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Uses of Diaryliodonium Salts and Methods for their Synthesis

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USES OF DIARYLIODONIUM SALTS AND METHODS FOR THEIR SYNTHESES

By

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USES OF DIARYLIODONIUM SALTS AND METHODS FOR THEIR SYNTHESES

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Diaryliodonium salts have been studied continuously since the first report of their synthesis in 1894. Diaryliodonium salts are I(III) derivatives that are air- and moisture-stable. The reactivity of these compounds resembles the organometallic chemistry of heavy transition metal ions such as Pb(IV), Hg(II), Th(III), and Pd(II). A significant advantage of diaryliodonium salts is that they can carry undergo many of the aryl functionalization reactions of heavy metal organometallic complexes, yet they have little to no toxicity and they are relatively inexpensive to prepare. The DiMagno laboratory uses diaryliodonium salts as precursors in the final synthetic step of radiopharmaceuticals; given that radiotracer prepared in this manner need to be injected into humans shortly after their synthesis, it is a virtual requirement that precursors and labeling reactions do not generate potentially toxic byproducts in radiotracer preparations.

This thesis comprises to two distinct projects. The first is the discussion of the synthesis of the highly electron-rich diaryliodonium salts in which one of the rings is an indole. Diaryliodonium salts featuring indole substituents constitute a relatively uncommon and poorly characterized class of compounds to date. The chapter will discuss the synthesis of diaryliodonium salts that feature 2- and 5-indole substituents, and will report nucleophilic substitution of these compounds with a variety of nucleophiles.

Progress towards synthesizing diaryliodonium salts that could serve as precursors to radiofluorinated or radioiodinated serotonin, tryptamine, and tryptophan derivatives, along with model studies that provide insight into the nature of nucleophilic substitution for these substrates, will be reported. Because of the electron-rich nature of the C-2 position of indole, conventional methods to synthesize diaryliodonium salts featuring this moiety failed. Here I discuss application of a novel synthetic approach to diaryliodonium salts, developed by Dr. Bao Hu in our group, which features condensation of Grignard reagents with aryl iodonium precursors. This reaction proved to be an extremely useful tool for the synthesis of extremely electron rich diaryliodonium salts that we were unable to prepare using the oxidative coupling methodology developed in our laboratory.

The second part of this thesis will discuss the synthesis of diaryliodonium salts on solid-phase resins, and the potential for using solid phase techniques for radiopharmaceutical synthesis Very little previous work has been done in synthesizing diaryliodonium salts on a solid support, so this work is quite new, and not fully developed at this time.

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NOMENCLATURE AND ABBREVIATIONS

PET	Positron Emission Tomography
HPLC	High Pressure Liquid Chromotography
TBA-X	Tetrabutylammonium-X
TMA-X	Tetramethylammonium-X
MCPBA	Meta-Chloroperoxybenzoic Acid
TMS-X	Trimethylsilyl-X
MIBG	Metaiodobenzylguanidine
DIAD/DEAD	Diisopropyl azodicarboxyl/Diethyl azodicarboxylate
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
FDG	[^{18}F]-2-Fluorodeoxyglucose

CHAPTER 1

SYNTHESIS OF INDOLE-BASED DIARYLIODONIUM SALTS

1.1.1 Introduction of Diaryliodonium Salts and Indoles

Iodine is the largest and most electropositive of the nonradioactive halogens. It is most commonly recognized in its I(I) oxidation state, however, it is also able to form multivalent compounds. Compounds containing hypervalent iodine have recently received increased attention in literature as alternatives to organometallic reagents.[1] Of particular interest to this thesis is iodine (III), which has similar reactivity to metals such as lead(IV), mercury(II), thallium(III) and palladium(II).[1] However, iodine(III) has lower toxicity (1100 μg for human adults)[2] than lead (no safe level for human adults)[3], mercury (10 μg/L)[4], and thallium (3 μg/L).[4] Iodine(III) is also relatively inexpensive ($0.08/g) compared to thallium ($0.48/g) and palladium ($58/g)[5].

Organic iodine(III) compounds are classified by the ligands attached to the iodine atom (Figure 1-1). Three types of organic iodine(III) compounds are used in this work. Iodosylarenes **3** and [bis(acyloxy)iodo]arenes **4** are strong oxidizing agents.[6] The most commonly used iodine (III) oxidizing agent is (diacetoxyiodo)benzene ($PhI(OAc)_2$). Aryliodonium salts **10** are used as arylation electrophiles and are also commonly used in lithography and as polymerization photoinitiators.[7] When R=Ar, these compounds are called diaryliodonium salts, which are most commonly used as arylating agents.

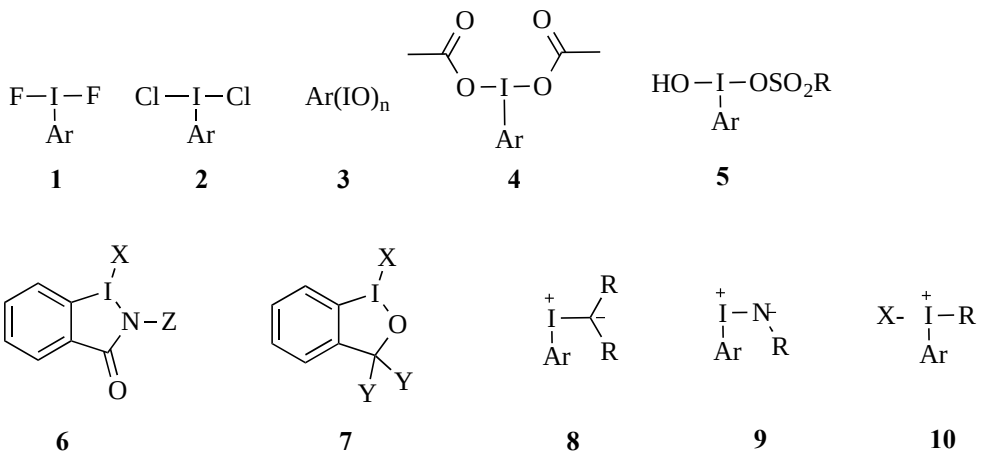

Figure 1-1 Classes of iodine (III) compounds

The accepted conformation of diaryliodonium salts is a T-shape (Figure 1-2).[6,8] Diaryliodonium compounds place the most electronegative substituent on the axial position and the two aryl groups on the remaining positions.[9] Exchange between the aryl groups are in rapid equilibrium, but it is dependent on solvent and the ion.[10] The distance between iodine and the nearest anion is approximately 2.6-2.8 Å,[8] giving the salt ionic character.

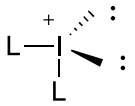

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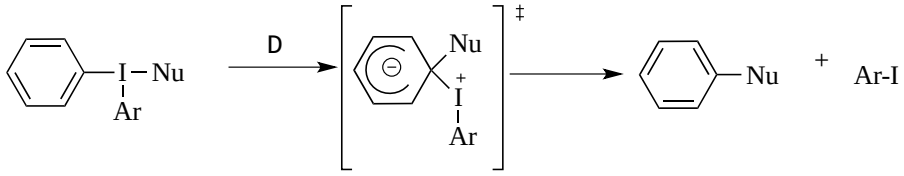
Figure 1-2 Structures of hypervalent iodine species

Data in the patent literature from the 1970's established the biocidal and antimicrobial activity of numerous diaryliodonium salts.[11-18] These salts also have low toxicity to mammals (LD_{50} = 56 mg/kg for Ph_2I-Cl in mice) and have potential as disinfectants and preservatives.[6] The low toxicity over similarly reactive, toxic metals has led to a resurgence of diaryliodonium salts in the literature. They are mainly used as an

aryl transfer reagent. In the DiMagno lab, diaryliodonium salts are used for the functionalization of highly electron-rich arenes.

When the diaryliodonium salt is heated, it undergoes thermolysis with nucleophiles through a Meisenheimer-like transition state (Scheme 1-1). Thermolysis of unsymmetrical diaryliodonium salts results in the nucleophile being directed towards the more electron-poor arene,[19] which is better able to tolerate the build-up of negative charge in the transition state.[20] Electron-rich arenes such as 4-methoxyphenyl[21] and thienyl[22] are commonly used as electron-rich directing groups. Thermolysis of diaryliodonium salts is a simple synthesis for the functionalization of electron-rich and electron-poor aromatic molecules at the ortho-, meta-, or para-positions.



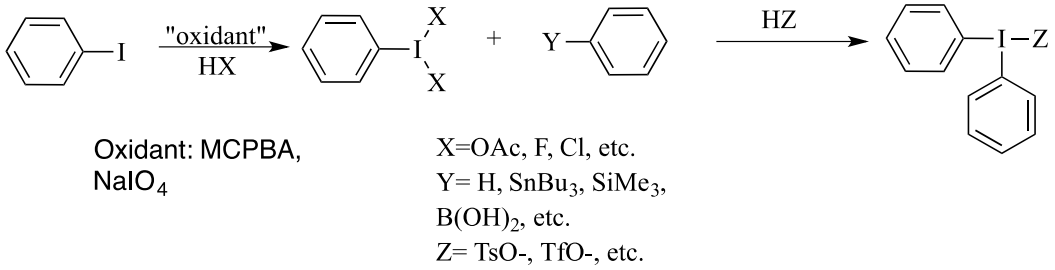
Scheme 1-1 General mechanism of diaryliodonium salt thermolysis

Diaryliodonium salts are used to functionalize arenes with a variety of nucleophiles including iodide,[23,24] bromide,[24,25] and fluoride.[26] Of these, the DiMagno group has particular interest in incorporating [^{18}F]-fluoride and [^{124}I]-iodide for Positron Emission Tomography (PET) imaging agents.

PET is a noninvasive molecular imaging technique that uses a radioactive tracer to study biological functions. Common radionuclides used in PET are carbon-11, fluorine-18, gallium-68, and iodine-124. Of these, fluorine-18 is one of the leading positron emitting radioisotopes because of its moderately short half-life (109.8 min.), and

high specific activity and high energy positron.[27] Diaryliodonium salts were first used to radiofluorinate tracers by Pike in 1995.[28]

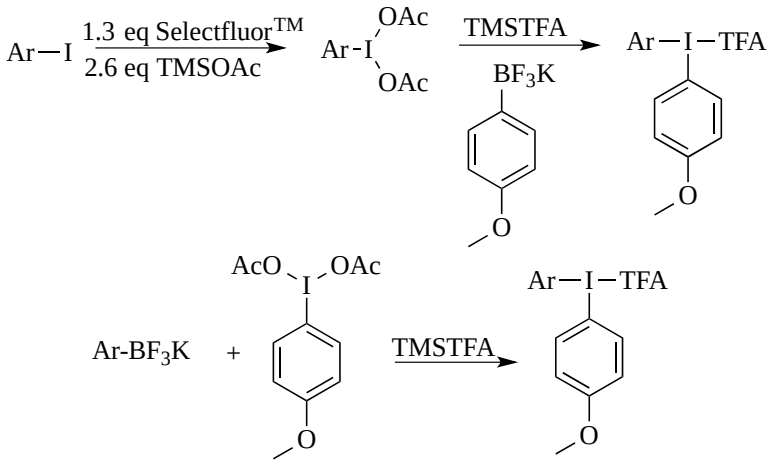
The most common synthetic strategy for diaryliodonium salts[6] begins with an iodoarene oxidized by MCPBA[29] or sodium periodate[30] and a moderate acid such as acetic acid.[31] This gives the oxidized iodosylarene (Ar-IX_2), which can be isolated or carried forward *in situ.*[6] The iodosylarene is introduced to an organometallic arene or a simple arene with a Brønsted acid such as tosylic acid[29] or triflic acid[30] and, in some cases, a metal catalyst[31] (Scheme 1-2).



Scheme 1-2 General synthetic strategy for synthesis of diaryliodonium salts

A major drawback of the traditional synthetic method is its incompatibility with acid sensitive functional groups. Many acid-labile protecting groups such as t-butyl carbamate (Boc) and ethoxymethyl ether cannot be used with acids such as tosylic acid (pKa=8.5 in acetonitrile) and triflic acid (pKa=0.7 in acetonitrile).[32] These protecting groups are ideal for PET because of their simple and fast deprotection. To synthesize diaryliodonium salts with acid sensitive protecting groups, the DiMagno lab has developed a synthetic approach[33] that avoids using Brønsted acids (Scheme 1-3). The iodoarene is oxidized using F-TEDA-BF_4 (*Selectfluor*™) in the presence of TMSOAc. The iodosylarene is introduced to the organometallic trifluoroborate with TMSTFA. Boronate compounds have low toxicity[34] and are air and moisture stable. TMSTFA and

TMSOAc are Lewis acids used in place of the strong Brønsted acids that are commonly used in diaryliodonium salt syntheses. Efficient functionalization of arenes via diaryliodonium salts requires an electron-rich directing group. In the DiMagno group, 4-methoxyphenyl is used.[33] The iodine (III) arene can be synthesized on the anisole directing group or the tracer (Scheme 1-3).



Scheme 1-3 General DiMagno lab methodology for synthesis of diaryliodonium salts

Using the DiMagno lab methodology, I turned my attention to synthesizing a diaryliodonium salt of an indole. Indoles are bicyclic, heterocyclic molecules that are sparingly studied in literature as ligands in diaryliodonium salts or radiotracers for PET. Indoles are relevant in pharmaceuticals,[35] agrochemicals,[36] and organic electronics.[37] Indole is the core structure of a large number of pharmaceutically relevant compounds (Figure 1-3), including tryptamine, a neuromodulator; 5-hydroxytryptamine (serotonin), a regulator of mood, appetite and sleep; *L*-Tryptophan, an essential amino acid; melatonin, a hormone that anticipates the daily onset of darkness; indomethacin, an NSAID; and N,N-Dimethyltryptamine, a hallucinogen.[35] I focused my attention on serotonin and *L*-Tryptophan.

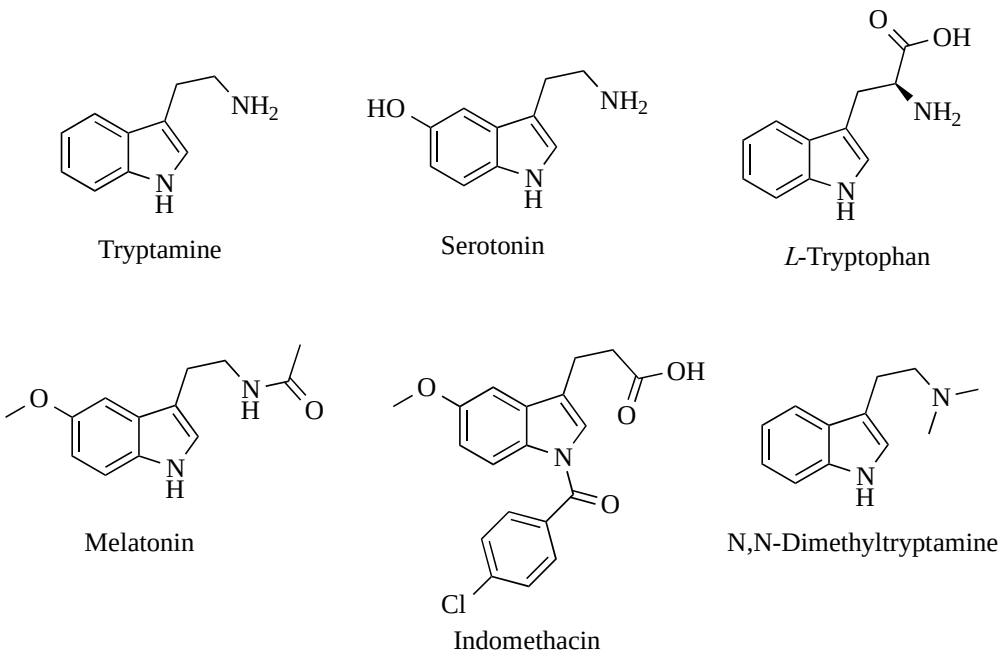
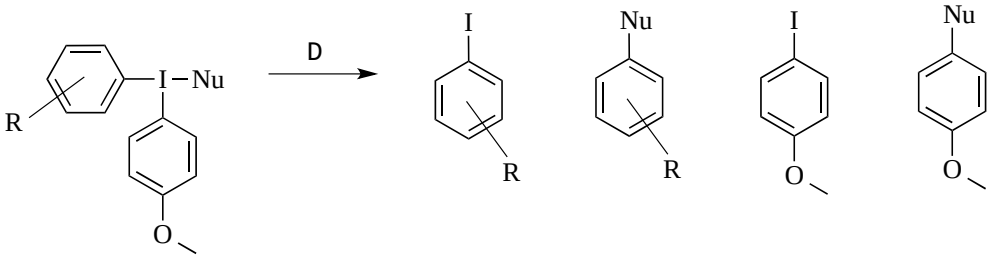


Figure 1-3 Indoles of pharmaceutical relevance

The electronic structure of indole, calculated by Pullman and Pullman,[37] has a high negative charge on C-2 and a lesser negative charge on C-1. Carbons C4 through C7 are much less electron-rich,[38] so I believed that thermolysis of diaryliodonium salts at the C4, C5, C6, or C7 positions would result in fewer side products. Synthesis of diaryliodonium salts at the highly electron-rich C2-position on indoles will be discussed in greater detail later in this chapter.

Thermolysis of diaryliodonium salts potentially produces four major products[39] (Scheme 1-4), but for radiosynthesis of tracers in PET, minimal side products are desired. Using an electron-rich directing group such as 4-methoxy phenyl limits these side products. However, with a highly electron rich arylating agents like indole, side products increase.



Scheme 1-4 Possible products of thermolysis

1.1.2 Synthesis of *tert*-butyl 3-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-λ^3-iodanyl)-1*H*-indole-1-carboxylate

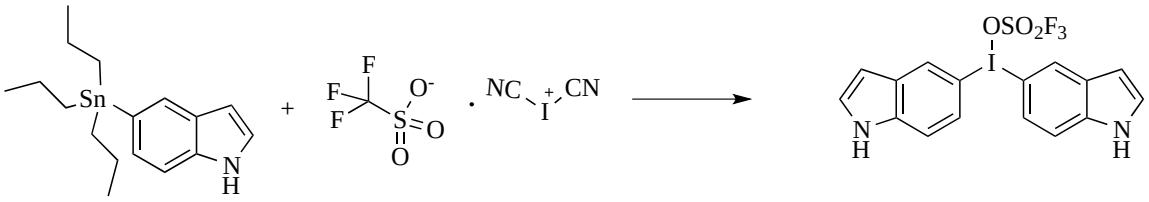
My first goal was to synthesize a radiotracer of serotonin. To quantify the side products, however, I needed to first synthesize a diaryliodonium salt at the C-5 position of indole. The C-F bond is similar in bond length and size to both C-H and C-OH groups (Table 1-1),[40] so it can be substituted for the bonds with minimal steric perturbation. By substituting the C-OH bond of serotonin with a C-^{18}F bond, we would be able to study the metabolism of serotonin via PET.

Bond	Length [Å]	van der Waals radius[Å]	Total Size [Å]
C-H	1.09	1.2	2.29
C=O	1.23	1.5	2.73
C-O-	1.43	1.52	2.95
C-F	1.35	1.47	2.82
O-H	0.96	1.2	2.16

Table 1-1 Steric consequences of fluorine

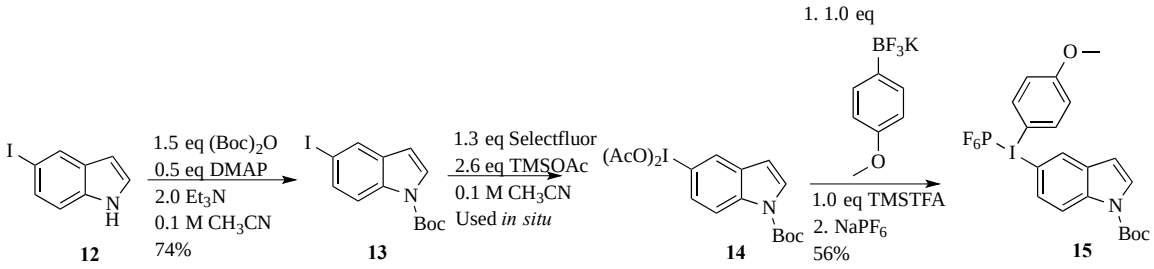
To estimate the electronics of serotonin, I synthesized two test compounds to determine what the selectivity of a thermolysis reaction would be. There has only been one previous synthesis of a diaryliodonium salt at the C-5 position of indole, which was

by Zhdankin[41] in 1992 (Scheme 1-5). He synthesized a symmetrical indole triflate diaryliodonium salt via a tin intermediate in 10% yield.



Scheme 1-5 Zhdankin synthesis of bis indole iodonium salt

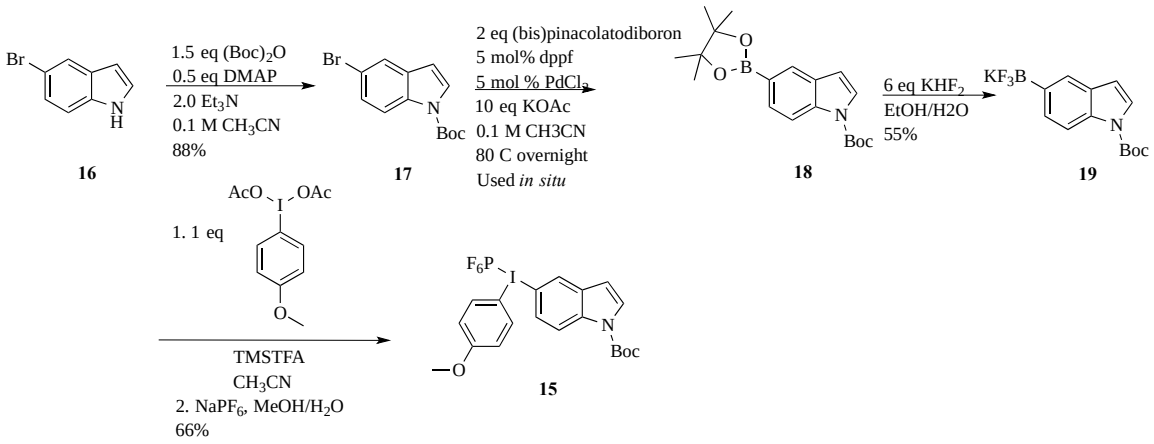
For the first test compound, I began with 5-iodoindole **12. I** synthesized *tert*-butyl-5-iodo-1*H*-indole-1-carboxylate **13,**[42] using a standard Boc protection. I synthesized the oxidized product **14** using 1.3 equivalents *Selectfluor*™ and 2.6 equivalents TMSOAc. The oxidation produced more than 90% oxidized product, which I carried forward *in situ* without further purification. I coupled the oxidized indole with trifluoro(4-methoxyphenyl)-λ^4-borane, potassium salt, and ion exchanged with sodium hexafluorophosphate to give the diaryliodonium salt **15** (Scheme 1-6).



Scheme 1-6 Synthesis of *tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate from 5-iodoindole

Synthesis from the oxidized iodo-indole forms the diaryliodonium salt using the (1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl)-λ^3-iodanediyl diacetate as an electrophile and trifluoro(4-methoxyphenyl)-l^4-borane, potassium salt as the nucleophile. However, the

diaryliodonium salt can also be synthesized from the oxidized anisole and the indole boronate. The boronate compound can easily be synthesized from 5-bromoindole by palladium cross-coupling.[43] Bromo-indoles are significantly cheaper ($130.50 for 25 g)[44] than iodo-indoles ($365.00/25 g).[45] Therefore, if the synthesis of *tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate from 5-bromoindole was successful, it would indicate that I could synthesize all serotonin and tryptophan diaryliodonium salts from the cheaper bromo precursors. To synthesize **17**, I Boc-protected 5-bromoindole[46] (Scheme 1-7) using common Boc protection methodology. I synthesized the boronic ester **18** using palladium catalysis with bis(pinacolato)diboron. The boronic ester was converted to the trifluoroborate **19** with potassium bifluoride. I coupled the trifluoroborate with (4-methoxyphenyl)-λ3-iodanediyl diacetate and TMSTFA. As was hoped, synthesis of the salt proceeded easily without issue, thus opening up a cheaper way to make these compounds(?).



Scheme 1-7 Synthesis of *tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate from 5-bromoindole

Thermolysis of *tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate, **15,** with tetra-butylammonium azide showed an incomplete selection for functionalization of the indole (Figure 1-4). The incomplete functionalization is shown by the presence of 1-azido-4-methoxybenzene in the crude NMR. The lower than expected selectivity suggests the C-5 position of indole ligand on a diaryliodonium salt with an anisole-directing group could be too electron-rich for PET radiosynthesis via diaryliodonium salts. To improve the selectivity of the thermolysis, a more electron-withdrawing protecting group such as tosyl or a more electron-rich directing group such as cyclophane[47] could be used. Cyclophane directs nucleophiles in thermolysis by regiochemical control. The out-of-plane steric bulk destabilizes the transition state, and permits regiospecific thermolysis[47]. The fault of diaryliodonium salts with a cyclophane ligand is the complexity of their synthesis. The synthesis requires formation of the cyclophane Zn complex.

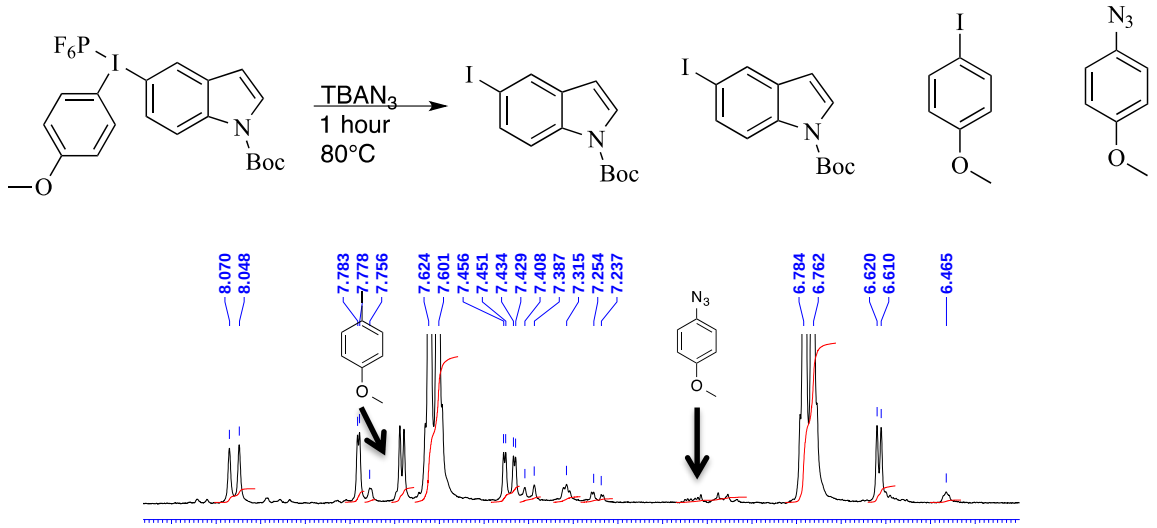


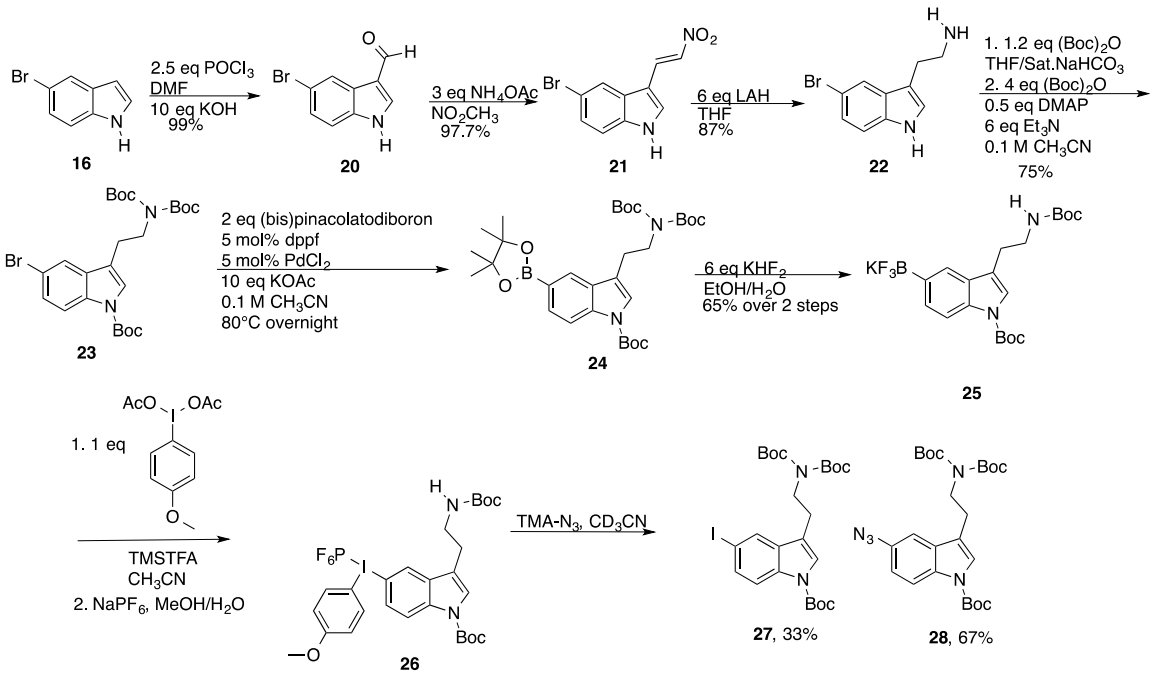
Figure 1-4 Thermolysis of *tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate with $TBAN_3$ in CD_3CN

1.1.3 Synthesis of *tert*-butyl 5-(2-((*tert*-butoxycarbonyl)amino)ethyl)-3-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-λ^3-iodanyl)-1*H*-indole-1-carboxylate

[^{18}F]-5-fluoro-tryptamine could serve as a radiotracer for either serotonin or tryptamine metabolism depending on its binding capacity. Minimal studies have been done on the binding capacity of 5-fluorotryptamine. James published in 1982[48] that 5-fluorotryptamine binds to normal and denatured DNA, but no *in vivo* studies have been completed to date. Serotonin is well known to be a target of many psychopharmaceuticals.[49-51] Tryptamine is biologically generated by decarboxylation of *L*-tryptophan by *L*-amino acid decarboxylase.[52] Tryptamine is also of pharmaceutical relevance in the psychopharmaceutical field. Tryptamine is highly metabolized by depressed patients;[53] however, it normalizes with treatment, while tryptophan and serotonin metabolism remain constant throughout.[54] An increase in tryptamine

metabolism is also shown in schizophrenics.[55] All studies showing abnormal tryptamine metabolism in psychiatric disorders have been by urinary analyses, and new studies have not been done using other technology. The goal of synthesizing [^{18}F]-5-fluorotryptamine would be to study the metabolism of tryptamine and serotonin in a healthy and depressed model. The results could lead to new revelations about tryptamine's role in depression and other psychiatric disorders. If there are different PET results between a depressed and normal model, the results could also validate PET as a diagnostic tool for depression.

