MODIFICATION OF HETEROAROTINOIDS TO ENHANCE THEIR RETINOIC ACID RECEPTOR-BINDING SPECIFICITY AND ANTI-CANCER ACTIVITY

By

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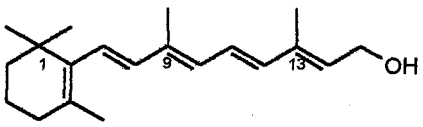
CHAPTER I

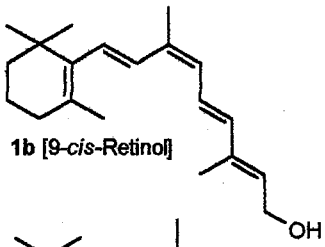
HISTORICAL

Introduction

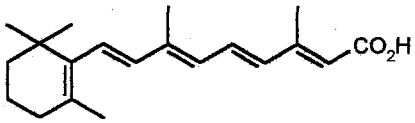
The retinoids are a group of compounds that can be defined as molecules (natural or synthetic) that are structurally similar to retinol (**1a**, vitamin A), 9-*cis*-retinol (**1b**), 11-*cis*-retinol, and 13-*cis*-retinol (see discussion on retinoid metabolism) and can elicit specific biological responses via binding to a specific receptor or set of receptors.[122] A natural retinoid molecule consists of four isoprenoid units [$H_2C{=}C(CH_3)CH{=}CH_2$] joined in a head-to-tail manner and can be divided into three parts, namely a trimethylated cyclohexene ring, a conjugated tetraene side chain, and a polar carboxylic acid end group. All-*trans*-retinoic acid (**2**, *t*-RA), 9-*cis*-retinoic acid (**3**, 9-*c*-RA), 11-*cis*-retinoic acid (**4**, 11-*c*-RA), and 13-*cis*-retinoic acid (**5**, 13-*c*-RA) are some of the examples of naturally occurring retinoids.[122]



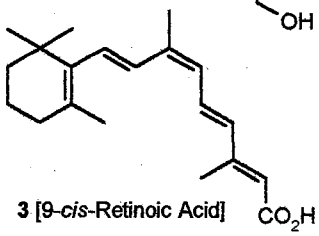
1a [Retinol, Vitamin A]



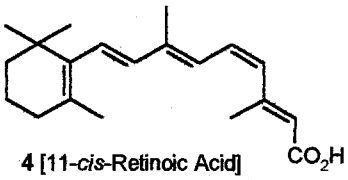
1b [9-*cis*-Retinol]



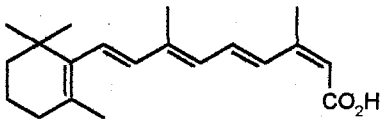
2 [*Trans*-Retinoic Acid]



3 [9-*cis*-Retinoic Acid]



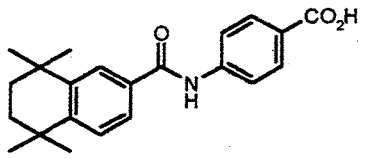
4 [11-*cis*-Retinoic Acid]



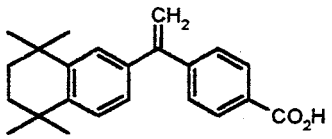
5 [13-*cis*-Retinoic Acid]

Molecular modifications of natural retinoids has led to a wide variety of synthetic retinoids including arotinoids (molecules that have at least one aryl group in their basic structure), such as Am-580 (**6**)[55] and Targretin (**7**, LGD 1069),[12] and heteroarotinoids (molecules with at least one aryl moiety and a heteroatom in a fused ring) such as **8**[9] and **9**.[8] Many others are known.[122]

AROTINOIDS

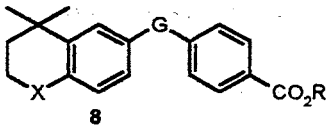


6 [Am 580]



7 [Targretin ™, LGD 1069]

HETEROAROTINOIDS



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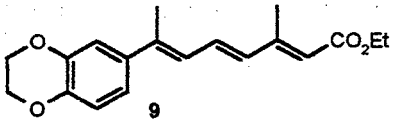

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X = O, S, NR'
R = H, Me, Et
R' = Me, iPr

G = $C(CH_3)$=CH, CO_2, C(O)NH
O_2C, NHC(O), C ≡ C

Experimentally, the role of vitamin A in regulating the epithelial cell differentiation and maintenance was first demonstrated by Wolbach and Howe.[135] They showed that feeding animals a diet deficient in vitamin A resulted in the appearance of hyperkeratinization, squamous metaplasia, and gross tumors in a variety of epithelial tissues in the experimental animals. This process resembled the induction of tumors by certain chemical carcinogens.[45] Since carcinogen-induced metaplasia appeared similar to that resulting from vitamin A deficiency, attempts have been made to study the effects ofretinoids on the inhibition of induction and progression of cancer in various organ tissues

including pancreas, esophagus, lung, stomach, intestine, liver, urinary bladder, nervous system, mammary gland, and skin.[60] Clinically, retinoids are useful for the treatment of skin disorders,[119] in the inhibition of early stages of tumor progression,[136] and are also being investigated in several other therapeutic areas including arthritis,[132] dyslipidimias,[115] and with prevention of HIV-induced lymphopenia.[138] The ability of retinoids to regulate proliferation and differentiation in both normal and malignant cells *in vitro* and *in vivo* presents the opportunity for the use of retinoids in the treatment of a variety disorders.

Nuclear Receptors for Natural and Synthetic Retinoids

The identification of cellular retinol and retinoic acid-binding proteins (CRBP and CRABP, respectively) led to the proposal that such retinoids might represent a specific intracellular receptor system.[85] However, despite extensive biochemical research, no evidence has been presented to establish a decisive role of CRBP and CRABP as direct mediators of retinoid action on transcription.[85] In late 1987, two independent groups were studying the steroid hormone receptors and discovered the novel nuclear receptors for retinoids, that is, retinoic acid receptor (RAR) and retinoid X receptor (RXR).[48,106] This discovery not only offered an opportunity to analyze in detail the structure of the two members of the nuclear receptors but it also provided the necessary tools to study the influence of retinoids on the developmental control of genes and cell differentiation.

Retinoic Acid Receptors (RARs)

The first isoform of the RAR family of nuclear receptors to be discovered was RARα, a polypeptide composed of 462 amino acid residues.[48] However, there was evidence that RARα was not the only nuclear receptor responsible for transduction of the retinoid signal. The discoveries of the several loci present in the human genome related to the

RARα and the family of RARα-related genes, together with a close resemblance of gene product to that of RARα, led to new evidence that another isotype of RAR family receptors existed.[92] The newly discovered, putative receptor has also been shown to respond to retinoic acid and was named RARβ.[5] In 1989, while attempting to clone the mouse homologs of RARα and RARβ, Chambon and colleagues discovered the third isotype of RARs and named it RARγ.[21] In addition to finding three different isotypes of the RAR family, each of the isotypes has different functional isoforms that are distinguished from each other in the number of amino acids that make up the amino terminus domain.[72,81,142] Thus, the RARα isotype has isoforms $RAR\alpha_1$ and $RAR\alpha_2$,[81] RARβ has four isoforms $RAR\beta_1$, $RAR\beta_2$, $RAR\beta_3$, and $RAR\beta_4$,[142] and RARγ isotype has isoforms $RAR\gamma_1$ and $RAR\gamma_2$.[72] Each isoform of the RAR can be divided into five domains:

- ligand-independent-activation function (AF-1) (domain A/B),
- DNA binding domain (DBD) (domain C),
- hinge (domain D),
- ligand binding domain (LBD) (domain E) which incorporates the ligand dependent-activation function (AF-2),
- and the functionally undefined C-terminus (F domain).[33]

The A/B domain, located at the amino terminus of the polypeptide chain, is rich in proline, serine, and threonine which are non-acidic amino acid residues. The A/B domain of RARs belongs to a distinct class of transcriptional regulators.[97] The sequence and number of amino acid residues of the A/B domain vary from one isoform of RAR to another. It is oneof the lowest conserved regions of the receptor (see Figure 1).[33] The central core of the RAR receptor contains the DNA-binding region (domain C), which is responsible for the

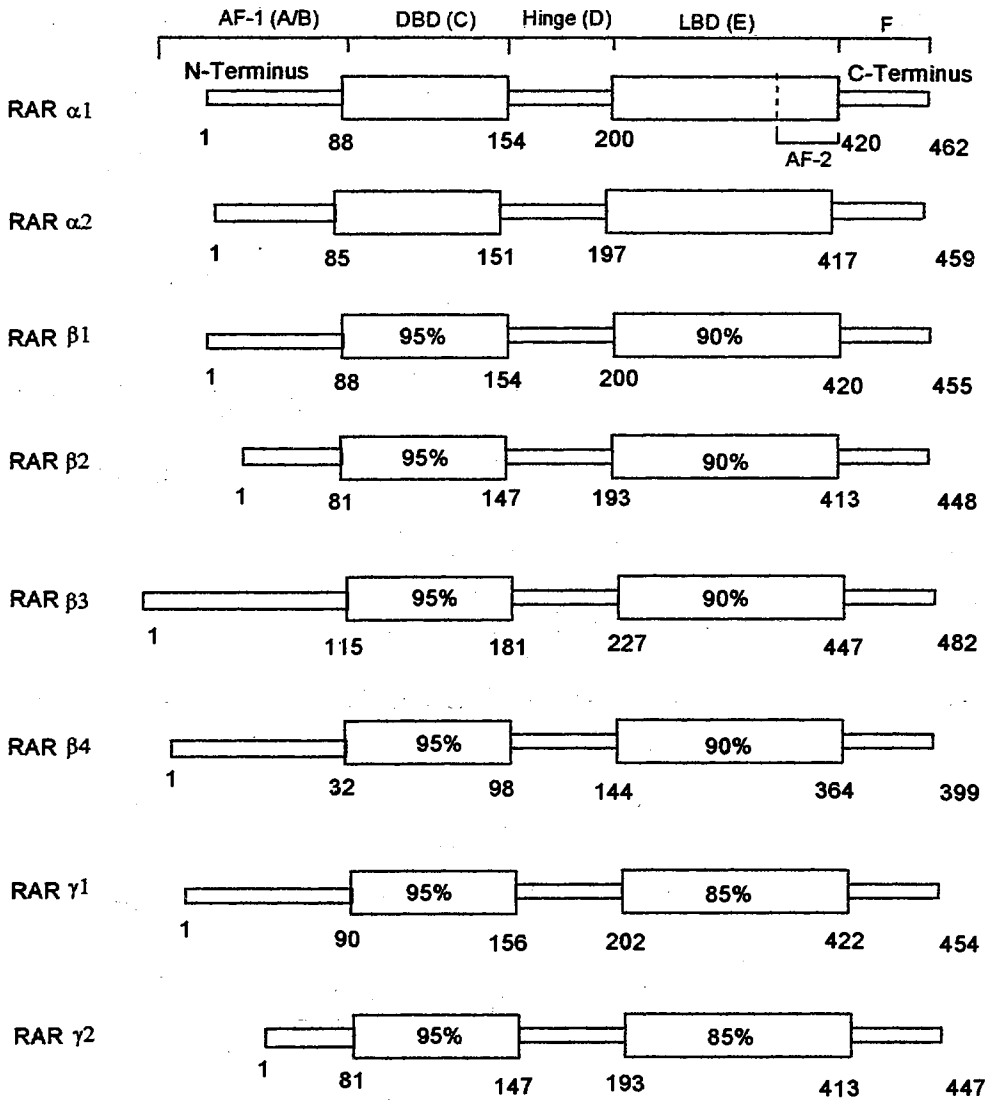


Figure 1. Schematic representation of mouse RAR isoforms. The highly conserved DNA-and ligand-binding domains are represented by large open boxes, and less conserved regions are represented by thin open boxes. The numbers within larger boxes are the percent amino acid identity when compared to RARα. The numbers below the boxes represent domains as well as total length (last number) of the receptor in the terms of amino acid residues.[72,81,142]

recognition of a DNA sequence, the so called hormone response element [HRE, in the case of retinoids is the retinoic acid response element (RARE)].[43] This domain consists of two

motifs known as the 'zinc finger'[32] and the 'zinc twist'(Figure 2).[131] The three amino acid residues, which are different among all isoforms of RAR isotypes, are located at the P-box

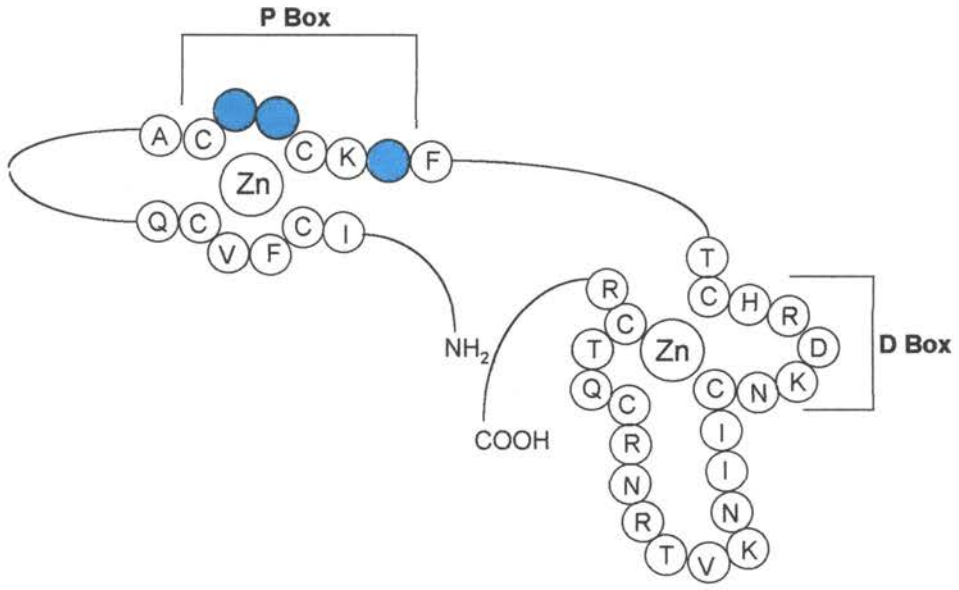


Figure 2. Schematic representation of P-Box and D-Box. The colored circles represent the amino acids responsible for specificity of binding to RARE.[131]

('zinc finger') and are responsible for the recognition and specificity of binding of RAR to the RARE[50] by insertion and making contact within the major groove of the DNA double helix.[128] The D-box ['zinc twist'] is required for the recognition of half-site spacing of RARE[130] and the formation of homo- or heterodimers with another nuclear receptor.[54] The ligand binding domain (LBD) of RAR is complex and fulfills multiple functions.[46] The LBD spans approximately 220 amino acid residues at the C-terminus of the receptor.[33] The degree of similarity of the LBD between RAR isoforms is about 85-95%, which suggests a different affinity for binding of the natural ligands *t*-RA (**2**) and 9-*c*-RA (**3**) to the RAR.

The crystal structure of the human LBD of RARγ_2 bound to *t*-RA (holo-LBD) has been determined by Renaud and co-workers (Figure 3).[14] The LBD is composed of 229 amino acid residues which make up 9 α-helical structures (H1 to H12), two Ω (omega) loops, and two β-sheets. The numbering system was adopted from the crystal structure of apo-RXRα,[15] and the α-helices were numbered according to the resemblance and in comparison to RXRα, but not sequentially. For example, helices H2, H5 and H11 were omitted from the holo-LBD of the RARγ crystallographic structure because their helices do not exist after the receptor is bound to a ligand.[14] The nine α-helices remaining were organized into a three-layered structure with H4, H6, H8, and H9 positioned between H1 and H3 on one side and H7, H10, and H11 on the other.[14]

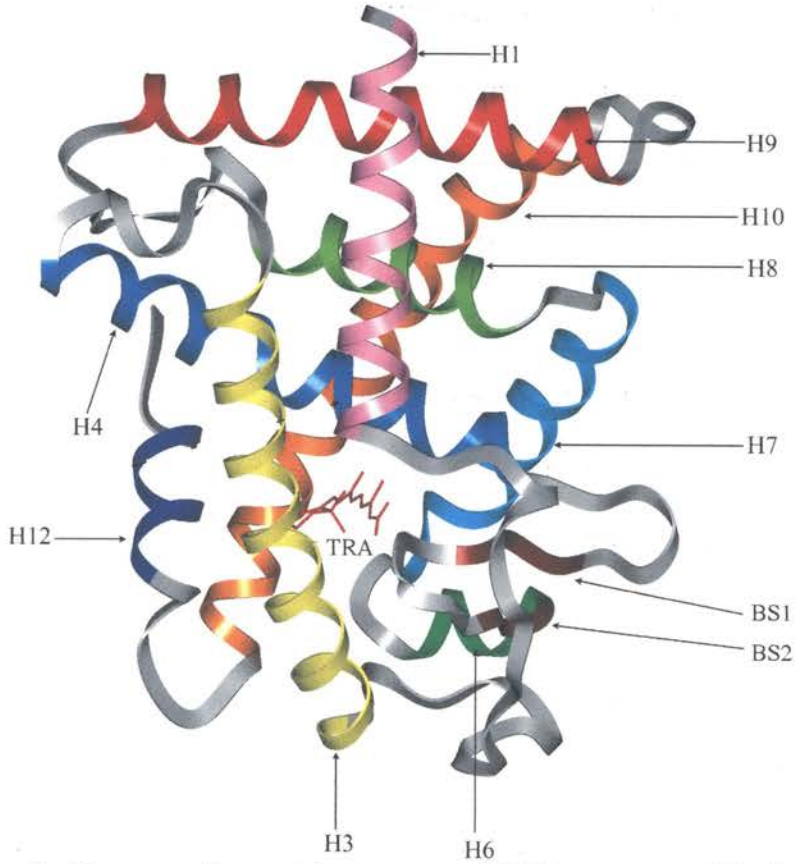


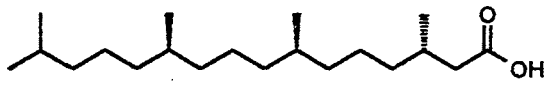
Figure 3. The crystallographic structure of RARγ co-crystallized with *t*-RA [(**2**), TRA].[14]

Two topologically conserved β-strands (BS1 and BS2) form the β-turn inserted between loop 1-3 (connecting H1 and H3) and H3.[14] Twenty four amino acid residues of the LBD, which include Phe 201, Thr 227, Phe 230, Ser 231, Leu 233, Ala 234, Lys 236, Cys 237, Leu271, Met 272, Arg 274, Ile 275, Arg 278, Phe 288, Ser 289, Gly 303, Phe 304, Ala 394, Arg 396, Ala 397, Leu 400, Me t408, Ile 412, and Met 415, make up the ligand-binding pocket (LBP).[14] The ligand-dependent activation-function 2 (AF-2) is located at the carbonyl terminus of the ligand binding domain (α-helix H12).[79] In addition to the two functionally important regions of the LBD (LBP, AF-2), the structural motif spanned by the amino terminus of α-helix H7, the amino terminus of H10, the loop between α-helices H9 and H10, and the carboxyl terminus of H9 provides a dimerization surface for the formation of homo- or heterodimers with other nuclear receptors including vitamin D_3, thyroid hormone receptor, RXR, and others.[35] This dimerization domain has features in common with both the leucine zipper and helix-loop-helix motif which has been proposed as the dimerization structure in other DNA binding proteins.[40]

Retinoic Acid X Receptors (RXR)

The studies of orphan nuclear receptors led to the discovery of a novel retinoic acid-responsive receptor with the same type of domain composition (domains A to F) as RAR and referred to as retinoid X receptor (RXR).[88] The family of RXR consists of three different isotypes, RXRα, RXRβ, and RXRγ, with sequence alignment homologies for DBDs of 92% and 95% and LBDs of 86% and 89% for RXRβ and RXRγ, respectively, as compared to RXRα.[90] Each isotype of the RXR family also has two isoforms, namely RXR$\alpha_{1,2}$, RXR$\beta_{1,2}$, and RXR$\gamma_{1,2}$.[90] Because of the low degree of homologies between RXRα and RARα over the entire length of the protein sequence, 27% for LBDs, and 61% for DBDs

(the highest),[53] it was discovered that 9-*c*-RA (**3**) was a natural activating ligand for the RXR family.[57] However, the 9-*c*-RA (**3**) can also activate RARs with equal potency,[9] which suggests that a more specific RXR ligand may exist. There is some evidence that phytanic acid (**10**) binds to RXRα, promotes the formation of the RXR/RAR response element



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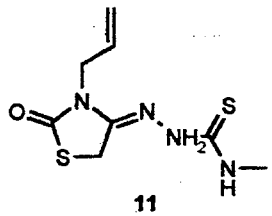

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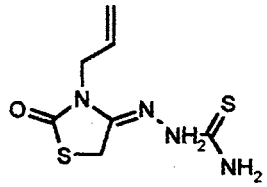

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complex, and induces RXRα conformational changes similar to that induced by 9-*c*-RA (**3**).[80]

The crystallographic structure of the LBD of RXRα (apo-LBD, not ligand bound to LBD-RXRα) has been elucidated by Bourguet and co-workers (Figure 4).[15] The LBD topology of RXRα can best be described as an antiparallel, α-helical sandwich with the dimension of 38 x 74 x 25 Å organized into a three-layered structure.[15] The α-helices H4, H5, H8, H9, and the N-terminus of H11 are sandwiched between H1, H2, and H3 on one side and H6, H7, and H10 on the other.[15] Two short β-strands (BS1 and BS2), forming a β-hairpin, are the only β-structures of the domain.[15] The LBD of RXRα also has a dimerization surface (α-helices H10, H5, and H8), the C-terminal activation domain AF-2 (amino acid residues sequence 450-FLMEMLE-458), and two proposed locations of the ligand binding pocket.[15] The letters in the 450-FLMEMLE-458 represent various amino acids.

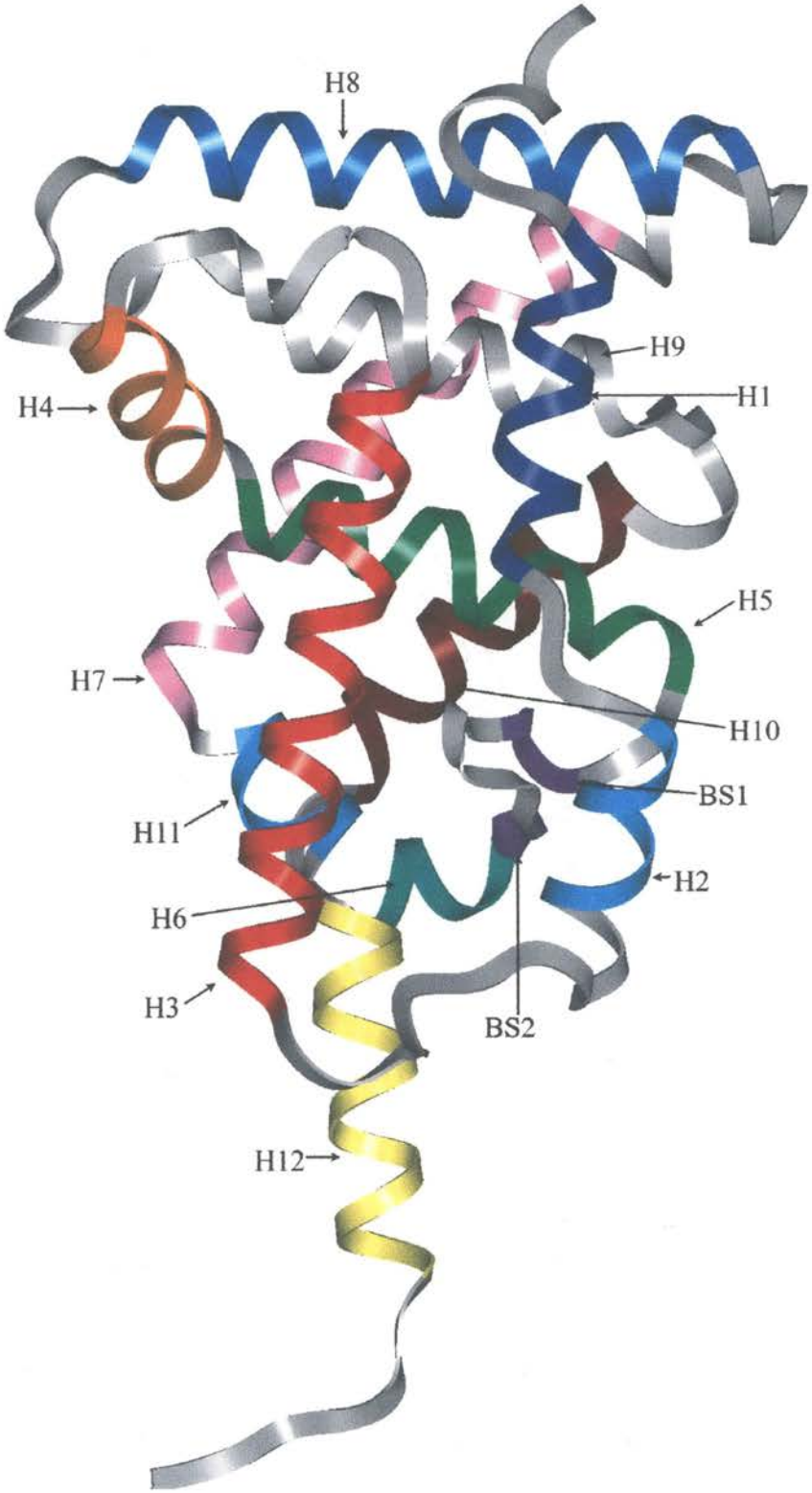


Figure 4. Crystallographic structure of the ligand binding domain (LBD) of RXRα.[15]

Retinoic Acid Z Receptor (RZR)

The RZR, whose name was proposed arbitrarily by its discoverer Carlberg and co-workers,[3] is a member of the orphan receptors and exhibits a highly restricted brain-specific expression pattern.[51] However, no natural ligand to activate this receptor has been identified, and the role and the function of RZR has yet to be determined.[3] Due to a high expression of RZR in the pineal, thalamus, and hypothalamus glands, it has been suggested that RZR is important for physiological and developmental regulation of the central nervous system and for regulation of the circadian rhythm.[4] Melatonin was suggested as a natural ligand for RZR, but more studies are needed to substantiate this claim.[3,51] The thiazolidine diones **11** and **12**, which are synthetic moieties, have proven to be RZR specific ligands and induce potent RZR antiarthritic activity.[96]

Distribution of the Retinoic Acid Receptors in Major Organ Tissues

A broad spectrum of biological activities are effected by retinoids, which suggests that these receptors play a unique role in mammalian development and homeostasis. The RARα isotype is highly concentrated in brain tissue, specifically in the hippocampus and cerebellum, suggesting importance in the development and maintenance of the central nervous system.[92] High levels of RARβ expression genes were found in the kidney, prostate, spinal cord, cerebral cortex, and pituitary gland, with average levels detected in the liver, spleen, uterus, ovary, brain, and testes.[4] The RARγ form was found in high levels in skin,[98] lung, and urogenital tissue,[66] as well as in average levels in cardiovascular tissue.[63] The RXR isoforms are widely distributed and display both unique and combinatorial patterns of regulating transcription.[89] The RXRα is abundant in visceral tissues such as the liver,

spleen, kidney, lung, and muscle.[66] The RXRβ is expressed in various levels in all tissues, and RXRγ predominates in liver, kidney, lung, brain, retina, and adrenal tissues.[61,98,116,118]

Metabolism of Retinoids and the Mechanism of Action for Retinoids and Retinoic Acid Receptors

The retinoids exert a variety of activities on the functions of numerous biological systems (Figure 5).[31] Metabolism of dietary β-carotene or hydrolysis of dietary retinyl esters produces the parent and major circulating, natural occurring retinol which has no known biological activity but rather serves as a parent substrate for the biosynthesis of functional retinoids.[17,18] β-Carotene is metabolized in the small intestine to retinal which then binds to a cellular retinol-binding protein (CRBP), which, in turn, protects the retinal from oxidizing

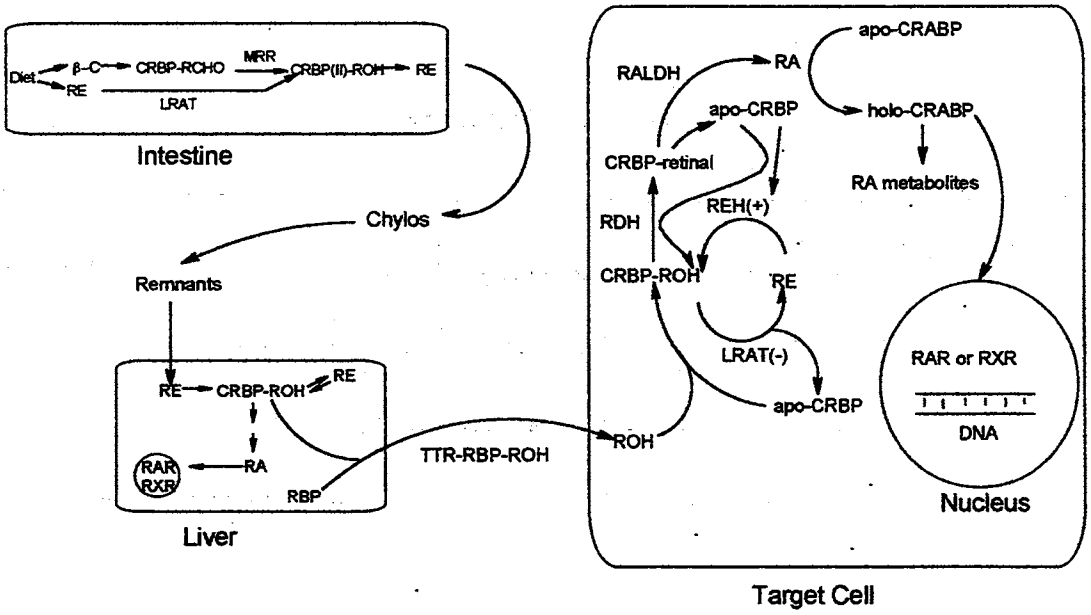


Figure 5. Schematic representation of dietary retinoid metabolism.[2,11,13,65,82,108,109]

to retinoic acid.[65] However, retinal is reduced to retinol by microsomal retinal reductase.[65] Retinol produced from the hydrolysis of retinyl esters also complexes with CRBP and serves

as a reserve for the production of retinyl ester in a reverse reaction catalyzed by the enzyme lecithin:retinol acyltransferase (LRAT).[86] The retinyl esters are then packaged into chylomicrones 22 with triacylglycerides and other fat-soluble vitamins and then are secreted into the lymph system.[11] Triacylglycerides are then removed from the chylomicrones by lipoprotein lipase, and the retinyl esters remain with chylomicrone remnants.[65] The retinyl esters are delivered to hepatic parenchyma cells of the liver where they are stored for future use or hydrolyzed back to retinol.[65] Retinol is then bound to a retinol binding protein (RBP), which protects it from oxidation and isomerization, and is secreted into the plasma where the RBP-ROH further complexes with transthyretin (TTR, a plasma transport protein), thus protecting retinol from degradation in the kidney.[65] Retinol palmitate constitutes 95% of stored retinyl ester in the liver.[122]

The precise mechanism of the uptake of retinol by a target cell is not known, but, there is some evidence for the existence of RBP receptors in the cell membrane.[2] Once inside the cell, retinol is bound by an apo-cellular retinoid-binding protein (apo-CRBP, different from mucosal CRBP II in the small intestine), specific for retinol and retinal only, and a holo-CRBP-retinol complex is formed.[82] The concentration ratio of holo-RBP/apo-RBP controls the conversion of retinol to either retinoic acid or to a cellular retinyl ester via the inhibition of enzymes LRAT by apo-CRBP and the subsequent activation of retinyl ester hydrolase (REH).[13,56] The holo-CRBP also serves as a substrate for microsomal retinol dehydrogenase (RDH) which oxidizes the retinol to retinaldehyde that remains bound to the CRBP, although with lesser affinity.[108] It is assumed that the CRBP also mediates the transfer of retinal from RDH to the retinal dehydrogenase (RALDH) which converts retinal to retinoic acid.[109] The newly formed retinoic acid is then bound with cellular apo-retinoic

acid-binding protein (apo-CRABP), resulting in holo-CRABP, and this complex plays a major role in retinoic acid metabolism and delivery to the nucleus of the cell.[16,103] Retinoic acid is metabolized oxidatively through dehydrogenation resulting in the formation of 4-oxo-retinoic acid or 18-hydroxyretinoic acid, which then undergoes further metabolism.[36] There is no evidence that 9-*cis*-RA (**3**), 11-*cis*-RA (**4**), or 13-*cis*-RA (**5**) are enzymatically isomerized from all-*trans*-retinoic acid,[101] with an exception of a proposal made by Hyaman and co-workers[57] that *t*-RA (**2**) may be isomerized to the 9-*c*-RA (**3**) in certain cells. The 9-*cis*-RA (**3**) originates from dietary 9-*cis* retinol (**1b**) or from the conversion of all-*trans*-retinyl esters, as in the case of 11- and 13-*cis*-retinol.[123]

The isomeric retinoic acids transported to the nucleus dissociate from CRABP and bind to one of the retinoic acid receptors [with *t*-RA (**2**) as the agonist, binding is restricted only to RAR isoforms, and 9-*c*-RA (**3**) as a pan-agonist binds to both RAR and RXR].[20,83] In unbound RARs or RXRs, helix H12 of the LBD points away from the core of the LBD.[14,15] This creates an opening for the retinoic acids to enter the ligand binding pocket (LBP) of the ligand binding domain (LBD).[14] The carboxylic end of the retinoic acids enters first by means of being drawn into the LBP via an electrostatic field gradient induced by basic amino acid residues in the LBP. These acids are then locked in this position through hydrophobic interactions induced by a bend of the α-helix H11 which creates a continuous loop between H10 and H12.[14] Helix H12 then covers and traps the ligand in the LBP by the formation of a salt bridge [CO_2^{-}···H-$N^{+}H_2$] between the glutamic residues of AF-2 (part of H12) and lysine residues in H4.[14] After binding of the ligand (retinoic acid or a synthetic retinoid which have agonistic effects), the receptors, which exist as tetramers[20] in the nucleus in the absence of a ligand, dissociate into monomers. This prompts dramatic conformational changes

throughout the LBD region and directs the receptor toward the formation of homo- or heterodimers via the D-box (located in DBD, Figure 2) and the newly formed dimerization surfaces at the LBD.[14,35,67,95,130] In addition to the dimer formation, the agonist-induced conformational change in the AF-2 domain (carboxyl-terminal of LBD, Figure 1) causes it to bind to and form complexes with transcriptional intermediary factors (TIF) such as estrogen recepter associating protein 160 (ERAP 160),[52] receptor interacting protein 140 (RIP 140),[27] TIF 1,[26,75] unidentified protein profile/thyroid hormone receptor interacting protein 1 (SUG1/TRIP1),[78] and the transcription recognition sequence TATA binding protein (TBP).[117] As a result of the complex formed between AF-2 and TIFs and the conformational change in the receptor, displacement of transcriptional silencing factors such as nuclear co-repressor (N-Cor) [59,101] and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT)[73] in RARs occurs which, in the absence of an agonist, are bound to the hinge region (domain D) of the RAR (not RXR).[24] Retinoic acid receptor homo- or heterodimers are then directed toward the DNA to initiate transcription.[101,123]

The release of the repressors (N-cor, SMRT) from the hinge region not only depends upon binding of the agonist to the RAR member of a heterodimeric pair but also upon the binding polarity of the heterodimer to the DNA (if the RAR occupies the 3' end of the DNA, a repressor is released; if the RAR member of a dimeric pair binds to the 5' side, the repressor remains bound to the RAR).[49] Once the tetramers dissociate into monomers because of retinoid binding, the ligand-independent-transactivation function AF-1 (A/B domain) complexes with transcriptional factors that are specific to the promoter of the target gene.[94] The homo- or heterodimeric pair of receptors binds to the DNA at a specific location of the promoter region named the retinoic acid response element (RARE).[91] RAREs are

nucleotide sequences arranged in direct or inverted polydromic repeats, spaced by one, two, four, or five nucleotides. For instance, a DR2 designation is assigned to direct polydrome repeats (AGGTCA) spaced by 2 nucleotides (AA) such as the DNA sequence AGGTCA(AA) AGGTCA.[59,73] The RAR/RXR heterodimer binds to DR2 and DR5 in such a manner that the RXR is positioned on the 5' end and the RAR on the 3' end of the DNA.[73] The polarity of binding is reversed in the case of association of the RAR/RXR heterodimer with DR1, where the RAR occupies the 5' position and RXR the 3' position.[59,123] The RXR/thyroid hormone receptor (THR) heterodimer recognizes the DR4,[91] and RXR/vitamin D_3 receptor (VD_3R) heterodimer recognizes DR3.[40] The crystallographic structure of the RXR/ THR heterodimer bound to the DNA has been solved (Figure 6).[42,112] The connecting loop of RXRα, made up of basic amino acid residues, runs perpendicular to the DNA, and, together with the basic residues of P-box, makes a series of H-bonds with the negatively charged backbone of the DNA.[42] Furthermore, the attachment of RXR in the major grove of the DNA is strengthen via a salt bridge formed at the dimerization surface which is made up of the THR's aspartate and the RXRα's argenine residues.[42] After binding of the homo- or heterodimeric pair to RARE, the DNA makes a loop and is positioned in such a manner that interaction of the TIFs bound to RAR or RXR, with transcriptional machinery (elements needed for initiation and specification of transcription), located up- and downstream from the TATA box, is possible (Figure 7).[59,73]

One major use of retinoids as potential anticancer agents is in their ability to induce programmed cell death (apoptosis) in malignant cells. The apoptosis of a cell is induced by the binding of an agonist and/or antagonist to the retinoic acid receptor and the receptor

acting through the mechanism as described above (Figure 7 and related description).[59,73,84,91] An antagonist is described as a compound that, after incorporation into the nuclear receptor,

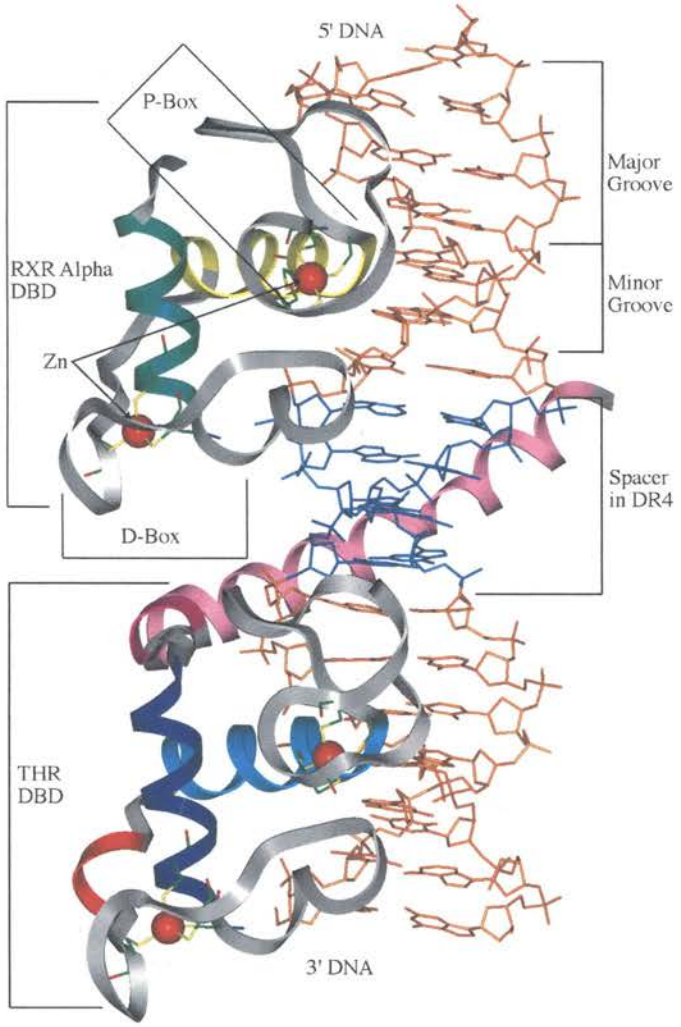
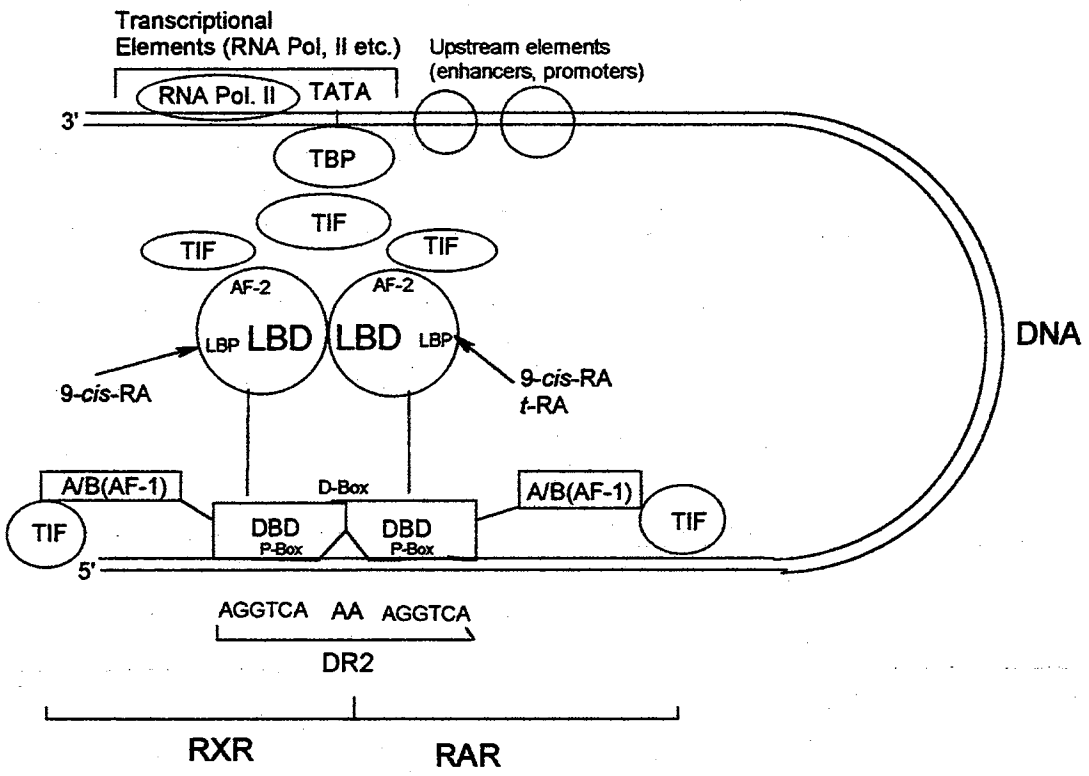


Figure 6. Crystallographic structure of RXR/THR heterodimer DNA binding domains bound to DNA.[42] Each Zn atoms (red balls) is coordinated to four cysteine residues.

abolishes or greatly reduces a basal transcriptional activity.[69] The mechanism for binding an antagonist to the LBP of RAR or RXR, and the subsequent receptor activity after the antagonist is bound, is not well understood. It has been proposed that an antagonist enters the LBP in the same way as an agonist.[47] However, because of structural differences

between the agonist and antagonist, the AF-2 of the LBD is not able to establish the same salt bridgebetween H12 and H4. This situation results in the receptor undergoing a different

Figure 7. Schematic representation of RXR/RAR heterodimer interaction with DNA and transcriptional machinery of DNA.[82,88] After activation of the



receptors by a ligand, the newly-formed heterodimer binds to the promoter region of the gene, located upstream from the TATA box, via DNA binding domains (DBD). Due to loop formation by DNA, the transcription intermediary factors (TIF) bound to the ligand binding domain (LBD) of the heterodimer are able to engage in chemical communication with transcriptional machinery proteins, such as TATA binding protein (TBP), etc. The A/B domain, which also recruits the TIFs, is responsible for specificity of DNA binding and cross-talk with enhancers of transcription.[40,59]

conformational change than the one induced by an agonist.[42] The induced conformational changes by ligands depend upon the structure of the LBP, which in turn means that what is perceived as an antagonist for one isotype of receptor may act as an agonist in another.[42,91]

The differences in conformational changes of the receptors' dimeric pair, induced by antagonist binding, may cause the receptors to be incapable of complex formation with RAREs.[40,91] However, a new antagonist-induced conformation of a receptor can bind the activation protein-1 [(AP-1), c-fos and c-jun genes products], nuclear factor-kappaB [(NF-κB) activator for c-myc, egr-1, LRF-1 cancer genes], and nuclear factor-IL6 (NF-IL6) proteins which are associated with the malignant transformation of cells.[37] The binding of RAR/RXR heterodimer to AP-1, and/or NF-κB, and/or NF-IL6, or binding with transcription intermediary factors, such as cyclic-AMP binding protein (CBP), and competitively displacing these oncogenic proteins, protects DNA from such influence and essentially silences the activity of AP-1, NF-κB, and NF-IL6.[94] Deactivation of the oncogenic proteins (AP-1, NF-κB), or their activity, reverses the action of the transcriptional machinery, and normal cell differentiation, which includes apoptosis induced by the agonist activated nuclear receptor, takes place.[94]

A third avenue by which retinoids can influence the homeostasis of cell is through the action of inverse agonism.[40] An inverse agonist is defined as a compound which, upon binding to the retinoic acid receptor, causes a shift of receptor activity towards that of an active repressor as opposed to an active enhancer of transcription when the receptor is activated by an agonist.[40] The conformational change of the receptor that is induced by the inverse agonist does not displace the co-repressor from the hinge (domain D), and, as a result, the retinoic acid receptor is actively involved in the transcriptional repression of target genes.[42]

In addition to these proposed mechanisms of action for the biological activity of retinoic acid receptors and their heterodimeric partners, RAR and RXR is believed to be

involved in a variety of positive and negative cross-talks mediated by the transcriptional integrator c-AMP binding protein (CBP), RNA polymerase II, and other transcription activating proteins.[25,143]

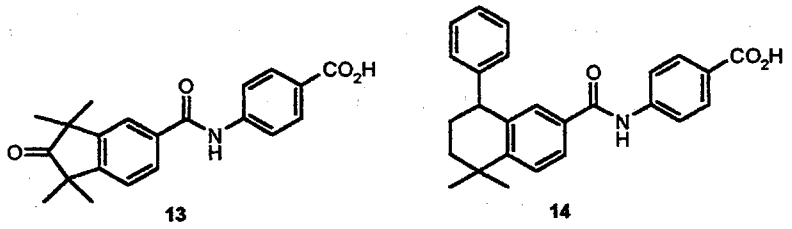
Classification of Synthetic Retinoids Based on Their Biological Effect on Retinoic Acid Receptor

Since the discovery of retinoic acid receptors and because of a high interest in retinoids as potential anticancer agents, many new compounds have been synthesized to gain a better understanding in the nature of biological activity of retinoic acid receptors. Synthetic retinoids can be described according to RAR or RXR biological activity when induced by a retinoid in four ways:

- synthetic retinoids that can act as an agonist or an antagonist,
- retinoids that can exhibit either RAR or RXR selectivity or act as pan-agonists,
- retinoids that can show RARα, RARβ, or RARγ isotype selectivity,
- and some retinoids that can preferentially induce target gene transactivation or AP-1 trans-repression.[47]

The existence of different types of receptors, response elements, and intermediary transcriptional proteins implies that retinoid physiology is mediated not by a single pathway, but by multiple pathways. Non-selective retinoids that can activate multiple pathways are likely to be associated with a high incident of adverse effects, and therefore the design of

new retinoids is aimed at specificity of ligand binding to only one isotype of retinoic acid receptor. These compounds and their agonist/antagonist activities are then separated into two classes of synthetic retinoids–Class I and Class II.[47] Class I retinoids are defined as mono-specific agonistic or antagonistic ligands, like BMS753 (**13**), that act specifically on a given isotype within the retinoic acid family (RAR or RXR families of receptors). Moreover, this Class I group, even at the highest concentration tested, do not bind or only



weakly bind and activate other isotypes within the given family.[47] Class II retinoids, such as BMS411 (**14**), bind with the same or similar affinity to all isotypes of the retinoic acid family (RAR or RXR family) but act as agonists for one isotype within the family and as antagonists for other isotypes.[91]

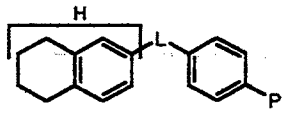
Mutational studies and sequence alignments of the LBDs of RARα, RAR-β, and RAR-γ show that only three residues inside the binding pocket of the LBD are different for each isotype.[14] The alanine 234 (Ala 234) in RARγ corresponds to serine 232 (Ser 232) and alanine 225 (Ala 225) in RARα and -β, respectively.[14] Furthermore, methionine 272 (Met 272) and alanine 397 (Ala 397) in RARγ correspond to isoleucine 270 (Ile 270) and valine 395 (Val 395), respectively, for RARα residues and to isoleucine 263 (Ile 263) and valine 388 (Val 388) for RARβ residues.[14] Therefore, these residues were considered as prime candidates responsible for ligand binding selectivity within the RAR family. This hypothesis

was further supported by mutational studies by Ostrovsky and co-workers.[104] However, the same sequence alignment also pointed to additional differences in the LBD of RAR's, but such may be of lesser importance in ligand binding selectivity. Site-directed mutagenesis of RARα (and RAR*β* and RARγ) strongly suggests that polar amino acid residues, such as arginine and/or lysine, are needed for proper hydrogen bonding or salt-bridge formation between the carboxylic end of the ligand and the receptor.[74]

Due to the conformational adaption of 9-*cis*-RA (**3**) and the spacial arrangement of the RARs' binding pocket, RARs are also able to bind this pan-agonist. However, the activation by 9-*cis*-RA (**3**) of RARγ was less than the activation of this receptor by *t*-RA (**2**), whereas with RARα and RARβ, the activation by 9-*cis*-RA (**3**) equaled or in some cases surpassed the activation by *t*-RA (**2**) of these two receptors.[68] From the crystallographic structures of RARγ [co-crystallized with *t*-RA (**2**) and 9-*cis*-RA(**3**)], it was pointed out that a possible reason for the activity difference is that RARγ binds the 9-*cis*-RA (**3**) less favorably than RARα and RAR*β*, a situation due to the interaction of 9-*cis*-RA (**3**) with amino acid residue Met 272.[47] This interaction of the Met 272 residue with the ligand in RARγ corresponds to an interaction of the 9-*cis*-RA (**3**) with less bulkier residues in RARα (Ile 270) and RAR*β* (Ile 263), which in turn results in a smaller distortion of the "active" conformation of the binding pocket.[47] Mutation of the amino acid residue phenylalanine 230 (Phe 230) by glycine (Phe 230/Gly 230) in RARγ resulted in the inactivation of the receptor.[112] This fact was further substantiated by docking the RARγ specific ligand into the LBP, where, in a ligand-receptor flexible system, the orientation of the phenyl group of Phe 230 did not change. However, in docking a ligand that does not initiate biological activity of the receptor, the orientation of the phenyl group changed by a rotation of

approximately 60 degrees.[9] Therefore, P230, although not important for selectivity of ligand binding, has to be taken into consideration because of its function as a "switch" between activity and inactivity of the receptor and its close 3-D proximity to the Ala 234, and Met 272.[9]

The activation of the RXR family receptors by *t*-RA (**2**) has not been observed.[57] One possible explanation for this phenomenon is that homologues of the Ala 397 (valines in RARα and RARβ) are leucine residues in all RXRs.[57] In RXRs, these leucine residues interact directly with the C(19) methyl group of 9-*cis*-RA (**3**) and, as a result, these bulkier residues restrict the size of the ligand bound to the receptor.[137] Moreover, isoleucine 275 (Ile 275) in the LBP of RARs corresponds to phenylalanine 313 (Phe 313) in RXR, and the orientation of Phe 313 sterically interferes with the binding of the more extended *t*-RA (**2**). This problem is overcome with 9-*cis*-RA (**3**) because it can assume a low energy "curved" conformation.[9] However, in contrast to RARs, the amino acid sequence alignment of the LBD of RXRs does not reveal any major differences within the RXR family subtypes.[137] This fact would suggest potential difficulties in designing specific ligands for RXRα, RXRβ, or RXRγ. If the RAR specific subtype activation stems from the interaction of the whole hydrophobic region of the ligand involving certain amino acid residues in the binding pocket and the simultaneous interaction between the linker of the ligand and the amino acid residues, ligand design should concentrate on an alteration of the hydrophobic region (heterocyclic ring fused to aryl ring) of a ligand. The hydrophilic, polar tail of the ligand



H = Hydrophobic Region
L = Linker
P = Hydrophilic Region (Polar Tail)

should remain intact so as to mimic the property of natural ligands [*t*-RA (**2**) and 9-*cis*-RA (**3**)]. If part of the linker and hydrophilic moiety of a ligand prove to be vulnerable to the activity of isomerases *in vivo* such as, for example, where a trans conformation is easily converted to a *cis* and vice versa, more rigid linkers (e.g. L = aryne or aryl) might be required in the ligand in order to avoid isomerization and to allow P313 in RXRs to exclude the RAR specific ligands from binding. Designs of RAR specific Class I antagonists (having a large group in the hydrophobic region of the molecule) and Class II antagonists (having bulky hydrophobic and acidic moieties) are also feasible.[129] Since agonists and antagonists have different mechanisms of action, co-administration of agonists and antagonists for the treatment of an undesirable condition may have a synergistic effect of value in chemotherapy. The benefit of co-administration of both types of ligands could arise from attack on a cancerous cell via induction of normal cell differentiation (action of agonist), induction of apoptosis (action of agonist and antagonist), and via disrupting the transcriptional machinery of the cancerous cell by competitive deactivation of AP-1 and NF-κB cancer cell messenger proteins (action of antagonist).

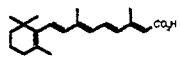
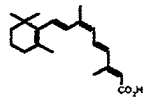
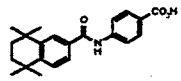
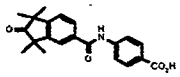
Multiple compounds, which act on a retinoic acid receptor either as an agonist or antagonist with specificity of binding to only one family of receptors or only one isoform, have been synthesized.[122] The Am 580 (**6**, page 2)[10,55] has 70 times higher affinity for binding to RARα than to RARβ or to RARγ. Another highly specific agonist for RARα is BMS 753 (**13**, Table 1).[47] This compound possesses a structural resemblance to compound **6**. BMS 411 (**14**, Table 1)[47] is an interesting compound because it acts as an antagonist for RARα and RARγ, but at the same time has an agonistic effect on RARβ, which would suggest large conformational differences between RARβ and the remaining two isotypes or

perhaps the conformation of the AF-2 region in RARβ's LDB can complex to TIFs without a major change induced by ligand binding.

The compounds LE 135 (**15**)[84] and LE 540 (**16**)[84] have bulky residues which bind to the RARβ with high affinity and are potent AP-1 activity inhibitors (Table I). Amides **17**[129] and **18**[62] have very good activity via inducing differentiation in human promyelotic leukemia cells and in mouse embryonal carcinoma. Arotinoids **19-22**,[10] with locked geometries and additional bulky moieties at the hydrophobic region of the ligand, possess excellent inverse and antagonistic effects and structurally resemble **15** which also possesses similar effects on RARβ and RARγ.

TABLE I

THE COLLECTION OF ENDOGENOUS RETINOIDS, AROTINOIDS, AND HETEROAROTINOIDS THAT EXHIBIT SOME OR TOTAL SPECIFICITY FOR ISOFORMS OF RAR OR RXR.[a]

Compound Structure, Name and Number		Isoform Selectivity						Activity Comments	Ref.
		RAR			RXR				
		α	β	γ	α	β	γ		
	*t*-RA (2)	A	A	A				Natural ligand; binds and transactivates RAR family of receptors only.	122
	9-*c*-RA (3)	A	A	A	A	A	A	Pan-agonist; activates both families of receptors RXR and RAR (slight lower).	122
	Am 580 (4)	A						EC_{50} = 0.36 n*M* in assay where EC_{50} = 2.12 n*M* for *t*-RA (2).	55
	BMS 753 (13)	A						As active as *t*-RA (2) in transcription activity at 10-fold higher concentration.	47

	BMS 411 (14)	T	A	T				The binding affinity to RAR receptors is compatible to *t*-RA (2), activation of transcription in RARβ is the same as in *t*-RA (2).	47
	LE 135 (15)		T					Anti-AP-1 activity in breast cancer cell lines when co-administered with *t*-RA (2).	84
	LE 540 (16)		T					Anti-AP-1 activity in breast cancer cell lines when co-administered with *t*-RA (2).	84
	9 O (17)	A	A	A				Induction differentiation in HL60 and P19 cell lines 83.5%, and 92.5%, respectively, as compared to *t*-RA (2). ED_{50} = 8. 3 n*M*	129
	10 A (18)	A	A	A				Induction differentiation in HL60 and P19 cell lines by 83.5% and 79% , respectively, as compared to *t*-RA (2). ED_{50} = 32 n*M*	62
	AGN 192817 (19)		A	T				Binding IC_{50} = 32 n*M* in an antagonism assay using 10 n*M* *t*-RA (2).	10
	AGN 193840 (20)		A	T				Binding IC_{50} = 32 n*M* in an antagonism assay using 10 n*M* *t*-RA (2).	10
	AGN 193109 (21)			I				Binding IC_{50} = 32 n*M* in an antagonism assay using 10 n*M* *t*-RA (2).	10
	AGN 193385 (22)			I				Binding IC_{50} = 32 n*M* in an antagonism assay using 10 n*M* *t*-RA (2).	10
	GGA (23)	A	A	A				90% upregulation of transcription of RARβ in CAT assay as compared to *t*-RA (2). Much less toxic.	1
	4,5-dd- GGA (24)	A	A	A				100% upregulation of transcription of RARβ in CAT assay as compare to *t*-RA (2). Much less toxic.	1

	UAB 7 (25)			A				At EC_{50} = 2. 5 n*M*, UAB8 is 5% better in preventing mouse skin papiloma than *t*-RA (2) whose EC_{50} = 3. 0 n*M*; Lower toxicity than *t*-RA (2).	99
	]UAB 8 (26)			A				At EC_{50} = 1. 5 n*M*, UAB8 is 5% better in preventing mouse skin papiloma than *t*-RA (2) whose EC_{50} = 3. 0 n*M*; Lower toxicity than *t*-RA (2).	99
	(9Z) UAB 7 (27)				A	A	A	At 1 m*M* concentration, 95% as effective as 9-*c*-RA (3) which is 7 nM in transcription activation, advantage RXR specific, not an pan-agonist.	99
	BMS 961 (28)		A	A				Compatible to *t*-RA (2) in initiation of transcription assay which is at 10-fold higher concentration.	47
	BMS 614 (29)	T						At 1 μ*M* concentration completely antagonizes *t*-RA (2) (10 n*M*) transcriptional activity.	47
	Tazarotine (30)		A	A				In clinical trial to treat skin disorders; highly receptor specific; very low toxicity and high RARγ selectivity.	23
	4 HPR (31)			A				Used in clinical trials in combination with tamoxifen, same transactivation CAT activity as *t*-RA (2)	34
	S1 (32)			A				Stereoselective, at 100 n*M* concentration achieves 90% efficacy in transactivation of transcription as compared to *t*-RA (2) which is 1 m*M*	140
	14 B (33)				A	A	A	Efficacy is over 120% in α and β isotype and 233% in γ isotype of RXR as compared to 9-*c*-RA (3).	58
	I 14 B (34)				T	T	T	Low transactivation activity, but superior inducer of apoptosis 4 times as good as apoptotic activities of 9-*c*-RA (3).	120
	C 3 (35)				A	A	A	Co-transfection activity EC_{50} values are low, total RXR selectivity, EC_{50} compatible to 9-*c*-RA (3).	70

	C15 (36)					A		RXR β selectivity with EC_{50} values is 5 times lower than that for RXR α and RXRγ, although not as good as for 9-*c*-RA (3).	70
	AGN 194574 (37)	T						Low concentration of AGN 194574 are needed to repress the *t*-RA (3) transcriptional activity, competetively displaces *t*-RA from RARα.	127
	SL-I-50 (38)	A	A	A	A			Partial pan-agonist, interestingly the efficacy for RXRβ and RXRγ are low. Excellent repressor of AP-1 activity, and RARE transactivator with low toxicity.	8
	CD 417 (39)		A					EC_{50} = 3.56 m*M* in assay where EC_{50} = 3.62 n*M* for *t*-RA (2)	140
	CD 666 (40)			A				EC_{50} = 1.40 m*M* in assay where EC_{50} = 2.46 n*M* for *t*-RA (2)	140
	SL-I-70 (41)			A				Believed to be RARγ-specific because of it s excellent activity in inhibition of growth in vulvar cancer cell lines	u
	SL-I-72 (42)			A				Believed to be RARγ-specific because of it s excellent activity in inhibition of growth in vulvar cancer cell lines	u

[a]Retinoids and their specificity of binding.
A = agonist, T = antagonist, I = inverse agonist, u = unpublished data. IC_{50} = concentration of the retinoid that is required to displace 50% bound *t*-RA (2) from a receptor; EC_{50} = concentration that is required to induce 50% of maximal retinoic acid receptor activity. Empty blocks indicate no or minimal binding or activation of a receptor by a retinoid. For more details please see recommended references.

Somewhat unusual acyclic and highly flexible retinoids that are very active in the CAT assay (see page 30) are compounds **23** and **24**.[1] These compounds are not bound by CRABP and have very low toxicity toward the environment.[129] Somewhat flexible retinoids, such as **25-27**,[99] mimic the structural features of *t*-RA (2) and 9-*c*-RA (3). However, the

specificity of binding by these compounds is only enhanced marginally whereas **25** and **26** are RARγ specific, and **27** recognizes only the RXR family receptors.

A three-atom linker compound (three atoms between the aryl groups), namely BMS 961 (**28**),[47] proved to be a specific agonist for RARγ and also bound with lesser affinity to RARβ (Table 1). The highly specific RARα antagonistic effects of **29**[47] were accomplished by the presence of a large naphthalene residue in the hydrophobic region of this ligand. Tazarotine (**30**) is a rigid, RARγ and RARβ specific agonist that is currently in clinical trials for the treatment of skin diseases.[23] Compound **31**,[34] whose mechanism of action is not well understood, but appears to bind selectively the RARγ and transactivate it through an agonistic effect, has a 10 atom linker between the hydrophobic moiety and aryl group. This structural feature is in agreement with that found in other RARγ specific ligands whose linker groups between aryl moieties are also longer than that for the ligands that are specific for RARα or RAR*β*.

The stereospecific arotinoid **32**,[140] which has the S configuration at the linker, specifically activates RARγ and to a lesser extent RAR*β*, but not RARα, whereas its R isomer is less active. This would suggest that the molecular geometry of the ligand will enhance the receptor's specificity.

A flourine atom has also been incorporated in the synthesis of flexible compounds, such as **33**, with structures resembling the 9-*c*-RA (**3**), but unlike 9-*c*-RA (**3**), which also binds to the RAR family of receptor, **33** (Table I) is only RXR specific.[58] Heteroarotinoid **34** containing a 5-membered heterocyclic ring did not induce the activation of transcription. However, compound **34** is one of the most potent inducers of apoptosis, perhaps through an

antagonistic effect on the RXR receptors.[120] Compounds **35** and **36**, with C=N systems, are RXR specific, the latter being one of the few compounds that is isotype-specific within the RXR family.[70]

Heteroarotinoid **37**, a complex structure with an amide linker, exhibits high binding affinity for RARα and influences the receptor through the induction of antagonistic activities.[127] Interestingly, heteroarotinoid **38** is a partial agonist, where it induces activity in all of the RAR isoform, but is somewhat selective for the α-isoform in the RXR family.[8] These compounds are reported to have the same transactivation effect on the RAR family of receptors as does *t*-RA (**2**).[34,140] The structural differences of the very recent RARβ specific **39** and RARγ specific **40** are believed to be major contributors to their specificity.[140] Compounds **41** and **42** exhibited excellent inhibition of cancer growth in vulvar cancer cell lines (unpublished data from Dr. Benbrook). Due to a high expression of RARγ in urogenital tissue[66] and an unusually high inhibition of cancer growth, these compounds are believed to express specificity for the RARγ.

Detection and Measurement of Retinoic Acid Receptor Activity

There are several methods for the detection of RAR or RXR ligand-induced activities. One of the most frequently used methods is the use of reporter assay to measure quantitatively the transcriptional activity of RAR, and RXR homo- or heterodimers.[134] The reporter plasmid construct (Figure 8) consists of a reporter gene, such as *lac*Z or luciferase, driven by a minimal promoter containing a TATA motif on RARE.[134] At the 5' end position of the RARE is a silencer (S) which acts to dampen any transcriptional activity originating upstream from the RARE.[134] Additionally, there are several antibiotic selective genes (Ab^r),

restriction sites (RS), and an origin of replication (ORI) to ensure proper analysis of RARE's transcriptional influence on the reporter gene.[134]

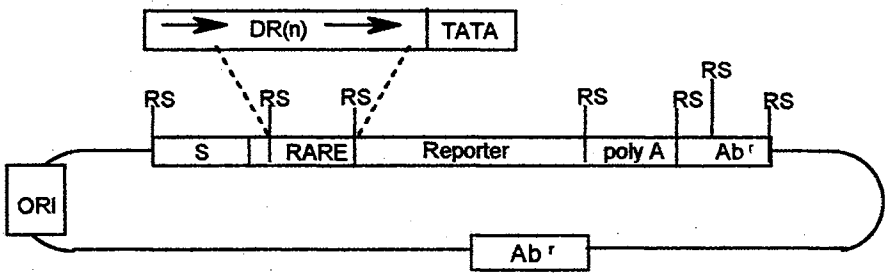
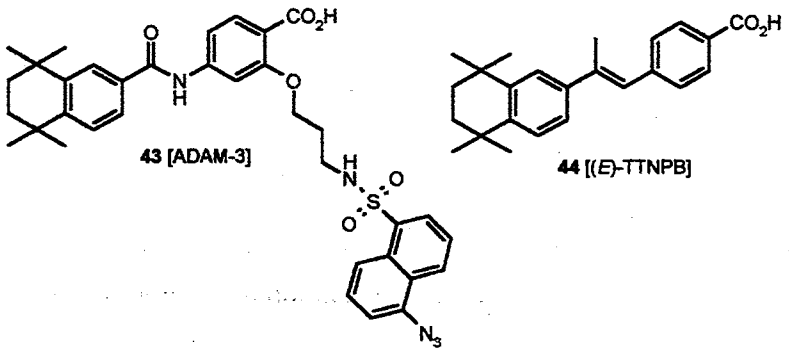


Figure 8. Schematic representation of reporter plasmid for measuring the transcriptional activity of RAR or RXR after activation by a ligand.[134]

A superior and convenient method in investigating the structural features of ligand-receptor complexes is the photoaffinity labeling assay.[134] The sequence of events for the photoaffinity assay are as follows: (1) design and synthesis of an isoform specific,



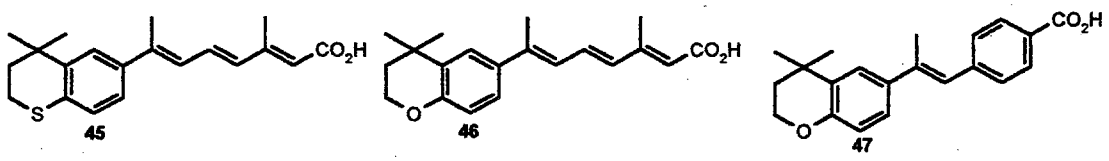
photoreactive ligand, (2) photoaffinity labeling of the receptor, (3) sequential digestion of the labeled receptor by endoproteinases, (4) HPLC separation of digests to determine the amino acid sequence of the labeled site, and (5) mapping of the labeled site for comparison with the known amino acid sequence of the receptor.[134] The compound ADAM-3 (**43**),

which is a photo-labeled derivative of the RARα specific agonist Am 580 (**6**), was successfully utilized in the mapping of the ligand-receptor complex.[134]

Toxicity of Retinoids

Many retinoids are administered primarily for dermatological conditions, such as psoriasis, acne, and disorders of keratinization.[6,124] Toxicity has proven to be a significant problem in the long-term administration of retinoids.[102] The most common, unwanted side-effects from the administration of higher than normal doses of retinoids (hypervitaminosis) are skin desquamation, hyperbilirunemia, transaminase elevation, leupenia, diarrhea, headaches, mucocutaneous toxicity, and hypercalcemia.[114] The synthetic retinoid TTNPB (**44**) is a more potent inducer of RAR transcriptional activity than *t*-RA (**2**) despite the fact that the binding affinity of TTNPB (**44**) to RARs is 10 times lower. However, arotinoid **44** is 1000 times more toxic then *t*-RA (**2**).[107] It has been suggested that the higher activity and toxicity of TTNPB is due to an inability to complex with CRABP.[124] The CRABP regulates the levels of retinoic acid in the cell and its transport to the nucleus where the *t*-RA (**2**) interacts with RARs.[107] Since the concentration of TTNBP (**44**), which can't bind to CRABP, is not regulated and its metabolism is slowed down, TTNBP (**44**) remains in the cell and nucleus for long periods of time and therefore interacts more significantly with RARs. This may well be the major contributing factor for the TTNPB (**44**) teratogenecity.[107] Intriguingly, when RARα specific antagonist AGN 193109 (**21**) was co-administered with TTNBP (**44**) or administered to mice with preexisting toxicity from **44**, **21** was able to accelerate significantly the recovery of the mice from the toxic effects of TTNPB.[124]

Targretin (**7**, page 2) is a RXR specific agonist and has an organic composition and structure which only slightly differs from TTNPB, but is much less toxic then TTNPB (**44**).[70]



Another possible avenue for decreasing the toxicological effect of retinoids is the utility of heteroarotinoids which are comparable in receptor activation to that activation induced by natural retinoids.[6] Nearly full toxicity studies of heteroarotinoids **45, 46,** and **47** revealed that the maximum tolerated dose (MTD) was 34 mg/kg/day, 32 mg/kg/day, and 9.4 mg/kg/day, respectively.[6] These data compared to the MTD of *t*-RA (**2**), which is 10 mg/kg/day, shows reduced toxicity of **45** and **46**. Therefore **45** and **46** are 3-fold less toxic than *t*-RA (**2**) and 3000-fold less toxic than TTNPB (**44**) whose MTD is 0.01mg/kg/day.[6] Design and synthesis of isoform-specific arotinoids or heteroarotinoids can also significantly decrease the unwanted side effect of retinoic acid receptors.[23]

Molecular Modeling of Retinoids

Molecular modeling is a useful tool for the investigation of structure-activity relationships (SAR) in a variety of proteins-ligands complexes. Unfortunately, with exception of unrelated modeling work to our type of research, not much molecular modeling in the field of retinoid research has been done.[39] Only in a recently published work by Gronemeyer and colleagues was consideration given to a study of SAR via docking of synthetic arotinoids into RAR isotypes in combination with mutagenic studies of the receptors.[47] The data from docking of synthetic arotinoids were in agreement with the

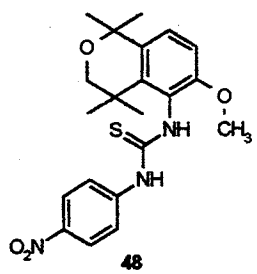
biological data, where the specificity of binding was dependent only on a few residues. The computer-aided analysis was based on the existence of the LBD crystallographic structure of human holo-RARγ co-crystallized with *t*-RA (**2**). The LBP of RARγ was prepared for modification by extraction of **2** to obtain apo-RARγ LBP.[14] The apo-RARγ was then modified by computer-aided mutagenesis to obtain the LBPs for RARα and RARβ. The use of QUANTA/CHARMS, a module in a molecular modeling software package from Molecular Simulation Inc. (MSI),[30] was utilized, and the amino acid residues of the LBP in RARγ that are responsible for selectivity were substituted with homologous amino acids of RARα and RARβ (see Experimental for details).[47] The computer-aided mutation allowed for creation of the new LBP of RARα and RARβ with different amino acid composition which essentially translates to different shapes of the hydrophobic surface of the binding pockets of the receptors which resulted in new interaction property (energy of interaction, positioning of in the LBP) with the ligand. Conformational searches and evaluations of the selected arotinoids provided conformations of various energies which was done before the ligands were docked into the LBPs of RAR isotypes. The interaction energy values and visual inspection of docked ligands in the LBPs provided a possible explanation as to how the ligand might interact with the receptors. These data could then serve as valuable tools for the future design of RAR isotype-specific retinoids.

CHAPTER II

RESULTS AND DISCUSSION

RAR and RXR Isotype Specific Heteroarotinoids

The work addressed in this thesis had two central themes, namely the synthesis of several receptor-specific, or projected receptor-specific, heteroarotinoids and the development of a computer assisted analysis of the heteroarotinoids as a ligand in binding to a specific receptor. The new compounds **48-68** which were prepared are listed below.



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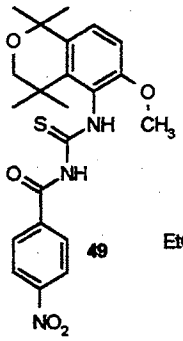

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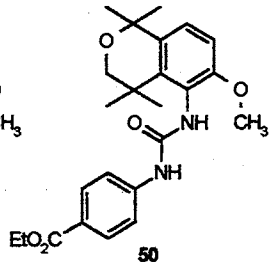

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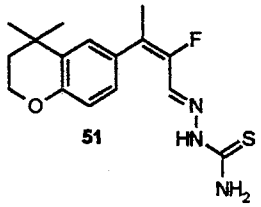

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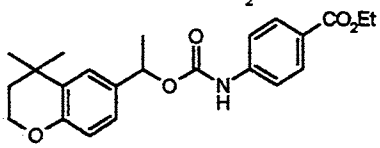

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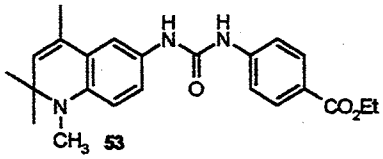

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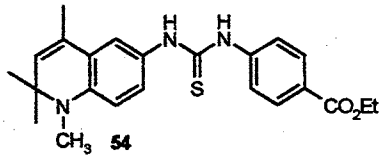

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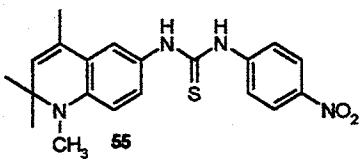

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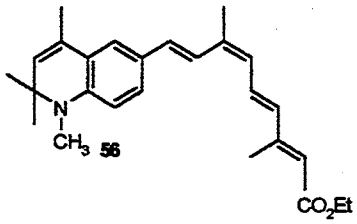

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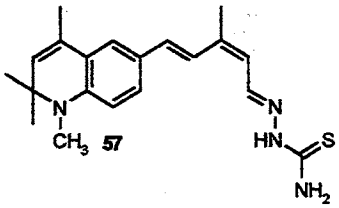

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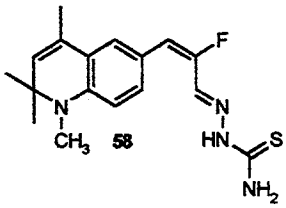

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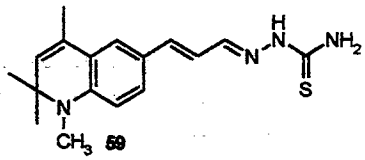
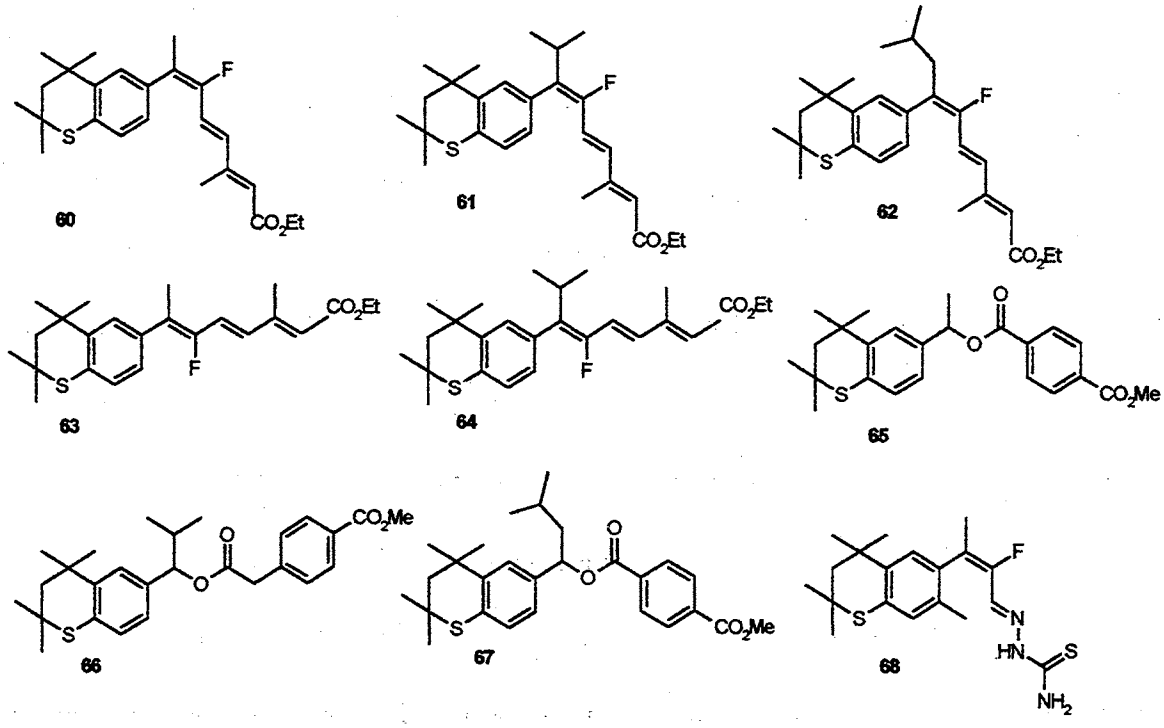


59

An approach to determine the suitability of a heteroarotinoid as a ligand to bind with the retinoic acid receptor was developed using several commercial programs and the computer in the Department of Biochemistry. Such programs addressed the following situations with respect to creating a "fixed" and "flexible" binding pocket in the receptor as well as a "fixed" and "flexible" ligand such as a heteroarotinoid. These programs were as follows along with their particular function in the analysis: The Molecular Simulation Inc. (MSI)[30] molecular modeling software package and its program modules were used in drawing and optimizing the conformations of compounds (Builder, MOPAC and Conformational Search Engine) and modification of the LBD of RARγ crystallographic structure (Biopolymer). The Sybyl 6.5[126] molecular modeling package, which has modules QSAR with Comfa, Flexidock, and Superimposition, were used in predicting the activity, docking, and analysis of resulting ligand and receptor conformations, respectively.

The goal of the research was to synthesize a number of heteroarotinoids to be RAR isotype (RARα, RARβ, or RARγ) or RXR isotype specific. The structure-activity investigation of previously prepared compounds in our laboratory, via the aid of computer modeling programs described later in this chapter and biological data published by us and other research groups, served as guide in designing heteroarotinoids **48-68**. The ligand binding domain (LBD) of the crystallographic structure of RARγ bound to *t*-RA (**2**) also provided a means for further exploration of the ligand-receptor interaction via docking of the ligands into the ligand binding pocket (LBP) of the receptor. Based on the type of heteroatom contained in the fused ring system, heteroarotinoids **48-68** were divided into three groups:

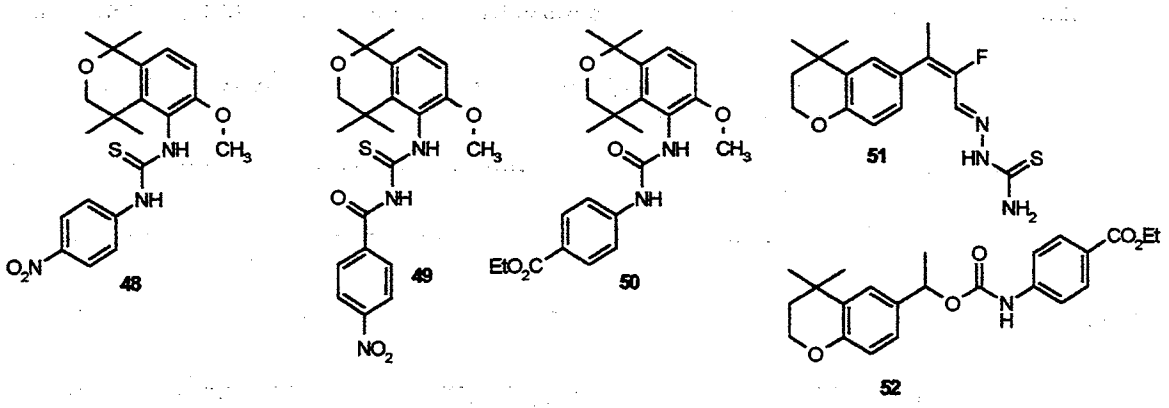


- oxygen heteroarotinoids, compounds **48-52**,
- nitrogen heteroarotinoids, **53-59**, and
- sulfur heteroarotinoids, **60-68**.

Oxygen Heteroarotinoids

Oxygen heteroarotinoids **48-50**, where oxygen is part of the isochroman ring and the linker group is placed at the C5 position of the hydrophobic aryl moiety (which is different from previously made retinoids) were synthesized to map the hydrophobic region of the ligand binding pocket. Furthermore the methoxy group at the C6 position was added to the enhance the bulk of the ligands in the hydrophobic region and to alter the bond rotational barrier of the linker group. The unusual nature of the linker group, with respect to the hydrophobic aryl moieties, was expected to reduce binding to the RAR family of receptors, and thus, the compounds might be RXR family specific. The other assumption was that if

the ligand was drawn into the binding pocket of RARγ, via an electrostatic attraction of its anionic tail to the basic residues, such as arginine 278 (R278) and arginine 274 (R274) in the LBP, to form hydrogen bonds, the hydrophobic bulk of the ligand would prevent the receptor from trapping the ligand through a conformational change of α-helix H12, which could ultimately lead to antagonistic activity of the RAR receptors. The results from the docking of these compounds by rendering them as flexible molecules (the ligand was allowed three degrees of freedom to translate within the LBP, and possessed free rotation around single bonds with restrained dihedral angles being altered) into the LBP of RARγ being rendered as "fixed ," with the exception of **48**, suggest that these compounds might not be RARγ active due to the unfavorable energies of interaction (see Experimental).



However, heteroarotinoid **48** interacted favorably with the receptor's binding site without any significant steric hindrance. Compound **49**, which differs from **48** in that the linker is extended by one carbonyl moiety, did *not* dock favorably. Sufficiently strong H-bonds formed by the nitro group of **49** with basic residues of the LBP, the extra atom in the linker, and the limiting space in the LBP resulted in repulsive energies between the region of the amino acids that make up α-helix H12 and the hydrophobic region of the ligand. After

deleting α-helix H12 from the LBD of the crystallographic structure of the RARγ, **49** interacted favorably with the receptor. This would suggest that **49** may express its influence on the receptor in the form of antagonistic activities.[47] Compound **50**, which has a urea linker and a carboxylic ester at the polar end, instead of a thiourea linker and a nitro group, respectively (as compared to **48**), did not exhibit the same binding property as heteroarotinoid **48** when docked in the RARγ LBP (for details, see discussion on pages 46-51).

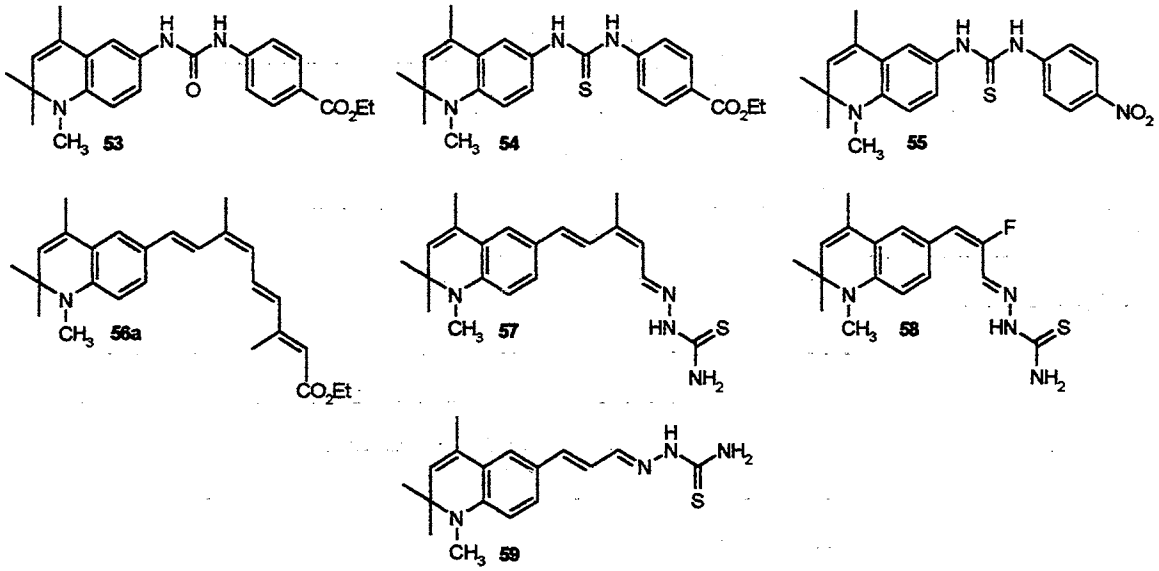
Heteroarotinoid **51**, in which the replacement of hydrogen by a larger fluorine atom at the C10 position could influence the E/Z isomer ratio at the C9-C10 double bond, was designed as a ligand to specifically bind only to the RXR family of receptors. Additionally, a polyene side chain was retained in **51**, and the terminal group was changed to a semicarbazone. This change switches the function of the ligand's polar tail from being an H-bond acceptor to an H-bond donor at a physiological pH via interaction of NH_2 group with the hydroxy group of serine 289 (Ser 289) and the carbonyl oxygen in the receptor's backbone moieties located at the polar end binding region. This agent allowed a study of the importance of electrostatic interactions between the receptor and the ligand. Docking of **51** into the LBP of RARγ resulted in a positive (unfavorable) energy of interaction which suggested steric hindrance between the ligand and the receptor due to bending of the side chain, and thus **51** could be specific for RXR.

The behavior of **52** with a four-atom linker between the aryl groups resembled that of compound **49** when the former was docked into the LBP of RARγ. Thus, it could be concluded that a four-atom linker between two aryl moieties may be slightly too long for

receptor activation. However, these compounds may act as antagonists.

Nitrogen Heteroarotinoids

Nitrogen heteroarotinoids **53-59** have a double bond incorporated into the fused ring



of the hydrophobic region. This addition to the heterocyclic ring changes the conformation of *the hydrophobic portion of the ligand*, as compared to previously synthesized retinoids. The double bond also serves as a probe in terms of the possible interaction or stacking of the π-electrons of the ligand with the phenyl rings of phenylalanine residues in the hydrophobic region of the LBP. It is not known what influence the latter has on the receptor activity. Additionally, the 3-D geometry of the hydrophobic region in **53-59** was altered by deleting one methyl group from the C4 position. Moreover, different bond lengths and conformations of the flexible linkers and the side chain were varied slightly for comparison of effects on activity. Modulation of the polar tails of the ligand was done to explore the

region of the LBP which is responsible for H-bonding.

Compounds **53-55**, which have three-atom linkers between aryl moieties, showed excellent interaction energies when docked as flexible molecules in the rigid LBP of RARγ (Figure 9, see Experimental for energy of interaction data). Heteroarotinoids **53-55** with a 3-atom linker between the aryl groups are similar to previously designed arotinoids with 3-atom linkers in exhibiting RARγ specificity.[47,140] However, the urea and thiourea groups provide a semi-flexible linker region of the ligand for possible enhanced adaptation of the compounds around the amino acid residues responsible for selectivity in the RARγ. Furthermore, possible H-bonding with the receptor is likely strengthened by the heteroatoms of the urea group present in the linker.

Based on visual inspection, the docked heteroarotinoids **56** and **57**, which were designed to discriminate against the RAR family, resembled the docked 9-*c*-RA (**3**) in the LBP of RARγ. However, due to the *cis* double bond arrangement at the C11-C12 position in **56** and **57**, which is different from the *cis* double bond position in 9-*c*-RA [(**3**), C9-C10], an unfavorable interaction of **56** and **57** with RARγ occurred. This differs from the interaction of **3** with RARγ. Considerable steric hindrance was observed with both heteroarotinoids between the hydrophobic region of the ligands and the residues Met 272, Ala 397, and Ile 275 of the LBP of RARγ. In addition to being RXR specific, **56** and **57**, which have linker moieties extended by two atoms compared to the polyene chain of 9-*cis*-RA (**3**), were originally designed to explore the LBP of RXRs and, hopefully, bind to only one of the RXR isoforms.

Compound **58** was conceived as being RXR specific due to its *E* conformation

around the C9-C10 double bond. However, unlike 9-*c*-RA (**3**), compound **58** did not show a favorable interaction with the LBP of RARγ upon docking into the receptor (see Experimental). Placement of heteroarotinoid **59** within the cavity of the LBP of RARγ was

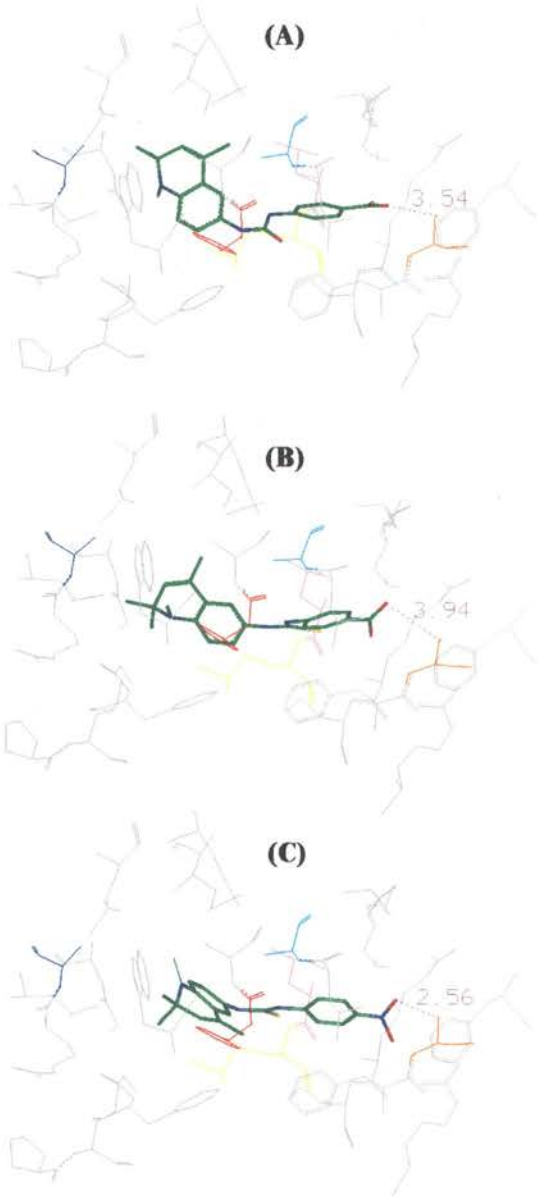
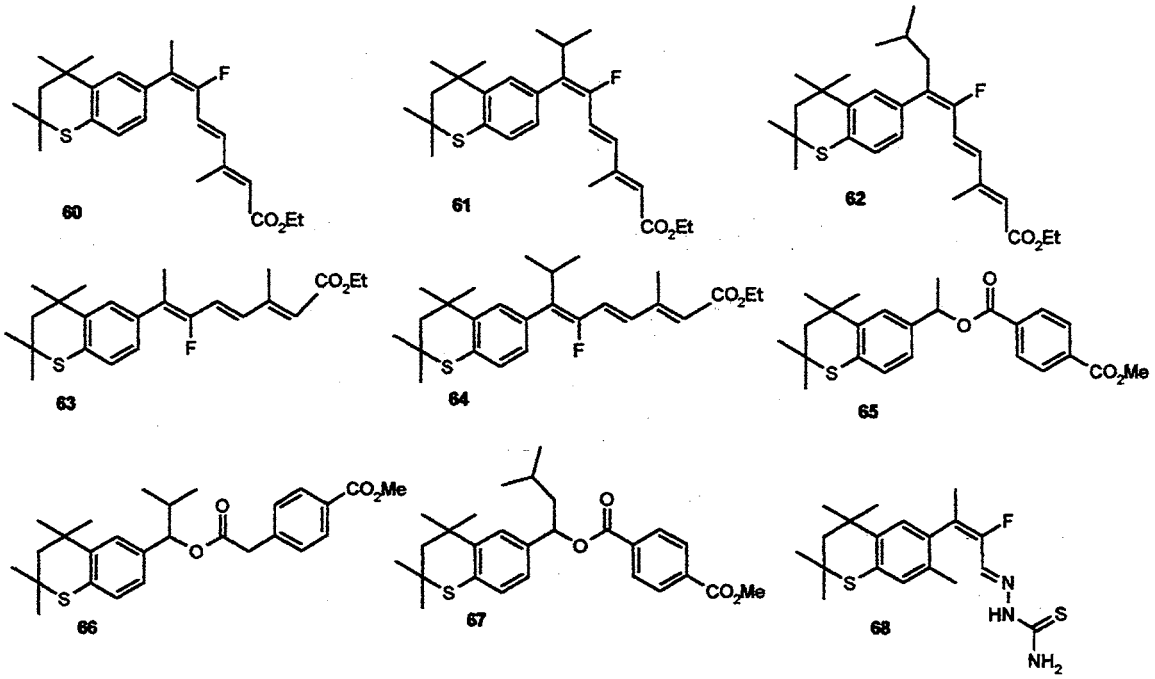


Figure 9. Docking of heteroarotinoids **53** (**A**), **54** (**B**), and **55** (**C**) into the LBP of the crystallographic structure of RARγ. The distance (Å) from Ser 289 to the closest polar end oxygen of the ligand is shown for comparison.

accomplished without any major steric or electrostatic repulsion of the ligand by the receptor (see Exper-imental). Consequently, **59** may act as an pan-agonist, with possible lower toxicity then 9-*c*-RA (**3**).[44]

Sulfur Heteroarotinoids

The synthesis of sulfur heteroarotinoids **60-68** added yet another structural variation to studies on the mechanism of activation of retinoic acid receptors. The differences in stereochemistry of the linker groups due, in part, to the influence of the incorporated fluorine atom, were designed to discern activity differences among the two families of receptors RAR and RXR. The difference in size and electronic density of the fluorine atom at the C9 position, as compared to hydrogen, was also intended to explore the interactions of the ligand with the amino acid residues (such as Ala 234, Met 272, Leu 271, Ala 397, and Phe 230) which were responsible for ligand selectivity and the flexibility in the LBD of RARγ.[14]



Docking of flexible **60** into the rigid LBP of RARγ did not result in a favorable interaction, and the results worsened as docking progressed to **61** and then to **62**. However, heteroarotinoids **63** and **64**, which are the *Z*-isomer counterparts of compounds **60** and **61**, respectively, showed excellent interactive energies with RARγ when docked in the LBD of RARγ(see Experimental). Compounds **60**, **61**, and **62** were designed specifically to activate the RXR family due to their *E* configuration, and **63** and **64**, because of the *Z* configuration about the C9-10 double bond, should activate the RAR. Furthermore, **64** was intended to be RARβ specific since similar compounds with bulky groups around the C9 position had shown RARβ specificity.[47] Heteroarotinoid **65**, a three-atom linker ligand, showed marginal energies of interaction when docked into the LBP of RARγ, and thus could be RARγ specific.[47] Interestingly, **66** and **67**, in which the bulk of the substituent group at C9 was increased, were rejected by the receptor's LBP due to spacial limitations. The intention to modify **65** at the C9 position with larger substituents (and progress to **66** and **67**) was to explore the limit of selectivity of the RAR receptors, since the ligands interact near the C9 area with the amino acid residues responsible for selectivity.[14] The 3-atom linker system with an ester moiety in **65-67** was devised to achieve RARγ specificity.[47]

Compound **68** was expected to have pan-agonist activity, since the linker and polar end are somewhat flexible. However, some restrictions on single bond rotations within the ene side chain were discovered when a computer-aided search for other conformations of the ligand was performed. One restriction arose from the addition of the methyl group at the C7 position which forced the fluoro-substituted linker and thiosemicarbazone polar tail into *only one conformation with minimum energy*. Docking of flexible **68** into the rigid LBP

of RARγ was unfavorable, and the behavior of the compound did not resemble that of 9-*c*-RA (**3**) with respect to interaction with RARγ (see Experimental). Therefore, heteroarotinoid **68** was expected to have preferential binding for the RXR family.

Computer-Aided Activity Prediction

In addition to docking flexible ligands into LBP of the rigid crystallographic structure of RARγ,[14] attempts were made to predict the activity of RAR and RXR isotypes (RARα, RARβ, and RARγ) upon induction by heteroarotinoids **48-68**. The Comparative Molecular Field Analysis (CoMFA) is a three-dimensional, Quantitative Structure-Activity Relationship (QSAR) technique which ultimately allows the design and prediction of biological activities of molecules (see user manual for CoMFA use, also see reference 39). The idea underlying CoMFA is that *differences in a target property are often related to the shapes of the non-covalent fields surrounding the test molecules.* In order to input the shape of the molecular field into a QSAR table, the magnitudes of its steric (Lennard-Jones) and electrostatic (Coulomb) energy fields were sampled at regular intervals throughout a defined region. The most important parameter for the CoMFA calculation is the relative alignment of individual molecules when their molecular fields are calculated. The alignment of the ligands was done by mimicking the positioning of *t*-RA (**2**) in the LBP of RARγ in the absence of receptor. This resulted in the X, Y, and Z, coordinates of the hydrophobic and hydrophilic moieties of ligands to be in close approximation to X, Y, and Z coordinates of *t*-RA (**2**), respectively. Therefore, properly aligned molecules have similar orientations in Cartesian space, and the generation of a QSAR by Partial Least Square (PLS) analysis gives a higher cross-validation number q^2. The number q^2 obtained from cross-validation of a

PLS analysis is a number which represents a percentage of "explained variation" in a ligand-activity relationship. For example, $q^2 = 0.55$, means, that the variation in activity exerted on the receptor by ligands can be explained (with 55% certainty) with respect to the variation in the hydrophobic and electrostatic force field (arrangements in 3-D space) of the aligned ligands. The same q^2 also implies that 45 % of the variation in structure-activity relationship cannot be justified. With a correlation coefficient of $r^2 = 0.95$ applied to the cross-validated PLS analysis, accuracy of about 52 % (55 x 0.95) would be predicted for activity of new molecules. The $q^2 = 0.4$ (minimum) and $r^2 = 0.95$ (minimum) are acceptable numbers for this type of calculation.[100]

The database of retinoids (conformations obtained from docking ligands in the RARγ and in pseudo-RARα and in RARβ; see Experimental for the latter two receptor modifications) with known and unknown biological activity was aligned through structural superimposition using the command "Align Database" in Sybyl 6.5.[126] The same type of alignment of the database was performed for the compounds to be correlated in the prediction of activity in RXR isotypes. However, since the location of the LBP of RXR has not been elucidated,[15] several different conformations of the same ligand had to be evaluated for this type of calculation (see Experimental for details). The CoMFA for each compound was calculated and stored in a molecular spread sheet. The known biological data, which in this case were EC_{50} values for the induction of transcription in CV-1 cells, were entered as $\log(1/EC_{50})$ and saved in a molecular spread-sheet. The summary of predicted EC_{50} values [the $\log(1/EC_{50})$ was converted back to EC_{50} values] for heteroarotinoids **48-68** are in Table II. The cross-validation q^2 values ranged from 0.43 to 0.58, and the correlation

coefficient r^2 values range from 0.95 to 0.98. This indicated that the accuracy percentage for prediction ranged from 41% to 58%.

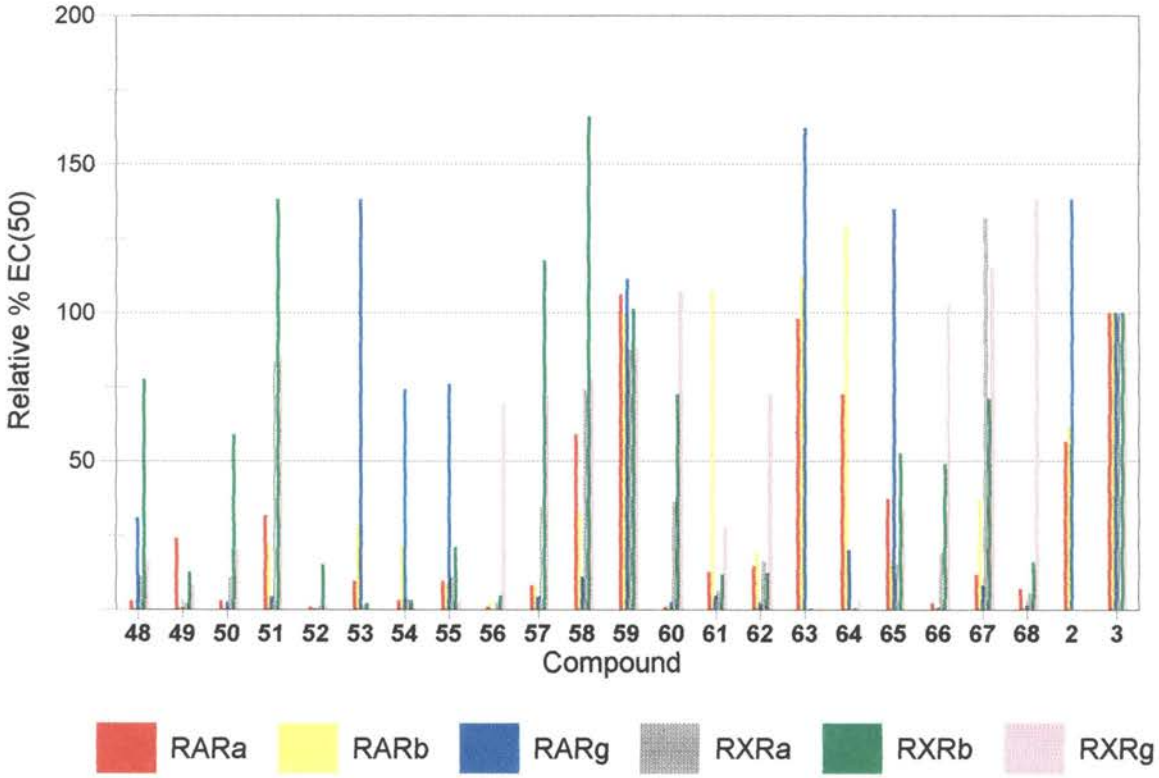
TABLE II

PREDICTED EC_{50} VALUES FOR COMPOUNDS 48-68 IN ACTIVATING TRANSCRIPTION OF THE CV-1 CELL LINE [a].

Compound	Predicted EC_{50} (μM)					
	RARα	RARβ	RARγ	RXRα	RXRβ	RXRγ
t-RA (**2**)	0.347	0.080	0.030	N/A	N/A	N/A
9-*c*-RA(**3**)	0.195	0.050	0.040	0.100	0.200	0.140
48	6.610	14.500	0.140	0.890	0.260	0.870
49	0.813	7.760	8.910	5.010	1.620	1.700
50	6.460	10.700	2.240	0.930	0.350	0.710
51	0.617	0.220	1.050	0.120	0.150	0.170
52	22.390	9.330	13.500	7.410	1.350	12.000
53	2.040	0.180	0.030	6.760	9.550	89.100
54	6.310	0.230	0.060	2.950	6.760	41.700
55	2.040	0.590	0.060	0.930	0.980	5.750
56	22.390	1.860	30.900	4.900	4.370	0.200
57	2.400	0.660	1.050	0.290	0.170	0.190
58	0.330	0.150	0.410	0.130	0.120	0.180
59	20.890	4.270	1.820	0.280	0.280	0.130
60	0.350	0.040	0.030	72.400	70.800	166.000
62	0.520	0.310	0.030	0.650	0.350	0.420
62	0.148	0.040	0.220	67.600	42.700	4.680
63	1.550	0.050	0.980	1.620	1.740	0.510
64	1.350	0.260	2.450	0.620	1.660	0.190
65	8.910	9.550	7.760	0.520	0.420	0.140
66	1.660	0.130	0.550	0.080	0.290	0.120
67	2.820	5.750	3.470	1.820	1.290	0.100
68	3.450	5.980	4.123	2.134	2.412	0.095

[a]The EC_{50} (μM) values for *t*-RA (**2**) and 9-*c*-RA (**3**) are experimental values.[28] The EC_{50}

Graph 1 represents the predicted relative activity of heteroarotinoids **48-68** and *t*-RA [(**2**), actual experimental value] to that of 9-*c*-RA (**3**) which was arbitrarily set to 100% for each RAR and RXR receptor isotype. Heteroarotinoids **59**, **63** and **64** appear to have predictable good activity with RARα as seen from Graph 1. However, compound **59**



Graph 1. Relative percentage of EC_{50} for compounds **2** and **45-65** when compared to pan-agonist 9-*c*-RA (**3**) which is 100%. When isotype bars are missing for a specific compound, this signifies that the predicted activity is close to zero with respect to 9-*c*-RA (**3**). a = α, b = β, g = γ.

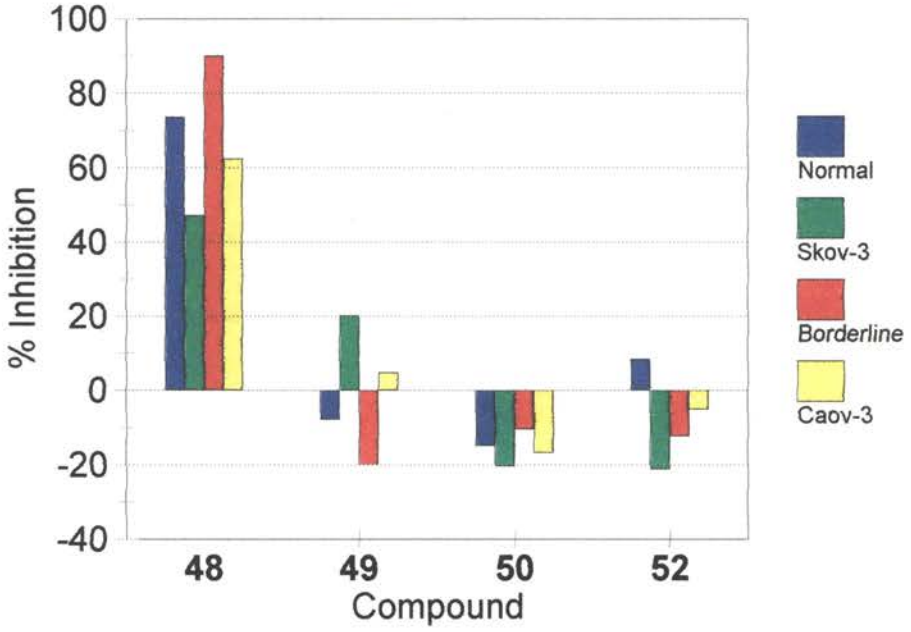
appears to have predictable pan-agonist activity, and **63** and **64** are also predicted to be RARγ and RARβ active, respectively. Besides moderate predicted activity of compound

appears to have predictable pan-agonist activity, and **63** and **64** are also predicted to be RARγ and RARβ active, respectively. Besides moderate predicted activity of compound **64** in RARα, it would appear that **64** may be RARβ specific (yellow bar). Heteroarotinoids **53-55** and **65** have predictable specificity for activation of RARγ (blue bar). None of the compounds seem to be specific for RXRα (gray bar). Nevertheless, moderate RXRα activity is predicted for heteroarotinoids **51** and **58**, and high activity is predicted with **59** and **67**. The RXRβ specific activity (green bar) would appear to be true for **48** and **50**, although with low activity inducement. Heteroarotinoids **51**, **57**, and **58** would have high predicted RXRβ activity and specificity.

Somewhat surprising are the predictions for compounds **66** and **68** as RXRγ (magenta bar) specific. Another highly active, but non-specific RXRγ ligand, appears to be compound **67**, and heteroarotinoids **56** and **67** are also envisioned to be highly selective and with high activity for RXRγ.

Of the tested heteroarotinoids **48-50** and **52**, only **48** showed promising activity in the inhibition of cancer growth (Graph 2) in ovarian cancer cells. This finding is in agreement with the data (see Experimental) obtained from docking ligand **48** into the LBP of RARγ, in which **48** interacted in a favorable fashion with the receptor. However, compounds **49**, **50**, and **52** did not. Compound **50**, which differs from **48** in having oxygen instead of sulfur in the linker moiety and a carboxylic anion instead of a nitro group at the polar end of the molecule, expressed a different mode of docking than did **48** despite conformational similarities (Figure 10). The orientation of the hydrophobic region of ligand **50**, with respect to the amino acid residues of the LBP, was different from the

orientation in **48**. *The C6 methoxy group in **48** lays parallel to the Phe 230 (red) whereas in **50** the C6 methoxy is orthogonal to the same residue.* The distances between the the Ser 289 residue and carbonyl group of **50** and the nitro group of **48**, with which active retinoids H-bond, are 4.38 Å and 3.07 Å, respectively. Perhaps this is a major reason why compound



Graph 2. Percent inhibition of cancer growth in ovarian cancer cell lines by compounds **48-52**.

50 did not dock favorably into the LBP of RARγ and why **50** exhibited a poor inhibition effect on the cancer cell lines tested. The nitro group of **48**, because of its polarity, makes stronger H-bonds than the carbonyl group of **50**. After ligand **50** was taken into the LBP, H-bonds were established, and the conformational change that took place resulted in strong hydrophobic interactions between the ligand and the receptor at the *non-polar region of the*

ligand. Because of weaker H-bonds in **50** versus **48** and the strong hydrophobic interaction, the former was pulled deeper into the hydrophobic core of the receptor, which may have caused a weakening in the H-bond. A reorientation of **50** occurred in such a way that it no longer exhibited the same effect on the receptor as did **48**.

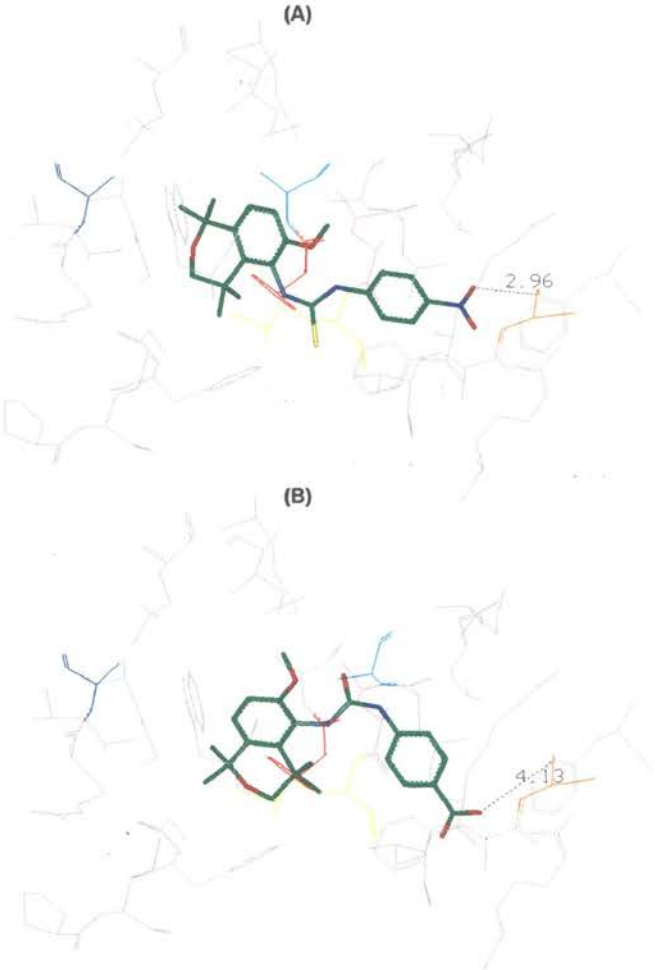
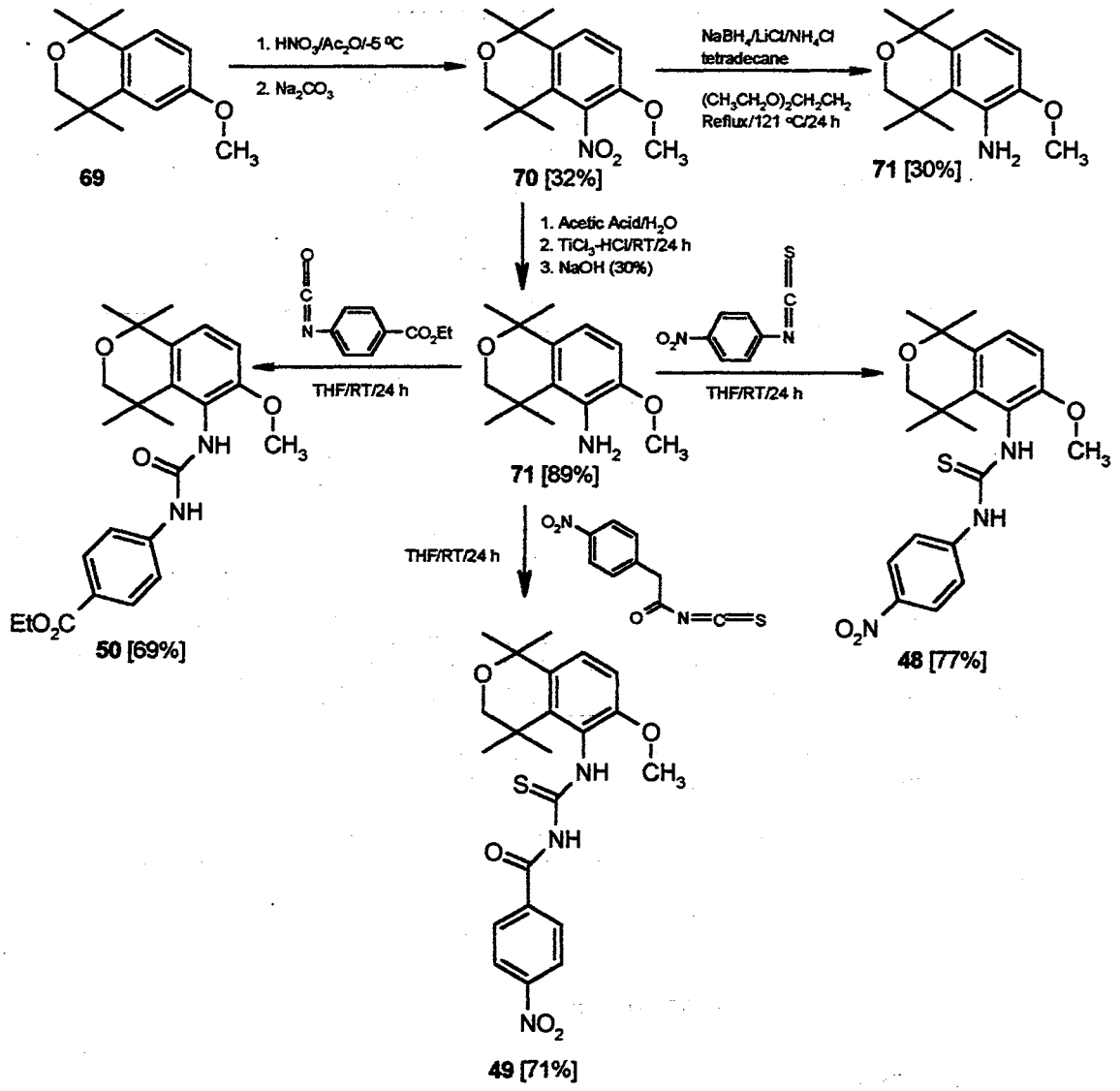


Figure 10. Docking of flexible heteroarotinoid **48** (**A**) and **50** (**B**) into the rigid LBP of the crystallographic structure of RARγ. The nitro group of active **48** in RARγ was positioned in closer proximity (2.96 Å) to the OH group of Ser 289 (H-bonding site) than was the carbonyl group of RARγ inactive **50** (4.13 Å). The corresponding distance in the crystallographic structure in the LBP of RARγ co-crystallized with *t*-RA (**2**), was 2.76 Å.[14]

Synthesis of Oxygen Heteroarotinoids

The key starting material for heteroarotinoids **48-50** was 6-methoxy-1,1,4,4-tetramethylisochromane (**69**), which was synthesized using a published methods (Scheme I).[87] Nitration of **69** with a mixture of acetic anhydride and concentrated nitric acid at -5 °C yielded a mixture of products with nitro groups being added at the C5 (30%), and the C7

Scheme I

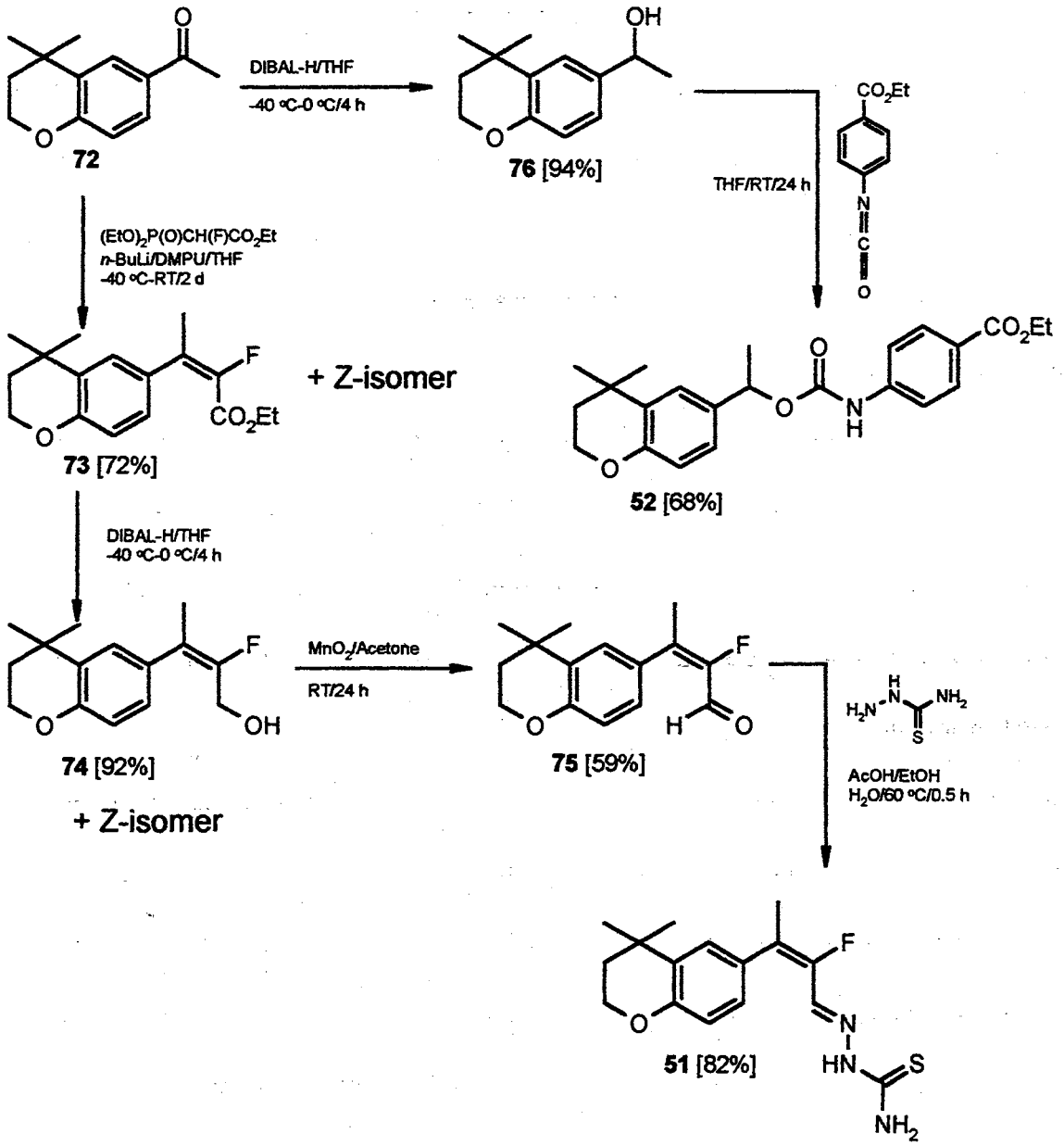


(50%) positions, along with a compound dinitrated at the C5 and C7 (10%) positions of the

benzene ring. The nitrated 5-isomer **70** was separated from the mixture via flash chromatography and then reduced with a $NaBH_4/LiCl/NH_4^+Cl^-$ complex in ethylene glycol diethyl ether.[113] However, this type of reduction failed to give a reasonable yield (30%) of **71** even at reflux (121 °C) for 24 hours. Reduction of **70** with a titanium (III) chloride-HCl complex[125] in acetic acid-water as a solvent, followed by workup of the reaction mixture with 30% NaOH, gave 6-methoxy-1,1,4,4,-tetramethylisochroman-5-yl-amine (**71**) in good yield (89%). The reaction of **71** with 4-nitrophenylisothiocyanate, (4-nitrophenyl)oxomethane isothiocyanate, and ethyl 4-isocyanatobenzoate in dry THF at room temperature afforded compounds **48**, **49**, and **50**, respectively, in reasonable yields as shown.

1-(4,4-Dimethylchroman-6-yl)ethan-1-one (**72**), which was synthesized according to a previously published method from our laboratory,[87] was used as an intermediate for the synthesis of **51** (Scheme II). A Horner-Emmons type reaction of **72** with triethyl 2-fluorophosphono- acetate, in the presence of *n*-BuLi and DMPU in dry THF, gave ester **73** as a mixture of *E* and *Z* isomers.[120] The separation of the *E* isomer **73** from its *Z* counterpart proved to be more difficult then separating the *E* and *Z* isomers of alcohol **74**. The latter was obtained by the reduction of **73** with DIBAL-H at -40 °C. The *E*-isomer of **74** made up 57%of the mixture. Several attempts to reduce the unsaturated ester **73** directly to aldehyde **75**, as reported by Zakharin and coworkers, failed.[141] The product was a mixture of an alcohol and an aldehyde even when 1.0 equivalent of DIBAL-H was added dropwise to **73** at -78 °C, and yields of the desired aldehyde (<10%), after separation from the alcohol, were unacceptable. However, the *E*-aldehyde **75** was obtained from **74** through oxidation with

Scheme II



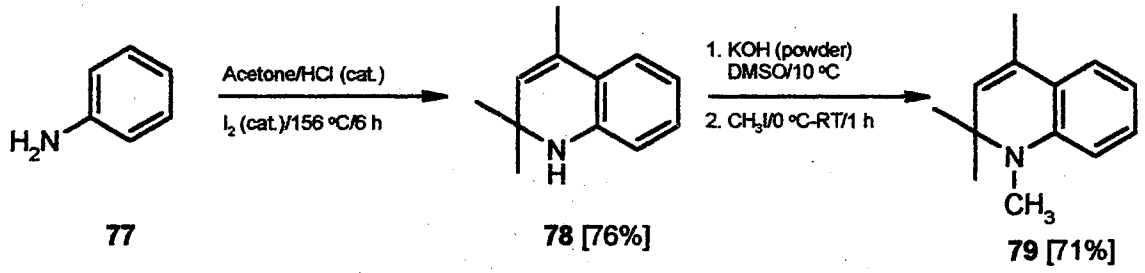
MnO_2 in acetone at room temperature with an overall yield of 54% from **73**. Reacting aldehyde **75** with thiosemicarbazide dissolved in water with few drops of acetic acid afforded heteroarotinoid **51** as a white solid in good yield (82%).[44] The reduction of ketone **72**, which was followed by a reaction of the resulting alcohol **76** with ethyl isocyanatobenzoate in THF, yielded the 4-atom linker heteroarotinoid **52** as a white solid

(69%).

Synthesis of Nitrogen Heteroarotinoids

A somewhat unusual reaction of aniline (**77**) with acetone, which was added at 156 °C and in the presence of catalytic amounts of HCl and iodine, led to the formation of 2,2,4-trimethyl-1,2-dihydroquinoline (**78**) (Scheme III). Interestingly, compound **78** was obtained

Scheme III

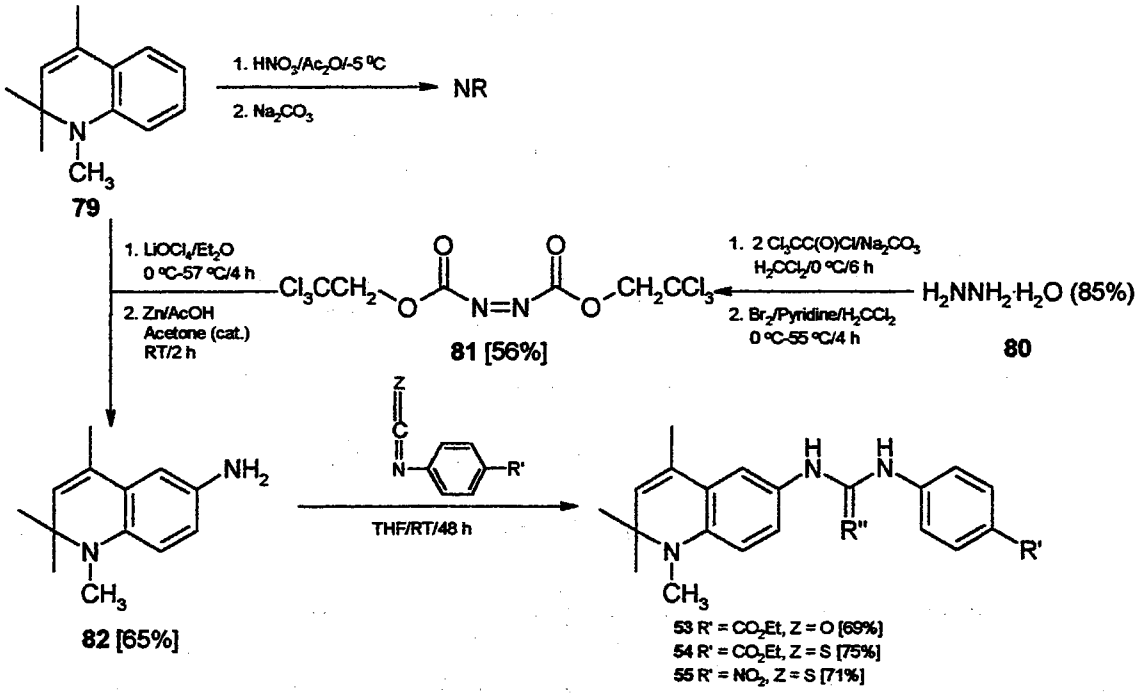


as a by-product as reported by deKoning and co-workers[29] in attempts to synthesize 4-(*N*-phenylamino)-4-methyl-2-pentanone [even in absence of HCl, **78** (identified by ^{1}H NMR) made up 80% of the mixture (52% overall yield) when separated from 4-(*N*-phenylamino)-4-methyl-2-pentanone].[29] However, the above method was convenient for our purposes where unsaturation in the heterocyclic ring was desired, and an addition of two equivalents of acetone and the subsequent cyclization of the ring allowed a one pot reaction. The yield (76%) of **78** from **77** was increased by addition of catalytic amount of HCl as compared to reported yields (40%).[29] On average, the *N*-methylation of **78** with dimethyl sulfate to give **79** resulted in 20% lower yields as opposed to methylation with methyl iodide in DMSO and KOH. 1,2,2,4-Tetramethyl-1,2-dihydroquinoline (**79**) was the key precursor for the nitrogen heteroarotinoids.

The amination procedure used in the reaction sequence **69**→**70**→**71** (Scheme I) was

not successful for the preparation of amine **82**. Perhaps the harsh acidic conditions for nitration and successive reduction of the nitro moiety to an amine group were responsible for the reaction failure. After reviewing several amination procedures for an arene ring, the most suitable method for **79**→**82**→**53** (**54**,**55**) appeared to be that reported by Leblanc and co-workers.[77] The conversion of **80** to **81** [bis(2,2,2-trichloroethyl) azodicarboxylate (**81**)] gave an excellent source of positive nitrogen for electron rich arenes (Scheme IV).[77] Reagent **81** was synthesized from the reaction of hydrazine hydrate (**80**) with two equivalents of 2,2,2-trichloroethyl chloroformate in the presence of sodium carbonate. Interestingly, after

Scheme IV

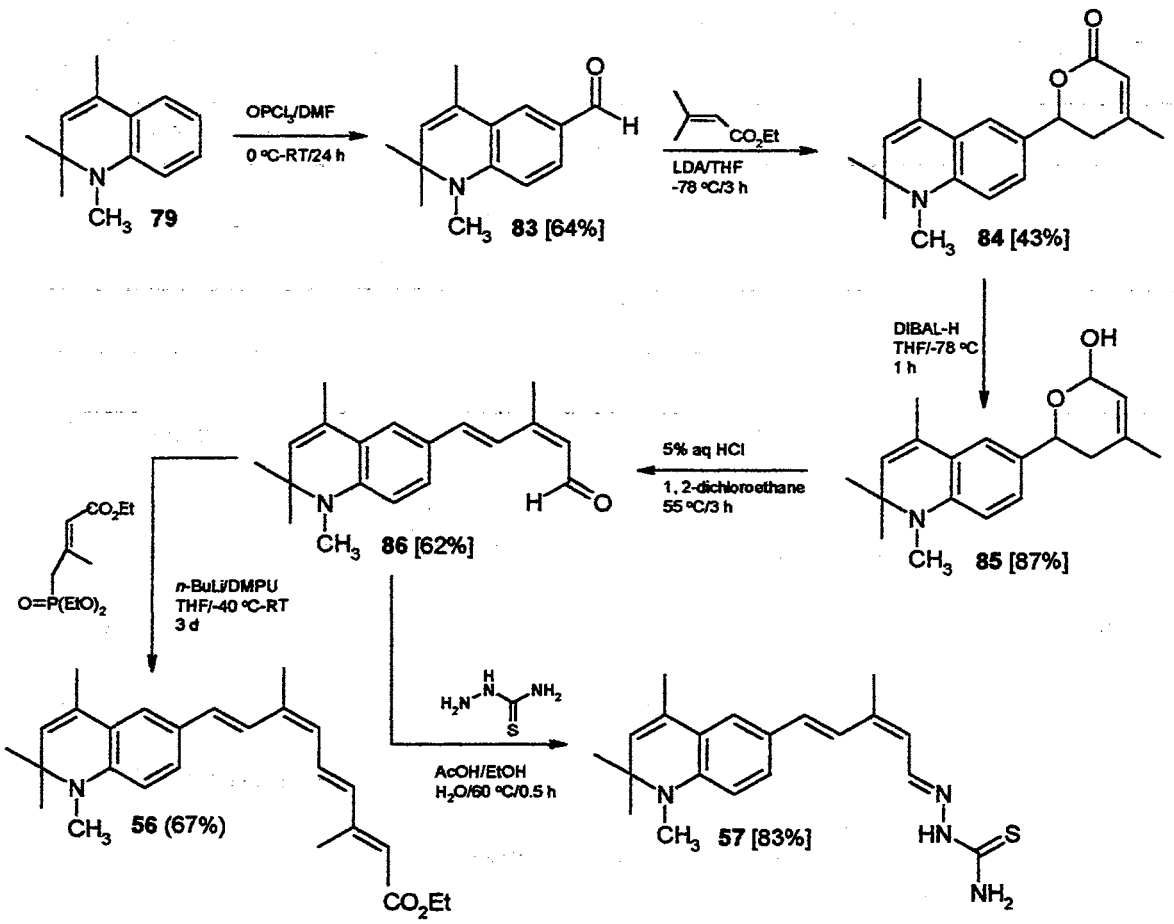


workup, the resulting intermediate from **80** was oxidized with Br_2 in pyridine[76,121] to yield **81** (56% from **80**). Amine **82** was obtained via a convergent synthesis involving **79** and **81**. 1,2,2,4-Tetramethyl-1,2-dihydroquinoline (**79**) was allowed to react with azo derivative **81** in a solution (3*M*) of lithium perchloride dissolved in dry diethyl ether, a process which was

followed by reduction of the product with zinc in acetic acid.[76] Three-atom linker heteroarotinoids **53-55** were then procured via a reaction of amine **82** with the respective isocyanates or isothiocyanates.

Heteroarotinoids **56** and **57** differ somewhat from 9-*c*-RA (**3**) where the *cis* arrangement of the double bond was moved from the C9 position to C11. Treatment of 1,2,2,4-tetramethyl-1,2 dihydroquinoline (**79**) with a DMF-$OPCl_3$ complex at 0 °C in a Vilsmeier-Haack reaction resulted in the production of aldehyde **83** (64%) (Scheme V).[19]

SchemeV

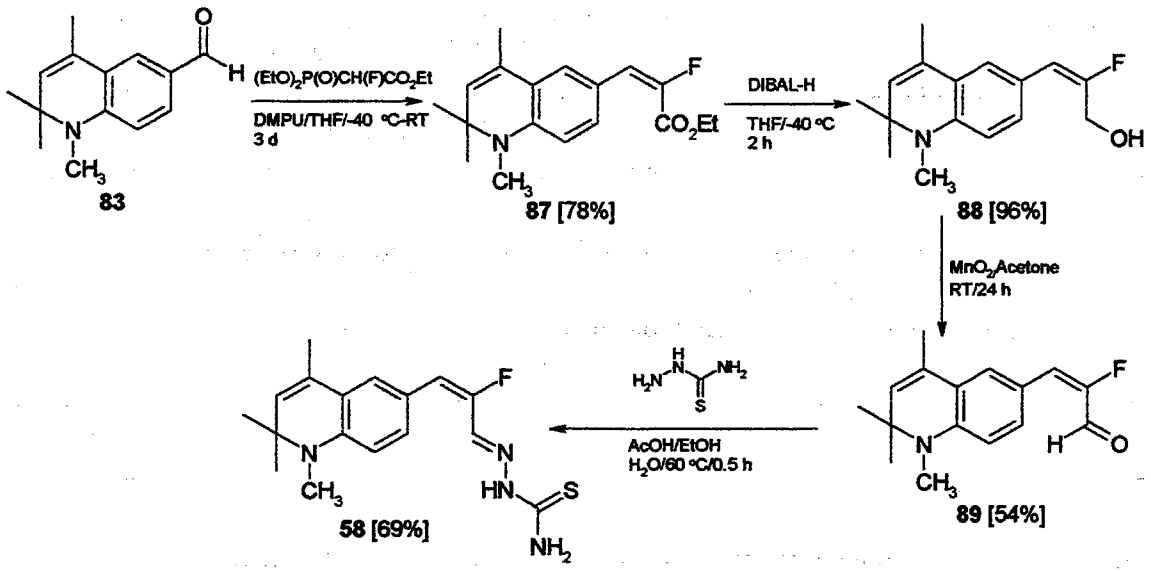


Reaction of aldehyde **83** with the lithium anion derived from ethyl 3,3-dimethylacrylate gave

lactone **84**.[7] The strategic introduction of the 11-*cis* double bond was efficiently performed by means of a DIBAL-H reduction of **84** to give lactol **85** (87%) which was then transformed upon treatment with HCl in dichloroethane to 11-*cis* aldehyde **86**.[7] The chain extension of **86** into ester **56** was accomplished by a Horner-Emmons type reaction of triethyl 3-methyl-4-phosphonocrotonate (*trans*:*cis*, 4:1) with aldehyde **86** in the presence of *n*-BuLi and DMPU. Heteroarotinoid **57** was obtained when 11-*cis*-aldehyde **86** and thiosemicarbazide were allowed to react in an ethanol-water mixture as solvents at 60 °C.

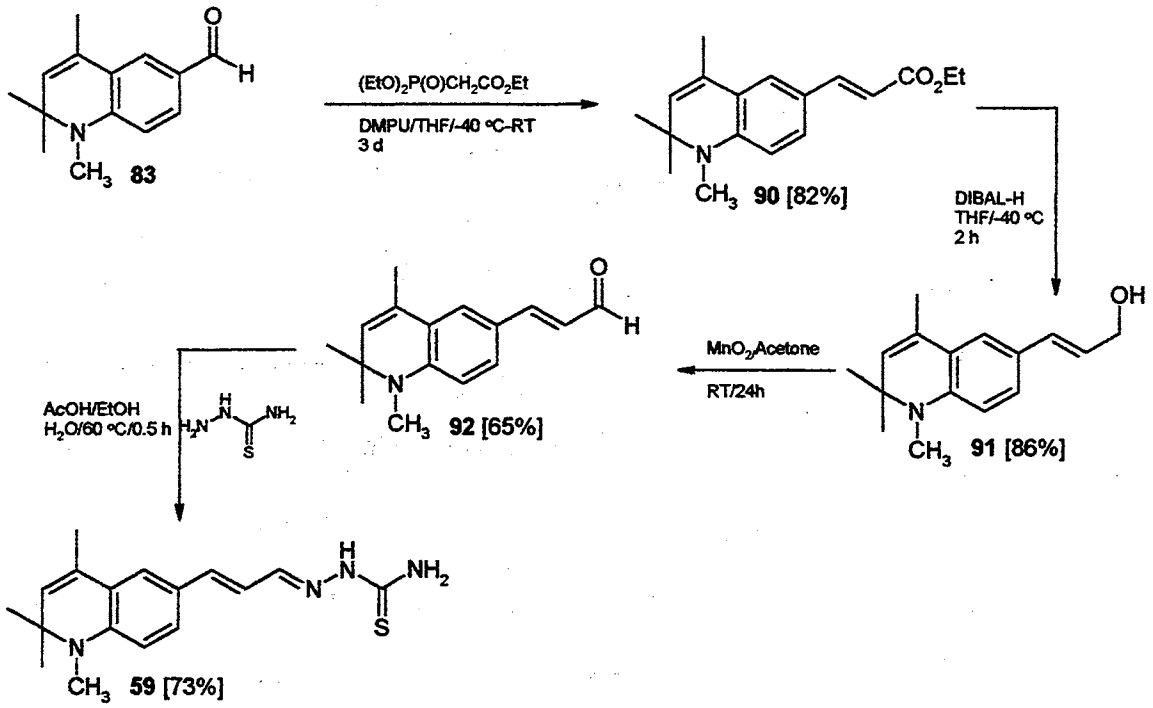
Treatment of aldehyde **83** with the anion of triethyl 2-fluoro-2-phosphonoacetate in THF at -40 °C generated ester **87** as an *E* isomer only (Scheme VI) as opposed to the generation of ester **73** in which both *E* and *Z* isomers were formed (Scheme II) for reasons unknown. The reduction of **87** to **88**, and subsequent oxidation, resulted in aldehyde **89** which was converted to **58** as shown.

