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**LAIELI DOS SANTOS MUNARETTO**

# NOVAS TRANSFORMAÇÕES ENVOLVENDO DIAZO COMPOSTOS

**CAMPINAS**

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**LAIELI DOS SANTOS MUNARETTO**

# NOVAS TRANSFORMAÇÕES ENVOLVENDO DIAZO COMPOSTOS

Tese de Doutorado apresentada ao Instituto de Química da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutora em Ciências.

**Orientador: Prof. Dr. Igor Dias Jurberg**

**O arquivo digital corresponde à versão final da Tese defendida pela aluna Laieli do Santos Munaretto e orientada pelo Prof. Dr. Igor Dias Jurberg.**

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## Resumo

Reações de transferência de carbeno empregando arildiazoacetatos representam uma estratégia geral que tem apresentado um grande desenvolvimento nos últimos anos. Geralmente, essas transformações ocorrem termicamente através de catálise metálica (Rh, Cu, Pd, Au, Ag, etc) resultando em uma grande variedade de produtos com alta estereosseletividade e eficiência.

Recentemente, o uso de radiação azul tem se mostrado uma alternativa mais branda para promover reações de transferência de carbeno, sendo assim uma estratégia complementar à catálise metálica para acessar moléculas complexas de interesse.

Nesse contexto, nos tornamos interessados no emprego sequencial de transformações fotoquímicas a partir de diazocompostos para a geração modular de heterociclos complexos, como a síntese de β-lactamas e de furan-3(2H)-onas polissubstituídas.

Nesse trabalho também foi explorado a transformação de diazo compostos para o preparo de novas moléculas fluoradas de forma simples e eficiente, já que estruturas moleculares contendo um ou mais átomos de flúor podem apresentar importantes atividades biológicas e propriedades físicas. Com isso, novos protocolos que permitem a fluoração de compostos orgânicos são de grande importância, pois podem impactar diretamente nos campos de química medicinal, agricultura, e ciência de materiais.

## Abstract

Carbene reactions transfer employing aryldiazoacetates represent a general strategy that has shown great development in recent years. In general, these transformations occur thermally through metal catalysis (Rh, Cu, Pd, Au, Ag, etc) resulting in a wide variety of products with high stereoselectivity and efficiency.

Recently, the use of blue radiation has been shown to be a milder alternative to promote carbene transfer reactions, thus being a complementary strategy to metal catalysis to access complex molecules of interest.

In this context, we became interested in the sequential use of photochemical transformations from diazo compounds for the modular generation of complex heterocycles, such as the synthesis of β-lactams and polysubstituted furan-3(2H)-ones.

During this work, we also explored the transformation of diazo compounds for the preparation of new fluorinated molecules in a simple and efficient way. Since molecular structures containing one or more fluorine atoms may have important biological activities and relevant physical properties.

Based on this, new protocols that allow the fluorination of organic compounds are of great importance, which can directly impact the fields of medicinal chemistry, agriculture, and materials science.

**Sumário**

## 1. Introdução

Carbenos são intermediários reativos amplamente explorados em várias transformações orgânicas, desde reações de cicloadição e rearranjos sigmatrópicos até funcionalização de ligações C–H, assim permitindo a construção de moléculas mais funcionalizadas.

A elevada reatividade dos carbenos está relacionada com o octeto incompleto do átomo de carbono, uma vez que possui somente seis elétrons na camada de valência.[1] Carbenos podem apresentar duas multiplicidades de spin: singleto (par de elétrons de spins contrários) ou tripleto (par de elétrons com mesmo spin) (Figura 1).[1]

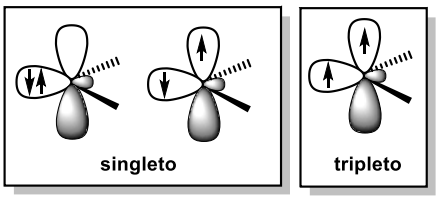



**Figura 1.** Exemplos representativos de diferentes estados de spin em carbenos.

Com base na teoria da ligação de valência, o átomo de carbono do carbeno pode apresentar hibridização $sp^2$ quando possui em sua estrutura substituintes doadores de elétrons, por exemplo, diaminocarbenos. Por outro lado, o átomo de carbono do carbeno pode ter hibridização sp quando substituído com grupos retiradores de elétrons, como em diborilcarbenos. [1]

Além de influenciar a hibridização do átomo de carbono que origina o carbeno os substituintes podem favorecer uma das duas multiplicidades de spin, são elas singleto ou tripleto. De modo geral, substituintes que possam doar elétrons ao orbital *p* vazio vizinho favorecem a formação de carbenos singletos. Por outro lado, substituintes retiradores de elétrons geralmente favorecem o estado de spin tripleto.[1]

Em termos de reatividade, carbenos singletos apresentam características ambífilicas. (*i.e.* podem reagir tanto como eletrófilo ou como nucleófilo). Por outro lado, carbenos tripletos apresentam características de diradical.[1]

Alguns exemplos de compostos precursores de carbenos incluem dihalogênios, sais de imidazólio, aminofosfocalcanos, ilídios de sulfoxônio,

diazirinas e diazo compostos (Figura 2). Ambos os dihalogênios e os sais de imidazólio formam carbenos a partir de uma desprotonação. Aminofosfoalcanos podem gerar carbenos a partir da fragmentação da dupla ligação C=P. Enquanto os ilídios de sulfoxônio podem originar carbenos a partir de catálise metálica, diazirinas tipicamente são fotolizadas. Finalmente, diazo compostos podem gerar carbenos a partir de catálise metálica, termólise ou fotólise.[1,2]

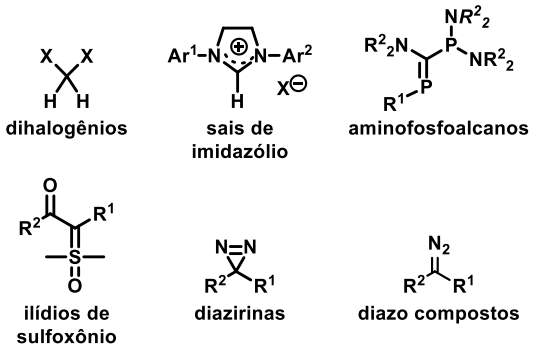
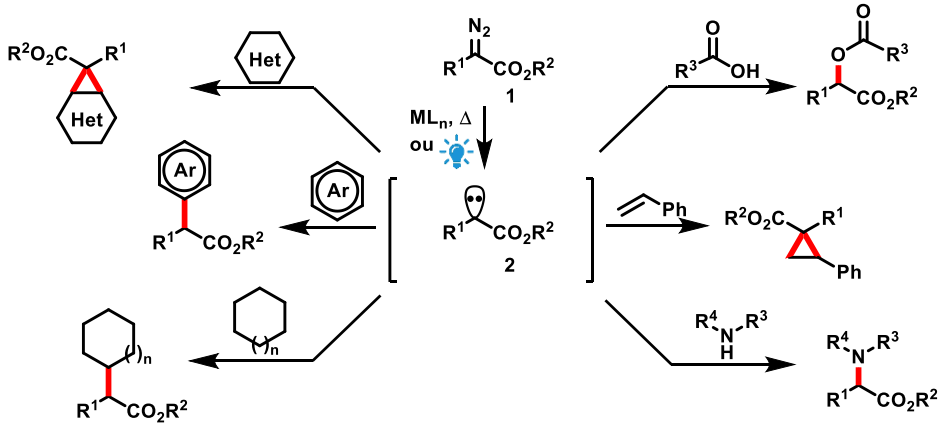



**Figura 2.** Exemplos selecionados dos precursores mais comuns de carbenos.

A utilização de diazo compostos **1** (Esquema 1) como precursores de carbenos **2** é uma estratégia sintética que tem ganhado destaque nas últimas décadas. Os diazo compostos podem originar carbenóides metálicos utilizando por exemplo, ródio e rutênio, enquanto carbenos livres podem ser formados a partir de termólise (> 80 ºC) ou por meio de fotólise com luz visível.[3]




**Esquema 1.** Exemplos selecionados de transformações fotoquímicas envolvendo diazo compostos **1**.

Atualmente, existe um extenso estudo sobre transformações térmicas utilizando diazo compostos, empregando métodos racêmicos[4] ou altamente

estereosseletivos para ciclopropanação,[5] inserção de ligações O–H,[6] N–H[7] e C–H,[8] além de cicloadições[9] e rearranjos.[10]

Em contraste ao grande número de protocolos reportados para processos térmicos (tipicamente catalisado por metais), estudos fotoquímicos utilizando diazo compostos[11] foram consideravelmente menos frequentes durante as últimas décadas; e aplicações sintéticas utilizando carbenos gerados por via fotoquímica ainda são relativamente escassas.[12,13]

Em 2018, Jurberg e Davies desenvolveram um protocolo utilizando luz visível no comprimento de onda do azul ($\lambda$ = 450 - 470 nm) para a geração de carbenos livres a partir de arildiazoacetatos.[14] Dessa maneira, uma série de funcionalizações puderam ser realizadas na ausência de catalisadores metálicos.[15]

Em termos de métodos sintéticos, esta estratégia pode ser entendida como uma contribuição interessante à química de carbenos. O método é insensível ao ar e a humidade e é suave; assim potencialmente permitindo a funcionalização de moléculas mais complexas. Assim, a irradiação de diazo compostos com luz visível para a geração de carbenos livres é uma estratégia complementar aos métodos anteriormente estabelecidos na literatura, como catálise metálica, fotoquímica (empregando luz ultravioleta) e aquecimentos elevados.[16,17]

# 2. Estratégias Mediadas por Luz Visível para o Preparo de β-Lactamas Trissubstituídas e Furanonas a partir de Arildiazoacetatos e Arildiazocetonas.

## 2.1 Distribuição de créditos

O trabalho apresentado neste capítulo foi desenvolvido em colaboração com o mestrando Caio Y. dos Santos, o doutorando Celso Y. Okada Jr.; e o pesquisador de pós-doutorado, o Dr. Rafael D. C. Gallo.

O mestrando Caio Y. dos Santos **foi o responsável pela otimização** da reação para a **formação de ilídios de sulfoxônio** e avaliou **todo o escopo** desta transformação (**22 exemplos de ilídios de sulfoxônio**). Ele também realizou as aplicações sintéticas descritas envolvendo estes ilídios (**2 exemplos**), e sintetizou **4 exemplos** de furanonas.

O pesquisador de pós-doutorado Dr. Rafael D. C. Gallo **foi o responsável** pela **descoberta de reatividade** entre arildiazoacetatos e azidas aromáticas e realizou estudos preliminares de otimização para esta reação.

O doutorando Celso Y. Okada Jr. **foi responsável** por **descobrir a reatividade** entre ilídios de sulfoxônio e diazocetonas levando à formação de furanonas e realizar estudos preliminares de otimização para esta reação.

A doutoranda Laiéli dos Santos Munaretto **foi responsável por otimizar** as seguintes reações: **formação de iminas**, de β **-lactamas** e de **furanonas**. Com relação ao desenvolvimento do escopo das transformações, ela preparou **18 exemplos de iminas**, **10 exemplos de β-lactamas**, **5 exemplos de furanonas** e estudou os **4 exemplos reportados de aplicações sintéticas** de iminas. Ela também obteve os **2 cristais** que foram utilizados para a determinação inequívoca da estrutura de **β-lactama 9i** e a **furanona 10i**. Todos os compostos sintetizados e caracterizados pela Laiéli estão destacados em azul neste capítulo.

O Professor Victor M. Deflon (Instituto de Química São Carlos – USP/ São Carlos) foi responsável pelas **análises de Raio-X** realizadas neste trabalho.

## 2.2 Introdução

Reações de transferência de carbeno empregando arildiazoacetatos representam uma estratégia geral que tem apresentado um grande desenvolvimento nos últimos anos. Geralmente, essas transformações ocorrem termicamente através de catálise metálica (Rh, Cu, Pd, Au, Ag, etc) resultando em uma grande variedade de produtos com alta estereosseletividade e eficiência.[16]

Recentemente, o uso de luz visível na região do azul (aproximadamente 450-470 nm) tem se mostrado uma alternativa suave e prática para gerar carbenos a partir de arildiazoacetatos. Desta forma, o uso da luz visível pode ser considerado uma estratégia complementar aos métodos baseados em catálise metálica ou puramente térmicos estabelecidos na literatura; e pode ser considerado uma estratégia particularmente atraente para o preparo de moléculas racêmicas ou aquirais; ou em potenciais aplicações em química biológica.[17]

É interessante notar que ao compararmos a reatividade de carbenos livres gerados a partir deste método fotoquímico e carbenos metálicos, algumas diferenças pronunciadas de seletividade e eficiência podem ser algumas vezes encontradas.[14] De fato, reações térmicas catalisadas por metais podem oferecer um mecanismo diferente como consequência da presença do metal (formando o carbeno metálico) influenciando sua estabilidade e a seletividade da transformação.[18]

Em termos mais práticos, protocolos promovidos por luz azul podem ser considerados como alternativas experimentais mais simples e práticas, uma vez que são tolerantes à umidade e ao ar. Além disso, como já mencionado, a fotólise pode ser considerada uma abordagem mais branda, pois permite a formação de carbenos em temperaturas mais baixas, tipicamente temperatura ambiente.

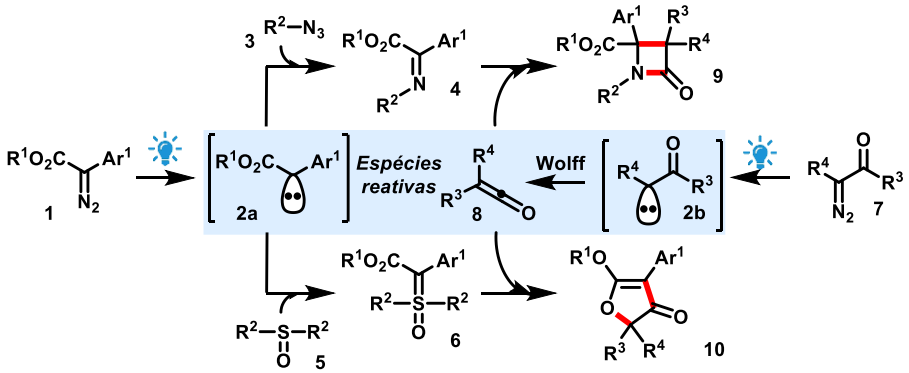
Por fim, estratégias que utilizam luz visível são frequentemente consideradas mais viáveis do ponto de vista econômico, pois não requerem o uso de materiais especiais como quartzo,[19] que é necessário quando se faz o uso de luz ultravioleta (adicionalmente à maior seletividade da reação que normalmente acompanha o uso da luz azul *vis-à-vis* da luz UV), ou do uso de metais preciosos como catalisadores.[16]

Por outro lado, reações envolvendo a fotólise com luz visível não permitem o controle da estereoquímica absoluta (pelo menos até o presente momento, com as estratégias já reportadas); o que em contraste está bem estabelecido com o uso de catalisadores metálicos com ligantes enantiomericamente puros.[15]

Nesse contexto,[14,20] nós nos tornamos interessados no emprego sequencial de transformações fotoquímicas a partir de diazo compostos para a geração modular de heterociclos complexos. Nosso plano inicial visou a geração de β-lactamas e furan-3(2H)-onas polissubstituídas.

### 2.3 Resultados e Discussão

Inicialmente, nossa hipótese de trabalho é que a fotólise de arildiazoacetatos **1** com luz azul permitiria a geração de carbenos **2a**, que poderiam reagir com azidas **3** ou sulfóxidos **5** resultando em iminas **4**[21] e ilídios de sulfoxônio **6**,[22,23] respectivamente. Na sequência, a fotólise de diazocetonas **7** levaria à formação do carbeno **2b**, que poderia sofrer um rápido rearranjo 1,2 (rearranjo de Wolff), assim originando o ceteno **8**. Em seguida, este ceteno poderia reagir com iminas **4** levando à formação de β-lactamas **9**.[24] De modo similar, ilídios de sulfoxônio **6** poderiam reagir com o intermediário **8** resultando em furan-3(2H)-onas **10**[25] (Esquema 2).




**Esquema 2:** Plano sintético para geração de β-lactamas **9** e furan-3(2H)-onas **10**.

Com o propósito de colocar nossa ideia na prática, iniciamos o estudo da reação entre o arildiazoacetato **1a** e a azida **3a** sob radiação da luz azul com o objetivo de preparar a imina correspondente **4a** (Tabela 1).

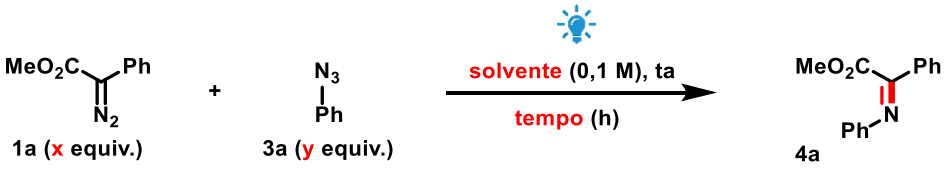
Inicialmente, exploramos a variação estequiométrica entre os reagentes empregados. Para todos esses testes preliminares, diclorometano (DCM) foi utilizado como solvente, em tempo reacional de 24 h e sob temperatura ambiente Tabela 1, Entradas 1-6). Nesse estudo, a condição ótima foi observada utilizando 1 equivalente do diazo composto **1a** e 2 equivalentes da azida **3a** com rendimento estimado de 50%, a partir de análise do espectro de RMN de $^{1}$H bruto reacional utilizando 1,3,5-trimetoxibenzeno como padrão interno, para averiguar a precisão do rendimento estimado por RMN, o produto **4a** foi isolado por cromatografia em coluna de sílica, e o rendimento obtido do produto **4a** foi de 47%.

Uma vez que os dados de rendimento estimado (análise do bruto reacional por RMN de $^{1}$H) e o rendimento isolado estavam suficientemente próximos, seguimos com o estudo de otimização. É importante destacar que esse procedimento de comparar rendimentos estimados utilizando um padrão interno, com os dados obtidos dos produtos isolados foram realizados em todos os estudos de otimização deste trabalho.

Os rendimentos mais baixos observados ao utilizar excesso de **1** em relação à azida **3a** podem ser explicados com relação a maior reatividade de arildiazoacetato **1a** no meio reacional, pois diversos subprodutos de difícil identificação foram observados no bruto reacional analisado por RMN de $^{1}$H (Tabela 1, Entradas 5 e 6).

Prosseguindo com os estudos de otimização, decidimos avaliar o aumento do tempo reacional para 48 h, no entanto não foi observado um incremento significativo no rendimento, indicando que a imina **4a** é estável nessas condições reacionais, sendo novamente observado 50% de rendimento (Tabela 1, Entrada 7). Experimentos utilizando tempos reacionais de 6 h e de 16 h também foram realizados. No entanto, menores rendimentos foram observados, de 24% e 40%, respectivamente.

**Tabela 1:** Otimização da reação fotoquímica entre arildiazoacetato **1a** e azida **3a** para o preparo da imina **4a**.



| Entrada | x | y | Solvente (0,1 M) | Tempo (h) | 4a (%)[a] |
|---|---|---|---|---|---|
| 1 | 1 | 1 | DCM | 24 | 37 |
| **2** | **1** | **2** | **DCM** | **24** | **50 (47)[b]** |
| 3 | 1 | 3 | DCM | 24 | 45 |
| 4 | 1 | 5 | DCM | 24 | 40 |
| 5 | 2 | 1 | DCM | 24 | 35 |
| 6 | 3 | 1 | DCM | 24 | 25 |
| 7 | 1 | 2 | DCM | 48 | 50 |
| 8 | 1 | 2 | 1,2-DCE | 24 | 35 |
| 9 | 1 | 2 | tolueno | 24 | 24 |
| 10 | 1 | 2 | MeCN | 24 | 25 |
| 11[c] | 1 | 2 | DCM | 24 | < 30 |
| 12[d] | 1 | 2 | DCM | 24 | < 40 |
| 13[e] | 1 | 2 | DCM | 24 | 0 |

[a]Rendimento estimado por RMN de $^1$H a partir do bruto reacional utilizando 1,3,5-trimetoxibenzeno como padrão interno e escala de 0,1 mmol com relação ao reagente limitante. [b] Rendimento isolado. [c]Utilizando 1, 3 ou 5 equiv. de $MgSO_4$. [d]Utilizando diferentes quantidades de peneira molecular 4Å. [e]Reação realizada no escuro.

Considerando o uso de solventes, 1,2-dicloroetano (1,2-DCE) resultou em 35% de **4a** (Tabela 1, Entrada 8), tolueno forneceu 24% de **4a** (Tabela 1, Entrada 9) e utilizado acetonitrila (MeCN) foi observado um rendimento de 25% (Tabela 1, Entrada 10). Os menores rendimentos observados ao utilizar tolueno e acetonitrila podem ser explicados devido à formação de subprodutos envolvendo carbeno formado e o solvente.[14]

Estudos utilizando agentes secantes também foram realizados, pois imaginamos que a umidade residual presente no meio reacional poderia estar ocasionando menor rendimento a partir da hidrólise da imina formada.[26] Para esses experimentos, $MgSO_4$ ou peneira molecular 4 Å em várias quantidades foram investigados, no entanto em nenhum dos experimentos realizados foi observado aumento no rendimento (Tabela 1, Entradas 11 e 12).

Por fim, o estudo de controle realizando a reação no escuro não levou à formação da imina de interesse em nenhuma extensão. De fato, após 24 h, somente os materiais de partida foram recuperados virtualmente em sua

totalidade (Tabela 1, Entrada 13), demonstrando que essa transformação necessita da luz azul.

Com um protocolo otimizado para a formação da imina **4a**, outras azidas aromáticas foram avaliadas, as quais levaram à geração de iminas em rendimentos similares entre si: **4g** (50%), **4h** (60%), **4i** (50%), **4k** (50%). A síntese de iminas derivadas de azidas alifáticas apresentou rendimentos mais elevados para os compostos correspondentes: **4b** (70%), **4c** (64%), **4d** (60%), **4e** (60%), **4f** (71%), **4q** (74%), **4s** (77%) e **4t** (54%). Vale a pena mencionar que a estereoquímica *Z* do diastereoisômero majoritário das iminas preparadas neste trabalho foi determinada comparando **4a** com os dados espectroscópicos já reportados na literatura, em que outros métodos (*i.e.* análise de difração de Raio-X de um mono cristal) foram utilizados para a determinação da estereoquímica, e generalizado para as demais iminas por analogia (Esquema 3A).[27]

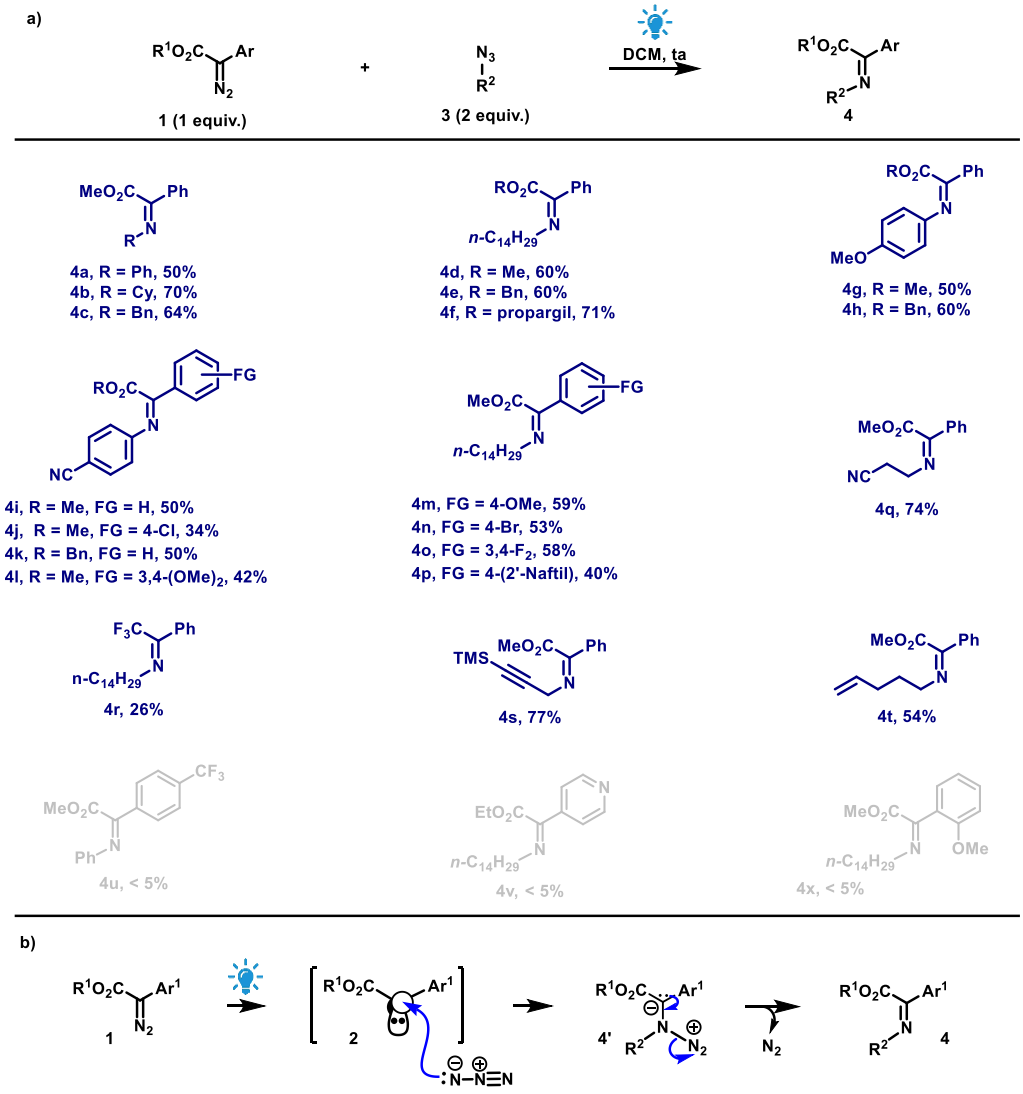
O maior rendimento observado para as iminas obtidas a partir das azidas derivadas de cadeias alifáticas ligadas diretamente ao átomo de nitrogênio do grupamento azido pode ser explicado devido à maior estabilidade dessas azidas no meio reacional. Ao analisar o espectro de RMN de $^{1}$H do bruto reacional desses experimentos era tipicamente possível observar a formação do produto esperado, a azida remanescente usada em excesso e a degradação parcial do arildiazoacetato.

Por outro lado, quando o bruto reacional analisado por RMN de $^{1}$H das reações empregando azidas aromáticas foram analisados observou-se a formação de diferentes subprodutos, além do consumo total da azida utilizada em excesso. Tentativas de isolar os subprodutos formados falharam.

Acreditamos que um dos subprodutos formados seja a dimerização de **1**, já reportada na literatura.[28]

É importante destacar que essa estratégia se mostrou compatível com diferentes grupos funcionais sobre a azida, tais como nitrila (**4q**), alcinil silano (**4s**) e alceno (**4t**) (Esquema 3A). O composto **4t** é um bom exemplo para demonstrar o potencial desse método no que diz respeito à quimiosseletividade. Carbenos são conhecidos por reagirem com alcenos para o preparo de ciclopronanos, no entanto não foi observada a formação do ciclopropano correspondente em nenhuma extensão, pois ao analisar o bruto reacional

utilizando RMN de $^{1}H$ não foi observado sinais característicos da formação desse composto.[5]




**Esquema 3. a)** Avaliação do escopo da reação fotoquímica entre arildiazoacetatos **1** e azidas **3** levando à formação das iminas correspondentes **4**. Rendimentos isolados para **4a**-**4t** em escala de 0,1 mmol do reagente limitante **1**. **b)** Proposta de Mecanismo.

Ao explorar a variação estrutural no grupo sobre o anel aromático do arildiazoacetato **1** foram observados rendimentos de moderados a bons: **4j** (34%), **4l** (42%), **4m** (59%), **4n** (53%), **4o** (58%), **4p** (40%). Notavelmente, rendimentos maiores foram obtidos quando o anel aromático possui grupos doadores de elétrons em sua estrutura. Por outro lado, rendimentos menores foram observados quando grupos retiradores de elétrons estão presentes no anel aromático do arildiazoacetato **1**. Possivelmente, efeitos eletrônicos estão

envolvidos nessa transformação e grupos doadores de elétrons favorecem a formação da imina de interesse.

A imina **4r**, que possui o grupo $CF_3$, foi preparada com um rendimento modesto (26%). Acreditamos que o menor rendimento observado é resultado das características singulares do substituinte trifluorometila.[29] Entre elas podemos citar o forte efeito indutivo retirador de elétrons. Leadbeater e colaboradores reportaram que o grupo $CF_3$ na posição alfa à carbonila de cetona aumenta a carga positiva no carbono da carbonila, e assim o ataque nucleofílico ao carbono é facilitado.[30]

Com relação à absorção na luz azul, o diazo composto **1r** apresenta absorção máxima na luz azul em 467 nm, que é próxima à absorção do arildiazoacetato **1a** que ocorre em 431 nm, ou seja, ambos os compostos apresentam absorção na radiação azul e possivelmente não seja esse o motivo do menor rendimento.[31]

Análise de RMN de $^1H$ do bruto reacional da reação de formação de **4r** foi realizada e notou-se apenas os sinais referentes ao produto e à azida utilizada em excesso, devido à volatilidade de **1r** e a potencial geração de subprodutos voláteis, a análise do bruto reacional utilizando RMN de $^1H$ não apresentou muita informação para auxiliar a racionalização sobre o rendimento mais baixo observado. É importante destacar que o preparo de **4r** foi realizado em triplicata e resultados semelhantes foram observados.

Apesar da modularidade demonstrada com a síntese de 20 exemplos bem-sucedidos, algumas limitações foram identificadas, onde o preparo dos compostos **4u**, que possui grupo retirador de elétrons ($CF_3$); **4v**, que possui um anel heteroaromático com nitrogênio básico; e **4x**, que possui um substituinte metoxila na posição *orto* do anel aromático, produziram apenas traços das iminas correspondentes (Esquema 3A).

Para **4u**, **4v** e **4x** foram observados a formação de diversos produtos de difícil identificação. No espectro de RMN de $^1H$ e de RMN de $^{19}F$ do bruto reacional da reação de formação **4u** foi possível notar a formação de diferentes produtos que contém o átomo de flúor.[29,30] No caso da reação de formação de **4v**, o caráter básico do átomo de nitrogênio no anel heteroaromático pode estar favorecendo reações paralelas levando a diferentes produtos, como observado

no espectro de RMN de $^{1}H$ do bruto reacional. De modo similar, ao analisar o espectro de RMN de $^{1}H$ do bruto reacional da reação de formação de **4x** observou-se a formação de diferentes produtos que contém o grupamento metoxila em sua estrutura (pelo menos 6). Esforços para isolar os compostos obtidos nas tentativas de formação de **4u**, **4v** e **4x** foram feitos, no entanto falharam (Esquema 3A).

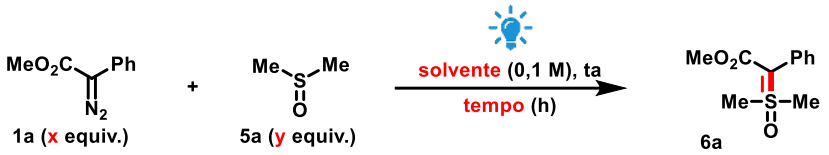
A quantificação dos produtos formados **4u**, **4v** e **4x** foi realizada utilizando a técnica de RMN de $^{1}H$ a partir do bruto reacional, onde foi possível observar sinais característicos dos produtos desejados (Esquema 3A).

Considerando a formação de iminas **4**, nossa proposta mecanística se inicia com a formação do carbeno **2** mediado pela luz azul. Em seguida, ocorre um ataque nucleofílico do átomo de nitrogênio do grupamento azido presente em **3**, fornecendo o intermediário **4'**, que a partir do ataque nucleofílico do átomo de carbono carregado negativamente presente na estrutura de **4'** seguido da liberação de gás nitrogênio resulta na formação da imina **4** (Esquema 3B).[32]

Considerando o preparo dos ilídios de sulfoxônio **6**, iniciamos os estudos da reação desejada empregando o arildiazoacetato **1a** e dimetilsulfóxido (DMSO) **5a**, com o objetivo de preparar o ilídio de sulfoxônio **6a** para nossa reação-modelo. Investigando a variação da quantidade de DMSO **5a** enquanto a quantidade de diazo composto **1a** permanece inalterada (Tabela 2, Entradas 1-4). Durante um tempo reacional de 12 h, sob temperatura ambiente, o melhor rendimento observado foi de 65% empregando 5 equiv. de DMSO, como um compromisso razoável entre eficiência da reação e economia dos reagentes (Tabela 2, Entrada 3). Ao utilizar 10 equivalentes do sulfóxido **5a** observa-se um aumento marginal no rendimento de **6a** para 67% (Tabela 2, Entrada 4).

Ao avaliar o uso de um número diferente de equivalentes do arildiazoacetato **1a**, enquanto a quantidade de DMSO **5a** permanece constante (Tabela 2, Entradas 6 e 7), os melhores rendimentos observados são de 66% e 68%, respectivamente. Assim, um pequeno aumento é produzido ao utilizarmos 3 e 5 equivalentes de **1a** (Tabela 2, Entradas 6 e 7) em comparação com o rendimento de 65% previamente observado (Tabela 2, Entrada 3).

**Tabela 2.** Estudos de otimização para a reação fotoquímica entre **1a** e **5a** visando o preparo do ilídio de sulfoxônio **6a**.




| Entrada | x | y | Solvente (0,1 M) | Tempo (h) | 4a (%)[a] |
|---|---|---|---|---|---|
| 1 | 1 | 1 | DCM | 12 | 41 |
| 2 | 1 | 2 | DCM | 12 | 52 |
| **3** | **1** | **5** | **DCM** | **12** | **65 (66)[b]** |
| 4 | 1 | 10 | DCM | 12 | 67 |
| 5 | 2 | 1 | DCM | 12 | 60 |
| 6 | 3 | 1 | DCM | 12 | 66 |
| 7 | 5 | 1 | DCM | 12 | 68 |
| 8 | 1 | 5 | DCM | 3 | 6 |
| 9 | 1 | 5 | DCM | 6 | 50 |
| 10 | 1 | 5 | DCM | 24 | 65 |
| 11 | 1 | 5 | 1,2-DCE | 12 | 40 |
| 12 | 1 | 5 | tolueno | 12 | 63 |
| 13 | 1 | 5 | MeCN | 12 | 0 |
| 14 | 1 | 5 | DCM[c] | 12 | 0 |

[a]Rendimento estimado por RMN de $^1$H a partir do bruto reacional utilizando 1,3,5-trimetoxibenzeno como padrão interno e escala de 0,1 mmol do reagente limitante. [b]Rendimento isolado. [c]Reação realizada no escuro.

Uma vez que DMSO e outros sulfóxidos utilizados nesse trabalho são tipicamente mais abundantes comparados aos diazo compostos **1**, decidimos utilizar os sulfóxidos em excesso para continuar o estudo de otimização. Ao avaliarmos se seria possível reduzir o tempo reacional para 3 h ou 6 h (Tabela 2, Entradas 8 e 9), ou aumentar o tempo reacional para 24 h (Tabela 2, Entrada 10), não foi observada nenhuma melhoria nos rendimentos para a síntese de **6a**: 5%, 50% e 65%, respectivamente. O uso de outros solventes, tais como 1,2-DCE, tolueno ou MeCN forneceram rendimentos de 40%, 63% e 0%,

respectivamente (Tabela 2, entradas 11-13). Finalmente, quando o experimento de controle foi realizado no escuro, não houve formação do ilídio de sulfoxônio **6a** (Tabela 2, entrada 14).

A avaliação do escopo dos ilídios de sulfoxônio **6** preparados a partir das condições reacionais otimizadas provou-se bastante abrangente, apresentando rendimentos variando de moderados a bons (Esquema 4a).

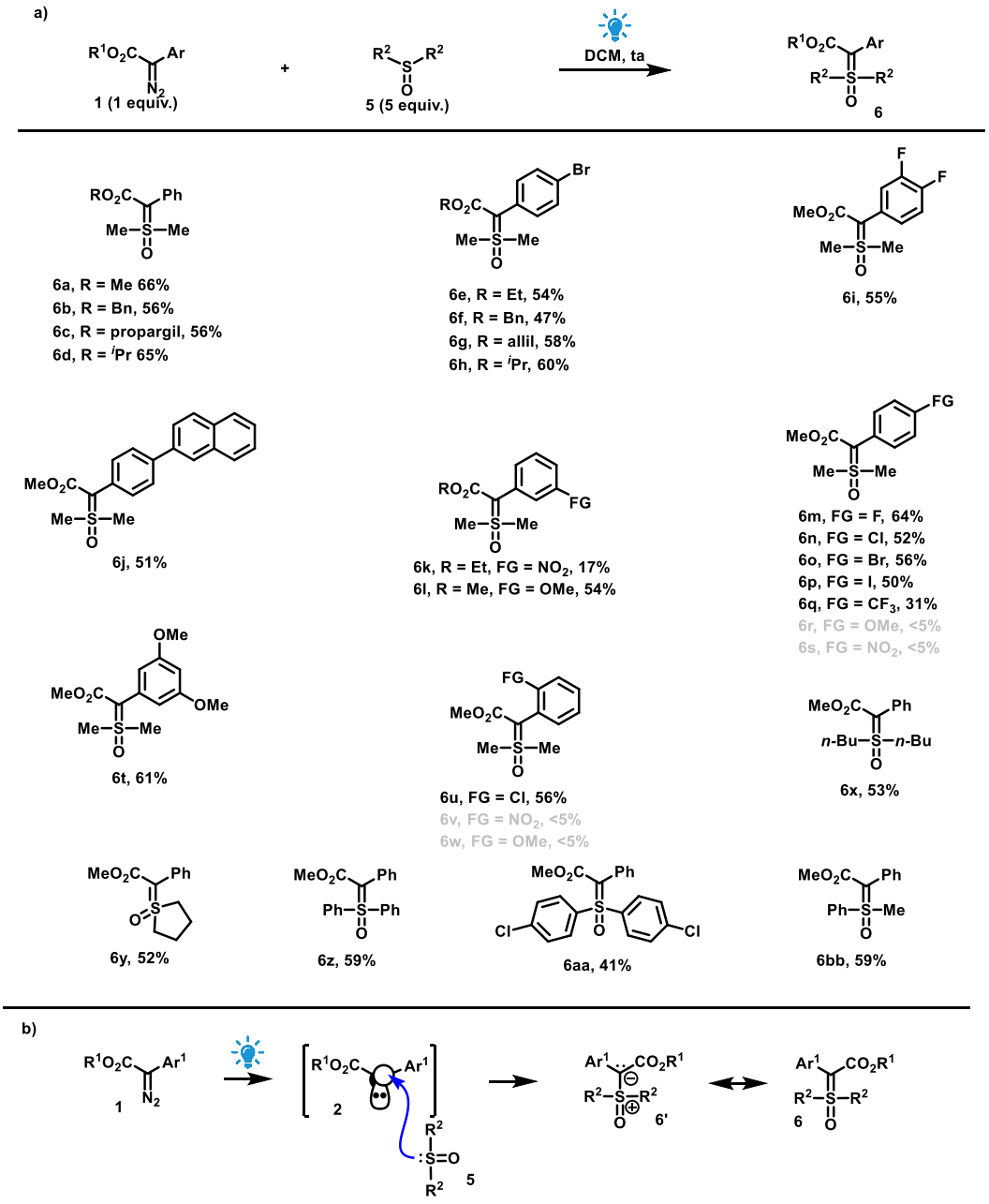
Uma variedade de grupamento ésteres do arildiazoacetato **1** são compatíveis com a metodologia desenvolvida nesse trabalho, como evidenciado a partir da preparação de **6a** (66%), **6b** (56%), **6c** (56%), **6d** (65%), **6e** (54%), **6f** (47%), **6g** (58%) e **6h** (60%). Além disso, diversos grupos funcionais também são tolerados no anel aromático presente na estrutura molecular dos arildiazoacetatos: **6i** (55%), **6j** (51%), **6l** (54%), **6m** (64%), **6n** (52%), **6o** (56%), **6p** (50%), **6t** (61%), **6u** (56%) (Esquema 4a).

Ao avaliar a compatibilidade da nossa estratégia em moléculas que apresentam grupos retiradores de elétrons *m*-$NO_2$ em **6k** (17%); *p*-$CF_3$ em **6q** (31%); *p*-$NO_2$ em **6s** (< 5%), *o*-$NO_2$ em **6v** (< 5%) notou-se rendimentos menores em comparação com outros grupos funcionais. Os menores rendimentos observados podem ser explicados devido à possibilidade do carbeno gerado reagir com o oxigênio do grupo nitro presente na estrutura do anel, levando à formação de diferentes produtos (Esquema 4a).

Similarmente, grupos fortemente doadores *p*-OMe em **6r** (< 5%) ou *o*-OMe em **6w** (< 5%) não resultaram nos produtos desejados em nenhuma das reações ou somente em rendimentos muito baixos. Notavelmente, carbenos livres gerados termicamente a partir de arildiazoacetatos contendo grupos OMe tem sido reportado como reativos com DMSO, mas preferencialmente resultando em $\alpha$-ceto-ésteres.[33] De acordo com outras estratégias previamente reportadas,[23a,34] a preparação dos ilídios de sulfoxônio tem falhado quando utilizados esse tipo de substrato (Esquema 4a).

Em contrapartida, diversos sulfóxidos **5** são compatíveis com a nossa estratégia sintética e resultaram no produto desejado **6** em rendimentos, no geral, sinteticamente úteis: **6x** (53%), **6y** (52%), **6z** (59%), **6aa** (41%) e **6bb** (59%) (Esquema 4). Esta observação sugere que essa transformação é mais

sensível às mudanças na estrutura do arildiazoacetatos **1** em comparação com as mudanças na estrutura dos sulfóxidos **5** (Esquema 4a).




**Esquema 4. a)** Avaliação do escopo da reação fotoquímica entre arildiazoacetatos **1** e sulfóxidos **5** levando à formação de ilídios de sulfoxônio **6**. Rendimentos isolados em escala de 0,1 mmol com relação ao reagente limitante **1**, com exceção de **6r**, **6s**, **6v** e **6w** em que os rendimentos foram estimados por RMN de $^{1}H$ utilizando 1,3,5-trimetoxibenzeno como padrão interno. **b)** Mecanismo proposto.

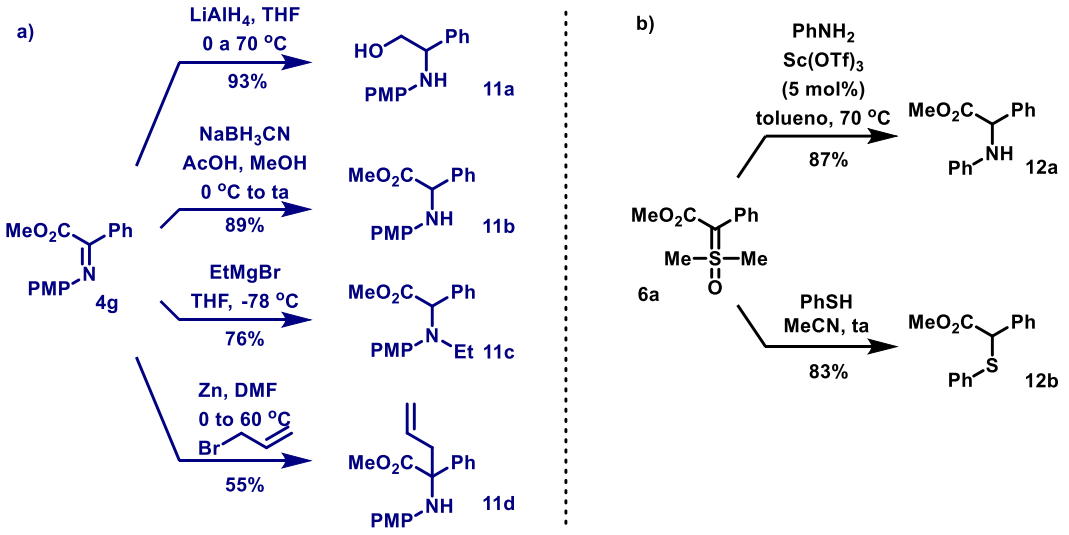
Com respeito a formação de **6**, nossa proposta mecanística se inicia com a formação do carbeno **2** mediado pela luz azul. Em seguida, ocorre um ataque

nucleofílico do par de elétrons não ligante presente no átomo de enxofre de **5**, fornecendo diretamente o produto **6**, o qual pode ser representado como estruturas de ressonância **6** e **6'** (Esquema 4b).[35]

Iminas **4** e ilídios de sulfoxônio **6** podem ser empregados como intermediários versáteis em uma variedade de transformações químicas, assim resultando em moléculas mais funcionalizadas como apresentado no Esquema 5. Exemplos de aplicações sintéticas envolvendo a imina **4g** incluem a redução com hidreto de lítio e alumínio ($LiAlH_4$)[36] resultando no aminoálcool **11a** (93%) ou utilizando cianoborohidreto de sódio ($NaBH_3CN$)[37] como redutor mais brando levando a formação de **11b** (89%).

A adição de espécies organometálicas também foi avaliada, para isso reagentes como brometo de etil magnésio (EtMgBr)[38] ou brometo de alil zinco (alilZnBr)[39] foram empregados e com isso foram sintetizados **11c** (76%) e **11d** (55%), respectivamente (Esquema 5a). A regiosseletividade observada para essa transformação (*C*- alquilação *versus N*- alquilação) foi observada na literatura e as origens para esse fenômeno ainda não estão claras, pois dependem dos substituintes na estrutura das iminas e do reagente organometálico utilizado. Contudo, geralmente, reagentes alquil magnésio tendem a privilegiar a *N*-alquilação (Esquema 5a).[38,40]

Reações de inserção empregando os ilídios de sulfoxônio **6a** foram avaliadas. Nessas transformações, a anilina[22a] ou o tiofenol[22b] foram usados para resultar em **12a** (87%) e **12b** (83%), respectivamente (Esquema 5b).




**Esquema 5. a)** Exemplos de aplicações sintéticas empregando a imina **4g**. **b)** ilídio de sulfoxônio **6a**. Rendimentos isolados em escala de 0,1 mmol do reagente inicial, **4g** ou **6a**.

Motivados pelo nosso interesse no desenvolvimento de novos métodos para o preparo de heterociclos,[41] decidimos explorar a possibilidade de acessar β-lactamas **9**, utilizando iminas **4**; e furan-3(2H)-onas **10** utilizando ilídios de sulfoxônio **6**. Essas reações utilizariam cetenos como intermediários reativos, os quais poderiam ser obtidos a partir do rearranjo de Wolff dos carbenos produzidos a partir da fotólise de diazocetonas **7**.

Com o objetivo de preparar β-lactamas **9**, estudos de otimização foram realizados. Inicialmente, variações das quantidades estequiométricas da imina **4g** e arildiazocetona **7a** foram avaliadas visando a preparação de **9a** (Tabela 3). Ao utilizar excesso de 2 equivalentes de **7a** em comparação à quantidade de **1a**, em apenas 2 h de reação, a β-lactama **9a** foi obtida com rendimento de 40% (Tabela 3, Entrada 1). Ao analisar o espectro de RMN de $^{1}$H do bruto reacional foi possível identificar **4g** e **7a**. Com base nesse resultado decidimos avaliar um tempo reacional mais longo de 16 h. Após análise do bruto reacional por RMN de $^{1}$H foi observado o rendimento estimado de 98% para β-lactama **9a** e rendimento isolado de 97% (Tabela 3, Entrada 2).

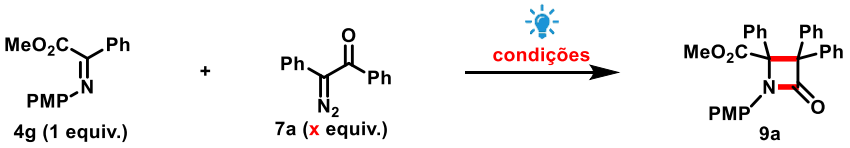
Similarmente, um pequeno excesso de 1,2 equivalentes de arildiazocetona **7a** em relação à imina **4g** apresentou um rendimento de 42% para **9a** com tempo reacional de 2 h; enquanto um maior tempo reacional de 16 h apresentou um rendimento significativamente maior, 98% (Tabela 3, Entradas 3 e 4). Dessa forma, a Entrada 4 da Tabela 3 apresentou as melhores condições

para essa série de experimentos, sendo assim escolhida como condição ótima para a avaliação do escopo desta transformação.

É importante destacar que a reação realizada no escuro, em DCM, sob temperatura ambiente, apresenta um rendimento modesto de 40% para o preparo do heterociclo de interesse (Tabela 3, Entrada 5). O rendimento para essa transformação pode ser maior (72% e 78%) empregando temperaturas mais elevadas, tais como 40 ºC (Tabela 3, Entrada 6); ou 60 ºC (Tabela 3, Entrada 7). No entanto, esses rendimentos são significativamente menores quando comparados ao método fotoquímico, 98% (Tabela 3, Entrada 4).

Além disso, ao analisar o espectro de RMN de $^{1}$H do bruto reacional das transformações térmicas, é possível notar a formação de diversos subprodutos de difícil identificação, o que não foi observado na transformação mediada por luz azul. Ou seja, o método fotoquímico permitiu o acesso à uma estratégia mais seletiva de síntese dos heterociclos **9**.

**Tabela 3.** Estudos de otimização voltados para a reação fotoquímica da imina **4g** com arildiazocetona **7a** levando à formação da β-lactama **9a**.




| Entrada | x | Condições | 10a (%)[a] |
|---|---|---|---|
| 1 | 2 | DCM, ta, 2 h | 40 |
| 2 | 2 | DCM, ta, 16 h | 98 |
| 3 | 1,2 | DCM, ta, 2 h | 42 |
| **4** | **1,2** | **DCM, ta, 16 h** | **98 (99)[b]** |
| 5 | 1,2 | DCM, ta, 16 h[c] | 40 |
| 6 | 1,2 | DCM, 40 ºC, 16 h[c] | 72 |
| 7 | 1,2 | 1,2-DCE, 60 ºC, 16 h[c] | 78 |

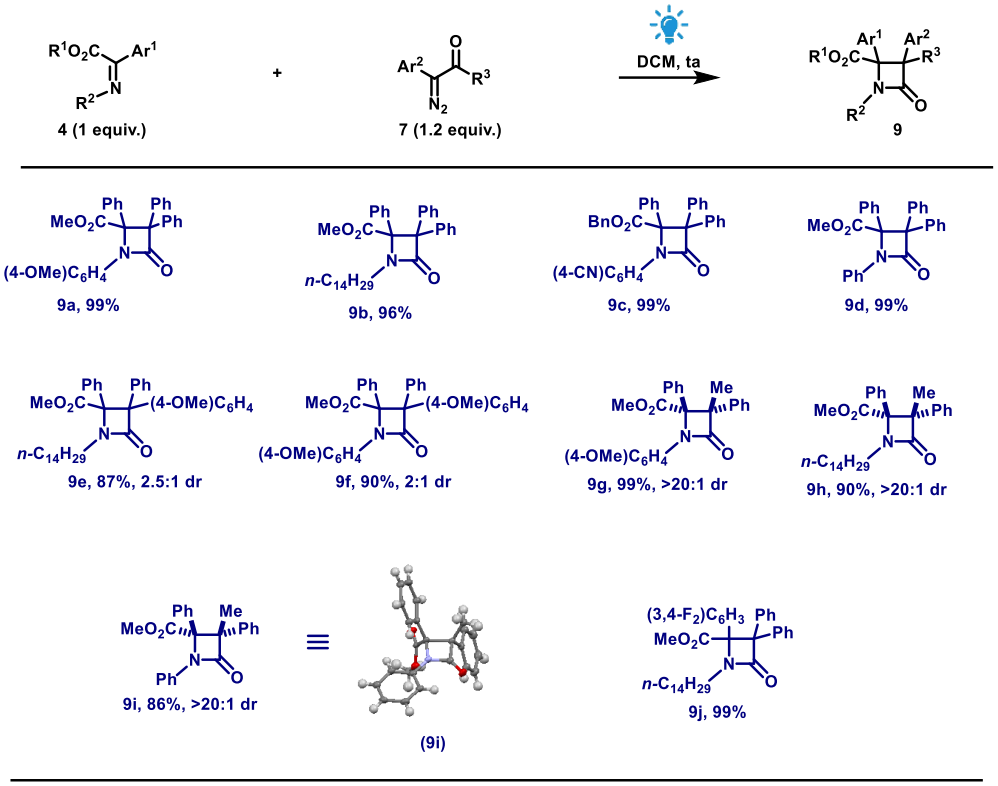
[a]Rendimento estimado por RMN de $^{1}$H a partir do bruto reacional utilizando 1,3,5-trimetoxibenzeno como padrão interno em escala de 0,1 mmol de **4g**. [b]Rendimento isolado. [c]Reação realizada no escuro.

Com as condições otimizadas em mãos (Tabela 3, Entrada 4) foi possível preparar uma variedade de β-lactamas **9** em elevados rendimentos (87 - 98%) a partir da reação entre iminas **4** e arildiazocetonas **7** utilizando DCM como

solvente, na temperatura ambiente e sob irradiação com luz azul (Esquema 6). Utilizando as condições ótimas foi possível sintetizar dez β-lactamas **9** inéditas em elevados rendimentos

Arildiazocetonas substituídas com dois grupos arila apresentaram baixa diasterosseletividade (evidenciado por **9e** e **9f**, produzindo 2.5:1 dr e 2:1 dr, respectivamente, Esquema 6). De modo oposto, quando grupamentos metila e fenila estão presentes na arquitetura molecular de arildiazocetona **7**, apenas um diastereoisômero da β-lactama **9** é observado (**9g**, **9h** e **9i**, todos > 20:1 dr, Esquema 6). A configuração relativa pôde ser determinada de forma inequívoca por difração de Raio-X de um monocristal de **9i**. (Esquema 6).

A reação envolvendo ilídios de sulfoxônio **6a** e arildiazocetonas **7b** sob luz azul resultou na formação da furan-3(2H)-ona **10a**. Estudos de otimização foram realizados variando as quantidades dos reagentes **6a** e **7b** (Tabela 4, Entradas 1-5), e revelaram que as condições ótimas para o preparo do heterociclo **10a** envolve 3 equivalentes de arildiazocetona **7b** em relação ao ilídio **6a** (Tabela 4, Entrada 5). Nessas condições um rendimento estimado de 71% foi detectado pela RMN de $^{1}H$ e o rendimento isolado foi de 67%. Vale mencionar que ao utilizar 1 ou 2 equivalentes de diazocetona notou-se no espectro de RMN de $^{1}H$ do bruto reacional que o ilídio de sulfoxônio **6a** não havia sido consumido em sua totalidade.

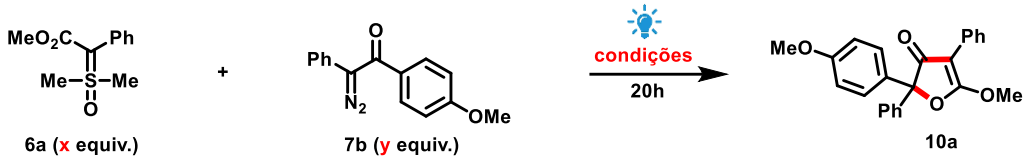



**Esquema 6.** Preparação de β-lactamas mediada por luz azul empregando iminas **4** e arildiazocetonas **7**. Rendimentos isolados em escala de 0,1 mmol de **4**.

Imaginando que ilídio de sulfoxônio pudesse ser menos reativo frente a reação com arildiazocetona e que esta estaria sendo consumida por reações paralelas, realizamos um experimento fazendo 3 adições de 1 equivalente de arildiazocetona **7b**, ou seja, 1 equivalente no início da reação, 1 equivalente após 4 h e outro equivalente após 8 h (em relação ao início da reação), no entanto rendimento similar foi observado quando 3 equivalentes de **7a** são adicionados de uma só vez no início do experimento.

Com relação ao experimento de controle no escuro, observou-se baixa formação de **10a**, de 20% (Tabela 4, Entrada 6). Nos estudos de controle, utilizando DCM como solvente e temperatura de 40 $^{o}$C ou 1,2-DCE como solvente e temperatura de 60 $^{o}$C, não foi observada a formação do heterociclo **10a**, apenas degradação de **6a** e **7b** foi constatado no espectro de RMN de $^{1}$H do bruto reacional (Tabela 4, Entradas 7 e 8).

**Tabela 4.** Estudos de otimização envolvendo a reação fotoquímica entre o ilídio de sulfoxônio **6a** com arildiazocetona **7b** visando a síntese da furan-3(2H)-ona **10a**.

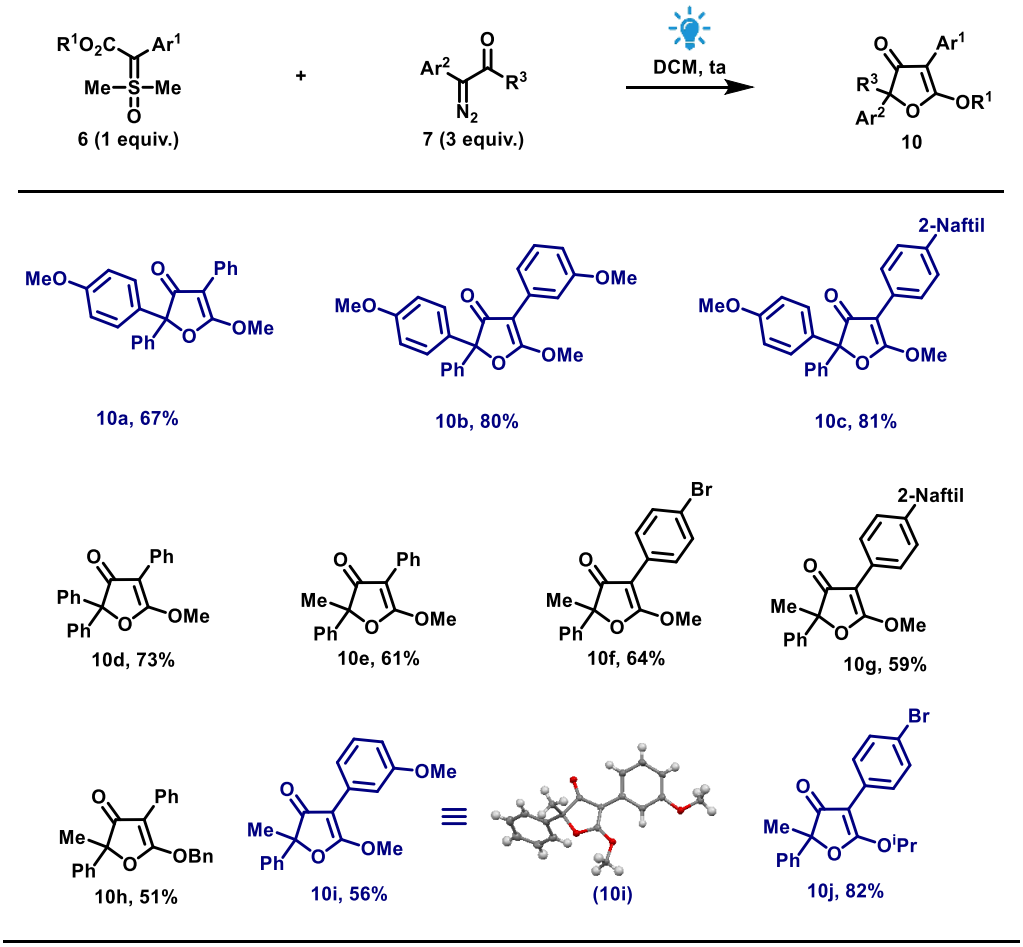



| Entrada | x | y | Condições | 10a (%)[a] |
|---|---|---|---|---|
| 1 | 1 | 1 | DCM, ta | 29 |
| 2 | 2 | 1 | DCM, ta | 42 |
| 3 | 3 | 1 | DCM, ta | 40 |
| 4 | 1 | 2 | DCM, ta | 56 |
| **5** | **1** | **3** | **DCM, ta** | **71 (67)[b]** |
| 6 | 1 | 3 | DCM, ta[b] | 20 |
| 7 | 1 | 3 | DCM, 40 °C[b] | < 5 |
| 8 | 1 | 3 | 1,2-DCE, 60 °C[b] | < 5 |

[a]Rendimento estimado por RMN de $^1$H a partir do bruto reacional utilizando 1,3,5-trimetoxibenzeno como padrão interno em escala de 0,1 mmol do reagente limitante. [b]Rendimento isolado. [c]Reação realizada no escuro.

Uma vez estabelecido um protocolo otimizado para essa transformação, esforços voltaram-se para avaliação de diferentes ilídios de sulfoxônio **6** e arildiazocetonas **7**, assim resultando nas furan-3(2H)-onas correspondentes **10** com rendimentos variando de moderados a bons, 51-82% (Esquema 7). A estrutura desses heterociclos pôde ser confirmada de modo inequívoco a partir da análise de difração de Raio-X de um monocristal de **10i**.

O novo protocolo para a síntese dos heterociclos **10** estabelecido pelo nosso grupo de pesquisa permitiu a síntese e caracterização completa de dez novos heterociclos inéditos. Além disso, essa estratégia se mostrou compatível com diferentes substituintes, tais como, haletos, grupos arila e alquila, bem como metoxila.



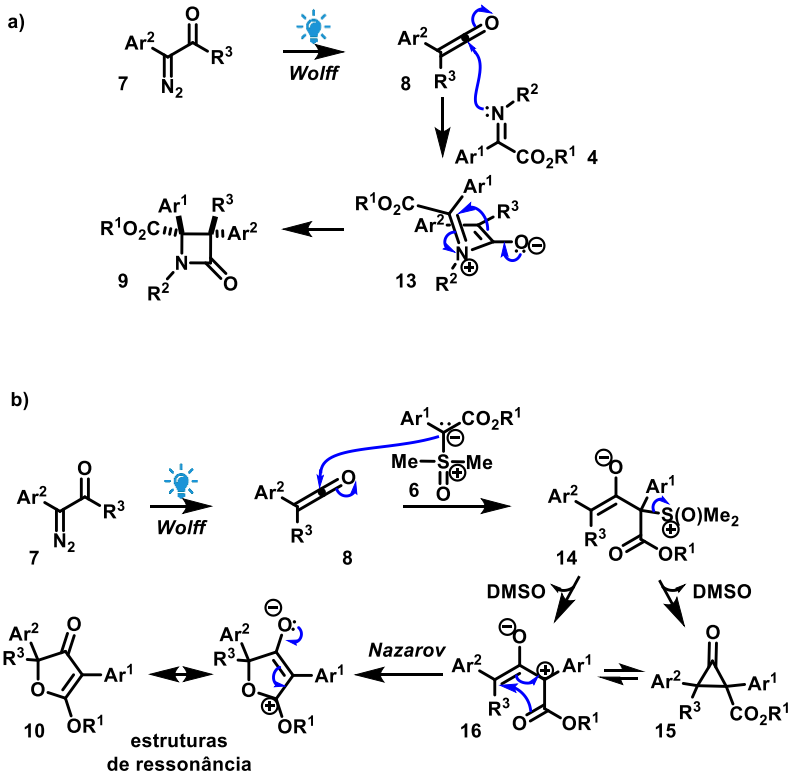

**Esquema 7.** Preparo de furan-3(2H)-onas **10** a partir da reação fotoquímica entre ilídios de sulfoxônio **6** e arildiazocetonas **7**. Rendimentos isolados em escala de 0,1 mmol de **6**.

Com respeito ao mecanismo de formação das β-lactamas **9**, nossa proposta envolve o rearranjo de Wolff mediado por luz azul visível, permitindo a conversão de arildiazocetonas **7** no ceteno intermediário **8**.[25] Esse intermediário pode reagir com a imina **4**, assim resultando na formação da espécie zwitteriônica **13**. Por fim, uma etapa de ciclização intramolecular resulta a formação da β-lactama **9**.

Essa etapa de ciclização intramolecular é que determina a razão diastereoisomérica observada no Esquema 6. Quando dois grupos arila distintos estão presentes na estrutura da arildiazocetona **7** a razão diastereoisomérica é modesta (2:1), uma vez que ambos os grupos são planares e não exibem grande diferença espacial. No entanto, ao utilizar arildiazocetona **7** substituída com grupo arila e metila ocorre uma diferenciação no volume que esses grupos ocupam no espaço, e, assim, favorecendo a formação preferencial de um dos

produtos (Esquema 8A). Essa observação já foi constatada por outros pesquisadores.[42]

Considerando a formação de furan-3(2H)-onas **10**, nossa proposta mecanística se inicia com o rearranjo de Wollf mediada pela luz azul visível permitindo a conversão de arildiazocetona **7** no ceteno **8**.[25] Em seguida, um ataque nucleofílico do ilídio de sulfoxônio **6** fornece presumidamente o intermediário **14**, que a partir do evento de fechamento de anel pode gerar uma ciclopropanona **15**,[43] seguido de uma rápida abertura do anel resultando na espécie zwitteriônica **16**. Alternativamente, o intermediário **14** pode potencialmente eliminar DMSO levando à formação direta de **16**, o qual pode sofrer processo pericíclico do tipo Nazarov resultando na formação do heterociclo **10** (Esquema 8B).




**Esquema 8.** Propostas mecanísticos para **a)** Síntese de β-lactamas **9** e **b)** furan-3(2H)-onas **10**.

## 2.4 Conclusão Parcial

No trabalho discutido neste capítulo foi possível desenvolver duas novas estratégias sintéticas promovidas por luz visível na região do azul, ambas utilizando arildiazoacetato **1** como precursor para geração de carbenos livres. Essas estratégias são simples e eficientes, permitindo a preparação de intermediários sintéticos valiosos (iminas **4** e ilídios de sulfoxônio **6**) e heterociclos polissubstituídos (β-lactamas **9** e furan-3(2H)-ones **10**), e assim, possivelmente contribuindo para o maior uso desses compostos em síntese orgânica.

Os resultados apresentados neste capítulo foram recentemente publicados no periódico *Organic Letters* (Munaretto, L. S.; dos Santos, C. Y.; Gallo, R. D. C.; Okada Jr., C. Y.; Deflon, V. M.; Jurberg, I. D. *Org. Lett.* **2021**, *23*, 9292-9296).

# 3. Inserção de H–F em Diazo Compostos via Condições Térmicas

## 3.1 Distribuição de Créditos

O trabalho apresentado neste capítulo foi desenvolvido em colaboração com o doutorando Luiz Paulo M. O. Leão e com o pesquisador de pós-doutorado Dr. Rafael D. C. Gallo.

O doutorando Luiz Paulo M. O. Leão **foi o responsável** pela **descoberta de reatividade** entre arildiazoacetatos e HF.pir, além de sintetizar **4 exemplos** do escopo dessa transformação.

O pesquisador de pós-doutorado Dr. Rafael D. C. Gallo preparou um grande número dos diazo compostos empregados como materiais de partida deste trabalho, **foi o responsável** por sintetizar **1 exemplo** do escopo dessa transformação, realizou o experimento em escala preparativa (3 mmol), e realizou todos os experimentos adicionais necessários solicitados pelos revisores para a publicação do manuscrito referente a este trabalho.

A doutoranda Laiéli dos Santos Munaretto **foi responsável por otimizar** a reação descrita nesse capítulo. Com relação ao escopo, a aluna Laiéli dos Santos Munaretto preparou **30 exemplos** e realizou os experimentos necessários para o estudo do mecanismo. Todos os compostos sintetizados e caracterizados pela Laiéli estão destacados em azul neste capítulo.

## 3.2 Introdução

Moléculas contendo um ou mais átomos de flúor podem apresentar importantes atividades biológicas e propriedades físicas.[44] Essas características estão relacionadas com a alta eletronegatividade e o pequeno raio de Van der Waals do átomo de flúor (1,47 Å), o qual não é significativamente maior comparado ao átomo de hidrogênio (1,20 Å).[45]

Devido a essas propriedades não usuais, novos protocolos que permitem a fluoração de compostos orgânicos são de grande importância, podendo impactar diretamente os campos de química medicinal,[46] agricultura,[47] e ciência de materiais.[48]

No que diz respeito à química medicinal, inúmeros fármacos contêm em sua estrutura um ou mais átomos de flúor. Isto pode ser explicado devido às

características intrínsecas do flúor. Entre elas, podemos destacar a força da ligação C–F de 439 kJ.mol$^{-1}$, que frequentemente aumenta a estabilidade de fármacos fluorados (a título de comparação, a força de ligação entre C–O é de 350 kJ.mol$^{-1}$ e entre C–C é de 345 kJ.mol$^{-1}$).[49]

Outro ponto que merece destaque é a capacidade do átomo de flúor influenciar na polarização da ligação C–F. Isso é resultado da sua elevada eletronegatividade, de 4,0 na escala de Pauling. Essa polarização da ligação pode alterar a lipofilicidade dos fármacos. Além disso, o flúor pode atuar como aceptor de ligações de hidrogênio. Essa característica pode ser explorada em Química Medicinal, onde por exemplo, um átomo de flúor pode ser considerado um bioisóstero de um grupo hidroxila.[50]

Alguns exemplos de medicamentos que contém um ou mais átomos de flúor em sua estrutura são levofloxacina, florfenicol, efavirenz, lascufloxaxina, fluordeoxiglucose-F18 e fluorodopa (Figura 3).[50]

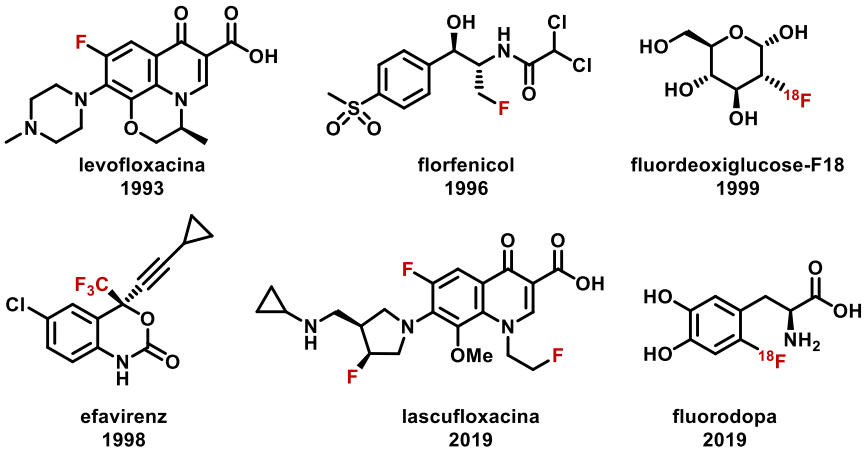



**Figura 3.** Exemplos de medicamentos que contém um ou mais átomos de flúor em sua estrutura e o ano de aprovação pelo FDA (*Food and Drug Administration* – agência federal do Departamento de Saúde e Serviços Humanos dos Estados Unidos.

Uma aplicação muito interessante dos fármacos fluorados é a possibilidade de acessar procedimentos baseados em tomografia por emissão de pósitrons (PET, *Positron Emission Tomography*). Essa estratégia fundamenta-se em medicina nuclear com o objetivo de medir a emissão de pósitrons. No caso do átomo de flúor, o isótopo $^{18}$F é um importante emissor de pósitrons que tem um curto tempo de meia-vida (110 minutos), o que permite ser

utilizado como rádio marcador. Exemplos de radiomedicamentos incluem fluordeoxiglucose-F18 e fluorodopa-F18 (Figura 3).[50,51]

Devido às numerosas aplicações de moléculas fluoradas, diversos métodos sintéticos vêm sendo reportados na literatura, por exemplo: fluoração de compostos aromáticos catalisada por paládio,[52] fluoração de ligações C–H em estágio avançado,[53] fluoração de amino ácidos[54] e deoxifluoração.[55]

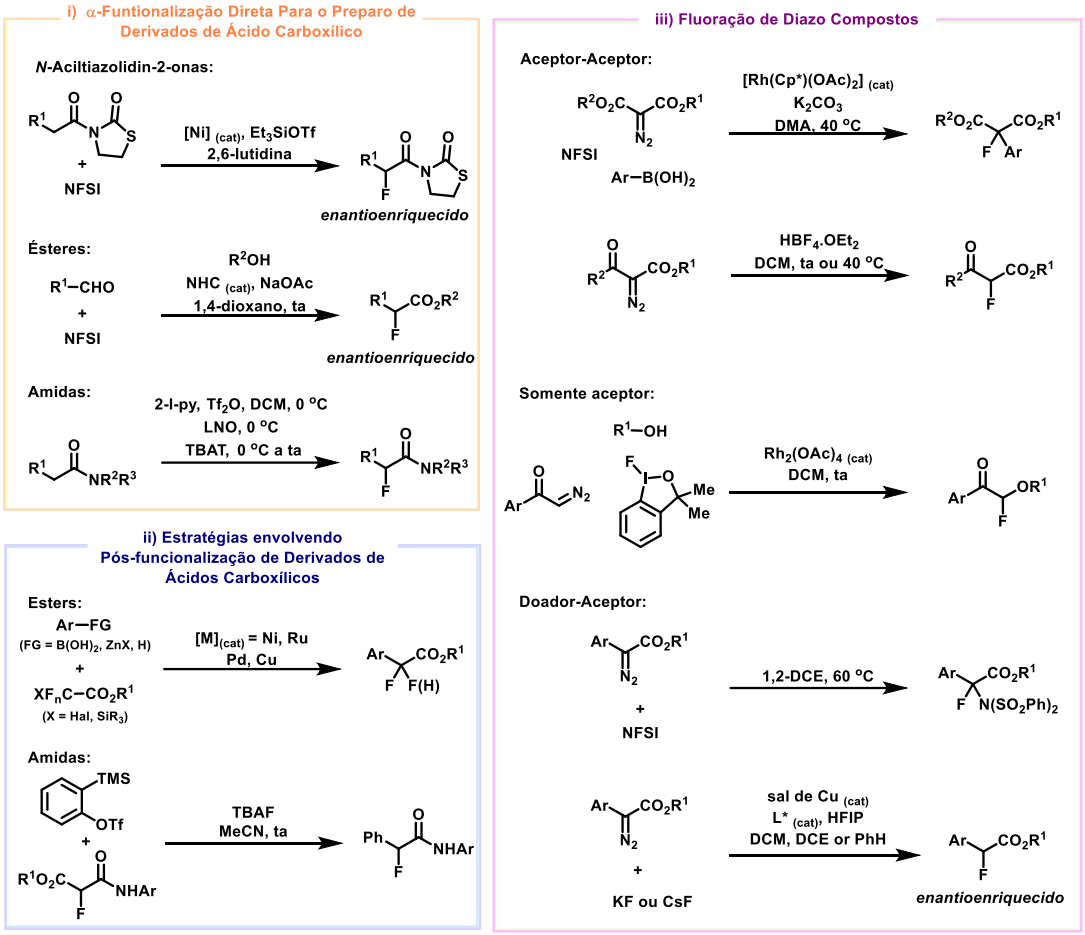
Entre os protocolos reportados para a preparação de diferentes classes de moléculas fluoradas, a síntese de derivados de ácidos carboxílicos $\alpha$-fluorados é uma delas.

Abordagens sintéticas que permitem a síntese desses compostos geralmente são fundamentadas em três categorias principais: i) fluoração direta do composto carbonilado adequado (Esquema 9a); ii) posterior modificação de moléculas previamente $\alpha$-fluoradas ou $\alpha,\alpha$-difluoradas (Esquema 9b); iii) fluoração dieta de diazo compostos (Esquema 9c).

Métodos representativos podem ser sumarizados como a seguir. Para i) Sodeoka e colaboradores descreveram a preparação assimétrica de $\alpha$-fluoro *N*-aciltiazolidin-2-onas mediada por níquel através da reação entre *N*-aciltiazolidin-2-ona e o agente de fluoração eletrofílico *N*-fluorobezenesulfonimida (NFSI).[56a] Rotas sintéticas para a funcionalização de ésteres $\alpha$-fluorados foram reportadas por Wang e colaboradores via catálise assimétrica empregando NHC envolvendo aldeídos e NFSI na presença de álcoois.[56b] A preparação de amidas $\alpha$-fluoradas foi reportada por Maulide e colaboradores empregando amidas em uma sequência reacional com 2-I-piridina e $Tf_2O$, seguido pelo tratamento com *N*-óxido de 2,6-lutidina (LNO) e tetrabutilamônio difluorotrifenilsilicato (TBAT)[56c] (Esquema 9a).

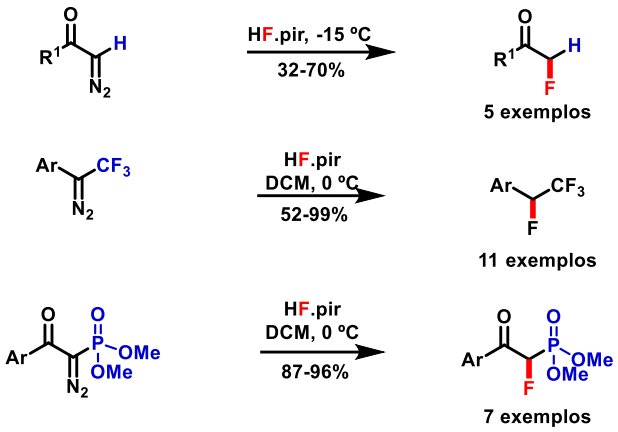
Para ii), muitos pesquisadores tem reportado reações de acoplamento cruzado envolvendo 2-fluoroacetatos ou 2,2-difluoroacetatos com arenos funcionalizados (Ar-FG, FG = $B(OH)_2$, ZnX) ou arenos não funcionalizados (ArH) por meio de estratégias baseadas em funcionalização de ligações C–H, explorando o uso de diversos catalisadores metálicos (Ni,[57a,b] Ru,[57c,d] Pd,[57e,f] Cu[57g,h]). Vale destacar que Mojanan e colaboradores reportaram o preparo de fluoromalonatos explorando a arilação descarboxilativa promovida por TBAF[57i] (Esquema 9b).

Para iii), métodos envolvendo diazo compostos podem ser separados em três categorias, de acordo com a natureza eletrônica (doador ou retirador) dos substituintes vizinhos ao grupo diazo.[58] Huang, Yu e colaboradores reportaram a reação utilizando diazo compostos com substituintes aceptores-aceptores, NFSI e ácidos aril borônicos, na presença de um catalisador de Rh(III), para o preparo dos 2-aril-2-fluoro diésteres correspondentes.[58a] Hayes, Moody e colaboradores reportaram o uso de $HBF_4$ como agente de fluoração nucleofílico para a obtenção de 2-diazo-β-cetoesteres[58b] (uma estratégia do tipo Balz-Schiemann[59]). Szabó e colaboradores descreveram uma reação empregando diazo compostos apenas com substituintes aceptores a partir do reagente benziodoxol na presença de álcoois, possibilitando a obtenção de 2-alcoxi-2-fluoro-cetonas.[58c] Li, Huang e colaboradores reportaram um protocolo empregando diazo compostos doadores-aceptores e NFSI sob condições puramente térmicas (aquecimento de 60 ºC) em 1,2-DCE para a síntese dos acetatos de 2-fluoro-2-(*N*-(fenilsulfonil) fenilsulfonamidoíla correspondentes.[58d] O grupo de pesquisas liderado por Doyle desenvolveu um novo método via catálise de cobre e KF como fonte de flúor nucleofílico;[58e] e Fürstner e colaboradores desenvolveram um método mediado por cobre para fluoração assimétrica de diazo compostos doadores-aceptores empregando CsF como fonte de flúor[58f] (Esquema 9c).




**Esquema 9.** Estratégias representativas para sintetizar compostos carbonílicos α-fluorados.

Em 1974, George Olah descreveu o uso de HF.pir como solvente e reagente para a fluoração nucleofílica de diferentes classes de moléculas orgânicas,[60] incluindo um número limitado de diazo compostos somente-aceptores, que foram isolados em rendimentos moderados.[61] Gouverneur e colaboradores[62] reportaram a fluoração de diazo compostos doadores-aceptores empregando HF.pir como agente de fluoração para o preparo de arenos tetrafluorados. O grupo de pesquisas liderado por Wang explorou a fluoração de α-diazo arilmetilfosfonatos também utilizando HF.pir como fonte de flúor nucleofílico (Esquema 10).[63]




**Esquema 10.** Métodos de fluoração de diazocompostos utilizando HF.pir anteriormente descritos na literatura.

Inspirados pelos resultados anteriores, nós decidimos explorar a fluoração de diferentes diazo compostos. Para isso, foram investigados arildiazoacetatos, diazoacetamidas, arildiazoacetamidas e diazocetonas.

O nosso objetivo para esse trabalho foi desenvolver uma abordagem complementar aos procedimentos já reportados. Além disso, gostaríamos de contribuir com uma nova metodologia simples e eficiente, utilizando um reagente de fluoração nucleofílica economicamente acessível, e que permitisse o preparo de compostos fluorados inéditos.

### 3.3 Resultados e Discussão

A reação entre o diazocomposto **1a** e HF.pir **17** foi empregada como nossa reação modelo para o preparo do éster $\alpha$-fluorado **18a** (Tabela 1). Uma investigação inicial sobre a eficiência desse protocolo foi realizada utilizando 3 equivalentes de HF.pir **17** em um recipiente reacional de vidro (vial de 4 mL) por 5 h, sob temperatura ambiente. Nessas condições, o produto desejado foi obtido em 15% de rendimento (Tabela 1, Entrada 1). Ao analisar o bruto reacional utilizando RMN de $^{1}$H observou-se a formação de diversos produtos de difícil interpretação, já o espectro de RMN de $^{19}$F indicava apenas a formação do produto **18a**.

Uma vez percebendo que o HF poderia reagir com as paredes de vidro do vaso reacional, sendo consumido de forma não-produtiva, realizamos a mudança do recipiente de vidro para um de plástico do tipo Eppendorf. Com essa

simples alteração, o rendimento aumentou significativamente para 85% de **18a** durante o mesmo tempo reacional (Tabela 1, Entrada 2). Essa mudança de recipiente reacional de vidro para recipiente de plástico foi inspirada no trabalho original de George Olah.[60]

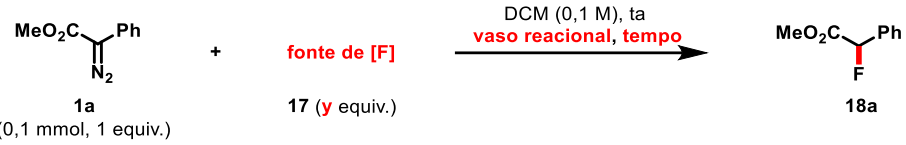
Interessantemente, um tempo reacional menor (1 h) resultou em um rendimento similar de 80% ao do experimento com duração de 5 h (Tabela 1, Entrada 3). Com isso, a eficácia da reação aumentou consideravelmente quando performada em recipiente de plástico e com menor tempo reacional (maior rendimento em menor tempo), uma vez que rendimentos similares foram observados tanto em 5 h como em 1 h de reação.

Uma vez otimizado o recipiente reacional, estudos envolvendo as quantidades dos reagentes foram realizados. Ao utilizar 6 equivalentes de HF.pir com tempo de reação de 5 h, tanto o teste realizado no recipiente de vidro, quanto no recipiente de plástico apresentaram melhores rendimentos para a formação de **18a**, 30% e 92%, respectivamente (Tabela 5, Entradas 4 e 5).

Prosseguindo com estudos de otimização dessa transformação, a avaliação de diferentes quantidades de HF.pir **17** em tempos reacionais menores (30 min e 1 h; Tabela 5, Entradas 6-13) indicou que o melhor resultado para essa série de estudos foi o rendimento de 95% para **18a**, utilizando 6 equivalentes de HF.pir com tempo reacional de 1 h. (Tabela 5, Entrada 13).

A irradiação com luz azul desse sistema reacional[64] não apresentou nenhuma melhoria adicional ao rendimento e **18a** foi obtido em 94% (Tabela 5, Entrada 14). Finalmente, outros agentes de fluoração também foram avaliados sob condições térmicas, no entanto, nenhum desses reagentes proporcionaram uma conversão significativa para a formação de **18a**; e uma mistura complexa de produtos foi observada ao analisar o bruto reacional por RMN de $^{1}H$ e por RMN de $^{19}F$ (Tabela 5, Entradas 15-19).

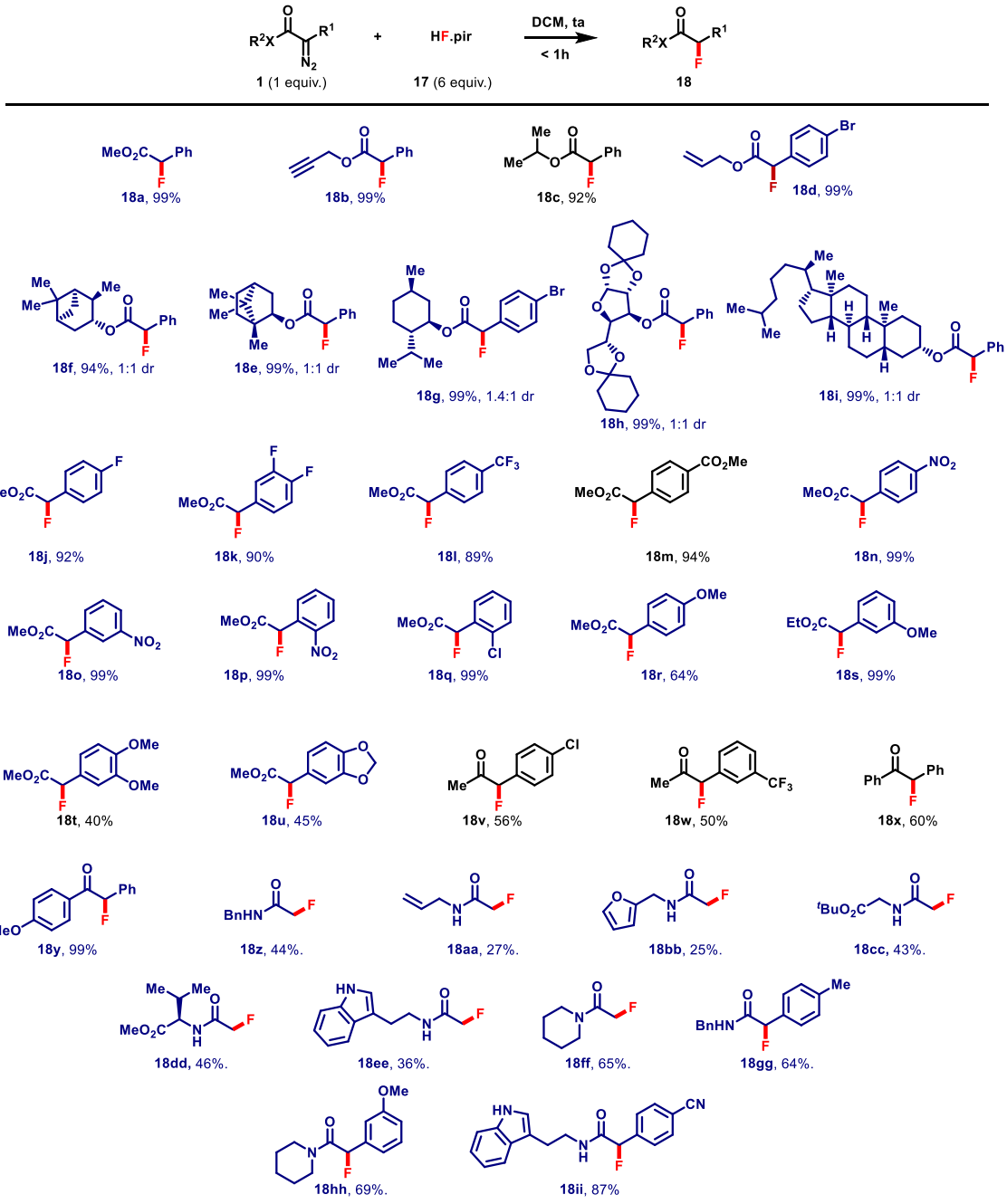
**Tabela 5.** Estudos de otimização para obtenção do composto fluorado **18a** a partir de **1a** e **17**.




| Entrada | x | y | Vaso reacional | Tempo (h) | 18a (%)[a] |
|---|---|---|---|---|---|
| 1 | HF·pir | 3 | vial de vidro | 5 | 15 |
| 2 | HF·pir | 3 | plástico | 5 | 85 |
| 3 | HF·pir | 3 | plástico | 1 | 80 |
| 4 | HF·pir | 6 | vial de vidro | 5 | 30 |
| 5 | HF·pir | 6 | plástico | 5 | 92 |
| 6 | HF·pir | 1 | plástico | 0.5 | 37 |
| 7 | HF·pir | 2 | plástico | 0.5 | 67 |
| 8 | HF·pir | 3 | plástico | 0.5 | 80 |
| 9 | HF·pir | 6 | plástico | 0.5 | 80 |
| 10 | HF·pir | 1 | plástico | 1 | 66 |
| 11 | HF·pir | 2 | plástico | 1 | 80 |
| 12 | HF·pir | 3 | plástico | 1 | 80 |
| 13 | HF·pir | 6 | plástico | 1 | 95 |
| **14[b]** | **HF·pir** | **6** | **plástico** | **1** | **94** |
| 15 | HF·$Et_3N$ | 6 | plástico | 1 | 5 |
| 16 | $KHF_2$ | 6 | plástico | 1 | < 5 |
| 17 | $KHF_2$/TFA (6eq) | 6 | plástico | 1 | < 5 |
| 18 | KF (6 eq) | 6 | plástico | 1 | < 5 |
| 19 | KF/ HFIP (6 eq) | 6 | plástico | 1 | < 5 |

[a]Rendimento determinado por análise de $^1$H RMN do bruto reacional utilizando 1,3,5-trimetoxibenzeno como padrão interno em escala de 0,1 mmol de **1a**. [b]Reação realizada sob irradiação de luz azul.

Com as condições otimizadas em mãos (Tabela 5, Entrada 14) avançamos para a avaliação do escopo. A transformação proposta mostrou-se bem abrangente e diversos diazo compostos foram eficientemente fluorados (Esquema 11).




**Esquema 11.** Escopo reacional para o protocolo térmico de α-fluoração de diazo compostos **1** com HF.pir **17**. Rendimentos isolados em escala de 0,1 mmol de **1**.

Diazo compostos doadores-aceptores **1** contendo diferentes grupos ésteres tipicamente apresentaram excelentes resultados, como evidenciado na preparação dos compostos **18a**-**18i**, onde todos os rendimentos obtidos foram superiores a 90%.

O uso de diazocompostos assimétricos empregando auxiliares quirais na porção do éster também foi avaliado a partir de álcoois enantiomericamente puros. No entanto, os excessos diastereoisoméricos observados foram baixos

para o preparo de **18e**-**18i**, com os valores das razões diastereoisoméricas variando de 1:1 a 1,4:1 (Esquema 11).

Com relação aos diferentes substituintes no anel aromático de arildiazoacetatos, notou-se que grupamentos retiradores de elétrons ou grupamentos fracamente doadores foram geralmente bem tolerados nessa transformação. Por exemplo, ésteres $\alpha$-fluorados **18l** (92%), **18m** (90%), **18n** (89%), **18o** (94%), **18p** (99%), **18q** (99%), **18r** (99%), **18s** (99%) e **18u** (99%) foram sintetizados em excelentes rendimentos e tempos reacionais de 1 h - 3 h, apenas no caso de **18n** (*p*-$NO_2$) o tempo total da reação foi de 24 h.

De modo oposto, grupamentos fortemente doadores apresentaram rendimentos modestos para essa transformação, como evidenciado nas reações de preparo dos compostos **18t** (64%), **18v** (40%) e **18w** (45%).

Além disso, tempos reacionais extremamente curtos são necessários quando utilizados os diazo compostos **1t**, **1v** e **1w** (5 min - 30 min). Essa constatação pode ser explicada devido a maior reatividade de arildiazoacetatos substituídos com grupos doadores de elétrons.

Com o objetivo de verificar a escalabilidade do método, um experimento utilizando 3 mmol de **1a** também foi avaliado para a obtenção de **18a**. Para esse estudo foi obtido um rendimento de 85%, o que representa apenas uma pequena perda em relação ao rendimento observado quando a reação é realizada em escala de 0,1 mmol de **1a** (95%).

Vale destacar que a maioria de arildiazocetonas também puderam ser fluoradas com rendimentos variando de moderados a bons: **18x** (46%), **18y** (50%), **18z** (56%) e **18aa** (60%); enquanto **18bb** foi preparada em excelente rendimento de 99% (Esquema 11). Durante essa avaliação, não foram observados subprodutos oriundos do rearranjo de Wolff, indicando que um carbeno livre não deve ser formado nestas condições reacionais. Notavelmente, diversos métodos reportados na literatura são incompatíveis com arildiazocetonas para obtenção dos correspondentes produtos fluorados,[41e] sendo esse também um dos diferenciais positivos da nossa metodologia.

O uso de diazo compostos contendo apenas grupos aceptores também foi avaliada. Para esse estudo, diazoamidas foram empregadas e novos derivados α-fluorados foram obtidos, agora em rendimentos mais baixos quando

comparados às transformações utilizando arildiazoacetatos: **18z** (44%), **18aa** (27%), **18bb** (25%), **18cc**(43%), **18dd** (46%), **18ee** (36%), **18ff** (65%), **18gg** (64%), **18hh** (69%) e **18ii** (87%).

Rendimentos superiores foram observados para diazo compostos doadores-aceptores quando comparados com diazo compostos somente aceptores. Tentativas de racionalizar os dados obtidos foram realizadas e imaginamos que diazoamidas com grupo somente aceptores sejam estruturas mais reativas, uma vez que para esses compostos observou-se a formação de diferentes produtos ao analisar o bruto reacional por RMN de $^{1}H$. Resultados similares foram constatados ao analisar o espectro RMN de $^{19}F$ do bruto reacional.

Apesar da nossa metodologia envolver o uso de um ácido (HF.pir), grupos funcionais tipicamente sensíveis se mostraram compatíveis, como o grupo acetal presente em **18h**, e o éster de *terc*-butila presente em **18cc**. Além disso, a fluoração de moléculas complexas tais como, **18i, 18ii** e derivados de amino ácidos, **18cc** e **18dd** sugerem o potencial uso desse protocolo para a fluoração em moléculas mais sofisticadas, carregando outros grupos funcionais.

Outro ponto que merece destaque deste novo método é o processo de purificação simples e rápido, em que na maioria dos casos, apenas uma filtração em uma pequena coluna de sílica feita em uma pipeta é suficiente para garantir que o produto desejado tenha um elevado grau de pureza.

Tentativas de obter derivados α-fluorados utilizando diazo compostos aceptores-aceptores resultando em **18nn** e **18oo** sob as condições otimizadas falharam, e os materiais de partida foram recuperados praticamente em sua totalidade (Figura 4). Essa reatividade pode ser explicada devido ao baixo caráter nucleofílico dessas estruturas. Com isso, eles não são prontamente protonados por HF.pir, como no caso dos diazo compostos avaliados anteriormente.

Alquildiazoacetato, alquildiazocetona e vinildiazoacetato também falharam no preparo dos produtos fluorados correspondentes: **18pp**, **18qq** e **18rr**. Nestes casos, somente misturas complexas de produtos foram observadas, tanto no espectro de RMN de $^{1}H$ quanto no espectro de RMN de $^{19}F$ do bruto reacional (Figura 4).

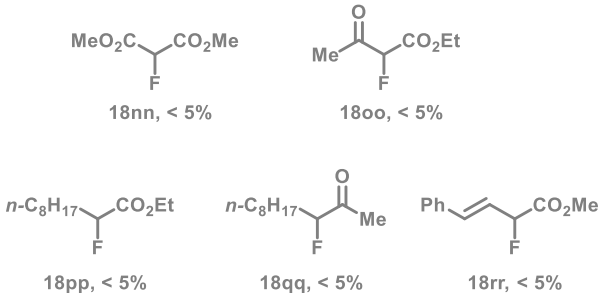
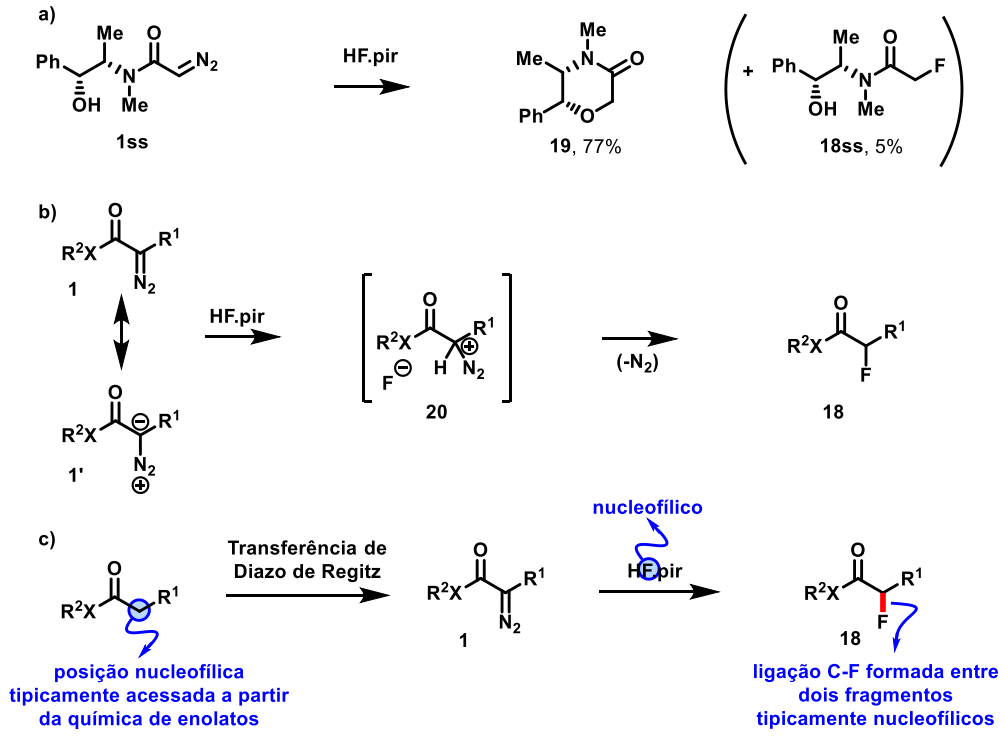



**Figura 4.** Exemplos de compostos α-fluorados que não puderam ser preparados utilizando as condições otimizadas.

Tentativas de fluoração do diazo composto **1ss** sob as condições otimizadas não resultaram no derivado fluorado correspondente. No entanto, o composto cíclico **19** foi obtido com rendimento de 77%, em combinação com apenas 5% de amida α-fluorada **18ss** (Esquema 12a). Nesse caso, a adição nucleofílica intramolecular do grupo hidroxila é presumidamente mais rápida do que a adição nucleofílica intermolecular do íon fluoreto.




**Esquema 12. a)** Distribuição de produtos observadas quando a fluoração do diazo composto **1ss** foi realizada. **b)** Mecanismo proposto para a reação. **c)** Conceito de *Umpolung* para reações de inserção de H–F em diazo compostos.

Com isso, fundamentados na reatividade geral observada anteriormente (Esquema 11 e Figura 4) e com base na formação do composto cíclico **19**, propomos que o mecanismo se inicia com a protonação do diazo composto **1** pelo reagente HF.pir **17**, levando ao intermediário **20**, o qual pode sofrer uma reação de substituição nucleofílica (via $S_N1$ ou $S_N2$) pelo fluoreto, resultando no composto $\alpha$-fluorado desejado **18** (Esquema 12b).

Vale mencionar que a maioria dos diazo compostos **1** empregados nesse trabalho são preparados utilizando como precursores ésteres e cetonas via a estratégia de transferência do grupo diazo (síntese de Regitz). Nesses casos, o protocolo de α-fluoração reportado aqui pode ser entendido como uma estratégia *Umpolung* (inversão de polaridade),[65] em que o éster ou a cetona é $\alpha$-fluorada utilizando uma fonte de flúor nucleofílica (Esquema 12c).

### 3.4 Conclusão Parcial

Inspirados pelo trabalho de George Olah,[60,61] desenvolvemos um método altamente prático, eficiente e versátil para a síntese de compostos carbonilados $\alpha$-fluorados, com rendimentos variando de bons a excelentes, utilizando como precursores diazo compostos e o agente de fluoração nucleofílica HF.pir (Reagente de Olah).

Elementos essenciais responsáveis pela eficiência desse método de fluoração são o emprego do recipiente reacional de plástico e o uso de diazo compostos com elevado caráter nucleofílico. Vale destacar que para vários casos não há a necessidade de posterior purificação do derivado fluorado.

Devido à simplicidade operacional desse método, ou seja, resistente à umidade e ao ar (método “open-flask”), além do uso de reagentes comercialmente disponíveis e/ ou acessíveis, aliados à eficiência sintética (rendimentos de bons a excelentes em curtos tempos reacionais), acreditamos que poderá ser amplamente empregado pela comunidade de químicos orgânicos sintéticos em diversas aplicações potenciais. Adicionalmente, o curto tempo reacional e a conhecida disponibilidade de $H^{18}F$.pir[66] podem fornecer uma nova avenida para radiofluoração no futuro.

Os resultados apresentados nesta seção publicados no jornal *Organic & Biomolecular Chemistry*: Munaretto, L. S.; Gallo, R. D. C.; Leão, L. P. M. O.; Jurberg, I. D.; *Org. Biomol. Chem.* **2022**, *aceito. DOI:* 10.1039/D2OB00400C.

## 4. Conclusão Geral

No capítulo 1 apresentamos e discutimos novos métodos sintéticos mediados pela luz visível na região do azul, empregando arildiazoacetatos **1** como precursores para carbenos livres. Essas estratégias são consideradas simples e eficientes, uma vez que não necessitam de cuidados especiais, tais como a exclusão de ar e umidade, além de apresentar rendimentos sinteticamente úteis em todos os casos.

Dessa forma, podemos preparar intermediários sintéticos importantes (iminas **4** e ilídios de sulfoxônio **6**) e heterociclos polissubstituídos (β-lactamas **9** e furan-3(2H)-onas **10**), assim contribuindo potencialmente para a maior aplicação desses compostos em síntese orgânica. Os resultados apresentados nesse capítulo foram publicados no jornal *Organic Letters*.

No capítulo 2, inspirados pelo trabalho de George Olah,[60,61] apresentamos e discutimos uma nova estratégia sintética para a síntese de compostos carbonilados α-fluorados com rendimentos variando de bons a excelentes, utilizando como precursores diazo compostos e HF.pir (Reagente de Olah). Para essa transformação diazoacetatos, diazoamidas e diazocetonas foram empregados como precursores.

Pontos fortes desta metodologia incluem a simplicidade operacional, o curto tempo reacional (geralmente menor do que 1 hora) e rendimentos variando de bons a excelentes na maioria dos casos. Adicionalmente, uma etapa de purificação simples e rápida é geralmente possível, assim permitindo o fácil acesso a produtos com elevado grau de pureza. Os dados reportados nesse capítulo foram publicados no jornal *Org. Biomol. Chem.*

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# 6. Apêndice

### 6.1.1 Publicação referente ao trabalho: Estratégias Mediadas por Luz Visível para o Preparo de β-Lactamas Trissubstituídas e Furanonas a partir de Arildiazoacetatos e Arildiazocetonas

OL | Organic Letters

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# Visible-Light-Mediated Strategies to Assemble Alkyl 2-Carboxylate-2,3,3-Trisubstituted β-Lactams and 5-Alkoxy-2,2,4-Trisubstituted Furan-3(2H)-ones Using Aryldiazoacetates and Aryldiazoketones

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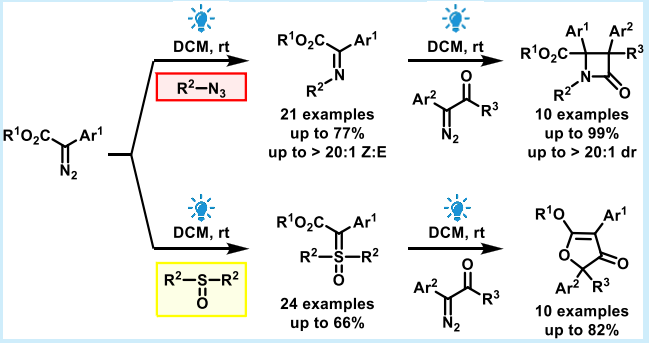
**ABSTRACT:** Two new visible-light-mediated strategies are described starting from aryldiazoacetates. The first approach describes their reaction with azides to afford the corresponding imines, and then reaction with aryldiazoketones produces alkyl 2-carboxylate-2,3,3-trisubstituted β-lactams. The second approach describes the reaction with sulfoxides to afford the corresponding sulfoxonium ylides, followed by reaction with aryldiazoketones to produce 5-alkoxy-2,2,4-trisubstituted furan-3(2H)-ones. These protocols take advantage of the photolysis of aryldiazoacetates and the photochemically promoted Wolff rearrangement of aryldiazoketones.






Carbene transfer reactions employing aryldiazoacetates represent a general thermal strategy promoted in the presence of metal catalysts (Rh, Cu, Pd, Au, Ag, among others) that has experienced tremendous development in recent years. This strategy has allowed the preparation of a wide variety of products with general high stereoselectivity and efficiency.[1]

More recently, the use of visible light has been disclosed as an exceptionally mild reaction promoter, thus affording a complementary approach to access the desired target molecules.[2] Although the formation of free carbenes is certainly occurring under visible-light irradiation,[3] alternative photoinduced proton transfer events followed by substitution reactions have been claimed as a dominant pathway for some insertion reactions involving more acidic O−H bonds.[4]

In addition to the different selectivities and efficiencies that might sometimes be expected,[3a] comparisons between such photochemical transformations and metal-catalyzed, thermally promoted reactions can possibly offer additional mechanistic views of the role of the metal.[5] In more practical terms, blue-light-promoted protocols are straightforward and robust, as they generally tolerate the presence of air and moisture (because of the major involvement of singlet carbenes, rather than triplet carbenes).[6] They can typically be run at lower temperatures (e.g., at room temperature) and can often be more cost-effective, as they do not require the use of precious metals. In particular, these photochemical strategies can be currently considered especially attractive when synthesizing achiral molecules or racemic mixtures.

In this context,[3a,7] we became interested in the blue-light-mediated photolysis of aryldiazoacetates **1** to afford carbenes **2**, which could sequentially react either with azides **3** or sulfoxides **5** to afford imines **4**[8] or sulfoxonium ylides **6**,[9,10] respectively. Sequential reaction with diazoketones **7**, also under blue light irradiation, could then potentially convert imines **4** to β-lactams **9**[11] (some members of this class of compounds have been previously accessed via metal catalysis)[8f,12] and sulfoxonium ylides **6** to furan-3(2H)-ones **10**[13] by taking advantage of a ketene intermediate **8** generated from a photochemically promoted Wolff rearrangement[14] (Scheme 1).

To reduce our initial idea into practice, we started our investigations by optimizing the reaction between aryldiazoacetate **1a** and azide **3a** under blue light irradiation, aiming at the preparation of imine **4a** (see the Supporting Information for details).

Having established the optimal conditions for this reaction, we evaluated the scope of imines **4** accessible by this method. This protocol allowed access to the desired compounds in a range of 26−77% yields, all examples with high *Z* selectivity

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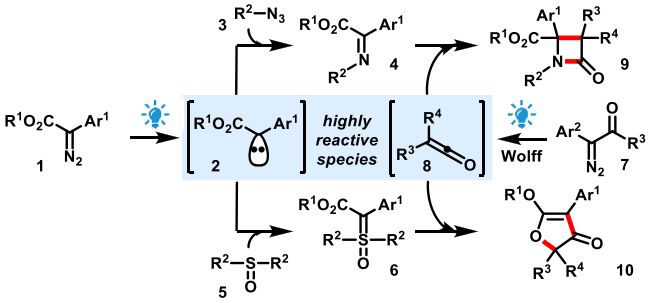
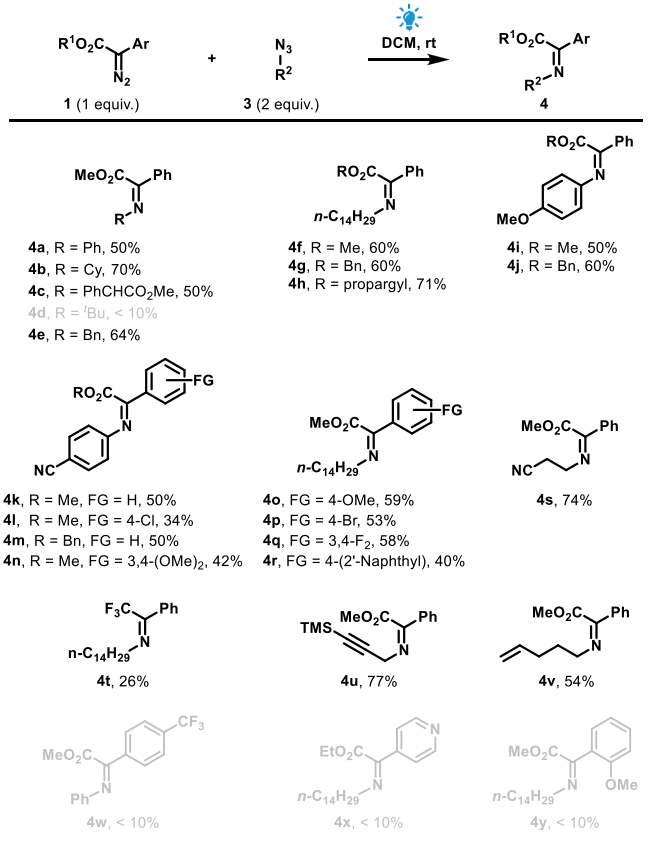
**Scheme 1. Proposed Synthetic Plan**




(Scheme 2, also see the Supporting Information for more details).

**Scheme 2. Evaluation of the Scope for the Photochemical Conversion of Aryldiazoacetates 1 and Azides 3 to the Corresponding Imines 4**[a]



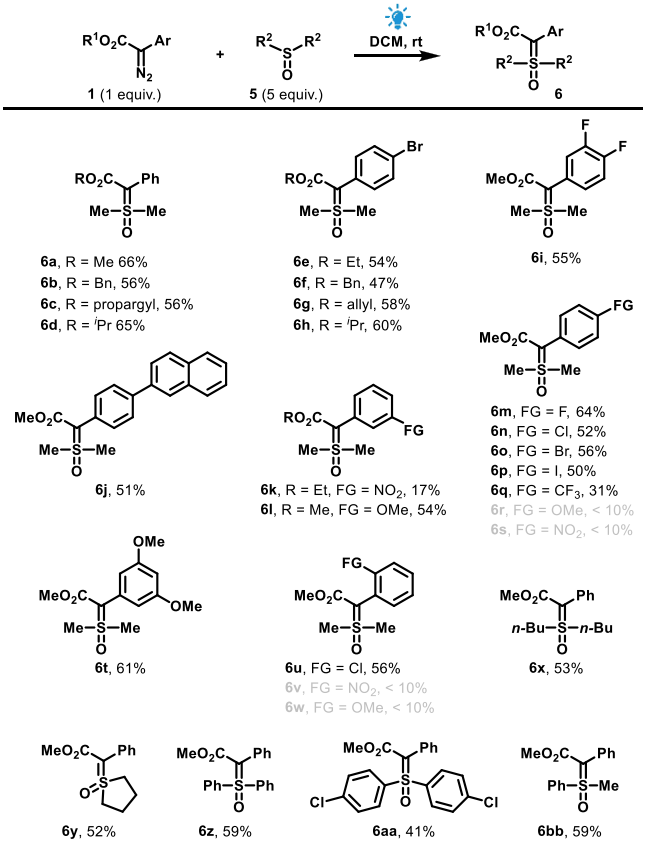

[a]Reaction conditions: **1** (0.2 mmol), **3** (0.4 mmol), DCM (2 mL).

Although the optimal yield found for imine **4a** was moderate, 50%, and other imines carrying aromatic groups on the nitrogen atom produced somehow similar yields (**4i** (50%), **4j** (60%), **4k** (50%), and **4m** (50%)), the synthesis of imines carrying nonaromatic groups on the azide partner **3** could afford slightly improved results for the corresponding imines: **4b** (70%), **4c** (50%), **4e** (64%), **4f** (60%), **4g** (60%), **4h** (71%), **4s** (74%), **4u** (77%), and **4v** (54%). The use of more-hindered $^{t}BuN_3$ did not allow a productive reaction when attempting the synthesis of **4d** (< 10%). Structural variations on the aromatic ring of the aryldiazoacetate partner **1** produced yields in a range of modest to good: **4l** (34%), **4n** (42%), **4o** (59%), **4p** (53%), **4q** (58%), and **4r** (40%). Imine **4t** carrying a $CF_3$ group could be produced only in a poor 26% yield. Stronger limitations of this method were identified when attempting the synthesis of imines **4w**, **4x**, and **4y**, which produced only trace amounts of the desired products (Scheme 2).

Considering the preparation of sulfoxonium ylides **6**, we performed our optimization studies by examining the reaction of aryldiazoacetate **1a** with dimethyl sulfoxide **5a**, aiming at the preparation of sulfoxonium ylide **6a** (see the Supporting Information for details).

With the optimal reaction conditions in hand, we moved forward to evaluate the scope of sulfoxonium ylides **6** that could be accessed. This method proved to be broad, producing the desired compounds in a range of moderate to good yields, 40−64% (Scheme 3).

**Scheme 3. Evaluation of the Scope for the Photochemical Conversion of Aryldiazoacetates 1 and Sulfoxides 5 to the Corresponding Sulfoxonium Ylides 6**[a]




[a]Reaction conditions: **1** (0.2 mmol), **5** (1 mmol), DCM (2 mL).

Different ester groups were tolerated, on the aryldiazoacetates **1** as evidenced by the preparation of **6a** (66%), **6b** (56%), **6c** (56%), **6d** (65%), **6e** (54%), **6f** (47%), **6g** (58%), and **6h** (60%). A variety of functional groups were also tolerated on the aromatic ring of aryldiazoacetates: **6i** (55%), **6j** (51%), **6l** (54%), **6m** (64%), **6n** (52%), **6o** (56%), **6p** (50%), **6t** (61%), and **6u** (56%). However, electron-withdrawing groups m-$NO_2$ in **6k** (17%), p-$CF_3$ in **6q** (31%), p-$NO_2$ in **6s** (< 10%), and o-$NO_2$ in **6v** (< 10%) or donor groups p-OMe in **6r** (< 10%) or o-OMe in **6w** (< 10%) produced poor yields or did not afford any productive reactions. Notably, thermal reactions of



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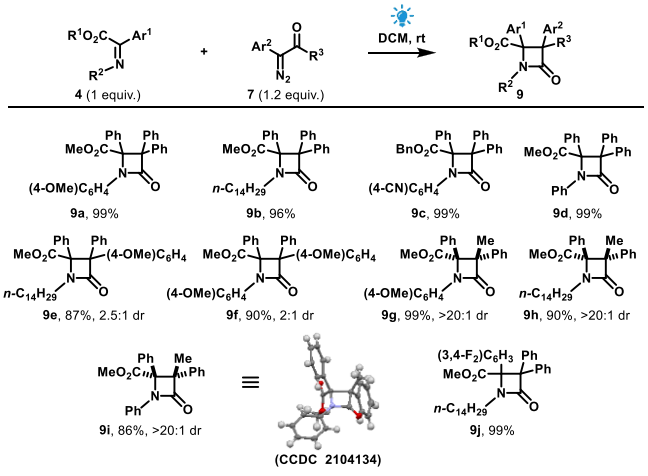
aryldiazoesters **1** containing OMe groups on the aromatic ring have been already reported to preferentially react with DMSO, leading to ketones,[15] and in agreement with other previous strategies,[9a,c,16] the tentative preparation of related sulfoxonium ylides has been met here only with failure. On the other hand, the use of other sulfoxides **5** are well-tolerated and can provide the corresponding sulfoxonium ylides **6** in generally synthetically useful yields **6x** (53%), **6y** (52%), **6z** (59%), **6aa** (41%), and **6bb** (59%) (Scheme 3).

Imines **4** and sulfoxonium ylides **6** can be employed in a variety of chemical transformations affording densely functionalized molecules (see the Supporting Information for examples of such applications, **11a**−**11d**, **12a**, and **12b**). On the basis of our interest in the chemistry of heterocycles,[17] we decided to explore the possibility of accessing *β*-lactams **9** starting from imines **4** and furan-3(2H)-ones **10** starting from sulfoxonium ylides **6**, also using visible-light-mediated transformations.

Aiming at the preparation of *β*-lactams **9**, we carried out optimization studies using different relative amounts of imine **4i** and aryldiazoketone **7a** toward the preparation of **9a** (see the Supporting Information for details). With the optimal reaction conditions in hand, it was possible to prepare a variety of *β*-lactams **9** in high yields (87−99%) starting from a reaction mixture containing an imine **4** and a freshly prepared aryldiazoketone **7** in DCM, at room temperature, under blue light irradiation (Scheme 4). When two aryl substituents are

**Scheme 4. Blue-Light-Mediated Preparation of *β*-Lactams Employing Imines 4 and Aryldiazoketones 7[a]**




[a]Reaction conditions: **1** (0.1 mmol), **7** (0.12 mmol), DCM (1 mL).

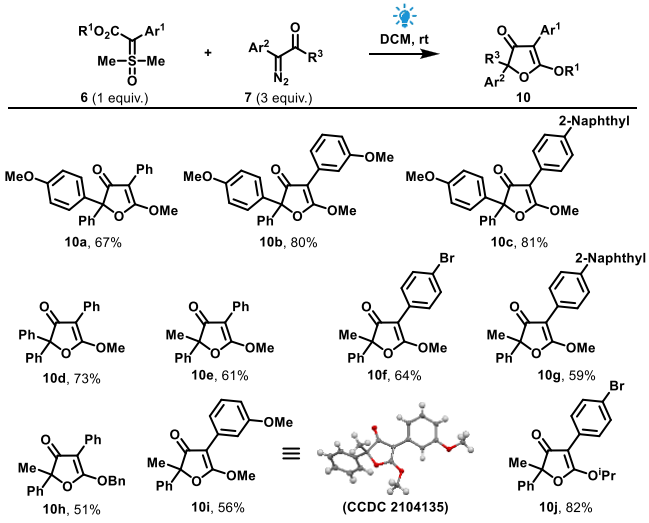
present at the aryldiazoketone **7**, poor diastereoselectivities are observed (as evidenced by **9e** and **9f**, showing 2.5:1 dr and 2:1 dr, respectively, Scheme 4). However, when a methyl and a phenyl group are present in the aryldiazoketone **7**, only one diastereoisomer of the *β*-lactam **9** is observed (**9g**, **9h**, and **9i**, all >20:1 dr, Scheme 4).

In addition, the one-pot preparation of *β*-lactams **9a** and **9b** was also attempted starting from the corresponding aryldiazoacetates and azides, and then followed by sequential addition of the diazoketone partner. This strategy afforded somehow competitive overall yields of 45 and 40%, respectively (also see the Supporting Information for details).

Finally, we investigated the reaction of sulfoxonium ylide **6a** with aryldiazoketone **7b** under blue light irradiation, which leads to furan-3(2H)-one **10a**. Studies using varying stoichiometries of reagents revealed the use of 1 equiv. of sulfoxonium ylide **6a** and 3 equiv. of aryldiazoketone **7b** as the optimal condition (see the Supporting Information for details).

Having established a promising protocol for this transformation, we advanced to evaluate the use of different sulfoxonium ylides **6** and aryldiazoketones **7**, thus producing the corresponding furan-3(2H)-ones **10** in a range of moderate to good yields, 51−82% (Scheme 5).

**Scheme 5. Blue-Light-Mediated Preparation of Furan-3(2H)-ones 10 Employing Sulfoxonium Ylides 6 and Aryldiazoketones 7[a]**




[a]Reaction conditions: **1** (0.1 mmol), 7 (0.3 mmol), DCM (1 mL).

When attempting the one-pot preparation of furan-3(2H)-ones **10d** and **10e** starting from the corresponding aryldiazoacetates and sulfoxides, followed by the addition of the diazoketone partners, we obtained only poor overall yields of 13 and 10%, respectively. It is conceivable that the excess of the sulfoxide reagent employed in the first step lowers the efficiency of the second step.

Concerning the formation of *β*-lactams **9**, our mechanistic proposal involves a blue light promoted Wolff rearrangement allowing the conversion of aryldiazoketone **7** to a ketene intermediate **8**.[14] This highly reactive intermediate is attacked by the imine **4**, thus leading to the formation of a putative zwitterionic intermediate **13**, which then evolves via an intramolecular cyclization event to produce the observed *β*-lactam **9** (Scheme 6a).

Considering the formation of furan-3(2H)-ones **10**, our mechanistic proposal also starts with a photochemical Wolff rearrangement allowing the conversion of aryldiazoketone **7** to the corresponding ketene **8**.[14] Nucleophilic attack of the sulfoxonium ylide **6** then leads presumably to intermediate **14**, which can possibly evolve via a ring-closure event to afford a highly reactive cyclopropanone intermediate **15**,[18] followed by rapid ring-opening to afford a zwitterionic intermediate **16**, or intermediate **14** can possibly eliminate DMSO to directly form the zwitterionic intermediate **16**. This species can now undergo a Nazarov-like pericyclic process to afford the observed furan-3(2H)-one **10** (Scheme 6b).

In summary, we have developed two new synthetic strategies promoted by blue light irradiation, both starting from an aryldiazoacetate precursor **1**. These strategies are simple and



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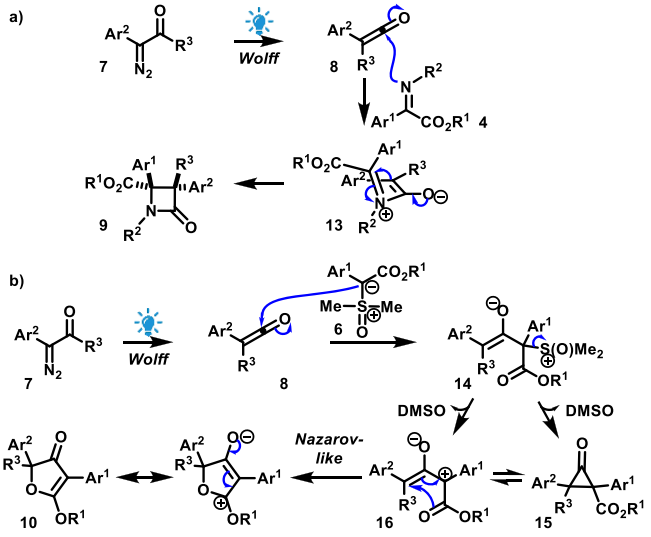
**Scheme 6. Mechanistic Proposals for the Synthesis of (a) β-Lactams 9 and (b) Furan-3(2H)-ones 10**




straightforward and allow the preparation of valuable intermediates (imines **4** and sulfoxonium ylides **6**) and heterocycles (β-lactams **9** and furan-3(2H)-ones **10**), thus possibly contributing to their broader use in organic synthesis and applications thereof.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03662.

Experimental procedures, analytical data, copies of NMR spectra of all new compounds and crystallographic data (PDF)

### Accession Codes

CCDC 2104134−2104135 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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(3) See for instance: (a) Jurberg, I. D.; Davies, H. M. L. Blue Light-Promoted Photolysis of Aryldiazoacetates. *Chem. Sci.* **2018**, *9*, 5112−5118. (b) Hommelsheim, R.; Guo, Y.; Yang, Z.; Empel, C.; Koenigs, R. M. Blue-Light-Induced Carbene-Transfer Reactions of Diazoalkanes. *Angew. Chem., Int. Ed.* **2019**, *58*, 1203−1207.

(4) (a) Jana, S.; Yang, Z.; Li, F.; Empel, C.; Ho, J.; Koenigs, R. M. Photoinduced Proton-Transfer Reactions for Mild O-H Functionalization of Unreactive Alcohols. *Angew. Chem., Int. Ed.* **2020**, *59*, 5562−5566. (b) Empel, C.; Jana, S.; Pei, C.; Nguyen, T. V.; Koenigs, R. M. Photochemical O-H Functionalization of Aryldiazoacetates with Phenols via Proton Transfer. *Org. Lett.* **2020**, *22*, 7225−7229.

(5) See for instance: (a) Jana, S.; Guo, Y.; Koenigs, R. M. Recent Perspectives on Rearrangement Reactions of Ylides via Carbene Transfer Reactions. *Chem. - Eur. J.* **2021**, *27*, 1270−1281. (b) Qi, Z.; Wang, S. Chemodivergent Synthesis of Oxazoles and Oxime Ethers Initiated by Selective C-N/ C-O Formation of Oximes and Diazo Esters. *Org. Lett.* **2021**, *23*, 8549.

(6) Jana, S.; Pei, C.; Empel, C.; Koenigs, R. M. Photochemical Carbene Transfer Reactions of Aryl/ Aryl Diazoalkanes - Experiment and Theory. *Angew. Chem., Int. Ed.* **2021**, *60*, 13271−13279.

(7) For examples of previous contributions of our group to this field, see: (a) Stivanin, M. L.; Fernandes, A. A. G.; Silva, A. F.; Okada, C. Y.; Jurberg, I. D. Blue Light-Promoted N-H Insertion of Carbazoles, Pyrazoles and 1,2,3-Triazoles into Aryldiazoacetates. *Adv. Synth. Catal.* **2020**, *362*, 1106−1111. (b) Silva, A. F.; Afonso, M. A. S.;

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(8) For previous syntheses of imines, mostly relying on thermal Rh-catalyzed protocols, see: (a) Hashimoto, T.; Yamamoto, K.; Maruoka, K. Development of a Practical Synthetic Method for N-*tert*-Butoxycarbonyl a-Ketimino Esters. *Chem. Lett.* **2011**, *40*, 326−327. (b) Huang, H.; Wang, Y.; Chen, Z.; Hu, W. H. A Novel Synthesis of Aryl a-Imino Esters from Aryl Diazoacetate. *Synlett* **2005**, *16*, 2498−2500. (c) Huang, H.; Wang, Y.; Chen, Z.; Hu, W. Rhodium-Catalyzed, Three-Component Reaction of Diazo Compounds with Amines and Azodicarboxylates. *Adv. Synth. Catal.* **2005**, *347*, 531−534. (d) Chen, L.; Zhang, L.; Shao, Y.; Xu, G.; Zhang, X.; Tang, S.; Sun, J. Rhodium-Catalyzed C = N Bond Formation through a Rebound Hydrolysis Mechanism and Application in b-Lactam Synthesis. *Org. Lett.* **2019**, *21*, 4124−4127. (e) Qian, Y.; Jing, C.; Zhai, C.; Hu, W.-h. A Novel Method for Synthesizing N-Alkoxycarbonyl Aryl a-Imino Esters and Their Applications in Enantioselective Transformations. *Adv. Synth. Catal.* **2012**, *354*, 301−307. (f) Mandler, M. D.; Truong, P. M.; Zavalij, P. Y.; Doyle, M. P. Catalytic Conversion of Diazocarbonyl Compounds to Imines: Applications to the Synthesis of Tetrahydropyrimidines and β-Lactams. *Org. Lett.* **2014**, *16*, 740−743.

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(11) For a selection of articles on the chemistry of β-lactams, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. β-Lactams: Versatile Building Blocks for the Stereoselective Synthesis of Non-β-Lactam Products. *Chem. Rev.* **2007**, *107*, 4437−4492. (b) Pitts, C. R.; Lectka, T. Chemical Synthesis of β-Lactams: Asymmetric Catalysis and Other Recent Advances. *Chem. Rev.* **2014**, *114*, 7930−7953. (c) Hosseyni, S.; Jarrahpour, A. Recent Advances in β-Lactam Synthesis. *Org. Biomol. Chem.* **2018**, *16*, 6840−6852. (d) Lima, L. M.; da Silva, B. N. M.; Barbosa, G.; Barreiro, E. J. β-Lactam Antibiotics: An Overview from a Medicinal Chemistry Perspective. *Eur. J. Med. Chem.* **2020**, *208*, 112829.

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*Org. Lett.* 2021, 23, 9292−9296

### 6.1.2 Material Suplementar para Estratégias Mediadas por Luz Visível para o Preparo de β-Lactamas Trissubstituídas e Furanonas a partir de Arildiazoacetatos e Arildiazocetonas

**Preparation of Aryldiazoacetates 1**

The following aryldiazoacetates have been prepared as previously described in the literature, being numbered following their order of appearance in the manuscript: *methyl 2-diazo-2-phenylacetate* (**1a**),[1] *benzyl 2-diazo-2-phenylacetate* (**1b**),[1] *prop-2-yn-1-yl 2-diazo-2-phenylacetate* (**1c**),[1] *2-(4-chlorophenyl)-2-diazoacetate* (**1d**),[2] *methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate* (**1e**),[2] *methyl 2-diazo-2-(4-methoxyphenyl)acetate* (**1f**),[2] *methyl 2-(4-bromophenyl)-2-diazoacetate* (**1g**),[2] *methyl 2-diazo-2-(3,4-difluorophenyl)acetate* (**1h**),[2] *(1-diazo-2,2,2-trifluoroethyl)benzene* (**1j**),[3] *2-diazo-2-(4-(trifluoromethyl)phenyl)acetate* (**1k**),[2] *ethyl 2-diazo-2-(pyridin-4-yl)acetate* (**1l**),[4] *methyl 2-(2-methoxyphenyl)-2*-diazoacetate (**1m**),[5] *isopropyl 2-diazo-2-phenylacetate* (**1n**),[1] *ethyl 2-(4-bromophenyl)-2-diazoacetate* (**1o**),[1] *benzyl 2-(4-bromophenyl)-2-diazoacetate* (**1p**),[1] *allyl 2-(4-bromophenyl)-2-diazoacetate* (**1q**),[2] *isopropyl 2-(4-bromophenyl)-2-diazoacetate* (**1r**),[2] *ethyl 2-diazo-2-(3-nitrophenyl)acetate* (**1s**),[6] *methyl 2-diazo-2-(3-methoxyphenyl)acetate* (**1t**),[2] *methyl 2-diazo-2-(4-fluorophenyl)acetate* (**1u**),[7] *methyl 2-diazo-2-(4-iodophenyl)acetate* (**1v**),[2] *methyl 2-diazo-2-(4-nitrophenyl)acetate* (**1w**),[8] *methyl 2-diazo-2-(3,5-dimethoxyphenyl)acetate* (**1x**),[7] *methyl 2-(2-chlorophenyl)-2-diazoacetate* (**1y**).[2]

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[1] Thurow, S.; Fernandes, A. A. G.; Quevedo-Acosta, Y.; de Oliveira, M. F.; de Oliveira, M. G.; Jurberg, I. D. *Org. Lett.* **2019**, *21*, 6909-6913.
[2] Stivanin, M. L.; Fernandes, A. A. G.; da Silva, A. F.; Okada Jr., C. Y.; Jurberg, I. D. *Adv. Synth. Catal.* **2020**, 362, 1106-1111.
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[5] Tsoi, Y.-T.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *13*, 5370-5373.
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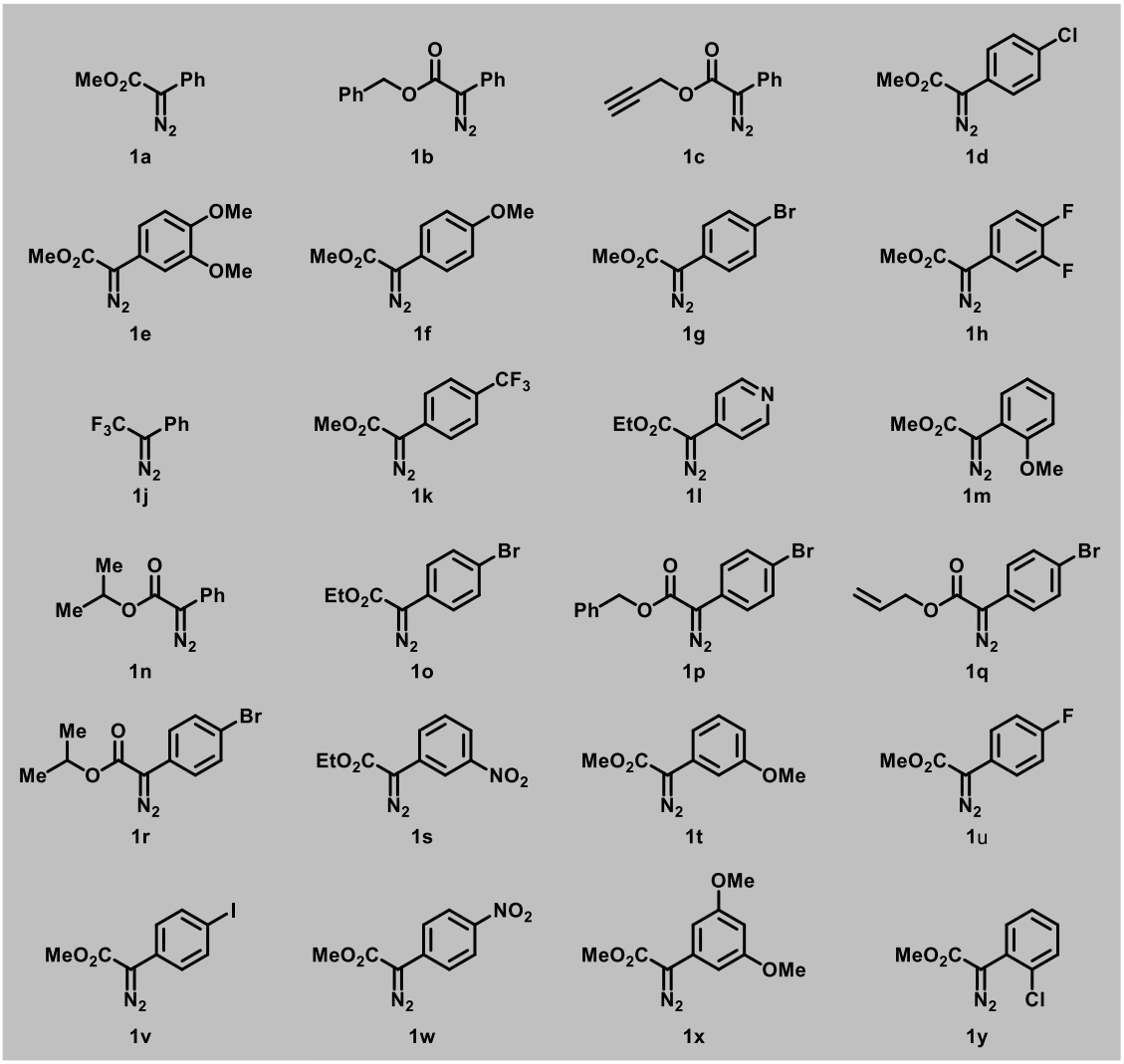
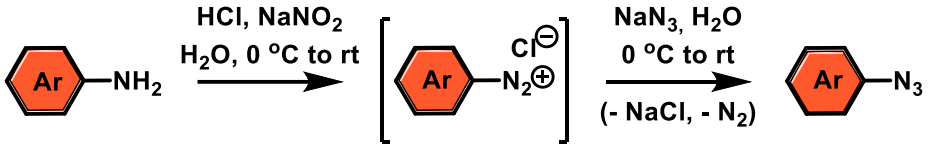
[7] Da Silva, A. F.; Afonso, M. A. S.; Cormanich, R. A.; Jurberg, I. D. *Chem. Eur. J.* **2020**, *26*, 5648.
[8] Chen, P.-A.; Setthakarn, K.; May, J. A. *ACS Catal.* **2017**, *7*, 6155-6161.

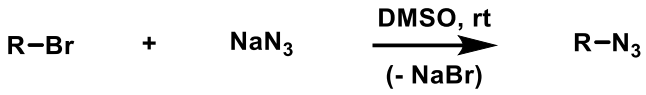



**Preparation of Azides**

**Caution!** Organic azides and diazonium salts are potentially explosive substances. We did not have any explosion when manipulating the azides mentioned in this work, but they should be handled with care and preferentially stored in the freezer.

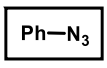


**General Procedure A**:[9] At room temperature, under nitrogen, a round bottom flask is charged with aniline (3 mmol, 1 equiv.) and 3M aqueous solution of HCl (0.1 M, 10 mL), and the mixture is cooled to 0 °C. Then, a solution of $NaNO_2$ (4.5 mmol, 310 mg, 1.5 equiv.) in distilled water (7.5 mL) is slowly added. The reaction mixture is stirred at room temperature for 30 min. Then, the mixture is cooled to 0 °C and a solution of $NaN_3$ (12 mmol, 780 mg, 4 equiv.) in distilled water (15 mL) is added dropwise. The resulting mixture is stirred at room temperature for 2h. Then, the mixture is extracted with DCM (3x). The combined organic phases are washed with brine, dried ($MgSO_4$), filtered, and carefully concentrated under reduced pressure (the azide produced can be volatile). The crude aryl azide obtained is used as such in the next step without further purification.




**General Procedure B:**[10] At room temperature, under air, a round bottom flask is charged with $NaN_3$ (3 or 4 equiv.) and DMSO (10 mL, 0.2 M). The resulting suspension is stirred at this temperature until the complete dissolution of the $NaN_3$ (approximately 40 min.). Then, the alkyl bromide (2 mmol, 1 equiv.) is added. The reaction mixture is stirred at room temperature for 24 - 48h. Then, $H_2O$ and $Et_2O$ are added, and the organic layer is separated. The aqueous layer is extracted with $Et_2O$ (3x). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and carefully concentrated under reduced pressure (the azide product can be volatile). The obtained crude alkyl azide is used as such in the next step without further purification.

**Molecule 3a:** *Azidobenzene*[10]



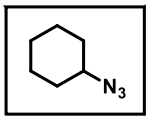

**General Procedure A** is employed with aniline (273 mL, 3 mmol, 1 equiv.), 3M aqueous solution of HCl (10 mL), $NaNO_2$ (4.5 mmol, 310

[9] Muraca, A. C. A.; Raminelli, C. *ACS Omega* **2020**, *5*, 2440-2457.
[10] Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413-414.

mg, 1.5 equiv.) in $H_2O$ (7.5 mL) and $NaN_3$ (12 mmol, 780 mg, 4 equiv.). The title compound is isolated as a brownish oil (321 mg, 90%).

**$^1$H NMR (250 MHz, $CDCl_3$) *δ*:** 7.39 – 7.33 (m, 2H), 7.17 – 7.11 (m, 1H), 7.06 – 7.02 (m, 2H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 140.0, 129.7, 124.9, 119.0.

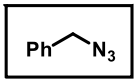
**Molecule 3b:** *Azidocyclohexane*[11]




**General Procedure B** is employed with bromocyclohexane (246 mL, 2 mmol, 1 equiv.), $NaN_3$ (520 mg, 8 mmol, 4 equiv.) and DMSO (10 mL, 0.2 M). Reaction time: 48h. The title compound is isolated as a transparent oil (138 mg, 55%). This compound was remarked to be volatile.

