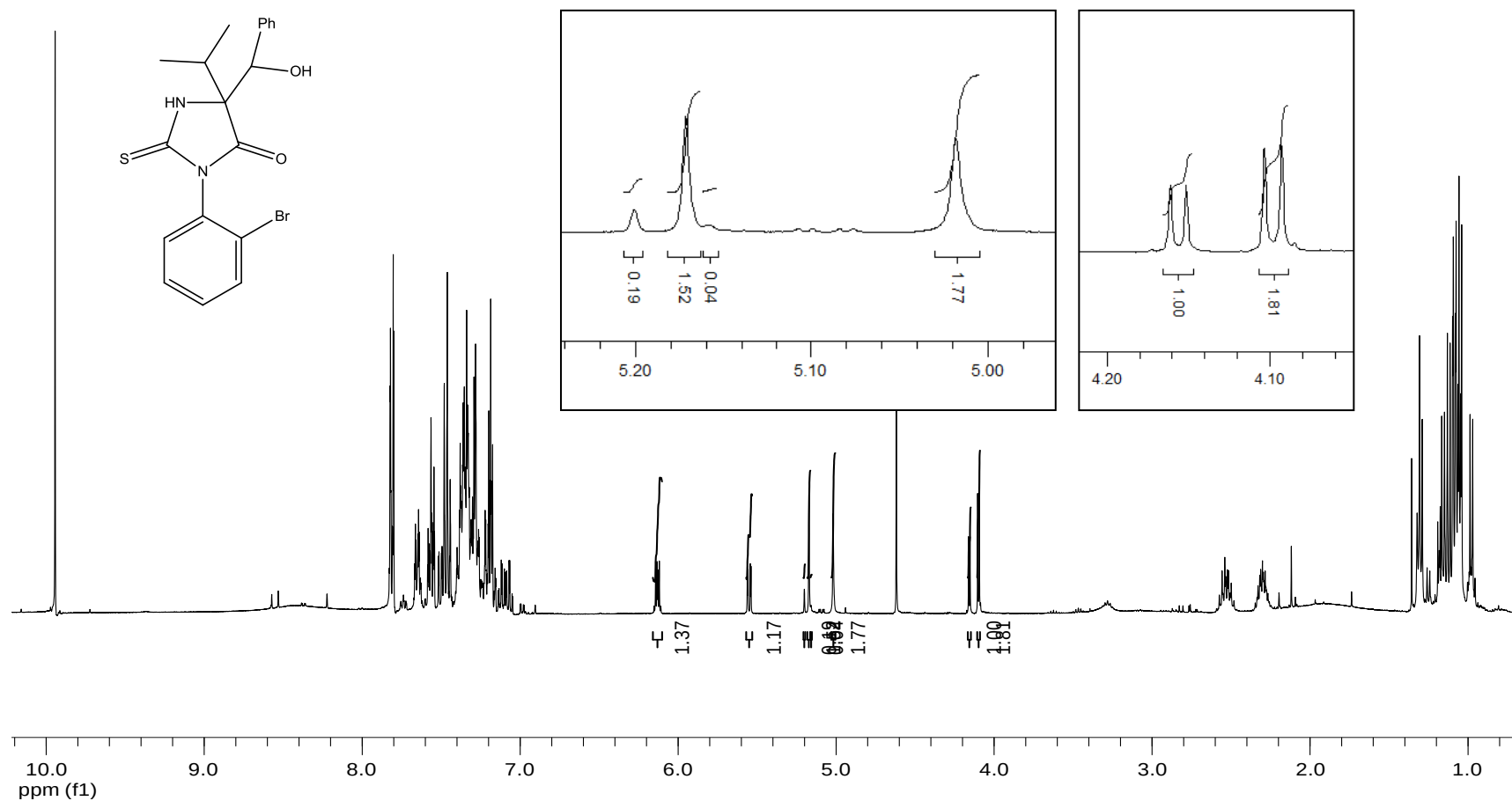


Figure A.54. 400 MHz ¹H NMR of crude 400 MHz ¹H NMR of crude 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-o-bromophenyl thiohydantoin (**24**) in CDCl₃.

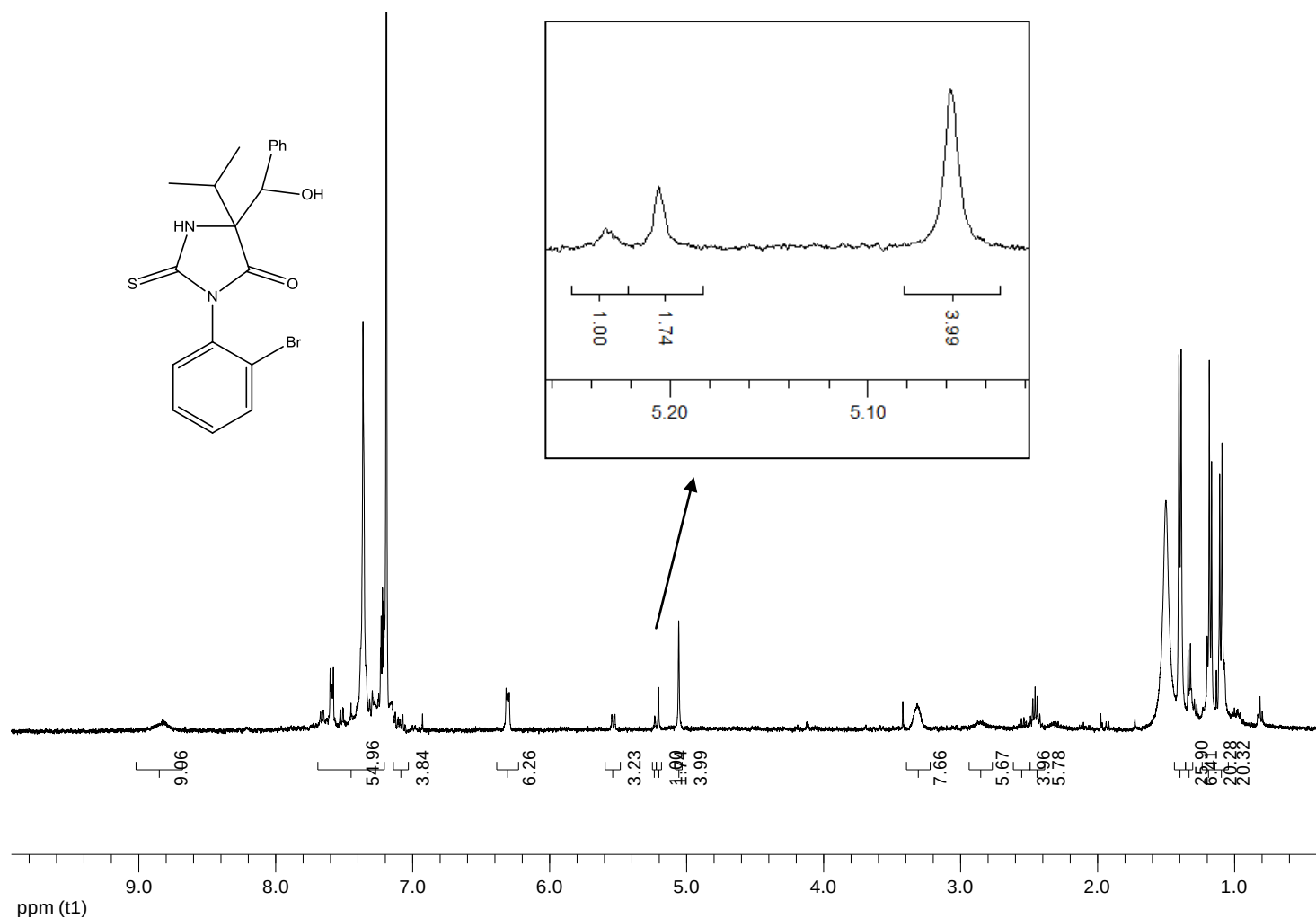


Figure A.55. 400 MHz ¹H NMR of crude 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-bromophenyl thiohydantoin (**24**) in CDCl₃ after purification.

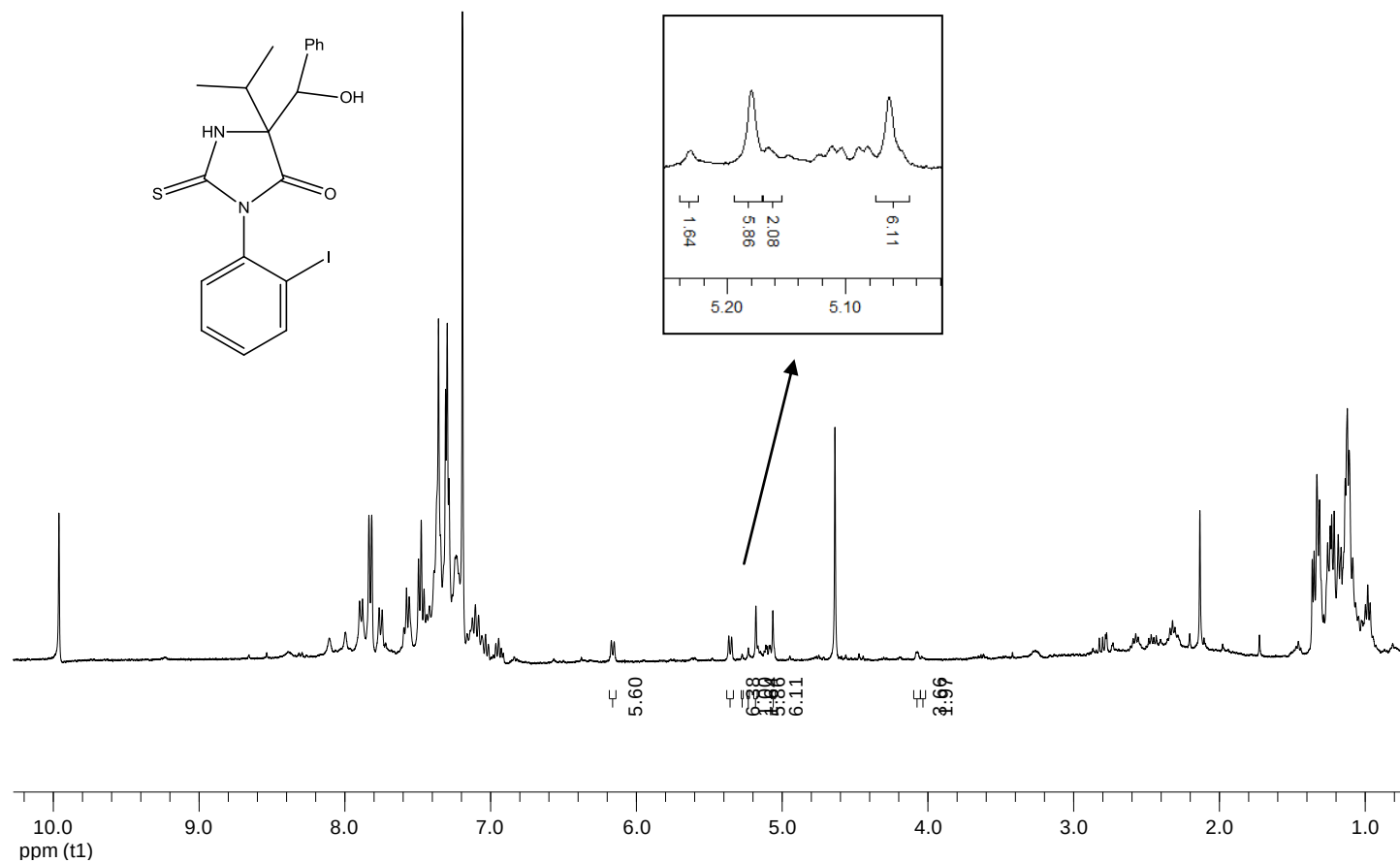
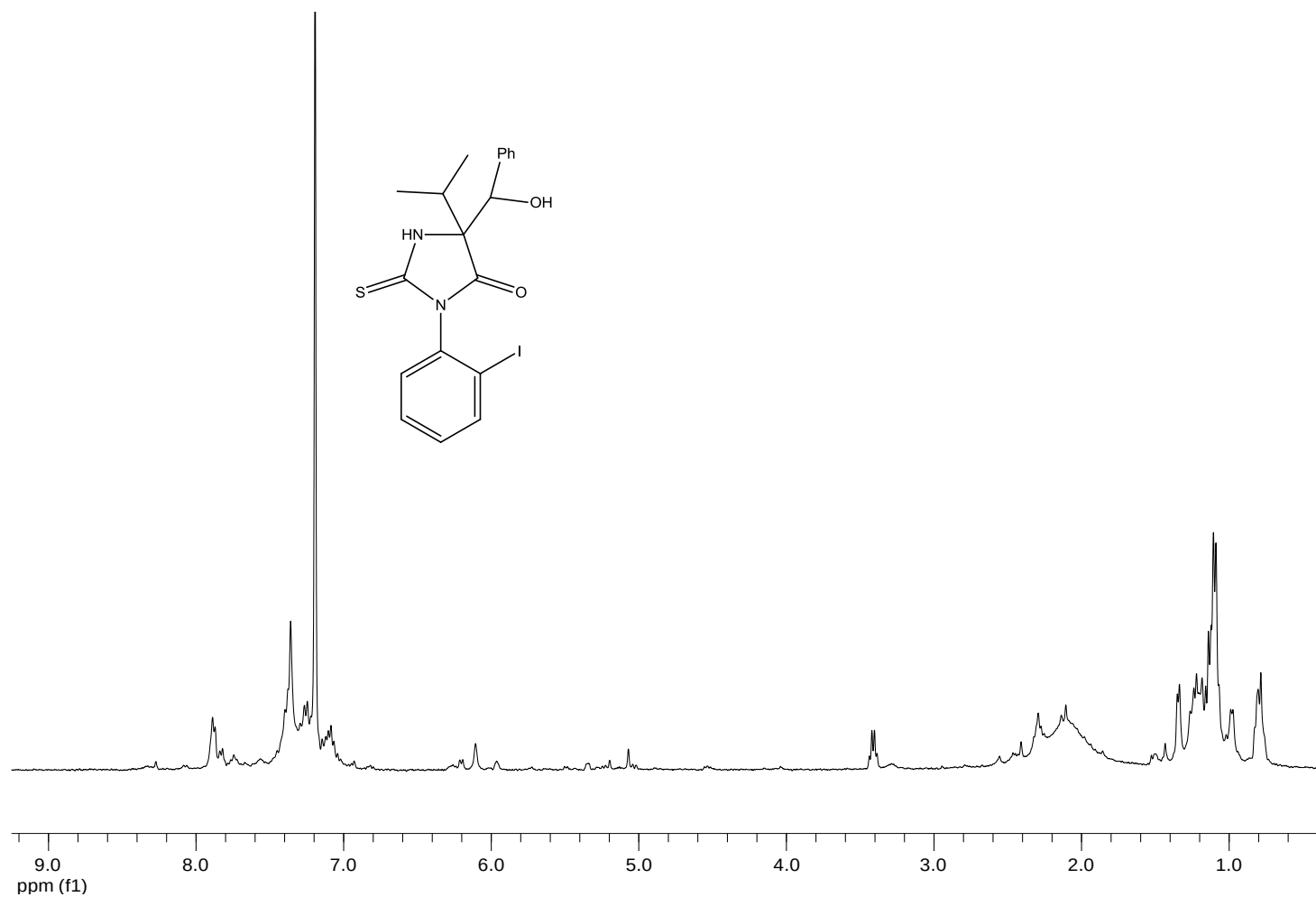


Figure A.56. 400 MHz ^1H NMR of crude 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-*o*-iodophenyl thiohydantoin (**25**) in CDCl_3 .



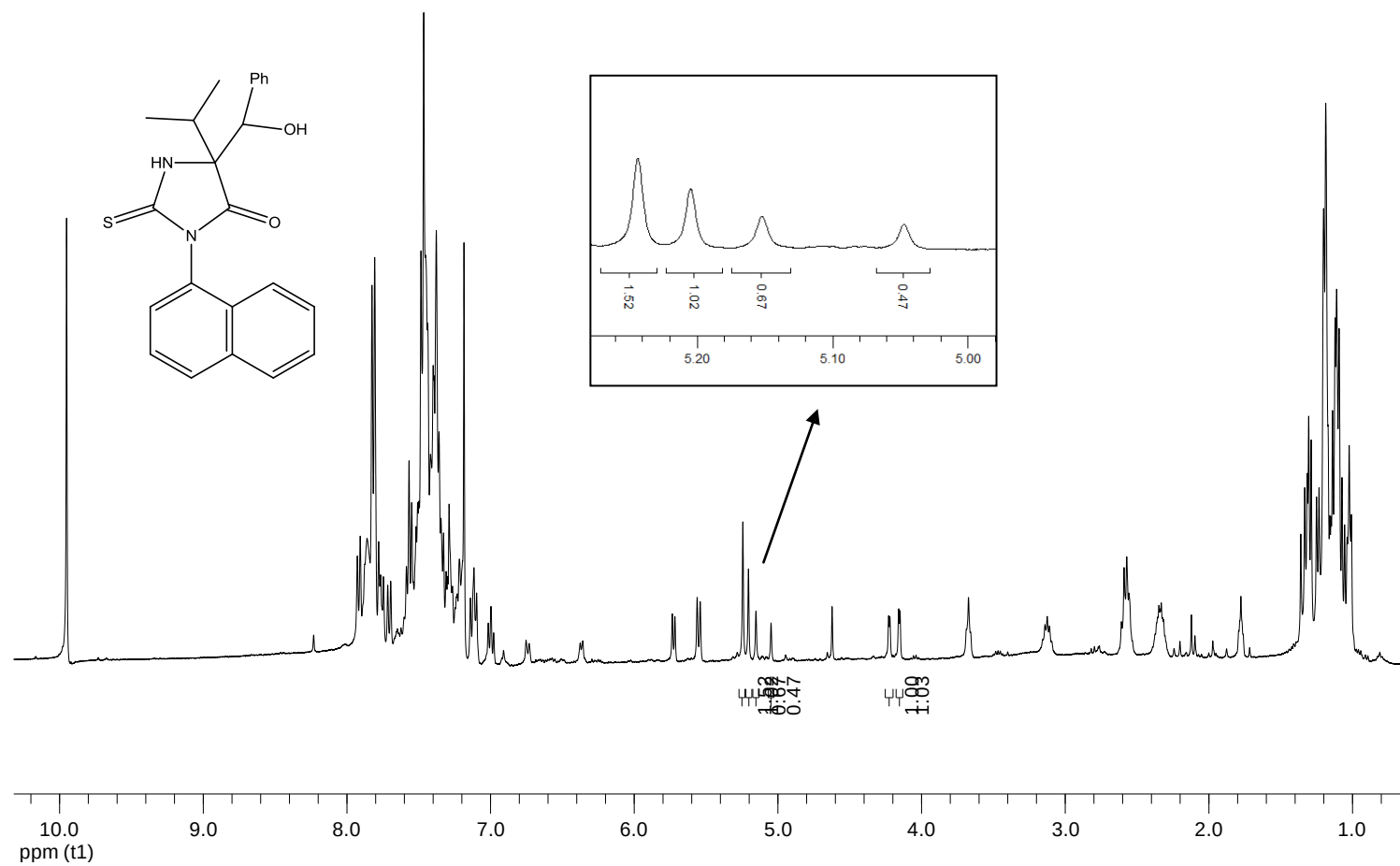
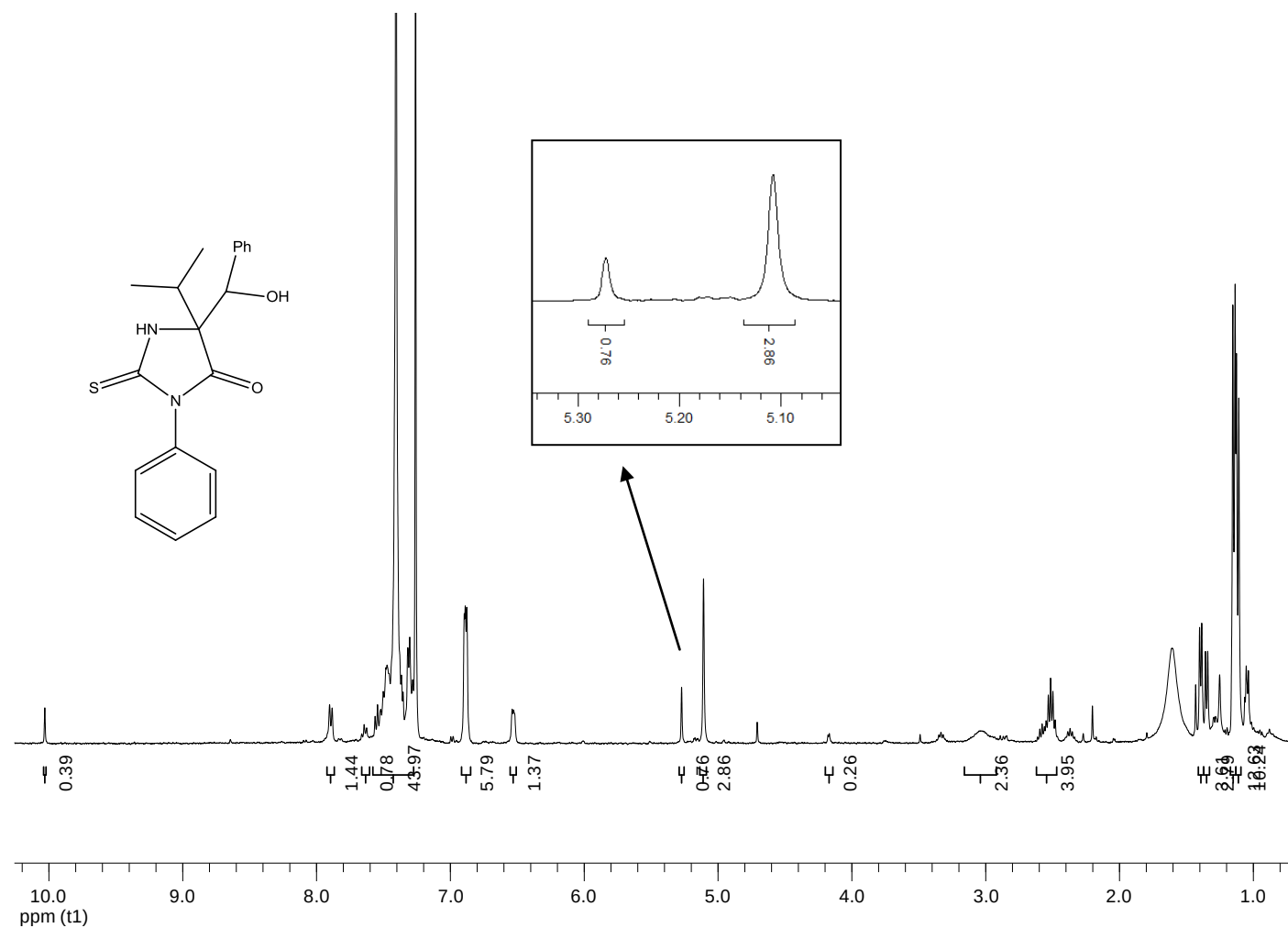


Figure A.58. 400 MHz ^1H NMR of crude 5-(hydroxy(phenyl)methyl)-5-isopropyl-3- α -naphthyl thiohydantoin (**26**) in CDCl_3 .



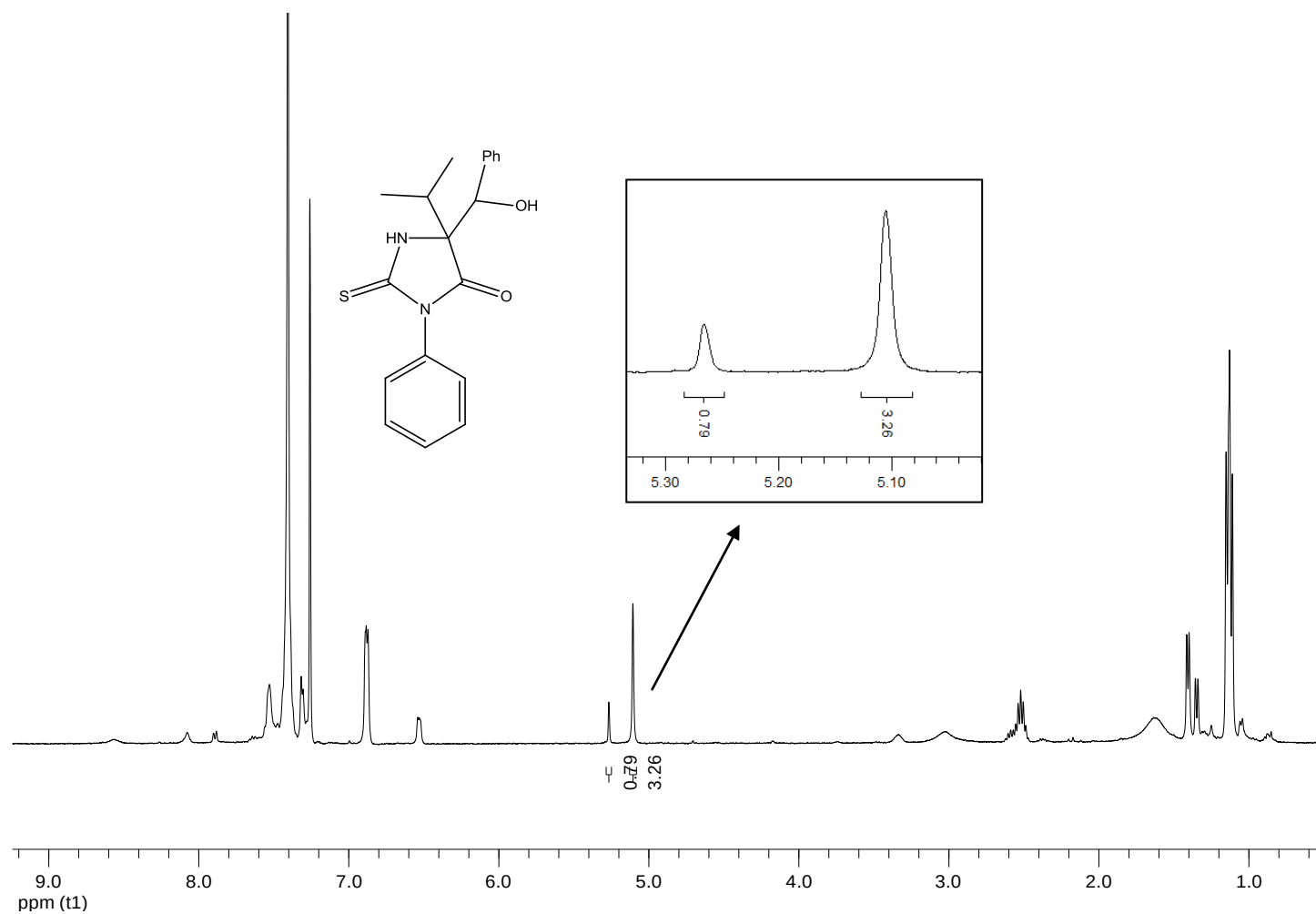


Figure A.60. 400 MHz ^1H NMR of 5-(hydroxy(phenyl)methyl)-5-isopropyl-3-phenyl thiohydantoin (27) in CDCl_3 after precipitation from diethyl ether.

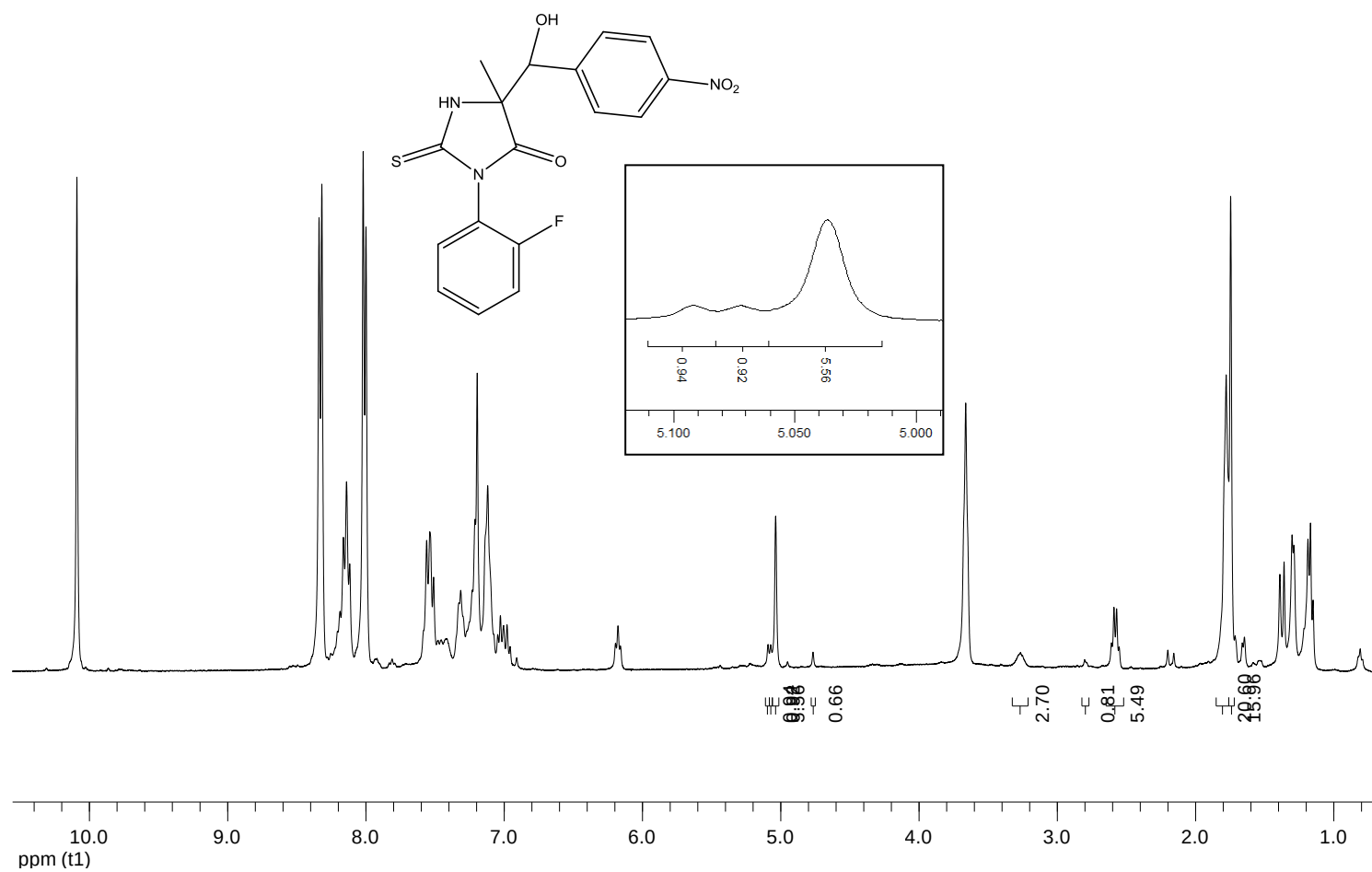


Figure A.61. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-o-florophenyl thiohydantoin (**28**) in CDCl₃.

