THE EFFECT OF STRUCTURAL MODIFICATIONS ON SIGMA RECEPTOR BINDING

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In Partial Fulfillment of

The Requirements for the Degree

Doctor of Philosophy

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by

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The undersigned, appointed by the dean of the graduate school, have examined the dissertation entitled,

THE EFFECT OF STRUCTURAL MODIFICATIONS ON

SIGMA RECEPTOR BINDING

presented by Rong Xu

a candidate for the degree of Doctor of Philosophy

and hereby certify that in their opinion it is worthy of acceptance.

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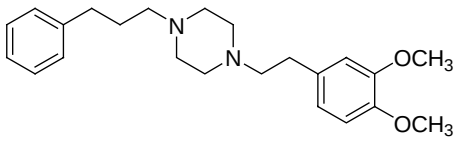
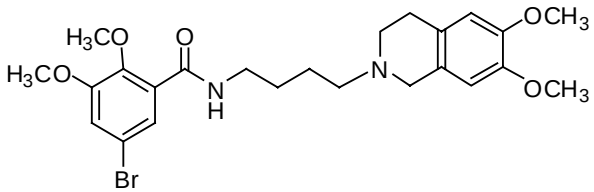
ABSTRACT

The sigma receptor is a unique receptor family that has two subtypes: sigma1 and sigma2. The selective sigma1 ligands are found to have potential usage in central nervous system diseases, while sigma2 selective ligands can play an important role as biomarkers and therapeutic agents of tumor proliferation.

Based on two well characterized lead compounds, structural modifications were conducted in order to find new ligands that can bind sigma receptor subtypes with both high affinity and high selectivity; the possibility of new ligands as potential SPECT imaging agents was also explored.



Lead I SA4503



Lead II Conformationally flexible benzamide

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INTRODUCTION

1.1 The sigma receptor and its pharmacological functions

The sigma receptor (σ) was originally classified as an opioid receptor subtype.[1] Because most of the sigma receptor-mediated effects are not sensitive to the opioid antagonist naloxane,[2, 3] this classification was discarded. At present, the sigma receptor is considered to be a unique receptor family in which two subtypes, sigma1 and sigma2, have been recognized. The existence of a sigma3 subtype has been discussed,[4, 5] but experimental evidence indicates this binding site is actually the histamine H_1 receptor.[6]

Sigma1 and sigma2 subtypes are different in their tissue distribution pattern, drug selectivity and, accordingly, their pharmacological functions. Visualized by different radioligands such as [^{3}H] NE100, [^{3}H] SKF 10, 047, [^{3}H]-(+) pentazocine and [^{3}H] DTG,[7-9] the sigma1 receptor has been well characterized in the central nervous system. It is concentrated in brain areas involved in motor functions, limbic areas, sensory areas and areas associated with endocrine functions, thus they may be involved in several diseases of the central nervous system (CNS), as well as in peripheral nervous system diseases. On the basis of their neuroregulatory and neuroprotective functions, a sigma1 ligand can be potentially used for the treatment of depression and psychiatric disorders, as well as amnesia and mental improvement.[10, 11]

On the other hand, cocaine was found to bind with both subtypes in micromolar concentration and has about 10-fold higher affinity for sigma1 compared to the sigma2 receptor in mouse brain.[12] This suggests that the sigma receptor is involved in the

physiological action of cocaine. So, antagonists of sigma receptors can produce anti-cocaine effects and be used in the treatment of cocaine-induced convulsion, lethality and locomotor activity and depressions.[13, 14] Sigma1 selective agonists have also found its potential role in the treatment of age-related cognitive impairment.[15]

In contrast, sigma2 receptor suffers from a lower degree of knowledge because of the lack of high-affinity and highly selective ligands. Nevertheless, sigma2 receptors are expressed in a variety of human tumors. This suggests that sigma2 selective ligands, when radiolabelled, can play an important role as tracer for in vivo visualization of sigma2 receptors, as biomarkers of tumor proliferation, and for imaging tumor diagnosis with SPECT and PET imaging (see section **1.3.2a**). Therefore, finding high affinity and highly selective sigma2 agents is a stimulating target in the area of current sigma receptor research.

1. 2 Progress in identification of the sigma receptor binding site

Since sigma receptors have such great potential in treating diseases, people have made many endeavors in constructing selective sigma receptor ligands. The knowledge about the active binding site of the sigma receptor will definitely help design molecules with high affinity.

In the process to identify an active binding site in a target macromolecule, a very important step is to define the receptor's three-dimensional structure by crystallization and X-ray diffraction. But no such investigation on the sigma receptor is reported to date. Nevertheless, plenty of efforts have been made. The sigma1 subtype was cloned from various sources.[16-21] Based on the analysis of its predicted 223 amino acid sequence, two

different models have been proposed: a single transmembrane domain with an extracellular N-terminus and intracellular C-terminus[20] or two transmembrane segments with both N- and C-terminus inside the membrane and a loop of 50 amino acids outside.[22] Although cloning of the sigma2 receptor has not been reported, its molecular size is estimated to be 18~21kDa.[23, 24]

It is not necessary to wait until the final 3-dimensional structure of the target is resolved. A comparison of muptiple lead compounds may result in the identification of the core of the pharmacophore.

Since the first characterization of sigma receptors by Martin in 1976,[1] many structurally diverse compounds have been found to bind with sigma receptors, but not all drugs within a class bind to sigma receptors. For those compounds that can bind with sigma receptors, it has always been difficult to obtain a ligand with both high selectivity and high affinity. Cross-reactivity with other receptor families such as the dopamine (DA) receptor and phencylidine (PCP) receptor are common. Nevertheless, the potential functional roles for sigma sites have accelerated the research in this area.

1. 3 The aim of our work

As most other groups working in the structure-activity relationship (SAR) area, we expect to gain a better understanding of the features that influence affinity and selectivity. This may help find new ligands, that can bind the target with both high affinity and high selectivity for only one receptor subtype. To approach this goal, we carefully picked two well characterized compounds from two different structural classes as leads and tried to study the SAR effect by modifying certain moieties.

The first lead compound **SA4503** (Figure 1), belonging to the 1,4-disubstituted piperazines, was reported to have high affinity and high selectivity toward the sigma1 receptor. **SA4503** is now in phase II clinical trial as therapeutic agent for functional recovery after stoke.[25] The slight modification of the methoxy by a fluoroethoxy (**FESA4503**) converts a sigma1 selective ligand into a sigma2 selective ligand, and the selectivity changes by about 300-fold (Table 1). On the other hand, the *in vivo* evaluation experiments showed that ^{11}C labelled **SA4503** and ^{18}F labelled **FESA4503** have high specific binding for sigma1 receptor in the brain.[26, 27] Thus, **SA4503** and its analog **FESA4503** were chosen as our lead compound to further explore the effects of phenolic side chain substituents.

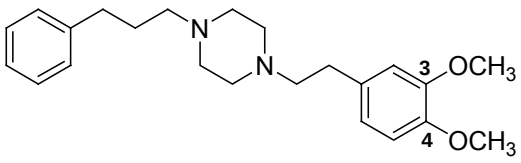


Figure 1 Structure of Lead I (SA4503)

Very recently, Mach's group reported a highly selective sigma2 ligand (Lead **II**, Figure 2) that belongs to the benzamide structural class. This compound has the highest sigma2 selectivity among all of the sigma ligands reported so far. The skeletal overlap of this benzamide with **SA4503** (Figure 16) makes us wonder whether similar structural modifications will cause the sigma affinity to change in the same direction. Also, the rigid conformation of the tetrahydroisoquinoline ring in Lead **II** is a spot of interest in order to understand the determinant of high sigma2 selectivity.

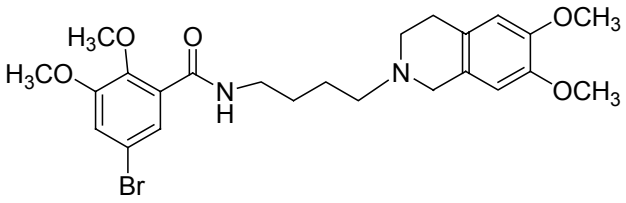


Figure 2 Structure of Lead II

1.3.1a Background of Lead I: SA4503

Since 1991, certain phenylamine, aminotetralin, piperazine, piperidine and related derivatives were found to have high binding to sigma receptors and low binding to PCP and DA receptors. Being one of the most potent structural classes binding to sigma receptors, piperazine and piperidine derivatives have attracted a lot of attention due to their synthetic availability.

The Glennon research group, one of the earliest groups to investigate the pharmacophore for sigma receptors, with "deconstruction-reconstruction-elaboration" approach, proposed a sigma1 binding model for phenylpiperazine and phenylpiperidine structural classes (Figure 3). This model has significant influence on the future modifications of congeners in this class. In this model, the sigma1 receptor is composed of an amine site flanked by a primary and a secondary hydrophobic regions. For a ligand to have good binding to the sigma1 subtype, a basic nitrogen linked with a phenylalkyl chain is necessary. When the alkyl chain has 5 methylene units in length, the sigma1 binding is optimal. This alkyl chain is tolerated with different embedded moieties such as olefin, alkyne, chiral center, ester. The other nitrogen does not affect the binding affinity as long as it is alkylated. [28-31]

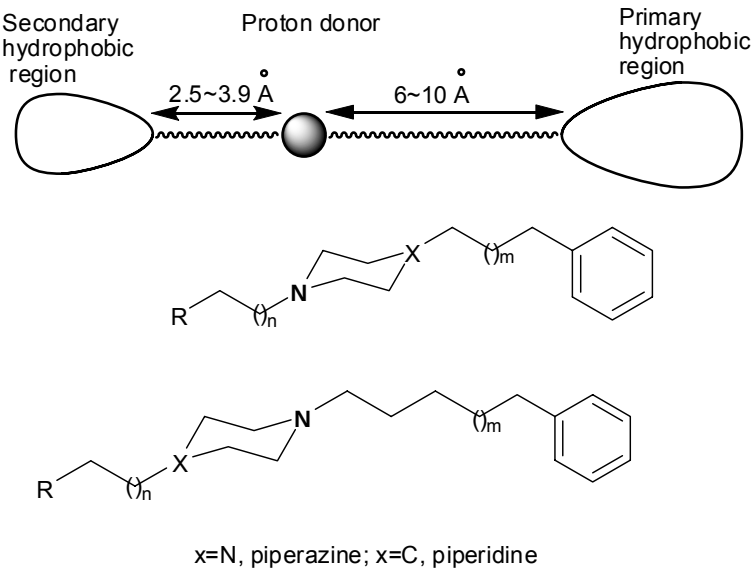


Figure 3 Glennon's sigma1 binding model

Most of the structural modifications on the piperazine analogs were done on its N-1, 4 substituents. **SA4503** (Figure 1), first synthesized in 1995, is one of the earliest in this series exhibiting high affinity toward sigma receptor (IC_{50}=0.34 nM against [^{3}H]-(+)SKF-10047 in GPB).[32]

In the systematic binding studies carried out in 1996, **SA4503** was found to have not only high affinity to the (+)-[^{3}H] pentazocine labeled sigma1 receptor but 100-fold higher selectivity over the [^{3}H]-DTG labeled sigma2 subtype. Furthermore, it showed little affinity for 36 other receptors, ion channels and second messenger systems.[33] These results suggested that **SA4503** is a potent ligand for binding sigma receptor in the body. Since then, extensive biological and radiopharmaceutical studies have been investigated to test the possibility of employing **SA4503** as an imaging and therapeutic agent. Some of these results[15, 34-38] are shown in Figure 4.

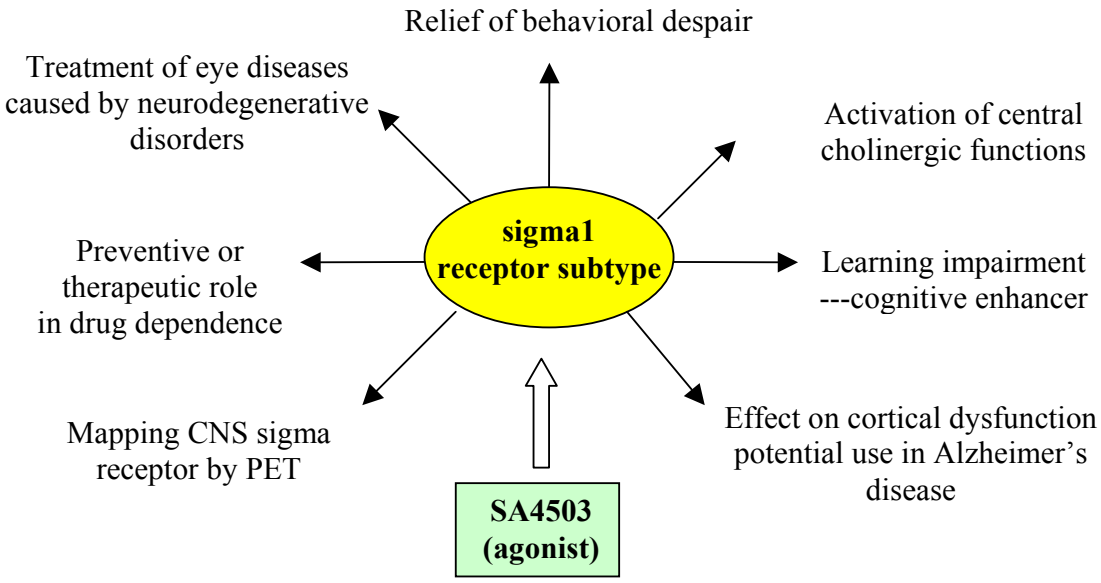


Figure 4 Biological functions of sigma1 receptor mediated by SA4503

Several research groups were encouraged to discover more potent sigma ligands by using **SA4503** as a lead compound. In summary, the SAR studies (Figure 5) were conducted mainly through 4 modifications:[27, 39-44] 1. the substituents on both hydrophobic regions, where R_1~R_4 could be electron withdrawing groups (NO_2, halogen, CF_3), electron donating groups (OCH_3, NH_2, OH) or neutral atom like H; 2. the replacement of a phenyl ring by other hydrophobic moieties, such as cyclohexane and tetralin. Replacement of one phenyl ring by small groups like amino or BOC protected amino groups have also been investigated; 3. The length of the alkyl chain connecting the two hydrophobic regions to the central piperazine ring; and 4. The restriction of N by forming an amide bond.

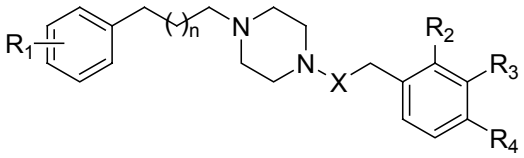
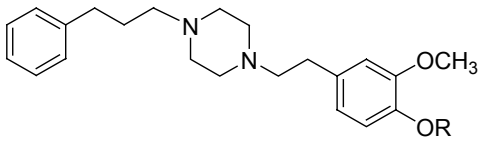


Figure 5 Previous structure modifications using SA4503 as Lead

Among these SAR studies, a result published in 2002[27] attracted our attention. In this study, the replacement of the 4-methoxy group in **SA4503** by a fluoroethoxy group (**FESA4503**) resulted in a 300-fold increase in sigma2 binding selectivity and converted a sigma1 selective ligand into a sigma2 selecetive ligand (Table 1). This dramatic change in binding properties indicated that the phenyl alkoxy position is very sensitive to structural modification. The studies on ^{18}F labelled **FESA4503** suggested that **FESA4503** has high specific binding to the sigma receptor in the brain. [26, 27]

Table 1 Comparison of sigma receptor binding properties of SA4503 and FESA4503



Compound	R	IC_{50} (nM)		Selectivity (σ_2/σ_1)
		σ_1	σ_2	
SA4503	$-CH_3$	17.4	1784.1	103[33]
FESA4503	$-CH_2CH_2F$	6.48	2.11	0.33[27]

1.3.1b Specific aims in Lead I modifications

Interested by the pharmacological functions and potential applications of **SA4503** and its analog **FESA4503**, we want to explore more on the phenyl alkoxy moiety of **SA4503** with the expectation of finding more potent sigma ligands.

1.3.1b.1 Exploration of the bulk tolerance of the hydrophobic region

The first target of structural modification is the phenyl 4-alkoxy position. As shown in Figure 6, **SA4503** fits into Glennon's sigma binding model well: a basic amine center connected by a 5-methylene-unit alkyl chain, except one of methylene is replaced by a tertiary N atom. According to Glennon's model, the primary hydrophobic region on the right side of **SA4503** interacts with a hydrophobic binding site of sigma receptor. To shed

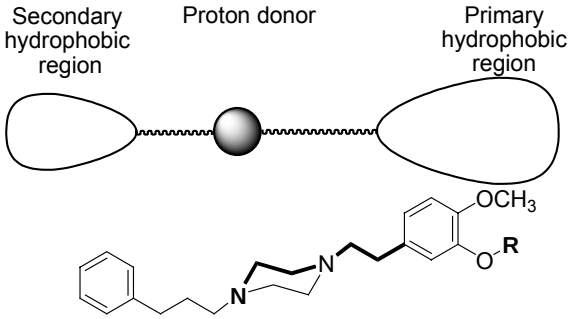


Figure 6 SA4503 analogs and Glennon's model

light on the size of space around this binding site, we decide to make a systematic investigation by using different-sized groups.

The first R group comes into mind is H. The phenol has been used as a synthetic intermediate in this category during the past. Its binding properties has never been reported. Although it is too small to be used as a bulk endurance detector, the phenol group, capable of forming a hydrogen bond with receptor molecule under physiological

conditions, will help us to understand whether such a functional group is useful in increasing the binding profile of a ligand.

To explore the size of the cavity around one of the hydrophobic binding site, we proposed several phenylalkoxy analogs, which are different only in the length of methylene chain. This difference in stucture causes different extension into the hydrophobic area, thus will help us understand the optimistic length of alkoxy side chain when interacting within that area. In addition, the incorporation of lipophilic phenylalkoxy groups might enhance the interaction of ligand with the hydrophobic binding site.

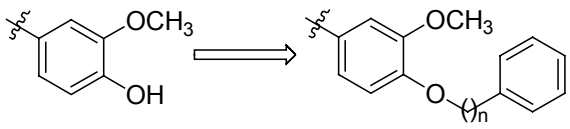


Figure 7 The incorporation of phenylalkoxy groups into phenol precursor

Nevertheless, the presence of phenyl ring as part of the side chain is not enough to indicate the bulk tolerance of the hydrophobic area inside sigma receptor. So we decide to introduce a diamine metal chelate by incorporating the chelate into the phenolic side chain. The complex incorporated a nonradioactive rhenium will be synthesized first and used to test the *in vitro* binding affinities. Rhenium belongs to the same group with Technetium and thus has similar chemical properties. If this complex has appropriate binding properties, it will be radiolabelled with ^{99m}Tc and further studied for the suitability as a potential candidate for Single Photon Computed Tomography (SPECT) imaging. The reason to choose ^{99m}Tc is because of its convinience of production and short decay half life (6 hours). The 140 keV gamma ray it emitted is also appropriate for

SPECT imaging. In a word, the incorporation of big-sized metal complex into phenolic side chain will give us not only some idea about the bulk tolerance of the hydrophobic binding site, but also the chance to first explore the possibility of designing **SA4503** analogs as novel SPECT agent. Before us, people only studied the feasibility of radiolabelled **SA4503** and its analogs as positron emission tomography (PET) imaging agent. [26, 27, 43, 45-48]

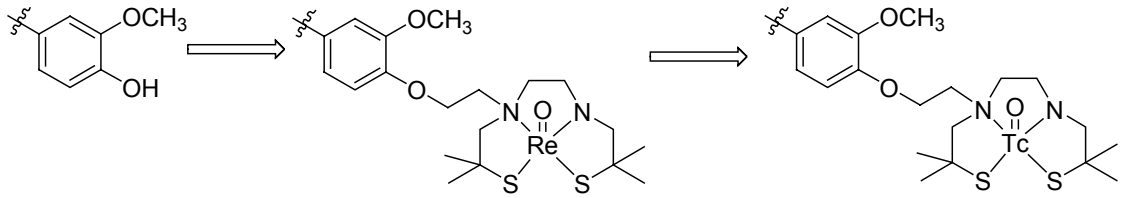


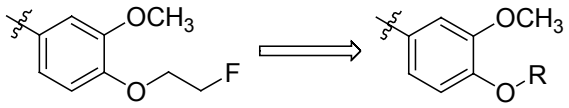
Figure 8 The incorporation of metal complex into phenol precursor

1.3.1b.2 Exploration of the importance of halogens on the phenolic side chain

The dramatic change in binding properties from **SA4503** to **FESA4503** makes us wonder what is the structural factor that causes this huge change. Since the size of methoxy has no big difference with that of ethoxy, the presence of fluorine in **FESA4503** might attribute to the greatly increased sigma2 affinity. The size and electronegativity of fluorine atom not only make it special in organic reactions but also finds its own application in drug and pesticide discovery. It interests us to find out whether the properties of fluorine performs an important role in increasing sigma2 subtype selectivity as compared to other halogen. Thus we proposes bromoethoxy and iodoethoxy as comparison to fluroethoxy. However, different from fluorine and bromine, iodine is known to be a good leaving group. In order to increase the stability of C-I bond, a p-π conjugated system, iodoallyloxy, is introduced to replace iodoethoxy. The

stereochemistry of *cis/trans* double bond changes the orientation of the alkoxy branch, which might cause a difference in binding affinity. It would be interesting to see whether the sigma receptor subtypes have any preference to one of the stereoisomers.

On the other hand, the importance of having a halogen on the phenolic side chain can be proven by using a counterpart that does not contain any halogen, e.g. propyloxy analog and allyloxy analog.



R=Bromoethyl, Iodoallyl, propyl

Figure 9 The modification of phenolic side chain by groups w or w/o halogen

1.3.1b.3 Incorporation of a double bond into the phenolic side chain

Compared to single bond, double bond increases the rigidity of a chain. To understand whether this rigid element on the phenolic side chain plays a role in sigma binding, we designed three compounds containing double bond as counterparts of two previously designed ligands.

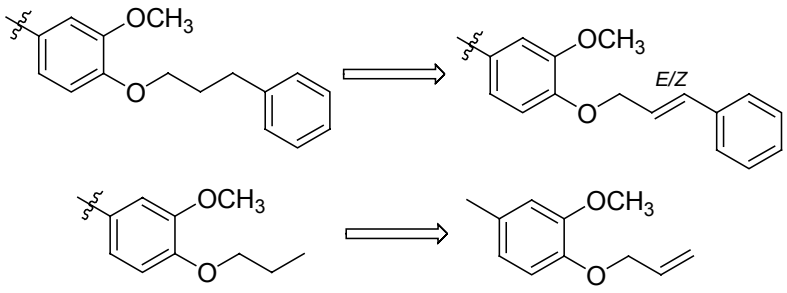


Figure 10 The incorporation of double bond into phenolic side chain

1.3.1b.4 Transformation from 3,4-phenyl dialkoxy open chains into rigid 3,4-phenyl dioxy rings

Except the above modifications proposed for the phenyl-4-alkoxy position, we want to incorporate both the 3- and 4-alkoxy moiety together. It is a common approach in drug design to replace two open chains with a cycle, or vice versa.[49] But in the case of **SA4503**, nobody has yet reported such kind of modification. We plan to synthesize several fused ring analogs with the size ranging from 5 member to 7 member. With increased rigidity, these analogs are expected to show different binding properties compared to their open chain congeners.

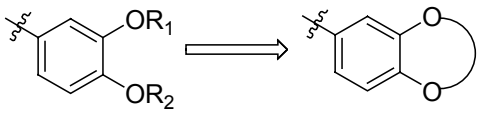


Figure 11 The transformation from 3,4-phenyl dialkoxy open chains into rigid 3,4-phenyl dioxy ring

Besides, we have also noticed that the most rigid methylenedioxy analog (5-membered) has a almost planar fused ring structure, while the least rigid propylenedioxy analog (7-membered) more resembles the structure of **SA4503**. So it is predicted that the propylenedioxy analog might have similar binding properties like **SA4503**.

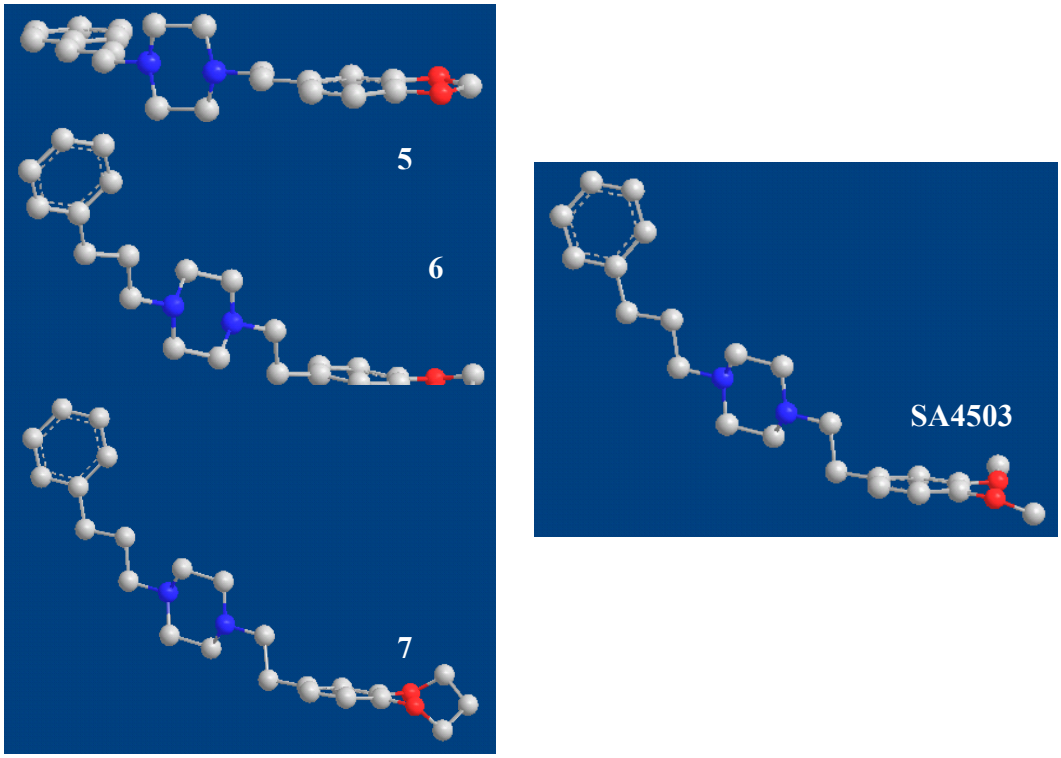


Figure 12 The 3D comparison of SA4503 with three rigid phenyl dioxy ring analogs

1.3.2a Background of Lead II: 5-bromo-N-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-2,3-dimethoxy-benzamide

Since sigma receptors were first characterized by Martin in 1976, enormous ligands from different structural classes have been synthesized and tested for their binding properties, most of which are more selective for sigma1 subtype. It was reported recently that sigma2 subtype is over expressed in a variety of tumor cell lines[50] and its density in proliferative cells is 8-10 fold higher than in quiescent counterpart in *vitro*.[51] Thus it is obvious that highly sigma2 selective ligand would play an important role in tumor cell imaging and anticancer therapy. Figure 13 lists several sigma2 selective ligand reported in literatures. [42, 52-55]

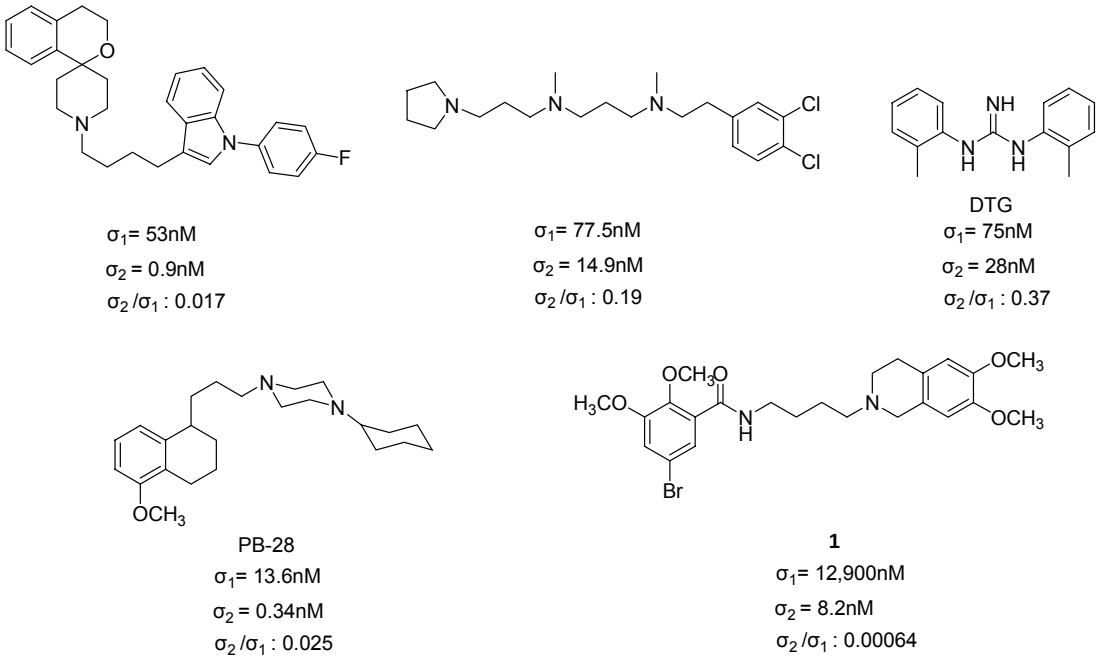
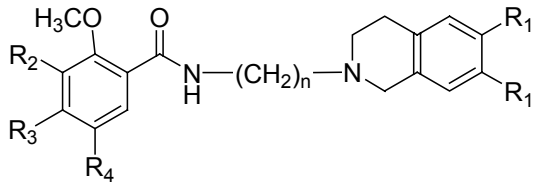


Figure 13 Some examples of sigma2 selective ligands

A series of conformationally flexible tetrahydroisoquinolinyl benzamides was first reported by Mach's group in 2004 (Figure 14).[54] Structural modifications were concentrated on three components: a. the length of the methylene chain that connects two nitrogen atoms; b. the substituents on tetrahydroisoquinoline phenyl ring; c. the substituents on benzamide phenyl ring.



R_1= H, OCH_3; R_2=OCH_3 or R_2-R_3=phenyl; R_4= Br, CH_3; n=2~4

Figure 14 Previous structural modifications on conformationally flexible Benzamide

Structure-activity relationship studies indicated that sigma receptor subtypes are sensitive to these structural changes. Among its congeners, compound 5-bromo-N-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-2,3-dimethoxy-benzamide (Figure 2, and **1** in Figure 13) was found to have the highest sigma2 selectivity than any other ligands reported to date. Soon after this discovery, several tetrahydroisoquinolinyl benzamides have been radiolabelled by ^{125}I, ^{76}Br, ^{11}C and ^{3}H (Figure 15). *In vivo* experiments shows they bind specifically to sigma2 receptors and are feasible to be used as potential marker for measuring proliferative status associated with sigma2 receptor expression.[56-59]

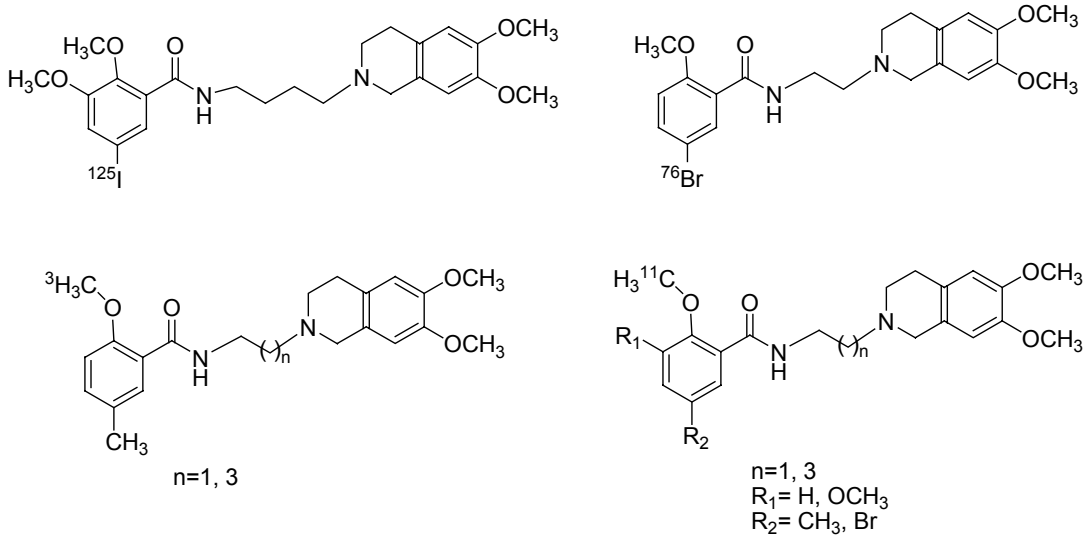


Figure 15 Radiolabelled benzamide series compounds

1.3.2b Specific aims in Lead II modifications

In order to explore further more on the core structural elements for this series of compound, we decide to use **1** (Figure 13) as a lead compound and make some structural changes.

1.3.2b.1 Transformation of the phenyl dimethoxy open chain into a rigid phenyl dioxy ring

When comparing the structure of Lead **I** and Lead **II**, we found they share some common characteristics, e.g., two Nitrogen atoms are separated by a carbon chain; both Nitrogens are connected by a hydrophobic site. Especially, the rotation of alkyl chain in Lead **II** may lead to a complete overlap with Lead **I** skeleton (Figure 16). Although their binding affinity and selectivity are completely different, the coincident skeleton overlap of two leads interests us to find out whether the modification on the same spot with the same groups will elicit similar binding effect in these two structural classes.

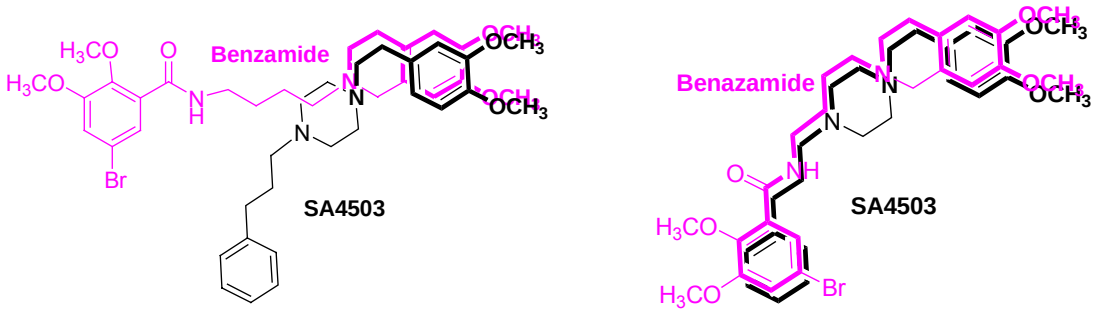


Figure 16 The skeleton overlap of Lead I and Lead II

The first modification comes into our mind is the phenyl dimethoxy on the right side of Benzamide. With the design previously proposed for Lead **I** in mind (Figure 11), we decide to make the same change on Lead **II**. We are curious to know: will the transformation of open chain into rigid dioxy ring cause the sigma binding of benzamide analogs to change in the same direction just like that of Lead **I** counterparts (Figure 17)? will the resulted tricyclic system contribute in binding with sigma receptor?

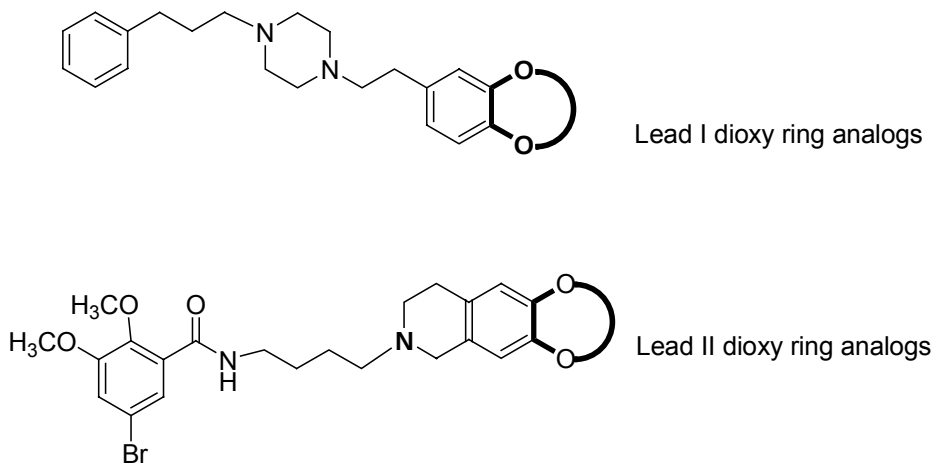


Figure 17 Proposed rigid ring analogs of Lead I and Lead II

1.3.2b.2 Transformation from the rigid tetrahydroisoquinoline ring into a freely rotated amine chain

In **1.3.2b.1**, we use the idea of increasing the rigidity of molecule to study the structure-activity relationship. Can the opposite idea: decreasing the rigidity, be applied to Lead **II**? The confined structure of tetrahydroisoquinoline is the right spot to consider.

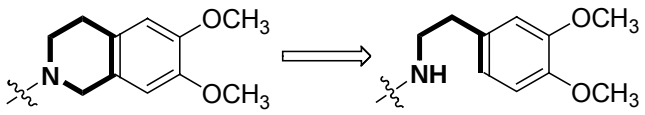


Figure 18 Deconstruction of tetrahydroisoquinoline ring

By employing "Deconstruction" method, a methylene unit will be removed so that the N atom that originally fixed by tetrahydroisoquinoline ring will have more freedom of rotation (Figure 18). This modification will help us to understand how important a rigid tetrahydroisoquinoline ring is to maintain high sigma2 selectivity in this series. On the other side, if the basic N is a core binding element, the change from a tertiay amine to a

secondary amine would most likely cause a difference in binding with sigma receptor due to the decreased steric hindrance when approaching N atom (Figure 19). This change is supposed to increase the easiness of forming hydrogen bond between sigma receptor and the benzamide ligand. Will this convenience contribute to the binding of either subtype?

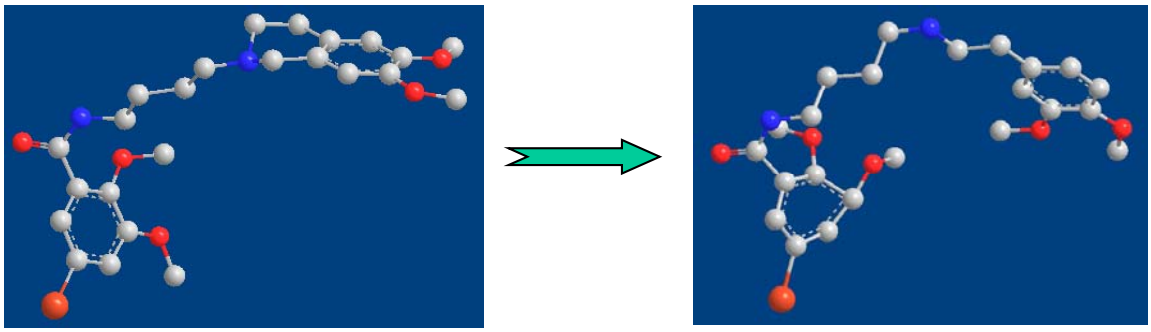


Figure 19 The 3D comparison of Lead II and its less rigid amine analog

1.3.3 Summary on our goals

This reseach project is about the structural modifications of two lead compounds. The modification of Lead **I**, **SA4503**, is based on the study of Elsinga et al in 2002,[27] where the replacement of a methoxy group of **SA4503** by fluoroethoxy resulted in a dramatic change in binding properties. The radiolabelled **SA4503** and its fluoroethoxy analog **FESA4503** have both shown great potential as PET imaging agents. The sensitivity of sigma receptor to the structural change of **SA4503** phenolic side chain interests us to make a deeper SAR investigation on this moiety. Our plan includes the exploration of bulk tolerance of the hydrophobic binding site, the effect of halogen and double bond, and the effect of rigidity. The possibility of finding new SPECT imaging agent by using **SA4503** analogs will also be discussed.

Lead **II** is a conformationally flexible benzamide that is reported to be a highly sigma2 selective ligand. Considering about the skeleton similarity of Lead **I** and Lead **II**, we want to investigate the effect of rigidity with the same method used for Lead **I** series compounds. Another modification made by transforming a tetrahydroisoquinoline ring into a chain will be able to indicate how important the tetrahydroisoquinoline is for selective sigma2 binding.

The methods that will be involved in this project will include organic synthesis, *in vitro* binding assay, radiolabelling, lipophilicity measurement, and biodistribution study (Figure 20).

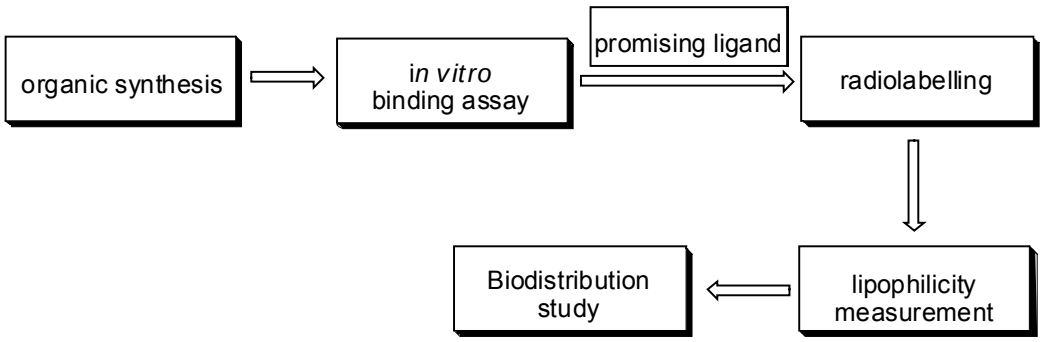


Figure 20 The flowchart of working process

In the process of doing the above investigation, the result obtained at each stage may affect the original proposal to change toward different directions, e.g. if the structure-activity relationship study on the phenolic side chain of **SA4503** doesn't yield any selective ligand, we may switch our interest to another spot; or if the lipophilicity of ligand is too high, we may work on different groups to lower the lipophilicty, and so on.

CHAPTER 2

EXPERIMENTAL

2.1 Organic Synthesis

Chemicals and solvents were reagent grade and used as received from commercial sources unless otherwise stated. 4-*O*-desmethyl **SA4503** (**1a-5**) was synthesized by using the procedure of Kawamura.[43] Known compounds such as **SA4503** (**1a-6**),[60] **FESA4503** (**1a-7**),[61] E/Z vinylstannylated alkylating agents (**1b-4, 1b-5**)[62, 63] and 5-bromo-N-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl)]-2,3-dimethoxy-benzamide[54] were prepared according to the same methods of literature. Melting points were determined in open glass capillaries with a melting-point apparatus and were uncorrected. ^{1}HNMR spectra were obtained on a Bruker ARX-250 (250 MHz), DRX-300 (300 MHz), DRX-500 (500 MHz) spectrometer. Copies of all spectra are found in **Appendix I**. Chemical shifts are reported in ppm (δ) relative to internal Me_4Si in $CDCl_3$ unless otherwise stated. HRMS via electron ionization was performed at the University of Missouri-Columbia Mass spectrometry Facility. Elemental analysis was determined by Atlantic Microlab, Inc. Norcross, GA. Analytical TLC was conducted on Polygram SIL G/UV254. Preparative TLC was conducted on silica gel plate (20×20 cm, 1000 microns) bought from Analtech Inc. Newark, DE. with preabsorbent zone and UV 254. Chromatography was performed using Silicycle ultra pure silica gel (230-400 mesh) under air pressure. Radial chromatography was carried out using a Chromatotron® (Harrison Research) equipped with 4-mm silica gel 60 with gypsum (EM Science) thick-layer plates. Analytical reversed-phase HPLC equipment consisted of a Rheodyne 7125 injector,

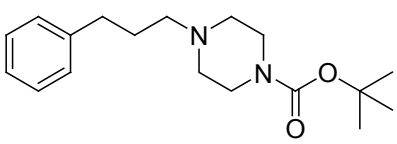
Waters 1525 EF binary pump, Waters 2487 dual λ absorbance detector, and a Waters symmetry® C-18 Nova-Pak stainless steel column (4.6 x 150 mm, 5 μm).

The 1,4-disubstituted piperazines **1a-5**~**1h-4** (except **1c-1** and **1c-4**) were made into diHCl salts to make them easier to dry and weigh. A general method was to first dissolve the piperazine free base into EtOH, and then to this solution was added an excess amount of concentrated hydrochloric acid. The mixture was evaporated to dryness to yield a white salt. This diHCl salt was then recrystallized from EtOH or a mixture of solvents to give the pure salt.

The benzamide series compounds **2a-5**~**2b-6** were made into oxalate salts. A general method was to dissolve the benzamide free base into EtOH, to this solution was added 0.9 equivalent of oxalic acid. The mixture was then evaporated to dryness and the oxalate salt was recrystallized by EtOAc or EtOH.

The full names of chemicals with abbreviations are found in **Appendix II**.

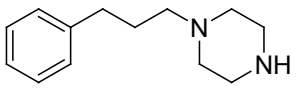
tert-butyl 4-(3-phenylpropyl)piperazine-1-carboxylate (1a-2)



The oil 1-chloro-3-phenylpropane (**1a-1**, 9.50 g, 65 mmol), and tert-butyl 1-piperazine carboxylate (11.50 g, 65 mmol) was reacted in the presence of potassium carbonate (26 g, 190 mmol) and sodium iodide (9.50 g, 65 mmol) in N, N-dimethyl formamide (280 mL) at 50º C overnight. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and then dried on $MgSO_4$, filtered and evaporated to dryness. The

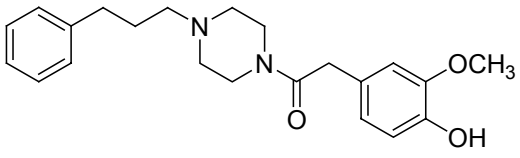
residue was purified by column chromatography (n-hexane/ethyl acetate, 1:4) to give **1a-2** as oil (10.80 g, 63% recovery). R_f=0.36 (n-hexane/ethyl acetate, 1:2). ^{1}H NMR: ($CDCl_3$, δ) 1.46 (s, 9H, CH_3), 1.76-1.88 (m, 2H, CH_2), 2.33- 2.39 (m, 6H,CH_2), 2.61-2.67 (t, 2H, CH_2), 3.41-3.45 (t, 4H, CH_2), 7.15-7.31 (m, 5H, CH).

1-(3-phenylpropyl)piperazine (1a-3)



The oil of **1a-2** (10.80 g, 35.48 mmol), 4N hydrochloric acid (78 mL) and 1,4-dioxane (31.25 g, 355 mmol) were mixed at 0º C, and then diluted with methanol (78 mL). The mixture was stirred at room temperature overnight, then evaporated to dryness. Recrystallization gave **1a-3** as diHCl salt (6.10 g, 84%). ^{1}H NMR: (free base, $CDCl_3$, δ) 1.75 (s, 1H, NH), 1.76-1.86 (m, 2H, CH_2), 2.32-2.39 (m, 6H,CH_2), 2.60-2.65 (t, 2H, CH_2), 2.87-2.90 (t, 4H, CH_2), 7.14-7.19 (m, 3H, CH), 7.24-7.29 (m, 2H, CH).

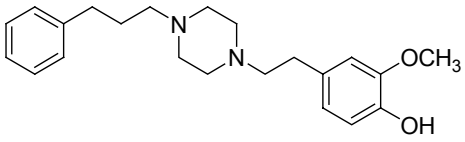
2-(4-hydroxy-3-methoxyphenyl)-1-(4-(3-phenylpropyl)piperazin-1-yl)ethanone (1a-4)



The HCl salt of **1a-3** (6.10 g, 29.9 mmol), homovanillic acid (5.45 g, 29.9 mmol), 1-hydroxy benzotriazole hydrate (4.02 g, 29.9 mmol), 4-methylmorpholine, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.74 g, 29.9 mmol) and dichloromethane (246 mL) were mixed under nitrogen at 0º C. The mixture was stirred at room temperature overnight, and then evaporated to dryness. The residue was diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated

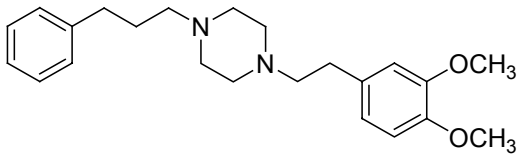
sodium chloride solution, dried on $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography ($CHCl_3$/MeOH, 25:1) to give **1a-4** as oil (9.20 g, 84%). ^{1}H NMR: ($CDCl_3$, δ) 1.75-1.84 (m, 2H, CH_2), 2.22- 2.39 (m, 6H, CH_2), 2.59-2.65 (t, 2H, CH_2), 3.43-3.47 (t, 2H, CH_2), 3.62-3.66 (t, 4H, CH_2), 3.86 (s, 3H, CH_3), 5.67 (br, 1H, OH), 6.65-6.66 (dd, 1H, CH), 6.77-6.78 (d, 1H, CH), 6.82-6.85 (d, 1H, CH), 7.14-7.20 (m, 3H, CH), 7.24-7.30 (m, 2H, CH).

2-methoxy-4-(2-(4-(3-phenylpropyl)piperazin-1-yl)ethyl)phenol (4-*O*-desmethyl SA4503, 1a-5)



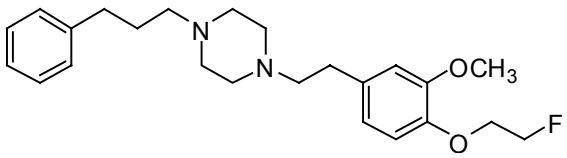
A solution of **1a-4** (9.20 g, 25 mmol) in THF (230 mL) was added dropwise into a solution of lithium aluminum hydride (2.81g, 73.6 mmol) in THF (230 mL) under nitrogen at 0º C. The mixture was stirred at room temperature overnight, then ethyl acetate (92 mL) and 2N hydrochloric acid (23 mL) was added at 0º C. Then sodium hydrogen carbonate was added into the mixture until no more bubble formed. The filtered solution was diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried on $MgSO_4$, filtered and evaporated to dryness. The residue was diluted with absolute ethanol and precipitated with 47% hydrobromic acid to give compound **1a-5** (7.70 g, 87%) as an HBr salt. ^{1}H NMR: (free base, $CDCl_3$, δ) 1.77-1.89 (m, 2H, CH_2), 2.36- 2.76 (m, 16H,CH_2), 3.86 (s, 3H, CH_3), 6.65-6.69 (dd, 1H, CH), 6.77-6.78 (d, 1H, CH), 6.82-6.85 (d, 1H, CH), 7.14-7.20 (m, 3H, CH), 7.24-7.30 (m, 2H, CH).

1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine (SA4503, 1a-6)



The mixture of **1a-5** HBr salt (218 mg, 0.424 mmol) and NaH (195 mg, 8.13 mmol, washed by hexane) in DMF (63 mL) was heated at 80 ºC for 10 min in sealed tube before CH_3I (240 mg, 1.692 mmol) was added into this solution. The mixture was reacted for 5 min at 120º C and then 2 hours at room temperature. The solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, saturated sodium chloride solution, and dried on $MgSO_4$. The ethyl acetate solution was filtered and evaporated to dryness. The residue was purified by preparative TLC ($CHCl_3/CH_3OH$, 20:1) to give **1a-6** (100 mg, 64%). ^1H NMR: ($CDCl_3$, δ) 1.80-1.89 (m, 2H, CH_2), 2.36- 2.78 (m, 16H,CH_2), 3.84 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.71-6.80 (m, 3H, CH), 7.14-7.30 (m, 5H, CH).

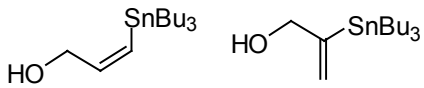
1-(4-(2-fluoroethoxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine (FESA4503, 1a-7)



To a sodium methanolate solution (sodium: 55 mg, 2.4 mmol; Methanol: 1.8 mL), **1a-5** HBr salt (200 mg, 0.389 mmol) and 1-bromo-2-fluoroethane (98 mg, 0.778 mmol) were added. The mixture was refluxed under the protection of dry nitrogen for 16 h. The reaction mixture was passed into water and extracted with ethyl acetate. The organic layer was dried on $MgSO_4$ and evaporated to dryness. The crude was applied to a preparative TLC to give **1a-7** as an oil (93 mg, 60%). ^1H NMR: ($CDCl_3$, δ) 1.79-1.89 (m, 2H, CH_2), 2.38- 2.77 (m, 16H,CH_2), 3.85 (s,

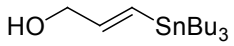
3H, CH_3), 4.18-4.30 (dt, 2H, CH_2, *J*=4.3, 27.6Hz), 4.66-4.84 (dt, 2H, CH_2F, *J*=4.3, 47.4Hz), 6.70-6.85 (m, 3H, CH), 7.15-7.30 (m, 5H, CH).

(*Z*)-3-(tributylstannyl)prop-2-en-1-ol (1b-2)



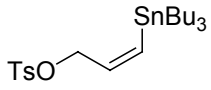
Propargyl alcohol (2.42 g, 43.2 mmol) was treated with tributyltin hydride (4.19 g, 14.4 mmol) and AIBN (52 mg, 0.31 mmol). After heating at 60º C for 2 h, the excess propargyl alcohol was removed under reduced pressure. The crude was applied to a column and eluted with n-hexane/ethyl acetate (96:4, R_f=0.52). Eluent was monitored by TLC (hexane/EtOAc, 8:1) and visualized by ethanolic phosphomolybdic acid. The **1b-2** and terminal alkene isomer were obtained as an inseparable mixture (2.0 g, 40%).

(*E*)-3-(tributylstannyl)prop-2-en-1-ol (1b-3)



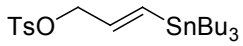
Propargyl alcohol (5.60 g, 100 mmol) was treated with tri-n-butyltin hydride (37.84 g, 130 mmol) and AIBN (0.10 g, 0.73 mmol). After heating at 80° C for 2 h, the excess propargyl alcohol was removed under reduced pressure. The crude was purified by the same method described for **1b-2** to yield **1b-3 (**9.9 g, 36%, R_f=0.33). ^{1}H NMR: ($CDCl_3$, δ) 0.85-0.93 (m, 15H, n-Bu), 1.28-1.54 (m, 12H, n-Bu), 3.91-4.03 (dd, 2H, CH_2, J=1.1, 4.9Hz), 6.03-6.27 (m, 2H, CH=CH).

(*Z*)-3-(tributylstannyl)allyl 4-methylbenzenesulfonate (1b-4)



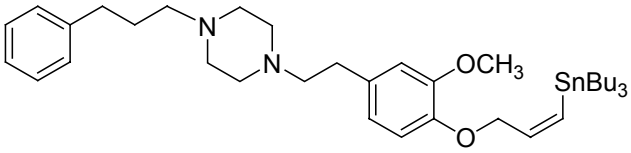
To a solution of **1b-2** (9.15 g, 26.36 mmol) in diethyl ether (60 mL) under N_2 and cooled to -25° C was added TsCl (5.59 g, 29.3 mmol) in diethyl ether (40 mL). Potassium trimethylsilanolate (17.00 g, 132.3 mmol) was added in portions over 30 min. The mixture was stirred vigorously at -25° C for 2 h, poured into ice water, and extracted with diethyl ether. The combined organic extracts were washed with ice cold water and dried by Na_2SO_4. Filtration, concentration by rotoevaporator at room temperature and chromatography (hexane/ethyl acetate, 98:2) gave **1b-4** (3.97 g, 30%) as colorless oil. ^{1}H NMR: ($CDCl_3$, δ) 0.81-0.88 (m, 15H, n-Bu), 1.20-1.48 (m, 12H, n-Bu), 2.42 (s, 3H, CH_3), 4.41-4.44 (dd, 2H, CH_2, J=0.76, 5.74Hz), 6.20-6.25 (d, 1H, CH, J=12.98Hz), 6.43-6.50 (dt, 1H, CH, J=6.4Hz, 13.0Hz), 7.30-7.34 (d, 2H, aromatic CH, J= 10 Hz), 7.75-7.79 (d, 2H, aromatic CH, J=6.6Hz).

(*E*)-3-(tributylstannyl)allyl 4-methylbenzenesulfonate (1b-5)



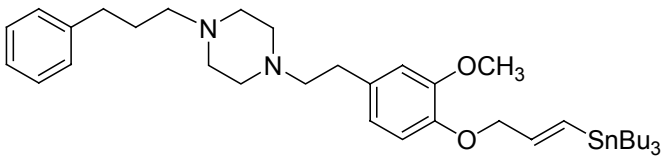
As described for **1b-4**, treatment of **1b-3** (18.80 g, 54.24 mmol) with TsCl (11.17 g, 58.64 mmol) and Potassium trimethylsilanolate (34.86 g, 271.4 mmol) gave **1b-5** (11.00 g, 40%) as a colorless oil. ^{1}H NMR: ($CDCl_3$, δ) 0.82-0.89 (m, 15H, n-Bu), 1.21-1.49 (m, 12H, n-Bu), 2.45 (s, 3H, CH_3), 4.53-4.55 (dd, 2H, CH_2, J=1.2, 6.0Hz), 5.88-5.96 (m, 1H, CH), 6.26-6.33 (d, 1H, CH, *J*=21.0Hz), 7.33-7.35 (d, 2H, aromatic CH, *J*= 8.1 Hz), 7.75-7.79 (d, 2H, aromatic CH, *J*=6.4Hz).

(*Z*)-1-(3-methoxy-4-(3-(tributylstannyl)allyloxy)phenethyl)-4-(3-phenylpropyl) piperazine (1b-6)



NaH (70 mg, 3 mmol) was added to a stirred solution of 4-*O*-desmethyl **SA4503** (**1a-5**) HCl salt (76 mg, 0.18 mmol) in 5 mL DMF under N_2 at ambient temperature. After 1 min, a solution of **1b-4** (180 mg, 0.36 mmol) in 1 ml DMF was added. After 90 min, the reaction was quenched by slow addition of saturated NH_4Cl and extracted with CH_2Cl_2. The extracts were washed with saturated $NaHCO_3$ and concentrated under reduced pressure. Chromatography ($CHCl_3$/MeOH, 20:1) gave **1b-6** (74 mg, 70%) as a yellow oil. ^{1}H NMR: ($CDCl_3$, δ) 0.85-0.96 (m, 15H, n-Bu), 1.27-1.46 (m, 12H, n-Bu), 1.79-1.95 (m, 2H, CH_2), 2.56-2.63 (m, 16H, CH_2), 3.84 (s, 3H, CH_3), 4.49-4.51 (dd, 2H, CH_2, *J*=1.1, 5.9Hz), 6.17-6.22 (dt, 1H, CH, *J*=1.1, 13.1Hz), 6.68-6.82 (m, 4H, alkene CH, aromatic CH), 7.17-7.29 (m, 5H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 7.93, 13.57, 27.19, 29.02, 33.16, 33.63, 53.11, 55.68, 57.93, 60.57, 72.32, 111.35, 114.13, 120.32, 125.64, 128.18, 133.01, 133.48, 142.01, 143.74, 146.31, 149.47.

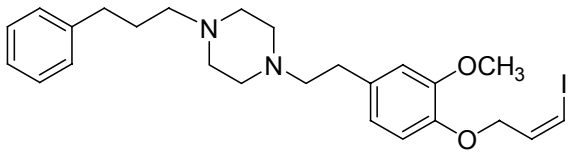
(*E*)-1-(3-methoxy-4-(3-(tributylstannyl)allyloxy)phenethyl)-4-(3-phenylpropyl) piperazine (1b-7)



As described for **1b-6**, NaH (48 mg, 1.98 mmol) was added to a stirred solution of 4-O-desmethyl **SA4503** HCl salt (51 mg, 0.12 mmol) in 3 mL DMF under N_2 at ambient temperature. After 1 min, a solution of **1b-5** (120 mg, 0.24 mmol) in 1 ml DMF was added. After 90 min, the reaction was quenched by slow addition of saturated NH_4Cl and extracted with

CH_2Cl_2. The extracts were washed with saturated $NaHCO_3$ and concentrated under reduced pressure. Chromatography ($CHCl_3$/MeOH, 20:1) gave **1b-7** (67 mg, 0.097 mmol) as yellow oil in 80% yield. ^{1}H NMR: ($CDCl_3$, δ) 0.86-0.93 (m, 15H, n-Bu), 1.26-1.51 (m, 12H, n-Bu), 1.79-1.90 (m, 2H, CH_2), 2.57-2.68 (m, 16H, CH_2), 3.87 (s, 3H, CH_3), 4.61-4.63 (dd, 2H, CH_2, *J*=1, 4.6Hz), 5.95-6.45 (m, 2H, CH=CH), 6.71-6.81 (m, 3H, aromatic CH), 7.18-7.28 (m, 5H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 9.35, 13.60, 27.16, 29.01, 33.13, 33.63, 53.09, 55.78, 57.93, 60.57, 72.52, 112.18, 113.59, 120.33, 125.66, 128.28, 131.83, 132.96, 142.00, 143.04, 146.34, 149.11.

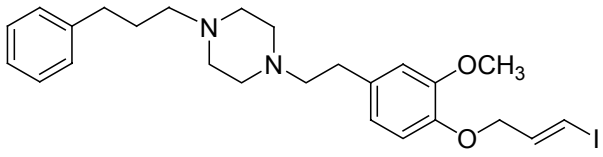
(*Z*)-1-(4-(3-iodoallyloxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine (1b-8)



To a solution of **1b-6** in CH_2Cl_2, was added 1.1 eq. I_2 in CH_2Cl_2. The reaction was stirred for 10 min at ambient temperature and quenched with 5% solution of $Na_2S_2O_5$. The organic layer was collected and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts was dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. Preparative TLC separation gave **1b-8** as a yellow oil in 55% yield. ^{1}H NMR: ($CDCl_3$, δ) 1.81-1.90 (m, 2H, CH_2), 2.37-2.85 (m, 16H, CH_2), 3.87 (s, 3H, OCH_3), 4.66-4.68 (dd, 2H, CH_2, *J*=1.8, 5.2 Hz), 6.43-6.47 (dt, 1H, *J*= 7.9, 1.8 Hz, CH), 6.59-6.66 (dt, 1H, *J*=7.9, 5.2 Hz, CH), 6.71-6.80 (m, 3H), 7.15-7.31 (m, 5H); ^{13}C NMR: ($CDCl_3$, δ) 28.56, 33.19, 33.68, 53.17, 55.83, 57.98, 60.55, 71.95, 83.09, 112.43, 113.66, 120.49, 125.69, 128.24, 128.32, 133.88, 137.60, 142.07, 145.76, 149.25; HRMS-EI: m/z calcd, 520.1587; found 521.1482 (MH^+);

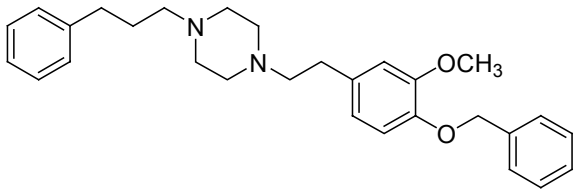
Anal. Calcd for $C_{25}H_{33}IN_2O_2 \cdot 2HCl$: C, 50.60; H, 5.95; N, 4.72. Found: C, 50.46; H, 5.92; N, 4.65; m.p. 228 °C.

(*E*)-1-(4-(3-iodoallyloxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine (1b-9)



As described for **1b-8**, treatment of **1b-7** with 1.1 eq. I_2 in CH_2Cl_2, gave, after work up and chromatography, **1b-9** as yellow oil in 56% yield. ^{1}H NMR: ($CDCl_3$, δ) 1.78-1.88 (m, 2H, CH_2), 2.37-2.78 (m, 16H, CH_2), 3.85 (s, 3H,OCH_3), 4.45-4.47 (dd, 2H, CH_2, *J*=1.4, 5.5Hz), 6.47-6.52 (dt, 1H, *J*= 1.4, 14.6 Hz, CH), 6.69-6.80 (m, 4H), 7.15-7.30 (m, 5H); ^{13}C NMR: ($CDCl_3$, δ) 28.53, 33.18, 33.64, 53.13, 55.80, 57.93, 60.48, 70.86, 79.86, 112.48, 113.99, 120.47, 125.68, 128.22, 128.30, 134.07, 140.85, 142.02, 145.65, 149.37; HRMS-EI: m/z calcd, 520.1587; found 521.1278 (MH^+); Anal. Calcd for $C_{25}H_{33}IN_2O_2 \cdot 2HCl$: C, 50.60; H, 5.95; N, 4.72. Found: C, 50.50; H, 5.91; N, 4.70; m.p. 233°C.

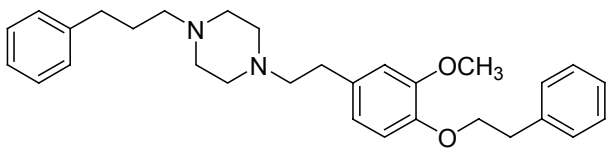
1-(4-(benzyloxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine (1c-1)



To a stirring solution of **1a-5** (250 mg, 0.70 mmol) in absolute EtOH (2.5 mL) was added K_2CO_3 (193 mg, 1.40 mmol) and benzyl bromide (192 mg, 1.12 mmol). The mixture was reacted under N_2 overnight and filtered through celite. After the evaporation of solvent, the crude was separated by prep TLC to give **1c-1** as yellowish solid (110 mg, 35%). m.p. 213 °C; ^{1}H NMR: ($CDCl_3$,

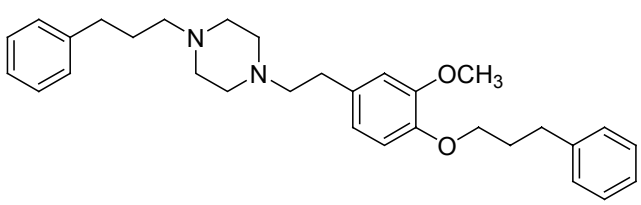
δ) 1.82-1.88 (m, 2H, CH_2), 2.38-2.77 (m, 16H, CH_2), 3.89 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 6.68-6.83 (m, 3H, CH), 7.19-7.46 (m, 10H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.60, 33.23, 33.70, 53.22, 55.94, 58.01, 60.61, 71.15, 112.63, 114.25, 120.51, 125.70, 127.20, 127.68, 128.25, 128.34, 128.44, 133.65, 137.36, 142.11, 146.47, 149.54.

1-(3-methoxy-4-phenethoxyphenethyl)-4-(3-phenylpropyl)piperazine (1c-2)



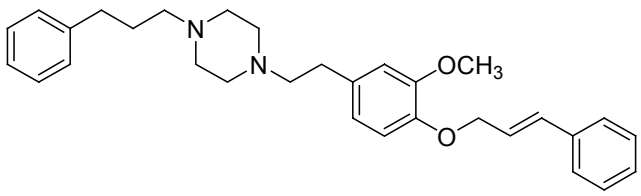
A mixture of **1a-5** (200 mg, 0.56 mmol), 40% KOH (1.12 mL), tetrabutylammonium hydroxide (TBAH, 1 M in methanol, 0.112 mL), and (2-bromoethyl)-benzene (1.80 g, 9.744 mmol) was heated at 50° C for 50 min. The reaction mixture was diluted with water (30 mL), extracted with dichloromethane (3×20 mL), washed with brine, dried by $MgSO_4$, and evaporated to dryness by vacuum. The residue was purified by column chromatography over silica gel ($CHCl_3$: Methanol=20:1) to give **1c-2** (113 mg, 82%). m.p. 252 °C; ^{1}H NMR: ($CDCl_3$, δ) 1.82-1.89 (m, 2H, CH_2), 2.38-2.78 (m, 16H, CH_2), 3.13-3.19 (t, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.18-4.24 (t, 2H, CH_2), 6.74-6.83 (m, 3H, CH), 7.19-7.31 (m, 10H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.61, 33.24, 33.71, 35.85, 53.22, 56.01, 57.99, 60.64, 69.99, 112.80, 113.55, 120.66, 125.68, 125.75, 126.43, 127.33, 128.29, 128.38, 128.45, 129.03, 133.43, 138.08, 142.10, 146.61, 149.41; Anal.Calcd for $C_{30}H_{38}N_2O_2 \cdot 2HCl$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.53; H, 7.64; N, 5.24.

1-(3-methoxy-4-(3-phenylpropoxy)phenethyl)-4-(3-phenylpropyl)piperazine (1c-3)



A mixture of **1a-5** (200 mg, 0.56 mmol), 40% KOH (1.1 mL), TBAH (1 M in methanol, 0.11 mL), and 1-bromo-3-phenylpropane (1.46 g, 7.308 mmol) was heated at 50 °C for 50 min. The reaction mixture was diluted with water (30 mL), extracted with dichloromethane (3×20 mL), washed with brine, dried by $MgSO_4$, and evaporated to dryness by vacuum. The residue was purified by column chromatography over silica gel ($CHCl_3$: Methanol=20:1) to give **1c-3** (214 mg, 81%). m.p. 227 °C; ^{1}HNMR: ($CDCl_3$, δ) 1.86-1.91 (p, 2H, CH_2), 2.13-2.18 (p, 2H, CH_2), 2.43-2.85 (m, 16H, CH_2), 3.86 (s, 3H, CH_3), 3.97-4.02 (t, 2H, CH_2), 6.71-6.80 (m, 3H, CH), 7.16-7.31 (m, 10H, CH); ^{13}CNMR: ($CDCl_3$, δ) 28.25, 30.77, 32.30, 33.59, 34.42, 52.80, 55.99, 58.52, 61.48, 68.23, 112.68, 113.58, 120.64, 125.77, 125.86, 125.88, 128.37, 128.39, 128.43, 128.49, 132.81, 141.53, 141.83, 146.89, 149.48; Anal.Calcd for $C_{31}H_{40}N_2O_2 \cdot 2HCl$: C, 68.24; H, 7.76; N, 5.13. Found: C, 67.94; H, 7.77; N, 5.12.

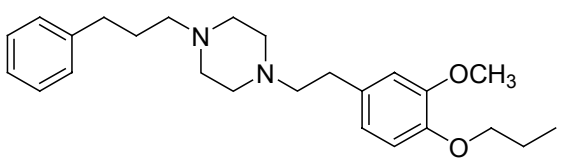
(*E*)-1-(4-(cinnamyloxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine (1c-4)



To a stirring solution of **1a-5** (250 mg, 0.70 mmol) in absolute EtOH, was added potassium carbonate (193 mg, 1.4mmol) and cinamyl bromide (220 mg, 1.12 mmol) at room temperature. After stirred for 28 h, the reaction mixture was diluted with 50 mL H_2O, and extracted with 3×20 mL CH_2Cl_2, dried on $MgSO_4$. The crude is separated by column

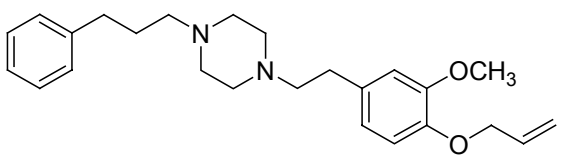
chromatography ($CHCl_3$: Methanol=20:1) to give **1c-4** as a white solid (187 mg, 56%). It was recrystallized by using EtOH. ^{1}H NMR: ($CDCl_3$, δ) 1.82-1.88 (p, 2H, CH_2), 2.38-2.80 (m, 16H, CH_2), 3.88 (s, 3H, OCH_3), 4.74-4.77 (dd, 2H, CH_2, J=1.2, 5.7Hz), 6.49 (dt, 1H, CH, J=5.7, 16Hz), 6.69-6.79 (m, 3H, CH), 6.86-6.89 (d, 1H, CH), 7.22-7.43 (m, 10H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.58, 33.24, 33.69, 53.20, 55.86, 58.00, 60.61, 69.84, 112.40, 113.72, 120.48, 124.77, 125.70, 126.53, 127.75, 128.24, 128.33, 128.47, 133.02, 133.51, 136.46, 142.10, 146.29, 149.34; Anal.Calcd for $C_{31}H_{38}N_2O_2$: C, 79.11; H, 8.14; N, 5.95. Found: C, 78.71; H, 8.10; N, 5.97.

1-(3-methoxy-4-propoxyphenethyl)-4-(3-phenylpropyl)piperazine (1d-1)



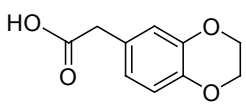
A mixture of **1a-5** (200 mg, 0.56 mmol), 40% KOH (1.1 mL), tetrabutylammonium hydroxide (1 M in methanol, 0.11 mL), and 1-Bromopropane (1.20 g, 9.744 mmol) was heated at 50 °C for 50 min. The reaction mixture was diluted with water (30 mL), extracted with dichloromethane (3×20 mL), washed with brine, dried by $MgSO_4$, and evaporated to dryness by vacuum. The residue was purified by column chromatography over silica gel ($CHCl_3$: Methanol=20:1) to give **1d-1** (201 mg, 90%). ^{1}H NMR: ($CDCl_3$, δ) 0.99-1.05 (t, 3H, CH_3), 1.77-1.89 (m, 4H, CH_2), 2.35-2.78 (m, 16H, CH_2), 3.84 (s, 3H, OCH_3), 3.91-3.96 (t, 2H, OCH_2), 6.70-6.80 (m, 3H, CH), 7.13-7.29 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 10.43, 22.49, 28.59, 33.20, 33.67, 53.20, 55.92, 57.96, 60.65, 70.57, 112.59, 113.19, 120.53, 125.68, 128.23, 128.32, 132.97, 142.07, 146.85, 149.29; Anal.Calcd for $C_{25}H_{36}N_2O_2 \cdot 2HCl$: C, 63.96; H, 8.16; N, 5.97. Found: C, 63.91; H, 8.13; N, 5.91; m.p. 212 °C.

1-(4-(allyloxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine (1d-2)



To a mixture of **1a-5** (250 mg, 0.70 mmol), 40% KOH (1.4 mL) and tetrabutylammonium hydroxide (1 M in methanol, 0.14 mL), Allyl bromide (1.5 g, 12.40 mmol) was added dropwise at 0° C. The mixture was then stirred at room temperature for 50 min. The reaction mixture was diluted with water (50 mL), extracted with dichloromethane (5×20 mL), washed with brine, dried by $MgSO_4$, and evaporated to dryness by vacuum. The residue was purified by column chromatography over silica gel ($CHCl_3$: Methanol=20:1) to give **1d-2** (160 mg, 57%). ^{1}H NMR: ($CDCl_3$, δ) 1.81-1.86 (m, 2H, CH_2), 2.36-2.76 (m, 16H, CH_2), 3.85 (s, 3H, OCH_3), 4.55-4.58 (ddd, 2H, CH_2, J=5.4, 1.5, 1.5Hz), 5.23-5.28 (ddt, 1H, J=10.5, 1.5, 1.5Hz), 5.35-5.42 (ddt, 1H, J=17.1, 1.5, 1.5Hz), 6.00-6.13 (ddt, 1H, J=17.4, 10.5, 5.4Hz), 6.70-6.81 (m, 3H, CH), 7.17-7.29 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.58, 33.21, 33.69, 53.18, 55.85, 57.97, 60.61, 69.94, 112.43, 113.60, 117.72, 120.44, 125.72, 128.26, 128.35, 133.37, 133.53, 142.07, 146.27, 149.30; Anal. Calcd for $C_{25}H_{34}N_2O_2 \cdot 2HCl$: C, 64.23; H, 7.76; N, 5.99. Found: C, 64.33; H, 7.71; N, 5.96; m.p. 222 °C.

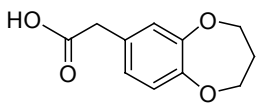
3,4-(Ethylenedioxy)phenylacetic acid (1e-2)



To a solution of 3,4-dihydroxyphenylacetic acid (500 mg, 3 mmol) and 1,2–dibromoethane (1.13 g, 6 mmol) in 5 mL of ethylene glycol was added anhydrous K_2CO_3 (1.24 g, 9 mmol). The mixture was heated at 120° C for 4.5 h. After cooling, the reaction mixture was added 50 mL water to dilute, acidified by 2N

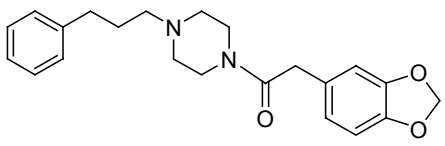
HCl to pH<1, and extracted by 3×20 mL EtOAc. The organic layer was evaporated to dryness and purified by column chromatography (EtOAc: Hexane=40:60, stained by Cerium molybdate solution) to give **1e-2** as a light yellow oil (301 mg, 52%). ^{1}H NMR: ($CDCl_3$, δ) 3.56 (s, 2H, CH_2), 4.23 (s, 4H, CH_2), 6.75-6.87 (m, 3H, CH), 11.64 (s, 1H, -COOH).

3,4-(Propylenedioxy)phenylacetic acid (1e-3)



To a solution of 3,4-dihydroxyphenylacetic acid (500 mg, 3 mmol) and 1,3–dibromopropane (1.21 g, 6 mmol) in 5 mL of ethylene glycol was added anhydrous K_2CO_3 (1.24 g, 9 mmol). The mixture was heated at 120 °C for 4.5 h. After cooling, the reaction mixture was added 50 mL water to dilute, acidified by 2N HCl to PH<1, and extracted by 3×20 mL EtOAc. The organic layer was evaporated to dryness and purified by column chromatography (EtOAc: Hexane=40:60, stained by Cerium molybdate solution) to give **1e-3** as a light yellow solid (260 mg, 42%). ^{1}H NMR: (CDCl3, δ) 2.14-2.23 (p, 2H, CH_2), 3.55 (s, 2H, CH_2), 4.18-4.24 (m, 4H, CH_2), 6.81-6.95 (m, 3H, CH), 10.50 (br, 1H, -COOH).

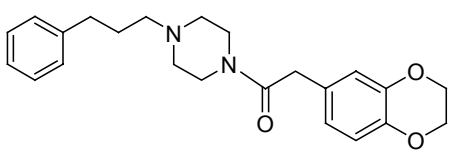
2-(3,4-methylenedioxy)phenyl-1-(4-(3-phenylpropyl)piperazin-1-yl)ethanone (1e-4)



Phenylpropyl piperazine (170 mg, 0.833 mmol), 3,4-(methylenedioxy)phenylacetic acid (150 mg, 0.833 mmol), 1-hydroxy benzotriazole hydrate (112 mg, 0.833 mmol), 4-methylmorpholine (251 mg, 2.51 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (160 mg, 0.833 mmol) and

dichloromethane (7 mL) were mixed under nitrogen at 0 °C. The mixture was stirred at room temperature overnight, and then evaporated to dryness. The residue was diluted saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution. The solution of ethyl acetate was dried on $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography to **1e-4** (288 mg, 94%) ^{1}H NMR: ($CDCl_3$, δ) 1.76-1.81 (m, 2H, CH_2), 2.25-2.39 (m, 6H, CH_2), 2.60-2.65 (t, 2H, CH_2), 3.43-3.46(t, 2H, CH_2), 3.62-3.65 (t, 4H, CH_2), 5.92 (s, 2H, OCH_2O), 6.66-6.75 (m, 3H, CH), 7.15-7.27 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.32, 33.40, 40.37, 41.69, 45.95, 52.62, 53.05, 57.53, 100.89, 108.26, 109.04, 121.52, 125.73, 128.24, 128.28, 128.61, 141.84, 146.31, 147.79, 169.32.

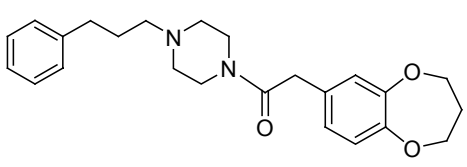
2-(3,4-ethylenedioxy)phenyl-1-(4-(3-phenylpropyl)piperazin-1-yl)ethanone (1e-5)



Phenylpropyl piperazine (316 mg, 1.55 mmol), **1e-2** (301 mg, 1.55 mmol), 1-hydroxy benzotriazole hydrate (209 mg, 1.55 mmol), 4-methylmorpholine (470 mg, 4.65 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (298 mg, 1.55 mmol) and dichloromethane (15 mL) were mixed under nitrogen at 0 °C. The mixture was stirred at room temperature overnight, and then evaporated to dryness. The residue was diluted saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution. The solution of ethyl acetate was dried on $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography to **1e-5** (577 mg, 98%) ^{1}H NMR: ($CDCl_3$, δ) 1.72-1.84 (p, 2H, CH_2), 2.24-2.39 (m, 6H, CH_2), 2.59-2.65 (t, 2H, CH_2), 3.41-3.45 (t, 2H, CH_2), 3.61-3.65 (t, 2H,

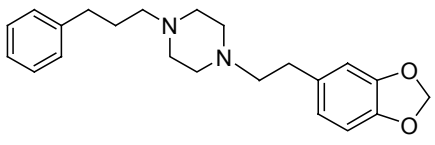
CH_2), 3.59 (s, 2H, CH_2), 4.20 (s, 4H, OCH_2CH_2O), 6.66-6.81 (m, 3H, CH), 7.15-7.30 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.35, 33.44, 40.04, 41.71, 46.02, 52.66, 53.07, 57.54, 64.22, 64.26, 117.31, 121.46, 125.75, 128.15, 128.26, 128.33, 141.91, 142.33, 143.52, 169.41.

2-(3,4-propylenedioxy)phenyl-1-(4-(3-phenylpropyl)piperazin-1-yl)ethanone (1e-6)



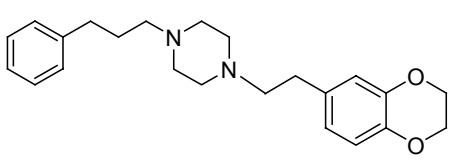
Phenylpropyl piperazine (255 mg, 1.25 mmol), **1e-3** (260 mg, 1.25 mmol), 1-hydroxy benzotriazole hydrate (169 mg, 1.25 mmol), 4-methylmorpholine (379 mg, 3.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (240 mg, 1.25 mmol) and dichloromethane (12 mL) were mixed under nitrogen at 0 °C. The mixture was stirred at room temperature overnight, and then evaporated to dryness. The residue was diluted saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution. The solution of ethyl acetate was dried on $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography to **1e-6** (443 mg, 90%) ^1H NMR: ($CDCl_3$, δ) 1.60-1.66 (p, 2H, CH_2), 1.95-2.00 (p, 2H, CH_2), 2.01-2.11 (t, 2H, CH_2), 2.15-2.18 (t, 2H, CH_2), 2.20-2.22 (t, 2H, CH_2), 2.45-2.48 (t, 2H, CH_2), 3.24-3.28 (, 2H, CH_2), 3.45 (s, 2H, CH_2), 3.47-3.49 (t, 2H, CH_2), 3.98-4.01 (m, 4H, CH_2), 6.62-6.77 (m, 3H, CH), 7.00-7.15 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.33, 31.85, 33.39, 39.82, 41.68, 46.00, 52.62, 53.01, 57.47, 70.43, 121.65, 123.40, 125.72, 128.24, 130.19, 141.88, 149.91, 151.14, 169.22.

1-(3,4-methylenedioxy phenethyl)-4-(3-phenylpropyl)piperazine (1e-7)



The solution of **1e-4** (288 mg, 0.787 mmol) in THF (7 mL) was dropped into the suspension of $LiAlH_4$ (89.6 mg, 2.36 mmol) in THF (7 mL) under nitrogen at 0 °C. The mixture was stirred at room temperature for 7.5 h and then added ethyl acetate (3 mL), 2N HCl (1 mL) at 0°C followed by the addition of $NaHCO_3$ until formation of CO_2 stopped. The mixture was filtered, diluted with $NaHCO_3$ and extract with ethyl acetate, dried on $MgSO_4$. The crude was separated by preparative TLC to give **1e-7** as a yellow oil (90 mg, 32.5%). m.p. 230 °C; ^{1}H NMR: (diHCl salt, D_2O, δ) 1.96-2.03 (p, 2H, CH_2), 2.63-2.69 (t, 2H, CH_2), 2.90-2.96 (t, 2H, CH_2), 3.11-3.17 (t, 2H, CH_2), 3.32-3.38 (t, 2H, CH_2), 3.50 (br, 8H, CH_2), 5.88 (s, 2H, OCH_2O), 6.70-6.81 (m, 3H, CH), 7.19-7.34 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.57, 33.27, 33.65, 53.17, 57.94, 60.68, 100.66, 108.08, 109.07, 121.33, 125.67, 128.22, 128.31, 134.05, 142.06, 145.69, 147.46; Anal.Calcd for $C_{22}H_{28}N_2O_2 \cdot 2HCl$: C, 62.12; H, 7.11; N, 6.59. Found: C, 61.85; H, 7.04; N, 6.55.

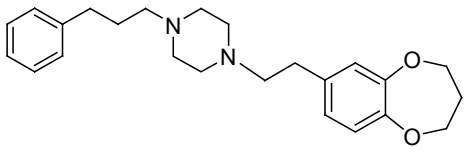
1-(3,4-ethylenedioxy phenethyl)-4-(3-phenylpropyl)piperazine (1e-8)



The solution of **1e-5** (484 mg, 1.27 mmol) in THF (12 mL) was added dropwise to a the suspension of $LiAlH_4$ (145 mg, 3.81 mmol) in THF (12 mL) under nitrogen at 0 °C. The mixture was stirred at room temperature for 7.5 h and then added ethyl acetate (10 mL), 2N HCl (10 mL) at 0 °C followed by the addition of $NaHCO_3$ until formation of CO_2 stopped. The mixture was filtered, diluted with $NaHCO_3$

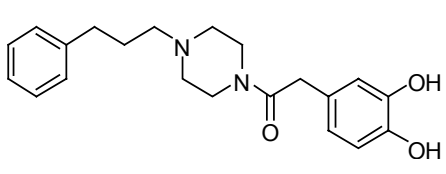
and extract with 3×10 mL ethyl acetate, dried on $MgSO_4$. The crude was separated by column chromatography to give **1e-8** as a light yellow oil (340 mg, 73%). ^{1}H NMR: ($CDCl_3$, δ) 1.81-1.90 (p, 2H, CH_2), 2.36-2.74 (m, 16H, CH_2), 4.19 (s, 4H, OCH_2CH_2O), 6.65-6.80 (m, 3H, CH), 7.15-7.31 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.61, 32.81, 33.69, 53.19, 57.97, 60.60, 64.21, 117.02, 117.24, 121.53, 125.70, 128.25, 128.35, 133.56, 141.77, 142.12, 143.26; Anal.Calcd for $C_{23}H_{30}N_2O_2$·2HCl: C, 62.87; H, 7.34; N, 6.38. Found: C, 63.14; H, 7.49; N, 6.39; m.p. 213 °C.

1-(3,4-propylenedioxy phenethyl)-4-(3-phenylpropyl)piperazine (1e-9)



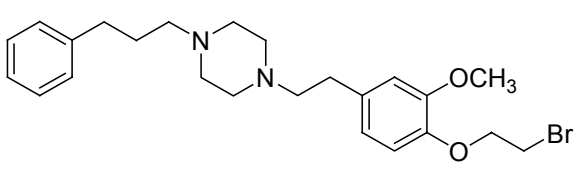
The solution of **1e-6** (390 mg, 0.99 mmol) in THF (12 mL) was added dropwise into the suspension of $LiAlH_4$ (113 mg, 2.97 mmol) in THF (12 mL) under nitrogen at 0 °C. The mixture was stirred at room temperature for 7.5 h and then added ethyl acetate (10 mL), 2N HCl (10 mL) at 0°C followed by the addition of $NaHCO_3$ until formation of CO_2 stopped. The mixture was filtered, diluted with $NaHCO_3$ and extract with 3×10 mL ethyl acetate, dried on $MgSO_4$. The crude was separated by column chromatography to give **1e-9** as a light yellow oil (321 mg, 85%). ^{1}H NMR: ($CDCl_3$, δ) 1.79-1.89 (p, 2H, CH_2), 2.11-2.19 (p, 2H, CH_2), 2.37-2.75 (m, 16H, CH_2), 4.14-4.20 (2t, 4H, -CH_2O), 6.74-6.91(m, 3H, CH), 7.15-7.30 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.63, 31.97, 32.69, 33.71, 53.20, 58.00, 60.46, 70.43, 121.34, 121.56, 123.42, 125.72, 128.27, 128.36, 135.60, 142.12, 149.38, 150.95; Anal.Calcd for $C_{24}H_{32}N_2O_2$·2HCl: C, 63.57; H, 7.56; N, 6.18. Found: C, 63.44; H, 7.71; N, 6.16; m.p. 212 °C.

2-(3,4-dihydroxyphenyl)-1-(4-(3-phenylpropyl)piperazin-1-yl)ethanone (1e'-1)



Phenylpropyl piperazine (1.5 g, 7.35 mmol), 2-(3,4-dihydroxyphenyl) acetic acid (1.24 g, 7.35 mmol), 1-hydroxy benzotriazole hydrate (1.0 g, 7.35 mmol), 4-methylmorpholine (2.5 g, 22 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 g, 7.82 mmol) and dichloromethane (60 mL) were mixed under nitrogen at 0 °C. The mixture was stirred at room temperature overnight, and then evaporated to dryness. The residue was diluted saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution. The solution of ethyl acetate was dried on $MgSO_4$, filtered and evaporated to dryness to give a solid. The solid was recrystallized from a mixture of EtOH and EtOAc to give **1e'-1** as a crystal in pink color (1.27 g, 49%) m.p. 168-169 °C. ^{1}H NMR: (DMSO, δ) 1.62-1.74 (p, 2H, CH_2), 2.20-2.25 (t, 6H, CH_2), 2.49-2.58 (t, 2H, CH_2), 3.36-3.48 (m, 6H, CH_2), 6.43-6.65 (m, 3H, CH), 7.11-7.28 (m, 5H, CH), 8.75 (br, 2H, OH); ^{13}C NMR: (DMSO, δ) 28.43, 33.23, 45.94, 52.82, 53.27, 57.37, 115.87, 116.34, 119.79, 126.03, 126.74, 128.61, 128.69, 142.39, 144.13, 145.51, 169.54. Anal.Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.89; H, 7.36; N, 7.85.

