Instytut Chemii Organicznej
Polskiej Akademii Nauk

Nowe reakcje karboanionów 2-nitroarylowych i ich azotowych analogów z wybranymi czynnikami elektrofilowymi prowadzące do powstania azotowych związków heterocyklicznych

mgr Magdalena Walewska-Królikiewicz

Spójny tematycznie cykl artykułów opublikowanych w czasopismach naukowych
przedstawiony Radzie Naukowej Instytutu Chemii Organicznej Polskiej Akademii Nauk
w celu uzyskania stopnia doktora

Promotor: dr hab. Zbigniew Wróbel, prof. IChO PAN

WARSZAWA 2024

Chciałabym serdecznie podziękować prof. Zbigniewowi Wróblowi.

Jestem niezmiernie wdzięczna, że miałam możliwość współpracować z Panem.

Dziękuję za cierpliwość, wsparcie, wiarę w moje możliwości

i pokazanie, że nauka może być prawdziwą pasją.

Dziękuję również dr Andrzejowi Kwastowi

za nieocenioną pomoc przy powstaniu tej pracy, ogrom rad i wsparcia.

Dla mojego dziadka

SPIS TREŚCI

1. Spis publikacji wchodzących w skład rozprawy doktorskiej

1. **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel *Tetrahedron Lett.* **2021**, *86*, 153515.

   Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes.

2. **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel *Synlett* **2022**, *33*, 1092.

   (2-Aminoaryl)iminophosphoranes as Versatile Starting Materials for the Synthesis of 1-Aryl-2-trifluoromethylbenzimidazoles.

3. **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel *Tetrahedron Lett.* **2023**, *146*, 133632.

   Comprehensive approach to the multigram, heavy-metal-free synthesis of 4-EWG-substituted quinoline derivatives.

4. **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel *J. Heterocycl. Chem.* **2024** DOI: 10.1002/jhet.4830

   Synthesis of various 1-alkylbenzimidazole derivatives directly from 2-alkylaminonitroarenes via a two-steps, one-pot procedure.

2. Spis publikacji niewchodzących w skład rozprawy doktorskiej

1. Karolina Anczkiewicz, **Magdalena Królikiewicz**, Zbigniew Wróbel, Krzysztof Wojciechowski *Tetrahedron* **2015**, *71*, 3924.

   Synthesis of 4-(4-toluenesulfonyl)quinolines from nitroarenes and allyl sulfones using step-by-step procedure.

2. Zbigniew Wróbel, **Magdalena Królikiewicz** *J. Heterocycl. Chem.* **2014**, *51*, 123.

   Simple Synthesis of Quinoxalin- 2(1H)-one N-Oxides from N-Aryl-2-nitrosoanilines and Alkylated Cyanoacetic Esters.

3. **Magdalena Królikiewicz**, Piotr Cmoch, Zbigniew Wróbel *Synlett* **2013**, *24*, 973.

   A Short Way to Pyrroloquinoxalinones via a Cascade Reaction of N-Aryl-5-alkylamino-2-nitrosoanilines with Methyl 2-Cyanoalkanoates. Unexpected Direction of Nucleophilic Substitution of Hydrogen.

4. **Magdalena Królikiewicz**, Kacper Błaziak, Witold Danikiewicz, Zbigniew Wróbel *Synlett* **2013**, *24,* 1945.

   A Two Step Synthesis of Selected 1,2,3,4-Tetrahydroquinoxaline Derivatives From N-Aryl-2-nitrosoanilines and Arylidenecyanoacetic Esters.

5. Zbigniew Wróbel, Karolina Stachowska, Andrzej Kwast, Agata Gościk, **Magdalena Królikiewicz**, Robert Pawłowski, Izabela Turska *Helv. Chim. Acta* **2013**, *96,* 956.

   Efficient Synthesis of N-Arylquinoxalin-2(1H)-ones via Cyclocondensation of 2-Nitroso-N-arylanilines with Functionalized Alkyl Acetates.