Scheme VI



Heteroarotinoid **59** was synthesized by the reaction sequence **83→90→91→92→59** (Scheme VII) which is similar to the reaction sequence **83→87→88→89→58** described earlier (Scheme VI). Thiosemicarbazide reacted with aldehyde **92** (Scheme VII) and afforded the locked, fluorinated *E*- isomer **59** with different properties at the polar end.

Scheme VII

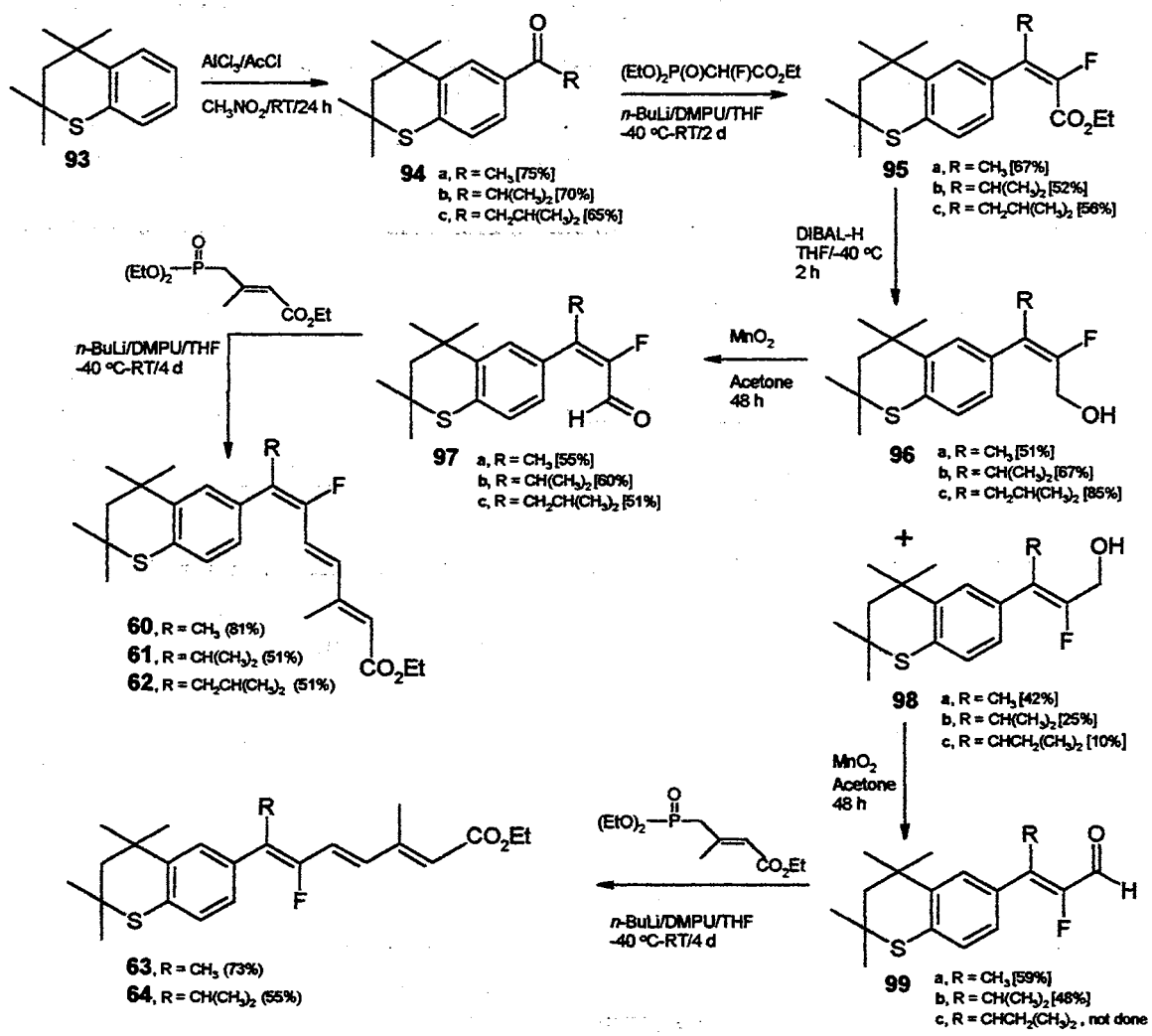


Synthesis of Sulfur Heteroarotinoids

Thiochroman **93** was synthesized (Scheme VIII) according to modified procedures reported from our laboratory.[125] Acylation of **93** by acetyl chloride, isobutyryl chloride, or isovaleryl chloride in the presence of a Lewis acid, resulted in ketones **94a**, **94b**, and **94c**, respectively,. The yields from these reactions were directly proportional to the size of the R group in the acylating reagent. The condensation of the Horner-Emmons reagent, triethyl 2-fluoro-2-phosphonoacetate, with ketones **94a-c** yielded esters **95a-c**. The DIBAL-H reduction of these esters afforded the easily separable *E*- and *Z*-isomers of alcohols **96a-c**

plus **98a** and **98 b**, respectively. Interestingly, the size of the R group may also play a role in determining the *E/Z* isomeric ratio. The larger the R group, the less *Z*-isomer could be recovered. A conformational search, done via computer modeling using the program Discover[30] where the torsional force and the V092 algorithm were options for searching and minimizing new conformations, respectively, revealed that the larger the R group, the more the side chain was displaced from conjugation with the arene ring. When the R group was methyl, the angle between the benzene ring and the double bond of the chain for minimal

Scheme VIII

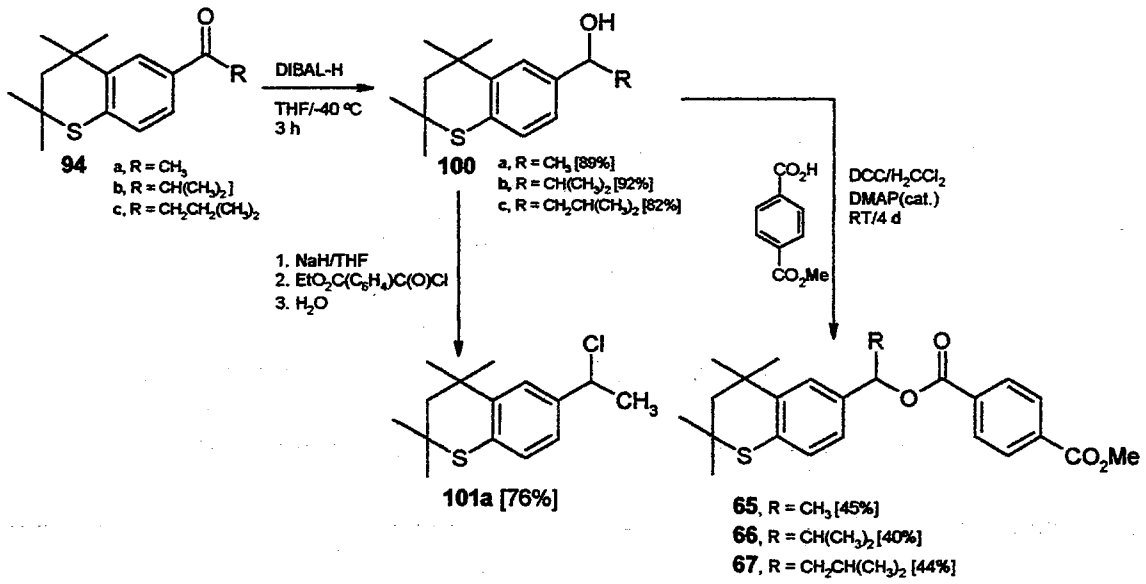


energy conformation was approximately 15 degrees. This angle became ~45° and ~ 60° when the R groups were isopropyl and isovaleryl, respectively. Perhaps it may be the combination of the out of plane angle between the arene ring and the side chain double bond and the presence of fluorine that are responsible for the direction of the Horner-Emmons anion attack on the carbonyl carbon. Only a small amount of the alcohol *Z*-isomer **98c** could be recovered after separation from the *E*-isomer **96c**. The alcohols **96a-c** and **98a,b** were oxidized to aldehydes **97a-c** and to **99a,b**, respectively. These aldehydes were then converted to the final heteroarotinoids **60-62**, **63**, and **64**, respectively.

Reduction of ketones **94a-c** by DIBAL-H led to the formation of alcohols **100a-c** in very good yields (Scheme IX). Treatment of alcohol **100a** with sodium hydride in THF, followed by the addition of methyl 4-(chlorocarbonyl)benzoate and workup with water, led to a substitution reaction of the alcohol functional group by chlorine and production of **101a**. The required final product **65** was not obtained (reaction procedure is described in Experimental).Diesters **65-67** were the products of an alternative procedure where alcohols **100a-c** were esterified via the addition of monomethyl terephthalate in the presence of DCC and a catalytic amount of DMAP. However, the yields of these reactions were low possibly due to steric hindrance of the R groups. When R was the isopropyl group, the yields were the lowest, a possible indication that the isopropyl moiety presents a larger bulk than the isovaleryl group in which the tertiary carbon is further removed from the OH group in **100**.

The synthetic procedure to obtain the 7-methylthiochroman **102** was essentially the same as that used to produce thiochroman **93**.[125] The presence of a methyl group at the C7 -position was reasoned to possibly increase the selectivity of the ligand **68** by the RARγ

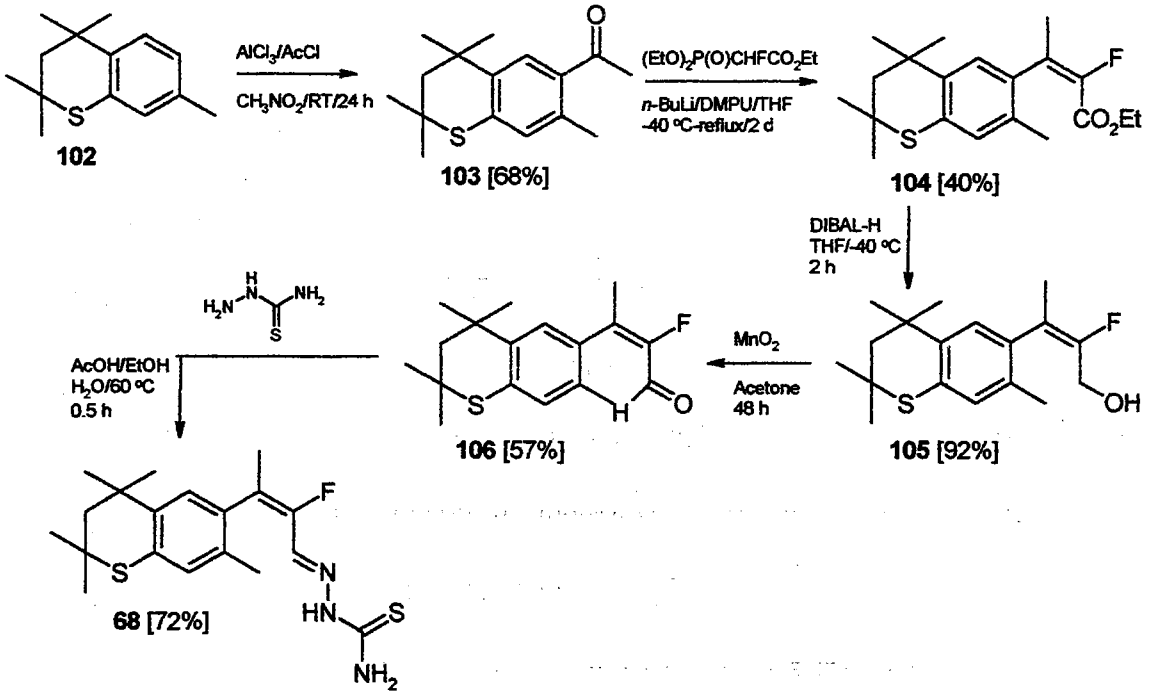
Scheme IX



receptor via altering the rotational barrier of the side chain. The reaction sequence **93→94→95→96→97**described previously (Scheme VIII) was the model for the conversion of **102→103→104→105→106** (Scheme X). However, the yields for the Horner-Emmons reactionto produce ester **104** were lower (even at reflux) than for its counterpart **95** which does not have a C7 methyl group. Intriguingly, in addition to inducing lower yields, the C7 group may play a vital role in *E/Z* isomer selectivity. The Horner-Emmons reagent used in the condensation with ketone **103** produced an *E/Z* isomer ratio (85:15) that was much higher than in the unmethylated C7 counterpart **95a** (55:45) (Scheme VIII). Molecular modeling also showed that the conformations of intermediates **103-106** had a 20 degree larger angle (35 degrees compared to 15 degrees), with respect to the side chain and the aryl ring than in intermediates **92a-95a**. Therefore, besides reduction of the conjugation between the arene ring and the double bonds of the side chain, the C7 methyl group may also direct the attack of the Horner-Emmons anion on the carbonyl group in **103**.

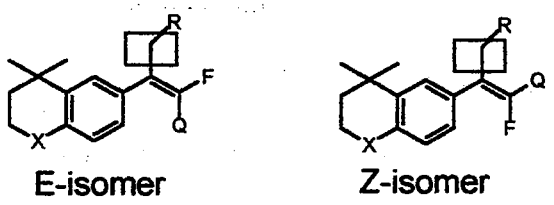
The *E/Z* isomeric ratio for compounds **74**, **96a-c**, **98a-c**, and **105** and proton chemical shifts of the groups attached to the C=C are in the Table III. The ^{19}F chemical shifts were

Scheme X



referenced to the trifluoroacetic acid-OD. It appears that the ^{19}F absorbance in the *E*-isomer is at a lower frequency than in the *Z*-isomer.[58] This is consistent with the proximity of the fluorine atom to the aryl ring as seen from molecular modeling.

In the *Z* isomers, the fluorine atom is positioned closer to the plane of the benzene ring and more deshielded. Therefore, one might expect ^{19}F chemical shifts to be more downfield in the *Z* isomers than in the *E* isomers. Interestingly, in the *Z* isomers the methyl,



the methylene, and the methine hydrogens (square box in representative compounds below) adjacent to the double bond appear to be more de-shielded than in the respective *E* isomers analogs. The coupling constants between the adjacent hydrogen(s) and fluorine were larger for the *E* isomer, and these values were consistent for all isomeric pairs. This could imply

TABLE III

NMR ANALYSIS OF $^{4}J_{^{1}H-^{19}F}$ COUPLING IN THE *E/Z* ISOMERS. [a]

Compound	*E/Z* Ratio	$\delta_{^{1}H}$ (ppm)	$^{4}J_{^{1}H-^{19}F}$ (Hz)	$\delta_{^{19}F}$ (ppm)
(*E*)-**74**	57:43	1.84	3.4	-118.49
(*Z*)-**74**		1.97	2.7	-117.21
(*E*)-**96a**	55:45	2.02	3.9	-117.76
(*Z*)-**98a**		2.03	3.3	-117.58
(*E*)-**96b**	61:39	2.86	2.7	-121.86
(*Z*)-**98b**		3.15	1.5	-115.28
(*E*)-**96c**	90:10	2.26	2.3	-128.49
(*Z*)-**98c**		2.64	1.4	-118.86
(*E*)-**105**	85:15	1.93	3.3	-120.93
(*Z*)-**105**		1.95	2.2	-114.64

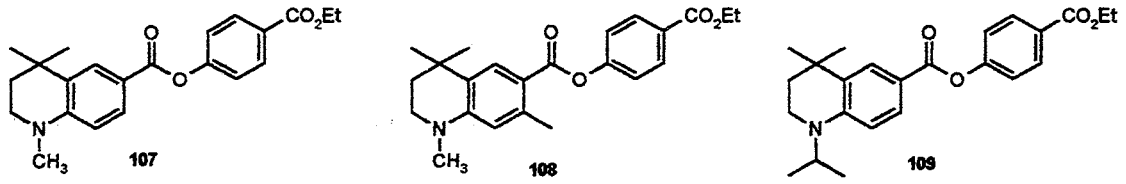
[a]The assigment of stereochemistry was by the Pawson method.[105]

that the primary influence of fluorine on the hydrogen atoms mentioned above is due to the size and proximity of the former to the latter, and heteronuclear influence via bond proximity may play role in hydrogen splitting.

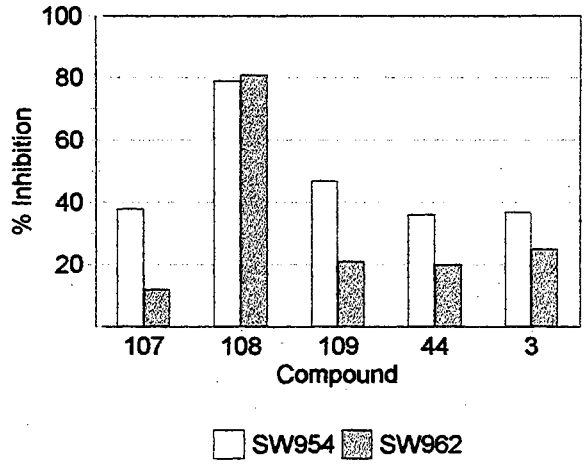
Structure-Activity Relationship (SAR) Study Via Molecular Modeling

The use of computer-aided analyses is becoming a standard method for evaluating structure-activity relationship analysis of new drugs and in the design of new medicinal

agents. To gain better insight into retinoic acid receptor interaction with ligands for the purpose of drug design, the binding of three compounds previously synthesized in our laboratory was assessed in terms of developing a rationale for the interaction with RARγ. The heteroarotinoids 4-(ethoxycarbonyl)phenyl 1,4,4-trimethyl-1,2,3,4-tetrahydroquino-line-6-carboxylate (**107**),4-(ethoxycarbonyl)phenyl1,4,4,7-tetramethyl-1,2,3,4-tetrahydroquino-



line-6-carboxylate (**108**), and 4-(ethoxycarbonyl)phenyl 4,4-dimethyl-1-isopropyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (**109**) were examined for docking in the RARγ receptor via the use of the SYBYL 6.5[126] software package along with the docking program "Flexidock." Due to the structural variations among compounds **107**, **108**, and **109**, differences in the activity of these compounds exist in terms of inhibiting cancer proliferation in two different cancerous vulvar cell lines (Graph 3).[9] The heteroarotinoid **108** exhibited greater growth inhibition of the various cancer cell lines than did 9-*c*-RA (**3**) or one of the most potent synthetic retinoids TTNPB (**45**).[9] Such differences in biological activity may be directly proportional to the ability of an agent to bind and activate the RARγ. As the data indicated, heteroarotinoid **108** activated the RARγ better than did 9-*cis*-RA (**3**) (Table IV).[9] In comparison to compounds **107** and **109**, which transactivate all receptors only moderately and without any specificities, considerable difference can be seen between the activation of RARγ and the rest of receptors by **108**, where the latter appears to be a RARγ specific transactivating ligand.[9]



Graph 3. Percent of Growth Inhibition of Cancerous Vulvar Cell Lines SW954 (Empty Bars) and SW962 (Gray Bars)

The activation of RARγ by **108** posed questions in term of conformations involving the ligand-receptor interaction and differences in receptor activation of **108** from **107** since the former has only an additional methyl group at the C7 position. The latter heteroarotinoid has little or no influence on the activity of the receptor. The heteroarotinoid **109**, which differs from **108** in that an isopropyl moiety is bound to the heteroatom instead of a methyl group and is void of a C7 methyl group, also did not activate the RARγ to any measurable extent.[9]

Using the Flexidock program, heteroarotinoids **107-109** were docked into the LBP of RARγ (data taken from the crystallographic structural information)[14] to investigate the ligand-receptor interaction. Compounds *t*-RA (**2**), which is an RAR family agonist, 9-*c*-RA (**3**), (pan-agonist), **6** (RARα specific), **39** (RARβ specific), **32**, and **40** (RARγ specific) were docked for comparison purposes (Table I). In addition, the docking of *t*-RA (**2**) was to test the validity of the Flexidock program (see Experimental for molecular modeling). All of the compounds were docked as a carboxylic anion for the closest simulation of the biological

TABLE IV

EC_{50} VALUES AND EFFICACY DATA FOR THE TRANSACTIVATION OF RETINOIC ACID RECEPTORS BY COMPOUNDS 107- 109.[a]

Heteroarotinoid		RAR			RXR		
		α	β	γ	α	β	γ
107	EC_{50} (n*M*)[a]	1128	256	NA	601	33	20
	(% efficacy)[b]	45	64	0	47	53	52
108	EC_{50} (n*M*)[a]	796	92	6	102	70	40
	(% efficacy)[b]	64	63	103	53	55	52
109	EC_{50} (n*M*)[a]	217	41	NA	12	47	27
	(% efficacy)[b]	59	71	0	62	45	47

[a] The potency (EC_{50}) is the concentration of the compound that can induce one half of the maximal activity of the receptor. [b]The efficacy is derived from dividing the maximal activity induced by the heteroarotinoid by the maximal activity induced by the 9-*c*-RA (**3**). NA = not active.[9]

condition where carboxylic esters of retinoids were hydrolyzed and ligands exist as anions at a physiological pH of 7.4.[17,52] Data from docking of a flexible ligand (a ligand has three degrees of translation, rotational degrees of freedom around each single bond and torsional degrees of freedom around dihedral angles) into the fixed crystallographic structure of the LBD of RARγ are summarized in Table V. A total of five calculation trials revealed that the interaction energies (interaction energy is equal to the energy of ligand-receptor complex minus the sum of the energy of a receptor before docking plus the energy of the ligand before docking) of heteroarotinoid **108** with RARγ were better then **107** but not better than for **109** or 9-*c*-RA (**3**).[4] These results did not agree with the biological data (Table 4) where the efficacy of **108** was 103% in the vulvar cell line in comparison to **3** and superior in comparison to **109** which did not transactivate the RARγ. These discrepancies

would suggest that the interaction energies of the flexible ligand-fixed receptor complex may be representative of the binding affinities of the ligand and receptor, but such may not be an indication of the level of receptor activation by the ligand.

TABLE V.

DATA FROM DOCKING THE FLEXIBLE LIGANDS INTO THE FIXED CONFORMATION OF RARγ LBD CRYSTALLOGRAPHIC STRUCTURE.[a]

Ligand	Energy of Interaction (Kcal/mol)				
	R1 (25,000)	R2 (20,000)	R3 (15,000)	R4 (30,000)	R5 (10,000)
t-RA (**2**)	-64.64	- 58.29	- 34.71	- 75.73	- 33.5
9-*c*-RA (**3**)	-15.38	- 9.32	- 7.44	- 17.33	- 5.38
107	8.35	12.58	21.49	5.38	22.98
108	2.47	3.61	5.72	- 1.36	9.34
109	-37.52	- 30.63	- 29.51	- 45.29	-25.61

[a]The notation R1 is the designation for the first trial, R2 for second, etc. The number following the trial designation (25,000) is the generation number, that is the number of calculations which the program generates through adjustments of the translation of ligand in the LPB, rotation around ligand single bonds, and torsion about dihedral angles. Exactly10,000 new conformations of the ligand are then generated for each generation. The calculation of interaction energies between 10,000 different conformations of the ligand and receptor is followed by scoring the results by picking the 20 conformations of the ligand with the best interaction energies with respect to the receptor. This process is then repeated 25,000 times. The higher the generation number, the more conformations are generated until the program examined that number of conformations where the energies of interaction remain essentially constant, and the results converge toward the 20 best ligand-receptor interacting conformations. Once the receptor is fixed, its conformation does not change.

One of the options for explaining the above observation is that the resulting crystal structure[14] of RARγ, which was co-crystallized with *t*-RA (**2**), although it may be in a minimal energy conformation, is not the active conformation of RARγ. Another possibility is that some of the amino acid conformations within the crystal structure of the LBP of RARγ are not important in the selectivity and activity of RARγ. In addition, the more rigid

nature of the system in a flexible ligand-fixed receptor type of docking could prevent **108** from proper orientation for interaction with receptor. Conceivably, the crystal structure of RARγ may deviate slightly from the active conformation of the receptor. Actually, computer matching of the crystal structure of RARγ to the resulting conformation of RARγ *after* a flexible ligand-flexible receptor docking with *t*-RA (**2**), and the subsequential removal of the ligand, revealed only small differences in conformational energies. The root-mean-square-deviations (RMSD) of the LBP of RARγ crystal structural amino acid residues superimposed upon the resulting conformation of the residues of the flexible LBP of RARγ, after *t*-RA (**2**) docking, were less than 0.01 Å in most of the cases with only a few differences as in: Phe 201 (RMS = 0.1931 Å), Lys 236 (0.452 Å), Cys 237 (0.420 Å), Arg 278 (0.185 Å), Ser 289 (0.423 Å), Leu 400 (0.128Å), Ile 412 (0.236 Å), and Met 415 (0.121 Å) observed. These small deviations of RMS values of less then 0.5 Å were considered to be a match via modeling of non-related systems.[139] The resulting conformation of the LBP of RARγ after *flexible-flexible* docking, agreed reasonably well with that of the crystallographic structure of the LBP of RARγ. Nevertheless, the crystallographic structure[14] of RARγ co-crystallized with *t*-RA (**2**) may or may not be the active conformation of RARγ in solution.

The conformations of *all* the amino acids in the LBP of RARγ, with deviation values noted above, are not considered to play a major role in ligand selectivity and receptor activity.[14] This notion was further supported by mutagenic studies done on the LBD of RARγ where three amino acid residues (Ala 234, Met 272, Ala 396) were found to be responsible for the selectivity of a ligand and one amino acid (Phe 230) was found to be responsible for the activation of receptor RARγ.[14,68,74,104] The interpretation of the results

from Tables 4 and 5 could then imply that compounds **109** and 9-*c*-RA (**3**), which activate RARγ less than **108**, favorably interact with residues of the LBP which are not important for activation of RARγ. In contrast, **108** does not interact to the same extend with the same residues of the LBP as do **109** and **3**.

The direct consequence of favorable interactions of compounds **109** and 9-*c*-RA (**3**) with amino acid residues that are *not* important for activation of RARγ is the unfavorable interaction of **109** and **3** with residues that *are important* for the activation of receptor. This proposition was further supported via docking flexible ligands into the flexible LBP of RARγ where all bonds in the crystallographic structure of RARγ were allowed to have the same degree of freedom as a ligand, and backbone rotation was also allowed (Table VI; the lower energy, the more favorable the interactions between the ligand and the amino acid residues; also see Figure 11). The *flexible-flexible* method of docking was to permit the atoms of the ligand and amino acid residues of the LBP to rearrange so as to obtain the minimum interaction energy. The resulting conformations of the LBP of RARγ (void of the ligand), after docking **107**, **108**, **109**, and **3**,were mathematically analyzed and visually compared with the resulting conformation of the LBP of RARγ after docking *t*-RA (**2**) which was then removed after docking (Figure 12).

Superimposition of the resulting conformations of the receptor's LBP, after **108** was docked and then removed, on the resulting conformation of the LBP of RARγ, after *t*-RA (**2**) was docked and removed, revealed only slight differences in RMSD values within the following residues: Phe 201 (0.397Å), Leu 233 (0.805Å), Lys 236 (1.192Å), Cys 237 (0.42Å), Ile 275 (0.185Å), Arg 278 (0.595Å), Ser 289 (0.339Å), Phe 304 (0.134Å), and Met

408 (0.478Å). However, the RMSD values resulting from the superimposition for the amino acid residues important in the selectivity and activity of RARγ were less then 0.1Å, which signifies a reasonable match. The spacial arrangements of Phe 230, Ala 234, Met 272, and Ala397 residues in the LBP with **108** docked, in comparison to the same residues of the

TABLE VI

INTERACTION ENERGIES BETWEEN THE LIGANDS AND THE LBP OF RARγ IN THE FLEXIBLE LIGAND-FLEXIBLE RECEPTOR DOCKING MODE.[a]

Ligand	Interaction Energy (Kcal/mol)	
	R1 (60,000)	R2 (45,000)
t-RA (**2**)	- 140.34	- 123.56
9-*c*-RA (**3**)	- 120.36	- 99.97
107	- 57.08	- 46.24
108	- 122.49	- 117.69
109	- 88.52	- 85.53

[a] In the flexible-flexible docking mode, all ligands docked favorably with different energetic changes for the ligands and receptors, which ultimately produced conformations of receptors that were analyzed.

LBP with docked *t*-RA **2**), were essentially the same. The receptor conformation of RARγ, after 9-*c*-RA (**3**) was docked, removed, and compared to the conformation of the receptor after *t*-RA (**2**) was docked, differed in several (residues Phe 230 (0.202Å), Lys 236 (0.698Å), Phe 230 (0.501Å), Ser 231 (0.415Å), Met 272 (1.061Å), Ser 289 (0.378Å), Phe 304 (0.143Å), Leu 307 (0.263Å), Arg 396 (0.151Å), Ile 412 (0.462Å), and Ile 275 (0.435Å). The RMSD values for the amino acid residues for the RARγ-inactive heteroarotinoid **107** from *t*-RA-induced conformation of the receptor were: Phe 201 (0.274Å), Phe 230 (0.832Å), Ser 231

(0.364Å), Lys 236 (1.655Å), Cys 237 (0.420Å), Met 272 (1.358Å), Ile 275 (0.235Å), Ser 289 (0.524Å), Phe 304 (0.154Å), Arg 396 (0.146Å), Leu 400 (0.338Å), Met 408 (0.174Å), Ile 412 (0.144Å), and Met 415 (0.121Å). The RMSD values for the conformations of residues of the LBP of RARγ, after the RARγ-quiescent heteroarotinoid **109** was docked, as

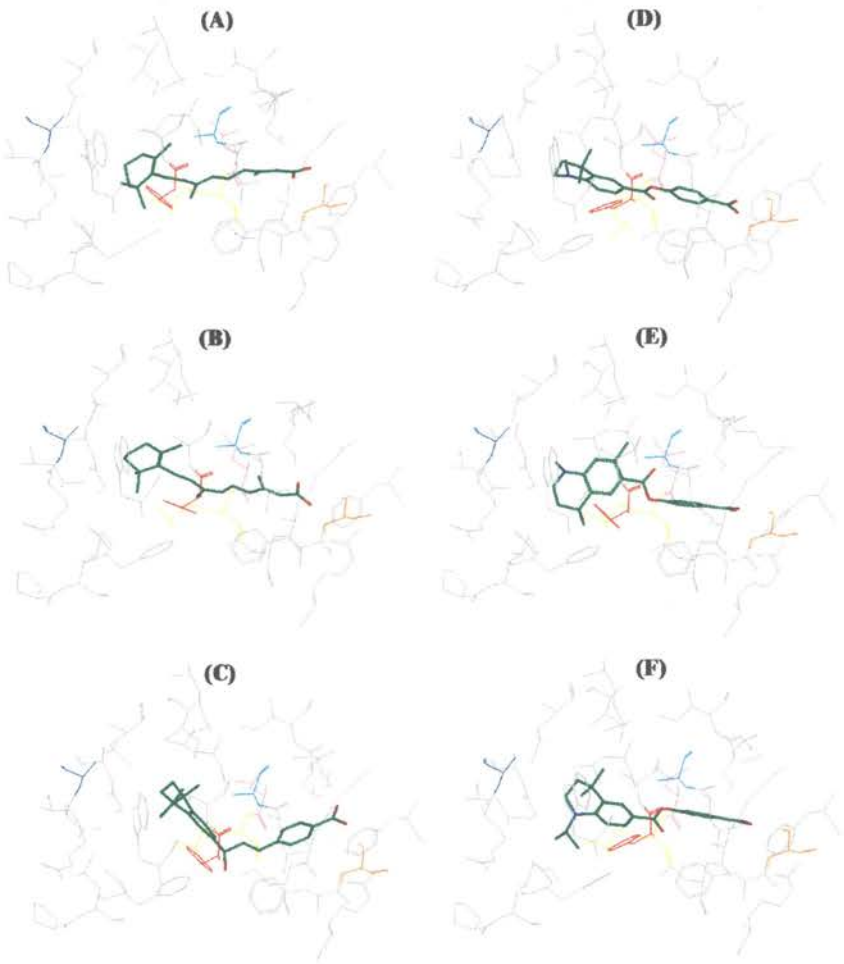


Figure 11. Compounds **2** (**A**), **3** (**B**), **40** (**C**), **107** (**D**), **108** (**E**), and **109** (**F**) docked into the flexible LBP of RARγ. The amino acids Phe 230 (red), Ala 234 (light blue), Leu 271(magenta), Met 272 (yellow), Ser 289 (orange), and Ala 397 (dark blue) are highlighted.

compared to the amino acids residues of the LBP of RARγ after **2** was docked, were: Phe 201 (0.182Å), Trp 227 (0.45Å), Phe 230 (0.893Å), Lys 236 (1.320Å), Cys 237

(0.420Å), Leu 271 (0.244Å), Ile 275 (0.185Å), Ser 289 (0.524Å), Leu 400 (0.128Å), and Met415 (0.121Å).

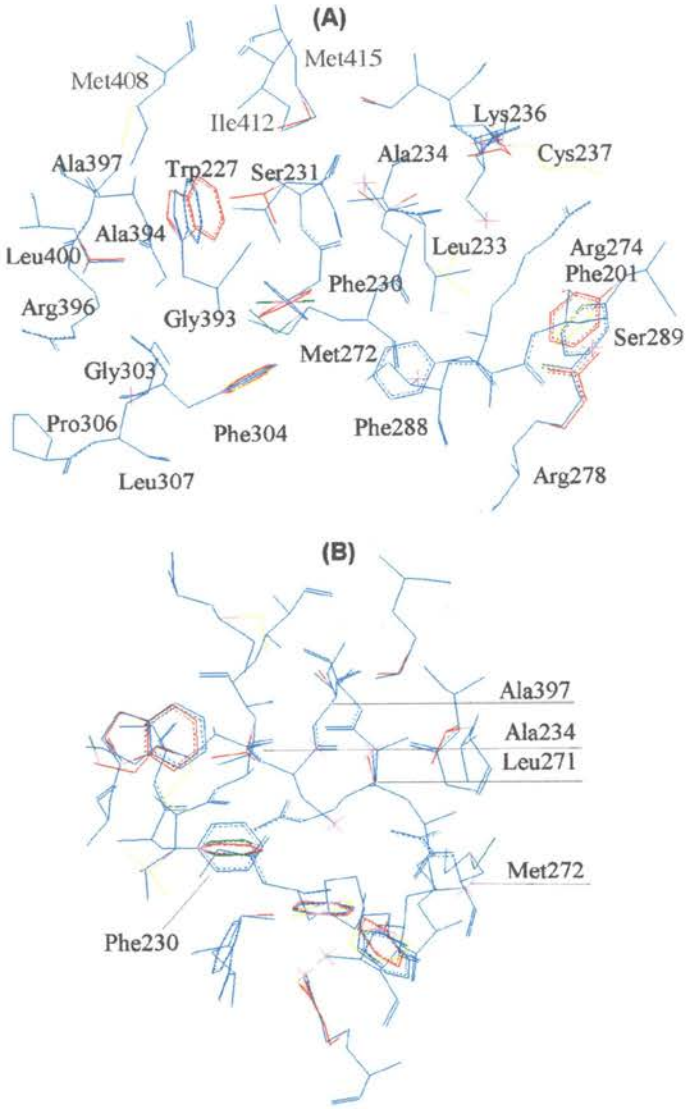


Figure 12. The LBP conformation resulting from *t*-RA (**2**) docking (blue) was superimposed upon conformations of the LBP which resulted from docking of **107** (magenta), **108** (yellow), **109** (red), and **3** (green). (**A**) side view; (**B**) view which resulted from (**A**) after a 90° clockwise rotation about the vertical axis.

After visual inspection and cross-checking the conformational differences where the RMSD value was larger then 0.1Å, it would be appropriate to suggest that in addition to

residues Phe 230, Met 272, Ala 234, and Ala 397, which were responsible for RARγ activity and selectivity, amino acid residue Leu 271 may also be important in the selectivity of the ligand. If Leu 271 was included as a ligand-selectivity factor residue, this could fill the void in the oval shape conformation within the LBP created by residues Phe 230, Ala 234, and Met 272. However, this conclusion is based only upon visual inspection of the LBP of RARγ conformation after docking the ligands and needs to be further verified through site-directed mutagenesis of the LBP of RARγ. Docking the arotinoids **32** and **40** (Table 1), RARγ specific ligands, via a flexible ligand-flexible receptor method, resulted in similar conformations of the LBP of RARγ to those conformations of the LBP which were obtain after docking the *t*-RA (**2**) and heteroarotinoid **108**. The docking of arotinoids **6** and **39** (Table I), which are RARα and RARβ specific, respectively, induced conformational changes in the LBP of RARγ similar to the conformations of the LBP of RARγ generated after **107** and **109** were docked (when compared by superimposition and visual inspection).

The orientation of the Phe230 phenyl ring was different with respect to the remaining residues in the LBP of RARγ after docking the inactive ligands as compared to the orientation found after biologically active ligands were docked into the RARγ. This fact supports findings from mutagenic studies which implicate Phe 230 as the primary residue responsible for the activity or inactivity of the RARγ receptor.[14,37,68,104] The mutation of the Phe 230 residue to Ala 230 or to Gly 230 rendered the receptor inactive.[14] In contrast, mutations in Ala 234, Met 272, and Ala 397 to different residues only partially abolished the activity of the receptor.[14,37,68,104] In addition to the above mentioned mutagenic studies, a proposal can be made that it is not only the presence of Phe 230 in the LBP that is important

for receptor activity, but it is also the orientation of the Phe 230 towards the remaining residues which may play a role regarding the extent to which the receptor is activated. In other words, Phe 230 can act as a "switch" that regulates the level of RARγ activity, and that activity can be switched off to deactivate the receptor.

The orientation difference of the Phe 230 phenyl ring between the LBP of RARγ conformations resulting from docking activating ligands (**2**, **108**) of RARγ, and conformations that resulted from docking inactive ligands (**107**, **109**) of RARγ, was a rotation of the ring approximately 60 degrees. This small shift in position of the Phe230 phenyl ring was perhaps of major importance since Phe 230 is part of the loop between α-helices H1 and H3, which in turn is important for the *ligand binding domain's dimerization surface*. Therefore, any changes that occur at the dimerization surface may prevent the formation of homo- or heterodimers and consequently disrupt the proper activity of the receptor. In the case of docking 9-*c*-RA (**3**), the phenyl ring of Phe 230 was rotated nearly 35 degrees apart from that of the active conformation of the receptor when *t*-RA (**2**) was docked. However, this change may not be significant enough to prevent receptor dimer formation. Moreover the interaction between heterodimeric partners at the dimerization surface may be only slightly weakened, and essentially the activity of 9-*cis*-RA-induced RARγ is not as strong as the activity induced by *t*-RA (**2**). The smaller change in the rotation of the Phe 230 phenyl ring caused by **3** could be due to the conformational change of the Met 272 residue which is pushed away from the core of the LBP cavity by the C19 methyl group of **3**. As a result, the rest of the curved and distorted conformation of 9-*c*-RA (**3**) can be incorporated into the LBP without major disruption of the Phe230 conformation.

The selectivity role of residues Ala 234, Met 272, Ala 397, and Leu 271 would appear to be exhibited through a series of hydrophobic interactions involving parts of the ligand. Since certain amino acid residues occupy the inner core of the LBP of RARγ, the flexibility of such residues, with the exception of Met272, is somewhat limited. It is this limited flexibility of Ala 234, Leu 271, and Ala 397, that may direct the positioning of the ligand within the binding pocket. *If part of the ligand is positioned in such manner that it can interact with these residues through van der Waals repulsion and attraction forces, as in the case of* ***108*** *where the C7 methyl group interacts with Ala 234 and Leu 271, then the rest of the ligand is positioned so as to induce the best interaction with the rest of the LBP.* However, if the structure of the ligand is void of certain groups at specific locations, then the best interactions between the ligand and receptor must come from sources other then from the residues responsible for selectivity, which, in retrospect, may influence the conformation of the remaining residues, such as Phe 230, of the LBP of RARγ and eventually prevent activation of the RARγ receptor.

Understanding the ligand-receptor structure-activity relationship is very important in designing isoform specific agents for alleviating of unwanted side-effects. However, more research is needed, and perhaps the discovery of a new method that would enable studies of the dynamic nature of the receptor activities would be a step in the right direction.

Summary

Computer-aided modeling was a good guide in the design of new heteroarotinoids with various linkage groups. The twenty-one new heteroarotinoids should serve as models in the understanding of the role of RAR and RXR families of receptors and, in general, the

mechanisms of action for all nuclear receptors. Furthermore the design of compounds described above was aimed at one receptor isotype-specific activation which eventually could serve as a platform for the invention of potentially effective anticancer agents with high activity and low toxicity. The refinement of heteroarotinoid structures, via adaptation of a fluorine atom property, repositioning of the key groups at the ligands non-polar end, altering the linker flexibility, and changing the polar end functionality could lead to better interaction between the receptor and the ligand.

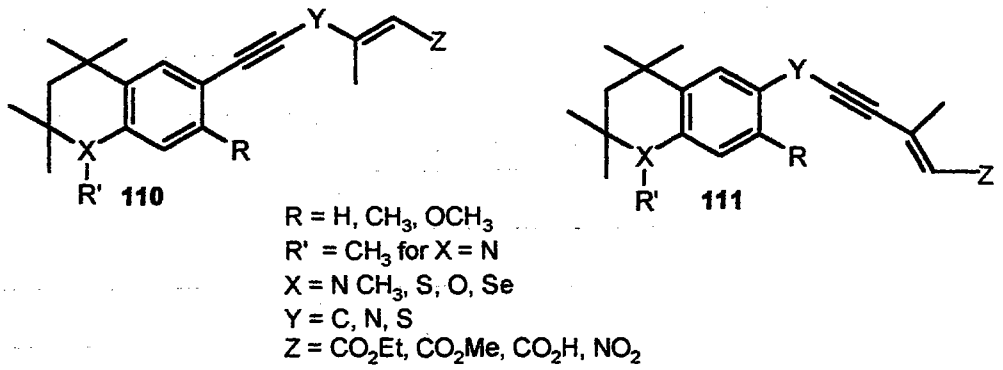
Suggestions for Future Work

Future research in retinoid chemistry should be focused on the generation of isoform specific, non-toxic heteroarotinoids. The specificity of the retinoid could be enhanced either by increasing the rigidity or by fine-tuning and manipulating the structure of ligands so as to create a good match for the three dimensional structure of only one isotype of RAR or of RXR. The former might be accomplished by the attachment of unsaturated rings structures to the linker which could reduce or minimize the ligand flexibility and lock the ligand into one conformation. One problem with this approach, however, is that the toxicity associated with poly-aryl moieties and their metabolites is known to cause variety of disorders.[133] The introduction of a triple bond in the linker (as in **30**) of a ligand structure may be another way to increase the rigidity of the heteroarotinoids.[23]

Matching the 3-D space of the active conformation in a receptor's LBP can be accomplished through careful studies of the LBP found in the crystallographic structures of a receptor as such become available, mapping the LBP with the aid of computer modeling software, and then deciding which part of the ligand structure needs alteration. A

combination of avenues for ligand design is perhaps a another way to address the problem.

Sulfur and nitrogen heteroarotinoids appear to have promising activity with an additional advantage being that the nitrogen compounds can easily be converted to their corresponding water soluble salts (added HX) which is helpful in drug formulation. Heteroarotinoids **110** and **111** are suggested structures for future exploration in retinoid research. Compound **110** has a semi-rigid linker whose orientation and conformation



mimics that of *t*-RA (**2**) (Figure 13) and may specifically bind to the RAR family only. The placement of the Y group in the linker may further reduce the toxic effects of retinoids. When the Y is nitrogen or sulfur, the increased polarity of the compound as a whole may reduce its fat soluble property, and thus the half life of the ligand stored in the fat tissue might be shortened.[22] Additionally, such a Y moiety could provide a functional group that could be utilized for further refinement of structures to enhance the receptor selectivity via attachment of different moieties. Rigidity is increased through the introduction of a triple bond (as in **30**) which could also enhance the selectivity by restraining the rotational freedom of the ligand and prohibiting conformational adaptation toward other isotypes. The overall dimensions and conformations of the ligands are still in close proximity to those of

t-RA (**2**) (Figure 13). Heteroarotinoid **111** has the same basic functionality as **110**. However, due to its conformational resemblance to 9-*c*-RA (**3**), the former would likely bind to RXR whereas the latter should bind to RAR only.[22]

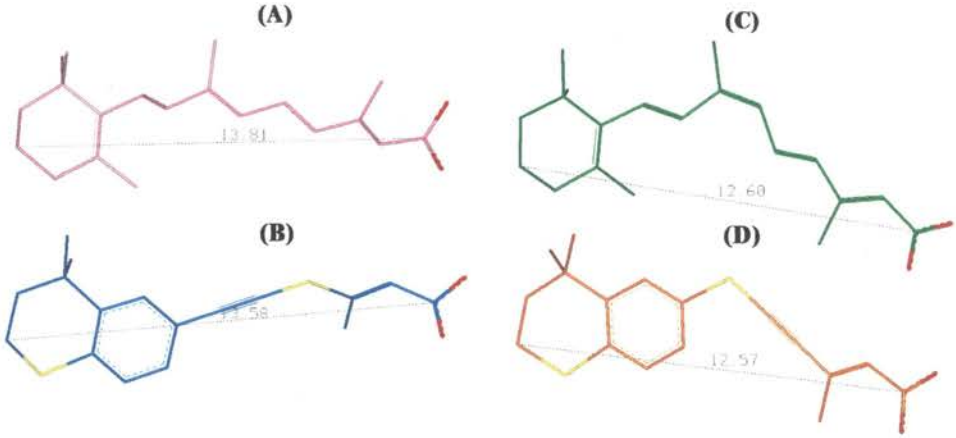


Figure 13. Comparison of *t*-RA [(**2**), **A**] with **110** (**B**) and 9-*c*-RA [(**3**), **C**] with **111** (**D**). The distances (Å) and overall conformation similarities between the two pairs of compounds were noted.

CHAPTER III

EXPERIMENTAL SECTION

Molecular Modeling

Compound Drawing and Energy Minimization

All ligands were drawn using the Builder module and fragment library in Insight II Discover 97 (Molecular Simulation Inc. (MSI) 9685 Scranton Road, San Diego, CA, 92121-2777).[30] The atom and bond types were assigned accordingly using the consistent valence force-field (cvff) parameters. The geometries of the ligands were optimized with the program MOPAC, a calculation module in the Insight II modeling package. The MOPAC parameters were set as follows:

- The electronic energy state was set to the "lowest" energy level with unrestricted electron spins where different spins use different orbitals,
- the calculation method was AM1,
- the convergent gradient was set to 0.1 kcal/mol Å,
- the gradient minimizing type was Non Linear Least Square (NLLSQ) method which can detect transition state and local minimums, and
- the minimizer for geometry optimization of the ligands was the Broyden-Fletcher-Goldfarb-Shano (BFGS) method.[38]

The charges of the ligands were calculated using the Gasteiger-Huckel method with pre-assigned formal charges for the carboxylate anion as -0.5 kcal/mol electrons for each oxygen

atom. After the geometry optimization for the ligands, the ligands were saved in "mol2" format for further use in Sybyl 6.5 (Tripos, Inc. 1699 Hanly Road, St. Louis, Mo, 63144-2913).[126]

Protein Modification

The crystallographic structure of RARγ was obtained from the Protein Data Bank (PDB, Brookhaven National Laboratory, Upton, NY, 11973). The PDB ID number for RARγ crystallographic structure was "2LBD", and the molecule was downloaded with the co-crystallized *t*-RA (**2**) and water molecules (~100). The protein was modified with the Biopolymer module in Sybyl 6.5 by deleting water molecules,[126] extracting *t*-RA (**2**), checking atom and bond types, adding hydrogens and valencies, and calculating charges via the Kollman method.[71] The total resulting electronic charge of modified RARγ was -3.04 kcal/mol electrons. The pseudo-LBP of RARα and pseudo-LBP of RARβ were obtained from a modified LBP of RARγ by the mutation of three and two amino acid residues, respectively.[47] The conversion of RARγ to pseudo-RARα was done by mutating Ala 234 to Ser 234, Met 272 to Ile 272, and Ala 397 to Val 397. Similarly, the RARγ to pseudo-RARβ conversion was done by changing two amino acid residues, Met 272 and Ala 397 to Ile 272, and Val 397, respectively. Since Ala 225 in RARβ corresponds to Ala 234 in RARγ, the change was not made at this position. This mutation procedure was performed by using the Biopolymer module in Sybyl 6.5, and the mutated receptors were then minimized in Sybyl 6.5 via use of Amber force field with the Powell method of line search and the gradient RMS set to 0.005 kcal/mol Å.[64] The minimization was allowed to proceed for 1000 iterations to give the final pseudo LBPs of RARα and RARβ.

Docking

The program Fexidock, which is a component of the Biopolymer module in the Sybyl 6.5 molecular modeling software package, was used for docking the ligands into the modified crystallographic structure of RARγ, pseudo-RARα, and pseudo-RARβ. Flexidock is a docking program that attempts to fit a mobile, usually flexible, ligand into a region of a fixed or flexible receptor. This can be viewed as a global optimization problem for which Flexidock's genetic algorithm calculation method is well suited. The genetic algorithm mimics evolutionary behavior and expresses potential solutions which are different conformations of a ligand-receptor complexes known as a population of "chromosomes".[110] Each chromosome consists of a number of "genes" which are parameters to be optimized, such as torsional angles, rotations around bonds, or translation of the ligand in the binding pocket of the receptor. A fitness scoring function rates each chromosome, and the competition between chromosomes yields a set of results.[71] Evolution occurs by a random change in the numerical value of the gene, referred to as a "mutation" or by chromosomes exchanging genes, known as a "crossover". Since the best solutions of the fittest generation are kept, the quality of the solution increases with time. Flexidock incorporates the van der Waals, electrostatic, torsional and constraint energy terms of the Tripos force field, while the bond stretching, angle bending, and out of plane bending terms, which are invariant in torsion-space optimization, are ignored. To calculate the interaction energy between the site and the ligand atoms, coordinates of the atoms are converted to an index in the lattice field. A simple linear expression then yields the energy of interaction between the site and a particular atom of the ligand, which, when summarized, yields the overall site-ligand

interaction energy. More precisely, the total energy of steric and electrostatic interactions between the ligand and the receptor is given by :

$$E_{interaction} = \sum_i \sum_j \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{Bij}{r_{ij}^{6}} + \frac{q_i q_j}{r_{ij}\varepsilon} \right)$$

where:

- A_{ij} and B_{ij} are the Lennard-Jones steric attractive and repulsive contributions between atoms of the ligand and the receptor (units are: kcal mol^{-1} $Å^{12}$ and kcal mol^{-1} $Å^{6}$, respectively, for A_{ij} and B_{ij}),
- r_{ij} is the distance between the receptor atom and the grid point nearest to the atom of the ligand (Å),
- the ϵ is the potential well depth for ligand and receptor (kcal mol^{-1})
- the q_i and q_j are the atomic charges (kcal/mol-electrons) in the ligand and receptor, respectively.

Docking Procedure

The validity of the Flexidock program was checked by removing the *t*-RA (**2**) from the crystallographic structure of RARγ and docking it back to the rigid structure of RARγand then comparing the results (energies and conformations) from docking with the original crystallographic structure. Before re-docking the *t*-RA (**2**), the receptor was modified as described previously. In addition, the *t*-RA (**2**) was also modified by adding hydrogen atoms, charges, and checking for correct atom and bond types. The resulting conformation and the positioning of *t*-RA (**2**) into the binding pocked after docking was

analyzed and compared with the original LBD of RARγ co-crystallized with *t*-RA (**2**), via superimposition. The overall RMSD of the docked conformational complex was not larger than 0.4Å for any atoms of *t*-RA (**2**), a situation generally considered to validate a good match.

For docking the flexible ligand into the rigid receptor, the default parameters of the Flexidock program were used with the exception that the non-rotational ("non_rot")bonds were activated to allow for rotation around amide and ester bonds in the ligand. The ligands were pre-positioned in the ligand binding pocket (LBP) defined by the following residues: Phe 201, Thr 227, Phe 230, Ser 231, Leu 233, Ala 234, Lys 236, Cys 237, Leu 271, Met 272, Arg 274, Ile 275, Arg 278, Phe 288, Ser 289, Gly 303, Phe 304, Pro 306, Leu 307, Gly 393, Ala 394, Arg 396, Ala 397, Leu 400, Met 408, Ile 412, and Met 415 with a radius of about 6 Å around the defined binding pocket. The random seed number, which specifies the initial population of ligand conformations, was set to 15,000, and the generation number was different for each series of calculations (see Table III in the Discussion).

The tournament method, where a new parent conformation is chosen by competition between pairs of all conformations and the conformation with a predetermined potential that it would produce more-fit conformations of a new generation when mutated, was chosen as the scoring method (See the Flexidock manual). After the calculation was completed, 20 ligand-receptor complexes with the best interaction energies were saved and compared with the resulting conformations involving the same ligand and receptor from previous series of calculations. The energies of interaction energies for compounds **48-68** with RARγ are in Table VII. The positive energies of interaction signified bad steric hindrance between the atoms of the ligand and the atoms of RARγ. *The results in Table VII are a representation*

TABLE VII

ENERGIES OF INTERACTION FROM DOCKING FLEXIBLE LIGAND INTO FIXED LBP OF RARγ[a]

Heteroarotinoid	Interaction Energies (kcal/mol)	
	R1 (35,000)	R2 (65,000)
t-RA (2)	-55.45	-78.63
48	- 23.92	-39.39
49	59.32	48.91
50	24.48	16.92
51	16.34	6.98
52	79.34	66.83
53	-98.45	-129.73
54	-87.32	-138.37
55	-123.99	-166.88
56	89.32	76.15
57	97.66	93.41
58	3.73	-1.39
59	-145.43	-177.82
60	18.49	14.72
61	56.94	44.38
62	101.87	72.45
63	-93.45	-98.71
64	2.76	-1.83
65	-21.38	-32.59
66	49.21	44.82
67	87.38	56.81
68	1.38	-9.42

[a]The negative Energy of Interaction = Favorable; Positive Energy of Interaction = Not favorable

of only the best values for energy of interaction of two separate series of calculations. Each series of calculations resulted in twenty final conformations (millions of conformations are generated during calculations) of the ligand-receptor complex which were then ranked in descending order for energies of interaction between the ligand and the RARγ.

Docking of a flexible ligand into the flexible receptor required some changes in the parameter default set of the Flexidock program, namely:

- to press for a more rigorous calculation of the interactive energy between the ligand and the receptor,
- the hydrogen van der Waals radii were change from 1.0 Å to 1.5 Å,
- the hydrogen van der Waals epsilon was changed from 0.03 to 0.042,
- and the van der Waals cutoff distance was adjusted from 16 Å to 8 Å,
- the parameter options "use_backbone" and "use_constrains" were turned on.
- the mutational windows for torsion and rotation were changed from 60 degrees to 30 degrees to assure the generation of additional ligand-receptor conformations and
- the generation number for two series of calculations for each docking procedure for a ligand was set at 45,000 and 60,000.

The data from these calculation were saved in an appropriate database for future comparison and analysis.

Superimposition of the Receptor Conformations

Following the flexible ligand-flexible receptor docking operations, the resulting conformations of the LBP of RARγ were analyzed by superimposition onto the LBP of the RARγ conformation that resulted from docking *t*-RA (**2**). Prior to the superimposition of

receptor conformations on each other, the ligand structures were extracted and saved for future use. The Superimpose module in Sybyl 6.5 was used and "all" of the atoms from the ligand docked LBP of RARγ conformation were chosen to be superimposed on "all" the atoms of the LBP of RARγ that resulted from docking *t*-RA (**2**). A database with the Root Mean Square Deviations (RMSD) between two LBPs of RARγ conformations was created and saved.

Conformational Search

The compounds used in the QSAR and CoMFA calculations and also 9-*c*-RA (**3**) used for docking purposes were searched for the minimal energy conformations that were best matched to the crystallographic structure[14] of *t*-RA (**2**) co-crystallized with RARγ. The crystallographic structure of **2** was then retrieved and modified via the addition of hydrogen atoms and charges. The program "Discover", which is a module of Insight II from MSI, was used for the conformational search. The method used for this conformational search was "Torsional Force" which is a subroutine of Discover. The Torsional Force employs an external force field that is applied about a specific dihedral angle during minimization. The force constant for this type of calculation was set to 200. The grid scan algorithm of each dihedral angle was set from 0 degrees to 360 degrees with an 18 degree step size. This implies that for each dihedral angle, 20 new conformations were created which were then minimized. Thus, with this set up for ligands with n dihedral angles, 20^n conformations were generated for each ligand. The quasi-Newton-Rapshon algorithm (VA09A),[38] which is time efficient, was chosen for the minimization with the derivative set to 0.001 kcal/mol Å, and the minimization of each new conformation was run for 100 iterations. The resulting conformations of the compounds were then screened by the creation of a Ramachandran

plot[111] with the two torsional angles as the X and Y axes and the energy value as a gradient with an energy rise of 1 kcal/mol. For compounds with more than two torsional angles, the process of screening conformations was repeated until all of the conformations with different tortional angles were evaluated. Twenty conformations of each ligand, which were energetically low, and resembled the crystallographic 3-D orientation of *t*-RA (**2**) retrieved from RARγ, were used for QSAR calculations. The conformation of 9-*c*-RA (**3**) which most resembled that of *t*-RA (**2**), which was slightly more "linearly stretched" than the minimal energy conformation of 9-*c*-RA (**3**) and deviated from the minimal energy conformatiom 9-*c*-RA (**3**) by only 0.87 kcal/mol (larger, than minimal conformation energy) in energy value, was chosen for the docking.

Activity Prediction

The programs QSAR, CoMFA, and Molecular Spread Sheet were used for predicting the activity of RAR and RXR isotype receptors in the CV-1 cell by compounds **45-65**. For predicting the activity in the receptor isotypes of RXR, 20 conformations of each compound with a known EC_{50} were used, and from these 20 conformations only one, in which the predicted EC_{50} value was the closest to the actual value, was used in the prediction of activity of the EC_{50} for the untested compounds **45-65**. In the prediction of EC_{50} values for the RAR isotypes (α, β, and γ), only the conformations of the ligands that were docked into RARγ, pseudo RARα, and pseudo-RARβ, and then extracted from the RARs ligand binding pockets (LBPs), were used. A total of six predictions, one for each isotype of RAR and RXR, were run for each heteroarotinoid **45-65**. Before the CoMFA calculation were applied, the database with all the compounds (compounds with known EC_{50} values and **45-65**) and their conformations were aligned via the command "Align Database",

with additional manual positioning for the thiosemicarbazone compounds. The CoMFA field of ligand sets was calculated using the default set-up (Sybyl 6.5) and then entered into the Molecular Spread Sheet. The known EC_{50} values were entered as log ($1/EC_{50}$), and a Partial Least Square (PLS) analysis was done twice, first with cross-validation analysis (which gave q^2) and second with "non-validation" analysis (which gave r^2). The q^2 and r^2 values are summarized in Table VIII.

The data from QSAR analysis were analyzed via the command "View CoMFA" in which the graphic representation of the compound in steric and electrostatic fields could be viewed

TABLE VIII

THE Q^2 AND R^2 VALUES FROM PLS ANALYSIS.[a]

Receptor Isotype	q^2	r^2	% certainty
RARα	0.43	0.97	42
RARβ	0.58	0.95	55
RARγ	0.51	0.99	50
RXRα	0.49	0.95	47
RXRβ	0.56	0.99	55
RXRγ	0.45	0.96	43

[a]q^2 is the correlation coefficient of explained variation in activity-structure relationship, r^2 is the correlation coefficient, and the percent certainty is (q^2 x r^2) x 100. The equation for calculating q^2 is given below where Y_{pred} is a predicted value, Y_{actual} is the actual experimental value, and Y_{mean} is the best of the mean of all values that might be predicted.

$$q^2 = 1 - \frac{\sum_Y (Y_{pred} - Y_{actual})^2}{\sum_Y (Y_{actual} - Y_{mean})^2}$$

of the ligands allowed for more detailed analysis and possible explanations of the

predicted activities as opposed to just superimposition of the ligands on each other and then trying to correlate the difference in activity to RMSD of atoms in the ligands. The predicted values were saved for further use.

Chemistry

General Information

Some ^{1}H, and ^{13}C NMR spectra were recorded on a ^{UNITY}*INOVA* 400 NB NMR spectrometer operating at 399.99 Hz and 100.01Hz, respectively. The broadband Gemini 2000 High-Resolution NMR (300 MHz) spectrometer was also used for obtaining a few ^{1}H, ^{13}C, and ^{19}F spectra operating at 299.97 Hz, 75.12 Hz, and 282.32 Hz, respectively. All ^{1}H and ^{13}C signals were referenced to TMS, and ^{19}F spectra were referenced to $F_3CC(O)OD$. The common refference for ^{19}F is F_3CCO_2H.[105] The instrument's name and the nucleic examined appear in the parameter table which is at the top-left corner of a ^{1}H and ^{13}C NMR spectra. IR spectra were recorded on a Perkin Elmer 2000 FT-IR as 'neat' or as KBr pellets. GC-MS spectra were obtained using an HP G1800A GCD system with acetone as the solvent of choice. Melting points were determined with a Thomas-Hoover melting point apparatus and were not corrected. All synthesis where carried out under N_2, unless indicated otherwise, and with the aid of magnetic stirrer.

All commercial reagents and reagent grade solvents were used without further purification unless described otherwise. The chromatography support used was J. T. Baker 40 μm mesh flash chromatographic packing. Elemental analysis were performed by Atlantic Microlabs, Inc. Norcross, GA, 30091.

[(6-Methoxy-1,1,4,4-tetramethylisochroman-5-yl)amino][(4-nitrophenyl)amino]methane-1-thione (**48**)

(6-Methoxy-1,1,4,4-tetramethylisochroman-5-yl)amine [(**71**), 200 mg, 0.85 mmol] dissolved in 5 mL of dry THF was placed in an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and addition funnel. The reaction mixture was then cooled to –5 °C (ice and NaCl), and 4-nitrophenylisothiocyanate (160.7 mg, 8.92 mmol, 1.05 eq) dissolved in 6 mL of dry THF was then added dropwise (1 h). After the addition, the reaction mixture was allowed to warm to RT and was then stirred for 24 h. The solvent was evaporated (rotovap), and resulting solid was recrystallized (H_2CCl_2:pentane, 1:1) to afford **48** as a light yellow solid (mp 181-2 °C, 251 mg, 71%). IR (KBr pellet) 3368 [N-H], 3214 [N-H] cm^{-1}; ^1H NMR [$D_3C(O)CD_3$] δ 1.24 [s, 6 H, $C(CH_3)_2$], 1.46 [s, 6 H, $C(CH_3)_2$], 3.56 [s, 2 H, OCH_2], 3.87 [s, 3 H, Ar-OCH_3], 7.01 [d, 1 H, J = 8.7 Hz, Ar-*H*], 7.25 [d, 1 H, J = 8.7 Hz, Ar-*H*], 7.60 [bs, 1 H, N-*H*], 8.01 [d, 2 H, J = 8.5 Hz, Ar-*H*], 8.15 [d, 2 H, J = 8.5 Hz, Ar-*H*], 8.48 [bs, 1 H, N-*H*]; ^{13}C NMR [$D_3C(O)CD_3$] ppm 18.06 [$C(CH_3)_2$], 26.72 [$C(CH_3)_2$], 28.91 [$C(CH_3)_2$], 34.54 [$C(CH_3)_2$], 56.10 [$C(CH_3)_2OCH_2$], 75.55 [$C(CH_3)_2OCH_2$], 108.65 [Ar-OCH_3], 122.11-145.87 [Ar-*C*], 181.15 [*C*=S]; Anal. Calcd for $C_{21}H_{25}O_4N_3S$: C, 60.70; H, 6.06; N, 10.11; S, 7.71. Found: C, 60.63; H, 6.01; N, 10.11; S, 7.69.

N-{[(6-Methoxy-1,1,4,4-tetramethylisochroman-5-yl)amino]tioxomethyl}(4-nitrophenyl)-carboxamide (**49**)

(6-Methoxy-1,1,4,4-tetramethylisochroman-5-yl)amine [(**71**), 200 mg, 0.85 mmol] dissolved in 5 mL of dry THF was placed in an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and addition funnel. The reaction

mixture was then cooled to –5 °C (ice and NaCl), and ethyl (4-nitrophenyl)oxomethanisocyanate (186 mg, 8.92 mmol, 1.05 eq) dissolved in 5 mL of dry THF was then added dropwise (1 h). After the addition, the reaction mixture was allowed to warm to RT and was then stirred for 24 h. The solvent was evaporated (rotovap), and the resulting solid was recrystallized ($HCCl_3$:pentane, 1:2) to afford **49** as a yellow solid [mp 179 °C (dec), 305 mg, 81%]. IR (KBr pellet) 3229 [N-H], 3171 [N-H], 1686 [C=O] cm^{-1}; ^1H NMR [$D_3C(O)CD_3$] δ 1.33 [s, 6 H, $C(CH_3)_2$], 1.56 [s, 6 H, $C(CH_3)_2$], 3.57 [s, 2 H, OCH_2], 3.80 [s, 3 H, Ar-OCH_3], 6.85 [d, 1 H, J = 8.3 Hz, Ar-*H*], 7.10 [d, 1 H, J = 8.3Hz, Ar-*H*], 8.10 [d, 1 H, J = 7.8 Hz, Ar-*H*], 8.39 [dd, 1 H, J = 7.8 Hz, Ar-*H*], 10.85 [s, 1 H, N-*H*], 11.82 [s, 1 H, N-*H*]; ^{13}C NMR ($D_3C(O)CD_3$) ppm 24.10 [$C(CH_3)_2$], 26.67 [$C(CH_3)_2$], 34.55 [$C(CH_3)_2$], 56.05 [$(CH_3)_2OCH_2$], 71.34 [$OC(CH_3)$], 111.19 [Ar-OCH_3], 124.24-135.77 [Ar-*C*], 168.77 [*C*=O], 182.56 [*C*=S]; Anal. Calcd for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.68; N, 9.47; S, 7.23. Anal. Calcd for $C_{22}H_{25}N_3O_5S \cdot 0.6\ H_2O$: C, 58.16; H, 5.70; N, 9.24; S, 7.05. Found: C, 57.98; H, 5.47; N, 9.15; S, 7.02.

<u>Ethyl 4-{[*N*-(6-Methoxy-1,1,4,4-tetramethylisochroman-5-yl)carbamoyl]amino}benzoate-(**50**)</u>

(6-Methoxy-1,1,4,4-tetramethylisochroman-5-yl)amine [(**71**), 200 mg, 0.85 mmol] dissolved in 5 mL of dry THF was placed in an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and addition funnel. The reaction mixture was then cooled to –5 °C (ice NaCl), and ethyl 4-isocyanatobenzoate (170.6 mg, 8.92 mmol, 1.05 eq) dissolved in 5 mL of dry THF was the added dropwise (1 h). After the addition, the reaction mixture was allowed to warm to RT and was then stirred for 24

h. The solvent was evaporated (rotovap), and the resulting solid was recrystallized (H_2CCl_2:pentane, 2:1) to afford **50** as a white solid (mp 147-9 °C,. 265 mg, 73%).; IR (KBr) 3343 [N-H], 3201 [N-H], 1713 [C=O], 1673 [C=O], cm^{-1}; ^1H NMR [$D_3C(O)CD_3$] δ 1.23 [s, 6 H, $C(CH_3)_2$], 1.26[t, 3 H, OCH_2CH_3], , 1.36 [s, 6 H, $C(CH_3)_2$], 3.47 [s, 2 H, OCH_2], 3.85 [s, 3 H, Ar-OCH_3], 4.33 [q, 2 H, OCH_2], 6.90 [d, 1 H, J = 7.3Hz, Ar-*H*], 7.15 [d, 1 H, J = 7.3 Hz, Ar-*H*], 7.58 [d, 2 H, J = 7.6 Hz, Ar-*H*], 7.84 [d, 2 H, J = 7.6 Hz, Ar-*H*], 8.23 [s, 1 H, N-*H*], 8.98 [bs, 1 H, N-*H*]; ^{13}C NMR [$D_3C(O)CD_3$] ppm 14.52 [OCH_2CH_3] 27.93 [$C(CH_3)_2$], 28.66 [$C(CH_3)_2$], 54.81 [$C(CH_3)_2$], 60.88 [OCH_2CH_3], 71.73 [$(CH_3)_2OCH_2$], 75.37 [$OC(CH_3)$], 107.24 [Ar-OCH_3], 116.80-145.71 [Ar-*C*], 153.4 [*C*=O], 156.47 [*C*=O]; Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 67.58; H, 7.08; N, 6.56. Found: C, 67.50; H, 7.10; N, 6.48.

<u>{[(1*E*,3*E*)-1-Aza-4-(4,4-dimethylchroman-6-yl)-3-fluoropenta-1,3-dienyl]amino}amino-methane-1-thione (**51**)</u>

Thiosemicarbazide (35.0 mg, 0.38 mmol) dissolved into 4 mL of water and AcOH (1 drop) was placed in a 10-mL beaker. Then aldehyde [(**75**), 95 mg, 0.38 mmol] was dissolved in 5 mL of EtOH (95%). The latter solution was warmed to 60 °C and then was added dropwise to the thiosemicarbazide solution while hot. A precipitate formed immediately. The reaction mixture was set aside for 24 h at 0 °C, and then the solid was filtered off. Recrystallization (EtOAc:diethyl ether, 1:1) of the solid afforded an white solid **51** (mp 231-2 °C, 100.1 mg, 82 %). IR (neat) 3444 [N-H], 3304 [N-H], 3205 [N-H] cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.30 [s, 6 H, $C(CH_3)_2$], 1.78 [t, 2 H, OCH_2CH_2], 2.10 [d, 3 H, =C-CH_3,], 4.19 [t, 2 H, OCH_2CH_2], 6.27 [d, 1 H, J = 8.4 Hz, Ar-*H*], 6.98 [dd, 1 H, J = 8.4 Hz, J = 2.1 Hz, Ar-*H*], 7.24 [d, 1 H, J = 2.1 Hz, Ar-*H*], 7.44 [s, 1 H, N-*H*], 7.65 [d, 1 H, J =

20.7 Hz, FC=C*H*], 8.21 [s, 1H, N-*H*], 11.31 [s, 1 H, N-*H*], ^{13}C NMR (DMSO-d_6) ppm, 17.22 [=C-CH_3], 30.27 [*C*-(CH_3)$_2$], 30.57 [C-(CH_3)$_2$], 36.83 [OCH_2CH_2], 62.58 [OCH_2CH_2], 116.58 [=*C*H], 121.81-131.67 [CH=*C*-Ph], 153.32 [F*C*=CH] 178.75 [*C*=S]. Anal. Calcd for $C_{16}H_{20}FN_3OS$: C, 59.79; H, 6.27; N, 13.07. Found: C, 59.67; H, 6.37; N, 13.10.

Ethyl 4-{[(4,4-Dimethylchroman-6-yl)ethoxy]carbonylamino}benzoate (**52**)

Powdered sodium hydride (23 mg, 0.97 mmol, 95%) was suspended in 5 mL of freshly distilled THF (5 mL) in an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and two addition funnels. The reaction mixture was then cooled to 0 °C, and 1-(4,4-dimethylchroman-6-yl)ethanol (200 mg, 0.97 mmol) dissolved in 5 mL of THF was added dropwise (30 min). The reaction mixture was stirred at this temperature (1 h) after which time ethyl 4-isocyanatobenzoate (185 mg, 0.97 mmol) dissolved in 5 mL of dry THF was added dropwise (1 h). The reaction mixture was allowed to warm to RT with continuous stirring for 8 h, followed by cooling to 0 °C and quenching with a solution of saturated, aqueous ammonium chloride (4 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were then washed with H_2O (2 x 5 mL) and brine (1 x 10 mL) and dried ($MgSO_4$, 24 h). Evaporation (rotovap) of the solvent and recrystallization (ethyl acetate:H_2CCl_2:hexane, 1:1:1) afforded **52** as a white solid (mp 109-11 °C, 262 mg, 68%). IR (KBr pellet) 3302 [N-H], 1744 [C=O], 1732 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.41 [s, 6 H, C(CH_3)$_2$], 1.54 [t, 3 H, OCH_2CH_3], 1.90 [d, 2 H, OCH_2CH_2] 4.02 [d, 2 H, OCH_2CH_2], 4.02 [q, 2 H, OCH_2CH_3], 5.81 [q, 1 H, $CHCH_3$], 6.85 [dd, 1 H, J = 8.3Hz, J = 2.7 Hz, Ar-*H*], 7.05 [d, 1 H, J = 2.7 Hz, Ar-*H*], 7.25 [d, 1 H, J = 8.3 Hz, Ar-*H*], 7.65 [d, 1 H, J = 7.4 Hz, Ar-

H], 8.05 [d, 1 H, J = 7.4 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.02 [OCH_2CH_3], 14.10 [$C(CH_3)_2$], 60.97 [OCH_2CH_2], 61.17 [OCH_2CH_2], 120.32-141.14 [Ar-*C*], 165.68 [*C*=O], 178.93 [*C*=O]; Anal. Calcd for $C_{23}H_{26}NO_5$: C, 69.40; H, 6.84; N, 3.52. Found: C, 69.27; H, 6.92; N, 3.45.

Ethyl 4-{[(1,2,2,4-Tetramethyl(1,2-dihydroquinol-6-yl)carbamoyl]amino]benzoate (**53**)

(1,2,2,4-Tetramethyl-1,2-dihydroquinol-6-yl)amine (**82**, 150 mg, 0.74 mmol) dissolved in 4 mL of dry THF was placed in an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and addition funnel. The reaction mixture was then cooled to -5 °C (ice and NaCl), and ethyl 4-isocyanatobenzoate (148.5 mg, 7.78 mmol, 1.05 eq) dissolved in 5 mL of dry THF was then added dropwise (30 min). After the addition, the reaction mixture was allowed to warm to RT and was then stirred for 24 h. The solvent was evaporated (rotovap), and the resulting solid was recrystallized ($HCCl_3$:pentane, 1:1) to afford **53** as a white, flaky solid (mp 211-12 °C, 206 mg, 71%). IR (KBr pellet) 3352 [N-H], 3262 [N-H], 1709 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.29 [s, 6 H, N-C-(CH_3)], 1.36 [t, 3 H, OCH_2CH_3], 1.63 [bs, 1 H, N-*H*], 1.94 [s, 3 H, =C-CH_3], 2,87 [s, 3 H, N-CH_3], 4.37 [q, 2 H, OCH_2CH_3], 5.33 [s, 1 H, =C*H*], 6.47 [d, 1 H, J = 8.3 Hz, Ar-*H*], 6.67 [bs, 1 H, N-*H*], 6.97 [d, 1 H, J = 1.9 Hz, Ar-*H*], 7.13 [q, 1 H, J = 1.9 Hz, J = 8.3 Hz, Ar-*H*], 7.4 [d, 2 H, J = 9.0 Hz, Ar-*H*], 7.92 [d, 2 H, J = 9.0 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.33 [OCH_2CH_3], 18.50 [=C-CH_3], 27.21 [2 C, $C(CH_3)_2$], 30.75 [N-CH_3], 56.39 [=C-$C(CH_3)_2$], 60.70 [OCH_2CH_3], 111.11 [=*C*-CH_3], 118.14 [=*C*-$C(CH_3)_2$], 120.64-143.96 [Ar-*C*], 154.23 [*C*=O], 180.45 [*C*=S]. TLC Analysis for $C_{23}H_{27}N_3O_3$ showed one spot in the following solvent systems: hexane:diethyl ether:H_2CCl_2, (1:1:1),R_f 0.46; chloroform:pen-

tane, (2:1), R_f 0.40; hexane:EtOAc, (2:1), R_f 0.18. Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.65. Anal. Calcd for $C_{23}H_{27}N_3O_3 \cdot 0.3\ H_2O$: C, 68.63; H, 7.01; N, 10.44. Found: C, 68.63; H, 6.75; N, 10.35.

Ethyl 4-({[(1,2,2,4-Tetramethyl-1,2-dihydroquinol-6-yl)amino]thioxomethyl}amino)-benzoate (**54**)

(1,2,2,4-Tetramethyl-1,2-dihydroquinol-6-yl)amine (**82**, 150 mg, 0.74 mmol) dissolved in 4 mL of dry THF, was placed in an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and addition funnel. The reaction mixture was then cooled to -5 °C (ice and NaCl), and ethyl 4-isothiocyanatobenzoate (161 mg, 7.78 mmol, 1.05 eq) dissolved in 5 mL of dry THF was then added dropwise (30 min). After the addition, the reaction mixture was allowed to warm to RT and was then stirred for 24 h. The solvent was evaporated (rotovap), and the resulting solid was recrystallized (H_2CCl_2:pentane, 1:2) to afford **54** as a pale yellow solid (mp 161-2 °C, 275 mg, 91%). IR (KBr pellet) 3344 [N-H], 3289 [N-H], 1712 [*C=O*] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.34 [s, 6 H, N-C-(CH_3)], 1.37 [t, 3 H, OCH_2CH_3], 1.60 [bs, 1 H, N-*H*], 1.95 [s, 3 H, =C-CH_3], 2,83 [s, 3 H, N-CH_3], 4.35 [q, 2 H, OCH_2CH_3], 5.36 [s, 1 H, =C*H*], 6.51 [d, 1 H, J = 8.7 Hz, Ar-*H*], 6.94 [d, 1 H, J = 2.4 Hz, Ar-*H*], 7.13 [q, 1 H, J = 2.4 Hz, J = 8.7 Hz, Ar-*H*], 7.60 [d, 2 H, J = 8.7 Hz, Ar-*H*], 7.75 [bs, 1 H, N-*H*], 8.01 [d, 2 H, J = 8.7 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.30 [OCH_2CH_3], 18.53 [=C-CH_3], 27.77 [2 C, $C(CH_3)_2$], 30.86 [N-CH_3], 56.75 [=C-$C(CH_3)_2$], 60.92 [OCH_2CH_3], 111.04 [=*C*-CH_3], 121.66 [=*C*-$C(CH_3)_2$], 123.06-143.56 [Ar-*C*], 165.97 [*C*=O], 179.92 [*C*=S]. Anal. Calcd for $C_{23}H_{27}N_3O_2S$: C, 67.45; H, 6.65; N, 10.26. Found: C, 67.47; H, 6.66; N, 10.17.

[(4-Nitrophenyl)amino][(1,2,2,4-tetramethyl(1,2-dihydroquinol-6-yl))amino]methane-1-thione (**55**)

(1,2,2,4-Tetramethyl-1,2-dihydroquinol-6-yl)amine (**82**, 150 mg, 0.74 mmol) dissolved in 5 mL of dry THF was placed in an oven-dried, 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and addition funnel. The reaction mixture was then cooled to -5 °C (ice and NaCl), and 4-nitrophenylisothiocyanate (141 mg, 7.78 mmol, 1.05 eq) dissolved in 5 mL of dry THF was then added dropwise (30 min). After the addition, the reaction mixture was allowed to warm to RT and was then stirred for 24 h. The solvent was evaporated (rotovap), and the resulting solid was recrystallized (EtOAc:hexane, 1:1) to afford **55** as an orange-yellow solid (mp 172-3.5 °C, 184 mg, 65%). IR (KBr pellet) 3338 [N-H], 3181 [N-H] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, N-C-(CH_3)], 1.93 [s, 3 H, =C-CH_3], 2,82 [s, 3 H, N-CH_3], 5.30 [s, 1 H, =C*H*], 6.52 [d, 1 H, J = 8.7 Hz, Ar-*H*], 6.92 [d, 1 H, J = 2.4 Hz, Ar-*H*], 7.02 [q, 1 H, J = 2.4 Hz, J = 8.7 Hz, Ar-*H*], 7.67 [bs, 1 H, N-*H*], 7.77 [d, 2 H, J = 9.0 Hz, Ar-*H*], 7.87 [bs, 1 H, N-*H*], 8.19 [d, 2 H, J = 9.0 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.52 [=C-CH_3], 27.89 [C(CH_3)$_2$], 30.91 [N-CH_3], 56.85 [=C-*C*(CH_3)$_2$], 111.08 [=*C*-CH_3], 121.61 [=*C*-C(CH_3)$_2$], 122.81-145.44 [Ar-*C*], 179.65 [*C*=S]. TLC Analysis for $C_{20}H_{22}N_4O_2S$ showed one spot in following solvent systems: hexane:diethyl ether:H_2CCl_2, (1:1:1), R_f 0.40; chloroform:pentane, (2:1), R_f 0.19; hexane:EtOAc, (2:1), R_f 0.14. Anal. Calcd. for $C_{20}H_{22}N_4O_2S$: C, 62.81; H, 5.80; N, 14.05. Anal. Calcd. for $C_{20}H_{22}N_4O_2S \cdot 1.37\ H_2O$: C, 59.50; H, 5.95; N, 13.82. Found: C, 59.26; H, 5.57; N, 13.47.

Ethyl (6*Z*,2*E*,4*E*,8*E*)-3,7-Dimethyl-9-(1,2,2,4-tetramethyl(1,2-dihydroquinolyl))nona-2,4,6,8-

tetraenoate (**56**)

In a 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet was placed a solution of triethyl 3-methyl-4-phosphonocrotonate (145 mg, 0.62 mmol) dissolved in 1 mL of THF which was cooled to 0 °C and then was treated with DMPU (100 mg, 0.78 mmol) and *n*-BuLi (0.4 mL, 0.62 mmol, 1.6 *M* solution in toluene). The mixture was stirred for 20 min and then cooled to -78 °C. A solution of aldehyde **86** (87 mg, 0.31 mmol) dissolved in 1 mL of THF was added, and the reaction mixture was stirred at -78 °C for an additional 1 h. This mixture was allowed to warm to 0 °C, and a saturated, aqueous solution of ammonium chloride (1.5 mL) was added. An extraction with EtOAc (3 x 1.5 mL) was followed by washing the extracts with water (1 x 2 mL) and brine (1x 1.5 mL each). The organic layer was then dried ($MgSO_4$, 12 h). The residue was purified with column chromatography (silica gel, hexane:diethyl ether, 2:1, drop rate = 1 drop/s) and then recrystallized (H_2CCl_2:pentane, 1:2) to yield **56** as a bright red solid (mp 52-54 °C, 37 mg, 42%). IR (neat) 1705 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.26 [t, 3 H, OCH_2CH_3], 1.29 [s, 6 H, $C(CH_3)_2$], 2.03 [d, 3 H, $=CCH_3$, J = 10.8 Hz], 2.36 [d, 3 H, $=C-CH_3$, J = 7.8 Hz], 2.83 [s, 3 H, $N-CH_3$], 4.18 [q, 2 H, OCH_2CH_3], 5.25 [s, 1 H, =*CH*], 5.77 [s, 1 H, =*CH*] 6.31 [d, 1 H, =*CH*], 6.45 [d, 1 H, =*CH*], 6.50 [d, 1 H, Ph-*H*], 7.45 [m, 3 H, Ph-*H*]; ^{13}C NMR ($DCCl_3$) ppm 12.98 [OCH_2CH_3], 18.57 [$=C-CH_3$], 26.78 [$C(CH_3)_2$], 27.75 [$C-CH_3$], 31.21 [$N-CH_3$], 56.43 [$CH_3-C=C$], 59.53 [$CH_3-C=C$], 110.58 [=*C*H], 118.20-155.04 [CH=*C*-Ph], 167.17 [O-*C*=O]. Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.76; H, 8.97; N, 3.57. Found: C, 79.68; H, 9.06; N, 3.23.

{[(3*Z*,1*E*,5*E*)-1-Aza-4-methyl-6-(1,2,2,4-tetramethyl(1,2-dihydroquinolyl))hexa-1,3,5-trienyl]amino}aminomethane-1-thione (**57**)

Thiosemicarbazide (71.31 mg, 0.76 mmol) dissolved into 4 mL of water and AcOH (1 drop) was placed in a 10-mL beaker. Then 200 mg (0.71 mmol) of aldehyde **86** was dissolved in 5 mL of EtOH (95%). The latter solution was warmed to 60 °C and then added dropwise to the thiosemicarbazide solution while hot. A precipitate formed immediately. The reaction mixture was set aside for 24 h at 0 °C, and then the solid was filtered off. Recrystallization (EtOAc:diethyl ether, 1:1) of the solid afforded an light orange solid **57** (mp 177-179 °C, 123 mg, 41 %). IR (neat) 3428 [N-H], 3254 [N-H], 3156 [N-H] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.32 [s, 6 H, $C(CH_3)_2$], 2.01 [d, 3 H, $=CCH_3$,], 2.06 [d, 3 H, $=C-CH_3$,], 2.84 [s, 3 H, $N-CH_3$], 5.32 [d, 1 H, =*CH*], 6.17 [d, 1 H, =*CH*], 6.47 [d, 1 H, =*CH*], 6.72 [s, 1 H, =C-*H*], 7.14-7.25 [m, 3 H, Ph-*H*]; 7.88 [s, 1 H, N-*H*], 7.91 [s, 1H, N-*H*], 9.28 [s, 1 H, N-*H*], ^{13}C NMR ($DCCl_3$) ppm, 18.57 [$=C-CH_3$], 27.64 [$C-CH_3$], 30.79 [$N-CH_3$], 56.63 [$CH_3-C=C$], 110.55 [=*C*H], 121.81-155.04 [CH=*C*-Ph], 177.75 [*C*=S]. Anal. Calcd for $C_{20}H_{26}N_4S$: C, 67.08; H, 7.39; N, 15.64. Found: C, 66.95; H, 7.37; N, 15.52.

<u>{[(1*E*,3*E*)-1-Aza-3-fluoro-4-(1,2,2,4-tetramethyl(6-1,2-dihydroquinolyl))buta-1,3-dienyl] amino}aminomethane-1-thione (**58**)</u>

Thiosemicarbazide (33.6 mg, 0.37 mmol) dissolved into 3 mL of water and AcOH (1 drop) was placed in a 10-mL beaker. Then aldehyde [(**89**), 200 mg, 0.77 mmol) was dissolved in 4 mL of EtOH (95%). The latter solution was warmed to 60 °C and then added dropwise to the thiosemicarbazide solution while hot. A precipitate formed immediately. The reaction mixture was set aside for 24 h at 0 °C, and then the solid was filtered off. Recrystallization (EtOAc:diethyl ether, 1:1) of the solid afforded an light yellow solid **58** (mp 77-79 °C, 86 mg, 69 %). IR (neat) 3429 [N-H], 3258 [N-H], 3148 [N-H] cm^{-1}; ^1H

NMR ($DCCl_3$) δ 1.36 [s, 6 H, C(CH_3)$_2$], 2.01 [d, 3 H, =CHCH_3,], 2.84 [s, 3 H, N-CH_3], 5.36 [d, 1 H, =C*H*], 5.83 [d, 1 H, FC=C*H*], 6.47 [d, 1 H, =C*H*], 7.14-7.25 [m, 3 H, Ph-*H*]; 7.78 [s, 1 H, N-*H*], 9.11 [s, 1H, N-*H*], 9.41 [s, 1 H, N-*H*], ^{13}C NMR ($DCCl_3$) ppm, 18.62 [=C-CH_3], 28.12 [C-CH_3], 30.98 [C(CH_3)$_2$], 40.79 [N-CH_3], 56.63 [C-CH=C], 110.08 [=*C*H], 121.08-145.04 [CH=*C*-Ph], 150.22 [HC=*C*F], 177.75 [*C*=S]. Anal. Calcd for $C_{17}H_{21}FN_4S$: C, 61.42; H, 6.37; N, 16.85. The compound decomposed very quickly, and no satisfactory elemental analysis could be obtained.

<u>{[(1*E*,3*E*)-1-Aza-4-(1,2,2,4-tetramethyl(6-1,2-dihydroquinolyl))buta-1,3-dienyl]amino}aminomethane-1-thione (59)</u>

Thiosemicarbazide (56.68 mg, 0.62 mmol) dissolved into 4 mL of water and AcOH (1 drop) was placed in a 10-mL beaker. Then aldehyde **92** (150 mg, 0.62 mmol) was dissolved in 5 mL of EtOH (95%). The latter solution was warmed to 60 °C and then added dropwise to the thiosemicarbazide solution while hot. A precipitate formed immediately. The reaction mixture was set aside for 24 h at 0 °C, and then the solid was filtered off. Recrystallization (EtOAc:diethyl ether, 1:1) of the solid afforded an light yellow solid **59** (mp 51-52.5 °C, 150 mg, 73 %). IR (neat) 3426 [N-H], 3262 [N-H], 3151 [N-H] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.26 [s, 6 H, C(CH_3)$_2$], 2.01 [d, 3 H, =CHCH_3,], 2.81 [s, 3 H, N-CH_3], 5.36 [d, 1 H, =C*H*], 5.80 [q, 1 H, HC=C*H*], 6.50 [d, 1 H, =C*H*], 6.78 [d, 1 H, =C*H*], 6.84-7.25 [m, 3 H, Ph-*H*], 7.38 [bs, 1 H, N-*H*], 8.20 [bs, 1H, N-*H*], 10.71 [bs, 1 H, N-*H*], ^{13}C NMR ($DCCl_3$) ppm, 16.62 [C-CH_3], 18.12 [=C-CH_3], 28.98 [C(CH_3)$_2$], 30.63 [C-CH=C], 58.79 [N-CH_3], 110.08 [=*C*H], 116.56 [=*C*H], 121.08-143.04 [CH=*C*-Ph], 178.35 [*C*=S]. Anal. Calcd for $C_{17}H_{22}FN_4S$: C, 64.93; H, 7.05; N, 17.81. The compound decomposed very quickly, and

no satisfactory elemental analysis could be obtained.

Ethyl (2*E*,4*E*,6*E*)-6-Fluoro-3-methyl-7-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))octa-2,4,6-trienoate (**60**)

A 25-mL, three-necked, round-bottomed flask equipped with a N_2 inlet and an addition funnel was charged with triethyl 3-methyl-4-phosphonocrotonate (119 mg, 0.45 mmol), DMPU (58 mg, 0.45 mmol), and THF (2 mL). The mixture was cooled to 0 °C, and 0.42 ml (0.67 mmol) of *n*-BuLi (1.6 *M*) was added by syringe. After stirring for 1 h at 0 °C, 120 mg (0.41 mmol) of aldehyde **97a** dissolved in 2 mL of dry THF was added (addition funnel). The new reaction mixture was allowed to warm to RT and was then stirred for 4 days. Quenching the reaction mixture with saturated, aqueous solution of ammonium chloride (1 mL) and extraction of the mixture with ethyl acetate (3 x 10 mL) was followed by washing the organic extracts with water (2 x 2 mL) and brine (1 x 3 mL). The organic extract was then dried ($MgSO_4$, 12 h), the solvent was evaporated (rotovap), and the residual oil was purified by flash chromatography (H_2CCl_2:hexane, 1:1, drop rate = 1 drop/s) to give 122 mg (81%) of ester **60** as a thick light yellow oil. IR (neat) 1712 [OC=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.28 [t, 3 H, OCH_2CH_3], 1.39 [s, 6 H, $C(CH_3)_2$], 1.44 [s, 6 H, $SC(CH_3)_2$], 1.98 [s, 2 H, $SC(CH_3)_2CH_2$], 2.18 [2s, 6 H, $=CCH_3$], 4.18 [q, 2 H, OCH_2CH_3], 5.87 [s, 1 H, =C*H*], 6.5 [d, 1 H, =C*H*], 6.59 [d, 1 H, =C*H*], 6.90-7.26 [m, 3 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.29 [OCH_2CH_3], 31.15 [$C(CH_3)_2$], 32.85 [$C(CH_3)_2$], 54.17 [$=CCH_3$], 59.77 [$=CCH_3$], 63.74 [$=CCH_3$], 120.45-123.21 [=*C*], 126.23-151.32 [Ar-*C*], 166.92 [O*C*=O]; ^{19}F NMR ($DCCl_3$) (ref $C_6H_5CF_3$ in C_6D_6) ppm -120.99 [m, 1 F, =C*F*]. Anal. Calcd for $C_{24}H_{31}FO_2S$: C, 71.60; H, 7.76. Found: C, 71.53; H, 7.82.

Ethyl (2*E*,4*E*,6*E*)-6-Fluoro-3,8-dimethyl-7-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))nona-2,4,6-trienoate (**61**)

A 25-mL, three-necked, round-bottomed flask equipped with a N_2 inlet and an addition funnel was charged with triethyl 3-methyl-4-phosphonocrotonate (58 mg, 0.22 mmol), DMPU (28 mg, 0.22 mmol), and THF (2 mL). The mixture was cooled to 0 °C, and 0.15 ml (24 mmol) of *n*-BuLi (1.6 *M*) was added by syringe. After stirring for 1 h at 0 °C, aldehyde **97b** (65 mg, 0.20 mmol) dissolved in 2 mL of dry THF was added (addition funnel). The new reaction mixture was allowed to warm to RT, and then it was stirred for 4 days. Quenching the reaction mixture with a saturated, aqueous solution of ammonium chloride (1 mL) and extraction of the mixture with ethyl acetate (3 x 10 mL) was followed by washing the organic extracts with water (2 x 2 mL) and brine (1 x 3 mL). The organic extract was then dried ($MgSO_4$, 12 h). Evaporation (rotovap) of the solvent and purification of the major component in the residue by flash chromatography (diethyl ether:hexane, 1:1, drop rate = 1 drop/s) gave **63** (1.44 mg, 51%) as a thick, light yellow oil. IR (neat) 1711 [OC=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.16 [d, 3 H, $CH(CH_3)_2$], 1.32[t, 3 H, OCH_2CH_3], 1.45 [s, 6 H, $C(CH_3)_2$], 1.44 [s, 6 H, $SC(CH_3)_2$], 1.57 [d, 3 H, $=CCH_3$], 1.96 [s, 2 H, $SC(CH_3)_2CH_2$], 2.16 [d, 3 H, $=CCH_3$], 2.37 [d, 3 H, $=CCH_3$], 4.27 [q, 2 H, OCH_2CH_3], 5.80 [s, 1 H, =C*H*], 6.6 [d, 1 H, =C*H*], 6.78 [d, 1 H, =C*H*], 6.82 [q, 1 H, J = 8.6 Hz, J = 2.2 Hz, Ar-*H*], 7.02 [d, 1 H, J = 8.6 Hz, Ar-*H*], 7.15 [d, 1 H, J = 2.2 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 13.41 [OCH_2CH_3], 14.29 [$=CCH_3$], 21.13 [$=CCH_3$], 29.70 [$C(CH_3)_2$], 30.51 [$C(CH_3)_2$], 54.20 [$=CCH_3$], 59.77 [$=CCH_3$], 120.96-125.21 [=*C*], 127.74-151.07 [Ar-*C*], 166.88 [O*C*=O]; ^{19}F NMR ($DCCl_3$) (ref $C_6H_5CF_3$ in C_6D_6) ppm -110.50 [m, 1 F, =C*F*]. Anal. Calcd for $C_{26}H_{35}FO_2S$: C, 72.52; H, 8.19. Found: C, 72.66; H, 8.19.

Ethyl (2*E*,4*E*,6*E*)-6-Fluoro-3,9-dimethyl-7-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))deca-2,4,6-trienoate (**62**)

A 25-mL, three-necked, round-bottomed flask equipped with a N_2 inlet and an addition funnel was charged with triethyl 3-methyl-4-phosphonocrotonate (58 mg, 0.22 mmol), DMPU (28 mg, 0.22 mmol), and THF (2 mL). The mixture was cooled to 0 °C, and 0.15 ml (24 mmol) of *n*-BuLi (1.6 *M*) was added by syringe. After stirring for 1 h at 0 °C, aldehyde **97c** (67 mg, 0.20 mmol) dissolved in 2 mL of dry THF was added (addition funnel). The new reaction mixture was allowed to warm to RT, and then it was stirred for 5 days. Quenching the reaction mixture with a saturated, aqueous solution of ammonium chloride (1 mL) and extraction of the mixture with ethyl acetate (3 x 10 mL) was followed by washing the organic extracts with water (2 x 2 mL) and brine (1 x 3 mL). The organic extract was then dried ($MgSO_4$, 12 h). Evaporation (rotovap) of the solvent and purification of the major component in the residue by flash chromatography (diethyl ether:hexane, 1:1, drop rate = 1 drop/s) gave **62** (44.3 mg, 51%) as a thick, light yellow oil. IR (neat) 1710 [OC=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.96 [d, 3 H, $CH(CH_3)_2$], 1.12 [d, 3 H, $CH(CH_3)_2$], 1.38[t, 3 H, OCH_2CH_3], 1.45 [s, 6 H, $C(CH_3)_2$], 1.44 [s, 6 H, $SC(CH_3)_2$], 1.62 [m, 1 H, $CH(CH_3)_2$], 2.13 [d, 3 H, $=CCH_3$], 2.22 [s, 2 H, $SC(CH_3)_2CH_2$], 2.66 [m, 2 H, $=CCH_2CH$], 2.89 [d, 3 H, $=CCH_3$], 4.21 [q, 2 H, OCH_2CH_3], 5.80 [s, 1 H, =C*H*], 6.60 [d, 1 H, =C*H*], 6.688 [d, 1 H, =C*H*], 6.82 [q, 1 H, J = 8.5 Hz, J = 2.1 Hz, Ar-*H*], 7.02 [d, 1 H, J = 8.5 Hz, Ar-*H*], 7.15 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 13.41 [OCH_2CH_3], 14.29 [$=CCH_3$], 21.13 [$=CCH_3$], 22.36 [$CH(CH_3)_2$], 29.70 [$C(CH_3)_2$], 30.55 [$C(CH_3)_2$], 53.24 [$=CCH_3$], 59.77 [$=CCH_3$], 120.96-125.21 [=*C*], 127.74-142.07 [Ar-*C*], 151.37 [F*C*=CH], 166.88 [O*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -122.13.50 [m, 1 F, =C*F*]. Anal. Calcd for $C_{27}H_{37}FO_2S$: C, 72.93; H,

8.39. Found: C, 72.66; H, 8.19.

Ethyl (6*Z*,2*E*,4*E*)-6-Fluoro-3-methyl-7-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))octa-2,4,6-trienoate (**63**)

A 25-mL, three-necked, round-bottomed flask equipped with a N_2 inlet and an addition funnel was charged with triethyl 3-methyl-4-phosphonocrotonate (96 mg, 0.36 mmol), DMPU (42 mg, 0.36 mmol), and THF (2 mL). The mixture was cooled to 0 °C, and 0.32 ml (0.51 mmol) of *n*-BuLi (1.6 *M*) was added by syringe. After stirring for 1 h at 0 °C, aldehyde **99a** (96 mg, 0.41 mmol) dissolved in 2 mL of THF was added (addition funnel). The new reaction mixture was allowed to warm to RT, and then it was stirred for 4 days. Quenching the reaction mixture with saturated, aqueous solution of ammonium chloride (1 mL) and extraction of the mixture with ethyl acetate (3 x 10 mL) was followed by washing the combined organic extracts with water (2 x 2 mL) and brine (1 x 3 mL). The organic extract was then dried ($MgSO_4$, 12 h), the solvent was evaporated (rotovap), and the residual oil was purified by flash chromatography (H_2CCl_2:hexane, 1:1, drop rate = 1 drop/s) to give 97 mg (73%) of **63** as a thick, light yellow oil. IR (neat) 1710 [OC=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.24 [t, 3 H, OCH_2CH_3], 1.40 [s, 6 H, $C(CH_3)_2$], 1.43 [s, 6 H, $SC(CH_3)_2$], 1.98 [s, 2 H, $SC(CH_3)_2CH_2$], 2.16 [d, 3 H, $=CCH_3$], 2.36 [d, 3 H, $=CCH_3$], 4.20 [q, 2 H, OCH_2CH_3], 5.92 [s, 1 H, =C*H*], 6.6 [s, 1 H, =C*H*], 6.81 [d, 1 H, =C*H*], 7.11-7.56 [m, 3 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.32 [OCH_2CH_3], 31.64 [$C(CH_3)_2$], 32.55 [$C(CH_3)_2$], 54.29 [$=CCH_3$], 59.86[$=CCH_3$], 61.38 [$=CCH_3$], 120.88-123.21 [=*C*-C], 125.74-151.11 [Ar-*C*], 166.93 [O*C*=O]; ^{19}F NMR ($DCCl_3$) (ref $C_6H_5CF_3$ in C_6D_6) ppm -122.32 [d, 1 F, =C*F*]. Anal. Calcd for $C_{24}H_{31}FO_2S$: C, 71.60; H, 7.76. Found: C, 71.48; H, 7.62.

Ethyl (6*Z*,2*E*,4*E*)-6-Fluoro-3,8-dimethyl-7-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))nona-2,4,6-trienoate (**64**)

A 25-mL, three-necked, round-bottomed flask equipped with a N_2 inlet and an addition funnel was charged with triethyl 3-methyl-4-phosphonocrotonate (124 mg, 0.47 mmol), DMPU (60 mg, 0.47 mmol), and THF (2 mL). The mixture was cooled to 0 °C, and 0.30 ml (0.48 mmol) of *n*-BuLi (1.6 *M*) was added by syringe. After stirring for 1 h at 0 °C, aldehyde **99b** (137 mg, 0.43 mmol) in 2 mL of THF was added (addition funnel). The new reaction mixture was allowed to warm to RT, and then it was stirred for 4 days. Quenching the reaction mixture with a saturated, aqueous, solution of ammonium chloride (1 mL) and extraction of the mixture with ethyl acetate (3 x 10 mL) was followed by washing the combined organic extracts with water (2 x 2 mL) and brine (1 x 3 mL). The organic extracts were then dried ($MgSO_4$, 12 h). Evaporation (rotovap) of the solvent and purification of the major component in the residue by flash chromatography ($(Et)_2O$:hexane, 1:1, drop rate = 1 drop/s) gave **64** (101 mg, 55%) as a thick, light yellow oil. IR (neat) 1712 [OC=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.06 [d, 3 H, $CH(CH_3)_2$], 1.24 [t, 3 H, OCH_2CH_3], 1.37 [s, 6 H, $C(CH_3)_2$], 1.44 [s, 6 H, $SC(CH_3)_2$], 1.57 [d, 3 H, $=CCH_3$], 1.98 [s, 2 H, $SC(CH_3)_2CH_2$], 2.16 [d, 3 H, $=CCH_3$], 2.36 [d, 3 H, $=CCH_3$], 4.25 [q, 2 H, OCH_2CH_3], 5.65 [s, 1 H, =*CH*], 6.6 [d, 1 H, =*CH*], 6.81 [d, 1 H, =*CH*], 6.88 [q, 1 H, J = 8.6 Hz, J = 2.2 Hz, Ar-*H*], 7.05 [d, 1 H, J = 8.6 Hz, Ar-*H*] 7.45 [d, 1 H, J = 2.2 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 13.41 [OCH_2CH_3], 14.29 [$=CCH_3$], 21.13 [$=CCH_3$], 29.70 [$C(CH_3)_2$], 30.51 [$C(CH_3)_2$], 54.20 [$=CCH_3$], 59.77 [$=CCH_3$], 120.37-125.21 [=*C*], 127.74-151.34 [Ar-*C*], 166.90 [O*C*=O]; ^{19}F NMR ($DCCl_3$) (ref $C_6H_5CF_3$ in C_6D_6) ppm -125.01 [d, 1 F, =*CF*]. Anal. Calcd for $C_{26}H_{35}FO_2S$: C, 72.52;

H, 8.19. Found: C, 72.32; H, 8.54.

(2,2,4,4-Tetramethyl(3*H*-benzo[3,4-*e*]thian6-yl))ethyl 4-(methoxycarbonyl)benzoate (**65**)

In a 50-mL, one-necked, round-bottomed flask equipped with a condenser and a N_2 inlet was added at RT 2-methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))propan-1-ol [(**101a**), 294.4 mg, 0.88 mmol] and 4-(methoxycarbonyl)benzoic acid (158 mg, 0.88 mmol) dissolved in 20 mL of CH_2Cl_2. To this solution were added *N,N'*-dicyclohexylcarbodiimide (DCC) (462 mg, 2.2 mmol, 2.5 eq) and DMAP (10.0 mg, catalytic amount), and the reaction mixture was stirred for 5 days at RT. Filtration of the reaction mixture, evaporation (rotovap) of solvent from the filtrate, and purification of the residue by flash chromatography (hexane:diethyl ether, 10:1, drop rate = 1 drop/s) of the residue after solvent evaporation afforded **65** (200 mg, 51%) as a pale yellow, thick oil. IR (neat) 1729 [C=O], 1722 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.69 [d, 3 H, $CHCH_3$] 1.94 [s, 2 H, CCH_2C], 3.94 [s, 3 H, OCH_3], 6.19 [q, 1 H, $OCHCH_3$], 7.18 [q, 1 H, J = 7.8 Hz, J = 2.1 Hz, Ar-*H*], 7.09 [d, 1 H, J = 7.8 Hz, Ar-*H*] 7.46 [d, 1 H, J = 2.1 Hz, Ar-*H*], 8.12 [s, 2 H, Ar-*H*], 8.13 [s, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 14.25 [$OCHCH_3$], 31.65 [$CH_2C(CH_3)_2$], 32.50 [$SC(CH_3)_2$], 34.85 [$CH_2C(CH_3)_2$], 35.37 [$SC(CH_3)_2$], 42.05 [$CH(CH_3)_2$] 52.39 [C, OCH_3], 54.23 [$CH_2C(CH_3)_2$], 81.94 [$HOCH_2$], 124.37-142.22 [Ar-*C*], 165.74 [*C*=O], 166.29 [*C*=O]. Anal. Calcd. for $C_{24}H_{28}O_4S$: C, 69.87; H, 6.84. Found: C, 70.11; H, 6.74.

2-Methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian6-yl))propyl 4-(methoxycarbonyl) benzoate (**66**)

In a 50-mL, one-necked, round-bottomed flask equipped with a condenser and a N_2 inlet was added at RT 2-methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))propan-1-ol [(**101b**), 300 mg 1.08 mmol] and 4-(methoxycarbonyl)benzoic acid (194 mg, 1.08 mmol) dissolved in 20 mL of CH_2Cl_2. To this solution were added *N,N'*-dicyclohexylcarbodiimide (DCC) (557 mg, 2.7 mmol, 2.5 eq) and DMAP (10.0 mg, catalytic amount), and the reaction mixture was stirred for 4 days at RT. Filtration of the reaction mixture, evaporation (rotovap) of solvent from the filtrate, and purification of the residue by flash chromatography (hexane:diethyl ether, 10:1, drop rate = 1 drop/s) of the residue after solvent evaporation afforded **66** as a pale yellow solid (mp 52-3°C, 190 mg, 40%). IR (neat) 1726 [C=O], 1723 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.89 [d, 3 H, $CH(CH_3)_2$], 1.04 [d, 3 H, $CH(CH_3)_2$] 1.34 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.94 [s, 2 H, CCH_2C], 2.25 [m, 1 H, $CH(CH_3)_2$], 3.94 [s, 3 H, OCH_3], 5.79 [d, 1 H, OCHCH], 7.08 [q, 1 H, J = 7.8 Hz, J = 2.1 Hz, Ar-*H*], 7.09 [d, 1 H, J = 7.8 Hz, Ar-*H*] 7.36 [d, 1 H, J = 2.1 Hz, Ar-*H*], 8.12 [s, 2 H, Ar-*H*], 8.13 [s, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 18.55 [$CH(CH_3)_2$], 18.68 [$CH(CH_3)_2$], 31.50 [$CH_2C(CH_3)_2$], 32.53 [$SC(CH_3)_2$], 34.85 [$CH_2C(CH_3)_2$], 35.37 [$SC(CH_3)_2$], 41.95 [$CH(CH_3)_2$] 52.37 [OCH_3], 54.46 [$CH_2C(CH_3)_2$], 81.94 [$HOCH_2$], 124.37-142.22 [Ar-*C*], 164.94 [*C*=O], 166.22 [*C*=O]. Anal. Calcd. for $C_{26}H_{32}O_4S$: C, 70.88; H, 7.32. Found: C, 70.81; H,7.74.

<u>3-Methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))butyl 4-(methoxycarbonyl)-benzoate (67)</u>

In a 50-mL, one-necked, round-bottomed flask equipped with a condenser and a N_2 inlet was added at RT 3-methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))butan-1-ol [(**100c**), 300 mg, 1.03 mmol] and 4-(methoxycarbonyl)benzoic acid (185 mg, 1.03 mmol)

dissolved in 20 mL of CH_2Cl_2. To this solution were added, *N,N'*-dicyclohexylcarbodiimide (DCC) (531 mg, 2.57 mmol, 2.5 eq) and DMAP (9.0 mg, catalytic amount), and the reaction mixture was stirred for 4 days at RT. Filtration of the reaction mixture, evaporation (rotovap) of solvent from the filtrate, and purification of the residue by flash chromatography (hexane:diethyl ether, 8:1, drop rate = 1 drop/s) afforded **67** as a white solid (mp 61-3 °C, 200 mg, 43%). IR (neat) 1732 [C=O], 1723 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.89 [dd, 6 H, $CH(CH_3)_2$], 1.36 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.84 [m, 2 H, $O{=}CCH_2CH$], 1.94 [s, 2 H, CCH_2C], 2.25 [m, 1 H, $CH(CH_3)_2$], 3.93 [s, 3 H, OCH_3], 6.05 [m, 1 H, OC*H*CH], 7.18 [q, 1 H, J = 7.9 Hz, J = 2.0 Hz, Ar-*H*], 7.19 [d, 1 H, J = 7.9 Hz, Ar-*H*] 7.340 [d, 1 H, J = 2.0 Hz, Ar-*H*], 8.1 [s, 2 H, Ar-*H*], 8.10 [s, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 22.39 [$CH(CH_3)_2$], 23.82 [$O\text{-}CCH_2CH$], 31.62 [$CH_2C(CH_3)_2$], 32.50 [$SC(CH_3)_2$], 35.55 [$CH_2C(CH_3)_2$], 42.05 [$SC(CH_3)_2$], 52.43 [OCH_3], 54.44 [$CH_2C(CH_3)_2$], 75.78 [*C*-OC=O], 124.07-142.62 [Ar-*C*]. 165.08 [*C*=O], 166.31 [*C*=O]. Anal. Calcd. for $C_{27}H_{34}O_4S$: C, 71.33; H, 7.54. Found: C, 71.36; H, 7.65.

<u>{[(1*E*,3*E*)-1-Aza-3-fluoro-4-(2,2,4,4,7-pentamethyl(3*H*-benzo)[3,4-*e*]thian-6-yl))penta-1,3-dienyl]amino}aminomethane-1-thione (**68**)</u>

Thiosemicarbazide (60.00 mg, 0.65 mmol) dissolved into 4 mL of water and AcOH (1 drop) was placed in a 10-mL beaker. Then 200 mg (0.65 mmol) of aldehyde **106** was dissolved in 5 mL of EtOH (95%). The latter solution was warmed to 60 °C and then was added dropwise to the thiosemicarbazide solution while hot. A precipitate formed immediately. The reaction mixture was set aside for 24 h at 0 °C, and then the solid was filtered off. The recrystallization of the solid (EtOAc:diethyl ether, 2:1) afforded an white

solid **68** (mp 162-3 °C, 178 mg, 72 %). IR (neat) 3379 [N-H], 3233 [N-H], 3151 [N-H] cm^{-1}; ^1H NMR (DMSO-d_6) 1.89 [s, 6 H, $C(CH_3)_2$], 1.90 [s, 6 H, $C(CH_3)_2$], 2.05 [d, 3 H, $CHCH_3$] 2.10 [s, 2 H, CCH_2C], 3.34 [s, 3 H, Ar-CH_3], 6.98 [s, 1 H, Ar-*H*], 7.09 [s, 1 H, Ar-*H*] 7.35 [d, 1 H, J = 14.1 Hz, FC=C*H*], 7.51 [s, 1 H, N-*H*], 7.99 [s, 1 H, N-*H*], 9.91 [s, 1 H, N-*H*]; ^{13}C NMR (DMSO-d_6) ppm, 17.57 [=CCH_3], 25.05 [Ar-CH_3] 31.30 [$CH_2C(CH_3)_2$], 32.52 [$SC(CH_3)_2$], 34.68 [$CH_2C(CH_3)_2$], 42.05 [$SC(CH_3)_2$], 53.63 [$CH_2C(CH_3)_2$] 128.37-142.22 [Ar-*C*], 151.61 [F*C*=CH], 179.83.74 [*C*=S]. Anal. Calcd for $C_{19}H_{26}FN_3S_2$: C, 60.12; H, 6.90; N, 11.07. Found: C, 60.35; H, 7.07; N, 11.22.

<u>6-Methoxy-1,1,4,4-tetramethyl-5-nitroisochromane (**70**)</u>

Into a 500-mL, singled necked, round bottomed flask, fitted with a condenser, magnetic stirrer, and N_2 inlet was added 6-methoxy-1,1,4,4-tetramethylisochromane [(**69**), 18.0 g, 81.70 mmol] dissolved in Ac_2O (36 mL) at -5 °C (ice/salt bath). A mixture of ice-cold concentrated HNO_3 (18 mL) and Ac_2O (36 mL) was added dropwise to the reaction mixture (-5 °C, 10 min) which was then stirred (1 h). The reaction mixture was poured into a solution of saturated $NaHCO_3$ (300 mL) and extracted with H_2CCl_2 (3 x 120 mL). The organic layer was washed with water (150 mL) and brine (150 mL) and then dried (Na_2SO_4, 12 h). The solvent was evaporated (rotovap) to give a thick yellow oil. The oil was triturated with pentane to give a light yellow solid. Recrystallization (95 % EtOH) gave **70** (6.91 g, 32%) as a white solid; mp 82-83 °C IR (KBr) 1241 [NO_2] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.28 [s, 6 H, $C(CH_3)_2$], 1.51 [s, 6 H, $OC(CH_3)_2$], 3.48 [s, 2 H, CH_2], 3.83 [s, 3 H, OCH_3], 6.88 [d, 1 H, J = 2.5 Hz, Ar-*H*], 7.12 [d, 1 H, J = 2.5 Hz, Ar-*H*]; ^{13}C NMR ($CDCl_3$) ppm 24.09 [$(CH_3)_2$] 30.05 [$(CH_3)_2$], 56.35 [O-CH_2], 71.68 [O-$C(CH_3)_2$], 110.65 [Ar-O-CH_3],

128.18-159.34 [Ar-*C*]; MS (EI) calcd *m/z* (M^+) for $C_{14}H_{19}NO_4$: 265; Found: 265.

(6-Methoxy-1,1,4,4-tetramethylisochromane-5-yl)amine (**71**)

Into a 1-L, single-necked, round bottomed flask, equipped with N_2 inlet, condenser, and a magnetic stirrer was placed 6-methoxy-1,1,4,4-tetramethyl-5-nitroisochromane [(**70**) 5.7 g, 17.71 mmol] dissolved in acetic acid (206 mL) and water (42 mL). Then the $TiCl_3$/HCl complex (30% solution, 120 g, 177.1 mmol) was added dropwise, and the resulting purple reaction mixture was stirred (13 h, RT). The new mixture was cooled (0 °C), and NaOH (30%, 500 mL) was added (dropwise, 4 h). The reaction mixture was separated, and the aqueous layer was extracted with EtOAc (8 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and saturated $NaHCO_3$ (2 x 100 mL), and then the organic extract was dried ($MgSO_4$, 12 h). Recrystallization (95 % EtOH) gave amine **71** (4.6 g, 89%) of as a white solid; mp 110-112 °C. IR (KBr) 3449 [NH_2], 3338 [NH_2], cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.37 [s, 6 H, $C(CH_3)_2$], 1.49 [s, 6 H, $OC(CH_3)_2$], 3.53 [s, 2H, CH_2], 3.83 [s, 3 H, OCH_3], 3.98 [s, 1 H, NH_2], 6.50 [d, 1 H, J =8.5 Hz, Ar-*H*], 7.69 [d, 1 H, J = 8.5 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 27.02 [$(CH_3)_2$], 29.73 [$(CH_3)_2$], 55.41 [O-CH_2], 71.16 [$C(CH_3)_2$], 74.83 [O-$C(CH_3)_2$], 111.79 [Ar-O-CH_3], 122.73-146.24 [Ar-*C*]; MS (EI) calcd *m/z* (M^+) for $C_{14}H_{19}NO_4$: 235. Found: 235.

Ethyl (2*E*)-3-(4,4-Dimethylchroman-6-yl)-2-fluorobut-2-enoate (**73**)

Into a 25-mL, three-necked, round-bottomed flask fitted with a condenser, magnetic stirrer, and N_2 inlet, was added ethyl-2-fluorophosphonoacetate (260 mg, 1.08 mmol) and DMPU (138 mg, 1.08 mmol) dissolved in 3 mL of dry THF. The reaction mixture was cooled to

0 °C, and *n*-BuLi (1.6 *M*, 0.68 mL, 1.08 mmol) was added dropwise by syringe. After stirring the reaction mixture for 1 h, 1-(4,4-dimethylchroman-6-yl)ethan-1-one [(**72**), 200 mg, 0.98 mmol] dissolved in 4 mL of dry THF was added. The reaction mixture was then stirred for 6 days at RT and then was quenched with a saturated, aqueous solution of ammonium chloride. Extraction with ethyl acetate (3 x 25 mL) was followed by washing the combined organic layers with H_2O (1 x 20 mL) and brine (1 x 25 mL) and then drying ($MgSO_4$, 5 h). After flash chromatography (hexane:diethyl ether, 2:1, drop rate = 1 drop/s) of the residue and, after solvent evaporation, **7** (206 mg, 72%) was recovered as a clear oil. IR (neat) 1728 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.15 [t, 3 H, OCH_2CH_3], 1.30 [s, 6 H, CH_3CCH_3], 1.82 [q, 2 H, CH_2CH_2], 2.09 [d, H, $=CCH_3$], 4.07 [q, 2 H, OCH_2CH_3], 4.20 [q, 2 H, CH_2CH_2], 6.73 [d, 1 H, J = 8.4 Hz, Ar-*H*], 6.88 [q, 1 H, J = 8.4 Hz, J = 2.4 Hz, Ar-*H*], 7.07 [d, 1 H, J = 2.4 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 13.75 [OCH_2CH_3], 19.20 [$CHCH_3$], 30.55 [$C(CH_3)_2$], 30.97 [$C(CH_3)_2$], 37.47 [CH_2CH_2], 60.88 [OCH_2CH_3], 63.05 [CH_2CH_2], 116.50 [FC=CH], 126.41-145.77 [Ar-*C*], 153.38 [F*C*=CH], 160.34 [O-*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -124.15 [q, 1 F, *F*C=CCH_3].

<u>(2*E*)-3-(4,4-dimethylchroman-6-yl)-2-fluorobut-2-en-1-ol (**74**)</u>

Ester **73** (206 mg, 0.70 mmol) dissolved in 5 mL of dry THF was placed in 25-mL, three-necked, round-bottomed flask fitted with a condenser, magnetic stirrer, and N_2 inlet, and then cooled to -40 °C. A solution (1.5 *M*, 0.93 mL, 1.40 mmol) of DIBAL-H in toluene was then added by syringe. The reaction mixture was stirred for 2 h, and the reaction was monitored by TLC (hexane:ethyl acetate, 1:1). After all of the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 2 mL of a saturated, aqueous

solution of Rochelle salt (sodium-potassium tartrate). The bi-phasic mixture was extracted with ethyl acetate (3 x 25 mL), followed by washing the organic extracts with H_2O (1 x 15 mL) and brine (1 x 20 mL) and then drying ($MgSO_4$, 12 h). Separation of the major component in the residue, via flash chromatography (hexane:diethyl ether, 1:3, drop rate = 1 drop/s) and, after solvent evaporation, afforded **74** (160 mg, 92%) as a colorless oil. IR (neat) 3412 [O-H], 1651 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.32 [s, 6 H, CH_3CCH_3], 1.82 [q, 2 H, CH_2CH_2], 2.00 [bs, 1H, O-*H*], 2.09 [d, H, =CCH_3], 4.19 [m, 2 H, H_2COH], 4.20 [q, 2 H, CH_2CH_2], 6.53 [d, 1 H, J = 8.4 Hz, Ar-*H*], 6.78 [q, 1 H, J = 8.4 Hz, J = 2.4 Hz, Ar-*H*], 7.27 [d, 1 H, J = 2.4 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 16.20 [=$CHCH_3$], 30.53 [$C(CH_3)_2$], 30.97 [$C(CH_3)_2$], 37.47 [CH_2CH_2], 58.88 [$HOCH_2$], 63.05 [CH_2CH_2], 116.76 [FC=CH], 118.69-152.77 [Ar-*C*], 156.38 [FC=CH]; ^{19}F NMR ($DCCl_3$) ppm -118.51 [m, 1 F, *F*C=CCH_3].

<u>(2*E*)-3-(4,4-Dimethylchroman-6-yl)-2-fluoro-2-butenal (75)</u>

Alcohol **74** (162 mg, 0.65 mmol) dissolved in 5 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask, and MnO_2 (0.75 g, 17.25 mmol, activated grade, size<5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and then was filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification via flash chromatography (hexane:diethyl ether:ethyl acetate, 1:1:1, drop rate = 1 drop/s) of the major component in the residue, afforded aldehyde **75** (95mg, 59%) as a light yellow oil. IR (neat) 2834 [O=C-H], 1674 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.37 [s, 6 H, CH_3CCH_3], 1.83 [q, 2 H, CH_2CH_2], 2.09 [d, H, =CCH_3], 4.21 [q, 2 H, CH_2CH_2], 6.73 [d, 1 H, J = 8.1 Hz, Ar-*H*], 6.98 [q, 1 H, J = 8.1 Hz, J = 2.2 Hz, Ar-*H*], 7.24 [d, 1 H, J = 2.1

Hz, Ar-*H*], 9.01 [s, 1H, *H*C=O]; ^{13}C NMR ($DCCl_3$) ppm 17.20 [=CH*C*H_3], 30.43 [*C*(CH_3)$_2$], 30.87 [C(*C*H_3)$_2$], 37.34 [*C*H_2CH$_2$], 63.05 [*C*H_2CH$_2$], 116.76 [FC=*C*H], 118.69-152.77 [Ar-*C*], 156.38 [F*C*=CH], 188.87 [H*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -121.51 [m, 1 F, *F*C=CCH$_3$].

1-(4,4-Dimethylchroman-6-yl)ethan-1-ol (**76**)

Ketone **72** (150 mg, 0.73 mmol) dissolved in 3 mL of dry THF was placed in a 25-mL, three-necked, round-bottomed flask fitted with a condenser, magnetic stirrer, and N_2 inlet, and cooled to -40 °C. A solution of DIBAL-H in toluene(1.5 *M*, 1.63 mL, 2.44 mmol) was then added by syringe. The reaction mixture was then stirred for 2 h, and it was monitored by TLC (hexane:ethyl acetate, 1:3). After all of the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 4 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate). The bi-phasic mixture was then extracted with ethyl acetate (3 x 25 mL), followed by washing the extracts with H_2O (2 x 10 mL) and brine (1 x 15 mL) and then drying ($MgSO_4$, 12 h). Separation of the major component after evaporation (rotovap) of the solvent and flash chromatography (hexane:diethyl ether, 1:3, drop rate = 1 drop/s) afforded alcohol **76** (142 mg, 94%) as a clear oil. IR (neat) 3401 [O-H], cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.23 [s, 6 H, C*H*$_3$CC*H*$_3$], 1.42 [d, 3 H, HCC*H*$_3$], 1.65 [bs, 1H, O-*H*], 1.82 [q, 2 H, C*H*$_2$CH$_2$], 4.20 [q, 2 H, C*H*$_2$CH$_2$], 4.81 [q, 1 H, *H*COH], 6.79 [d, 1 H, J = 8.2 Hz, Ar-*H*], 7.08 [q, 1 H, J = 8.2 Hz, J = 2.1 Hz, Ar-*H*], 7.27 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 24.85 [(HO)HC*C*H$_3$], 30.58 [*C*(CH_3)$_2$], 30.97 [C(*C*H$_3$)$_2$], 37.459[*C*H$_2$CH$_2$], 63.08 [*C*H$_2$CH$_2$], 70.29 [HO*C*H$_2$], 116.76 [FC=*C*H], 118.69-152.77 [Ar-*C*].

2,2,4-Trimethyl-1,2-dihydroquinoline (**78**)

Into a 500-mL, 4-necked, round-bottomed flask equipped with a thermometer, condensor, N_2 inlet, and addition funnel connected to N_2 and placed on top of another condensor, and distillation apparatus was added freshly distilled aniline (20.0 g, 0.21 mol) together with a catalytic amount of iodine (0.3 g) and concentrated HCl (0.2 mL). The reaction mixture was heated to 155 °C, and then acetone (~ 400 mL) was added slowly and at such a rate so that the temperature of the mixture did not fall bellow 140 °C. The unreacted acetone and H_2O (a reaction byproduct) distilled off during the addition process. After addition of acetone (250 mL, ~3.5 h), the reaction mixture was stirred for an additional 1 h and was then allowed to cool to RT. Extraction with hexane (3 x 100 mL) was followed by washing the combined organic extracts with H_2O (1 x 100 mL) and brine (1 x 100 mL) and then drying ($MgSO_4$, 12 h). The hexane was evaporated (rotovap), and the resulting product was purified by distillation (bp 109-111 °C/0.75 mm Hg) to yield **78** as a pale yellow oil (27.9 g, 76%). IR (neat) 3301 [N-H] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.41 [s, 6 H, N-C-(CH_3)], 2.18 [s, 3 H, =C-CH_3], 3.79 [bs, 1 H, N-*H*], 5.45 [s, 1 H, =CH], 6.55-7.15 [m, 4 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.64 [=C-CH_3], 23.44 [2 C, C(CH_3)$_2$], 54.34 [=C-*C*(CH_3)$_2$], 110.53 [=*C*-CH_3], 111.91 [=*C*-C(CH_3)$_2$], 116.12-145.07 [Ar-*C*].

.1,2,2,4-Tetramethyl-1,2-dihydroquinoline (79)

In a 25-mL, three-necked, round-bottomed flask equipped with a condenser, magnetic stirrer, and N_2 inlet, was added powdered KOH (299 mg, 5.7 mmol) dissolved in 10 mL of DMSO. The mixture was stirred at RT until all KOH dissolved, and then the temperature was adjusted to 10 °C (water bath and ice). 2,2,4-Trimethyl-1,2-dihydroquinoline (1.00 g, 5.77 mmol) dissolved in 5 mL of DMSO was added dropwise,

followed immediately by the addition of CH_3I (1.09 g, 7.7 mmol). The reaction mixture was allowed to stir for 30 min and then was poured into 10 mL of ice-cold water. The mixture was extracted with H_2CCl_2 (3 x 5 mL). The combined organic extracts were washed with water (1 x 10 mL) and brine (1 x 10 mL) and then dried (Na_2SO_4, 12 h). Evaporation (rotovap) of solvent and flash chromatography (silica gel, hexanes as only solvent, drop rate = 1 drop/s) of the residue afforded **2** as a yellow oil (0.784 g, 71 %). IR (neat) 1048 [C-N] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.37 [s, 6 H, N-C-(C*H*$_3$)], 2.23 [s, 3 H, =C-C*H*$_3$], 2,96 [s, 3 H, N-CH_3], 5.36 [s, 1 H, =CH], 6.87-7.24 [m, 4 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.64 [=C-*C*H$_3$], 25.74 [2 C, C(*C*H$_3$)$_2$], 30.60 [N-*C*H$_3$], 54.53 [=C-*C*(CH$_3$)$_2$], 111.43 [=*C*-CH$_3$], 112.51 [=*C*-C(CH$_3$)$_2$, 118.12-144.56 [Ar-*C*].

Bis(2,2,2-trichloroethyl) Azodicarboxylate (**81**)

In a 50-mL, three-necked flask equipped with magnetic stirrer, thermometer, and 25-mL and 25-mL dropping funnels was placed a solution of 1.0 g (0.023 mol) of 85% hydrazine hydrate in 6 mL of 95% ethanol. The reaction flask was cooled in an ice bath, and 9.6 g (0.046 mol) of 2,2,2-trichloroethyl chloroformate was added dropwise so that the temperature was kept below 20 °C. During the addition of 1 equivalent of the chloroformate, a white precipitate formed. After exactly one-half of the chloroformate had been added, a solution of of sodium carbonate (2.5 g, 0.024 mol) in 10.0 mL of water was added dropwise (2 h) along with the remaining chloroformate. The rate of addition of these two reagents was such that the flow of the chloroformate was faster than that of the sodium carbonate so that there was always an excess of chloroformate present. The temperature was kept below 20 °C during the addition. As the second equivalent of chloroformate was

added, the white precipitate dissolved. After the addition of the reactants was complete (4 h), the reaction was allowed to stir for an additional 30 min while the solution warmed to RT. The reaction mixture was then transferred to a separatory funnel. The viscous, organic layer (bottom) was separated from the aqueous layer and was dissolved in 20 mL of ether. The reaction vessel was washed with 10 mL of ether, and this ether portion was used to extract the aqueous layer again. The ether layers were combined, dried ($MgSO_4$, 5 h), and then filtered, and the solvent was removed under reduced pressure (rotovap).

Bromine (1.6 g, 20.0 mmol) in 150 mL of dichloromethane was added dropwise (1 h) to a dichloromethane (500 mL) solution of hydrazide (7.0 g, 18.2 mmol) and pyridine (1.50 g, 20.0 mmol), and solution was cooled to 0 °C (ice bath) under argon. The reaction mixture turned from colorless to yellow upon the addition. The reaction was complete after 30-60 min at RT as determined by TLC (silica gel, EtOAc:hexane, 1:1). The reaction mixture was then diluted to 1000 mL with dichloromethane, washed with 5% HCl (2 x 300 mL), saturated sodium bicarbonate (300 mL), water (3 x 300 mL) and saturated NaCl (1 x 300 mL) to give azide **81** as light yellow solid [4.26 g, 56%, mp 115-6 °C (lLit.[76] 116.5-117 °C). IR (KBr pellet) 1786 [C=O], 1723 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 5.08 [s, 4 H, Cl_3CCH_2]; ^{13}C NMR ($DCCl_3$) ppm 77.45 [Cl_3CCH_2], 93.09 [Cl_3CCH_2], 158.42 [C=O].

[1,2,2,4-Tetramethyl-1,2-dihydroquinol-6-yl]amine (**82**)

1,2,2,4-Tetramethyl-1,2-dihydroquinoline (1.00 g, 5.3 mmol) dissolved in 5 mL of a 3 *M* solution of $LiOCl_4$ in diethyl ether was placed in a 25-mL, three-necked, round-bottomed flask equipped with a condensor, addition funnel, and N_2 inlet. To this solution was added dropwise bis(2,2,2-trichloroethyl) azodicarboxylate (4.5 g, 11.8 mmol, prepared

in our lab (see above) via reaction of 2,2,2,trichloroacetyl chloride and hydrazine (85%), followed by reduction with Br_2 in pyridine) dissolved in 5 mL of diethyl ether at 0 °C. The solution was then carefully warmed to 55 °C and stirred at this temperature for 3 h. The new reaction mixture was cooled to 0 °C, and 5 mL of ice water was added. Extraction with H_2CCl_2 (3 x 10 mL), followed by washing the extracts with brine (1 x 5 mL) and drying (Na_2SO_4) overnight, yielded an aryl azide (2.58 g, 85%). This aryl azide was reduced, without purification, by dissolving it in 5 mL of concentrated acetic acid. To this solution was added approximately 1 equivalent by weight of Zn dust (2.6 g). The reaction mixture was stirred for 15 min, and 9 μL of acetone was added by micro-pipette. After stirring the reaction mixture for 3 h at RT, the new mixture was filtered through a 1-cm thick pad of celite. Then 5 mL of a saturated, aqueous solution of $NaHCO_3$ was added, and the mixture was extracted (H_2CCl_2, 3 x 10 mL). Flash chromatography of the concentrated extracts with silica gel (hexane:EtOAc, 1:1) was used to purify the resulting amine obtained as a light brown solid **3**, (mp 87-9 °C, 546 mg, 51% from **79**). IR (neat) 3338 [N-H], 3224 [N-H] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.30 [s, 6 H, N-C-(C*H*$_3$)], 1.97 [s, 3 H, =C-C*H*$_3$], 2,78 [s, 3 H, N-CH_3], 5.38 [s, 1 H, =CH], 6.42 [d, 1 H, J = 9.3 Hz, Ar-*H*], 6.48 [d, 1 H, J = 2.3 Hz, Ar-*H*], 6.55 [q, 1 H, J = 2.1 Hz, J = 9.3 Hz, Ar-*H*], 6.56 [s, 1 H, N-*H*], 6.8 [bs, 1 H, N-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.53 [=C-*C*H$_3$], 25.70 [C(*C*H$_3$)$_2$], 30.68 [N-*C*H$_3$], 55.60 [=C-*C*(CH$_3$)$_2$], 111.91 [=*C*-CH$_3$], 112.14 [=*C*-C(CH$_3$)$_2$, 115.72-138.78 [Ar-*C*].

<u>1,2,2,4-Tetramethyl-1,2-dihydroquinoline-6-carbaldehyde (**83**)</u>

Phosphorus oxychloride (4.1 g, 0.026 mol) was added dropwise to DMF (12 mL) at 0 °C in a 50-mL, three-necked, round-bottomed flask equipped with a condenser and N_2

inlet. After the reaction of $OPCl_3$ with DMF had subsided, 1,2,2,4-tetramethyl-1,2-dihydroquinoline [(**79**), 5 g, 0.026 mol] dissolved in 30 mL of DMF was slowly added at 0 °C. The reaction mixture was allowed to stir for 24 h at RT and was then cooled to 0 °C, after which cold water (5 mL) was carefully added. The reaction mixture was extracted with methylene chloride (3 x 30 mL), and the combined organic layers were washed with water (1 x 10 mL) and brine (1 x 10 mL) and dried ($MgSO_4$, overnight). After evaporation (rotovap) of the solvents and refrigeration for 24 h, aldehyde **83** crystallized as a pale yellow solid (no purification required, 3.57 g, 64%), mp 39-41 °C. IR (pellet) 2733 [H-C=O], 1669 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.38 [s, 6 H, $C(CH_3)_2$], 2.03 [s, 3 H, $=CCH_3$], 2.91 [s, 3 H, $N-CH_3$], 5.30 [s, 1 H, =*CH*], 6.50 [d, 1 H, J = 8.4 Hz, Ar-*H*], 7.52 [d, 1 H, J = 2.4 Hz, Ar-*H*], 7.52 [q, 1 H, J = 8.4 Hz, J = 2.4 Hz, Ar-*H*], 9.67 [s, 1 H, O=C-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.57 [$=C-CH_3$], 28.75 [$C-(CH_3)_2$], 31.21 [$N-CH_3$], 57.60 [$=C-C(CH_3)_2$], 109.14 [=*C*H], 121.76-150.04 [CH=*C*-Ph], 190.19 [*C*=O].

<u>4-Methyl-6-(1,2,2,4-tetramethyl(1,2-dihydroquinolyl))-5,6-dihydropyran-2-one (**84**)</u>

To a solution of of ethyl 3,3-dimethylacrylate (205 mg, 1.5 mmol) and 3 mL of dry THF in a 25-mL, three-necked, round-bottomed flask equipped with a condenser and N_2 inlet was added dropwise (syringe) LDA (0.51 mL, 1.53 mmol, 3 *M* solution in toluene) at -78 °C. After the addition, the reaction mixture was stirred for 1 h, after which **83** (0.3 g, 1.46 mmol) dissolved in 2 mL of THF was added. After stirring the reaction mixture for 1 h at -78 °C, the reaction was quenched with 1.5 mL of a saturated, aqueous solution of ammonium chloride. The resulting mixture was allowed to warm to RT and was then stirred for an additional 1 h. Extraction of the mixture with EtOAc (3 x 3 mL) was followed by washing

the combined organic extracts with water (1 x 1 mL) and brine (1 x 1 mL). After drying ($MgSO_4$, 5 h), the solvent was removed (rotovap), and a thick, dark-red oil was recovered as **84** (171 mg, 43%). IR (neat) 1725 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.28 [s, 6 H, $C(CH_3)_2$], 2.03 [s, 3 H, $=CCH_3$], 2.05 [s, 3 H, $=C-CH_3$], 2.91 [s, 3 H, $N-CH_3$], 5.25 [s, 1 H, =*CH*], 5.91 [s, 1 H, =*CH*], 6.50 [d, 1 H, Ph-*H*], 7.45 [m, 2 H, Ph-*H*], 9.85 [s, 1 H, O=C-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.57 [$=C-CH_3$], 28.75 [$C-CH_3$], 31.21 [s, 1 C, $N-CH_3$], 56.60 [$=C-C(CH_3)_2$], 109.14 [=*C*H], 121.76-150.04 [Ph-CH=*C*], 168.35 [O-*C*=O].