**$^1$H NMR (250 MHz, $CDCl_3$) *δ*:** 3.37 – 3.28 (m, 1H), 1.92 – 1.88 (m, 2H), 1.77 – 1.75 (m, 2H), 1.58 – 1.56 (m, 1H), 1.40 – 1.25 (m, 5H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 59.9, 31.6, 25.2, 24.2.

**Molecule 3c:** *Benzyl azide*[12]

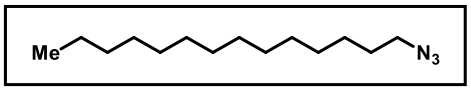



**General Procedure B** is employed with benzyl bromide (238 mL, 2 mmol, 1 equiv.), $NaN_3$ (520 mg, 8 mmol, 4 equiv.) and DMSO (10 mL, 0.2 M). Reaction time: 36h. The title compound is isolated as a transparent oil (216 mg, 81%).

**$^1$H NMR (250 MHz, $CDCl_3$) *δ*:** 7.41 – 7.32 (m, 5H), 4.35 (s, 2H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 135.3, 128.8, 128.3, 128.2, 54.8.

[11] Spectroscopic data is in good agreement with the literature. See: Asano, K.; Matsubara, S. *Org. Lett.* **2010**, *12*, 4988-4991.
[12] Spectroscopic data is in good agreement with the literature. See: Sebest, F.; Casarrubios, L.; Rzepa, H. S.; White, A. J. P.; Díez-González, S. *Green Chem.* **2018**, *20*, 4023-4035.

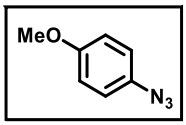
**Molecule 3d:** *1-Azidotetradecane*[13]




**General Procedure B** is employed with 1-bromotetradecane (595 mL, 2 mmol, 1 equiv.), $NaN_3$ (390 mg, 6 mmol, 3 equiv.) and DMSO (10 mL, 0.2 M). Reaction time: 36h. The title compound is isolated as a transparent oil (469 mg, 98%).

**$^1$H NMR (250 MHz, $CDCl_3$) $\delta$:** 3.25 (t, *J* = 7.0 Hz, 2H) 1.61 – 1.57 (m, 2H), 1.36 – 1.26 (m, 22H), 0.88 (t, *J* = 7.0 Hz, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$:** 51.5, 31.9, 29.7, 29.6 (x3), 29.5 (x2), 29.3, 29.1, 28.8, 26.7, 22.7, 14.1.

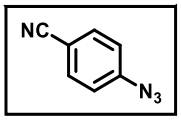
**Molecule 3e:** *1-azido-4-methoxybenzene*[14]




**General Procedure A** is employed with 4-methoxyaniline (369 mg, 3 mmol, 1 equiv.), 3M aqueous solution of HCl (10 mL), $NaNO_2$ (4.5 mmol, 310 mg, 1.5 equiv.) in $H_2O$ (7.5 mL), and $NaN_3$ (12 mmol, 780 mg, 4 equiv.). The title compound is isolated as a brown oil (467 mg, 82%).

**$^1$H NMR (250 MHz, $CDCl_3$) $\delta$:** 6.96 (d, *J* = 9.0 Hz, 2H), 6.88 (t, *J* = 9.0 Hz, 2H), 3.80 (s, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$:** 157.0, 132.3, 120.0, 115.1, 55.6.

**Molecule 3f:** *4-azidobenzonitrile*[15]




**General Procedure A** is employed with 4-aminobenzonitrile (355 mg, 3 mmol, 1 equiv.), 3M aqueous solution of HCl (10 mL), $NaNO_2$ (4.5 mmol, 310 mg, 1.5 equiv.) in $H_2O$ (7.5 mL), and $NaN_3$ (12 mmol, 780 mg, 4 equiv). The title compound is isolated as a yellow solid (302 mg, 70%).

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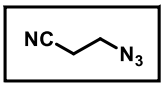
[13] Spectroscopic data is in good agreement with the literature. See: Pajk, S.; Garvas, M.; Štrancar, J.; Pečar, S. *Org. Biomol. Chem*. **2011**, *9*, 4150-4159.
[14] Spectroscopic data is in good agreement with the literature. See: Barral, K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett.* **2007**, *9*, 1809-1811.

**$^{1}$H NMR (500 MHz, CDCl3) *δ*:** 7.63 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 8.4 Hz, 2H).
**$^{13}$C NMR (125 MHz, CDCl3) *δ*:** 144.8, 133.7, 119.6, 118.3, 108.2.

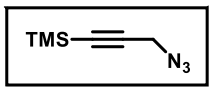
**Molecule 3g:** *3-azidopropanenitrile*[15]




**General Procedure B** is employed with 3-bromopropanenitrile (166 mL, 2 mmol, 1 equiv.), $NaN_3$ (520 mg, 8 mmol, 4 equiv.) and DMSO (10 mL, 0.2 M). Reaction time: 48h. The title compound is isolated as a yellow oil (148 mg, 77%). This compound was remarked to be volatile.

**$^{1}$H NMR (250 MHz, $CDCl_3$) *δ*:** 3.58 (t, *J* = 6.8 Hz, 2H), 2.60 (t, *J* = 6.8 Hz, 2H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 116.9, 46.5, 18.3.
**IR (ATR, cm$^{-1}$):** 2114, 1289, 909.
**HRMS (ESI+):** Calcd. for $[C_3H_4N_4 + H]^+$: 97.0509, found: 97.0512.

**Molecule 3h:** *(3-azidoprop-1-yn-1-yl)trimethylsilane*

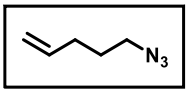



**General Procedure B** is employed with (3-bromoprop-1-yn-1-yl)trimethylsilane (326 mL, 2 mmol, 1 equiv.), $NaN_3$ (520 mg, 8 mmol, 4 equiv.) and DMSO (10 mL, 0.2 M). Reaction performed at 40 ºC for 48h. The title compound is isolated as a transparent oil (184 mg, 60%). This compound was remarked to be volatile and was isolated with a minor amount of DMSO.

**$^{1}$H NMR (250 MHz, $CDCl_3$) *δ*:** 3.90 (s, 2H), 0.19 (s, 9H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 96.9, 93.0, 40.5, -0.3.
**IR (ATR, cm$^{-1}$):** 2961, 2124, 1251, 1026.
**HRMS (ESI+):** Calcd. for $[C_6H_{11}N_3Si + H]^+$: 154.0795, found: 154.0794.

[15] Spectroscopic data is in good agreement with the literature, $^{1}$H NMR. See: Carboni, B.; Vaultier, M.; Carrié, *Tetrahedron,* **1987**, *43*, 1799-1810.

**Molecule 3i:** *5-azidopent-1-ene*[16]



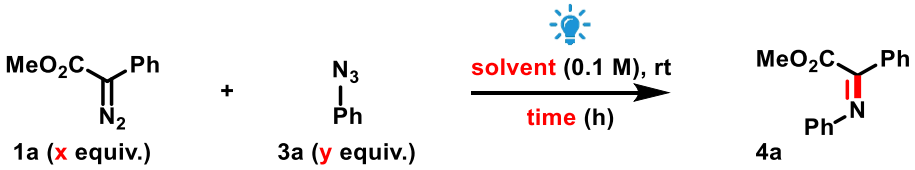
**General Procedure B** is employed with 5-bromopent-1-ene (237 mL, 2 mmol, 1 equiv.), $NaN_3$ (390 mg, 6 mmol, 3 equiv.) and DMSO (10 mL, 0.2 M). Reaction time: 24h. The title compound is isolated as a transparent oil (100 mg, 45%). This compound was remarked to be volatile and was isolated with a minor amount of DMSO.

**$^1$H NMR (250 MHz, $CDCl_3$) *δ*:** 5.83 – 5.70 (m, 1H), 5.09 – 4.99 (m, 2H), 3.28 (t, *J* = 7.0 Hz, 2H), 2.18 – 2.10 (m, 2H), 1.75 – 1.63 (m, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 137.1, 115.6, 50.7, 30.7, 28.0.

## Synthesis of Imines 4

Optimization studies aiming at the photochemical reaction of aryldiazoacetate **1a** with azide **3a** to produce imine **4a**.

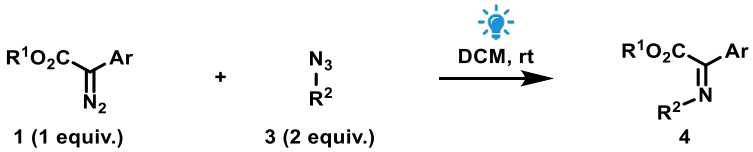



| entry | x | y | solvent (0.1 M) | time (h) | yield **4a** (%)[a] |
|---|---|---|---|---|---|
| 1 | 1 | 1 | DCM | 24 | 37 |
| **2** | **1** | **2** | **DCM** | **24** | **50** |
| 3 | 1 | 3 | DCM | 24 | 45 |
| 4 | 1 | 5 | DCM | 24 | 40 |
| 5 | 2 | 1 | DCM | 24 | 35 |
| 6 | 3 | 1 | DCM | 24 | 25 |
| 7 | 1 | 2 | DCM | 48 | 50 |
| 8 | 1 | 2 | 1,2-DCE | 24 | 40 |
| 9 | 1 | 2 | toluene | 24 | 24 |
| 10 | 1 | 2 | MeCN | 24 | 25 |

[16] Spectroscopic data is in good agreement with the literature. See: Mathia, F.; Szolcsányi, P. *Org. Biomol. Chem.* **2012**, *10*, 2830-2839.

| | | | | | |
|---|---|---|---|---|---|
| 11[b] | 1 | 2 | DCM | 24 | < 30 |
| 12[c] | 1 | 2 | DCM | 24 | < 40 |
| 13[d] | 1 | 2 | DCM | 24 | < 5 |

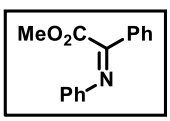
[a]Estimated yield by $^1$H NMR of the reaction crude using 1,3,5-trimethoxybenzene as internal standard. [b]Using 1, 3 or 5 equiv. of $MgSO_4$. [c]Using various amounts of 4Å MS. [d]Reaction performed in the dark.




**General Procedure C:** Under air, at room temperature, a 4 mL-vial is charged with aryldiazoacetate **1** (1 equiv.), an aryl or alkyl azide **3** (2 equiv.) and DCM (0.1 M). The reaction mixture is stirred at room temperature under blue light irradiation for 24h (using two blue LED lamps, 15 W each, displaced at approximate distances of 5 cm each from the reaction vessel). Then, the reaction mixture is concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding imine **4** in the stated yield.

- *General observation:* The imine products **4** derived from alkyl azides have shown to be more sensitive to hydrolysis and had their NMR analyses made in $CDCl_3$ pre-treated with $K_2CO_3$.

**Molecule 4a:** *methyl (Z)-2-phenyl-2-(phenylimino)acetate*[17]




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), azidobenzene **3a** (48 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a yellow oil: 24 mg, 50%, 16:1 Z:E.

[17] Spectroscopic data is in good agreement with the literature. See: Tindall, D. J.; Werlé, C.; Goddard, R.; Philipps, P.; Farès, C.; Fürstner, A. *J. Am. Chem. Soc.* **2018**, *140*, 1884-1893.

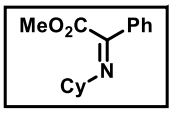
**$^{1}$H NMR (250 MHz, $CDCl_3$) *δ*:** 7.90 – 7.86 (m, 2H), 7.53 – 7.43 (m, 3H), 7.37 – 7.31 (m, 2H), 7.19 – 7.11 (m, 1H), 6.99 – 6.95 (m, 2H), 3.64 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 165.4, 159.9, 150.0, 133.8, 131.8, 128.9, 128.7, 128.0, 125.0, 119.5, 51.9.

**IR (ATR, $cm^{-1}$):** 2915, 1735, 1623, 1484, 1227, 1010.

**HRMS (ESI+):** Calcd. for $[C_{15}H_{13}NO_2 + H]^+$: 240.1019, found: 240.1019.

**Molecule 4b:** *methyl (Z)-2-(cyclohexylimino)-2-phenylacetate*




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), azidocyclohexane **3b** (50 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 34 mg, 70%, >20:1 Z:E.

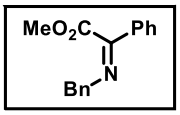
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.71 – 7.67 (m, 2H), 7.43 – 7.36 (m, 3H), 3.92 (s, 3H), 3.29 – 3.20 (m, 1H), 1.81 – 1.56 (m, 8H), 1.36 – 1.29 (m, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 166.4, 157.5, 134.6, 130.7, 128.5, 127.1, 64.2, 51.7, 33.7, 25.6, 24.3.

**IR (ATR, $cm^{-1}$):** 2929, 1734, 1634, 1449, 1207, 1007.

**HRMS (ESI+):** Calcd. for $[C_{15}H_{19}NO_2 + H]^+$: 246.1489, found: 246.1490.

**Molecule 4c:** *methyl (Z)-2-(benzylimino)-2-phenylacetate*




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), benzylazide **3c** (53 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as transparent oil: 32 mg, 64%, 17:1 Z:E. (This compound was remarked to hydrolyze quite easily and was isolated in the presence of *ca.* 15% of the corresponding ketone.)

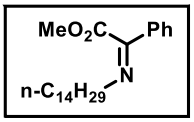
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.81 – 7.77 (m, 2H), 7.48 – 7.29 (m, 8H), 4.76 (s, 2H), 3.98 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.9, 160.4, 138.7, 134.1, 131.1, 128.5, 128.4, 127.9, 127.3, 127.0, 58.6, 51.9.

**IR (ATR, $cm^{-1}$):** 2911, 1733, 1634, 1450, 1208, 1041.

**HRMS (ESI+):** Calcd. for $[C_{16}H_{15}NO_2 + H]^+$: 254.1176, found: 254.1179.

**Molecule 4d:** *methyl (Z)-2-phenyl-2-(tetradecylimino)acetate*




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), 1-azidotetradecane **3d** (96 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 43 mg, 60%, >20:1 Z:E.

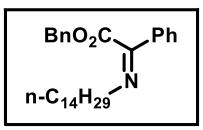
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.71 – 7.67 (m, 2H), 7.44 – 7.39 (m, 3H), 3.92 (s, 3H), 3.51 (t, *J* = 7.5 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.37 - 1.26 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (3C cannot be unambiguously assigned) δ:** 166.1, 159.6, 134.4, 130.8, 128.5, 127.1, 55.4, 51.7, 31.9, 30.7, 29.7, 29.6 (x2), 29.4, 29.3, 27.4, 22.7, 14.1

**IR (ATR, $cm^{-1}$):** 2923, 2853, 1737, 1635, 1448, 1208, 1039.

**HRMS (ESI+):** Calcd. for $[C_{23}H_{37}NO_2 + H]^+$: 360.2897, found: 360.2902.

**Molecule 4e:** *benzyl (Z)-2-phenyl-2-(tetradecylimino)acetate*




**General Procedure C** is employed with benzyl 2-diazo-2-phenylacetate **1b** (25 mg, 0.1 mmol, 1 equiv.), 1-azidotetradecane **3d** (48 mg, 0.2 mmol, 2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 26 mg, 60%, >20:1 Z:E.

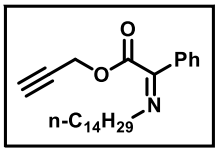
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.68 – 7.64 (m, 2H), 7.45 – 7.32 (m, 8H), 5.38 (s, 2H), 3.47 (t, *J* = 7.5 Hz, 2H), 1.70 – 1.65 (m, 2H), 1.35 – 1.26 (m, 22H), 0.89 (t, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (2C cannot be unambiguously assigned) δ:** 165.6, 159.3, 134.9, 134.4, 130.7, 128.8, 128.7 (x2), 128.5, 127.1, 66.9, 55.2, 31.9, 30.7, 29.7, 29.6 (x3), 29.4, 29.3, 27.4, 22.7, 14.1.

**IR (ATR, cm$^{-1}$):** 2922, 2851, 1734, 1691, 1455, 1194, 1002.

**HRMS (ESI+):** Calcd. for $[C_{29}H_{41}NO_2 + H]^+$: 436.3210, found: 436.3216.

**Molecule 4f:** *prop-2-yn-1-yl (Z)-2-phenyl-2-(tetradecylimino)acetate*




**General Procedure C** is employed with propargyl 2-diazo-2-phenylacetate **1c** (20 mg, 0.1 mmol, 1 equiv.), 1-azidotetradecane **3d** (48 mg, 0.2 mmol, 2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 27 mg, 71%, 10:1 Z:E.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.73 – 7.69 (m, 2H), 7.45 – 7.40 (m, 3H), 4.93 (d, *J* = 2.5 Hz, 2H), 3.55 (t, *J* = 7.5 Hz, 2H), 2.56 (t, *J* = 2.5 Hz, 1H), 1.76 – 1.71 (m, 2H), 1.38 – 1.23 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

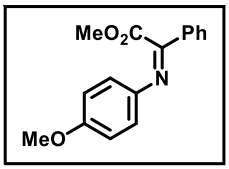
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (3C cannot be unambiguously assigned) δ:** 164.8, 158.5, 134.2, 130.9, 128.6, 127.1, 76.7, 75.8, 55.2, 52.2, 31.9, 30.7, 29.7, 29.6 (x2), 29.4, 29.3, 27.4, 22.7, 14.1.

**IR (ATR, cm$^{-1}$):** 2923, 2853, 1742, 1635, 1448, 1189, 1038.

**HRMS (ESI+):** Calcd. for $[C_{25}H_{37}NO_2 + H]^+$: 384.2897, found: 384.2902.

**Molecule 4g:** *methyl (Z)-2-((4-methoxyphenyl)imino)-2-phenylacetate*[18]

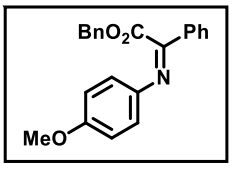
[18] Spectroscopic data is in good agreement with the literature. See: Mandler, M. D.; Truong, P. M.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2014**, *16*, 740-743.




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), 1-azido-4-methoxybenzene **3e** (60 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a yellow oil: 27 mg, 50%, 10:1 Z:E.

**$^1$H NMR (500 MHz, $CDCl_3$) δ:** 7.86 – 7.84 (m, 2H), 7.52 – 7.44 (m, 3H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 3.69 (s, 3H).
**$^{13}$C NMR (125 MHz, $CDCl_3$) δ:** 166.1, 159.1, 157.3, 143.1, 134.1, 131.6, 128.7, 127.8, 121.2, 114.2, 55.4, 52.0.
**IR (ATR, cm$^{-1}$):** 2955, 1732, 1614, 1504, 1245, 1033.
**HRMS (ESI+):** Calcd. for $[C_{16}H_{15}NO_3 + H]^+$: 270.1125, found: 270.1129.

**Molecule 4h:** *benzyl (Z)-2-((4-methoxyphenyl)imino)-2-phenylacetate*[19]



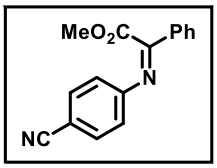

**General Procedure C** is employed with benzyl 2-diazo-2-phenylacetate **1b** (51 mg, 0.2 mmol, 1 equiv.), 1-azido-4-methoxybenzene **3e** (60 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a yellow oil: 41 mg, 60%, >20:1 Z:E.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.86 – 7.82 (m, 2H), 7.49 – 7.43 (m, 3H), 7.30 – 7.26 (m, 3H), 7.11 – 7.08 (m, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 5.14 (s, 2H), 3.79 (s, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (2C cannot be unambiguously assigned) δ:** 165.3, 159.0, 157.3, 143.1, 134.4, 134.1, 131.5, 128.7, 128.5, 127.8, 121.2, 114.1, 67.1, 55.4.
**IR (ATR, cm$^{-1}$):** 2915, 1731, 1503, 1449, 1245, 1032.

[19] Spectroscopic data is in good agreement with the literature. See: Kang, Q.; Zhao, Z.-A.; You, S.-L. *Adv. Synth. Catal.* **2007**, *349*, 1657-1660.

**HRMS (ESI+):** Calcd. for $[C_{22}H_{19}NO_3 + H]^+$: 346.1438, found: 346.1438.

**Molecule 4i:** *methyl (Z)-2-((4-cyanophenyl)imino)-2-phenylacetate*




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (18 mg, 0.1 mmol, 1 equiv.), 4-azidobenzonitrile **3f** (29 mg, 0.2 mmol, 2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a yellow oil: 13 mg, 50%, 15:1 Z:E.

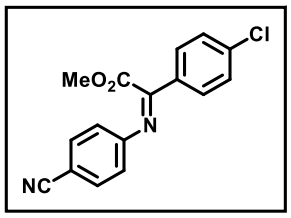
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.88 – 7.84 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.57 – 7.45 (m, 3H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 164.3, 161.0, 154.0, 133.0, 132.9, 132.6, 128.9, 128.3, 120.1, 118.9, 108.2, 52.1.

**IR (ATR, cm$^{-1}$):** 2226, 1735, 1629, 1598, 1232, 1165, 1033.

**HRMS (ESI+):** Calcd. for $[C_{16}H_{12}N_2O_2 + H]^+$: 265.0972, found: 265.0976.

**Molecule 4j:** *methyl (Z)-2-(4-chlorophenyl)-2-((4-cyanophenyl)imino)acetate*




**General Procedure C** is employed with methyl 2-diazo-2-(4-chlorophenyl)acetate **1d** (42 mg, 0.2 mmol, 1 equiv.), 4-azidobenzonitrile **3f** (58 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a yellow oil: 20 mg, 34%, >20:1 Z:E.

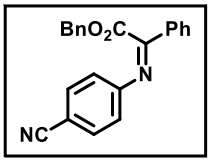
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.81 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 164.0, 159.8, 153.7, 138.9, 133.1, 131.4, 129.6, 129.2, 120.0, 118.8, 108.4, 52.3.

**IR (ATR, cm$^{-1}$):** 2226, 1736, 1600, 1591, 1233, 1165, 1021.

**HRMS (ESI+):** Calcd. for $[C_{16}H_{11}ClN_2O_2 + H]^+$: 299.0582, found: 299.0587.

**Molecule 4k:** *benzyl (Z)-2-((4-cyanophenyl)imino)-2-phenylacetate*




**General Procedure C** is employed with benzyl 2-diazo-2-(4-chlorophenyl)acetate **1b** (51 mg, 0.2 mmol, 1 equiv.), 4-azidobenzonitrile **3f** (58 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a yellow oil: 34 mg, 50%, >20:1 Z:E.

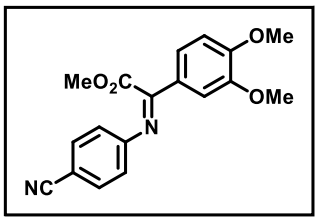
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.88 – 7.84 (m, 2H), 7.56 – 7.26 (m, 8H), 7.08 – 7.05 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.12 (s, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 163.6, 160.7, 153.5, 133.9, 132.9, 132.8, 132.5, 129.1, 128.9, 128.8, 128.6, 128.3, 120.1, 118.9, 108.1, 67.5.

**IR (ATR, cm$^{-1}$):** 2923, 1777, 1736, 1559, 1448, 1190, 1031.

**HRMS (ESI+):** Calcd. for $[C_{22}H_{16}N_2O_2 + H]^+$: 341.1285, found: 341.1287.

**Molecule 4l:** *methyl (Z)-2-((4-cyanophenyl)imino)-2-phenylacetate*




**General Procedure C** is employed with methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate **1e** (47 mg, 0.2 mmol, 1 equiv.), 4-azidobenzonitrile **3f** (58 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 98:2 Hex:AcOEt - 95:5 Hex:AcOEt) affords the title compound as a yellow solid: 27 mg, 42%, >20:1 Z:E.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.64 – 7.59 (m, 3H), 7.26 – 7.24 (m, 1H), 7.01 – 6.89 (m, 3H), 3.96 (s, 6H), 3.63 (s, 3H).

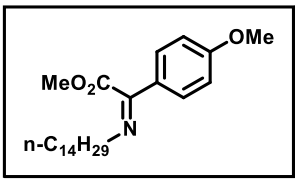
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 164.5, 160.3, 154.3, 153.1, 149.5, 133.0, 125.8, 123.4, 120.4, 119.0, 110.3, 109.3, 107.9, 56.1, 56.0, 52.1.

**IR (ATR, cm$^{-1}$):** 2226, 1735, 1593, 1514, 1258, 1147, 1023.

**M.P.:** 104 - 106 ºC.

**HRMS (ESI+):** Calcd. for $[C_{18}H_{16}N_2O_4 + H]^+$: 325.1183, found: 325.1183.

**Molecule 4m:** *methyl (Z)-2-(4-methoxyphenyl)-2-(tetradecylimino)acetate*




**General Procedure C** is employed with methyl 2-diazo-2-(4-methoxyphenyl)acetate **1f** (21 mg, 0.1 mmol, 1 equiv.), 1-azidotetradecane **3d** (48 mg, 0.2 mmol, 2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a white solid: 23 mg, 59%, >20:1 Z:E.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.63 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.46 (t, *J* = 7.5 Hz, 2H), 1.76 - 1.61 (m, 2H), 1.33 - 1.25 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

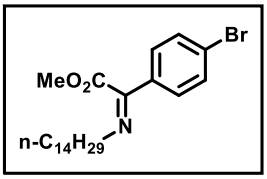
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (3C cannot be unambiguously assigned) δ:** 166.4, 161.7, 159.0, 128.7, 127.2, 113.9, 55.4, 55.2, 51.6, 31.9, 30.8, 29.7, 29.6 (x2), 29.4, 29.3, 27.4, 22.7, 14.1.

**M.P.:** 45 - 47 ºC.

**IR (ATR, cm$^{-1}$):** 2923, 2852, 1736, 1605, 1512, 1255, 1053.

**HRMS (ESI+):** Calcd. for $[C_{24}H_{39}NO_3 + H]^+$: 390.3003, found: 390.3007.

**Molecule 4n:** *methyl (Z)-2-(4-bromophenyl)-2-(tetradecylimino)acetate*




**General Procedure C** is employed with methyl 2-diazo-2-(4-bromo)phenylacetate **1g** (26 mg, 0.1 mmol, 1 equiv.), 1-azidotetradecane **3d** (48 mg, 0.2 mmol, 2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ – 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as transparent oil: 23 mg, 53%, >20:1 Z:E.

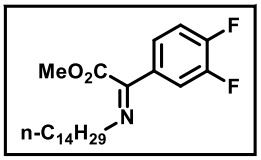
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.58 – 7.50 (m, 4H), 3.92 (s, 3H), 3.49 (t, *J* = 7.5 Hz, 2H), 1.77 – 1.60 (m, 2H), 1.33 - 1.25 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (4C cannot be unambiguously assigned) δ:** 165.7, 158.5, 133.3, 131.7, 128.6, 125.4, 55.4, 51.9, 31.9, 30.6, 29.7, 29.5, 29.4, 29.3, 27.3, 22.7, 14.1.

**IR (ATR, cm$^{-1}$):** 2923, 2853, 1740, 1456, 1259, 1167.

**HRMS (ESI+):** Calcd. for $[C_{23}H_{36}BrNO_2 + H]^+$: 438.2002, found: 438.2009.

**Molecule 4o:** *methyl (Z)-2-(3,4-difluorophenyl)-2-(tetradecylimino)acetate*




**General Procedure C** is employed with methyl 2-diazo-2-(3,4-difluorophenyl)acetate **1h** (42 mg, 0.2 mmol, 1 equiv.), 1-azidotetradecane **3d** (48 mg, 0.2 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ – 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 46 mg, 58%, >20:1 Z:E.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.66 – 7.57 (m, 1H), 7.39 – 7.33 (m, 1H), 7.22 – 7.12 (m, 1H), 3.92 (s, 3H), 3.49 (t, *J* = 7.5 Hz, 2H), 1.76 – 1.63 (m, 2H), 1.33 - 1.25 (m, 22H), 0.87 (t, *J* = 6.5 Hz, 3H).

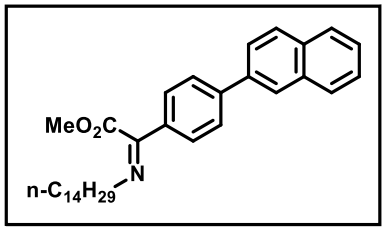
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (3C cannot be unambiguosly assigned) δ:** 165.4, 157.3 (dd, *J* = 1.9 Hz, *J* = 2.5 Hz), 152.1 (dd, *J* = 251.9 Hz, *J* = 13.1 Hz), 150.5 (dd, *J* = 247.5 Hz, *J* = 13.1 Hz), 131.6 (dd, *J* = 5.6 Hz, *J* = 3.8 Hz), 123.7 (dd, *J* = 6.3 Hz, *J* = 3.1 Hz), 117.3 (d, *J* = 17.5 Hz), 116.1 (d, *J* = 18.8 Hz), 55.3, 51.9, 31.9, 30.6, 29.7, 29.6, 29.5, 29.4, 29.3, 27.3, 22.7, 14.1.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** -133.9 (d, *J* = 21.2 Hz), -136.6 (d, *J* = 21.2 Hz).

**IR (ATR, cm$^{-1}$):** 2924, 2854, 1738, 1516, 1430, 1273, 1157.

**HRMS (ESI+):** Calcd. for $[C_{23}H_{35}F_2NO_2 + H]^+$: 396.2709, found: 396.2714.

**Molecule 4p:** *methyl (Z)-2-(4-(naphthalen-2-yl)phenyl)-2-(tetradecylimino)acetate*




**General Procedure C** is employed with methyl 2-diazo-2-(4-(naphthalen-2-yl)phenyl)acetate **1i** (61 mg, 0.2 mmol, 1 equiv.), 1-azidotetradecane **3d** (96 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ – 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 39 mg, 40%, >20:1 Z:E.

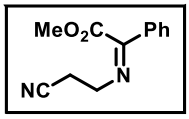
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 8.07 – 8.06 (m, 1H), 7.95 – 7.83 (m, 4H), 7.80 – 7.73 (m, 4H), 7.53 – 7.50 (m, 2H), 3.96 (s, 3H), 3.55 (t, *J* = 7.5 Hz, 2H), 1.82 – 1.71 (m, 2H), 1.40 - 1.24 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (4C cannot be unambiguosuly assigned) δ:** 166.1, 159.3, 143.5, 137.5, 133.6, 133.4, 132.8, 128.6, 128.3, 127.6, 127.5, 126.4, 126.2, 126.0, 125.3, 55.4, 51.8, 31.9, 30.8, 29.7, 29.6 (x2), 29.4, 29.3, 27.4, 22.7, 14.1.

**IR (ATR, $cm^{-1}$):** 2923, 2852, 1735, 1604, 1466, 1214, 1040.

**HRMS (ESI+):** Calcd. for $[C_{33}H_{43}NO_2 + H]^+$: 486.3367, found: 486.3367.

**Molecule 4q:** *methyl (Z)-2-((2-cyanoethyl)imino)-2-phenylacetate*




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), 3-azidopropanenitrile **3g** (87 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ – 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 32 mg, 74%, >20:1 Z:E.

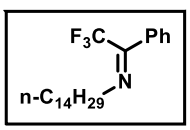
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.73 – 7.70 (m, 2H), 7.52 – 7.38 (m, 3H), 3.96 (s, 3H), 3.77 (t, *J* = 7.0 Hz, 2H), 2.79 (t, *J* = 7.0 Hz, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.0, 162.1, 133.5, 131.6, 128.7, 127.5, 118.2, 52.2, 49.8, 19.4.

**IR (ATR, $cm^{-1}$):** 2971, 1734, 1636, 1449, 1217, 1035.

**HRMS (ESI+):** Calcd. for $[C_{12}H_{12}N_2O_2 + H]^+$: 217.0972, found: 217.0975.

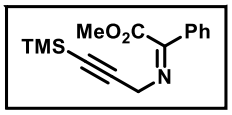
**Molecule 4r:** *2,2,2-trifluoro-1-phenyl-N-tetradecylethan-1-imine*




**General Procedure C** is employed with (1-diazo-2,2,2-trifluoroethyl)benzene **1j** (37 mg, 0.2 mmol, 1 equiv.), 1-azidotetradecane **3d** (96 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ – 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 19 mg, 26%, >20:1 Z:E.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.48 – 7.44 (m, 3H), 7.24 – 7.21 (m, 2H), 3.40 – 3.34 (m, 2H), 1.67 – 1.60 (m, 2H), 1.25 – 1.26 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (2C cannot be unambiguously assigned) δ:** 158.0 (q, *J* = 33.1 Hz), 130.6, 129.9, 128.7, 127.7, 119.7 (q, *J* = 277.5 Hz), 53.3, 31.9, 30.2, 29.7, 29.6 (x2), 29.5, 29.3, 29.2, 27.2, 22.7, 14.1.
**$^{19}$F (235 MHz, $CDCl_3$) δ:** -71.1.
**IR (ATR, $cm^{-1}$):** 2924, 2853, 1466, 1333, 1195, 1132.
**HRMS (ESI+):** Calcd. for $[C_{22}H_{34}F_3N + H]^+$: 370.2716, found: 370.2721.

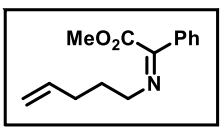
**Molecule 4s:** *methyl (Z)-2-phenyl-2-((3-(trimethylsilyl)prop-2-yn-1-yl)imino)acetate*




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), (3-azidoprop-1-yn-1-yl)trimethylsilane **3h** (61 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ – 98:1:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 42 mg, 77%, >20:1 Z:E.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.75 – 7.71 (m, 2H), 7.47 – 7.37 (m, 3H), 4.38 (s, 2H), 3.94 (s, 3H), 0.18 (s, 9H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 164.9, 162.2, 134.0, 131.4, 128.5, 127.5, 101.6, 88.3, 52.1, 44.3, -0.1.
**IR (ATR, $cm^{-1}$):** 1739, 1435, 1250, 1211.
**HRMS (ESI+):** Calcd. for $[C_{15}H_{19}NO_2Si + H]^+$: 274.1258, found: 274.1261.

**Molecule 4t:** *methyl (Z)-2-(pent-4-en-1-ylimino)-2-phenylacetate*




**General Procedure C** is employed with methyl 2-diazo-2-phenylacetate **1a** (35 mg, 0.2 mmol, 1 equiv.), 5-azidopent-1-ene **3i** (45 mg, 0.4 mmol, 2 equiv.) and DCM (2 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ – 98:1:1

Hex:AcOEt:$Et_3N$) affords the title compound as a transparent oil: 25 mg, 54%, >20:1 Z:E.

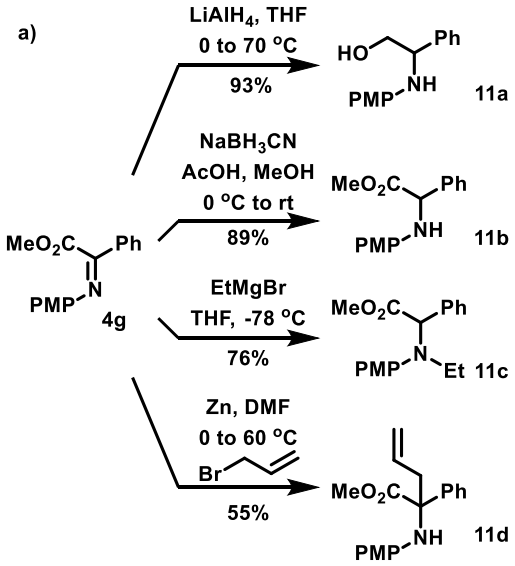
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.71 – 7.67 (m, 2H), 7.45 – 7.36 (m, 3H), 5.91 – 5.77 (m, 1H), 5.09 – 4.96 (m, 2H), 3.92 (s, 3H), 3.53 (t, *J* = 7.5 Hz, 2H), 2.22 – 2.13 (m, 2H), 1.90 – 1.78 (m, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 166.1, 159.9, 138.2, 134.3, 130.9, 128.5, 127.1, 114.8, 54.5, 51.8, 31.4, 29.8.

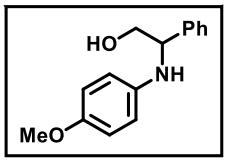
**IR (ATR, cm$^{-1}$):** 2917, 2849, 1738, 1638, 1462, 1210, 1038.

**HRMS (ESI+):** Calcd. for $[C_{14}H_{17}NO_2 + H]^+$: 232.1332, found: 232.1337.

## Synthetic Applications of Imines 4




**Molecule 11a:** *2-((4-methoxyphenyl)amino)-2-phenylethan-1-ol*[20]



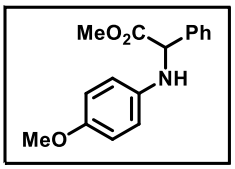

Under nitrogen, at room temperature, a round bottom flask is charged with methyl *(Z)*-2-((4-methoxyphenyl)imino)-2-phenylacetate **4g** (150 mg, 0.55 mmol, 1 equiv.), dry THF (5 mL, 0.1 M). The reaction temperature is cooled to 0 °C. Then, $LiAlH_4$ (84 mg, 2.2 mmol, 4 equiv.) is slowly added. The reaction mixture is heated to 70 °C overnight. Then, the reaction temperature is cooled to 0 °C. and the reaction is

[20] Spectroscopic data is in good agreement with the literature. See: Yamada, K.-I.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805-3808.

carefully quenched with water. The reaction mixture is diluted in AcOEt, washed with water (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography ($SiO_2$, gradient: DCM – 98:2 DCM:MeOH) affords the title compound as a brown oil: 124 mg, 93%.

**$^1$H NMR (250 MHz, $CDCl_3$) (2H cannot be unambiguously assigned) *δ*:** 7.38 – 7.26 (m, 5H), 6.71 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 4.43 (dd, *J* = 7.4 Hz, *J* = 4.2 Hz, 1H), 3.91 (dd, *J* = 11.0 Hz, *J* = 4.2 Hz, 1H), 3.71 (dd, *J* = 11.0 Hz, *J* = 7.4 Hz, 1H), 3.70 (s, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 152.3, 141.3, 140.3, 128.7, 127.5, 126.7, 115.3, 114.7, 67.3, 60.8, 55.7.
**IR (ATR, cm$^{-1}$):** 3394, 2834, 1511, 1238, 1034.
**HRMS (ESI+):** Calcd. for $[C_{15}H_{17}NO_2 + H]^+$: 244.1332, found: 244.1335.

**Molecule 11b:** *methyl 2-((4-methoxyphenyl)amino)-2-phenylacetate*[21,22]




Under nitrogen, at room temperature, a round bottom flask is charged with methyl *(Z)*-2-((4-methoxyphenyl)imino)-2-phenylacetate **4g** (135 mg, 0.5 mmol, 1 equiv.), MeOH (5 mL, 0.1 M), and AcOH (200 µL, 3.5 mmol, 7 equiv.). The reaction temperature is cooled to 0 $^o$C. Then, $NaBH_3CN$ (47 mg, 0.75 mmol, 1.5 equiv.) is carefully added. The reaction mixture is allowed to warm up to room temperature and is stirred at this temperature for 1h. Finally, the mixture is concentrated under reduced pressure. The residue is diluted in AcOEt, washed with saturated aqueous solution of $NaHCO_3$ (2x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography ($SiO_2$, gradient: Hex – 95:5 Hex:AcOEt – 9:1 Hex:AcOEt – 8:2 Hex:AcOEt) affords the title compound as a yellow oil: 121 mg, 89%.

[21] For procedure, see: U.S. Pat. Appl. Publ., 20160237042, 18 Aug 2016.
[22] Spectroscopic data is in good agreement with the literature. See: Rueping, M.; Azap, C.; Sugiono, E.; Theissmann, T. *Synlett* **2005**, *15*, 2367-2369.

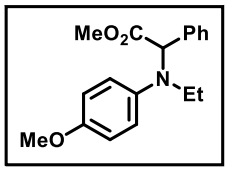
**$^{1}$H NMR (250 MHz, $CDCl_3$) *δ*:** 7.51 – 7.47 (m, 2H), 7.39 – 7.30 (m, 3H), 6.73 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 5.02 (s, 1H), 4.66 (br s, 1H), 3.72 (s, 3H), 3.71 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 172.5, 152.5, 140.2, 137.8, 128.8, 128.3, 127.2, 114.8, 114.7, 61.6, 55.7, 52.7.

**IR (ATR, $cm^{-1}$):** 1734, 1513, 1237, 1031.

**HRMS (ESI+):** Calcd. for $[C_{16}H_{17}NO_3 + H]^+$: 272.1281, found: 272.1284.

**Molecule 11c:** *methyl 2-(ethyl(4-methoxyphenyl)amino)-2-phenylacetate*[23]




Under nitrogen, at room temperature, a round bottom flask is charged with methyl *(Z)*-2-((4-methoxyphenyl)imino)-2-phenylacetate **4g** (54 mg, 0.2 mmol, 1 equiv.), dry THF (1 mL, 0.1 M). The reaction temperature is cooled to -78 $^{o}$C. Then, EtMgBr (300 µL, 0.3 mmol, 1.5 equiv., 1 M in THF) is slowly added. The mixture is warmed to room temperature and allowed to stir at this temperature for 1h. Then, the reaction temperature is cooled to 0 $^{o}$C and the reaction is quenched with a saturated aqueous solution of $NH_4Cl$, extracted with EtOAc (3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography ($SiO_2$, gradient: Hex - 98:2 Hex:AcOEt) affords the title compound as a brown oil: 46 mg, 76%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) *δ*:** 7.40 – 7.31 (m, 5H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.29 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.31 – 3.03 (m, 2H), 0.88 (t, *J* = 7.0 Hz, 3H).

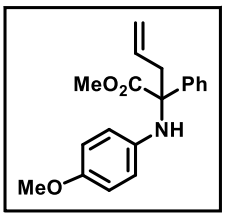
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 172.6, 153.8, 142.5, 136.4, 128.7, 128.5, 128.1, 119.8, 114.4, 68.6, 55.5, 51.9, 43.8, 13.0.

**IR (ATR, $cm^{-1}$):** 2914, 1745, 1510, 1244, 1167, 1038.

**HRMS (ESI+):** Calcd. for $[C_{18}H_{21}NO_3 + H]^+$: 300.1594, found: 300.1595.

[23] Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose, B. J.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 15794-15795.

**Molecule 11d:** *methyl 2-((4-methoxyphenyl)amino)-2-phenylpent-4-enoate*[24,25]




Under nitrogen, at room temperature, a round bottom flask is charged with methyl *(Z)*-2-((4-methoxyphenyl)imino)-2-phenylacetate **4g** (27 mg, 0.1 mmol, 1 equiv.) and DMF (5 mL mL, 0.02 M). Then, the reaction mixture is cooled to 0 ºC and allyl bromide (11 µL, 0.13 mmol, 1.3 equiv.) is added, followed by the addition of activated Zn powder (10 mg, 0.15 mmol, 1.5 equiv). The reaction mixture is heated to 60 ºC and is stirred at this temperature for 1h. Then, the reaction temperature is cooled to 0 ºC and the reaction is quenched with a saturated aqueous solution of $NH_4Cl$. Finally, the reaction mixture is extracted with AcOEt (3x), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography ($SiO_2$, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a brown solid: 17 mg, 55%.

For the activation of Zn: Zn powder is stirred with 2M HCl solution for *ca.* 15 minutes. Then, it is washed sequentially with $H_2O$, EtOH and $Et_2O$. Then, it is dried under vacuum before use.

**$^1$H NMR (250 MHz, $CDCl_3$) (1H cannot be unambiguously assigned) *δ*:** 7.62 – 7.58 (m, 2H), 7.40 – 7.29 (m, 3H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.34 (d, *J* = 8.6 Hz, 2H), 5.72 – 5.61 (m, 1H), 5.10 – 4.99 (m, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 3.21 – 3.18 (m, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 173.8, 152.2, 140.6, 138.2, 132.4, 128.6, 127.6, 127.1, 119.3, 116.9, 114.4, 66.8, 55.5, 52.9, 38.0.

**IR (ATR, cm$^{-1}$):** 2953, 1734, 1511, 1236, 1179, 1038.

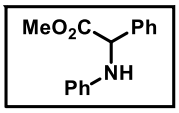
**M.P.:** 69 - 70 ºC.

**HRMS (ESI+):** Calcd. for $[C_{19}H_{21}NO_3 + H]^+$: 312.1594, found: 312.1598.

[24] For procedure, see: Kidd, S. L.; Fowler, E.; Reinhardt, T.; Compton, T.; Mateu, N.; Newman, H.; Bellini, D.; Talon, R.; McLoughlin, J.; Krojer, T.; Aimon, A.; Bradley, A.; Fairhead, M.; Brear, P.; Díaz- Sáez, L.; McAuley, K.; Sore, H. F.; Madin, A.; O'Donovan, D. H.; Huber, K. V. M.; Hyvonen, M.; von Delft, F.; Dowson, C. G.; Spring, D. R. *Chem. Sci.* **2020**, *11*, 10792-10801.

[25] Spectroscopic data is in good agreement with the literature. See: Bhakta, U.; Kattamuri, P. V.; Siitonen, J. H.; Alemany, L. B.; Kürti, L. *Org. Lett.* **2019**, *21*, 9208-9211.

**Molecule 12a:** *methyl 2-phenyl-2-(phenylamino)acetate*[22]

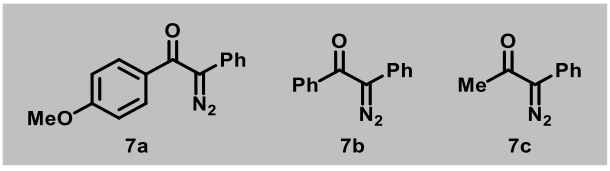


Under air, at room temperature, a round bottom flask is charged with the sulfoxonium ylide **6a** (61 mg, 0.22 mmol, 1.1 equiv.), $PhNH_2$ (19 µL, 0.2 mmol, 1 equiv.), $Sc(OTf)_3$ (5 mg, 0.01 mmol, 5 mol%) and toluene (1 mL). The resulting reaction mixture is stirred at 70 ºC for 12h. Then, the reaction mixture is concentrated under reduced pressure and the resulting residue is purified by flash column chromatography ($SiO_2$, gradient: Hex – 95:5 Hex:AcEt – 9:1 Hex:AcOEt – 8:2 Hex:AcOEt) to afford the title compound as a white solid: 42 mg, 87%.

**$^1$H NMR (500 MHz, $CDCl_3$) *δ*:** 7.53 – 7.51 (m, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 2H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 2H), 5.10 (s, 1H), 4.98 (s, 1H), 3.74 (s, 3H).
**$^{13}$C NMR (125 MHz, $CDCl_3$) *δ*:** 172.3, 145.9, 137.6, 129.2, 128.8, 128.3, 127.2, 118.1, 113.4, 60.7, 52.8.

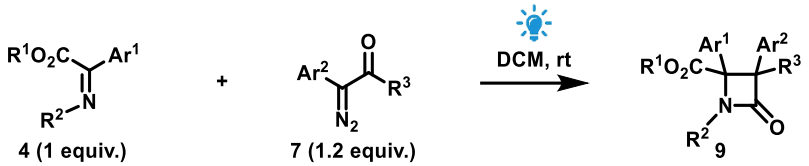
**Preparation of Aryldiazoketones 7**

The following aryldiazoketones have been prepared as previously described in the literature, being numbered following their order of appearance in the manuscript: *2-diazo-1-(4-methoxyphenyl)-2-phenylethan-1-one* (**7a**),[26,27] *2-diazo-1,2-diphenylethan-1-one* (**7b**)[2] and *1-diazo-1-phenylpropan-2-one* (**7c**)[2]




[26] For the synthesis of the ketone precursor via an acylation procedure, see: Gupton, J. T.; Shimozono, A.; Crawford, E.; Ortolani, J.; Clark, E.; Mahoney, M.; Heese, C.; Noble, J.; Mandry, C. P.; Kanters, R.; Dominey, R. N.; Goldman, E. W.; Sikorski, J. A. Fisher, D. C. *Tetrahedron* **2018**, *74*, 2650-2663.
[27] For the diazo transfer procedure, see: Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972-8981.

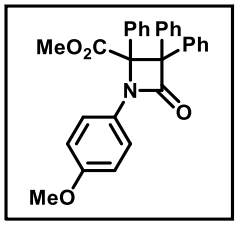
**Synthesis of Alkyl 2-Carboxylate-2,3,3-Trisubstituted β-Lactams 9**




**General procedure E:** Under air, at room temperature, a 4 mL-vial is charged with imine **4** (1 equiv.), aryldiazoketone **7** (1.2 equiv.) and DCM (0.1 M in relation to the imine **4**). The reaction mixture is stirred at room temperature under blue light irradiation for 16h (using two blue LED lamps, 15 W each, displaced at approximate distances of 5 cm each from the reaction vessel). Then, the reaction mixture is concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding β-lactam **9** in the stated yield.

Remarkably, higher yields are observed when freshly prepared aryldiazoketones **7** are used.

**Molecule 9a:** *methyl 1-(4-methoxyphenyl)-4-oxo-2,3,3-triphenylazetidine-2-carboxylate*




**General Procedure E** is employed with methyl (*Z*)-2-((4-methoxyphenyl)imino)-2-phenylacetate **4g** (27 mg, 0.1 mmol, 1 equiv.), 2-diazo-1,2-diphenylethan-1-one **7b** (27 mg, 0.12 mmol, 1.2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 95:4:1 Hex:AcOEt:$Et_3N$ - 90:9:1 Hex:AcOEt:$Et_3N$) affords the title compound as a white solid: 46 mg, 99%.

**$^1$H NMR (250 MHz, $CDCl_3$) *δ*:** 7.53 – 7.49 (m, 2H), 7.42 (d, *J* = 9.1 Hz, 2H), 7.37 – 7.23 (m, 7H), 7.11 – 7.03 (m, 6H), 6.78 (d, *J* = 9.1 Hz, 2H), 3.74 (s, 3H), 3.27 (s, 3H).

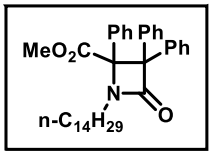
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) *δ*:** 169.3, 166.6, 156.2, 137.9, 135.2, 133.3, 130.4, 129.3, 128.7, 128.2 (x2), 127.8, 127.7, 127.6, 127.0, 119.9, 113.9, 77.8, 77.7, 55.3, 52.1.

**IR (ATR, cm$^{-1}$):** 2919, 1747, 1511, 1248, 1171, 1032.

**M.P.:** 199 - 200 ºC.

**HRMS (ESI+):** Calcd. for $[C_{30}H_{25}NO_4 + H]^+$: 464.1856, found: 464.1857.

**Molecule 9b:** *methyl 4-oxo-2,3,3-triphenyl-1-tetradecylazetidine-2-carboxylate*




**General Procedure E** is employed with methyl (*Z*)-2-phenyl-2-(tetradecylimino)acetate **4d** (36 mg, 0.1 mmol, 1 equiv.), 2-diazo-1,2-diphenylethan-1-one **7b** (27 mg, 0.12 mmol, 1.2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 95:4:1 Hex:AcOEt:$Et_3N$ - 90:9:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 53 mg, 96%.

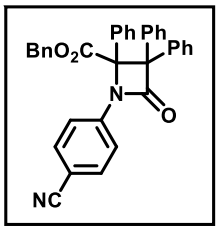
**$^1$H NMR (250 MHz, CDCl3) *δ*:** 7.31 – 7.24 (m, 7H), 7.16 – 7.07 (m, 8H), 3.41 – 3.32 (m, 1H), 3.35 (s, 3H), 3.08 – 2.96 (m, 1H), 1.99 – 1.88 (m, 2H), 1.31 - 1.25 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (3C cannot be unambiguously assigned) *δ*:** 169.8 (x2), 138.6, 135.3, 134.7, 129.6, 128.5, 128.4, 128.2, 127.9 (x2), 127.6, 126.7, 78.7, 77.2, 51.7, 43.2, 31.9, 29.7, 29.6 (x3), 29.4, 29.2, 28.2, 27.6, 22.7, 14.1.

**IR (ATR, cm$^{-1}$):** 2924, 2853, 1757, 1449, 1260.

**HRMS (ESI+):** Calcd. for $[C_{37}H_{47}NO_3 + H]^+$: 554.3629, found: 554.3630.

**Molecule 9c:** *benzyl 1-(4-cyanophenyl)-4-oxo-2,3,3-triphenylazetidine-2-carboxylate*




**General Procedure E** is employed with benzyl (*Z*)-2-((4-methoxyphenyl)imino)-2-phenylacetate **4k** (20 mg, 0.06 mmol, 1 equiv.), 2-diazo-1,2-diphenylethan-1-one **7b** (16 mg, 0.072 mmol, 1.2 equiv.) and DCM (600 µL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 95:4:1 Hex:AcOEt:$Et_3N$ - 90:9:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 32 mg, 99%.

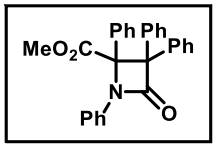
**$^{1}$H NMR (250 MHz, $CDCl_3$) $\delta$:** 7.49 – 7.44 (m, 6H), 7.32 – 7.20 (m, 10H), 7.15 – 7.04 (m, 6H), 6.94 – 6.90 (m, 2H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (2C cannot be unambigously assigned) $\delta$:** 168.1, 167.8, 140.5, 137.3, 134.5, 132.8, 132.5, 129.1, 128.6, 128.5, 128.4 (x3), 128.2, 128.1, 127.8, 127.7, 127.3, 118.8, 118.6, 107.4, 78.5, 77.9, 67.9.

**IR (ATR, cm$^{-1}$):** 2921, 2226, 1760, 1605, 1510, 1364.

**HRMS (ESI+):** Calcd. for $[C_{36}H_{26}N_2O_3 + H]^+$: 535.2016, found: 535.2016.

**Molecule 9d:** *methyl 1-(4-methoxyphenyl)-4-oxo-2,3,3-triphenylazetidine-2-carboxylate*




**General Procedure E** is employed with methyl *(Z)*-2-phenyl-2-(phenylimino)acetate **4a** (24 mg, 0.1 mmol, 1 equiv.), 2-diazo-1,2-diphenylethan-1-one **7b** (27 mg, 0.12 mmol, 1.2 equiv.) and DCM (1 mL, 0.1 M). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as a yellow oil: 43 mg, 99%.

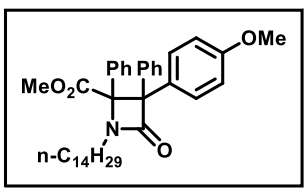
**$^{1}$H NMR (250 MHz, $CDCl_3$) $\delta$:** 7.55 – 7.45 (m, 4H), 7.37 – 7.22 (m, 9H), 7.12 – 7.03 (m, 7H), 3.26 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) $\delta$:** 169.3, 167.2, 137.8, 137.0, 135.1, 133.1, 129.2, 128.7, 128.3, 128.2, 127.9, 127.8 (x2), 127.6, 127.0, 124.3, 118.4, 77.8, 77.5, 52.2.

**IR (ATR, cm$^{-1}$):** 3057, 1751, 1494, 1370, 1264, 1021.

**HRMS (ESI+):** Calcd. for $[C_{29}H_{23}NO_3 + H]^+$: 434.1751, found: 434.1751.

**Molecule 9e:** *methyl 3-(4-methoxyphenyl)-4-oxo-2,3-diphenyl-1-tetradecylazetidine-2-carboxylate*




**General Procedure E** is employed with methyl *(Z)*-2-phenyl-2-(tetradecylimino)acetate **4d** (36 mg, 0.1 mmol, 1 equiv.), 2-diazo-1-(4-methoxyphenyl)-2-phenylethan-1-one **7a** (30 mg, 0.12 mmol, 1.2 equiv.) and DCM (1

mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 95:4:1 Hex:AcOEt: $Et_3N$ - 90:9:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 51 mg, 87%, 2.5:1 dr.

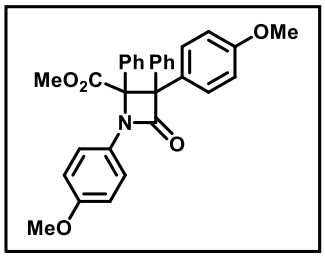
**$^1$H NMR (250 MHz, $CDCl_3$) (both diastereoisomers described) *δ*:** 7.30 – 7.06 (m, 12H), 6.79 (d, *J* = 9.0 Hz, 0.57H), 6.62 (d, *J* = 9.0 Hz, 1.43H), 3.76 (s, 0.85H), 3.70 (s, 2.15H), 3.43 – 3.31 (m, 4H), 3.11 – 2.93 (m, 1H), 1.98 – 1.88 (m, 2H), 1.37 – 1.25 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (both diastereoisomers described, 16C cannot be unambiguously assigned) *δ*:** 170.1, 169.9, 169.8 (x2), 158.9, 158.2, 139.0, 135.6, 134.8, 134.6, 130.6, 129.4, 129.2, 128.6, 128.5, 128.3 (x2), 128.1, 127.9 (x2), 127.8, 127.6, 127.5, 127.4, 126.6, 113.5, 113.0, 78.8, 78.7, 76.8, 76.7, 55.2, 55.1, 51.8, 51.6, 43.1, 43.2, 31.9, 29.7, 29.6 (x2), 29.5, 29.3, 29.2, 28.2, 27.5, 22.7, 14.1.

**IR (ATR, cm$^{-1}$):** 2924, 2853, 1756, 1512, 1251, 1181, 1035.

**HRMS (ESI+):** Calcd. for $[C_{38}H_{49}NO_4 + H]^+$: 584.3734, found: 584.3735.

**Molecule 9f:** *methyl 1,3-bis(4-methoxyphenyl)-4-oxo-2,3-diphenylazetidine-2-carboxylate*




**General Procedure E** is employed with methyl *(Z)*-2-((4-methoxyphenyl)imino)-2-phenylacetate **4g** (27 mg, 0.1 mmol, 1 equiv.), 2-diazo-1-(4-methoxyphenyl)-2-phenylethan-1-one **7a** (30 mg, 0.12 mmol, 1.2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 95:4:1 Hex:AcOEt: $Et_3N$ - 90:9:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 45 mg, 90%, 2:1 dr.

**$^1$H NMR (250 MHz, $CDCl_3$) *δ*: (both diastereoisomers described)** 7.53 – 7.28 (m, 8.76H), 7.21 – 7.05 (m, 5.34H), 6.88 – 6.77 (m, 2.66H), 6.60 (d, *J* = 8.8 Hz, 1.34H), 3.80 (s, 1H), 3.77 (s, 2H), 3.76 (s, 1H), 3.69 (s, 2H), 3.37 (s, 1H), 3.27 (s, 2H).

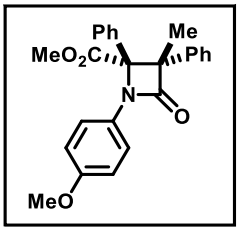
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (both diastereoisomers described, 3C cannot be unambiguosuly assigned) *δ*:** 169.9, 169.3, 166.8 (x2), 159.0, 158.3, 156.2,

156.1, 138.2, 135.4, 133.5, 133.3, 130.5, 130.4, 129.9, 129.3, 129.2, 128.7, 128.6, 128.2 (x2), 127.9 (x2), 127.8, 127.6 (x2), 127.4, 126.9, 120.0, 119.8, 113.9 (x2), 113.6, 113.0, 77.9, 77.7, 77.4 (x2), 55.4, 55.2, 55.1, 52.2, 52.1.

**IR (ATR, $cm^{-1}$):** 2916, 1746, 1510, 1248, 1179, 1033.

**HRMS (ESI+):** Calcd. for $[C_{31}H_{27}NO_5 + H]^+$: 494.1962, found: 494.1968.

**Molecule 9g:** *methyl 1-(4-methoxyphenyl)-3-methyl-4-oxo-2,3-diphenylazetidine-2 carboxylate*




**General Procedure E** is employed with methyl (*Z*)-2-((4-methoxyphenyl)imino)-2-phenylacetate **4g** (27 mg, 0.1 mmol, 1 equiv.), 1-diazo-1-phenylpropan-2-one **7c** (19 mg, 0.12 mmol, 1.2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 95:4:1 Hex:AcOEt:$Et_3N$) affords the title compound as a white solid: 40 mg, 99%, >20:1 dr.

**$^1$H NMR (250 MHz, $CDCl_3$) $\delta$:** 7.72 – 7.68 (m, 2H), 7.51 – 7.28 (m, 10H), 6.84 (d, *J* = 9.1 Hz, 2H), 3.78 (s, 3H), 3.05 (s, 3H), 1.23 (s, 3H).

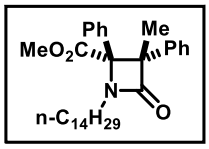
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$:** 169.7, 168.0, 156.1, 138.0, 133.0, 131.2, 128.5, 128.3 (x2), 128.2, 127.7, 126.7, 119.1, 114.1, 74.8, 69.3, 55.4, 52.0, 21.7.

**IR (ATR, $cm^{-1}$):** 1751, 1511, 1246, 1179, 1032.

**M.P.:** 145 - 146 ºC.

**HRMS (ESI+):** Calcd. for $[C_{25}H_{23}NO_4 + H]^+$: 402.1700, found: 402.1700.

**Molecule 9h:** *methyl 3-methyl-4-oxo-1,2,3-triphenylazetidine-2-carboxylate*




**General Procedure E** is employed with (*Z*)-2-phenyl-2-(tetradecylimino)acetate **4d** (18 mg, 0.05 mmol, 1 equiv.), 1-diazo-1-phenylpropan-2-one **7c** (10 mg, 0.06 mmol, 1.2 equiv.) and DCM (500 µL, 0.1 M). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 95:4:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 22 mg, 90%, >20:1 dr.

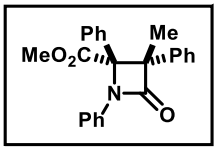
**$^{1}$H NMR (250 MHz, $CDCl_3$) $\delta$:** 7.66 – 7.63 (m, 2H), 7.49 – 7.27 (m, 8H), 3.55 – 3.31 (m, 2H), 3.17 (s, 3H), 2.17 – 2.07 (m, 2H), 1.38 - 1.26 (m, 22H), 1.18 (s, 3H), 0.88 (t, *J* = 6.5 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (3C cannot be unambiguously assigned) $\delta$:** 171.6, 170.1, 138.3, 134.6, 128.5, 128.3, 128.2, 127.6 (x2), 126.8, 76.7, 68.5, 51.8, 45.0, 31.9, 29.7, 29.6 (x2), 29.3, 29.2, 28.0, 27.6, 22.7, 19.7, 14.1.

**IR (ATR, cm$^{-1}$):** 2925, 2854, 1760, 1724, 1447, 1241, 1026.

**HRMS (ESI+):** Calcd. for $[C_{32}H_{45}NO_3 + H]^+$: 492.3472, found: 492.3472.

**Molecule 9i:** *methyl 3-methyl-4-oxo-1,2,3-triphenylazetidine-2-carboxylate*




**General Procedure E** is employed with (*Z*)-2-phenyl-2-(phenylimino)acetate **4a** (24 mg, 0.1 mmol, 1 equiv.), 1-diazo-1-phenylpropan-2-one **7c** (19 mg, 0.12 mmol, 1.2 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 95:4:1 Hex:AcOEt:$Et_3N$) affords the title compound as a white solid: 32 mg, 86%, >20:1 dr.

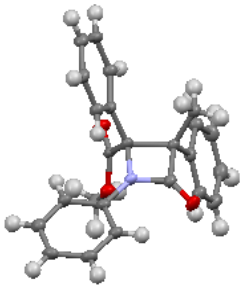
**$^{1}$H NMR (250 MHz, $CDCl_3$) $\delta$:** 7.74 – 7.50 (m, 2H), 7.46 – 7.27 (m, 12H), 7.15 – 7.09 (m, 1H), 3.05 (s, 3H), 1.25 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$:** 169.6, 168.5, 137.9, 137.7, 132.8, 128.9, 128.4, 128.3 (x2), 128.2, 127.7, 126.7, 124.1, 117.8, 74.7, 69.2, 52.1, 21.8.

**IR (ATR, cm$^{-1}$):** 1757, 1494, 1378, 1226, 1013.

**M.P.:** 166 - 167 ºC.

**HRMS (ESI+):** Calcd. for $[C_{24}H_{21}NO_3 + H]^+$: 372.1594, found: 372.1593.

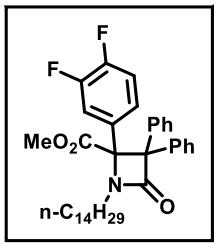


**Crystal data for 9i (CCDC 2104134)**

| | |
|---|---|
| Identification code | shelx |

| | | |
|---|---|---|
| Empirical formula | C24 H21 N O3 | |
| Formula weight | 371.42 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | P 21 21 21 | |
| Unit cell dimensions | a = 8.3874(6) Å | a = 90°. |
| | b = 10.0611(7) Å | b = 90°. |
| | c = 22.4185(17) Å | g = 90°. |
| Volume | 1891.8(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.304 $Mg/m^3$ | |
| Absorption coefficient | 0.689 $mm^{-1}$ | |
| F(000) | 784 | |
| Crystal size | 0.190 x 0.110 x 0.060 $mm^3$ | |
| Theta range for data collection | 3.943 to 69.610°. | |
| Index ranges | -9<=h<=10, -12<=k<=12, -27<=l<=26 | |
| Reflections collected | 11358 | |
| Independent reflections | 3450 [R(int) = 0.0936] | |
| Completeness to theta = 67.679° | 97.8 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7532 and 0.5848 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3450 / 0 / 256 | |
| Goodness-of-fit on $F^2$ | 1.060 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0433, wR2 = 0.1108 | |
| R indices (all data) | R1 = 0.0863, wR2 = 0.1321 | |
| Absolute structure parameter | 0.33(18) | |
| Extinction coefficient | 0.0058(11) | |
| Largest diff. peak and hole | 0.466 and -0.457 $e.Å^{-3}$ | |

**Molecule 9j:** *methyl 2-(3,4-difluorophenyl)-4-oxo-3,3-diphenyl-1-tetradecylazetidine-2-carboxylate*




**General Procedure E** is employed with methyl (*Z*)-2-(3,4-difluorophenyl)-2-(tetradecylimino)acetate **4o** (25 mg, 0.06 mmol, 1 equiv.), 2-diazo-1,2-diphenylethan-1-one **7b** (16 mg, 0.072 mmol, 1.2 equiv.) and DCM (600 µL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 95:4:1 Hex:AcOEt:$Et_3N$ - 90:9:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 35 mg, 99%.

**$^1$H NMR (250 MHz, $CDCl_3$) $\delta$:** 7.31 – 7.26 (m, 7H), 7.15 – 7.02 (m, 4H), 6.97 – 6.81 (m, 2H), 3.41 – 3.29 (m, 4H), 3.13 – 3.01 (m, 1H), 1.96 – 1.88 (m, 2H), 1.36 – 1.26 (m, 22H), 0.88 (t, *J* = 6.5 Hz, 3H).

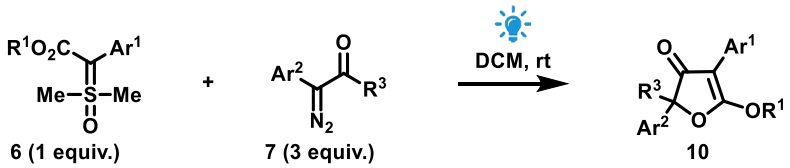
**$^{13}$C NMR (125 MHz, $CDCl_3$) (2C cannot be unambiguously assigned) $\delta$:** 169.4, 169.2, 150.0 (dd, *J* = 247.5 Hz, *J* = 10.0 Hz), 149.7 (dd, *J* = 251.3 Hz, *J* = 17.5 Hz), 137.9, 134.8, 131.9 (t, *J* = 5.0 Hz), 129.3, 128.3, 127.9 (x2), 127.8, 127.2, 124.8 (dd, *J* = 6.3 Hz, *J* = 3.8 Hz), 118.0 (d, *J* = 18.8 Hz), 116.8 (d, *J* = 17.5 Hz), 77.8, 77.7, 52.0, 43.3, 31.9, 29.7, 29.6 (x2), 29.5, 29.3, 29.1, 28.1, 27.5, 22.7, 14.1.

**$^{19}$F NMR (235 MHz, $CDCl_3$):** -136.6 (d, *J* = 21.2 Hz), -136.9 (d, *J* = 21.2 Hz).

**IR (ATR, cm$^{-1}$):** 2925, 2854, 1759, 1519, 1279.

**HRMS (ESI+):** Calcd. for $[C_{37}H_{45}F_2NO_3 + H]^+$: 590.3440, found: 590.3441.

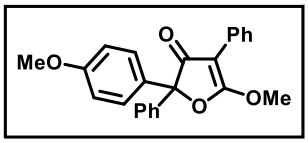
**Synthesis of 5-Alkoxy-2,2,4-Trisubstituted Furan-3(2H)-ones 10**




**General Procedure F:** Under air, at room temperature, a 4-mL vial is charged with sulfoxonium ylide **6** (1 equiv.), aryldiazoketone **7** (3 equiv.) and DCM (0.1 M in respect to sulfoxonium ylide **6**). The reaction mixture is stirred at room temperature under blue light irradiation for 24 h (using two blue LED lamps, 15 W each, displaced at approximate distances of 5 cm each from the reaction

vessel). Then, the reaction mixture is concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding furan-3(2H)-one **10** in the stated yield.

**Molecule 10a:** *5-methoxy-2-(4-methoxyphenyl)-2,4-diphenylfuran-3(2H)-one*




**General Procedure F** is employed with methyl 2-(dimethyl(oxo)-λ$^6$-sulfanylidene)-2-phenylacetate **6a** (22 mg, 0.1 mmol, 1 equiv.), 2-diazo-1-(4-methoxyphenyl)-2-phenylethanone **7a** (75 mg, 0.3 mmol, 3 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 94:5:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 25 mg, 67%.

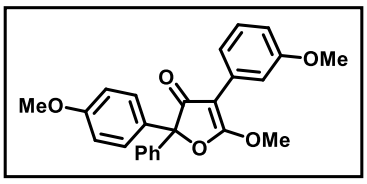
**$^1$H NMR (250 MHz, $CDCl_3$) $\delta$:** 7.91 (d, *J* = 9.0 Hz, 2H), 7.53 – 7.50 (m, 2H), 7.43 – 7.31 (m, 6H), 7.22 – 7.18 (m, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.30 (s, 3H), 3.80 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguosuly assigned) $\delta$:** 194.8, 178.8, 159.8, 137.9, 130.1, 129.5, 128.5, 128.4, 128.1, 126.6, 126.1, 126.0, 113.8, 93.9, 92.5, 56.8, 55.3.

**IR (ATR, cm$^{-1}$):** 1735, 1689, 1590, 1383, 1252, 1178, 1033.

**HRMS (ESI+):** Calcd. for $[C_{24}H_{20}O_4 + H]^+$: 373.1434, found: 373.1436.

**Molecule 10b:** *5-methoxy-2,2,4-triphenylfuran-3(2H)-one*




**General Procedure F** is employed with methyl 2-(dimethyl(oxo)-λ$^6$-sulfanylidene)-2-(3-methoxyphenyl)acetate **6l** (30 mg, 0.1 mmol, 1 equiv.), 2-diazo-1-(4-methoxyphenyl)-2-phenylethanone **7a** (75 mg, 0.3 mmol, 3 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 94:5:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 32 mg, 80%.

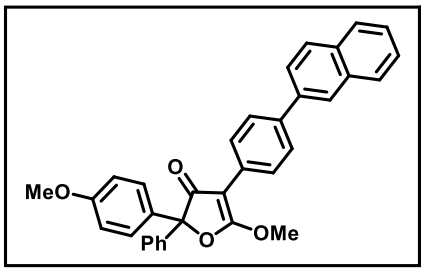
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.62 – 7.60 (m, 1H), 7.53 – 7.35 (m, 7H), 7.29 – 7.22 (m, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.78 – 6.73 (m, 1H), 4.31 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 194.8, 178.8, 159.9, 159.4, 137.8, 130.9, 130.0, 129.0, 128.5 (x2), 128.4, 126.6, 118.4, 113.8, 112.0, 111.2, 94.0, 92.3, 56.8, 55.3, 55.2.

**IR (ATR, $cm^{-1}$):** 1736, 1688, 1593, 1511, 1495, 1471, 1448, 1288, 1253, 1178, 1095, 1075, 1033, 1006.

**HRMS (ESI+):** Calcd. for $[C_{25}H_{22}O_5 + H]^+$: 403.1540, found: 403.1538.

**Molecule 10c:** *5-methoxy-2-(4-methoxyphenyl)-4-(4-(naphthalen-2-yl)phenyl)-2-phenylfuran-3(2H)-one*




**General Procedure F** is employed with methyl 2-(dimethyl(oxo)-λ$^6$-sulfanylidene)-2-(4-(naphthalen-2-yl)phenyl)acetate **6j** (35 mg, 0.1 mmol, 1 equiv.), 2-diazo-1-(4-methoxyphenyl)-2-phenylethanone **7a** (75 mg, 0.3 mmol, 3 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 94:5:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 45 mg, 81%.

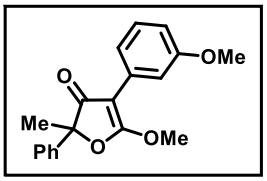
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 8.08 – 8.04 (m, 3H), 7.92 – 7.84 (m, 3H), 7.79 – 7.71 (m, 3H), 7.56 – 7.37 (m, 9H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.35 (s, 3H), 3.81 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 194.8, 178.8, 159.9, 138.4, 138.3, 137.8, 133.7, 132.5, 130.0, 128.8, 128.6 (x2), 128.4, 128.3, 128.1, 127.6, 127.0, 126.6, 126.4, 126.2, 125.8, 125.4 (x2), 113.9, 94.1, 92.3, 56.9, 55.3.

**IR (ATR, $cm^{-1}$):** 1687, 1591, 1511, 1475, 1448, 1380, 1345, 1308, 1254, 1216, 1178, 1088, 1075, 1033.

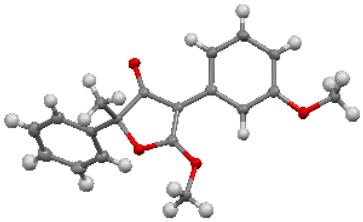
**HRMS (ESI+):** Calcd. for $[C_{34}H_{26}O_4 + H]^+$: 499.1904, found: 499.1904.

**Molecule 10i:** *5-methoxy-4-(3-methoxyphenyl)-2-methyl-2-phenylfuran-3(2H)-one*




**General Procedure F** is employed with methyl 2-(dimethyl(oxo)-λ$^6$-sulfanylidene)-2-(3-methoxyphenyl) acetate **6l** (30 mg, 0.1 mmol, 1 equiv.), 1-diazo-1-phenylpropan-2-one **7c** (48 mg, 0.3 mmol, 3 equiv.), and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 94:5:1 Hex:AcOEt:$Et_3N$) affords the title compound as a white solid: 17 mg, 56%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.58 – 7.54 (m, 3H), 7.47 (dt, *J* = 8.0 Hz, *J* = 1.3 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.28 – 7.21 (t, *J* = 8.0 Hz, 1H), 6.74 (ddd, *J* = 8.0 Hz, *J* = 2.5 Hz, *J* = 0.8 Hz, 1H), 4.29 (s, 3H), 3.82 (s, 3H), 1.90 (s, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 196.6, 178.6, 159.4, 137.7, 131.0, 129.0, 128.6, 128.4, 124.6, 118.3, 112.0, 111.1, 91.5, 91.1, 56.7, 55.2, 24.5.
**IR (ATR, cm$^{-1}$):** 1686, 1592, 1496, 1474, 1386, 1288, 1266, 1245, 1035.
**M.P.:** 102 - 103 °C.
**HRMS (ESI+):** Calcd. for $[C_{19}H_{18}O_4 + H]^+$: 311.1278, found: 311.1277.

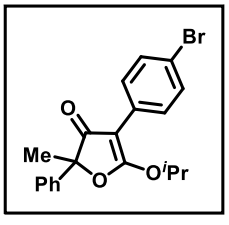


**Crystal data for 10i (CCDC 2104135).**

| | | |
|---|---|---|
| Identification code | shelx | |
| Empirical formula | C19 H18 O4 | |
| Formula weight | 310.33 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | P 21 21 21 | |
| Unit cell dimensions | a = 8.4510(5) Å | a = 90°. |
| | b = 10.9156(6) Å | b = 90°. |

| | |
|---|---|
| | c = 16.6836(10) Å g = 90°. |
| Volume | 1539.02(15) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.339 $Mg/m^3$ |
| Absorption coefficient | 0.763 $mm^{-1}$ |
| F(000) | 656 |
| Crystal size | 0.210 x 0.150 x 0.060 $mm^3$ |
| Theta range for data collection | 4.841 to 69.310°. |
| Index ranges | -10<=h<=10, -13<=k<=11, -19<=l<=20 |
| Reflections collected | 8923 |
| Independent reflections | 2864 [R(int) = 0.0290] |
| Completeness to theta = 67.679° | 99.7 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7532 and 0.6063 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2864 / 0 / 211 |
| Goodness-of-fit on $F^2$ | 1.075 |
| Final R indices [I>2sigma(I)] | R1 = 0.0280, wR2 = 0.0716 |
| R indices (all data) | R1 = 0.0287, wR2 = 0.0734 |
| Absolute structure parameter | 0.09(6) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.180 and -0.177 $e.Å^{-3}$ |

**Molecule 10j:** *5 4-(4-bromophenyl)-5-isopropoxy-2-methyl-2-phenylfuran-3(2H)-one*




**General Procedure F** is employed with isopropyl 2-(4-bromophenyl)-2-(dimethyl(oxo)-$λ^6$-sulfanylidene)acetate **6h** (33 mg, 0.1 mmol, 1 equiv.), 1-diazo-1-phenylpropan-2-one **7c** (48 mg, 0.3 mmol, 3 equiv.) and DCM (1 mL). Purification by flash column chromatography ($SiO_2$, gradient: 99:1 Hex:$Et_3N$ - 98:1:1 Hex:AcOEt:$Et_3N$ - 94:5:1 Hex:AcOEt:$Et_3N$) affords the title compound as a yellow oil: 32 mg, 82%.

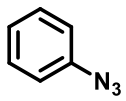
**$^{1}$H NMR (250 MHz, $CDCl_3$) *δ*:** 7.83 (d, *J* = 8.8 Hz, 2H), 7.57 – 7.53 (m, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.41 – 7.33 (m, 3H), 5.42 (sept., *J* = 6.2 Hz, 1H), 1.88 (s, 3H), 1.94 (d, *J* = 6.2 Hz, 6H).

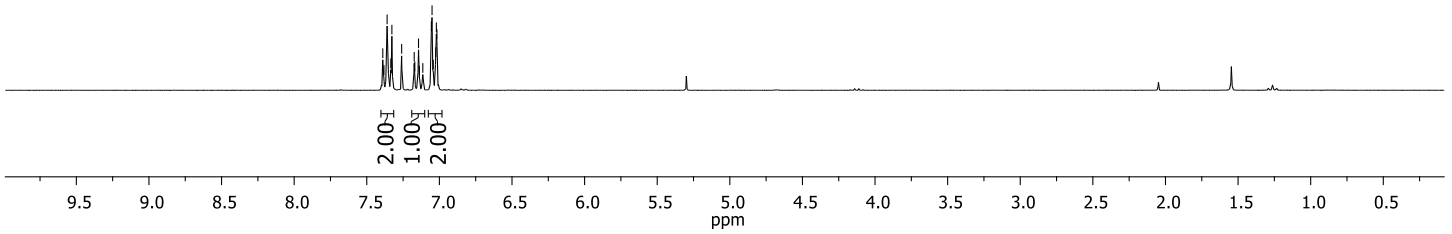
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ*:** 196.4, 177.9, 137.7, 131.1, 129.1, 128.6, 128.4, 127.3, 124.6, 119.1, 91.3, 90.4, 76.0, 24.5, 22.6 (x2).

**IR (ATR, cm$^{-1}$):** 2982, 1688, 1576, 1395, 1210, 1089, 1026.

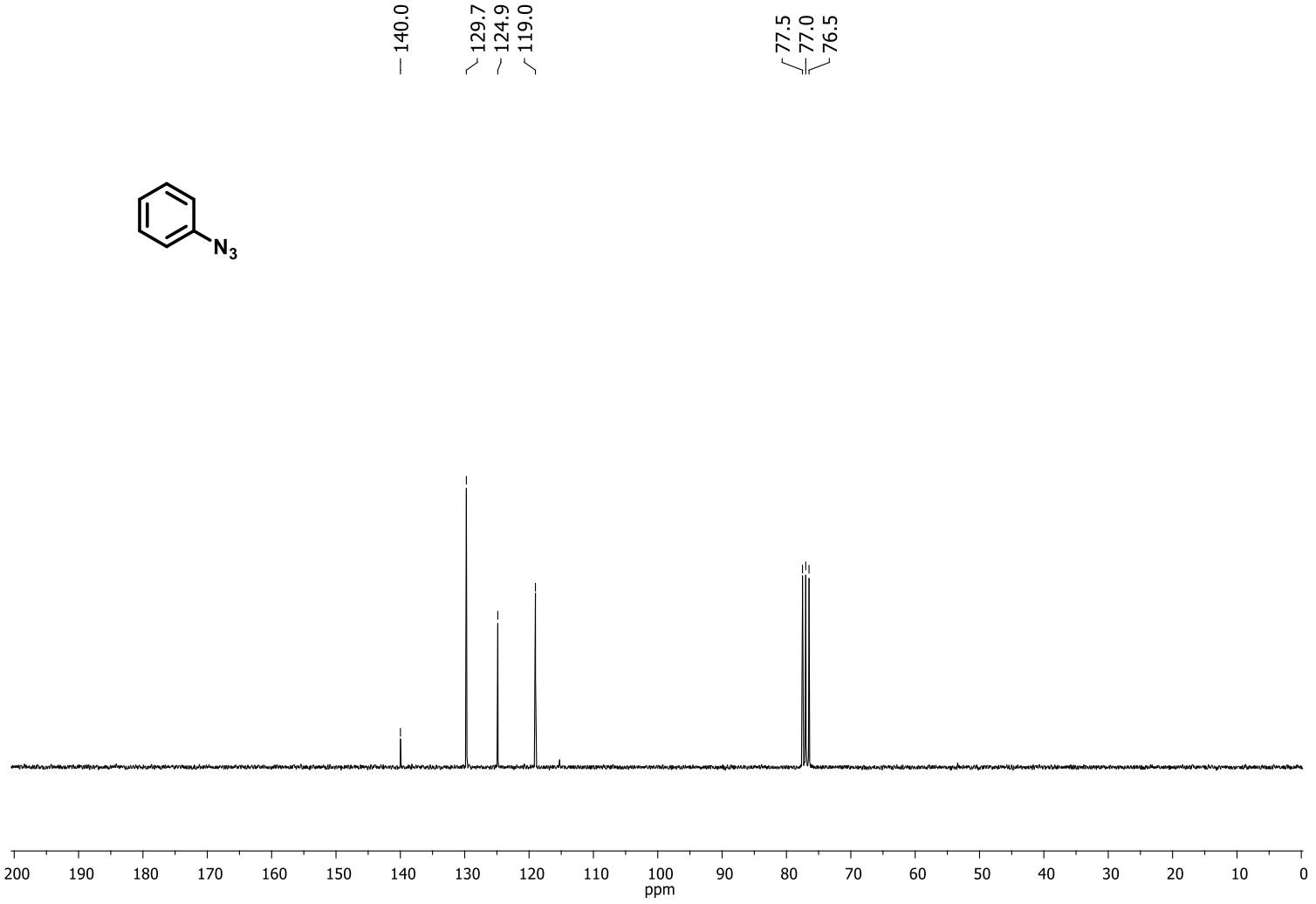
**HRMS (ESI+):** Calcd. for $[C_{20}H_{19}BrO_3 + H]^+$: 387.0590, found: 387.0591.

**Molecule 3a - $^{1}H$ NMR (250 MHz, $CDCl_3$)**

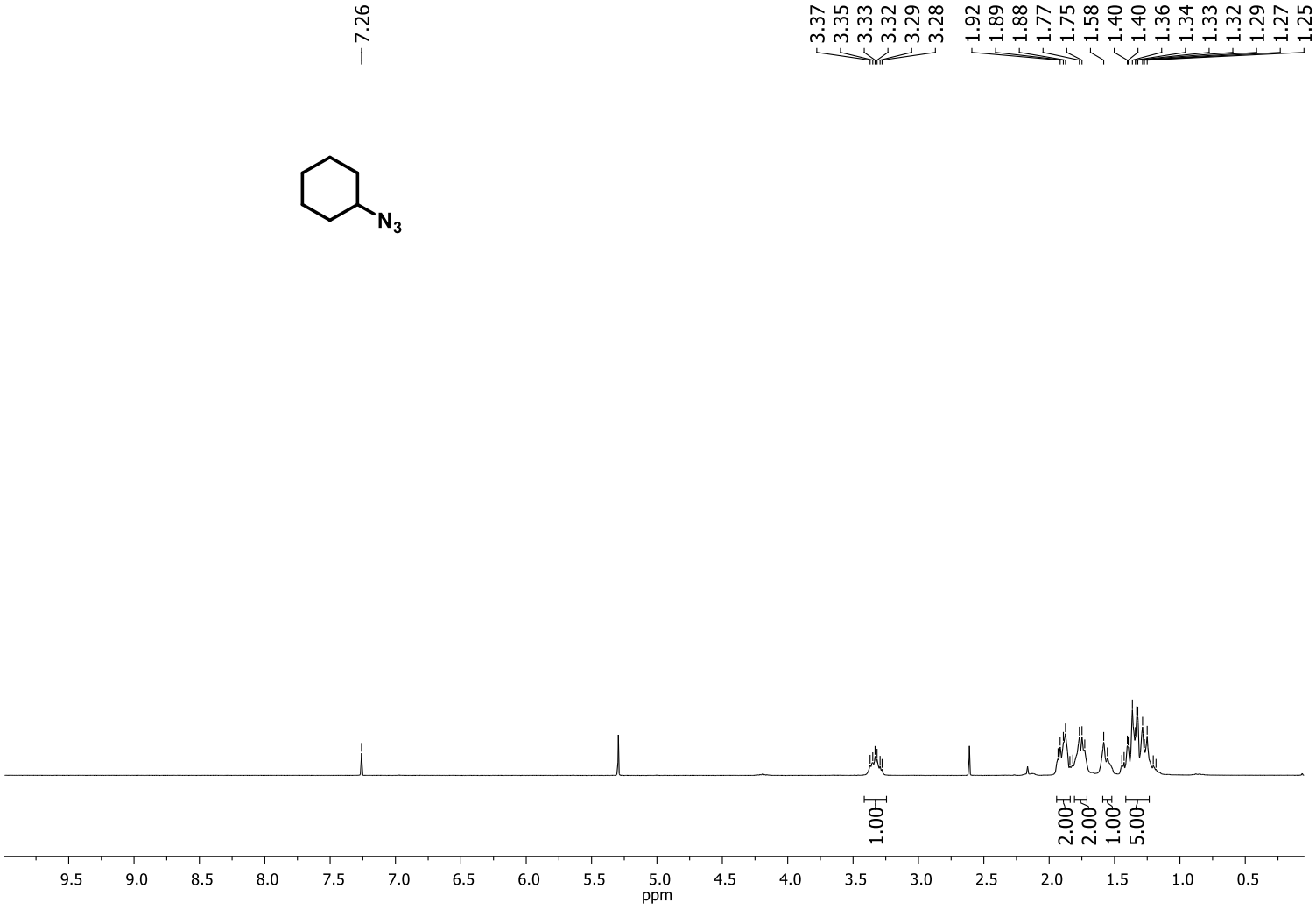



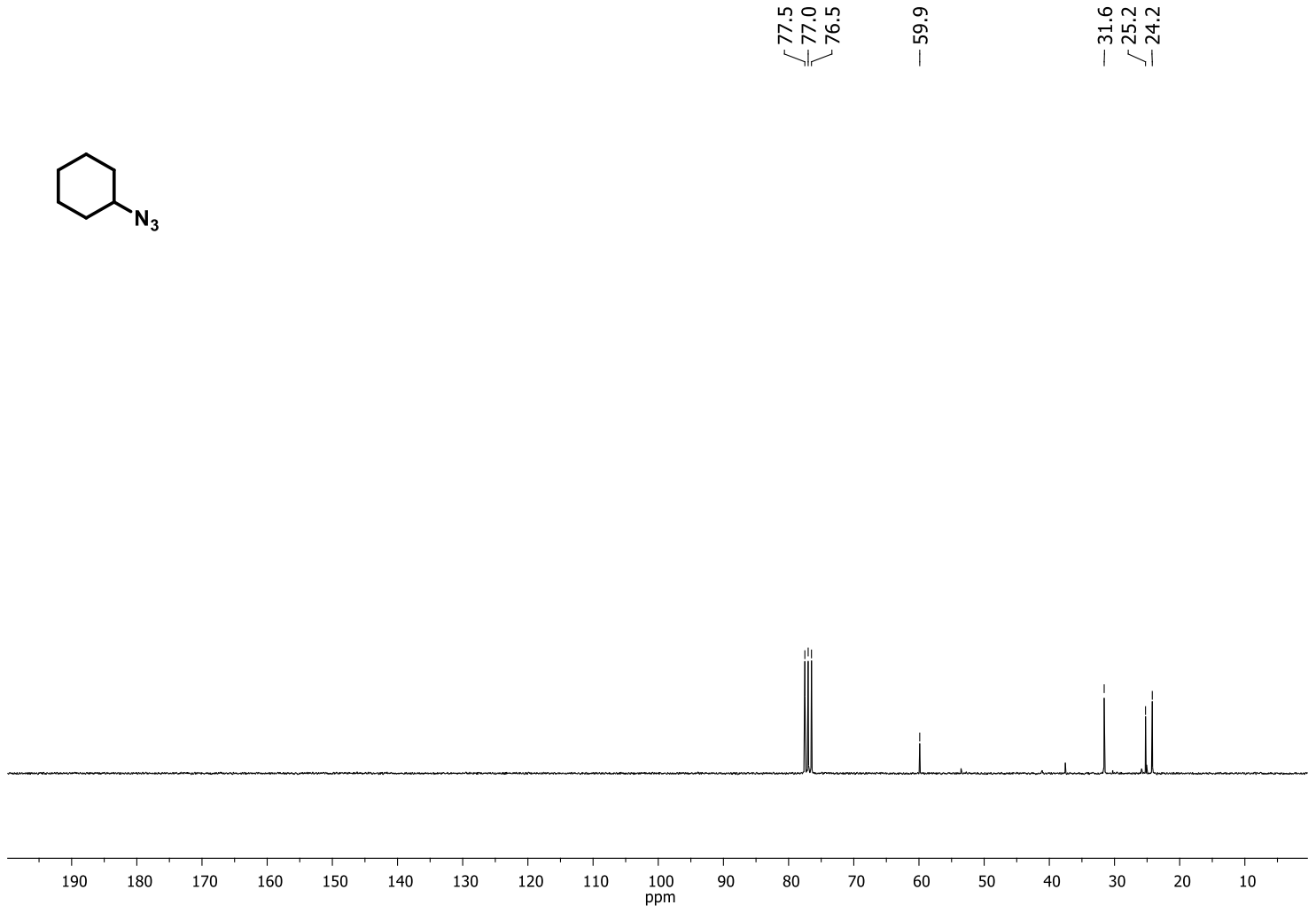
**Molecule 3a - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



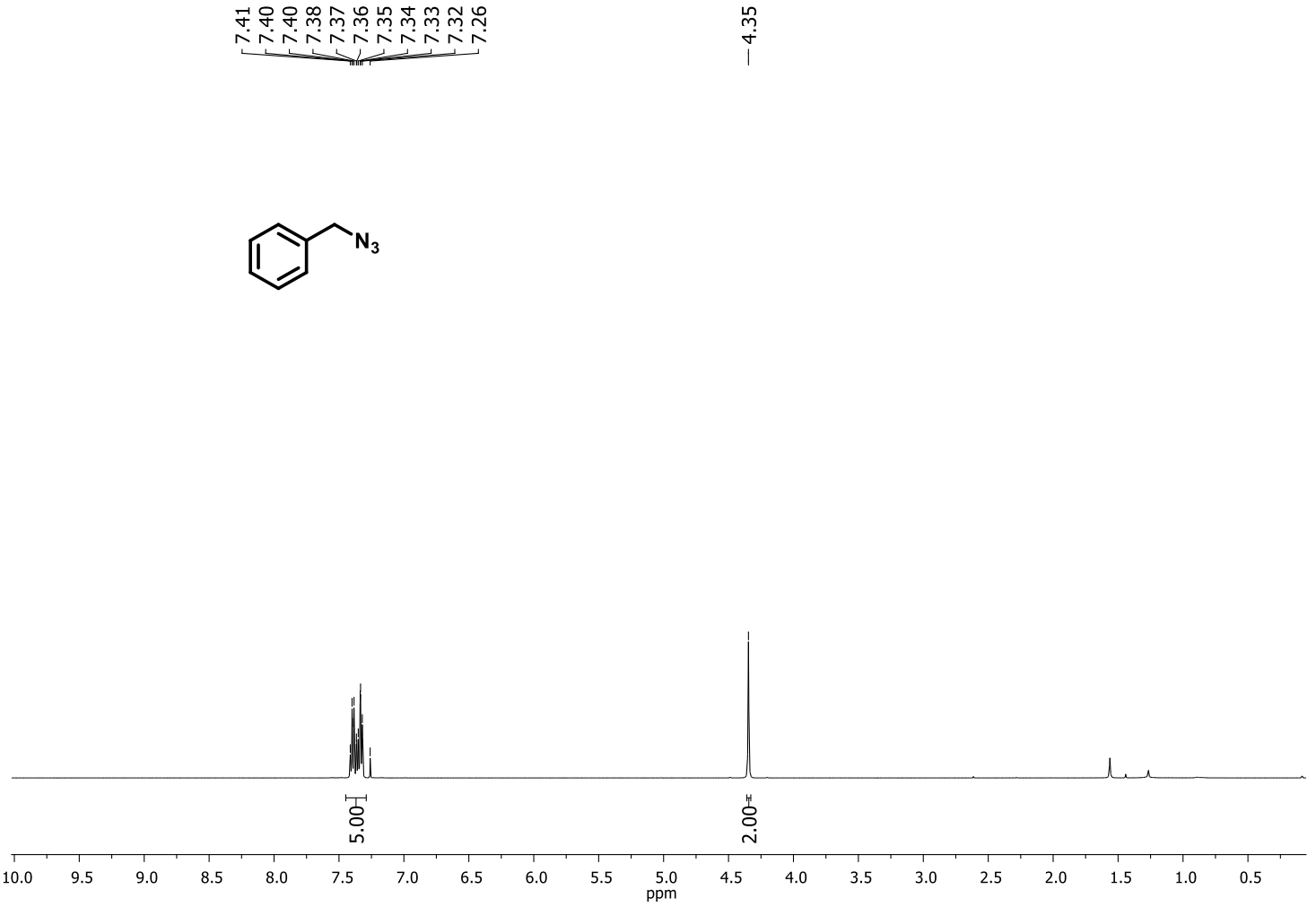
**Molecule 3b - $^{1}H$ NMR (250 MHz, $CDCl_3$)**



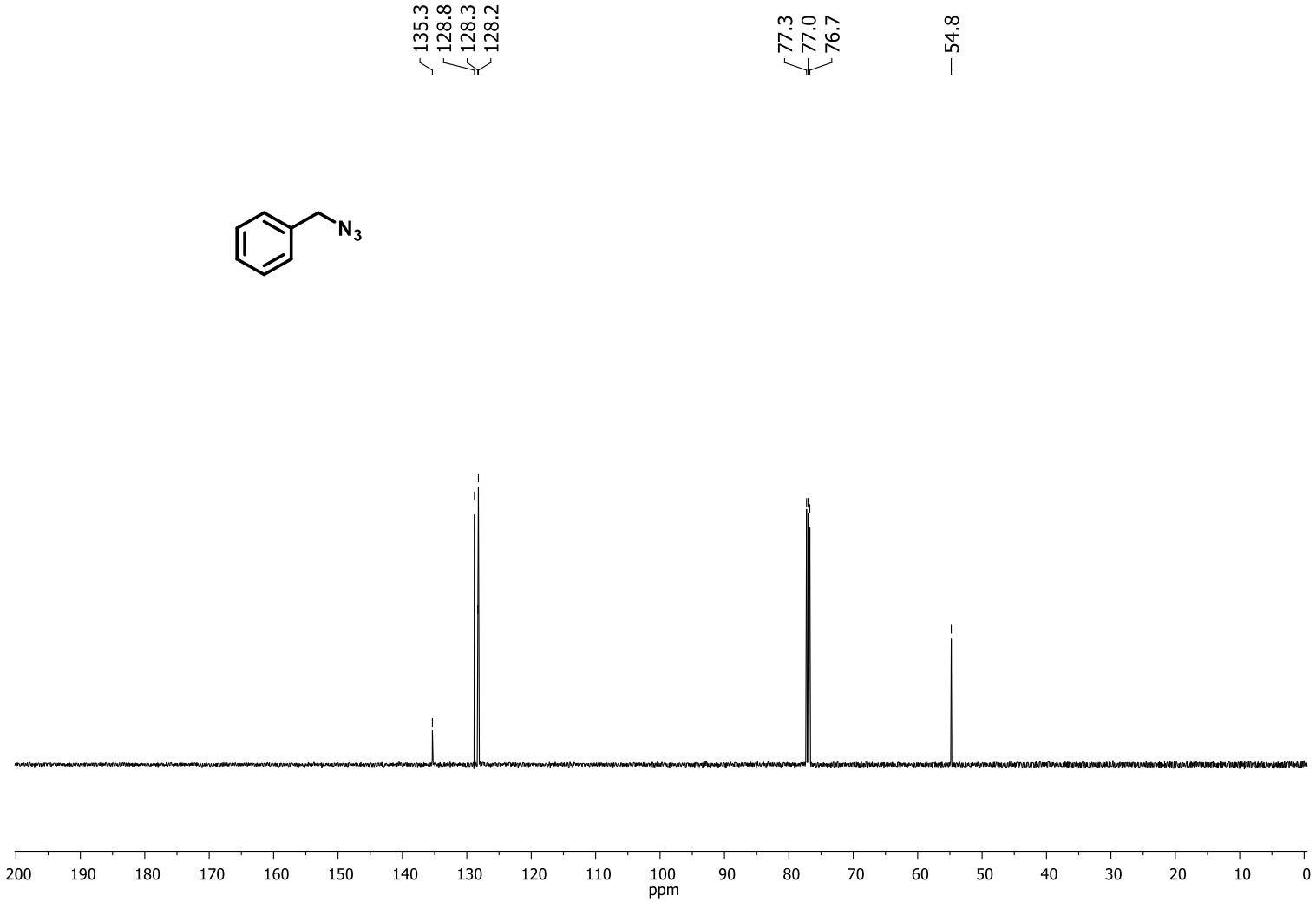
**Molecule 3b - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



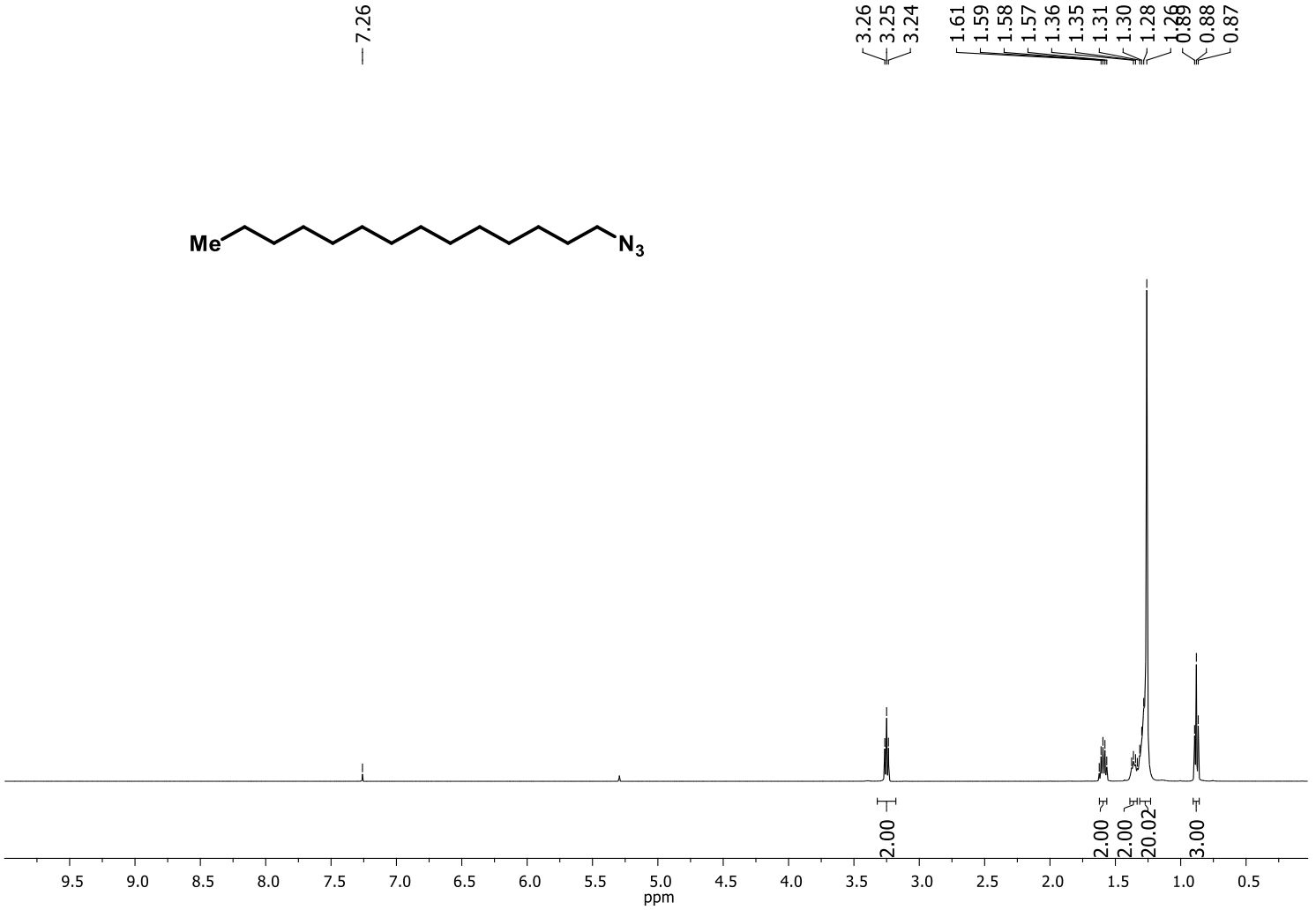
**Molecule 3c - $^{1}H$ NMR (250 MHz, $CDCl_3$)**



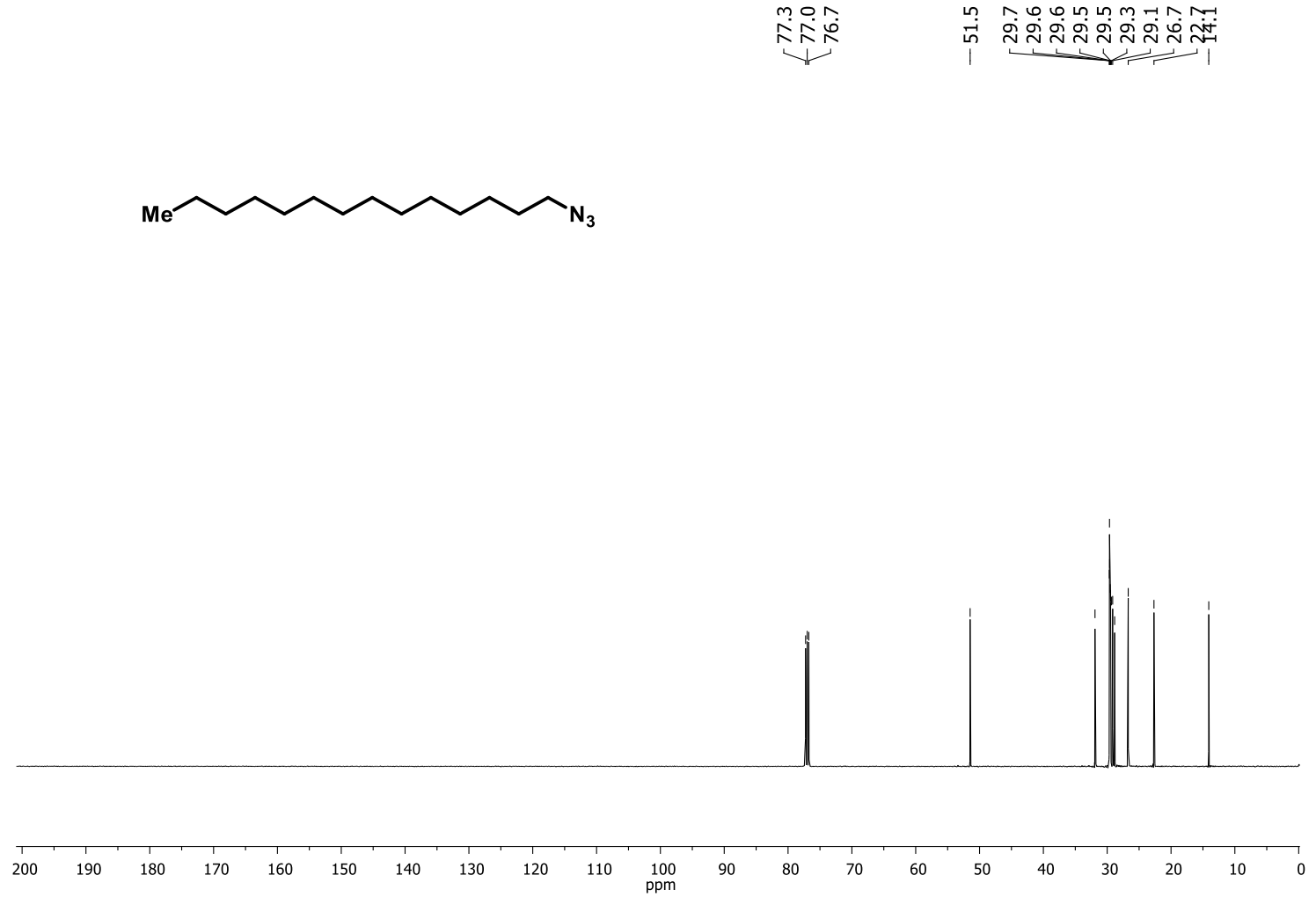
**Molecule 3c - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



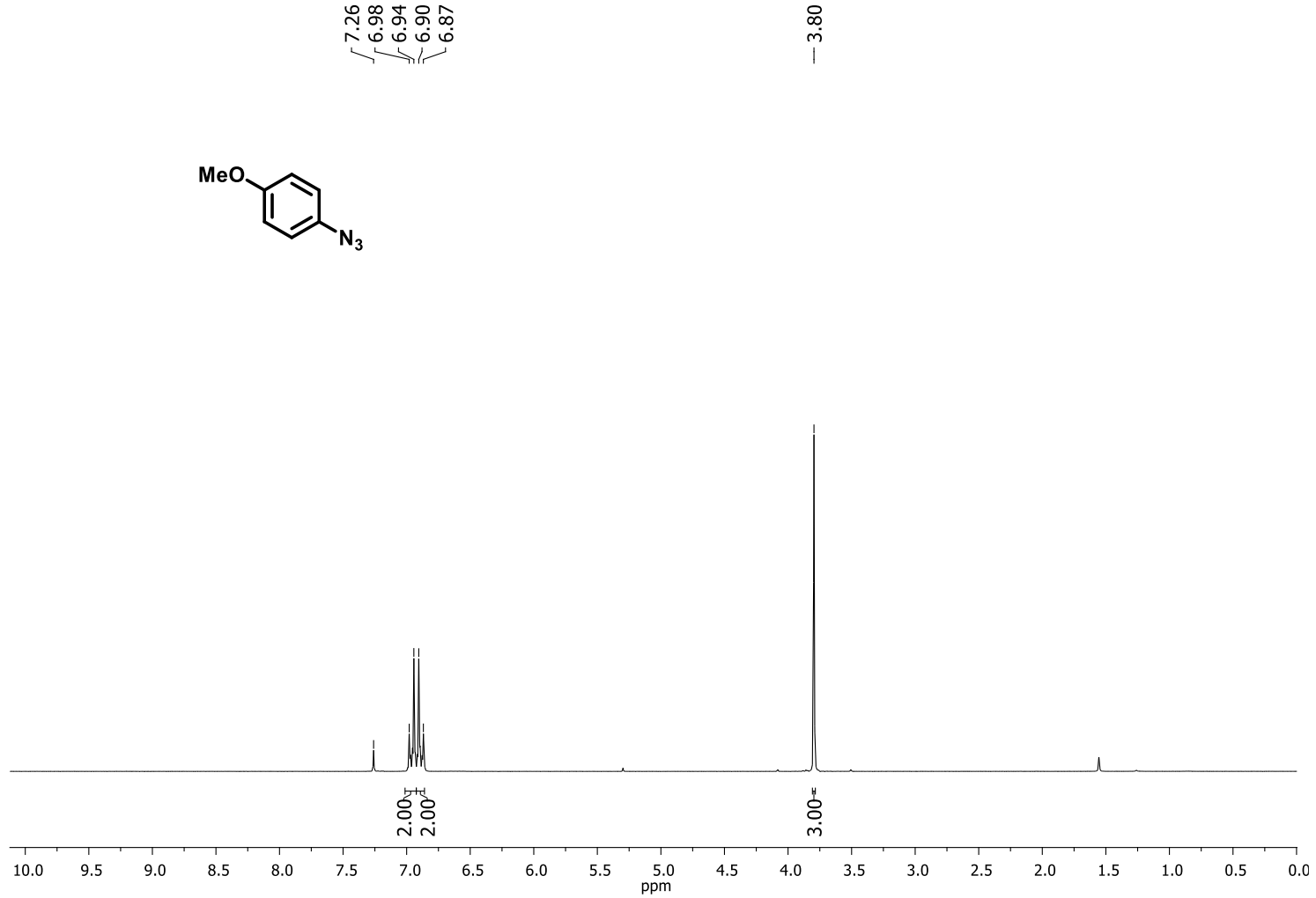
**Molecule 3d - $^{1}$H NMR (250 MHz, $CDCl_3$)**



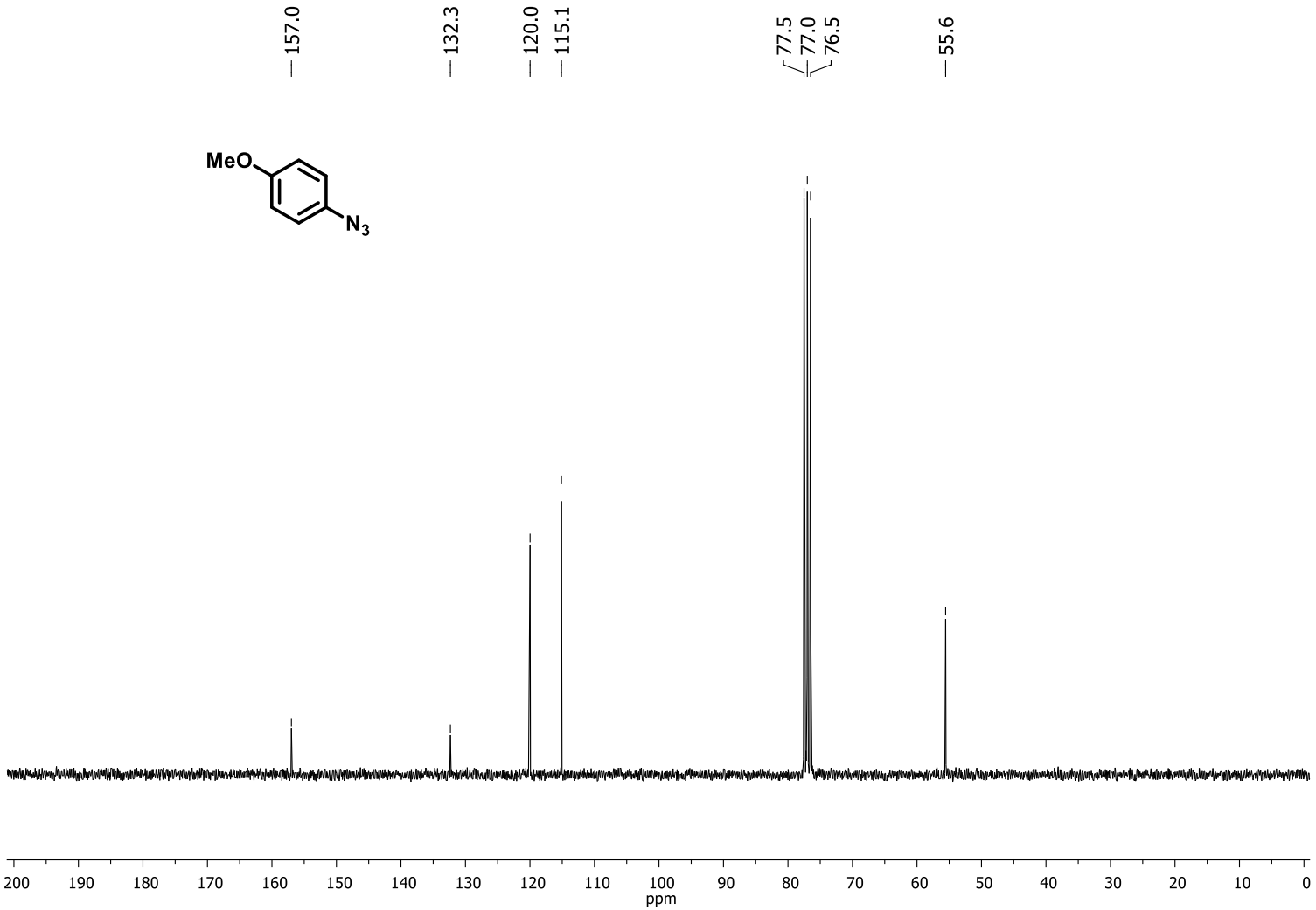
**Molecule 3d - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



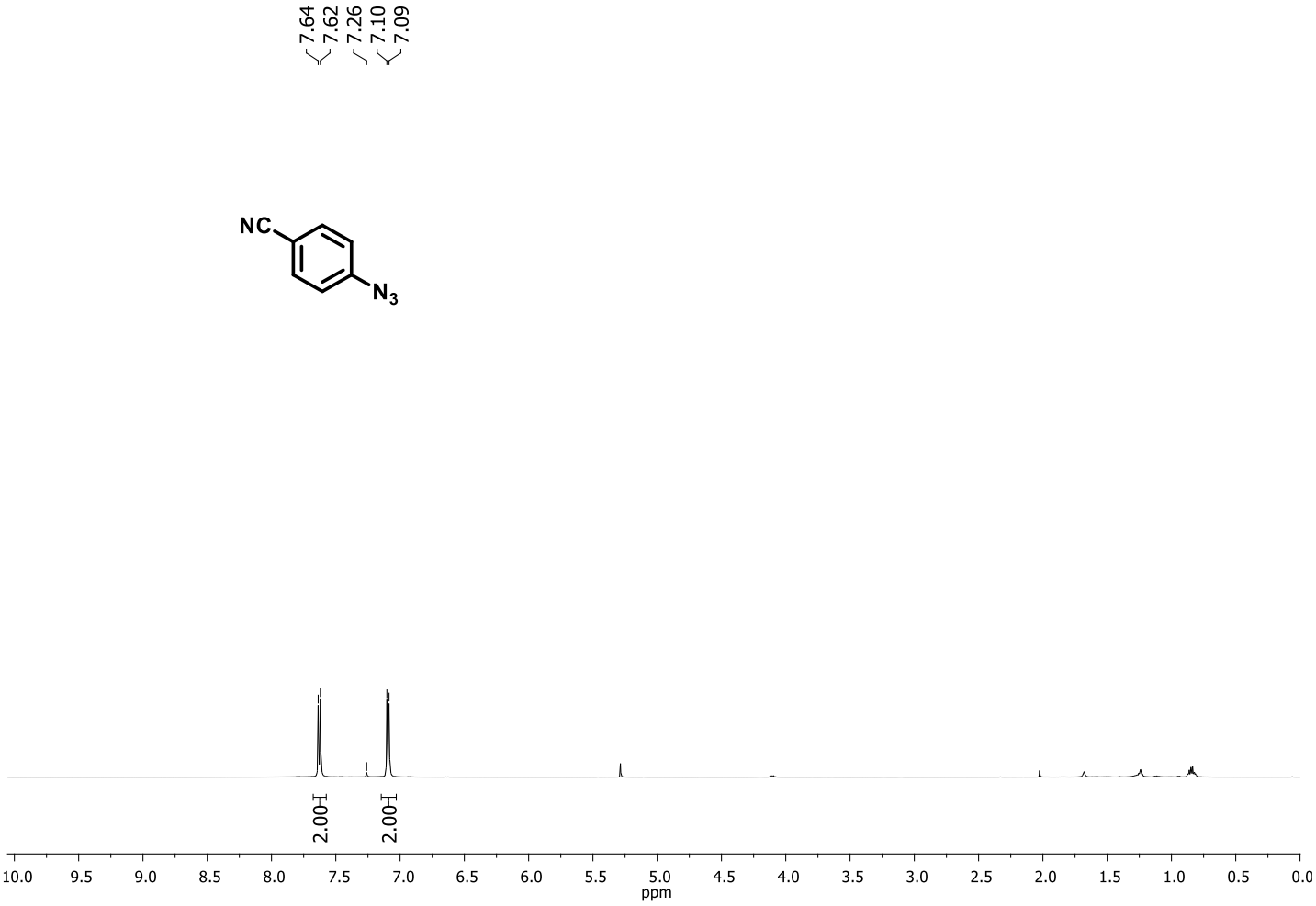
**Molecule 3e - $^{1}$H NMR (250 MHz, $CDCl_3$)**



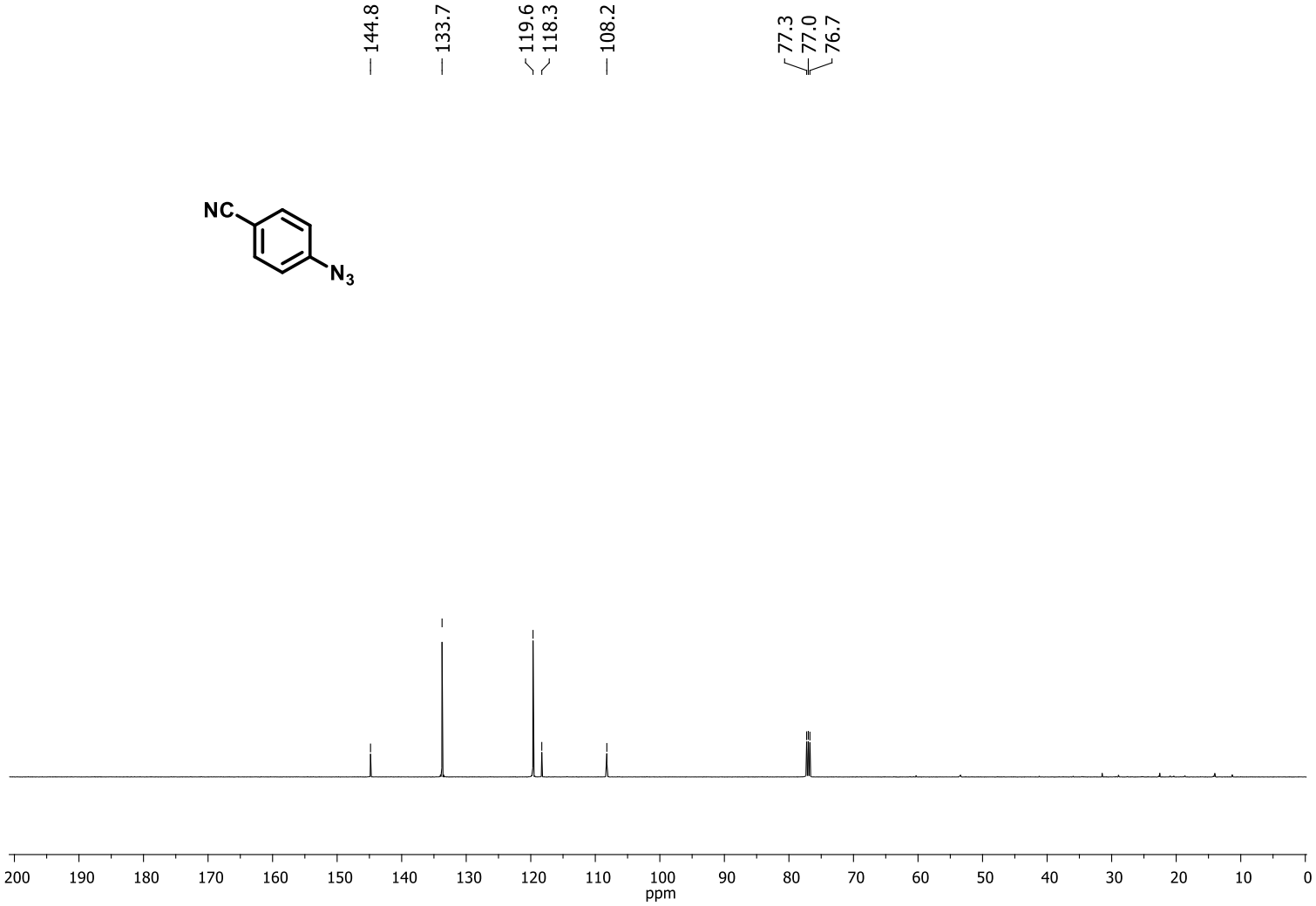
**Molecule 3e - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



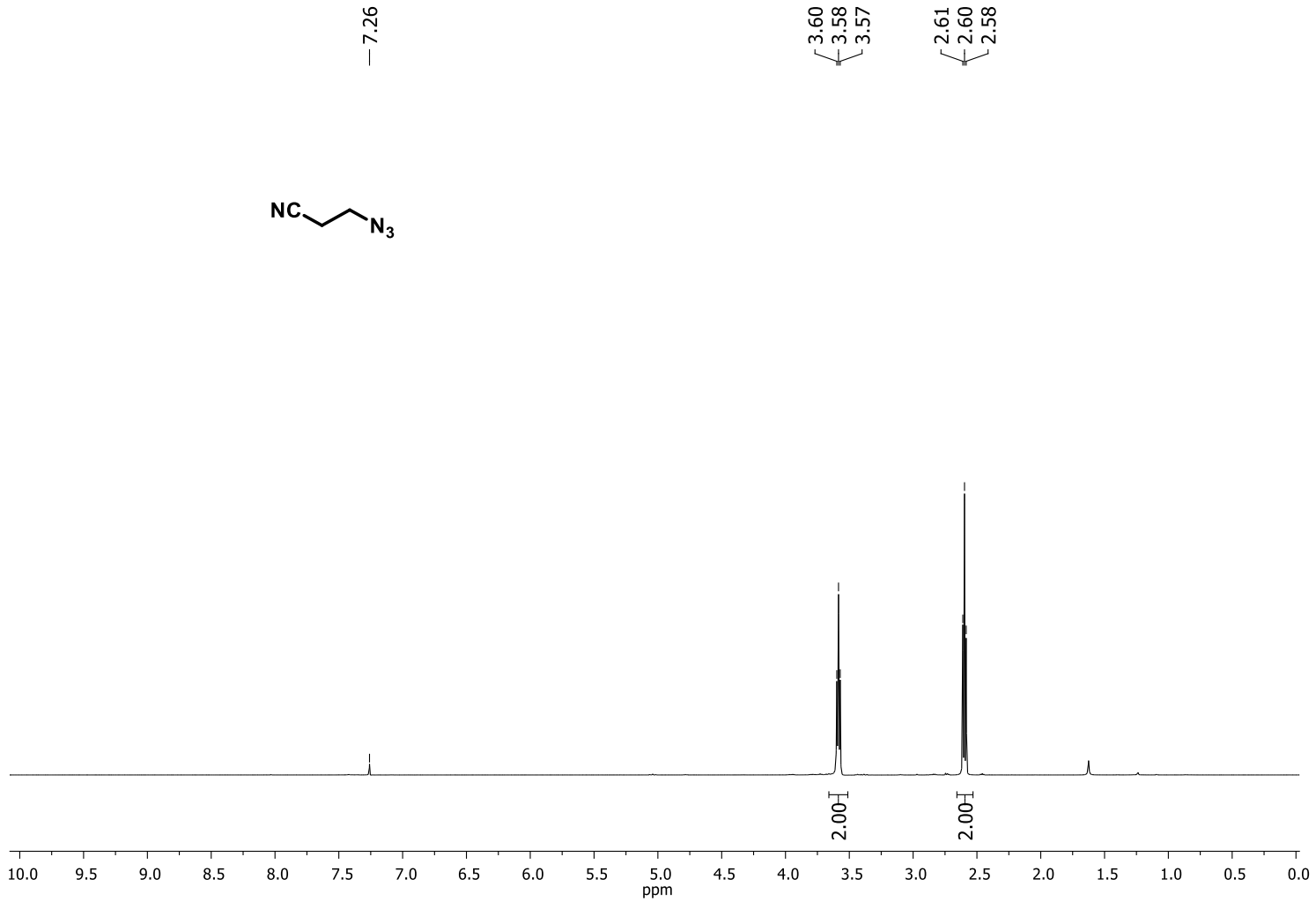
**Molecule 3f - $^{1}$H NMR (500 MHz, $CDCl_3$)**



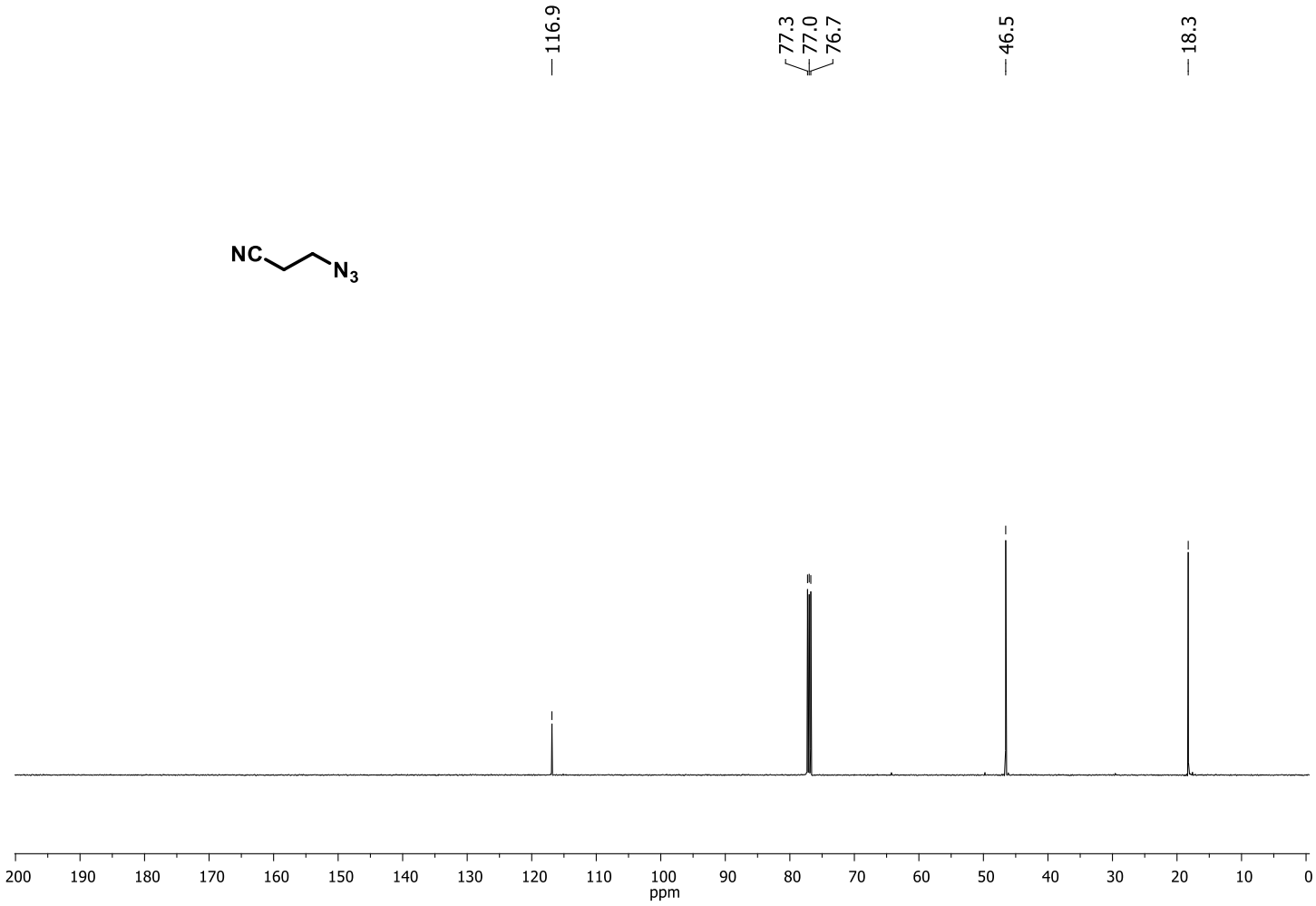
**Molecule 3f - $^{13}C$ NMR (125 MHz, $CDCl_3$)**



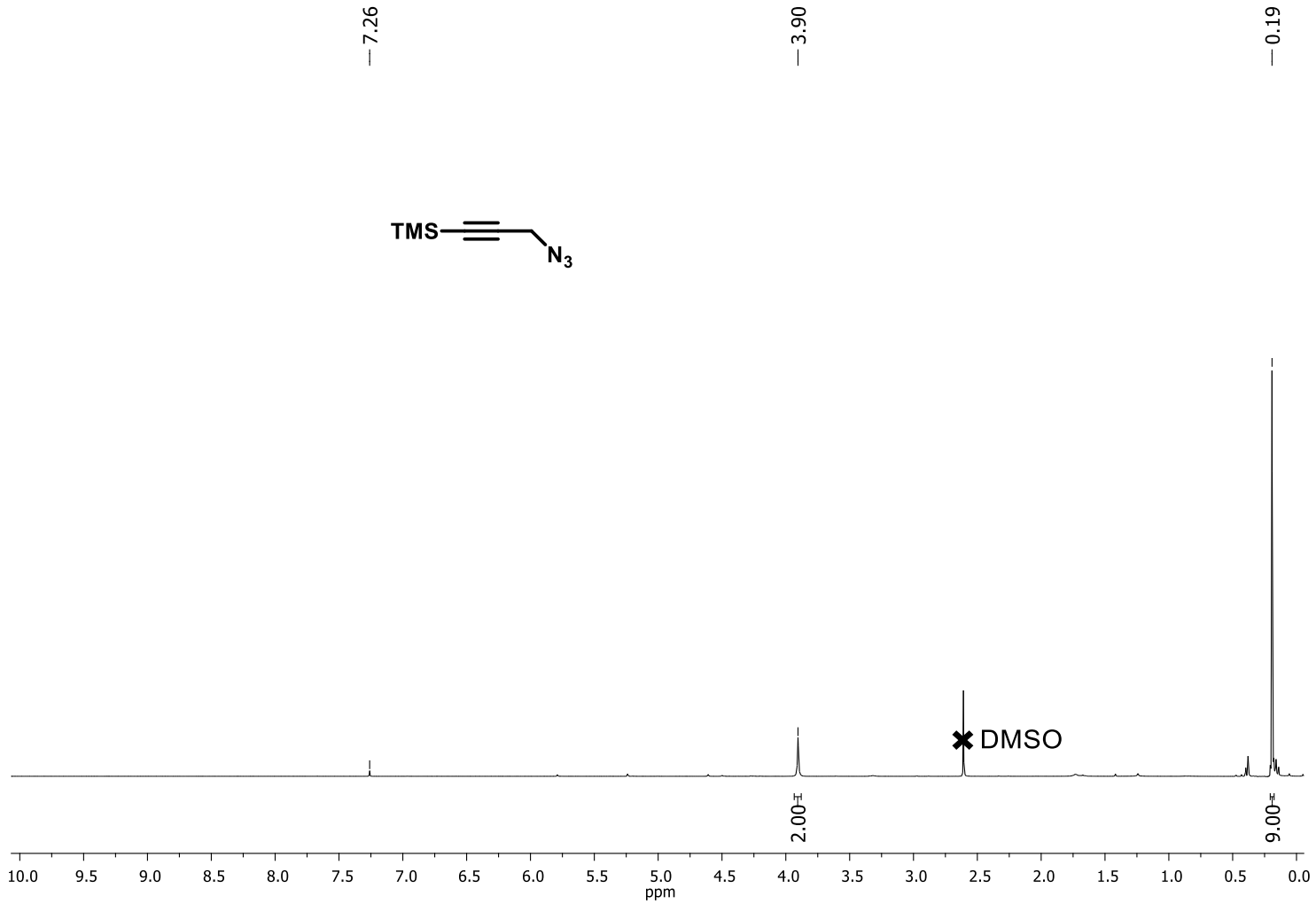
**Molecule 3g - $^{1}H$ NMR (250 MHz, $CDCl_3$)**



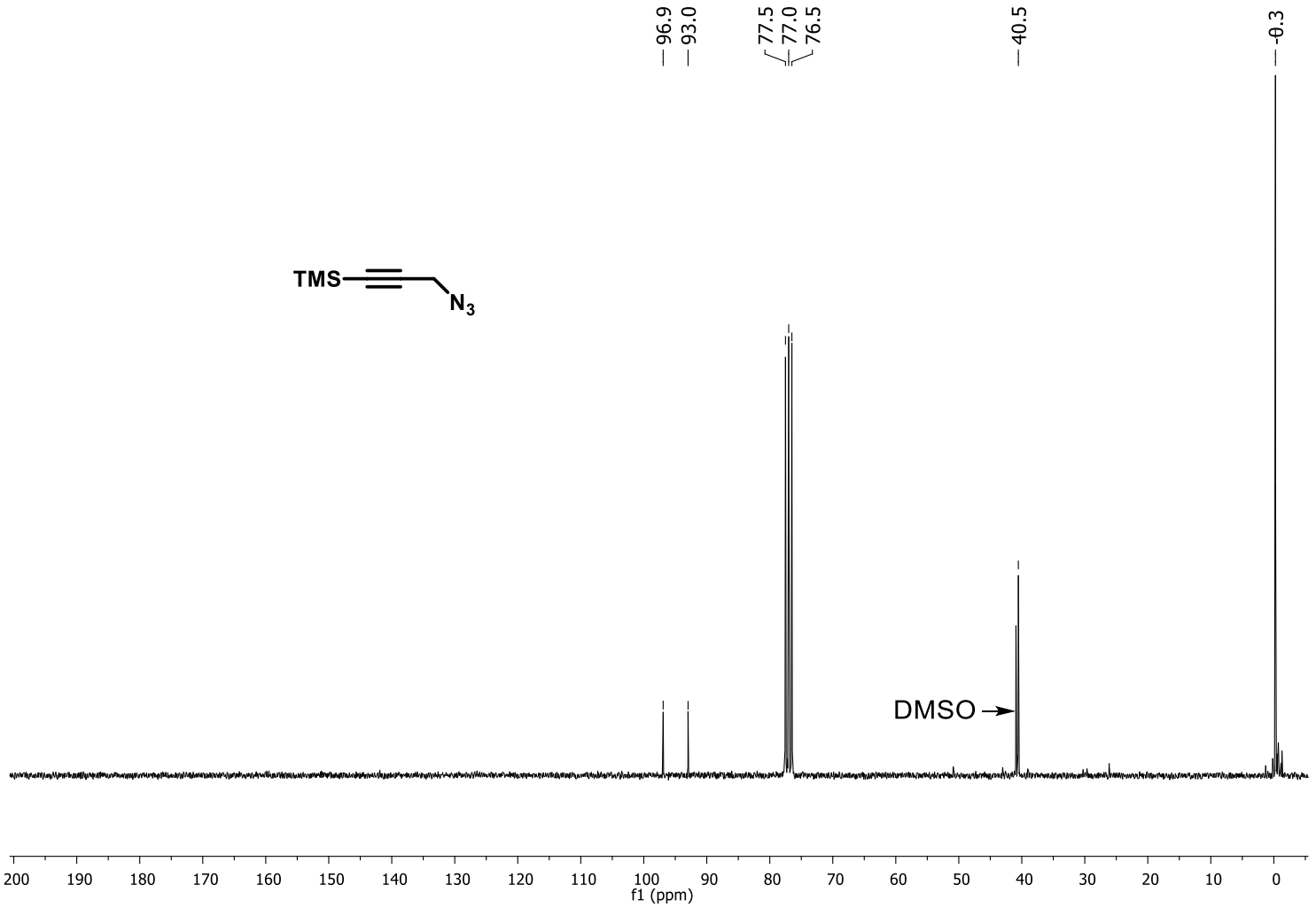
**Molecule 3g - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



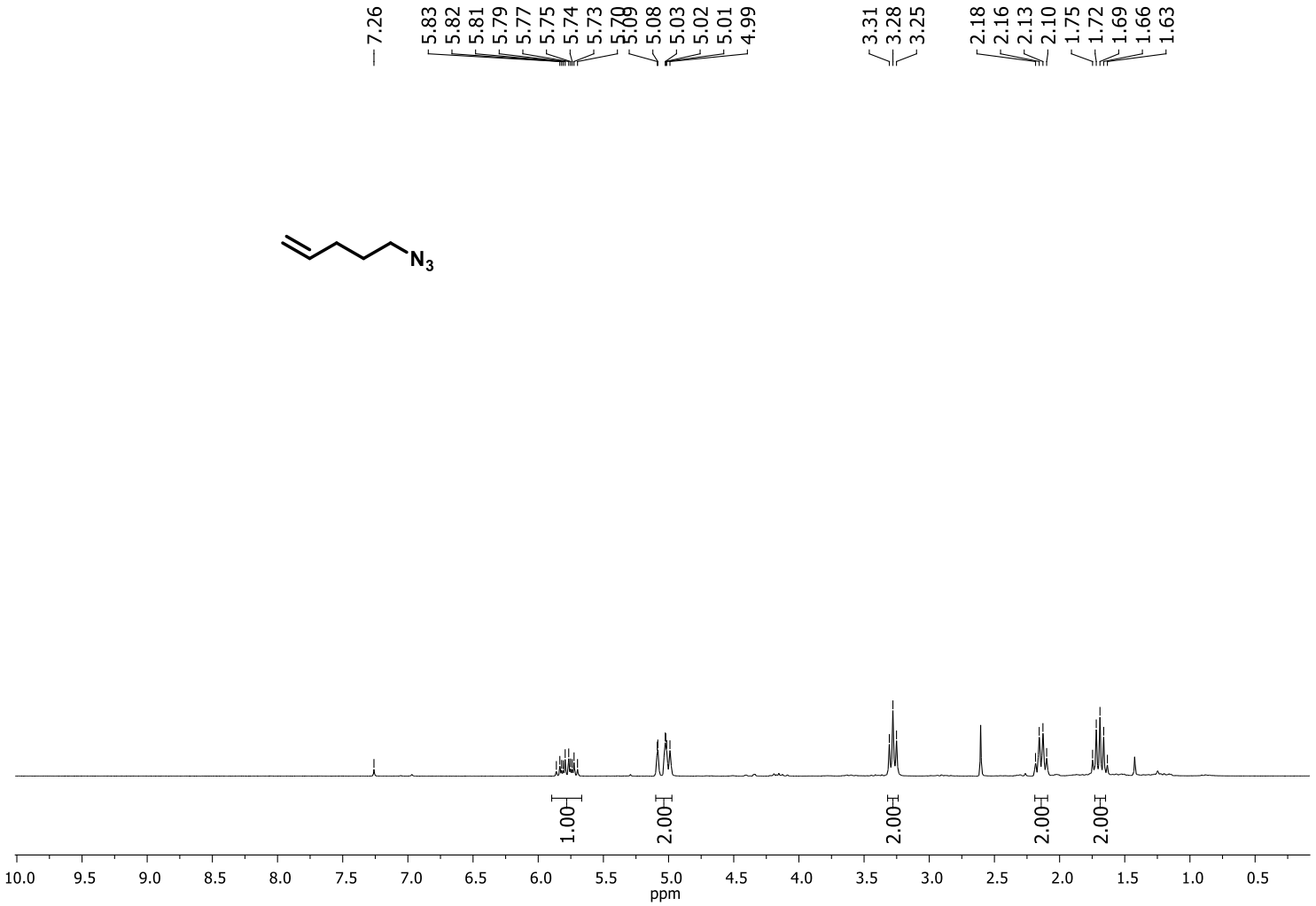
**Molecule 3h - $^{1}$H NMR (250 MHz, $CDCl_3$)**