3. Przewodnik po rozprawie doktorskiej

3.1. Założenia i cel pracy

Niniejszy przewodnik po rozprawie doktorskiej opisuje w głównej mierze pracę syntetyczną. Jej tematem było poszukiwanie nowych, użytecznych metod syntezy dwupierścieniowych związków heterocyklicznych, zwierających przynajmniej jeden atom azotu w układzie pierścieniowym. Azotowe związki heterocykliczne są niezwykle rozpowszechnione w organizmach żywych i pełnią w nich wielorakie, istotne dla prawidłowego działania organizmu funkcje. Z tego powodu mają też ogromne znaczenie w chemii biologicznej i farmakologii. Fakt ten powoduje niesłabnące zapotrzebowanie na dogodne, a więc wydajne, proste, tanie i możliwie nieszkodliwe dla środowiska metody syntezy związków heterocyklicznych o założonej budowie i spodziewanej aktywności biologicznej. Zebrane w tym zestawieniu prace wpisują się w odpowiedź na to zapotrzebowanie w zakresie syntezy podstawowych, dwupierścieniowych układów heterocyklicznych, zawierających także grupy funkcyjne umożliwiające dalsze funkcjonalizowanie i rozbudowę w kierunku struktur docelowych. Szczególną uwagę poświęcono również metodom umożliwiającym otrzymanie struktur zawierających grupę trifluorometylową, ze względu na jej szczególne własności i wyraźny wpływ na aktywność biologiczną zawierających ją związków.

W projektowaniu sekwencji reakcji prowadzących do zamierzonego celu brano pod uwagę dostępność i koszt wyjściowych związków jak i łatwość realizacji poszczególnych procesów. Ze względu na zamierzoną praktyczną przydatność planowanych metod, ważnym czynnikiem była możliwość realizacji syntezy w skali wielogramowej. Mankamentem bowiem wielu opisanych w literaturze, atrakcyjnych – wydawałoby się – metod syntezy, jest miligramowa jedynie skala w jakiej ich realizacja jest efektywna.

Istotnym założeniem była też eliminacja kosztownych bądź niedogodnych reagentów takich jak metale, drogie katalizatory, oraz drastycznych warunków reakcji. W efekcie, prawie we wszystkich przedstawionych przemianach, udało się te warunki spełnić.

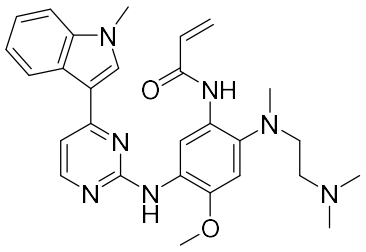
Wszystkie przedstawione tu prace za punkt wyjściowy planowanych syntez miały proste pochodne nitrobenzenu to jest podstawiony nitrotoluen i *o*-nitroanilinę. Docelowo posłużyły one do otrzymania rozmaicie podstawionych układów indolu, chinoliny i benzimidazolu.

3.2. Wstęp literaturowy

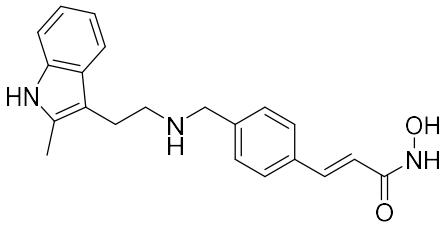
Chemia związków o potencjalnym znaczeniu biomedycznym odgrywa ogromną rolę w naukach przyrodniczych. Szczególnie ważną rolę pełnią związki heterocykliczne, a w szczególności te zawierające w swojej strukturze atom azotu. W literaturze możemy znaleźć informację, że ponad 75%, związków które mają znaczenie lecznicze zawiera w swojej strukturze układ heterocykliczny. Wiele z nich będąc antybiotykami, hormonami czy witaminami, zbudowana jest na heterocyklicznym szkielecie azotowym.[1] Tak jak zastosowanie – ważny jest sposób syntezy tych związków. Poniższy przegląd literaturowy ma na celu przedstawienie podstawowych metod otrzymywania niektórych aromatycznych azotowych związków heterocyklicznych. Jest to ogromny dział chemii który stale się rozwija, tak więc przegląd ten jest zaledwie szkicem tematu w kontekście późniejszego opisu badań własnych. Wybór przedstawionych metod jest subiektywny i całkowicie wyłącza z opisu metody rodnikowe.

Synteza indoli

Szkielet indolu jest bez wątpienia jednym z kluczowych azotowych związków heterocyklicznych. W chemii biomedycznej cząsteczka indolu występuje w wielu związkach o aktywności biologicznej, posiadających rożnorodne właściwości. Wiele struktur zawierających szkielet indolu można spotkać w wielu lekach o działaniu przeciwnowotworowym (np. Osimertinib lub Panobinostat, Rysunek 1).[2]



Osimertinib

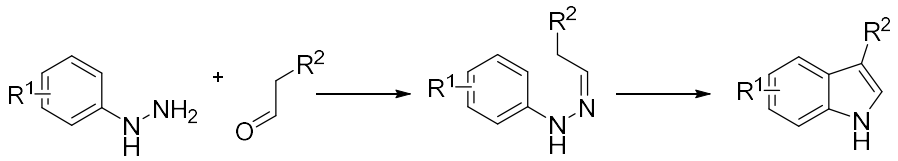


Panobinostat

Rysunek 1

[1] (a) E. Vitaku, D. Smith, J. Njardarson *J. Med. Chem*. **2014**, *57,* 10257. (b) M. Heravi, V. Zadsirjan *RSC Adv*. **2020**, *10,* 44247. (c) N. Kerru, L. Gummidi, S. Maddila, K. Gangu, S. Jonnalagadda *Molecules* **2020**, *25*, 1909.
[2] (a) N. Chadha, O. Silakari *Eur. J. Med. Chem.* **2017**, *134*, 159. (b) A. Kumari, R. Singh *Bioorg Chem.* **2019**, *89*, 103021.