4-Methyl-6-(1,2,2,4-tetramethyl(1,2-dihydroquinolyl))-5,6-dihydropyran-2-ol (**85**)

To a 25-mL, three-necked, round-bottomed flask equipped with a condenser and N_2 inlet was slowly added a solution of **84** (107 mg, 0.36 mmol) in 2 mL of dry THF to a chilled solution (-78 °C) of DIBAL-H in hexane (0.37 mL, 0.59 mmol, 1.6 *M*). The mixture was stirred for 20 min and was then quenched with 0.75 mL of a saturated, aqueous solution of Rochelle salt (saturated solution of sodium and potassium tartrate, 1:1). After allowing the reaction mixture to warm to RT, the mixture was extracted with EtOAc (2 x 2 mL), and the extracts were washed with water (1 x 1 mL) and brine (1 x 1 mL). After drying (Na_2SO_4, 12 h), the solvent was evaporated (rotovap) to give a thick, red oil **85** [the only product as seen from TLC (hexane:EtOAc, 2:1) (92 mg, 85%)]. Compound **85** was used in the next step without further purification. IR (neat) 3452 [O-H] cm^{-1}.

(2*Z*,4*E*)-3-Methyl-5-(1,2,2,4-tetramethyl(1,2-dihydroquinolyl))penta2,4-dienal (**86**)

In a 25-mL, three-necked, round-bottomed flask equipped with a condenser, N_2 inlet, and thermometer holder was placed lactol **85** (150 mg, 0.5 mmol) dissolved in 2 mL of

$ClCH_2CH_2Cl$ (1,2-dichloroethane), and then 2 mL of 5% HCl was added. The reaction mixture was warmed to 55 °C for 3 h. The reaction was monitored by TLC (hexane:EtOAc, 4:1) until completion. The mixture was then cooled to RT and carefully neutralized with a saturated, aqueous solution of $NaHCO_3$. The aqueous layer was extracted with H_2CCl_2 (2 x 3 mL), and the combined extracts were washed with water (1 x 2 mL) and brine (1 x 2 mL). After drying ($MgSO_4$, 12 h) and evaporating the solvent (rotovap), the residue was purified with silica gel chromatography (hexane:EtOAc, 1:1) to yield a bright red oil as **86** (87 mg, 62%). IR (neat) 2785 [H-C=O], 1655 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.28 [s, 6 H, $C(CH_3)_2$], 2.03 [s, 3 H, $=CCH_3$], 2.35 [s, 3 H, J = 0.3 Hz, $=C-CH_3$], 2.91 [s, 3 H, $N-CH_3$], 5.25 [s, 1 H, =*CH*], 5.91 [d, 1 H, =*CH*], 6.25 [s, 1 H, =*CH*], 6.50 [d, 1 H, Ar-*H*], 7.45 [m, 2 H, Ar-*H*], 10.15 [d, 1 H, O=C-*H*]; ^{13}C NMR ($DCCl_3$) ppm 13.06 [$=C-CH_3$], 18.57 [$=C-CH_3$], 27.90 [$C-(CH_3)_2$], 30.21 [$N-CH_3$], 56.86 [$=C-C(CH_3)_2$], 110.14 [=*C*H], 122.76-136.04 [CH=*C*-Ph], 191.04 [H-*C*=O].

<u>Ethyl (2*E*)-2-Fluoro-3-(1,2,2,4-tetramethyl(6-1,2-dihydroquinolyl))prop-2-enoate (**87**)</u>

Into a 25-mL, three-necked, round-bottomed flask fitted with a condenser, magnetic stirrer, and N_2 inlet, was added ethyl 2-fluorophosphono-acetate (224 mg, 0.93 mmol) and DMPU (120 mg, 0.93 mmol) dissolved in 3 mL of dry THF. The reaction mixture was cooled to 0 °C, and *n*-BuLi was added dropwise (0.6 mL, 0.94 mmol, 1.6 *M*) by syringe. After stirring the reaction mixture for 1 h, 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde [(**83**), 200 mg, 0.93 mmol] dissolved in 2 mL of dry THF was added. The reaction mixture was then stirred for 3 days at RT and was then quenched with a saturated, aqueous solution of ammonium chloride (1.0 mL). Extraction with ethyl acetate (3 x 25 mL)

was followed by washing the combined organic layers with H_2O (1 x 20 mL) and brine (1 x 25 mL) and then drying ($MgSO_4$, 5 h). After flash chromatography (hexane:diethyl ether, 1.5:1, drop rate = 1 drop/s) of the residue, and, after solvent evaporation (rotovap), ester **87** (220 mg 78%) of was recovered as a clear oil. IR (neat) 1724 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.85 [t, 3 H, OCH_2CH_3], 1.35 [s, 6 H, CH_3CCH_3], 1.98 [s, 3 H, $=CCH_3$], 2.81 [s, 3 H, N-CH_3], 4.27 [q, 2 H, OCH_2CH_3], 5.33 [s, 1 H, =*CH*], 6.50 [d, 1 H, J = 8.7 Hz, Ar-*H*], 6.85 [d, 1 H, J = 36.6 Hz, FC=C*H*], 7.42 [d, 1 H, J = 2.1 Hz, Ar-*H*], 7.52 [q, 1 H, J = 8.7 Hz, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.29 [OCH_2CH_3], 18.53 [=C-CH_3], 25.70 [$C(CH_3)_2$], 28.68 [N-CH_3], 56.60 [=C-$C(CH_3)_2$], 61.32 [OCH_2CH_3], 110.91 [=*C*-CH_3], 118.14 [=*C*-$C(CH_3)_2$, 127.72-131.78 [Ar-*C*], 146.34 [F*C*=CH], 162.45 [*C*=O].

<u>(2*E*)-2-Fluoro-3-[(1,2,2,4-tetramethyl-6-(1,2-dihydroquinolyl))]prop-2-en-1-ol (**88**)</u>

Ester **87** (220 mg, 0.72 mmol) dissolved in 5 mL of dry THF was placed in 25-mL, one-necked, round-bottomed flask, and was then cooled to -40 °C. A solution (1.8 mL, 1.2 mmol, 1.5 *M*) of DIBAL-H in toluene was then added by syringe. The reaction mixture was stirred for 2 h, and it was monitored by TLC (hexane:ethyl acetate, 1:2). After all of the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 1 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was extracted with ethyl acetate (3 x 25 mL), followed by washing the organic extracts with H_2O (1 x 15 mL) and brine (1 x 20 mL) and then drying ($MgSO_4$, 12 h). Separation of the major component in the residue, after solvent evaporation (rotovap), by flash chromatography (hexane:diethyl ether:EtOAc, 1:1:1, drop rate = 1 drop/s) afforded **88** (182 mg, 96%) as a colorless oil. IR (neat) 3371 [O-H] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.36

[s, 6 H, CH_3CCH_3], 1.98 [bs, 1 H, O-*H*], 1.98 [d, 3 H, =CCH_3], 2.86 [s, 3 H, N-CH_3], 4.41 [q, 2 H, H_2C-OH], 6.35 [d, 1 H, J = 20.4 Hz, FC=C*H*], 6.46 [d, 1 H, J = 8.4 Hz, Ar-*H*], 6.93 [d, 1 H, J = 2.1 Hz, Ar-*H*], 6.95 [q, 1 H, J = 8.4 Hz, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.53 [=C-CH_3], 27.70 [$C(CH_3)_2$], 29.68 [$C(CH_3)_2$], 30.68 [N-CH_3], 56.36 [=C-$C(CH_3)_2$], 58.83[$HOCH_2$], 110.48 [=*C*-CH_3], 111.34 [F*C*=CH] 111.54 [=*C*-$C(CH_3)_2$, 123.72-130.78 [Ar-*C*]; ^{19}F NMR ($DCCl_3$) ppm -113.65 [q, 1 F, $HOCH_2CF$].

<u>(2*E*)-2-Fluoro-3-[(1,2,2,4-tetramethyl-6-(1,2-dihydroquinolyl))]prop-2-enal (**89**)</u>

Alcohol **88** (180 mg, 0.70 mmol) dissolved in 5 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask and MnO_2 (0.75 g, 8.75 mmol, activated grade, size<5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue, after solvent evaporation, via flash chromatography (hexane:diethyl ether:ethyl acetate, 2:1:0.1, drop rate = 1 drop/s) afforded aldehyde **89** (98 mg, 54%), as a light yellow oil. IR (neat) 2864 [O=C-H], 1682 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.34 [s, 6 H, CH_3CCH_3], 1.98 [s, 3 H, =CCH_3], 2.81 [s, 3 H, N-CH_3], 5.33 [s, 1 H, =C*H*], 6.47 [d, 1 H, J = 8.4 Hz, Ar-*H*], 7.06 [d, 1 H, J = 2.4 Hz, Ar-*H*], 7.14 [q, 1 H, J = 8.4 Hz, J = 2.1 Hz, Ar-*H*]; 7.26 [d, 1 H, J = 18.3 Hz, FC=C*H*], 9.75 [d, 1 H, J = 19.8 Hz, FCC(O)*H*], ^{13}C NMR ($DCCl_3$) ppm 18.51 [=C-CH_3], 28.19 [$C(CH_3)_2$], 30.86 [N-CH_3], 38.68 [$C(CH_3)_2$], 57.36 [=C-$C(CH_3)_2$], 110.48 [=*C*-CH_3], 116.54 [=*C*-$C(CH_3)_2$, 123.72-130.78 [Ar-*C*], 151.34 [F*C*=CH], 182.35 [*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -131.44 [t, 1 F, O=CHC*F*].

<u>Ethyl (2*E*)-3-(1,2,2,4-tetramethyl(6-1,2-dihydroquinolyl))prop-2-enoate (**90**)</u>

Into a 25-mL, three-necked, round-bottomed flask fitted with a condenser, magnetic stirrer, and N_2 inlet, was added ethyl 2-phosphonoacetate (217 mg, 0.93 mmol) and DMPU (119 mg, 0.93 mmol) dissolved in 3 mL of dry THF. The reaction mixture was cooled to 0 °C, and *n*-BuLi was added dropwise (64 mL, 1.03 mmol, 1.6 *M*) by syringe. After stirring the reaction mixture for 1 h, 1,2,2,4-tetramethyl-1,2-dihydroquinoline-6-carbaldehyde [(**83**), 200 mg, 0.93 mmol] dissolved in 3 mL of dry THF was added dropwise (20 min). The reaction mixture was stirred for 3 days at RT and then was quenched with a saturated, aqueous solution of ammonium chloride (1 mL). Extraction with ethyl acetate (3 x 20 mL) was followed by washing the combined organic layers with H_2O (1 x 20 mL) and brine (1 x 20 mL) and then drying ($MgSO_4$, 12 h). After flash chromatography (hexane:diethyl ether, 1:2, drop rate = 1 drop/s) of the residue (after solvent evaporation), **90** (217 mg, 82%) was recovered as a clear oil. IR (neat) 1703 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.33 [t, 3 H, OCH_2CH_3], 1.34 [s, 6 H, CH_3CCH_3], 1.99 [d, 3 H, $=CCH_3$], 2.84 [s, 3 H, N-CH_3], 4.23 [q, 2 H, OCH_2CH_3], 5.30 [d, 1 H, =*CH*], 6.18 [d, 1 H, J = 15.9 Hz, HC=*CH*], 6.48 [d, 1 H, J = 8.4 Hz, Ar-*H*], 7.21 [d, 1 H, J = 2.1 Hz, Ar-*H*], 7.30 [q, 1 H, J = 8.7 Hz, J = 2.1 Hz, Ar-*H*], 7.60 [d, 1 H, J = 15.9 Hz, HC=*CH*]; ^{13}C NMR ($DCCl_3$) ppm 14.40 [OCH_2CH_3], 18.54 [=C-CH_3], 30.68 [N-CH_3], 56.60 [=C-$C(CH_3)_2$], 60.32 [OCH_2CH_3], 63.96 [$C(CH_3)_2$], 110.53 [=*C*-CH_3], 112.14 [=*C*-$C(CH_3)_2$, 121.72-147.78 [Ar-*C*], 167.92 [*C*=O].

<u>(2*E*)-3-[(1,2,2,4-Tetramethyl-6-(1,2-dihydroquinolyl))]prop-2-en-1-ol (**91**)</u>

Ester **90** (200 mg, 0.7 mmol) dissolved in 3 mL of dry THF was placed in 25-mL, three-necked, round-bottomed flask fitted with a condenser, magnetic stirrer, and N_2 inlet, and then cooled to -40 °C. A solution (1.20 mL, 1.75 mmol, 2.5 eq, 1.5 M) of DIBAL-H in

toluene was then added by syringe. The reaction mixture was stirred for 3 h, and it was monitored by TLC (hexane:ethyl acetate, 1:2). After the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 1 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was extracted with ethyl acetate (3 x 15 mL), followed by washing the organic extracts with H_2O (1 x 15 mL) and brine (1 x 20 mL) and then drying ($MgSO_4$, 12 h). Separation of the major component in the residue, after solvent evaporation, by flash chromatography (hexane:diethyl ether, 1:2, drop rate = 1 drop/s) afforded **91** (146 mg, 86%) as colorless oil. IR (neat) 3342 [O-H] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.29 [s, 6 H, CH_3CCH_3], 1.58 [bs, 1 H, O-*H*], 1.99 [d, 3 H, =CCH_3], 2.80 [s, 3 H, N-CH_3], 4.26 [d, 2 H, H_2C-OH], 5.31 [d, 1H, =C*H*], 6.35 [d, 1 H, J = 20.4 Hz, FC=C*H*], 6.46 [d, 1 H, J = 8.4 Hz, Ar-*H*], 6.93 [d, 1 H, J = 2.1 Hz, Ar-*H*], 6.95 [q, 1 H, J = 8.4 Hz, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.56 [=C-CH_3], 27.21 [$C(CH_3)_2$], 30.65 [N-CH_3], 56.29 [=C-$C(CH_3)_2$], 64.21 [$HOCH_2$], 110.49 [=*C*-CH_3], 121.54 [=*C*-$C(CH_3)_2$, 123.72-145.78 [Ar-*C*].

<u>(2*E*)-3-[(1,2,2,4-Tetramethyl-6-(1,2-dihydroquinolyl))]prop-2-enal (**92**)</u>

Alcohol **91** (140 mg, 0.57 mmol) dissolved in 3 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask and MnO_2 (0.55 g, 6.44 mmol, activated grade, size<5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and was then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue, after solvent evaporation, via flash chromatography (hexane:diethyl ether:ethyl acetate, 2:1:1, drop rate = 1 drop/s) afforded aldehyde **92** (90 mg, 65%), as a light yellow oil. IR (neat) 2837 [O=C-H], 1697 [C=O] cm^{-}

[1]; ^{1}H NMR ($DCCl_3$) δ 1.36 [s, 6 H, CH_3CCH_3], 1.98 [d, 3 H, =CCH_3], 2.87 [s, 3 H, N-CH_3], 5.32 [s, 1 H, =*CH*], 6.47 [d, 1 H, J = 8.4 Hz, Ar-*H*], 6.55 [dd, 1 H, J = 7.8 Hz, J = 15.9 Hz, =*CH*C(O)H], 7.21 [d, 1 H, J = 2.4 Hz, Ar-*H*], 7.30 [q, 1 H, J = 8.4 Hz, J = 2.1 Hz, Ar-*H*]; 7.26 [d, 1 H, J = 15.9 Hz, HC=*CH*], 9.57 [d, 1 H, J = 7.8 Hz, HCC(O)*H*], ^{13}C NMR ($DCCl_3$) ppm 18.50 [=C-CH_3], 28.36 [$C(CH_3)_2$], 31.86 [N-CH_3], 57.36 [=C-$C(CH_3)_2$], 110.48 [=*C*-CH_3], 121.54 [=*C*-$C(CH_3)_2$, 122.72-154.78 [Ar-*C*], 151.34 [F*C*=CH], 193.70 [*C*=O].

<u>1-(2,2,4,4-Tetramethyl-3*H*-benzo[*e*]thiane)ethan-1-one (**94a**)</u>

Into a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet, and an addition funnel was added $AlCl_3$ (5.17 g, 38.77 mmol) dissolved in 25 mL of freshly distilled CH_3NO_2. A solution of the 2,2,4,4-tetramethyl-3*H*-benzo[*e*]thiane [(**93**), 5.00 g, 24.24 mmol] and acetyl chloride (2.80 g, 40.11 mmol) in freshly distilled CH_3NO_2 (20 mL) was then added dropwise at RT over period of 1 h. The reaction mixture was stirred for 48 h and then poured into a 100-mL beaker containing ~30 g of crushed ice. The layers were separated, and the aqueous layer was then extracted with diethyl ether (2 x 50 mL). Combined organic layers were washed with water (2 x 30 mL) and brine (1 x 30 mL) and then dried (Na_2SO_4, 12 h). Evaporation (rotovap) of solvent and distillation (bp 132-34 °C/ 0.75 mm Hg) of the residual oil afforded ketone **94a** (4.29 g, 75%) as a light yellow oil. IR (neat) 1681 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.39 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.98 [s, 2 H, $CH_2C(CH_3)_2$], 2.55 [s, 3 H, $C(O)CH_3$], 7.18 [d, 1 H, J = 8.7 Hz, Ar-*H*], 7.62 [q, 1 H, J = 8.7 Hz, J = 1.9 Hz, Ar-*H*], 8.15 [d, 1 H, J = 1.9 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.21 [$C(O)CH_3$], 31.58 [$CH_2C(CH_3)_2$)], 32.53 [$SC(CH_3)_2$], 35.42 [$CH_2C(CH_3)_2$], 42.41 [$SC(CH_3)_2$], 53.78 [$CH_2C(CH_3)_2$], 125.70-142.51 [Ar-*C*], 196.78 [*C*=O].

2-Methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))propan-1-one (**94b**)

Into a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet, and an addition funnel was added $AlCl_3$ (5.17 g, 38.77 mmol) dissolved in freshly distilled CH_3NO_2 (25 mL). A solution of the 2,2,4,4-tetramethyl-3*H*-benzo[*e*]thiane [(**93**), 4.00 g, 19.38 mmol] and isobutyryl chloride (2.61 g, 21.32 mmol) in 20 mL of freshly distilled CH_3NO_2 was then added dropwise (1 h) at RT. The reaction mixture was stirred for 48 h and was then poured into a 100-mL beaker containing ~30 g of crushed ice. The layers were separated, and the aqueous layer was then extracted with diethyl ether (2 x 50 mL). Combined organic layers were washed with water (2 x 25 mL) and brine (1 x 30 mL) and then dried (Na_2SO_4, 12 h). Evaporation (rotovap) of solvent and distillation (bp 153-54 °C/ 0.75 mm Hg) of the residual oil afforded ketone **94b** (3.59 g, 70%) as a light yellow oil. IR (neat) 1679 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.21 [d, 3 H, $CH(CH_3)_2$], 1.42 [s, 6 H, $C(CH_3)_2$], 1.43 [s, 6 H, $C(CH_3)_2$], 3.53 [m, 1 H, $CH(CH_3)_2$], 7.18 [d, 1 H, J = 8.7 Hz, Ar-*H*], 7.62 [q, 1 H, J = 8.7 Hz, J = 1.9 Hz, Ar-*H*], 8.15 [d, 1 H, J = 1.9 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 19.21 [$CH(CH_3)_2$], 31.58 [$CH_2C(CH_3)_2$)], 32.53 [$SC(CH_3)_2$], 35.42 [$CH_2C(CH_3)_2$], 42.41 [$SC(CH_3)_2$], 53.78 [C, $CH_2C(CH_3)_2$], 125.70-142.51 [Ar-*C*], 203.59 [*C*=O].

3-Methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian6-yl))butan-1-one (**94c**)

Into a 100-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet and an addition funnel was placed $AlCl_3$ (6.5 g, 48.46 mmol) dissolved in 25 mL of freshly distilled CH_3NO_2. The solution of 2,2,4,4-tetramethyl-3*H*-benzo[*e*]thiane [(**93**), 5.00 g, 24.23 mmol] and isovaleryl chloride (3.21g, 26.65 mmol) in 20 mL of freshly distilled

CH_3NO_2 was then added at RT over period of 1 h. The reaction mixture was stirred for 48 h and was then poured into a 100-mL beaker containing ~30 g of crushed ice. The layers were separated, and the aqueous layer was then extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with water (2 x 25 mL) and brine (1 x 30 mL) and dried (Na_2SO_4, 12 h). Evaporation (rotovap) of the solvent and distillation (bp 182-85 °C/1.5 mm Hg) of the residual oil afforded ketone **94c** (mp 55-6 °C, 4.60 g, 65%) as a light yellow solid. IR (neat) 1680 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.01 [d, 6 H, $CH(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.41 [s, 6 H, $C(CH_3)_2$], 1.96 [s, 2 H, CCH_2C], 2.25 [m, 1 H, $CH(CH_3)_2$], 2.80 [d, 2 H, $O{=}CCH_2CH$], 7.18 [d, 1 H, J = 8.9 Hz, Ar-*H*], 7.62 [q, 1 H, J = 8.9 Hz, J = 2.0 Hz, Ar-*H*], 8.15 [d, 1 H, J = 2.0 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 22.76 [$CH(CH_3)_2$], 25.22 [$O{=}CCH_2CH$], 31.60 [$CH_2C(CH_3)_2$], 32.52 [$SC(CH_3)_2$], 35.47 [$CH_2C(CH_3)_2$], 42.44 [$SC(CH_3)_2$], 53.81 [$CH_2C(CH_3)_2$], 125.63-142.47 [Ar-*C*], 198.22 [*C*=O].

<u>Ethyl (2*E*)-2-Fluoro-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-enoate (**95a**)</u>

Into a 25-mL, three-necked, round-bottomed equipped with a condenser, a N_2 inlet and an addition funnel flask was added ethyl 2-fluorophosphono-acetate (536 mg, 2.21 mmol) and DMPU (283.2 mg, 2.21 mmol) dissolved in 3 mL of dry THF. The reaction mixture was cooled to 0 °C, and *n*-BuLi was added dropwise (1.38 mL, 2.21 mmol, 1.6 *M*) by syringe. After stirring the reaction mixture for 1 h, 1-(2,2,4,4-tetramethyl-3*H*-benzo[3,4-*e*]thian-1-one [(**94a**), 502 mg, 2.00 mmol] dissolved in 4 mL of dry THF was added dropwise (1h). The reaction mixture was stirred for 6 days at RT and was then quenched with a saturated, aqueous solution of ammonium chloride (2 mL). Extraction with ethyl acetate (3 x 25 mL) was followed by washing the combined organic layers with H_2O (1 x 20 mL) and

brine (1 x 25 mL) and then drying ($MgSO_4$, 12 h). After solvent evaporation (rotovap), and flash chromatography (hexane:di-ethyl ether, 1:1, drop rate = 1 drop/s) of the residue, **95a** (394 mg, 67%) was recovered as a clear oil which was a mixture of *E* and *Z* isomers clear oils (*E*:*Z*, 4:1). IR (neat) 1712 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.00 [t, 3 H, OCH_2CH_3], 1.40 [s, 6 H, CH_3CCH_3], 1.42 [s, 6 H, CH_3CCH_3], 1.98 [s, 2 H, CH_2], 2.15 [d, 3 H, $=CCH_3$], 4.07 [q, 2 H, OCH_2CH_3], 6.83 [q, 1 H, Ar-*H*]; 7.10 [d, 1 H, Ar-*H*], 7.15 [d, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.25 [OCH_2CH_3], 18.15 [$=CCH_3$], 26.39 [$C(CH_3)_2$], 30.43 [$C(CH_3)_2$], 55.59 [CH_2CS], 60.19 [OCH_2CH_3], 110.65 [=*C*H], 115.03-131.14 [Ar-*C*], 140.99 [F*C*=CH], 165.34 [RO-*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -123.6 [q, 1 F, *F*C=CCH_3].

<u>Ethyl (2*E*)-2-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-enoate (**95b**)</u>

Into a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet, and an addition funnel was added ethyl 2-fluorophosphonoacetate (482 mg, 1.99 mmol), DMPU (255 mg, 1.99 mmol), and 3 mL of dry THF. The reaction mixture was cooled to 0 °C, and *n*-BuLi (1.25 mL, 21.99 mmol, 1.6 *M*) was added by syringe. After stirring the reaction mixture for 1 h, 2-methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))propan-1-one [(**94b**), 495 mg, 1.98 mmol] dissolved in 4 mL of dry THF was added dropwise (30 min). The reaction mixture was then stirred for 4 days at RT and then 2 days at reflux, after which time it was cooled to RT and quenched with a saturated, aqueous solution of ammonium chloride (1 mL). Extraction with ethyl acetate (3 x 25 mL) was followed by washing the combined organic extracts with H_2O (1 x 20 mL) and brine (1 x 25 mL) and drying ($MgSO_4$, 12 h). After solvent evaporation (rotovap), and flash chromatography (hexane:diethyl ether, 1:1, drop rate = 1 drop/s) of the residue, ester **95b**

(342 mg, 52%) was recovered as a light yellow oil. IR (neat) 1702 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.35 [t, 3 H, OCH_2CH_3], 1.23 [d, 3 H, $CH(CH_3)_2$], 1.44 [s, 6 H, $C(CH_3)_2$], 1.43 [s, 6 H, $C(CH_3)_2$], 2.01 [s, 2 H, CCH_2C], 3.48 [m, 1 H, $CH(CH_3)_2$], 4.14 [q, 2 H, OCH2CH_3], 7.18 [d, 1 H, J = 8.9 Hz, Ar-*H*], 7.54 [q, 1 H, J = 8.9 Hz, J = 2.1 Hz, Ar-*H*], 8.02 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.25 [C, OCH_2CH_3], 19.34 [2 C, $CH(CH_3)_2$], 31.75 [2 C, $CH_2C(CH_3)_2$], 32.43 [2 C, $SC(CH_3)_2$], 35.56 [C, $CH_2C(CH_3)_2$], 42.41 [$SC(CH_3)_2$], 53.78 [C, $CH_2C(CH_3)_2$], 60.12 [C, OCH_2CH_3], 110.65 [C, CH_3C=CF], 110.65 [C, CH_3C=CF], 122.70-140.51 [6 C, Ar-*C*], 165.45 [*C*=O]; ^{19}F NMR ppm -123.8 [q, 1 F, *F*C=CCH_3].

<u>Ethyl (2*E*)-2-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-enoate (**95c**)</u>

Into a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet, and an addition funnel was added ethyl 2-fluorophosphonoacetate (530 mg, 2.20 mmol), DMPU (280 mg, 2.20 mmol), and 5 mL of dry THF. The reaction mixture was cooled to 0 °C, and *n*-BuLi (1.33 mL, 2.20 mmol, 1.6 *M*) was added by syringe. After stirring the reaction mixture for 1 h, 2-methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian6-yl))butan-1-one [(**94c**), 580 mg, 2.00 mmol] dissolved in 5 mL of dry THF was added dropwise (30 min). The reaction mixture was then stirred for 6 days at RT and then 2 days at reflux, after which it was cooled to RT and quenched with a saturated, aqueous solution of ammonium chloride (1 mL). Extraction with ethyl acetate (3 x 35 mL) was followed by washing the combined organic extracts with H_2O (1 x 30 mL) and brine (1 x 35 mL) and drying ($MgSO_4$, 12 h). After solvent evaporation (rotovap) and flash chromatography

(hexane:diethyl ether, 1:1, drop rate = 1 drop/s) of the residue, ester **95c** (423 mg, 56%) was recovered as a light yellow oil. IR (neat) 1702 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.85 [t, 3 H, OCH_2CH_3], 1.25 [d, 3 H, $CH(CH_3)_2$], 1.44 [s, 6 H, $C(CH_3)_2$], 1.43 [s, 6 H, $C(CH_3)_2$], 2.01 [s, 2 H, CCH_2C], 2.14 [m, 2 H, CH_2CH], 3.48 [m, 1 H, $CH(CH_3)_2$], 4.24 [q, 2 H, OCH2CH_3], 7.18 [d, 1 H, J = 8.7 Hz, Ar-*H*], 7.54 [q, 1 H, J = 8.7 Hz, J = 2.4 Hz, Ar-*H*], 8.02 [d, 1 H, J = 2.4 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.25 [C, OCH_2CH_3], 19.34 [2 C, $CH(CH_3)_2$], 31.75 [2 C, $CH_2C(CH_3)_2$], 32.43 [2 C, $SC(CH_3)_2$], 35.56 [C, $CH_2C(CH_3)_2$], 42.41 [$SC(CH_3)_2$], 53.78 [C, $CH_2C(CH_3)_2$], 60.12 [C, OCH_2CH_3], 110.65 [C, CH_3C=CF], 110.65 [C, CH_3C=CF], 122.70-140.51 [6 C, Ar-*C*], 165.45 [*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -125.8 [q, 1 F, *F*C=CCH_3].

<u>(2*E*)-2-Fluoro-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-en-1-ol (**96a**) and (2*Z*)-2-Fluoro-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-en-1-ol (**98a**)</u>

Ester **95a** (631 mg, 1.87 mmol) dissolved in 5 mL of dry THF was placed in 25-mL, three-necked, round-bottomed flask and then cooled to -40 °C. A solution of DIBAL-H in toluene (3.75 mL, 5.61 mmo, l 1.5 *M*) was then added by syringe. The reaction mixture was stirred for 2 h, and it was monitored by TLC (hexane:ethyl acetate, 1:1). After all of the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 2 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was extracted with ethyl acetate (3 x 25 mL), followed by washing the organic extracts with H_2O (1 x 15 mL) and brine (1 x 20 mL) and then drying ($MgSO_4$, 12 h). Separation of the major component in the residue, after solvent evaporation followed by flash chromatography (hexane:diethyl ether, 1:1, drop rate = 1 drop/s), afforded **96a** [(*E*

isomer) 390 mg, 70%] and **98a** [(*Z* isomer), 127 mg, 23%] as colorless oils. The *E*:*Z* ratio was 3:1; R_f's were 0.645 and 0.362, respectively, for TLC with hexane:diethyl ether, (1:1).

The spectrum of **96a**: IR (neat) 3402 [O-H], 1659 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.75 [bs, 1 H, O-*H*], 4.18 [d, 2 H, H_2COH], 6.9-7.3 [m, 3 H, Ar-*H*], ^{13}C NMR ($DCCl_3$) ppm 31.56 [2 C, CH_3CCH_3], 118.81 [=CCH_3], 119.05 [=*C*F], 125.70-156.44 [Ar-*C*]; ^{19}F NMR ($DCCl_3$) ppm -117.65 [d, 1 F, $HOCH_2CF$].

The spectrum of **98a**: IR (neat) 3404 [O-H], 1683 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.65 [bs, 1 H, O-*H*], 4.41 [d, 2 H, H_2COH], 7.1-7.45 [m, 3 H, Ar-*H*], ^{13}C NMR ($DCCl_3$) ppm 32.56[2 C, CH_3CCH_3], 120.81 [=CCH_3], 121.05 [=*C*F], 125.70-154.60 [Ar-*C*]; ^{19}F NMR ($DCCl_3$) ppm -117.57 [t, 1 F, $HOCH_2CF$].

(1*E*)-1-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-en-1-ol (**96b**) (1*Z*)-1-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-en-1-ol (**98b**)

Ester **95b** (402 mg, 1.1 mmol) dissolved in 4 mL of dry THF was placed in a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet and an addition funnel and then cooled to -40 °C. A solution of DIBAL-H (2.20 mL, 3.3 mmol, 1.5 *M* in toluene) was then added by syringe. The reaction mixture was stirred for 1 h and monitored by TLC (hexane:ethyl acetate, 1:1). After all of the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 2 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was extracted with ethyl acetate (3 x 20 mL), followed by washing the organic extracts with H_2O (1 x 10 mL) and brine (1 x 15 mL). Purification of the major component in the residue (after

solvent evaporation) by flash chromatography (hexane:diethyl ether, 2:1, drop rate = 1 drop/s) afforded 112 mg (31%) of **96b** (E isomer) and 191 mg (53%) of **98b** (Z isomer) (E:Z, 0.6:1, R_f's were 0.745 and 0.562, respectively) as oils.

The spectrum of **96b**: IR (neat) 3359 [O-H], 1686 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.01 [d, 3 H, $CH(CH_3)_2$], 1.36 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.58 [bs, 1 H, O-*H*], 1.96 [s, 2 H, CCH_2C], 3.18 [m, 1 H, $CH(CH_3)_2$], 3.97 [d, 2 H, $HOCH_2$], 6.98 [q, 1 H, J = 8.5 Hz, J = 2.3 Hz, Ar-*H*], 7.15 [d, 1 H, J = 8.5 Hz, Ar-*H*] 7.25 [d, 1 H, J = 2.3 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 20.98 [2 C, $CH(CH_3)_2$], 31.51 [2 C, $CH_2C(CH_3)_2$], 32.80 [2 C, $SC(CH_3)_2$], 33.56 [C, $CH_2C(CH_3)_2$], 35.31 [$SC(CH_3)_2$], 54.25 [C, $CH_2C(CH_3)_2$], 59.54 [C, $HOCH_2$], 112.34 [C, CH_3C=CF], 113.65 [C, CH_3C=CF], 127.70-142.16 [6 C, Ar-*C*]; ^{19}F NMR ($DCCl_3$) ppm -121.85 [t, 1 F, =C*F*].

The spectrum of **98b**: IR (neat) 3347 [O-H], 1688 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.98 [dd, 3 H, $CH(CH_3)_2$], 1.38 [s, 6 H, $C(CH_3)_2$], 1.44 [s, 6 H, $C(CH_3)_2$], 1.60 [bs, 1 H, O-*H*], 1.96 [s, 2 H, CCH_2C], 2.86 [m, 1 H, $CH(CH_3)_2$], 4.40 [d, 2 H, $HOCH_2$], 6.80 [q, 1 H, J = 8.0 Hz, J = 2.1 Hz, Ar-*H*], 7.10 [d, 1 H, J = 8.0 Hz, Ar-*H*], 7.25 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 21.89 [2 C, $CH(CH_3)_2$], 30.60 [2 C, $CH_2C(CH_3)_2$], 31.68 [2 C, $SC(CH_3)_2$], 32.76 [C, $CH_2C(CH_3)_2$], 41.96 [$SC(CH_3)_2$], 54.35 [C, $CH_2C(CH_3)_2$], 61.91 [C, $HOCH_2$], 110.34 [C, CH_3C=CF], 111.34 [C, CH_3C=CF], 127.23-142.16 [6 C, Ar-*C*], ^{19}F NMR ($DCCl_3$) ppm -115.28 [m, 1 F, =C*F*].

(1*E*)-1-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-en-1-ol (**96c**) and (1*E*)-1-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-en-1-ol (**98c**)

Ester **95c** (300 mg, 0.79 mmol) dissolved in 4 mL of dry THF was placed in a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet and an addition funnel and then cooled to -40 °C. A solution of DIBAL-H in toluene (1.35 mL, 1.98 mmol, 1.5 *M*) was then added by syringe. The reaction mixture was stirred for 1 h and monitored by TLC (hexane:ethyl acetate, 1:1). After all of the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 2 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was extracted with ethyl acetate (3 x 15 mL), followed by washing the organic extracts with H_2O (1 x 10 mL) and brine (1 x 15 mL). After solvent evaporation (rotovap) and separation of the major component in the residue by flash chromatography (hexane:diethyl ether, 1:1, drop rate = 1 drop/s), **96c** (225 mg, 85%) and **98c** (21 mg, 8%) were obtained as oils.

The spectrum of **96c**: IR (neat) 3369 [O-H], 1683 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.89 [d, 6 H, $CH(CH_3)_2$], 1.36 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.54 [m, 1 H, $CH(CH_3)_2$] 1.88 [bs, 1 H, O-*H*], 1.96 [s, 2 H, CCH_2C], 2.22 [d, 2 H, $CHCH_2$], 4.42 [d, 2 H, $HOCH_2$], 6.98 [q, 1 H, J = 8.5 Hz, J = 2.3 Hz, Ar-*H*], 7.15 [d, 1 H, J = 8.5 Hz, Ar-*H*] 7.30 [d, 1 H, J = 2.3 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 22.98 [$CH(CH_3)_2$], 24.90 [$CH(CH_3)_2$], 31.51 [$CH_2C(CH_3)_2$], 32.67 [$SC(CH_3)_2$], 39.56 [$CH_2C(CH_3)_2$], 41.31 [$SC(CH_3)_2$], 54.29 [$CH_2C(CH_3)_2$], 58.54 [$HOCH_2$], 120.16 [CH_3C=CF],, 126.70-142.16 [Ar-*C*], 155.21[CH_3C=*C*F]; ^{19}F NMR ($DCCl_3$) ppm -117.36 [t, 1 F, =C*F*].

The spectrum of **98c**: IR (neat) 3369 [O-H], 1683 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.82 [d, 6 H, $CH(CH_3)_2$], 1.36 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.69 [m, 1 H, $CH(CH_3)_2$] 1.82 [bs, 1 H, O-*H*], 1.94 [s, 2 H, CCH_2C], 2.32 [m, 2 H, $CHCH_2$], 4.17 [d, 2 H, $HOCH_2$], 6.95 [q, 1 H, J = 8.4 Hz, J = 2.1 Hz, Ar-*H*], 7.15 [d, 1 H, J = 8.4 Hz, Ar-*H*] 7.30

[d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 22.24 [CH(CH_3)$_2$], 24.79 [*C*H(CH_3)$_2$], 31.58 [CH_2C(CH_3)$_2$], 32.87 [SC(CH_3)$_2$], 38.56 [CH_2*C*(CH_3)$_2$], 42.31 [S*C*(CH_3)$_2$], 54.43 [*C*H_2C(CH_3)$_2$], 72.73 [HO*C*H_2], 122.16 [CH_3*C*=CF],, 126.16-142.38 [Ar-*C*], 156.21[CH_3C=*C*F]; ^{19}F NMR ($DCCl_3$) ppm -118.76 [t, 1 F, =C*F*].

(2*E*)-2-Fluoro-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-enal (**97a**)

Alcohol **96a** (390 mg, 1.32 mmol) dissolved in 5 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask, and MnO_2 (1.5 g, 17.25 mmol, activated grade, size<5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue (after solvent evaporation) via flash chromatography (hexane:diethyl ether:ethyl acetate, 1:1:0.1, drop rate = 1 drop/s) afforded aldehyde **97a** (212 mg, 55%), as a light yellow oil. IR (neat) 2874 [O=C-H], 1667 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.36 [s, 6 H, C(CH_3)$_2$], 1.40 [s, 6 H, C(CH_3)$_2$], 1.94 [s, 2 H, CCH_2C], 2.30 [d, 3 H, =CCH_3], 7.02 [q, 1 H, Ar-*H*], 7.12 [d, 1 H, Ar-*H*], 7.29 [d, 1 H, Ar-*H*], 9.31 [d, 1 H, *H*C=O]; ^{13}C NMR ($DCCl_3$) ppm, 17.98 [CH(CH_3)$_2$], 31.58 [CH_2C(CH_3)$_2$], 32.53 [SC(CH_3)$_2$], 35.49 [CH_2*C*(CH_3)$_2$], 42.31 [S*C*(CH_3)$_2$], 53.95 [*C*H_2C(CH_3)$_2$], 126.16 [CH_3*C*=CF], 126.16-142.86 [Ar-*C*], 155.70[CH_3C=*C*F]; 182.69 [*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -131.32 [m, 1 F, =C*F*].

(2*E*)-2-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-enal (**97b**)

Alcohol **96b** (112 mg, 0.35 mmol) dissolved in 3 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask, and MnO_2 (0.5 g, 6.75 mmol, activated grade, size:

<5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue via flash chromatography (hexane:diethyl ether 1:1, drop rate = 1 drop/s) afforded aldehyde **97b** (67 mg, 60%) as a yellow oil. IR (neat) 2814 [O=C-H], 1687 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.11 [d, 3 H, $CH(CH_3)_2$], 1.38 [s, 6 H, $C(CH_3)_2$], 1.42 [s, 6 H, $C(CH_3)_2$], 1.96 [s, 2 H, CCH_2C], 3.21 [m, 1 H, $CH(CH_3)_2$], 6.88 [q, 1 H, J = 8.5 Hz, J = 2.3 Hz, Ar-*H*], 7.05 [d, 1 H, J = 8.5 Hz, Ar-*H*] 7.45 [d, 1 H, J = 2.3 Hz, Ar-*H*], 9.78 [d, 1 H, O=C*H*]; ^{13}C NMR ($DCCl_3$) ppm, 20.78 [2 C, $CH(CH_3)_2$], 31.65 [2 C, $CH_2C(CH_3)_2$], 32.16 [2 C, $SC(CH_3)_2$], 32.56 [C, $CH_2C(CH_3)_2$], 35.45 [$SC(CH_3)_2$], 54.23 [C, $CH_2C(CH_3)_2$], 110.34 [C, CH_3C=CF], 111.45 [C, CH_3C=*CF*], 125.70-143.16 [6 C, Ar-*C*], 184.23 [*C*=O]; ^{19}F NMR ($DCCl_3$) (ref $C_6H_5CF_3$ in C_6D_6) ppm -128.3 [t, 1 F, =C*F*].

<u>(2*E*)-2-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-enal (**97c**)</u>

Alcohol **96c** (120 mg, 0.35 mmol) dissolved in 3 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask, and MnO_2 (0.55 g, 6.95 mmol, activated grade, size: <5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue via flash chromatography (hexane:diethyl ether 2:1, drop rate = 1 drop/s) afforded aldehyde **97c** (60 mg, 51%) as a light yellow oil. IR (neat) 2869 [O=C-H], 1687 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.90 [d, 3 H, $CH(CH_3)_2$], 1.34 [s, 6 H, $C(CH_3)_2$], 1.40 [s, 6 H, $C(CH_3)_2$], 1.72 [m, 1 H, $CH(CH_3)_2$], 1.96 [s, 2 H, CCH_2C], 2.59 [m, 2 H, $CHCH_2$], 6.88 [q, 1 H, J = 8.7 Hz, J = 2.1 Hz, Ar-*H*], 7.15 [d, 1 H, J = 8.5 Hz, Ar-*H*], 7.25 [d, 1 H, J = 2.3 Hz, Ar-*H*], 9.25 [d, 1 H, O=C*H*]; ^{13}C NMR ($DCCl_3$)

ppm, 22.38 [CH(CH_3)$_2$], 26. 98 [CCH_2C], 31.58 [2 C, CH_2C(CH_3)$_2$], 32.61 [SC(CH_3)$_2$], 32.56 [CH_2C(CH_3)$_2$], 35.45 [S*C*(CH_3)$_2$], 35.42 [CH_2H*C*(CH_3)$_2$], 53.93 [C, *C*H_2C(CH_3)$_2$], 125.70-142.16 [Ar-*C*], 183.23 [*C*=O]; ^{19}F NMR ($DCCl_3$) (ref $C_6H_5CF_3$ in C_6D_6) ppm -132.08 [m, 1 F, =C*F*].

(2*Z*)-2-Fluoro-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-enal (**99a**)

Alcohol **98a** (121 mg, 0.43 mmol) dissolved in 3 mL of acetone was placed in a 25-mL one-necked, round-bottomed flask, and MnO_2 (0.8 g, 9.8 mmol, activated grade, size<5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue (after solvent evaporation) via flash chromatography (hexane:diethyl ether:ethyl acetate, 1:1:0.1, drop rate = 1 drop/s) afforded aldehyde **99a** (74 mg, 59%) as a light yellow oil. IR (neat) 2874 [O=C-H], 1667 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.42 [s, 6 H, C(CH_3)$_2$], 1.44 [s, 6 H, C(CH_3)$_2$], 1.96 [s, 2 H, CCH_2C], 2.30 [d, 3 H, =CCH_3], 7.12-7.60 [m, 3 H, Ar-*H*], 9.98 [d, 1 H, *H*C=O]; ^{13}C NMR ($DCCl_3$) ppm, 17.98 [CH(CH_3)$_2$], 31.58 [CH_2C(CH_3)$_2$], 32.53 [SC(CH_3)$_2$], 35.49 [CH_2*C*(CH_3)$_2$], 42.31 [S*C*(CH_3)$_2$], 53.95 [CH_2C(CH_3)$_2$], 126.16 [CH_3*C*=CF], 126.16-142.86 [Ar-*C*], 155.70[CH_3C=*C*F]; 181.69 [*C*=O]; ^{19}F NMR ($DCCl_3$) ppm -131.86 [m, 1 F, =C*F*].

(2*Z*)-2-Fluoro-4-methyl-3-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))pent-2-enal (**99b**)

Alcohol **98b** (190 mg, 0.59 mmol) dissolved in 3 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask, and MnO_2 (1.00 g, 11.5 mmol, activated grade, size<5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and

then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue via flash chromatography (hexane:diethyl ether, 1:1, drop rate = 1 drop/s) afforded aldehyde **99b** (90 mg, 48%) as a light yellow oil. IR (neat) 2832[O=C-H] 1686 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.10 [d, 3 H, $CH(CH_3)_2$], 1.48 [s, 6 H, $C(CH_3)_2$], 1.52 [s, 6 H, $C(CH_3)_2$], 2.11 [s, 2 H, CCH_2C], 3.01 [m, 1 H, $CH(CH_3)_2$], 6.98 [q, 1 H, J = 8.4 Hz, J = 2.0 Hz, Ar-*H*], 7.25 [d, 1 H, J = 8.4 Hz, Ar-*H*] 7.68 [d, 1 H, J = 2.0 Hz, Ar-*H*], 9.94 [d, 1 H, O=C*H*]; ^{13}C NMR ($DCCl_3$) ppm, 21.78 [$CH(CH_3)_2$], 33.65 [$CH_2C(CH_3)_2$], 34.16 [$SC(CH_3)_2$], 34.56 [$CH_2C(CH_3)_2$], 35.45 [$SC(CH_3)_2$], 54.23 [$CH_2C(CH_3)_2$], 112.34 [CH_3C=CF], 113.42 [CH_3C=CF], 126.70-144.89 [Ar-*C*], 188.92 [*C*=O]; ^{19}F NMR ($DCCl_3$) (ref $C_6H_5CF_3$ in C_6D_6) ppm -129.53 [m, 1 F, =C*F*].

<u>2-Methyl-1-(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian6-yl))ethan-1-ol (**100a**)</u>

Ketone **94a** (300 mg, 1.20 mmol) dissolved in 5 mL of dry THF was placed in a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet and an addition funnel and then cooled to -40 °C. A solution of DIBAL-H in toluene (2.42 mL, 3.63 mmol 1.5 *M*) was then added by syringe. The reaction mixture was then stirred for 2 h, and it was monitored by TLC (hexane:ethyl acetate, 1:4). After the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 4 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was then extracted with ethyl acetate (3 x 30 mL), followed by washing the extracts with H_2O (1 x 30 mL) and brine (1 x 30 mL) then drying ($MgSO_4$, 12 h). After evaporation (rotovap) and separation of the major component of the solvent by flash chromatography (hexane:diethyl ether, 1:2, drop rate = 1 drop/s), alcohol **100a** (269 mg, 89%) was obtained

as a clear oil. IR (neat) 3352 [O-H], cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, $C(CH_3)_2$], 1.41 [s, 6 H, $C(CH_3)_2$], 1.46 [d, 3 H, $HOCH_2CH_3$], 1.82 [bs, 1 H, O-*H*], 1.95 [s, 2 H, CCH_2C], 1.98 [m, 1 H, $CH(CH_3)_2$], 4.84 [dd, 2 H, $HOCH_2CH_3$], 7.07 [q, 1 H, J = 7.8 Hz, J = 2.1 Hz, Ar-*H*], 7.09 [d, 1 H, J = 7.8 Hz, Ar-*H*] 7.38 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 24.98 [$HOCH_2CH_3$], 31.61 [$CH_2C(CH_3)_2$], 32.53 [$SC(CH_3)_2$], 35.60 [$CH_2C(CH_3)_2$], 41.99 [$SC(CH_3)_2$], 54.42 [$CH(CH_3)_2$], 70.38 [$HO\ CH_2C(CH_3)_2$], 123.27-142.19 [Ar-*C*].

<u>2-Methyl-1-[(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))]propan-1-ol (**100b**)</u>

Ketone **94b** (500 mg, 1.81 mmol) dissolved in 6 mL of dry THF was placed in a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet and an addition funnel and then cooled to -40 °C. A solution of DIBAL-H in toluene (3.63 mL, 5.43 mmol, 1.5 *M*) was then added by syringe. The reaction mixture was then stirred for 2 h, and it was monitored by TLC (hexane:ethyl acetate, 1:3). After the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 5 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was then extracted with ethyl acetate (3 x 35 mL), followed by washing the extracts with H_2O (1 x 30 mL) and brine (1 x 25 mL) then drying ($MgSO_4$, 12 h). After evaporation (rotovap) and separation of the major component of the solvent by flash chromatography (hexane:diethyl ether, 1:4, drop rate = 1 drop/s), alcohol **100b** (462 mg, 92%) was obtained as a clear oil. IR (neat) 3425 [O-H], cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.78 [d, 3 H, $CH(CH_3)_2$], 1.01 [d, 3 H, $CH(CH_3)_2$] 1.26 [s, 6 H, $C(CH_3)_2$], 1.32 [s, 6 H, $C(CH_3)_2$], 1.85 [bs, 1 H, O-*H*], 1.96 [s, 2 H, CCH_2C], 1.98 [m, 1 H, $CH(CH_3)_2$], 4.27 [d, 1 H, HOCHCH], 6.98 [q, 1 H, J = 7.8 Hz, J = 2.1 Hz, Ar-*H*], 7.09 [d, 1 H, J = 7.8 Hz, Ar-*H*] 7.32 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR

($DCCl_3$) ppm, 18.36 [$CH(CH_3)_2$], 18.92 [$CH(CH_3)_2$] 31.51 [$CH_2C(CH_3)_2$], 32.70 [$SC(CH_3)_2$], 35.19 [$CH_2C(CH_3)_2$], 35.36 [$SC(CH_3)_2$], 41.95 [$CH(CH_3)_2$], 54.46 [$CH_2C(CH_3)_2$], 80.35 [$HOCH_2$], 124.27-140.19 [Ar-*C*].

3-Methyl-1-[(2,2,4,4-tetramethyl(3*H*-benzo[3,4-*e*]thian-6-yl))]butan-1-ol (**100c**)

Ketone **94c** (500 mg, 1.72 mmol) dissolved in 6 mL of dry THF was placed in a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet and an addition funnel and then cooled to -40 °C. A solution of DIBAL-H in toluene (3.44 mL, 5.15 mmol, 1.5 *M*) was then added by syringe. The reaction mixture was then stirred for 2 h, and it was monitored by TLC (hexane:ethyl acetate, 1:2). After the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 5 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was then extracted with ethyl acetate (3 x 35 mL), followed by washing the extracts with H_2O (1 x 30 mL) and brine (1 x 35 mL) then drying ($MgSO_4$, 12 h). After evaporation (rotovap) and separation of the components in the residue, of solvent, by flash chromatography (EtOAc, 1:4, drop rate = 1 drop/s), alcohol **100c** (412 mg, 82%) was obtained as a clear oil. IR (neat) 3385 [O-H] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.95 [d, 6 H, $CH(CH_3)_2$], 1.39 [s, 6 H, $C(CH_3)_2$], 1.41 [s, 6 H, $C(CH_3)_2$], 1.47 [m, 1 H, $CH(CH_3)_2$], 1.65 [bs, 1 H, O-*H*], 1.78 [m, 2 H, CH_2CH], 1.96 [s, 2 H, CCH_2C], 4.87 [m, 1 H, $HOCHCH_2$], 7.12 [q, 1 H, J = 7.8 Hz, J = 2.1 Hz, Ar-*H*], 7.19 [d, 1 H, J = 7.8 Hz, Ar-*H*] 7.40 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 22.21 [$CH(CH_3)_2$], 123.16 [$CH(CH_3)_2$] 24.82 [CH_2CH], 31.59 [$CH_2C(CH_3)_2$], 32.60 [$SC(CH_3)_2$], 35.59 [$CH_2C(CH_3)_2$], 42.00 [$SC(CH_3)_2$], 48.95 [$CH(CH_3)_2$], 54.45 [$CH_2C(CH_3)_2$], 72.35 [$HOCH_2$], 123.27-142.19 [Ar-*C*].

6-(1-Chloro-2-isobutyl)-2,2,4,4-tetramethyl-3*H*-benzo[*e*]thione (**101b**)

Into a 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet, and an addition funnel NaH (17.00 mg, 0.72 mmol) was added to 5 mL of dry THF at 0 °C. The reaction mixture was stirred for 2 h, and then ethyl 4-(chlorocarbonyl)benzoate [(**101b**), 153 mg, 0.72 mmol] dissolved in 4 mL of dry THF was added dropwise. A cloudy precipitate formed during the addition, and the reaction mixture was then stirred for 4 hours after which time 2 drops of de-ionized water were added at RT. The cloudy reaction mixture cleared and was diluted with diethyl ether (20 mL). The organic mixture was then washed with $NaHCO_3$ (3 x 10 mL), H_2O (1 x 10 mL), and brine (1 x 10 mL) and the dried ($MgSO_4$, 12 h). Evaporation of solvent (rotovap) and and flash chromatography (hexane:EtOAc, 1:1, drop rate = 1 drop/s) afforded **101b** (163 mg, 76%) as a clear oil. IR (neat) 1474 [C-Cl], cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.82 [d, 3 H, $CH(CH_3)_2$], 1.05 [d, 3 H, $CH(CH_3)_2$] 1.40 [s, 6 H, $C(CH_3)_2$], 1.42 [s, 6 H, $C(CH_3)_2$], 1.96 [s, 2 H, CCH_2C], 2.20 [m, 1 H, $CH(CH_3)_2$], 4.60 [d, 2 H, $ClCH_2CH$], 7.05 [q, 1 H, J = 8.1 Hz, J = 2.1 Hz, Ar-*H*], 7.07 [d, 1 H, J = 8.1 Hz, Ar-*H*] 7.32 [d, 1 H, J = 2.1 Hz, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm, 19.61 [$CH(CH_3)_2$], 20.07 [$CH(CH_3)_2$] 31.56 [$CH_2C(CH_3)_2$], 32.62 [$SC(CH_3)_2$], 35.46 [$CH_2C(CH_3)_2$], 36.63 [$CH(CH_3)_2$], 42.34 [$SC(CH_3)_2$], 54.28 [$CH_2C(CH_3)_2$], 71.04 [$ClCH_2$], 124.97-142.30 [Ar-*C*].

1-(2,2,4,4,7-Pentamethyl-3*H*benzo[*e*]thiane)ethan-1-one (**103**)

Into a 50-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet, and an addition funnel was added $AlCl_3$ (2.53 g, 19.33 mmol) and dissolved in 25 mL of freshly distilled CH_3NO_2. A solution of the 2,2,4,4,7-pentamethyl-3*H*-benzo[*e*]thiane [(**102**), 2.00 g, 9.08 mmol] and acetyl chloride (850 mg, 10.56 mmol) dissolved in 20 mL

of freshly distilled CH_3NO_2 was then added dropwise (1 h) at RT. The reaction mixture was stirred for 48 h and then poured into a 100-mL beaker containing ~30 g of crushed ice. The layers were separated, and the aqueous layer was then extracted with diethyl ether (3 x 50 mL). Combined organic layers were washed with water (2 x 25 mL) and brine (1 x 30 mL) and then dried (Na_2SO_4, 12 h). Evaporation (rotovap) of solvent and distillation (bp 163-64 °C/ 0.75 mm Hg) of the residual oil afforded ketone **103** (mp 78-9 °C, 1.47 g, 68%) as a light yellow solid. IR (neat) 1600 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.42 [s, 6 H, $C(CH_3)_2$], 1.43 [s, 6 H, $C(CH_3)_2$], 1.98 [s, 2 H, CCH_2C], 2.45 [s, 3 H, $C(O)CH_3$], 2.57 [s, 3 H, Ar-CH_3], 6.97 [s, 1 H, Ar-*H*], 7.75 [s, 1 H, Ar-*H*], ^{13}C NMR ($DCCl_3$) ppm 21.22 [$C(O)CH_3$], 29.12 [$CH_2C(CH_3)_2$] 31.54 [$CH_2C(CH_3)_2$)], 32.70 [$SC(CH_3)_2$], 35.42 [$CH_2C(CH_3)_2$], 42.31 [$SC(CH_3)_2$], 53.87 [$CH_2C(CH_3)_2$], 128.70-139.40 [Ar-*C*], 200.59 [*C*=O].

<u>Ethyl (2*E*)-2-Fluoro-3-(2,2,4,4,7-pentamethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-enoate (**104**)</u>

Into a 25-mL, three-necked, round-bottomed equipped with a condenser, a N_2 inlet and an addition funnel flask was added ethyl 2-fluorophosphono-acetate (505 mg, 2.10 mmol) and DMPU (267 mg, 2.10 mmol) dissolved in 3 mL of dry THF. The reaction mixture was cooled to 0 °C, and *n*-BuLi (1.31 mL, 2.10 mmol, 1.6 *M*) was added dropwise by syringe. After stirring the reaction mixture for 1 h, 1-(2,2,4,4,7-pentamethyl-3H-benzo[3,4-*e*]thian-1-one (500 mg, 1.90 mmol) dissolved in 4 mL of dry THF was added dropwise (1 h). The reaction mixture was stirred for 6 days at RT and was then quenched with a saturated, aqueous solution of ammonium chloride (3 mL). Extraction with ethyl acetate (3 x 25 mL) was followed by washing the combined organic layers with H_2O (1 x 20 mL) and brine (1 x 25 mL) and then drying ($MgSO_4$, 5 h). After solvent evaporation

(rotovap), followed by flash chromatography (hexane:diethyl ether, 1:1, drop rate = 1 drop/s) of the residue and after solvent evaporation, **104** (266 mg, 40%) was recovered as a clear oil. IR (neat) 1712 [C=O] cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.85 [t, 3 H, OCH_2CH_3], 1.42 [s, 6 H, $C(CH_3)_2$], 1.43 [s, 6 H, $C(CH_3)_2$], 1.98 [s, 2 H, CCH_2C], 2.45 [s, 3 H, CCH_3], 2.57 [s, 3 H, Ar-CH_3], 3.97 [q, 2 H, OCH_2CH_3], 6.97 [s, 1 H, Ar-*H*], 7.75 [s, 1 H, Ar-*H*], ^{13}C NMR ($DCCl_3$) ppm 13.61 [OCH_2CH_3], 21.22 [$C(O)CH_3$], 29.12 [$CH_2C(CH_3)_2$] 31.54 [$CH_2C(CH_3)_2$)], 32.70 [$SC(CH_3)_2$], 36.45 [$CH_2C(CH_3)_2$], 43.31 [$SC(CH_3)_2$], 52.87 [$CH_2C(CH_3)_2$], 60.88 [OCH_2CH_3], 128.70-139.40 [Ar-*C*], 145.88 [F*C*=CH], 160.98 [*C*=O]. ^{19}F NMR ($DCCl_3$) ppm -124.77 [d, 1 F, *F*C=CCH_3].

<u>(2*E*)-2-Fluoro-3-(2,2,4,4,7-pentamethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-en-1-ol (**105**)</u>

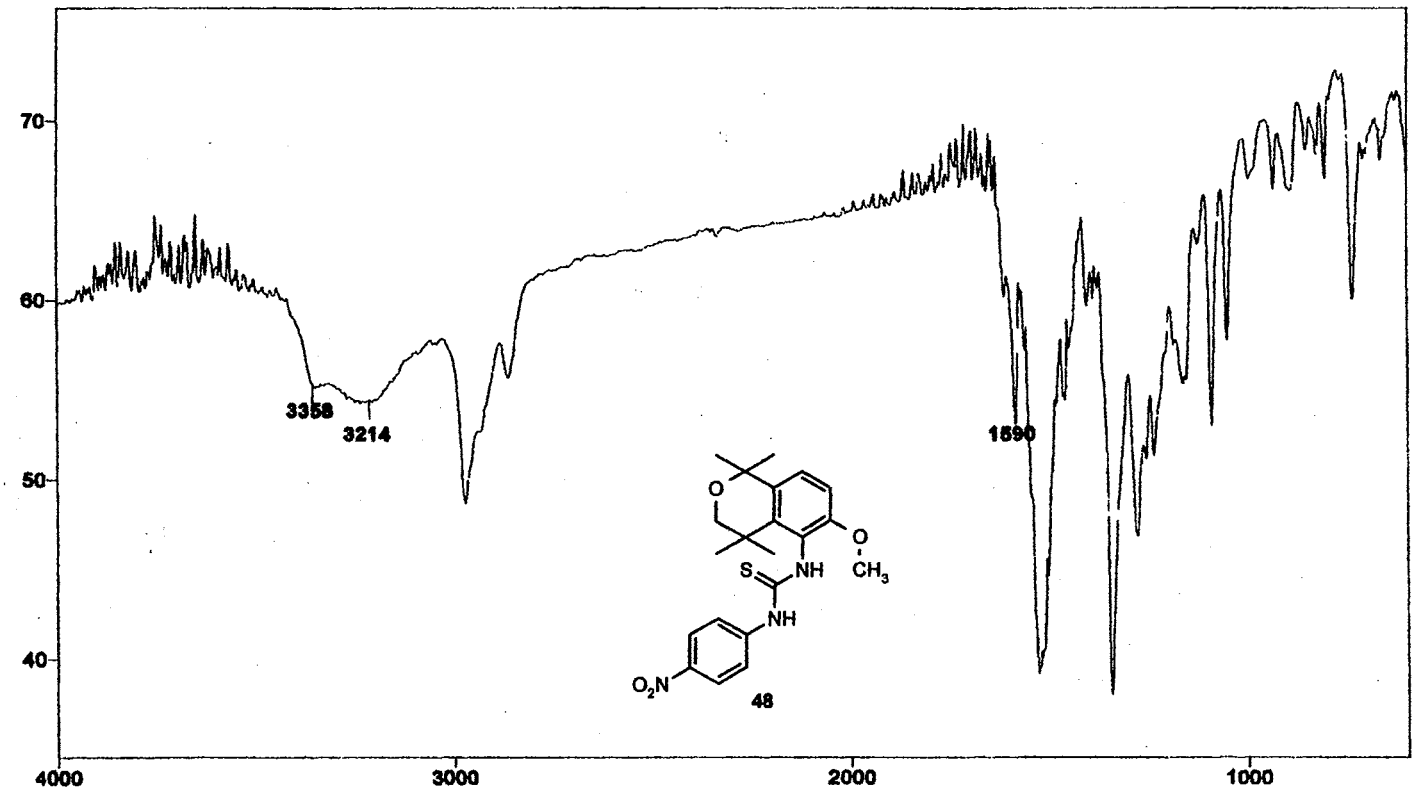
Ester **104** (266 mg, 0.76 mmol) dissolved in 5 mL of dry THF was placed in 25-mL, three-necked, round-bottomed flask equipped with a condenser, a N_2 inlet and an addition funnel and then cooled to -40 °C. A solution of DIBAL-H in toluene (1.27 mL, 1.90 mmol, 1.5 *M*) was then added by syringe. The reaction mixture was stirred for 2 h, and it was monitored by TLC (hexane:ethyl acetate, 1:2). After all of the starting material appeared to have reacted (TLC), the reaction mixture was quenched with 2 mL of a saturated, aqueous solution of Rochelle salt (sodium-potassium tartrate, 1:1). The bi-phasic mixture was extracted with ethyl acetate (3 x 25 mL), followed by washing the organic extracts with H_2O (1 x 15 mL) and brine (1 x 20 mL) and then drying ($MgSO_4$, 12 h). Separation of the major component in the residue, after solvent evaporation, by flash chromatography (hexane:diethyl ether, 1:1, drop rate = 1 drop/s) afforded alcohol **105** (216 mg, 92%) as a colorless oil. IR (neat) 3353 [O-H], 1659 [C=C-F] cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.35 [s, 6 H,

C(CH_3)$_2$], 1.42 [s, 6 H, C(CH_3)$_2$], 1.87 [bs, 1 H, O-*H*], 1.97 [d, 3 H, CCH_3], 1.98 [s, 2 H, CCH_2C], 2.14 [s, 3 H, Ar-CH_3], 3.97 [d, 2 H, HOCH_2], 6.94 [s, 1 H, Ar-*H*], 7.07 [s, 1 H, Ar-*H*], ^{13}C NMR ($DCCl_3$) ppm 16.61 [=CCH_3], 18.68 [CCH_3], 31.54 [$CH_2C(CH_3)_2$)], 32.61 [S$C(CH_3)_2$], 35.04 [$CH_2C(CH_3)_2$] 42.05 [$CH_2C(CH_3)_2$], 54.27 [S$C(CH_3)_2$], 58.88 [HOCH_2], 117.66 [FC=*C*H], 127.70-140.05 [Ar-*C*], 156.28 [F*C*=CH]. ^{19}F NMR ($DCCl_3$) ppm -120.93 [td, 1 F, *F*C=CCH_3].

<u>(2*E*)-2-Fluoro-3-(2,2,4,4,7-pentamethyl(3*H*-benzo[3,4-*e*]thian-6-yl))but-2-enal (**106**)</u>

Alcohol **105** (200 mg, 0.65 mmol) dissolved in 3 mL of acetone was placed in a 25-mL, one-necked, round-bottomed flask, and MnO_2 (1.0 g, 11.52 mmol, activated grade, size <5 μm) was then added to the solution at RT. The suspension was stirred for 24 h and then filtered through a 1-inch thick celite pad. Evaporation (rotovap) of the solvent and purification of the major component in the residue, after solvent evaporation, via flash chromatography (hexane:diethyl ether:ethyl acetate, 1:1:1, drop rate = 1 drop/s), afforded aldehyde **106** (113 mg, 57%) as a light yellow oil. IR (neat) 2834 [O=C-H], 1692 [C=O] cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.35 [d, 6 H, C(CH_3)$_2$], 1.43 [d, 6 H, C(CH_3)$_2$], 1.96 [s, 2 H, CCH_2C], 2.19 [d, 3 H, CCH_3], 2.21 [s, 3 H, Ar-CH_3], 7.00 [s, 1 H, Ar-*H*], 7.17 [s, 1 H, Ar-*H*], 9.15 [d, 1 H, *H*C(O)], ^{13}C NMR ($DCCl_3$) ppm 18.22 [=CCH_3], 18.82 [CCH_3], 31.52 [$CH_2C(CH_3)_2$)], 32.47 [S$C(CH_3)_2$], 35.03 [$CH_2C(CH_3)_2$] 42.15 [$CH_2C(CH_3)_2$], 54.01 [S$C(CH_3)_2$], 127.66-140.05 [FC=*C*H, Ar-*C*], 154.73 [F*C*=CH]. 182.44 [H*C*(O)]; ^{19}F NMR ($DCCl_3$) ppm -132.98 [m, 1 F, *F*C=CCH_3].

Plate I



IR Spectrum of **48**

Plate II

```
STANDARD 1H OBSERVE

expl  stdih

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file           exp   dpwr            38
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tn              H1   dmm              c
at            9.747  dmf            200
np            33728      PROCESSING
sw          4500.5   wtfile
fb            2600   proc            ft
bs              16   fn        not used
tpwr            48
pw             6.9   werr
d1               0   wexp
tof              0   wbs
nt              16   wnt
ct              16
alock            n
gain       not used
      FLAGS
il               n
in               y
dp               y
     DISPLAY
sp           -13.8
wp          3831.8
vs              78
sc               0
wc             250
hzmm         14.52
is          500.00
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rfp          612.2
th              20
ins         180.000
nm  cdc  ph
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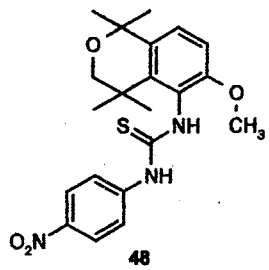
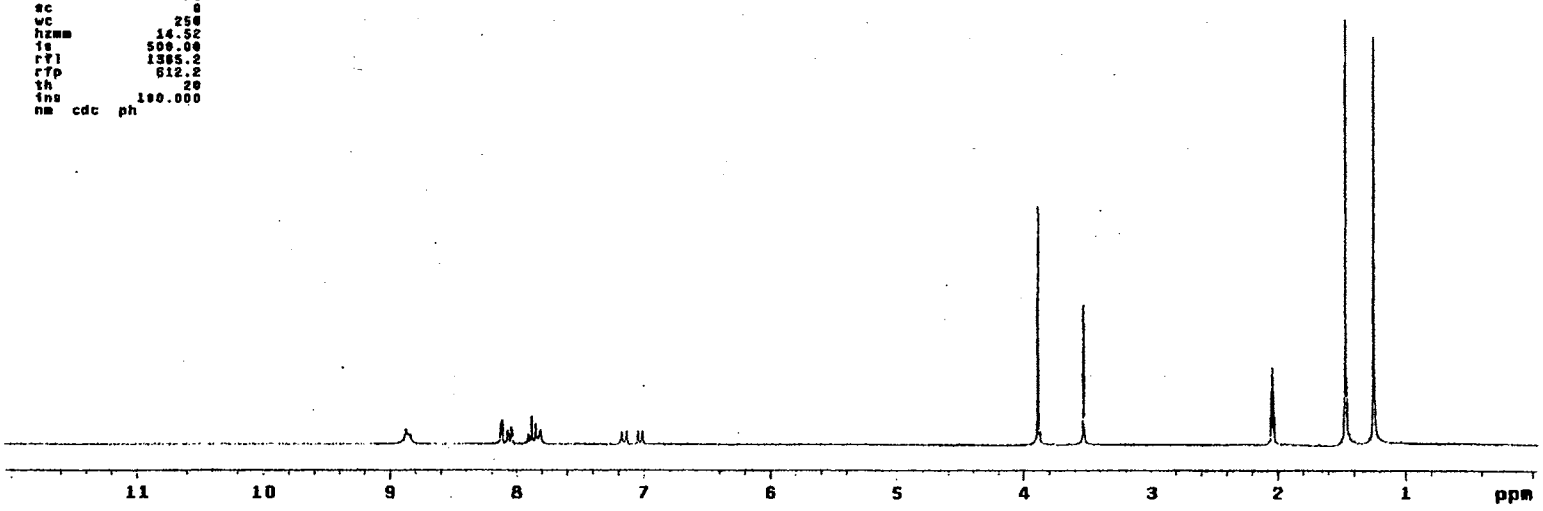
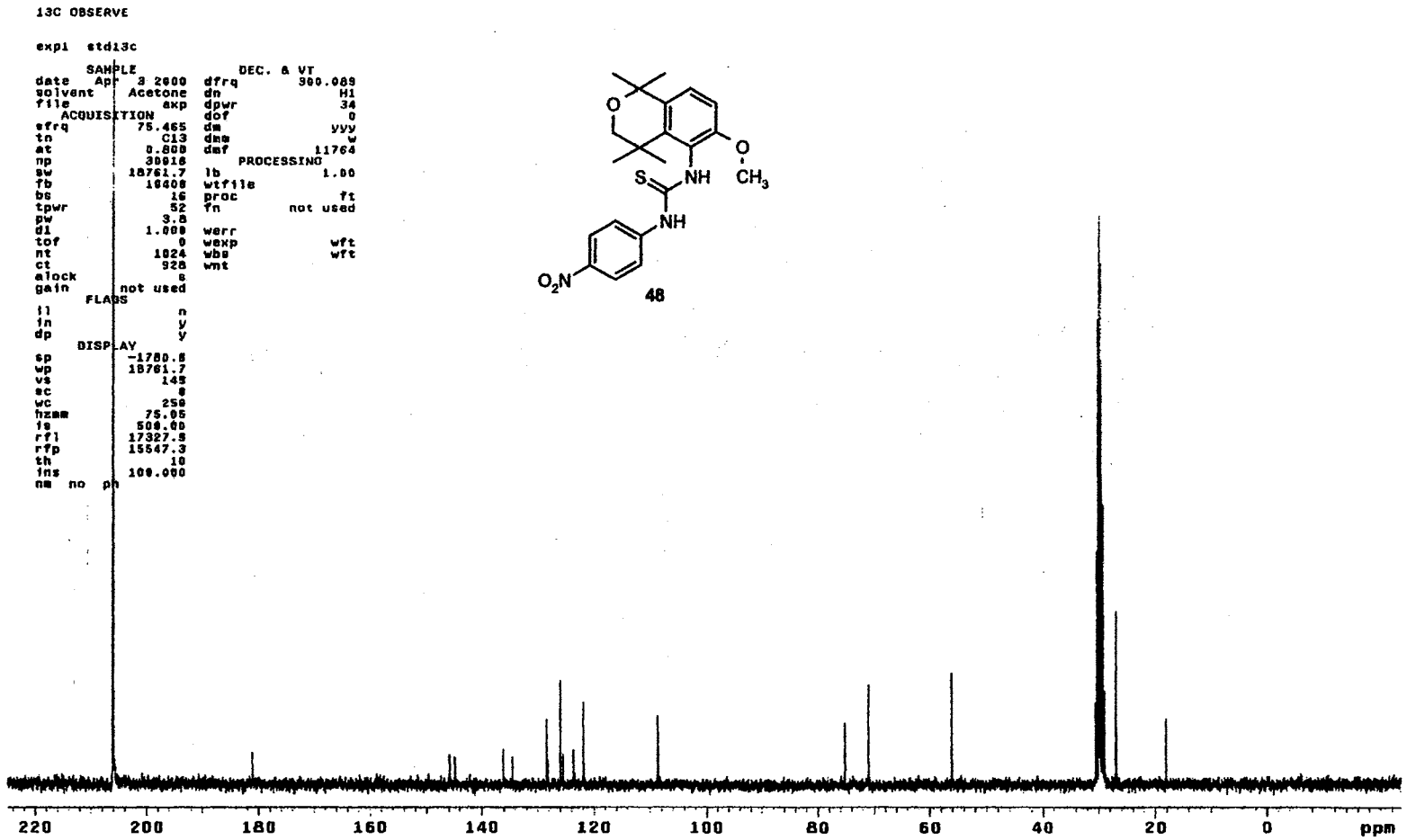




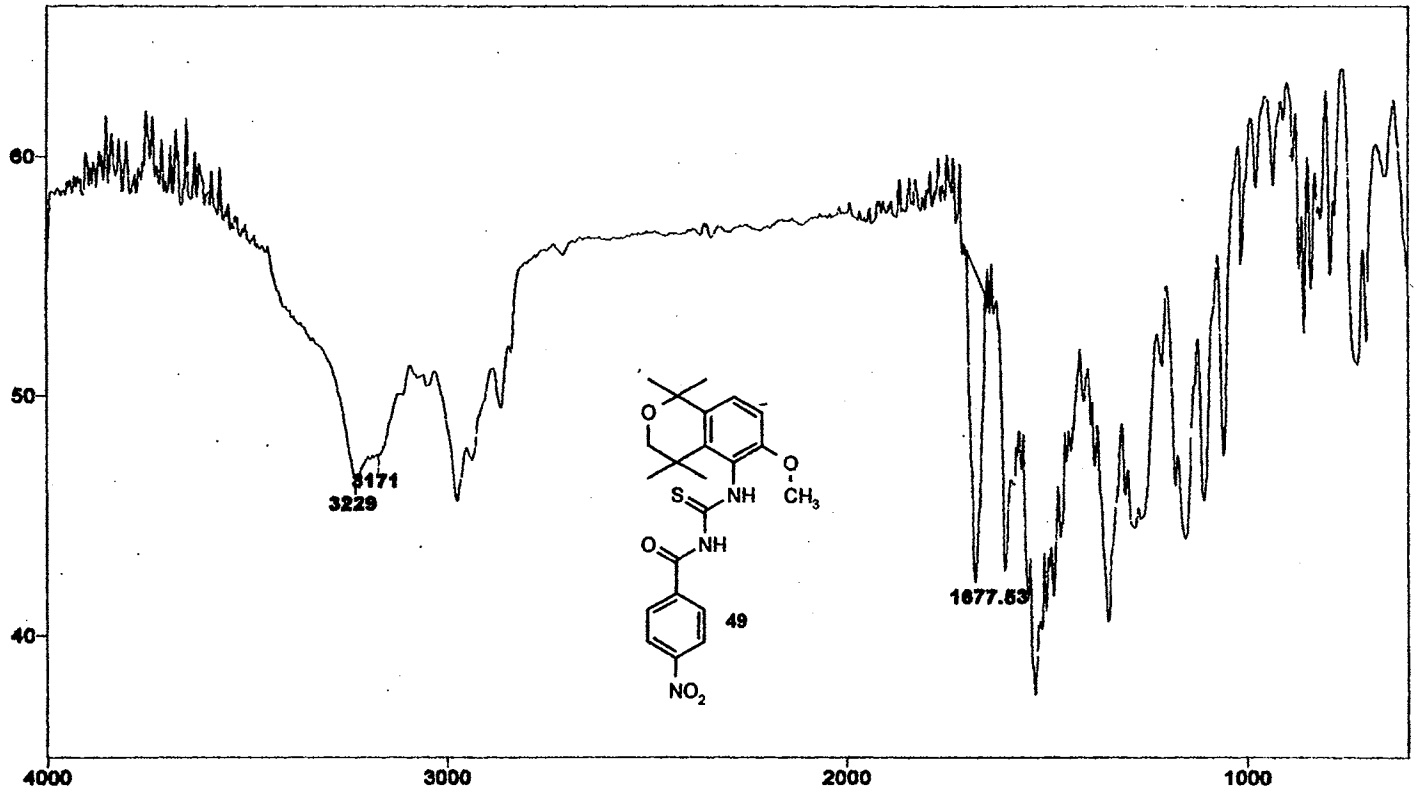
^{1}H NMR Spectrum of **48**

Plate III



^{13}C NMR Spectrum of **48**

Plate IV



IR Spectrum of **49**

Plate V

STANDARD 1H OBSERVE

exp1 std1h

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solvent	Acetone	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.089	dm	nnn
tn	H1	dmm	c
at	3.747	dmf	200
np	33728	PROCESSING	
sw	4500.5	wtfile	
fb	2600	proc	ft
bs	16	fn	not used
tpwr	48		
pw	6.9	werr	
d1	0	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	y		
dp	y		
DISPLAY			
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wp	3702.1		
vs	89		
sc	0		
wc	250		
hzcm	14.81		
is	322.13		
rf1	1365.2		
rfp	612.2		
th	26		
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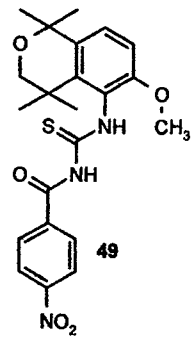
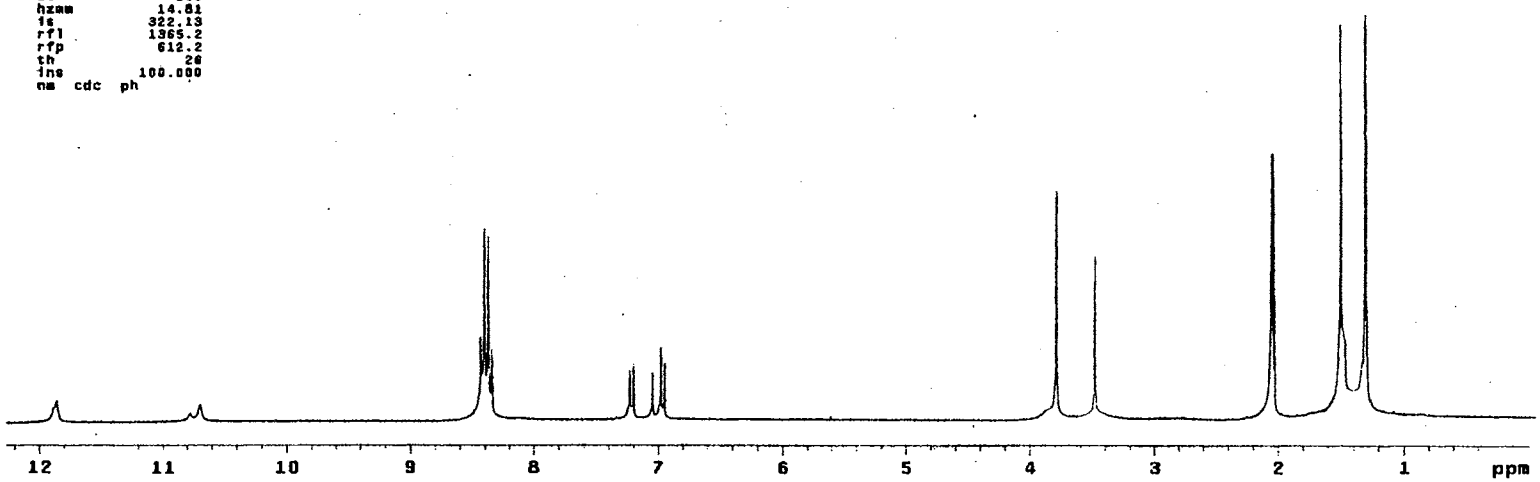
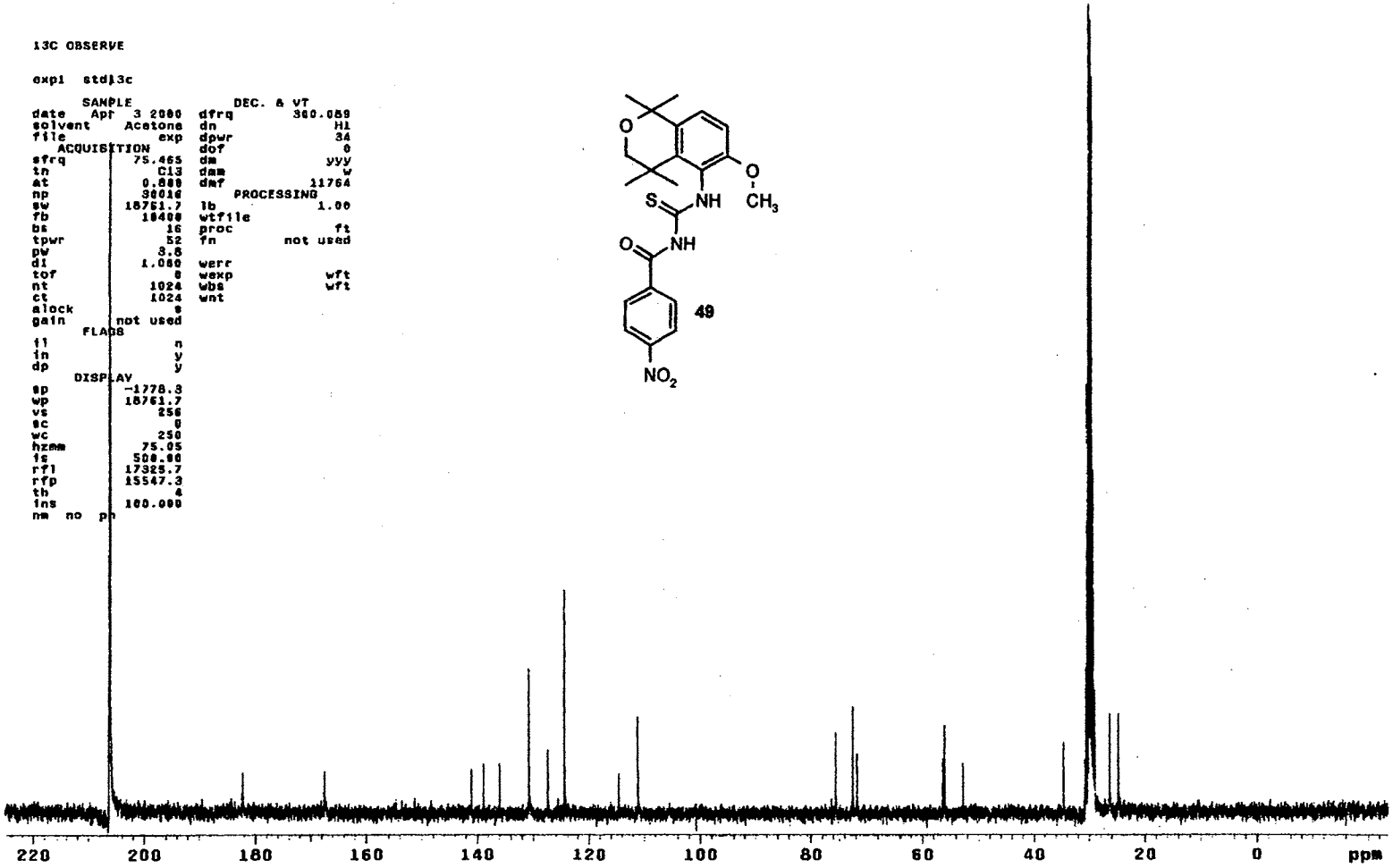
nm cdc ph			





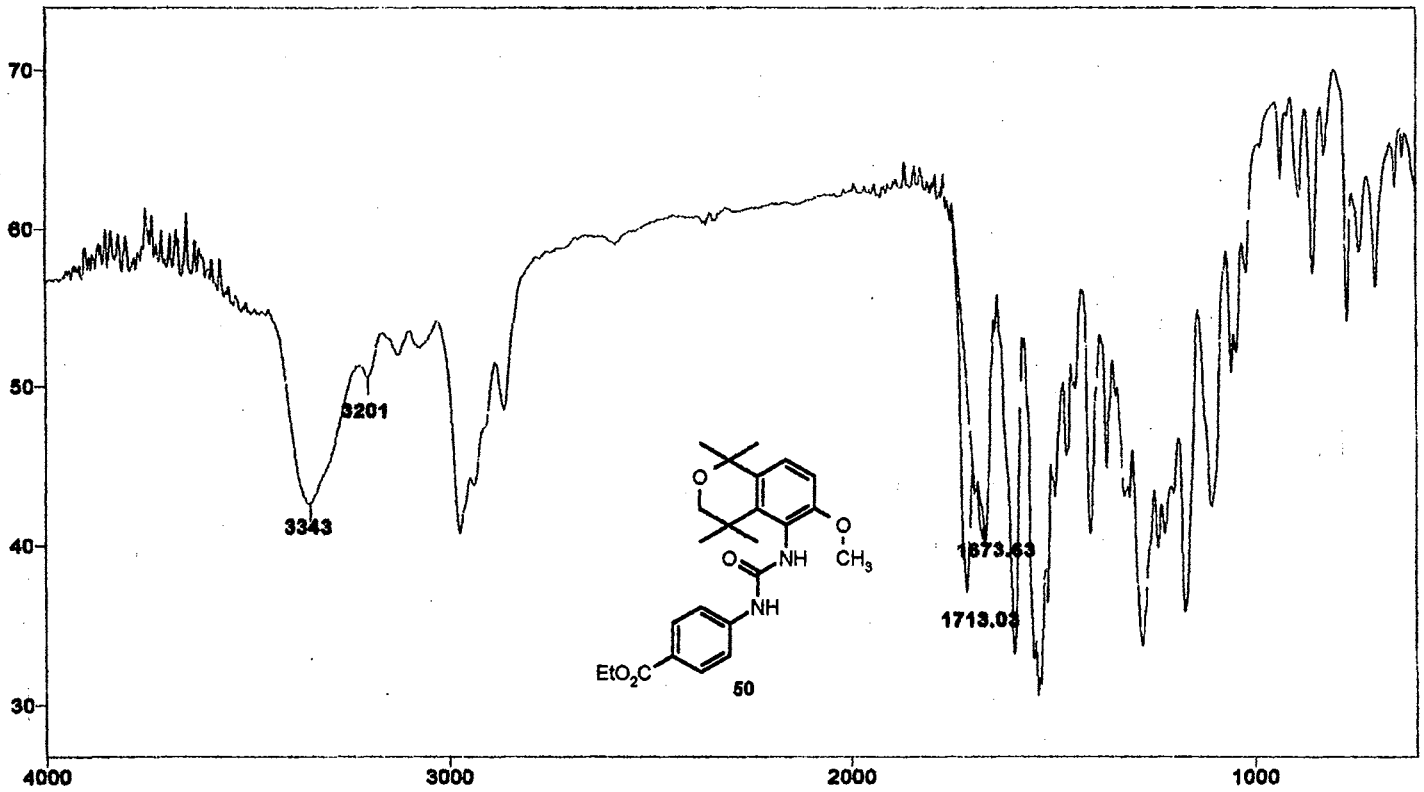
^{1}H NMR Spectrum of **49**

Plate VI



^{13}C NMR Spectrum of **49**

Plate VII



IR Spectrum of **50**

Plate VIII

STANDARD 1H OBSERVE

expl stdih

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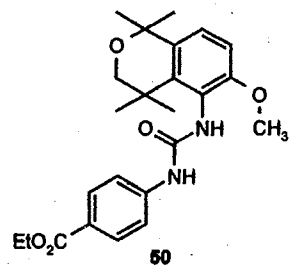
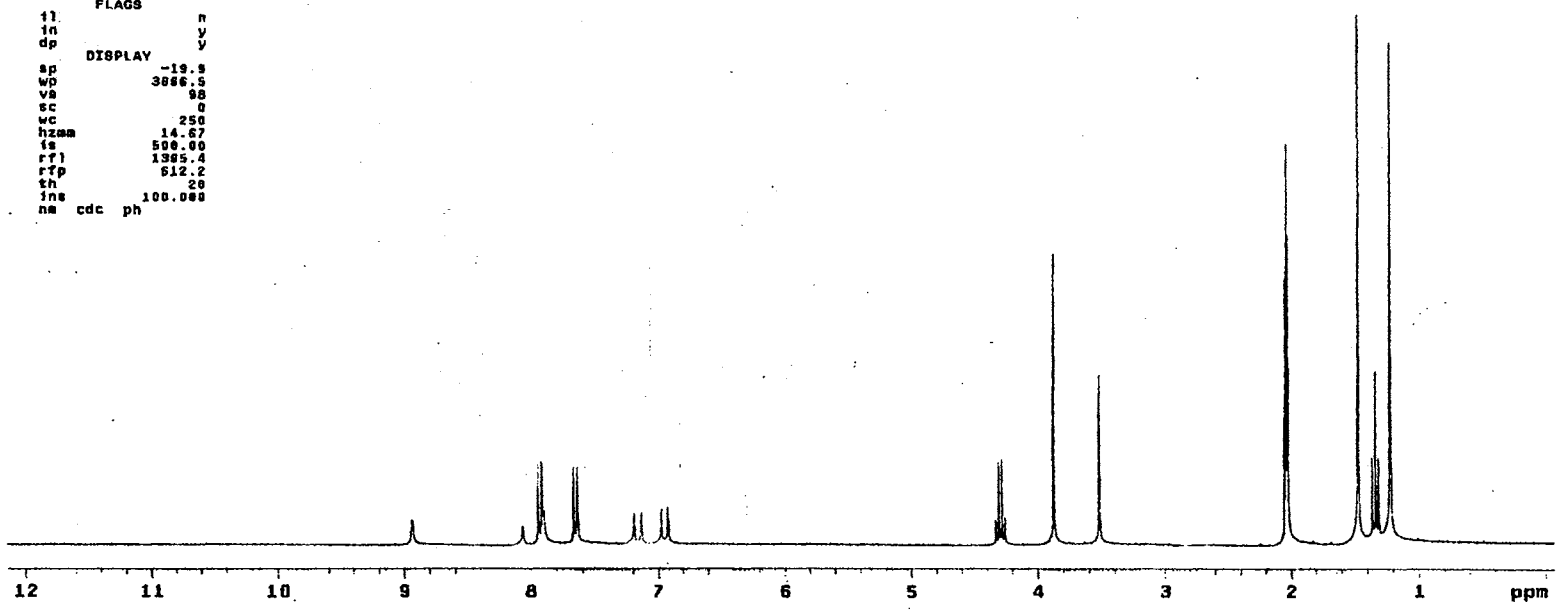
tn	H1	dmm	c
at	3.747	dmf	200
np	33728	PROCESSING	
sw	4500.5	wtfile	
fb	2600	proc	ft
bs	16	fn	not used
tpwr	48		
pw	6.9	werr	
dl	0	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	y		
dp	y		
DISPLAY			
sp	-19.9		
wp	3886.5		
vs	98		
sc	0		
wc	250		
hzcm	14.67		
is	500.00		
rfl	1385.4		
rfp	612.2		
th	20		
ins	100.000		
nm cdc ph			

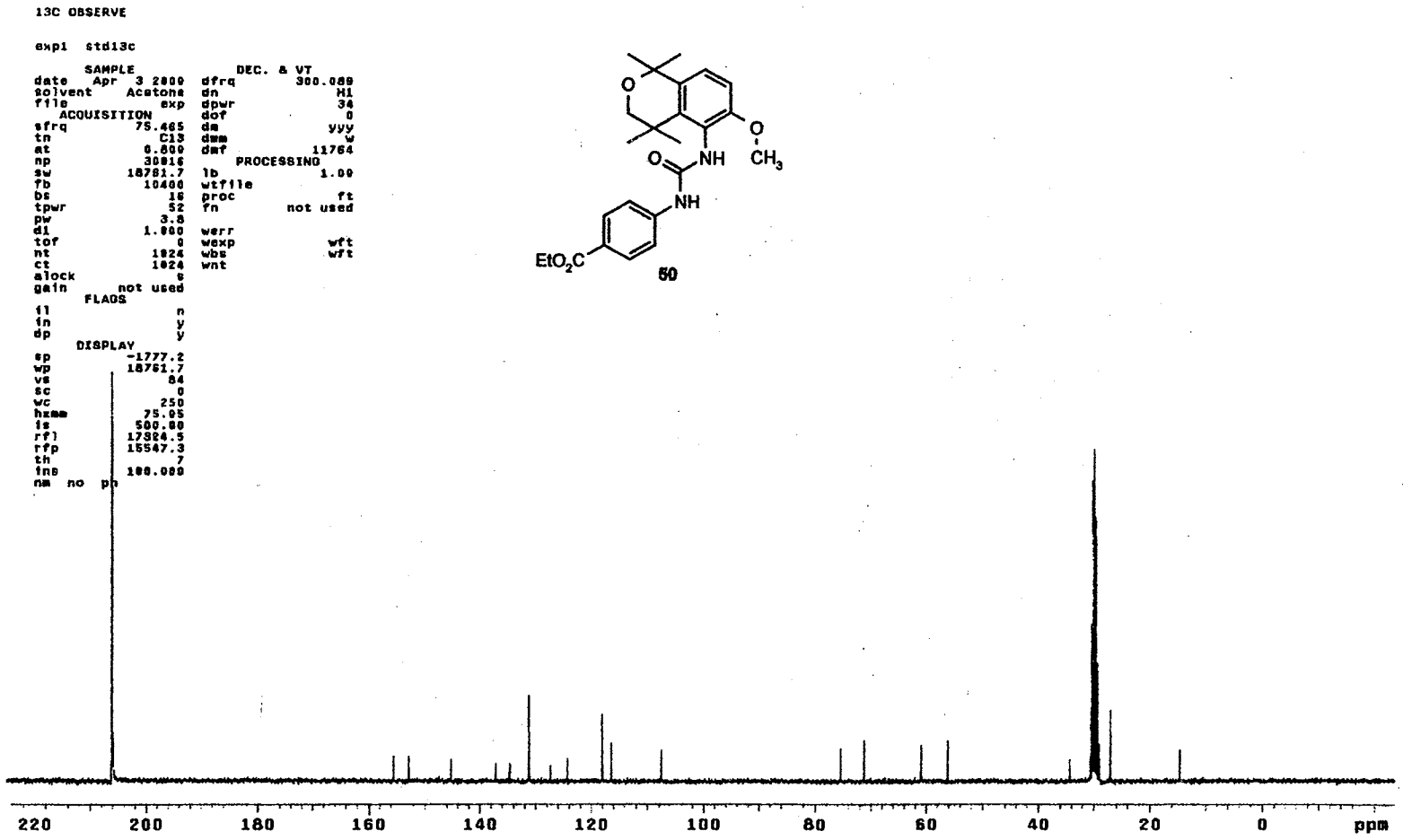


50



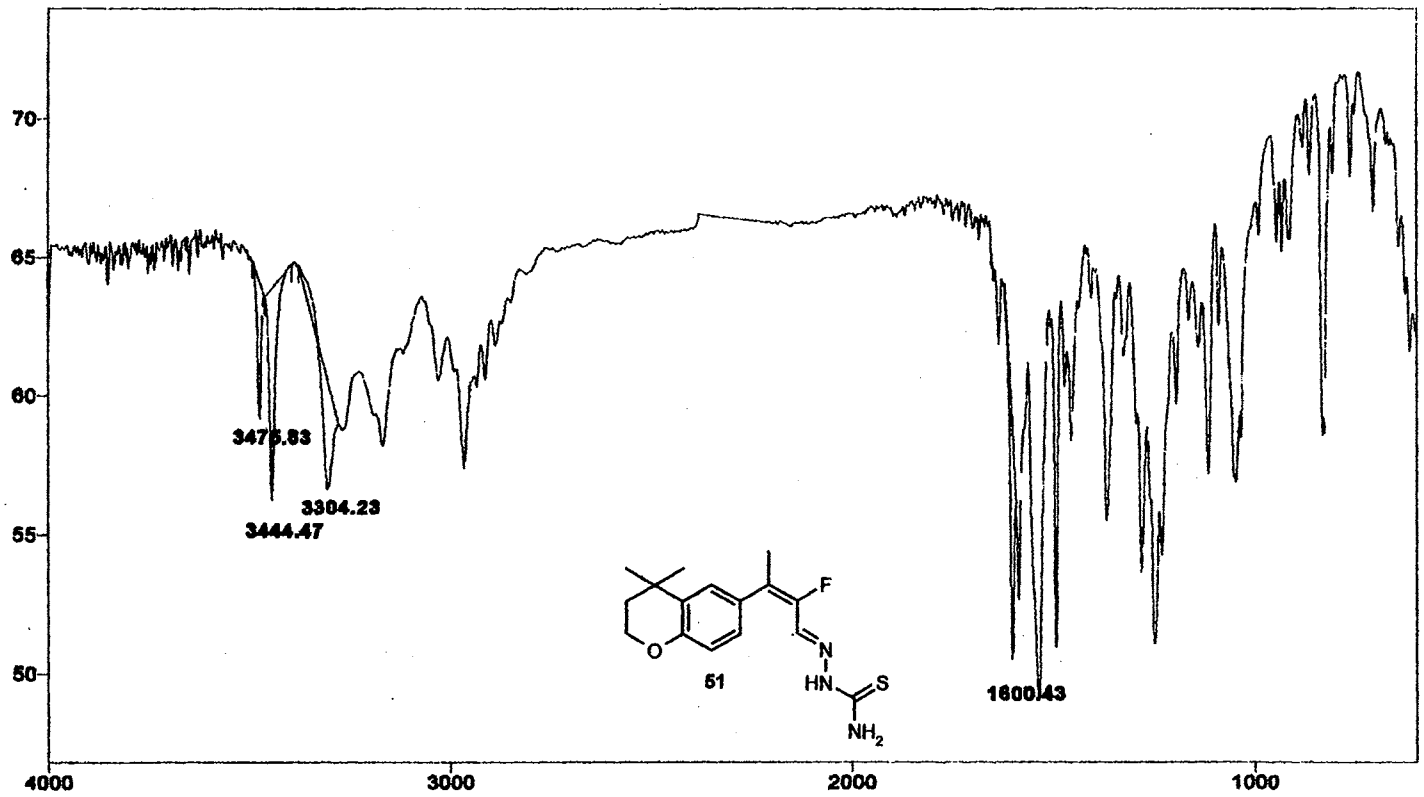
^{1}H NMR Spectrum of **50**

Plate IX



^{13}C NMR Spectrum of **50**

Plate X



IR Spectrum of **51**

Plate XI

```
STANDARD 1H OBSERVE

expl  stdih

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sfrq        300.089  dm               nnn
tn               H1  dmm                c
at            3.747  dmf              200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2600  proc              ft
bs               16  fn          not used
tpwr             48
pw              6.9  werr
dl                0  wexp
tof               0  wbs
nt               84  wnt
ct               64
alock             n
gain        not used
      FLAGS
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in                y
dp                y
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sp            -97.1
wp           3772.9
vs              354
sc                0
wc              250
hzcm          15.09
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rfl          1494.6
rfp           747.2
th               20
ins         100.000
nm  cdc  ph
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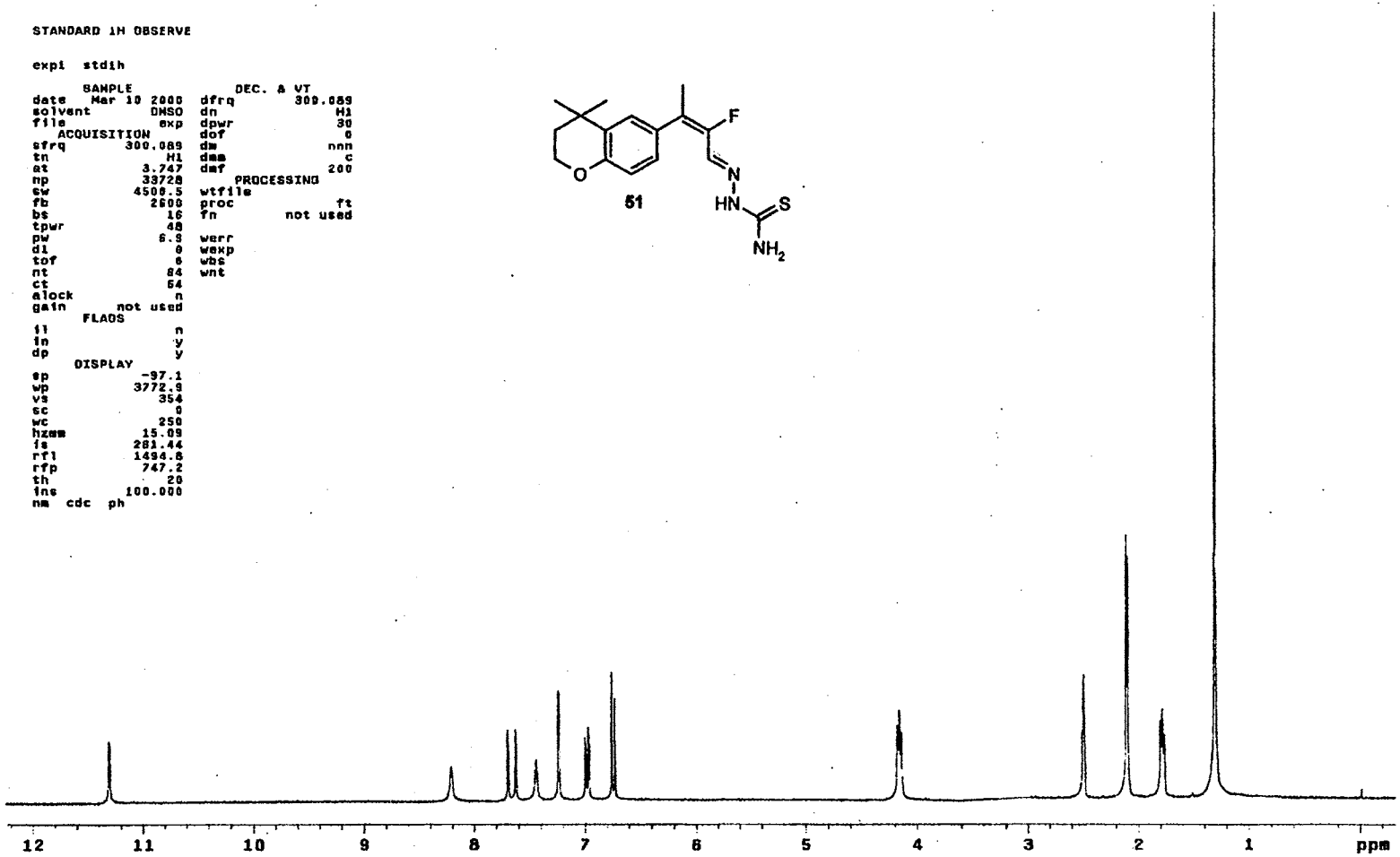

^{1}H NMR Spectrum of **51**

Plate XII

```
13C OBSERVE

expl  std13c

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solvent        DMSO
file            exp
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at             0.800
np             39016
sw           18761.7
fb             10400
bs                16
tpwr              52
pw               3.8
d1             1.000
tof                0
nt              4096
ct              3535
alock              s
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1869.5
wp           18761.7
vs               111
sc                 0
wc               250
hzcm           75.05
is             500.0
rfl            4850.0
rfp            2980.6
th                 2
ins            100.000
nm  no  ph

      DEC. & VT
dfrq         300.085
dn                H1
dpwr              34
dof                0
dm               yyy
dmm                w
dmf            11764
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lb               1.00
wtfile
proc               ft
fn          not used
werr
wexp             wft
wbs              wft
wnt
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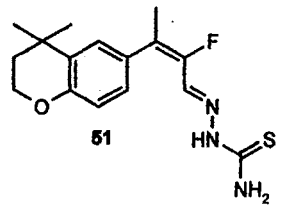

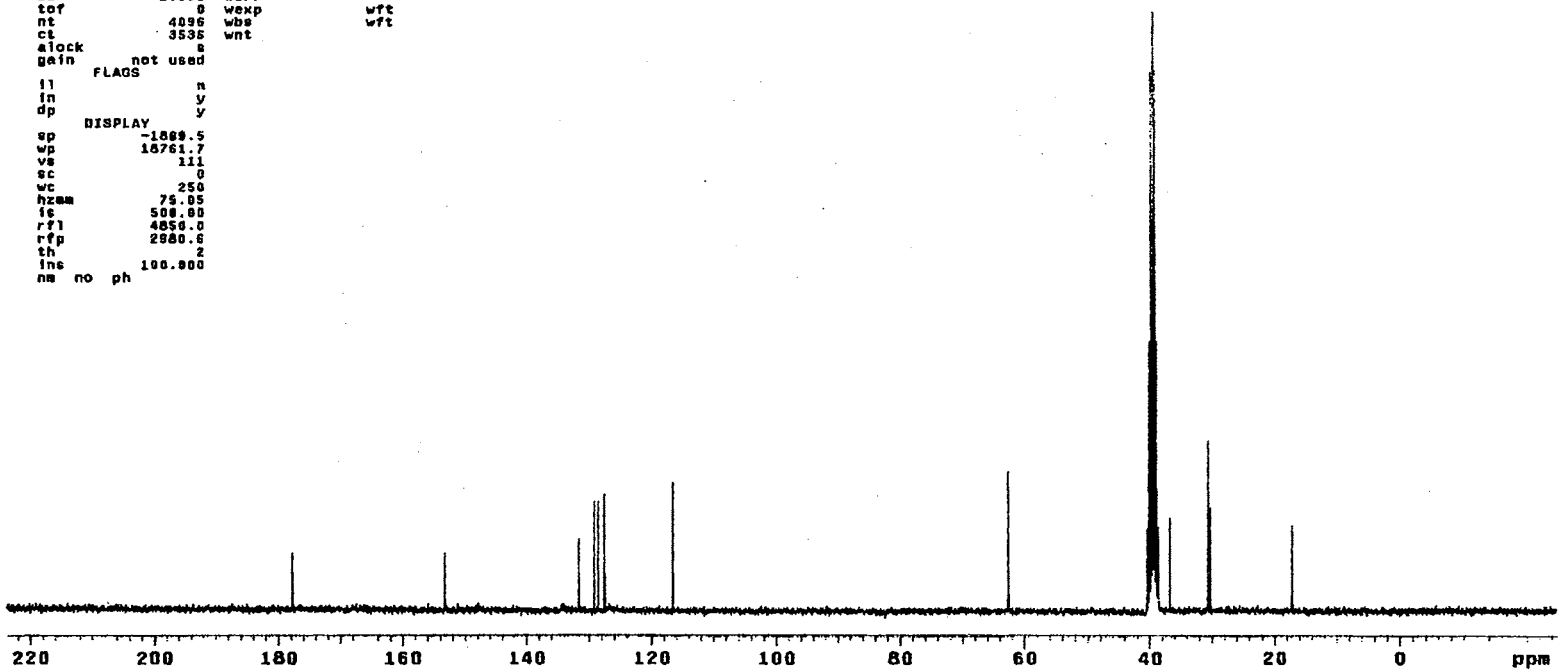

^{13}C NMR Spectrum of **51**

Plate XIII

```
13C OBSERVE

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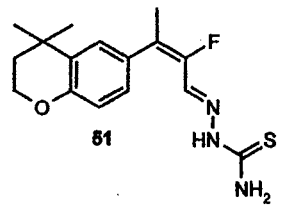
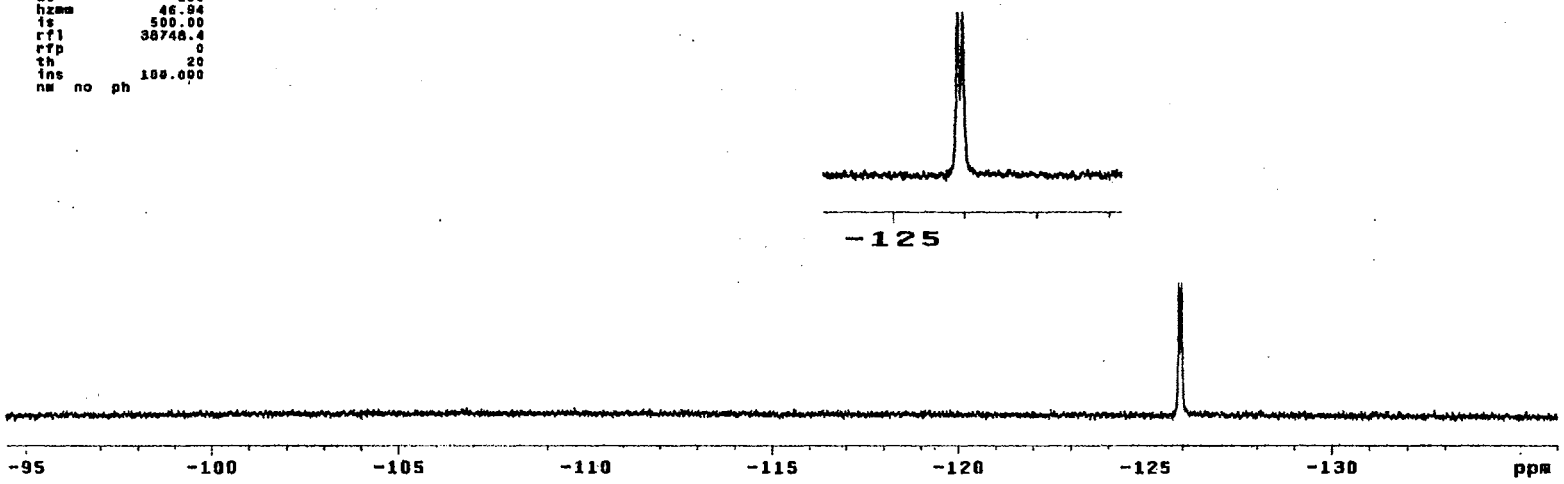
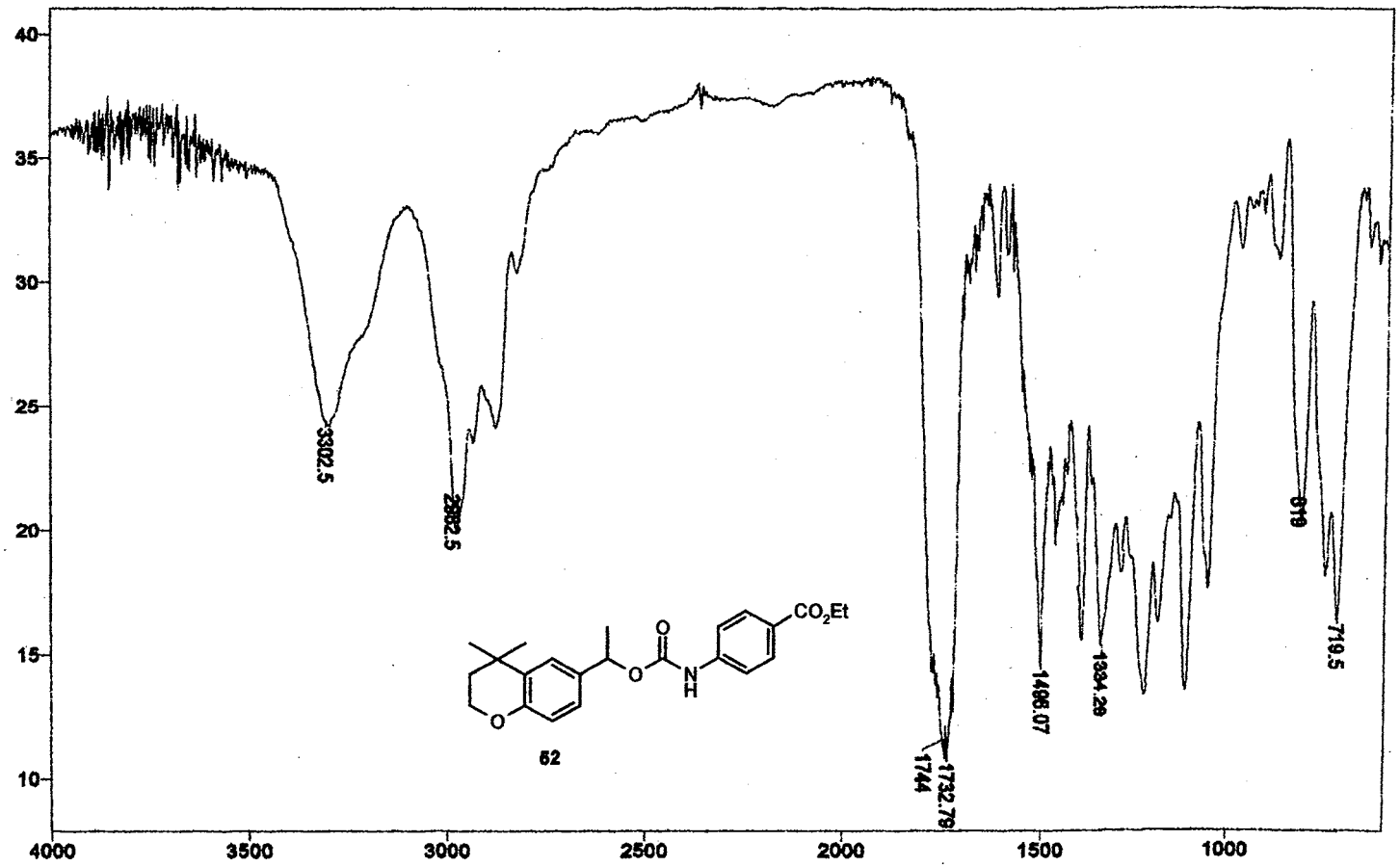
tn              F19  dmm                 w
at            0.600  dmf             11784
np            30016      PROCESSING
sw          18761.7  lb                1.00
fb            10400  wtfile
bs               16  proc              ft
tpwr             52  fn          not used
pw              3.8
d1            1.000  warr
tof               0  wexp             wft
nt             1024  wbs              wft
ct               96  wnt
alock             n
gain        not used
      FLAGS
fl                n
in                y
dp                y
     DISPLAY
sp         -38403.7
wp          11734.8
vs               25
sc                0
wc              250
hzcm          46.94
is           500.00
rfl         38748.4
rfp               0
th               20
ins         100.000
nm  no  ph
```





^{19}F NMR Spectrum of **51**

Plate XIV



IR Spectrum of **52**

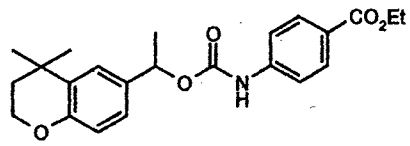
Plate XV

STANDARD 1H OBSERVE

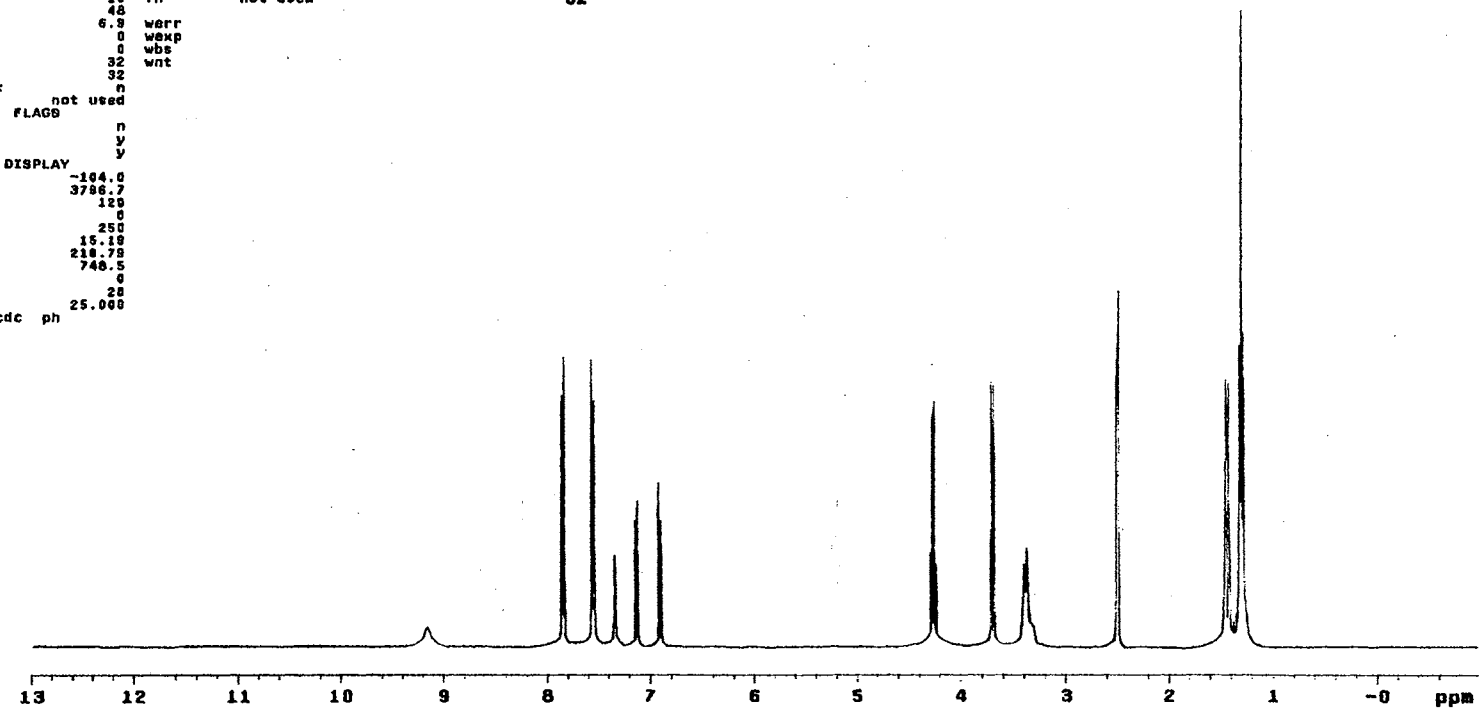
```
expl  stdlh

        SAMPLE
date    Nov 11 1989
solvent        CDCl3
file           exp
    ACQUISITION
sfrq         300.067
tn              H1
at             3.747
np             33728
sw            4500.5
fb              2600
bs                16
tpwr              48
pw               6.9
d1                 0
tof                0
nt                32
ct                32
alock              n
gain        not used
      FLAGS
ll                 n
in                 y
dp                 y
      DISPLAY
sp            -104.0
wp            3786.7
vs               129
sc                 0
wc               250
hzmm           15.19
is            218.79
rfl            748.5
rfp                0
th                28
ins           25.000
nm  cdc  ph