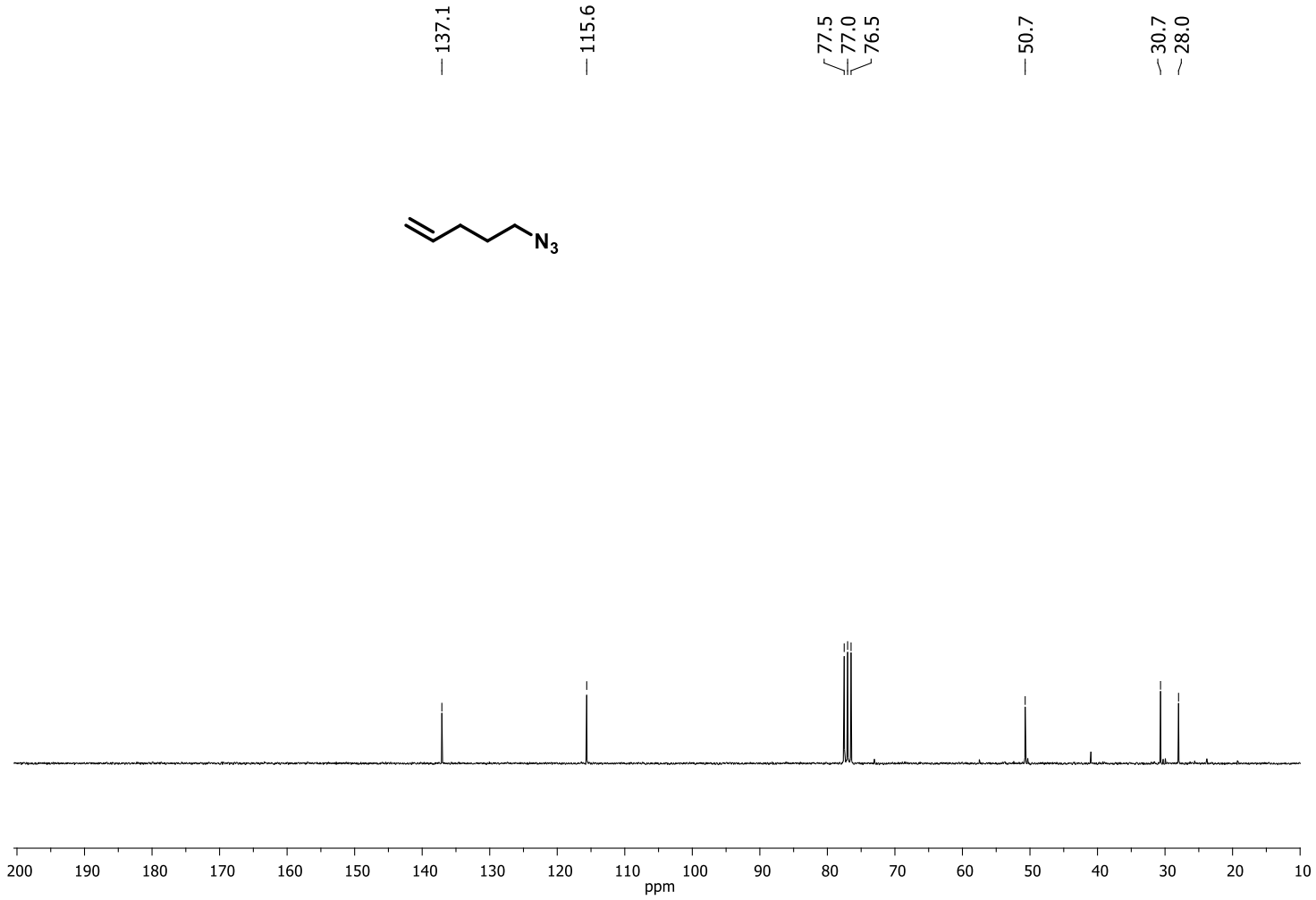
**Molecule 3h - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



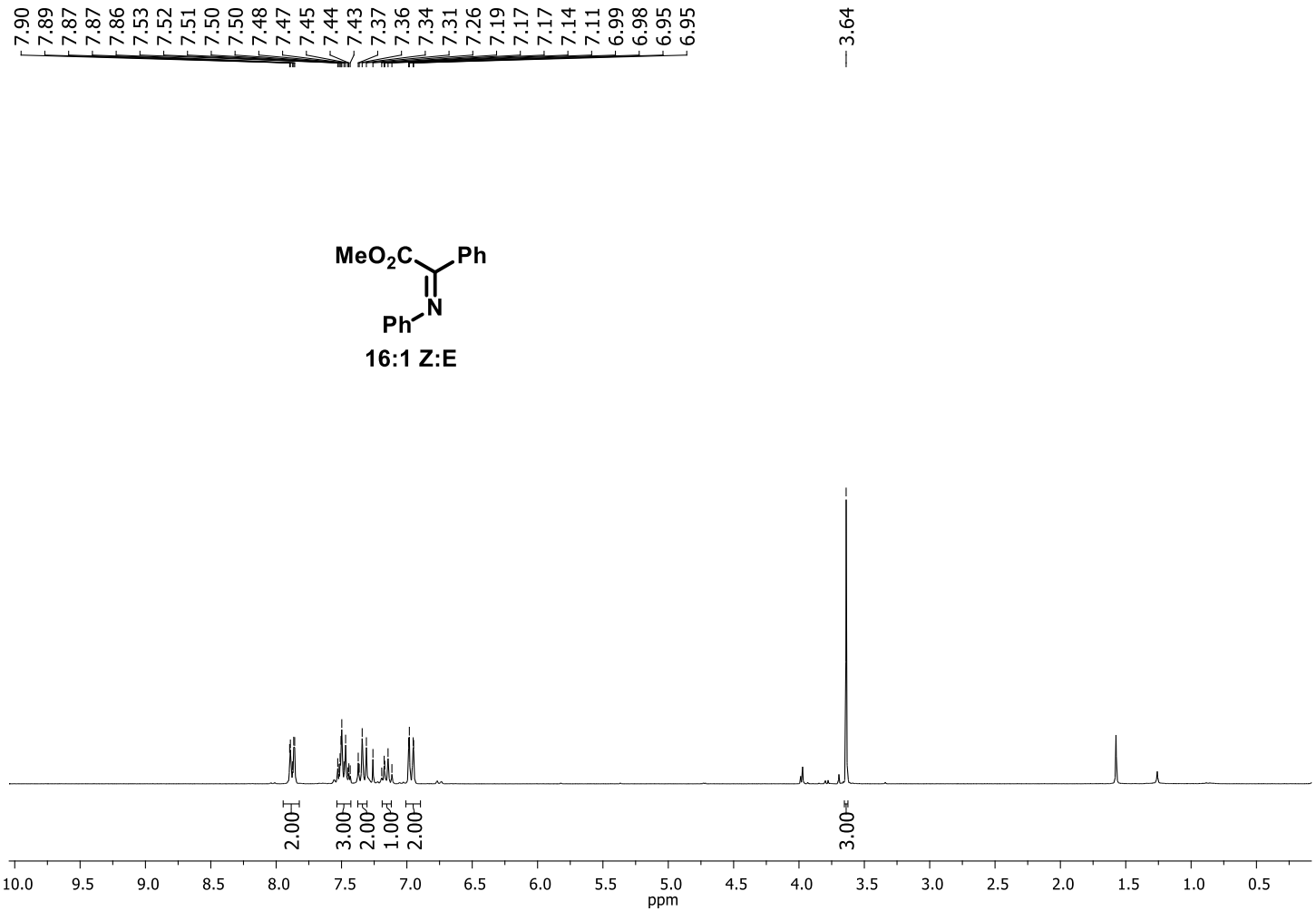
**Molecule 3i - $^{1}$H NMR (250 MHz, $CDCl_3$)**



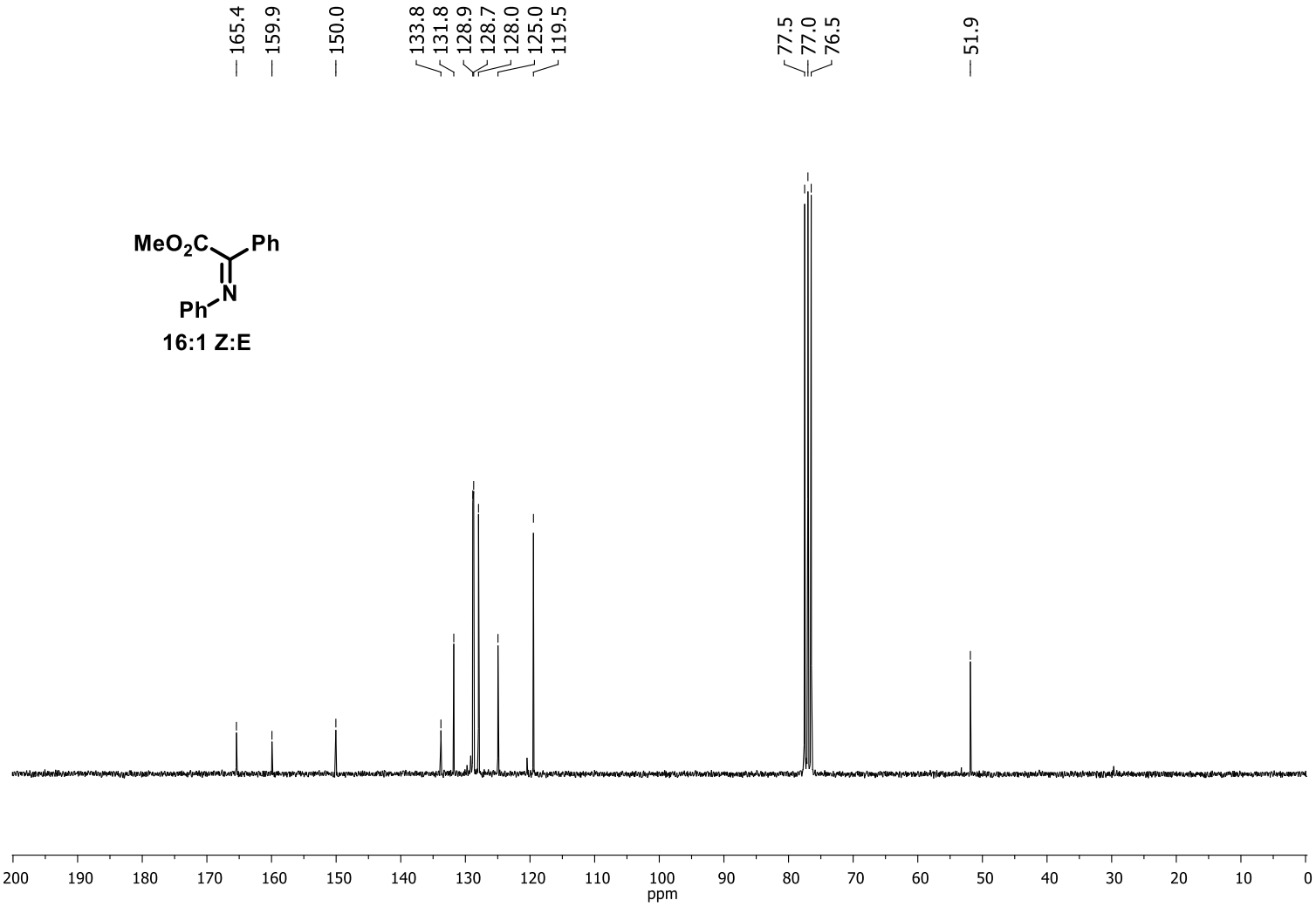
**Molecule 3i - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



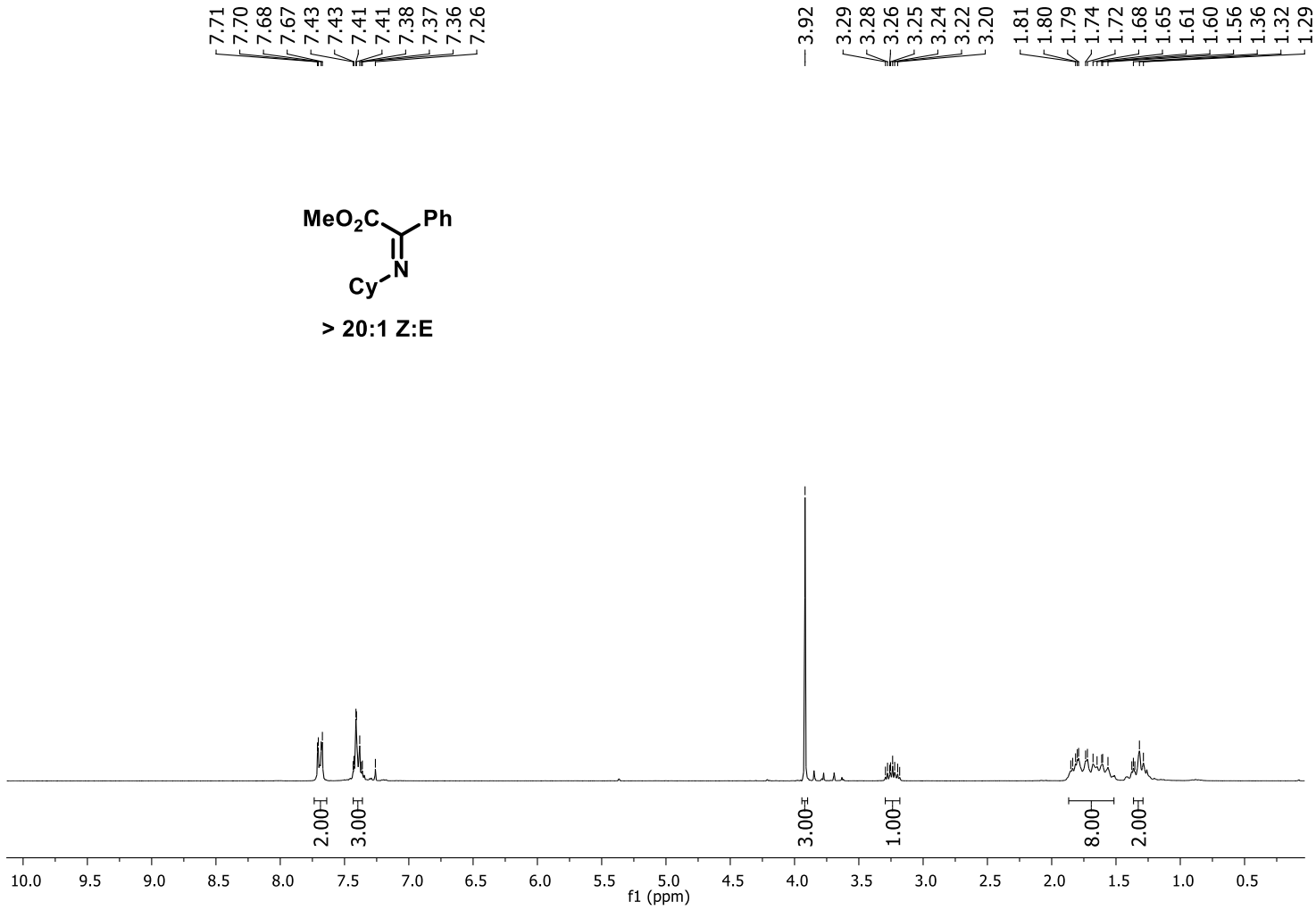
**Molecule 4a - $^{1}$H NMR (250 MHz, $CDCl_3$)**



**Molecule 4a - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**

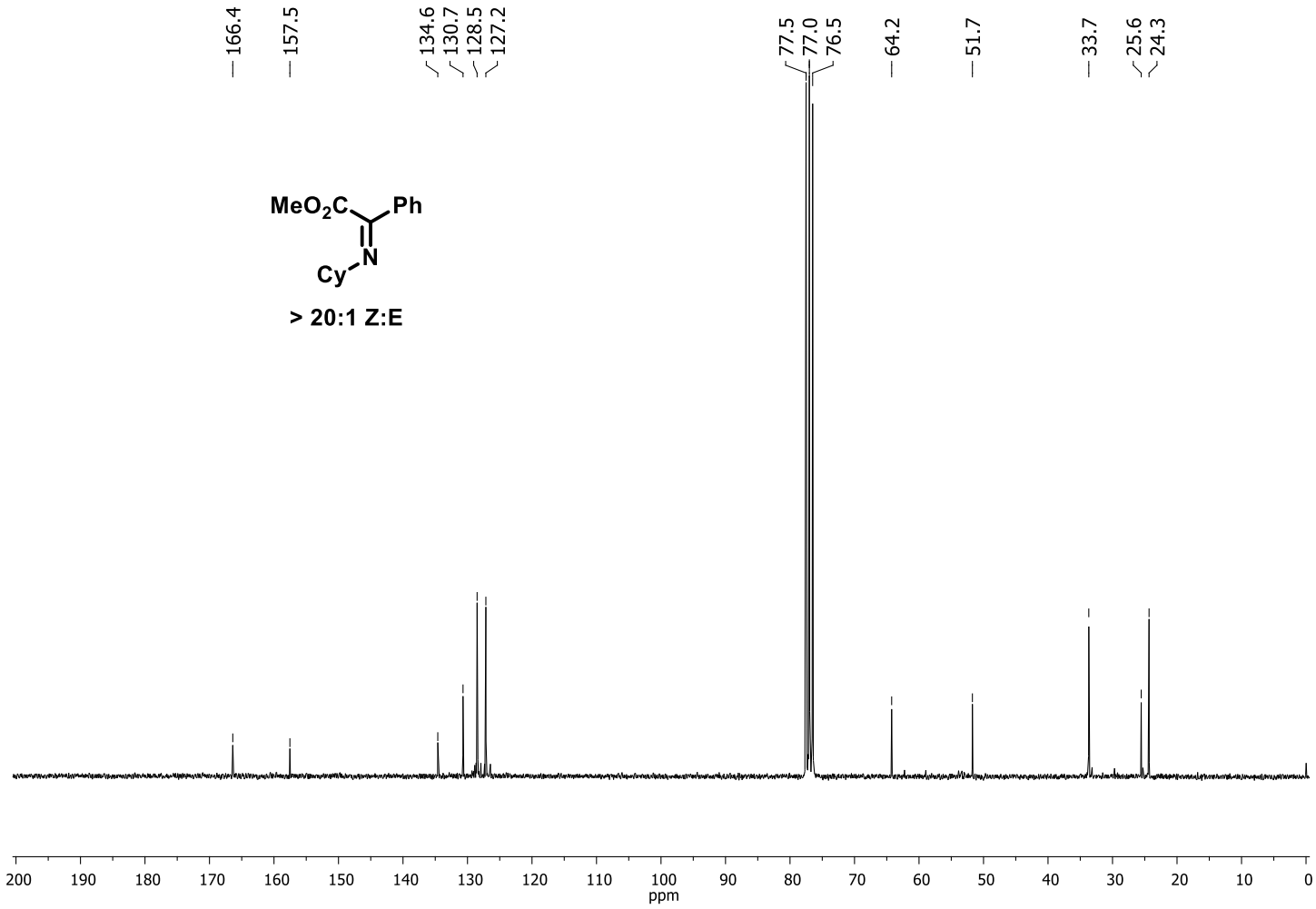


**Molecule 4b - $^{1}$H NMR (250 MHz, $CDCl_3$)**

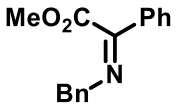



**> 20:1 Z:E**

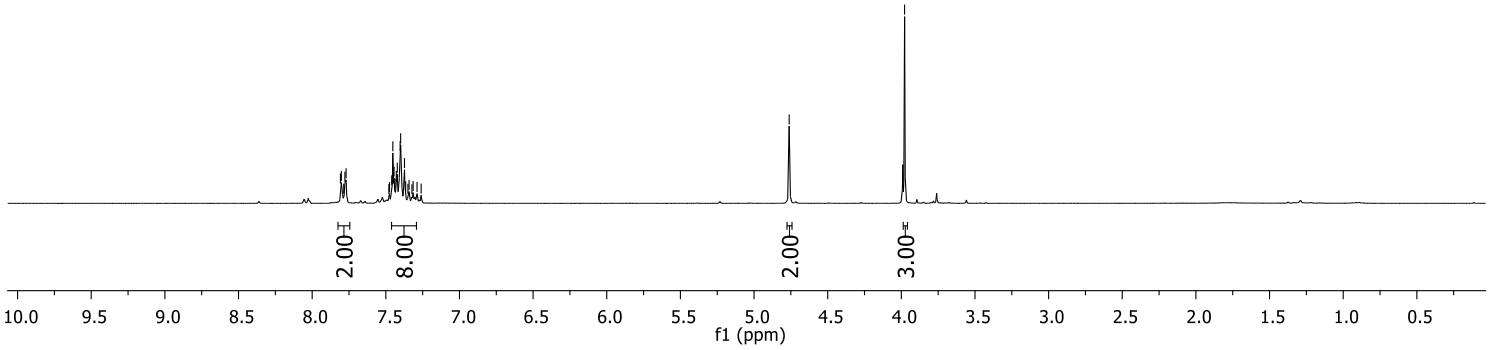
**Molecule 4b - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



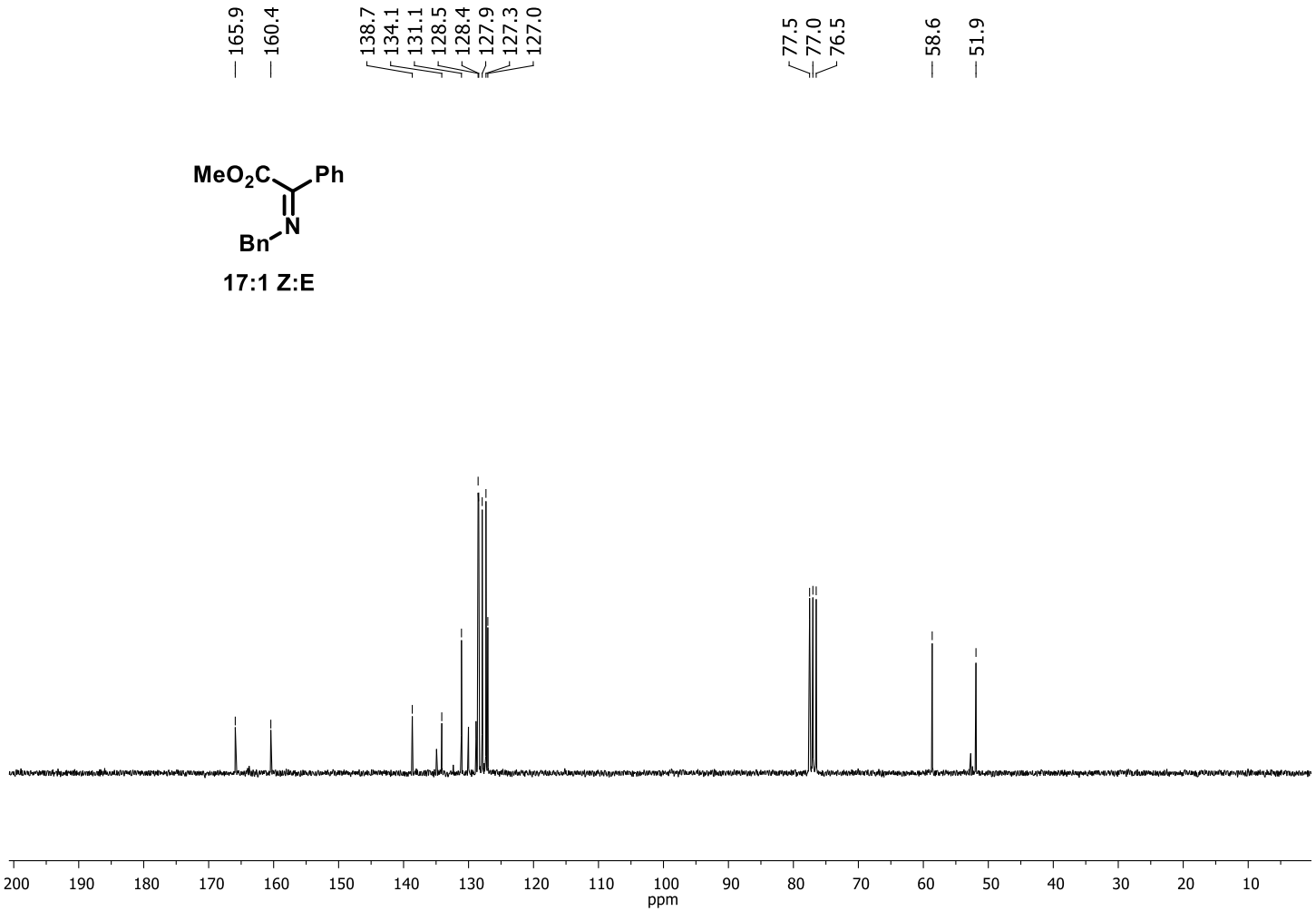
**Molecule 4c - $^{1}$H NMR (250 MHz, $CDCl_3$)**

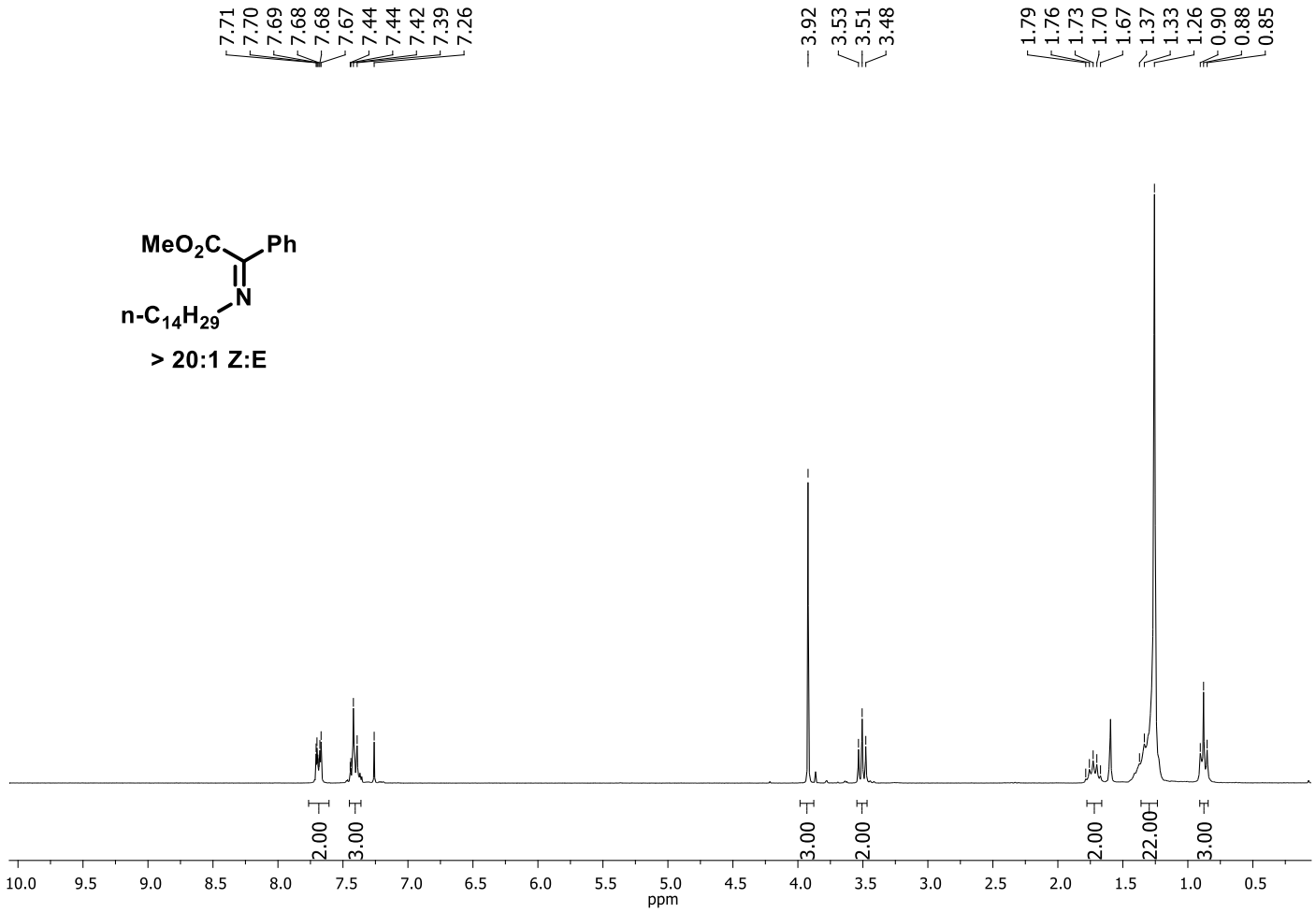

**17:1 Z:E**



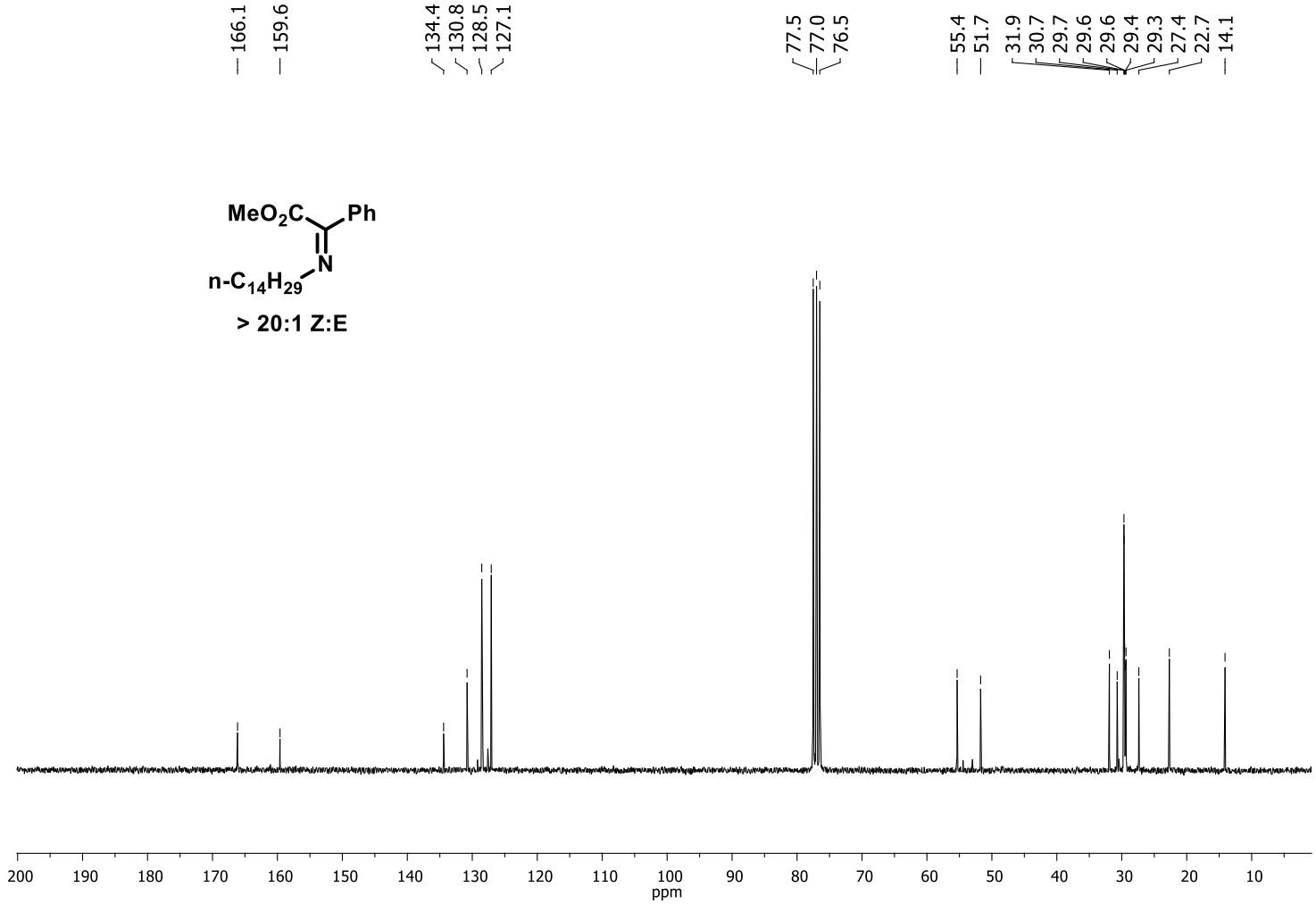
**Molecule 4c - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



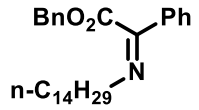
**Molecule 4d - $^{1}$H NMR (250 MHz, $CDCl_3$)**



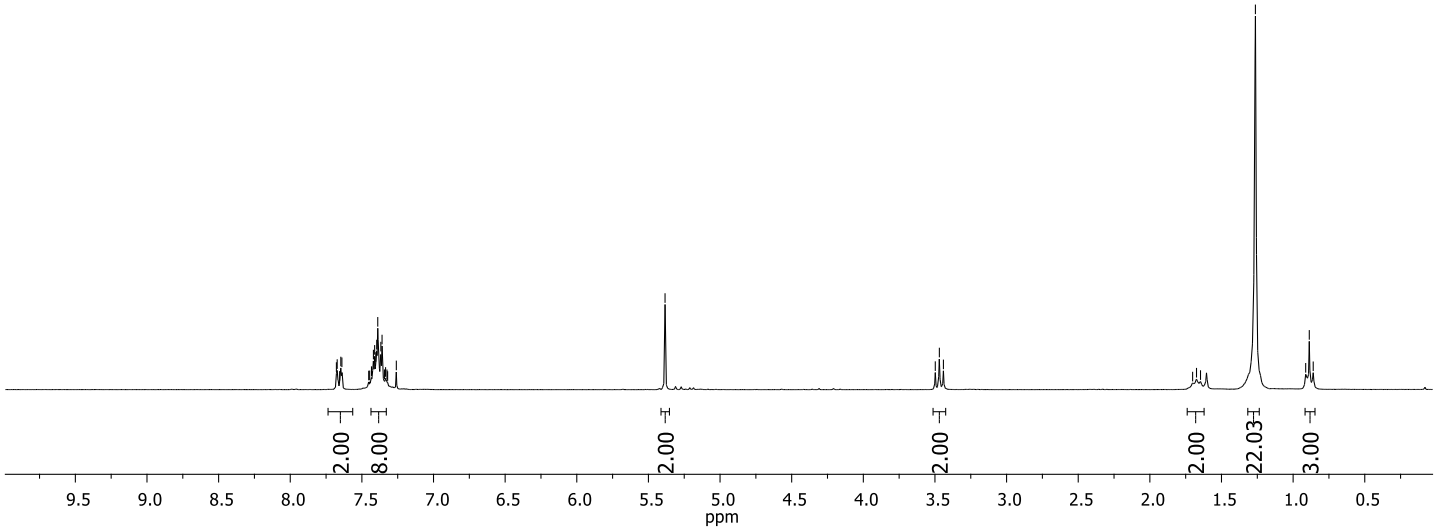
**Molecule 4d - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



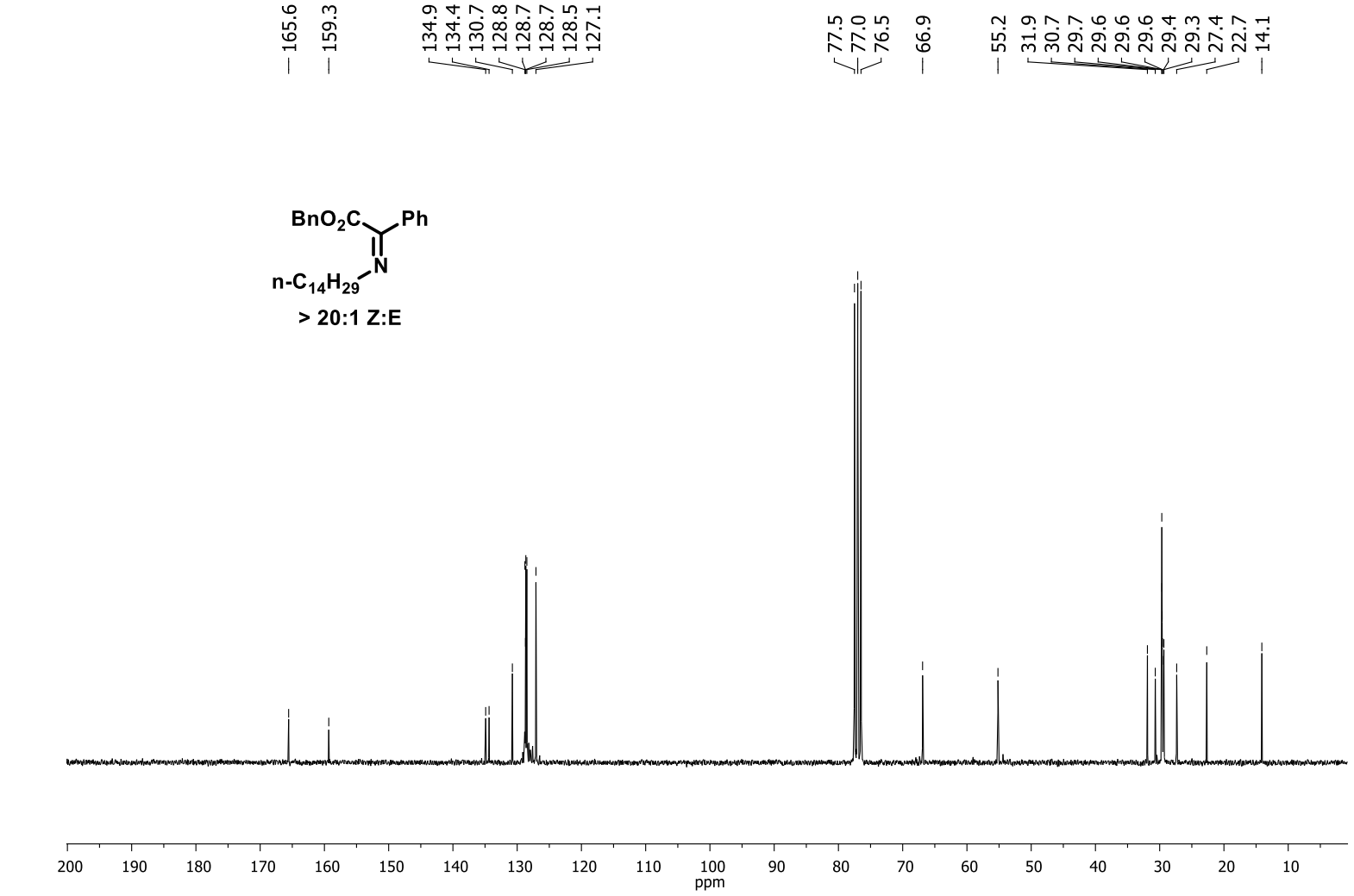
**Molecule 4e - $^{1}$H NMR (250 MHz, $CDCl_3$)**

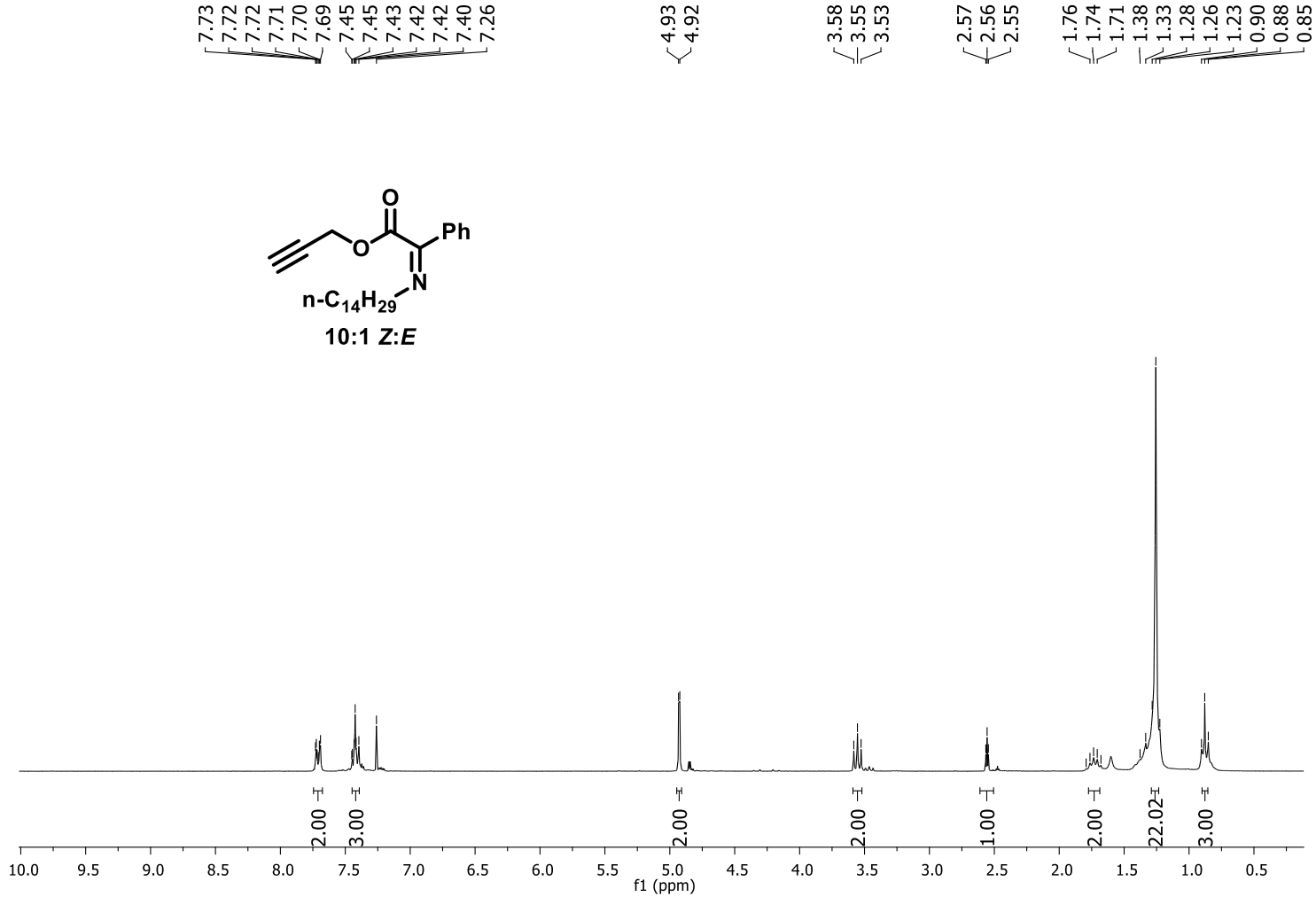

**> 20:1 Z:E**



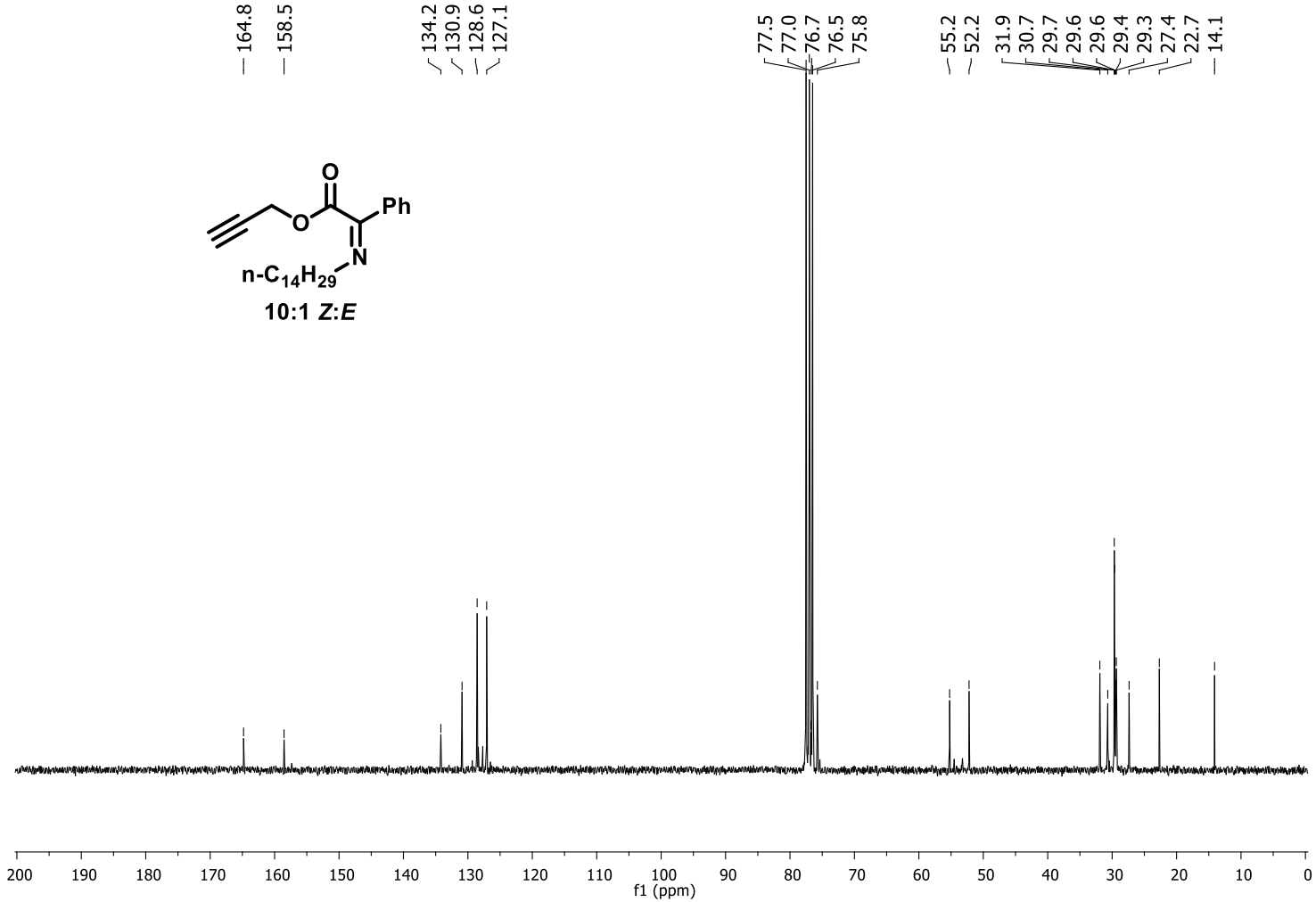
**Molecule 4e - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



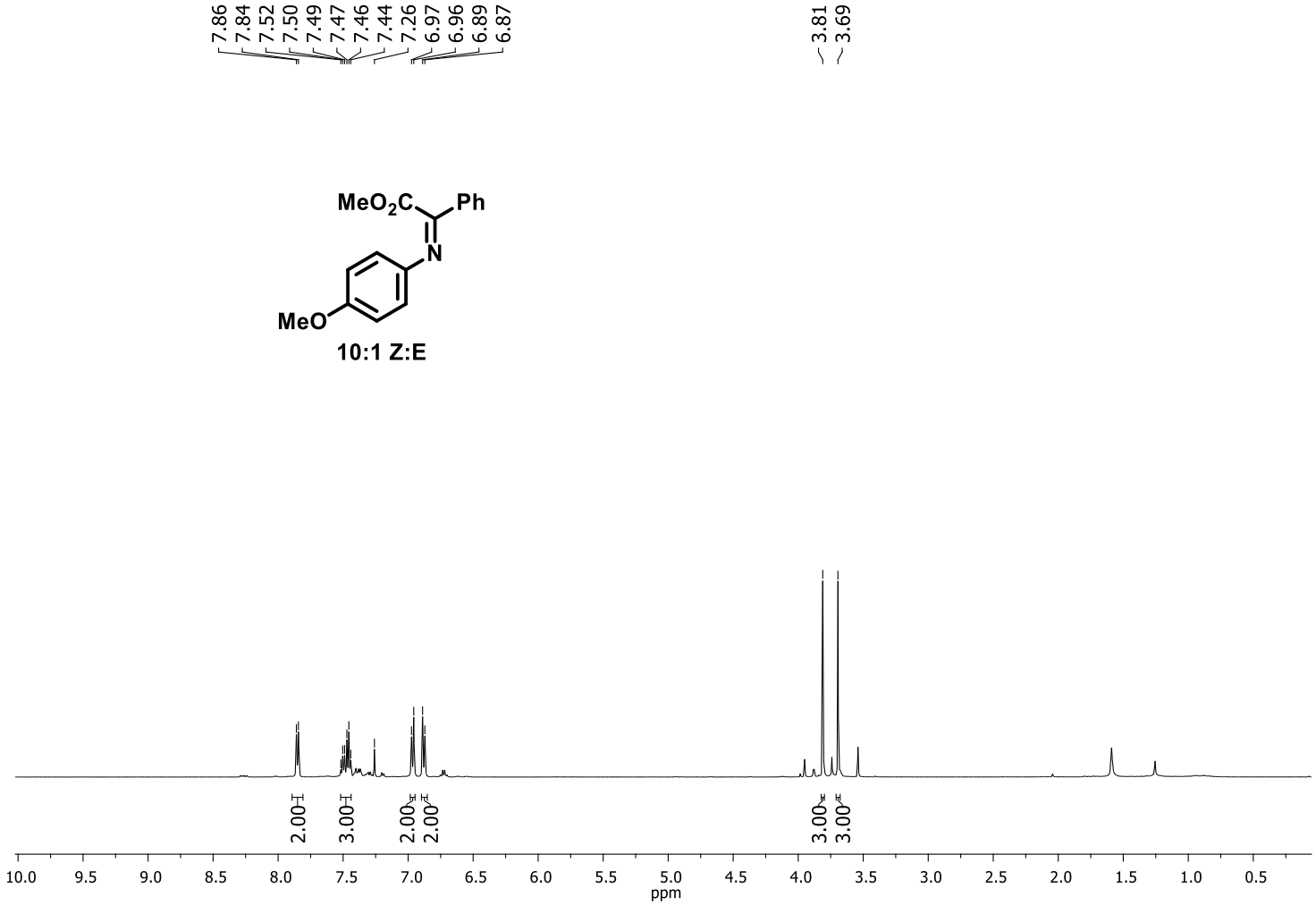
**Molecule 4f - $^{1}$H NMR (250 MHz, $CDCl_3$)**



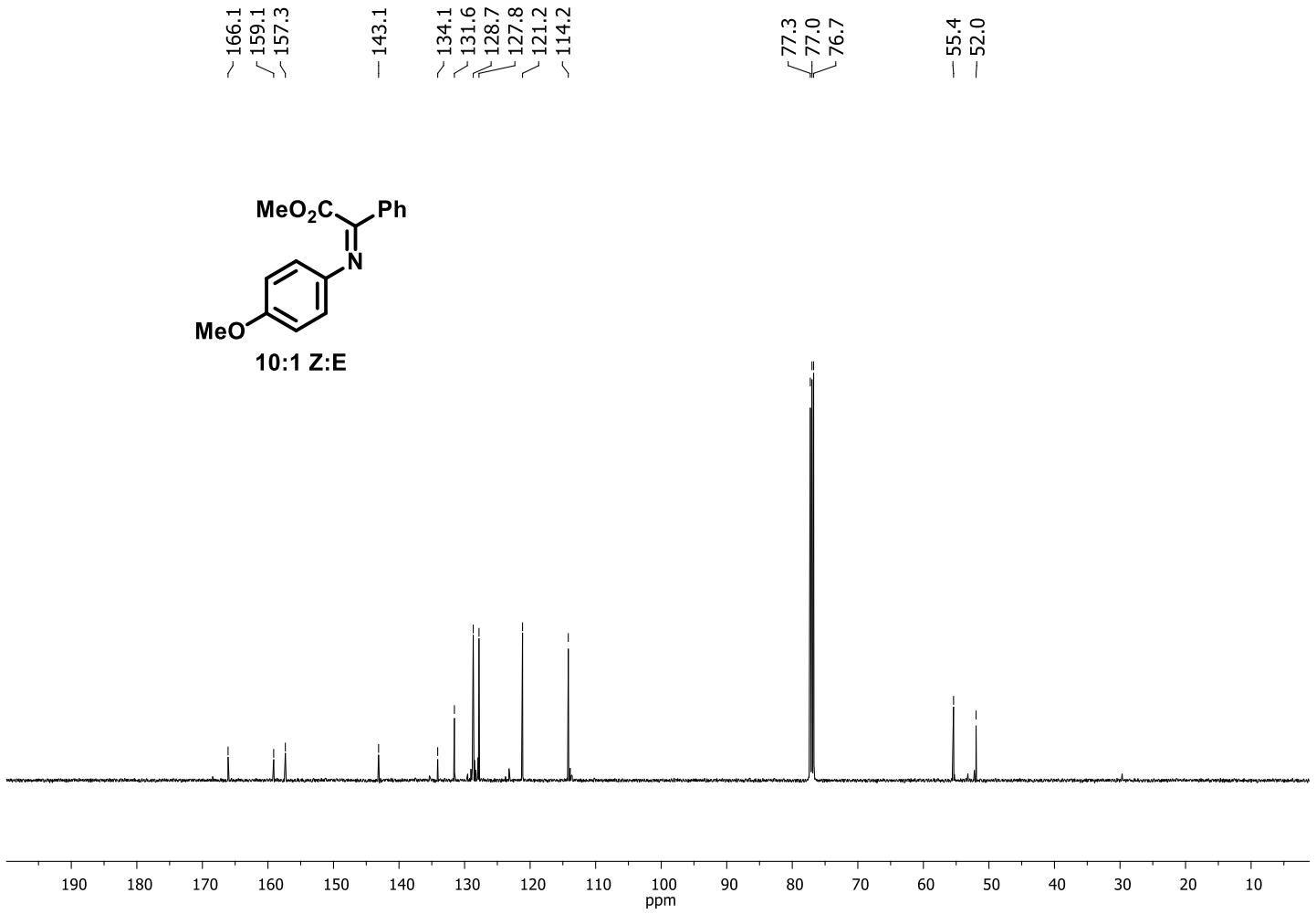
**Molecule 4f - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



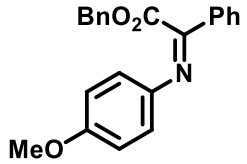
**Molecule 4g - $^{1}$H NMR (500 MHz, $CDCl_3$)**



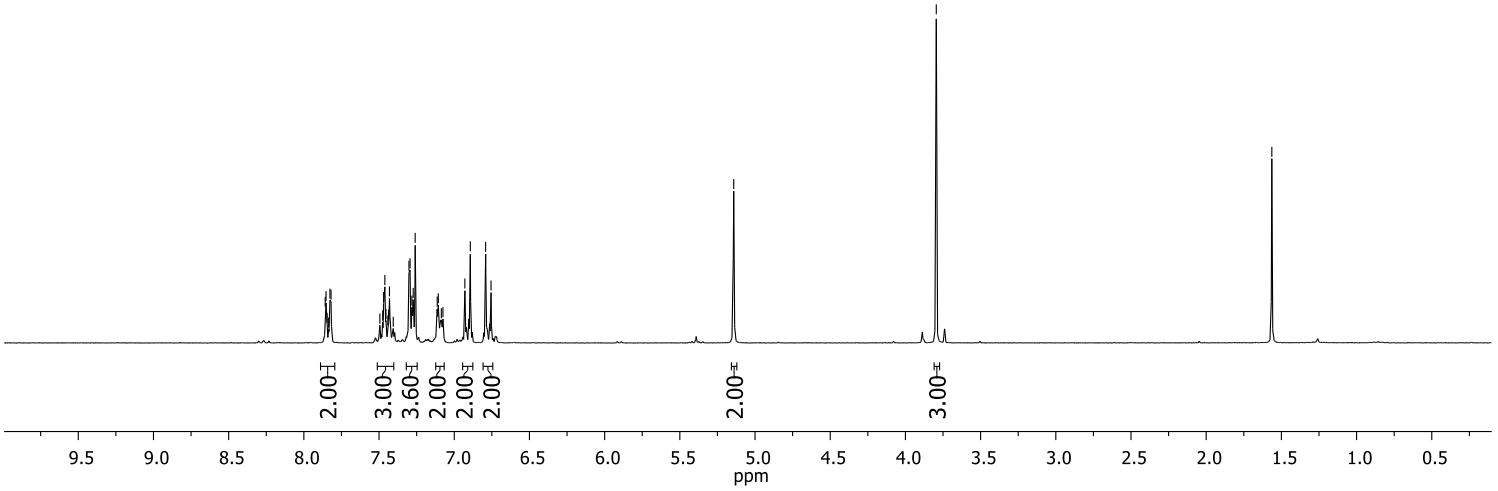
**Molecule 4g - $^{13}C$ NMR (125 MHz, $CDCl_3$)**



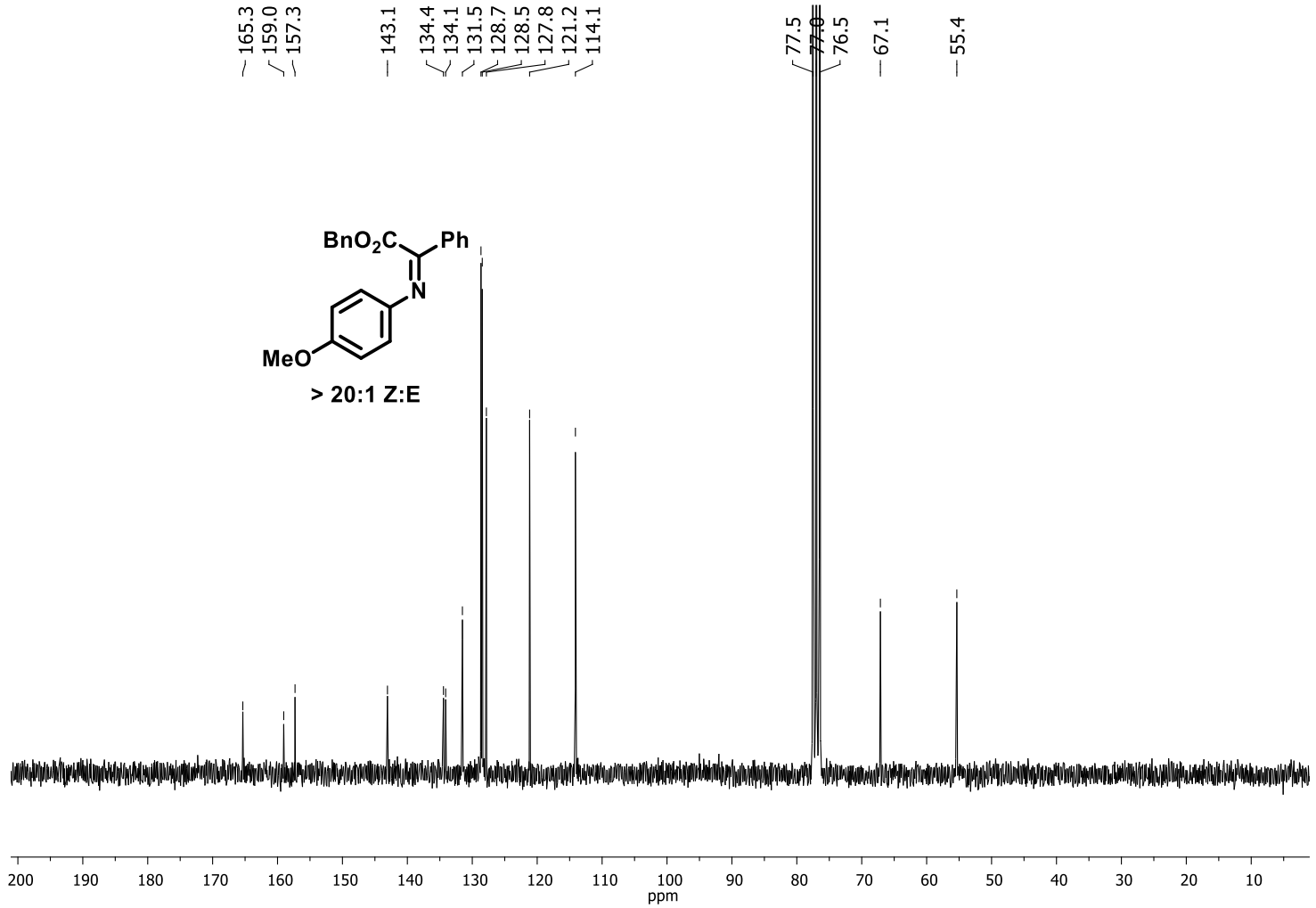
**Molecule 4h - $^{1}$H NMR (250 MHz, $CDCl_3$)**

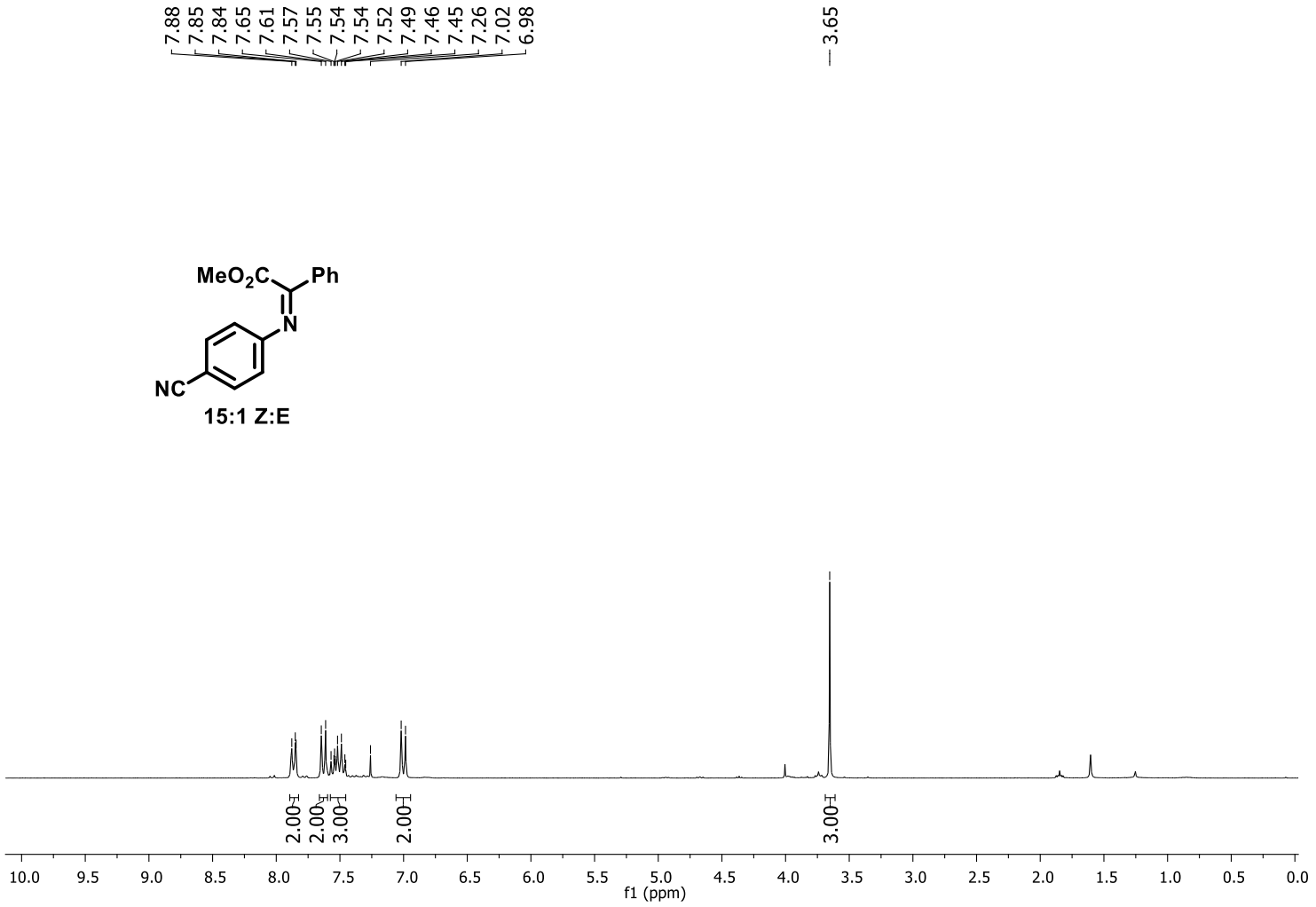

**> 20:1 Z:E**



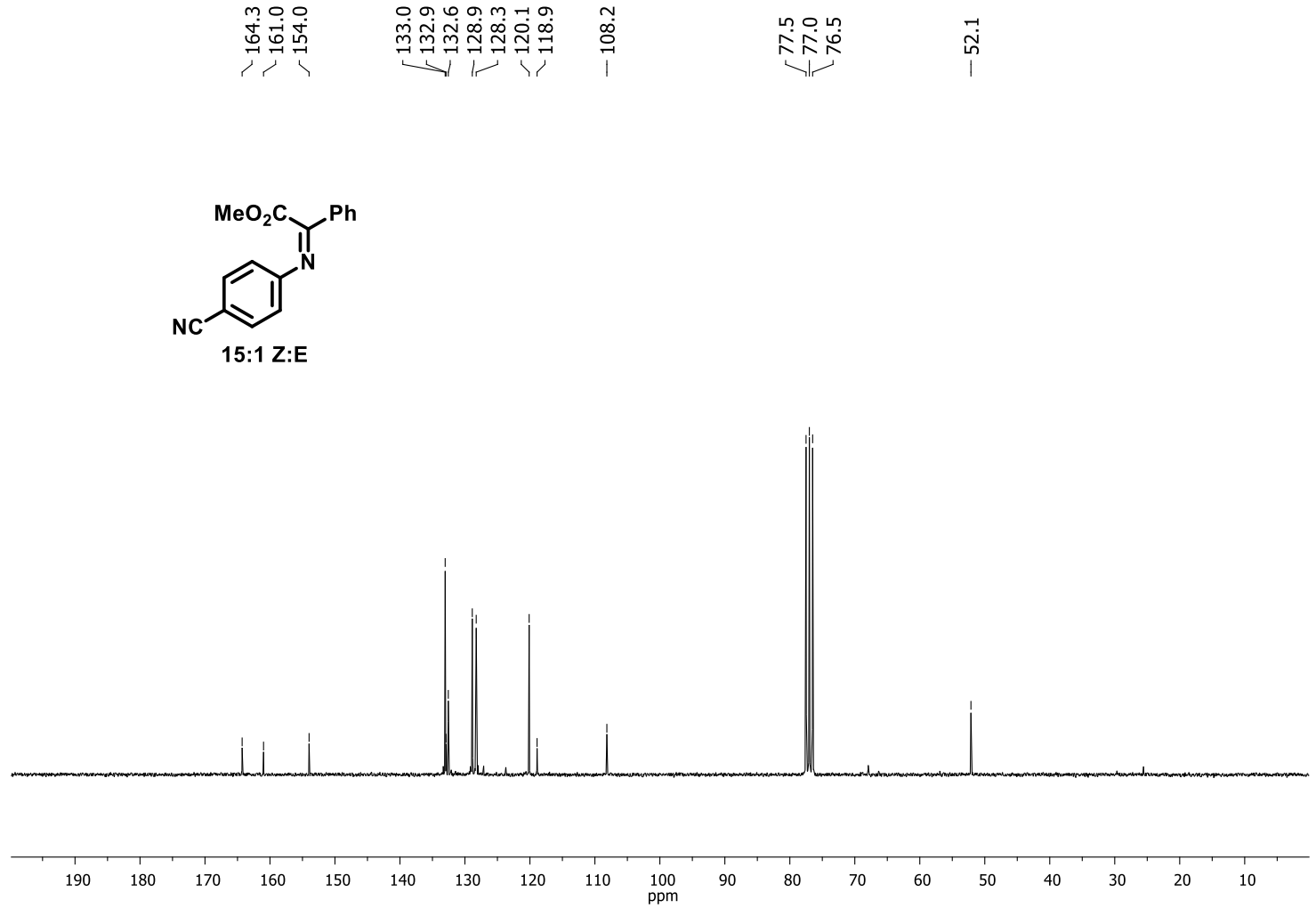
**Molecule 4h - $^{13}C$ NMR (125 MHz, $CDCl_3$)**



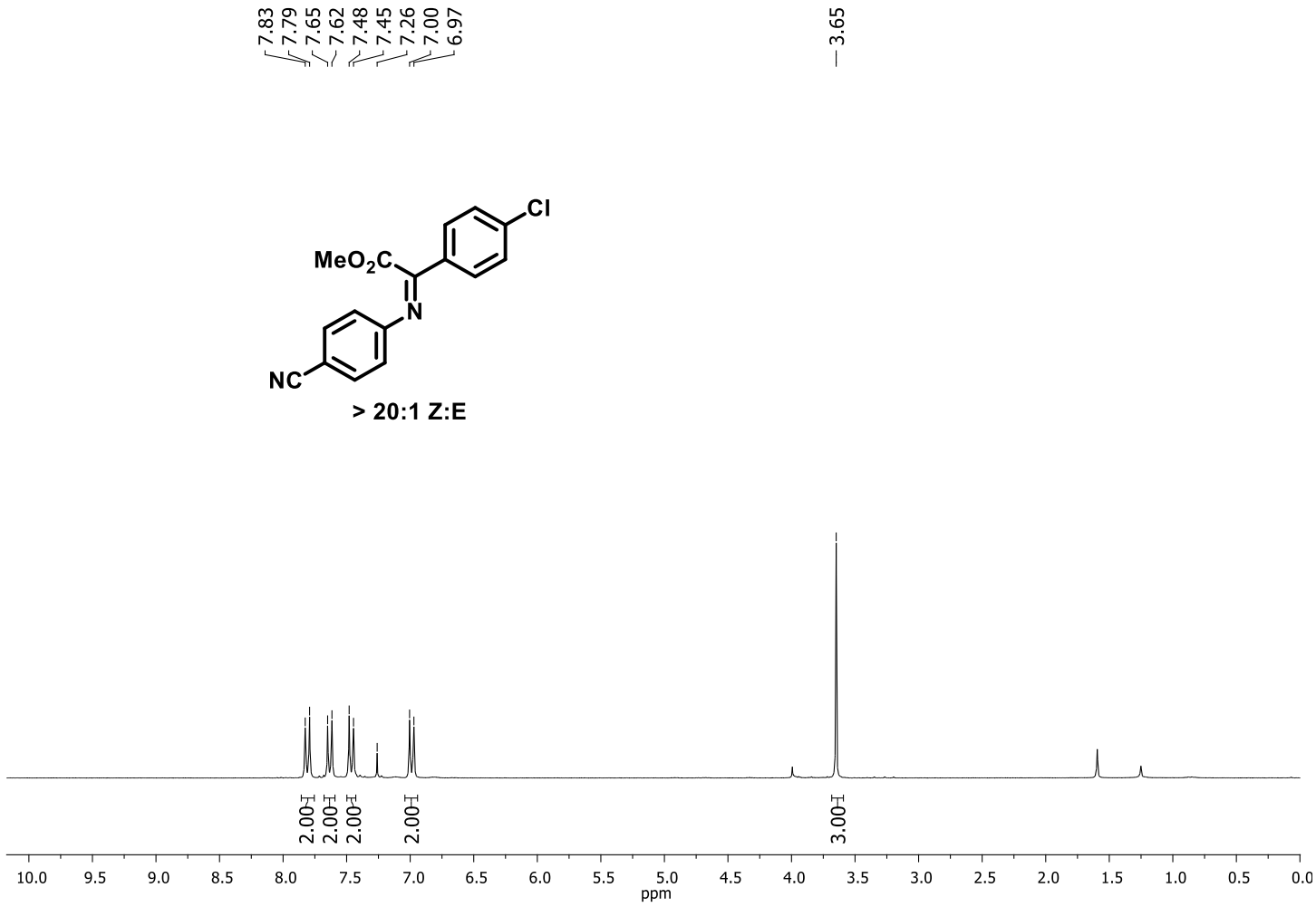
**Molecule 4i - $^{1}$H NMR (250 MHz, $CDCl_3$)**



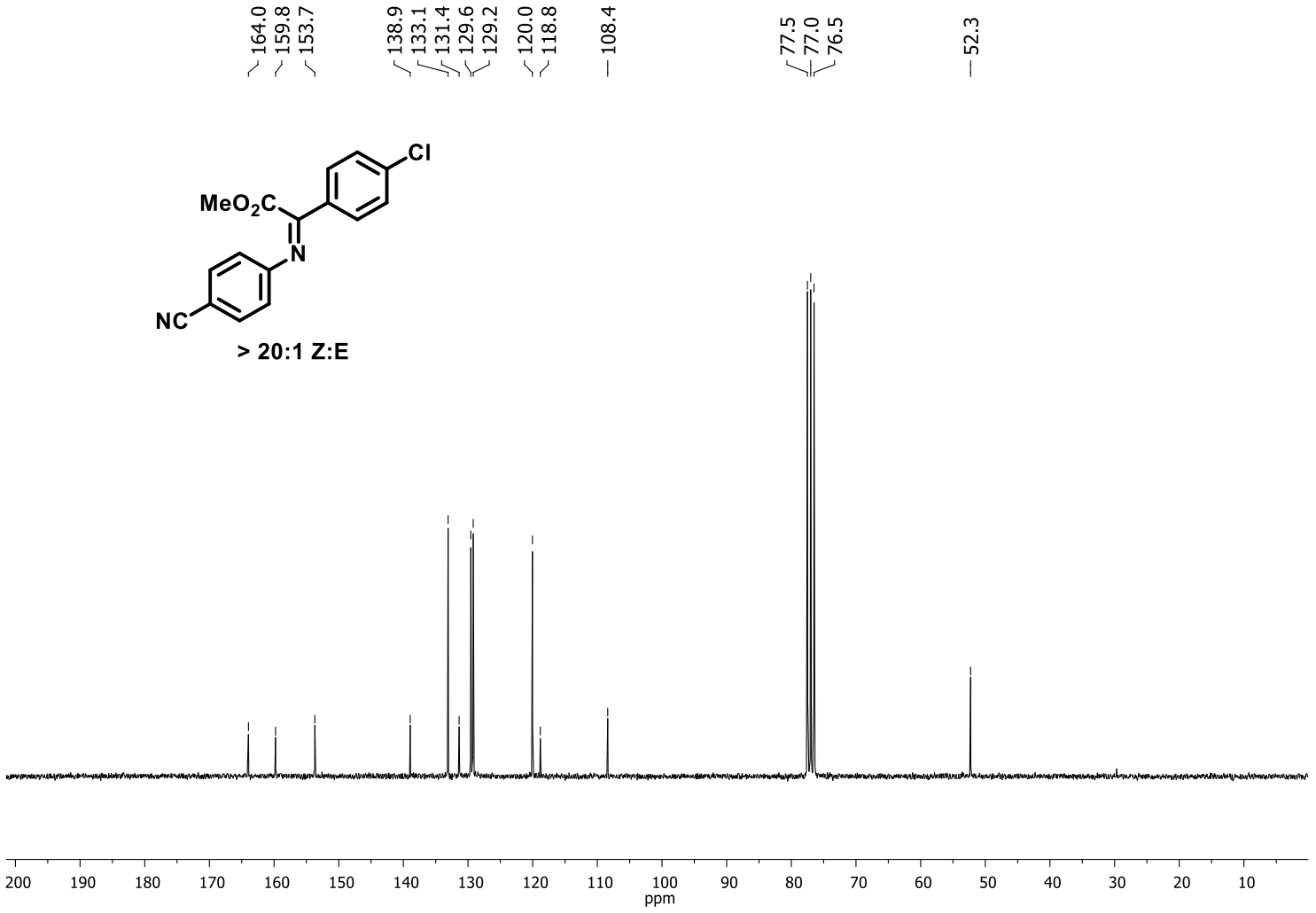
**Molecule 4i - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



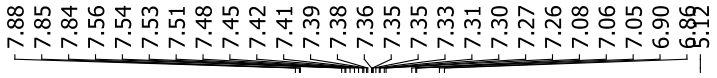
**Molecule 4j - $^{1}$H NMR (250 MHz, $CDCl_3$)**

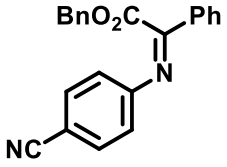


**Molecule 4j - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**

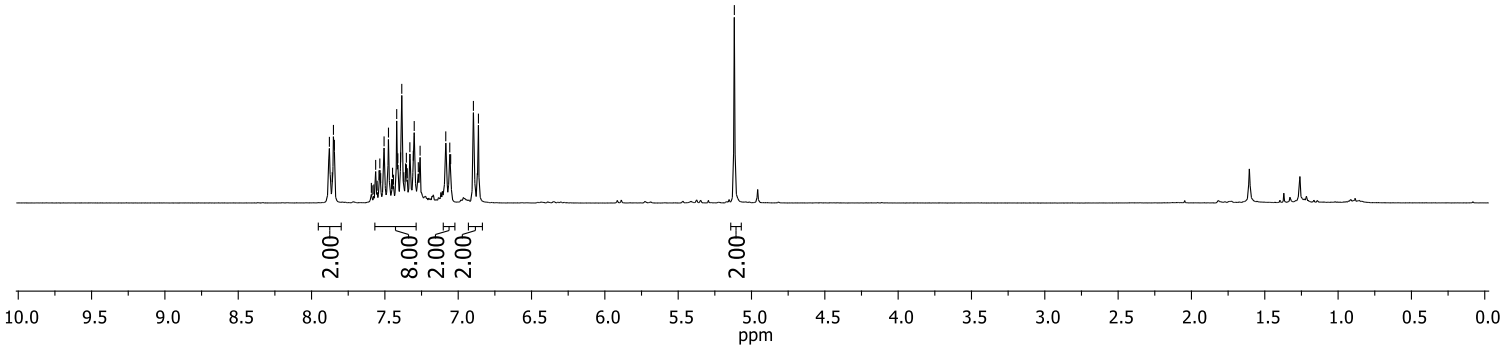


**Molecule 4k - $^{1}$H NMR (250 MHz, $CDCl_3$)**

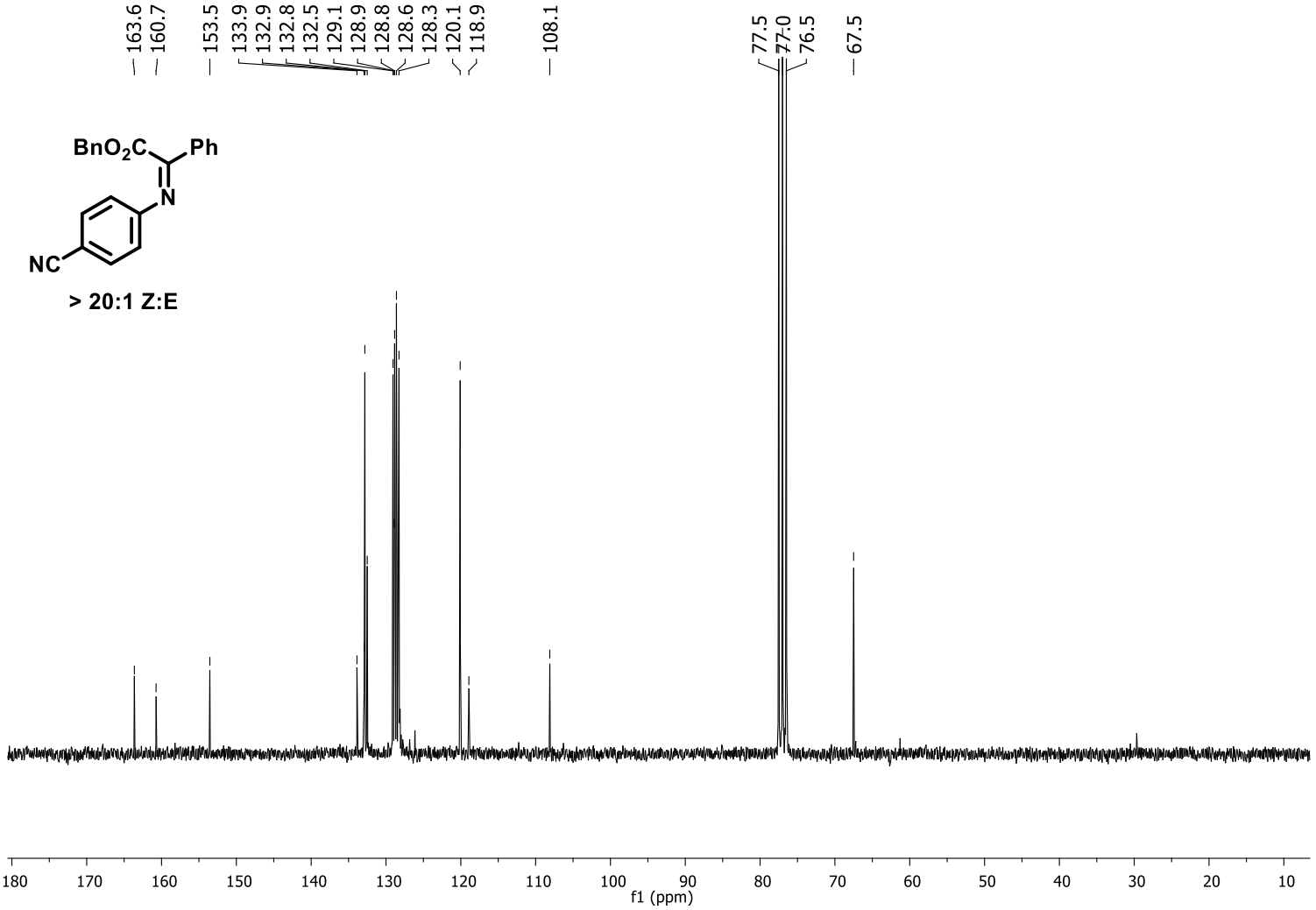


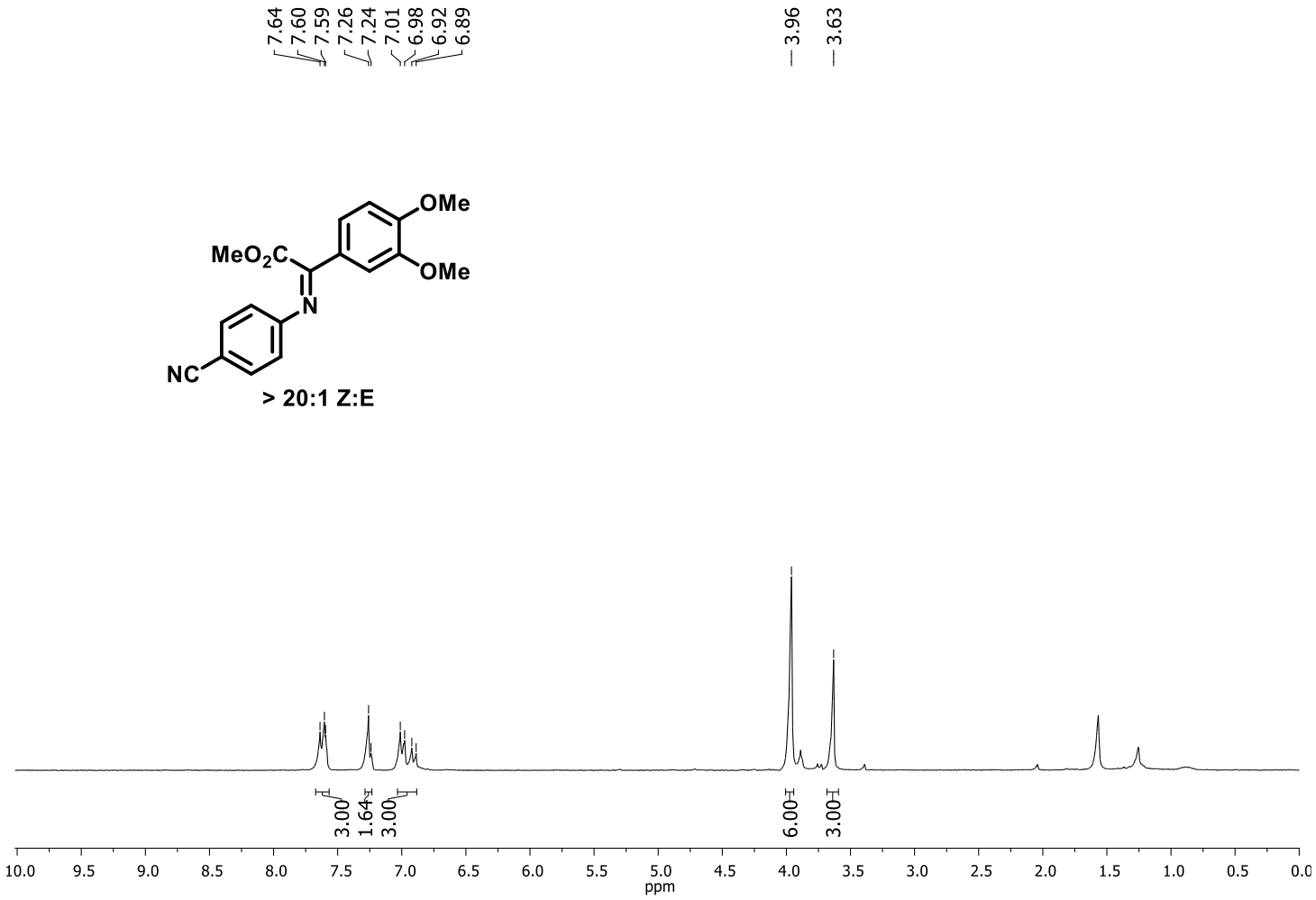

**> 20:1 Z:E**



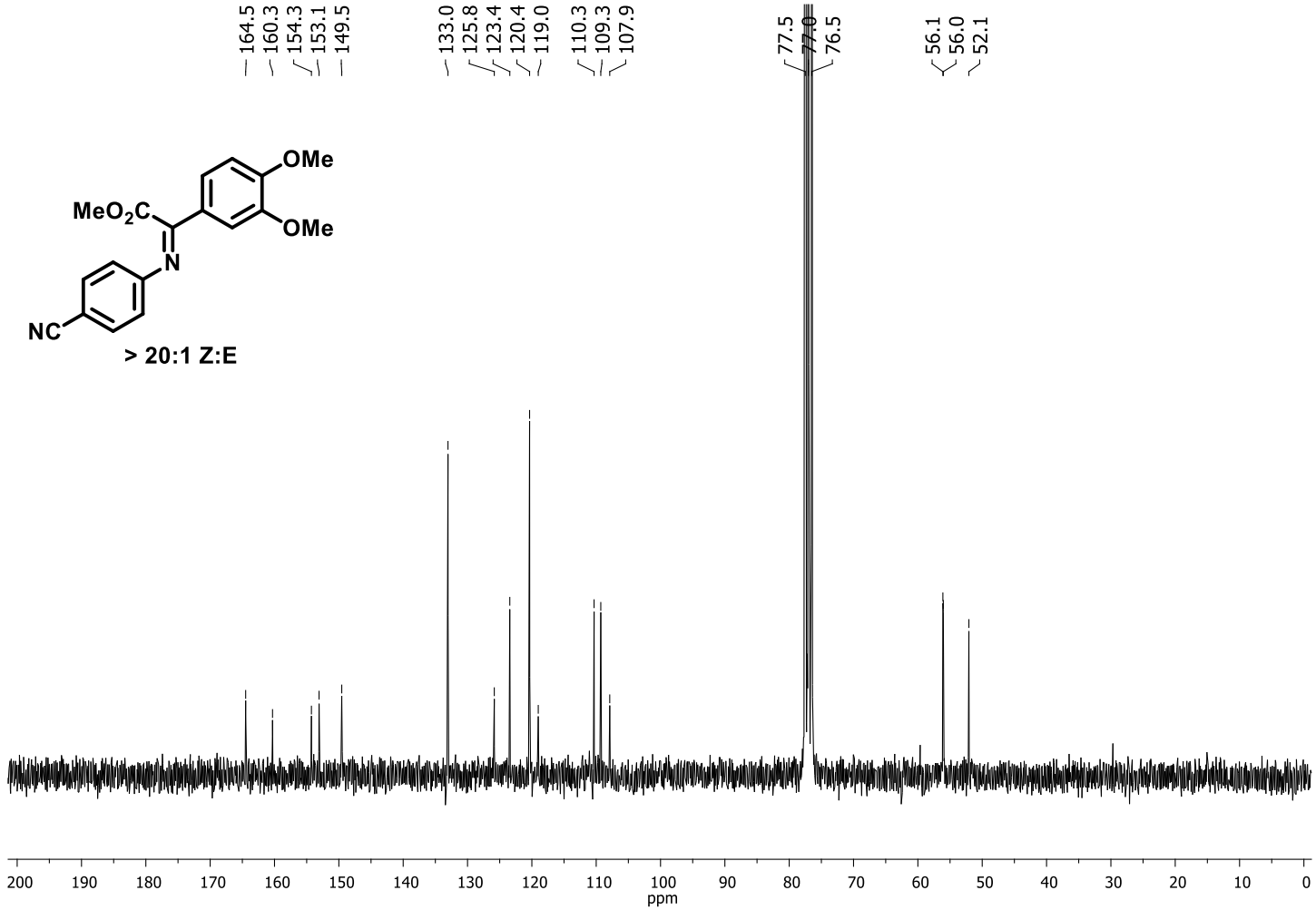
**Molecule 4k - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



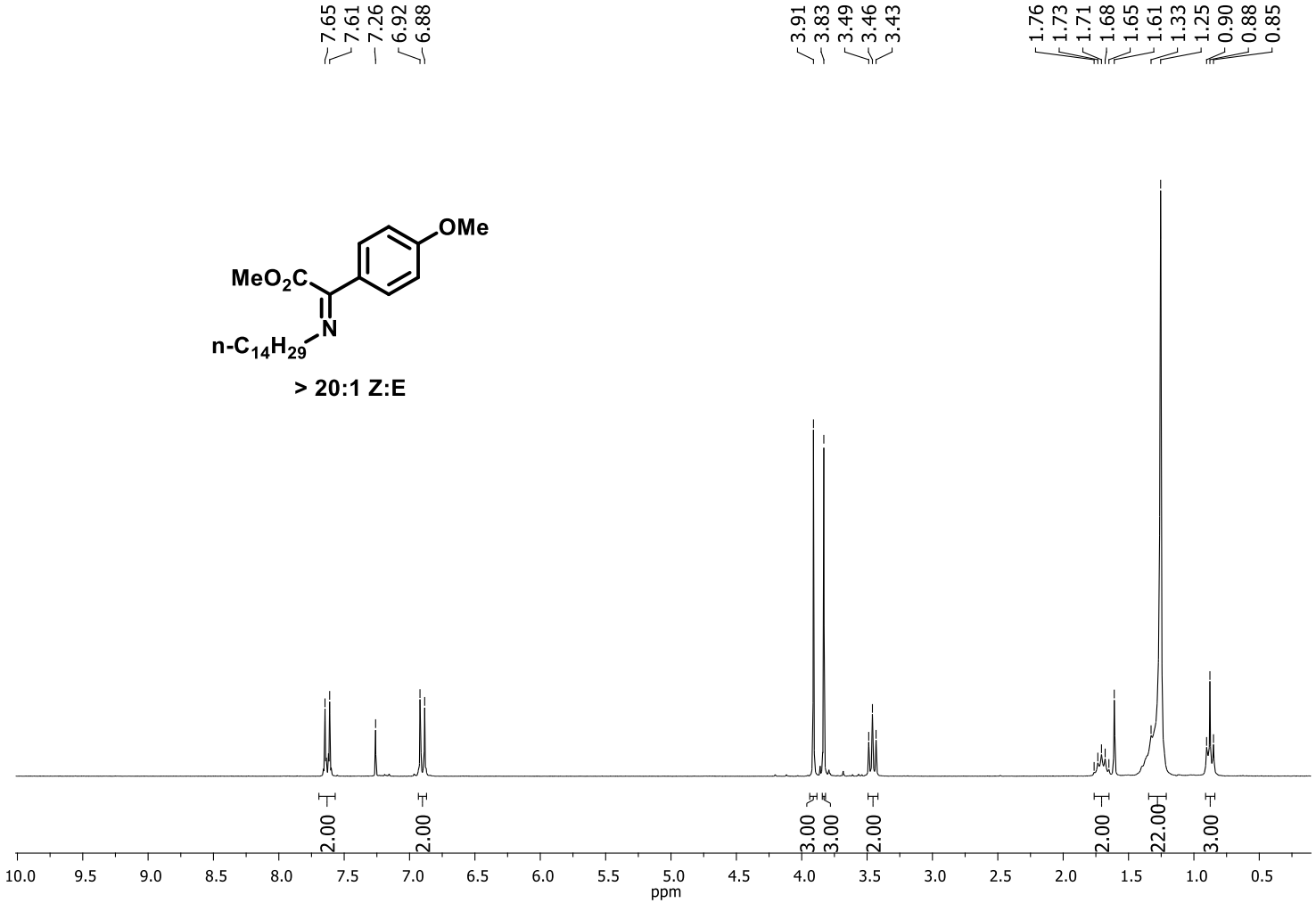
**Molecule 4l - $^{1}$H NMR (250 MHz, $CDCl_3$)**



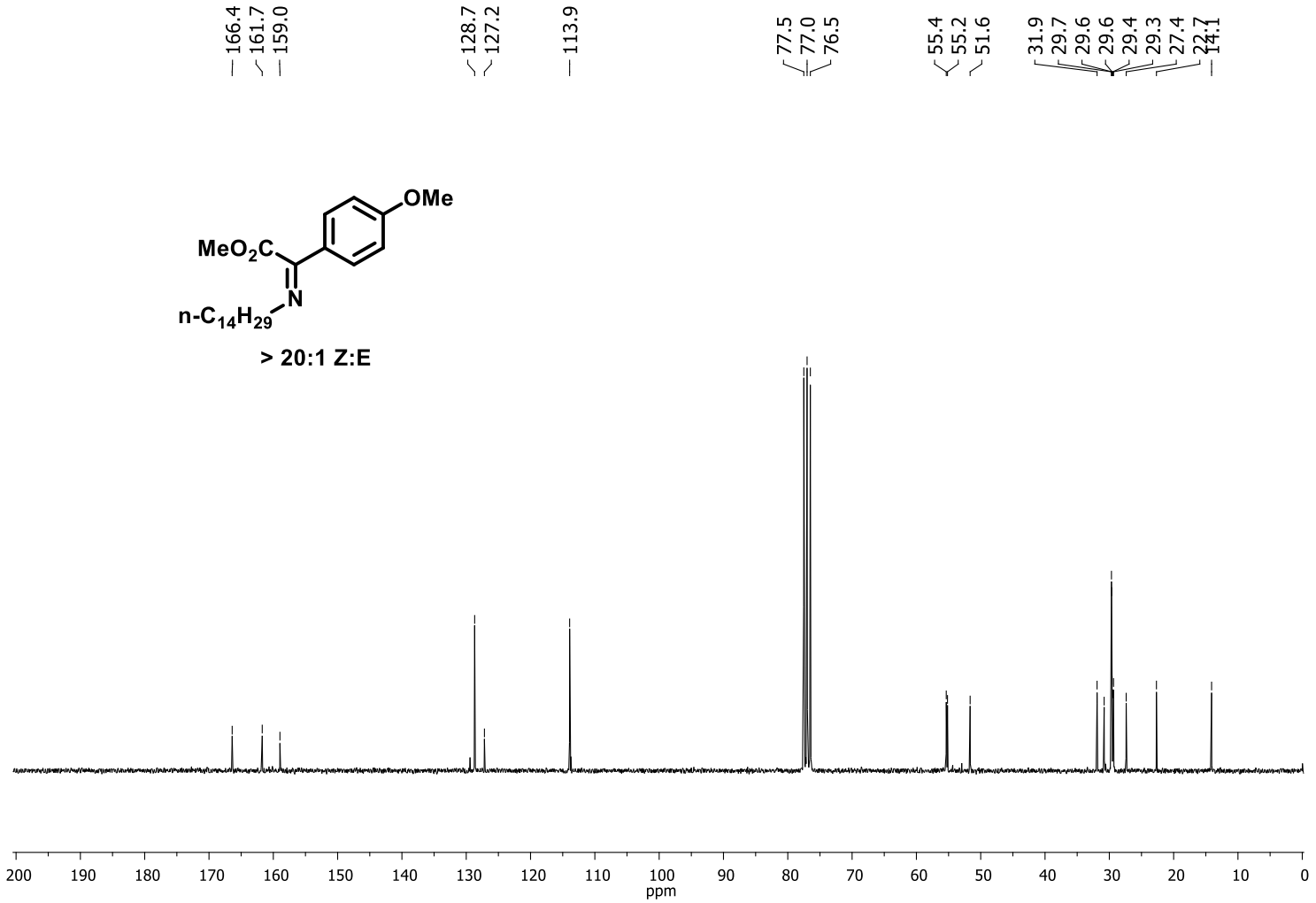
**Molecule 4l - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



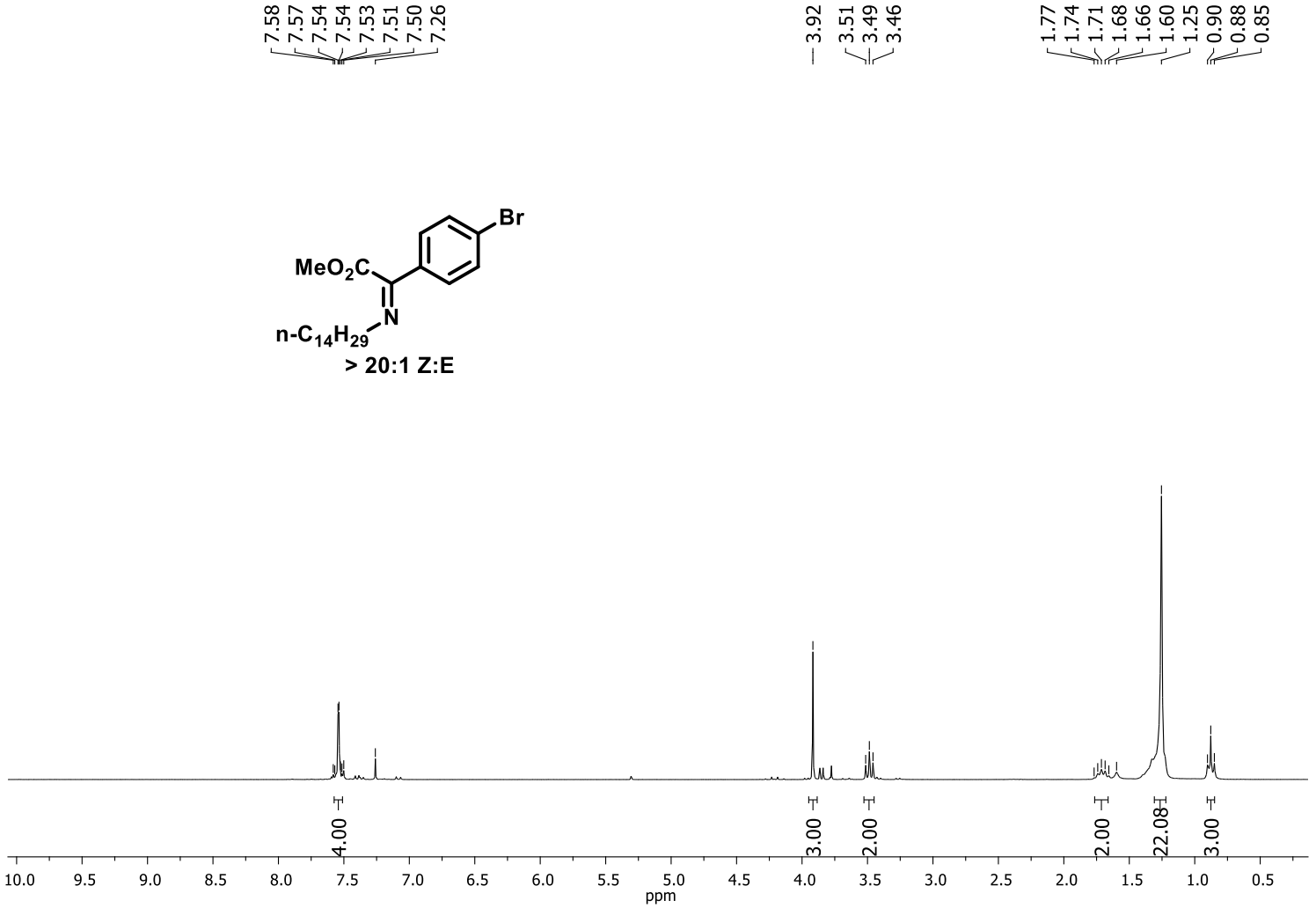
**Molecule 4m - $^{1}$H NMR (250 MHz, $CDCl_3$)**



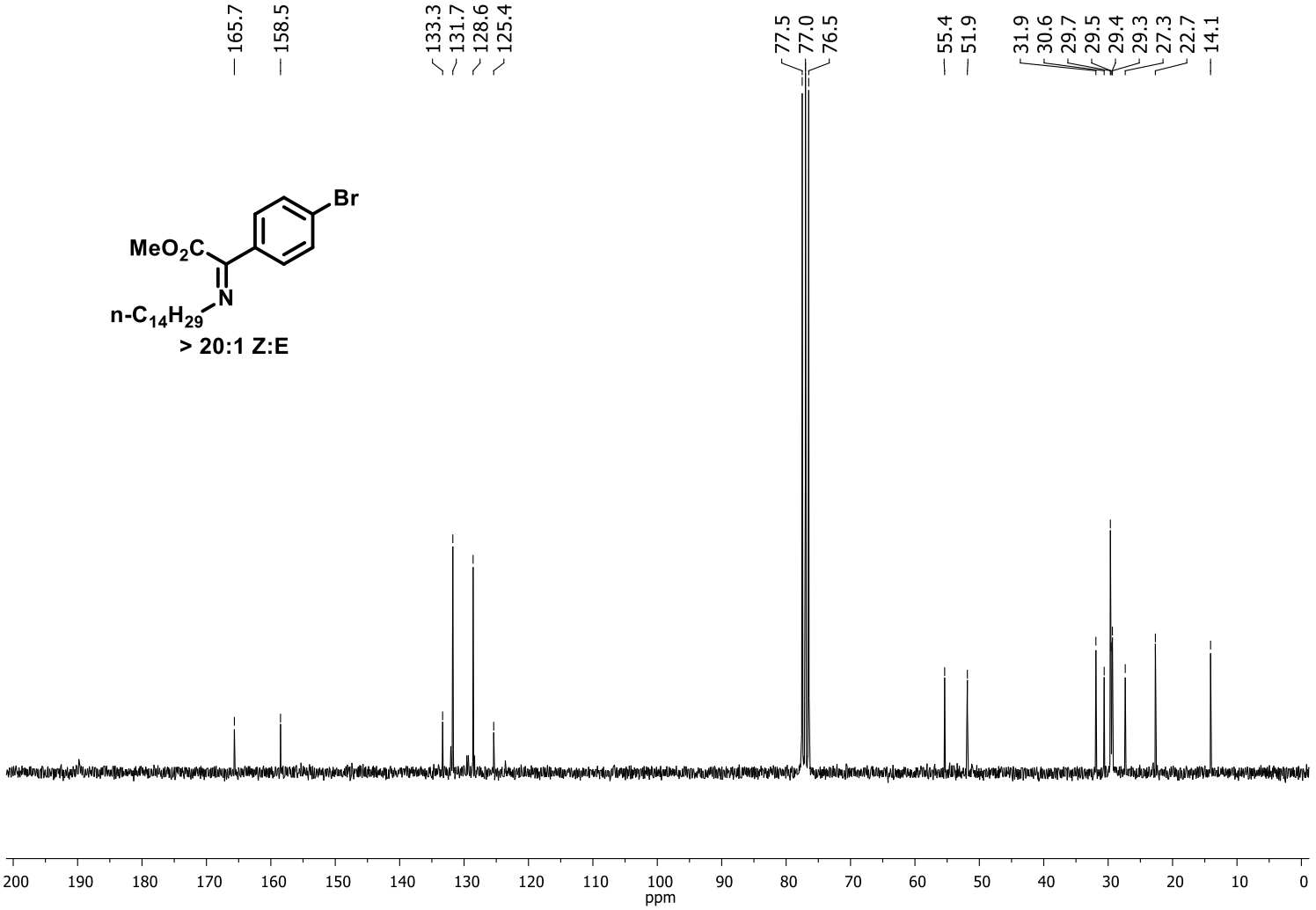
**Molecule 4m - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



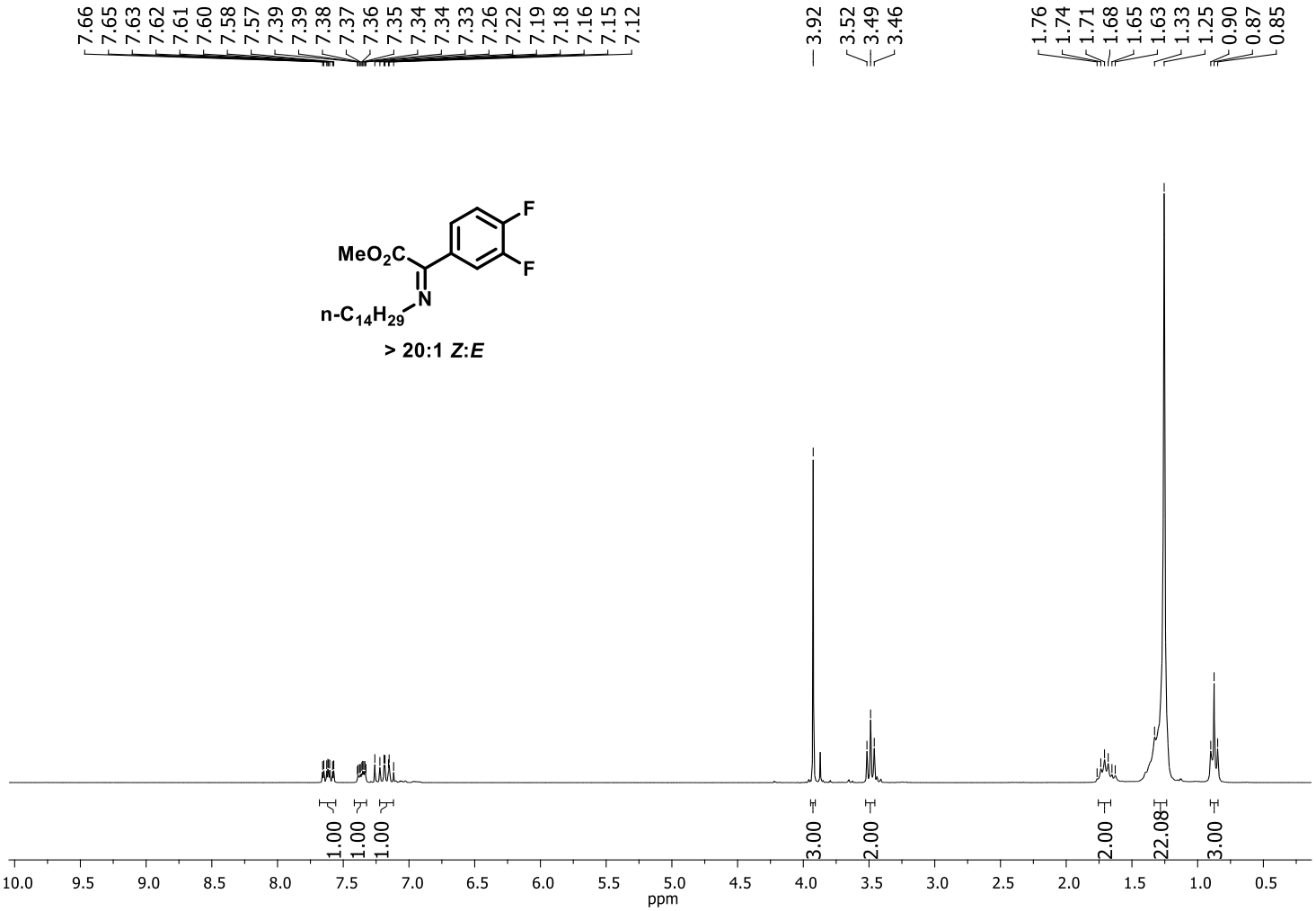
**Molecule 4n - $^{1}$H NMR (250 MHz, $CDCl_3$)**



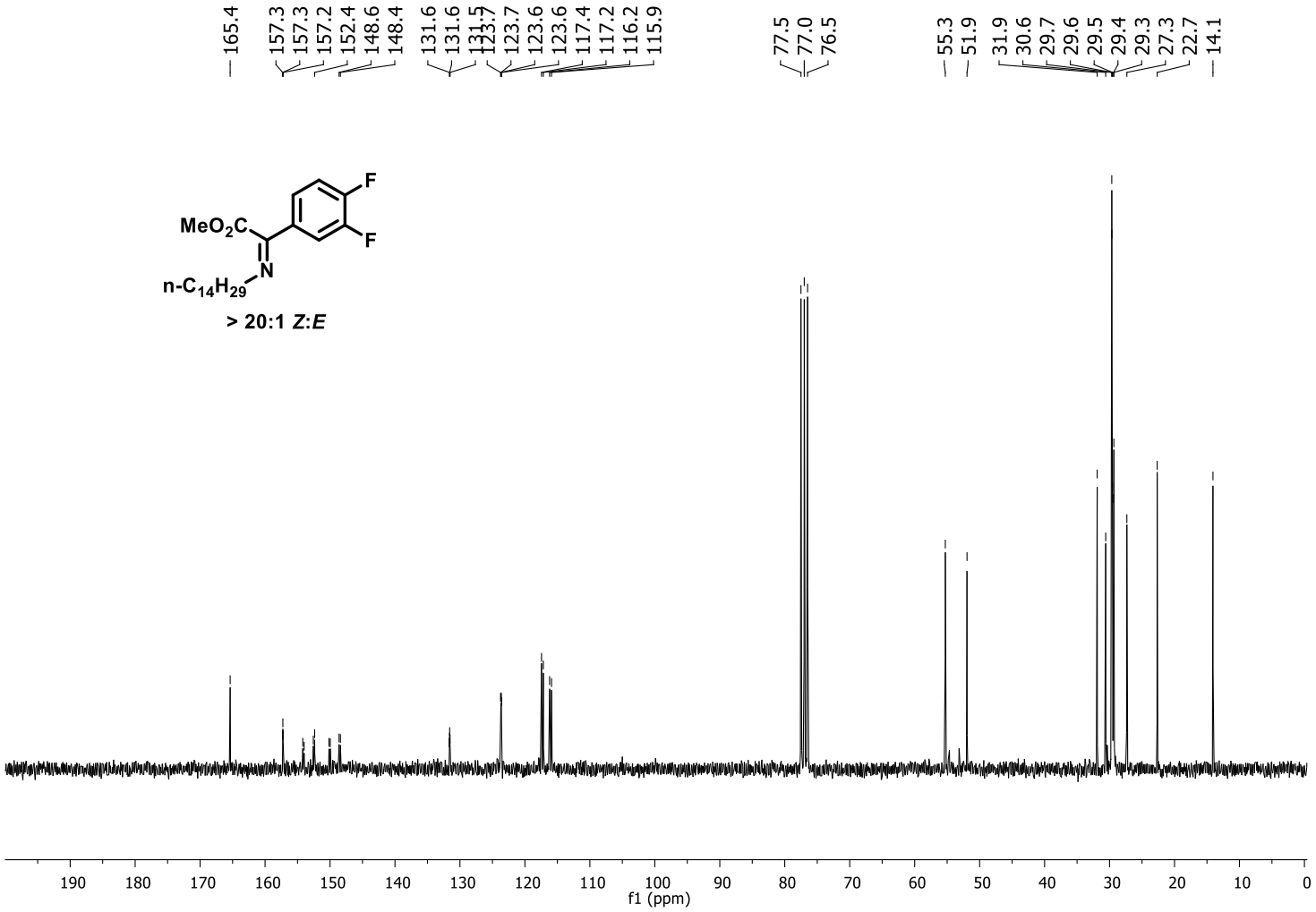
**Molecule 4n - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



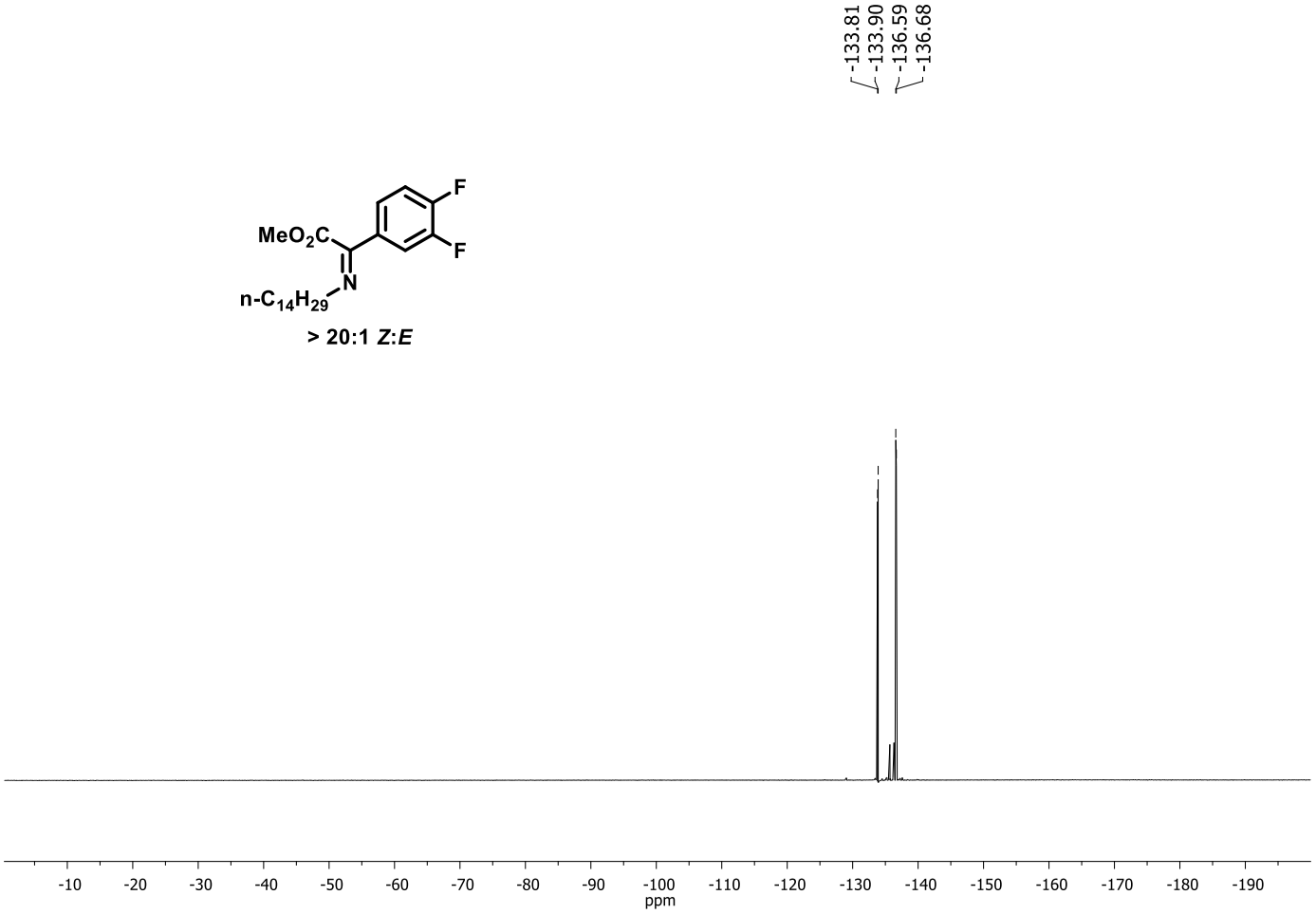
**Molecule 4o - $^{1}$H NMR (250 MHz, $CDCl_3$)**



**Molecule 4o - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**

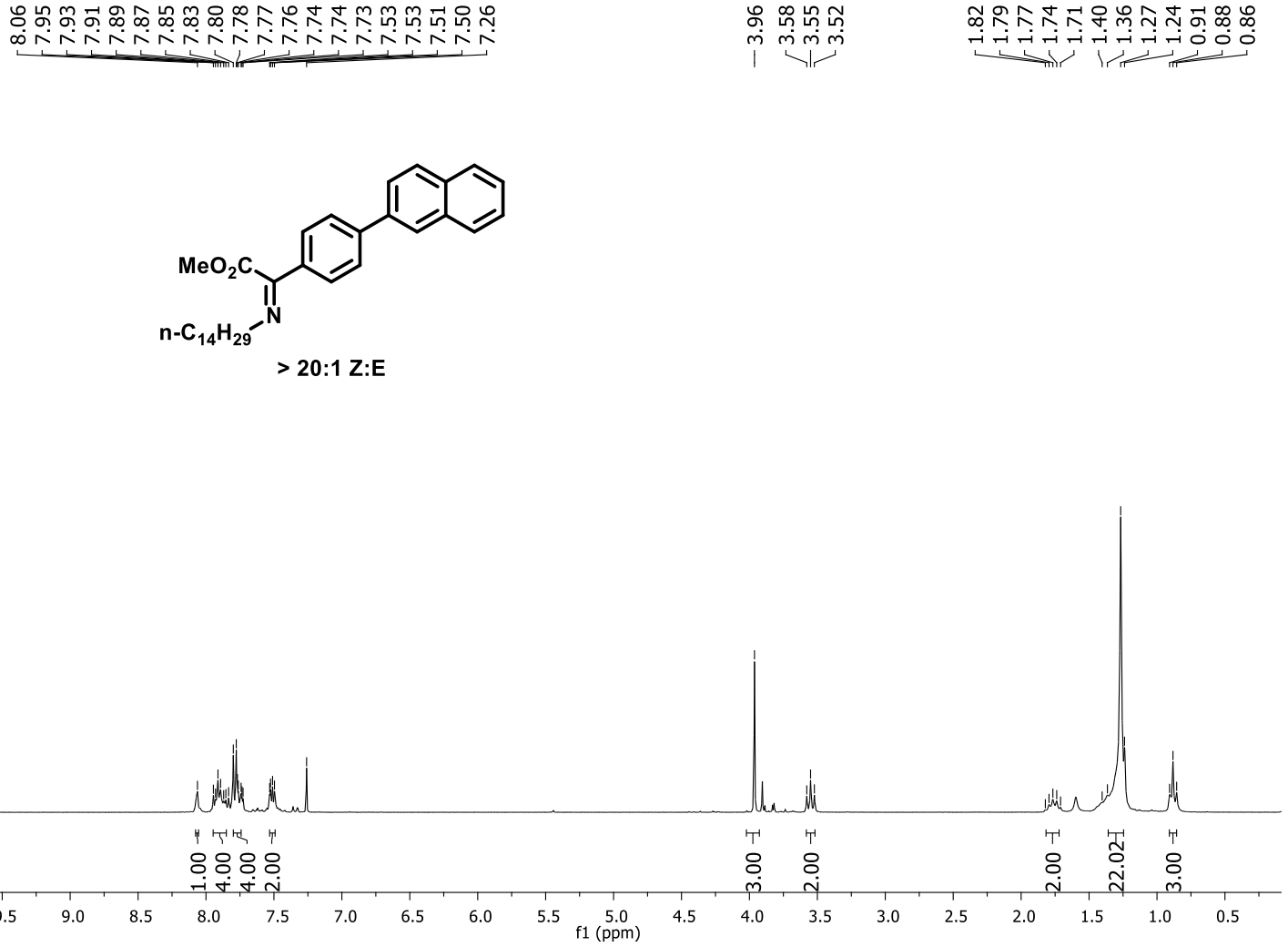


**Molecule 4o - $^{19}$F NMR (235 MHz, $CDCl_3$)**



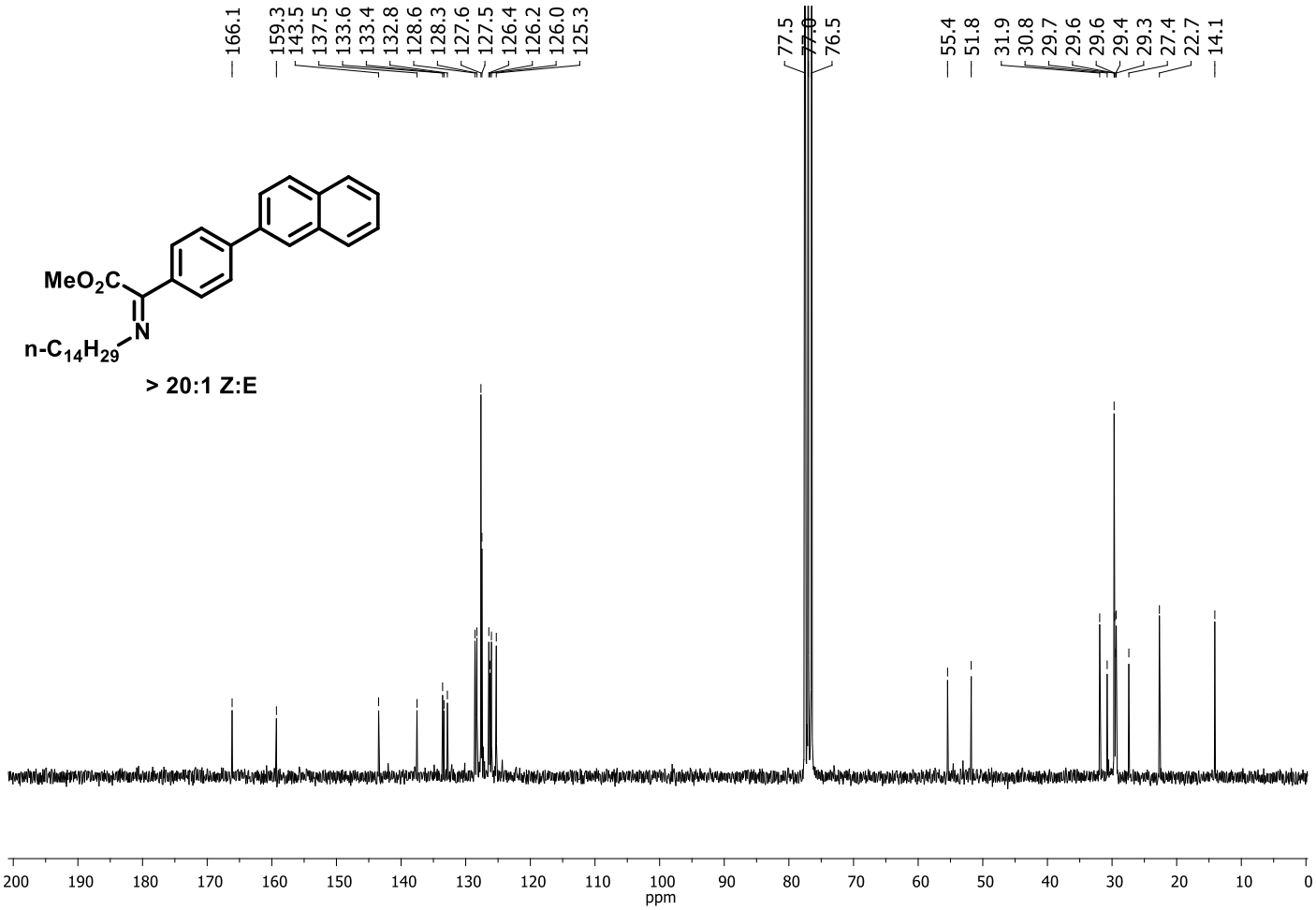

> 20:1 *Z*:*E*

**Molecule 4p - $^{1}$H NMR (250 MHz, $CDCl_3$)**

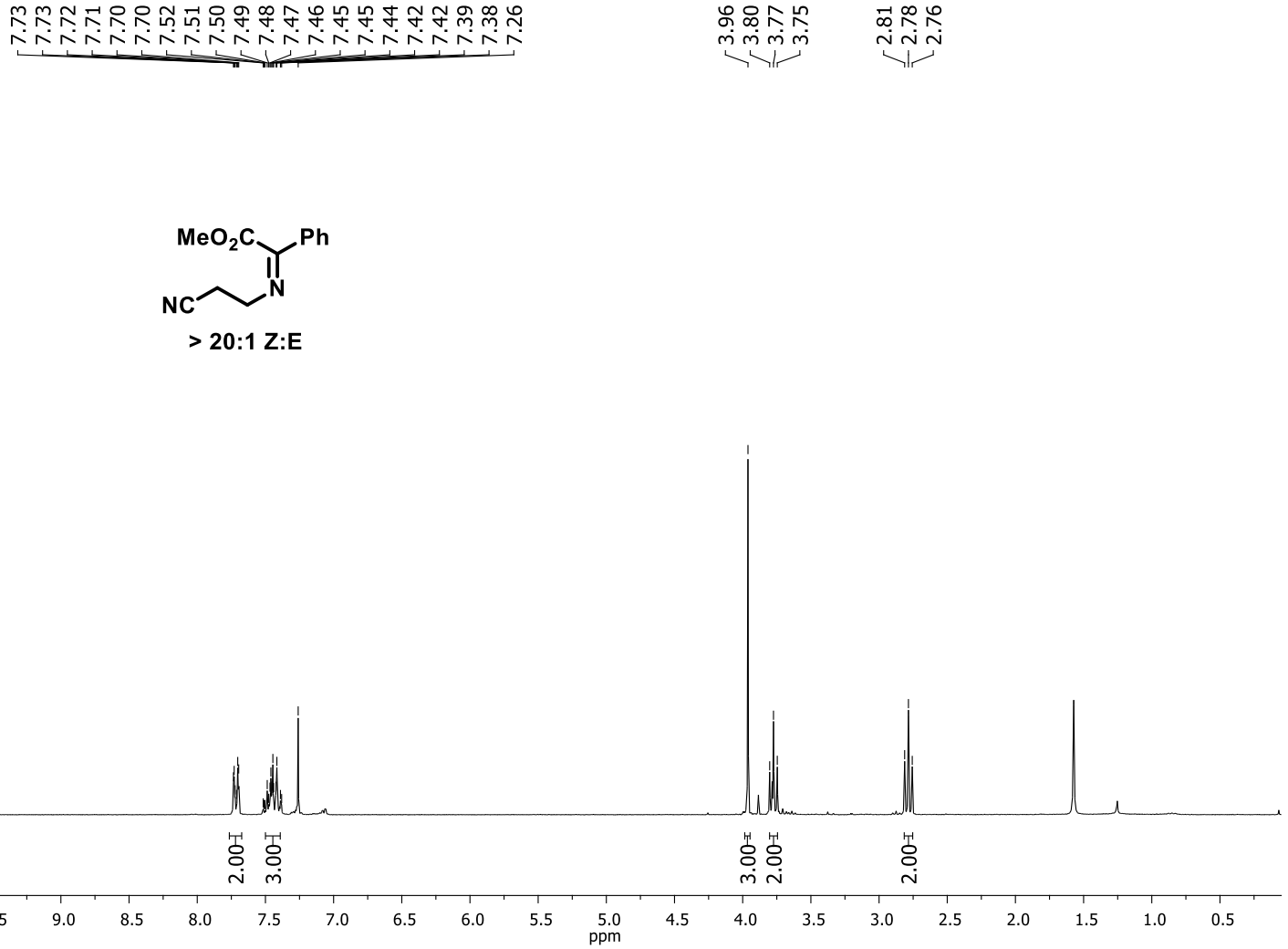



**> 20:1 Z:E**

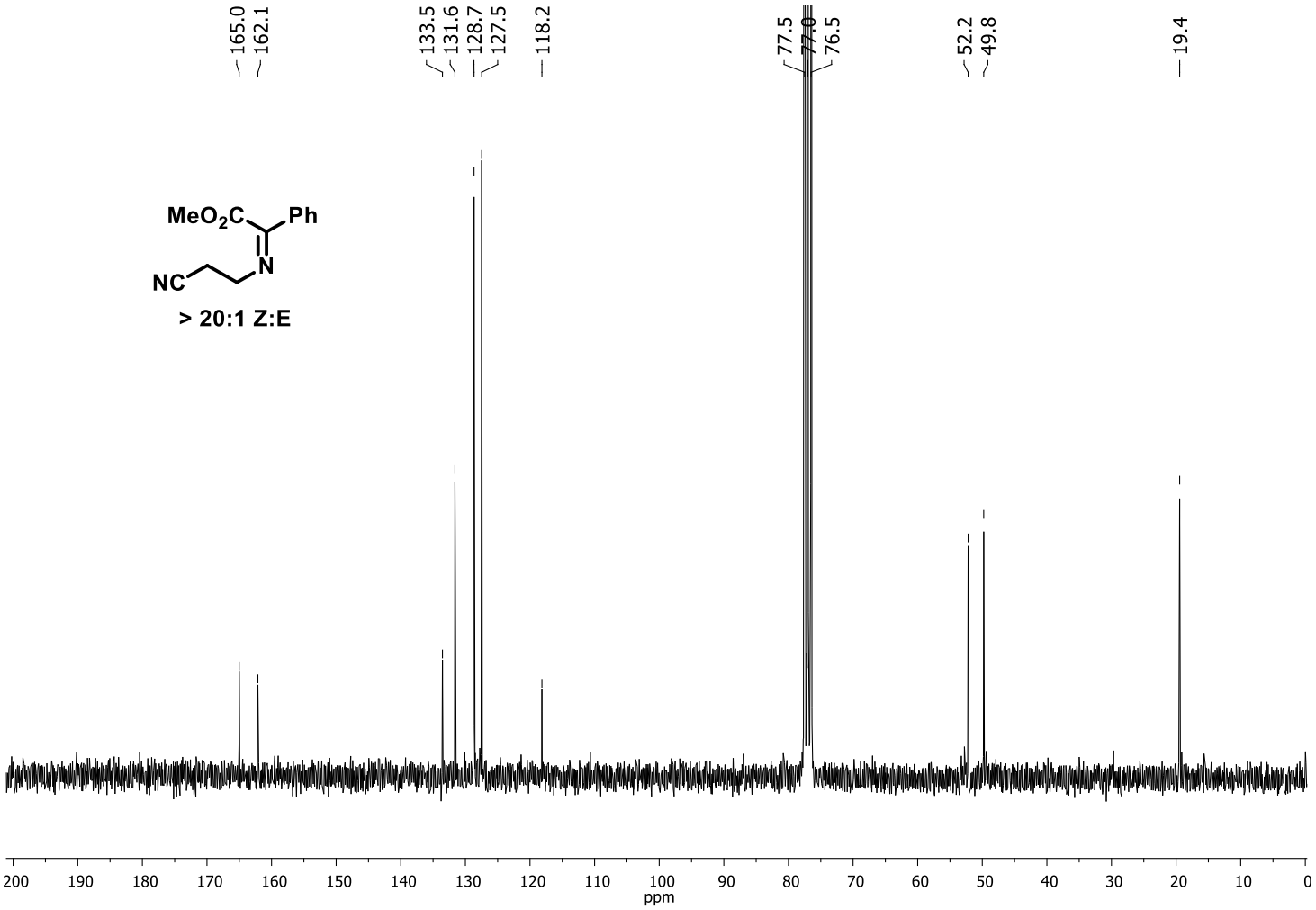
**Molecule 4p - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



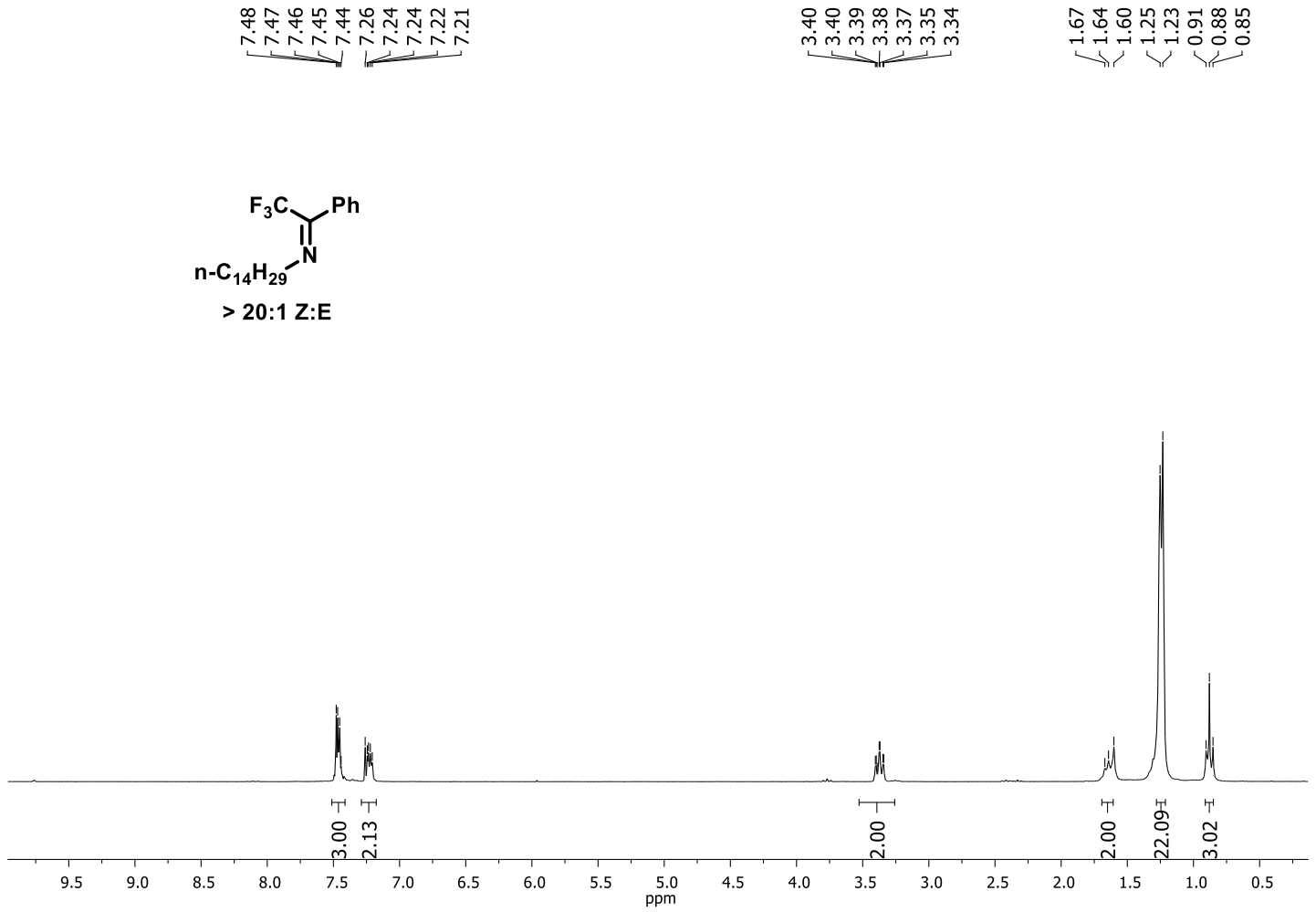
**Molecule 4q - $^{1}$H NMR (250 MHz, $CDCl_3$)**



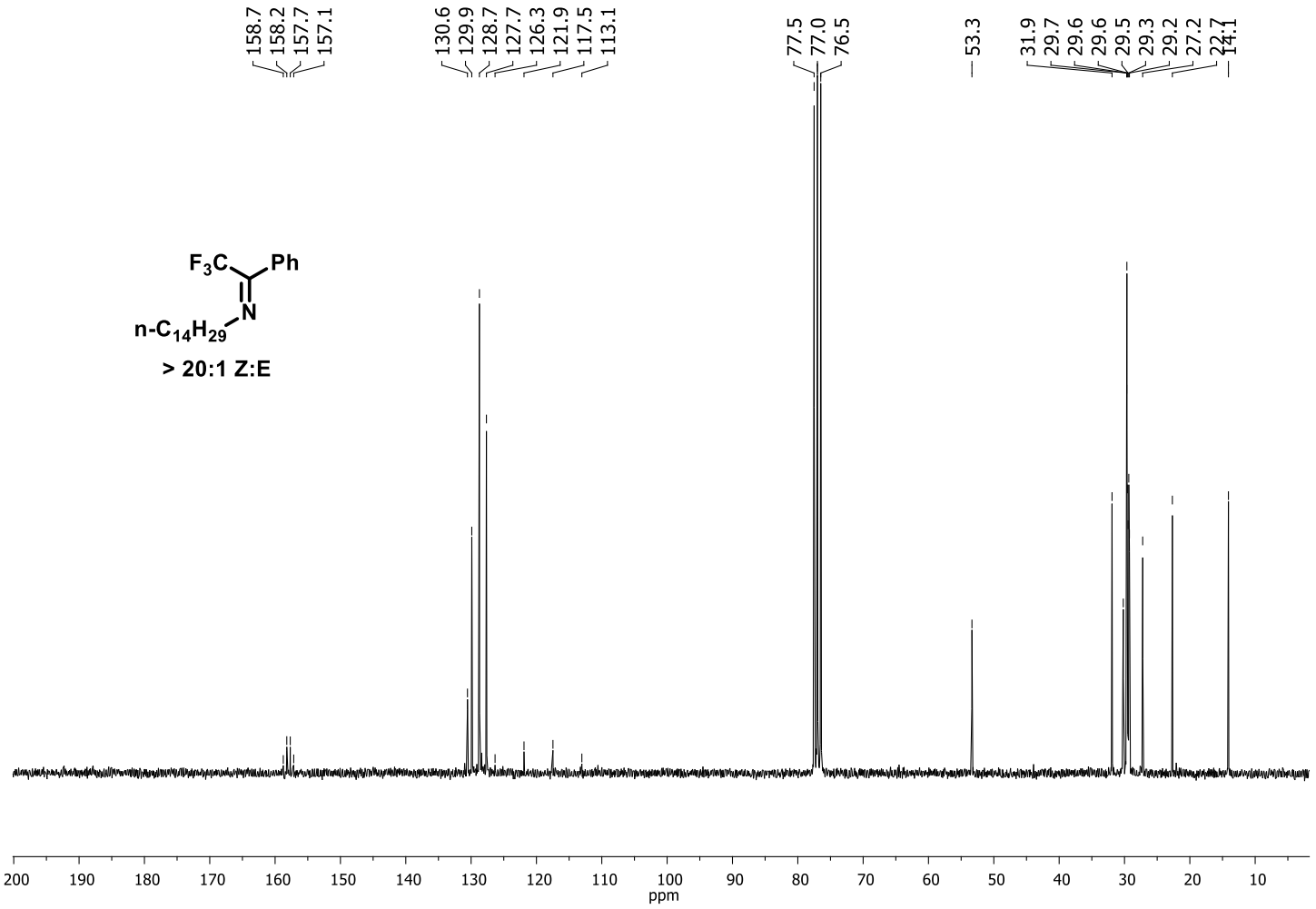
**Molecule 4q - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