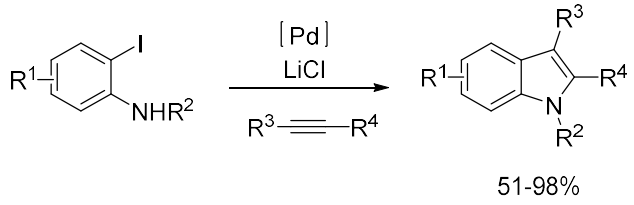
Do tej pory zostało opracowanych wiele metod otrzymywania indolu.[3] Można pokusić się o stwierdzenie, że najsłynniejszą metodą otrzymywania indolu jest synteza Fischera[4] opisana w 1883 roku. Klasyczna synteza Fischera polega na ogrzewaniu fenylohydrazyny z ketonem lub aldehydem w środowisku kwaśnym (Schemat 1).



Schemat 1 Synteza Fischera

W literaturze możemy znaleźć liczne modyfikacje podstawowej syntezy indoli Fishera. Znaczna część opisanej metodologii uwzględnia oprócz wykorzystania ketonów i aldehydów, również użycie alkinów oraz alkenów, a także zabezpieczonych związków karbonylowych takich jak acetale a nawet ketoestrów. Ważną część literatury dotyczącej tego tematu zajmuje również otrzymanie odpowiedniej wyjściowej hydrazyny – na ogół z soli diazoniowych.[5] Warto zaznaczyć, że gdy obie pozycje *orto* | w pochodnej fenylohydrazyny są niepostawione, cyklizacja może zachodzić nieselektywnie z utworzeniem mieszaniny izomerycznych produktów. Tej wady pozbawione są metody przedstawione w dalszej części rozdziału.

Kolejną ważną, imienną syntezą prowadzącą do otrzymania szkieletu indolu jest heteroannulacja Larocka.[6] *o*-Jodoanilina i di-podstawiony alkin ulegają sprzęganiu w obecności katalizatora palladowego (Schemat 2).

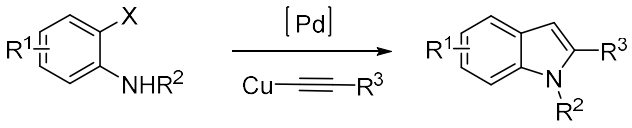


Schemat 2 Synteza Larocka

[3] (a) G. Humphrey, J. Kuethe *Chem. Rev.* **2006**, *106*, 2875. (b) D. Tabera, P. Tirunaharib *Tetrahedron* **2011**, *67*, 7195.
[4] (a) E. Fischer, F. Jourdan *Ber. Dtsch Chem. Ges.* **1883,** *16.* (b) B. Robinson *Chem. Rev.* **1969**, *69*, 227.
[5] J. Jampilek *Molecules* **2019**, *24*, 3839.
[6] (a) R. Larock, E. Yum *J. Am. Chem. SOC.* **1991**, *113*, 6690. (b) K. Chuang, M. Kieffer, S. Reisman *Org. Lett.* **2016**, *18*, 4750.

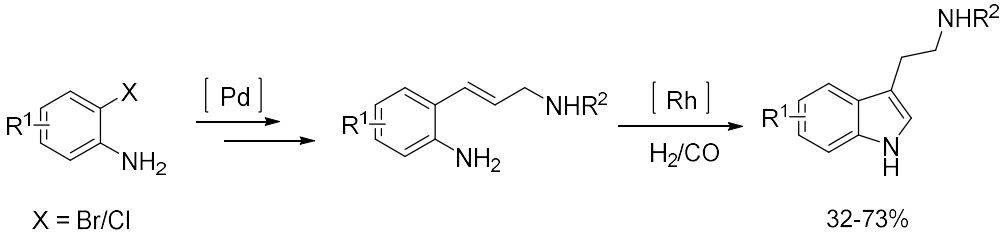
Sporym ograniczeniem klasycznej wersji syntezy Larocka jest fakt, że reakcji ulegają jedynie jodo-aniliny. Reakcje przeprowadzone z bromo- lub chloro-aniliną wymagają zmodyfikowania warunków reakcji.[7]

W przypadku klasycznych metod otrzymywania indolu, opartych na mechanizmie sprzęgania Hecka, warto również wspomnieć o syntezie Castro[8] Reakcja dla pochodnych jodoaniliny prowadzi z bardzo dobrymi rezultatami do otrzymania indolu (Schemat 3). Na przestrzeni lat również w przypadku tej syntezy powstały modyfikacje warunków reakcji oraz bardzo dokładnie sprawdzono zakres stosowalności metody.