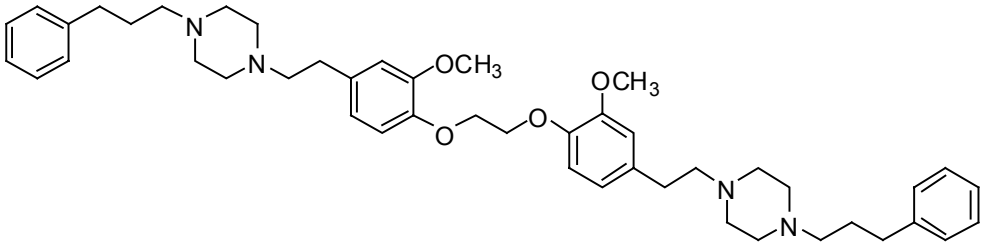
1-(4-(2-bromoethoxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine (1f-1a)



A mixture of **1a-5** (400 mg, 1.13 mmol), 40% KOH (2.2 mL), TBAH (1 M in methanol, 0.22 mL), and 1,2-dibromoethane (0.69 g, 3.66 mmol) was heated at 50° C for 50 min. The reaction mixture

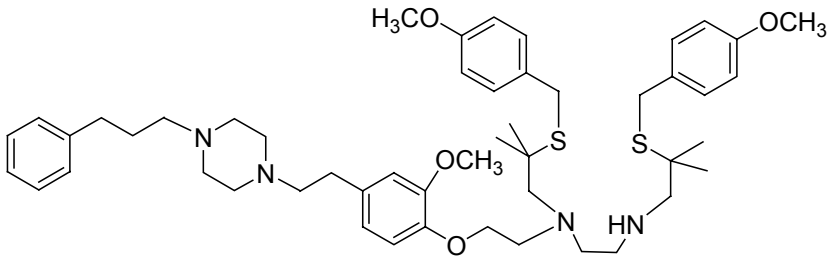
was diluted with water (60 mL), extracted with dichloromethane (3×20 mL), washed with brine, dried by $MgSO_4$, and evaporated to dryness by vacuum. The residue was purified by column chromatography over silica gel ($CHCl_3$: Methanol=20:1) to give **1d-1** (430 mg, 82.5%). ^{1}H NMR: ($CDCl_3$, δ) 1.77-1.89 (m, 2H, CH_2), 2.35-2.78 (m, 16H, CH_2), 3.59-3.64 (t, 2H, CH_2), 3.84 (s, 3H, CH_3), 4.25-4.31 (t, 2H, CH_2), 6.70-6.84 (m, 3H, CH), 7.14-7.30 (m, 5H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.58, 29.02, 33.23, 33.67, 53.19, 55.95, 57.97, 60.51, 69.47, 112.96, 115.25, 120.68, 125.69, 128.24, 128.33, 134.74, 142.08, 145.67, 149.76; Anal.Calcd for $C_{24}H_{33}BrN_2O_2 \cdot 2HCl$: C, 53.94; H, 6.60; N, 5.24. Found: C, 53.94; H, 6.70; N, 5.24.

1,2-bis(2-methoxy-4-(2-(4-(3-phenylpropyl)piperazin-1-yl)ethyl)phenoxy)ethane (1f-1b)



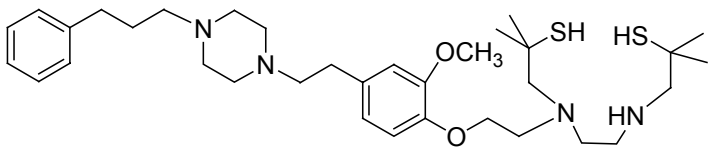
A mixture of **1a-5** (1.10 g, 3.10 mmol), 40% KOH (6 mL), TBAH (1M in methanol, 0.6 mL), and 1,2-dibromoethane (1.88 g, 10 mmol) was heated at 50°C overnight. The reaction mixture was diluted with water (90 mL), extracted with dichloromethane (3×60 mL), washed with brine, dried by $MgSO_4$, and evaporated to dryness under vacuum. The residue was purified by column chromatography over silica gel ($CHCl_3$: methanol=20:1) to give **1f-1b** (1.79 g, 80%). ^{1}HNMR: ($CDCl_3$, δ) 1.79-1.89 (m, 2H, CH_2), 2.34-2.78 (m, 16H, CH_2), 3.85 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 6.71-6.91 (m, 3H, CH), 7.16-7.31 (m, 5H, CH); ^{13}C NMR ($CDCl_3$, δ) 28.6, 33.2, 33.7, 53.2, 55.9, 60.6, 67.7, 112.7, 114.2, 120.6, 125.7, 128.2, 128.3, 133.9, 142.1, 146.4, 149.5.

N^1-(2-(2-methoxy-4-(2-(4-(3-phenylpropyl)piperazin-1-yl)ethyl)phenoxy)ethyl)-N^1,N^2-bis(2-(4-methoxybenzylthio)-2-methylpropyl)ethane-1,2-diamine (1f-2)



A mixture of **1f-1a** (476 mg, 1.03 mmol), N^1, N^2-bis(2-(4-methoxybenzyl thio)-2-methylpropyl)ethane-1,2-diamine free base (309 mg, 0.65 mmol), NaI (488 mg, 3.25 mmol), anhydrous K_2CO_3 (449 mg, 3.25 mmol) in 5 mL DMF was stirred under nitrogen at 50 °C for 72 h. After the evaporation of DMF under vacuum, the reaction crude was diluted with 30 mL water, extracted with 3×20 mL methylene chloride and dried over $MgSO_4$. The residue was purified by column chromatography over silica ($CHCl_3$: MeOH=20:1) to give **1f-2** as a yellowish oil (139 mg, 25%). ^{1}H NMR ($CDCl_3$, δ) 1.30 (s, 6H), 1.35 (s, 6H), 1.78-1.90 (m, 3H), 2.36-2.78 (m, 24H), 3.04 (t, *J* = 6.5 Hz, 2H), 3.65 (s, 2H), 3.73 (s, 2H), 3.76 (s, 6H), 3.81 (s, 3H), 4.08 (t, *J* = 6.5 Hz, 2H), 7.18-7.31 (m, 10H), 6.67-6.81 (m, 7H); ^{13}C NMR ($CDCl_3$, δ) 26.9, 27.2, 28.5, 32.0, 33.1, 33.6, 46.8, 47.7, 48.4, 53.1, 54.9, 55.1, 55.8, 56.9, 58.0, 59.8, 60.6, 66.9, 67.1, 112.4, 113.0, 113.8, 120.5, 125.6, 128.2, 128.3, 129.8, 129.9, 130.3, 133.1, 142.0, 146.6, 149.1, 158.4.

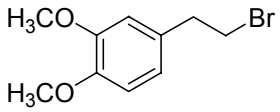
1-(2-((2-mercapto-2-methylpropyl)(2-(2-methoxy-4-(2-(4-(3-phenylpropyl)piperazin-1-yl)ethyl)phenoxy)ethyl)amino)ethylamino)-2-methylpropane-2-thiol (1f-3)



To a stirring solution of **1f-2** (139 mg, 0.16 mmol) and anisole (52 mg, 0.48 mmol) in TFA (1.6 mL), was added methanesulfonic acid (0.5 mL). The mixture was stirred for 1 h

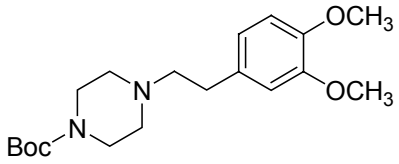
at ambient temperature. The volatile components were evaporated under vacuum. The residue was dissolved in 15 mL H_2O and extracted with 2×10 mL ether. Then the aqueous phase was adjusted to neutral pH and extracted by 3×15 mL chloroform. The organic layer was washed by 2×20 mL of water and dried over Na_2SO_4. The evaporation of solvent yielded an oil (77 mg, 77%). ^{1}H NMR ($CDCl_3$, δ) 7.18-7.30 (m, 6H), 6.86 (d, 1H), 6.73-6.75 (m, 2H), 4.58-4.63 (m, 1H), 4.23-4.28 (m, 1H), 3.82 (s, 3H), 3.39-3.55 (m, 5H), 2.36-3.02 (m, 25H), 1.81-1.88 (m, 4H), 1.53 (s, 3H), 1.47 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H).

4-(2-bromoethyl)-1,2-dimethoxybenzene (1h-1)[64]



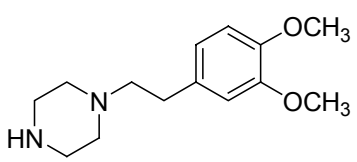
To a stirring ice-cooled solution of triphenylphosphine (17.3 g, 65.86 mmol) in 80 mL of CH_2Cl_2 was added dropwise a solution of bromine (10.4 g, 65.86 mmol) in 30 mL of CH_2Cl_2. A white precipitate formed immediately. After the reaction was stirred at room temperature for 0.5 h and cooled to ice bath temperature, a solution of 3,4-dimethoxyphenyl ethanol (10 g, 54.88 mmol) in 30 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for an additional hour at room temperature and concentrated by rotoevaporator. The residue was washed several times with hexane followed by separation with chromatography (hexane: EtOAc=40:10) to give **1h-1** (12.36 g, 92%). ^{1}H NMR: ($CDCl_3$, δ) 3.09-3.14 (t, 2H, CH_2), 3.53-3.57 (t, 2H, CH_2), 3.87-3.89 (2s, 6H, OCH_3), 6.74-6.85 (m, 3H, aromatic CH).

1-*tert*butylcarboxylate-4-(3,4-dimethoxyphenethyl)piperazine (1h-2)[43]



3,4-dimethoxyphenyl ethyl bromide (12.36 g, 50.45 mmol) and 1-Boc-piperazine (9.4 g, 50.45 mmol) were reacted in the presence of potassium carbonate (20.4 g, 147 mmol) and sodium iodide (7.56 g, 50.45 mmol) in DMF (220 mL) at 50 °C overnight. The reaction mixture was filtered and evaporated to dryness. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, saturated NaCl solution, then dried on $MgSO_4$, followed by filtration and evaporation. The residue was purified by chromatography with pure EtOAc to give **1h-2** (12.36 g, 70%). ^{1}H NMR: ($CDCl_3$, δ) 1.46 (s, 9H, $3CH_3$), 2.45-2.48 (t, 4H, $2CH_2$), 2.56-2.61 (t, 2H, CH_2), 2.73-2.78 (t, 2H, CH_2), 3.45-3.48 (t, 4H, $2CH_2$), 3.85-3.87 (2s, 6H, OCH_3), 6.73-6.81 (m, 3H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 28.32, 33.05, 52.91, 55.72, 60.55, 79.52, 111.15, 111.92, 120.40, 132.66, 147.29, 148.74, 154.64.

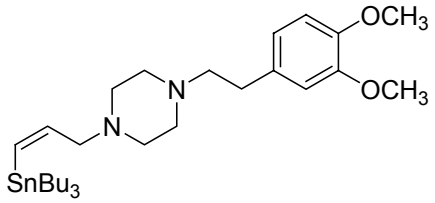
1-(3,4-dimethoxyphenethyl)piperazine (1h-3)



1h-2 (12.36 g, 35.2 mmol), 4N hydrochloric acid (77 mL), and 1,4-dioxane (30 mL) were mixed at 0 °C. The mixture was diluted with MeOH (77 mL) and then stirred at room temperature for 8.5 hours, followed by evaporation to dryness. The HCl salt was turned into the free base by basification and then extraction with EtOAc. After the evaporation of the solvent, the resulted solid was recrystallized from EtOAc. ^{1}H NMR: ($CDCl_3$, δ) 1.69 (s, 1H, NH), 2.50-2.60 (m, 6H, CH_2), 2.73-2.79 (t, 2H, CH_2), 2.92-2.96 (t, 4H,

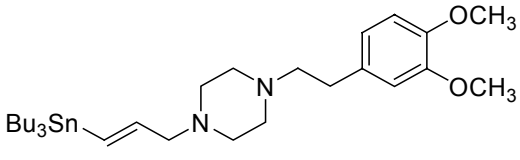
2CH_2), 3.86-3.88 (2s, 6H, OCH_3), 6.72-6.82 (m, 3H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 32.89, 46.01, 54.46, 55.70, 61.20, 111.13, 111.93, 120.39, 132.89, 147.21,147.21, 148.70.

(*Z*)-1-(3,4-dimethoxyphenethyl)-4-(3-(tributylstannyl)allyl)piperazine (1h-4)



The mixture of **1f-3** (592 mg, 2.51 mmol), **1b-4** (1.89 g, 3.77 mmol) and K_2CO_3 (740 mg, 5.35 mmol) were reacted in absolute ethanol (35 mL) at reflux for 13 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure and then purified by chromatography ($CHCl_3$: MeOH=80:1) to give **1h-4** (883 mg, 64%). ^{1}H NMR: ($CDCl_3$, δ) 0.85-0.92 (m, 15H, n-Bu), 1.22-1.54 (m, 12H, n-Bu), 2.55-2.60 (m, 10H, CH_2), 2.71-2.78 (t, 2H, CH_2), 2.98-3.00 (dd, 2H, CH_2, J=1.0Hz, 6.3Hz), 3.83-3.85 (2s, 6H, OCH_3), 6.00-6.05 (d, 1H, CH, J=12.5Hz), 6.54-6.59 (dt, 1H, CH, J=12.5Hz, 6.3Hz), 6.71-6.76 (m, 3H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 10.37, 13.66, 27.23, 29.10, 33.19, 53.13, 55.70, 60.66, 64.01, 111.09, 111.88, 120.40, 131.86, 132.85, 145.35, 147.22, 148.71.

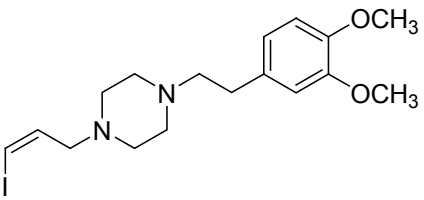
(*E*)-1-(3,4-dimethoxyphenethyl)-4-(3-(tributylstannyl)allyl)piperazine (1h-5)



The mixture of **1h3** (555 mg, 2.22 mmol), **1b-5** (1.67 g, 3.33 mmol) and K_2CO_3 (654 mg, 4.73 mmol) were reacted in absolute ethanol (30 mL) at reflux for 13 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure and then purified by chromatography ($CHCl_3$: MeOH=60:1) to give **1h-5** (754 mg, 58%). ^{1}H NMR: ($CDCl_3$,

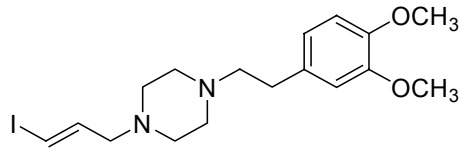
δ) 0.81-0.88 (m, 15H, n-Bu), 1.19-1.52 (m, 12H, n-Bu), 2.52-2.74 (m, 10H, CH_2), 2.71-2.78 (t, 2H, CH_2), 3.02-3.04 (dd, 2H, CH_2, 5.25 Hz), 3.80-3.82 (2s, 6H, OCH_3), 5.98-6.13 (m, 2H, CH), 6.68-6.76 (m, 3H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 9.33, 13.64, 27.58, 29.02, 33.13, 52.99, 55.66, 60.60, 65.44, 111.07, 111.87, 120.38, 132.30, 132.84, 144.93, 147.19, 148.68.

(*Z*)-1-(3,4-dimethoxyphenethyl)-4-(3-iodoallyl)piperazine (1h-6)



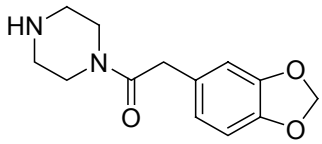
To **1h-4** (626 mg, 1.08 mmol) in CH_2Cl_2 (15 mL) was added iodine (310 mg, 1.22 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred at room temperature for 10 minutes and then quenched by 5% $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was dried on anhydrous Na_2SO_4 and purified by column chromatography ($CHCl_3$: MeOH=60:1) to give **1h-6** (394 mg, 88%). ^{1}H NMR: (di-HCl salt, D_2O, δ) 3.08-3.13 (t, 2H, CH_2), 3.55-3.74 (m, 10H, CH_2), 3.86-3.87 (2s, 6H, OCH_3), 4.03-4.06 (d, 2H, CH_2, J=7.2 Hz), 6.48-6.56 (dt, 1H, CH, J=7.2, 15.3Hz), 6.93-7.06 (m, 3H, aromatic and alkene CH), 7.21-7.23 (d, 1H, aromatic CH, J=7.8 Hz); ^{13}C NMR: (di-HCl salt, D_2O, δ) 29.13, 48.28, 48.87, 55.68, 57.58, 59.55, 95.45, 112.18, 121.39, 128.08, 128.55, 147.33, 148.31; Anal.Calcd for $C_{17}H_{25}IN_2O_2 \cdot 2HCl$ (corrected): C, 40.25; H, 5.76; N, 5.52. Found: C, 40.41; H, 5.36; N, 5.53; m.p. 166-167 °C.

(*E*)-1-(3,4-dimethoxyphenethyl)-4-(3-iodoallyl)piperazine (1h-7)



To **1f-5** (450 mg, 0.78 mmol) in CH_2Cl_2 (10 mL) was added iodine (224 mg, 0.88 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at room temperature for 10 minutes and then quenched with 5% $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was dried on anhydrous Na_2SO_4 and purified by chromatography ($CHCl_3$: MeOH=60:1) to give **1h-7** (268 mg, 83%). ^{1}HNMR: (di-HCl salt, D_2O, δ) 3.03-3.09 (t, 2H, CH_2), 3.49-3.84 (m, 18H, CH_2), 6.63-6.75 (dt, 1H, CH, J=14.6Hz, 7.6Hz), 6.89-7.10 (m, 4H, CH); ^{13}CNMR: (di-HCl salt, D_2O, δ) 29.07, 47.87, 48.84, 55.58, 57.54, 59.40, 90.42, 112.07, 121.32, 128.50, 132.22, 147.24, 148.22; Anal.Calcd for $C_{17}H_{25}IN_2O_2 \cdot 2HCl$ (corrected): C, 38.87; H, 5.95; N, 5.33. Found: C, 38.91; H, 5.55; N, 5.36; m.p. 176-177 °C.

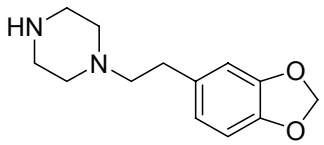
2-(3,4-methylenedioxy phenyl)-1-(piperazin-1-yl)ethanone (1i-1)



1-Boc piperazine (827 mg, 4.44 mmol), 3,4-(methylenedioxy) phenylacetic acid (800 mg, 4.44 mmol), 1-hydroxy benzotriazole hydrate (600 mg, 4.44 mmol), 4-methylmorpholine (1.35 g, 13.32 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (851 mg, 4.44 mmol) and dichloromethane (40 mL) were mixed under nitrogen at 0 °C. The mixture were stirred at room temperature overnight, and then evaporated to dryness. The residue was diluted by saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution. The solution of ethyl acetate was dried over $MgSO_4$, filtered and

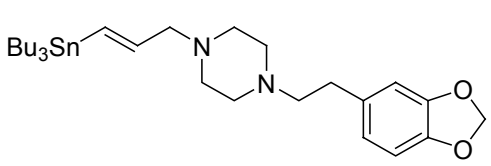
evaporated to dryness. The crude was then mixed with 4N HCl (10 mL), 1,4-dioxane (4 mL) and then diluted by MeOH (25 mL). The mixture was stirred at room temperature overnight and then evaporated to dryness. It was used for next reaction without further purification (674 mg, 61%) ^{1}H NMR: ($CDCl_3$, δ) 2.61-2.65 (t, 2H, CH_2), 2.72-2.76 (t, 2H, CH_2), 3.34-3.37 (t, 2H, CH_2), 3.51-3.56 (m, 4H, CH_2), 5.83 (s, 2H, OCH_2O), 6.58-6.70 (m, 3H, CH); ^{13}C NMR: ($CDCl_3$, δ) 40.32, 42.61, 45.52, 45.89, 46.99, 100.91, 108.24, 108.99, 121.52, 128.57, 146.29, 147.77, 169.41.

1-(3,4-methylenedioxy phenethyl) piperazine (1i-2)



The solution of **1i-1** (320 mg, 1.29 mmol) in THF (7 mL) was added dropwise into the suspension of $LiAlH_4$ (147 mg, 3.87 mmol) in THF (7 mL) under nitrogen at 0 °C. The mixture was stirred overnight at room temperature, then Glauber's salt was added into the mixture slowly until no bubble were given off. The mixture was filtered, diluted with water and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and dried by high vaccum (210 mg). The crude was used in next reaction without further purification.

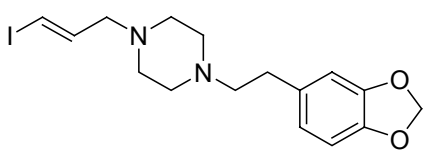
(*E*)-1-(3,4-methylenedioxy phenethyl)-4-(3-(tributylstannyl)allyl)piperazine (1i-3)



The mixture of **1i-2** (200 mg, 0.855 mmol), **1b-5** (643 mg, 1.282 mmol) and K_2CO_3 (252 mg, 1.82 mmol) were reacted in absolute ethanol (12 mL) at reflux for 18 h. After cooled to room temperature, the mixture was filtered and the

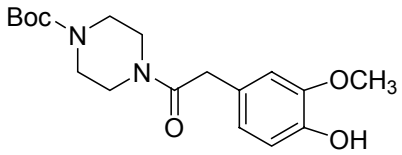
filtrate was concentrated under reduced pressure and then purified by column chromatography ($CHCl_3$: MeOH=60:1) to give **1i-3** (200 mg, 41%). ^{1}H NMR: ($CDCl_3$, δ) 0.81-0.88 (m, 15H, n-Bu), 1.19-1.52 (m, 12H, n-Bu), 2.51-2.56 (m, 8H, CH_2), 2.67-2.75 (m, 2H, CH_2), 3.04-3.06 (d, 2H, CH_2, 5.4 Hz), 5.87 (s, 2H, OCH_2O), 5.96-6.14 (m, 2H, alkene CH), 6.60-6.70 (m, 3H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 9.35, 13.66, 27.17, 29.04, 33.19, 52.93, 60.66, 65.42, 100.66, 108.07, 109.04, 121.35, 132.36, 133.97, 144.91, 145.67, 147.43.

(*E*)-1-(3,4-methylenedioxy phenethyl)-4-(3-iodoallyl)piperazine (1i-4)



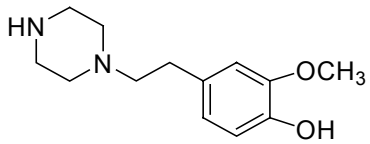
To **1g-3** (200 mg, 0.35 mmol) in CH_2Cl_2 (2.5 mL) was added iodine (100 mg, 0.395 mmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred at room temperature for 10 minutes and then quenched by 5% $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layer was dried over anhydrous Na_2SO_4 and purified by column chromatography ($CHCl_3$: MeOH=50:1) to give **1i-4** (135 mg, 95%). ^{1}H NMR: (di-HCl salt, D_2O, δ) 2.95-2.98 (t, 2H, CH_2), 3.41-3.44 (t, 2H, CH_2), 3.52-3.59 (d, broad, 7H), 3.72-3.74 (d, 2H, CH_2, J=7.5 Hz), 5.88 (s, 2H, OCH_2O), 6.61-6.63 (dt, 1H, alkene CH, J_1=7.5, J_2=14.5 Hz), 6.72-6.80 (m, 3H, aromatic CH), 6.99-7.02 (d, 1H, CH, J=14.5 Hz); ^{13}C NMR: ($CDCl_3$, δ) 29.22, 47.85, 48.81, 57.58, 59.40, 90.44, 101.04, 108.71, 108.96, 121.96, 129.13, 132.19, 146.25, 147.44; Anal.Calcd for $C_{16}H_{21}IN_2O_2 \cdot 2HCl$: C, 40.61; H, 4.90; N, 5.92. Found: C, 40.32; H, 4.90; N, 5.70; m.p. 197-199 °C.

2-(3-methoxy-4-hydroxy phenyl)-1-(4-*tert*-butyl carboxylate piperazin-1-yl)ethanone (1j-1)



1-Boc piperazine (1.64 g, 8.78 mmol), Homovanillic acid (1.60 g, 8.78 mmol), 1-hydroxy benzotriazole hydrate (1.35 g, 8.78 mmol), 4-methylmorpholine (2.66 g, 26.30 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.68 g, 8.78 mmol) and dichloromethane (80 mL) were mixed under nitrogen at 0 °C. The mixture was stirred at room temperature overnight, and then evaporated to dryness. The residue was diluted saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated NaCl solution. The solution of ethyl acetate was dried over $MgSO_4$, filtered and evaporated to dryness and followed by recrystallization from pure ethyl acetate. ^{1}H NMR: ($CDCl_3$, δ) 1.44 (s, 9H, t-butyl), 3.22-3.24 (m, 2H, CH_2), 3.35-3.42 (m, 2H, CH_2), 3.58-3.62 (m, 4H, CH_2), 3.86 (s, 3H, OCH_3), 5.75 (br, 1H, OH), 6.66-6.86 (m, 3H, CH); ^{13}C NMR: ($CDCl_3$, δ) 28.18, 40.48, 41.50, 45.75, 55.72, 80.16, 111.13, 114.78, 121.03, 126.00, 144.81, 147.13, 154.36, 170.13.

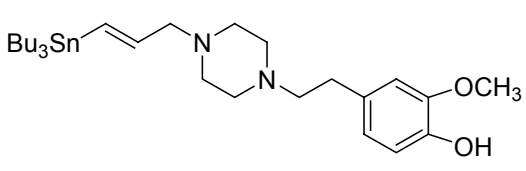
1-(3-methoxy-4-hydroxy phenethyl) piperazine (1j-2)



The solution of **1j-1** (660 mg, 1.88 mmol) in THF (15 mL) was added dropwise into the suspension of $LiAlH_4$ (215 mg, 5.66 mmol) in THF (15 mL) under nitrogen at room temperature. The mixture was stirred for 5 h when the TLC showed the completion of reaction (solvent system: $CHCl_3$: MeOH=10:1). The mixture was filtered through celite and then the celite was washed with THF three times. The filtrate was evaporated to dryness to yield a white foam like solid. The solid was mixed with 4N HCl (4 mL),

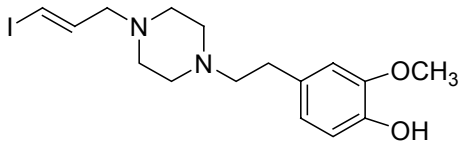
1,4-dioxane (1.7 mL) and diluted with MeOH (4 mL). The mixture was stirred at room temperature overnight and then dried to give a white salt. Further recrystallization gave **1j-2** as white solid. It was used in next reaction without further purification.

(*E*)-1-(3-methoxy-4-hydroxy phenethyl)-4-(3-(tributylstannyl)allyl)piperazine (1j-3)



The mixture of **1j-2** (367 mg, 1.19 mmol), **1b-5** (1.03 g, 2.05 mmol) and K_2CO_3 (654 mg, 4.74 mmol) were reacted in absolute ethanol (14 mL) at reflux for 12 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure and then purified by column chromatography ($CHCl_3$: MeOH=20:1) to give **1j-3** (240 mg, 36%). ^{1}H NMR: ($CDCl_3$, δ) 0.78-0.90 (m, 16H, n-Bu), 1.28-1.55 (m, 12H, n-Bu), 2.58-2.74 (m, 12H, CH_2), 3.07-3.09 (d, 2H, CH_2), 6.04-6.09 (m, 2H, alkene CH), 6.65-6.81 (m, 3H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 7.19, 13.64, 27.19, 29.05, 33.22, 46.02, 53.14, 55.13, 55.80, 60.59, 72.54, 112.22, 113.64, 120.37, 131.82, 133.06, 143.09, 146.36, 149.15.

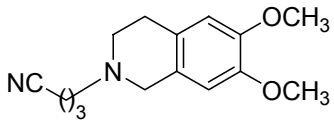
(*E*)-1-(3-methoxy-4-hydroxy phenethyl)-4-(3-iodoallyl)piperazine (1j-4)



To **1j-3** (240 mg, 0.424 mmol) in CH_2Cl_2 (2 mL) was added iodine (131 mg, 0.52 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 10 minutes and then evaporated to dryness. The crude was purified by preparative TLC ($CHCl_3$: MeOH=50:1) to give **1j-4** as a yellow oil (120 mg, 70%). ^{1}H NMR: (Di-HCl salt, D_2O, δ) 2.95-3.02 (t, 2H, CH_2), 3.42-3.50 (m, 10H, CH_2), 3.70-3.73

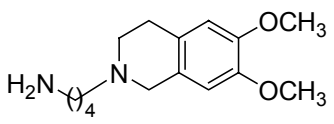
(d, 2H, CH_2, J=7.5 Hz), 3.72-3.74 (d, 2H, CH_2, J=7.5 Hz), 3.80 (s, 3H, OCH_3), 6.58-6.70 (dt, 1H, alkene CH, J_1=7.5, J_2=14.5 Hz), 6.72-6.80 (m, 4H, aromatic and alkene CH); ^{13}C NMR: ($CDCl_3$, δ) 13.50, 16.35, 26.55, 29.07, 33.02, 52.53, 52.93, 55.80, 60.53, 62.52, 78.74, 111.26, 114.41, 121.15, 131.74, 142.52, 146.48; Anal.Calcd for $C_{16}H_{21}IN_2O_2 \cdot 2HCl$ (corrected): C, 38.49; H, 5.59; N, 5.61. Found: C, 38.45; H, 5.10; N, 5.58; m.p. 185-187 °C.

4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butanenitrile (2a-1)



A mixture of commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2 g, 8.71 mmol), 4-bromobutyronitrile (1.29 g, 8.71 mmol), K_2CO_3 (4.83 g, 35 mmol) and NaI (1.31 g, 8.71 mmol) in 40 mL of DMF was stirred at 50 °C for 10 h. After evaporation of the DMF under reduced pressure, the crude was diluted with water, and extracted with EtOAc. The organic layer was dried overnight and evaporated to dryness to gave a solid, which was then recrystallized by hexane and EtOAc to give **2a-1** as a yellowish crystalline solid (1.9 g, 84%). ^{1}H NMR: ($CDCl_3$, δ) 1.88-1.97 (p, 2H, CH_2), 2.46-2.51 (t, 2H, CH_2), 2.61-2.66 (t, 2H, CH_2), 2.70-2.73 (t, 2H, CH_2), 2.81-2.84 (t, 2H, CH_2), 3.56 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.53 (s, 1H, CH), 6.61 (s, 1H, CH).

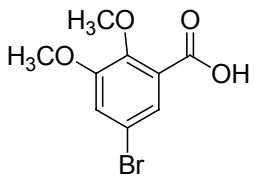
4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-amine (2a-2)



A solution of **2a-1** (500 mg, 1.92 mmol) in THF (10 mL) was added dropwise to a solution of $LiAlH_4$ (220 mg, 5.75

mmol) in THF (10 mL), and then stirred at room temperature overnight. To consume the excess LAH, Glauber's salt was added slowly and carefully until no bubbles were produced. The suspension was filtered through celite and washed with ether. The HCl salt of **2a-2** was formed by passing dry HCl gas through the solution. After evaporation of all solvent, the solid was dried under vaccum to give **2a-2** as the HCl salt (341mg, 67%). ^{1}H NMR: (D_2O, δ) 1.39-1.57 (m, 4H, CH_2), 2.13 (s, br, 2H, NH_2), 2.38-2.43 (t, 2H, CH_2), 2.58-2.74 (m, 6H, CH_2), 3.45 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 6.42 (s, 1H, CH), 6.49 (s, 1H, CH).

5-bromo-2,3-dimethoxybenzoic acid (2a-3)

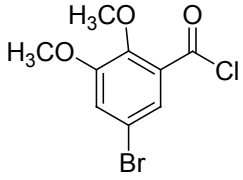


To a solution of 2, 3-dimethoxybenzoic acid (544 mg, 2.98 mmol) in acetic acid (5 mL) was added bromine dropwise. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo to give a solid, which was recrystalized from hexane and ethyl acetate to give 2-hydroxy-3-methoxy-5-bromobenzoic acid (580 mg, 80%). ^{1}H NMR: (MeOD, δ) 3.85 (s, 3H, CH_3), 5.06 (s, br, phenol-OH), 7.17-7.18 (s, 1H, CH), 7.48-7.49 (s, 1H, CH).

2-hydroxy-3-methoxy-5-bromobenzoic acid (560 mg, 2.28 mmol) was then refluxed with dimethyl sulfate (0.99 g, 7.88 mmol), and K_2CO_3 (1.09 g, 7.88 mmol) in acetone (4 mL) overnight. The solution was filtered through celite and condensed to give a liquid, which was then dissolved in 5 mL of MeOH and added 40% NaOH (250 μL), refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in water and extracted with EtOAc three times. The aqueous layer was acidified to pH<2 and extracted

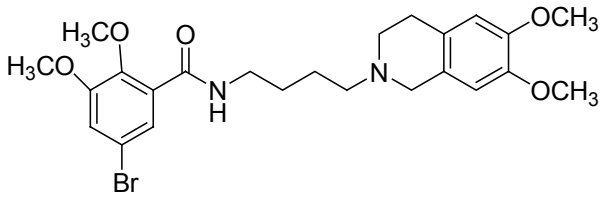
with EtOAc, dried over Na_2SO_4. The solvent was removed and the residue (244 mg, 41%) was recrystalized from ethyl acetate and hexane. ^{1}H NMR: (MeOD, δ) 3.96 (s, 3H, OCH_3), 4.1 (s, 3H, OCH_3), 7.28 (d, 1H, CH), 7.88 (d, 1H, CH), 11.2 (s, br, 1H, COOH).

5-bromo-2,3-dimethoxybenzoyl chloride (2a-4)



A solution of **2a-3** (244 mg, 0.94mmol) and $SOCl_2$ (224 mg, 1.88 mmol) in Benzene (5 mL) was refluxed overnight. Benzene and $SOCl_2$ is removed by distillation to give benzoyl chloride **2a-4**.

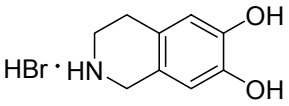
5-bromo-N-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butyl)-2,3-dimethoxy benzamide (2a-5)



To a solution of benzoyl chloride **2a-4** in dry CH_2Cl_2 (5 mL), was added **2a-2** free base (300 mg, 1.14 mmol) in CH_2Cl_2 (2 mL) solution and triethylamine (57 µL) dropwise. After 6.5 h, the solvent was evaporated and the residue was dissolved in CH_2Cl_2, washed by 0.5 N NaOH, H_2O and dried on $NaSO_4$. After evaporation of the solvent, the crude was purified by preparative TLC ($CHCl_3$: MeOH=15:1) to give **2a-5** (180 mg, 41%). ^{1}H NMR: ($CDCl_3$, δ) 1.66-1.71 (p, 4H, CH_2), 2.50-2.56 (t, 2H, CH_2), 2.66-2.70 (t, 2H, CH_2), 2.76-2.80 (t, 2H, CH_2), 3.46-3.52 (m, 4H, CH_2), 3.82 (2s, 6H, OCH_3), 3.85 (2s, 6H, OCH_3), 6.48 (s, 1H, CH), 6.55 (s, 1H, CH), 7.10 (d, 1H, CH), 7.73 (d, 1H, CH), 8.01-8.05 (t, 1H, amide NH); ^{13}C NMR: ($CDCl_3$, δ) 24.68, 27.53, 28.53, 39.67, 50.81, 55.72, 55.81, 55.84, 56.23, 57.72, 61.31, 109.37, 111.25, 116.94, 118.06, 125.06, 126.05, 126.41, 128.49, 146.39, 147.07,

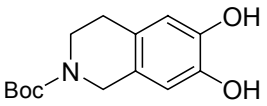
147.38, 153.21, 163. 86; Anal.Calcd for $C_{24}H_{31}BrN_2O_5 \cdot (COOH)_2$: C, 52.27; H, 5.57; N, 4.69. Found: C, 51.98; H, 5.56; N, 4.60. m.p. 170-171 °C.

1,2,3,4-tetrahydroisoquinoline-6, 7-diol (2b-1)



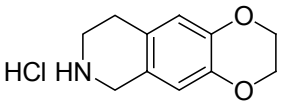
A mixture of 6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (10 g, 43.5 mmol) and 48% HBr (138 mL) was heated at 120 °C for 2 h, and then cooled to room temperature. The precipitate was filtered and the filtrate was evaporated to dryness to afford a white solid **2b-1** in quantitative yield. ^{1}H NMR: (DMSO, δ) 2.79 (t, 2H, CH_2), 3.26 (s, 2H, CH_2), 4.05 (s, 2H, CH_2), 6.54 (s, 2H, CH), 8.93 (br, 4H, HBr); ^{13}C NMR: (DMSO, δ) 24.33, 41.33, 43.75, 113.65, 115.61, 119.14, 122.43, 144.63, 145.34.

N-tertbutyl carboxylate 6,7-dihydroxy-3,4-dihydroisoquinoline (2b-2)



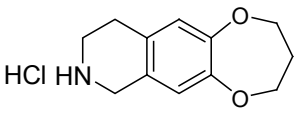
To a mixture of Et_3N (1.25 g, 12.22 mmol) and **2b-1** (2 g, 8.15 mmol) in MeOH (10 mL) was added the solution of di-tert-butyl dicarbonate (2.68 g, 12.22 mmol) in MeOH (5 mL). The reaction mixture was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was diluted with water and extracted with EtOAc three times. The organic layer was washed with 1N HCl and saturated $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (hexane: EtOAc=7:3) yielded **2b-2** (1.07 g, 50%) as a light yellow solid. ^{1}H NMR: ($CDCl_3$, δ) 1.50 (s, 9H, CH_3), 2.70 (t, 2H, CH_2), 3.60 (t, 2H, CH_2), 4.44 (s, 2H, CH_2), 5.71 (br, 1H, phenol OH), 6.66 (s, 2H, CH).

6,7-ethylenedioxy-1,2,3,4-tetrahydroisoquinoline (2b-3)



The mixture of **2b-2** (610 mg, 2.29 mmol), 1,2-dibromoethane (1.29 g, 6.87 mmol), K_2CO_3 (948 mg, 6.87 mmol), and tetrabutylammonium bromide (TBAB, 74 mg, 0.23 mmol) in toluene (15 mL) was stirred under nitrogen at 80 °C for 24 h, after cool down, the reaction mixture was diluted with water and extracted with ethyl ether three times. The organic layer was washed with 2N NaOH solution and dried on Na_2SO_4 to give an oil. The oil was mixed with 4N HCl (7 mL) and 1,4-dioxane (2 mL), then diluted with 7 mL MeOH. After stirred at room temperature overnight, the solution was evaporated to get rid of solvent and dried on vacuum. The HCl salt of **2b-3** (400 mg, 77%) is recrystallized from MeOH. ^{1}H NMR: (DMSO, δ) 2.87 (t, 2H, CH_2), 3.25 (t, 2H, CH_2), 3.38 (s, 1H, NH), 4.07 (s, 2H, CH_2O) 4.21 (s, 4H, OCH_2CH_2O), 6.70 (s, 1H), 6.73 (s, 1H), 9.73 (s, H from HCl); ^{13}C NMR: (DMSO, δ) 24.34, 40.86, 43.24, 64.48, 64.50, 115.16, 116.90, 121.81, 125.11, 142.46, 143.04.

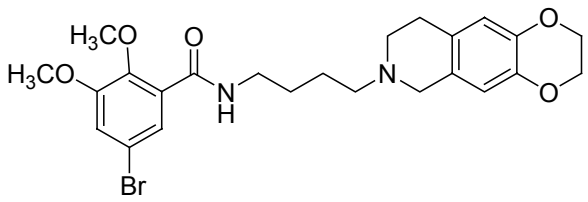
6,7-propylenedioxy-1,2,3,4-tetrahydroisoquinoline (2b-4)



A mixture of **2b-2** (715 mg, 2.69 mmol), 1,3- dibromopropane (1.63 g, 8.07 mmol), K_2CO_3 (1.11 g, 8.07 mmol), and TBAB (96 mg, 0.29 mmol) in toluene (15 mL) was stirred under nitrogen at 80 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl ether three times. The organic layer was washed with 2N NaOH solution and dried over anhydrous Na_2SO_4 to give a crude, which was purified by column chromatography (hexane: ethyl acetate=7:3) to give an oil (420 mg, 52%). The oil was

mixed with 4N HCl (5 mL) and 1,4-dioxane (1.2 mL), then diluted with 5 mL MeOH. After stirred at room temperature overnight, the solution was evaporated to remove solvent and dried under vacuum. The HCl salt of **2b-4** (270 mg, 82%) was precipitated out by EtOAc from EtOH. ^{1}H NMR: (DMSO, δ) 2.09 (t, 2H, CH_2), 2.89 (t, 2H, CH_2), 3.27 (t, 2H, CH_2), 4.08 (m, 6H, CH_2O, CH_2), 4.21 (s, 4H, OCH_2CH_2O), 6.83 (s, 1H), 6.86 (s, 1H), 9.59 (s, H from HCl); ^{13}C NMR: (DMSO, δ) 24.31, 31.99, 40.80, 43.31, 70.96, 70.99, 119.87, 121.68, 124.08, 127.36, 150.13, 150.72.

5-bromo-N-(4-(6,7-ethylenedioxy-3,4-dihydroisoquinolin-2(1H)-yl)butyl)-2,3-dimeth oxy benzamide (2b-5)

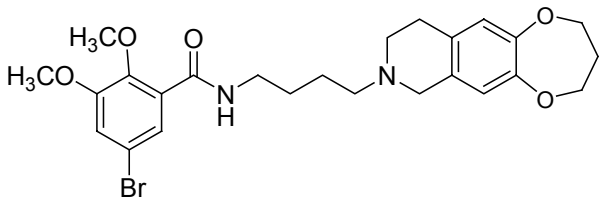


A mixture of **2b-3** (400 mg, 1.75 mmol), K_2CO_3 (968 mg, 7.02 mmol), 4-bromobutyronitrile (259 mg, 1.75 mmol), and NaI (262 mg, 1.75 mmol) in 10 mL of DMF was stirred at 50 °C for overnight. After evaporation of the DMF under reduced pressure, the crude was diluted with water, and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give a colorless oil (330 mg). The oil was dissolved in 5 mL of THF and added slowly into the THF (10 mL) solution of LAH (145 mg, 3.82 mmol) slowly at room temperature. After reacting overnight, the suspension was quenched carefully by Glauber's salt and filtered through celite. The crude was obtained as colorless oil (290 mg) after evaporation of solvent.

To the solution of 5-bromo-2, 3-dimethoxy benzoyl chloride (208 mg, 0.74 mmol) in 2 mL of dry CH_2Cl_2 was added a mixture of triethylamine (38 mg, 0.37 mmol), dichloromethane (3 mL) and the oil (290 mg) reduced from the last step. The mixture was

stirred at room temperature overnight and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed by 0.5N NaOH, water, then dried over Na_2SO_4. After evaporation of the solvent, the crude was purified by chromatotron ($CHCl_3$: MeOH=100:1) to give **2b-5** as a light yellow oil (213 mg, 57%). The oxalate salt of **2b-5** was recrystallized from the mixture of ethanol, ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$, δ) 1.68 (p, 4H, CH_2), 2.52 (t, 2H, CH_2), 2.66 (t, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.49 (m, 4H, CH_2), 3.86 (2s, 6H, OCH_3), 4.20 (s, 4H, OCH_2CH_2O), 6.49 (s, 1H, CH), 6.57 (s, 1H, CH), 7.10 (d, 1H, CH), 7.75 (d, 1H, CH), 7.99 (t, 1H, amide NH); ^{13}C NMR: ($CDCl_3$, δ) 24.65, 27.49, 28.27, 39.67, 50.87, 55.56, 56.25, 57.69, 61.31, 64.34, 114.51, 116.45, 117.00, 118.15, 125.19, 127.16, 127.61, 128.44, 141.48, 141.82, 146.41, 153.20, 163.81; Anal.Calcd for $C_{24}H_{29}BrN_2O_5 \cdot (COOH)_2$: C, 52.45; H, 5.25; N, 4.70. Found: C, 52.66; H, 5.30; N, 4.61; m.p. 146-147 °C.

5-bromo-N-(4-(6,7-propylenedioxy-3,4-dihydroisoquinolin-2(1H)-yl)butyl)-2,3-dimethoxy benzamide (2b-6)

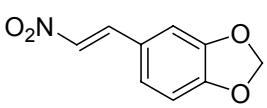


A mixture of **2b-5** (270 mg, 1.12 mmol), K_2CO_3 (618 mg, 4.48 mmol), 4-bromobutyronitrile (166 mg, 1.12 mmol), and NaI (168 mg, 1.12 mmol) in 5 mL of DMF was stirred at 50 °C overnight. After the evaporation of DMF under reduced pressure, the crude was diluted with water, and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give a colorless oil (430 mg). The oil was dissolved in 7 mL THF and added slowly into the THF (7 mL) solution of LAH (180 mg, 4.73 mmol) at room temperature. After reacting overnight, the suspension was quenched carefully with Glauber's salt and

filtered through celite. The crude was obtained as colorless oil (150 mg) after evaporation of the solvent.

To the solution of 5-bromo-2, 3-dimethoxy benzoyl chloride (101 mg, 0.36 mmol) in 2 mL dry CH_2Cl_2 was added the mixture of triethylamine (18 mg, 0.18 mmol), dichloromethane (3 mL) and the oil (150 mL) reduced from the last step. The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed by 0.5 N NaOH, water, then dried over Na_2SO_4. After the evaporation of solvent, the crude was purified by preparative TLC plate ($CHCl_3$: MeOH=20:1) to give **2b-6** as a light yellow oil (109 mg, 58%). The oxalate salt of **2b-6** was recrystallized from ethanol and ethyl acetate. ^{1}H NMR ($CDCl_3$, δ) 1.66 (p, 4H, CH_2), 2.13 (p, 2H, CH_2), 2.50 (t, 2H, CH_2), 2.65 (t, 2H, CH_2), 2.77 (t, 2H, CH_2), 3.40-3.48 (m, 4H, CH_2), 3.84-3.86 (2s, 6H, OCH_3), 4.12 (s, 4H, CH_2O), 6.61 (s, 1H, CH), 6.69 (s, 1H, CH), 7.10 (d, 1H, CH), 7.75 (d, 1H, CH), 7.98 (t, 1H, amide NH); ^{13}C NMR: ($CDCl_3$, δ) 24.63, 27.48, 28.26, 32.15, 39.67, 50.49, 50.79, 55.50, 56.28, 57.71, 61.32, 70.66, 117.01, 118.18, 119.05, 121.00, 125.17, 128.37, 129.25, 129.68, 146.44, 149.24, 149.58, 153.23, 163.83; Anal.Calcd for $C_{27}H_{33}BrN_2O_9 \cdot (COOH)_2$: C, 53.21; H, 5.46; N, 4.60. Found: C, 53.26; H, 5.48; N, 4.60; m.p. 163-164 °C.

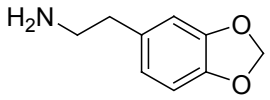
(*E*)-1-(2-nitrovinyl)-3,4-methylenedioxy benzene (2c-1)[65]



Commercially available piperonal (2 g, 13.3 mmol) was mixed with nitromethane (812 mg, 13.3 mmol) in methanol (5 mL) at 0 °C. An aqueous solution of NaOH (596 mg, 14.9 mmol) was added slowly to the stirring solution. The stirring was continued for another 40 min at 0 °C. The mixture was then

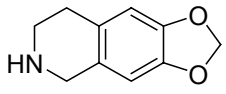
diluted with water and poured into ice cold water containing 2 mL of concentrated HCl. The yellow solid precipitated was filtered, dried under vacuum and recrystallized from EtOH and EtOAc. ^{1}H NMR: ($CDCl_3$, δ) 6.07 (s, 2H, OCH_2O), 6.87 (d, 1H, trans alkene, J=8.0Hz), 7.00 (d, 1H, aromatic CH, J=1.7Hz), 7.08 (dd, 1H, trans alkene, J_1=8.0Hz, J_2=1.7Hz), 7.47 (d, 1H, aromatic CH), 7.92 (d, 1H, aromatic CH).

1-(2-amino ethyl)-3,4-methylenedioxy benzene (2c-2)[66]



To a suspension of LAH in 6 ml of THF under N_2 was added dropwise **2c-1** (1.0 g, 5.18 mmol) in THF (14 mL) at –30 °C. After removal of the cooling bath, the mixture was stirred at room temperature for 3 h, and then heated to 65-70 °C for 1 h. Ice was added to quench the reaction under dry ice bath, then the mixture was stirred overnight at room temperature and the precipitate was removed by filtration through celite. The filtrate was extracted with Et_2O. The combined organic layer was washed by brine and dried over $MgSO_4$, evaporated to dryness to give the amine **2c-2** (0.62 g, 73%) as a light yellow oil. ^{1}H NMR: ($CDCl_3$, δppm) 2.66 (t, 2H, CH_2), 2.91(t, 2H, CH_2), 5.93(s, 2H, OCH_2O), 6.69 (m, 3H, aromatic CH); ^{13}C NMR: ($CDCl_3$, δ) 39.71, 43.64, 100.76, 108.17, 109.08, 121.62, 133.55, 145.86, 147.62.

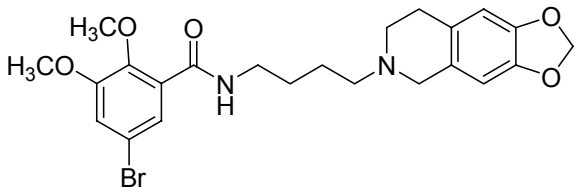
6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (2c-3)[67]



A mixture of amine **2c-2 (**620 mg, 3.76 mmol), paraformaldehyde (116 mg) and formic acid (4.1 mL) was heated in an oil bath at 40 °C for 24 h. Most of the formic acid was removed in vacuo. The residue was dissolved in EtOH (14 mL) and added to a solution of oxalic acid (685 mg) in EtOH (7 mL), The

resulting oxalate salt was filtered and dried to give **2c-3 (**660 mg, 65%)**.** ^{1}H NMR: (DMSO, δ) 2.86 (t, 2H, CH_2), 3.29 (t, 2H, CH_2), 4.12 (s, 2H, CH_2), 5.99 (s, 2H, OCH_2O), 6.78 (d, 2H, aromatic CH); ^{13}C NMR: (DMSO, δ) 25.12, 44.07, 101.37, 106.90, 108.83, 122.23, 125.66, 146.42, 147.06, 164.90.

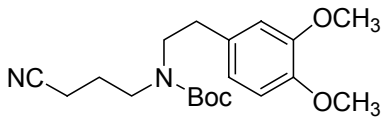
5-bromo-N-(4-(6,7-methylenedioxy-3,4-dihydroisoquinolin-2(1H)-yl)butyl)-2,3-dimethoxy benzamide (2c-4)



A mixture of **2c-3** (660 mg, 2.96 mmol), K_2CO_3 (1.64 g, 11.84 mmol), 4-bromobutyronitrile (438 mg, 2.96 mmol), and NaI (444 mg, 2.96 mmol) in 12 mL of DMF was stirred at 50 °C for overnight. After evaporation of the DMF under reduced pressure, the crude was diluted with water, and extracted with EtOAc. The organic layer was dried on Na_2SO_4 and evaporated to dryness to give a colorless oil (695 mg). The oil was dissolved in 15 mL of THF and added slowly into the THF (15 mL) solution of LAH (324 mg, 8.52 mmol) slowly at room temperature. After reacting overnight, the suspension was quenched carefully with Glauber's salt and filtered through celite. The crude was obtained as a colorless oil (370 mg) after evaporation of solvent. To the solution of 5-bromo-2, 3-dimethoxy benzoyl chloride (279 mg, 0.99 mmol) in 3 mL of dry CH_2Cl_2 was added the mixture of triethylamine (51 mg, 0.50 mmol), dichloromethane (4 mL) and the oil (370 mg) reduced from the last step. The mixture was stirred at room temperature overnight and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed by 0.5 N NaOH, water, then dried over Na_2SO_4. After evaporation of the solvent, the crude was purified by preparative TLC plate ($CHCl_3$: MeOH=20:1) to give **2c-4** as a light yellow oil (300

mg, 61%). The oxalate salt of **2c-4** was recrystallized from the ethanol. ^{1}H NMR ($CDCl_3$, δ) 1.67 (p, 4H, CH_2), 2.51 (t, 2H, CH_2), 2.65 (t, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.44-3.48 (m, 4H, CH_2), 3.84-3.86 (2s, 6H, OCH_3), 5.86 (s, 2H, OCH_2O), 6.44 (s, 1H, aromatic CH), 6.52 (s, 1H, aromatic CH), 7.08 (d, 1H, CH), 7.74 (d, 1H, aromatic CH), 8.01 (t, 1H, amide NH); ^{13}C NMR: ($CDCl_3$, δ) 24.67, 27.53, 29.01, 39.68, 50.73, 56.19, 57.69, 61.33, 100.50, 106.37, 108.29, 117.00, 118.12, 125.14, 127.12, 127.45, 128.46, 145.56, 145.92, 146.41, 163.90; Anal.Calcd for $C_{23}H_{27}BrN_2O_5 \cdot (COOH)_2$: C, 51.64; H, 5.03; N, 4.82. Found: C, 51.80; H, 5.15; N, 4.80; m.p. 174-175 °C.

N-3-cyanopropyl-(3,4-dimethoxyphenethyl) *tert*-butyl carbamate (2d-1)

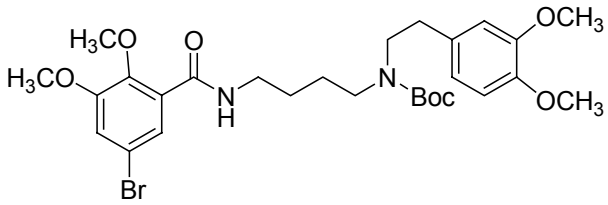


A mixture of 3,4-dimethoxyphenethylamine (1.0 g, 5.52 mmol), K_2CO_3 (3.04 g, 22 mmol), 4-bromobutyronitrile (816 mg, 5.52 mmol), and NaI (828 mg, 5.52 mmol) in 24 mL of DMF was stirred at 50 °C for overnight. After the evaporation of DMF under reduced pressure, the crude was diluted with water, and extracted with EtOAc. The organic layer was dried on Na_2SO_4 and evaporated to dryness to give a yellowish oil without further purification (1.32 g) (decomposes on column, so was not purified). ^{1}H NMR: ($CDCl_3$, δ) 1.98 (p, 2H, CH_2), 2.41 (t, 2H, CH_2), 2.76 (t, 2H, CH_2), 3.42 (q, 2H, CH_2), 3.86-3.87 (2s, 6H, OCH_3), 4.16 (t, 2H, CH_2), 4.79 (br, 1H, NH), 6.71-6.83 (m, 3H, aromatic CH).

To a mixture of the above oil (520 mg, 2.11 mmol), and Et_3N (323 mg, 3.17 mmol) in MeOH (5 mL) was added di-tertbutyl dicarbonate (698 mg, 3.17 mmol). The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the crude was purified by column chromatography (hexane: EtOAc=1:1) to give **2d-1** as a

light yellow oil (350 mg, 48%). ^{1}H NMR: ($CDCl_3$, δ) 1.32 (s, 9H, CH_3), 1.65 (p, 2H, CH_2), 2.15 (t, 2H, CH_2), 2.63 (t, 2H, CH_2), 3.08 (t, 2H, CH_2), 3.23 (t, 2H, CH_2), 3.68-3.71 (2s, 6H, OCH_3), 4.16 (t, 2H, CH_2), 4.79 (br, 1H, NH), 6.58-6.67 (m, 3H, aromatic CH).

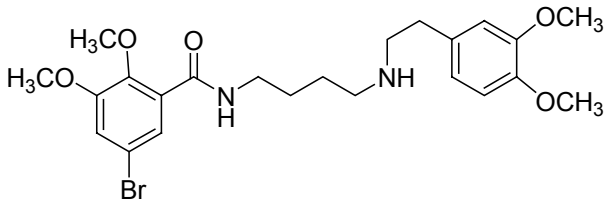
4-(5-bromo-2,3-dimethoxybenzamido)butyl-(3,4-dimethoxyphenethyl) tertbutyl carbamate (2d-2)



A solution of **2d-1** (280 mg, 0.81 mmol) in THF (6 mL) was added dropwise into the THF (4 mL) solution of LAH (92 mg, 2.43 mmol) at 0 °C. The mixture was stirred at room temperature overnight. The suspension was quenched carefully with Glauber's salt and filtered through celite. The crude was obtained as a colorless oil (290 mg) after evaporation of solvent.

To a solution of benzoyl chloride **2a-4** in dry CH_2Cl_2 was added the CH_2Cl_2 solution of the above oil and TEA dropwise. The mixture was stirred overnight and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed by 0.5 N NaOH, water, then dried over Na_2SO_4. After the evaporation of solvent, the crude was purified by column chromatography ($CHCl_3$: MeOH=80:1) to give a colorless oil **2d-2** (210 mg, 71%). ^{1}H NMR: ($CDCl_3$, δ) 1.41 (s, 9H, CH_3), 1.54 (m, 4H, CH_2), 2.71 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 3.31 (t, 2H, CH_2), 3.41(m, 2H, CH_2), 3.78-3.85 (4s, 12H, OCH_3), 6.68-6.77 (m, 3H, aromatic CH), 7.07 (d, 1H, aromatic CH), 7.75 (d, 1H, aromatic CH), 7.87(t, 1H, NH); ^{13}C NMR: ($CDCl_3$, δ) 26.89, 28.35, 39.34, 55.72, 55.82, 56.24, 61.23, 79.15, 111.27, 112.01, 116.98, 118.26, 120.65, 125.24, 127.99, 131.76, 146.48, 147.40, 148.77, 153.21, 155.30, 163.68.

5-bromo-N-(4-(3,4-dimethoxyphenethylamino)butyl)-2,3-dimethoxybenzamide (2d-3)



A solution of **2d-2 (**210 mg, 0.35 mmol) in CH_2Cl_2 (9 mL) was stirred at 0°C for 30 min. Then a solution of trifluoroacetic acid (1.85 mL) in CH_2Cl_2 (6 mL) was added dropwise slowly with vigorous stirring. The mixture was stirred at room temperature for 3 h and then evaporated to dryness. The residue was diluted with water and extracted by CH_2Cl_2 at pH 8.0-9.0. The organic layer was concentrated in vacuo and purified by preparative TLC ($CHCl_3$: MeOH=10:1) to give **2d-3** as a light brown oil (140 mg, 80%). ^{1}HNMR: ($CDCl_3$, δ) 1.66 (br, 4H, CH_2); 2.85 (t, 2H, CH_2); 2.96 (t, 2H, CH_2); 3.43 (t, 2H, CH_2); 3.83-3.86 (4s, 12H, OCH_3); 5.75 (br, 1H, NH); 6.70-6.80 (m, 3H, aromatic CH); 7.11 (d, 1H, aromatic CH); 7.74 (d, 1H, aromatic CH); 7.99 (t, 1H, amide NH); ^{13}CNMR: ($CDCl_3$, δ) 25.66, 27.07, 34.17, 39.24, 48.49, 50.40, 55.75, 55.83, 55.26, 61.27, 111.32, 111.81, 117.00, 118.35, 120.50, 125.17, 127.89, 130.88, 146.53, 147.64, 148.94, 153.23, 163.99; Anal.Calcd for $C_{23}H_{31}BrN_2O_5 \cdot (COOH)_2$: C, 51.29; H, 5.68; N, 4.79. Found: C, 51.07; H, 5.72; N, 4.75; m.p. 176-177 °C.

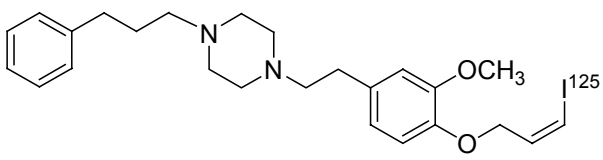
2.2 Radioiodination

Chemicals and solvents were reagent grade and used as received from commercial sources. No carrier added [^{125}I] NaI was obtained from Amersham Biosciences (104 mCi/mL of dilute NaOH). HPLC equipment consisted of a Rheodyne 7125 injector, Water 510EF pump, and a Waters 490 UV absorbance detector (280nm). A Waters C-18

Nova-Pak radial compression module column (8 x 100 mm, 4 μm) was used for preparative separation and a Waters C-18 Nova-Pak stainless steel column (3.9 x 150 mm, 4 μm) was used for analytical reversed-phase HPLC. Solid Phase extraction (SPE) cartridges (Waters SEP-PAK Light t-C-18) were activated prior to use by sequential elution with 2.5 mL of ethanol and 2.5 mL of distilled water. Radioactivity was measured with a dose calibrator (Capintec CRC-15W) employing similar counting geometries, coupled with attenuation correction factors as necessary for each reading.

2.2.1 Radiosynthesis, HPLC purification and Solid Phase Extraction

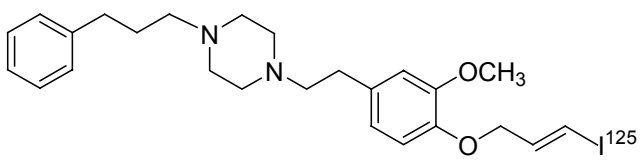
(*Z*)-1-(4-(3-[^{125}I]-iodoallyloxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine ([^{125}I] 1b-8)



The **1b-6** (1.5 mg, 2.2 μmol) oil was diluted with MeOH (364 μL). 25 μL of this solution was transferred into a glass vial sealed with a Teflon-faced septum, to which [^{125}I] NaI (15 μL, 1.55 mCi, 0.75 nmol), 75 μL of MeOH containing 3% HOAc, and aqueous chloromine-T (10 μL, 70 nmol) were added sequentially while stirring. After reacting for 1 min at room temperature, the reaction was quenched by 5% $Na_2S_2O_5$ solution. Semipreparative reversed-phase HPLC using the mobile phase: MeOH (20%), CH_3CN (20%), and an aqueous solution (60%) of Et_3N (2.1% v/v) and HOAc (2.8% v/v) at an elution speed of 2 mL/min gave **[^{125}I] 1b-8** (t_R=21.2 min) in a volume of 11 mL (containing 40% organic solvent). This solution was diluted by 25.6 mL of water (containing 15% organic solvent) and filtered through the activated C-18 Sep-Pak. The Sep-Pak was flushed once with 2.5 mL water and twice with air. The radioligand was eluted from the Sep-Pak with 1.0 mL

of ethanol into a clean 4 mL glass vial. The isolated radiochemical yield of [^{125}I] **1b-8** was 58% with a radiochemical purity of >97%.

(*E*)-1-(4-(3-[^{125}I]-iodoallyloxy)-3-methoxyphenethyl)-4-(3-phenylpropyl)piperazine ([^{125}I] 1b-9)



Similar treatment of **1b-7** with [^{125}I] NaI and chloramine-T as for **1b-6** gave [^{125}I] **1b-9** (t_R= 23.4 min) in 57% radiochemical yield.

2.2.2 The determination of specific radioactivity

The non-radioactive **1b-8** HCl salt was dissolved in water to make a 1.00E-3 M stock solution. A series of dilutions were made by using HPLC buffer (as described in **2.2.1**) to obtain 7 solutions: 2.26E-6 M, 4.50E-6 M, 7.50E-6 M, 1.05E-5 M, 1.35E-5 M, 1.50E-5 M and 2.50E-5 M. 20 μL of each of these solutions was injected into an analytical HPLC system and the height of each UV absorbance peak was measured (Figure 30). Then a standard curve with mass injected (pmol) vs. peak height (cm) was established (Figure 31). 714 μCi of radioiodinated **1b-8** was injected into the HPLC and the height of UV absorbance peak was measured to be 24 mm. From the standard curve obtained above, the mass of [^{125}I] **1b-8** was calculated to be 339 pmol. The specific radioactivity, 2105 mCi/μmol, can then be derived by dividing the radioactivity by the mass.

For the *trans* isomer, a standard curve was first established as described for the *cis* isomer (Figure 32 and 33). 475 μCi of radioiodinated **1b-9** was injected and the UV

absorbance peak was measured to be 16 mm. The mass of **[^{125}I] 1b-9** was calculated to be 199 pmol from the standard curve. Specific radioactivity, 2100 mCi /μmol, was then calculated as described above.

2.3 Measurement of lipophilicity[68, 69]

Lipophilicity was measured as the distribution coefficient (**Log D**) between a 1-octanol phase and a pH 7.4 Dulbecco's phosphate buffered saline phase. The octanol and buffer were pre-saturated (stirred overnight, and allowed to completely separate) with a minimum amount of aqueous phase and organic phase, respectively, prior to use. The radioactivity was measured in a Wallac Wizard, 1480 Automatic Gamma Scintillation Counter at a I-125 efficiency of 78%.

LogD of [^{125}I] 1b-8. 3.5 mL of octanol was added into a 15 mL plastic centrifuge tube A1. 4 μCi of [^{125}I] **1b-8** obtained from radioiodination was transferred to A1, to which 3.5 mL of phosphate buffer (pH 7.4) was then added. A1 was vortexed for 45 seconds and then centrifuged for 2 min at 2500 rpm to make sure that the phases had completely separated. A1 was removed from the centrifuge carefully without disturbing the two layers. The aqueous layer (bottom) was removed and discarded by using a 5 mL polypropylene syringe with a spinal needle (the purpose of this step was to wash away water-soluble impurities), then 3.5 mL fresh buffer was added. A1 was vortexed and centrifuged as before. 2×100 μL of the top layer (organic) were pipetted into 2 plastic scintillation vials (labeled as Oct A1). 2.5 mL of the bottom layer (aqueous) was transferred to a glass test tube, from which 2×1000 μL samples were pipetted into another 2 plastic scintillation vials (labeled as Buff A1).

6×0.5 mL of buffer-equilibrated octanol and 6×3.5 mL of octanol-equilibrated buffer were pipetted into 6 additional tubes A2-A6 sequentially. Then 3.0 mL of the remaining top layer (organic) from tube A1 was transferred into tube A2. The vortexing, centrifuging, pipetting and transferring procedures were repeated for A2-A6.

The resulting 24 vials (Oct A1-Oct A6, Buff A1-Buff A6) were counted in a gamma scintillation counter. The distribution coefficient logD was then calculated by the following equation:

$$\text{logD} = \log \frac{\text{radioactivity in octanol phase} \times 10}{\text{radioactivity in buffer}}$$

The same procedure was repeated for [^{125}I] **1b-9**, [^{125}I] **1f-6** and [^{125}I] **1f-7**. Values for radioactivity counts (cpm) are found in **Appendix III**.

2.4 *In vitro* binding assays

Haloperidol, (+)-pentazocine, and 1,3-di(2-tolyl)guanidine (DTG) were purchased from Sigma-Aldrich (St. Louis, MO). [^{3}H]-DTG and [^{3}H] (+) pentazocine were obtained from Perkin-Elmer Life Sciences (Boston, MA). Other chemicals and solvents were the best grade available, and were used as received from commercial sources. Stock solutions (1 mM) of ligands were prepared in water. For haloperidol and (+)-pentazocine, acetic acid (~5%) was added for solubilization. Serial dilutions of competing ligands and the radioligands were prepared in tris-HCl buffers (50 mM, pH 7.4 or pH 8.0 at 25 °C). Radioactivity was measured using a Wallac 1409 liquid scintillation counter and OptiPhase1HiSafe 2 cocktail (Perkin-Elmer) at a tritium efficiency of 44%.

2.4.1 Membrane preparation and BCA protein assay

Brain tissues for use in both sigma1 and sigma2 binding assays were prepared from English Hartley guinea pigs by minor modifications of procedures described previously.[70, 71]

Protein concentrations were determined using the bicinchoninic acid (BCA) colorimetric assay[72] against a bovine serum albumin (BSA) standard curve using a commercially available kit (Pierce Biotechnology, Rockford, IL).

Membranes prepared from guinea pigs of mixed sex were used for the binding assays of 1,4-disubstituted piperazines, while those from male guinea pigs were used for the benzamide series compounds.

2.4.1.1 Membrane preparation

Whole, fresh-frozen guinea pig brains (Rockland Immunochemicals, Gilbertsville, PA) were thawed, and then homogenized in 10 volumes (w/v) of ice-cold 0.32 M sucrose in Tris-HCl buffer (50 mM; pH 7.4, 25 °C) using a Polytron® (Brinkmann Instruments, Westbury, NY) at setting 5 for 30 s. The homogenate was centrifuged at low speed (900 g, 10 min; 4 °C), and the pellet discarded. The supernatant was centrifuged (22,000 g, 20 min; 4 °C), and the pellet suspended in 10 volumes of tris-HCl buffer (50 mM; pH 7.4, 25 ºC) and then incubated at 37 ºC for 30 min. After centrifugation (22,000 g, 20 min; 4 ºC), the pellet was suspended in Tris buffer as before, and divided into 5 – 12 mL aliquots that were stored until use at –80 ºC.

2.4.1.2 BCA protein assay

In 8 glass test tubes, 8 protein standards (2000, 1500, 1000, 750, 500, 250, 125, 25 μg/mL) were prepared by diluting the 2000 μg/mL BSA standard stock with 50 mM pH 7.4 tris buffer at 25 ºC. 2×100 μL (duplicates) of each of these standards were pipetted into test tubes numbered 1-16.

5 unknown protein samples were prepared by diluting the membrane suspension obtained from **2.4.1.1** in a ratio of $1:2^n$ (n=1-4) with tris buffer. For example, to get a 1:2 dilution, add 150 μL of membrane suspension and 150 μL of buffer; to get a 1:4 dilution, add 75 μL of membrane suspension and 225 μL of buffer, and so on. 2×100 μL of each of these unknown samples were pipetted into test tubes numbered 17-26.

55 mL of BCA reagent A were mixed with 1.1 mL of BCA reagent B to obtain a fresh working reagent (WR).

After added 2 mL of WR, tubes 1~26 were incubated at 37 ºC for 30 min and then cooled to room temperature. The absorbance at 562 nM of each tube (use water reference as blank) was measured quickly within 10 minutes. Data is found in **Appendix IV**.

2.4.2 Radiotracer solution preparation

2.4.2.1 The preparation of 10 nM [^{3}H]-(+) pentazocine

9.42 μL (volume is obtained by using graphpad online radioactivity calculator: http://www.graphpad.com/quickcalcs/radcalcform.cfm) of [^{3}H]-(+) pentazocine stock (34 Ci/mmol, 1 mCi/mL) was pipetted into 20 mL of pH 7.4 tris buffer in a 50 mL centrifuge tube. The mixture was vortexed and then 2×100 μL of this solution were pipetted into two glass scintillation vials. 10 mL of cocktail was added to each vial and vortexed. The

samples were counted in a beta scintillation counter (5 min/vial). The concentration of radiotracer was calculated to be 12.6 nM by the following equation:

$$\frac{Radioactivity(dpm)}{100\,\mu L} \times \frac{1\,\mu Ci}{2.22 \times 10^6\,dpm} \times \frac{1 mmol}{34 Ci \times remaining\%} \times \frac{1000 mL}{L} = X\ nmol/L$$

To adjust the concentration to the desired 10 nM, 4.8 mL ($M_1V_1=M_2V_2$) of buffer was added to dilute the above solution. The precise concentration of 9.88 nM was obtained by repeating the counting and calculation step.

2.4.2.2 The preparation of 30 nM [^{3}H]-DTG in the presence of 2000 nM (+)-pentazocine as sigma1 mask

68 μL of [^{3}H]-DTG stock (56 Ci/mmol, 1 mCi/mL) was pipetted into 30 mL of pH 8.0 tris buffer in a 50 mL centrifuge tube. Counting, calculation and adjustment by buffer (12.98 mL) were carried out as described in **2.4.2.1** to obtain a precise concentration of 30.08 nM. Then 170 μL of 0.5 mM (+)-pentazocine was pipetted into the [^{3}H]-DTG solution to make the sigma1 mask 2000 nM.

2.4.3 The Determination of IC_{50}

2.4.3.1 Sigma1 binding assay using [^{3}H]-(+) Pentazocine as the radiotracer[71]

Guinea pig brain (GPB) membrane aliquots were thawed, and then suspended at a concentration of 1 mg protein/mL by adding fresh 50 mM tris-HCl buffer (pH 7.4, 25 ºC). Each glass assay tube was kept at a final volume of 1.0 mL. The GPB (1 mg protein/mL, 250 μL/tube) was incubated for 150 min at 37 ºC with [^{3}H] (+)-pentazocine (10 nM, 100 μL/tube). Nonspecific binding was defined by haloperidol (10 μM, 100 μL/tube). Competing ligands (100 μL/tube) were used at 10 concentrations that were

equally spaced on the log scale, centered on the anticipated K_i, covering 5 orders of magnitude. Assays were terminated by addition of 5 mL of ice-cold 50 mM tris-HCl buffer (pH7.4) and filtration, using a cell harvester (Brandel, Gaithersburg, MD), through glass fiber filters (GF/B) that had been pretreated with polyethyleneimine (0.5%) for 60 min. Tubes and filter discs were washed three times with 5mL ice-cold assay buffer, and the filter discs were dried under vacuum. Each circular glass fiber filter piece was transferred into glass scintillation vials. 10 mL of Hisafe2 scintillation cocktail was added to each vial. Scintillation counting was carried out after equilibration of the glass fiber filter discs with cocktail for at least 24 h. The determination of the equilibration time was described in **2.4.3.2**.

2.4.3.2 The determination of equilibration time for sigma1 binding assay

To a 20 mL glass scintillation vial were first added 100 μL of 10 nM [^{3}H]-(+) pentazocine and then 10 mL of Hisafe2 scintillation cocktail (1 duplicate). The mixture was vortexed to mix well.

To another 20 mL glass scintillation vial was added one circle of glass fiber filter paper. 100 μL of [^{3}H]-(+) Pentazocine solution was pipetted onto this filter paper (3 duplicates). 10 mL cocktail was added into the vial and the mixture was vortexed.

The vials were counted in a liquid scintillation counter (counting time=1 min) at time intervals of 15 min, 60 min, 150 min, 270 min, 360 min, 1460 min and 2795 min to obtain the optimum equilibration time.

2.4.3.3 Sigma2 binding assay using [^{3}H]-DTG as the radiotracer[55, 70, 73, 74]

Thawed membranes were suspended at 1 mg protein/ml using 50 mM Tris-HCl (pH 8.0, 25 ºC). Each glass assay tube was kept at a final volume of 0.5 mL. The GPB (1 mg protein/mL, 250 μL/tube) was incubated for 120 min at 25 ºC with [^{3}H]-DTG (30 nM, 50 μL/tube) in the presence of (+)-pentazocine (200 nM, final concentration). Nonspecific binding was defined by DTG (1000 μM, 50 μL/tube). Competing ligands (50 μL/tube) were used at 10 concentrations. Assays were terminated by addition of ice-cold 50 mM tris-HCl (pH 8.0) assay buffer, followed by filtration and wash steps as described earlier. Scintillation counting was carried out after equilibration of the glass fiber filter discs with cocktail for at least 24 h. The determination of equilibration time was described in **2.4.3.4**.

2.4.3.4 The determination of equilibration time for sigma2 binding assay

To a 20 mL glass scintillation vial were first added 100 μL 30 nM [^{3}H]-DTG and then 10 mL of Hisafe2 scintillation cocktail (1 duplicate). The mixture was vortexed to mix well.

To another 20ml glass scintillation vial was added one circle of glass fiber filter paper. 100 μL of [^{3}H]-DTG solution was pipetted onto this filter paper (3 duplicates). 10 mL cocktail was added into the vial and the mixture was vortexed.

The vials were counted in a liquid scintillation counter (counting time=1 min) at the time interval of 15 min, 60 min, 150 min, 270 min, 360 min, and 1460 min to obtain the optimum equilibration time.

2.4.4 Sigma1 agonism/antagonism assays[75, 76]

Guinea pig brain membrane aliquots were thawed, and then suspended at a concentration of 1 mg protein/mL by adding fresh 50 mM tris-HCl buffer (pH 7.4, 25 ºC). Each glass assay tube was kept at a final volume of 1.0 mL. The GPB (1 mg protein/mL, 250 μL/tube) was incubated for 150 min at 37ºC with [^{3}H] (+)-pentazocine (10 nM, 100 μL/tube), and phenytoin (DPH, 20 mM, 50 μL/tube) or its solvent (0.15 mM NaOH, 50 μL/tube). Nonspecific binding was defined by haloperidol (10 μM, 100 μL/tube). Competing ligand were used at 10 concentrations. Assays were terminated by addition of ice-cold 50 mM tris-HCl (pH 8.0) assay buffer, followed by filtration and wash steps as described earlier. Scintillation counting was carried out after incubation of the discs with cocktail for at least 24 h.

CHAPTER 3

RESULTS AND DISCUSSION

In this section, the results obtained from the experimental sections described in **Chapter 2** are discussed, including organic synthesis, radiosynthesis, lipophilicity and *in vitro* binding assays. The *in vivo* experiments, cited from colleagues' work, is also described.

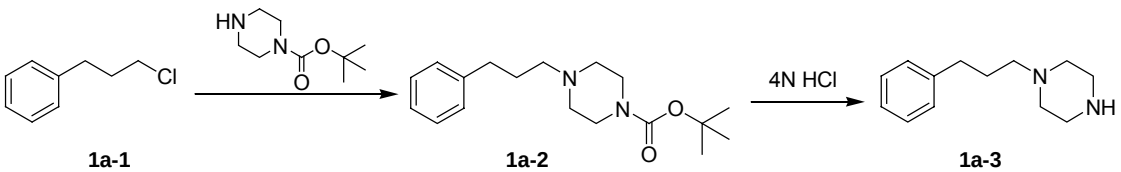
Most of the ligands were thick oils when in the free base form. The transformation from oils into white salts made them easier to dry and weigh. More important, the salt form had much better solubility in the assay buffer. The piperazine analogs were made into their diHCl salts and the benzamide analogs were made into their oxalate salts.

3.1 Structural modifications on Lead I and the related biological studies

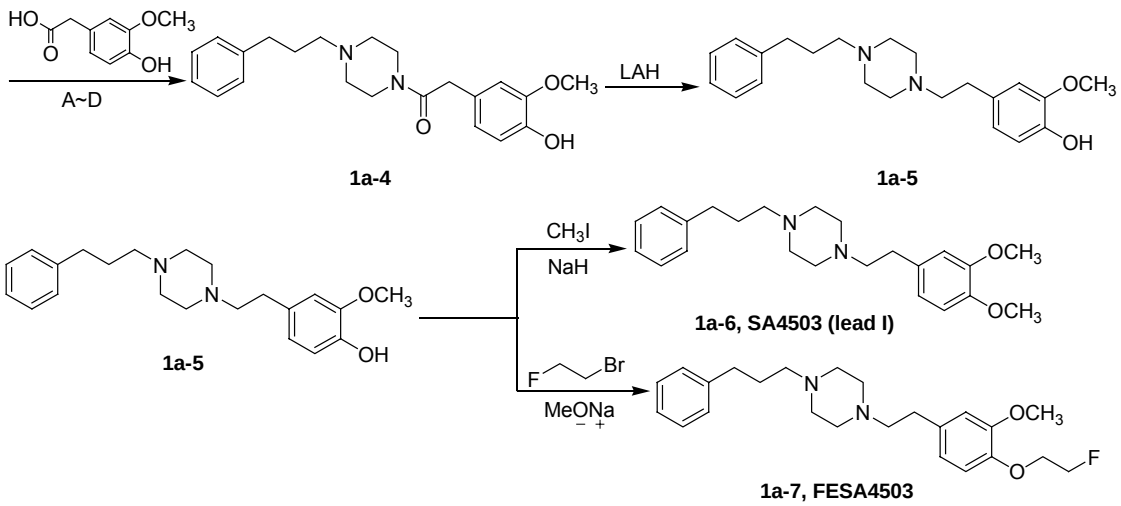
3.1.1 Structural modifications on SA4503 (Lead I analogs)

Generally, the **SA4503** analogs were synthesized by the alkylation of 4-*O*-desmethyl **SA4503** (**1a-5)** with alkyl bromides or *cis/trans* tributyltin tosylate under different basic conditions.

Scheme 1a The synthesis of 4-*O*-desmethyl SA4503 and two reference compounds



1a-1 **1a-2** **1a-3**



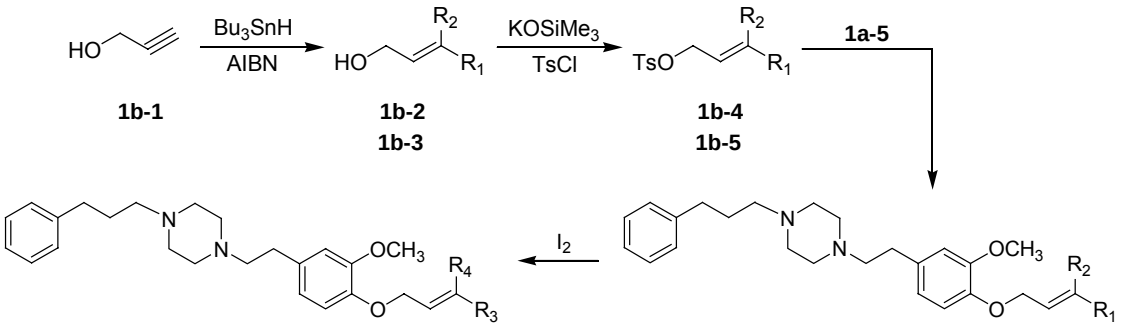
A, 1-hydroxy benzotriazole hydrate; B, 4-methylmorpholine; C, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; D, dichloromethane

In this scheme, 4-*O*-desmethyl **SA4503** (**1a-5**) was synthesized by the alkylation of 3-chlorophenylpropane with 1-Boc piperazine, followed by acid hydrolysis of the protecting group, amidation with carboxylic acid and then LAH reduction. **1a-5** was used as a synthetic precursor for the phenolic side chain modifications.

Two known compounds, **SA4503** (**Lead I**, **1a-6**) and its analog **FESA4503** (**1a-7**) were synthesized as refernce compounds for *in vitro* binding experiments. **SA4503**, was made by the method indicated in the literature[43] and no problems were encountered. The synthesis of **FESA4503** was reported in the literature by the reaction of **1a-5** with 2-fluoroethyl tosylate.[27] This tosylate intermediate, however, was not obtained in satisfactory yield by the reaction of 1, 2-ditosylate ethane with KF with the presence of the phase transfer reagent kryptofix 2.2.2. A possible explanation is that both tosylate groups in 1, 2-ditosylate had been replaced by fluorines. A different alkylating reagent, commercially available 1-bromo-2-fluoroethane, when reacted in freshly made sodium

methanolate solution with a phenol precursor, was reported to give a fluoroethoxy compound in 69% yield.[61] In our case, this method gave **1a-7** in 60% yield.

Scheme 1b The synthesis of cis/trans iodoallyl SA4503



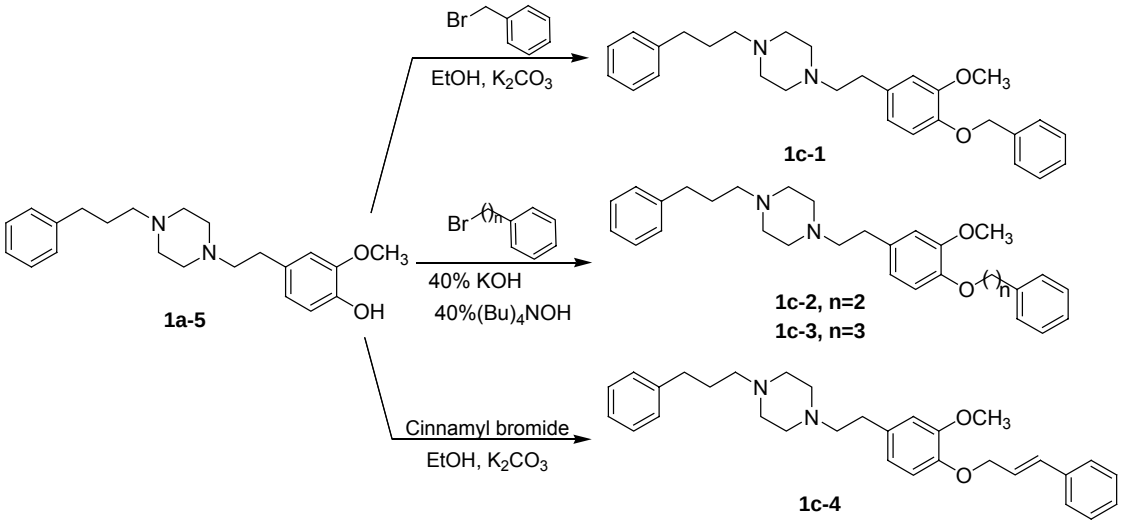
The *cis* and *trans* allylic alcohols (**1b-2**, **1b-3**) were prepared by the free radical reaction of propargyl alcohol with tributyltin hydride and AIBN. **1b-2** was obtained as an inseparable mixture with its terminal alkene isomer (2:1 from ^{1}H NMR). As reported by Jung,[63] **1b-2** and **1b-3** can be obtained in different ratios under different temperatures. The *trans* isomer **1b-3** was obtained in higher yield at higher temperature (80°C vs. 60°C), while lower temperature favored the *cis* isomer.

The esterification of allylic alcohols with tosylate chloride and potassium trimethylsilanolate at –25 °C proceeded well as indicated by the complete conversion of starting material on analytical TLC. The terminal alkene isomer, unable to be separated with **1b-2** in the previous step did not react with TsCl and thus became separable in this step. However, it was found that both **1b-4** and **1b-5** suffered from partial decomposition during chromatographic purification (the mass of eluted material decreased by 30-50% every time). Considering their acid sensitivity, we buffered silica gel with 5% triethylamine, but the decomposition still occurred. The purification by reduced pressure

distillation (160˚C, 3.2 torr) was not successful due to decomposition under high temperature. The *trans* tosylate **1b-5,** although stored in refrigerator, was still found to decompose and form gel like polymer after two months. The *cis* and *trans* tributyltin tosylates served as important intermediate for the synthesis of N- or O-iodoallyl compounds. The stereospecific iodo-destannylation made them especially useful.

We incorporated the *cis/trans* iodoallyl groups on the phenolic side chain as a comparison to the fluoroethyl group in **FESA4503** in order to understand the effects of different halogens on binding affinity.

Scheme 1c The synthesis of 4-*O*-phenylalkyl analogs of SA4503



To explore the bulk tolerance of the hydrophobic region in sigma receptor, we proposed several phenyl alkyl analogs. Phenethyl analog **1c-2** and phenylpropyl analog **1c-3** were synthesized by the optimized alkylation condition indicated in Scheme **1d**.

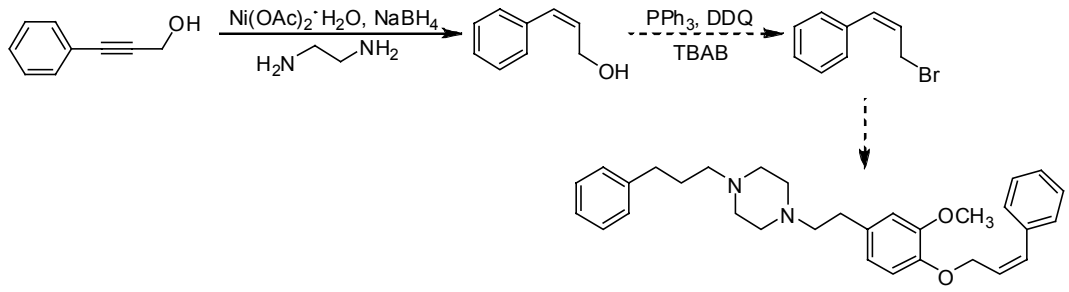
When the same conditions were used for preparing benzyl analog **1c-1** and cinnamyl analog **1c-4,** no products were obtained. During the synthesis**,** it was found that the phenol starting material **1a-5** was consumed completely after one hour, but instead of

forming less polar O-alkylated compounds, more polar compounds were formed as indicated by analytical TLC.

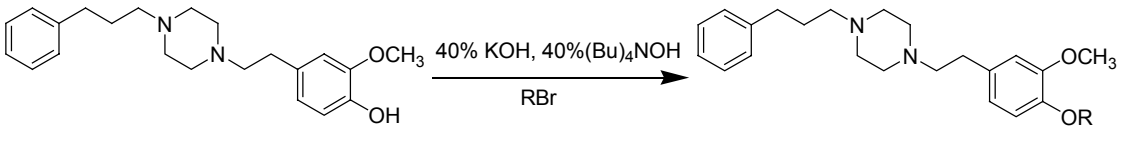
Finally, **1c-1** and **1c-4** were synthesized in low to moderate yields (35%, 56%) by reacting with the mild base K_2CO_3 in EtOH.[77] The moderate yield of **1c-4** was probably due to poor solubility of cinnamyl bromide in EtOH.

The (*Z*)-**1c-4**, was not obtained due to a problem present in synthesizing an intermediate, the *cis* isomer of cinnamyl bromide. The synthesis was carried out first by the $NaBH_4$ reduction of 3-phenyl-2-propyn-1-ol with the presence of Ni^{2+} as catalyst.[78] The amount of ethylenediamine was found to affect the outcome of this hydrogenation reaction. When 0.2 equivalent of ethylenediamine was used, the desired allylic alcohol was obtained in 86% yield as indicated by GC-MS, with the over-hydrogenation product as an impurity. When using 0.4 equivalent of ethylenediamine, allylic alcohol was produced as the only product. The followed bromination reaction[79] gave the allylic bromide in very low yield. It was found later that the (*E*)-**1c-4** was decomposed in binding assay solution (section **3.1.3**), so we thought that the (*Z*)-**1c-4** might have the same problem. Thus the synthesis of (*Z*)-**1c-4** was given up at this stage.

Scheme 1c' The synthesis of (*Z*)-1c-4



Scheme 1d The synthesis of 4-*O*-alkyl analogs of SA4503



1a-5

1d-1, R= propyl, T= 50 °C
1d-2, R=Allyl, T= 0 °C

Different solvents and bases were used to optimize the phenol alkylation reaction. The following table showed the conditions tried for the propyl analog **1d-1** as an example.

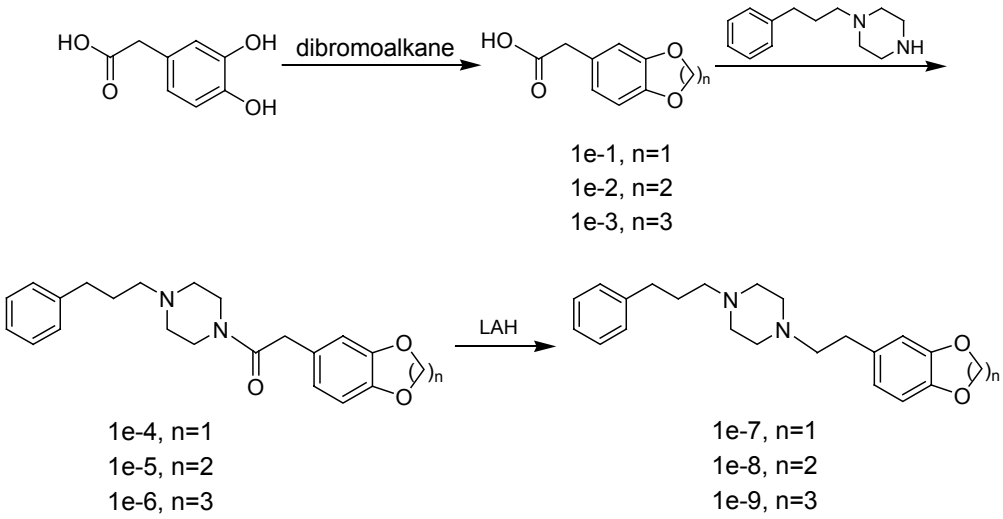
Table 2 Optimization of phenol alkylation reaction

	Base	ROH: Base: RBr: NaI: TBAH	Solvent	t (min)	T (˚C)	Yield (%)
1	NaH	1:300:100:0: 0	DMF	5	80	Trace
2	NaH	1:50:100:100: 0	DMF	50	120	Trace
3	NaOH	1: 14: 2: 0: 0	H_2O:MeOH (1:50)	300	80-90	24
4	KOH	1: 14: 17: 0: 0.2	H_2O	60	50	90

When using NaH (entries 1 and 2)[60] as base, only trace amount of products were produced. The change from NaH to NaOH (entry 3)[80] improved the yield to 24%. A significant improvement in yield was observed when using aqueous KOH as base and TBAH as phase transfer reagent at a temperature of 50 ˚C (entry 4).[81] This optimized condition worked well with most of the alkyl bromides except allyl bromide (**1d-2**), cinnamyl bromide (**1c-4**) and benzyl bromide (**1c-1**), where many side products were produced. The yield for the allyl analog (**1d-2**) was improved to 57% by lowering the

temperature to 0 ˚C when adding allyl bromide. This optimization reduced the amount of impurities in the reactions of **1c-1** and **1c-4**, but still no target products were observed.