          DEC. & VT
dfrq         300.067
dn              H1
dpwr            39
dof              0
dm             nnn
dmm              c
dmf            200
     PROCESSING
wtfile
proc            ft
fn         not used
werr
wexp
wbs
wnt
```

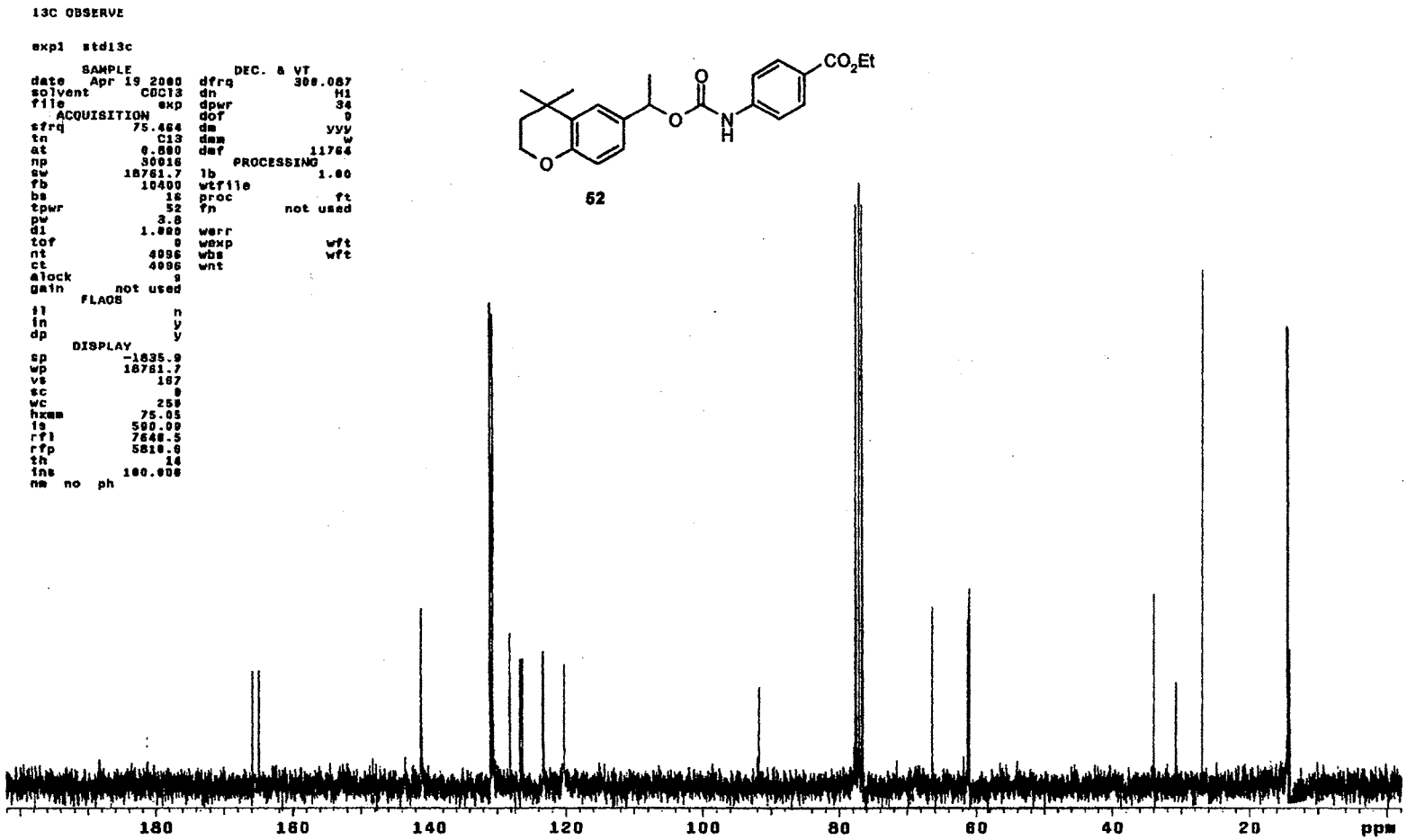


52



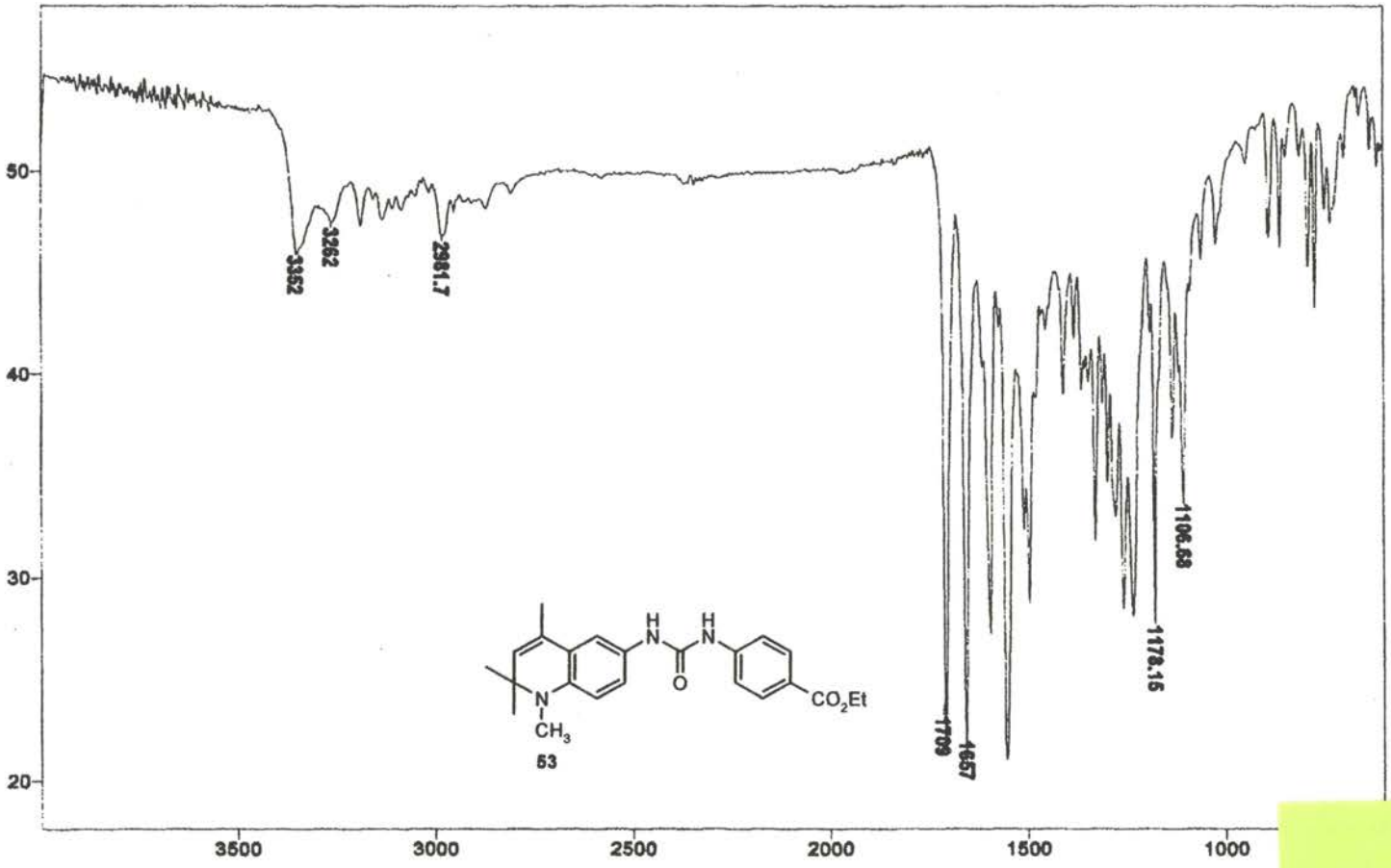
^{1}H NMR Spectrum of **52**

Plate XVI



^{13}C NMR Spectrum of **52**

Plate XVII



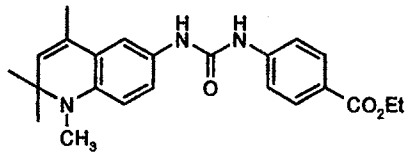
IR Spectrum of **53**

Plate XVIII

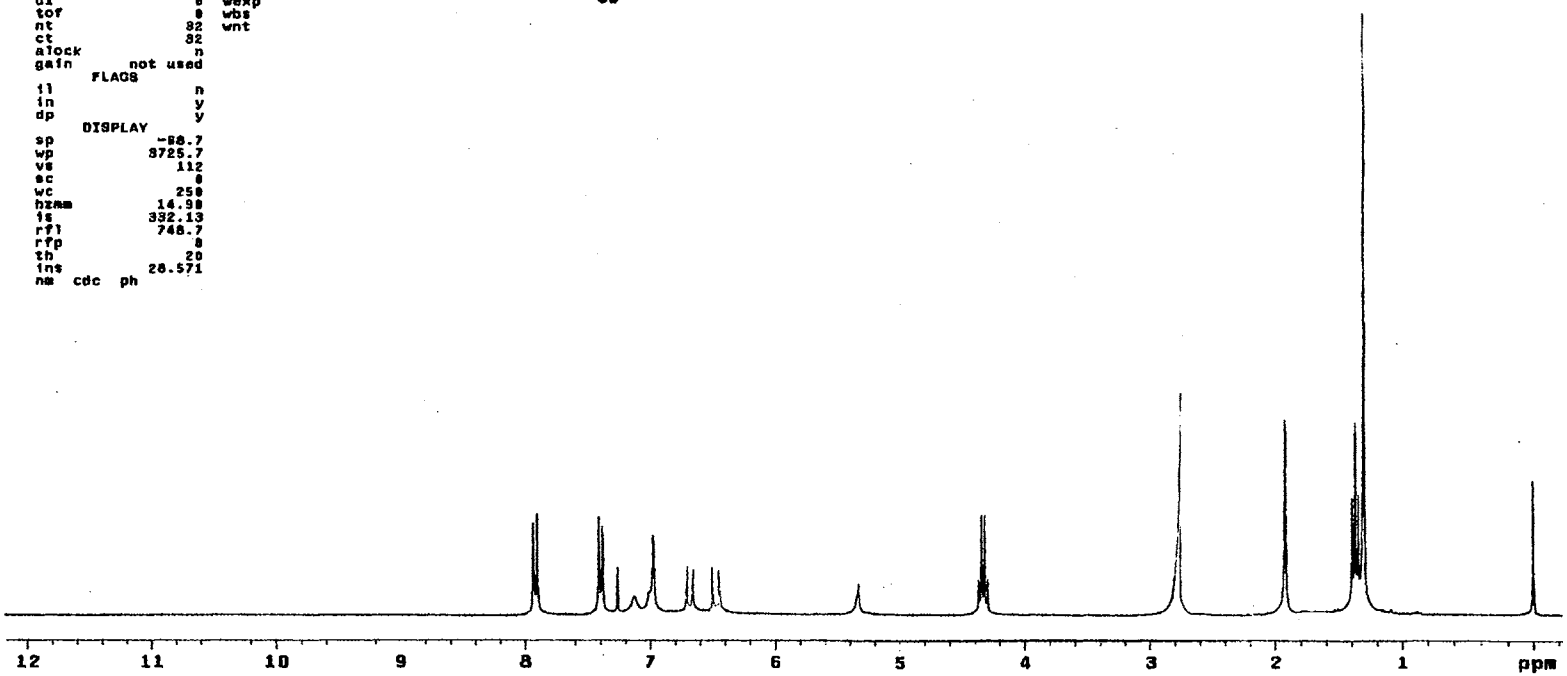
```
STANDARD 1H OBSERVE

exp1  stdih

      SAMPLE                 DEC. & VT
date   Nov 11 1999   dfrq          300.087
solvent       CDCl3  dn                 H1
file           exp   dpwr               30
   ACQUISITION       dof                 0
sfrq         300.087 dm                nnn
tn                H1 dmm                 c
at             3.747 dmf               200
np             33728    PROCESSING
sw            4508.5 wtfile
fb             2600 proc                ft
bs               16 fn          not used
tpwr             48
pw              6.9 werr
d1                0 wexp
tof               0 wbs
nt               32 wnt
ct               32
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp            -98.7
wp           3725.7
vs              112
sc                0
wc              250
hzmm          14.98
is           332.13
rf1           748.7
rfp               0
th               20
ins          28.571
nm  cdc  ph
```



53



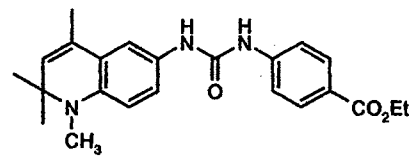
^{1}H NMR Spectrum of **53**

Plate XIX

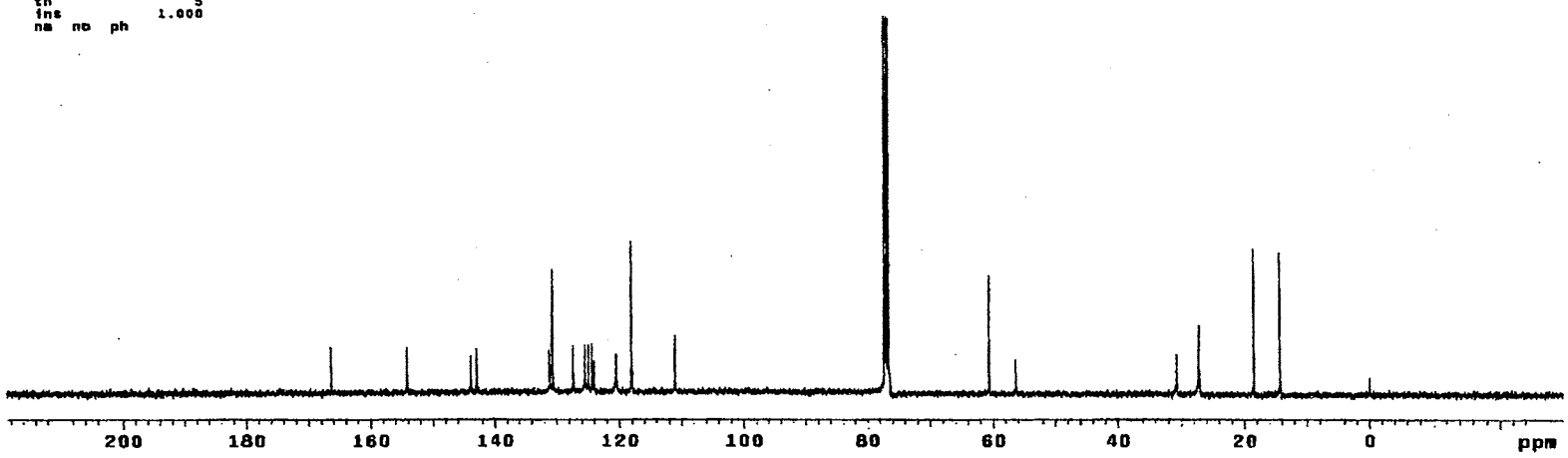
```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date    Nov 11 1999  dfrq          399.925
solvent       CDCl3  dn                 H1
file            exp  dpwr               40
   ACQUISITION       dof                 0
sfrq          100.570 dm                nyy
tn                C13 dmm                 w
at              1.199 dmf           12000
np              59968 dseq
sw           25000.0  dres              1.0
fb              14000 homo                n
bs                 16
tpwr               53   PROCESSING
pw               7.0  lb               1.00
d1              1.000 wtfile
d2              0.500 proc               ft
tof                 0 fn          not used
nt              10000 math                f
ct              10000 werr
alock               n wexp              wft
gain         not used wbs               wft
      FLAGS           wnt
il                  n
in                  n
dp                  y
hs                 nn
     DISPLAY
sp            -3008.4
wp           25000.0
vs                 71
sc                  0
wc                250
hzcm           108.00
is             500.00
rfl           18750.1
rfp            7743.8
th                  5
ins             1.000
ns  no  ph
```

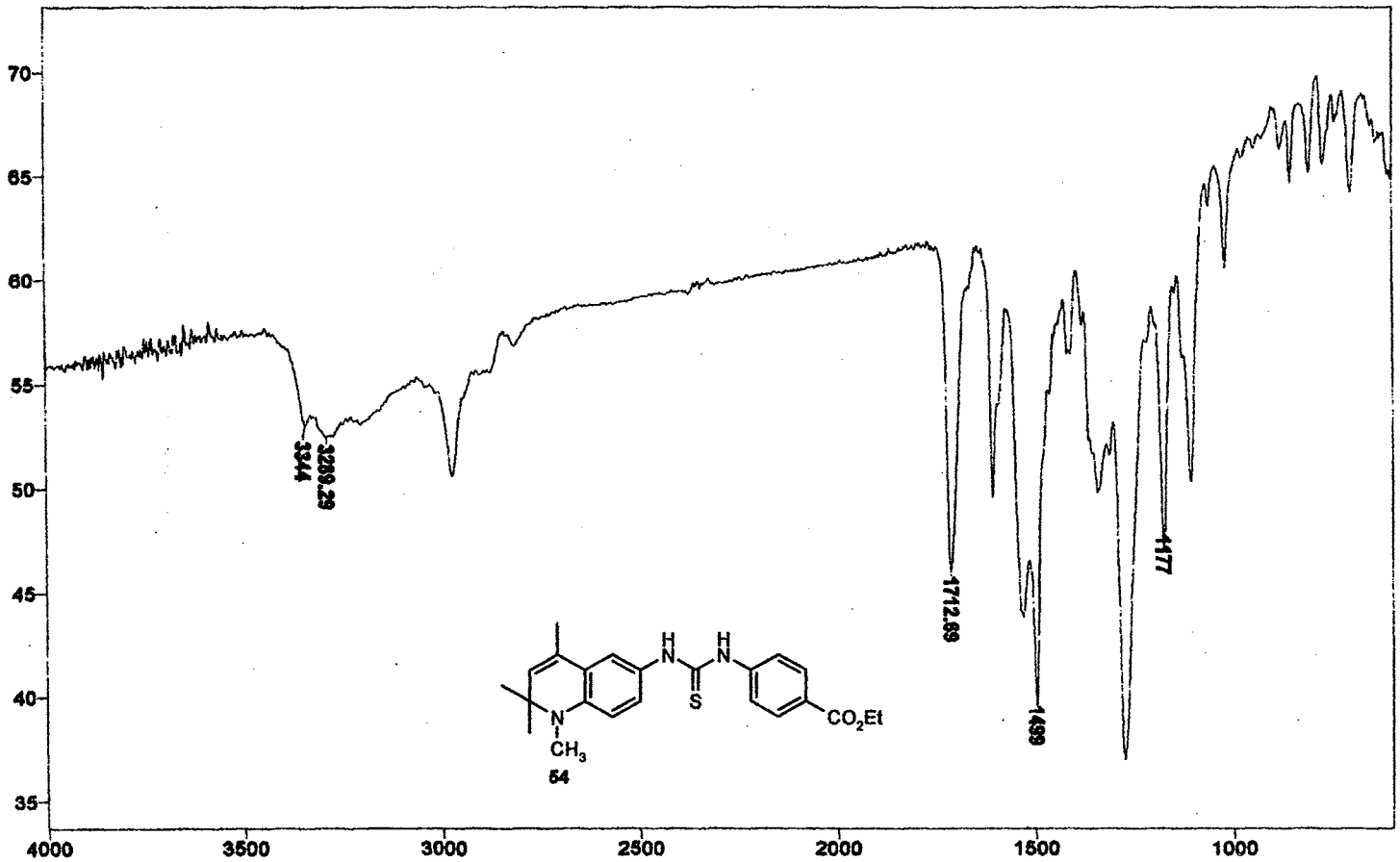


53



^{13}C NMR Spectrum of **53**

Plate XX



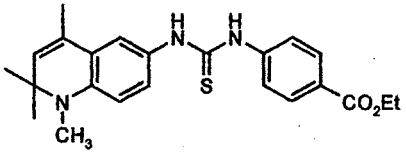
IR Spectrum of **54**

Plate XXI

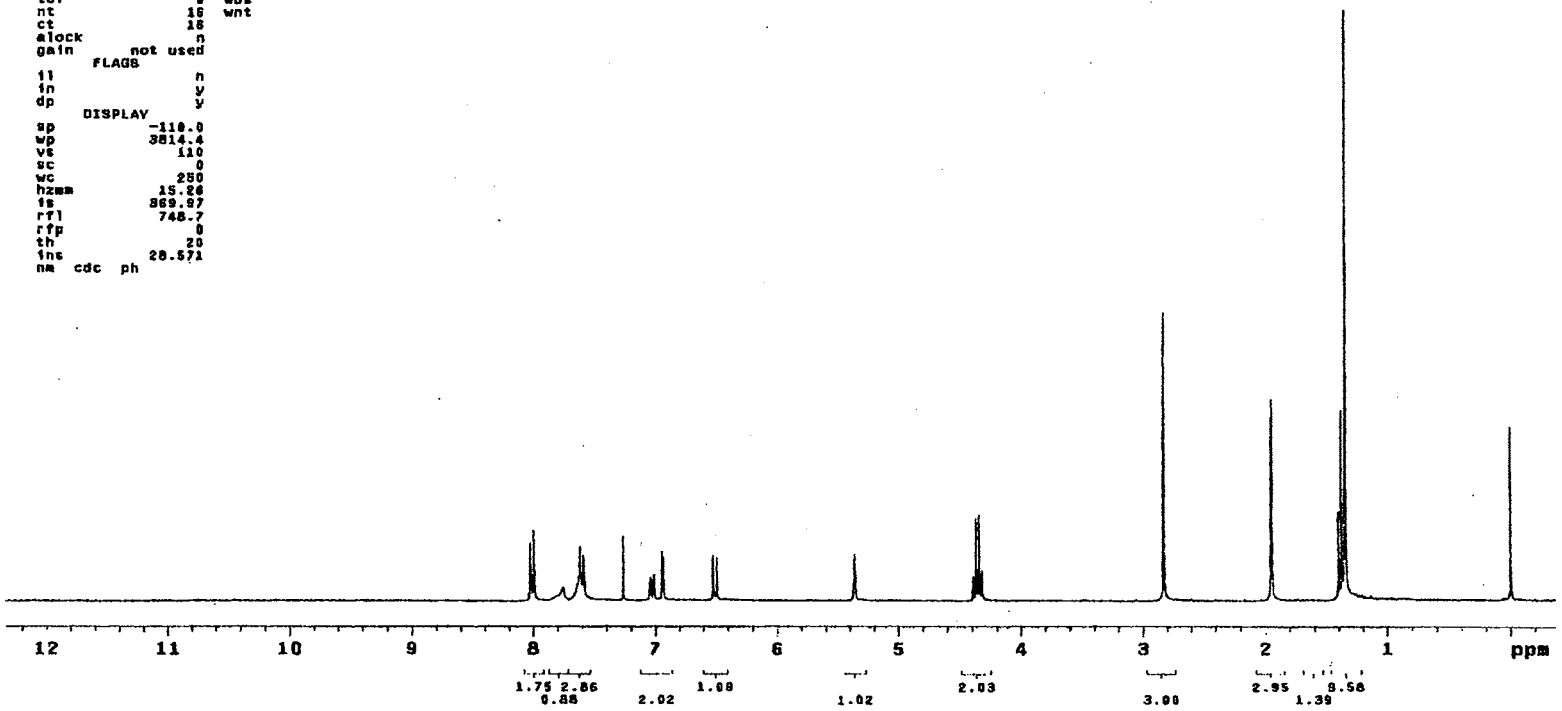
```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                 DEC. & VT
date   Nov 11 1999   dfrq        300.087
solvent        CDCl3  dn              H1
file             exp  dpwr            30
   ACQUISITION       dof               0
sfrq         300.087  dm              nnn
tn              H1    dmm               c
at            3.747   dmf             200
np            33728      PROCESSING
sw           4500.5   wtfile
fb             2600   proc             ft
bs               16   fn         not used
tpwr             48
pw              6.5   werr
d1                0   wexp
tof               0   wbs
nt               16   wnt
ct               16
alock             n
gain        not used
      FLAGS
ii                n
in                y
dp                y
      DISPLAY
sp           -110.0
wp           3814.4
vs              110
sc                0
wc              250
hzmm          15.26
is            369.97
rfl            748.7
rfp                0
th                20
ins           28.571
nm  cdc  ph
```

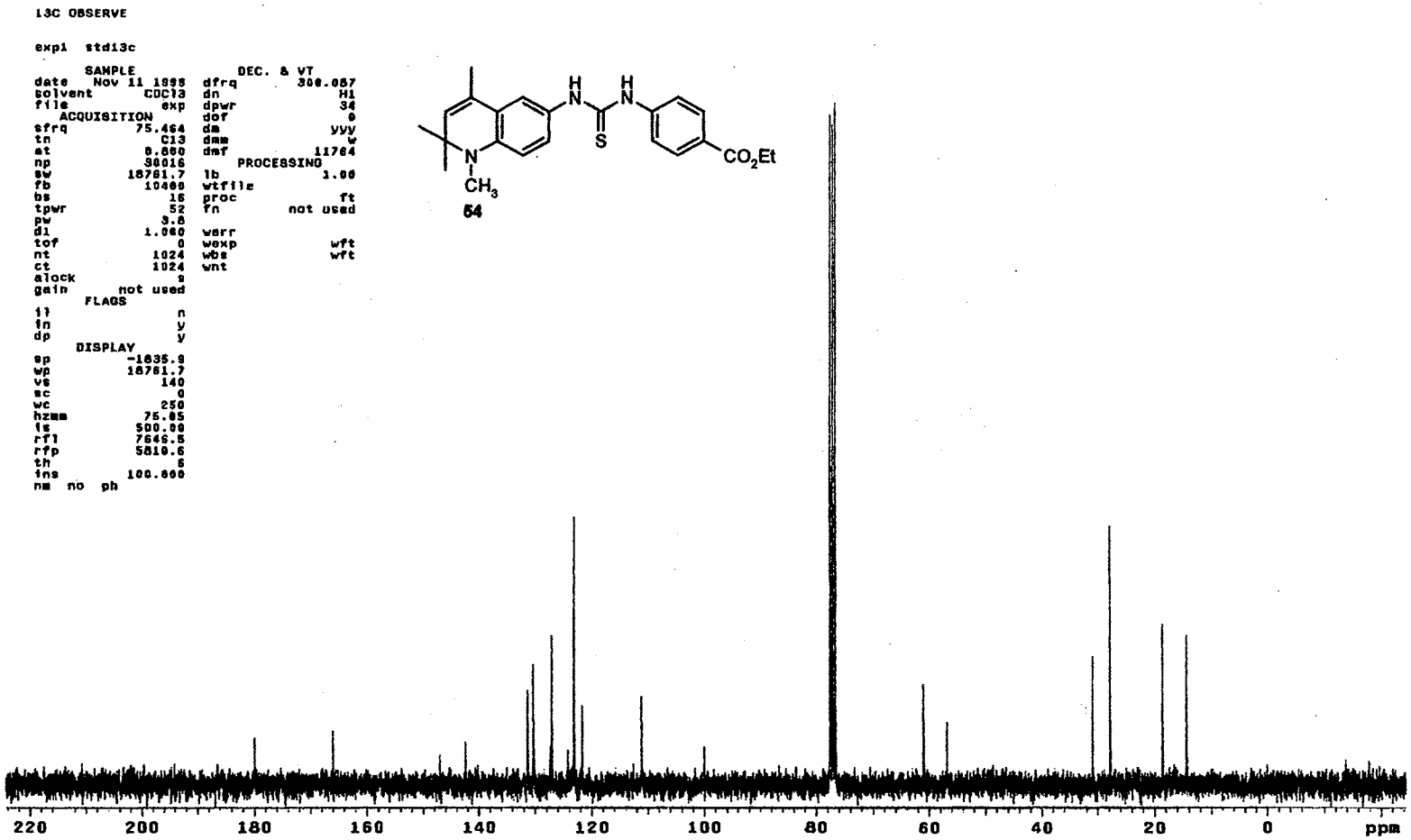


54



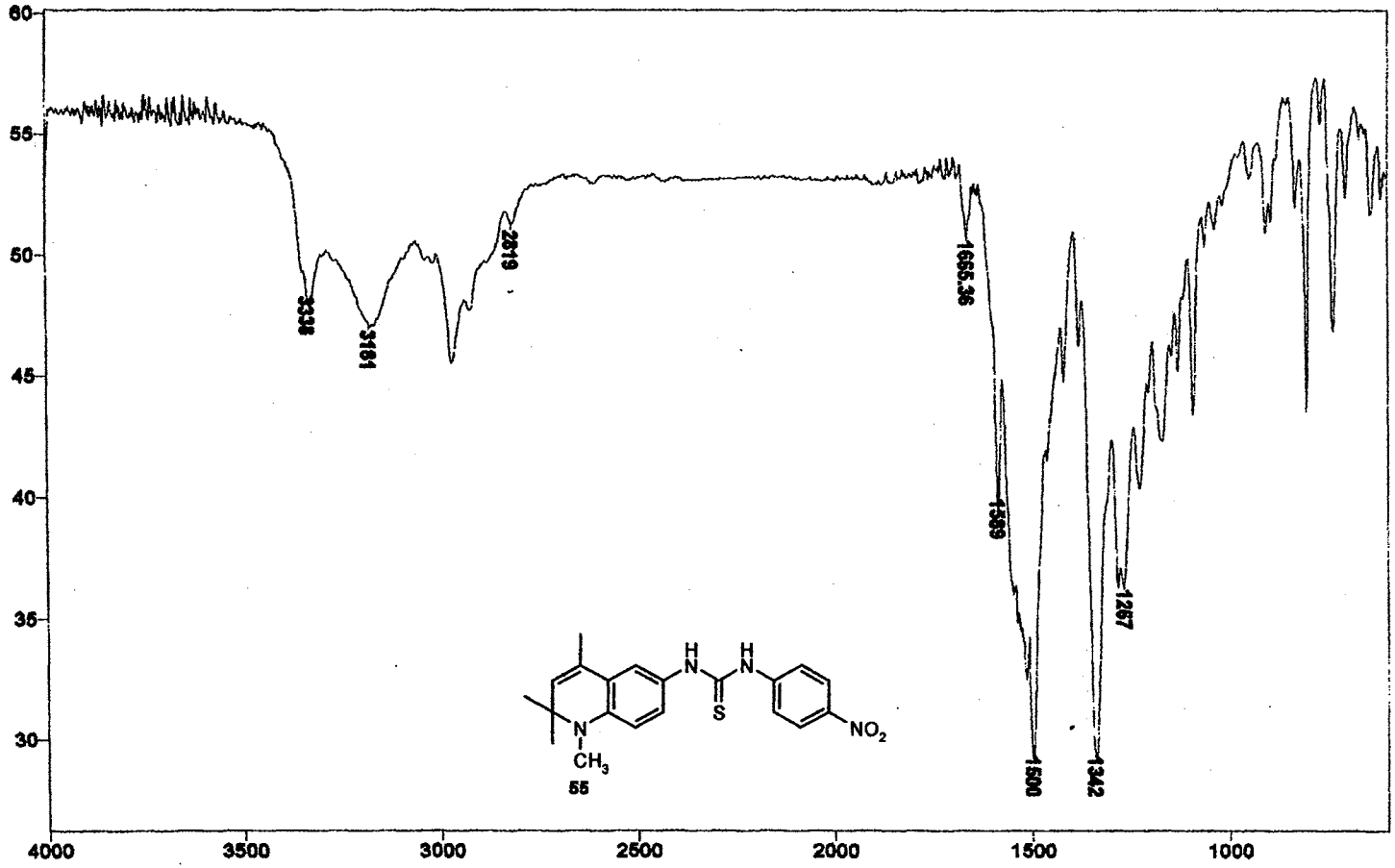
^{1}H NMR Spectrum of **54**

Plate XXII



^{13}C NMR Spectrum of **54**

Plate XXIII



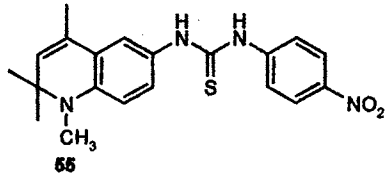
IR Spectrum of **55**

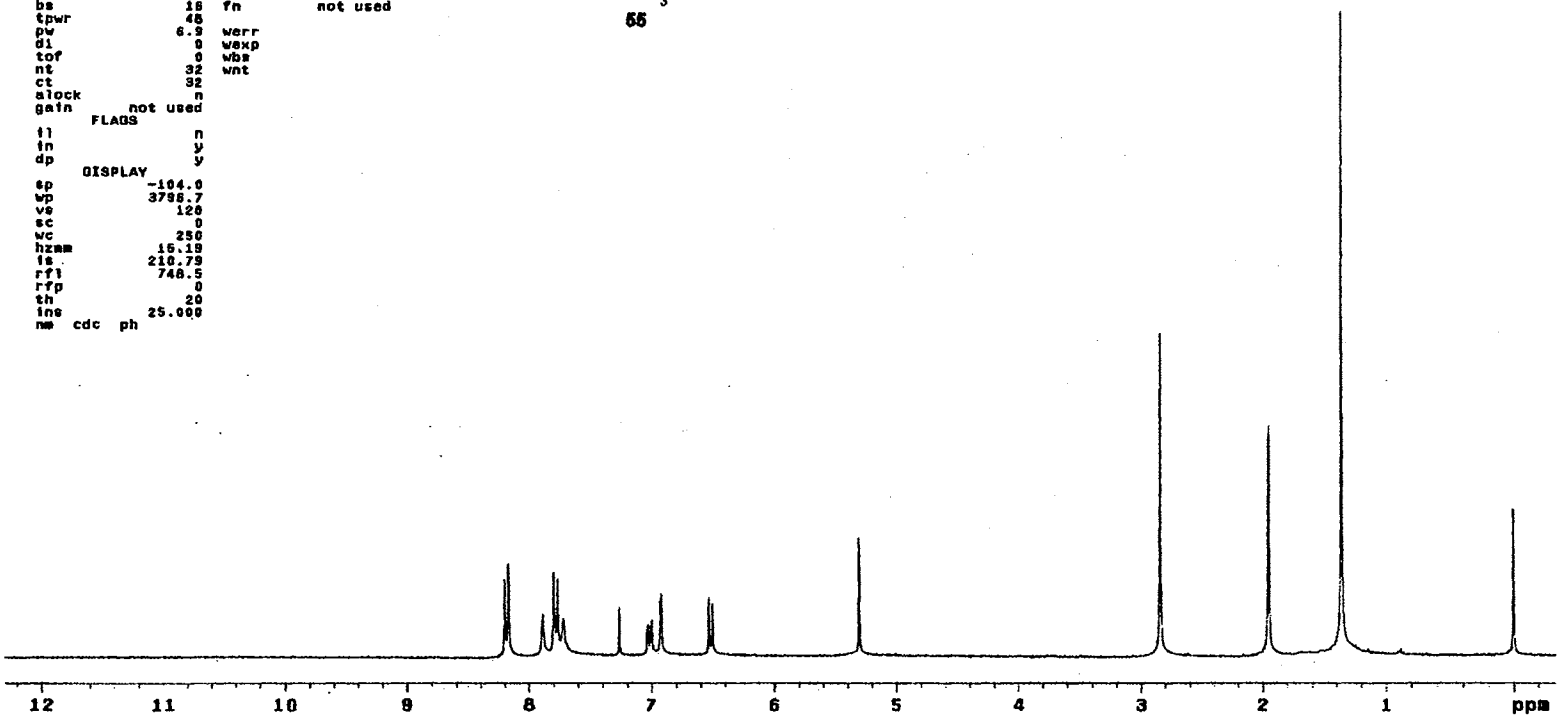
Plate XXIV

```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date    Nov 11 1999   dfrq        300.087
solvent       CDCl3   dn              H1
file            exp   dpwr            30
   ACQUISITION        dof              0
sfrq        300.087   dm             nnn
tn               H1   dmm              c
at            3.747   dmf            200
np           33728       PROCESSING
sw           4500.5   wtfile
fb             2000   proc            ft
bs               16   fn        not used
tpwr             46
pw              6.9   werr
d1                0   wexp
tof               0   wbs
nt               32   wnt
ct               32
alock             n
gain       not used
      FLAGS
ii                n
in                y
dp                y
      DISPLAY
sp           -104.0
wp           3796.7
vs              120
sc                0
wc              250
hzmm          16.19
is           210.79
rf1          748.5
rfp               0
th               20
ins          25.000
nm  cdc  ph
```





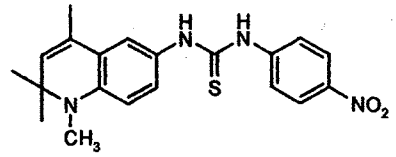
^{1}H NMR Spectrum of **55**

Plate XXV

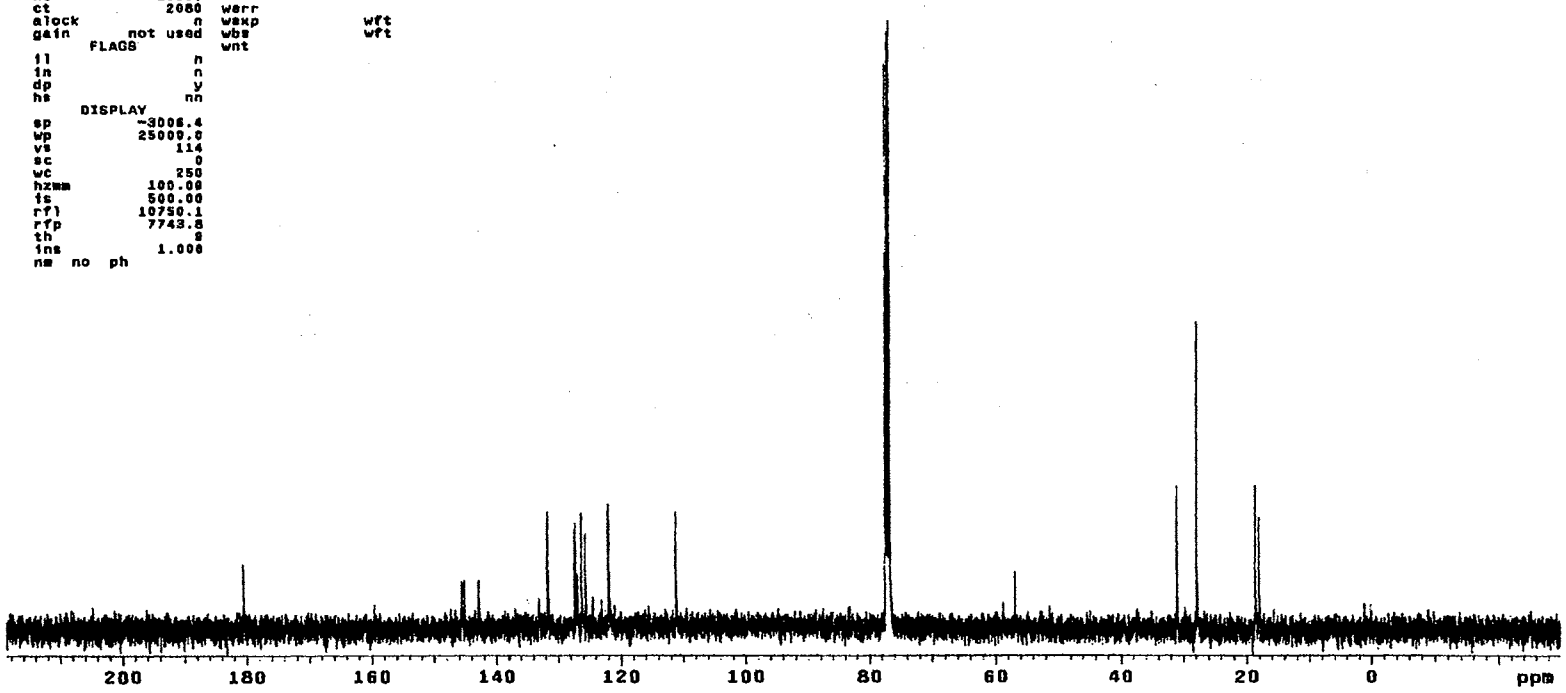
```
13C OBSERVE

exp1  std13c

        SAMPLE                  DEC. & VT
date   Nov 11 1999      dfrq          398.926
solvent        CDCl3    dn                 H1
file             exp    dpwr               40
    ACQUISITION         dof                 0
sfrq         100.578    dm                nyy
tn               C13    dmm                 w
at             1.198    dmf             12900
np             59368    dseq
sw           25000.0    dres              1.0
fb             14000    homo                n
bs                16        PROCESSING
tpwr              53    lb               1.00
pw               7.8    wtfile
d1             1.000    proc              ft
d2             0.500    fn          not used
tof                0    math               f
nt             10000    werr
ct              2080    wexp             wft
alock              n    wbs              wft
gain       not used     wnt
       FLAGS
il                 n
in                 n
dp                 y
hs                nn
      DISPLAY
sp           -3006.4
wp           25009.0
vs               114
sc                 0
wc               250
hzmm          100.00
is            500.00
rfl          10750.1
rfp           7743.8
th                 9
ins           1.000
nm  no  ph
```

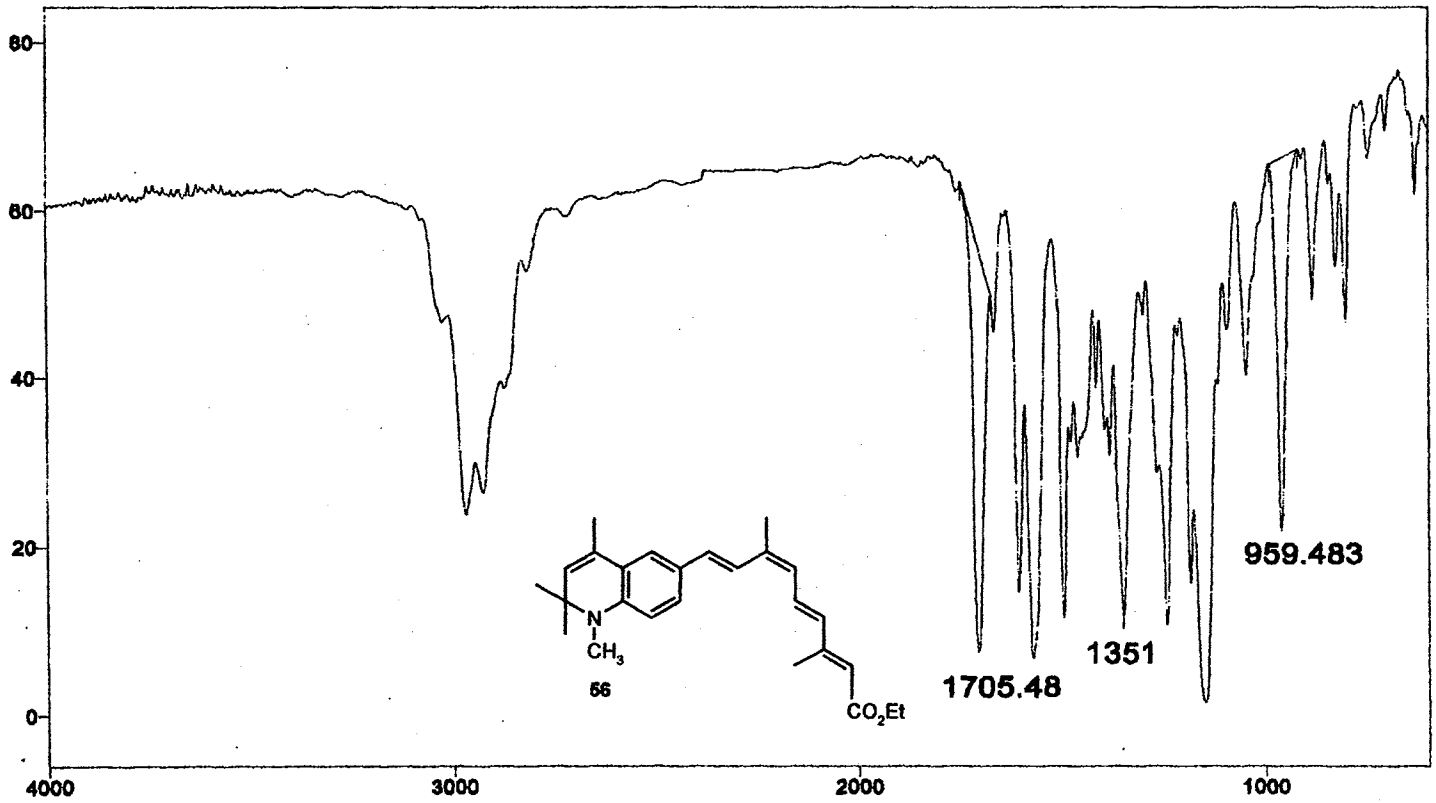


55



^{13}C NMR Spectrum of **55**

Plate XXVI



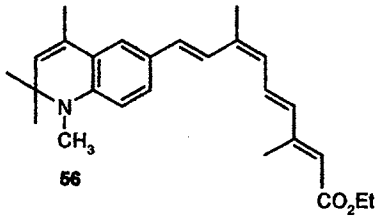
IR Spectrum of **56**

Plate XXVII

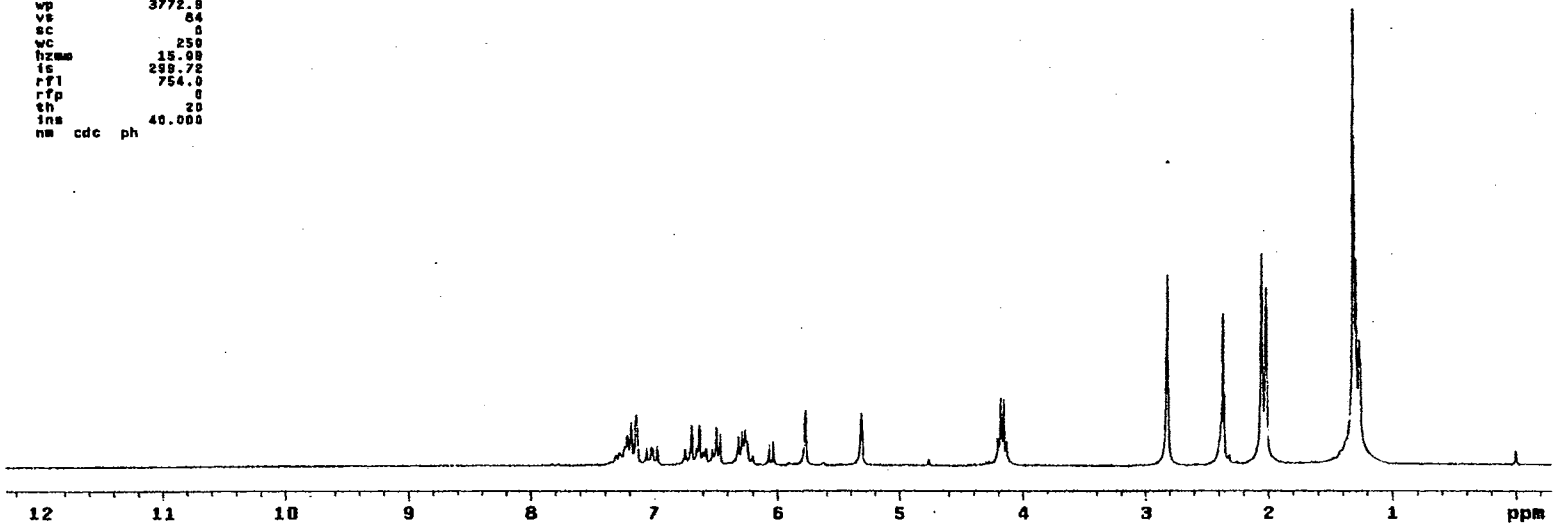
```
STANDARD 1H OBSERVE

expl  std1h

      SAMPLE                    DEC. & VT
date   Nov 22 1995        dfrq          300.087
solvent        CDCl3      dn                 H1
file             exp      dpwr               30
    ACQUISITION           dof                 0
sfrq          300.087     dm                nnn
tn                 H1     dmm                 c
at               3.747    dmf               200
np               33728        PROCESSING
sw              4500.5    wtfile
fb                2600    proc               ft
bs                  16    fn          not used
tpwr                48
pw                 4.0    werr
d1                   0    wexp
tof                  0    wbs
nt                  16    wnt
ct                  16
alock                n
gain          not used
      FLAGS
fl                   n
in                   y
dp                   y
     DISPLAY
sp               -85.5
wp              3772.8
vs                  84
sc                   0
wc                 250
hzcm             15.08
is               299.72
rfl              754.0
rfp                  0
th                  20
ins              40.000
nm  cdc  ph
```



56



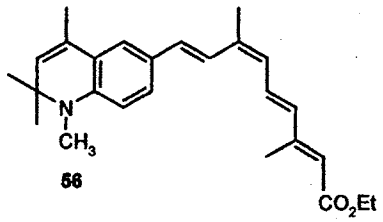
^{1}H NMR Spectrum of **56**

Plate XXVIII

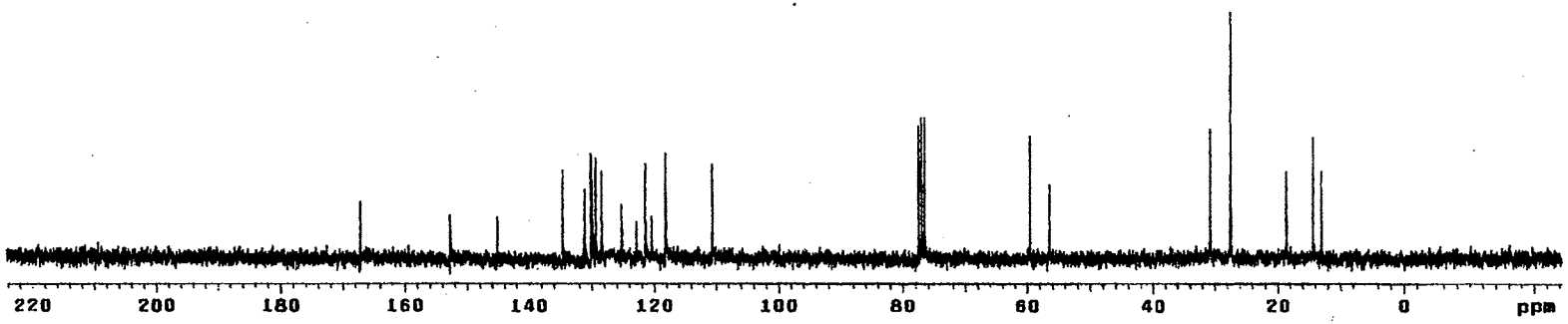
```
13C OBSERVE

exp1  std13c

        SAMPLE                  DEC. & VT
date   Nov 22 1999      dfrq          300.087
solvent        CDCl3    dn                 H1
file             exp    dpwr               34
   ACQUISITION          dof                 0
sfrq          75.464    dm                yyy
tn               C13    dmm                 w
at             0.800    daf             11764
np             30016       PROCESSING
sw           18761.7    lb               1.00
fb             16408    wtfile
bs                16    proc               ft
tpwr              52    fn           not used
pw               3.8
d1             1.000    werr
tof                0    wexp              wft
nt              1024    wbs               wft
ct               128    wnt
alock              s
gain        not used
       FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp            -1640.4
wp           18761.7
vs                46
sc                 0
wc               250
hzcm           75.05
is             500.00
rfl            7651.0
rfp            5810.6
th                 20
ins            100.000
nm  no  ph
```

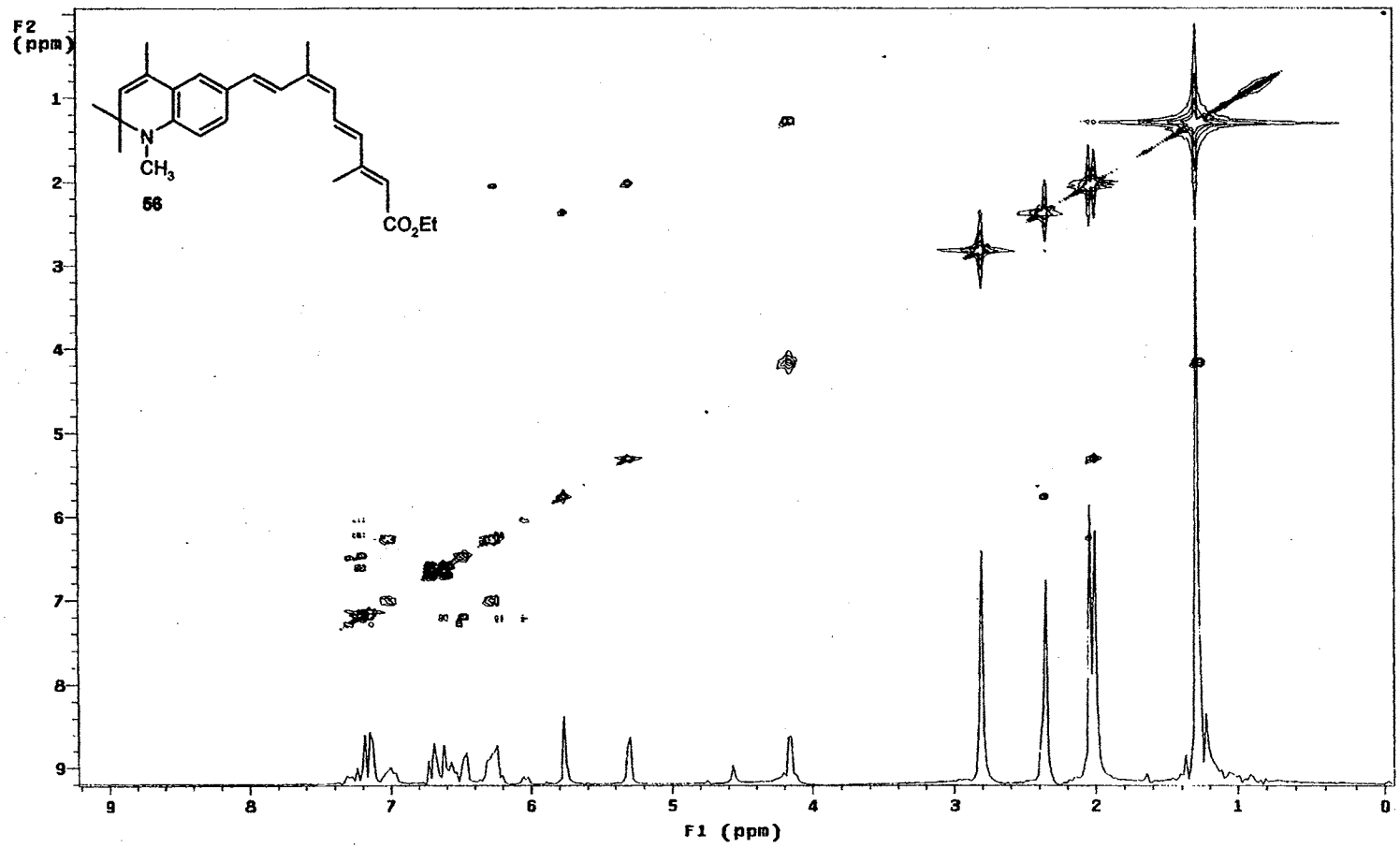


56



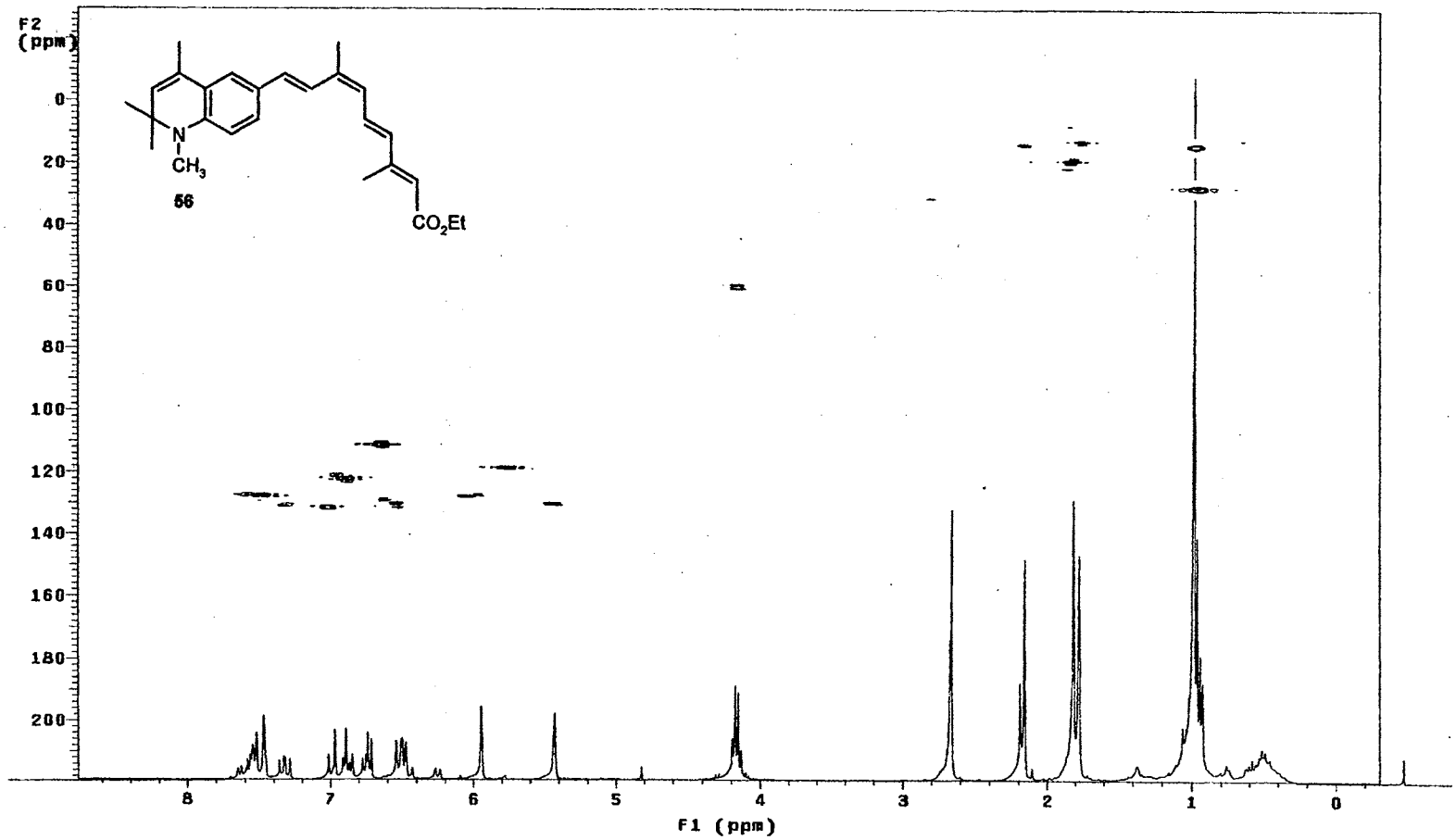
^{13}C NMR Spectrum of **56**

Plate XXIX



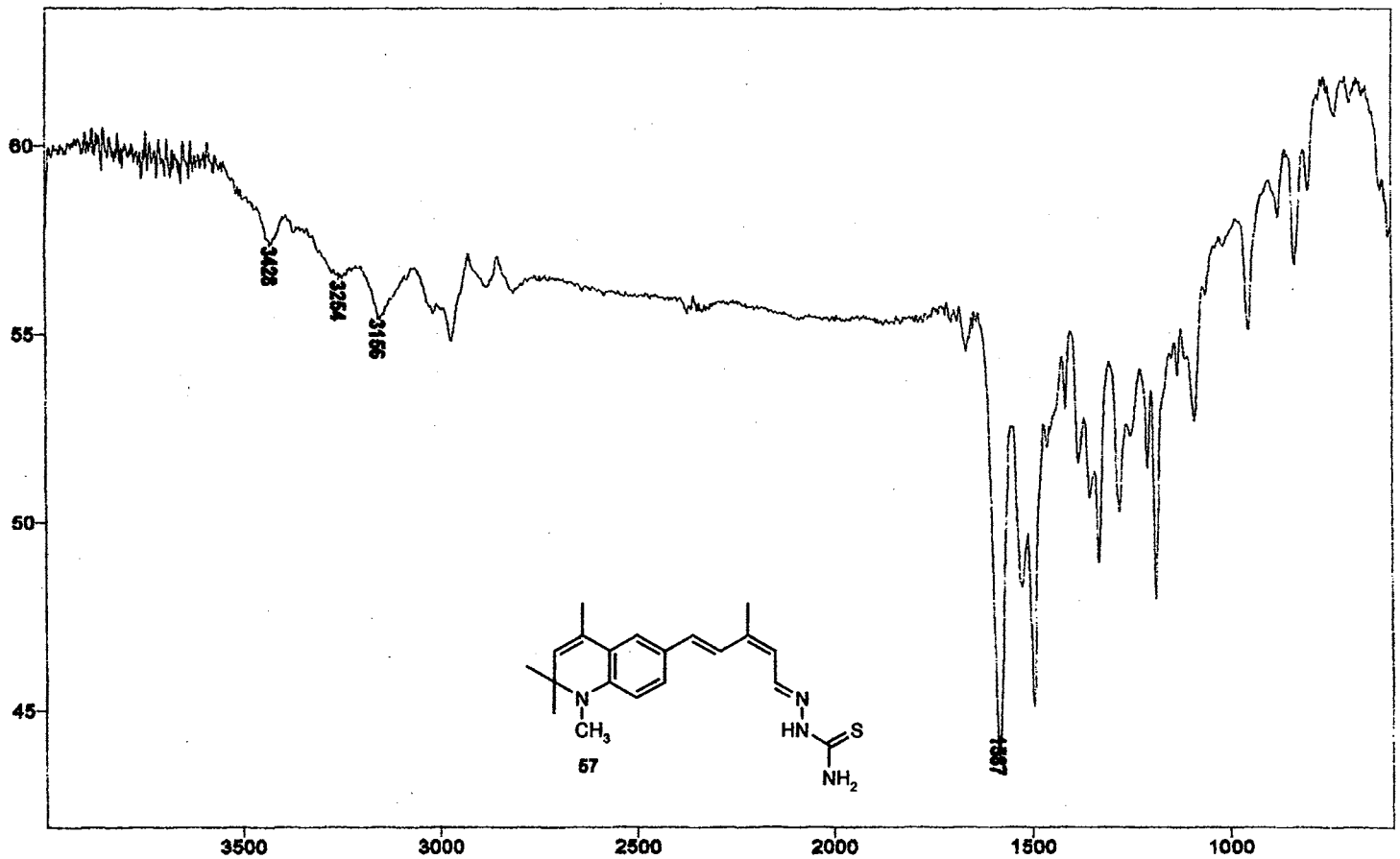
2D COSY NMR Spectrum of **56**

Plate XXX



2D HETCOR NMR Spectrum of **56**

Plate XXXI



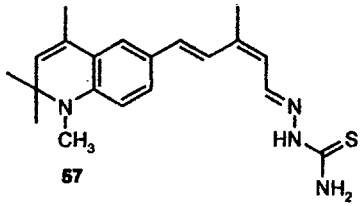
IR Spectrum of **57**

Plate XXXII

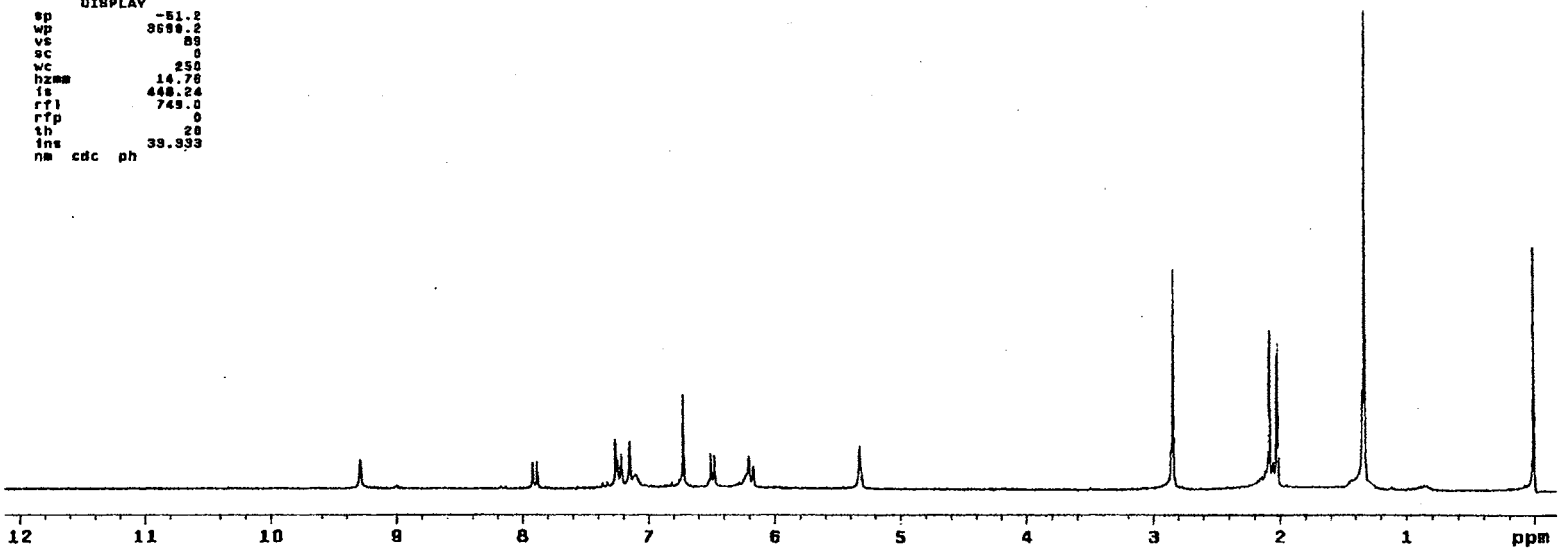
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date   Nov 12 1999   dfrq          300.057
solvent       CDCl3  dn                H1
file            exp  dpwr              30
   ACQUISITION       dof                0
sfrq          300.057 dm               nnn
tn                H1  dmm                c
at            3.747   dmf              200
np            33728      PROCESSING
sw           4500.5   wtfile
fb            2800   proc              ft
bs              16   fn          not used
tpwr            48
pw             6.9   werr
d1               0   wexp
tof              0   wbs
nt              64   wnt
ct              64
alock            n
gain        not used
      FLAGS
ii               n
in               y
dp               y
      DISPLAY
sp            -51.2
wp           3680.2
vs               89
sc                0
wc              250
hzmm          14.76
is           448.24
rf1           749.0
rfp               0
th               28
ins           39.333
nm  cdc  ph
```



57



^{1}H NMR Spectrum of **57**

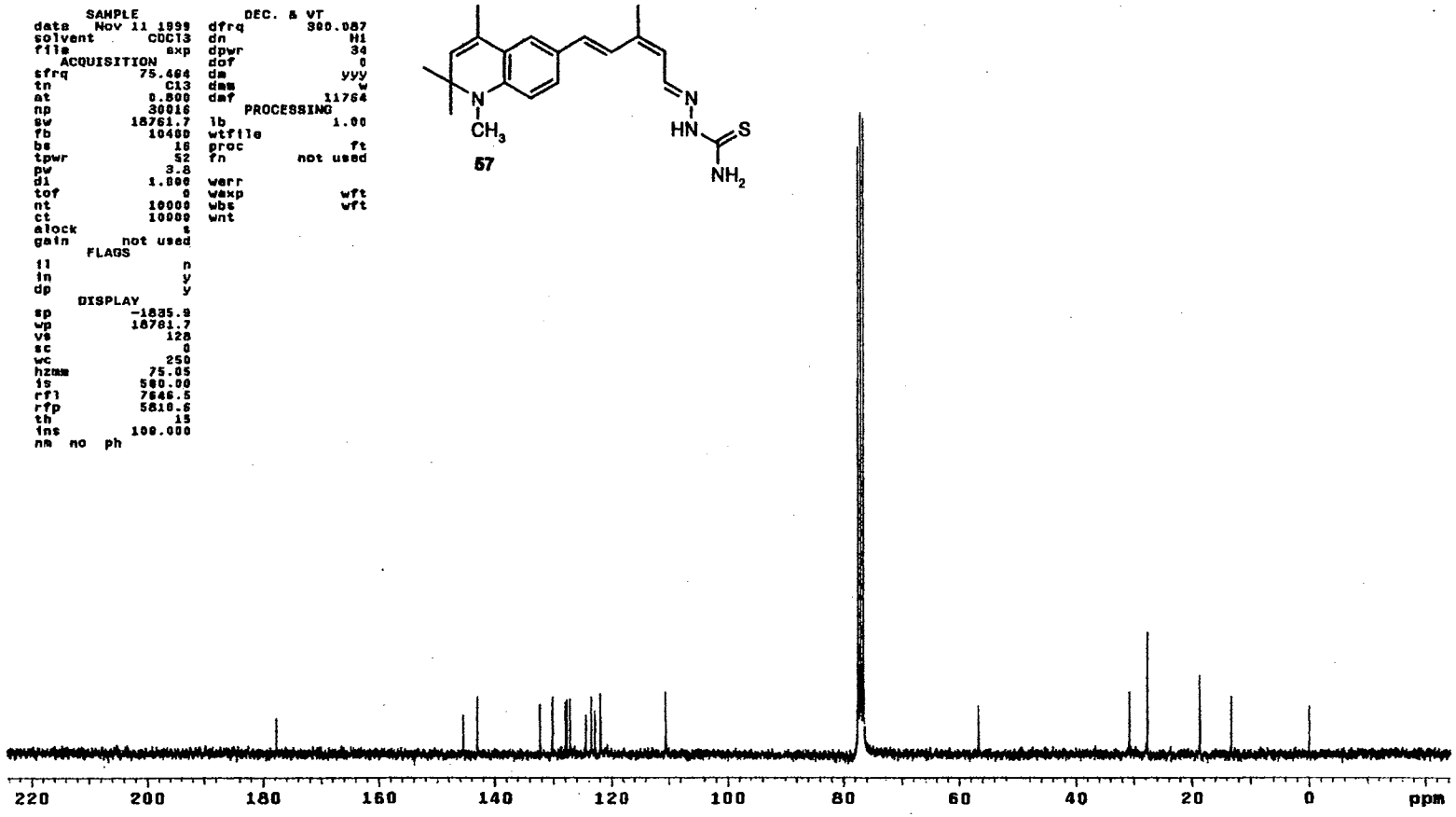
Plate XXXIII

```
13C OBSERVE

exp1  std13c

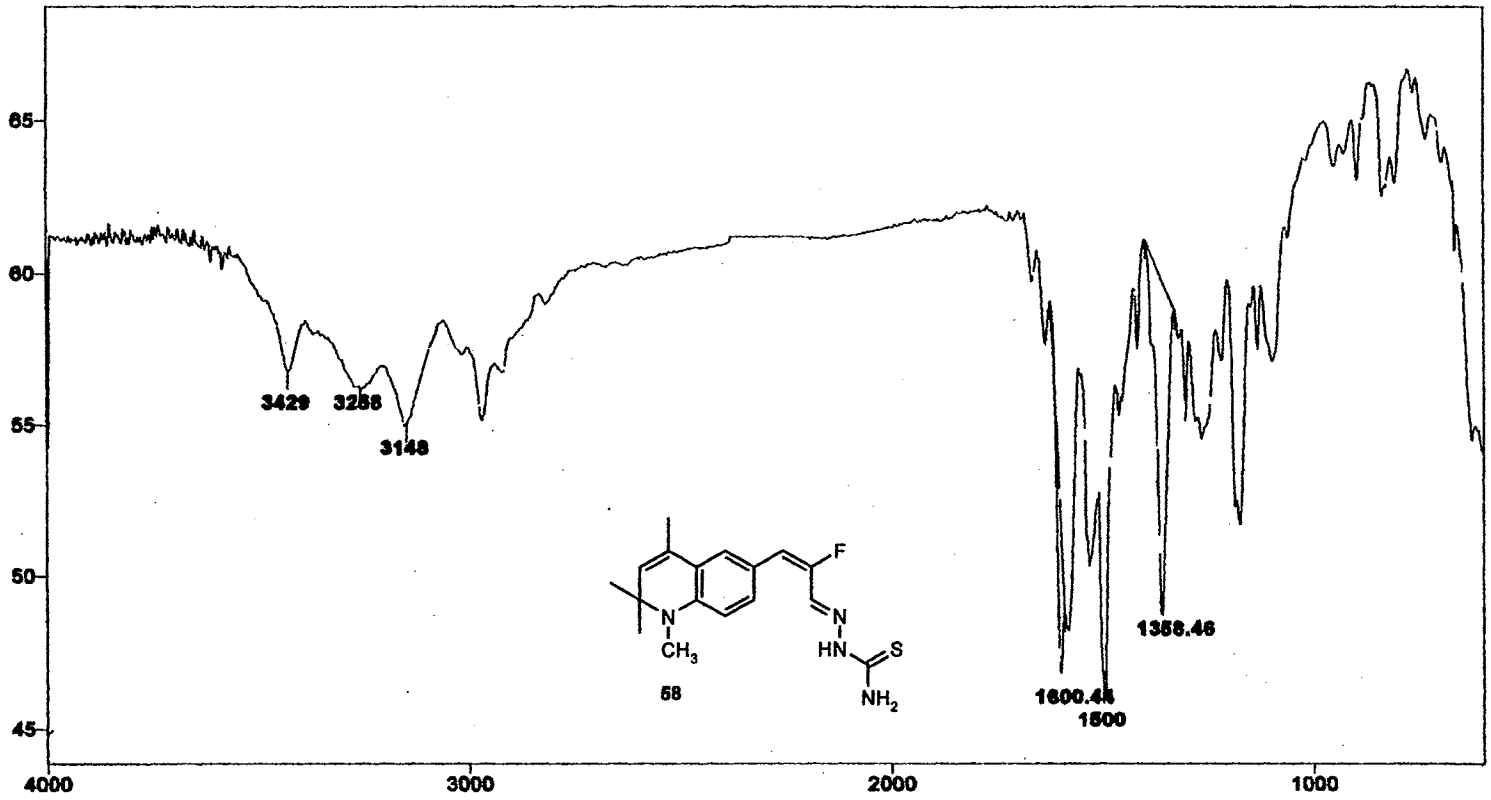
        SAMPLE                DEC. & VT
date   Nov 11 1999   dfrq          300.087
solvent       CDCl3  dn                Hi
file            exp  dpwr              34
    ACQUISITION      dof               0
sfrq          75.464 dm               yyy
tn               C13 dmm                w
at             0.800 dmf            11764
np             30016     PROCESSING
sw           18761.7 lb             1.00
fb             10400 wtfile
bs                16 proc              ft
tpwr              52 fn         not used
pw               3.8
di             1.800 werr
tof                0 wexp             wft
nt             10000 wbs              wft
ct             10000 wnt
alock              s
gain        not used
        FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp           -1885.9
wp           18781.7
vs               128
sc                 0
wc               250
hzmm           75.05
is             500.00
rfl            7646.5
rfp            5810.6
th                15
ins           100.000
nm  no  ph
```


57



^{13}C NMR Spectrum of **57**

Plate XXXIV



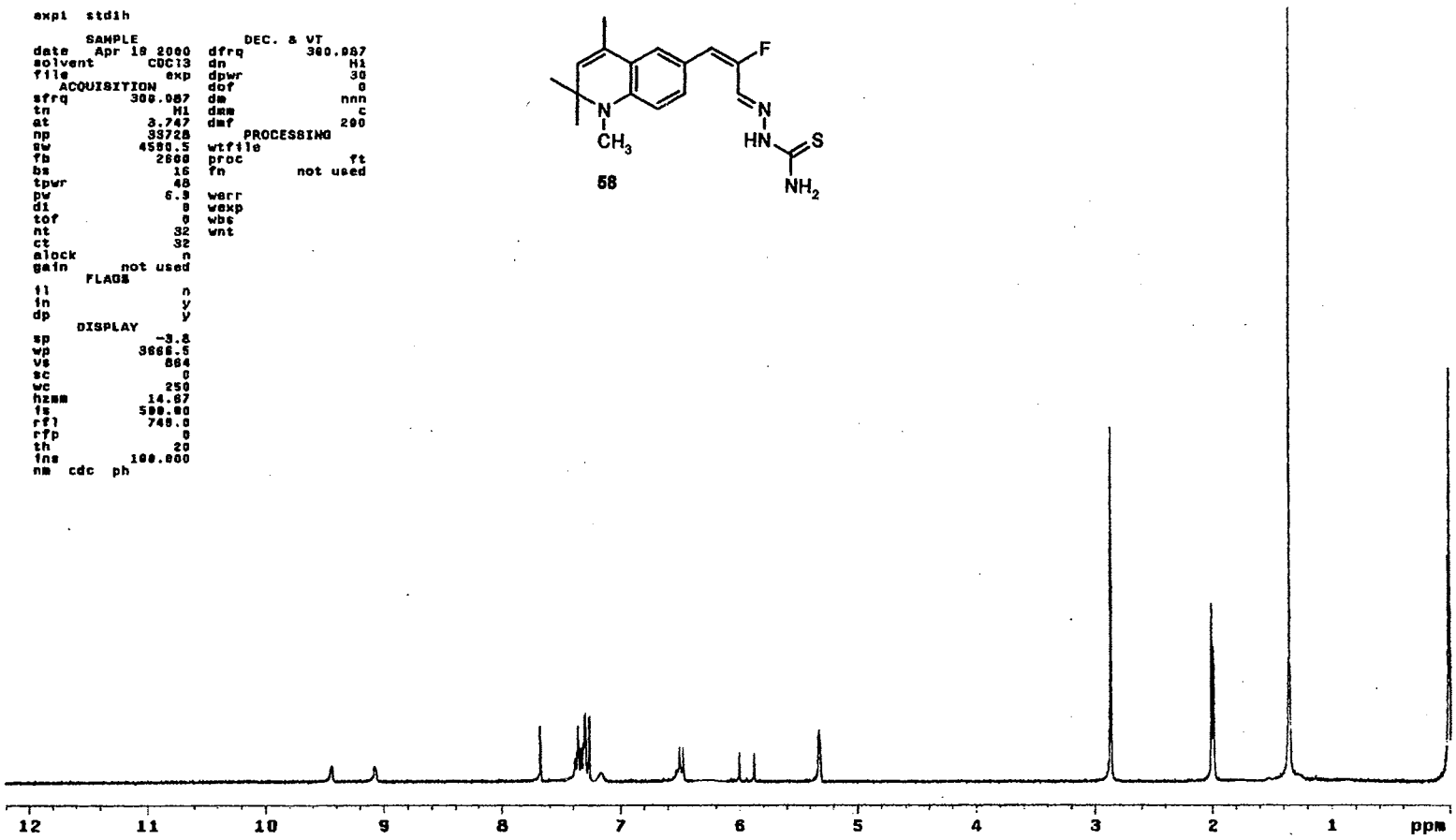
IR Spectrum of **58**

Plate XXXV

```
STANDARD 1H OBSERVE

expl  std1h

      SAMPLE                    DEC. & VT
date   Apr 18 2000   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               30
   ACQUISITION       dof                 0
sfrq        300.087  dm                nnn
tn               H1  dmm                 c
at            3.747  dmf               200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2000  proc              ft
bs               16  fn          not used
tpwr             48
pw              6.3  werr
d1                0  wexp
tof               0  wbs
nt               32  wnt
ct               32
alock             n
gain        not used
      FLAGS
fl                n
in                y
dp                y
      DISPLAY
sp             -3.8
wp           3666.5
vs              864
sc                0
wc              250
hzmm          14.67
is            500.00
rfl           749.0
rfp               0
th               20
ins          100.000
nm  cdc  ph
```

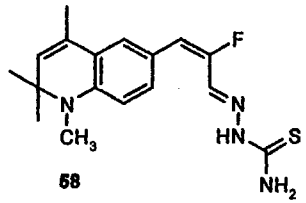
^{1}H NMR Spectrum of **58**

Plate XXXVI

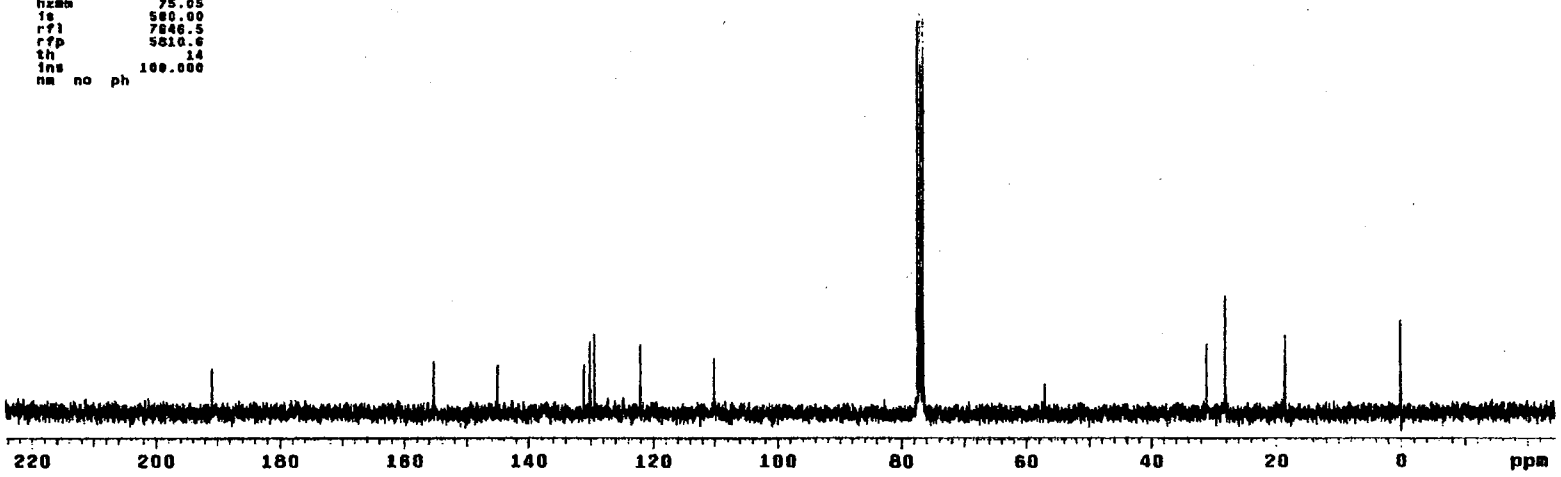
```
13C OBSERVE

expl  std13c

        SAMPLE                DEC. & VT
date   Apr 19 2000  dfrq          300.087
solvent       CDCl3 dn                 H1
file            exp dpwr               34
   ACQUISITION      dof                 0
sfrq         75.464 dm                yyy
tn              C13 dmm                 w
at            0.800 dmf             11764
np            30016      PROCESSING
sw          18761.7 lb              1.00
fb            10400 wtfile
bs               16 proc               ft
tpwr             52 fn          not used
pw              3.8
d1            1.000 werr
tof               0 wexp              wft
nt             4056 wbs               wft
ct             4096 wnt
alock             s
gain        not used
       FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -1835.9
wp          18761.7
vs              167
sc                0
wc              250
hzmm          75.05
is            500.00
rfl           7846.5
rfp           5810.6
th                14
ins          100.000
nm  no  ph
```



58



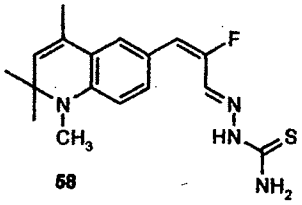
^{13}C NMR Spectrum of **58**

Plate XXXVII

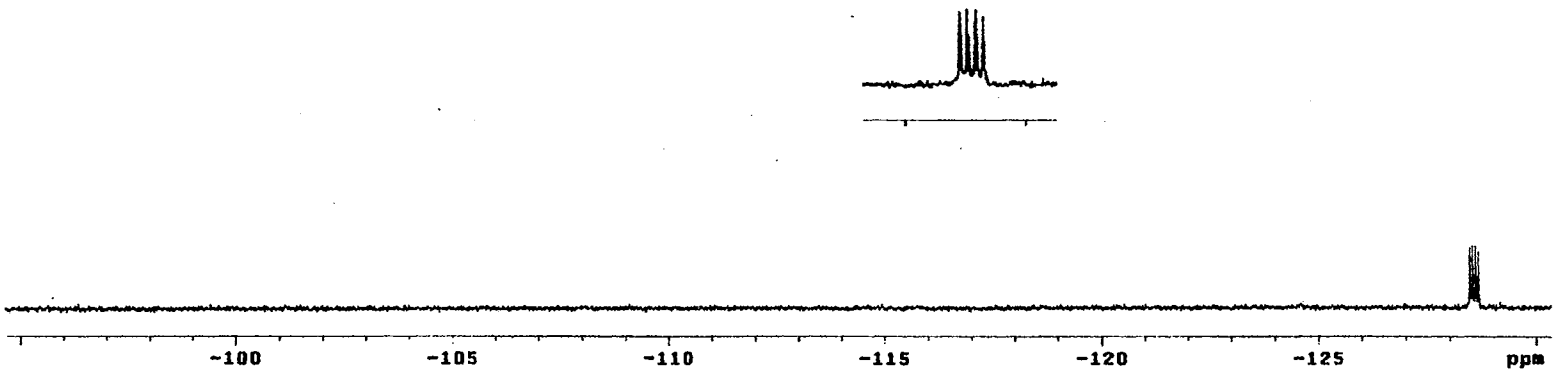
```
13C OBSERVE

expl  std13c

        SAMPLE                DEC. & VT
date    Feb 22 2008   dfrq          300.087
solvent        CDCl3  dn                 H1
file             exp  dpwr               34
   ACQUISITION        dof                 0
sfrq          282.333 dm                nnn
tn                F19 dmm                 w
at              0.800 dmf             11764
np              30016     PROCESSING
sw            18761.7 lb                1.00
fb              10400 wtfile
bs                 16 proc                ft
tpwr               52 fn          not used
pw               3.8
d1              1.000 werr
tof                 0 wexp               wft
nt               1024 wbs               wft
ct                112 wnt
alock               n
gain        not used
       FLAGS
i1                  n
in                  y
dp                  y
      DISPLAY
sp          -35801.4
wp           10083.4
vs                 12
sc                  0
wc                250
hzcm            40.33
is             500.00
rf1          38748.2
rfp                 0
th                 10
ins            100.000
nm  no  ph
```

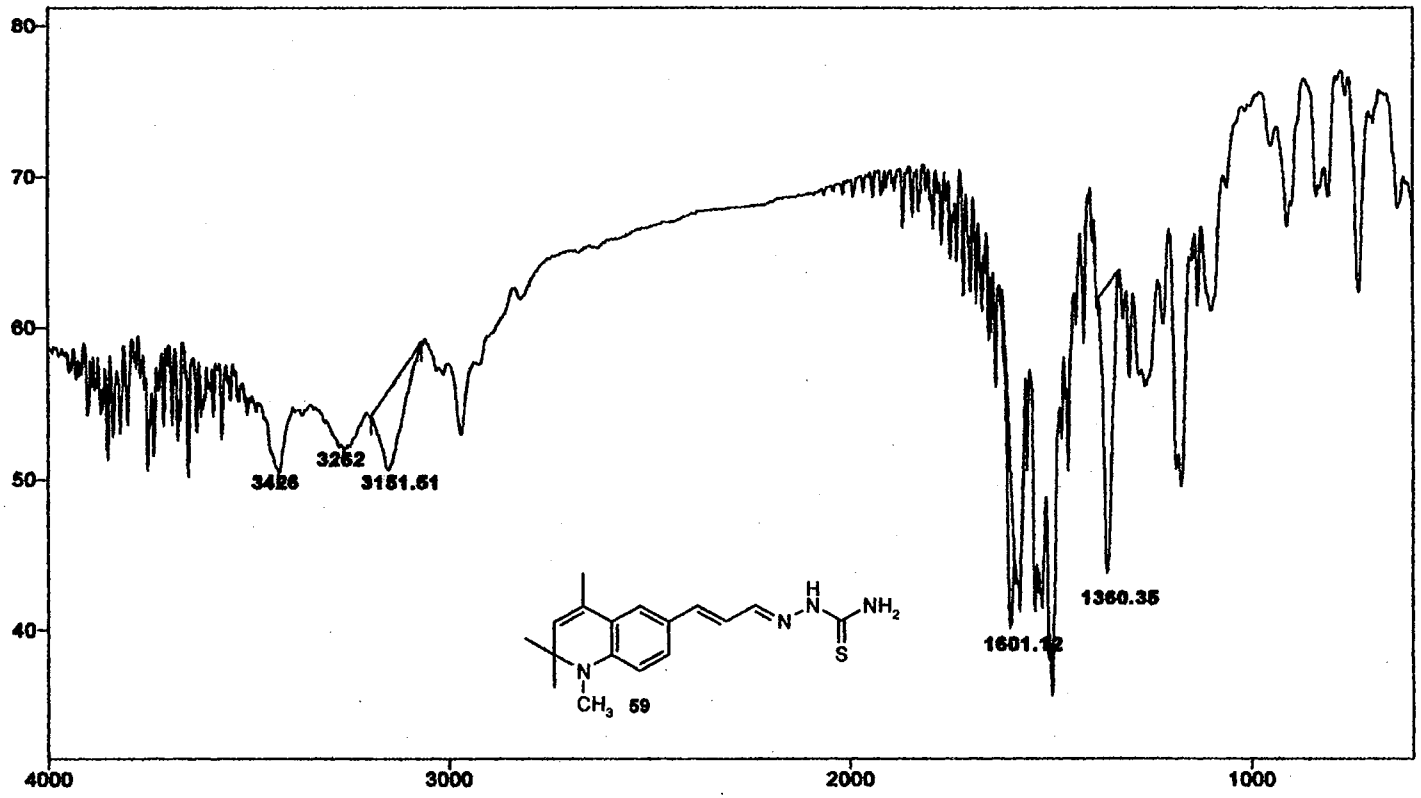


58



^{18}F NMR Spectrum of **58**

Plate XXXVIII

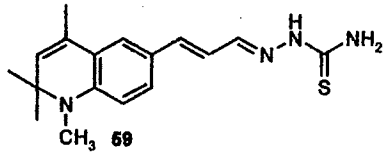


IR Spectrum of **59**

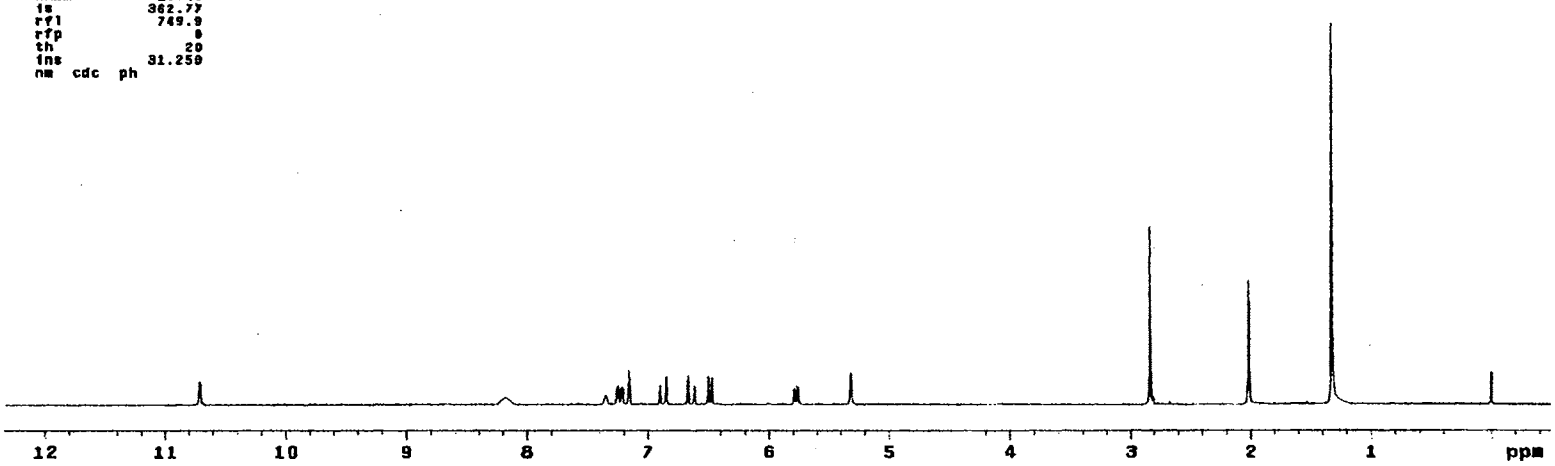
Plate XXXIX

```
STANDARD 1H OBSERVE

exp1  std1h
      SAMPLE
date    Jul  8 1999
solvent       CDCl3
file            exp
   ACQUISITION
sfrq        300.087
tn               H1
at             3.747
np             33728
sw            4500.5
fb              2600
bs                16
tpwr              48
pw               3.0
d1                 0
tof                0
nt                16
ct                16
alock              n
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp            -146.8
wp            3849.8
vs                 81
sc                 0
wc               250
hzmm           15.49
is            362.77
rf1            749.9
rfp                0
th                 20
ins            31.250
nm  cdc  ph
      DEC. & VT
dfrq        300.087
dn               H1
dpwr             39
dof               0
dm              nnn
dmm               c
dmf             200
      PROCESSING
wtfile
proc             ft
fn         not used
werr
wexp            wft
wbs
wnt
```



59



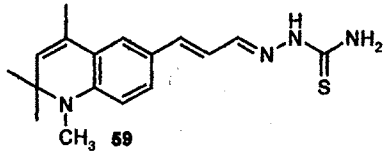
^{1}H NMR Spectrum of **59**

Plate XL

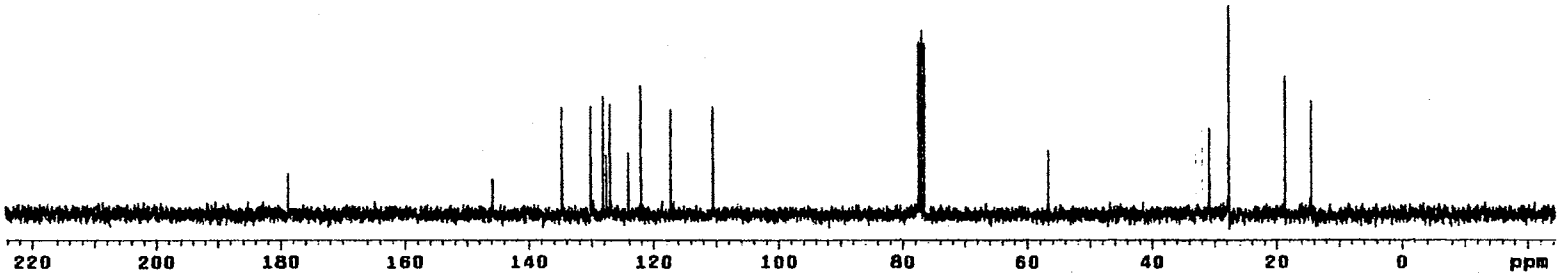
```
13C OBSERVE

expl  std13c

      SAMPLE                 DEC. & VT
date   Jul  8 1989  dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof               0
efrq          75.464  dm              yyy
tn               C13  dmm               w
at             0.880  dmf           11764
np            30016      PROCESSING
sw          18761.7  lb             1.00
fb           10498  wtfile
ba              18  proc              ft
tpwr            52  fn          not used
pw             3.8
d1           1.000  werr
tof              0  wexp            wft
nt            1024  wbs             wft
ct             256  wnt
alock            s
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -1837.0
wp          18761.7
vs               52
sc                0
wc              250
hzmm          75.05
is           500.00
rfl          7647.6
rfp          5810.6
th                4
ins         100.000
nm  no  ph
```

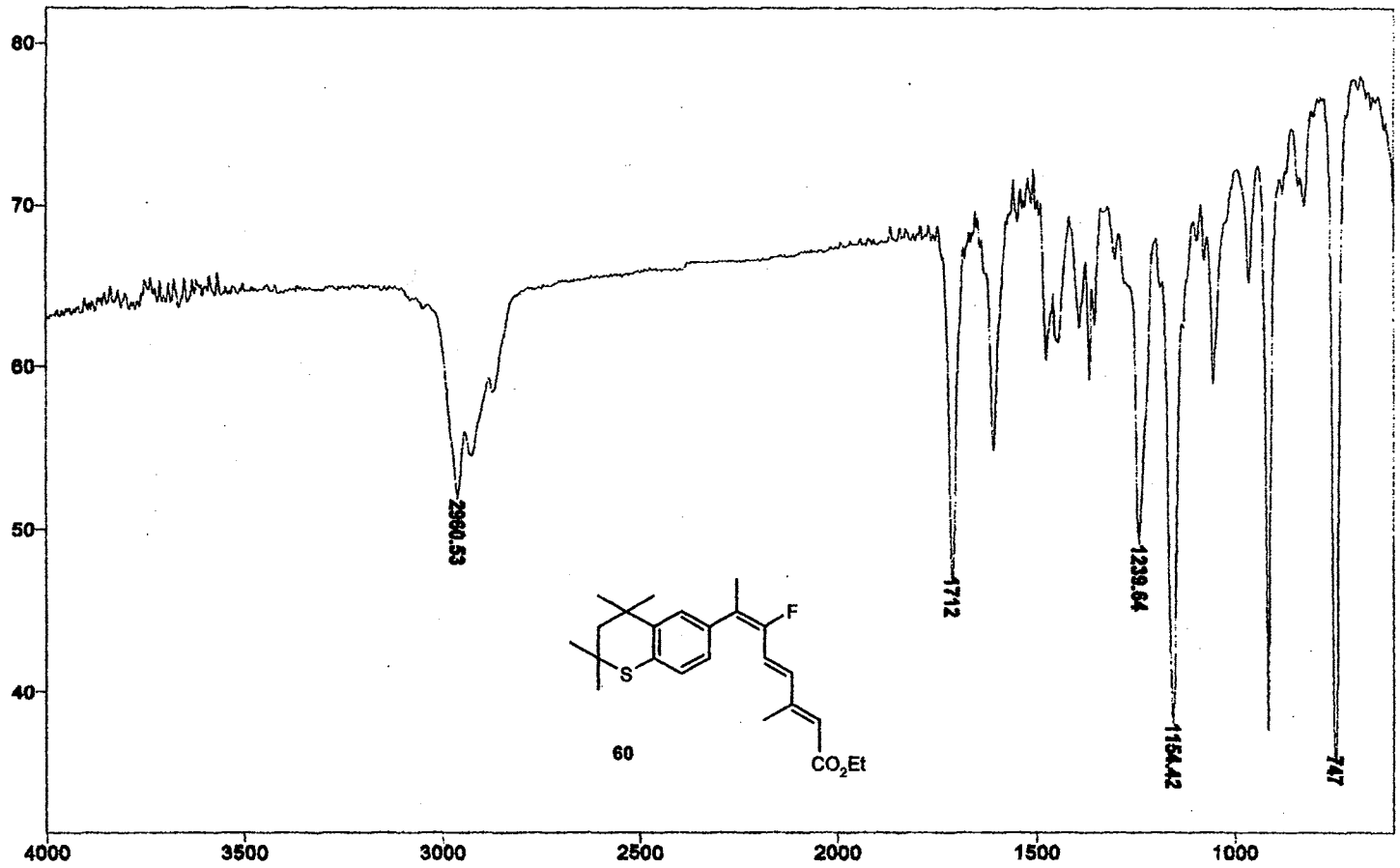


59



^{13}C NMR Spectrum of **59**

Plate XLI



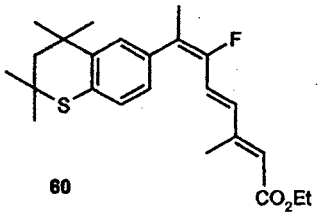
IR Spectrum of **60**

Plate XLII

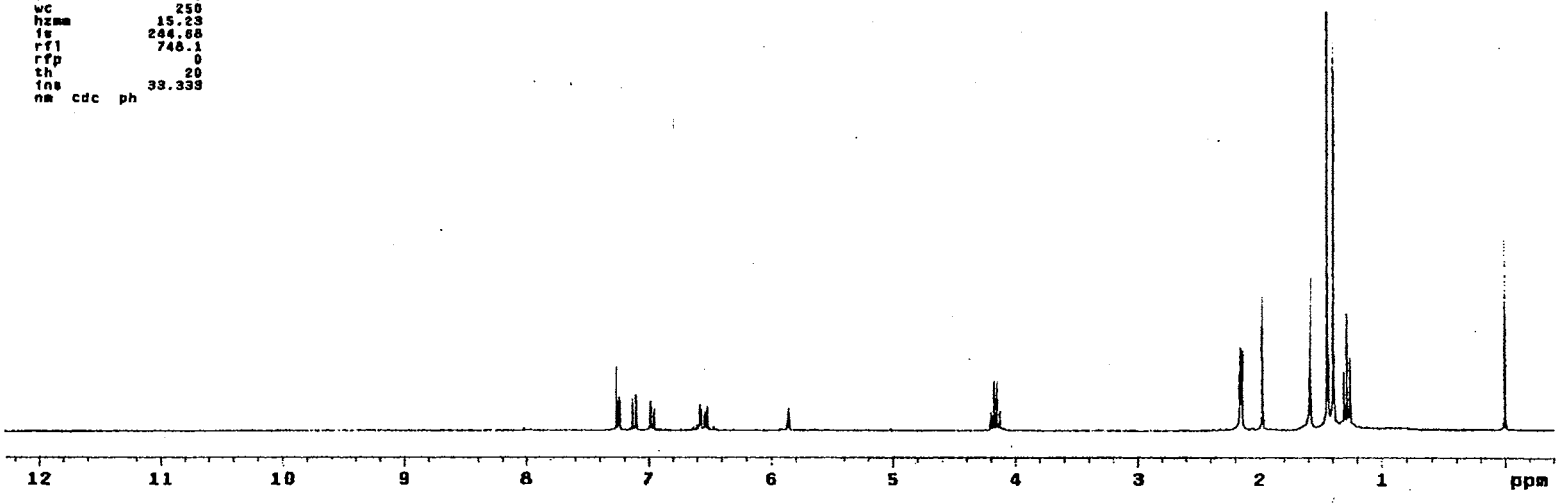
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date   Oct 30 1995   dfrq        300.057
solvent      CDCl3   dn              H1
file           exp   dpwr            30
   ACQUISITION       dof              0
sfrq        300.057  dm             nnn
tn              H1   dmm              c
at           3.747   dmf            200
np           39728      PROCESSING
sw          4500.5   wtfile
fb            2000   proc            ft
bs              16   fn        not used
tpwr            48
pw             5.9   werr
d1               0   wexp
tof              0   wbs
nt              32   wnt
ct              32
alock            n
gain      not used
      FLAGS
i1               n
in               y
dp               y
      DISPLAY
sp          -121.3
wp          3608.5
vs              78
sc               0
wc             250
hzcm         15.23
ls          244.68
rf1          748.1
rfp              0
th              20
ins         33.333
nm  cdc  ph
```

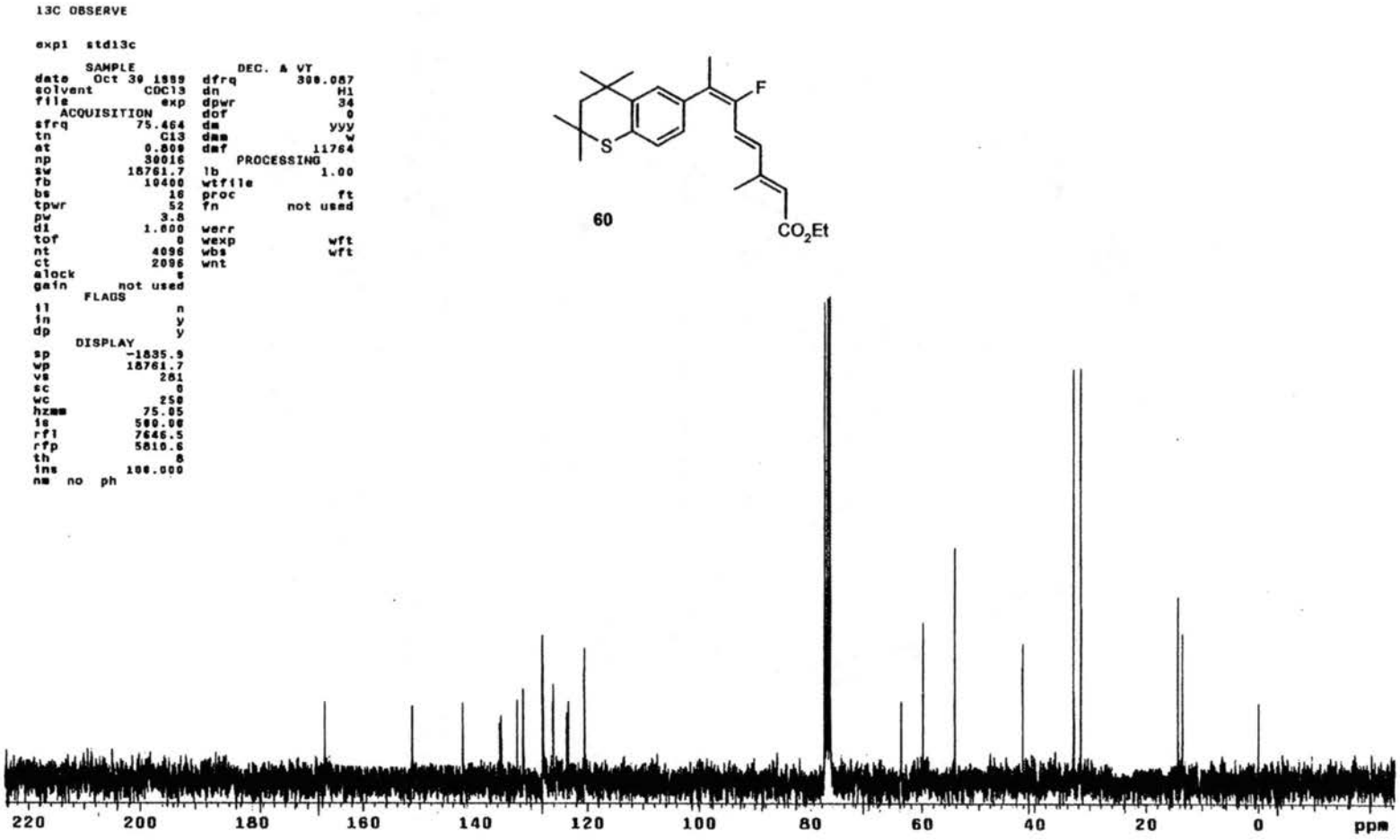


60



^{1}H NMR Spectrum of **60**

Plate XLIII



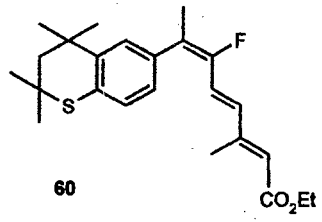
^{13}C NMR Spectrum of **60**

Plate XLIV

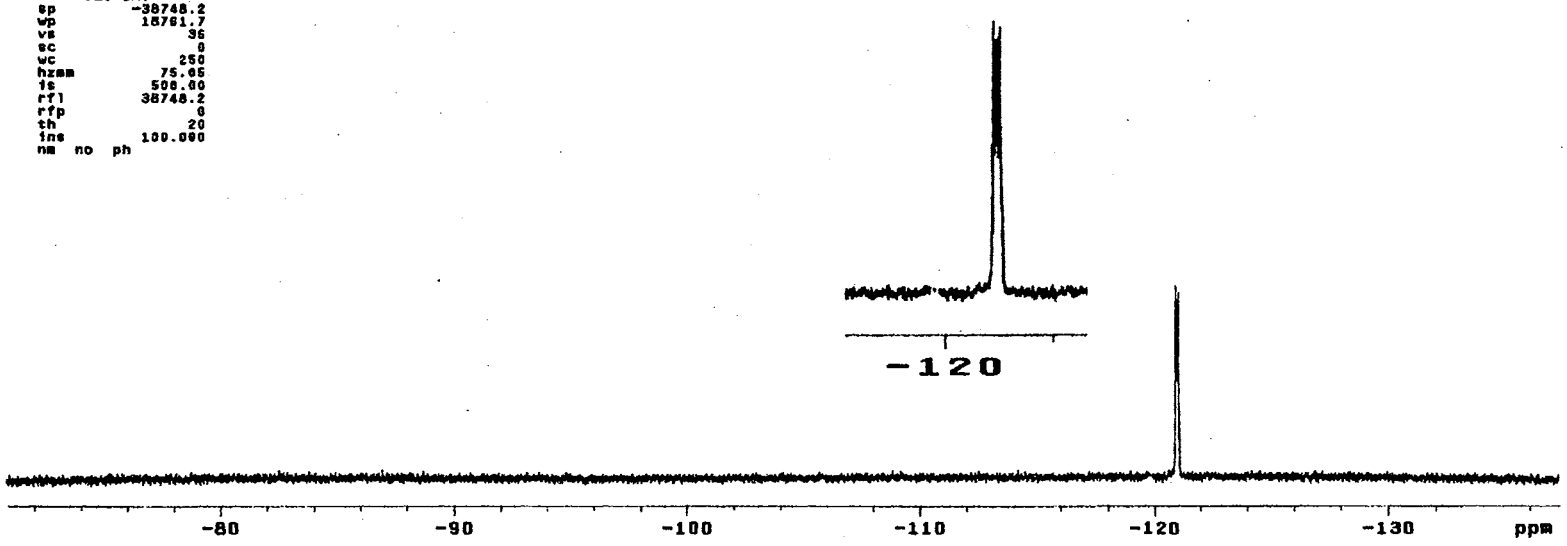
```
13C OBSERVE

expl  std13c

      SAMPLE                 DEC. & VT
date   Oct 30 1999   dfrq          300.087
solvent       CDCl3  dn                Hl
file            exp  dpwr              34
   ACQUISITION       dof               0
sfrq        282.333  dm              nnn
tn              F19  dmm               w
at            8.600  dmf           11764
np            30816     PROCESSING
sw          18761.7  lb             1.00
fb            10400  wtfile
bs               16  proc             ft
tpwr             52  fn         not used
pw              3.8
d1            1.000  werr
tof               0  wexp            wft
nt             1024  wbs             wft
ct              112  wnt
alock             n
gain        not used
      FLAGS
fl                n
fn                y
dp                y
      DISPLAY
sp          -38748.2
wp           18761.7
vs                36
sc                 0
wc               250
hzcm           75.05
is             500.00
rfl         38748.2
rfp                0
th                20
ins           100.000
nm  no  ph
```

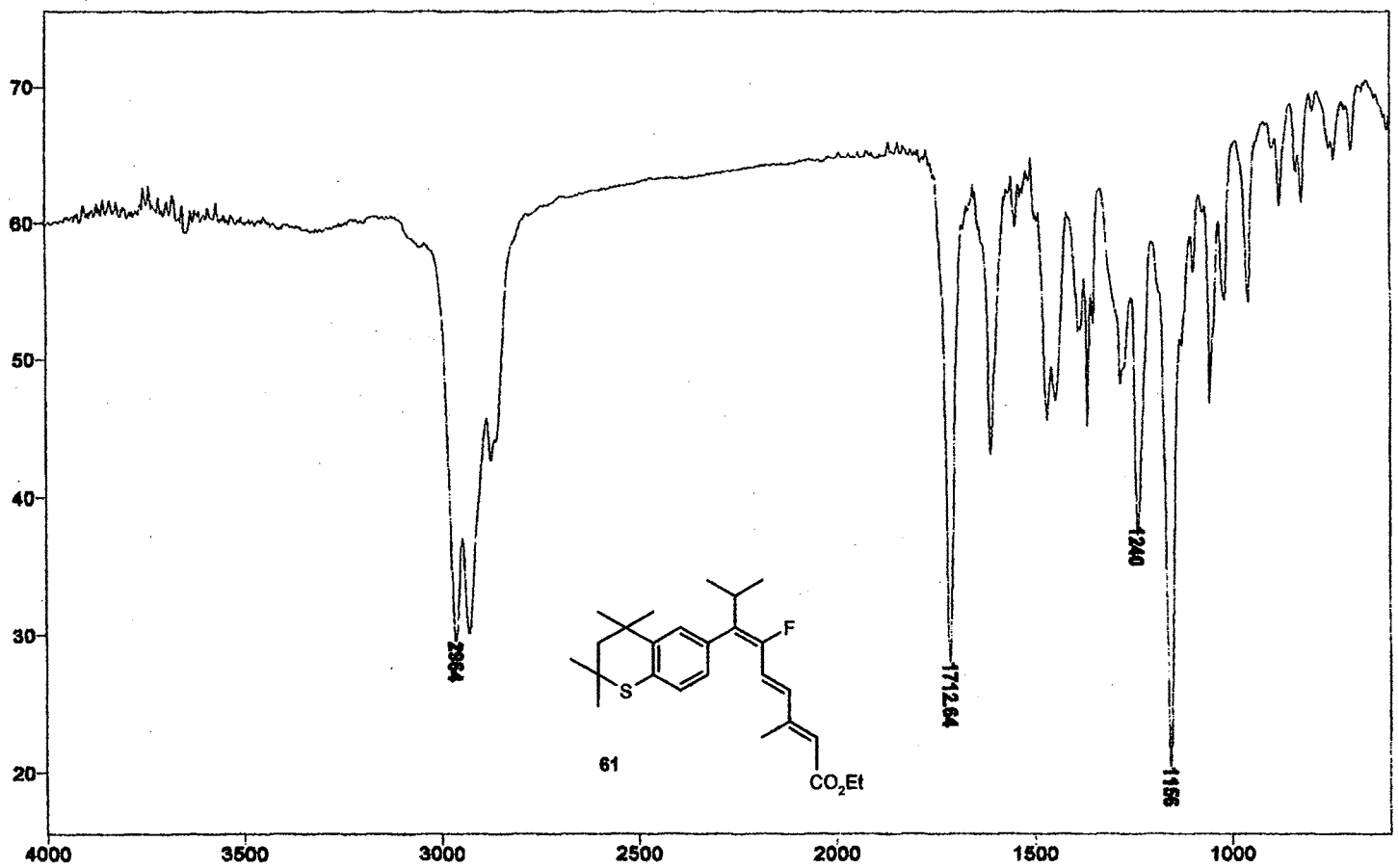


60



^{19}F NMR Spectrum of **60**

Plate XLV



IR Spectrum of **61**

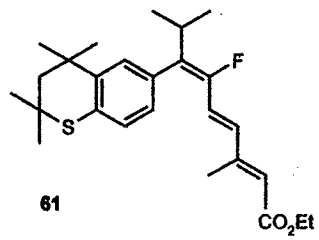
Plate XLVI

```
STANDARD 1H OBSERVE

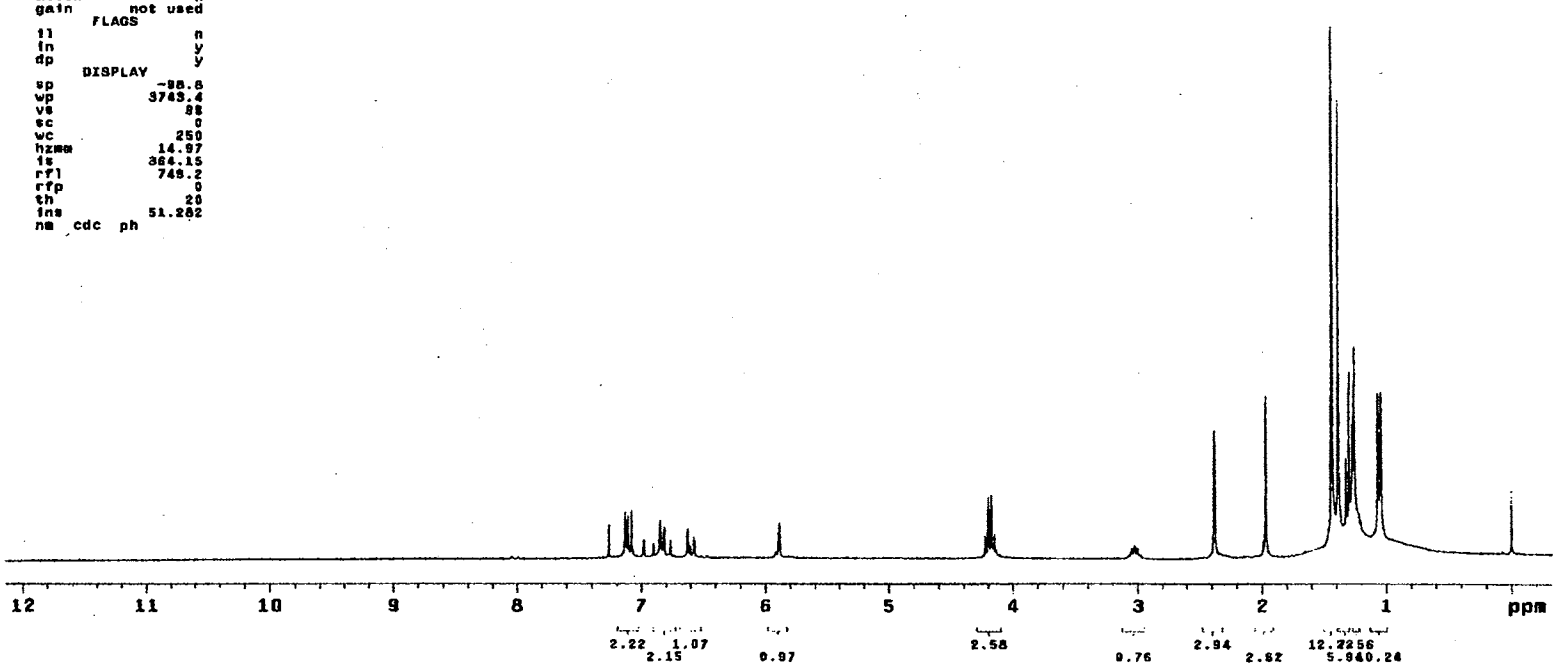
exp1  std1h

      SAMPLE
date   Nov 10 1999
solvent       CDCl3
file            exp
   ACQUISITION
sfrq        300.067
tn               H1
at             3.747
np             33728
sw            4500.5
fb             2880
bs                16
tpwr              48
pw               8.9
d1                 0
tof                0
nt                16
ct                16
alock              n
gain       not used
      FLAGS
fl                 n
in                 y
dp                 y
     DISPLAY
sp            -88.8
wp            3743.4
vs                88
sc                 0
wc               250
hzmm           14.97
is            364.15
rfl            748.2
rfp                0
th                20
ins            51.282
nm  cdc  ph

      DEC. & VT
dfrq         300.067
dn               H1
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
     PROCESSING
wtfile
proc              ft
fn         not used
werr
wexp
wbs
wnt
```

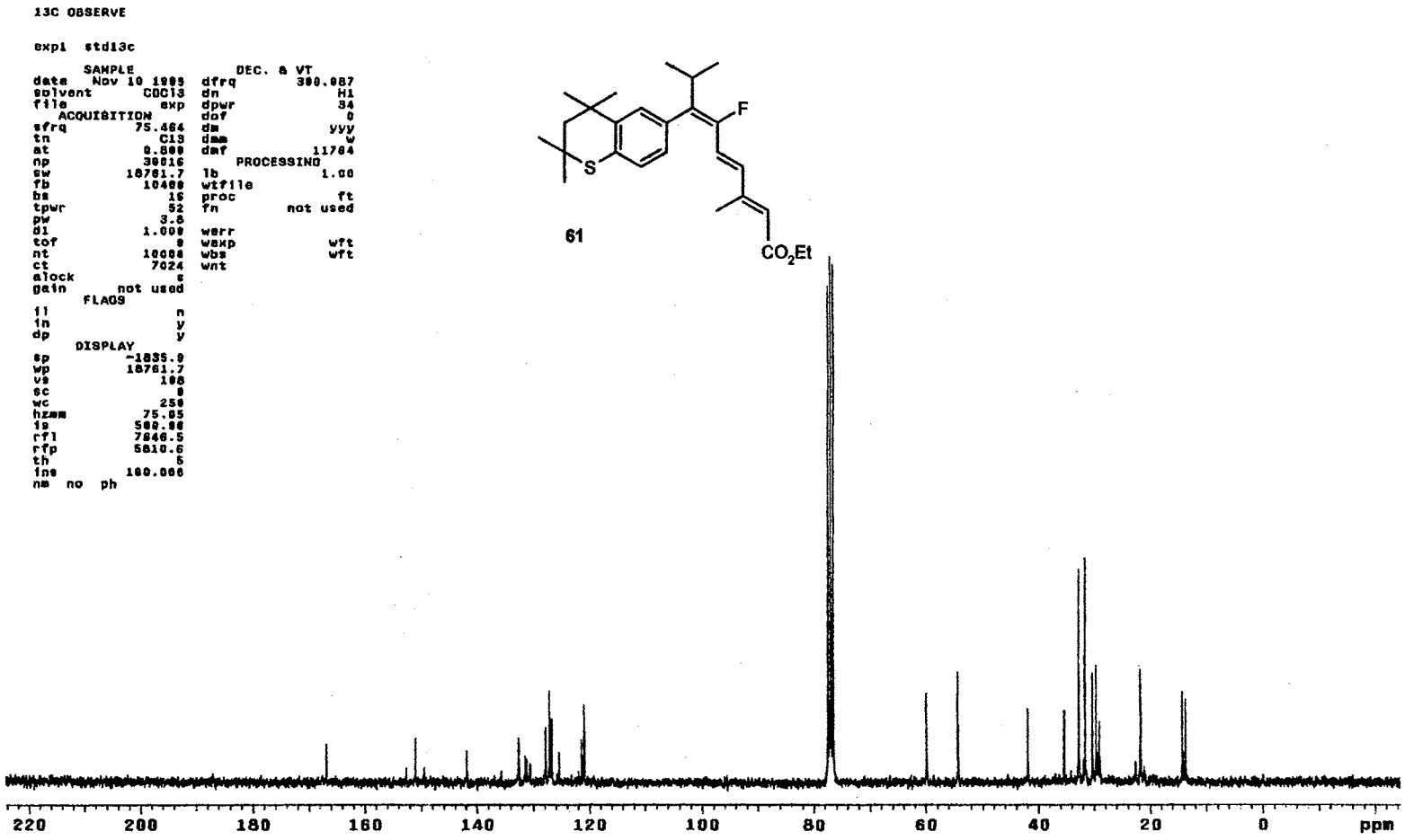


61



^{1}H NMR Spectrum of **61**

Plate XLVII



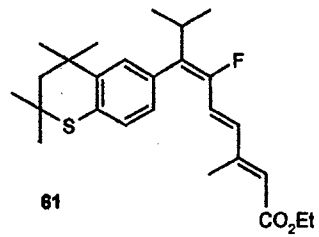
^{13}C NMR Spectrum of **61**

Plate XLVIII

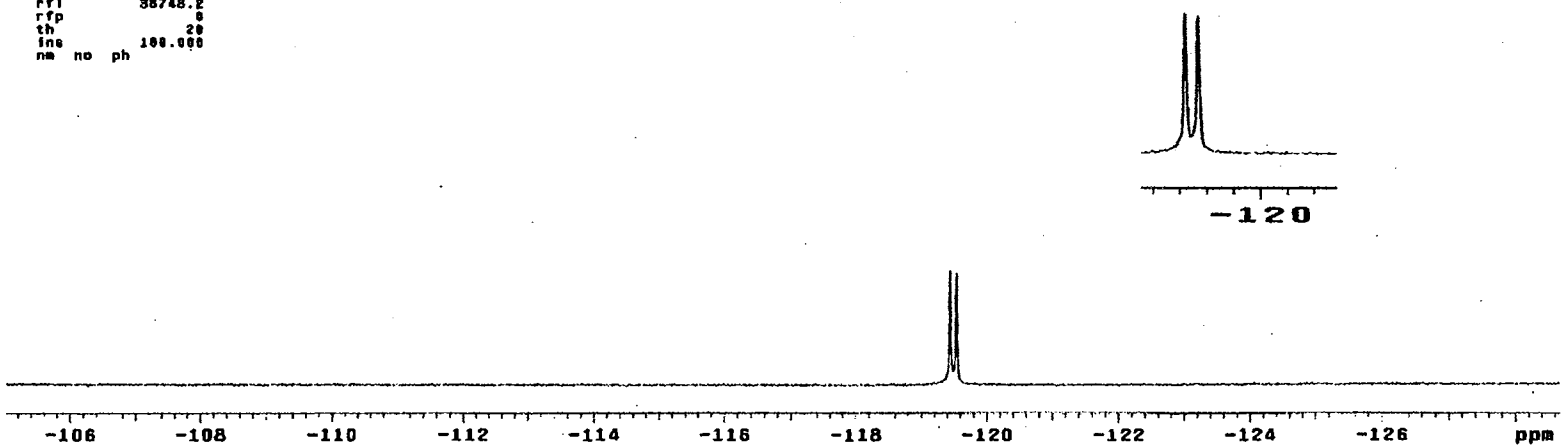
```
13C OBSERVE

expl  std13c

        SAMPLE                DEC. & VT
date   Nov 10 1999   dfrq          380.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
    ACQUISITION      dof                 0
sfrq        282.333  dm                nnn
tn              F19  dmm                 w
at            0.800  dmf             11764
np            38016      PROCESSING
sw          18761.7  lb                1.00
fb            10400  wtfile
bs               16  proc                ft
tpwr             52  fn           not used
pw              3.8
d1            1.000  werr
tof               0  wexp               wft
nt             1024  wbs               wft
ct              112  wnt
alock             n
gain        not used
       FLAGS
f1                n
in                y
dp                y
      DISPLAY
sp          -36333.0
wp           6681.1
vs                22
sc                 0
wc               250
hzcm           26.72
is            500.00
rfl          35748.2
rfp                0
th                20
ins          100.000
nm  no  ph
```

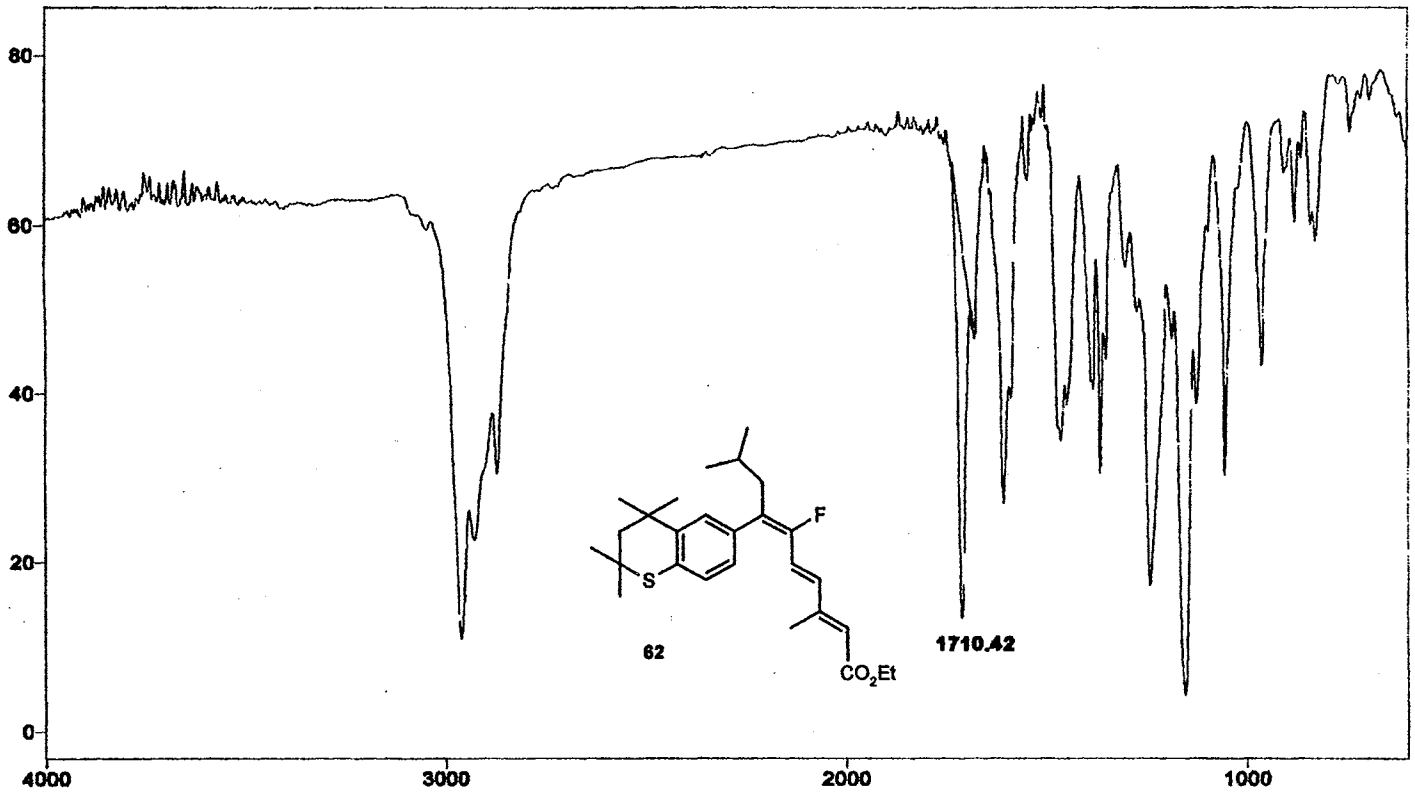


61



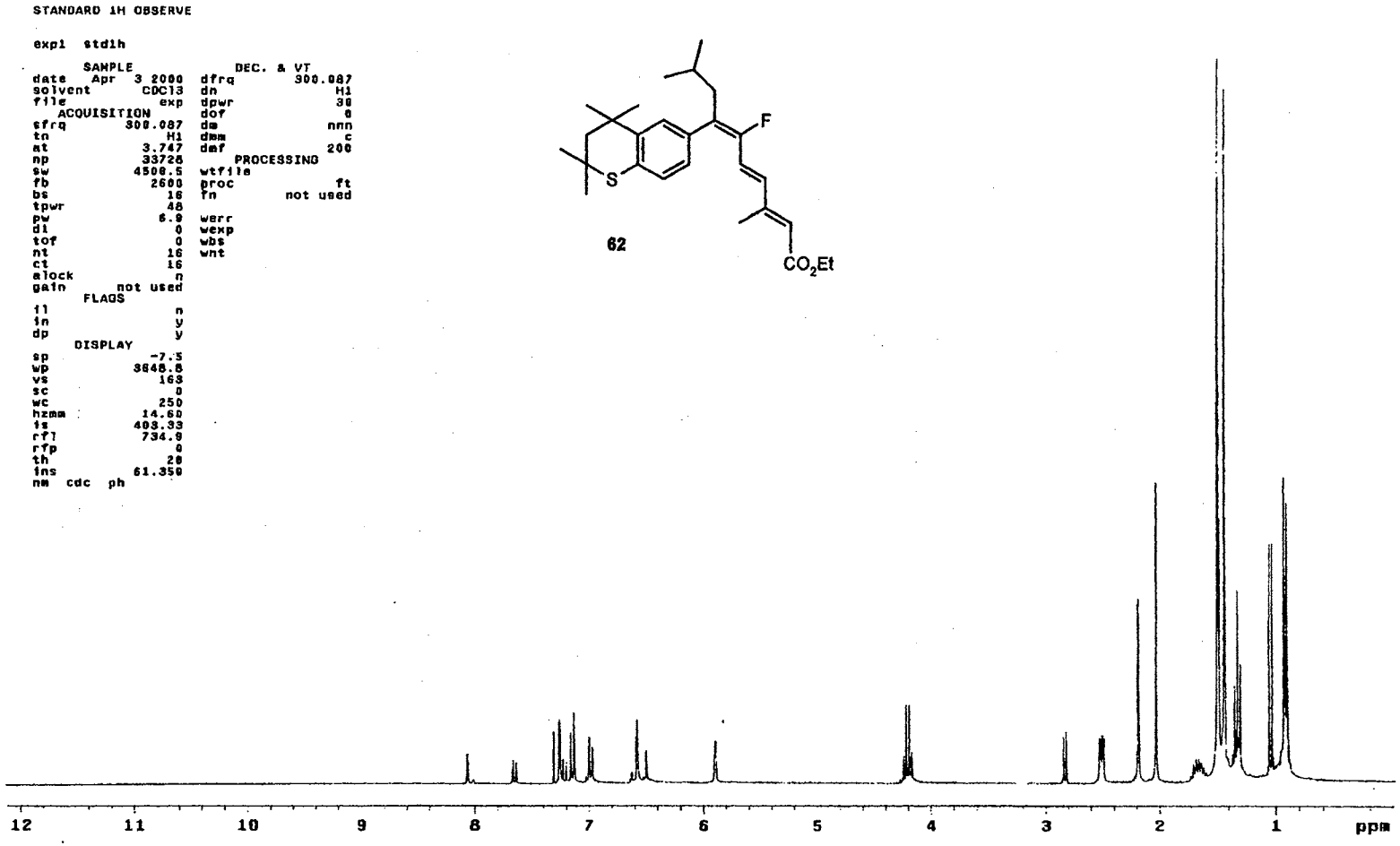
^{19}F NMR Spectrum of **61**

Plate XLIX



IR Spectrum of **62**

Plate L



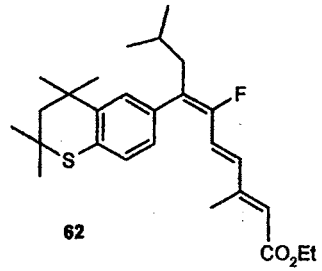
^{1}H NMR Spectrum of **62**

Plate LI

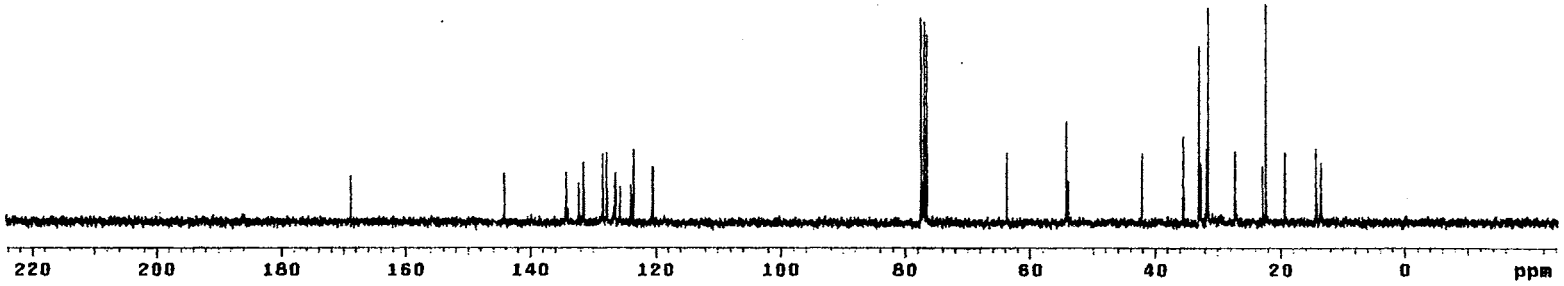
```
13C OBSERVE

expl  std13c

        SAMPLE                DEC. & VT
date    Apr  3 2000   dfrq        300.087
solvent       CDCl3   dn             H1
file            exp   dpwr           34
   ACQUISITION        dof             0
sfrq         75.464   dm            yyy
tn              C13   dmm             w
at            9.500   dmf         11764
np            30016      PROCESSING
sw          18761.7   lb           1.00
fb            10400   wtfile
bs               16   proc           ft
tpwr             52   fn       not used
pw              3.8
d1            1.000   werr
tof               0   wexp          wft
nt             1024   wbs           wft
ct              736   wnt
alock             s
gain        not used
       FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -1835.9
wp          18761.7
vs               40
sc                0
wc              250
hzmm          75.05
is           500.00
rfl          7646.5
rfp          5810.6
th                4
ins         100.000
nm  no  ph
```



62



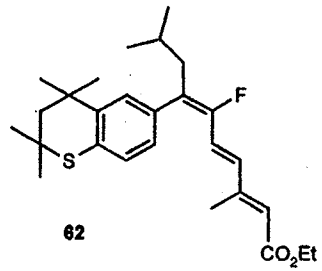
^{13}C NMR Spectrum of **62**

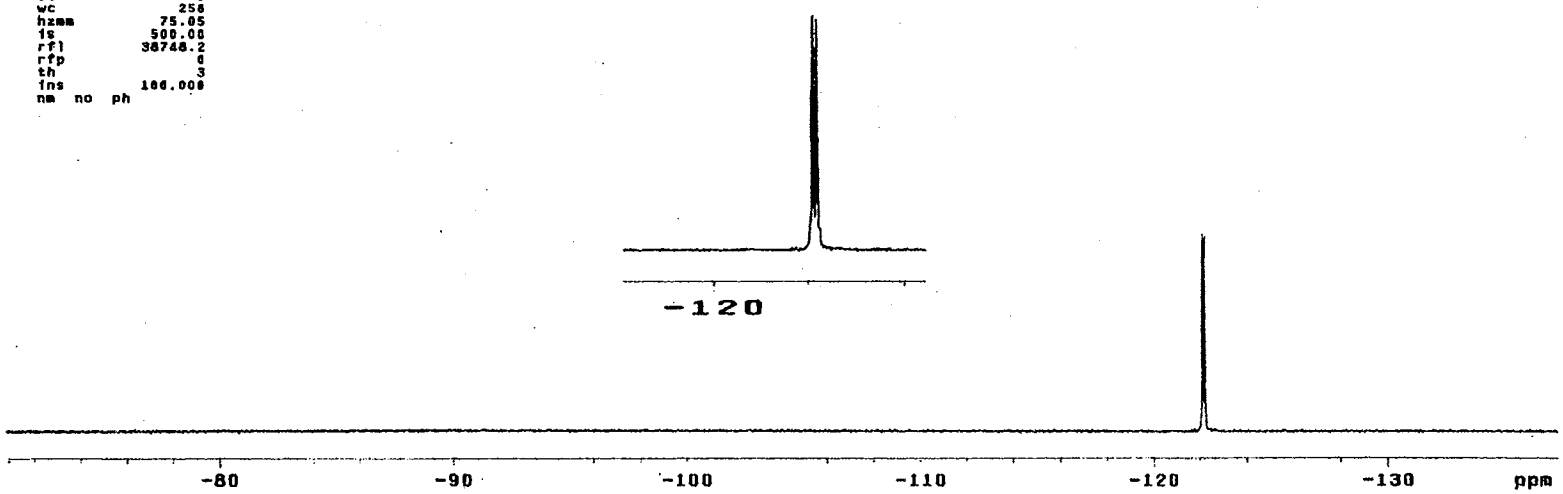
Plate LII

```
13C OBSERVE

exp1  std13c

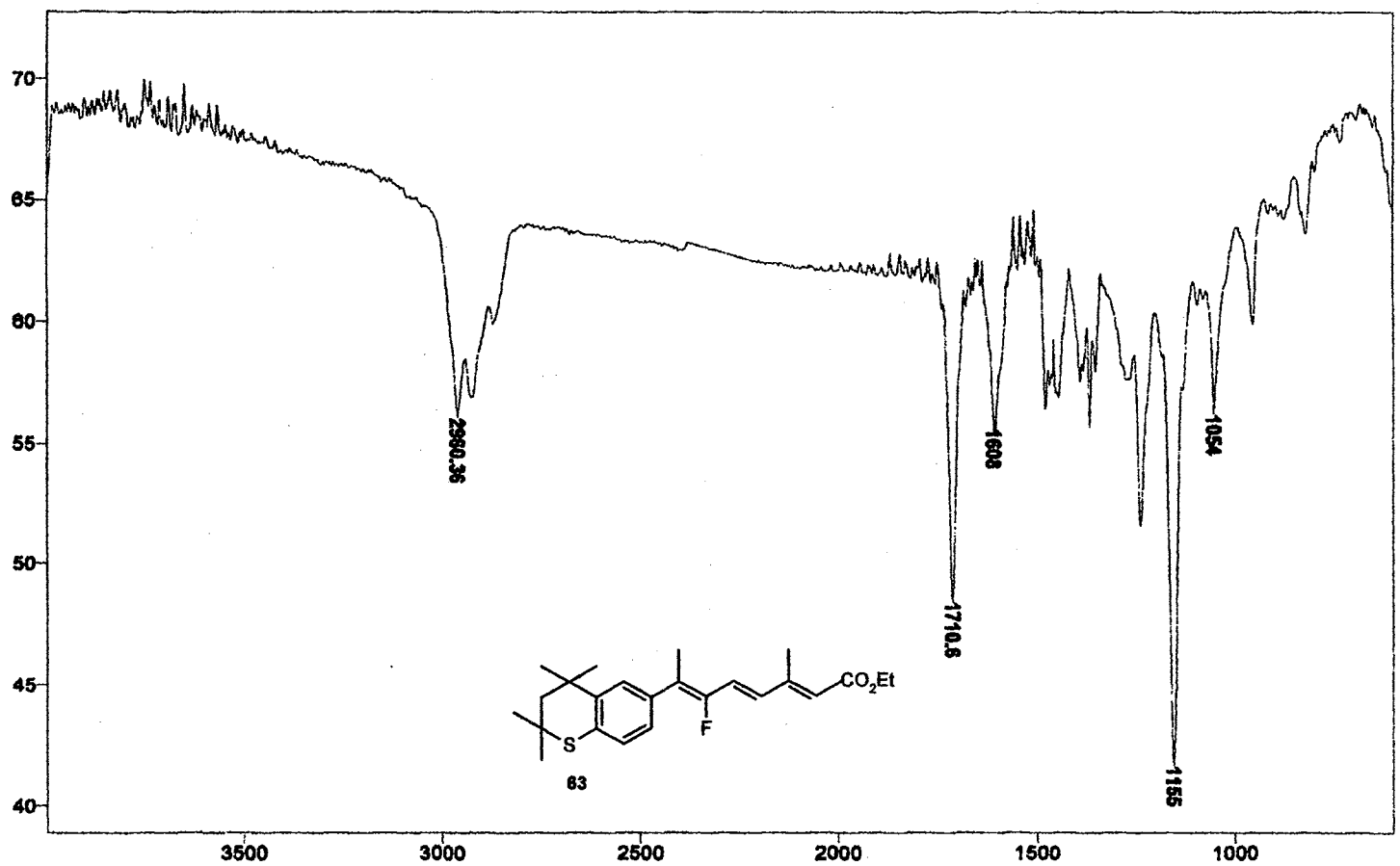
      SAMPLE                    DEC. & VT
date    Apr  3 2000   dfrq          380.087
solvent       CDCl3   dn                 H1
file            exp   dpwr               34
   ACQUISITION        dof                 0
sfrq          282.333 dm                  n
tn                F19 dmm                 w
at              0.808 dmf             11764
np              38016     PROCESSING
sw           18761.7  lb               1.00
fb             10400  wtfile
bs                16  proc               ft
tpwr              52  fn         not used
pw               3.8
d1             1.000  werr
tof                0  wexp             wft
nt              1024  wbs              wft
ct                48  wnt
alock              n
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp          -38748.2
wp           18761.7
vs                97
sc                 0
wc               256
hzmm           75.05
is            500.00
rfl           38748.2
rfp                0
th                 3
ins            100.000
nm  no  ph
```





^{19}F NMR Spectrum of **62**

Plate LIII



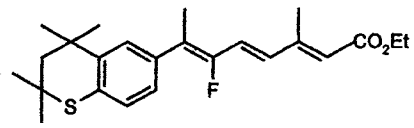
IR Spectrum of **63**

Plate LIV

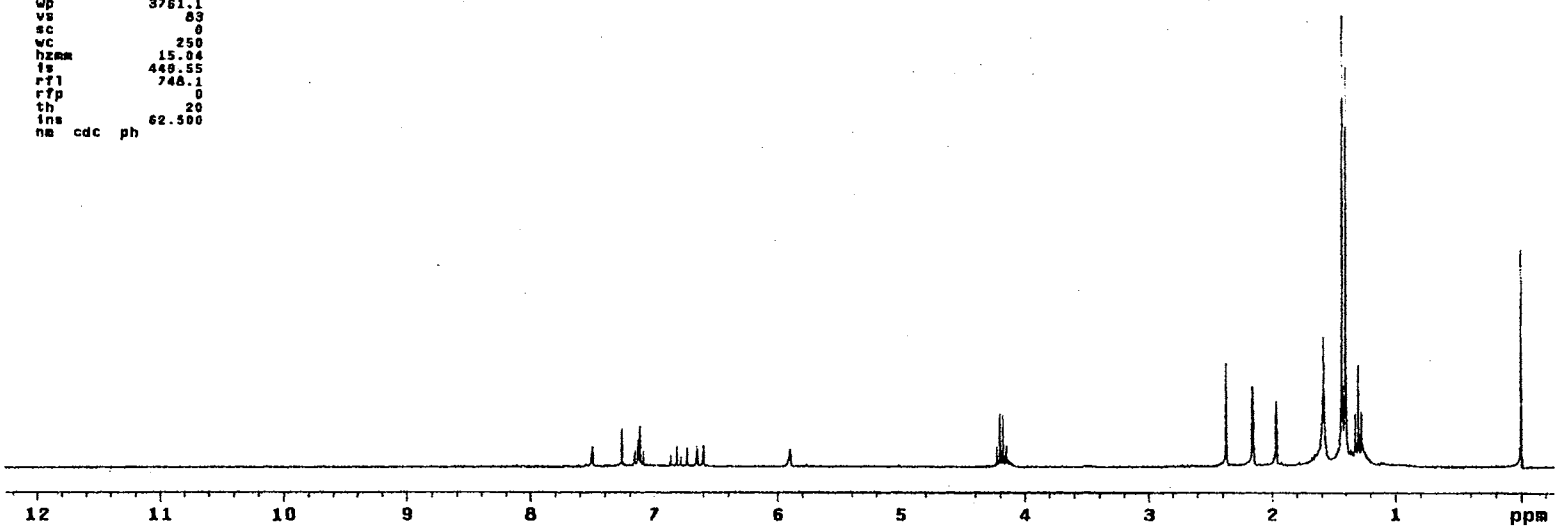
```
STANDARD 1H OBSERVE

exp1  stdih

        SAMPLE                  DEC. & VT
date    Oct 30 1999     dfrq        380.087
solvent        CDCl3    dn               H1
file             exp    dpwr             30
   ACQUISITION          dof               0
sfrq        380.087     dm              nnn
tn               H1     dmm               c
at             3.747    dmf             200
np             33728        PROCESSING
sw            4580.5    wtfile
fb             2600     proc             ft
bs               16     fn          not used
tpwr             48
pw              6.9     werr
d1                0     wexp
tof               0     wbs
nt               32     wnt
ct               32
alock             n
gain        not used
       FLAGS
ii                n
in                y
dp                y
     DISPLAY
sp            -79.9
wp           3761.1
vs               83
sc                0
wc              250
hzcm          15.04
hs           449.55
rf1           748.1
rfp               0
th               20
ins          62.500
nm  cdc  ph
```



63



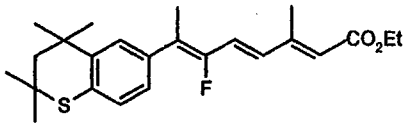
^{1}H NMR Spectrum of **63**

Plate LV

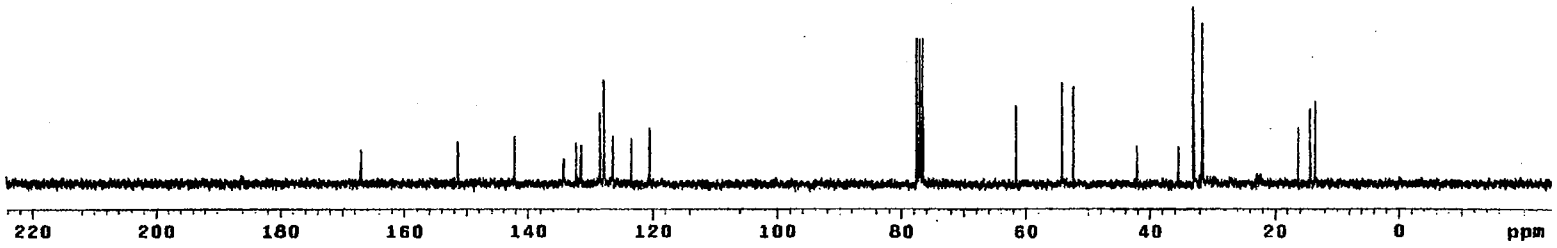
```
13C OBSERVE

expl  std13c

        SAMPLE                    DEC. & VT
date   Apr  3 2000        dfrq          300.087
solvent       CDCl3       dn                 H1
file            exp       dpwr               34
   ACQUISITION            dof                 0
sfrq          75.464      dm                yyy
tn             C13        dmm                 w
at            0.800       dmf             11764
np            30016          PROCESSING
sw          18761.7       lb               1.00
fb            10400       wtfile
bs               16       proc               ft
tpwr             52       fn          not used
pw              3.8
d1            1.000       werr
tof               0       wexp              wft
nt             1024       wbs               wft
ct              736       wnt
alock             s
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -1835.9
wp          18761.7
vs               40
sc                0
wc              250
hzmm          75.05
is            500.00
rf1           7846.5
rfp           5810.6
th                4
ins          160.000
nm  no  ph
```



63



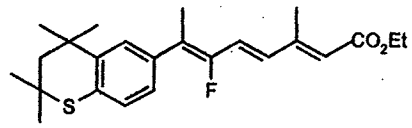
^{13}C NMR Spectrum of **63**

Plate LVI

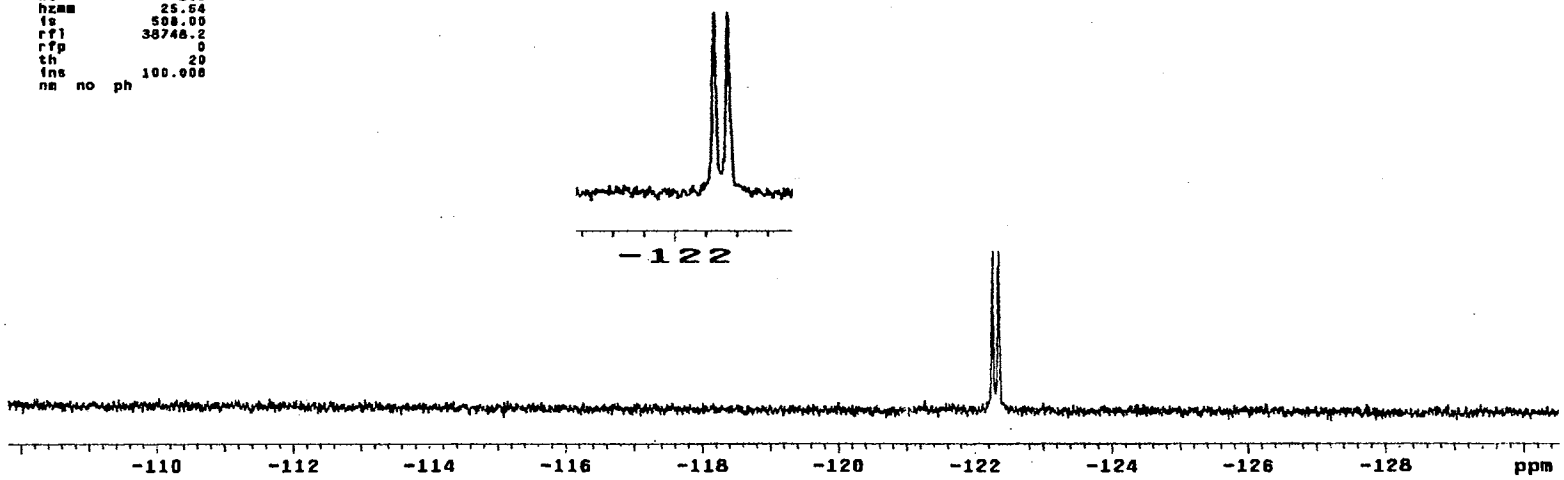
```
13C OBSERVE

expl  std13c

        SAMPLE                 DEC. & VT
date   Oct 30 1999      dfrq          300.087
solvent       CDCl3     dn                 H1
file            exp     dpwr               34
   ACQUISITION          dof                 0
sfrq        282.333     dm                nnn
tn              F19     dmm                 w
at            0.800     dmf             11764
np            38016        PROCESSING
sw          16761.7     lb               1.00
fb            19400     wtfile
bs               16     proc              ft
tpwr             52     fn          not used
pw              3.8
d1            1.000     werr
tof               0     wexp             wft
nt             1024     wbs              wft
ct              144     wnt
alock             n
gain        not used
       FLAGS
ll                n
in                y
dp                y
     DISPLAY
sp         -39858.6
wp          8409.7
vs               31
sc                0
wc              250
hzcm          25.54
fs           598.09
rfl         38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```