Schemat 3 Synteza Castro

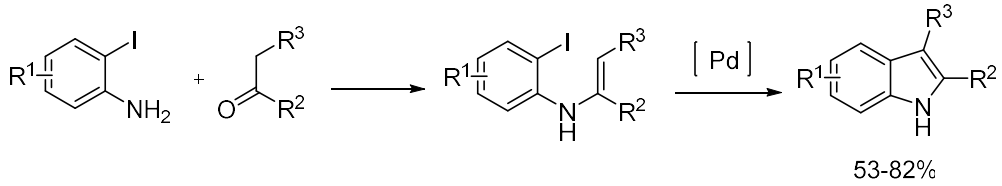
W literaturze możemy znaleźć również inne reakcje otrzymywania indolu oparte na reakcjach sprzęgania. Przykładem takiej syntezy może być opisane przez Donga i Busaccę[9] hydroformylowanie uprzednio sfunkcjonalizowanej aniliny (Schemat 4).



Schemat 4 Synteza Donga i Busacca

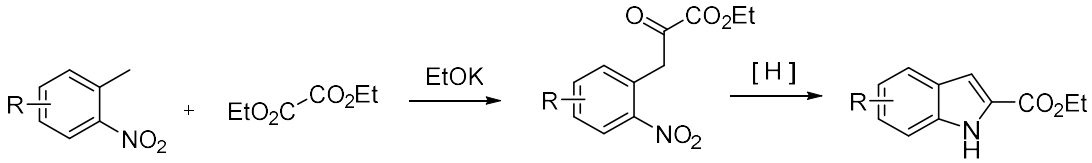
Reakcja Hecka znalazła zastosowanie również w syntezie indolu z wykorzystaniem ketonów oraz jodoaniliny.[10] Jest to tzw. wewnątrzcząsteczkowa cyklizacja Hecka. Sprzęganie halogenku arylu z alkenem zachodzi w tej samej cząsteczce (Schemat 5).

[7] J. Herraiz-Cobo, F. Albericio, M. Alvarez *Adv. Heterocycl Chem.* **2015,** *116,* 1.
[8] C. Castro, E. Gaughan, D. Owsley *J. Org. Chem.* **1966**, *31*, 4071.
[9] Y. Dong, C. Busacca *J. Org. Chem*. **1997**, *62*, 6464.
[10] C. Chen, D. Lieberman, R. Larsen, T. Verhoeven, P. Reider *J. Org. Chem* **1997**, *62*, 2676.



Schemat 5 Wewnątrzcząsteczkowa reakcja Hecka

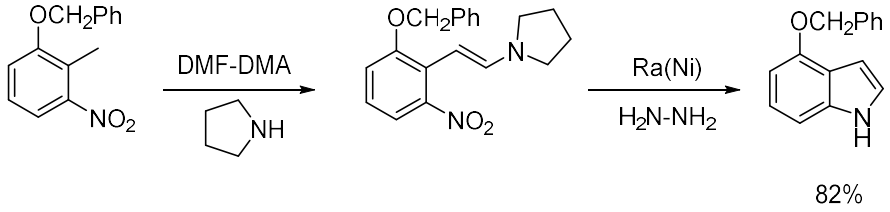
Na wyróżnienie zasługuje również reduktywna cyklizacja aromatycznych nitrozwiązków.[11] Jedną z najstarszych metod syntezy indoli, oczywiście oprócz już opisanej syntezy Fishera jest synteza Reisserta.[12] Otrzymanie indolu jest oparte na reakcji *o*-nitrotoluenu i szczawianu dietylu z utworzeniem produktu pośredniego, który następnie ulega reduktywnej cyklizacji pod wpływem czynnika redukującego (Schemat 6).



Schemat 6 Synteza Reisserta

Etanolan jest dostatecznie mocną zasadą, aby oderwać proton od grupy metylowej w nitrotoluenie, a wytworzony anion jest na tyle reaktywny, aby mogła zajść reakcja acylowania. Najpopularniejszym czynnikiem redukującym wykorzystanym w tym typie reakcji jest cynk w kwasie octowym. Synteza opracowana w 1897 roku doczekała się wielu modyfikacji.