To synthesize *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-((hexafluoro-l^7-phosphanyl)(4-methoxyphenyl)-λ3-iodanyl)-1*H*-indole-1-carboxylate **26**, I began with a modified synthesis of 5-bromotryptamine[56] (Scheme 1-8). With the modified synthesis, I had a fully protected 5-bromotryptamine, which could be converted to the trifluoroboronate and coupled (4-methoxyphenyl)-l^3-iodanediyl diacetate to give the diaryliodonium salt.



Scheme 1-8 Synthesis of tert-butyl 3-(2-((tert-butoxycarbonyl)amino)ethyl)-5-((hexafluoro-l7-phosphanyl)(4-methoxyphenyl)-λ3-iodanyl)-1H-indole-1-carboxylate

It is known that the 2-position of indole is the most electron-rich position.[37] Because of the high electron density, formylation via a Villsmeier-Haack reaction of **16** proceeded in a quantitative fashion at room temperature to give **19**. Using a Henry reaction, I synthesized the nitro alkene **20** nearly quantitatively. I reduced with lithium aluminum hydride to give the amine **21**. Schotten-Baumann Boc protection gave the mono-protected tryptamine **22**. I then proceeded with Boc-protecting the remaining amines **23**. Using the same methodology for synthesis of diaryliodonium salts that I had used for the indole, I synthesized the boronic ester using palladium-catalyzed cross coupling. The boronic ester **24** was found to be unstable, and I carried it forward without purification. I synthesized the fluoro-boronate **25** with potassium bifluoride, and coupled **25** with (4-methoxyphenyl)-λ3-iodanediyl diacetate to give the salt **26**.

Previous work in the DiMagno lab by Dr. Linlin Qin[57] had shown that thermolysis to the functionalized azide proceeded fastest, at the lowest temperature, and with the best selectivity. Because the test indole compounds proceeded with imperfect selection, I tried the thermolysis of *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-((hexafluoro- λ ^{7}-phosphanyl)(4-methoxyphenyl)-λ3-iodanyl)-1*H*-indole-1-carboxylate with azide to estimate the selectivity. However, selectivity proceeded with a 2:1 functionalization of the indole **28** to the iodinated indole **29**. The incomplete selectivity is most obvious looking at the anisole peaks, where iodo-anisole is in 2:1 ratio with the functionalized anisole (Figure 1-5).

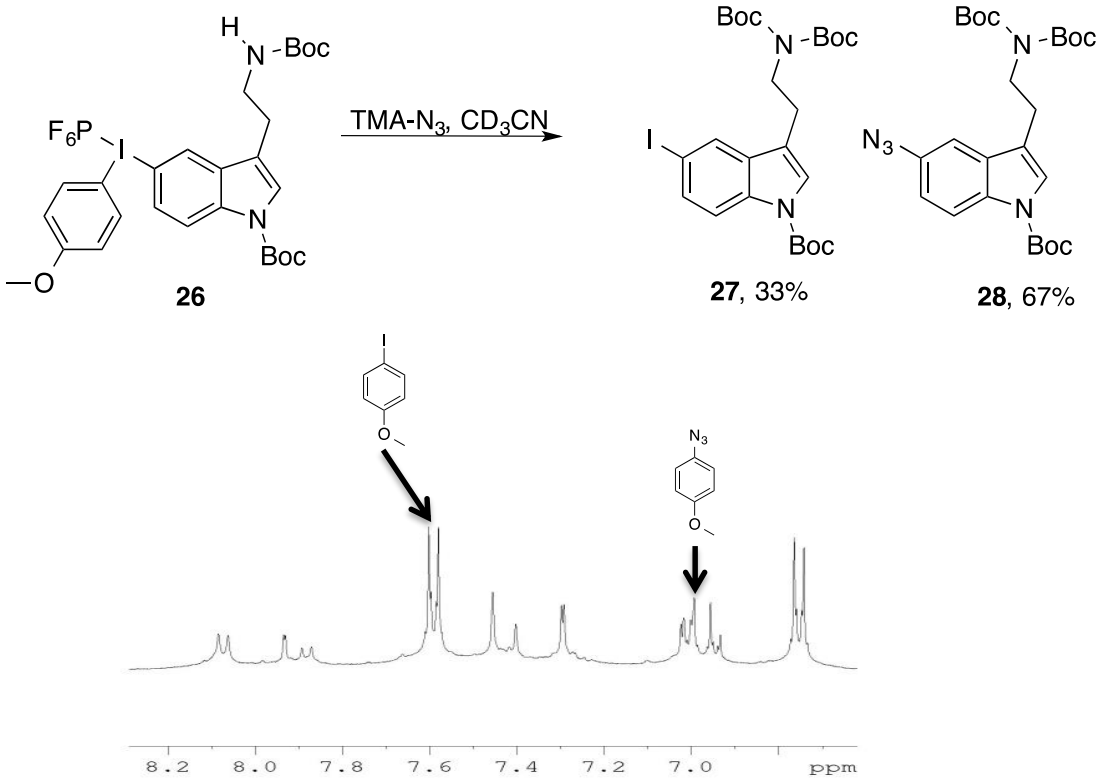


Figure 1-5 Crude thermolysis of Tryptamine with $TBAN_3$ in CD_3CN

Because of the incomplete selectivity, continuing forward with the indole project was impractical without a more electron-withdrawing protecting group or a better directing group. Different protecting group options, such as acetate, tosyl, and triflate, are available to withdraw electron density from the aromatic ring. However, most other protecting groups are not plausible for use with radiofluorination, as all require long and harsh deprotection strategies.[59]

1.1.4 Radiofluorination of Tryptophan and Future Studies

The final goal of the indole project was to synthesize a radiofluorinated tryptophan. Tryptophan is an essential amino acid, and it is of interest in PET imaging because of its increased metabolism in tumor cells.[59-61] It is known that Large Amino Acid Transporter 1 (LAT1) transports large neutral amino acids such as tyrosine,

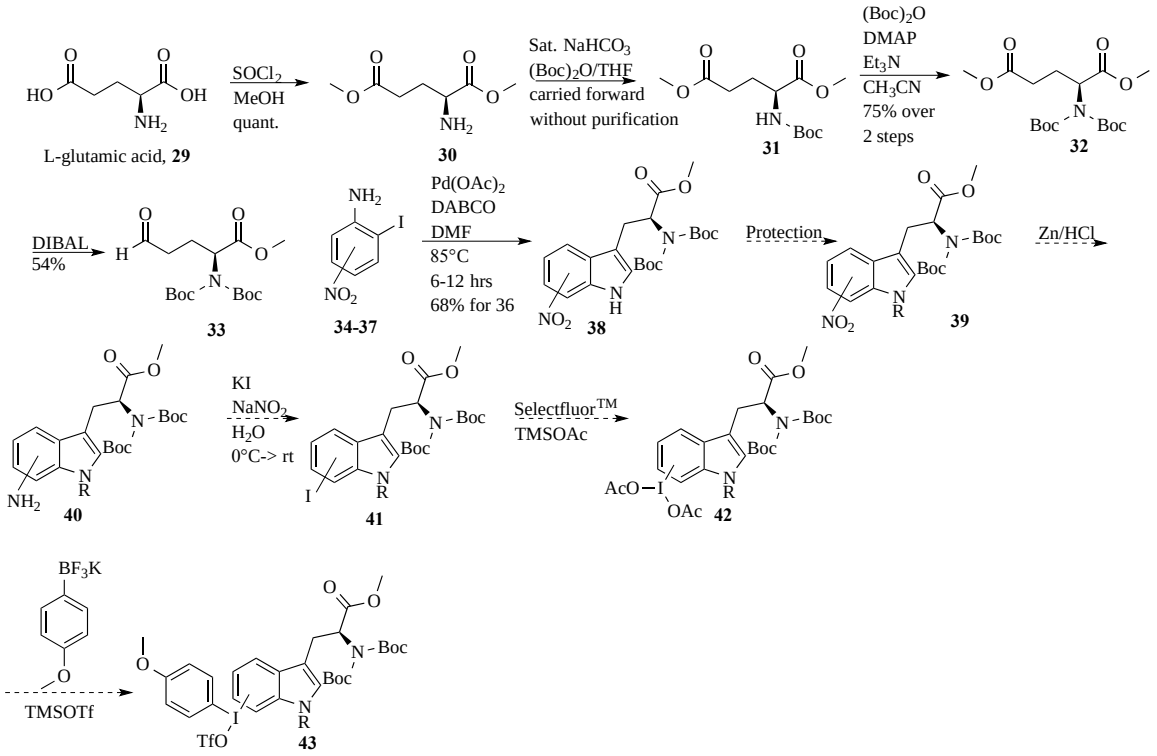
tryptophan, and phenylalanine, with high affinity (15-50microM).[62] LAT1 also transports chemotherapy drugs that mimic amino acids like melphalan.[63, 64] I wanted to synthesis [^{18}F]-Fluoro-*L*-Tryptophan because it has potential to be used alongside [^{18}F]-2-F-fluorodeoxyglucose ([^{18}F]-FDG) in PET.

[^{18}F]-FDG is the number one radiotracer used in PET imaging studies[65]. Currently, over 90% of PET scans use [^{18}F]-FDG for imaging the metastasis of cancer. However, [^{18}F]- FDG is also used for the assessment of glucose metabolism in the heart,[66] brain,[67] and lungs.[68] Tumors in these major organs are unable to be scanned with [^{18}F]-FDG because of the organ's high glucose uptake. The large uptake by the heart, brain, and lungs leads to a large amount of background noise, which hides any tumors. There is a need for general PET imaging tools that can scan tumors in glucose high-uptake organs. LAT1 is increased in tumor cells because of their high amino acid metabolism.[69] Tryptophan metabolism is increased in meningiomas,[70] breast cancer,[71] and neuroepithelial tumors.[72] Because of the increased metabolism of tryptophan in tumor cells, I believe that a [^{18}F]-fluoro-*L*-tryptophan could be a useful tracer for PET imaging.

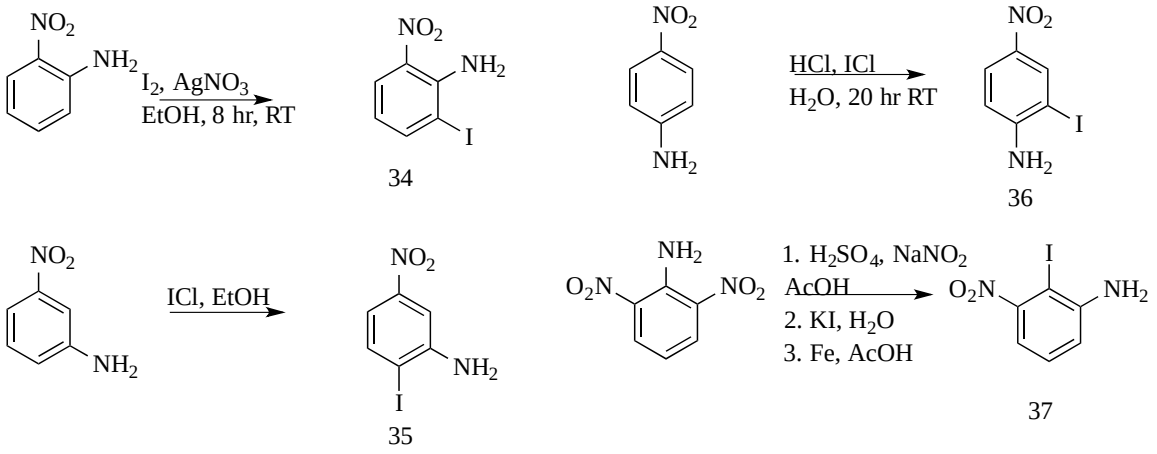
Given the incomplete selectivity of the indole and tryptamine thermolyses, the synthesis of a diaryliodonium salt tryptophan needs to be different than the test compounds. More electron-withdrawing groups such as acetyl or tosyl would need to be used. The problem is that electron-withdrawing groups require harsh, long deprotection. Acetyl is a strong, base-labile protecting group that would likely require overnight refluxing in strong base to completely remove.[73] Tosyl would require a more difficult deprotection with a reducing group like Na/NH_3 or Zn/HCl.[73] In PET, time is of the essence. Deprotection occurs after the introduction of the radionuclide. The longer the

deprotection, the less radioactivity is maintained for introduction into the patient. A better directing group such as cyclophane[47] could be used.

My proposed synthesis (Scheme 1-9) includes flexibility of the protecting group on the indole ring.[74-75] I synthesized all precursors up to **38,** which requires a new protection strategy. I begin with L-Glutamic Acid **29**, an amino acid that is both cheap and accessible. Ester protection with thionyl chloride gave the diester **30** quantitatively. I protected the first free amine with Schotten-Baumann Boc protection **31**, and a standard Boc protection would gave the desired **32**. Reduction of the single ester with DIBAL would give the aldehyde **33.**[74] Next, the aldehyde would be coupled with a 2-iodo-nitroaniline **34**-**37**[76-79] to give nitrotryptophan **38**. I successfully synthesized methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-nitro-1*H*-indol-3-yl)propanoate with this strategy. Because the aniline can be used with the nitro group at any position, the iodonium salt could be synthesized at the C4, C5, C6, or C7 position of tryptophan.[80] The unprotected nitrogen of the indole would need to be protected with an electron-withdrawing protecting group to avoid the incomplete thermolysis seen in the indole test compounds. Reduction of the nitro group to the amine would be done with Zn and 5% HCl to avoid deprotection of the Boc group **40.**[75] The diazo compound would be formed and converted to the iodide **41**. To synthesize the final desired salt **42**, I would oxidize the iodo-tryptophan with *Selectfluor* and TMSOAc, and couple it with (4-methoxyphenyl)-λ3-iodanediyl diacetate.



Scheme 1-9 Proposed Synthesis of Iodonium Tryptophan

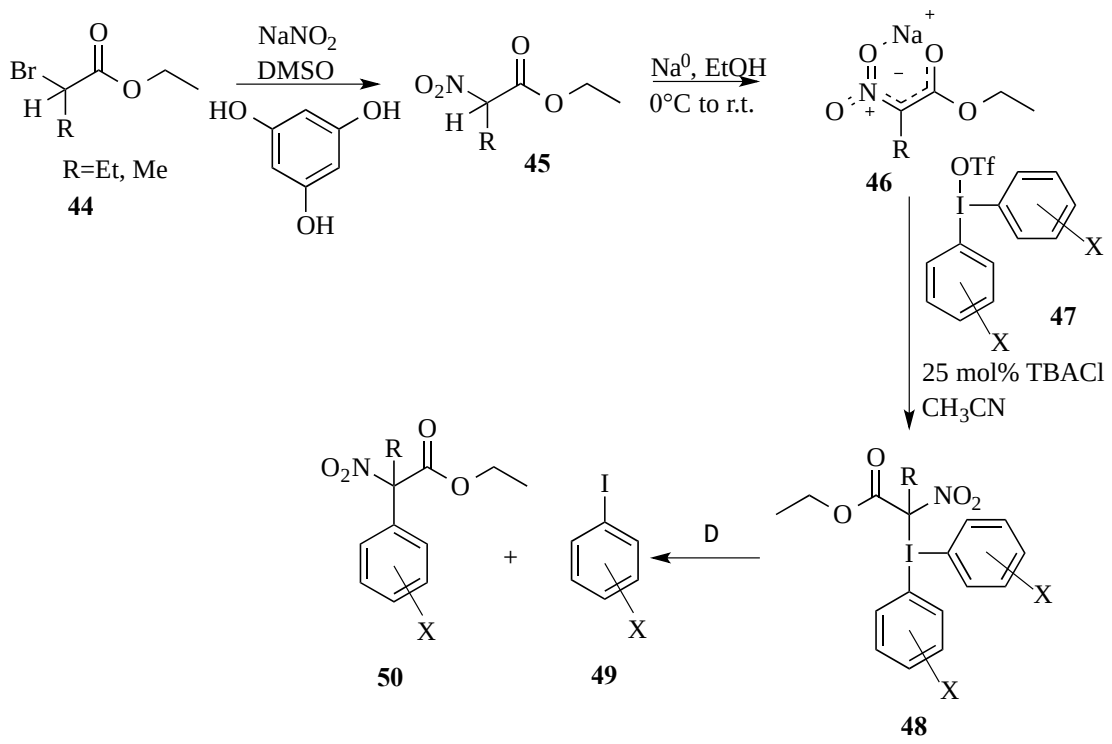


Scheme 1-10 Synthesis of 2-iodonitroaniline Precursors

1.2.1 Introduction to the Synthesis of Indole Iodonium Salts via Novel Grignard Reagent

Quaternary α-alkyl α-aryl amino acids are of biological interest because of their increased stability[81] and use as inhibitors for enzymes not usually inhibited by simple amino acids.[82]

The formation of C-C bonds via diaryliodonium salts is sparsely studied,[83] and thus presents a synthetic challenge. My lab mate Jayson Kempinger developed a general synthetic strategy (Scheme 1-11) that could be used to synthesize a vast number of functionalized quaternary aromatic amino acids via diaryliodonium salts. Synthesis begins with either ethyl 2-bromopropanoate or ethyl 2-bromobutanoate **44**, which are reacted with sodium nitrite to give **45.**[84] Reaction with sodium metal gives the carbanion **46**. When the carbanion is added to a diaryliodonium salt **47** with 25 mol% phase transfer catalyst TBACl, the carbanion replaces the triflate anion. Thermolysis of the exchanged salt gives the desired quaternary amino acid **49** and the iodinated product **50**. His work included functionalized phenylalanine and tyrosine. Of particular interest to me, because of my work with indoles, was a quaternary tryptophan.



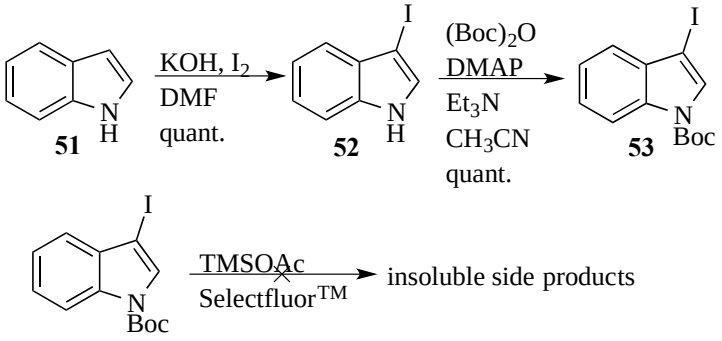
Scheme 1-11 General Synthetic Strategy for synthesis of quaternary amino acids via diaryliodonium salts

Multiple quaternary α-alkyl α-aryl tryptophans have been synthesized for biological purposes. The tryptophan analogues are reverse transcriptase inhibitors[85] and Beta amyloid self-assembly inhibitors.[86] among many others. However, many are synthesized under harsh conditions with heavy metals[85] or strong acids.[86] Simple, protecting group stable synthetic conditions could make the tryptophan analogue compounds more available and useful.

Kempinger's work focused on using symmetrical salts for the synthesis, so I began with a synthetic design for a bis-diaryliodonium indole salt at the C-2 position. The C-2 position has been significantly more studied than the C-4 through C-7 positions, however, there have been no symmetrical salts of indole at the C-2 position synthesized.

The high electron-density at the C-2 position makes it challenging as it is very common for one-electron reduction and polymerization to occur.[87]

Synthesis of the symmetrical salt requires an oxidized I(III) indole, so I began with the oxidation of the 2-iodo protected indole (Scheme 1-12). I synthesized 2-iodoindole from indole using potassium hydroxide and iodine in DMF to give **52**. The reaction, as previously reported,[88] proceeded quantitatively. I then protected the amine with a Boc group to give **53.**[89] When I attempted to oxidize the iodo-indole, however, the reaction produced a myriad of soluble and insoluble side products, most likely from the known polymerization that occurs at the C-2 position of indole[87]. There are no published syntheses of an oxidized 2-Iodoindole, and other common synthetic strategies require strong acids, which would deprotect the Boc. The protecting group incompatibility hindered further progress on the synthesis, and a bis salt became unobtainable.



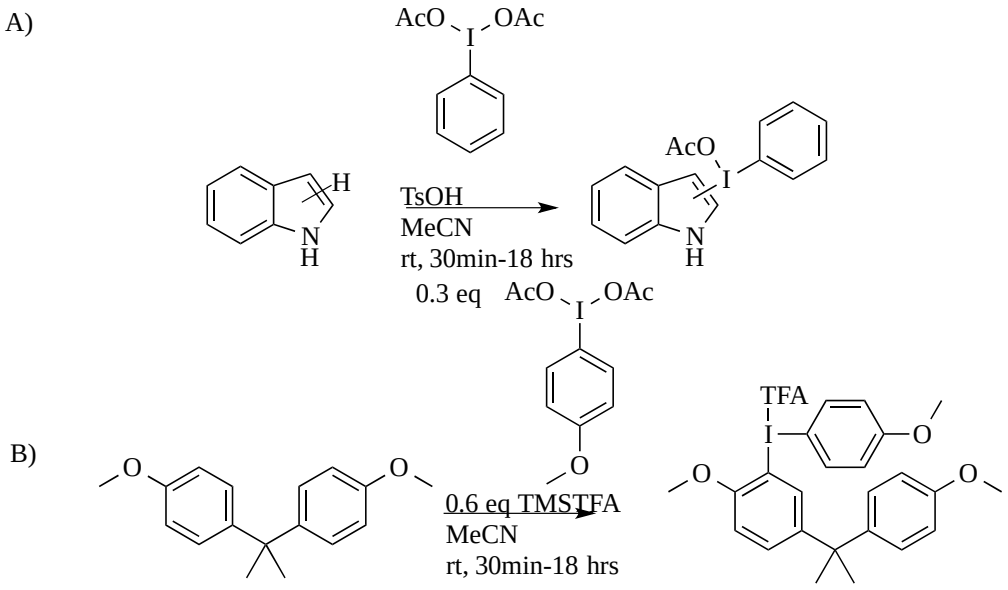
Scheme 1-12 Attempted synthesis of oxidized 3-iodoindole

1.2.2 Use of Transmetalation for Diaryliodonium Salt Synthesis

Synthesis of diaryliodonium salts proceeds with a general strategy of an oxidized iodo-compound coupled to a metal[6]. Different metals used are tin(IV),[90] boron,[33] and zinc.[47] The metal can be synthesized on either the substrate or the directing group, which

allows for flexibility in synthesis. The metal and oxidized iodoarene are coupled using a strong acid.

The syntheses of diaryliodonium salts at the C-2 position of indole have been reported using acids such as tosylic acid[91] and acetic acid.[92] Using tosylic acid, Suna[92] synthesized a tosylic diaryliodonium salt strategy that was similar to that developed in the DiMagno lab[93] (Scheme 1-13).



Scheme 1-13 A) Suna approach to synthesis of indole diaryliodonium approach

B) General DiMagno approach to synthesis of diaryliodonium salts

The former synthetic approach includes strong acid that would interfere with the acid-labile protecting groups. The methodology developed in our lab requires a Lewis acid, avoiding deprotection of the compounds. I attempted to use the DiMagno approach, however, in my hands, the reaction was unsuccessful in synthesizing an iodonium salt at the C-2 position of indole. Because of the unsuccessful reaction, there was a need to develop a new heavy-metal and Brønsted-acid-free synthetic approach.

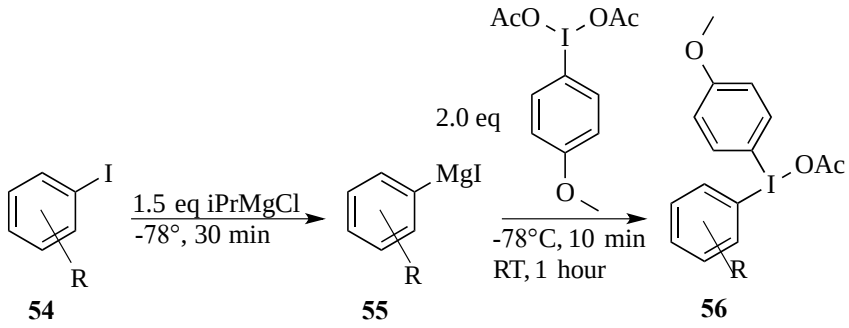
Magnesium offers an interesting alternative to the heavy metals commonly used in the synthesis of diaryliodonium salts. Previous work in the DiMagno lab[94] showed that lithium is too reactive of a metal for diaryliodonium salt synthesis, while zinc is a cumbersome reaction. Diaryliodonium salts from tin, copper, and platinum reagents are hard to purify and have toxicity problems. Magnesium is less reactive than lithium, and its side products are water-soluble.

Grignard reagents are well known to anyone in organic synthesis from the time they are undergraduate students. Generally, they are known to add into carbonyl groups or act as bases, limiting their usefulness in complex organic syntheses. They can however, undergo transmetalation reactions. Transmetalation Grignard reactions at low temperatures have low reactivity towards protecting groups,[95] and are therefore more useful for synthetic chemistry than standard Grignard reactions. Generally, transmetalation reactions are done with Iron,[96] Cadmium, or Cuprate[97] catalysts or co-reagents. Knochel,[95] however, published reactions of Grignard transmetalation without any co-reagents in highly functionalized, Grignard-sensitive molecules.

1.2.3 Structures of Novel Grignard

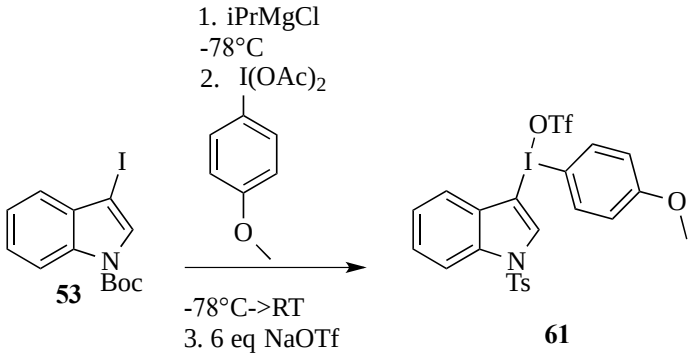
In our group, Dr. Bao Hu first discovered the usefulness of Grignard reagents for synthesis of diaryliodonium salts when trying to oxidize unreactive iodo arenes. After many failed attempts, Dr. Hu discovered that transmetalation with iso-propyl magnesium chloride and coupling with (4-methoxyphenyl)-λ^3-iodanediyl diacetate provided the desired diaryliodonium salt. I modified his approach by using fewer equivalents for longer periods of time (Scheme 1-14). Possibly most interesting was the high functional

group stability of this reaction. By cooling the reaction to -78°C, traditionally Grignard sensitive groups like amides and esters were unaffected by the reaction.



Scheme 1-14 Hu general synthetic strategy of diaryliodonium salts via a Grignard intermediate

Because of my failed attempts at oxidizing 2-iodo indole, I attempted to perform the transmetalation on *tert*-butyl 3-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-λ^3-iodanyl)-1*H*-indole-1-carboxylate (Scheme 1-15).



Scheme 1-15 Synthesis of *tert*-butyl 3-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy-λ^3-iodanyl)-1*H*-indole-1-carboxylate via Grignard transmetalation

After some optimization, I was able to synthesize the desired salt. I continued with a thermolysis using $TBAN_3$ to test nucleophile selectivity. The nucleophile selectivity surprisingly favored functionalization of anisole 9:1 (Figure 1-6). This is

easiest to quantify in the crude NMR by comparing the singlet peaks of the C-1 position of both indoles.

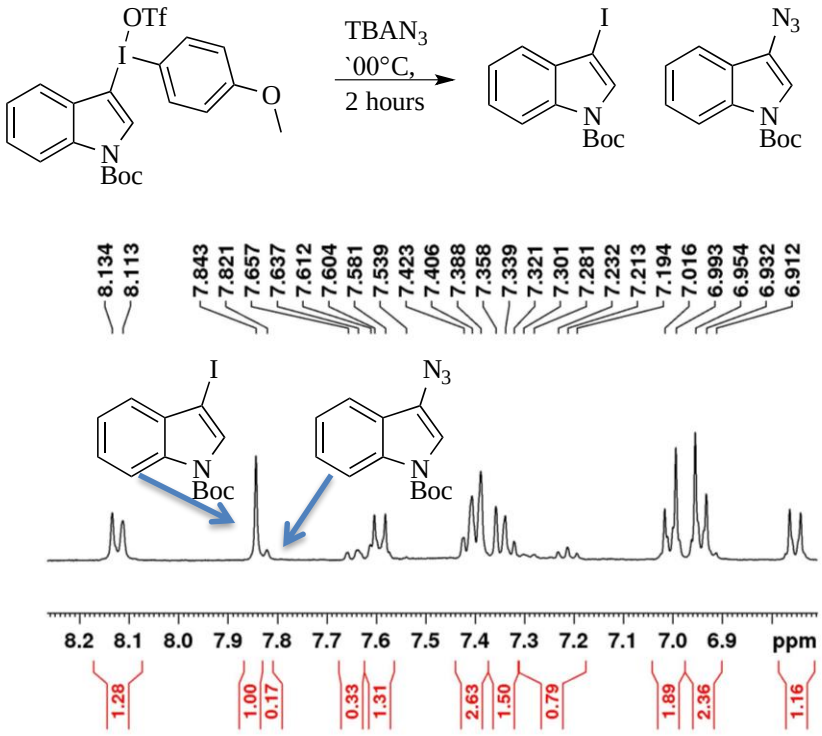
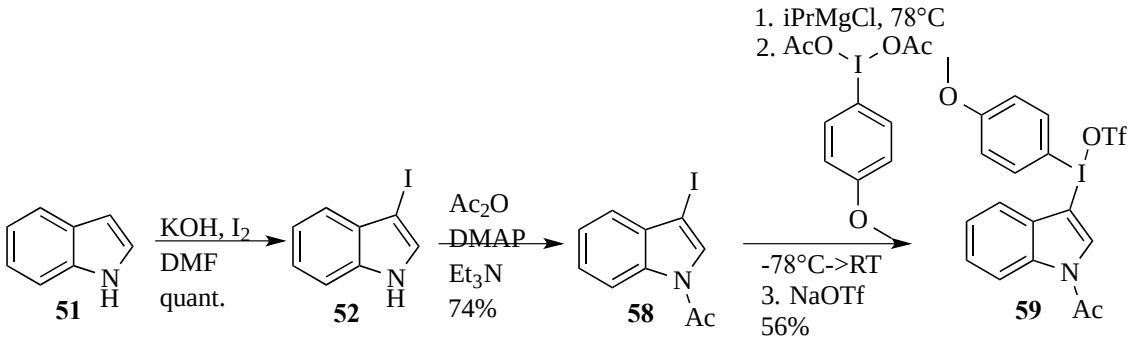


Figure 1-6 Crude Thermolysis of *tert*-butyl 3-((4-methoxyphenyl) (((trifluoromethyl)sulfonyl)oxy-λ^3-iodanyl)-1*H*-indole-1-carboxylate

Nucleophile selectivity relies on the electron-richness of the directing group. In this case, the results show the indole was more electron-rich than the anisole, limiting the functionalization capabilities of *tert*-butyl 3-((4-methoxyphenyl) (((trifluoromethyl)sulfonyl)oxy-λ^3-iodanyl)-1*H*-indole-1-carboxylate. To try to shift the electronics more towards indole functionalization, I attempted two more electron-withdrawing protecting groups: acetyl and tosyl.