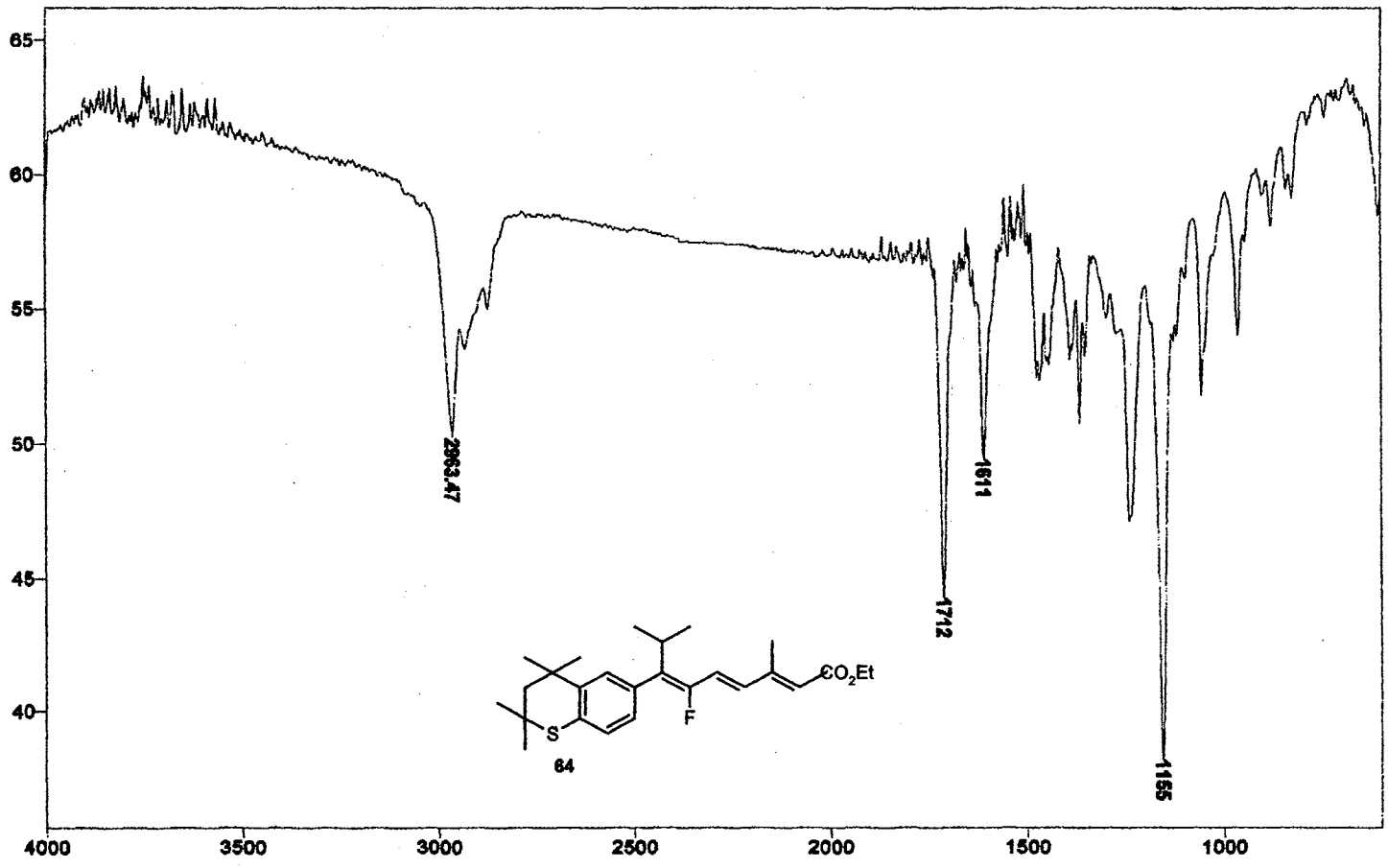


63



^{19}F NMR Spectrum of **63**

Plate LVII



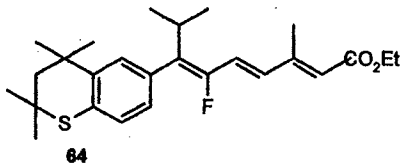
IR Spectrum of **64**

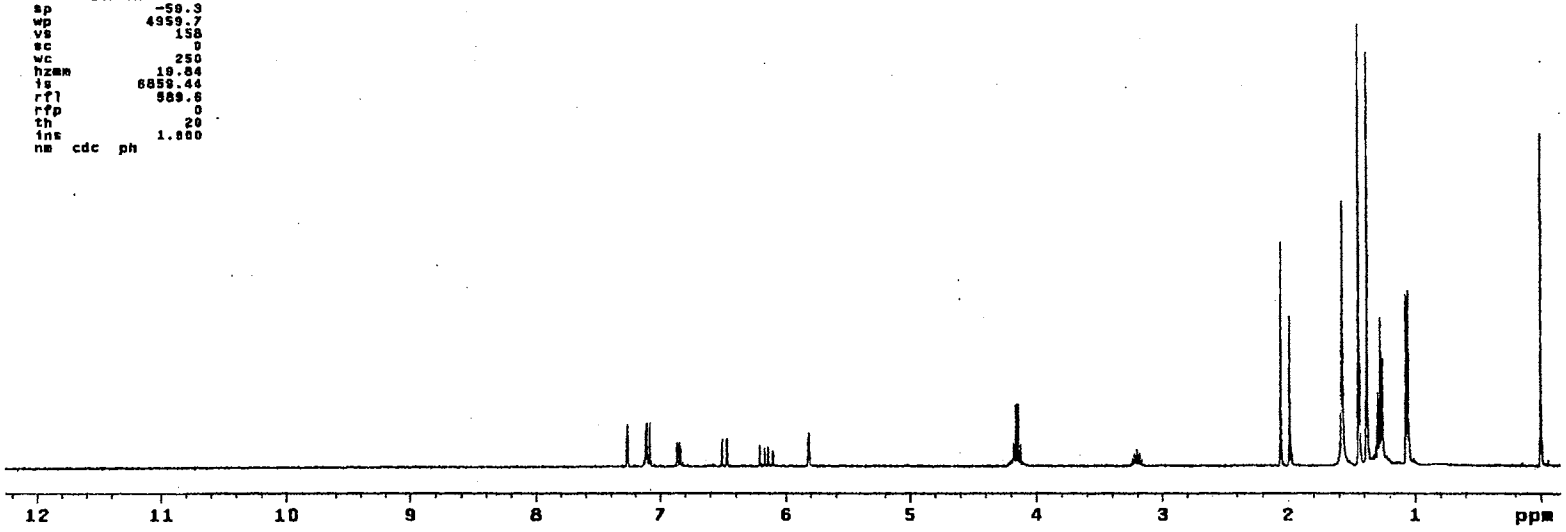
Plate LVIII

```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                    DEC. & VT
date   Nov 10 1999   dfrq          399.925
solvent       CDCl3  dn                Hi
file            exp  dpwr              30
   ACQUISITION       dof                0
afrq        399.925  dm               nnn
tn               Hi  dmm                c
at            3.744  dmf              200
np           44828   dseq
sw          6600.6   dres            1.0
fb            3080   homo              n
bs              16          PROCESSING
tpwr            52   wtfile
pw             6.0   proc              ft
d1               0   fn          not used
tof              0   math               f
nt              32
ct              32   werr
alock            n   wexp
gain            35   wbs
      FLAGS         wnt
il               n
in               n
dp               y
he              nn
     DISPLAY
sp            -59.3
wp           4959.7
vs              158
sc                0
wc              250
hzcm          19.84
is          6859.44
rfl           589.6
rfp               0
th               20
ins           1.860
nm  cdc  ph
```





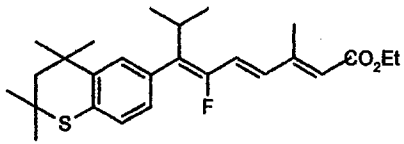
^{1}H NMR Spectrum of **64**

Plate LIX

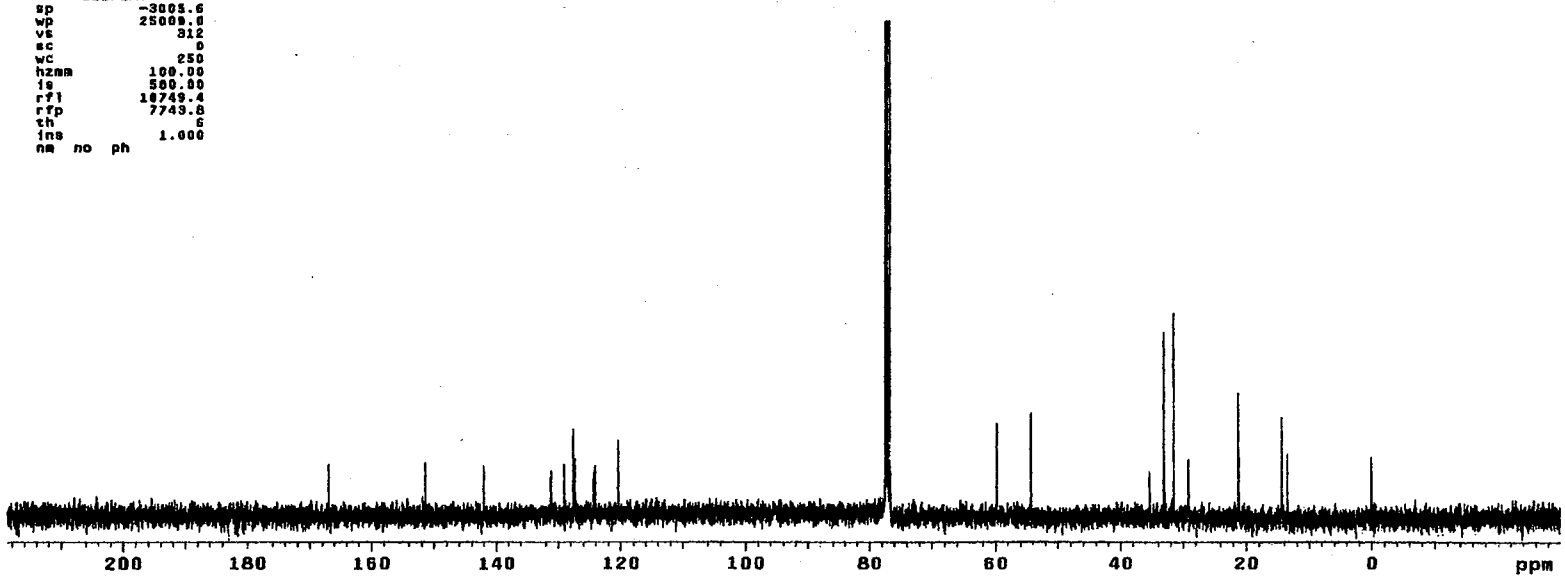
```
13C OBSERVE

exp1  std13c

      SAMPLE                DEC. & VT
date   Nov 10 1998   dfrq          399.925
solvent      CDCl3   dn               H1
file           exp   dpwr             40
   ACQUISITION       dof               0
sfrq        100.570  dm              nyy
tn              C13  dmm               w
at            1.199  dmf           12000
np            59868  dseq
sw          25000.0  dres            1.0
fb            14000  homo              n
bs               64      PROCESSING
tpwr             53  lb             1.00
pw              7.0  wtfile
d1            1.000  proc              ft
d2            0.500  fn         not used
tof               0  math              f
nt            10000
ct             6144  werr
alock             n  wsxp            wft
gain       not used  wbs             wft
      FLAGS          wnt
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -3005.6
wp          25009.0
vs              312
sc                0
wc              250
hzmm         100.00
is           500.00
rf1         10749.4
rfp          7749.8
th                6
ins           1.000
nm  no  ph
```



64



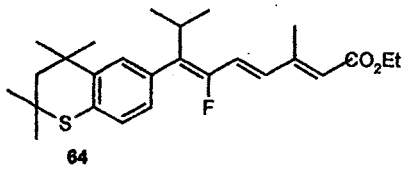
^{13}C NMR Spectrum of **64**

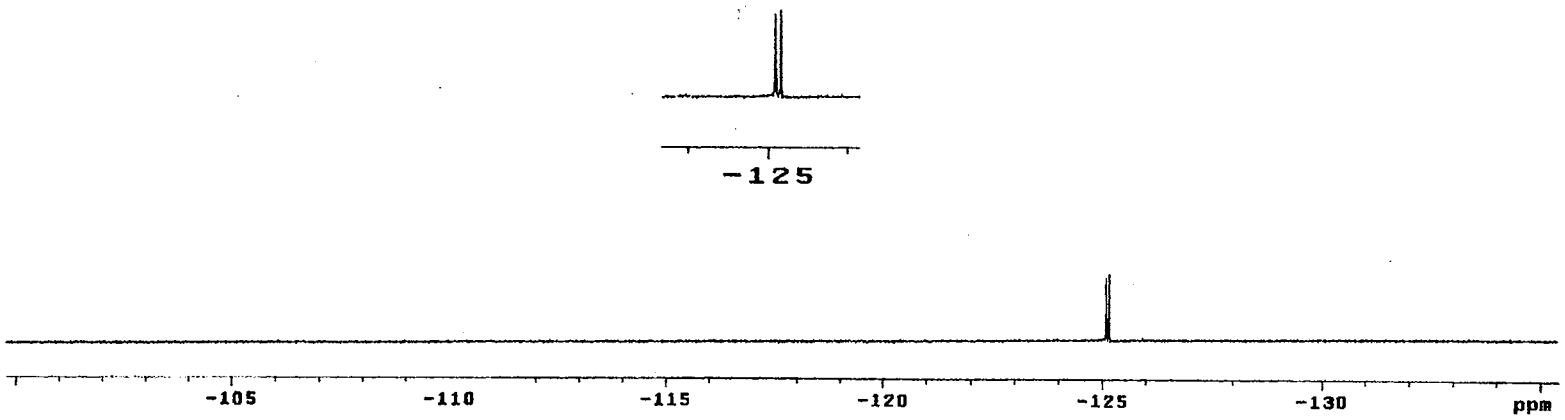
Plate LX

```
F19 OBSERVE
STANDARD PARAMETERS

exp1  s2pul

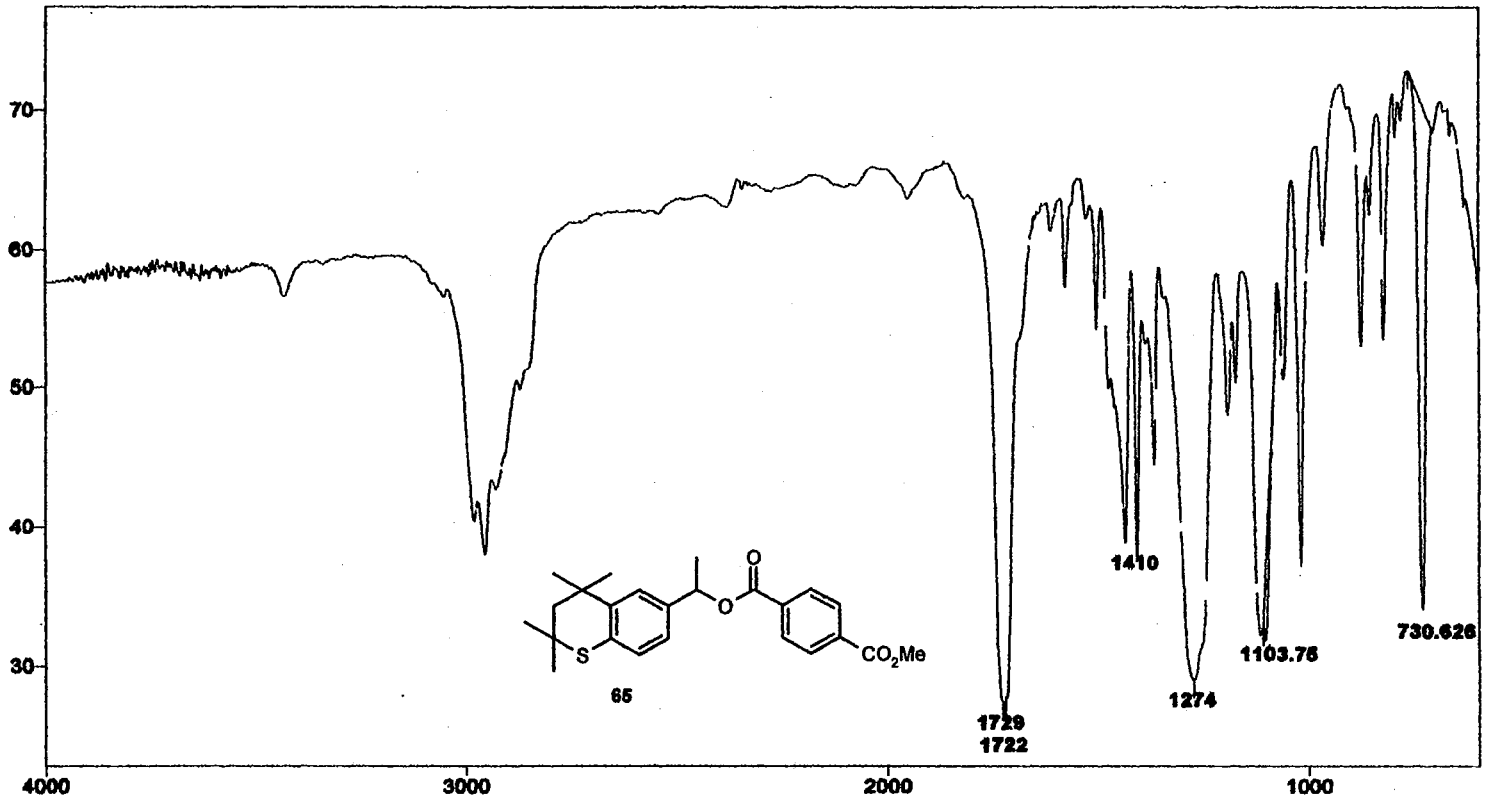
      SAMPLE                DEC. & VT
date    Nov 10 1999  dfrq          399.925
solvent       CDCl3  dn                 H1
file            exp  dpwr               30
   ACQUISITION       dof                 0
sfrq        376.263  dm                nnn
tn              F19  dmm                 c
at            0.600  dmf               200
np            59968  dseq
sw          50000.0  dres              1.0
fb            28000  homo                n
bs               16       PROCESSING
tpwr             55  lb               0.30
pw              5.0  wtfile
d1            4.000  proc               ft
tof               0  fn          not used
nt              128  math                f
ct              128
alock             n  werr
gain       not used  wexp              wft
      FLAGS          wbs               wft
il                n  wnt
in                n
dp                y
hs               nn
      DISPLAY
sp          -50050.4
wp          13402.2
vs               14
sc                0
wc              250
hzmm          53.61
is           500.00
rfl         65141.5
rfp               0
th               20
ins           1.000
nm  no  ph
```





^{19}F NMR Spectrum of **64**

Plate LXI



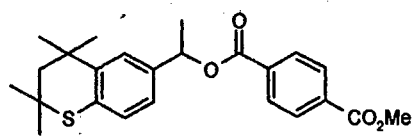
IR Spectrum of **65**

Plate LXII

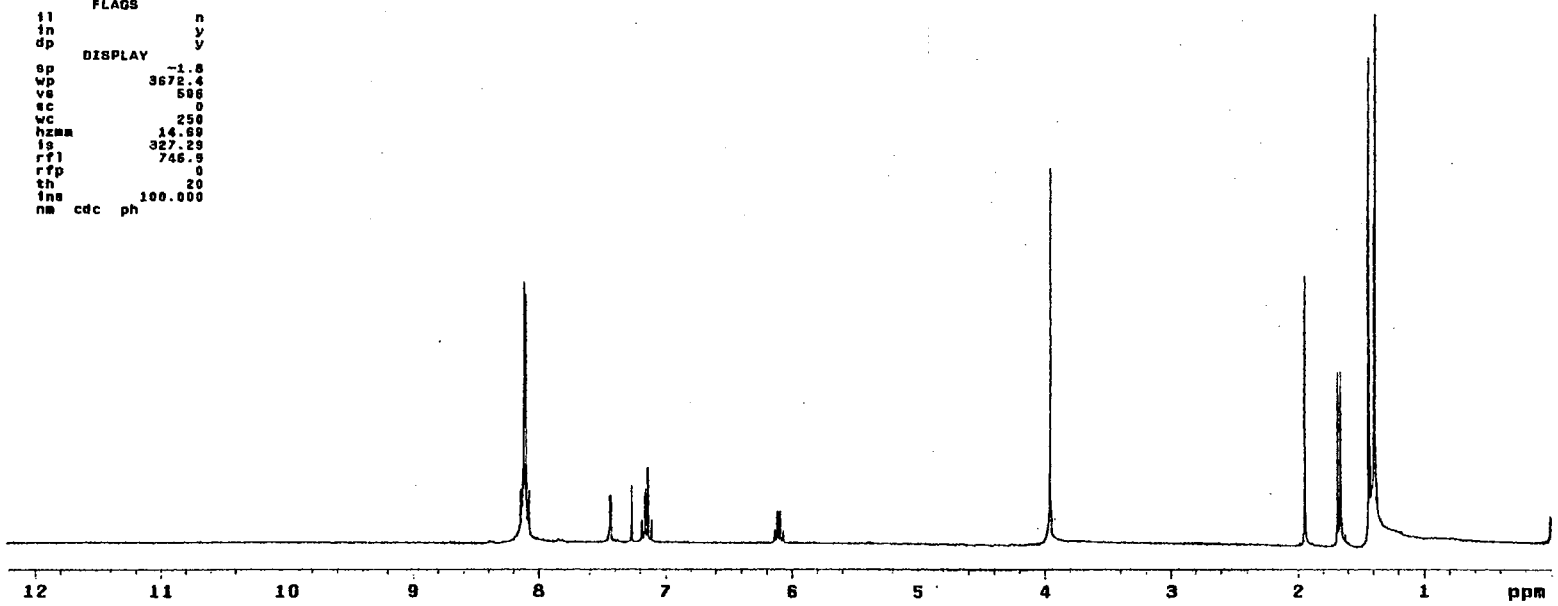
STANDARD 1H OBSERVE

expl stdih

SAMPLE		DEC. & VT	
date	Apr 13 2000	dfrq	300.087
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.087	dm	nnn
tn	H1	dmm	c
at	3.747	dmf	200
np	33728	PROCESSING	
sw	4500.5	wtfile	
fb	2600	proc	ft
bs	16	fn	not used
tpwr	48		
pw	6.9	werr	
d1	0	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	y		
dp	y		
DISPLAY			
sp	-1.8		
wp	3672.4		
vs	596		
sc	0		
wc	250		
hzmm	14.69		
is	327.29		
rfl	746.9		
rfp	0		
th	20		
ins	100.000		
nm cdc ph			



65



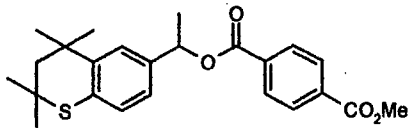
^{1}H NMR Spectrum of **65**

Plate LXIII

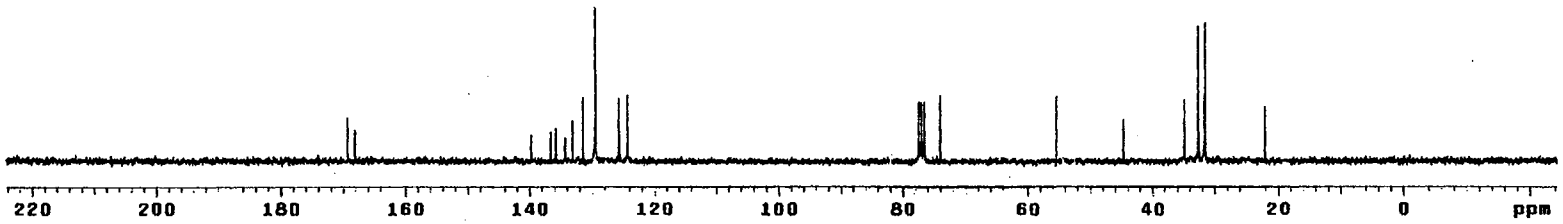
```
13C OBSERVE

expl  std13c

      SAMPLE                DEC. & VT
date   Nov 20 1999  dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof               0
sfrq          75.464  dm              yyy
tn               C13  dmm               w
at             8.800  dmf           11764
np             30016     PROCESSING
sw          18761.7  lb              1.00
fb             10400  wtfile
bs                16  proc              ft
tpwr              52  fn         not used
pw               3.8
d1             1.000  werr
tof                0  wexp             wft
nt              4096  wbs             wft
ct               368  wnt
alock              s
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp          -1839.3
wp          18761.7
vs               28
sc                0
wc              250
hzmm          75.05
is           500.00
rfl          7649.9
rfp          5810.6
th                5
ins          100.000
nm  no  ph
```

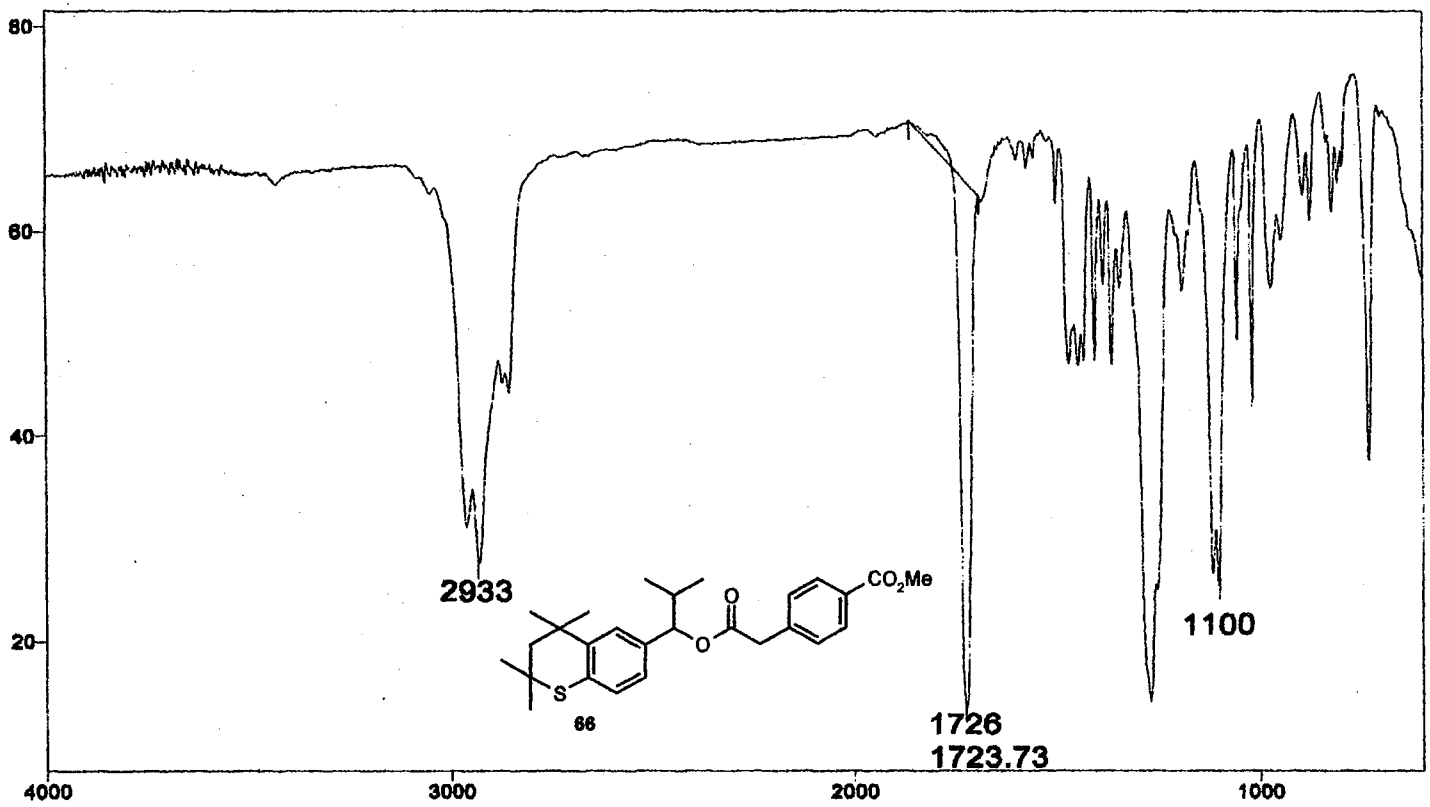


65



^{13}C NMR Spectrum of **65**

Plate LXIV



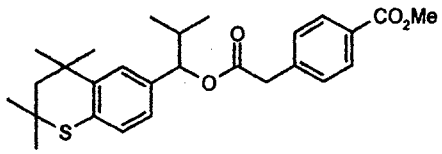
IR Spectrum of **66**

Plate LXV

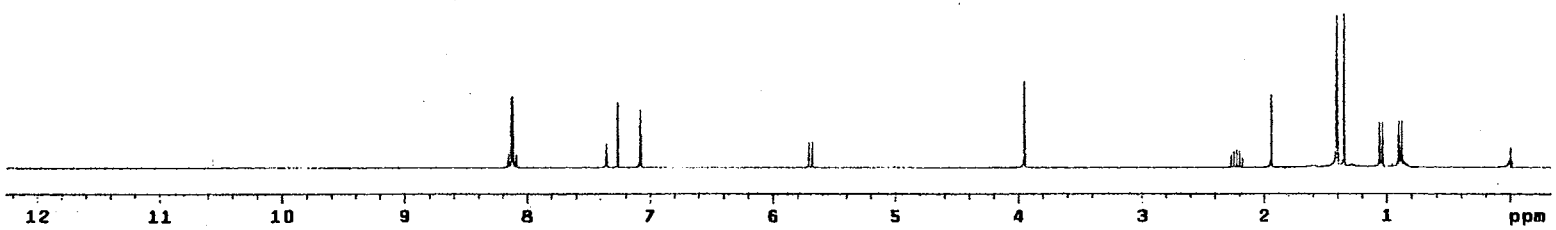
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                 DEC. & VT
date   Nov 30 1999   dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr              30
   ACQUISITION       dof               0
sfrq        300.087  dm              nnn
tn               H1  dmm               c
at            3.747  dmf             200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2800  proc            ft
bs               16  fn        not used
tpwr             46
pw              6.9  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain        not used
      FLAGS
fl                n
in                y
dp                y
     DISPLAY
sp            -184.2
wp           3764.9
vs               47
sc                0
wc              250
hzcm           15.14
is            338.21
rfl            748.8
rfp                0
th                20
ins            40.000
nm  cdc  ph
```



66



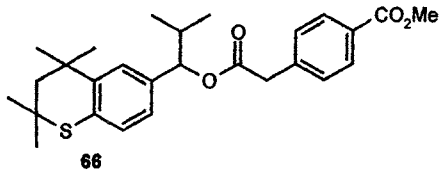
^{1}H NMR Spectrum of **66**

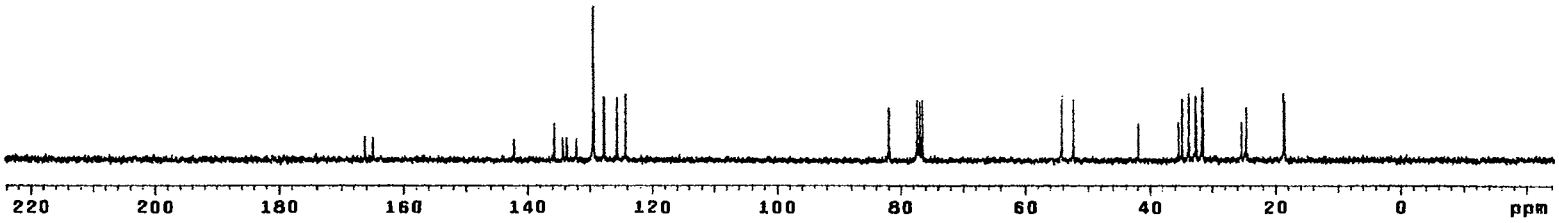
Plate LXVI

```
13C OBSERVE

exp1  std13c

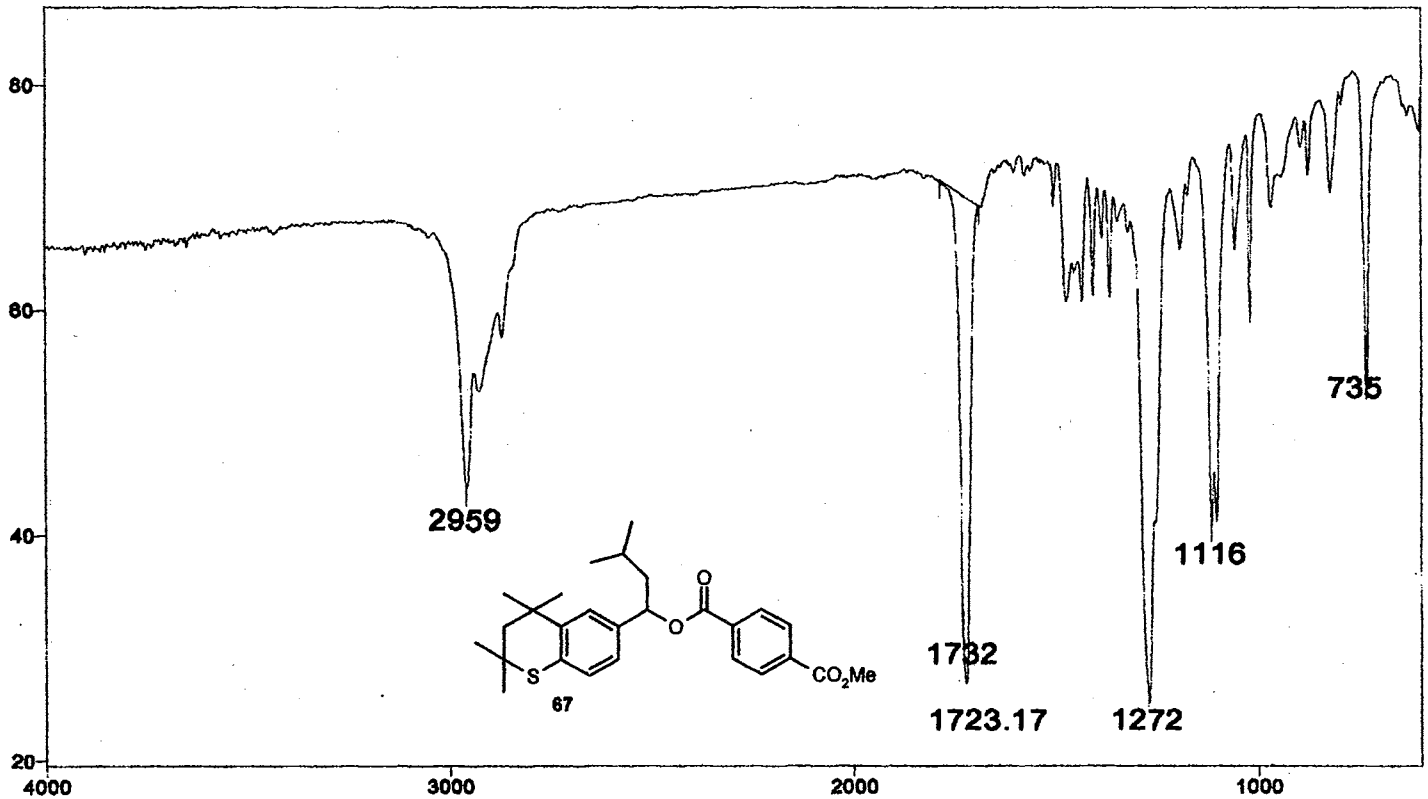
      SAMPLE                    DEC. & VT
date   Nov 20 1999  dfrq          380.087
solvent       CDCl3 dn                Hi
file            exp dpwr              34
    ACQUISITION     dof                0
sfrq         75.464 dm               yyy
tn              C13 dmm               w
at            0.800 dmf            11764
np            30016     PROCESSING
sw          18761.7 lb               1.00
fb            10400 wtfile
bs               16 proc              ft
tpwr             52 fn         not used
pw              3.8
d1            1.000 werr
tof               0 wexp             wft
nt             4088 wbs              wft
ct              368 wnt
alock             s
gain        not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -1839.3
wp          18761.7
vs               28
sc                0
wc              250
hzcm          75.05
is           500.00
rfl          7649.9
rfp          5810.8
th                5
ins         100.000
nm  no  ph
```





^{13}C NMR Spectrum of **66**

Plate LXVII



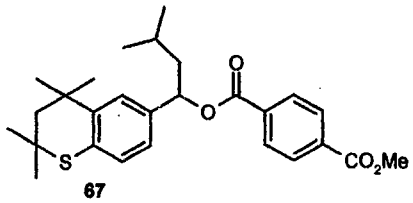
IR Spectrum of **67**

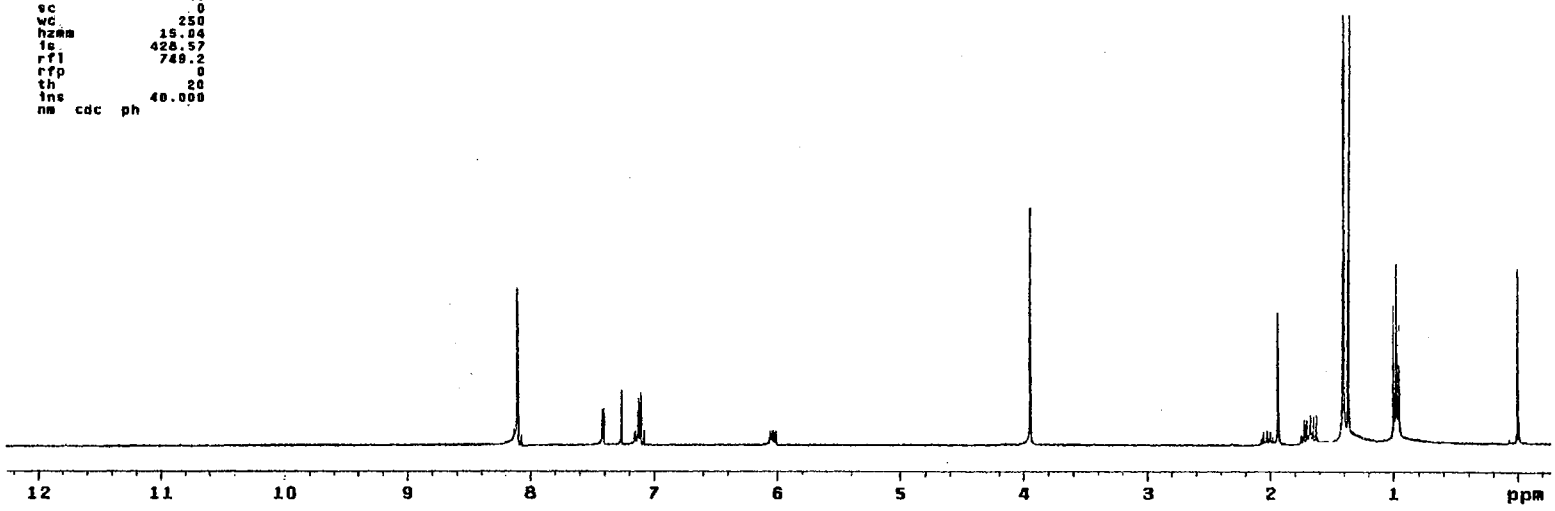
Plate LXVIII

```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                 DEC. & VT
date   Nov 20 1999   dfrq          300.087
solvent       CDCl3  dn                Hl
file            exp  dpwr              30
   ACQUISITION       dof               0
sfrq        300.067  dm              nnn
tn               Hl  dmm               c
at            3.747  dmf             280
np            33728        PROCESSING
sw           4500.5  wtfile
fb             2600  proc              ft
bs               16  fn          not used
tpwr             48
pw              6.9  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               18
alock             n
gain       not used
      FLAGS
ii                n
in                y
dp                y
     DISPLAY
sp            -81.0
wp           3761.1
vs               80
sc                0
wc              250
hzmm          15.04
is           428.57
rfl           749.2
rfp               0
th               20
ins          40.000
nm  cdc  ph
```





^{1}H NMR Spectrum of **67**

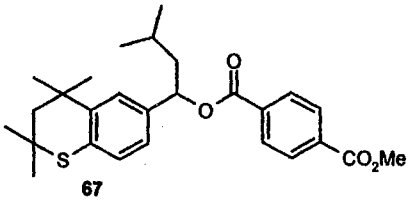
Plate LXIX

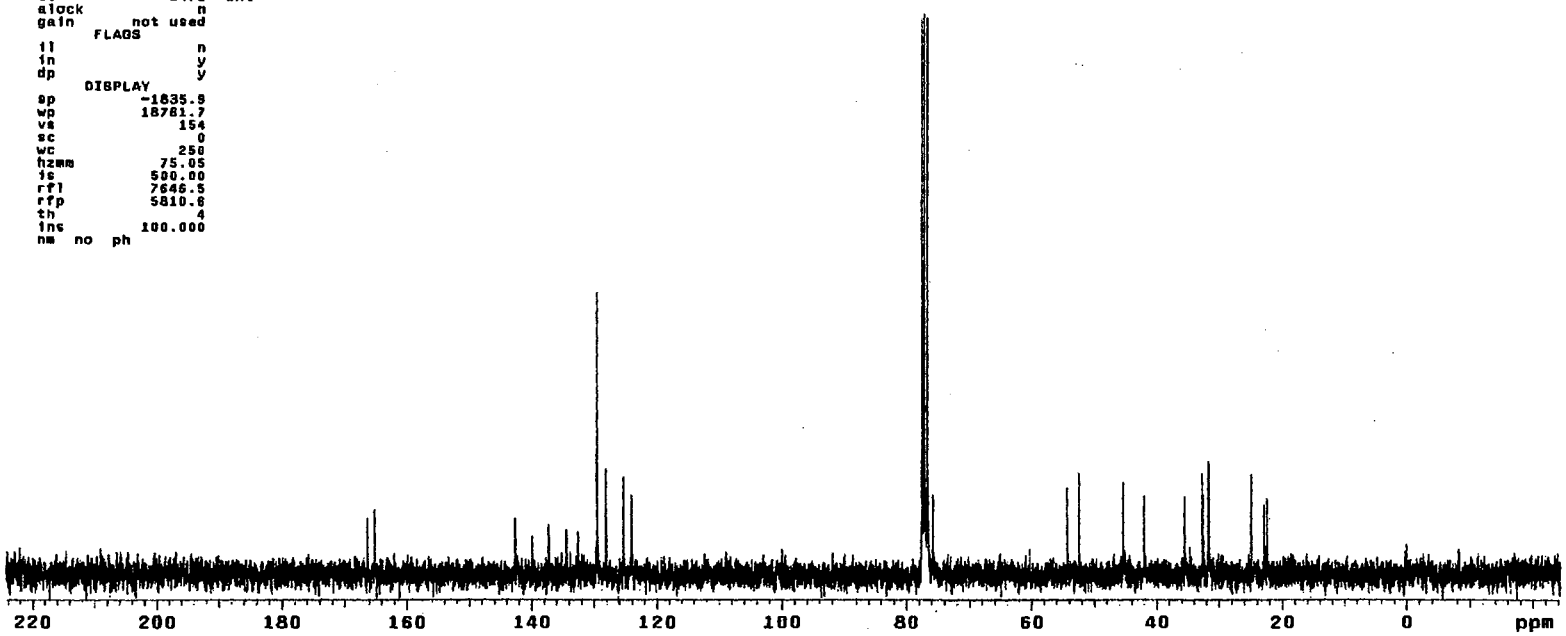
```
13C OBSERVE

exp1  std13c

      SAMPLE
date    Nov 20 1999
solvent        CDCl3
file             exp
   ACQUISITION
sfrq           75.464
tn               C13
at               0.800
np              30016
sw           18761.7
fb             19460
bs                16
tpwr              52
pw               3.8
d1               1.000
tof                0
nt              4096
ct              1472
alock              n
gain         not used
      FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp            -1635.5
wp           18781.7
vs               154
sc                 0
wc               250
hzmm           75.05
is            500.00
rfl           7646.5
rfp           5810.6
th                 4
ins           100.000
nm  no  ph

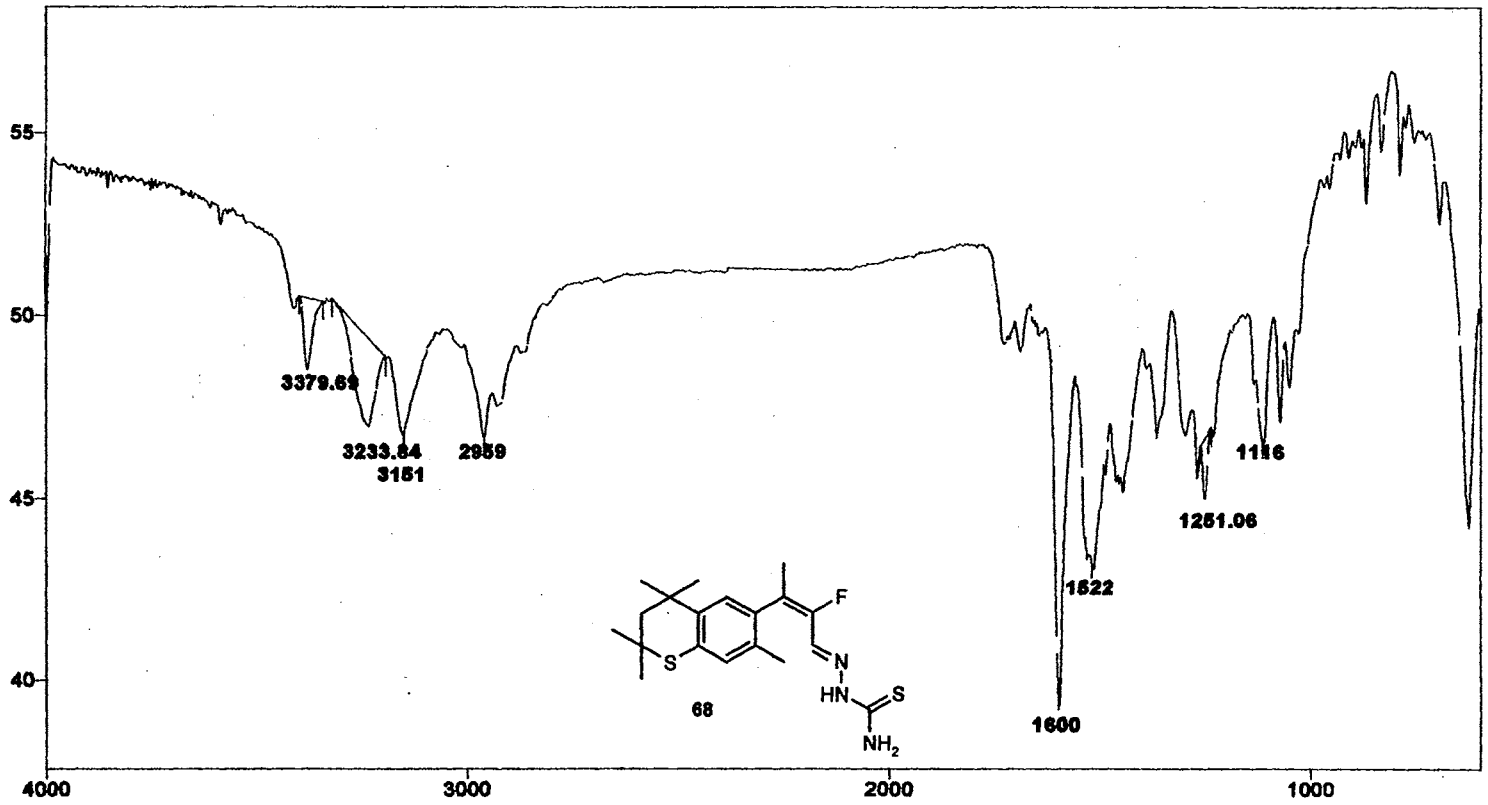
      DEC. & VT
dfrq          300.087
dn                 H1
dpwr               34
dof                 0
dm                yyy
dmm                 w
dmf             11764
      PROCESSING
lb                1.00
wtfile
proc               ft
fn          not used
werr
wexp              wft
wbs               wft
wnt
```





^{13}C NMR Spectrum of **67**

Plate LXX



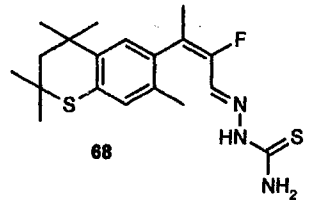
IR Spectrum of **68**

Plate LXXI

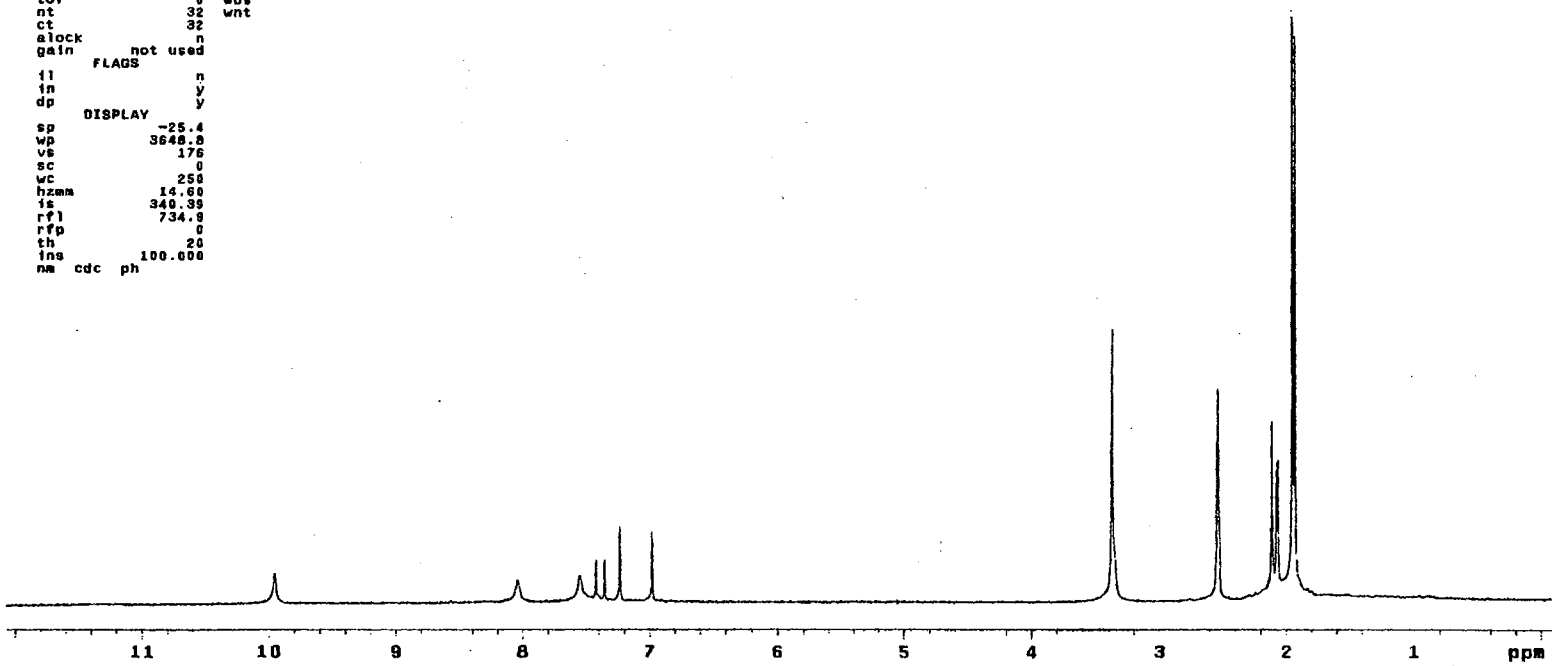
STANDARD 1H OBSERVE

exp1 std1h

SAMPLE		DEC. & VT	
date	Apr 4 2009	dfrq	300.089
solvent	DMSO	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.089	dm	nnn
tn	H1	dmm	c
at	3.747	dmf	200
np	33728	PROCESSING	
sw	4500.5	wtfile	
fb	2600	proc	ft
bs	16	fn	not used
tpwr	46		
pw	6.8	werr	
d1	0	wexp	
tof	0	wbs	
nt	32	wnt	
ct	32		
alock	n		
gain	not used		
FLAGS			
il	n		
in	y		
dp	y		
DISPLAY			
sp	-25.4		
wp	3648.8		
vs	176		
sc	0		
wc	250		
hzmm	14.60		
is	340.39		
rfl	734.9		
rfp	0		
th	20		
ins	100.000		
nm cdc ph			



68



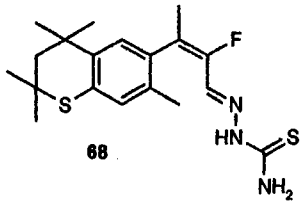
^{1}H NMR Spectrum of **68**

Plate LXXII

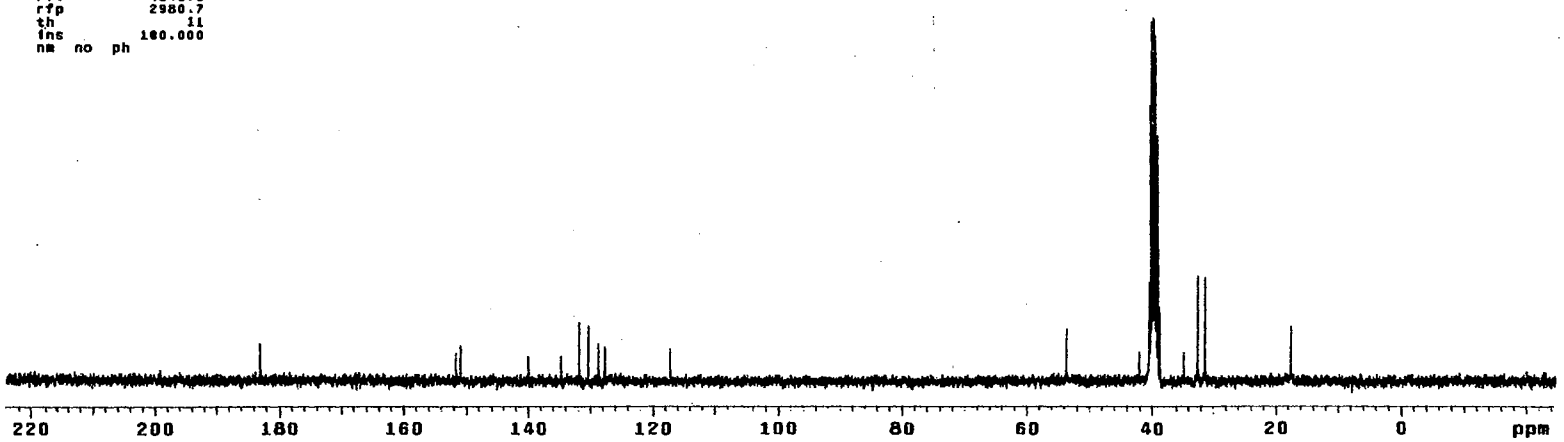
```
13C OBSERVE

expl  std13c

      SAMPLE                    DEC. & VT
date    Apr  4 2000  dfrq          300.089
solvent        DMSO  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                 0
sfrq          75.464 dm                 yyy
tn               C13 dmm                  w
at             0.800 dmf              11764
np             30016     PROCESSING
sw          18761.7  lb              1.00
fb            10400  wtfile
bs               16  proc               ft
tpwr             52  fn          not used
pw              3.8
d1            1.000  werr
tof               0  wexp             wft
nt             1024  wbs              wft
ct             1024  wnt
alock             s
gain       not used
       FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -1668.1
wp          18761.7
vs              107
sc                0
wc              250
hzmm          75.05
is           500.00
rfl          4848.8
rfp          2980.7
th                11
ins          100.000
nm  no  ph
```



68



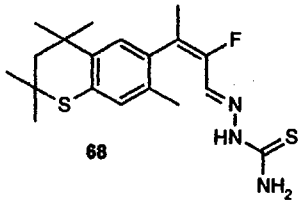
^{13}C NMR Spectrum of **68**

Plate LXXIII

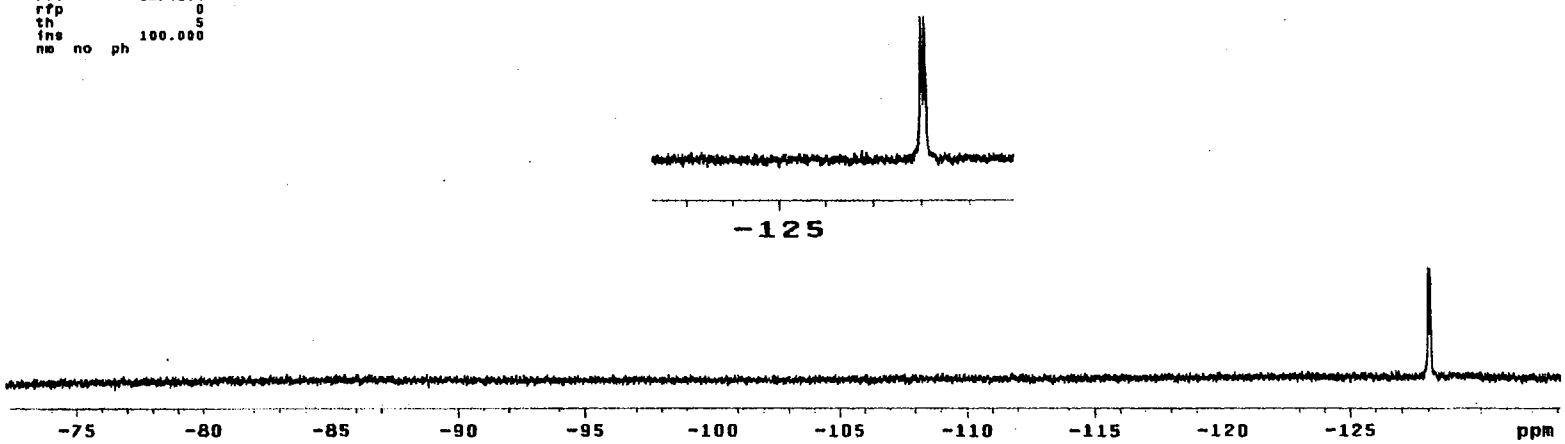
```
13C OBSERVE

expl  std13c

        SAMPLE                  DEC. & VT
date    Apr  4 2000   dfrq        300.089
solvent        DMSO   dn               H1
file            exp   dpwr             34
   ACQUISITION        dof               0
sfrq          282.335 dm                n
tn              F19   dmm               w
at            0.808   dmf           11764
np            30016       PROCESSING
sw          18761.7   lb             1.00
fb            10400   wtfile
bs               16   proc             ft
tpwr             52   fn         not used
pw              3.8
d1            1.000   werr
tof               0   wexp            wft
nt             1024   wbs             wft
ct               80   wnt
alock             n
gain       not used
        FLAGS
ii                n
in                y
dp                y
       DISPLAY
sp         -37598.6
wp          17207.7
vs               21
sc                0
wc              250
hzcm          66.83
is           500.00
rfl         38748.4
rfp               0
th                5
ins         100.000
nm  no  ph
```

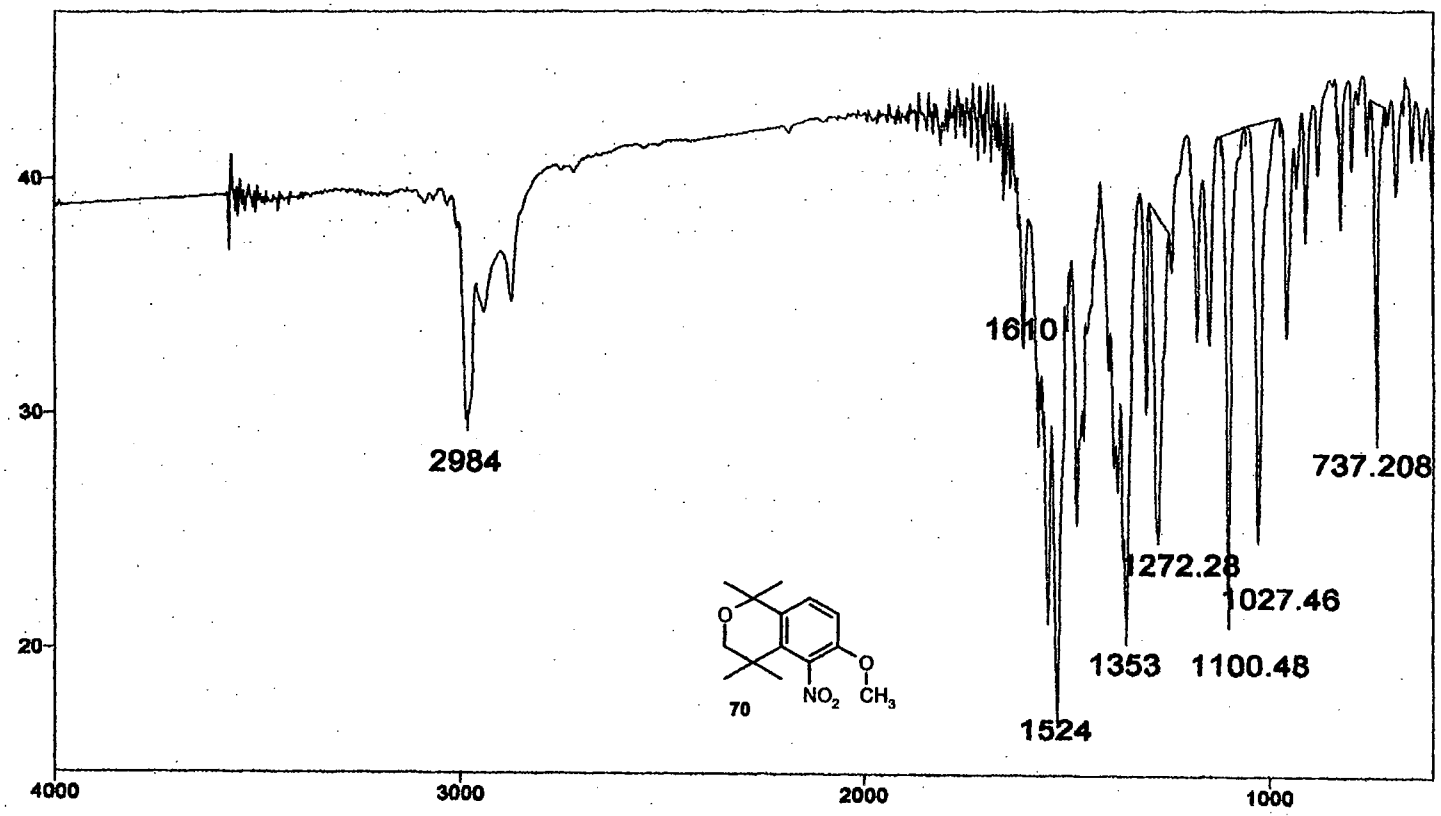


68



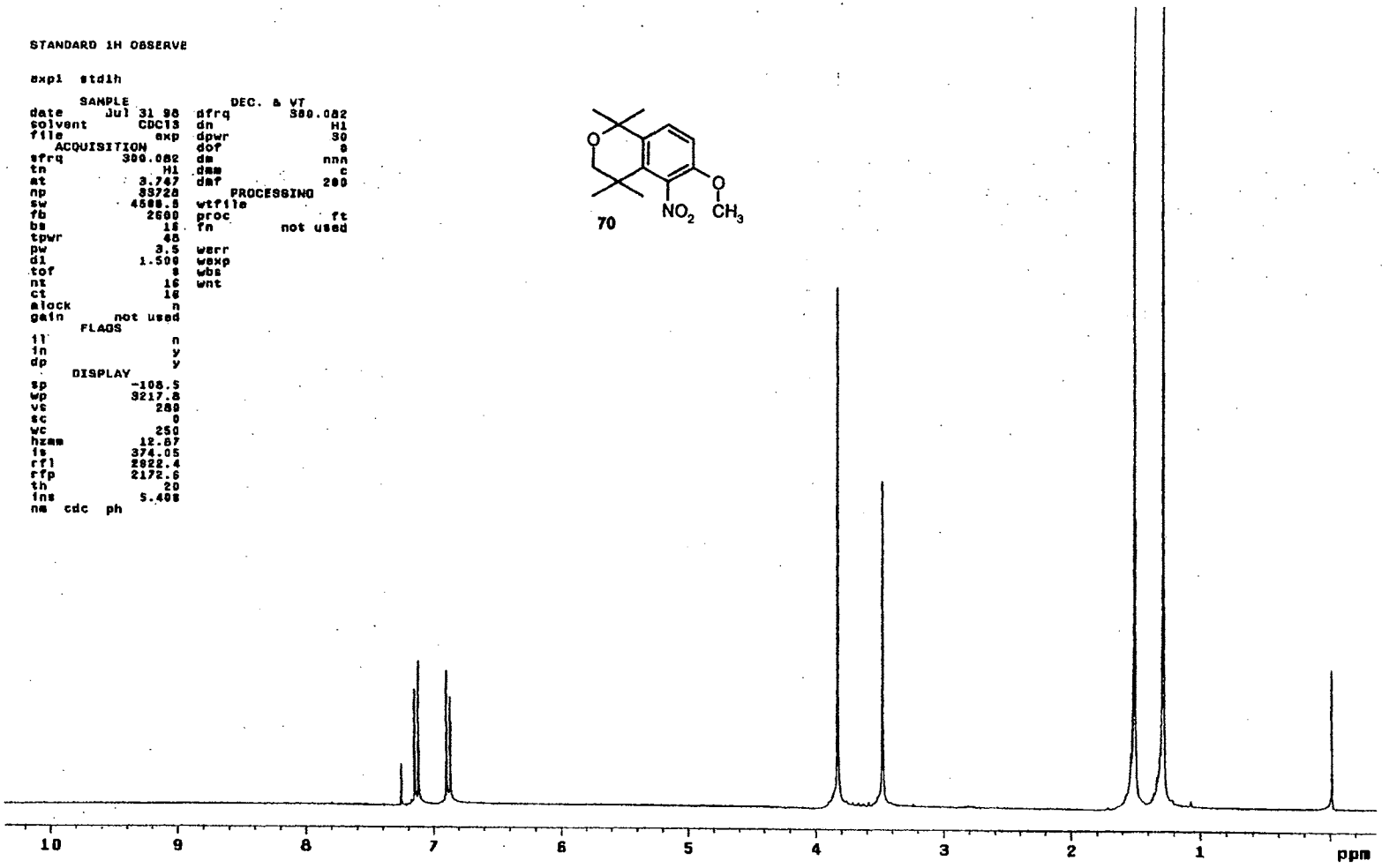
^{19}F NMR Spectrum of **68**

Plate LXXIV



IR Spectrum of **70**

Plate LXXV



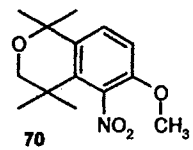
^{1}H NMR Spectrum of **70**

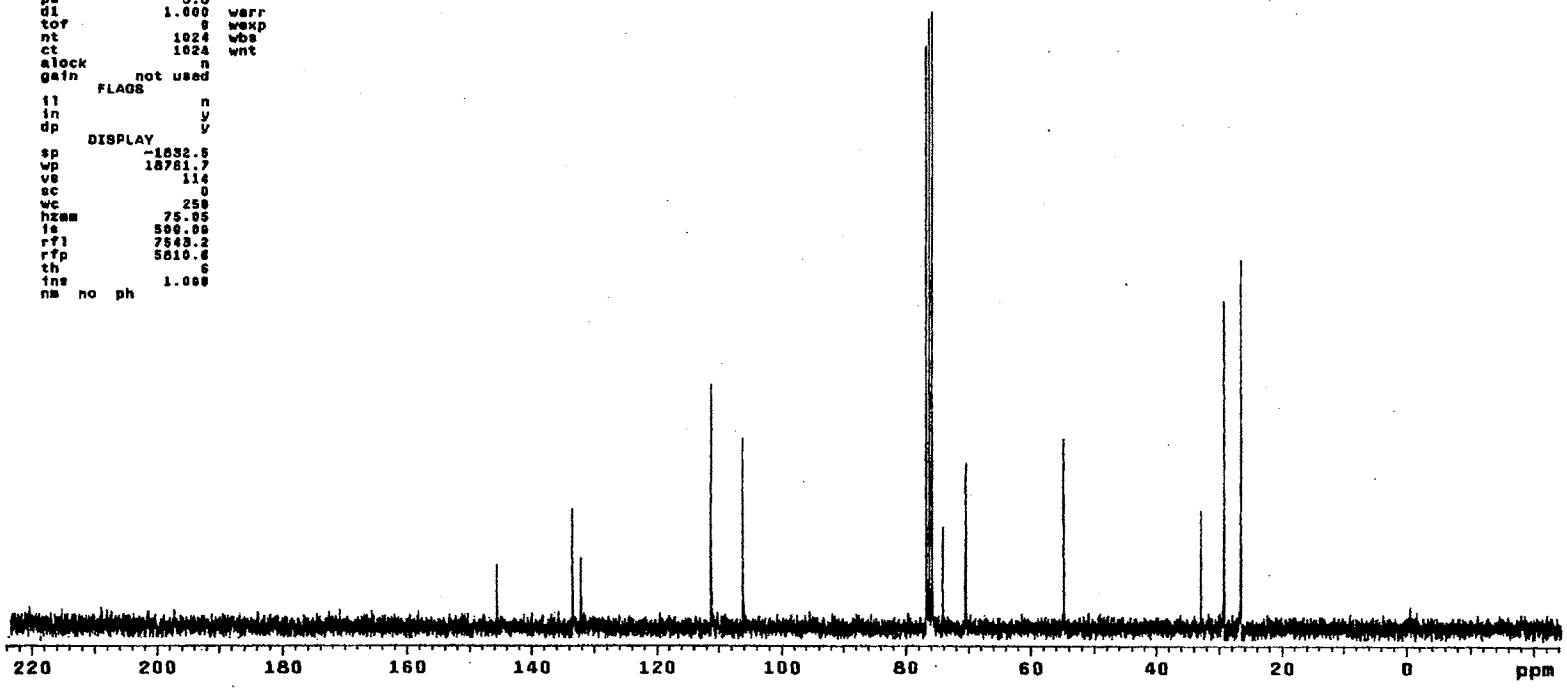
Plate LXXVI

```
13C OBSERVE

expl  std13c

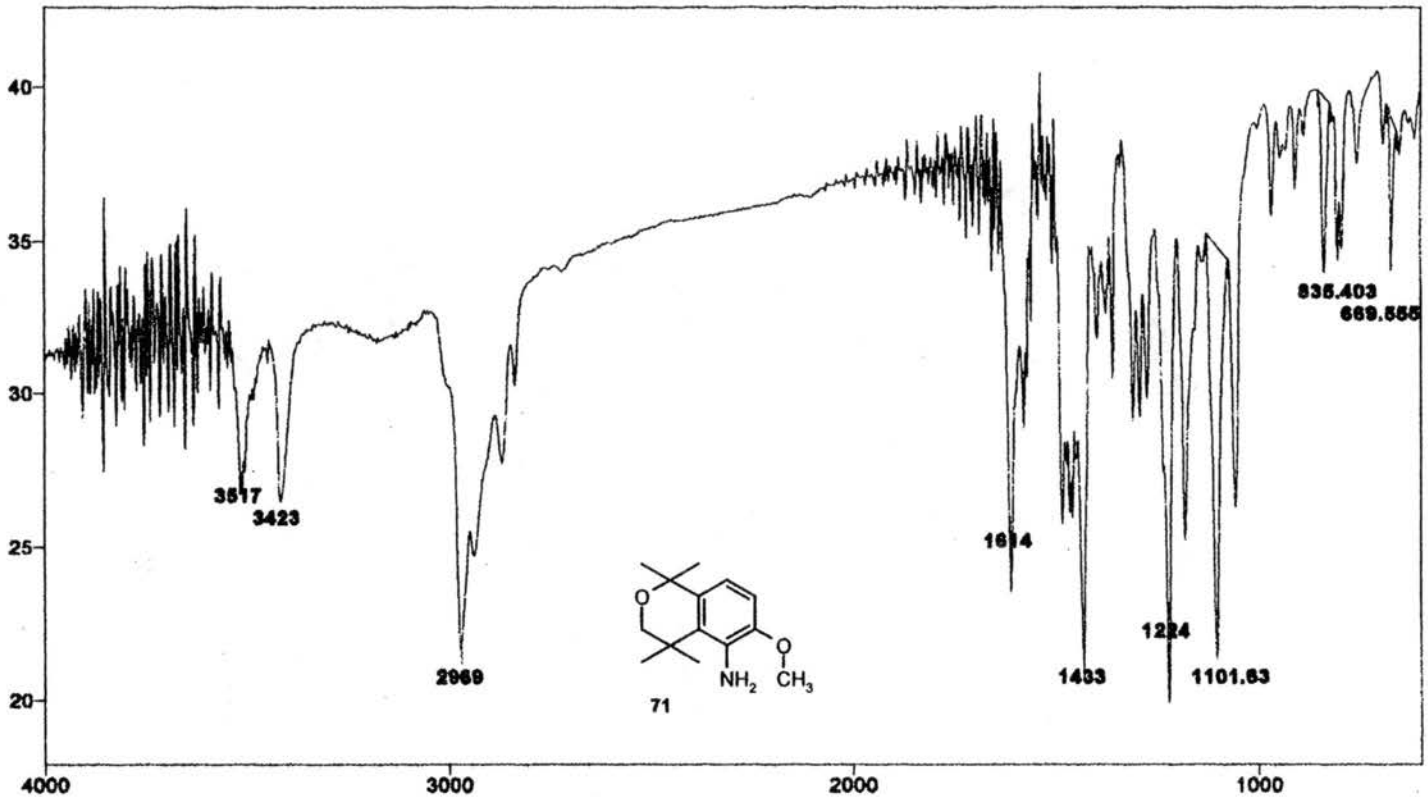
      SAMPLE                 DEC. & VT
date      Jul 30 96   dfrq        300.082
solvent       CDCl3   dn               H1
file            exp   dpwr             34
   ACQUISITION        dof               0
sfrq         75.463   dm              nyy
tn              C13   dmm               w
at            8.800   dmf           11784
np            30816      PROCESSING
sw          18781.7   lb             1.00
fb            10409   wtfile
bs               18   proc              ft
tpwr             52   fn        not used
pw              3.5
dl            1.000   werr
tof               0   wexp
nt             1024   wbs
ct             1024   wnt
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp          -1832.5
wp          18781.7
vs              114
sc                0
wc              250
hzcm          75.05
is            500.00
rfl           7543.2
rfp           5810.6
th                6
ins           1.000
nm  no  ph
```





^{13}C NMR Spectrum of **70**

Plate LXXVII



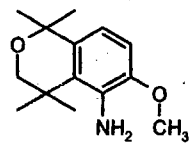
IR Spectrum of **71**

Plate LXXVIII

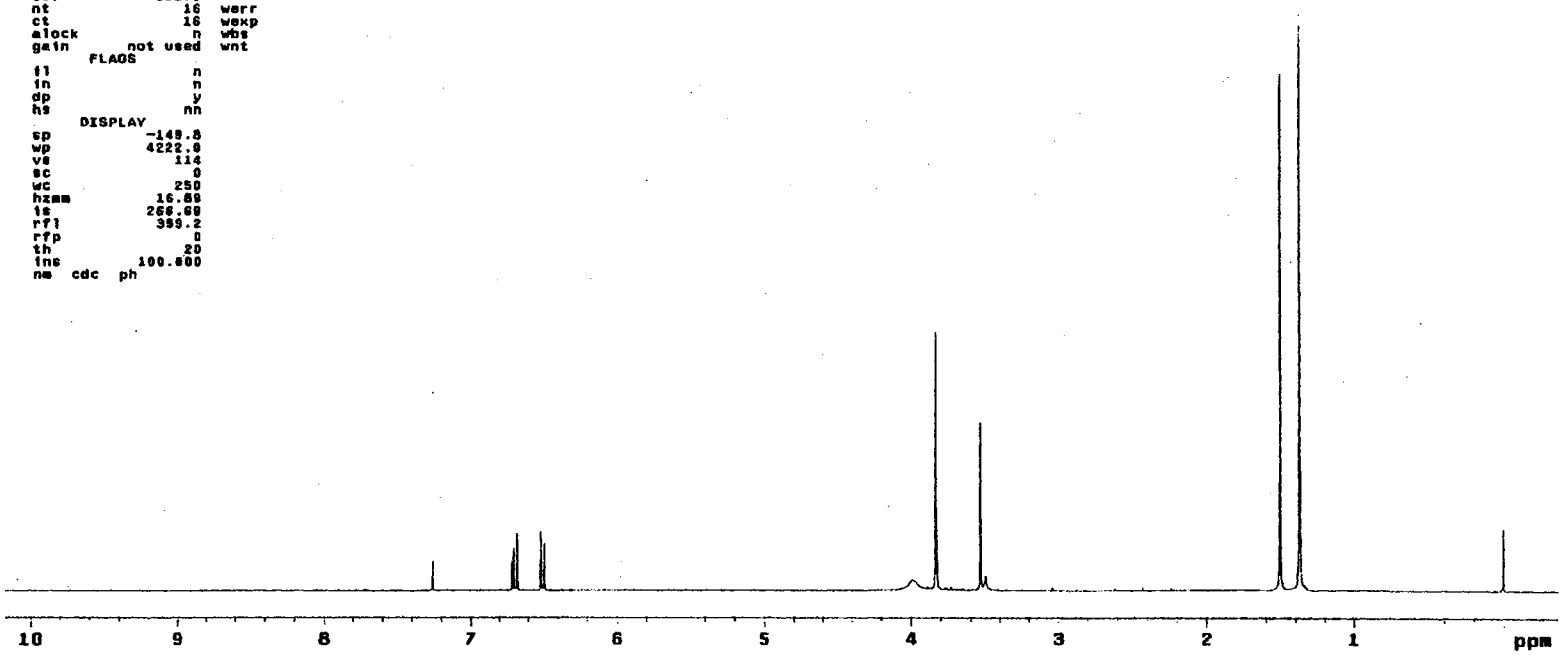
```
Std. 1H Inova400

expl  std1h

      SAMPLE                    DEC. & VT
date      Aug  5 98   dfrq          399.923
solvent       CDCl3   dn                 H1
file            exp   dpwr               30
   ACQUISITION        dof                 0
sfrq        399.924   dm                nnn
tn               H1   dmm                 c
at            2.731   dmf               200
np            32768   dseq
sw           6000.2   dres              1.0
fb             3000   homo                n
bs               16        PROCESSING
ss                2   wtfile
tpwr             52   proc               ft
pw              6.6   fn          not used
d1            1.000   math                f
tof           588.8
nt               16   werr
ct               16   wexp
alock             n   wbs
gain       not used   wnt
      FLAGS
fl                n
in                n
dp                y
hs               nn
      DISPLAY
sp            -149.5
wp            4222.0
vs               114
sc                 0
wc               250
hzmm           16.69
is            268.69
rfl           399.2
rfp                0
th                20
ins           100.000
nm  cdc  ph
```

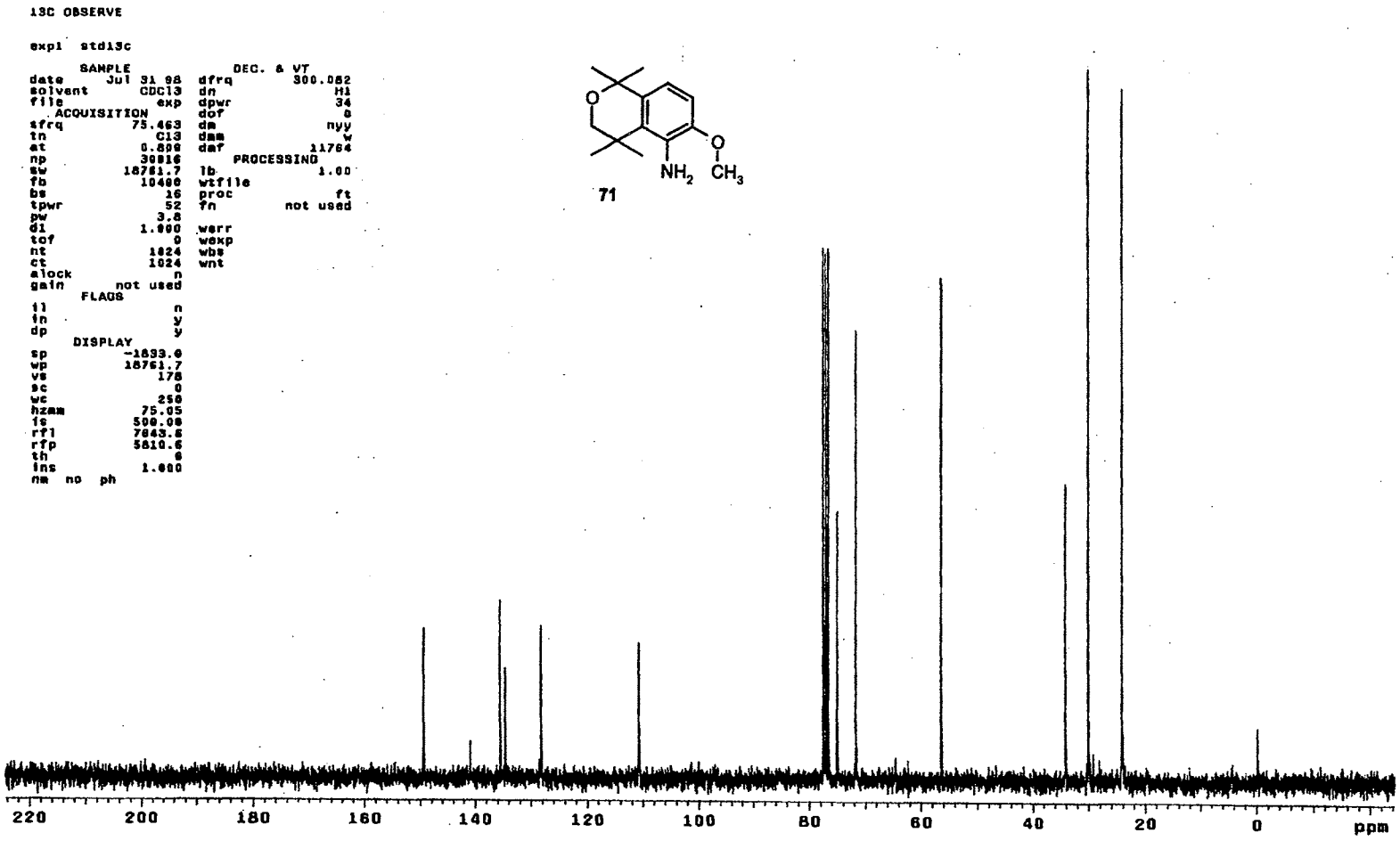


71



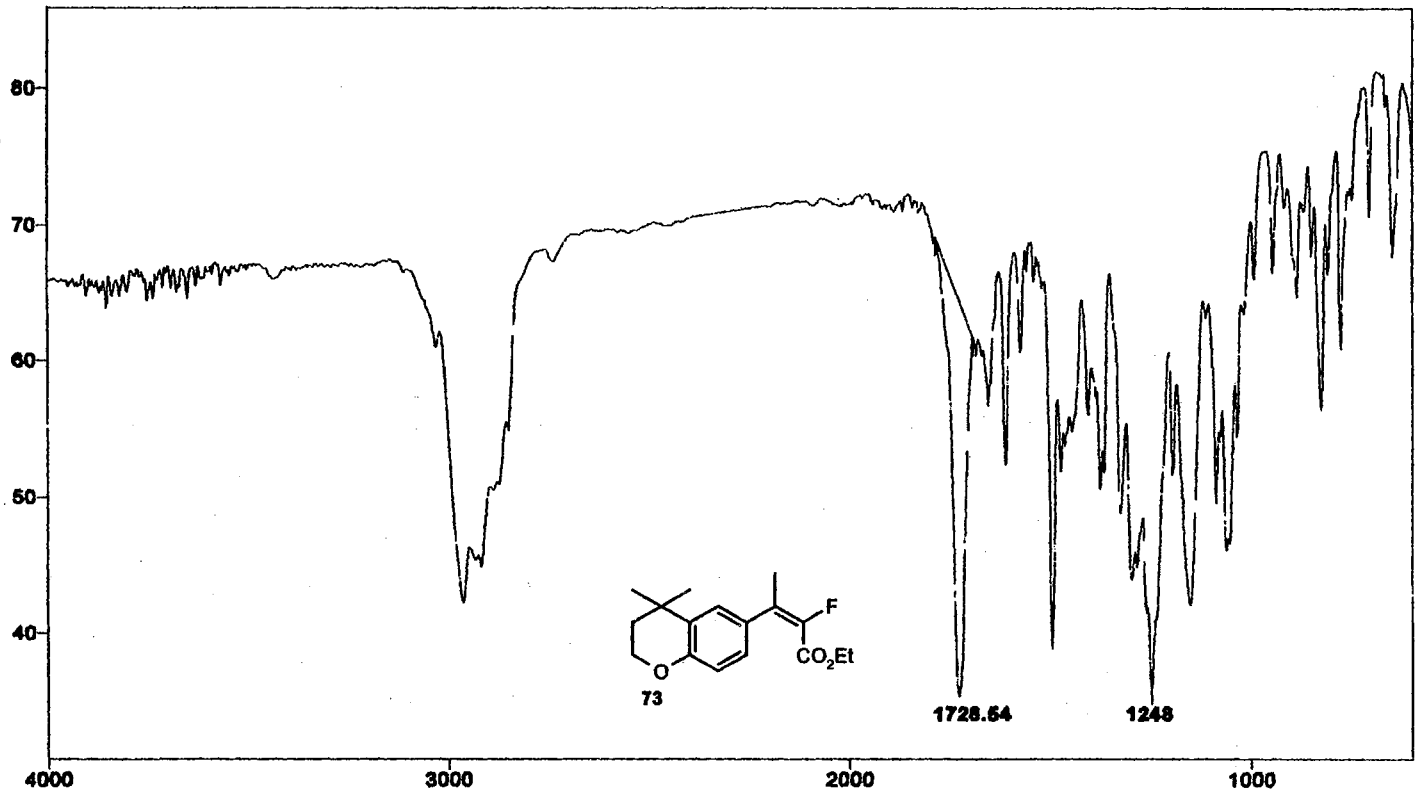
^{1}H NMR Spectrum of **71**

Plate LXXIX



^{13}C NMR Spectrum of **71**

Plate LXXX



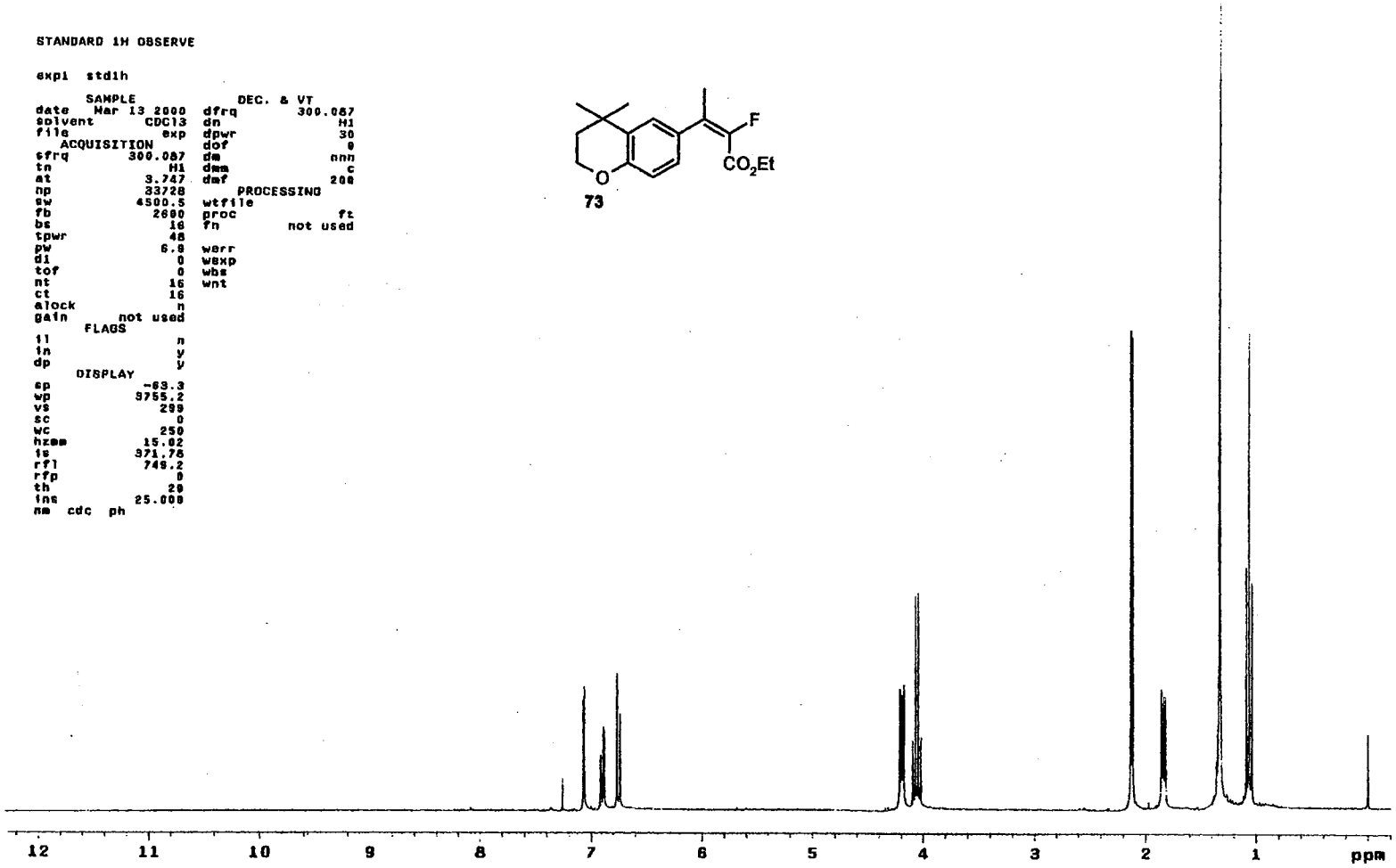
IR Spectrum of 73

Plate LXXXI

```
STANDARD 1H OBSERVE

expl  stdlh

        SAMPLE                DEC. & VT
date    Mar 13 2000   dfrq          300.087
solvent       CDCl3   dn               H1
file            exp   dpwr             30
    ACQUISITION       dof               0
sfrq        300.087   dm              nnn
tn               H1   dmm               c
at            3.747   dmf             200
np            33728       PROCESSING
sw           4500.5   wtfile
fb             2690   proc            ft
bs               16   fn         not used
tpwr             48
pw              6.8   werr
d1                0   wexp
tof               0   wbs
nt               16   wnt
ct               16
alock             n
gain       not used
       FLAGS
il                n
in                y
dp                y
       DISPLAY
sp            -63.3
wp           3755.2
vs              299
sc                0
wc              250
hzcm          15.02
is           371.76
rfl           749.2
rfp               0
th               20
ins           25.000
nm  cdc  ph
```

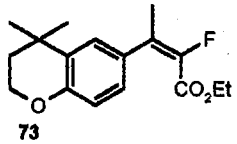
^{1}H NMR Spectrum of **73**

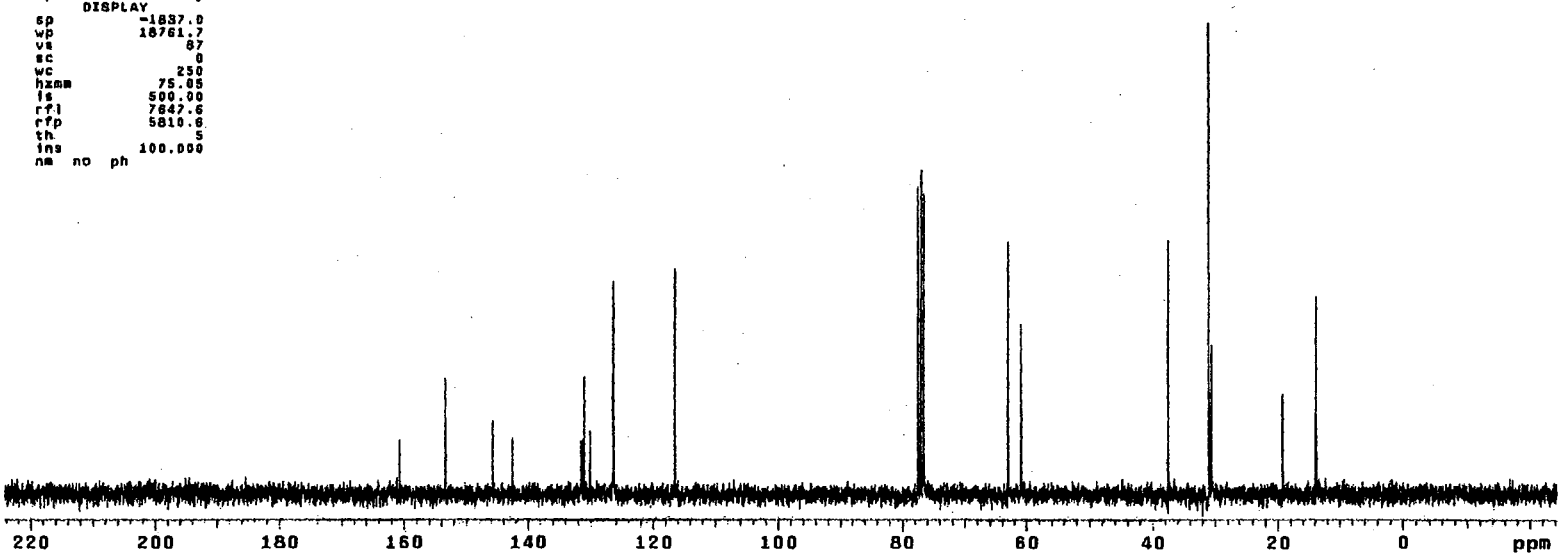
Plate LXXXI

```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date   Jan 24 2000  dfrq          300.087
solvent       CDCl3  dn                Hi
file            exp  dpwr              34
   ACQUISITION       dof               0
sfrq          75.464  dm              yyy
tn               C13  dmm               w
at             0.800  dmf           11764
np             30016     PROCESSING
sw          18761.7  lb              1.00
fb            10400  wtfile
bs               16  proc              ft
tpwr             52  fn         not used
pw              3.8
d1            1.000  werr
tof               0  wexp             wft
nt             1024  wbs             wft
ct              256  wnt
alock             s
gain        not used
      FLAGS
ii                n
in                y
dp                y
      DISPLAY
sp          -1837.0
wp          18761.7
vs               87
sc                0
wc              250
hzmm          75.05
is           500.00
rfl          7647.6
rfp          5810.6
th                5
ins         100.000
nm  no  ph
```





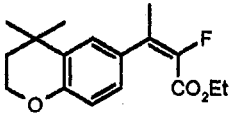
^{13}C NMR Spectrum of **73**

Plate LXXXIII

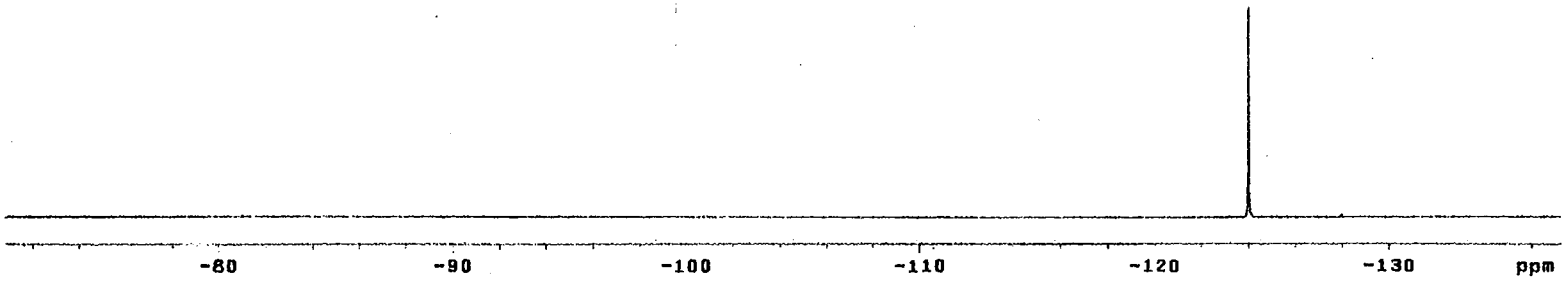
```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date    Jan 24 2000   dfrq        300.087
solvent       CDCl3   dn               H1
file            exp   dpwr             34
   ACQUISITION        dof               0
sfrq        282.333   dm              nnn
tn              F19   dmm               w
at            0.800   dmf           11764
np            30016       PROCESSING
sw          18761.7   lb             1.00
fb            10400   wtfile
bs               16   proc              ft
tpwr             52   fn         not used
pw              3.8
d1            1.000   werr
tof               0   wexp             wft
nt             1024   wbs              wft
ct               32   wnt
alock             n
gain        not used
      FLAGS
fl                n
in                y
dp                y
     DISPLAY
sp          -38748.2
wp          18761.7
vs               39
sc                0
wc              250
hzmm          75.05
is           500.00
rfl         38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```

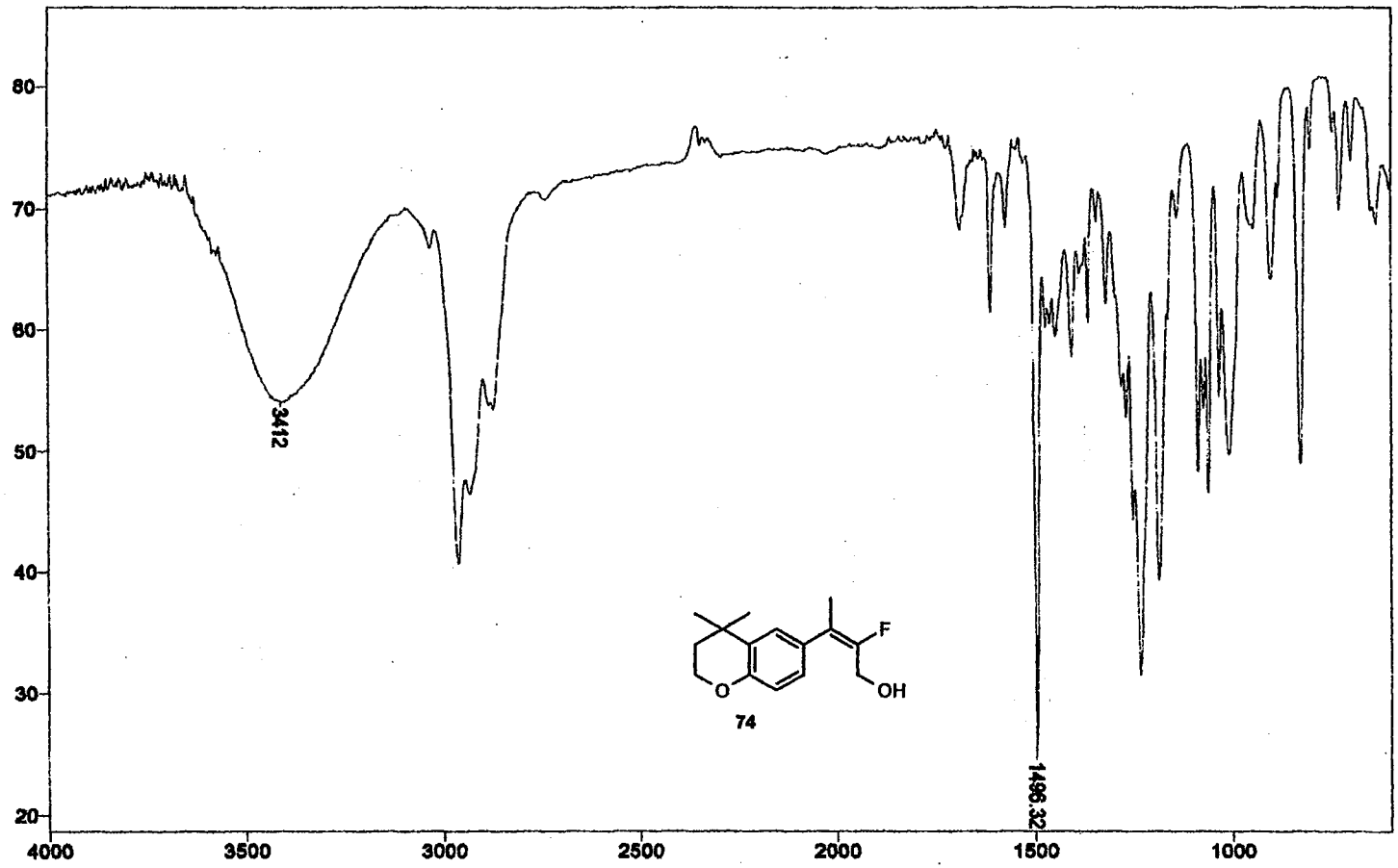


73



^{19}F NMR Spectrum of **73**

Plate LXXXIV



IR Spectrum of **74**

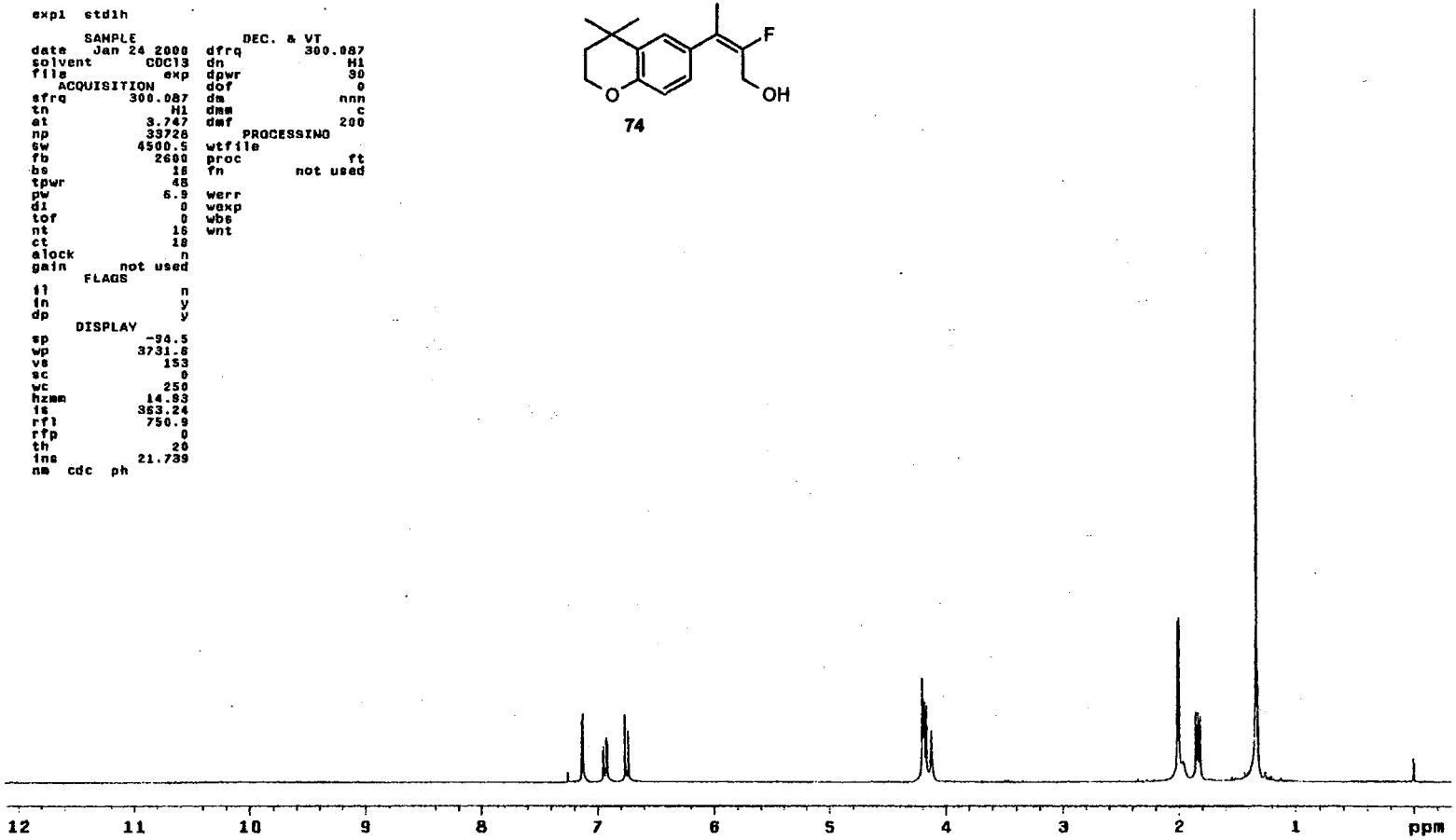
Plate LXXXV

```
STANDARD 1H OBSERVE

expl  std1h

      SAMPLE                    DEC. & VT
date   Jan 24 2000  dfrq          300.087
solvent       CDCl3 dn               H1
file            exp dpwr             30
   ACQUISITION      dof               0
sfrq        300.087 dm              nnn
tn               H1 dmm               c
at            3.747 dmf             200
np            33728      PROCESSING
sw           4500.5 wtfile
fb             2600 proc              ft
bs               16 fn         not used
tpwr             48
pw              6.9 werr
di                0 wexp
tof               0 wbs
nt               16 wnt
ct               18
alock             n
gain        not used
      FLAGS
ii                n
in                y
dp                y
      DISPLAY
sp            -94.5
wp           3731.6
vs              153
sc                0
wc              250
hzmm          14.93
is           363.24
rfl           750.9
rfp               0
th               20
ins          21.739
nm  cdc  ph
```


74

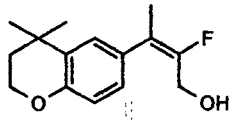


^{1}H NMR Spectrum of **74**

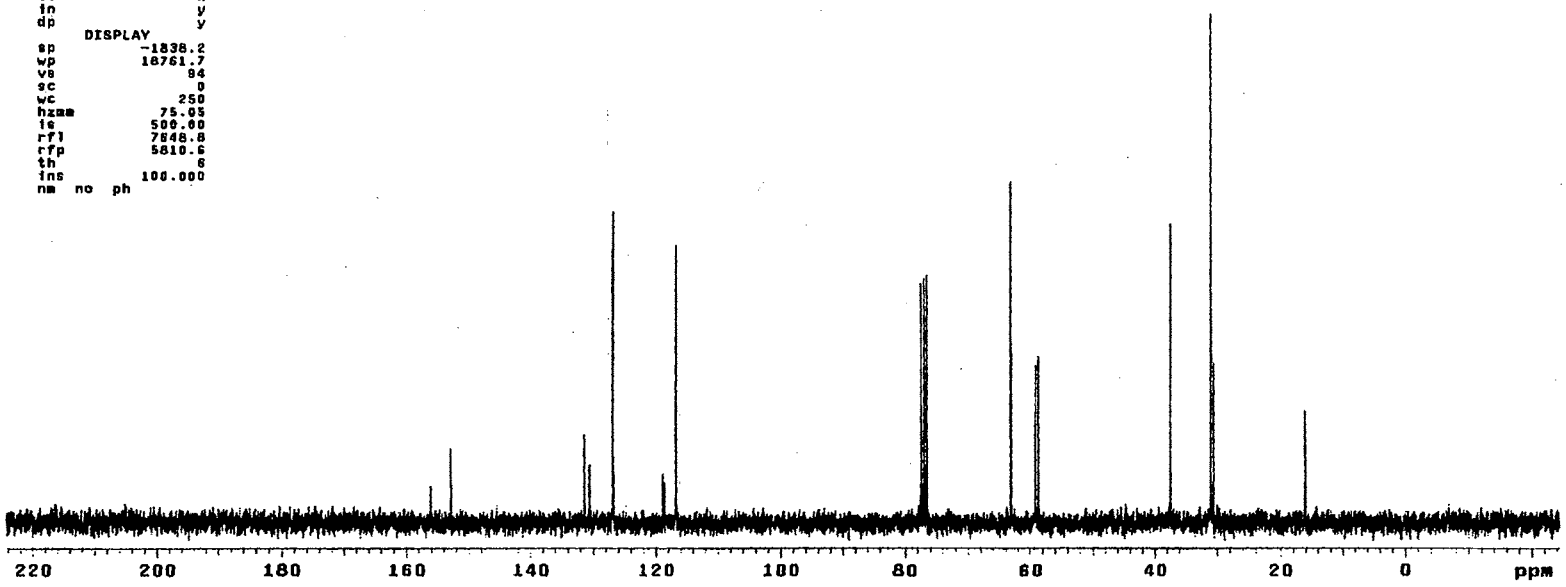
Plate LXXXVI

```
13C OBSERVE

exp1  std13c
        SAMPLE                DEC. & VT
date   Jan 24 2000   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof                 0
sfrq          75.464 dm                yyy
tn               C13 dmm                 w
at             0.800 dmf             11764
np             30016    PROCESSING
sw           18761.7 lb               1.00
fb             10400 wtfile
bs                16 proc               ft
tpwr              52 fn          not used
pw               3.8
d1             1.000 werr
tof                0 wexp              wft
nt              1024 wbs               wft
ct               128 wnt
alock              s
gain        not used
       FLAGS
ii                 n
in                 y
dp                 y
     DISPLAY
sp           -1838.2
wp           18761.7
vs                94
sc                 0
wc               250
hzcm           75.05
is             500.00
rf1            7848.8
rfp            5810.6
th                 6
ins            100.000
nm  no  ph
```



74



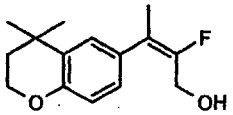
^{13}C NMR Spectrum of **74**

Plate LXXXVII

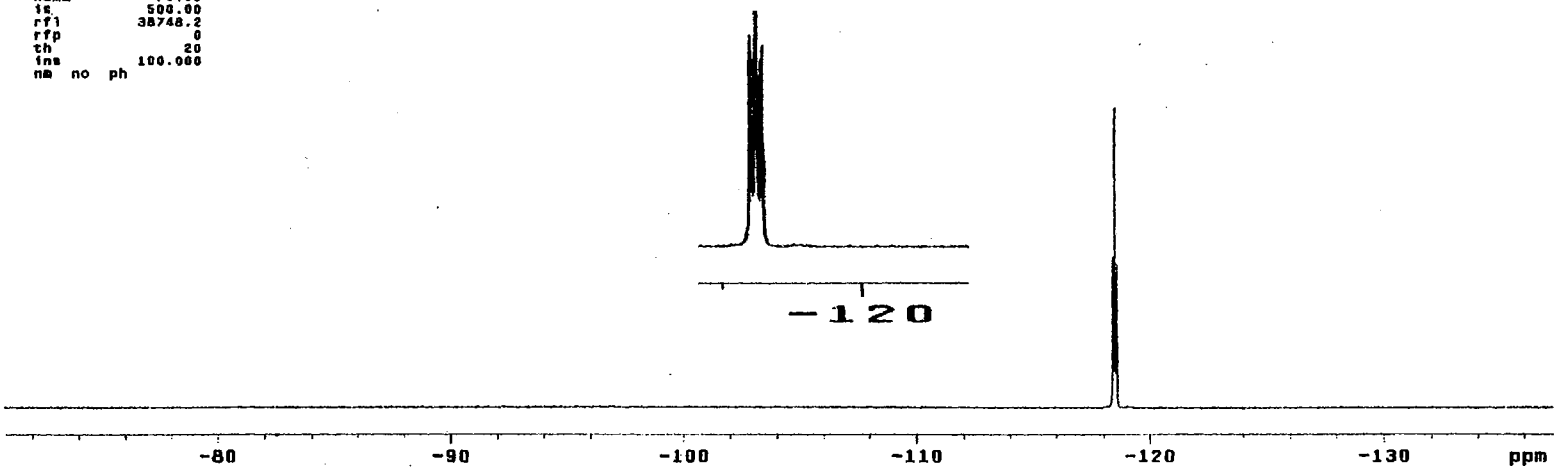
```
13C OBSERVE

expl  std13c

        SAMPLE                    DEC. & VT
date   Jan 24 2000.  dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                  0
sfrq        282.333  dm                 nnn
tn              F19  dmm                  w
at            0.800  dmf             11764
np            30016     PROCESSING
sw          18761.7  lb                1.00
fb            10490  wtfile
bs               16  proc                ft
tpwr             52  fn            not used
pw              3.8
d1            1.000  werr
tof               0  wexp               wft
nt             1024  wbs                wft
ct               48  wnt
alock             n
gain        not used
       FLAGS
fl                n
in                y
dp                y
      DISPLAY
sp          -38748.2
wp          18761.7
vs                55
sc                 0
wc               250
hzmm           75.05
is             500.00
rf1         38748.2
rfp                0
th                20
ins           100.000
nm  no  ph
```

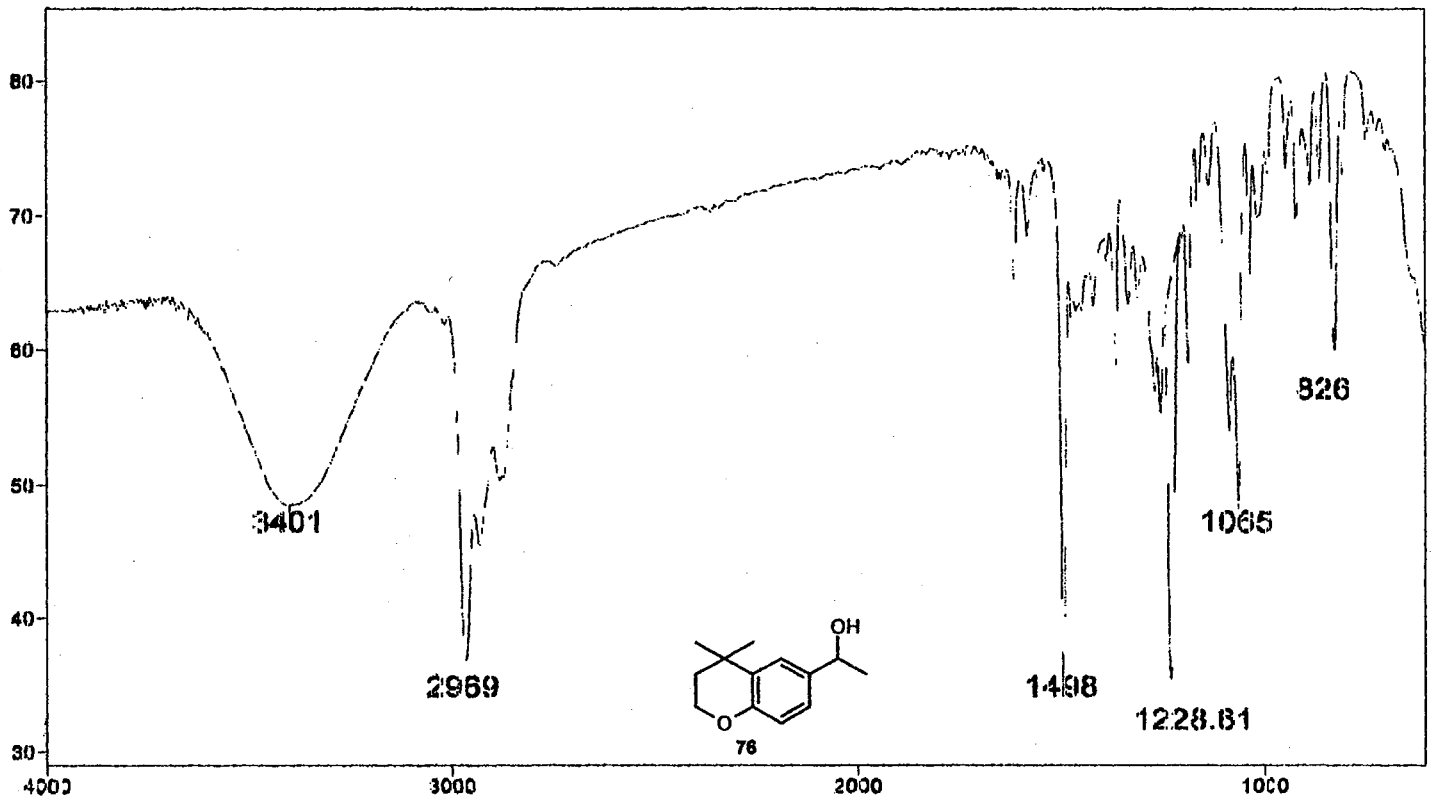


74



^{19}F NMR Spectrum of **74**

Plate LXXXVIII



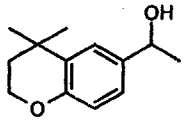
IR Spectrum of **76**

Plate LXXXIX

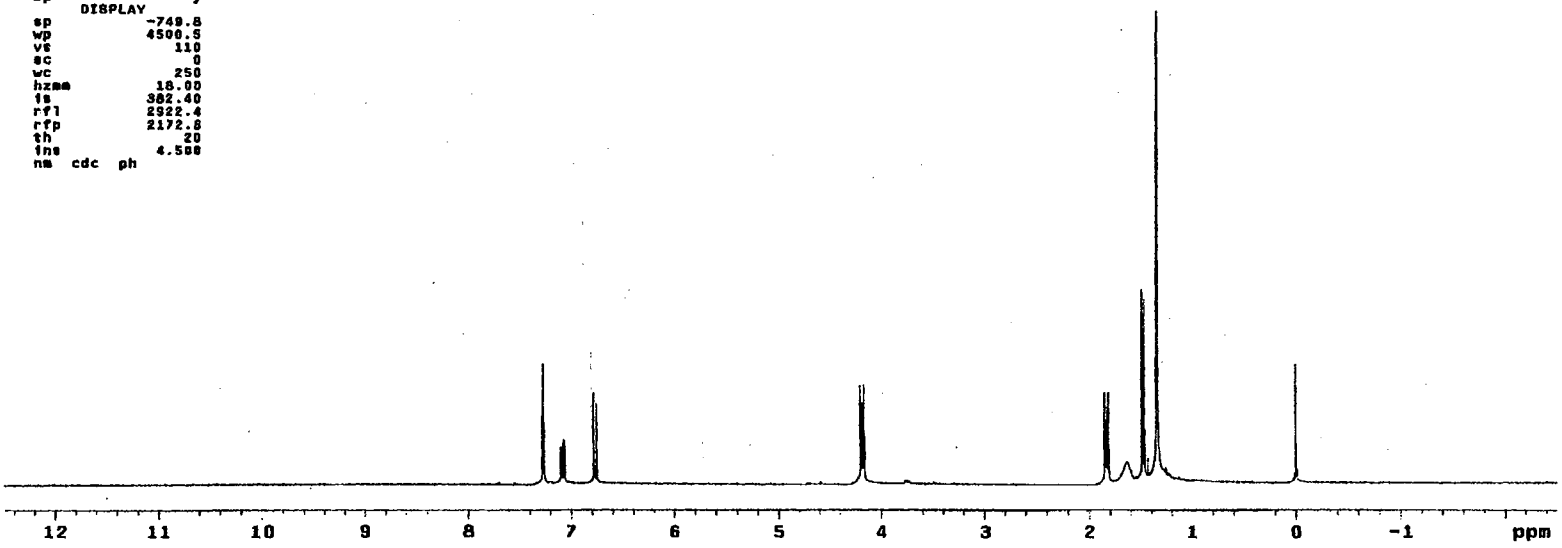
```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                 DEC. & VT
date      Aug 18 98   dfrq          300.082
solvent       CDCl3   dn               H1
file /export/home/~   dpwr             30
   Klucik/alcohol6    dof               0
   ACQUISITION        dm              nnn
sfrq        300.082   dmm               c
tn               H1   dmf             290
at             3.001        PROCESSING
np             27008   wtfile
sw            4500.5   proc            ft
fb             2600   fn         not used
bs               16
tpwr             48   werr
pw              4.5   wexp
d1            1.500   wbs
tof               0   wnt
nt               16
ct               16
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp            -749.8
wp            4500.5
vs               110
sc                 0
wc               250
hzcm           18.00
is            382.40
rfl           2922.4
rfp           2172.8
th                20
ins            4.500
nm  cdc  ph
```

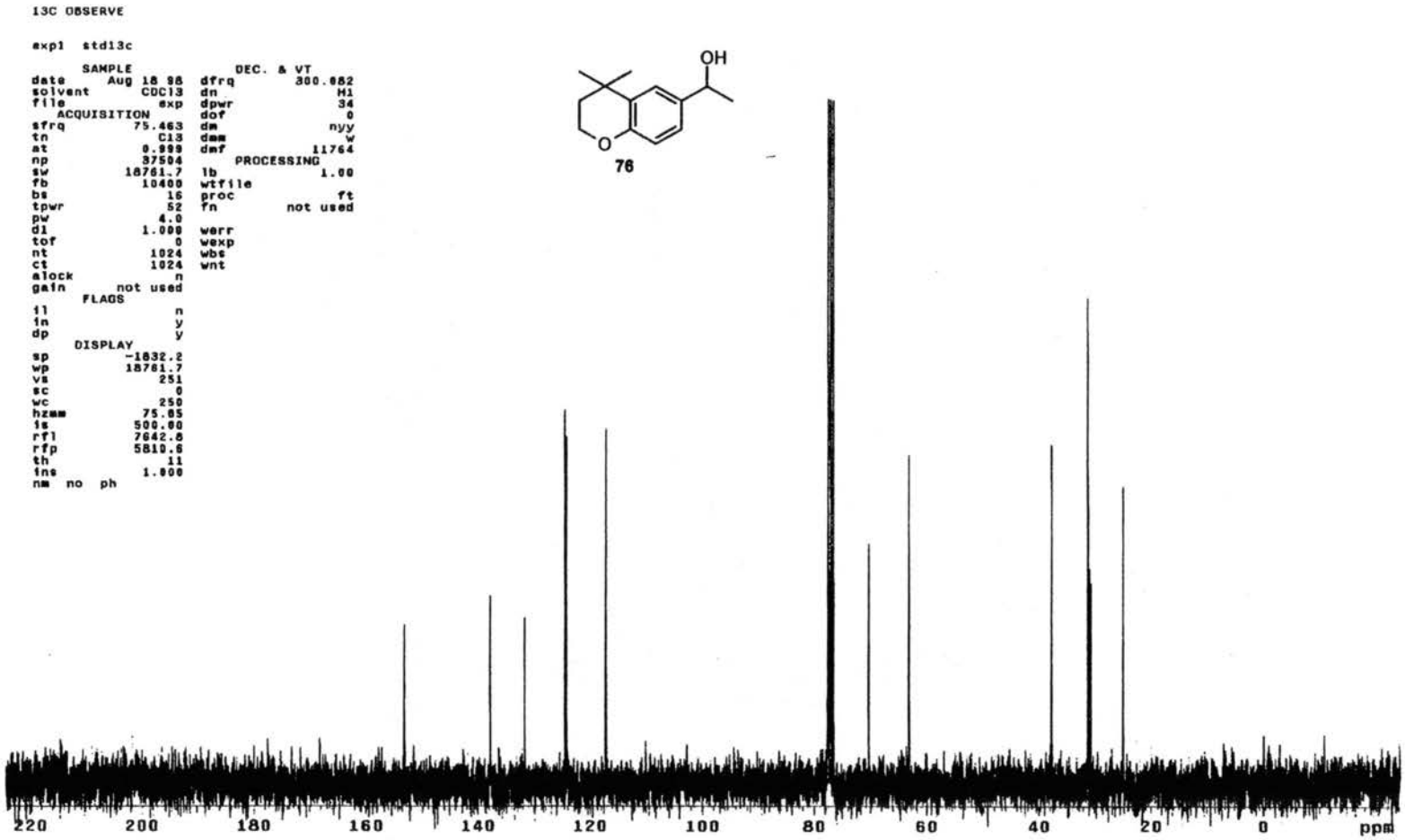


76



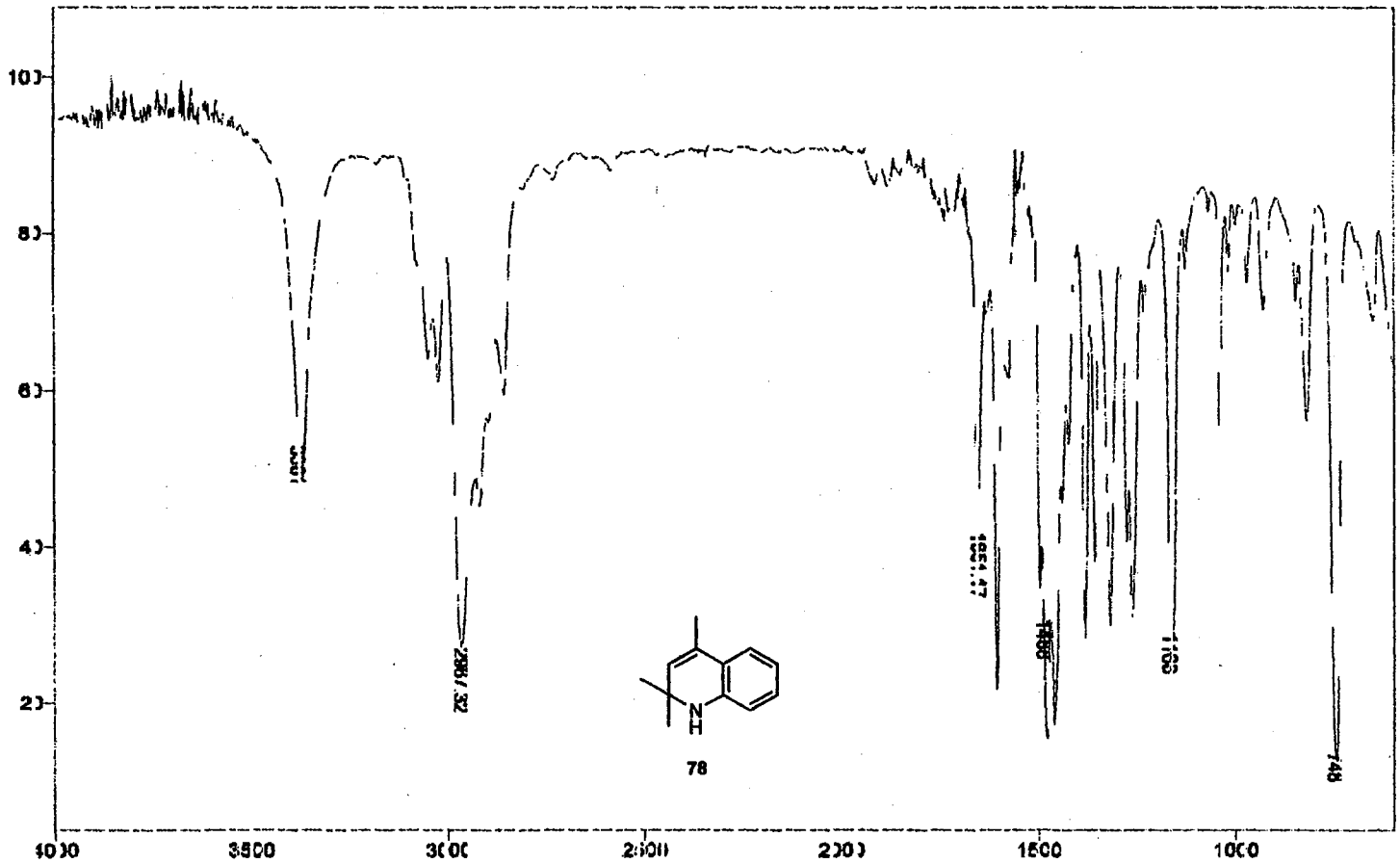
^{1}H NMR Spectrum of **76**

Plate XC



^{13}C NMR Spectrum of **76**

Plate XCI



IR Spectrum of **78**

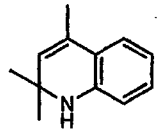
Plate XCII

STANDARD 1H OBSERVE

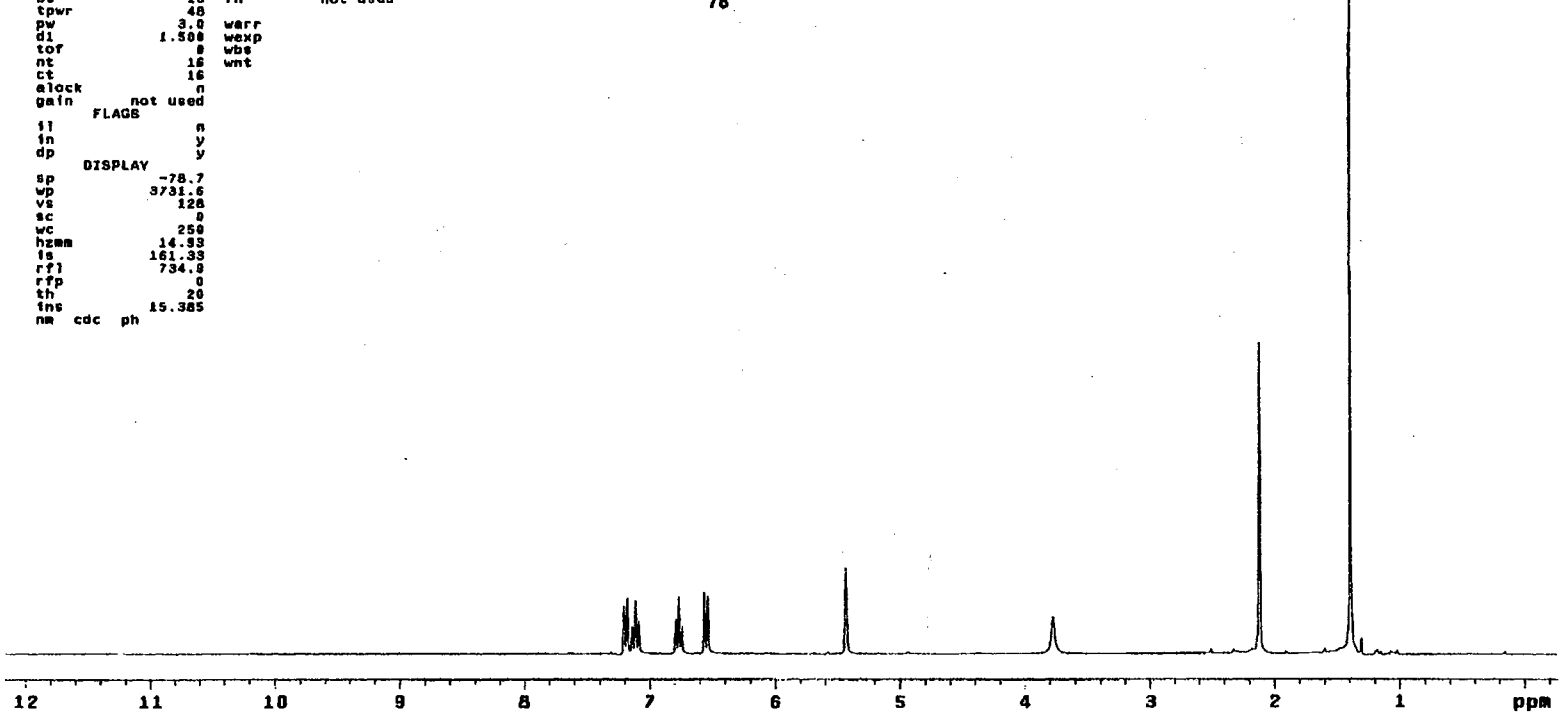
expl stdih

SAMPLE		DEC. & VT	
date	Feb 22 1999	dfrq	300.087
solvent	CDCl3	dn	H1
file	exp	dpwr	39
ACQUISITION		dof	0
sfrq	300.087	dm	nnn
tn	H1	dmm	c
at	3.001	dmf	200
np	27008	PROCESSING	
sw	4500.5	wtfile	
fb	2600	proc	ft
bs	16	fn	not used
tpwr	48		
pw	3.0	werr	
d1	1.500	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	y		
dp	y		
DISPLAY			
sp	-78.7		
wp	3731.6		
vs	128		
sc	0		
wc	250		
hzcm	14.93		
hs	161.33		
rfl	734.9		
rfp	0		
th	20		
ins	15.385		

nm cdc ph

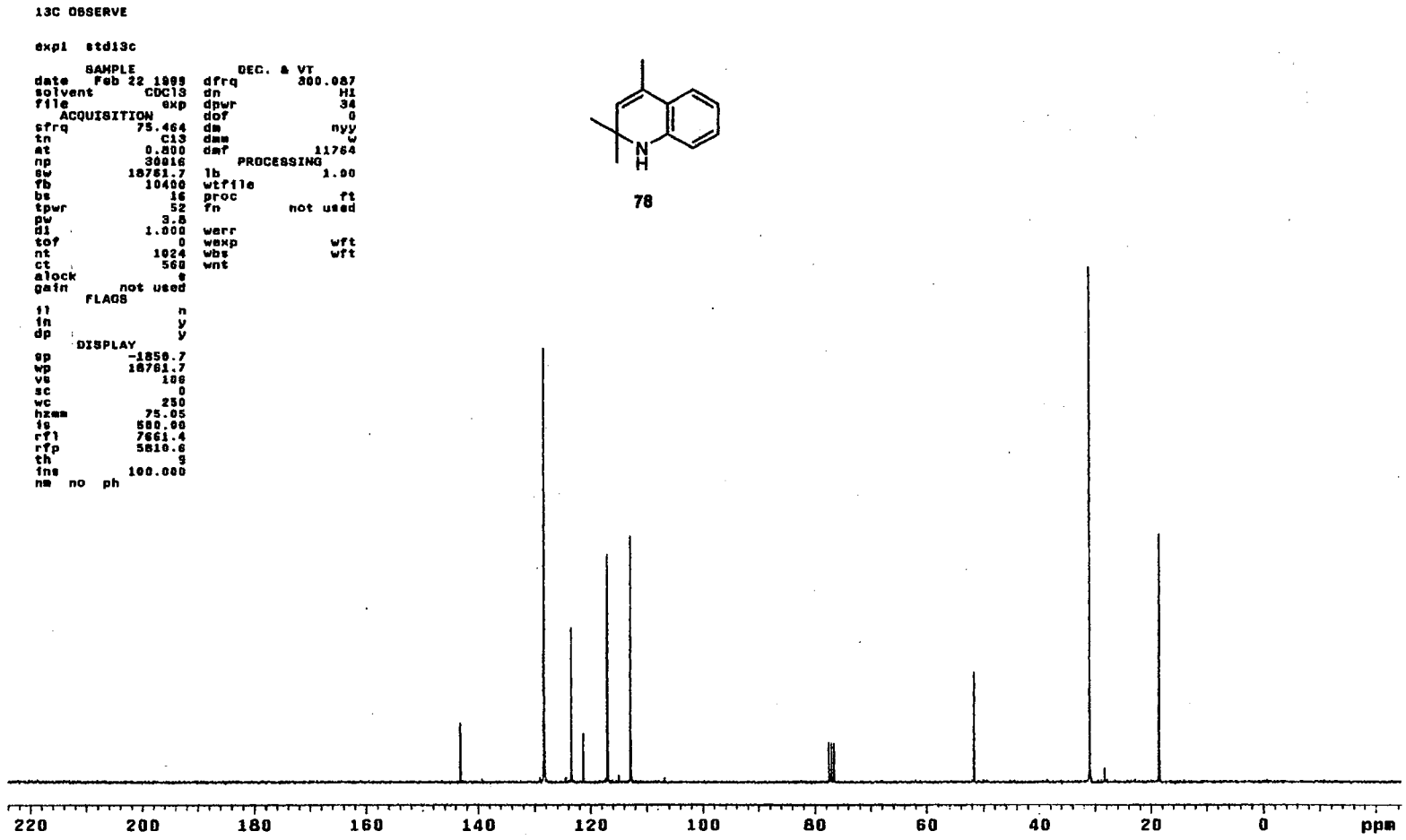


78



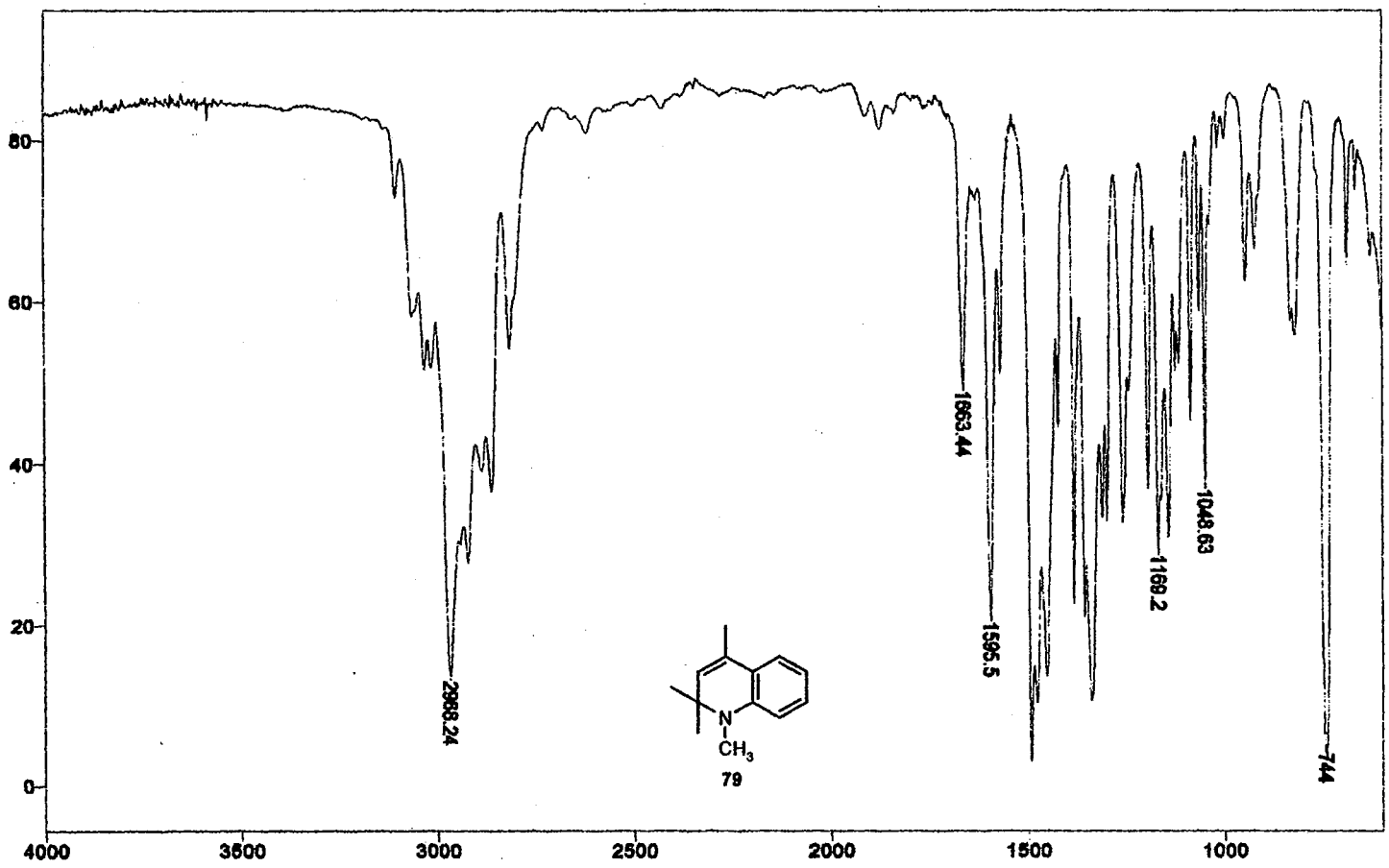
^{1}H NMR Spectrum of **78**

Plate XCIII



^{13}C NMR Spectrum of **78**

Plate XCIV



IR Spectrum of **79**

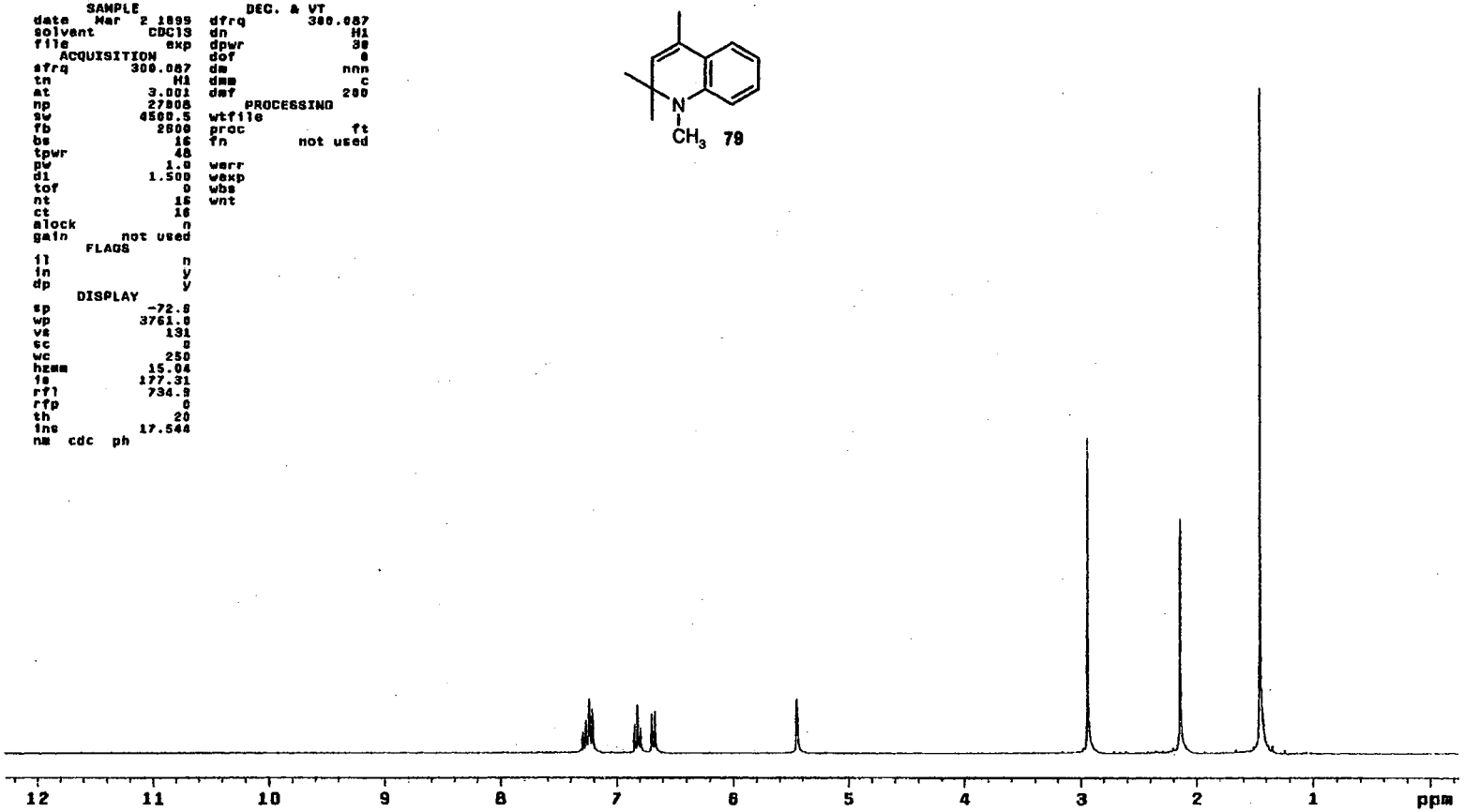
Plate XCV

```
STANDARD 1H OBSERVE

expl  std1h

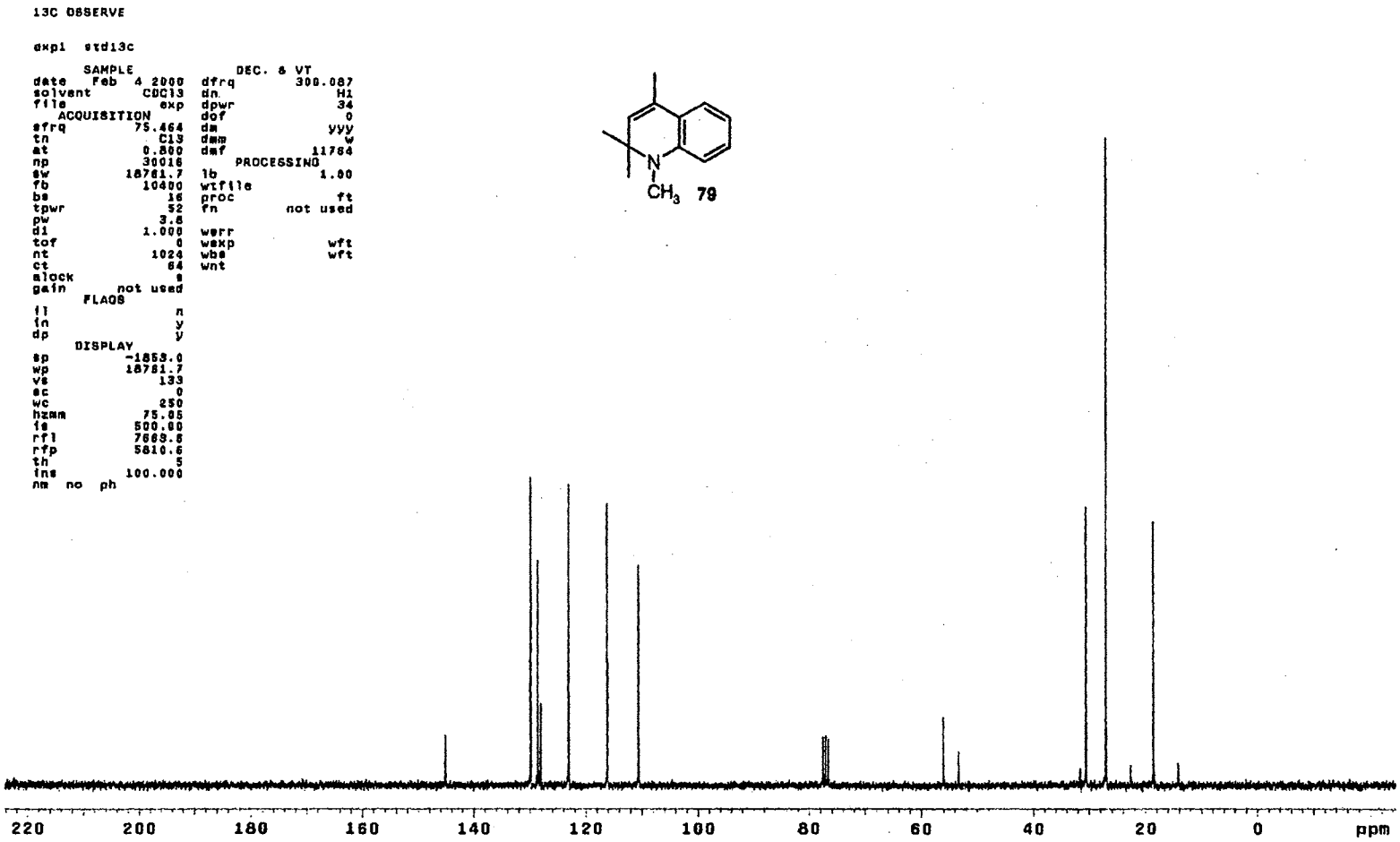
      SAMPLE                DEC. & VT
date   Mar  2 1899  dfrq          300.087
solvent       CDCl3 dn                 H1
file            exp dpwr               38
   ACQUISITION      dof                 0
sfrq        300.087 dm                nnn
tn               H1 dmm                 c
at            3.001 dmf               200
np            27808     PROCESSING
sw           4500.5 wtfile
fb             2800 proc               ft
bs               16 fn         not used
tpwr             48
pw              1.0 werr
d1            1.500 wexp
tof               0 wbs
nt               16 wnt
ct               16
alock             n
gain        not used
       FLAGS
il                n
in                y
dp                y
     DISPLAY
sp            -72.8
wp           3761.0
vs              131
sc                0
wc              250
hzcm          15.04
is           177.31
rfl           734.9
rfp               0
th               20
ins           17.544
nm  cdc  ph
```