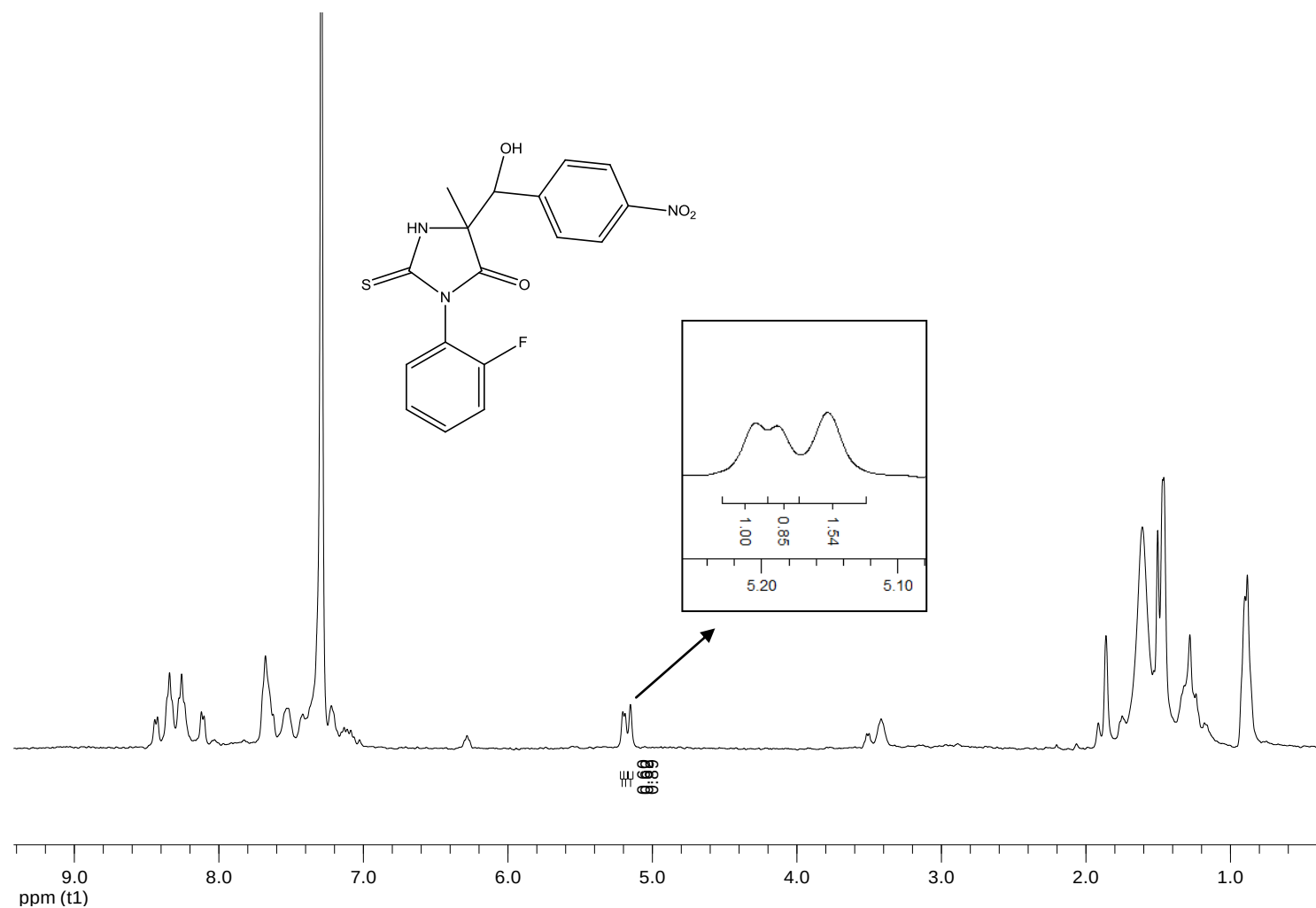


Figure A.62. 400 MHz ^1H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-o-florophenyl thiohydantoin (**28**) in CDCl_3 after precipitation from diethyl ether.

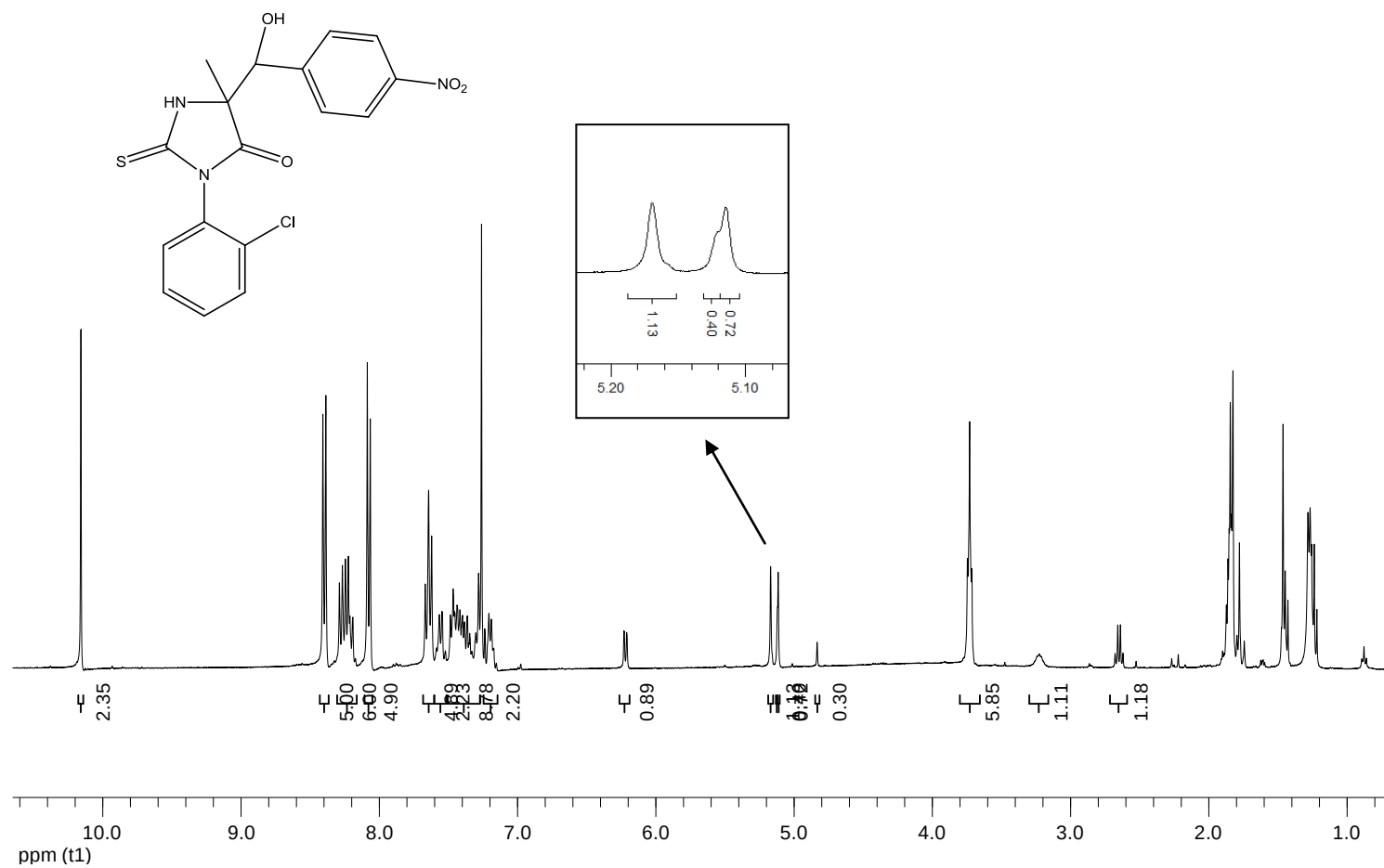


Figure A.63. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-o-chlorophenyl thiohydantoin (**29**) in CDCl₃.

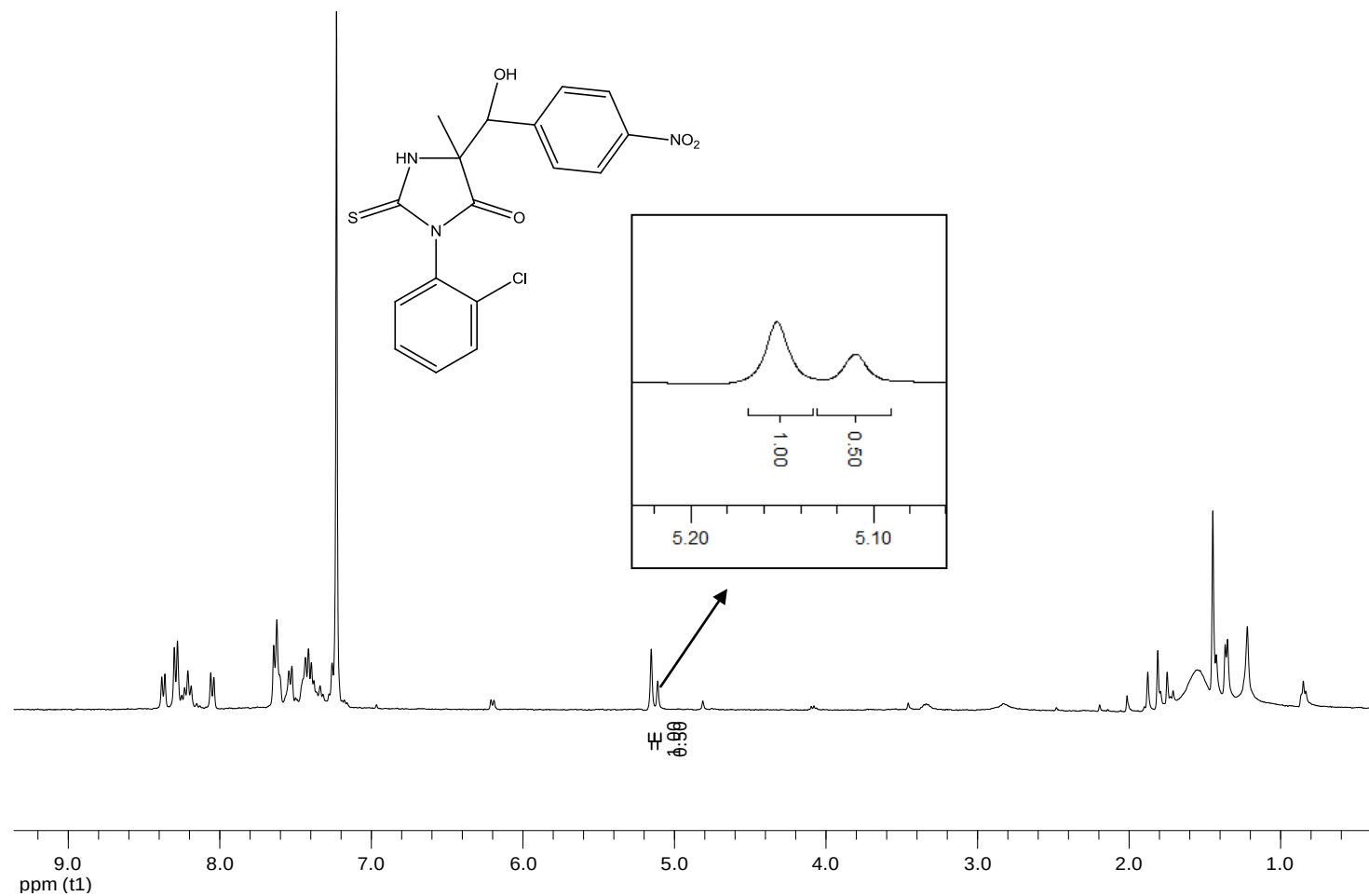


Figure A.64. 400 MHz ^1H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-o-chlorophenyl thiohydantoin (**29**) in CDCl_3 after purification.

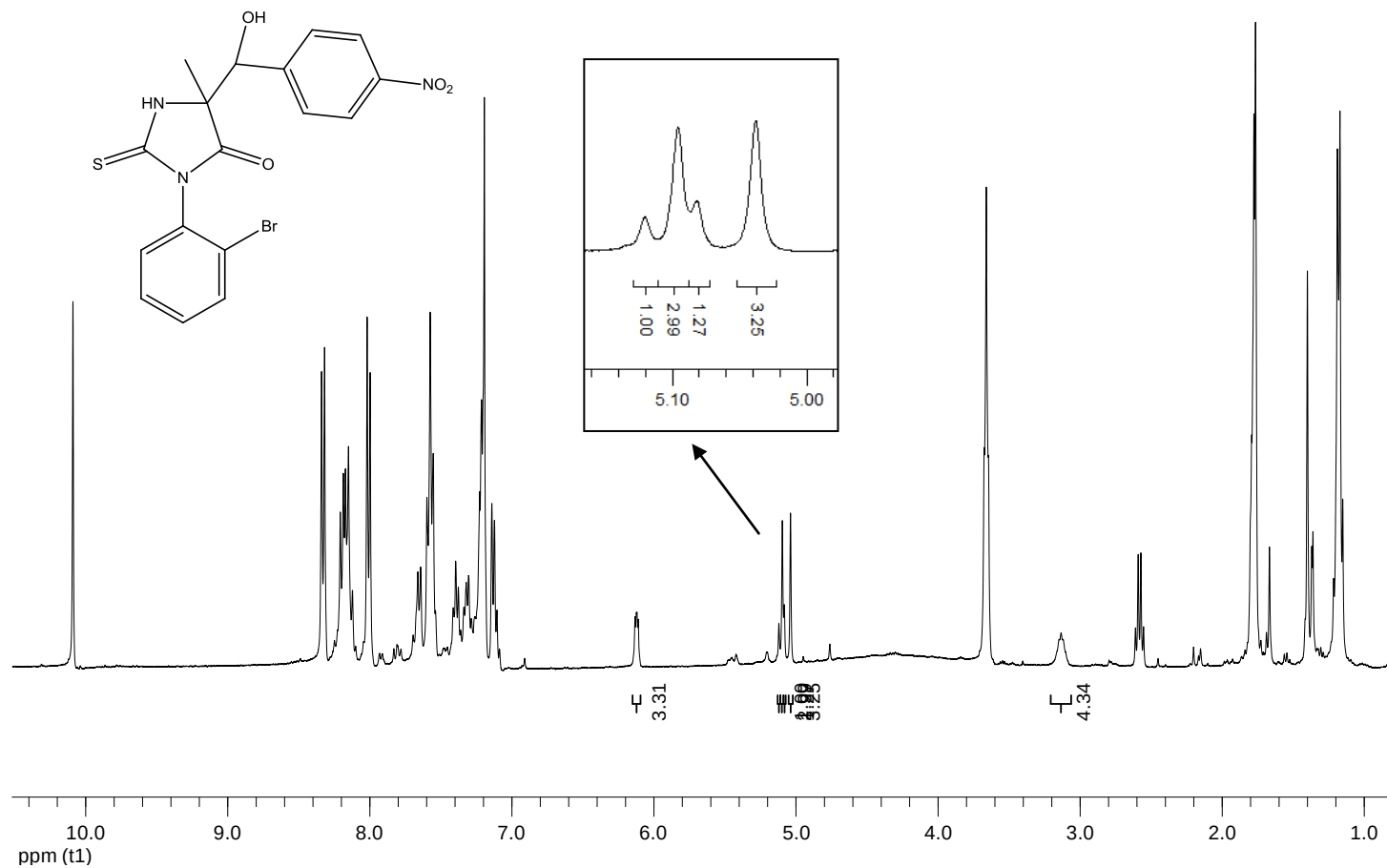


Figure A.65. 400 MHz ^1H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-*o*-bromophenyl thiohydantoin (**30**) in CDCl_3 .

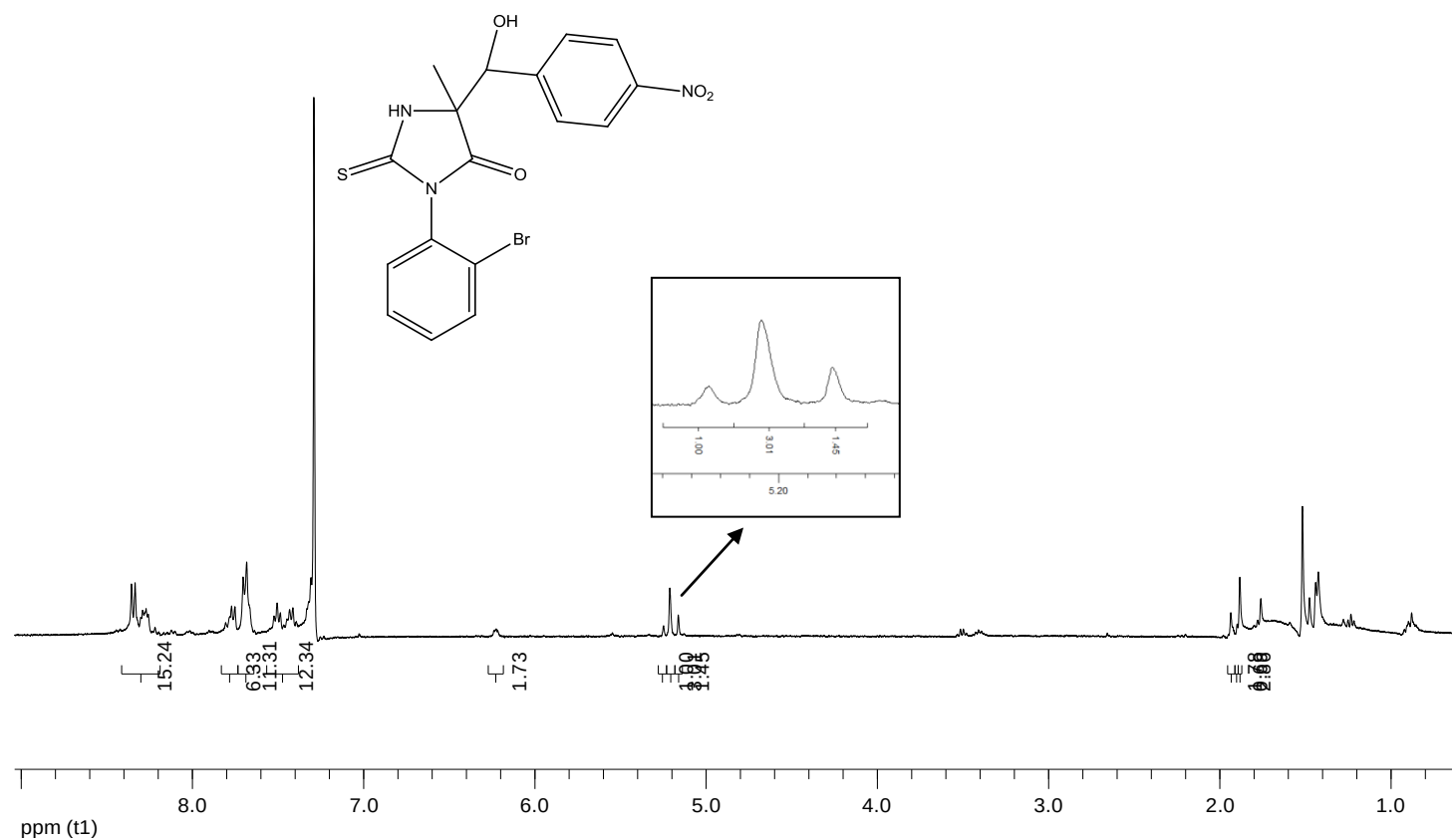


Figure A.66. 400 MHz ^1H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-o-bromophenyl thiohydantoin (**30**) in CDCl_3 after precipitation from diethyl ether&petroleum ether.

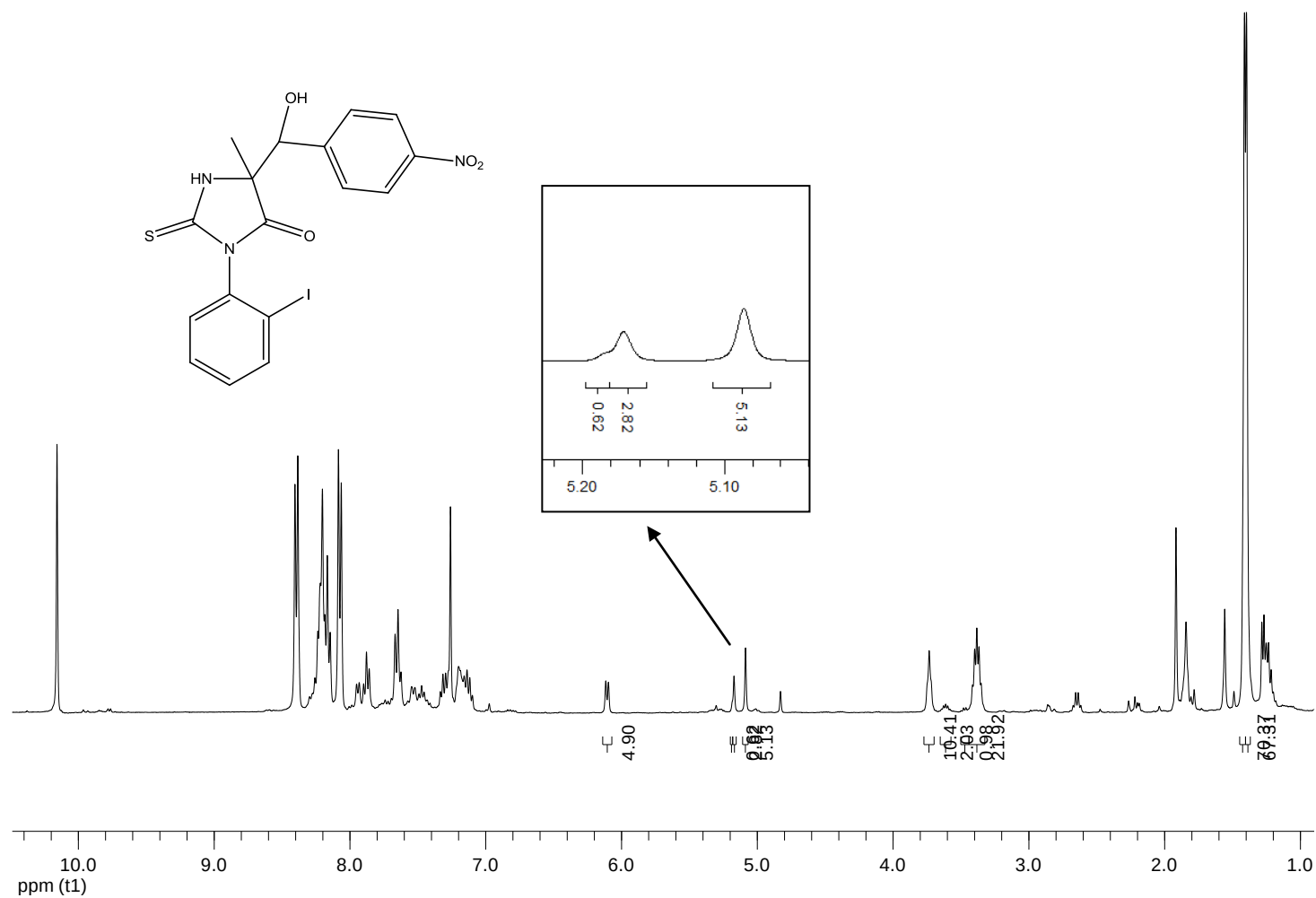


Figure A.67. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-*o*-iodophenyl thiohydantoin (**31**) in CDCl₃.

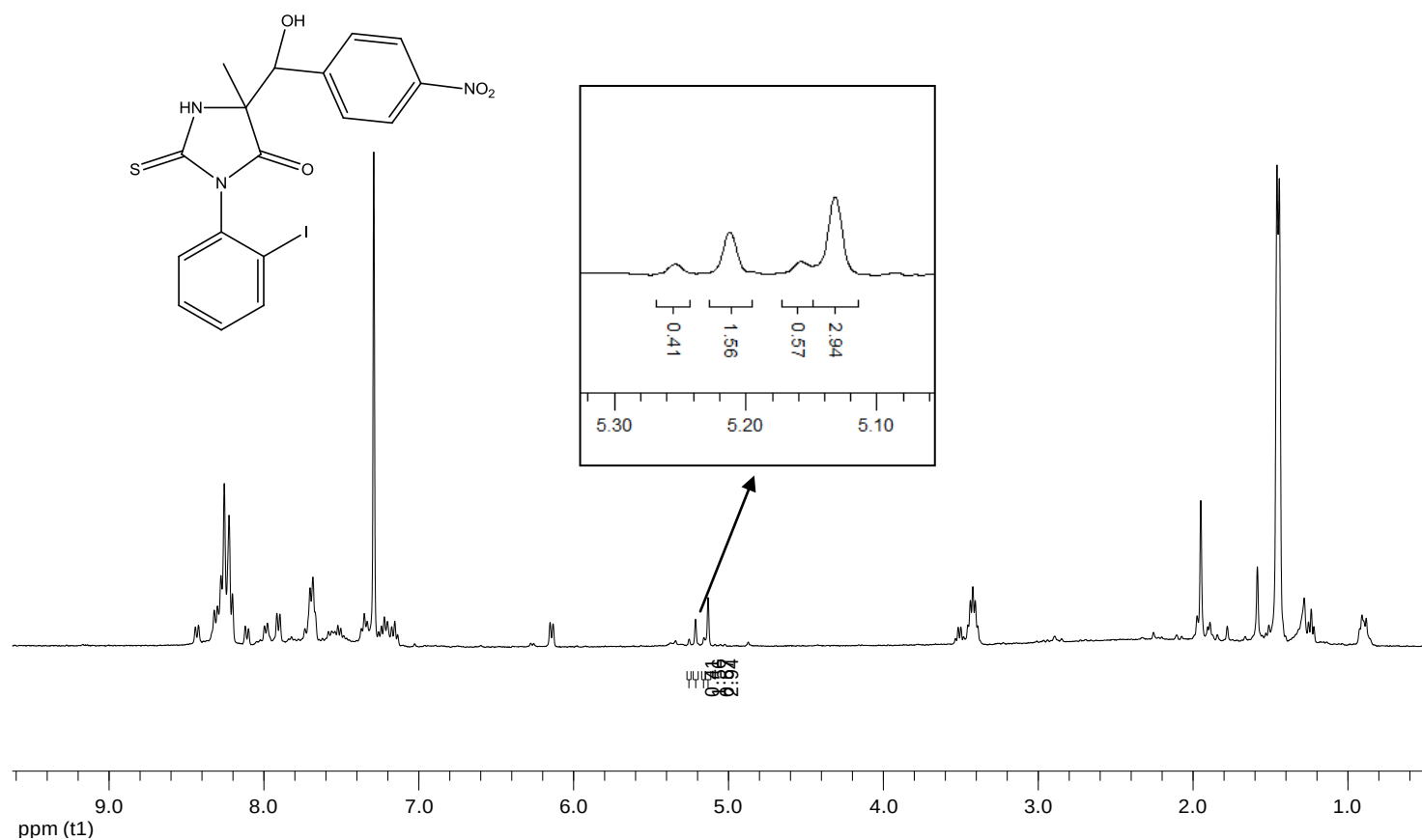


Figure A.68. 400 MHz ¹H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-o-iodophenyl thiohydantoin (**31**) in CDCl₃ after precipitation from diethyl ether&petroleum ether.

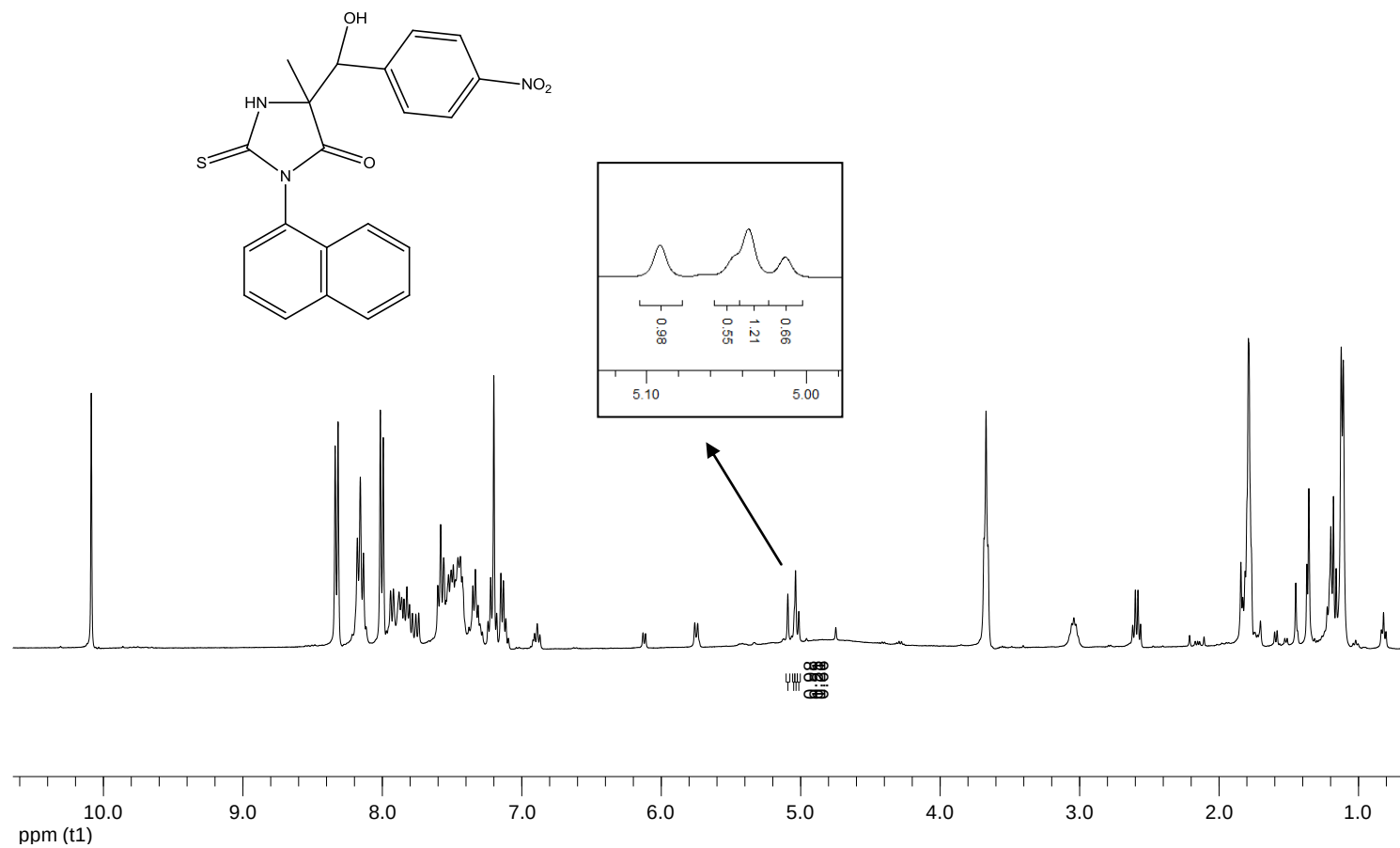


Figure A.69. 400 MHz ^1H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3- α -naphthyl thiohydantoin (**32**) in CDCl_3 .