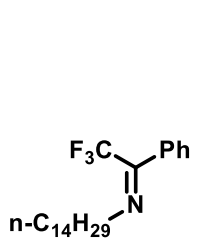
**Molecule 4r - $^{1}$H NMR (250 MHz, $CDCl_3$)**



**Molecule 4r - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**

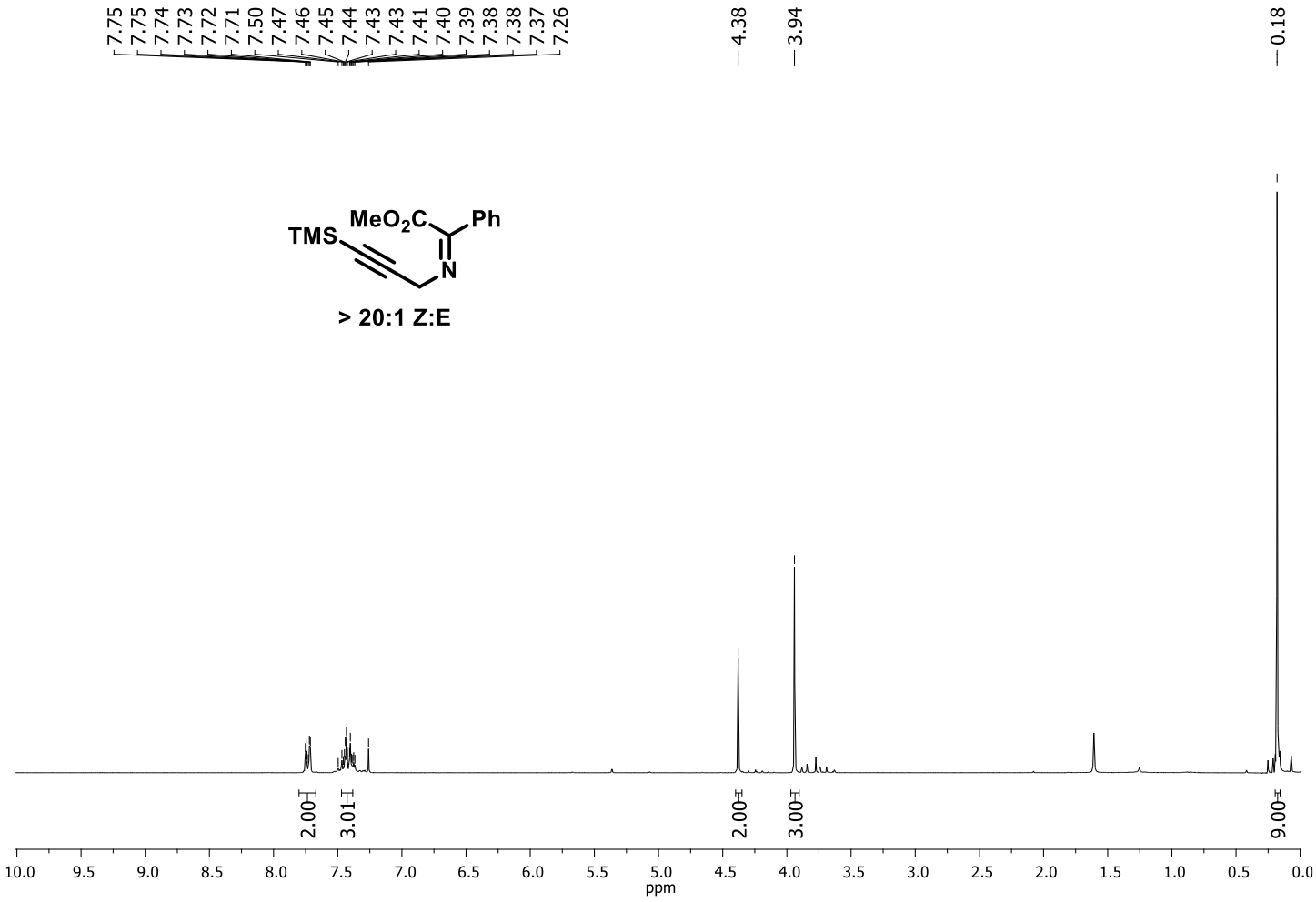


**Molecule 4r - $^{19}F$ NMR (235 MHz, $CDCl_3$)**

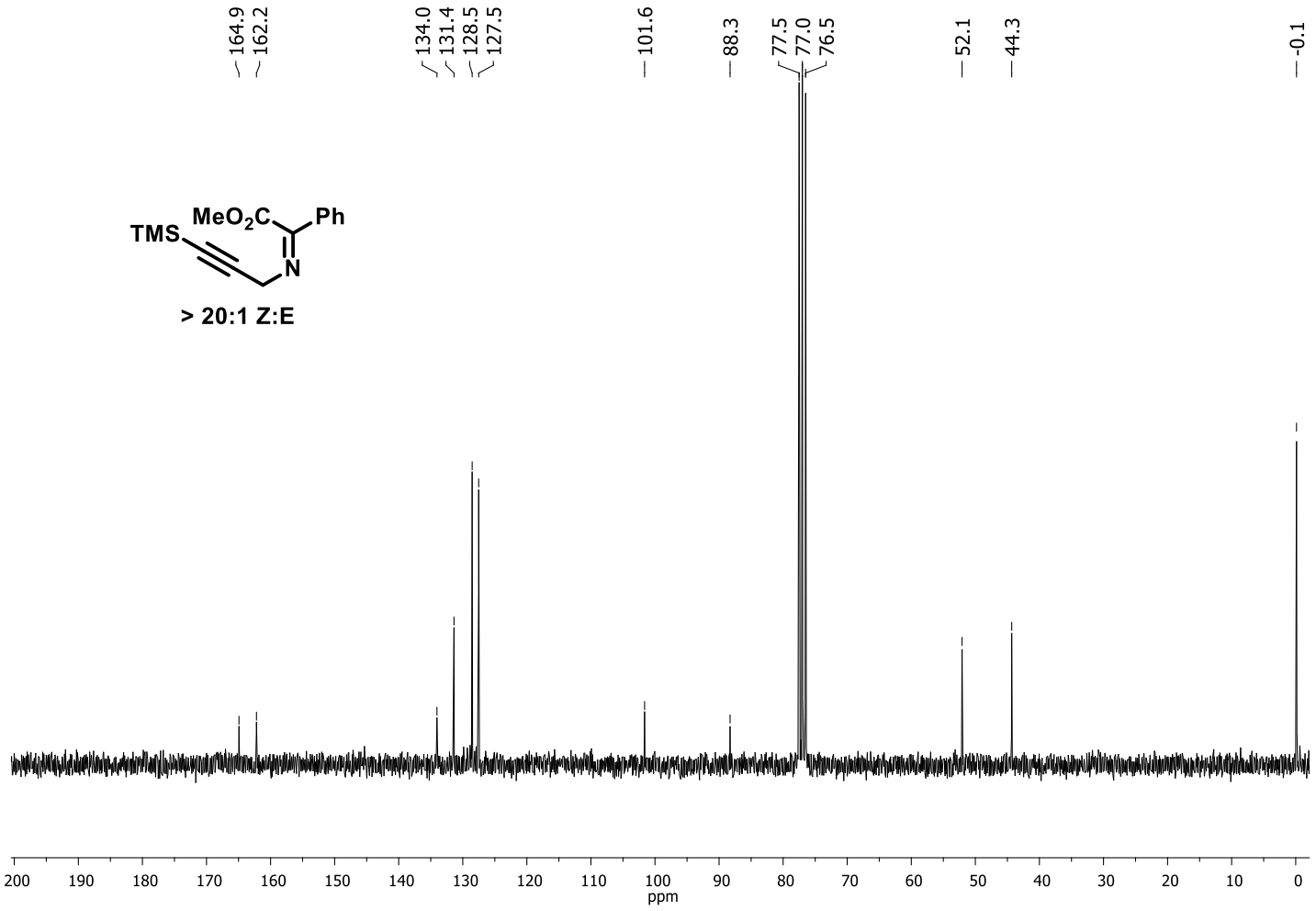



**> 20:1 Z:E**

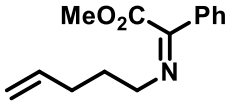
**Molecule 4s - $^{1}$H NMR (250 MHz, $CDCl_3$)**



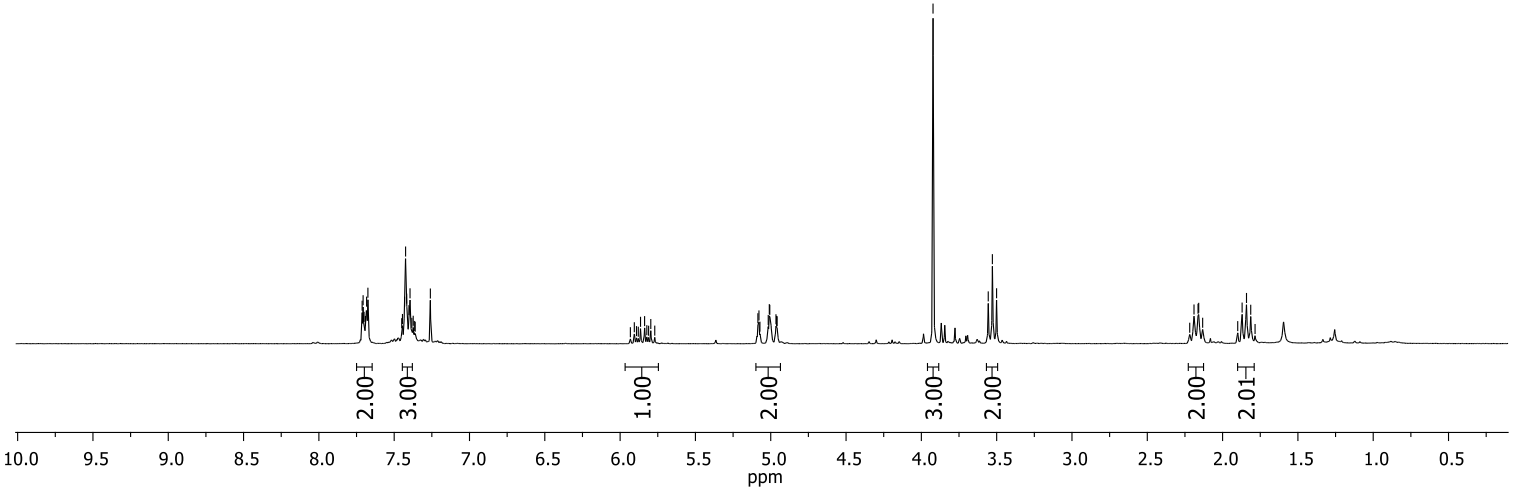
**Molecule 4s - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



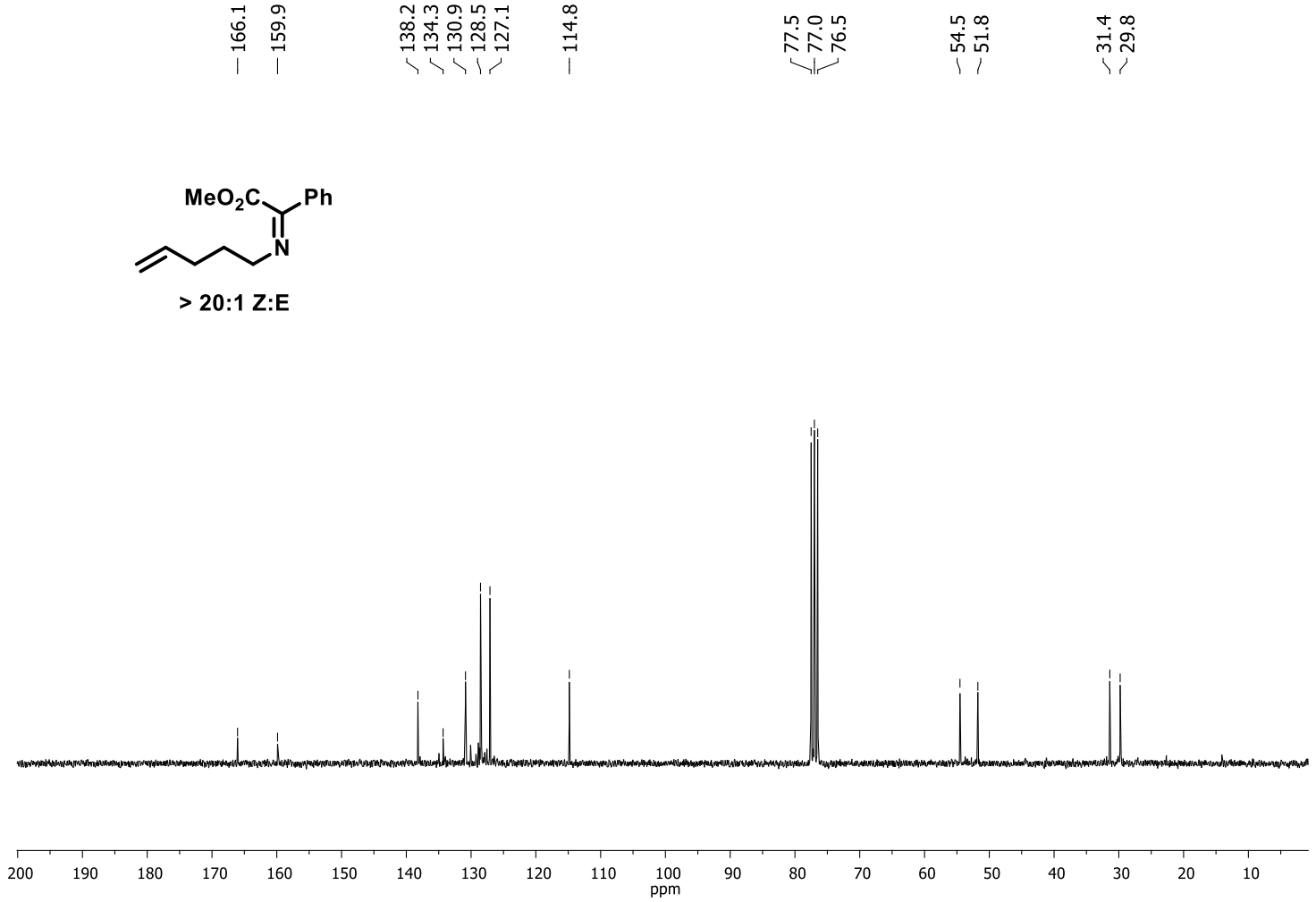
**Molecule 4t - $^{1}$H NMR (250 MHz, $CDCl_3$)**

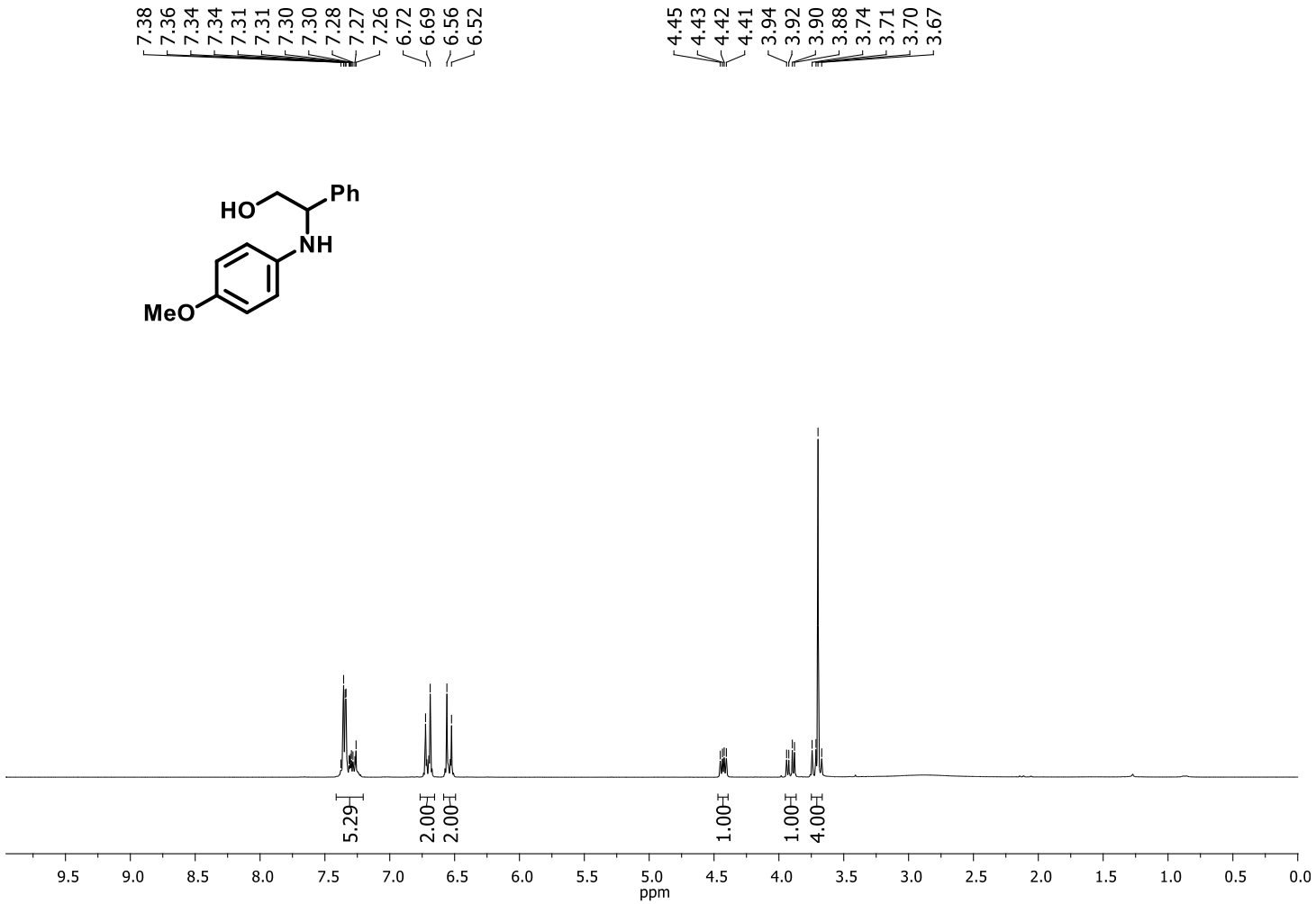

**> 20:1 Z:E**



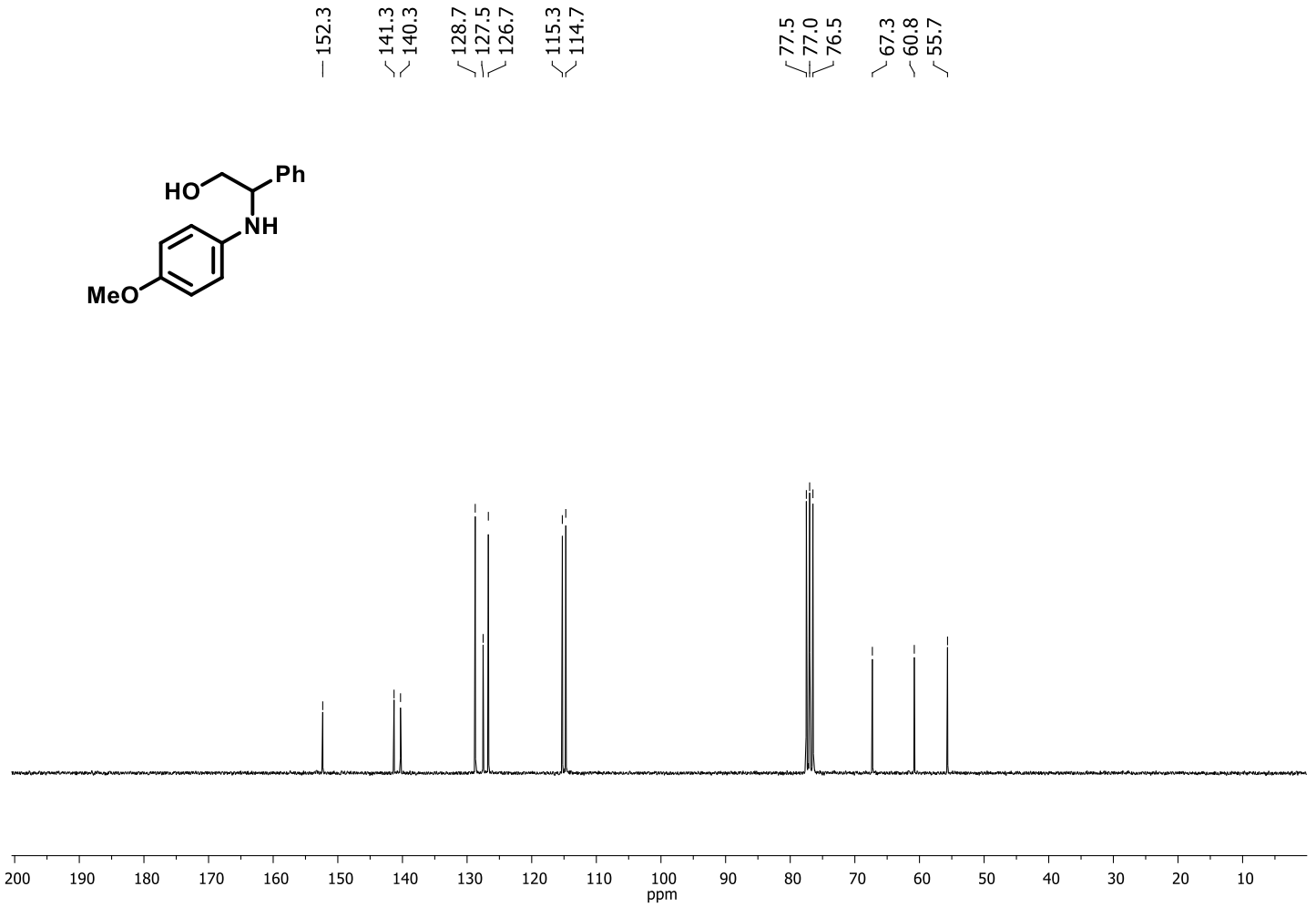
**Molecule 4t - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



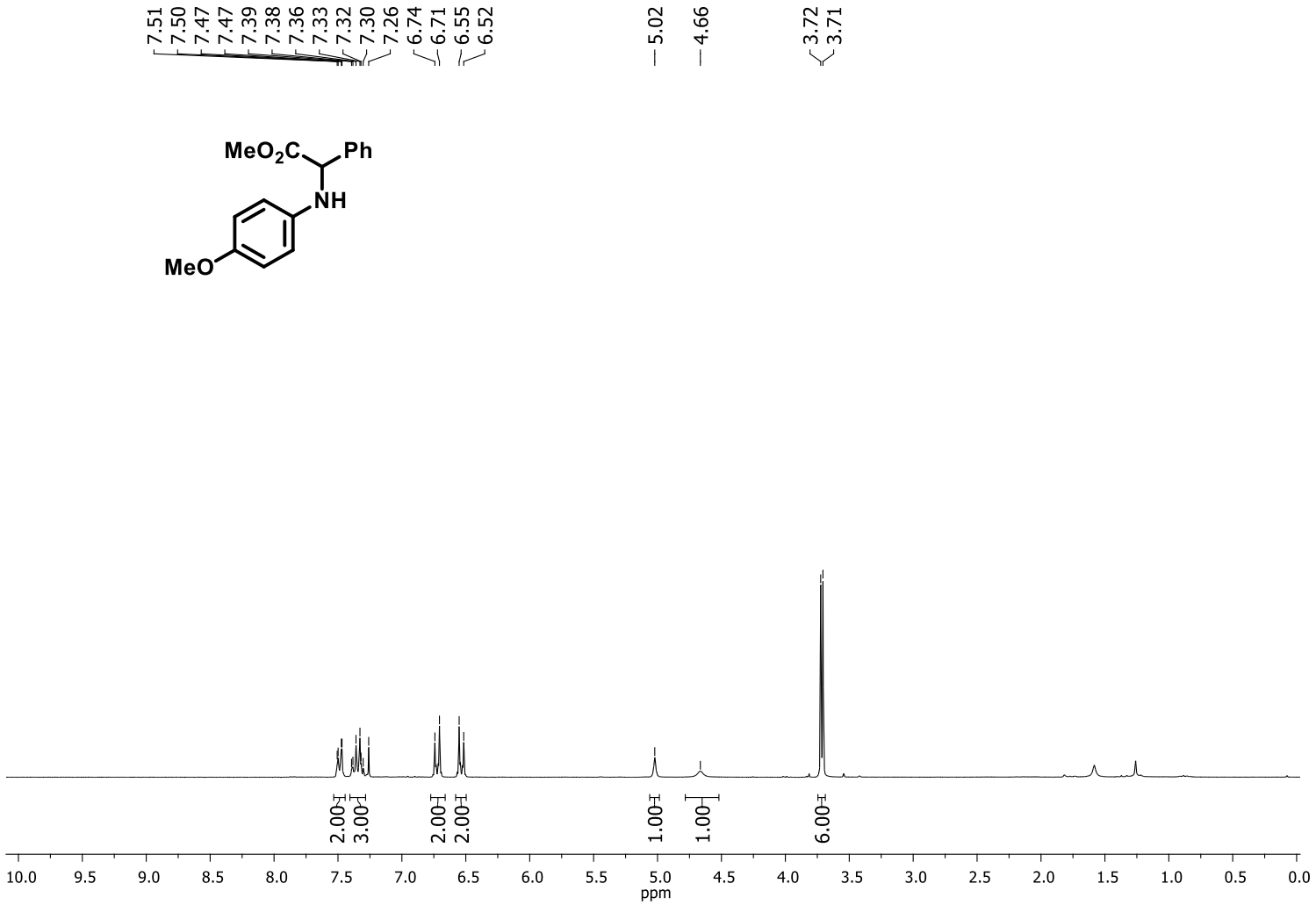
**Molecule 11a - $^{1}$H NMR (250 MHz, $CDCl_3$)**



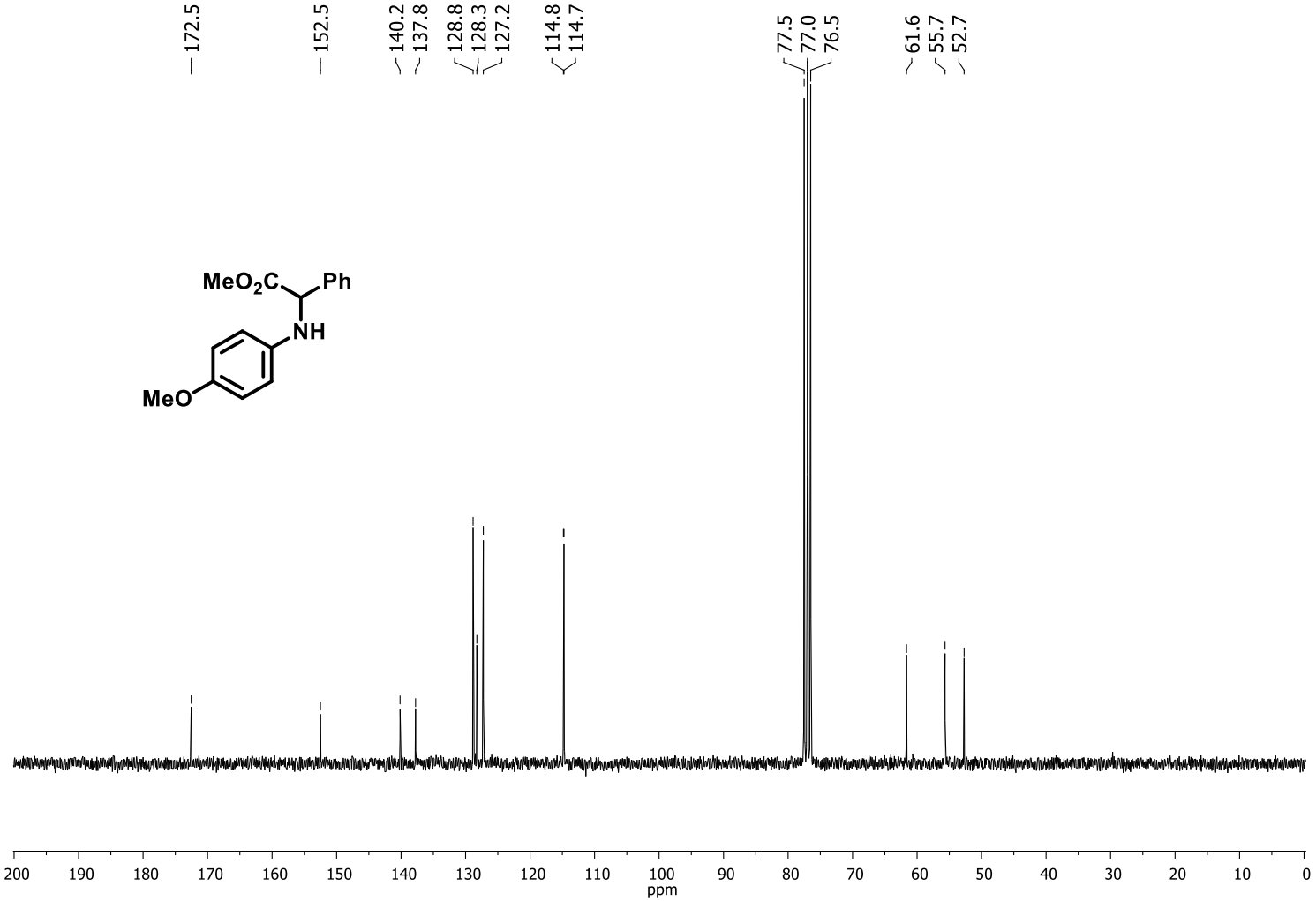
**Molecule 11a - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



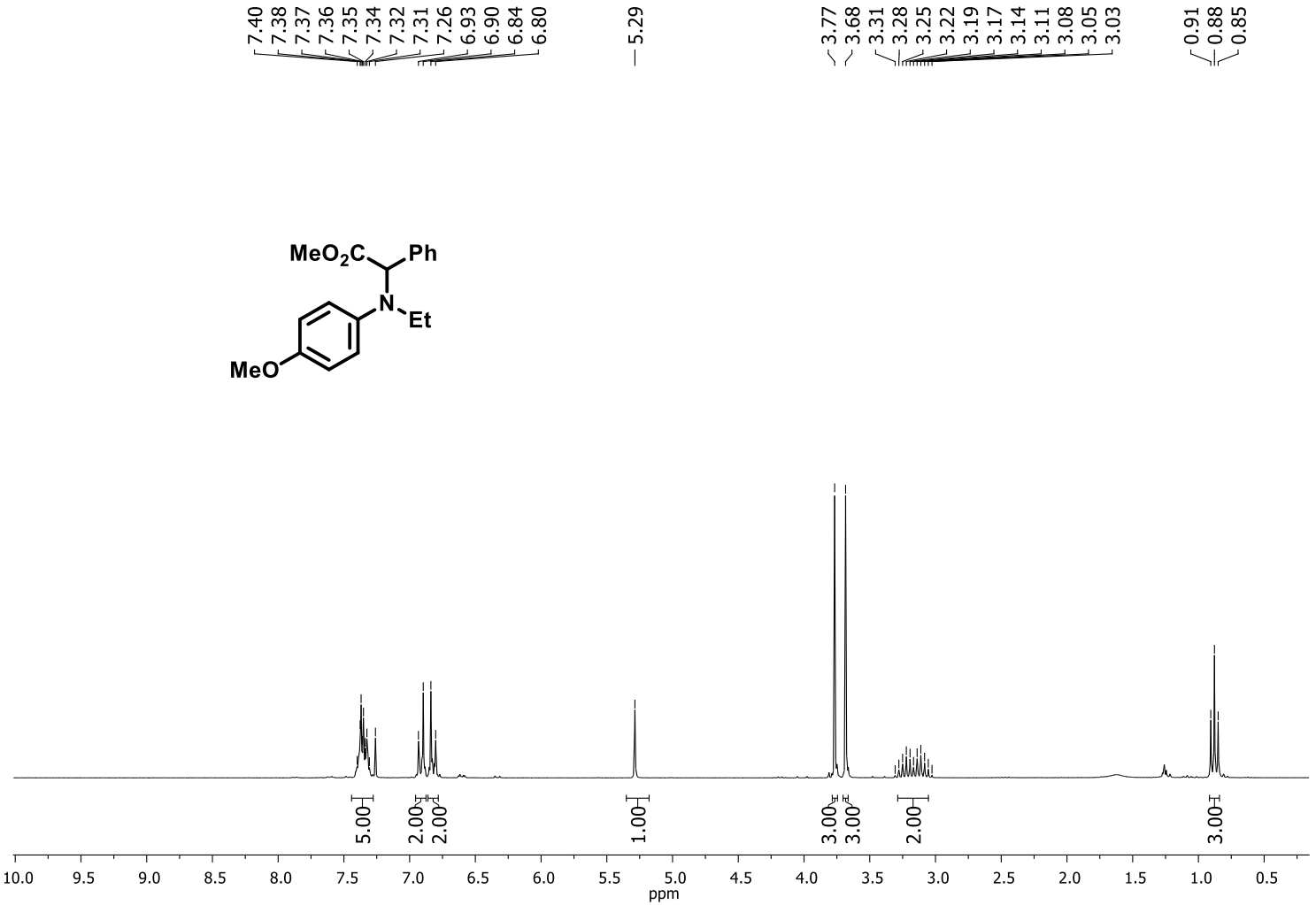
**Molecule 11b - $^{1}H$ NMR (250 MHz, $CDCl_3$)**



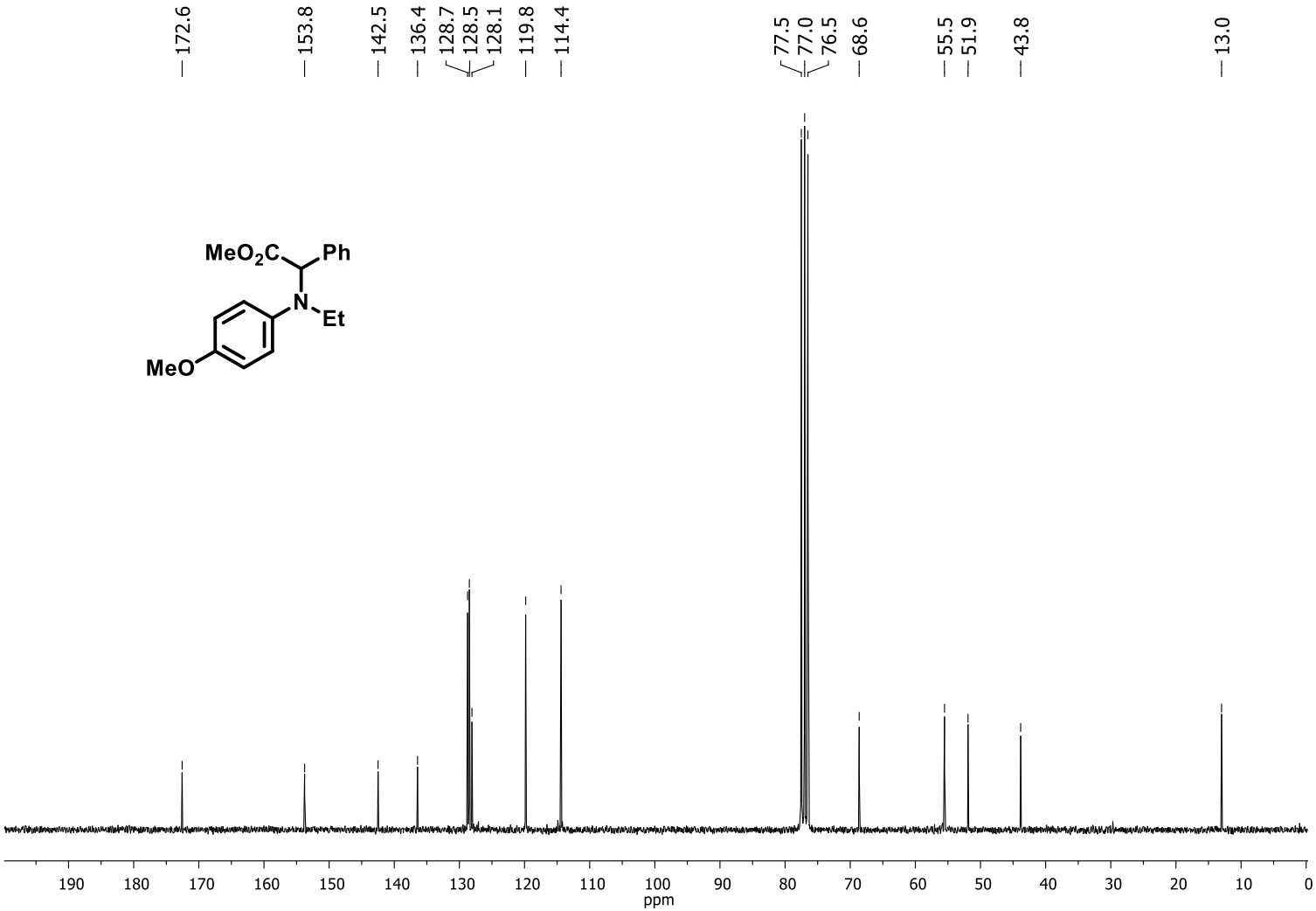
**Molecule 11b - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



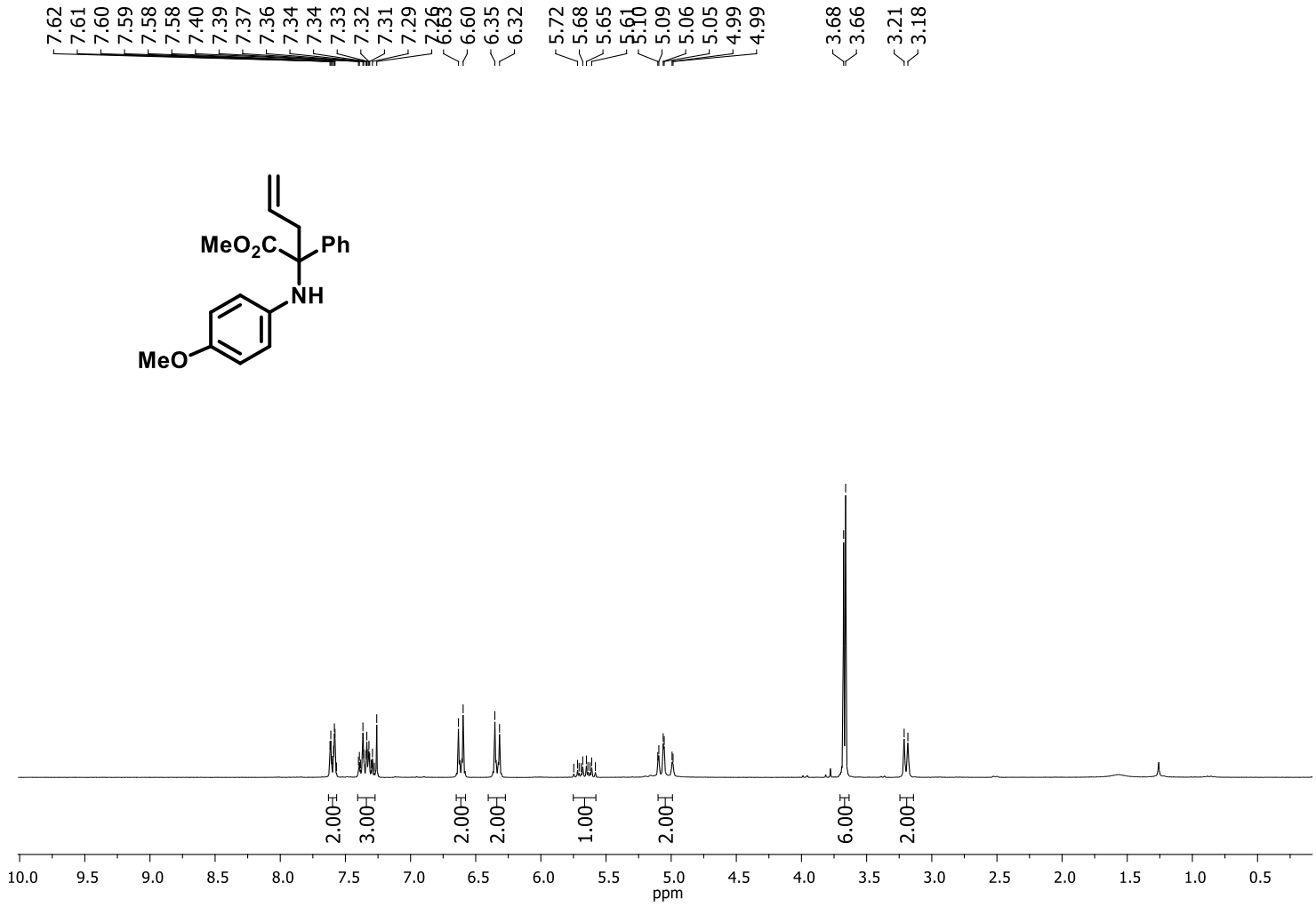
**Molecule 11c - $^{1}$H NMR (250 MHz, $CDCl_3$)**



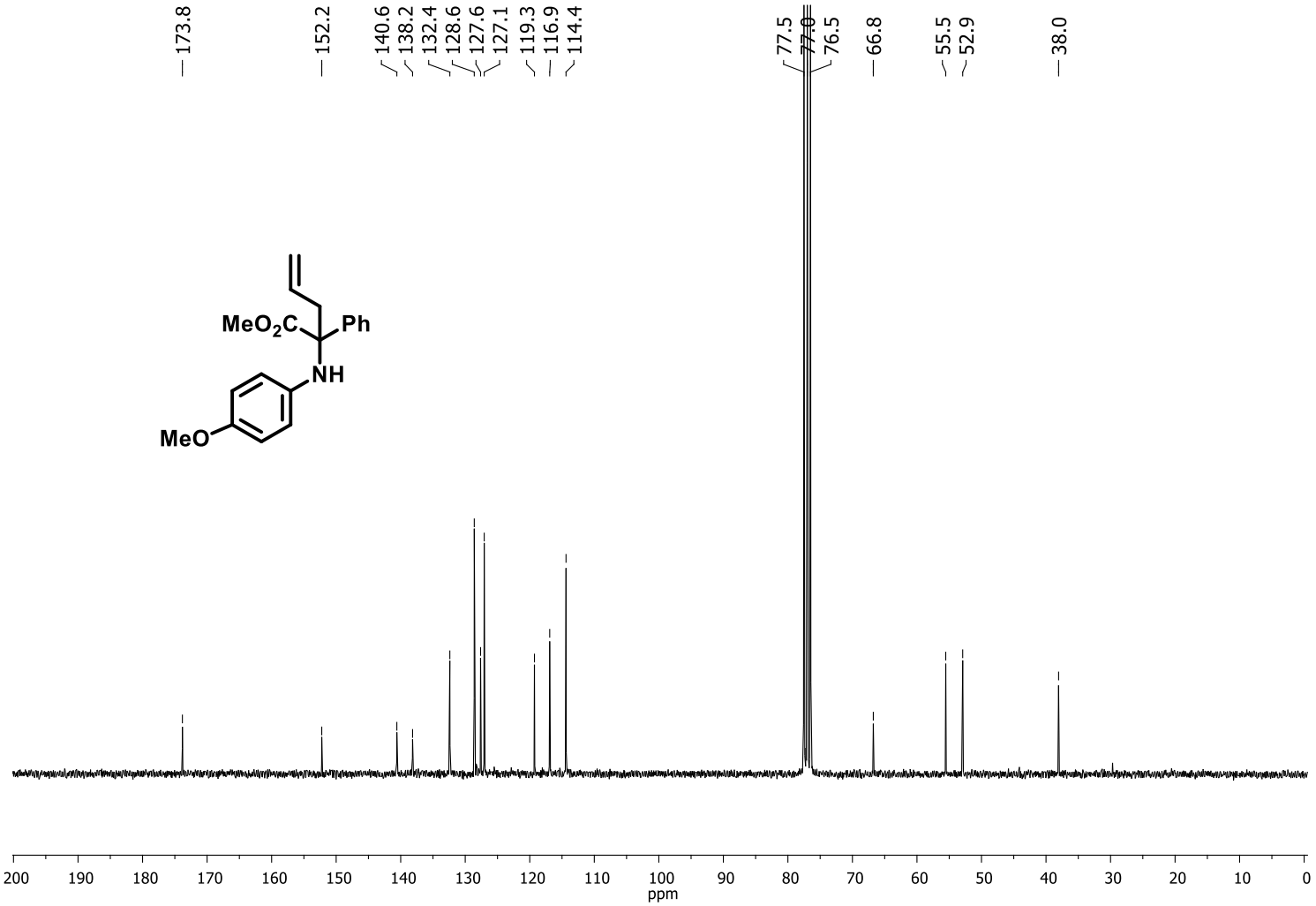
**Molecule 11c - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



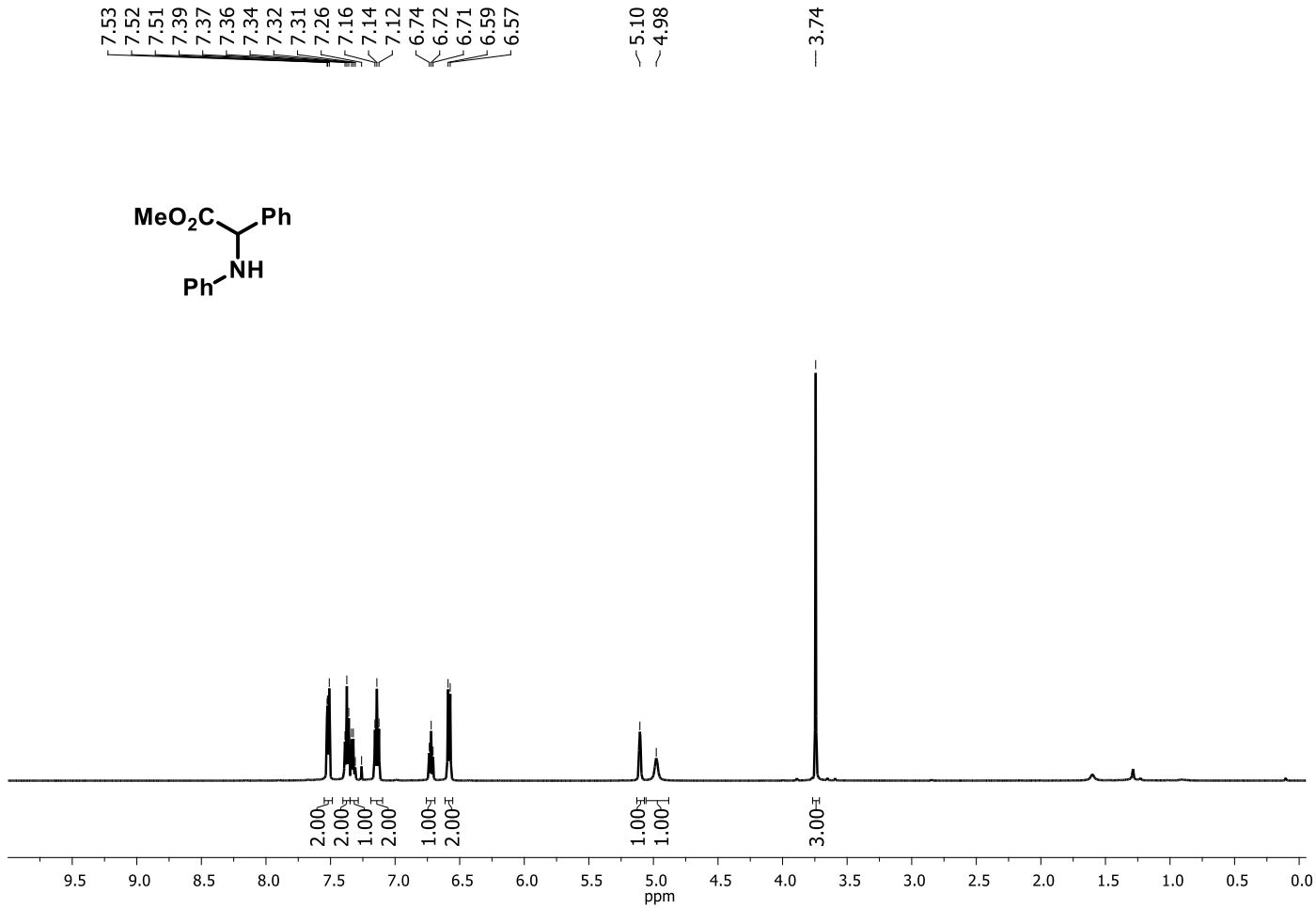
**Molecule 11d - $^{1}H$ NMR (250 MHz, $CDCl_3$)**



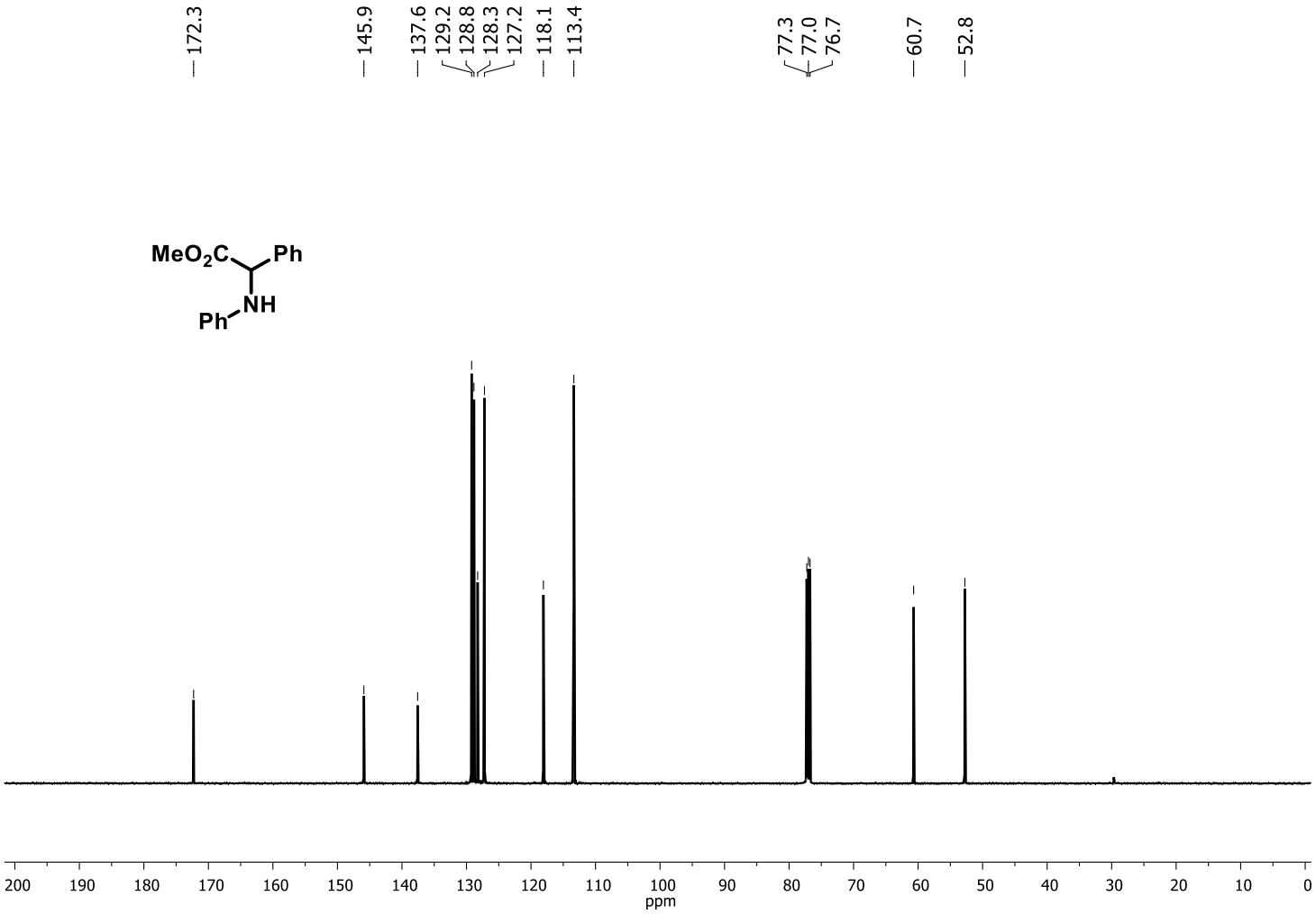
**Molecule 11d - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



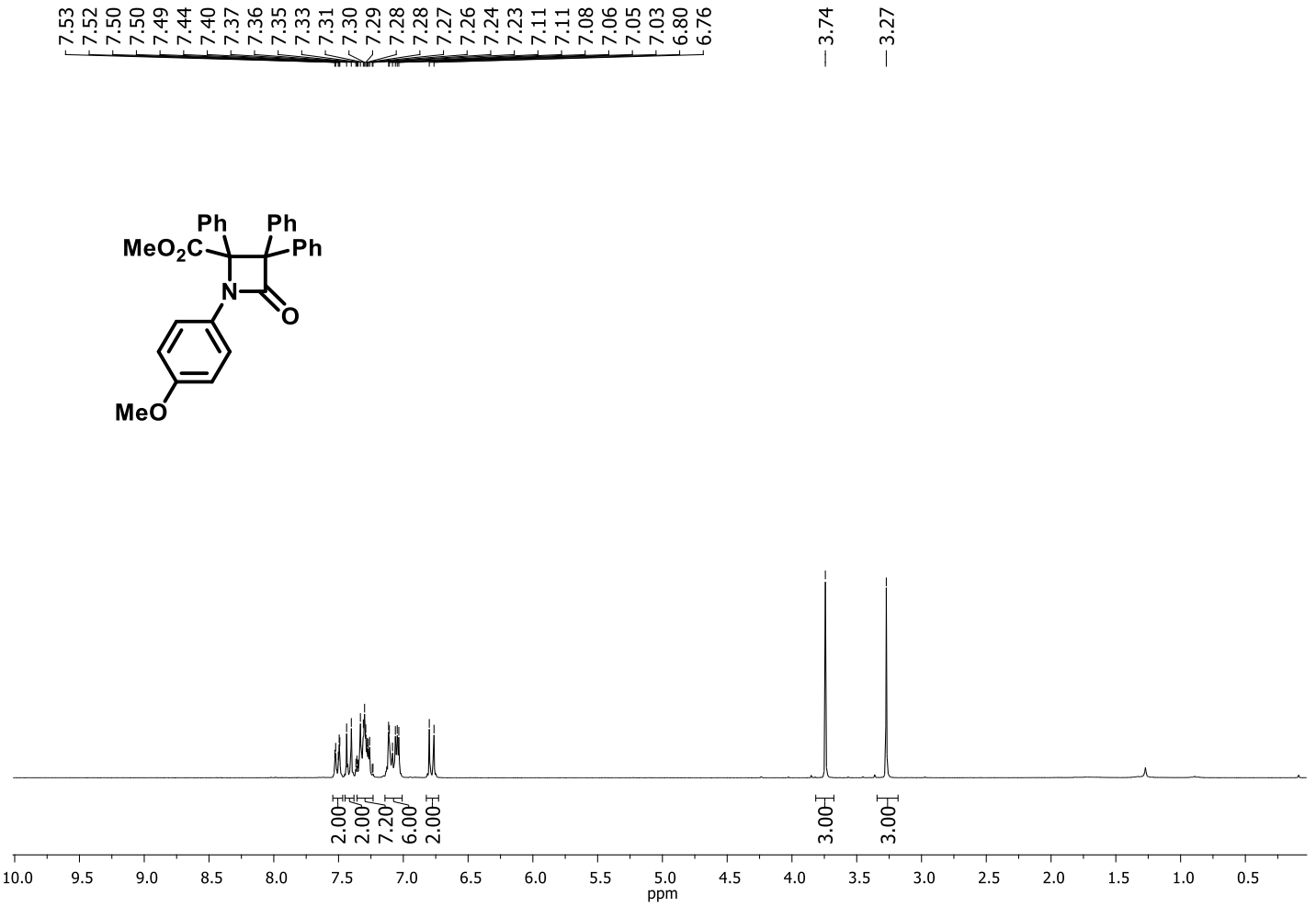
**Molecule 12a – $^{1}H$ NMR (250 MHz, $CDCl_3$)**



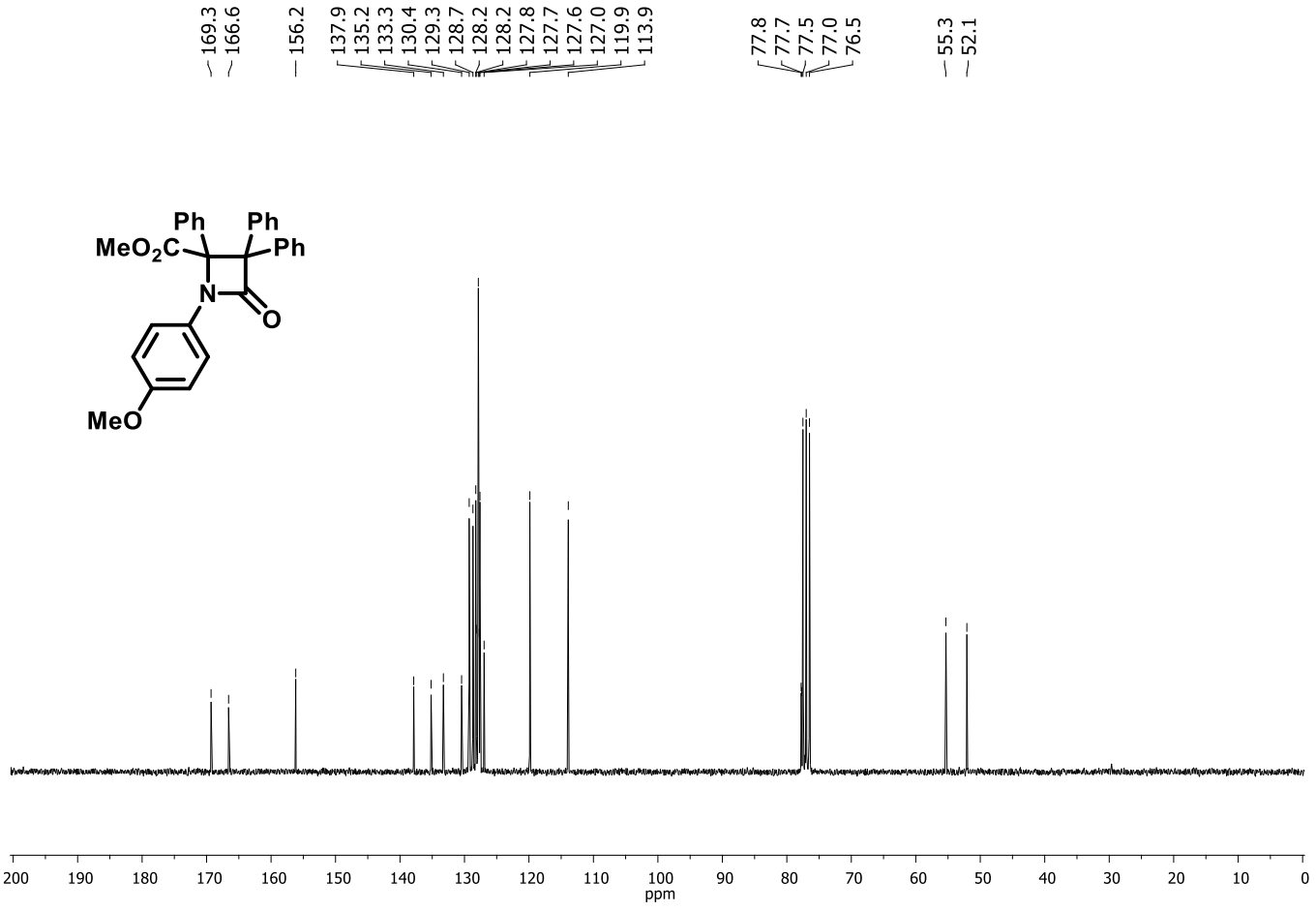
**Molecule 12a – $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



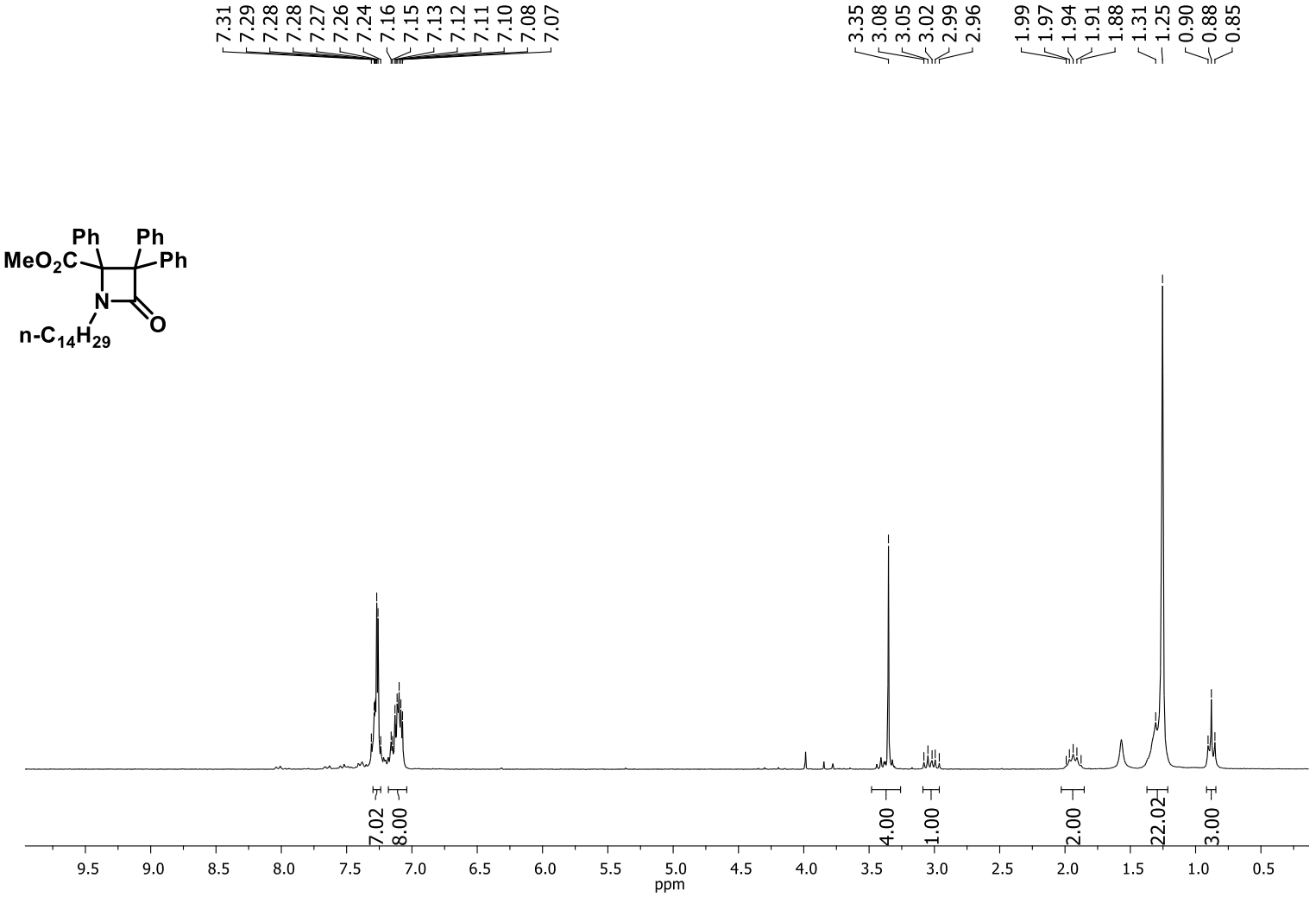
**Molecule 9a - $^{1}$H NMR (250 MHz, $CDCl_3$)**



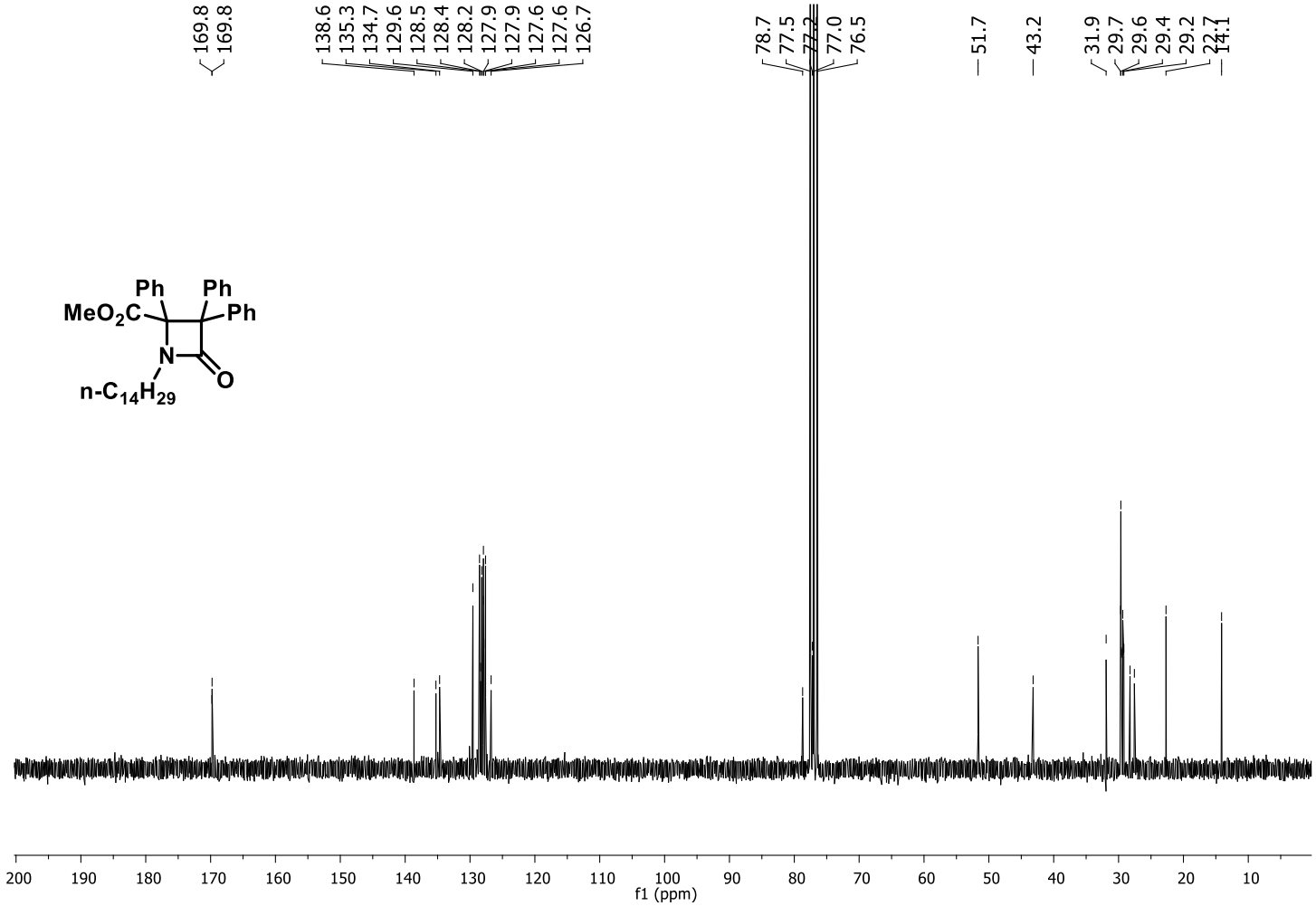
**Molecule 9a - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



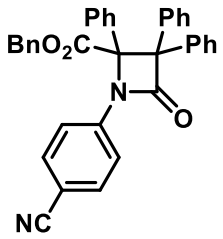
**Molecule 9b - $^{1}$H NMR (250 MHz, $CDCl_3$)**

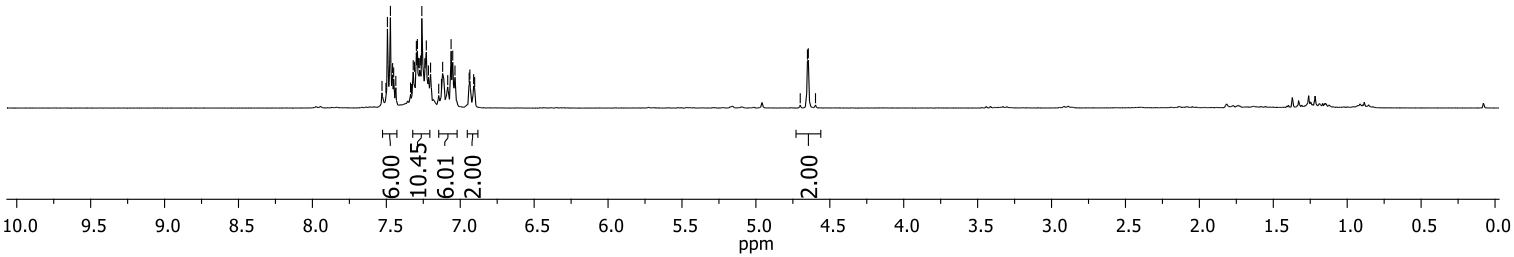


**Molecule 9b - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**

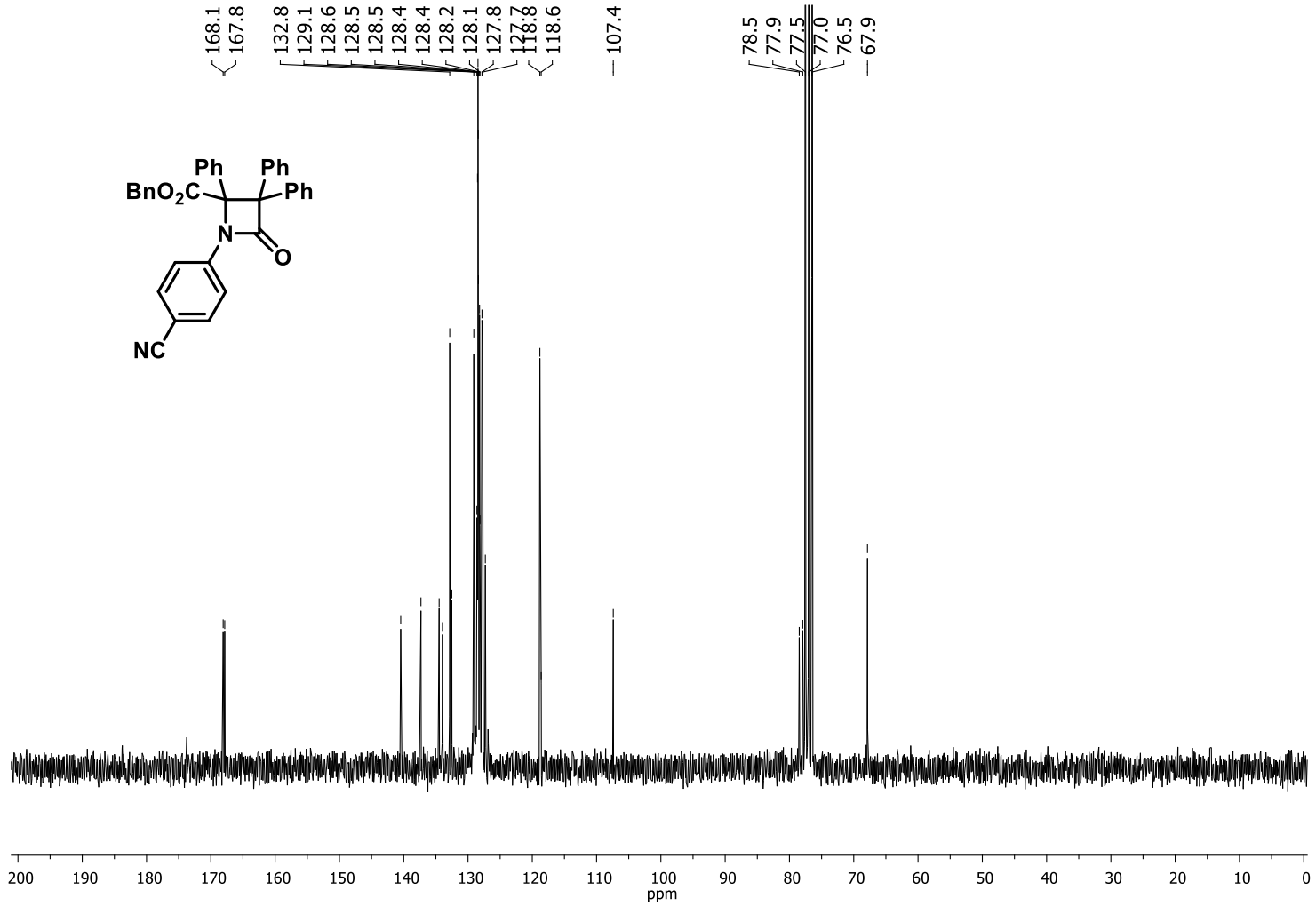


**Molecule 9c - $^{1}$H NMR (250 MHz, $CDCl_3$)**

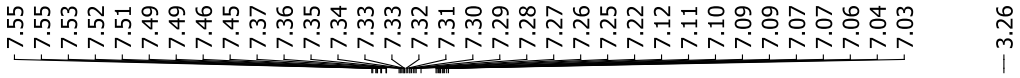



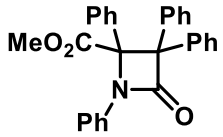



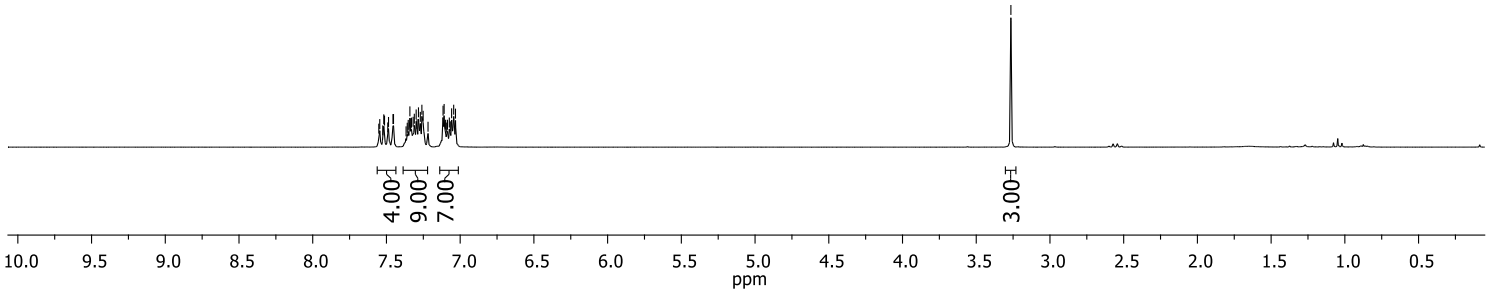
**Molecule 9c - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



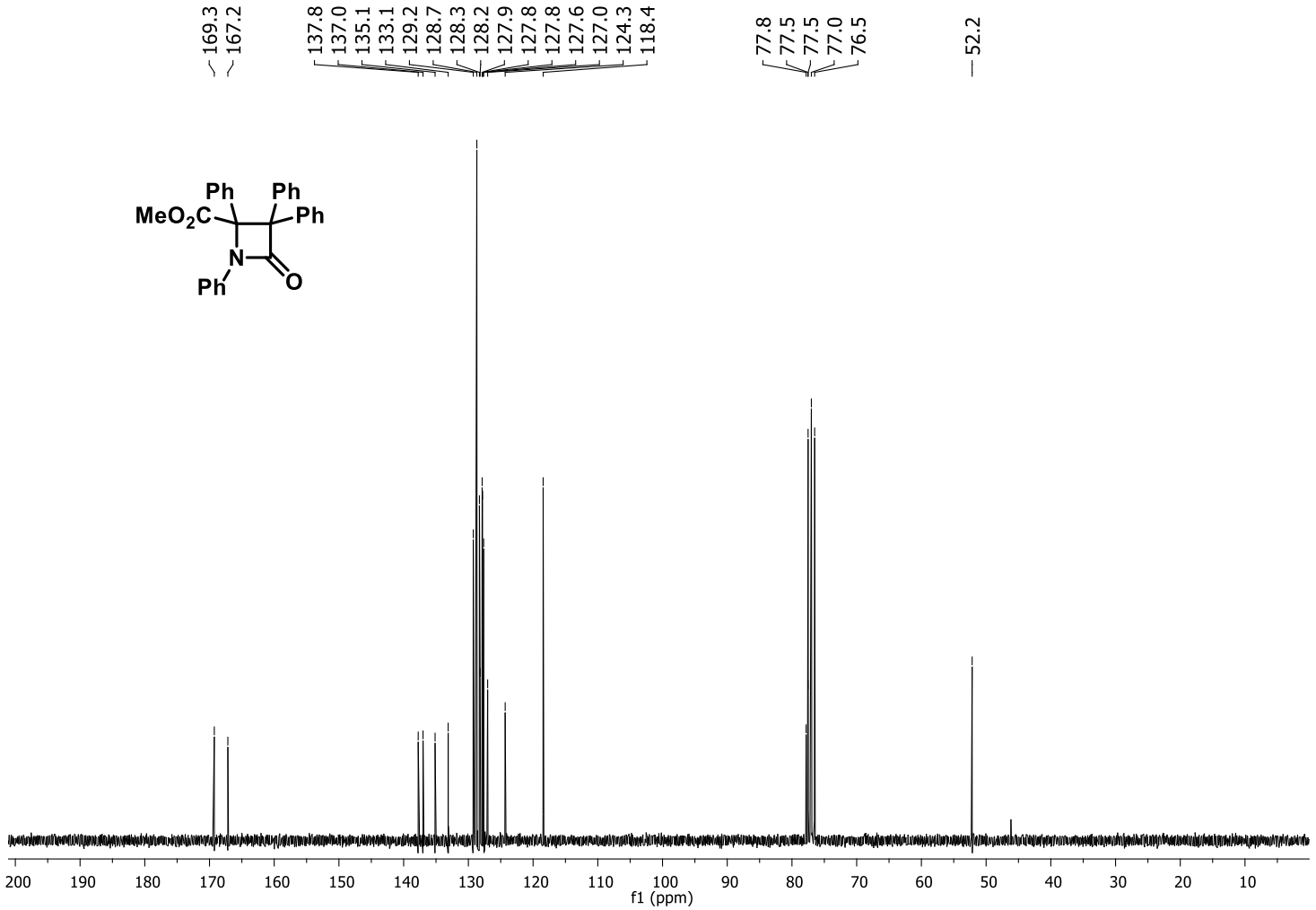
**Molecule 9d - $^{1}$H NMR (250 MHz, $CDCl_3$)**



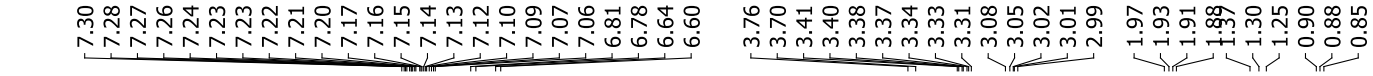



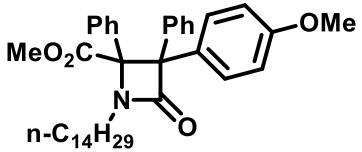



**Molecule 9d - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



**Molecule 9e - $^{1}$H NMR (250 MHz, $CDCl_3$)**

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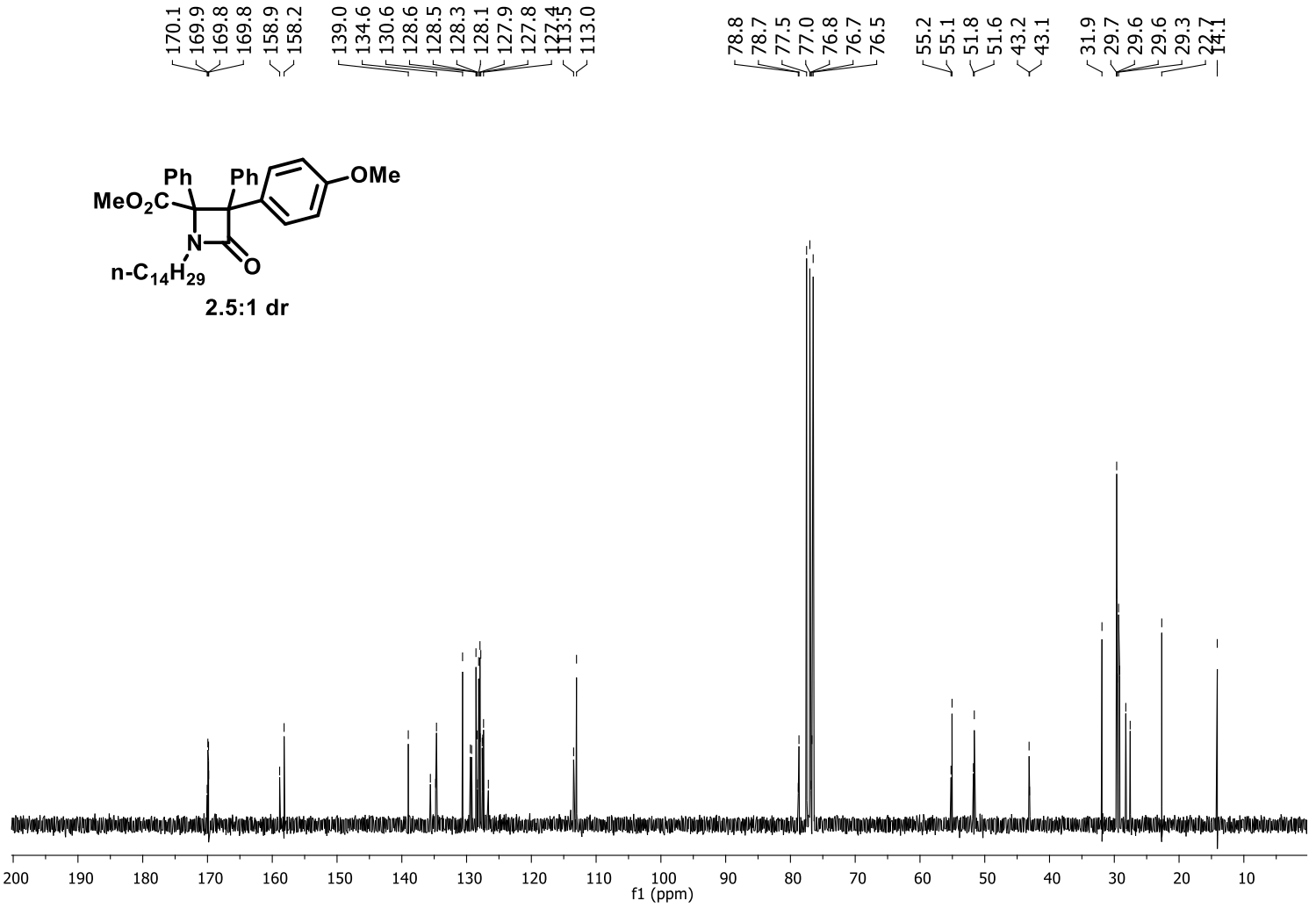
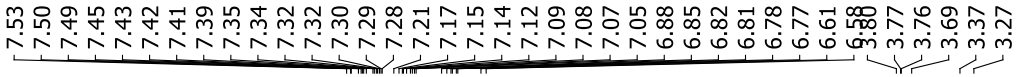
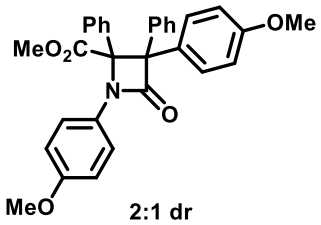
**Molecule 9e - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



**Molecule 9f - $^{1}$H NMR (250 MHz, $CDCl_3$)**

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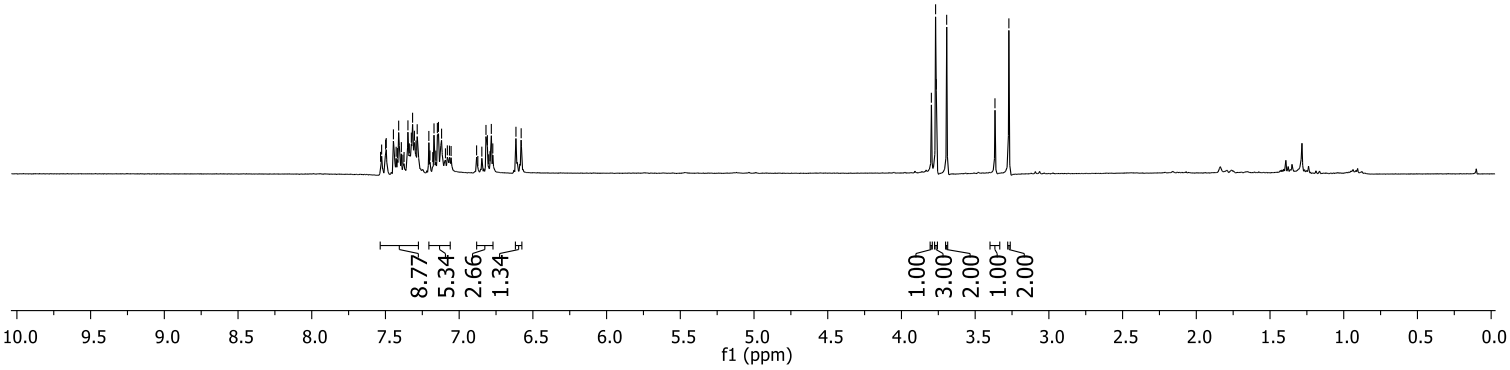
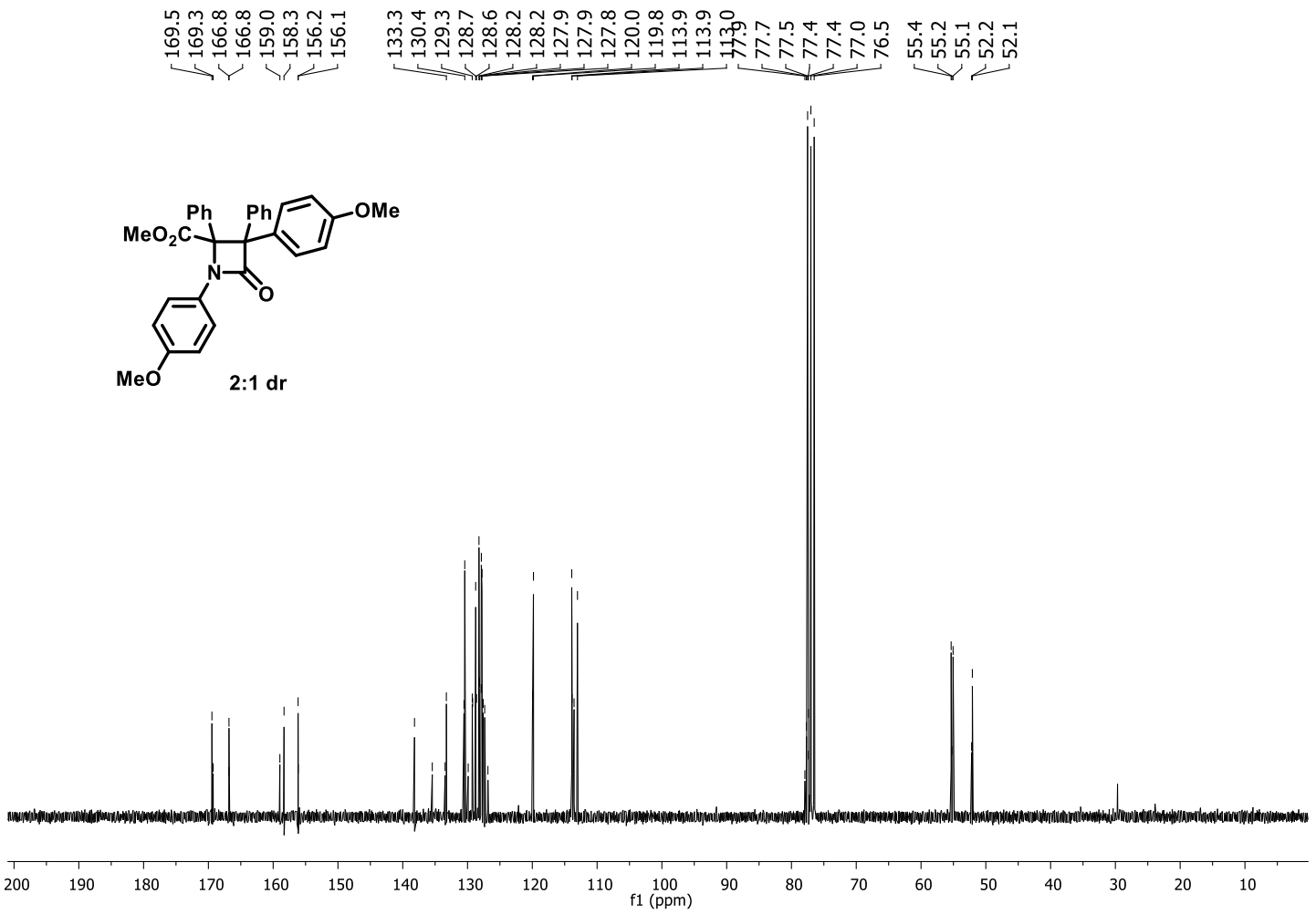
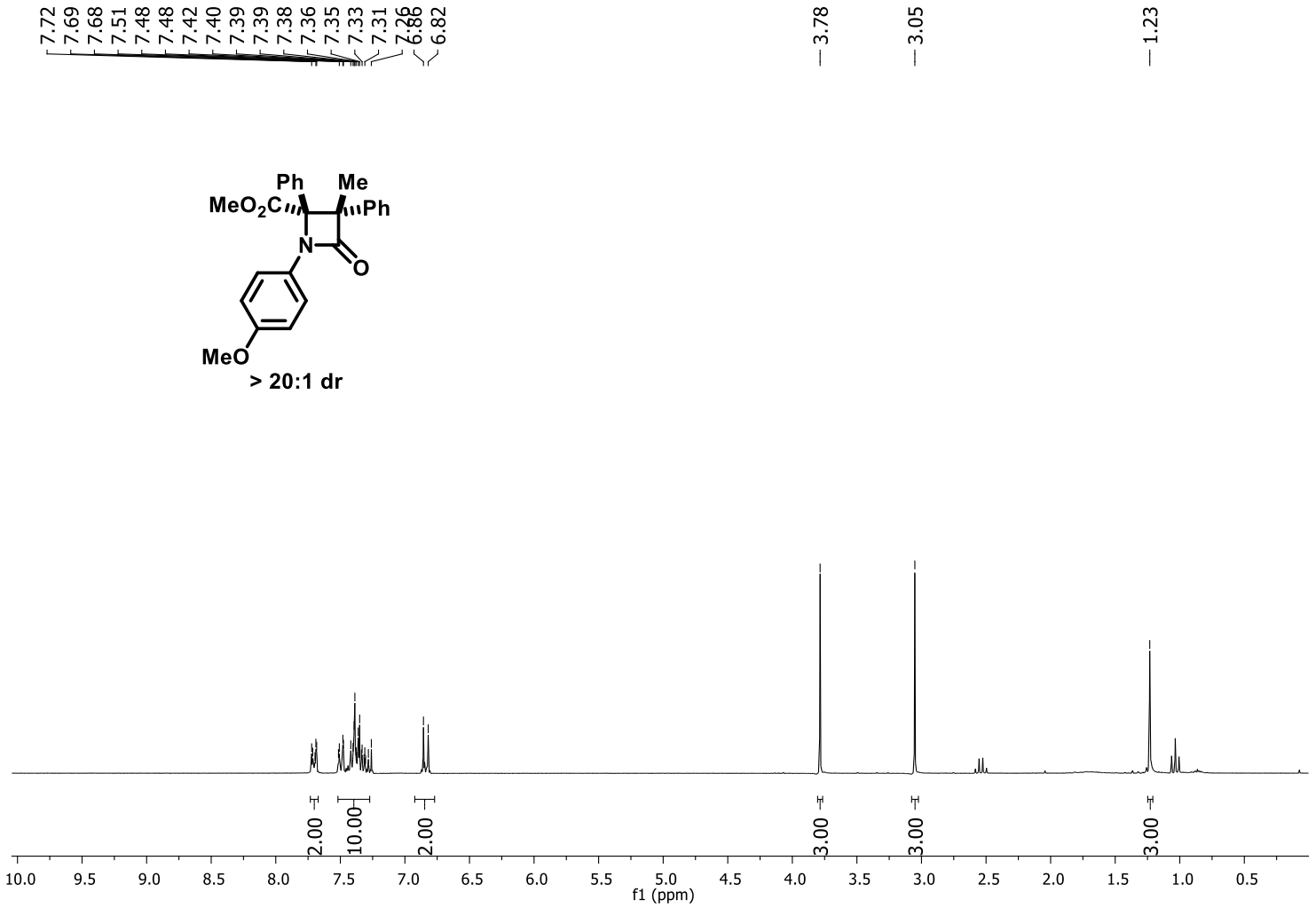


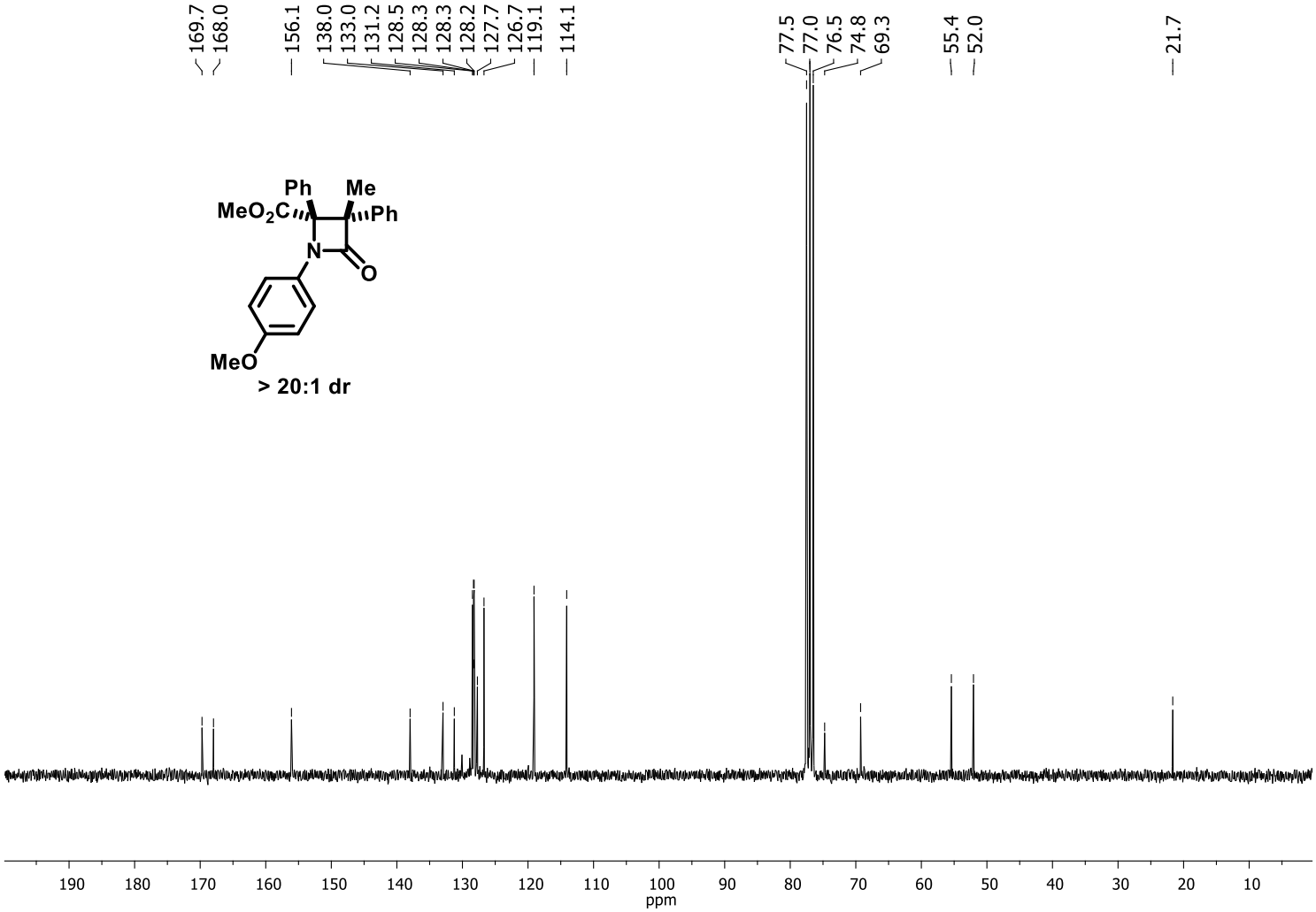
**Molecule 9f - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



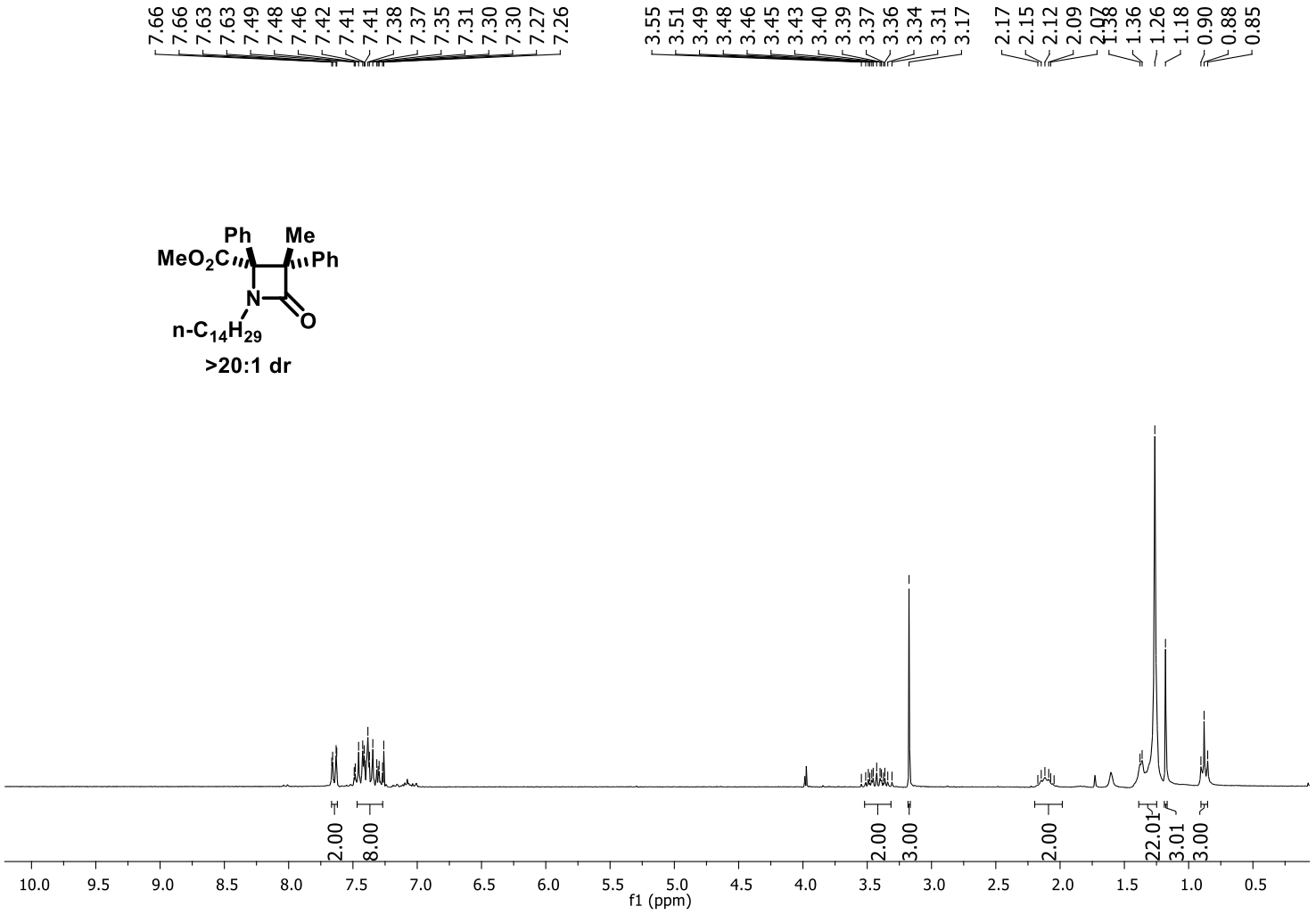
**Molecule 9g - $^{1}$H NMR (250 MHz, $CDCl_3$)**



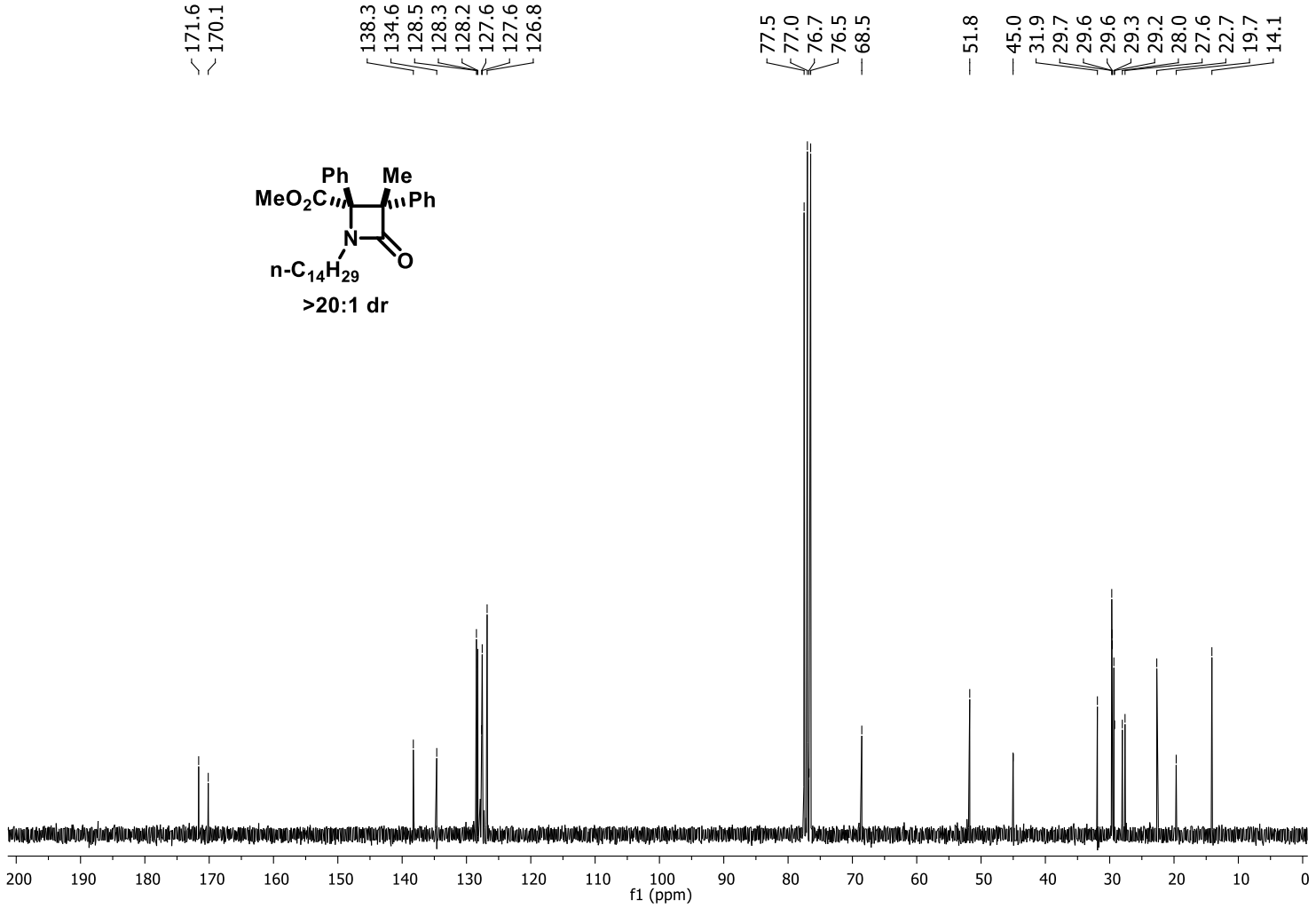
**Molecule 9g - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



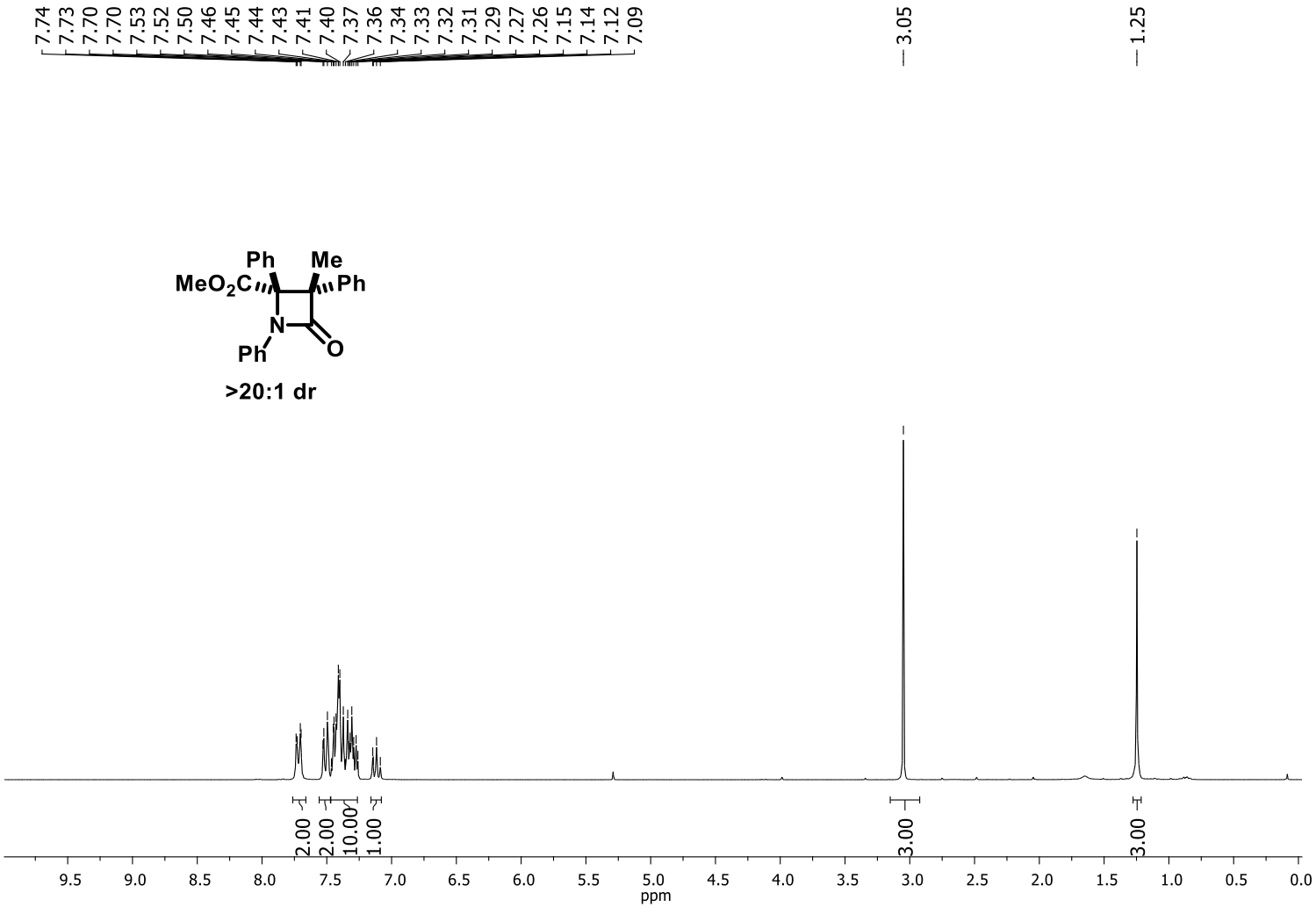
**Molecule 9h - $^{1}$H NMR (250 MHz, $CDCl_3$)**



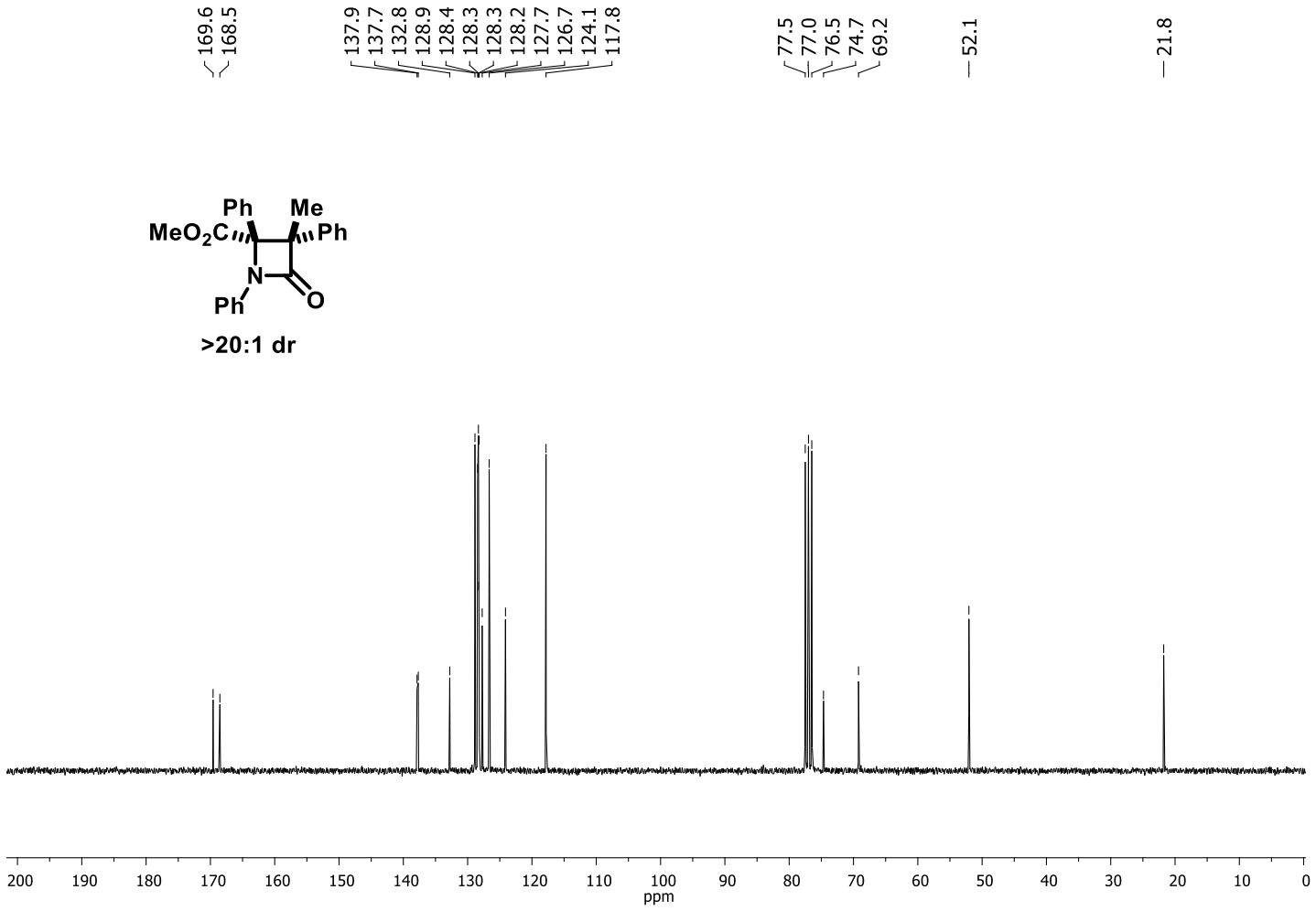
**Molecule 9h - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



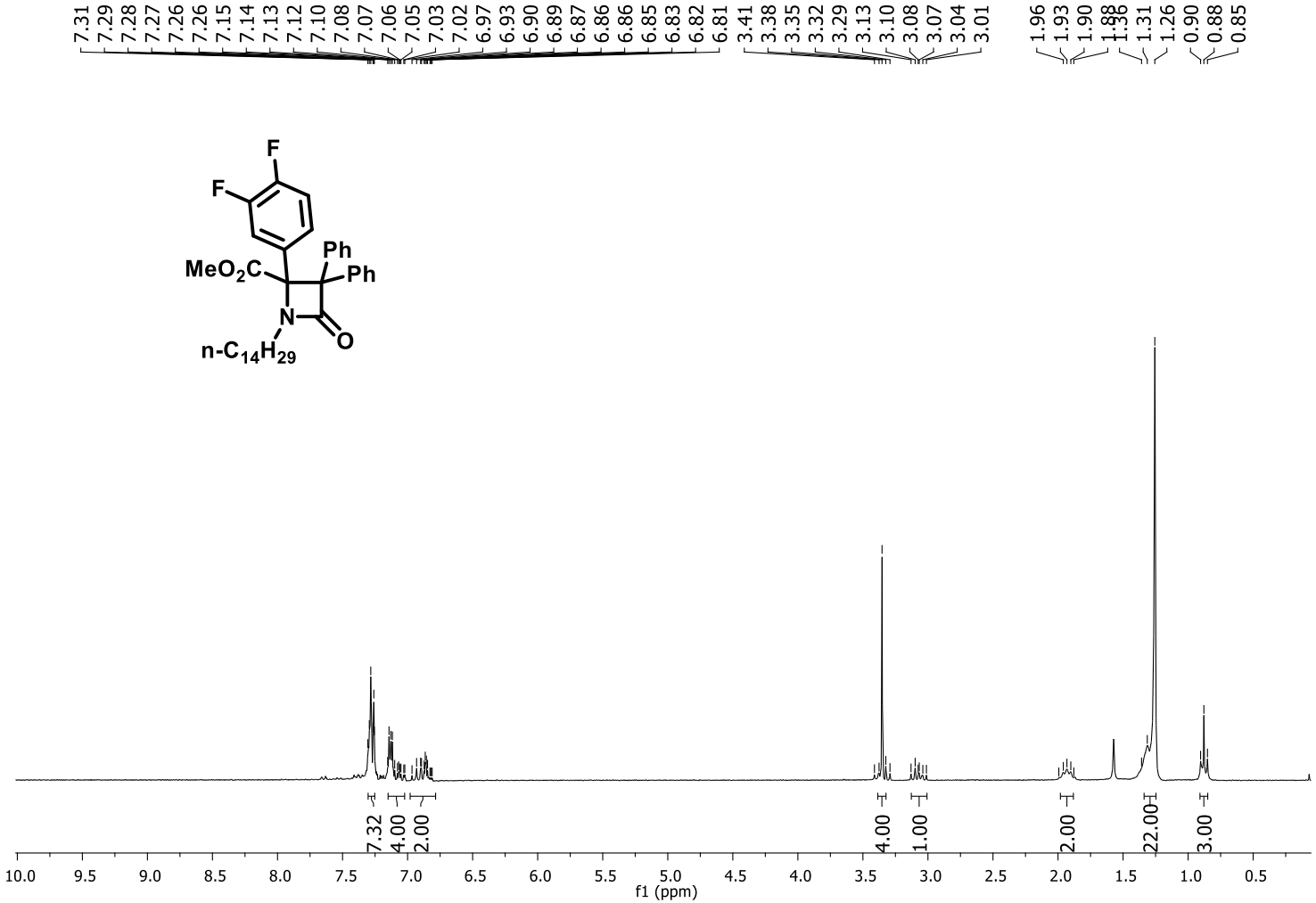
**Molecule 9i - $^{1}$H NMR (250 MHz, $CDCl_3$)**



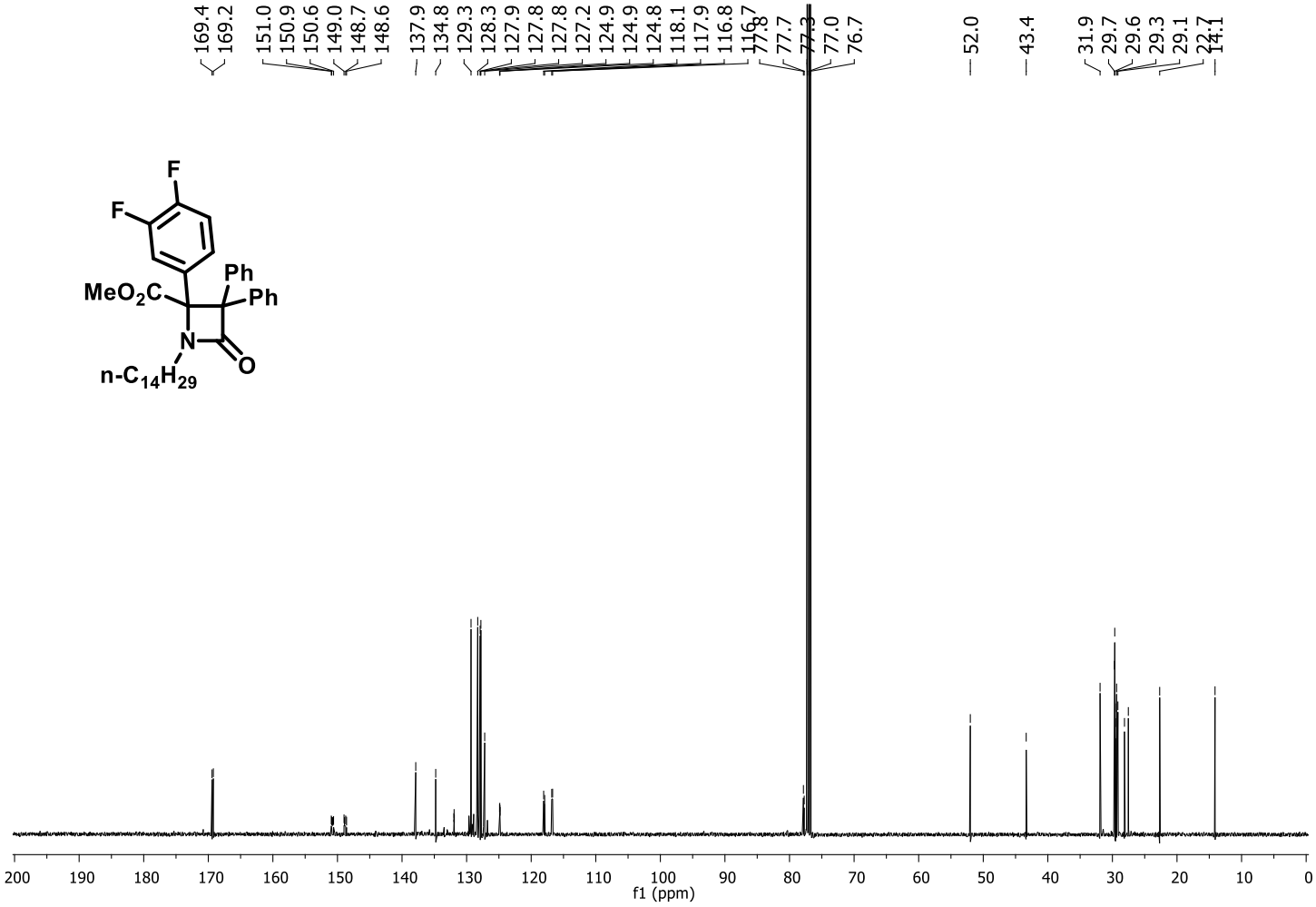
**Molecule 9i - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



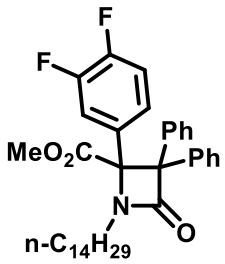
**Molecule 9j - $^{1}$H NMR (250 MHz, $CDCl_3$)**



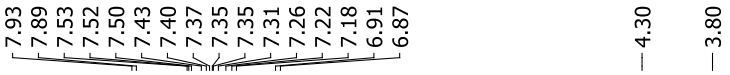
**Molecule 9j - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**

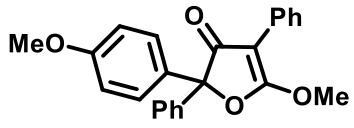


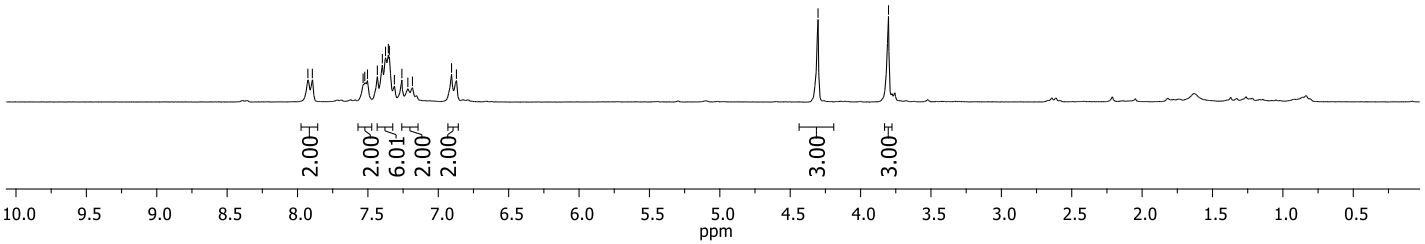
**Molecule 9j - $^{19}$F NMR (235 MHz, $CDCl_3$)**



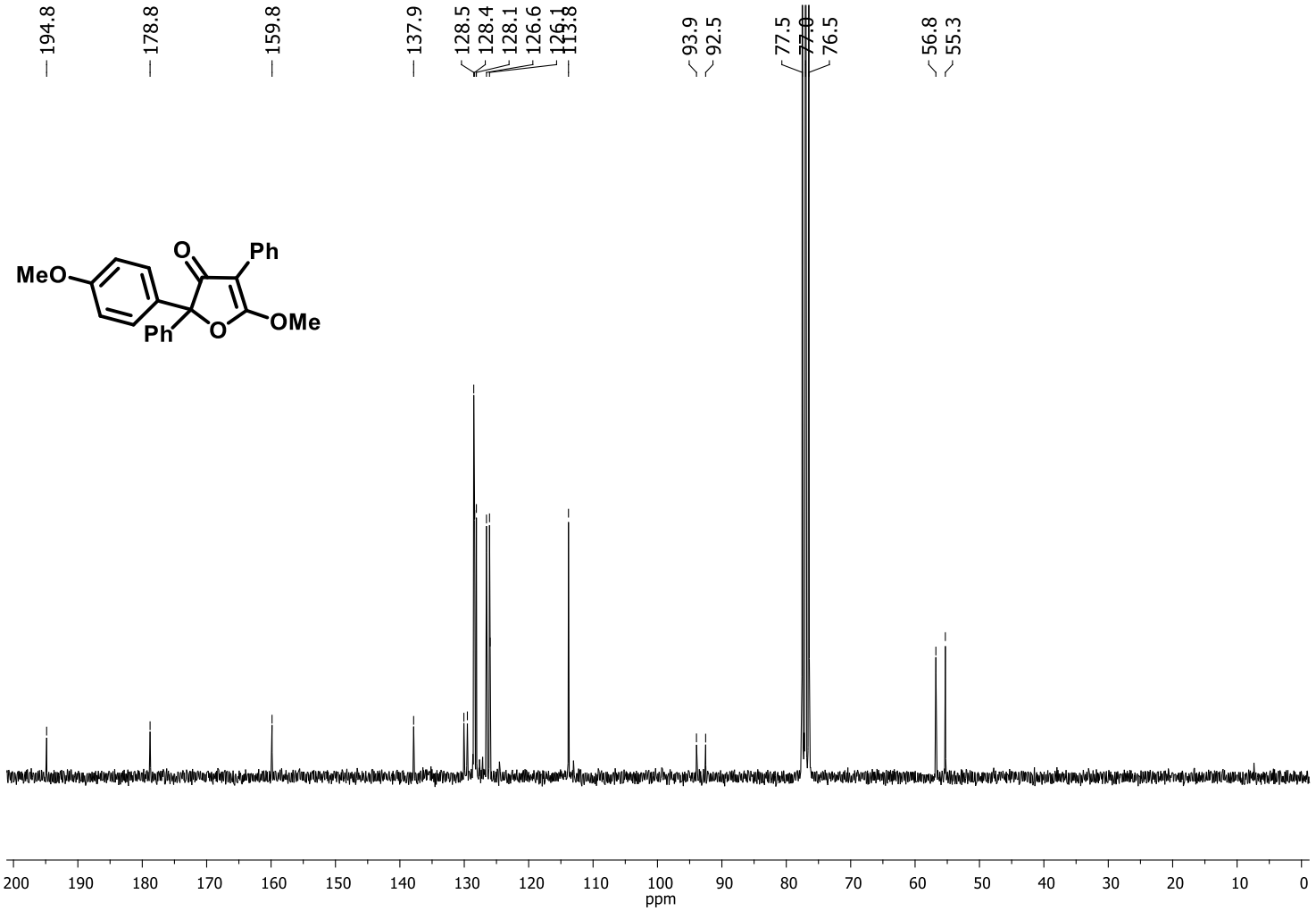
**Molecule 10a - $^{1}$H NMR (250 MHz, $CDCl_3$)**



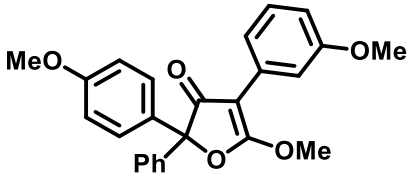



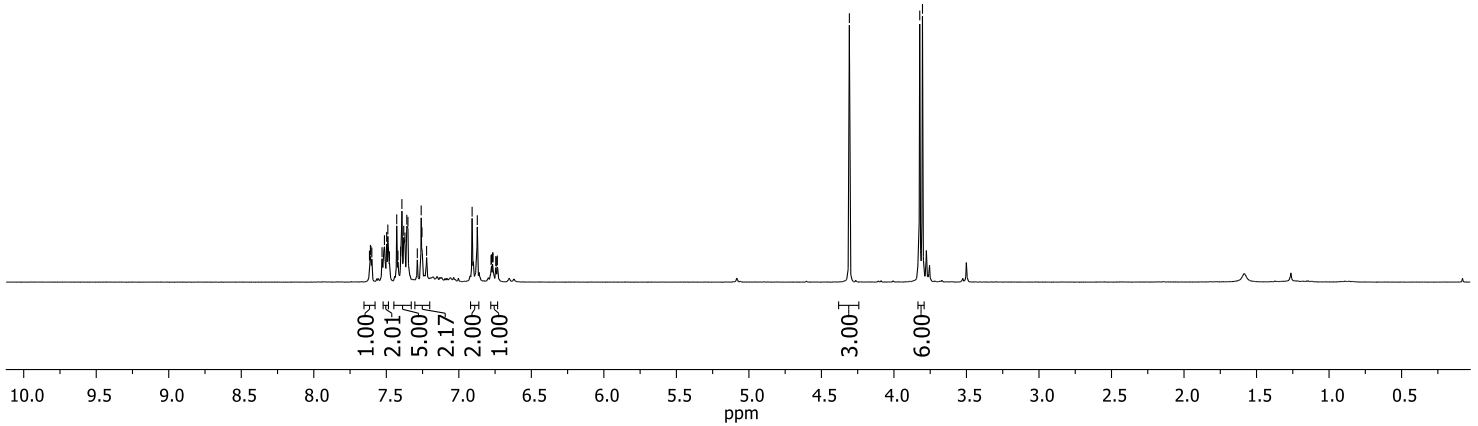



**Molecule 10a - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**

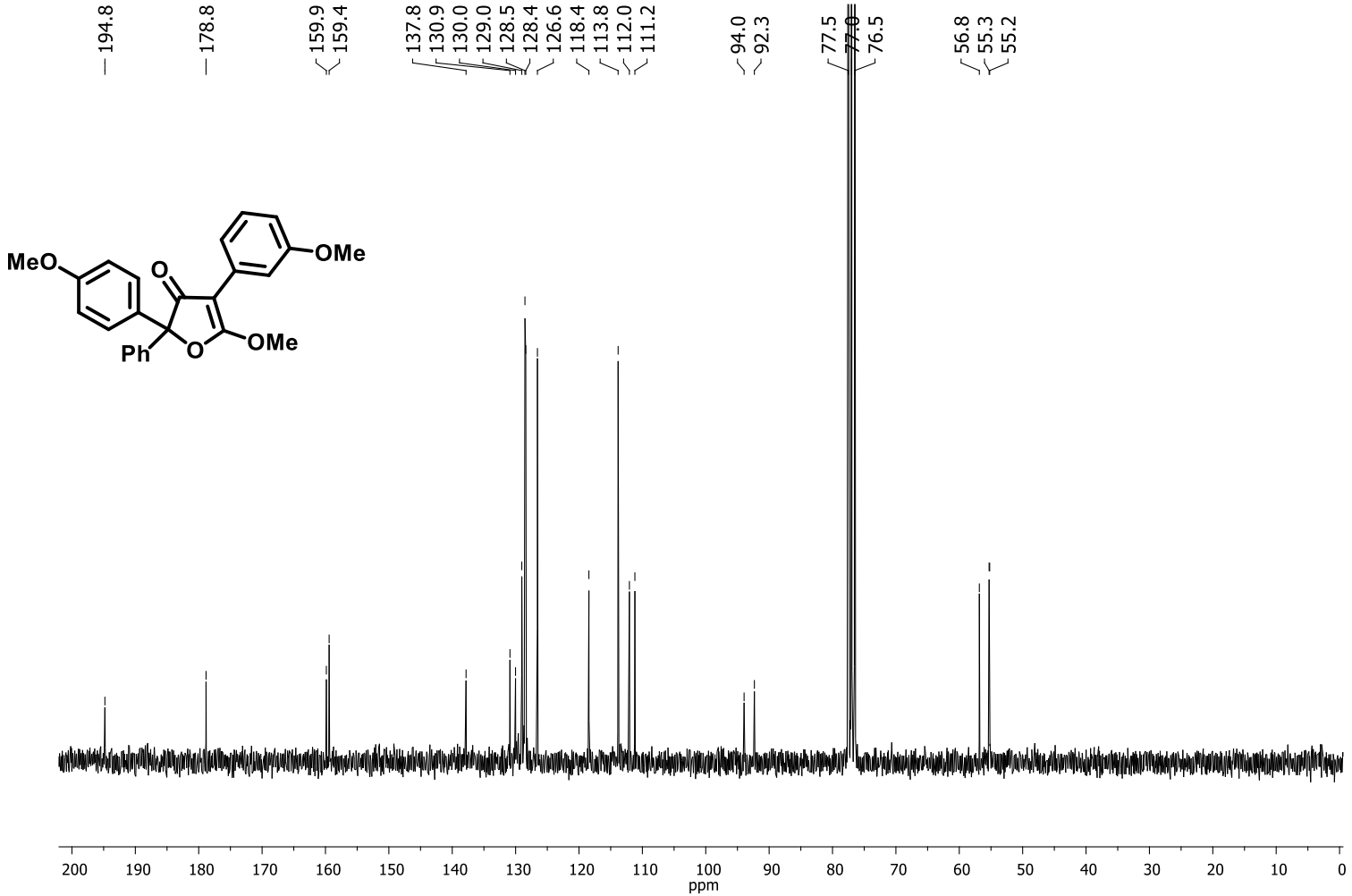


**Molecule 10b - $^{1}$H NMR (250 MHz, $CDCl_3$)**

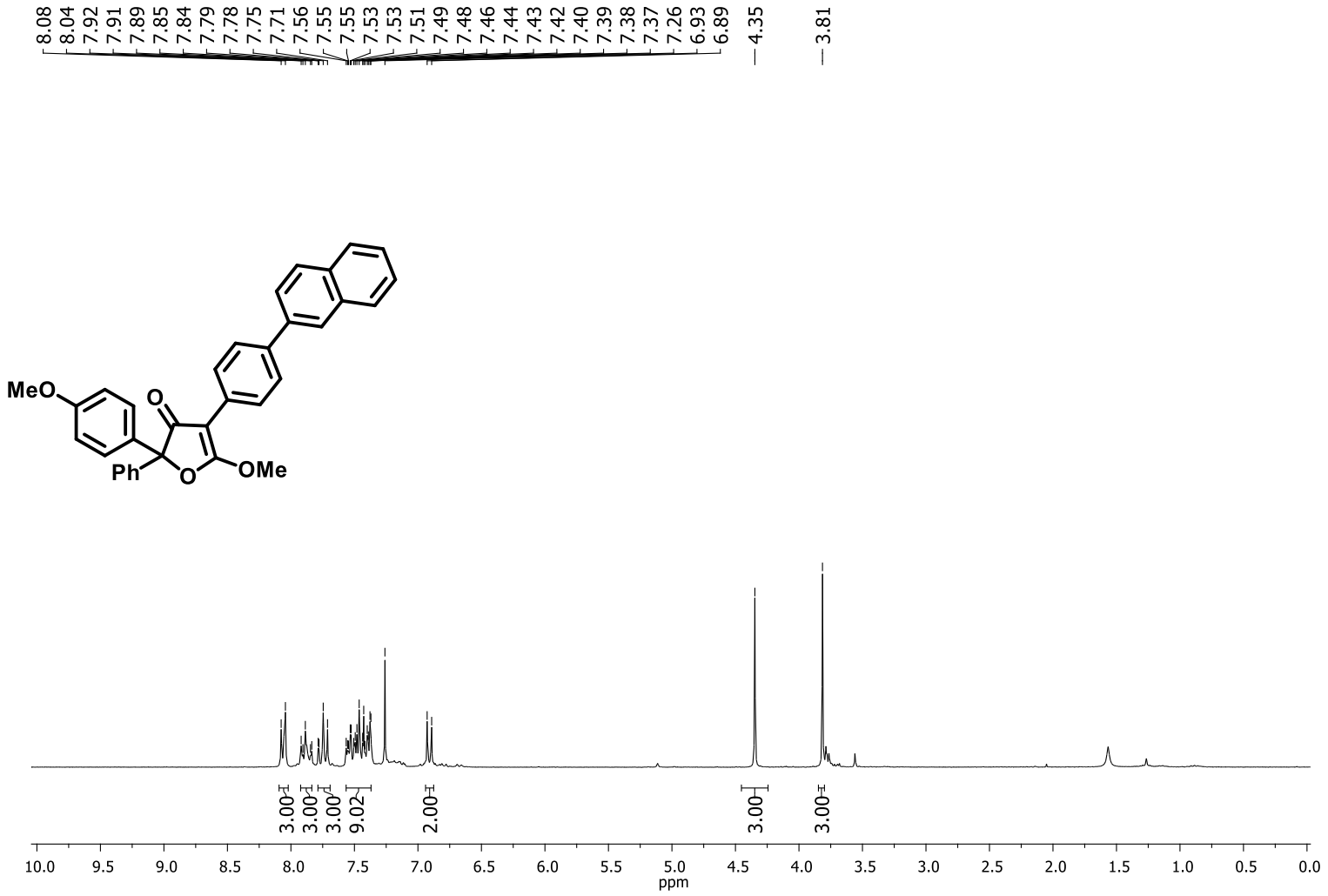



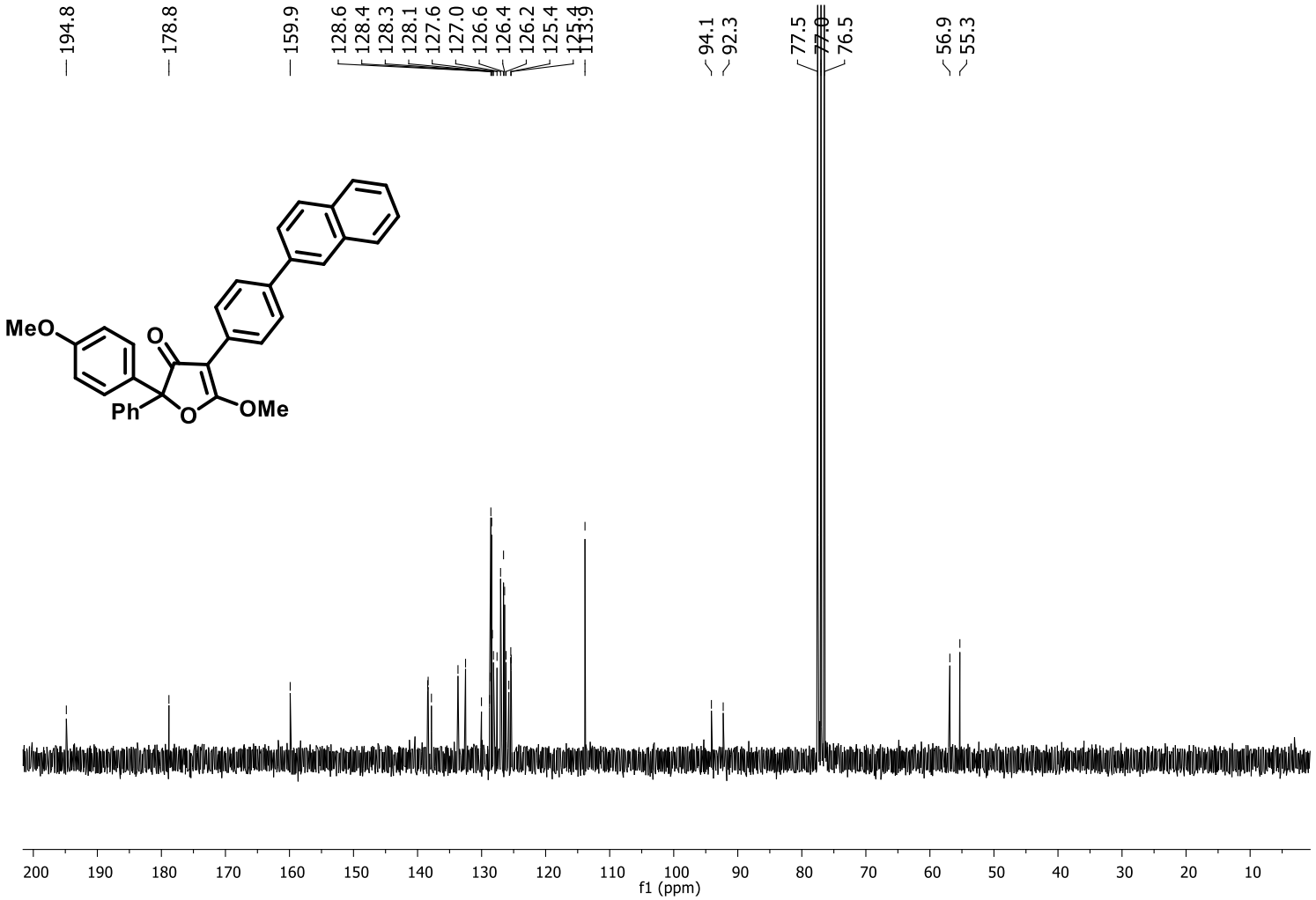
**Molecule 10b - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



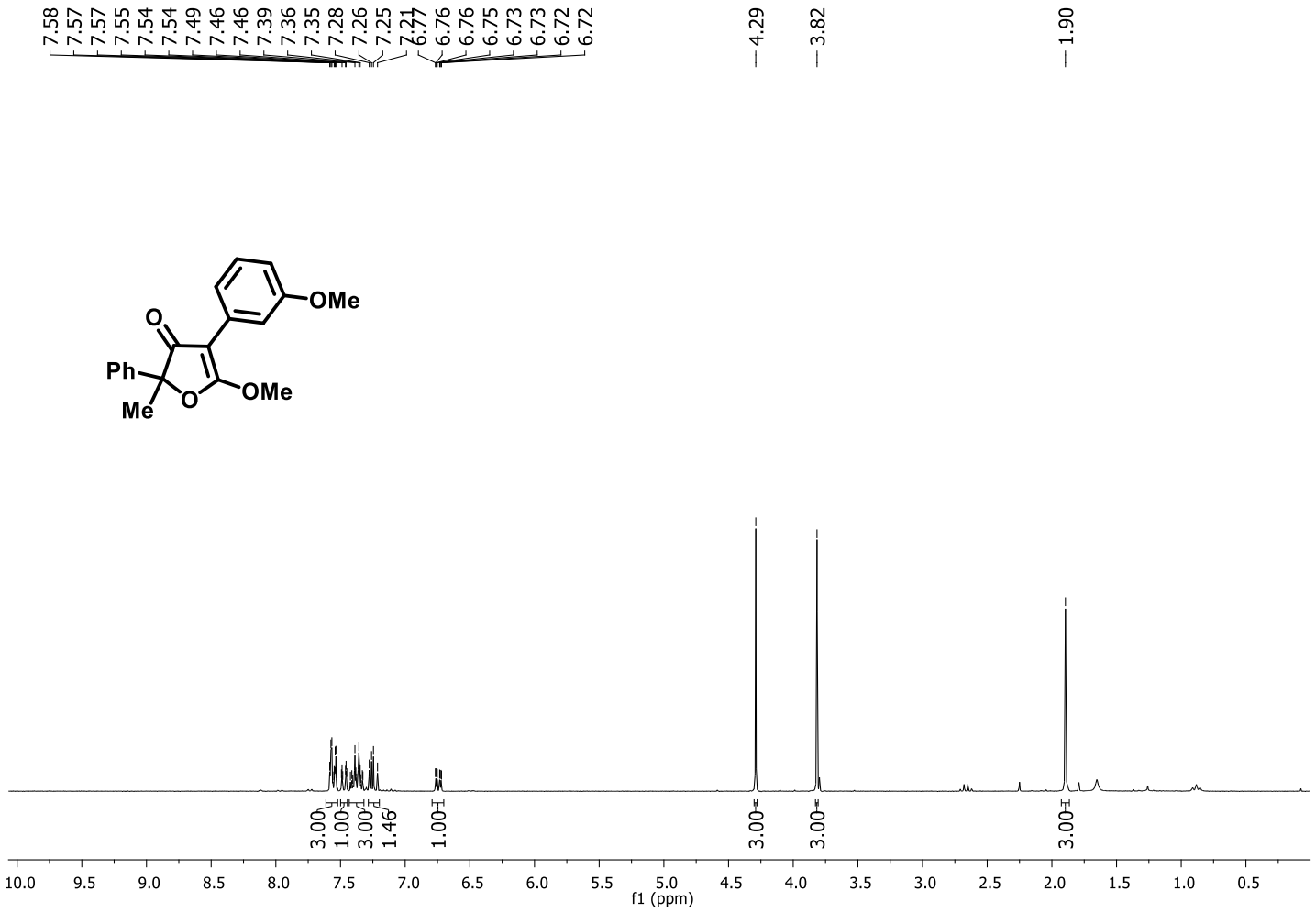
**Molecule 10c - $^{1}$H NMR (250 MHz, $CDCl_3$)**



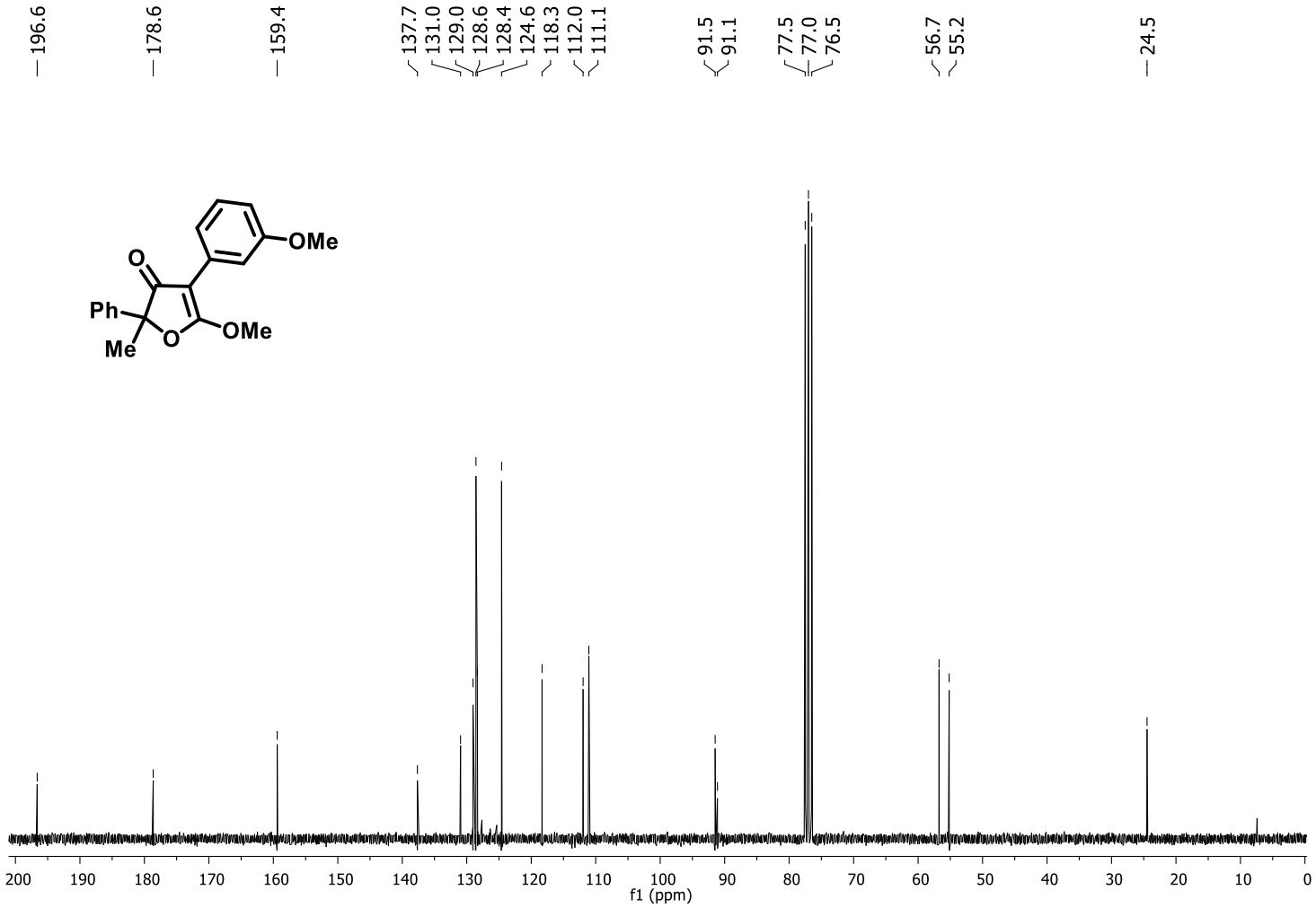
**Molecule 10c - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



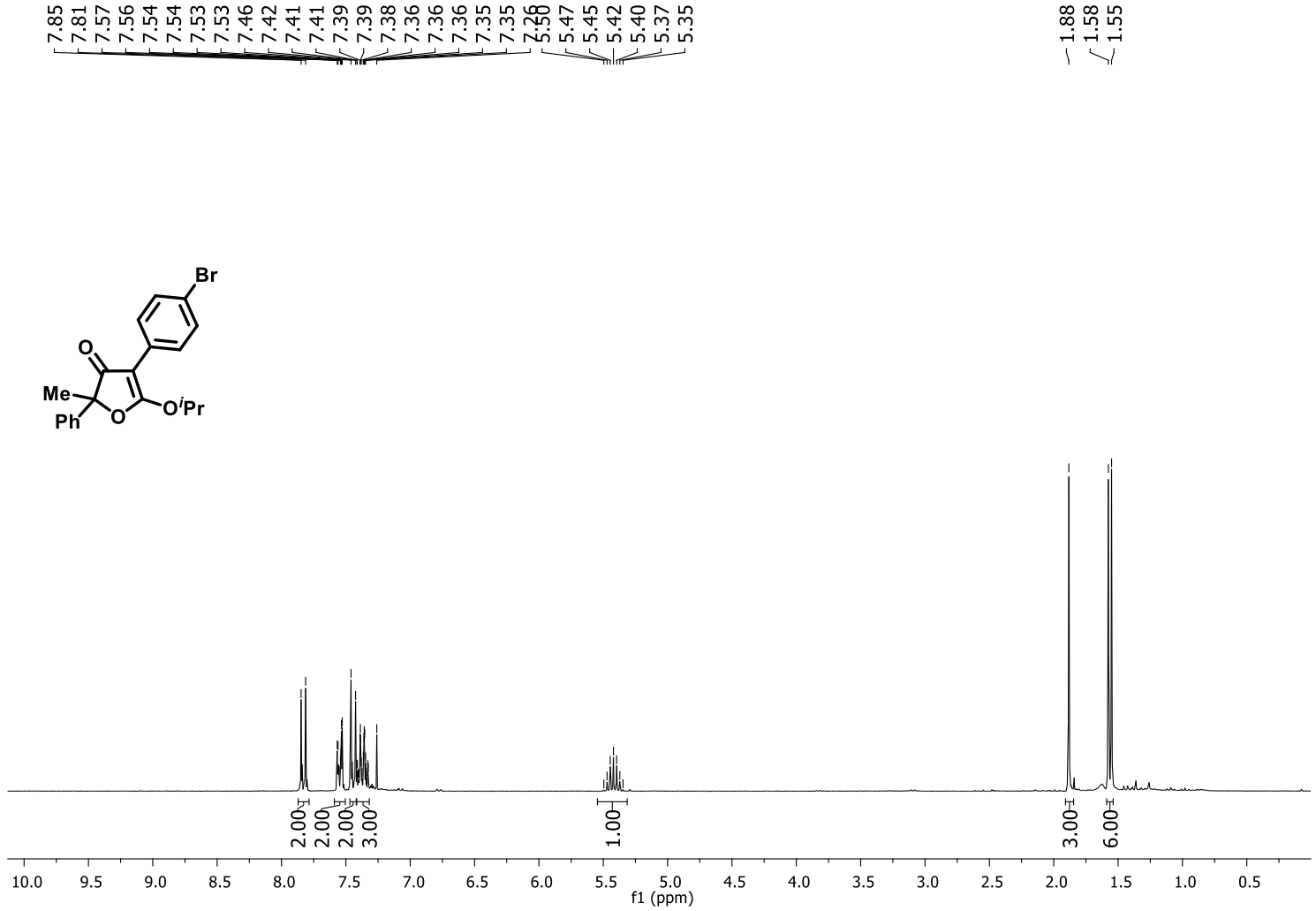
**Molecule 10i - $^{1}$H NMR (250 MHz, $CDCl_3$)**



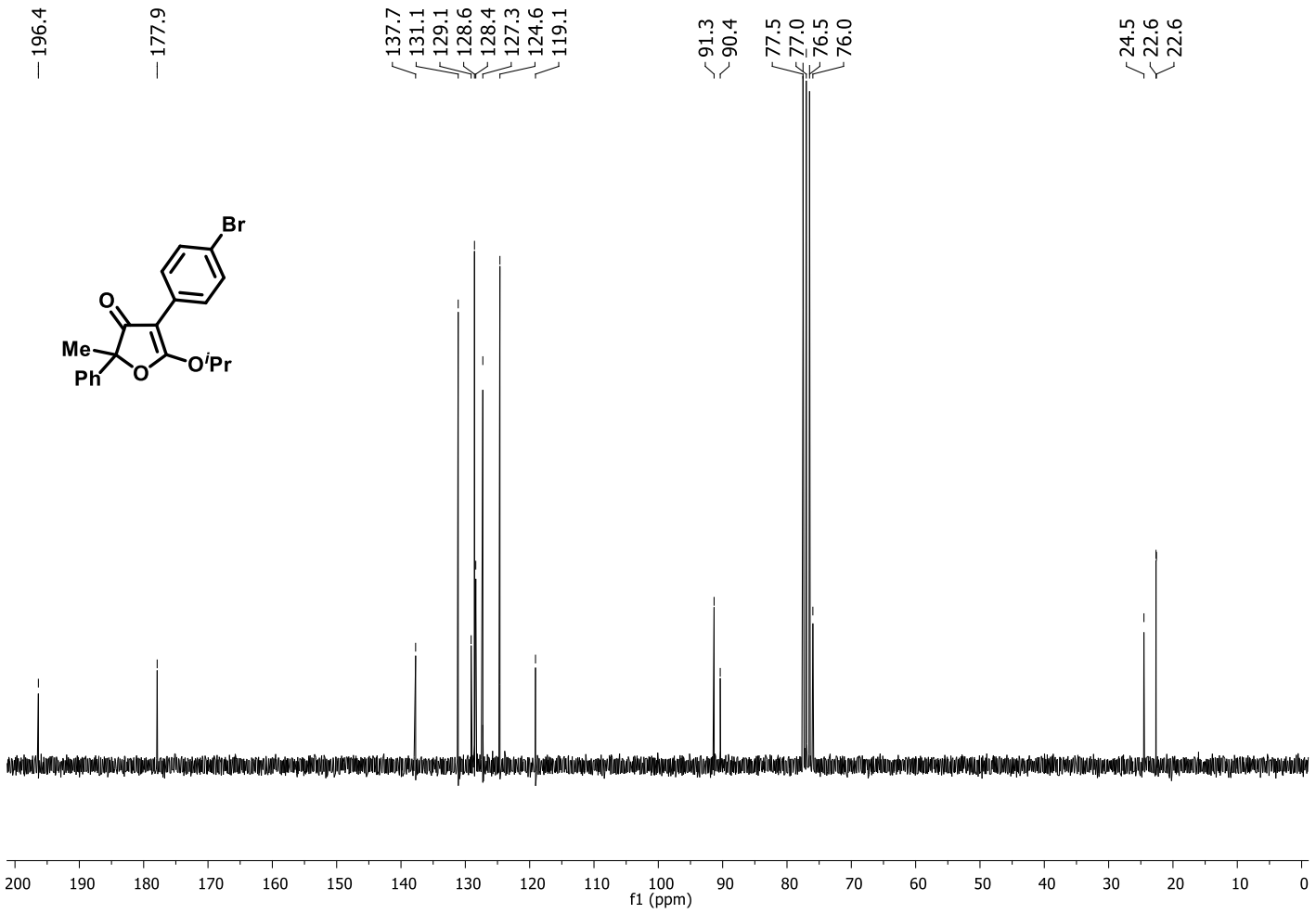
**Molecule 10i - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



**Molecule 10j - $^{1}$H NMR (250 MHz, $CDCl_3$)**



**Molecule 10j – $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



## 6.2 Publicação referente ao trabalho: Inserção de H–F em Diazo Compostos via Condições Térmicas

Organic & Biomolecular Chemistry

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# H–F bond insertions into α-diazo carbonyl compounds†

Laiéli S. Munaretto, Rafael D. C. Gallo, Luiz Paulo M. O. Leão and Igor D. Jurberg *

**A reaction for H–F bond insertion into α-diazo carbonyl compounds is reported. The protocol describes a simple reaction setup employing commercially available HF·pyr (Olah reagent) as the fluorine source. The method is rapid and practical, and allows access to a broad range of α-fluorinated carbonyl compounds in generally good yields.**

Molecules containing one or more fluorine atoms may display interesting physiological activities and physical properties.[1] These features can be arguably attributed to the high electronegativity of fluorine and its somewhat small van der Waal radius (1.47 Å), which is not significantly larger than that of hydrogen (1.20 Å).[2] Because of these unusual properties, perhaps not surprisingly, fluorination chemistry is considered today as an important research endeavor showing numerous potential applications in the fields of medicinal chemistry,[3] agriculture,[4] and materials science.[5] Remarkably, the broader use of fluorinated molecules in these areas is mostly limited by their synthetic availability.