I synthesized 1-(3-iodo-1*H*-indol-1-yl)ethan-1-one from 2-iodoindole (Scheme 1-16). Compound **58** had no synthetic precedence, so I modified the Boc protection using

acetic anhydride, DMAP, and triethylamine, neat. For the formation of (1-acetyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate, I did the transmetalation with iPrMgCl at -78°C, and quenched with a THF solution of (4-methoxyphenyl)-λ^3-iodanediyl diacetate at -78°C before warming to room temperature. After workup, I did an ion exchange with sodium triflate to get the desired product.



Scheme 1-16 Synthesis of (1-acetyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate

I attempted the thermolysis of (1-acetyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate with 1-ethoxy-1-hydroxy-2-(hydroxy(oxo)ammonio)propan-2-ide, which was the functional group for Kempinger's work. What I found was that the acetate diaryliodonium salt was not stable under thermolysis conditions, and a large amount of 4-iodoanisole was produced (Figure 1-7). Multiple attempts at the thermolysis reaction showed the same results, and I decided to move forward with the more electron-withdrawing tosyl.

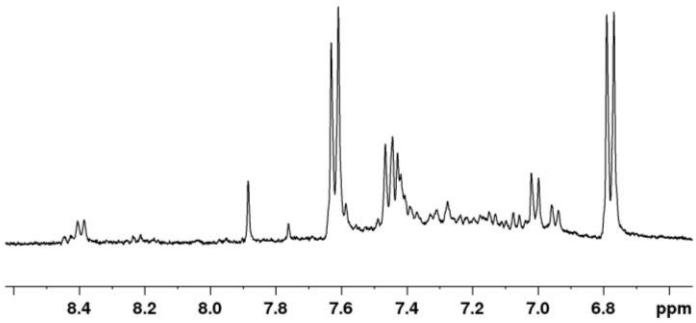
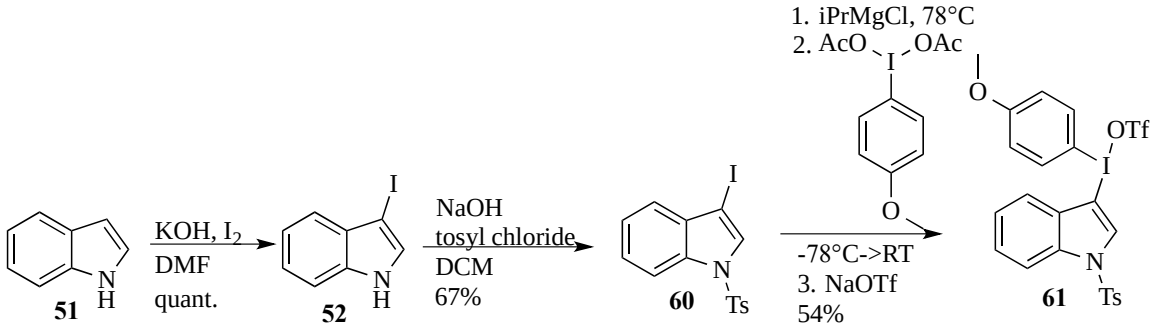


Figure 1-7 Crude thermolysis of (1-acetyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate with 1-ethoxy-1-hydroxy-2-(hydroxy(oxo)ammonio)propan-2-ide

Synthesis of (4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)-λ^3-iodanyl trifluoromethanesulfonate proceeded similarly to the Boc- and acetyl-protected compounds (Scheme 1-17). Indole was iodinated with KOH/I_2, and then protected with sodium hydroxide and tosyl chloride in dichloromethane[98]. For the formation of (4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)-λ^3-iodanyl, I did the transmetalation with iPrMgCl at -78°C and quenched with a THF solution of (4-methoxyphenyl)-λ^3-iodanediyl diacetate at -78°C before warming to room temperature. After workup, I did an ion exchange with sodium triflate to get the desired product.



Scheme 1-17 Synthesis of (4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)-λ^3-iodanyl

I attempted the thermolysis with 1-ethoxy-1-hydroxy-2-(hydroxy(oxo)ammonio)propan-2-ide to synthesize a quaternary tryptophan (Figure 1-8). The thermolysis showed better selectivity than the previous compounds. I was able to achieve approximately a 45% yield of the desired functionalized indole, (4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)-λ^3-iodanyl. However, I also had a 55% yield of the functionalized anisole.

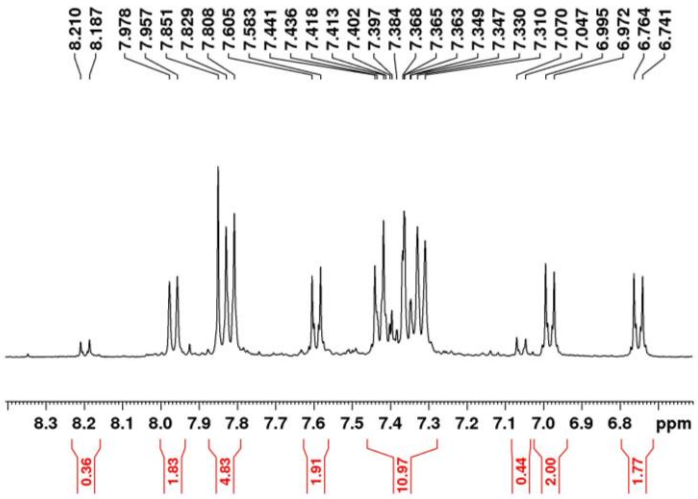
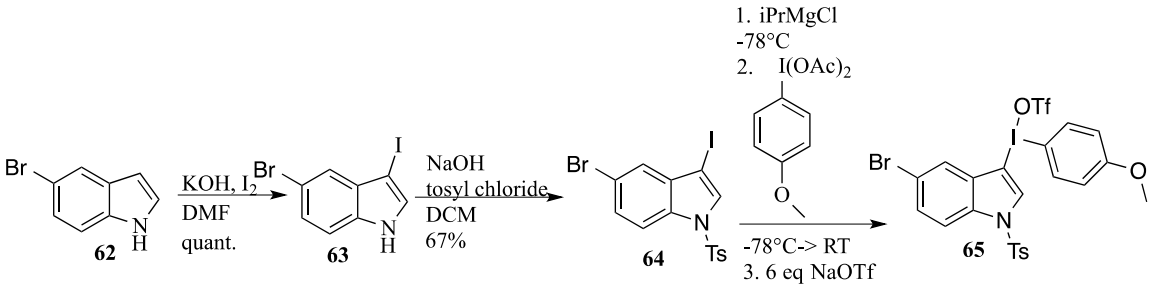


Figure 1-8 Crude thermolysis of (4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)-λ^3-iodanyl with 1-ethoxy-1-hydroxy-2-(hydroxy(oxo)ammonio)propan-2-ide

With the poorly-selective thermolysis data, continuing forward to attempt to synthesize a salt for the quaternary amino acid project was not feasible. The C-2 position of indole is too electron rich for selective thermolysis without a stronger directing group.

Finally, I wanted to synthesize an indole with a bromide to test the selectivity of the Grignard transmetalation (Scheme 1-18). The brominated-quaternary tryptophan is a known reverse transcriptase inhibitors.[85] I began with the iodination 5-bromoindole,[99] **62**, with KOH/I_2 **63** and protected with tosyl chloride/NaOH **64**. I performed the

transmetalation with iPrMgCl and quenched with (4-methoxyphenyl)-λ^3-iodanediyl diacetate to give (5-bromo-1-tosyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate **65**. After workup, I did an ion exchange with sodium triflate. The transmetalation was completely selective, and no diaryliodonium salt was detected at the C-5 position. With a successful thermolysis, the synthesis of a quaternary tryptophan via diaryliodonium salt could also be used to again form a diaryliodonium salt at the C5 position.



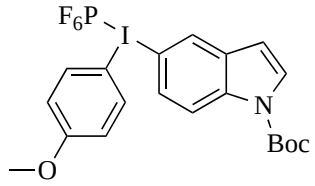
Scheme 1-18 Synthesis of(5-bromo-1-tosyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate

1.3.1 Conclusion

Indoles are of synthetic interest because of their electron rich properties and their vast uses in nature. By synthesizing a diaryliodonium salt on the benzene ring, diaryliodonium salts can be formed from drugs, neurotransmitters, psychedelic drugs, and many others. Indole diaryliodonium salts can be used in PET to study the metabolism of these tracers. Because of the electron-rich benzene ring of the indole, synthesis of a diaryliodonium salt will require an electron-withdrawing protecting group to be used for functionalization chemistry. Groups such as tosyl or acetate can be explored using the presented syntheses.

More interesting however, is the formation of diaryliodonium salts at the C-2 position. The electronics are too strong for selective functionalization of indole with anisole. However, it can be explored as alternative directing group for electron rich molecules. The electron-rich molecules presented in this chapter are stable, and may be explored in the future.

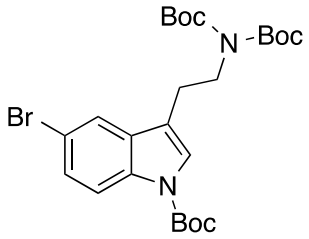
1.3.2 Experimentals



***tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate (via *tert*-butyl 5-iodo-1*H*-indole-1-carboxylate) (18)**

In a N_2 charged glove box, F-TEDA-BF_4 (134 mg, 0.38 mmol) was dissolved in 1 mL CH_3CN in a 2 mL vial. Trimethylsilyl acetate (100 mg, 0.76 mmol) in 1 mL CH_3CN was added dropwise to the solution with swirling. The solution was added to a suspension of 100 mg (0.29 mmol) *tert*-butyl 5-iodo-1*H*-indole-1-carboxylate[55] in 2 mL acetonitrile dropwise. The reaction mixture was placed in a 25 mL Schlenk flask charged with a magnetic stirbar, removed from the glove box, and stirred for 4 hours at 40 °C. The Schlenk flask was brought back into the glove box. Into the diacetate solution was added potassium (4-methoxyphenyl) trifluoroborate (62.3 mg, 0.29 mmol). Trimethylsilyl trifluoroacetate (49 mg, 0.29 mmol) was dissolved in 1 mL acetonitrile and added to the stirring solution dropwise. The reaction continued to stir for 30 minutes and was brought out of the glove box. The solution was transferred to a 50 mL round bottom flask. The solvent was removed via rotary evaporation. The resulting oil was dissolved in 10 mL dichloromethane and washed with 10 mL acetate buffer (NaOAc:HOAc = 0.5 M :0.5 M, pH = 5) and 15 mL DI water 3x. The organic layer was collected, dried with Na_2SO_4, and filtered. The filtrate was evaporated via rotary evaporation, and the oil was brought up in acetonitrile and washed with pentanes. Solvent was removed. To form the hexafluorophosphate salt, the trifluoroacetate salt was dissolved in 10 mL ethanol in a 50 mL round bottom flask charged with a magnetic stirbar. Sodium hexafluorophosphate

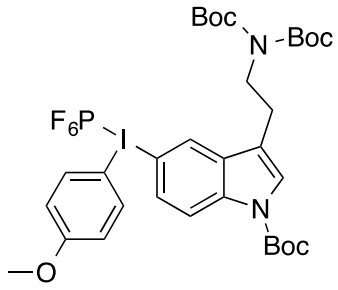
(382 mg, 2.28 mmol), was dissolved in 5 mL DI water and added dropwise to the stirring salt. The suspension was stirred for one hour at room temperature. Organic solvent was removed by rotary evaporation. The aqueous suspension was extracted with 10 mL dichloromethane 3x. The organic layers were combined, dried with $Na_2SO_,$, and filtered. The filtrate was evaporated via rotary evaporation and the residual oil was recrystallized from ethyl acetate/methyl tert butyl ether. (110 mg, 64%) ^{1}H NMR (CD_3CN, 700 MHz, 25°C): δ 8.37 (d, *J* = 1.8 Hz, 1 H), 8.2790 28 (d, *J* = 9.0 Hz, 1 H), 8.0293 03 (d, *J* = 9.2 Hz, 2 H), 7.9312 (dd, J = 9.0, 1.9 Hz, 1 H), 7.81714 (d, *J* = 3.8 Hz, 1 H), 7.0632 (d, *J* = 9.2 Hz, 2 H), 6.7600 (d, *J* = 3.8 Hz, 1 H), 3.8477 85 (s, 3 H), 1.6653 (s, 9 H). ^{13}C NMR (CD_3CN, 176 MHz, 25°C): δ 164.2, 150.0, 139.3, 138.4, 137.7, 134.3, 130.6, 130.2, 129.7, 119.0, 107.6, 107.5, 103.1, 86.3, 56.7, 28.2. ^{19}F NMR (CD_3CN, 276 MHz, 25°C) δ -73.0 (d, J = -706.2 Hz, PF_6^-, 6 F). HRMS (ESI) calculated for $C_{20}H_{21}INO_3^+$ $[M\text{-}PF_6^-]^+$ 450.0556, found 450.0568.



tert-butyl 5-bromo-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate (27)

In a 100 mL round bottom flask charged with a magnetic stirbar, 2-(5-bromo-1*H*-indol-3-yl)ethan-1-amine[56] (943 mg, 3.962 mmol) was dissolved in 6.6 mL tetrahydrofuran. 6.6 mL of saturated sodium bicarbonate was added dropwise, and the solution was stirred vigorously until no bilayer remained. The solution was cooled to

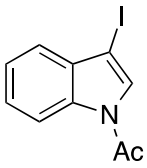
0°C. $(Boc)_2O$ (1.037 g, 4.754 mmol) was dissolved in 4.75 mL tetrahydrofuran and added dropwise. The solution was stirred for two hours at room temperature. The solution was poured into a 100 mL separator funnel. The solution was allowed to separate, and the organic layer removed. The aqueous layer was extracted with ethyl acetate (3x 20 mL). The organic layers were combined and washed with DI water (3x 30 mL) and brine (1x 30 mL). The organic layers were dried with Na_2SO_4, filtered, and solvent was removed via rotary evaporation. The yellow oil was dissolved in 40mL CH_3CN and dimethylamino pyridine (0.2870 g, 2.2565 mmol) and triethylamine (2.740 g, 27.0786 mmol) were added. The solution was cooled to 0°C and $(Boc)_2O$ (3.940 g, 18.0524 mmol) was added. The solution was stirred for 18 hours at room temperature. The solvent was removed via rotary evaporation, and the crude oil was cleaned via flash chromotography (9:1 hexanes:ethyl acetate). The remaining colorless oil was dissolved in pentane and cooled in a freezer overnight to produce 1.840 g (80%) white crystals. ^{1}HNMR (CD_3CN, 400 MHz, 25°C): δ 8.01(d, *J* = 8.8, 1 H), δ7.76 (s, 1 H), δ7.46 (s, 1 H), δ 7.43 (d, *J* = 8.8 1 H), δ 3.84 (t, *J* = 6.7, 2 H), δ 2.95 (t, *J* = 6.7, 2 H), δ 1.44 (s, 9 H), δ 1.39 (s, 18 H) ^{13}C NMR (276 MHz): 152.7, 149.5, 134.5, 132.6, 127.3, 134.7, 122.0, 117.2, 116.9, 116.1, 84.1, 82.6, 46.5, 34.3, 28.4, 28.2, 24.7, 22.5, 14.3 HRMS (ESI) calculated for $C_{25}H_{35}BrN_2O_6$ 563.1678 found 563.1553



tert-butyl 3-(2-((_tert_-butoxycarbonyl)amino)ethyl)-5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1_H_-indole-1-carboxylate (30)

In a 100 mL Schlenk flask charged with magnetic stirbar, tert-butyl 3-(2-((tert-butoxycarbonyl)amino)ethyl)-5-(trifluoro-λ^4-boranyl)-1H-indole-1-carboxylate, potassium salt (2.0 g, 3.5321 mmol) and (4-methoxyphenyl)-λ^3-iodanediyl diacetate (1.24 g, 3.5321 mmol) were dissolved in 30 mL CH_3CN. TMSTFA (0.600 g, 3.5321 mmol) was dissolved in 5 mL CH_3CN and added dropwise to the stirring solution. The solution was stirred for 1 hour at room temperature. The solution was transferred to a 100 mL found bottom flask. The solvent was removed by rotary evaporation, and the remaining oil was again dissolved in 10 mL CH_3CN with a magnetic stirbar. Sodium hexafluorophosphate (3.527 g, 21.926 mmol) was dissolved 10 mL DI water and was added to the stirring solution dropwise. The solution was stirred for two hours at room temperature. Acetonitrile was removed via rotary evaporation, and the aqueous suspension was extracted with dichloromethane (3x 15 mL). The organic layers were combined, dried with Na_2SO_4, filtered and solvent removed via rotary evaporation. The remaining oil was recrystallized from ethyl acetate/ether. ^{1}HNMR (CD_3CN, 400 MHz, 25°C): δ 8.37 (d, *J* = 1.8, 1 H), δ 8.21 (d, *J* = 8.9, 1 H), δ 8.02 (d, *J* = 9.1, 2 H), δ 7.92 (dd, J = 8.9, 1.9), δ 7.57 (s, 1 H) δ 7.02 (d, *J* = 9.2, 2 H) δ 3.85 (t, *J* = 6.7, 2 H), δ 3.81 (s, 3 H) δ 2.98 (t, *J* = 6.7, 2 H), δ 1.62 (s, 9 H) δ 1.31 (s, 18 H) ^{13}C NMR (276 MHz): 164.5,

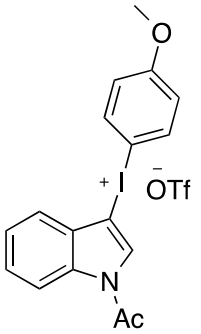
153.8, 138.6, 134.9, 131.2, 128.8, 128.0, 120.1, 119.4, 119.0, 117.9, 107.5, 103.4, 86.5, 83.3, 57.0, 49.8, 46.9, 28.5, 28.4, 28.4, 27.6, 25.2 HRMS (ESI) $C_{32}H_{42}N_2O_7I$, calculated 393.2037, found 393.2046



1-(3-iodo-1*H*-indol-1-yl)ethan-1-one (62)

In a 100 mL round bottom flask charged with magnetic stirbar, indole (0.500 g, 4.268 mmol) and crushed potassium hydroxide (0.599 g, 10.6701 mmol) were dissolved in dimethylformamide (0.5 M, 10 mL). The reaction was stirred at room temperature for 20 minutes. Iodine (1.086 g, 4.268 mmol) was dissolved in 5 mL dimethylformamide and added to indole solution. After 45 minutes, the reaction was poured over DI water and filtered.

The precipitate was dried *in vacuo* in a 50 mL round bottom flask charged with a magnetic stirbar. 2.2 mL of acetic anhydride, 4-dimethyl aminopyridine (0.028 g, 0.2227 mmol) and triethylamine (0.72 mL) were added. The reaction was stirred overnight. Solvent was removed *in vacuo* and the product was purified by column chromatography (9:1 hexanes:ethyl acetate). (2.250 g, 74.2% over 2 steps). ^{1}H NMR (CD_3CN, 400 MHz, 25°C): δ 8.35 (d, J = 7.8, 1 H), 7.83 (s, 1 H), 7.38 (m, J = 8.3, 3 H), 2.58 (s, 3 H). ^{13}C NMR (CD_3CN, 176 MHz 25°C): δ 169.8, 136.0, 133.0, 132.3, 126.9, 125.1, 122.1, 117.1, 67.0, 24.4. HRMS (ESI) calculated for $C_{10}H_8NOI$: 284.9651, found 284.9659.

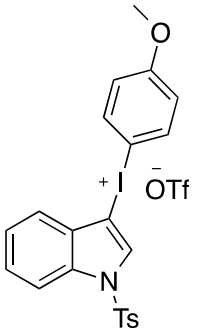


(1-acetyl-1*H*-indol-3-yl)(4-methoxyphenyl)iodonium trifluoromethanesulfonate (63)

Under inert N_2 atmosphere in a 50 mL Schlenk flask charged with a stirbar, 1-(3-iodo-1*H*-indol-1-yl)ethan-1-one (1.0 g, 3.5091 mmol) was dissolved in 2 mL dry THF. The solution was cooled to -78°C, and *i*PrMgCl (2.0 M, 5.2635 mmol, 2.63 mL) was added. The solution was stirred for 5 minutes at -78°C. The solution was added quickly to a suspension of (4-methoxyphenyl)-λ^3-iodanediyl diacetate (3.5807 g, 10.5274 mmol) in 3 mL dry THF in a 50 mL Schlenk flask. The solution was stirred at -78 C for 10 minutes. The ice bath was removed and the solution was stirred for 1 hour at room temperature.

The solvent was removed *in vacuo* over 18 hours. The yellow oil was dissolved in 5 mL methanol. Sodium trifluoromethane sulfonate (2.470 g, 7.0182 mmol) was dissolved in 5 mL DI water and added dropwise with stirring. The solution was stirred for 1 hour and the organic solvent was removed by rotary evaporation. The aqueous solution was extracted 3x with 10 mL dichloromethane. The organic layers were combined, dried with Na_2SO_4, and filtered. The filtrate was dried *in vacuo*. The crude oil was recrystallized from ethyl acetate/ether. (1.063 g, 56%) ^{1}H NMR (CD_3CN, 700 MHz, 25°C): δ 8.60 (s, 1 H), 8.47 (d, J = 8.3, 1 H), 8.05 (d, J = 9.1, 2 H), 7.69 (d, J = 7.8, 1 H), 7.55 (dd, J = 7.7, 1 H), 7.51 (dd, J = 7.6, 1 H), 7.03 (d, J = 9.2, 2 H), 3.82 (s, 3 H), 2.72

(s, 3 H) ^{13}C NMR (276 MHz): δ 170.3, 164.2, 138.0, 137.5, 136.1, 129.0, 128.3, 126.4, 120.4, 119.0, 118.0, 103.2, 85.1, 56.8, 24.4 HRMS (ESI) calculated for $C_{17}H_{15}NO_2I$: 392.0148, found 392.0161.

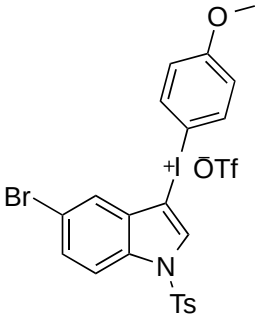


(4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)iodonium trifluoromethanesulfonate (75)

Under inert N_2 atmosphere in a 50 mL Schlenk flask charged with a stirbar, 3-iodo-1-tosyl-1*H*-indole[98] (0.500g, 1.2596 mmol) was dissolved in 2 mL dry THF. The solution was cooled to -78°C, and *i*PrMgCl (2.0 M, 1.8894 mmol, .95 mL) was added dropwise. The solution was stirred for 5 minutes at -78°C, and cannulated into a suspension of (4-methoxyphenyl)-λ^3-iodanediyl diacetate in dry THF at -78°C. The solution was stirred for 10 minutes at -78°C. The ice bath was removed and solution was stirred for 1 hour at room temperature.

The solvent was removed *in vacuo*, and the remaining yellow oil was dissolved in 5 mL methanol. Sodium trifluoromethane sulfonate (1.300 g, 7.5574 mmol) was dissolved in 5 mL DI water and added dropwise. The solution was stirred for 1 hour at room temperature. The organic solvent was removed by rotary evaporation. The remaining aqueous solution was extracted with 10 mL dichloromethane 3x. The organic layers were combined, dried with Na_2SO_4, and filtered. The filtrate was dried *in vacuo*, and the remaining crude oil was recrystallized from ethyl acetate/ether. ^{1}H NMR

(CD_3CN, 700 MHz, 25°C): δ 8.59 (s, 1 H), 8.02 (d, J = 8.4, 1 H), 7.98 (d, J = 9.0, 2 H), 7.87 (d, J = 8.3, 2 H), 7.60 (d, j = 7.9, 1 H), 7.50 (dd, J = 7.8, 1 H), 7.43 (dd, J = 7.6, 1 H), 7.35 (d, J = 8.1, 2 H), 6.96 (d, J = 9.0, 2 H), 3.79 (s, 3 H), 2.34 (s, 3 H). ^{13}C NMR (CD_3CN, 176 MHz, 25°C): δ 164.2, 148.3, 138.3, 138.0, 136.5, 135.0, 134.4, 131.6, 129.5, 129.4, 128.4, 128.3, 128.2, 126.6, 119.0, 103.6, 86.5, 56.7, 21.7. HRMS (ESI) calculated for $C_{22}H_{19}NO_3SI$ 504.0106, found 504.0114



(5-Bromo -1-tosyl-1*H*-indol-3-yl)(4-methoxyphenyl)iodonium hexafluorophosphate(V) (79)

Under inert N_2 atmosphere in a 50 mL Schlenk flask charged with a stirbar, 5-bromo-3-iodo-1-tosyl-1*H*-indole[99] (2.0 g, 4.21167 mmol) was dissolved in 2 mL dry THF. The solution was cooled to -78°C, and *i*PrMgCl (2.0 M, 6.3175 mmol, 3.16 mL) was added dropwise. The solution was stirred for 10 minutes at -78°C. The Grignard solution was cannulated into a 50 mL Schlenk flask charged with magnetic stirbar and a solution of (4-methoxyphenyl)-λ^3-iodanediyl diacetate (2.865 g, 8.4233 mmol) in 2 mL THF at -78°C. The solution was stirred for ten minutes at -78°C. The ice bath was removed, and the solution was allowed to stir for 1 hour at room temperature.

The solvent was removed *in vacuo*, and dissolved in 5 mL methanol. Sodium trifluoromethane sulfonate (4.34 g, 25.27 mmol) was dissolved in 5 mL DI water and added dropwise. The solution was stirred for 1 hour at room temperature. The organic

solvent was removed by rotary evaporation. The remaining aqueous solution was extracted with 3x with 10 mL dichloromethane. The organic extractions were combined, dried with Na_2SO_4, and filtered. The filtrate solvent was removed *in vacuo*, and the remaining crude oil was recrystallized from ethyl acetate/ether.

δ 8.58 (s, 1H), 7.99 (d, *J* = 9.1 Hz, 2 H), 7.94 (d, *J* = 8.9 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 2 H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.61 (m, *J* = 3.6, 1.7 Hz 1 H), 7.37 (d, J = 8.2 Hz, 2 H), 6.99 (d, *J* = 9.2 Hz, 2 H), 3.81 (s, 3 H), 2.36 (s, 3 H). ^{13}C NMR (276 MHz): δ 164.1, 148.5, 139.3, 138.1, 137.7, 134.2, 131.6, 131.2, 131.0, 128.4, 123.9, 119.0, 117.6, 116.8103.9, 85.3, 56.7, 21.7. HRMS (ESI) calculated for $C_{22}H_{19}INO_3S$ 581.9236, found 581.9233

CHAPTER 2

TOWARDS THE DEVELOPMENT OF POLYMERS FOR DIARYLIODONIUM SALT THERMOLYSIS FOR USE IN POSITRON EMISSION TOMOGRAPHY

2.1 Introduction of Resins for PET

A radiotracer's success is dependent on its binding to a target and visibility on a PET scan. Binding and visibility can be improved by other factors like purity, enantiopurity, and time of synthesis. Purity and time of synthesis can be improved by manipulation of protecting groups and synthetic strategies before radiosynthesis.

Radiochemical yield (RCY) is the yield of radiochemical separation divided by the activity originally present.[100] Specific activity is the activity per set amount of nucleotide.[100] These two values are most commonly used to discuss the usefulness of a radiotracer. While some commercial syntheses are used with radiochemical yields of under 10%,[101-103] more successful syntheses have greater than a 50% yield.[104,105] Factors like time of synthesis and purity play a large part in yields. Shorter syntheses result in lower decay of the radioisotopes, and more pure compounds require less time after introduction of the radionucleotide.

To optimize radiochemical yields and specific activity, I developed methodology that could decrease time of synthesis and increase purity. I planned to do this by functionalizing diaryliodonium salts on a resin as a precursor for PET.

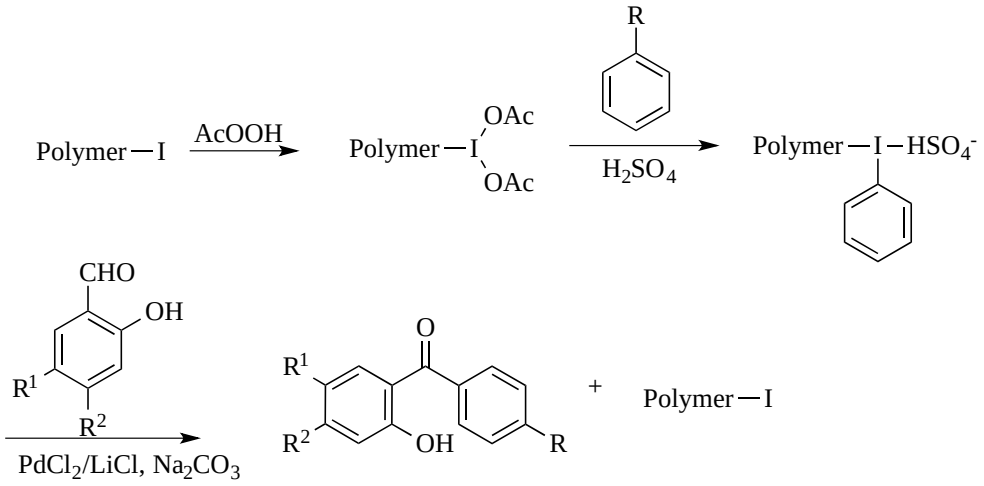
[^{18}F]-Fluorine is synthesized by bombarding $H_2{}^{18}O$ with a high-energy proton beam.[106] Protons displace the ^{18}O neutrons from the nucleus, which produces an aqueous ^{18}F-. The fluoride anion is trapped on an exchange resin to remove excess water. The fluoride is coordinated to a cryptand, usually 1,10-diaza-4,7,13,16,21,24-

hexaoxabicyclo[8.8.8]hexacosane (Kryptofix). Water is removed by distillation with an apolar aprotic solvent such as acetonitrile. The tracer is then introduced. For the DiMagno group, the tracer is a diaryliodonium salt. After thermolysis, the products are purified. The products are loaded onto a silica separation pack, the reactor vial is rinsed, and the separation pack is eluted back into the reactor vial. Solvent is evaporated, and the products are deprotected, neutralized and purified by HPLC. The purification process should give a pure product, but may take upwards of an hour to complete. The main issue using diaryliodonium salts for radiofluorination is dilution of the products of the thermolysis reaction. Up to 3 side products are formed and require purification after introduction of the radionucleotide. By using a resin, all side products from thermolysis (Figure 1-4 in Chapter 1) would remain on the resin, and theoretically only the functionalized tracer would be washed off.