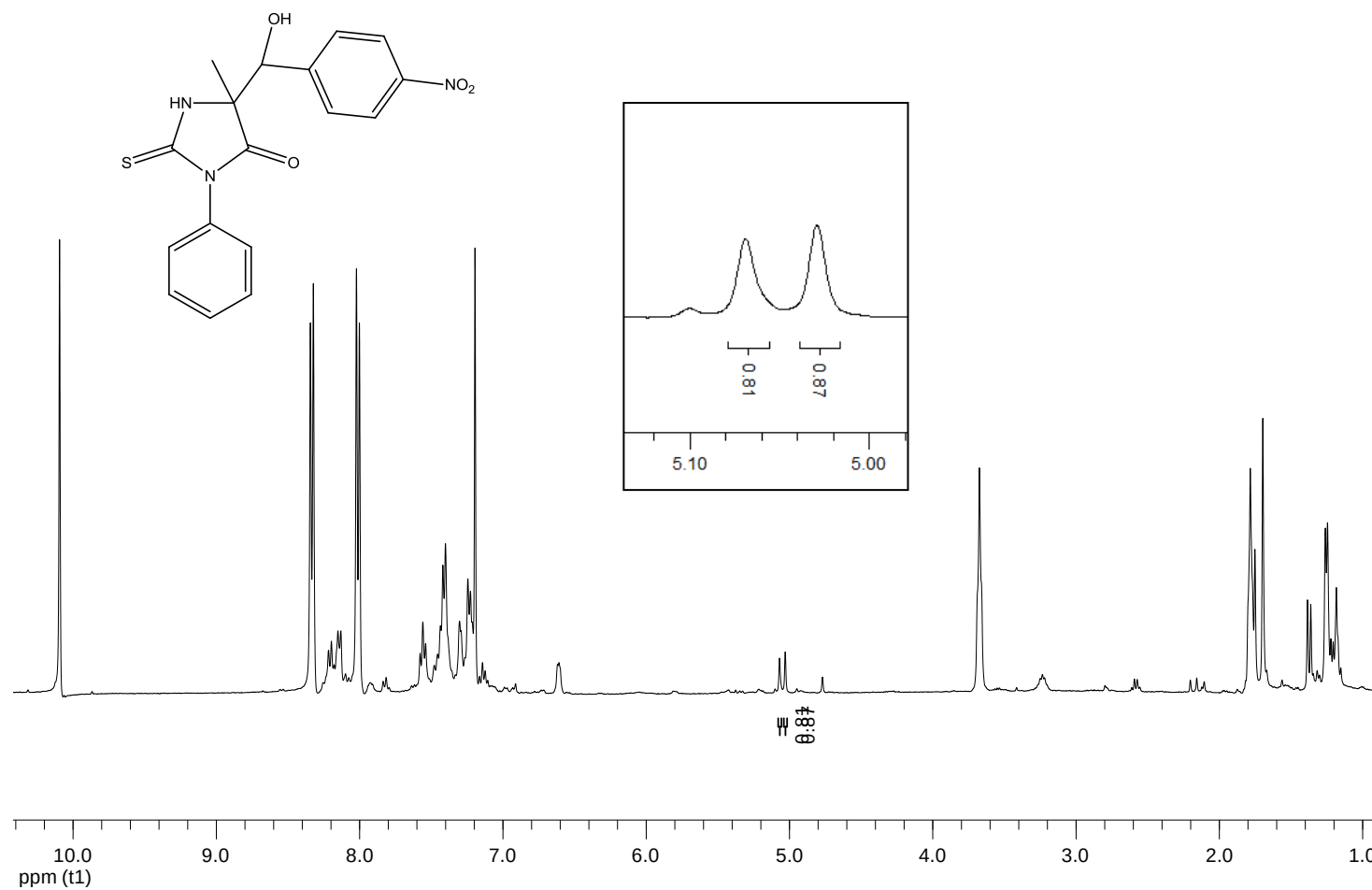


Figure A.70. 400 MHz ^1H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-phenyl thiohydantoin (**33**) in CDCl_3 .

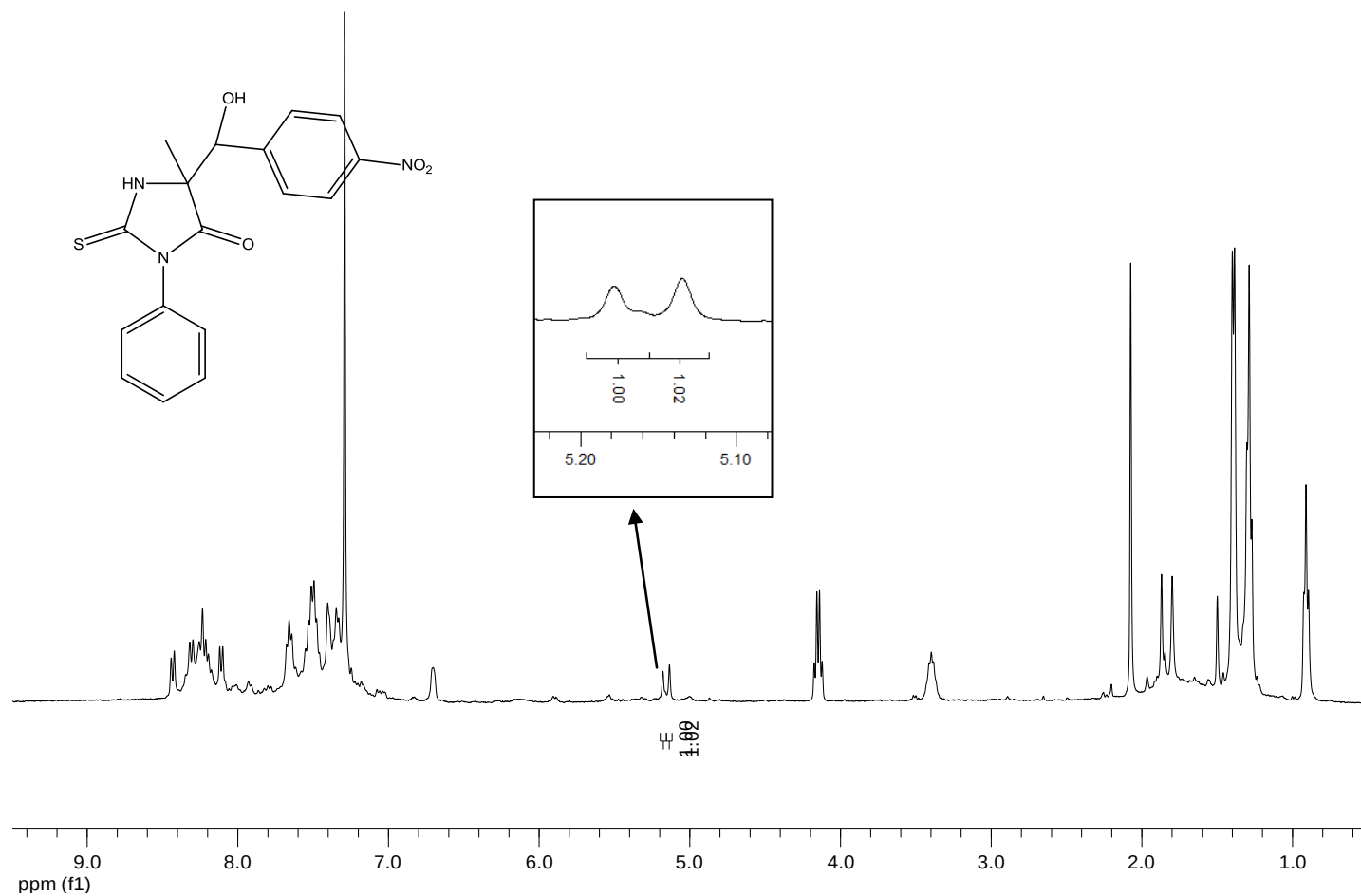


Figure A.71. 400 MHz ^1H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-methyl-3-phenyl thiohydantoin (**33**) in CDCl_3 after precipitation from ethyl acetate&hexane.

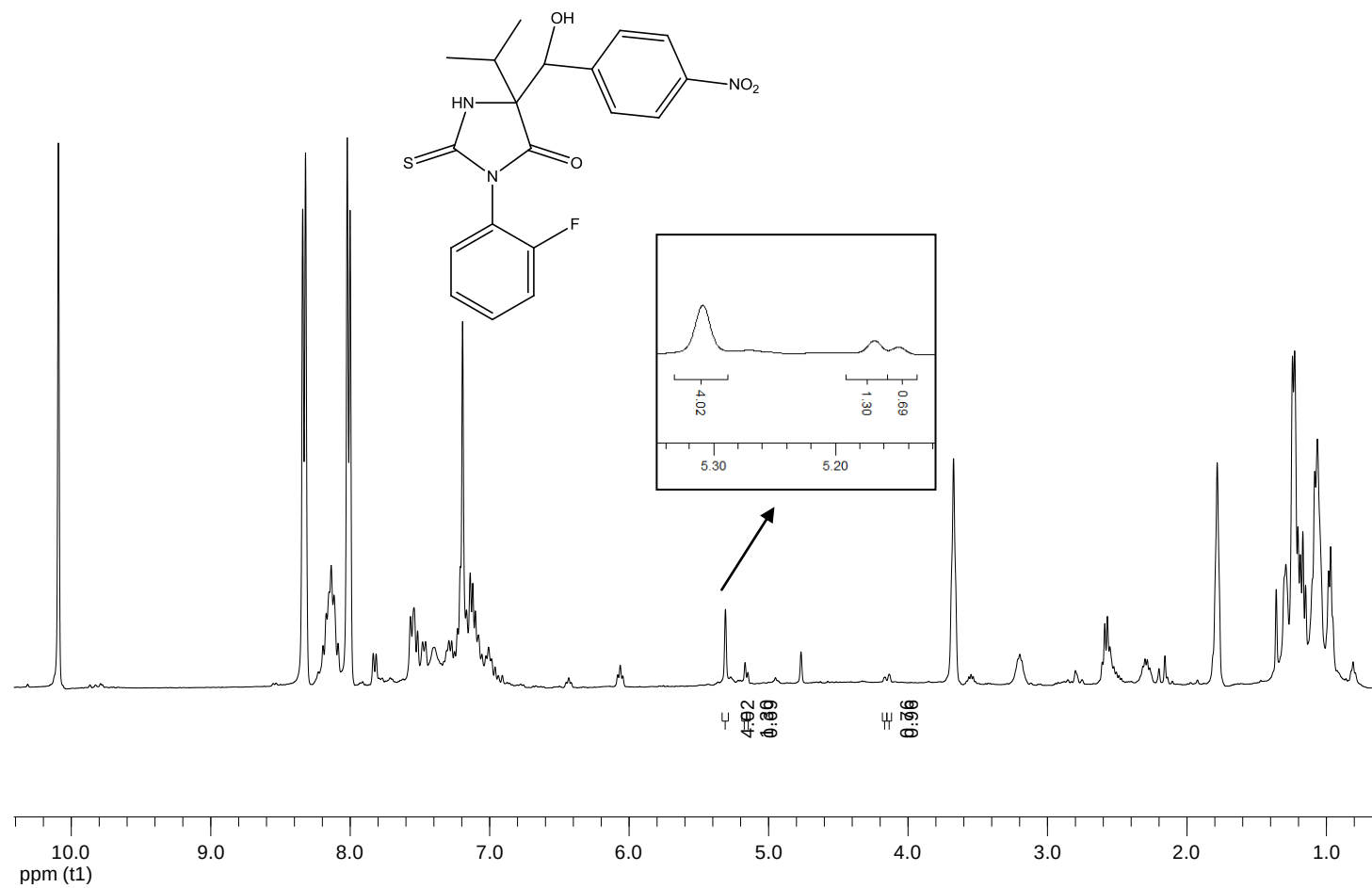


Figure A.72. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-o-florophenyl thiohydantoin (**34**) in CDCl₃.

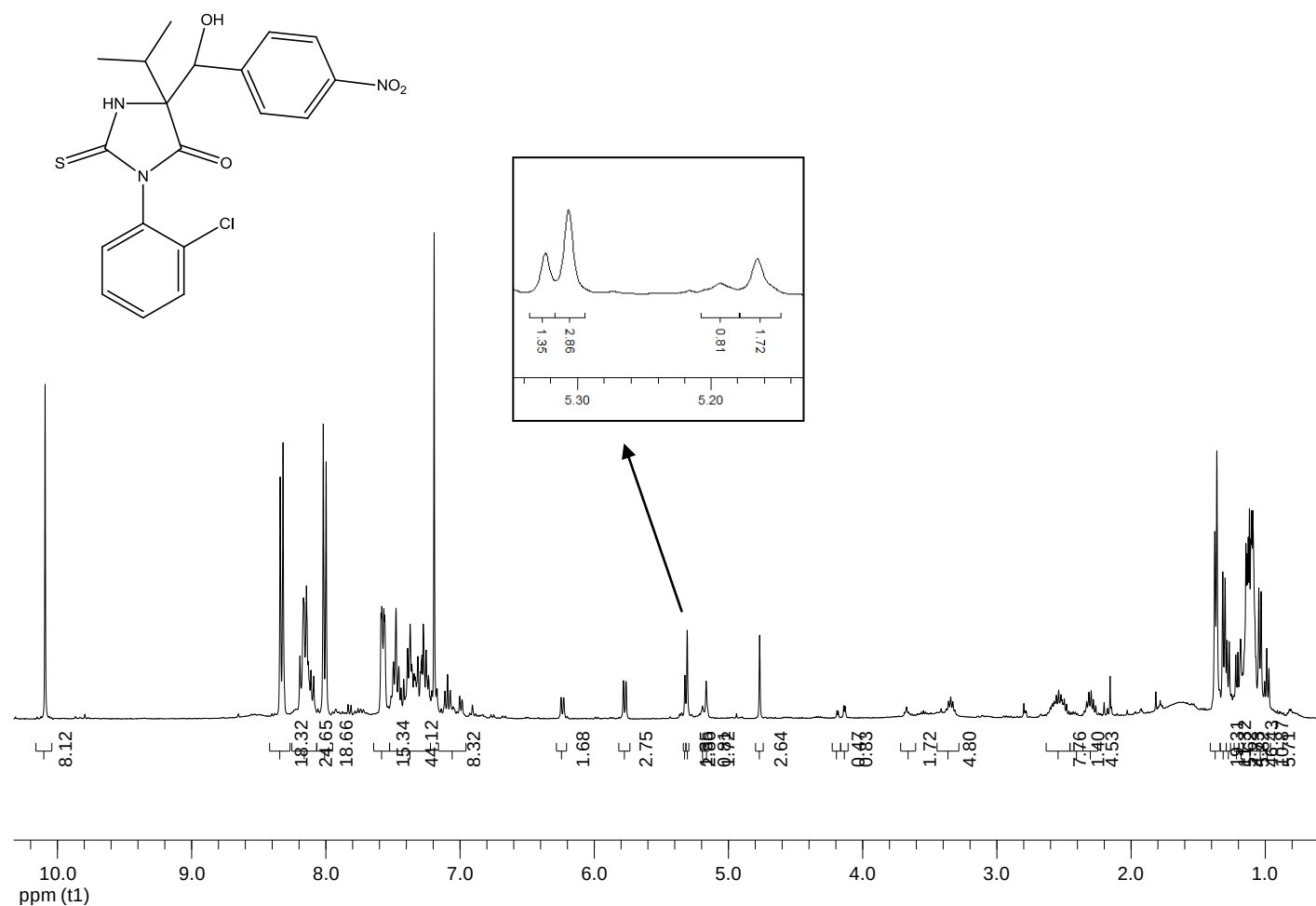


Figure A.73. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-*o*-chlorophenyl thiohydantoin (35) in CDCl₃.

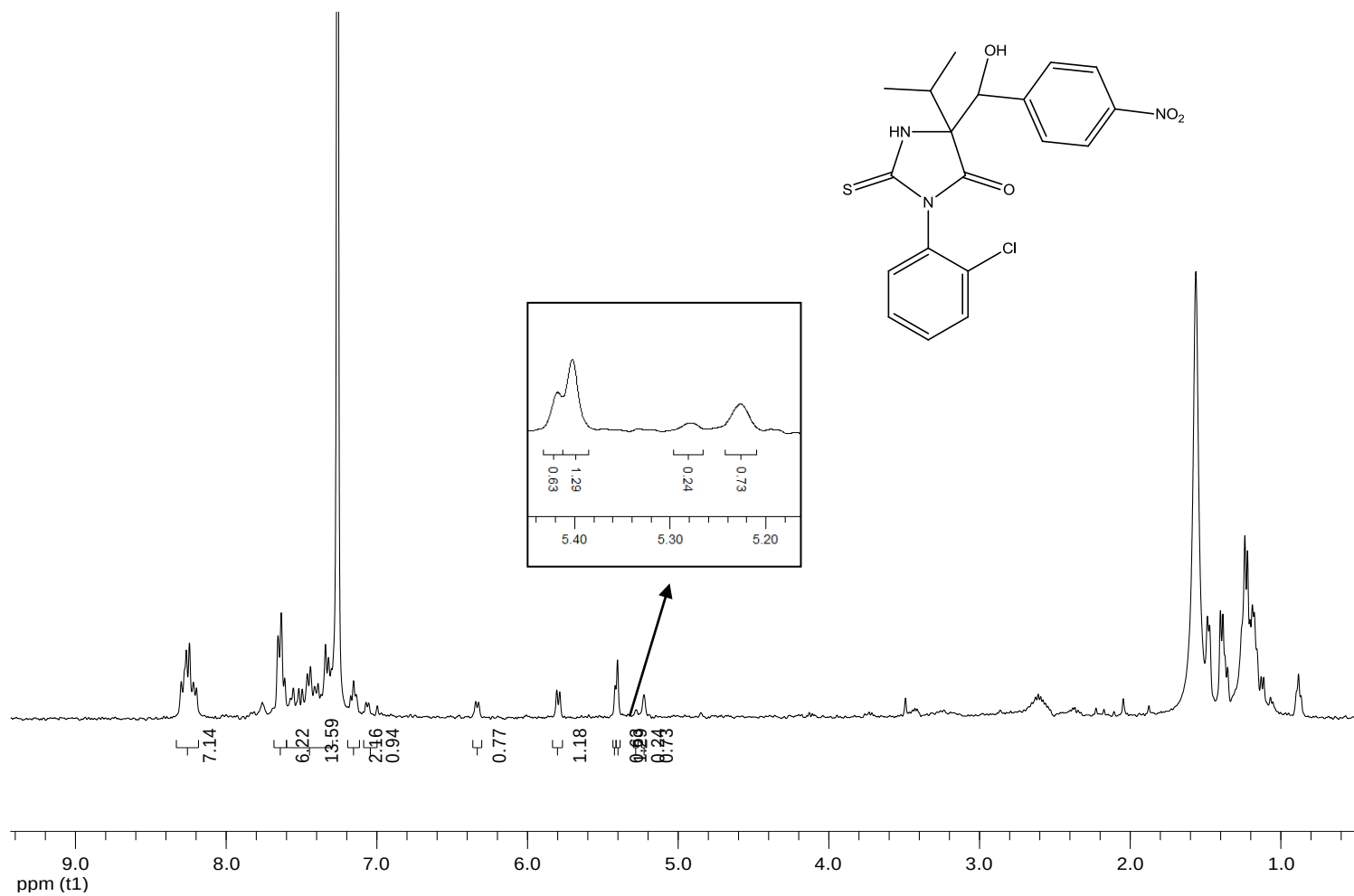


Figure A.74. 400 MHz ¹H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-o-chlorophenyl thiohydantoin (**35**) in CDCl₃ after purification.

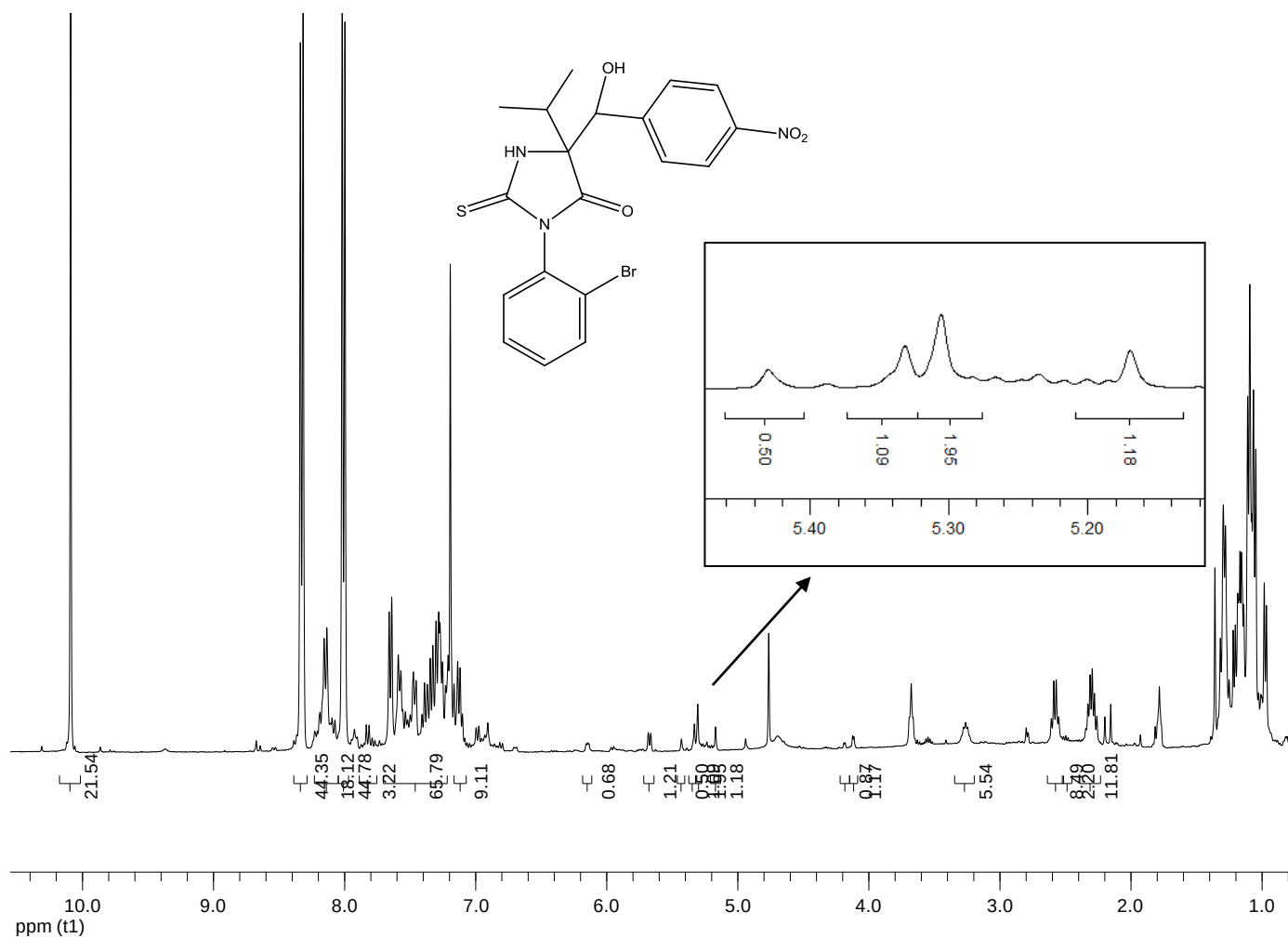


Figure A.75. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-*o*-bromophenyl thiohydantoin (**36**) in CDCl₃.

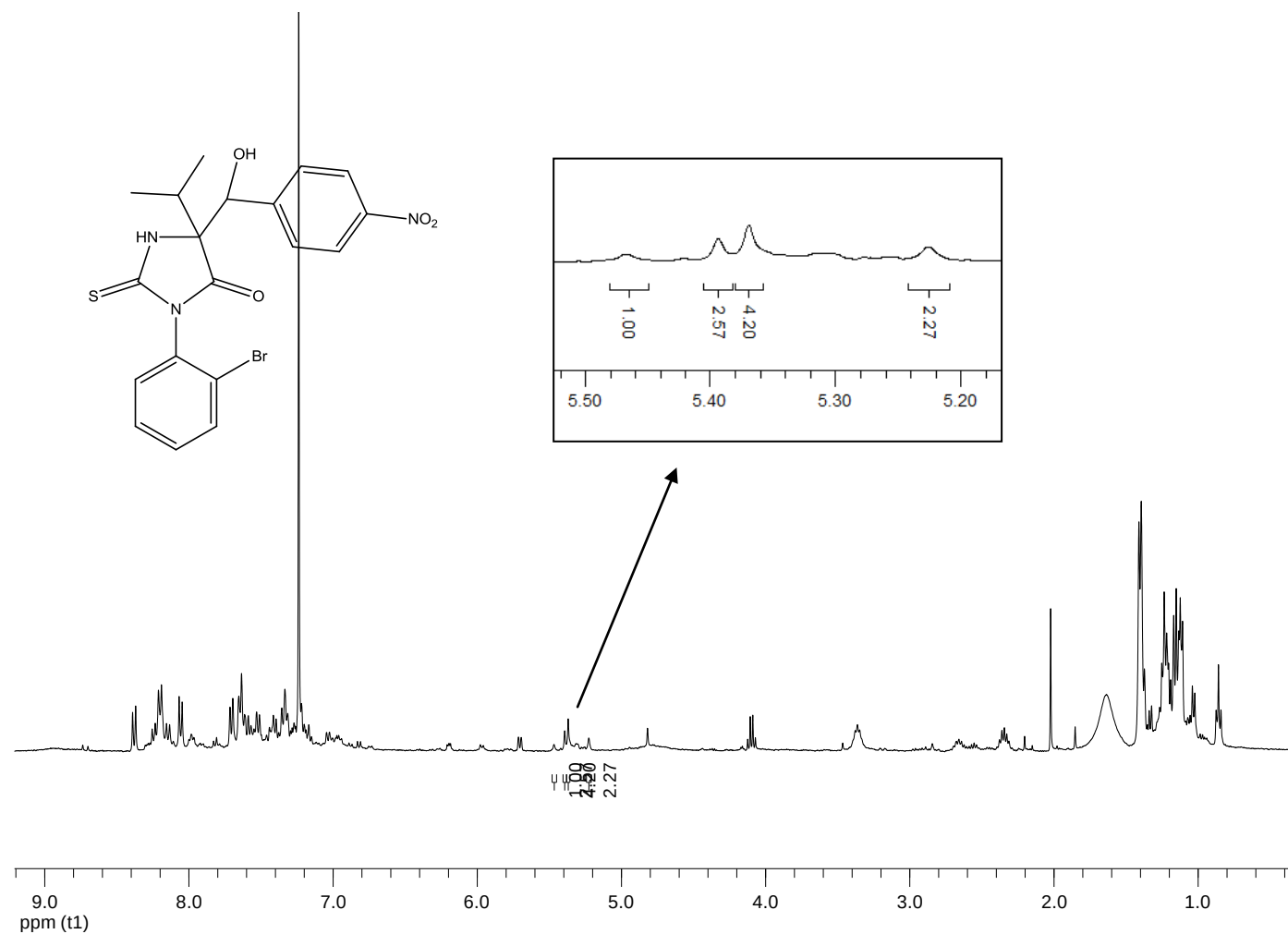


Figure A.76. 400 MHz ¹H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-o-bromophenyl thiohydantoin (**36**) in CDCl₃ after purification.

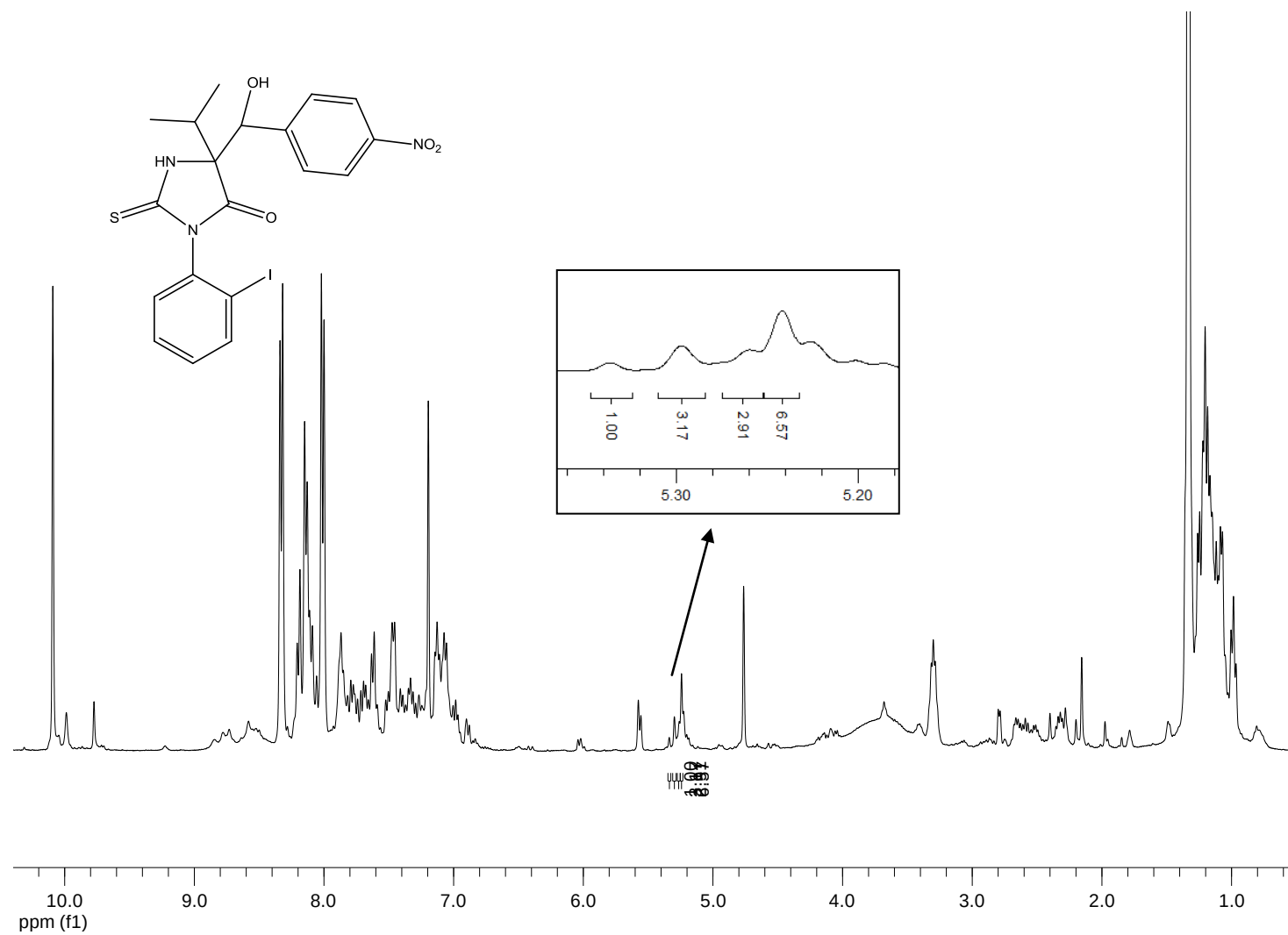


Figure A.77. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-*o*-iodophenyl thiohydantoin (**37**) in CDCl₃.