79



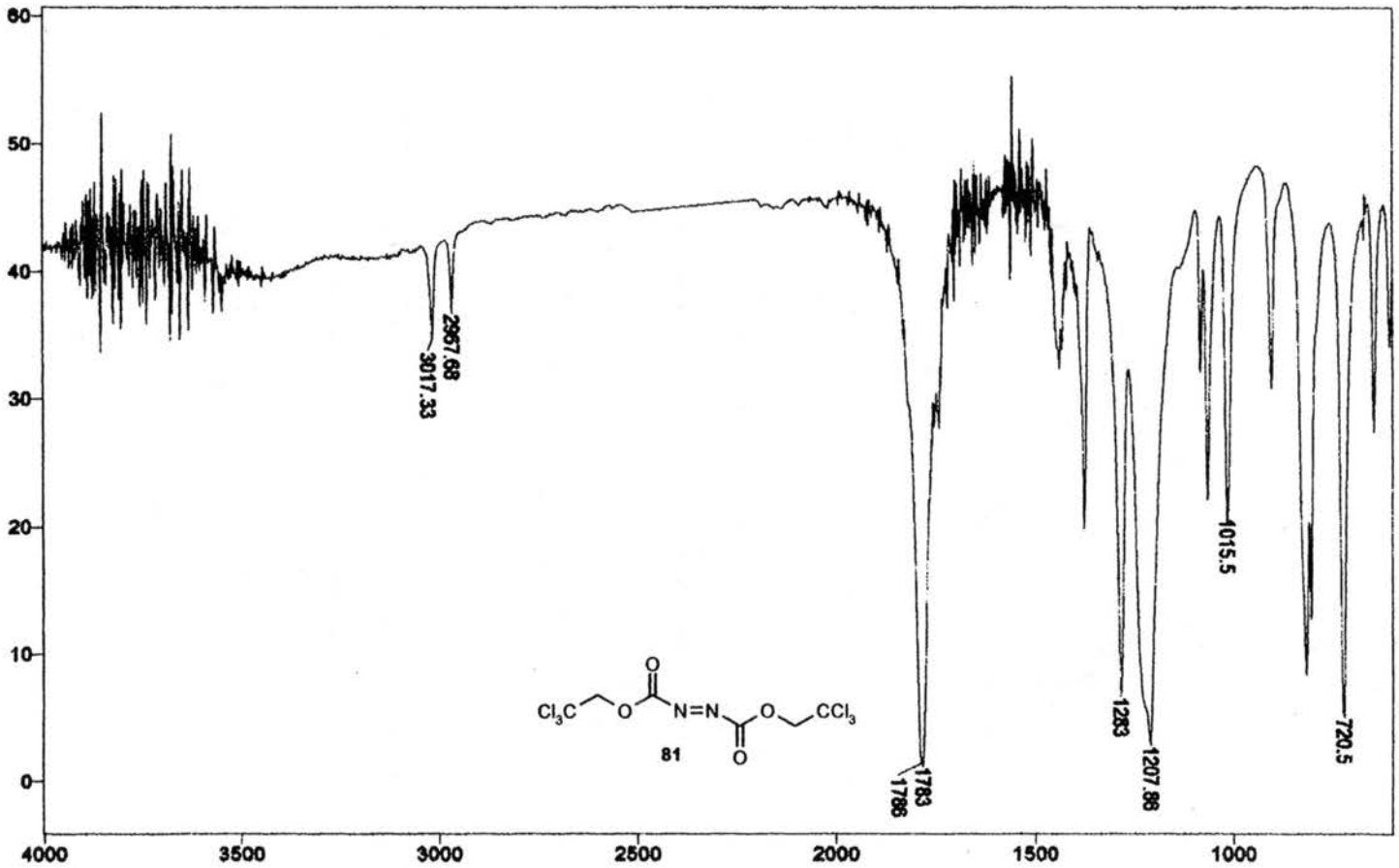
^{1}H NMR Spectrum of **79**

Plate XCVI



^{13}C NMR Spectrum of **79**

Plate XCVII



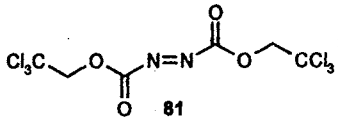
IR Spectrum of **81**

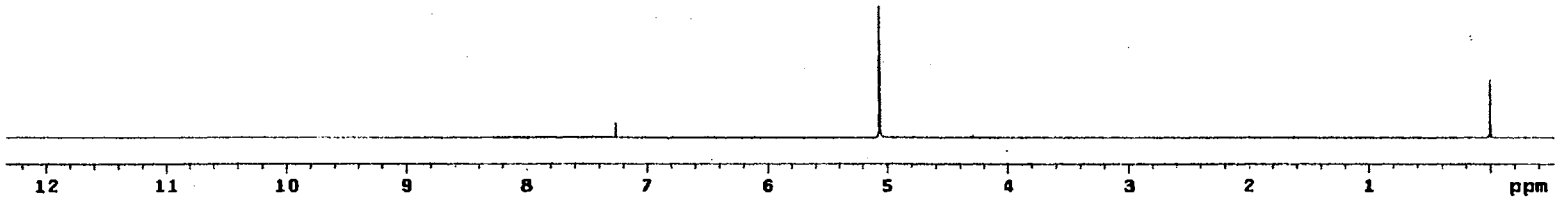
Plate XCVIII

```
STANDARD 1H OBSERVE

exp1  stdih

      SAMPLE                 DEC. & VT
date    Mar 31 1999  dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr              38
   ACQUISITION       dof               0
sfrq        300.087  dm              nnn
tn               H1  dmm               c
at            3.001  dmf             200
np            27008      PROCESSING
sw           4500.5  wtfile
fb             2000  proc             ft
bs               18  fn         not used
tpwr             48
pw              3.0  werr
d1            1.500  wexp
tof               0  wbs
nt                8  wnt
ct                8
alock             n
gain       not used
      FLAGS
ii                n
in                y
dp                y
     DISPLAY
sp           -157.7
wp           3861.5
vs               24
sc                0
wc              250
hzcm          15.45
fs           302.26
rfl           748.8
rfp               0
th               20
ins           4.000
nm  cdc  ph
```





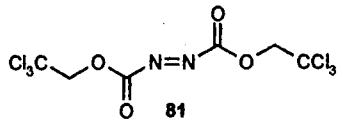
^{1}H NMR Spectrum of **81**

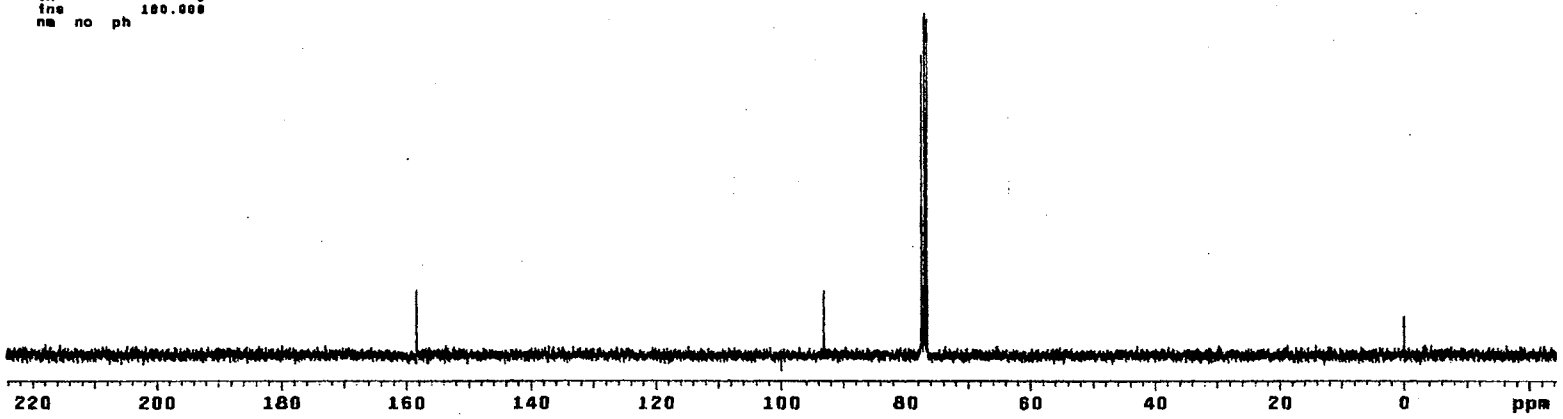
Plate XCIX

```
13C OBSERVE

exp1  std13c

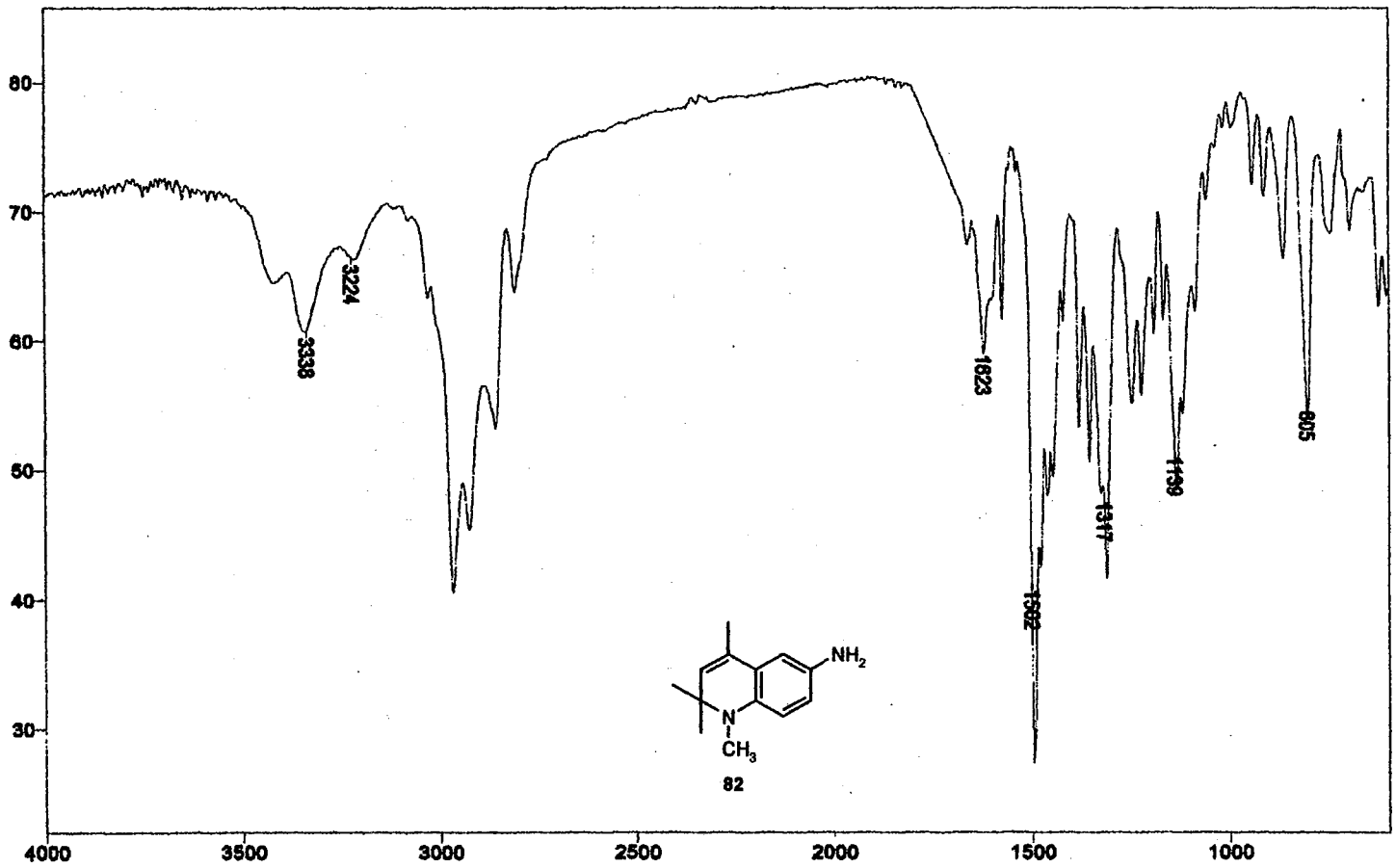
      SAMPLE                    DEC. & VT
date   Mar 31 1888   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                 0
sfrq         75.464  dm                yyy
tn              C13  dmm                 w
at            9.000  dmf             11764
np            30816     PROCESSING
sw          18761.7  lb               1.00
fb            10400  wtfile
bs               16  proc               ft
tpwr             52  fn          not used
pw              3.6
d1            1.000  werr
tof               0  wexp              wft
nt             1024  wbs               wft
ct              844  wnt
alock             s
gain        not used
      FLAGS
i1                n
in                y
dp                y
     DISPLAY
sp          -1885.9
wp          18761.7
vs               63
sc                0
wc              250
hzmm          75.05
is            500.00
rfl           7646.5
rfp           5810.6
th                8
ins         180.000
nm  no  ph
```





^{13}C NMR Spectrum of **81**

Plate C



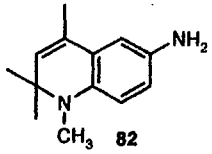
IR Spectrum of **82**

Plate CI

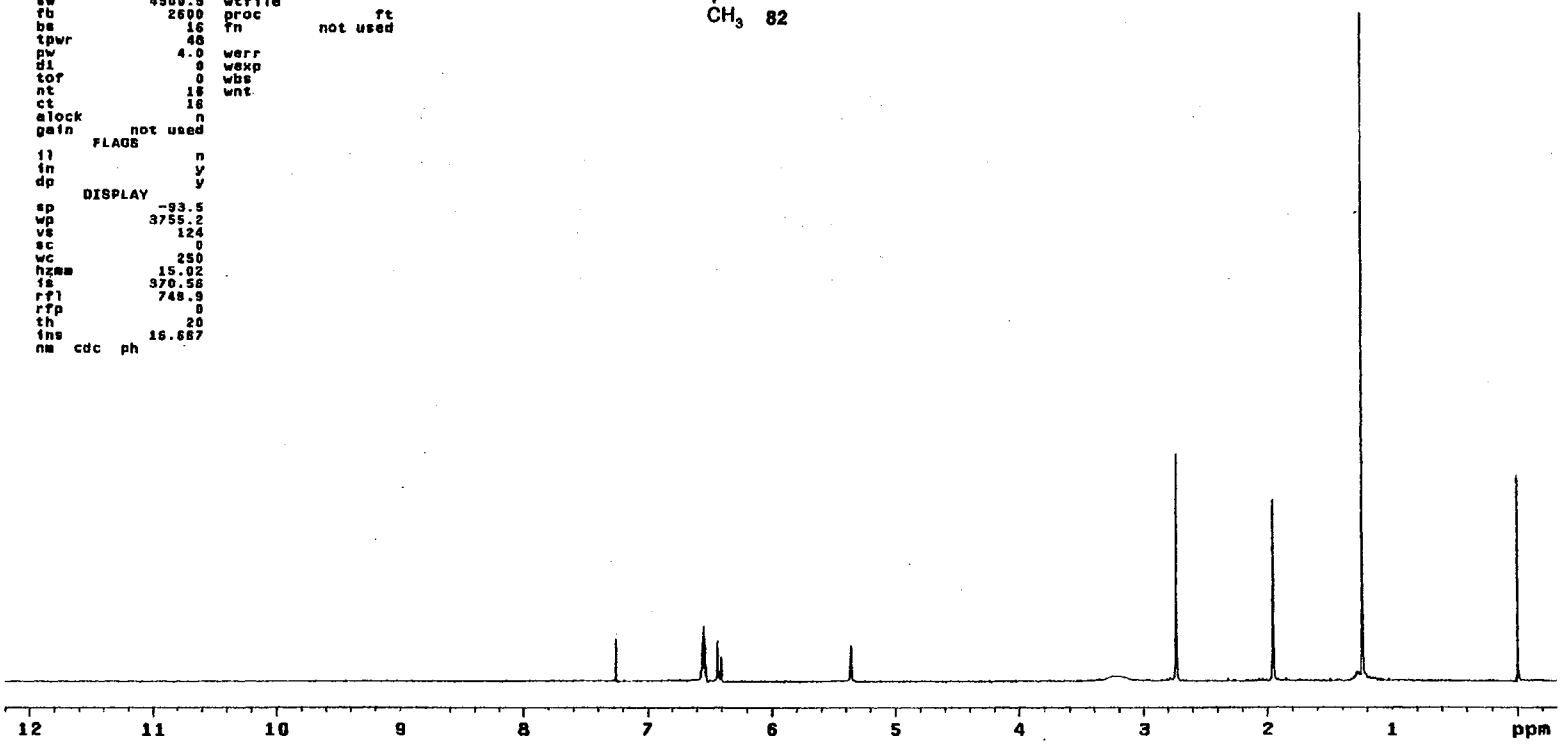
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date   Apr 12 1999   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               30
   ACQUISITION       dof                  0
sfrq        300.087  dm                 nnn
tn               H1  dmm                  c
at            3.747  dmf                zod
np           33728       PROCESSING
sw           4500.5  wtfile
fb             2600  proc                ft
bs               16  fn          not used
tpwr             46
pw              4.0  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp            -93.5
wp           3755.2
vs              124
sc                0
wc              250
hzcm          15.02
is           370.56
rfl           748.9
rfp               0
th               20
ins           16.687
nm  cdc  ph
```



82



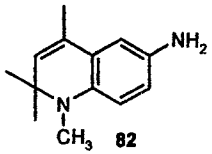
^{1}H NMR Spectrum of **82**

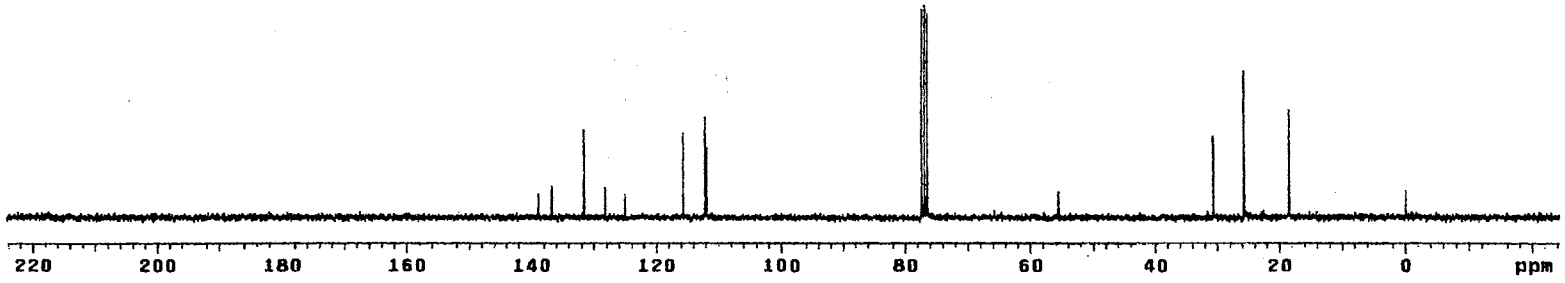
Plate CII

```
13C OBSERVE

expl  std13c

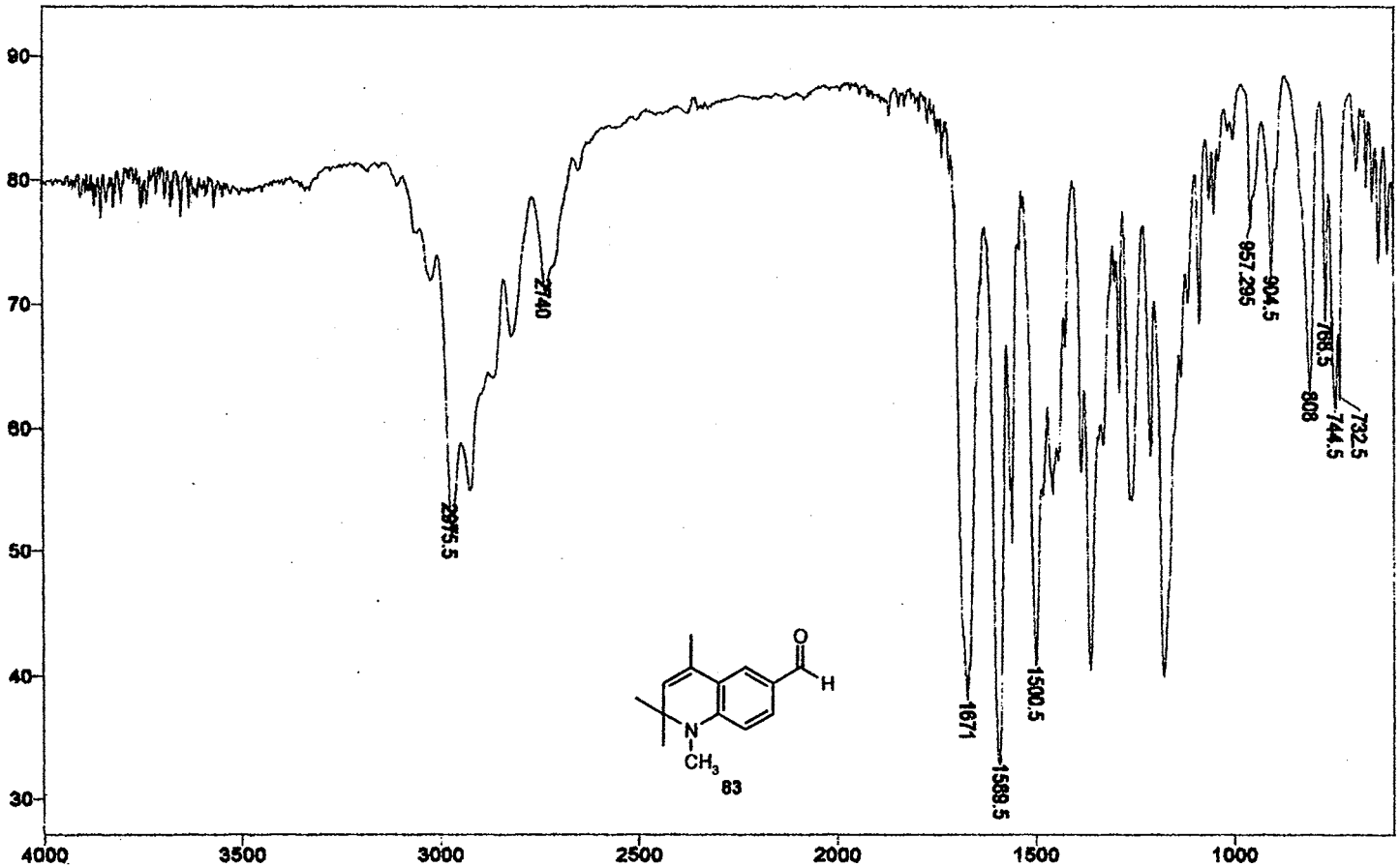
      SAMPLE                 DEC. & VT
date   Apr 12 1999   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof                0
sfrq         75.464  dm               yyy
tn              C13  dmm                w
at            0.800  dmf            11764
np            30016     PROCESSING
sw          18761.7  lb             1.00
fb           10400  wtfile
bs              16  proc              ft
tpwr            52  fn         not used
pw             3.8
d1           1.000  werr
tof             0   wexp            wft
nt           1024   wbs             wft
ct           1024   wnt
alock            s
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp          -1835.9
wp          18761.7
vs               39
sc                0
wc              250
hzmm          75.05
is           500.00
rfl          7646.5
rfp          5810.6
th                4
ins          100.000
nm  no  ph
```





^{13}C NMR Spectrum of **82**

Plate CIII



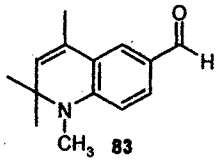
IR Spectrum of **83**

Plate CIV

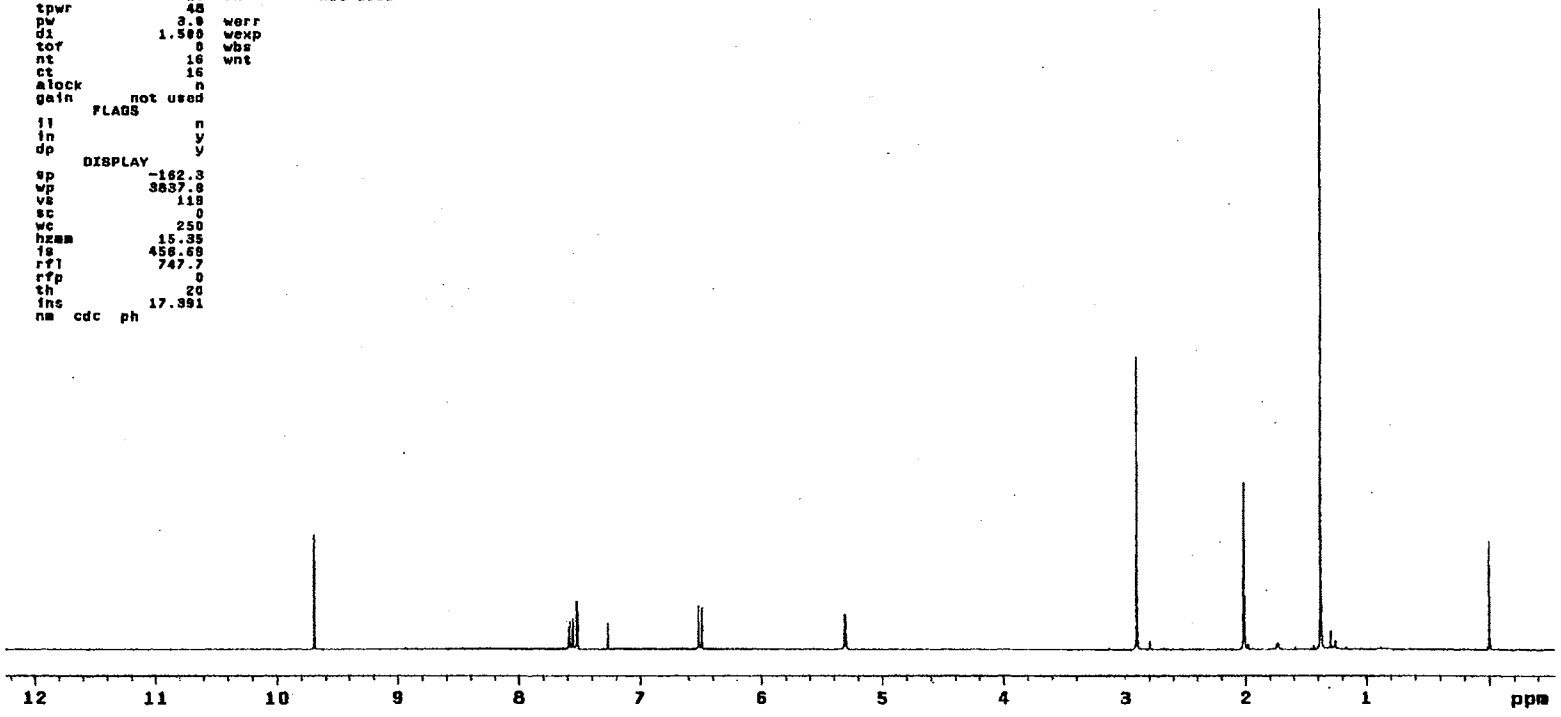
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                 DEC. & VT
date   Mar 31 1995   dfrq          300.087
solvent      CDCl3   dn                H1
file           exp   dpwr              38
   ACQUISITION       dof                0
sfrq         300.087 dm               nnn
tn               H1  dmm                c
at            3.001  dmf              200
np            27688      PROCESSING
sw           4500.5  wtfile
fb             2600  proc              ft
bs               16  fn         not used
tpwr             48
pw              3.0  werr
d1            1.500  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain        not used
      FLAGS
ii                n
in                y
dp                y
     DISPLAY
sp           -162.3
wp           3837.6
vs              118
sc                0
wc              250
hzcm          15.35
is           456.68
rfl           747.7
rfp               0
th               20
ins           17.391
nm  cdc  ph
```



83



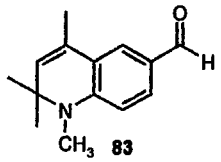
^{1}H NMR Spectrum of **83**

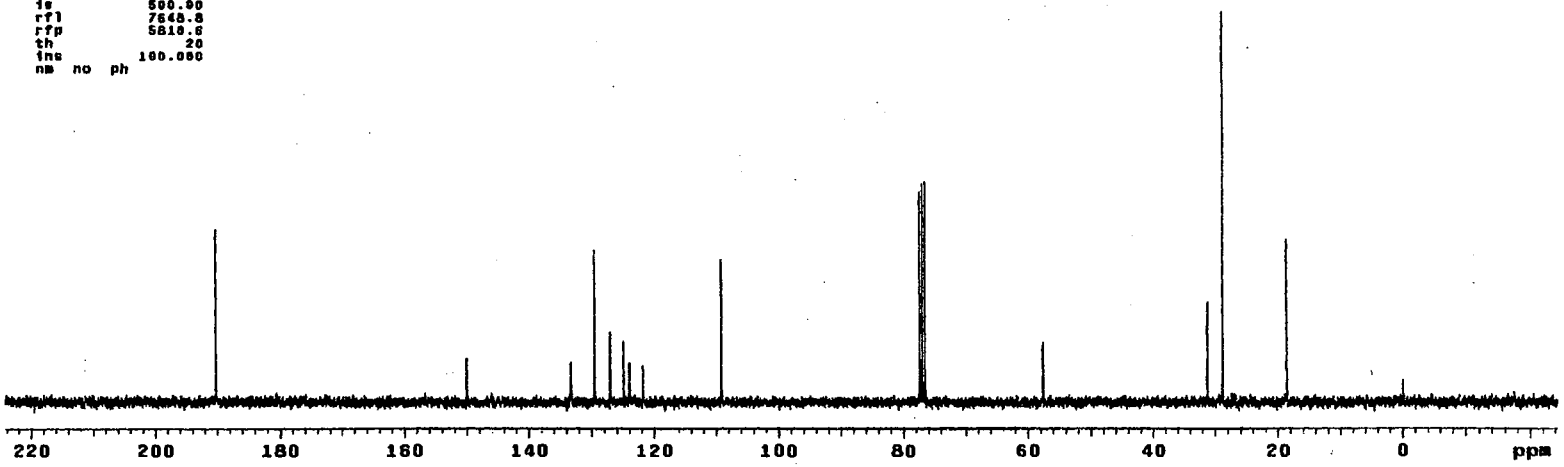
Plate CV

```
13C OBSERVE

exp1  std13c

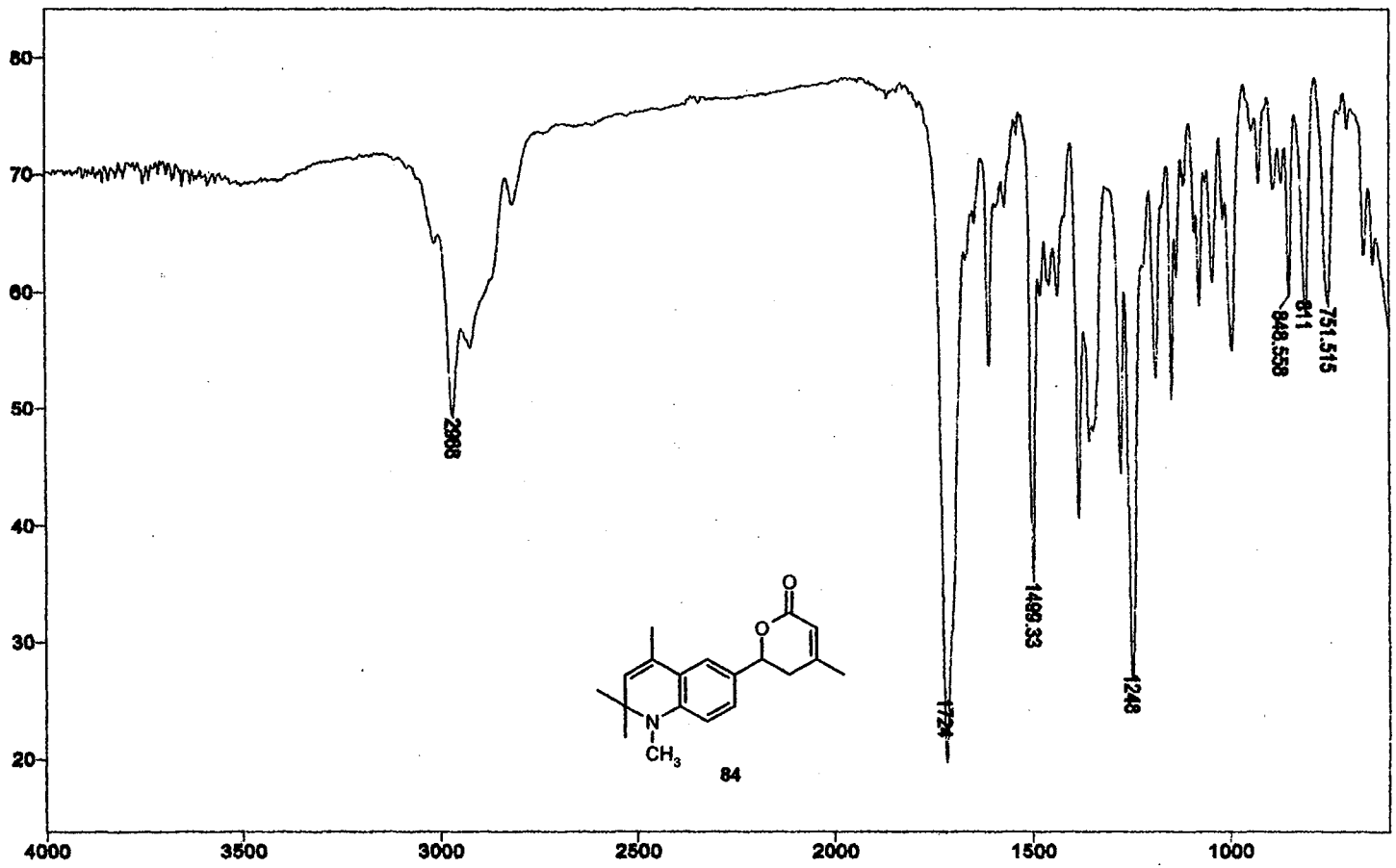
        SAMPLE                  DEC. & VT
date    Mar 31 1999     dfrq          300.087
solvent        CDCl3    dn                H1
file             exp    dpwr               34
   ACQUISITION          dof                 0
sfrq           75.464   dm                yyy
tn                C13   dmm                 w
at              0.800   dmf             11764
np             30816       PROCESSING
sw           18761.7    lb                1.00
fb             10400    wtfile
bs                16    proc                ft
tpwr              52    fn            not used
pw               3.0
d1              1.000   werr
tof                0    wexp               wft
nt              1024    wbs                wft
ct               288    wnt
alock              s
gain         not used
        FLAGS
i1                 n
in                 y
dp                 y
       DISPLAY
sp            -1838.2
wp           18761.7
vs                72
sc                 0
wc               250
hzcm           73.05
is             500.00
rf1            7648.8
rfp            5810.6
th                20
ins           100.000
nm  no  ph
```





^{13}C NMR Spectrum of **83**

Plate CVI



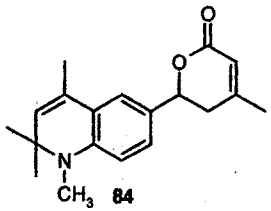
IR Spectrum of **84**

Plate CVII

```
STANDARD 1H OBSERVE

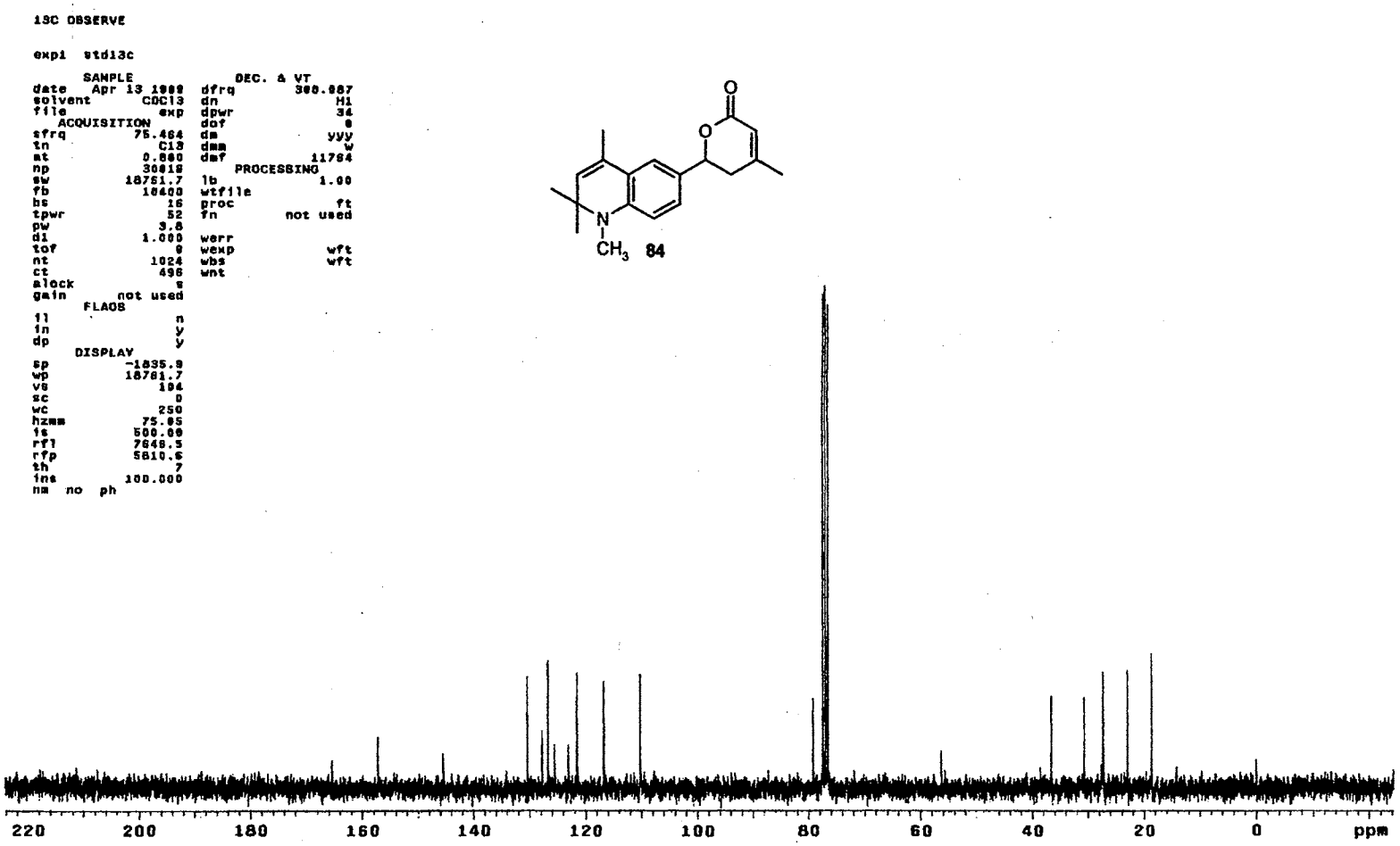
expl  std1h

      SAMPLE                DEC. & VT
date   Apr 13 1988   dfrq          300.087
solvent       CDCl3  dn                Hi
file            exp  dpwr              30
   ACQUISITION       dof               0
sfrq        300.087  dm               nnn
tn               H1  dmm               c
at            3.747  dmf             200
np           33728      PROCESSING
sw          4500.5   wtfile
fb            2600   proc             ft
bs              16   fn         not used
tpwr            48
pw             4.0   werr
d1               0   wexp
tof              0   wbs
nt              16   wnt
ct              16
alock            n
gain       not used
      FLAGS
il               n
in               y
dp               y
     DISPLAY
sp          -123.8
wp          3790.8
vs              38
sc               0
wc             250
hzmm          7.84
is          500.00
rfl          750.7
rfp              0
th              34
ins         25.000
nm  cdc  ph
```



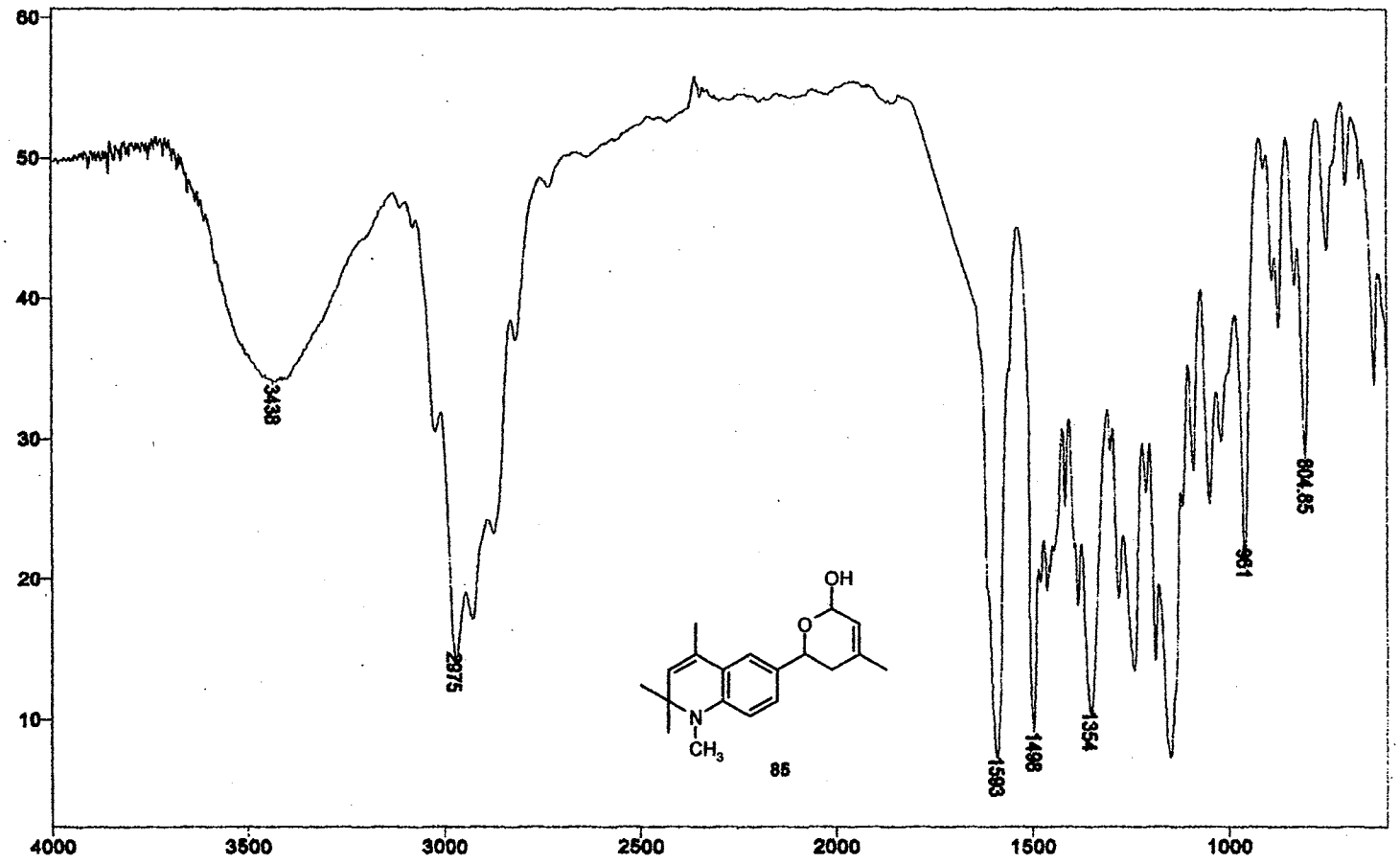
^{1}H NMR Spectrum of **84**

Plate CVIII



^{13}C NMR Spectrum of **84**

Plate CIX



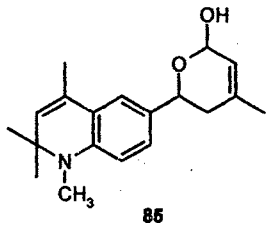
IR Spectrum of **85**

Plate CX

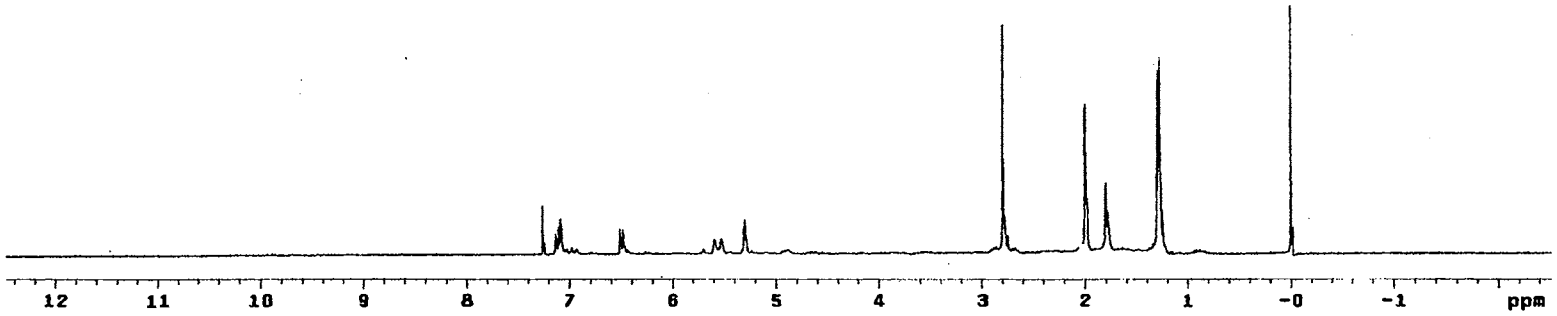
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                 DEC. & VT
date   Jun 16 1999  dfrq          300.087
solvent       CDCl3  dn               H1
file            exp  dpwr             30
   ACQUISITION       dof               0
sfrq        300.087  dm              nnn
tn               H1  dmm               c
at            3.747  dmf             200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2600  proc             ft
bs               16  fn          not used
tpwr             46
pw              6.9  werr
d1                0  wexp
tof               0  wbs
nt               32  wnt
ct               32
alock             n
gain       not used
      FLAGS
i1                n
in                y
dp                y
     DISPLAY
sp           -755.9
wp           4500.5
vs               46
sc                0
wc              250
hzmm          18.00
is           500.00
rf1           755.9
rfp               0
th               28
ins          100.000
nm  cdc  ph
```



85



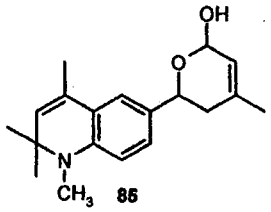
^{1}H NMR Spectrum of **85**

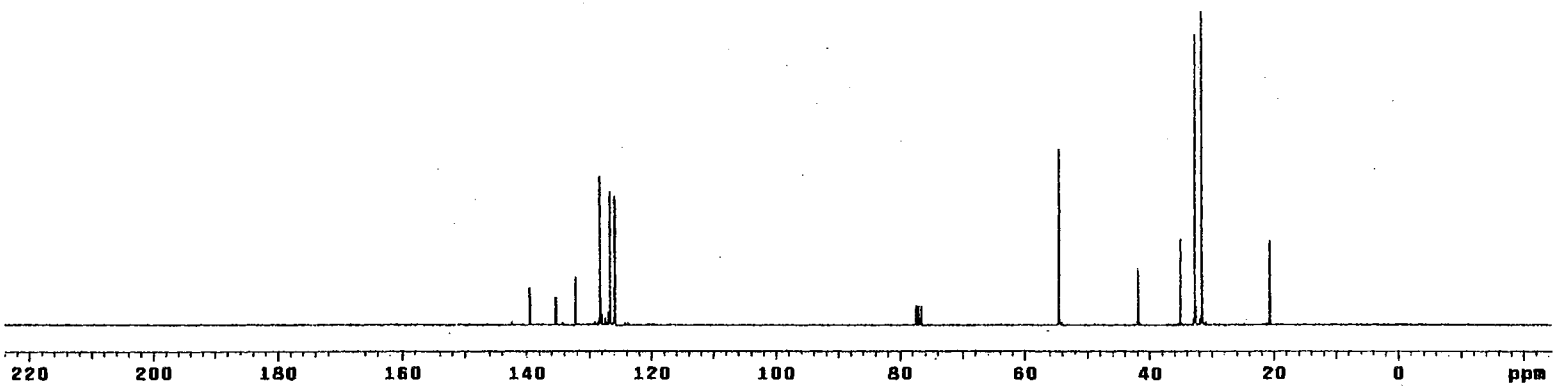
Plate CXI

```
13C OBSERVE

exp1  std13c

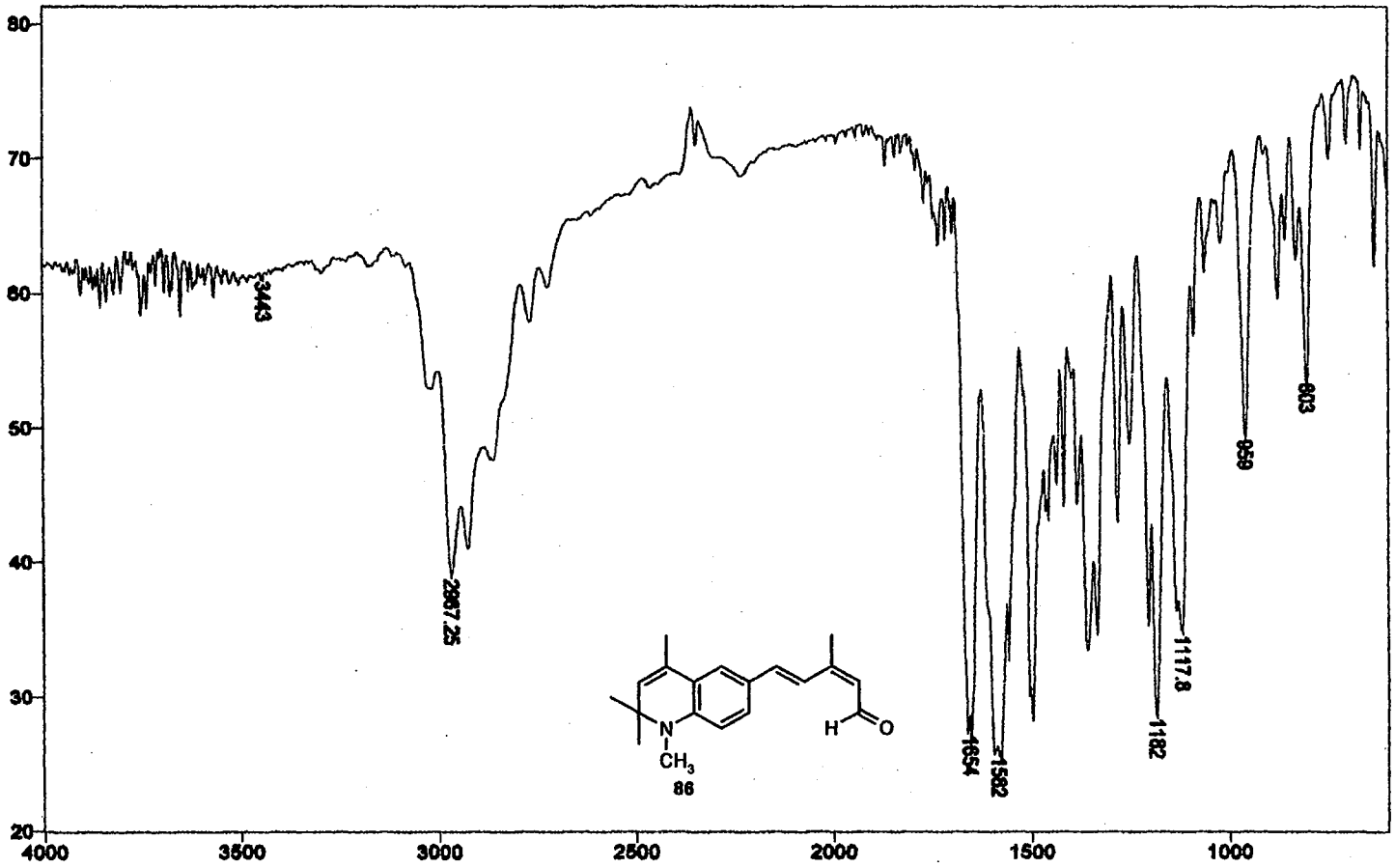
      SAMPLE                 DEC. & VT
date   Jul  6 1999   dfrq          300.087
solvent       CDCl3  dn                Hi
file            exp  dpwr              34
   ACQUISITION       dof               0
sfrq         75.464  dm               yyy
tn              C13  dmm               w
at            0.800  dmf            11764
np            30016     PROCESSING
sw          18761.7  lb              1.00
fb            10400  wtfile
bs               16  proc              ft
tpwr             52  fn          not used
pw              3.8
d1            1.000  werr
tof               0  wexp             wft
nt             1024  wbs              wft
ct              576  wnt
alock             s
gain        not used
      FLAGS
ii                n
in                y
dp                y
      DISPLAY
sp          -1854.2
wp          18761.7
vs               58
sc                0
wc              250
hzmm          75.05
is            500.00
rf1          7664.8
rfp          5810.6
th                3
ins          100.000
nm  no  ph
```





^{13}C NMR Spectrum of **85**

Plate CXII



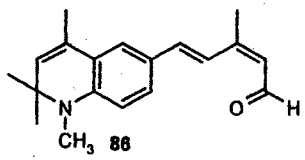
IR Spectrum of **86**

Plate CXIII

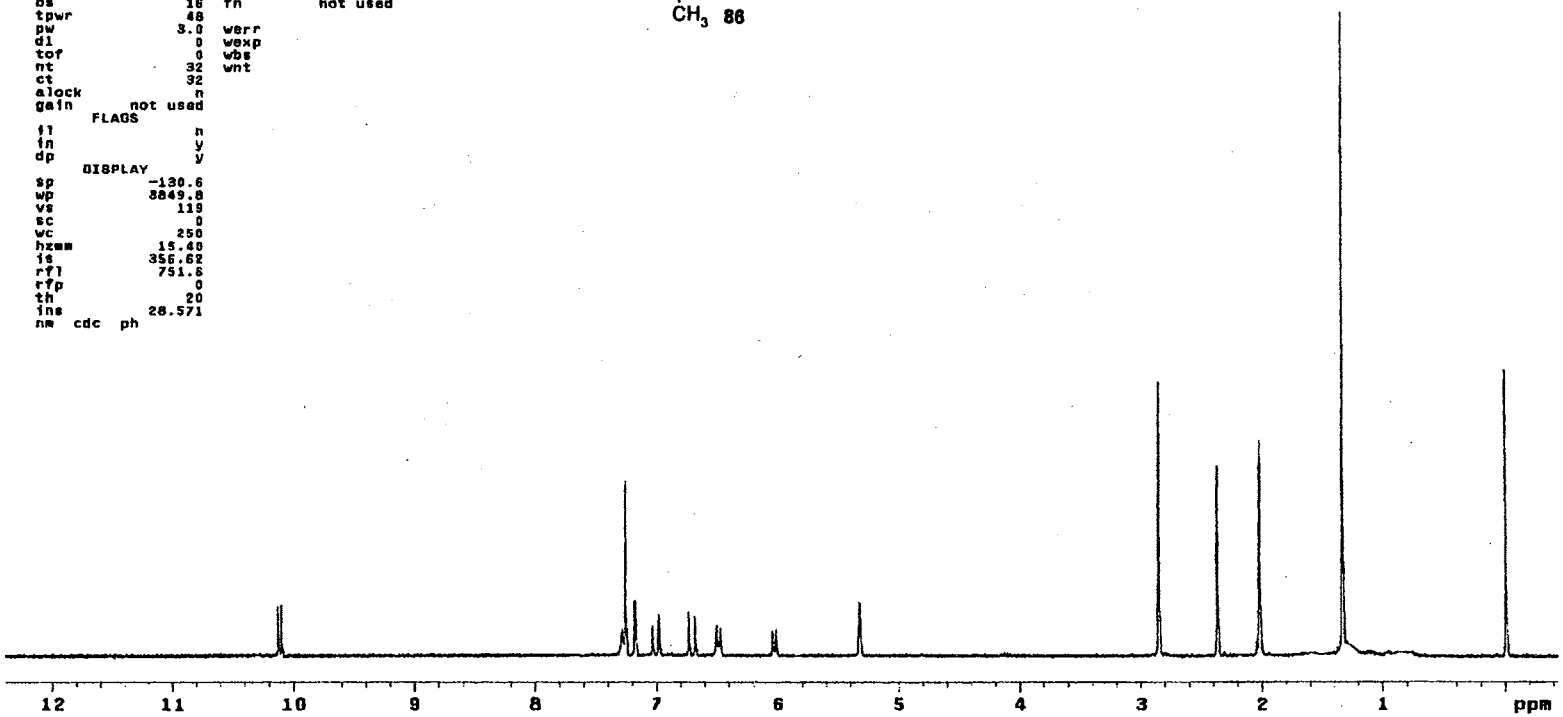
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                    DEC. & VT
date    May 10 1999   dfrq          300.087
solvent       CDCl3   dn                 H1
file            exp   dpwr               38
   ACQUISITION        dof                 0
sfrq          300.087 dm                nnn
tn                 H1 dmm                 c
at             3.747  dmf               200
np             33728      PROCESSING
sw            4500.5  wtfile
fb             2600   proc               ft
bs               16   fn          not used
tpwr             48
pw              3.0   werr
d1                0   wexp
tof               0   wbs
nt               32   wnt
ct               32
alock             n
gain       not used
       FLAGS
f1                n
in                y
dp                y
     DISPLAY
sp            -130.6
wp            3849.8
vs               119
sc                 0
wc               250
hzmm           15.40
is            356.62
rf1            751.6
rfp                0
th                20
ins            28.571
nm  cdc  ph
```



86



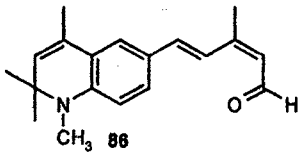
^{1}H NMR Spectrum of **86**

Plate CXIV

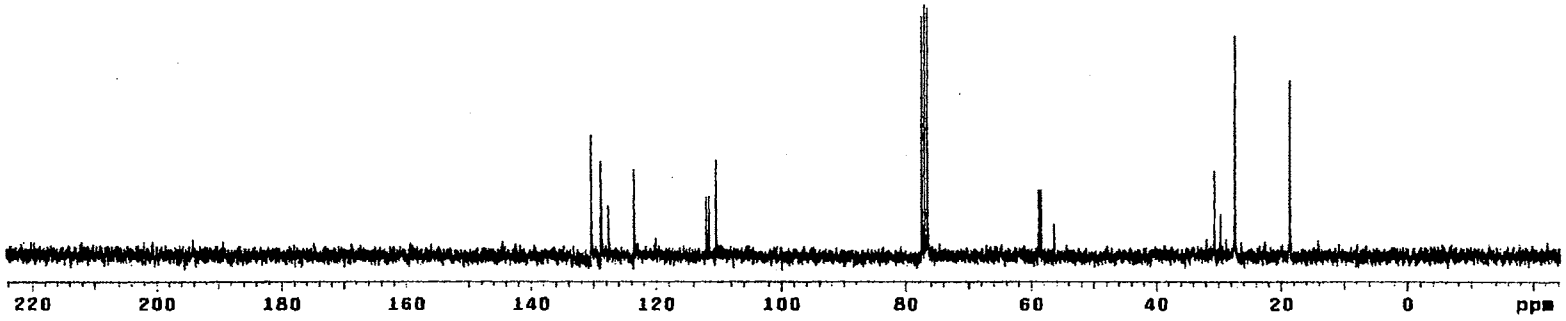
```
13C OBSERVE

exp1  std13c

        SAMPLE                  DEC. & VT
date   Jan 24 2000      dfrq          300.087
solvent        CDCl3    dn                 H1
file             exp    dpwr               34
   ACQUISITION          dof                 0
sfrq          75.464    dm                yyy
tn               C13    dmm                 w
at             0.800    dmf             11764
np             30016       PROCESSING
sw          18781.7     lb                1.00
fb            10400     wtfile
bs               16     proc                ft
tpwr             52     fn            not used
pw              3.8
d1            1.000     werr
tof               0     wexp               wft
nt             1024     wbs                wft
ct              368     wnt
alock             s
gain        not used
       FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -1837.0
wp          18761.7
vs               46
sc                0
wc              250
hzmm          75.05
fs           500.08
rfl          7647.8
rfp          5810.6
th                5
ins         100.000
nm  no  ph
```

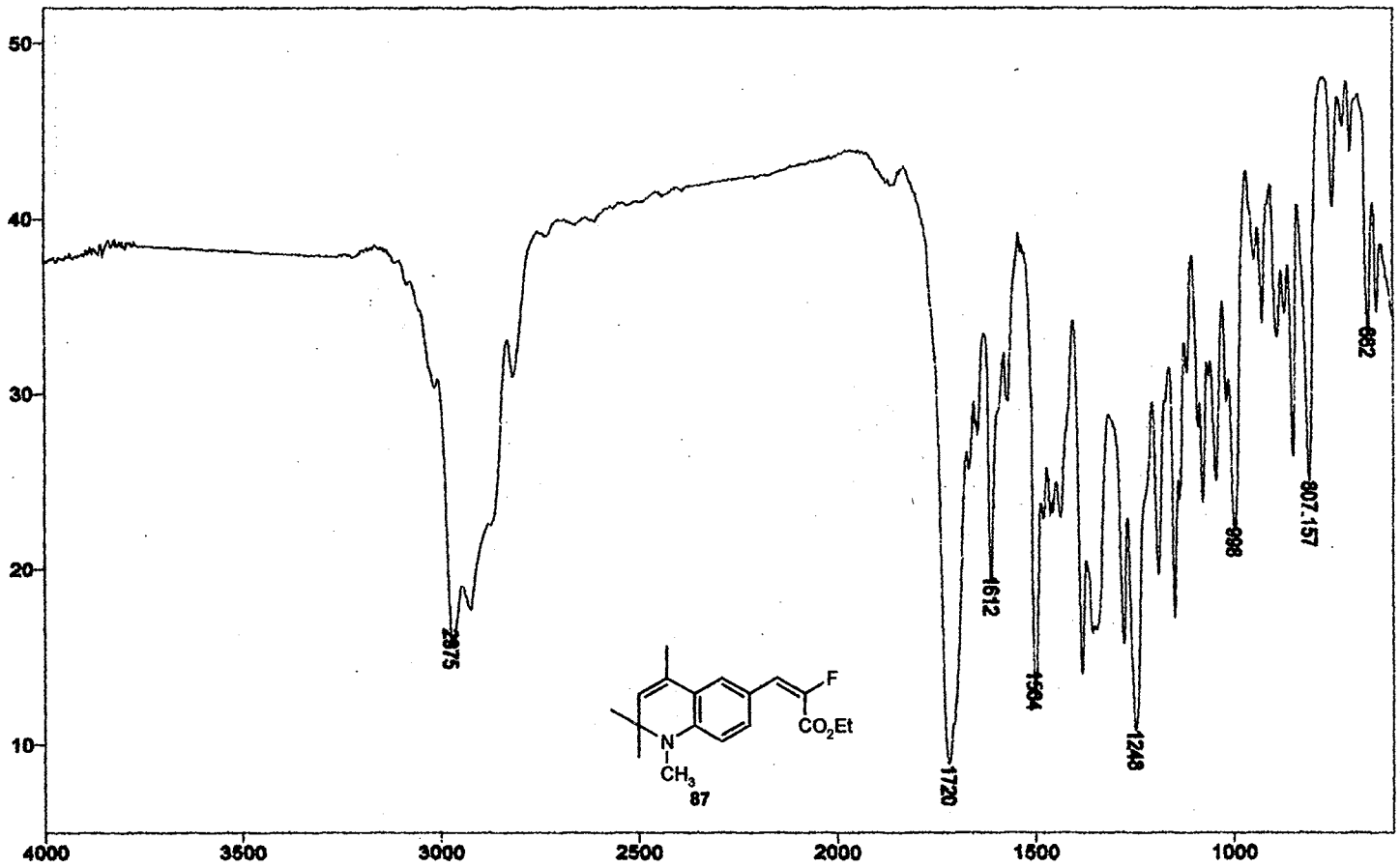


86



^{13}C NMR Spectrum of **86**

Plate CXV



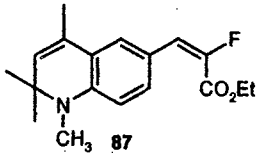
IR Spectrum of **87**

Plate CXVI

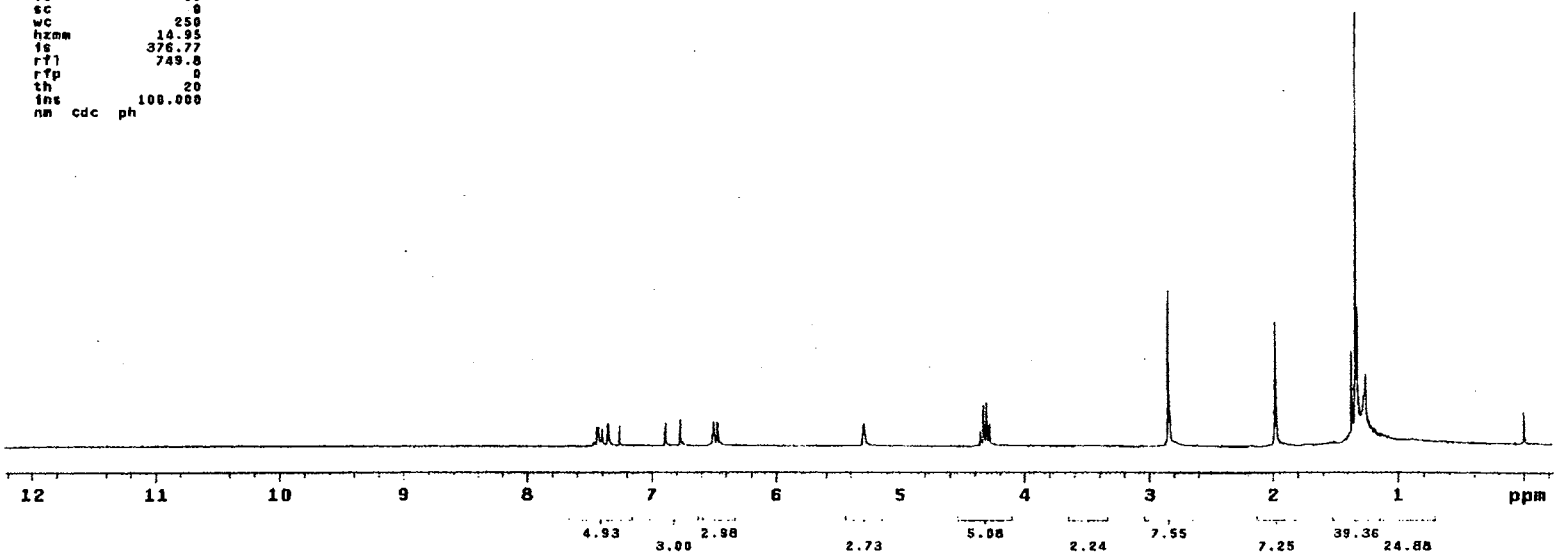
```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                DEC. & VT
date    Jan 24 2000   dfrq        300.087
solvent       CDCl3   dn              H1
file            exp   dpwr            30
   ACQUISITION        dof              0
sfrq        300.087   dm             nnn
tn               H1   dmm              c
at            3.747   dmf            200
np            33728        PROCESSING
sw           4500.5   wtfile
fb             2600   proc            ft
bs               16   fn        not used
tpwr             48
pw              6.9   werr
d1               9   wexp
tof              0   wbs
nt              16   wnt
ct              16
alock            n
gain       not used
      FLAGS
il               n
in               y
dp               y
      DISPLAY
sp           -69.8
wp          3737.5
vs              59
sc               0
wc             250
hzcm         14.95
is          376.77
rf1          749.8
rfp              0
th              20
ins         100.000
nm  cdc  ph
```



87



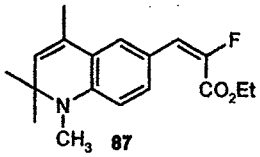
^{1}H NMR Spectrum of **87**

Plate CXVII

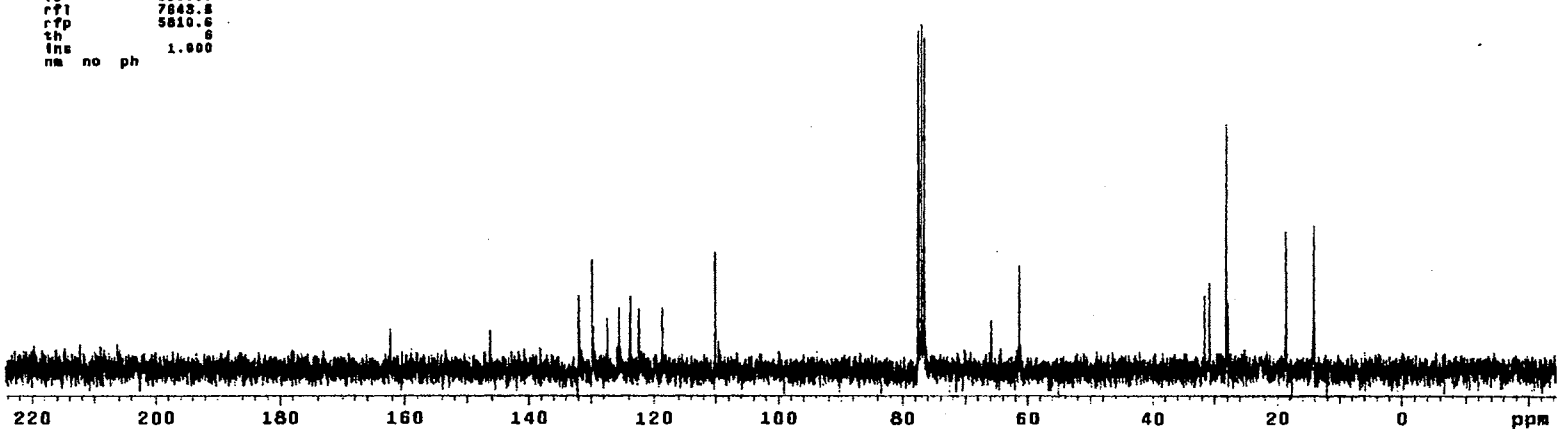
```
13C OBSERVE

expl  std13c

      SAMPLE                    DEC. & VT
date        Jul 31 95   dfrq          300.082
solvent        CDCl3    dn               H1
file             exp    dpwr             34
  ACQUISITION           dof               0
sfrq           75.463   dm              nyy
tn                C13   dmm               w
at              0.800   dmf           11764
np              30816       PROCESSING
sw           18761.7    lb              1.00
fb              10400   wtfile
bs                 16   proc              ft
tpwr               52   fn          not used
pw                3.0
d1              1.000   werr
tof                 0   wexp
nt               1024   wbs
ct               1024   wnt
alock               n
gain          not used
      FLAGS
il                  n
in                  y
dp                  y
      DISPLAY
sp            -1833.0
wp           18761.7
vs                 178
sc                   0
wc                 250
hzcm             75.05
is              500.00
rfl             7843.8
rfp             5810.6
th                   6
ins             1.000
nm  no  ph
```

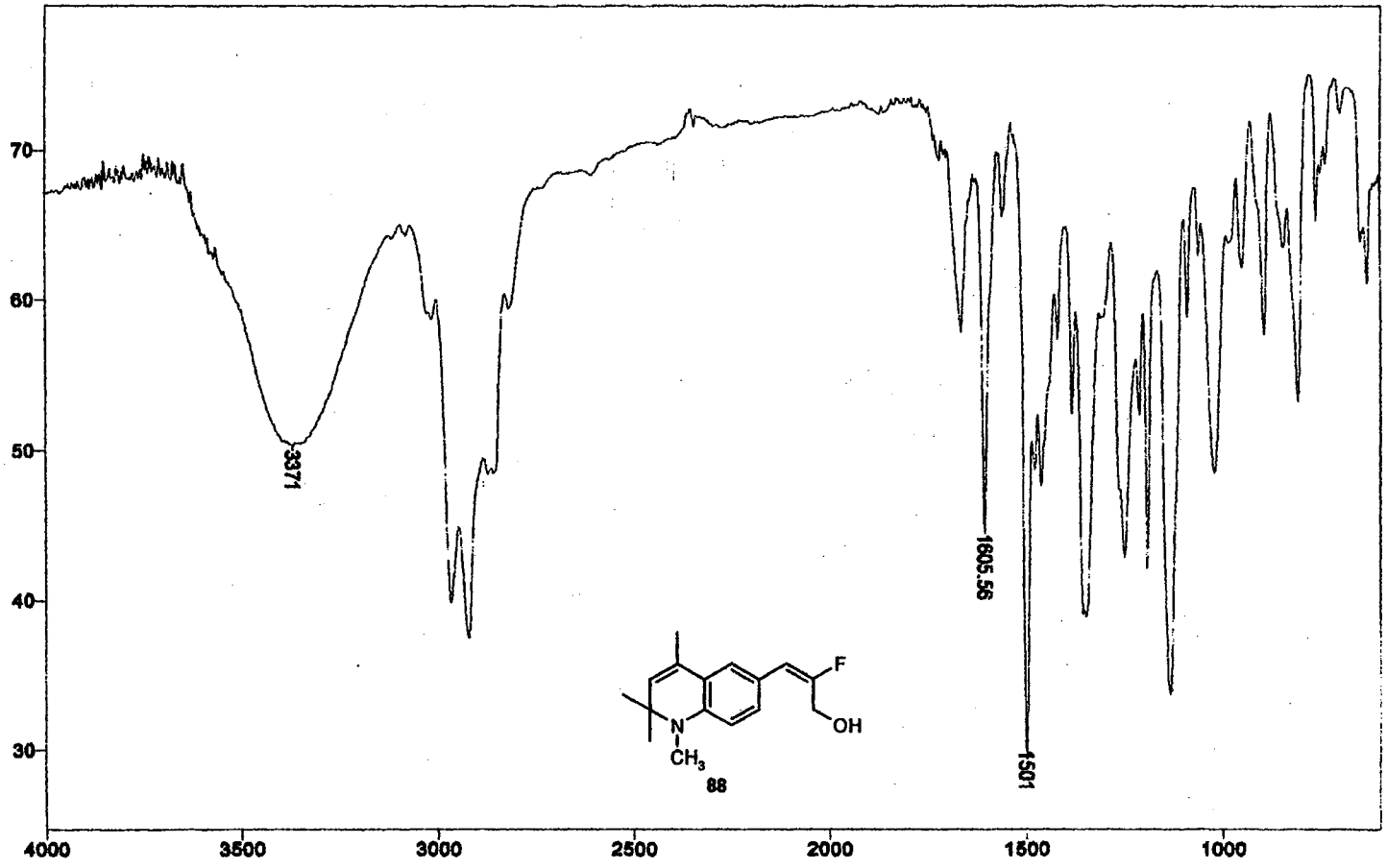


87



^{13}C NMR Spectrum of **87**

Plate CXVIII



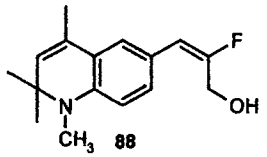
IR Spectrum of **88**

Plate CXIX

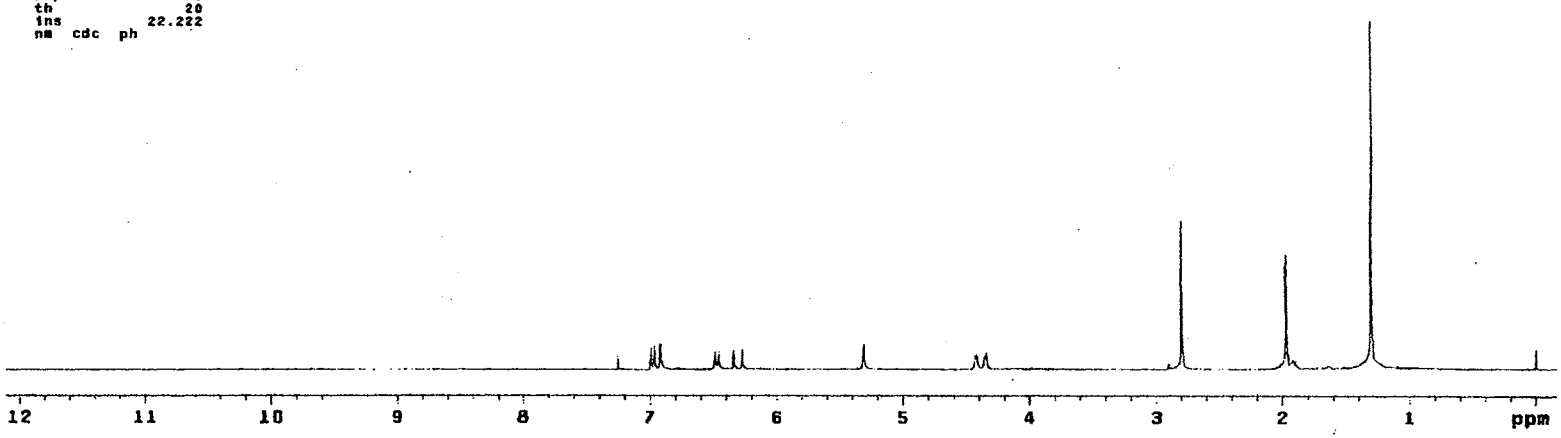
```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                 DEC. & VT
date   Jan 24 2000   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               30
   ACQUISITION       dof                 0
sfrq         300.087 dm                nnn
tn                H1 dmm                 c
at             3.747 dmf               200
np             33728     PROCESSING
sw            4500.5 wtfile
fb             2600  proc               ft
bs               16  fn          not used
tpwr             48
pw              8.3  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain       not used
      FLAGS
fl                n
in                y
dp                y
      DISPLAY
sp            -47.8
wp           3684.3
vs               64
sc                0
wc              250
hzcm          14.74
is           259.53
rfl           751.4
rfp               8
th               20
ins          22.222
nm  cdc  ph
```



88



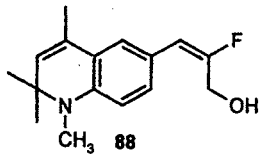
^{1}H NMR Spectrum of **88**

Plate CXX

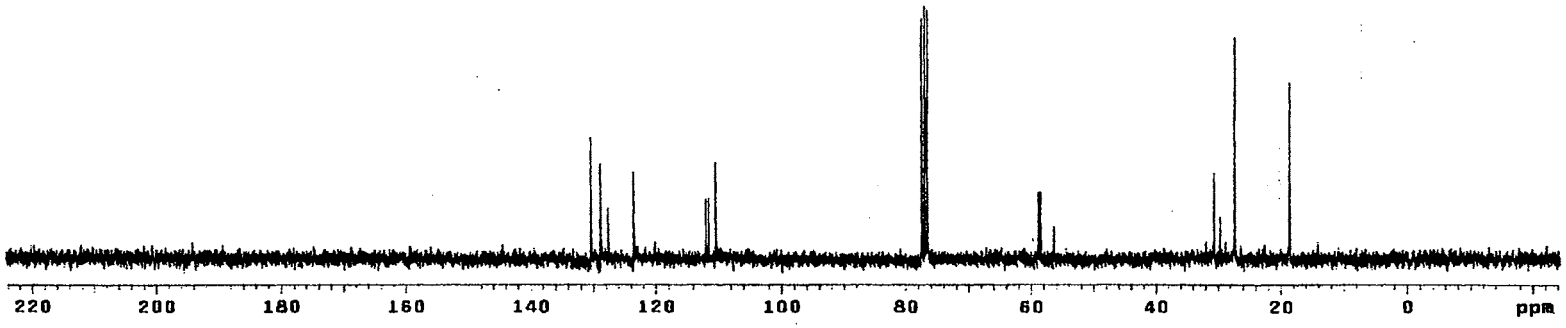
```
13C OBSERVE

expl  std13c

      SAMPLE                    DEC. & VT
date   Jan 24 2000   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof                 0
sfrq          75.464 dm                yyy
tn               C13 dmm                 w
at             0.800 dmf             11764
np             30016    PROCESSING
sw           18761.7 lb              1.00
fb             10400 wtfile
bs                16 proc               ft
tpwr              52 fn          not used
pw               3.8
d1             1.000 werr
tof                0 wexp              wft
nt              1024 wbs               wft
ct               368 wnt
alock              s
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp           -1837.0
wp           18761.7
vs                46
sc                 0
wc               250
hzcm           75.05
is             500.00
rfl            7847.6
rfp            5810.6
th                 5
ins          100.000
nm  no  ph
```



88



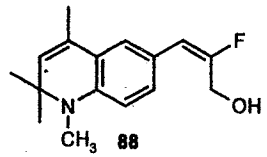
^{13}C NMR Spectrum of **88**

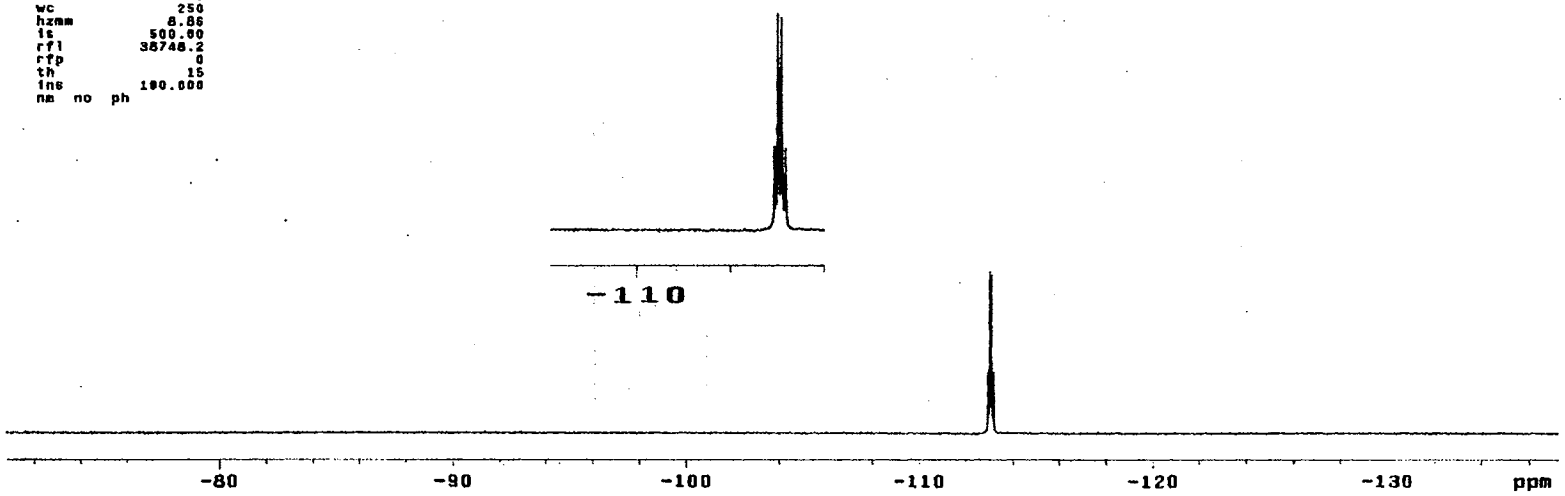
Plate CXXI

```
13C OBSERVE

expl  std13c

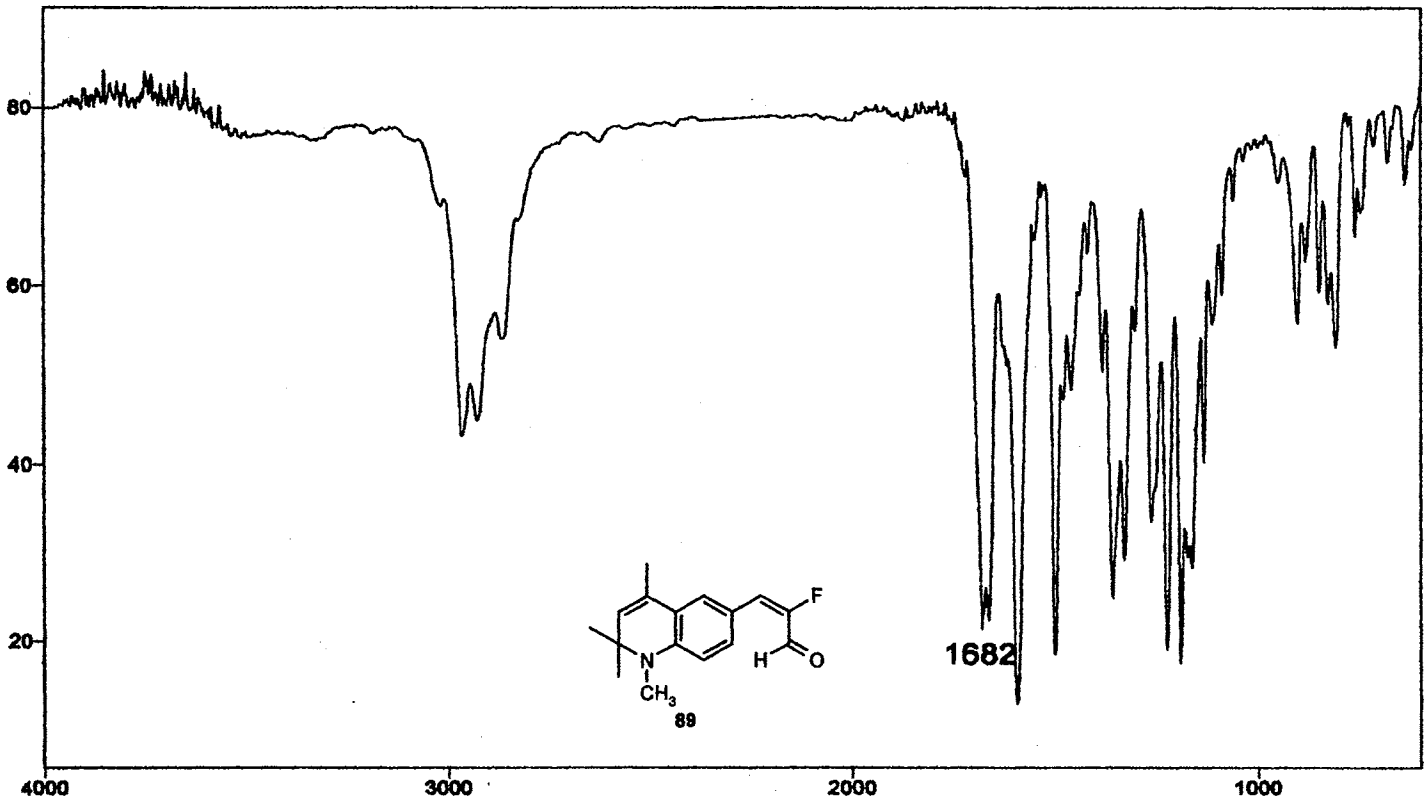
      SAMPLE                DEC. & VT
date   Jan 24 2000   dfrq        300.067
solvent       CDCl3  dn              H1
file            exp  dpwr            34
   ACQUISITION       dof             0
sfrq        282.333  dm            nnn
tn              F18  dmm             w
at            0.500  dmf         11764
np            30016      PROCESSING
sw          18761.7  lb            1.00
fb            10400  wtfile
bs               16  proc            ft
tpwr             52  fn        not used
pw              3.8
d1            1.000  werr
tof               0  wexp           wft
nt             1024  wbs            wft
ct               32  wnt
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp         -38748.2
wp          18761.7
vs               30
sc                0
wc              250
hzmm           8.86
is           500.00
rfl         38748.2
rfp               0
th               15
ins          100.000
nm  no  ph
```





^{19}F NMR Spectrum of **88**

Plate CXXII



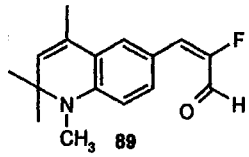
IR Spectrum of **89**

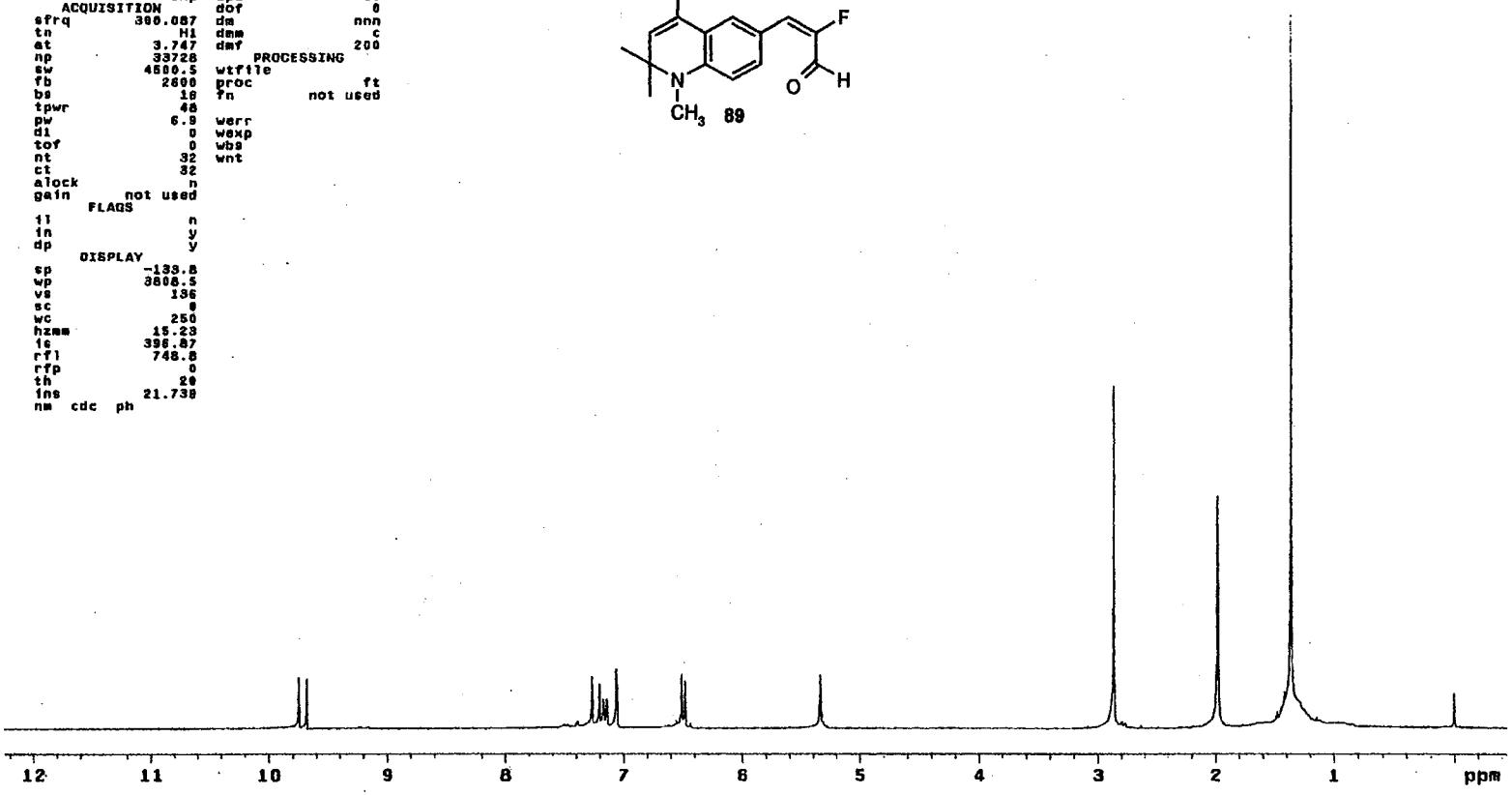
Plate CXXIII

```
STANDARD 1H OBSERVE

expl  std1h

        SAMPLE                  DEC. & VT
date   Feb  8 2000  dfrq          300.087
solvent       CDCl3 dn                 H1
file            exp dpwr               30
   ACQUISITION      dof                 0
sfrq        300.087 dm                nnn
tn               H1 dmm                 c
at            3.747 dmf               200
np            33728    PROCESSING
sw           4500.5 wtfile
fb             2600 proc               ft
bs               16 fn          not used
tpwr             48
pw              6.9 werr
d1                0 wexp
tof               0 wbs
nt               32 wnt
ct               32
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp           -133.8
wp           3808.5
vs              136
sc                0
wc              250
hzmm          15.23
is           398.87
rfl           748.8
rfp               0
th               20
ins          21.738
nm  cdc  ph
```





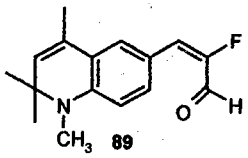
^{1}H NMR Spectrum of **89**

Plate CXXIV

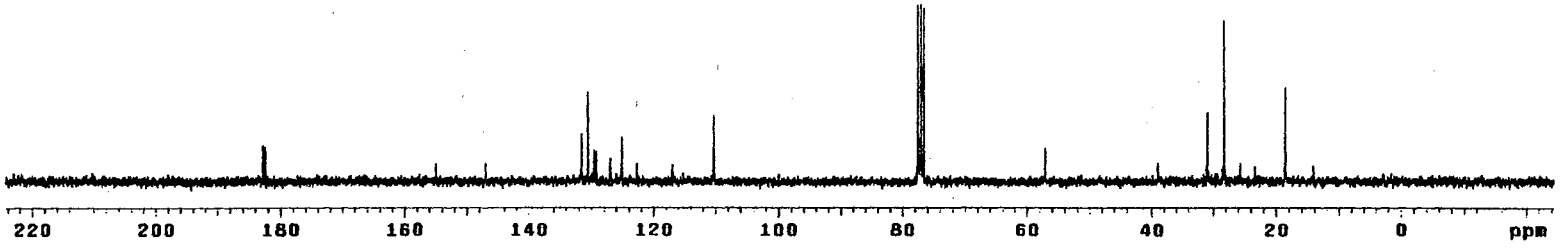
```
13C OBSERVE

exp1  std13c

        SAMPLE                  DEC. & VT
date   Feb  8 2000      dfrq          300.087
solvent       CDCl3     dn                 H1
file            exp     dpwr               34
   ACQUISITION          dof                 0
sfrq          75.464    dm                yyy
tn               C13    dmm                 w
at             0.800    dmf             11764
np             30016      PROCESSING
sw           18761.7    lb               1.00
fb             10400    wtfile
bs                16    proc               ft
tpwr              52    fn        not used
pw               3.8
d1             1.000    werr
tof                0    wexp              wft
nt              1024    wbs               wft
ct               704    wnt
alock              s
gain        not used
       FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp           -1837.0
wp           18761.7
vs                32
sc                 0
wc               250
hzcm           75.05
fs            500.00
rf1           7647.5
rfp           5810.6
th                 s
ins          100.000
nm  no  ph
```



89



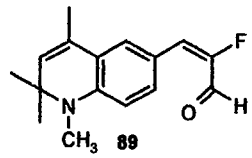
^{13}C NMR Spectrum of **89**

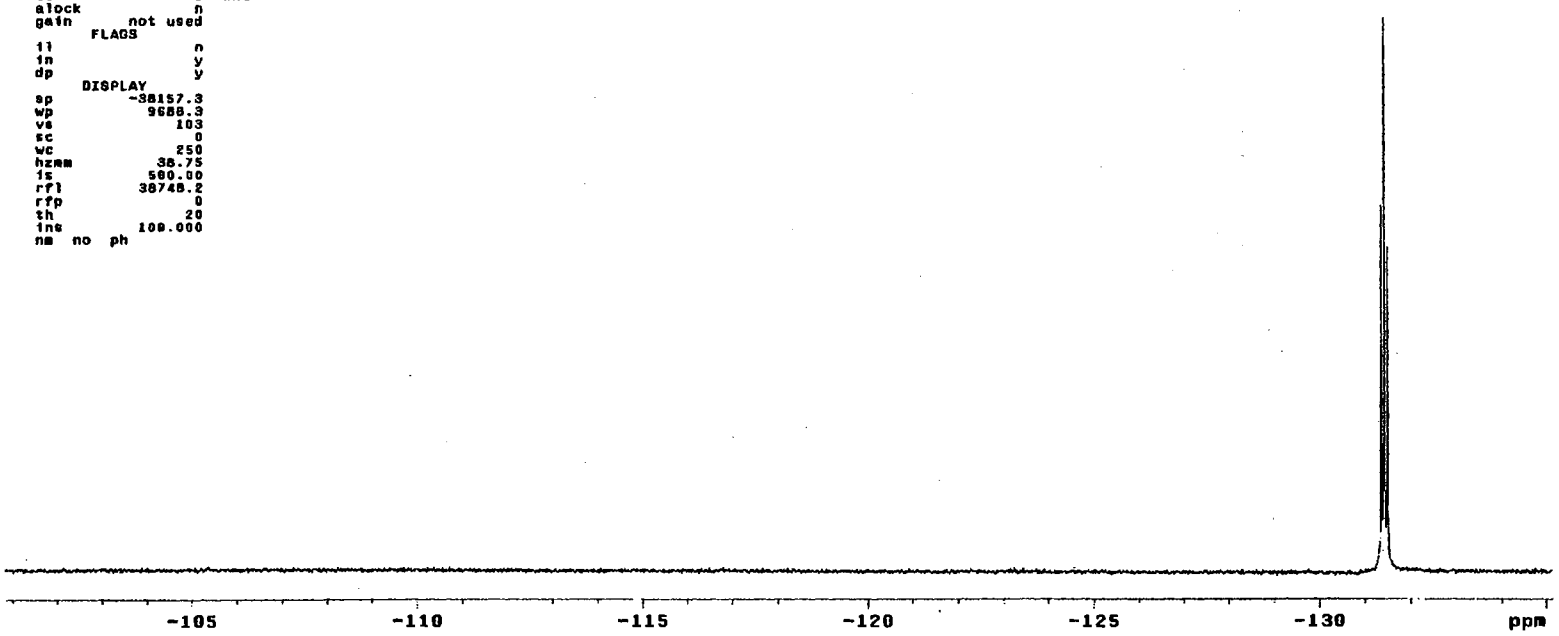
Plate CXXV

```
13C OBSERVE

exp1  std13c

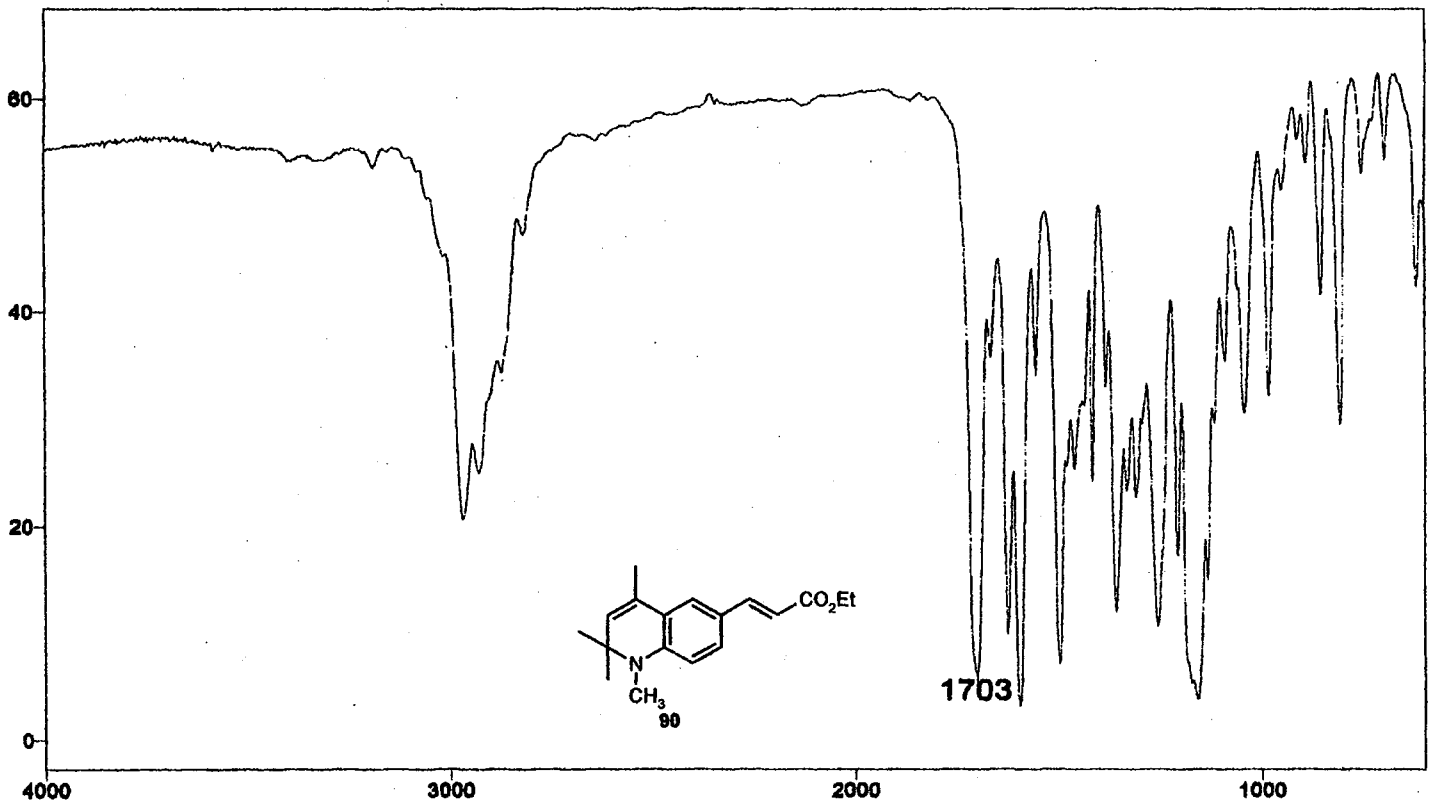
        SAMPLE                  DEC. & VT
date   Feb  8 2000   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                 0
sfrq        282.333  dm                nnn
tn              F19  dmm                 w
at            0.800  dmf             11764
np            30016  PROCESSING
sw          18761.7  lb               1.00
fb            10400  wtfile
bs               16  proc              ft
tpwr             52  fn          not used
pw              3.8
d1            1.000  werr
tof               0  wexp             wft
nt             1024  wbs              wft
ct               48  wnt
alock             n
gain       not used
      FLAGS
ii                n
in                y
dp                y
      DISPLAY
sp         -38157.3
wp          9688.3
vs              103
sc                0
wc              250
hzcm          38.75
is           500.00
rf1         38748.2
rfp               0
th               20
ins         109.000
nm  no  ph
```





^{19}F NMR Spectrum of **89**

Plate CXXVI



IR Spectrum of **90**

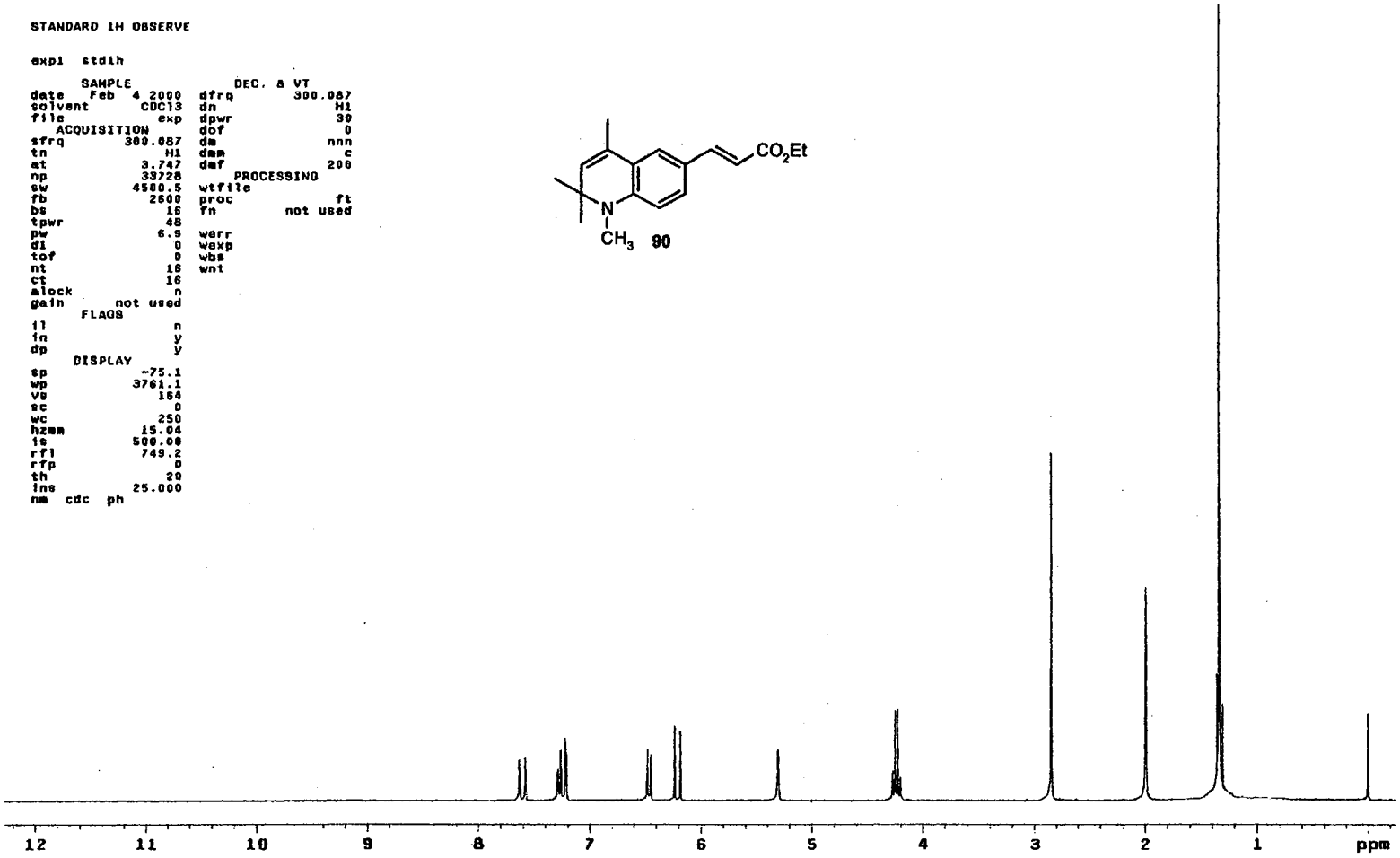
Plate CXXVII

```
STANDARD 1H OBSERVE

exp1  stdih

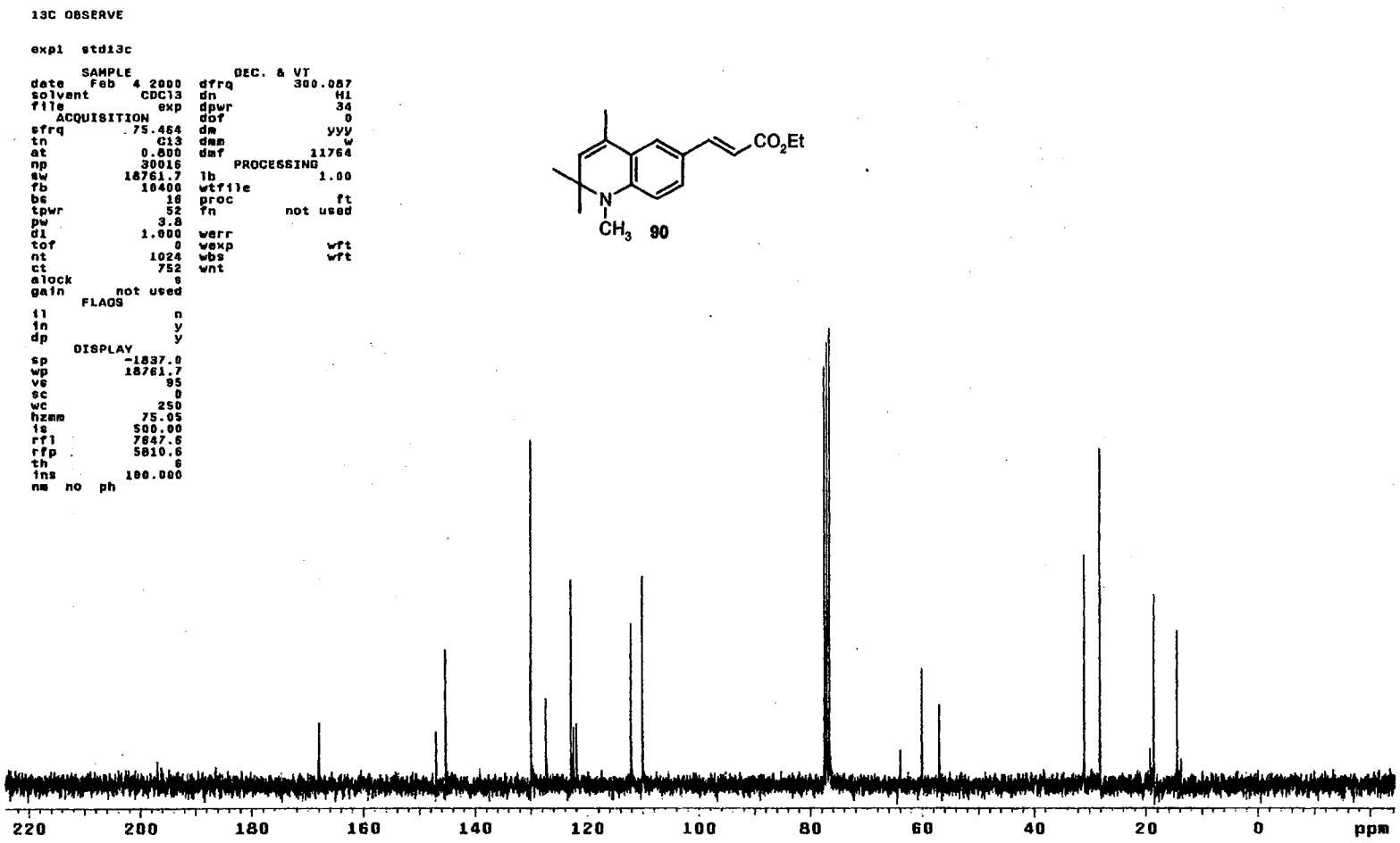
      SAMPLE                 DEC. & VT
date   Feb  4 2000   dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr            30
   ACQUISITION       dof              0
sfrq        300.087  dm             nnn
tn               H1  dmm              c
at            3.747  dmf            200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2500  proc            ft
bs               16  fn        not used
tpwr             48
pw              6.9  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain        not used
      FLAGS
i1                n
in                y
dp                y
      DISPLAY
sp            -75.1
wp           3761.1
vs              164
sc                0
wc              250
hzcm          15.04
is           500.00
rfl           749.2
rfp               0
th               20
ins          25.000
nm  cdc  ph
```


90



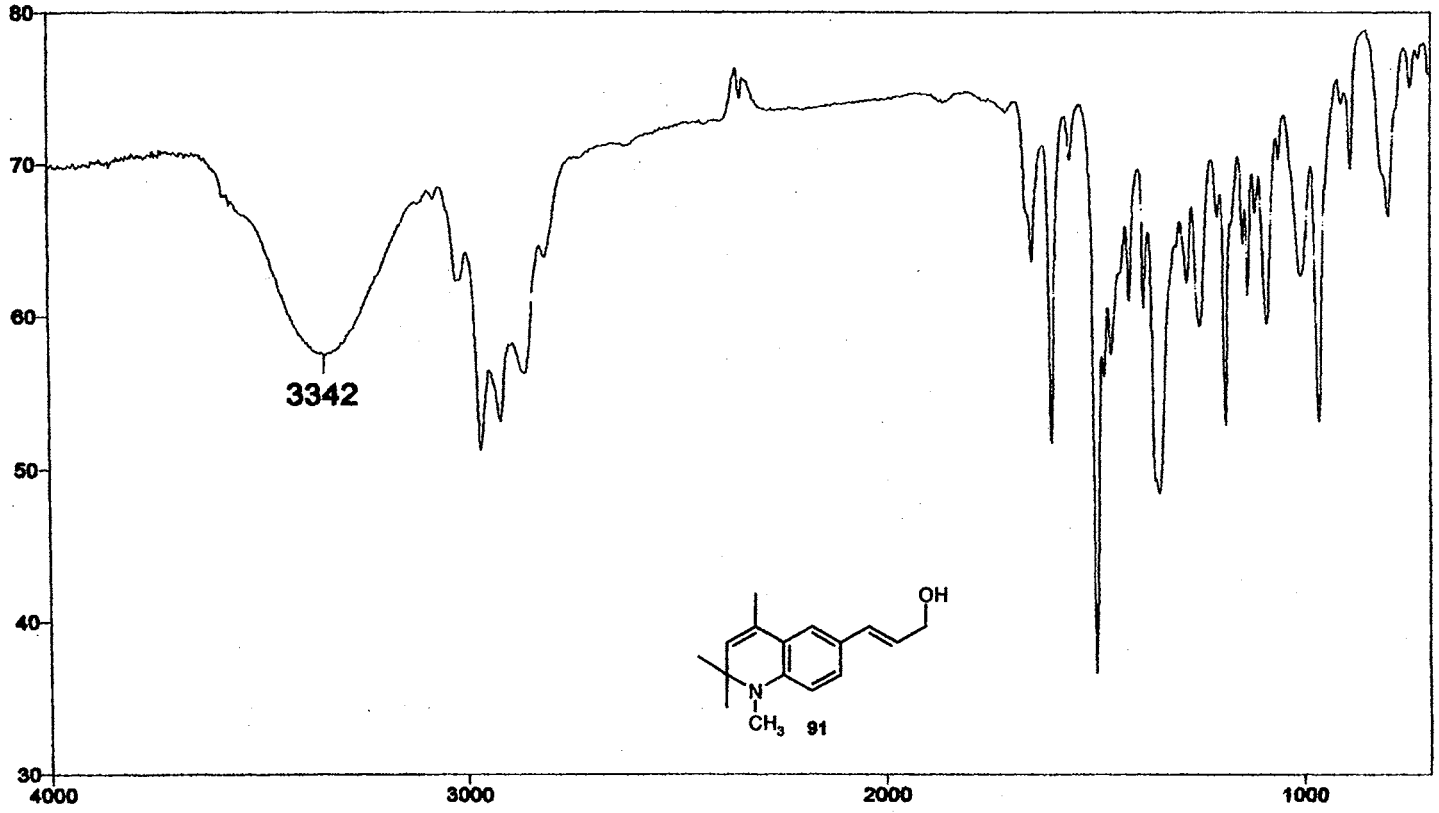
^{1}H NMR Spectrum of **90**

Plate CXXVIII



^{13}C NMR Spectrum of **90**

Plate CXXIX



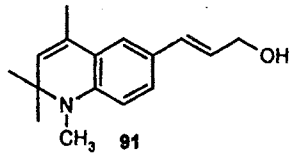
IR Spectrum of **91**

Plate CXXX

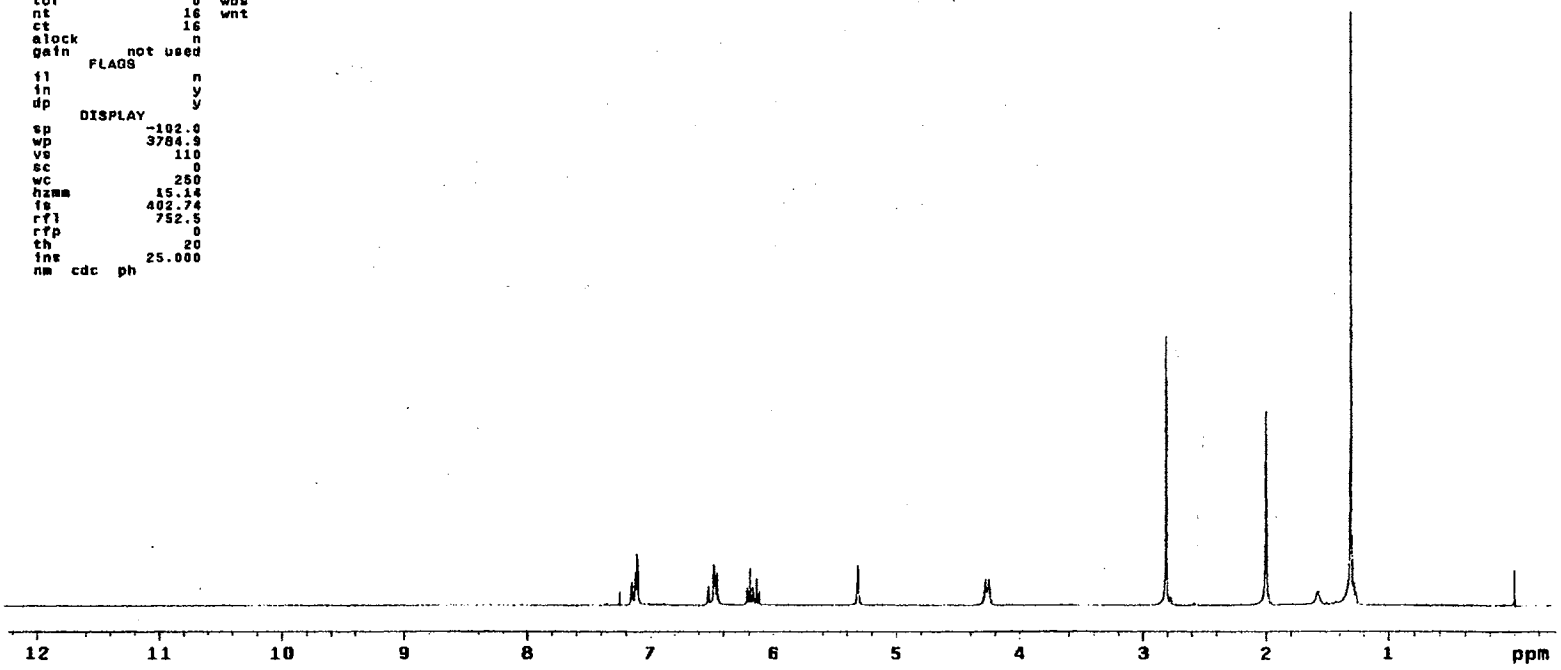
STANDARD 1H OBSERVE

```
exp1  std1h

        SAMPLE                    DEC. & VT
date   Feb  5 2000   dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr            30
    ACQUISITION      dof             0
sfrq        300.087  dm            nnn
tn               H1  dmm             c
at            3.747  dmf           200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2600  proc           ft
bs               16  fn        not used
tpwr             48
pw              6.9  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain        not used
       FLAGS
i1                n
in                y
dp                y
      DISPLAY
sp           -102.0
wp           3784.9
vs              110
sc                0
wc              250
hzmm          15.14
fs           402.74
rf1           752.5
rfp               0
th               20
ins          25.000
nm  cdc  ph
```



91



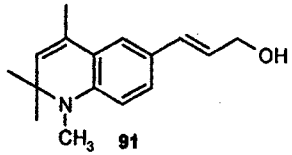
^{1}H NMR Spectrum of **91**

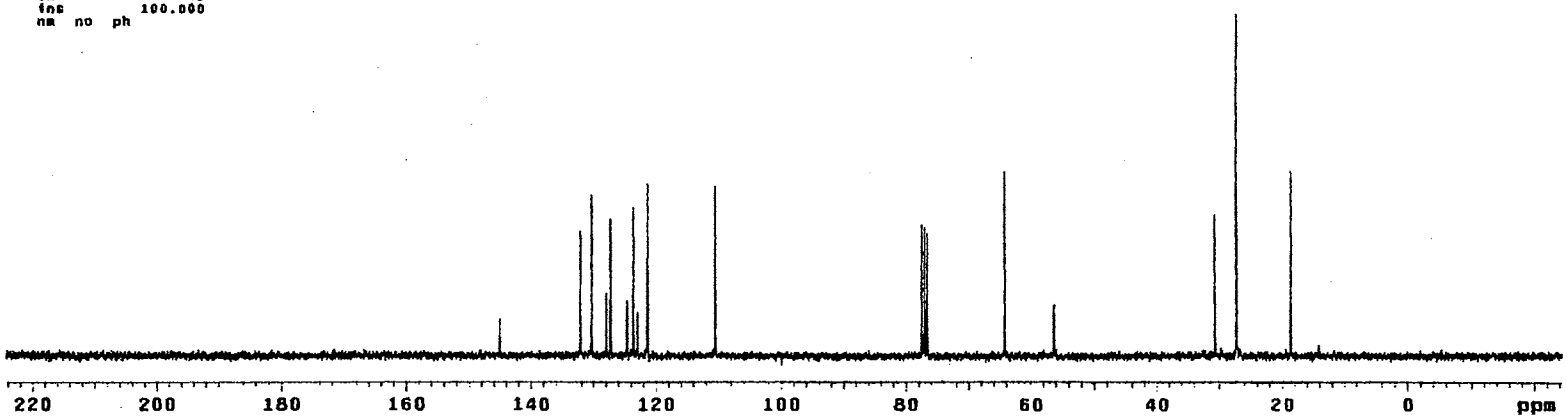
Plate CXXXI

```
13C OBSERVE

exp1  std13c

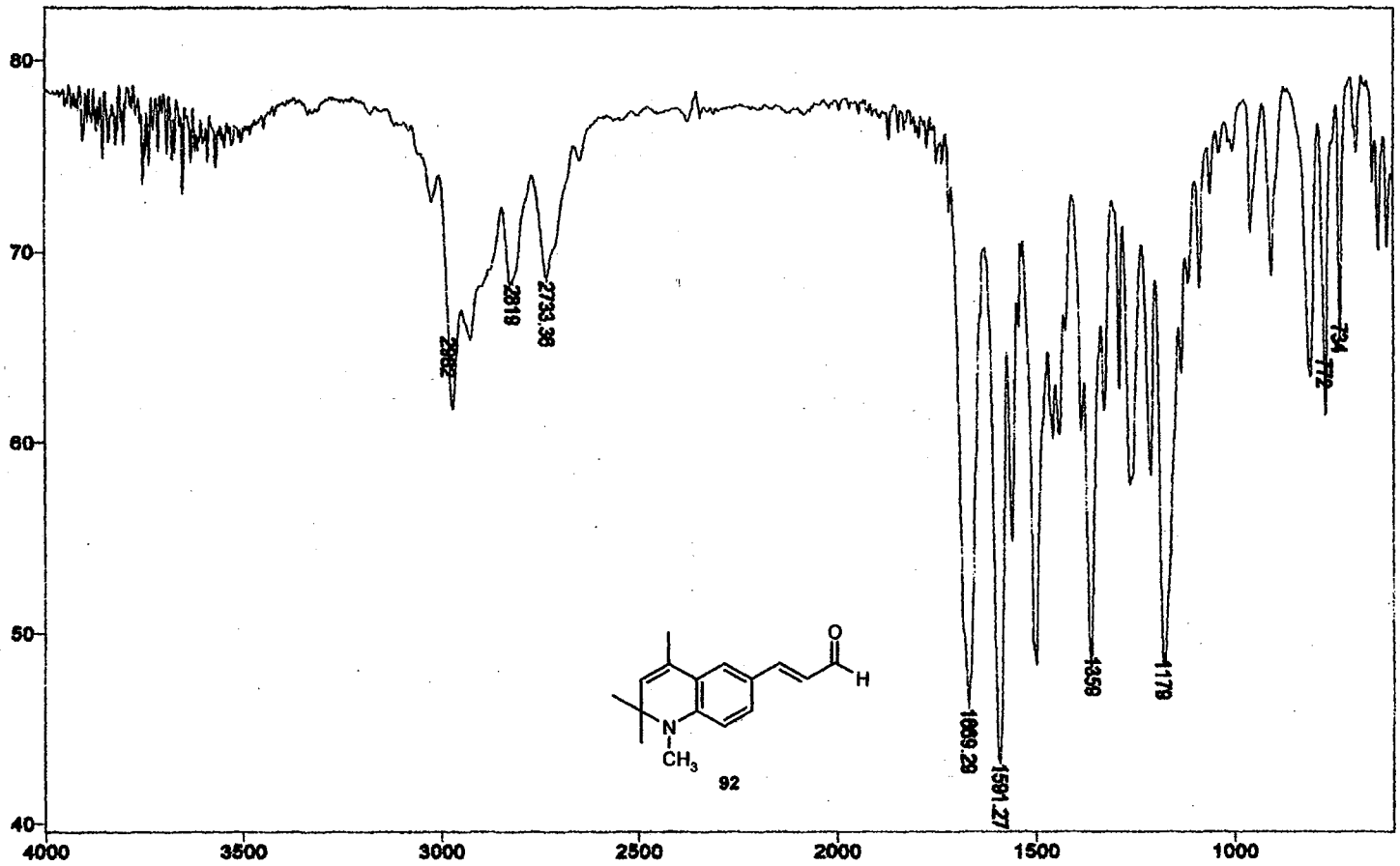
      SAMPLE                DEC. & VT
date   Feb  5 2000   dfrq          300.087
solvent       CDCl3  dn               H1
file            exp  dpwr             34
    ACQUISITION      dof              0
sfrq          75.484 dm             yyy
tn               C13 dmm              w
at             0.800 dmf          11764
np             30016     PROCESSING
sw           18761.7 lb             1.00
fb             10400 wtfile
bs                16 proc             ft
tpwr              52 fn         not used
pw               3.8
d1             1.000 werr
tof                0 wexp            wft
nt              1024 wbs             wft
ct               512 wnt
alock              s
gain        not used
      FLAGS
i1                 n
in                 y
dp                 y
     DISPLAY
sp           -1839.3
wp           18761.7
vs                63
sc                 0
wc               250
hzcm           75.05
is             508.00
rf1            7649.9
rfp            5810.6
th                 .5
ins            100.000
nm  no  ph
```





^{13}C NMR Spectrum of **91**

Plate CXXXII



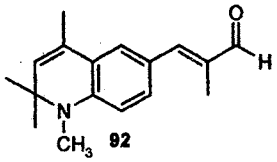
IR Spectrum of **92**

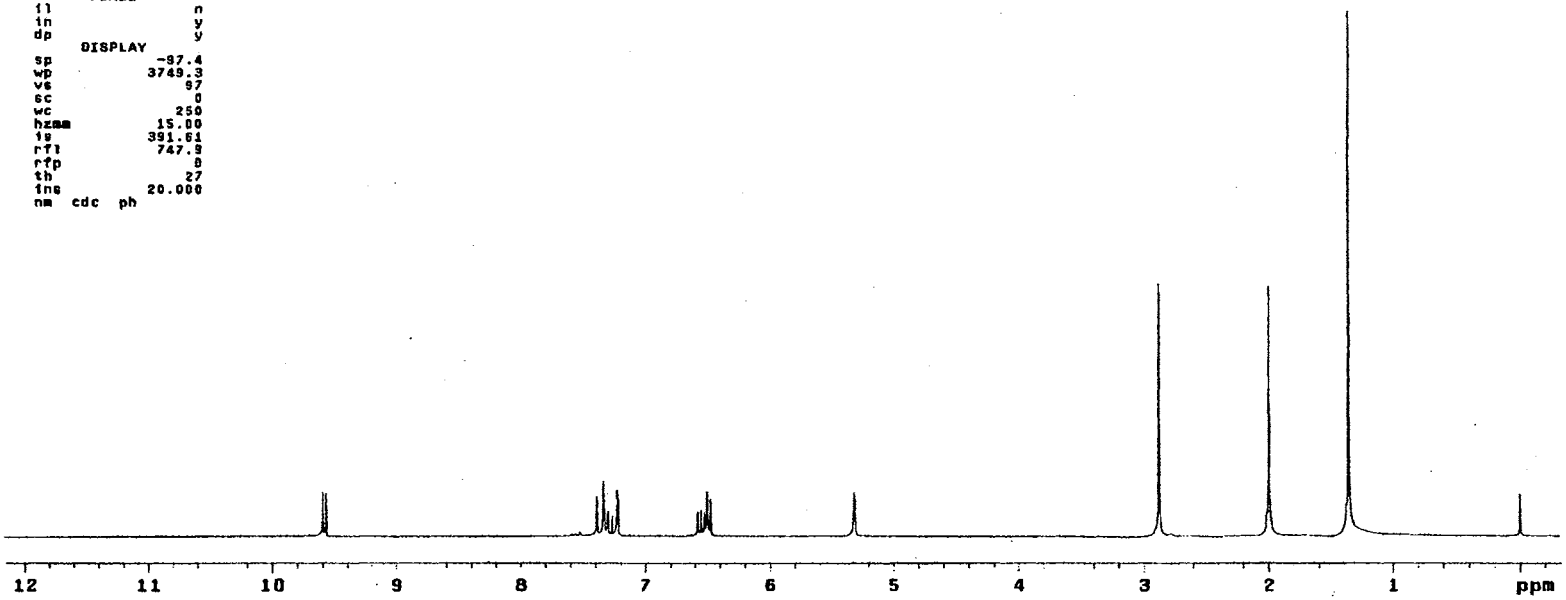
Plate CXXXIII

```
STANDARD 1H OBSERVE

expl  std1h

        SAMPLE                DEC. & VT
date    Feb  6 2000   dfrq          300.087
solvent        CDCl3  dn                 H1
file             exp  dpwr               38
   ACQUISITION         dof                 0
sfrq          300.087  dm                nnn
tn                 H1  dmm                 c
at              3.747  dmf               200
np              39728        PROCESSING
sw             4500.5  wtfile
fb               2600  proc              ft
bs                 16  fn         not used
tpwr               48
pw                6.9  werr
d1                  0  wexp
tof                 0  wbs
nt                 16  wnt
ct                 16
alock               n
gain         not used
       FLAGS
il                  n
in                  y
dp                  y
      DISPLAY
sp              -97.4
wp             3749.3
vs                 97
sc                  0
wc                250
hzcm            15.00
is             391.61
rfl             747.9
rfp                 0
th                 27
ins             20.000
nm  cdc  ph
```