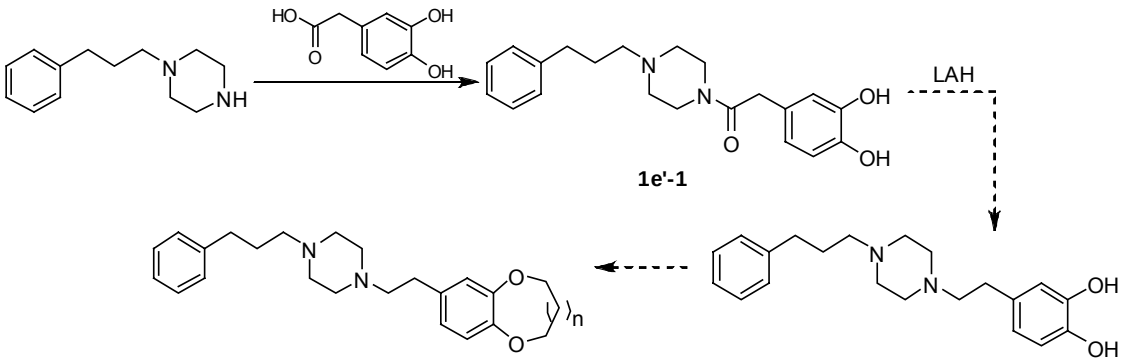
Scheme 1e The synthesis of phenyldioxy analogs of SA4503



The synthesis of the phenyl 3,4-dioxy ring analogs was straightforward by the amidation of the carboxylic acid with phenylpropyl piperazine followed by LAH reduction. **1e-1** was commercially available. **1e-2** and **1e-3** were made by ring closure of the ortho diphenol with dibromoalkane[82].

An alternative method of making dioxy ring analogs **1e-8** and **1e-9** had also been proposed as shown below:

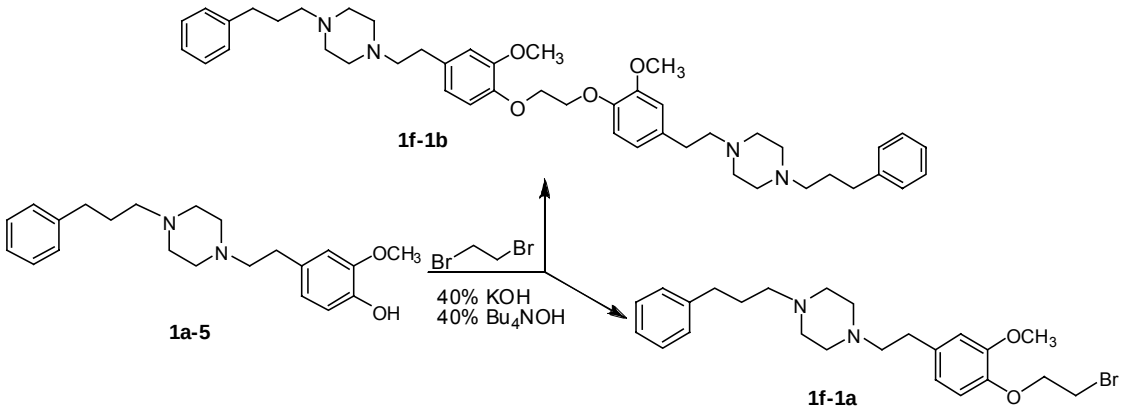
Scheme 1e' An alternative method of synthesizing phenyldioxy ring analogs

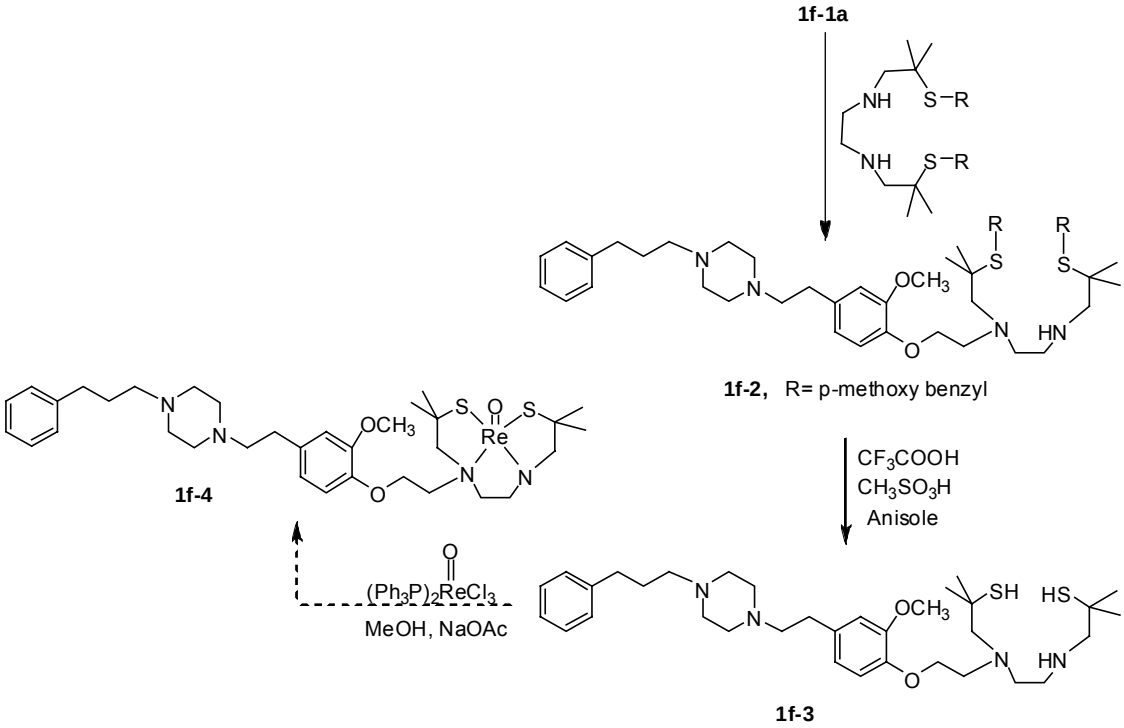


The amide **1e'-1** was obtained as a pink colored crystalline solid in 49% yield. However, its poor solubility in THF made the LAH reduction impossible to proceed and the amphoteric property of the reduction product also caused many problems during the extraction.

In Scheme **1f**, the bromoethyl analog of **SA4503** (**1f-1a**) was synthesized by the optimized conditions described in Scheme **1d**. An unexpected dimer product **1f-1b** was formed in high yield (80%) when the reaction was scaled up from 1 mmol to 3 mmol. **1f-1b** had the same R_f value as its starting material **1a-5** on analytical TLC plates but different retention times by HPLC (**1a-5**: 1.9 min; **1f-1a**: 2.28 min; **1f-1b:** 2.39 min).

Scheme 1f The synthesis of diamine metal chelate as SA4503 ananlogs





The formation of **1f-2** was monitored by HPLC (Figure 21). After reacting for 43 h at 50 °C, the growth of product became slow. The percentage of product increased when the temperature was increased from 50 °C to 80 °C, but another 77 hours of reaction did not seem to increase the percentage of product significantly. An equilibrium had probably been reached at that point.

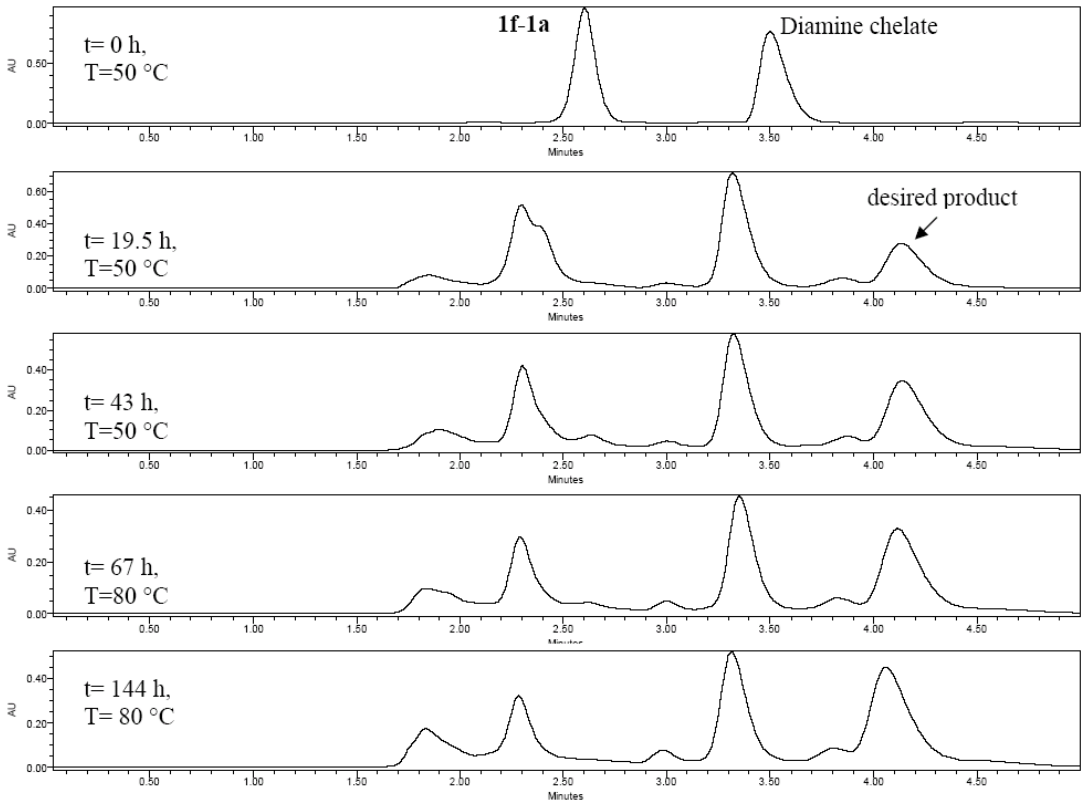


Figure 21 HPLC monitored alkylation reaction of 1f-1a with diamine chelate

The LC-MS for the reaction crude also confirmed that the desired product **1f-2** had been produced (Figure 22). However, a problem was encountered during purification. Although the HPLC indicated only 4 major components in the reaction crude, many more impurities with similar R_f values were observed on the analytical TLC plate. The column chromatographic purification was monitored by HPLC (Figure 23). After the first separation, some of the diamine reactant was removed and the percentage of product was increased slightly. However, the second separation resulted in increased amount of the diamine reactant, suggesting that part of product **1f-2** had decomposed into its diamine precursor. Other purification methods such as chromototron and preparative TLC had

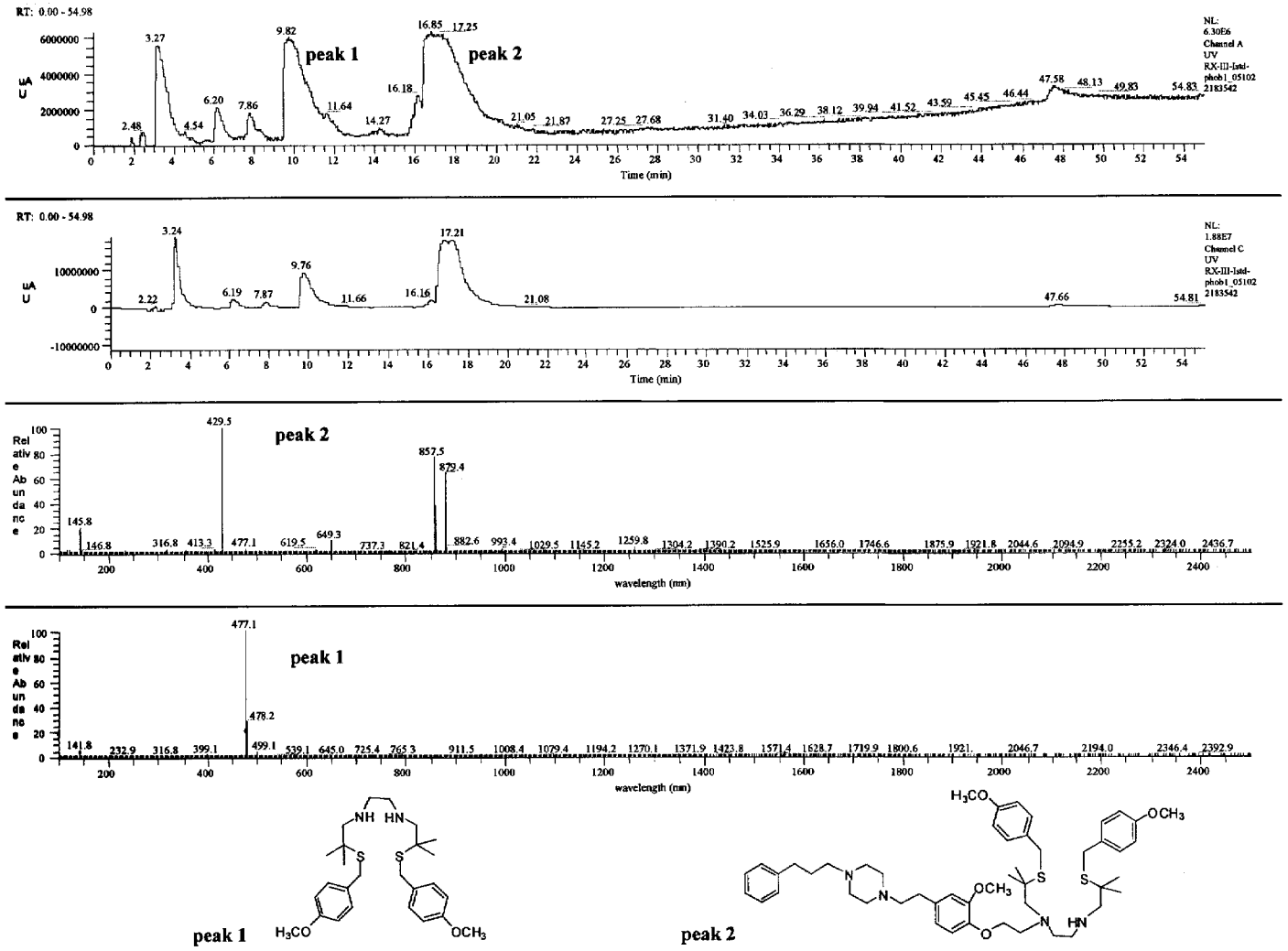


Figure 22 LC-MS of 1f-2 crude

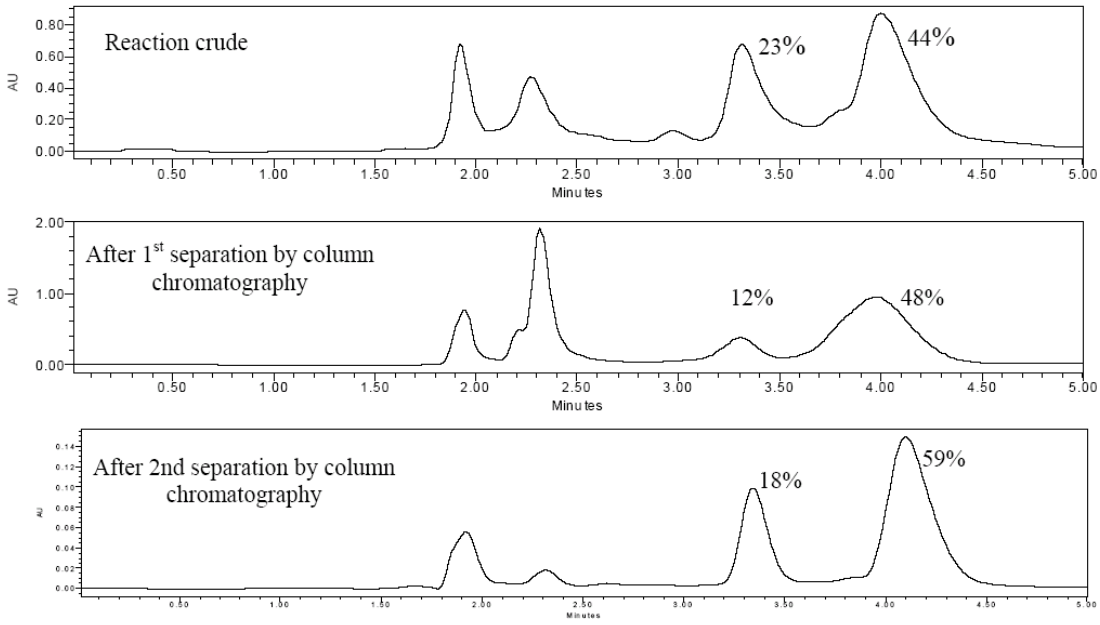


Figure 23 HPLC monitored column chromatographic purification of 1f-2

been used, but this problem still existed. The reaction and purification were repeated several times, but only once, was **1f-2** obtained as a clean compound in 25% yield.

The reaction crude of **1f-4** was purified by preparative TLC to give a product purple in color. Due to the tiny amount, characterization was not possible.

3.1.2 *In vitro* binding assay results for Lead I analogs

3.1.2.1 BCA protein assay

The BCA protein assay was conducted in order to get the concentration of protein in the membrane suspension prepared from whole GPB (described in **2.4.1.1)**. With 8 concentrations of standard protein samples and their corresponding UV absorbances at 562 nm (Figure 24, data is found in **Appendix IV**), a standard curve was first established.

Then the unknown samples were analyzed by Radlig 6.0 software (KELL, Suite, Biosoft, Inc., Ferguson, MO) to get the protein concentration.

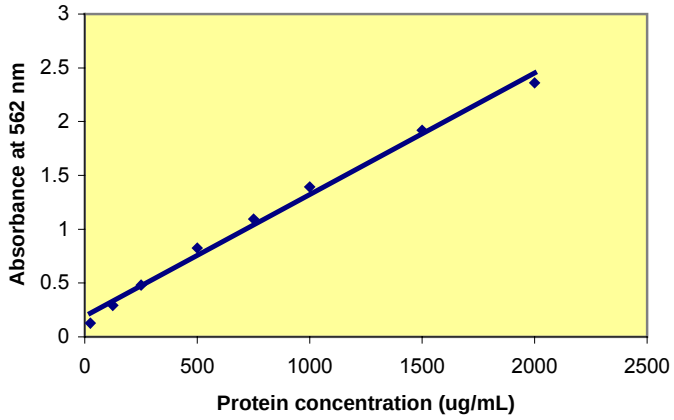


Figure 24 BCA standard curve

For most cases, a concentration of about 4 mg/mL is needed. In this experiment, the concentration obtained was 3416 µg/mL. A further 1: 3.4 dilution of this membrane suspension with tris buffer resulted in a concentration of 1 mg/mL that was used in the *in vitro* binding assays.

3.1.2.2 The determination of optimum equilibration time

The equilibration time is the time that is needed to extract the receptor-radioligand complex from the glass fiber filter discs into scintillation cocktail. Before an equilibrium is reached, the amount of receptor-radioligand complex that is transferred from filter paper into cocktail will keep increasing as time goes by. If radioactivity is measured during this time, inaccurate results will be obtained. The purpose of this experiment is to determine the least time needed for the equilibration.

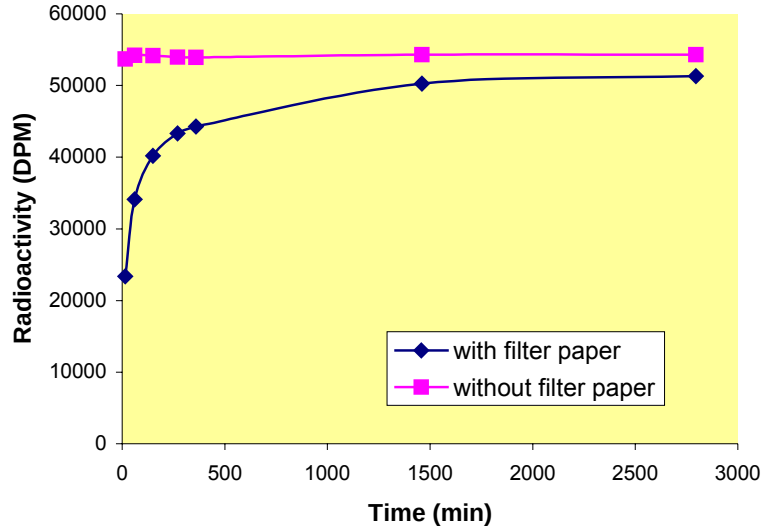


Figure 25 The equilibration of [^{3}H] (+)-pentazocine between glass fiber filter paper and scintillation cocktail

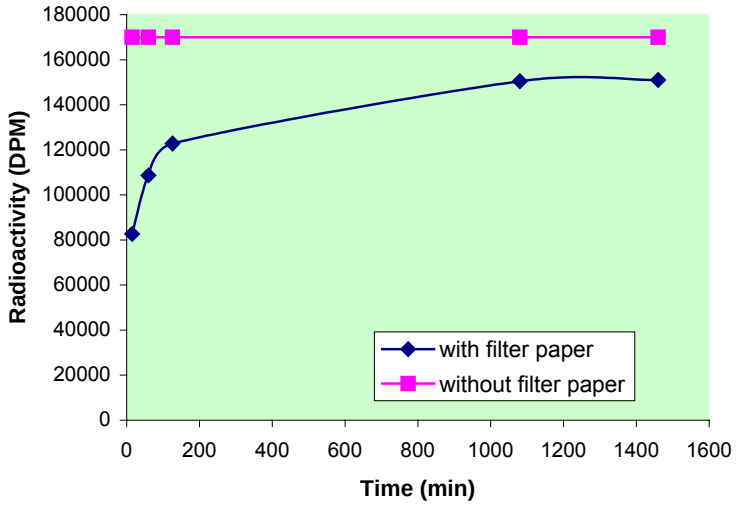


Figure 26 The equilibration of [^{3}H]-DTG between glass fiber filter paper and scintillation cocktail

As shown in Figures 25 and 26, the amount of radiotracer that was extracted from the glass fiber into cocktail kept increasing as a parameter of time until equilibrium was reached, at which time, the radioactivity should be measured. The least equilibration time

for the sigma1 assay using [^{3}H]-(+) Pentazocine is 24 h, and the time for the sigma2 assay using [^{3}H] DTG is 18 h.

3.1.2.3 Sigma binding assay results for the SA4503 analogs

Binding data were analyzed with the nonlinear curve-fitting computer programs Prism 4.0 b (GraphPad Software, San Diego, CA) and Radlig 6.0 (KELL Suite, Biosoft, Inc., Ferguson, MO). Statistical analyses were performed with the program Prism. Each experiment was performed in duplicate, and repeated three to six times to provide means and standard errors. Apparent affinities (K_i) were calculated by the equation of Cheng and Prusoff using IC_{50} values, the concentration of radioligand, and the experimentally determined K_D of the radioligand.

SA4503 and its analog **FESA4503** were synthesized as reference compounds in order to obtain standard binding data. The binding results (Table 3) showed that the replacement of a methoxy by a fluoroethoxy group decreased sigma1 affinity by about 2-fold. While in the literature, this structural modification resulted in a 3-fold increase in sigma1 affinity. Even though, the difference between the reported data and ours was within a reasonable range. However, the sigma2 affinities have a big discrepancy with the literature values, for example, **SA4503** has a 25-fold higher affinity than Mastuno's data[33] and **FESA4503** has 61 fold less affinity than Elsinga's data.[27] Both of these two leads showed only moderate selectivity for sigma1, thus the replacement of methoxy by fluoroethoxy group seems unlikely to convert a sigma1 ligand into a sigma2 ligand. To make sure our assay protocol was reliable, haloperidol purchased from a commercial source was tested and the result showed no significant difference with literature values.

Then we used the same protocol reported in Mastuno's paper, the data still agreed with our previous result. In order to find out the reason that caused different binding properties, we also tried both male GPB membrane and mixed sex GPB membrane, but results were consistent with our previous findings.

Table 3 Comparison of binding affinities of SA4503 and FESA4503 with the literature values

Compound	(IC_{50}, nM)		Selectivity (σ_2/σ_1)
	σ_1	σ_2	
SA4503	17.4	1784.1	103*
	6.67 ± 0.30	70.93 ± 4.86	10.6
FESA4503	6.48	2.11	0.33*
	11.50 ± 0.56	128.9 ± 12.5	11.2

* reported data[27, 33]

Beradi's group, published in 2001 the sigma affinities of a series of piperidine ligands. In their paper, **SA4503** was used as a reference compound and its sigma2 affinity was 77.5 nM.[83] This was in good agreement with our data. Additionally, it had been described in Elsinga's paper[27] that there was a discrepancy between the *in vitro* and *in vivo* affinities for **FESA4503**. Their *in vivo* observation, that ^{18}F-**FESA4503** had lower affinities than ^{11}C-**SA4503**, however, was consistent with our results. We published a detailed discussion about the discrepancies of binding properties of **SA4503** and **FESA4503** in *Synapse*. [84]

Most of the phenyl 4-*O*-alkylated analogs showed moderate affinities for both sigma receptors, and almost no selectivity between sigma subtypes (Table 4).

The replacement of fluorine (**1a-7**) by bromine (**1f-1a**) causes a 3-fold decrease in sigma1 affinity while 4-fold increase in sigma2 affinity. *E* and *Z* iodoallyl groups (**1b-8**,

1b-9) have similar effects as bromoethyl (**1f-1a**). These results indicate that the chemical properties of fluorine attribute to the selective sigma1 binding. The modification of fluorine by other halogens, such as bromine and iodine, can diminish the selectivity between sigma1 and sigma2 subtypes.

Compared to the alkyl substituent (**1d-1**), the incorporation of alkene (**1d-2**) slightly decreases affinities for both sigma subtypes. Nevertheless, the introduction of iodine in conjugation with double bond (**1b-8**, **1b-9**) can slightly increase affinities. The stereochemistry of the iodoallyl does not make big difference, as seen from their similar binding affinities and selectivities.

Bulky phenol substituents such as benzyl (**1c-1**), phenethyl (**1c-2**) and phenylpropyl (**1c-3**) are tolerated by both subtypes. Compared to **SA4503**, their increased sigma2 affinities might be attributed to a better interaction of the hydrophobic phenolic side chains with the hydrophobic region of sigma receptor. The different length of methylene unit (n=1 to 3) in **1c-1** to **1c-3** does not show big difference in sigma binding, suggesting that these three analogs have almost the same extension into the hydrophobic pocket of sigma receptor.

The modification of the 3, 4-alkoxy open chain by 3, 4-rigid dioxy ring leads to a slight increase in sigma1 selectivity. The methylenedioxy analog (**1e-7**), being the most rigid, has higher binding affinity and selectivity for both subtypes than its six (**1e-8**) and seven (**1e-9**) membered ring analogs. Additionally, as we mentioned in **1.3.1b.4** that since the 3D structure of **1e-9** more resembles that of **SA4503** than **1e-7** and **1e-8**, thus **1e-9** might have similar binding properties to **SA4503**. The result shows **1e-9** does have similar sigma2 binding properties with **SA4503**.

Desmethyl **SA4503** (**1a-5**), a synthetic precursor for the phenolic side chain alkylation, has not had its binding properties reported before. In our hands, it showed nanomolar affinity toward both sigma1 and sigma2 receptors. Thus, a hydrogen bond donor at the phenolic side chain is useful in increasing binding affinities for both sigma subtypes.

Except the above observations, we have also noticed that all of the **SA4503** analogs in this study showed higher sigma2 affinities than their lead compound **SA4503**.

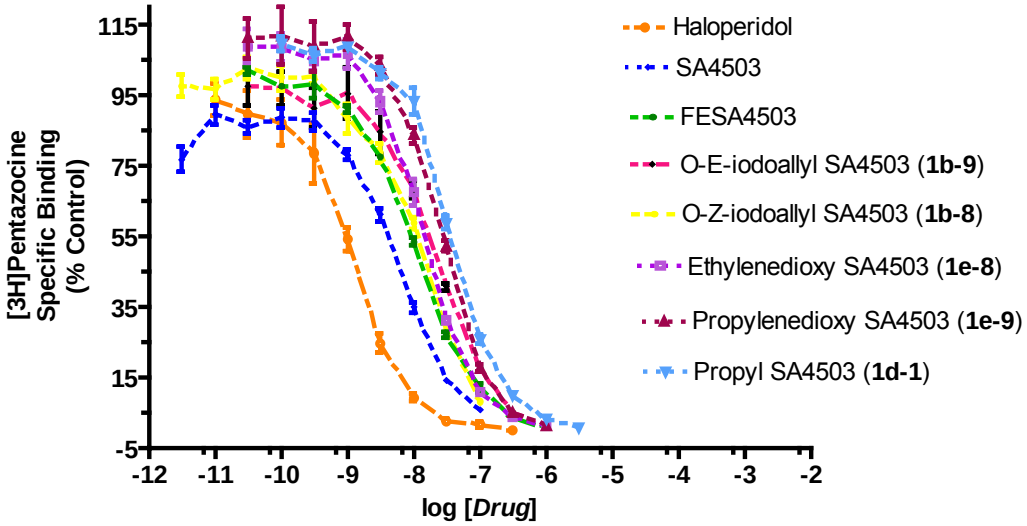


Figure 27 The displacement curves for SA4503 analogs against [^{3}H]-(+) pentazocine binding to sigma1 sites in GPB membranes

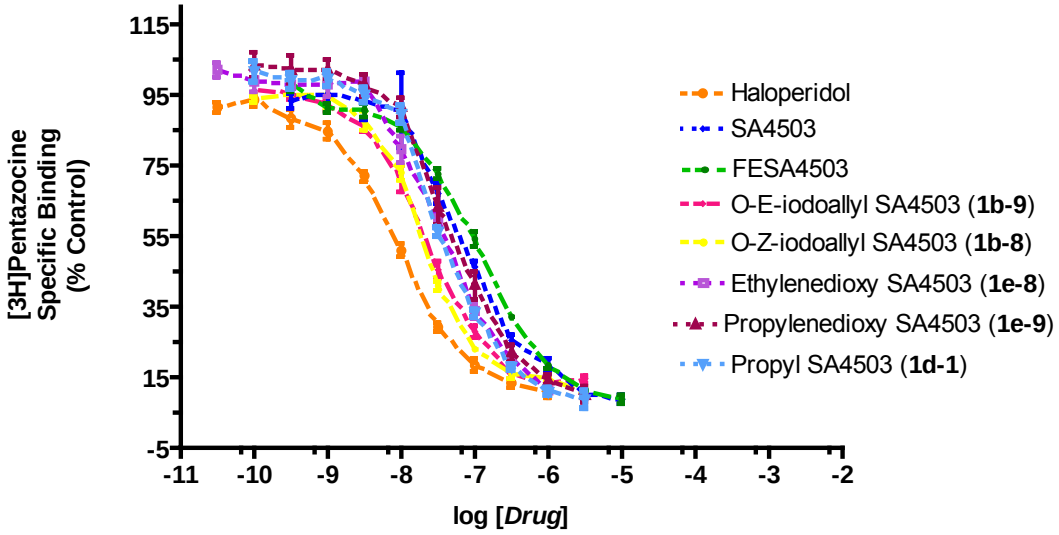
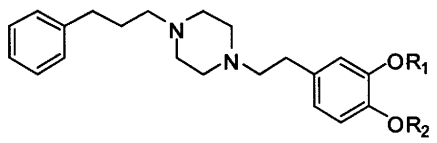


Figure 28 The displacement curves for SA4503 analogs against [^{3}H] DTG binding to sigma2 sites in GPB membranes using 200 nM (+)-pentazocine as sigma1 mask

Table 4 Sigma receptor binding affinity and sigma2 / sigma1 selectivity for 1,4-disubstituted piperazines in GPB



Compound			# of assays	Sigma1			Sigma2			σ_2 / σ_1 (IC_{50})
	R_1	R_2		IC_{50} (nM)	K_i (nM)	n_H*	IC_{50} (nM)	K_i (nM)	n_H	
1a-5	OCH_3	H	4	2.51 ± 0.25#	1.75 ± 0.17	1.25 ± 0.04	7.59 ± 0.24	6.72 ± 0.21	0.87 ± 0.06	3.0
1a-6 (SA4503)	OCH_3	OCH_3	6	6.67 ± 0.30	4.63 ± 0.21	1.23 ± 0.06	70.93 ± 4.86	63.09 ± 4.33	0.88 ± 0.05	13.6
1a-7 (FESA4503)	OCH_3	fluoroethyl	4	11.50 ± 0.56	8.03 ± 0.41	0.93 ± 0.19	128.9 ± 12.5	113.2 ± 11.7	0.95 ± 0.07	14.1
1b-8	OCH_3	*(Z)*-iodoallyl	6	15.45 ± 1.91	10.67 ± 1.32	1.01 ± 0.09	18.78 ± 1.24	16.71 ± 1.20	1.15 ± 0.04	1.2
1b-9	OCH_3	*(E)*-iodoallyl	4	24.48 ± 1.85	16.91 ± 1.28	1.06 ± 0.08	20.45 ± 2.23	18.20 ± 1.99	0.96 ± 0.01	0.8
1c-1	OCH_3	benzyl	4	29.73 ± 1.57	20.79 ± 1.10	1.32 ± 0.05	18.55 ± 1.27	16.43 ± 1.13	0.82 ± 0.04	0.6
1c-2	OCH_3	phenethyl	4	18.97 ± 1.18	13.26 ± 0.82	1.20 ± 0.11	18.72 ± 0.72	16.57 ± 0.64	0.78 ± 0.06	1.0
1c-3	OCH_3	phenylpropyl	4	26.38 ± 0.68	18.45 ± 0.48	1.28 ± 0.05	26.31 ± 3.78	23.31 ± 3.34	0.96 ± 0.09	1.0
1d-1	OCH_3	propyl	3	34.1±7.36	25.6±2.56	-1.27±0.26	37.8±1.26	33.4±1.11	-1.22±0.34	1.1
1d-2	OCH_3	allyl	3	43.10 ± 1.77	30.13 ± 1.24	1.05 ± 0.05	47.65 ± 0.75	42.10 ± 0.66	0.95 ± 0.05	1.1
1e-7	CH_2		3	3.65 ± 0.26	2.55 ± 0.19	1.23 ± 0.05	16.74 ± 0.49	14.83 ± 0.43	1.06 ± 0.03	4.6
1e-8	CH_2CH_2		3	14.8±0.76	10.2±0.52	-1.22±0.04	39.8±1.91	35.2±1.69	-1.00±0.17	2.7
1e-9	$CH_2CH_2CH_2$		3	27.3±4.29	19.1±3.11	-1.21±0.20	58.9±5.56	52.1±4.91	-1.06±0.22	2.1
1f-1a	OCH_3	bromoethyl	3	36.29 ± 2.88	25.37 ± 2.02	1.11 ± 0.06	30.61 ± 1.09	27.12 ± 0.96	0.99 ± 0.05	0.8

* Hill slope; # Standard error

3.1.2.4 A stability examination of the phenylallyl SA4503 analog 1c-4

Due to its heat sensitive nature, the *trans* phenylallyl **SA4503** analog (**1c-4)** free base (white solid), instead of its HCl salt, was used for the biological study to avoid the heat required during salt recrystallization. Unlike its phenylpropyl analog **1c-3** and allyl analog **1d-2** that had only moderate affinity for the sigma1 receptor, **1c-4** showed nanomolar affinity. This unusual observation arose the thought that **1c-4** might have decomposed into its phenol precursor **1a-5** during storage, as **1a-5** had nanomolar affinity as well. The purity examination by analytical HPLC (30A70B, A=H_2O: HOAc: TEA (32:1:0.75, v/v/v), B=MeOH: MeCN (1:1, v/v), 1mL/min, UV 280 nM) (Figure 29) showed that **1c-4** was indeed under decomposition after storage for a certain period even though different dissolution conditions were employed. Another possibility was to prepare fresh assay solution and conduct the binding assay right away to avoid the decomposition. However, nanomolar binding affinity was again observed as before. An explanation was: for the purpose of dissolving the lipophilic phenylallyl analog **1c-4** free base into aqueous phase, acid was an unavoidable reagent (EtOH and DMSO alone did not show good solubility in small volume), which in turn caused the acid sensitive **1c-4** to decompose although the solution was freshly made.

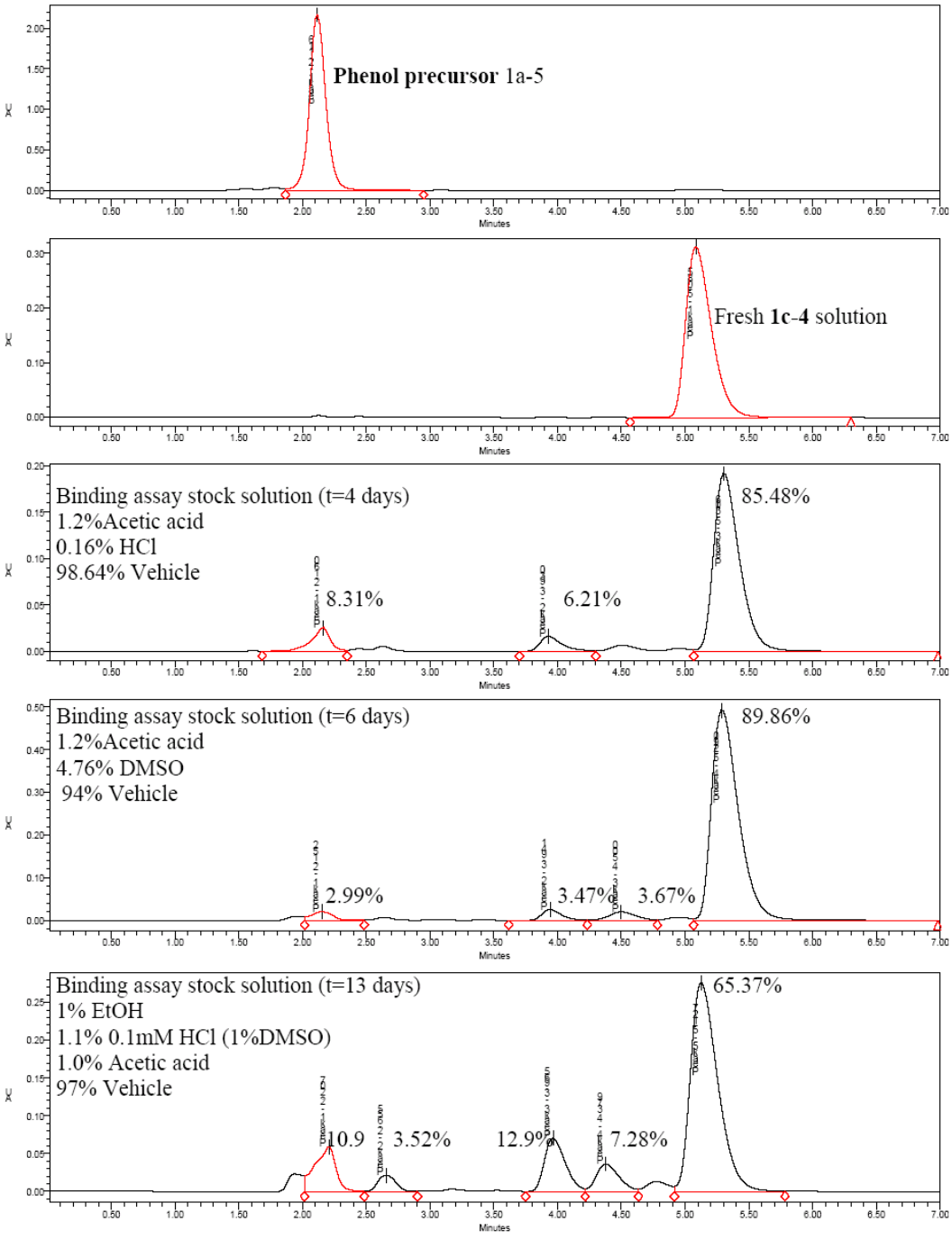


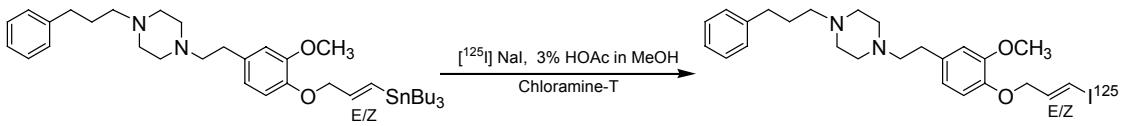
Figure 29 The stability examination on phenylallyl analog 1c-4 in assay solution

3.1.3 Radioiodination and related studies

Radioiodinated compounds are useful as diagnostic reagents. For organic substrates, commonly used radioiodination methods include iodine monochloride iodination and chloramine-T iodination. In both cases, the iodine cation is generated and undergoes electrophilic substitution to yield an iodine-labeled compound. Two major considerations in radioiodination are the reactivity of the nucleophile in electrophilic substitution and the stability of resultant iodinated product. Thus, a group such as vinylstanne and arylstanne is desired in order to improve reactivity and stability. Especially, the iododestannylation of vinylstannylated agent can maintain the original stereochemistry of the alkene, so it has great applications in radioiodination.

As described in Chapter 1, we designed the *cis/trans* iodoallyl analogs of **SA4503** to understand the binding effects of halogens. The *in vitro* binding study showed both *cis* and *trans* isomer had similar moderate binding affinities (Table 4). Would they be feasible to be used in the next step, the biodistribution studies? Did they have the appropriate lipophilicities, one of the important parameters for a brain imaging agent? Radioiodination of both isomers would be the first step in order to answer these questiones.

Scheme 1g Radioiodination of *E/Z* O-iodoallyl SA4503



1b-6, Z
1b-7, E

[^{125}I]1b-8, Z
[^{125}I]1b-9, E

The iododestannylation reaction proceeded fast and smoothly by the method reported. [62] Good yields, 58% for the *cis* isomer and 57% for *trans* isomer, were obtained.

3.1.3.1 The Determination of Specific activity for [^{125}I] 1b-8 and [^{125}I] 1b-9

Specific activity (SA) is the radioactivity per unit mass. To determine the SA of [^{125}I] **1b-8 and** [^{125}I] **1b-9**, the standard curves (Figures 31 and 33) were first established using nonradioactive standards containing different masses and their corresponding HPLC response peak heights (Figures 30 and 32).

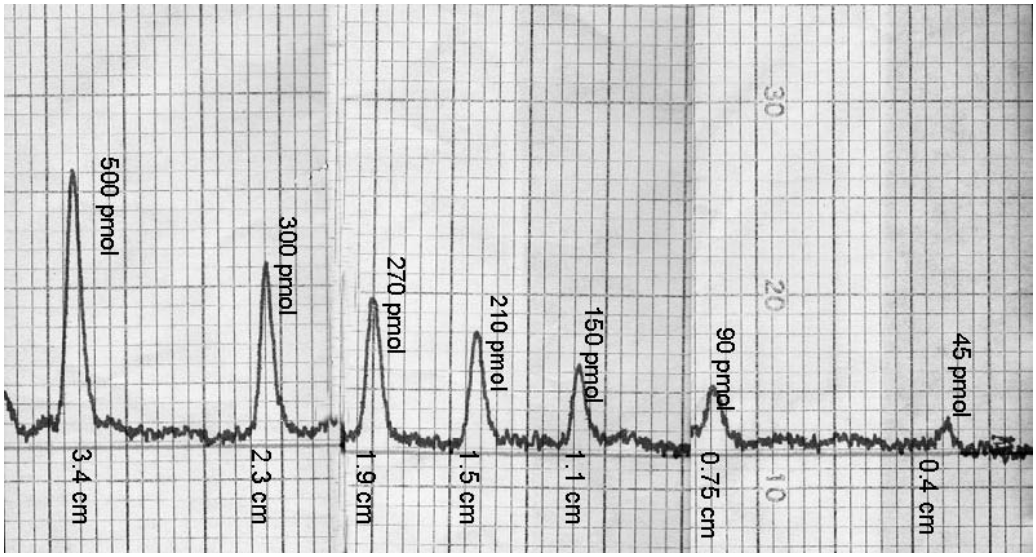


Figure 30 HPLC UV absorbance of nonradioactive *cis* 1b-8 with different mass

cis-IA SA4503 (1b-8, pmol/20µl)	Peak height (cm)
45	0.4
90	0.75
150	1.1
210	1.5
270	1.9
300	2.3
500	3.4
Unkown (radiolabeled)	2.4

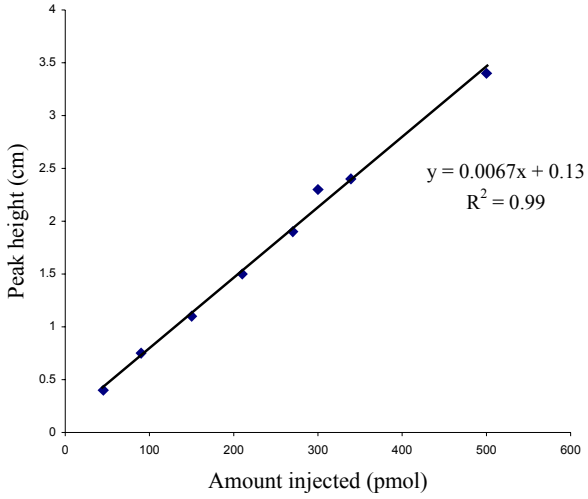


Figure 31 The standard curve for *cis*-IA-SA4503

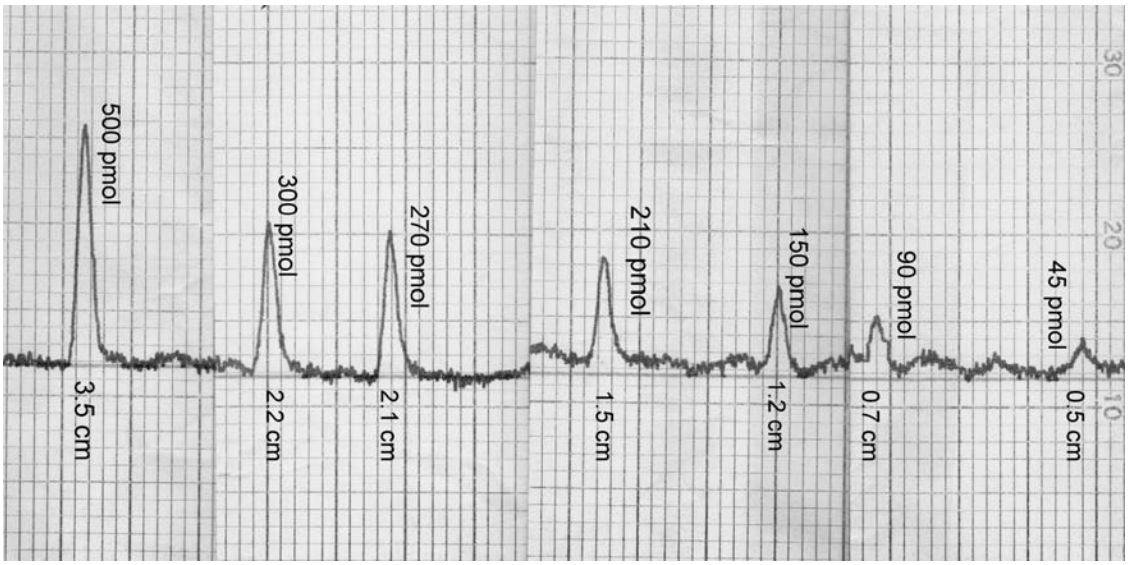


Figure 32 HPLC UV absorbance of nonradioactive *trans* 1b-9 with different mass

trans-IA SA4503 (1b-9, pmol/20µl)	Peak height (cm)
45	0.5
90	0.7
150	1.2
210	1.5
270	2.1
300	2.2
500	3.5
Unkown (radiolabeled)	1.5

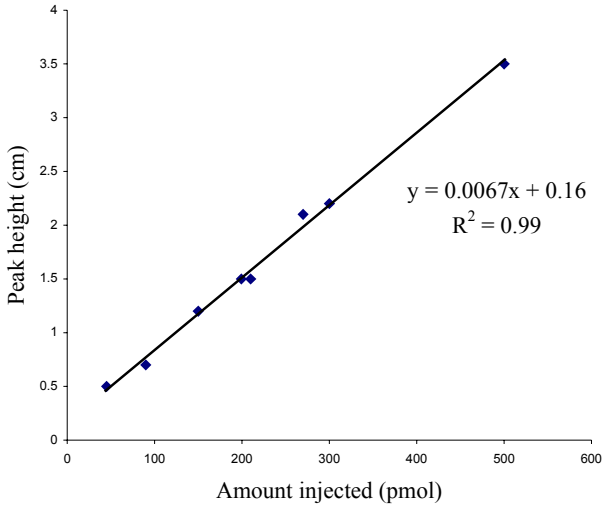


Figure 33 The standard curve for *trans*-IA-SA4503

From the linear equation derived and the HPLC peak heights of the radioiodinated sample of known radioactivity, the mass associated with the UV absorbance peak was obtained. The SA was then calculated by using the following equation:

$$\text{Specific radioactivity} = \frac{\text{Measured radioactivity } (\mu\text{Ci})}{\text{Amount (pmol)}}$$

The SA for [^{125}I] **1b-8** and [^{125}I] **1b-9** was 2105 and 2097 mCi/µmol respectively. Compared to the theoretical value "2175mCi/µmol", the SA of both radioiodinated products were high.

3.1.3.2 Lipophilicity of [^{125}I] 1b-8 and [^{125}I] 1b-9

The lipophilicity experiments using octanol-buffer system showed that the *cis* 4-*O*-iodoallyl ligand (**[^{125}I] 1b-8**) has almost the same log D as its *trans* isomer (**[^{125}I] 1b-9**) (3.57 vs. 3.60). Their logDs are off the ideal range (2-3) for brain penetration and high specific binding. The biodistribution studies in male CD1 mice confirmed that the *O*-

iodoallyl analogs had low uptake in brain (Figure 36). Thus the *O*-iodoallyl analogs were unlikely to be used as SPECT agents.

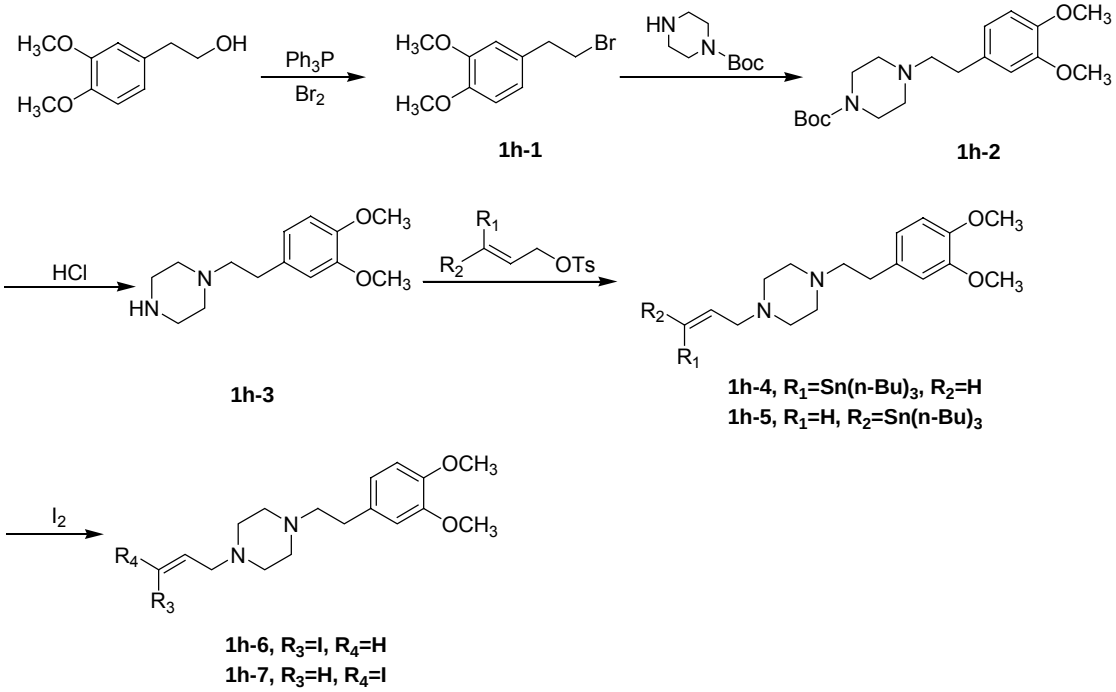
To this point, we found that most of the designed phenolic side chain analogs of **SA4503** had only moderate affinities and almost no selectivity between sigma1 and sigma2. So we decided to modify our original proposal. It was stated in Glennon's sigma binding model that it was not necessary to have both Ns of piperazine alkylated with phenylalkyl groups. The structure of **SA4503** had two phenylalkyl groups, which one was the less important one? With the thought of utilizing our previous work, we decided to replace the phenylpropyl on the left side of piperazine with *cis/trans* N-iodoallyl group, and incorporate the functional groups in **SA4503**, desmethyl **SA4503** (**1a-5**) and 3, 4-methylenedioxy **SA4503** (**1e-7**), which showed higher affinity and selectivity than others in previous studies. This change will not only make radioiodination feasible, but also decrease the lipophilicity, making the ligand more appropriate to bind with sigma1 receptors in CNS. Also, it was possible to have improved binding affinities.

3.2 The structural modifications on the N-iodoallyl piperazines and related biological studies

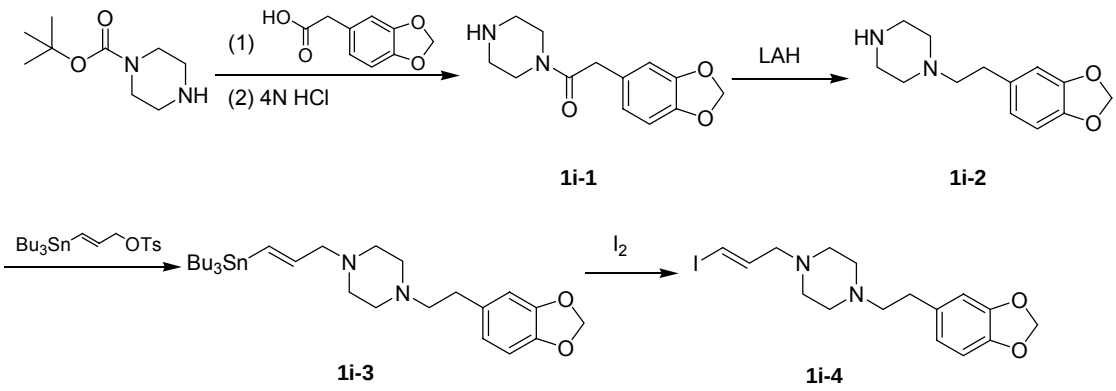
3.2.1 The structural modifications on the N-iodoallyl piperazines

For the N-iodoallyl analogs, the general synthetic approach was the amidation or alkylation of Boc protected piperazine, followed by (reduction and) hydrolysis, N-alkylation with **1b-4** or **1b-5** and then stereospecific iododestannylation[62]. This synthesis route was straightforward for all the other three compounds except the phenyl 3-methoxy-4-hydroxy analog **1j-4**.

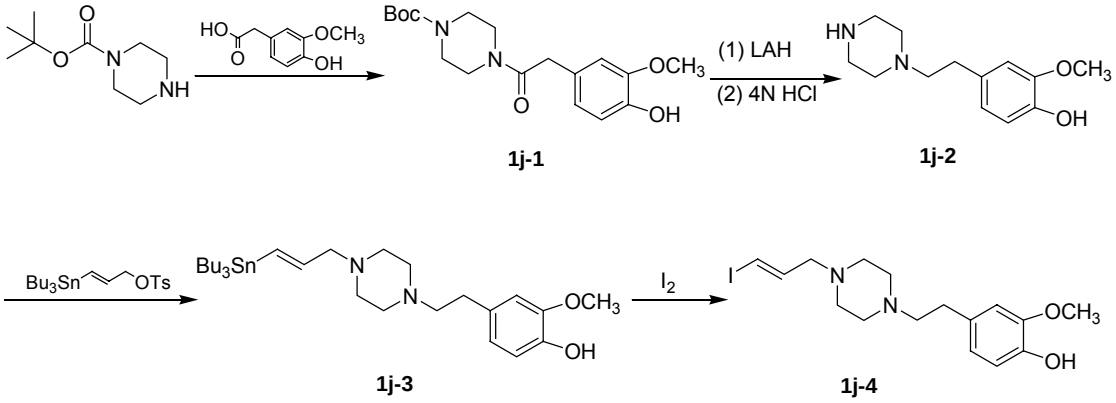
Scheme 1h The synthesis of 1-(*cis/trans* iodoallyl)-4-(3,4-dimethoxyphenethyl) piperazine



Scheme 1i The synthesis of 1-(*trans*-iodoallyl)-4-(3, 4-methylenedioxyphenethyl) piperazine



Scheme 1j The synthesis of 1-(*trans*-iodoallyl)-4- (3-methoxy-4-hydroxyphenethyl) piperzine



In the second step, after LAH reduction and acid work up, the piperazine N was found to be deprotected. Both the N and the phenol O in **1j-2** could theoretically be alkylated and nitrogen is more nucleophilic than oxygen, so a N-alkylated is expected to be the major product. However, a compound with phenol O alkylated was isolated as the major product.

This observation led to the thought of protecting the phenol with a TBDMS group. The method of N-alkylation in the presence of a TBDMS protecting group was referenced from Musachio's paper.[85] However, this reaction with NaH as base produced too many impurities to be worth of purification. The TBDMS protected phenol was later found to be unstable and could decompose back to phenol under the storage of refrigerator. Also, the decomposition of tributyltin tosylate, after long time storage might attribute to the low yield of this reaction.

In order to find out the actual reason that caused the N-alkylation reaction fail, a freshly made tribtuyltin tosylate was used to react with the 3-methoxy-4-hydroxy piperazine HCl salt. This time, although still low in yield (36%), the N-alkylated

compound was isolated as the major product, and no O-alkylated compound was observed from analytical TLC.

3.2.2 Sigma binding assay results for the N-iodoallyl piperazines

The binding assay results show that the sigma receptor is very sensitive to the structural alteration from phenylpropyl to iodoallyl (Table 5). Both *cis* and *trans* N-iodoallyl 3, 4-dimethoxy phenethyl piperazine (**1h-6**, **1h-7**) have similar moderate affinities for the sigma1 receptor. However, as far as sigma2 affinity is concerned, the *trans* isomer (**1h-7**) has 3.5 fold less affinity than the cis isomer (**1h-6**), indicating that the stereochemistry of the double bond plays an important role in selective sigma1 binding. Thus, we decided to use *trans* iodoally on the other two proposed ligands. The rigid methylenedioxy analog (**1i-4**) with a *trans* iodoallyl increases sigma1 affinity to nanomolar range while still maintaining high selectivity. The 3-methoxy-4-hydroxy analog (**1j-4**) shows a 29-fold less selectivity for sigma1 as compared to the 3, 4-dimethoxy counterpart (**1h-7**), suggesting that the alkylation of the phenol is an important element for selective sigma1 binding.

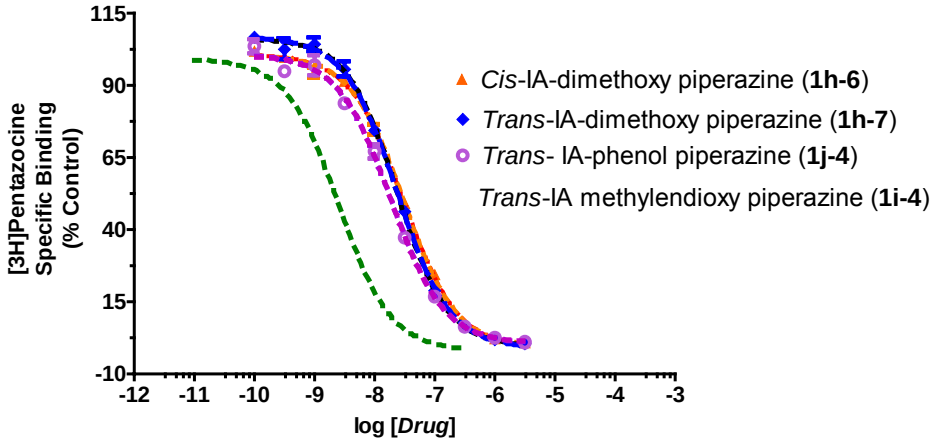


Figure 34 The displacement curves for N-iodoallyl piperazine analogs against [^{3}H]-(+) pentazocine binding to sigma1 sites in GPB membranes

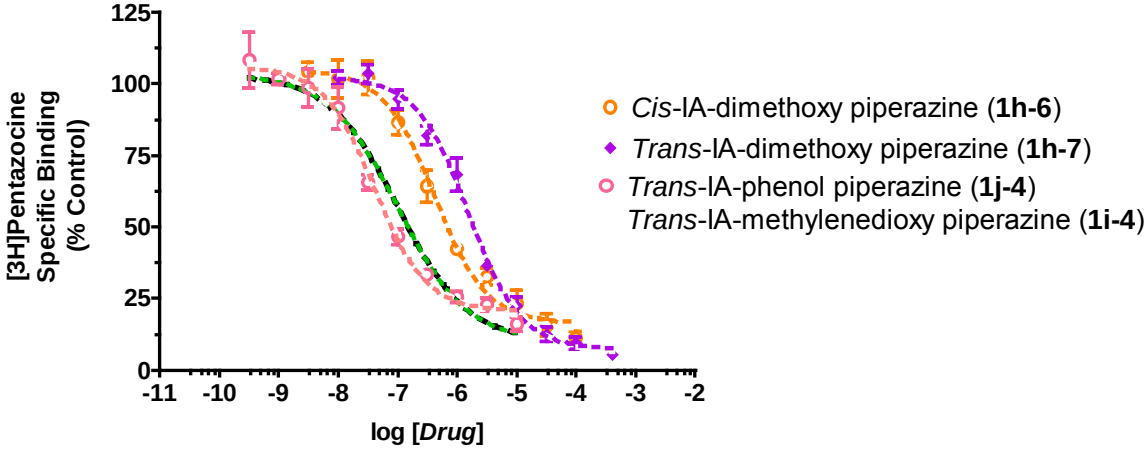
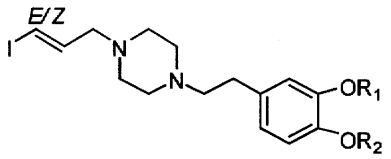


Figure 35 The displacement curves for N-iodoallyl piperazines against [^{3}H]-DTG binding to sigma2 sites in GPB membranes using 200 nM (+)-pentazocine as sigma1 mask

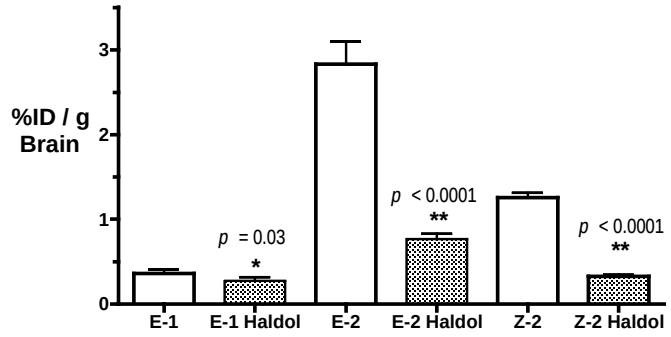
Table 5 Sigma receptor binding affinity and sigma2 / sigma1 selectivity for N-iodoallyl piperazines in GPB



Compound				# asssays	Sigma1			Sigma2			σ_2 / σ_1 (IC_{50})
	E/Z	R_1	R_2		IC_{50} (nM)	K_i (nM)	n_H	IC_{50} (nM)	K_i (nM)	n_H	
1h-6	*Z*	OCH_3	OCH_3	3	30.78±1.60	21.52±1.12	-0.97±0.025	437±13.92	386±12.32	-0.81±0.063	14.2
1h-7	*E*	OCH_3	OCH_3	3	23.95±1.01	16.74±0.70	-1.05±0.029	1531±207	1352±183	-0.88±0.054	63.9
1i-4	*E*	CH_2		3	2.50±0.015	1.74±0.010	-1.20±0.21	110±7.26	97.8±6.47	-0.79±0.13	44.0
1j-4	*E*	OCH_3	OH	4	18.65±0.69	13.04±0.48	-0.96±0.049	41.18±1.14	36.59±1.02	-0.85±0.034	2.2

3.2.3 Lipophilicity and *in vivo* studies of ^{125}I labeled *cis/trans* iodoallyl dimethoxy phenethyl piperazines (IA-DM-PE-PIPZ)

The *cis* N-iodoallyl 3, 4-dimethoxy phenethyl piperazines (**1h-6**) have similar lipophilicty with its *trans* isomer (**1h-7**) (2.27 vs. 2.25), both falling in the optimum range for penetrating blood brain barrier. They are less lipophilic than the O-iodoallyl ones (**1b-8**, **1b-9**) as predicted. The biodistribution studies (Figure 34) showed the *trans* IA-DM PE PIPZ (**1h-**7, E-2 in Figure 36) had not only higher %ID/g brain than its *cis* isomer (**1h-**7, Z-2) but much higher uptake than the *trans* O-iodoallyl **SA4503** (**1b-9**, E-1). The blockade effect of haloperidol (2.5 mmol/kg) caused significant decrease in the %ID/g brain, indicating that the N-iodoallyl analogs bound to sigma1 receptor specifically.



[^{125}I]-*E*-IA-SA4503 (***E*-1**); [^{125}I]-*E*-IA-DM-PE-PIPZ (***E*-2**); [^{125}I]-*Z*-IA-DM- PE-PIPZ (***Z*-2**)

Figure 36 Blocking study of *cis/trans* IA-DM-PE-PIPZ and *trans* IA SA4503

In the pharmacokinetic studies (Figure 37), [^{125}I]-*E*-IA-DM-PE-PIPZ (**1h-7**) exhibited higher brain uptake and longer retention than the *Z*-isomer (**1h-7**). Uptake was 5.8% ± 1.2 %ID/g at 15 min and fell to 1.5% ± 0.1 %ID/g by 120 min as a single phase exponential ($r^2 = 0.99$). This indicated a pseudo-equilibrium for binding to σ_1 receptors is

reached *in vivo*, as long as most of the observed signal can be attributed to specific receptor binding.

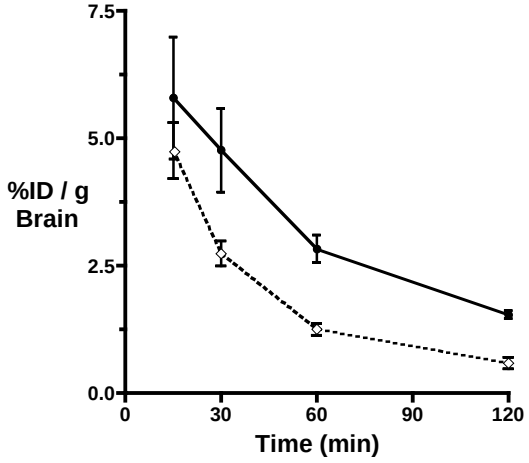


Figure 37 Pharmacokinetic comparison of whole brain uptake for [^{125}I]-*E*-IA-DM-PE-PIPZ (*E*-2) and [^{125}I]-*Z*-IA-DM-PE-PIPZ (*Z*-2)

The pharmacology of [^{125}I]-*E*-**IA-DM-PE-PIPZ** proved it has high specific binding (*ca*. 85 - 90%) *in vivo* for sigma1 receptor in various regions of the mouse brain. The brain uptake of [^{125}I]-*E*-**IA-DM-PE-PIPZ** was blocked by its own cold ligand, haloperidol (sigma1/sigma2) and sigma1 selective **BD1063**, but unaffected by the highly sigma2 selective tetrahydroisoquinolinyl benzamide (Lead **II**).

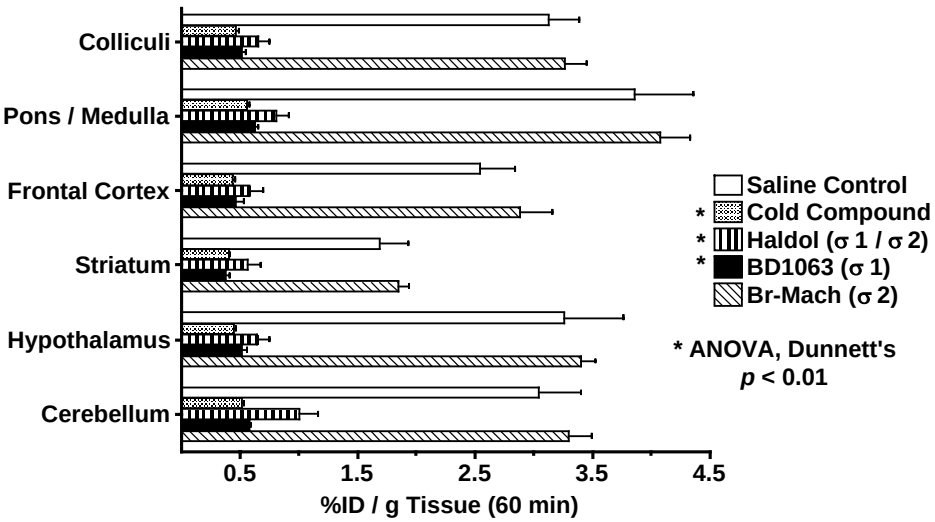


Figure 38 Effects of pretreatments on [^{125}I]-*E*-IA-DM-PE-PIPZ uptake in various mouse regions (t=60 min)

3.3.3 Agonism/Antagonism study

It was reported in 2005 that phenytoin (DPH) was able to differentiate sigma1 agonist and antagonist by an *in vitro* binding assay[75]. The allosteric modulation of DPH enhances sigma1 agonist binding affinity while slightly decreasing the affinity of the sigma1 antagonist. This observation was explained on the basis of two-state model of receptor activation.

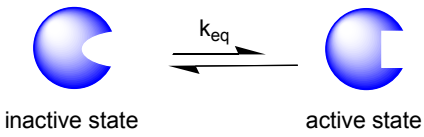


Figure 39 An equilibrium of inactive state and active state of receptor

The receptor exists in an equilibrium of active and inactive states, in which the latter is favored. The competitive agonist binds to the active state with higher affinity. In contrast, the antagonist has almost the same binding affinity for either state. The

modulator DPH can promote the active state of the receptor, which in turn increases the binding of the agonist.

To determine the reliability of this point of view, the commercially available sigma1 agonist dextromethorphan and sigma1 antagonist rimcazole were tested for their agonism/antagonism using DPH in our group (work done by colleagues). The result showed dextromethorphan had a 15-fold increase in sigma1 affinity in the presence of DPH, while rimcazole had a slightly decreased affinity. This experiment supported that this method is an easy and simple way to differentiate sigma1 agonist and antagonist.

The most potent sigma1 ligand in our study, *trans*-iodoallyl phenethyl piperazine (**1f-7**), had a similar response like rimcazole to the mediation of DPH, thus we concluded at this point that this ligand may be an antagonist.

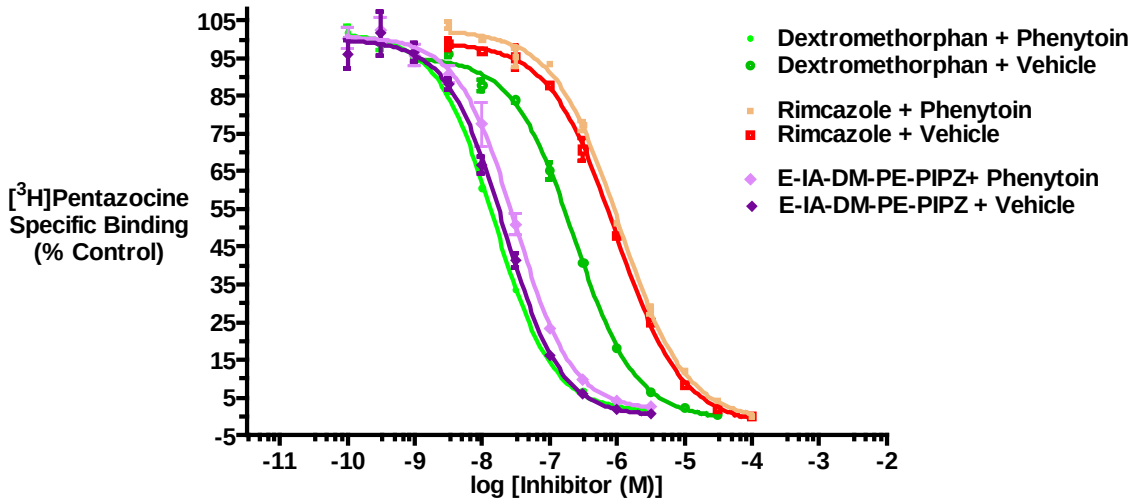


Figure 40 Agonism/ Antagonism study by using Phenytoin

In conclusion, by modifying two different sites of **SA4503** (Lead **I**), a sigma1 selective ligand (**1h-7**) that had appropriate lipophilicity for passing through the blood

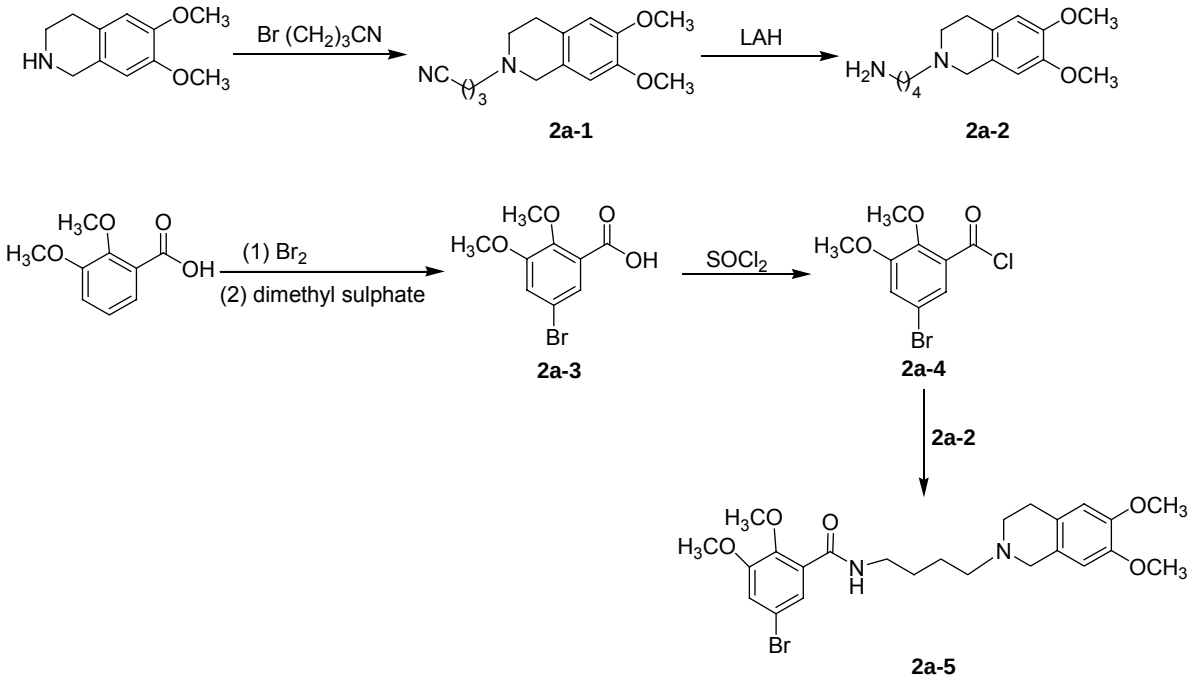
brain barrier was developed. The biodistribution studies on **1h-7** proved that it had potential value for future examination as SPECT imaging agent.

3.3 Structural modifications on the tetrahydroisoquinoline benzamide and the sigma binding assay results

3.3.1 Structural modifications on the tetrahydroisoquinoline benzamides

For the benzamide series of compounds, the general synthetic method was the alkylation of tetrahydroisoquinoline with 4-bromo-butylnitrile, followed by the reduction of the nitrile into an amine by LAH, and then amidation with 5-bromo-2, 3-dimethoxy benzoyl chloride[54].

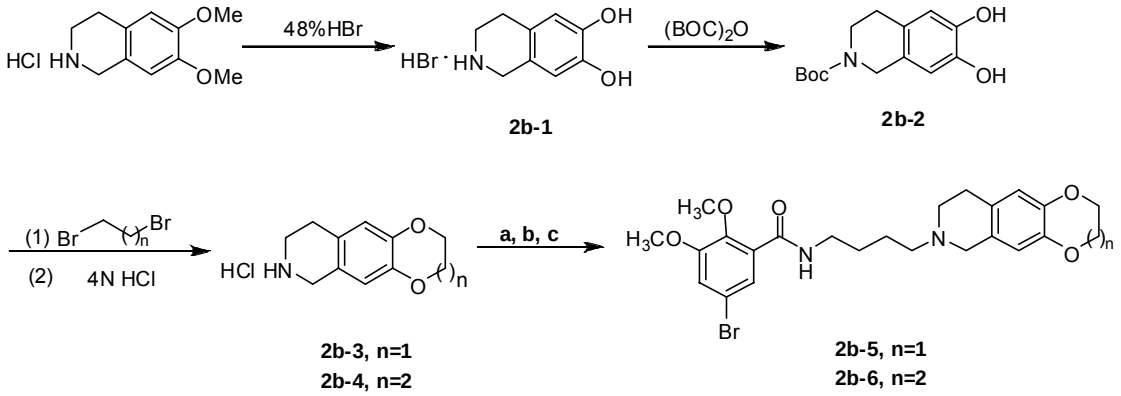
Scheme 2a The synthesis of 5-Bromo-N-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl)]-2,3-dimethoxy-benzamide



The lead compound **2a-5** was synthesized for reference using reported method.

Unlike the reported method[54], where the bromination of 2, 3-dimethoxy benzoic acid directly yielded **2a-3**, our synthesis resulted in the hydrolysis of one of the methoxy group into a hydroxy group. Thus it was necessary to conduct a methylation reaction with dimethyl sulphate after the bromination to get **2a-3**.

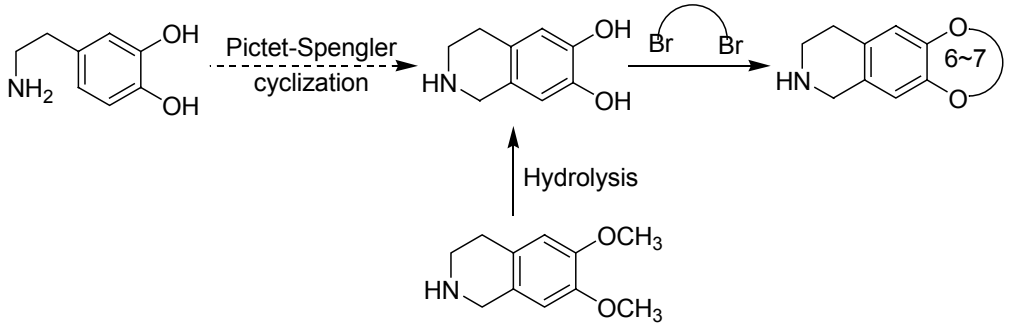
Scheme 2b The synthesis of 5-bromo-N-[4-(6,7-ethylenedioxy(and propylenedioxy)-3,4-dihydro-1H-isoquinolin-2-yl)-butyl)]-2,3-dimethoxy-benzamide



a=4-bromobutylnitrile; b=LAH; c=**2a-4**

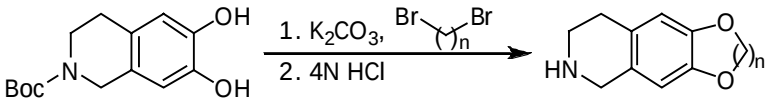
The synthesis of tetrahydroisoquinolines with a fused dioxy ring on the aromatic ring was the key step. The cyclization of dopamine by a Pictet-Spengler reaction did not take place (Scheme 2b'), although different conditions (acid, solvent, temperature, time; reactions was monitored by HPLC) were tried.

Scheme 2b' The synthesis of tetrahydroisoquinolines with fused 6~7 membered dioxy ring



In the other attempt (Scheme 2b'), commercially available 6, 7-dimethoxy tetrahydroisoquinoline was found to hydrolyze into the desired diphenol compound in quantitative yield when treated with 48% HBr.[86] The cyclization reaction of this ortho diphenol by dibromoalkane was optimized as shown in Table 6.

Table 6 Optimization of the diphenol cylization reaction

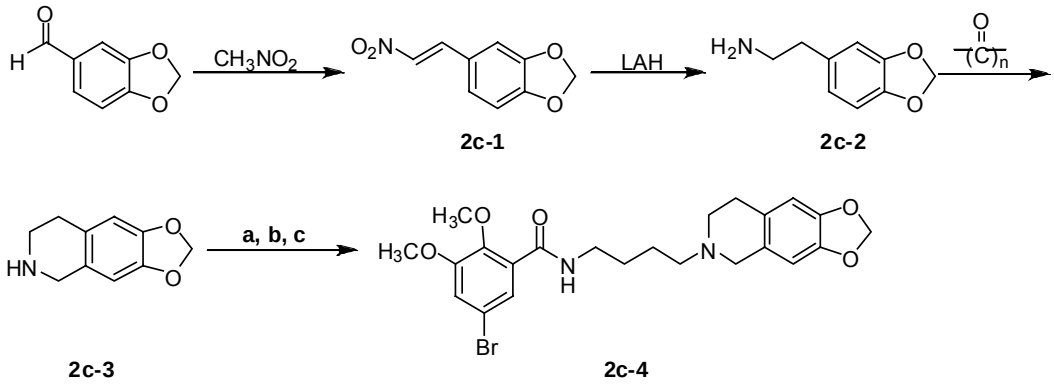


entry	n	Reagent	Solvent	t (h)	T (°C)	Result
1	2	NaI	acetone	overnight	reflux	Trace
2*	2	NaI	Ethylene glycol	12	120	Trace
3#	2	TBAB	Toluene	22	80	77% yield
4	3	TBAB	Toluene	22	80	43% yield
5	1	TBAB	Toluene	22	80	trace

* reference [82]; # reference[87]

The optimized conditions worked well for ethylenedioxy and propylenedioxy tetrahydroisoquinolines, but no methylenedioxy analog was obtained by using this method. The strain of forming a five membered ring may account for the failure of this reaction. Thus, a different method of synthesizing the methylenedioxy analog was proposed as shown in Scheme 2c.

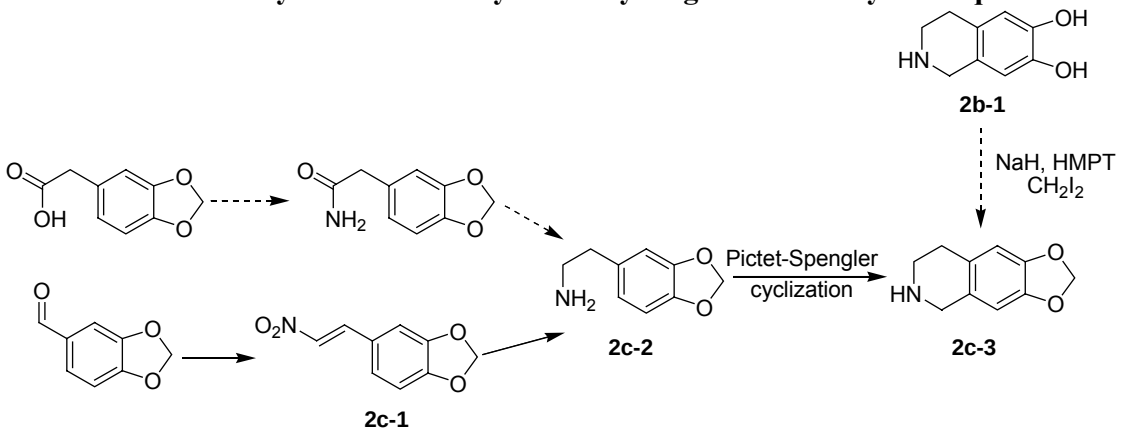
Scheme 2c The synthesis of 5-bromo-N-[4-(6,7-methylenedioxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl)]-2,3-dimethoxy-benzamide



a=4-bromobutylnitrile; b=LAH; c=**2a-4**

The optimized ring closure reaction of ortho diphenol by dibromoalkane described previously did not work for the synthesis of methylenedioxy tetrahydroisoquinoline **2c-3**. A method employing the methylenation of o-dihydroxyaromatic compound[88] had also been tried to make **2c-3**, but no product was observed (Scheme 2c'). So we had to go back to the Pictet-Spengler cyclization to find a solution.

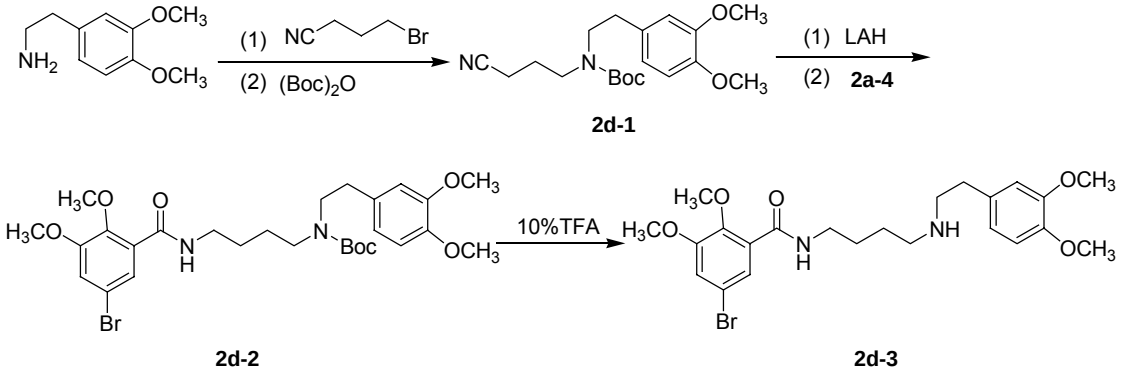
Scheme 2c' The synthesis of methylenedioxy ring fused tetrahydroisoquinoline



In order to make methylenedioxy phenethylamine (**2c-2**) as Pictet-Spengler precursor, two different methods were tried: the amidation of carboxylic acid followed by

reduction; the generation of vinyl nitro group followed by reduction. The first method, reported to have high yield under the assistance of 300W microwave, didn't give the expected product. In the second method, the reduction of vinyl nitro group by LAH gave much better yield than by iron and HCl. The Pictet-Spengler reaction, using paraformaldehyde and formic acid, gave the product **2c-2** in moderate yield. Compared to the previous failed Pictet-Spengler cyclization (Scheme 2b'), it was found that except for the difference in the form of formaldehyde (37% aqueous solution vs. powder of polymer), the phenyl substituent (hydroxy vs. alkoxy) might be the reason that led to the success of the latter reaction.

Scheme 2d 5-bromo-N-(4-(3,4-dimethoxyphenethylamino)butyl)-2,3-dimethoxybenz-amide



2d-3 was prepared by alkylation, followed by N-Boc protection, LAH reduction, amidation and deprotection[89]. The synthesis worked smoothly and no problem was encountered.

3.3.2 Sigma binding assay results for the tetrahydroisoquinoline benzamide analogs

5-bromo-N-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-butyl]-2,3-dimethoxy-benzamide (**2a-5**) was reported to be a highly sigma2 selective ligand. In

order to get consistent results, we synthesized this lead compound by the reported method and analyzed its binding properties. In our hand, **2a-5** showed nanomolar affinity and a 417-fold selectivity for the sigma2 subtype. Although it was somewhat off the reported 1573 fold selectivity, our data supported that this ligand was indeed a highly selective sigma2 ligand.

Opening of the tetrahydroisoquinoline ring by removal of a methylene unit led to a secondary amine that was sterically less hindered. This change was thought to make the formation of hydrogen bonding easier, thus an increased binding affinity for one of the sigma subtypes was expected to be observed. However, this amine (**2d-3**) maintained unaffected sigma1 binding, while dropping sigma2 binding remarkably by 1712-fold from nanomolar to micromolar concentration. Although it is hard to explain, but this observation suggested that a restricted tetrahydroisoquinoline ring is an important element for highly selective sigma2 binding in this class of compounds.

The replacement of the phenyl dimethoxy open chain by a rigid methylenedioxy (**2c-4**) and ethylene dioxy (**2b-5**) rings increased sigma1 affinity by 11- and 3-fold, respectively, while propylenedioxy (**2b-6**) decreased sigma1 affinity by about 2-fold, revealing sigma1 binding is sensitive to the orientation of the oxygen atom in this region. The sigma2 binding affinity was dropped by 8- to 11-fold from the change of the dimethoxy to a closed dioxy ring, but different sized ring did not cause significant difference in sigma2 binding.