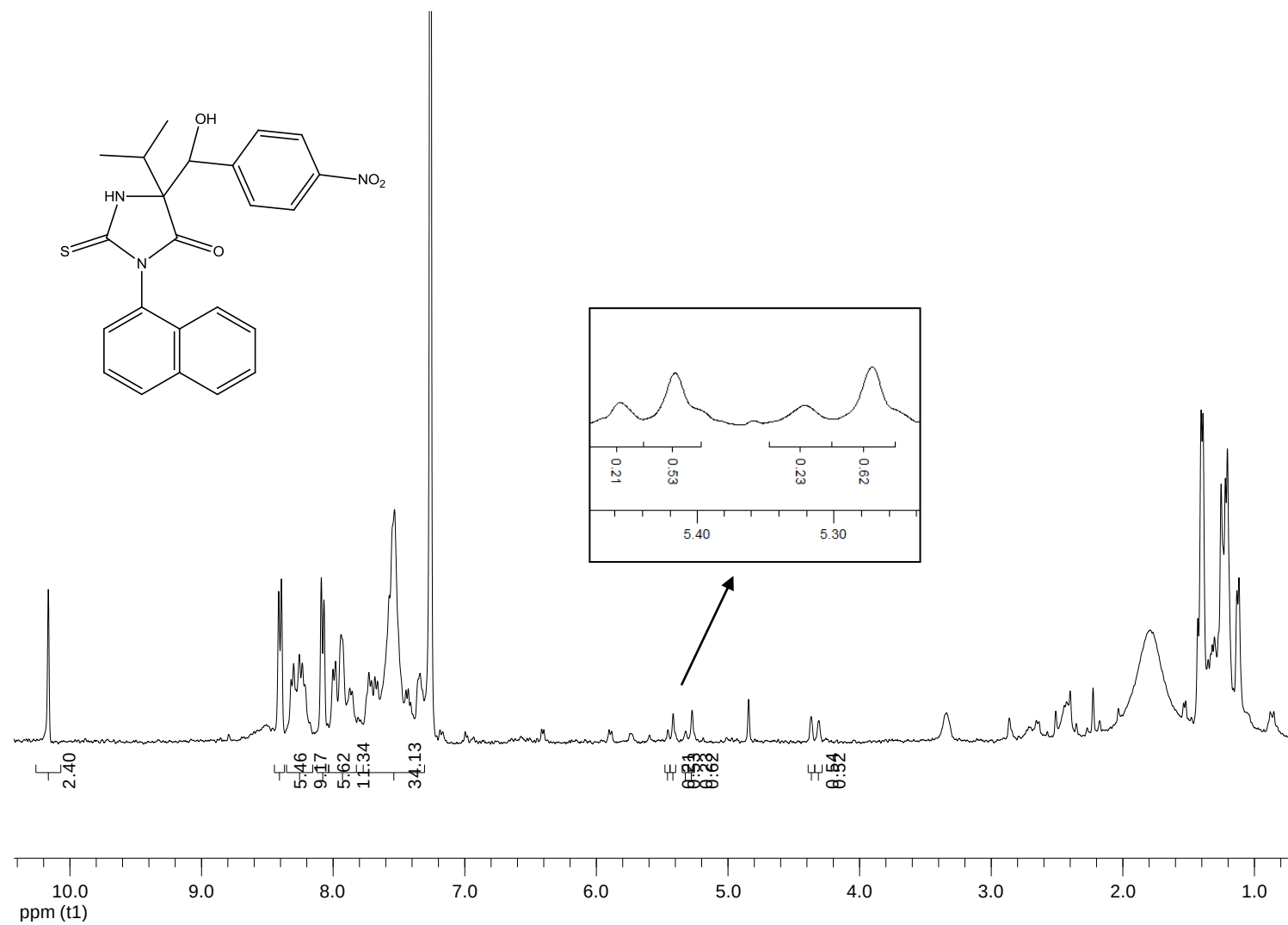


Figure A.78. 400 MHz ¹H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3- α -naphthylthiohydantoin (**38**) in CDCl₃.

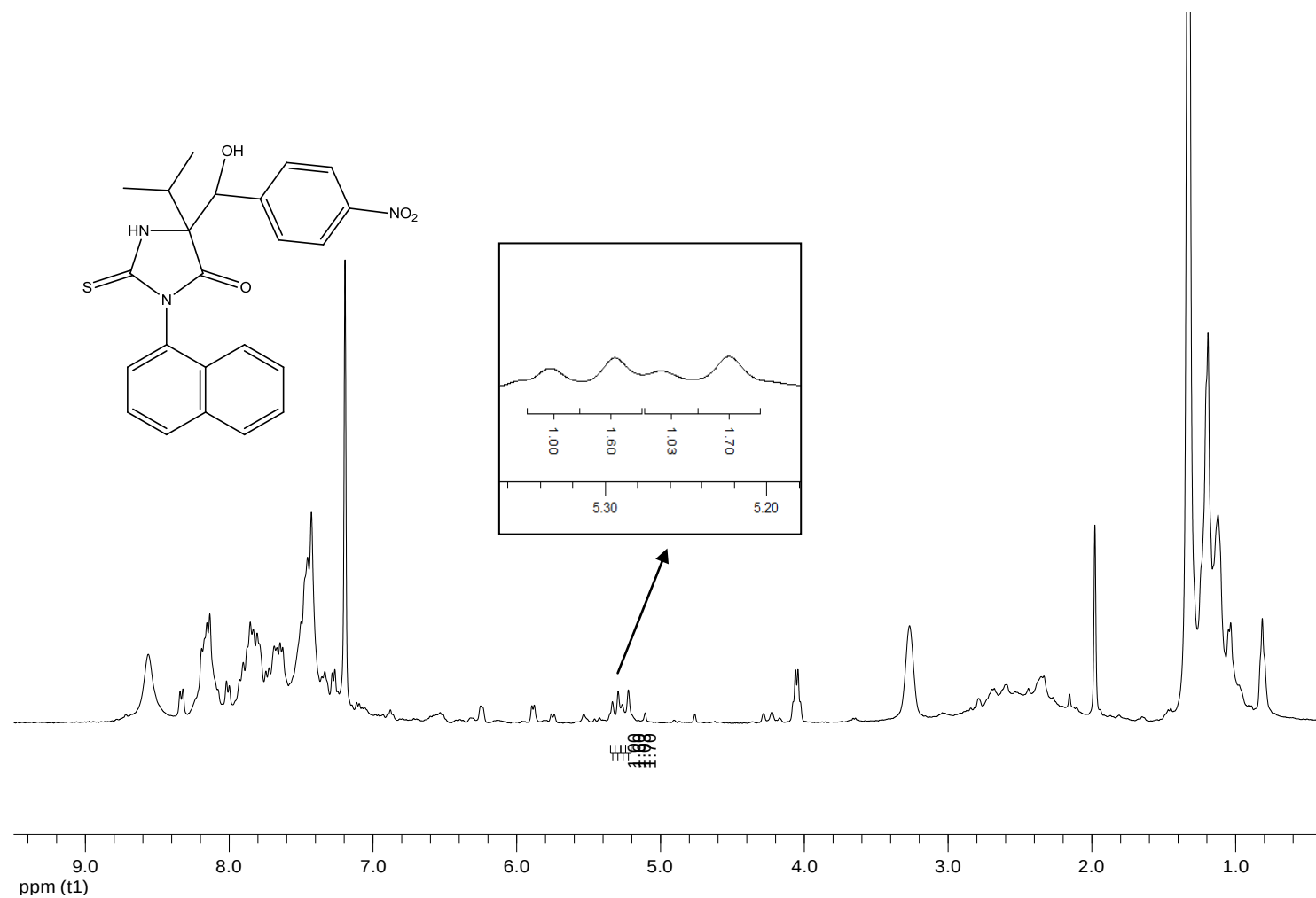


Figure A.79. 400 MHz ¹H NMR of 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3- α -naphthylthiohydantoin (**38**) in CDCl₃ after precipitation from ethyl acetate&hexane.

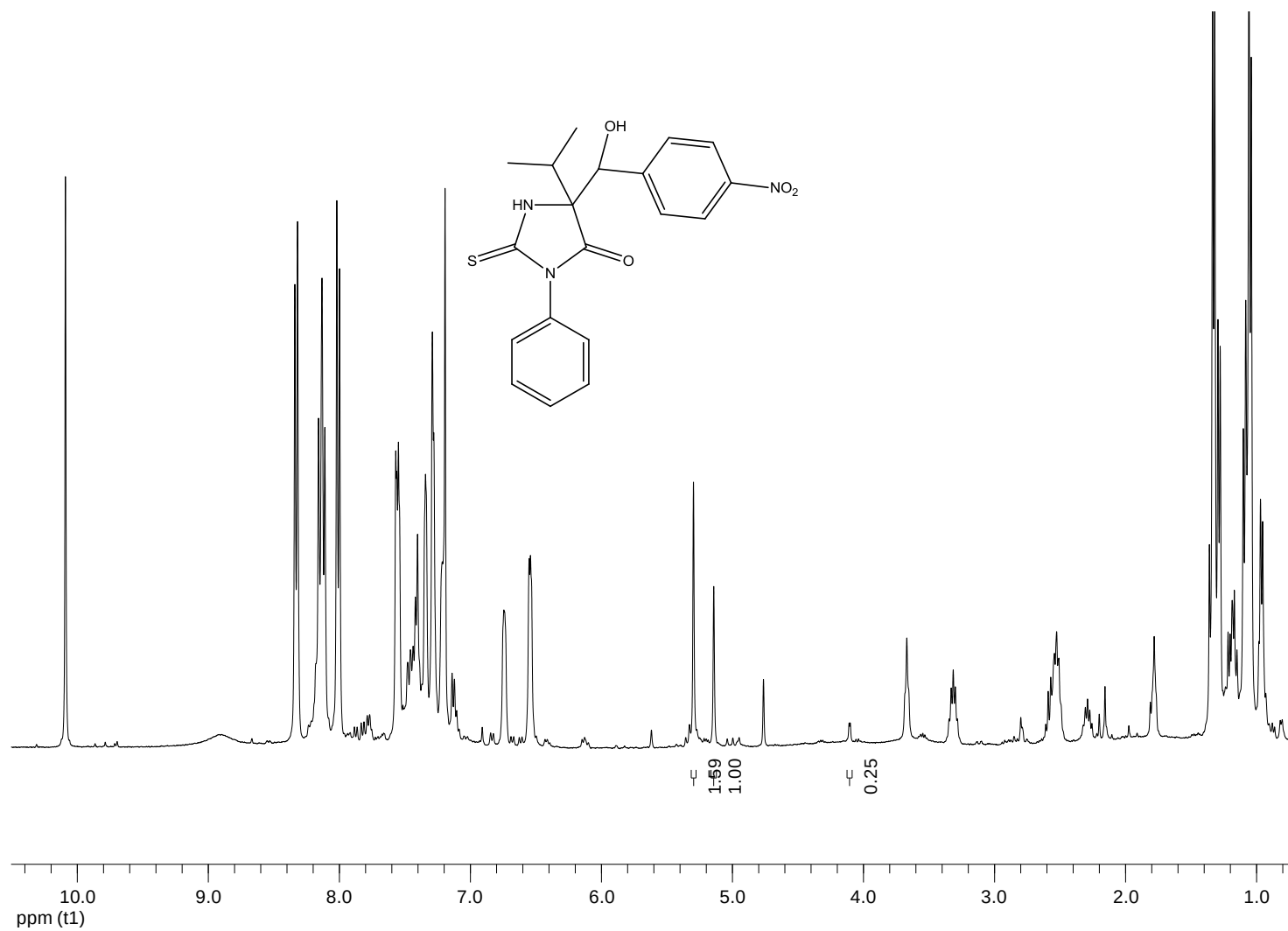


Figure A.80. 400 MHz ^1H NMR of crude 5-(hydroxy(4-nitrophenyl)methyl)-5-isopropyl-3-phenyl thiohydantoin (**39**) in CDCl_3 .

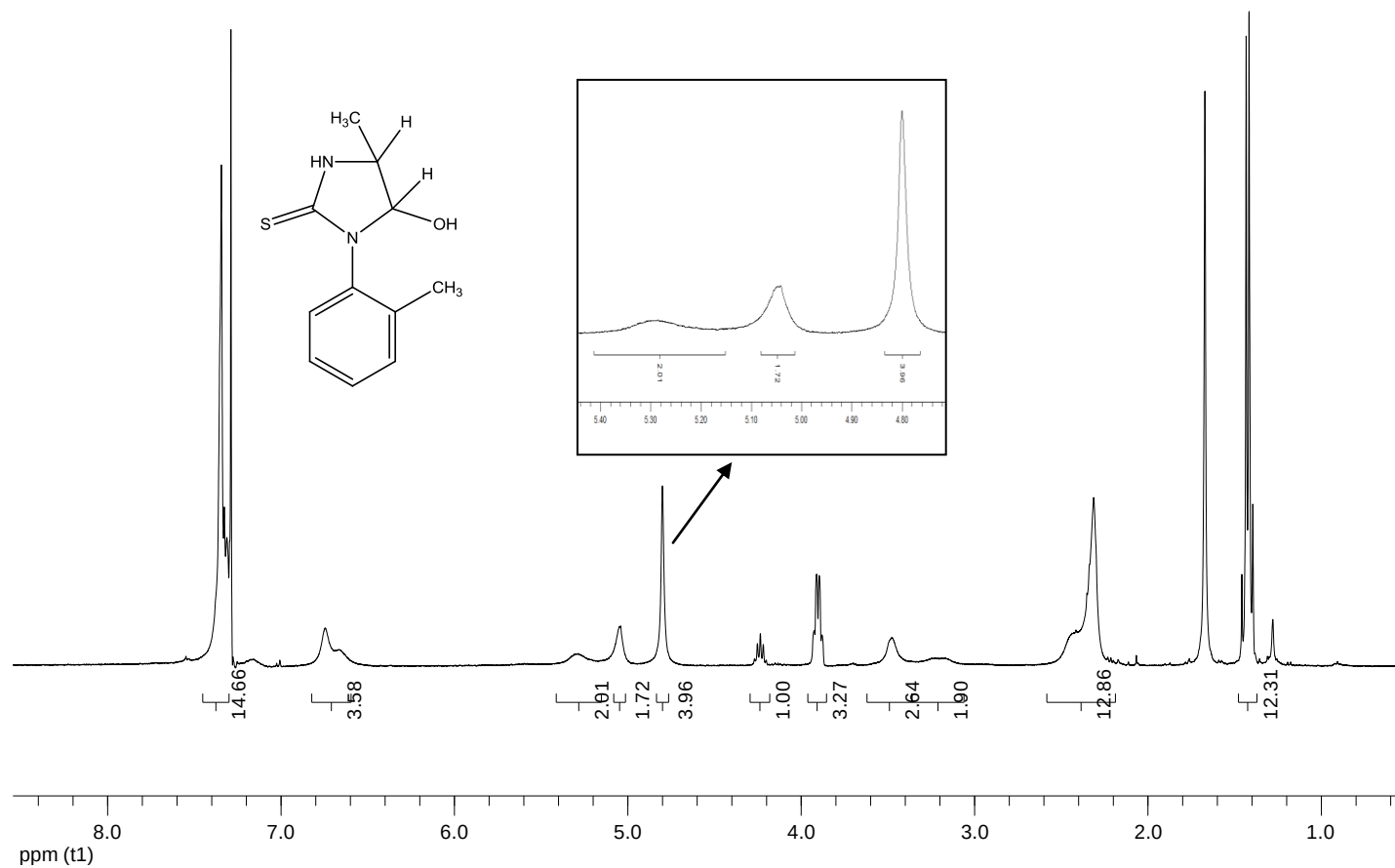


Figure A.81. 400 MHz ^1H NMR of crude 4-hydroxy-5-methyl-3-o-tolyl-2-imidazolidinethione (**40**) in CDCl_3 .

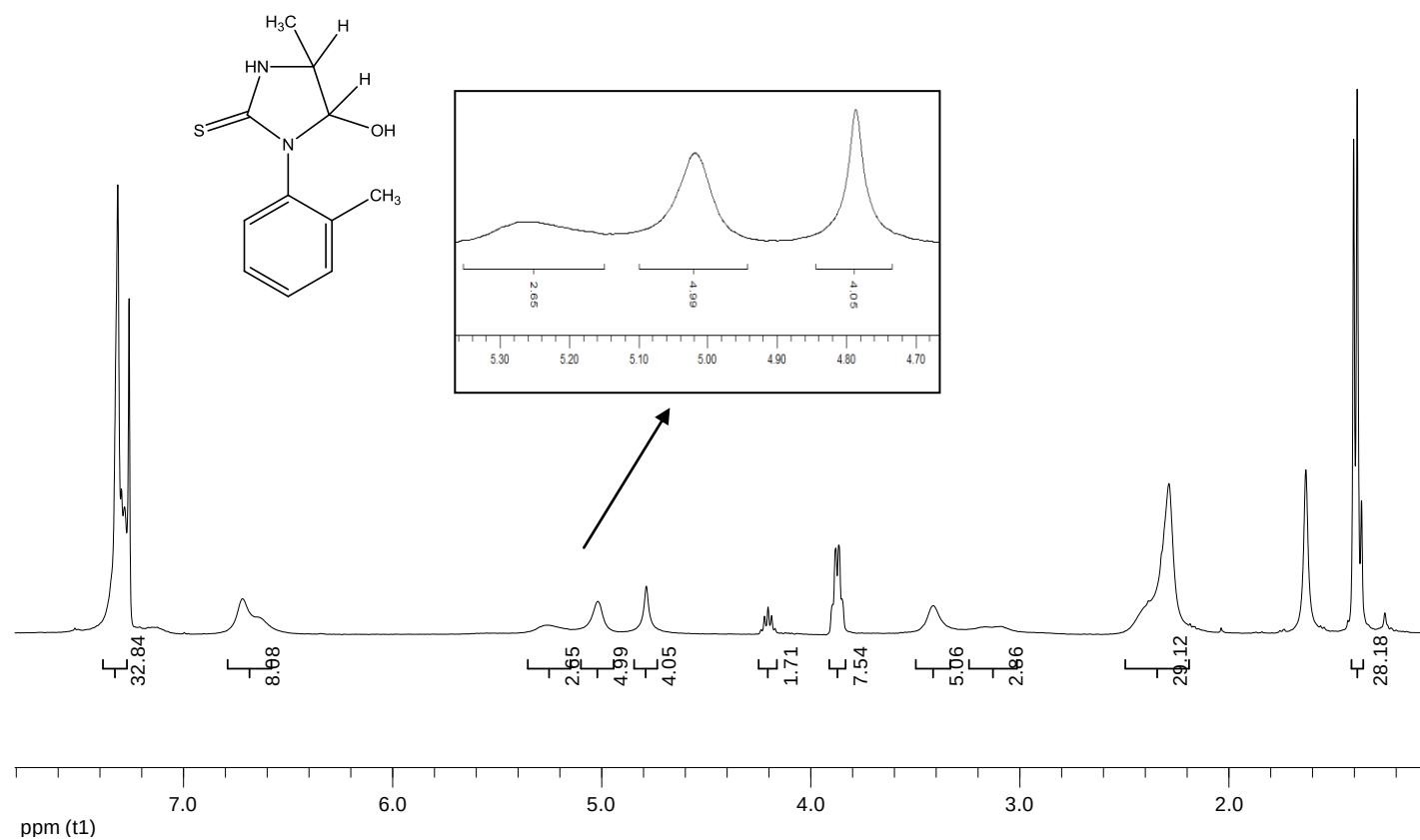


Figure A.82. 400 MHz ¹H NMR of 4-hydroxy-5-methyl-3-*o*-tolyl-2-imidazolidinethione (**40**) in CDCl₃ after purification.

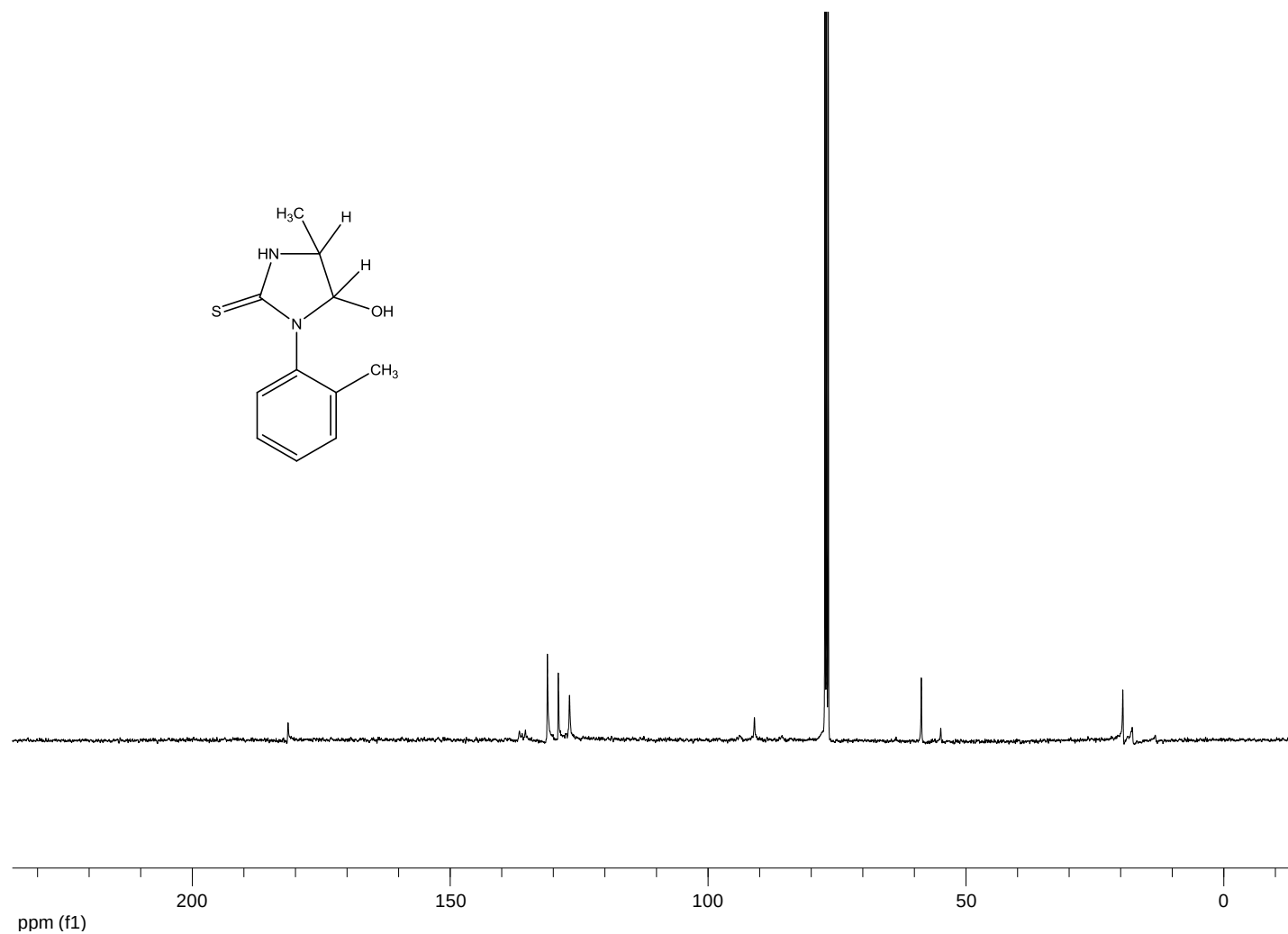


Figure A.83. 100 MHz ¹³C NMR of 4-hydroxy-5-methyl-3-*o*-tolyl-2-imidazolidinethione (**40**) in CDCl₃.

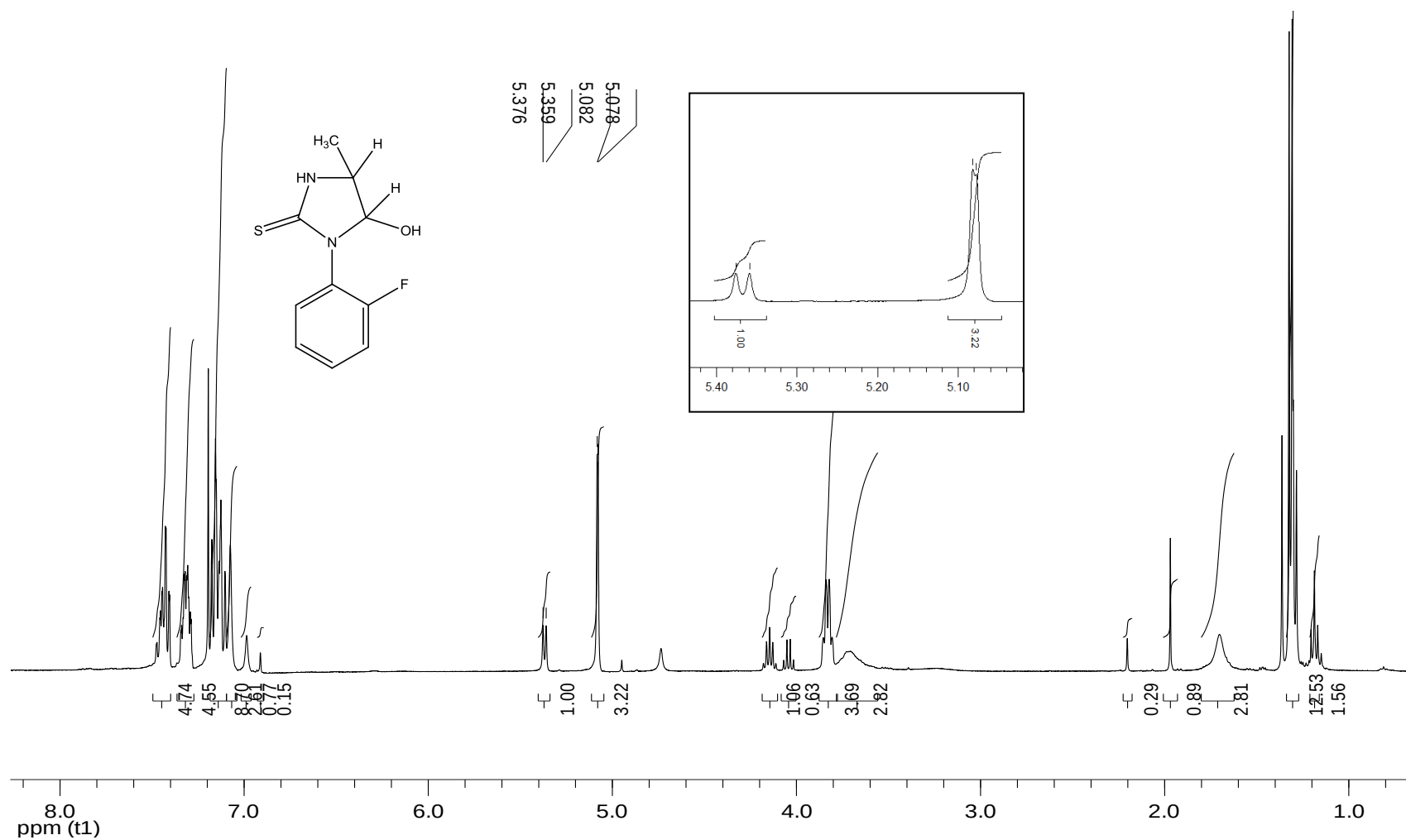


Figure A.84. 400 MHz ¹H NMR of crude 4-hydroxy-5-methyl-3-o-fluorophenyl-2-imidazolidinethione (**41**) in CDCl₃.

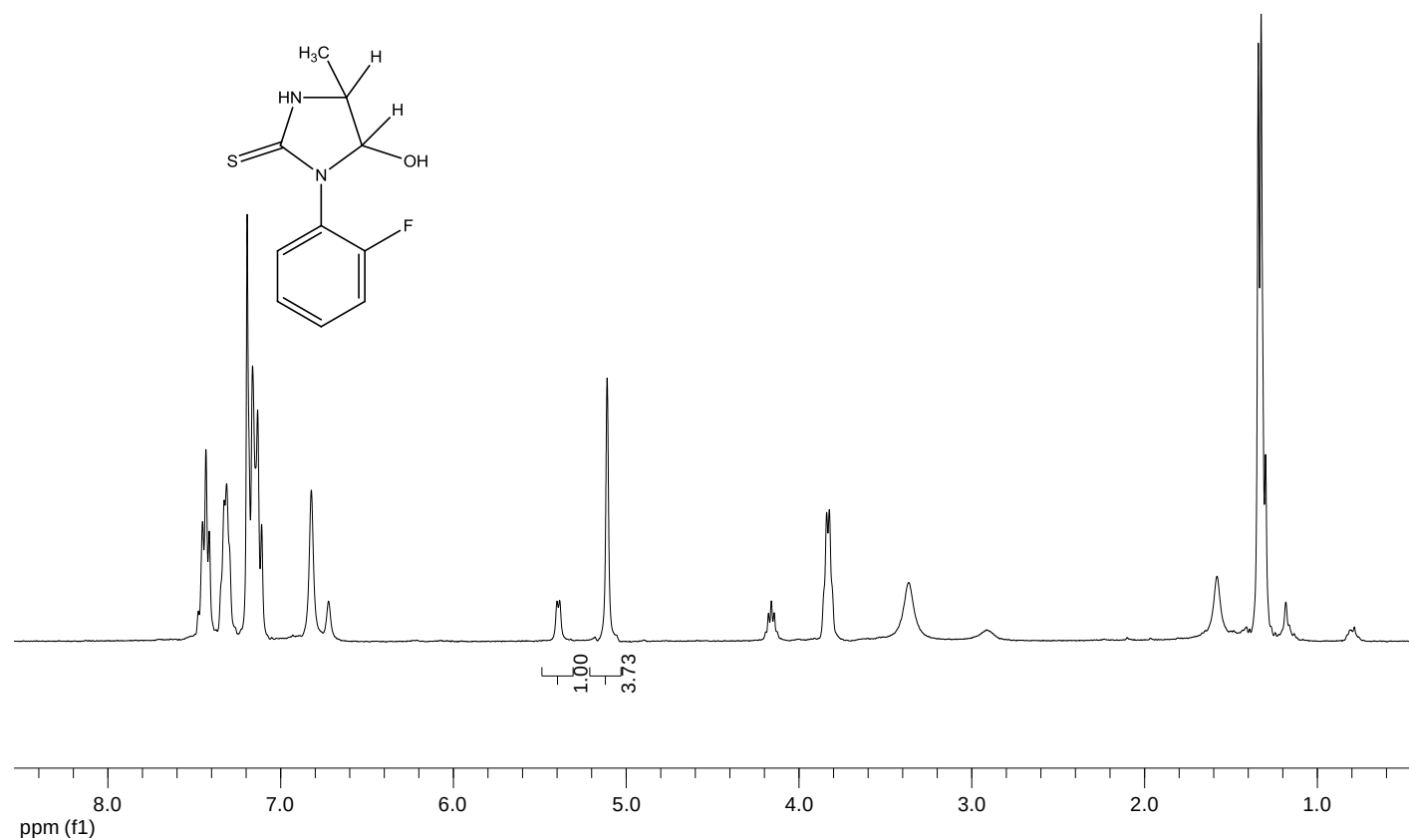


Figure A.85. 400 MHz ¹H NMR of 4-hydroxy-5-methyl-3-*o*-fluorophenyl-2-imidazolidinethione (**41**) in CDCl₃ after purification.