Synthesis of iodine (III) on resins have been successfully accomplished for use as oxidants[107,108] and for the synthesis of heterocycles.[109] Polymer-supported hypervalent iodine reagents are useful in the pharmaceutical and agrochemical industries because of their low toxicity and high yields.[110] Phenyliodine(III) diacetate was the first hypervalent iodine compound synthesized on a polymer-support by Chen in 1994.[111] Since then, polymer-supported iodine(III) compounds have been vastly used for oxidation in a wide variety of solvents, including water[112] and methanol,[113] proving their stability and usefulness to a broad spectrum of reagents.

Fewer syntheses have been accomplished for diaryliodonium salts on polymer support. Chen published syntheses[114] of diaryliodonium salts used for functionalized of

Carbon and Sulfur ions. Their standard synthesis (Scheme 2-1) included oxidation by acetic acid and coupling with a functionalized arene.

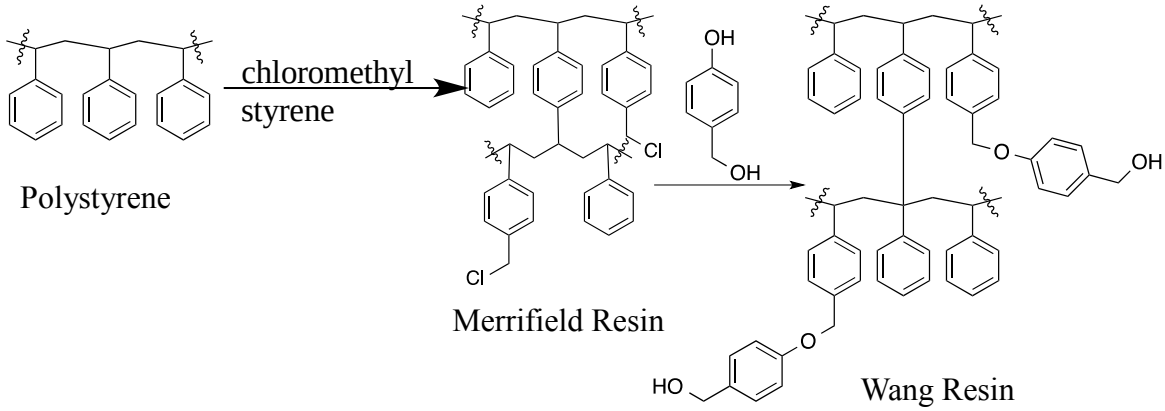


Scheme 2-1 Chen Synthesis and Thermolysis of Polymer-Supported Diaryliodonium Salts

Knowing that diaryliodonium salts could be synthesized on a polymer, I believed we could use DiMagno methodology to synthesize diaryliodonium salts with similar success to our solid-state syntheses.

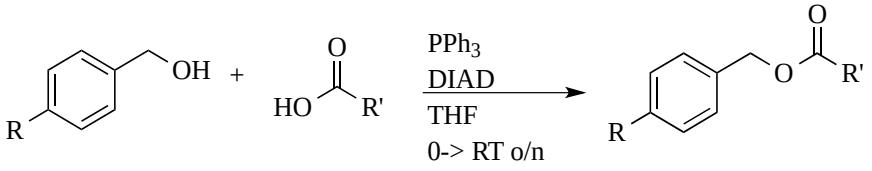
An ideal synthesis of a functionalized solid-phase resin would need to be relatively simple, efficient, and scalable. We chose to begin with the Wang resin because it met these criteria. The Wang resin is commercially available and often used on a large scale for peptide synthesis.[115] It is also useful because of its easy decoupling by trifluoroacetic acid to show the yield of labeling.[116]

The commercial synthesis of the Wang Resin (Scheme 2-2) begins with the coupling polystyrene with chloromethyl styrene. This gives the commercially Merrifield resin. The Merrifield resin is then coupled with 4-(hydroxymethyl)phenol to give Wang Resin.[117]



Scheme 2-2 Synthesis of Wang Resin from Polystyrene

Synthesis of the Wang Resin from Merrifield resin is not quantitative, and remaining chloride ions are present on the resin. The remaining benzyl chloride can later undergo S_N2 reaction with the radioactive $^{18}F^-$ source, and therefore has to be exchanged prior to synthesis. To remove all remaining chloride ions, I began my synthesis by "pre-treating" the Wang resin with refluxing potassium hydroxide/water. I then coupled the desired substrate by Mitsunobu esterification (Scheme 2-3). To accommodate the reaction, I synthesized each of the substrates with a terminal carboxylic acid.

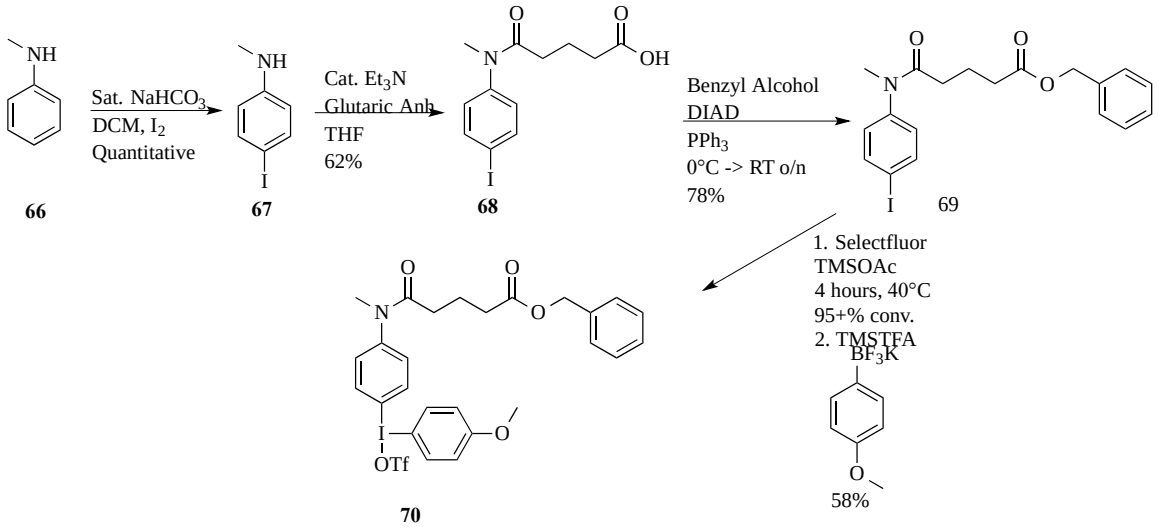


Scheme 2-3 General Mitsunobu Procedure for Functionalizing Wang Resin

After coupling each substrate onto the resin, I needed to cap any remain terminal alcohols groups. I esterified all the benzyl alcohols by stirring in acetic anhydride.

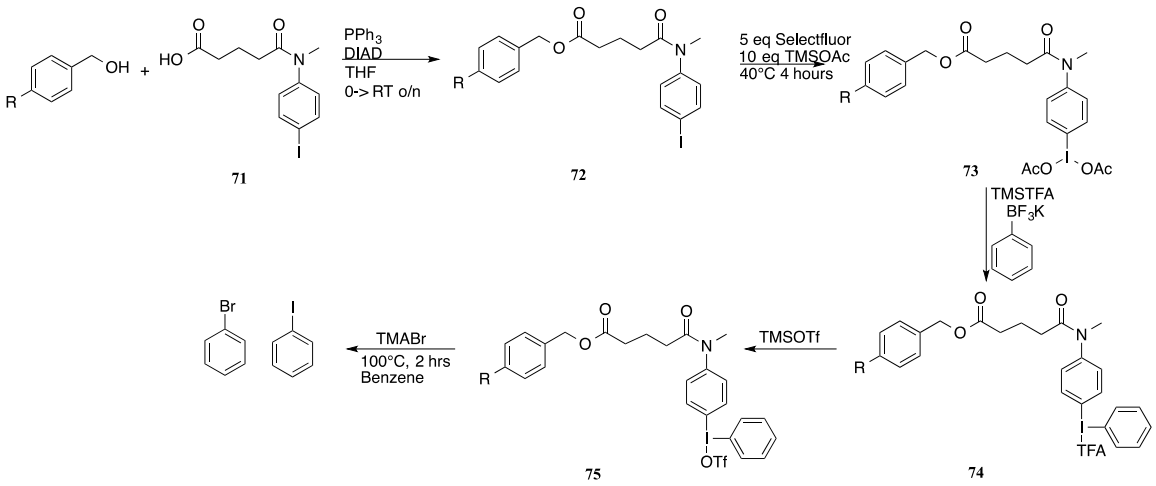
2.2 Synthesis of Aniline Test Compound and Aniline Based Wang Resin

I first chose an aniline-based moiety because of its simplicity of synthesis. Synthesis (Scheme 2-4) began with the iodination of N-methyl aniline[118] **66** with saturated bicarbonate/iodine in dichloromethane to give **67**. I then protected the moderately unstable aniline with glutaric anhydride and catalytic triethylamine in tetrahydrofuran to give the desired aniline **68** with terminal carboxylic acid in 62% yield. To mock the Wang resin, I used benzyl alcohol to synthesize the test compounds for Mitsunobu esterification. To synthesize **69**, I used the Mitsunobu esterification with triphenyl phosphine and diisopropyl azodicarboxylate neat. I oxidized **69** with *Selectfluor*™ and TMSOAc for 4 hours at 40°C and then coupled with trifluoro(phenyl)-λ^4-borane, potassium salt to successfully synthesize benzyl 5-((4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-λ^3-iodanyl)phenyl)(methyl)amino)-5-oxopentanoate **70**. The successful synthesis of **70** and subsequent thermolysis of the aniline test compound proved that synthesis of this aniline moiety on a resin should be hypothetically possible.



Scheme 2-4 Synthesis of benzyl 5-((4-((4-methoxyphenyl)(2,2,2-trifluoroacetyl)-λ^3-iodanyl)phenyl)(methyl)amino)-5-oxopentanoate

I continued by using the Mitsunobu reaction to couple 5-((4-iodophenyl)(methyl)amino)-5-oxopentanoic acid to the Wang resin (Scheme 2-5). Using an excess of *Selectfluor* ™ and TMSOAc, I oxidized the resin, washed away the excess oxidant, and coupled with TMSTFA and trifluoro(phenyl)-λ^4-borane, potassium salt. I chose the phenyl to test the electronics of the resin. We know that aniline is less electron-rich than anisole, however, I did not know the directing-group ability of the aniline compared to less electron-rich compounds such as phenyl.



Scheme 2-5 Synthesis of Aniline Diaryliodonium Salt on Wang Resin

I exchanged the trifluoroacetate counterion to triflate. To do this, I passed through TMSOTf in acetonitrile until no trifluoroacetate was detected by NMR of the flitrate. I proceeded with the thermolysis reaction with tetra butylammonium bromide, which after 2 hours at 100°C showed incomplete selectivity in benzene solvent.

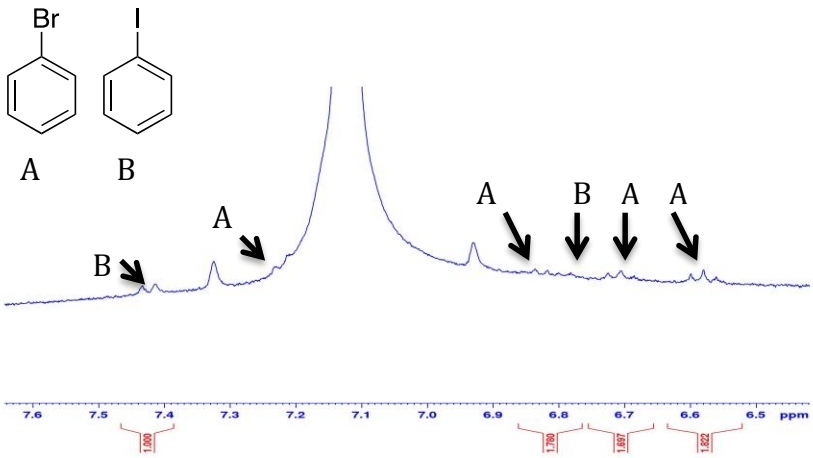
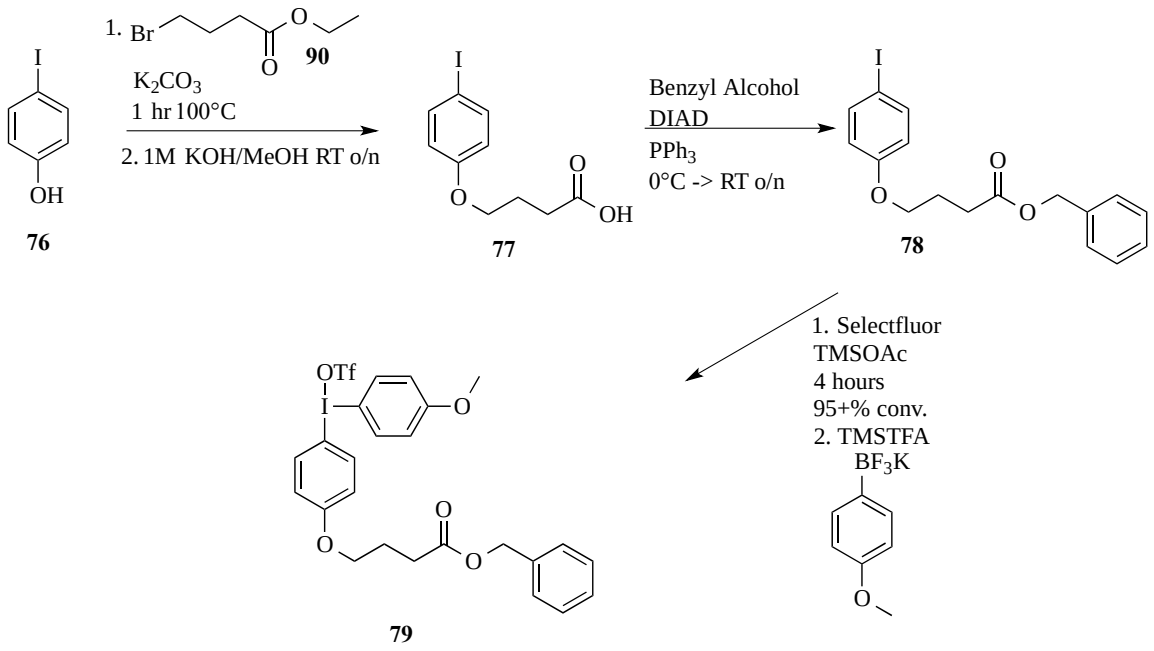


Figure 2-1 Thermolysis of Aniline Resin with TMABr

In the small quantities that are used in an NMR reaction of the resin, it was not possible to quantify the exact ratio. However, comparison with the NMRs of both bromobenzene and iodobenzene, it was confirmed that both of these were present in the filtrate. Because of the incomplete selectivity, I knew that continuing with the aniline resin would not be useful due to its incomplete selectivity for even electron poor substrates.

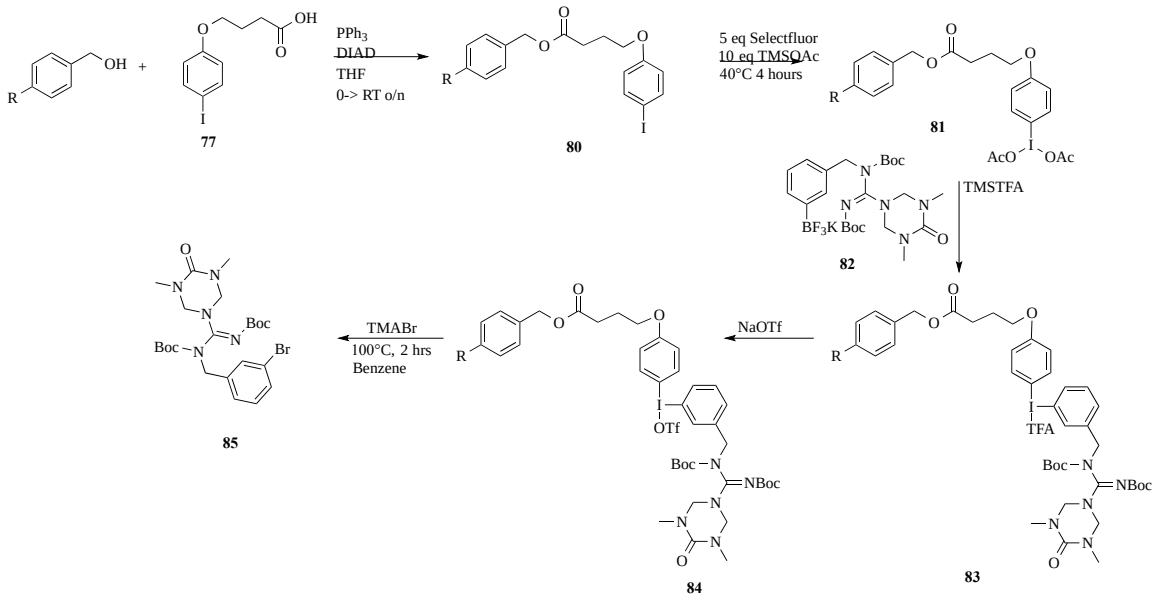
2.3 Synthesis of Anisole Test Compound and Anisole Based Wang Resin

Because of the lack of selectivity in the aniline resin, I carried forward with the more electron rich anisole. Anisole is the standard electron-rich directing group in the DiMagno lab (Scheme 2-6). I began with the etherification of 4-iodo phenol **76** with ethyl-4-bromobutanoate **77**[119] to give 4-(4-iodophenoxy)butanoic acid **78**. Esterification by Mitsunobu reaction with benzyl alcohol gave the desired test compound benzyl 4-(4-iodophenoxy)butanoate **79**. Oxidation and coupling of the anisole compound with trifluoro(4-methoxyphenyl)-λ^4-borane, potassium salt, potassium salt gave the desired benzyl 4-(4-((4-methoxyphenyl)(2,2,2-trifluoroacetyl)-λ^3-iodanyl)phenoxy)butanoate.



Scheme 2-6 Synthesis and functionalization of benzyl 4-(4-((4-methoxyphenyl)(2,2,2-trifluoroacetyl)-λ^3-iodanyl)phenoxy)butanoate

Because we knew that this resin was equivalent anisole, our standard nucleophile director for diaryliodonium salt thermolysis, I decided to try the reaction using the pharmaceutically relevant compound metaiodobenzyl guanidine (MIBG) on the Wang resin. MIBG will be discussed in greater detail later in chapter 2. The MIBG diaryliodonium salt had been previously synthesized and radiofluorinated and radioiodinated by Dr. Bao Hu from our group. Using his compound, *tert*-butyl (*E*)-(((*tert*-butoxycarbonyl)imino)(3,5-dimethyl-4-oxo-1,3,5-triazinan-1-yl)methyl)(3-(trifluoro-l^4-boranyl)benzyl)carbamate, potassium salt **82**, we hoped to anchor it onto a resin, making an already highly desirable radiotracer even more useful.



Scheme 2-7 Functionalization of Wang Resin with MIBG diaryliodonium salt

I did a Mitsunobu esterification using Wang resin and 4-(4-iodophenoxy)butanoic acid **77**. I oxidized the resin with an excess of TMSOAc and *Selectfluor*^{TM}, washed it with acetonitrile, and coupled it with *tert*-butyl (*E*)-(((*tert*-butoxycarbonyl)imino)(3,5-dimethyl-4-oxo-1,3,5-triazinan-1-yl)methyl)(3-(trifluoro-λ^4-boranyl)benzyl)carbamate, potassium salt **82**. I tried passing dilute TMSOTf in acetonitrile like I had done with the aniline resin, however, the anisole resin decomposed. Instead, I stirred the resin in an aqueous solution of sodium triflate until there was complete exchange by NMR of the filtrate (Scheme 2-7).

I did a thermolysis of the resin with TMABr overnight at 100°C. What I found was that the only MIBG product observed was the brominated product. However, there was also other observable side products presumed to be from the resin (Figure 2-2).

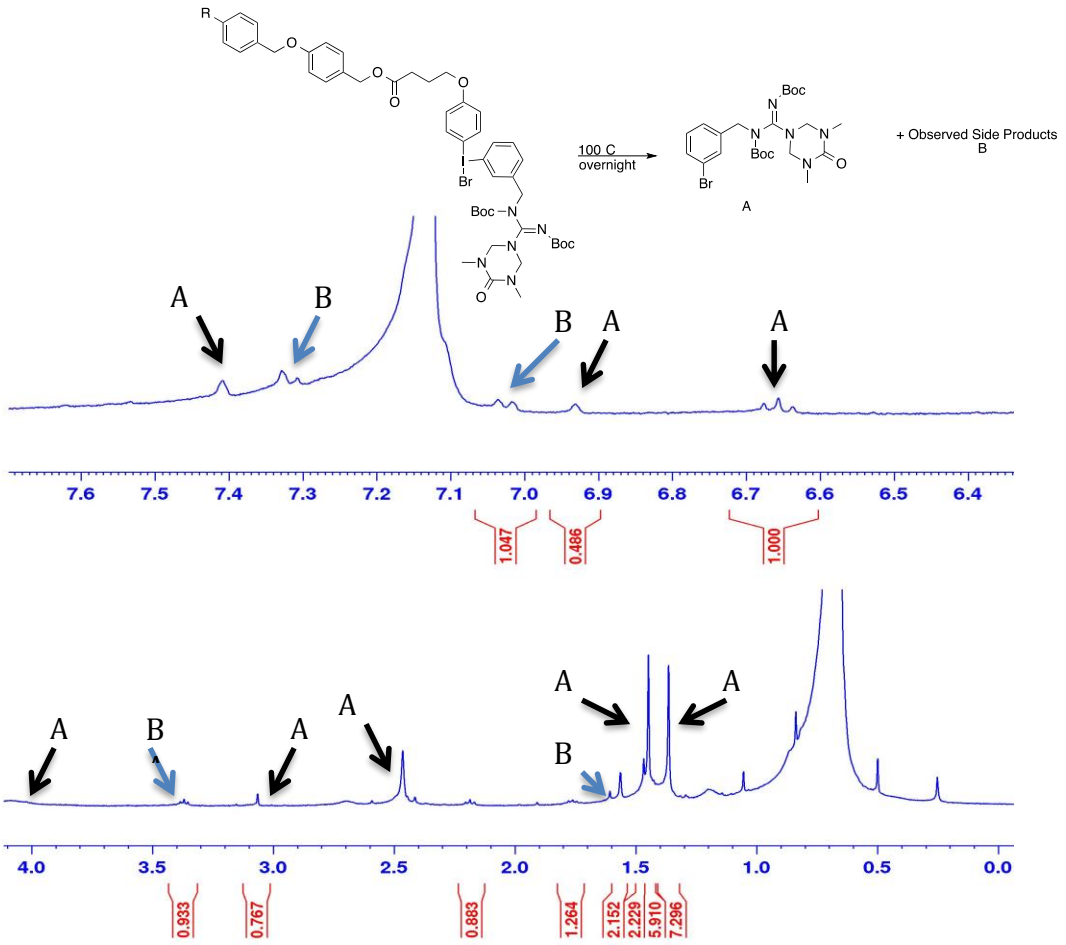


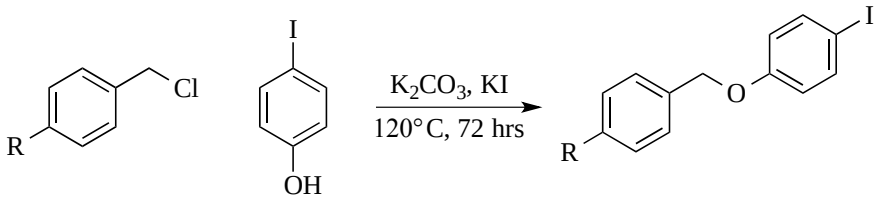
Figure 2-2 Thermolysis of Wang Resin with MIBG diaryliodonium salt

After multiple attempts with this reaction, there seemed to be no solution for the extra-cleaved products. Because of the issue, another synthetic strategy needs to be pursued.

2.4 Synthesis of Anisole Based Merrifield Resin

The Merrifield resin, as previously discussed, is synthesized by reacting polystyrene with chloromethyl styrene. By using this resin, my synthesis was simplified because it was only necessary to do an S_N2 reaction with 4-iodophenol (Scheme 2-8). I stirred the Merrifield resin, 4-iodophenol, potassium carbonate, and potassium iodide in

DMF, and after 72 hours at 120°C, I filtered and washed the resin. I capped the resin by refluxing methanol with potassium carbonate.



Scheme 2-8 Functionalization of Merrifield Resin

The Merrifield resin has potential moving forward as a resin option. We believed that the side products produced by the Wang Resin was from cleaving across the ester bond, which is not present in the Merrifield Resin.

2.5 Introduction of Meta-iodobenzyl Guanidine and Future Directions

MIBG is a radiolabelled molecule similar to noradrenaline (Figure 2-3). It is taken up through the neuronal uptake I system and is stored in the noradrenergic neuorsecretory granules, also similar to noradrenaline.[119] It is well-known that its I-123 and I-131 radioisotopes can be used to image adrenergic tissues,[120] pheochromocytomas,[121] and neuroblastomas.[122] It has largely overtaken CT scans and MRI scans for detecting these tumors. CT scans can detect tumors 2 cm in diameter, however, this leaves a substantial number of smaller, and often-malignant tumors undetected.[120] ($^{123/125/131}$I) MIBG is used and treat to detect these tumors.

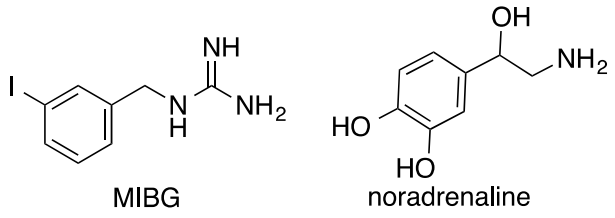
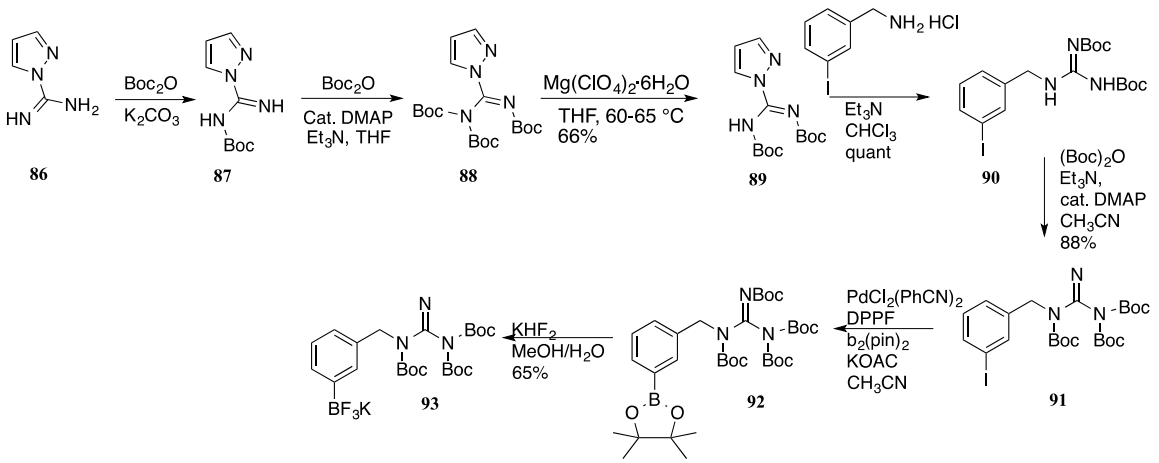


Figure 2-3 MIBG and Noradrenaline

^{131}I-MIBG was first developed for the imaging of the sympathetic innervation of the heart[123] and as well as the adrenal medulla.[120] In 1985, Shapiro[124] showed that in large doses ^{131}I-MIBG could also be used for tumor regression in malignant pheochromocytomas. Approximately 90% of I-131 decay is beta radiation, which causes tissue damage to the cells it penetrates as well as cells up to several millimeters away. It is also visible by imaging techniques in large doses because the remaining 10% of decay is via gamma radiation. ^{123}I-MIBG is used in SPECT-CT[125] for diagnosis of neuroblastoma. ^{18}F-MFBG has also become of recent interest to our lab[126] because of its low half-life and superior imaging quality[127-129].

Because of the large amount of work in our lab and the interest that is growing in MIBG, the future goal is to functionalize MIBG on a finalized resin. Previous work by Dr. Hu in our lab[125] guided my synthesis of a boronate precursor of the desired salt. Dr. Hu originally synthesized the tetrakis-Boc protected diaryliodonium salt, but was only able to obtain a 95% yield that was unable to be purified by recrystallization[126]. The "greasiness" of this compound makes it unable to be used as a radiochemical precursor. Because of this, **82** was synthesized for non-polymer use. However, while pursuing these compounds on a polymer, I knew that recrystallization and purity would not be an issue, and that the tetra-kis Boc protected MIBG had a less harsh deprotection strategy. I chose to carry forward with a new synthesis of the **93**, which had not previously been synthesized by our lab or others (Scheme 2-9).



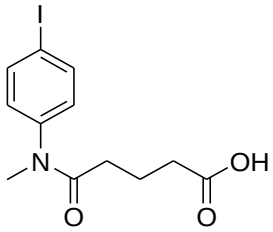
Scheme 2-9 Synthesis of *tert*-butyl ((λ^2-azanylidene)(bis(*tert*-butoxycarbonyl)amino)methyl)(3-(trifluoro-λ^4-boranyl)benzyl)carbamate, potassium salt

The commercially available 1*H*-pyrazole-1-carboximidamide **86** was Boc protected to give *tert*-butyl (*E*)-(*tert*-butoxycarbonyl)(((*tert*-butoxycarbonyl)imino)(1*H*-pyrazol-1-yl)methyl)carbamate **87**.[130] Using magnesium perchlorate hexahydrate, I did a single Boc deprotection for **88**, followed by a coupling with (3-iodophenyl)methanamine hydrochloride[126] to give **89**. I then did a final Boc protection **90**, synthesized the boronic ester using palladium catalysis **91**, and fluorinated with potassium bifluoride **92**.

Because of this work, future works can be done to synthesize an array of compounds on different resins. While I was unable to synthesize a resin with a pharmaceutically relevant compound on it, I did discover that oxidation by *Selectfluor*™ and TMSOAc and our thermolysis are possible. This has shown that this chemistry is very applicable for solid-phase work, and can be used in the future to even possibly design a radiosynthesis on a polymer.