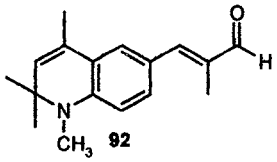
^{1}H NMR Spectrum of **92**

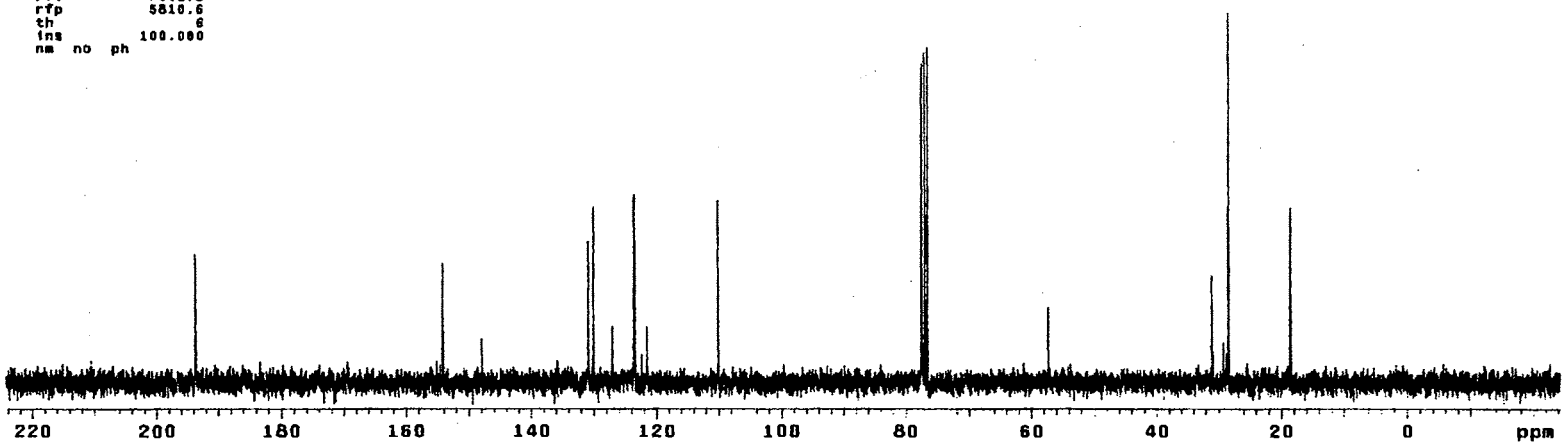
Plate CXXXIV

```
13C OBSERVE

expl  std13c

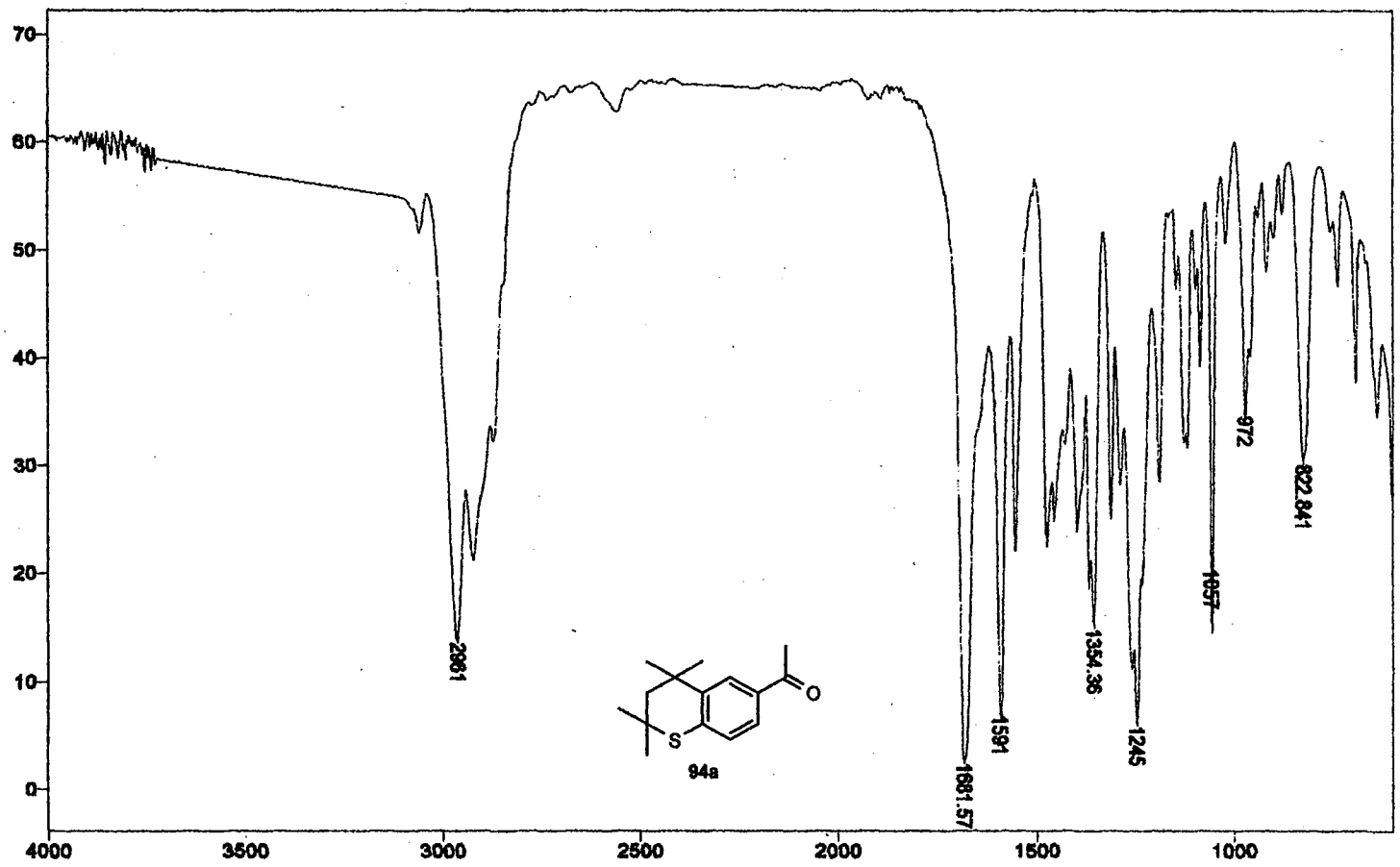
        SAMPLE                DEC. & VT
date   Feb  6 2000   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                 0
sfrq          75.464 dm                yyy
tn               C13 dmm                 w
at             0.800 dmf             11764
np             30018    PROCESSING
sw           18761.7 lb               1.00
fb             10400 wtfile
bs                16 proc               ft
tpwr              52 fn          not used
pw               3.8
d1             1.000 werr
tof                0 wexp              wft
nt              1024 wbs               wft
ct               256 wnt
alock              s
gain         not used
       FLAGS
fl                 n
in                 y
dp                 y
      DISPLAY
sp           -1838.2
wp           18761.7
vs                68
sc                 0
wc               250
hzmm           75.05
is            500.00
rf1           7648.8
rfp           5810.6
th                 6
ins           100.000
nm  no  ph
```





^{13}C NMR Spectrum of **92**

Plate CXXXV



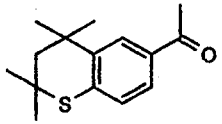
IR Spectrum of **94a**

Plate CXXXVI

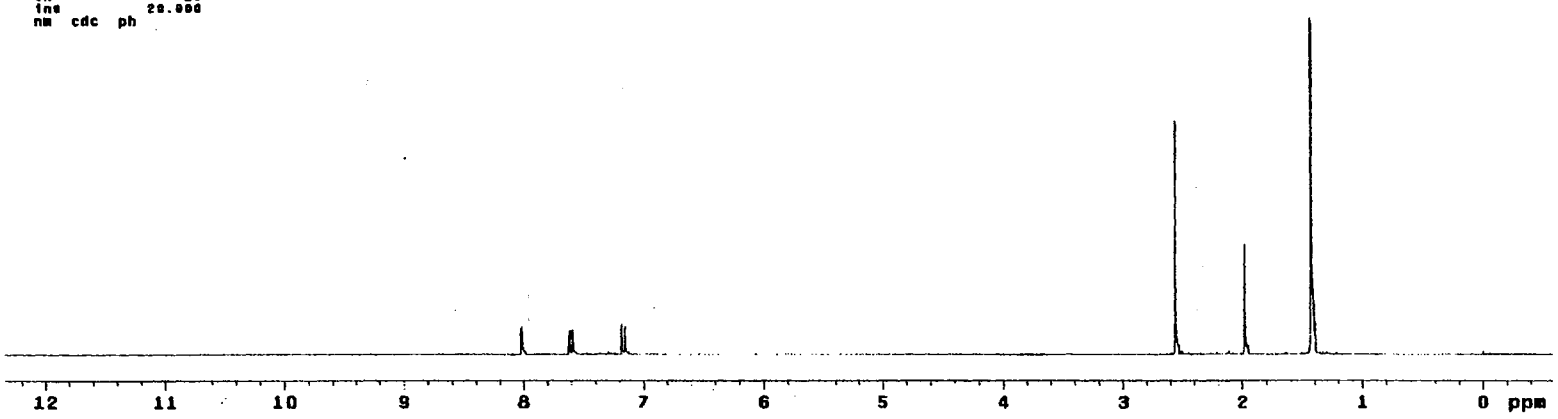
```
STANDARD 1H OBSERVE

exp1  stdih

      SAMPLE                DEC. & VT
date   Jul 13 1999  dfrq          300.087
solvent      CDCl3  dn               H1
file           exp  dpwr             30
   ACQUISITION      dof               0
sfrq        300.087 dm              nnn
tn               H1 dmm               c
at            3.747 dmf             200
np            33728     PROCESSING
sw           4500.5 wtfile
fb            2600  proc            ft
bs              16  fn         not used
tpwr            48
pw             3.0  werr
di               0  wexp
tof              0  wbs
nt              16  wnt
ct              16
alock            n
gain      not used
      FLAGS
il               n
in               y
dp               y
     DISPLAY
sp           -173.9
wp           3879.4
vs              62
sc               0
wc             250
hzmm         15.52
ts           370.48
rf1           741.5
rfp               0
th               20
ins          28.000
nm  cdc  ph
```



94a



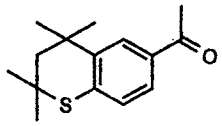
^{1}H NMR Spectrum of **94a**

Plate CXXXVII

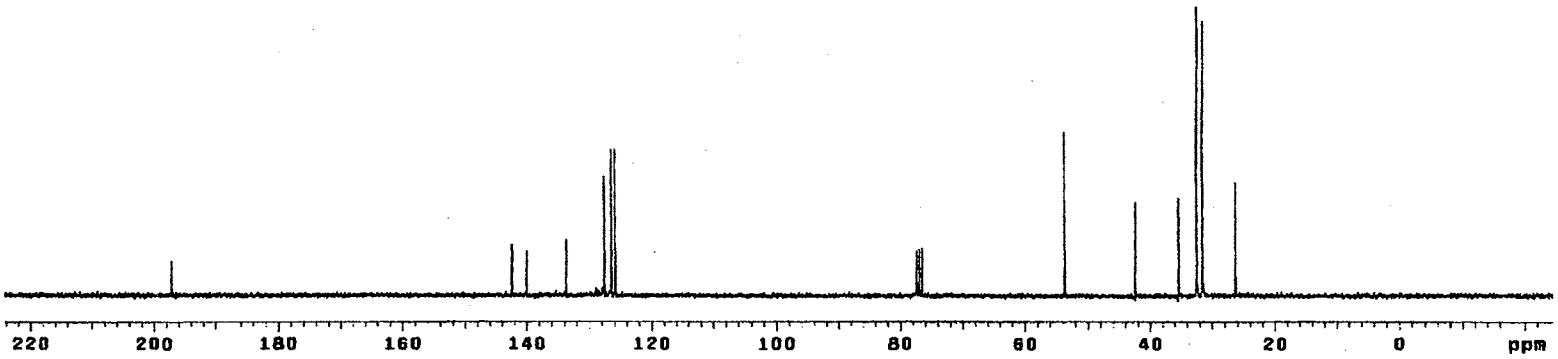
```
13C OBSERVE

exp1  std13c

      SAMPLE                DEC. & VT
date    Jul 13 1999  dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dgwr            34
   ACQUISITION       dof             0
sfrq          75.484  dm            yyy
tn               C13  dmm             w
at             0.800  dmf         11764
np             30016      PROCESSING
sw           18781.7  lb           1.00
fb             10408  wtfile
bs                16  proc           ft
tpwr              52  fn        not used
pw               9.8
d1             1.000  werr
tof                0  wexp          wft
nt              1024  wbs           wft
ct               112  wnt
alock              s
gain       not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1845.0
wp           18781.7
vs                53
sc                 8
wc               250
hzmm           75.05
is             500.00
rf1            7655.6
rfp            5810.0
th                 3
ins            100.000
nm  no  ph
```

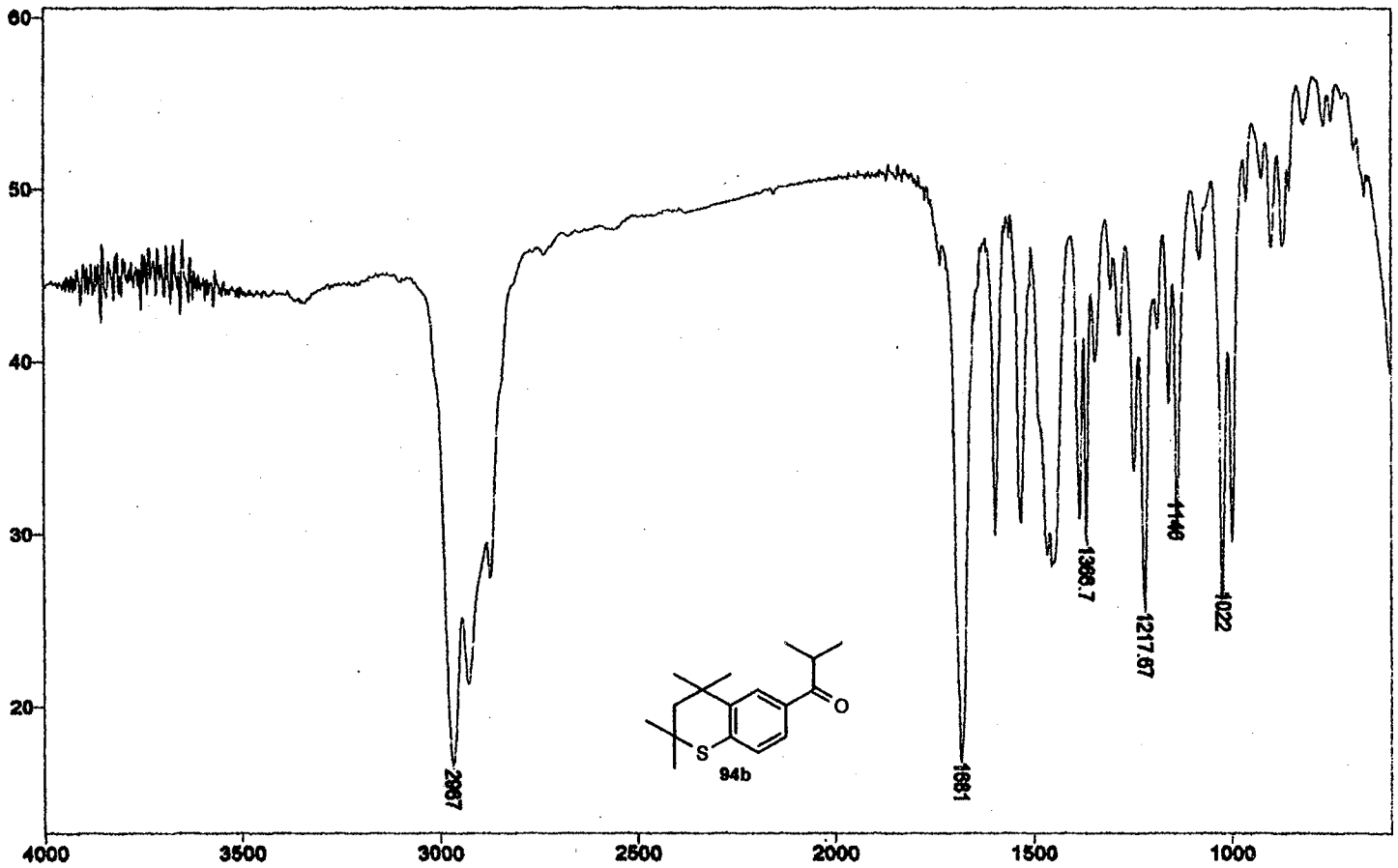


94a



^{13}C NMR Spectrum of **94a**

Plate CXXXVIII



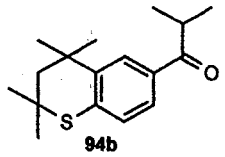
IR Spectrum of **94b**

Plate CXXXIX

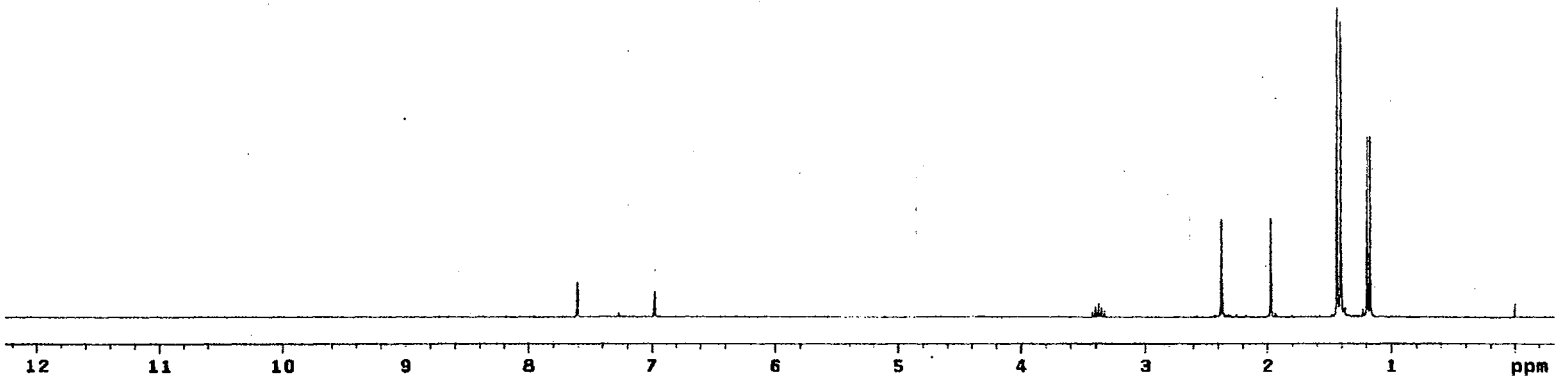
```
STANDARD 1H OBSERVE

expl  std1h

      SAMPLE                  DEC. & VT
date    Jul  9 1999   dfrq        300.087
solvent       CDCl3   dn              H1
file            exp   dpwr            30
   ACQUISITION        dof              0
afrq          300.087 dm             nnn
tn              H1    dmm              c
at            3.747   dmf            200
np            33728       PROCESSING
sw           4500.5   wtfile
fb             2600   proc            ft
bs               16   fn        not used
tpwr             46
pw              5.9   werr
d1                0   wexp
tof               0   wbs
nt               16   wnt
ct               16
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp            -97.5
wp           3778.8
vs               57
sc                0
wc              250
hzmm          15.12
is           282.93
rfl           748.8
rfp               0
th               20
ins          31.250
nm  cdc  ph
```

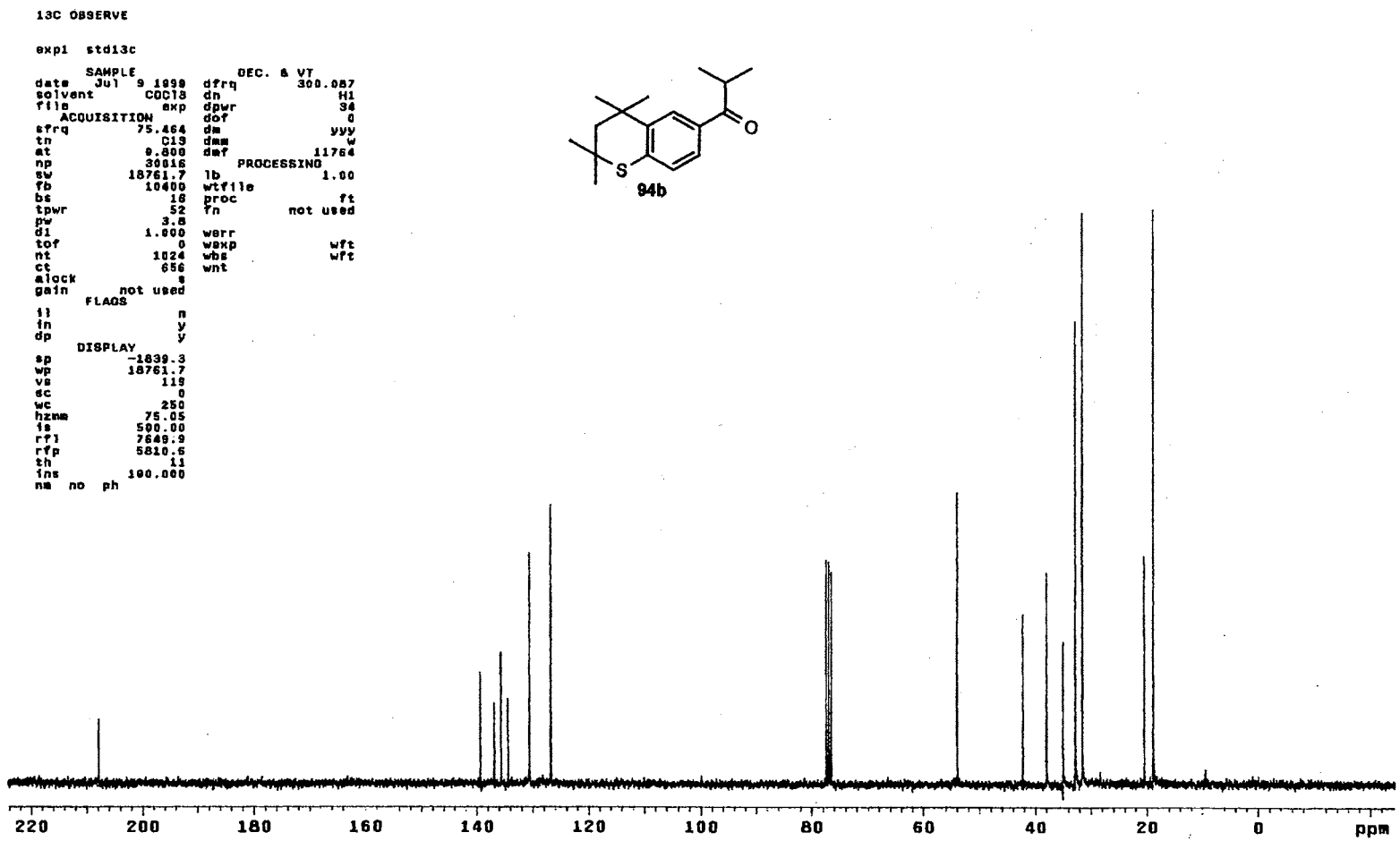


94b



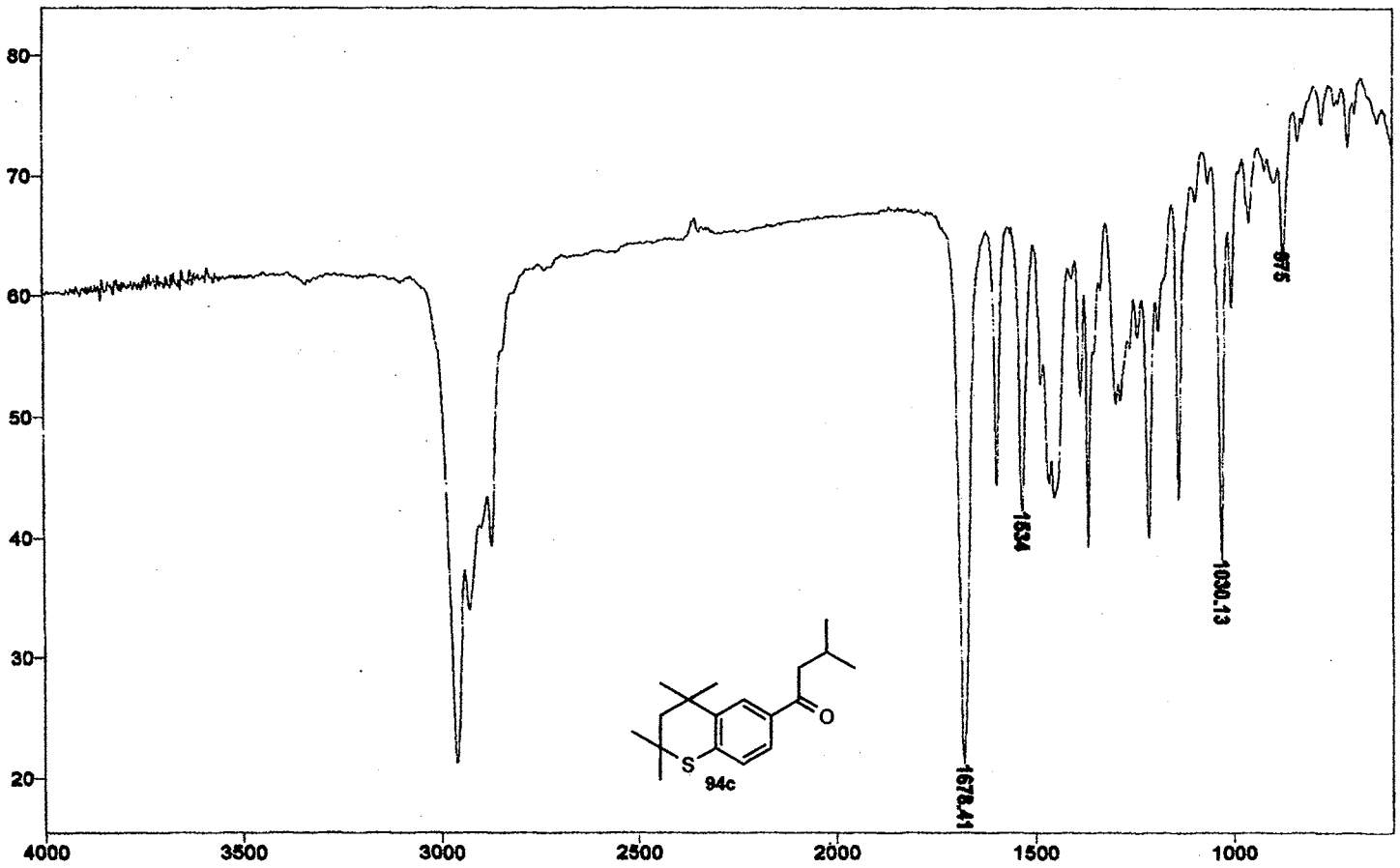
^{1}H NMR Spectrum of **94b**

Plate CXL



^{13}C NMR Spectrum of **94b**

Plate CXLI



IR Spectrum of **94c**

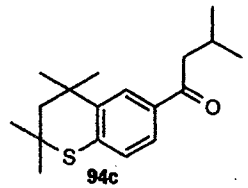
Plate CXLII

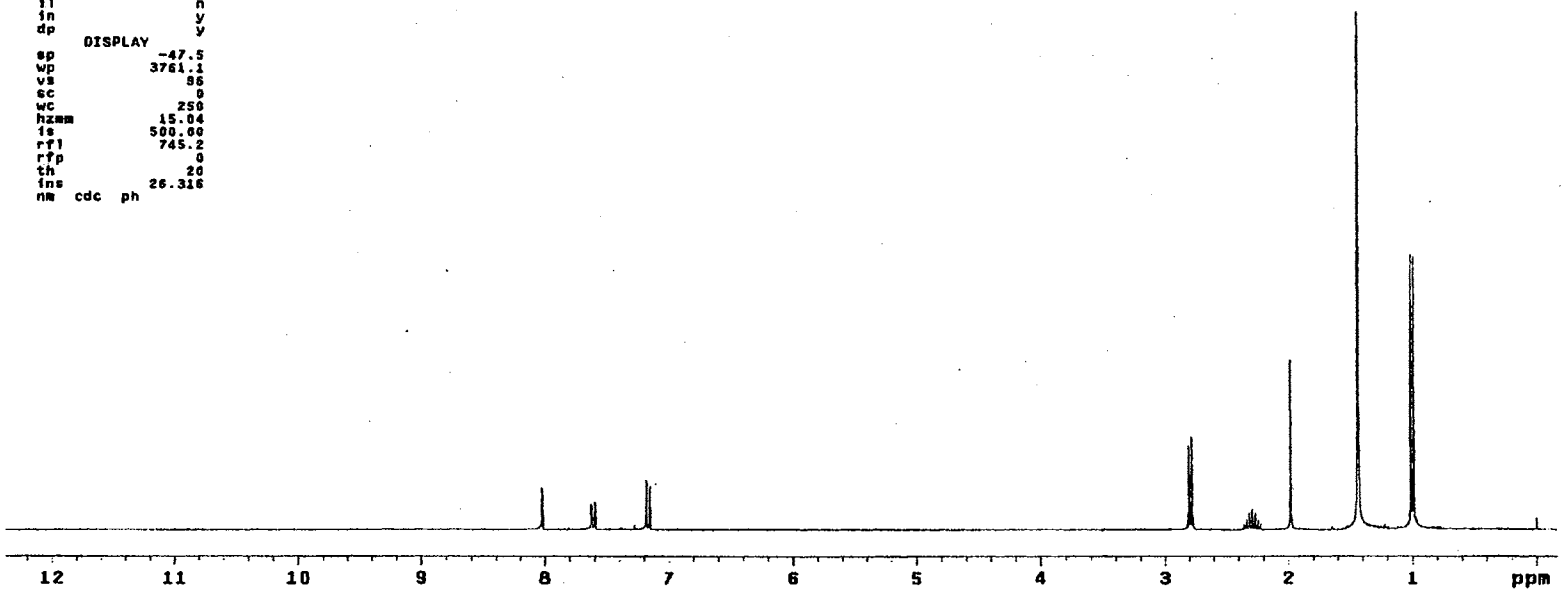
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE
date    Nov  8 1999
solvent       CDCl3
file           exp
   ACQUISITION
sfrq        300.087
tn               H1
at            3.747
np            33728
sw           4500.5
fb             2600
bs               16
tpwr             48
pw              2.0
d1                0
tof               0
nt               16
ct               16
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp            -47.5
wp           3761.1
vs               86
sc                0
wc              250
hzmm          15.04
is           500.00
rf1           745.2
rfp               0
th               20
ins           26.316
nm  cdc  ph

      DEC. & VT
dfrq        300.087
dn               H1
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
     PROCESSING
wtfile
proc             ft
fn        not used
werr
wexp
wbs
wnt
```





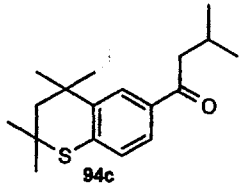
^{1}H NMR Spectrum of **94c**

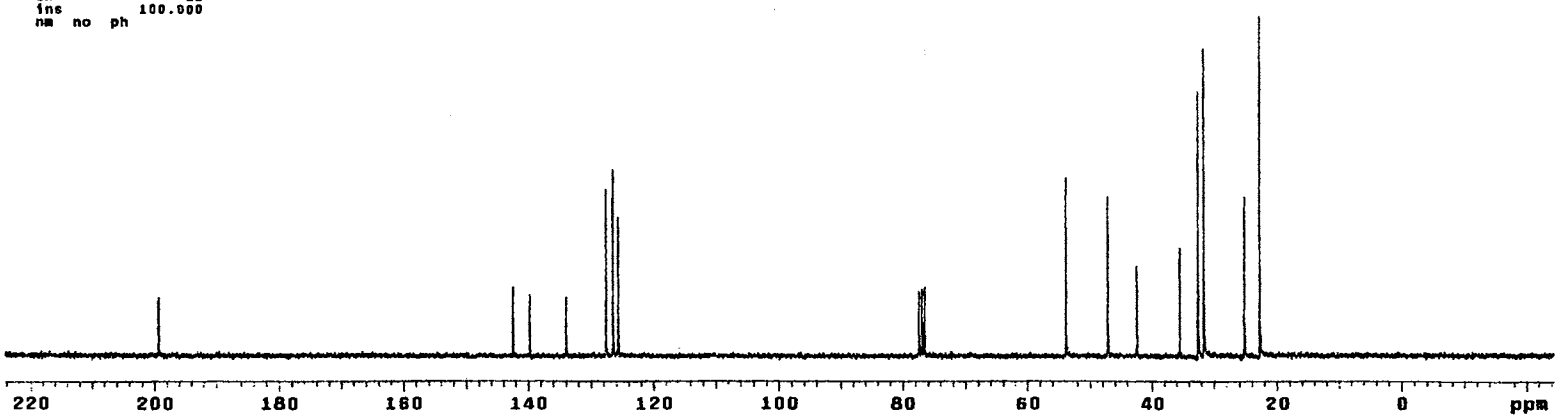
Plate CXLIII

```
13C OBSERVE

expl  std13c

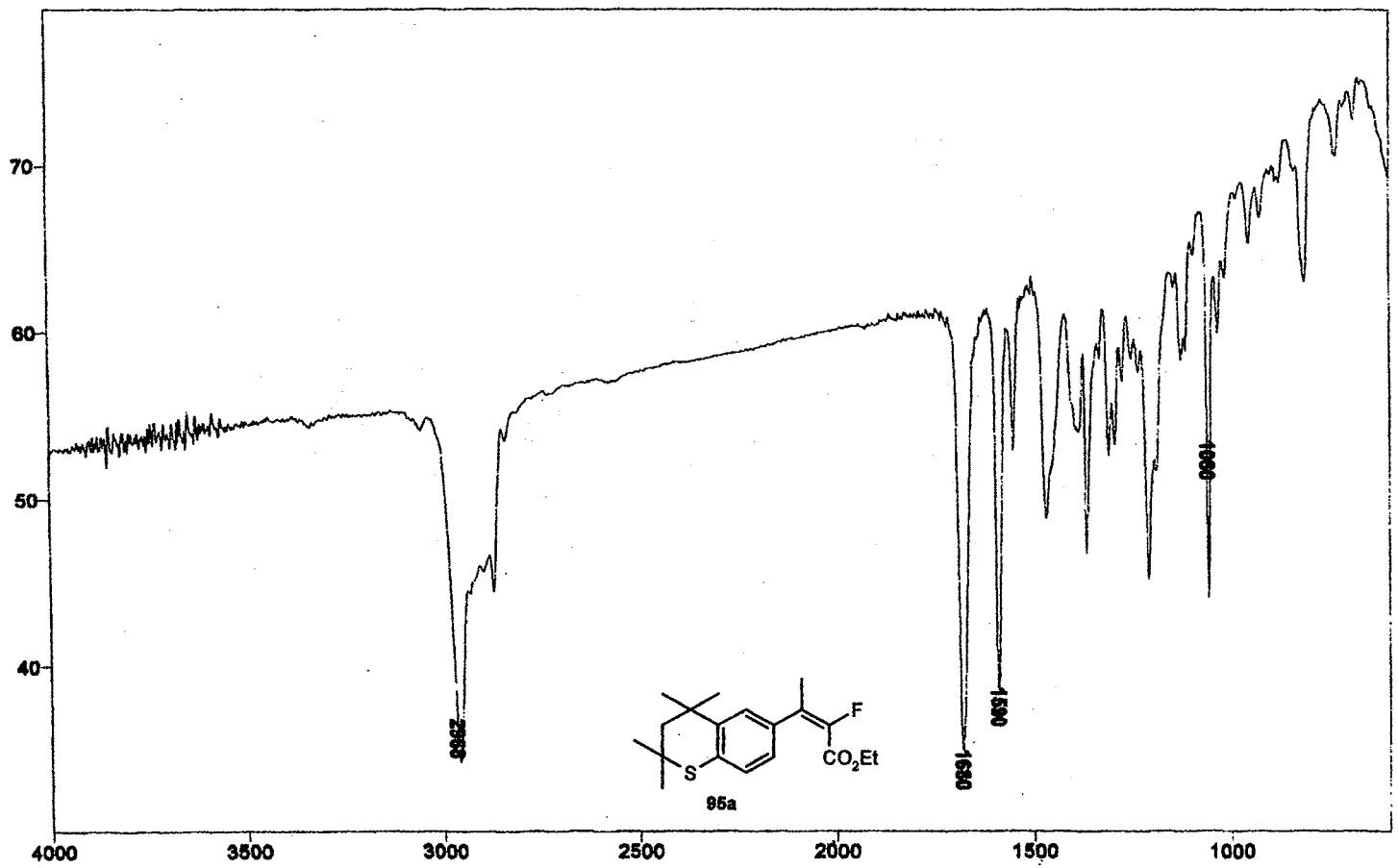
      SAMPLE                 DEC. & VT
date   Nov  5 1999   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                  0
sfrq          75.464 dm                 yyy
tn               C13 dmm                  w
at             0.800 dmf              11764
np             30016     PROCESSING
sw           18761.7 lb                1.00
fb             10400 wtfile
bs                16 proc                 ft
tpwr              52 fn          not used
pw               3.8
d1             1.000 werr
tof                0 wexp                wft
nt              1024 wbs                 wft
ct               256 wnt
alock              s
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1840.4
wp           18761.7
vs                63
sc                 0
wc               250
hzmm           75.05
is             500.00
rfl            7651.0
rfp            5810.6
th                11
ins           100.000
nm  no  ph
```





^{13}C NMR Spectrum of **94c**

Plate CXLIV



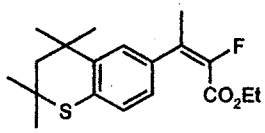
IR Spectrum of **95a**

Plate CXLV

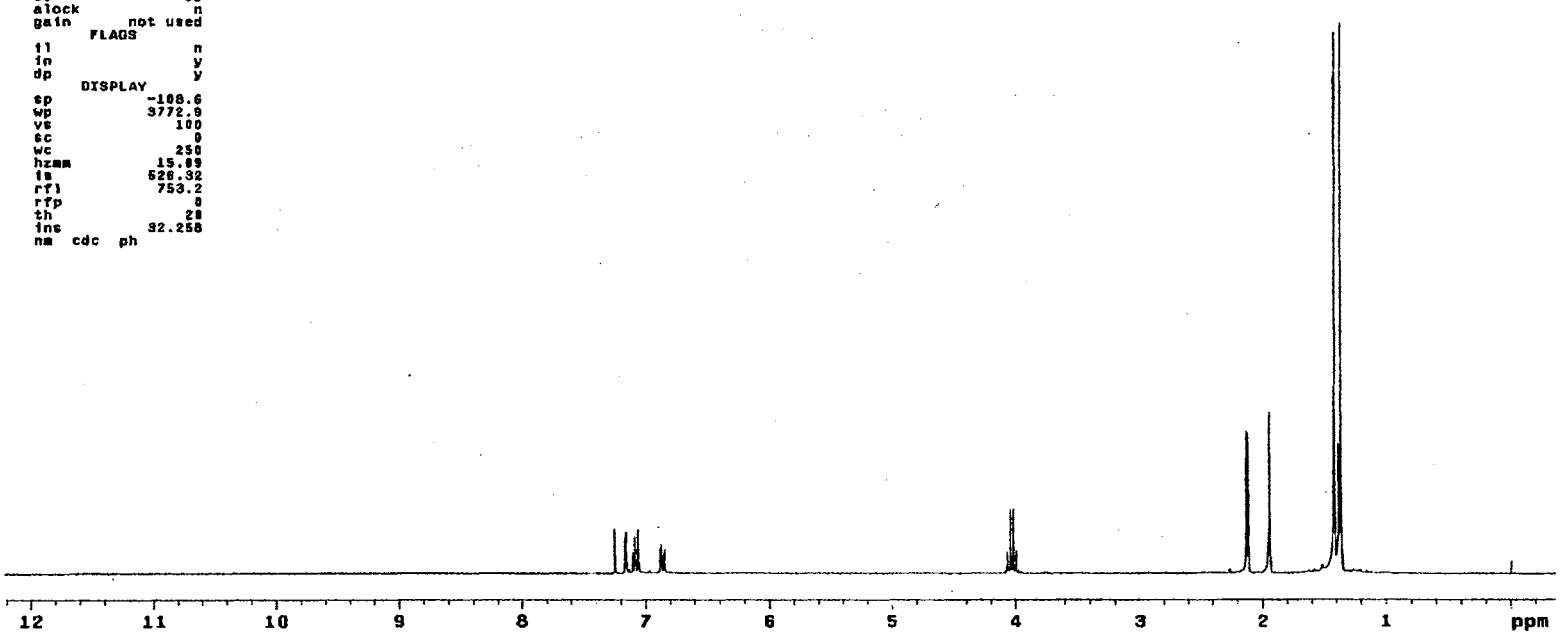
```
STANDARD 1H OBSERVE

expl  std1h

      SAMPLE                 DEC. & VT
date   Sep 29 1999   dfrq          300.087
solvent      CDCl3   dn               H1
file           exp   dpwr             30
   ACQUISITION       dof               0
sfrq        300.087  dm              nnn
tn               H1  dmm               c
at            3.747  dmf             200
np           33728      PROCESSING
sw          4500.5   wtfile
fb            2600   proc            ft
bs              16   fn        not used
tpwr            48
pw             6.9   werr
d1               0   wexp
tof              0   wbs
nt              32   wnt
ct              32
alock            n
gain      not used
      FLAGS
i1               n
in               y
dp               y
      DISPLAY
sp          -108.6
wp          3772.9
vs             100
sc               0
wc             250
hzmm         15.09
fn          526.32
rf1          753.2
rfp              0
th              28
ins         32.258
nm  cdc  ph
```



95a



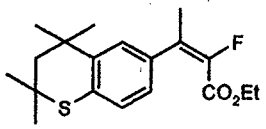
^{1}H NMR Spectrum of **95a**

Plate CXLVI

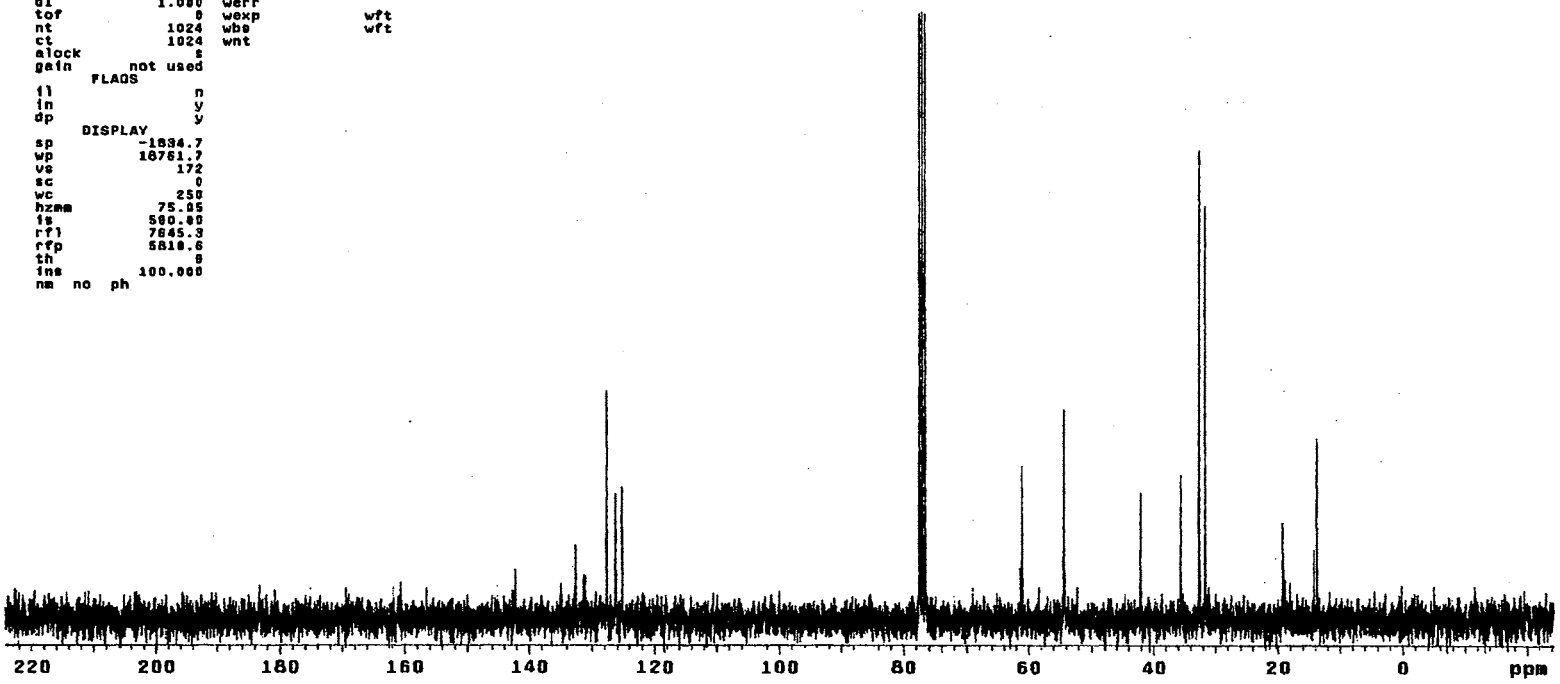
```
13C OBSERVE

exp1  std13c

      SAMPLE                    DEC. & VT
date   Sep 29 1999      dfrq          300.057
solvent        CDCl3    dn                 H1
file             exp    dpwr               34
   ACQUISITION          dof                 0
sfrq           75.464   dm                yyy
tn                C13   dmm                 w
at              0.800   dmf             11764
np              30016      PROCESSING
sw           18761.7    lb                1.00
fb              10400   wtfile
bs                 16   proc                ft
tpwr               52   fn          not used
pw                3.8
d1              1.000   werr
tof                 0   wexp               wft
nt               1024   wbs                wft
ct               1024   wnt
alock               s
gain         not used
      FLAGS
il                  n
in                  y
dp                  y
      DISPLAY
sp            -1834.7
wp            18761.7
vs                172
sc                  0
wc                250
hzcm            75.05
is             500.00
rf1            7645.3
rfp            5818.6
th                  8
ins           100.000
nm  no  ph
```



95a



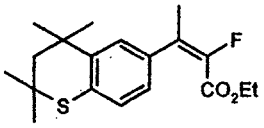
^{13}C NMR Spectrum of **95a**

Plate CXLVII

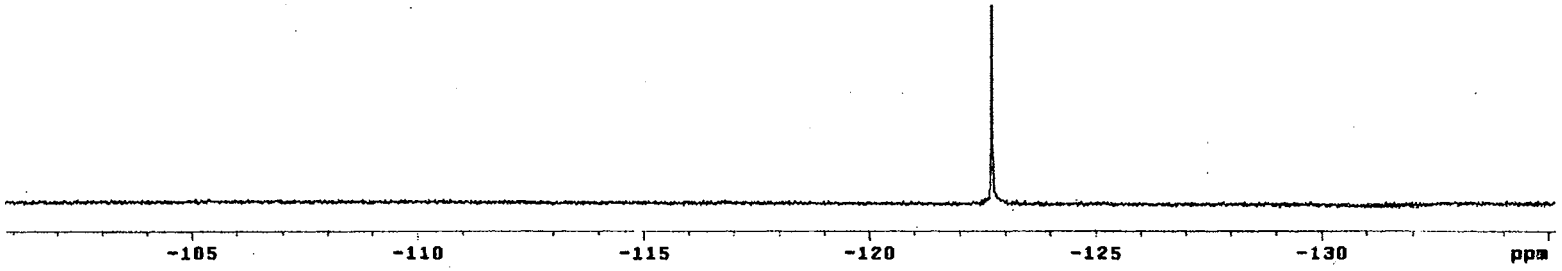
```
13C OBSERVE

expl  std13c

      SAMPLE                    DEC. & VT
date   Feb  8 2000  dfrq          300.087
solvent       CDCl3 dn                 H1
file            exp dpwr               34
   ACQUISITION      dof                 0
sfrq        282.333 dm                nnn
tn              F19 dmm                 w
at            0.800 dmf             11764
np            30016      PROCESSING
sw          16761.7 lb             1.00
fb            16400 wtfile
bs               16 proc               ft
tpwr             52 fn          not used
pw              3.8
d1            1.000 werr
tof               0 wexp             wft
nt             1024 wbs              wft
ct               48 wnt
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp         -38157.3
wp          9588.3
vs             103
sc               0
wc             250
hzcm         38.75
is          500.00
rfl         38748.2
rfp               0
th               20
ins         106.000
nm  no  ph
```

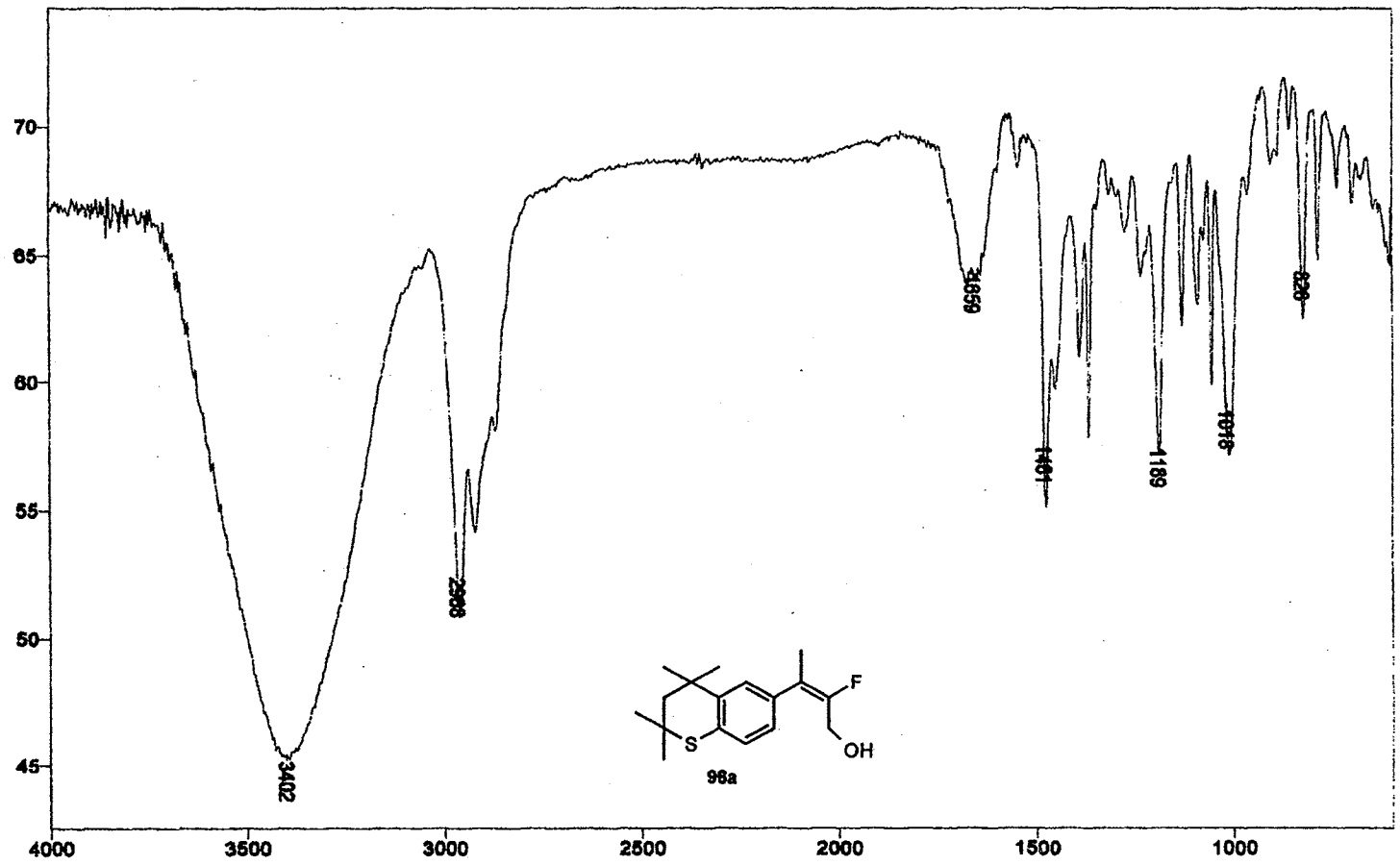


95a



^{19}F NMR Spectrum of **95a**

Plate CXLVIII



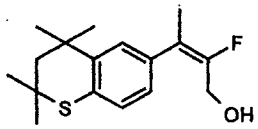
IR Spectrum of **96a**

Plate CXLIX

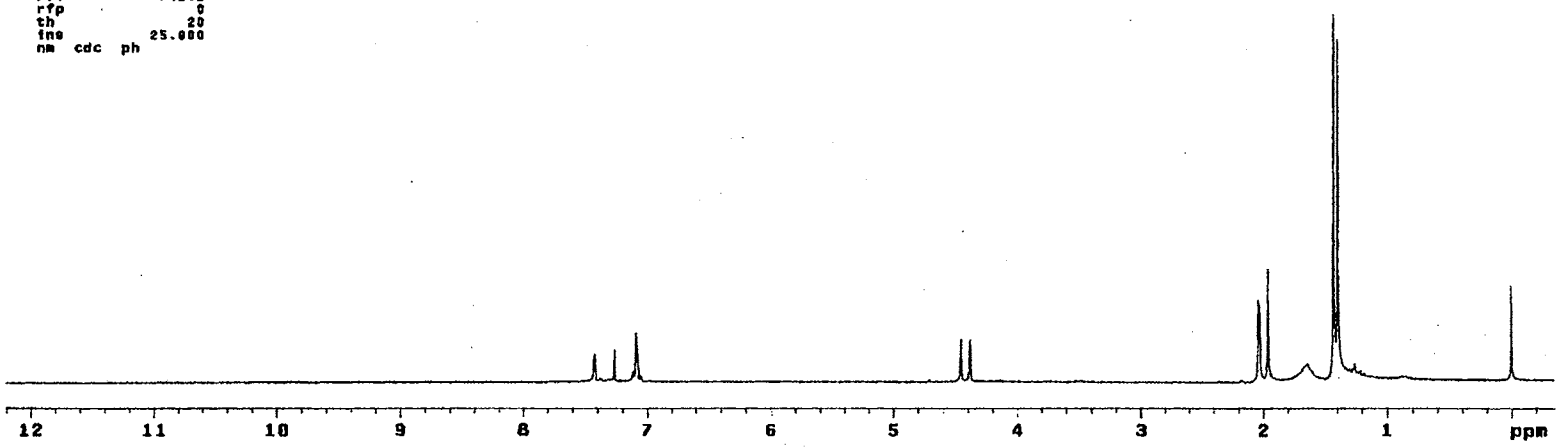
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date   Oct  8 1999   dfrq        300.067
solvent       CDCl3  dn              H1
file            exp  dpwr            30
   ACQUISITION       dof             0
sfrq         300.067 dm            nnn
tn              H1   dmm             c
at            3.747  dmf           200
np           33728      PROCESSING
sw          4500.5   wtfile
fb            2600   proc           ft
bs              16   fn        not used
tpwr            48
pw             6.9   werr
d1              0    wexp
tof             0    wbs
nt             16    wnt
ct             16
alock           n
gain       not used
      FLAGS
il              n
in              y
dp              y
     DISPLAY
sp          -104.2
wp          3787.0
vs             68
sc              0
wc            250
hzcm        15.07
is          500.00
rf1         748.8
rfp             0
th             20
ins         25.000
nm  cdc  ph
```



96a



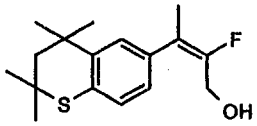
^{1}H NMR Spectrum of **96a**

Plate CL

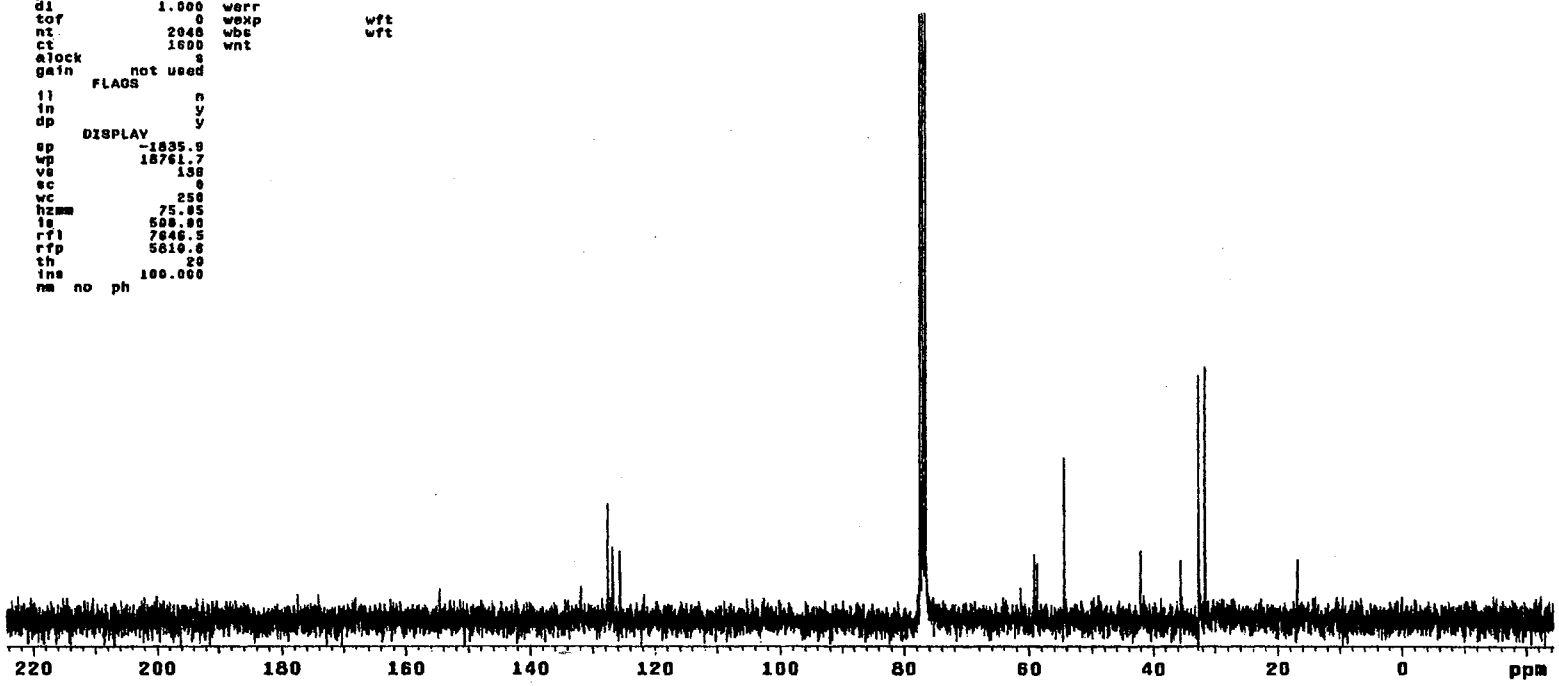
```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date   Oct  8 1999   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                  0
sfrq          75.464 dm                 yyy
tn               C13 dmm                  w
at             0.800 dmf             11764
np             38016    PROCESSING
sw           18761.7 lb                1.00
fb             10400 wtfile
bs                16 proc                 ft
tpwr              52 fn            not used
pw               3.8
d1             1.000 werr
tof                0 wexp                wft
nt              2048 wbs                 wft
ct              1600 wnt
alock              s
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1835.9
wp           18761.7
vs               138
sc                 0
wc               250
hzmm           75.85
is             508.8
rfl            7646.5
rfp            5610.6
th                20
ins           100.000
nm  no  ph
```



96a



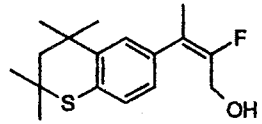
^{13}C NMR Spectrum of **96a**

Plate CLI

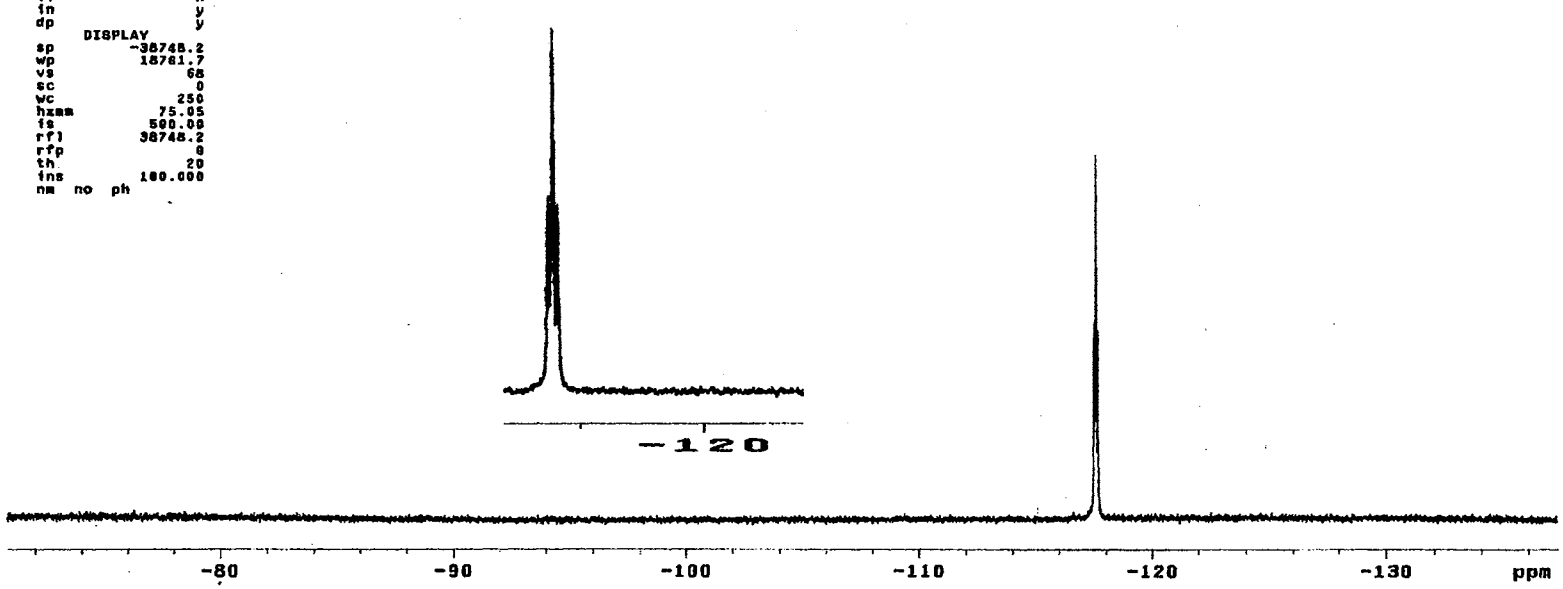
```
13C OBSERVE

exp1  std13c

      SAMPLE                DEC. & VT
date   Oct  8 1999  dfrq          300.087
solvent       CDCl3 dn                 H1
file            exp dpwr               34
   ACQUISITION      dof                 0
sfrq        282.339 dm                nnn
tn              F19 dmm                 w
at            6.800 dmf             11764
np            30016     PROCESSING
sw          18761.7 lb                1.00
fb            10408 wtfile
bs               16 proc                ft
tpwr             52 fn          not used
pw              3.8
d1            1.000 werr
tof               0 wexp               wft
nt             1024 wbs                wft
ct              336 wnt
alock             n
gain       not used
      FLAGS
fl                n
in                y
dp                y
     DISPLAY
sp         -38748.2
wp         18761.7
vs               68
sc                0
wc              250
hzcm          75.05
is           500.00
rfl        38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```

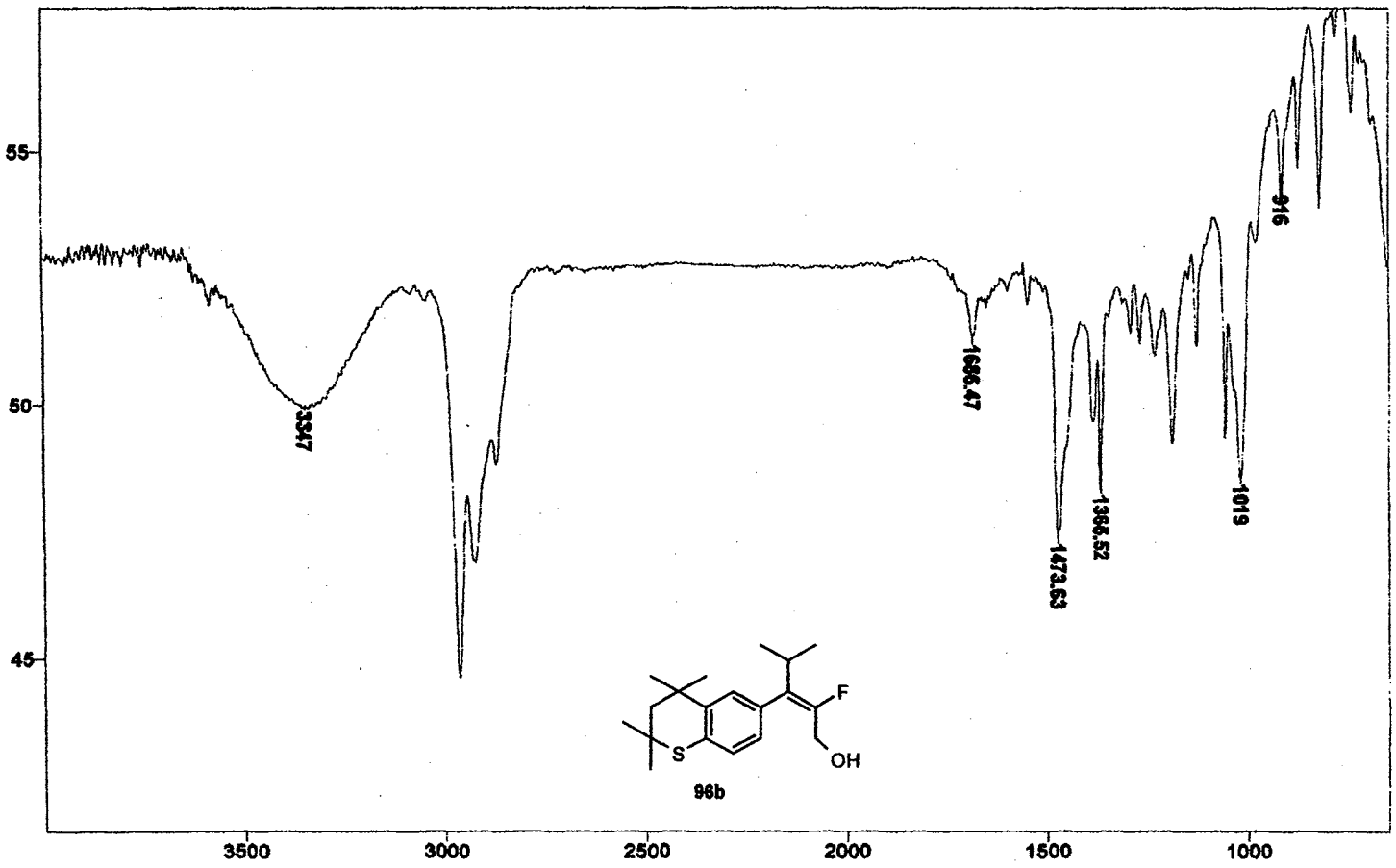


96a



^{19}F NMR Spectrum of **96a**

Plate CLII



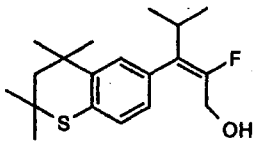
IR Spectrum of **96b**

Plate CLIII

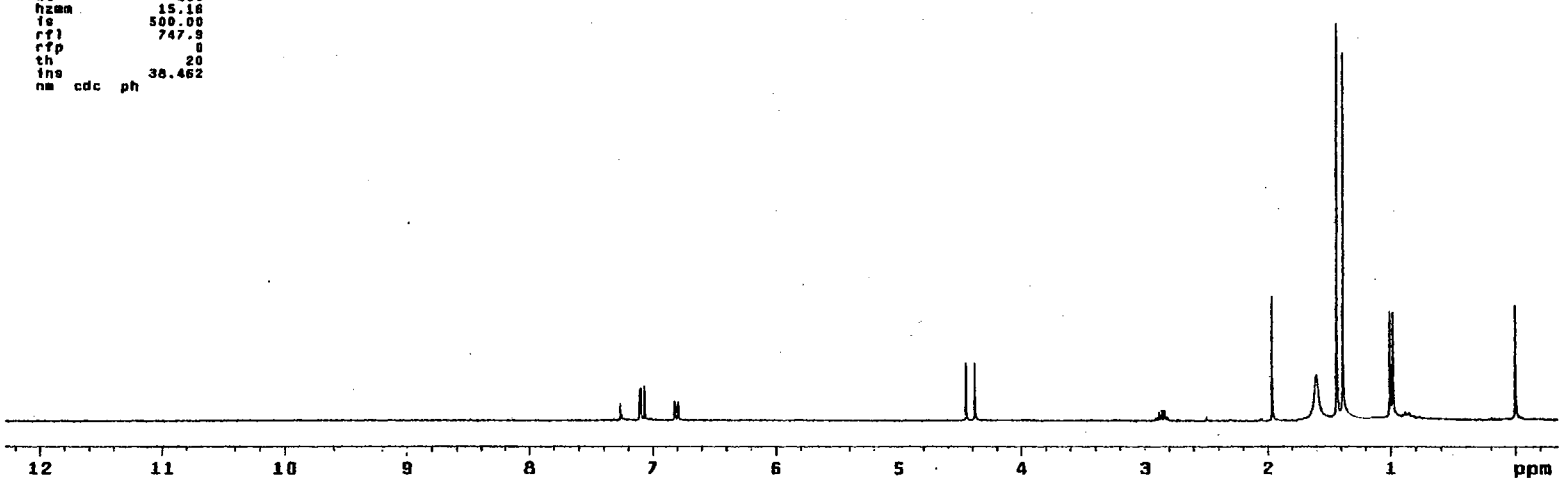
```
STANDARD 1H OBSERVE

exp1  stdih

      SAMPLE                 DEC. & VT
date   Nov  3 1999   dfrq        300.087
solvent      CDCl3   dn              H1
file           exp   dpwr            30
   ACQUISITION       dof              0
sfrq        300.087  dm             nnn
tn             H1    dmm              c
at           3.747   dmf            200
np           33728        PROCESSING
sw          4500.5   wtfile
fb            2600   proc            ft
bs              16   fn        not used
tpwr            46
pw             6.8   werr
di               0   wexp
tof              0   wbs
nt              32   wnt
ct              32
alock            n
gain       not used
      FLAGS
il               n
in               y
dp               y
     DISPLAY
sp          -103.3
wp          3780.8
vs              73
sc               0
wc             250
hzcm         15.18
ts          500.00
rfl          747.9
rfp              8
th              20
ins          38.462
nm  cdc  ph
```



96b



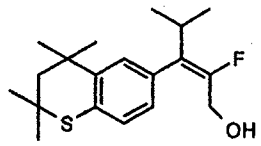
^{1}H NMR Spectrum of **96b**

Plate CLIV

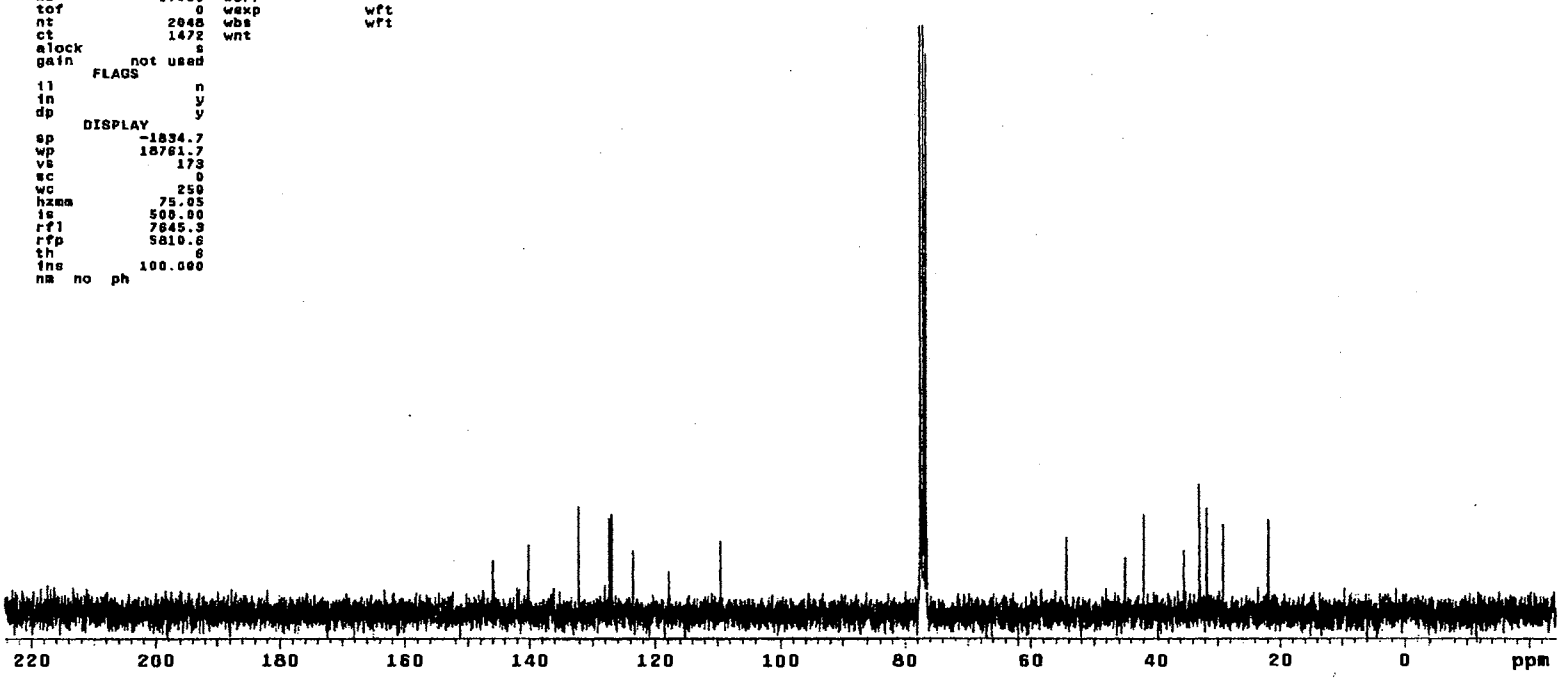
```
13C OBSERVE

exp1  std13c

        SAMPLE                DEC. & VT
date   Nov  3 1999   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr                34
    ACQUISITION      dof                  0
sfrq          75.464 dm                 yyy
tn               C13 dmm                  w
at             0.800 dmf             11764
np             30016     PROCESSING
sw           18761.7 lb                1.00
fb             18408 wtfile
bs                16 proc                 ft
tpwr              52 fn           not used
pw               3.8
d1             1.000 werr
tof                0 wexp               wft
nt              2048 wbs                wft
ct              1472 wnt
alock              s
gain        not used
        FLAGS
i1                 n
in                 y
dp                 y
        DISPLAY
sp           -1834.7
wp           18761.7
vs               173
sc                 0
wc               250
hzmm           75.05
is            500.00
rf1           7645.3
rfp           5810.6
th                 6
ins          100.000
nm  no  ph
```



96b



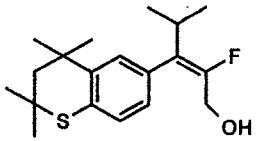
^{13}C NMR Spectrum of **96b**

Plate CLV

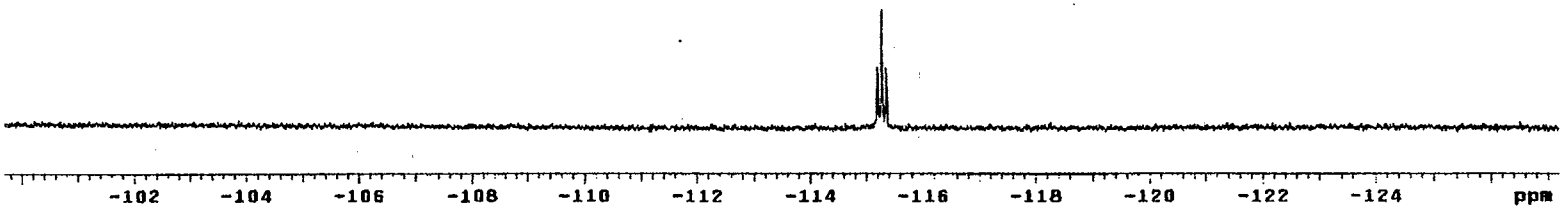
```
13C OBSERVE

expl  std13c

      SAMPLE                 DEC. & VT
date   Nov  3 1999   dfrq        300.087
solvent      CDCl3   dn              H1
file           exp   dpwr            34
    ACQUISITION      dof              0
sfrq        282.333  dm             nnn
tn              F19  dmm              w
at            0.800  dmf          11764
np            30016      PROCESSING
sw          16761.7  lb            1.00
fb            10400  wtfile
bs               16  proc            ft
tpwr             52  fn        not used
pw              3.6
d1            1.000  werr
tof               0  wexp          wft
nt             1024  wbs           wft
ct              144  wnt
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp         -35913.9
wp          7765.6
vs               25
sc                0
wc              250
hzmm          31.08
is           500.00
rfl         38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```

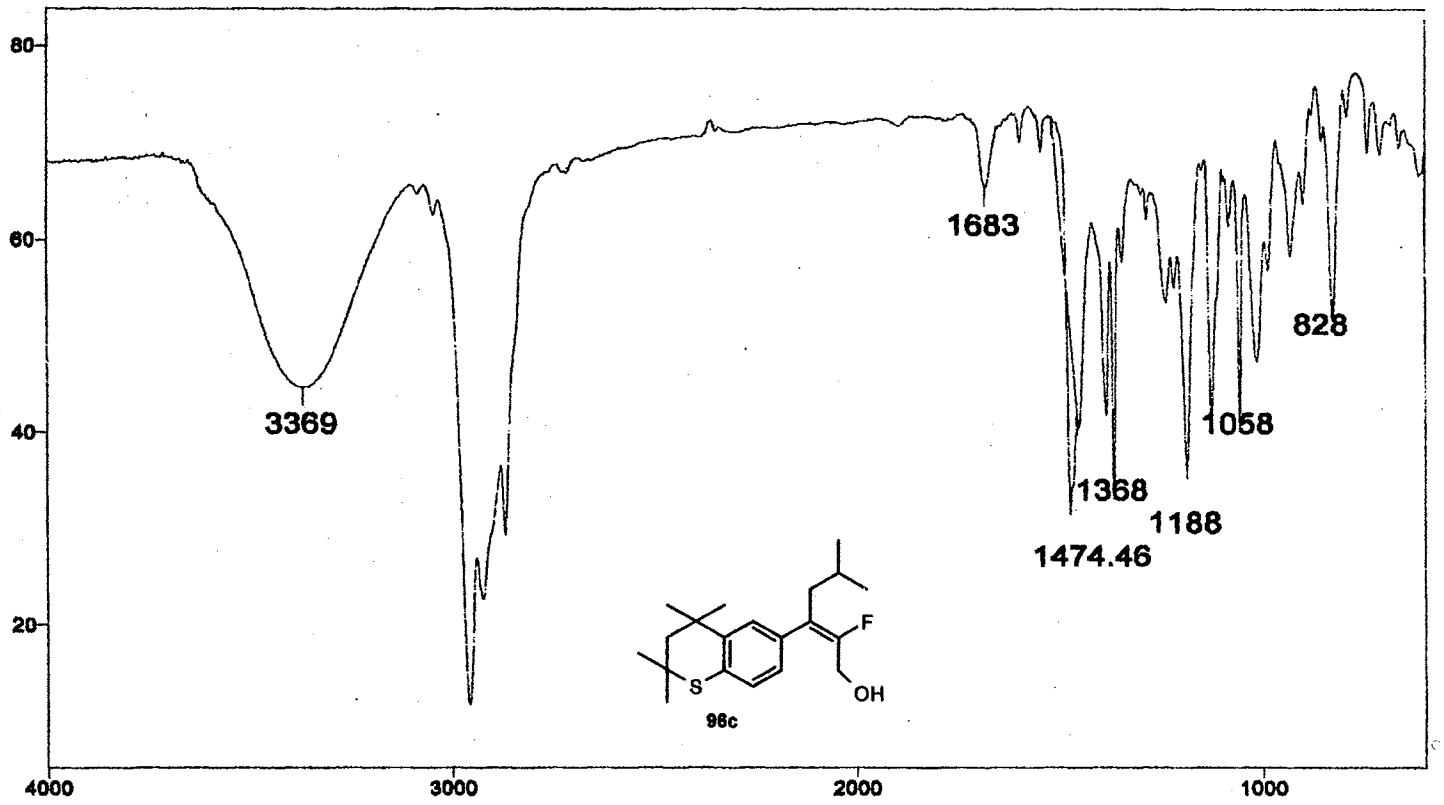


96b



^{19}F NMR Spectrum of **96b**

Plate CLVI



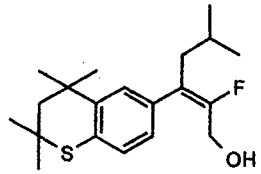
IR Spectrum of **96c**

Plate CLVII

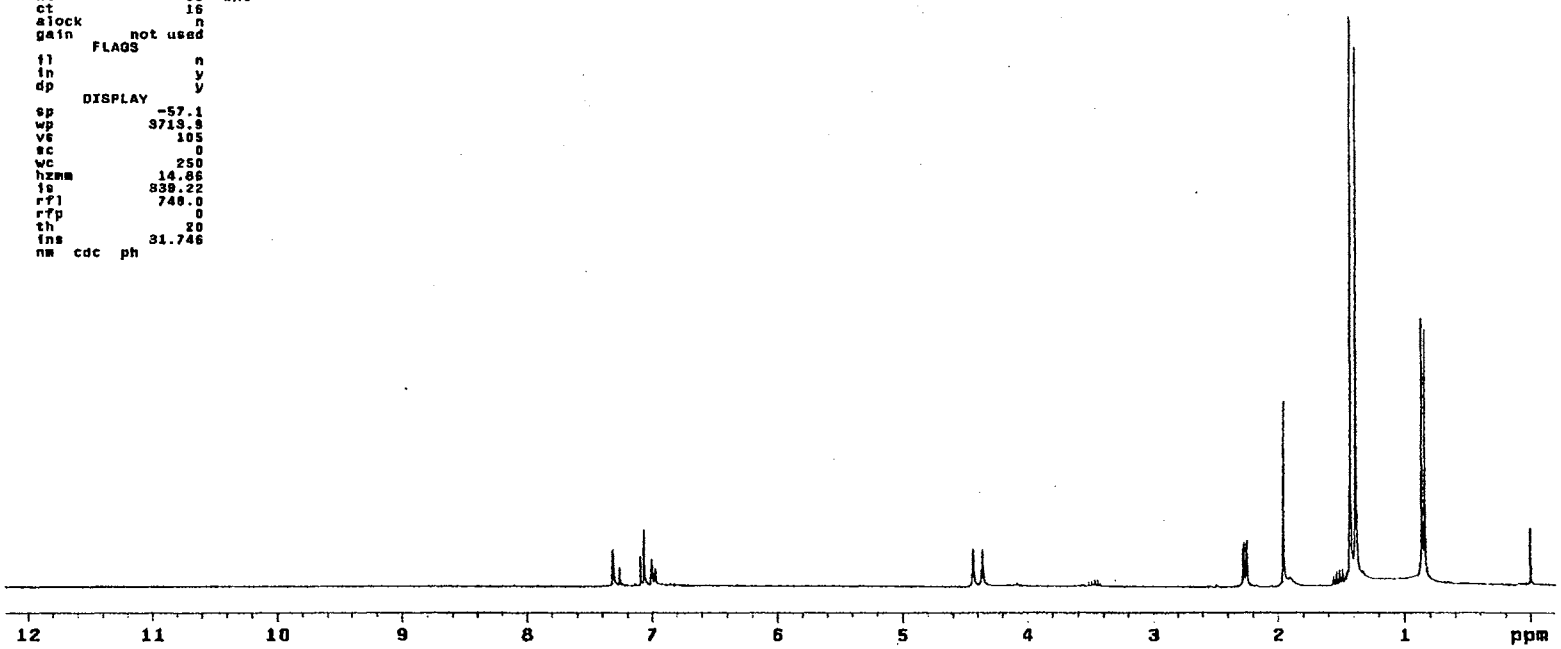
```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                DEC. & VT
date    Nov 23 1999   dfrq        300.087
solvent       CDCl3   dn              H1
file            exp   dpwr            30
   ACQUISITION        dof              0
sfrq          300.087 dm             nnn
tn              H1    dmm              c
at            3.747   dmf            200
np            33726       PROCESSING
sw           4500.5   wtfile
fb             2600   proc             ft
bs               16   fn        not used
tpwr             48
pw              6.9   werr
d1                0   wexp
tof               0   wbs
nt               16   wnt
ct               16
alock             n
gain       not used
      FLAGS
fl                n
in                y
dp                y
     DISPLAY
sp            -57.1
wp           3713.9
vs              105
sc                0
wc              250
hzmm          14.86
is           839.22
rfl           748.0
rfp               0
th               20
ins          31.746
nm  cdc  ph
```



96c



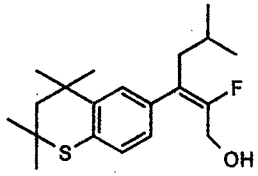
^{1}H NMR Spectrum of **96c**

Plate CLVIII

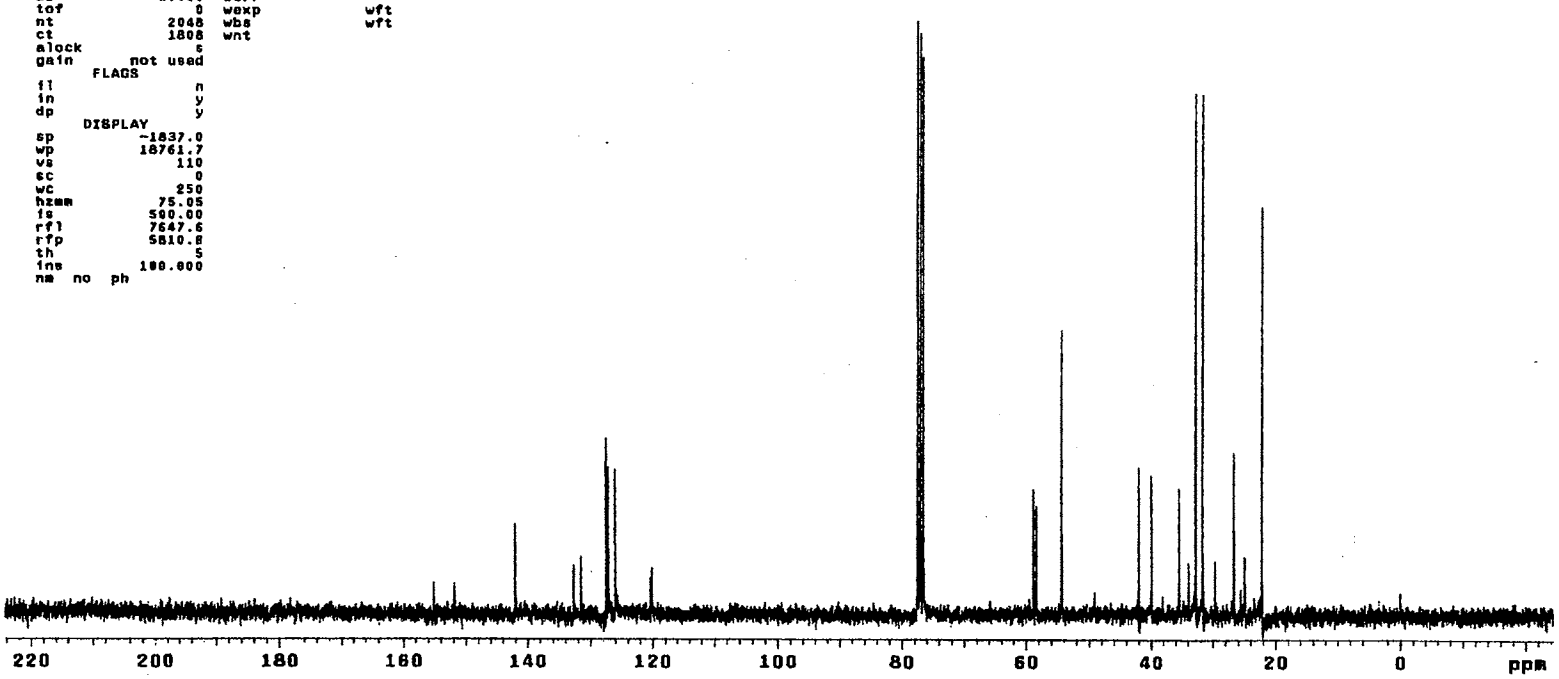
```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date   Nov 23 1996   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof                 0
sfrq         75.464  dm                yyy
tn              C13  dmm                 w
at            0.800  dmf             11764
np            30016     PROCESSING
sw          18761.7  lb              1.00
fb            10400  wtfile
bs               16  proc              ft
tpwr             52  fn          not used
pw              3.5
d1            1.000  werr
tof               0  wexp             wft
nt             2048  wbs             wft
ct             1808  wnt
alock             s
gain        not used
      FLAGS
fl                n
in                y
dp                y
      DISPLAY
sp          -1837.0
wp          18761.7
vs              110
sc                0
wc              250
hzmm          75.05
is           500.00
rfl          7647.6
rfp          5810.8
th                5
ins         100.000
nm  no  ph
```



96c



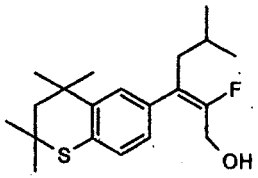
^{13}C NMR Spectrum of **96c**

Plate CLIX

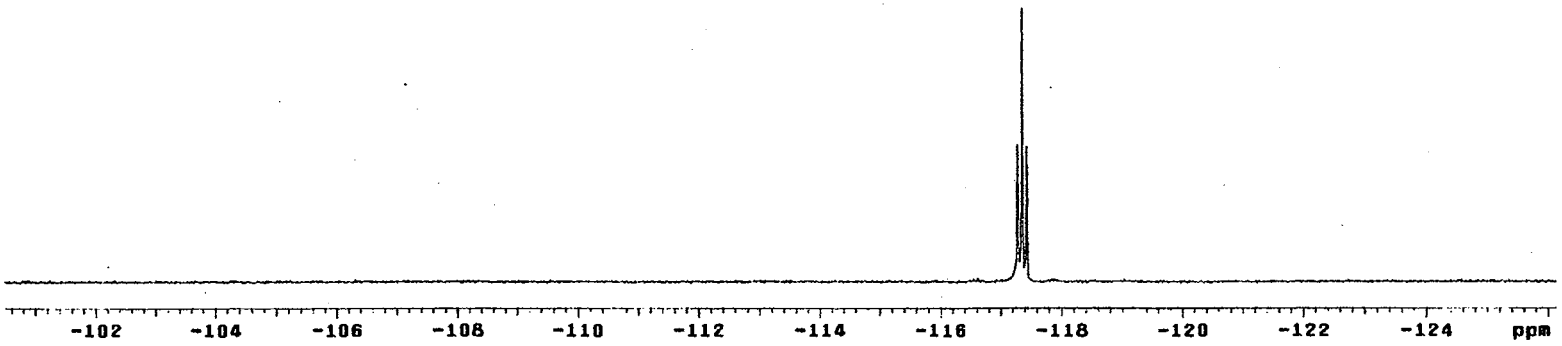
```
13C OBSERVE

expl  std13c

      SAMPLE                 DEC. & VT
date   Nov 23 1999  dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof               0
sfrq        282.333  dm              nnn
tn              F19  dmm               w
at            0.800  dmf           11764
np            30016     PROCESSING
sw          18781.7  lb             1.00
fb            10400  wtfile
hz               16  proc              ft
tpwr             52  fn         not used
pw              3.8
d1            1.000  werr
tof               0  wexp            wft
nt             1024  wbs             wft
ct               48  wnt
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp         -35617.3
wp          7247.9
vs               50
sc                0
wc              250
hzcm          28.99
is            500.00
rfl         38748.2
rfp               0
th               20
ins          100.000
nm  no  ph
```

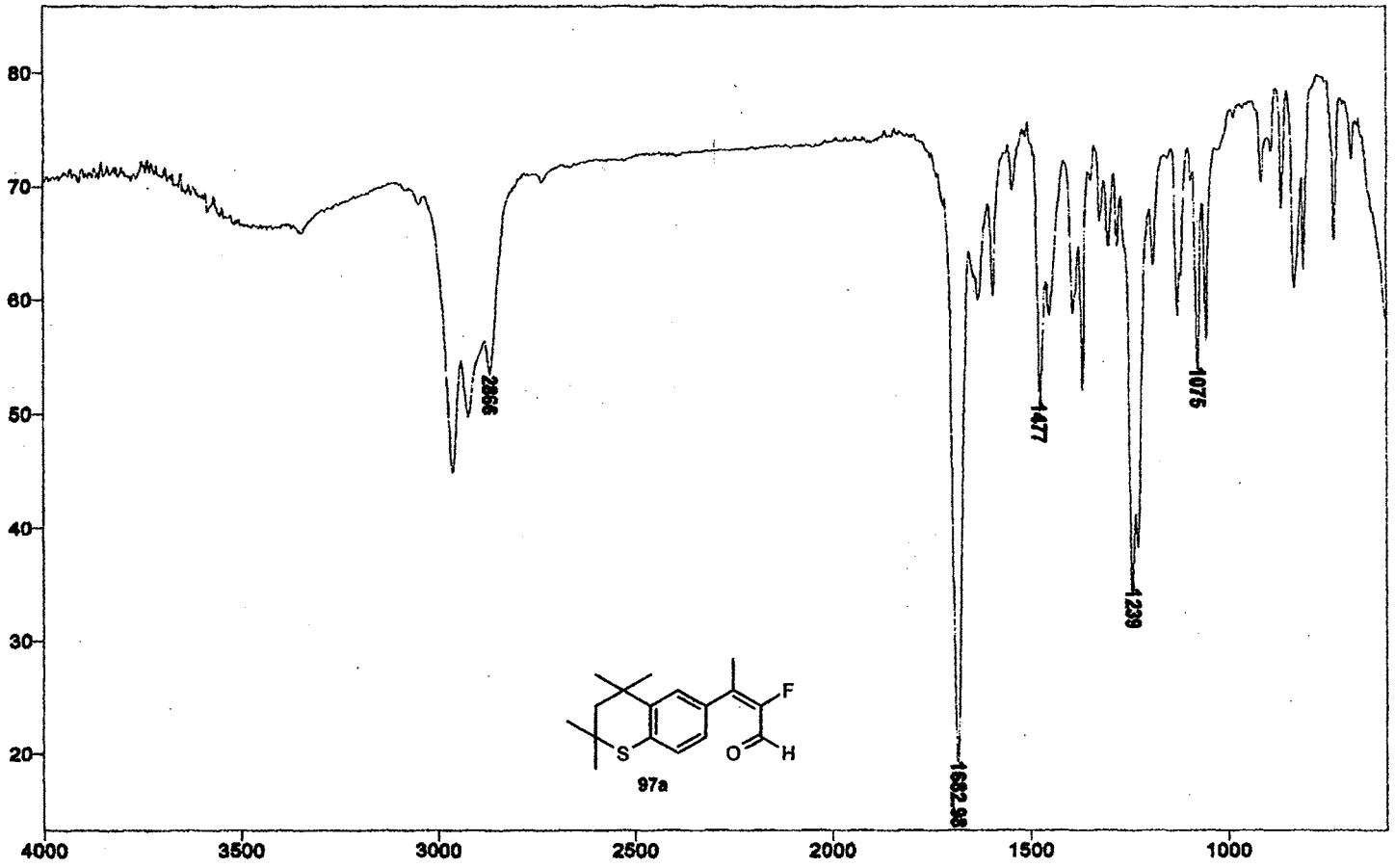


96c



^{19}F NMR Spectrum of **96cs**

Plate CLX



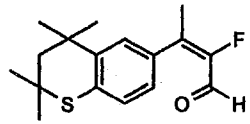
IR Spectrum of **97a**

Plate CLXI

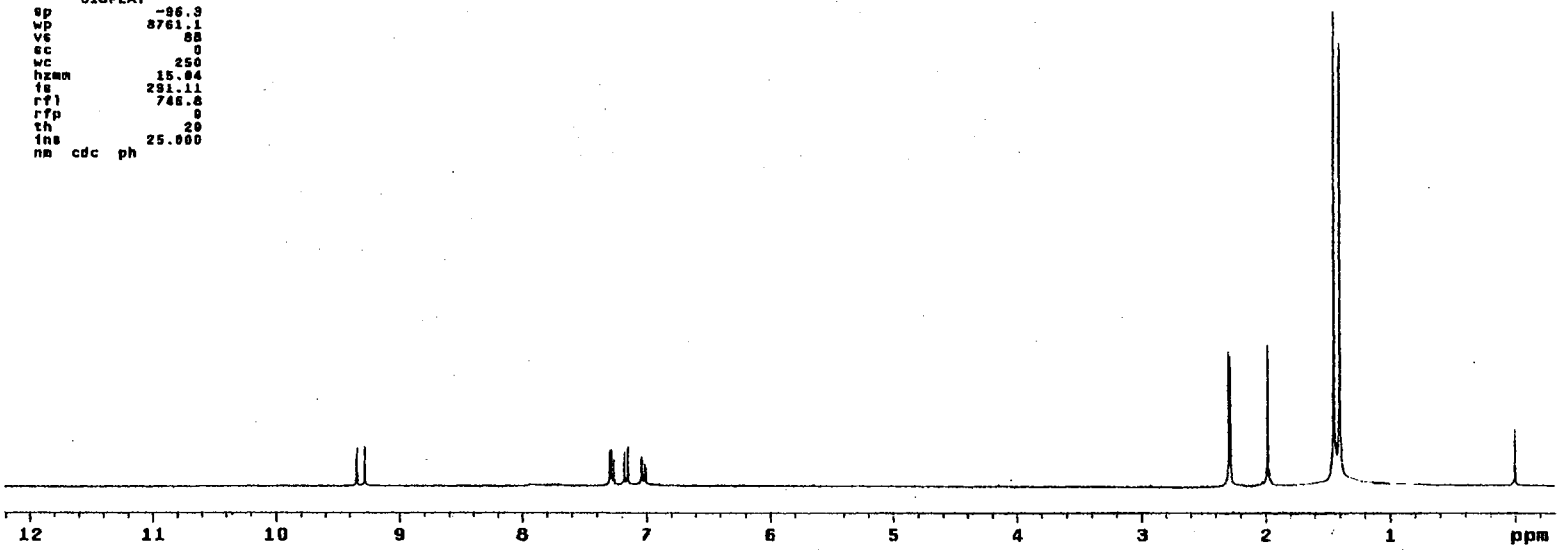
```
STANDARD 1H OBSERVE

exp1  stdih

      SAMPLE                DEC. & VT
date   Oct 28 1999   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              38
   ACQUISITION       dof                 0
sfrq        300.087  dm                nnn
tn               H1  dmm                 c
at            3.747  dmf               200
np            33728     PROCESSING
sw           4500.5  wtfile
fb             2600  proc              ft
bs               16  fn         not used
tpwr             48
pw              6.9  werr
d1                0  wexp            wft
tof               0  wbs             wft
nt               16  wnt
ct               16
alock             n
gain       not used
      FLAGS
ll                n
in                y
dp                y
     DISPLAY
sp            -96.3
wp           8761.1
vs               88
sc                0
wc              250
hzmm          15.04
is           291.11
rfl           746.8
rfp               0
th               20
ins          25.000
nm  cdc  ph
```



97a



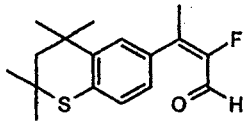
^{1}H NMR Spectrum of **97a**

Plate CLXII

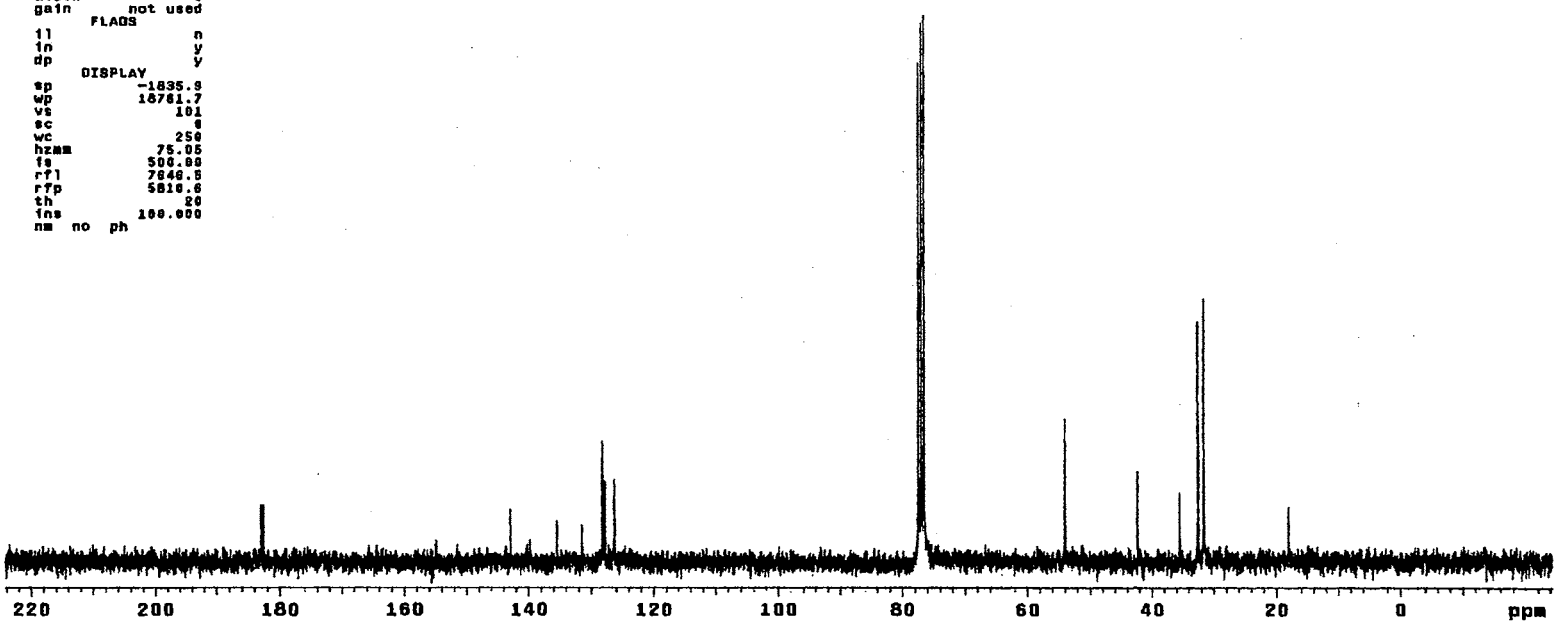
```
13C OBSERVE

expl  std13c

      SAMPLE                DEC. & VT
date    Oct 28 1999  dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr            34
   ACQUISITION       dof             0
sfrq          75.464 dm            yyy
tn               C13 dmm             w
at             0.600 dmf         11764
np             30016    PROCESSING
sw           18761.7  lb          1.00
fb             10400  wtfile
bs                16  proc          ft
tpwr              52  fn      not used
pw               3.8
d1             1.000  werr
tof                8  wexp        wft
nt              2048  wbs         wft
ct              2048  wnt
alock              s
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1835.9
wp           18761.7
vs               101
sc                 0
wc               250
hzmm           75.05
fs            500.00
rfl           7646.5
rfp           5816.6
th                20
ins          100.000
nm  no  ph
```



97a



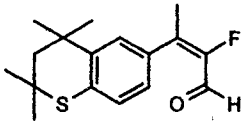
^{13}C NMR Spectrum of **97a**

Plate CLXIII

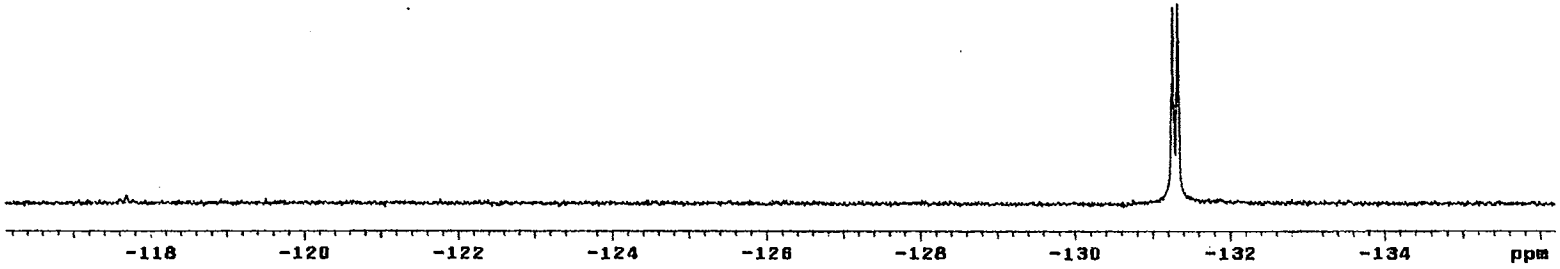
```
13C OBSERVE

expl  std13c

      SAMPLE                DEC. & VT
date   Oct 28 1988   dfrq        300.087
solvent      CDCl3   dn              H1
file           exp   dpwr             34
   ACQUISITION       dof              0
sfrq       282.333   dm             nnn
tn             F19   dmm              w
at           0.800   dmf          11764
np           30016      PROCESSING
sw         18761.7   lb            1.00
fb           10400   wtfile
bs              16   proc             ft
tpwr            52   fn        not used
pw             3.8
d1           1.000   werr
tof             0    wexp            wft
nt           1024   wbs             wft
ct             64   wnt
alock           n
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp        -38452.6
wp         5889.9
vs              37
sc               0
wc             250
hzcm         22.68
hz          500.88
rfl        38746.2
rfp              0
th              20
ins        100.000
nm  no  ph
```

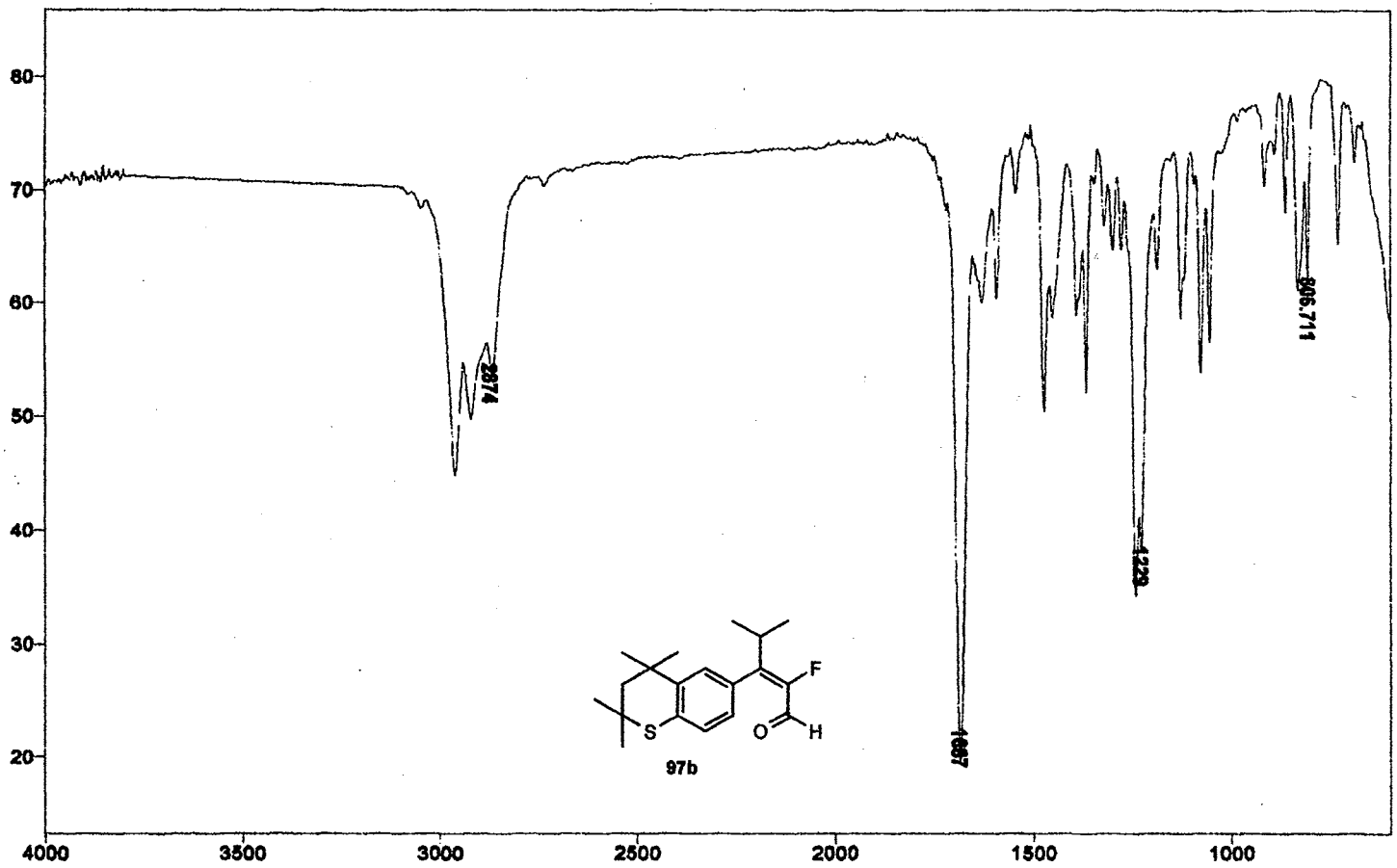


97a



^{19}F NMR Spectrum of **97a**

Plate CLXIV



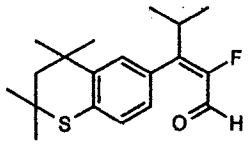
IR Spectrum of **97b**

Plate CLXV

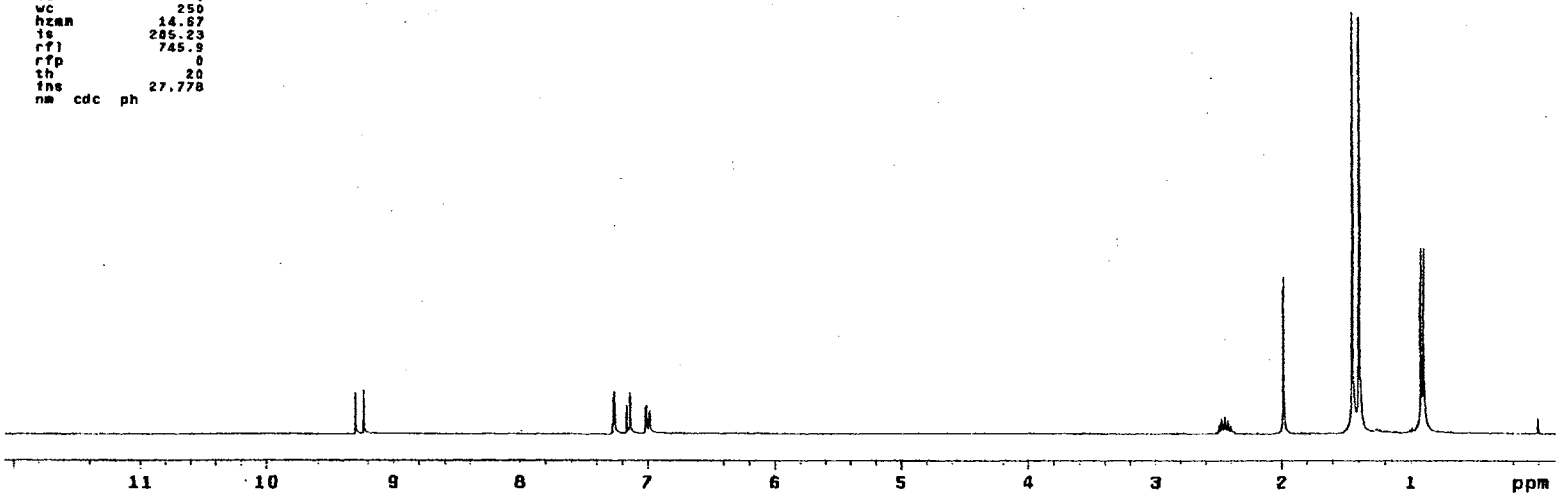
```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                 DEC. & VT
date    Jan 24 2000   dfrq        300.087
solvent       CDCl3   dn              H1
file            exp   dpwr              30
    ACQUISITION       dof                0
sfrq        300.087   dm               nnn
tn               H1   dmm                c
at            3.747   dmf              200
np            33728       PROCESSING
sw           4500.5   wtfile
fb             2600   proc              ft
bs               16   fn         not used
tpwr             48
pw              6.9   werr
d1                0   wexp
tof               0   wbs
nt               16   wnt
ct               16
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
    DISPLAY
sp            -42.3
wp           3866.5
vs               87
sc                0
wc              250
hzcm          14.67
is           285.23
rfl           745.9
rfp               0
th               20
ins           27.778
nm  cdc  ph
```



97b



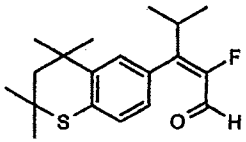
^{1}H NMR Spectrum of **97b**

Plate CLXVI

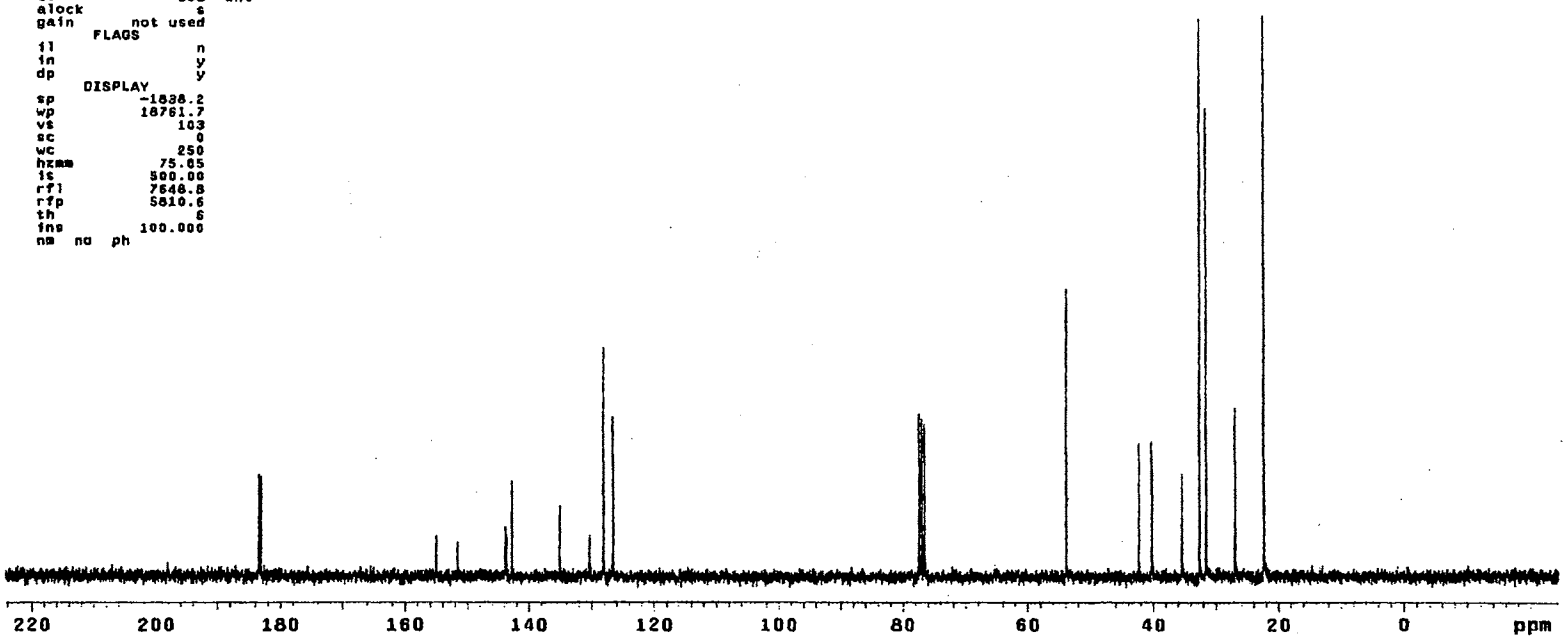
```
13C OBSERVE

exp1  std13c

      SAMPLE                DEC. & VT
date   Jan 24 2000   dfrq        300.087
solvent       CDCl3  dn.            H1
file            exp  dpwr           34
   ACQUISITION       dof            0
sfrq          75.464 dm            yyy
tn               C13 dmm             w
at             0.800 dmf         11764
np             30016     PROCESSING
sw           18761.7 lb           1.00
fb             10400 wtfile
bs                16 proc           ft
tpwr              52 fn       not used
pw               3.8
d1             1.000 werr
tof                0 wexp          wft
nt              1024 wbs           wft
ct               208 wnt
alock              s
gain        not used
      FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp          -1838.2
wp           18761.7
vs               103
sc                 0
wc               250
hzmm           75.65
is            500.00
rfl           7648.8
rfp           5810.6
th                 6
ins         100.000
nm  nc  ph
```



97b



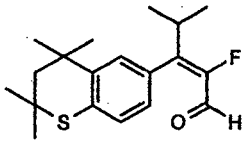
^{13}C NMR Spectrum of **97b**

Plate CLXVII

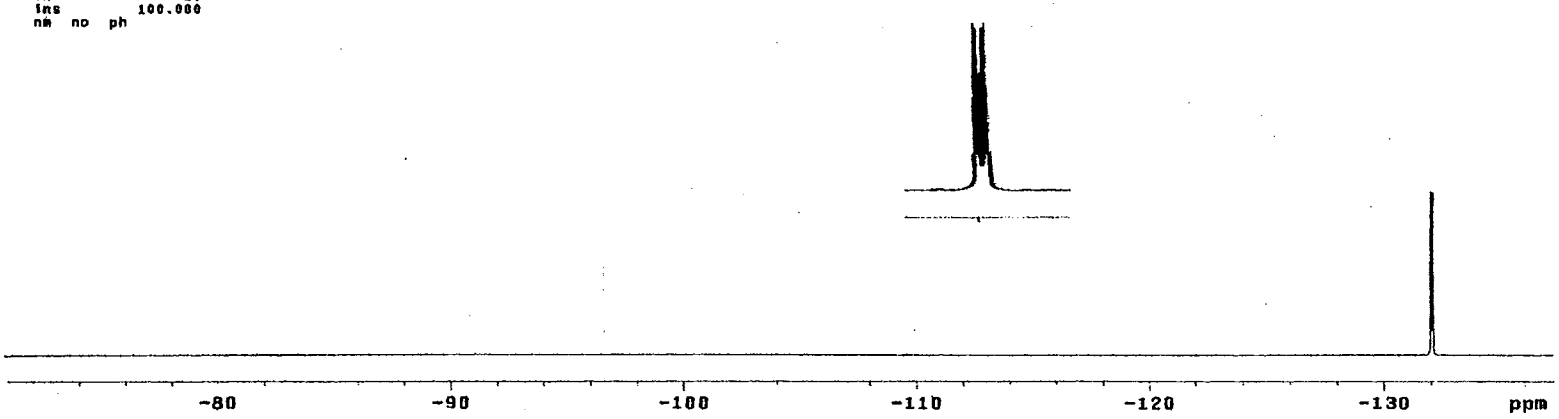
```
13C OBSERVE

expl  std13c

      SAMPLE                DEC. & VT
date   Jan 24 2000   dfrq        300.087
solvent      CDCl3   dn              H1
file           exp   dpwr            34
   ACQUISITION       dof              0
sfrq        282.333  dm             nnn
tn              F19  dmm              w
at            0.800  dmf          11764
np            30016     PROCESSING
sw          18761.7  lb            1.00
fb            10400  wtfile
bs               16  proc            ft
tpwr             52  fn        not used
pw              3.6  werr
d1            1.000  wexp           wft
tof               0  wbs            wft
nt             1024  wnt
ct               32
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp         -38748.2
wp          18761.7
vs               30
sc                0
wc              250
hzmm          75.05
is           500.00
rf1        38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```

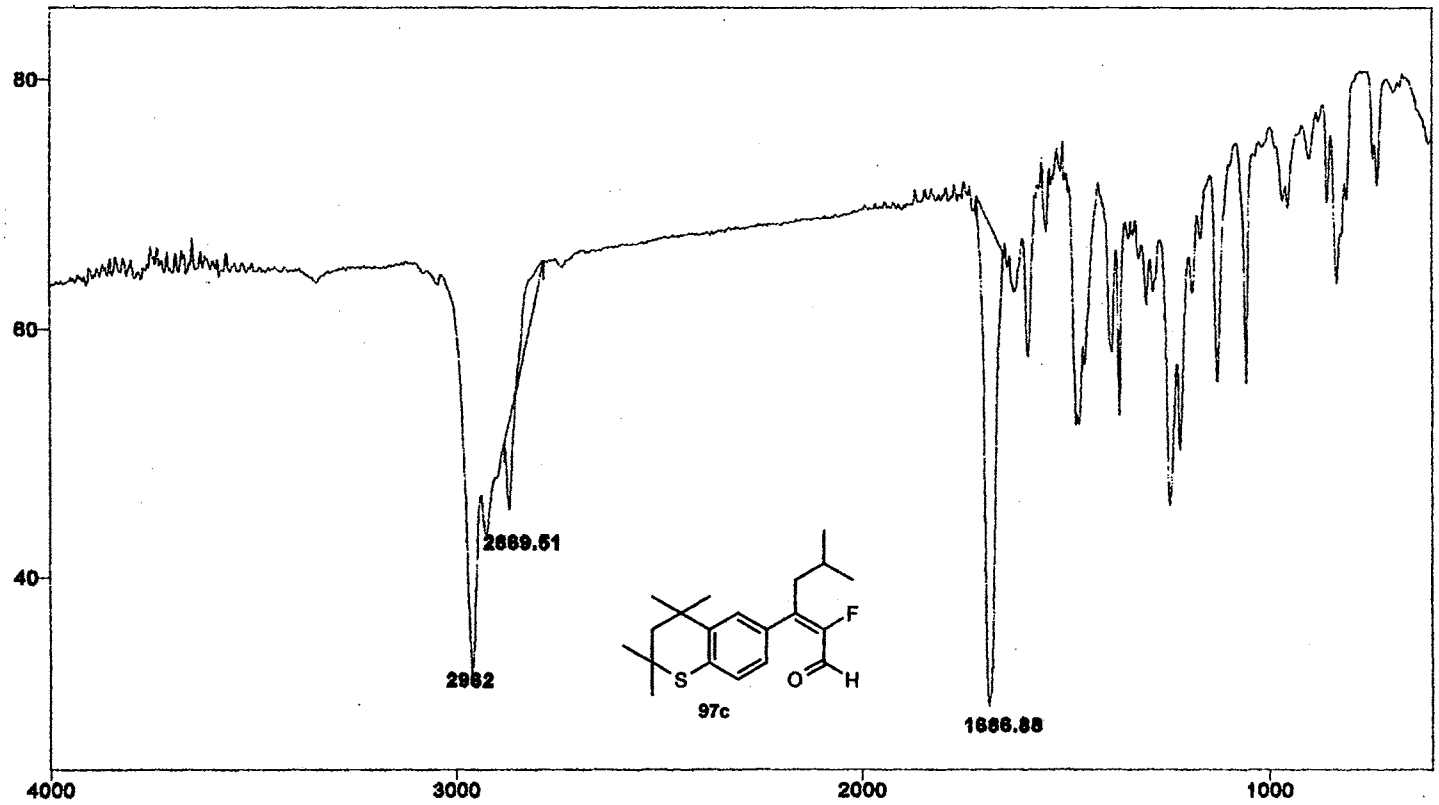


97b



^{19}F NMR Spectrum of **97b**

Plate CLXVIII



IR Spectrum of **97c**

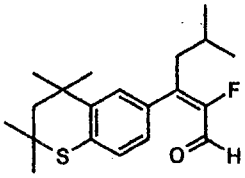
Plate CLXIX

```
STANDARD 1H OBSERVE

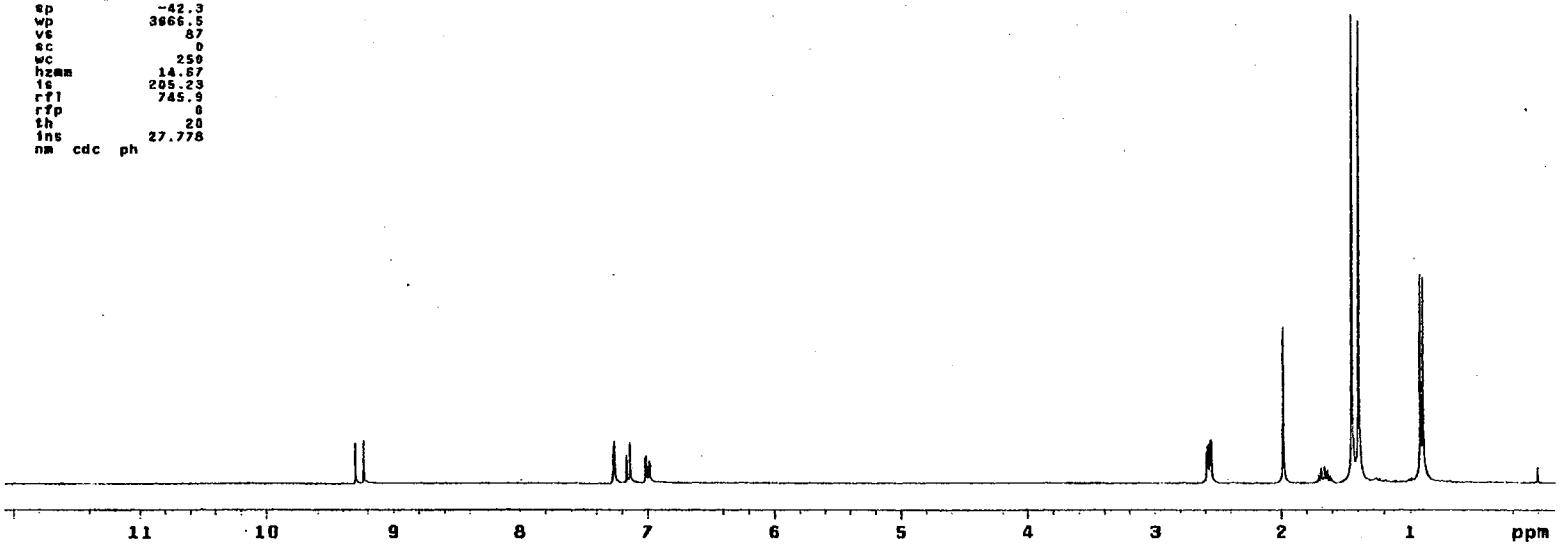
expl  std1h

      SAMPLE
date   Jan 24 2000
solvent       CDCl3
file             exp
   ACQUISITION
sfrq        300.087
tn               H1
at             3.747
np             33728
sw            4500.5
fb             2600
bs               16
tpwr             48
pw              6.9
d1                0
tof               0
nt               16
ct               16
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp            -42.3
wp           3666.5
vs               87
sc                0
wc              250
hzcm          14.67
is           205.23
rfl           745.9
rfp               0
th               20
ins           27.778
nm  cdc  ph

      DEC. & VT
dfrq        300.087
dn               H1
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
      PROCESSING
wtfile
proc             ft
fn         not used
werr
wexp
wbs
wnt
```



97c



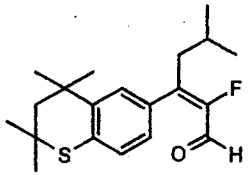
^{1}H NMR Spectrum of **97c**

Plate CLXX

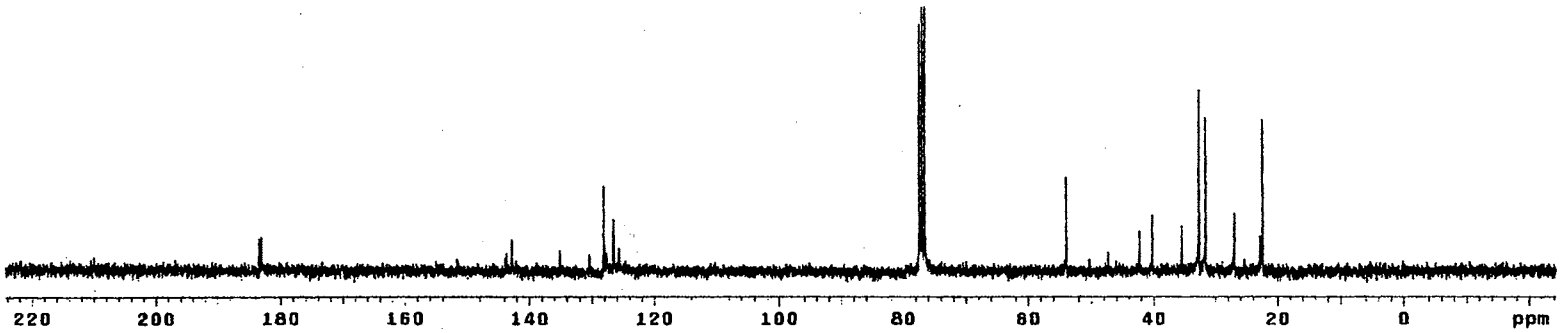
```
13C OBSERVE

expl  std13c

      SAMPLE                 DEC. & VT
date   Dec 20 1999   dfrq          300.087
solvent       CDCl3  dn               H1
file            exp  dpwr             34
    ACQUISITION      dof              0
sfrq         75.464  dm             yyy
tn              C13  dmm              w
at            0.800  dmf          11764
np            30016      PROCESSING
sw          18761.7  lb            1.00
fb            10400  wtfile
bs               16  proc             ft
tpwr             52  fn         not used
pw              3.8
d1            1.000  werr
tof               0  wexp            wft
nt             2048  wbs             wft
ct             1744  wnt
alock             s
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp          -1835.9
wp          18761.7
vs               49
sc                0
wc              250
hzcm          75.05
is           500.00
rfl          7646.5
rfp          5810.6
th                4
ins         100.000
nm  no  ph
```



97c



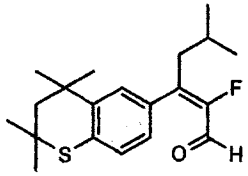
^{13}C NMR Spectrum of **97c**

Plate CLXXI

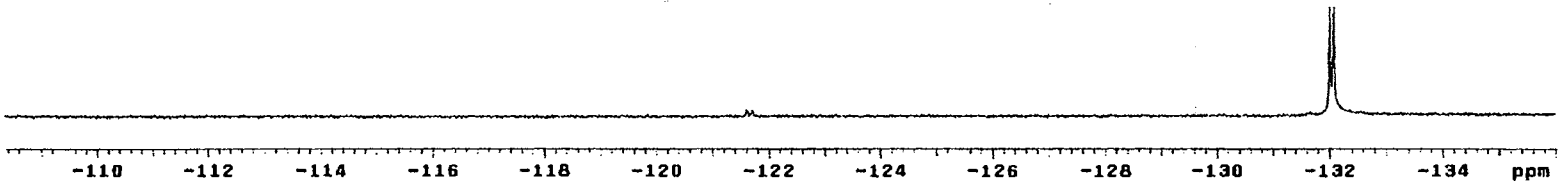
```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date   Dec 20 1999   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof               0
sfrq        282.333  dm              nnn
tn              F19  dmm               w
at            0.800  dmf           11764
np            30016      PROCESSING
sw          18761.7  lb             1.00
fb            19400  wtfile
bs               16  proc              ft
tpwr             52  fn         not used
pw              3.8
d1            1.000  werr
tof               0  wexp            wft
nt             1024  wbs             wft
ct               48  wnt
alock             n
gain       not used
      FLAGS
ii                n
in                y
dp                y
     DISPLAY
sp          -38493.5
wp           7814.8
vs               29
sc                0
wc              250
hzcm          31.26
is            500.00
rfl         38748.2
rfp               0
th                8
ins         100.000
nm  no  ph
```

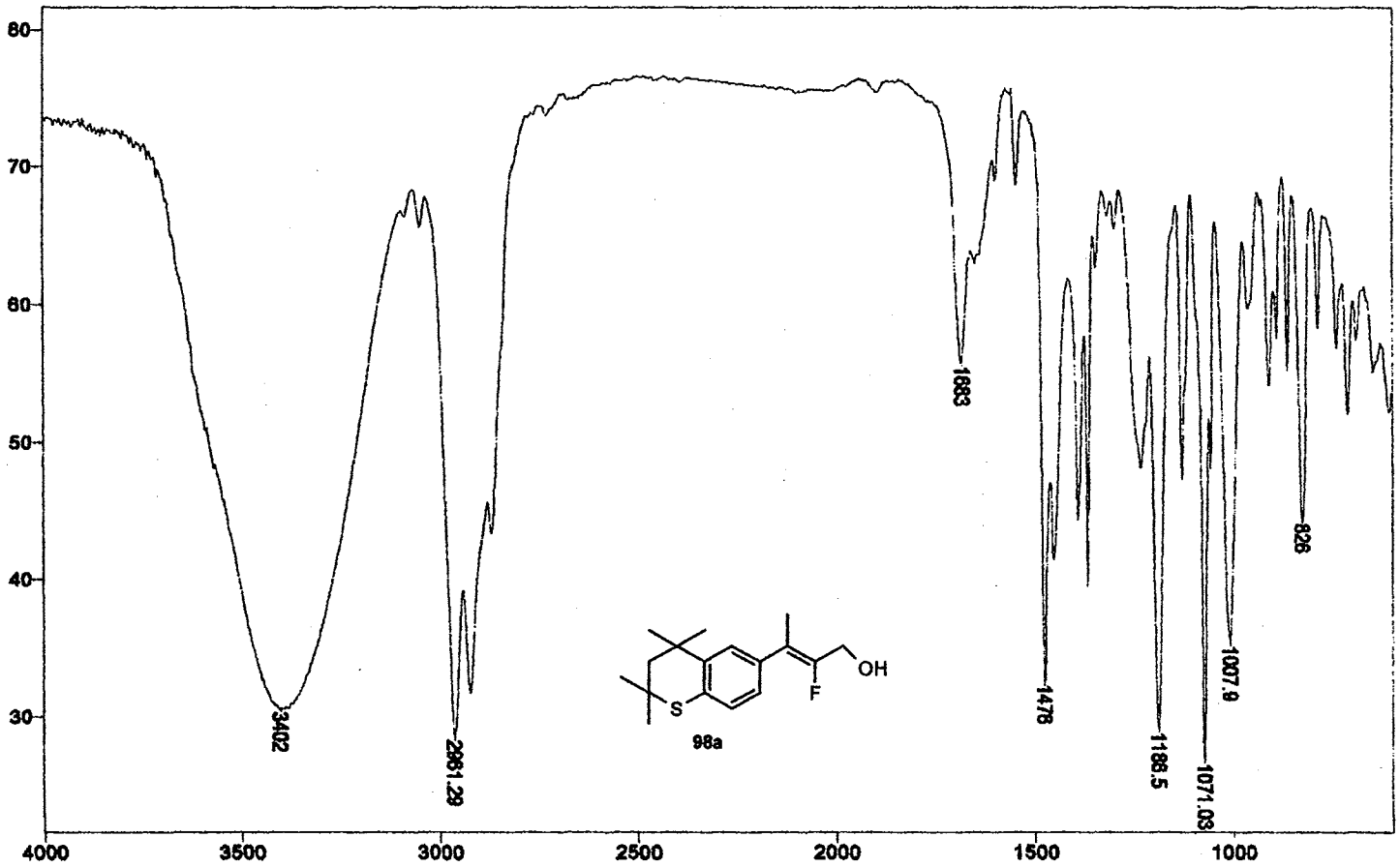


97c



^{19}F NMR Spectrum of **97c**

Plate CLXXII



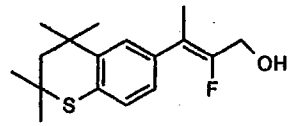
IR Spectrum of **98a**

Plate CLXXIII

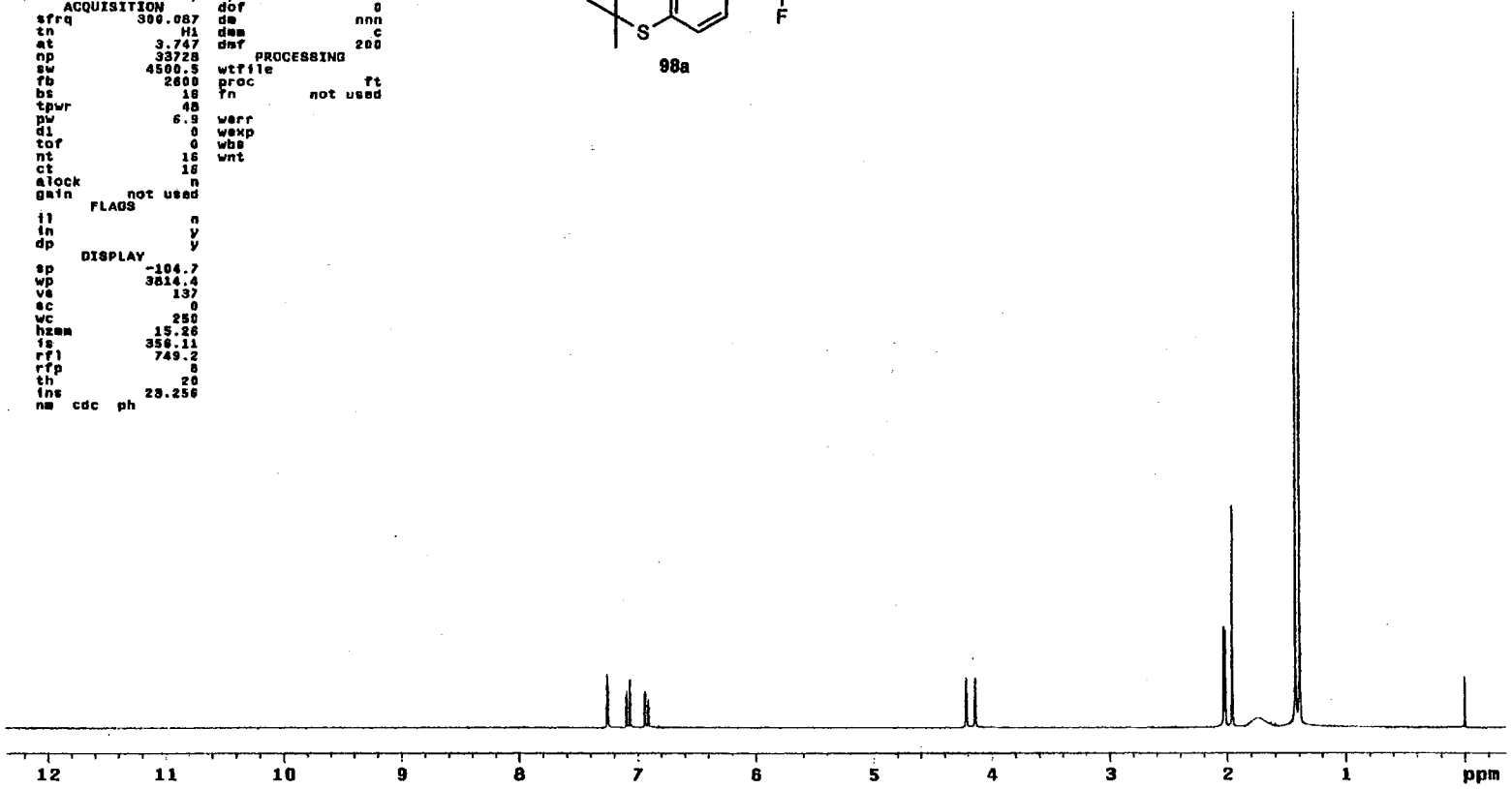
```
STANDARD 1H OBSERVE

expl  std1h

      SAMPLE                DEC. & VT
date   Oct  8 1999   dfrq        300.087
solvent      CDCl3   dn              H1
file           exp   dpwr            30
   ACQUISITION       dof              0
sfrq        300.087  dm             nnn
tn               H1  dmm              c
at            3.747  dmf            200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2600  proc            ft
bs               16  fn        not used
tpwr             48
pw              6.9  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp           -104.7
wp           3814.4
vs              137
sc                0
wc              250
hzcm          15.26
is           356.11
rfl           749.2
rfp               8
th               20
ins          23.256
nm  cdc  ph
```



98a



^{1}H NMR Spectrum of **98a**

Plate CLXXIV

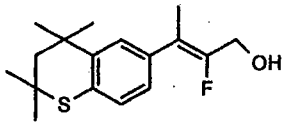
```
13C OBSERVE

expl  std13c

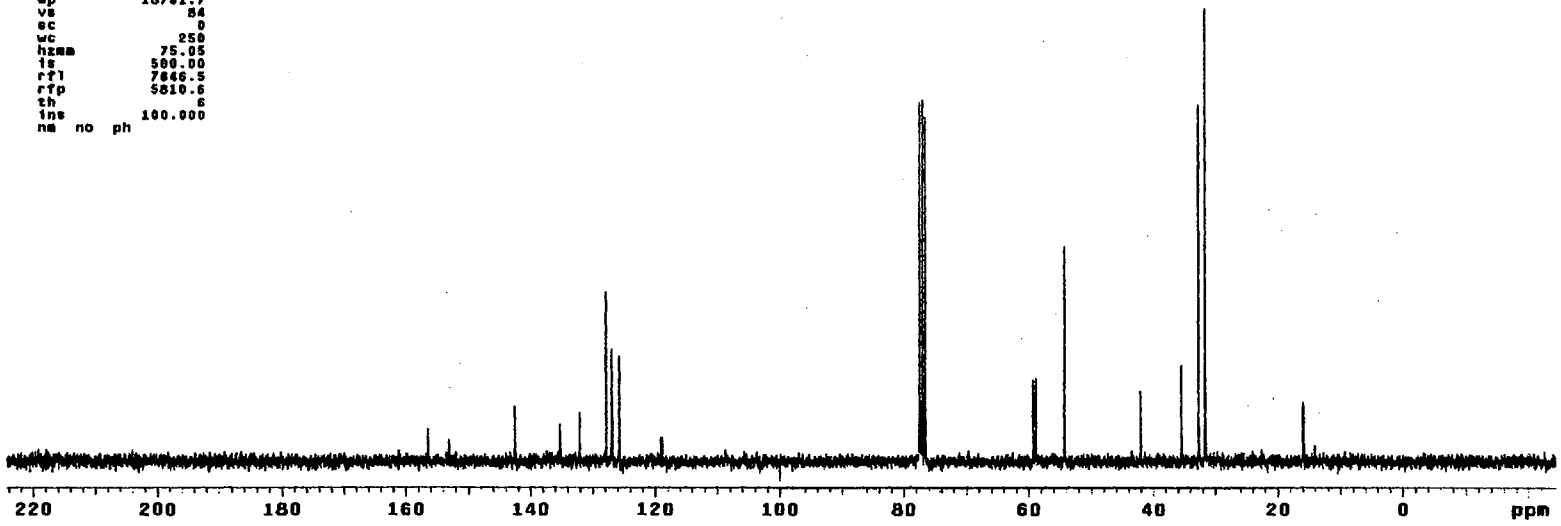
      SAMPLE
date   Oct  6 1999
solvent       CDCl3
file            exp
   ACQUISITION
sfrq         75.464
tn              C13
at              0.800
np              30016
sw           18761.7
fb             10400
bs                16
tpwr              52
pw               3.8
d1             1.000
tof                0
nt              2048
ct              1248
alock              s
gain       not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1835.9
wp           18761.7
vs                84
sc                 0
wc               250
hzmm           75.05
is             500.00
rfl            7846.5
rfp            5810.6
th                 6
ins            100.000
nm  no  ph