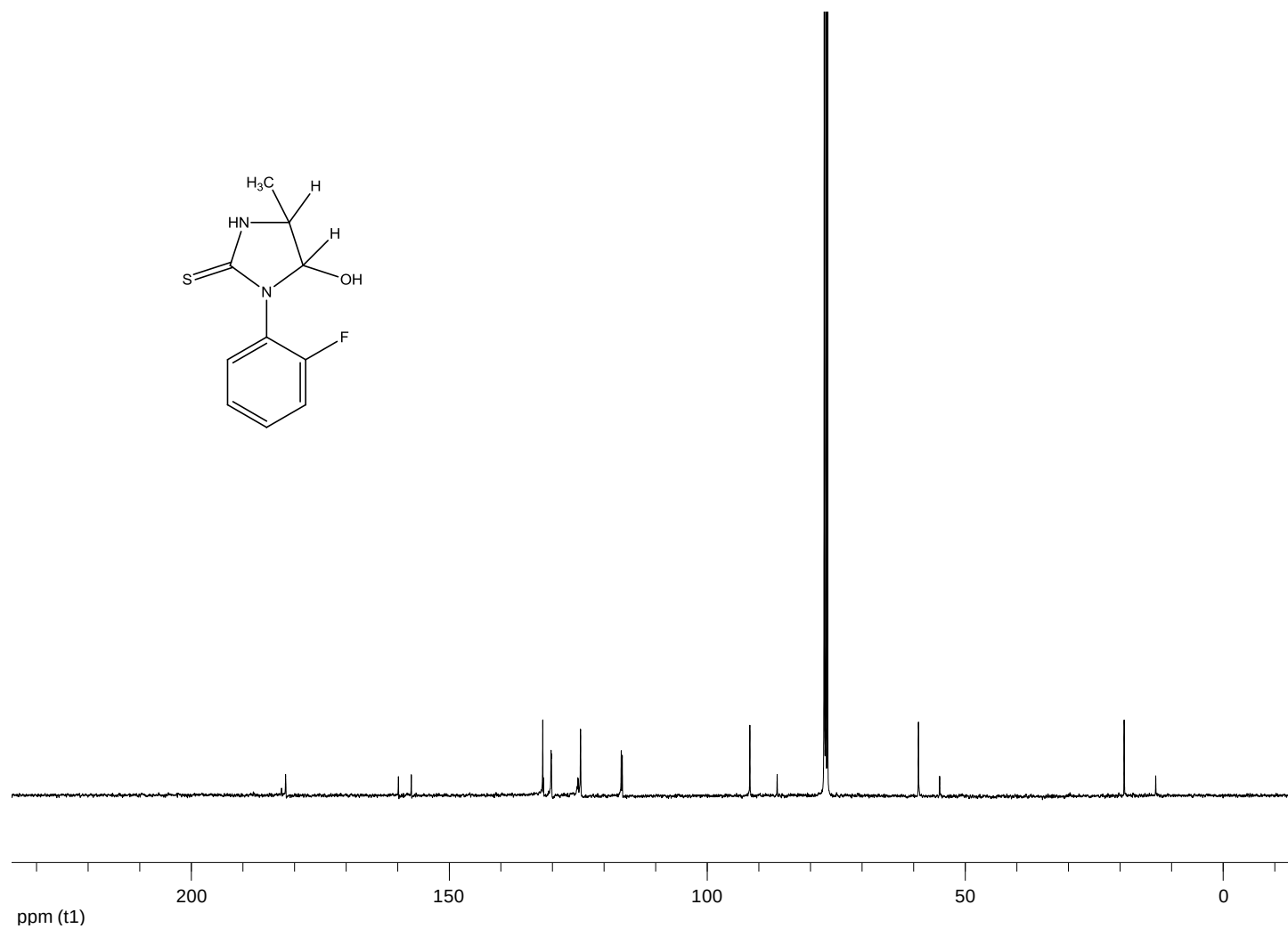


Figure A.86. 100 MHz ¹³C NMR of 4-hydroxy-5-methyl-3-o-fluorophenyl-2-imidazolidinethione (**41**) in CDCl₃.

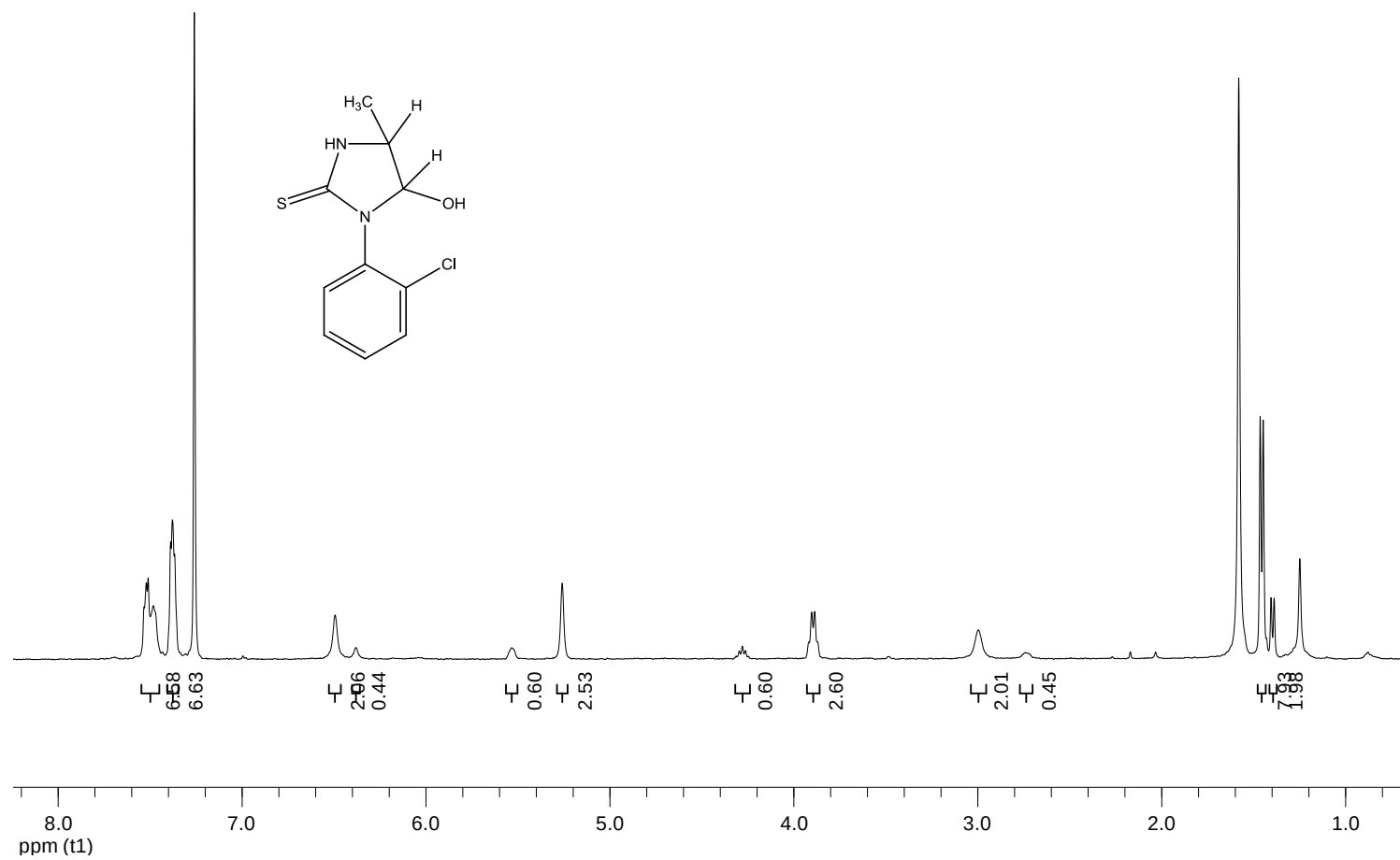


Figure A.87. 400 MHz ^1H NMR of 4-hydroxy-5-methyl-3-*o*-chlorophenyl-2-imidazolidinethione (**42**) in CDCl_3 after purification.

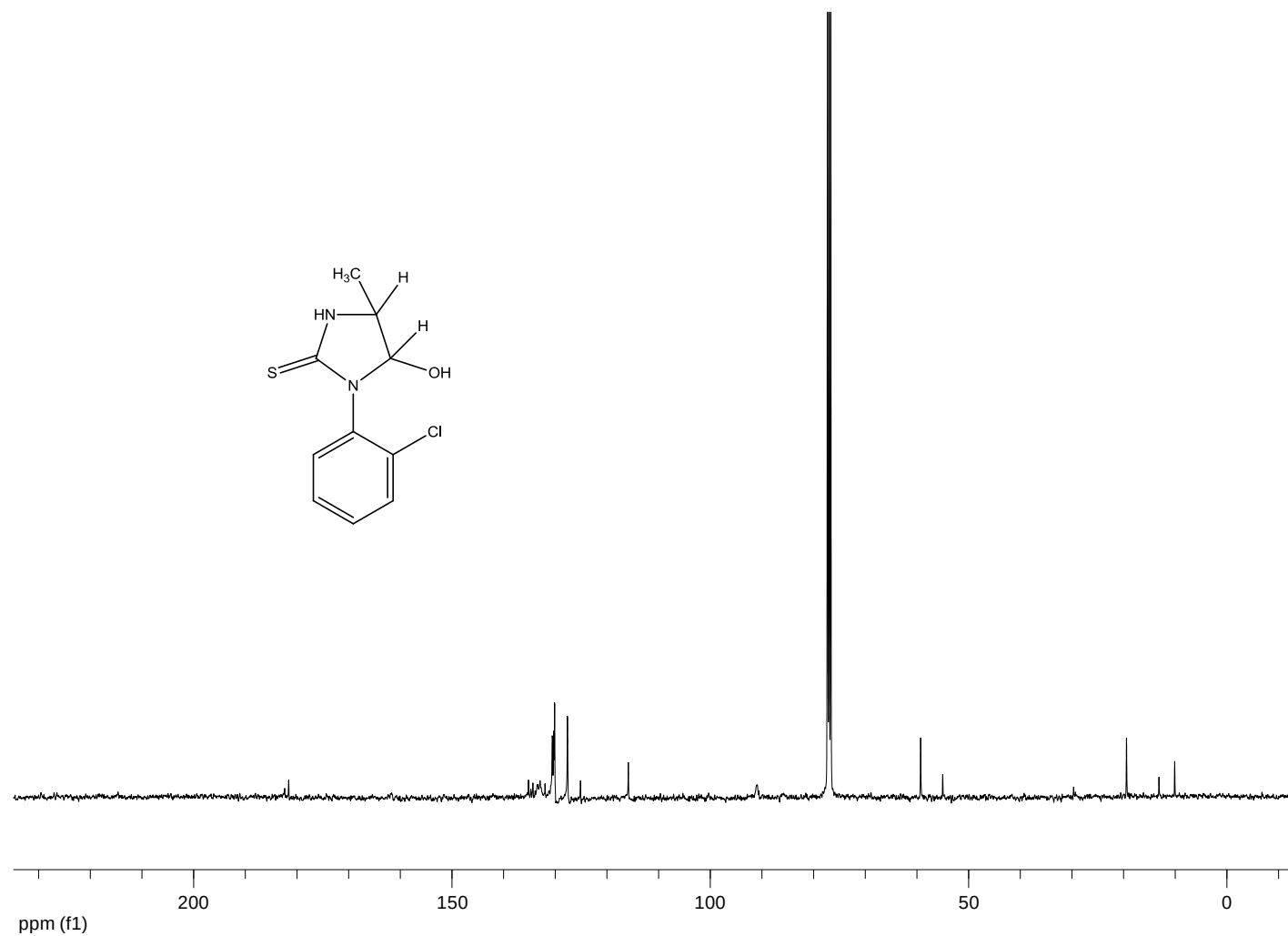


Figure A.88. 100 MHz ^{13}C NMR of 4-hydroxy-5-methyl-3-*o*-chlorophenyl-2-imidazolidinethione (**42**) in CDCl_3 .

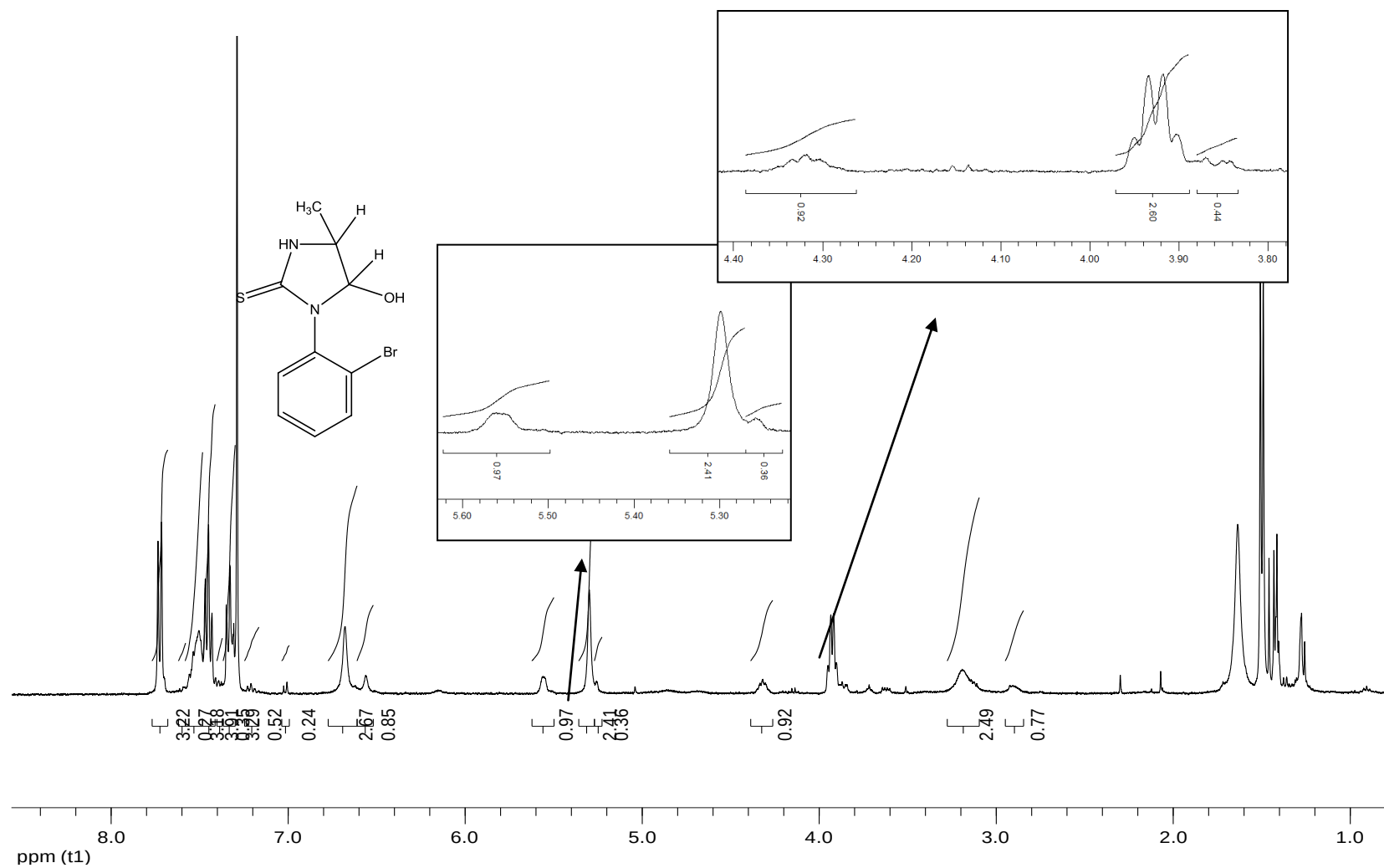


Figure A.89. 400 MHz ¹H NMR of crude 4-hydroxy-5-methyl-3-o-bromophenyl-2-imidazolidinethione (**43**) in CDCl₃.

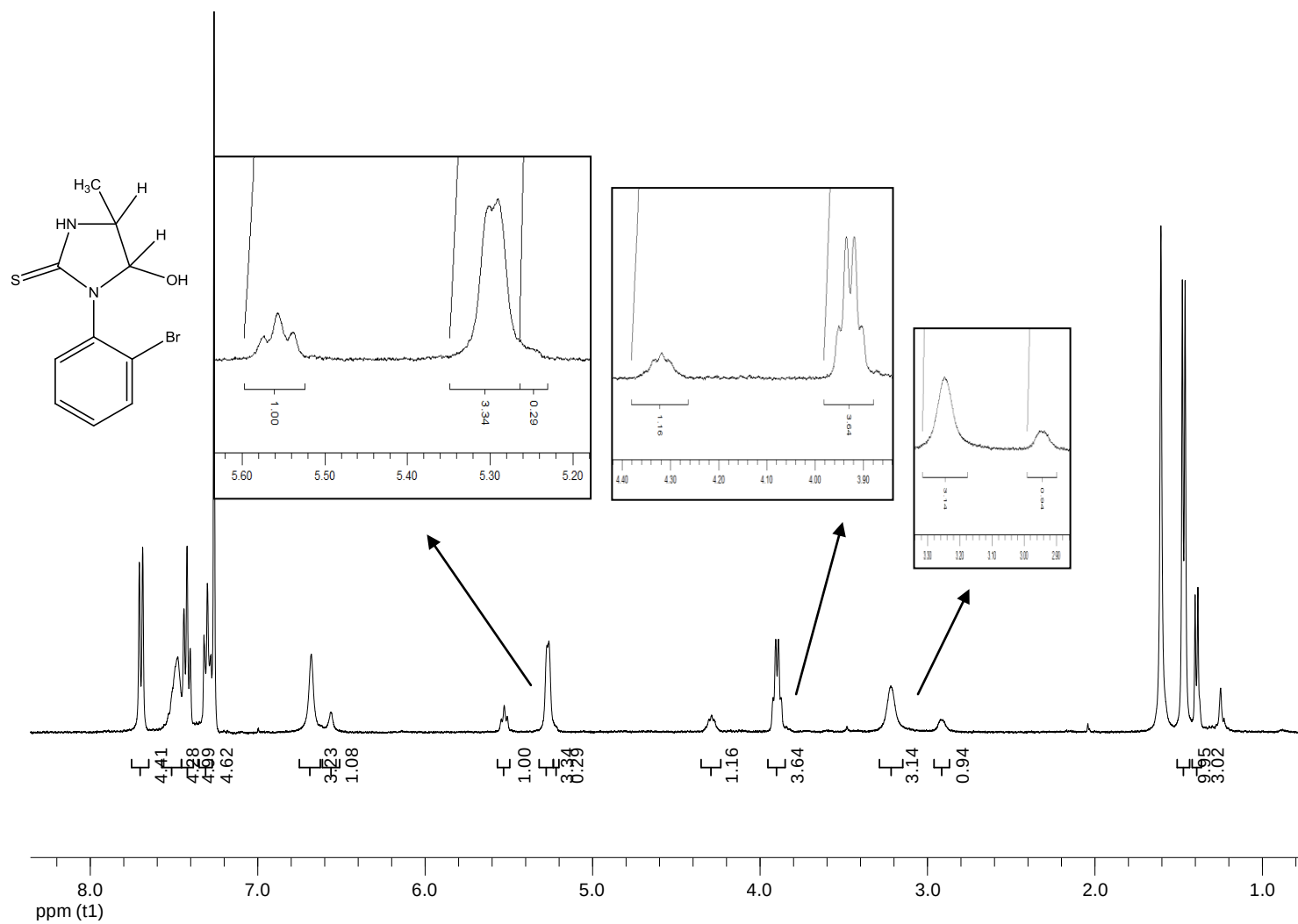


Figure A.90. 400 MHz ¹H NMR of 4-hydroxy-5-methyl-3-o-bromophenyl-2-imidazolidinethione (**43**) in CDCl₃ after purification.

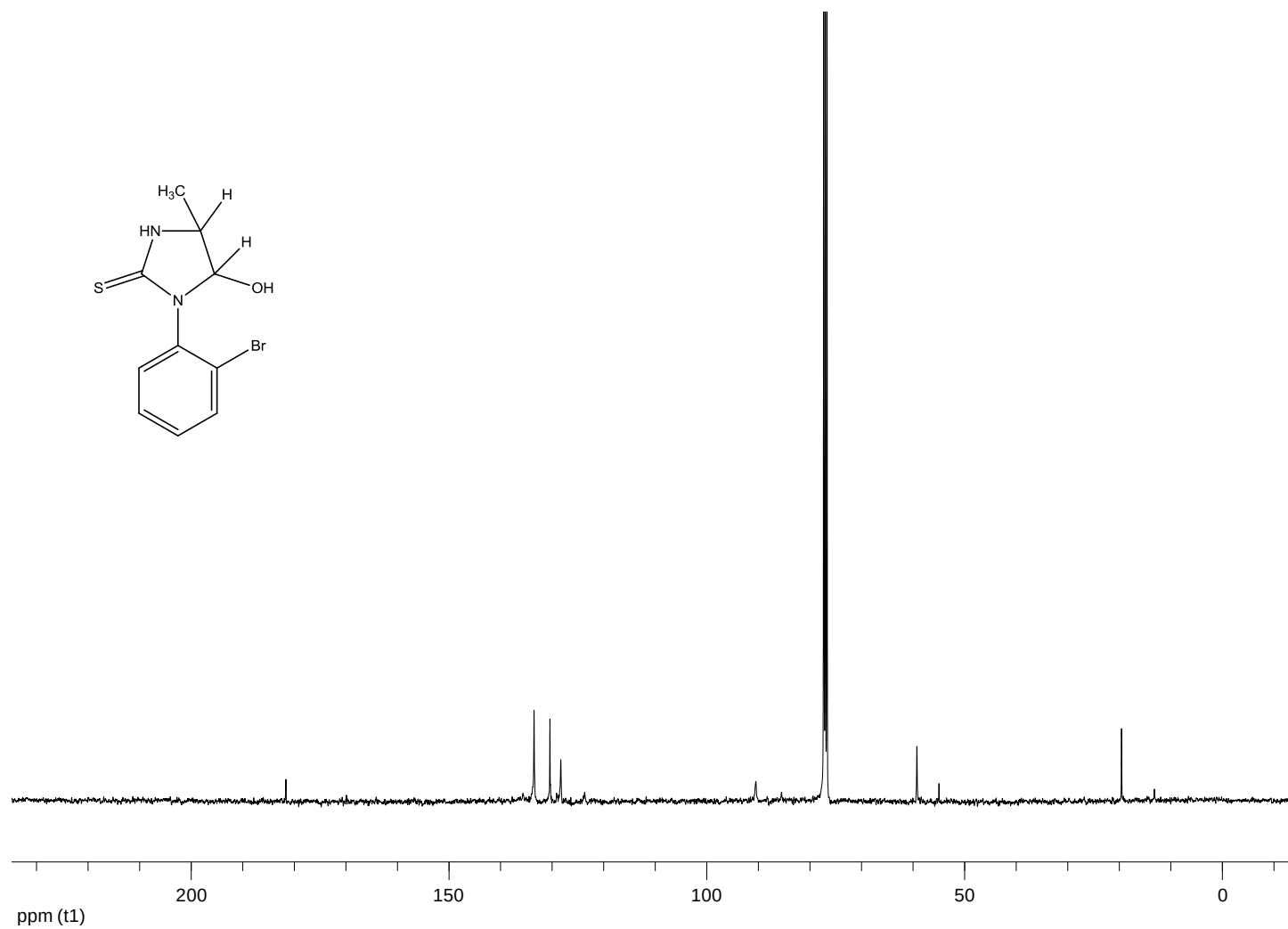


Figure A.91. 100 MHz ^{13}C NMR of 4-hydroxy-5-methyl-3-*o*-bromophenyl-2-imidazolidinethione (**43**) in CDCl_3 .

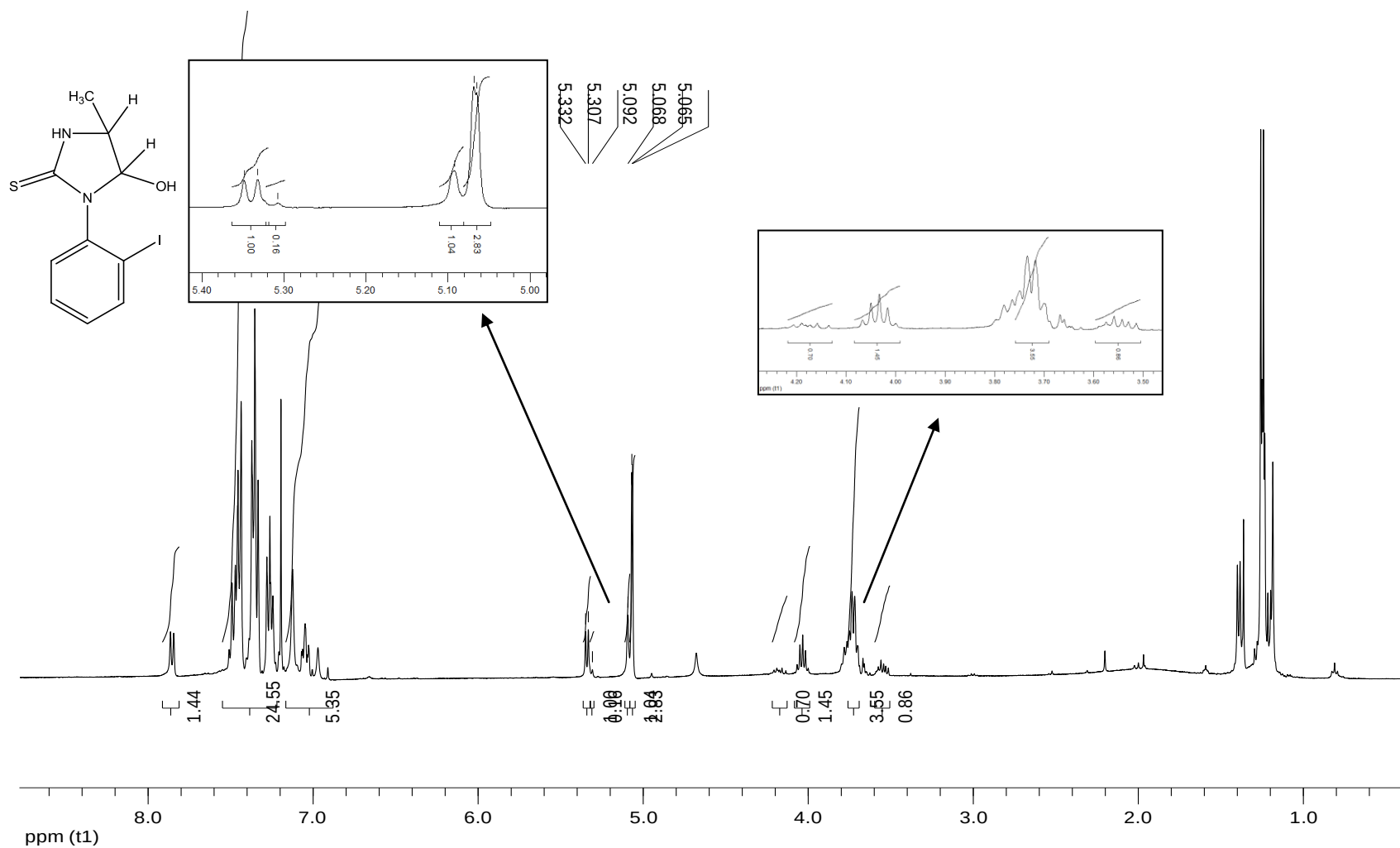


Figure A.92. 400 MHz ¹H NMR of crude 4-hydroxy-5-methyl-3-o-iodophenyl-2-imidazolidinethione (**44**) in CDCl₃.

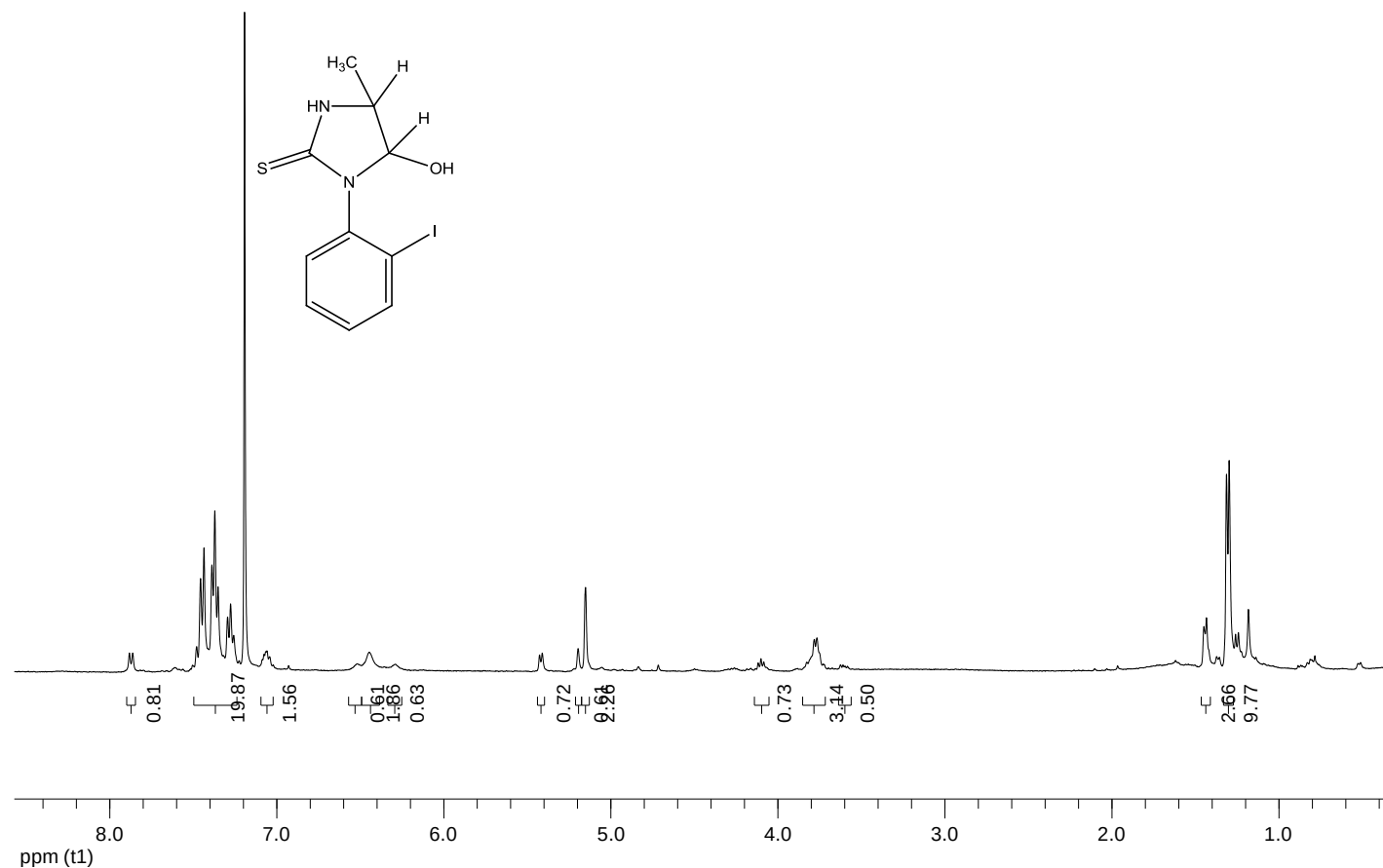


Figure A.93. 400 MHz ¹H NMR of 4-hydroxy-5-methyl-3-o-iodophenyl-2-imidazolidinethione (**44**) in CDCl₃ after purification.