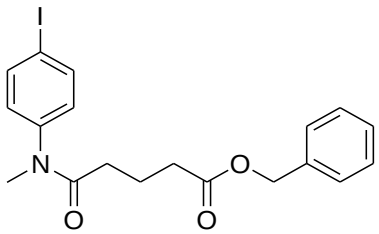
2.5 Experimentals

5-((4-Iodophenyl)(methyl)amino)-5-oxopentanoic acid



N-methyl-4-iodo-aniline (21.75 g, 93.33 mmol) was dissolved in 95 mL of acetonitrile. Triethylamine (9.44 g, 93.33 mmol) and glutaric anhydride (15.97 g, 139.99 mmol) were added. The solution was stirred overnight at room temperature. The solvent was removed and then purified by column chromatography (80:20 hexanes:ethyl acetate). Glutaric anhydride was left over after purification, and the brown oil was purified by recrystallization (THF/Hexanes) to produce a white solid (25.4 g, 62%). ^{1}H NMR (acetone, 700 MHz) δ 7.81 (d, *J* = 7.0, 2 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 3.78 (s, 1 H), 3.20 (s, 3 H), 2.26 (s, 2 H), 2.1413 (s, 2H), 1.807081 (, m, J = 6.61706 Hz, 2 H) ^{13}C NMR (acetone-d6, 276 MHz, 25° C) δ 174.4, 172.0, 145.3, 139.4, 130.7, 69.3, 54.7, 27.3, 33.4, 21.3. HRMS (ESI) calculated for $C_{12}H_{13}INO_3^-$ $[M+Na]^+$ 369.9916, found 369.9922.

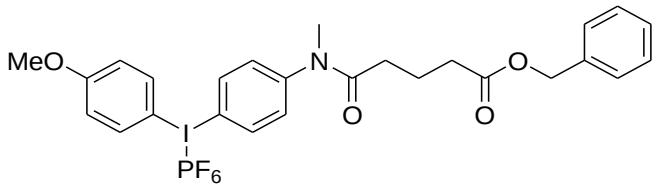
benzyl Benzyl 5-((4-iodophenyl)(methyl)amino)-5-oxopentanoate



5-((4-iodophenyl)(methyl)amino)-5-oxopentanoic acid (2.00 g, 5.40 mmol) and benzyl alcohol (0.64 g, 5.94 mmol), were dissolved in 25 mL dichloromethane. The solution was

cooled to 0 °C. N,N'-Dicyclohexylcarbodiimide was dissolved in 10 mL dichloromethane and added dropwise. The solution was stirred at 10 minutes at 0 °C and at room temperature for one hour. The suspension was filtered and the mother liquor was washed with DI water (3x). The crude oil was purified by column chromatography (90:10 hexanes:ethyl acetate). (1.98 g, 78%) ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.66 (d, *J* = 8.2 Hz, 2 H) 7.29 (m, *J* = 9.6 Hz, 5 H), 6.86 (d, *J* = 7.3 Hz, 2 H), 5.01 (s, 2 H), 3.17 (s, 3 H), 2.31 (s, 2 H), 2.07 (s, 2 H) 1.88 (s, 2 H); ^{13}C NMR ($CDCl_3$, 276 MHz,) δ 172.8, 171.7, 143.6, 135.9, 129.2, 128.5, 128.1, 66.0, 37.2, 33.3, 33.0, 25.7, 25.0, 20.5. HRMS (ESI) calculated for $C_{19}H_{20}INO_3$ $[M]^+$ 460.0386, found 437.0369.

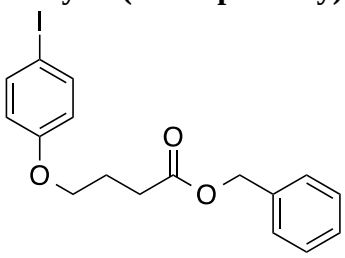
(4-(5-(Benzyloxy)-*N*-methyl-5-oxopentanamido)phenyl)(4-methoxyphenyl)iodonium hexafluorophosphate(V)



In a N_2-charged glove box, TEDA-BF_4 (179 mg, 0.39 mmol) is dissolved in 1 mL acetonitrile. Trimethylsilyl acetate (133 mg, 1.01 mmol) is added dropwise and the solution is stirred for 5 minutes. The solution was added to a solution of benzyl 5-((4-iodophenyl)(methyl)amino)-5-oxopentanoate (170 mg, 0.39 mmol) dissolved in 1 mL acetonitrile in a 100 mL Schlenk flask. The flask was removed from the glove box, and stirred for 6 hours at 40 °C. The flask was brought back into the glove box, and potassium (4-methoxyphenyl) trifluoroborate (83 mg, 0.39 mmol) was added. Trimethylsilyl trifluoroacetate (72 mg, 0.39 mmol) was added dropwise, and the solution was stirred for 10 minutes in the dark glove box. The flask was brought out of the glove

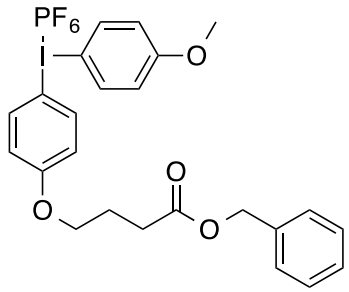
box, and the solvent was removed *in vacuo*. The yellow oil was dissolved in dichloromethane, washed with DI water (1x), acetate buffer (NaOAc : HOAc = 0.5 M:0.5 M, pH = 5) (3x) and DI water (2x). Solvent was again removed, and the clear oil was dissolved in acetonitrile. Sodium hexafluorophosphate (394 mg, 2.33 mmol) was dissolved in minimal DI water and added dropwise. The solution was stirred for 1 hour, and then organic solvent was removed *in vacuo*. The aqueous suspension was extracted with dichloromenthane, and the organic fractions were combined. Solvent was removed *in vacuo*. The crude oil was sonicated in pentane and recrystallized from ethyl acetate/ether. (155 mg, 58%) ^{1}H NMR (CD_3CN, 700 MHz) δ 8.06 (d, *J* = 8.6 Hz, 2 H), 8.05 (d, *J* = 9.0 Hz, 2 H) 7.41 (d, *J* = 8.6 Hz, 2 H), 7.38 (m, J = 7.0 Hz, 5 H), 7.09 (d, *J* = 9.5 Hz, 2 H), 5.05 (s, 2 H), 3.86 (s, 3 H), 3.22 (s, 3 H), 2.35 (m, *J* = 7.7 Hz, 2 H), 2.27 (s, 2 H), 1.84 (m, *J* = 7.4 Hz, 2 H) ^{13}C NMR ($CDCl_3$, 276 MHz) δ 173.9, 164.5, 149.3, 138.8, 137.6, 131.7, 129.6, 129.1, 129.1, 119.3, 102.5, 66.8, 56.8, 56.8, 37.8, 33.9, 21.3, 14.6. ^{19}F NMR (CD_3CN, 276 MHz, 25°C) δ -73.0 (d, *J* = -707.0 Hz, PF_6^-, 6 F). HRMS (ESI) calculated for $C_{19}H_{21}INO_4^+$ $[M]^+$ 544.0985, found 544.0992

benzyl 4-(4-iodophenoxy)butanoate



4-(4-iodophenoxy)butanoic acid (1.0 g, 3.268 mmol), triphenyl phosphine (1.559 g, 5.94216 mmol), and benzyl alcohol (0.321 g, 2.971 mmol) were dissolved in 30 mL tetrahydrofuran, and cooled to 0°C. Diisopropylazodicarboxylate (0.600 g, 2.971 mmol) was added dropwise, and the solution was stirred for 18 hours at room temperature.

Solvent was removed and the residue was dissolved in diethyl ether, washed with DI water, and the organic layers were collected. Solvent was removed in vacuo and purified by flash chromatography (100% hexanes). 1.24 g (quantitative yield. 1HNMR (CD3CN, 400 MHz, 25°C) δ 7.56 (d , *J* = 8.7, 2 H), δ 7.33 (m, *J* = 1.5, 5 H), δ 6.69 (d, *J* = 8.7, 2 H), δ 5.10 (s, 3 H), δ 3.96 (t , *J* = 6.3, 2 H) δ 2.50 (t, *J* = 7.3, 2 H) δ 2.18 (s, 2 H), δ 2.03 (m, *J* = 6.76, 2 H) ^{13}C NMR (CD_3CN, 276 MHz) 25.3, 31.3, 66.9, 67.9, 83.1, 118.1, 129.1, 129.1, 129.5, 137.6, 139.2, 159.9, 173.7 HRMS (ESI) calculated for $C_{17}H_{17}IO_3$ $[M]^+$ 419.0120, found 419.0112

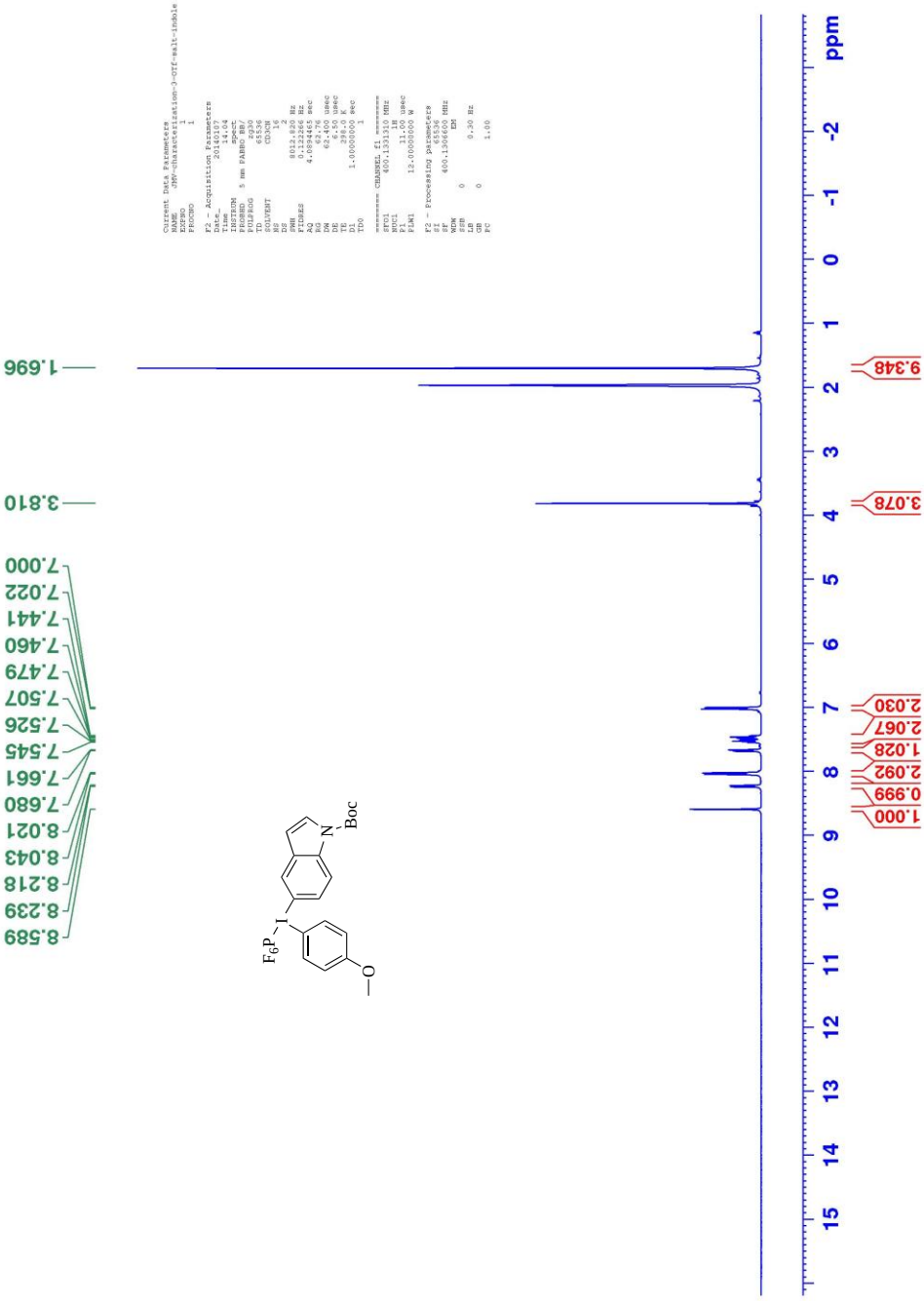


benzyl 4-(4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-ë3-iodanyl)phenoxy)butanoate

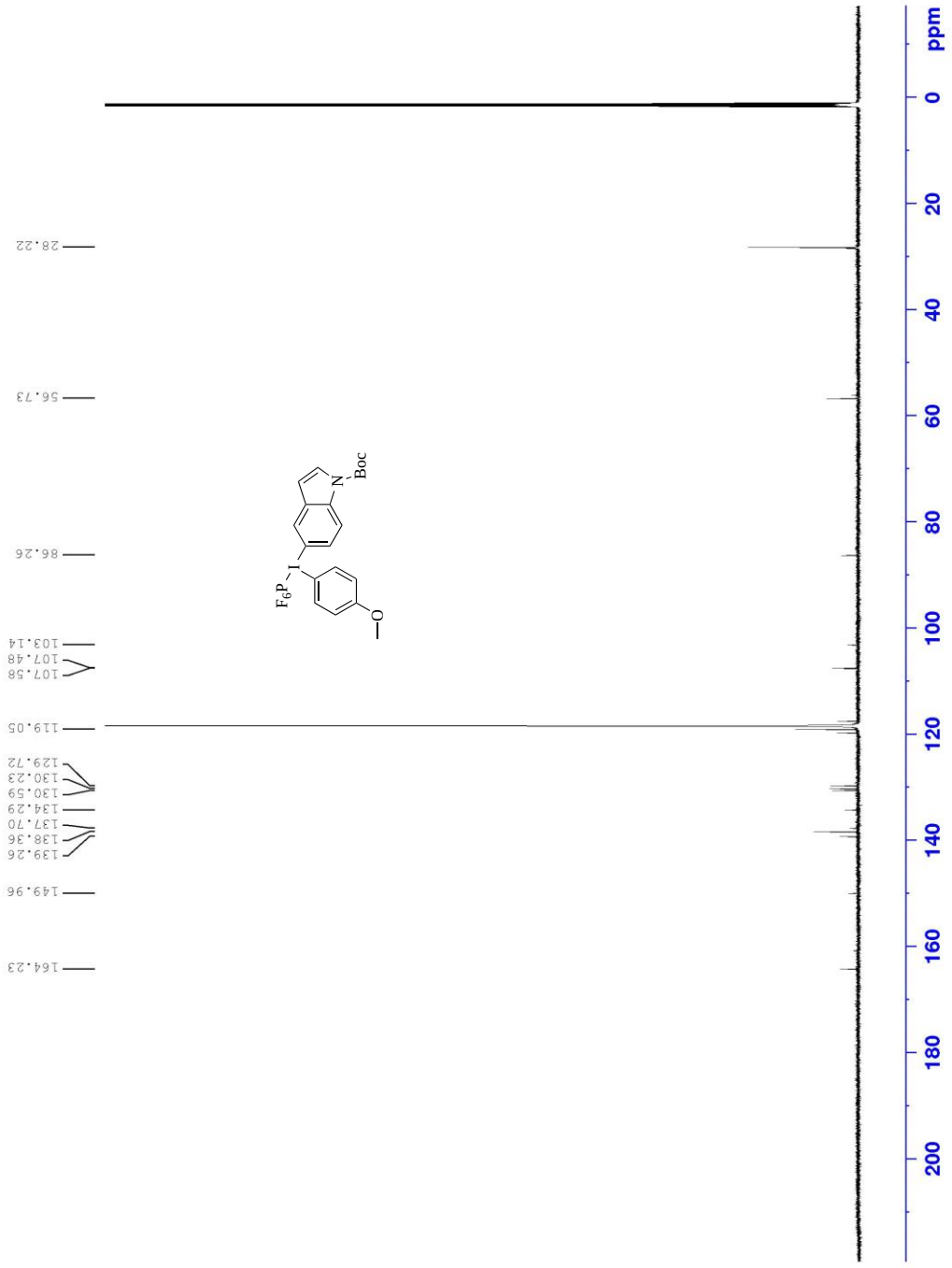
Under a N_2-charged glove box atmosphere, trimethylsilyl acetate (0.270 mg, 2.04183 mmol) was dissolved in 2 mL acetonitrile, and added dropwise to a stirring solution of F-TEDA-BF_4 (0.361 g, 1.02091 mmol) in acetonitrile. The solution was then added to benzyl 4-(4-iodophenoxy)butanoate (0.300 g, 0.785 mmol) was dissolved in 3 mL acetonitrile, and stirred at room temperature for 4 hours in the absence of light. Potassium (4-methoxyphenyl) trifluoroborate (0.168 g, 0.78532 mmol) was added, followed by a dropwise addition of a solution of Trimethylsilyl trifluoroacetate (0.132 g, 0.78532 mmol) dissolved in 1 mL acetonitrile. The solution was stirred for one hour and then removed from the N_2 atmosphere. The solvent was removed in vacuo, and the residual oil

was dissolved in ethyl acetate and washed with DI water. The organic solvent was removed in vacuo, and dissolved in minimal acetonitrile. Sodium hexafluorophosphate (0.791 g, 4.71192 mmol) was dissolved in minimal DI water and added dropwise. The solution was stirred for one hour. The organic solvent was removed in vacuo, and the aqueous suspension was extracted with ethyl acetate. The organic layers were combined, washed with DI water, dried with sodium sulfate, and evaporated in vacuo. The remaining oil was recrystallized from ethyl acetate/MTBE. (0.486 g, 62%)1HNMR (CD3CN, 400 MHz, 25°C) δ 7.98 (d, *J* = 10.8, 2 H), δ 7.96 (d, *J* = 10.8, 2 H), δ7.33 (m, *J* = 3.0, 5 H), δ 7.03 (d, *J* = 3.06, 2 H), δ 6.70 (d, *J* = 4.58, 2H), δ 5.08 (s, 3 H), δ 4.03 (t, *J* = 6.2, 2 H), δ 3.81 (s, 3 H), δ 2.50 (t, *J* = 7.2, 2 H), δ 2.31 (s, 2 H), δ 2.04 (m, *J* = 6.7, 2 H) ^{19}F NMR (CD_3CN, 276 MHz, 25°C) δ -73.0 (d, *J* = -707.0 Hz, PF_6^-, 6 F) HRMS (ESI) calculated for $C_{24}H_{24}IO_4^+$ $[M]^+$ 503.0695, found 503.0702

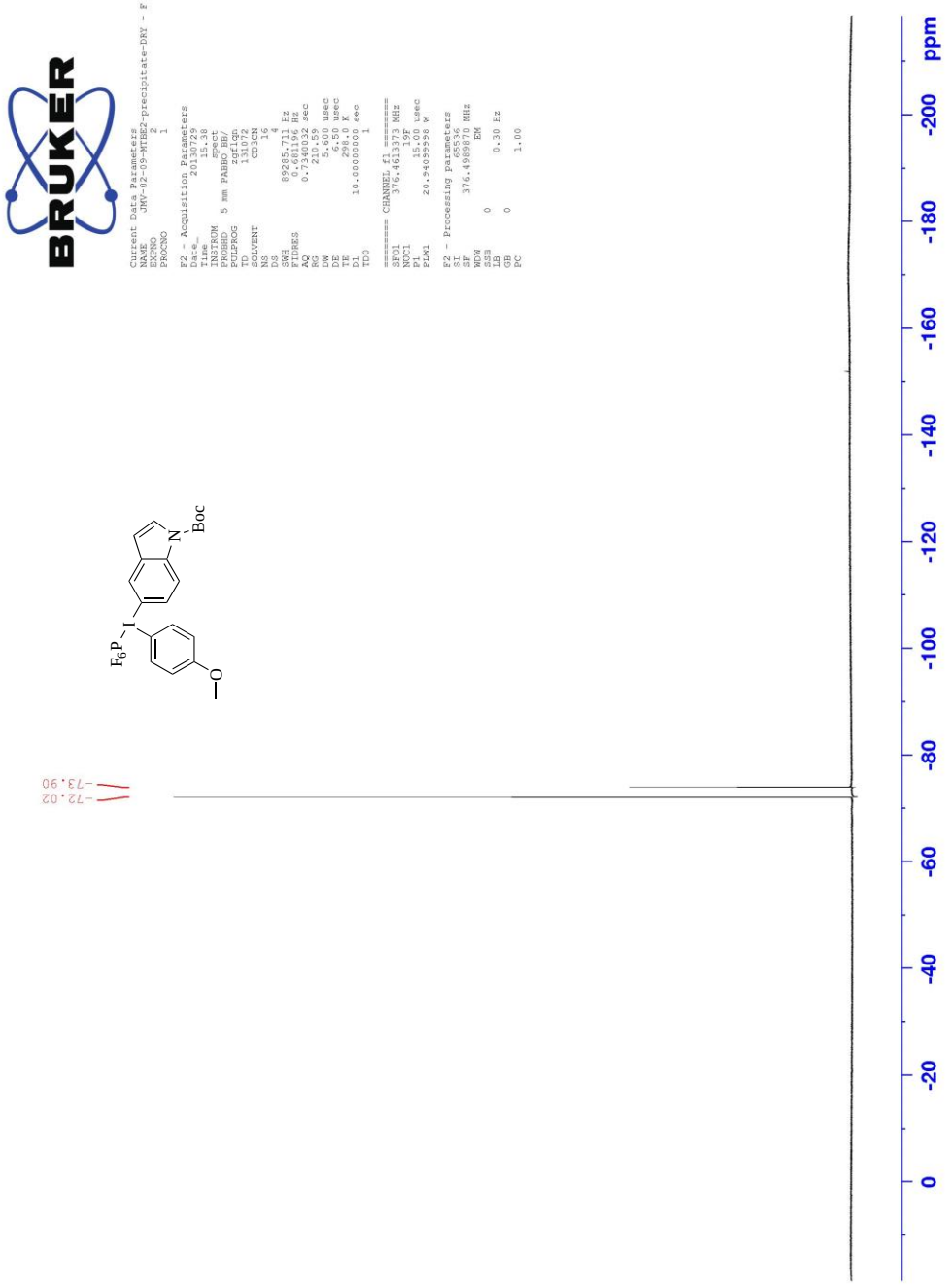
^{1}H NMR Spectrum of *tert*-butyl 5-((hexafluoro-λ^{7}-phosphanyl)(4-methoxyphenyl)-λ^{3}-iodanyl)-1*H*-indole-1-carboxylate



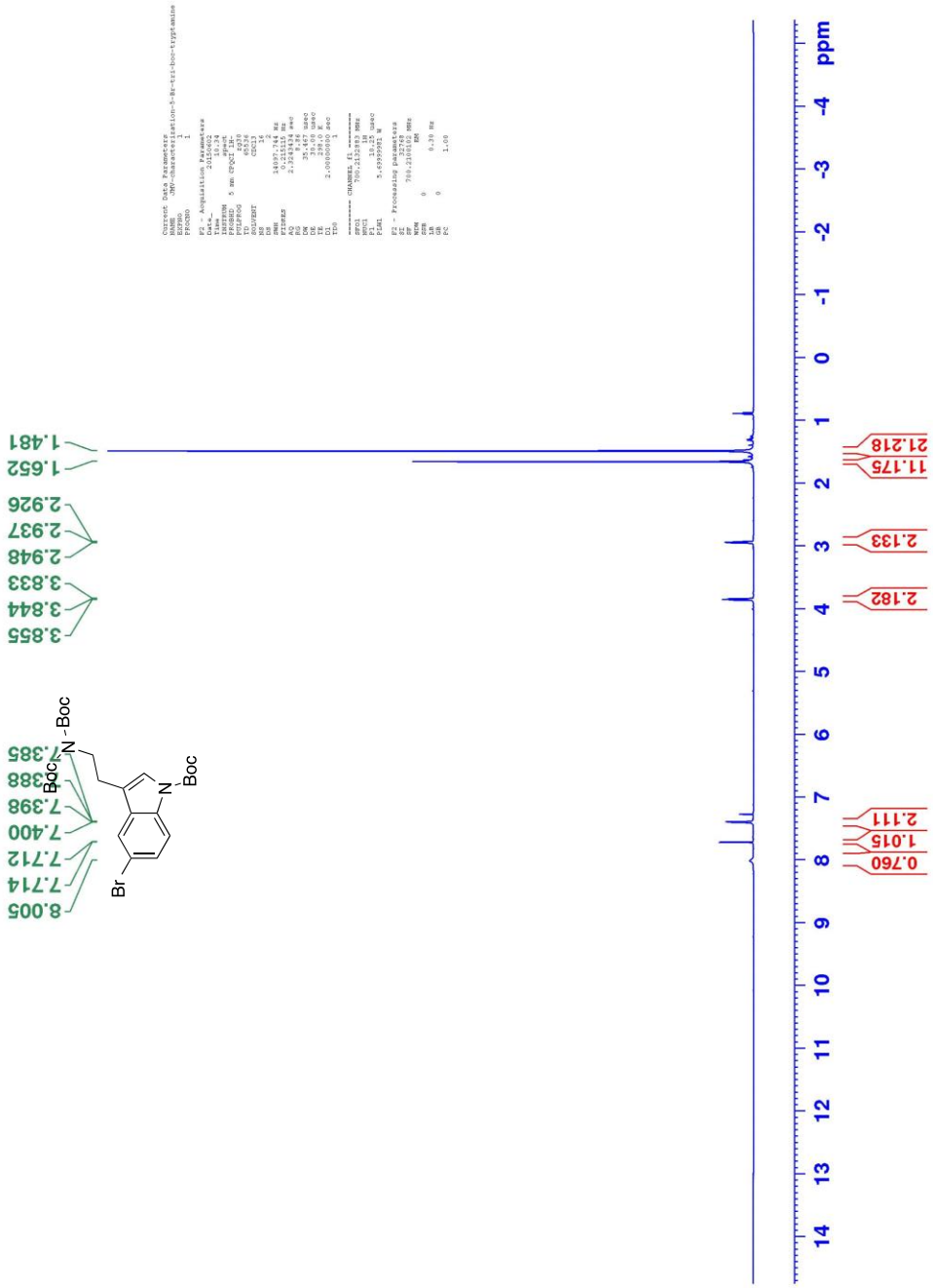
^{13}C NMR Spectrum of *tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate



^{19}F NMR Spectrum of *tert*-butyl 5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate



[1]H NMR Spectrum of *tert*-butyl 5-bromo-3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-1*H*-indole-1-carboxylate