The synthesis and binding assay results were published in *Bioorganic & Medicinal Chemistry Letters.*[90]

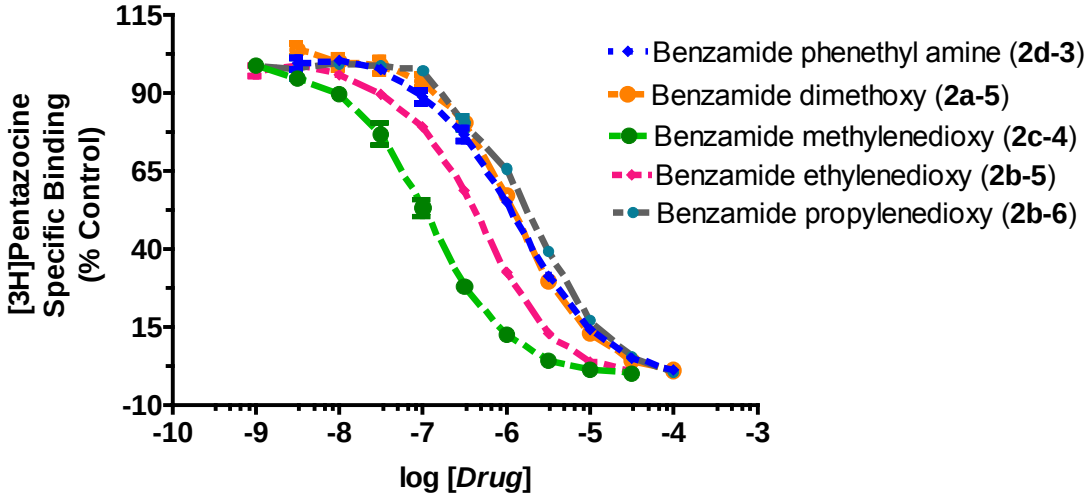


Figure 41 The displacement curves for N-iodoallyl piperazine analogs against [^{3}H]-(+) pentazocine binding to sigma1 sites in GPB membranes

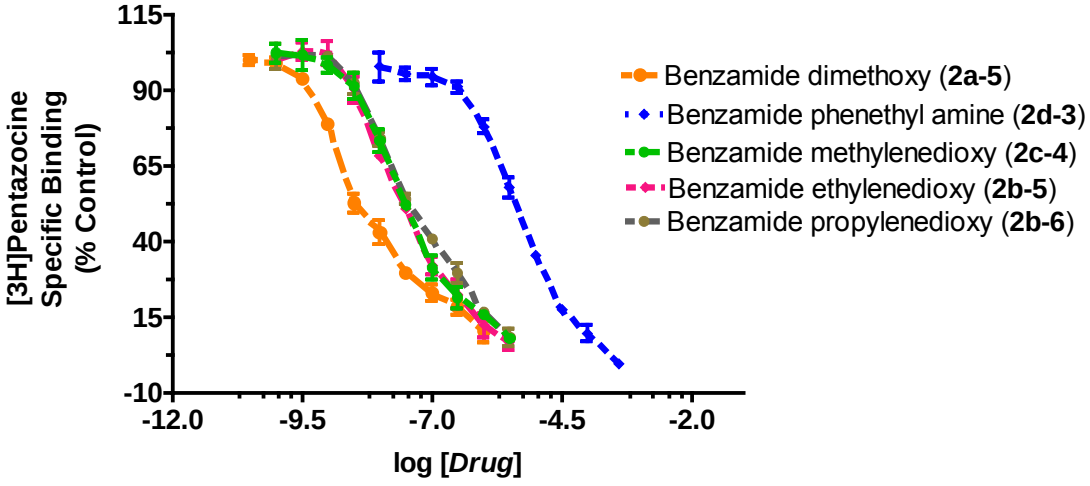
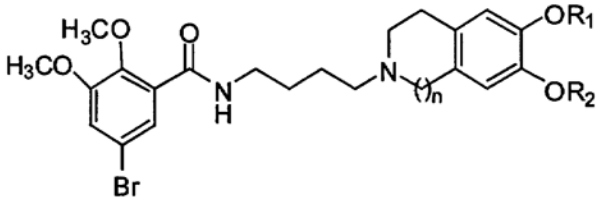


Figure 42 The displacement curves for N-iodoallyl piperazine analogs against [^{3}H] DTG binding to sigma2 sites in GPB membranes using 200 nM (+)-pentazocine as sigma1 mask

Table 7 Sigma receptor binding affinity and sigma2 / sigma1 selectivity for Benzamide series ligands in GPB



	Compound			# of assays	Sigma1			Sigma2			σ_2 / σ_1 (IC_{50})
	n	R_1	R_2		IC_{50} (nM)	K_i (nM)	n_H	IC_{50} (nM)	K_i (nM)	n_H	
2a-5	1	OCH_3	OCH_3	3	1273±22.19	887.3±15.31	-0.94±0.031	3.05±0.11	2.71±0.094	-0.68±0.025	0.0024
2d-3	0	OCH_3	OCH_3	3	1272±87.3	886.6±60.81	-0.83±0.012	5224±279.7	4642±248.5	-0.82±0.062	4.1
2c-4	1	CH_2		3	118.5±11.34	82.61±7.91	-0.92±0.010	25.48±0.54	22.64±0.48	-0.82±0.059	0.2
2b-5	1	CH_2 CH_2		3	488.9±12.10	340.7±8.43	-0.92±0.011	24.58±1.37	21.84±1.22	-0.75±0.032	0.05
2b-6	1	CH_2 CH_2 CH_2		3	2066±52.52	1440±36.68	-0.90±0.04	36.90±1.71	32.78±1.52	-0.64±0.068	0.02

3.4 An overall summary on this project

In conclusion, three structural modifications were made based on two lead compounds.

Most of the **SA4503** phenolic side chain analogs had moderate affinity and no selectivity between sigma1 and sigma2 receptor subtype. All of these analogs showed increased binding affinity for sigma2 subtype than their lead compound **SA4503**. The radioiodinated **SA4503** analogs, **1b-8** and **1b-9**, are a little too lipophilic to be suitable for *in vivo* studies.

The modifications made by replacing the left phenylpropyl group of **SA4503** with an N-iodoallyl group yielded a sigma1 selective ligand (**1h-7**) that had appropriate lipophilicity for penetrating the blood brain barrier in the CNS. The *in vivo* studies using radioiodinated **1h-7** showed that it had high specific binding to the sigma1 receptor in the mouse brain and thus it had great potential as SPECT agent for brain imaging.

The modifications on the benzamide series of compounds by rigid dioxy rings showed similar trend in binding affinities as observed in the similar modification made on the **SA4503** phenolic side chain, the most rigid methylenedioxy analog had the highest affinity and the least rigid propylenedioxy had the lowest affinity for sigma1 subtype. Sigma2 affinity was not affected significantly by the size of the dioxy ring. The modification of the strained tetrahydroisoquinoline ring with a freely rotating amine chain maintained the sigma1 affinity unchanged, while decreasing the sigma2 binding affinity dramatically. Thus a rigid tetrahydroisoquinoline is an important structural element for selective sigma2 binding in the benzamides series compounds.

3.5 Prospect for future studies

3.5.1 N-iodoallyl series of compounds

As mentioned in **3.4**, a potent sigma1 ligand, **1h-7**, had been discovered. Although it had high selectivity (sigma2/sigma1, 64-fold) toward sigma1 subtype, its affinity was only moderate (23.95 nM). So future research may use this compound as a lead and continue the structure-activity relationship study in order to improve the sigma1 affinity. As we have observed from the binding properties of **1h-7** and its analogs (Table 5), the phenolic side chain is a sensitive area for sigma1 binding. The change of one of the phenyl methoxy group into a hydroxy decreased sigma1 selectivity dramatically, indicating that the alkylation at this position is fairly important. Additionally, the replacement of dimethoxy open chain with a methylenedioxy group increased the sigma1 affinity by ~10-fold and resulted in a compound (**1i-4**) that has both nanomolar sigma1 affinity and high selectivity. Thus, it would be interesting to further explore how different structural features at this position affect the sigma binding. For example, whether the oxygen atoms of **1i-4** plays a role in increasing sigma1 binding affinity? If so, whether both oxygen atoms are necessary? Will the sigma1 affinity be maintained or increased if the phenyl methylenedioxy ring moiety of **1i-4** is replaced by other heterocycles such as pyrrole, imidazole and furan et al.

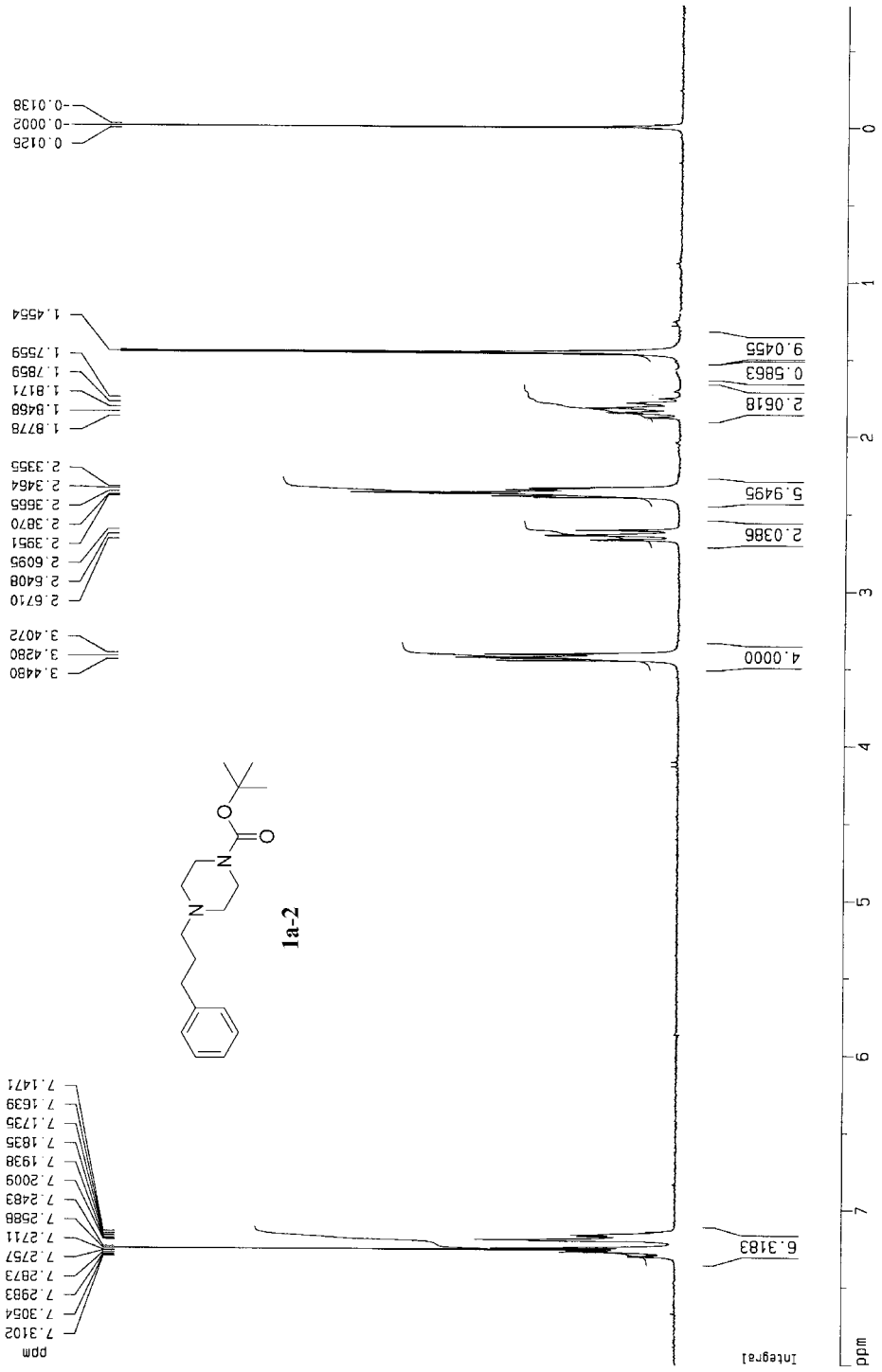
3.5.2 Benzamide series of compounds

As shown in our binding assay results, the rigid tetrahydroisoquinoline is an important structural feature in highly selective sigma2 binding in the benzamide series compounds. It would be interesting to see how different rigidity of this N-containing ring

affects sigma binding properties. Also, the importance of nitrogens can be explored by replacing the nitrogen atom with carbon. Besides, the amide bond in Lead **II** might be an interesting spot to explore.

In summary, the goals of this thesis were accomplished: structural modifications led to differences in sigma 1 and sigma2 binding affinity and selectivity.

Appendix I ^{1}H NMR and ^{13}C NMR Spectra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7
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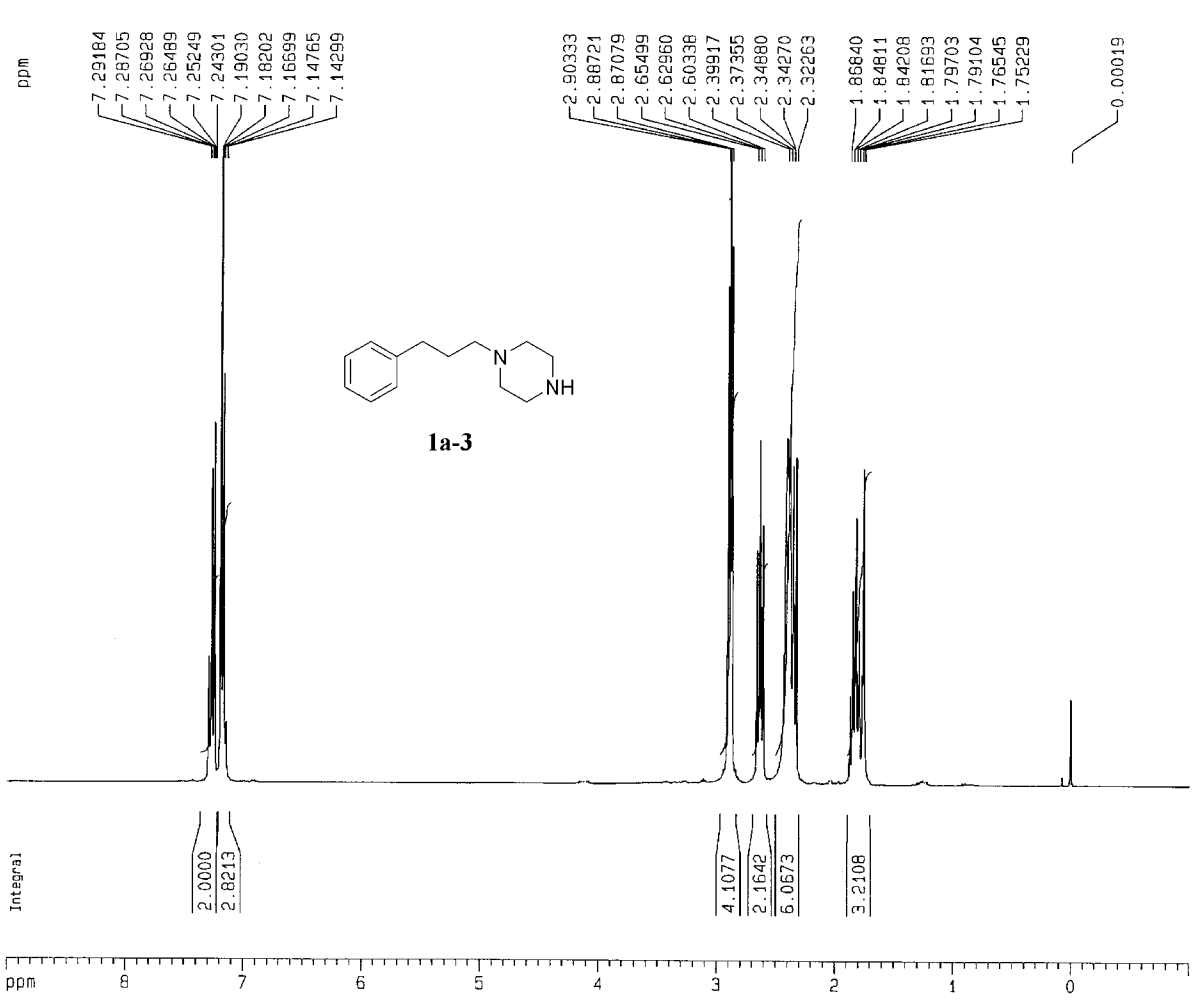


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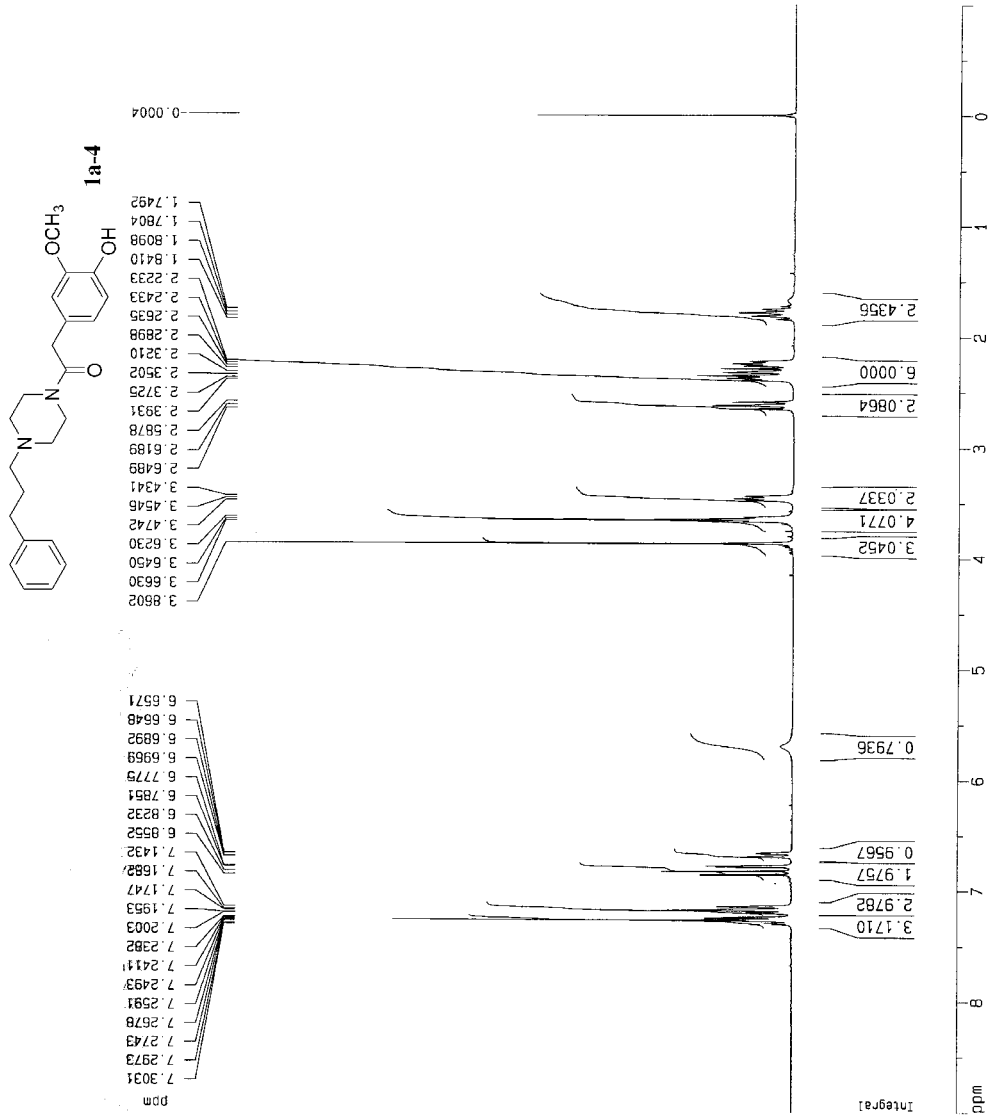
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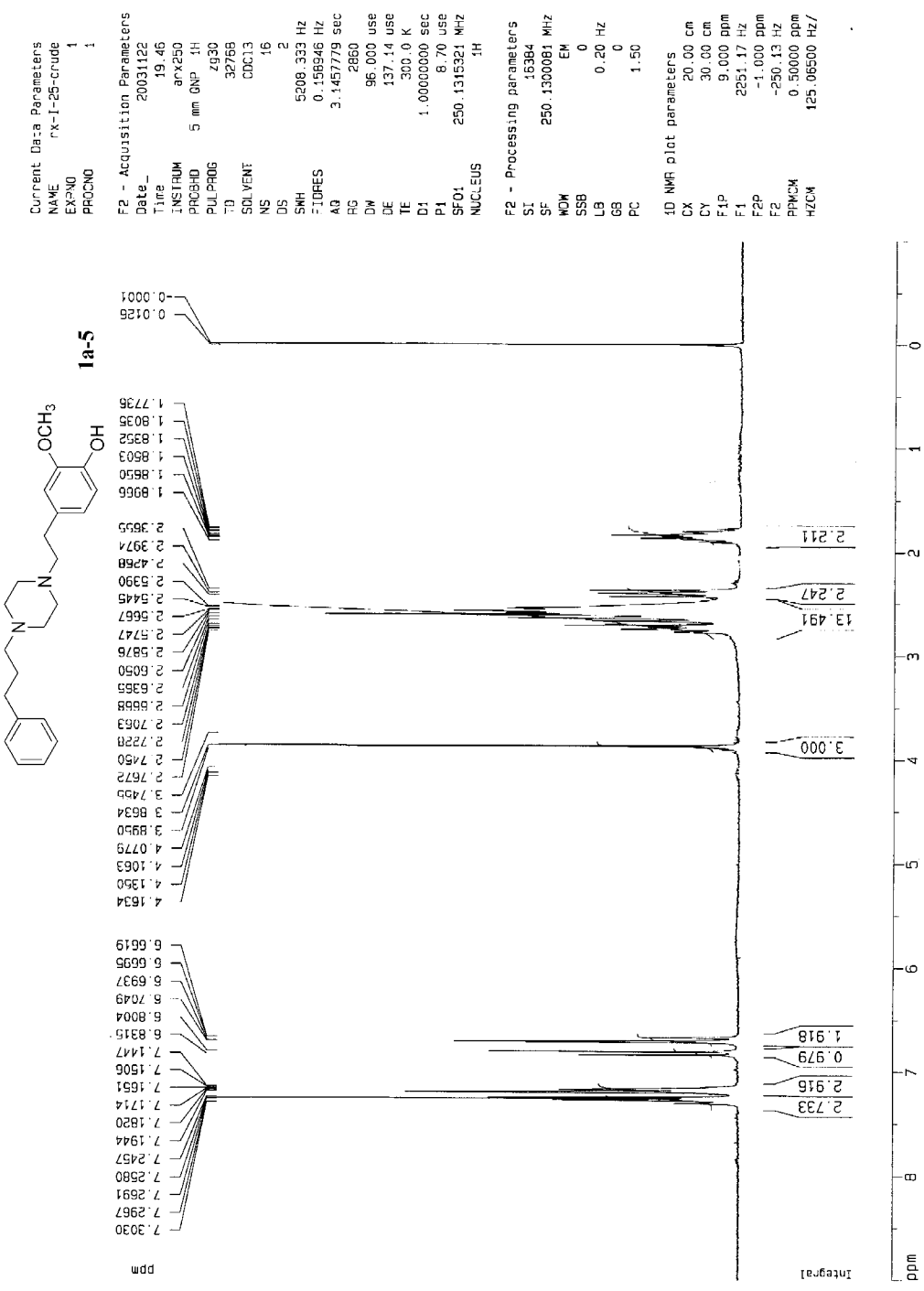
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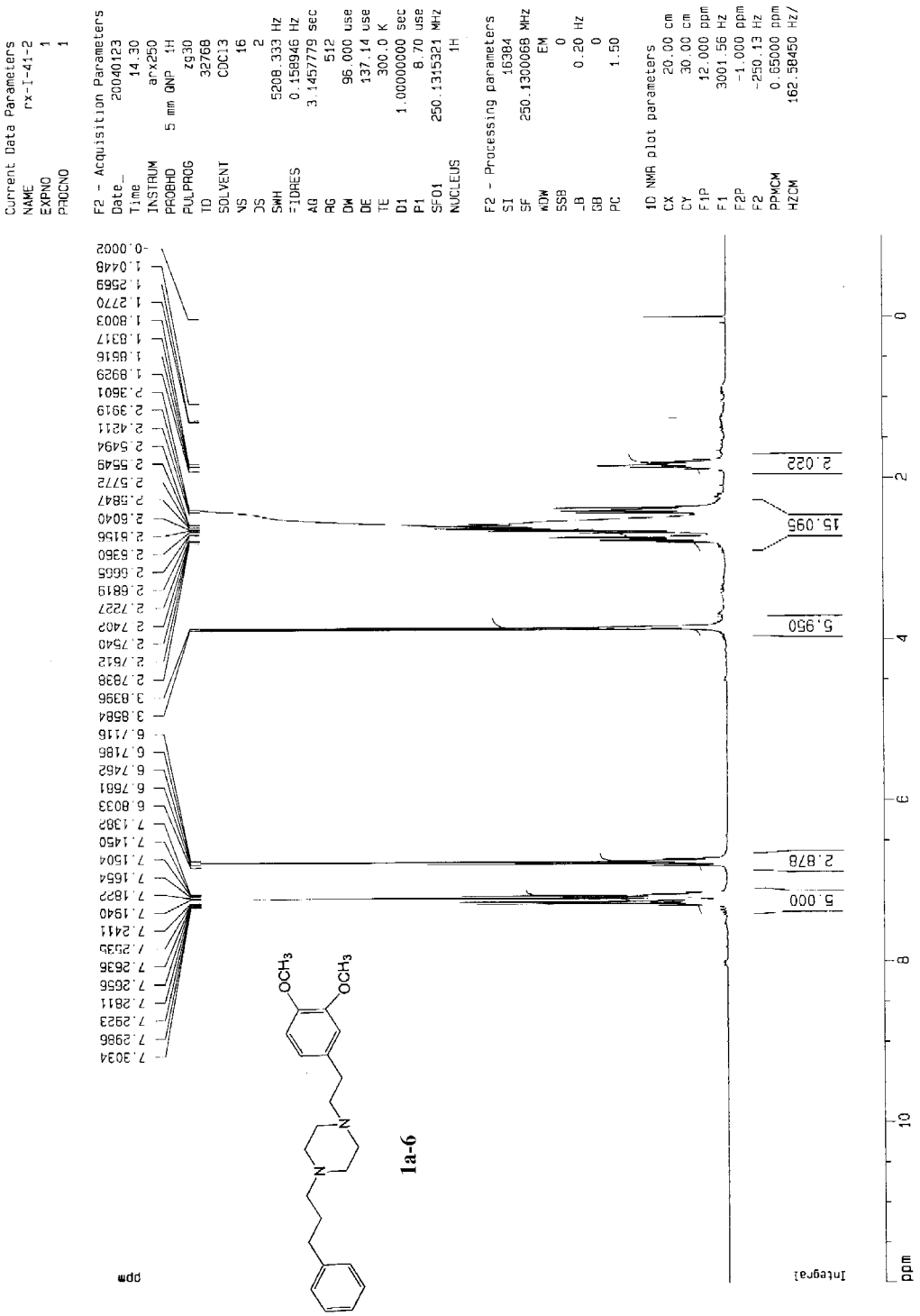
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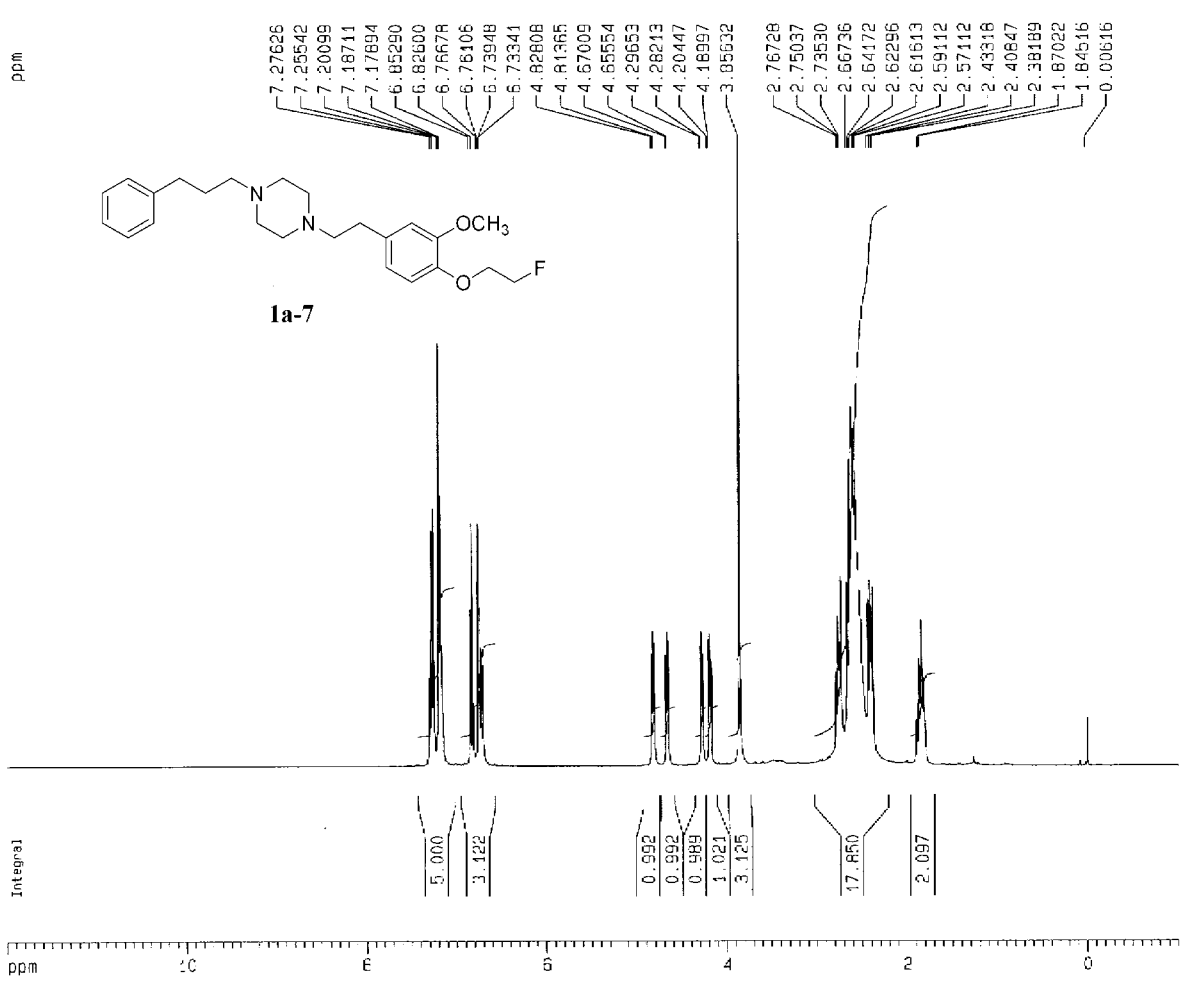


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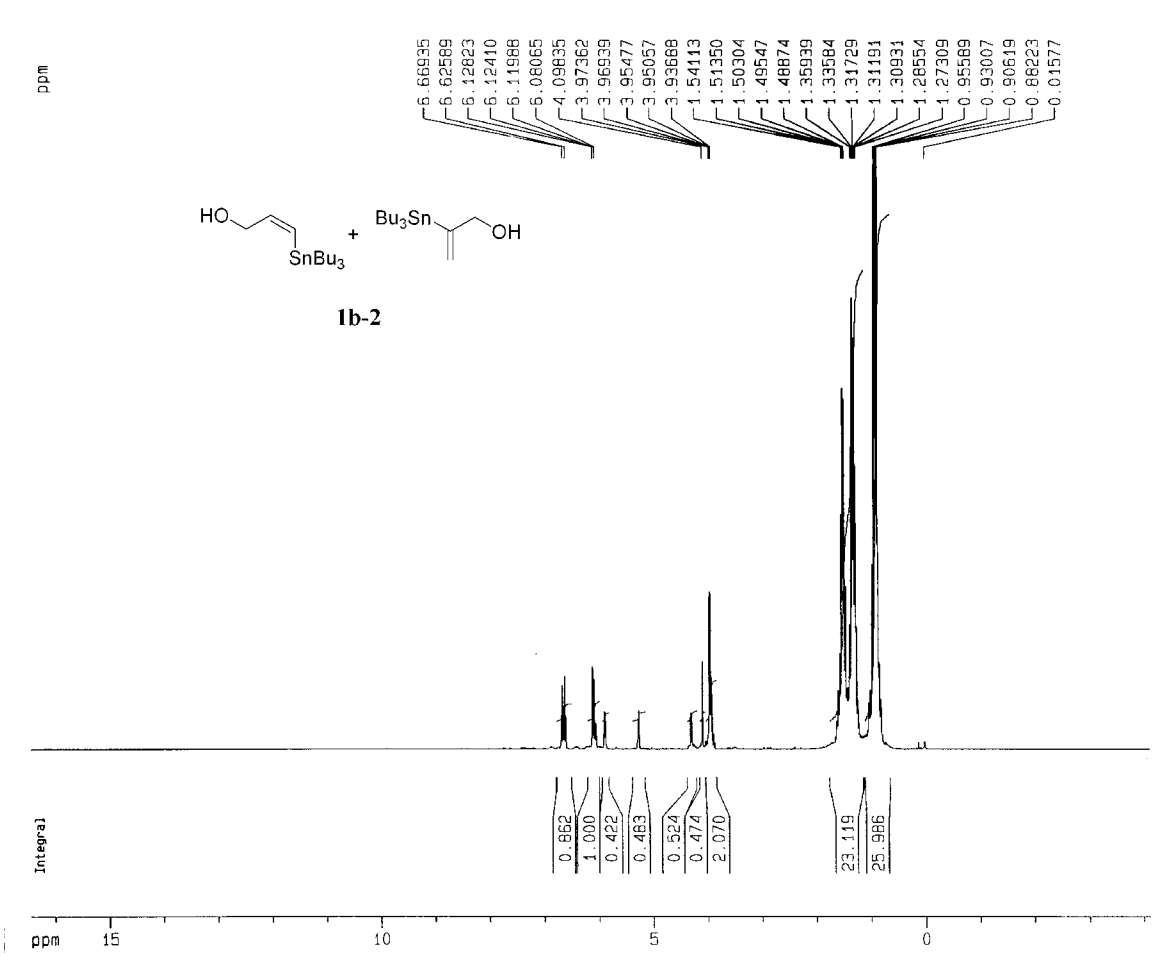

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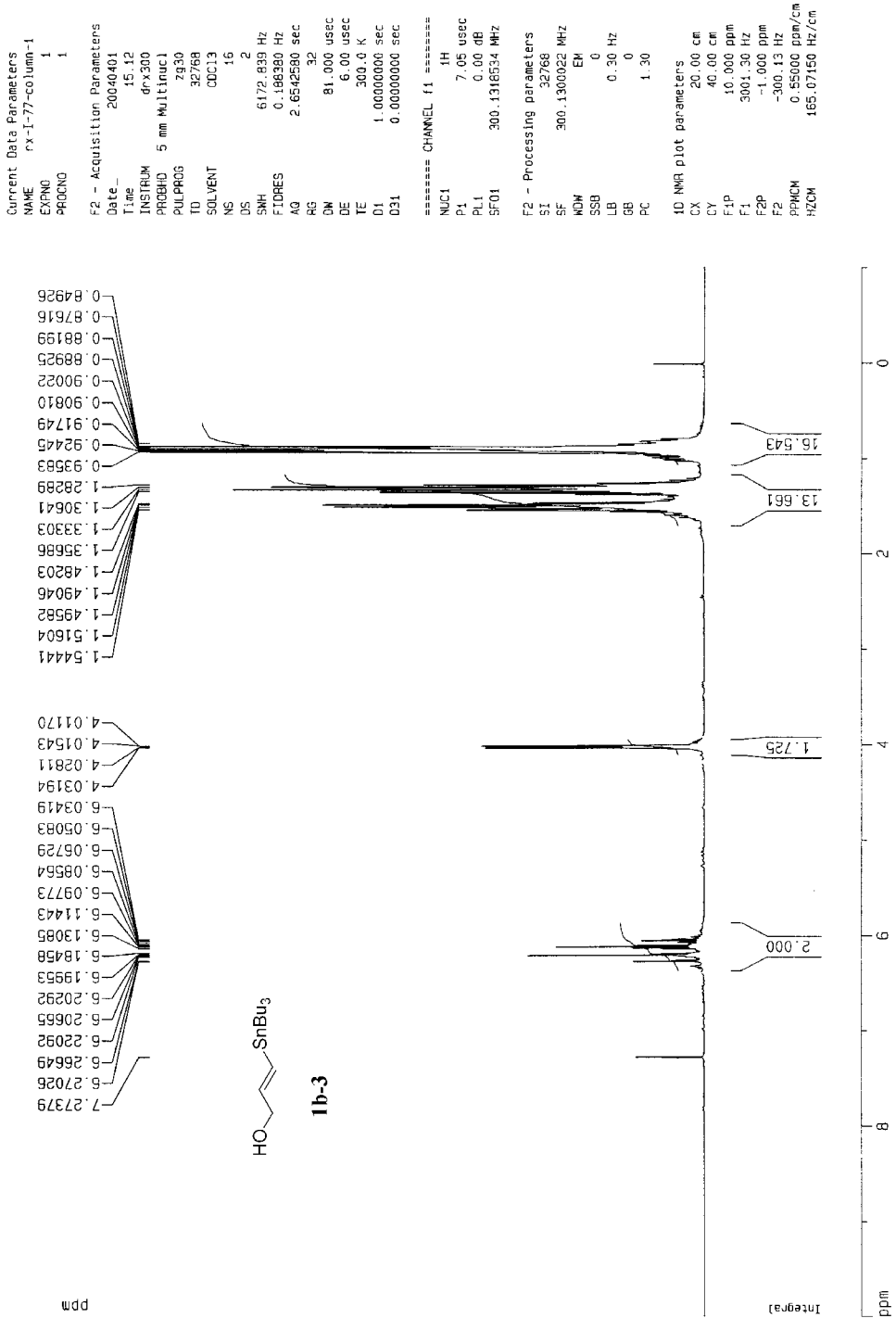
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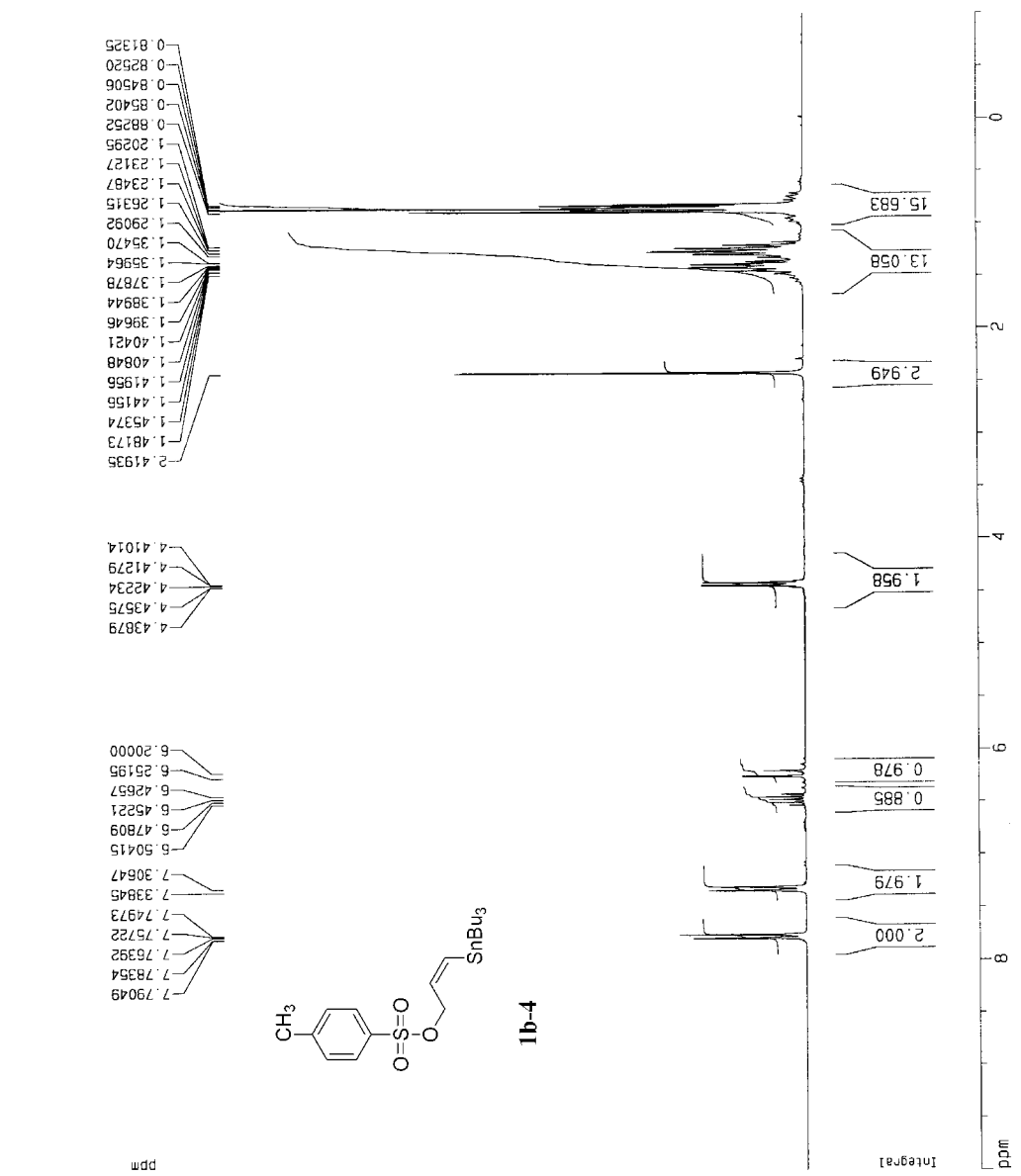
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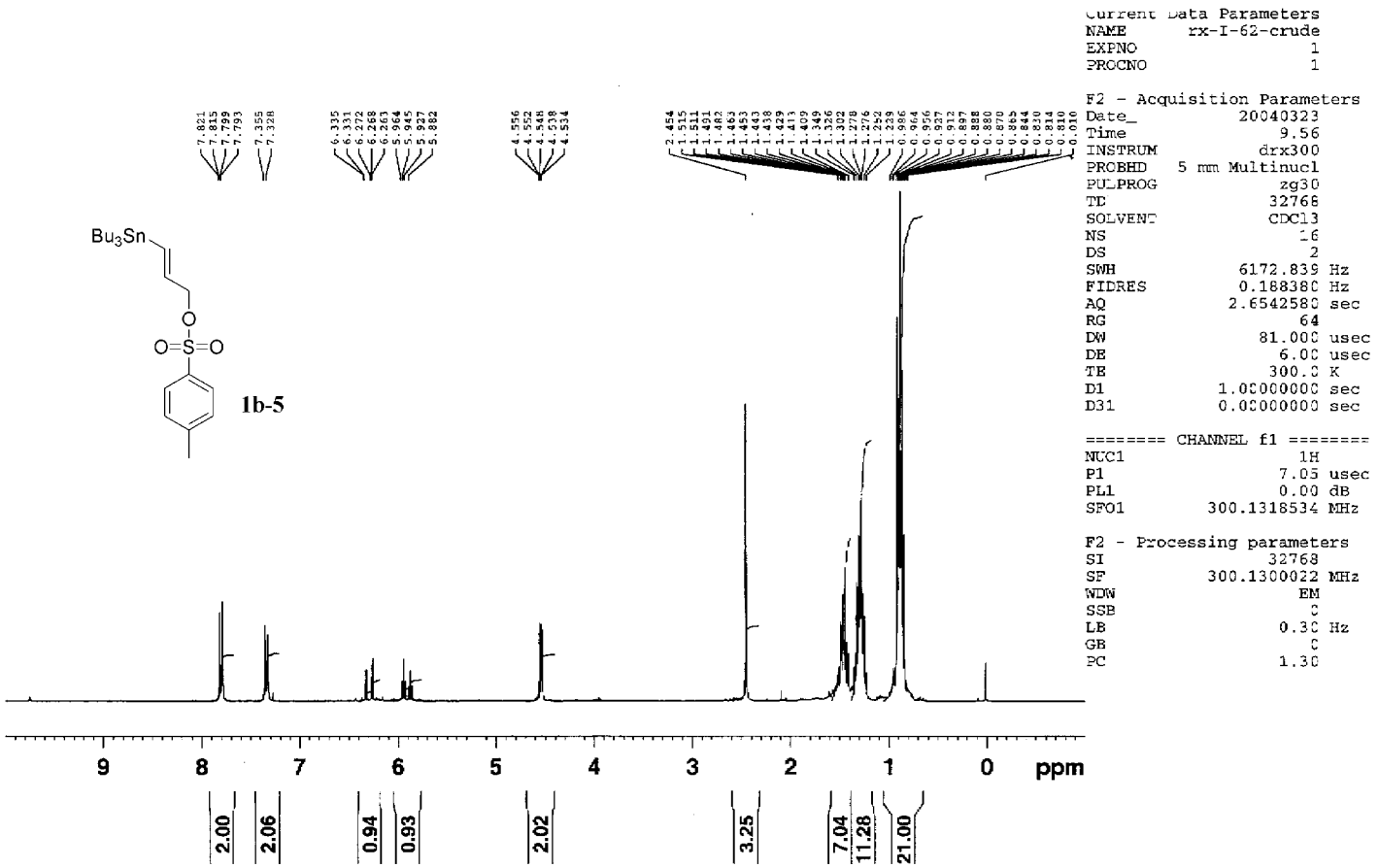
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D31 0.00000000 sec
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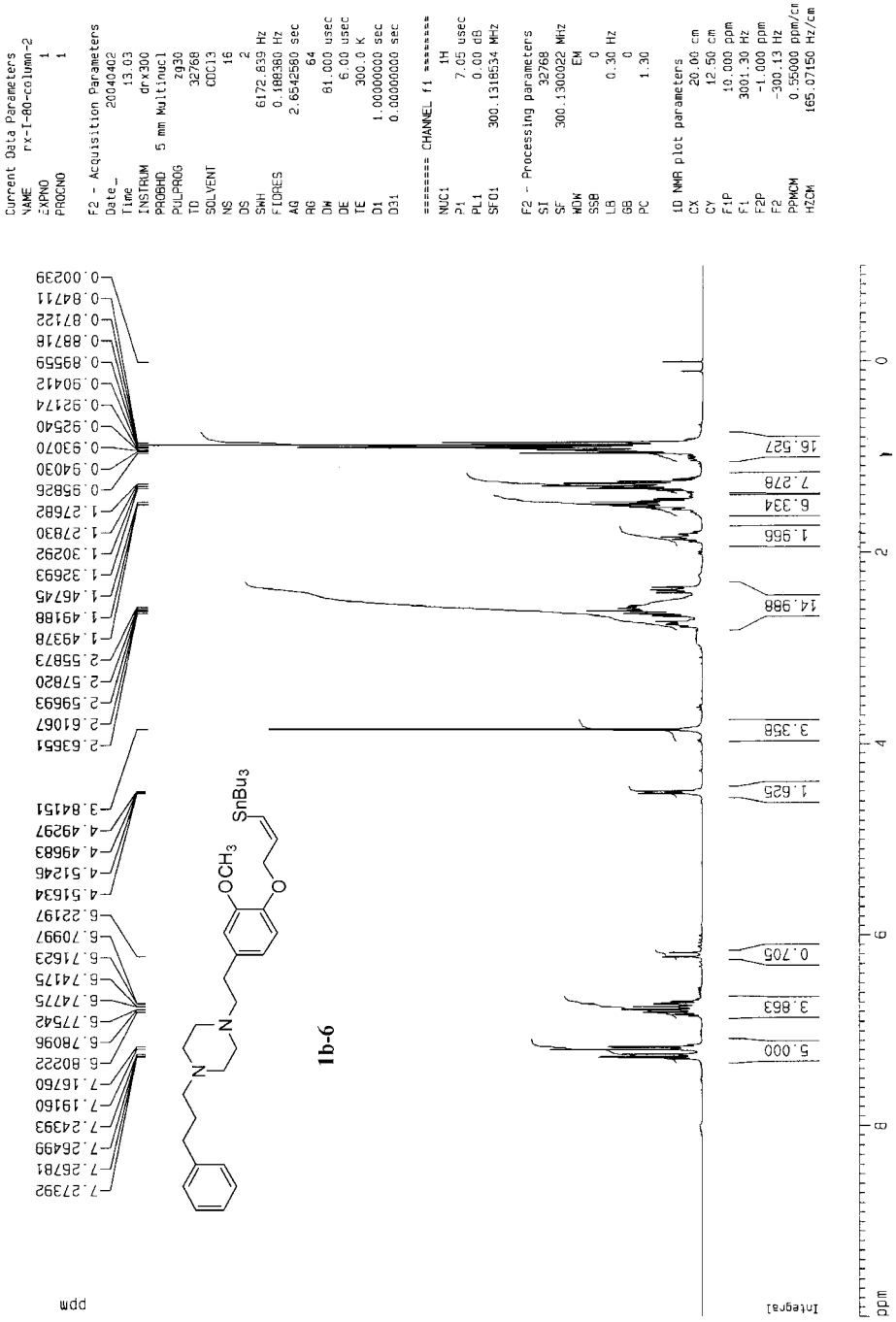
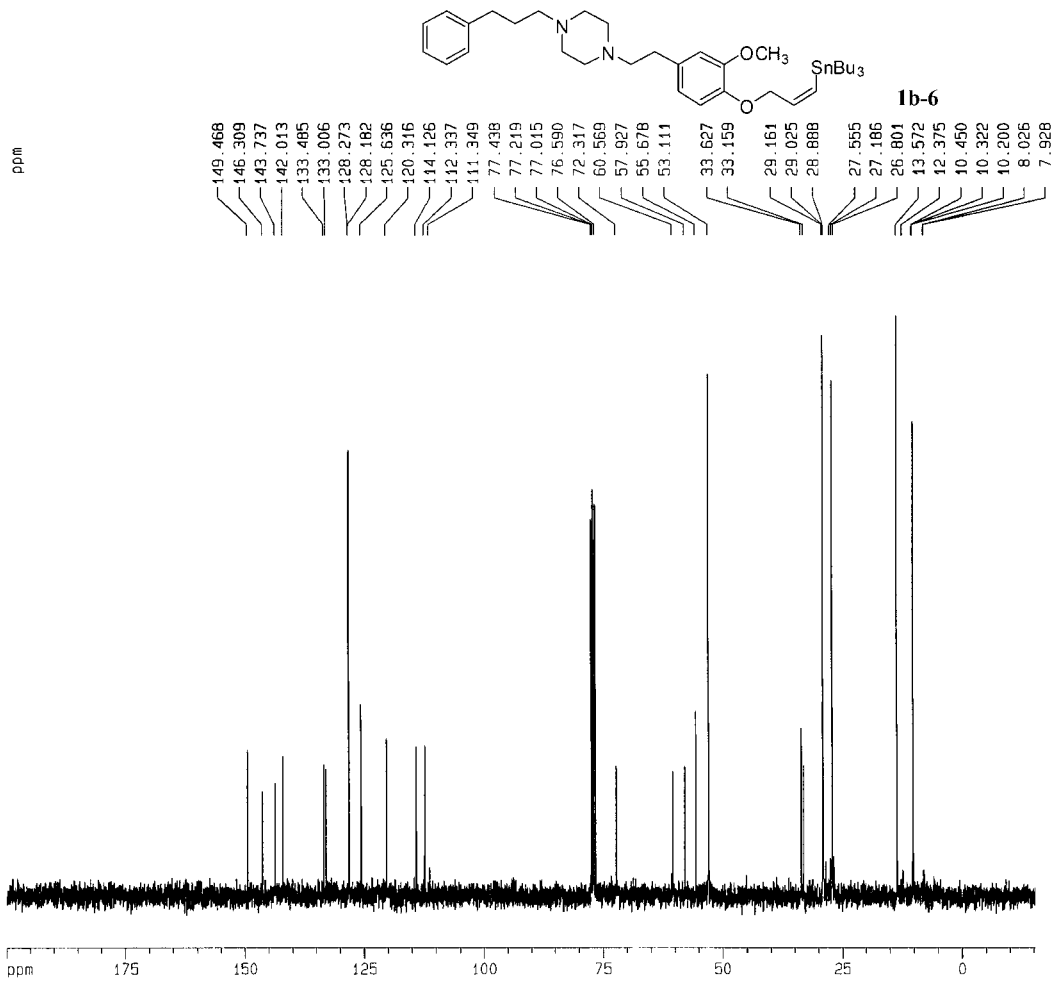
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30


Current Data Parameters
NAME rx-1-80-column-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040402
Time 13.03
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 64
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 3001.30 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 165.07150 Hz/cm
0.00239
0.84711
0.87122
0.88718
0.89559
0.90412
0.92174
0.92540
0.93070
0.94030
0.95826
1.27682
1.27830
1.30292
1.32693
1.46745
1.49188
1.49378
2.55873
2.57820
2.59693
2.61067
2.63651
3.84151
4.49297
4.49683
4.51246
4.51634
6.22197
6.70997
6.71623
6.74175
6.74775
6.77542
6.78096
6.80222
7.16760
7.19160
7.24393
7.26499
7.26781
7.27392
SnBu3
OCH3
1b-6
16.527
7.278
6.334
1.966
14.988
3.358
1.625
0.705
3.863
5.000
Integral
ppm

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Current Data Parameters
NAME      rx-I-80-column-2
EXPNO                    2
PROCNO                   1

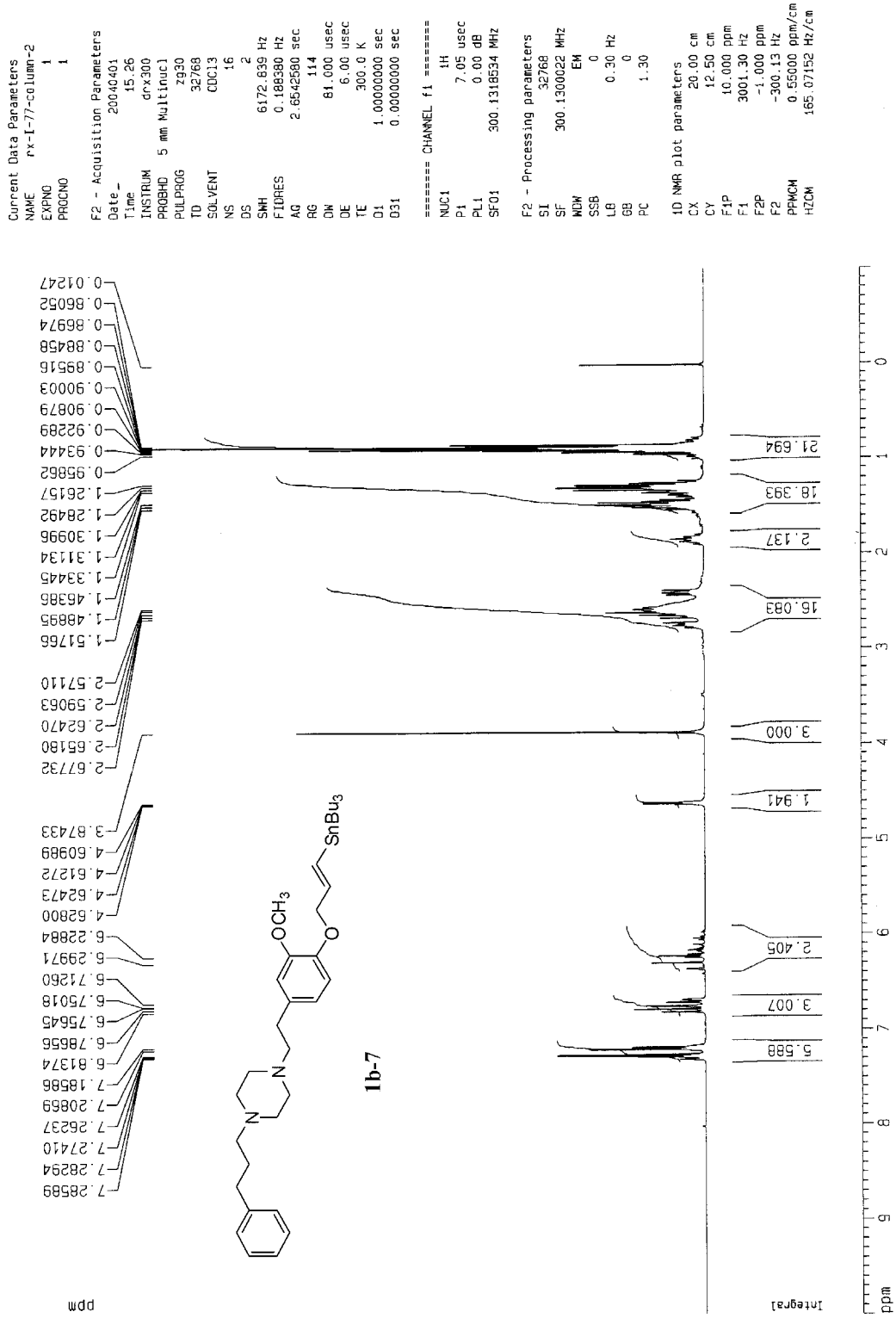
F2 - Acquisition Parameters
Date_          20040402
Time                13.07
INSTRUM          drx300
PROBHD   5 mm Multinucl
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                   69
DS                    4
SWH           18832.393 Hz
FIDRES        0.287360 Hz
AQ            1.7400308 sec
RG                22528
DW               26.550 usec
DE                6.00 usec
TE               297.1 K
D1            1.29999995 sec
d11           0.03000000 sec
D31           0.00000000 sec

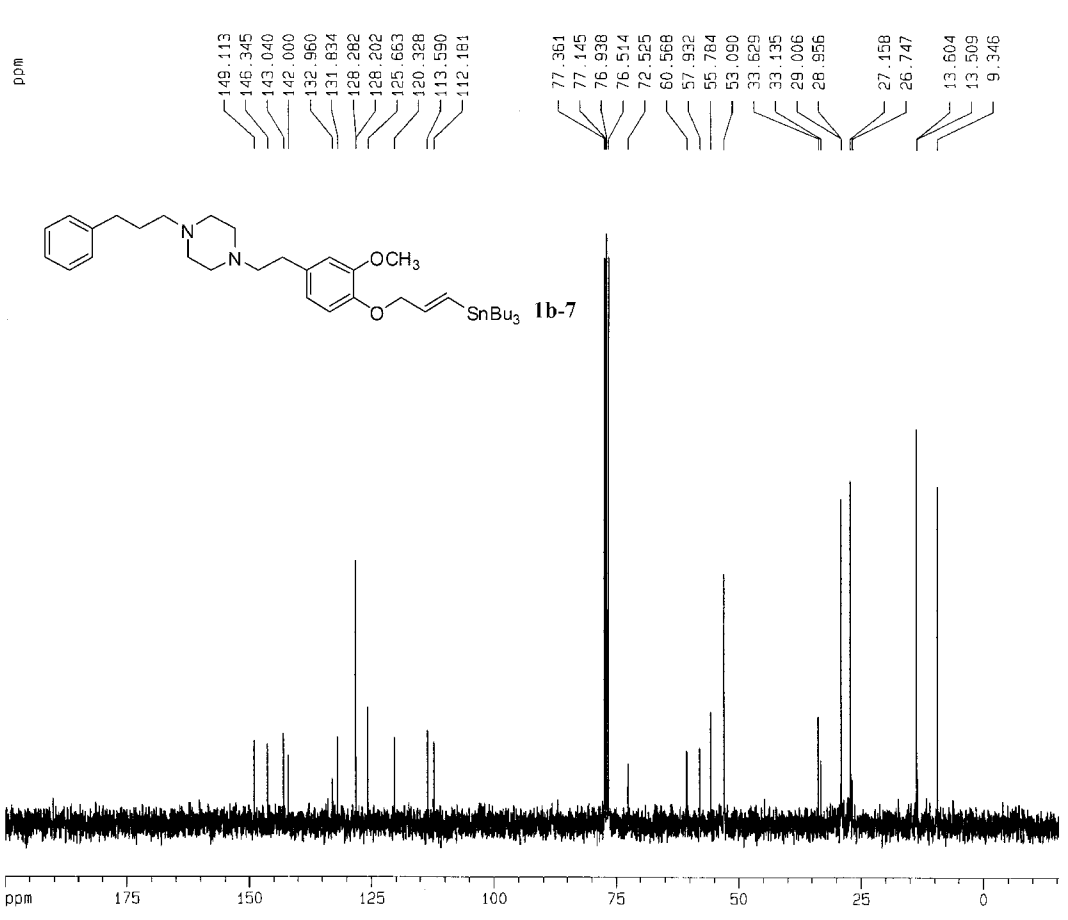
======== CHANNEL f1 ========
NUC1                 13C
P1                  8.50 usec
PL1                 5.00 dB
SFO1         75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2               120.00 dB
PL12               25.60 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI                32768
SF           75.4677571 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
CY                11.00 cm
F1P              200.000 ppm
F1              15093.55 Hz
F2P              -20.000 ppm
F2              -1509.36 Hz
PPMCM          11.00000 ppm/cm
HZCM          830.14532 Hz/cm
```


Current Data Parameters
NAME px-I-77-column-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040401
Time 15.26
INSTRUM drx300
PROBHD 5 mm Multinuc1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 114
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 3001.30 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 165.07152 Hz/cm
0.01247
0.86052
0.86974
0.88458
0.89516
0.90003
0.90879
0.92289
0.93444
0.95862
1.26157
1.28492
1.30996
1.31134
1.33445
1.46386
1.48895
1.51766
2.57110
2.59063
2.62470
2.65180
2.67732
3.87433
4.60989
4.61272
4.62473
4.62800
6.22884
6.29971
6.71260
6.75018
6.75645
6.78656
6.81374
7.18586
7.20869
7.26237
7.27410
7.28294
7.28589
21.694
18.393
2.137
16.083
3.000
1.941
2.405
3.007
5.588
OCH3
SnBu3
N
N
O
1b-7
ppm
Integral



Current Data Parameters
NAME rx-I-77-column-2
EXPNO 2
PROCNO 1

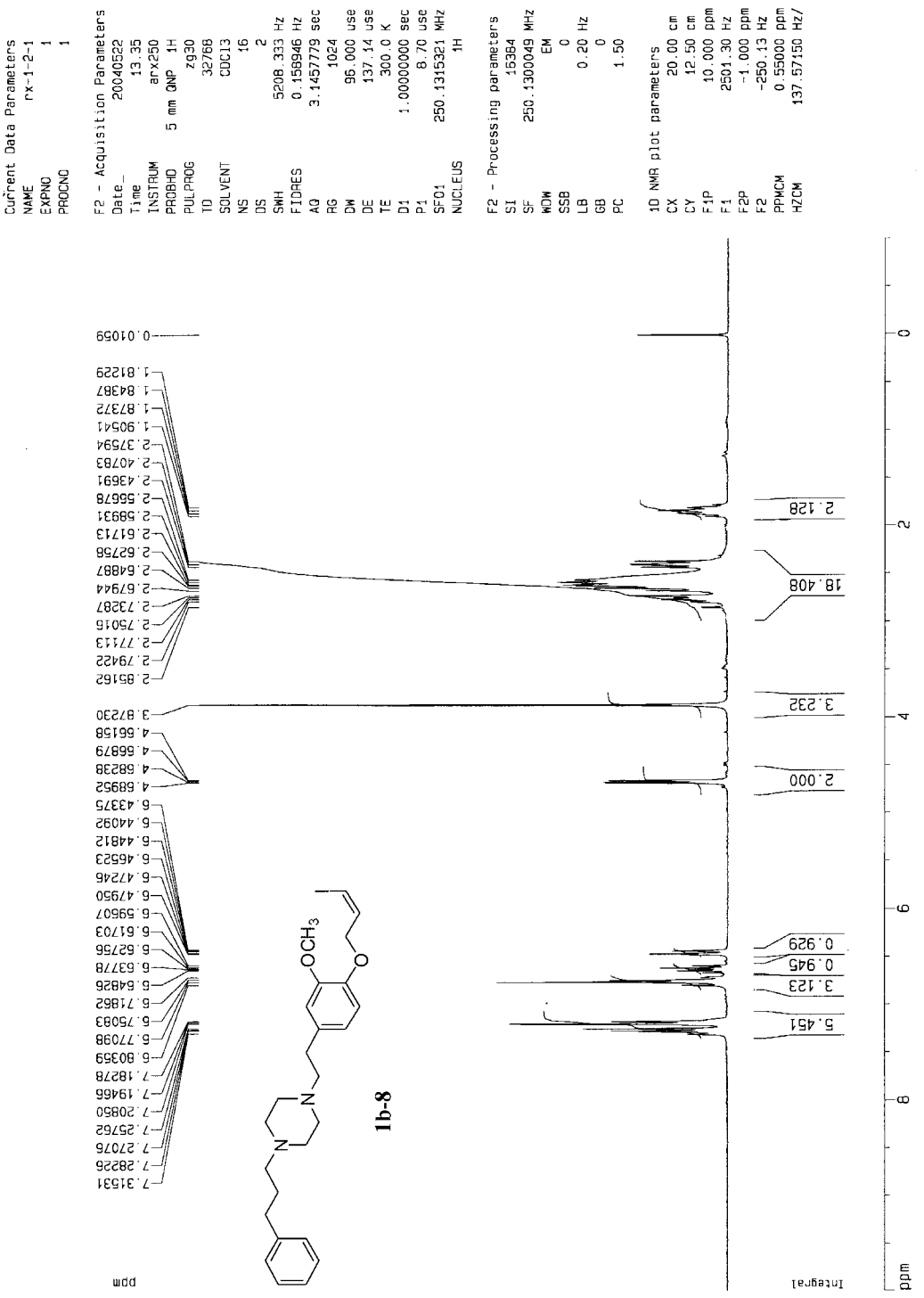
F2 - Acquisition Parameters
Date_ 20040401
Time 15.33
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 297.1 K
D1 1.29999995 sec
d11 0.03000000 sec
D31 0.00000000 sec

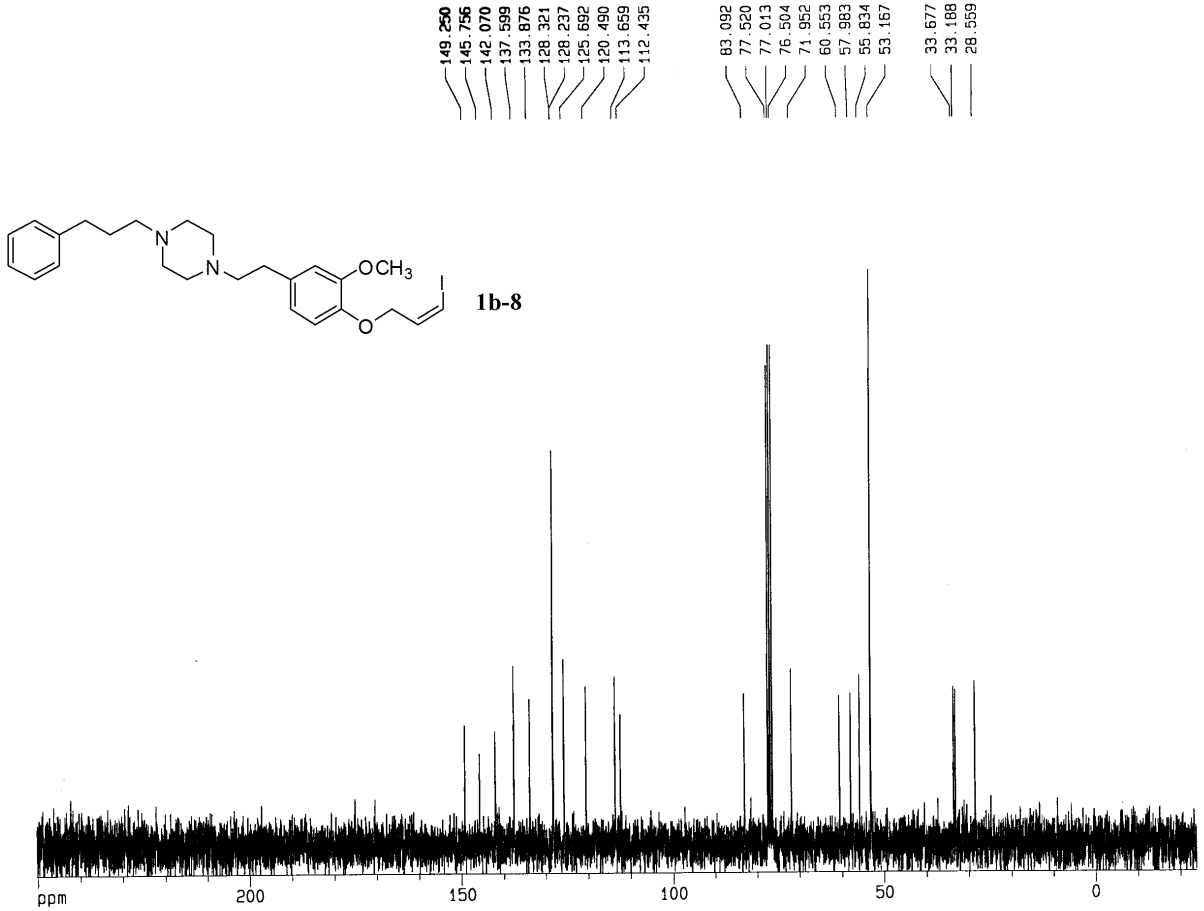
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 5.00 dB
SFO1 75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 11.00 cm
F1P 200.000 ppm
F1 15093.55 Hz
F2P -20.000 ppm
F2 -1509.36 Hz
PPMCM 11.00000 ppm/cm
HZCM 830.14532 Hz/cm


Current Data Parameters
NAME rx-1-2-1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040522
Time 13.35
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 1024
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
0.01059
1.81229
1.84387
1.87372
1.90541
2.37594
2.40783
2.43691
2.56678
2.58931
2.61713
2.62758
2.64887
2.67944
2.73287
2.75015
2.77113
2.79422
2.85162
3.87230
4.66158
4.66879
4.68238
4.68952
6.43375
6.44092
6.44812
6.46523
6.47246
6.47950
6.59607
6.61703
6.62756
6.63778
6.64826
6.71862
6.75083
6.77098
6.80359
7.18278
7.19466
7.20850
7.25762
7.27076
7.28226
7.31531
OCH3
N
N
O
1b-8
2.128
18.408
3.232
2.000
0.929
0.945
3.123
5.451
ppm
Integral
8
6
4
2
0



Current Data Parameters

NAME	rx-I-1-1-1b
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

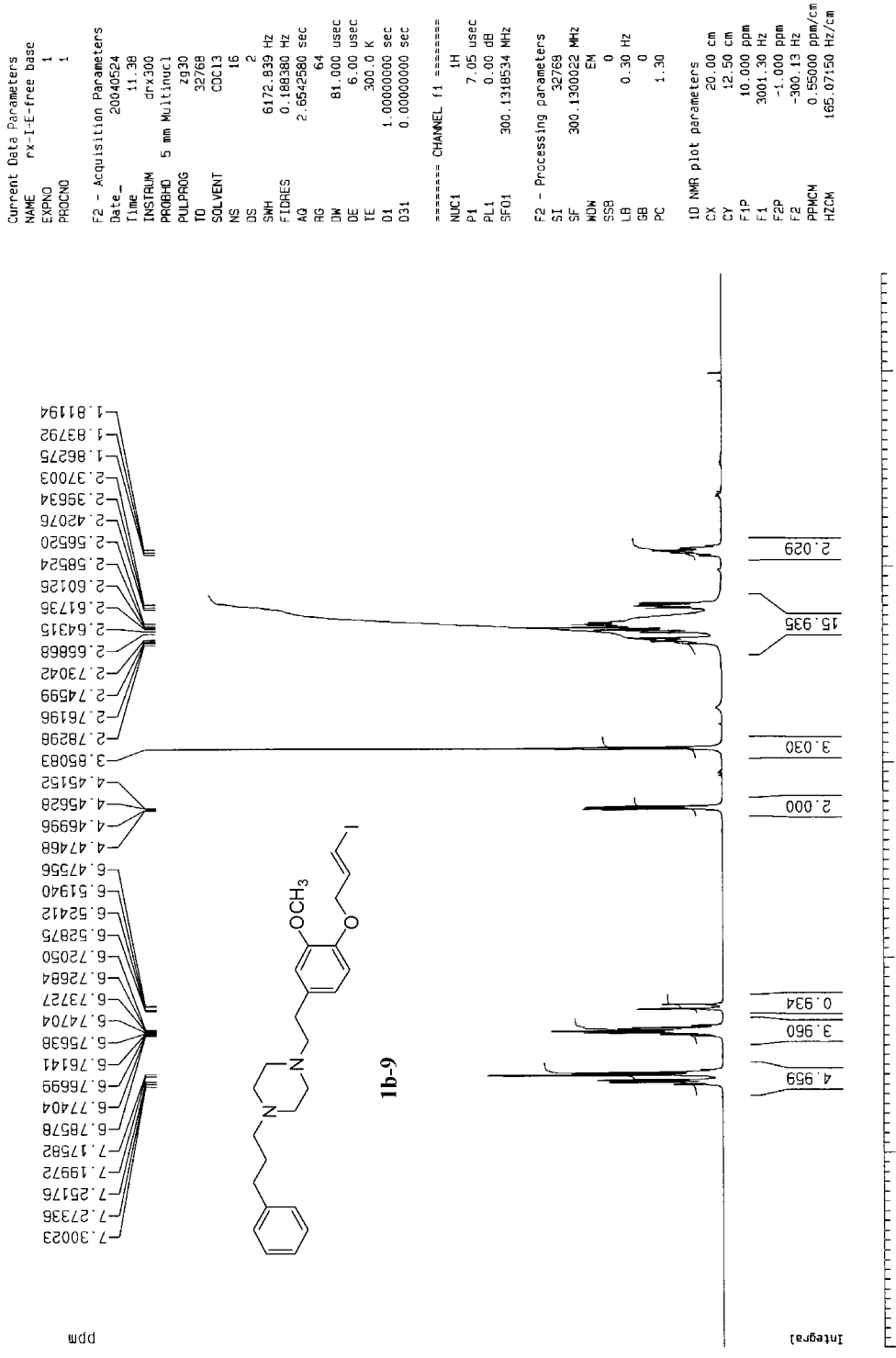
Date_	20040522
Time	23.09
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	95
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	1.00000000 sec
P1	5.35 use
SF01	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

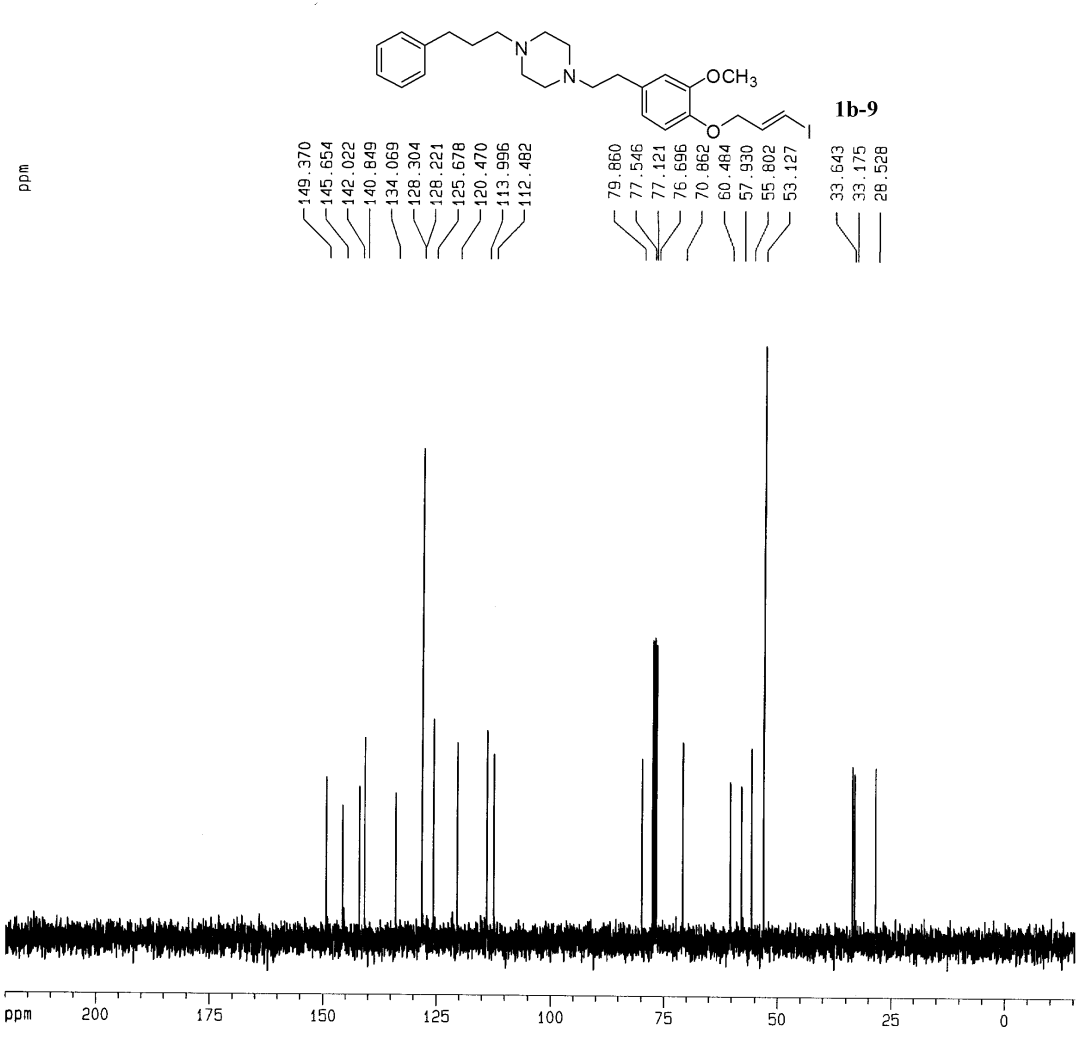
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	250.354 ppm
F1	15746.05 Hz
F2P	-23.775 ppm
F2	-1495.33 Hz
PPMCM	13.70643 ppm
HZCM	862.06897 Hz/


Current Data Parameters
NAME rx-I-E-free base
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040524
Time 11.38
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 64
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 3001.30 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 185.07150 Hz/cm
7.30023
7.27336
7.25176
7.19972
7.17582
6.78578
6.77404
6.76699
6.76141
6.75638
6.74704
6.73727
6.72684
6.72050
6.70875
6.52412
6.51940
6.47556
4.47468
4.46996
4.46628
4.45152
3.85083
2.78298
2.76196
2.74599
2.73042
2.65868
2.64315
2.61736
2.60126
2.58524
2.56520
2.42076
2.39634
2.37003
1.86275
1.83792
1.81194
OCH3
N
N
O
I
1b-9
2.029
15.935
3.030
2.000
0.934
3.960
4.959
Integral
ppm
8
6
4
2
0




```
Current Data Parameters
NAME      rx-I-E-free base
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20040524
Time                 11.41
INSTRUM              drx300
PROBHD   5 mm Multinucl
PULPROG              zgdc30
TD                    65536
SOLVENT               CDCl3
NS                        8
DS                        4
SWH              18832.393 Hz
FIDRES            0.287360 Hz
AQ                1.7400308 sec
RG                    22528
DW                   26.550 usec
DE                    6.00 usec
TE                   297.1 K
D1               1.29999995 sec
d11              0.03000000 sec
D31              0.00000000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                   8.50 usec
PL1                  5.00 dB
SFO1            75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2              100.00 usec
PL2                120.00 dB
PL12                25.60 dB
SFO2           300.1312005 MHz

F2 - Processing parameters
SI                     32768
SF              75.4677571 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                     1.40

1D NMR plot parameters
CX                   20.00 cm
CY                   11.00 cm
F1P                220.000 ppm
F1                 16602.91 Hz
F2P                -20.000 ppm
F2                 -1509.35 Hz
PPMCM             12.00000 ppm/cm
HZCM             905.61310 Hz/cm
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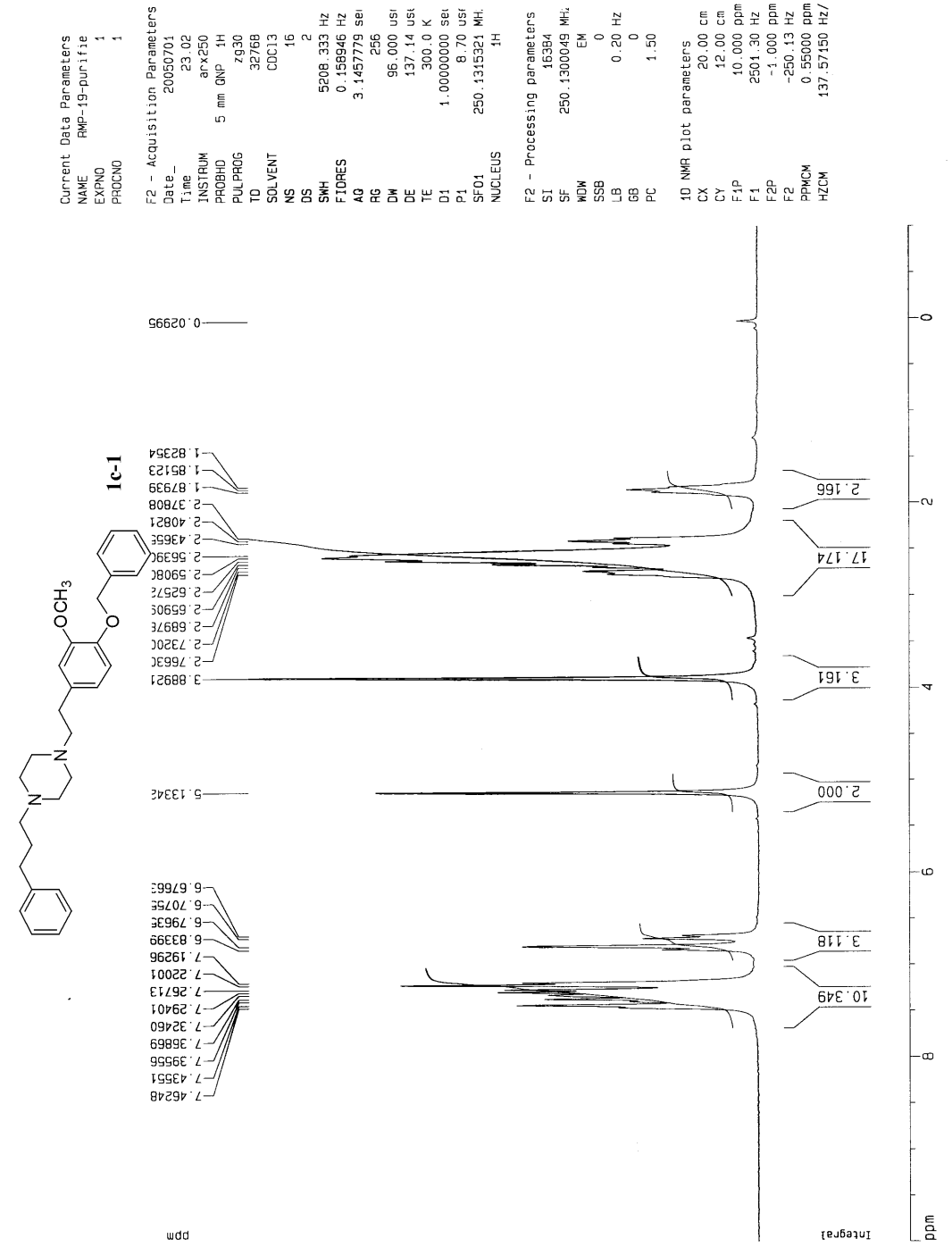
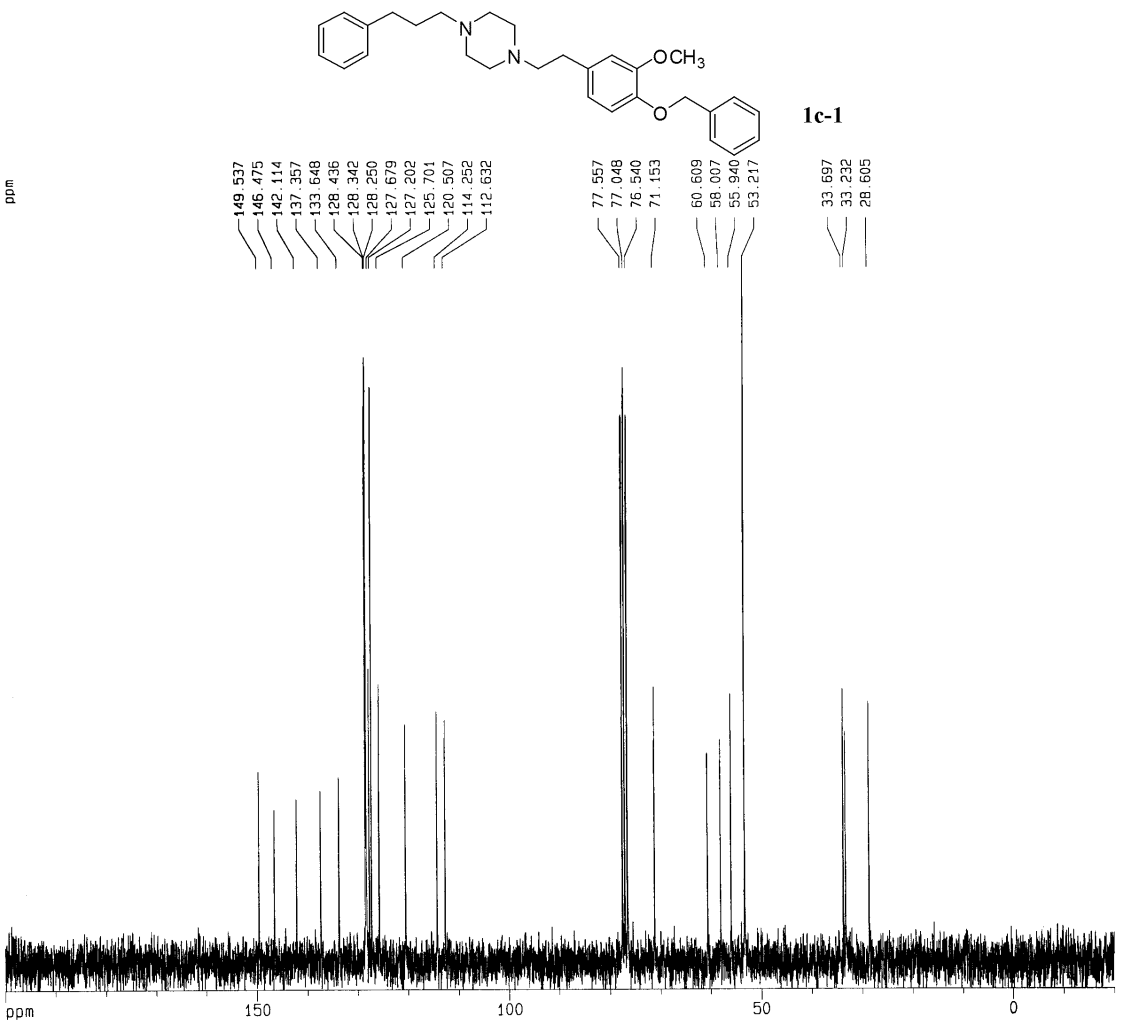

Current Data Parameters
NAME AMP-19-purifie
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050701
Time 23.02
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AG 3.1457779
RG 256
DW 96.000
DE 137.14
TE 300.0 K
D1 1.00000000
P1 8.70
SFO1 250.1315321 MH
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MH
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
1c-1
OCH3
O
N
N
0.02995
1.82354
1.85123
1.87939
2.37808
2.40821
2.43656
2.56390
2.59080
2.62572
2.65906
2.68976
2.73200
2.76630
3.88921
5.13342
6.67663
6.70756
6.79636
6.83399
7.19296
7.22001
7.26713
7.29401
7.32460
7.36869
7.39556
7.43551
7.46248
2.166
17.174
3.161
2.000
3.118
10.349
ppm
Integral
ppm
0
2
4
6
8

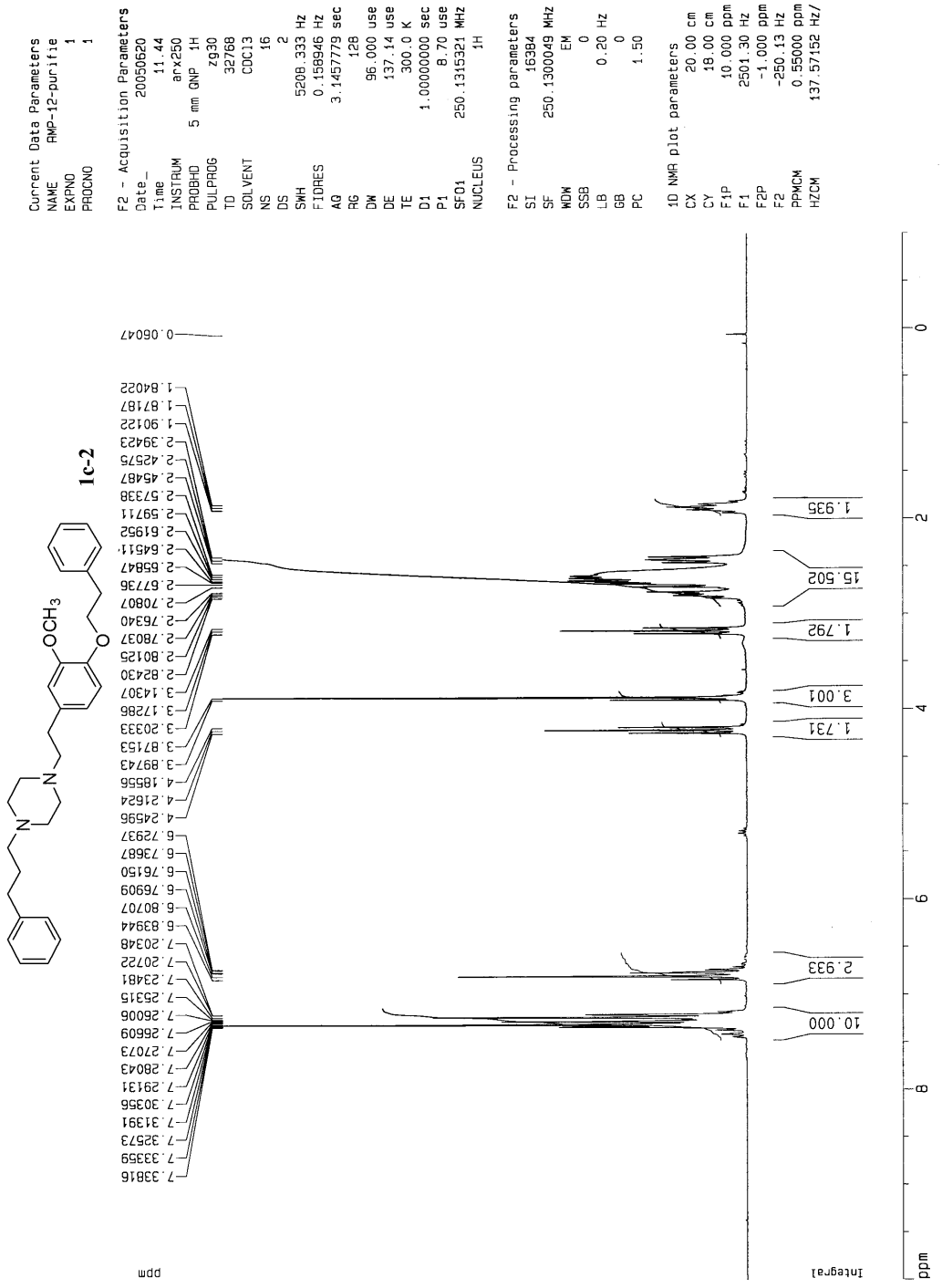


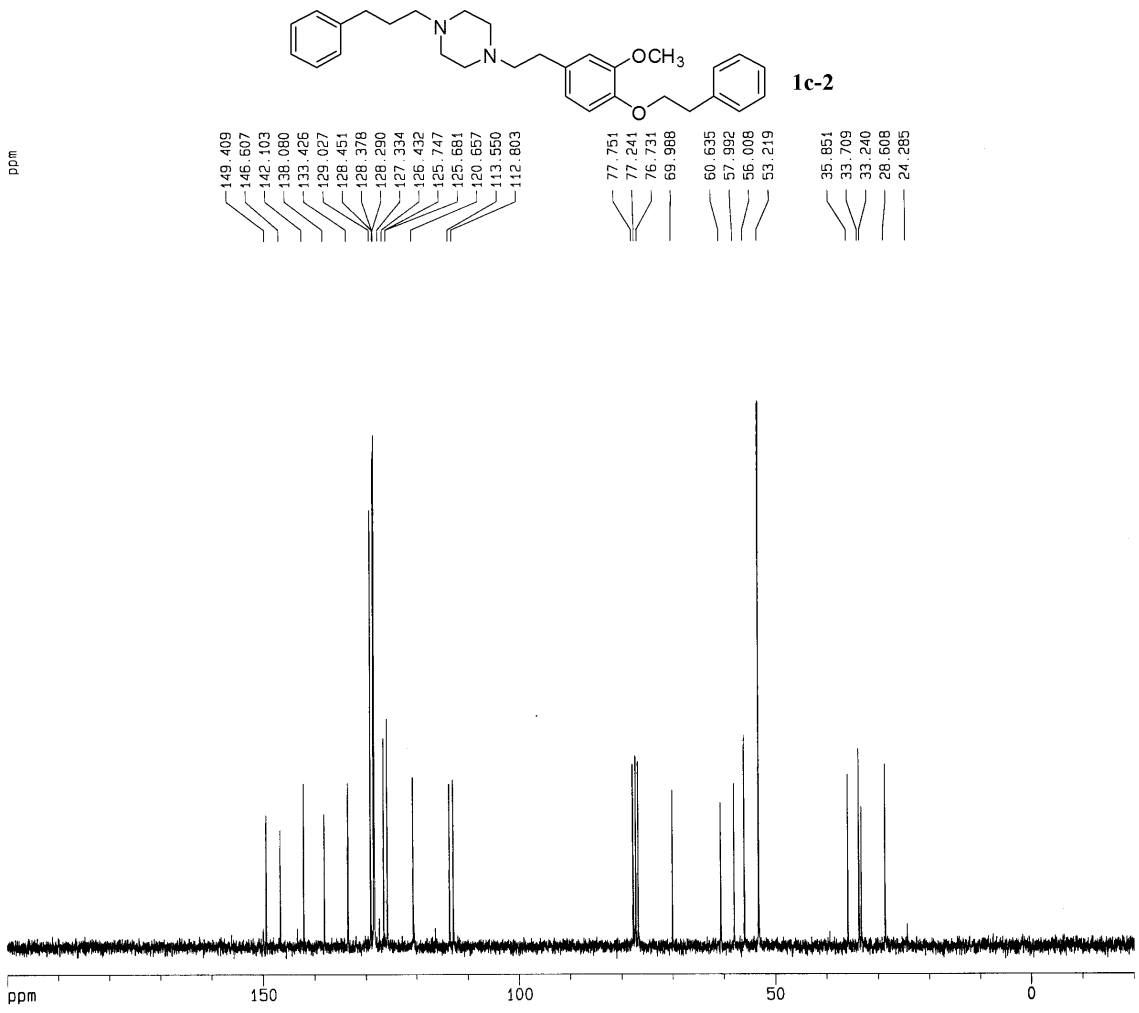
Current Data Parameters
NAME AMP-19-purifie
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050701
Time 23.06
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zgdc30
TD 36864
SOLVENT CDCl3
NS 84
DS 4
SWH 17241.379 Hz
FIDRES 0.467702 Hz
AQ 1.0691060 sec
RG 22800
DW 29.000 use
DE 41.43 use
TE 300.0 K
D12 0.00002000 sec
DL5 23.00 dB
CPDPRG waltz16
P31 103.00 use
D1 2.00000000 sec
P1 6.00 use
SFO1 62.9023694 MHz
NUCLEUS 13C
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 62.8952440 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 16.00 cm
F1P 200.000 ppm
F1 12579.05 Hz
F2P -20.000 ppm
F2 -1257.91 Hz
PPMCM 11.00000 ppm
HZCM 691.84772 Hz/