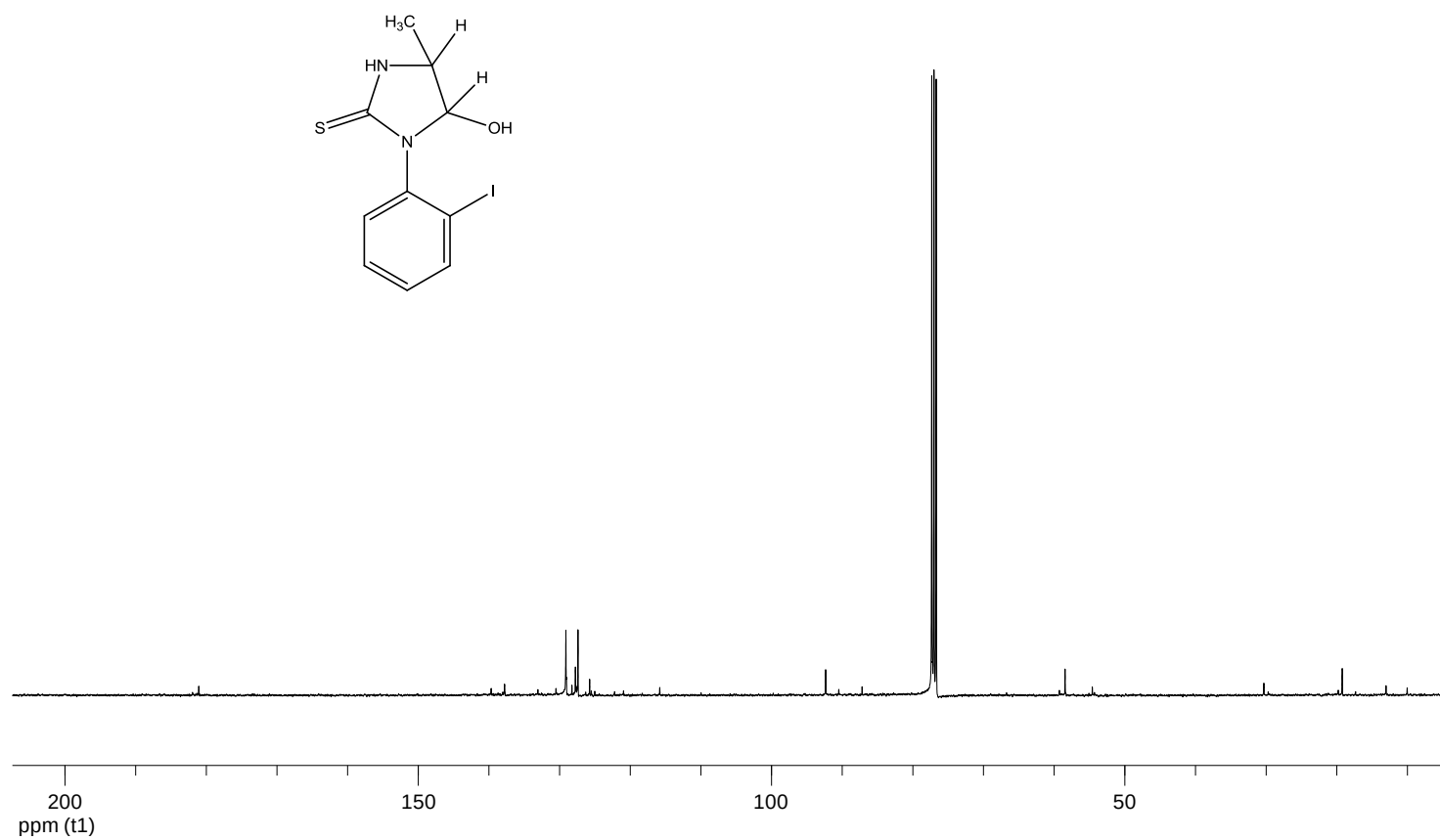


Figure A.94. 100 MHz ^{13}C NMR of 4-hydroxy-5-methyl-3-o-iodophenyl-2-imidazolidinethione (**44**) in CDCl_3 .

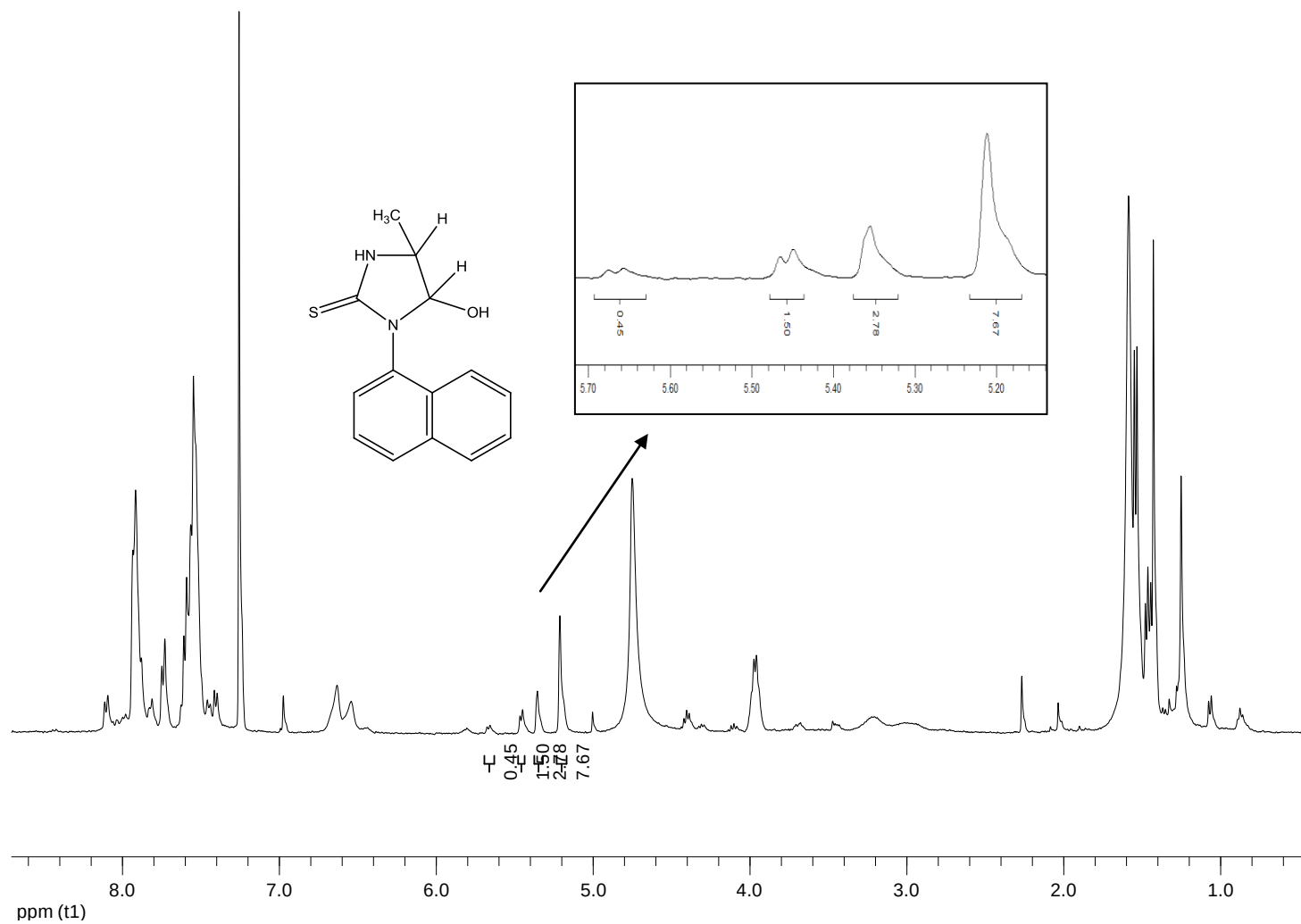


Figure A.95. 400 MHz ¹H NMR of crude 4-hydroxy-5-methyl-3- α -naphtyl-2-imidazolidinethione (**45**) in CDCl₃.

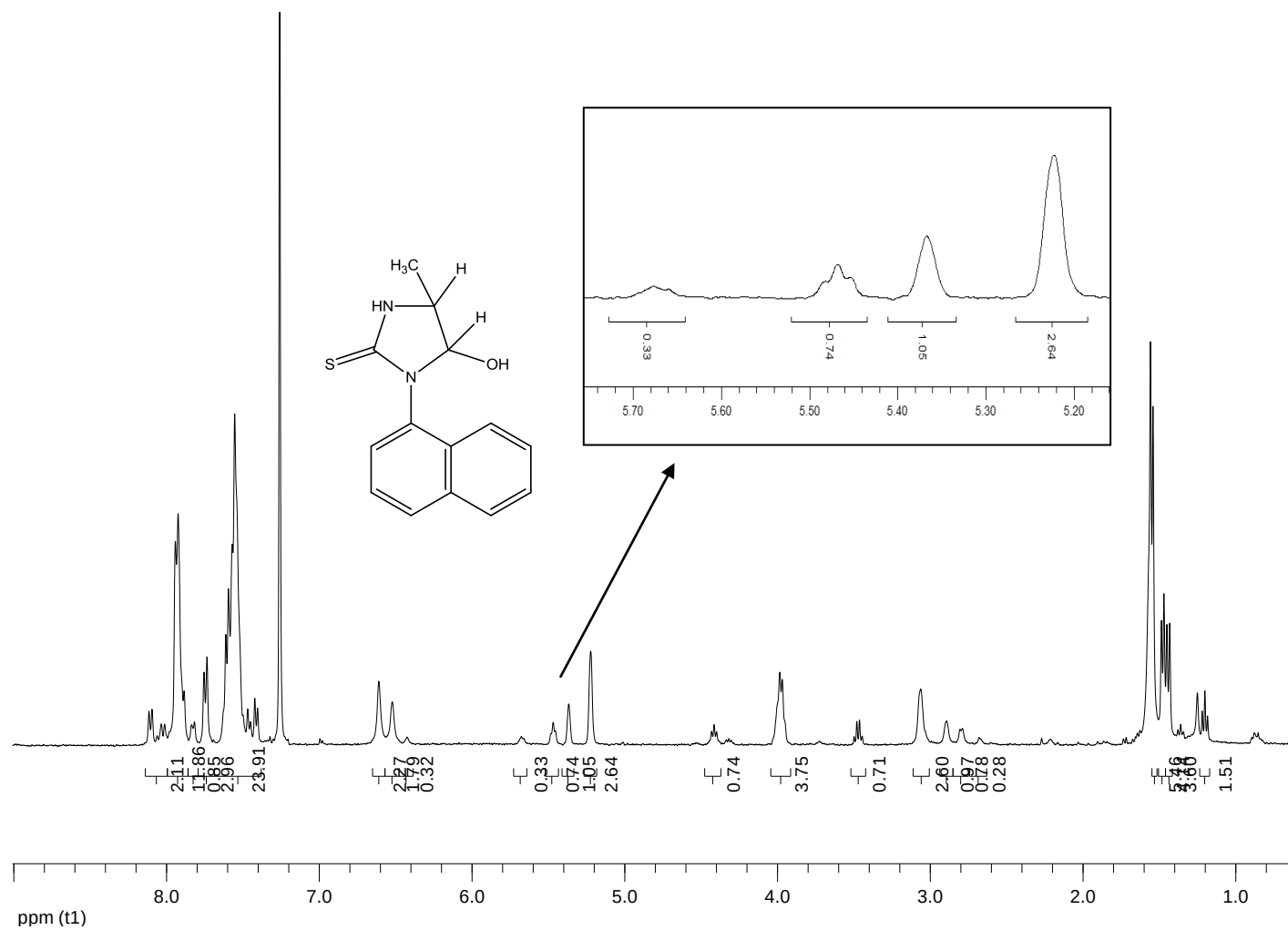


Figure A.96. 400 MHz ¹H NMR of 4-hydroxy-5-methyl-3- α -naphthyl-2-imidazolidinethione (**45**) in CDCl₃ after purification.

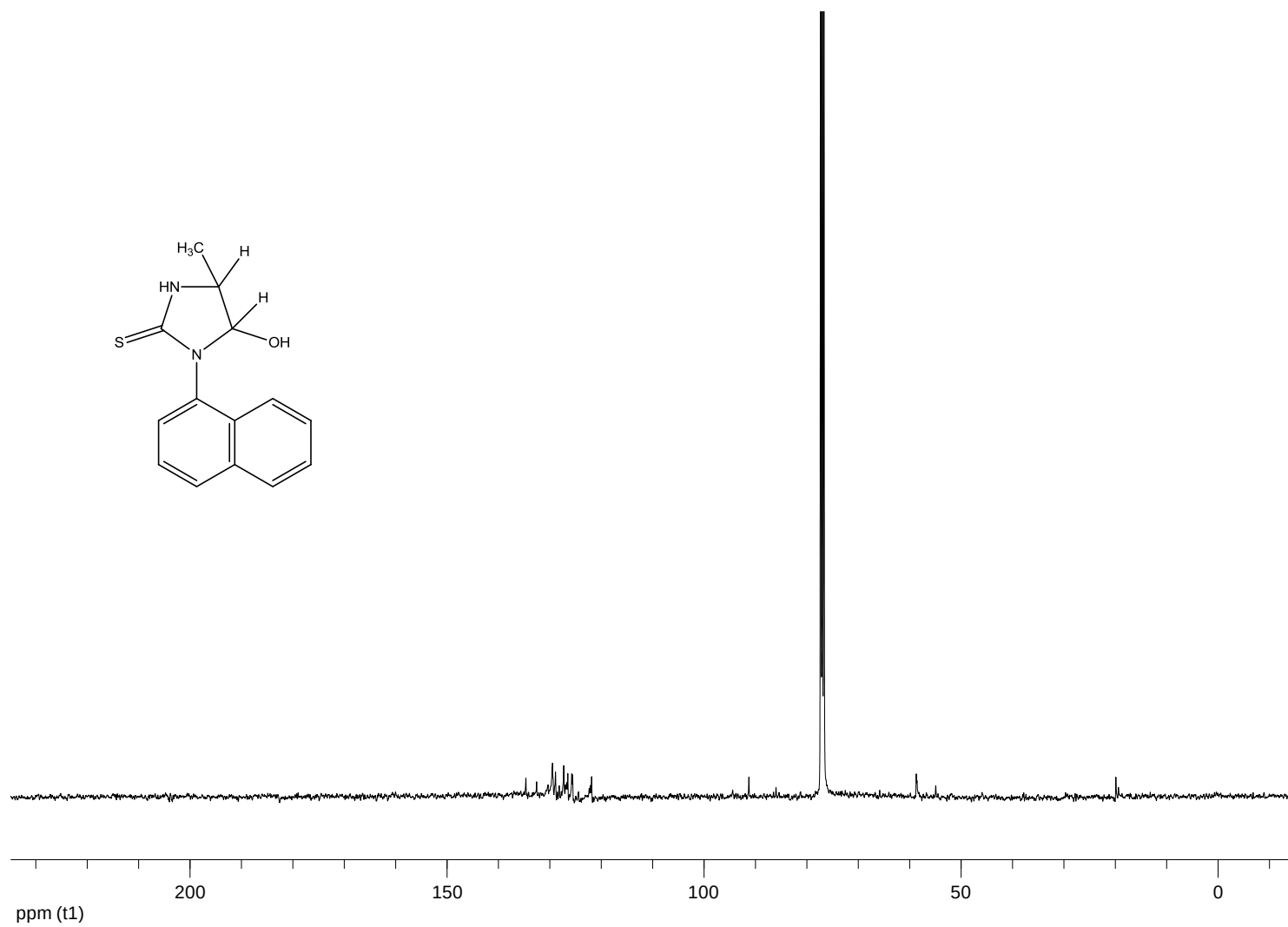


Figure A.97. 100 MHz ^{13}C NMR of 4-hydroxy-5-methyl-3- α -naphtyl-2-imidazolidinethione (**45**) in CDCl_3 .

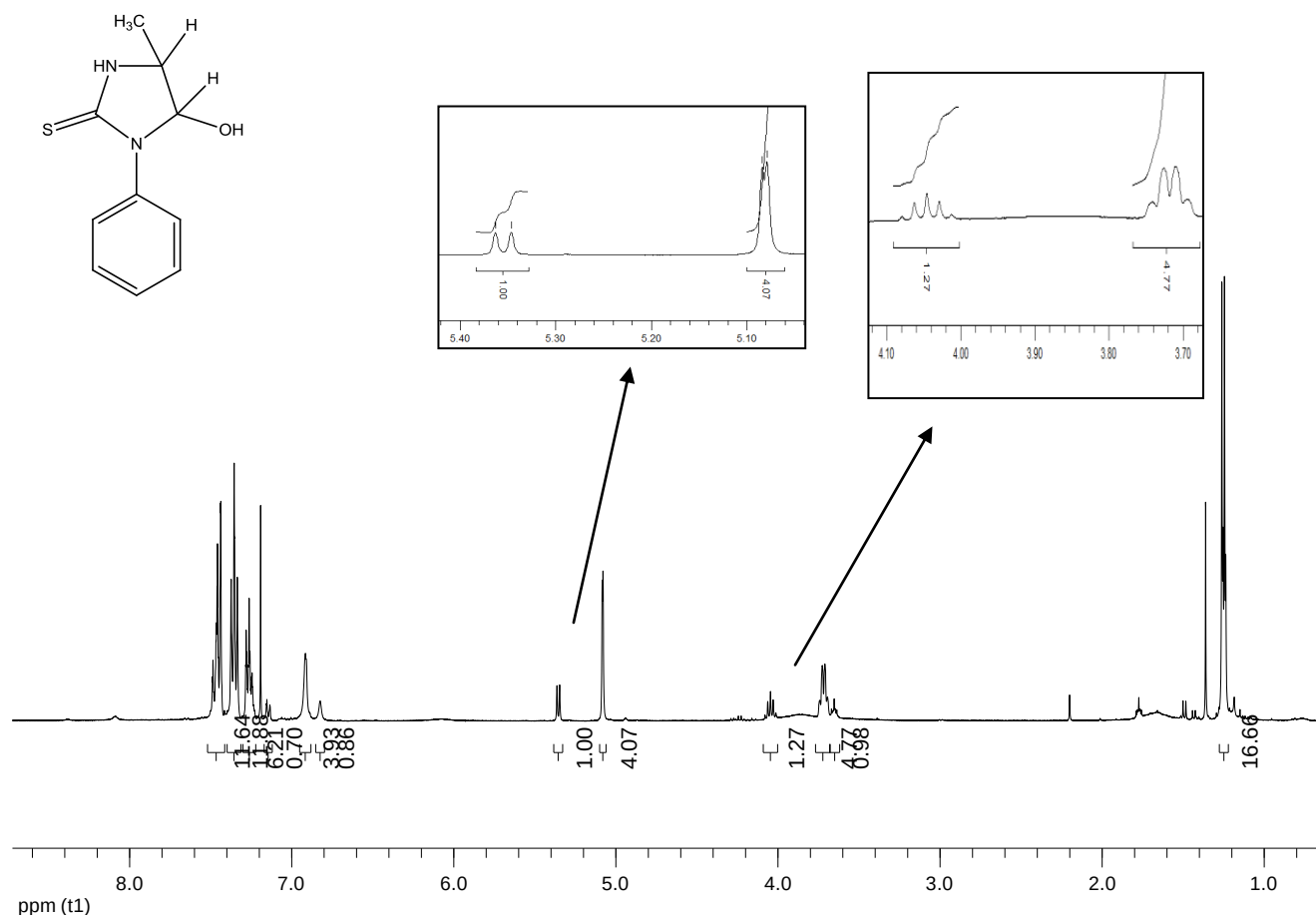


Figure A.98. 400 MHz ¹H NMR of 4-hydroxy-5-methyl-3-phenyl-2-imidazolidinethione (**46**) in CDCl₃.

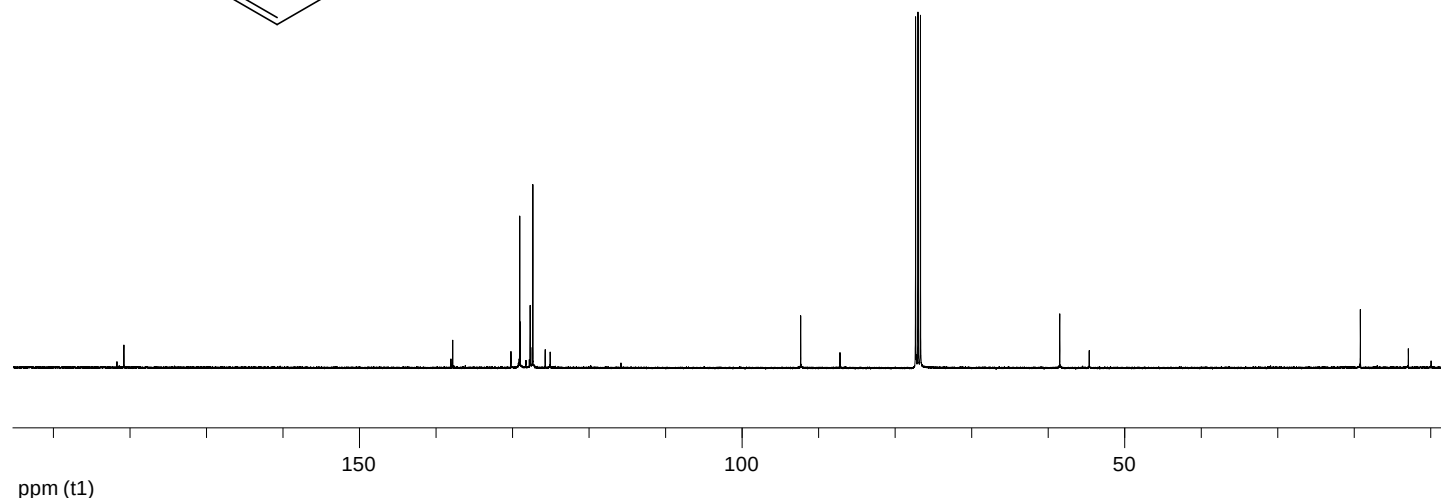
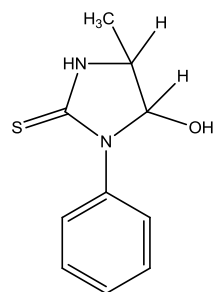


Figure A.99. 100 MHz ¹³C NMR of 4-hydroxy-5-methyl-3-phenyl-2-imidazolidinethione (**46**) in CDCl₃.

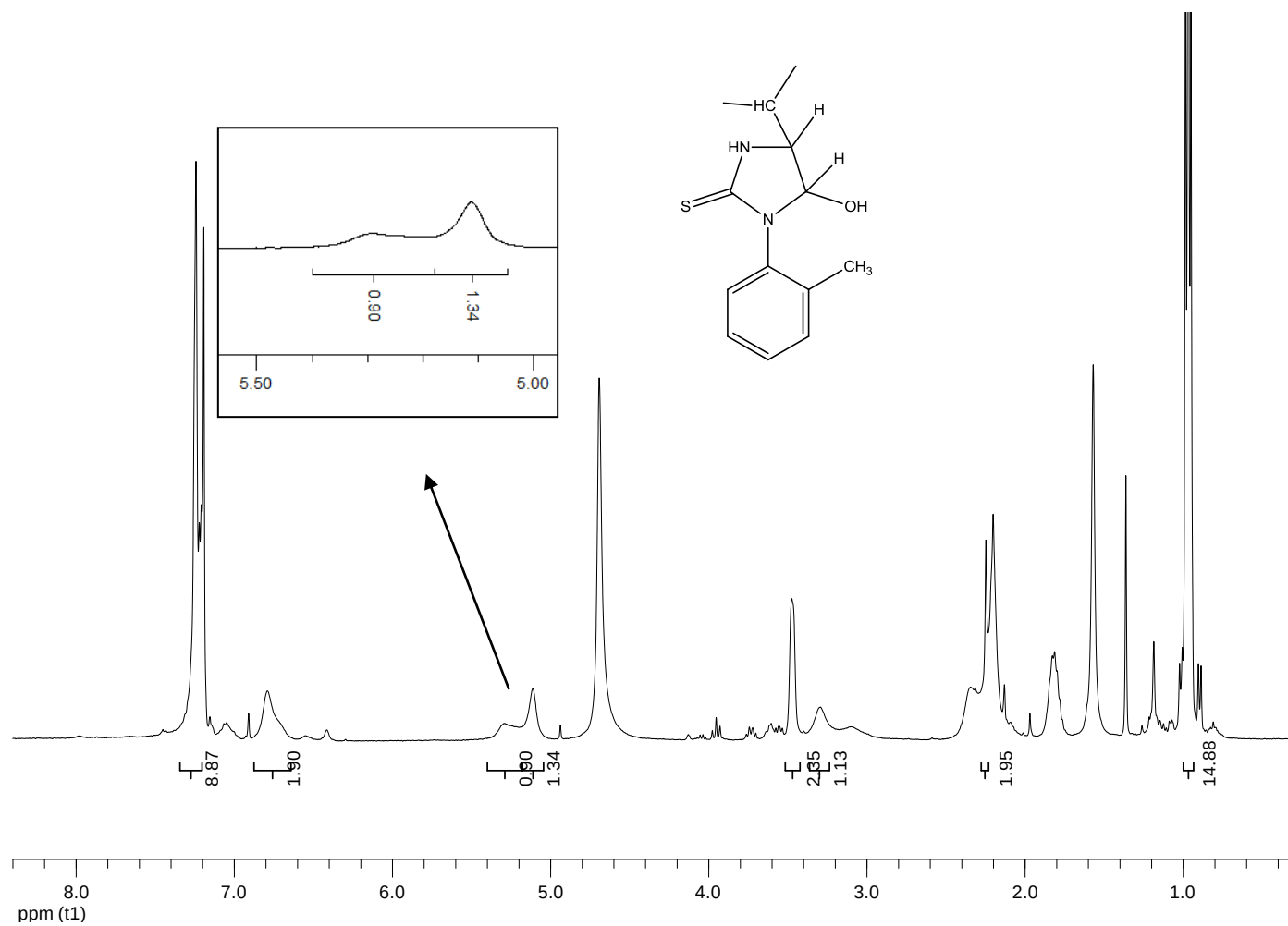


Figure A.100. 400 MHz ¹H NMR of crude 4-hydroxy-5-isopropyl-3-o-tolyl-2-imidazolidinethione (**47**) in CDCl₃.

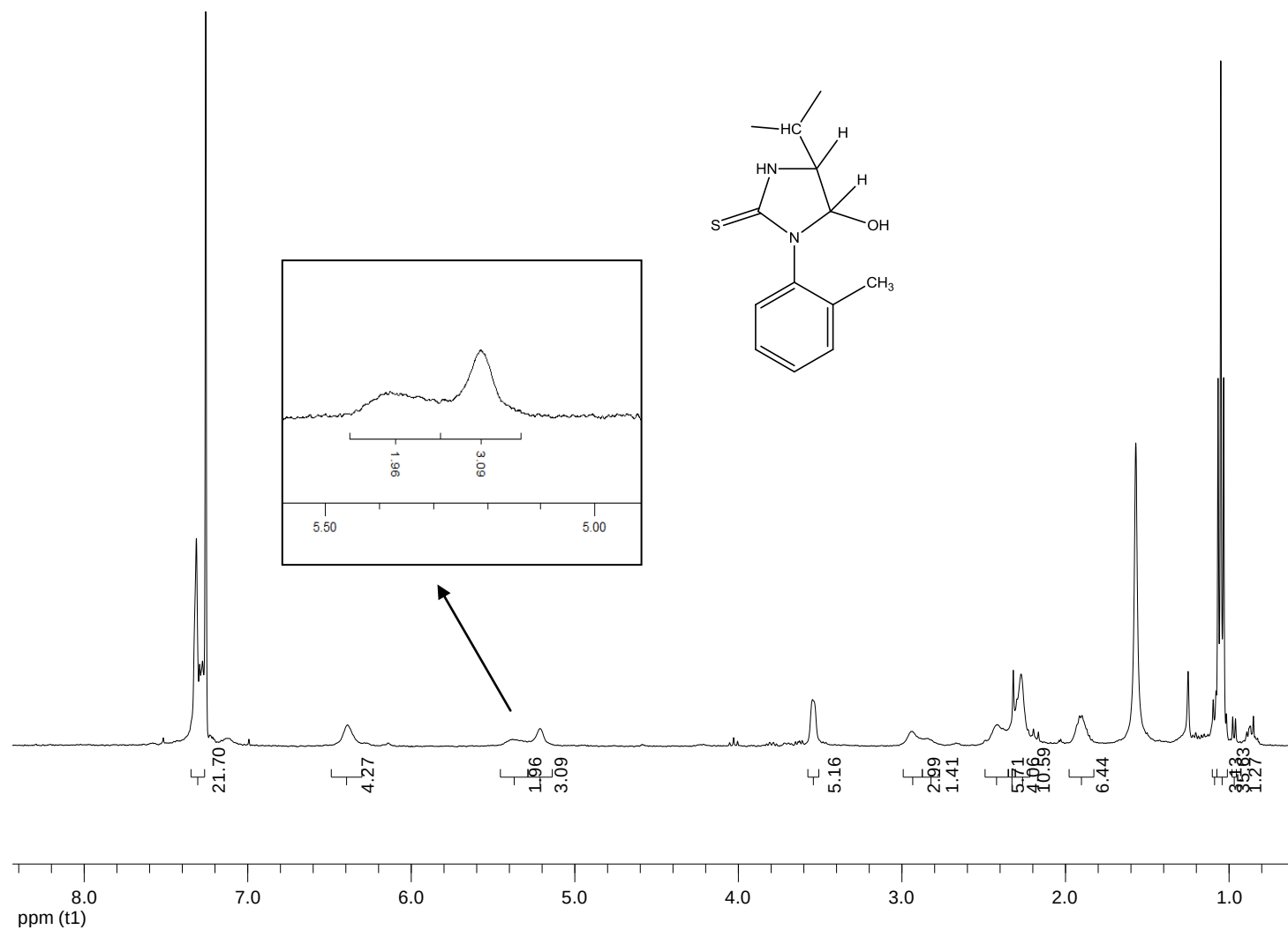


Figure A.101. 400 MHz ¹H NMR of 4-hydroxy-5-isopropyl-3-o-tolyl-2-imidazolidinethione (**47**) in CDCl₃.