      DEC. & VT
dfrq         300.087
dn                H1
dpwr              34
dof                0
dm               yyy
dmm                w
dmf            11764
     PROCESSING
lb               1.00
wtfile
proc               ft
fn          not used

warr
wexp             wft
wbs              wft
wnt
```



98a



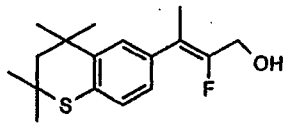
^{13}C NMR Spectrum of **98a**

Plate CLXXV

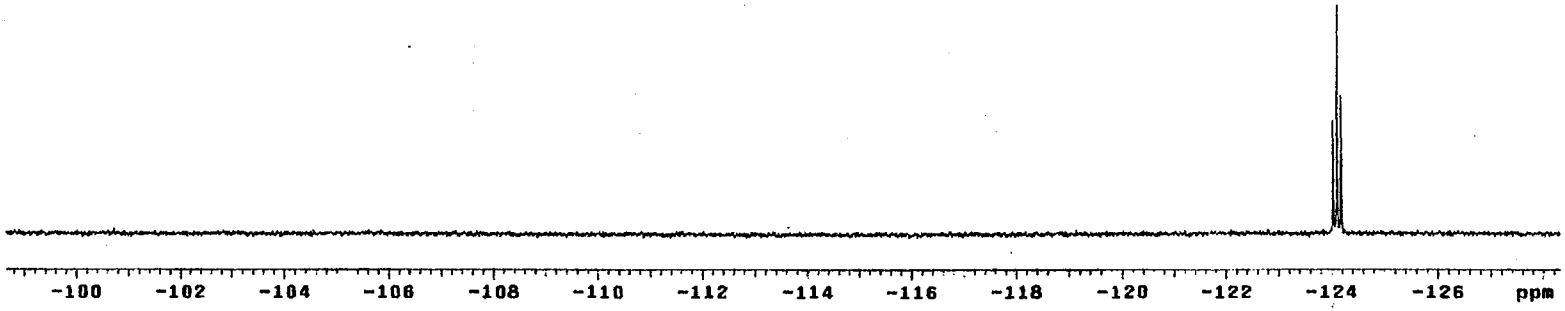
```
13C OBSERVE

expl  std13c

      SAMPLE                DEC. & VT
date   Nov  3 1999   dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr            34
   ACQUISITION       dof             0
sfrq          282.333 dm            nnn
tn              F19  dmm             w
at            0.800  dmf         11764
np            30016      PROCESSING
sw          18761.7  lb           1.00
fb            10400  wtfile
bs               16  proc          ft
tpwr             52  fn      not used
pw              3.8
d1            1.000  werr
tof               0  wexp         wft
nt             1024  wbs          wft
ct               48  wnt
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp          -38234.5
wp           8381.7
vs               32
sc                0
wc              250
hzmm          33.53
is           500.00
rfl         38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```

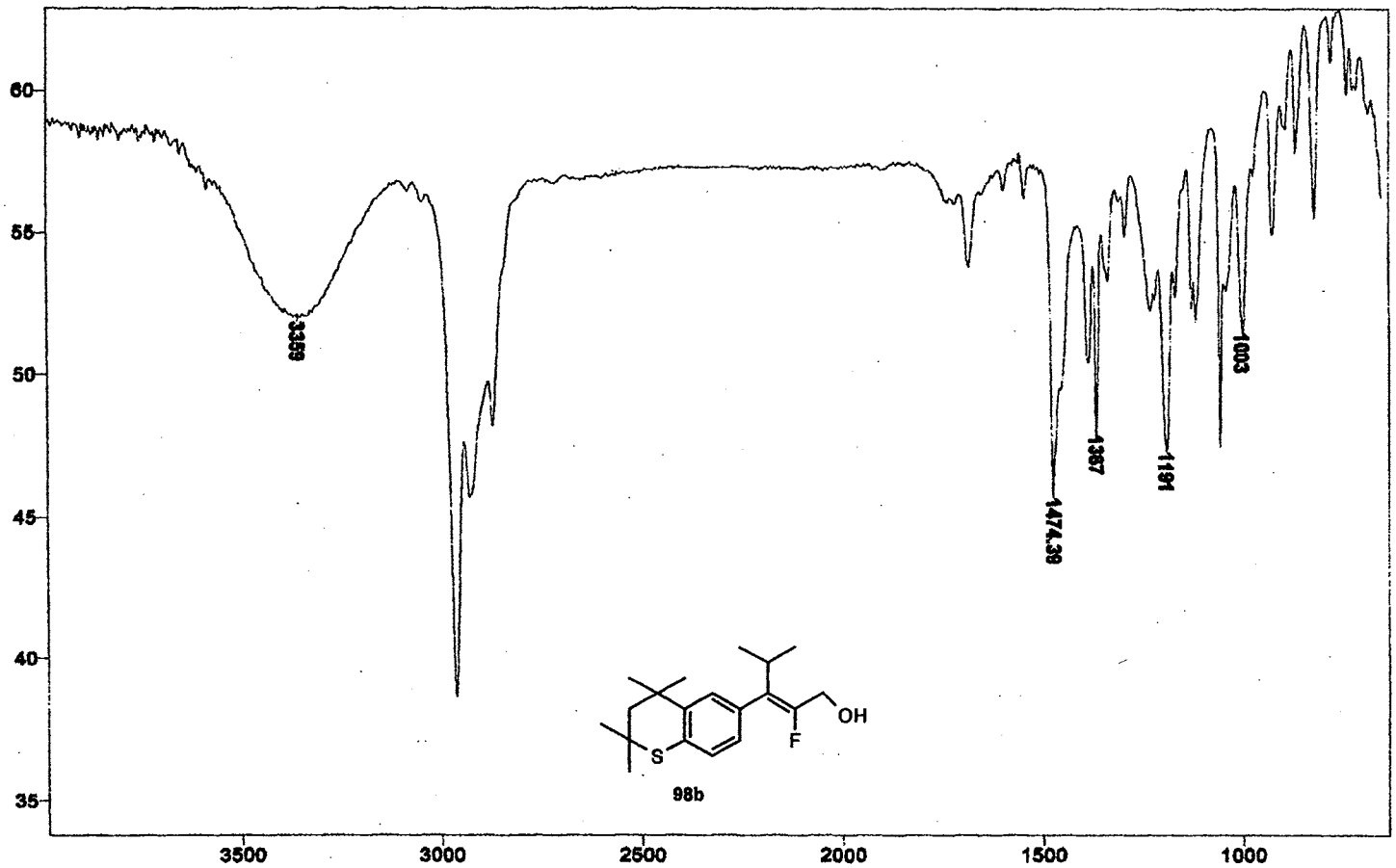


98a



^{19}F NMR Spectrum of **98a**

Plate CLXXVI



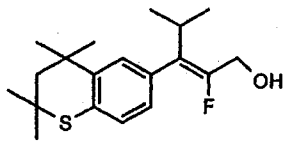
IR Spectrum of **98b**

Plate CLXXVII

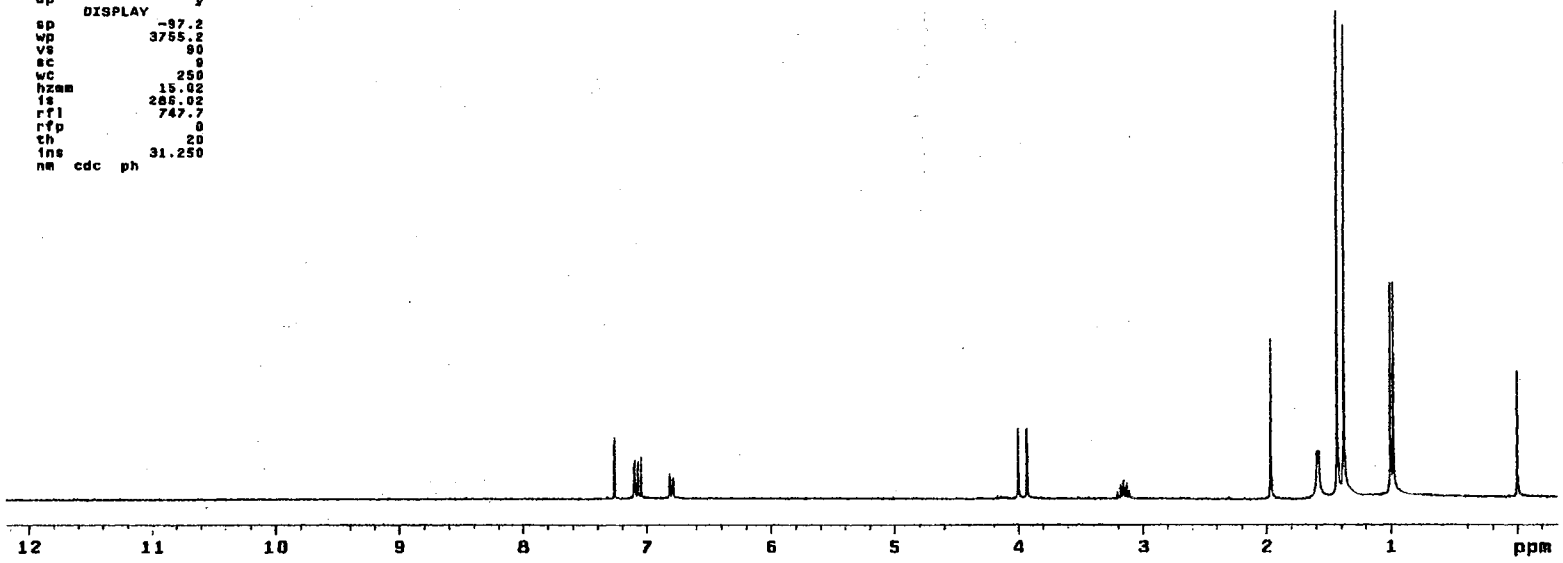
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                DEC. & VT
date   Nov  3 1998   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              30
   ACQUISITION       dof                 0
sfrq          300.087 dm               nnn
tn                H1  dmm                c
at            3.747   dmf              200
np            33728      PROCESSING
sw           4500.5   wtfile
fb            2600   proc               ft
ds              16   fn          not used
tpwr            48
gw             6.9   werr
d1              0    wexp
tof             0    wbs
nt             16    wnt
ct             16
alock           n
gain       not used
      FLAGS
il              n
in              y
dp              y
     DISPLAY
sp           -97.2
wp          3755.2
vs             90
sc              9
wc            250
hzcm        15.02
is          286.02
rfl         747.7
rfp             0
th             20
ins         31.250
nm  cdc  ph
```

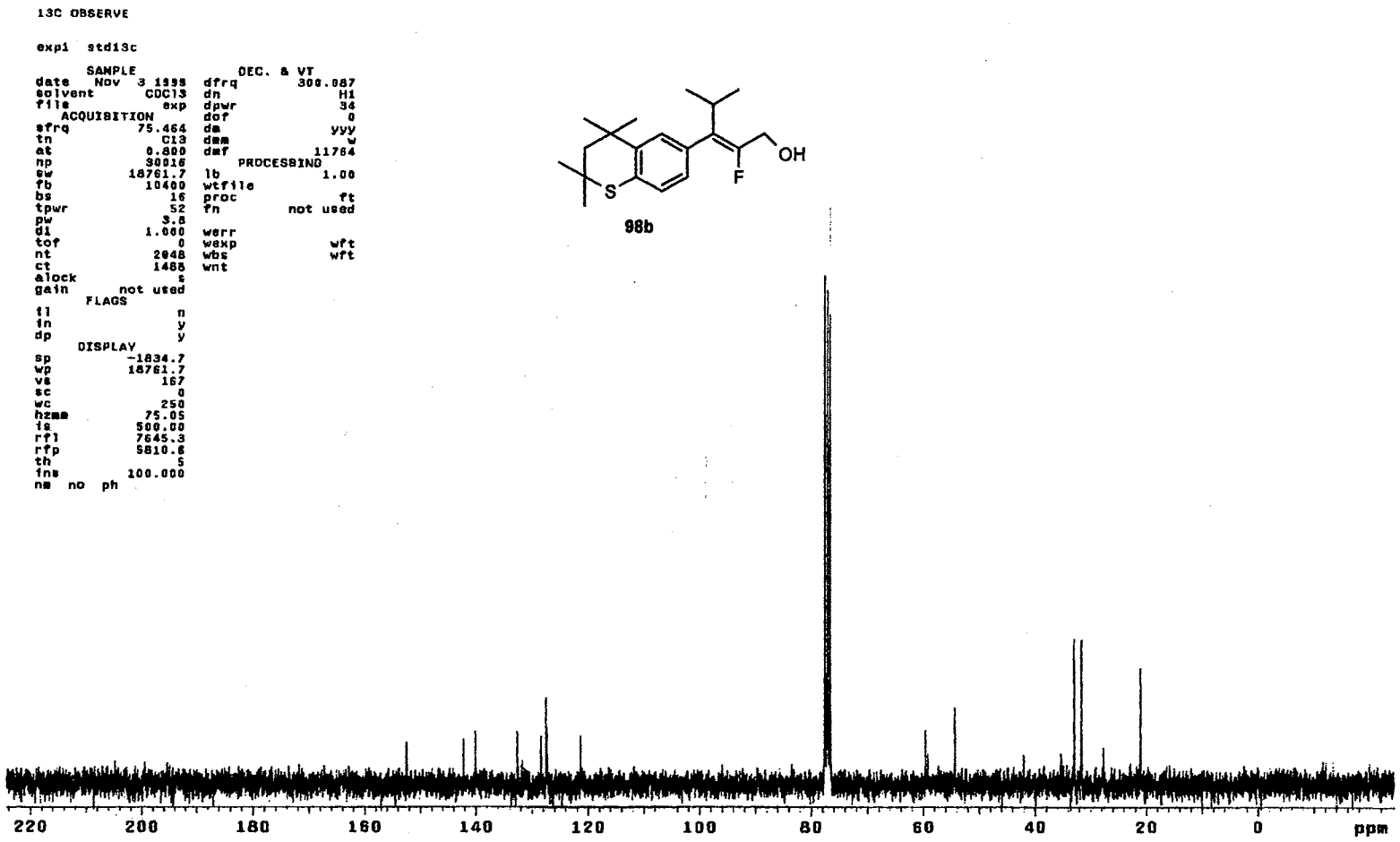


98b



^{1}H NMR Spectrum of **98b**

Plate CLXXVIII



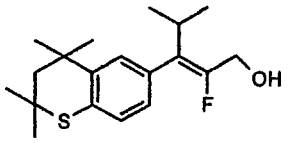
^{13}C NMR Spectrum of **98b**

Plate CLXXIX

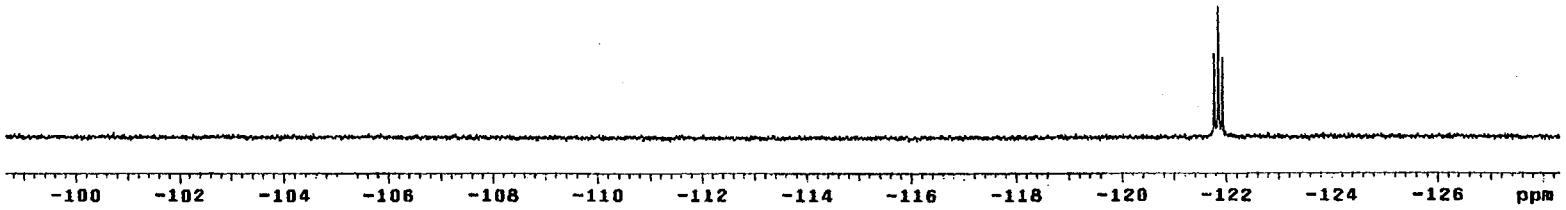
```
13C OBSERVE

expl  std13c

      SAMPLE                DEC. & VT
date   Nov  3 1999   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                 0
sfrq        282.333  dm                nnn
tn              F19  dmm                 w
at            0.800  dmf             11764
np            30016      PROCESSING
sw          18761.7  lb               1.00
fb            10400  wtfile
bs               16  proc               ft
tpwr             52  fn          not used
pw              3.6
d1            1.000  werr
tof               0  wexp              wft
nt             1024  wbs              wft
ct               48  wnt
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp         -38234.5
wp          8381.7
vs               32
sc                0
wc              250
hzmm          33.53
is           500.00
rfl         38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```



98b



^{19}F NMR Spectrum of **98b**

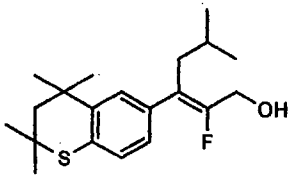
Plate CLXXX

STANDARD 1H OBSERVE

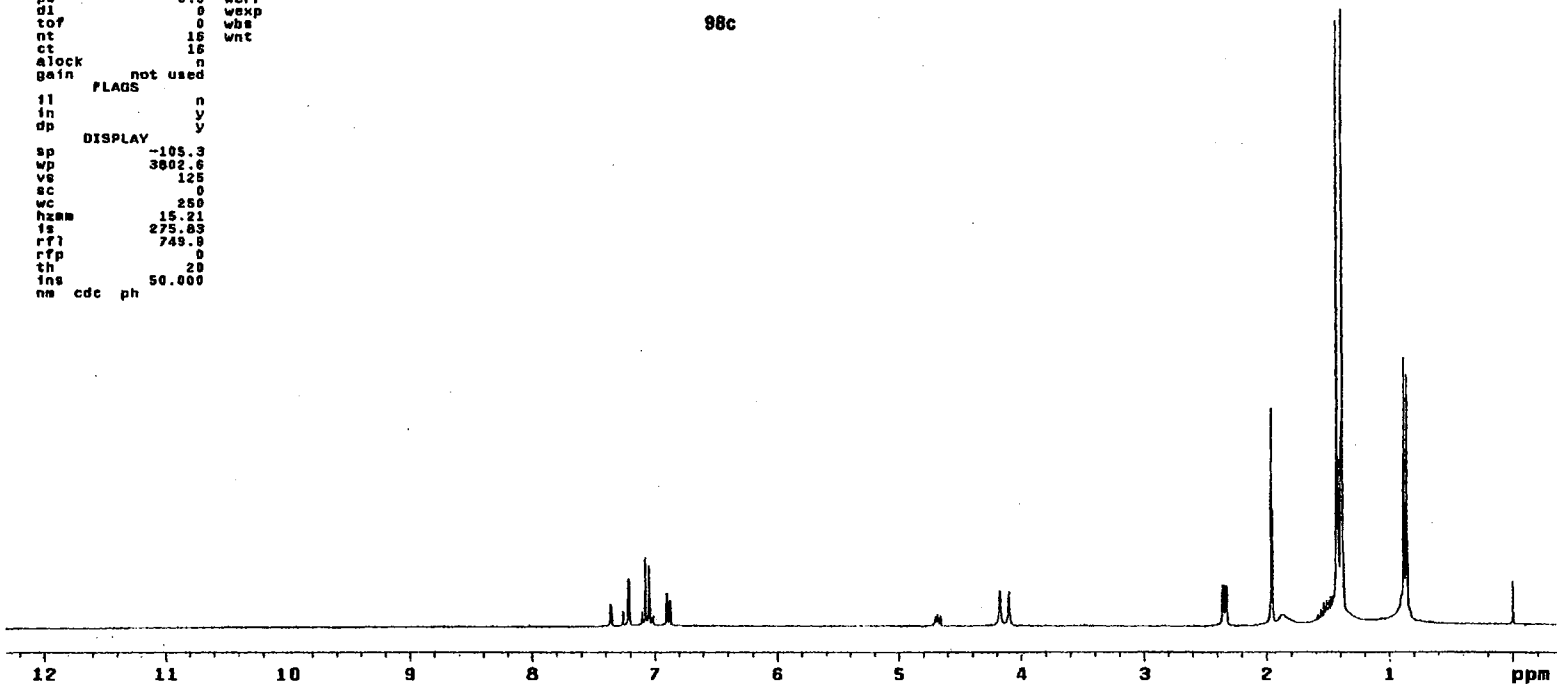
expl stdlh

SAMPLE		DEC. & VT	
date	Nov 17 1989	dfrq	300.087
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.087	dm	nnn
tn	H1	dmm	c
at	3.747	dmf	200
np	33728	PROCESSING	
sw	4500.5	wtfile	
fb	2800	proc	ft
bs	16	fn	not used
tpwr	48		
pw	6.9	werr	
d1	0	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
fl	n		
in	y		
dp	y		
DISPLAY			
sp	-105.3		
wp	3602.6		
vs	125		
sc	0		
wc	250		
hzcm	15.21		
is	275.83		
rfl	749.8		
rfp	0		
th	20		
ins	50.000		

nm cdc ph



98c



^{1}H NMR Spectrum of **98c**

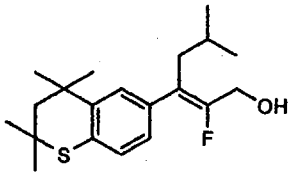
Plate CLXXXI

```
13C OBSERVE

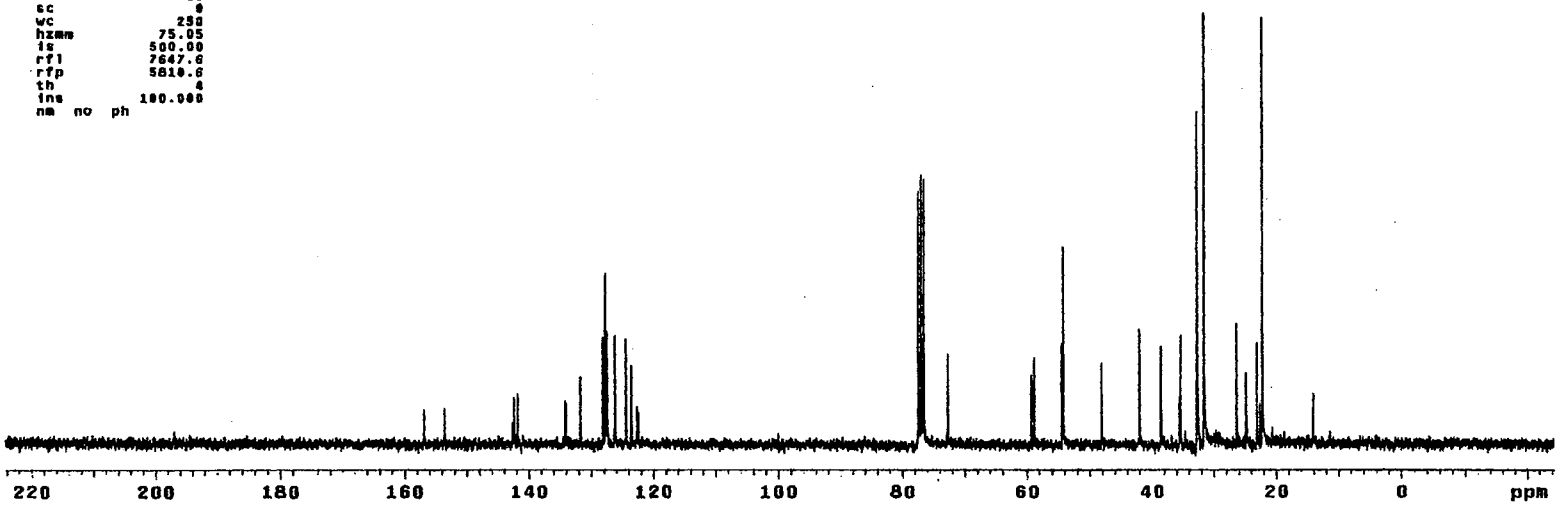
expl  std13c

      SAMPLE
date   Nov 17 1999
solvent       CDCl3
file            exp
    ACQUISITION
sfrq         75.464
tn            C13
at            0.800
np            30016
sw          18761.7
fb            10409
bs                16
tpwr              52
pw               3.8
d1             1.000
tof                0
nt              2096
ct              1120
alock              y
gain       not used
     FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1837.0
wp           18761.7
vs                89
sc                 0
wc               250
hzmm           75.05
is            500.00
rf1           7647.6
rfp           5810.6
th                 4
ins           100.000
nm  no  ph

      DEC. & VT
dfrq         300.067
dn              H1
dpwr            34
dof              0
dm             yyy
dmm              w
dmf          11764
    PROCESSING
lb             1.00
wtfile
proc             ft
fn         not used
werr
wexp           wft
wbs            wft
wnt
```



98c



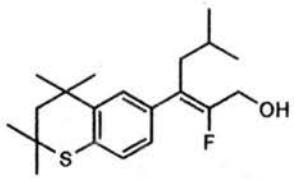
^{13}C NMR Spectrum of **98c**

Plate CLXXXII

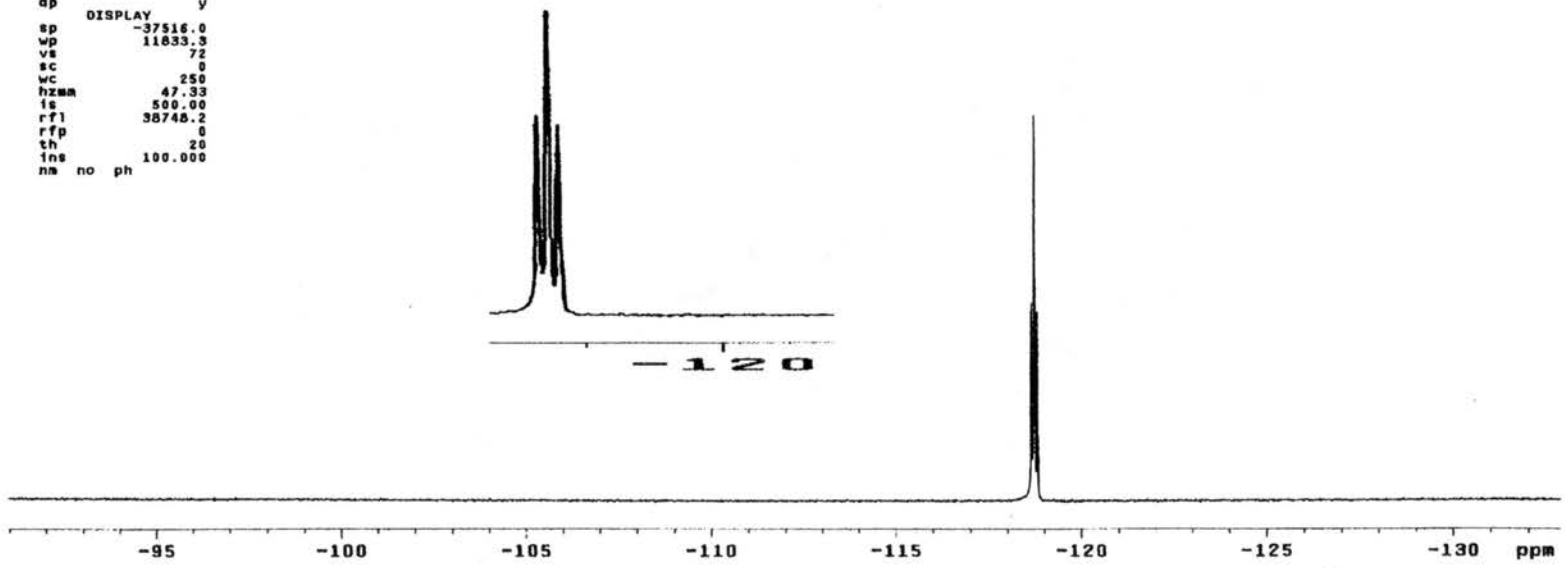
```
13C OBSERVE

expl  std13c

      SAMPLE                DEC. & VT
date   Nov 17 1999   dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr            34
   ACQUISITION       dof               0
sfrq        282.333  dm              nnn
tn              F19  dmm               w
at            0.880  dmf           11764
np            30016      PROCESSING
sw         18761.7   lb             1.00
fb            10400  wtfile
bs               16  proc             ft
tpwr             52  fn         not used
pw              3.8
d1            1.000  werr
tof               0  wexp            wft
nt             1024  wbs            wft
ct               64  wnt
alock             n
gain        not used
      FLAGS
i1                n
in                y
dp                y
      DISPLAY
sp         -37516.0
wp         11833.3
vs               72
sc                0
wc              250
hzmm          47.33
is           500.00
rf1        38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```



98c



^{19}F NMR Spectrum of **98c**

Plate CLXXXIII

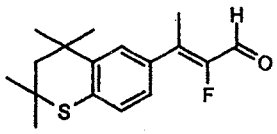
```
STANDARD 1H OBSERVE

expl  std1h

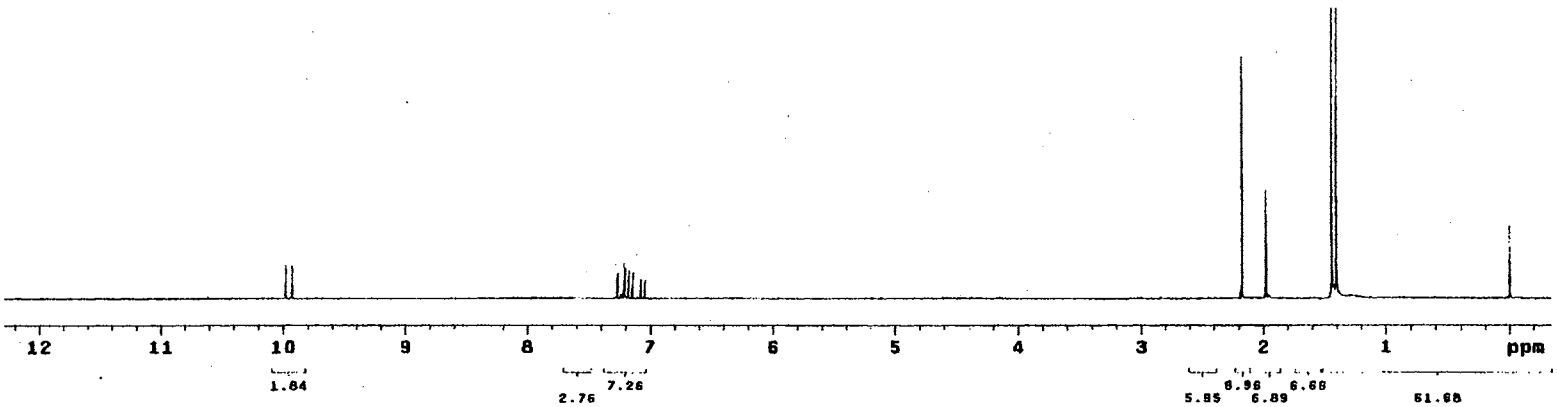
      SAMPLE
date   Oct 28 1999
solvent       CDCl3
file            exp
   ACQUISITION
sfrq        300.087
tn               H1
at             3.747
np             33728
sw            4500.5
fb              2600
bs                16
tpwr              48
pw               6.9
d1                 0
tof                0
nt                16
ct                16
alock              n
gain       not used
     FLAGS
il                 n
in                 y
dp                 y
    DISPLAY
sp            -103.1
wp            3790.6
vs                38
sc                 0
wc               250
hzcm           15.18
is            475.82
rfl            747.7
rfp                0
th                20
ins           100.000
nm  cdc  ph

      DEC. & VT
dfrq        300.087
dn               H1
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
     PROCESSING
wtfile
proc              ft
fn        not used

werr
wexp
wbs
wnt
```

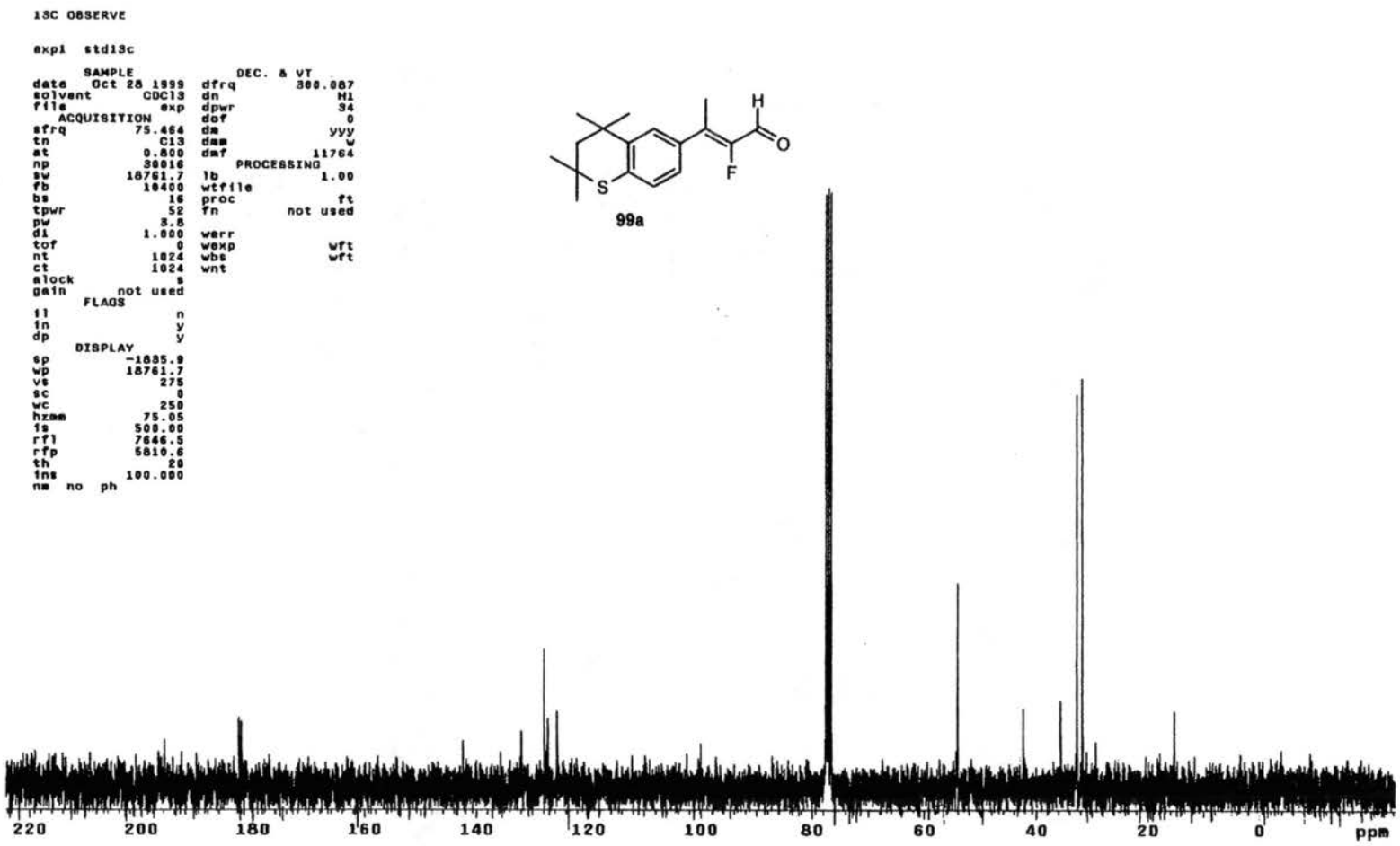


99a



^{1}H NMR Spectrum of **99a**

Plate CLXXXIV



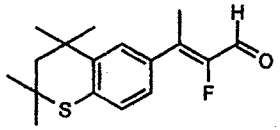
^{13}C NMR Spectrum of **99a**

Plate CLXXXV

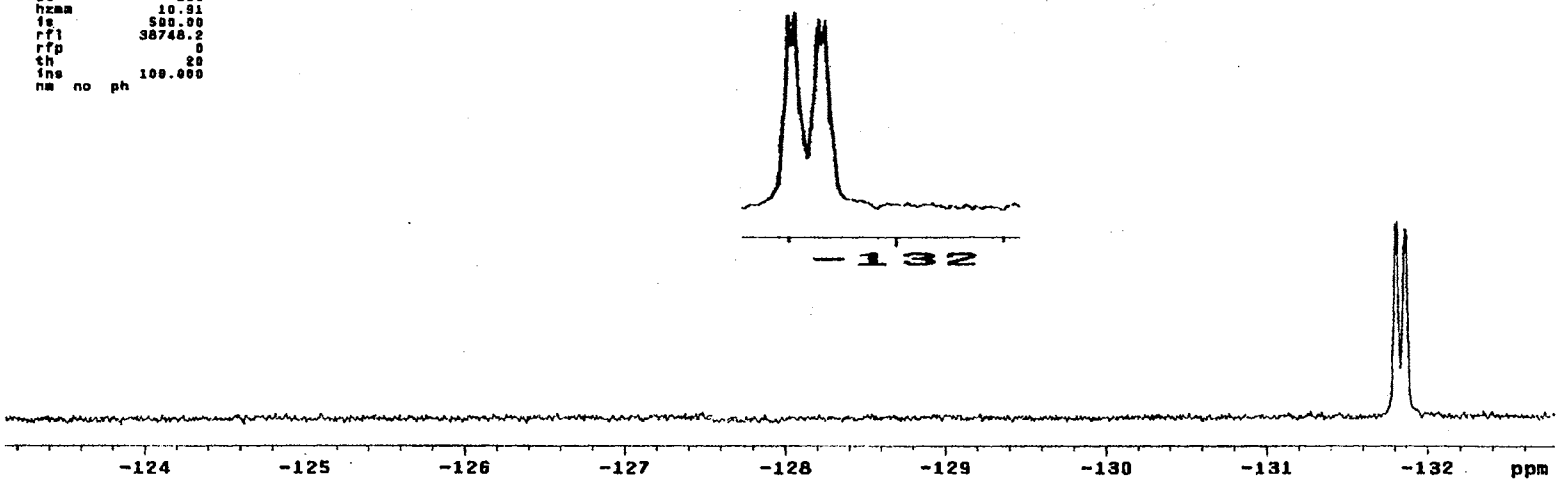
```
13C OBSERVE

exp1  std13c

      SAMPLE                DEC. & VT
date   Oct 26 1999  dfrq        300.087
solvent       CDCl3  dn              H1
file            exp  dpwr            34
   ACQUISITION       dof              0
sfrq        282.333  dm             nnn
tn              F19  dmm              w
at            0.500  dmf          11764
np            30016     PROCESSING
sw          18761.7  lb            1.00
fb            10400  wtfile
bs               16  proc            ft
tpwr             52  fn        not used
pw              3.8
d1            1.000  werr
tof               0  wexp          wft
nt             1024  wbs           wft
ct               80  wnt
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp         -37494.2
wp           2727.9
vs                36
sc                 0
wc               250
hzcm           10.91
is            500.00
rf1         38748.2
rfp                0
th                20
ins          100.000
nm  no  ph
```

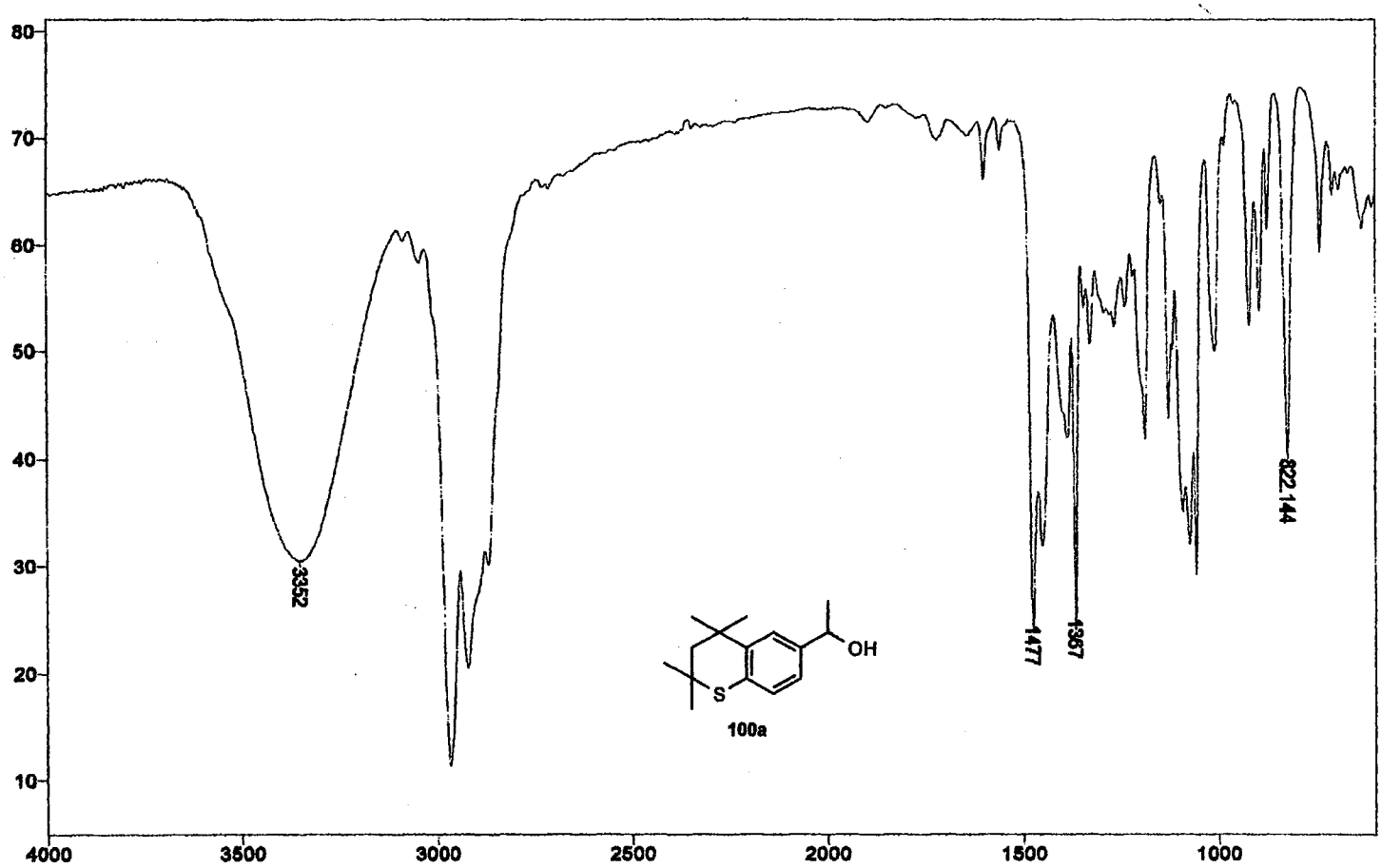


99a



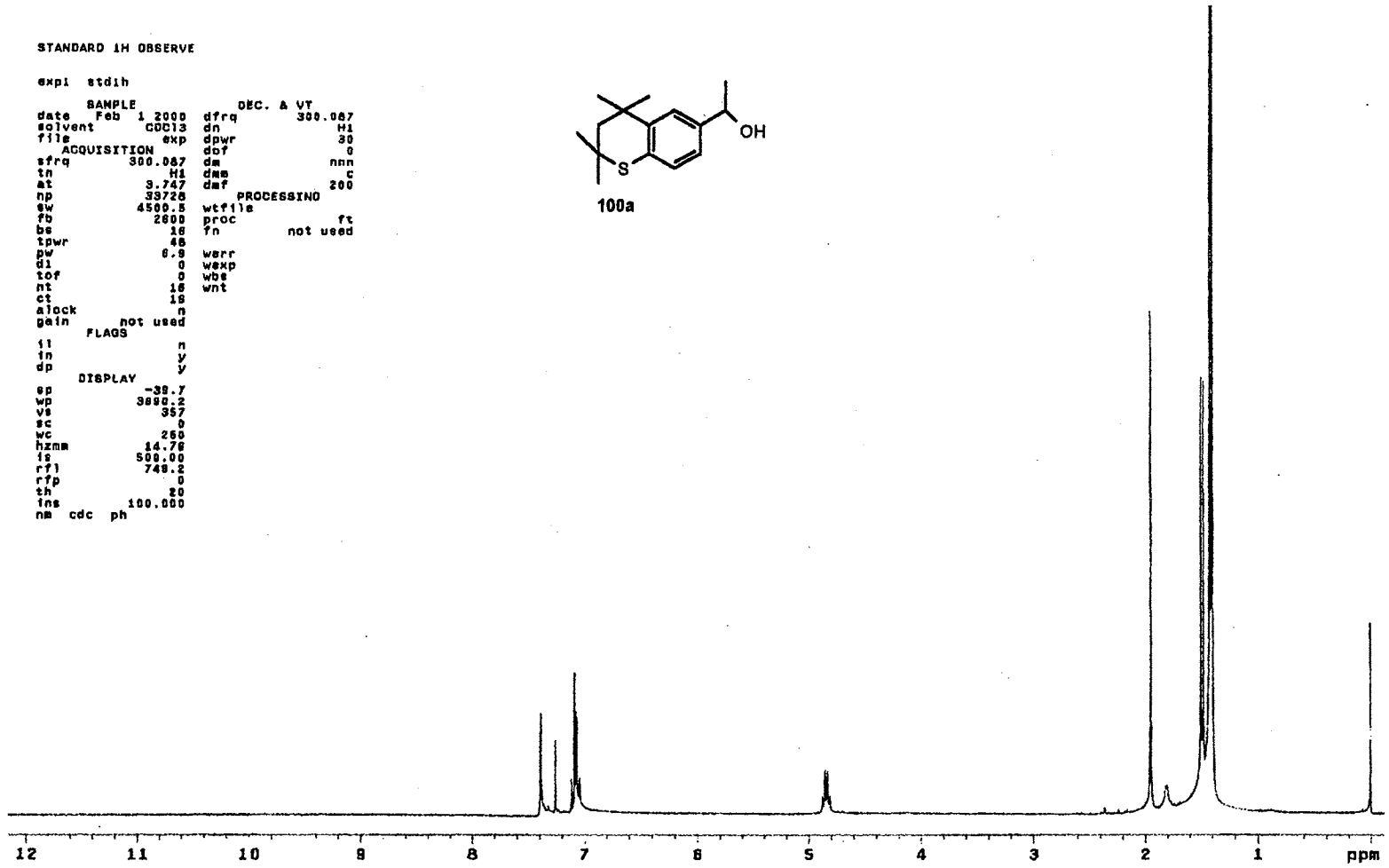
^{19}F NMR Spectrum of **99a**

Plate CLXXXVI



IR Spectrum of **100a**

Plate CLXXXVII



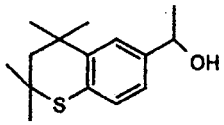
^{1}H NMR Spectrum of **100a**

Plate CLXXXVIII

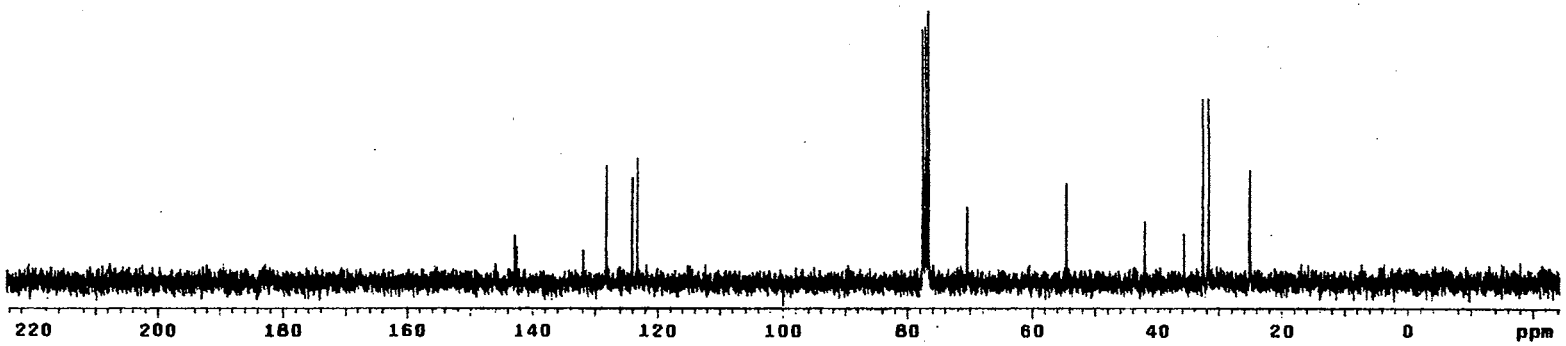
```
13C OBSERVE

exp1  std13c

        SAMPLE                  DEC. & VT
date   Feb  1 2000   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
    ACQUISITION      dof                 0
sfrq          75.464 dm                yyy
tn               C13 dmm                 w
at             0.800 dmf             11764
np             30016     PROCESSING
sw           18761.7 lb               1.00
fb             10400 wtfile
bs                16 proc               ft
tpwr              52 fn          not used
pw              3.8
d1            1.000  werr
tof               0  wexp              wft
nt             1024  wbs              wft
ct              256  wnt
alock             6
gain        not used
       FLAGS
ii                n
in                y
dp                y
      DISPLAY
sp          -1837.0
wp          18761.7
vs               50
sc                0
wc              250
hzcm          75.05
is            500.00
rfl           7647.6
rfp           5810.6
th                5
ins          100.000
nm  no  ph
```

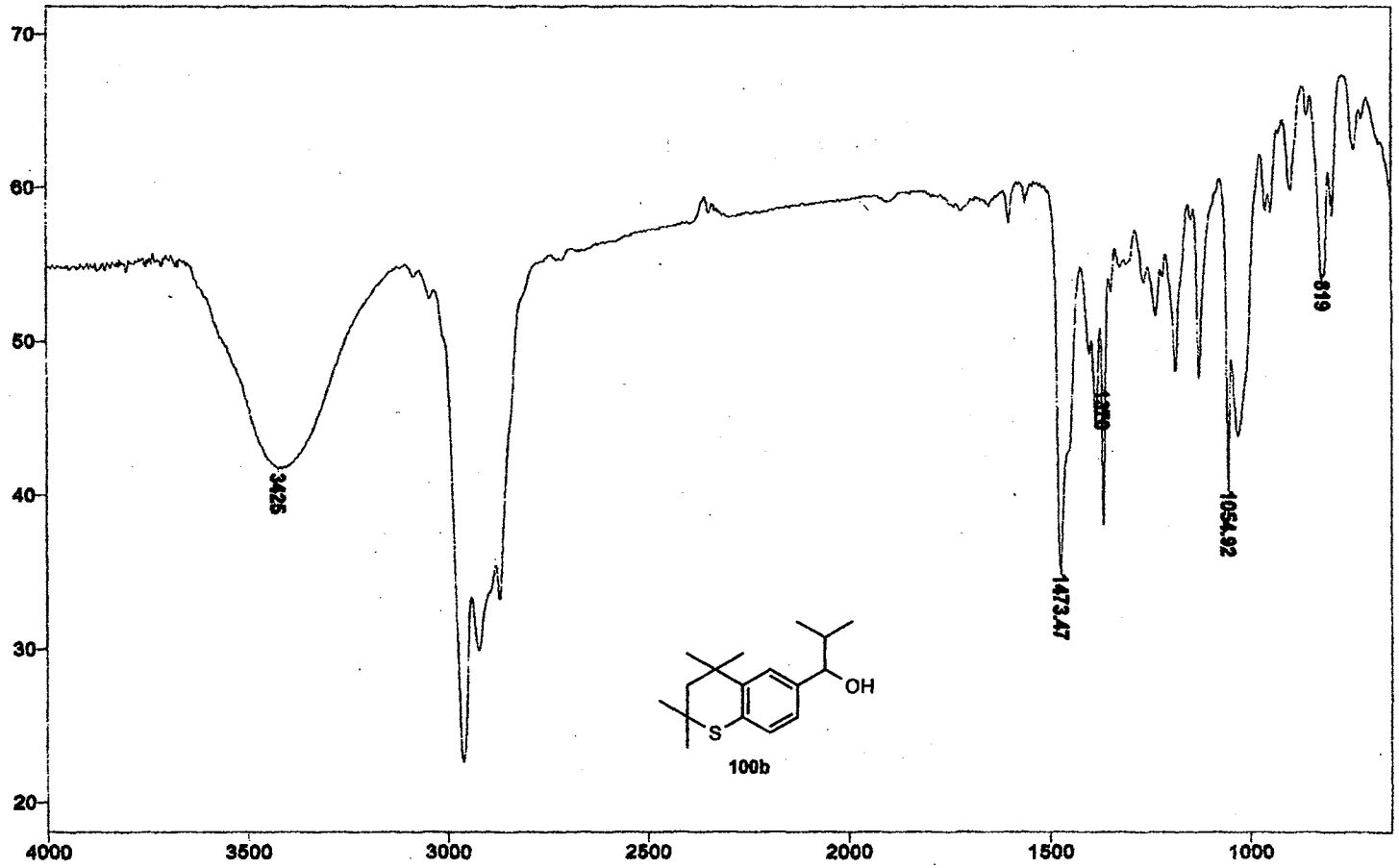


100a



^{13}C NMR Spectrum of **100a**

Plate CLXXXIX



IR Spectrum of **100b**

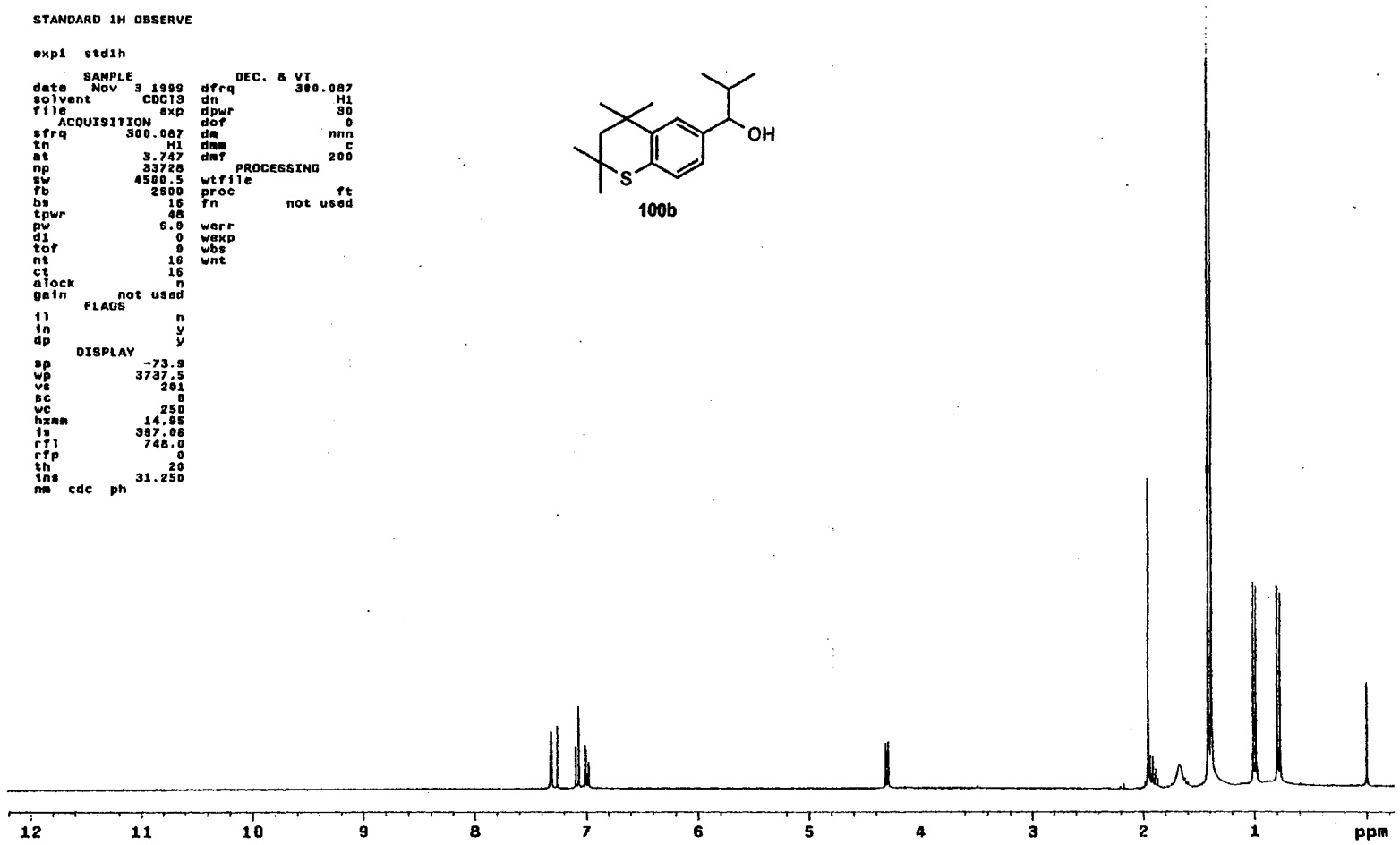
Plate CXC

```
STANDARD 1H OBSERVE

expl  stdih

      SAMPLE                DEC. & VT
date   Nov  3 1999   dfrq          300.087
solvent       CDCl3  dn                Hl
file            exp  dpwr              30
    ACQUISITION      dof               0
sfrq        300.087  dm               nnn
tn               Hl  dmm               c
at            3.747  dmf             200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2500  proc             ft
hs               16  fn          not used
tpwr             48
pw              6.0  werr
d1                0  wexp
tof               0  wbs
nt               10  wnt
ct               16
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp            -73.9
wp           3737.5
vs              201
sc                0
wc              250
hzmm          14.95
is           387.06
rfl           748.0
rfp               0
th               20
ins           31.250
nm  cdc  ph
```


100b



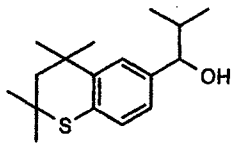
^{1}H NMR Spectrum of **100b**

Plate CXCI

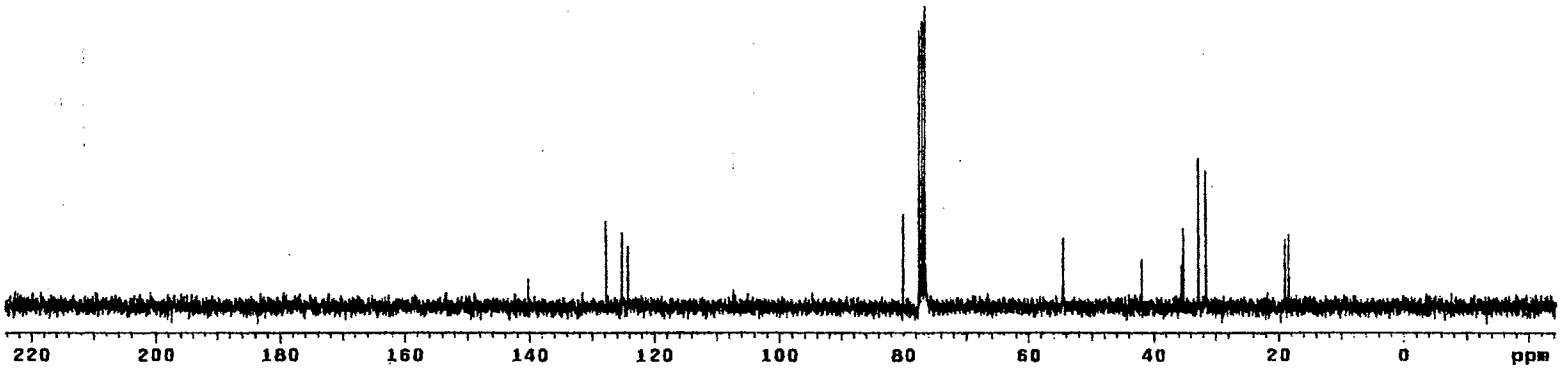
```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date   Nov  3 1999   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              34
   ACQUISITION       dof                 0
sfrq          75.484 dm               yyy
tn               C13 dmm                 w
at             0.808 dmf            11764
np             30916    PROCESSING
sw           18761.7  lb             1.00
fb             18400  wtfile
bs                16  proc              ft
tpwr              52  fn         not used
pw               3.8
d1             1.000  werr
tof                0  wexp            wft
nt              2048  wbs             wft
ct               512  wnt
alock              s
gain         not used
      FLAGS
il                 n
in                 y
dp                 y
     DISPLAY
sp           -1835.9
wp           18761.7
vs                56
sc                 0
wc               250
hzcm           75.05
is             500.00
rfl            7848.5
rfp            5810.6
th                 8
ins          100.000
nm  no  ph
```

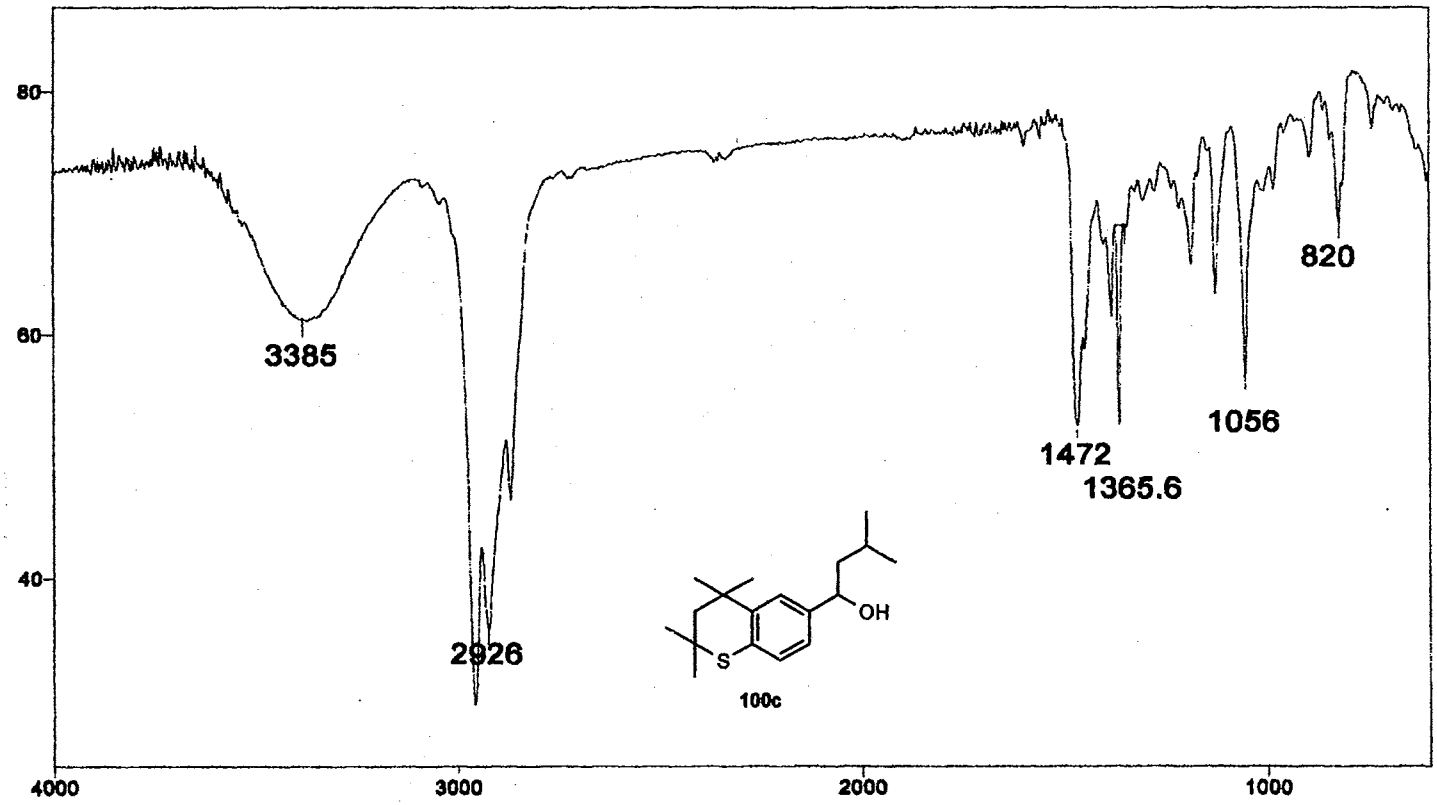


100b



^{13}C NMR Spectrum of **100b**

Plate CXCII



IR Spectrum of **100c**

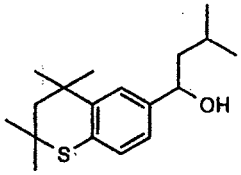
Plate CXCIII

STANDARD 1H OBSERVE

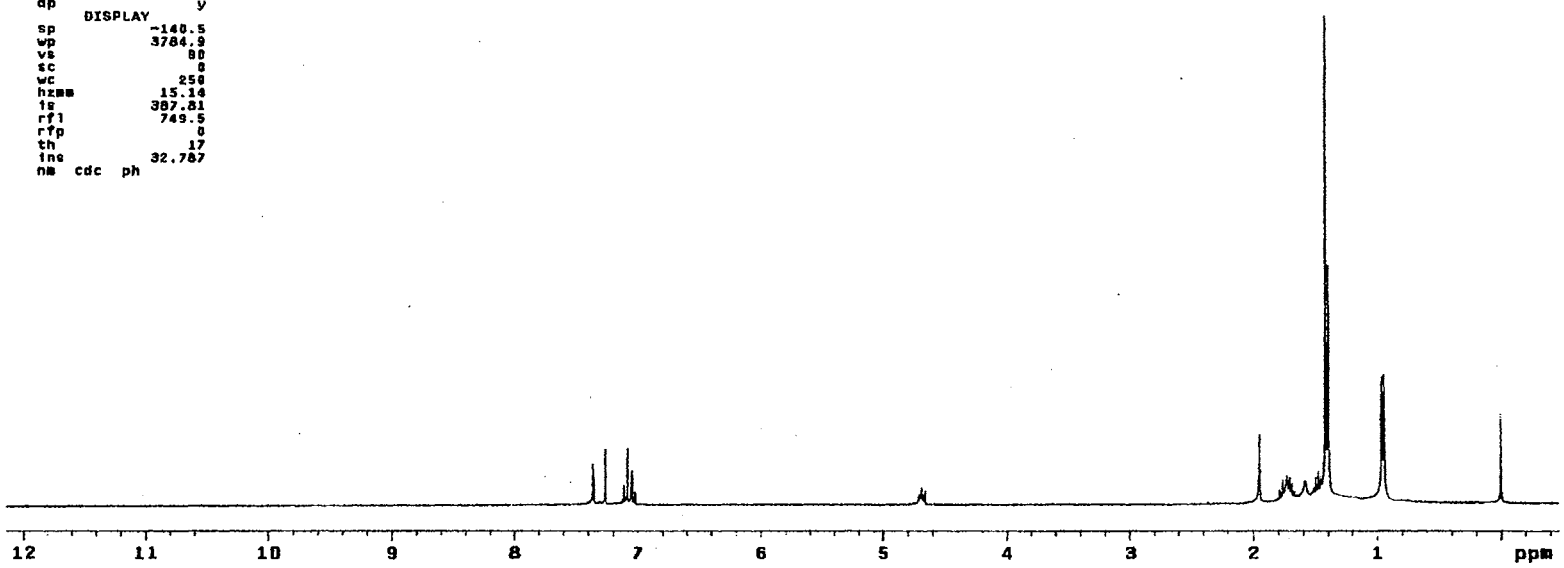
exp1 std1h

SAMPLE		DEC. & VT	
date	Nov 16 1999	dfrq	300.067
solvent	CDCl3	dn	H1
file	exp	dpwr	38
ACQUISITION		dof	0
sfrq	300.067	dm	nnn
tn	H1	dmm	c
at	3.747	dmf	200
np	33726	PROCESSING	
sw	4500.5	wtfile	
fb	2600	proc	ft
bs	16	fn	not used
tpwr	48		
pw	6.9	werr	
d1	0	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	y		
dp	y		
DISPLAY			
sp	-140.5		
wp	3784.9		
vs	80		
sc	0		
wc	250		
hzmm	15.14		
is	387.81		
rf1	749.5		
rfp	0		
th	17		
ins	32.787		

nm cdc ph



100c



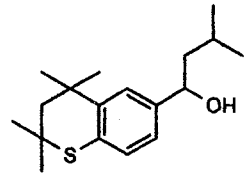
^{1}H NMR Spectrum of **100c**

Plate CXCIV

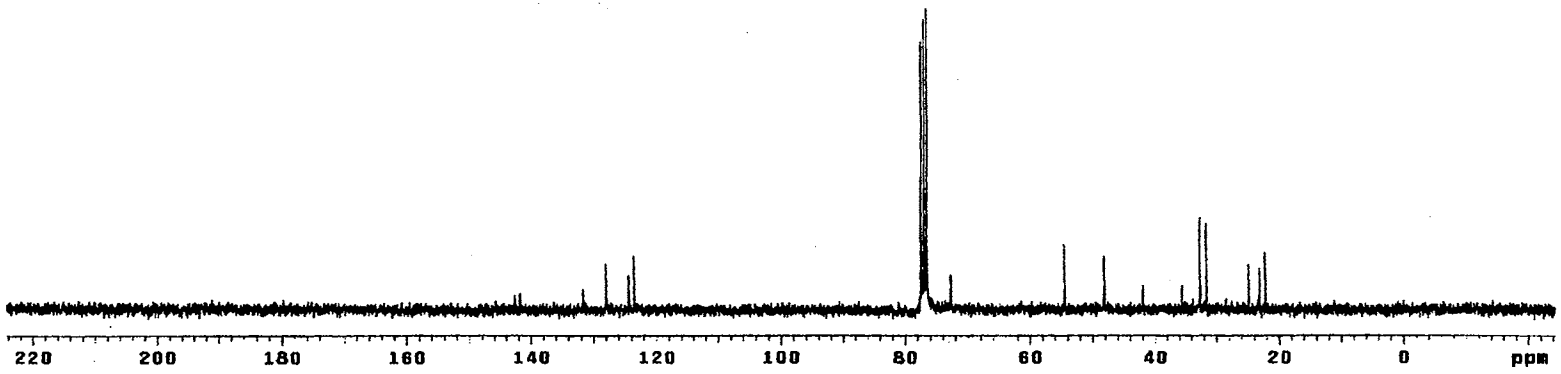
```
13C OBSERVE

expl  std13c

        SAMPLE                DEC. & VT
date   Nov 16 1998   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                 0
sfrq          75.464 dm                yyy
tn               C13 dmm                 w
at             0.800 dmf             11764
np             30016     PROCESSING
sw           18761.7 lb               1.00
fb             10400 wtfile
bs                16 proc                ft
tpwr              52 fn          not used
pw               3.8
d1             1.000 werr
tof                0 wexp               wft
nt              2048 wbs               wft
ct              2048 wnt
alock              s
gain        not used
       FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp          -1035.9
wp           18761.7
vs                56
sc                 0
wc               250
hzmm           75.05
is            500.00
rfl           7646.5
rfp           5819.6
th                20
ins          100.000
nm  no  ph
```

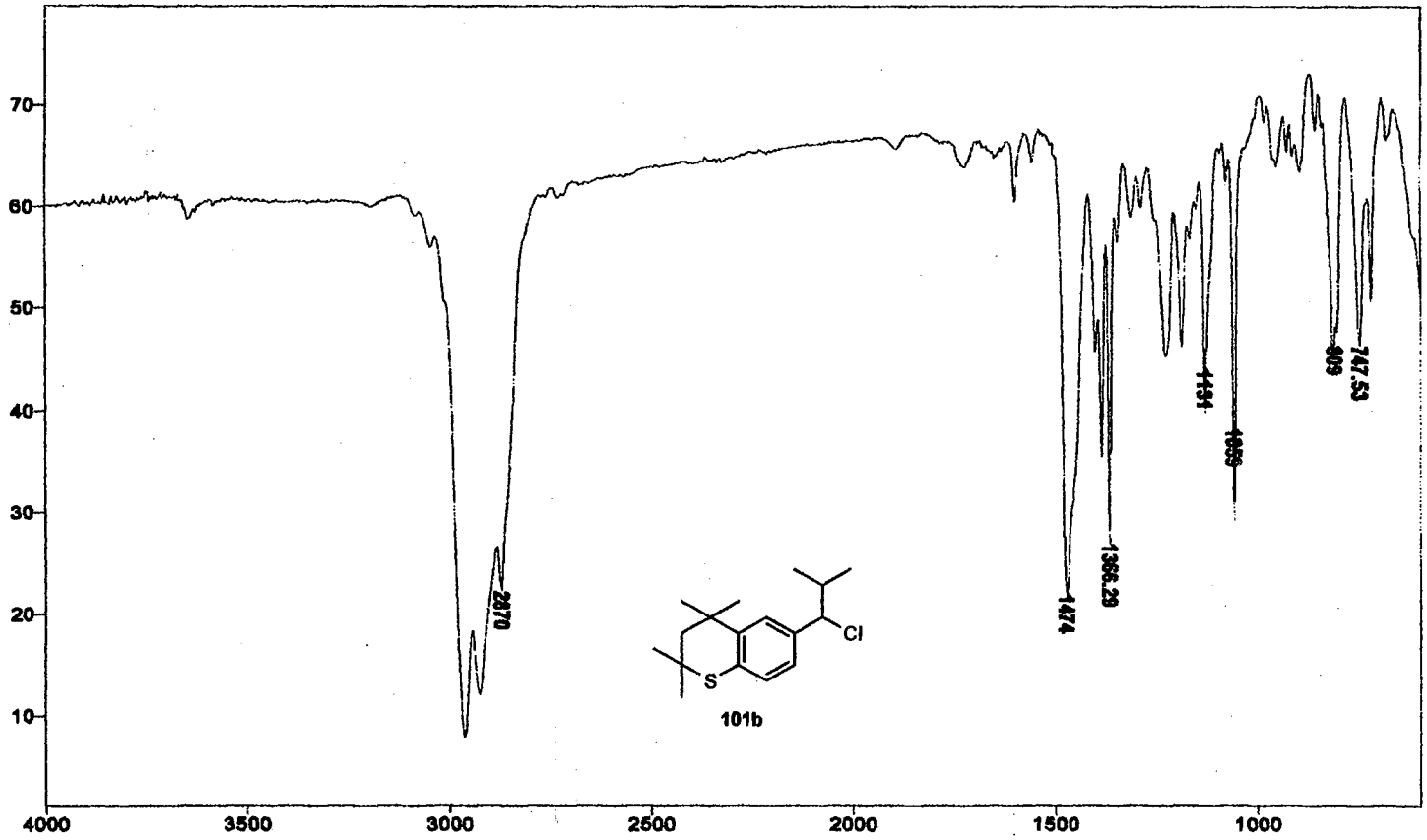


100c



^{13}C NMR Spectrum of **100c**

Plate CXCV



IR Spectrum of **101b**

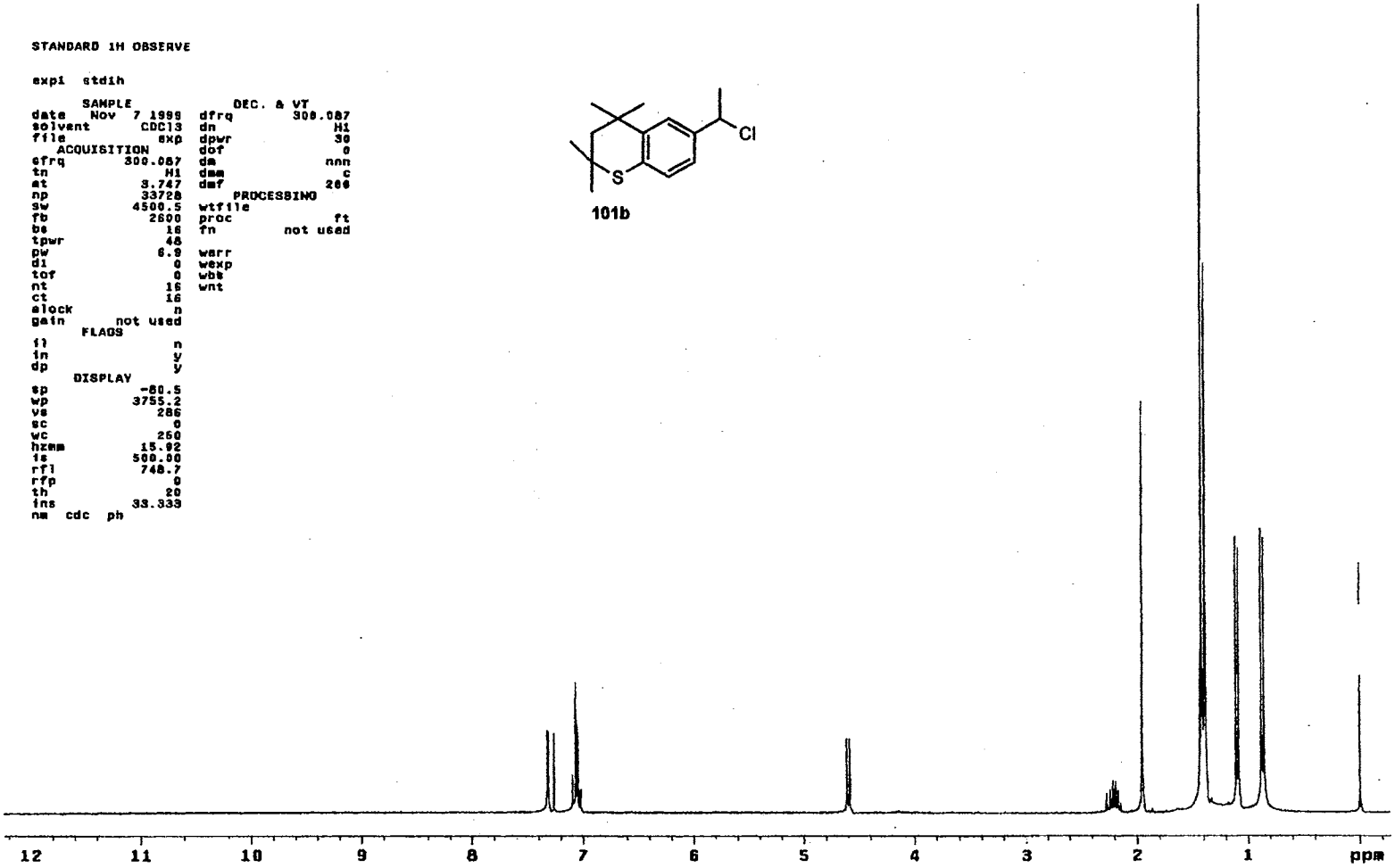
Plate CXCVI

```
STANDARD 1H OBSERVE

expl  stdih

        SAMPLE                 DEC. & VT
date   Nov  7 1999   dfrq          300.087
solvent       CDCl3  dn                H1
file            exp  dpwr              30
    ACQUISITION      dof                0
sfrq        300.087  dm               nnn
tn               H1  dmm                c
at            3.747  dmf              266
np            33728      PROCESSING
sw           4500.5  wtfile
fb            2600   proc              ft
bs              16   fn          not used
tpwr            48
pw             6.9   warr
d1               0   wexp
tof              0   wbk
nt              16   wnt
ct              16
slock            n
gain       not used
       FLAGS
fl               n
in               y
dp               y
      DISPLAY
sp           -80.5
wp          3755.2
vs             286
sc               0
wc             260
hzmm         15.92
is          500.00
rfl          748.7
rfp              0
th              20
ins          33.333
nm  cdc  ph
```


101b



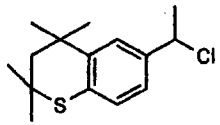
^{1}H NMR Spectrum of **101b**

Plate CXCVII

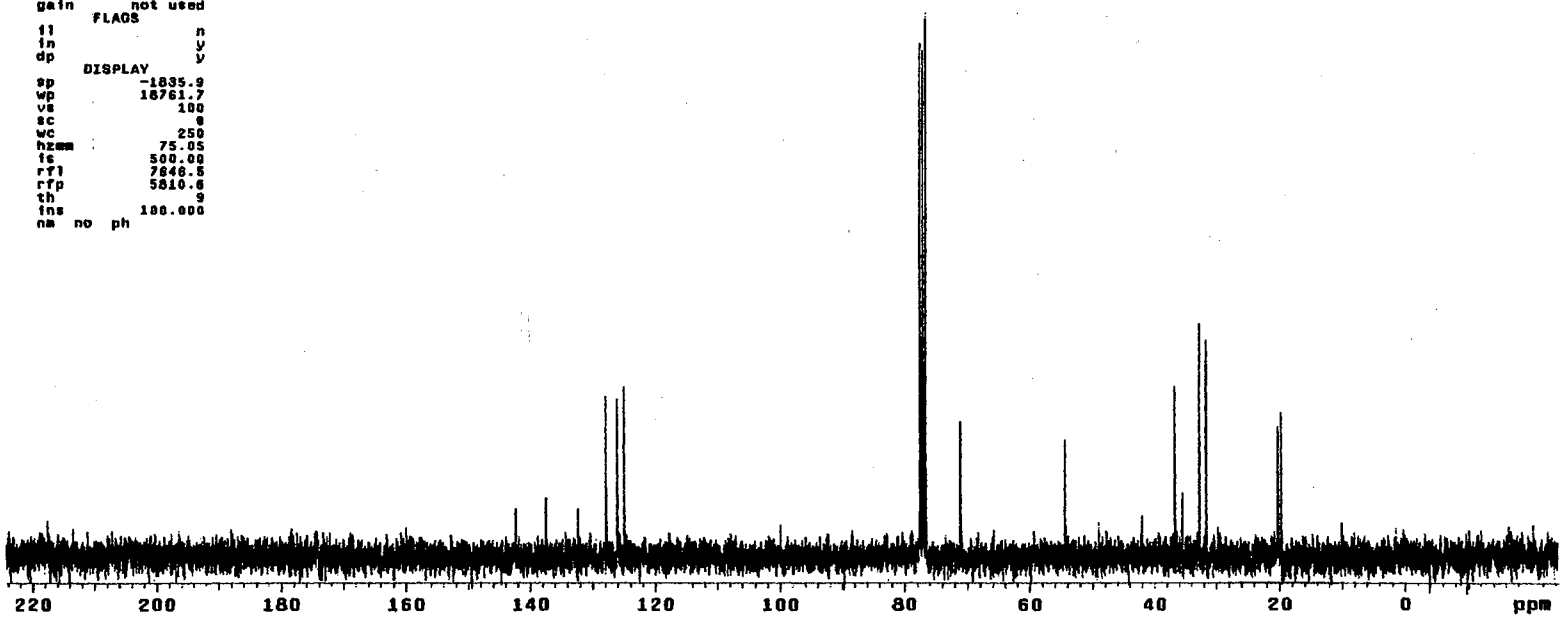
```
13C OBSERVE

exp1  std13c

      SAMPLE                 DEC. & VT
date   Nov  7 1999     dfrq        300.087
solvent       CDCl3    dn               H1
file            exp    dpwr             34
   ACQUISITION         dof               0
sfrq          75.464   dm              yyy
tn               C13   dmm               w
at             0.800   dmf           11764
np             30016       PROCESSING
sw           18761.7   lb             1.00
fb             10400   wtfile
bs                16   proc              ft
tpwr              52   fn         not used
pw               3.6   werr
d1             1.000   wexp            wft
tof                0   wbs             wft
nt              1024   wnt
ct               368
alock              s
gain         not used
      FLAGS
i1                 n
in                 y
dp                 y
      DISPLAY
sp           -1835.9
wp           18761.7
vs               100
sc                 0
wc               250
hzmm           75.05
is            500.00
rf1           7846.5
rfp           5810.6
th                 9
ins           188.000
nm  no  ph
```

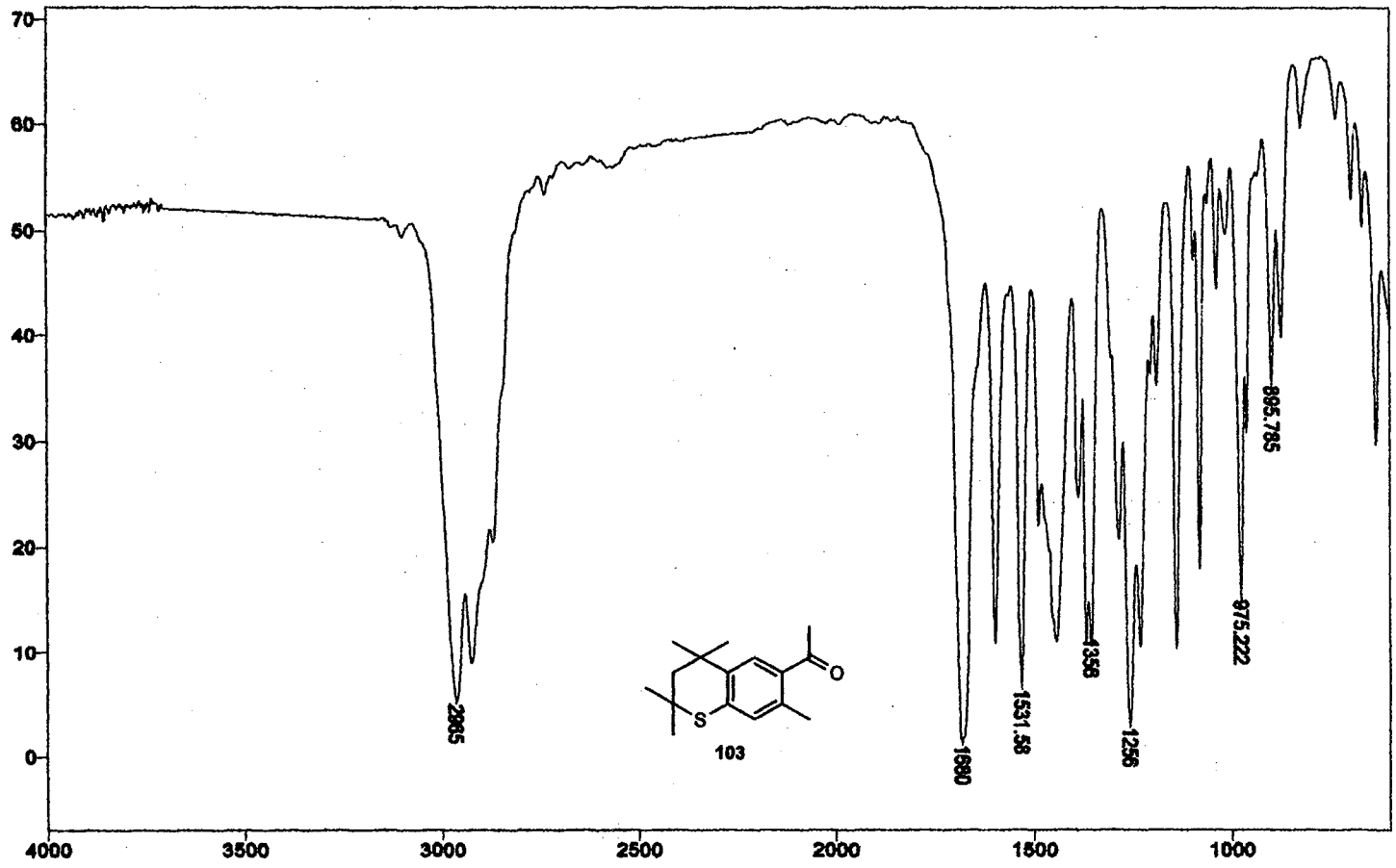


101b



^{13}C NMR Spectrum of **101b**

Plate CXCVIII



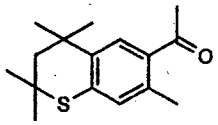
IR Spectrum of **103**

Plate CXCIX

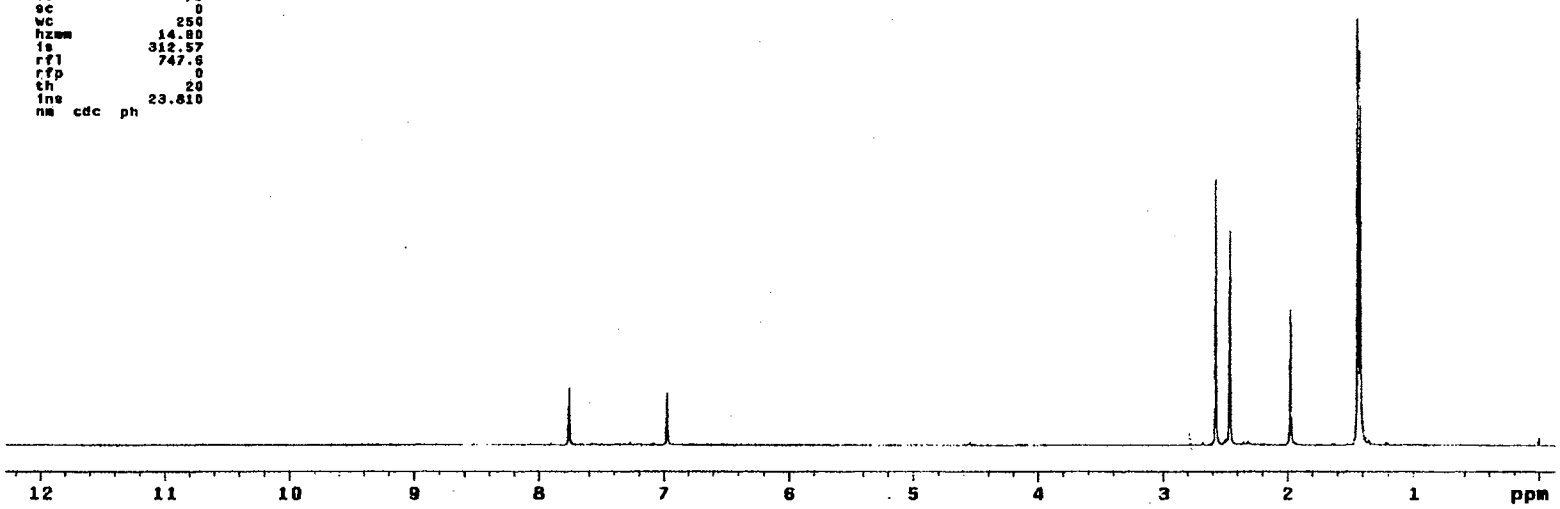
```
STANDARD 1H OBSERVE

expl  stdih

        SAMPLE                  DEC. & VT
date   Jul  9 1999   dfrq          300.087
solvent       CDCl3  dn                 H1
file            exp  dpwr               30
    ACQUISITION      dof                  0
sfrq        300.087  dm                 nnn
tn               H1  dmm                  c
at            3.747  dmf                200
np           33728       PROCESSING
sw           4500.5  wtfile
fb            2680   proc                ft
bs              16   fn            not used
tpwr            48
pw             3.0   werr
d1               0   wexp
tof              0   wbs
nt              16   wnt
ct              16
alock            n
gain        not used
        FLAGS
il               n
in               y
dp               y
      DISPLAY
sp           -38.6
wp          3725.7
vs              79
sc               0
wc             250
hzcm         14.80
is          312.57
rfl          747.6
rfp              0
th              20
ins          23.810
nm  cdc  ph
```



103



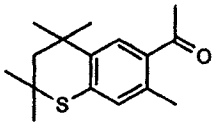
^{1}H NMR Spectrum of **103**

Plate CC

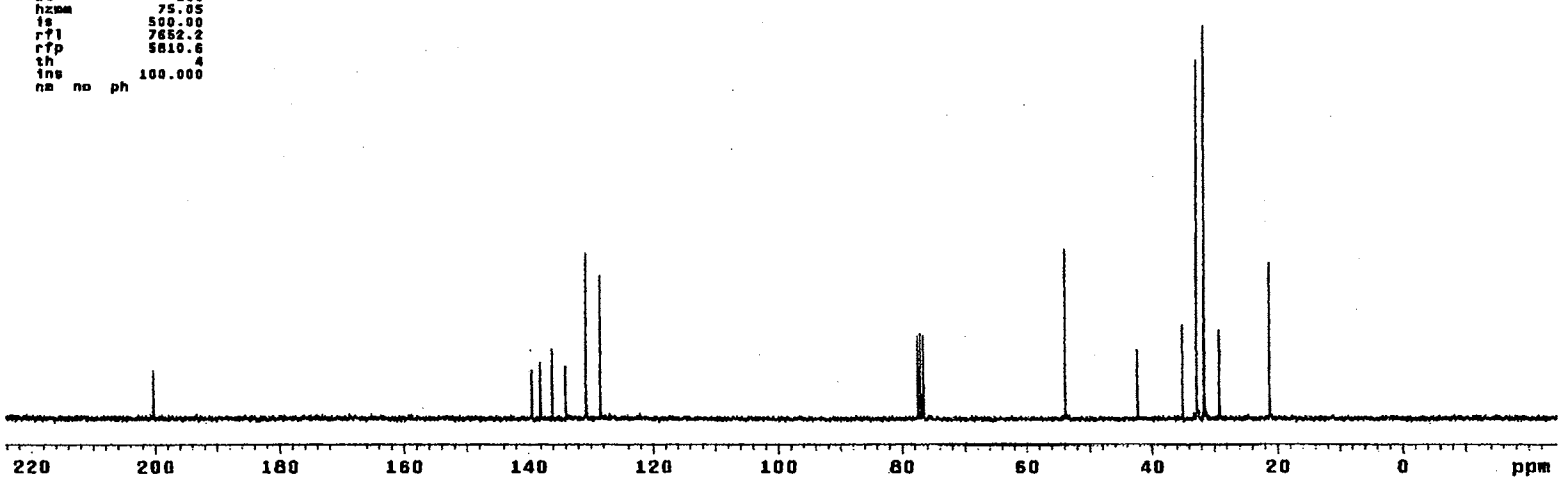
```
13C OBSERVE

exp1  std13c

      SAMPLE                    DEC. & VT
date   Jul  8 1993   dfrq          300.057
solvent      CDCl3   dn                 H1
file           exp   dpwr               34
   ACQUISITION       dof                 0
sfrq         75.464  dm                yyy
tn             C13   dmm                 w
at           0.800   dmf             11764
np           38016      PROCESSING
sw         18761.7   lb              1.00
fb           18400   wtfile
bs              16   proc              ft
tpwr            52   fn        not used
pw             3.8
d1           1.000   werr
tof             0    wexp             wft
nt           1024   wbs              wft
ct            258   wnt
alock           s
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp         -1841.6
wp         18761.7
vs              73
sc               0
wc             250
hzcm         75.05
is          500.00
rfl         7652.2
rfp         5810.6
th               4
ins         100.000
nm  no  ph
```



103



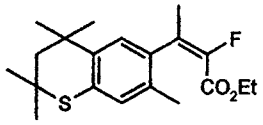
^{13}C NMR Spectrum of **103**

Plate CCI

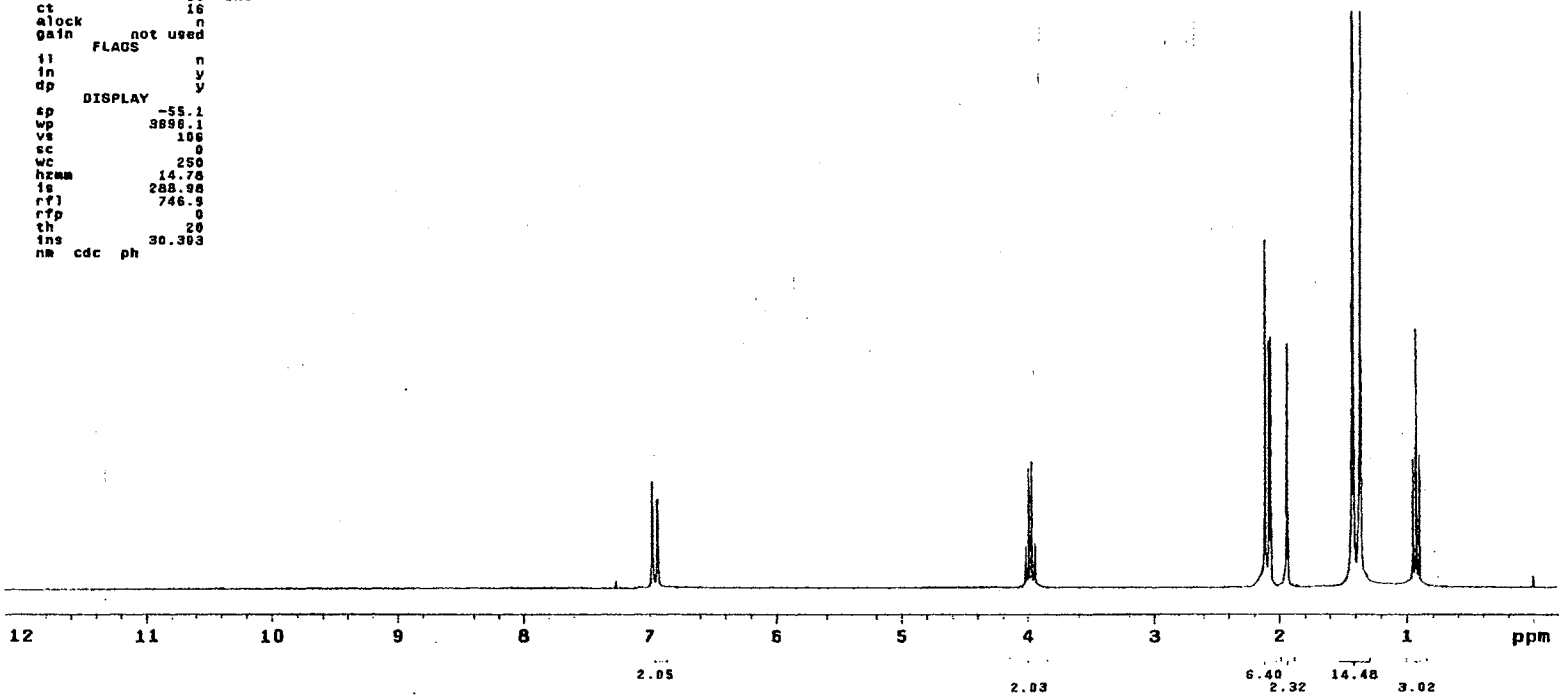
```
STANDARD 1H OBSERVE

exp1  std1h

      SAMPLE                 DEC. & VT
date   Jan 24 2000     dfrq        300.087
solvent       CDCl3    dn               H1
file            exp    dpwr             30
   ACQUISITION         dof               0
sfrq        300.087    dm              nnn
tn               H1    dmm               c
at            3.747    dmf             200
np            33728       PROCESSING
sw           4500.5    wtfile
fb             2600    proc             ft
bs               16    fn        not used
tpwr             48
pw              2.0    werr
d1                0    wexp
tof               0    wbs
nt               16    wnt
ct               16
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp            -55.1
wp           3898.1
vs              106
sc                0
wc              250
hzmm          14.78
is           288.98
rfl           746.9
rfp               0
th               20
ins          30.393
nm  cdc  ph
```



104



^{1}H NMR Spectrum of **104**

Plate CCII

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13C OBSERVE

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solvent       CDCl3   dn               H1
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sfrq          75.464  dm              yyy
tn               C13  dmm               w
at             0.800  dmf           11764
np             30016      PROCESSING
sw           18761.7  lb             1.00
fb             10400  wtfile
bs                16  proc             ft
tpwr              52  fn         not used
pw               3.8  werr
d1             1.000  wexp            wft
tof                0  wbs             wft
nt              1024  wnt
ct               112
alock              s
gain         not used
       FLAGS
il                 n
in                 y
dp                 y
      DISPLAY
sp           -1842.7
wp           18761.7
vs                52
sc                 0
wc               250
hzmm           75.05
is            500.00
rfl           7653.3
rfp           5810.6
th                 7
ins           100.000
nm  no  ph
```
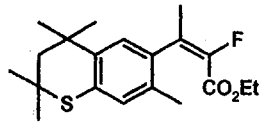
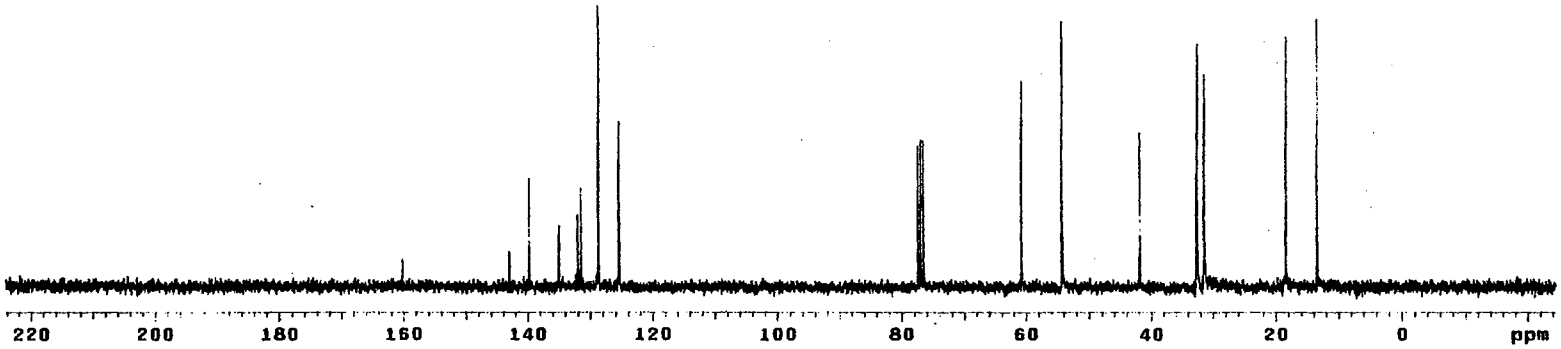



104



^{13}C NMR Spectrum of **104**

Plate CCIII

```
13C OBSERVE

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solvent       CDCl3  dn                H1
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   ACQUISITION       dof                0
sfrq        282.333  dm               nnn
tn              F19  dmm                w
at            0.500  dmf            11764
np            30019     PROCESSING
sw          18761.7  lb              1.00
fb            10400  wtfile
bs               16  proc              ft
tpwr             52  fn          not used
pw              3.8  werr
d1            1.000  wexp             wft
tof               0  wbs              wft
nt             1024  wnt
ct               16
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp         -38748.2
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vs               86
sc                0
wc              250
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rfl         38748.2
rfp               0
th               20
ins         100.000
nm  no  ph
```
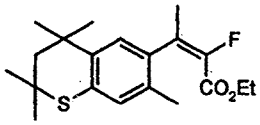
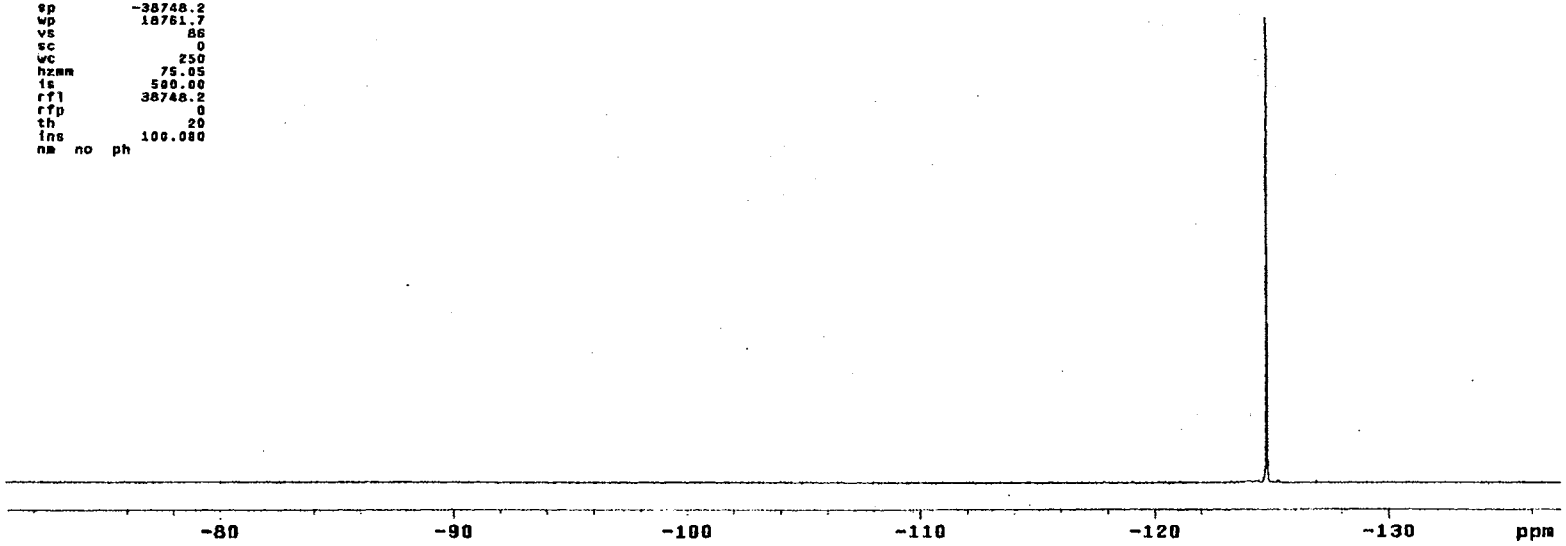
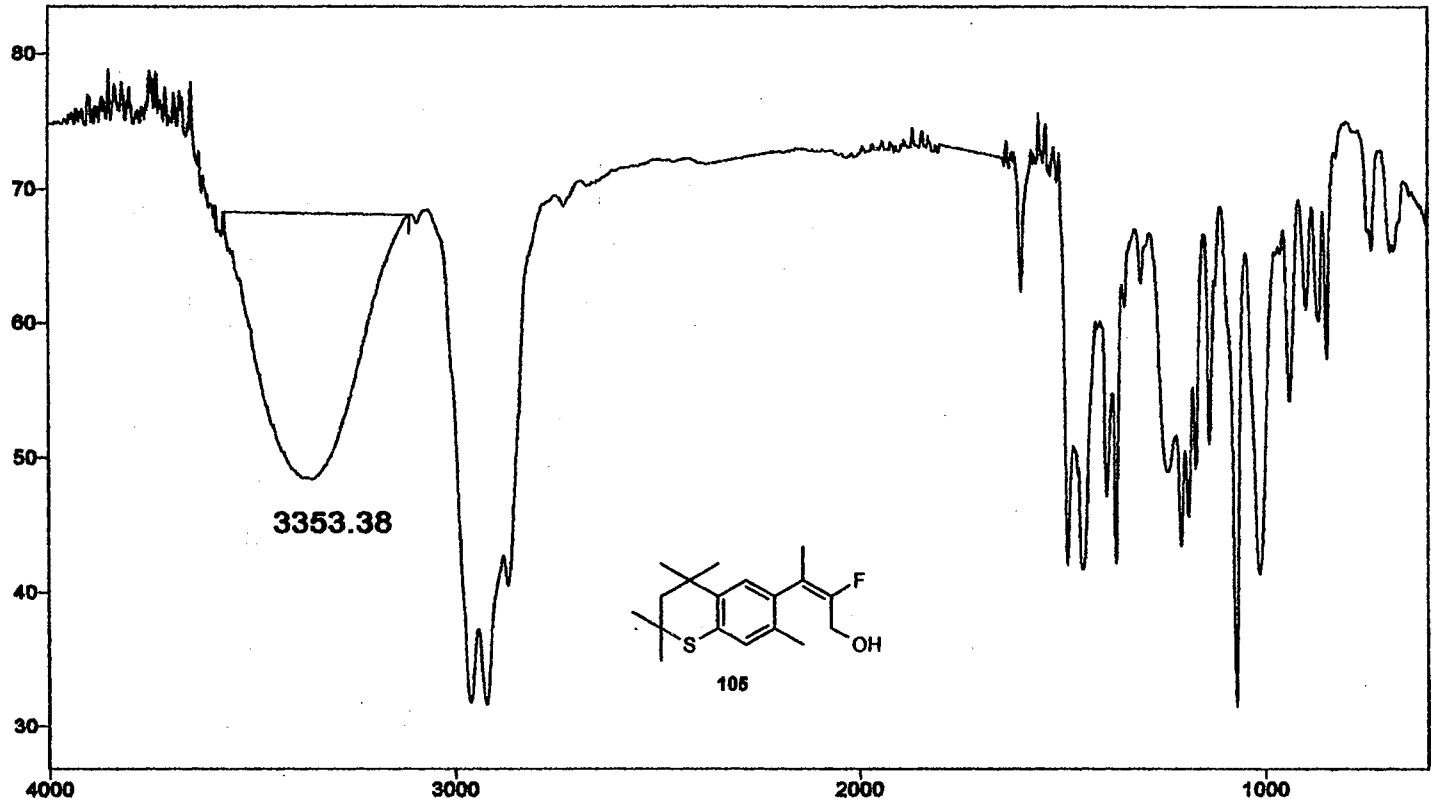



104



^{19}F NMR Spectrum of **104**

Plate CCIV



IR Spectrum of **105**

Plate CCV

```
STANDARD 1H OBSERVE

exp1  std1h

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solvent       CDCl3  dn               H1
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   ACQUISITION       dof               0
sfrq         300.087 dm              nnn
tn               H1  dmm               c
at            3.747  dmf             200
np            33728      PROCESSING
sw           4500.5  wtfile
fb             2600  proc            ft
bs               16  fn        not used
tpwr             48
pw              3.0  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain       not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp            -40.4
wp           3761.1
vs              103
sc                0
wc              250
hzcm          15.04
is           377.52
rfl           749.8
rfp               6
th               20
ins          25.000
nm  cdc  ph
```
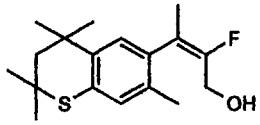
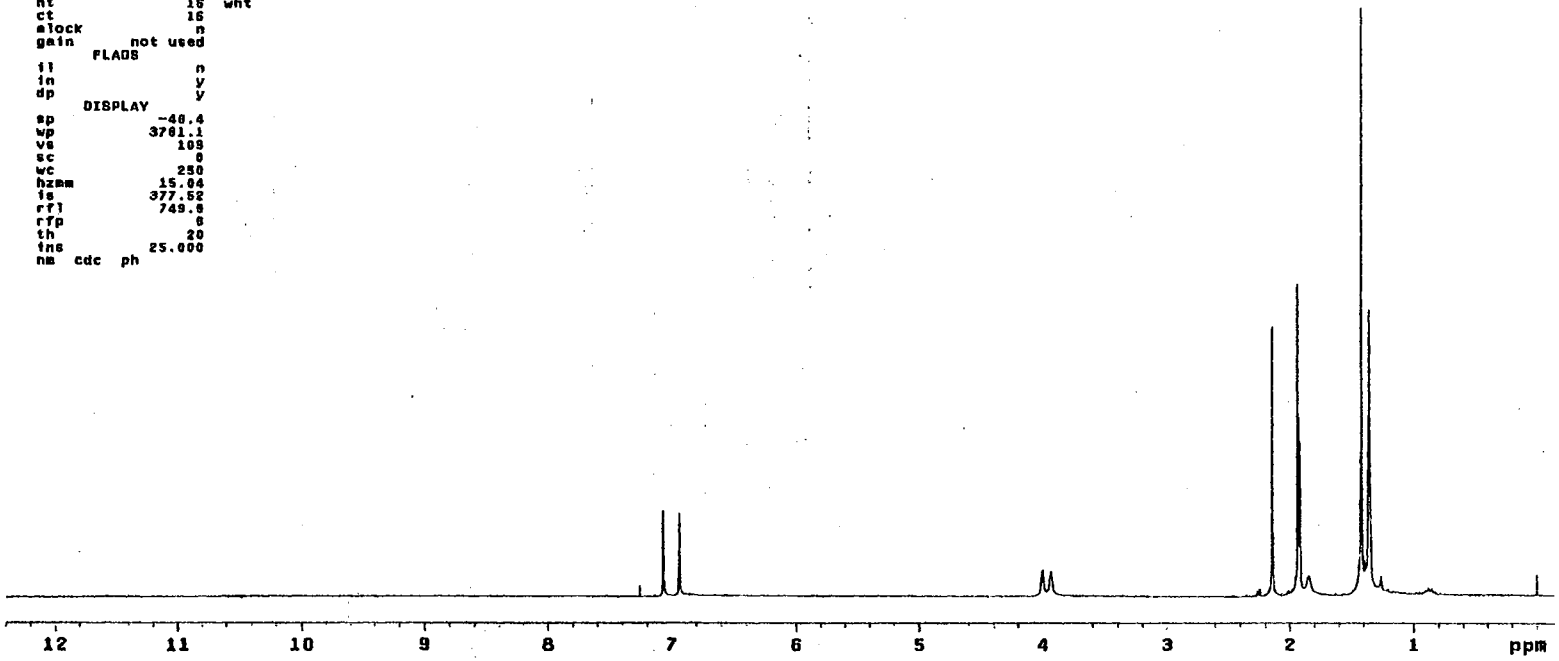



105



^{1}H NMR Spectrum of **105**

Plate CCVI

```
13C OBSERVE

expl  std13c
      SAMPLE                    DEC. & VT
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solvent       CDCl3  dn                 H1
file            exp  dpwr               34
   ACQUISITION       dof                  0
sfrq          75.464 dm                 yyy
tn             C13   dmm                  w
at           0.800   dmf             11764
np           30016      PROCESSING
sw         18761.7   lb               1.00
fb           10400   wtfile
bs              16   proc               ft
tpwr            52   fn           not used
pw             3.8
d1           1.000   werr
tof             0    wexp              wft
nt           1024    wbs               wft
ct            272    wnt
alock           s
gain       not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp         -1839.3
wp         18761.7
vs              38
sc               0
wc             250
hzmm         75.05
is          500.00
rfl         7649.9
rfp         5810.8
th               4
ins         100.000
nm  no  ph
```
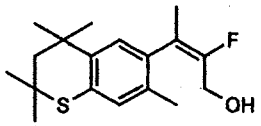
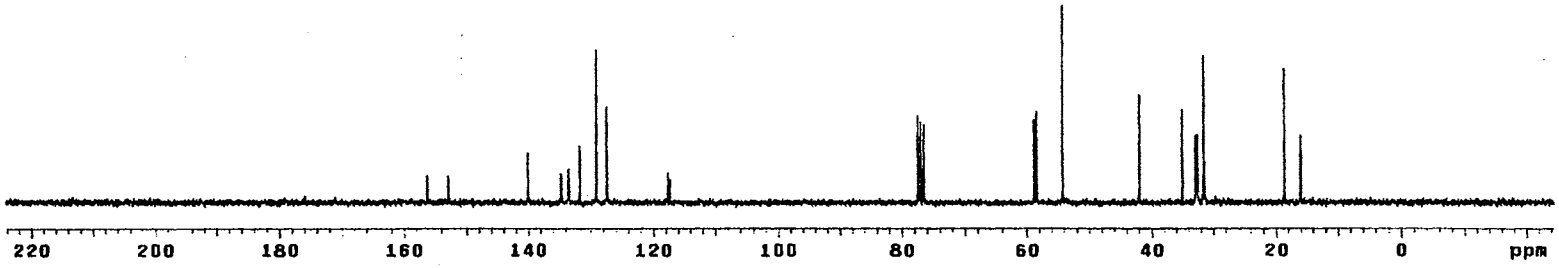



105



^{13}C NMR Spectrum of **105**

Plate CCVII

```
13C OBSERVE

exp1  std13c

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solvent       CDCl3  dn                 H1
file            exp  dpwr                34
   ACQUISITION       dof                   0
sfrq        282.333  dm                  nnn
tn              F19  dmm                   w
at            0.800  dmf               11764
np            30016      PROCESSING
sw          18761.7  lb                 1.00
fb            10400  wtfile
bs               16  proc                 ft
tpwr             52  fn          not used
pw              3.6
d1            1.000  werr
tof               0  wexp               wft
nt             1024  wbs                wft
ct               32  wnt
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
     DISPLAY
sp         -38746.2
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vs               34
sc                0
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th               20
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nm  no  ph
```

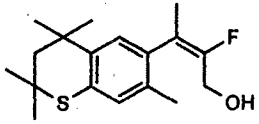

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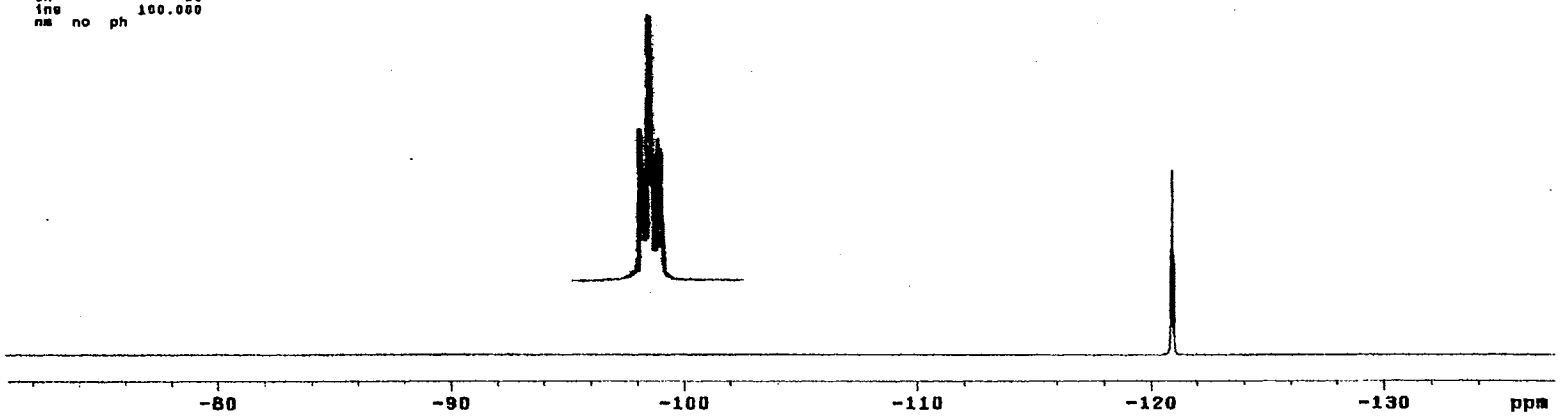
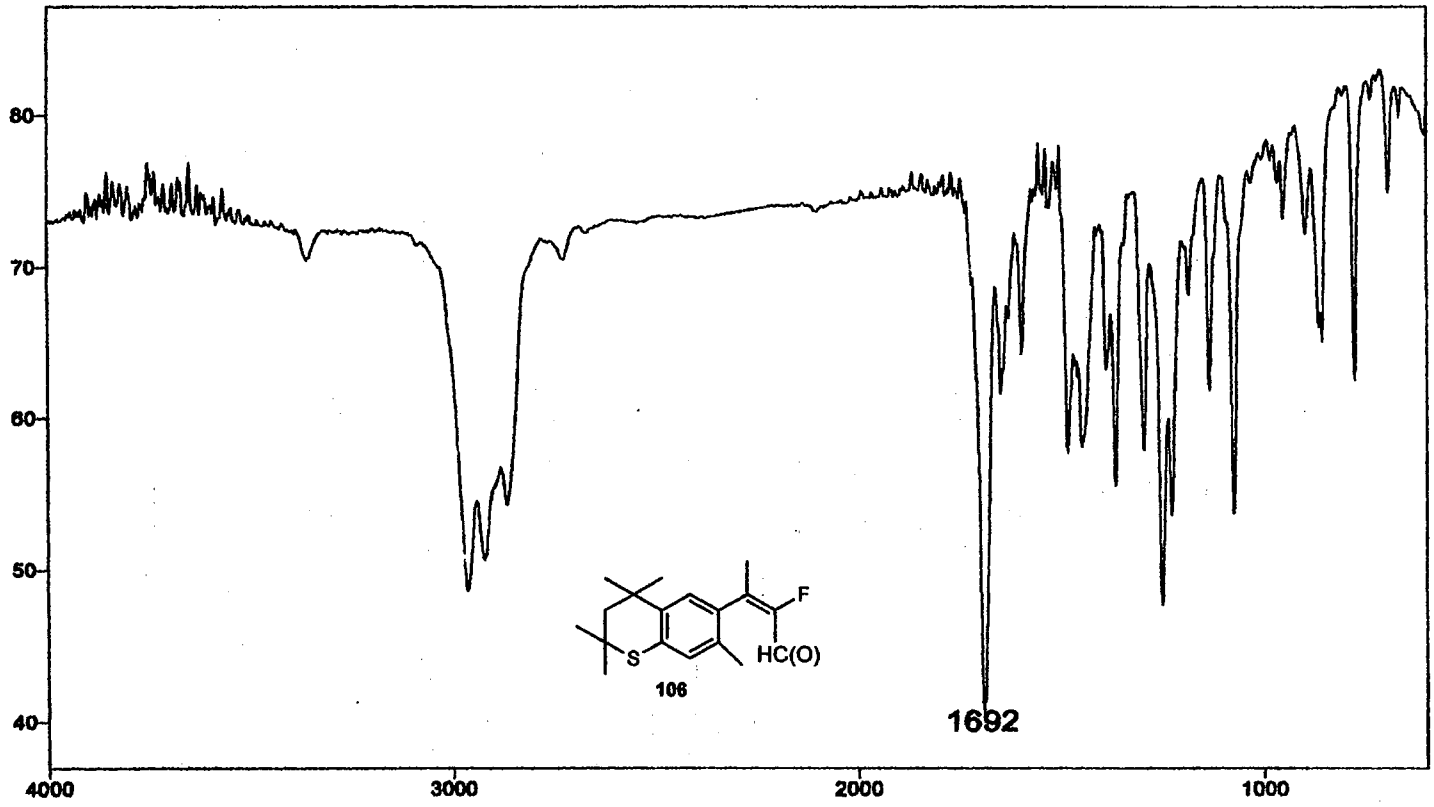


^{19}F NMR Spectrum of **105**

Plate CCVIII



IR Spectrum of **106**

Plate CCIX

```
STANDARD 1H OBSERVE

expl  stdih

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solvent       CDCl3  dn                H1
file            exp  dpwr              30
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sfrq        300.087  dm                nnn
tn               H1  dmm                 c
at            3.747  dmf               200
np            33728     PROCESSING
sw           4500.5  wtfile
fb             2600  proc              ft
bs               16  fn          not used
tpwr             48
pw              3.0  werr
d1                0  wexp
tof               0  wbs
nt               16  wnt
ct               16
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp            -40.9
wp           3713.9
vs               60
sc                0
wc              250
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rfl           744.6
rfp               0
th               20
ins          26.316
nm  cdc  ph
```
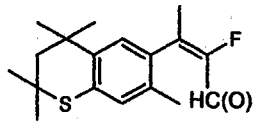
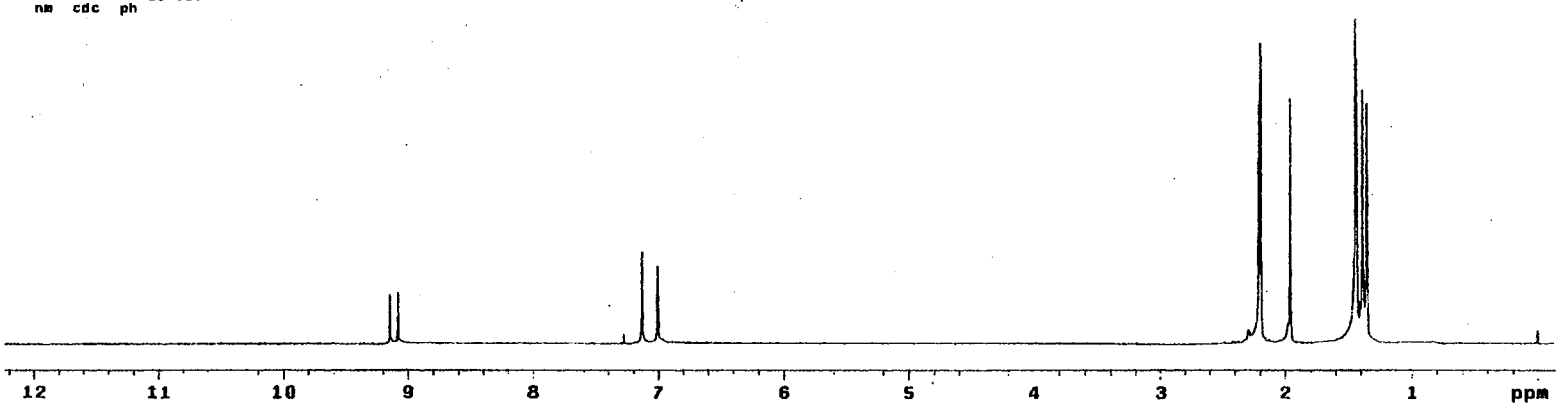
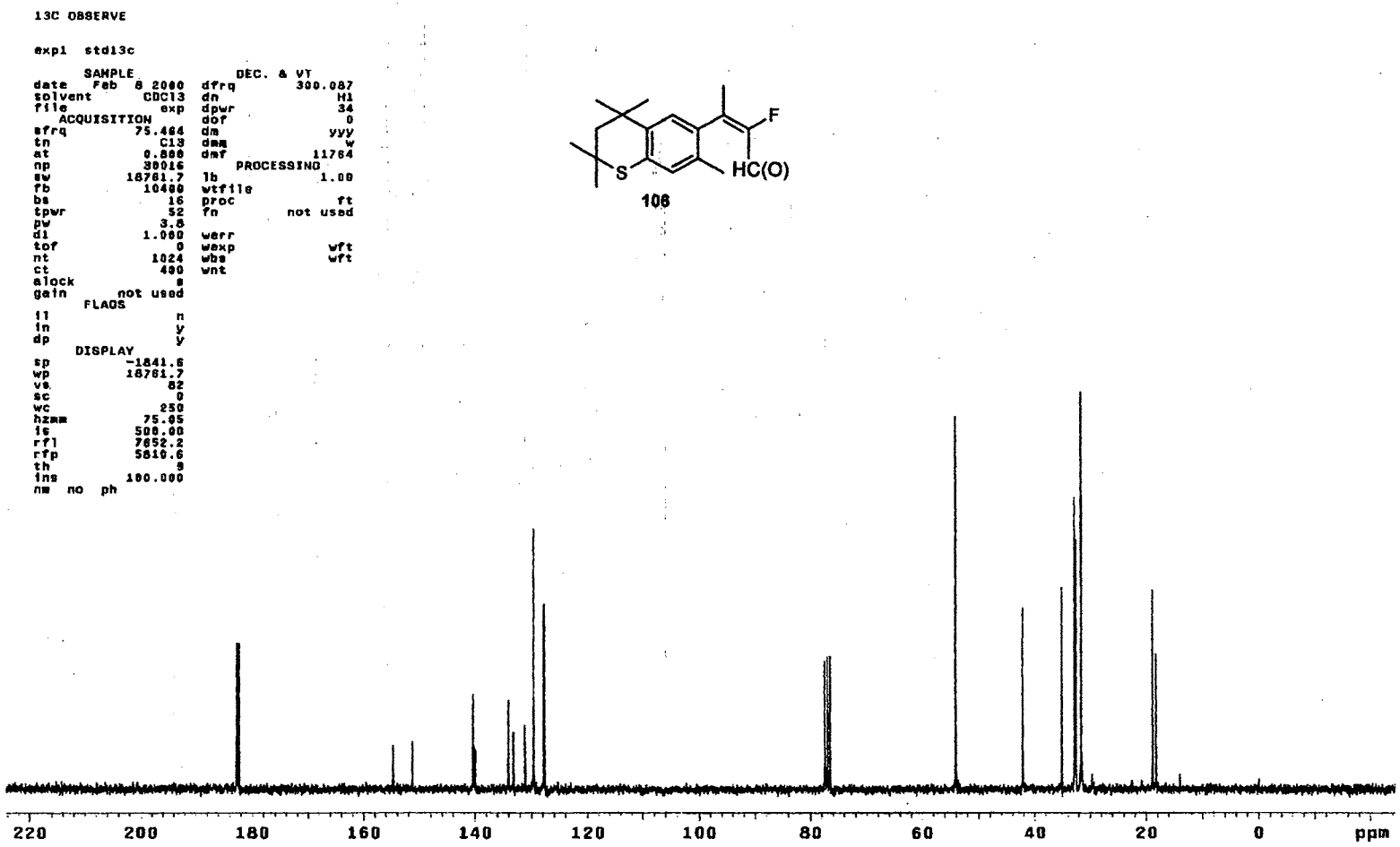



106



^{1}H NMR Spectrum of **106**

Plate CCX



^{13}C NMR Spectrum of **106**

Plate CCXI

```
13C OBSERVE

exp1  std13c

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solvent       CDCl3   dn               H1
file            exp   dpwr             34
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sfrq          282.333 dm              nnn
tn              F19   dmm               w
at            0.800   dmf           11764
np            30016       PROCESSING
sw          18761.7   lb             1.00
fb            10400   wtfile
bs               16   proc             ft
tpwr             52   fn         not used
pw              3.8   werr
d1            1.000   wexp            wft
tof               0   wbs             wft
nt             1024   wnt
ct               32
alock             n
gain        not used
      FLAGS
il                n
in                y
dp                y
      DISPLAY
sp         -38551.2
wp          9639.1
vs               42
sc                0
wc              250
hzmm          38.56
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rfp               0
th               20
ins         180.000
nm  no  ph
```
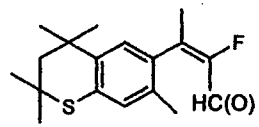
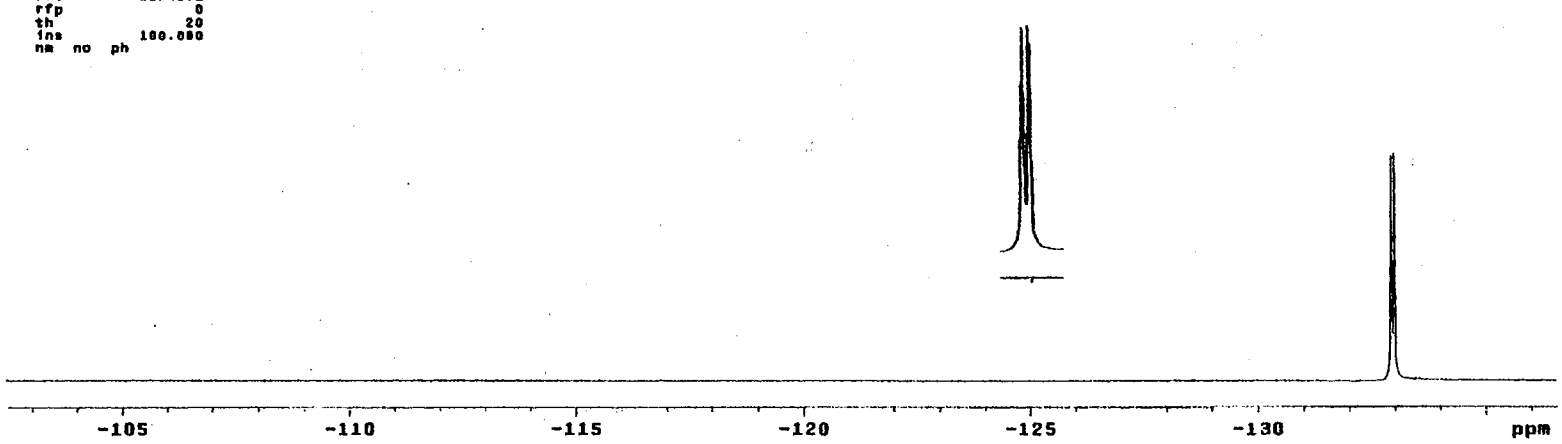



106



^{19}F Spectrum of **106**

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VITA 2

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Education: Received primary education in Czechoslovakia; received Bachelor of Science Degree in Chemistry from Cameron University, Lawton, Oklahoma, in May of 1996. Completed the requirements for the Doctor of Philosophy degree with a major in chemistry at Oklahoma State University in July of 2000.

Experience: Employed by Oklahoma State University, Department of Chemistry, as a graduate teaching assistant and as a research assistant from June, 1996, to present.

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