Inną metodą wykorzystującą nitrozwiązki jest synteza Leimgrubera-Batcho (Schemat 7).[13] Daje ona możliwość otrzymania indoli niepodstawionych w pozycjach 2 i 3.

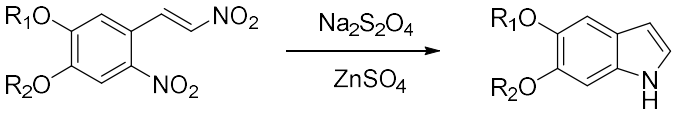


Schemat 7 Synteza Leimgrubera-Batcho

[11] B. Söderberg *Curr. Org. Chem.* **2000**, *4*, 727.
[12] A. Reissert *Ber. Dtsch Chem. Ges.* **1897**, *30,* 1030.
[13] A. Batcho, W. Leimgruber *Org. Synth.* **1990**, *7,* 34.

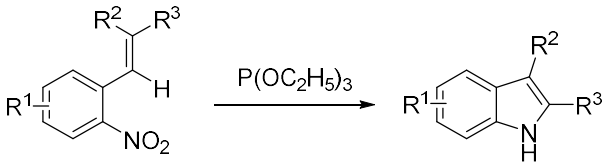
Klasyczna wersja reakcji oparta jest na kondensacji odpowiedniego *o*-nitrotoluenu z dimetyloacetalem *N,N* dimetyloformamidu (DMF-DMA) w obecności nadmiaru pirolidyny. Produkt pośredni zostaje poddany reduktywnej cyklizacji za pomocą Niklu Raneya, przekształcając się w odpowiedni indol. Warto zwrócić uwagę, że produkt pośredni jest stabilny w bardzo dużym zakresie podstawników w pierścieniu aromatycznym. W następnych latach powstało sporo prac modyfikujących warunki reakcji oraz sprawdzających czynniki redukujące – jednak klasyczna idea przebiegu reakcji pozostała bez zmian.

Na uwagę zasługuję synteza opisana przez Benigniego oraz Minnisa,[14] a następnie dopracowywana przez Prota w 1999 roku pod kątem zastosowania w większej skali oraz rozwiązania problemu oczyszczania produktów otrzymanych w trakcie syntezy.[15] Reakcje można potraktować jako ciekawą i praktyczną modyfikację syntezy Leimgrubera-Batcho – wykorzystuje ona nitrostyren jako substrat do syntezy indolu (Schemat 8). Sporym wyzwaniem w takiej syntezie jest opracowanie wydajnej metody otrzymywania odpowiedniej pochodnej dinitrostyrenu, ale autorzy rozwiązali ten problem, opisując wieloetapowa syntezę wychodzącą z pochodnej benzaldehydu.



Schemat 8 Synteza Prota

Opisano również reduktywną cyklizację podstawionych 2-nitrostyrenów prowadzącą do indoli (Schemat 9).[16]



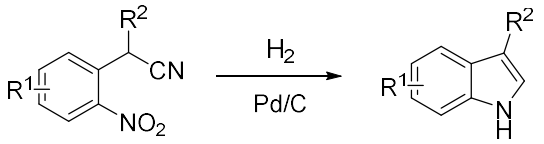
Schemat 9 Synteza Sundberga

W przypadku tej syntezy pierwszy raz jako czynnik redukujący został wykorzystany związek fosforu (III). Ogrzewanie aromatycznych związków nitrowych z fosforynem trietylu powoduje odtlenienie grupy nitrowej a w następstwie wewnątrzcząsteczkową cyklizacje. W przypadku obecności dwóch

[14] J. Benigni, R. Minnis *J. Heterocycl. Chem.* **1965**, *2,* 387.
[15] L. Novellino, M. d'Ischia, G. Prota *Synthesis* **1999**, 793.
[16] R. Sundberg. T. Tamazaki *J. Org. Chem.* **1967,** *32*, 290.

grup (alkil, aryl) przy węglu ß, w czasie cyklizacji następuję migracja jednej z grup do sąsiedniej pozycji. Reakcja przebiega prawdopodobnie poprzez przejściowe utworzenie i cyklizację nitrenu.