Among the protocols reported for the preparation of different classes of fluorinated molecules, α-fluoro carboxylic acid derivatives have been less explored. Synthetic strategies allowing the access to such compounds generally rely on three main approaches: (i) direct α-fluorination of an appropriate carbonyl compound[6] (Scheme 1a); (ii) post-modification of a previously assembled α-fluoro or α,α-difluoro carbonyl substrate (Scheme 1b);[7] or (iii) fluorination of diazo compounds[8] (Scheme 1c).

The representative methods for (i) are: the asymmetric preparation of α-fluoro *N*-acyl thiazolidin-2-ones described by Sodeoka and co-authors *via* a Ni-catalyzed reaction of *N*-acyl thiazolidin-2-ones with the electrophilic fluorinating agent *N*-fluorobenzenesulfonimide (NFSI);[6a] the synthesis of α-fluorinated esters *via* an N-heterocyclic carbene (NHC)-catalyzed asymmetric reaction between aldehydes and NFSI, in the presence of alcohols, described by Wang and co-authors;[6b] and the preparation of α-fluorinated amides *via* the reaction of an amide with 2-I-pyr and $Tf_2O$, followed by treatment with 2,6-lutidine *N*-oxide (LNO) and then with tetrabutylammonium difluorotriphenylsilicate (TBAT), as reported by Maulide and co-authors[6c] (Scheme 1a). For (ii), several authors have described the cross-couplings of 2-fluoroacetates or 2,2-difluoroacetates with functionalized arenes (Ar-FG, FG = $B(OH)_2$, ZnX, Br, I) or unfunctionalized arenes (ArH) *via* C–H functionalization strategies, using various metal catalysts (Ni,[7a,b] Ru,[7c,d] Pd,[7e,f] and Cu[7g,h]), or a TBAF-promoted decarboxylative arylation protocol of fluoromalonamates, as described by Mohanan and co-authors[7i] (Scheme 1b). For (iii), methods involving diazo compounds can be divided into categories according to the electron donating/withdrawing nature of their substituents.[8] Huang, Yu and co-authors reported the reaction of acceptor–acceptor diazo compounds with NFSI and aryl boronic acids, in the presence of a Rh(III) catalyst, to afford the corresponding 2-aryl-2-fluoro-derived compounds.[8a] Hayes, Moody and co-authors reported the use of $HBF_4$ as a nucleophilic fluorinating agent reacting with 2-diazo-β-ketoesters[8b] (a Balz–Schiemann-like approach[9]). Szabó and co-authors described the reaction of acceptor-only diazo compounds with 1-fluoro-3,3-dimethyl-1,2-benziodoxole in the presence of alcohols to afford the corresponding 2-alkoxy-2-fluoro ketones.[8c] Li, Huang and co-authors reported a protocol employing donor–acceptor diazo compounds and NFSI under purely thermal conditions (heating at 60 °C) in 1,2-dichloroethane to produce the corresponding 2-fluoro-2-(*N*-(phenylsulfonyl)phenylsulfonamido)acetates.[8d] Doyle and co-workers reported a virtually racemic (*i.e.* poorly enantioselective) Cu(I)-catalyzed fluorination of aryldiazoacetates (and other diazo compounds) using KF,[8e] and Fürstner and co-authors developed a Cu(I)-catalyzed asymmetric fluorination protocol of donor–acceptor diazo compounds employing CsF as the fluorine source[8f] (Scheme 1c).

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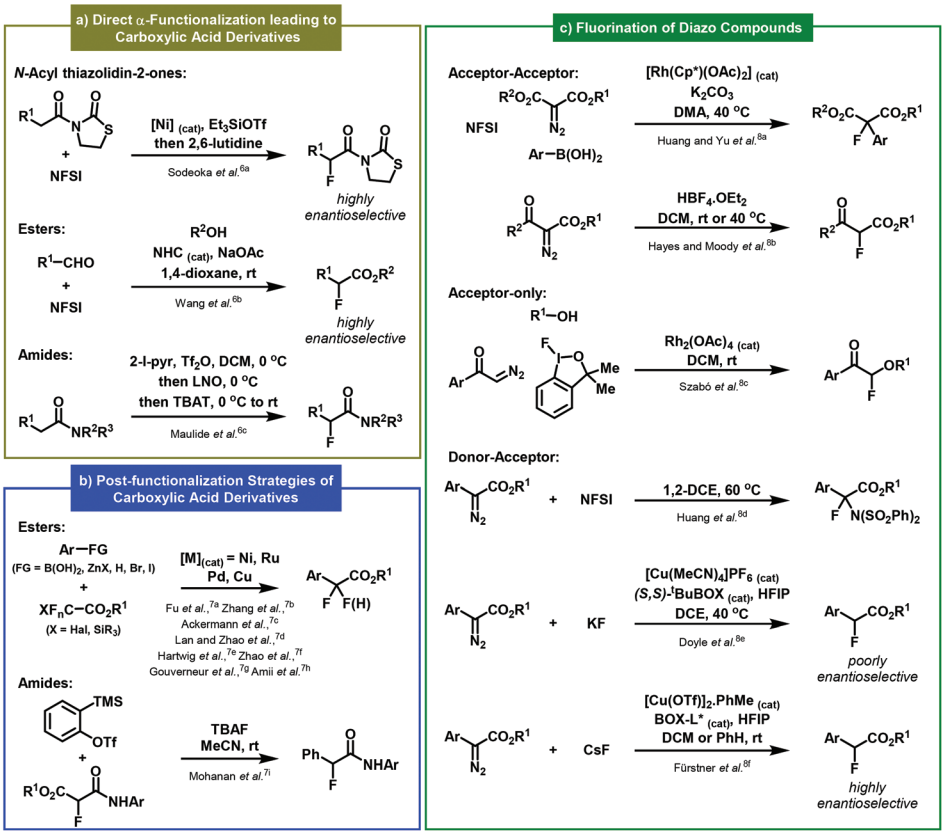
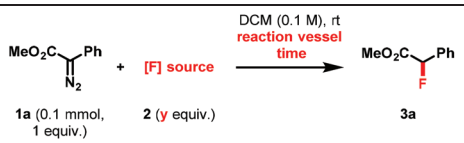
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2ob00400c




**Scheme 1** A selection of representative strategies to synthesize α-fluorinated carbonyl compounds.

**Table 1** Optimization studies




| Entry | [F] source | *y* | Reaction vessel | Time (h) | Yield **3a** [a] (%) |
|---|---|---|---|---|---|
| 1 | HF·pyr | 3 | Glass vial | 5 | 15 |
| 2 | HF·pyr | 3 | Plastic Eppendorf tube | 5 | 85 |
| 3 | HF·pyr | 3 | Plastic Eppendorf tube | 1 | 80 |
| 4 | HF·pyr | 6 | Glass vial | 5 | 30 |
| 5 | HF·pyr | 6 | Plastic Eppendorf tube | 5 | 95 |
| 6 | HF·pyr | 1 | Plastic Eppendorf tube | 0.5 | 37 |
| 7 | HF·pyr | 2 | Plastic Eppendorf tube | 0.5 | 67 |
| 8 | HF·pyr | 3 | Plastic Eppendorf tube | 0.5 | 80 |
| 9 | HF·pyr | 6 | Plastic Eppendorf tube | 0.5 | 80 |
| 10 | HF·pyr | 1 | Plastic Eppendorf tube | 1 | 66 |
| 11 | HF·pyr | 2 | Plastic Eppendorf tube | 1 | 80 |
| 12 | HF·pyr | 3 | Plastic Eppendorf tube | 1 | 80 |
| **13** | **HF·pyr** | **6** | **Plastic Eppendorf tube** | **1** | **99** |
| 14[b] | HF·pyr | 6 | Plastic Eppendorf tube | 1 | 95 |
| 15 | HF·$Et_3N$ | 6 | Plastic Eppendorf tube | 1 | 5 |
| 16 | $KHF_2$ | 6 | Plastic Eppendorf tube | 1 | < 5 |
| 17 | $KHF_2$/TFA (6 eq.) | 6 | Plastic Eppendorf tube | 1 | < 5 |
| 18 | KF | 6 | Plastic Eppendorf tube | 1 | < 5 |
| 19 | KF/HFIP (6 eq.) | 6 | Plastic Eppendorf tube | 1 | < 5 |

[a] Determined by $^1$H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b] Reaction was performed under blue light irradiation.

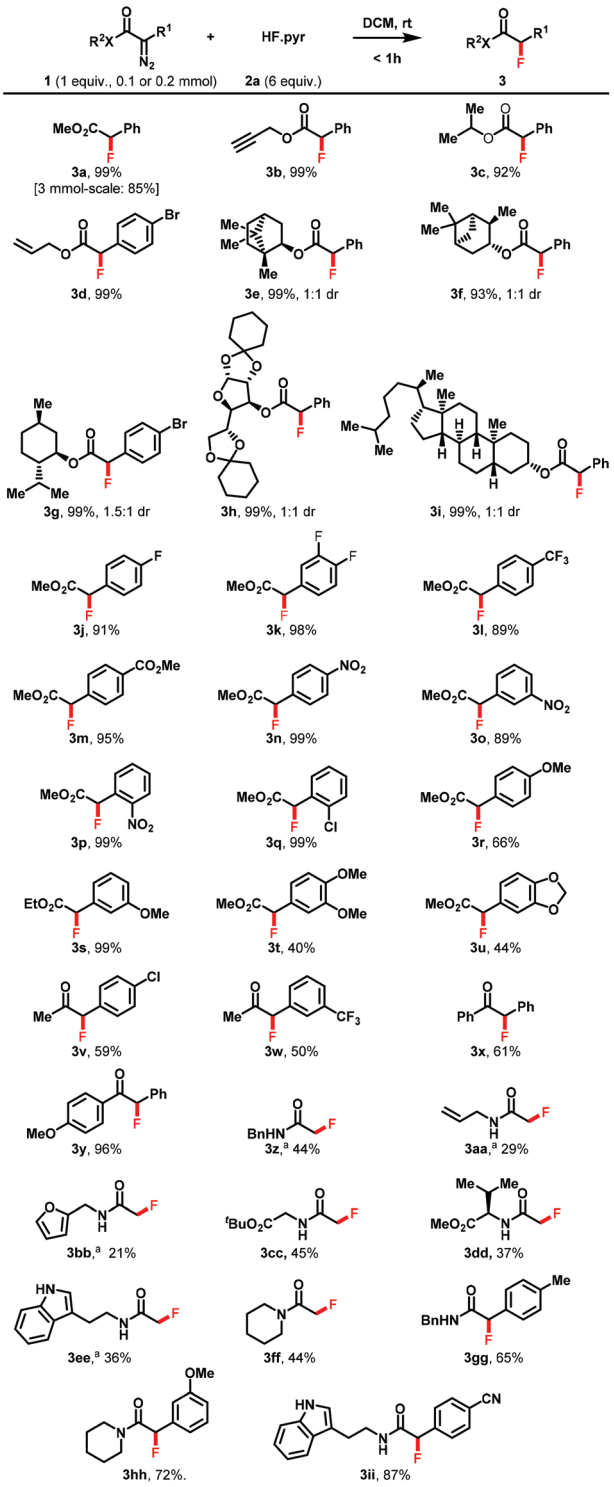
 

On the other hand, in 1974, George Olah described the use of HF·pyr as the reaction solvent employed for the nucleophilic fluorination of different classes of organic molecules,[10] including a limited number of acceptor-only diazo compounds, which have been isolated only in modest yields.[11] Inspired by these early results, we decided to investigate this preliminary reactivity in more detail aiming at the possibility of developing a new method having a significantly expanded scope.[12,13]

The reaction between diazo compound **1a** and HF·pyr **2a** was investigated as our model reaction aiming at the preparation of α-fluorinated ester **3a** (Table 1). Initial investigation on the reaction efficiency was performed in a glass vial for 5 h using 3 equiv. of HF·pyr **2a**, and only afforded a poor 15% yield of **3a** (Table 1, entry 1). On recognizing that HF can attack the glass walls of our reaction vessel and be inadvertently consumed, we changed the reaction vessel to a plastic Eppendorf tube, and a significantly higher yield of **3a** of 85% was obtained this time (Table 1, entry 2). Interestingly, a shorter reaction time of 1 h produced a somewhat similar yield of 80% of **3a** (Table 1, entry 3). The reaction efficiency increased when performing this fluorination approach in a glass or plastic reaction vessel with a larger excess of 6 equiv. of HF·pyr for 5 h to afford **3a** in 30% and 95% yields, respectively (Table 1, entries 4 and 5). Then, evaluating different stoichiometries of HF·pyr **2a** at shorter reaction times of 30 min and 1 h (Table 1, entries 6–13) showed that the best result of the series was 99% yield of **3a**, that was obtained when using 6 equiv. of HF·pyr for a reaction time of 1 h (Table 1, entry 13). Irradiation of this reaction system with blue light[14] did not offer any additional improvement, as a 95% yield of **3a** was obtained (Table 1, entry 14). Finally, other fluorinating agents were also tested in thermal reactions and did not produce any significant conversions toward **3a** (Table 1, entries 15–19).

With the optimal reaction conditions in hand, we moved forward to investigate the scope of this transformation. The reaction proved to be quite general, and a rich variety of α-diazo carbonyl compounds could be efficiently fluorinated (Scheme 2).

Donor–acceptor diazo compounds **1** containing different ester groups typically produced excellent results, as evidenced by the preparation of **3a–3i**, all in yields above 90%. α-Fluorinated ester **3a** was also synthesized on a preparative scale (using 3 mmol of **1a**) in a slightly lower 85% yield. When considering the use of chiral alcohols as possible chiral auxiliaries for this transformation, as evaluated in the preparation of compounds **3e–3i**, no marked diastereoselectivities were noted: varying values of dr from 1 : 1 to 1.5 : 1 were obtained. On considering different aryl substituents in aryldiazoacetates, electron-withdrawing or weakly electron-donating groups were generally well tolerated, but strong electron-donating groups could have a negative impact on the efficiency of the desired fluorination. For instance, α-fluorinated esters **3j** (91%), **3k** (98%), **3l** (89%), **3m** (95%), **3n** (99%), **3o** (89%), **3p** (99%), **3q** (99%) and **3s** (99%) were all produced in high yields, while reactions toward compounds **3r** (66%), **3t** (40%) and **3u** (44%) showed markedly lower efficiencies, even though they could still be prepared in synthetically useful yields. In addition, several aryldiazoketones could also be fluorinated in a range of moderate to good yields: **3v** (59%), **3w** (50%) and **3x** (61%), while **3y** was prepared in an excellent 96% yield. In addition,




**Scheme 2** Reaction scope of the fluorination protocol. [a] Reaction was performed using 3 equiv. of HF·pyr **2a**.

acceptor-only diazo compounds containing amide groups could also be fluorinated, albeit in lower yields: **3z** (44%), **3aa** (29%), **3bb** (21%), **3cc** (45%), **3dd** (37%), **3ee** (36%) and **3ff** (44%). Some additional tests were conducted with some of these acceptor-only diazo compounds, and it was possible to reduce the amount of HF·pyr employed to 3 equiv., because it produced virtually the same yields as those when 6 equiv. were employed (*cf.* **3z**, **3aa**, **3bb** and **3ee**, Scheme 2. See the ESI† for additional details). Finally, donor–acceptor diazo compounds containing amide groups afforded somewhat higher yields, thus showcasing the benefit of having an aryl ring on the structure of the substrate for the reaction efficiency: **3gg** (65%), **3hh** (72%) and **3ii** (87%) (Scheme 2).

Furthermore, attempts to fluorinate acceptor–acceptor diazo compounds **1jj**, **1kk**, and **1ll** leading to the corresponding compounds **3jj**, **3kk**, and **3ll**, respectively, using our optimized conditions were only met with failure, and the starting diazo compounds could be recovered untouched (Fig. 1). This reactivity might be possibly attributed to the lower nucleophilicity of such compounds, which cannot be as readily protonated by HF·pyr as the previously studied diazo compounds.[15] Other diazo compounds also failed to produce their corresponding fluorinated products **3mm**, **3nn**, **3oo**, **3pp** and **3qq**. Instead, only complex mixtures were observed (Fig. 1).

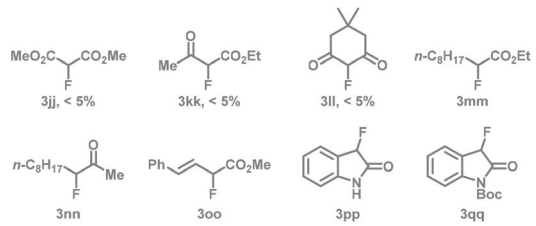
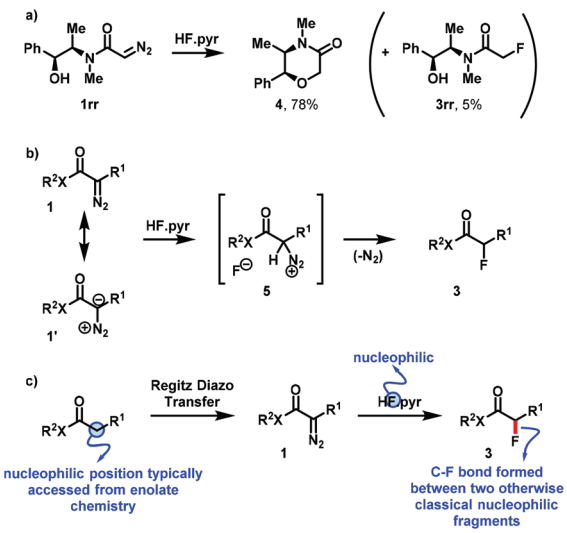



**Fig. 1** Examples of fluorinated compounds that could not be prepared under our optimized conditions.

Remarkably, when attempting the fluorination of diazo compound **1rr** using our optimized conditions, we obtained a 78% yield of non-fluorinated cyclic compound **4**, in combination with only a very poor 5% yield of the desired α-fluorinated amide **3rr** (Scheme 3a).

Therefore, based on the general reactivity observed previously (Scheme 2 and Fig. 1), and the formation of cyclic compound **4**, it seems reasonable to propose a mechanism initially starting with the protonation of diazo compound **1** with HF·pyr **2a**, thus leading to an intermediate **5**, which can undergo a substitution reaction leading to the corresponding α-fluorinated compound **3** (Scheme 3b). In addition, it is interesting to note that as most of the diazo compounds **1** employed in this work were prepared from the parent ester or ketone *via* a Regitz diazo transfer strategy (see the ESI† for details), in these cases, this overall strategy can be seen as an umpolung approach, where the parent ester or ketone is α-fluorinated using a nucleophilic fluorine source (Scheme 3c).




**Scheme 3** (a) Product distribution observed when attempting the fluorination of diazo compound **1rr**. (b) Proposed reaction mechanism. (c) Concept of umpolung for the reactions of H–F insertion into diazo compounds that are accessed from the parent ester or ketone *via* Regitz diazo transfer protocols.

## Conclusions

In summary, we developed a highly practical, fast and versatile approach to synthesize various α-fluorinated carbonyl compounds in a general range of good to excellent yields starting from the corresponding α-diazo carbonyl compounds and a readily available nucleophilic fluorinating agent HF·pyr (Olah reagent). The key elements of this efficient fluorination strategy are the use of a plastic-based reaction vessel and the use of more nucleophilic diazo compounds. Finally, the generally observed short reaction times and the availability of the reagent H[$^{18}$F]·pyr[16] may also possibly enable the corresponding radiofluorination chemistry.

## Author contributions

L. S. M. was mostly involved in the development of the methodology and investigation, with contributions of R. D. C. G. and L. P. M. O. L.. I. D. J. was involved in the supervision of the work and funding acquisition, and wrote the manuscript. All authors were involved in the conceptualization of this work and data curation.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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### 6.2.1 Material Suplementar para Inserção de H–F em Diazo Compostos via Condições Térmicas

**Diazo Esters 1a - 1u**

Diazo esters **1** have been numbered following their order of appearance in the manuscript. The following diazo esters were prepared as previously reported in the literature: *methyl 2-diazo-2-phenylacetate* (**1a**),[1] *prop-2-yn-1-yl 2-diazo-2-phenylacetate* (**1b**),[2] *isopropyl 2-diazo-2-phenylacetate* (**1c**),[2] *allyl 2-(4-bromophenyl)-2-diazoacetate* (**1d**),[1] *(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-diazo-2-phenylacetate* (**1e**),[3] *(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl 2-diazo-2-phenylacetate* (**1f**),[2] *methyl 2-diazo-2-(4-fluorophenyl)acetate* (**1j**),[4] *methyl 2-diazo-2-(3,4-difluorophenyl)acetate* (**1k**),[1] *methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate* (**1l**),[1] *methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate* (**1m**),[5] *methyl 2-diazo-2-(4-nitrophenyl)acetate* (**1n**),[6] *methyl 2-(2-chlorophenyl)-2-diazoacetate* (**1q**),[1] *methyl 2-diazo-2-(4-methoxyphenyl)acetate* (**1r**),[1] *ethyl 2-diazo-2-(3-methoxyphenyl)acetate* (**1s**),[2] *methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate* (**1t**),[4] *ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-diazoacetate* (**1u**).[2]

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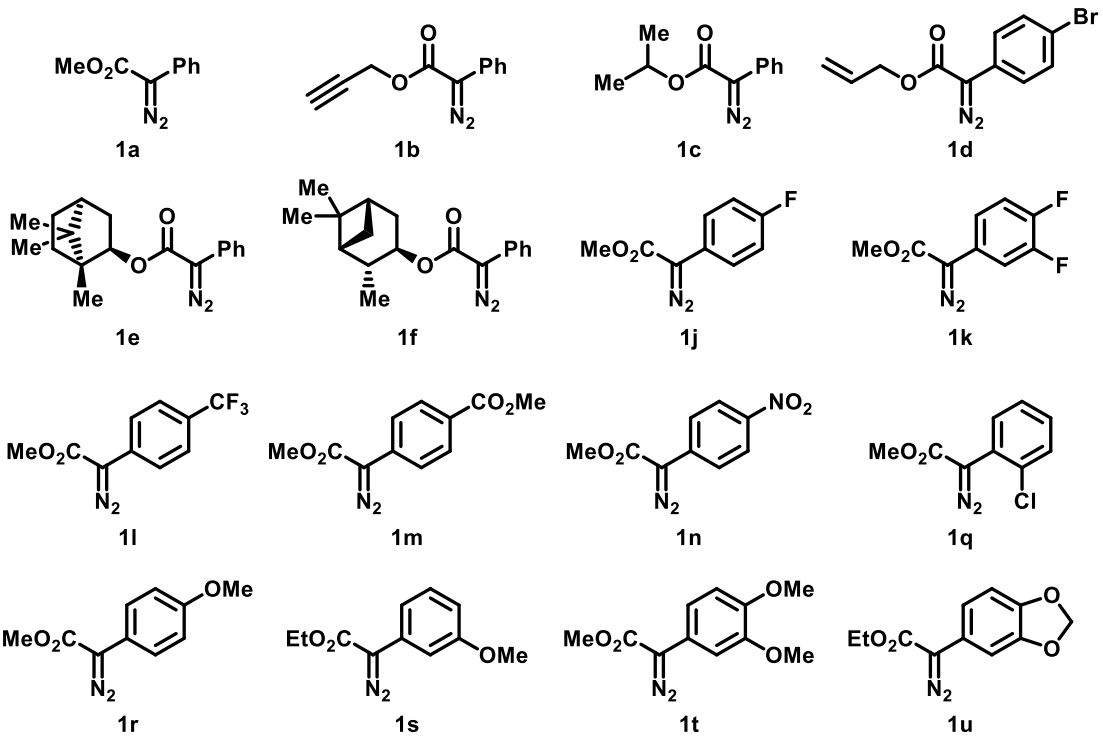
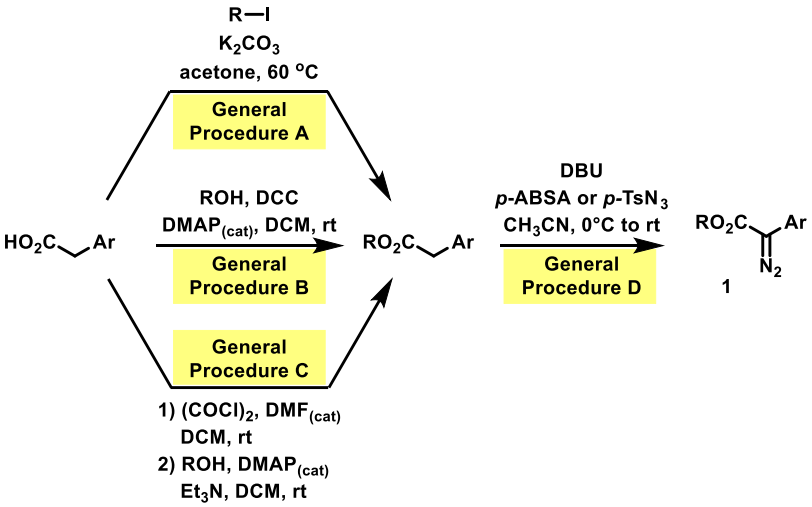



Diazo esters **1** used in this work were either prepared according to one of the following synthetic routes shown below (Scheme S1) or by specific procedures that will be detailed later, as appropriate.




**Scheme S1.** General synthetic routes employed for the preparation of aryldiazoacetates **1**.

**General Procedure A:** *Alkylation of Carboxylic Acids*

Under air, a round bottomed flask is charged with the carboxylic acid (1 equiv.), acetone (0.5 M), alkyl halide (1.2 equiv.) and $K_2CO_3$ (1 equiv.). The reaction mixture is heated at reflux (60 $^oC$) overnight. Then, the reaction is allowed to cool to room temperature and is concentrated under vacuum. The residue is dissolved in AcOEt, washed with $H_2O$ (1x), brine (1x), dried ($MgSO_4$) and concentrated again under vacuum. Purification by flash column chromatography affords the title compounds in the stated yields.

**General Procedure B:** *Steglich Esterification*

To a stirred, ice cooled solution of the phenylacetic acid (1.3 g, 10 mmol, 1 equiv.), and chiral alcohol (12 mmol, 1.2 equiv.) in 20 mL DCM was added a solution of DCC (13 mmol, 1.3 equiv.) and DMAP (1 mmol, 0.1 equiv.) in 10 mL DCM at once. The solution was stirred 6 h while slowly warming up to room temperature. After finishing the reaction, the solid was filtered off and washed with $Et_2O$. The solvent was evaporated, and the residue was purified by flash column chromatography to afford the corresponding ester.

**General Procedure C:** *Acyl Chloride Synthesis/ Nucleophilic Substitution*

Step 1: Under nitrogen, at room temperature, a round bottomed flask is charged with the carboxylic acid (1 equiv.), dry DCM (0.2 M), oxalyl chloride (2 equiv.). Then, DMF (2 drops) is add and the reaction is allowed to stir overnight at room temperature. Then, the reaction mixture is concentrated under vacuum. The corresponding acyl chloride is generally clean and can be directly employed in the next step.

Step 2: Under nitrogen, at room temperature, a round bottomed flask is charged with dry DCM (0.2 M), ROH (1.2 equiv.), $Et_3N$ (1.2 equiv.) and DMAP (10 mol%). Then, the temperature of the reaction mixture is cooled to 0 $^oC$ and the previously prepared acyl chloride (1 equiv., dissolved in a minimun amount of DCM) is added. The reaction is allowed to warm up to room temperature and to stir at this temperature overnight. Then, the reaction is quenched with a saturated aqueous solution of $NaHCO_3$, extracted with AcOEt (3x), dried ($MgSO_4$) and concentrated

under vacuum. Purification by flash column chromatography affords the title compounds in the stated yields.

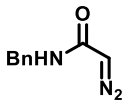
**General Procedure D:** *Regitz Diazo Transfer with p-ABSA or p-$TsN_3$*

Under nitrogen, a round-bottomed flask is charged with carboxylic acid (1 equiv.), dry $CH_3CN$ (0.1 M) and *p*-ABSA (1.3 equiv.) or $TsN_3$ (1.1 equiv.). The solution is cooled to 0 °C and DBU (1.3 equiv.) is added slowly. The temperature is allowed to warm up to 25 °C and the reaction mixture is stirred at this temperature overnight. Then, a saturated aqueous solution of $NH_4Cl$ is added. The resulting mixture is extracted with AcOEt (3x). The combined organic extracts are dried ($MgSO_4$) and concentrated under vacuum. Purification by flash column chromatography affords the title compounds in the stated yields.

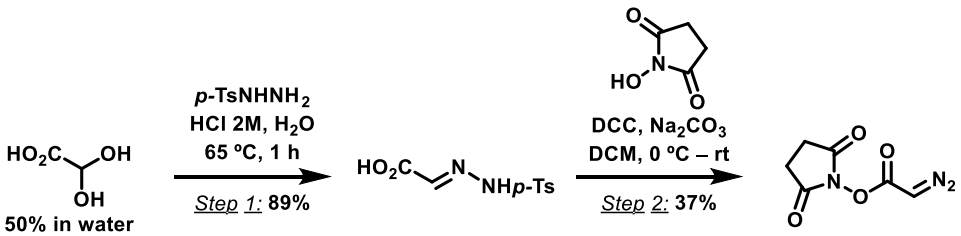
**Diazo Amides 1z – 1ii and 1rr**

Diazo amides **1z** – **1ii** and **1rr** are numbered following their order of appearance in the manuscript: The following diazo amides have been prepared as previously reported in the literature:

N-benzyl-2-diazoacetamide[7] (**1z**).




1z




pre-1z

[7] Adapted procedure from: Gupta, A. K.; Yin, X.; Mukherjee, M.; Desai, A. A.; Mohammadlou, A.; Jurewicz, K.; Wulff, W. D.; *Angew. Chem., Int. Ed.* **2019**, *58*, 3361-3367.

*Step 1:*[8] At room temperature, a round bottom flask is charged with *p*-toluenesulfonylhydrazide (2.79 g, 15 mmol, 1 equiv.), distilled water (15 mL), HCl 2M (24 mL). The reaction is allowed to stir at 65 ºC until total solubilization of the *p*-toluenesulfonylhydrazide. Then, glyoxylic acid 50% in water (3.3 mL, 30 mmol, 2 equiv.) is added and the reaction is stirred at 65 ºC for 1h. The reaction mixture is allowed to cool down to room temperature and then it is moved to the refrigerator and kept there for 1h to induce precipitation. The obtained solid is collected by vacuum filtration, washed with cold water (30 mL), then washed with DCM (to remove any trace of p-toluenesulfonylhydrazide) and dried under vacuum to afford 2-(2-tosylhydrazono)acetic acid as a white solid: 3.24 g, 13.4 mmol, 89%.

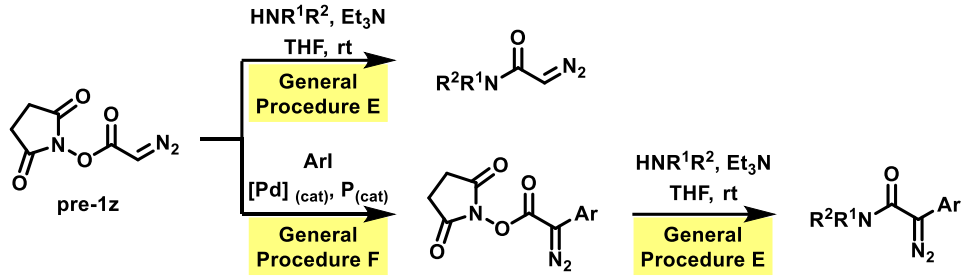
**$^1$H NMR (250 MHz, $CDCl_3$) δ:**[11] 8.79 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.16 (s, 1H), 2.46 (s, 3H).

*Step 2:*[11] Next, at room temperature, a round bottom flask is charged with the previously prepared hydrazone (3.24 g, 13.4 mmol, 1 equiv), *N*-hydroxysuccinimide (1.7 g, 14.7 mmol, 1.1 equiv) and anhydrous DCM (40 mL). The resulting reaction mixture is cooled to 0 °C. Then, *N*,*N*'-dicyclohexylcarbodiimide (DCC) (3.0 g, 14.7 mmol, 1.1 equiv) is added; and the reaction mixture is stirred at 0 °C for 1 h. Then, at this temperature, $Na_2CO_3$ (1.6 g, 14.7 mmol, 1.1 equiv) is added and the reaction mixture is allowed to warm up to room temperature and is stirred at this temperature overnight. At this moment, the reaction is moved to the refrigerator and kept there for 1h to induce precipitation. The resulting solid (urea by-product, DCU) is filtered off and the collected solution is concentrated under reduced pressure. The reaction mixture is extracted with AcOEt (3x) and washed with a saturated aqueous solution of $NaHCO_3$ (3x), brine (1x). Then, organic layer is dried ($MgSO_4$), and filtered. The solvent is removed under reduced pressure and the resulting residue is purified by flash column chromatography ($SiO_2$ 6:3:1 Hex:AcOEt:DCM) to afford 2,5-

[8] Adapted procedure from: Jun, J. V.; Raines, R. T.; *Org. Lett.* **2021**, *23*, 3110-3114.

dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** as a pale yellow crystalline solid: 907 mg, 37%.

**$^{1}$H NMR (500 MHz, $CDCl_3$) δ:**[9] 5.12 (br s, 1H), 2.83 (s, 4H).
**$^{13}$C NMR (125 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) δ:** 169.3, 45.1, 25.5.



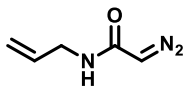

**General Procedure E:**[11] A round bottom flask is charged with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (1 equiv.) and THF (0.1M). Then, **$R^1R^2NH$** (or **$R^1R^2NH.HCl$**) (2 - 5 equiv) is added; accompanied by the eventual simultaneous addition of $Et_3N$ (2 - 5 equiv.) in THF (0.1 M) in one portion. The resulting reaction mixture is stirred at room temperature. Upon reaction completion (TLC), the solvent is removed under reduced pressure. Purification by flash column chromatography affords the corresponding diazo amide.

**General Procedure F:**[11] Under nitrogen, at room temperature, a round bottom flask is charged with aryl iodide (1.5 equiv.), tri(furan-2-yl)phosphane (10 mol%), $Pd(OAc)_2$ (5 mol%) and $Ag_2CO_3$ (0.7 equiv.). The resulting mixture is then evacuated and backfilled with $N_2$. In the sequence, a solution of 2,5-dioxopyrrolidin-1-yl 2-diazoacetate (1 equiv) and $Et_3N$ (1.5 equiv) in dry EtOAc (0.05M in relation to diazoacetate) is added in one portion. The reaction mixture is stirred at room temperature for 16 h under $N_2$. The progress of the reaction is monitored by TLC. Upon completion, the reaction mixture is filtered through a Celite pad, while being washed with AcOEt. The filtrate is concentrated under

[9] Spectroscopic data is in good agreement with reported literature. See: Mukherjee, M.; Gupta, A. K.; Lu, Z.; Zhang, Y.; Wulff, W. D.*; J. Org. Chem.* **2010**, *75*, 5643-5660.

reduced pressure and purified by silica gel chromatography to afford the targeted aryldiazoester in the stated yield.

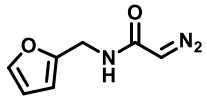
*N-allyl-2-diazoacetamide* (**1aa**)[10]



**General Procedure E** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (92 mg, 0.5 mmol, 1 equiv.), allylamine (75 mL, 1 mmol, 2 equiv.) and THF (5 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, 6:3:1 Hex:AcOEt:DCM) affords the title compound as an yellow oil: 61 mg, 98%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 5.88 – 5.77 (m, 1H), 5.75 (br s, 1H), 5.22 – 5.10 (m, 2H), 4.83 (s, 1H), 3.91 – 3.86 (m, 2H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.7, 134.3, 116.3, 47.0, 42.3.
**IR (ATR, cm$^{-1}$):** 3921, 2100, 1724, 1617, 1379, 1239.
**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_5H_8N_3O$ 126.0662; Found 126.0664.

*2-diazo-N-(furan-2-ylmethyl)acetamide* (**1bb**)



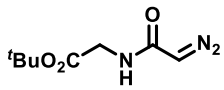
**General Procedure E** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (93 mg, 0.5 mmol, 1 equiv.), furfuryl amine (88 mL, 1 mmol, 2 equiv.) and THF (5 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, 5.5:4.5:0.5 Hex:AcOEt:DCM) affords the title compound as an yellow oil: 55 mg, 66%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.33 (d, *J* = 1.0 Hz, 1H), 6.30 (dd, *J* = 3.2 Hz, *J* = 1.8 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 5.71 (br s, 1H), 4.79 (s, 1H), 4.44 (d, *J* = 5.7 Hz, 2H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.7, 151.4, 142.1, 110.4, 107.3, 47.1, 36.7.
**IR (ATR, cm$^{-1}$):** 2100, 1616, 1551, 1381, 1244.

[10] NMR data only reported in $d_6$-acetone: Chow, S.; Green, A. I.; Liver, S.; Arter, C.; Leggott, A.; Trask, L.; Karageorgis, G.; Warriner, S.; Nelson, A. *Synthesis* **2020**, *52*, 1695-1706.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_7H_8N_3O_2$ 166.0611; Found 166.0611.

*tert-butyl (2-diazoacetyl)glycinate* (**1cc**)



**General Procedure E** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (92 mg, 0.5 mmol, 1 equiv.), *tert*-butyl glycinate hydrochloride (168 mg, 1 mmol, 2 equiv.), $Et_3N$ (557 mL, 4 mmol, 4 equiv.) and THF (5 mL, 0.1M). 16h, rt. Purification by flash column chromatography ($SiO_2$, 6:3:1 Hex:AcOEt:DCM) affords the title compound as an yellow oil: 49 mg, 45% (isolated with the starting ester as a minor impurity).

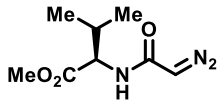
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 5.75 (br s, 1H), 4.83 (s, 1H), 3.97 (d, *J* = 5.2 Hz, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 169.4, 165.6, 82.4, 47.3, 42.3, 28.0.

**IR (ATR, cm$^{-1}$):** 3264, 2982, 2099, 1731, 1609, 1397, 1245.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_8H_{14}N_3O_3$ 200.1030; Found 200.1031.

*methyl (2-diazoacetyl)valinate* (**1dd**)



**General Procedure E** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (92 mg, 0.5 mmol, 1 equiv.), methyl L-valinate hydrochloride (334 mg, 1 mmol, 4 equiv.), $Et_3N$ (557 mL, 4 mmol, 4 equiv.) and THF (5 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, 6:3:1 Hex:EtOAc:DCM) affords the title compound as an yellow oil: 61 mg, 57%.

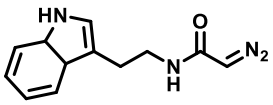
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 5.77 (br s, 1H), 4.84 (s, 1H), 4.64 – 4.59 (m, 1H), 3.73 (s, 3H), 2.18 – 2.08 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 173.0, 165.6, 57.3, 52.2, 47.4, 31.4, 18.9, 17.7.

**IR (ATR, cm$^{-1}$):** 3286, 2964, 2103, 1742, 1538, 1382, 1207.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_8H_{14}N_3O_3$ 200.1030; Found 200.1030.

*2-diazo-N-(2-(3a,7a-dihydro-1H-indol-3-yl)ethyl)acetamide* (**1ee**)



**General Procedure E** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (92 mg, 0.5 mmol, 1 equiv.) and tryptamine (160 mg, 1 mmol, 2 equiv.) and THF (5 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, 98:2 DCM:MeOH) affords the title compound as an yellow solid: 105 mg, 92%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 8.20 (br s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.10 (m, 2H), 7.02 (d, *J* = 2.0 Hz, 1H), 5.18 (br s, 1H), 4.60 (s, 1H), 3.64 – 3.62 (m, 2H), 2.98 (t, *J* = 6.8 Hz, 2H).

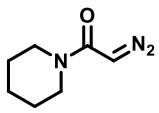
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.4, 136.4, 127.3, 122.2, 122.1, 119.5, 118.7, 112.8, 111.3, 47.1, 40.2, 25.6.

**M.P.:** 115 – 117 °C.

**IR (ATR, cm$^{-1}$):** 3405, 2917, 2104, 1609, 1365, 1094.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{12}H_{15}N_4O$ 231.1240; Found 231.1231.

*2-diazo-1-(piperidin-1-yl)ethan-1-one* (**1ff**)[11]



**General Procedure E** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (92 mg, 0.5 mmol, 1 equiv.), piperidine (99 mL, 1 mmol, 2 equiv.) and THF (5 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, 6:3:1 Hex:AcOEt:DCM) affords the title compound as an yellow oil: 68 mg, 89%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 5.01 (s, 1H), 3.31 (app s, 4H), 1.64 – 1.46 (m, 6H).

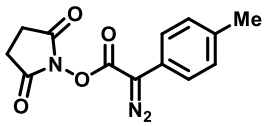
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 164.2, 46.1, 44.9, 25.7, 24.3.

**IR (ATR, cm$^{-1}$):** 2939, 2855, 2098, 1597, 1433, 1224, 1018.

[11] Spectroscopic data is in good agreement with the literature. See: Döben, N.; Yan, H.; Kischkewitz, M.; Mao, J.; Studer, A.; *Org. Lett.* **2018**, *20*, 7933-7936.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_7H_{12}N_3O$ 154.0975; Found 154.0975.

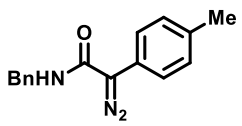
*2,5-dioxopyrrolidin-1-yl 2-diazo-2-(p-tolyl)acetate* (**pre-1gg**)[11]




**General Procedure F** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (183 mg, 1 mmol, 1 equiv.), 1-iodo-4-methylbenzene (327 mg, 1.5 mmol, 1.5 equiv.), tri(furan-2-yl)phosphane (23 mg, 0.1 mmol, 10 mol%), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), $Ag_2CO_3$ (189 mg, 0.7 mmol, 0.7 equiv.), $Et_3N$ (210 mL, 1.5 mmol, 1.5 equiv) and dry EtOAc (20 mL, 0.05M). Purification by flash column chromatography ($SiO_2$, 95.5:4:0.5 Hex:AcOEt:DCM) affords the title compound as yellow oil: 84 mg, 51%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.31 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 2.86 (s, 4H), 2.34 (m, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) δ:** 169.3, 160.5, 137.1, 129.9, 124.6, 119.8, 25.5, 21.0.

*N-benzyl-2-diazo-2-(p-tolyl)acetamide* (**1gg**)[12]



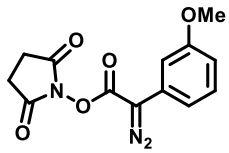

**General Procedure E** is employed with diazo compound **pre-1kk** (82 mg, 0.3 mmol, 1 equiv.), $Et_3N$ (210 mL, 1.5 mmol, 5 equiv.) and dry THF (3 mL, 0.1M), followed by the addition of benzylamine (164 mL, 1.5 mmol, 5 equiv.) and $Et_3N$ (210 mL, 1.5 mmol, 5 equiv.) in THF (3 mL, 0.1M, in relation to diazo compound **pre-1kk**). Purification by flash column chromatography ($SiO_2$, 8:2 Hex:AcOEt) affords the title compound as a yellow oil: 46 mg, 58%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.39 – 7.28 (m, 9H), 5.76 (br s,1H), 4.56 (d, *J* = 5.8 Hz, 2H), 2.37 (s, 3H).

[12] Mix, K. A.; Raines, R. T.; *Org. Lett.* **2015**, *17*, 2358-2361.

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) δ:** 165.0, 138.4, 138.0, 130.4, 128.7, 127.8, 127.6, 127.4, 122.9, 44.0, 21.1.

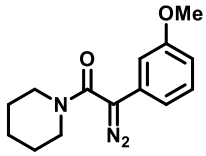
*2,5-dioxopyrrolidin-1-yl 2-diazo-2-(3-methoxyphenyl)acetate* (**pre-1hh**)[11]



**General Procedure F** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (183 mg, 1 mmol, 1 equiv.), 1-iodo-3-methoxybenzene (179 mL, 1.5 mmol, 1.5 equiv.), tri(furan-2-yl)phosphane (23 mg, 0.1 mmol, 10 mol%), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), $Ag_2CO_3$ (189 mg, 0.7 mmol, 0.7 equiv.), $Et_3N$ (210 mL, 1.5 mmol, 1.5 equiv) and dry AcOEt (20 mL, 0.05M). Purification by flash column chromatography ($SiO_2$, gradient: Hex – 96:3:1 Hex:AcOEt:DCM – 5:4:1 Hex:AcOEt:DCM) affords the title compound as an yellow oil: 260 mg, 90%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.31 (t, *J* = 8.0 Hz, 1H), 7.07 – 7.05 (m, 1H), 6.94 (ddd, *J* = 8.1 Hz, *J* = 1.8 Hz, *J* = 0.7 Hz, 1H), 6.78 (ddd, *J* = 8.1 Hz, *J* = 2.4 Hz, *J* = 0.7 Hz, 1H), 3.80 (s, 3H), 2.86 (s, 4H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 169.3, 160.1 (x2), 130.1, 124.6, 116.3, 112.6, 110.0, 61.6, 55.3, 25.5.

*2-diazo-2-(3-methoxyphenyl)-1-(piperidin-1-yl)ethan-1-one* (**1hh**)



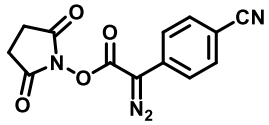
**General Procedure E** is employed with diazo compound **pre-1hh** (87 mg, 0.3 mmol, 1 equiv.), $Et_3N$ (210 mL, 1.5 mmol, 5 equiv.) and dry THF (3 mL, 0.1M), followed by the addition of piperidine (148 mL, 1.5 mmol, 5 equiv.) and $Et_3N$ (210 mL, 1.5 mmol, 5 equiv.) in THF (3 mL, 0.1M, in relation to diazo compound **pre-1hh**). Purification by flash column chromatography ($SiO_2$, Hex - 96.5:3.5:0.5 Hex:AcOEt:DCM) affords the title compound as an yellow oil: 24 mg, 30%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.27 (t, *J* = 8.3 Hz, 1H), 6.78 – 6.75 (m, 2H), 6.72 – 6.68 (m, 1H), 3.80 (s, 3H), 3.42 – 3.38 (m, 4H), 1.65 – 1.55 (m, 6H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 164.9, 160.2, 130.0, 129.5, 116.6, 111.1, 109.9, 63.0, 55.3, 46.6, 25.8, 24.5.

**IR (ATR, cm$^{-1}$):** 2937, 2854, 2060, 1627, 1415, 1264, 1037.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{14}H_{18}N_3O_2$ 260.1394; Found 260.1394.

*2,5-dioxopyrrolidin-1-yl 2-(4-cyanophenyl)-2-diazoacetate* (**pre-1ii**)



**General Procedure F** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (183 mg, 1 mmol, 1 equiv.), 4-iodobenzonitrile (229 mg, 1.5 mmol, 1.5 equiv.), tri(furan-2-yl)phosphane (23 mg, 0.1 mmol, 10 mol%), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol%), $Ag_2CO_3$ (189 mg, 0.7 mmol, 0.7 equiv.), $Et_3N$ (210 mL, 1.5 mmol, 1.5 equiv) and dry AcOEt (20 mL, 0.05M). Purification by flash column chromatography ($SiO_2$, gradient: Hex – 95.5:4.5 Hex:AcOEt - 4:6 Hex:AcOEt) affords the title compound as an yellow oil: 160 mg, 56%.

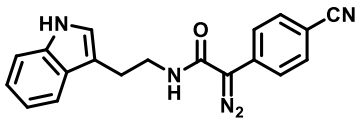
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.68 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 2.89 (s, 4H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) δ:** 169.0, 159.2, 132.8, 129.2, 123.7, 118.3, 110.0, 25.5.

**IR (ATR, cm$^{-1}$):** 2916, 2228, 2111, 1737, 1511, 1201, 1072.

**HRMS (ESI-Orbitrap) m/z:** $[M - N_2 + H]^+$ Calcd. for $C_{13}H_9N_2O_4$ 257.0557; Found 257.0555.

*2-(4-cyanophenyl)-2-diazo-N-(2-(3a,7a-dihydro-1H-indol-3-yl)ethyl)acetamide* (**1ii**)



**General Procedure E** is employed with diazo compound **pre-1ii** (85 mg, 0.3 mmol, 1 equiv.), $Et_3N$ (210 mL, 1.5 mmol, 5 equiv.) and dry THF (3 mL, 0.1M), followed by the addition of tryptamine (240 mg, 1.5 mmol, 5 equiv.) in THF (3 mL, 0.1M, in relation to diazo compound **pre-1ii**). Purification by flash column chromatography ($SiO_2$, 8:2 Hex:AcOEt) affords the title compound as an yellow oil: 46 mg, 58%.

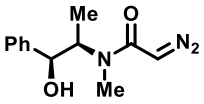
**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 8.15 (br s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.23 (m, 3H), 7.18 – 7.12 (m, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 5.53 (t, *J* = 5.0 Hz, 1H), 3.81 – 3.73 (m, 2H), 3.09 (t, *J* = 6.8 Hz, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (2C cannot be unambiguously assigned) δ:** 162.7, 136.4, 132.8, 132.2, 127.2, 125.2, 122.5, 122.1, 119.8, 118.6, 112.6, 111.4, 109.2, 40.6, 25.1.

**IR (ATR, cm$^{-1}$):** 2925, 2853, 2067, 1636, 1507, 1262, 1096, 1018.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{19}H_{16}N_5O$ 330.1349; Found 330.1349.

*2-diazo-N-(1-hydroxy-1-phenylpropan-2-yl)-N-methylacetamide* (**1rr**)




**General Procedure E** is employed with 2,5-dioxopyrrolidin-1-yl 2-diazoacetate **pre-1z** (92 mg, 0.5 mmol, 1 equiv.) and (*1S,2R*)-(+)-ephedrine hemihydrate (174 mg, 1 mmol, 2 equiv.), $Et_3N$ (557 mL, 4 mmol, 4 equiv.) and THF (5 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, 5:4:1 Hex:AcOEt:DCM) affords the title compound as an yellow oil: 98 mg, 84%.

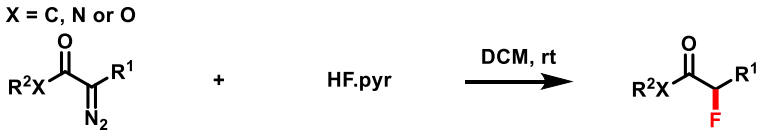
**$^{1}$H NMR (250 MHz, $CDCl_3$) (1H cannot be unambiguously assigned) δ:** 7.34 – 7.24 (m, 5H), 4.89 (s, 1H), 4.79 (br s, 1H), 4.46 (br s, 1H), 2.57 (app s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) δ:** 167.4, 141.6, 128.1, 127.4, 126.2, 57.9, 46.9, 32.0, 12.3.

**IR (ATR, cm$^{-1}$):** 3364, 2927, 2005, 1590, 1407, 1172.

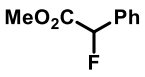
**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{12}H_{16}N_3O_2$ 234.1237; Found 234.1236.

**-Fluorinated Carbonyl Compounds 18a – 18ii**




**General Procedure G:** Under air, a plastic vessel (an Eppendorf for ~0.1 mmol scale; or a falcon tube for ~0.2 mmol or higher scale) is added the diazo compound **1** (1 equiv.) and DCM (0.1M). Then, at 0 ºC or rt, the Olah's reagent HF.pyr **17a**, (3 - 6 equiv., 70% HF/ 30% pyridine) is carefully added. The reaction mixture is typically stirred for 1h at room temperature. Upon reaction completion (TLC), silica ($SiO_2$, 20 mg/ 0.1 mmol of the diazo compound **1**) is added. The resulting mixture is filtrated using a pipette while washing with DCM. Then, the solvent is removed under reduced pressure. Purification by flash column chromatography affords the target α-fluorinated carbonyl compound **3** in the stated yield.

*methyl 2-fluoro-2-phenylacetate* (**18a**)[13]




**General Procedure G** is employed with methyl 2-diazo-2-phenylacetate **1a** (18 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as transparent oil: 17 mg, 99%.

This reaction has been also carried out in a preparative scale using methyl 2-diazo-2-phenylacetate **1a** (528 mg, 3 mmol, 1 equiv.), HF·pyr **17a** (480 mL, 18 mmol, 6 equiv.) and DCM (25 mL). Filtration using $SiO_2$ affords the title compound as transparent oil: 428 mg, 85%.

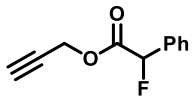
**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.45 – 7.40 (m, 5H), 5.80 (d, *J* = 48.2 Hz, 1H), 3.78 (s, 3H).

[13] Spectroscopic data is in good agreement with reported literature. See: Gray, E. E.; Nielsen, M. K., Choquette, K. A.; Kalow, J. A.; Graham, T. J. A.; Diyle, A. G.; *J. Am. Chem. Soc.* **2016**, *138*, 10802-10805.

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 169.0 (d, *J* = 27.5 Hz), 134.1 (d, *J* = 20.0 Hz), 129.6 (d, *J* = 2.5 Hz), 128.8, 126.6 (d, *J* = 6.9 Hz), 89.4 (d, *J* = 184.4 Hz), 52.6 (d, *J* = 1.3 Hz).

**$^{19}$F (235 MHz, $CDCl_3$) δ:** -179.91 (d, *J* = 47.8 Hz).

*prop-2-yn-1-yl 2-fluoro-2-phenylacetate* (**18b**)




**General Procedure G** is employed with methyl 2-diazo-2-(4-fluorophenyl)acetate **1b** (19 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as transparent oil: 19 mg, 99%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.50 – 7.40 (m, 5H), 5.83 (d, *J* = 47.4 Hz, 1H), 4.82 (dd, *J* = 15.4 Hz, *J* = 2.4 Hz, 1H) 4.72 (dd, *J* = 15.4 Hz, *J* = 2.4 Hz, 1H), 2.49 (t, *J* = 2.4Hz, 1H).

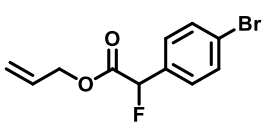
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (1C cannot be unambiguously assigned) δ:** 167.8 (d, *J* = 27.5 Hz), 133.7 (d, *J* = 20.6 Hz), 129.8 (d, *J* = 2.5 Hz), 128.9, 126.8 (d, *J* = 5.6 Hz), 89.2 (d, *J* = 185.0 Hz), 75.8, 53.1 (d, *J* = 1.3 Hz).

**$^{19}$F (235 MHz, $CDCl_3$) δ:** -179.62 (d, *J* = 47.2 Hz).

**IR (ATR, $cm^{-1}$):** 3298, 2924, 1770, 1457, 1182, 1058.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{11}H_9O_2$ 173.0597; Found 173.0598.

*allyl 2-(4-bromophenyl)-2-fluoroacetate* (**18d**)




**General Procedure G** is employed with allyl 2-(4-bromophenyl)-2-diazoacetate **1d** (21 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 95:5 Hex:AcOEt) affords the title compound as transparent oil: 27 mg, 99%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.55 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.92 – 5.81 (m, 1H), 5.76 (d, *J* = 47.5 Hz, 1H), 5.30 – 5.22 (m, 2H), 4.74 – 4.60 (m, 2H).

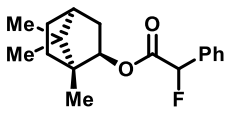
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.7 (d, *J* = 27.2 Hz), 133.1 (d, *J* = 21.0 Hz), 132.0, 130.9, 128.2 (d, *J* = 6.3 Hz), 123.9 (d, *J* = 2.7 Hz), 119.3, 88.6 (d, *J* = 187.8 Hz), 66.3.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −181.31 (d, *J* = 47.6 Hz).

**IR (ATR, cm$^{-1}$):** 2911, 1762, 1489, 1208, 1072.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{11}H_{10}BrO_2$ 252.9859; Found 252.9858.

*(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-fluoro-2-phenylacetate* (**18e**)




**General Procedure G** is employed with (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-diazo-2-phenylacetate **1e** (30 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 29 mg, 99%, 1:1 dr.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.47 – 7.40 (m, 5H), 5.80 (d, *J* = 47.7 Hz, 1H), 5.01 – 4.94 (m, 1H), 2.40 – 2.24 (m, 2H), 1.88 – 1.74 (m, 1H), 1.69 – 1.60 (m, 1H), 1.33 – 1.16 (m, 2H), 1.05 – 0.98 (m, 1H), 0.88 – 0.63 (m, 10H)

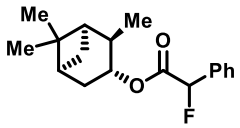
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (5C cannot be unambiguously assigned) δ:** 168.8 (d, *J* = 28.1 Hz), 168.7 (d, *J* = 27.5 Hz), 134.8 (d, *J* = 10.0 Hz), 134.4 (d, *J* = 10.6 Hz), 129.5 (d, *J* = 2.5 Hz), 129.4 (d, *J* = 2.5 Hz), 128.7, 126.5 (d, *J* = 6.9 Hz), 126.4 (d, *J* = 5.6 Hz), 89.4 (d, *J* = 184.4 Hz), 89.3 (d, *J* = 184.4 Hz), 81.6, 81.4, 49.0, 48.8, 47.9, 44.8, 44.7, 36.4, 27.9, 27.8, 27.0, 26.8, 19.6, 18.8, 13.4, 13.2.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −180.35 (d, *J* = 48.6 Hz), −181.30 (d, *J* = 49.3 Hz).

**IR (ATR, cm$^{-1}$):** 2957, 1759, 1455, 1251, 1060.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{18}H_{23}O_2$ 271.1693; Found 271.1698.

(*1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl 2-fluoro-2-phenylacetate* (**18f**)



**General Procedure G** is employed with (1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl2-diazo-2-phenylacetate **1f** (30 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 27 mg, 93%, 1:1 dr.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.48 – 7.40 (m, 5H), 5.78 (d, *J* = 47.7 Hz, 1H), 5.19 – 5.09 (m, 1H), 2.64 – 2.45 (m, 1H), 2.40 – 2.29 (m, 1H), 2.18 – 1.75 (m, 4H), 1.69 – 1.44 (m, 1H), 1.26 - 0.93 (m, 9H).

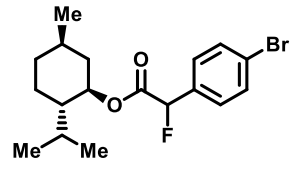
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (4C cannot be unambiguously assigned) δ:** 168.5 (d, *J* = 27.8 Hz), 168.4 (d, *J* = 27.5 Hz), 134.6 (d, *J* = 7.4 Hz), 134.3 (d, *J* = 7.3 Hz), 129.5, 128.7, 126.6 (d, *J* = 6.1 Hz), 126.5 (d, *J* = 6.0 Hz), 89.4 (d, *J* = 186.5 Hz, x2), 75.9, 75.8, 47.4, 47.3, 43.5, 41.1, 41.0, 38.2, 38.1, 35.5, 35.3, 33.4, 33.3, 27.4, 27.3, 23.7, 20.4, 20.3.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −179.97 (d, *J* = 49.1 Hz), −180.17 (d, *J* = 49.1 Hz).

**IR (ATR, cm$^{-1}$):** 2913, 1756, 1455, 1212, 1057.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{18}H_{23}O_2$ 271.1693; Found 271.1692.

*(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-(4-bromophenyl)-2-fluoroacetate* (**18g**)



**General Procedure G** is employed with (2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-(4-bromophenyl)-2-diazoacetate **1g** (38 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 37 mg, 99%, 1.5:1 dr.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.54 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 5.72 (d, *J* = 47.9 Hz, 0.4H), 5.68 (d, *J* = 47.9 Hz, 0.6H), 4.83 – 4.66 (m, 1H), 2.04 – 1.95 (m, 0.6 H), 1.85 – 1.76 (m, 1H), 1.72 – 1.59 (m, 2.4 H), 1.54 – 1.25 (m, 3H), 1.12 – 0.94 (m, 2H), 0.91 – 0.85 (m, 4.2H), 0.74 – 0.70 (m, 3H), 0.53 (d, *J* = 7.0 Hz, 1.8 H).

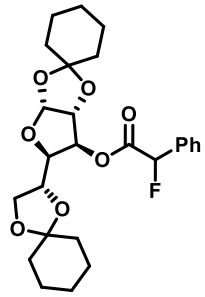
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.7 (d, *J* = 27.5 Hz), 167.6 (d, *J* = 26.9 Hz), 133.6 (d, *J* = 6.9 Hz), 133.3 (d, *J* = 6.9 Hz), 131.9, 131.8, 128.3 (d, *J* = 5.6 Hz), 128.1 (d, *J* = 6.3 Hz), 123.8 (d, *J* = 3.1 Hz), 123.7 (d, *J* = 1.9 Hz), 88.7 (d, *J* = 185.6 Hz), 88.6 (d, *J* = 185.6 Hz), 76.3 (x2), 46.9, 46.8, 40.6, 40.2, 34.0 (x2), 31.4, 31.3, 26.2, 25.8, 23.3, 23.1, 21.9 (x2), 20.6, 20.5, 16.2, 15.8.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −179.91 (d, *J* = 48.3 Hz), −181.08 (d, *J* = 45.8 Hz).

**IR (ATR, cm$^{-1}$):** 2957, 2871, 1756, 1488, 1214, 1072, 1012.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{18}H_{24}BrO_2$ 351.0954; Found 351.0954.

*(3a'R,5'R,6'S,6a'R)-5'-((R)-1,4-dioxaspiro[4.5]decan-2-yl)tetrahydrospiro [cyclohexane-1,2'-furo[2,3-d][1,3]dioxol]-6'-yl-2-fluoro-2-phenylacetate* (**18h**)




**General Procedure G** is employed with (3a'*R*,5'*R*,6'*S*,6a'*R*)-5'-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)tetrahydrospiro[cyclohexane-1,2'-furo[2,3-*d*][1,3]dioxol]-6'-yl 2-diazo-2-phenylacetate **1h** (48 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 47 mg, 99%, 1:1 dr.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.48 – 7.38 (m, 5H), 5.91 – 5.87 (m, 1H), 5.72 – 5.69 (m, 1H), 5.45 – 5.42 (m, 1H), 4.37 (d, *J* = 55.8 Hz, 0.5 H), 4.36 (d, *J* = 55.8 Hz, 0.5H), 4.17 – 4.05 (m, 2H), 3.99 – 3.94 (m, 0.5H), 3.88 – 3.84 (m, 1H), 3.73 – 3.65 (m, 0.5H), 2.34 (t, *J* = 6.3 Hz, 0.5H), 1.91 – 1.81 (m, 1H), 1.73 – 1.63 (m, 5H), 1.53 – 1.34 (m, 13H), 0.89 - 0.83 (m, 0.5H).

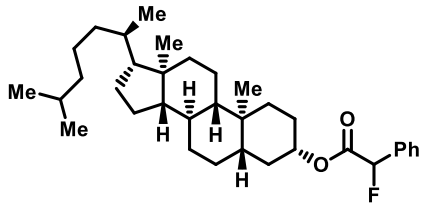
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (2C cannot be unambiguously assigned) δ:** 167.1 (d, *J* = 28.1 Hz), 166.9 (d, *J* = 27.5 Hz), 133.9 (d, *J* = 6.3 Hz), 133.6 (d, *J* = 6.3 Hz), 129.8 (x2), 128.8 (x2), 126.8 (d, *J* = 5.6 Hz), 126.6 (d, *J* = 5.6 Hz), 113.2 (x2), 110.0, 109.9, 104.8, 104.7, 89.2 (d, *J* = 185.0 Hz), 89.1 (d, *J* = 186.9 Hz), 82.7, 82.5, 80.2, 80.0, 77.2, 77.1, 72.0, 71.5, 67.2, 67.0, 42.0, 36.6, 36.5, 36.3 (x2), 35.6, 34.7, 34.5, 27.0, 25.1, 25.0, 24.8 (x2), 23.9 (x2), 23.8, 23.7, 23.5.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −178.63 (d, *J* = 46.8 Hz), −180.05 (d, *J* = 47.8 Hz).

**IR (ATR, cm$^{-1}$):** 2937, 2863, 1770, 1449, 1207, 1093.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{26}H_{34}FO_7$ 477.2283; Found 477.2283.

*(3S,5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-fluoro-2-phenylacetate* (**18i**)




**General Procedure G** is employed with (3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-diazo-2-phenylacetate **1i** (53 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 52 mg, 99%, 1:1 dr.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.46 – 7.38 (m, 5H), 5.73 (d, *J* = 48.0 Hz, 1H), 4.87 – 4.74 (m, 1H), 1.98 – 1.42 (m, 12H), 1.39 – 0.96 (m, 17H), 0.91 – 0.85 (m, 9H), 0.80 (s, 3H), 0.68 – 0.55 (m, 5H).

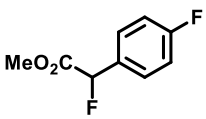
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) (28C cannot be unambiguously assigned) δ:** 168.1 (d, *J* = 26.9 Hz), 134.5 (d, *J* = 20.7 Hz), 129.4 (d, *J* = 2.2 Hz), 128.7, 126.6 (d, *J* = 6.0 Hz), 89.4 (d, *J* = 185.8 Hz), 75.5, 63.4, 56.4, 56.2, 54.1, 44.6 (x2), 42.6, 39.9, 39.5, 36.6 (x2), 36.1, 35.8, 35.4 (x2), 33.8, 33.5, 31.9, 28.5 (x2), 28.2, 28.0, 27.3, 27.1, 24.2, 23.8, 22.5, 21.2, 18.6, 12.2, 12.0.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −179.27 (d, *J* = 41.1 Hz), −179.47 (d, *J* = 41.1 Hz).

**IR (ATR, cm$^{-1}$):** 2945, 2868, 1757, 1468, 1213, 1002.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{35}H_{53}O_2$ 505.4040; Found: 505.4030

*methyl 2-fluoro-2-(4-fluorophenyl)acetate* (**18j**)[16]



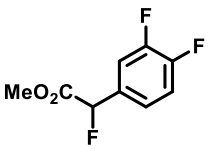

**General Procedure G** is employed with methyl 2-diazo-2-(4-fluorophenyl)acetate **1j** (19 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as transparent oil: 17 mg, 91%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.45 (dd, *J* = 8.2 Hz, *J* = 5.5 Hz, 2H), 7.10 (t, *J* = 8.2 Hz, 2H), 5.78 (d, *J* = 47.5 Hz, 1H), 3.78 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 168.8 (d, *J* = 27.5 Hz), 163.4 (dd, *J* = 248.1 Hz, *J* = 2.5 Hz), 130.0 (dd, *J* = 20.6 Hz, *J* = 3.1 Hz), 128.7 (dd, *J* = 8.8 Hz, *J* = 6.3 Hz), 115.9 (d, *J* = 21.9 Hz), 88.7 (d, *J* = 185.0 Hz), 52.7 (d, *J* = 0.6 Hz).

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −111.24 (app oct, *J* = 4.7 Hz), −178.49 (dd, *J* = 47.0 Hz, *J* = 2.4 Hz).

*methyl 2-(3,4-difluorophenyl)-2-fluoroacetate* (**18k**)




**General Procedure G** is employed with methyl 2-diazo-2-(3,4-difluorophenyl)acetate **1k** (21 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration through $SiO_2$ affords the title compound as transparent oil: 20 mg, 98%

**$^{1}$H NMR (250 MHz, $CDCl_3$) *δ:*** 7.35 - 7.27 (m, 1H), 7.26 - 7.18 (m, 2H), 5.75 (d, *J* = 47.5 Hz, 1H), 3.80 (s, 3H).

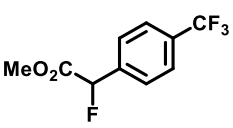
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) *δ:*** 168.4 (d, *J* = 11.3 Hz), 151.1 (ddd, *J* = 251.9 Hz, *J* = 14.4 Hz, *J* = 1.9 Hz), 150.4 (dd, *J* = 250.6 Hz, *J* = 15.0 Hz), 131.0 (ddd, *J* = 21.3 Hz, *J* = 5.6 Hz, *J* = 3.8 Hz), 122.9 (td, *J* = 6.3 Hz, *J* = 3.8 Hz), 117.8 (dd, *J* = *J* = 16.9 Hz, *J* = 1.3 Hz), 115.9 (ddd, *J* = 18.1 Hz, *J* = 6.9 Hz, *J* = 1.9 Hz), 88.0 (dd, *J* = 186.3 Hz, *J* = 0.9 Hz), 52.9 (d, *J* = 0.6 Hz).

**$^{19}$F NMR (235 MHz, $CDCl_3$) *δ*:** -135.88 (dm), -180.82 (dd, *J* = 47.0 Hz, *J* = 4.7 Hz).

**IR (ATR, $cm^{-1}$):** 2963, 1763, 1521, 1439, 1281.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_9H_7F_2O_2$ 185.0409; Found 185.0409.

*methyl 2-fluoro-2-(4-(trifluoromethyl)phenyl)acetate* (**18l**)[16]

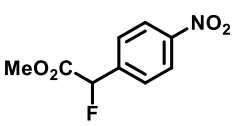



**General Procedure G** is employed with methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate **1l** (49 mg, 0.2 mmol, 1 equiv.), HF·pyr **17a** (32 mL, 1.2 mmol, 6 equiv.) and DCM (2 mL, 0.1M).

Purification by flash column chromatography ($SiO_2$, gradient: Hex - 95:5 Hex:AcOEt) affords the title compound as transparent oil: 42 mg, 89%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.68 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 5.86 (*d*, J = 47.5 Hz, 1H), 3.80 (s, 3H),
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 168.2 (d, *J* = 26.3 Hz), 137.9 (dq, *J* = 20.6 Hz, J = 1.3 Hz), 131.7 (qd, *J* = 32.5 Hz, *J* = 1.3 Hz), 126.7 (d, *J* = 6.9 Hz), 125.8 (q, *J* = 3.1 Hz), 123.7(q, *J* = 270.6 Hz), 88.5 (d, *J* = 186.3 Hz), 52.9 (d, *J* = 1.3 Hz).
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −62.89 (s), −184.31 (d, *J* = 47.0 Hz).

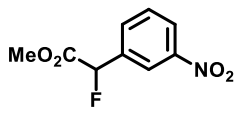
*methyl 2-fluoro-2-(4-nitrophenyl)acetate* (**18n**)[16]




**General Procedure G** is employed with methyl 2-diazo-2-(4-nitrophenyl)acetate **1n** (22 mg, 0.2 mmol, 1 equiv.), HF·pyr **17a** (32 mL, 1.2 mmol, 6 equiv.) and DCM (2 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 42 mg, 99%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 8.28 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 5.92 (d, *J* = 47.5 Hz, 1H), 3.81 (s, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.7 (d, *J* = 25.6 Hz), 148.6, 140.7 (d, *J* = 20.6 Hz), 127.1 (d, *J* = 6.9 Hz), 124.0, 88.1 (d, *J* = 188.1 Hz), 53.1.
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −185.95 (d, *J* = 47.0 Hz).

*methyl 2-fluoro-2-(3-nitrophenyl)acetate* (**18o**)[16]

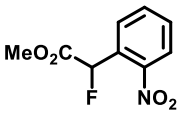



**General Procedure G** is employed with methyl 2-diazo-2-(3-nitrophenyl)acetate **1o** (22 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 19 mg, 89%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 8.35 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 5.92 (d, *J* = 47.0 Hz, 1H), 3.82 (s, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.8 (d, *J* = 26.3 Hz), 148.4, 136.1 (d, *J* = 21.9 Hz), 132.1 (d, *J* = 6.3 Hz), 129.9, 124.4 (d, *J* = 1.3 Hz), 121.5 (d, *J* = 6.9 Hz), 88.0 (d, *J* = 187.5 Hz), 53.1.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −184.40 (d, *J* = 47.0 Hz).

*methyl 2-fluoro-2-(2-nitrophenyl)acetate* (**18p**)[14]




**General Procedure G** is employed with methyl 2-diazo-2-(2-nitrophenyl)acetate **1p** (22 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 21 mg, 99%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 8.16 (d, *J* = 8.3 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.63 – 7.56 (m, 1H), 6.62 (d, *J* = 46.8 Hz, 1H), 3.79 (s, 3H).

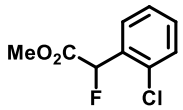
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.1 (d, *J* = 25.0 Hz), 146.8, 134.1 (d, *J* = 1.0 Hz), 130.3 (d, *J* = 21.0 Hz), 130.0, 127.7 (d, *J* = 14.0 Hz), 125.2, 86.5 (d, *J* = 183.0 Hz), 53.1.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −187.22 (d, *J* = 47.0 Hz).

**IR (ATR, cm$^{-1}$):** 2959, 2924, 1754, 1533, 1351, 1221, 1024.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_9H_9FNO_4$ 214.0510; Found 214.0510.

*methyl 2-(2-chlorophenyl)-2-fluoroacetate* (**18q**)




**General Procedure G** is employed with methyl 2-(2-chlorophenyl)-2-diazoacetate **1q** (21 mg, 0.2 mmol, 1 equiv.), HF·pyr **17a** (32 mL, 1.2 mmol, 6 equiv.) and DCM (2 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as transparent oil: 40 mg, 99%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.52 – 7.47 (m, 1H), 7.45 – 7.38 (m, 1H), 7.36 - 7.30 (m, 2H), 6.24 (d, *J* = 46.5 Hz, 1H), 3.80 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 168.4 (d, *J* = 27.5 Hz), 133.5 (d, *J* = 4.4 Hz), 132.2 (d, *J* = 20.6 Hz), 131.0 (d, *J* = 1.9), 129.9, 128.7 (d, *J* = 5.6 Hz), 127.3, 86.2 (d, *J* = 183.1 Hz), 52.7 (d, *J* = 0.6 Hz).

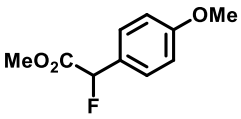
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −180.66 (d, *J* = 47.0 Hz).

[14] Zhu, F.; Xu, P.-W.; Zhou, F.; Wang, C.-H.; Zhou, J.; *Org. Lett.* **2015**, *17*, 972-975.

**IR (ATR, cm$^{-1}$):** 2956, 1763, 1438, 1222, 1070.

**HRMS (ESI-Orbitrap) m/z:** [M - F]$^+$ Calcd. for $C_9H_8ClO_2$ 183.0207; Found 183.0207.

*methyl 2-fluoro-2-(4-methoxyphenyl)acetate* (**18r**)[16]



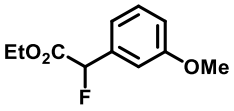

**General Procedure G** is employed with methyl 2-diazo-2-(4-dimethoxyphenyl)acetate **1r** (21 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 95:5 Hex:AcOEt) affords the title compound as transparent oil: 13 mg, 66%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.38 (dd, *J* = 8.8 Hz, *J* = 1.5 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.74 (d, *J* = 47.8 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 169.2 (d, *J* = 28.1 Hz), 160.7 (d, *J* = 1.9 Hz), 128.5 (d, *J* = 5.6 Hz), 126.2 (d, *J* = 20.6 Hz), 114.2, 89.1 (d, *J* = 183.1 Hz), 55.3, 52.5 (d, *J* = 0.6 Hz).

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −174.71 (d, *J* = 47.0 Hz).

*ethyl 2-fluoro-2-(3-methoxyphenyl)acetate* (**18s**)[15]




**General Procedure G** is employed with ethyl 2-diazo-2-(3-methoxyphenyl)acetate **1s** (22 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 21 mg, 99%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.32 (t, *J* = 7.8 Hz, 1H), 7.06 – 6.92 (m, 3H), 5.74 (d, *J* = 47.8 Hz, 1H), 4.35 – 4.14 (m, 2H), 3.82 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 168.4 (d, *J* = 27.5 Hz), 159.8, 135.6 (d, *J* = 20.6 Hz), 129.8, 118.9 (d, *J* = 6.3 Hz), 115.4 (d, *J* = 1.9 Hz), 111.7 (d, *J* = 6.3 Hz), 89.2 (d, *J* = 185.0 Hz), 61.8, 55.3, 14.0.

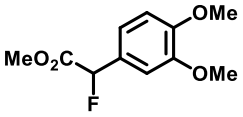
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −180.25 (d, *J* = 49.4 Hz).

[15] Xia, T.; He, L.; Liu, Y. A.; Hartwig, J. F.; Liao, X.; *Org. Lett.* **2017**, *19*, 2610-2613.

**IR (ATR, cm$^{-1}$):** 2926, 1759, 1603, 1491, 1265, 1044.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{11}H_{14}FO_3$ 213.0921; Found 213.0918.

*methyl 2-(3,4-dimethoxyphenyl)-2-fluoroacetate* (**18t**)




**General Procedure G** is employed with methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate **1t** (24 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, gradient: Hex – 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as transparent oil: 9 mg, 40%.

**$^1$H NMR (500 MHz, $CDCl_3$) δ:** 7.03 – 6.97 (m, 2H), 6.89 – 6.86 (m, 1H), 5.72 (d, *J* = 47.5 Hz, 1H), 3.90 (s, 6H), 3.79 (s, 3H).

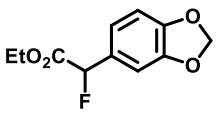
**$^{13}$C NMR (125 MHz, $CDCl_3$) δ:** 169.2 (d, *J* = 28.8.4 Hz), 150.2 (d, *J* = 3.8 Hz), 149.3, 126.5 (d, *J* = 21.3 Hz), 120.0 (d, *J* = 6.3 Hz), 111.0, 109.5 (d, *J* = 6.3 Hz), 89.3 (d, *J* = 185.0 Hz), 56.0, 55.9, 52.6.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −175.35 (d, *J* = 49.4 Hz).

**IR (ATR, cm$^{-1}$):** 2926, 1759, 1603, 1491, 1265, 1044.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{11}H_{14}FO_4$ 229.0871; Found 229.0873.

*ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-fluoroacetate* (**18u**)[16]

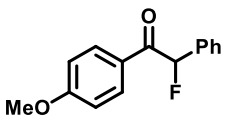



**General Procedure G** is employed with methyl ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-diazoacetate **1u** (22 mg, 0.1 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 6 equiv.) and DCM (1 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, gradient: Hex – 95:5 Hex:AcOEt - 9:1 Hex:AcOEt) affords the title compound as transparent oil: 10 mg, 44%.

[16] Guo, C.; Yue, X.; Qing, F.-L. *Synthesis* **2010**, *11*, 1837-1844.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 6.95 – 6.92 (m, 2H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.99 (s, 2H), 5.65 (d, *J* = 47.8 Hz, 1H), 4.35 – 4.14 (m, 2H), 1.27 (t, *J* = 6.7 Hz, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 168.6 (d, *J* = 29.1 Hz), 148.8 (d, *J* = 2.2 Hz), 148.0, 127.9 (d, *J* = 21.0 Hz), 121.3 (d, *J* = 6.5 Hz), 108.4, 107.2 (d, *J* = 5.2 Hz), 101.4, 89.2 (d, *J* = 183.9 Hz), 61.8, 14.0.
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −174.87 (d, *J* = 49.4 Hz).
**IR (ATR, $cm^{-1}$):** 2959, 2918, 1749, 1615, 1491, 1270, 1067.
**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{11}H_{11}O_4$ 207.0652; Found 207.0653.

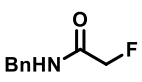
*2-fluoro-1-(4-methoxyphenyl)-2-phenylethan-1-one* (**18y**)[20]




**General Procedure G** is employed with 2-diazo-1-(4-methoxyphenyl)-2-phenylethan-1-one **18y** (15 mg, 0.06 mmol, 1 equiv.), HF·pyr **17a** (10 mL, 0.36 mmol, 6 equiv.) and DCM (600 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 14 mg, 96%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.95 (d, *J* = 8.8 Hz, 2H), 7.50 – 7.37 (m, 5H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 48.8 Hz, 1H), 3.84 (s, 3H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 192.7 (d, *J* = 20.6 Hz), 163.9, 134.7 (d, *J* = 20.0 Hz), 131.5 (d, *J* = 3.1 Hz), 129.4 (d, *J* = 2.5 Hz), 129.0, 127.2 (d, *J* = 5.0 Hz), 126.9, 113.9, 94.0 (d, *J* = 184.4 Hz), 55.5.
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −175.59 (d, *J* = 47.0 Hz).

*N-benzyl-2-diazoacetamide* (**18z**)[13]



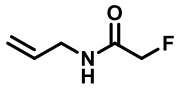

**General Procedure G** is employed with *N*-benzyl-2-diazoacetamide **1z** (53 mg, 0.3 mmol, 1 equiv.) HF·pyr **17a** (24 mL, 0.9 mmol, 3 equiv.) and DCM (3 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$, - 99:1 DCM:MeOH) affords the title compound as transparent oil: 22 mg, 44%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.36 – 7.29 (m, 5H), 6.57 (br s, 1H), 4.86 (d, *J* = 47.3 Hz, 2H), 4.53 (d, *J* = 5.8 Hz, 2H).

**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.4 (d, *J* = 16.3 Hz), 137.3, 128.8, 127.9 (d, *J* = 3.8 Hz), 127.8, 80.4 (d, *J* = 185.0 Hz), 43.0.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −224.85 (td, *J* = 47.0 Hz, *J* = 2.4 Hz).

*N*-allyl-2-diazoacetamide (**18aa**)



**General Procedure G** is employed with *N*-allyl-2-diazoacetamide **1aa** (38 mg, 0.3 mmol, 1 equiv.) HF·pyr **17a** (24 mL, 0.9 mmol, 3 equiv.) and DCM (3 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$, Hex - 6:3.5:0.5 Hex:AcOEt:DCM) affords the title compound as transparent oil (volatile): 10 mg, 29%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 6.38 (br s, 1H), 5.91 – 5.80 (m, 1H), 5.27 – 5.17 (m, 2H), 4.82 (d, *J* = 47.5 Hz, 2H), 3.97 (t, *J* = 5.8 Hz, 2H).

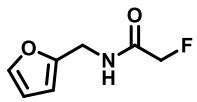
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.4 (d, *J* = 16.9 Hz), 133.3, 117.1, 80.3 (d, *J* = 184.4 Hz), 41.2.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −224.91 (td, *J* = 47.0 Hz, *J* = 2.4 Hz).

**IR (ATR, $cm^{-1}$):** 2450, 1676, 1079.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_5H_9FNO$ 118.0663; Found 118.0665.

*2-diazo-N-(furan-2-ylmethyl)acetamide* (**18bb**)



**General Procedure G** is employed with 2-diazo-N-(furan-2-ylmethyl)acetamide **1bb** (38 mg, 0.3 mmol, 1 equiv.) HF·pyr **17a** (24 mL, 0.9 mmol, 3 equiv.) and DCM (3 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$, Hex - 6:3.5:0.5 Hex:AcOEt:DCM) affords the title compound as transparent oil (volatile): 10 mg, 21%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.37 (dd, *J* = 1.8, *J* = 0.8, 1H), 6.61 (br s, 1H), 6.33 (dd, *J* = 3.3 Hz, *J* = 1.9 Hz, 1H), 6.26 (dd, *J* = 3.0 Hz, *J* = 0.5 Hz, 1H), 4.82 (d, *J* = 47.5 Hz, 2H), 4.52 (d, *J* = 5.8 Hz, 2H).

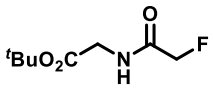
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.3 (d, *J* = 17.5 Hz), 150.3, 142.5, 110.5, 107.9, 80.2 (d, *J* = 185.0 Hz), 35.7.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −225.23 (td, *J* = 47.0 Hz, *J* = 4.7 Hz).

**IR (ATR, $cm^{-1}$):** 3304, 2957, 1668, 1544, 1046.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ $C_7H_9FNO_2$ 158.0612; Found 158.0612.

*tert-butyl (2-fluoroacetyl)glycinate* (**18cc**)



**General Procedure G** is employed with tert-butyl (2-diazoacetyl)glycinate **1cc** (40 mg, 0.2 mmol, 1 equiv.) HF·pyr **17a** (32 mL, 1.2 mmol, 6 equiv.) and DCM (2 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$, - 6:3:1 Hex:AcOEt:DCM) affords the title compound as transparent oil (volatile): 17 mg, 45%.

**$^{1}$H NMR (250 MHz, CDCl3) δ:** 6.78 (br s, 1H), 4.84 (d, *J* = 47.5 Hz, 2H), 4.01 (d, *J* = 5.3 Hz, 2H), 1.48 (s, 9H).

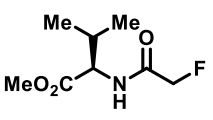
**$^{13}$C NMR (62.5 MHz, CDCl3) δ:** 168.3, 165.7 (d, *J* = 16.9 Hz), 82.7, 80.1 (d, *J* = 185.0 Hz), 41.3, 28.0.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −225.50 (td, *J* = 47.0 Hz, *J* = 2.4 Hz).

**IR (ATR, $cm^{-1}$):** 3264, 2982, 2099, 1731, 1609, 1397, 1245.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_8H_{15}FNO_3$ 192.1030; Found 192.1028.

*methyl (2-fluoroacetyl)valinate* (**18dd**)

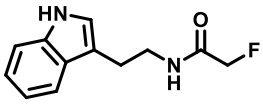


**General Procedure G** is employed with methyl (2-diazoacetyl)valinate **1dd** (40 mg, 0.2 mmol, 1 equiv.) HF·pyr **17a** (32 mL, 1.2 mmol, 6 equiv.) and DCM (2 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$,

- 6:3:1 Hex:AcOEt:DCM) affords the title compound as transparent oil: 14 mg, 37%.

**$^{1}$H NMR (250 MHz, CDCl3) δ:** 6.75 (br s, 1H), 4.84 (dd, *J* = 47.3 Hz, *J* = 1.3 Hz, 2H), 4.61 (ddd, *J* = 9.0 Hz, *J* = 5.0 Hz, *J* = 1.3 Hz, 1H), 3.76 (s, 3H), 2.28 – 2.13 (m, 1H), 0.95 (d, *J* = 7.1 Hz, 6H).
**$^{13}$C NMR (62.5 MHz, CDCl3) δ:** 171.8, 167.5 (d, *J* = 17.5 Hz), 80.2 (d, *J* = 185.0 Hz), 56.5, 52.3, 31.3, 18.9, 17.7.
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −225.00 (tdd, *J* = 47.2 Hz, *J* = 3.3 Hz, *J* = 1.2 Hz).
**IR (ATR, $cm^{-1}$):** 2959, 2923, 1751, 1685, 1464, 11260, 1044.
**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_8H_{15}FNO_3$ 192.1030; Found 192.1030.

*2-diazo-N-(2-(3a,7a-dihydro-1H-indol-3-yl)ethyl)acetamide* (**18ee**)[17]

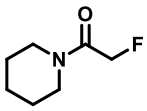



**General Procedure G** is employed with 2-diazo-N-(2-(3a,7a-dihydro-1H-indol-3-yl)ethyl)acetamide **1ee** (46 mg, 0.2 mmol, 1 equiv.), HF·pyr **17a** (11 mL, 0.4 mmol, 2 equiv.) and DCM (2 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$, DCM - 98:2 DCM:MeOH) affords the title compound as transparent oil: 16 mg, 36%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 8.09 (br s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.23 – 7.14 (m, 2H), 7.07 (s, 1H), 6.40 (br s, 1H), 4.76 (d, *J* = 47.5 Hz, 2H), 3.69 (td, *J* = 6.7 Hz, *J* = 6.3 Hz, 2H), 3.03 (t, *J* = 6.7 Hz, 2H).
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.5 (d, *J* = 16.9 Hz), 136.4, 127.2, 122.3, 122.0, 119.6, 118.6, 112.6, 111.3, 80.3 (d, *J* = 185.0 Hz), 39.0, 25.3.
**$^{19}$F (235 MHz, $CDCl_3$) δ:** −224.63 (td, *J* = 47.0 Hz, *J* = 4.7 Hz).
**IR (ATR, $cm^{-1}$):** 3409, 2928, 1664, 1546, 1262, 1093.
**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{12}H_{14}FN_2O$ 221.1085; Found 221.1086.

[17] Zheng, W.; Scheibner, K. A.; Ho, A. K.; Cole, P. A.; *Chem. Biol.* **2001**, *8*, 379-389.

*2-fluoro-1-(piperidin-1-yl)ethan-1-one* (**18ff**)



**General Procedure G** is employed with 2-diazo-1-(piperidin-1-yl)ethan-1-one **1ff** (46 mg, 0.3 mmol, 1 equiv.), HF·pyr **17a** (48 mL, 1.8 mmol, 6 equiv.) and DCM (3 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$, 98:2 DCM:MeOH) affords the title compound as transparent oil (volatile): 19 mg, 44%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 4.97 (d, *J* = 47.3 Hz, 2H), 3.58 – 3.56 (m, 2H), 3.34 – 3.32 (m, 2H), 1.68 – 1.56 (m, 6H).

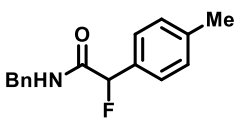
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.0 (d, *J* = 17.5 Hz), 80.0 (d, *J* = 178.1 Hz), 45.6, 43.0, 26.4, 25.4, 24.4.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −224.56 (t, *J* = 47.0 Hz).

**IR (ATR, cm$^{-1}$):** 2939, 2853, 1773, 1647, 1446, 1256.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_7H_{118f}NO$ 146.0976; Found 146.0976.

*N-benzyl-2-fluoro-2-(p-tolyl)acetamide* (**18gg**)



**General Procedure G** is employed with *N*-benzyl-2-diazo-2-(p-tolyl)acetamide **1gg** (40 mg, 0.15 mmol, 1 equiv.), HF·pyr **17a** (12 mL, 0.45 mmol, 6 equiv.) and DCM (1.5 mL, 0.1M). Purification by flash column chromatography ($SiO_2$, gradient: Hex - 95:5 Hex:AcOEt - 9:1 Hex:AcOEt - 8:2 Hex:AcOEt - 7:3 Hex:AcOEt) affords the title compound as transparent oil: 25 mg, 65%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.37 – 7.29 (m, 7H), 7.21 (d, *J* = 7.8 Hz, 2H), 6.79 (br s,1H), 5.80 (d, *J* = 48.5 Hz, 1H), 4.53 (d, *J* = 6.0 Hz, 2H), 2.36 (s, 3H).

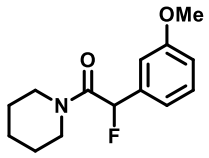
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 168.6 (d, *J* = 21.9 Hz), 139.5 (d, *J* = 3.1 Hz), 137.5, 131.8 (d, *J* = 18.8 Hz), 129.4, 128.8, 127.9, 127.8, 126.7 (d, *J* = 6.3 Hz), 91.9 (d, *J* = 185.6 Hz), 43.2, 21.3.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −175.42 (t, *J* = 49.4 Hz).

**IR (ATR, cm$^{-1}$):** 2939, 2853, 1773, 1647, 1446, 1256.

**HRMS (ESI-Orbitrap) m/z:** $[M - F]^+$ Calcd. for $C_{16}H_{16}NO$ 238.1226; Found 238.1228.

*2-fluoro-2-(3-methoxyphenyl)-1-(piperidin-1-yl)ethan-1-one* (**18hh**)




**General Procedure G** is employed with 2-diazo-2-(3-methoxyphenyl)-1-(piperidin-1-yl)ethan-1-one **1hh** (20 mg, 0.078 mmol, 1 equiv.), HF·pyr **17a** (13 mL, 0.47 mmol, 6 equiv.) and DCM (780 mL, 0.1M). Filtration using $SiO_2$ affords the title compound as a transparent oil: 14 mg, 72%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 7.32 (t, *J* = 7.8 Hz, 1H), 7.03 – 6.90 (m, 3H), 6.04 (d, *J* = 49.0 Hz, 1H), 3.82 (s, 3H), 3.69 – 3.64 (m, 1H), 3.54 – 3.48 (m, 1H), 3.37 – 3.23 (m, 2H), 1.63 – 1.49 (m, 4H), 1.33 – 1.23 (m, 2/H).

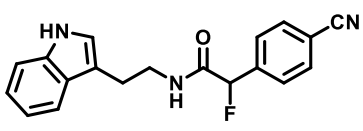
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 165.8 (d, *J* = 21.9 Hz), 160.0, 136.2 (d, *J* = 20.0 Hz), 129.9, 118.8 (d, *J* = 5.6 Hz), 115.1 (d, *J* = 2.5 Hz), 111.7 (d, *J* = 6.3 Hz), 90.8 (d, *J* = 183.1 Hz), 55.4, 46.1, 43.5, 25.8, 25.5, 24.3.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −173.77 (d, *J* = 49.4 Hz).

**IR (ATR, cm$^{-1}$):** 2940, 2856, 1655, 1601, 1455, 1262, 1044, 1007.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{14}H_{19}FNO_2$ 252.1394; Found 252.1393.

*N-(2-(1H-indol-3-yl)ethyl)-2-(4-cyanophenyl)-2-fluoroacetamide* (**18ii**)




**General Procedure G** is employed with *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(4-cyanophenyl)-2-diazoacetamide **1ii** (82 mg, 0.25 mmol, 1 equiv.), HF·pyr **17a** (40 mL, 1.5 mmol, 6 equiv.) and DCM (2.5 mL, 0.1 M). Purification by preparative TLC ($SiO_2$, DCM - 98:2 DCM:MeOH) affords the title compound as transparent oil: 70 mg, 87%.

**$^1$H NMR (250 MHz, $CDCl_3$) δ:** 8.07 (br s, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.54 (br s, 1H), 5.78 (d, *J* = 48.0 Hz, 1H), 3.67 (dt, *J* = 6.5 Hz, *J* = 6.3 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H).

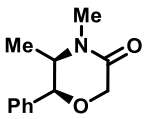
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 167.2 (d, *J* = 20.6 Hz), 139.7 (d, *J* = 19.4 Hz), 136.4, 132.3, 127.2, 126.6 (d, *J* = 7.5 Hz), 122.4, 122.0, 119.7, 188.6, 118.3, 113.0 (d, *J* = 1.9 Hz), 112.4, 111.3, 90.5 (d, *J* = 190.6 Hz), 39.4, 25.1.

**$^{19}$F (235 MHz, $CDCl_3$) δ:** −184.66 (dd, *J* = 47.0 Hz, *J* = 3.5 Hz).

**IR (ATR, cm$^{-1}$):** 3390, 2927, 2230, 1670, 1458, 1264.

**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{19}H_{17}FN_3O$ 322.1350; Found 322.1350.

*(5R,6S)-4,5-dimethyl-6-phenylmorpholin-3-one* (**19**)




**General Procedure G** is employed with 2-diazo-*N*-(1-hydroxy-1-phenylpropan-2-yl)-*N*-methylacetamide **1rr** (47 mg, 0.2 mmol, 1 equiv.), HF·pyr **17a** (16 mL, 0.6 mmol, 3 equiv.) and DCM (2 mL, 0.1M). The addition of HF.pyr **17a** is made at 0 ºC. Purification by flash column chromatography ($SiO_2$, DCM - 98:2 DCM:MeOH) affords the title compound as transparent oil: 32 mg, 78%.

**$^{1}$H NMR (250 MHz, $CDCl_3$) δ:** 7.40 – 7.27 (m, 5H), 4.96 (d, *J* = 2.8 Hz, 1H), 4.44 (d, *J* = 17.0 Hz, 1H), 4.32 (d, *J* = 17.0 Hz, 1H), 3.49 (qd, *J* = 6.5 Hz, *J* = 2.8 Hz, 1H), 3.03 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H).

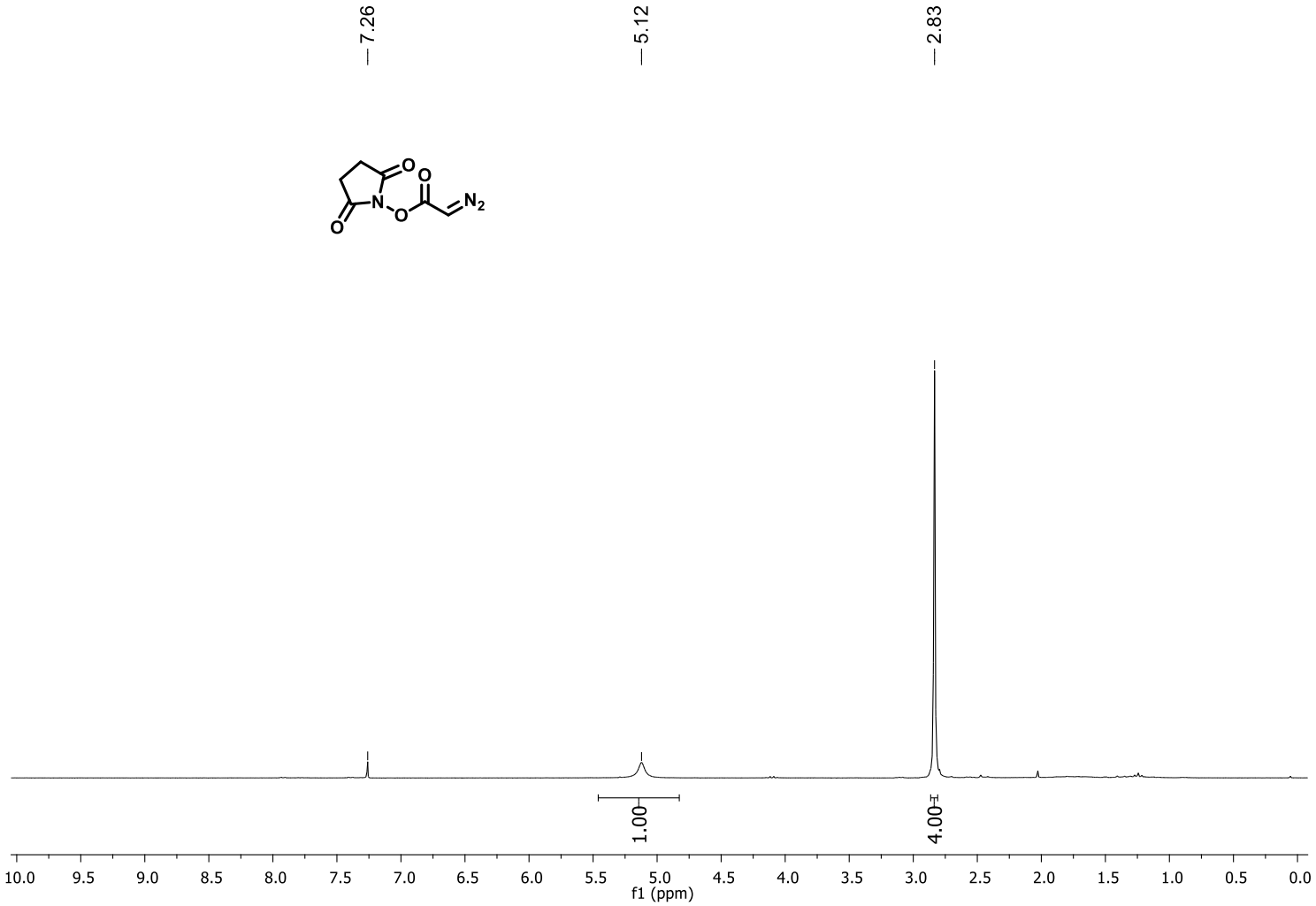
**$^{13}$C NMR (62.5 MHz, $CDCl_3$) δ:** 166.8, 137.5, 128.4, 127.7, 125.4, 77.4, 68.1, 58.3, 33.1, 12.5.

**IR (ATR, cm$^{-1}$):** 2925, 1653, 1452, 1253, 1149.

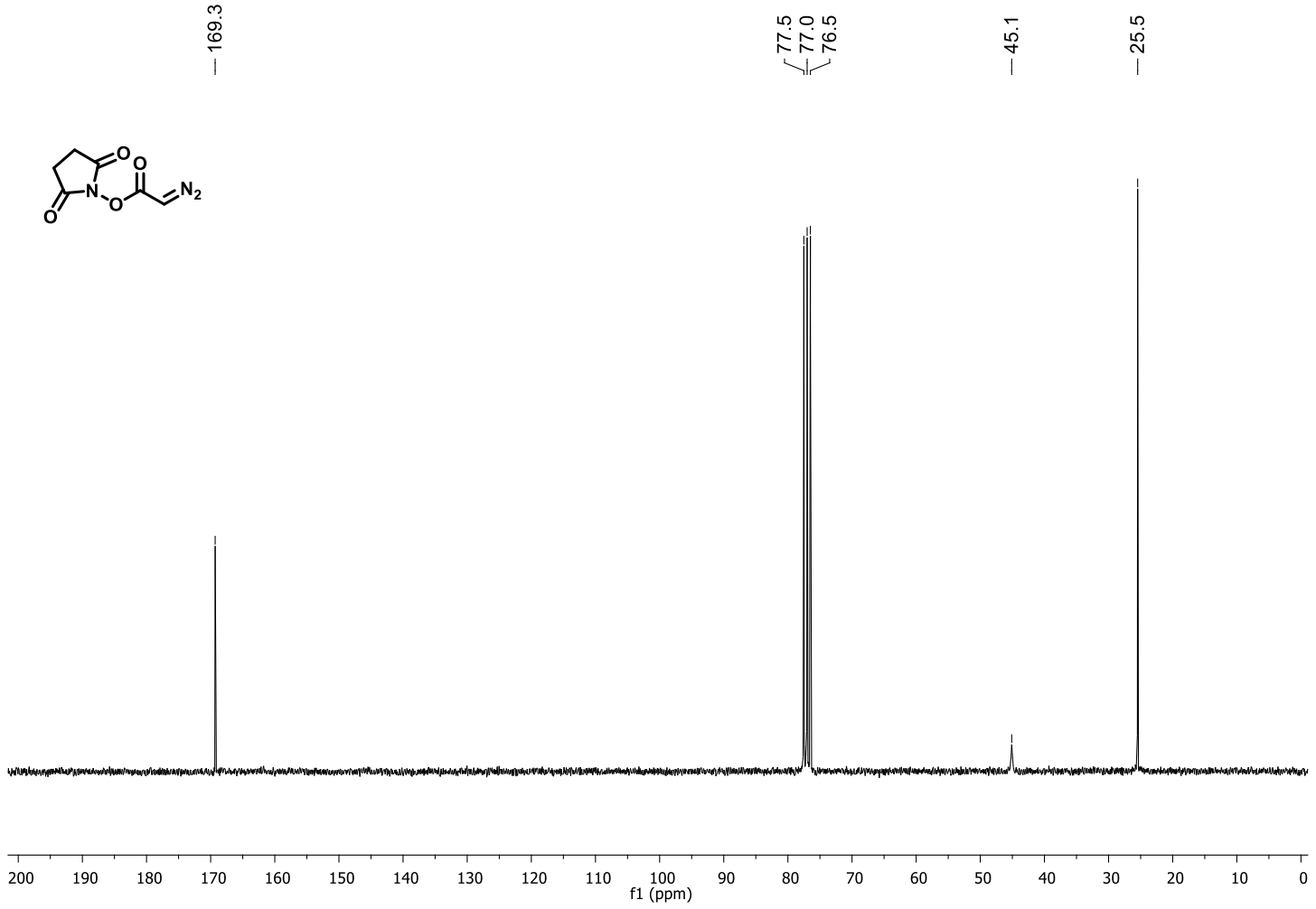
**HRMS (ESI-Orbitrap) m/z:** $[M + H]^+$ Calcd. for $C_{12}H_{16}NO_2$ 206.1176; Found 206.1176.