Current Data Parameters
NAME AMP-12-purifie
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050620
Time 11.44
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 128
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 18.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57152 Hz/
1c-2
OCH3
N
N
O
ppm
Integral
1.935
15.502
1.792
3.001
1.731
2.933
10.000
0
2
4
6
8
ppm

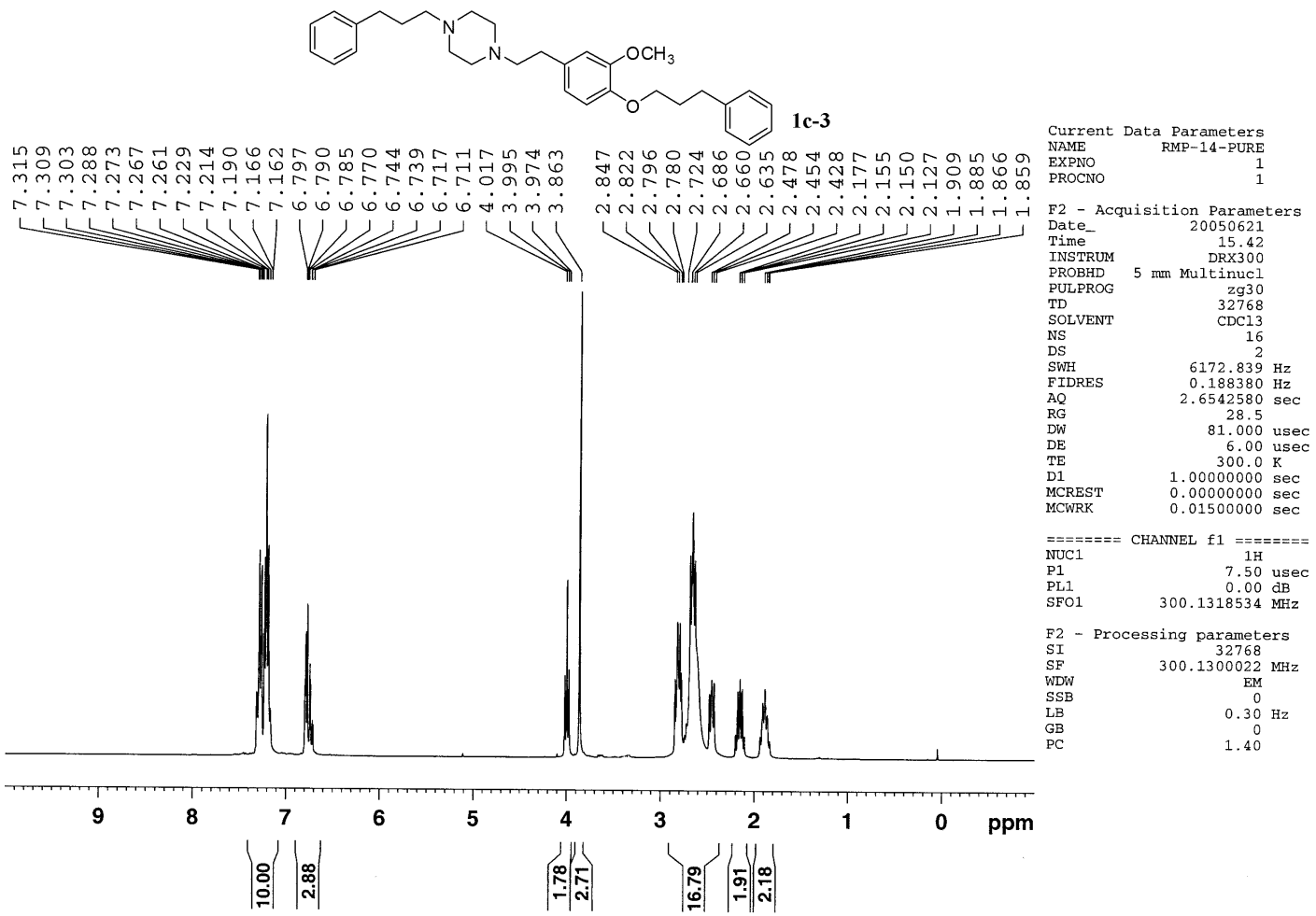


Current Data Parameters
NAME RMP-12-purifie
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050620
Time 11.48
INSTRUM arx250
PROBHD 5 mm GNP 1H
PULPROG zgdc30
TD 36864
SOLVENT CDCl3
NS 62
DS 4
SWH 17241.379 Hz
FIDRES 0.467702 Hz
AQ 1.0691060 sec
RG 22800
DW 29.000 use
DE 41.43 use
TE 300.0 K
D12 0.00002000 sec
DL5 23.00 dB
CPDPRG waltz16
P31 103.00 use
D1 2.00000000 sec
P1 6.00 use
SFO1 62.9023694 MHz
NUCLEUS 13C
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 62.8952440 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 200.000 ppm
F1 12579.05 Hz
F2P -20.000 ppm
F2 -1257.91 Hz
PPMCM 11.00000 ppm
HZCM 691.84772 Hz/

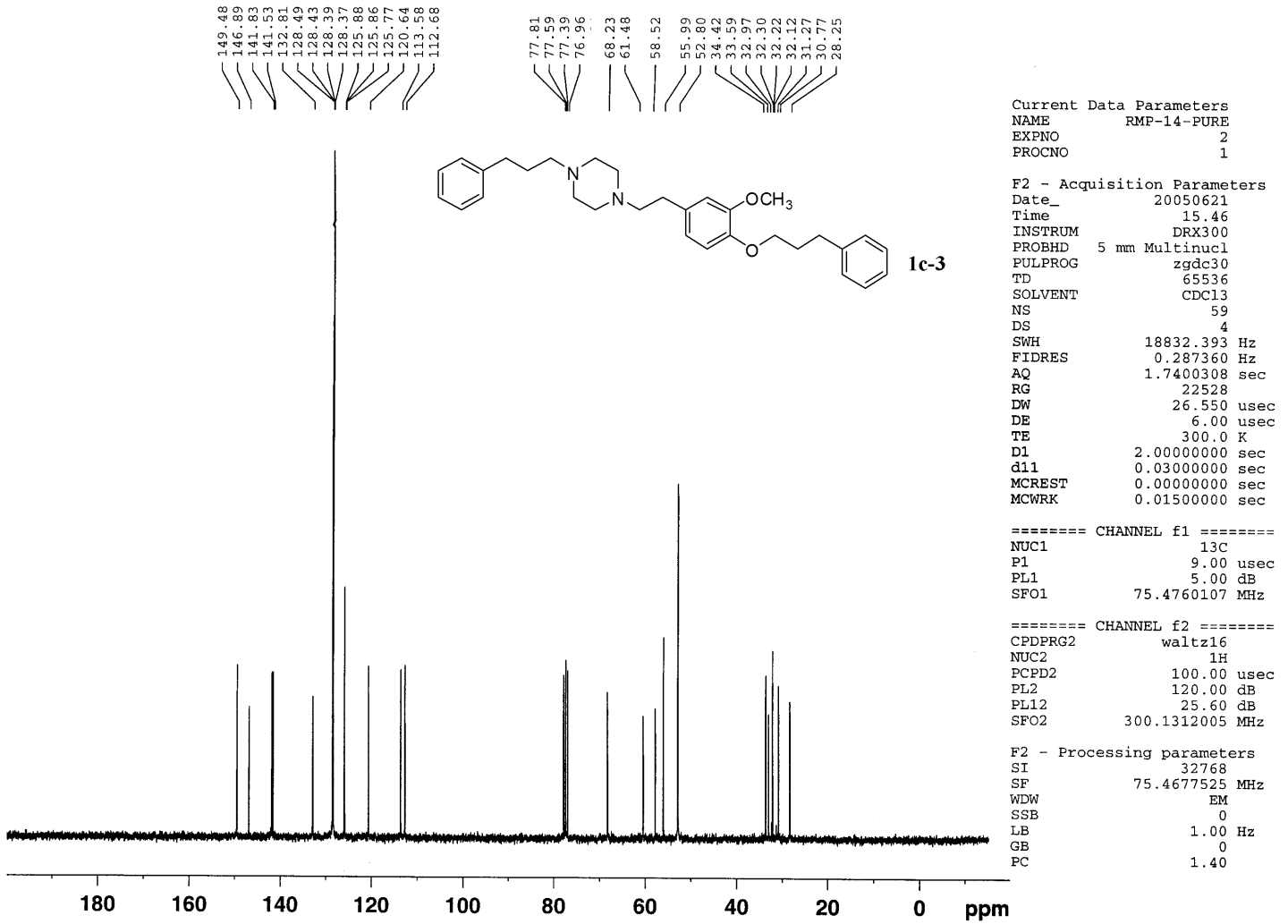



```
Current Data Parameters
NAME          RMP-14-PURE
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20050621
Time                15.42
INSTRUM           DRX300
PROBHD   5 mm Multinucl
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             6172.839 Hz
FIDRES          0.188380 Hz
AQ              2.6542580 sec
RG                   28.5
DW                 81.000 usec
DE                  6.00 usec
TE                 300.0 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   7.50 usec
PL1                  0.00 dB
SFO1          300.1318534 MHz

F2 - Processing parameters
SI                  32768
SF          300.1300022 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40
```

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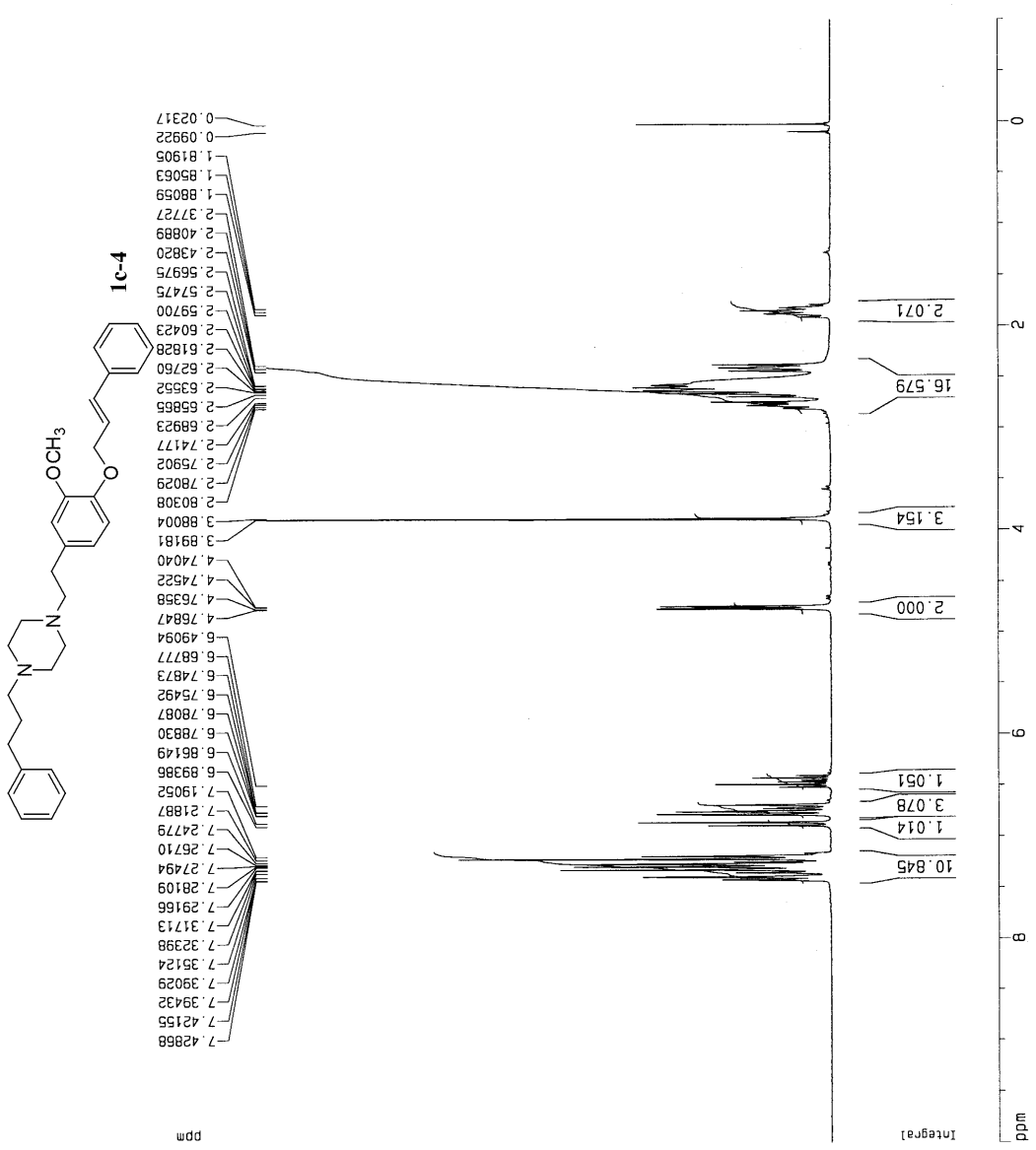
Current Data Parameters
NAME          RMP-14-PURE
EXPNO                   2
PROCNO                  1

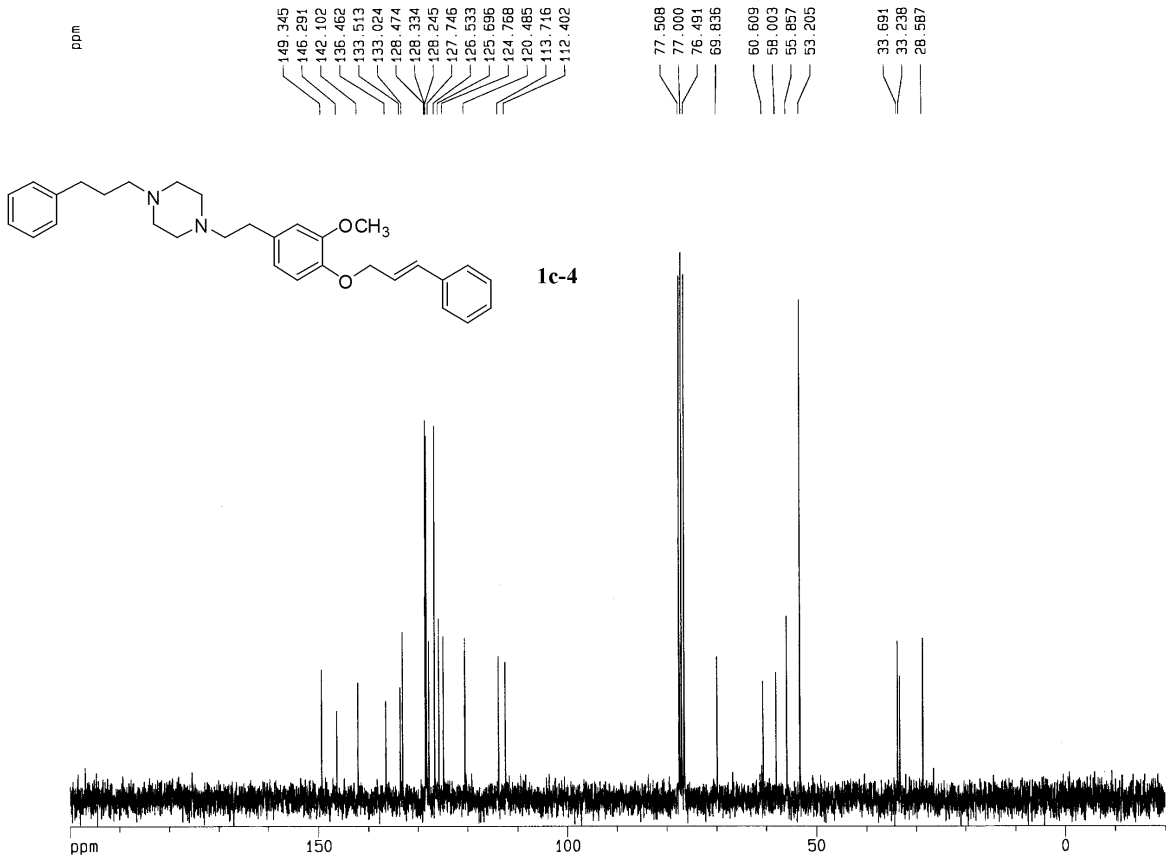
F2 - Acquisition Parameters
Date_            20050621
Time                15.46
INSTRUM           DRX300
PROBHD   5 mm Multinucl
PULPROG           zgdc30
TD                 65536
SOLVENT            CDCl3
NS                    59
DS                     4
SWH           18832.393 Hz
FIDRES         0.287360 Hz
AQ             1.7400308 sec
RG                 22528
DW                26.550 usec
DE                 6.00 usec
TE                300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                 9.00 usec
PL1                5.00 dB
SFO1         75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2            100.00 usec
PL2              120.00 dB
PL12              25.60 dB
SFO2        300.1312005 MHz

F2 - Processing parameters
SI                 32768
SF           75.4677525 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                 1.40
```


1c-4
OCH3
Current Data Parameters
NAME rx-II-99-pure
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050805
Time 10.13
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AG 3.1457779 sec
RG 715
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
ppm
Integral
2.071
16.579
3.154
2.000
1.051
3.078
1.014
10.845



Current Data Parameters

NAME	rx-II-99-pure
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

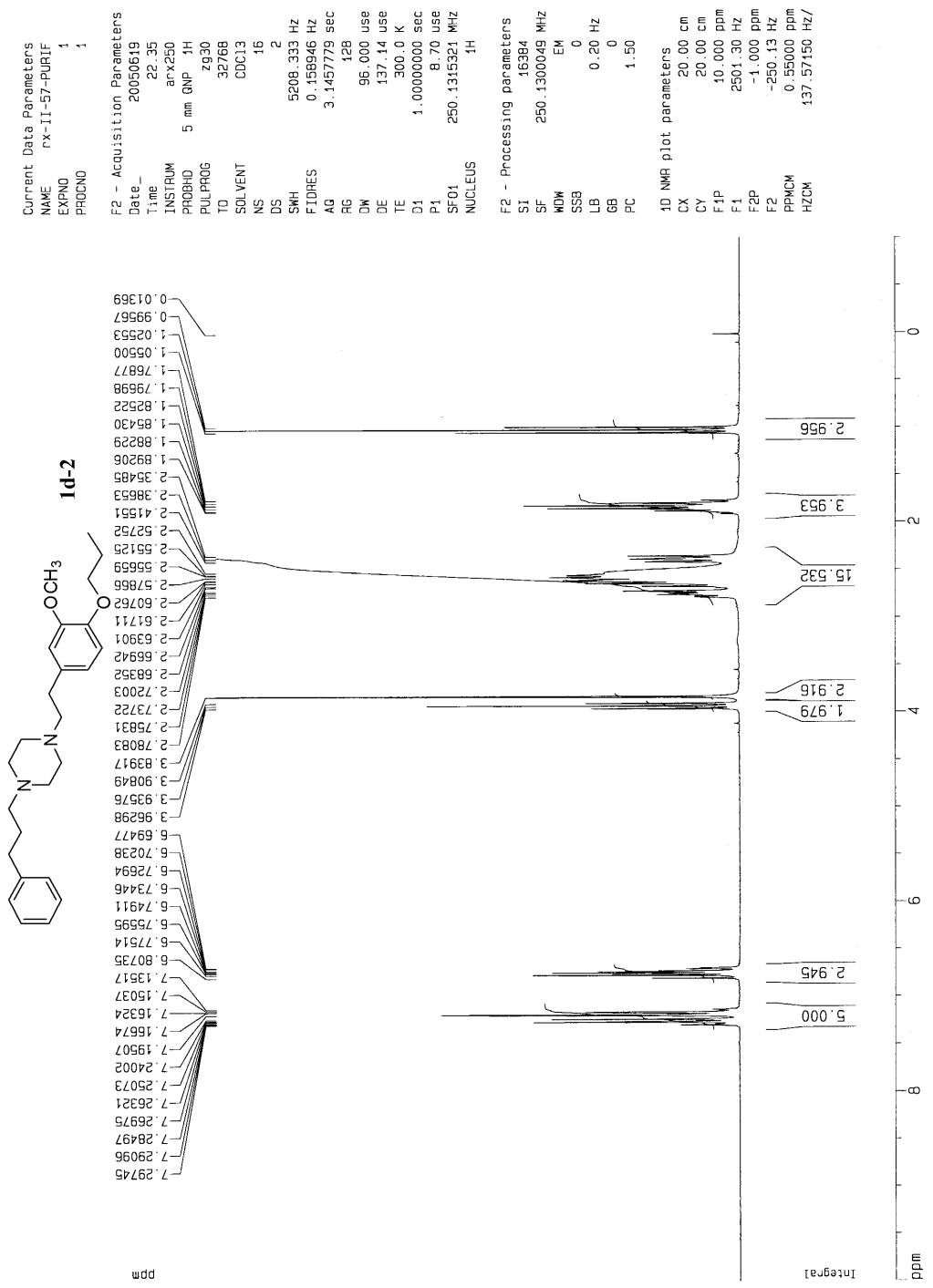
Date_	20050805
Time	10.17
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	122
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	2.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

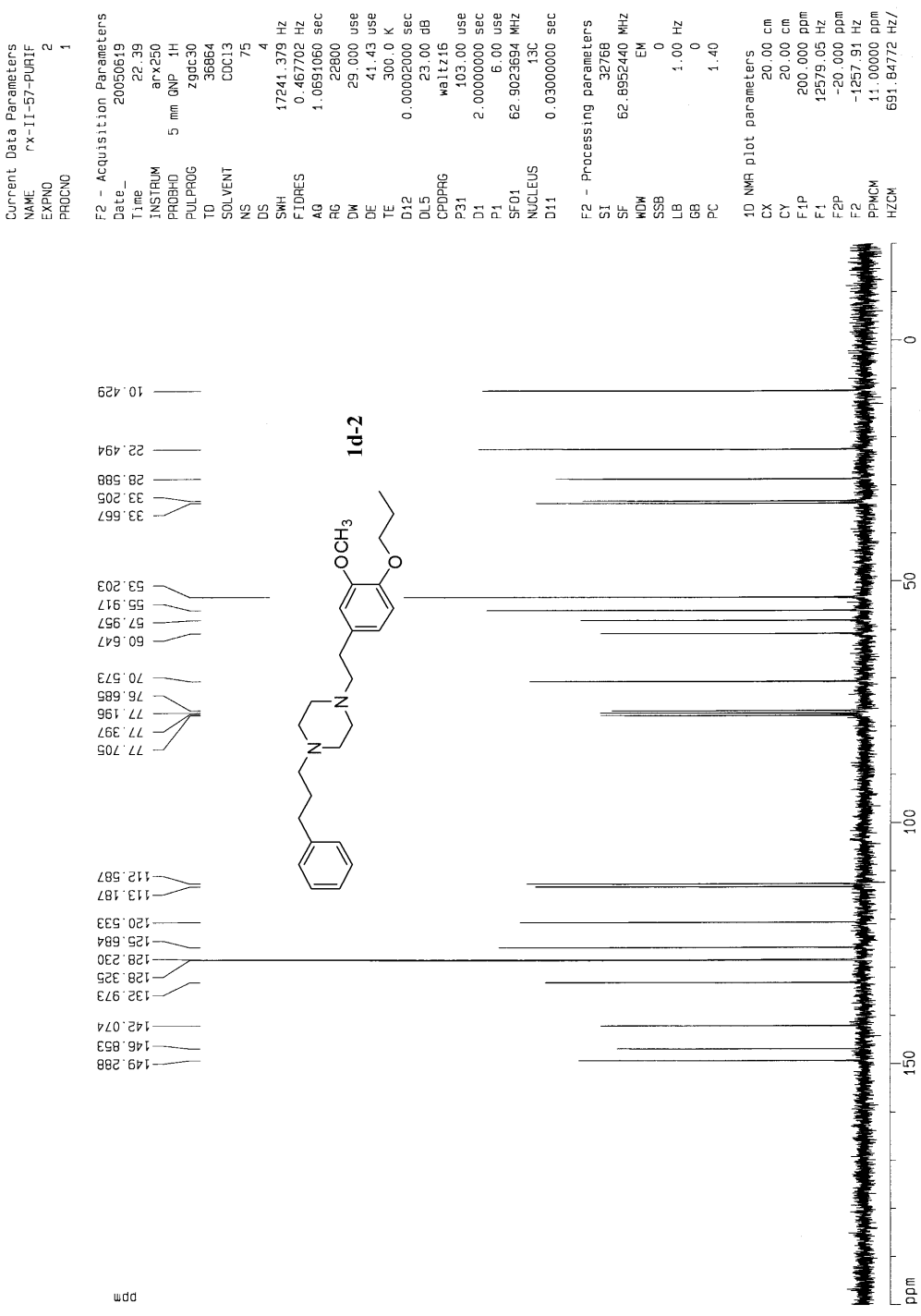
F2 - Processing parameters

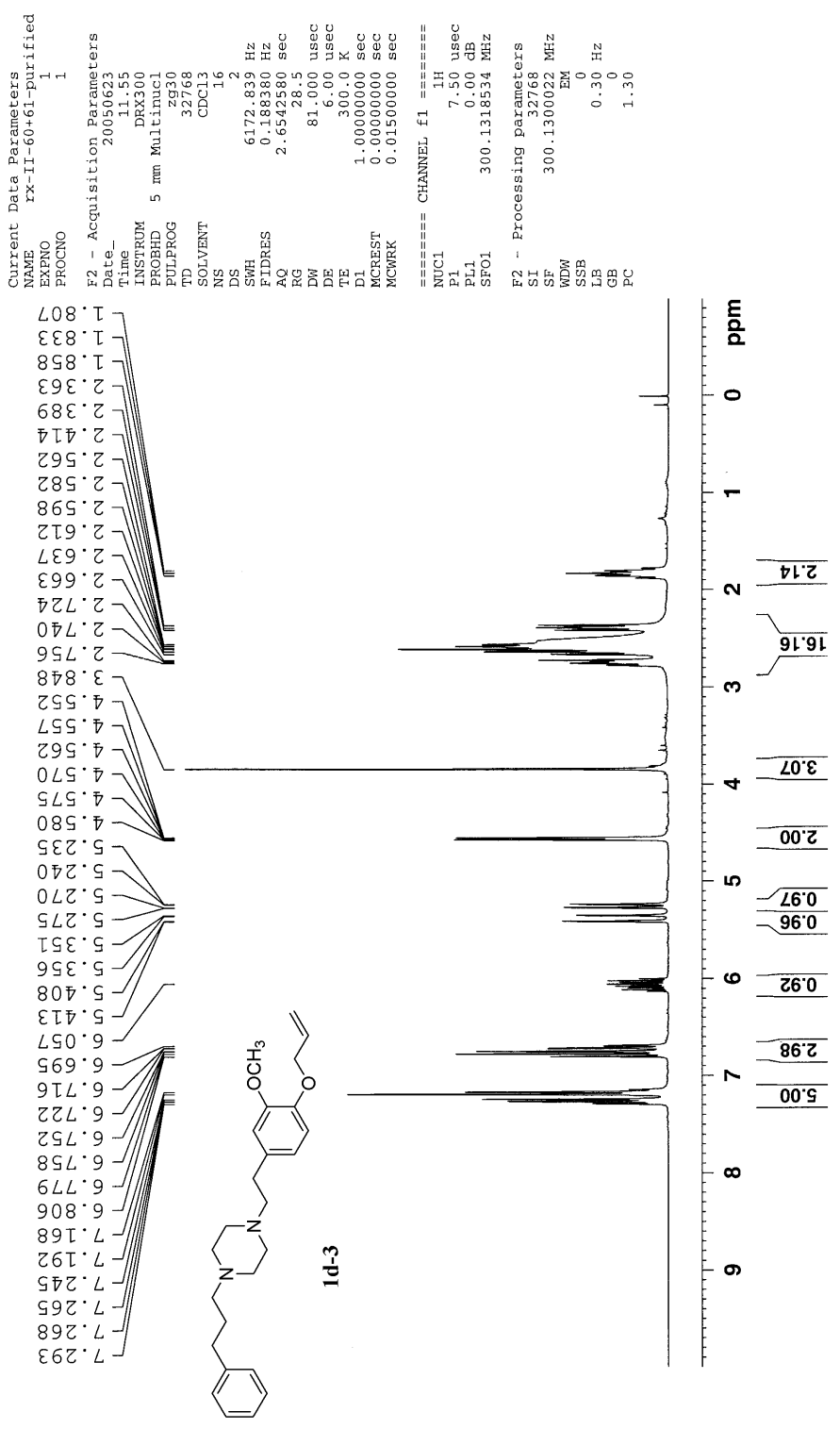
SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

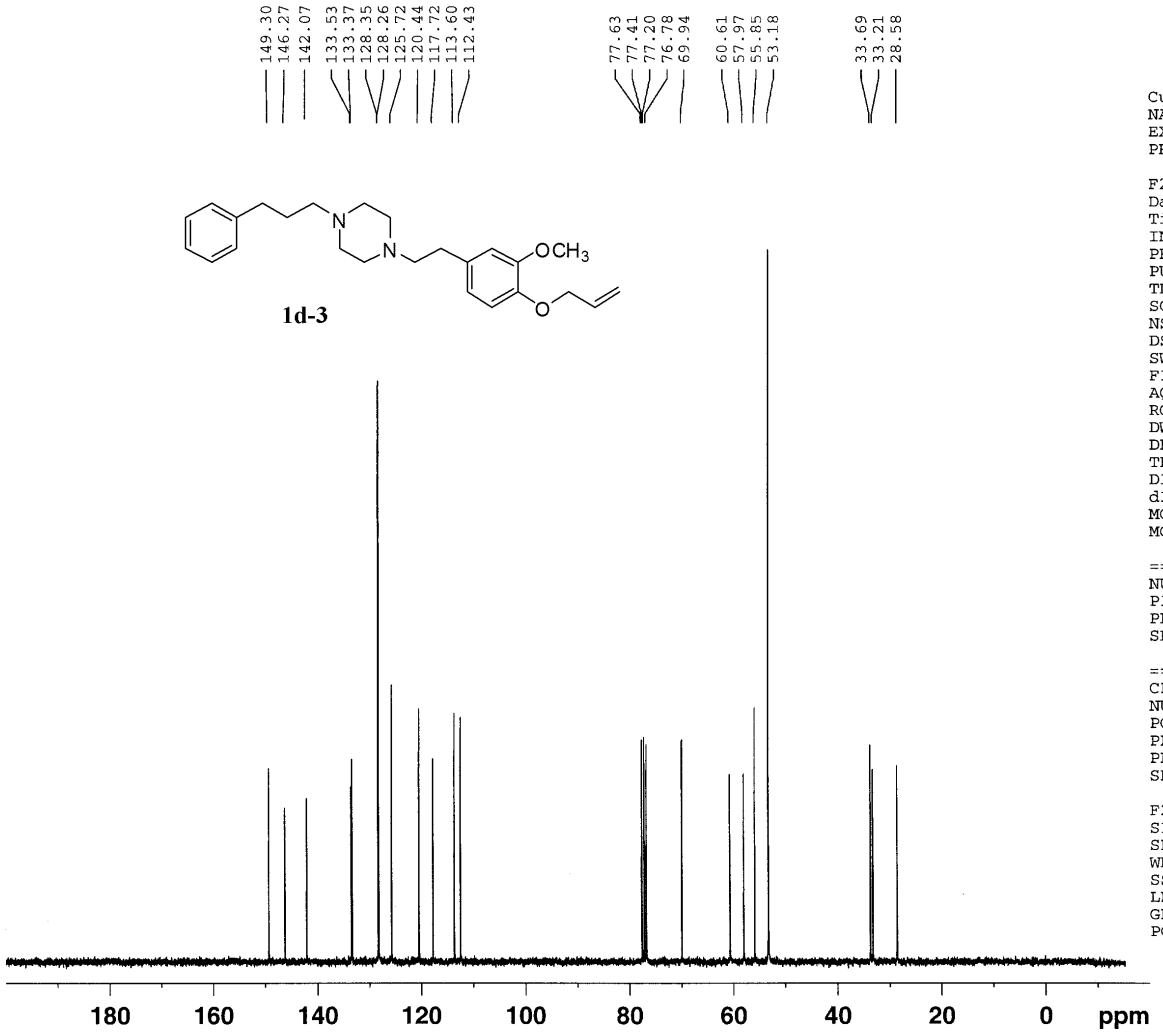
1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm
HZCM	691.84772 Hz/


Current Data Parameters
NAME rx-II-57-PURIF
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050619
Time 22.35
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 128
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
1d-2
OCH3
O
N
N
0.01369
0.99567
1.02553
1.05500
1.76877
1.79698
1.82522
1.85430
1.88229
1.89206
2.35485
2.38653
2.41551
2.52752
2.55125
2.55659
2.57866
2.60762
2.61711
2.63901
2.66942
2.68352
2.72003
2.73722
2.75831
2.78083
3.83917
3.90849
3.93576
3.96298
6.69477
6.70238
6.72694
6.73446
6.74911
6.75595
6.77514
6.80735
7.13517
7.15037
7.16324
7.16674
7.19507
7.24002
7.25073
7.26321
7.26975
7.28497
7.29096
7.29745
2.956
3.953
15.532
2.916
1.979
2.945
5.000
ppm
Integral
ppm
0
2
4
6
8


Current Data Parameters
NAME rx-II-57-PURIF
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050619
Time 22.39
INSTRUM arx250
PROBHD 5 mm GNP 1H
PULPROG zgdc30
TD 36864
SOLVENT CDCl3
NS 75
DS 4
SWH 17241.379 Hz
FIDRES 0.467702 Hz
AQ 1.0691060 sec
RG 22800
DW 29.000 use
DE 41.43 use
TE 300.0 K
D12 0.00002000 sec
DL5 23.00 dB
CPDPRG waltz16
P31 103.00 use
D1 2.00000000 sec
P1 6.00 use
SFO1 62.9023694 MHz
NUCLEUS 13C
D11 0.03000000 sec
F2 - Processing parameters
SI 32768
SF 62.8952440 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
F1P 200.000 ppm
F1 12579.05 Hz
F2P -20.000 ppm
F2 -1257.91 Hz
PPMCM 11.00000 ppm
HZCM 691.84772 Hz/
10.429
22.494
28.588
33.205
33.667
53.203
55.917
57.957
60.647
70.573
76.685
77.196
77.397
77.705
112.587
113.187
120.533
125.684
128.230
128.325
132.973
142.074
146.853
149.288
1d-2
OCH3
O
N
N
ppm
0
50
100
150


Current Data Parameters
NAME rx-II-60+61-purified
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050623
Time 11.55
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 28.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
7.293
7.268
7.265
7.245
7.192
7.168
6.806
6.779
6.758
6.752
6.722
6.716
6.695
6.057
5.413
5.408
5.356
5.351
5.275
5.270
5.240
5.235
4.580
4.575
4.570
4.562
4.557
4.552
3.848
2.756
2.740
2.724
2.663
2.637
2.612
2.598
2.582
2.562
2.414
2.389
2.363
1.858
1.833
1.807
OCH3
N
N
O
1d-3
ppm
0 1 2 3 4 5 6 7 8 9
5.00
2.98
0.92
0.96
0.97
2.00
3.07
16.16
2.14



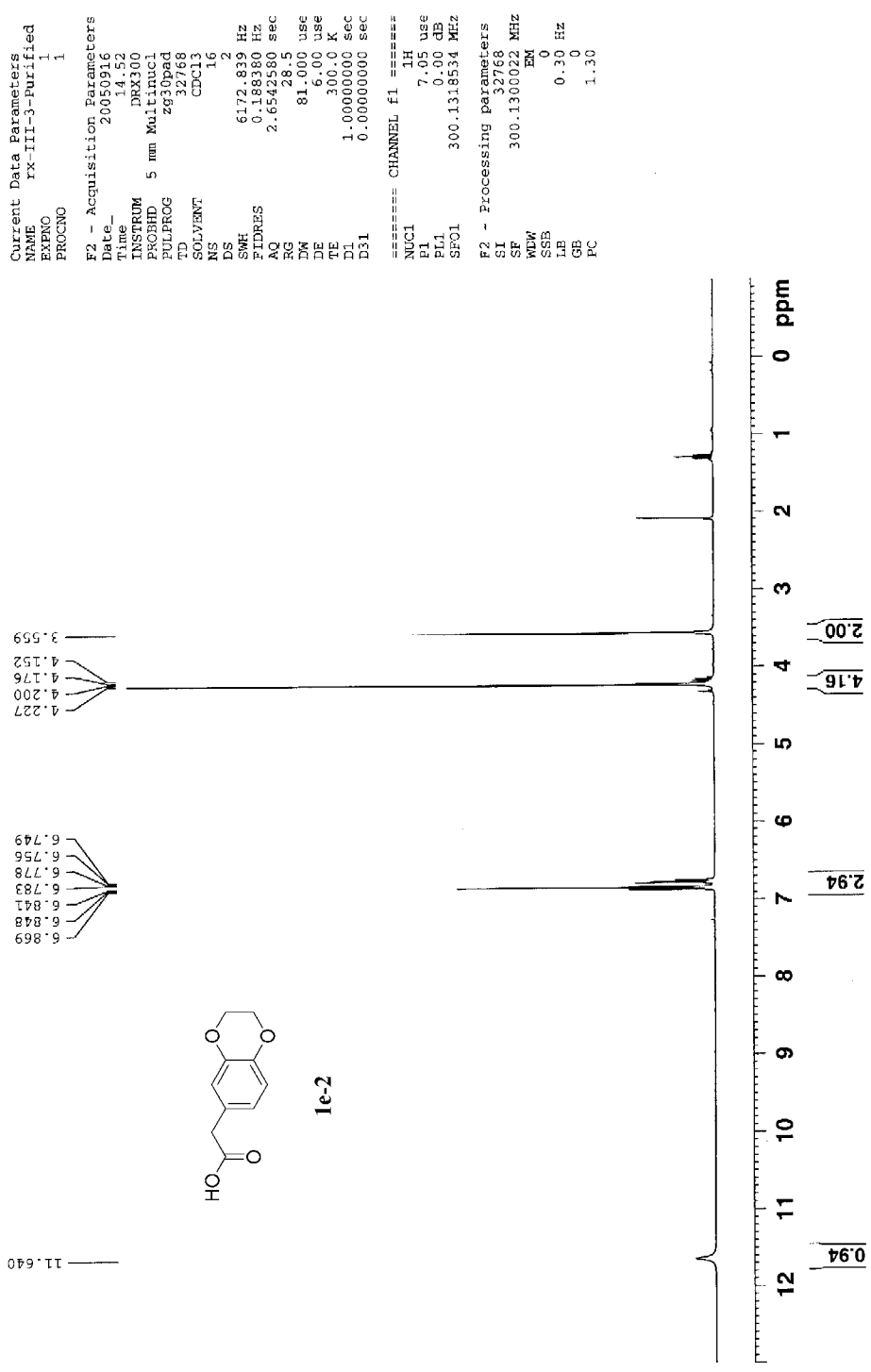

```
Current Data Parameters
NAME      rx-II-60+61-purified
EXPNO                        2
PROCNO                       1

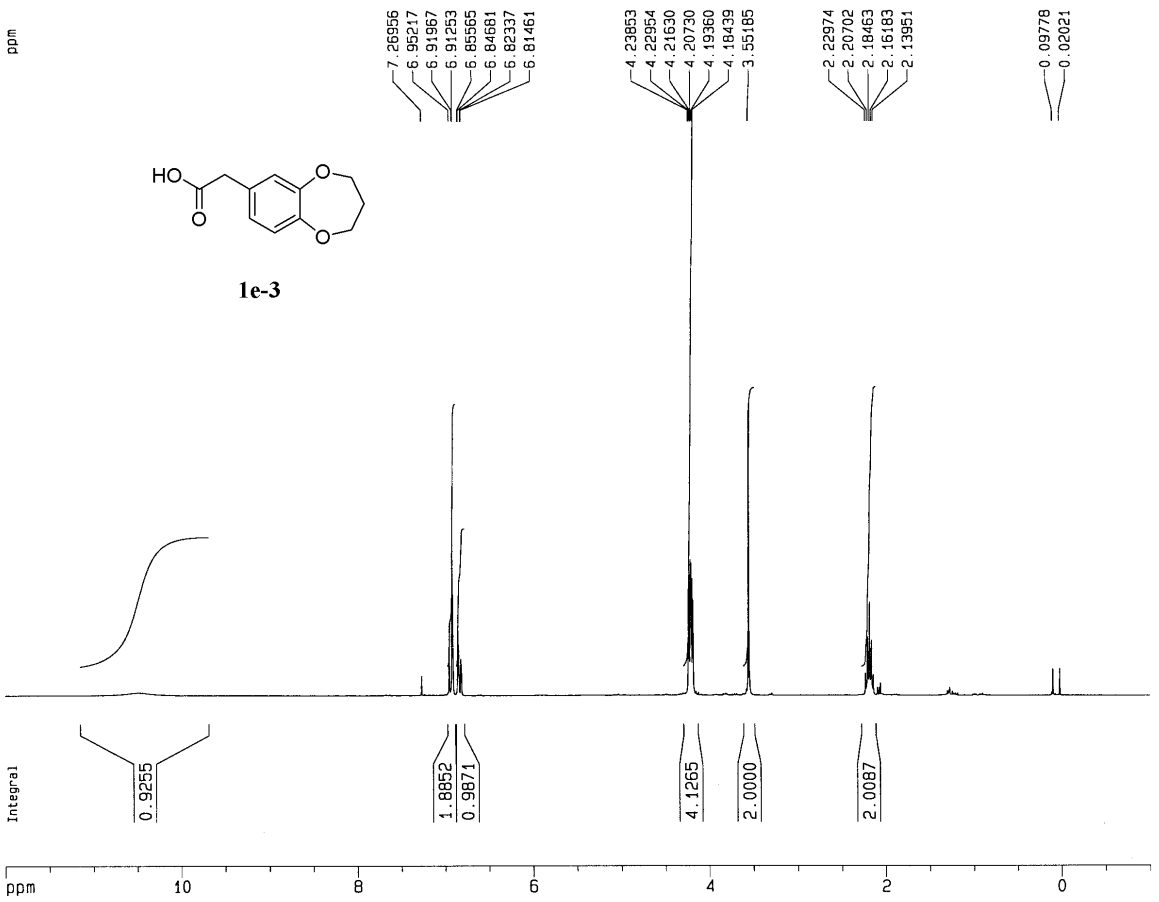
F2 - Acquisition Parameters
Date_              20050623
Time                 12.04
INSTRUM              DRX300
PROBHD   5 mm Multinucl
PULPROG              zgdc30
TD                    65536
SOLVENT               CDCl3
NS                      142
DS                        4
SWH              18832.393 Hz
FIDRES            0.287360 Hz
AQ                1.7400308 sec
RG                    22528
DW                   26.550 usec
DE                    6.00 usec
TE                   300.0 K
D1               2.00000000 sec
d11              0.03000000 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                   9.00 usec
PL1                  5.00 dB
SFO1          75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2              100.00 usec
PL2                120.00 dB
PL12                25.60 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI                    32768
SF            75.4677525 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.30
```


Current Data Parameters
NAME rx-III-3-Purified
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050916
Time 14.52
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 28.5
DW 81.000 use
DE 6.00 use
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 use
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
11.640
6.869
6.848
6.841
6.783
6.778
6.756
6.749
4.227
4.200
4.176
4.152
3.559
2.00
4.16
2.94
0.94
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
HO
O
O
O
1e-2



Current Data Parameters
NAME rx-III-5-Purif
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters

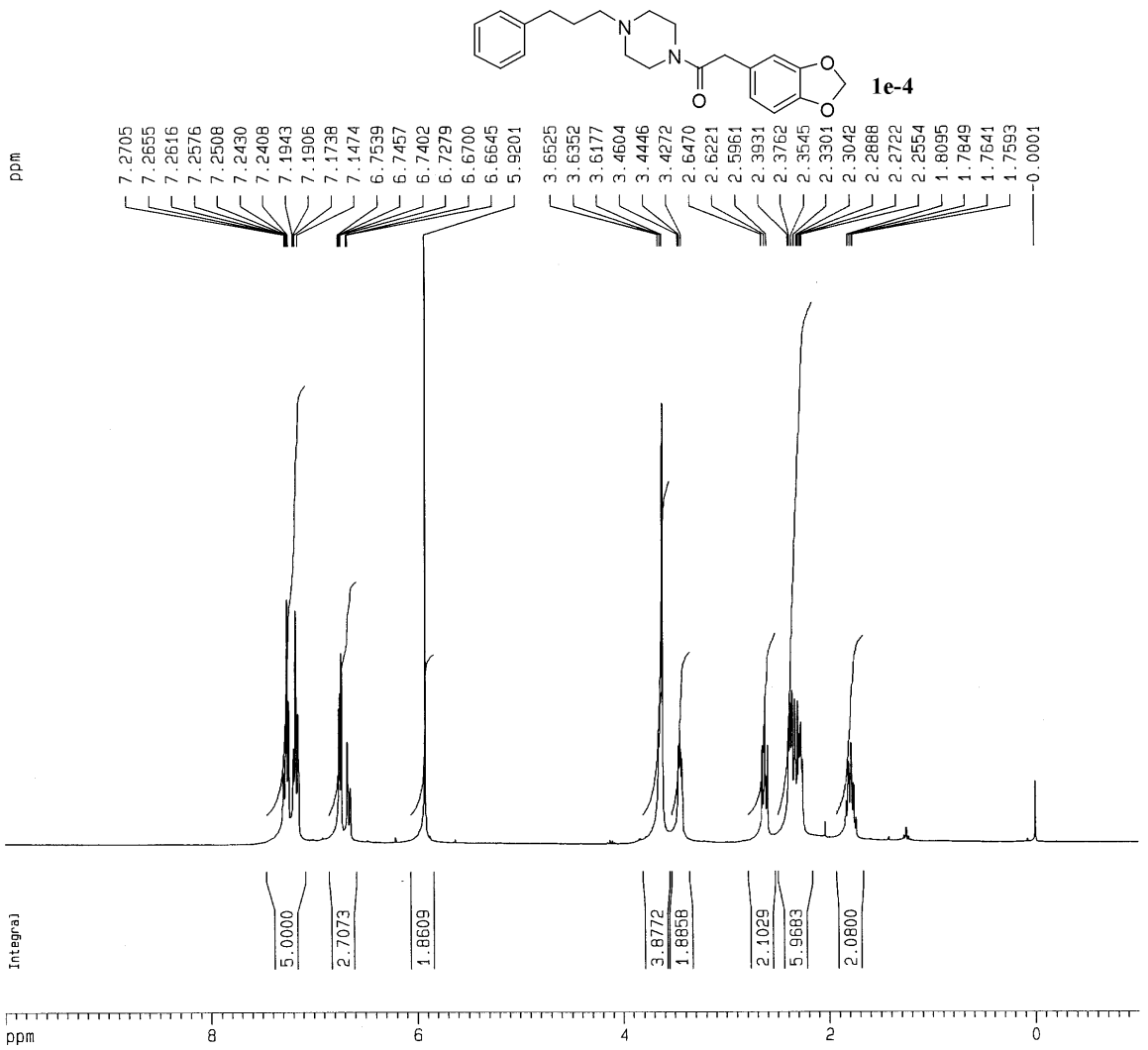
Date_	20050919
Time	16.20
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	512
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300049 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	5.00 cm
F1P	12.000 ppm
F1	3001.56 Hz
F2P	-1.000 ppm
F2	-250.13 Hz
PPMCM	0.65000 ppm
HZCM	162.58450 Hz/



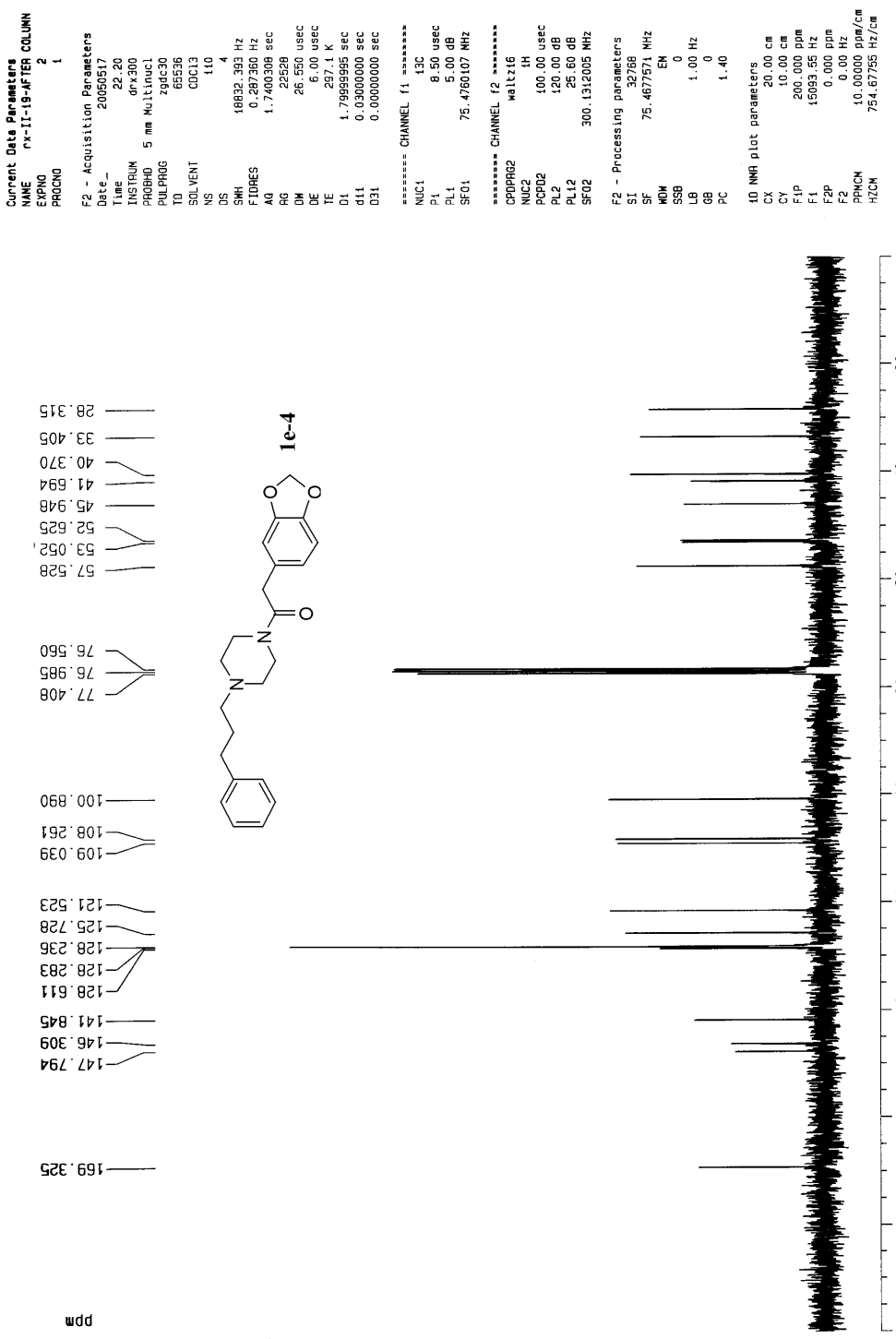

```
Current Data Parameters
NAME      rx-II-19-AFTER COLUMN
EXPNO                  1
PROCNO                 1

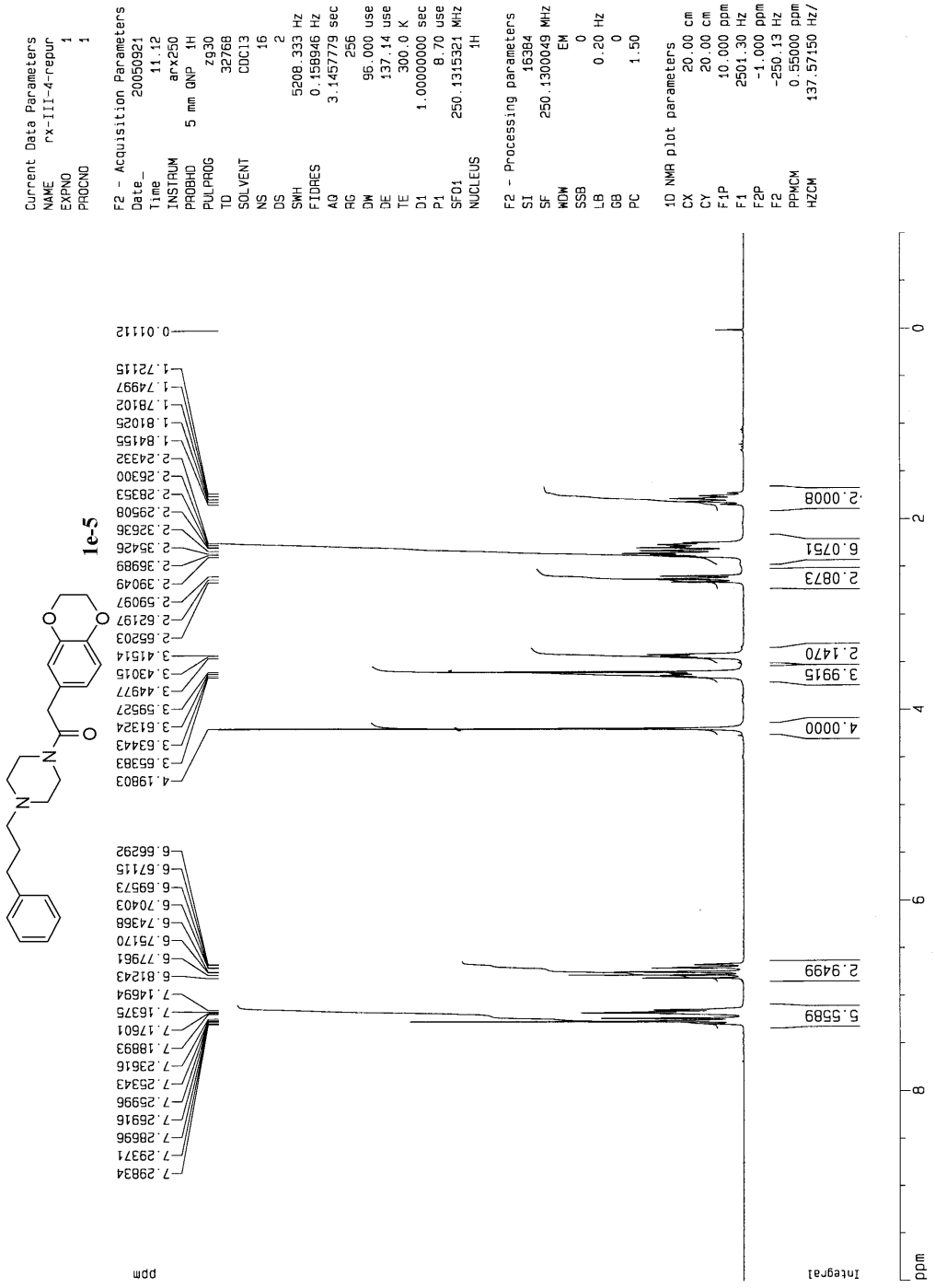
F2 - Acquisition Parameters
Date_           20050517
Time               22.28
INSTRUM           drx300
PROBHD   5 mm Multinucl
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             6172.839 Hz
FIDRES          0.188380 Hz
AQ              2.6542580 sec
RG                   114
DW                81.000 usec
DE                 6.00 usec
TE                300.0 K
D1             1.00000000 sec
D31            0.00000000 sec

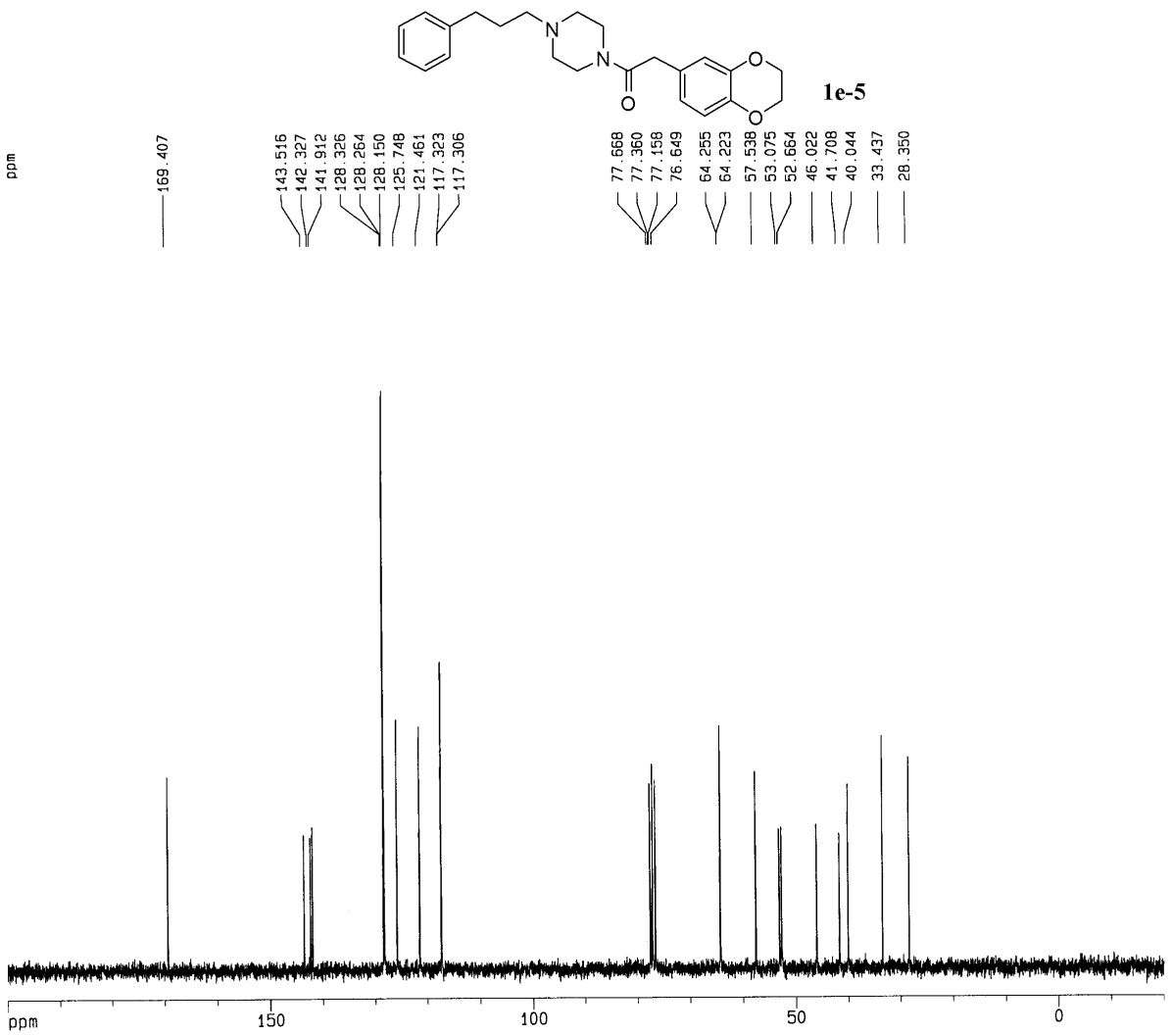
======== CHANNEL f1 ========
NUC1                  1H
P1                 7.05 usec
PL1                0.00 dB
SFO1         300.1318534 MHz

F2 - Processing parameters
SI                 32768
SF           300.1300067 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.30

1D NMR plot parameters
CX                20.00 cm
CY                12.50 cm
F1P               10.000 ppm
F1              3001.30 Hz
F2P               -1.000 ppm
F2              -300.13 Hz
PPMCM             0.55000 ppm/cm
HZCM            165.07150 Hz/cm
```


Current Data Parameters
NAME rx-II-19-AFTER COLUNN
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050517
Time_ 22.20
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 110
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 297.1 K
D1 1.79999995 sec
d11 0.03000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 5.00 dB
SFO1 75.4760107 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 200.000 ppm
F1 15093.55 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.00000 ppm/cm
HZCM 754.67755 Hz/cm
1e-4
28.315
33.405
40.370
41.694
45.948
52.625
53.052
57.528
76.560
76.985
77.408
100.890
108.261
109.039
121.523
125.728
128.236
128.283
128.611
141.845
146.309
147.794
169.325
ppm
ppm


Current Data Parameters
NAME rx-III-4-repur
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050921
Time 11.12
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 256
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
1e-5
ppm
Integral
2.0008
6.0751
2.0873
2.1470
3.9915
4.0000
2.9499
5.5589
ppm



Current Data Parameters

NAME	rx-III-4-repur
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

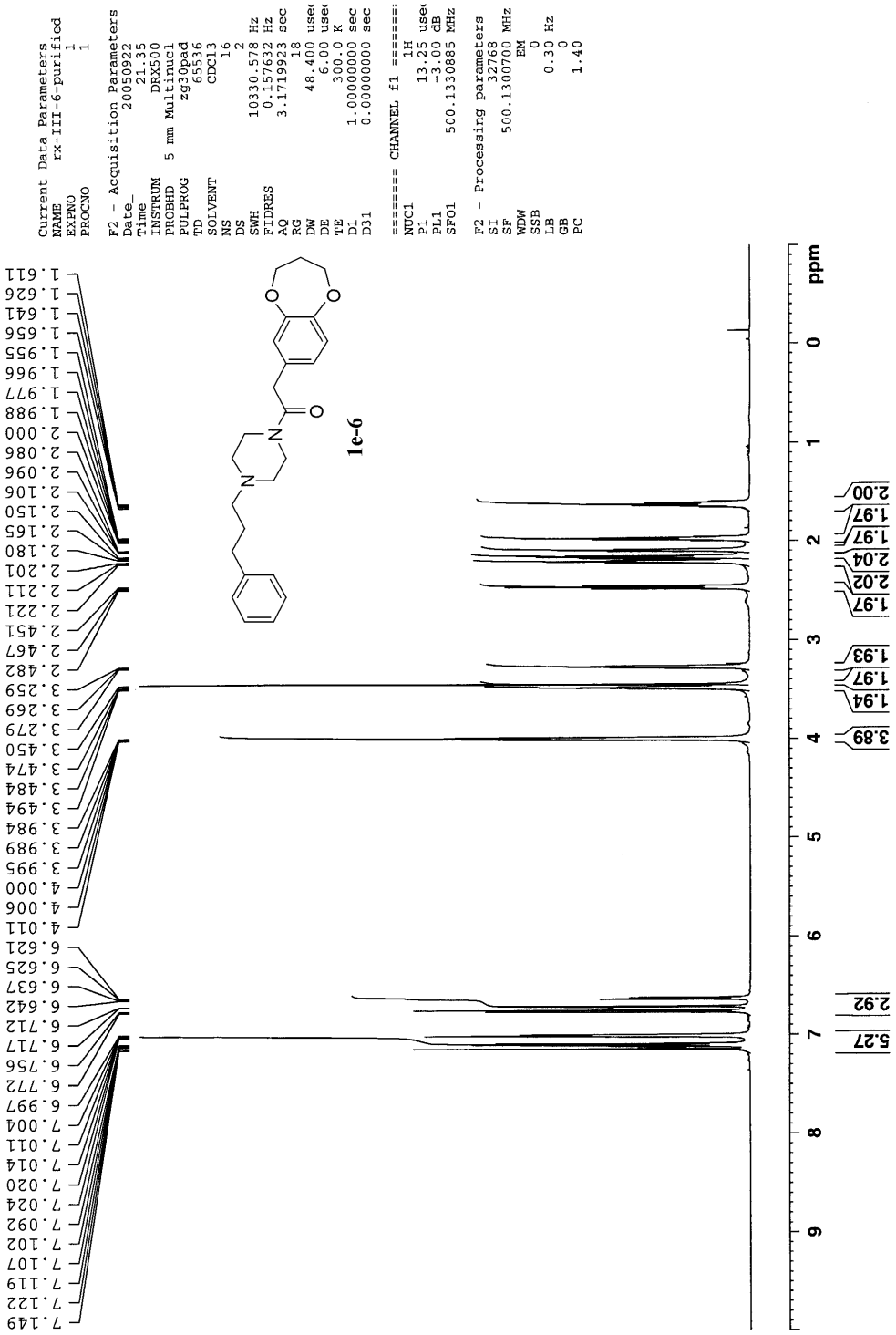
Date_	20050921
Time	11.15
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	66
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	2.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

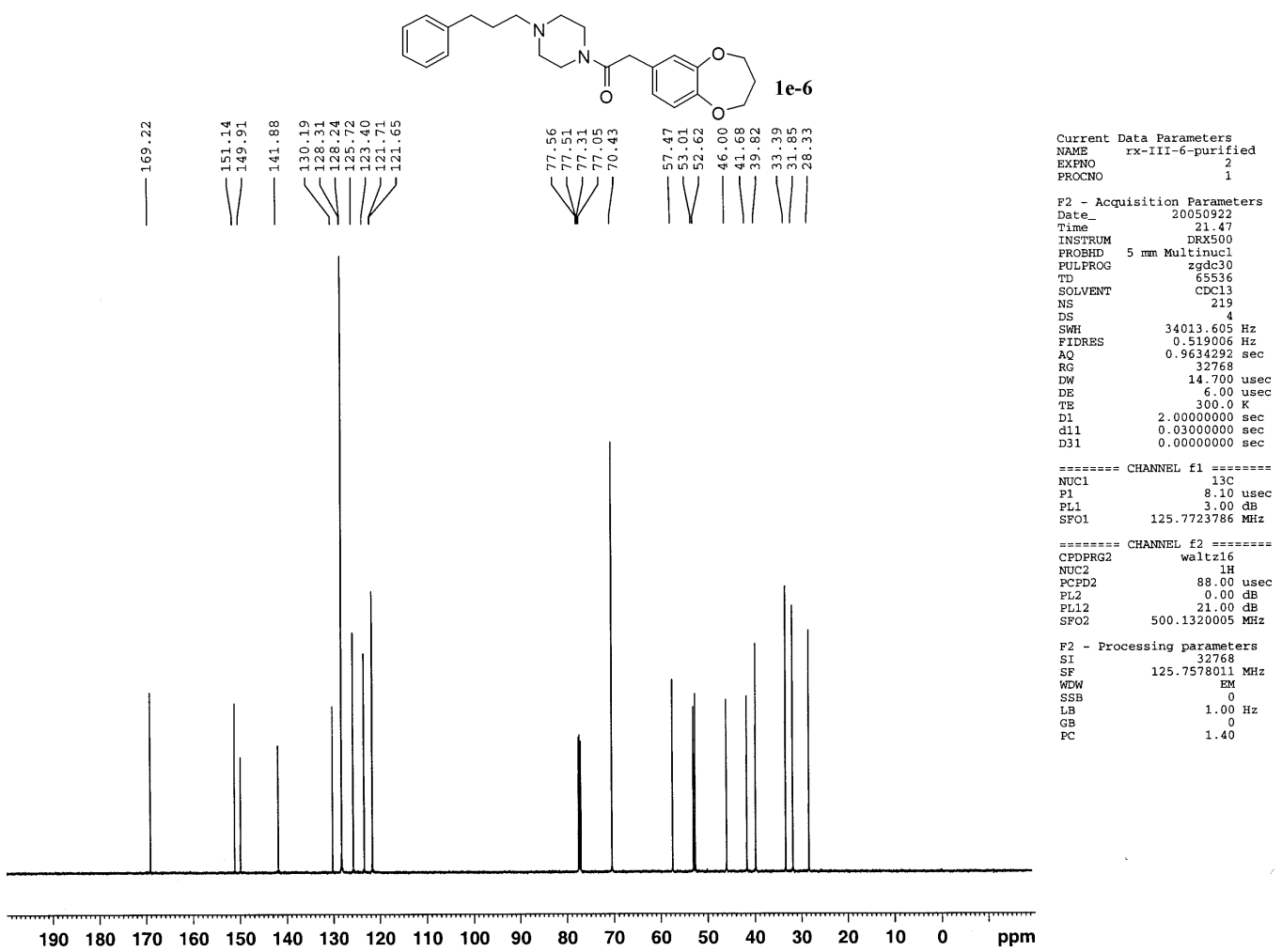
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm
HZCM	691.84772 Hz/


Current Data Parameters
NAME rx-III-6-purified
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050922
Time 21.35
INSTRUM DRX500
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 18
DW 48.400 use
DE 6.00 use
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 13.25 use
PL1 -3.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300700 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
1e-6
1.611
1.626
1.641
1.656
1.955
1.966
1.977
1.988
2.000
2.086
2.096
2.106
2.150
2.165
2.180
2.201
2.211
2.221
2.451
2.467
2.482
3.259
3.269
3.279
3.450
3.474
3.484
3.494
3.984
3.989
3.995
4.000
4.006
4.011
6.621
6.625
6.637
6.642
6.712
6.717
6.756
6.772
6.997
7.004
7.011
7.014
7.020
7.024
7.092
7.102
7.107
7.119
7.122
7.149
ppm
0
1
2
3
4
5
6
7
8
9
2.00
1.97
1.97
2.04
2.02
1.97
1.93
1.97
1.94
3.89
2.92
5.27



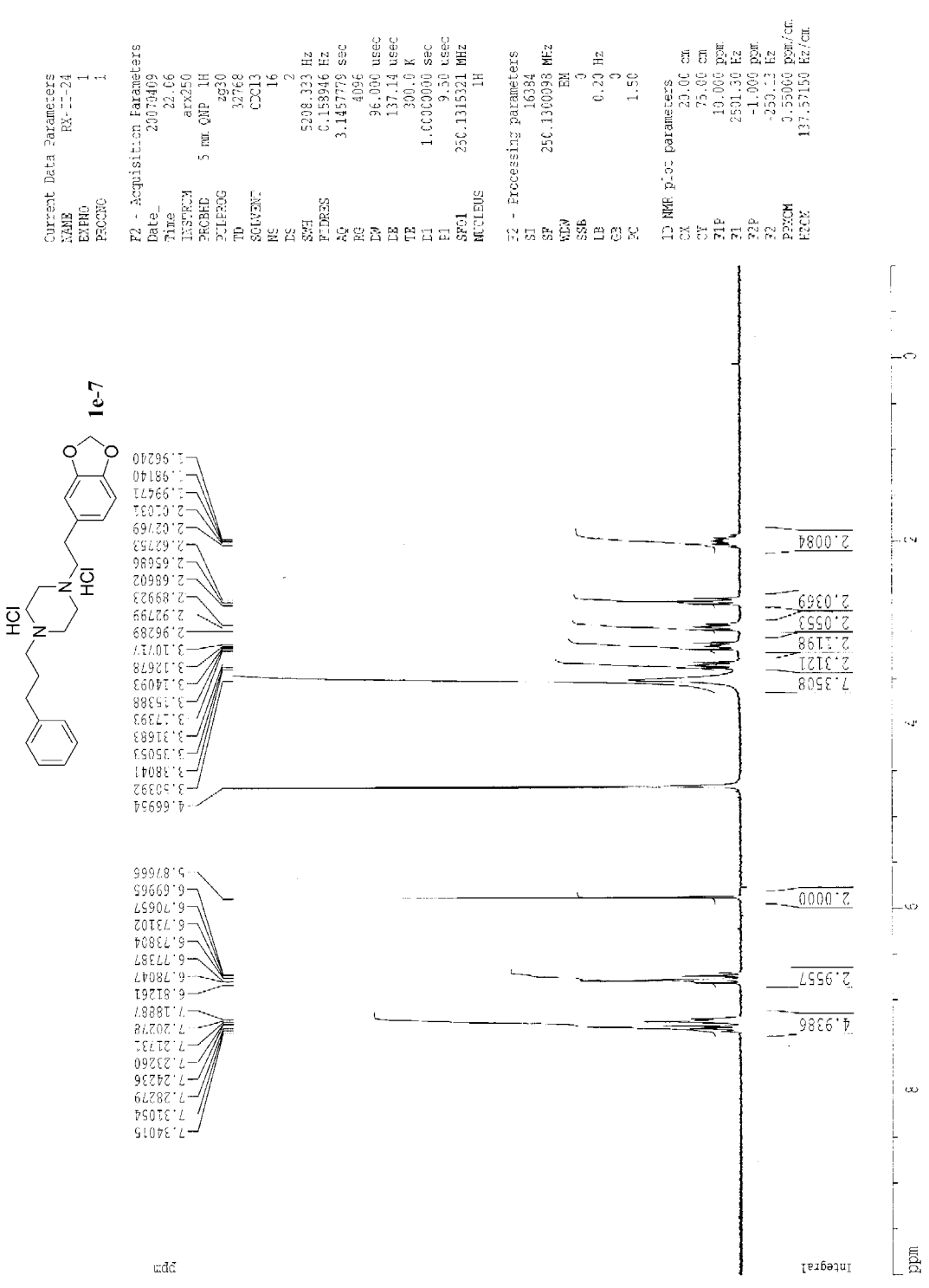

```
Current Data Parameters
NAME      rx-III-6-purified
EXPNO                    2
PROCNO                   1

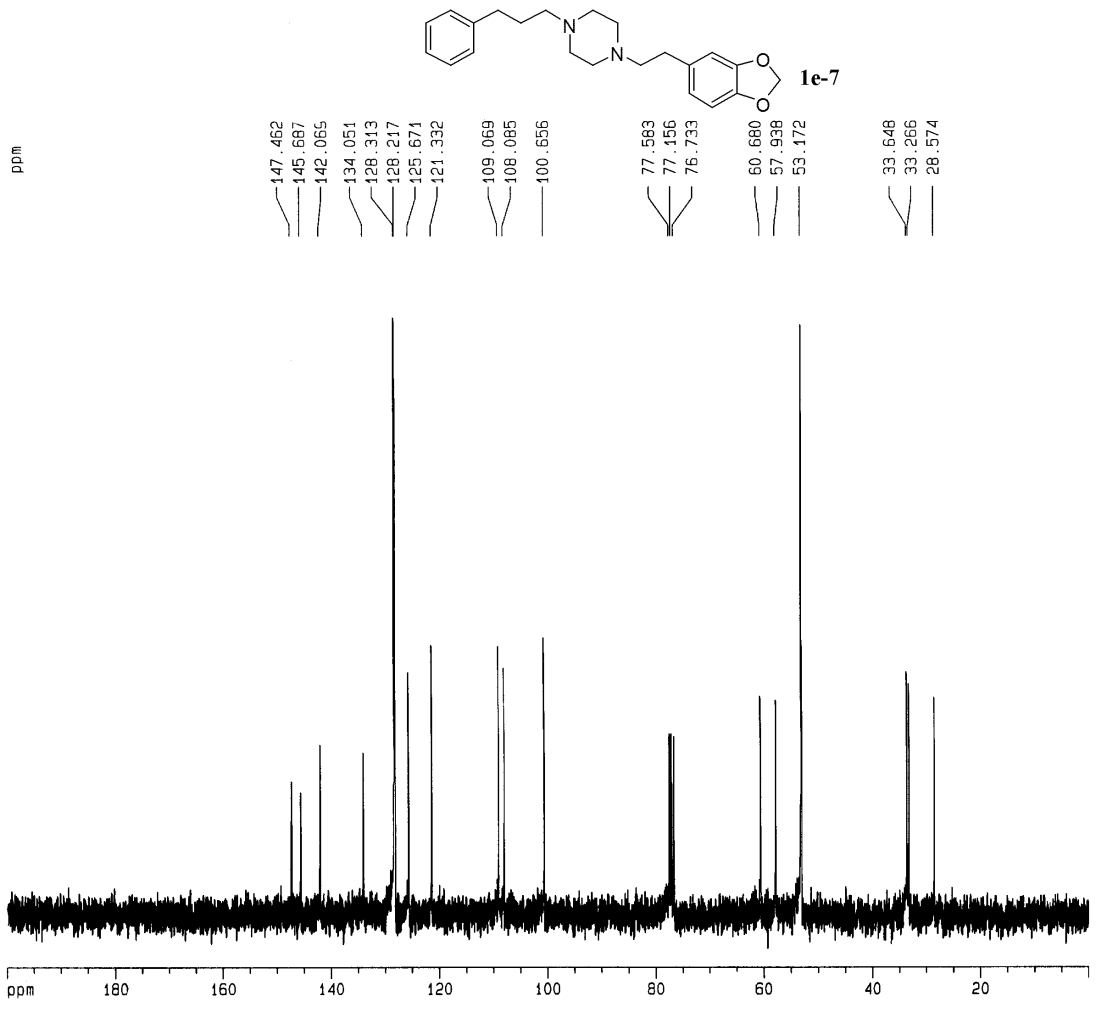
F2 - Acquisition Parameters
Date_             20050922
Time                 21.47
INSTRUM              DRX500
PROBHD   5 mm Multinucl
PULPROG              zgdc30
TD                    65536
SOLVENT               CDCl3
NS                      219
DS                        4
SWH              34013.605 Hz
FIDRES           0.519006 Hz
AQ               0.9634292 sec
RG                    32768
DW                14.700 usec
DE                 6.00 usec
TE                 300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
D31           0.00000000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                  8.10 usec
PL1                 3.00 dB
SFO1         125.7723786 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                   1H
PCPD2              88.00 usec
PL2                 0.00 dB
PL12               21.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                    32768
SF           125.7578011 MHz
WDW                     EM
SSB                      0
LB                  1.00 Hz
GB                       0
PC                    1.40
```


1e-7
HCl
HCl
Current Data Parameters
NAME RX---24
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070409
Time 22.06
INSTRM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT C2Cl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 4096
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
EI 9.30 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300098 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 23.00 cm
CY 75.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.53000 ppm/cm
HZCM 137.57150 Hz/cm
ppm
Integral
2.0084
2.0369
2.0553
2.1198
2.3121
7.3508
2.0000
2.9557
4.9386



Current Data Parameters
NAME rx-II-24-prep TLC
EXPNO 2
PROCNO 1

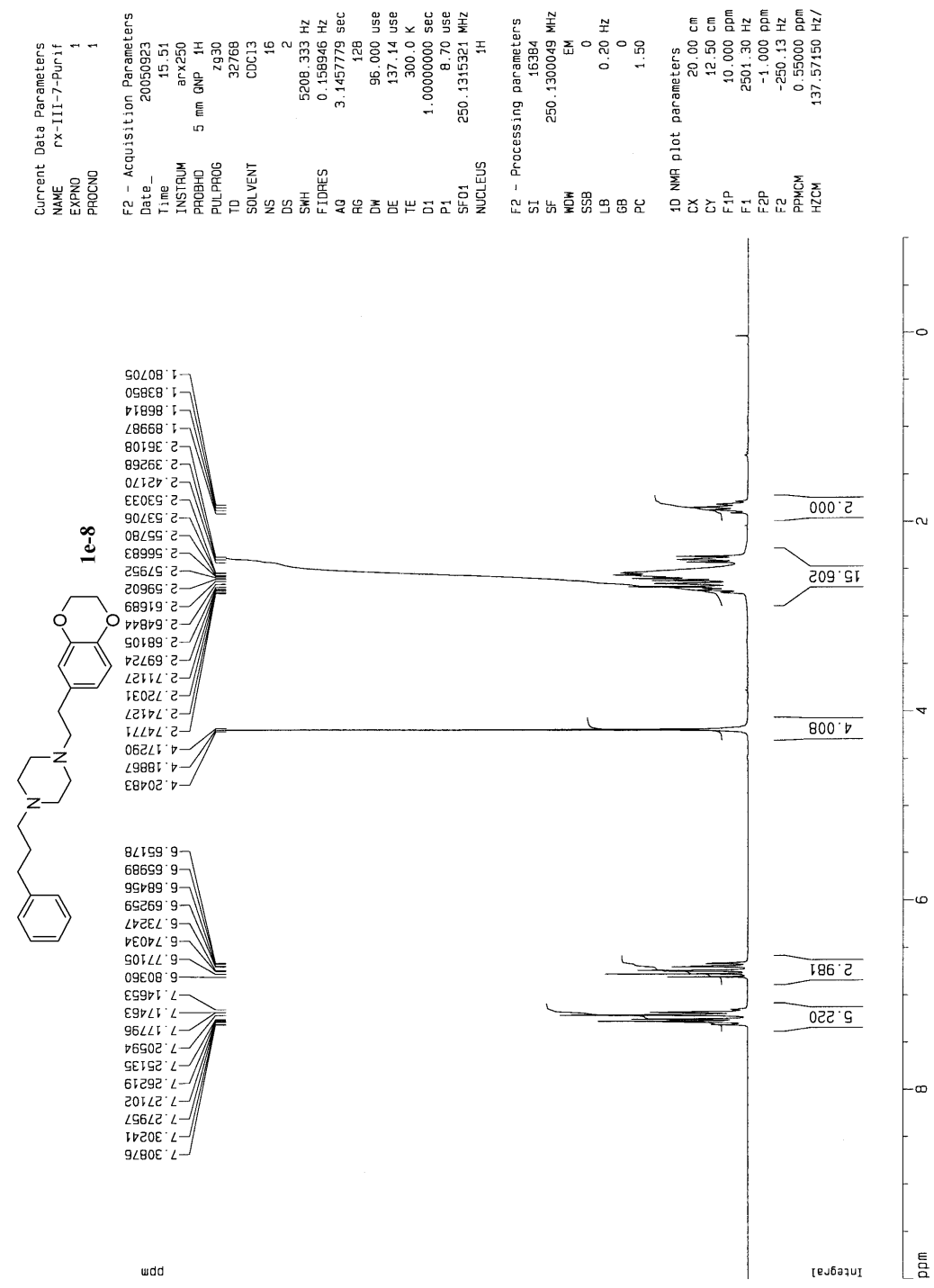
F2 - Acquisition Parameters
Date_ 20050519
Time 9.47
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 29
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 297.1 K
D1 1.79999995 sec
D11 0.03000000 sec
D31 0.00000000 sec

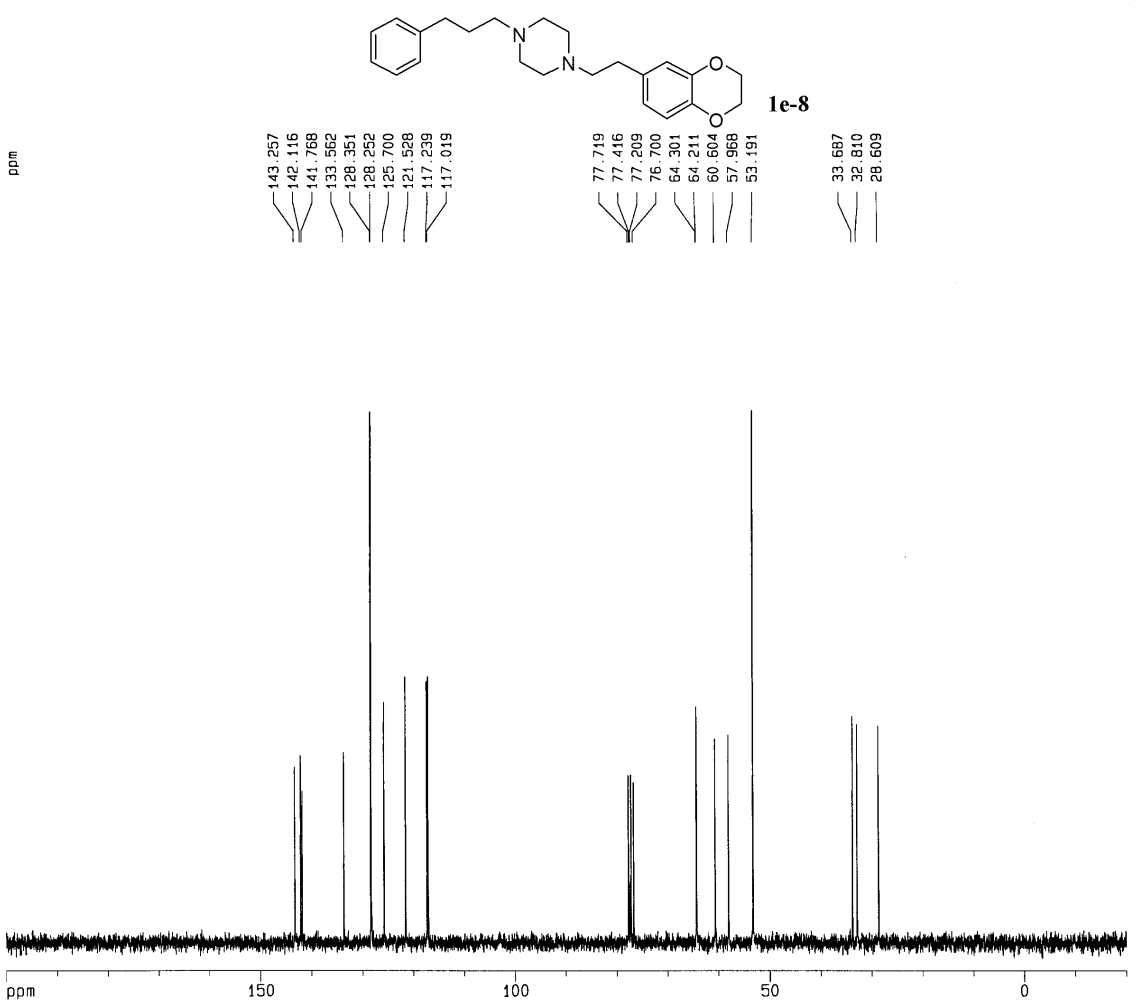
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 5.00 dB
SFO1 75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 11.00 cm
F1P 200.000 ppm
F1 15093.55 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.000[redacted]/cm
HZCM 754.677[redacted]cm


Current Data Parameters
NAME rx-III-7-Purif
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050923
Time 15.51
INSTRUM arx250
PROBHD 5 mm GNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 128
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
1e-8
ppm
Integral
2.000
15.502
4.008
2.981
5.220



Current Data Parameters
NAME rx-III-7-Purif
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters

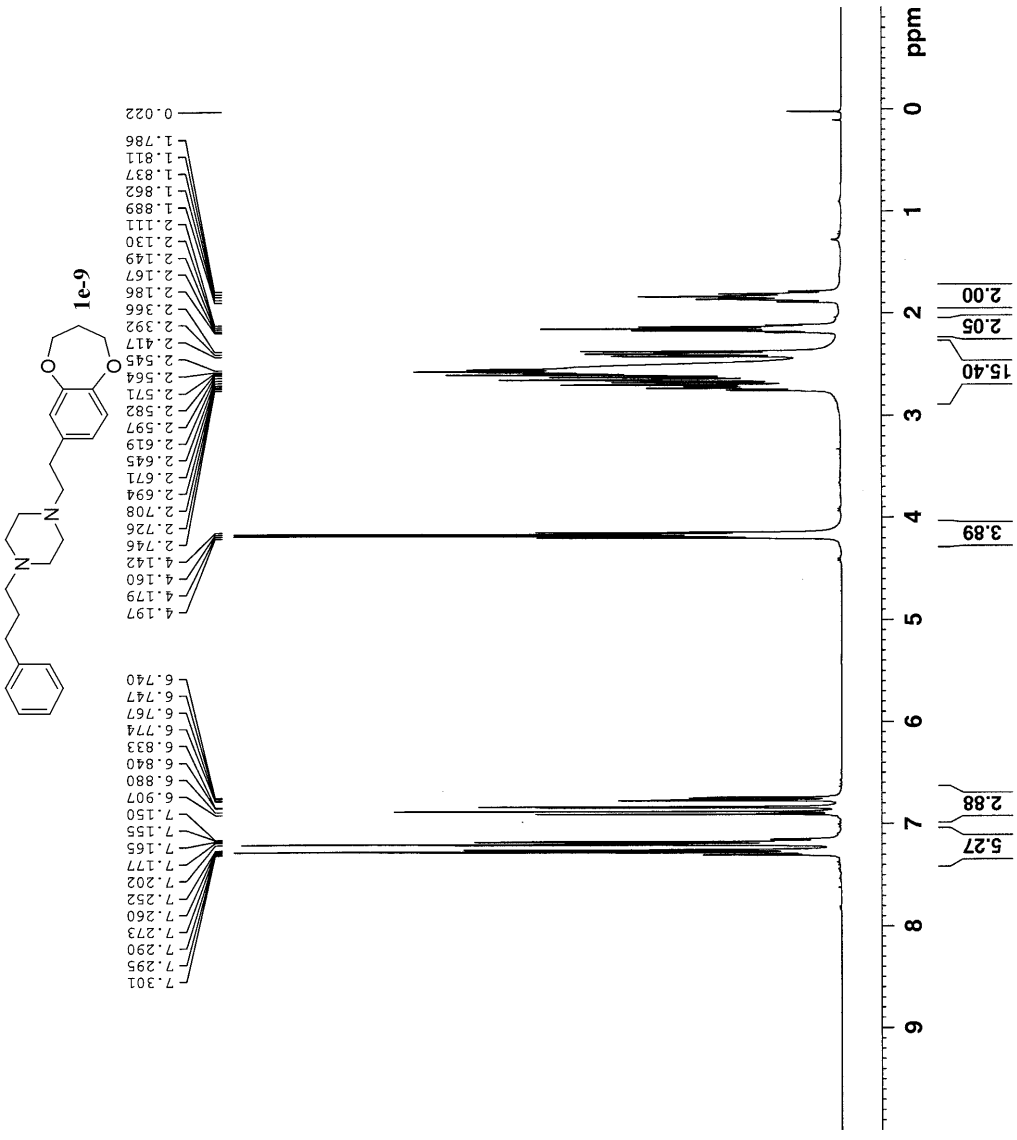
Date_	20050923
Time	15.54
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	39
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	2.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

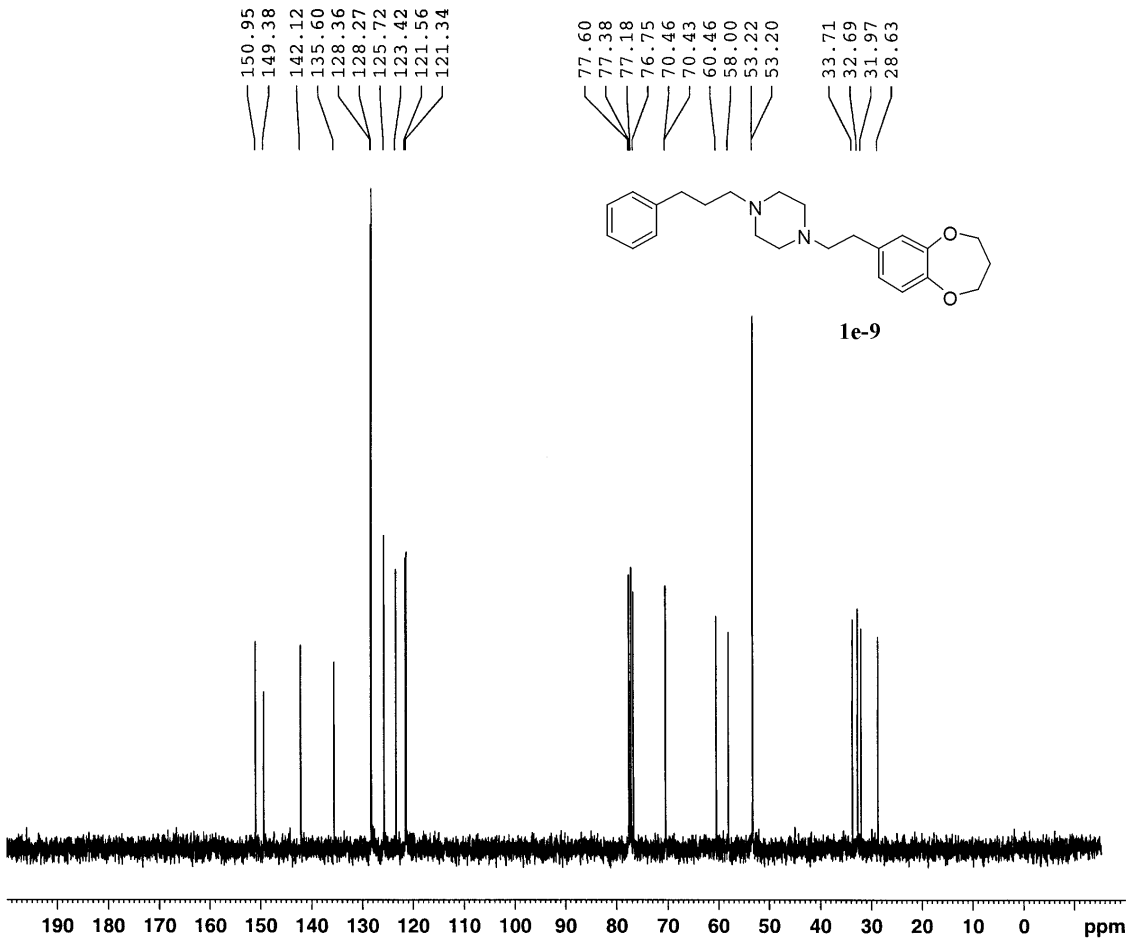
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm
HZCM	691.84772 Hz/


1e-9
Current Data Parameters
NAME rx-III-8-Purified
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050923
Time 17.06
INSTRUM DRX300
PROBHD 5 mm Multinuc1
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 28.5
DW 81.000 use
DE 6.00 use
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 use
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
0.022
1.786
1.811
1.837
1.862
1.889
2.111
2.130
2.149
2.167
2.186
2.366
2.392
2.417
2.545
2.564
2.571
2.582
2.597
2.619
2.645
2.671
2.694
2.708
2.726
2.746
4.142
4.160
4.179
4.197
6.740
6.747
6.767
6.774
6.833
6.840
6.880
6.907
7.150
7.155
7.165
7.177
7.202
7.252
7.260
7.273
7.290
7.295
7.301
2.00
2.05
15.40
3.89
2.88
5.27
ppm



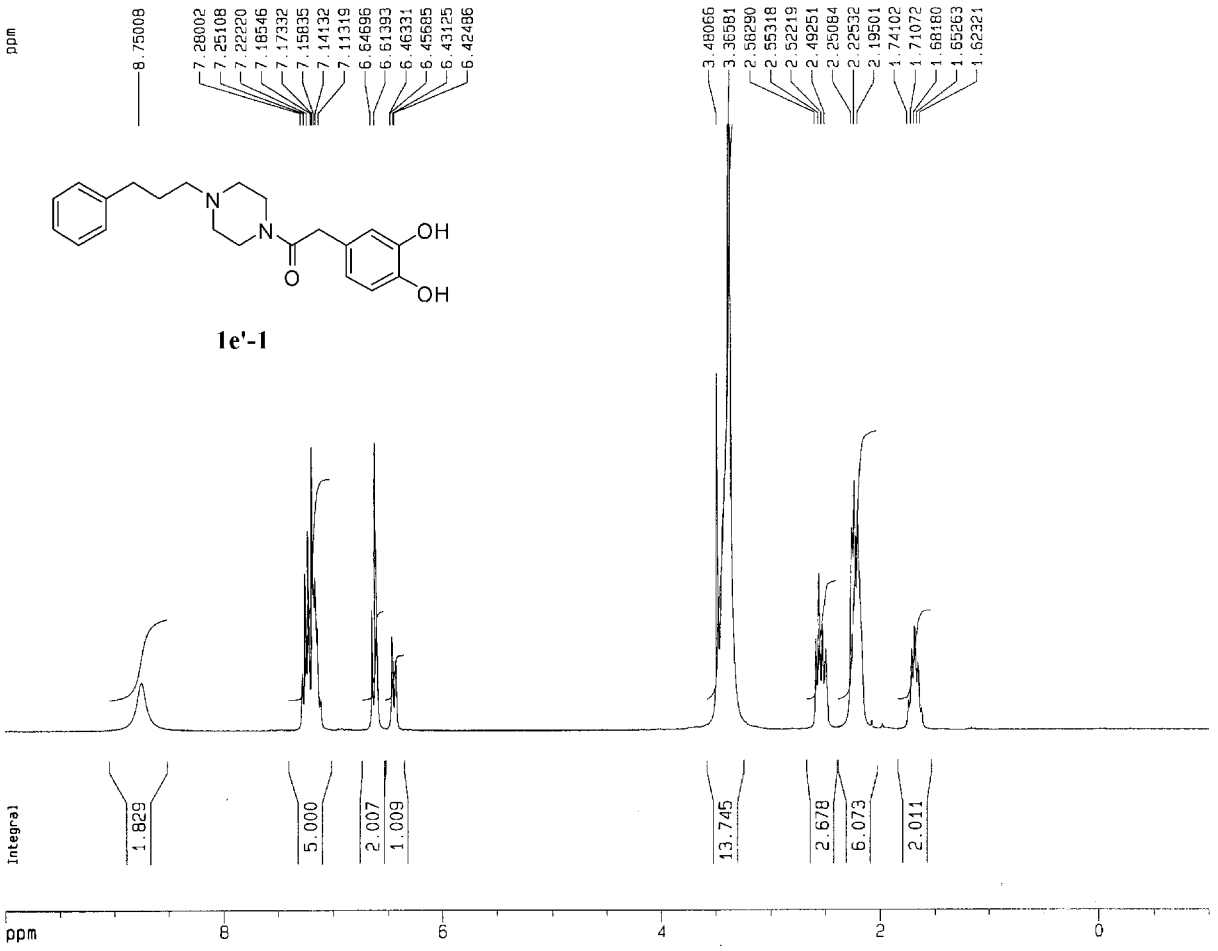