Duże znaczenie syntetyczne ma reakcja oparta na reduktywnej cyklizacji pochodnej *o*-nitrofenyloacetonitrylu, która w czasie katalitycznej redukcji wodorem ulega cyklizacji do indolu (Schemat 10).[17]



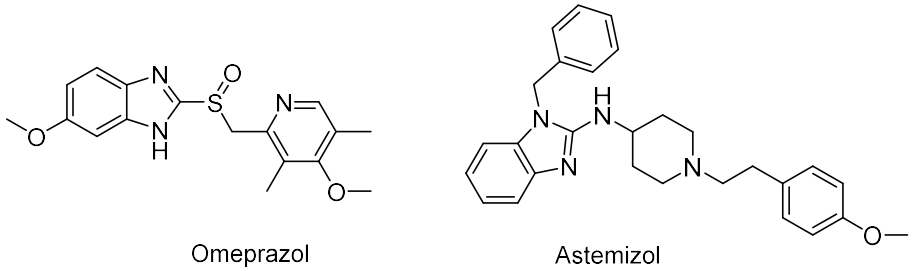
Schemat 10 Synteza indolu z wykorzystaniem pochodnej (2-nitrofenylo)acetonitrylu

Swoją popularność metoda zawdzięcza dostępności wyjściowych pochodnych fenyloacetonitrylu, które można łatwo otrzymać wykorzystując substytucję nukleofilową *o*-chlorowca w pierścieniu nitroaromatycznym[18] lub zastępcze podstawienie wodoru (VNS).[19]

Przedstawione powyżej klasyczne, wybrane spośród szerokiej palety możliwości, metody syntezy indoli były inspiracją dla wielu modyfikacji i ulepszeń przeprowadzonych w późniejszych latach. Walory praktyczne oraz szerokie zastosowanie, także w skali przemysłowej, zdecydowały o ich przedstawieniu w tym rozdziale.

Synteza benzimidazoli

Szkielet benzimidazolu można spotkać w wielu cząsteczkach związków biologicznie czynnych oraz znanych leków.[20]

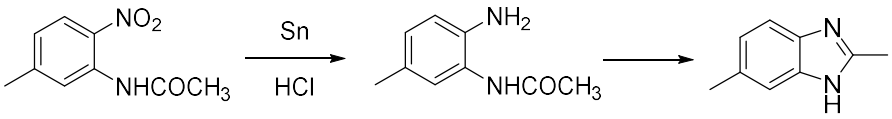


Rysunek 2

[17] (a) G. Walker *J. Am. Chem. Soc.* **1955**, *77*, 3844. (b) H. Snyder, E. Merica, C. Force, E. White *J. Am. Chem. Soc*. **1958**, *80*, 4622.
[18] A. Walkington, M. Gray, F. Hossner, J. Kitteringham M. *Voyle Synth. Commun.* **2003**, *33*, 2229.
[19] M. Mąkosza, K. Wojciechowski *Chem. Rev.* **2004,** *104*, 2631.
[20] Y. Bansal, O. Silakari *Bioorg. Med. Chem*. **2012**, *20,* 6208.

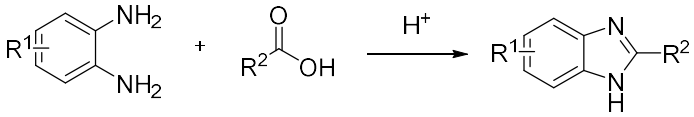
Przykładem takiego leku jest Omeprazol – inhibitor pompy protonowej stosowany w leczeniu choroby wrzodowej czy Astemizol – lek o działaniu przeciwhistaminowym (Rysunek 2). Z tego powodu, podobnie jak w przypadku opisanego wcześniej indolu, jest wiele prac w literaturze poświęconych metodologii otrzymywania benzimidazoli.[21]

Opisanie ich w sposób zwięzły i krótki nie jest łatwe. Na uwagę z pewnością zasługuje pierwsza synteza benzimidazolu opracowana w 1872 roku przez Hobreckera.[22] Reakcja polega na cyklizacji monoacetylowanej *o*-fenylenodiaminy w warunkach kwaśnych, a poprzedzona jest redukcją grupy nitrowej w acetylowanej *o*-nitroanilinie (Schemat 11).



Schemat 11 Synteza Hobreckera

Sama cyklizacja acylowanych *o*-fenylenodiamin w środowisku kwaśnym, prowadząca do rozmaicie 2-podstawionych benzimidazoli, jest także etapem kończącym inną znaną i szeroko stosowaną klasyczna reakcją opisaną w 1875 roku przez Ladenburga (Schemat 12).[23]



Schemat 12 Synteza Ladenburga

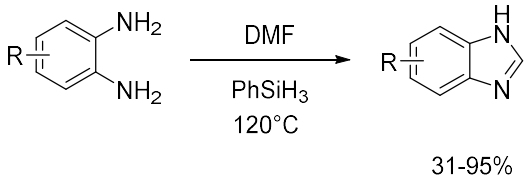
W reakcji tej do 2-podstawionego benzimidazolu prowadzi kondensacja *o*-aminoaniliny z kwasem karboksylowym. Ulegają jej kwasy alifatyczne, a w wyższej temperaturze również aromatyczne.