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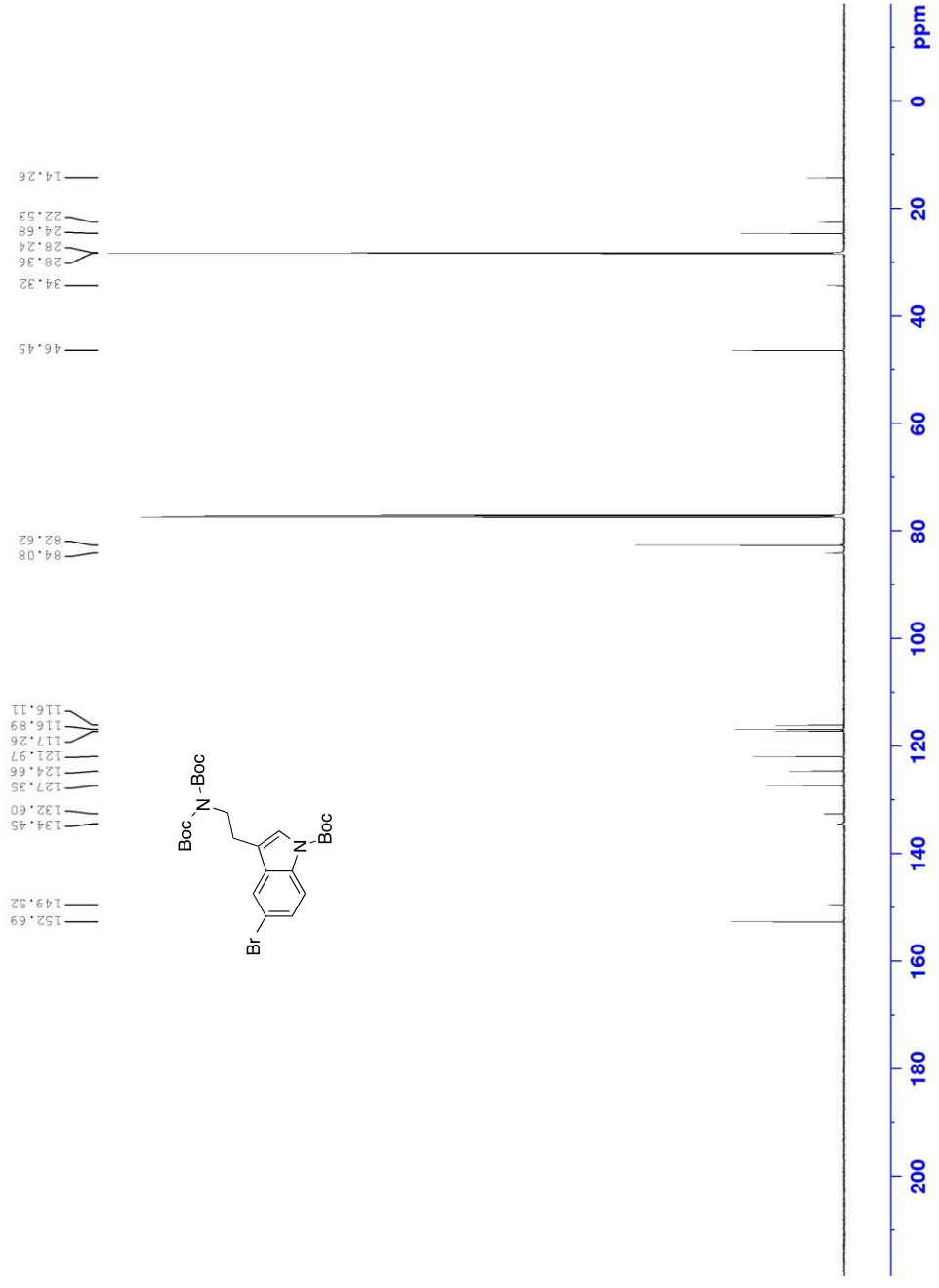
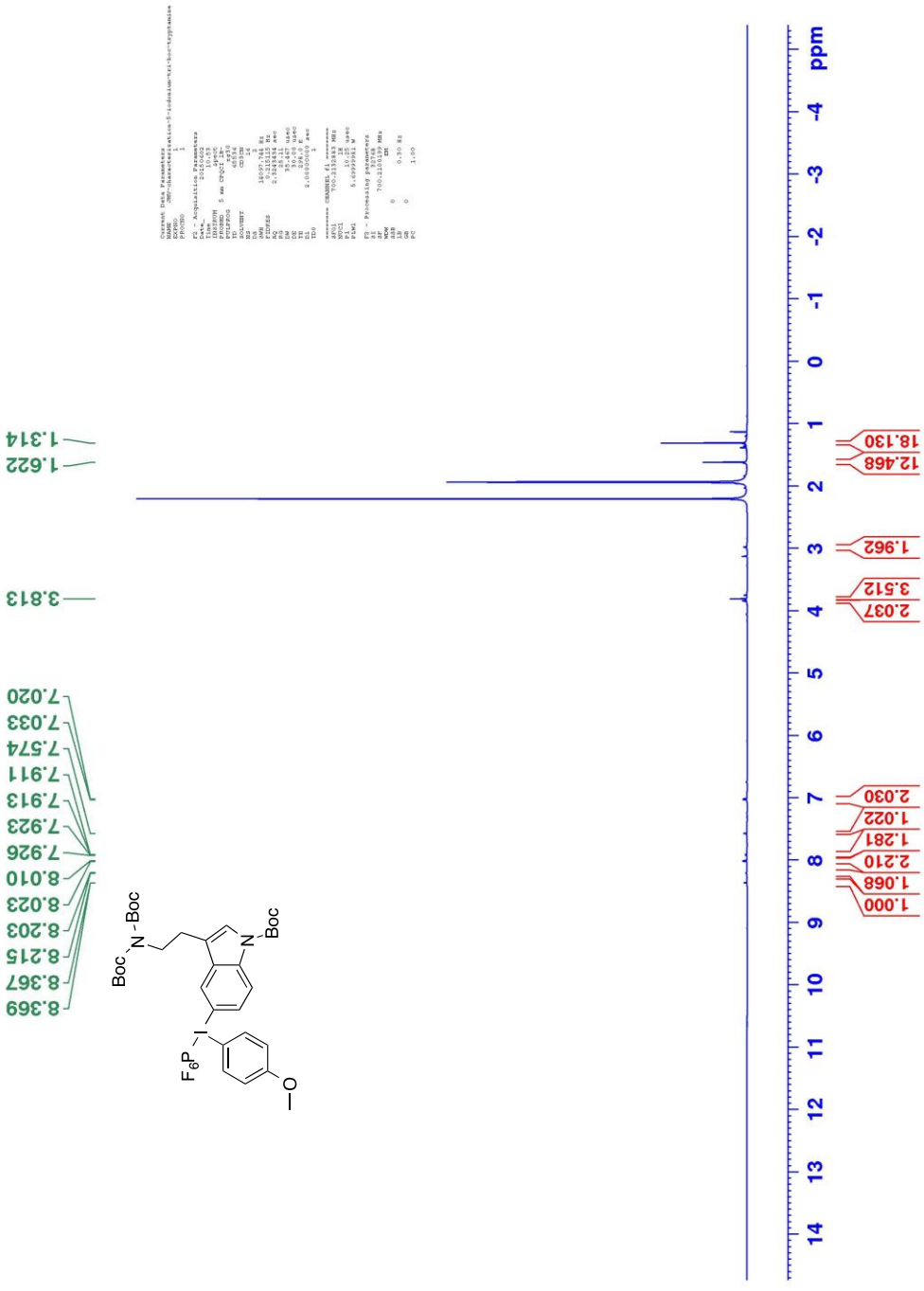
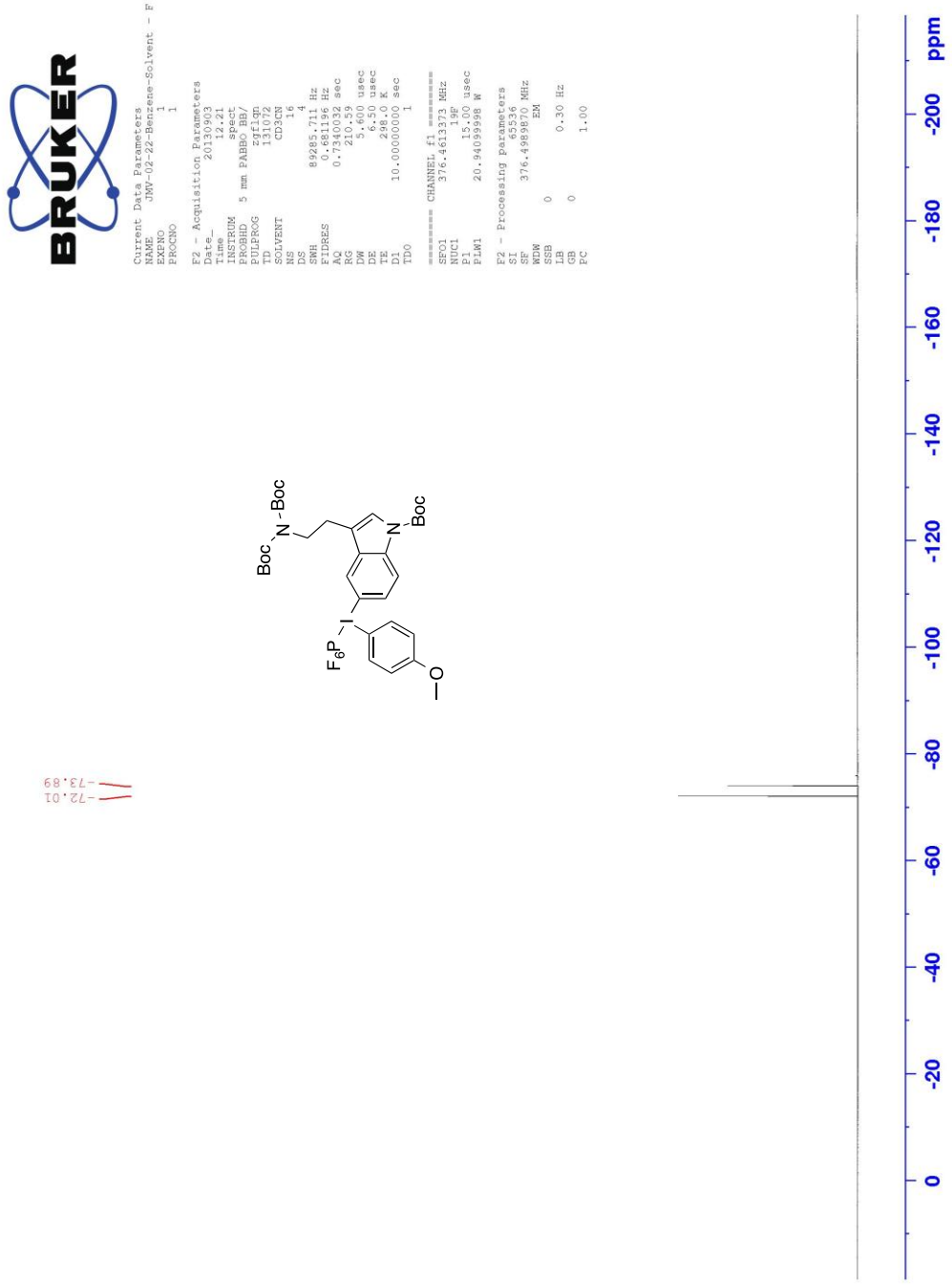


^{1}H NMR Spectrum of *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-((hexafluoro-λ^{7}-phosphanyl)(4-methoxyphenyl)-λ^{3}-iodanyl)-1*H*-indole-1-carboxylate

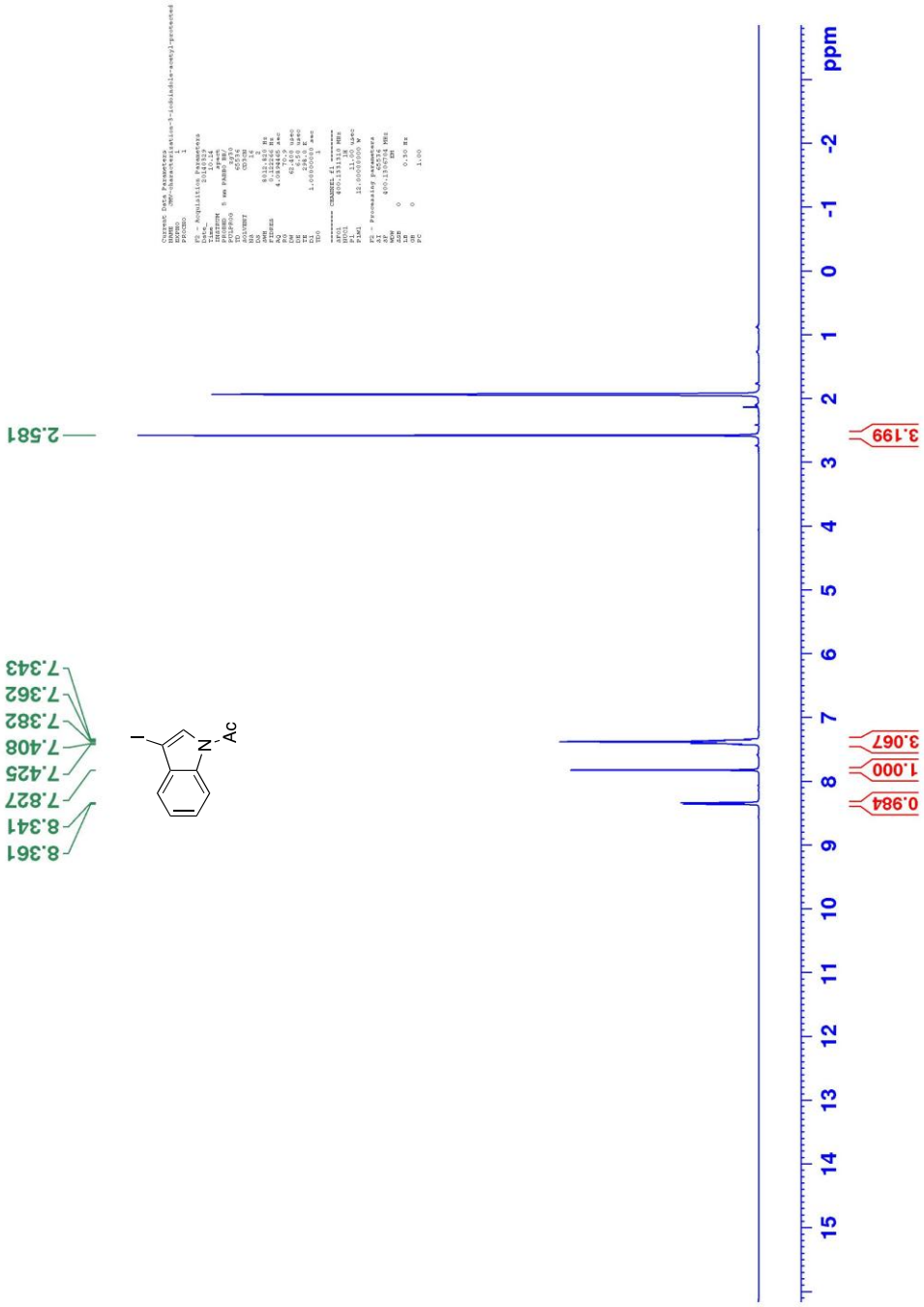


^{13}C NMR Spectrum of *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate

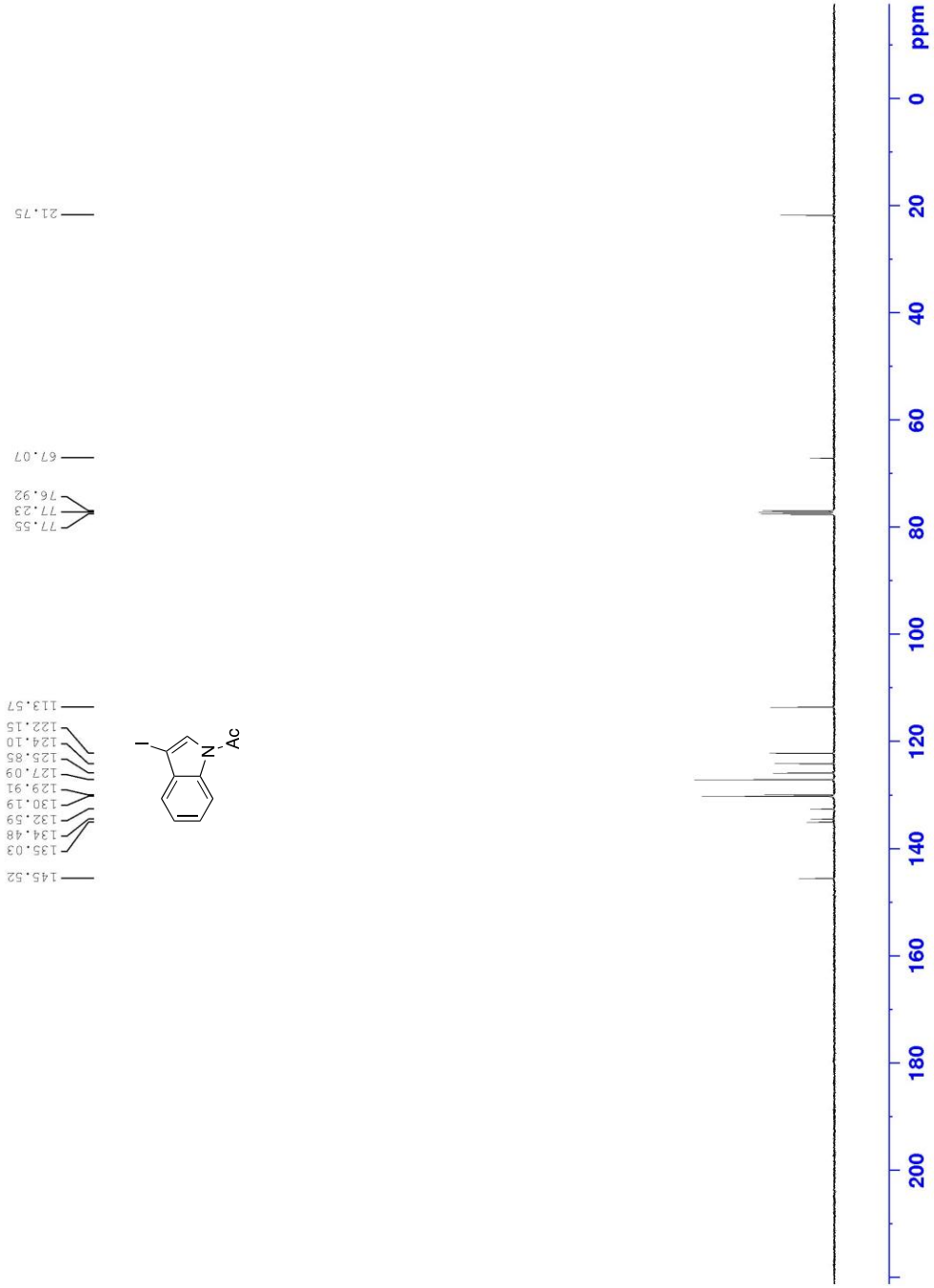
^{19}F NMR Spectrum of *tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-((hexafluoro-λ^7-phosphanyl)(4-methoxyphenyl)-λ^3-iodanyl)-1*H*-indole-1-carboxylate



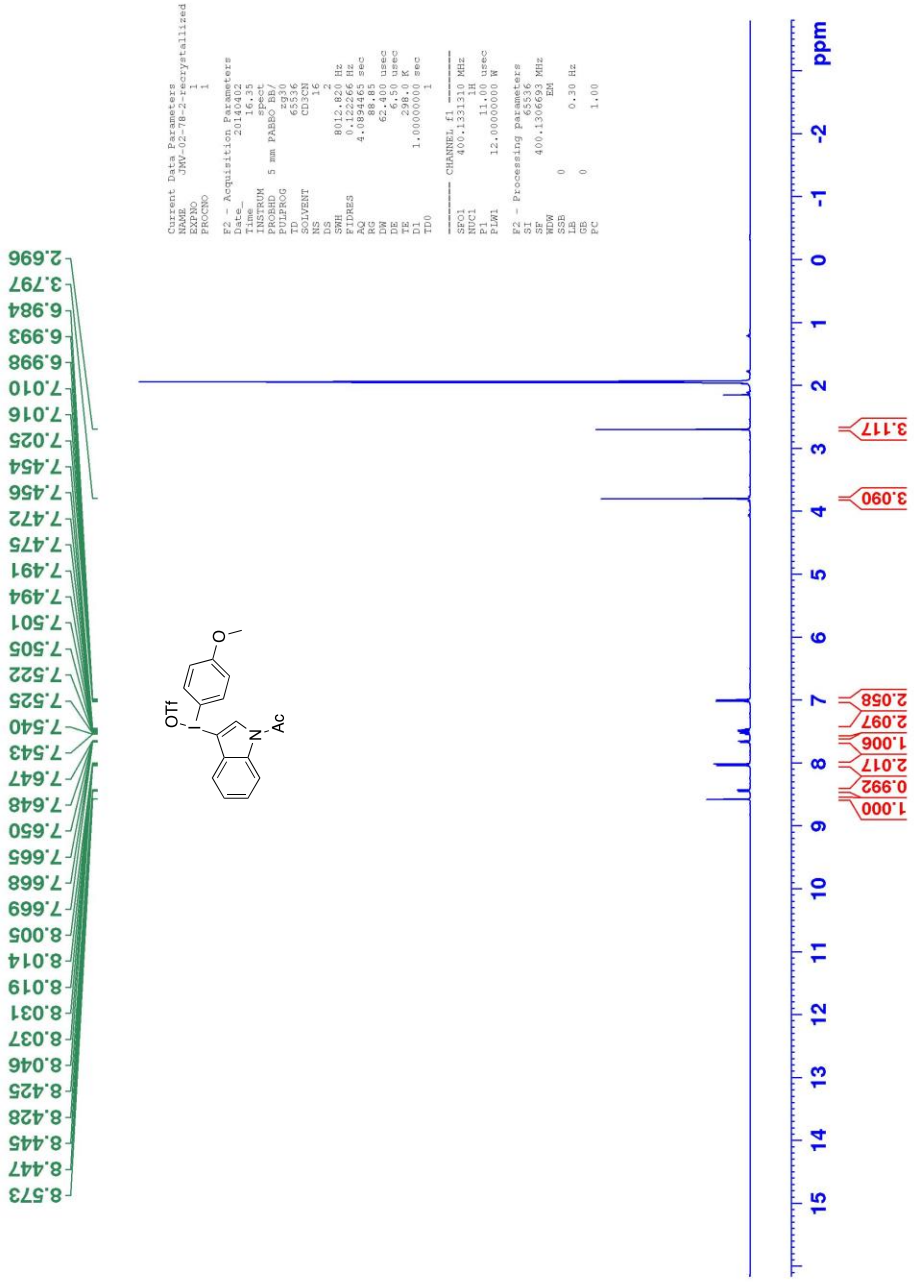
^{1}H NMR Spectrum of 1-(3-iodo-1*H*-indol-1-yl)ethan-1-one



^{13}C NMR Spectrum of 1-(3-iodo-1*H*-indol-1-yl)ethan-1-one



^{1}H NMR Spectrum of (1-acetyl-1H-indol-3-yl)(4-methoxyphenyl)-l3-iodanyl trifluoromethanesulfonate



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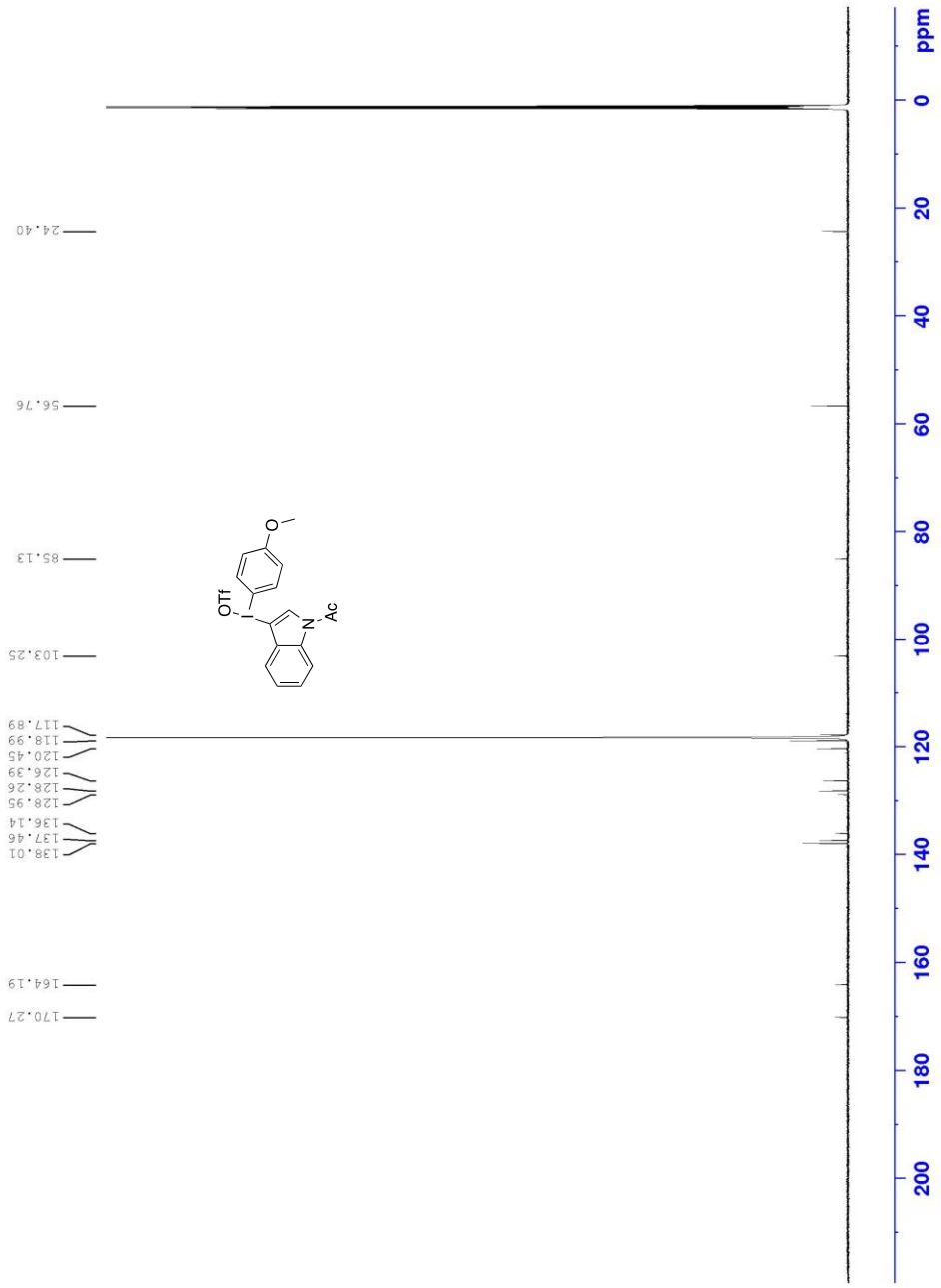

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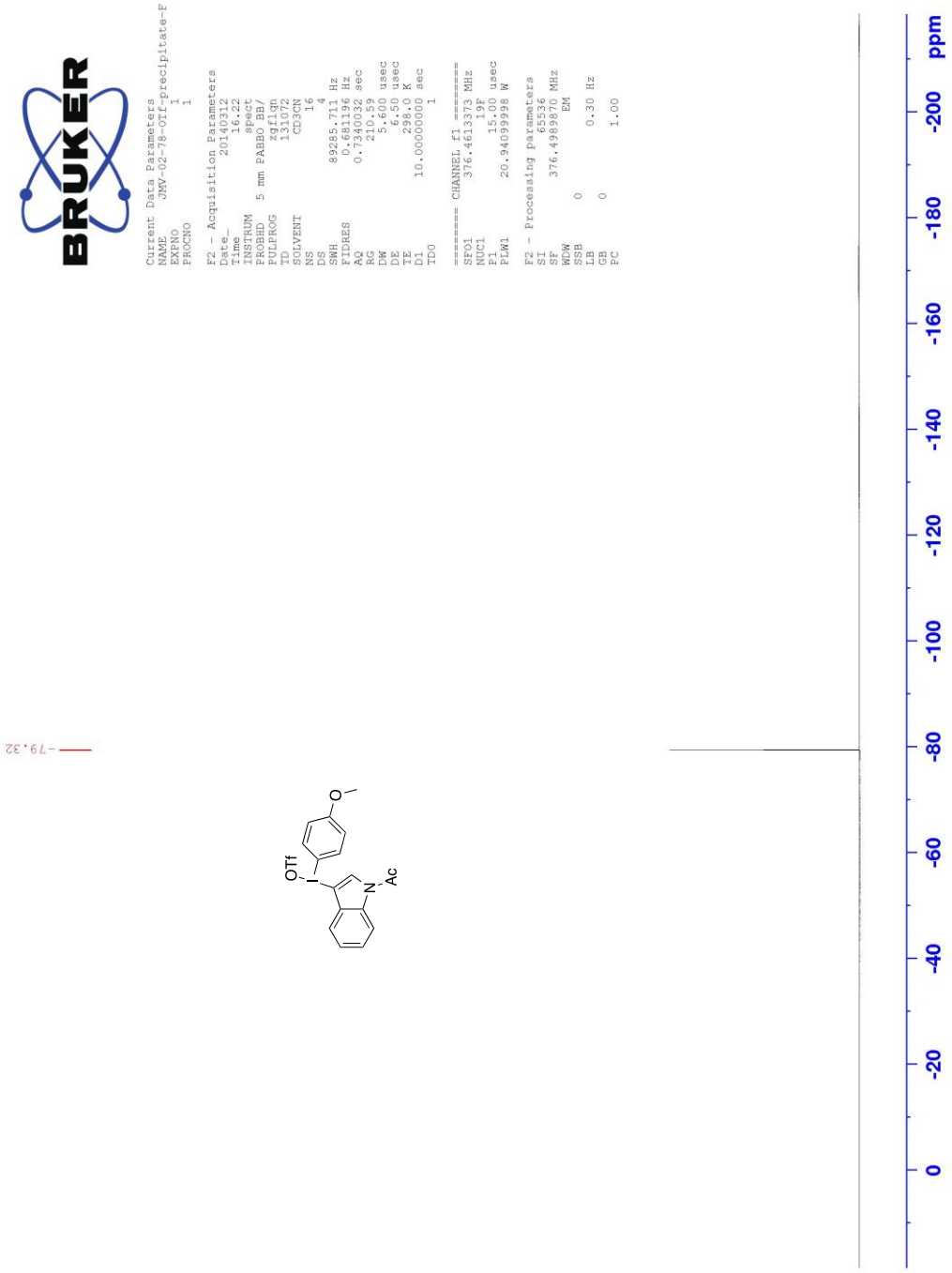
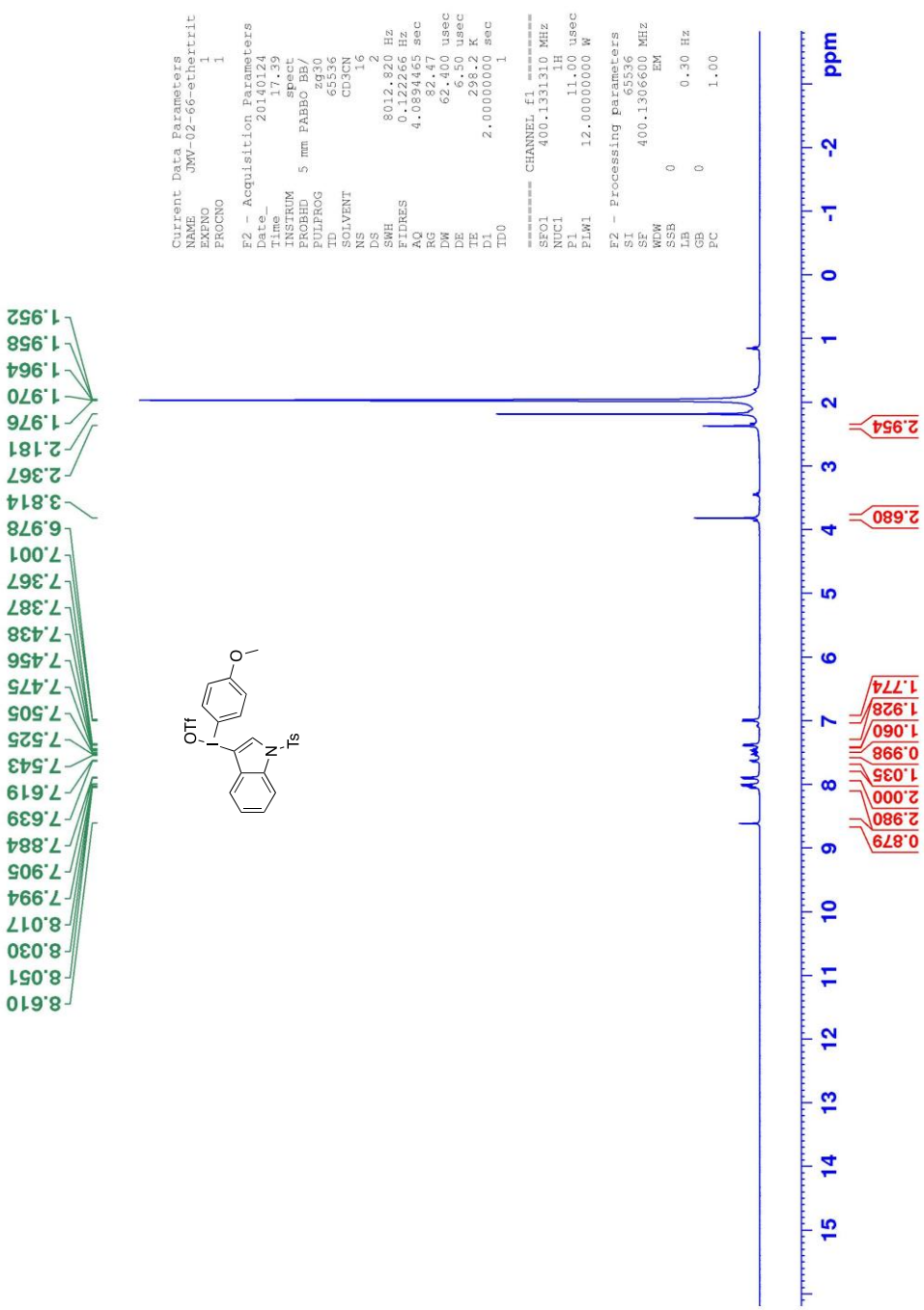