```
Current Data Parameters
NAME      rx-III-8-Purified
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20050923
Time                  17.11
INSTRUM              DRX300
PROBHD   5 mm Multinucl
PULPROG          zgdc30pad
TD                   65536
SOLVENT              CDCl3
NS                      13
DS                       4
SWH              18832.393 Hz
FIDRES           0.287360 Hz
AQ               1.7400308 sec
RG                   22528
DW                  26.550 usec
DE                   6.00 usec
TE                  300.0 K
D1              2.00000000 sec
D11             0.03000000 sec
D31             0.00000000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.00 usec
PL1                   5.00 dB
SFO1           75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2               100.00 usec
PL2                 120.00 dB
PL12                 25.60 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                   32768
SF             75.4677525 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.30
```



1e'-1

Current Data Parameters

NAME	nx-II-70-CRYST
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

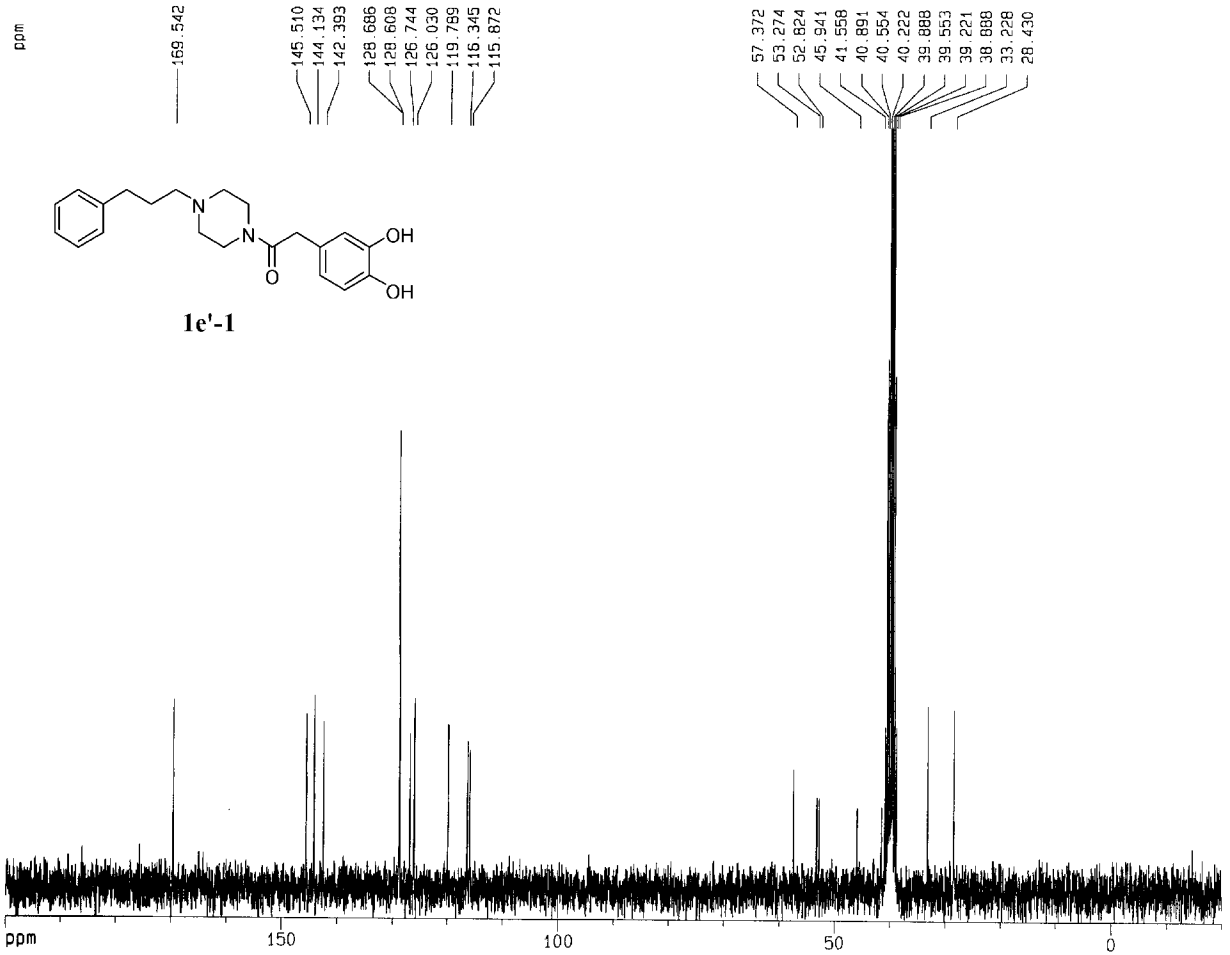
Date_	20050630
Time	22.24
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	715
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	8.70 use
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300049 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-1.000 ppm
F2	-250.13 Hz
PPMCM	0.55000 ppm
HZCM	137.57150 Hz/



1e'-1

Current Data Parameters

NAME	rx-II-70-CRYST
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

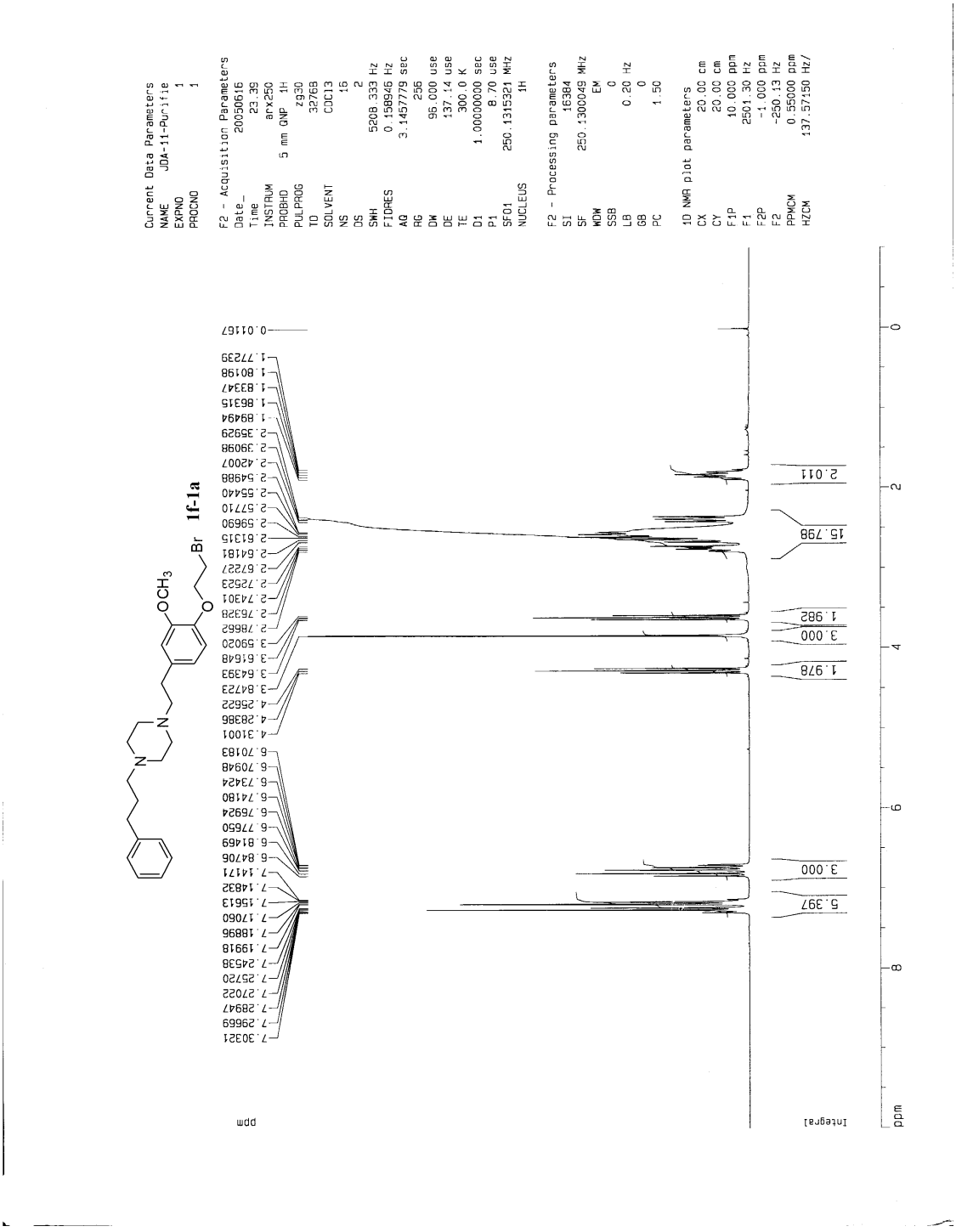
Date_	20050630
Time	22.29
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	123
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 use
DE	41.43 use
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 use
D1	2.00000000 sec
P1	6.00 use
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

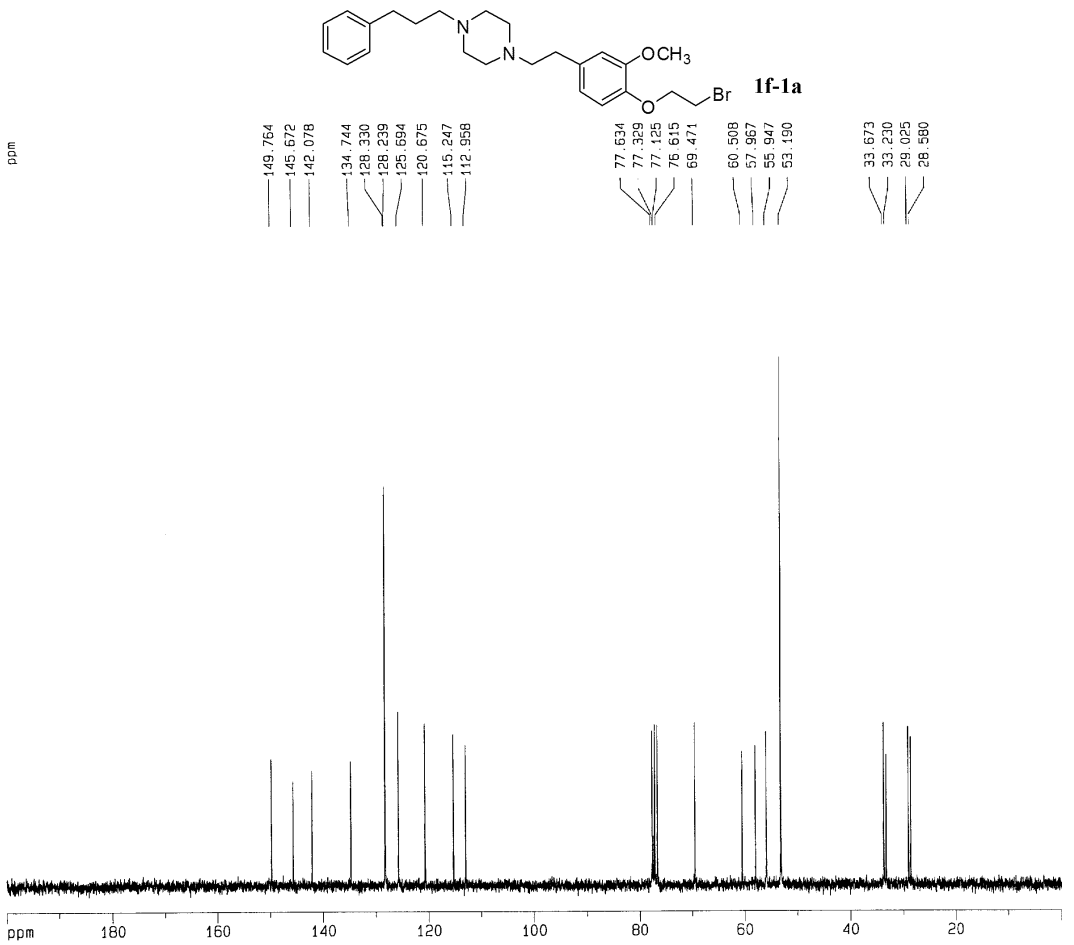
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	20.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm
HZCM	691.84772 Hz/


1f-1a
Br
OCH3
Current Data Parameters
NAME JDA-11-Purifie
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050616
Time 23.39
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 256
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
2.011
15.798
1.982
3.000
1.978
3.000
5.397
Integral
ppm

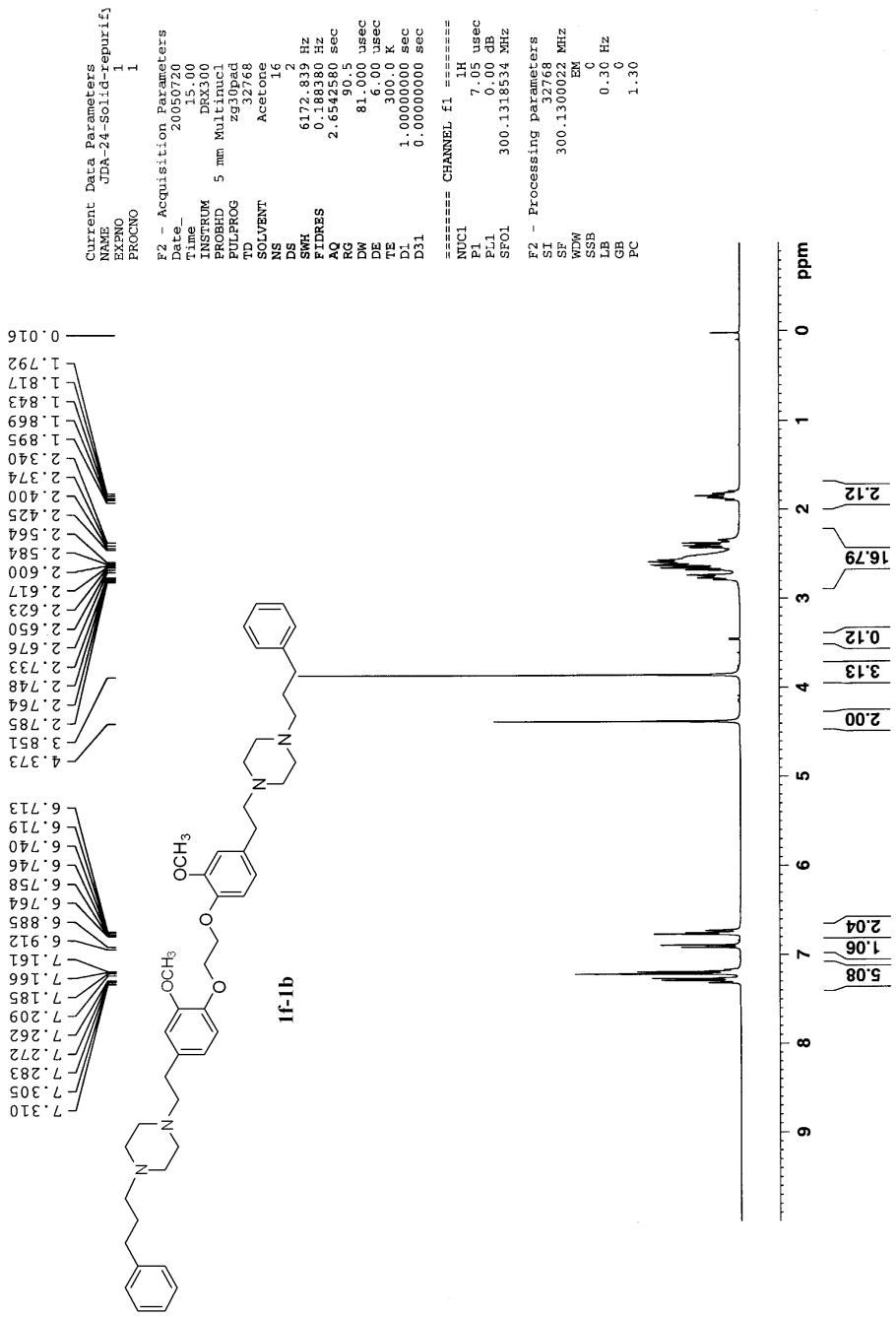


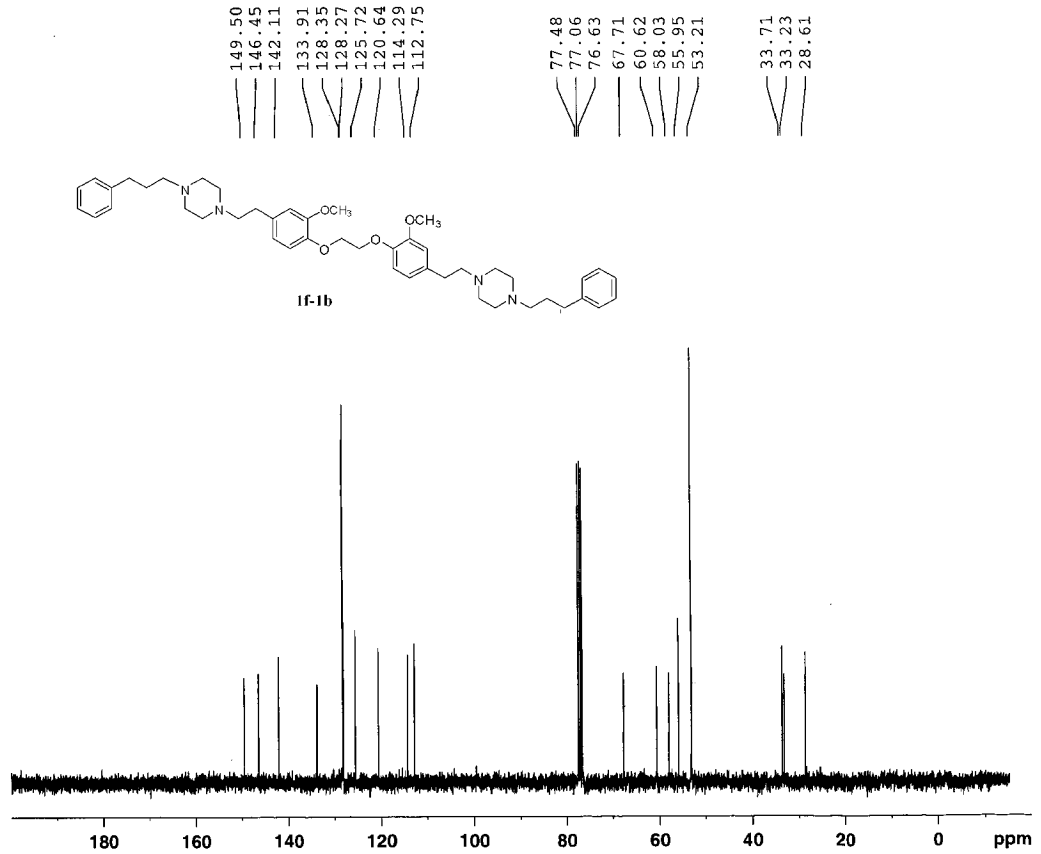

```
Current Data Parameters
NAME      JDA-11-Purifie
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20050616
Time               23.41
INSTRUM          arx250
PROBHD     5 mm QNP  1H
PULPROG         zgdc30
TD               36864
SOLVENT          CDCl3
NS                  74
DS                   4
SWH          17241.379 Hz
FIDRES        0.467702 Hz
AQ            1.0691060 sec
RG               22800
DW              29.000 use
DE               41.43 use
TE               300.0 K
D12          0.00002000 sec
DL5             23.00 dB
CPDPRG          waltz16
P31             103.00 use
D1           2.00000000 sec
P1               6.00 use
SFO1         62.9023694 MHz
NUCLEUS             13C
D11          0.03000000 sec

F2 - Processing parameters
SI                32768
SF           62.8952440 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
CY                10.00 cm
F1P              200.000 ppm
F1             12579.05 Hz
F2P              0.000 ppm
F2                0.00 Hz
PPMCM          10.00000 ppm
HZCM          628.95245 Hz/
```


Current Data Parameters
NAME JDA-24-Solid-repurifi
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050720
Time 15.00
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT Acetone
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 90.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
0.016
1.792
1.817
1.843
1.869
1.895
2.340
2.374
2.400
2.425
2.564
2.584
2.600
2.617
2.623
2.650
2.676
2.733
2.748
2.764
2.785
3.851
4.373
6.713
6.719
6.740
6.746
6.758
6.764
6.885
6.912
7.161
7.166
7.185
7.209
7.262
7.272
7.283
7.305
7.310
OCH3
OCH3
1f-1b
ppm
0
1
2
3
4
5
6
7
8
9
2.12
16.79
0.12
3.13
2.00
2.04
1.06
5.08



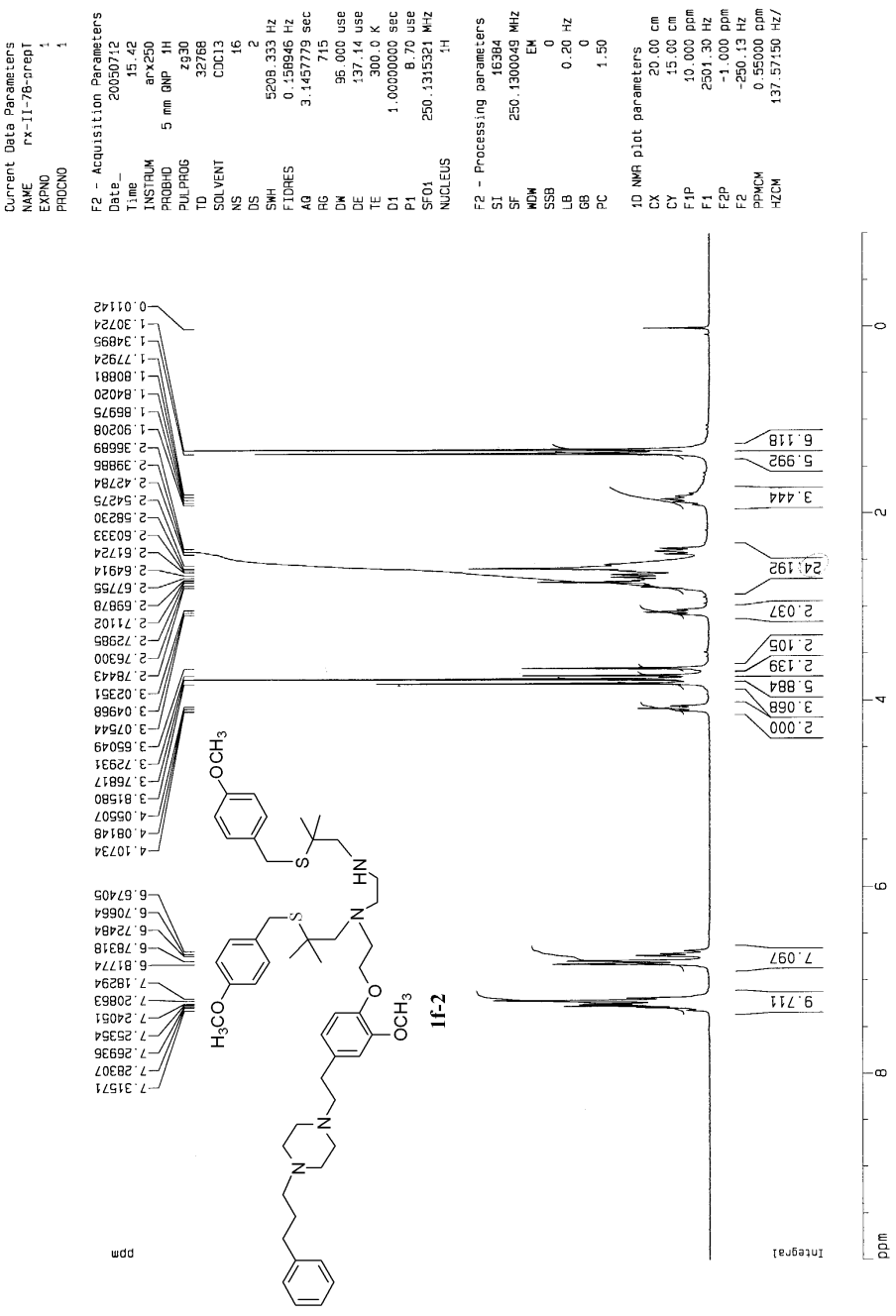
Current Data Parameters
NAME JDA-24-Solid-repurify
EXPNO 2
PROCNO 1

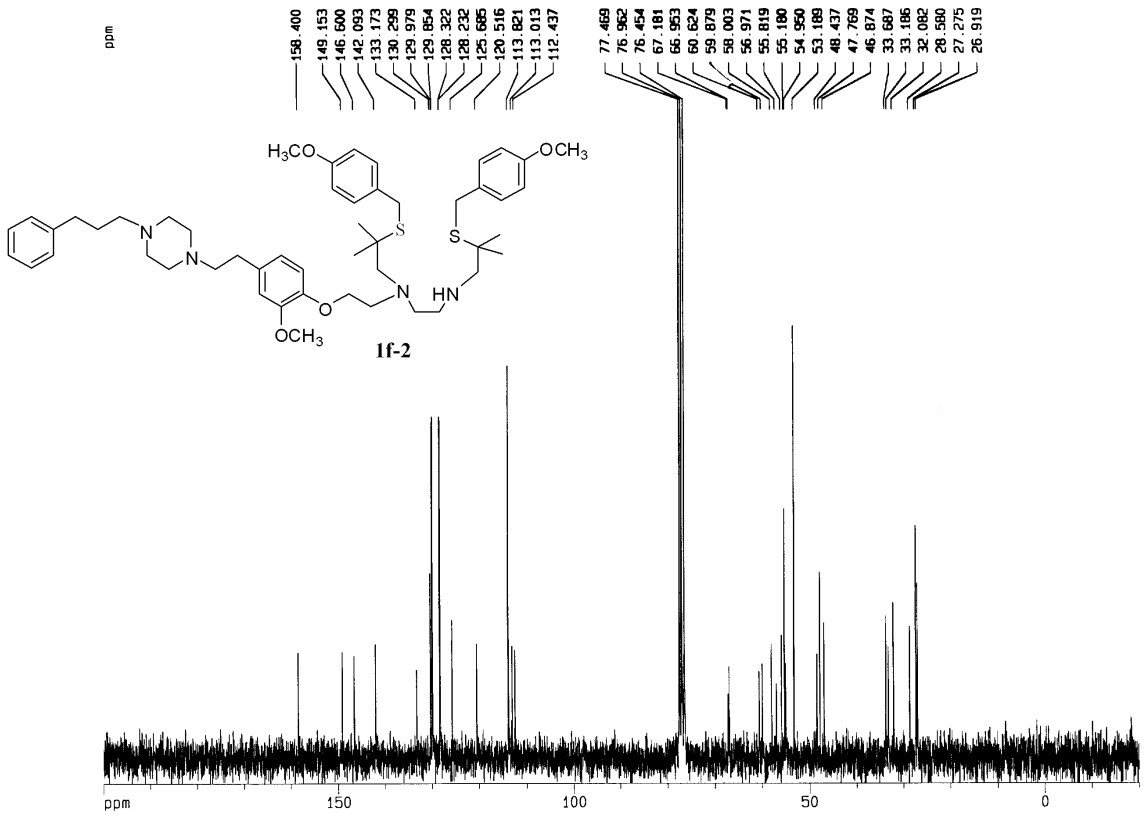
F2 - Acquisition Parameters
Date_ 20050720
Time 15.04
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zgdc30pad
TD 65536
SOLVENT CDCl3
NS 54
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
D31 0.00000000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 5.00 dB
SFO1 75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677525 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.30


Current Data Parameters
NAME rx-II-78-prepI
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050712
Time 15.42
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 715
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 8.70 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 15.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
0.01142
1.30724
1.34895
1.77924
1.80881
1.84020
1.86975
1.90208
2.36689
2.39886
2.42784
2.54275
2.58230
2.60333
2.61724
2.64914
2.67755
2.69878
2.71102
2.72985
2.76300
2.78443
3.02351
3.04968
3.07544
3.65049
3.72931
3.76817
3.81580
4.05507
4.08148
4.10734
6.67405
6.70664
6.72484
6.78318
6.81774
7.18294
7.20863
7.24051
7.25354
7.26936
7.28307
7.31571
ppm
1f-2
integral
6.118
5.992
3.444
24.192
2.037
2.105
2.139
5.884
3.068
2.000
7.097
9.711
ppm

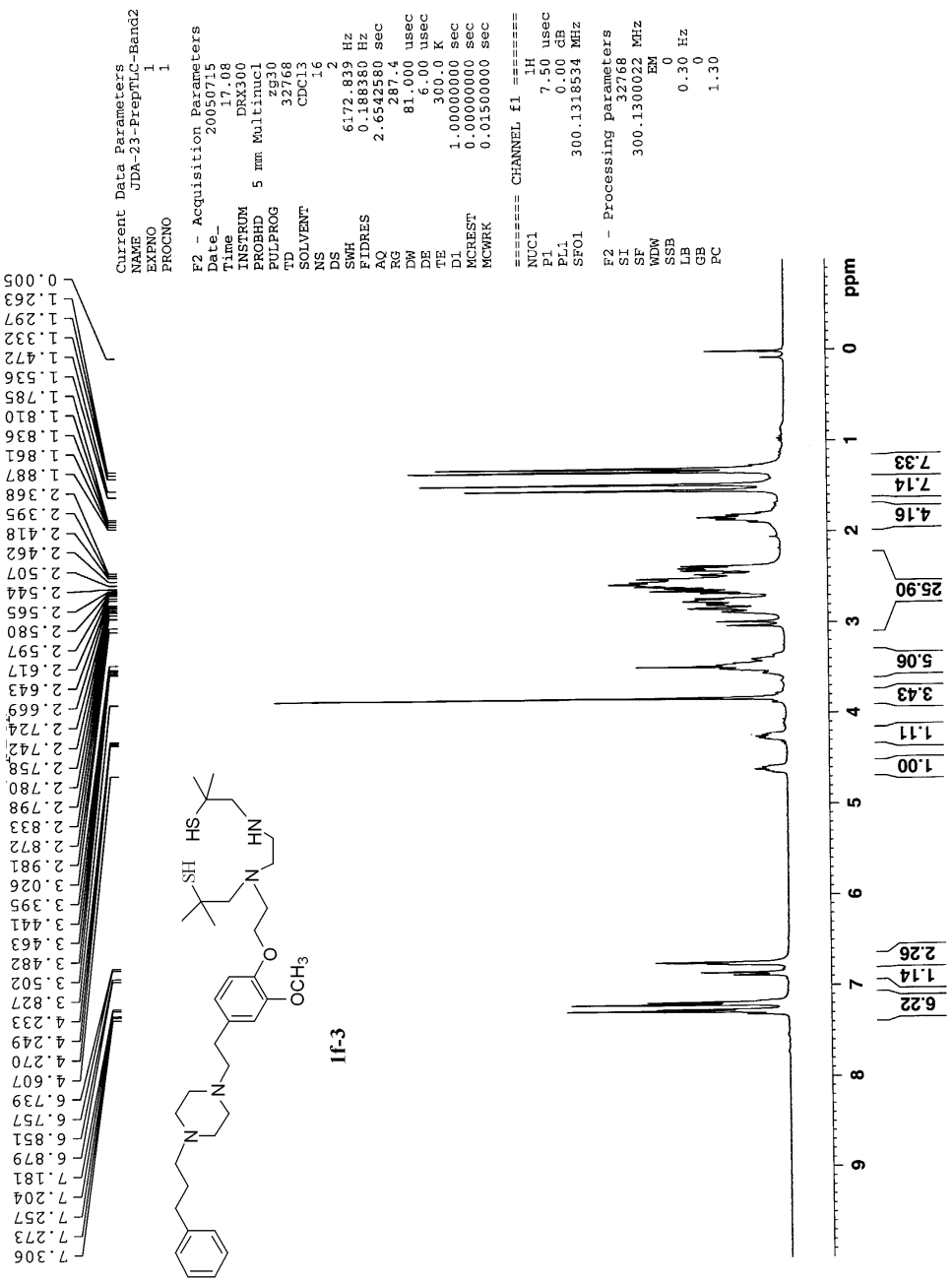


Current Data Parameters
NAME rx-II-78-prepT
EXPNO 2
PROCNO 1

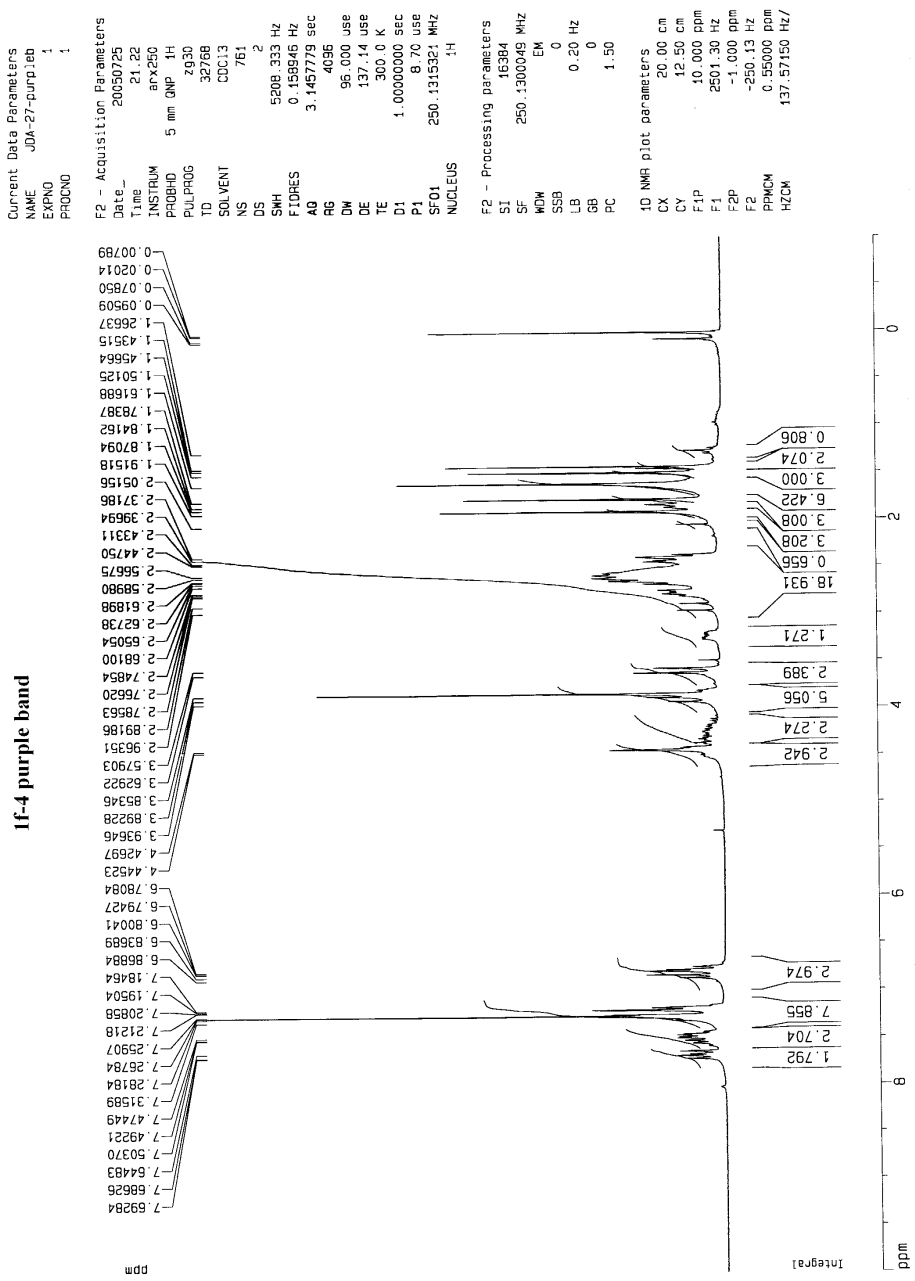
F2 - Acquisition Parameters
Date_ 20050712
Time 15.48
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zgdc30
TD 36864
SOLVENT CDCl3
NS 867
DS 4
SWH 17241.379 Hz
FIDRES 0.467702 Hz
AQ 1.0691060 sec
RG 22800
DW 29.000 use
DE 41.43 use
TE 300.0 K
D12 0.00002000 sec
DL5 23.00 dB
CPDPRG waltz16
P31 103.00 use
D1 2.00000000 sec
P1 6.00 use
SFO1 62.9023694 MHz
NUCLEUS 13C
D11 0.03000000 sec

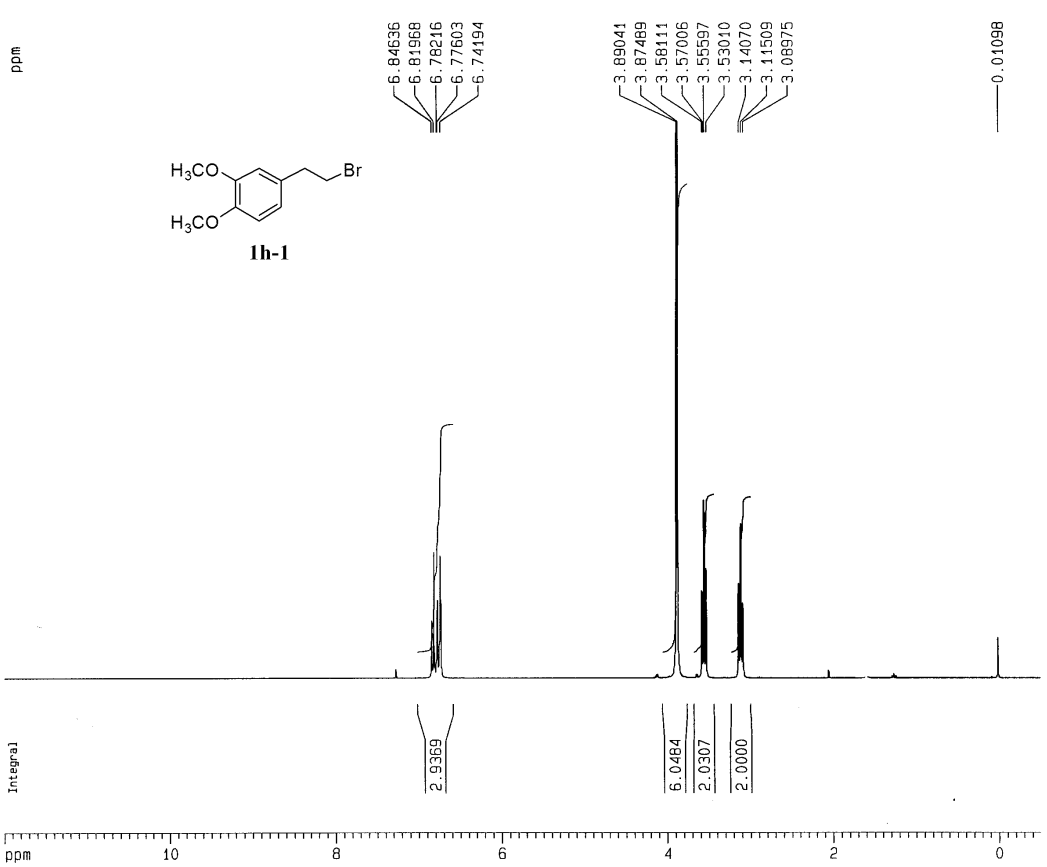
F2 - Processing parameters
SI 32768
SF 62.8952440 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 30.00 cm
F1P 200.000 ppm
F1 12579.05 Hz
F2P -20.000 ppm
F2 -1257.91 Hz
PPMCM 11.00000 ppm
HZCM 691.84772 Hz/


Current Data Parameters
NAME UDA-23-PrepTLC-Band2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050715
Time 17.08
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 287.4
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
0.005
1.263
1.297
1.332
1.472
1.536
1.785
1.810
1.836
1.861
1.887
2.368
2.395
2.418
2.462
2.507
2.544
2.565
2.580
2.597
2.617
2.643
2.669
2.724
2.742
2.758
2.780
2.798
2.833
2.872
2.981
3.026
3.395
3.441
3.463
3.482
3.502
3.827
4.233
4.249
4.270
4.607
6.739
6.757
6.851
6.879
7.181
7.204
7.257
7.273
7.306
HS
SH
HN
N
O
OCH3
1f-3
ppm
0
1
2
3
4
5
6
7
8
9
6.22
1.14
2.26
1.00
1.11
3.43
5.06
25.90
4.16
7.14
7.33

1f-4 purple band





Current Data Parameters
NAME rx-II-11-COLUMN
EXPNO 1
PROCNO 1

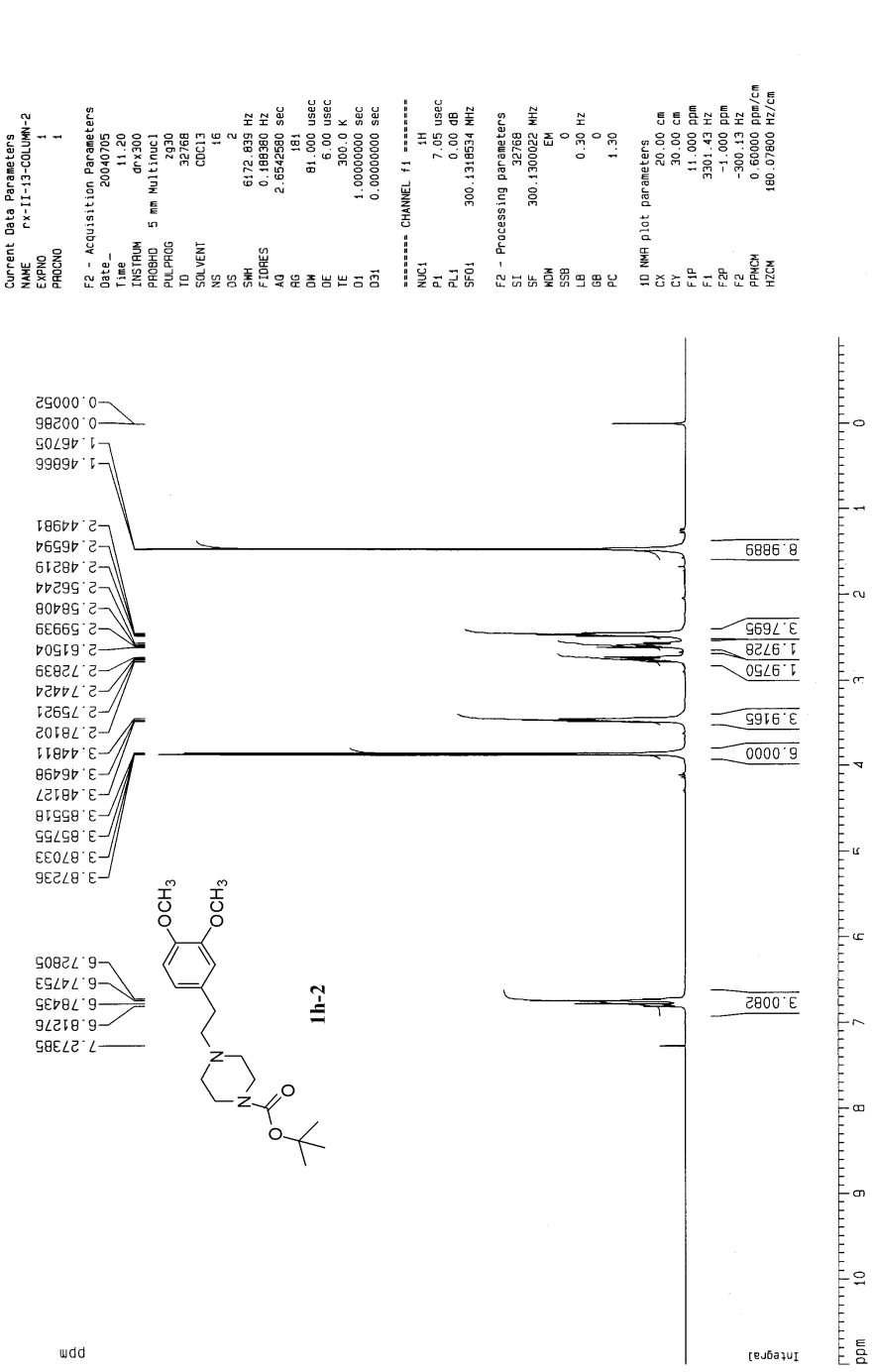
F2 - Acquisition Parameters
Date_ 20040703
Time 22.40
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 228.1
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec

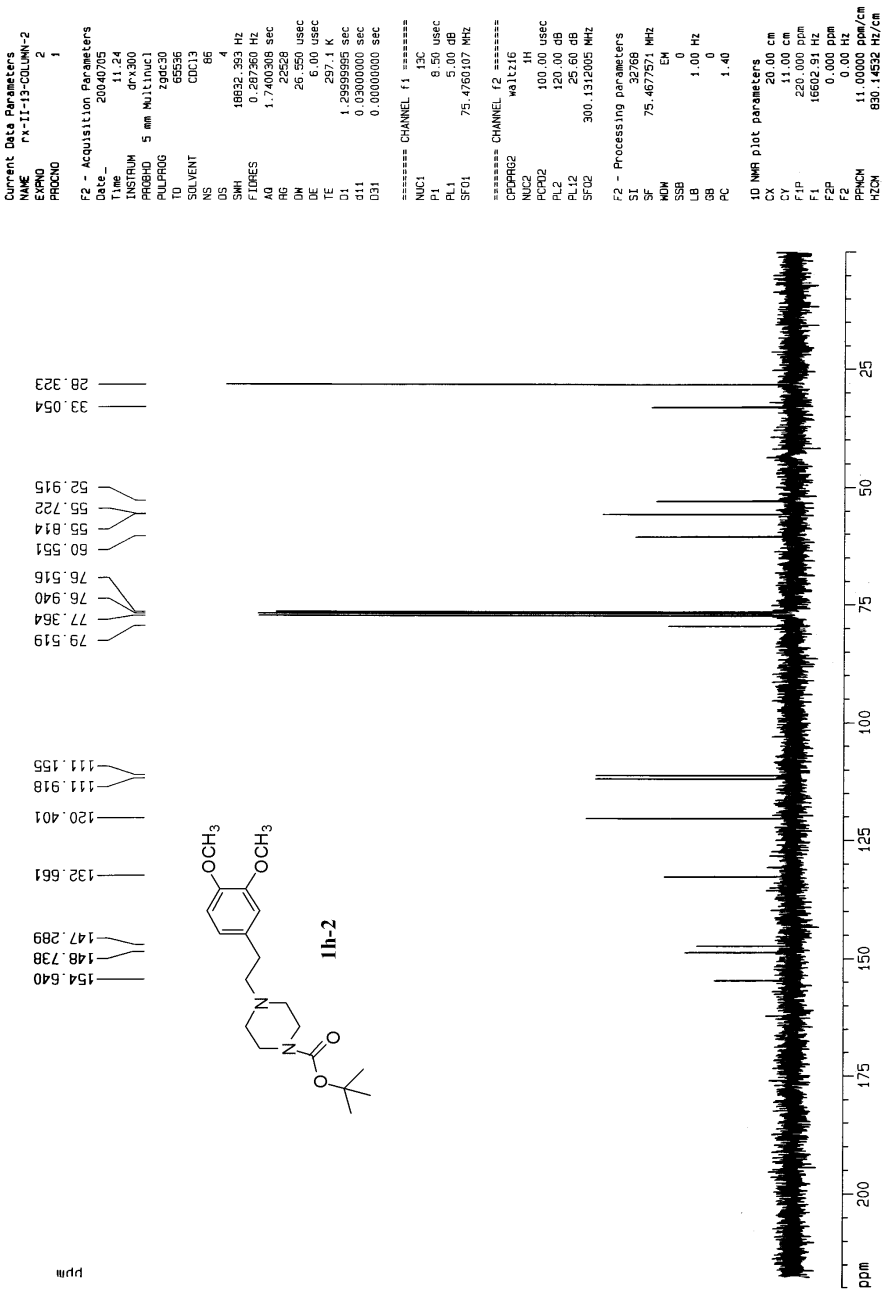
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz

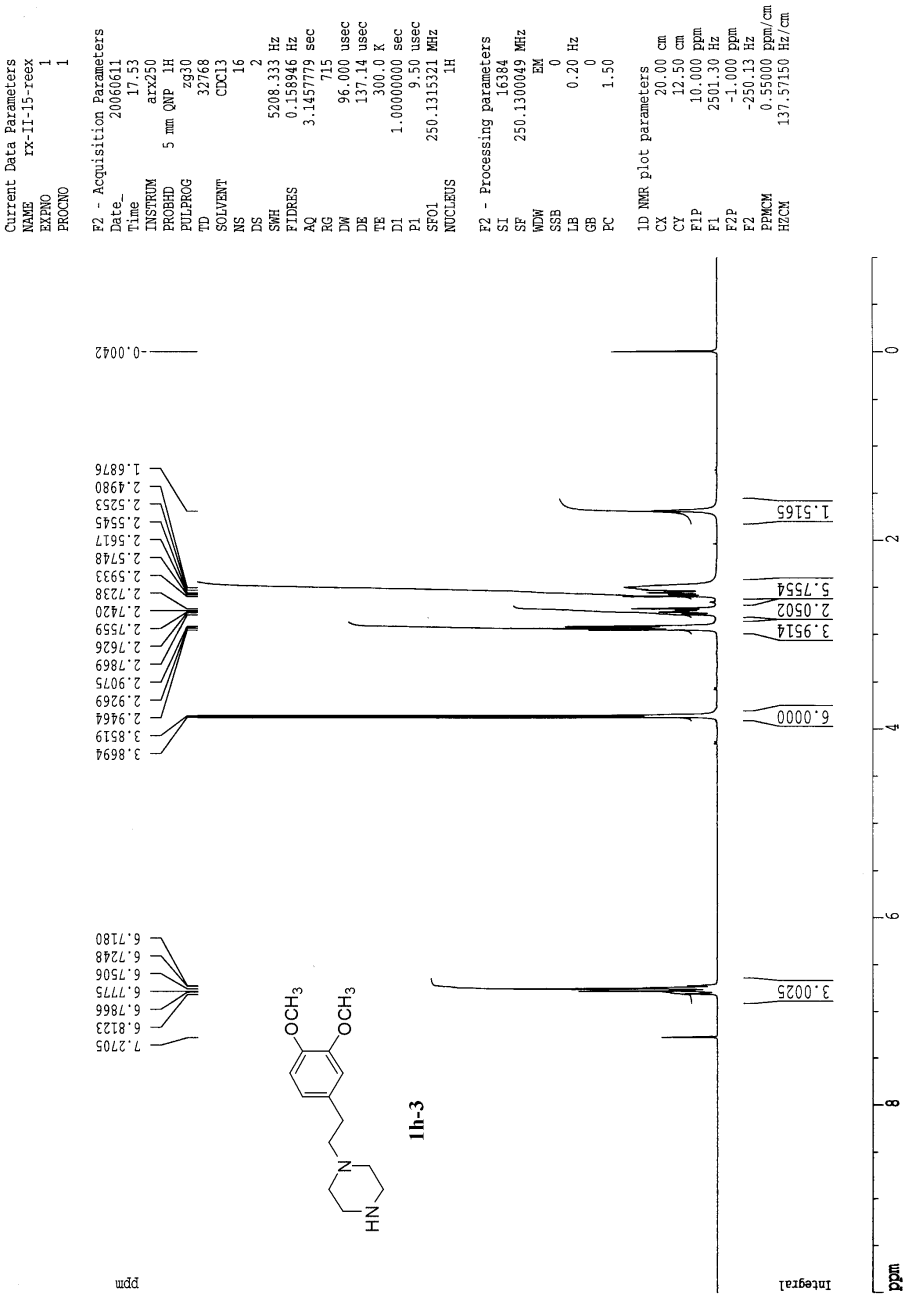
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30

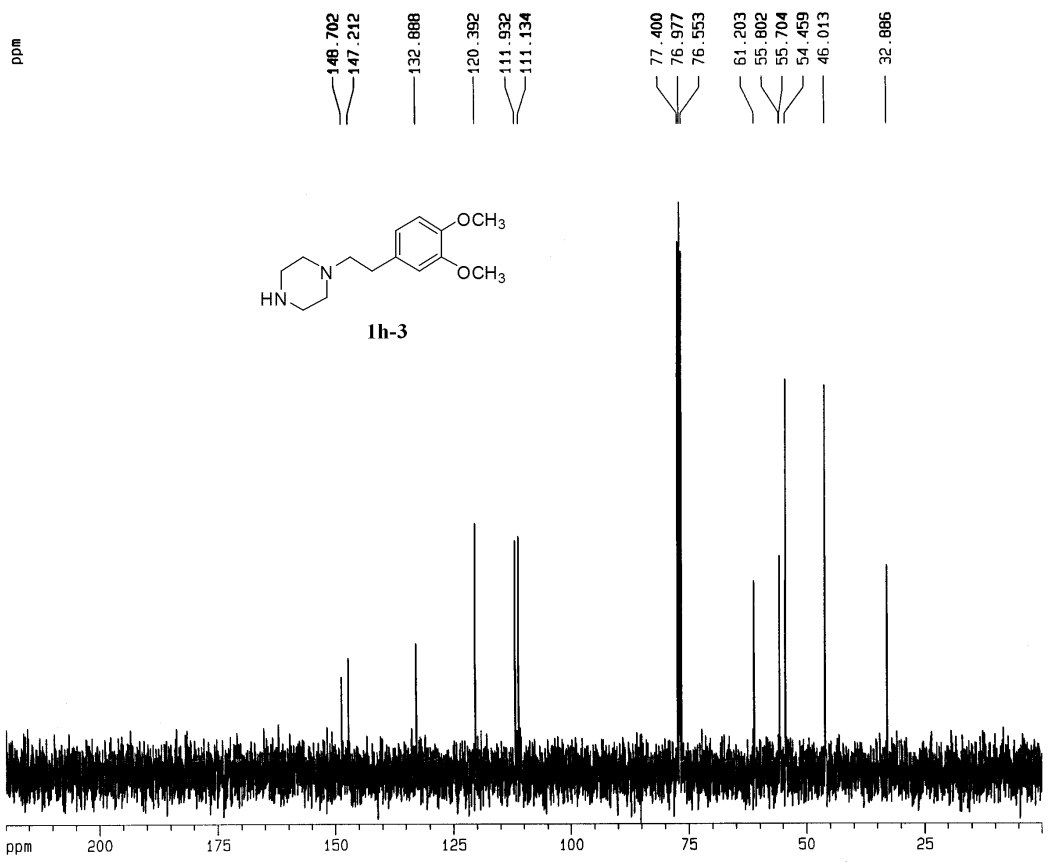
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 12.000 ppm
F1 3601.56 Hz
F2P -0.500 ppm
F2 -150.06 Hz
PPMCM 0.62500 ppm/cm
HZCM 187.58125 Hz/cm

Current Data Parameters
NAME rx-II-11-COLUMN
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040703
Time 22.44
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 32
DS 4
SWH 19832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 297.1 K
D1 1.29999995 sec
d11 0.03000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 5.00 dB
SFO1 75.4760107 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
CY 11.00 cm
F1P 220.000 ppm
F1 16602.91 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 11.00000 ppm/cm
HZCM 830.14532 Hz/cm
148.861
147.891
131.411
120.582
111.794
111.178
77.375
76.952
76.528
55.804
55.772
38.978
33.145
ppm
Br
H3CO
H3CO
1h-1


Current Data Parameters
NAME rx-II-13-COLUMN-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040705
Time 11.20
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 181
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
1D NMR plot parameters
CX 20.00 cm
CY 30.00 cm
F1P 11.000 ppm
F1 3301.43 Hz
F2P -1.000 ppm
F2 -300.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 180.07800 Hz/cm
0.00052
0.00286
1.46705
1.46866
2.44981
2.46594
2.48219
2.56244
2.58408
2.59939
2.61504
2.72839
2.74424
2.75921
2.78102
3.44811
3.46498
3.48127
3.85518
3.85755
3.87033
3.87236
6.72805
6.74753
6.78435
6.81276
7.27385
8.9889
3.7695
1.9728
1.9750
3.9165
6.0000
3.0082
OCH3
OCH3
1h-2
ppm
Integral


Current Data Parameters
NAME rx-II-13-COLUMN-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040705
Time 11.24
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 86
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 297.1 K
D1 1.29999995 sec
d11 0.03000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 5.00 dB
SFO1 75.4760107 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
CY 11.00 cm
F1P 220.000 ppm
F1 16602.91 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 11.00000 ppm/cm
HZCM 830.14532 Hz/cm
28.323
33.054
52.915
55.722
55.814
60.551
76.516
76.940
77.364
79.519
111.155
111.918
120.401
132.661
147.289
148.738
154.640
OCH3
OCH3
1h-2
ppm
25
50
75
100
125
150
175
200


Current Data Parameters
NAME rx-II-15-reex
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060611
Time 17.53
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 715
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 137.57150 Hz/cm
0.0042
1.6876
2.4980
2.5253
2.5545
2.5617
2.5748
2.5933
2.7238
2.7420
2.7559
2.7626
2.7869
2.9075
2.9269
2.9464
3.8519
3.8694
6.7180
6.7248
6.7506
6.7775
6.7866
6.8123
7.2705
1.5165
5.7554
2.0502
3.9514
6.0000
3.0025
OCH3
OCH3
N
HN
1h-3
ppm
Integral
ppm



1h-3

Current Data Parameters
NAME rx-ii-18-recrystal
EXPNO 2
PROCNO 1

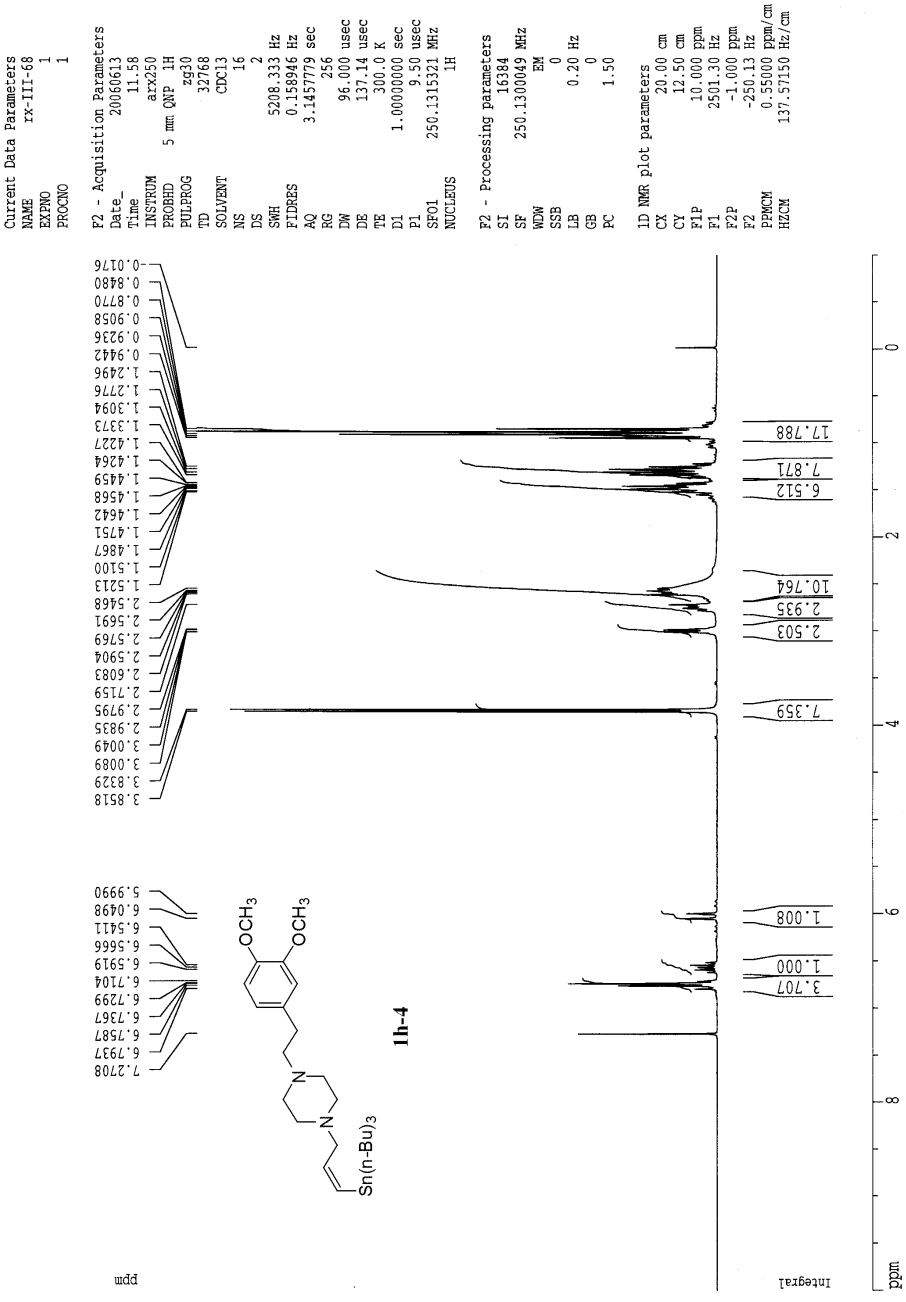
F2 - Acquisition Parameters
Date_ 20040706
Time 22.26
INSTRUM drx300
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 61
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 297.1 K
D1 1.29999995 sec
d11 0.03000000 sec
D31 0.00000000 sec

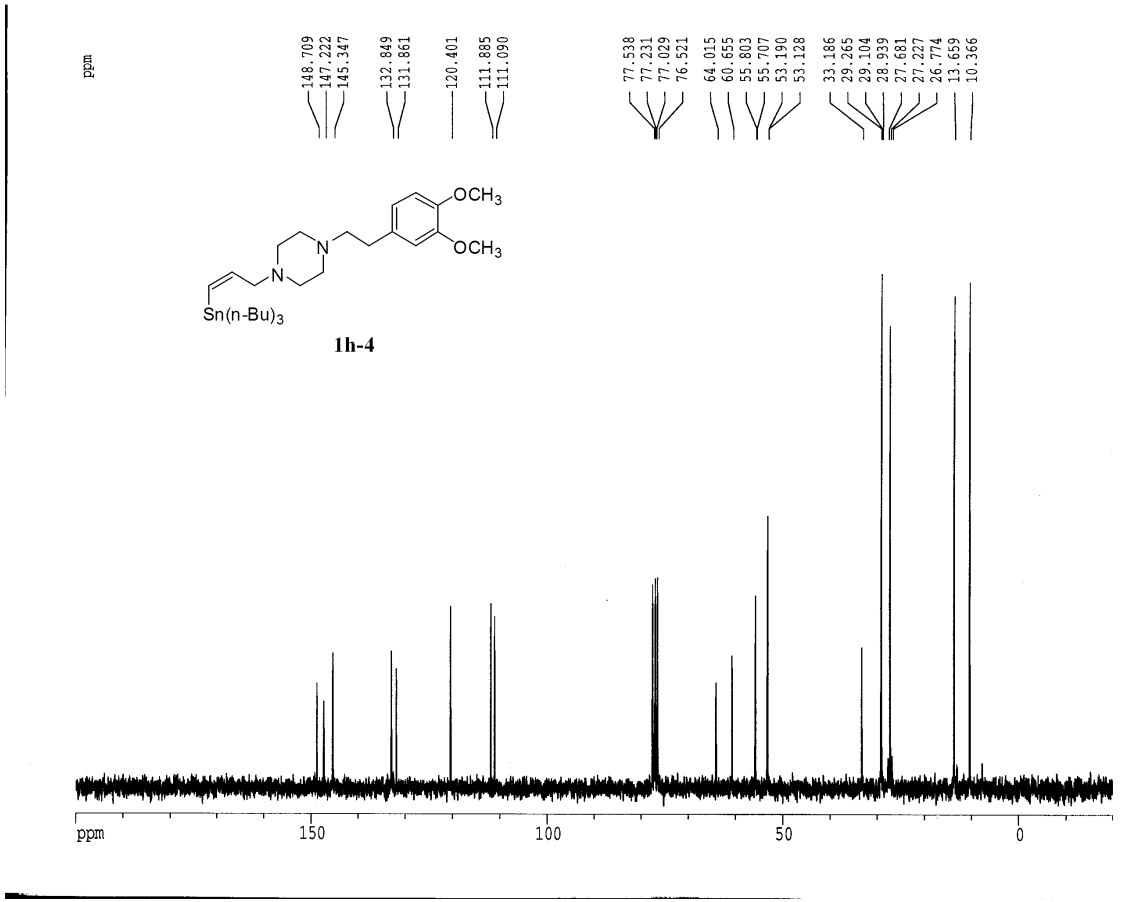
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 5.00 dB
SFO1 75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677571 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 11.00 cm
F1P 220.000 ppm
F1 16602.91 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 11.00000 ppm/cm
HZCM 830.14532 Hz/cm


Current Data Parameters
NAME rx-III-68
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060613
Time 11.58
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 256
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 137.57150 Hz/cm
0.0176
0.8480
0.8770
0.9058
0.9236
0.9442
1.2496
1.2776
1.3094
1.3373
1.4227
1.4264
1.4459
1.4568
1.4642
1.4751
1.4867
1.5100
1.5213
2.5468
2.5691
2.5769
2.5904
2.6083
2.7159
2.9795
2.9835
3.0049
3.0089
3.8329
3.8518
7.2708
6.7937
6.7587
6.7367
6.7299
6.7104
6.5919
6.5666
6.5411
6.0498
5.9990
17.788
7.871
6.512
10.764
2.935
2.503
7.359
1.008
1.000
3.707
OCH3
OCH3
N
N
Sn(n-Bu)3
1h-4
ppm
Integral
ppm
0
2
4
6
8



1h-4

Current Data Parameters

NAME	rx-III-68
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

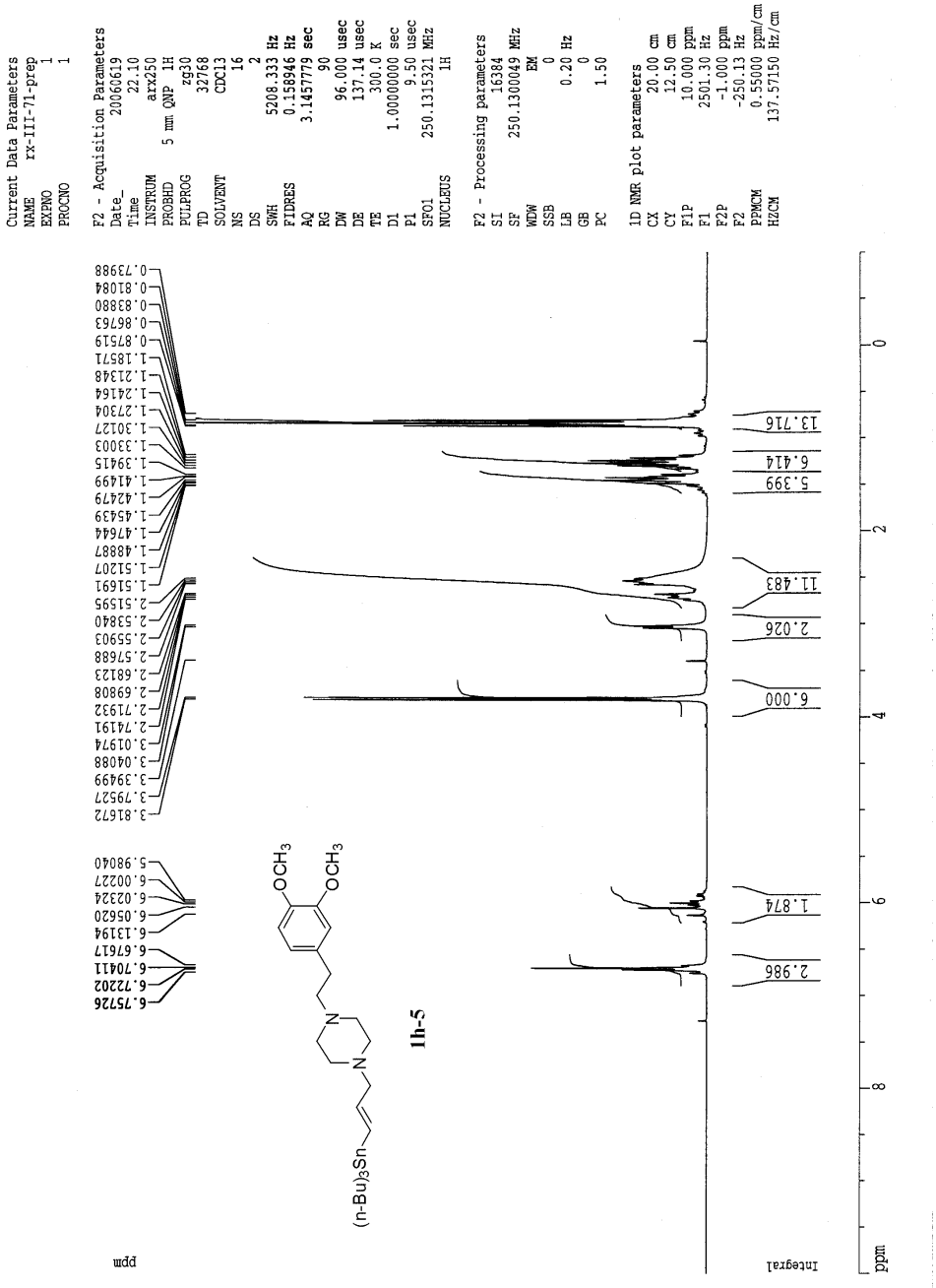
Date_	20060613
Time	12.00
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	66
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	8.00 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

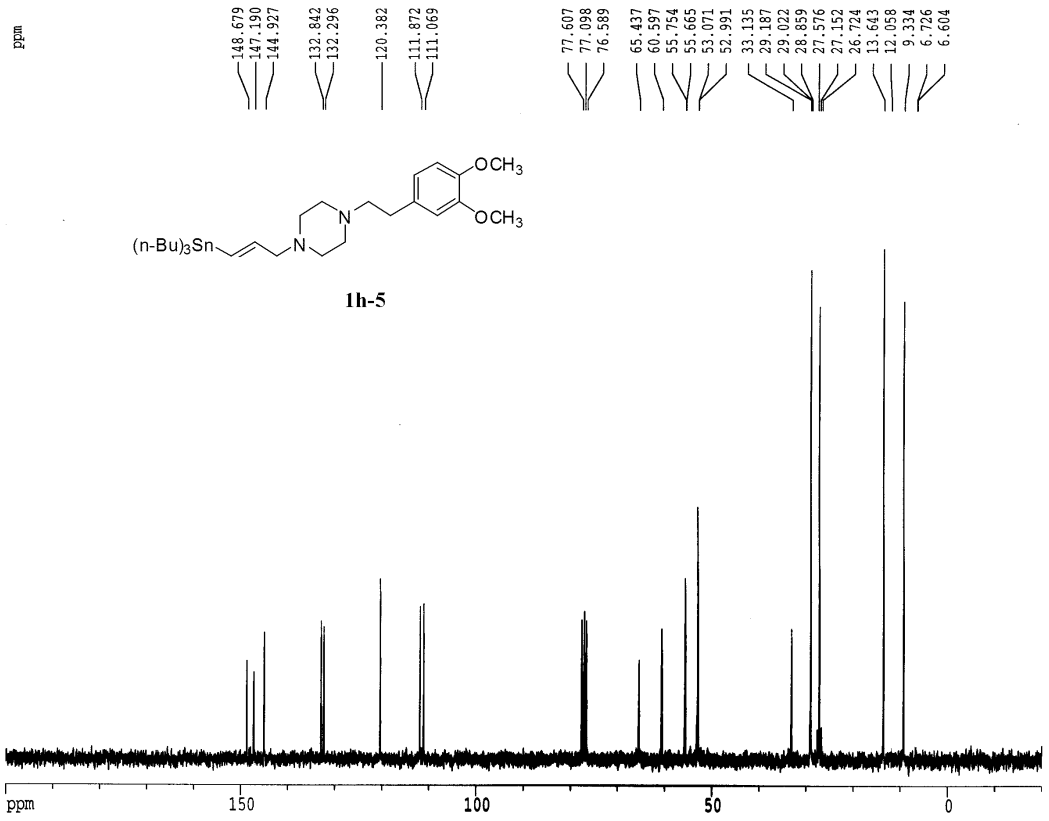
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm/cm
HZCM	691.84772 Hz/cm


Current Data Parameters
NAME rx-III-71-prep
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060619
Time 22.10
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.14457779 sec
RG 90
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 137.57150 Hz/cm
OCH3
OCH3
(n-Bu)3Sn
1h-5
ppm
Integral
13.716
6.414
5.399
11.483
2.026
6.000
1.874
2.986



1h-5

```
Current Data Parameters
NAME      rx-III-71-prep
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20060619
Time               22.13
INSTRUM          arx250
PROBHD     5 mm QNP  1H
PULPROG          zgdc30
TD                36864
SOLVENT           CDCl3
NS                   58
DS                    4
SWH           17241.379 Hz
FIDRES        0.467702 Hz
AQ            1.0691060 sec
RG                22800
DW               29.000 usec
DE               41.43 usec
TE               300.0 K
D12           0.00002000 sec
DL5              23.00 dB
CPDPRG          waltz16
P31              103.00 usec
D1            2.00000000 sec
P1                8.00 usec
SFO1          62.9023694 MHz
NUCLEUS             13C
D11           0.03000000 sec

F2 - Processing parameters
SI                32768
SF            62.8952440 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
CY                10.00 cm
F1P              200.000 ppm
F1             12579.05 Hz
F2P              -20.000 ppm
F2             -1257.91 Hz
PPMCM          11.00000 ppm/cm
HZCM          691.84772 Hz/cm
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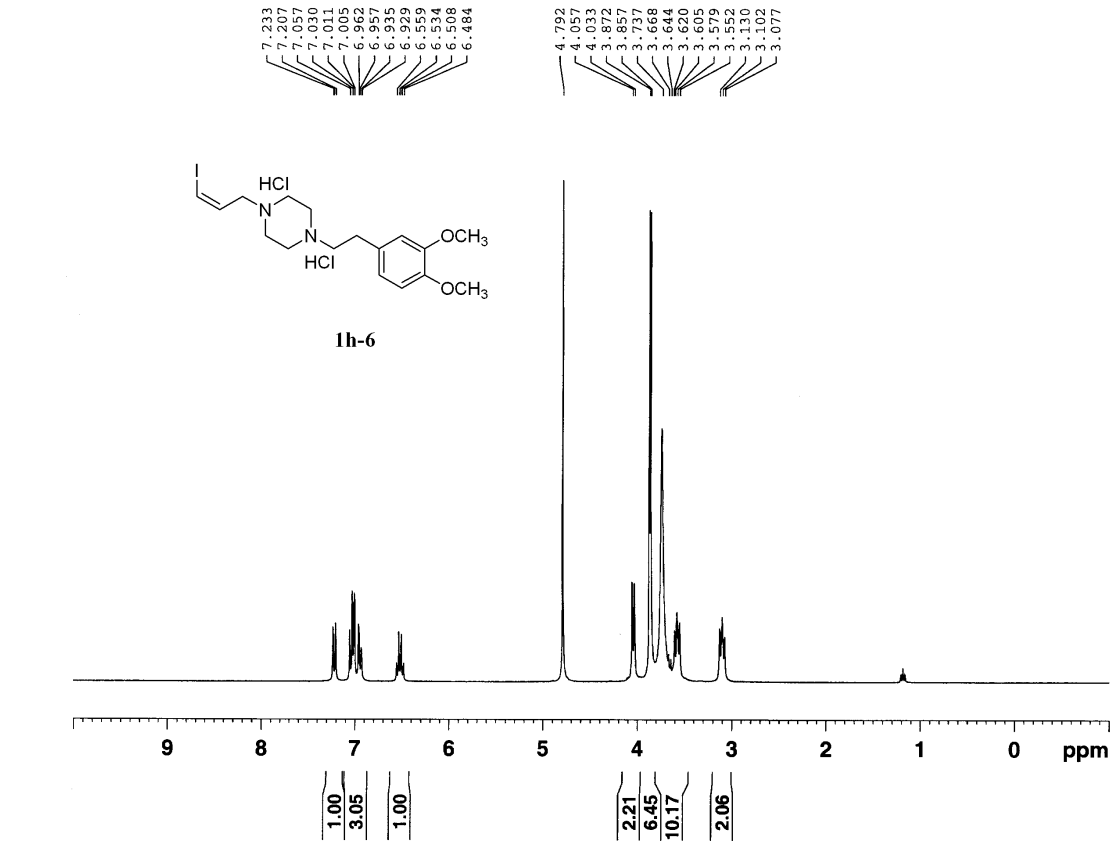
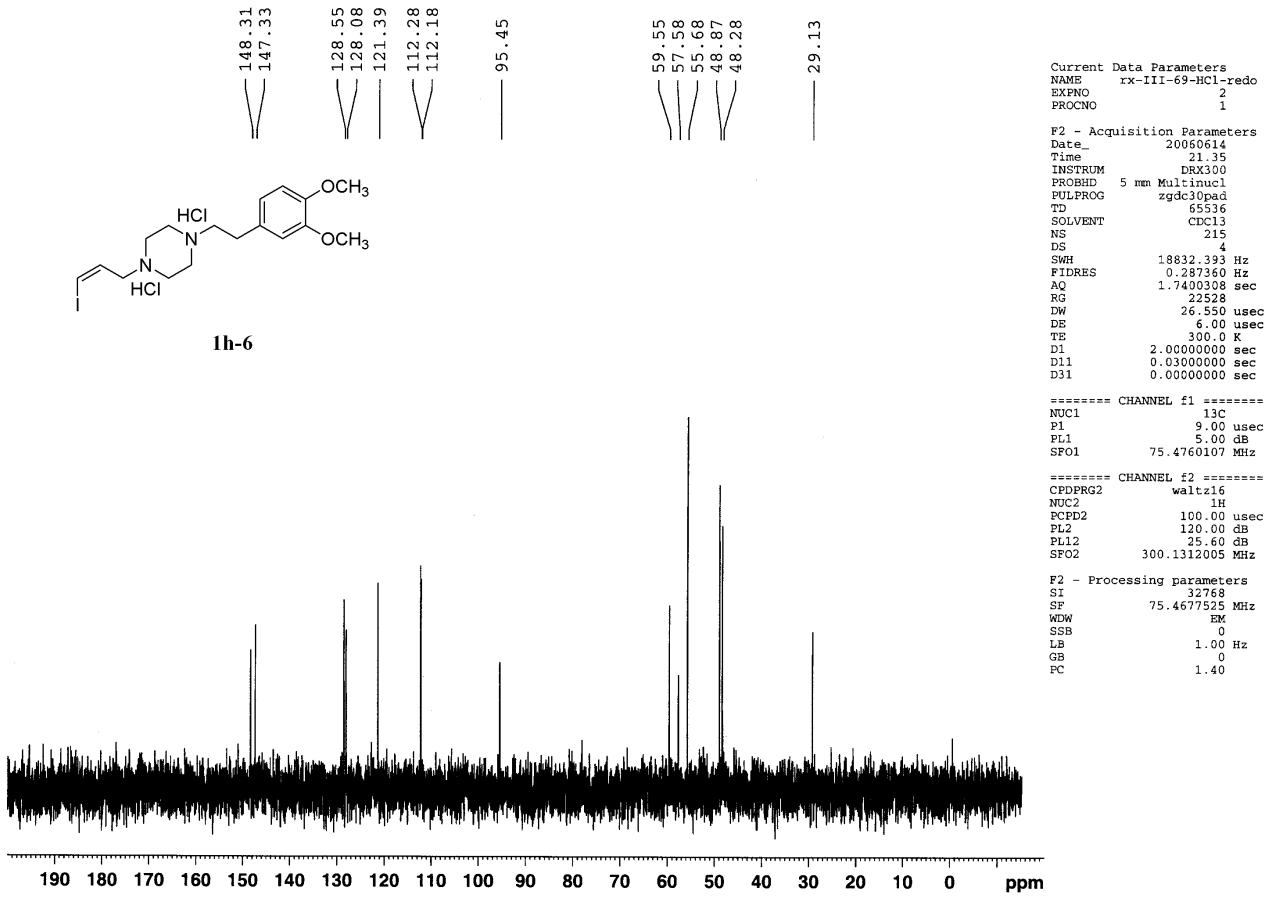