W odpowiednich warunkach w reakcje z *o*-aminoanilinami, także N-podstawionymi, wchodzą również inne związki karbonylowe takie jak chlorki kwasowe, estry, aldehydy czy ketony.[24]

Jednowęglowego elementu, łączącego oba atomy azotu w fenylenodiaminie może dostarczyć również DMF (Schemat 13).[25] Do tego typu przekształcenia mogą zostać wykorzystane również

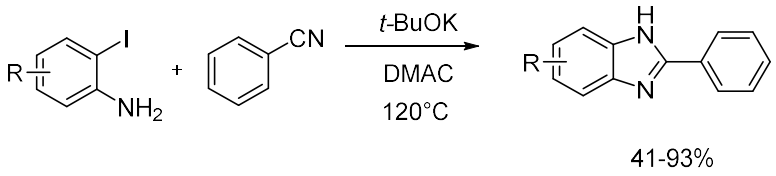
[21] N. Mahurkar, N. Gawhale, M. Kodape, M. Lokhande, S. Uke *Results Chem*. **2023**, *6,* 101139.
[22] (a) F. Hobrecker *Chem. Ber.* **1872**, *5*, 290. (b) J. Wright *Chem. Rev.* **1951**, *48,* 397. (c) K. Hofmann *The Chemistry of Heterocyclic Compounds, Imidazole and its Derivatives* **1953** *Part 1*.
[23] A. Ladenburg *Chem. Ber.* **1875**, *8*, 677.
[24] (a) L. Carvalho, E. Fernandes, M. Marques *Chem. Eur. J.* **2011**, *17*, 12544. (b) M. Alamgir, D. Black, N. Kumar *Top. Heterocycl. Chem.* **2007**, *9,* 87.
[25] J. Zhu, Z. Zhang, C. Miao, W. Liu, W. Sun *Tetrahedron* **2017**, *73,* 3458.

*o*nitroaniliny,[26] gdy warunki reakcji mają działanie redukujące ($DMF/H_2O/CuFe_2O_4$) i odpowiednia *o*-fenylenodiamina powstaje i reaguje *in situ*.



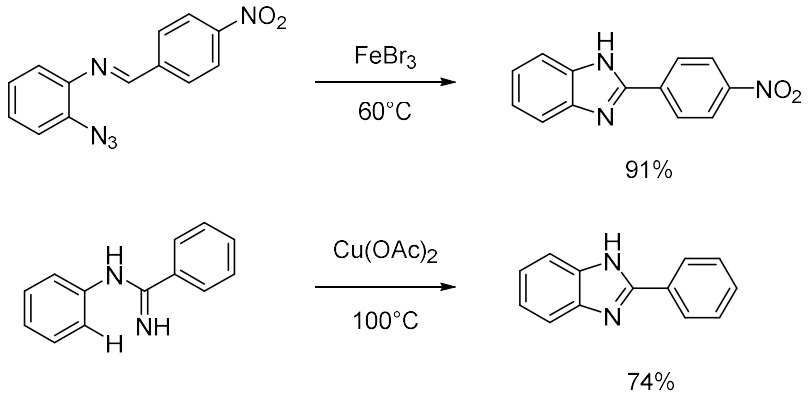
Schemat 13 Synteza benzimidazolu z wykorzystaniem fenylenodiaminy

Inną możliwością syntezy pierścienia imidazolowego jest zastosowanie reakcji cyklizacji z wykorzystaniem grupy cyjanowej w benzonitrylu. Reakcja zachodzi w obecności jedynie zasady i nie wymaga katalizy solami lub kompleksami metali (Schemat 14).[27]



Schemat 14 Synteza benzimidazolu z wykorzystaniem benzonitrylu

Benzimidazole można również otrzymać w wyniku katalizowanej solami metali reakcji wewnątrzcząsteczkowej (Schemat 15).



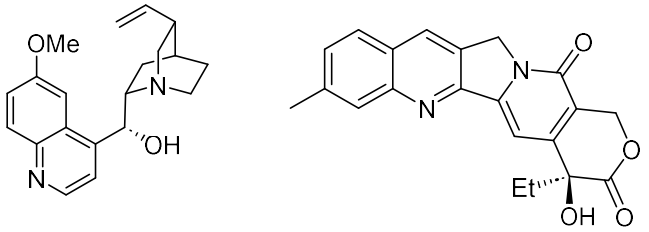
Schemat 15 Synteza benzimidazolu katalizowana solami metali

[26] K. Rasal, G. Yadav *Catal. Today* **2018**, *309,* 51.
[27] S. Xiang, W. Tan, D. Zhang, X. Tian, C. Feng, B. Wang, K. Zhao, P. Hu, H. Yang *Org. Biomol. Chem.* **2013**, *11*, 7271.