**NMR Spectra**

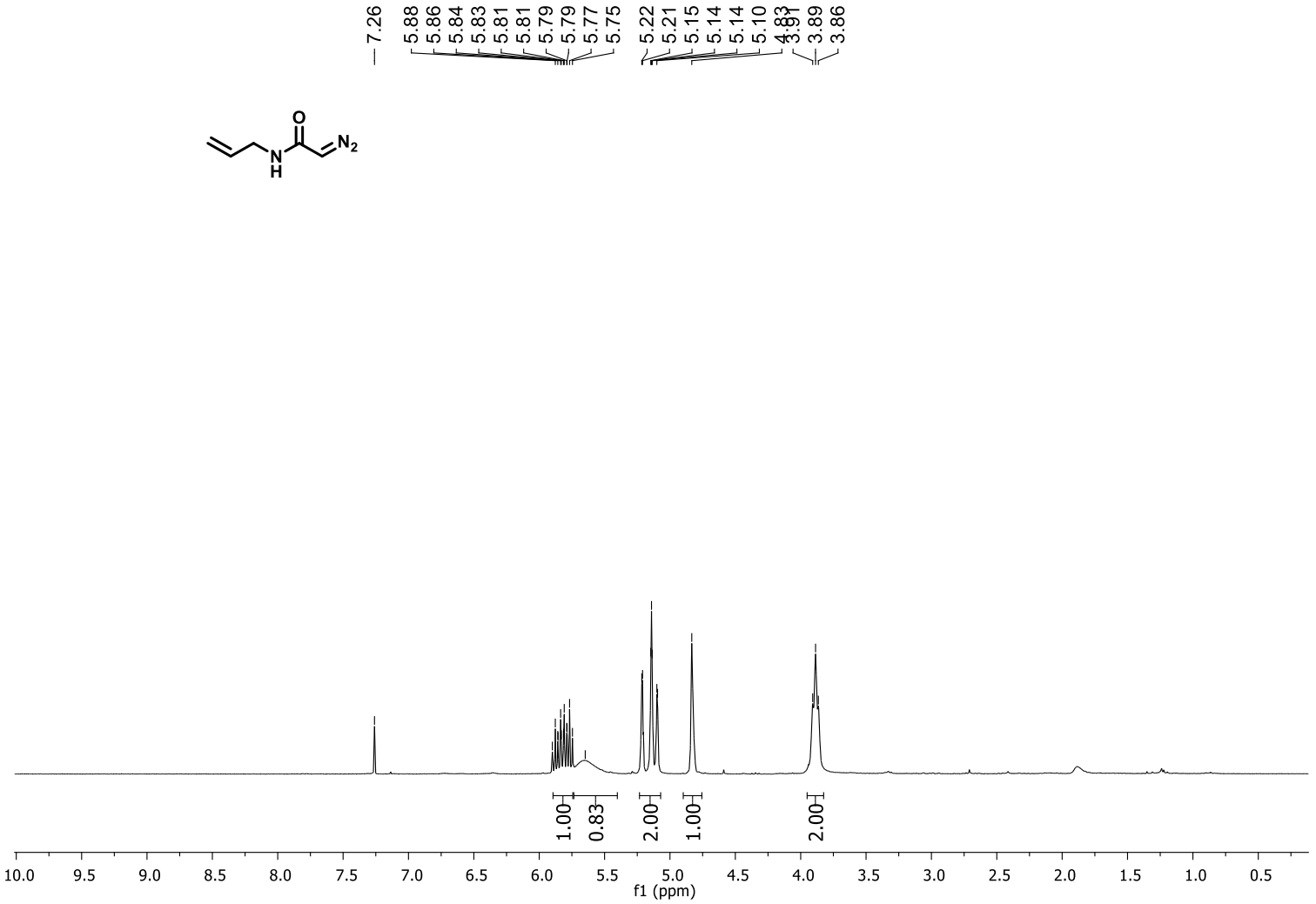
**pre-1z - $^{1}$H NMR (250 MHz, $CDCl_3$)**



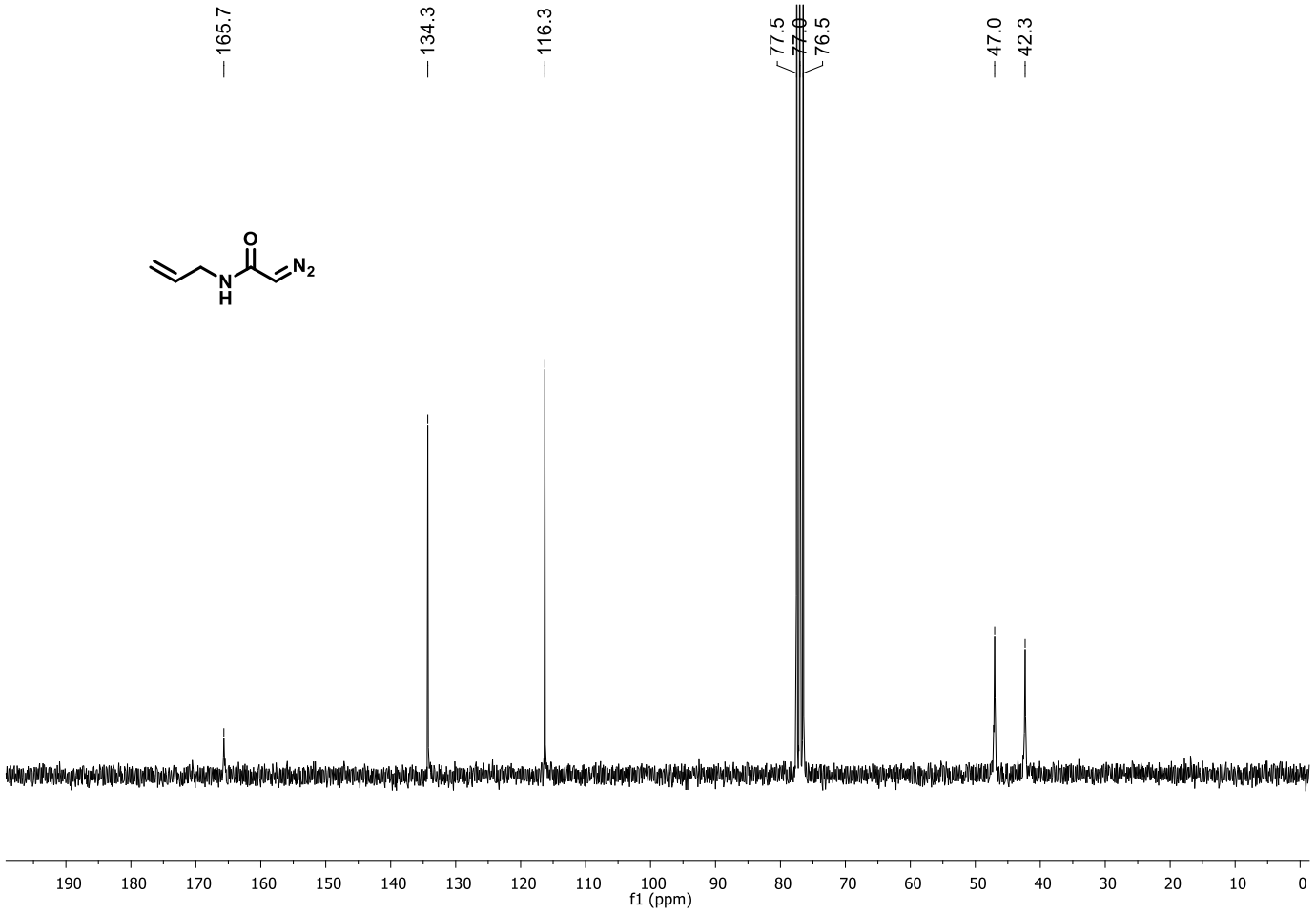
**pre-1z - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



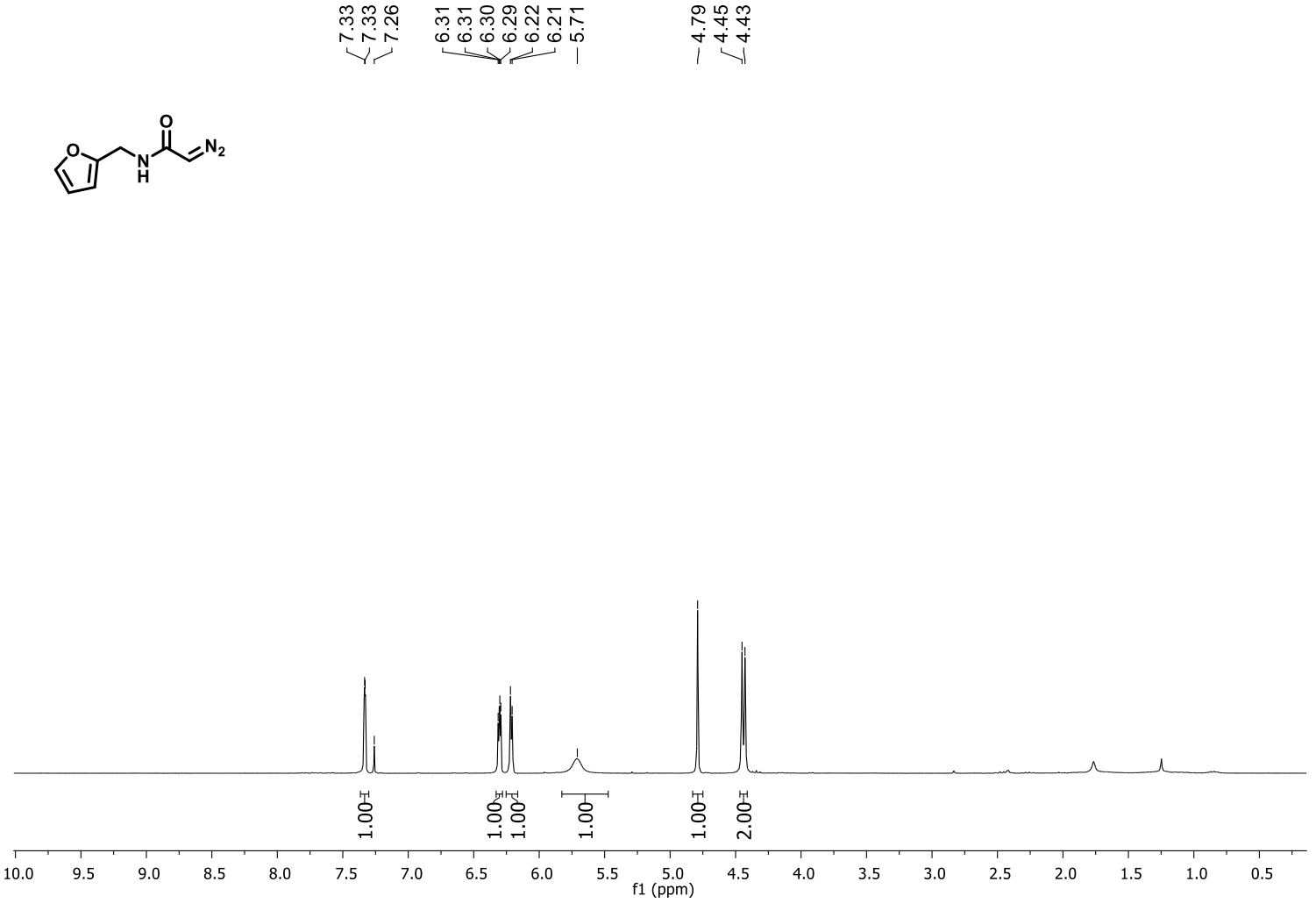
**1aa - $^{1}$H NMR (250 MHz, $CDCl_3$)**



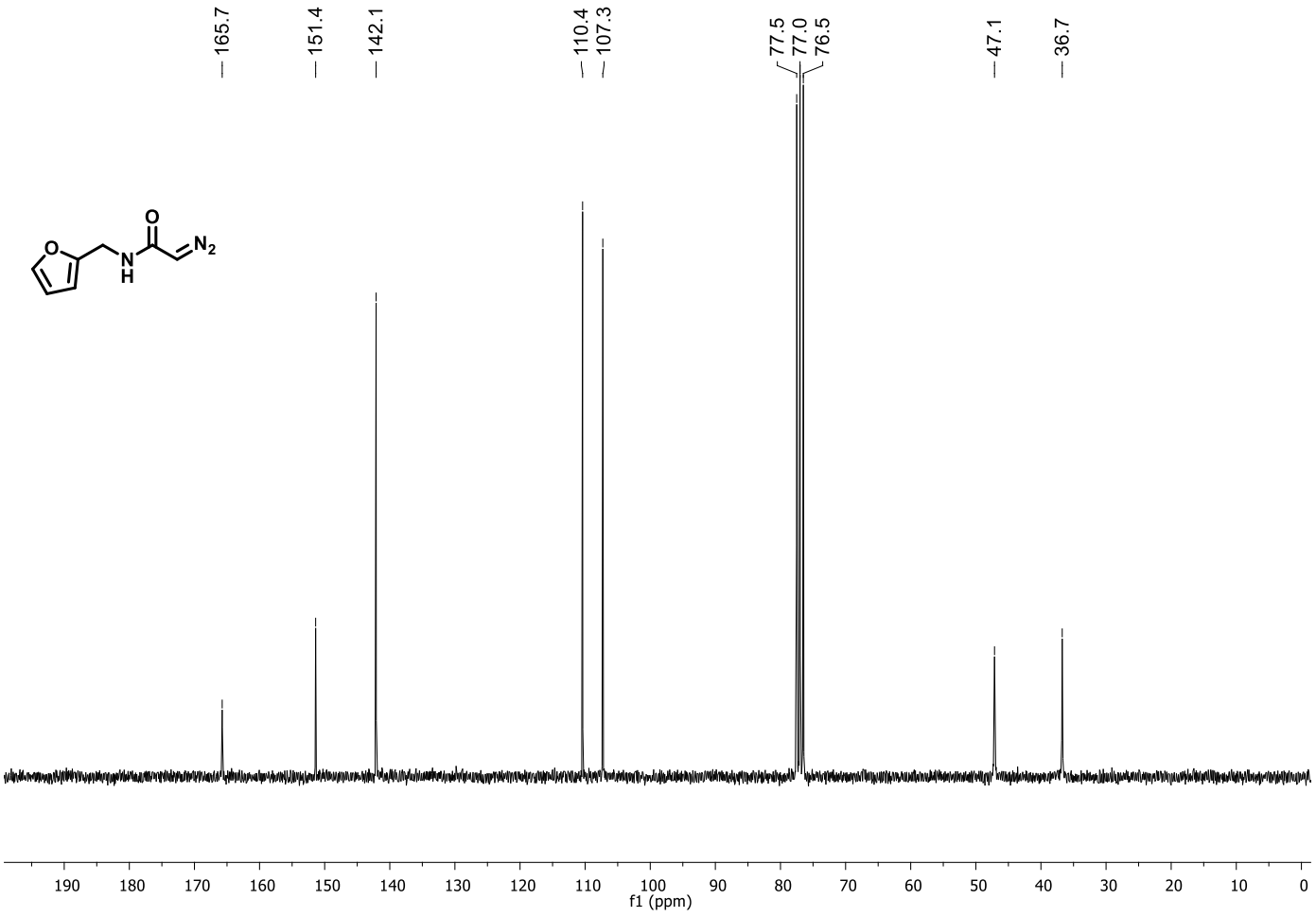
**1aa - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



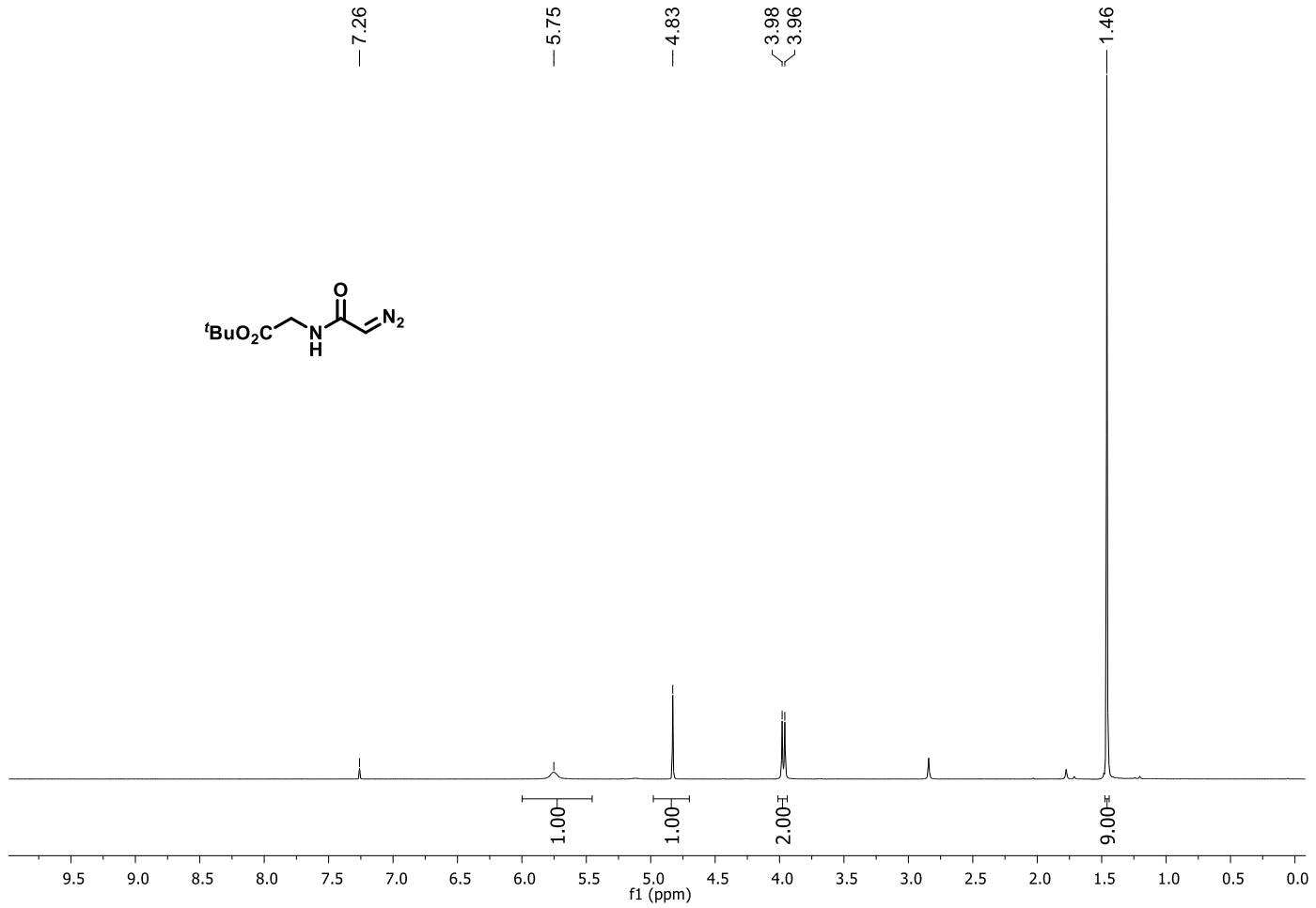
**1bb - $^{1}$H NMR (250 MHz, $CDCl_3$)**



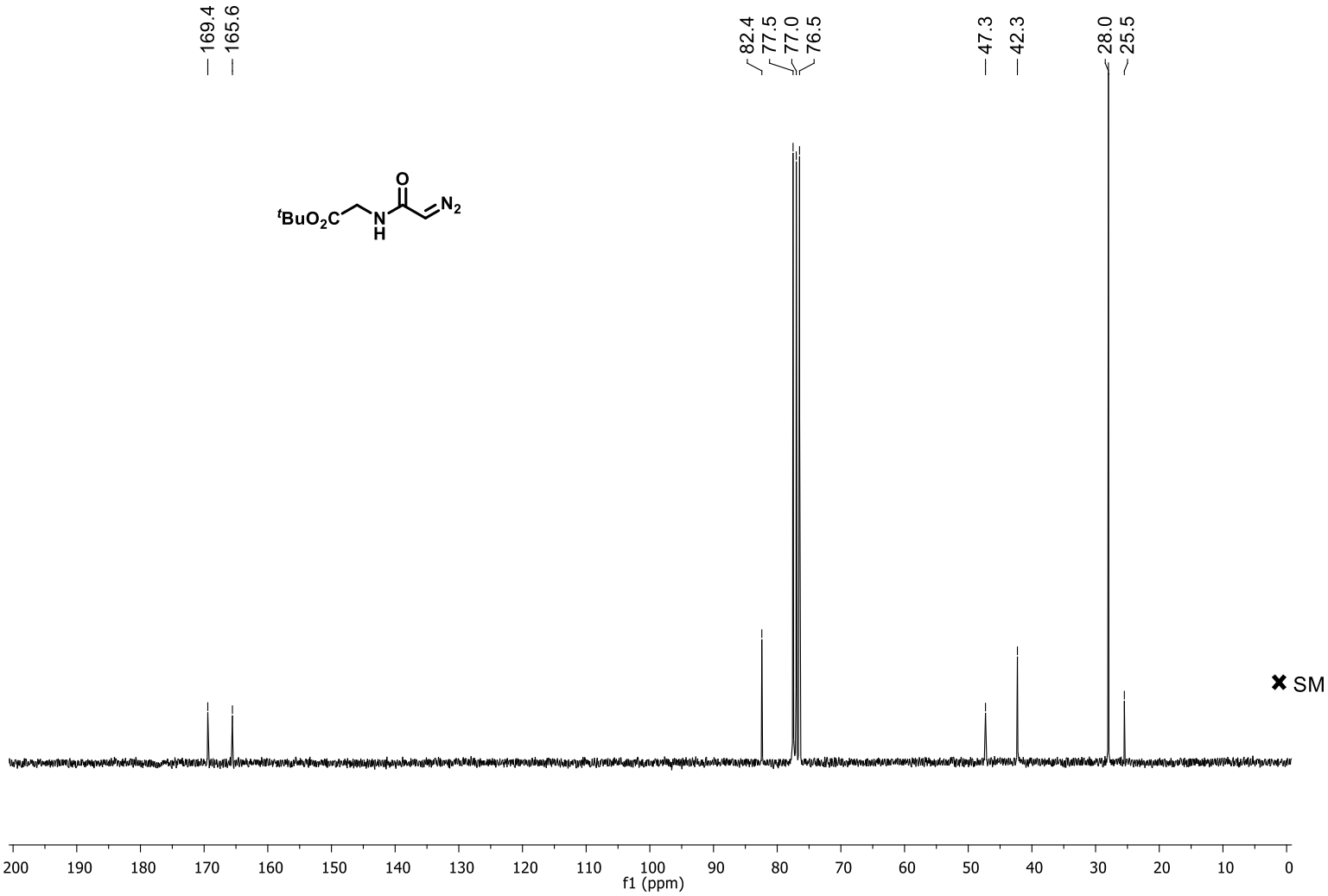
**1bb - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



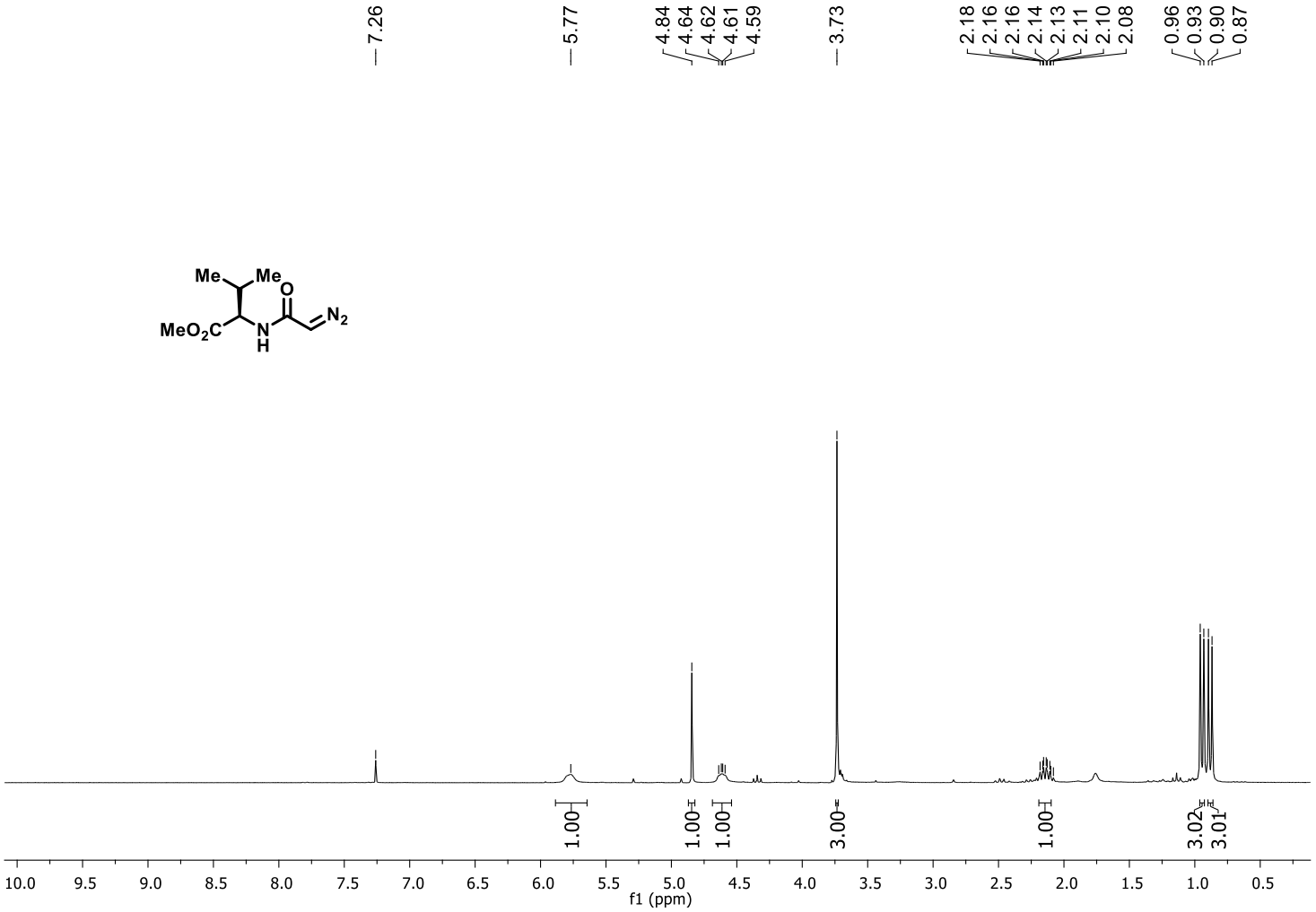
**1cc - $^{1}$H NMR (250 MHz, $CDCl_3$)**



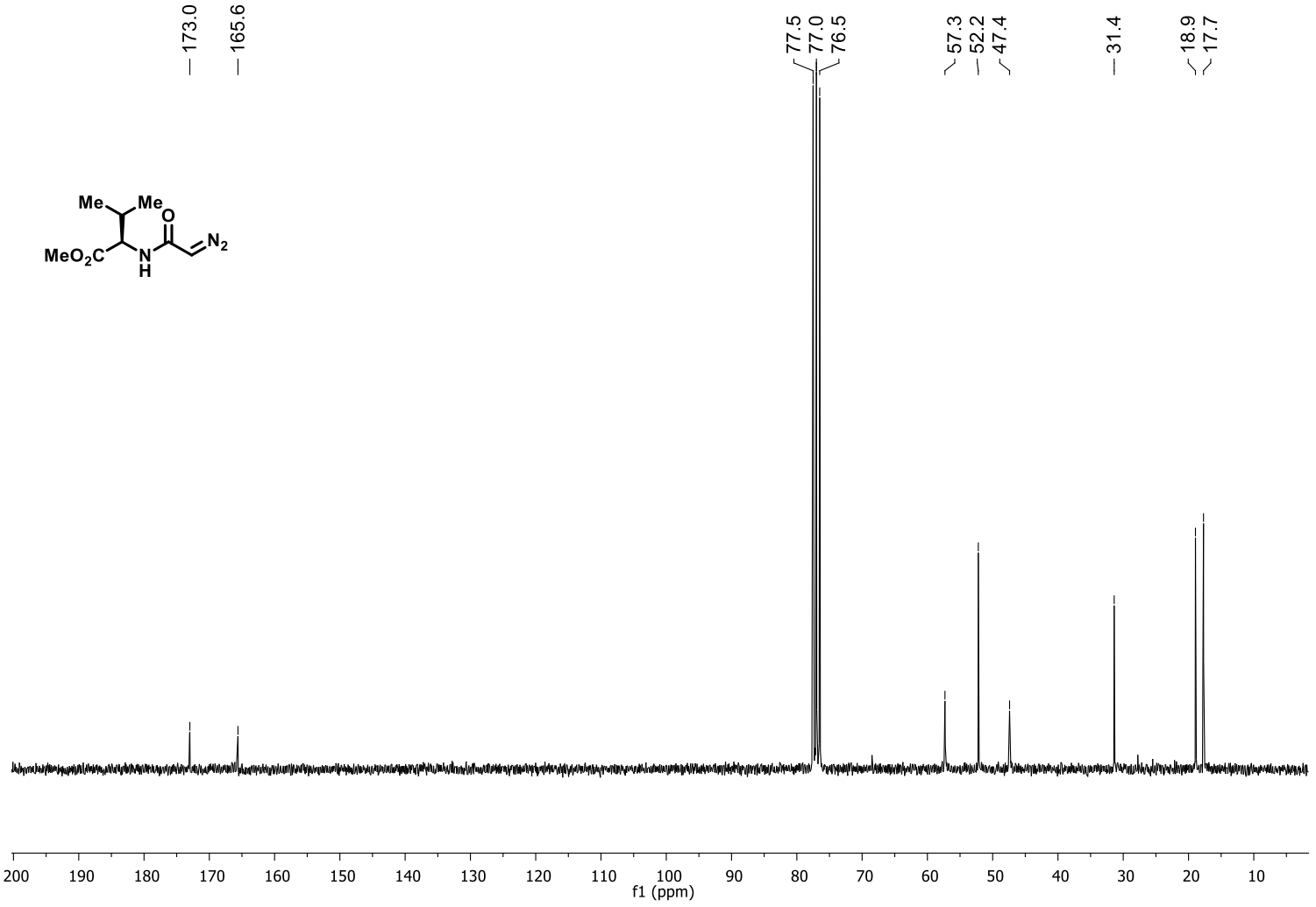
**1cc - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



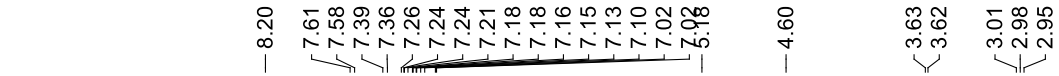
**1dd - $^{1}$H NMR (250 MHz, $CDCl_3$)**

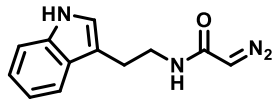


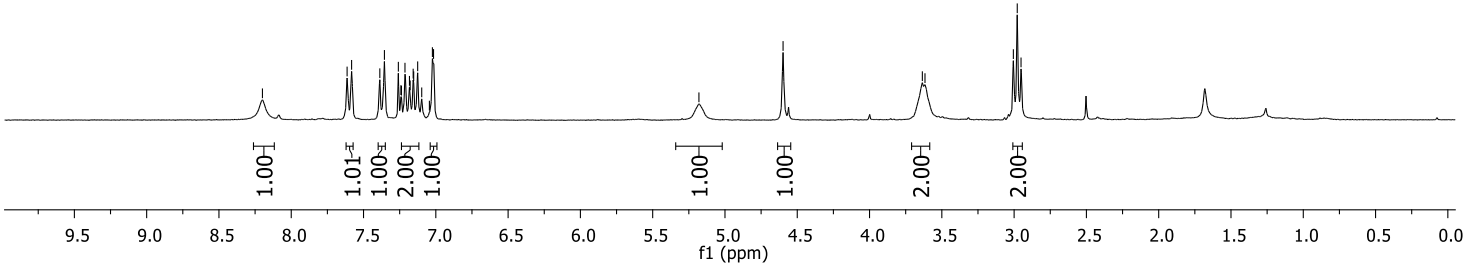
**1dd - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



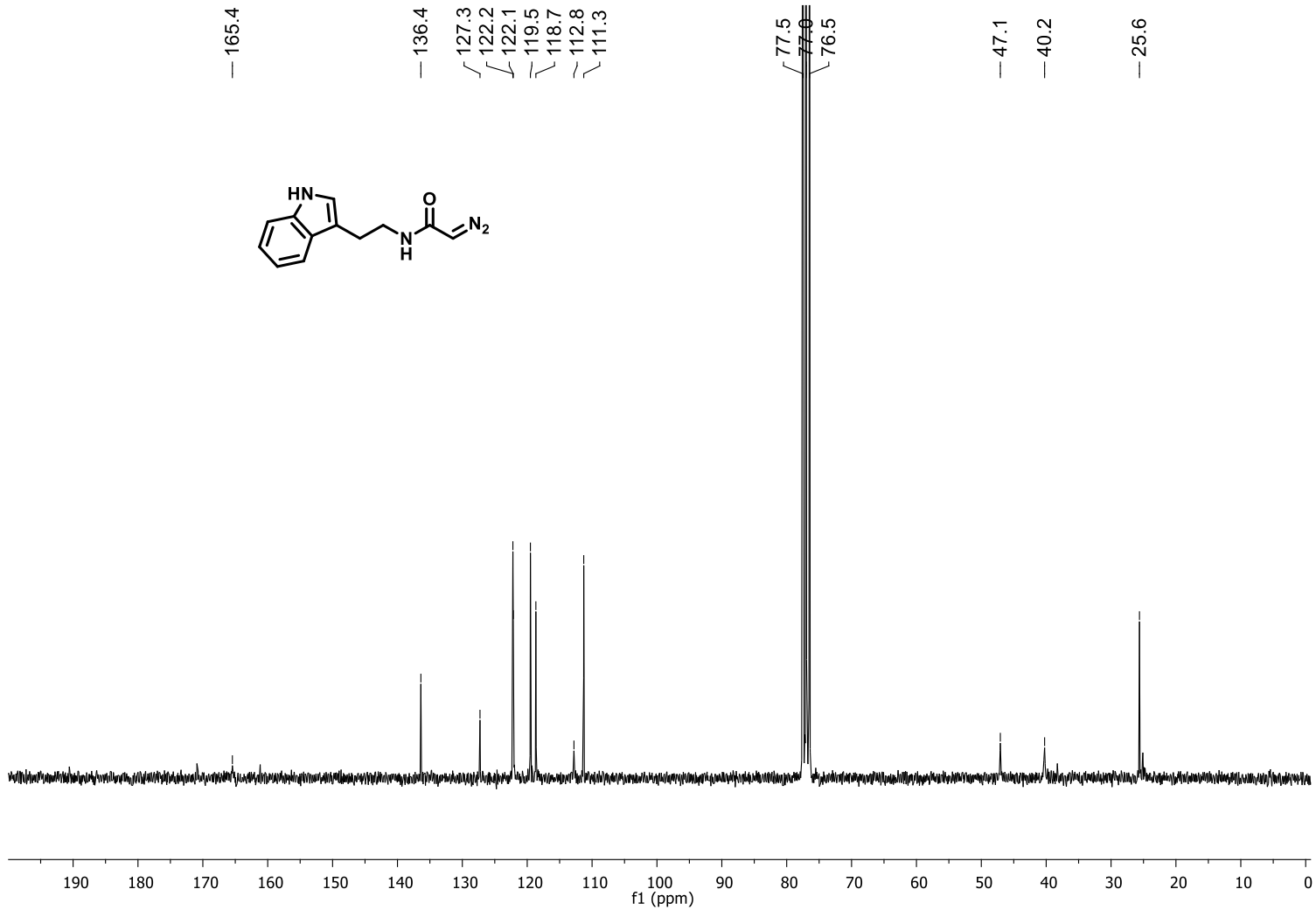
**1ee - $^{1}$H NMR (250 MHz, $CDCl_3$)**



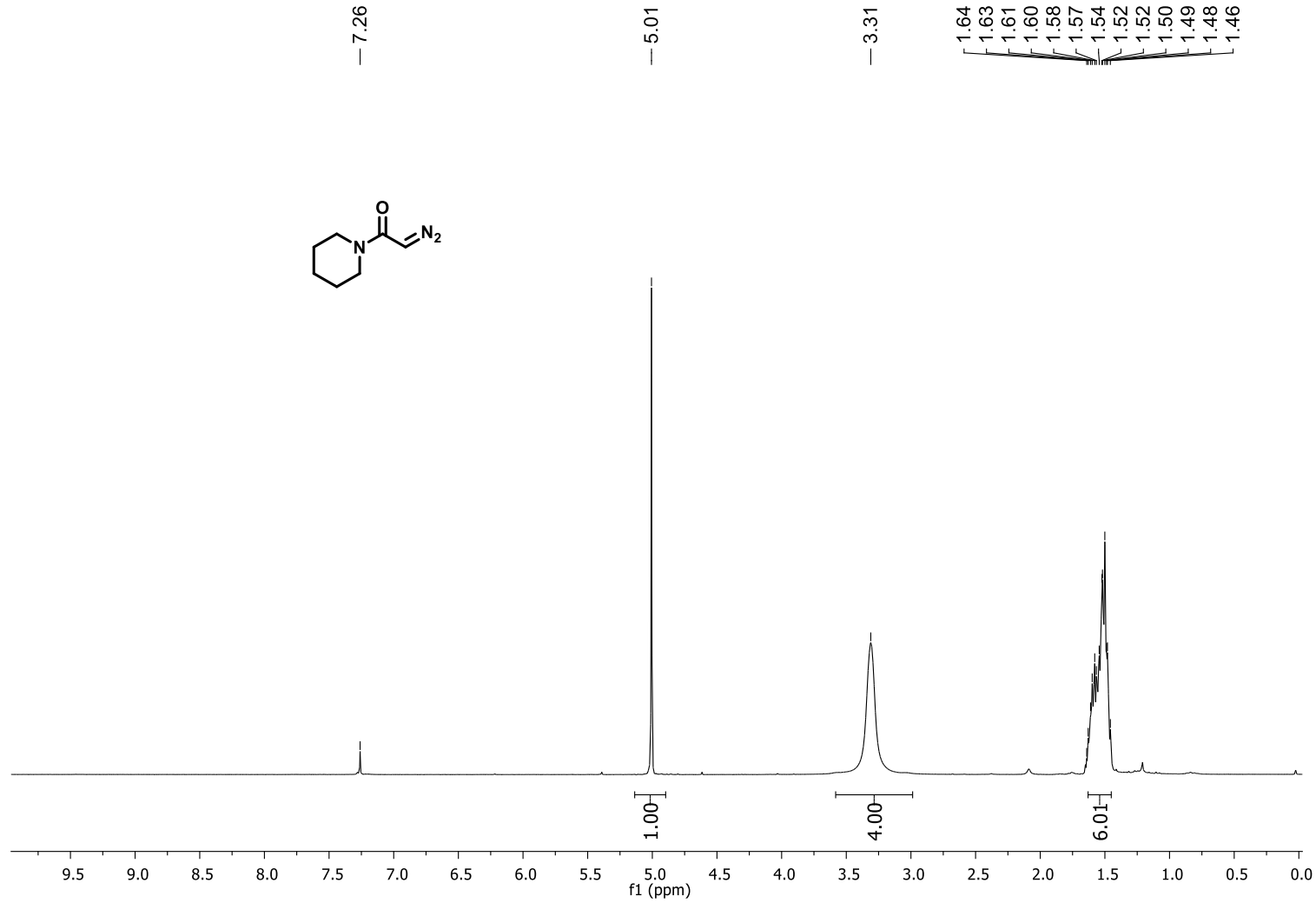



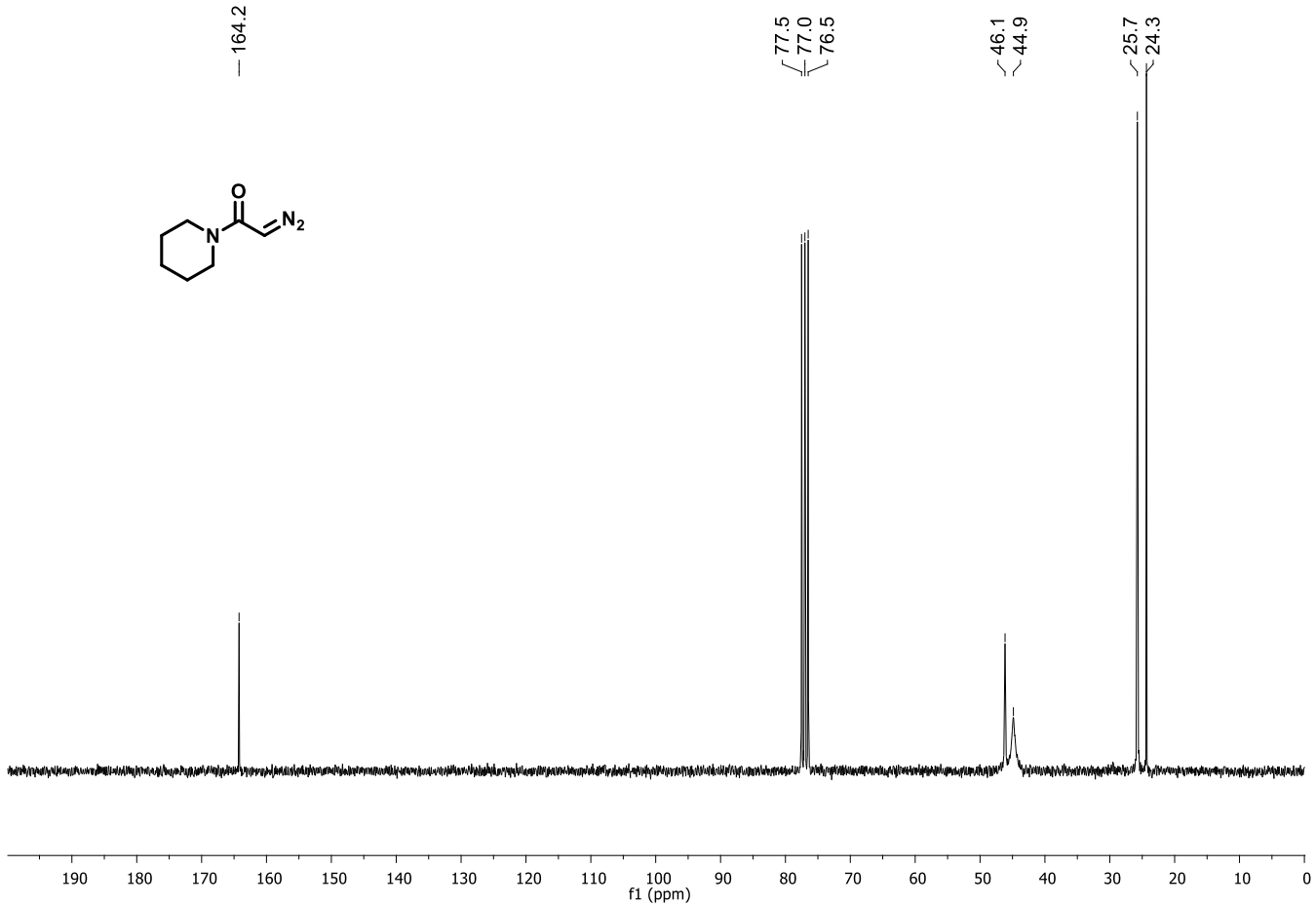
**1ee - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



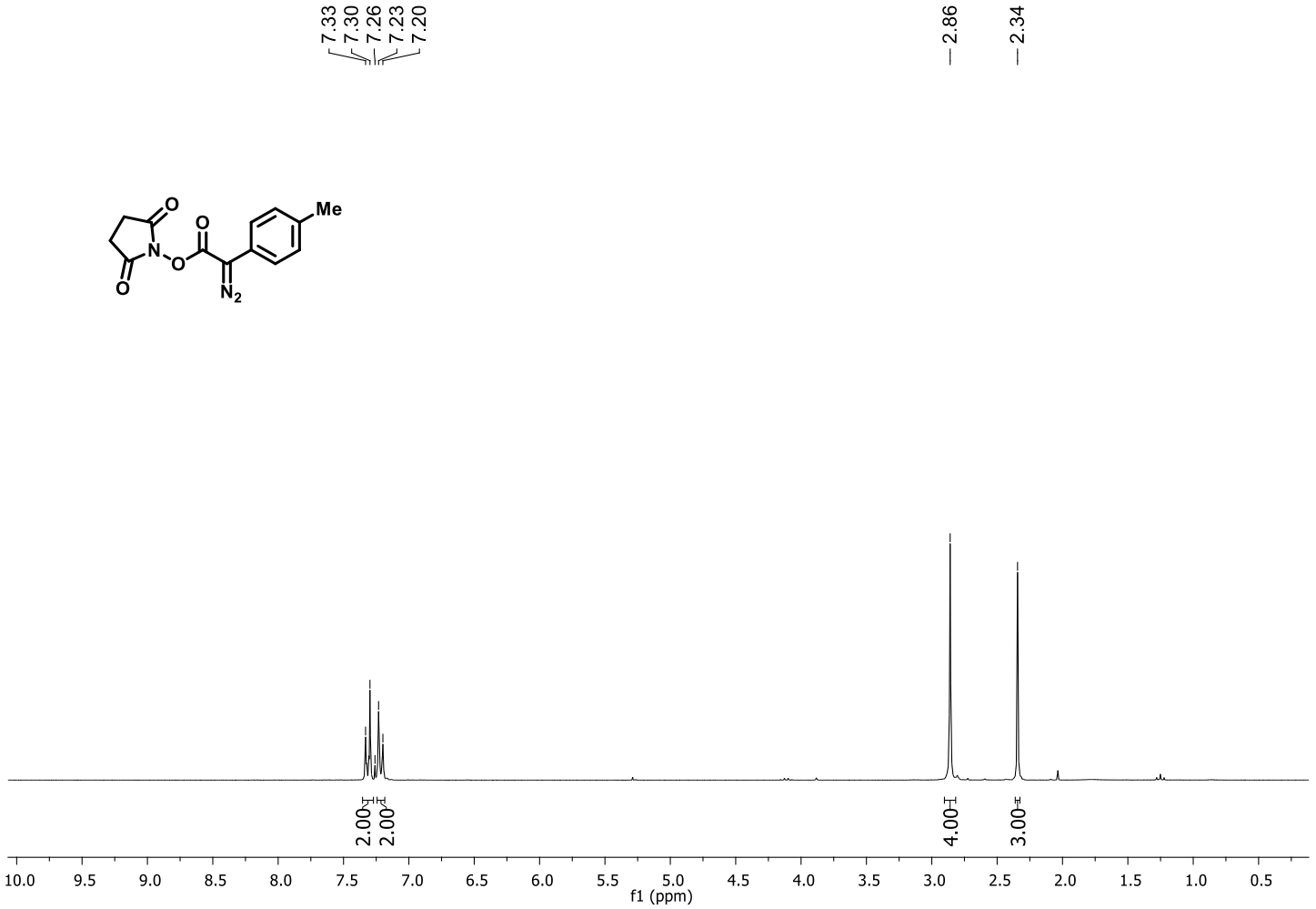
**1ff - $^{1}$H NMR (250 MHz, $CDCl_3$)**



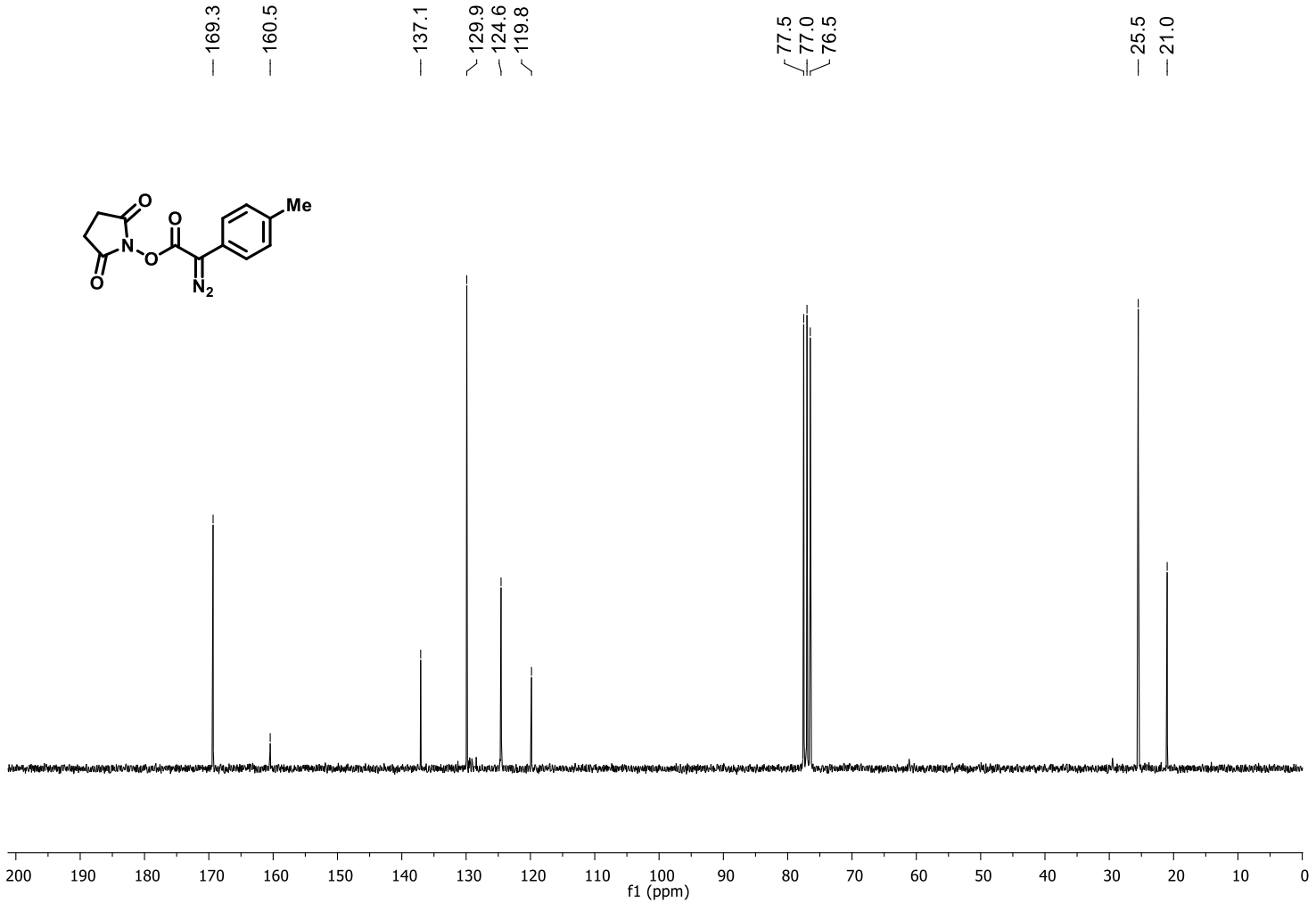
**1ff - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



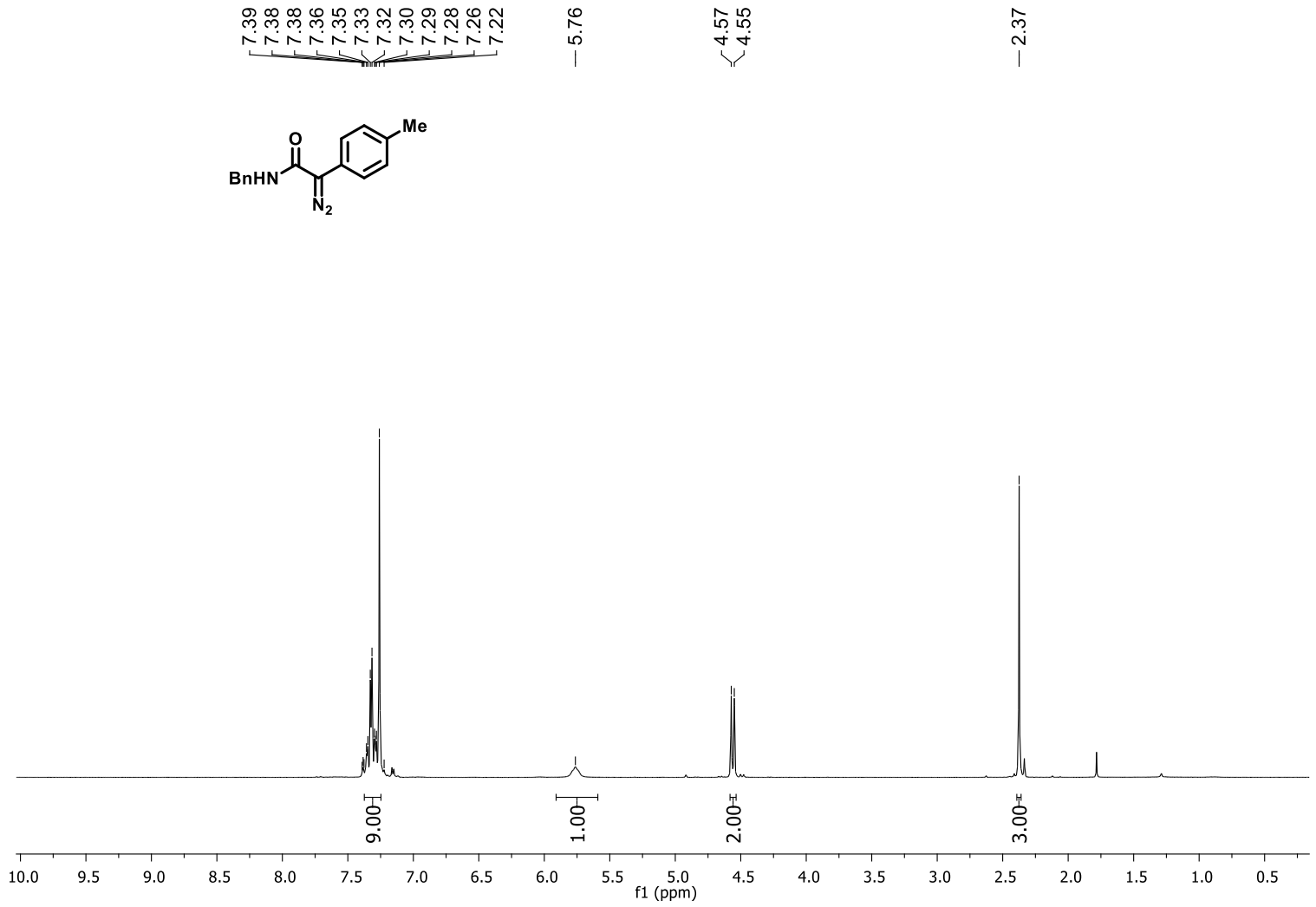
**Pre-1gg - $^{1}$H NMR (250 MHz, $CDCl_3$)**



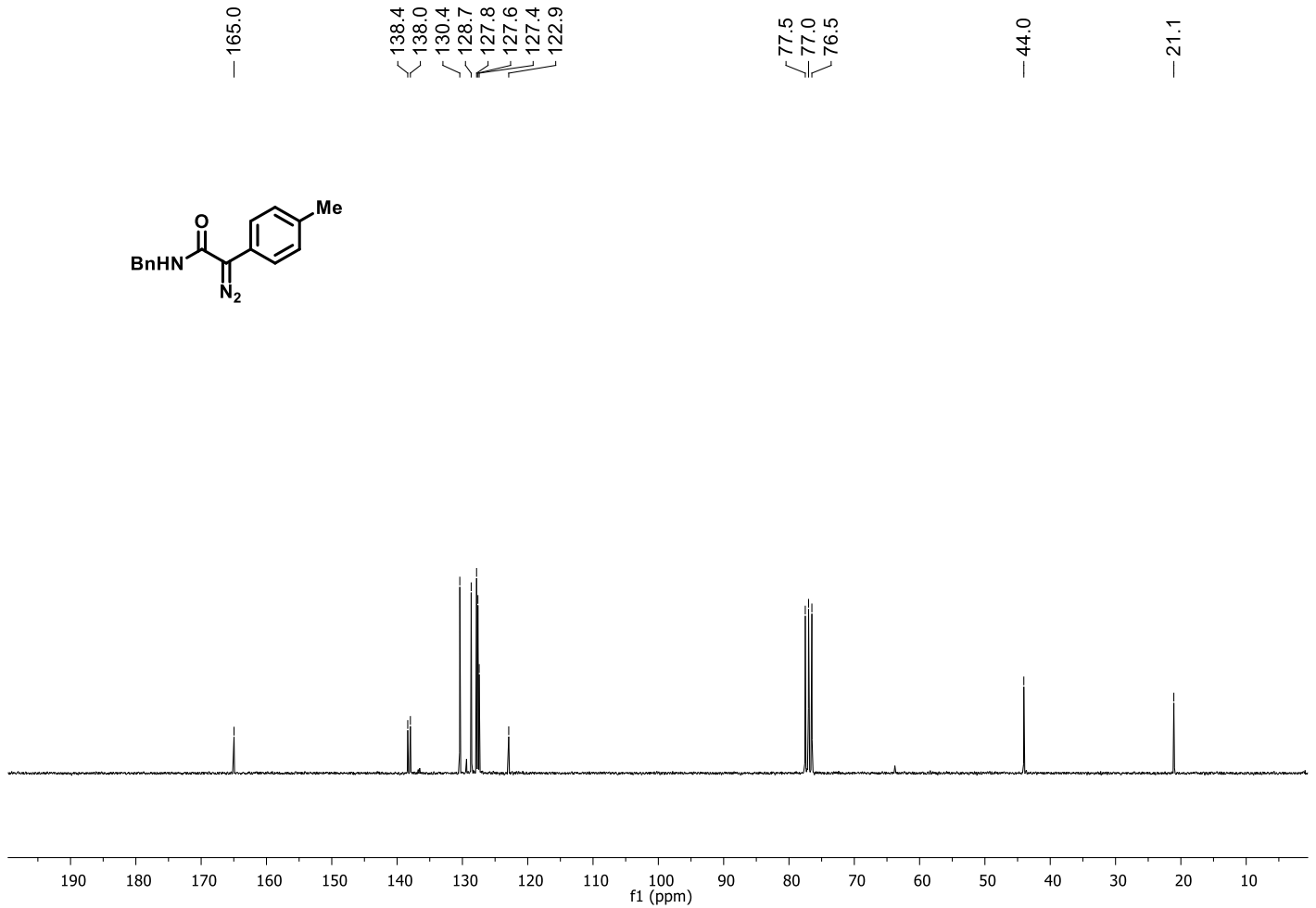
**Pre-1gg - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



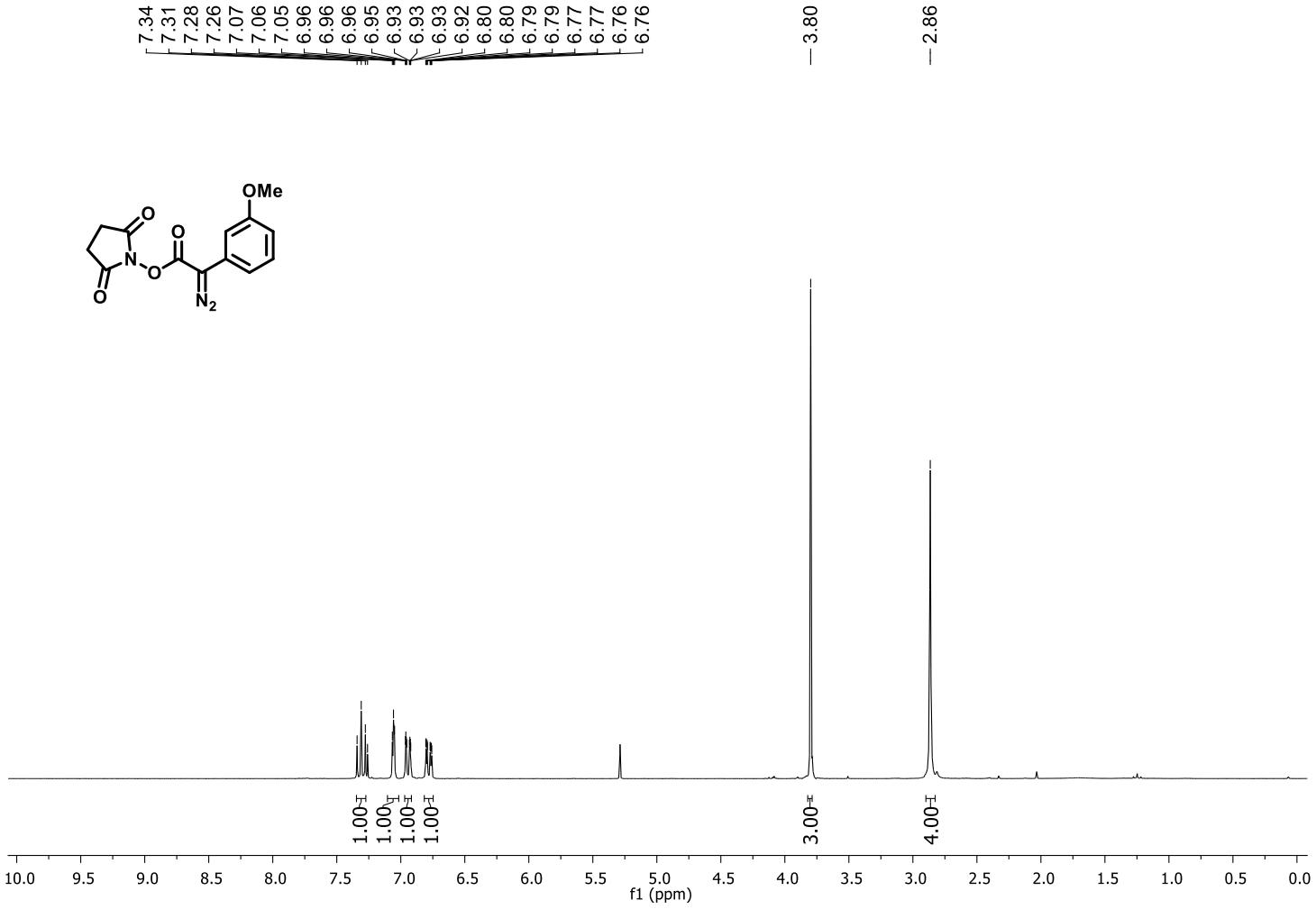
**1gg - $^{1}$H NMR (250 MHz, $CDCl_3$)**



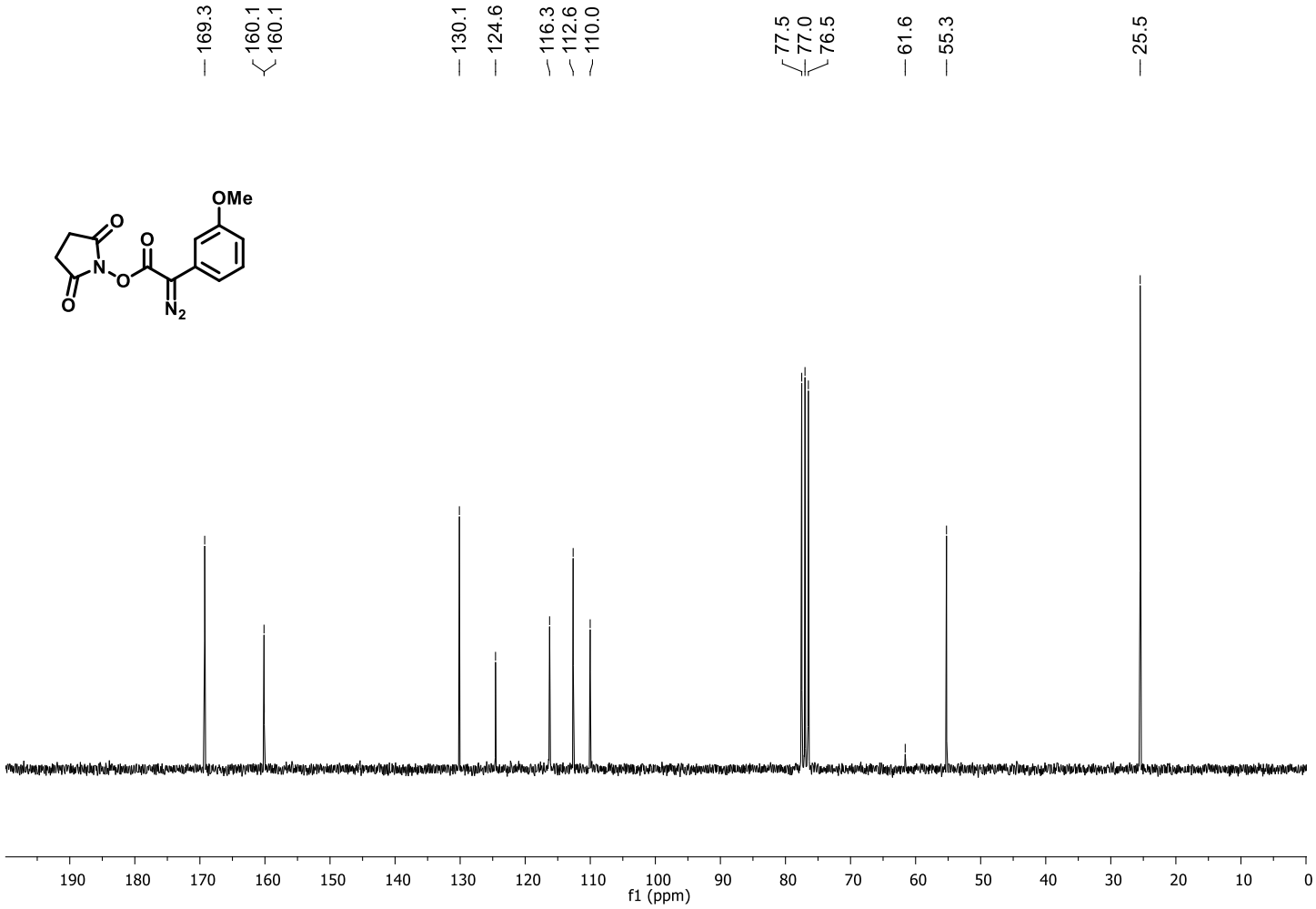
**1gg - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



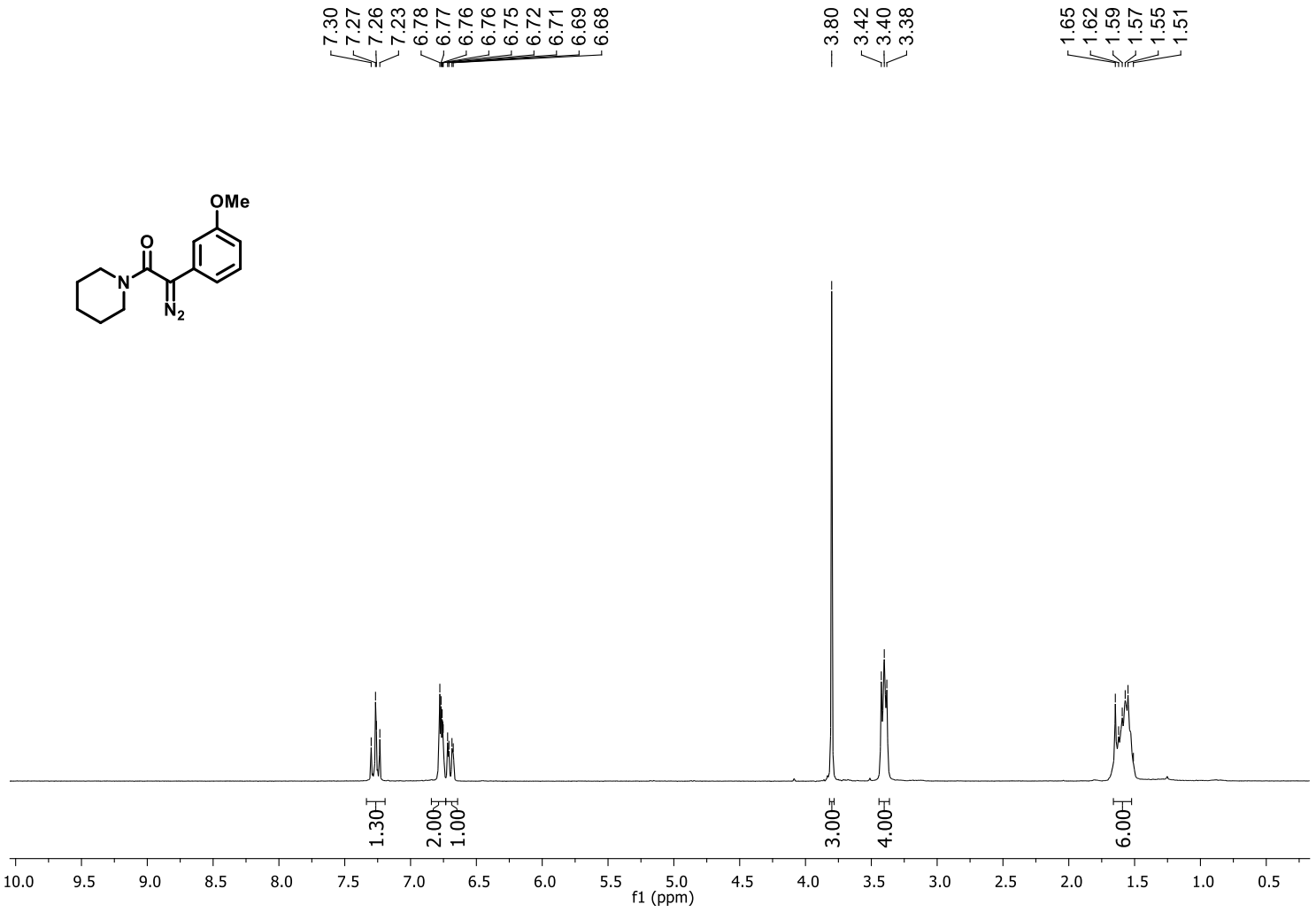
**pre-1hh - $^{1}$H NMR (250 MHz, $CDCl_3$)**



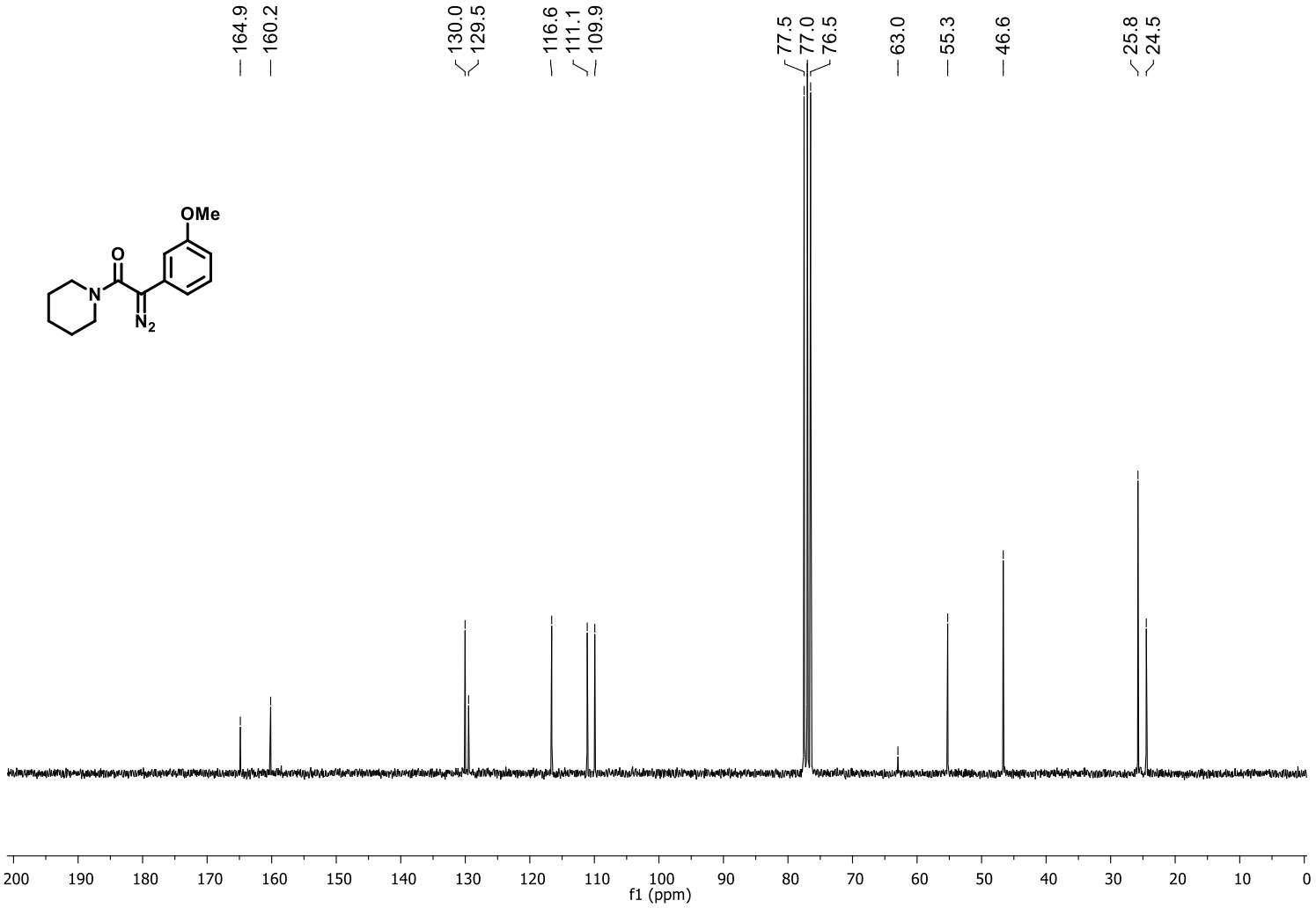
**pre-1hh - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



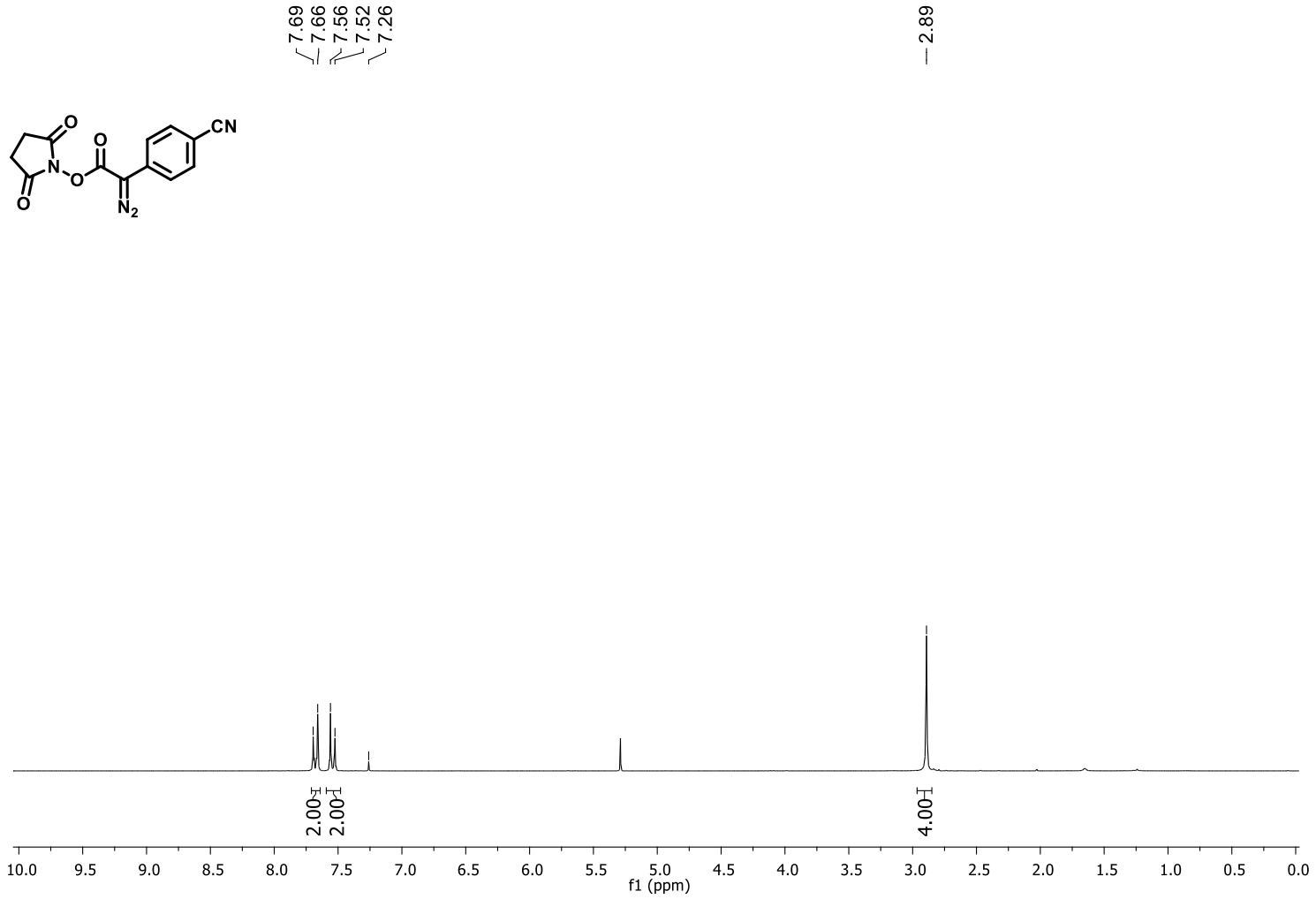
**1hh - $^{1}$H NMR (250 MHz, $CDCl_3$)**



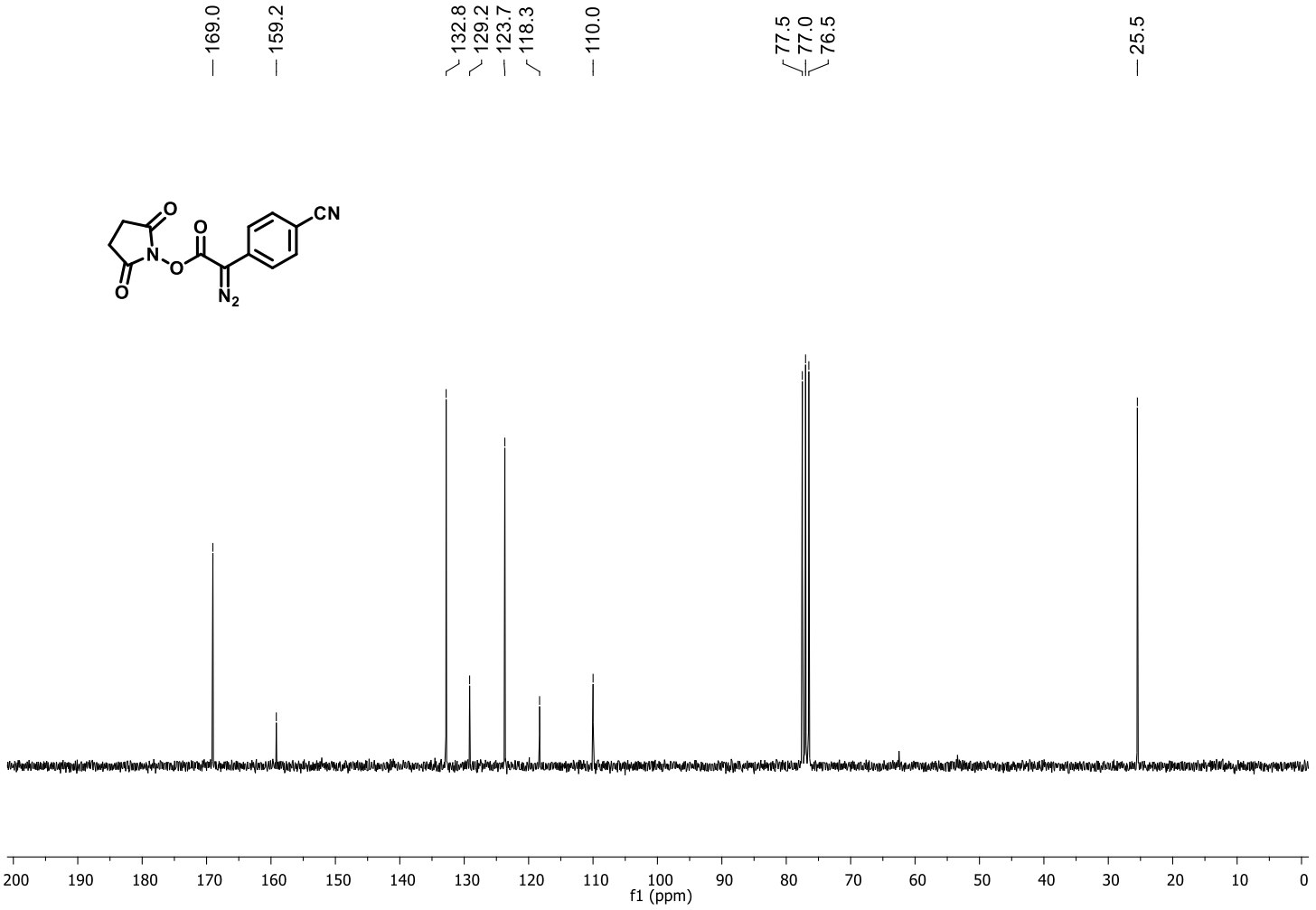
**1hh - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



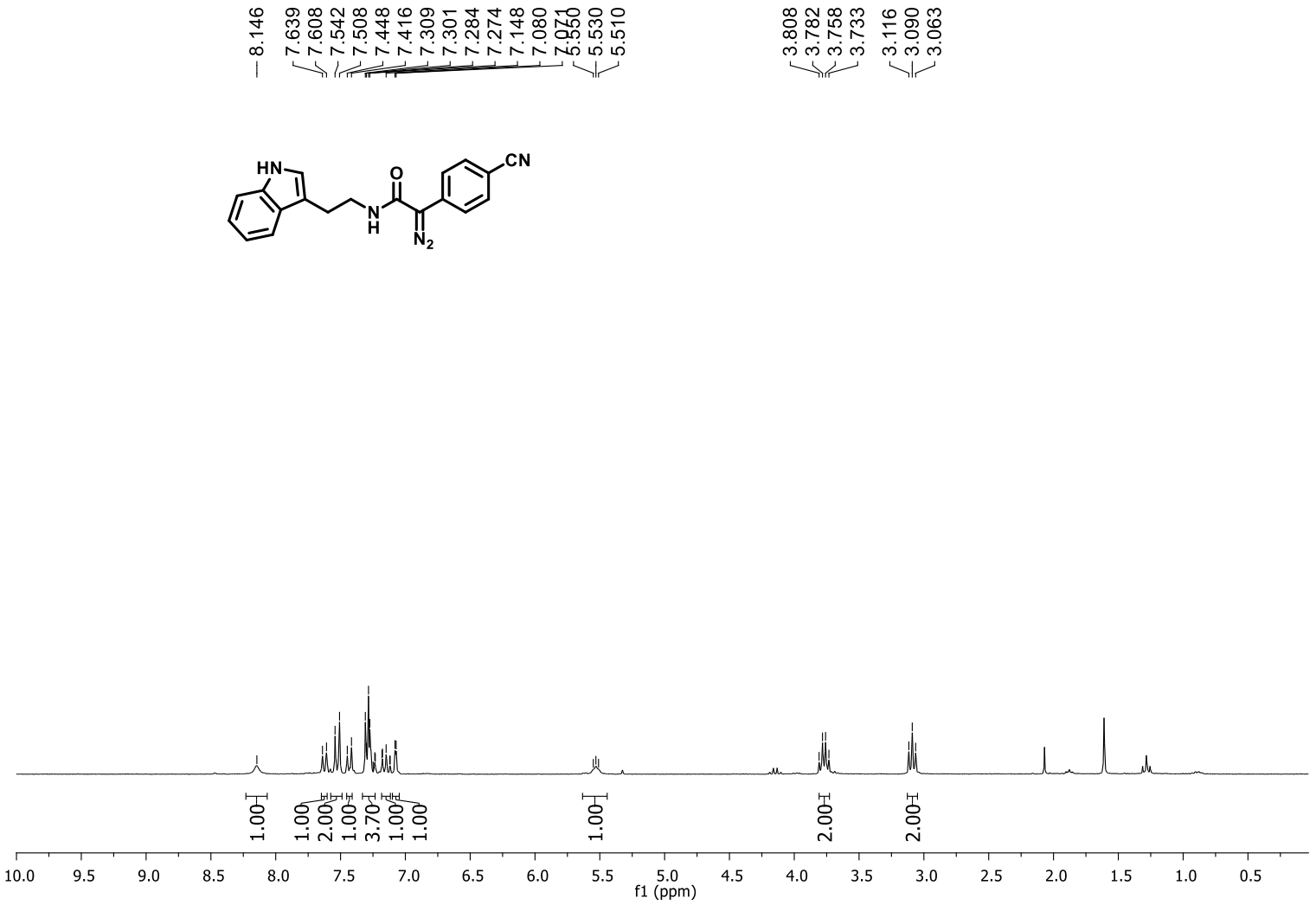
**pre-1ii - $^{1}$H NMR (250 MHz, $CDCl_3$)**



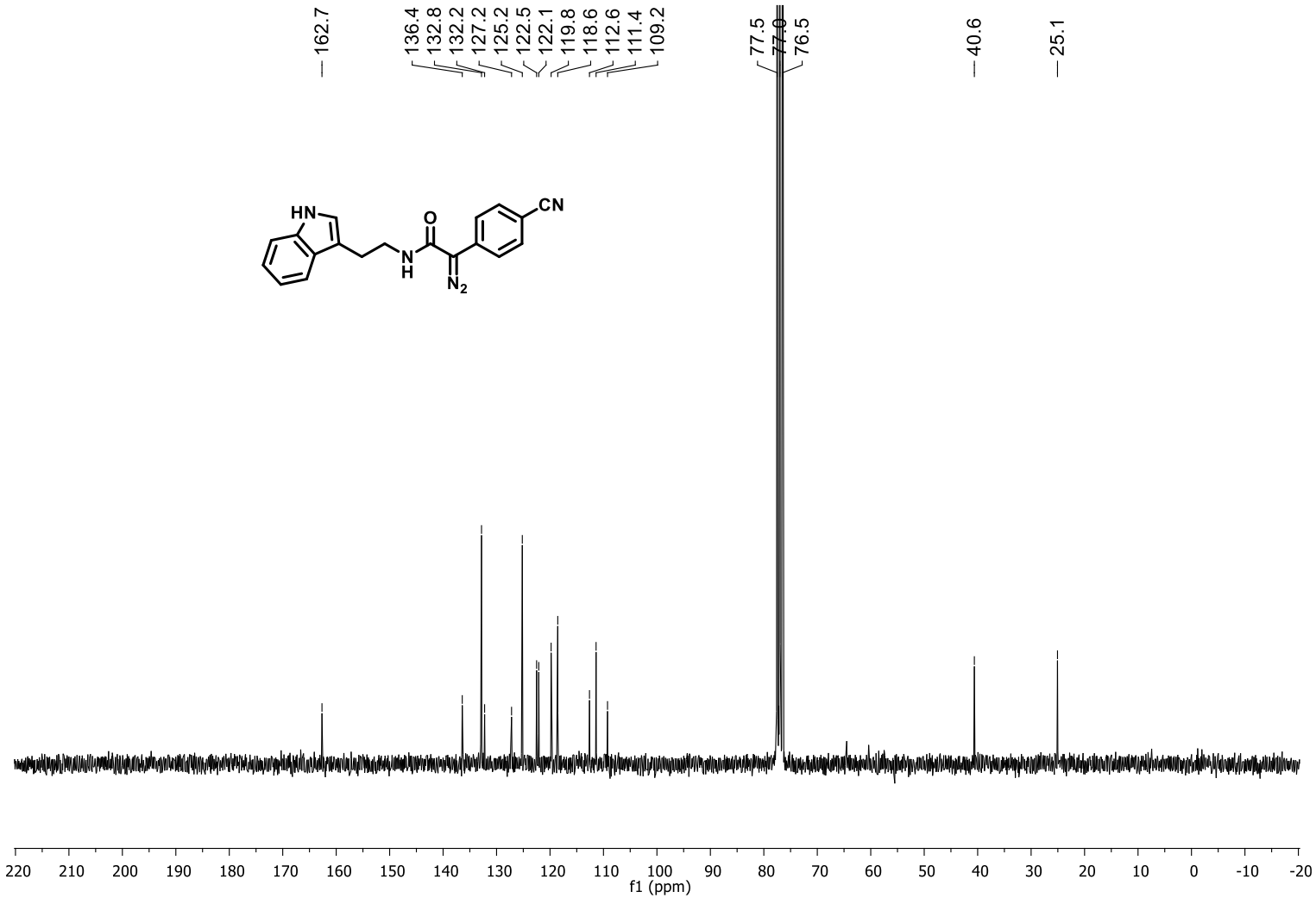
**pre-1ii - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



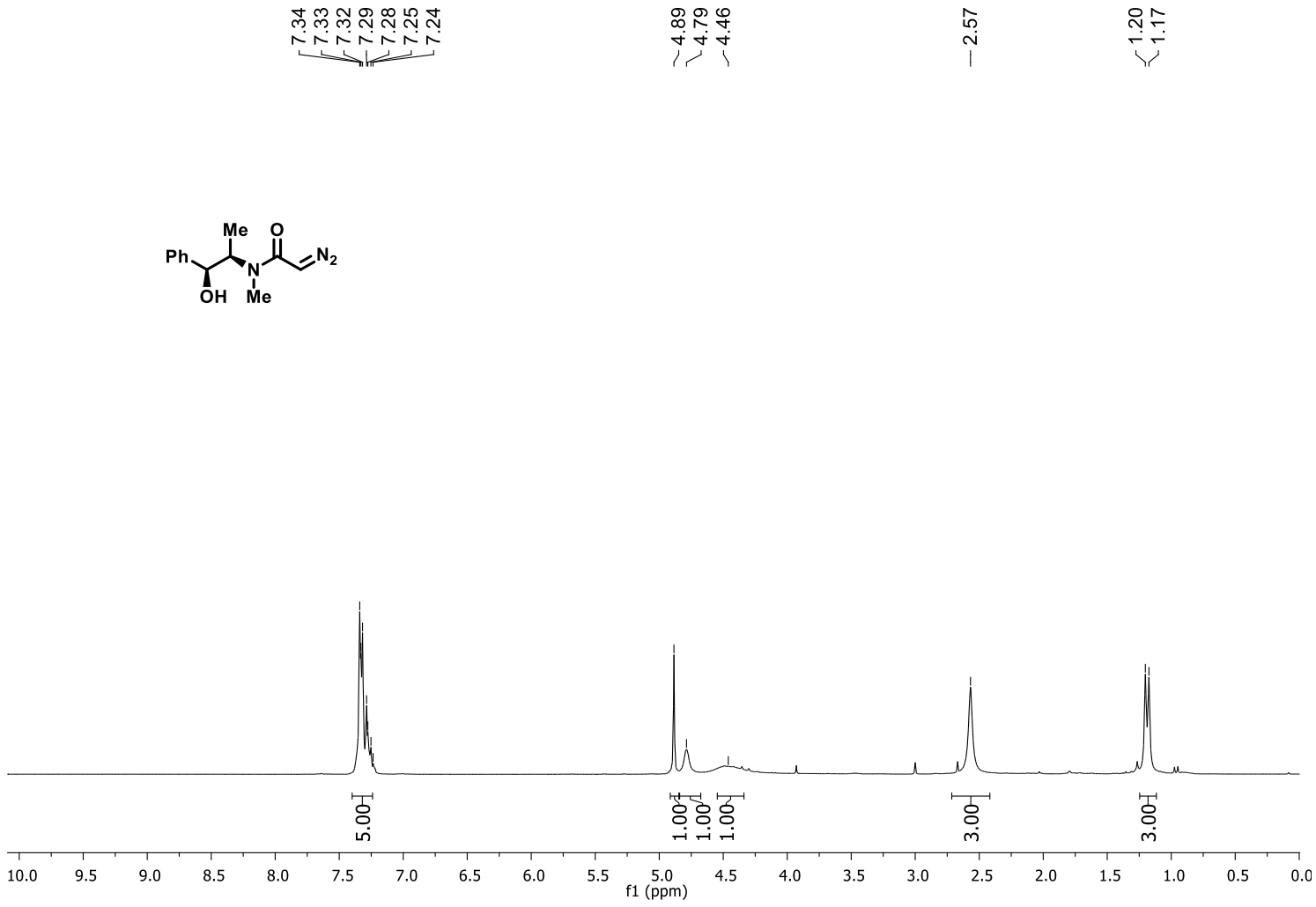
**1ii - $^{1}$H NMR (250 MHz, $CDCl_3$)**



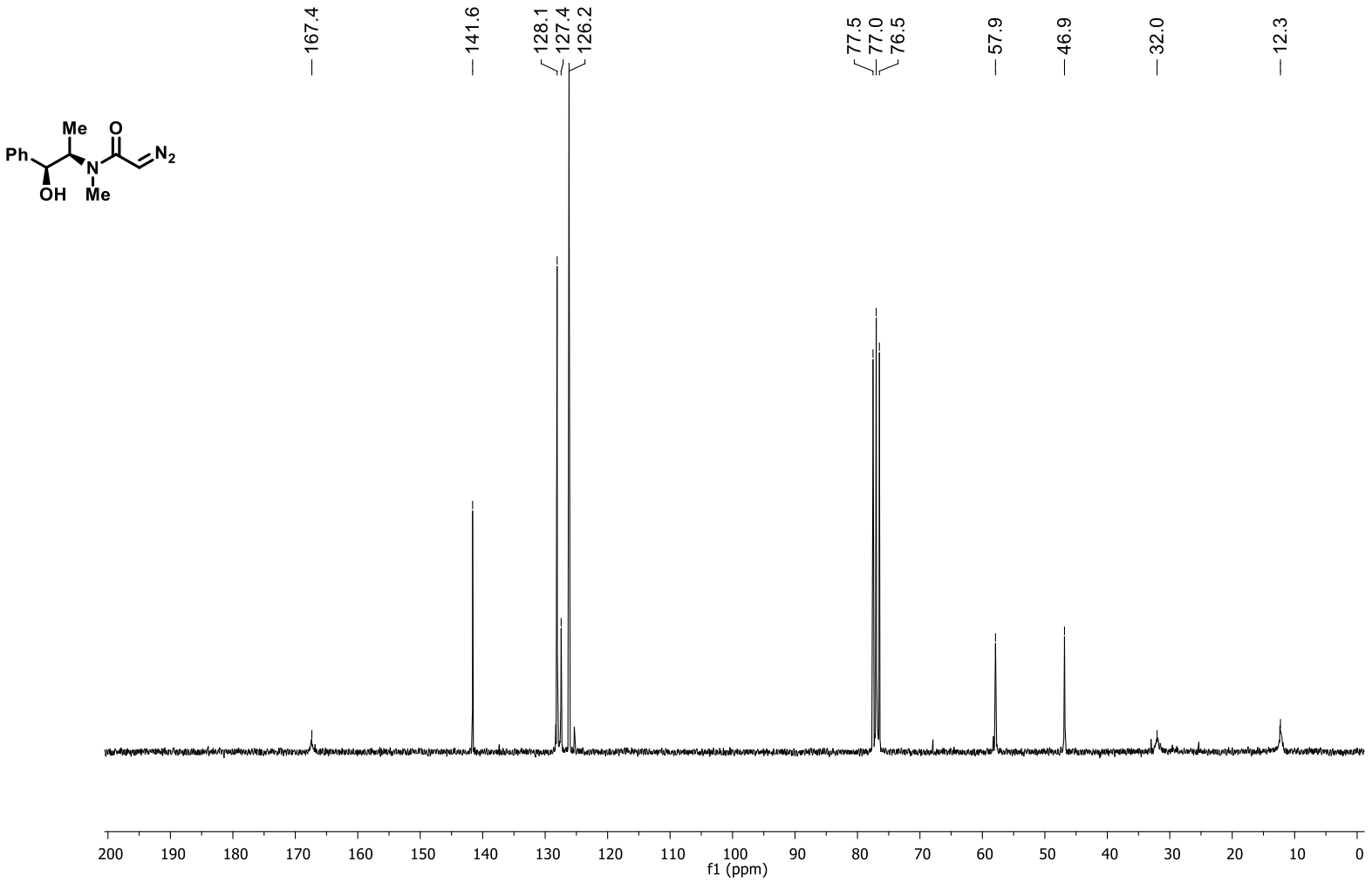
**1ii - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



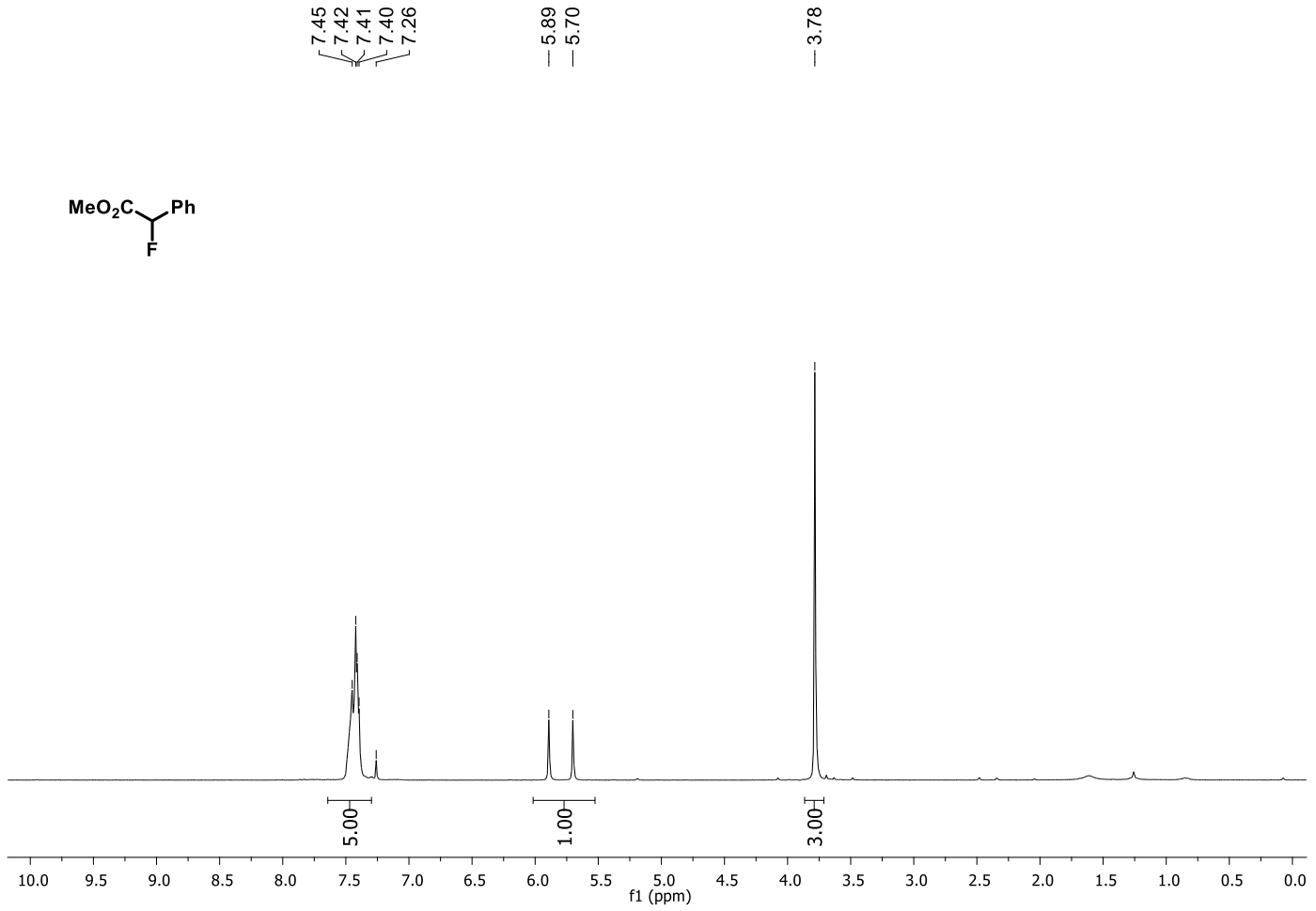
**1rr - $^{1}$H NMR (250 MHz, $CDCl_3$)**



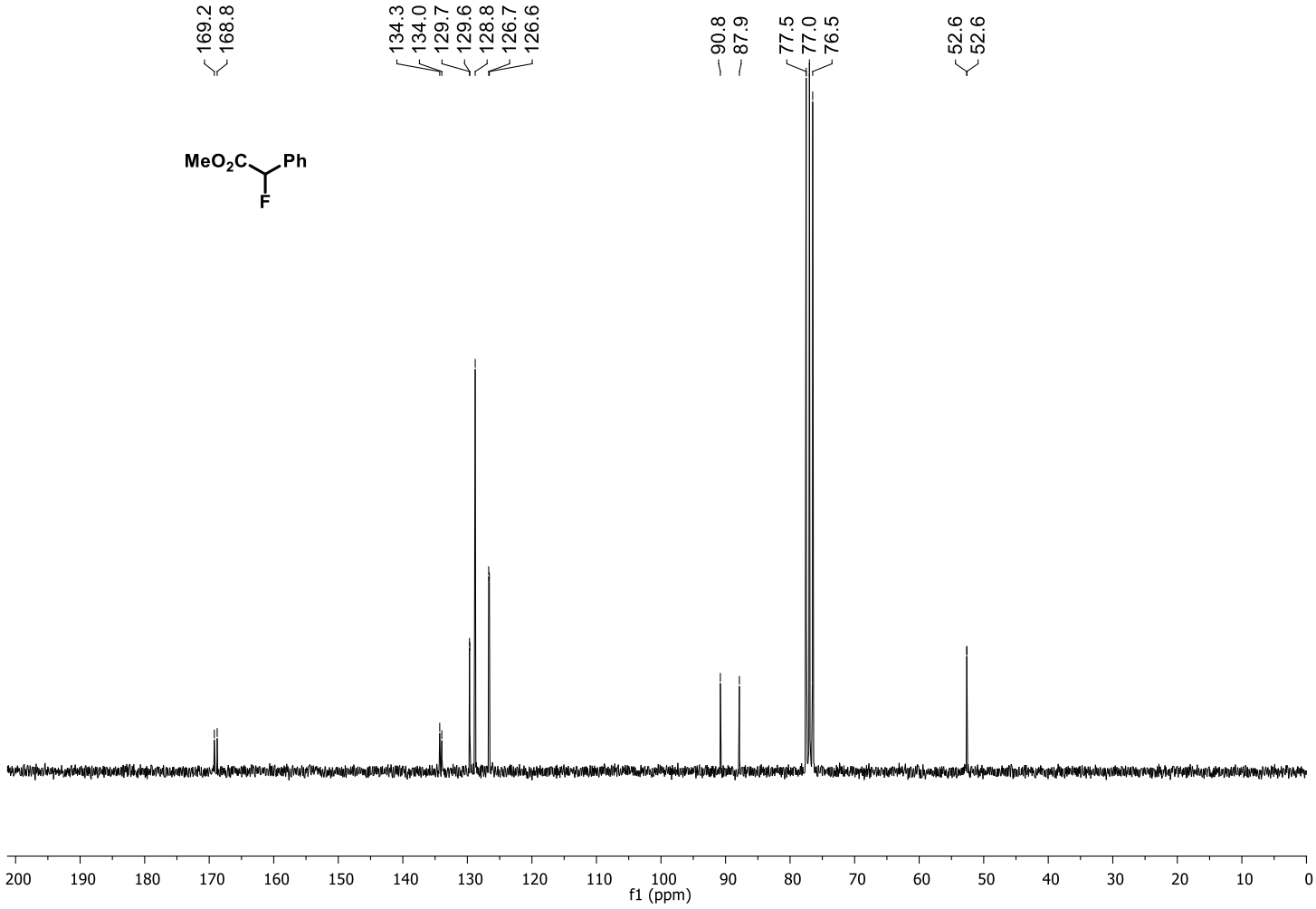
**1rr - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



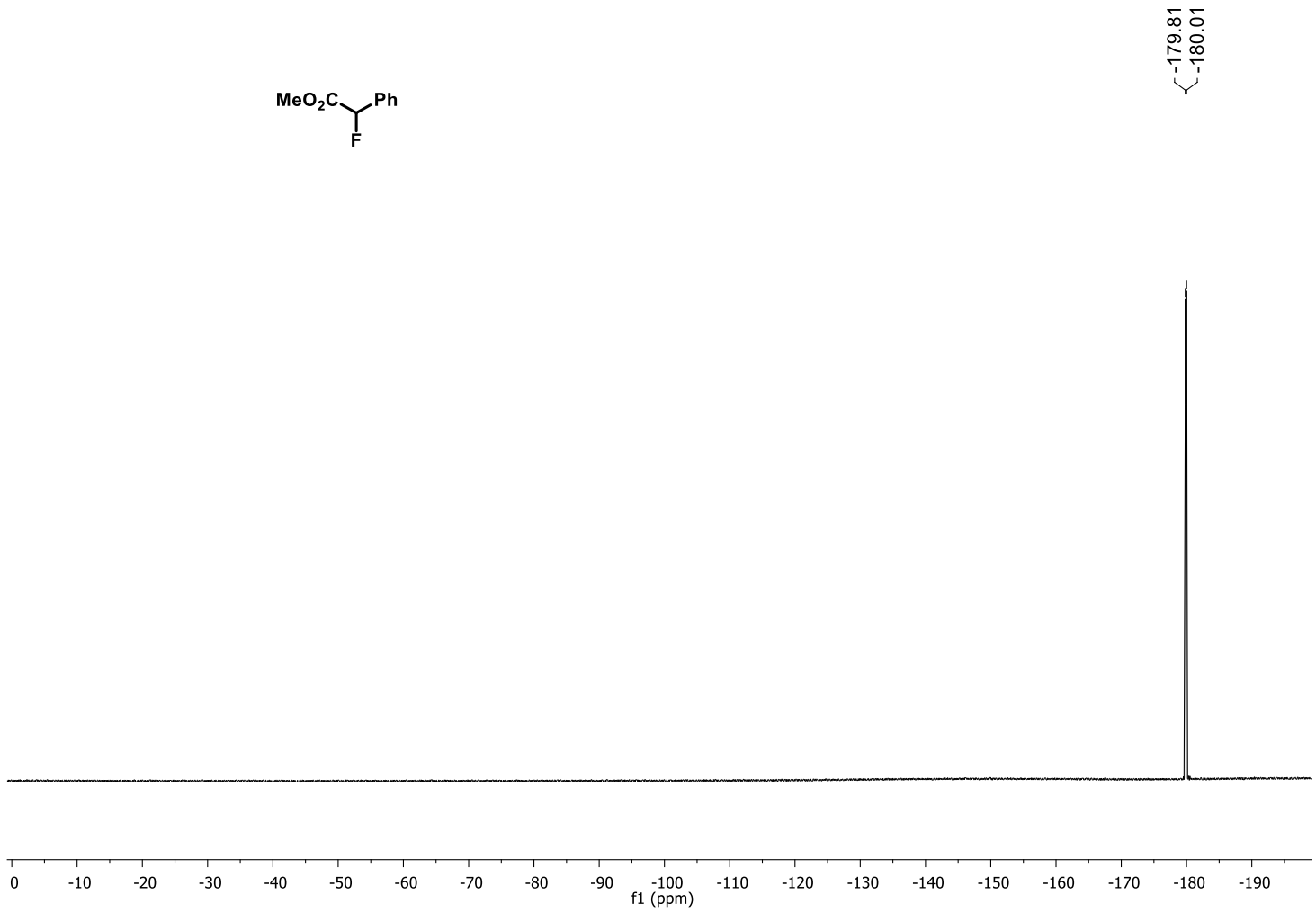
**18a - $^{1}$H NMR (250 MHz, $CDCl_3$)**



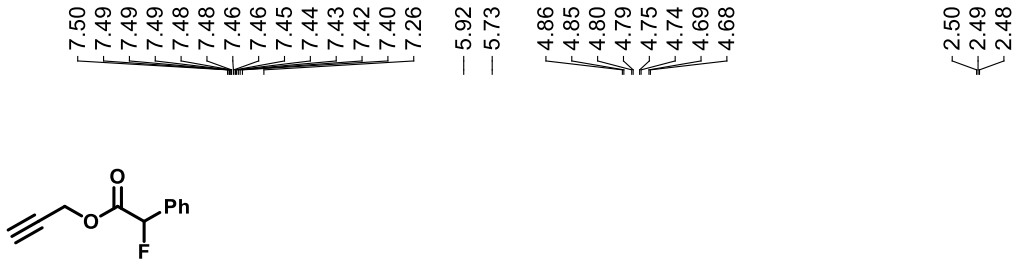
**18a - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**

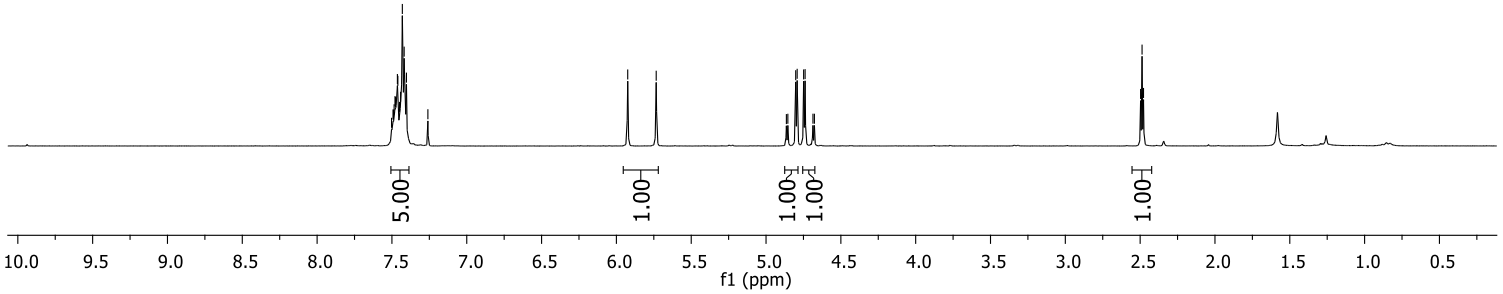



**18a - $^{19}$F NMR (235 MHz, $CDCl_3$)**

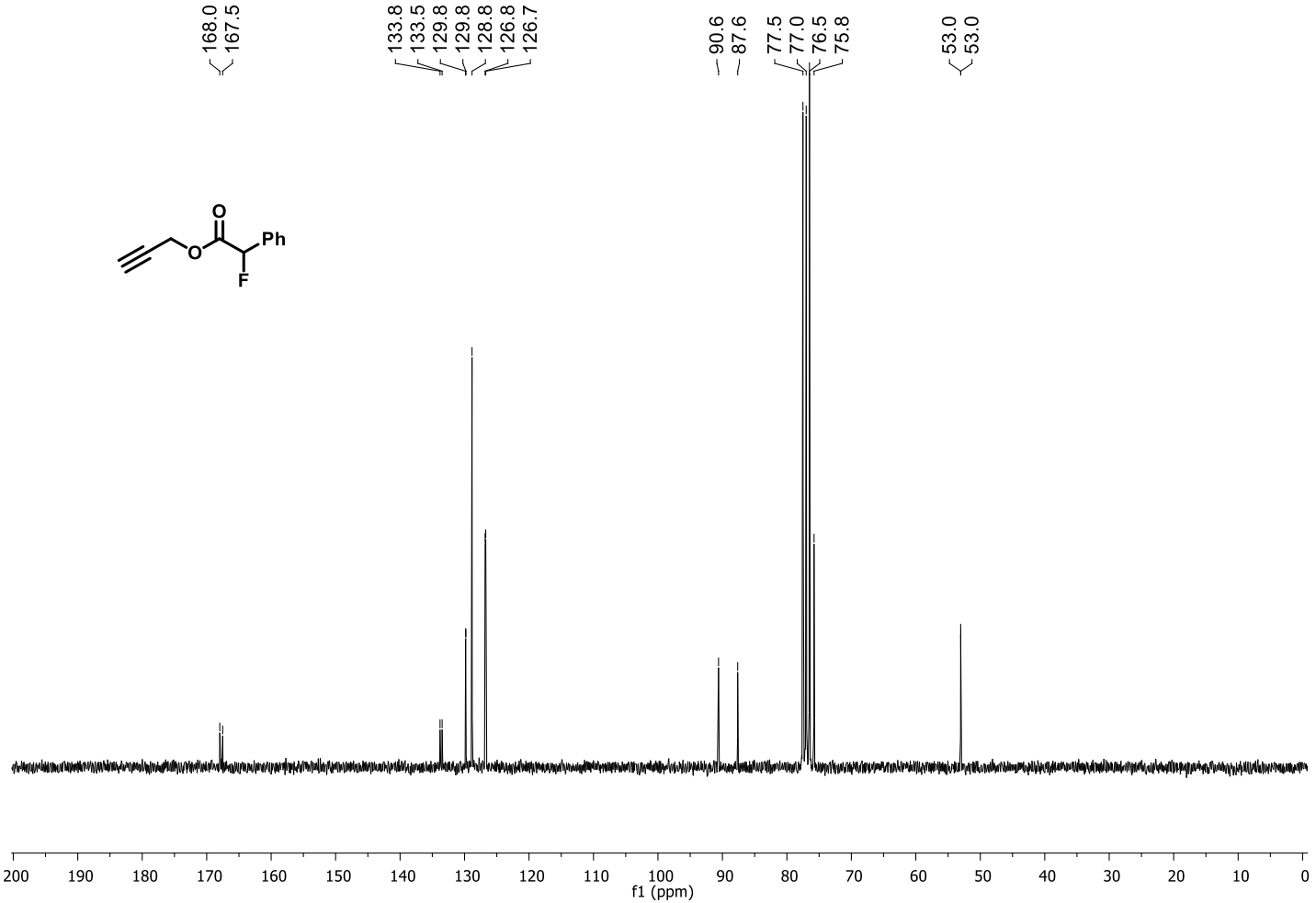

MeO2C
Ph
F
-179.81
-180.01
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

**18b - $^{1}$H NMR (250 MHz, $CDCl_3$)**

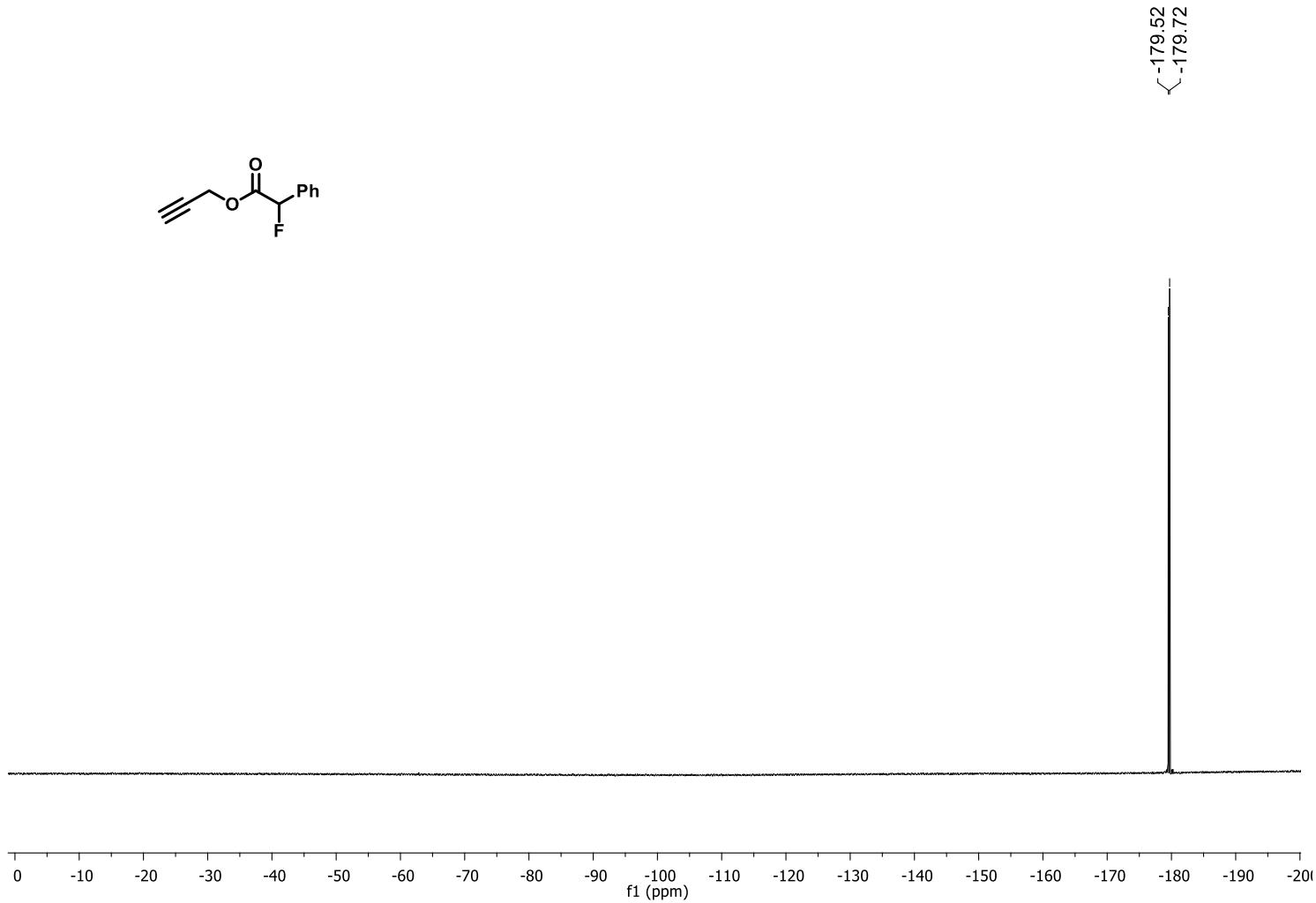


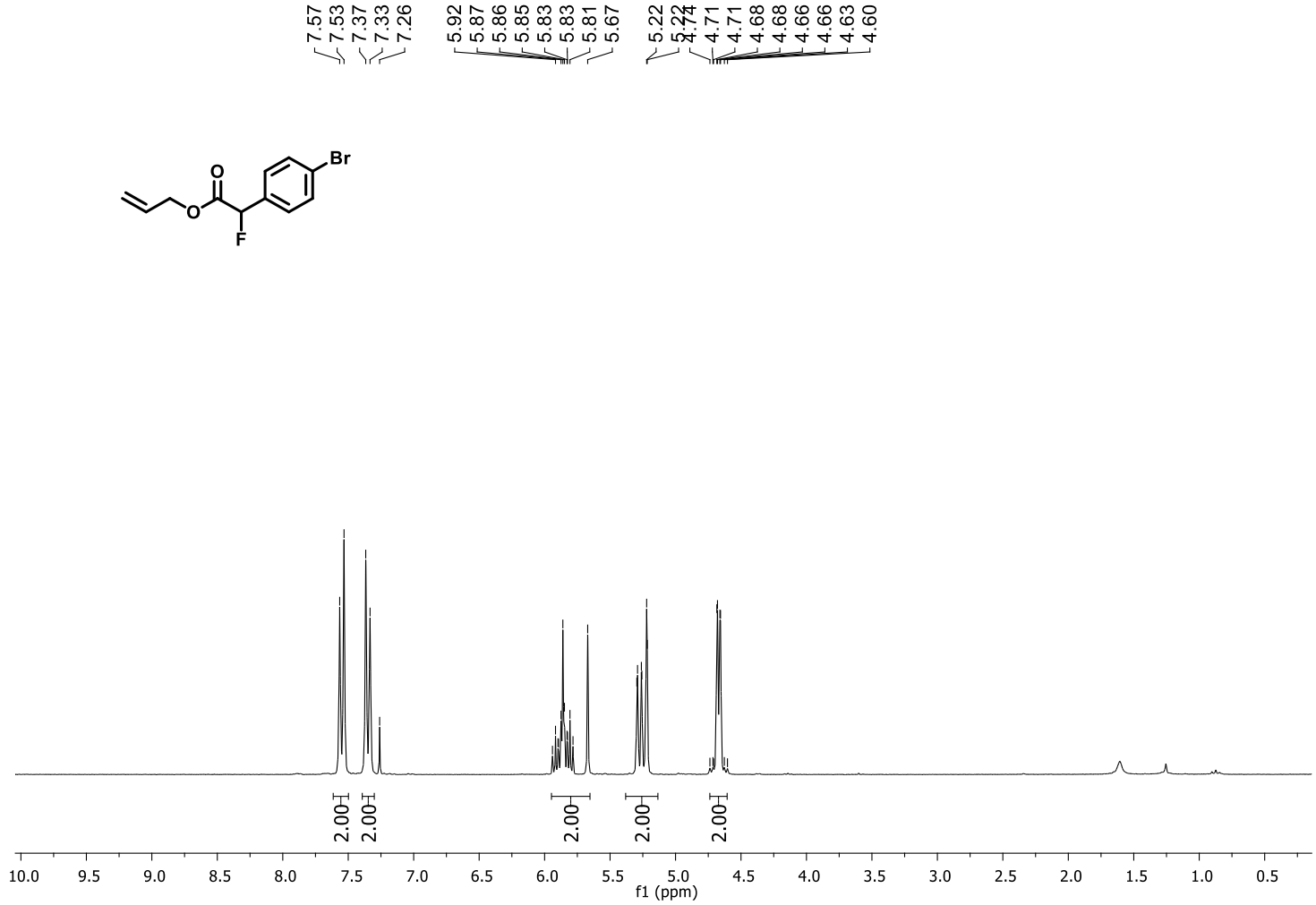
**18b - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



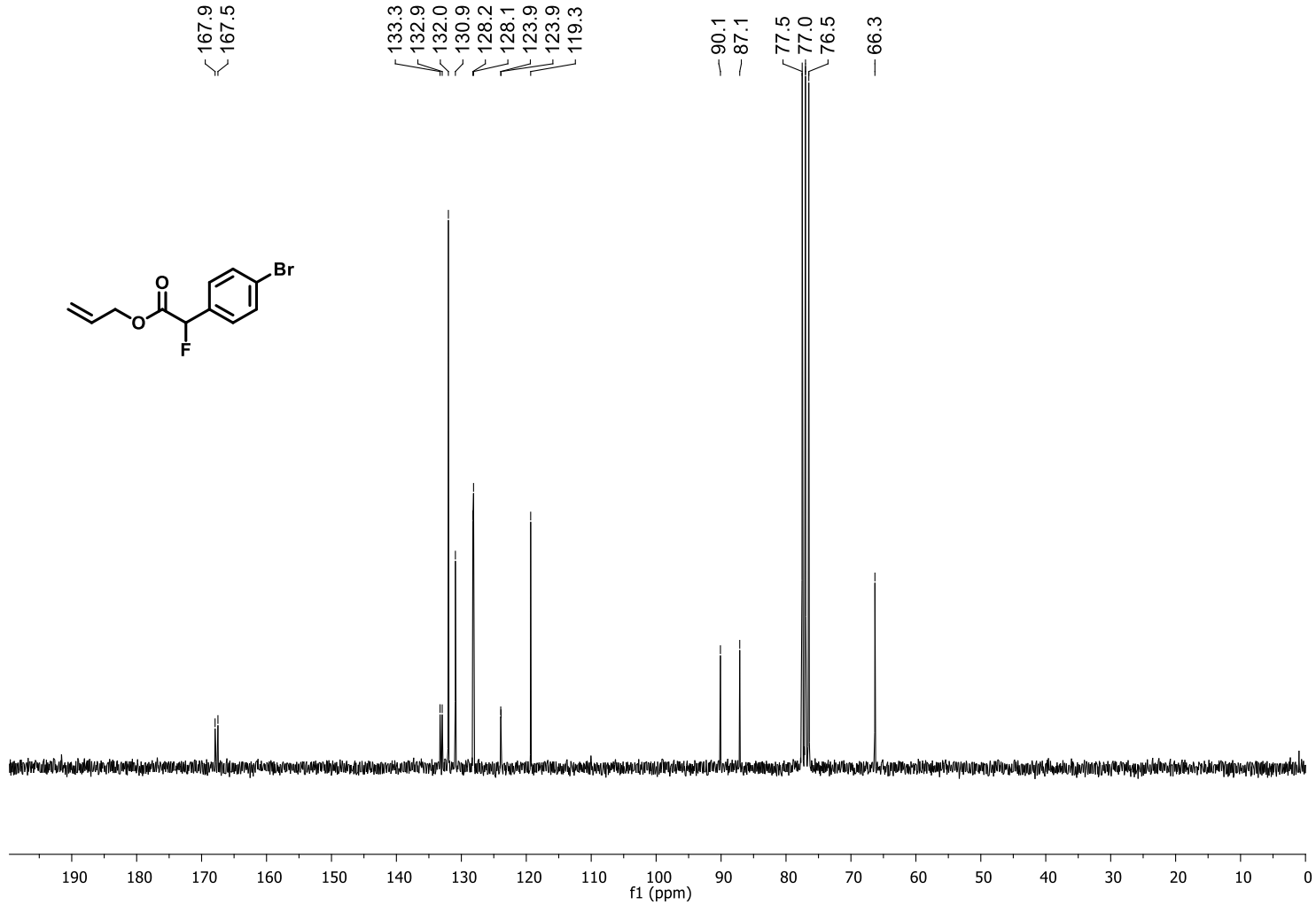

**18b - $^{19}F$ NMR (235 MHz, $CDCl_3$)**


-179.52
-179.72
O
O
Ph
F
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

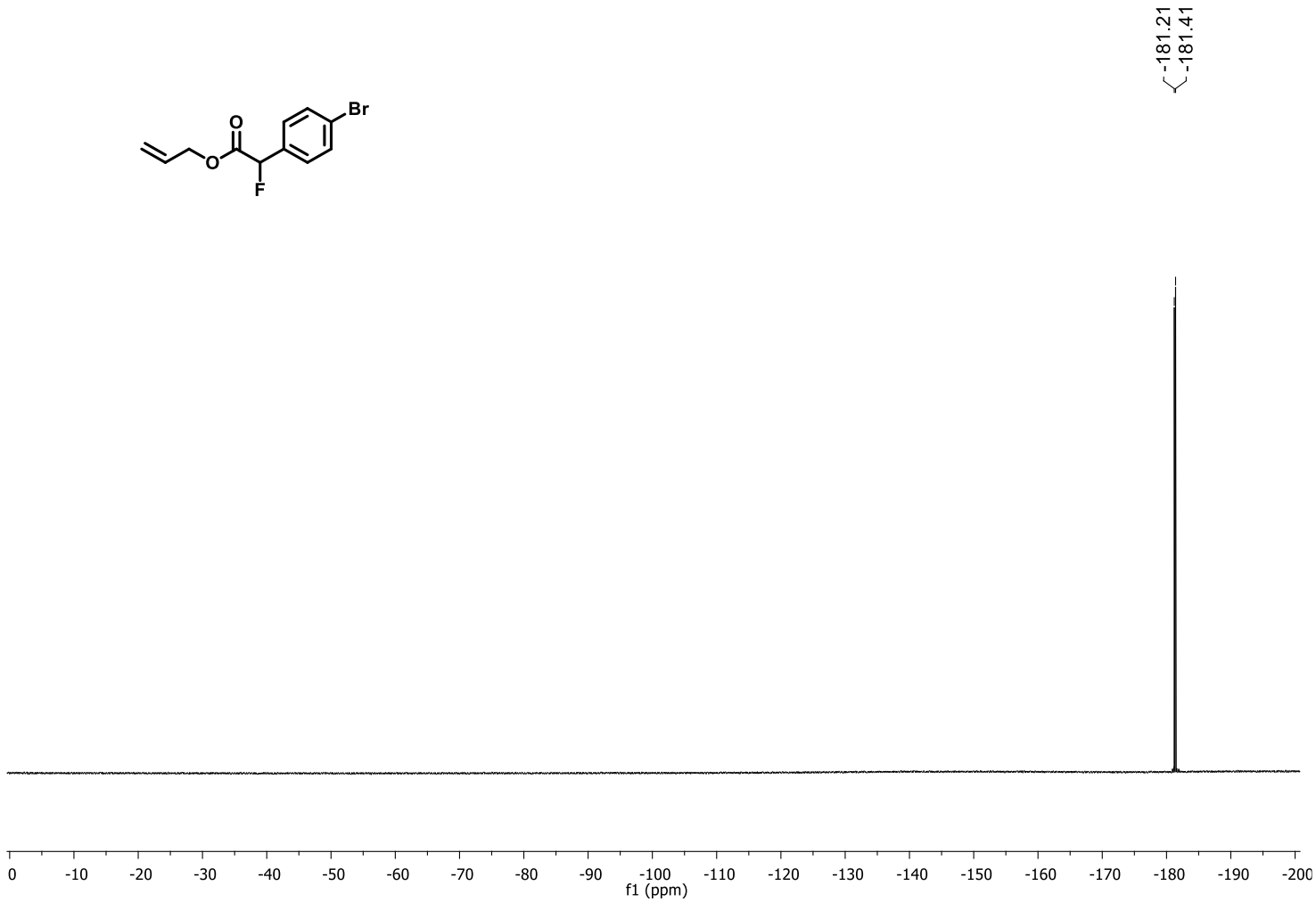
**18d - $^{1}$H NMR (250 MHz, $CDCl_3$)**



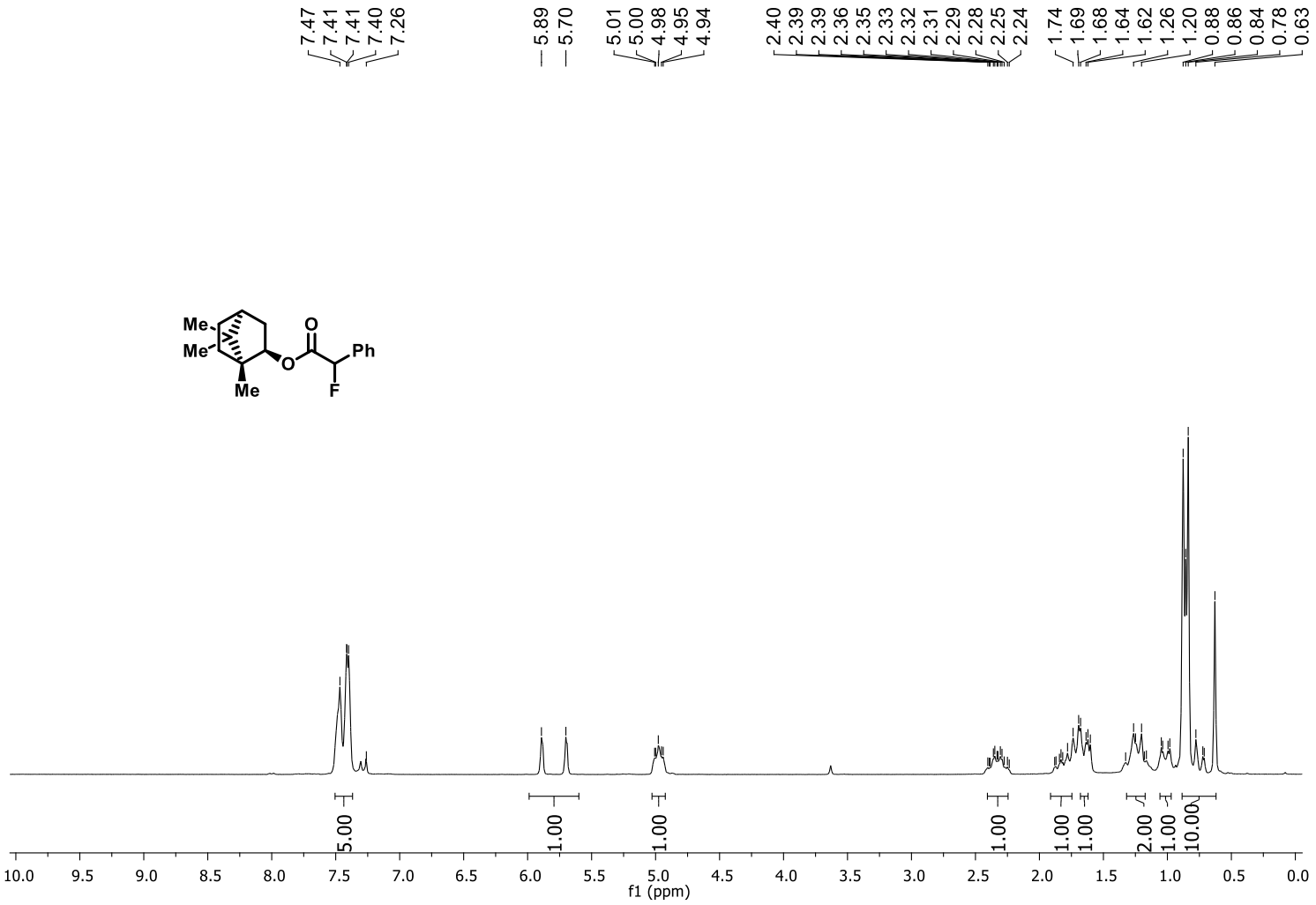
**18d - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



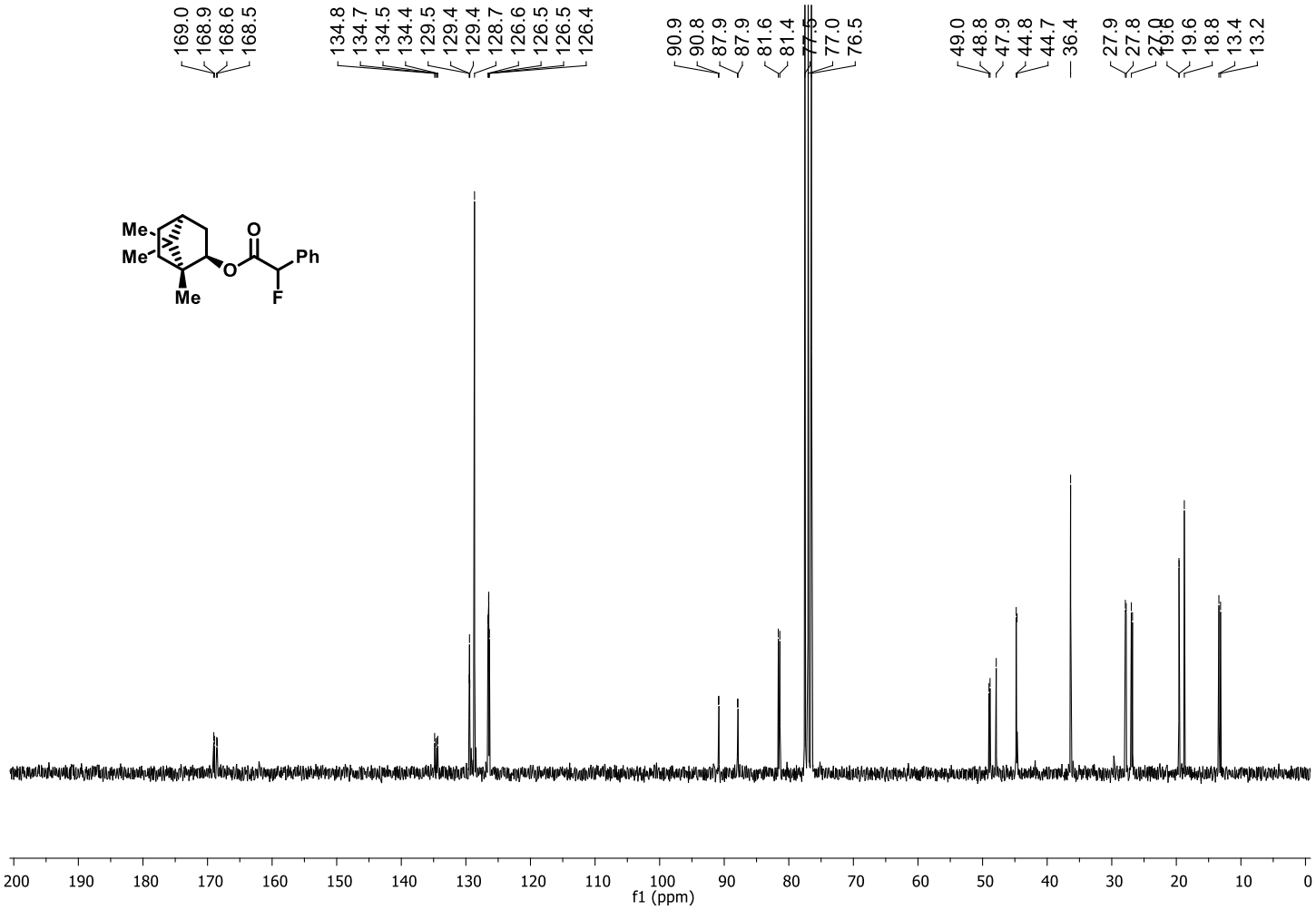
**18d - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



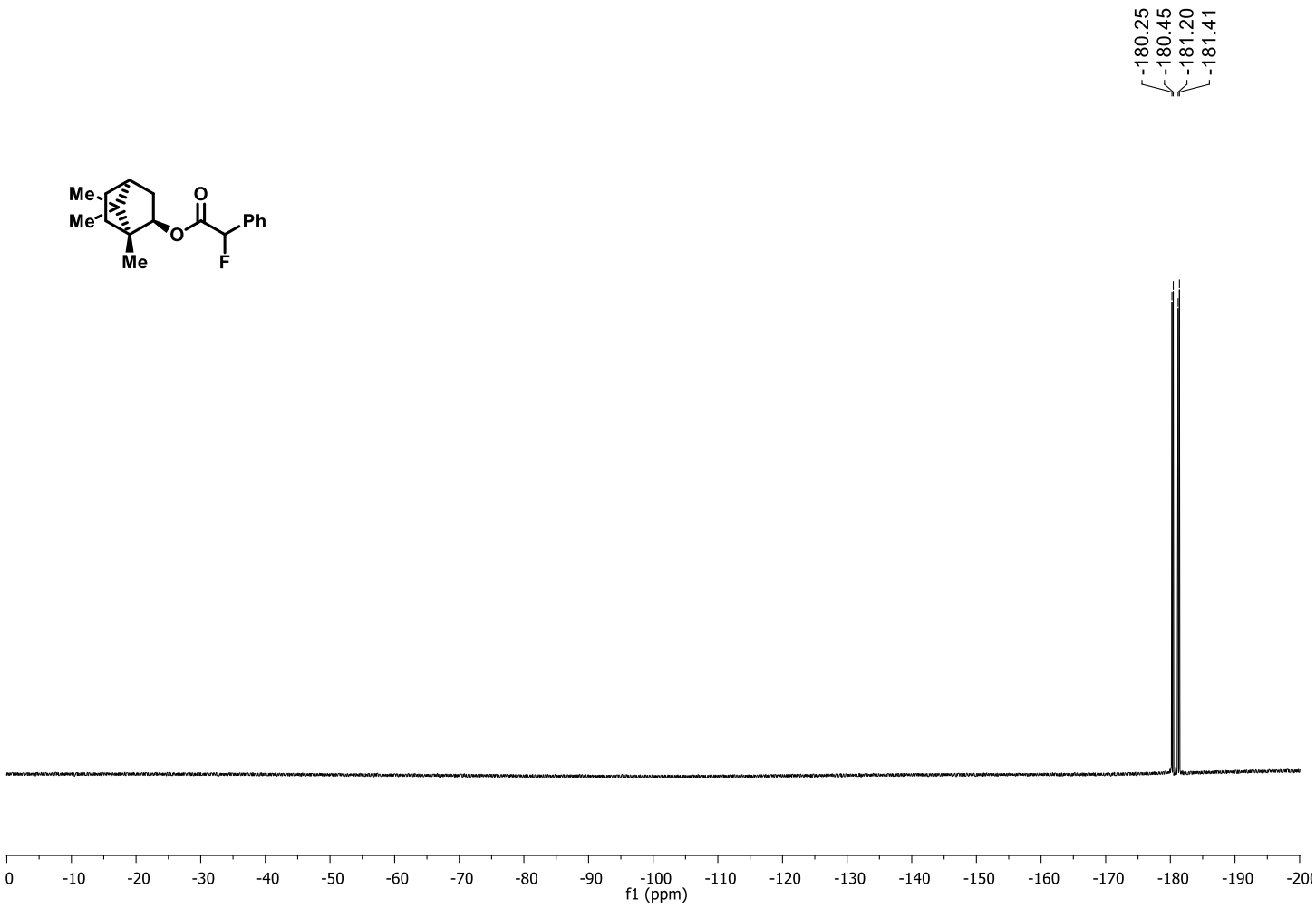
**18e - $^{1}H$ NMR (250 MHz, $CDCl_3$)**



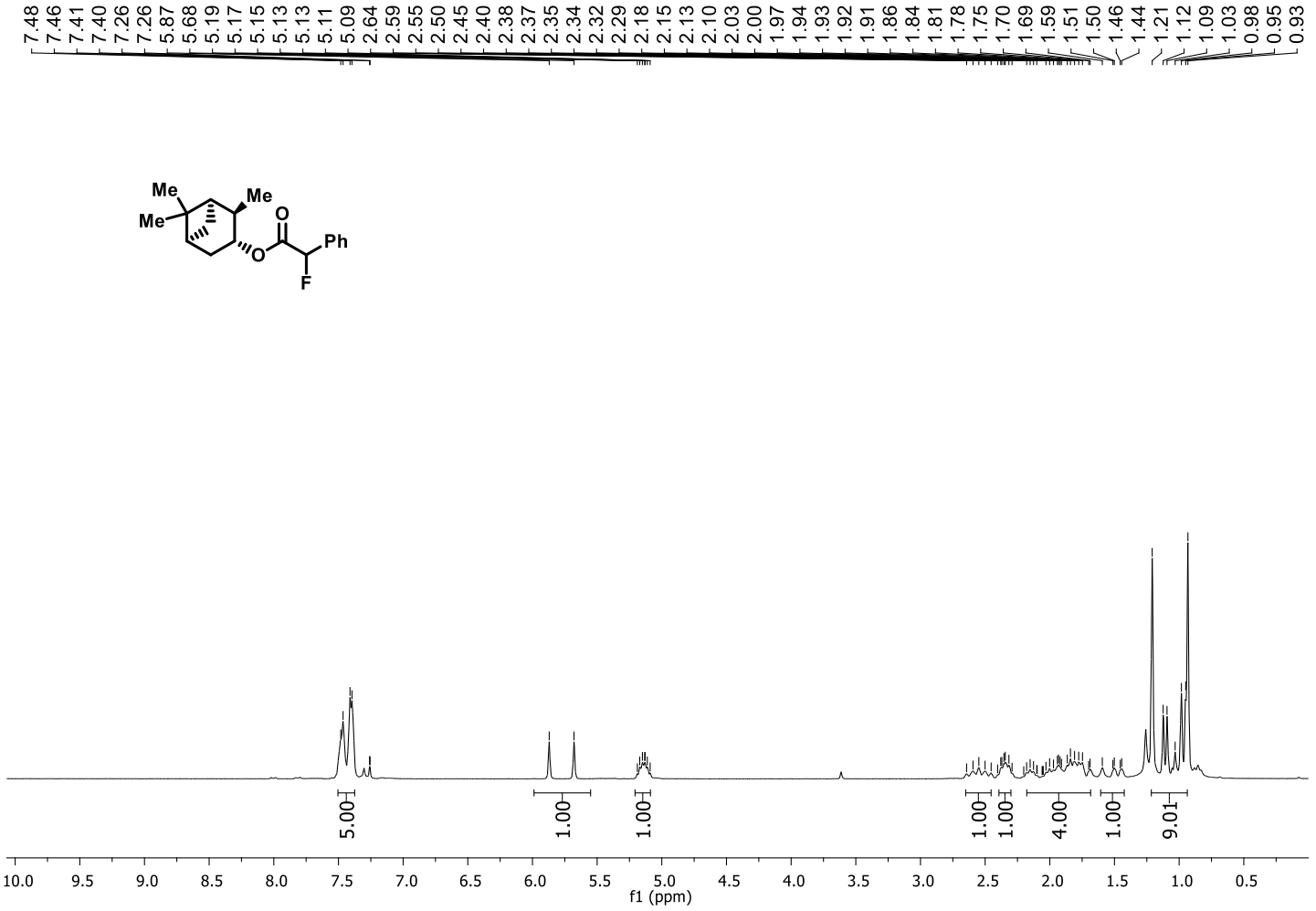
**18e - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



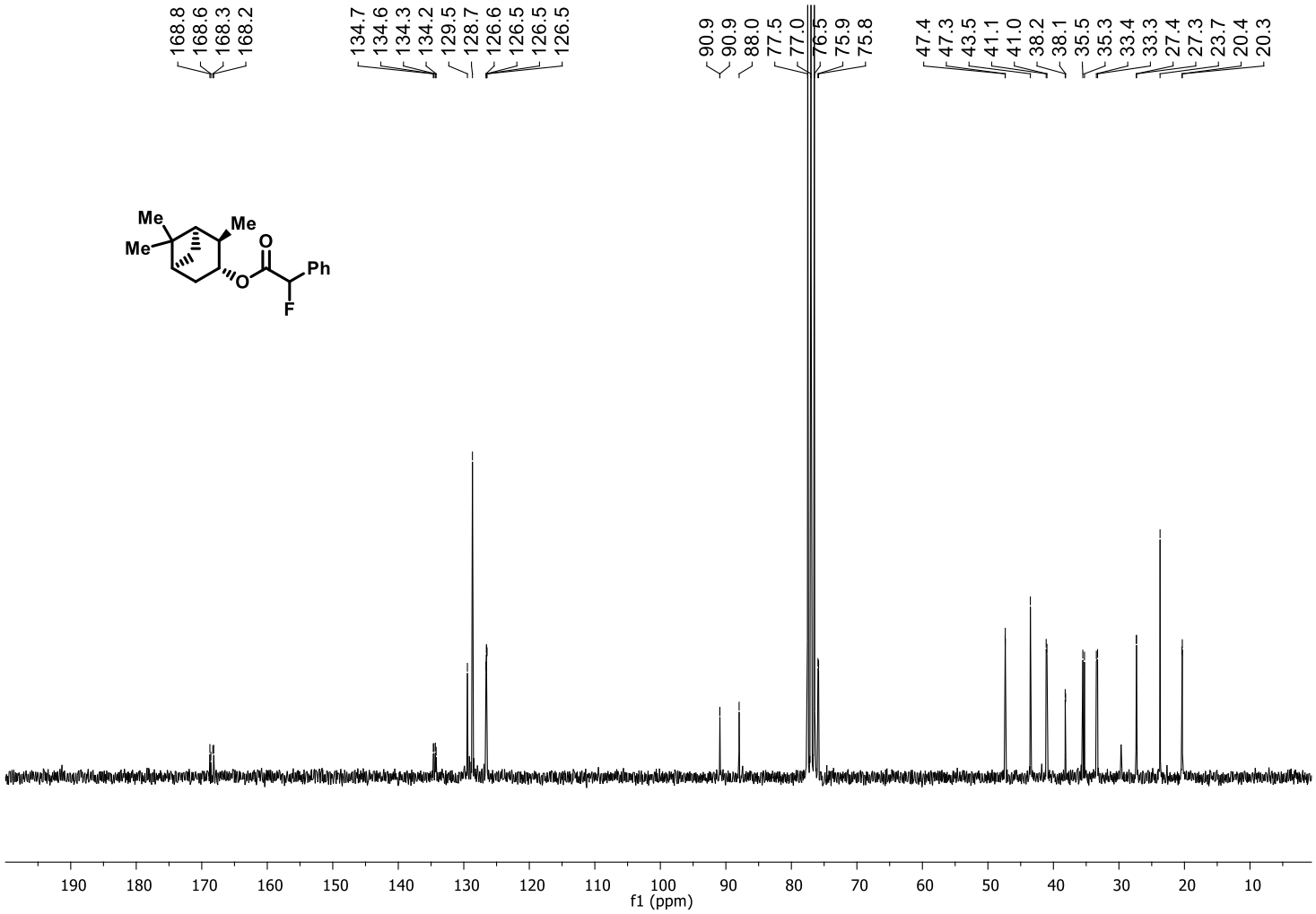

**18e - $^{19}F$ NMR (235 MHz, $CDCl_3$)**


-180.25
-180.45
-181.20
-181.41
Me
Me
Me
O
O
Ph
F
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

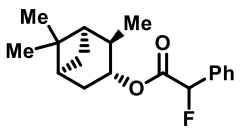
**18f - $^{1}$H NMR (250 MHz, $CDCl_3$)**



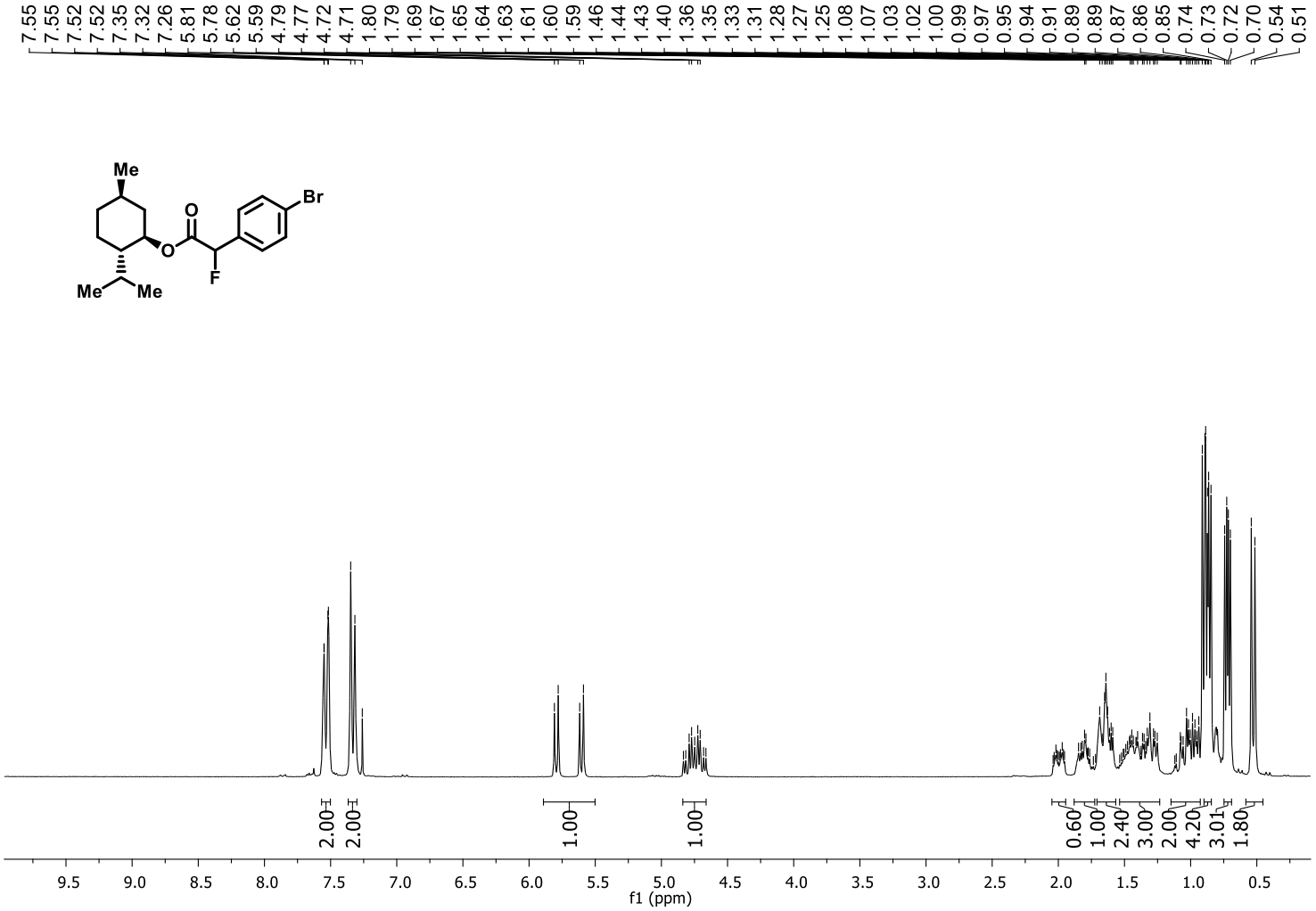
**18f - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



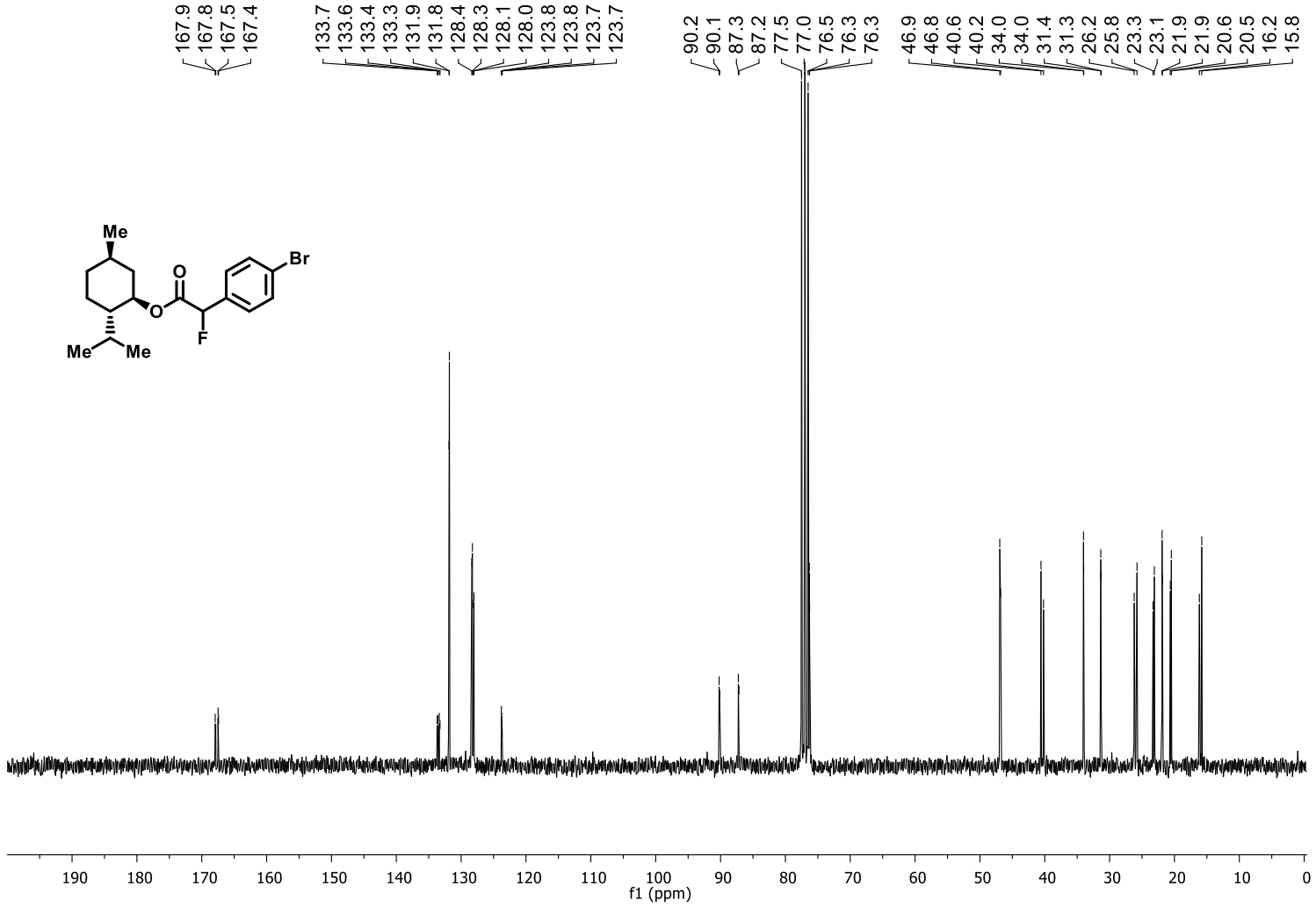
**18f - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



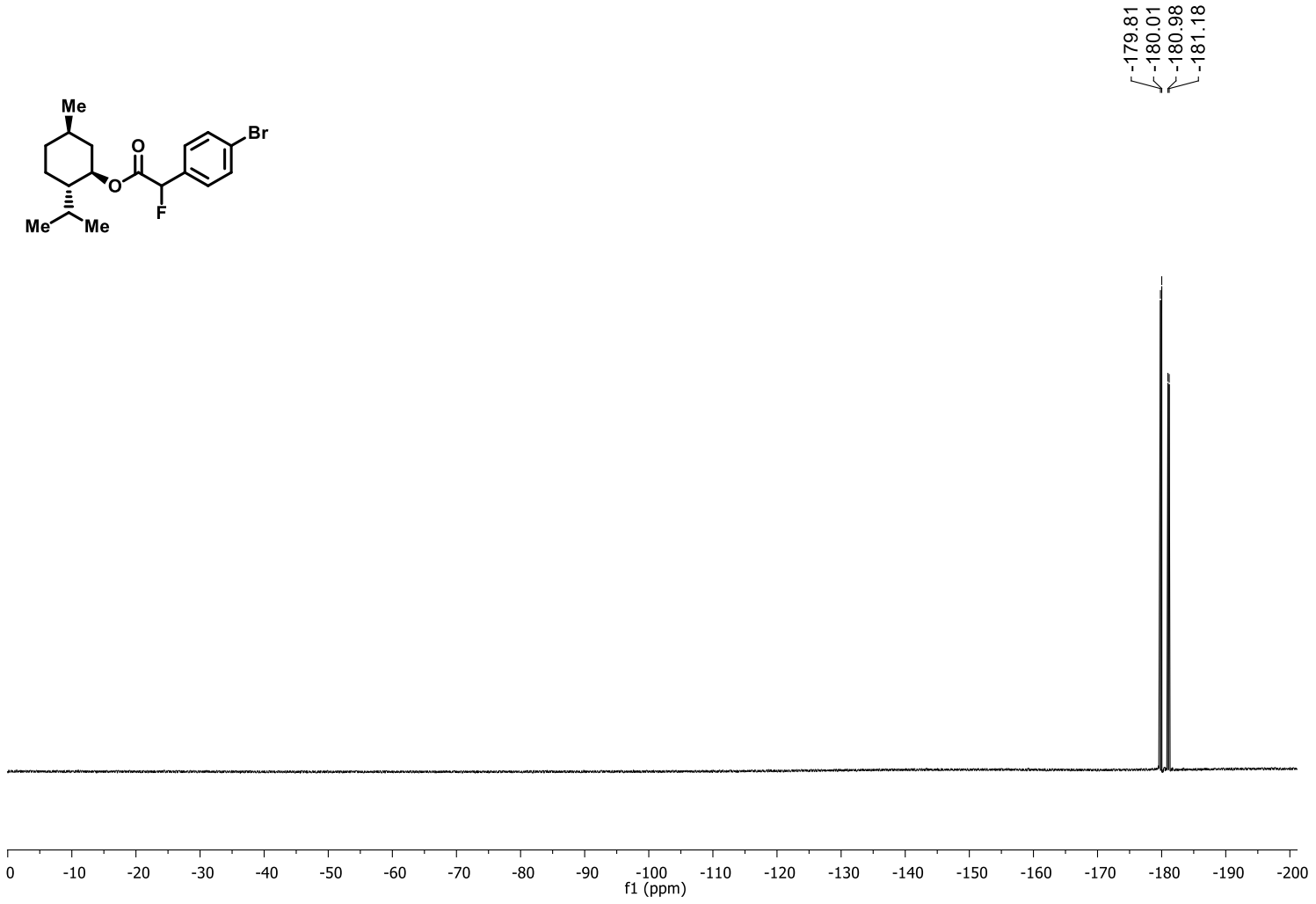
**18g - $^{1}$H NMR (250 MHz, $CDCl_3$)**