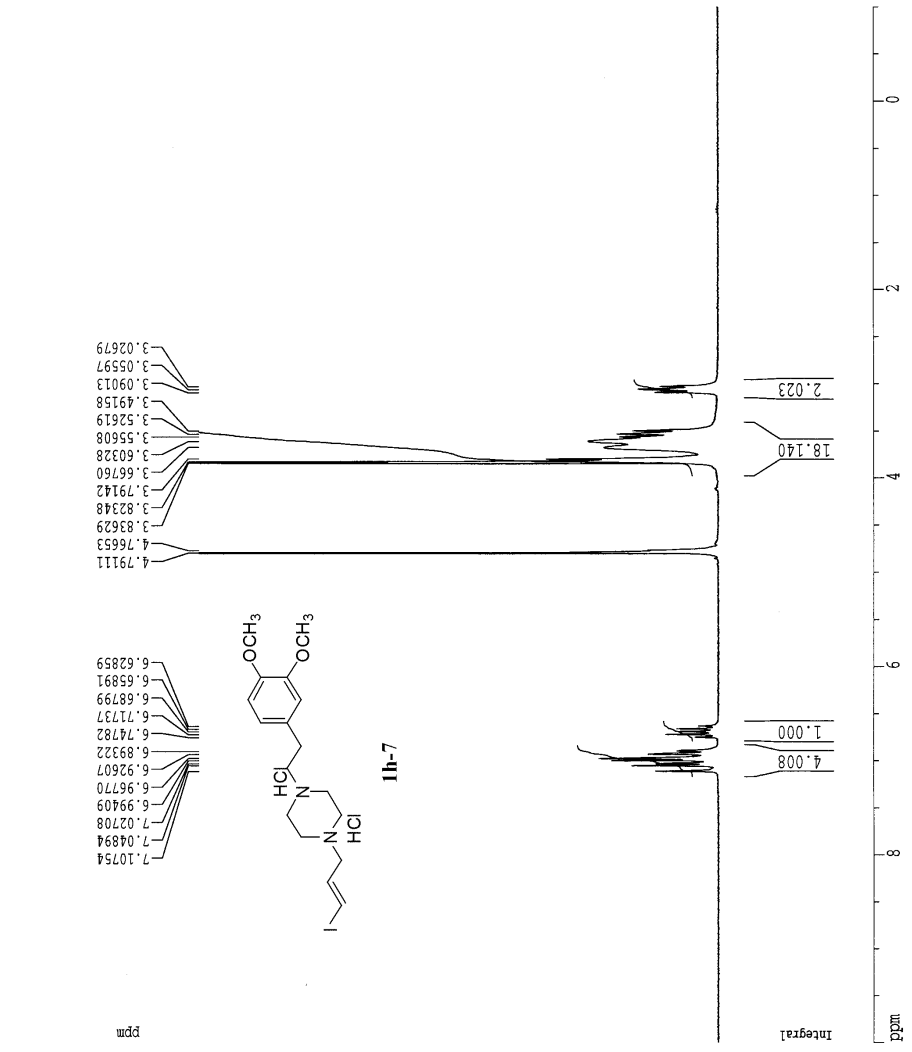
1h-6

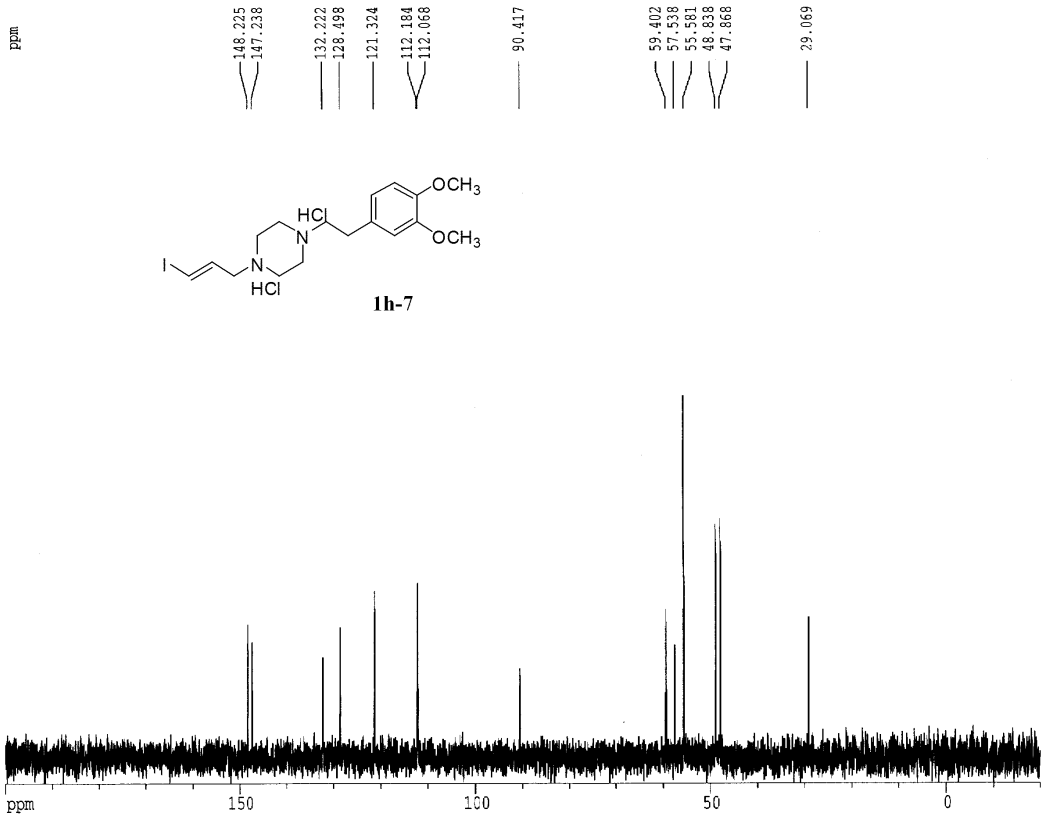
```
Current Data Parameters
NAME      rx-III-69-HCl-redo
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_               20060614
Time                   21.26
INSTRUM                DRX300
PROBHD   5 mm Multinucl
PULPROG              zg30pad
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                6172.839 Hz
FIDRES             0.188380 Hz
AQ                 2.6542580 sec
RG                     406.4
DW                    81.000 usec
DE                     6.00 usec
TE                    300.0 K
D1                 1.00000000 sec
D31                0.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                       7.05 usec
PL1                      0.00 dB
SFO1            300.1318534 MHz

F2 - Processing parameters
SI                     32768
SF              300.1299718 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.30
```



1h-6

```
Current Data Parameters
NAME      rx-III-69-HCl-redo
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_           20060614
Time              21.35
INSTRUM           DRX300
PROBHD   5 mm Multinucl
PULPROG        zgdc30pad
TD                65536
SOLVENT           CDCl3
NS                  215
DS                    4
SWH           18832.393 Hz
FIDRES         0.287360 Hz
AQ             1.7400308 sec
RG                22528
DW               26.550 usec
DE                6.00 usec
TE                300.0 K
D1            2.00000000 sec
D11           0.03000000 sec
D31           0.00000000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                 9.00 usec
PL1                5.00 dB
SFO1         75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2            100.00 usec
PL2              120.00 dB
PL12              25.60 dB
SFO2        300.1312005 MHz

F2 - Processing parameters
SI                32768
SF           75.4677525 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```


Current Data Parameters
NAME rx-III-72-HCl
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060621
Time 22.15
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 1430
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1299792 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 30.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 137.57149 Hz/cm
7.10754
7.04894
7.02708
6.99409
6.96770
6.92607
6.89322
6.74782
6.71737
6.68799
6.65891
6.62859
4.79111
4.76653
3.83629
3.82348
3.79142
3.66760
3.60328
3.55608
3.52619
3.49158
3.09013
3.05597
3.02679
OCH3
OCH3
HCl
HCl
1h-7
18.140
2.023
4.008
1.000
ppm
Integral



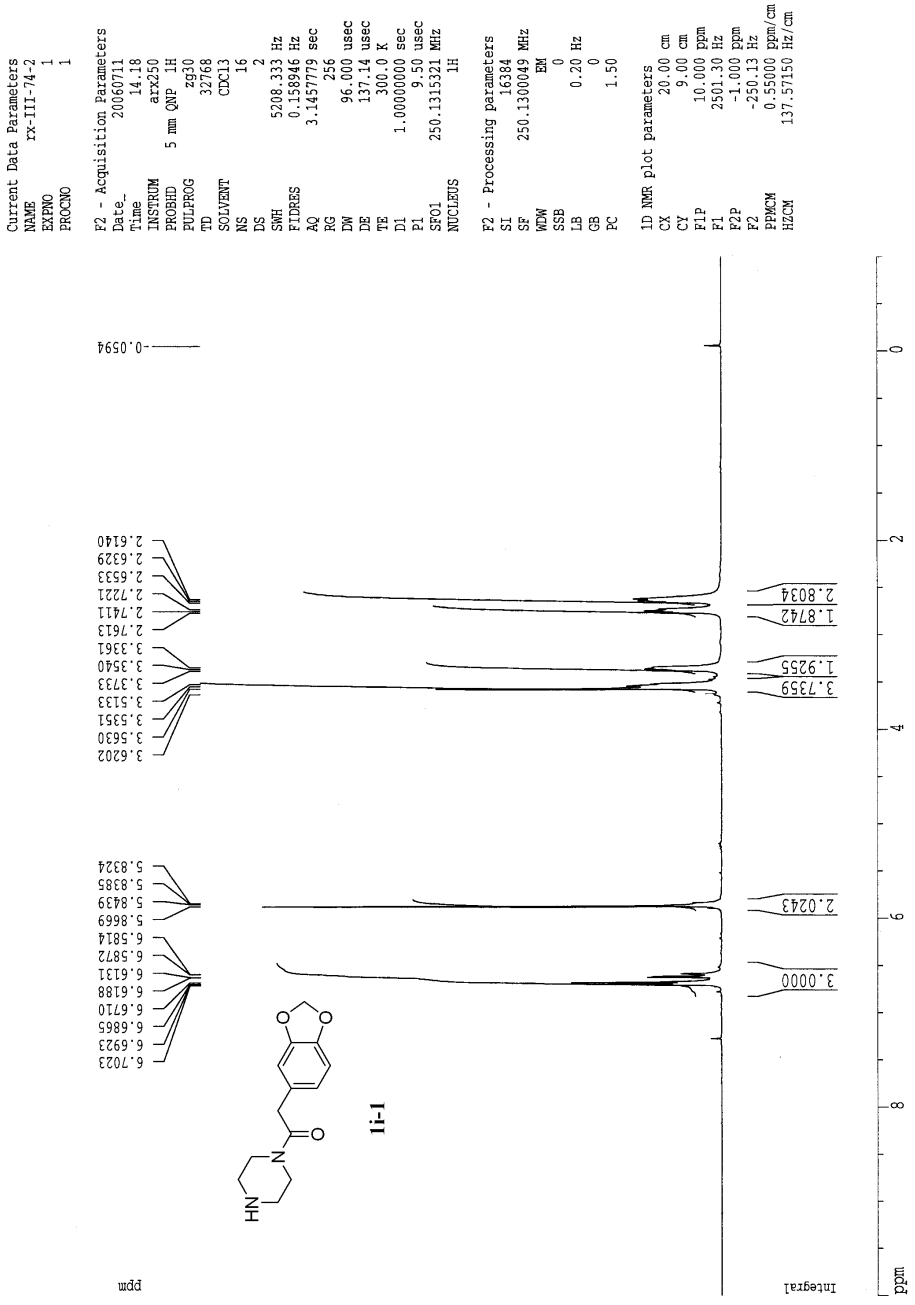
1h-7

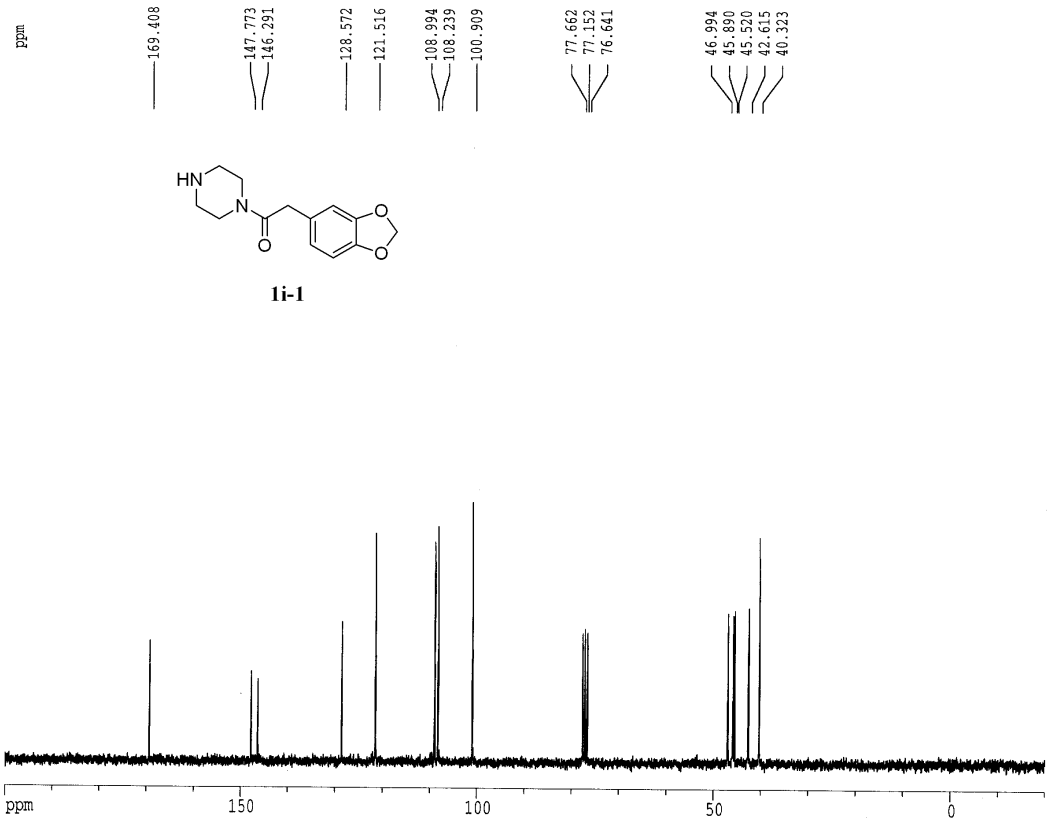
Current Data Parameters
NAME rx-III-72-HCl
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060621
Time 22.24
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zgdc30
TD 36864
SOLVENT CDCl3
NS 1695
DS 4
SWH 17241.379 Hz
FIDRES 0.467702 Hz
AQ 1.0691060 sec
RG 22800
DW 29.000 usec
DE 41.43 usec
TE 300.0 K
D12 0.00002000 sec
DL5 23.00 dB
CPDPRG waltz16
P31 103.00 usec
D1 2.00000000 sec
P1 8.00 usec
SFO1 62.9023694 MHz
NUCLEUS 13C
D11 0.03000000 sec

F2 - Processing parameters
SI 32768
SF 62.8952440 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
CY 7.00 cm
F1P 200.000 ppm
F1 12579.05 Hz
F2P -20.000 ppm
F2 -1257.91 Hz
PPMCM 11.00000 ppm/cm
HZCM 691.84772 Hz/cm


Current Data Parameters
NAME rx-III-74-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060711
Time 14.18
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 256
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 9.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 137.57150 Hz/cm
-0.0594
2.6140
2.6329
2.6533
2.7221
2.7411
2.7613
3.3361
3.3540
3.3733
3.5133
3.5351
3.5630
3.6202
6.7023
6.6923
6.6865
6.6710
6.6188
6.6131
6.5872
6.5814
5.8669
5.8439
5.8385
5.8324
2.8034
1.8742
1.9255
3.7359
2.0243
3.0000
1i-1
HN
N
O
O
O
ppm
Integral
ppm
0
2
4
6
8



1i-1

Current Data Parameters

NAME	rx-III-74-2
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

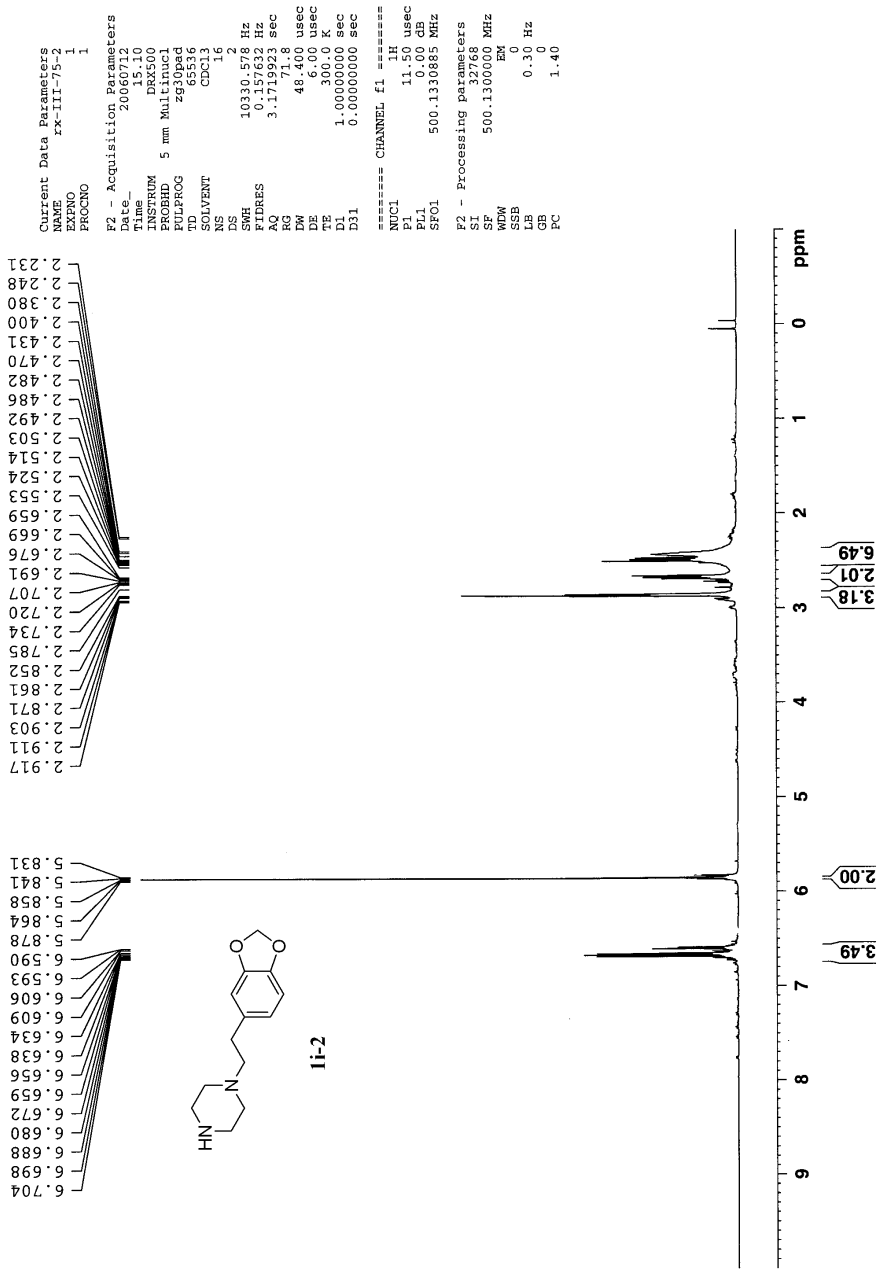
Date_	20060711
Time	14.22
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	118
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	8.00 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

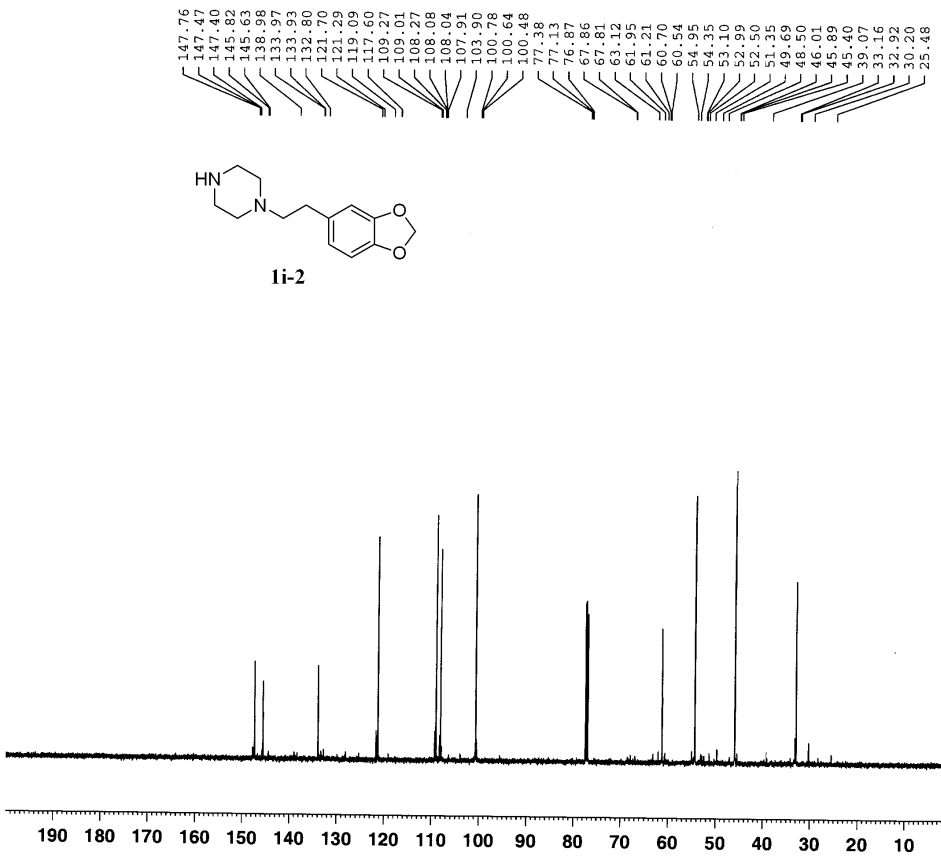
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

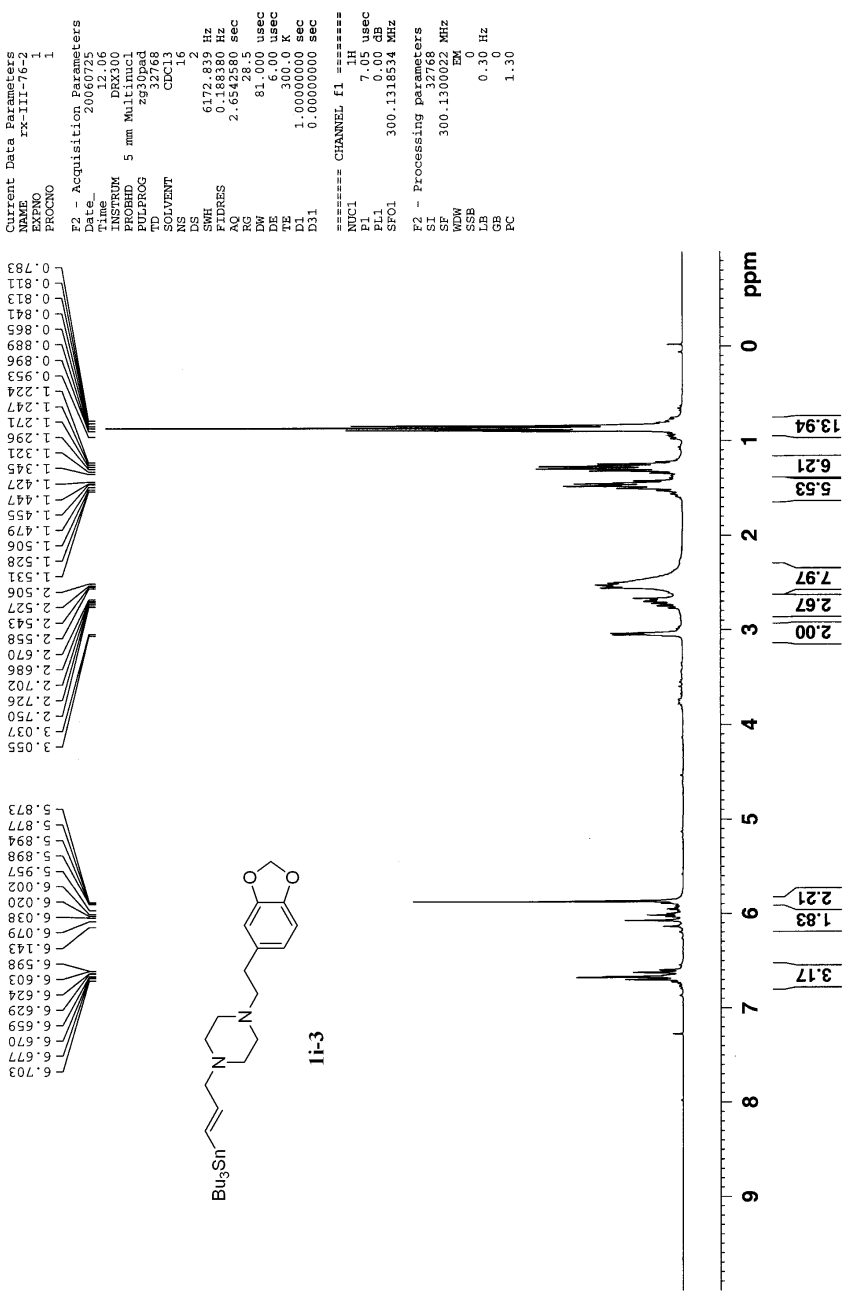
1D NMR plot parameters

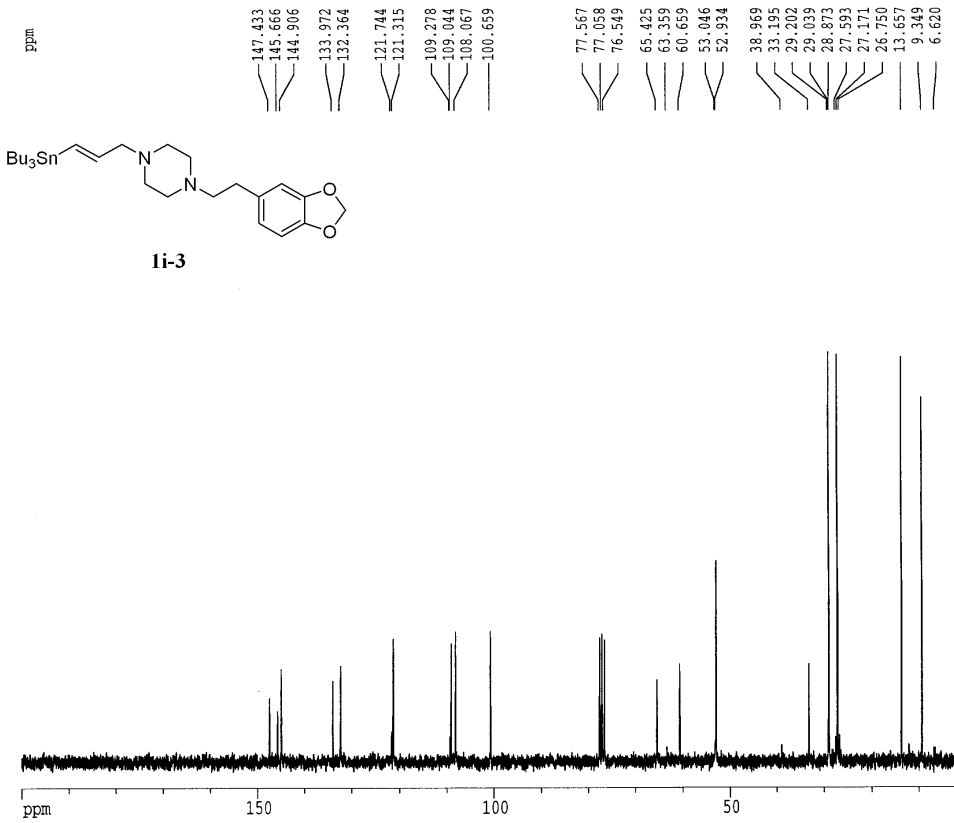
CX	20.00 cm
CY	5.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm/cm
HZCM	691.84772 Hz/cm


Current Data Parameters
NAME rx-III-75-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060712
Time 15.10
INSTRUM DRX500
PROBHD 5 mm Multinuc1
PULPROG zg30pad
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 71.8
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 11.50 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
2.917
2.911
2.903
2.871
2.861
2.852
2.785
2.734
2.720
2.707
2.691
2.676
2.669
2.659
2.553
2.524
2.514
2.503
2.492
2.486
2.482
2.470
2.431
2.400
2.380
2.248
2.231
5.831
5.841
5.858
5.864
5.878
6.590
6.593
6.606
6.609
6.634
6.638
6.656
6.659
6.672
6.680
6.688
6.698
6.704
3.49
2.00
3.18
2.01
6.49
ppm
1i-2




```
Current Data Parameters
NAME          rx-III-75-2
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_          20060712
Time              15.14
INSTRUM          DRX500
PROBHD  5 mm Multinucl
PULPROG         zgdc30
TD               65536
SOLVENT           CDCl3
NS                   54
DS                    4
SWH           34013.605 Hz
FIDRES        0.519006 Hz
AQ            0.9634292 sec
RG                32768
DW               14.700 usec
DE                6.00 usec
TE               300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
D31          0.00000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                  8.10 usec
PL1                 3.00 dB
SFO1       125.7723786 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              88.00 usec
PL2                 0.00 dB
PL12               21.00 dB
SFO2       500.1320005 MHz

F2 - Processing parameters
SI                32768
SF         125.7578011 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```


Current Data Parameters
NAME rx-III-76-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060725
Time 12.06
INSTRUM DRX300
PROBHD 5 mm Multinuc1
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542380 sec
RG 228.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
0.783
0.811
0.813
0.841
0.865
0.889
0.896
0.953
1.224
1.247
1.271
1.296
1.321
1.345
1.427
1.447
1.455
1.479
1.506
1.528
1.531
2.506
2.527
2.543
2.558
2.670
2.686
2.702
2.726
2.750
3.037
3.055
5.873
5.877
5.894
5.898
5.957
6.002
6.020
6.038
6.079
6.143
6.598
6.603
6.624
6.629
6.659
6.670
6.677
6.703
Bu3Sn
li-3
ppm
13.94
6.21
5.53
7.97
2.67
2.00
2.21
1.83
3.17



1i-3

Current Data Parameters

NAME	rx-III-76-2
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

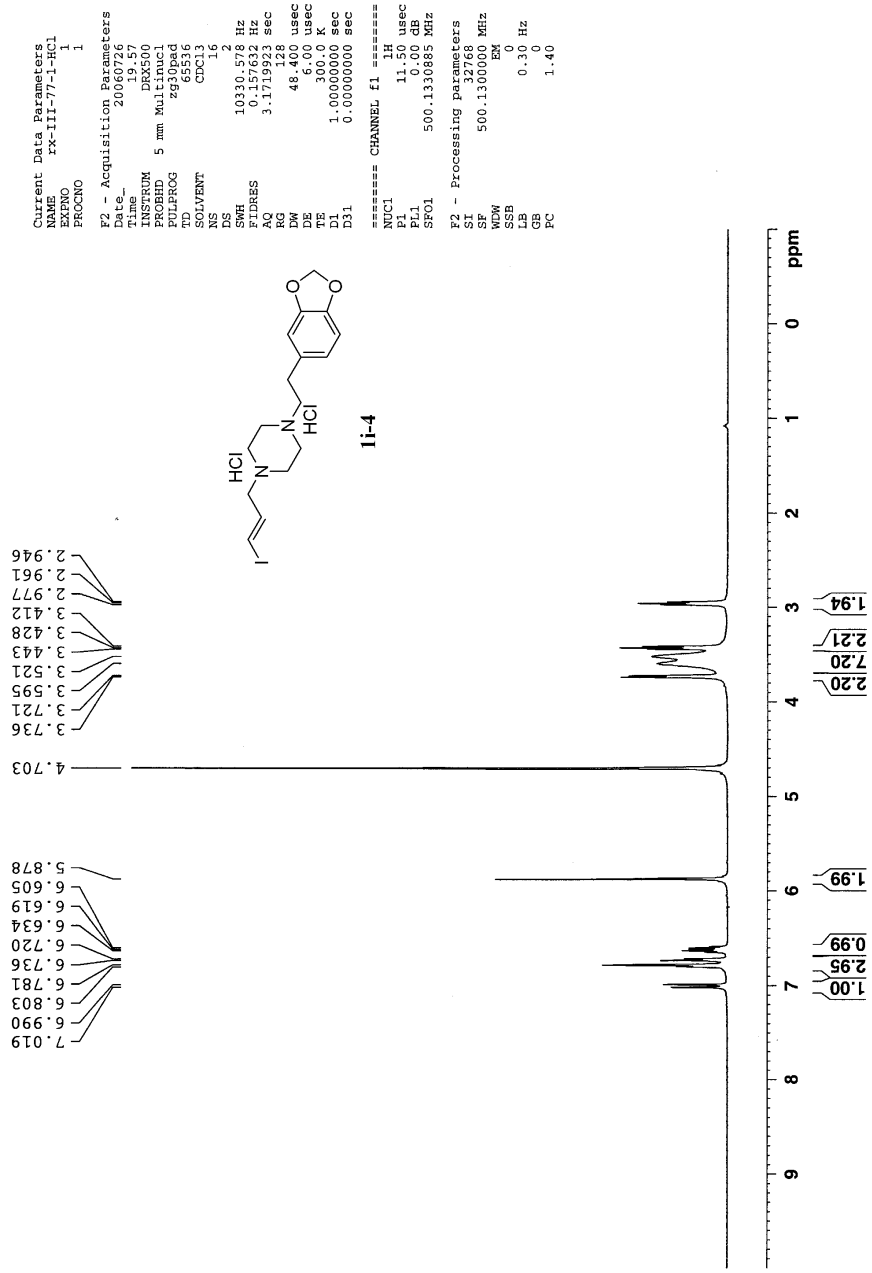
Date_	20060725
Time	13.37
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zgdc30
TD	36864
SOLVENT	CDCl3
NS	45
DS	4
SWH	17241.379 Hz
FIDRES	0.467702 Hz
AQ	1.0691060 sec
RG	22800
DW	29.000 usec
DE	41.43 usec
TE	300.0 K
D12	0.00002000 sec
DL5	23.00 dB
CPDPRG	waltz16
P31	103.00 usec
D1	2.00000000 sec
P1	8.00 usec
SFO1	62.9023694 MHz
NUCLEUS	13C
D11	0.03000000 sec

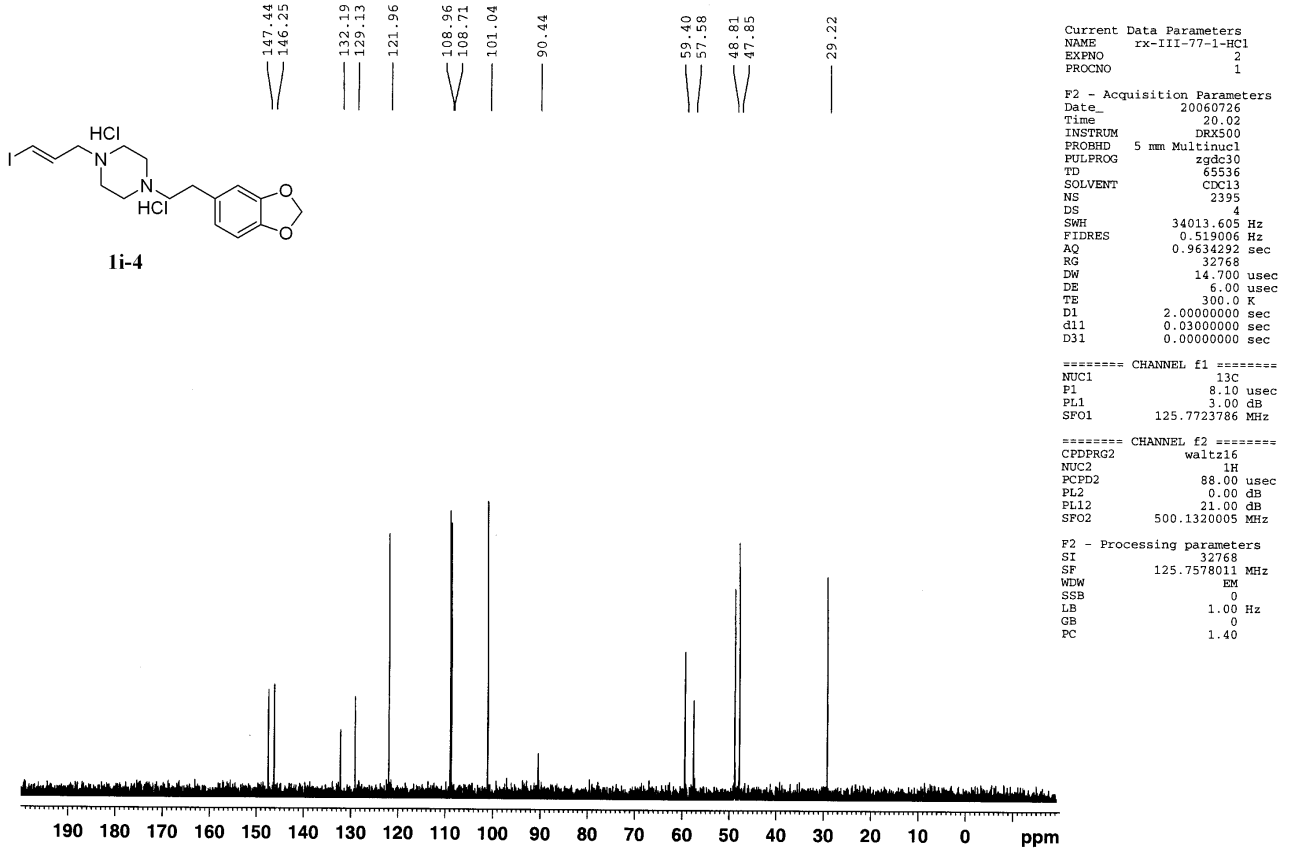
F2 - Processing parameters

SI	32768
SF	62.8952440 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

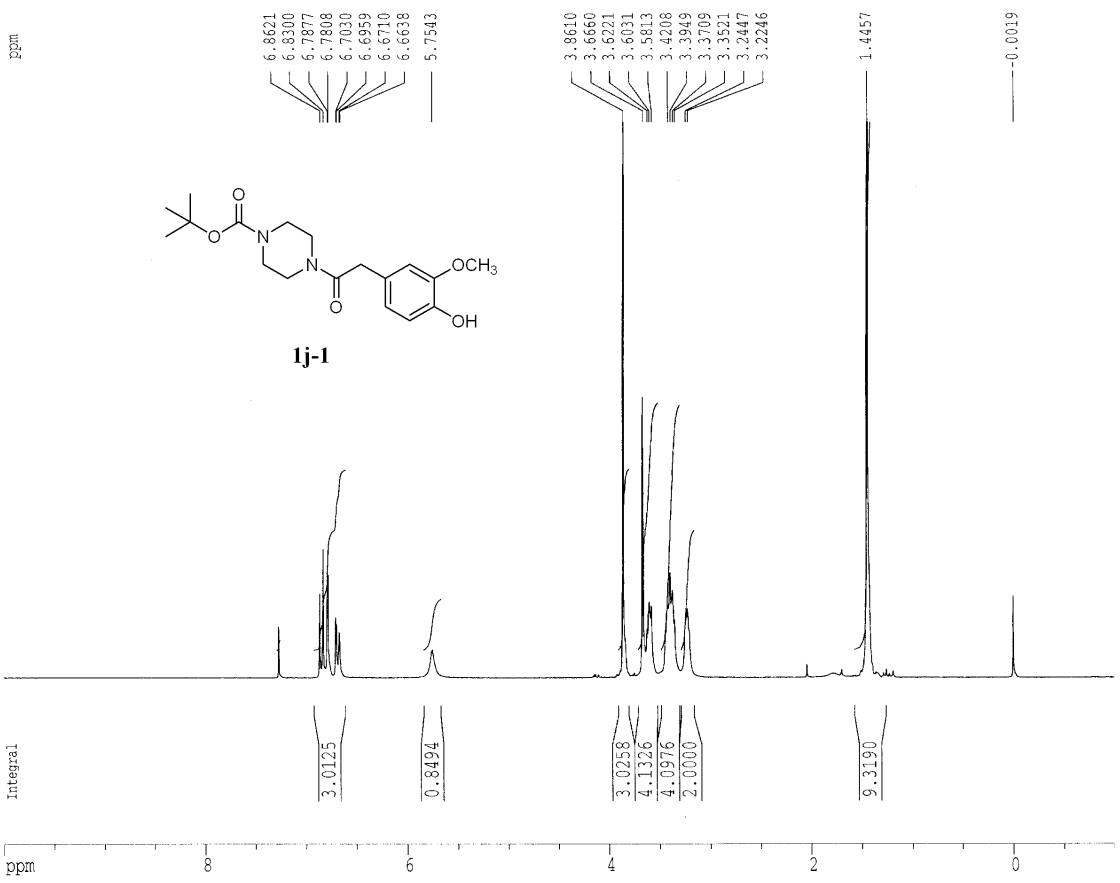
CX	20.00 cm
CY	8.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm/cm
HZCM	691.84772 Hz/cm


Current Data Parameters
NAME rx-III-77-1-HCl
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060726
Time 19.57
INSTRUM DRX500
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 128
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 11.50 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
HCl
HCl
1i-4
2.946
2.961
2.977
3.412
3.428
3.443
3.521
3.595
3.721
3.736
4.703
5.878
6.605
6.619
6.634
6.720
6.736
6.781
6.803
6.990
7.019
1.94
2.21
7.20
2.20
1.99
0.99
2.95
1.00
ppm



1i-4

```
Current Data Parameters
NAME      rx-III-77-1-HCl
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20060726
Time              20.02
INSTRUM          DRX500
PROBHD   5 mm Multinucl
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3
NS                 2395
DS                    4
SWH          34013.605 Hz
FIDRES        0.519006 Hz
AQ            0.9634292 sec
RG                32768
DW               14.700 usec
DE                6.00 usec
TE               300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
D31          0.00000000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 8.10 usec
PL1                3.00 dB
SFO1        125.7723786 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             88.00 usec
PL2                0.00 dB
PL12              21.00 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                32768
SF          125.7578011 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



1j-1

Current Data Parameters

NAME	rx-III-81-1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

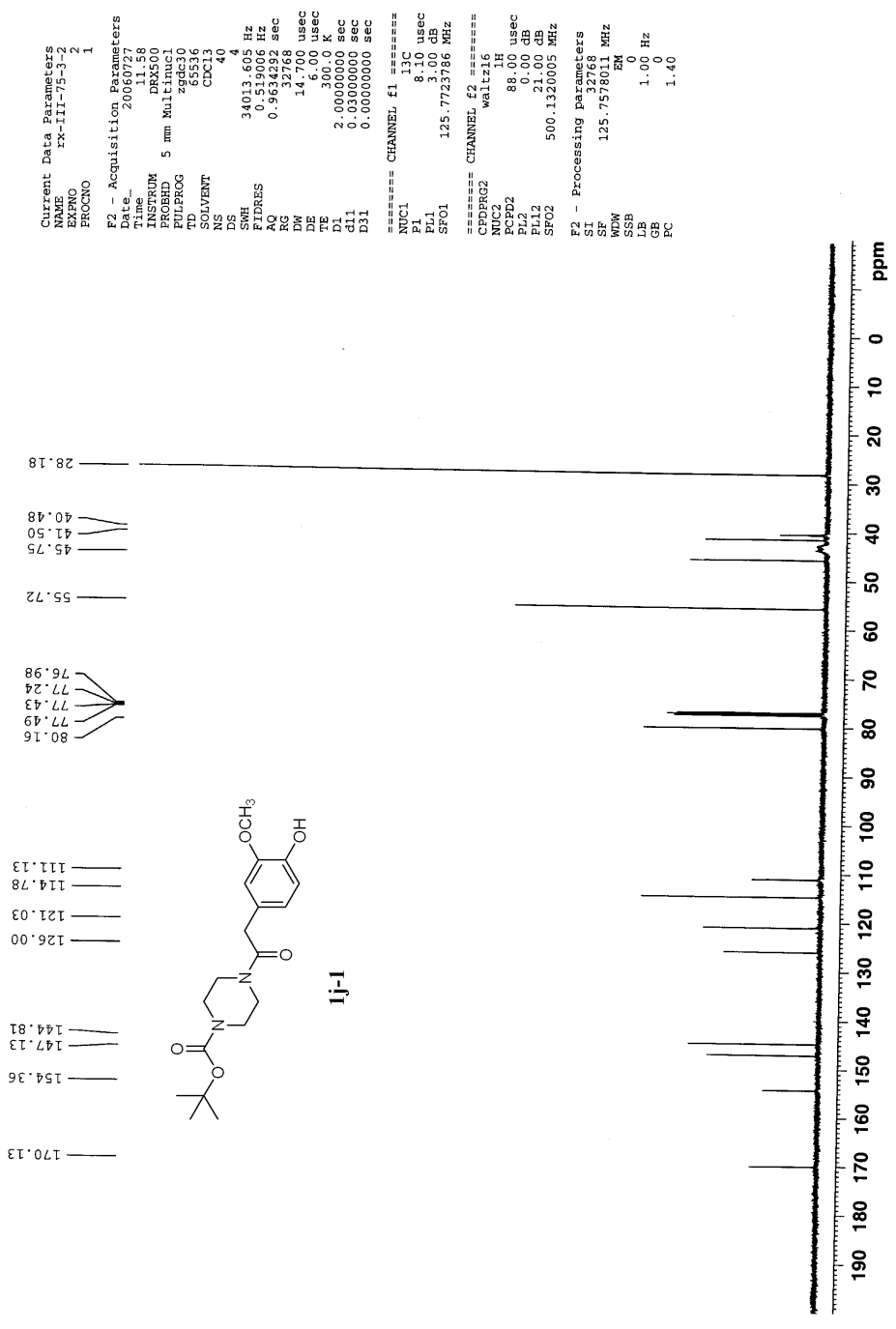
Date_	20060907
Time	13.03
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	715
DW	96.000 usec
DE	137.14 usec
TE	300.0 K
D1	1.00000000 sec
P1	9.50 usec
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

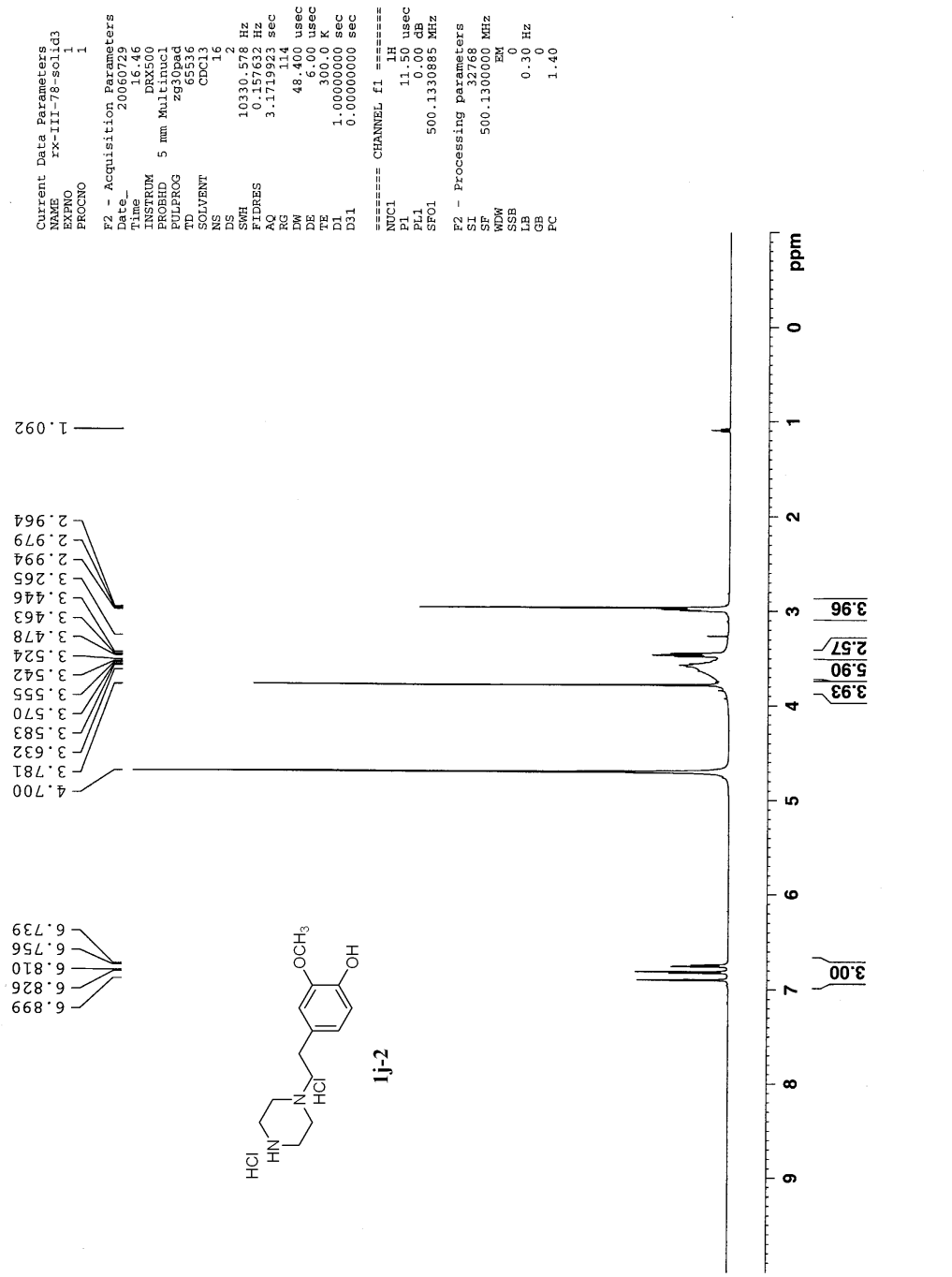
SI	16384
SF	250.1300049 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	30.00 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-1.000 ppm
F2	-250.13 Hz
PPMCM	0.55000 ppm/cm
HZCM	137.57150 Hz/cm


Current Data Parameters
NAME rx-III-75-3-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060727
Time 11.58
INSTRUM DRX500
PROBHD 5 mm Multinuc1
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 40
DS 4
SWH 34013.605 Hz
FIDRES 0.519006 Hz
AQ 0.9634292 sec
RG 32768
DW 14.700 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.10 usec
PL1 3.00 dB
SFO1 125.7723786 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 88.00 usec
PL2 0.00 dB
PL12 21.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578011 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
28.18
40.48
41.50
45.75
55.72
76.98
77.24
77.43
77.49
80.16
111.13
114.78
121.03
126.00
144.81
147.13
154.36
170.13
OCH3
OH
O
N
N
O
O
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

1j-1


Current Data Parameters
NAME rx-III-78-solid3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060729
Time 16.46
INSTRUM DRX500
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 114
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 11.50 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
1.092
2.964
2.979
2.994
3.265
3.446
3.463
3.478
3.524
3.542
3.555
3.570
3.583
3.632
3.781
4.700
6.739
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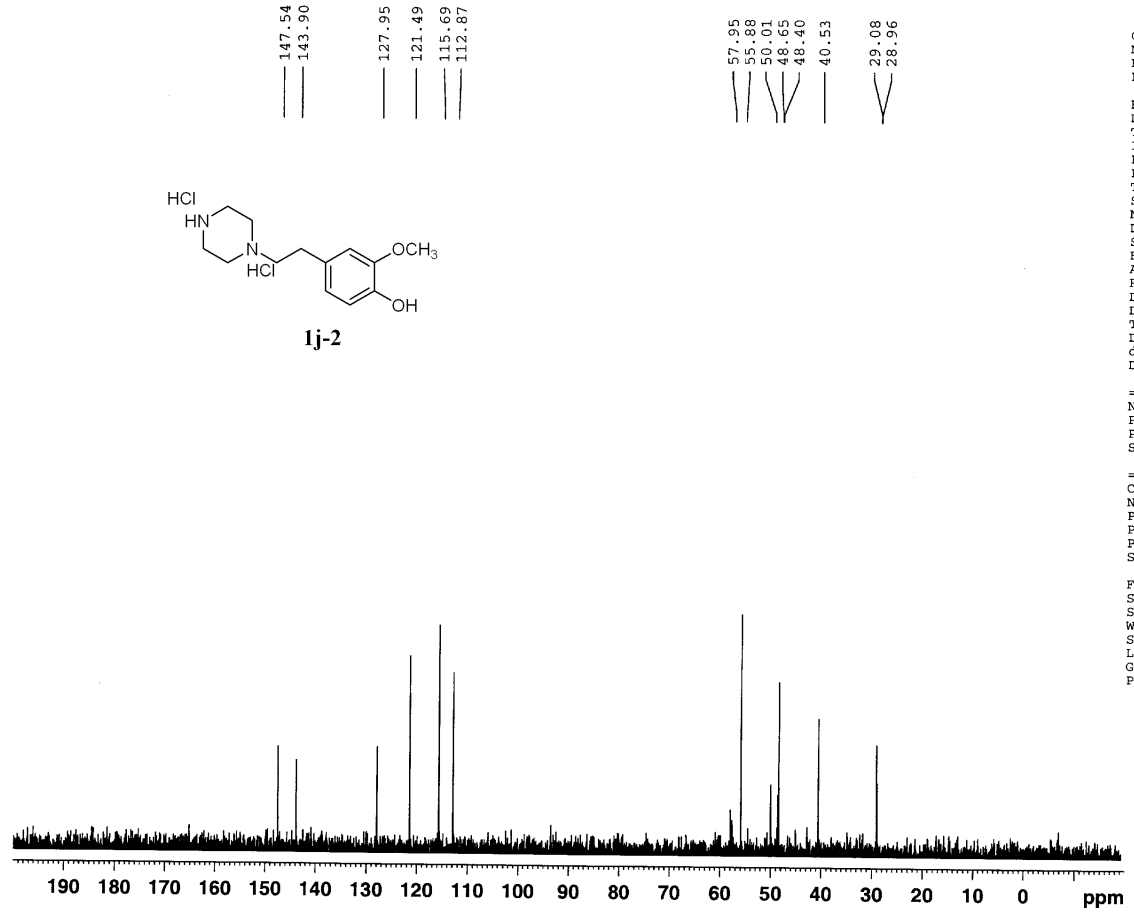
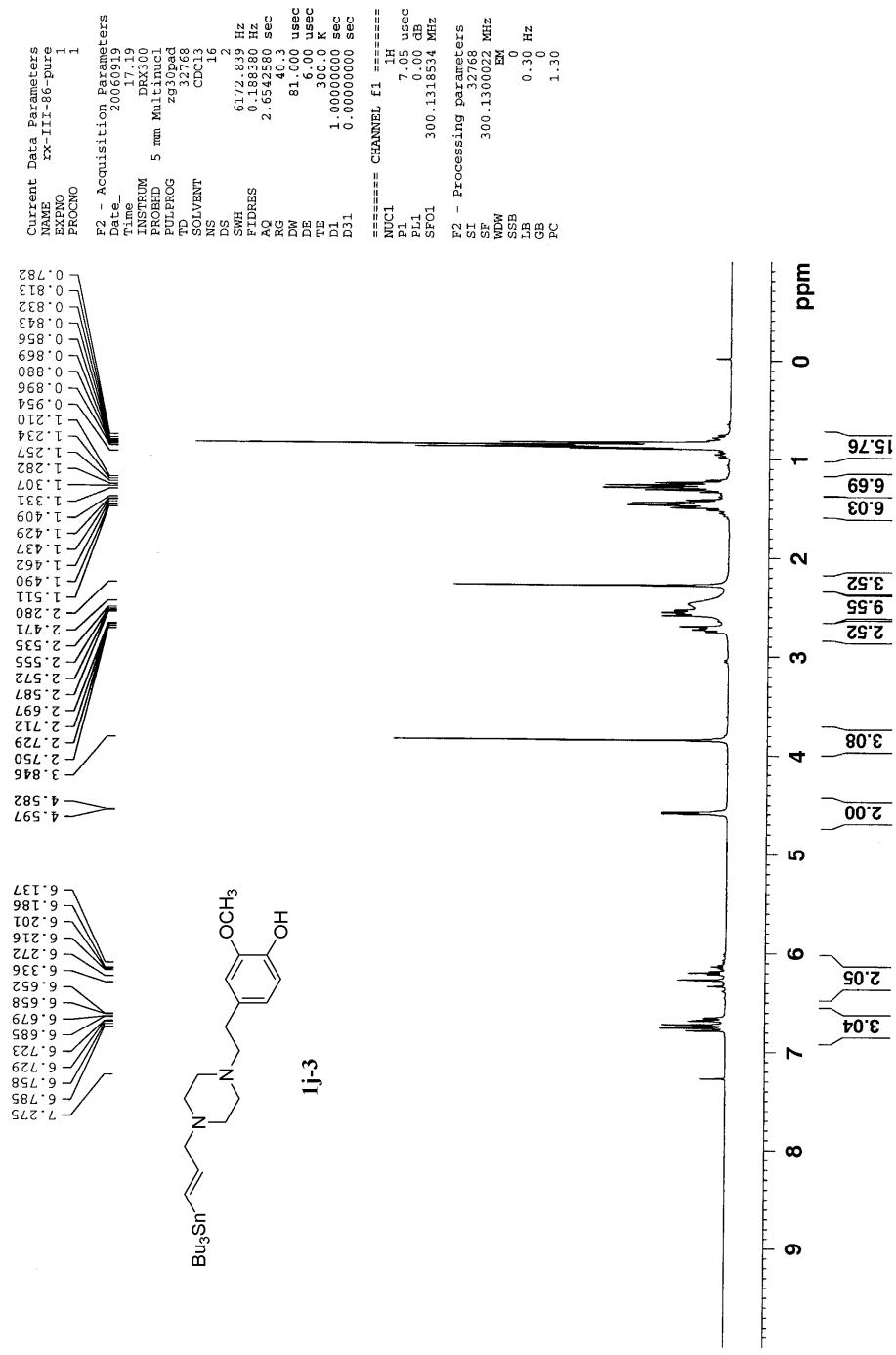
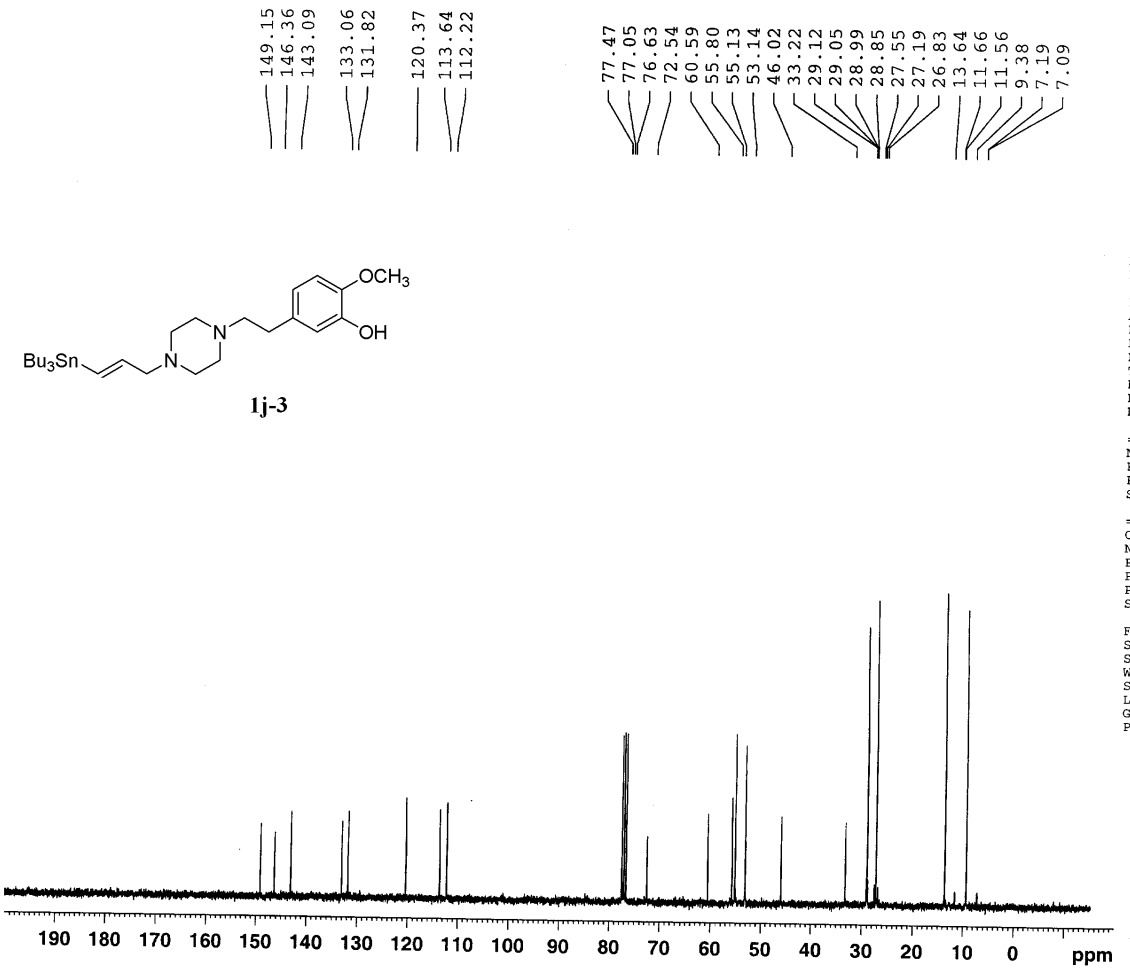
6.826
6.899
3.96
2.57
5.90
3.93
3.00
ppm
1j-2



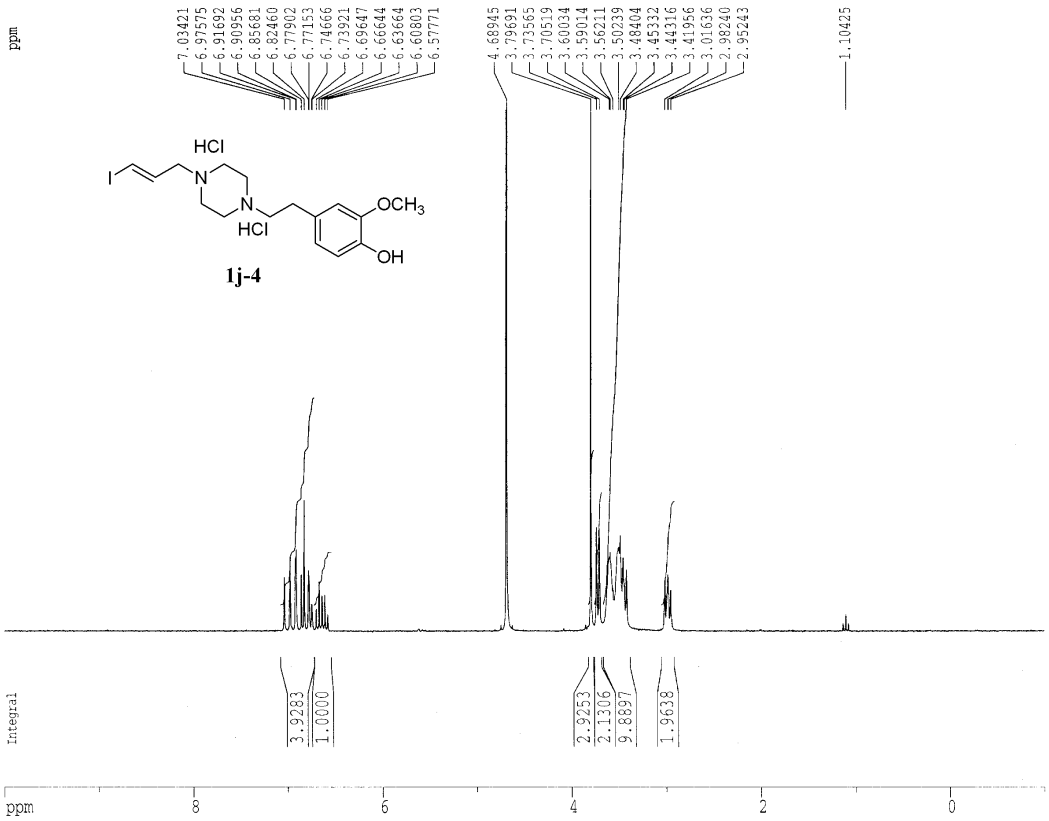

```
Current Data Parameters
NAME      rx-III-78-solid3
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20060729
Time                  16.50
INSTRUM              DRX500
PROBHD   5 mm Multinucl
PULPROG              zgdc30
TD                    65536
SOLVENT               CDCl3
NS                      106
DS                        4
SWH              34013.605 Hz
FIDRES            0.519006 Hz
AQ                0.9634292 sec
RG                    32768
DW                   14.700 usec
DE                    6.00 usec
TE                   300.0 K
D1                2.00000000 sec
d11               0.03000000 sec
D31               0.00000000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                    8.10 usec
PL1                   3.00 dB
SFO1           125.7723786 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                88.00 usec
PL2                   0.00 dB
PL12                 21.00 dB
SFO2           500.1320005 MHz

F2 - Processing parameters
SI                    32768
SF             125.7578011 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```


Current Data Parameters
NAME rx-III-86-pure
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060919
Time 17.19
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 40.3
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
0.782
0.813
0.832
0.843
0.856
0.869
0.880
0.896
0.954
1.210
1.234
1.257
1.282
1.307
1.331
1.409
1.429
1.437
1.462
1.490
1.511
2.280
2.471
2.535
2.555
2.572
2.587
2.697
2.712
2.729
2.750
3.846
4.582
4.597
6.137
6.186
6.201
6.216
6.272
6.336
6.652
6.658
6.679
6.685
6.723
6.729
6.758
6.785
7.275
OCH3
OH
N
N
Bu3Sn
1j-3
ppm
9
8
7
6
5
4
3
2
1
0
3.04
2.05
2.00
3.08
2.52
9.55
3.52
6.03
6.69
15.76



1j-3

```
Current Data Parameters
NAME          rx-III-86-pure
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_               20060919
Time                   17.23
INSTRUM               DRX300
PROBHD   5 mm Multinucl
PULPROG            zgdc30pad
TD                     65536
SOLVENT                CDCl3
NS                        76
DS                         4
SWH                18832.393 Hz
FIDRES             0.287360 Hz
AQ                 1.7400308 sec
RG                     22528
DW                    26.550 usec
DE                     6.00 usec
TE                    300.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
D31                0.00000000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                       9.00 usec
PL1                      5.00 dB
SFO1              75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  100.00 usec
PL2                    120.00 dB
PL12                    25.60 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF                75.4677525 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.30
```

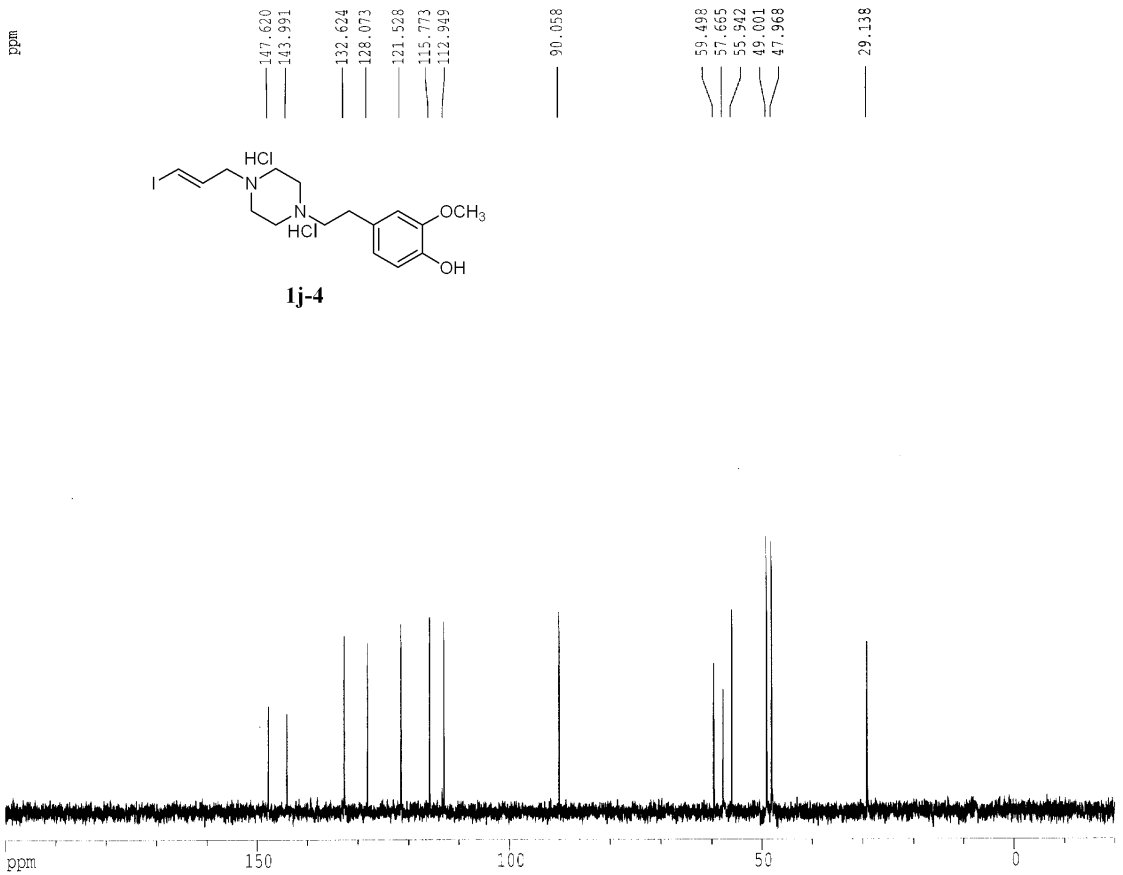


Current Data Parameters
NAME rx-III-89-HCl
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060924
Time 22.20
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 2860
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H

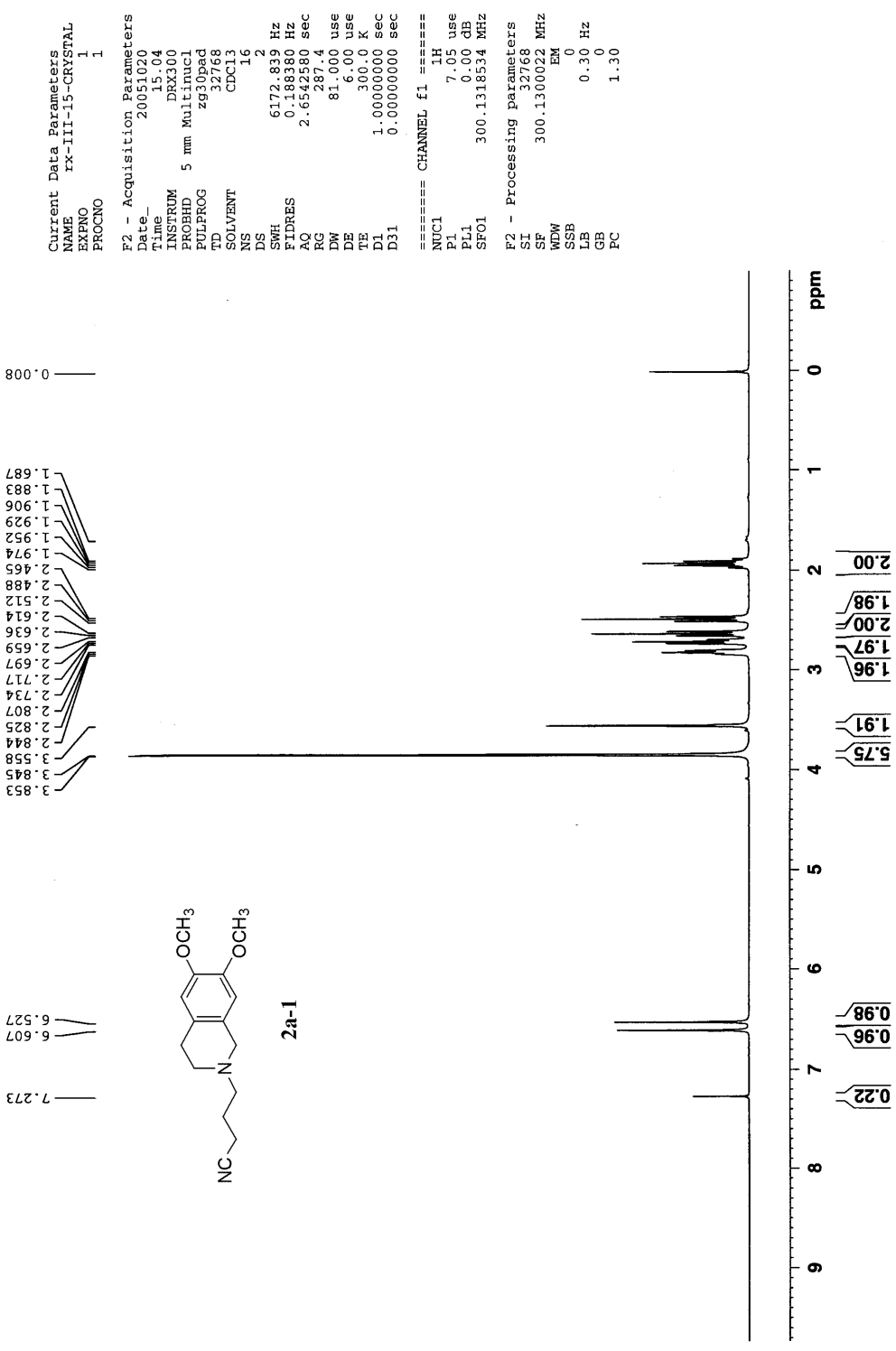
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50

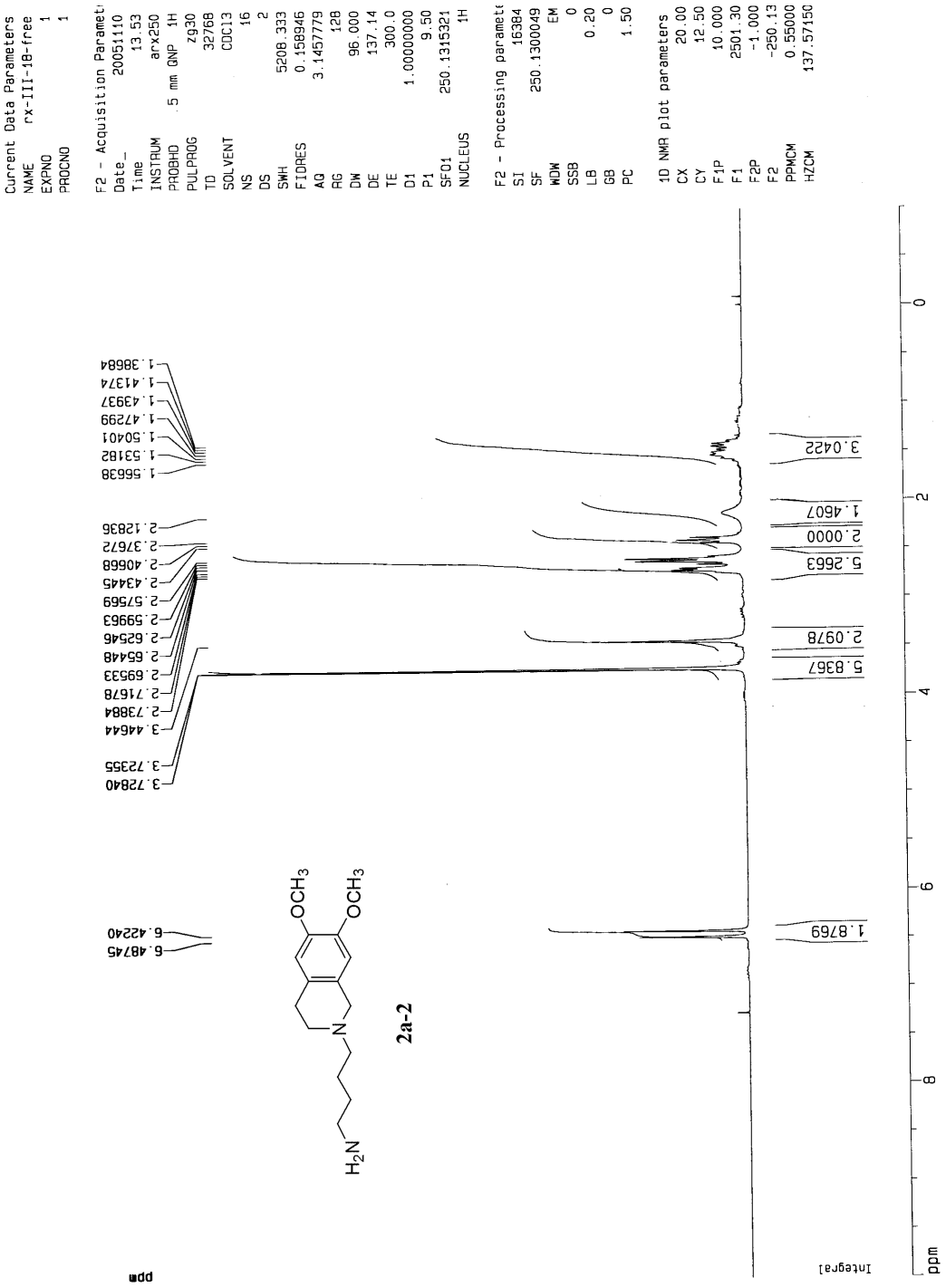
1D NMR plot parameters
CX 20.00 cm
CY 30.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 137.57150 Hz/cm

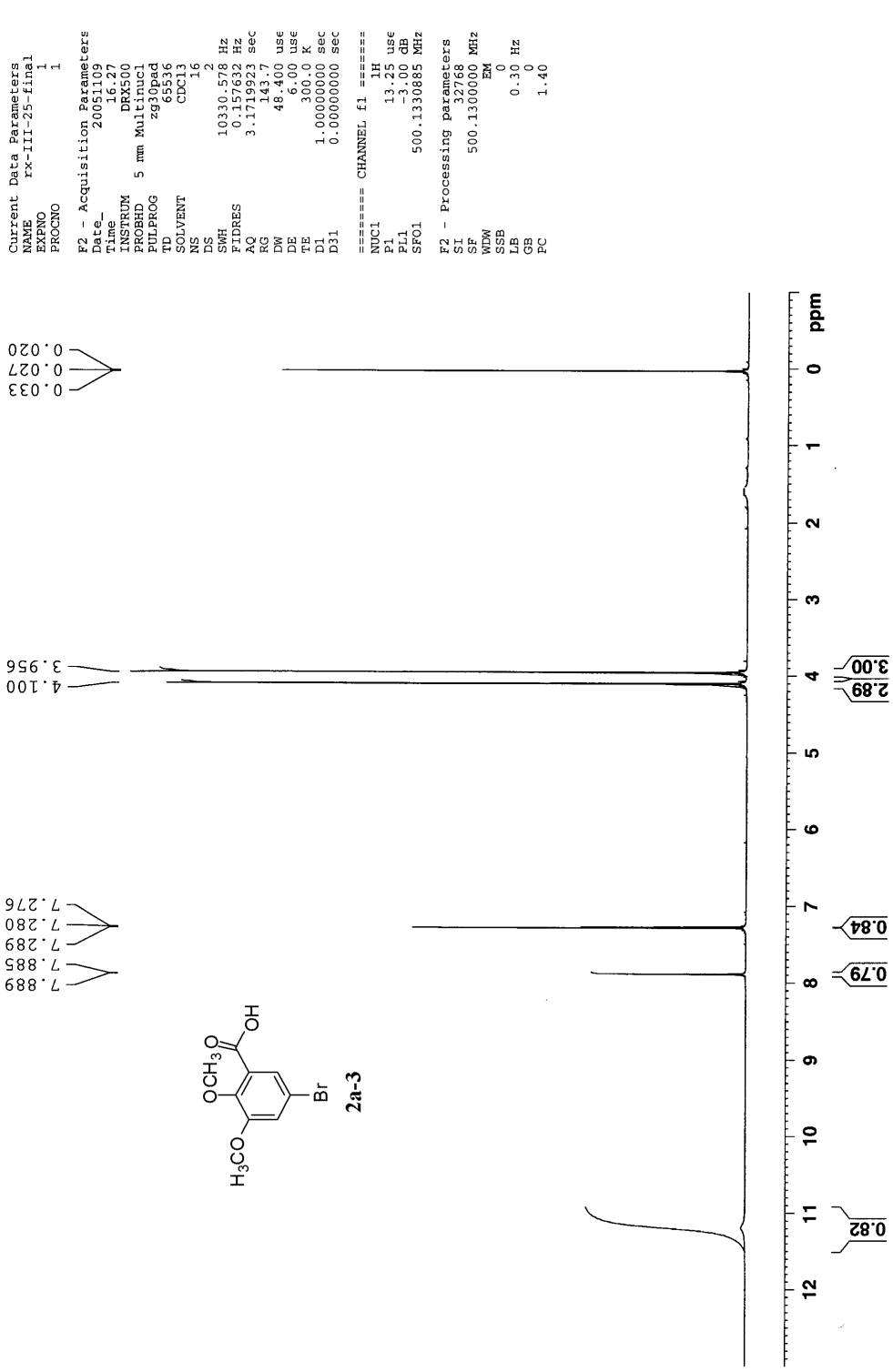


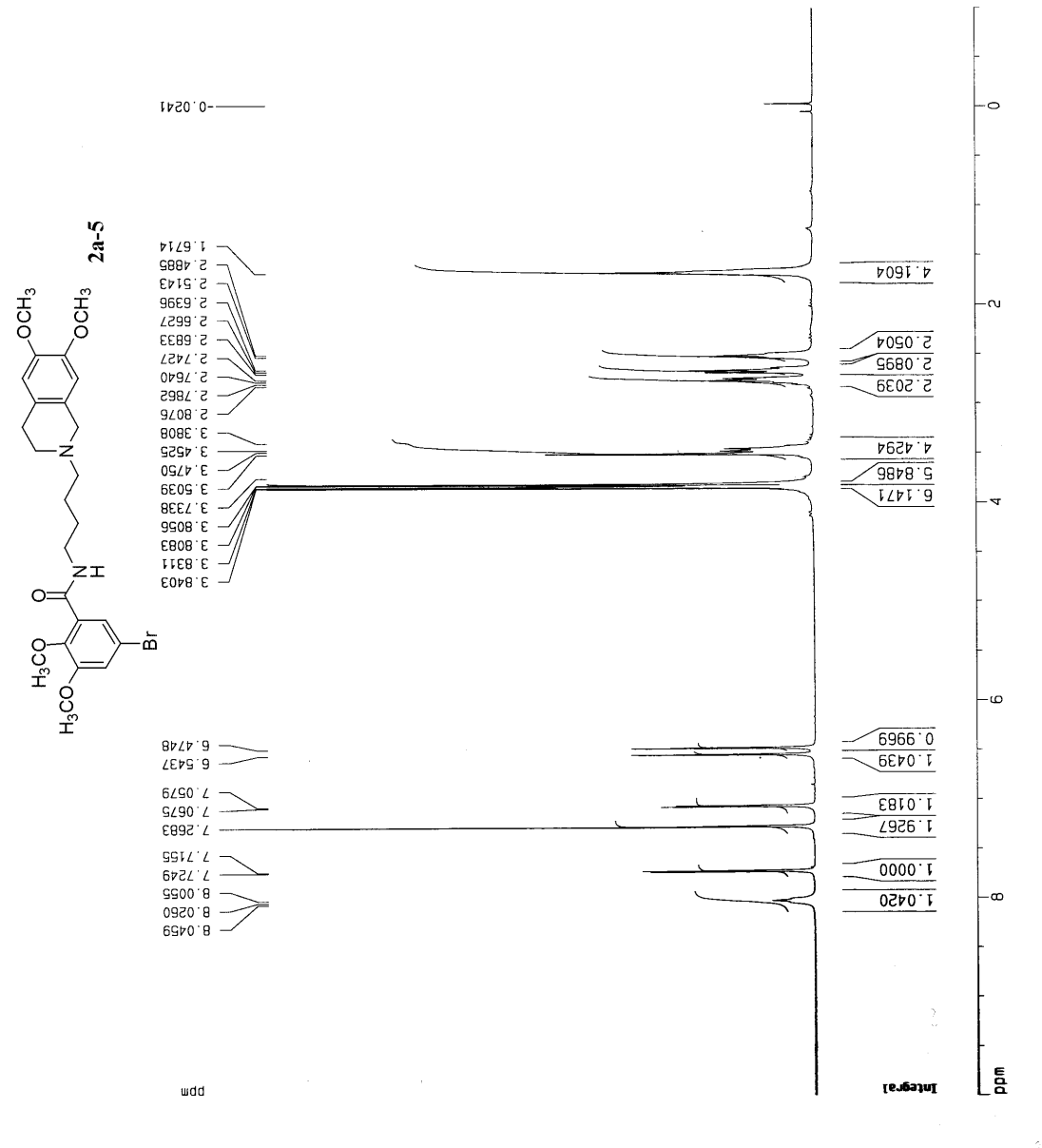
1j-4

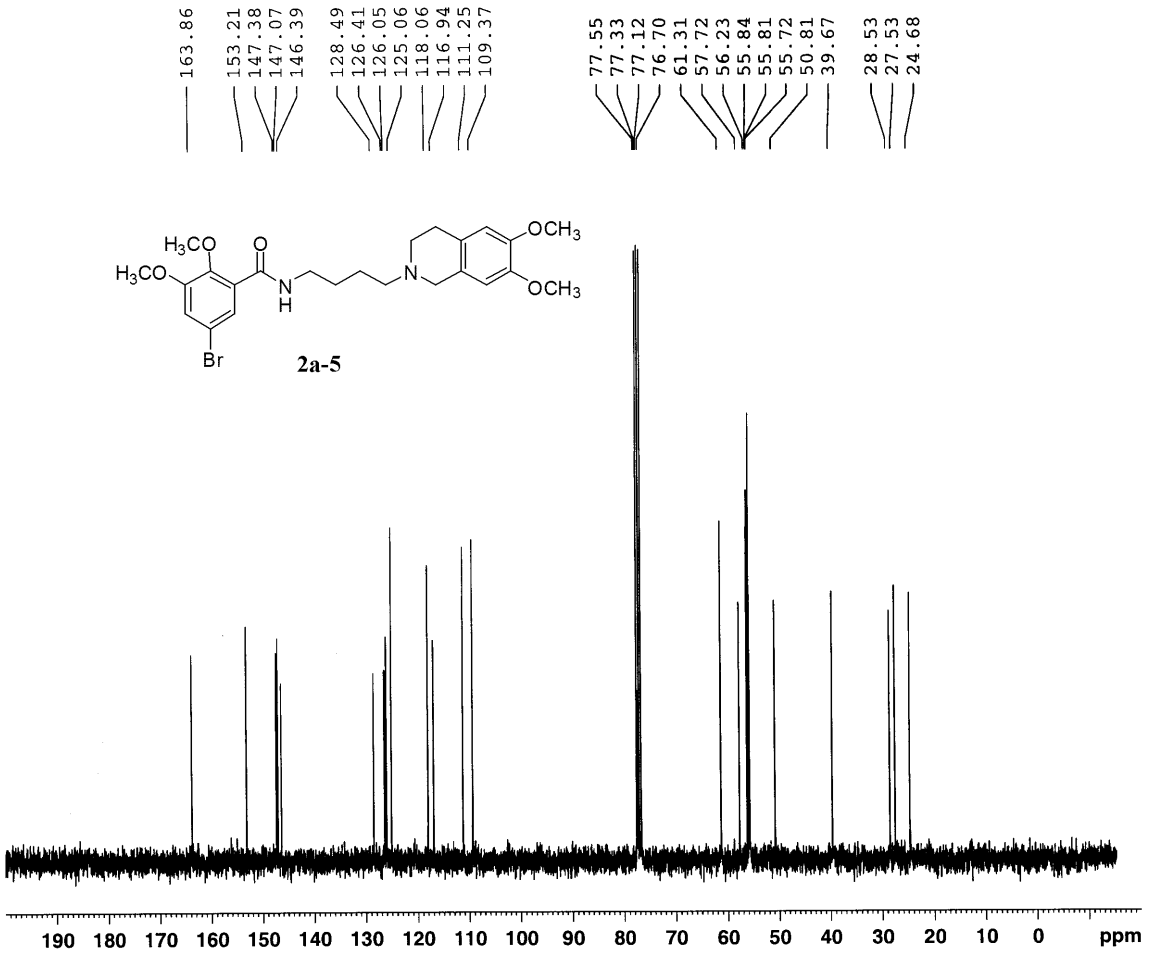
```
Current Data Parameters
NAME      rx-III-89-HCl
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20060924
Time              22.24
INSTRUM          arx250
PROBHD     5 mm QNP  1H
PULPROG          zgdc30
TD                36864
SOLVENT           CDCl3
NS                13560
DS                    4
SWH           17241.379 Hz
FIDRES        0.467702 Hz
AQ            1.0691060 sec
RG                22800
DW               29.000 usec
DE               41.43 usec
TE               300.0 K
D12           0.00002000 sec
DL5              23.00 dB
CPDPRG          waltz16
P31              103.00 usec
D1            2.00000000 sec
P1                8.00 usec
SFO1         62.9023694 MHz
NUCLEUS             13C
D11           0.03000000 sec

F2 - Processing parameters
SI                32768
SF           62.8952440 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
CY                 5.00 cm
F1P              200.000 ppm
F1             12579.05 Hz
F2P              -20.000 ppm
F2             -1257.91 Hz
PPMCM          11.00000 ppm/cm
HZCM          691.84772 Hz/cm
```


Current Data Parameters
NAME rx-III-15-CRYSTAL
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20051020
Time 15.04
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 287.4
DW 81.000 use
DE 6.00 use
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 use
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
0.008
1.687
1.883
1.906
1.929
1.952
1.974
2.465
2.488
2.512
2.614
2.636
2.659
2.697
2.717
2.734
2.807
2.825
2.844
3.558
3.845
3.853
6.527
6.607
7.273
OCH3
OCH3
N
NC
2a-1
ppm
0
1
2
3
4
5
6
7
8
9
2.00
1.98
2.00
1.97
1.96
1.91
5.75
0.98
0.96
0.22


Current Data Parameters
NAME rx-III-18-free
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20051110
Time 13.53
INSTRUM arx250
PROBHD .5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333
FIDRES 0.158946
AQ 3.1457779
RG 128
DW 96.000
DE 137.14
TE 300.0
D1 1.00000000
P1 9.50
SFO1 250.1315321
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049
WDW EM
SSB 0
LB 0.20
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00
CY 12.50
F1P 10.000
F1 2501.30
F2P -1.000
F2 -250.13
PPMCM 0.55000
HZCM 137.57150
1.87
2.09
5.83
2.00
1.46
3.04
5.26
OCH3
OCH3
N
H2N
2a-2
ppm
Integral


Current Data Parameters
NAME rx-III-25-final
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20051109
Time 16.27
INSTRUM DRX500
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 143.7
DW 48.400 use
DE 6.00 use
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 =======
NUC1 1H
P1 13.25 use
PL1 -3.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
0.033
0.027
0.020
4.100
3.956
7.889
7.885
7.289
7.280
7.276
OH
OCH3O
Br
H3CO
2a-3
3.00
2.89
0.84
0.79
0.82
ppm


2a-5
Current Data Parameters
NAME rx-III-35-crud
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060126
Time 23.51
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG z930
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 256
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 9.50 use
SF01 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 20.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 pp
HZCM 137.57150 Hz
-0.0241
1.6714
2.4885
2.5143
2.6396
2.6627
2.6833
2.7427
2.7640
2.7862
2.8076
3.3808
3.4525
3.4750
3.5039
3.7338
3.8056
3.8083
3.8311
3.8403
6.5437
6.4748
7.0579
7.0675
7.2683
7.7155
7.7249
8.0055
8.0260
8.0459
4.1504
2.0504
2.0895
2.2039
4.4294
5.8486
6.1471
0.9969
1.0439
1.0183
1.9267
1.0000
1.0420
ppm
Integral



Current Data Parameters

NAME	rx-III-28-PrepTLC
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20051121
Time	21.50
INSTRUM	DRX300
PROBHD	5 mm Multinucl
PULPROG	zgdc30pad
TD	65536
SOLVENT	CDCl3
NS	78
DS	4
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	22528
DW	26.550 usec
DE	6.00 usec
TE	300.0 K
D1	2.00000000 sec
D11	0.03000000 sec
D31	0.00000000 sec