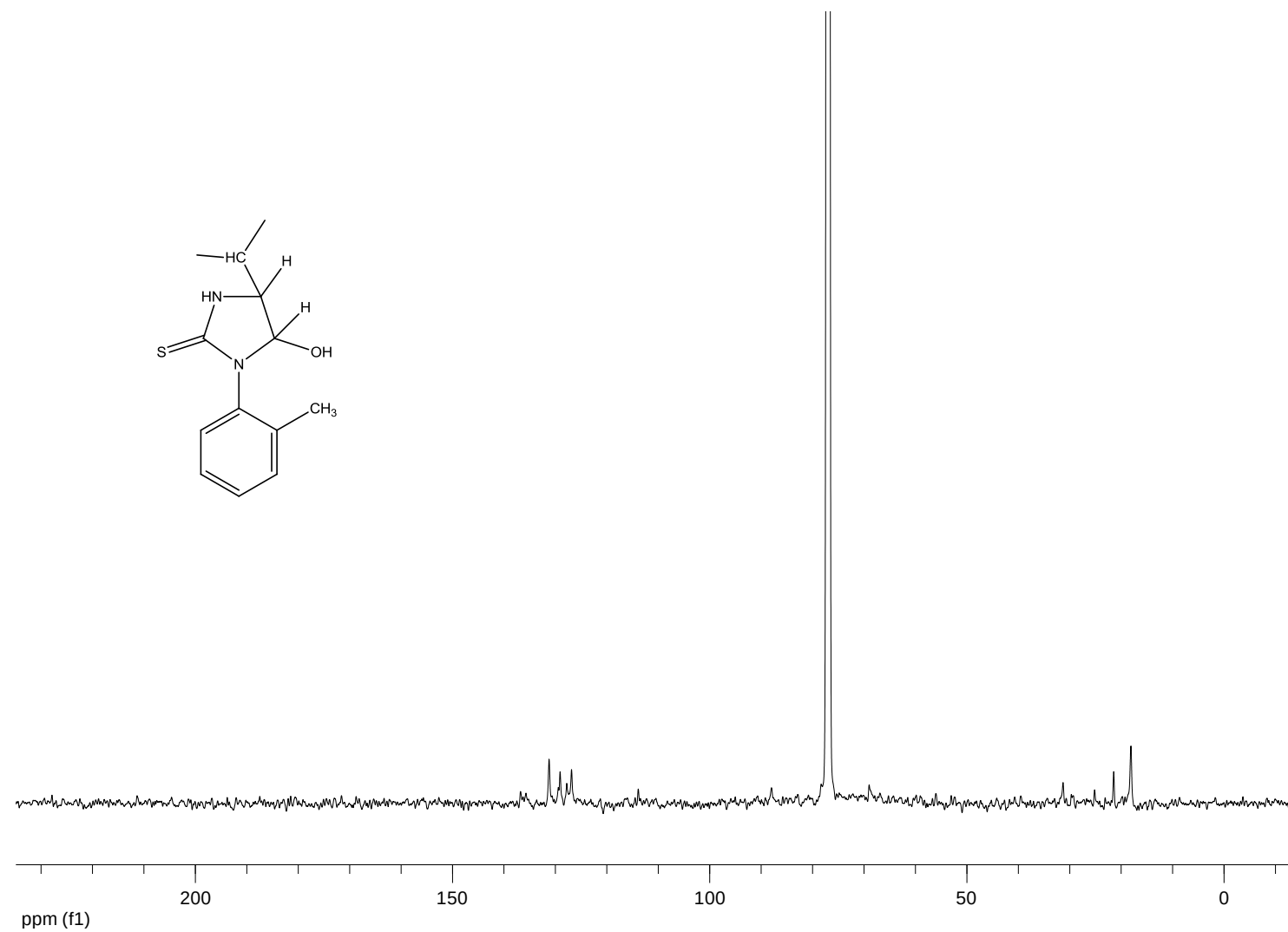
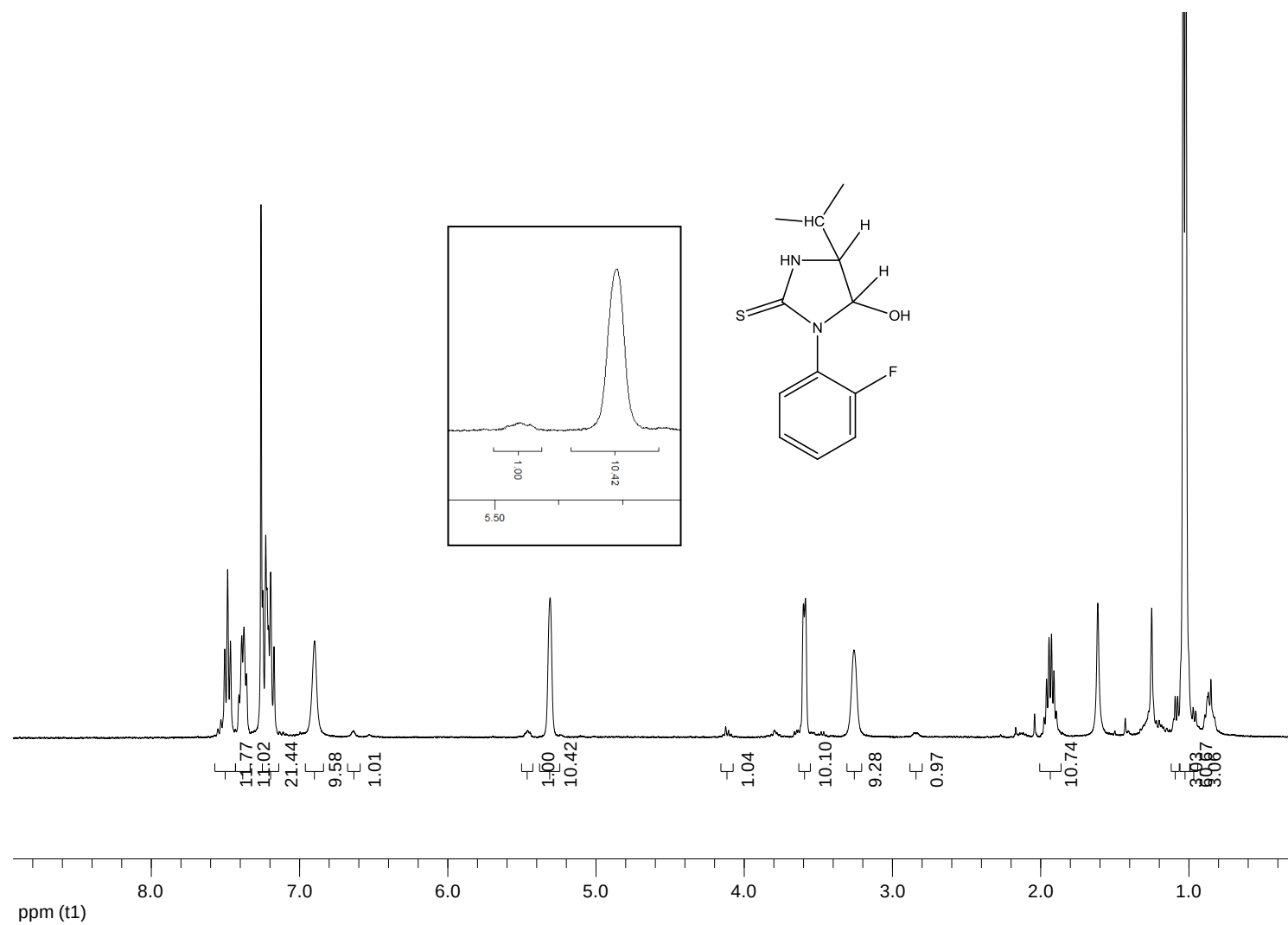


Figure A.102. 100 MHz ¹³C NMR of 4-hydroxy-5-isopropyl-3-*o*-tolyl-2-imidazolidinethione (**47**) in CDCl₃.



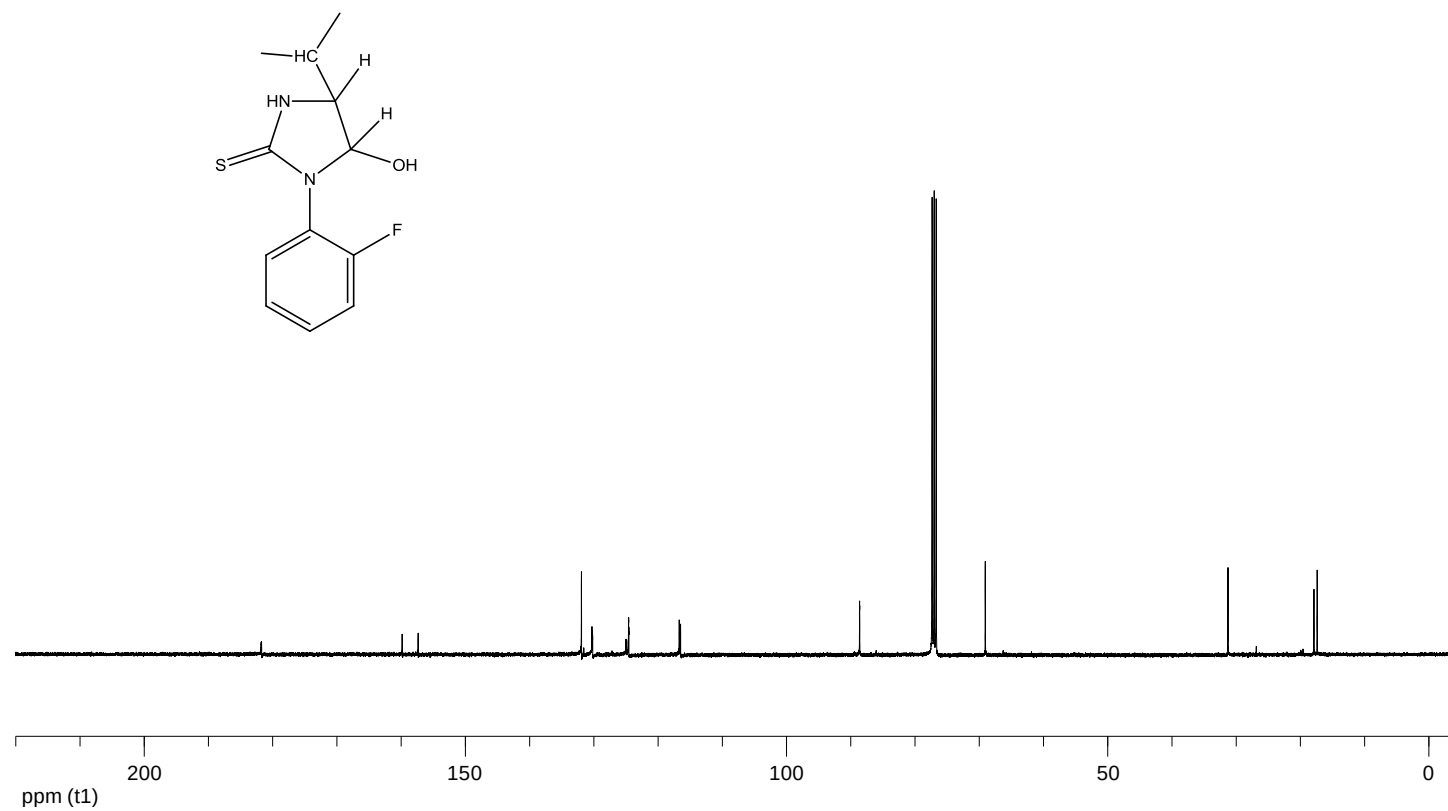


Figure A.105. 100 MHz ¹³C NMR of 4-hydroxy-5-isopropyl-3-o-fluorophenyl-2-imidazolidinethione (**48**) in CDCl₃.

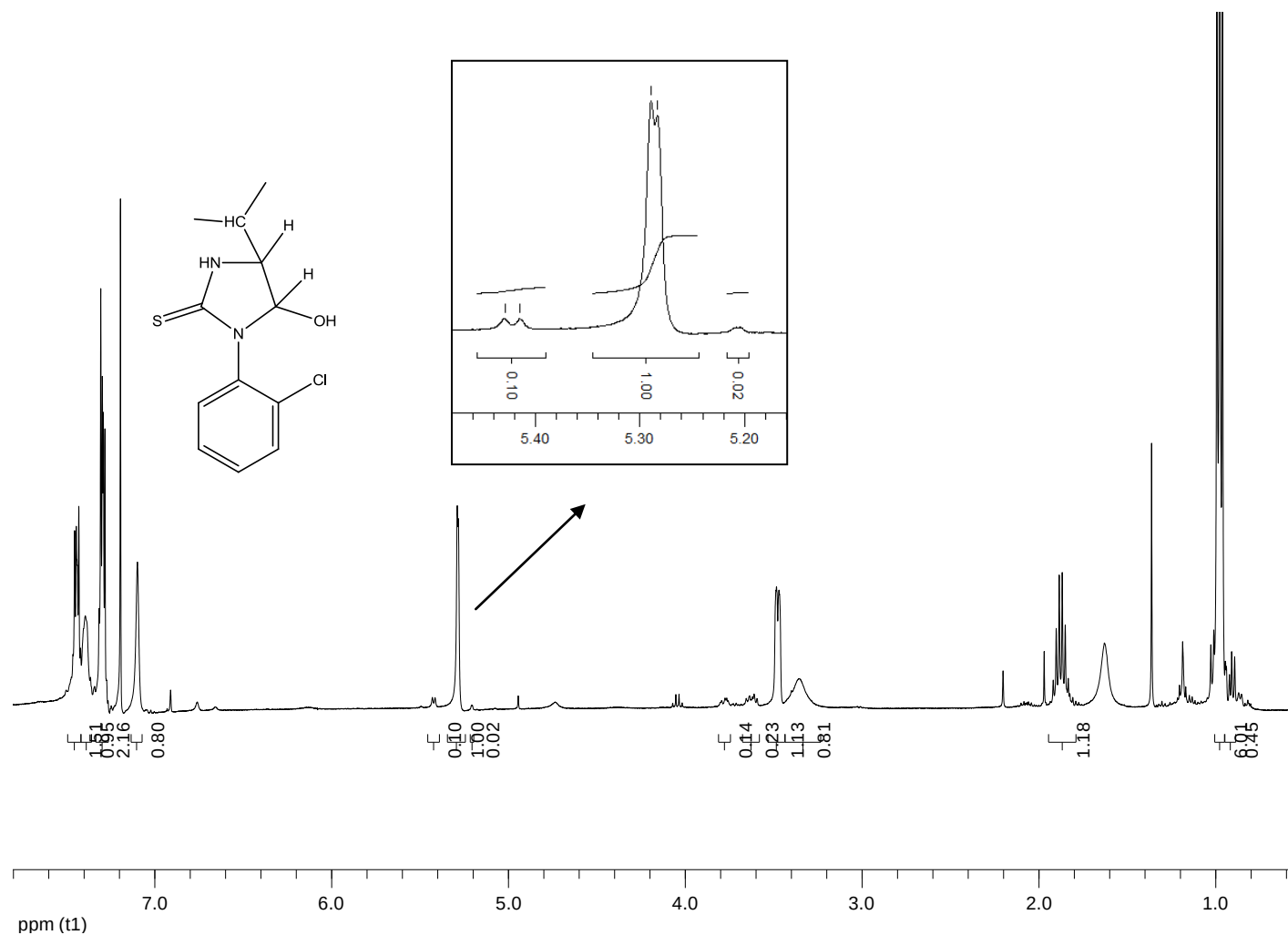


Figure A.106. 400 MHz ^1H NMR of crude 4-hydroxy-5-isopropyl-3-o-chlorophenyl-2-imidazolidinethione (**49**) in CDCl_3 .

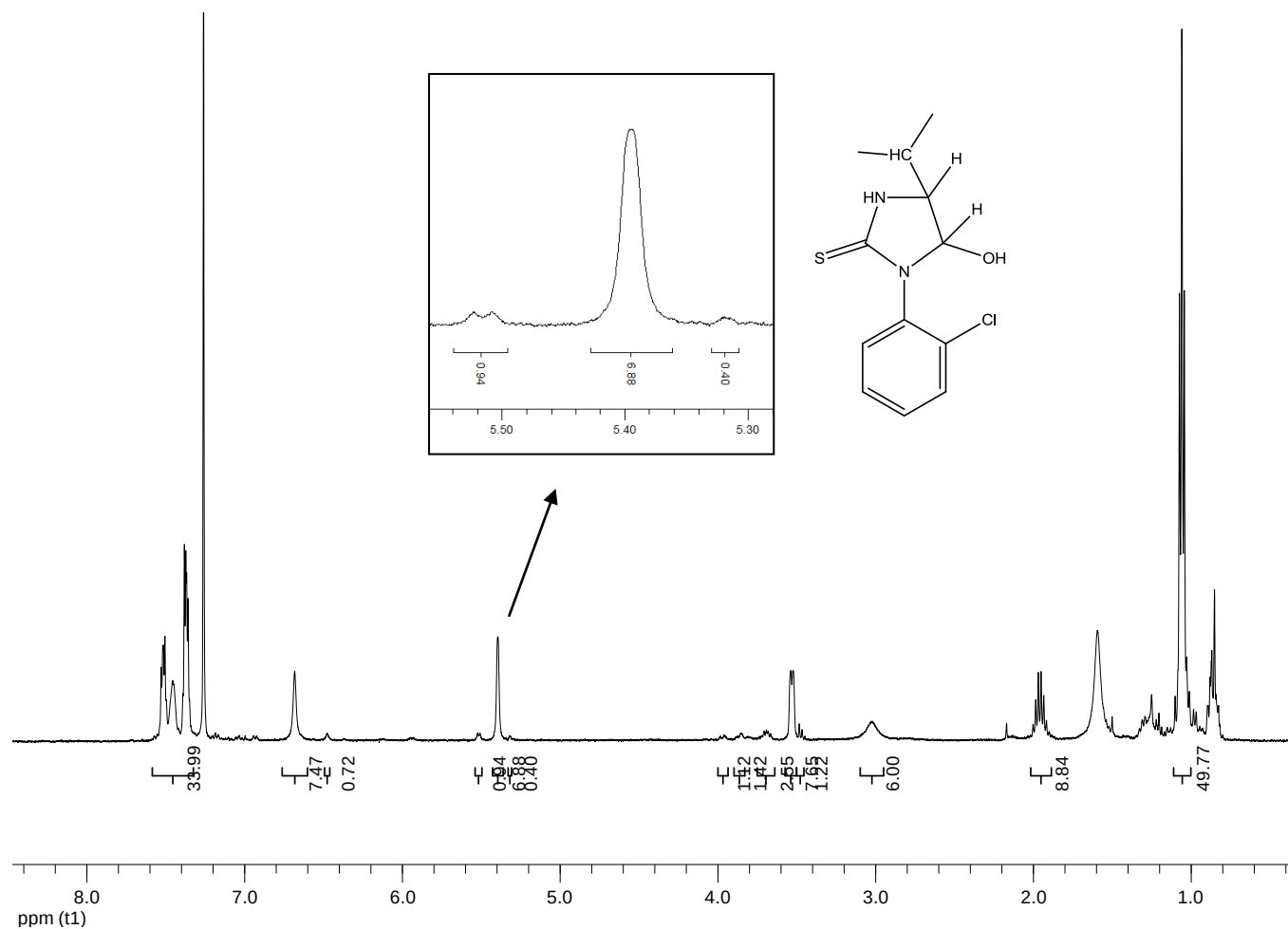


Figure A.107. 400 MHz ^1H NMR of 4-hydroxy-5-isopropyl-3-o-chlorophenyl-2-imidazolidinethione (**49**) in CDCl_3 after purification.

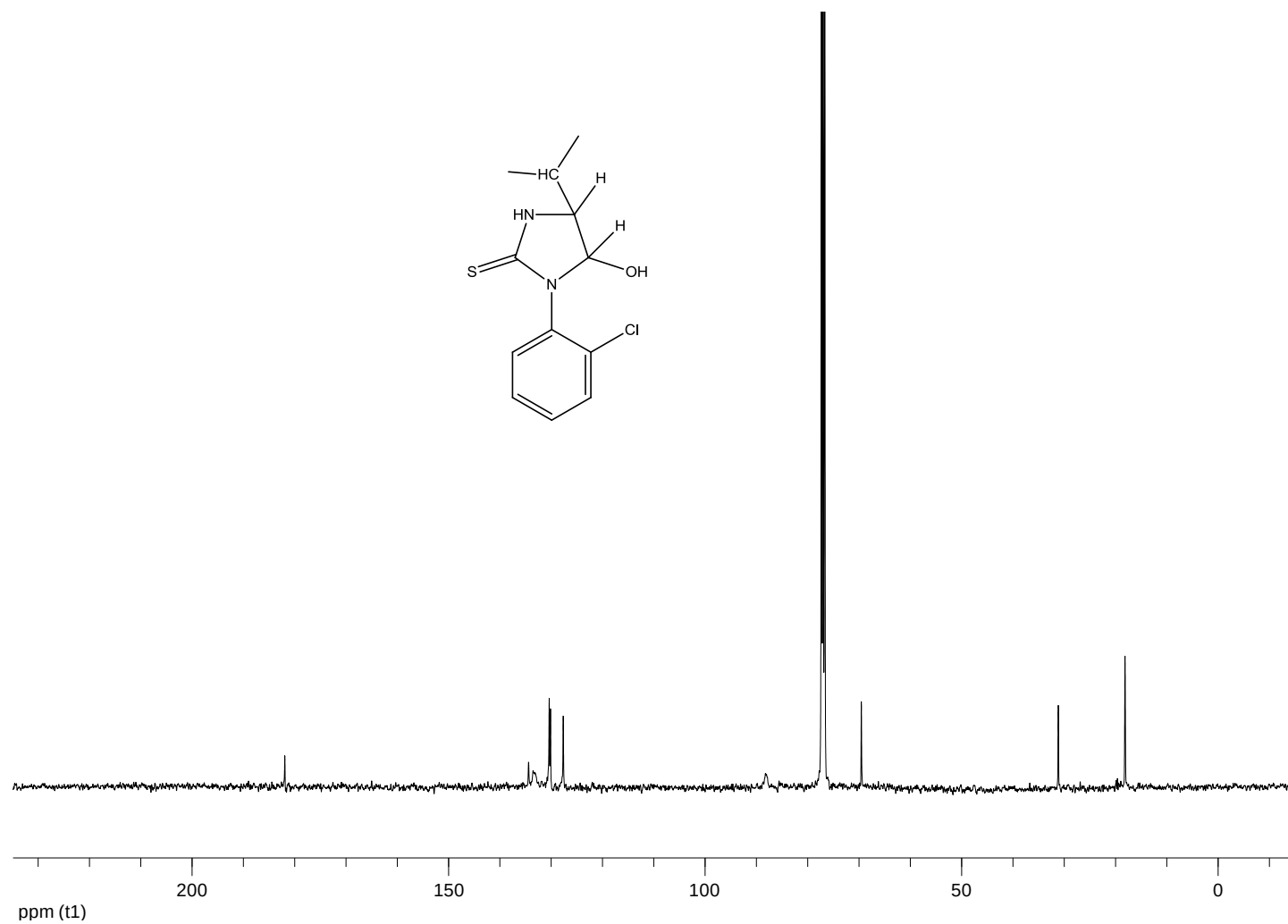


Figure A.108. 100 MHz ¹³C NMR of 4-hydroxy-5-isopropyl-3-o-chlorophenyl-2-imidazolidinethione (**49**) in CDCl₃.

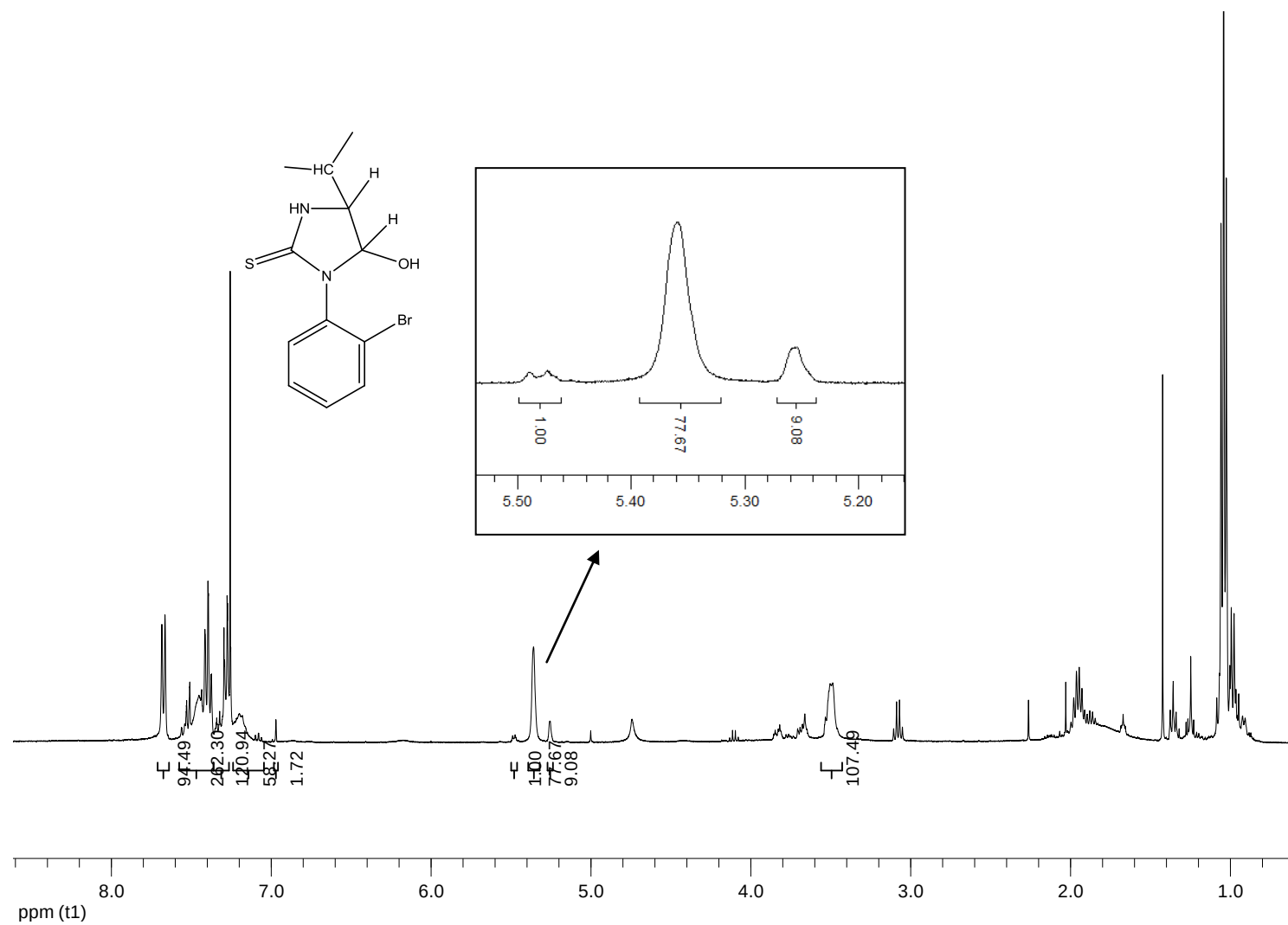


Figure A.109. 400 MHz ¹H NMR of crude 4-hydroxy-5-isopropyl-3-o-bromophenyl-2-imidazolidinethione (**50**) in CDCl₃.

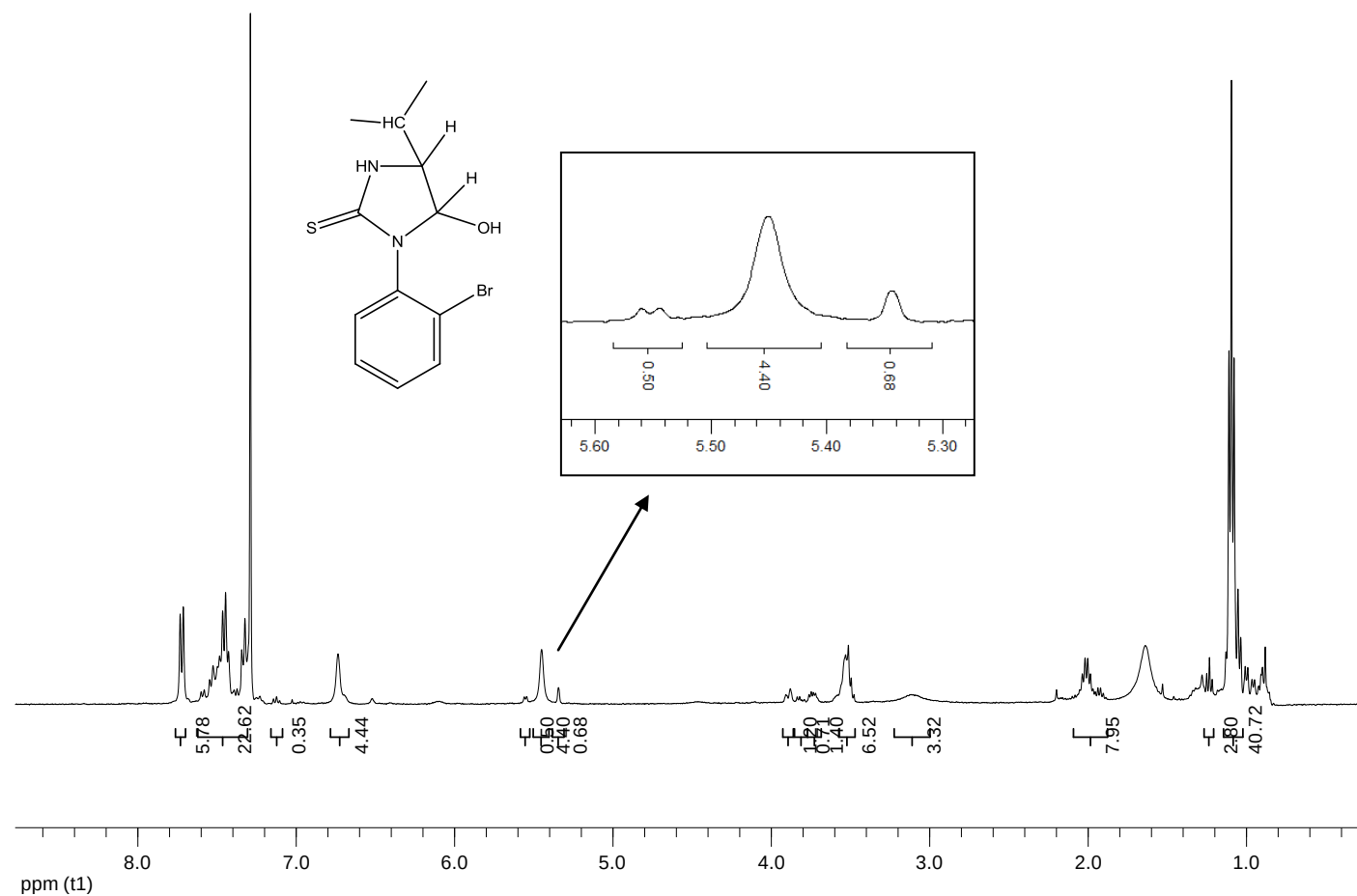


Figure A.110. 400 MHz ¹H NMR of 4-hydroxy-5-isopropyl-3-o-bromophenyl-2-imidazolidinethione (**50**) in CDCl₃ after purification.