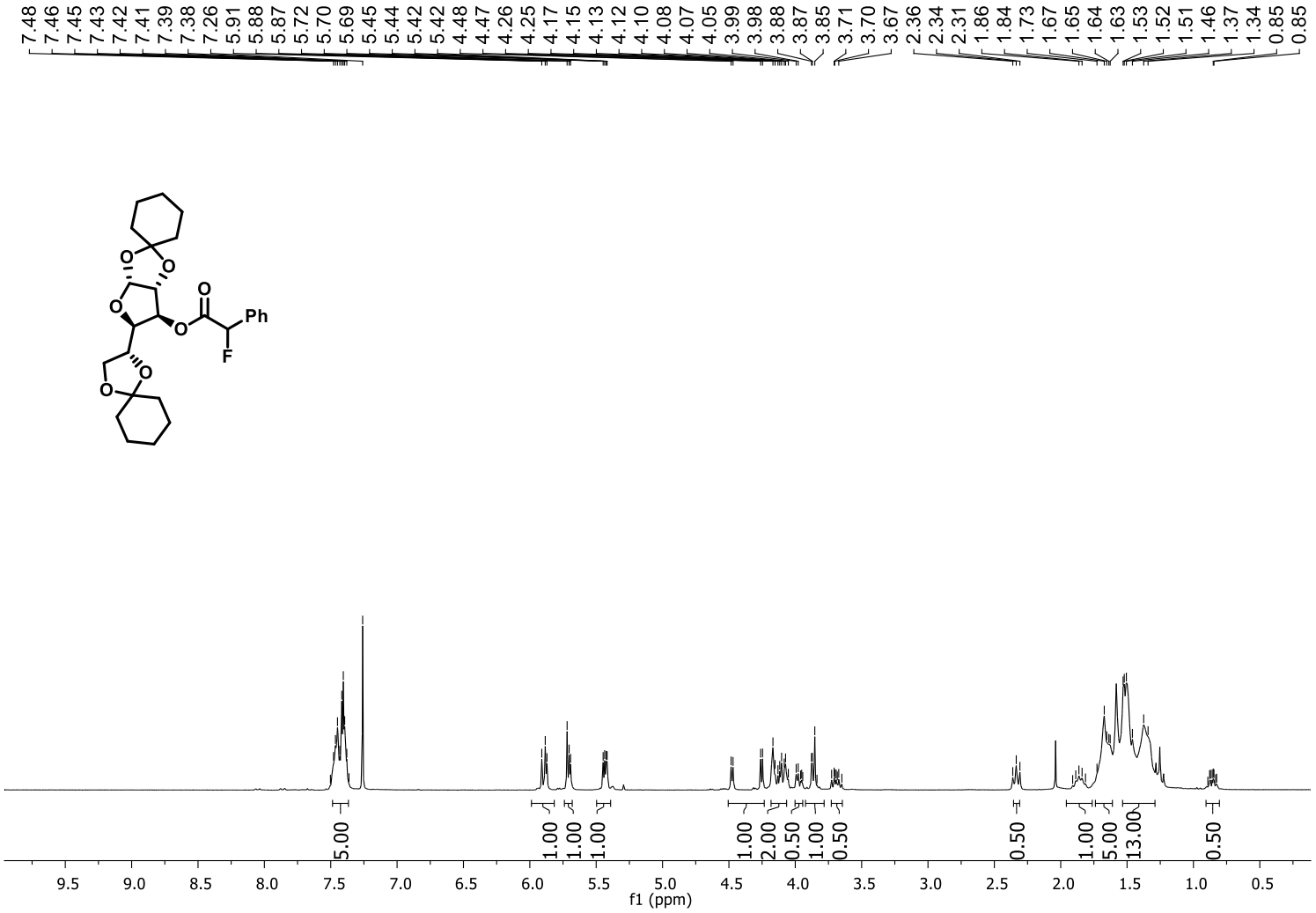
**18g - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



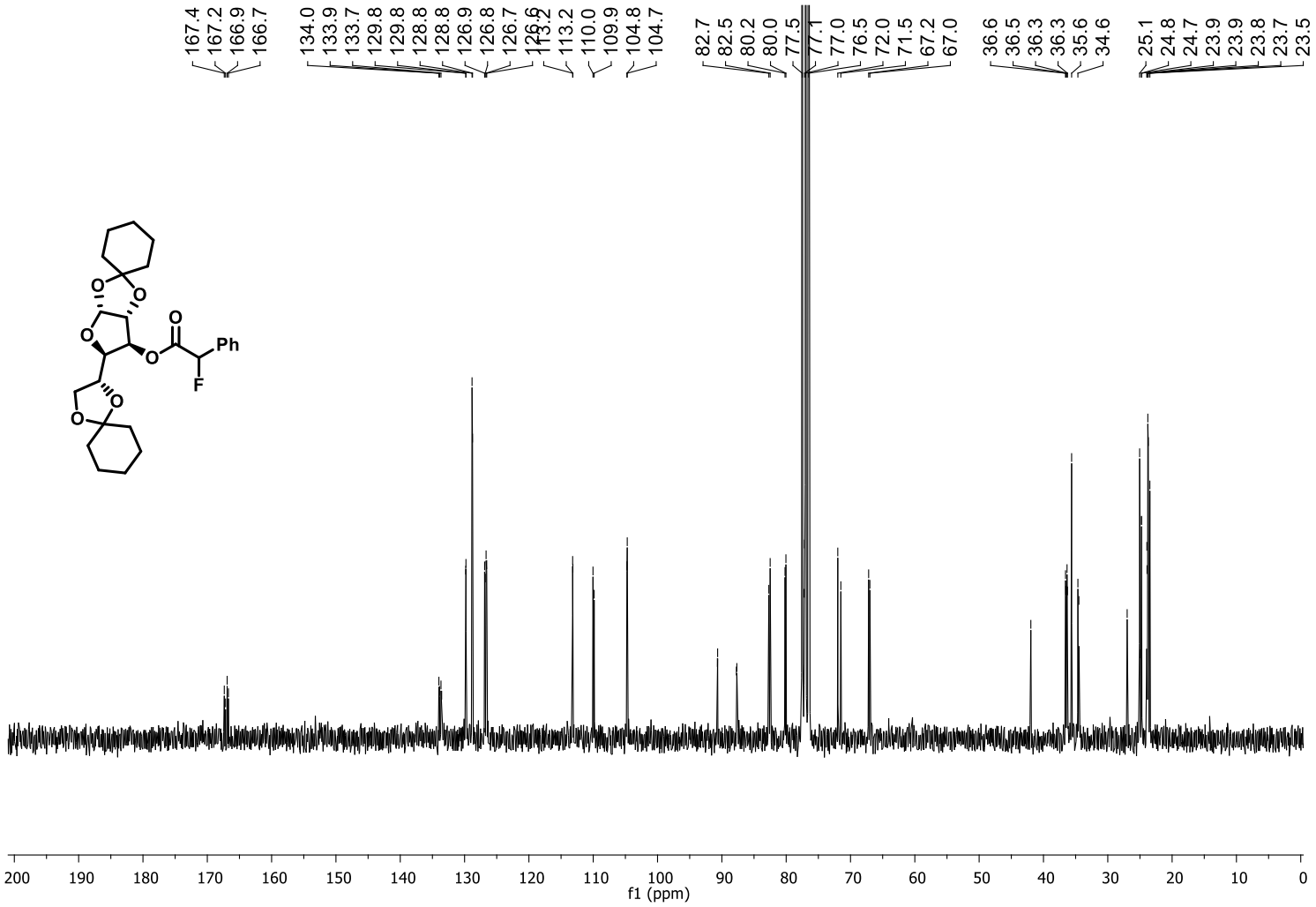
**18g - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



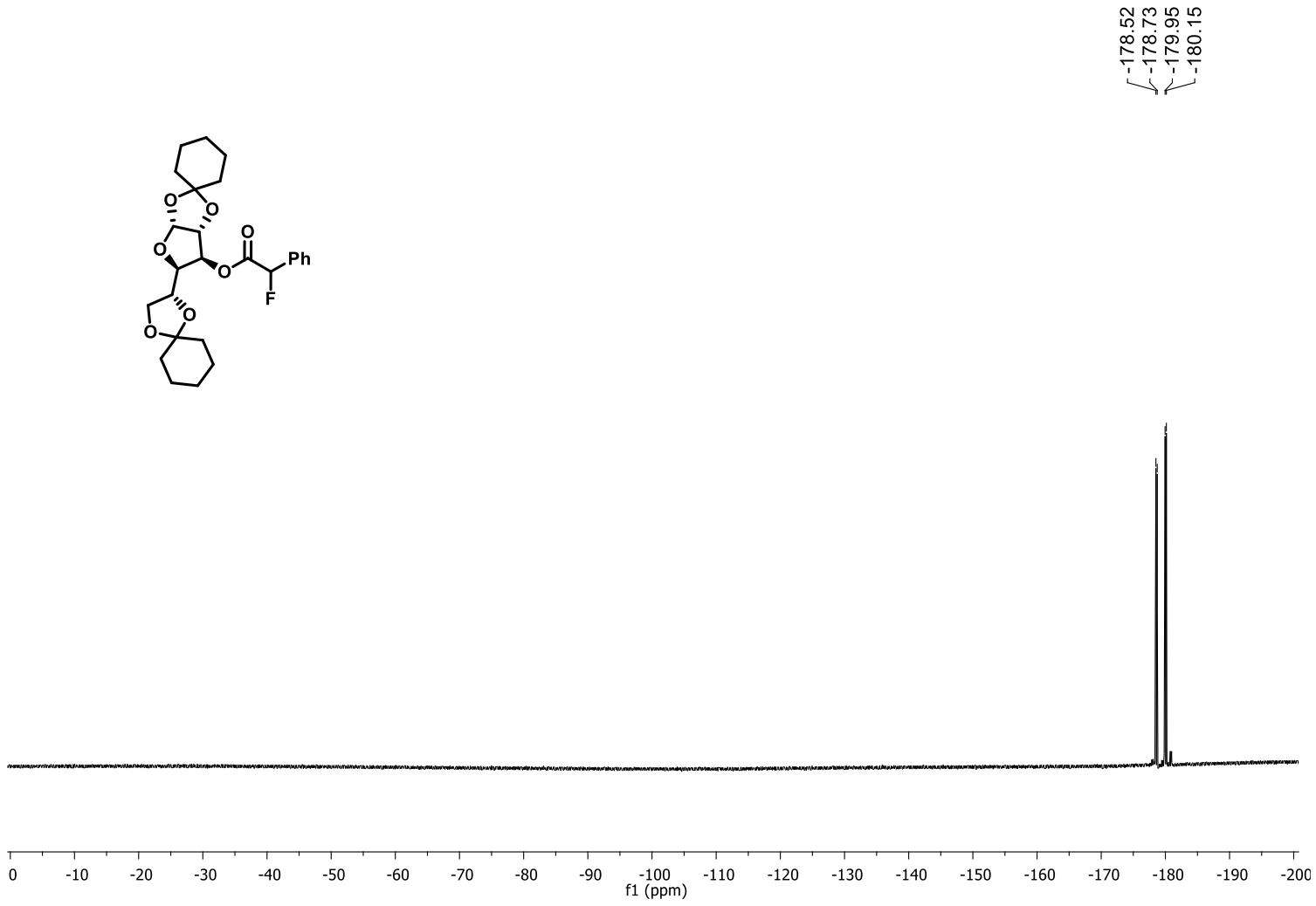
**18h - $^{1}$H NMR (250 MHz, $CDCl_3$)**



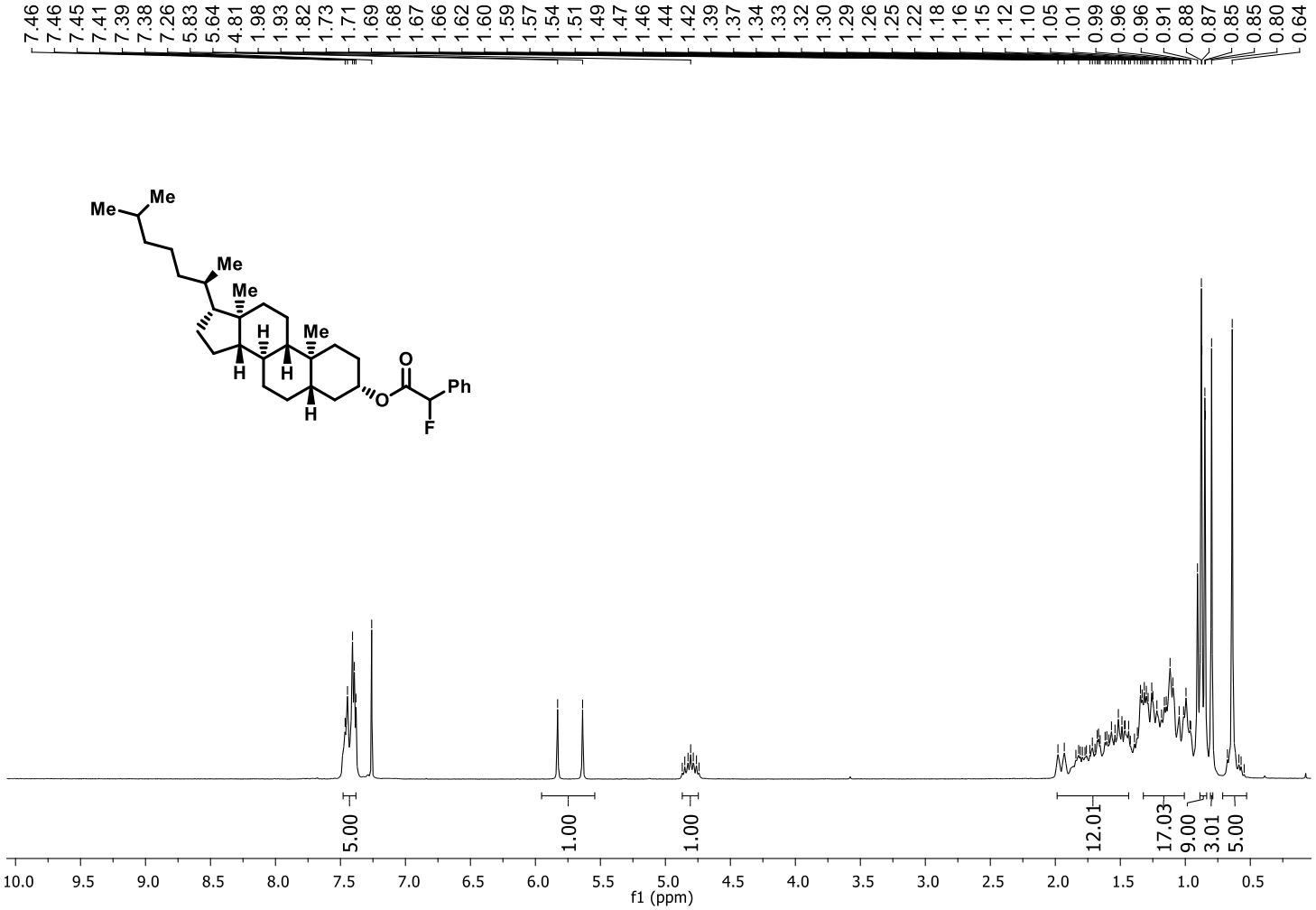
**18h - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



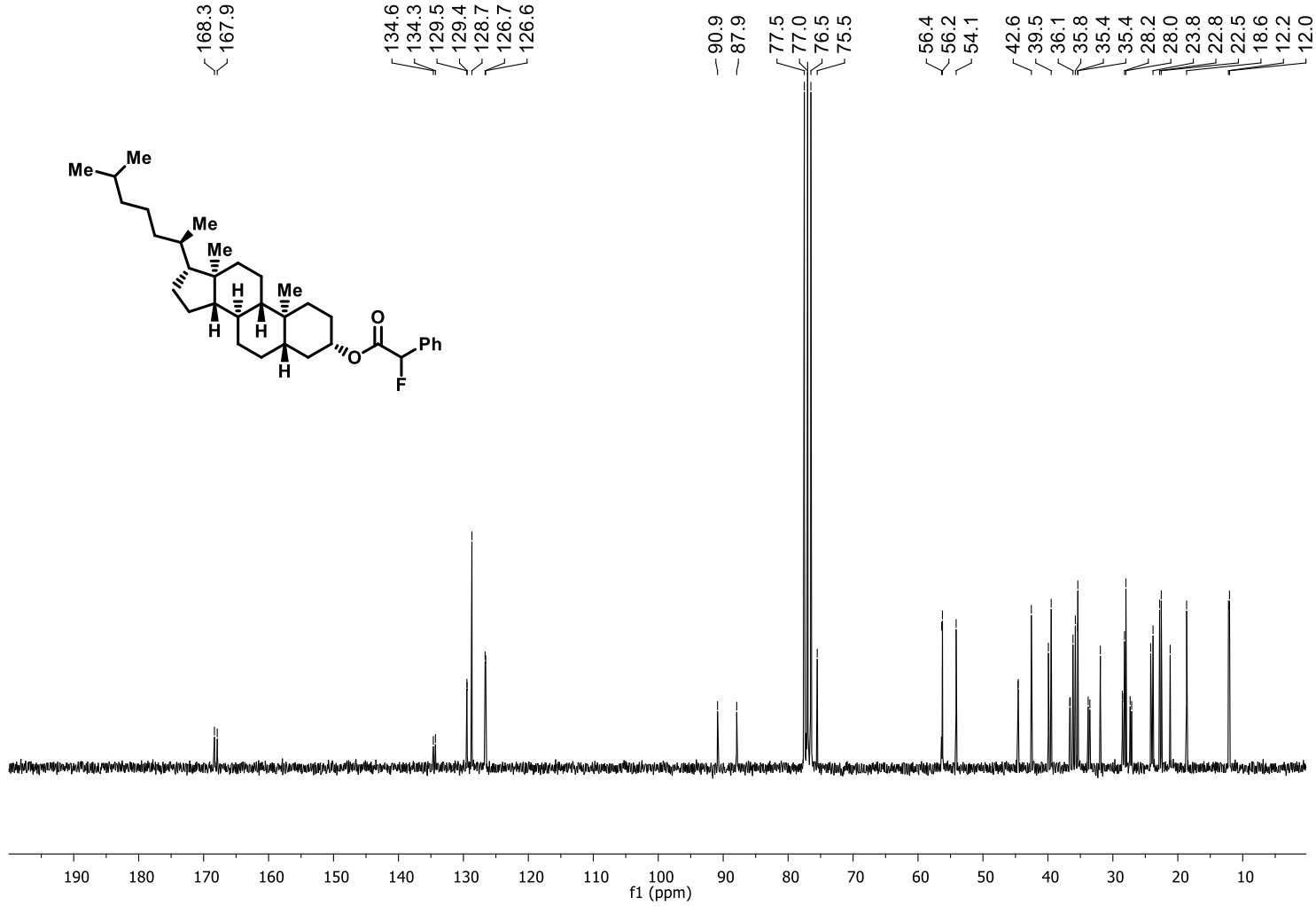
**18h - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



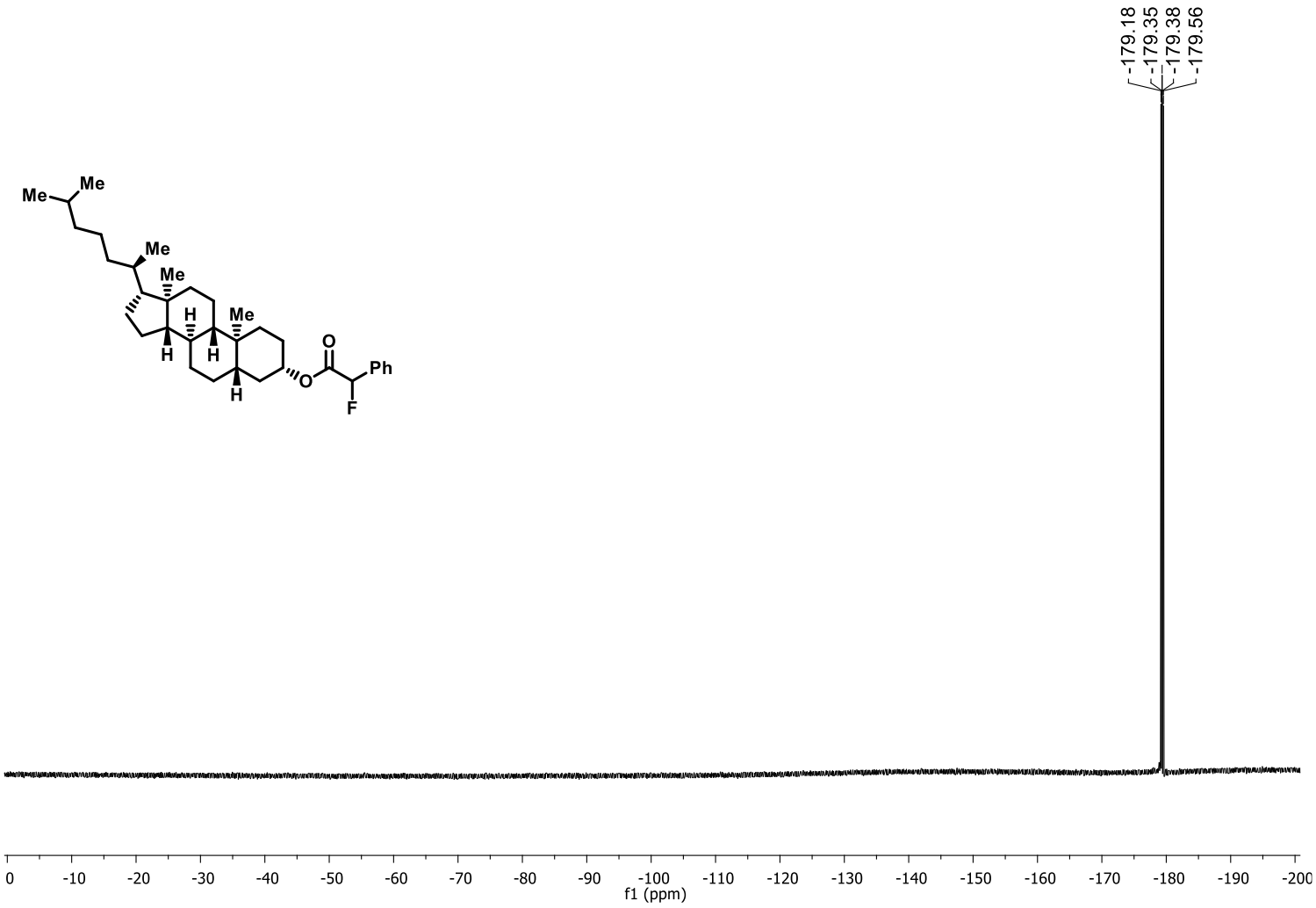
**18i - $^{1}$H NMR (250 MHz, $CDCl_3$)**



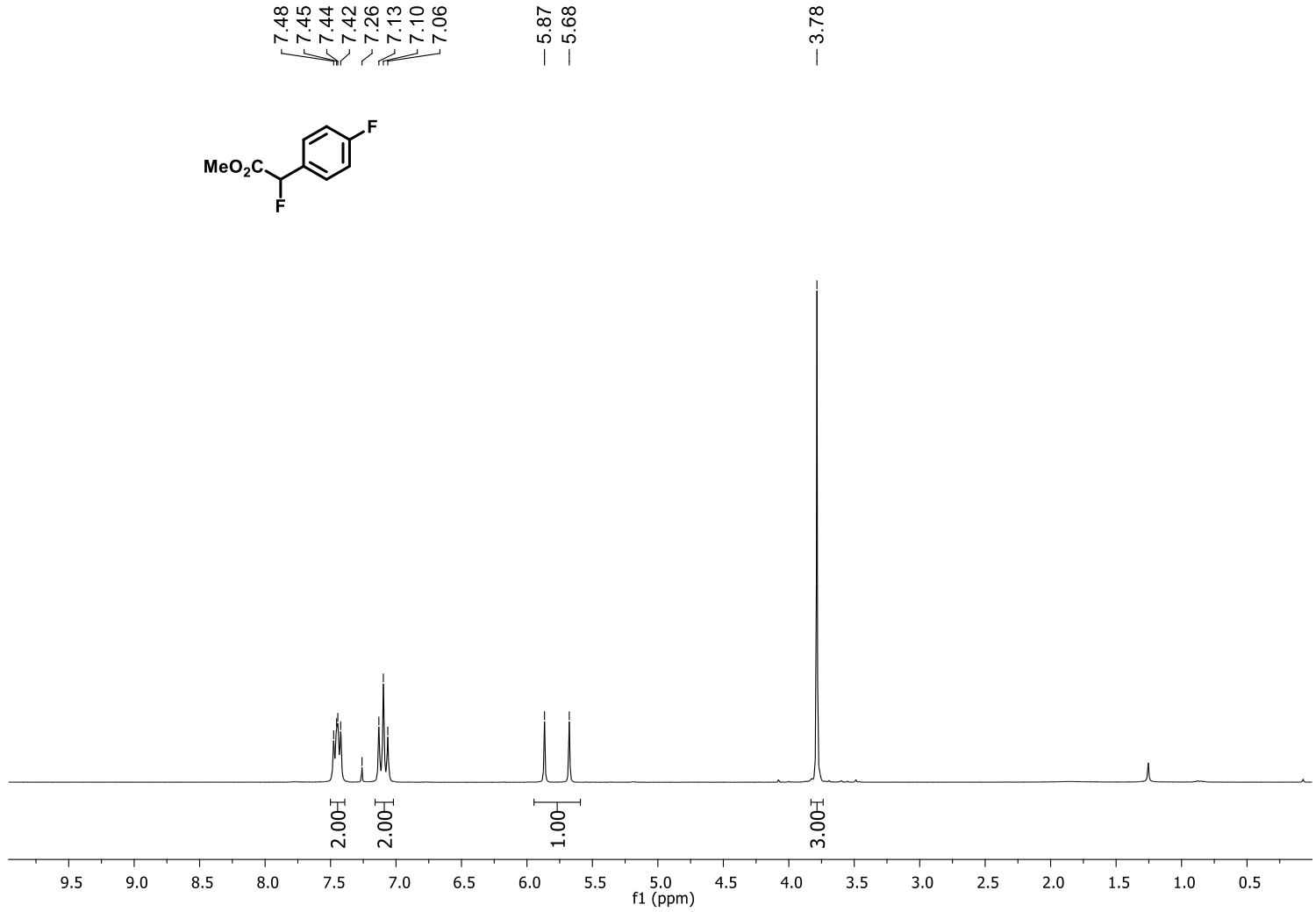
**18i - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



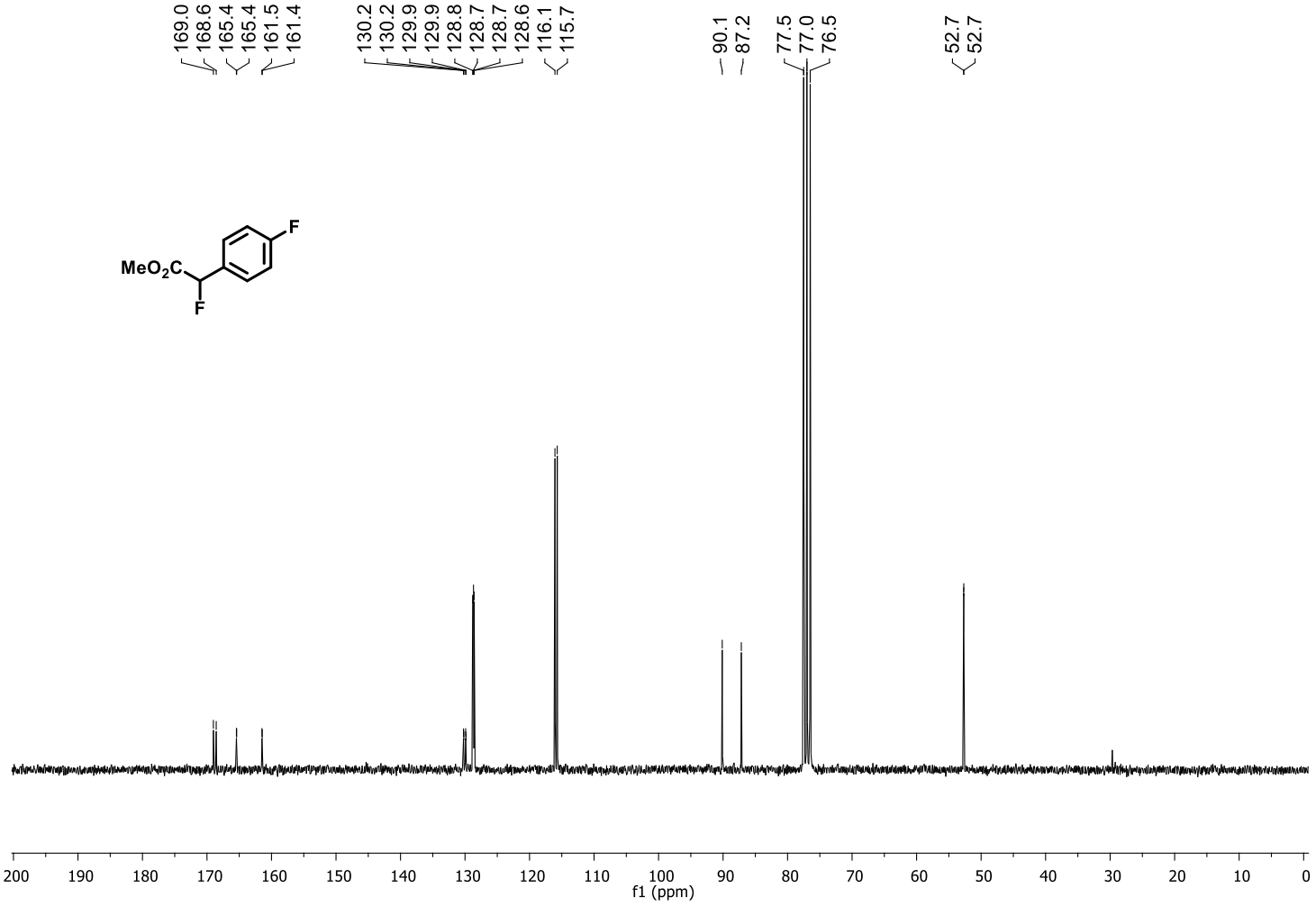
**18i - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



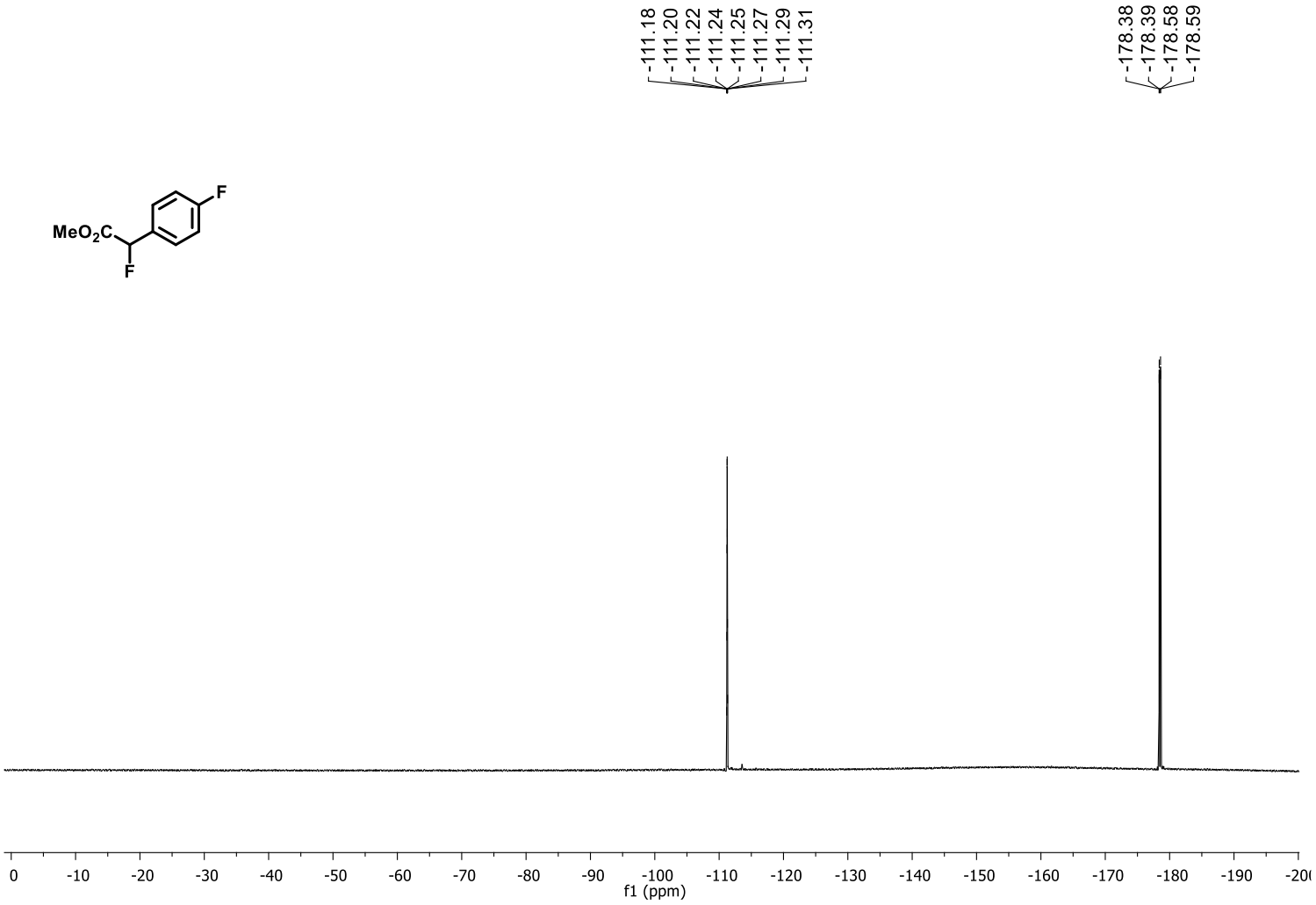
**18j - $^{1}$H NMR (250 MHz, $CDCl_3$)**



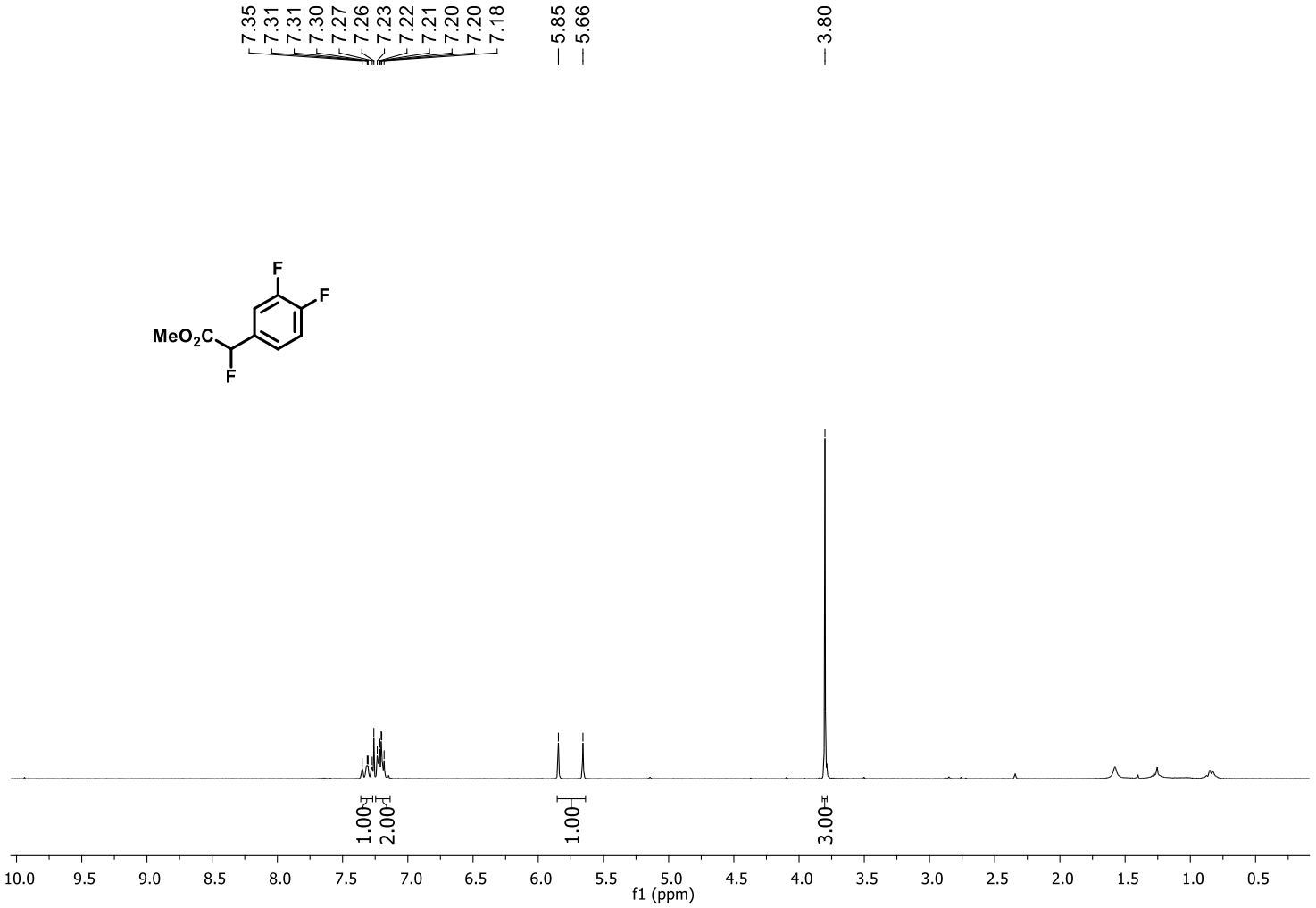
**18j - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



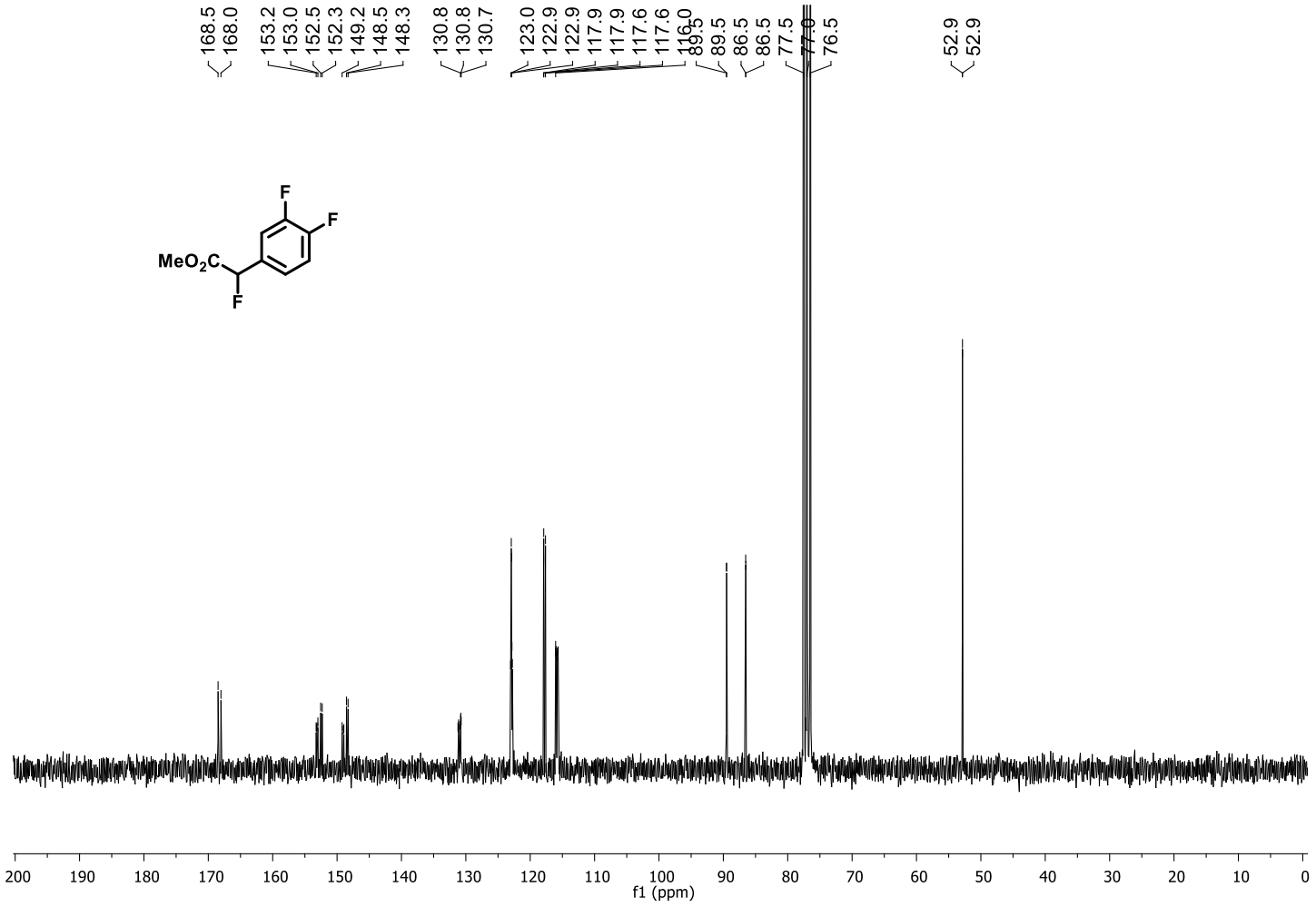
**18j - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



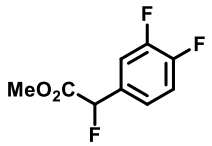
**18k - $^{1}$H NMR (250 MHz, $CDCl_3$)**



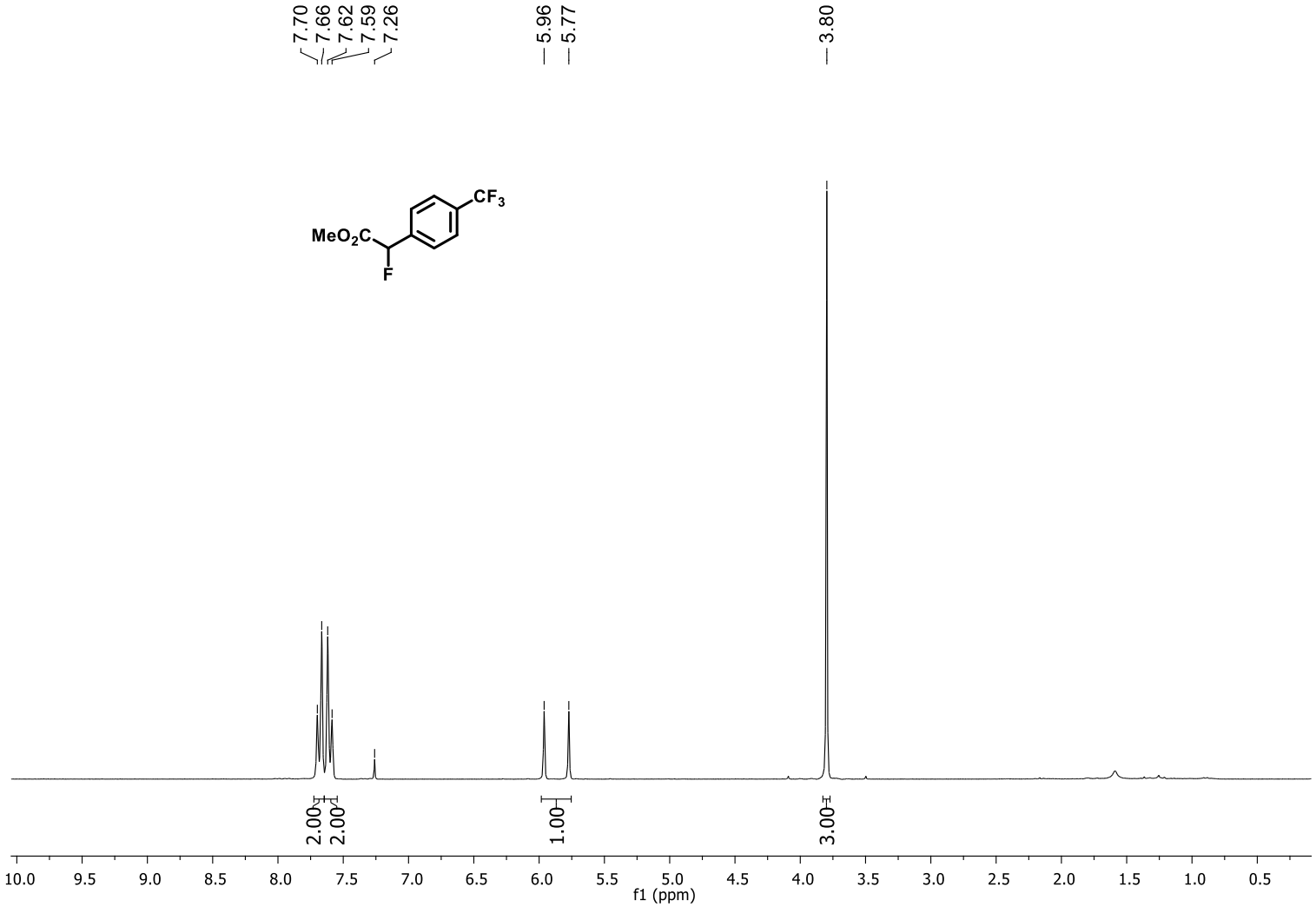
**18k – $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



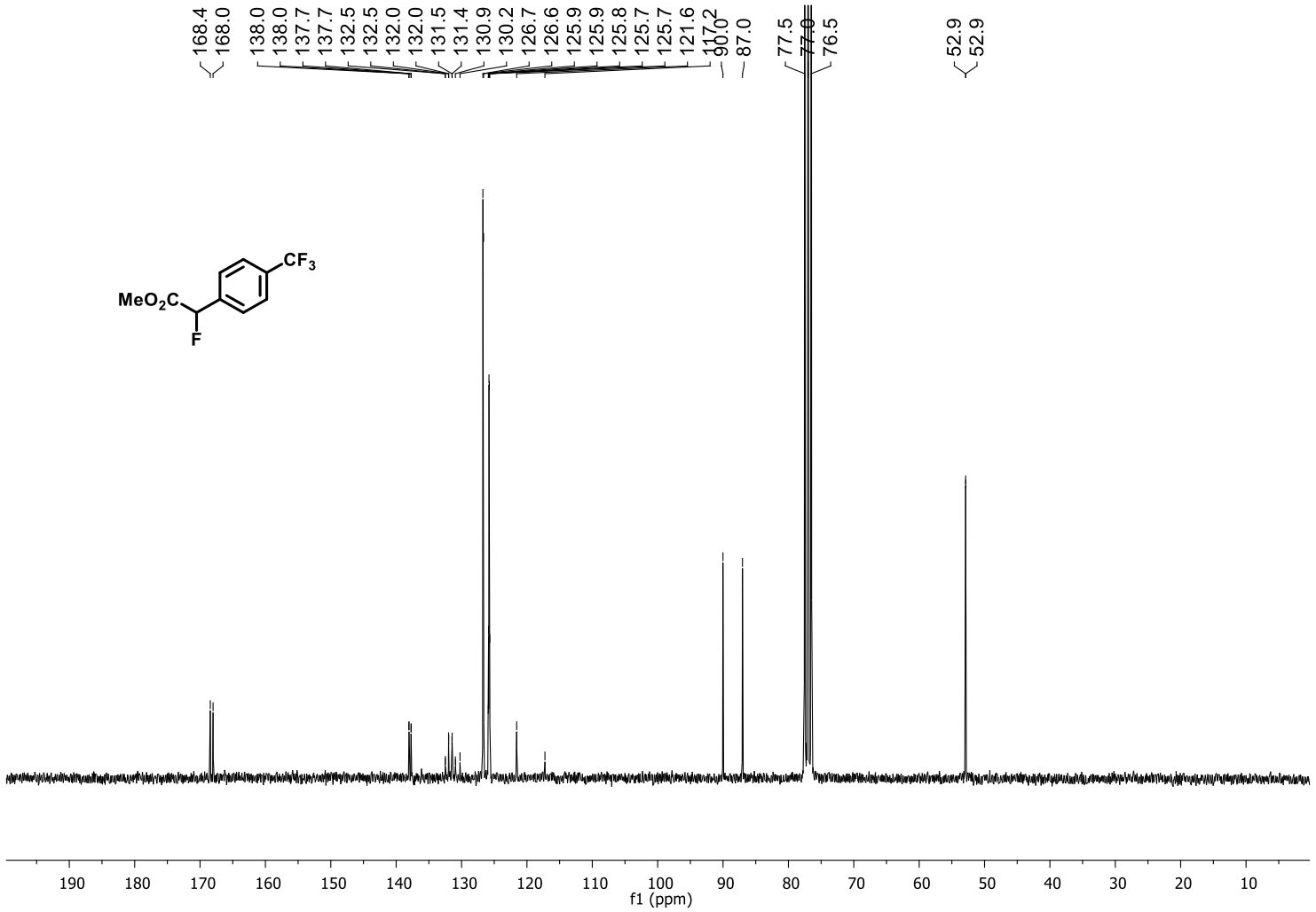
**18k – $^{19}$F NMR (235 MHz, $CDCl_3$)**



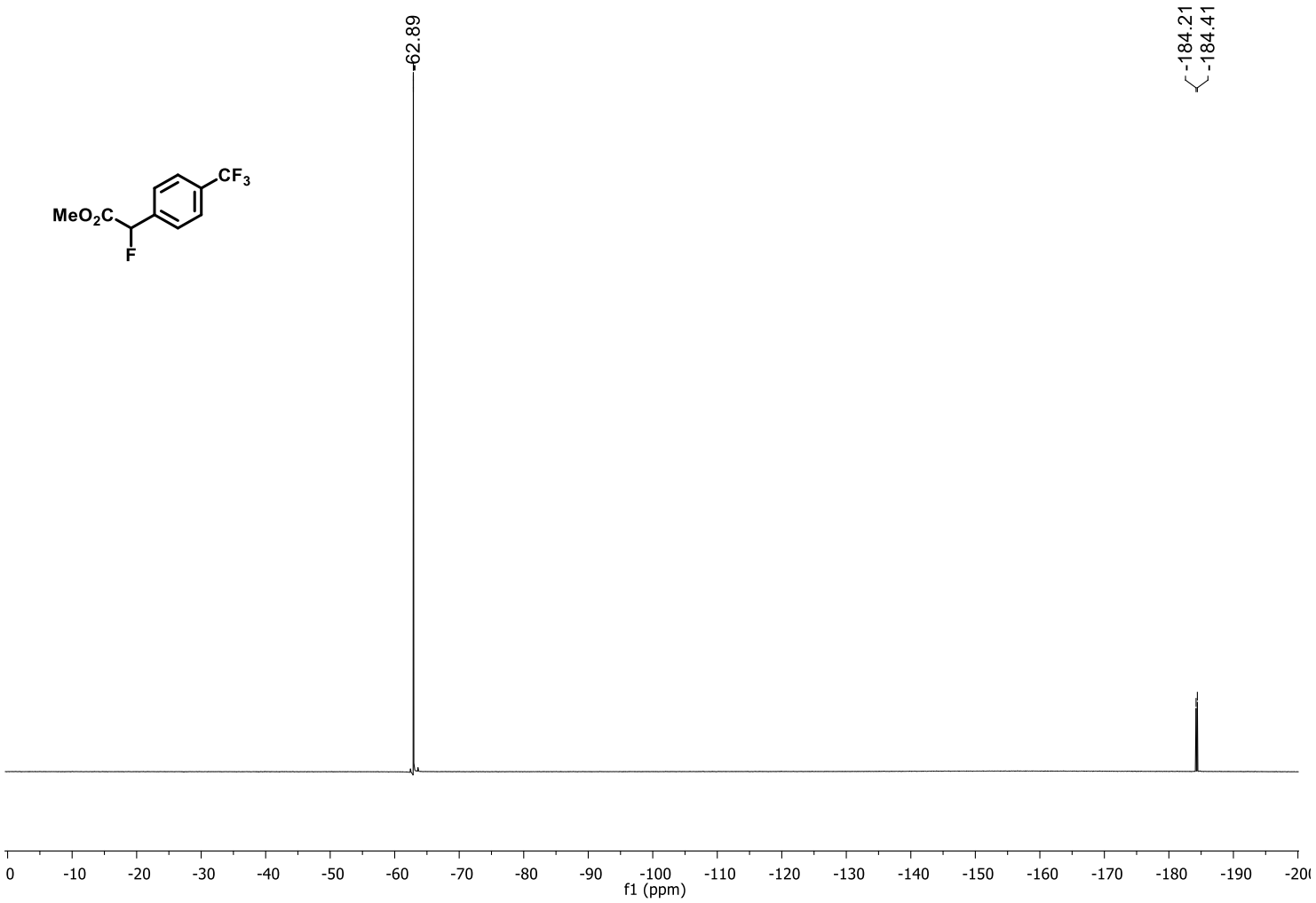
**18l - $^{1}$H NMR (250 MHz, $CDCl_3$)**



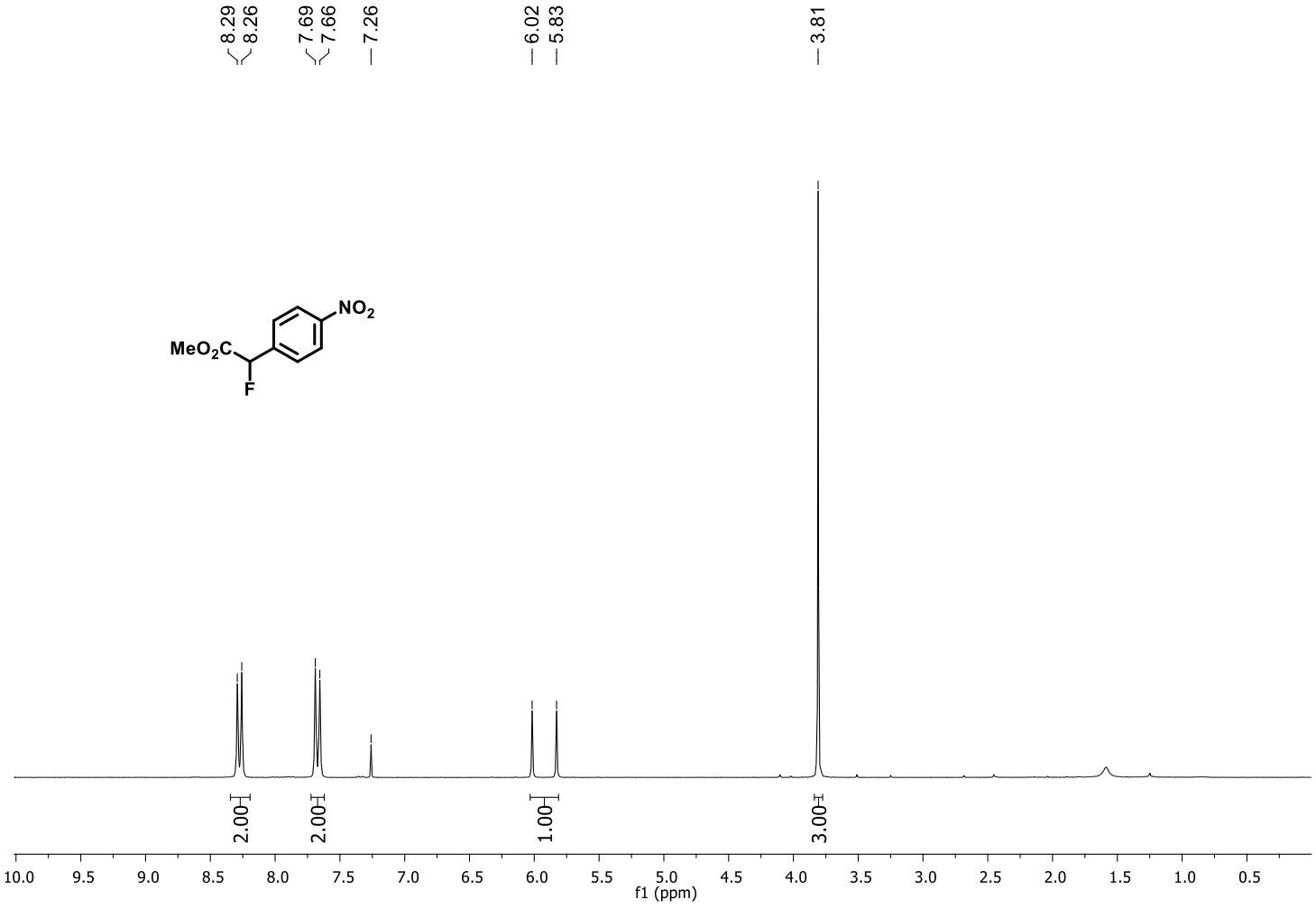
**18l - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



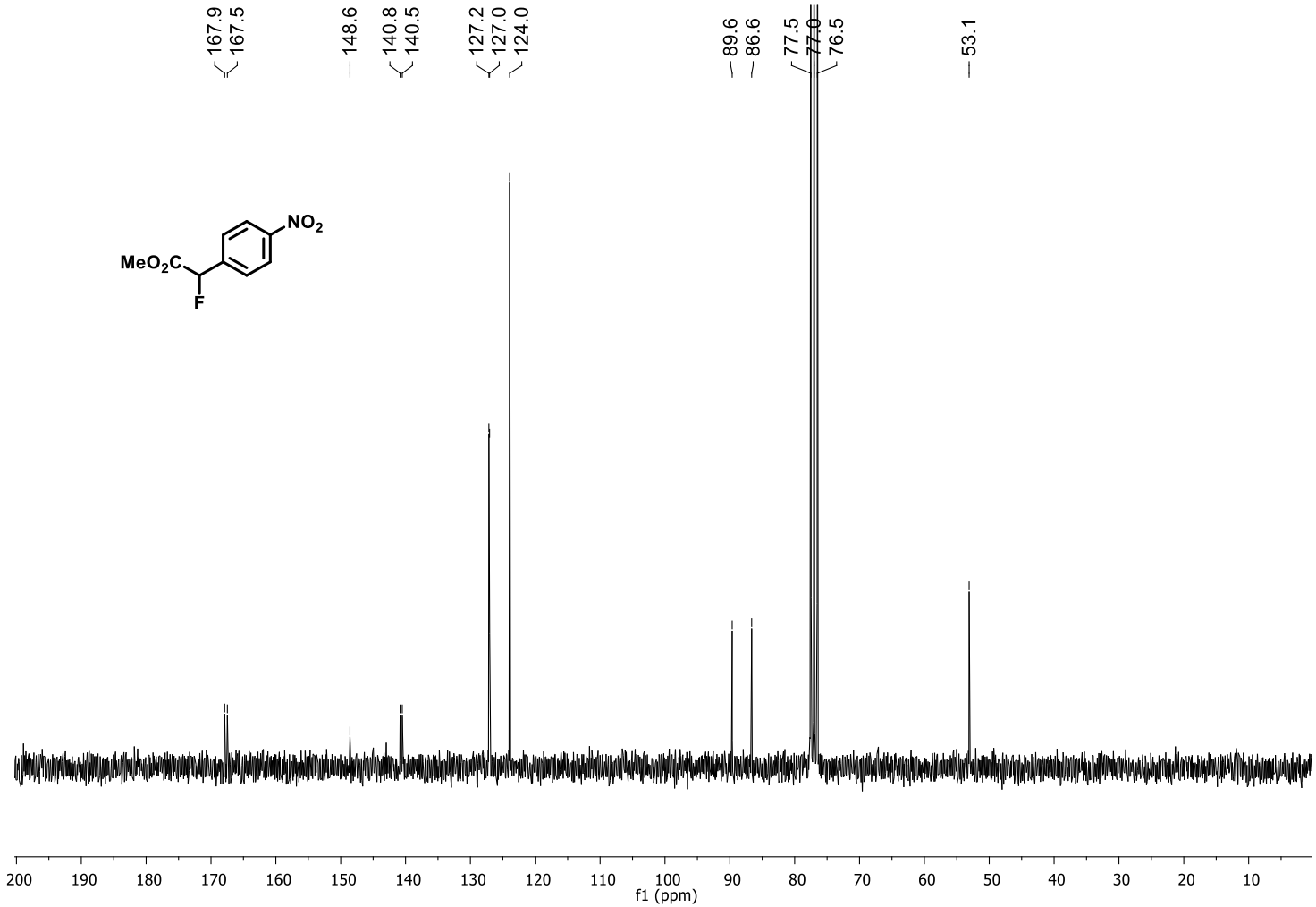
**18l - $^{19}$F NMR (235 MHz, $CDCl_3$)**



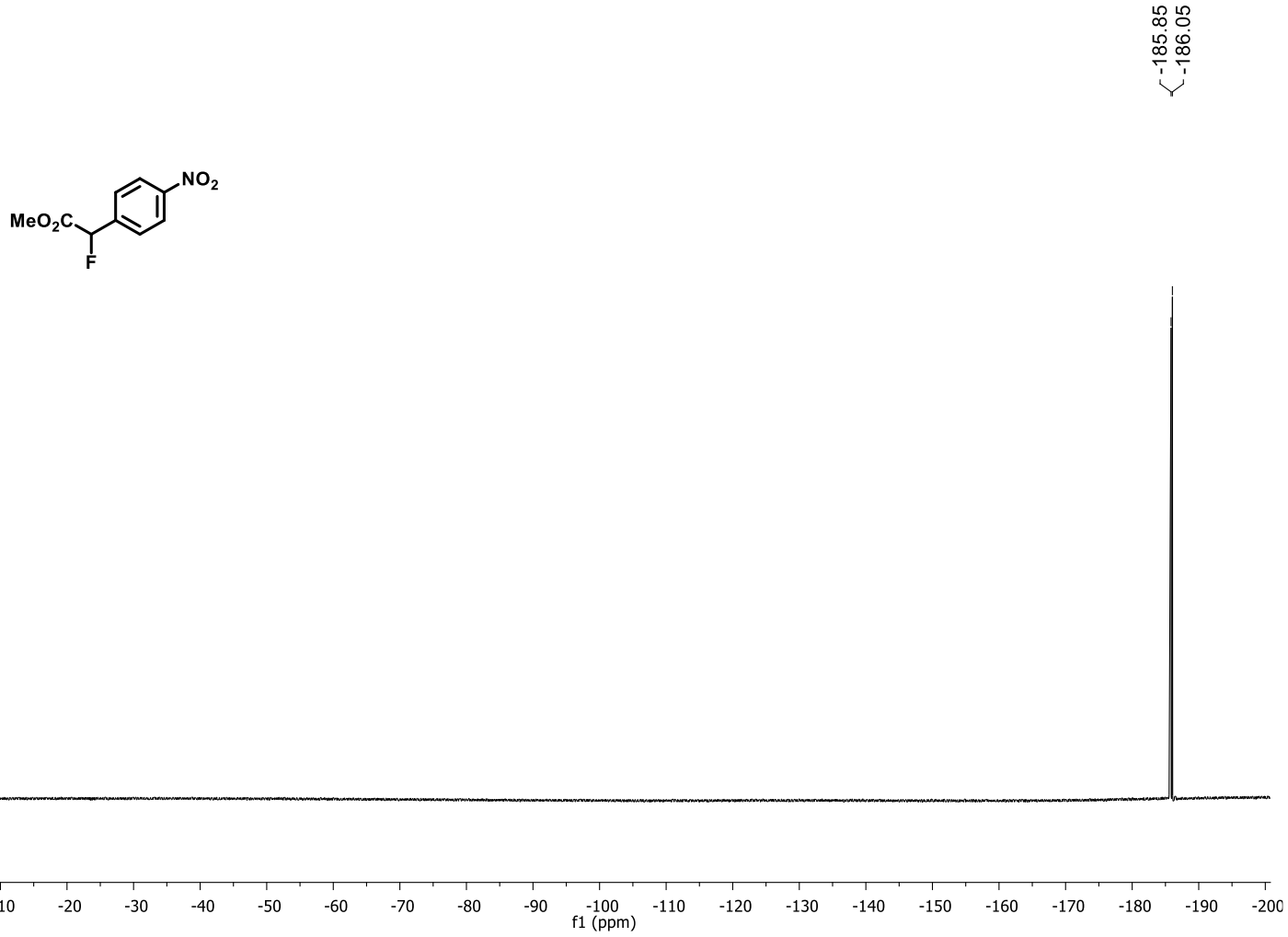
**18n - $^{1}$H NMR (250 MHz, $CDCl_3$)**



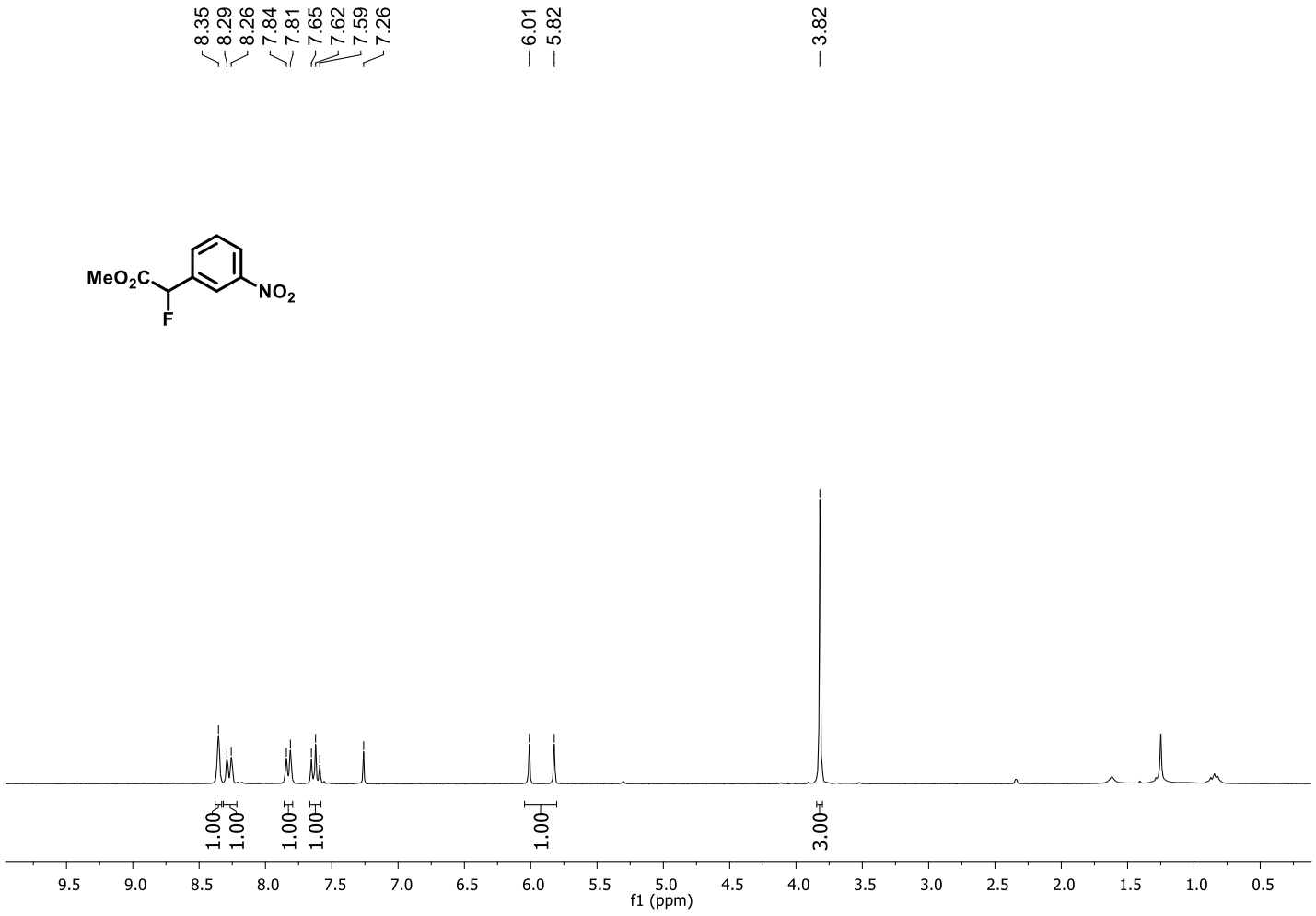
**18n - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



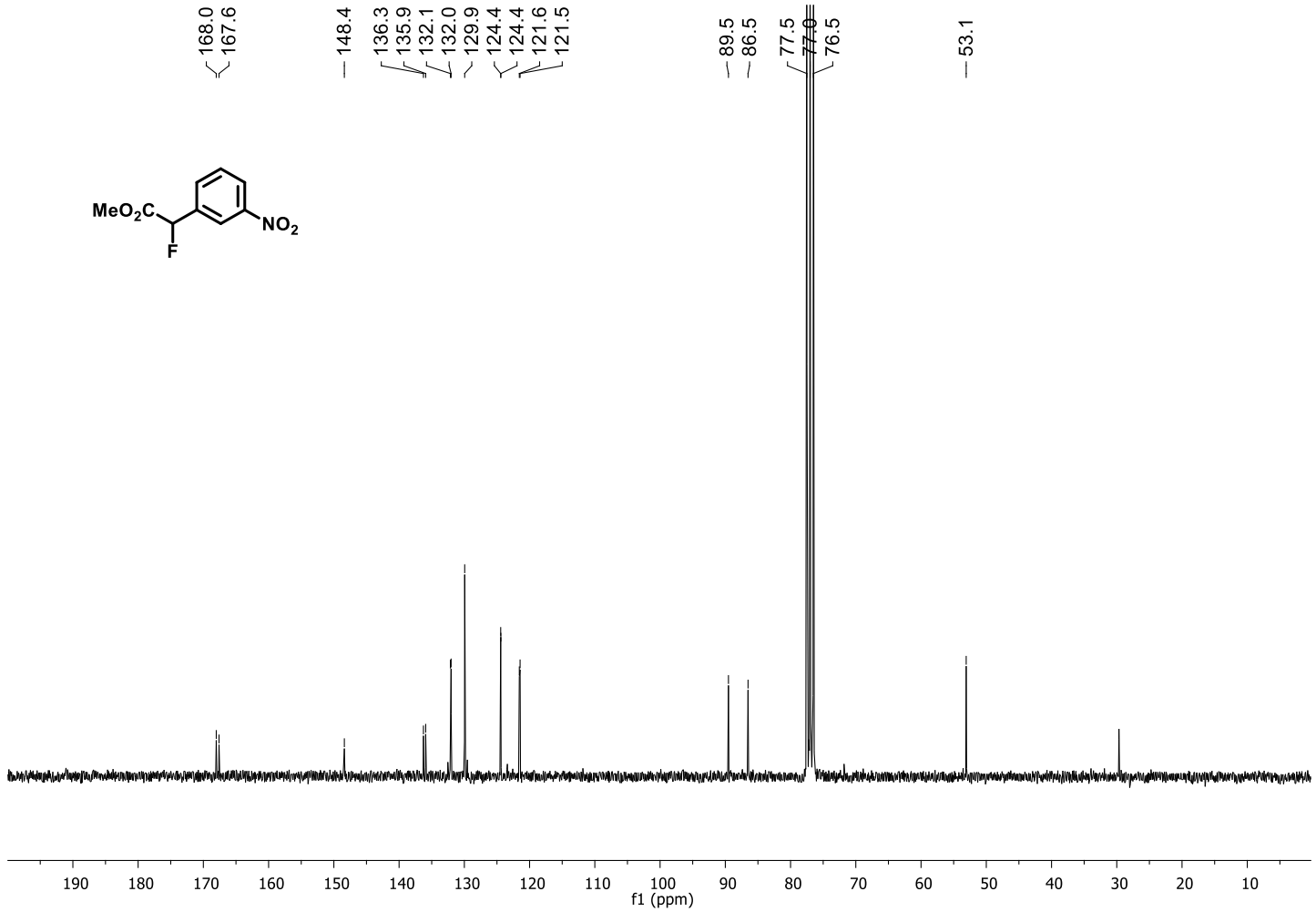
**18n - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



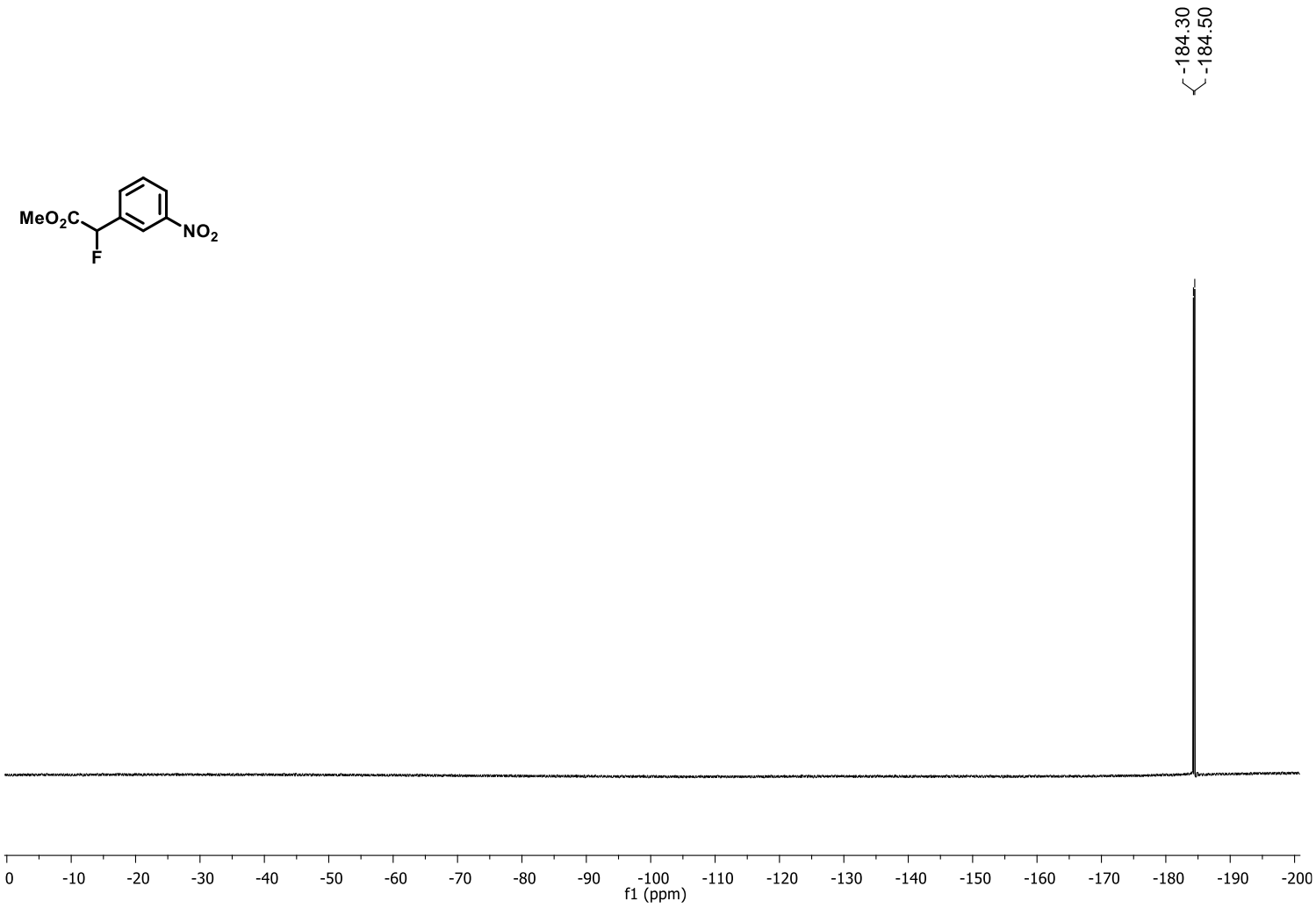
**18o - $^{1}$H NMR (250 MHz, $CDCl_3$)**



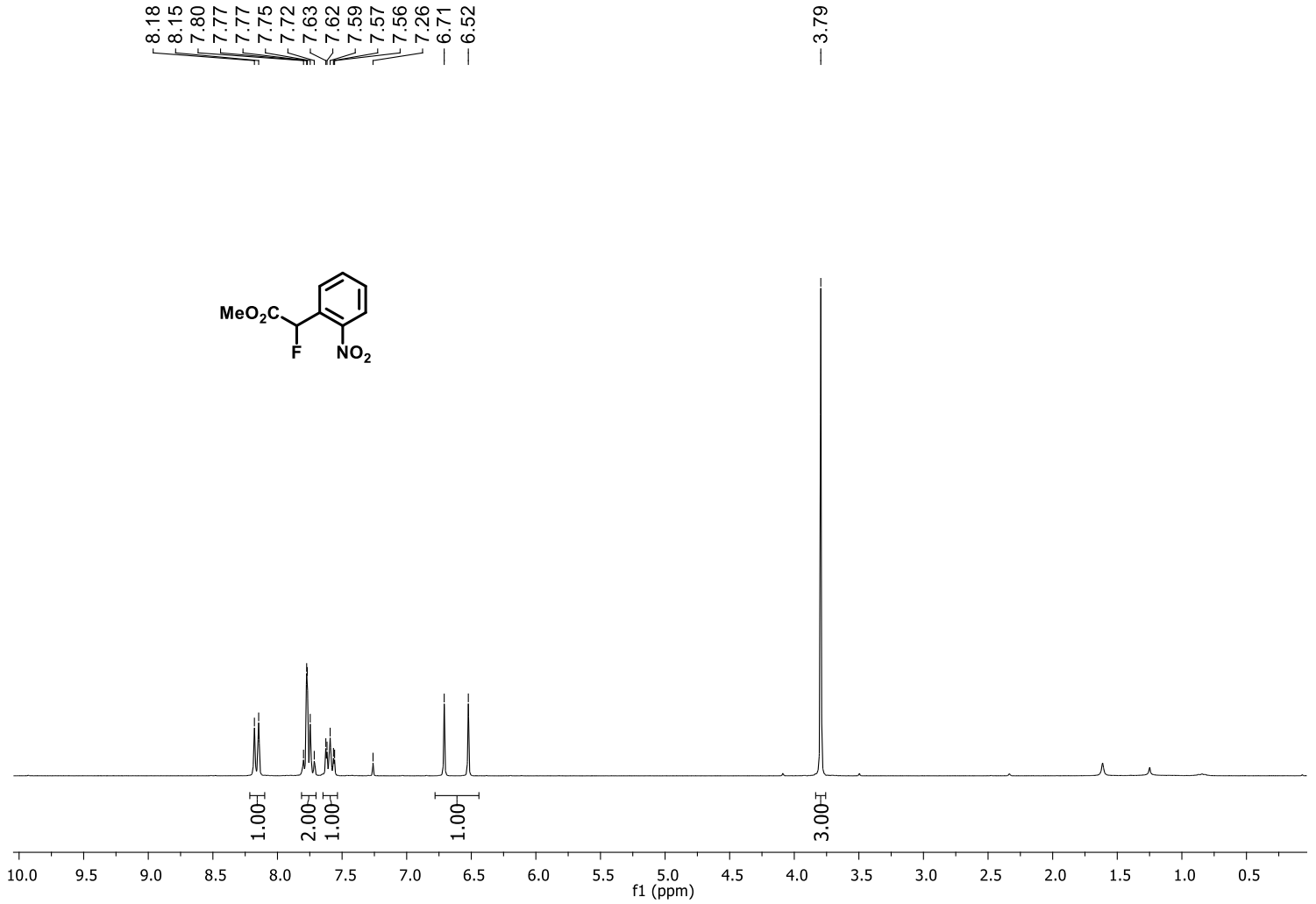
**18o - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



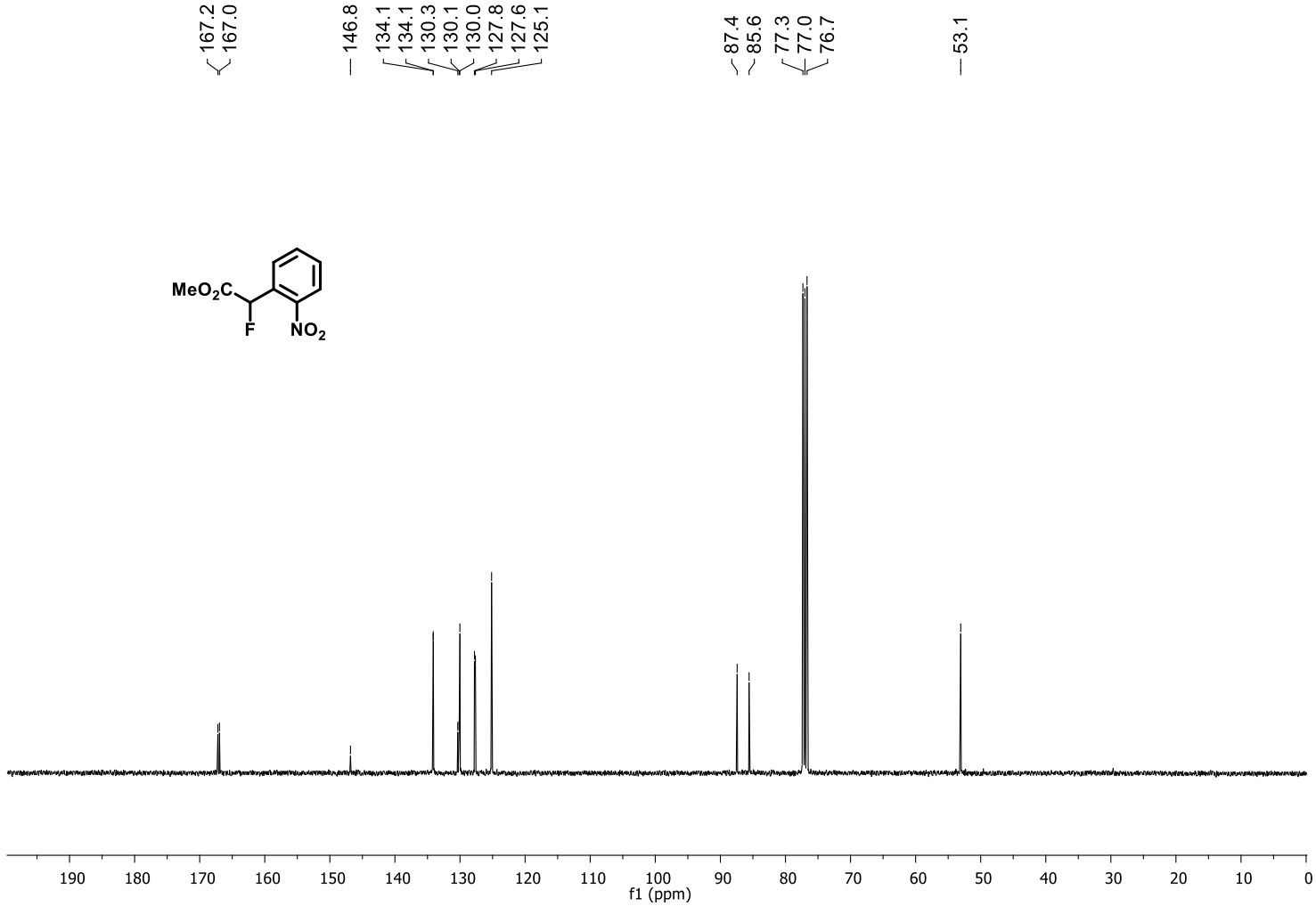
**18o - $^{19}$F NMR (235 MHz, $CDCl_3$)**



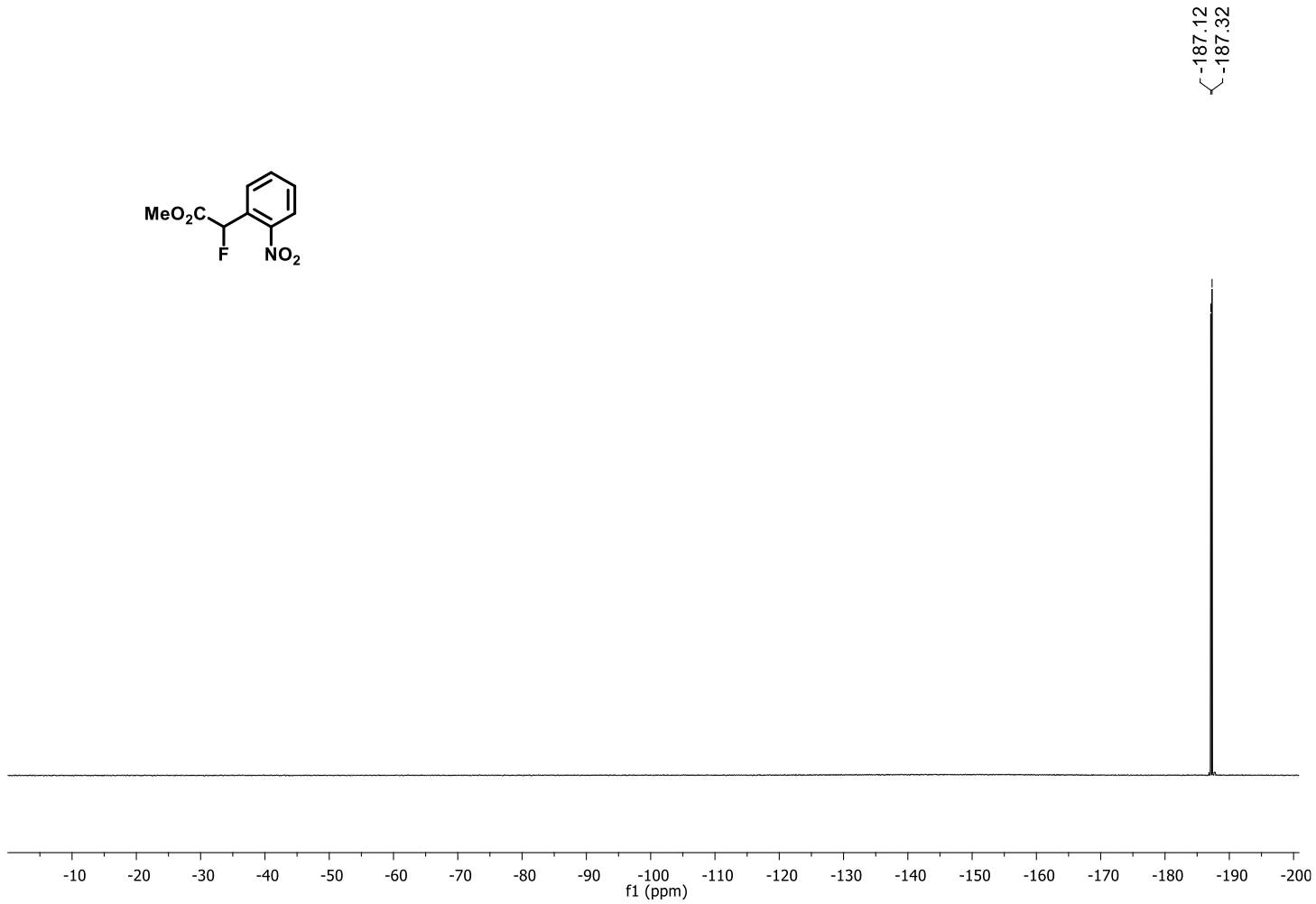
**18p - $^{1}$H NMR (250 MHz, $CDCl_3$)**



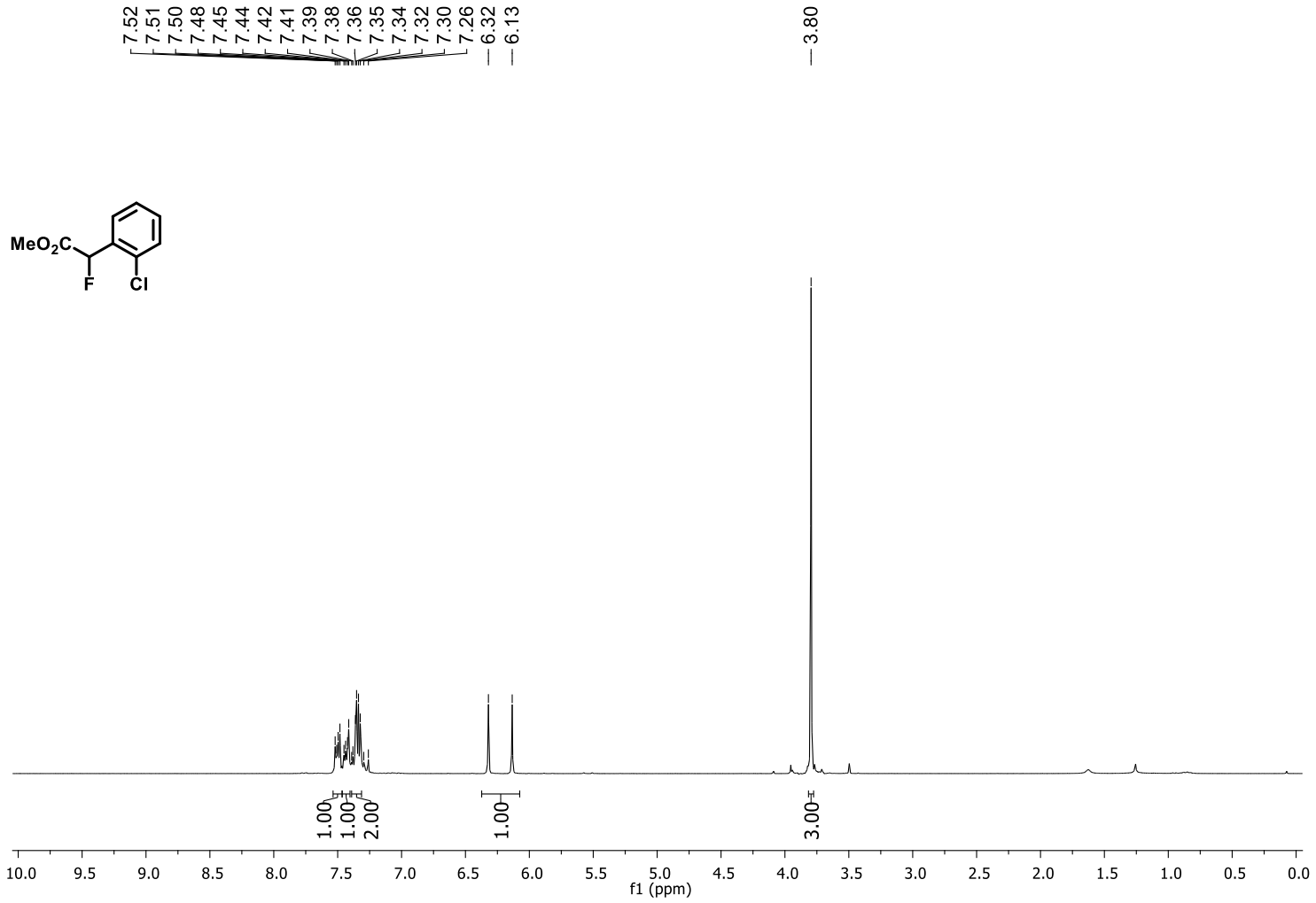
**18p - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



**18p - $^{19}$F NMR (235 MHz, $CDCl_3$)**




**18q - $^{1}$H NMR (250 MHz, $CDCl_3$)**


7.52
7.51
7.50
7.48
7.45
7.44
7.42
7.41
7.39
7.38
7.36
7.35
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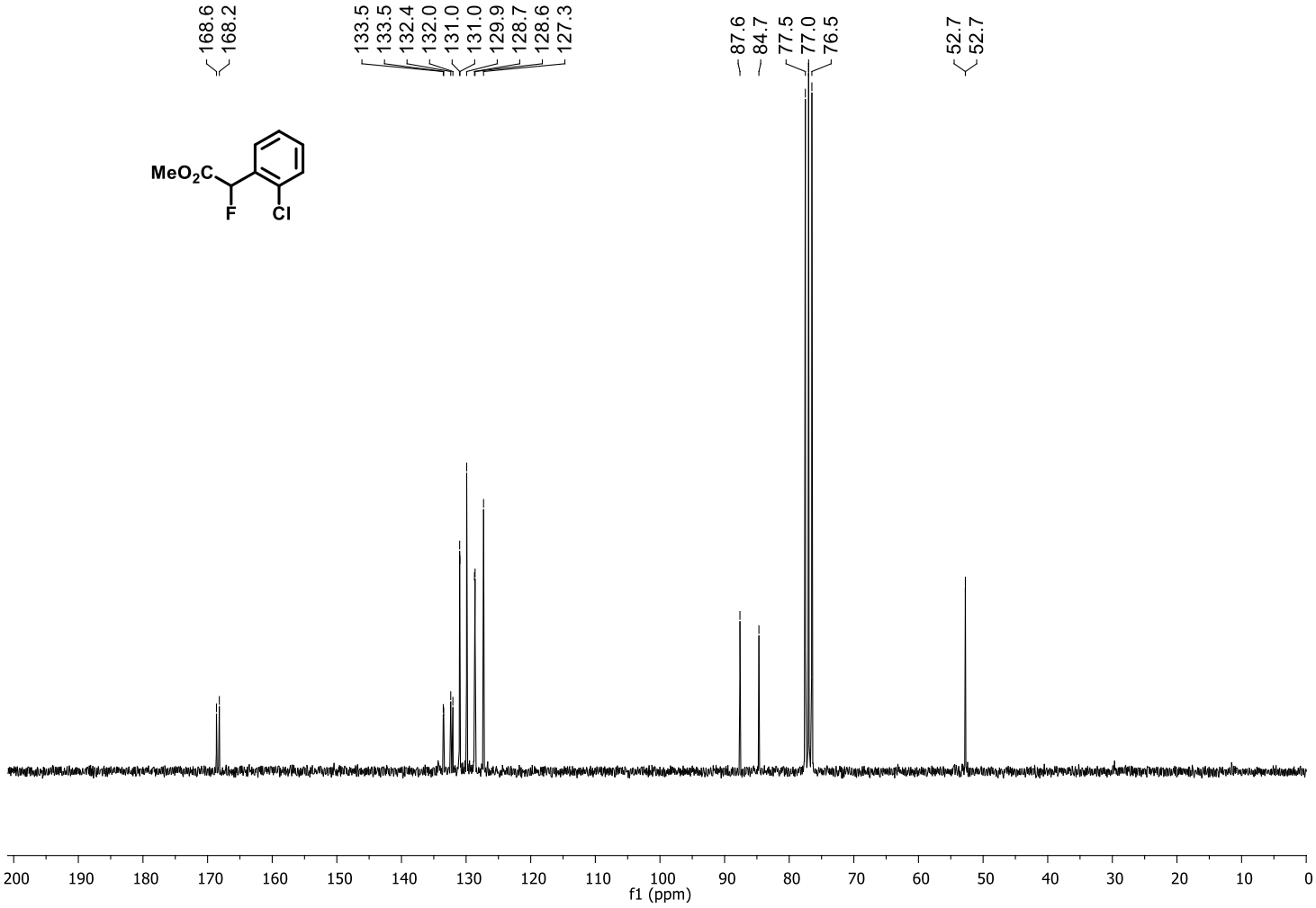
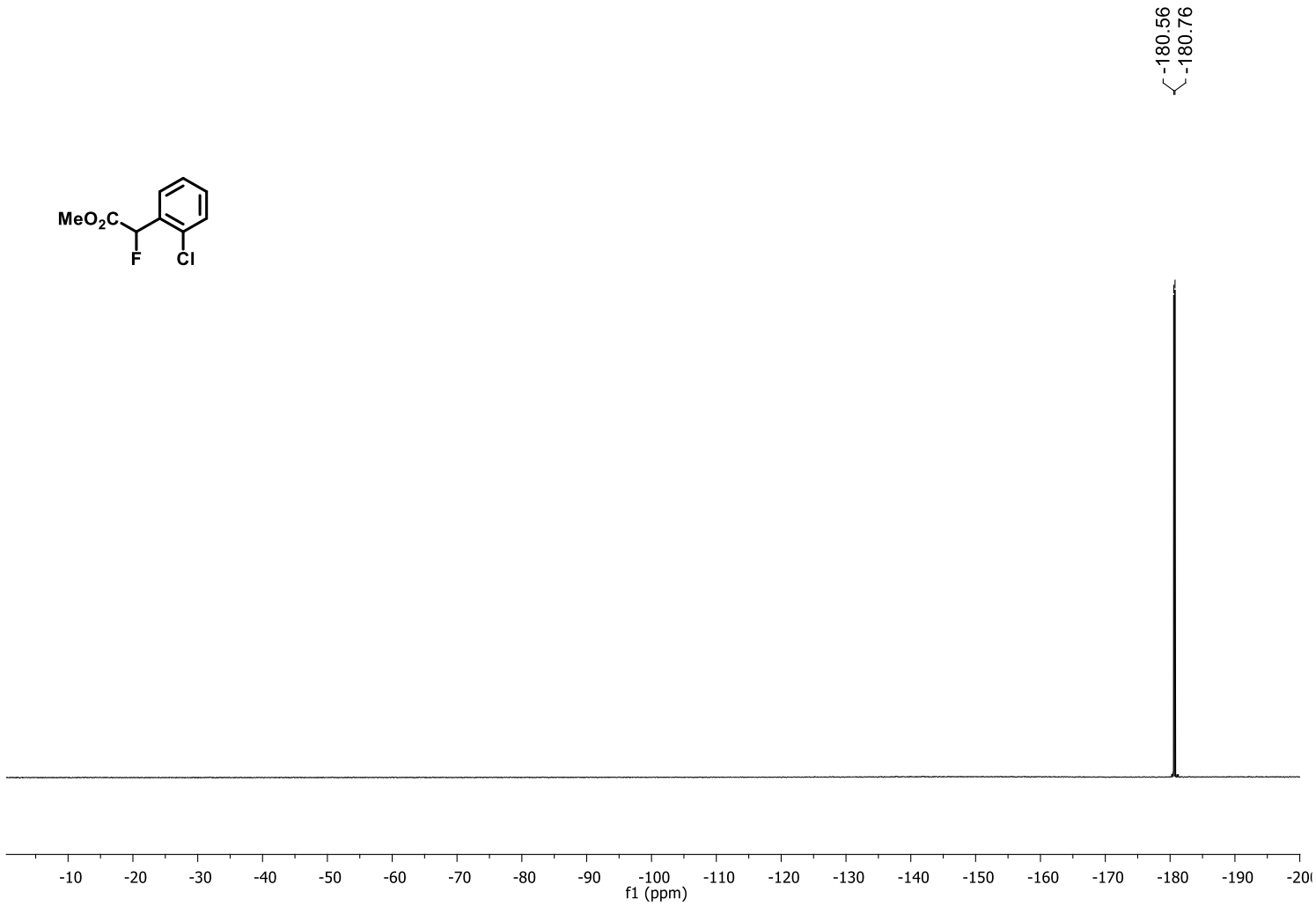
7.32
7.30
7.26
6.32
6.13
3.80
MeO2C
F
Cl
1.00
1.00
2.00
1.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

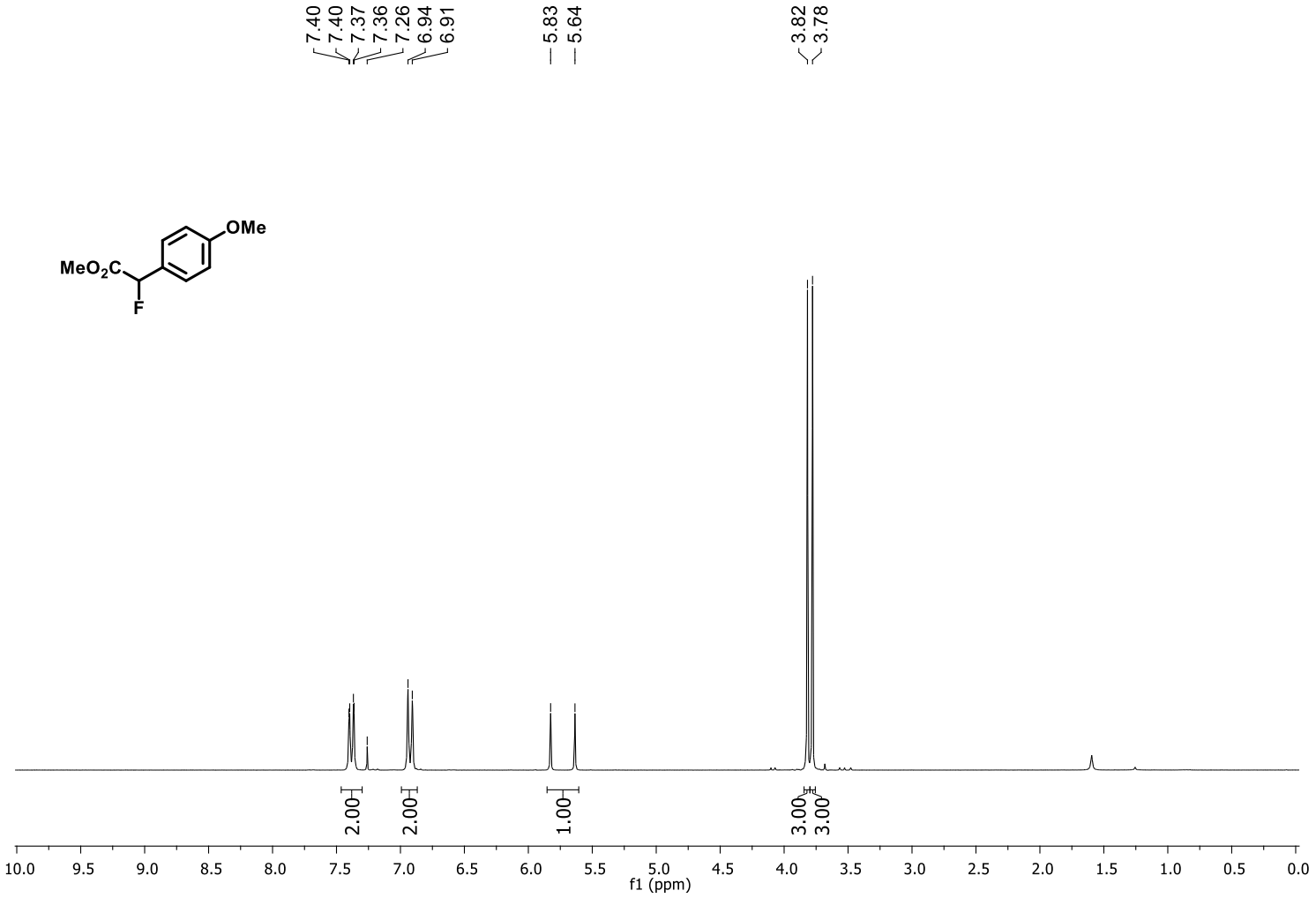
**18q - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



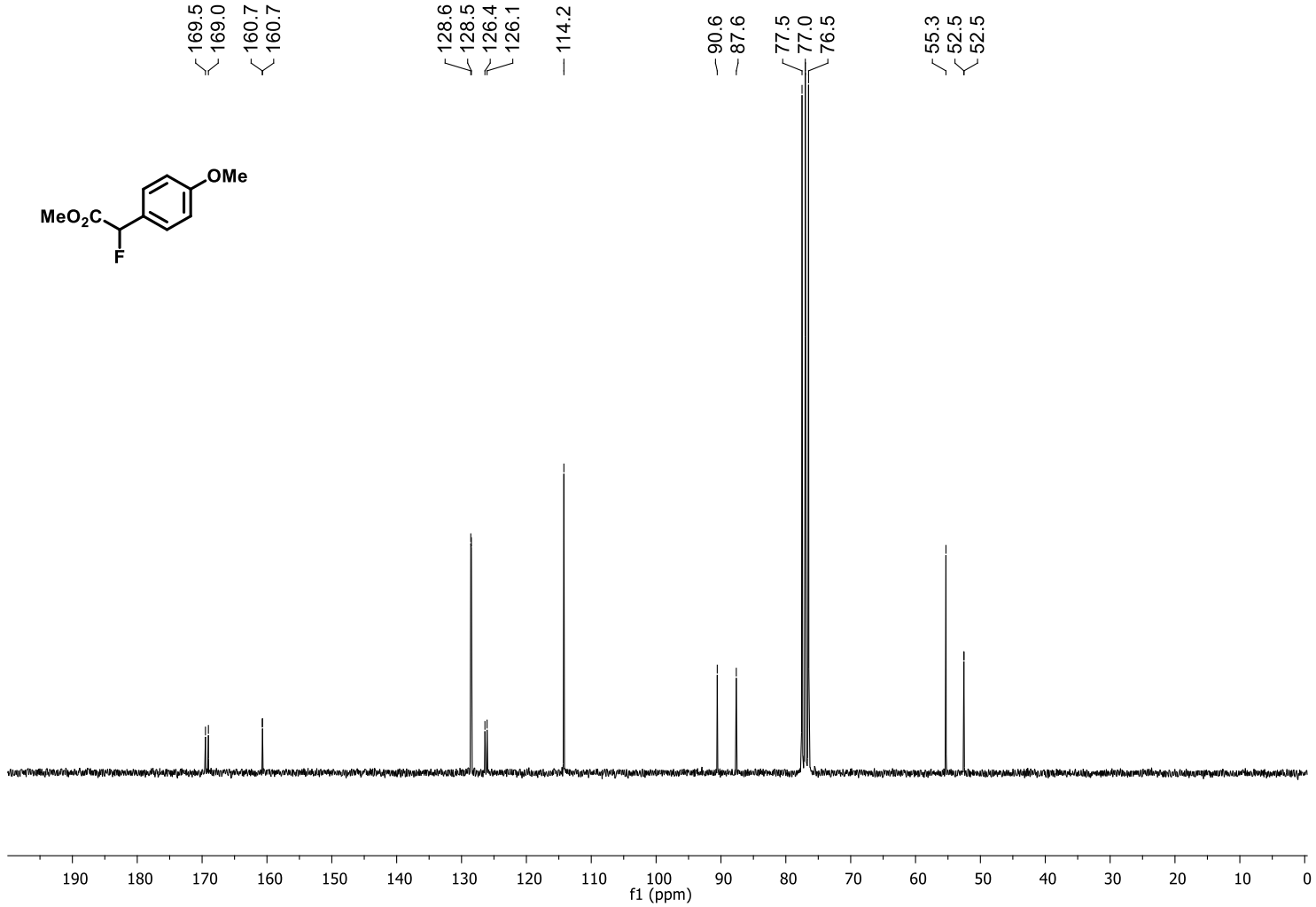
**18q - $^{19}$F NMR (235 MHz, $CDCl_3$)**



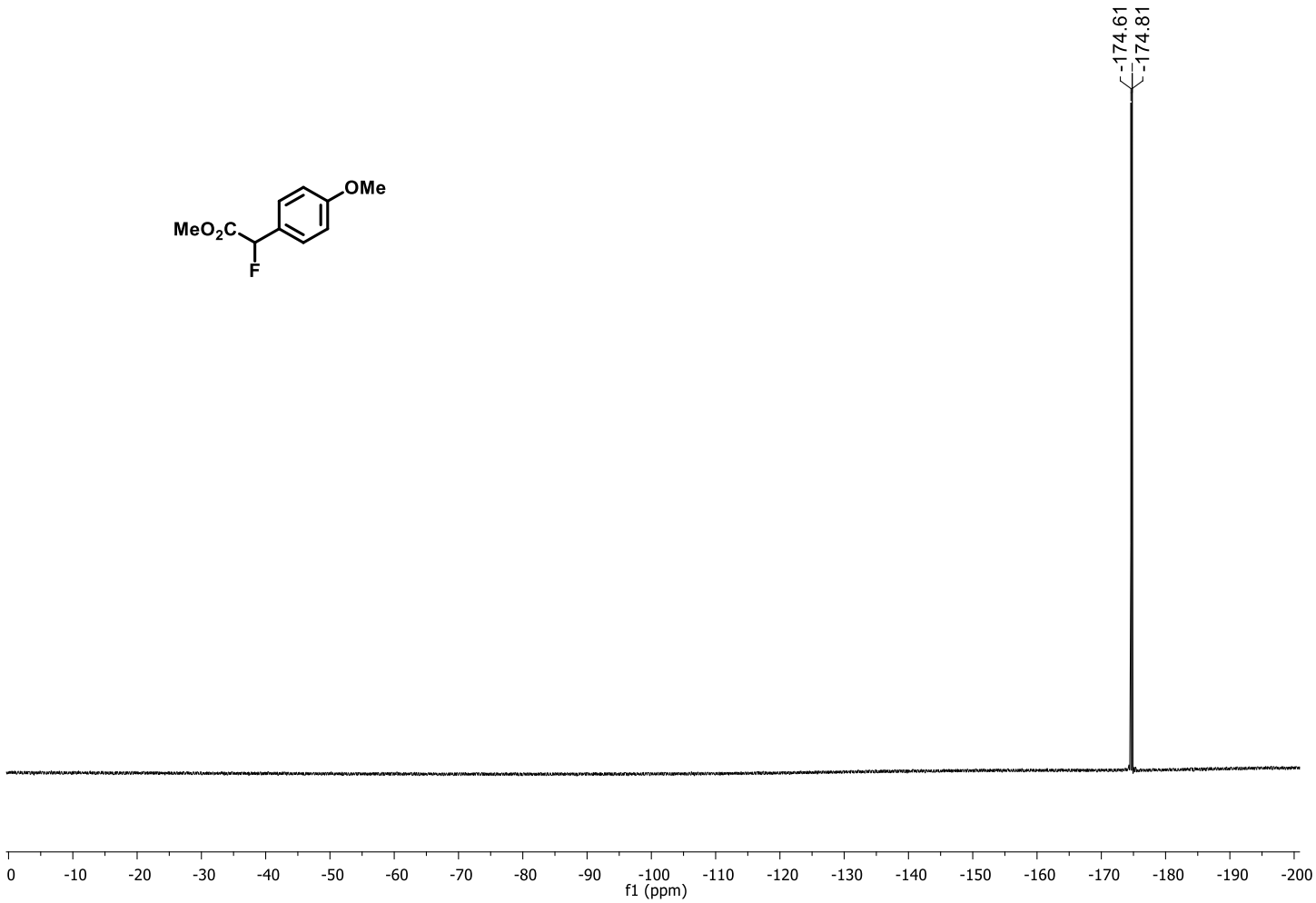
**18r - $^{1}$H NMR (250 MHz, $CDCl_3$)**



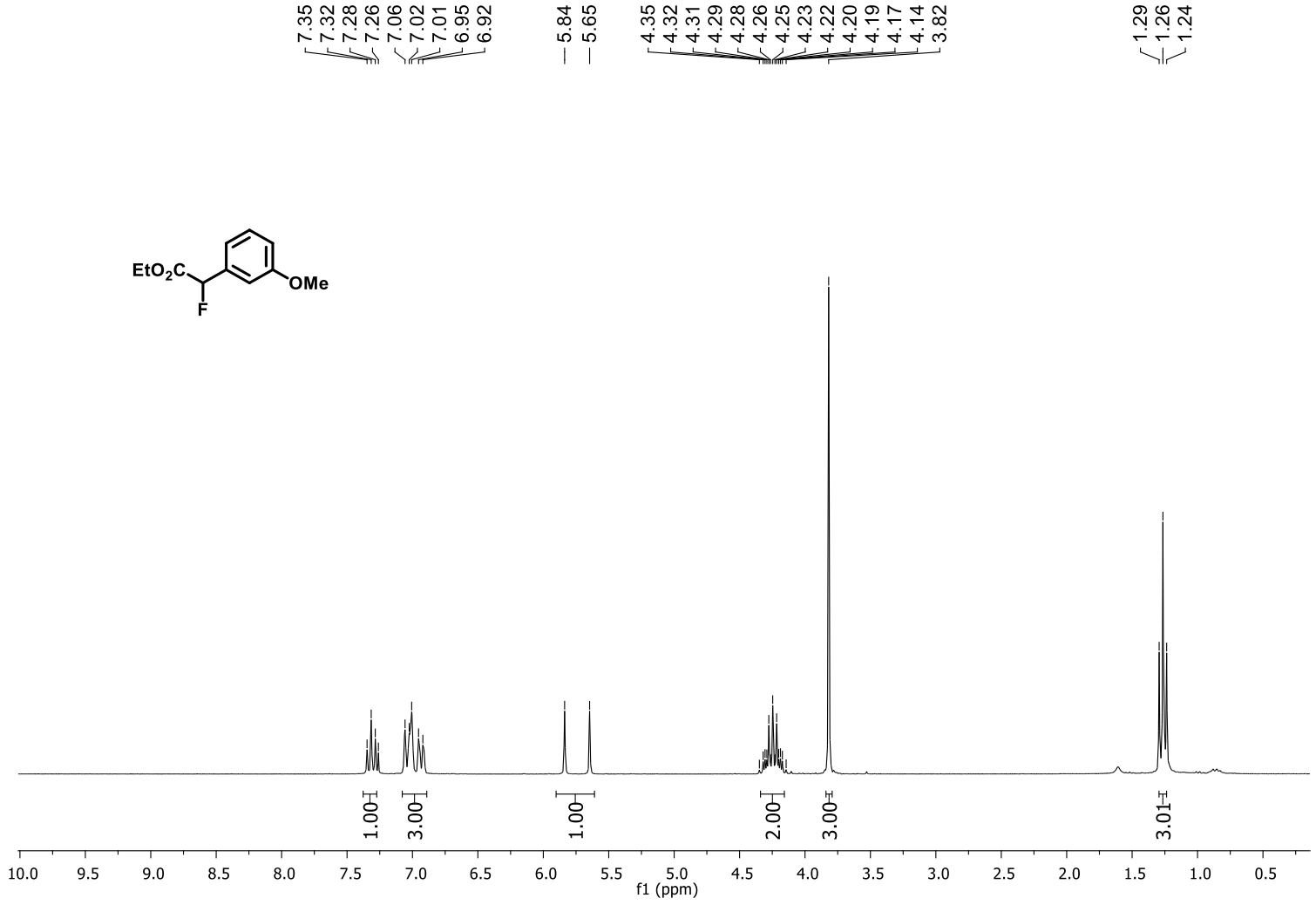
**18r - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



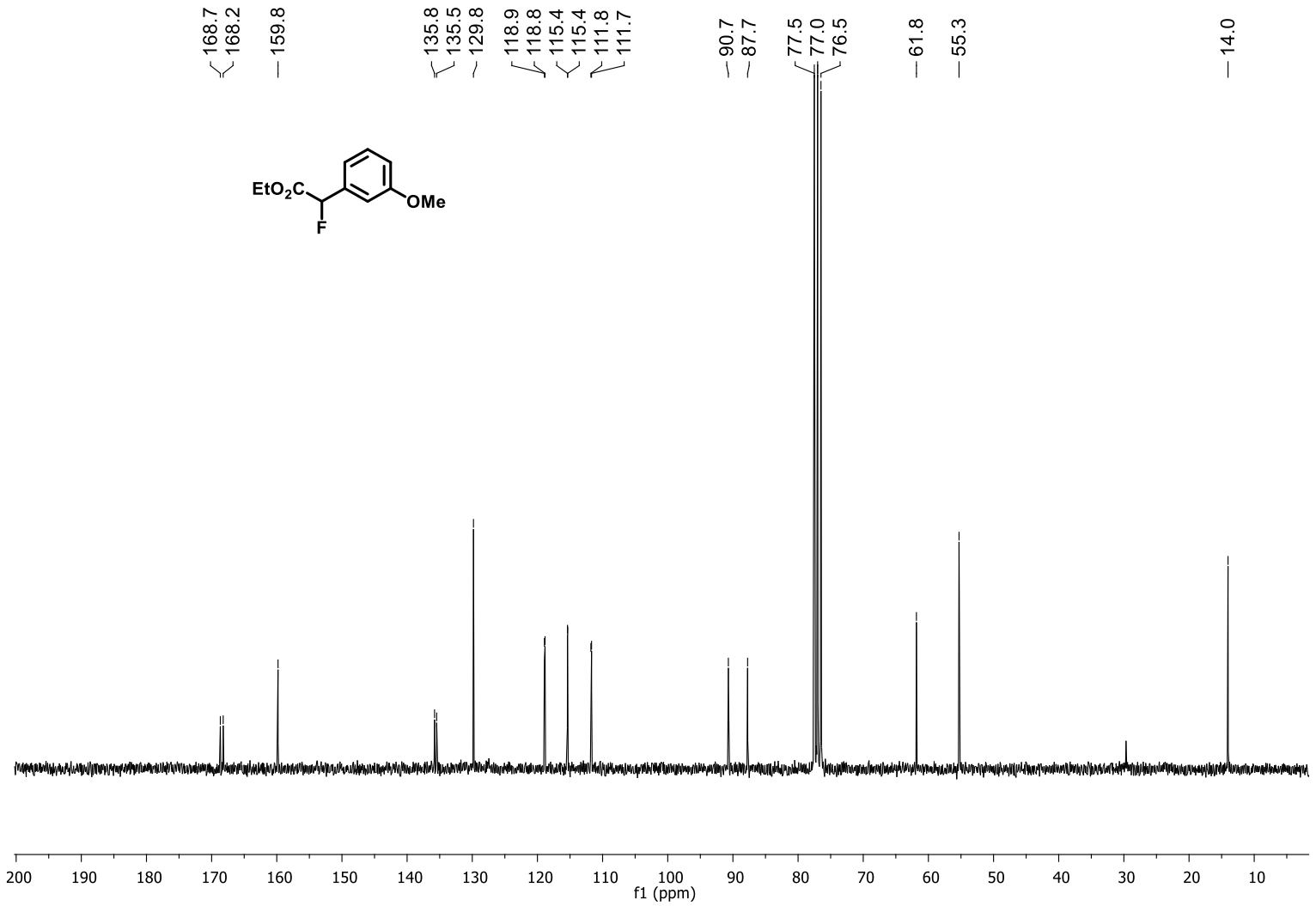
**18r - $^{19}$F NMR (235 MHz, $CDCl_3$)**



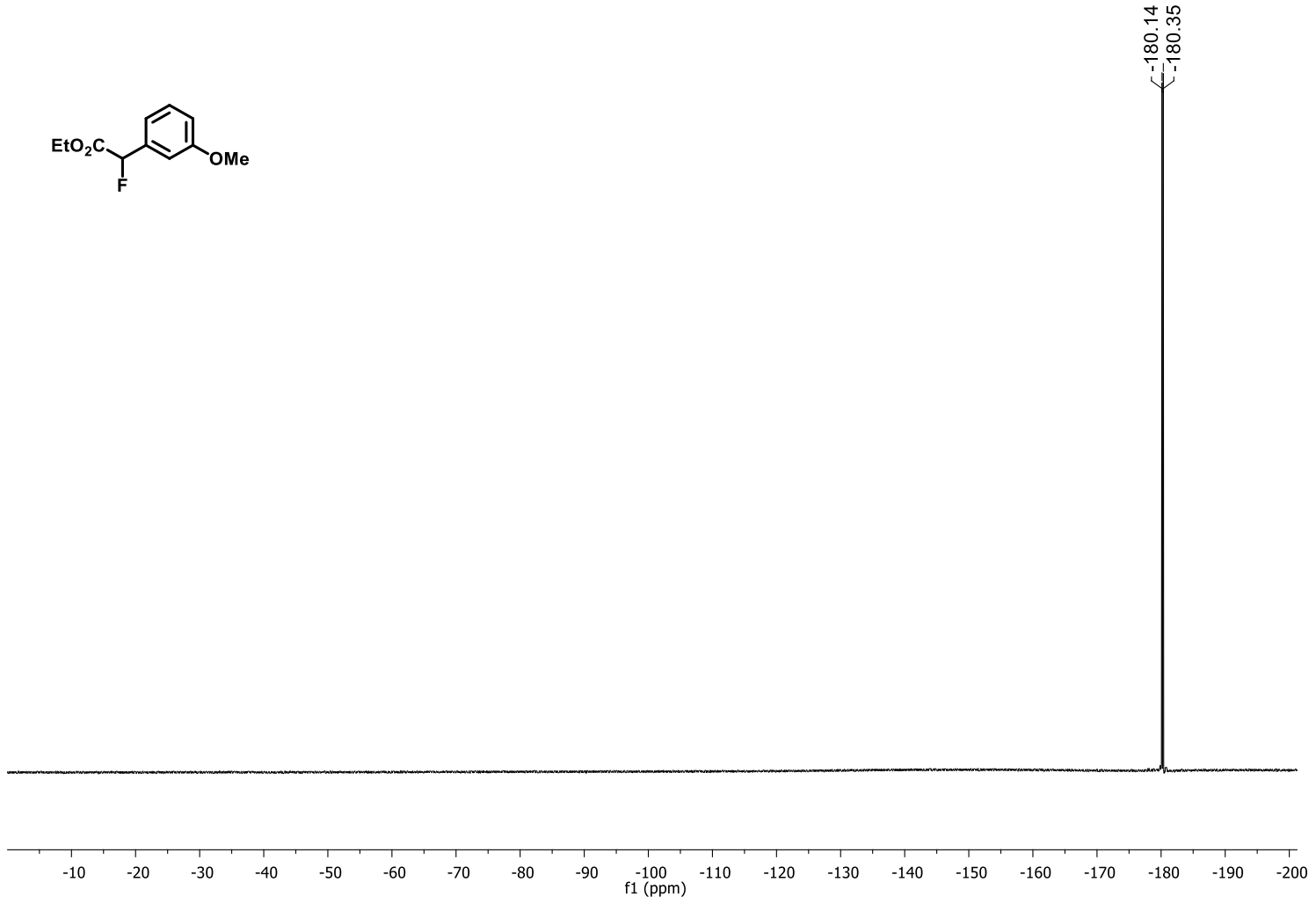
**18s - $^{1}$H NMR (250 MHz, $CDCl_3$)**



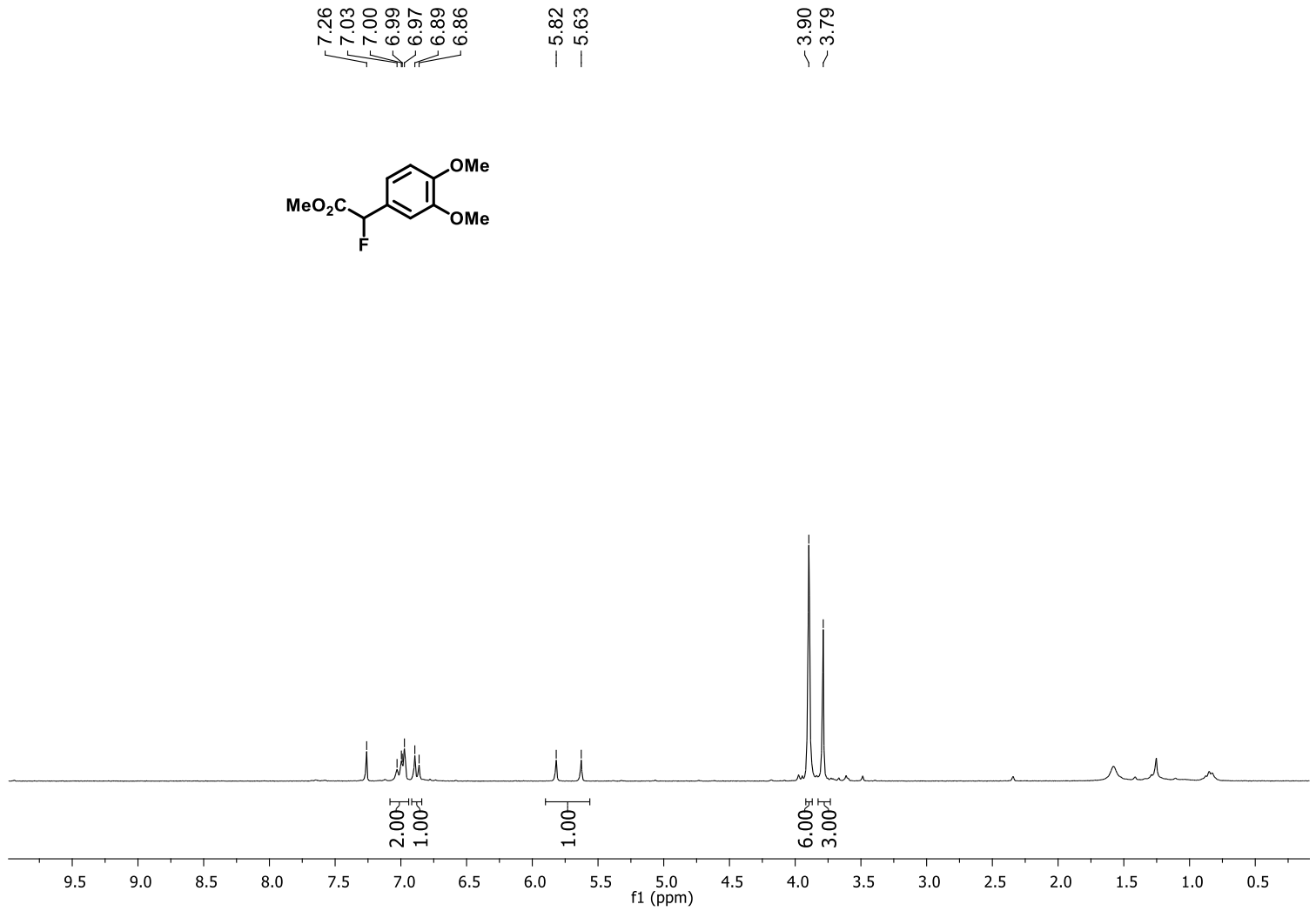
**18s - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



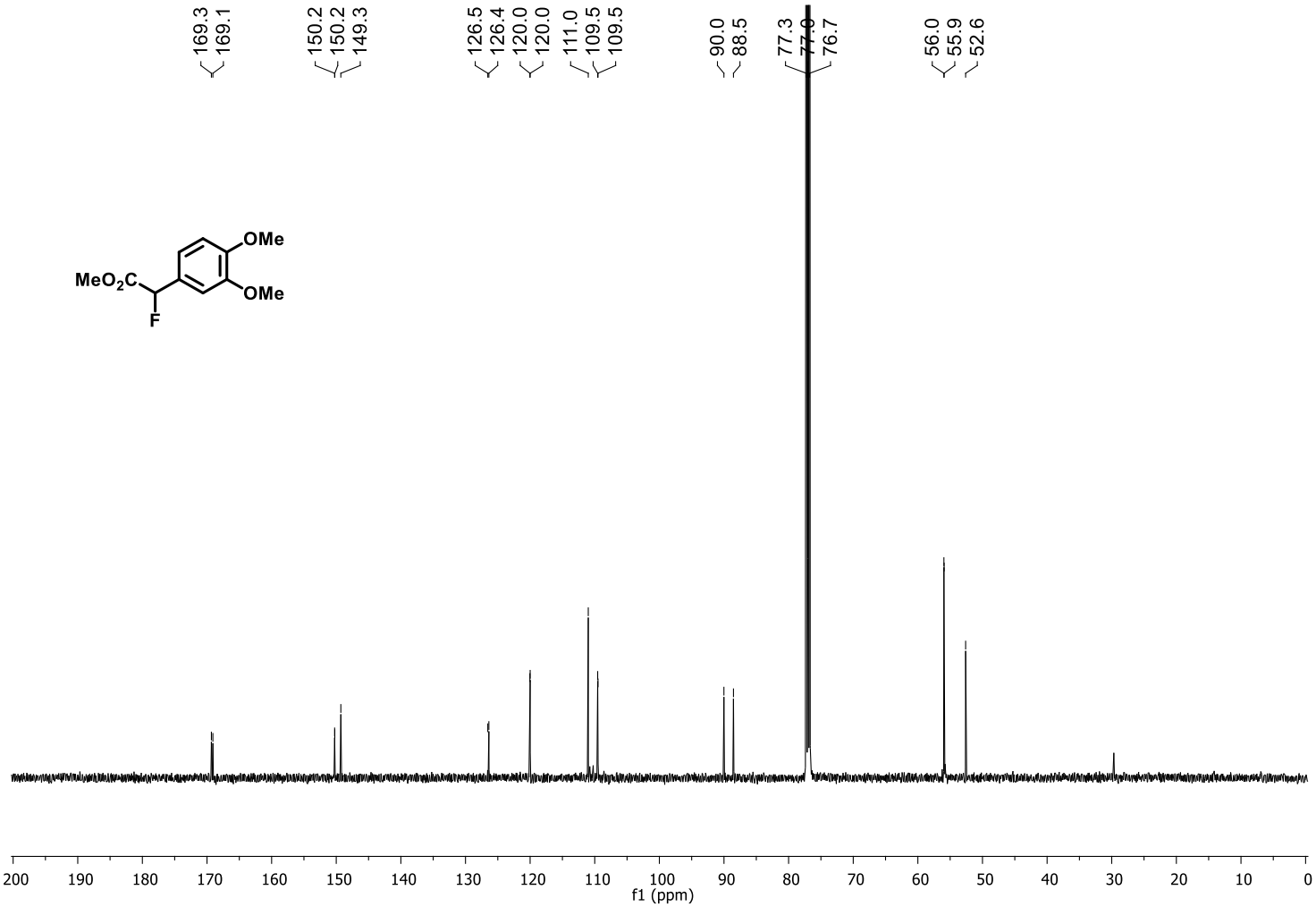
**18s - $^{19}$F NMR (235 MHz, $CDCl_3$)**



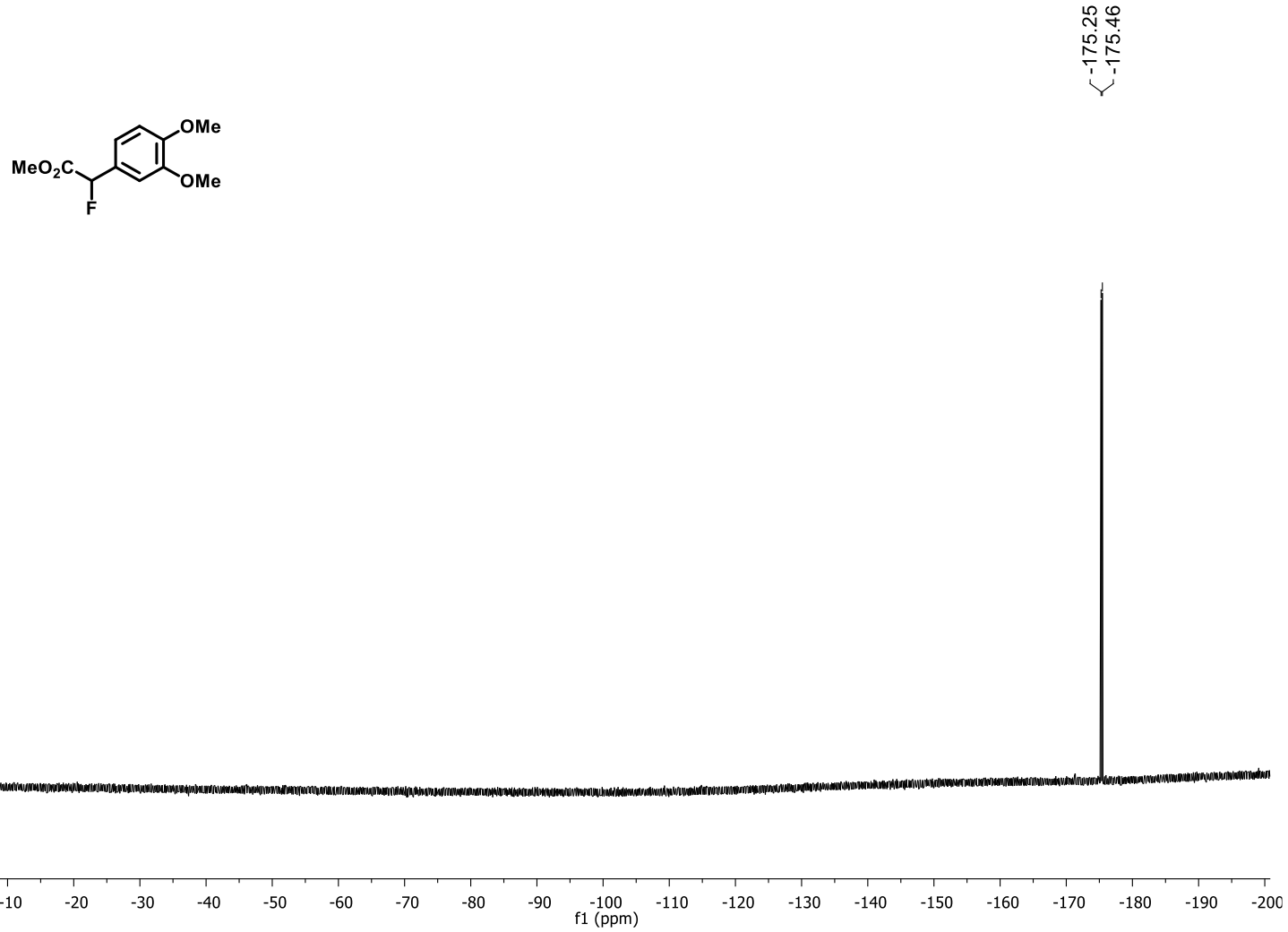
**18t -$^{1}$H NMR (250 MHz, $CDCl_3$)**



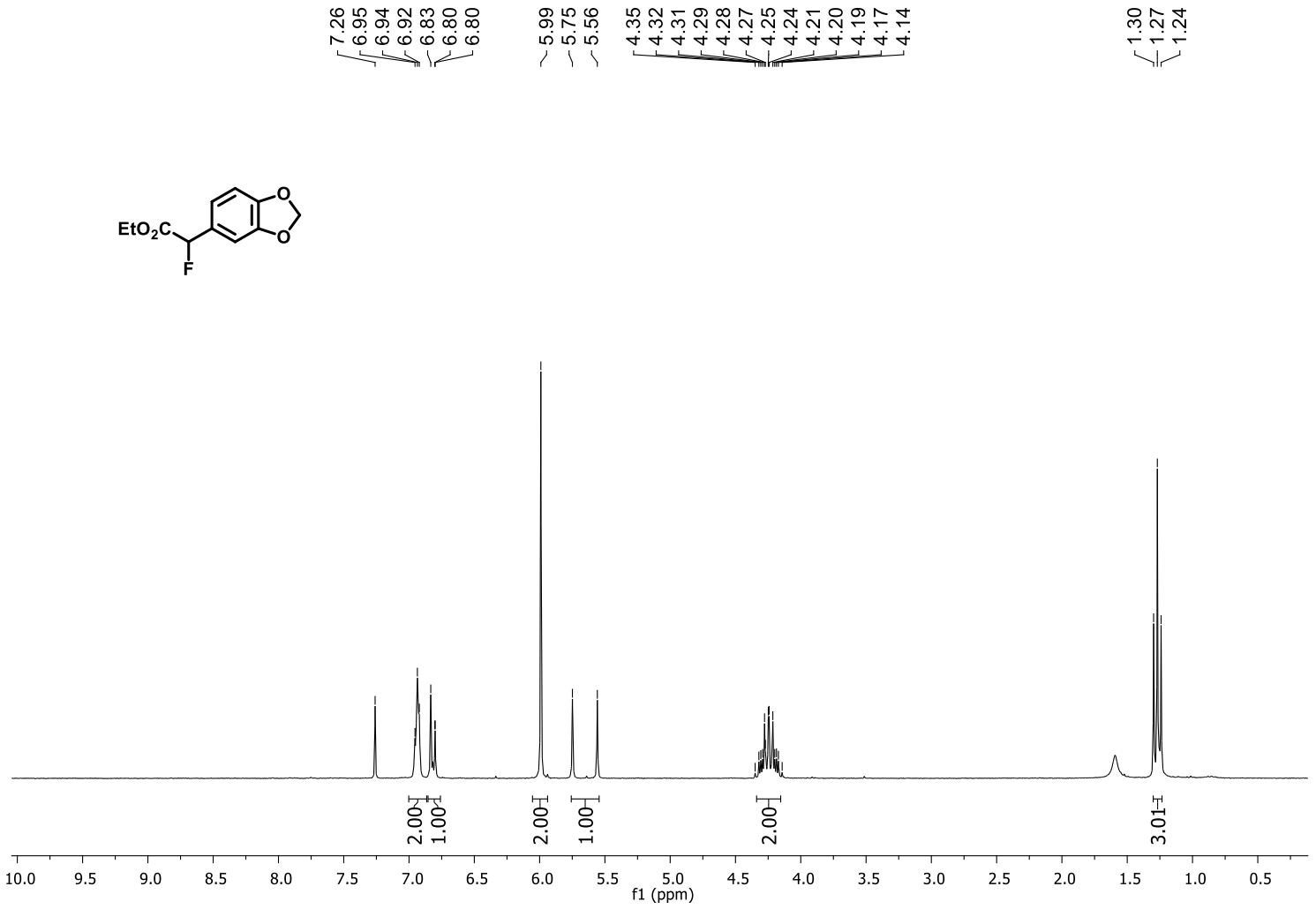
**18t - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