======== CHANNEL f1 ========

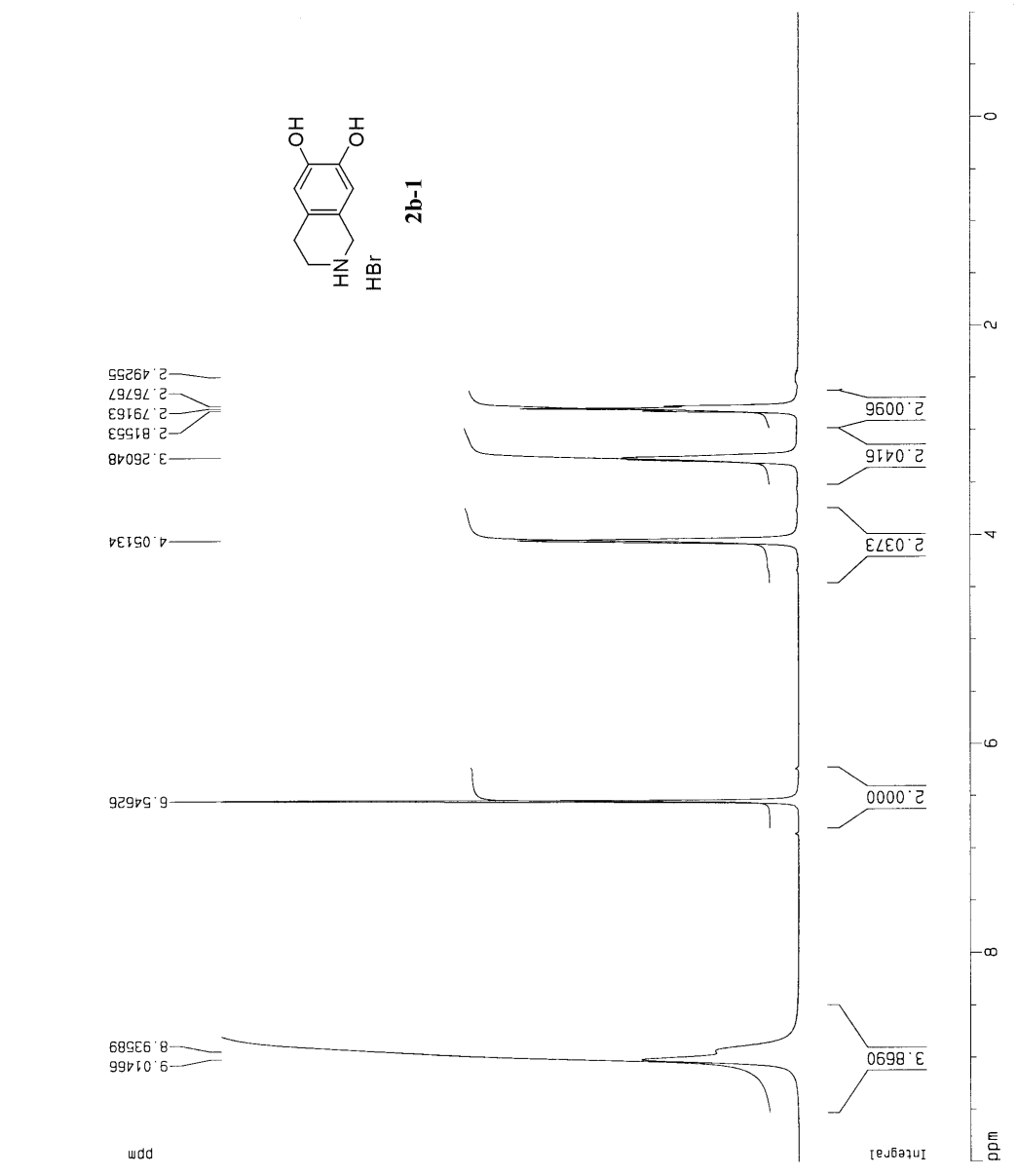
NUC1	13C
P1	9.00 usec
PL1	5.00 dB
SFO1	75.4760107 MHz

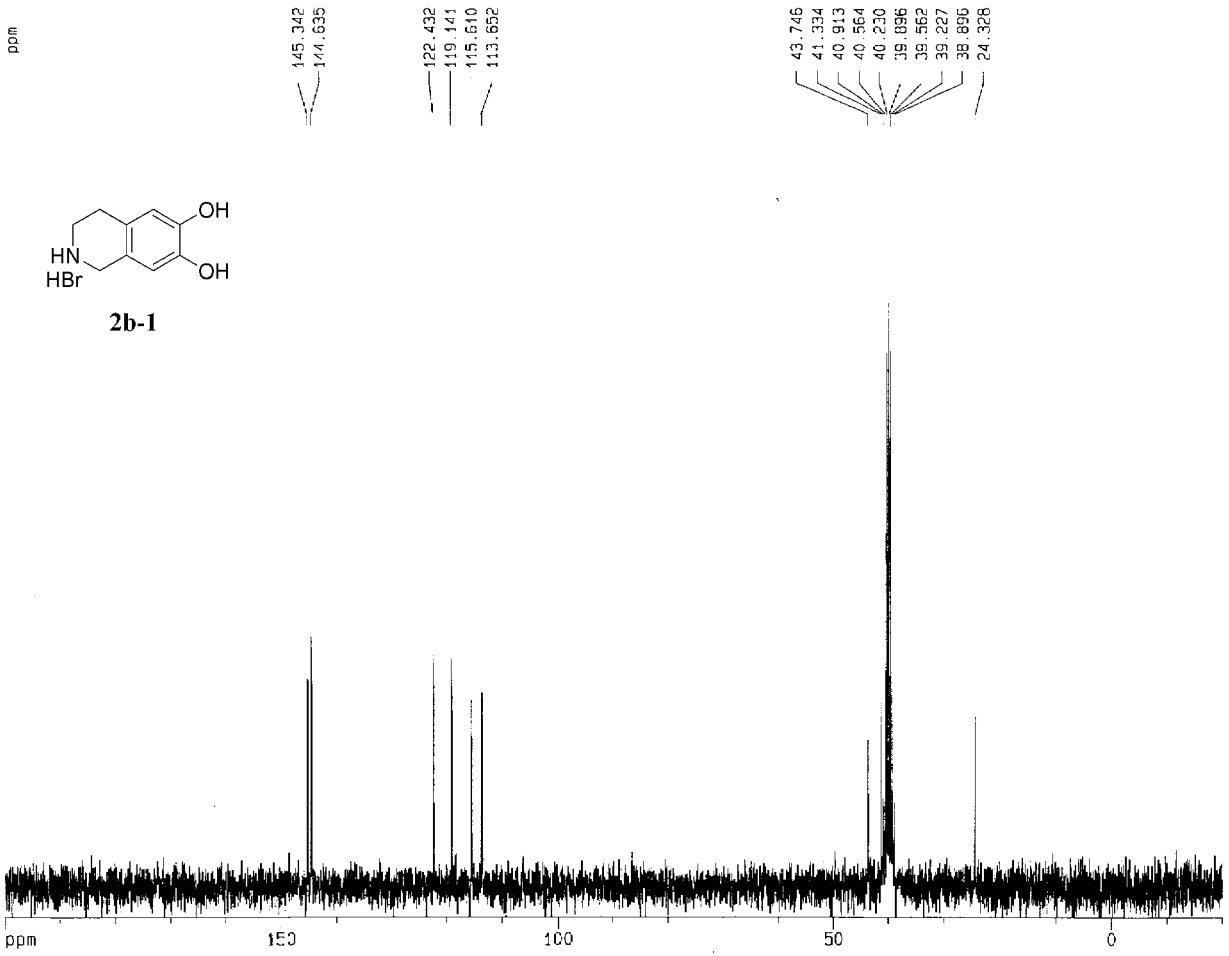
======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	120.00 dB
PL12	25.60 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

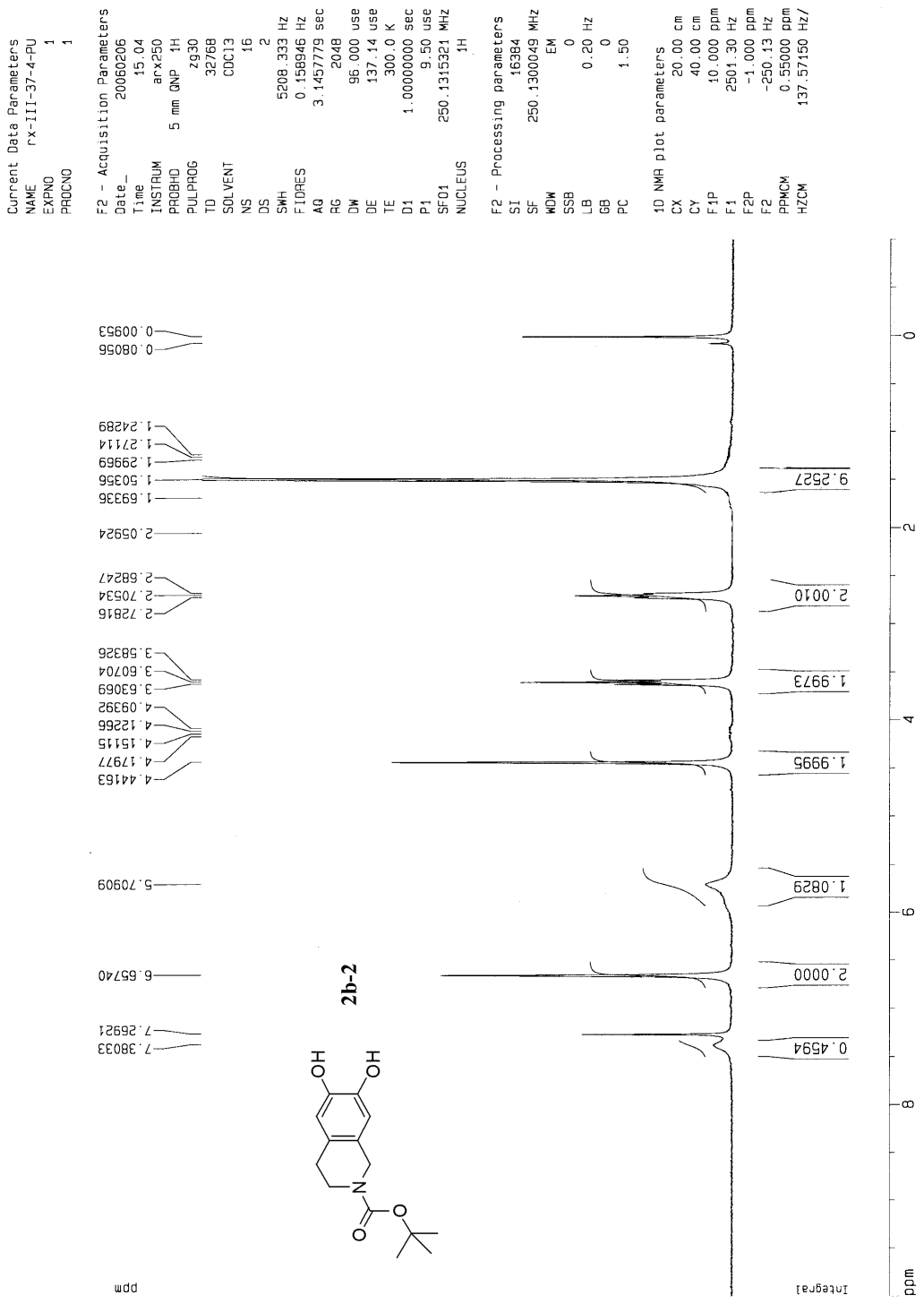
SI	32768
SF	75.4677525 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.30

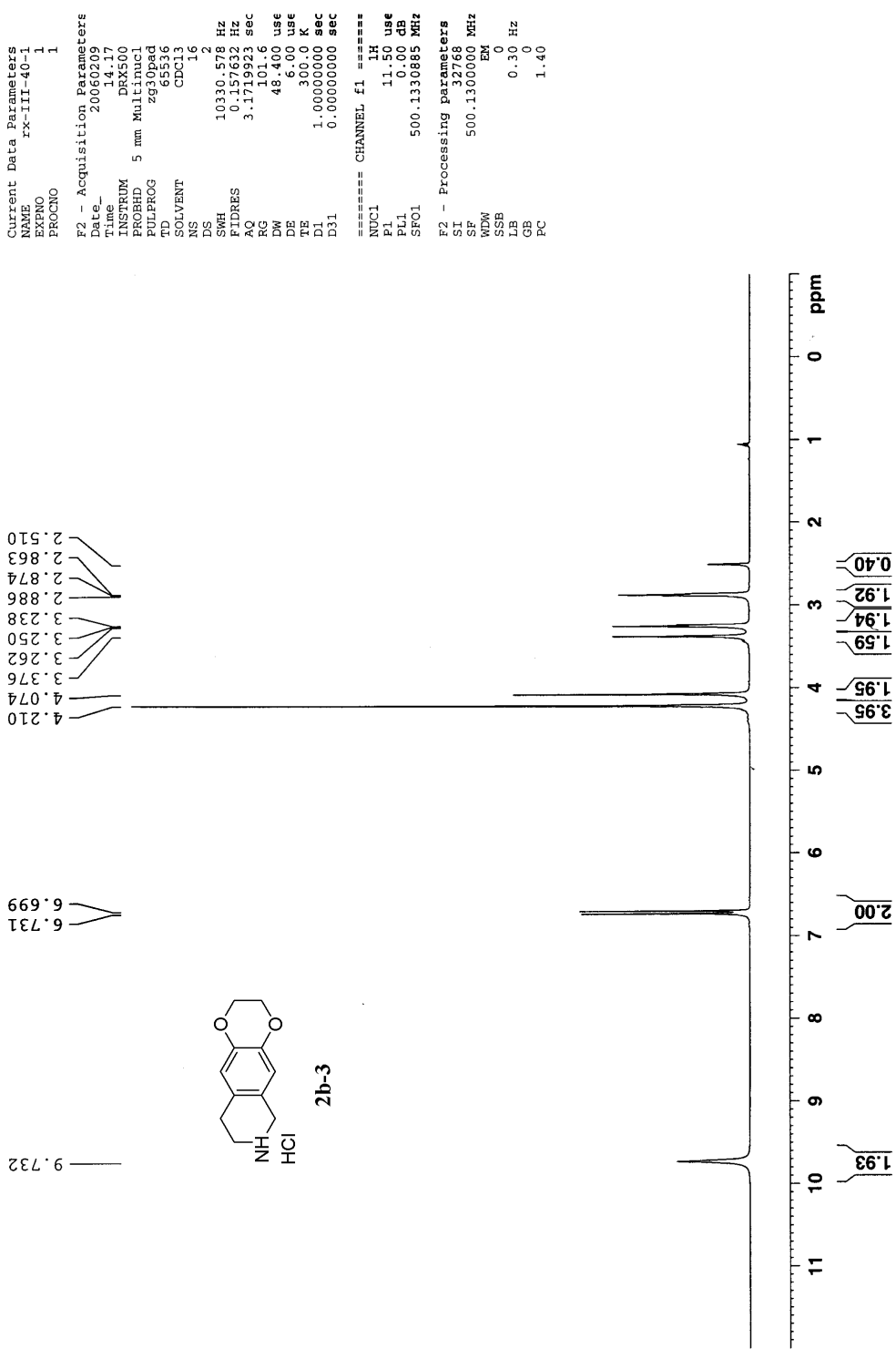

Current Data Parameters
NAME rx-III-40-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060209
Time 13.07
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 1024
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 9.50 use
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
OH
OH
HN
HBr
2b-1
9.01466
8.93589
6.54626
4.05134
3.26048
2.81553
2.79163
2.76767
2.49255
3.8690
2.0000
2.0373
2.0416
2.0096
ppm
Integral
ppm
0
2
4
6
8

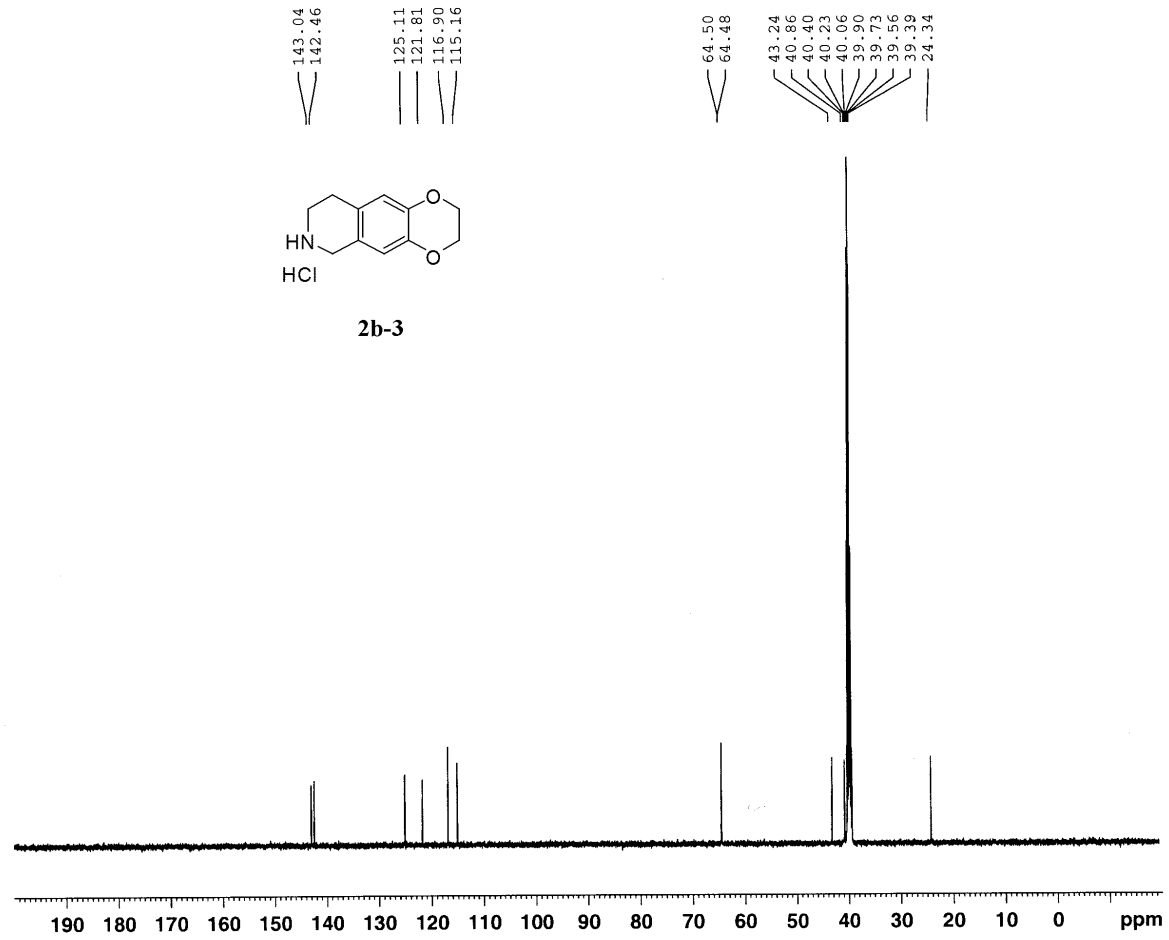


2b-1

```
Current Data Parameters
NAME          cx-III-40-2
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_          20060209
Time                13.10
INSTRUM           arx250
PROBHD     5 mm QNP  1H
PULPROG          zgdc30
TD                 36864
SOLVENT            CDCl3
NS                    44
DS                     4
SWH            17241.379 Hz
FIDRES         0.467702 Hz
AQ             1.0691050 sec
RG                 22800
DW                29.000 use
DE                41.43 use
TE                300.0 K
D12            0.00002000 sec
DL5                23.00 dB
CPDPRG           waltz16
P31               103.00 use
D1             2.00000000 sec
P1                 8.00 use
SFO1           62.9023694 MHz
NUCLEUS               13C
D11            0.03000000 sec

F2 - Processing parameters
SI                 32768
SF             62.8952440 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
CY                 10.00 cm
F1P              200.000 ppm
F1              12579.65 Hz
F2P              -20.000 ppm
F2              -1257.91 Hz
PPMCM            11.00000 ppm
HZCM            691.84772 Hz/
```

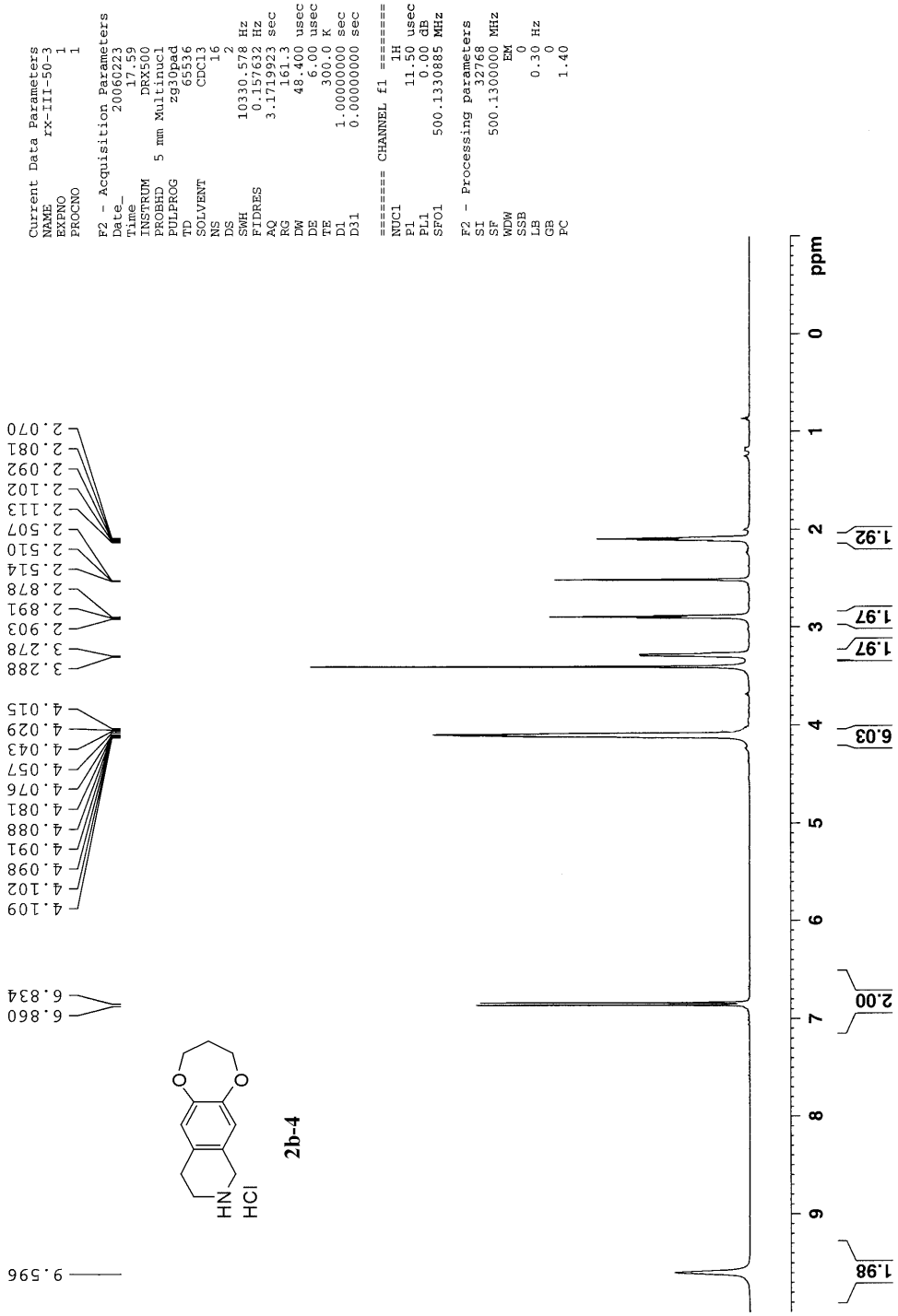

Current Data Parameters
NAME rx-III-37-4-PU
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060206
Time 15.04
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 2048
DW 96.000 use
DE 137.14 use
TE 300.0 K
D1 1.00000000 sec
P1 9.50 use
SF01 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 40.00 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
0.00953
0.08056
1.24289
1.27114
1.29969
1.50356
1.69336
2.05924
2.68247
2.70534
2.72816
3.58326
3.60704
3.63069
4.09392
4.12266
4.15115
4.17977
4.44163
5.70909
6.65740
7.26921
7.38033
9.2527
2.0010
1.9973
1.9995
1.0829
2.0000
0.4594
2b-2
OH
OH
N
O
O
ppm
Integral
ppm
0
2
4
6
8

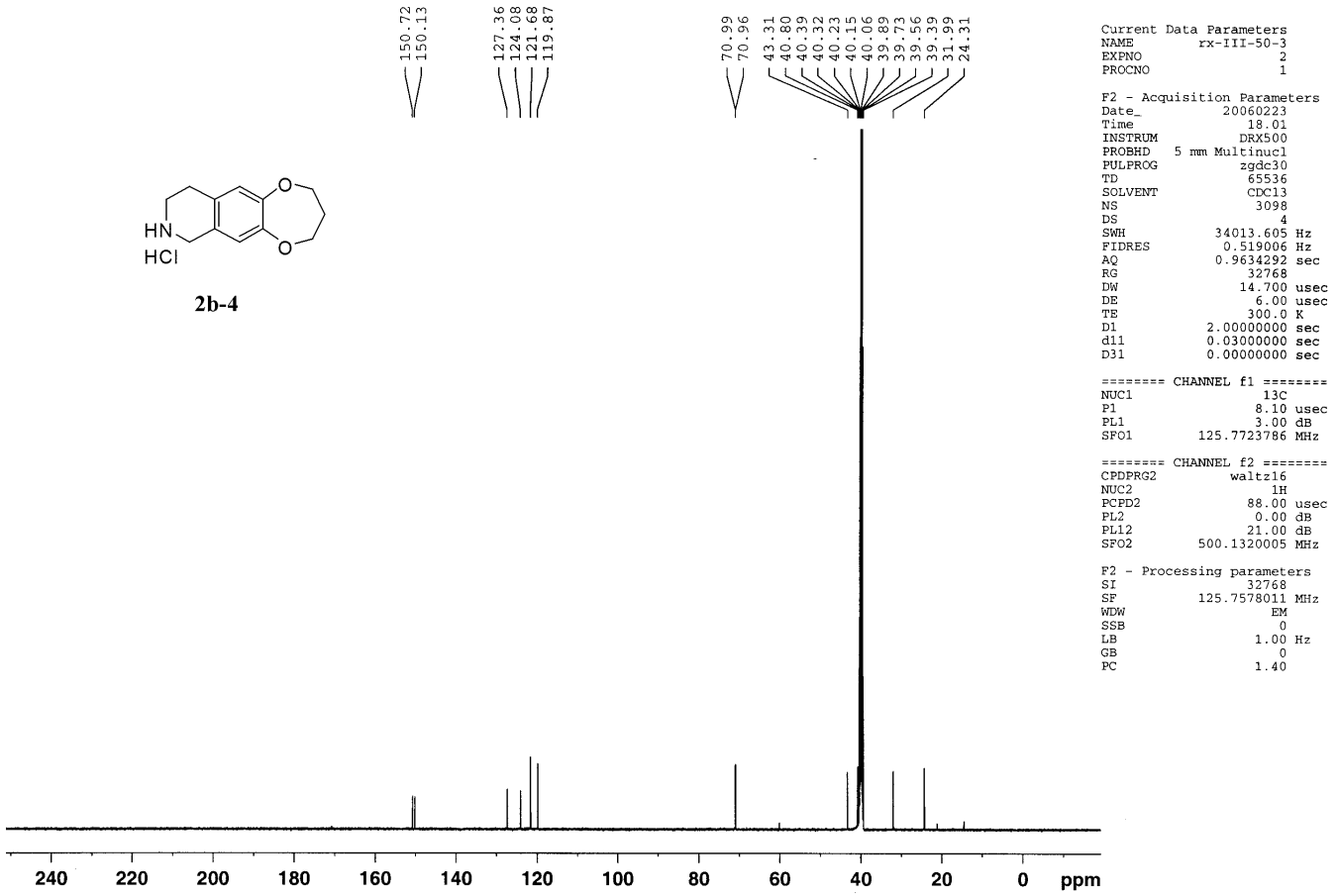

Current Data Parameters
NAME rx-III-40-1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060209
Time 14.17
INSTRUM DRX500
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 101.6
DW 48.400 use
DE 6.00 use
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 11.50 use
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
9.732
6.731
6.699
4.210
4.074
3.376
3.262
3.250
3.238
2.886
2.874
2.863
2.510
NH
HCl
2b-3
2.00
1.93
3.95
1.95
1.59
1.94
1.92
0.40
ppm



2b-3

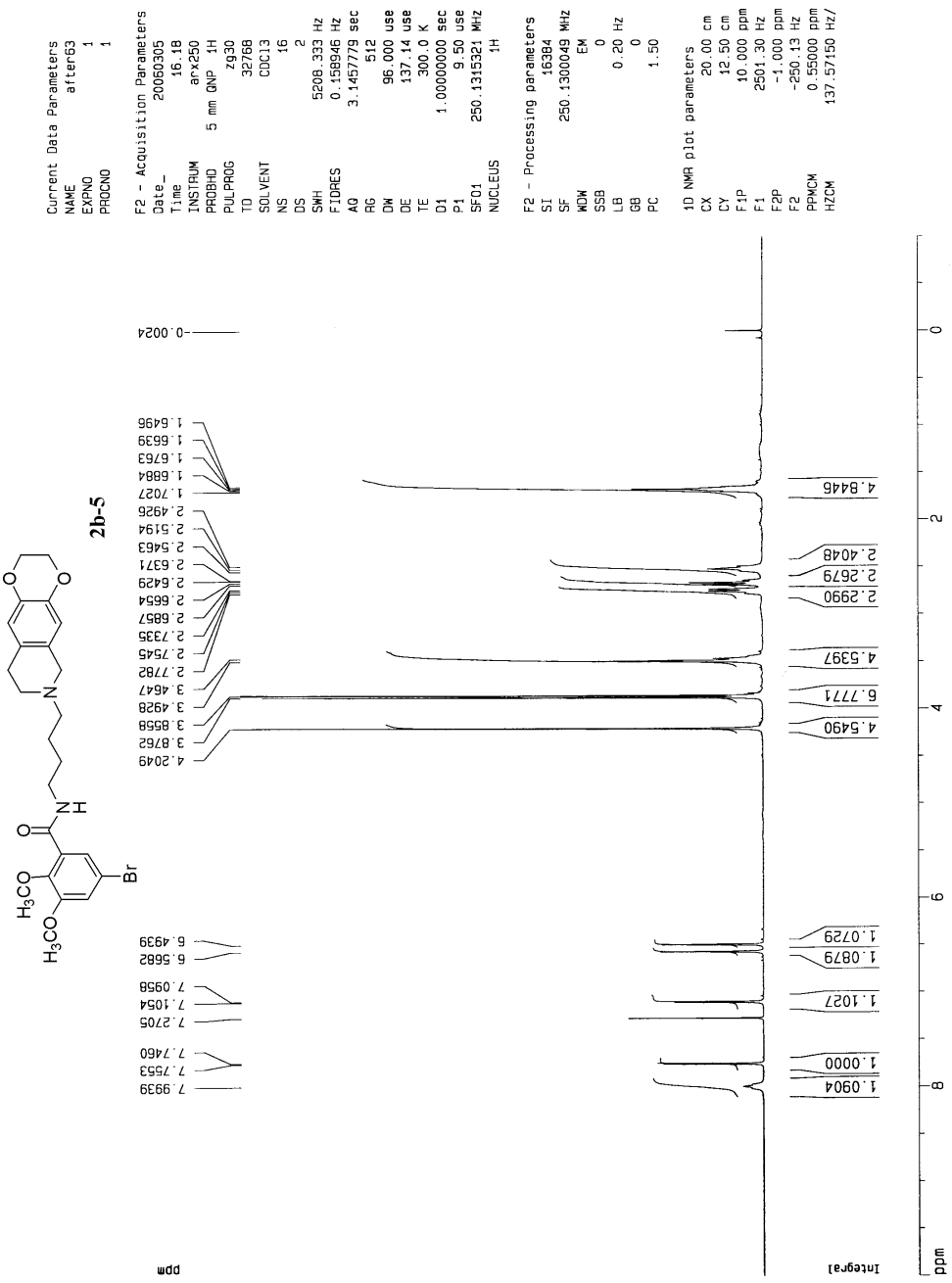
```
Current Data Parameters
NAME          rx-III-40-1
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20060209
Time                14.23
INSTRUM           DRX500
PROBHD   5 mm Multinucl
PULPROG           zgdc30
TD                 65536
SOLVENT            CDCl3
NS                   115
DS                     4
SWH            34013.605 Hz
FIDRES          0.519006 Hz
AQ              0.9634292 sec
RG                 32768
DW                14.700 usec
DE                 6.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
D31          0.00000000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                 8.10 usec
PL1                3.00 dB
SFO1        125.7723786 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2             88.00 usec
PL2                0.00 dB
PL12              21.00 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF          125.7578011 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

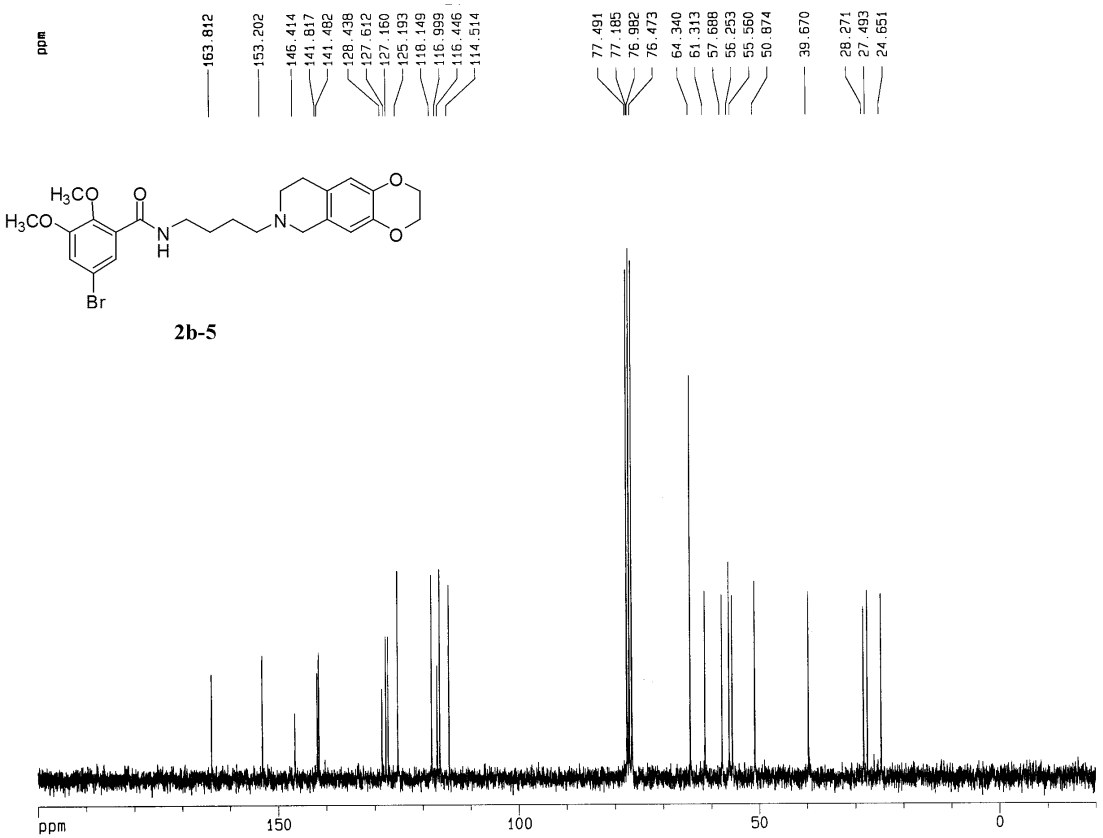

Current Data Parameters
NAME rx-III-50-3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060223
Time 17.59
INSTRUM DRX500
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 161.3
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 11.50 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
9.596
6.860
6.834
4.109
4.102
4.098
4.091
4.088
4.081
4.076
4.057
4.043
4.029
4.015
3.288
3.278
2.903
2.891
2.878
2.514
2.510
2.507
2.113
2.102
2.092
2.081
2.070
HN
HCl
2b-4
1.98
2.00
6.03
1.97
1.97
1.97
1.92
ppm



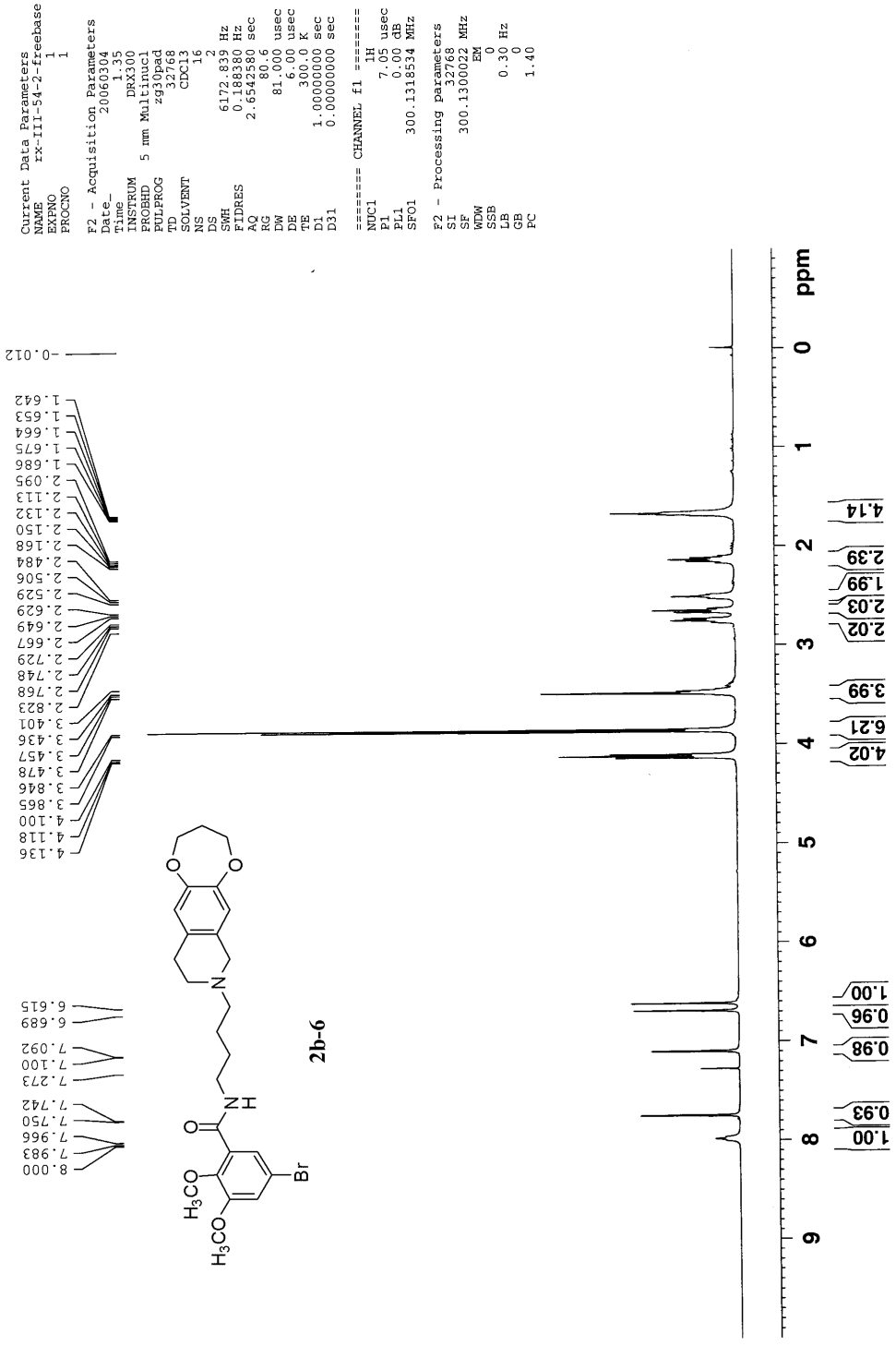
2b-4

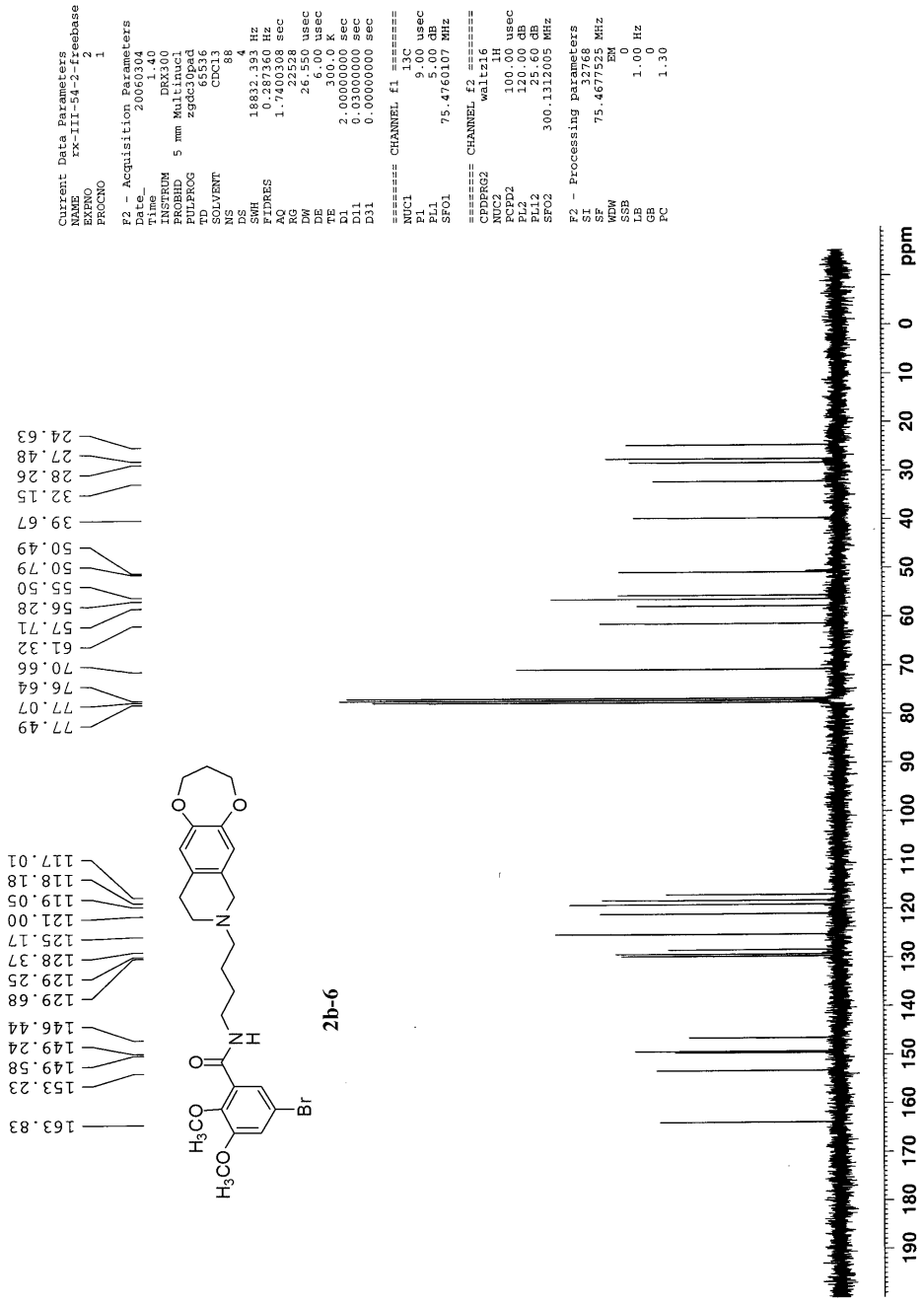
```
Current Data Parameters
NAME          rx-III-50-3
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20060223
Time                18.01
INSTRUM           DRX500
PROBHD   5 mm Multinucl
PULPROG           zgdc30
TD                 65536
SOLVENT            CDCl3
NS                  3098
DS                     4
SWH           34013.605 Hz
FIDRES         0.519006 Hz
AQ             0.9634292 sec
RG                 32768
DW                14.700 usec
DE                 6.00 usec
TE                300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
D31           0.00000000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                 8.10 usec
PL1                3.00 dB
SFO1        125.7723786 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             88.00 usec
PL2                0.00 dB
PL12              21.00 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF          125.7578011 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```


2b-5
Current Data Parameters
NAME afterG3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060305
Time 16.18
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 512
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 2501.30 Hz
F2P -1.000 ppm
F2 -250.13 Hz
PPMCM 0.55000 ppm
HZCM 137.57150 Hz/
0.0024
1.6496
1.6539
1.6763
1.6884
1.7027
2.4926
2.5194
2.5463
2.6371
2.6429
2.6654
2.6857
2.7335
2.7545
2.7782
3.4647
3.4928
3.8558
3.8762
4.2049
6.4939
6.5682
7.0958
7.1054
7.2705
7.7460
7.7553
7.9939
4.8446
2.4048
2.2679
2.2990
4.5397
6.7771
4.5490
1.0729
1.0879
1.1027
1.0000
1.0904
ppm
Integral
0
2
4
6
8

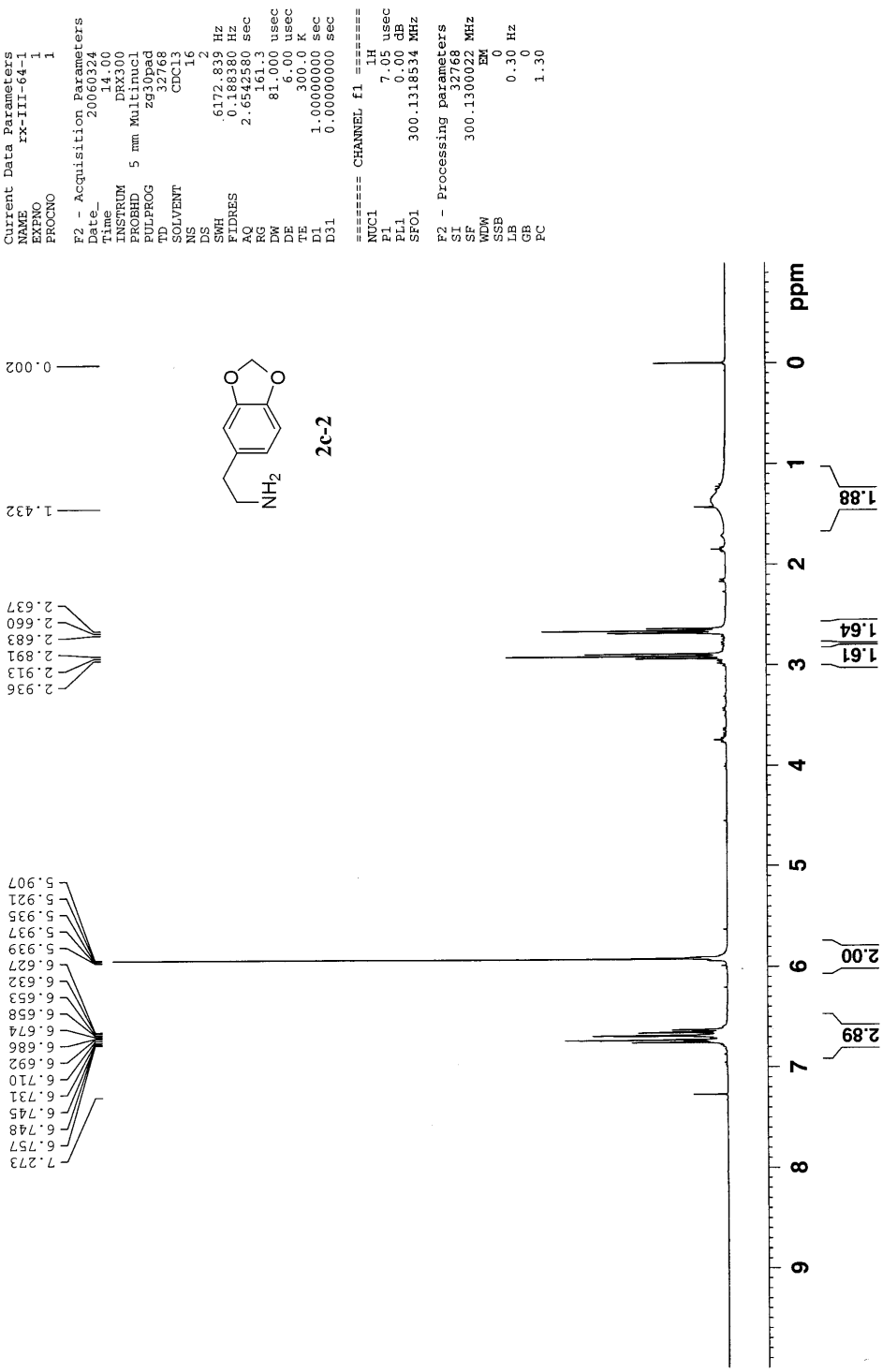


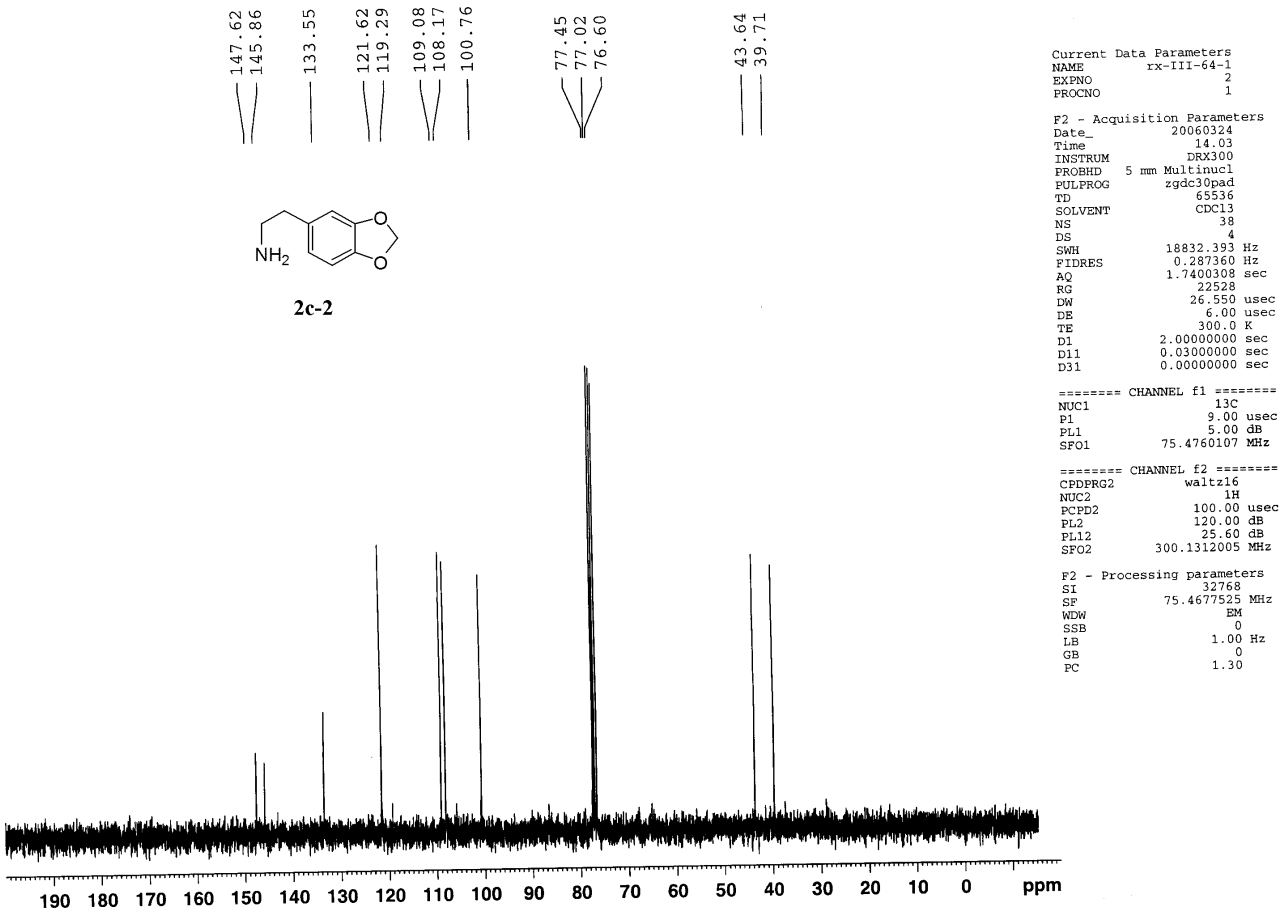

```
Current Data Parameters
NAME      rx-III-54-1-fr
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20060304
Time                1.59
INSTRUM           arx250
PROBHD     5 mm QNP  1H
PULPROG           zgdc30
TD                 36864
SOLVENT            CDCl3
NS                   489
DS                     4
SWH           17241.379 Hz
FIDRES        0.467702 Hz
AQ            1.0691060 sec
RG                 22800
DW                29.000 use
DE                41.43 use
TE                300.0 K
D12           0.00002000 sec
DL5                23.00 dB
CPDPRG            waltz16
P31               103.00 use
D1            2.00000000 sec
P1                 8.00 use
SFO1          62.9023694 MHz
NUCLEUS              13C
D11           0.03000000 sec

F2 - Processing parameters
SI                 32768
SF            62.8952440 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
CY                10.00 cm
F1P              200.000 ppm
F1              12579.05 Hz
F2P              -20.000 ppm
F2              -1257.91 Hz
PPMCM           11.00000 ppm
HZCM          691.84772 Hz/
```


Current Data Parameters
NAME rx-III-54-2-freebase
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060304
Time_ 1.35
INSTRUM DRX300
PROBHD 5 mm Multinuc1
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 80.6
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
-0.012
1.642
1.653
1.664
1.675
1.686
2.095
2.113
2.132
2.150
2.168
2.484
2.506
2.529
2.629
2.649
2.667
2.729
2.748
2.768
2.823
3.401
3.436
3.457
3.478
3.846
3.865
4.100
4.118
4.136
6.615
6.689
7.092
7.100
7.273
7.742
7.750
7.966
7.983
8.000
2b-6
ppm
4.14
2.39
1.99
2.03
2.02
3.99
6.21
4.02
1.00
0.96
0.98
1.00
0.93


Current Data Parameters
NAME rx-III-54-2-freebase
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060304
Time 1.40
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zgdc30pad
TD 65536
SOLVENT CDCl3
NS 88
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 5.00 dB
SFO1 75.4760107 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677525 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.30
77.49
77.07
76.64
70.66
61.32
57.71
56.28
55.50
50.79
50.49
39.67
32.15
28.26
27.48
24.63
163.83
153.23
149.58
149.24
146.44
129.68
129.25
128.37
125.17
121.00
119.05
118.18
117.01
2b-6
ppm

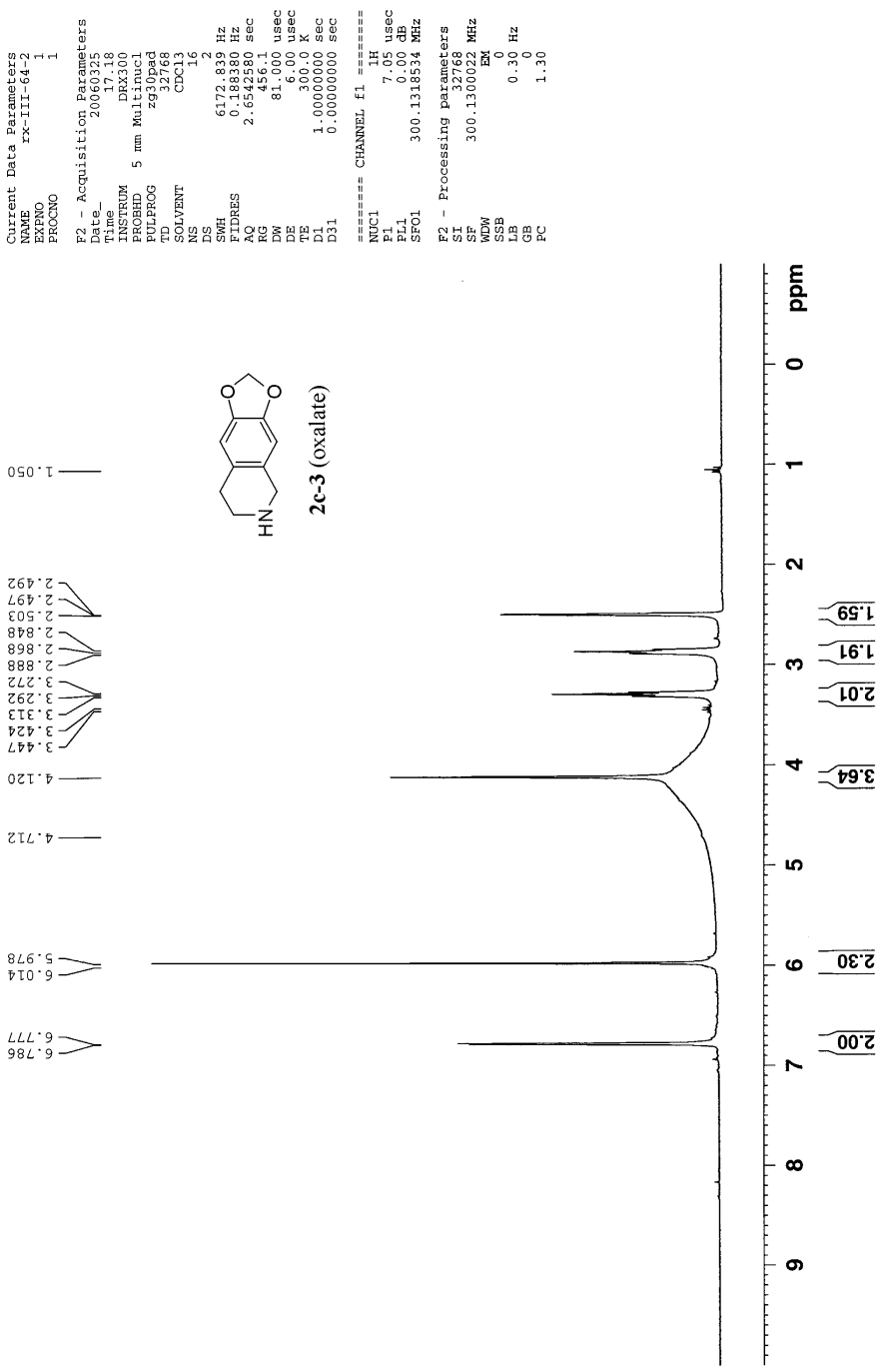
Current Data Parameters
NAME rx-III-63-1-cr
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060322
Time 21.58
INSTRUM arx250
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5208.333 Hz
FIDRES 0.158946 Hz
AQ 3.1457779 sec
RG 2048
DW 96.000 usec
DE 137.14 usec
TE 300.0 K
D1 1.00000000 sec
P1 9.50 usec
SFO1 250.1315321 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 250.1300049 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.50
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 8.844 ppm
F1 2212.20 Hz
F2P 5.057 ppm
F2 1264.79 Hz
PPMCM 0.18938 ppm
HZCM 47.37057 Hz/
2c-1
6.06701
7.95442
7.90014
7.46637
7.45067
7.27059
7.10656
7.09975
7.07450
7.06762
7.00693
7.00005
6.89247
6.86038
2.0000
0.9510
0.9605
0.9783
0.9600
0.9782
ppm
Integral

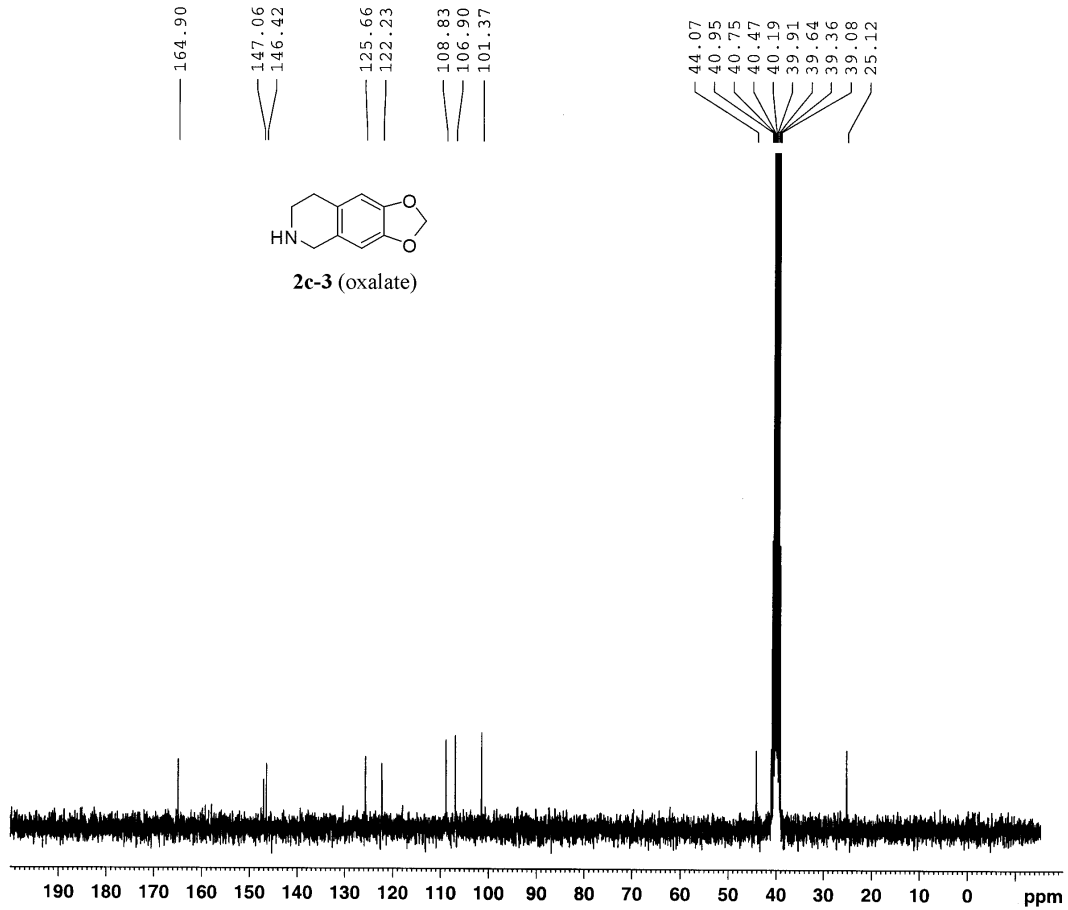

Current Data Parameters
NAME rx-III-64-1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060324
Time 14.00
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 161.3
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
0.002
1.432
2.637
2.660
2.683
2.891
2.913
2.936
5.907
5.921
5.935
5.937
5.939
6.627
6.632
6.653
6.658
6.674
6.686
6.692
6.710
6.731
6.745
6.748
6.757
7.273
NH2
2c-2
1.88
1.64
1.61
2.00
2.89
ppm



2c-2

```
Current Data Parameters
NAME                  rx-III-64-1
EXPNO                           2
PROCNO                          1

F2 - Acquisition Parameters
Date_                    20060324
Time                        14.03
INSTRUM                    DRX300
PROBHD   5 mm Multinucl
PULPROG                 zgdc30pad
TD                          65536
SOLVENT                     CDCl3
NS                             38
DS                              4
SWH                   18832.393 Hz
FIDRES                 0.287360 Hz
AQ                     1.7400308 sec
RG                          22528
DW                       26.550 usec
DE                        6.00 usec
TE                        300.0 K
D1                    2.00000000 sec
D11                   0.03000000 sec
D31                   0.00000000 sec

======== CHANNEL f1 ========
NUC1                         13C
P1                         9.00 usec
PL1                        5.00 dB
SFO1                 75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                    100.00 usec
PL2                       120.00 dB
PL12                       25.60 dB
SFO2                300.1312005 MHz

F2 - Processing parameters
SI                           32768
SF                   75.4677525 MHz
WDW                             EM
SSB                              0
LB                            1.00 Hz
GB                               0
PC                            1.30
```


Current Data Parameters
NAME rx-III-64-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060325
Time_ 17.18
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 456.1
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz
F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30
1.050
2.492
2.497
2.503
2.848
2.868
2.888
3.272
3.292
3.313
3.424
3.447
4.120
4.712
5.978
6.014
6.777
6.786
HN
2c-3 (oxalate)
1.59
1.91
2.01
3.64
2.30
2.00
ppm



2c-3 (oxalate)

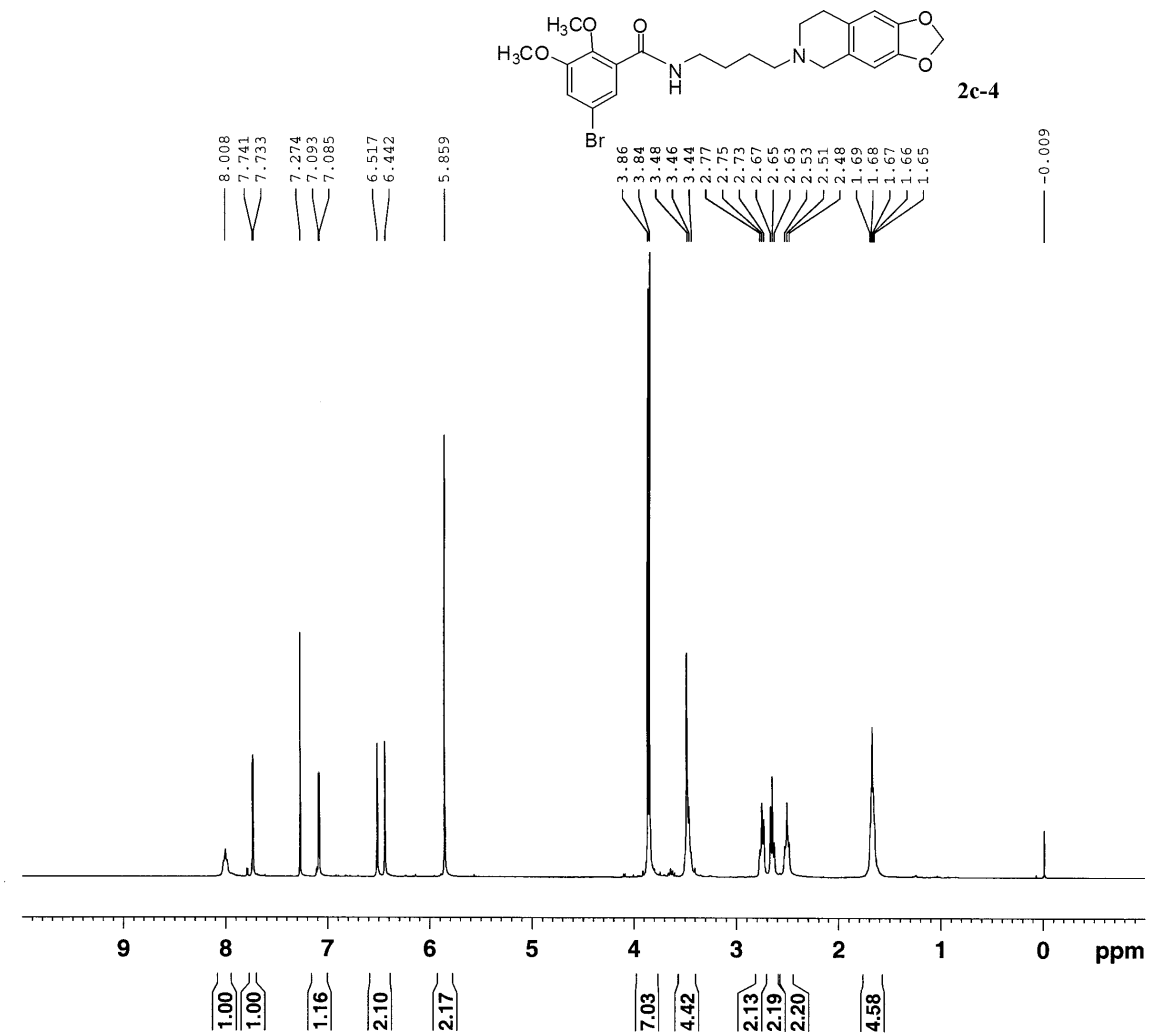
Current Data Parameters
NAME rx-III-64-2
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060325
Time 17.22
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zgdc30pad
TD 65536
SOLVENT CDCl3
NS 307
DS 4
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 22528
DW 26.550 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
D31 0.00000000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 5.00 dB
SFO1 75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 120.00 dB
PL12 25.60 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677525 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

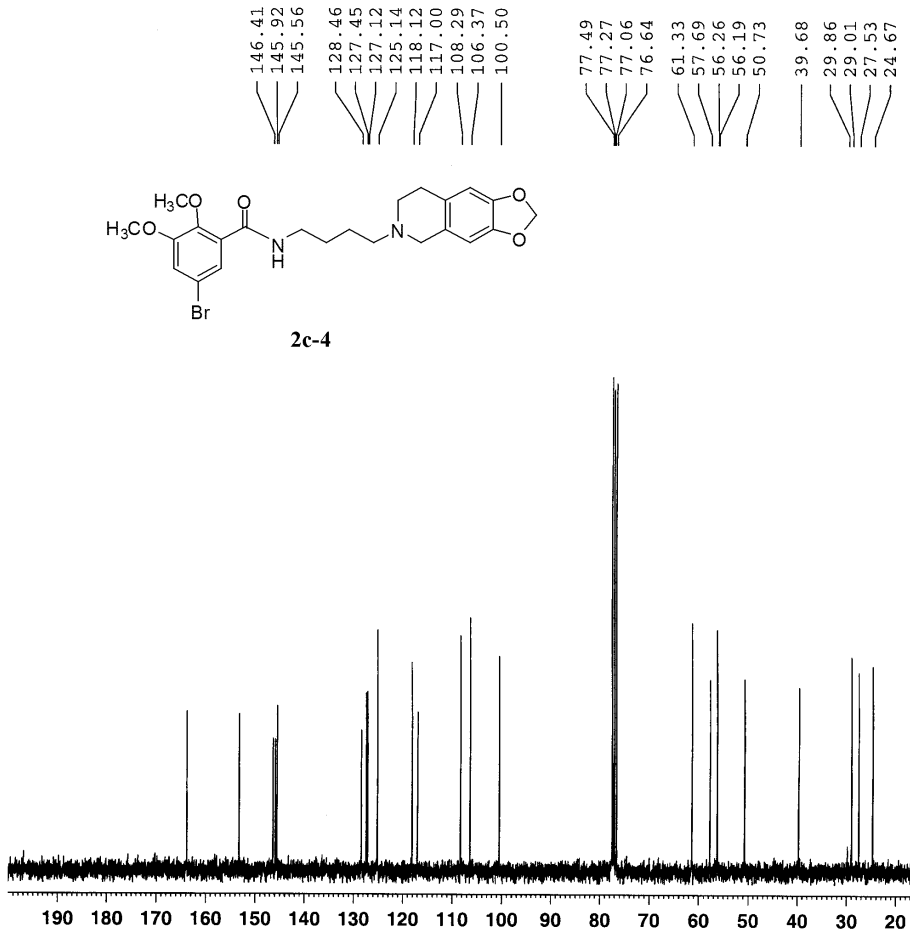


Current Data Parameters
NAME rx-III--65-3-freebase
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060403
Time 18.07
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 90.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec

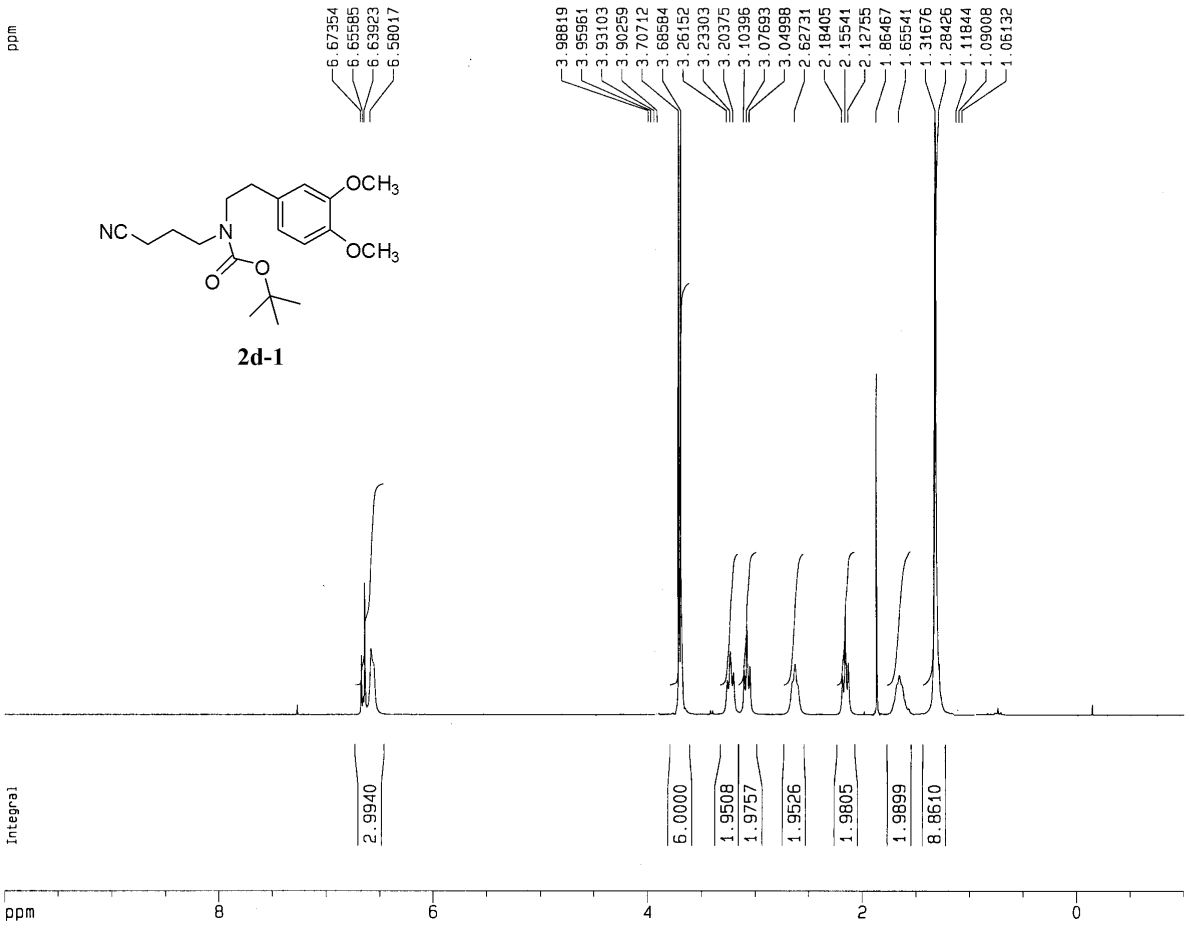
======== CHANNEL f1 ========
NUC1 1H
P1 7.05 usec
PL1 0.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.30



2c-4

```
Current Data Parameters
NAME      rx-III--65-3-freebase
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_               20060403
Time                   18.11
INSTRUM              DRX300
PROBHD    5 mm Multinucl
PULPROG          zgdc30pad
TD                   65536
SOLVENT              CDCl3
NS                      85
DS                       4
SWH               18832.393 Hz
FIDRES             0.287360 Hz
AQ                 1.7400308 sec
RG                     22528
DW                    26.550 usec
DE                     6.00 usec
TE                    300.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
D31                0.00000000 sec

======== CHANNEL f1 ========
NUC1                     13C
P1                      9.00 usec
PL1                     5.00 dB
SFO1              75.4760107 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                  120.00 dB
PL12                  25.60 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF                75.4677525 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.30
```



2d-1

Current Data Parameters

NAME	rx-III-57-1-cr
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

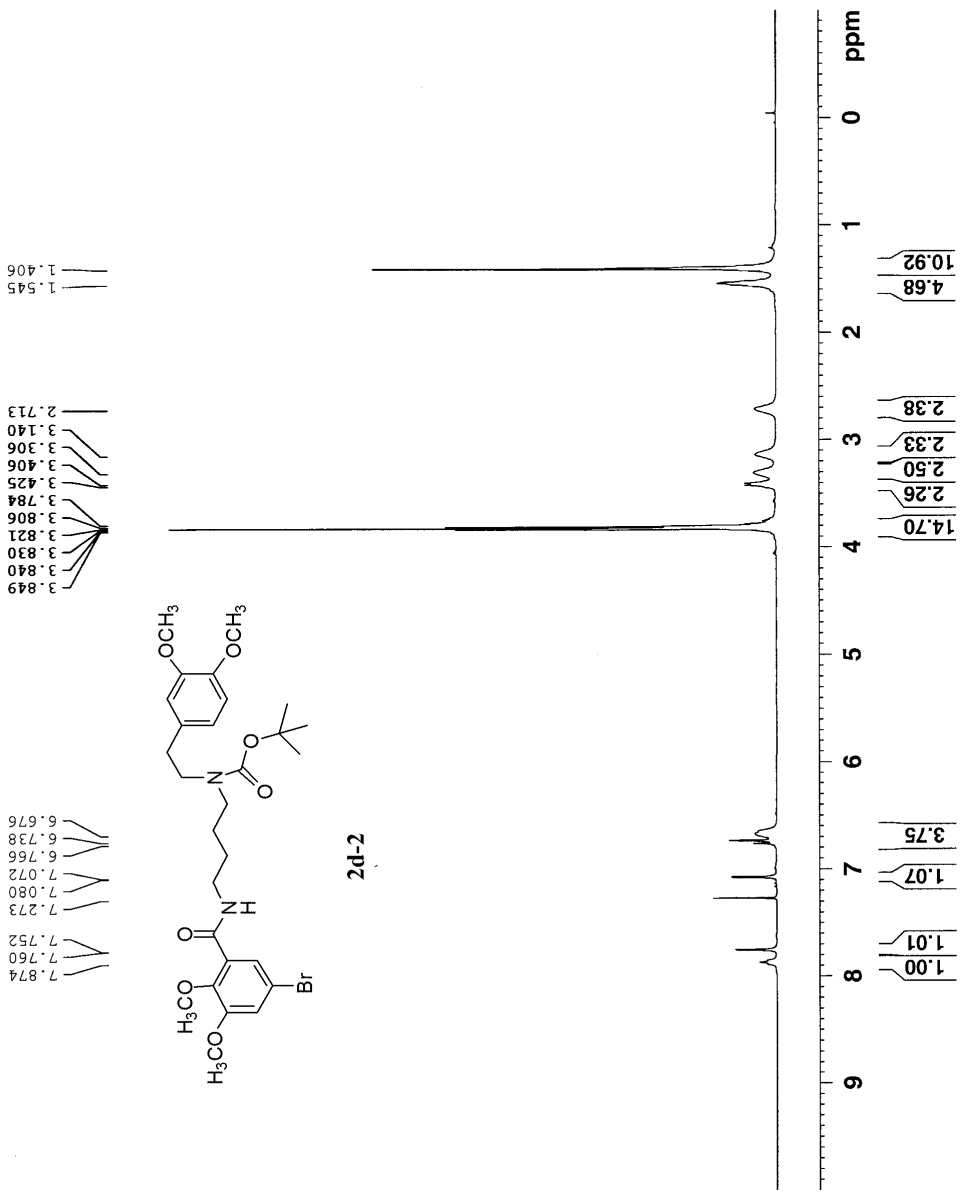
Date_	20060313
Time	17.11
INSTRUM	arx250
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5208.333 Hz
FIDRES	0.158946 Hz
AQ	3.1457779 sec
RG	64
DW	96.000 use
DE	137.14 use
TE	300.0 K
D1	1.00000000 sec
P1	9.50 use
SFO1	250.1315321 MHz
NUCLEUS	1H

F2 - Processing parameters

SI	16384
SF	250.1300049 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.50

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	10.000 ppm
F1	2501.30 Hz
F2P	-1.000 ppm
F2	-250.13 Hz
PPMCM	0.55000 ppm
HZCM	137.57150 Hz/


Current Data Parameters
NAME rx-III-58-1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060315
Time 21.43
INSTRUM DRX300
PROBHD 5 mm Multinucl
PULPROG zg30pad
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542560 sec
RG 28.5
DW 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D31 0.00000000 sec
======== CHANNEL f1 ========
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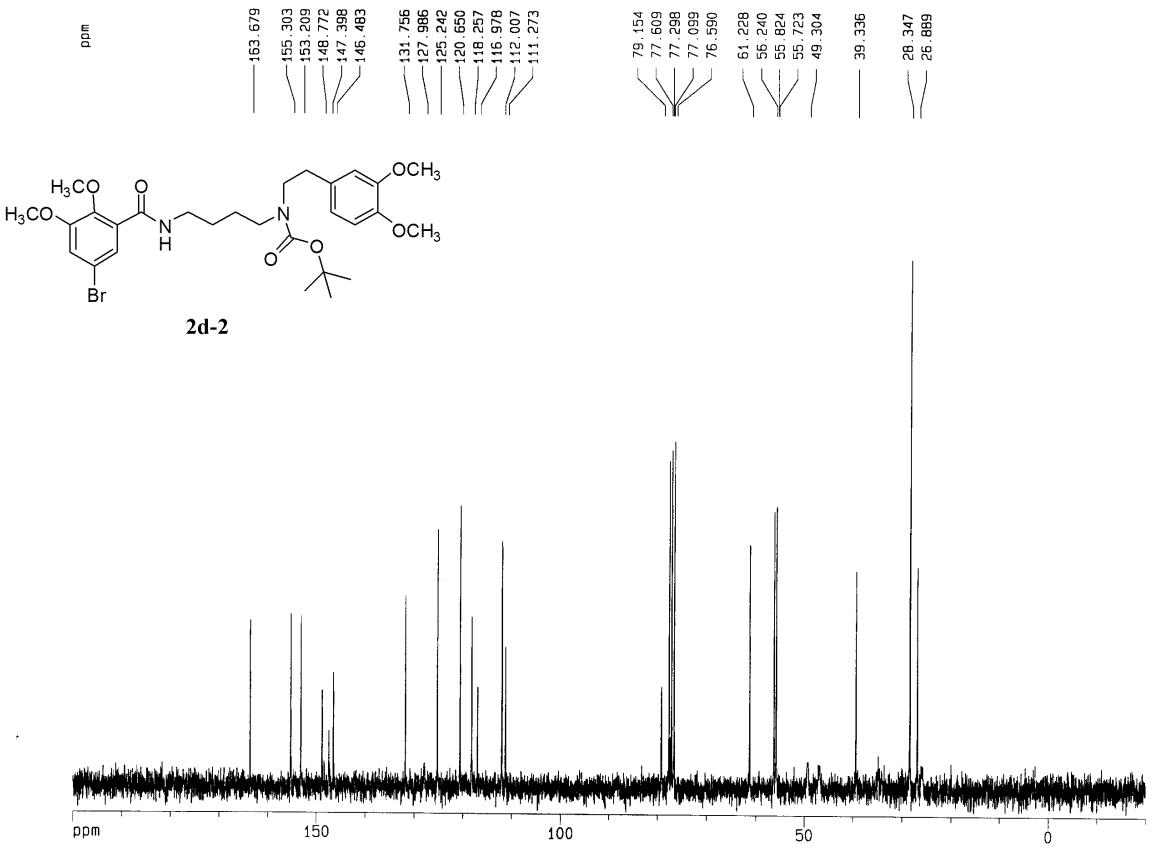

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1D NMR plot parameters
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F2             -1257.91 Hz
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1D NMR plot parameters

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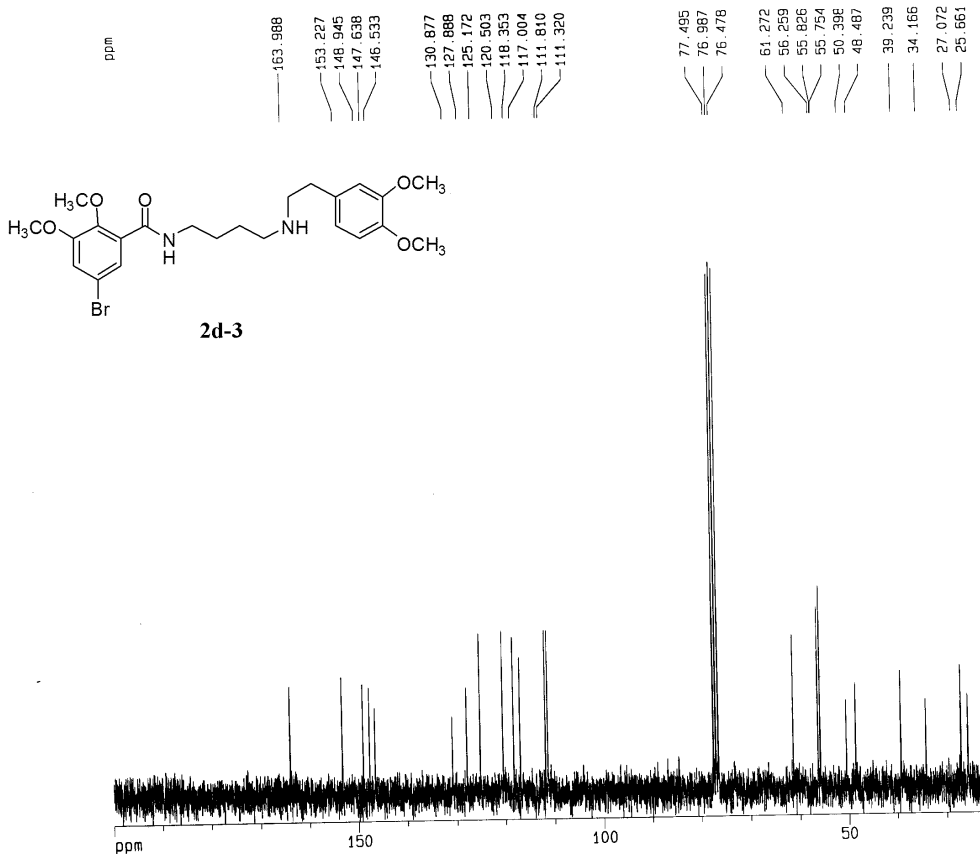

2d-3

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F2 - Processing parameters

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GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	10.00 cm
F1P	200.000 ppm
F1	12579.05 Hz
F2P	-20.000 ppm
F2	-1257.91 Hz
PPMCM	11.00000 ppm
HZCM	691.84772 Hz/

Appendix II Table of abbreviation

Abbreviation	Full name
DA	dopamine
PCP	phencyclidine
AIBN	2,2’-azo bisisobutyronitrile
TBAH	tetrabutyl ammonium hydroxide
TBAB	tetrabutyl ammonium bromide
TBDMS	tetrabutyldimethylsilyl

Appendix III The measurement of lipophilicities (pH 7.4)

$$\log D = \log \frac{\text{radioactivity in octanol phase} \times 10}{\text{radioactivity in buffer}}$$

	^{125}I-*Cis*-iodoallyl SA4503 ([^{125}I] 1b-8)			
Layer	**CPM**	**Layer avg**	**D***	**log D**
OCT A1	156003	158143		
OCT A1	160283		3444	3.54
Buff A1	501	459		
Buff A1	416			
OCT A2	129993	132839		
OCT A2	135684		3756	3.57
Buff A2	392	353		
Buff A2	314			
OCT A3	88745	92742		
OCT A3	96739		7866	3.89
Buff A3	118	117		
Buff A3	117			
OCT A4	75655	77315		
OCT A4	78975		3637	3.56
Buff A4	225	212		
Buff A4	199			
OCT A5	63616	63487		
OCT A5	63358		4182	3.62
Buff A5	158	151		
Buff A5	145			
OCT A6	168110	177536		
OCT A6	186961		1615	3.21
Buff A6	500	1098		
Buff A6	1697			
		log D	Mean ± SD =	3.57 ± 0.22

*Distribution coefficient

	^{125}I-*Trans*-iodoallyl SA4503 ([^{125}I] 1b-9)			
Layer	**CPM**	**Layer avg**	**D**	**log D**
OCT A1	165938	164602		
OCT A1	163266		4737	3.67
Buff A1	356	347		
Buff A1	338			
OCT A2	140549	144007		
OCT A2	147465		5014	3.70
Buff A2	311	287		
Buff A2	262			
OCT A3	118349	122040		
OCT A3	125731		4560	3.66
Buff A3	267	267		
Buff A3	267			
OCT A4	86522	84271		
OCT A4	82019		4683	3.67
Buff A4	208	180		
Buff A4	151			
OCT A5	73032	75341		
OCT A5	77651		2372	3.37
Buff A5	368	317		
Buff A5	267			
OCT A6	60840	61627		
OCT A6	62414		3232	3.51
Buff A6	191	190		
Buff A6	190			
		log D	Mean ± SD =	3.60 ± 0.13

^{125}I-*Cis*-iodoallyl dimethoxy phenethyl piperazine (1h-6)				
Layer	**CPM**	**Layer avg**	**D**	**log D**
OCT A1	143159	143463		
OCT A1	143767		184	2.26
Buff A1	7694	7785		
Buff A1	7876			
OCT A2	122565	122584		
OCT A2	122602		185	2.27
Buff A2	6679	6601		
Buff A2	6523			
OCT A3	102968	103514		
OCT A3	104060		185	2.27
Buff A3	5525	5570		
Buff A3	5615			
OCT A4	88273	88283		
OCT A4	88294		188	2.27
Buff A4	4705	4687		
Buff A4	4668			
OCT A5	75309	75186		
OCT A5	75063		190	2.28
Buff A5	3968	3952		
Buff A5	3937			
		log D	Mean ± SD =	2.27 ± 0.0055

	^{125}I-*Trans*-iodoallyl dimethoxy phenethyl piperazine (1h-7)			
Layer	**CPM**	**layer avg**	**D**	**log D**
OCT A1	145686	146002		
OCT A1	1463183		176	2.25
Buff A1	8182	82545		
Buff A1	8326			
OCT A2	123505	123159		
OCT A2	122813		175	2.24
Buff A2	7029	7012		
Buff A2	6996			
OCT A3	104748	104597		
OCT A3	104446		176	2.25
Buff A3	5907	5913		
Buff A3	5918			
OCT A4	88419	87910		
OCT A4	87402		182	2.26
Buff A4	4872	4815		
Buff A4	4759			
OCT A5	75137	75203		
OCT A5	75269		182	2.26
Buff A5	4129	4128		
Buff A5	4128			
		log D	Mean ± SD=	2.25 ± 0.0079

Appendix IV BCA data

Tube Number	Concentration of protein (µg/mL)	UV Absorbance at 562 nm	Average of UV Absorbance
1	2000	2.331 2.291	2.361
2	1500	1.906 1.933	1.919
3	1000	1.381 1.405	1.393
4	750	1.094 1.099	1.096
5	500	0.812 0.837	0.824
6	250	0.479 0.481	0.480
7	125	0.289 0.295	0.292
8	25	0.127 0.129	0.128
9	unknown	2.054 2.033	2.043
10	unknown	1.306 1.311	1.309
11	unknown	0.927 0.935	0.931
12	unknown	0.720 0.712	0.716
13	unknown	0.402 0.399	0.400

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VITA

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