^{1}H NMR Spectrum of (4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)-λ^{3}-iodanyl trifluoromethanesulfonate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OTf
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O
N
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8.017
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7.905
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1.958
1.952
2.954
2.680
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2.980
2.000
1.035
0.998
1.060
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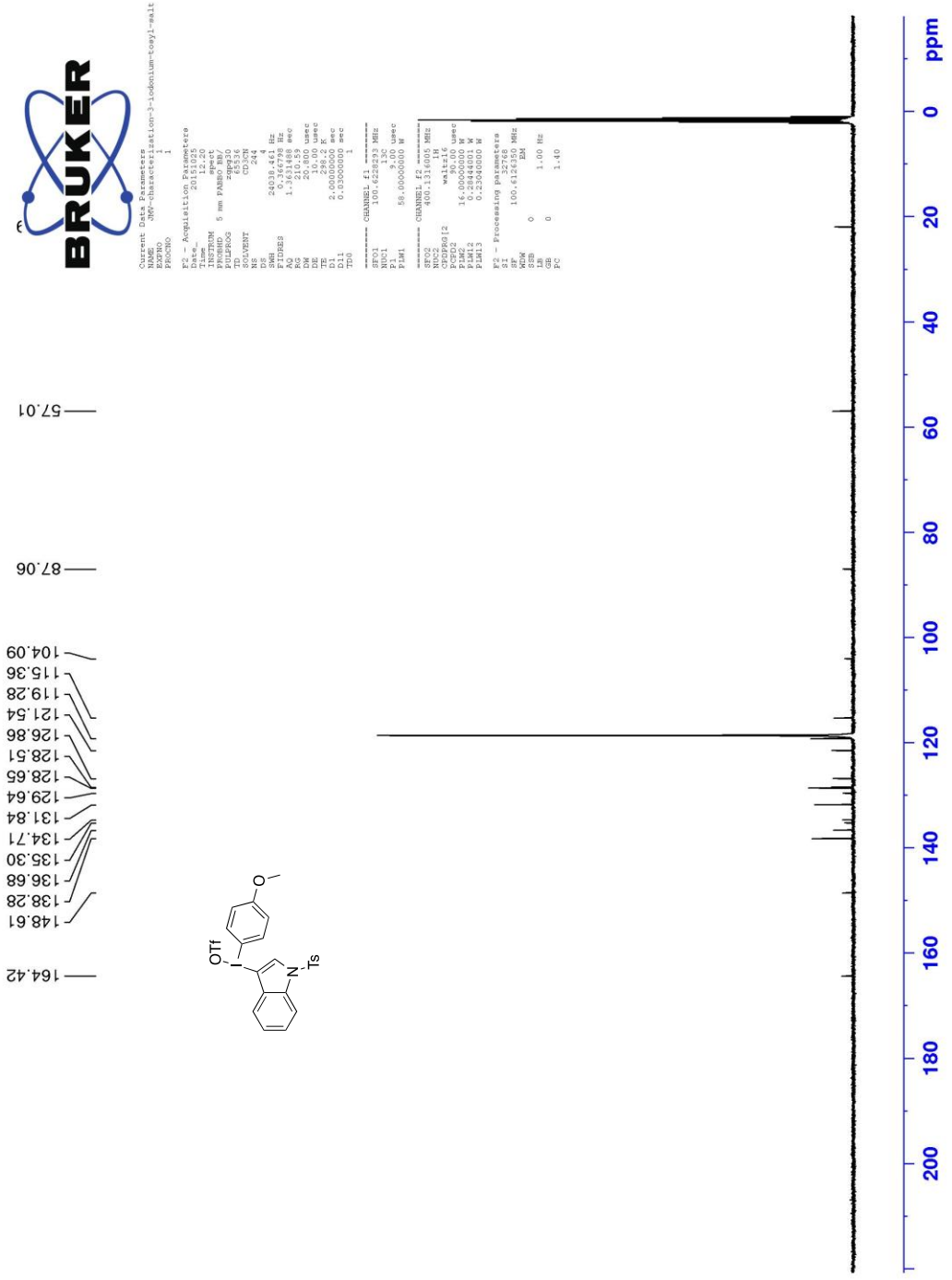
^{13}C NMR Spectrum of (4-methoxyphenyl)(1-tosyl-1*H*-indol-3-yl)-λ^3-iodanyl trifluoromethanesulfonate



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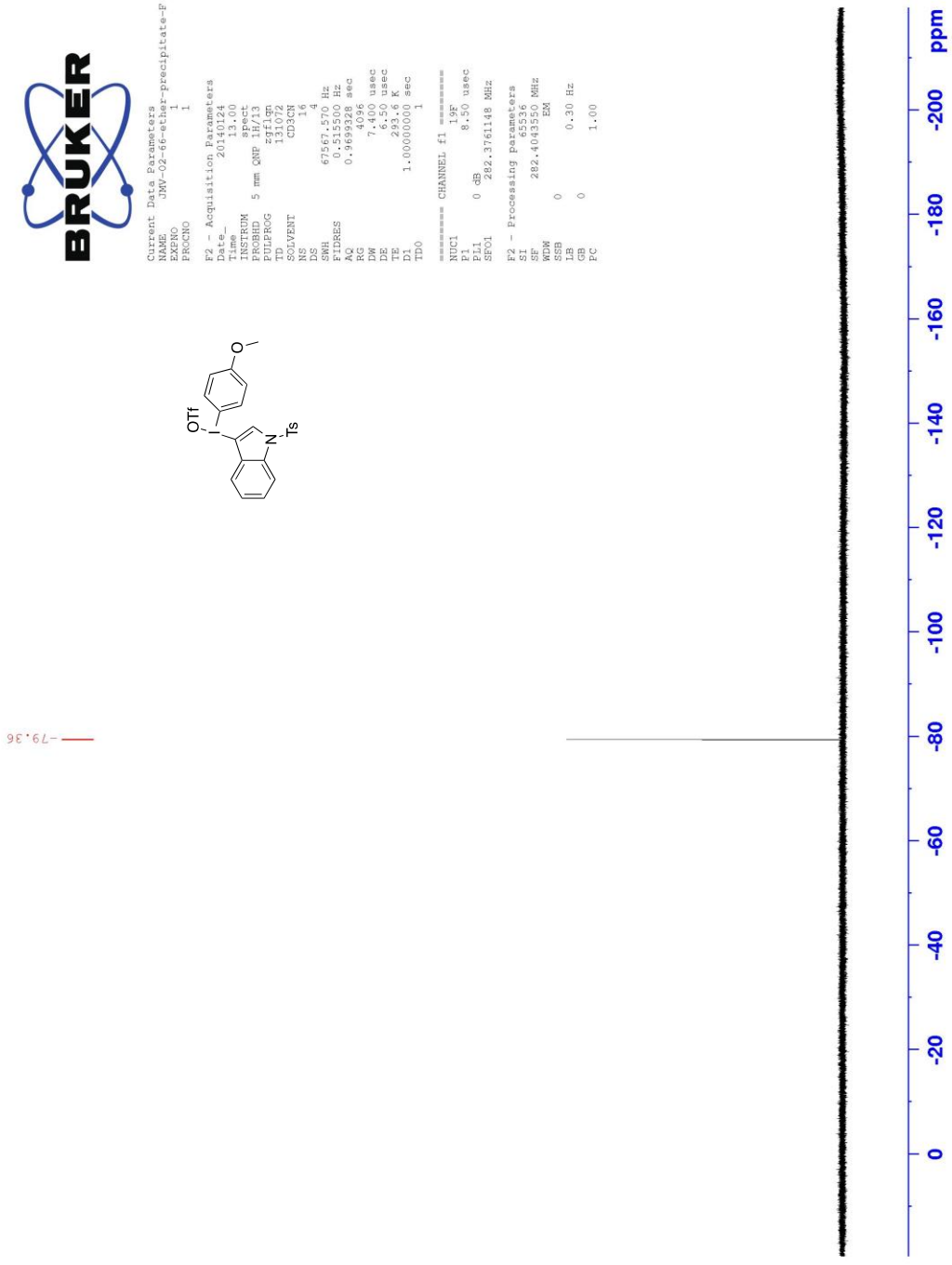
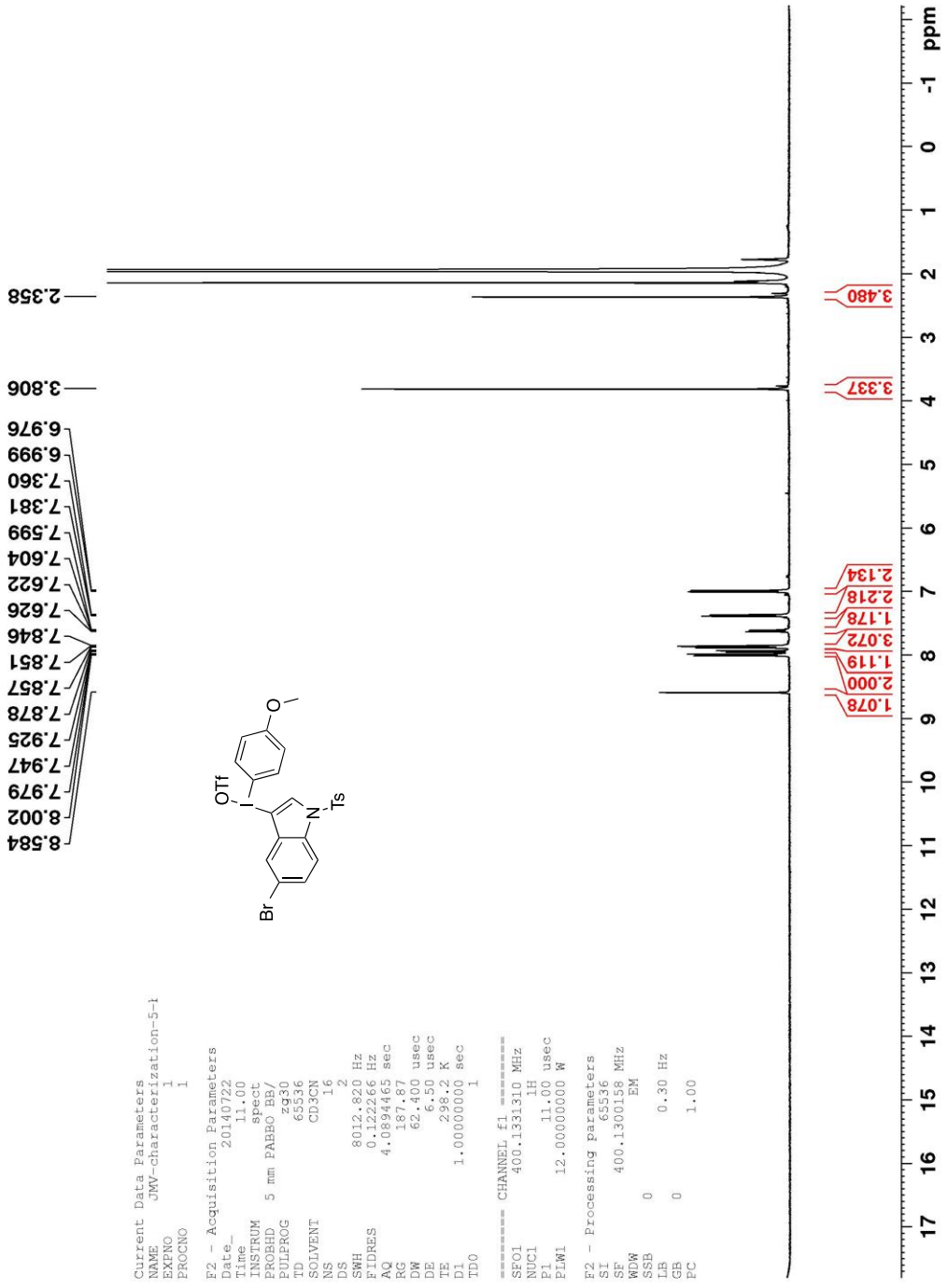
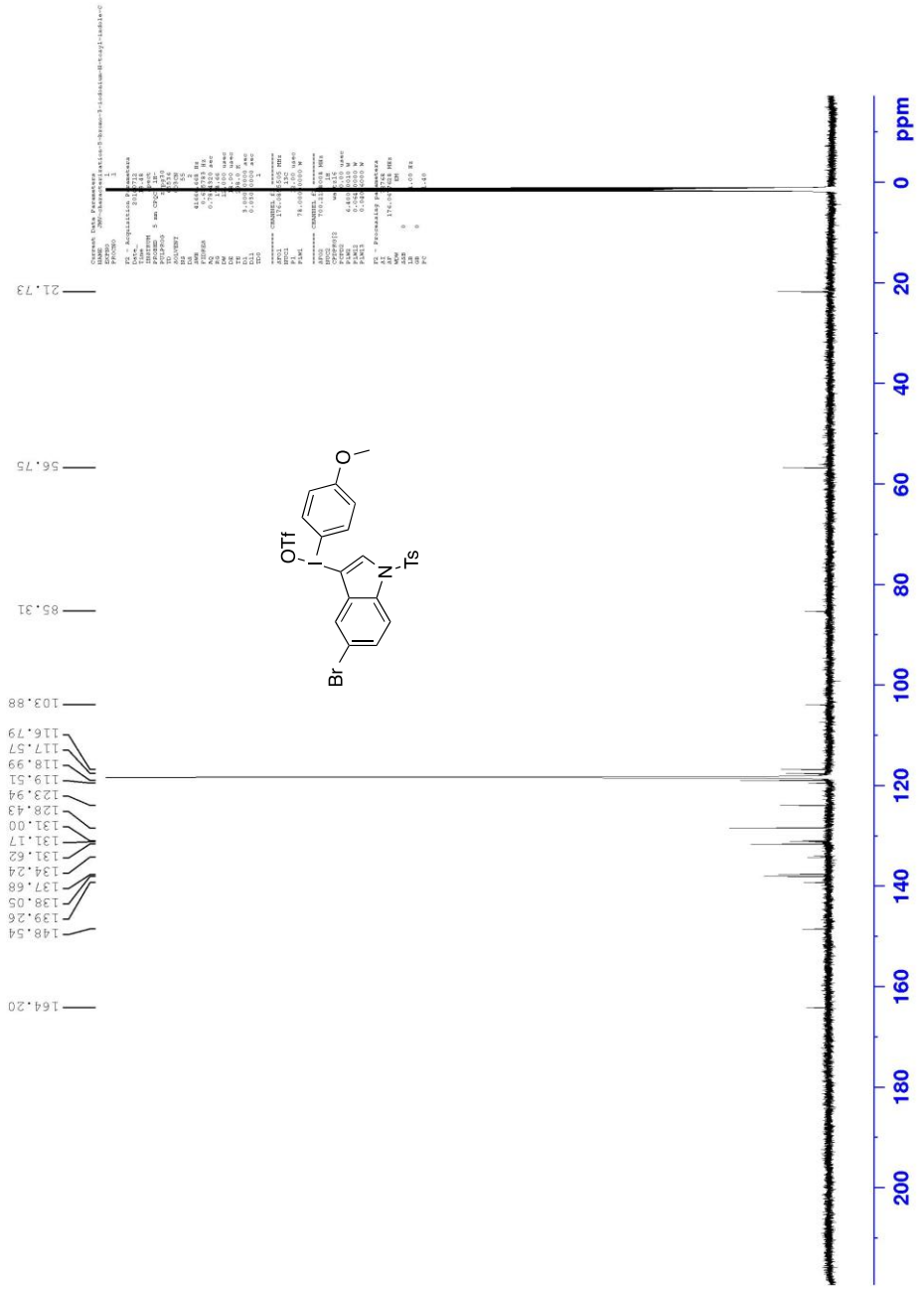


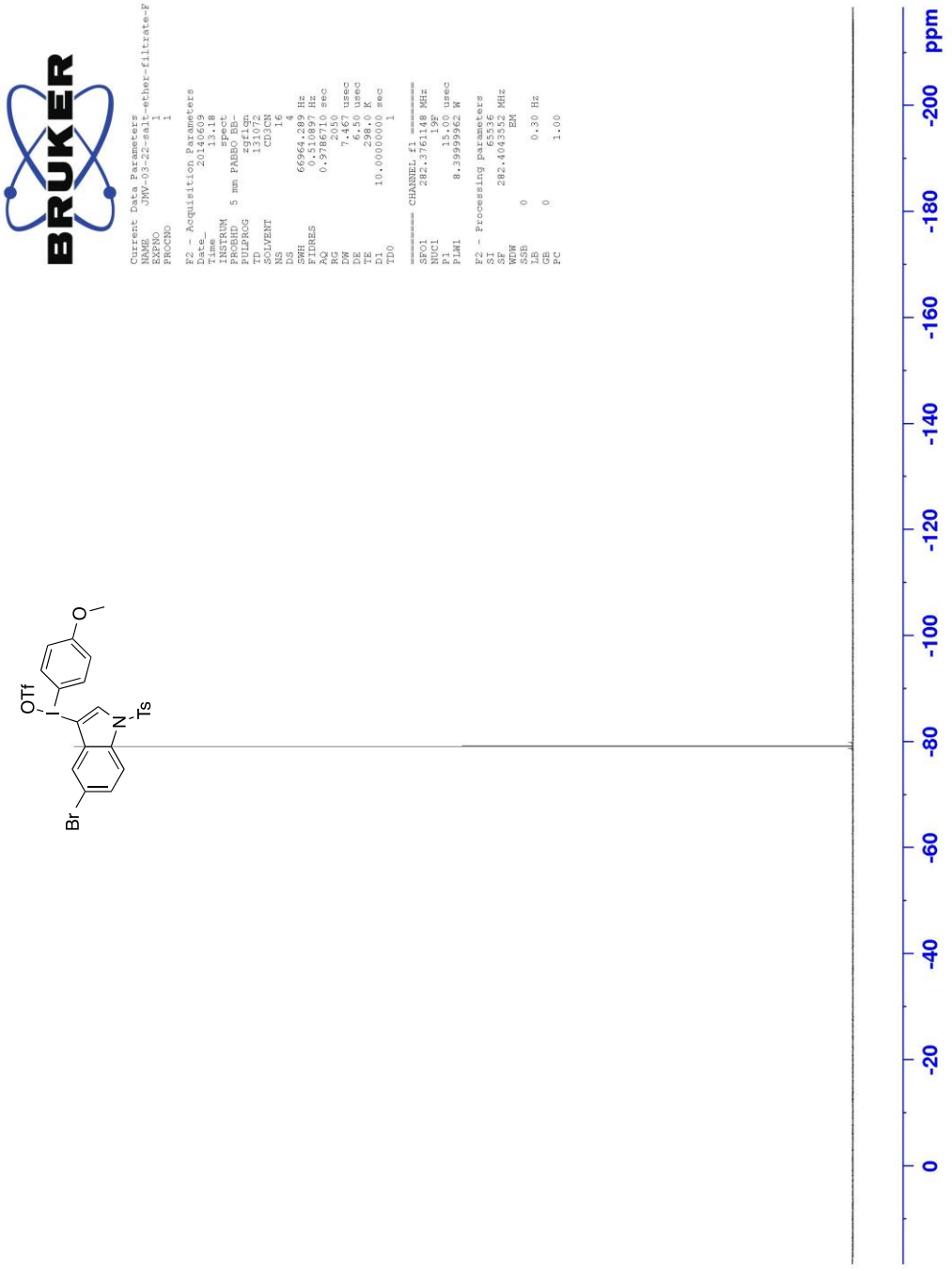
^{1}H NMR Spectrum of (5-bromo-1-tosyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^{3}-iodanyl trifluoromethanesulfonate



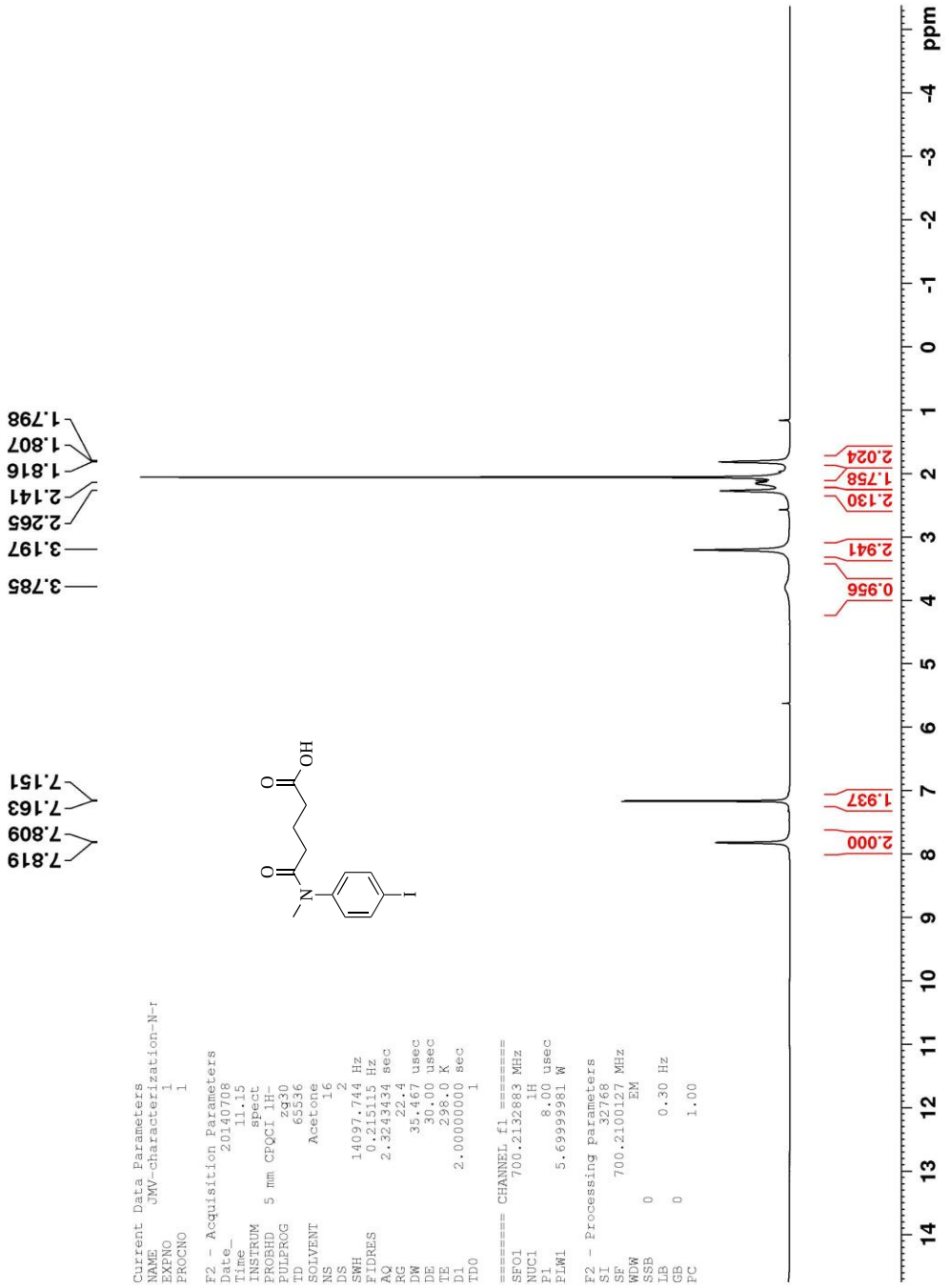
^{13}C NMR Spectrum of (5-bromo-1-tosyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate



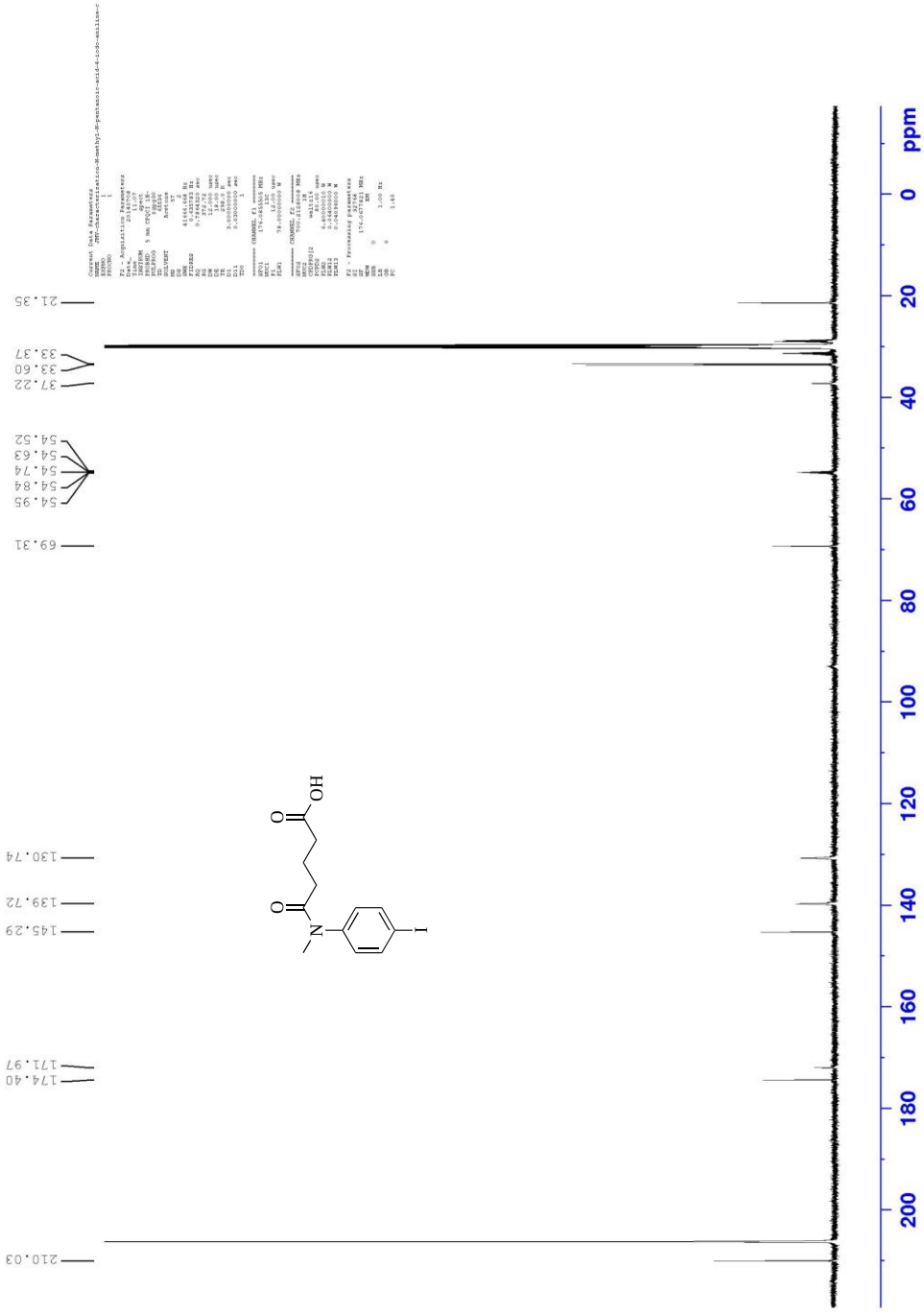
^{19}F NMR Spectrum of (5-bromo-1-tosyl-1*H*-indol-3-yl)(4-methoxyphenyl)-λ^3-iodanyl trifluoromethanesulfonate



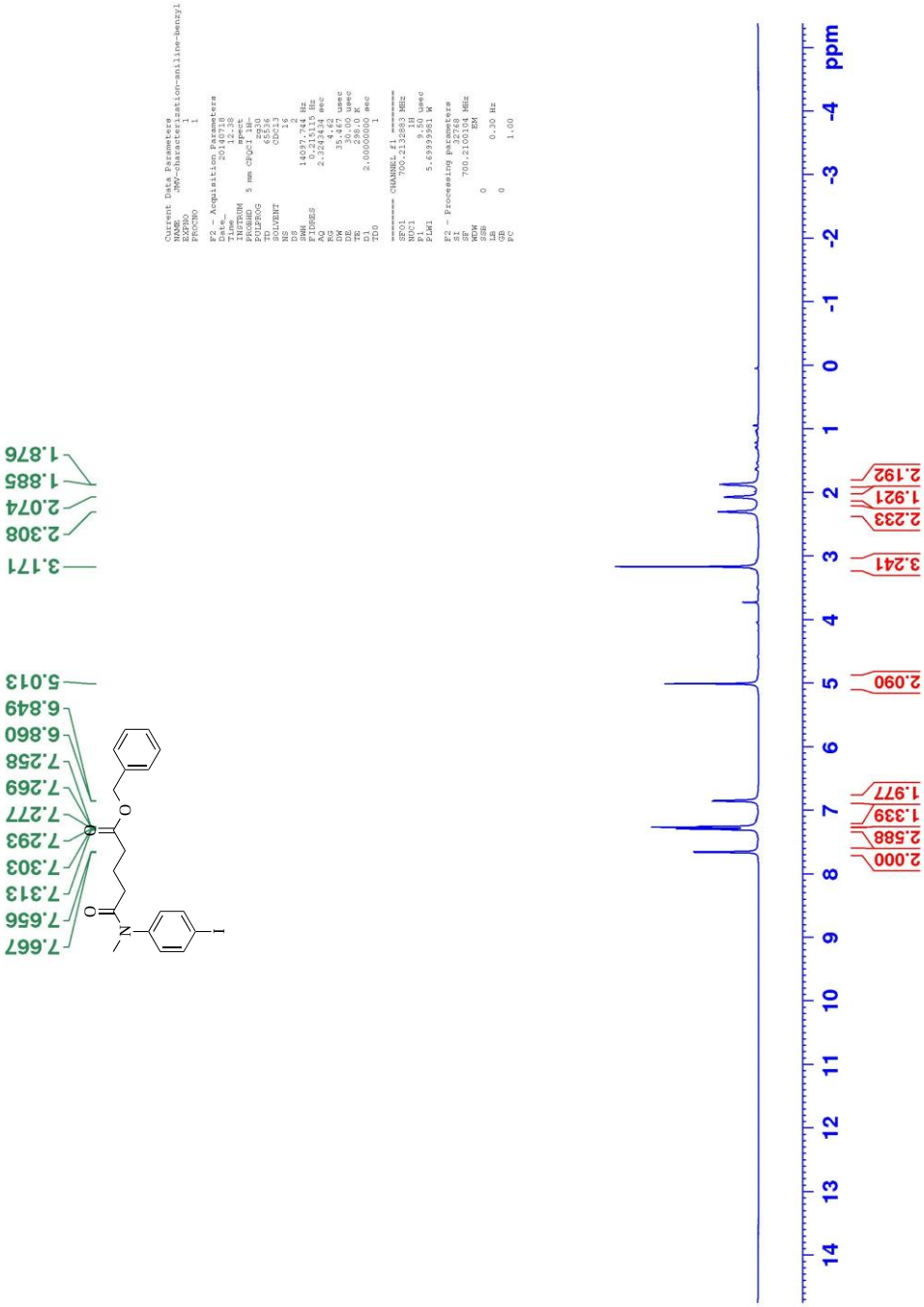
[1]H NMR Spectrum of 5-((4-iodophenyl)(methyl)amino)-5-oxopentanoic acid