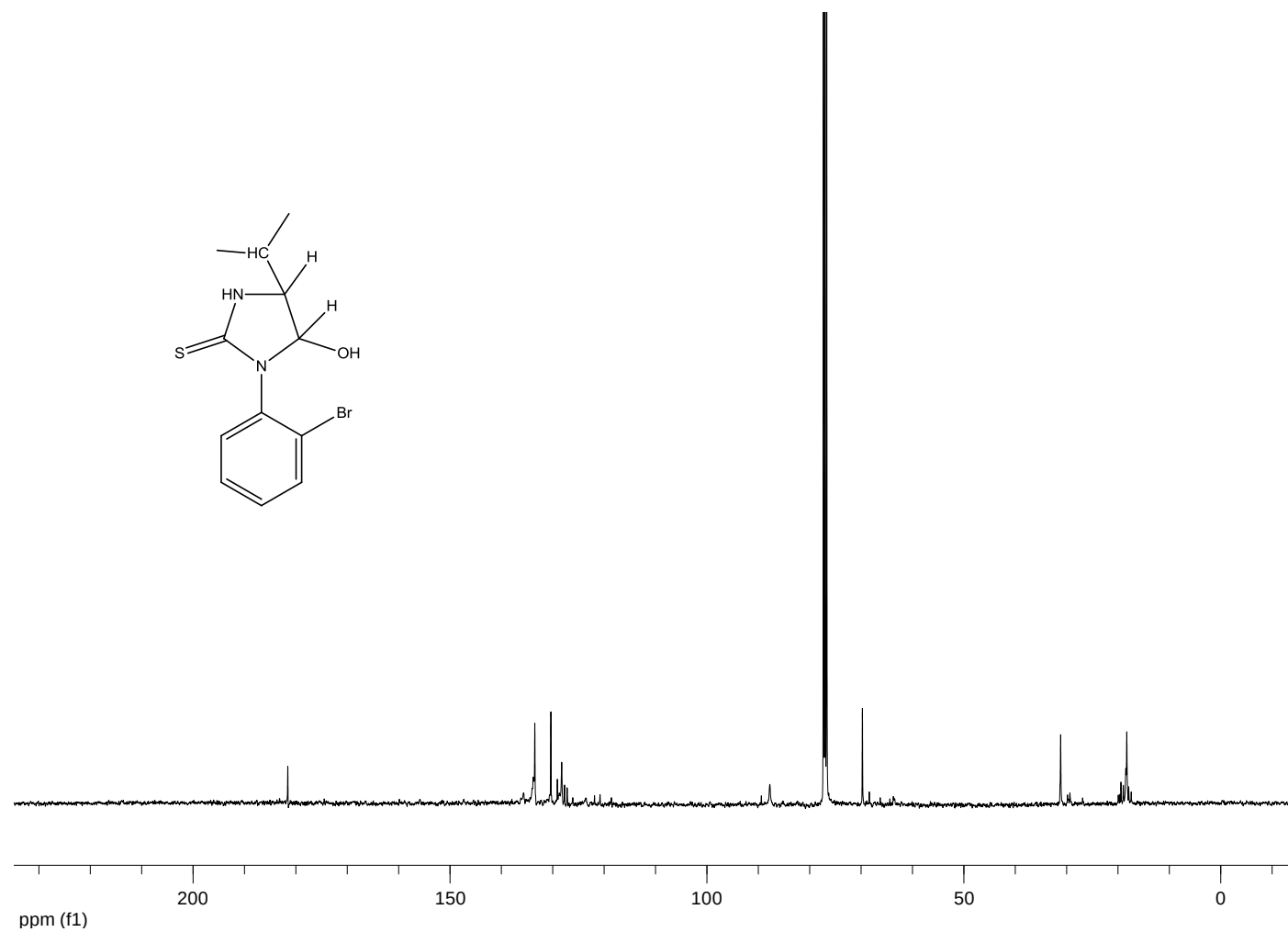


Figure A.111. 100 MHz ^{13}C NMR of 4-hydroxy-5-isopropyl-3-o-bromophenyl-2-imidazolidinethione (**50**) in CDCl_3 .

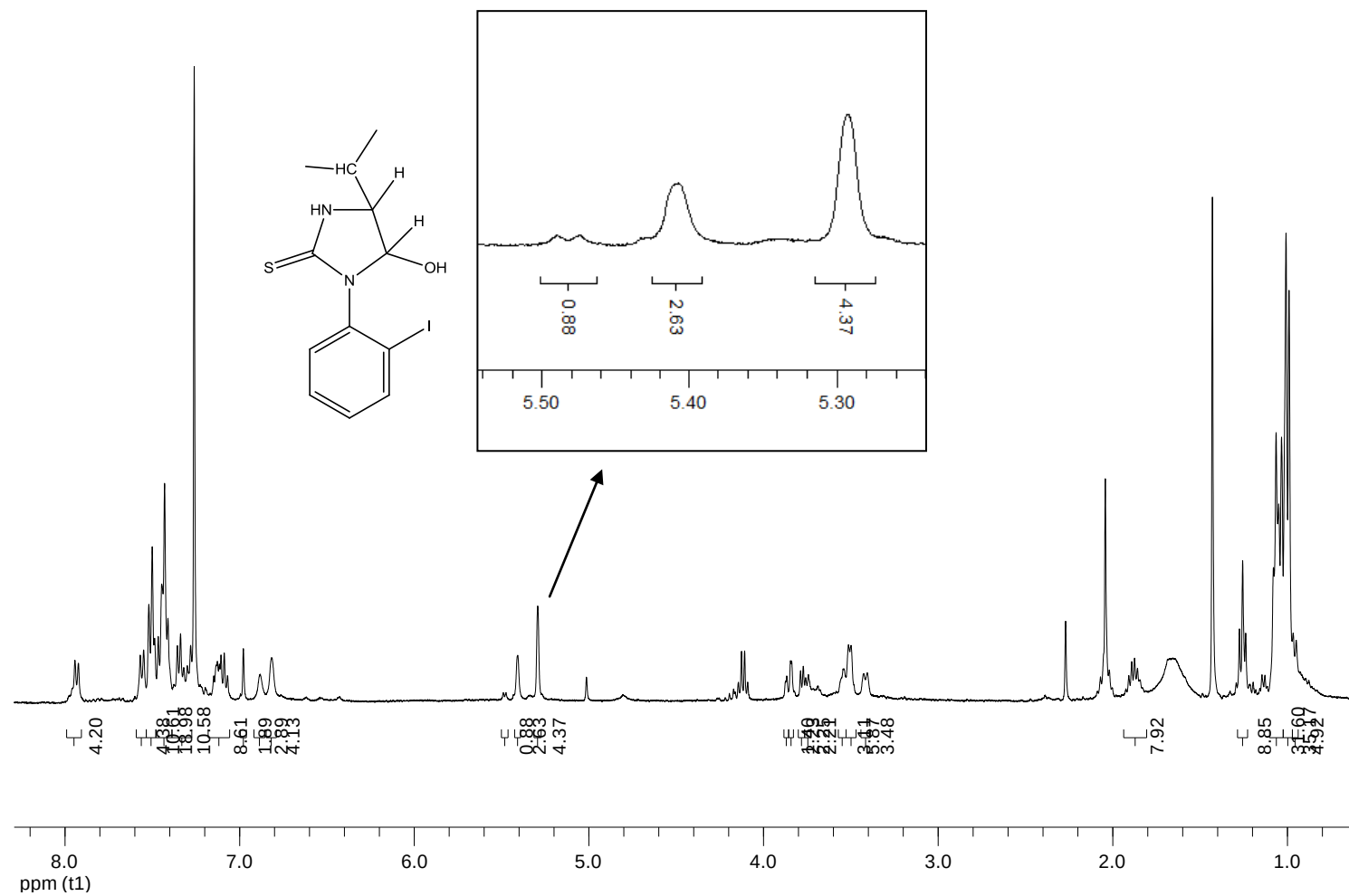


Figure A.112. 400 MHz ¹H NMR of crude 4-hydroxy-5-isopropyl-3-o-iodophenyl-2-imidazolidinethione (**51**) in CDCl₃.

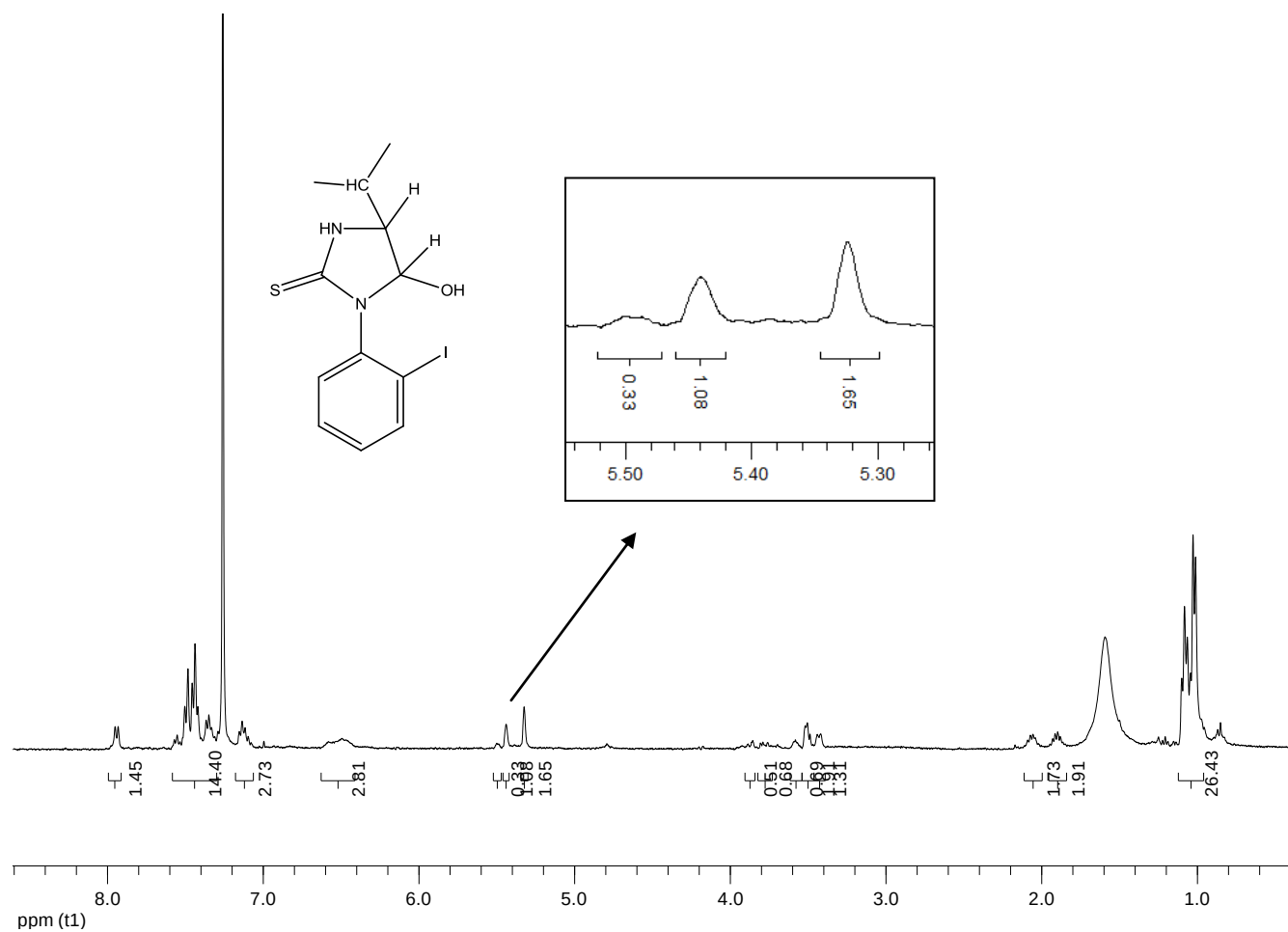


Figure A.113. 400 MHz ¹H NMR of 4-hydroxy-5-isopropyl-3-o-iodophenyl-2-imidazolidinethione (**51**) in CDCl₃ after purification.

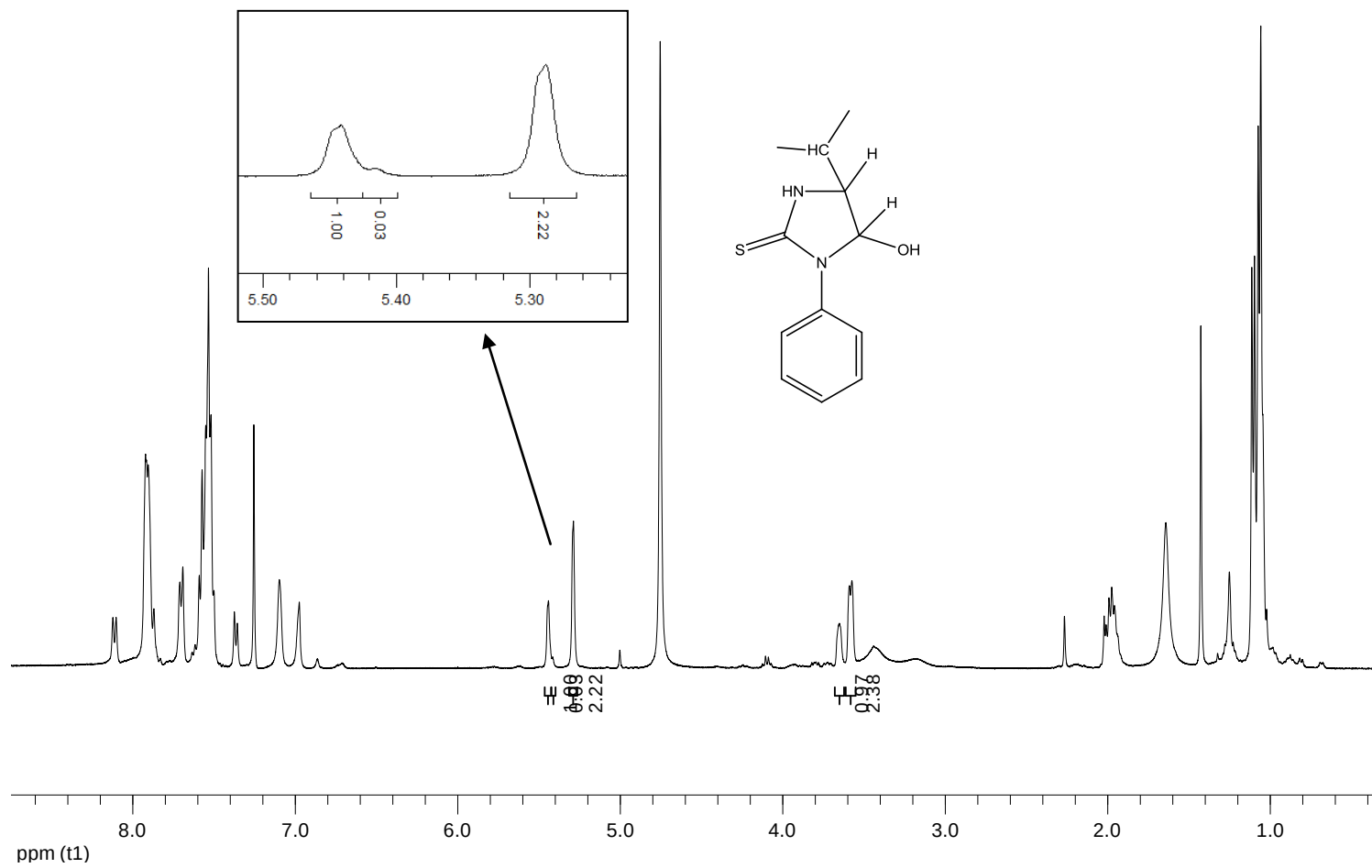


Figure A.114. 400 MHz ^1H NMR of crude 4-hydroxy-5-isopropyl-3- α -naphthyl-2-imidazolidinethione (**52**) in CDCl_3 .

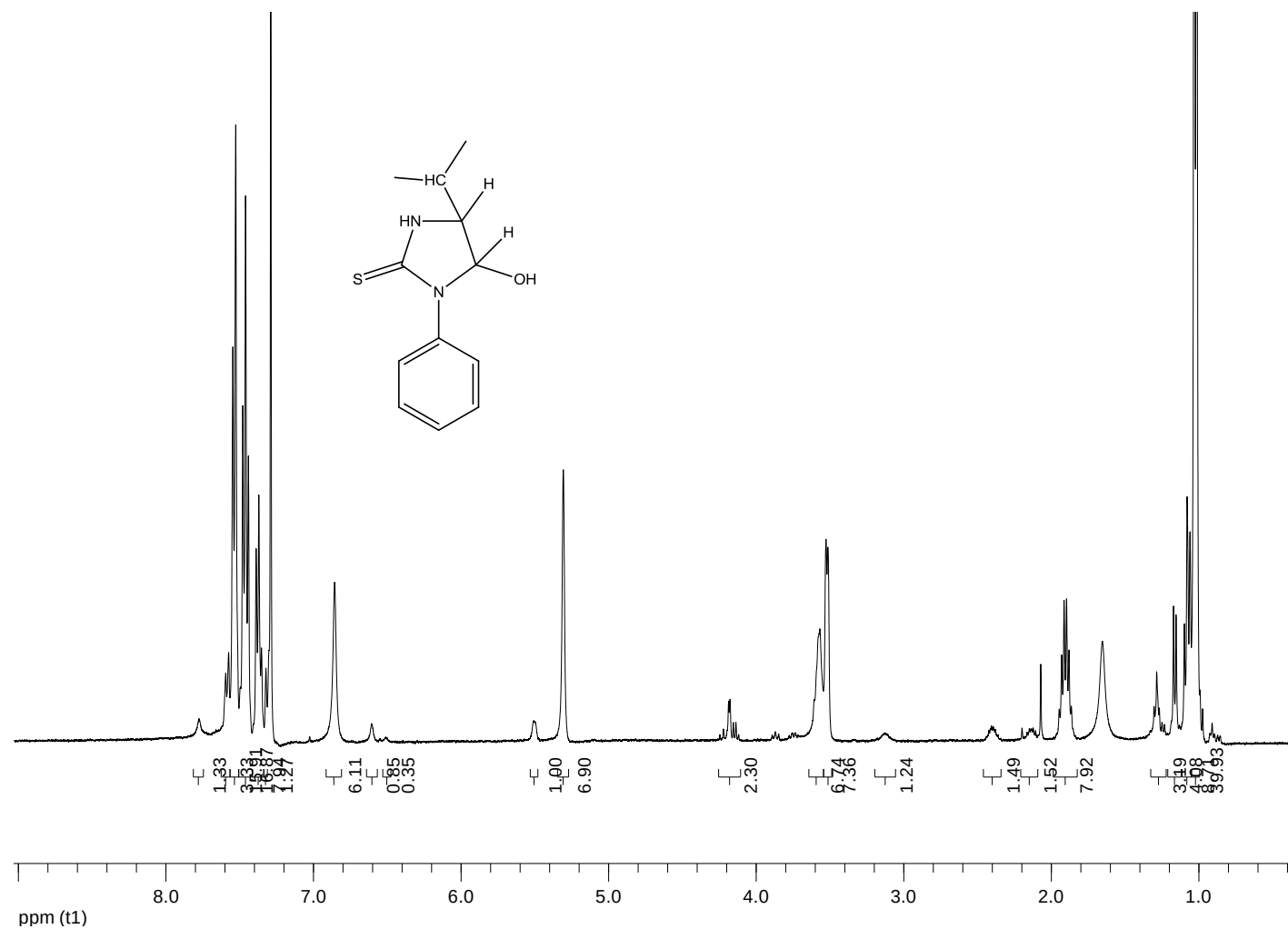


Figure A.115. 400 MHz ¹H NMR of crude 4-hydroxy-5-isopropyl-3-phenyl-2-imidazolidinethione (**53**) in CDCl₃.

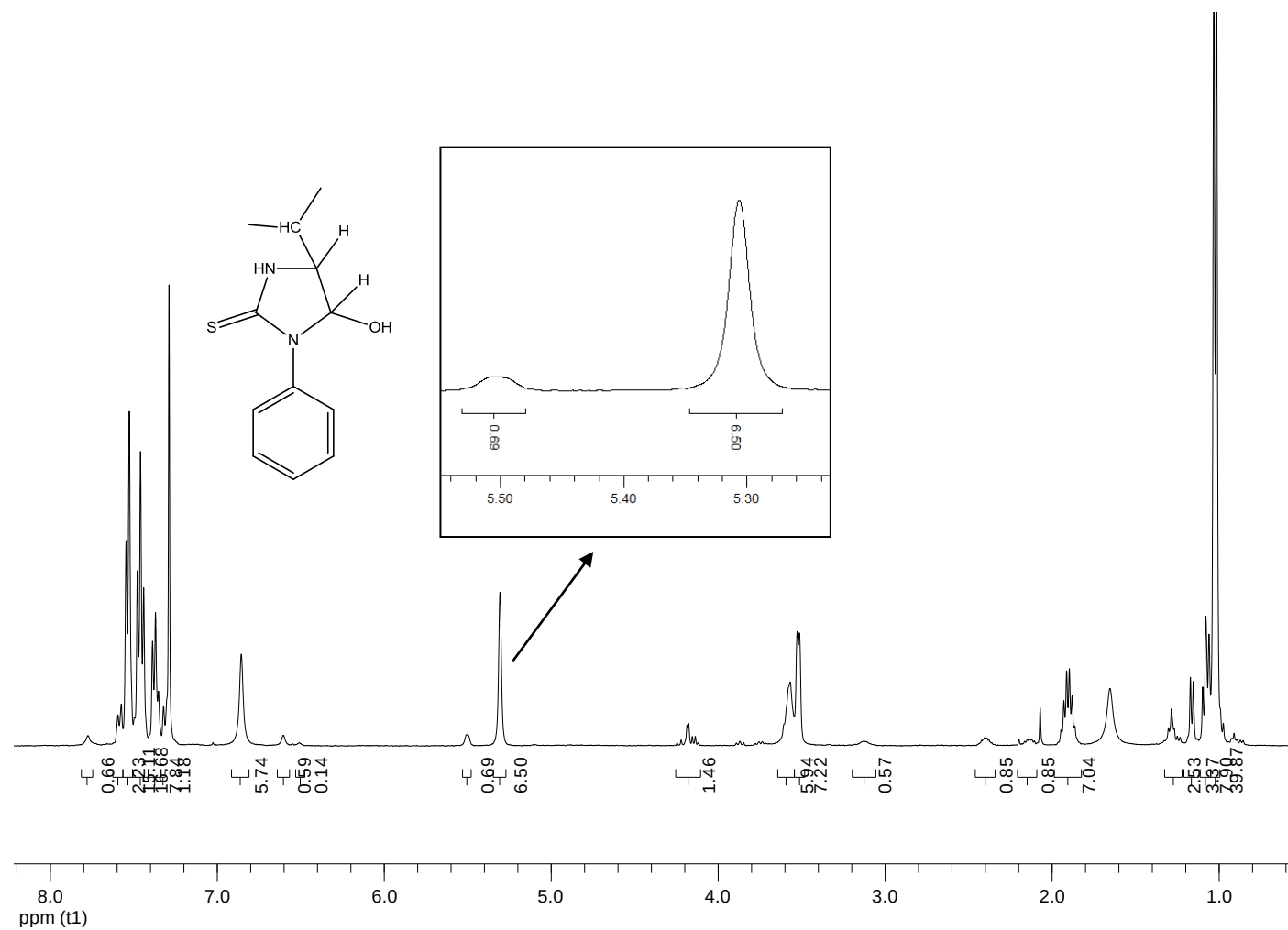


Figure A.116. 400 MHz ¹H NMR of 4-hydroxy-5-isopropyl-3-phenyl-2-imidazolidinethione (**53**) in CDCl₃ after purification.

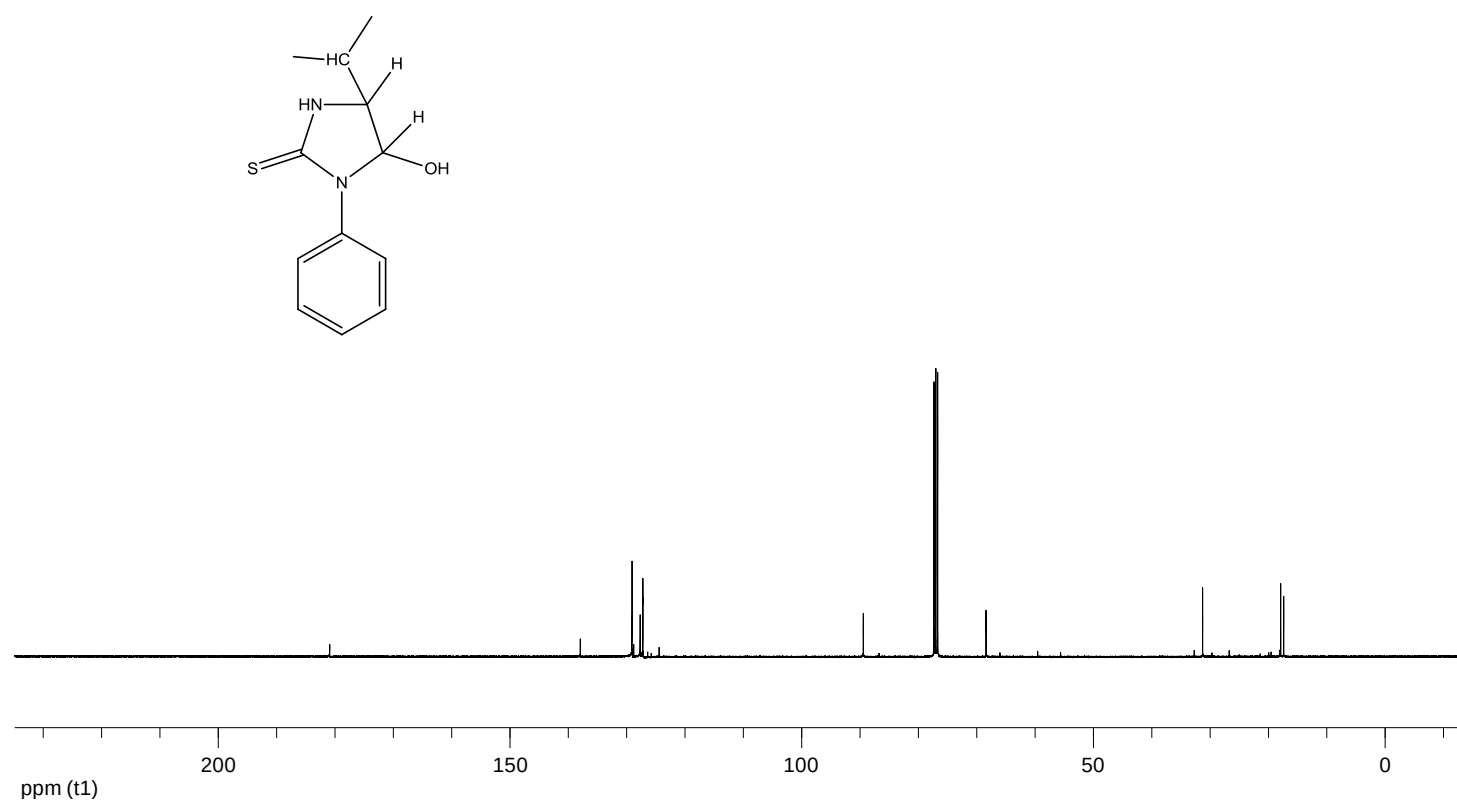


Figure A.117. 100 MHz ¹³C NMR of 4-hydroxy-5-isopropyl-3-phenyl-2-imidazolidinethione (**53**) in CDCl₃.

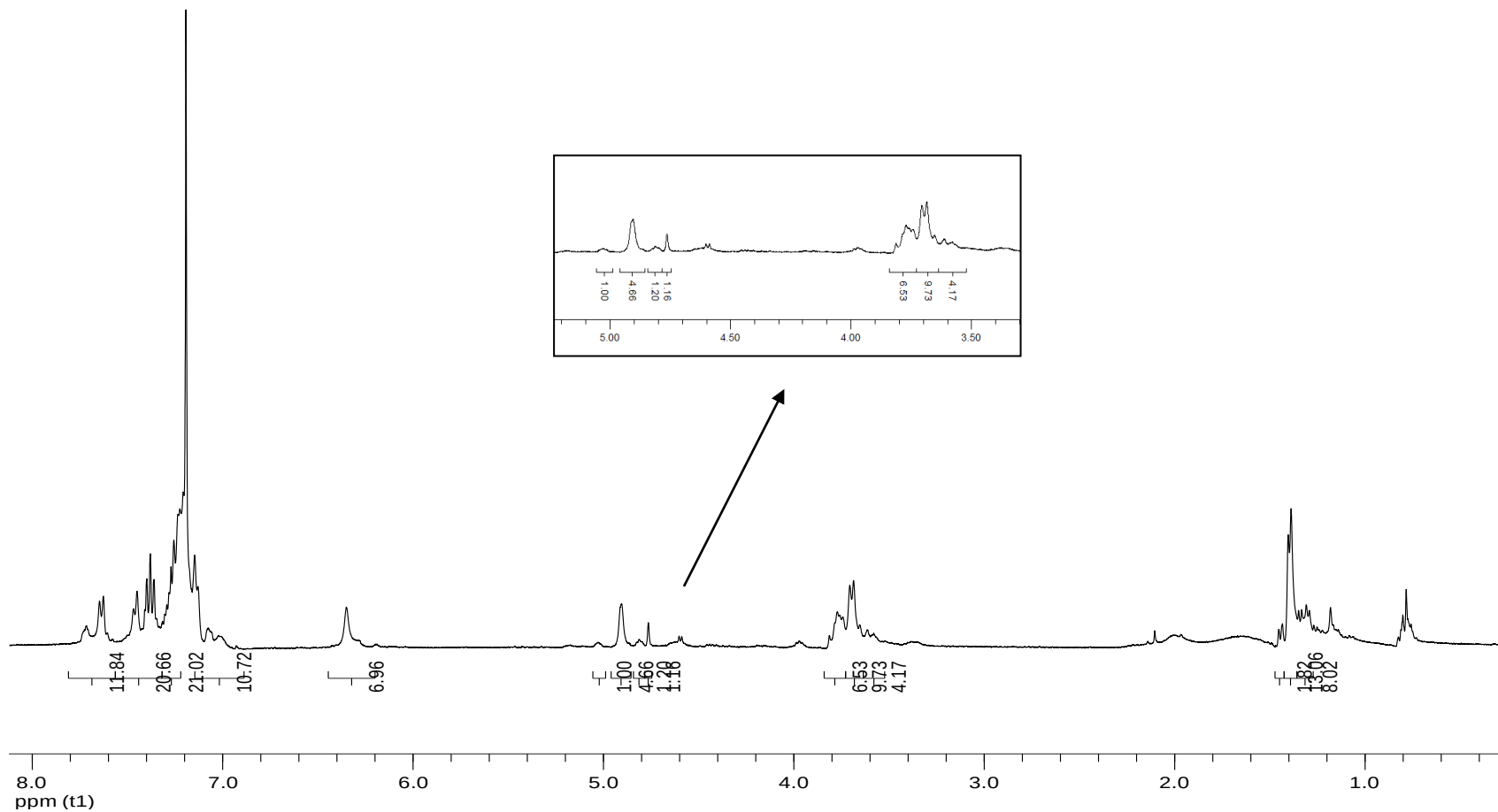


Figure A.118. 400 MHz ^1H NMR spectrum of 4-benzylamine-5-methyl-3-*o*-bromophenyl-2-imidazolidinethione (**54**) in CDCl_3 .