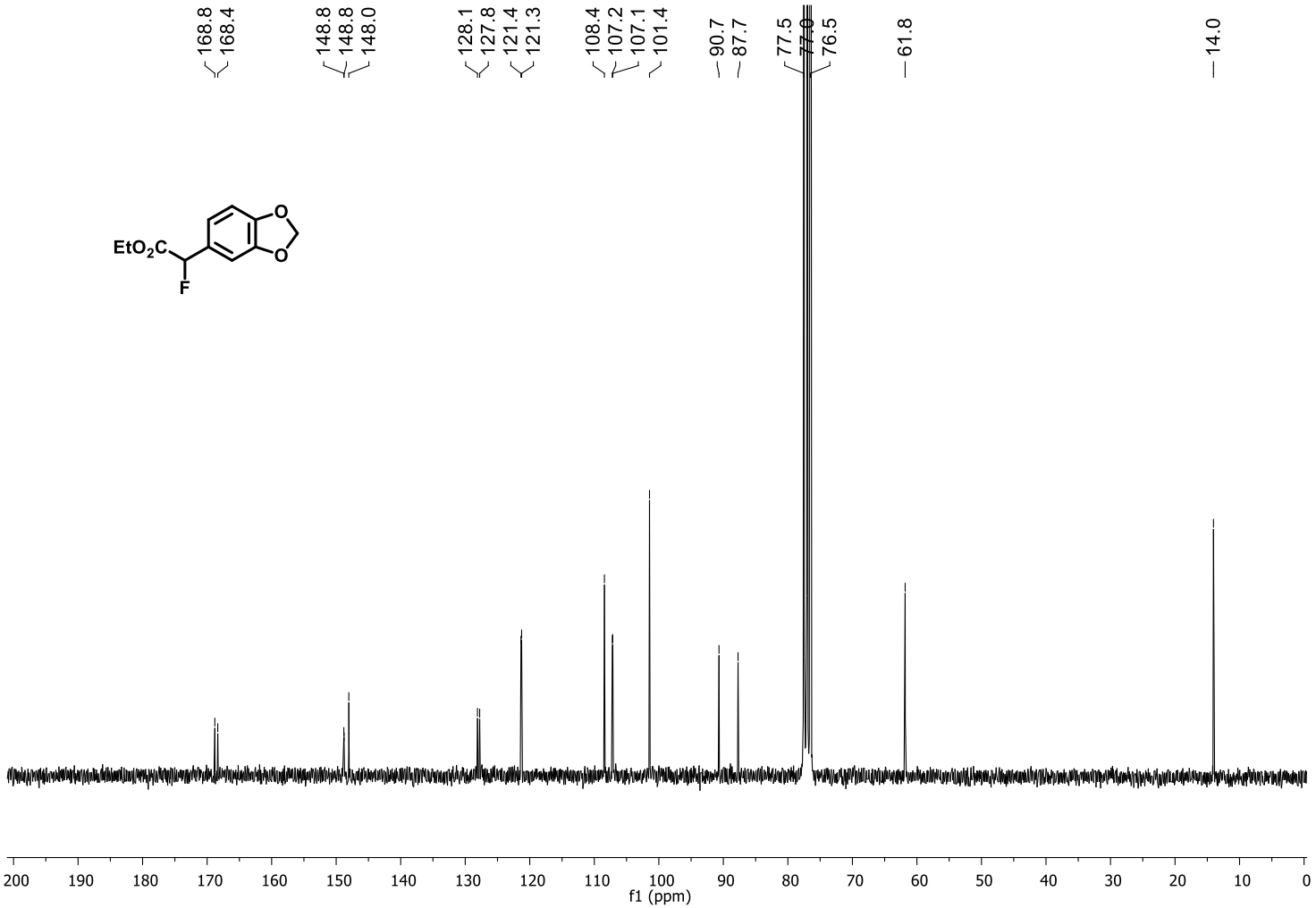
**18t - $^{19}$F NMR (235 MHz, $CDCl_3$)**



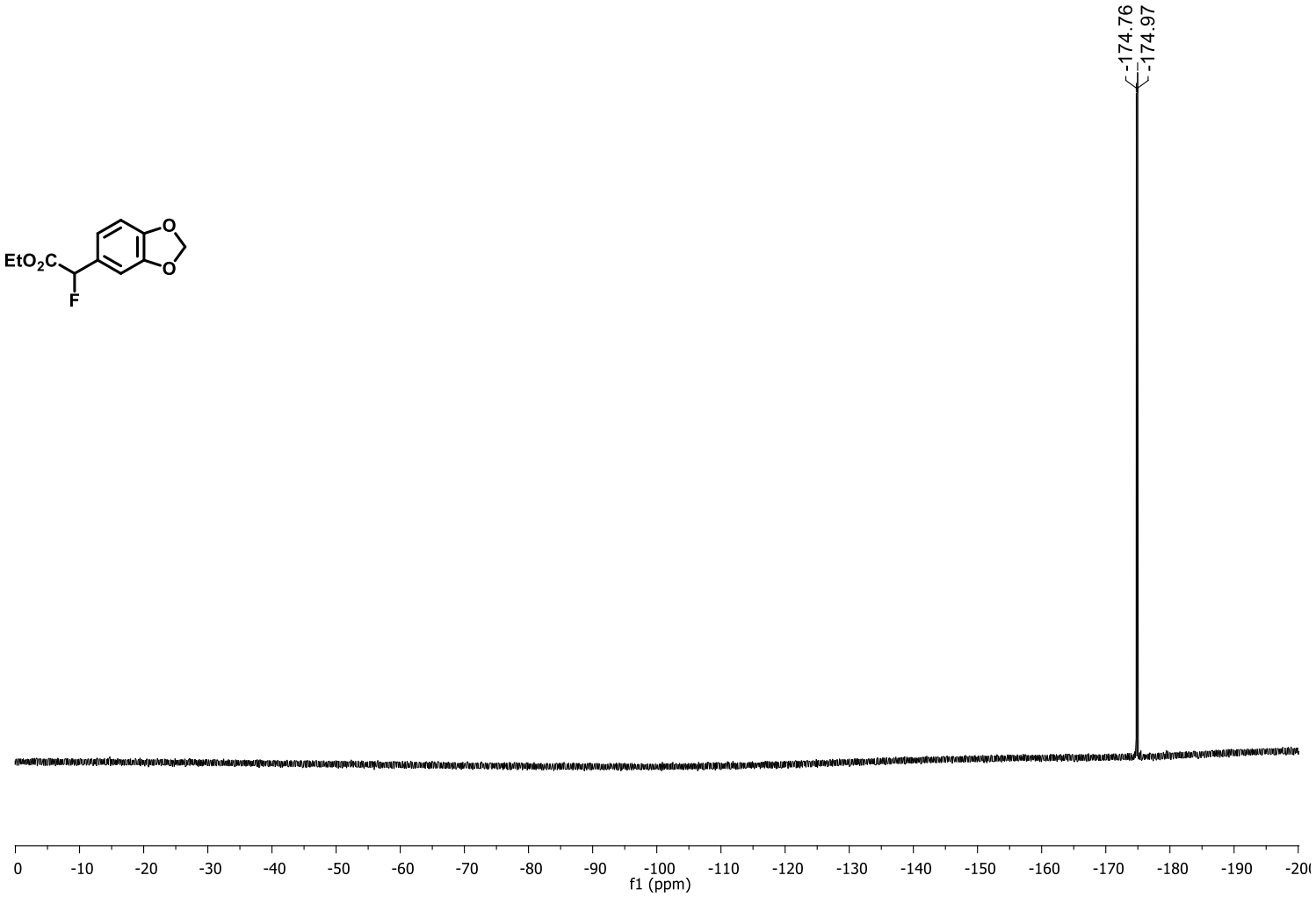
**18u - $^{1}$H NMR (250 MHz, $CDCl_3$)**



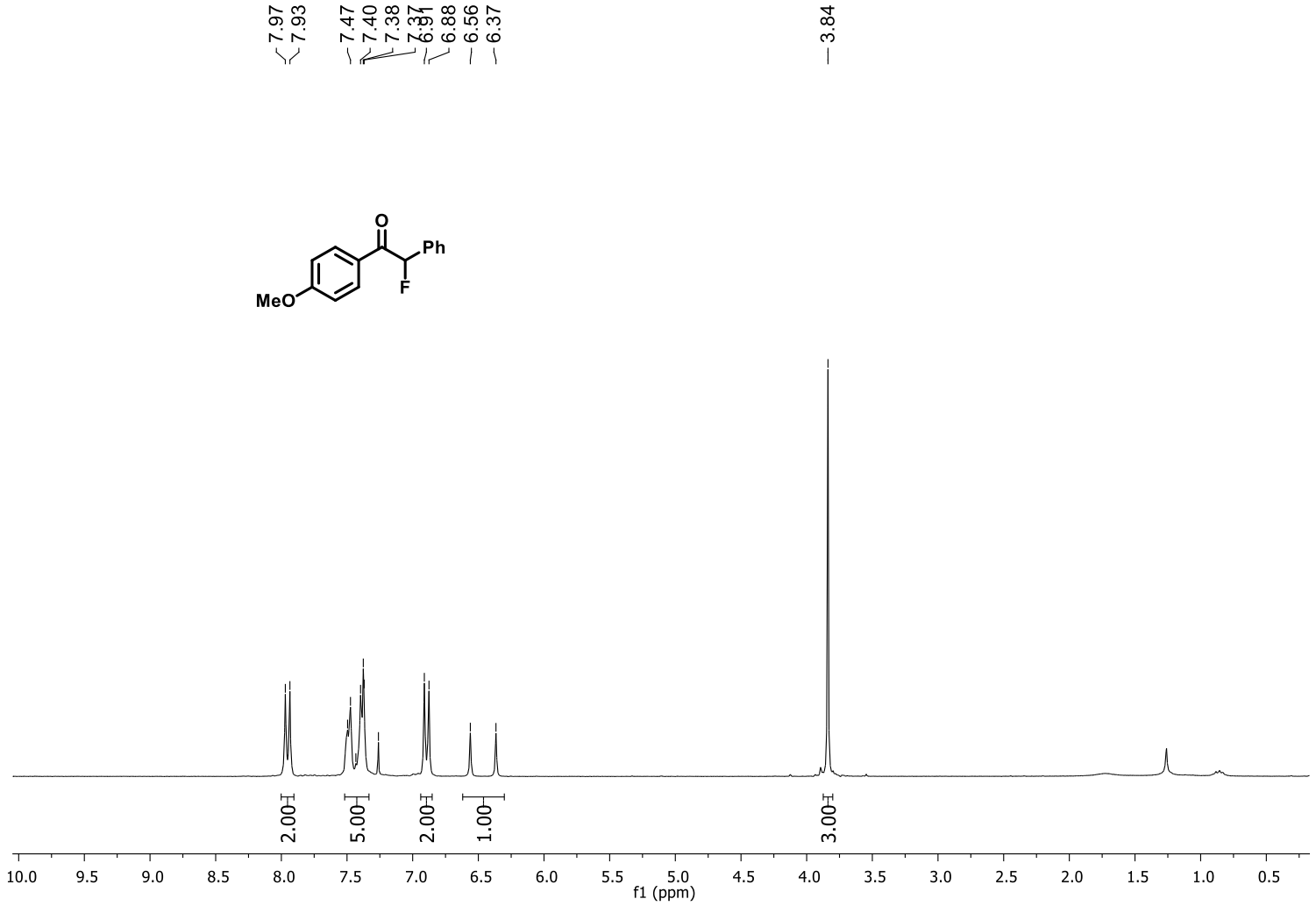
**18u - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



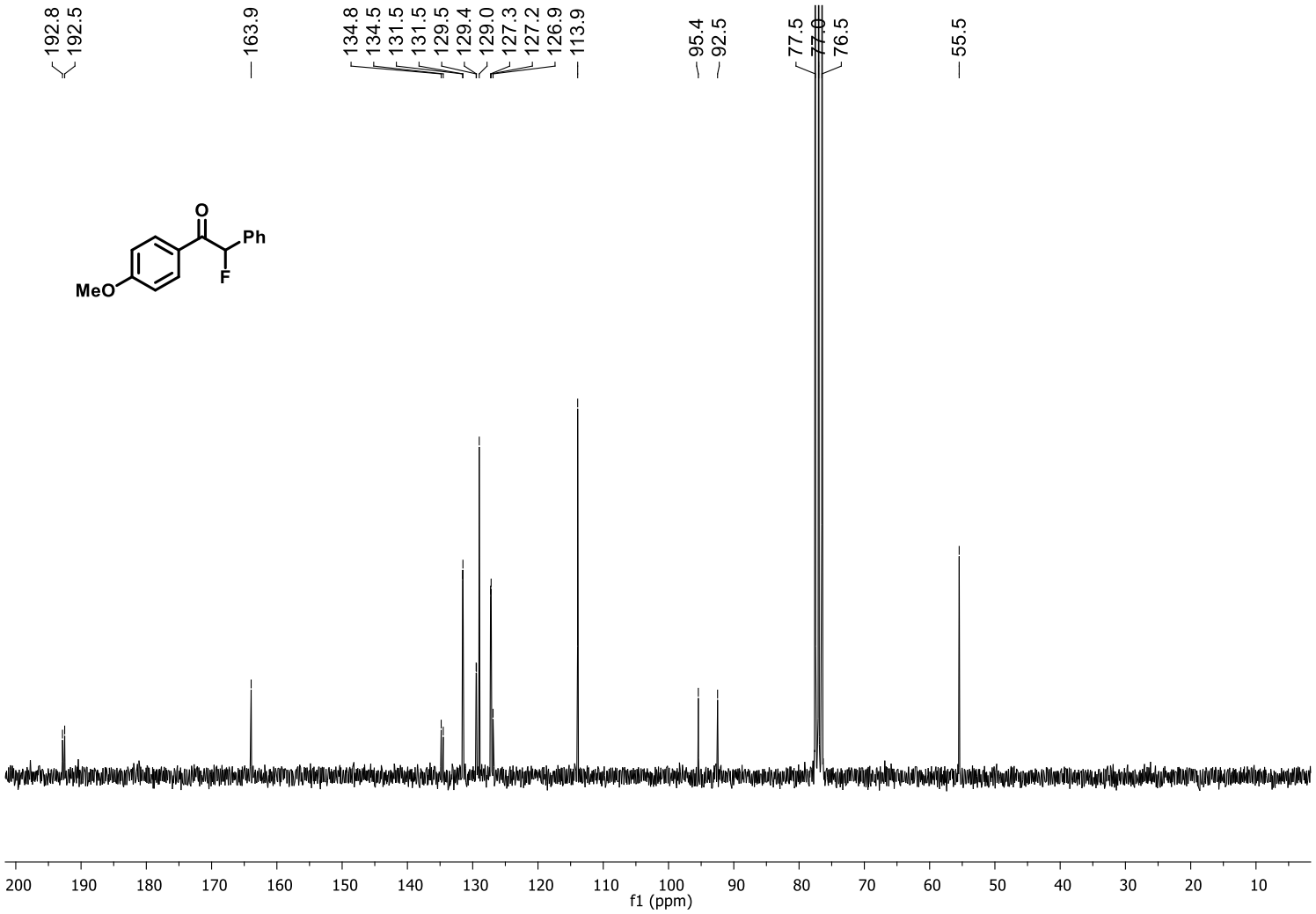
**18u - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



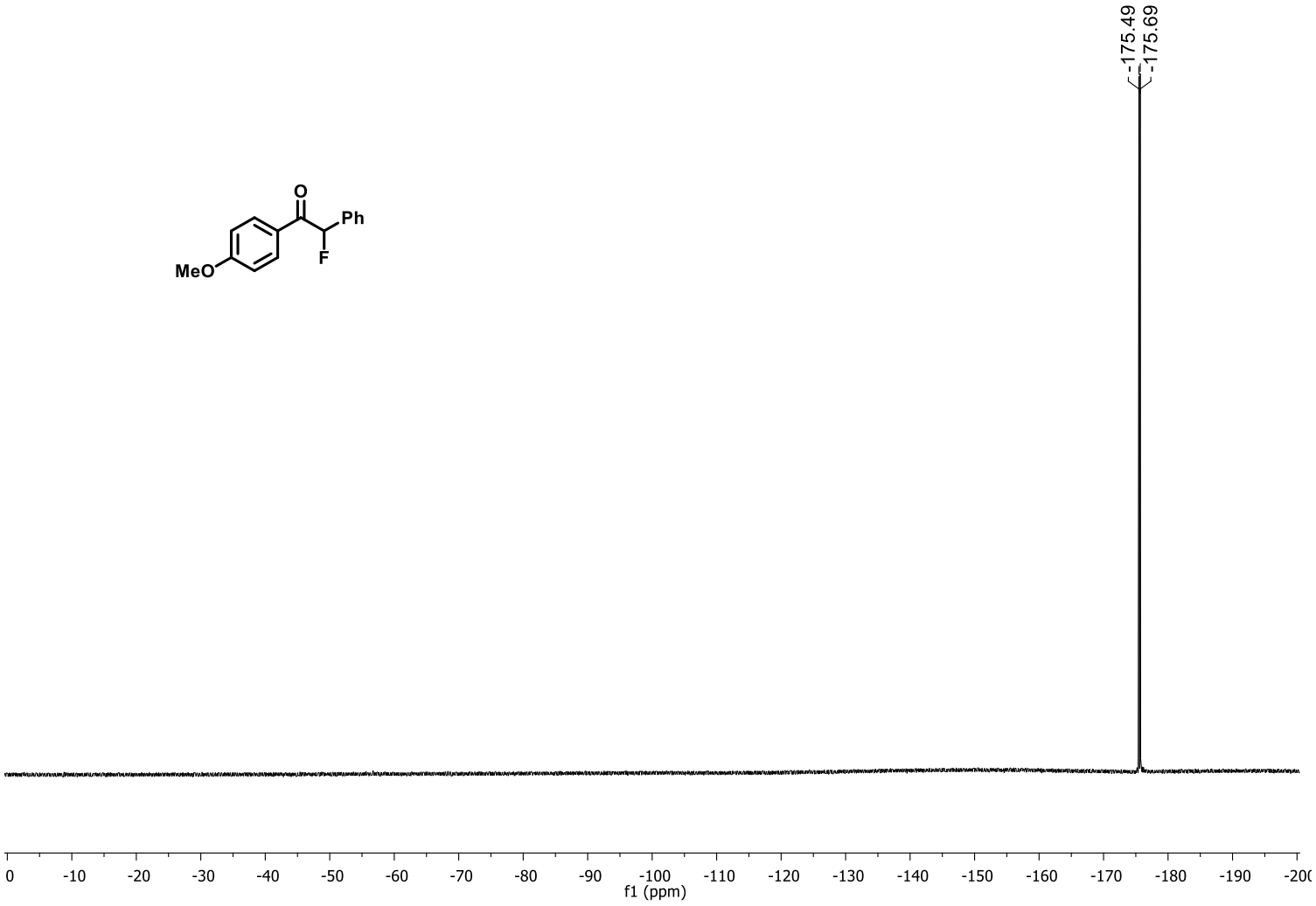
**18y - $^{1}$H NMR (250 MHz, $CDCl_3$)**



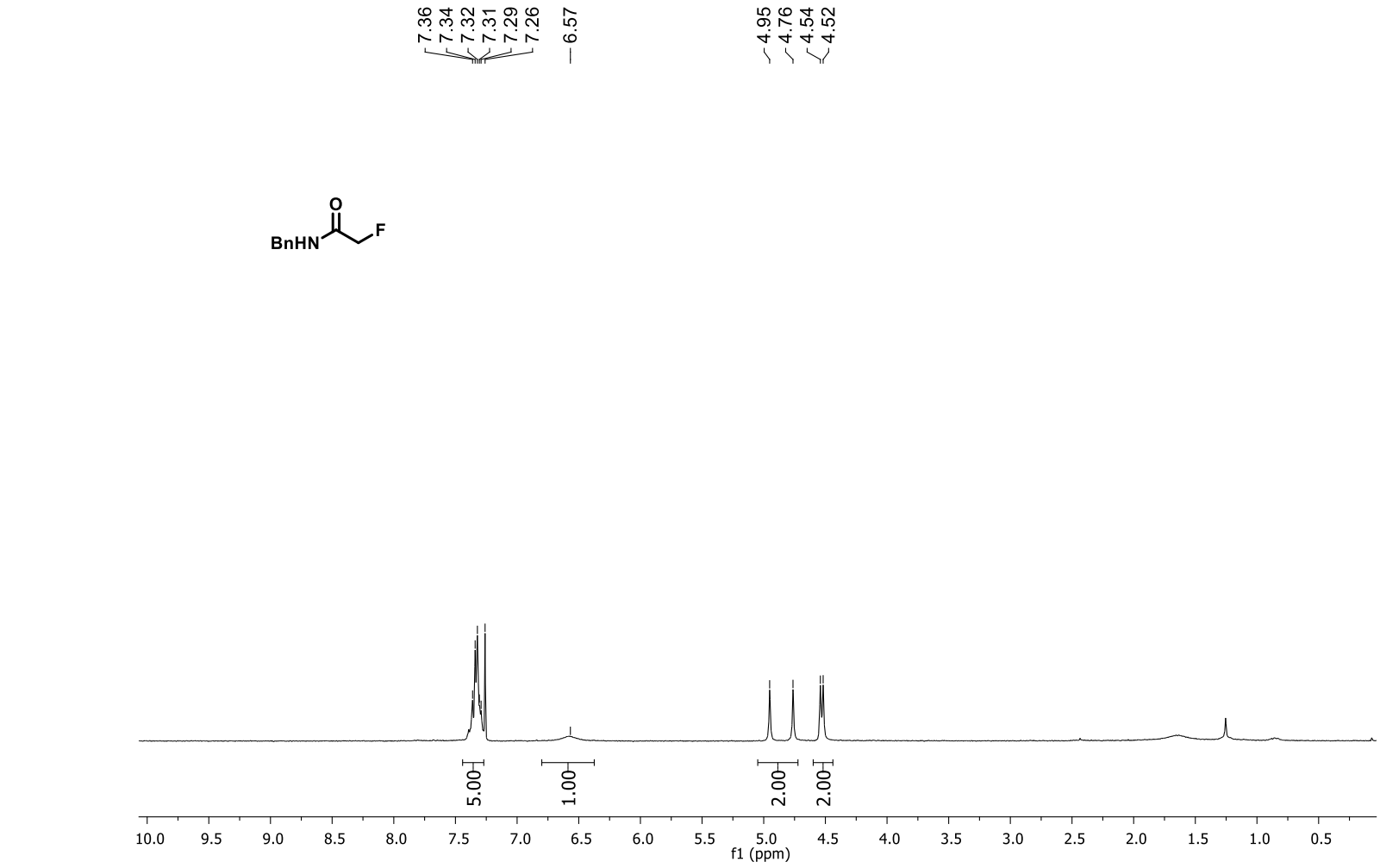
**18y - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



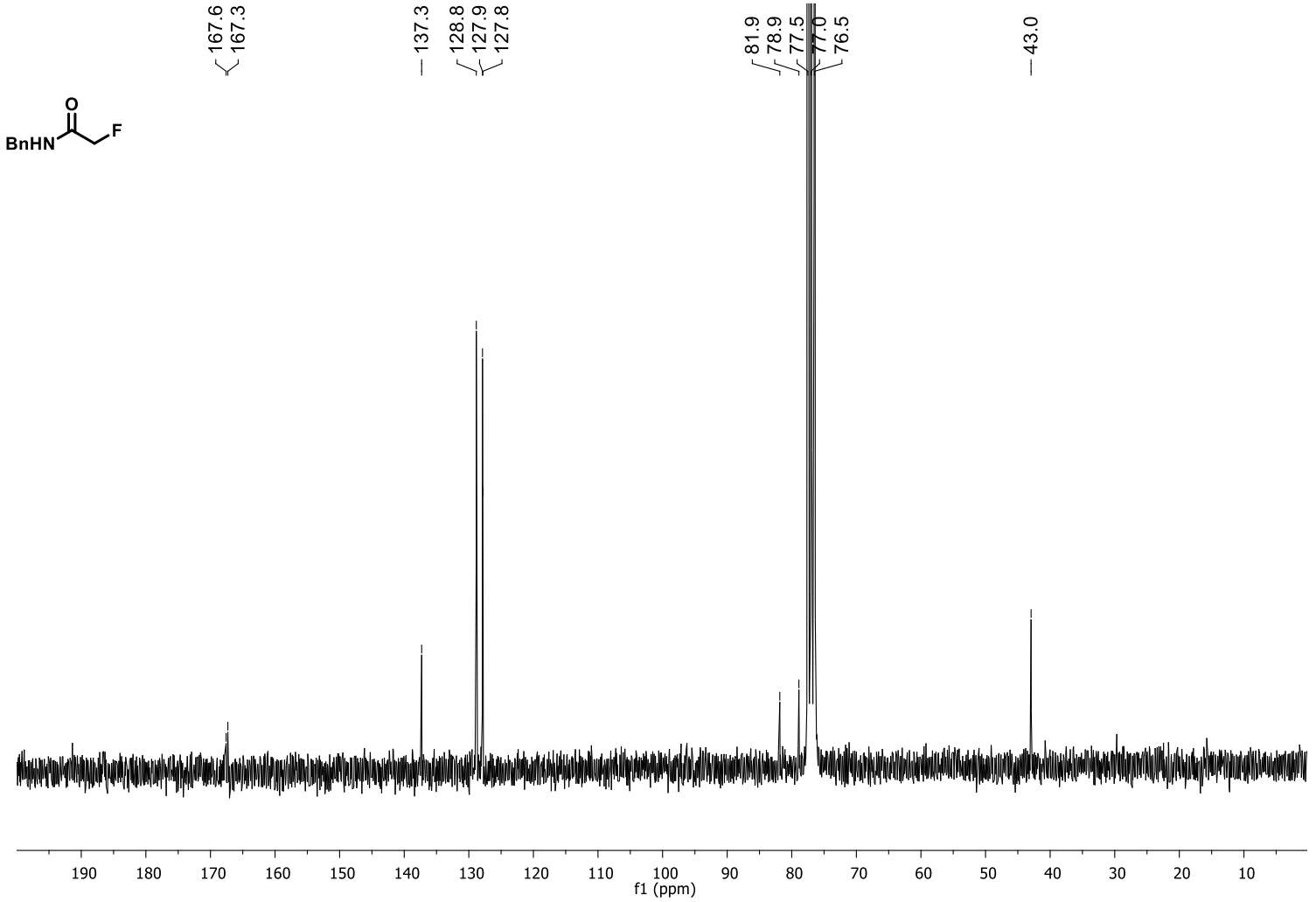
**18y - $^{19}$F NMR (235 MHz, $CDCl_3$)**



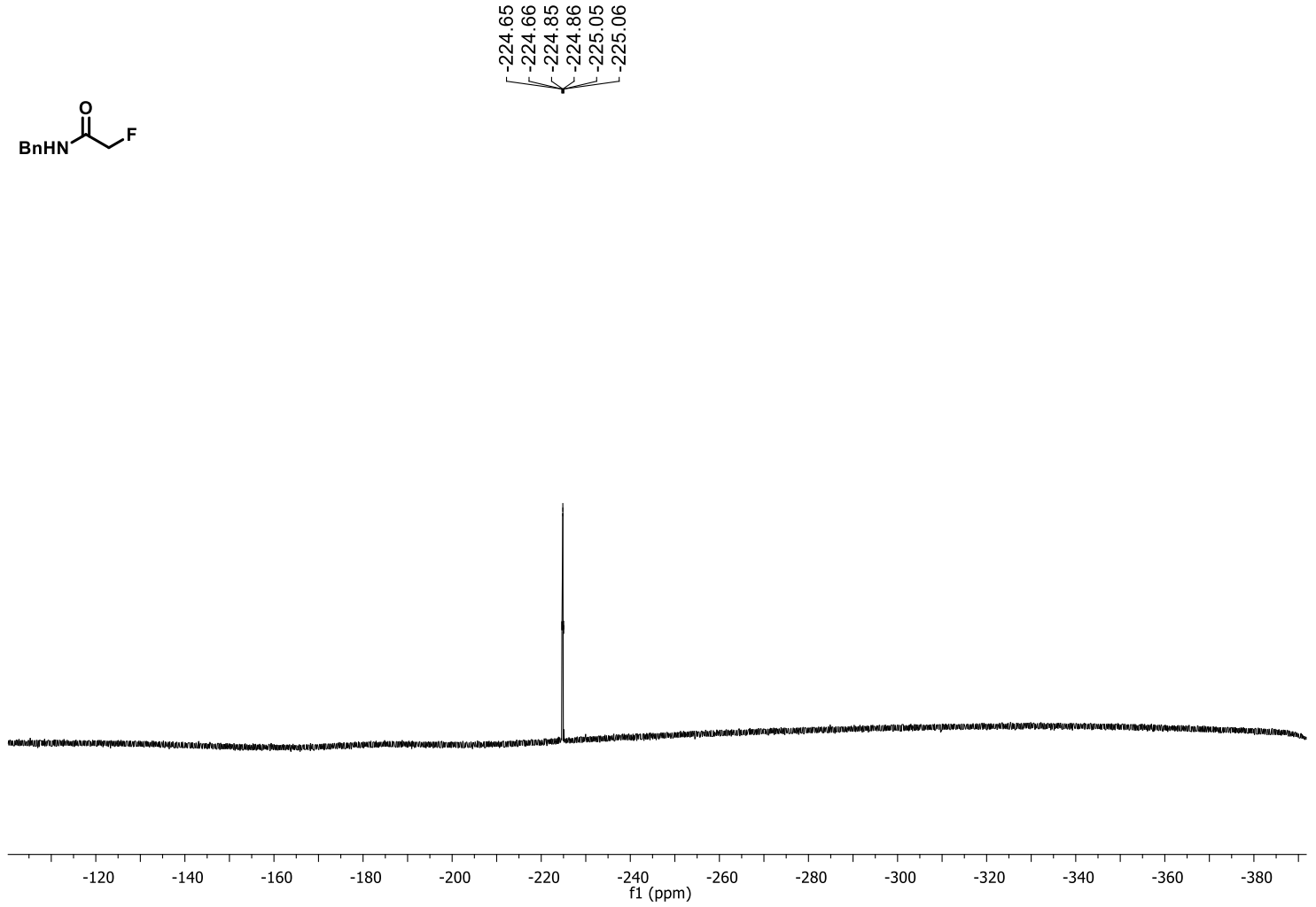
**18z - $^{1}$H NMR (250 MHz, $CDCl_3$)**



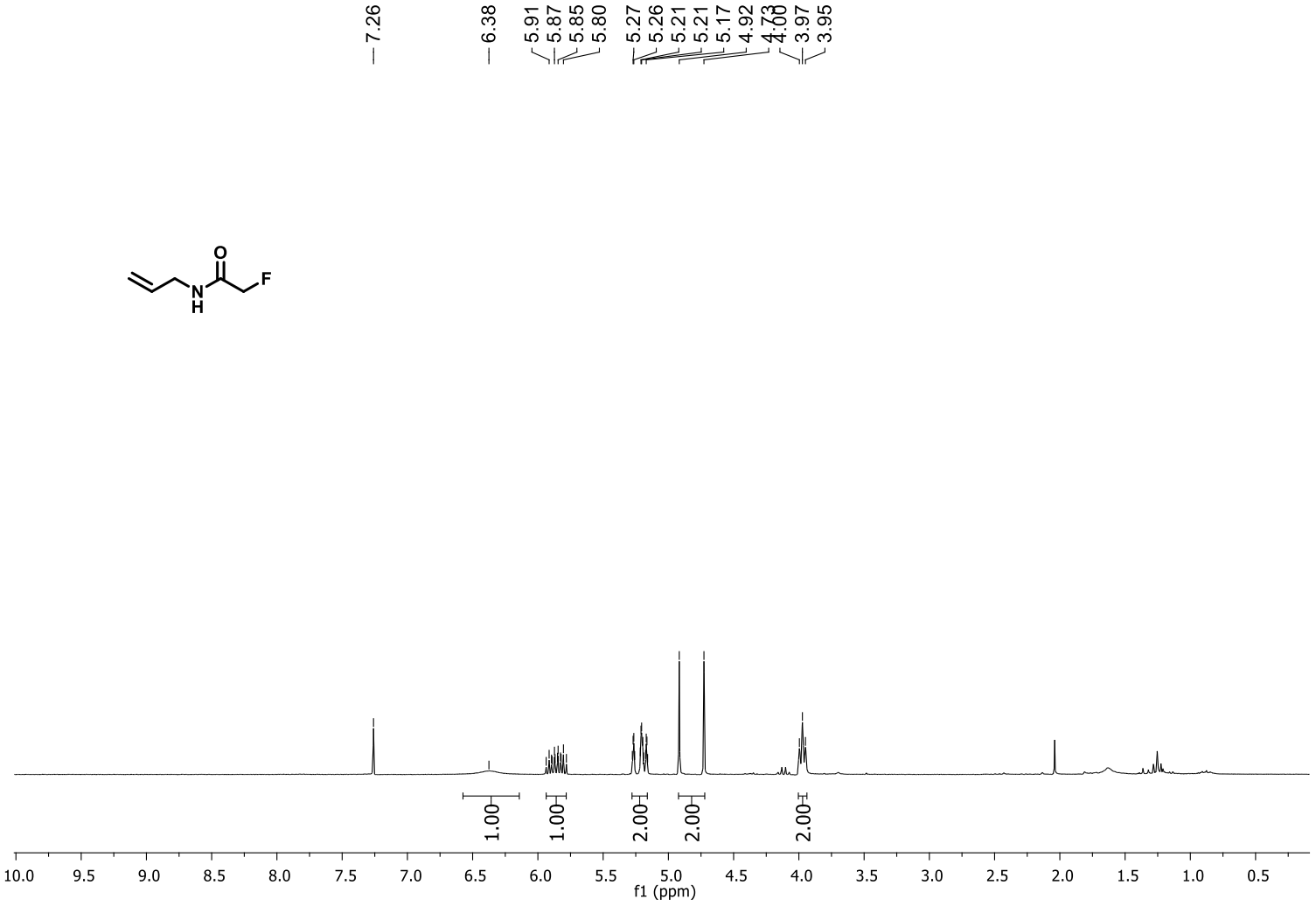
**18z - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



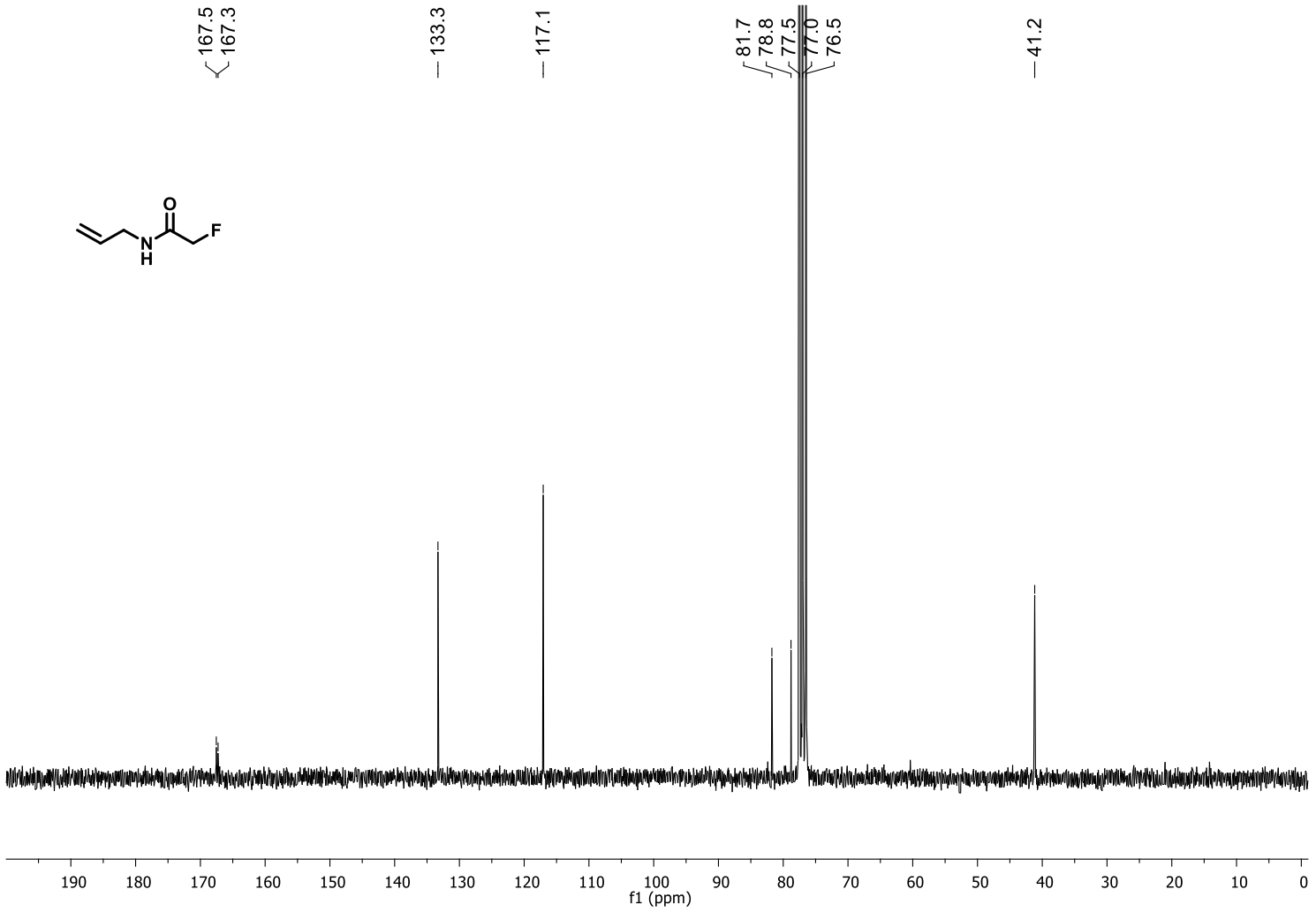
**18z - $^{19}F$ NMR (235 MHz, $CDCl_3$)**



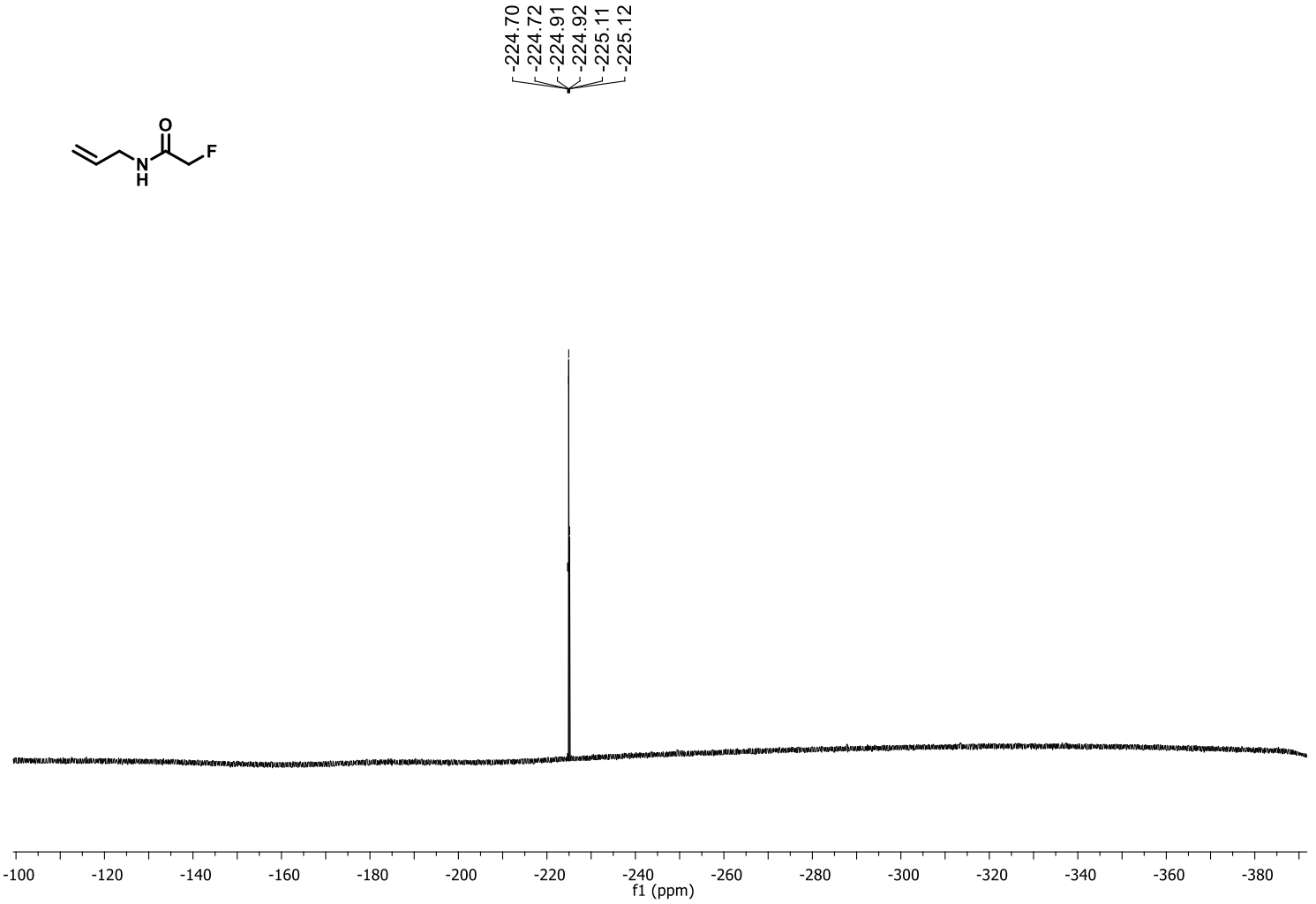
**3aa - $^{1}$H NMR (250 MHz, $CDCl_3$)**



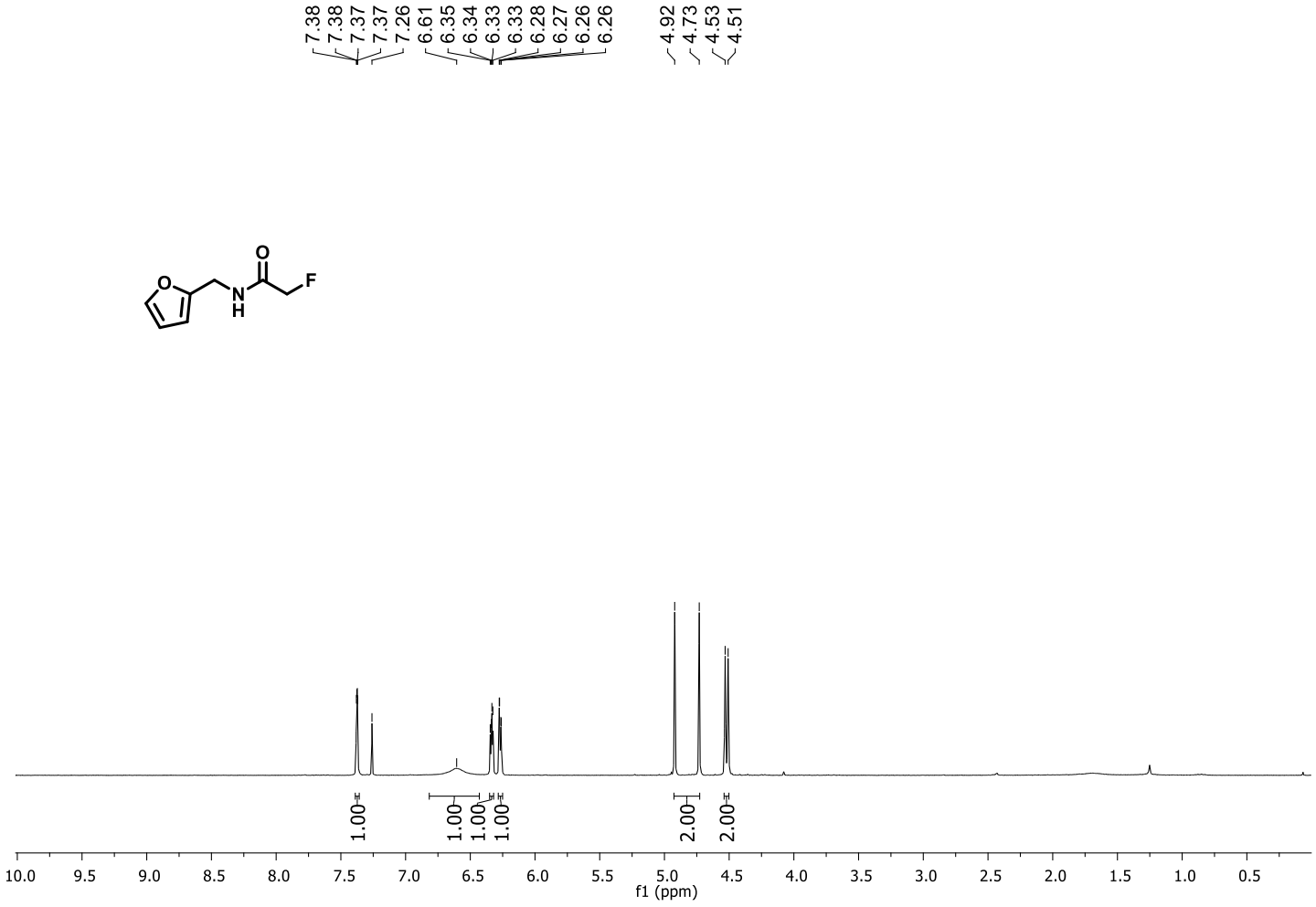
**3aa - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



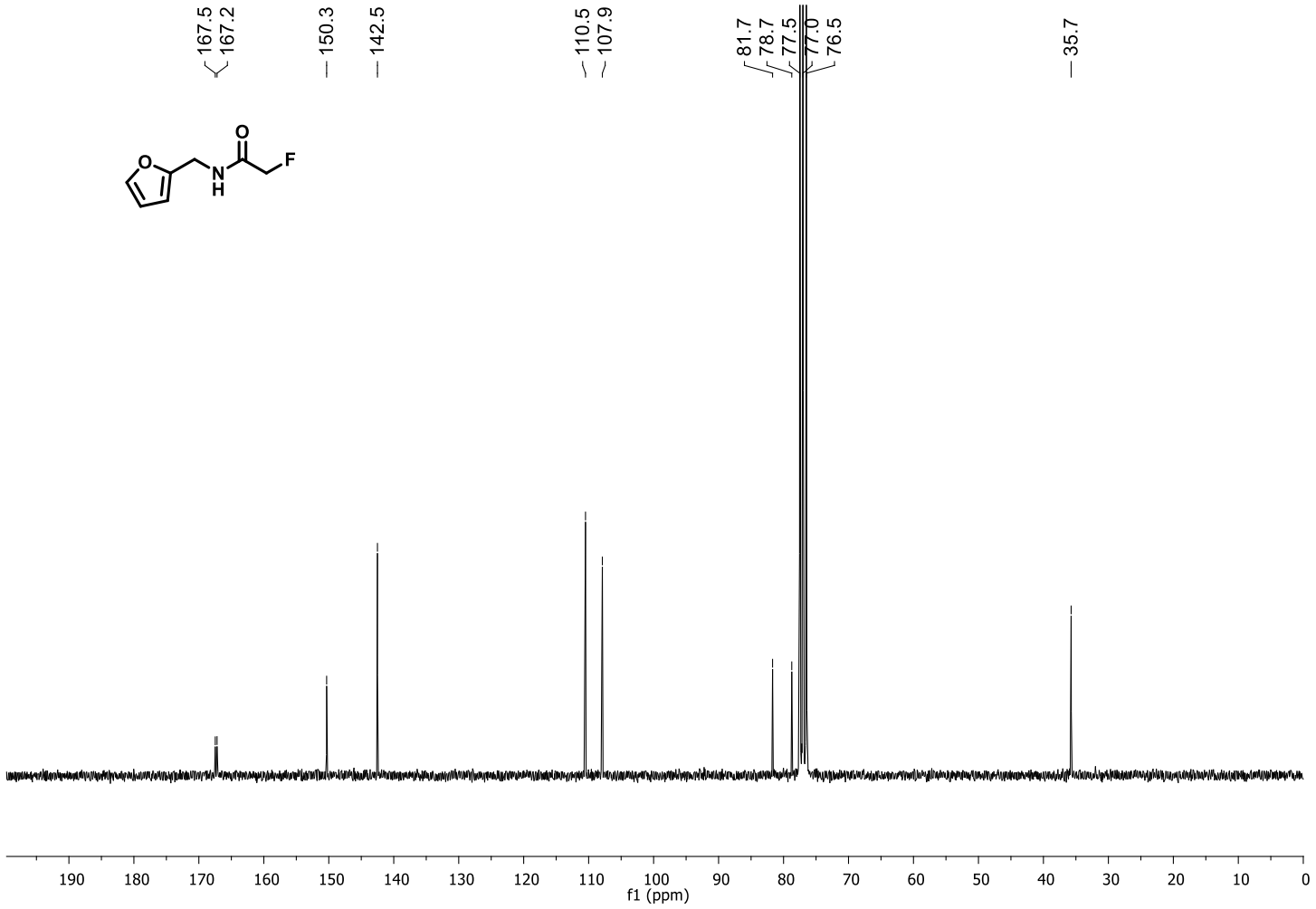
**3aa - $^{19}$F NMR (235 MHz, $CDCl_3$)**



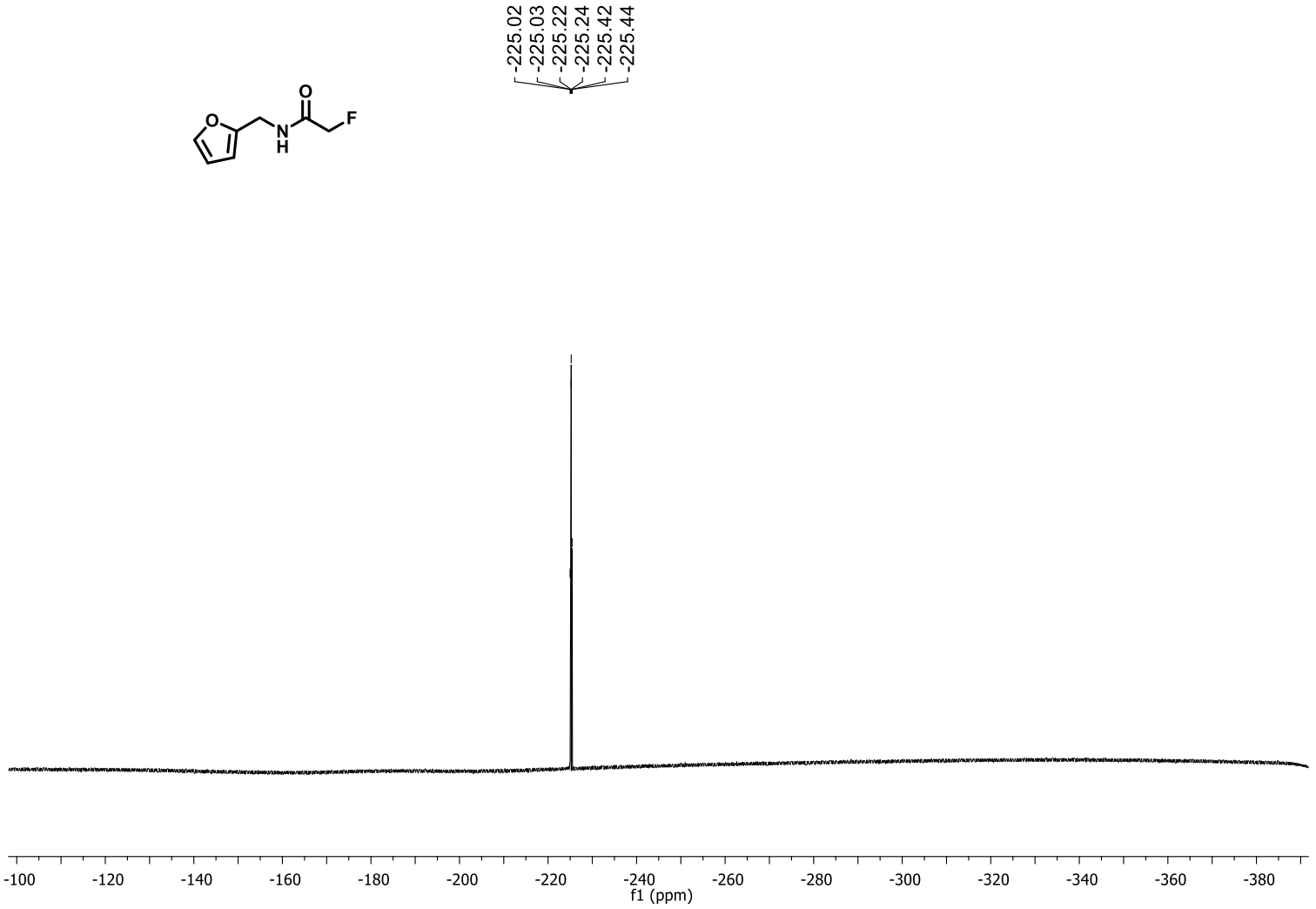
**18bb - $^{1}$H NMR (250 MHz, $CDCl_3$)**



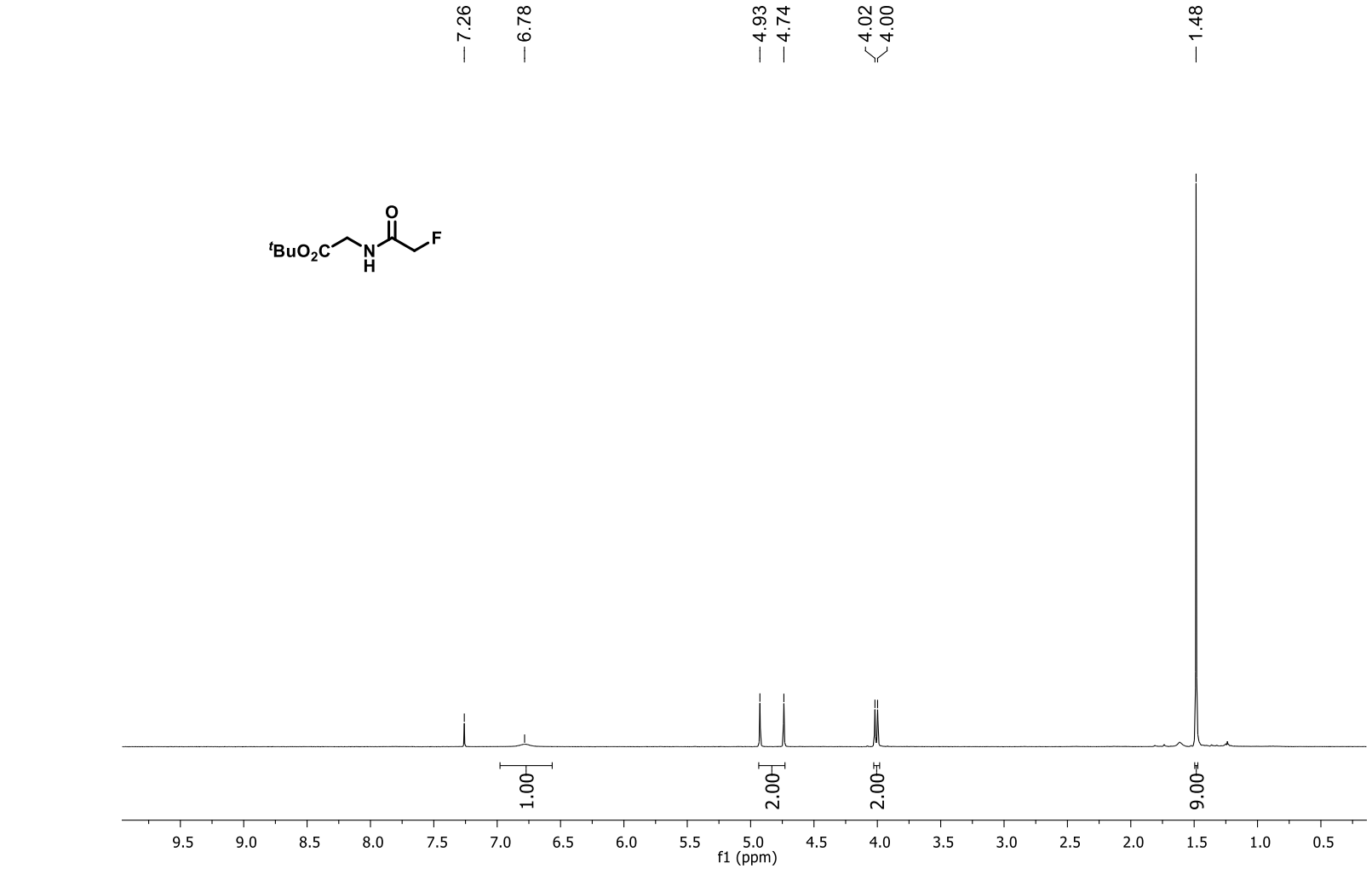
**18bb - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



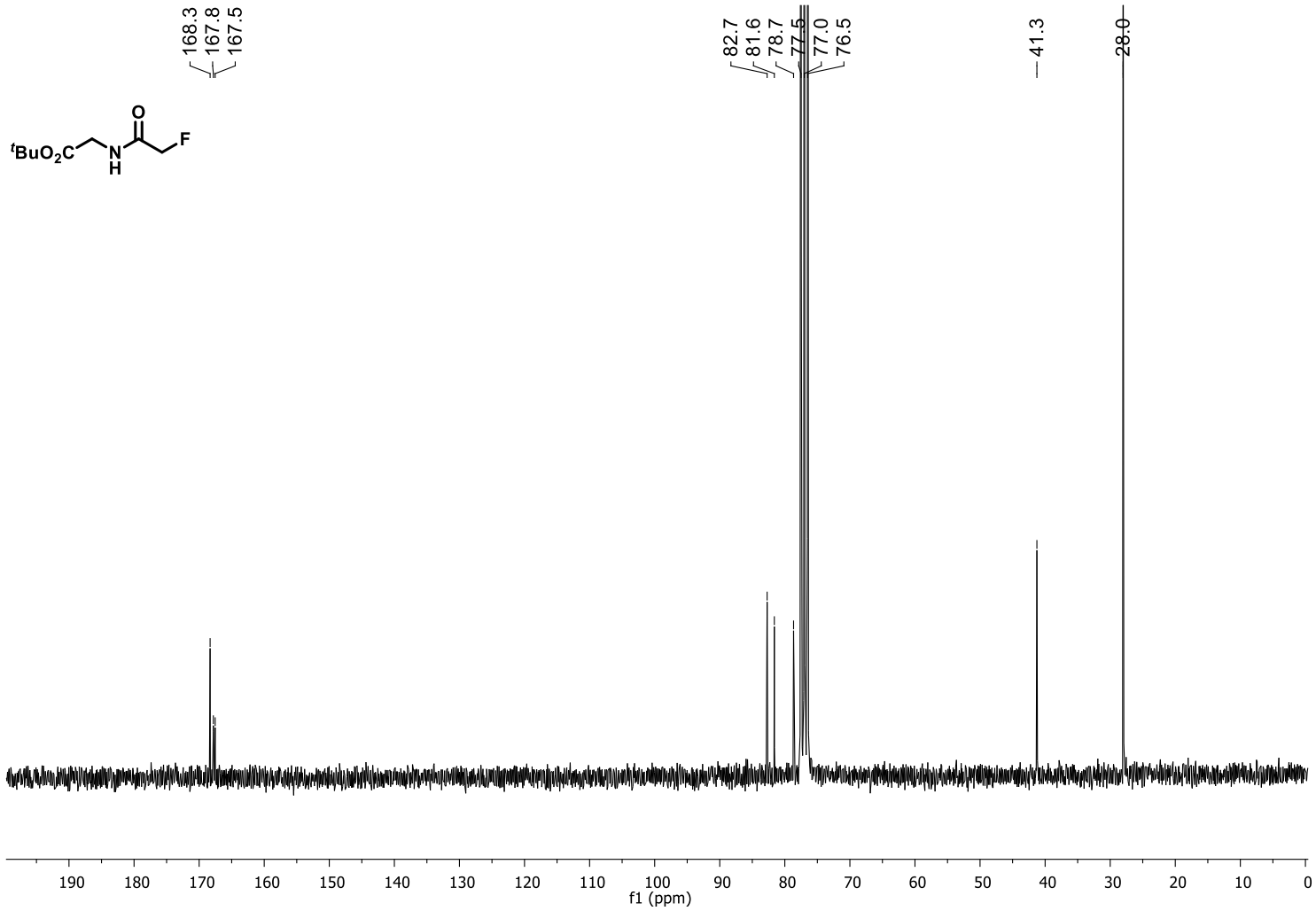
**18bb - $^{19}$F NMR (235 MHz, $CDCl_3$)**



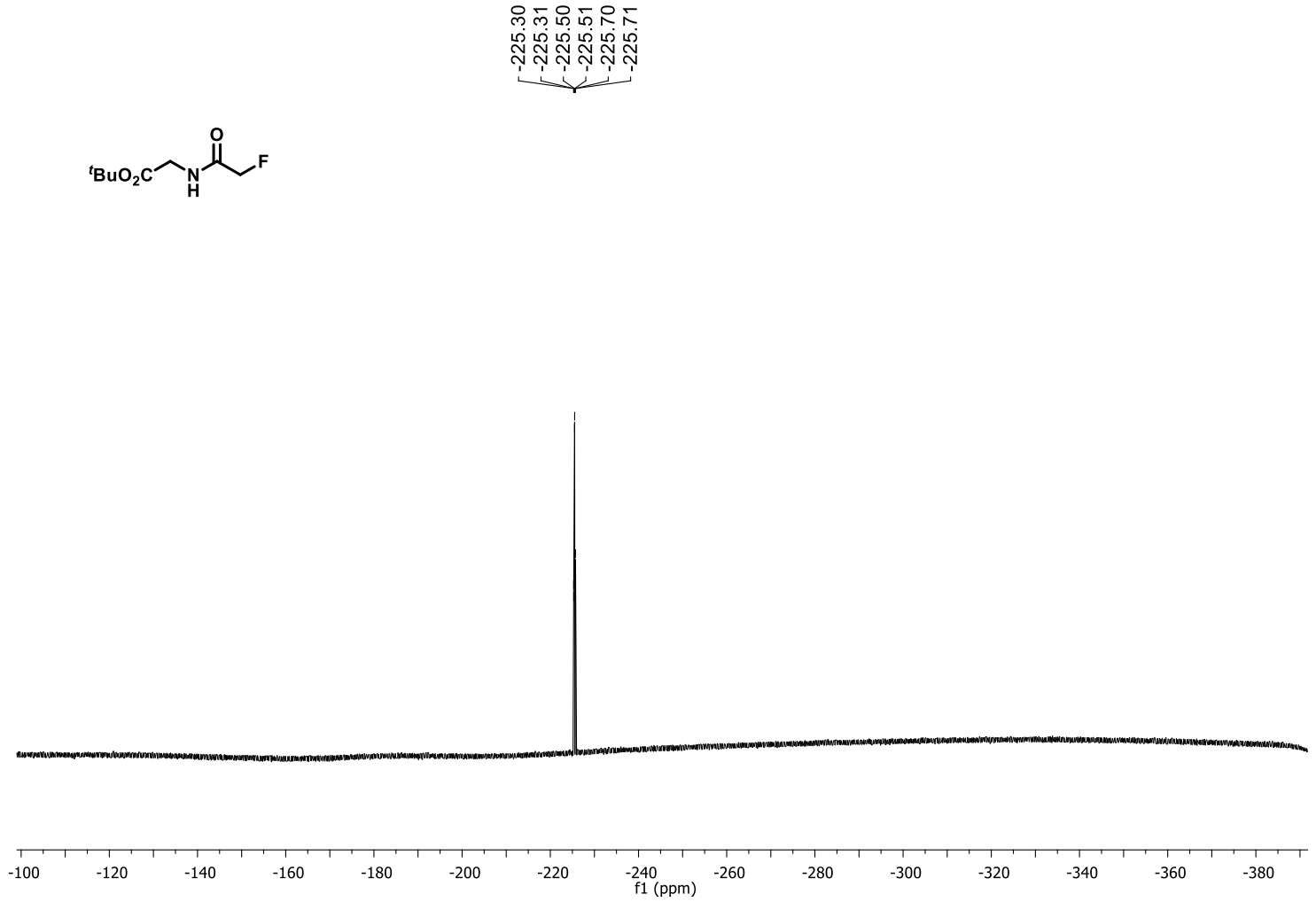
**3cc - $^{1}$H NMR (250 MHz, $CDCl_3$)**



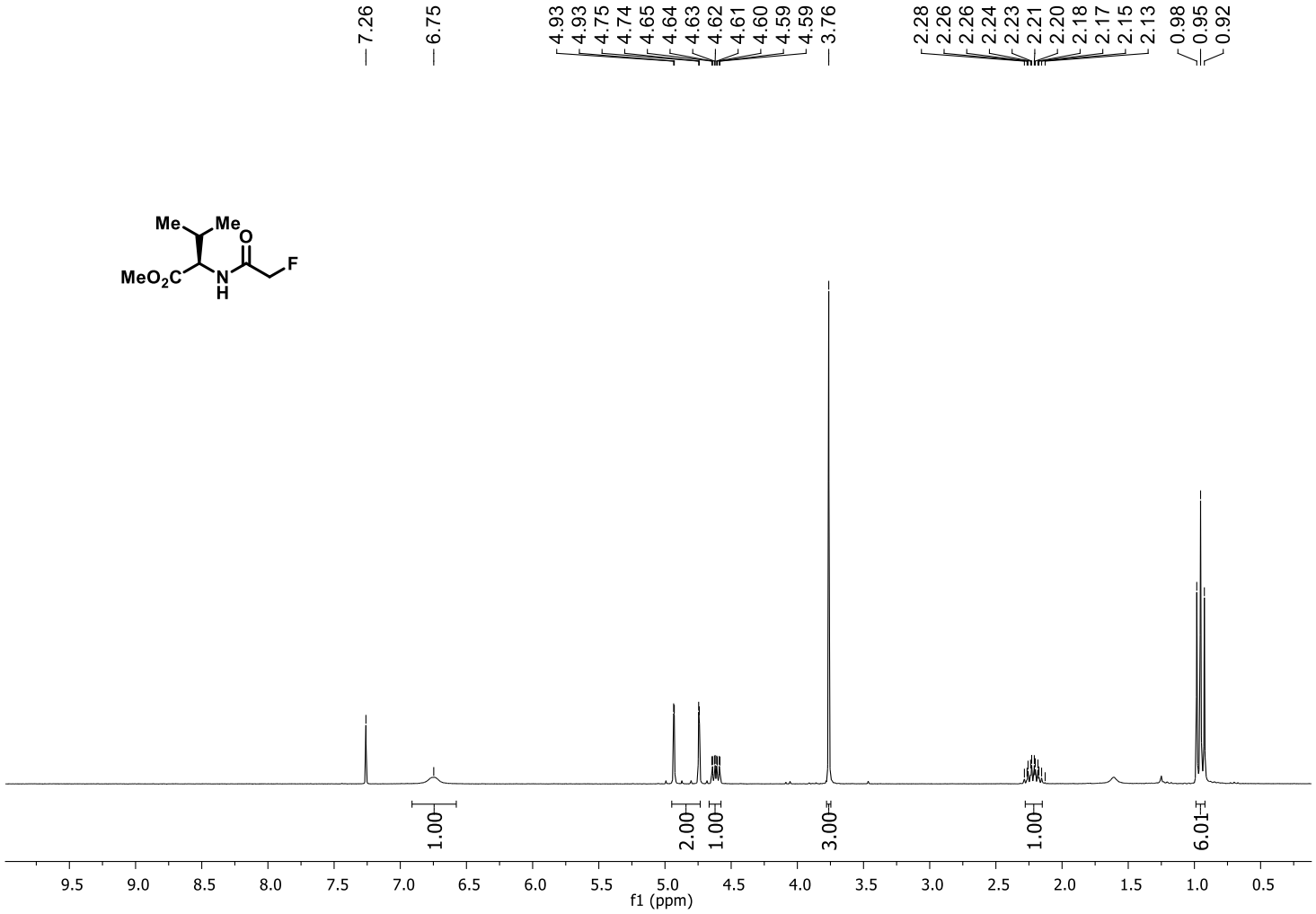
**3cc - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



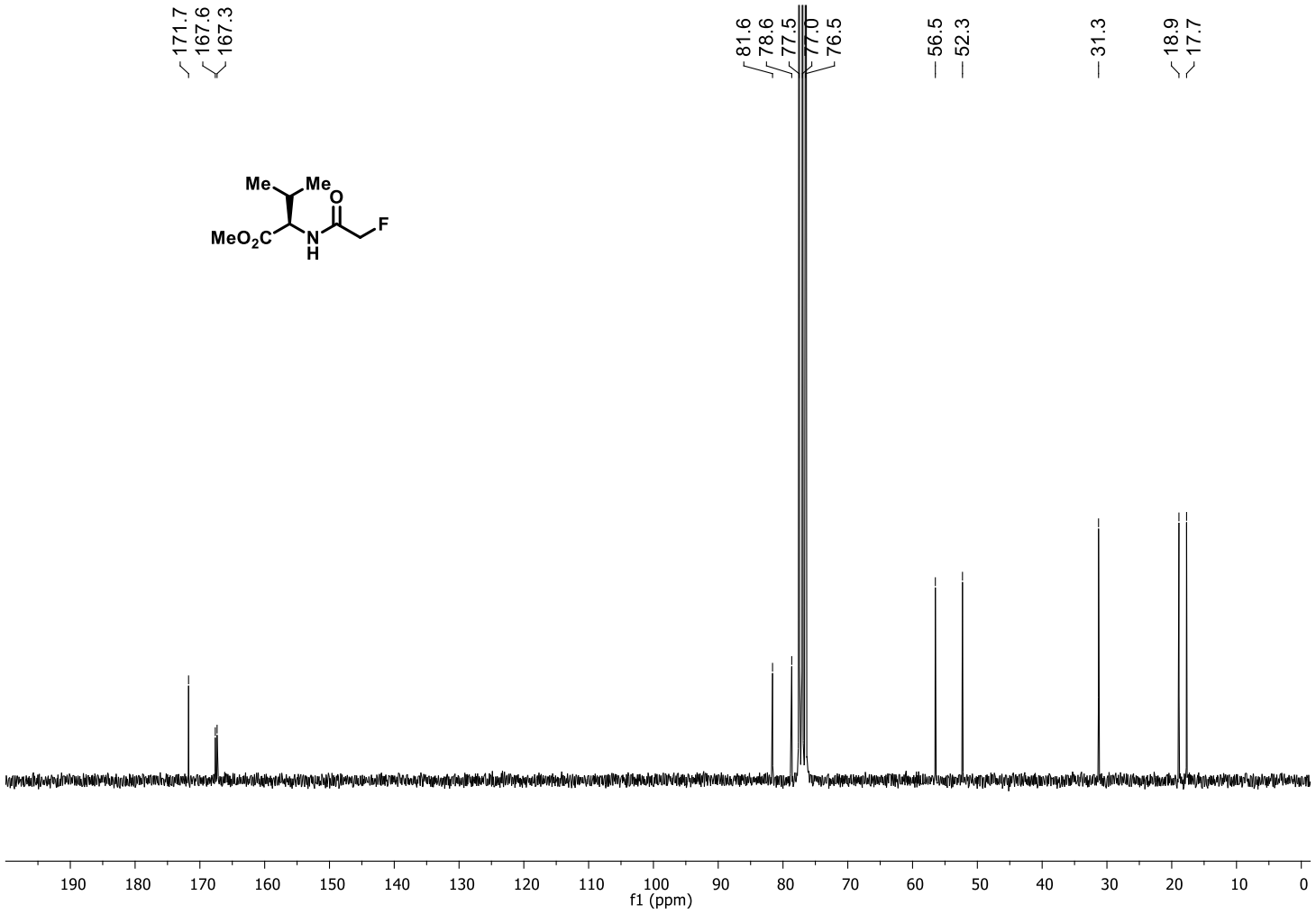
**3cc - $^{19}$F NMR (235 MHz, $CDCl_3$)**



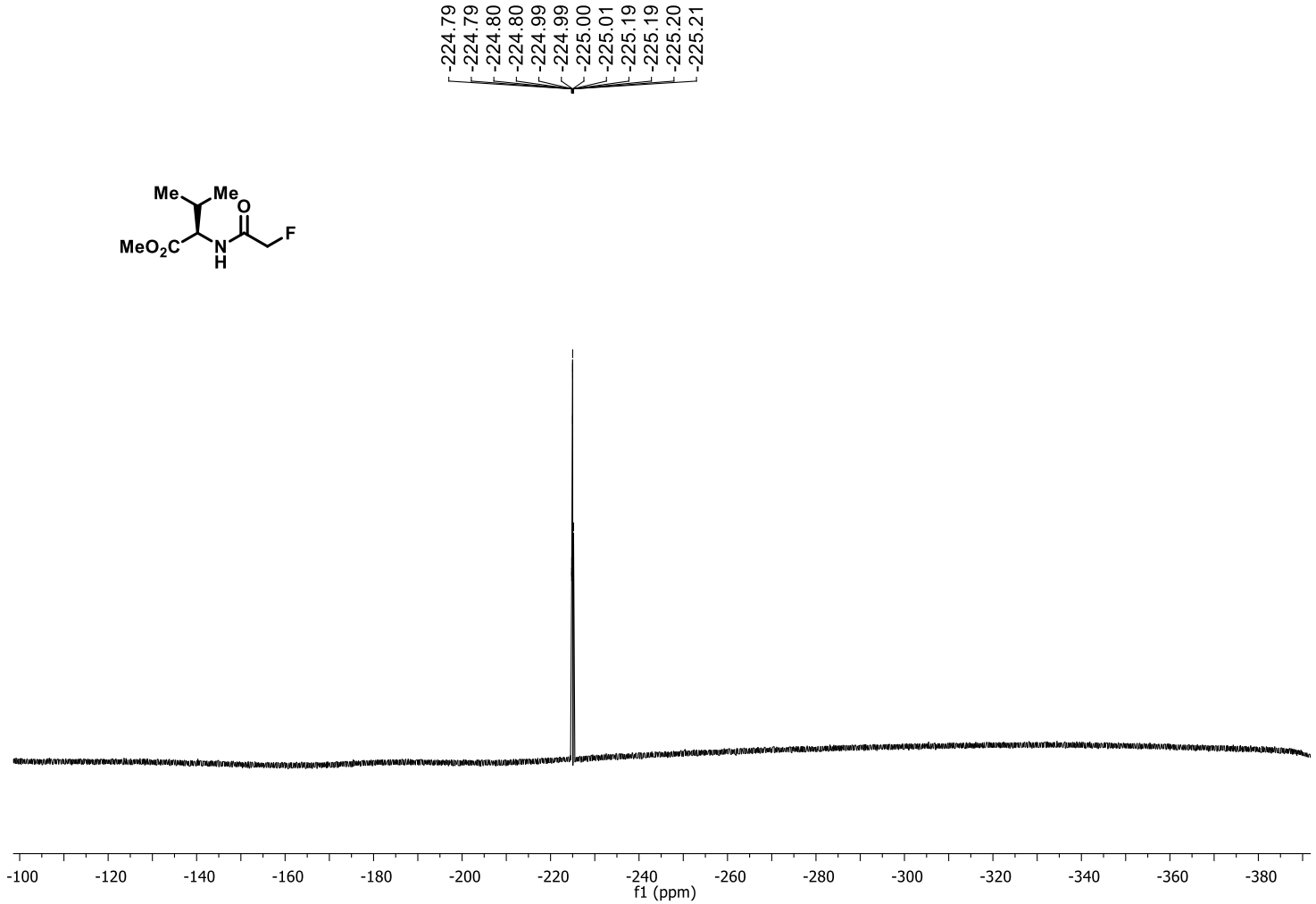
**18dd - $^{1}$H NMR (250 MHz, $CDCl_3$)**



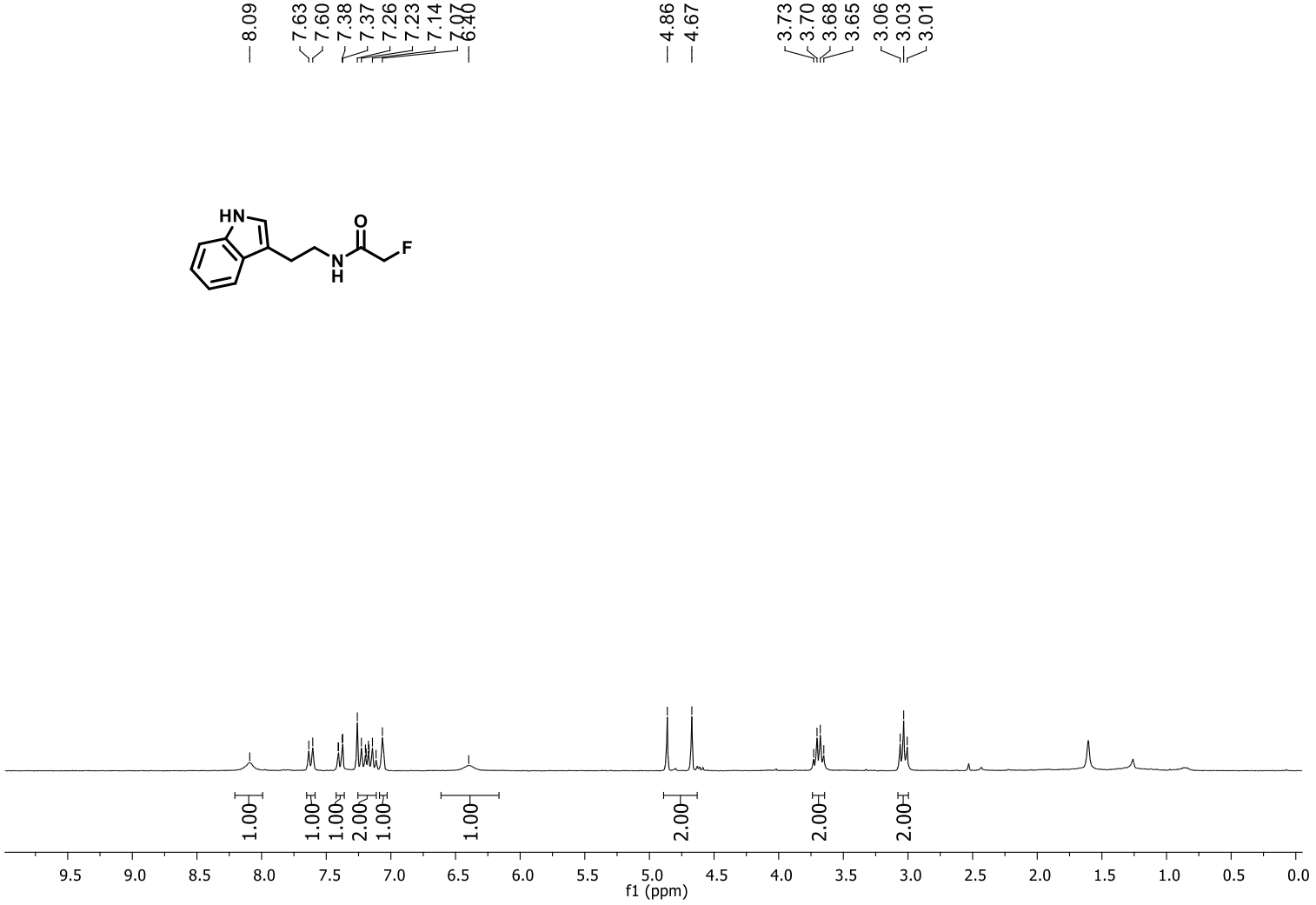
**18dd - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



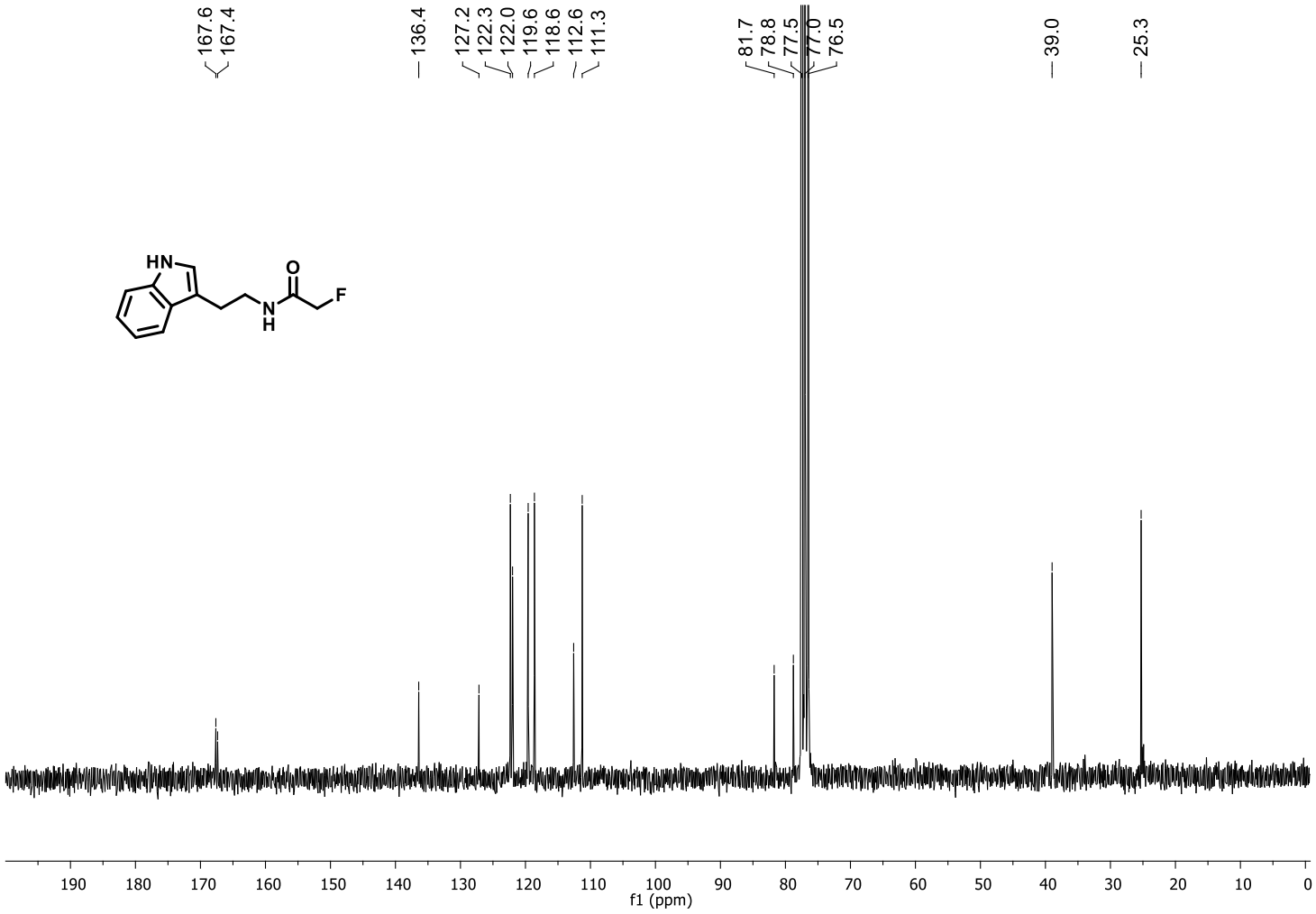
**18dd - $^{19}$F NMR (235 MHz, $CDCl_3$)**



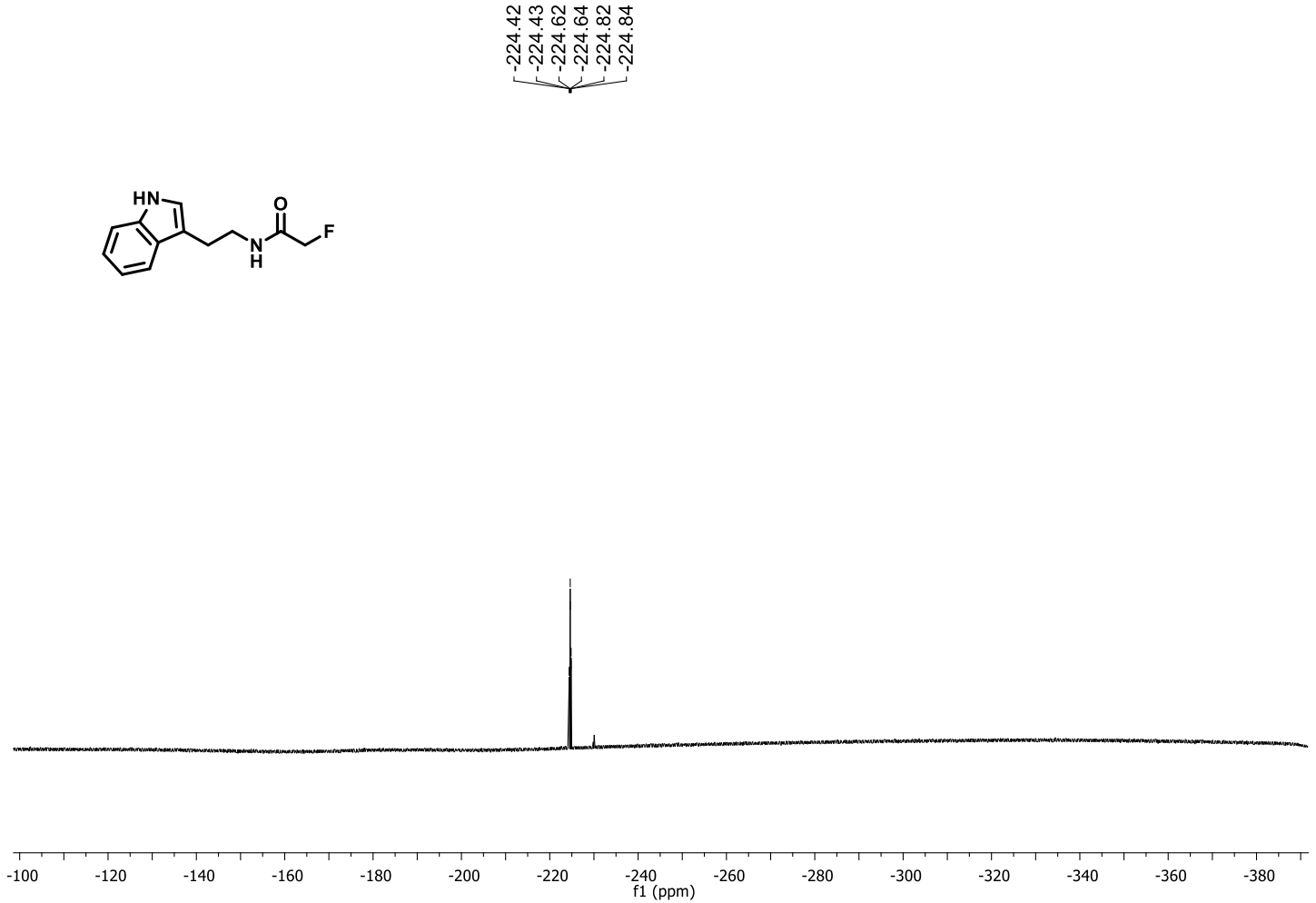
**18ee - $^{1}$H NMR (250 MHz, $CDCl_3$)**



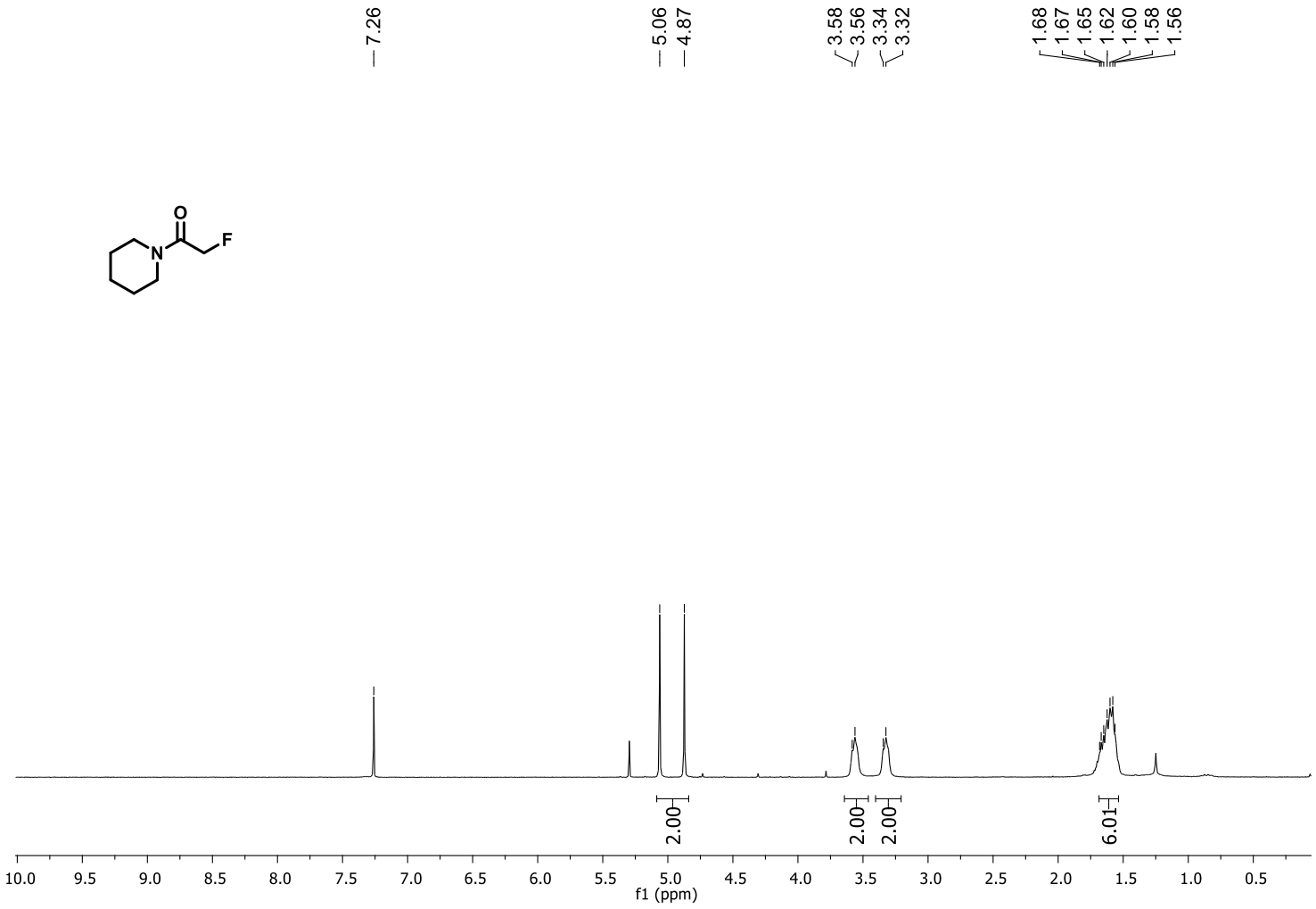
**18ee - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



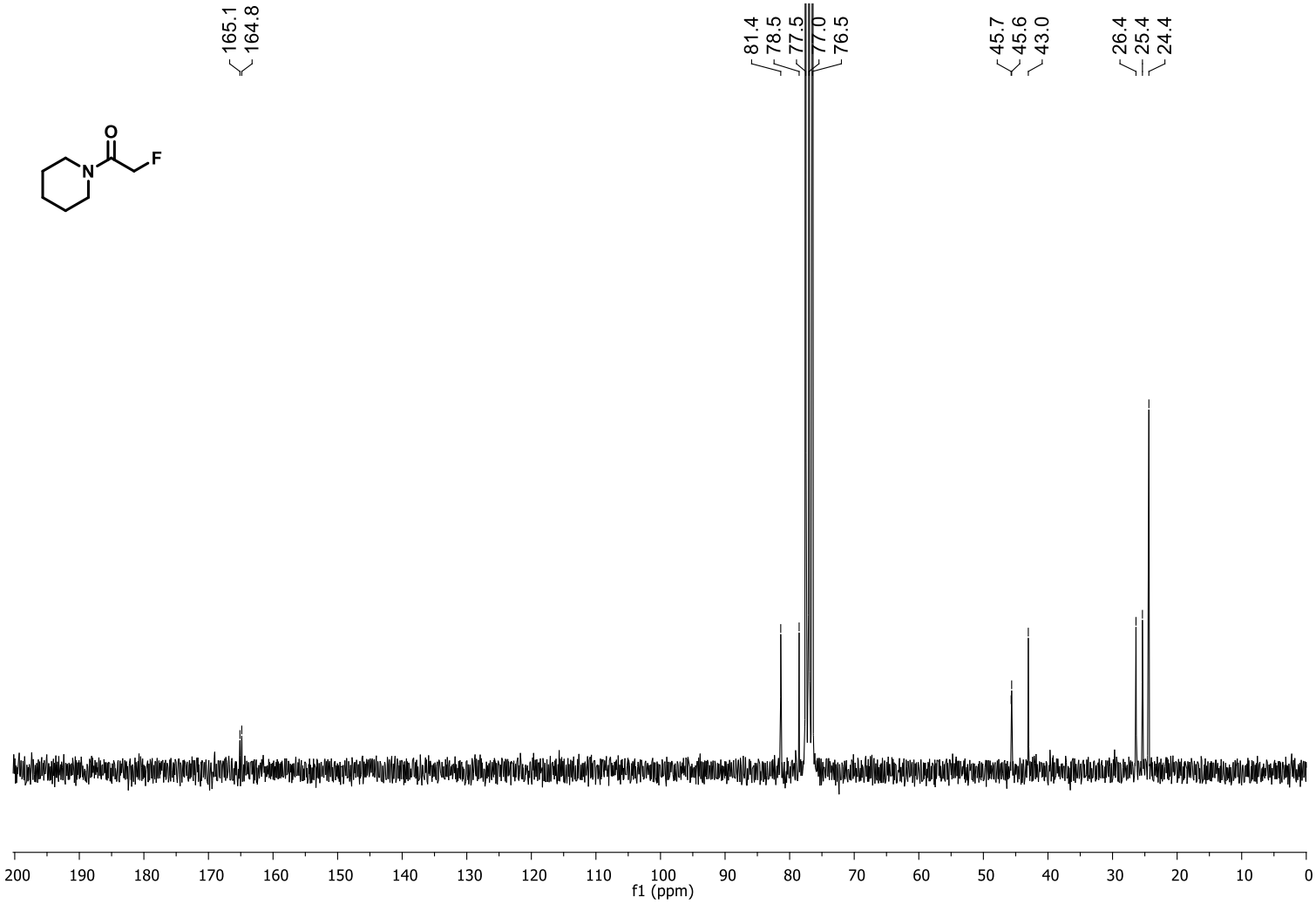
**18ee - $^{19}$F NMR (235 MHz, $CDCl_3$)**



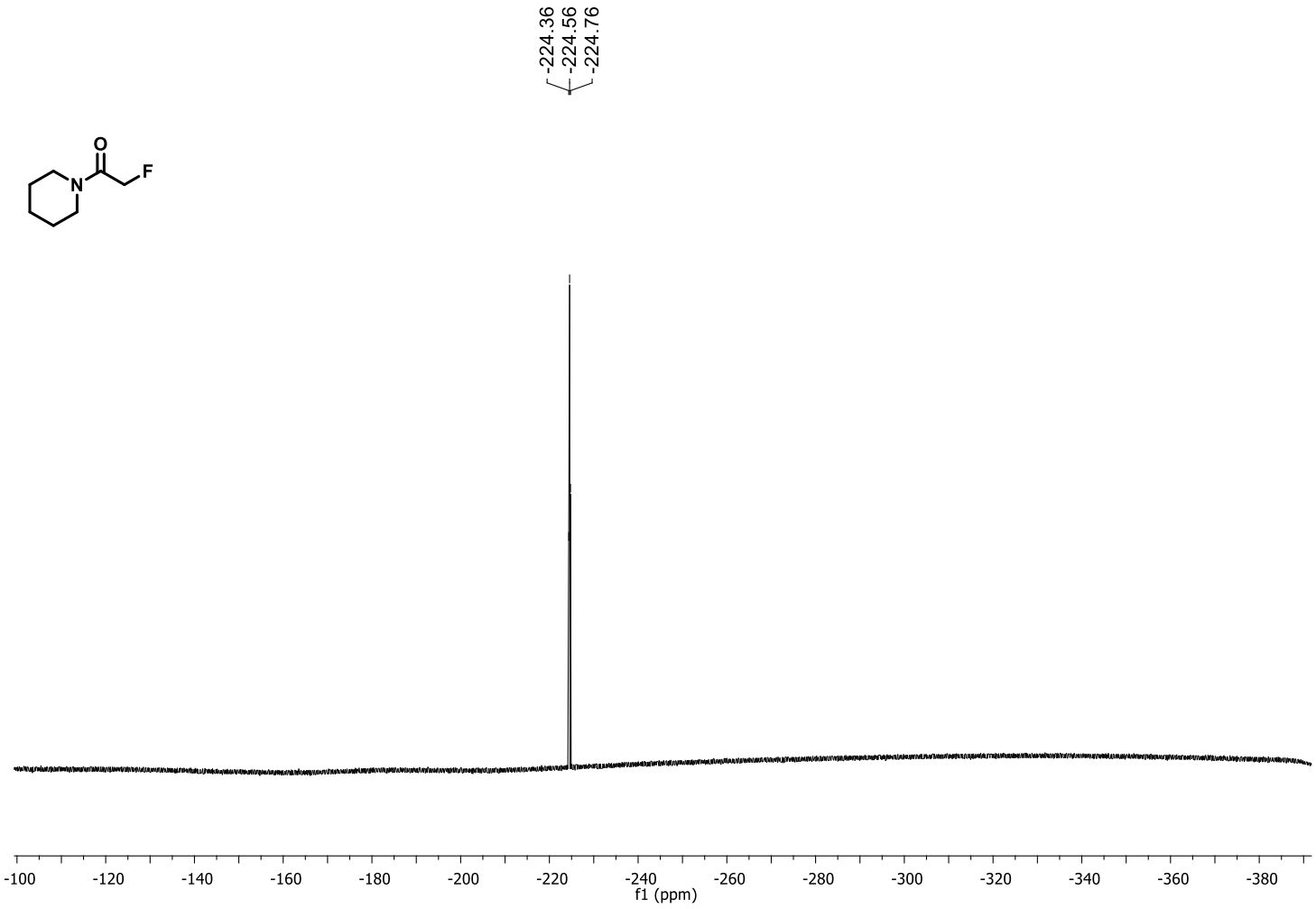
**18ff - $^{1}$H NMR (250 MHz, $CDCl_3$)**



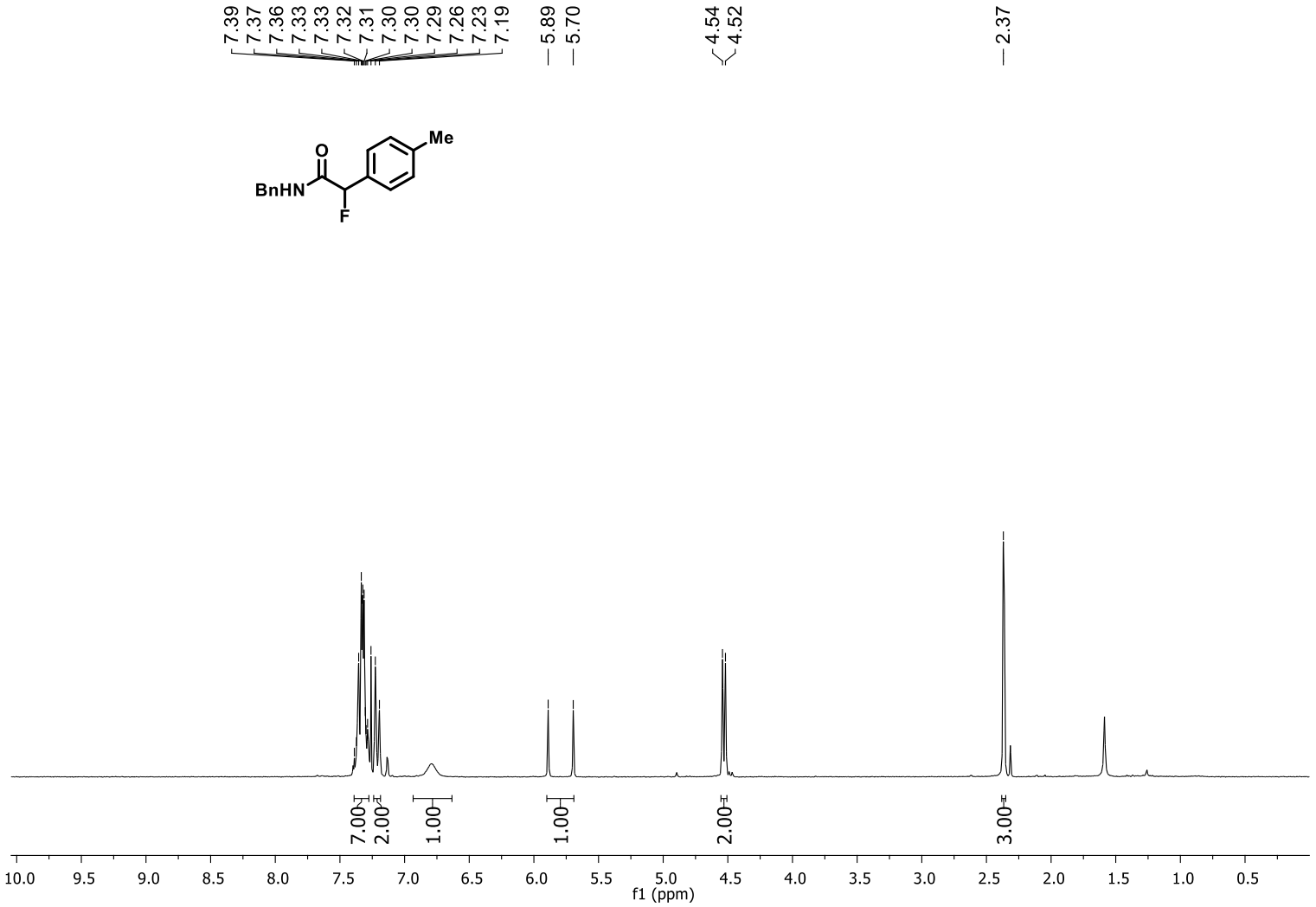
**18ff - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



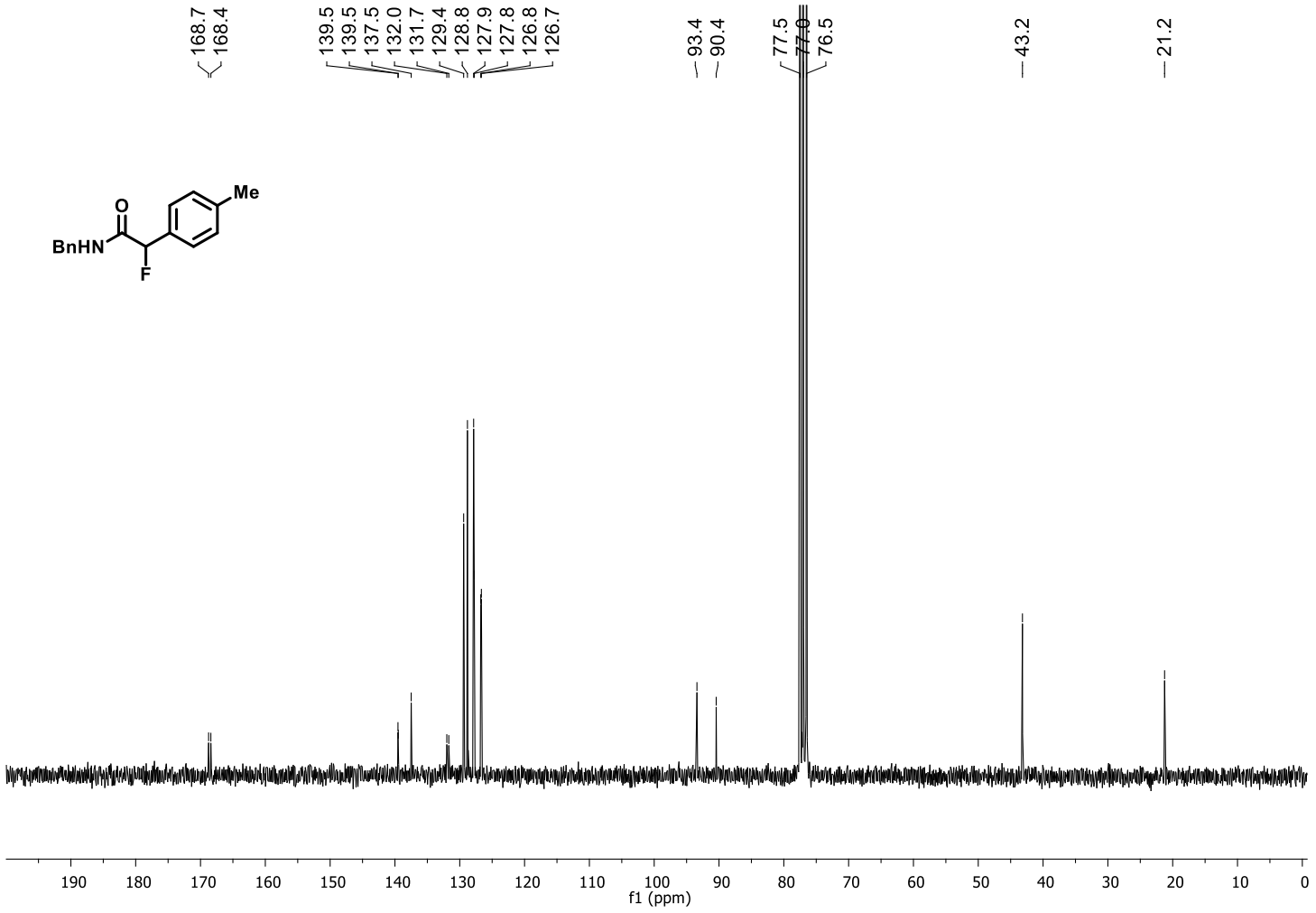
**18ff - $^{19}$F NMR (235 MHz, $CDCl_3$)**



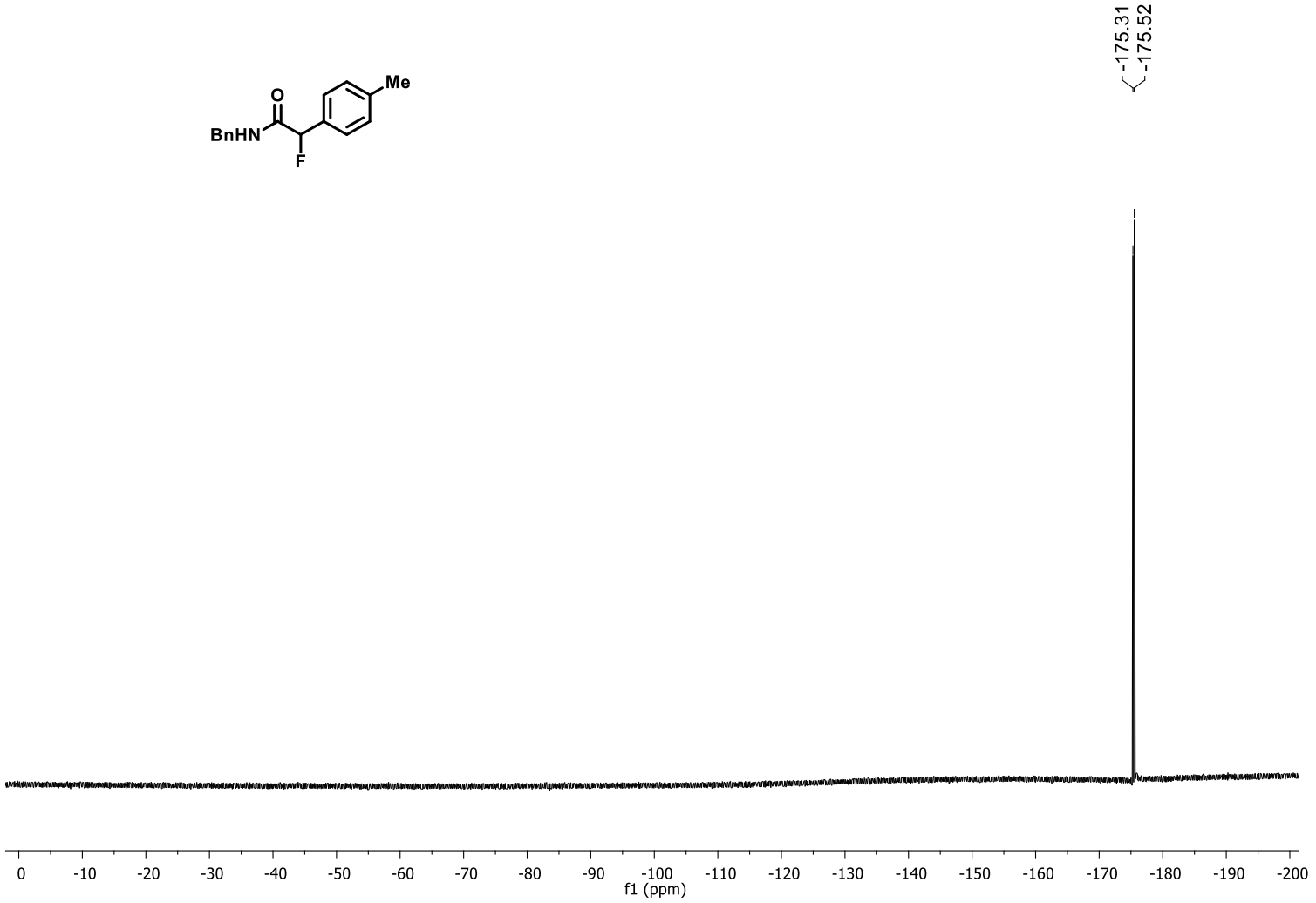
**18gg - $^{1}$H NMR (250 MHz, $CDCl_3$)**



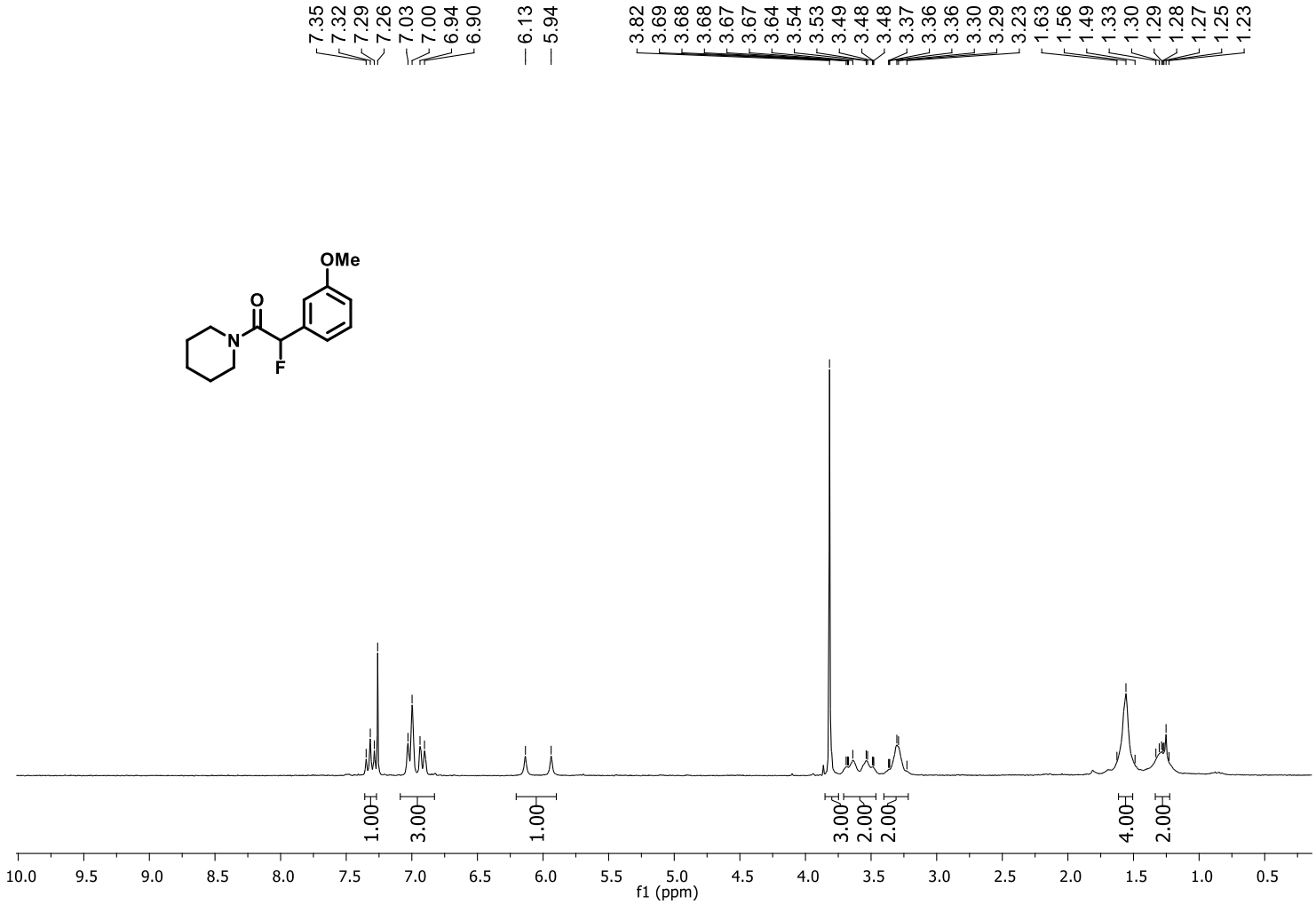
**18gg - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



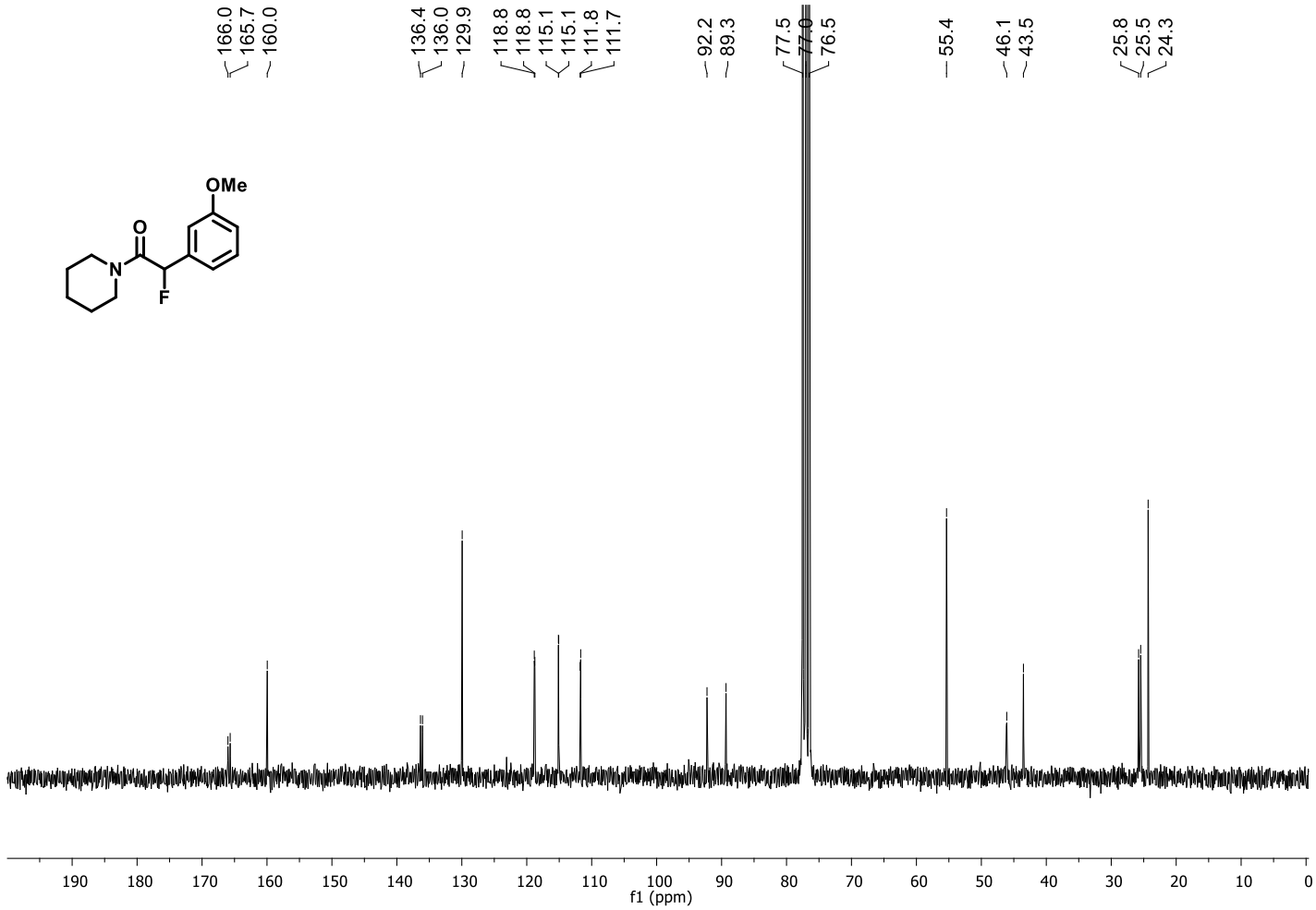
**18gg - $^{19}$F NMR (235 MHz, $CDCl_3$)**



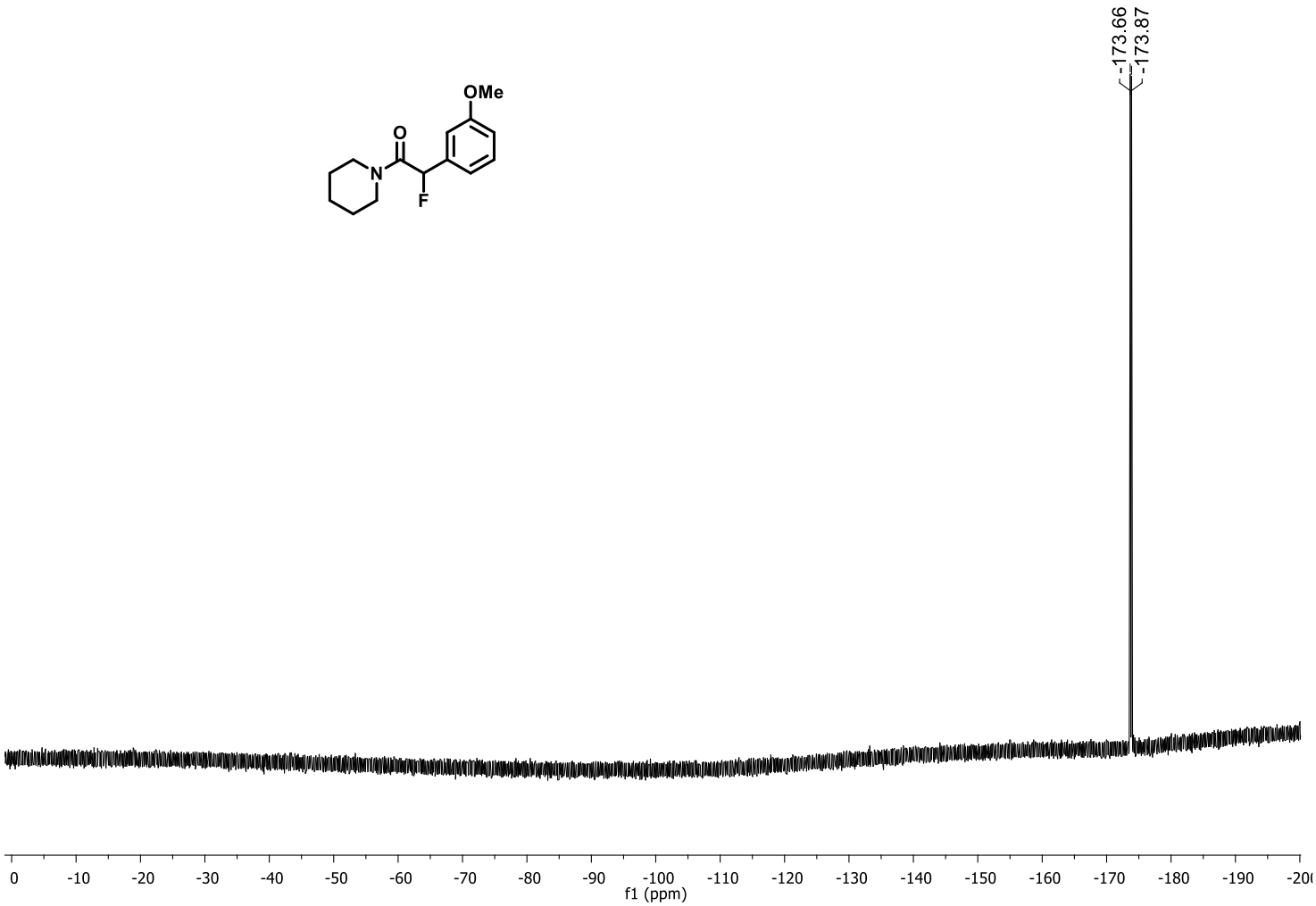
**3hh - $^{1}$H NMR (250 MHz, $CDCl_3$)**



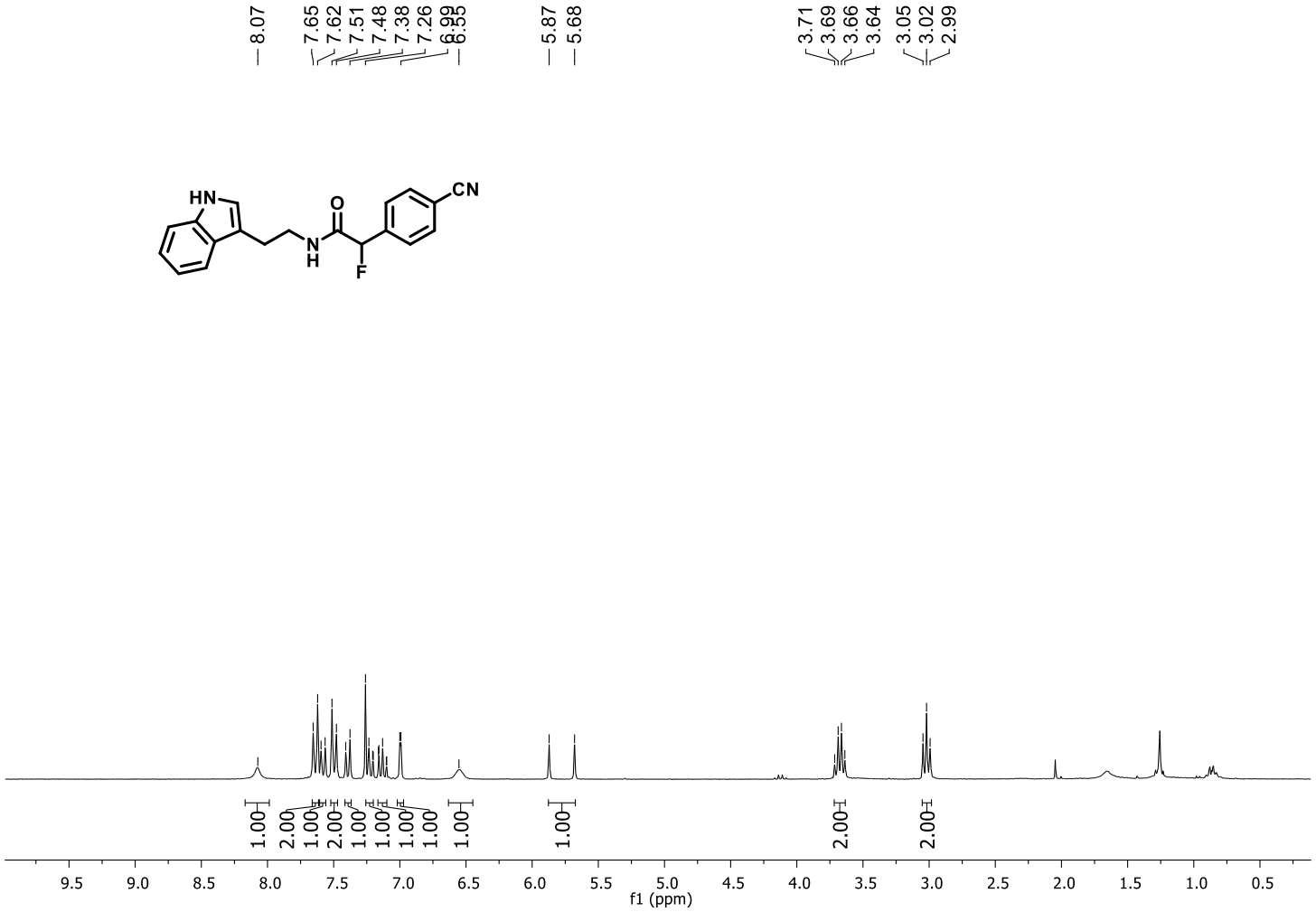
**3hh - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



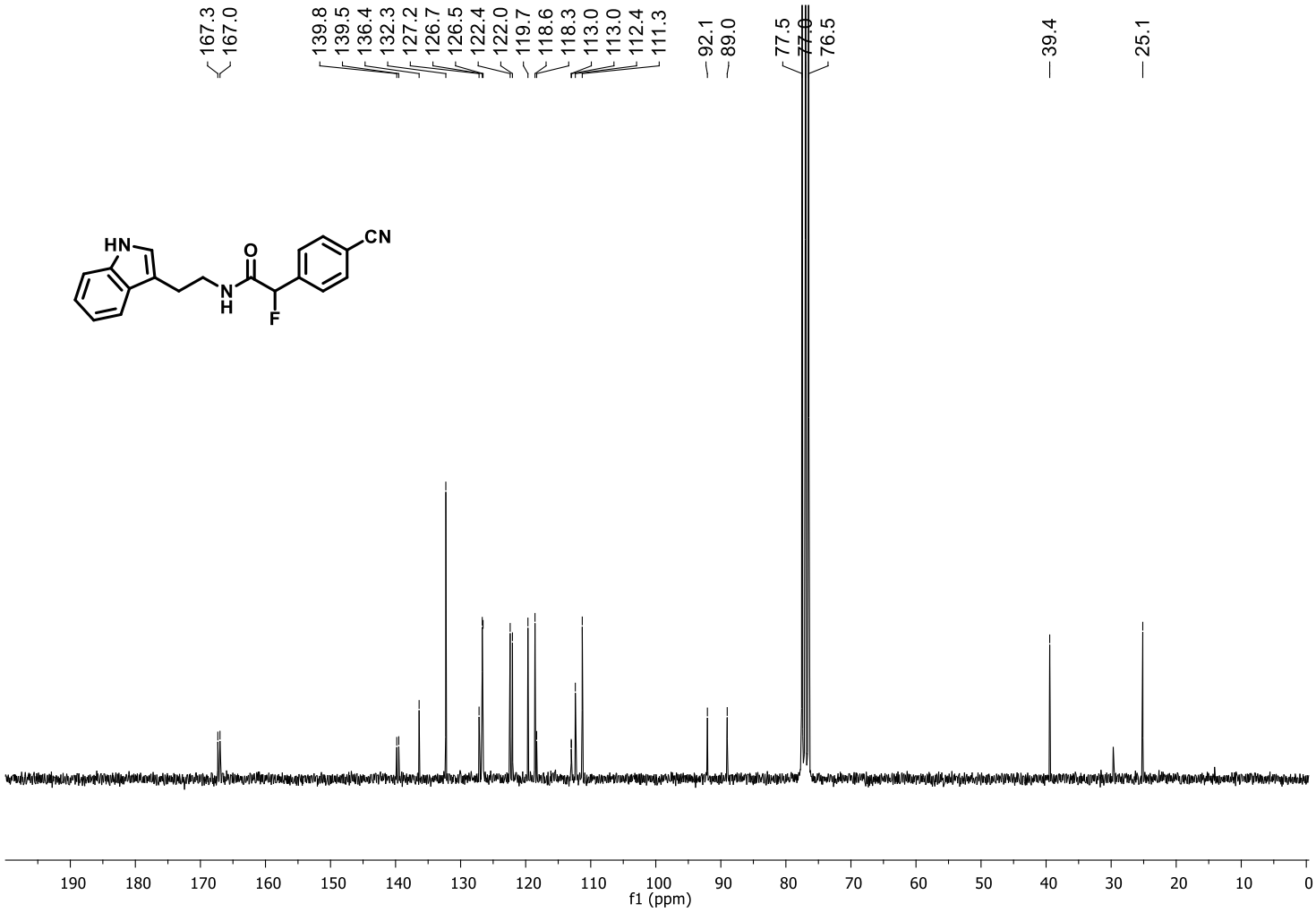
**3hh - $^{19}$F NMR (235 MHz, $CDCl_3$)**



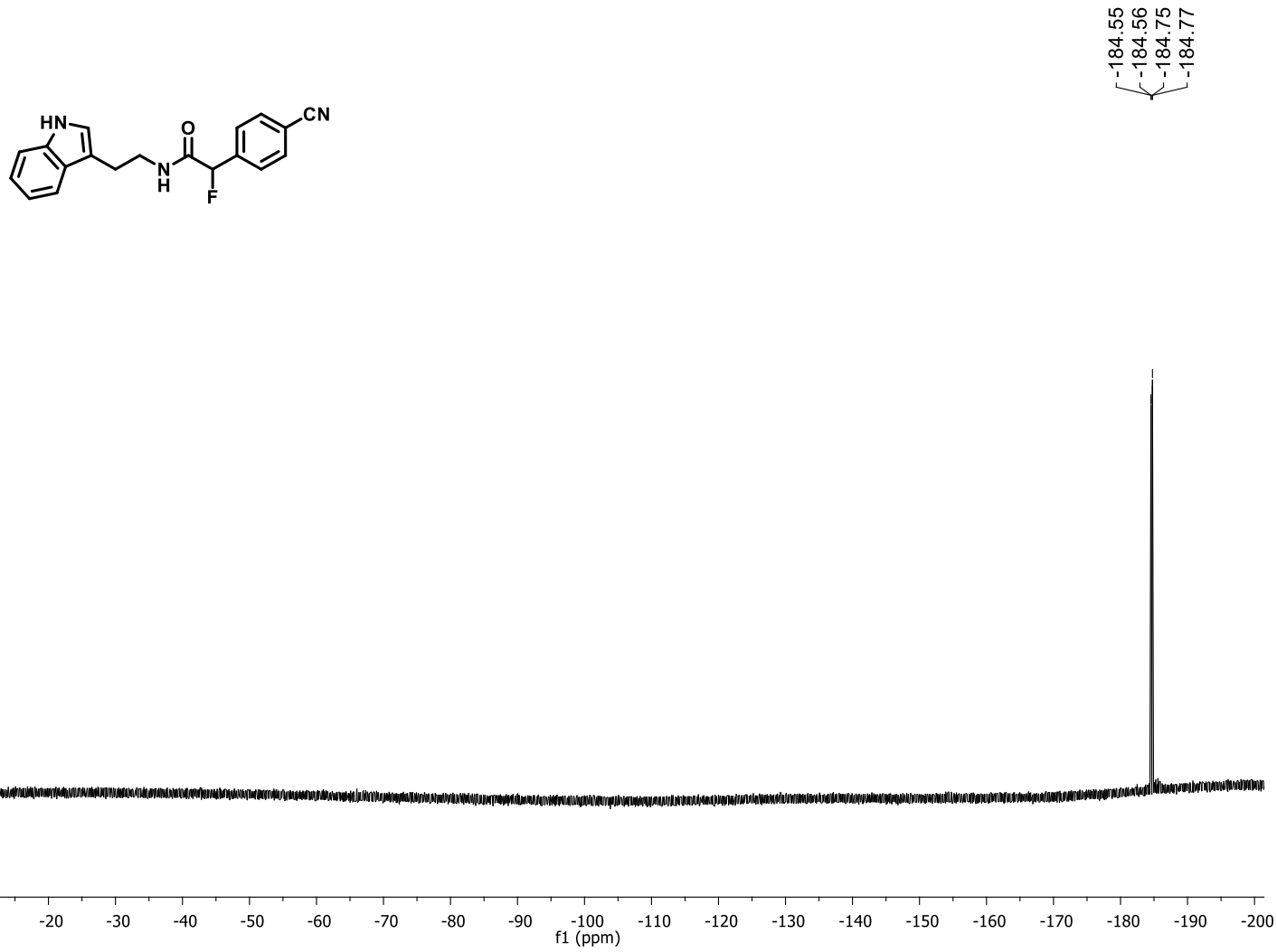
**18ii - $^{1}$H NMR (250 MHz, $CDCl_3$)**



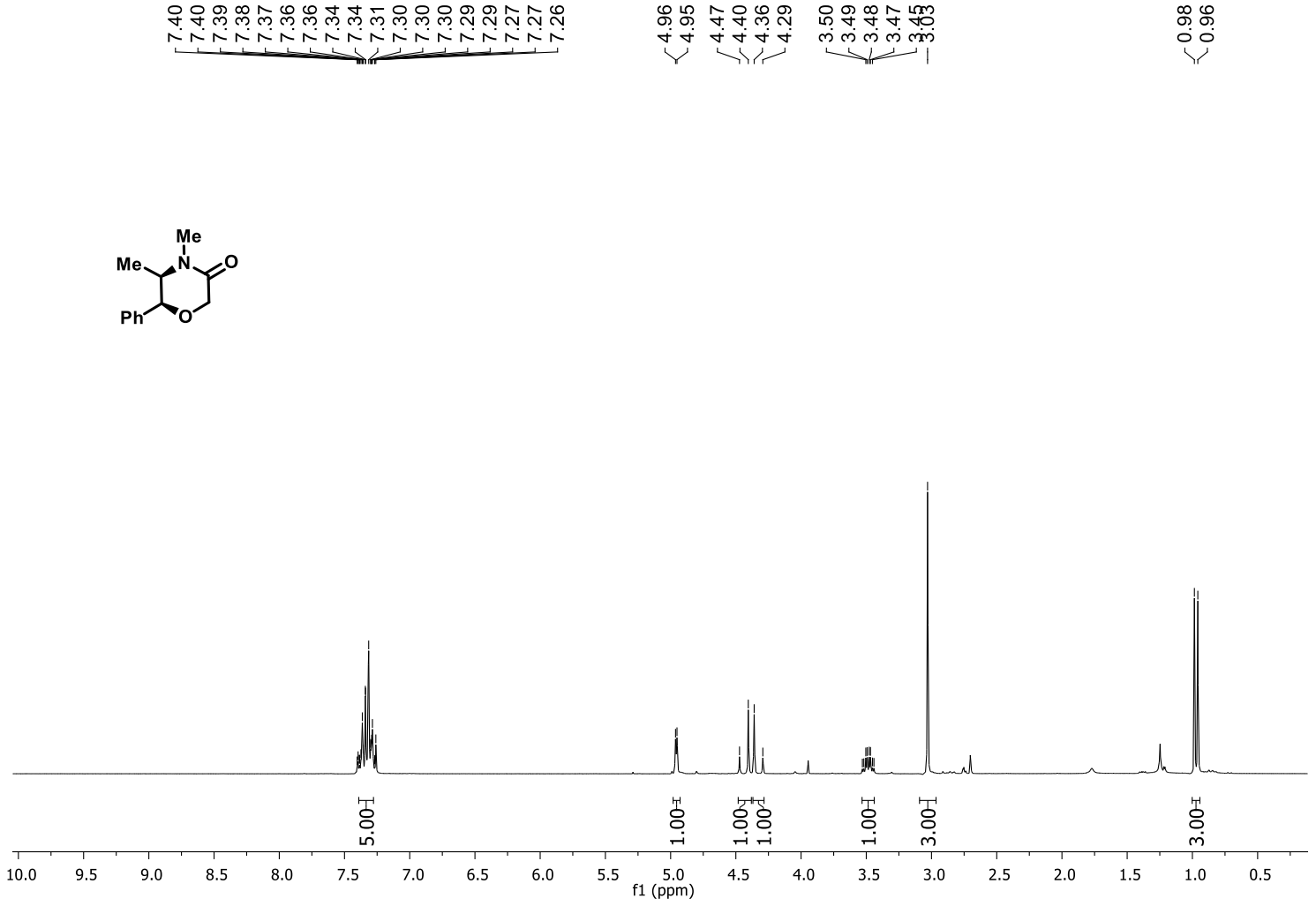
**18ii - $^{13}C$ NMR (62.5 MHz, $CDCl_3$)**



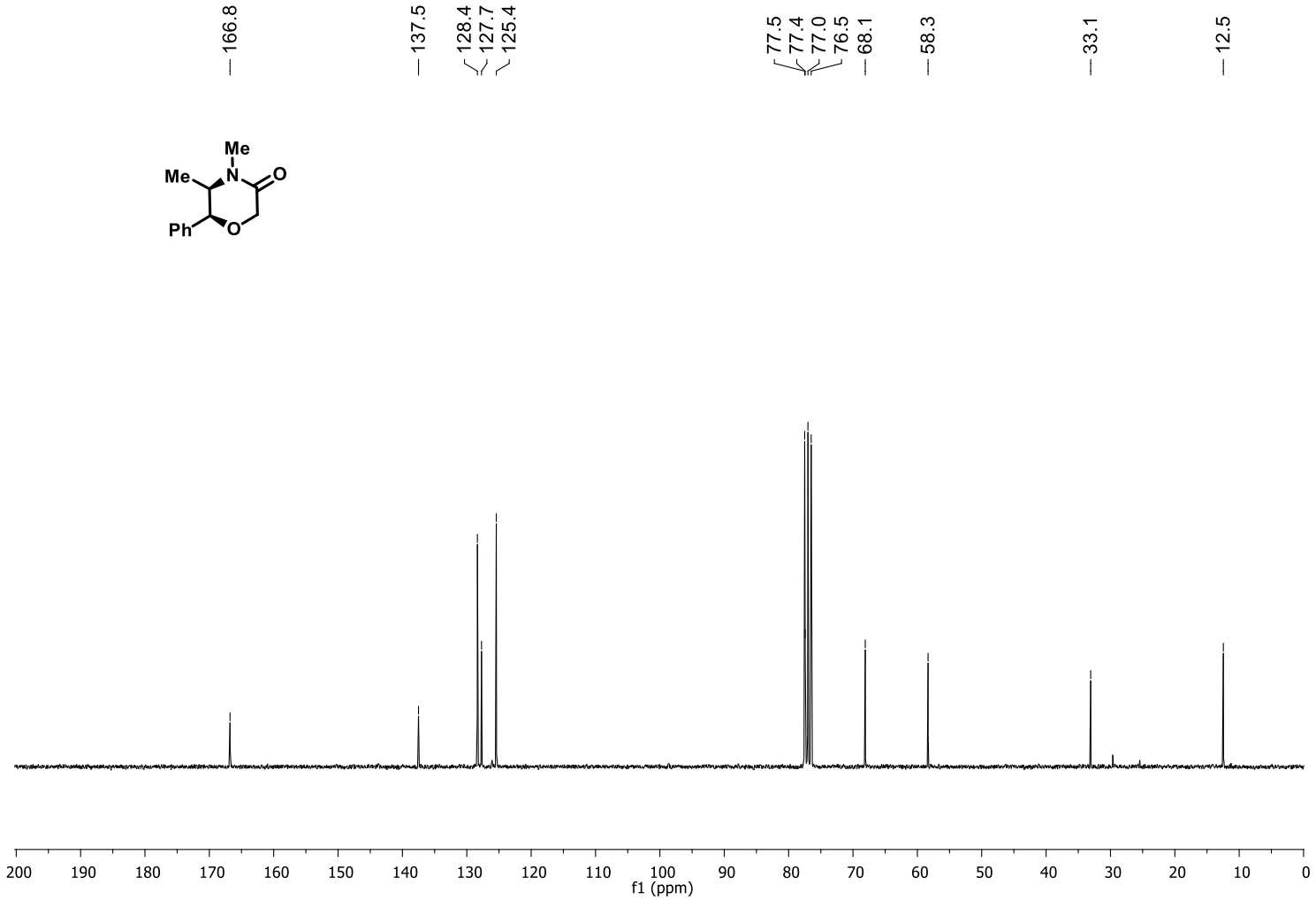
**18ii - $^{19}$F NMR (235 MHz, $CDCl_3$)**



**19 - $^{1}$H NMR (250 MHz, $CDCl_3$)**



**19 - $^{13}$C NMR (62.5 MHz, $CDCl_3$)**



# 7. Anexos

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