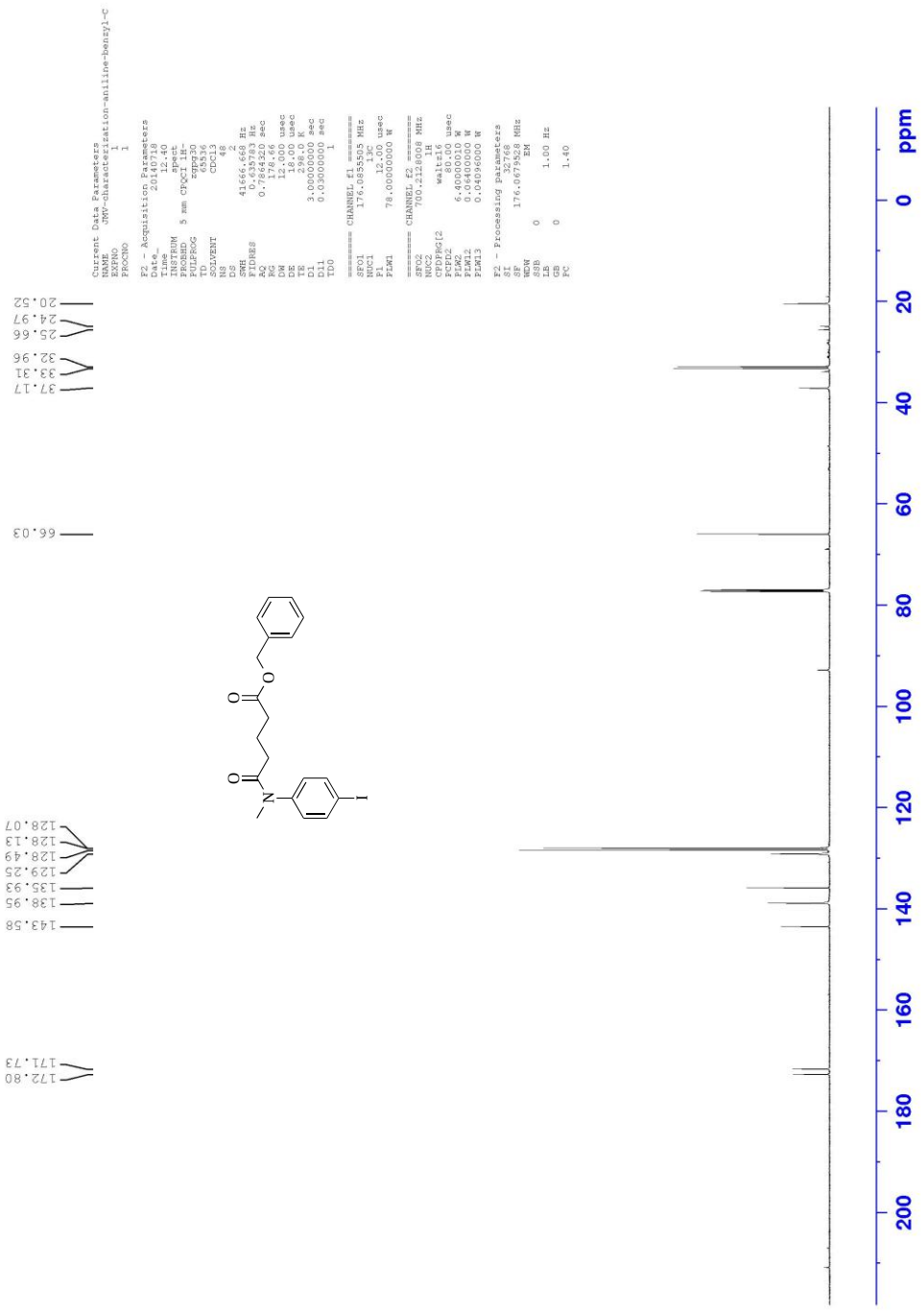
^{13}C NMR Spectrum of 5-((4-iodophenyl)(methyl)amino)-5-oxopentanoic acid



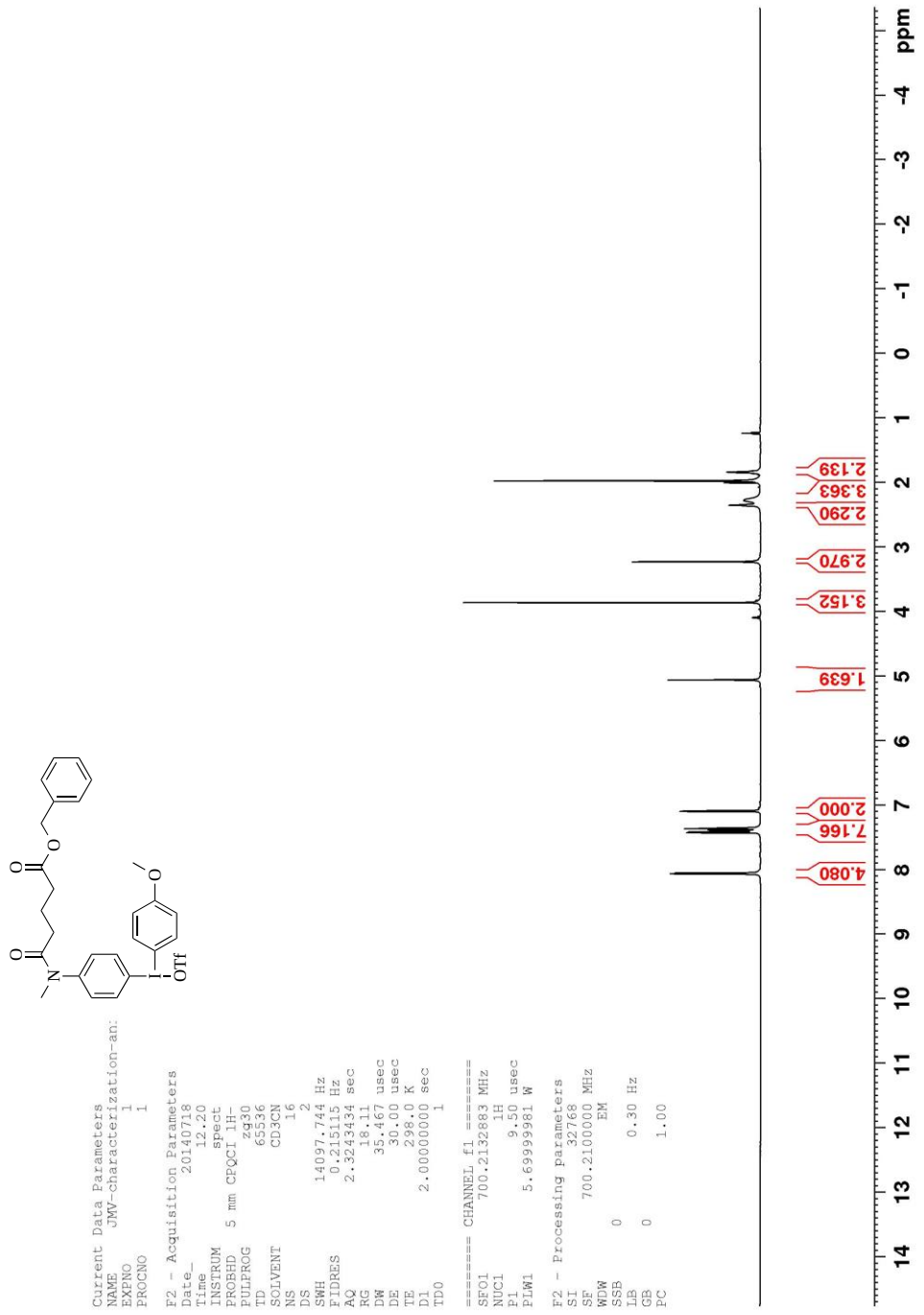
^{1}H NMR Spectrum of benzyl 5-((4-iodophenyl)(methyl)amino)-5-oxopentanoate



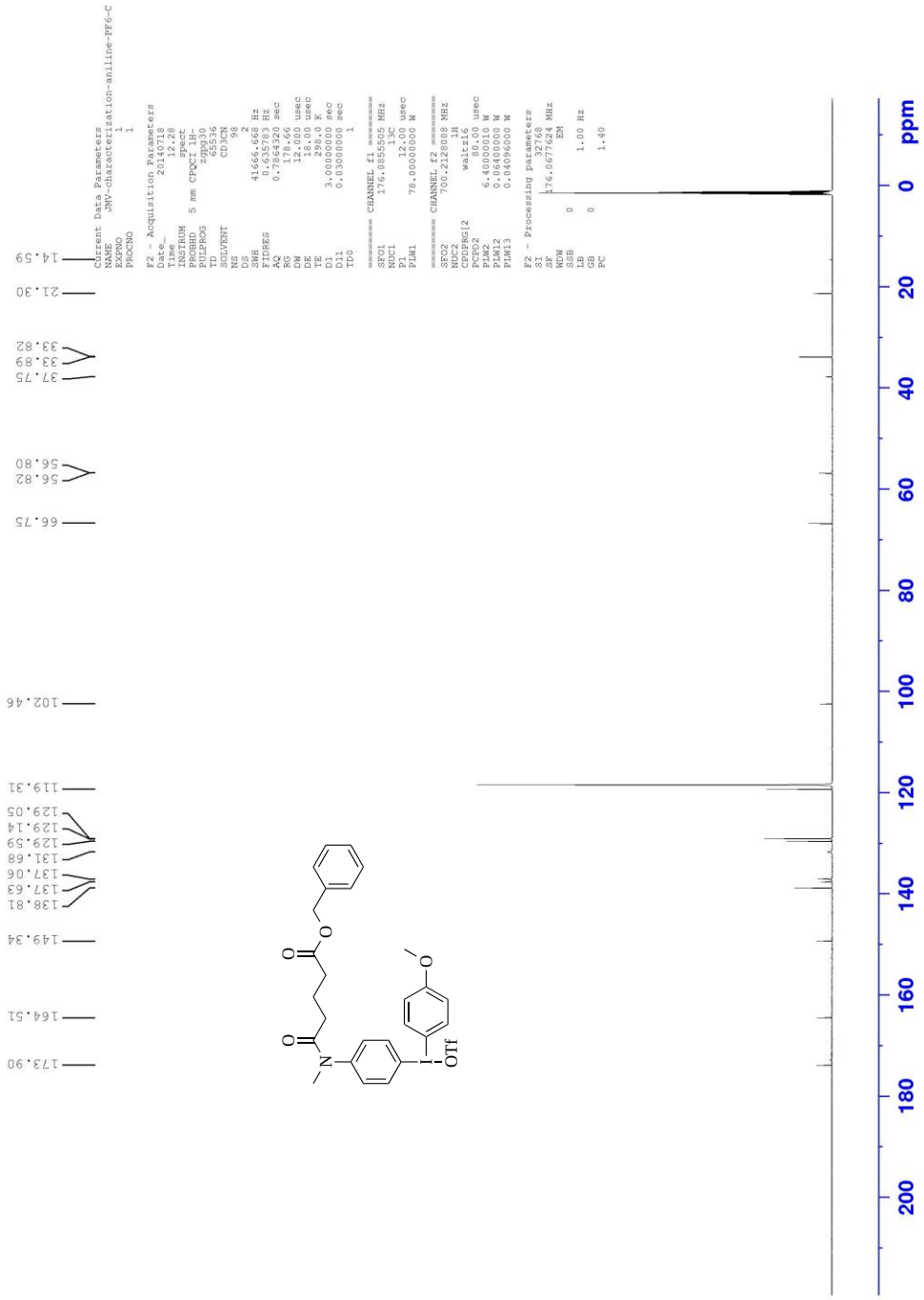
^{13}C NMR Spectrum of benzyl 5-((4-iodophenyl)(methyl)amino)-5-oxopentanoate



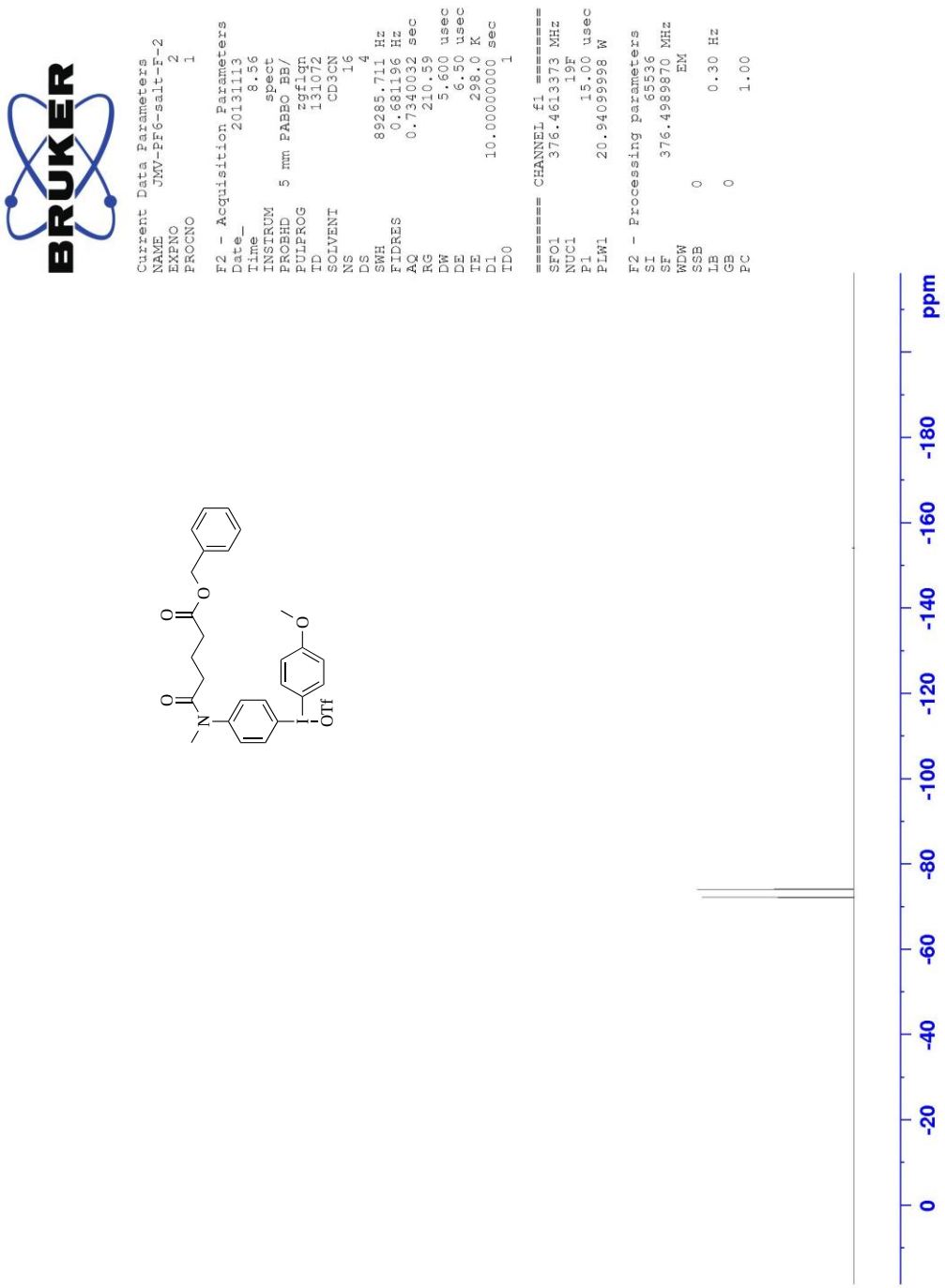
^{1}H NMR Spectrum of benzyl 5-((4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-λ^{3}-iodanyl)phenyl)(methyl)amino)-5-oxopentanoate



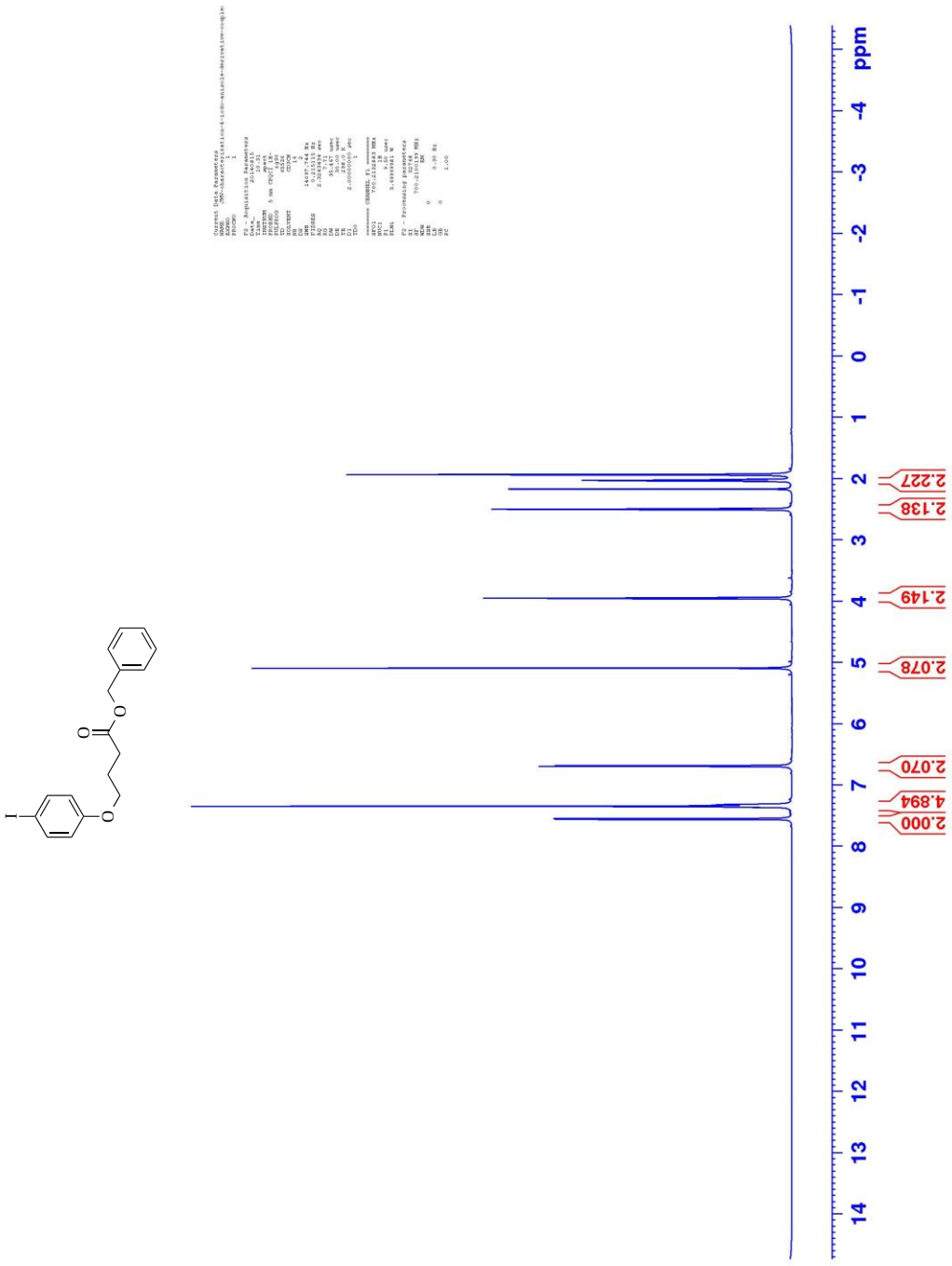
^{13}C NMR Spectrum of benzyl 5-((4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-λ^3-iodanyl)phenyl)(methyl)amino)-5-oxopentanoate



^{19}F NMR Spectrum of benzyl 5-((4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-λ^3-iodanyl)phenyl)(methyl)amino)-5-oxopentanoate



^{1}H NMR Spectrum of benzyl 4-(4-iodophenoxy)butanoate



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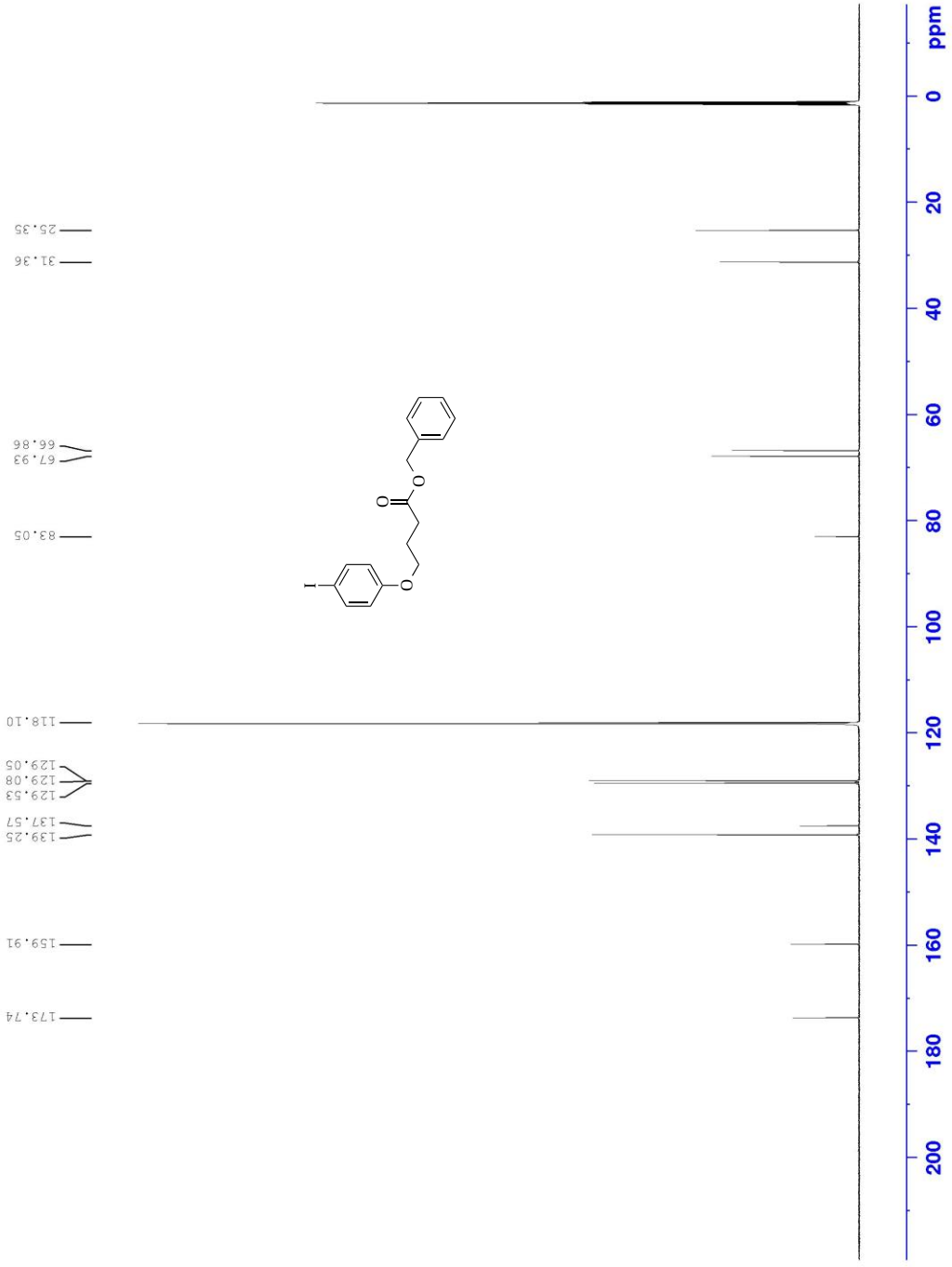
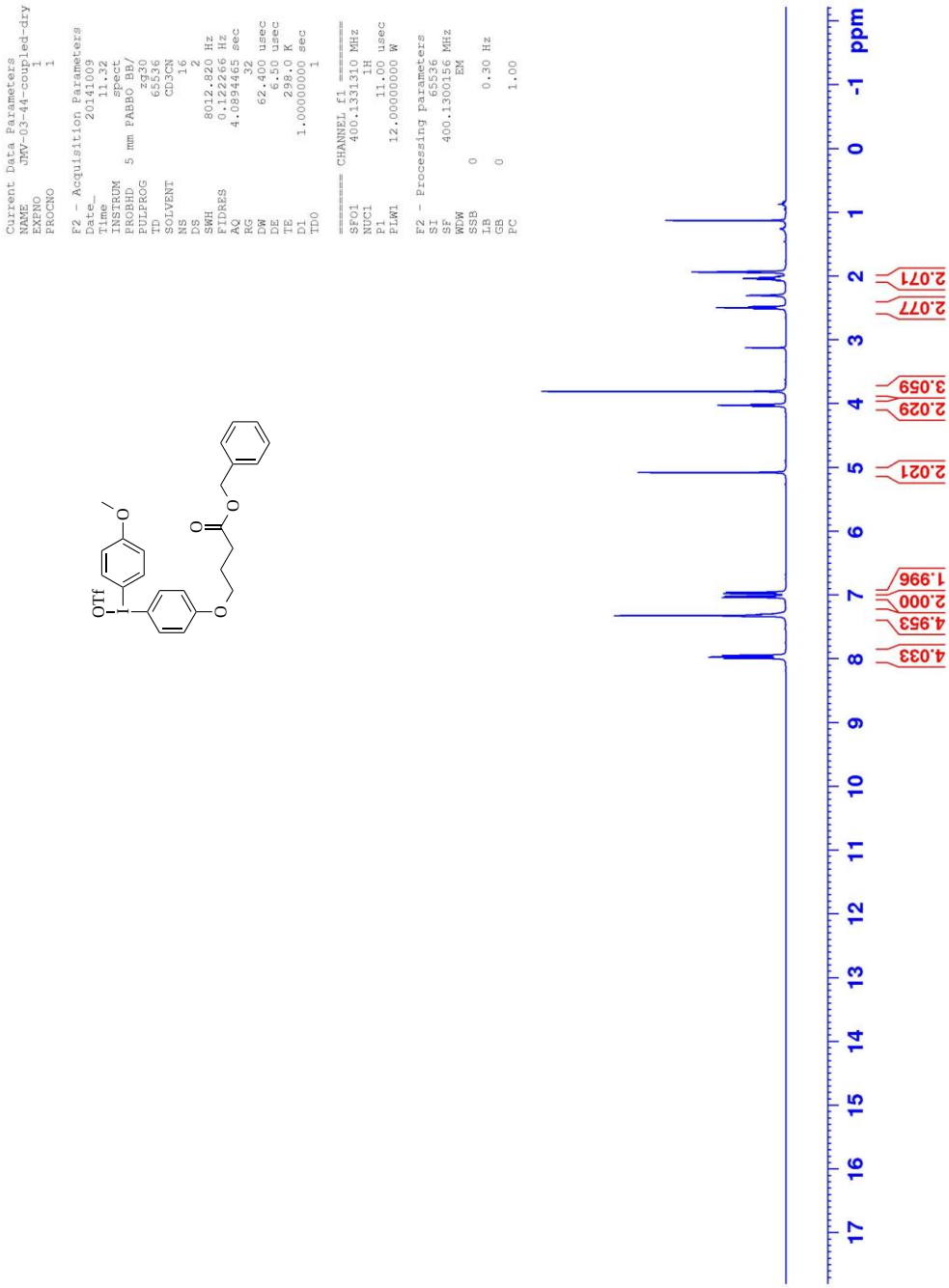
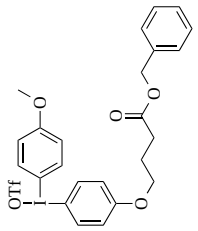


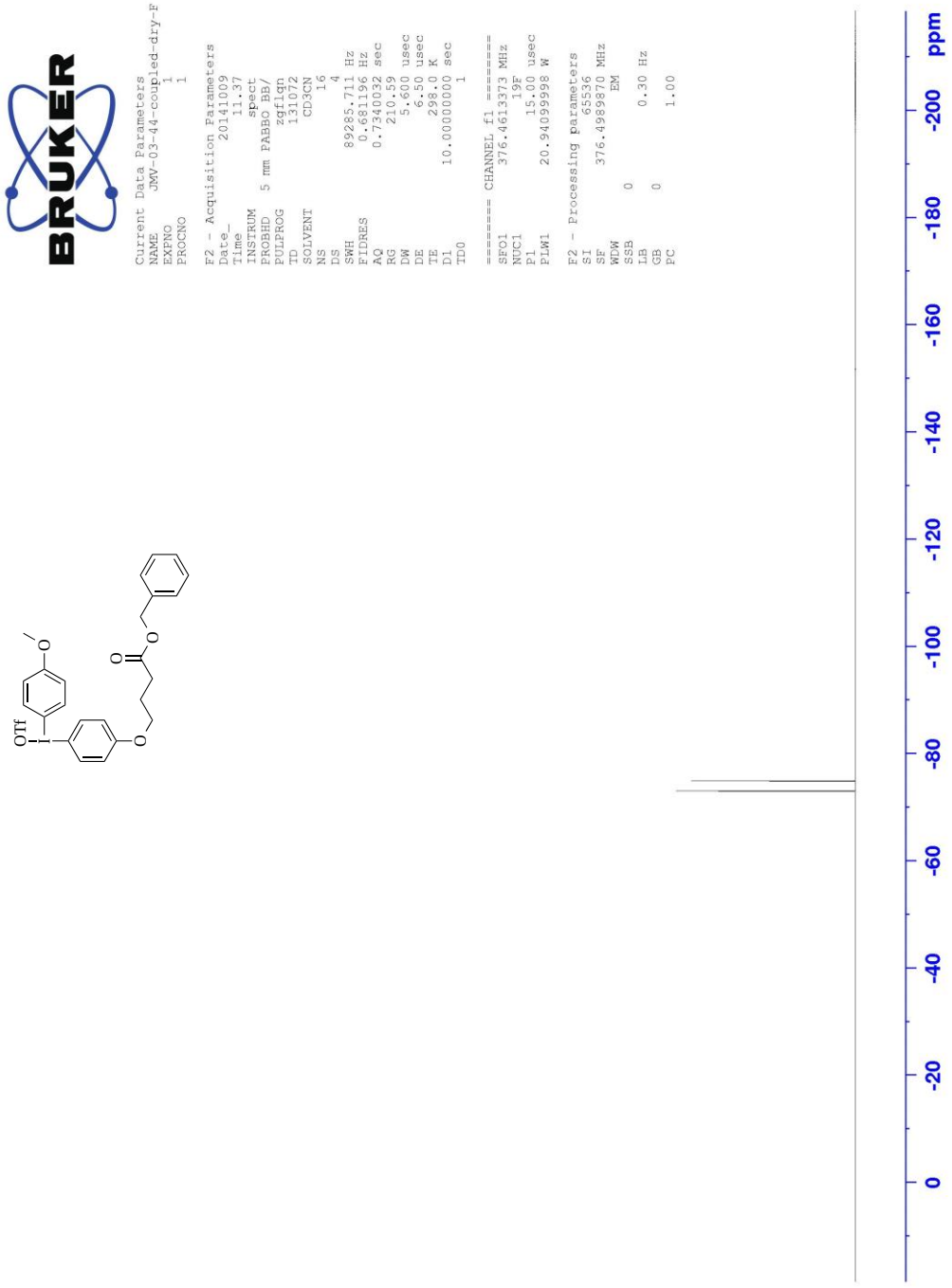
^{1}H NMR Spectrum of benzyl 4-(4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-l^{3}-iodanyl)phenoxy)butanoate



^{13}C NMR Spectrum of benzyl 4-(4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-l^3-iodanyl)phenoxy)butanoate



^{19}F NMR Spectrum of benzyl 4-(4-((4-methoxyphenyl)(((trifluoromethyl)sulfonyl)oxy)-l^3-iodanyl)phenoxy)butanoate



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