W pierwszym przypadku ma miejsce reakcja pomiędzy grupą azydkową oraz iminą znajdującymi się w jednej cząsteczce.[28] Prostota tej metody jest pozorna, gdyż odpowiedni wyjściowy azydek otrzymać trzeba w czterech przejściach z *o*-nitroaniliny. W drugim przykładzie cyklizacja amidyny następuje w wyniku CH funkcjonalizacji z utworzeniem wiązania C-N. Do katalitycznego działania soli miedzi niezbędne jest prowadzenie procesu w atmosferze tlenu.[29]

Synteza chinolin

Synteza szkieletu chinoliny jest kolejnym bardzo ważnym elementem chemii heterocyklicznej ze względu na jej obecność w bardzo wielu naturalnych oraz syntetycznych związkach o znaczeniu farmakologicznym.[30] Najsłynniejszym lekiem zawierającym strukturę chinoliny jest chinina[31] – lek antymalaryczny. Cząsteczka chinoliny występuje nie tylko w lekach o właściwościach przeciwpasożytniczych czy przeciwwirusowych, ale i przeciwnowotworowych jak np. w leku Kamptotecyna[32] (Rysunek 3). Co warto podkreślić, te i wiele innych pochodnych chinoliny to związki pochodzenia naturalnego.



Chinina Kamptotecyna

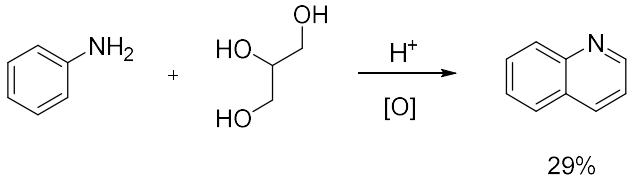
Rysunek 3

Z każdym rokiem przybywa nowych związków o potencjalnym znaczeniu biomedycznym. Struktura chinoliny odgrywa znaczną rolę nie tylko w chemii związków biologicznie czynnych, ale jest także kluczowym elementem szerokiej gamy organokatalizatorów, które od lat pozwalają przeprowadzać

[28] M. Shen, T. Driver *Org. Lett*. **2008**, *15*, 3367.
[29] G. Brasche , S. Buchwald *Angew. Chem. Int. Ed.* **2008**, *47*, 1932.
[30] (a) X. Shang, S. Morris-Natschke, Y. Liu, X. Guo, X. Xu, M. Goto, J. Li, G. Yang, K. Lee *Med. Res. Rev.* **2018**, *38,* 775. (b) B. Matada, R. Pattanashettar, N. Yernale *Bioorg. Med. Chem.* **2021**, *32,* 115973.
[31] A. Renslo *ACS Med. Chem. Lett.* **2013,** *4*, 1126.
[32] S. Rangappa, S. Patil *Biomed. pharmacother.* **2014***, 68,* 1161.

reakcje wydajnie i enancjoselektywnie.[33] Metod otrzymywania chinolin[34] jest wiele – poniżej zostały przedstawione najbardziej klasyczne.

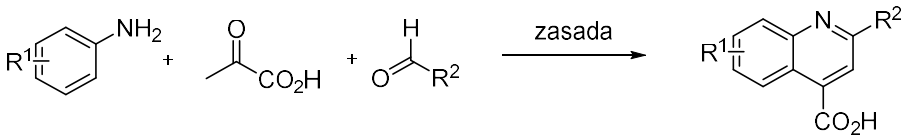
Przełomowym momentem w chemii związków heterocyklicznych było opracowanie pierwszej syntezy chinoliny przez Skraupa w 1880 roku (Schemat 16).[35] Reakcja pomiędzy aniliną i glicerolem zachodzi w obecności mocnego kwasu, utleniacza (na ogół chloranilu) w wysokiej temperaturze. Obecność mocnego kwasu powoduje odwodnienie glicerolu i powstanie akroleiny, która jest reaktywnym produktem pośrednim ulegającym dalszym przekształceniom.



Schemat 16 Synteza Skraupa

W modyfikacjach syntezy Skraupa wykorzystywane są enony lub enale zamiast glicerolu. Przykładem takiej modyfikacji jest reakcja Doebnera-Millera[36] – kondensacja pierwszorzędowej aminy aromatycznej z α,β-nienasyconymi związkami karbonylowymi (głównie α,β-nienasyconymi aldehydami) prowadzi do powstania 2,3-dipodstawionych chinolin.

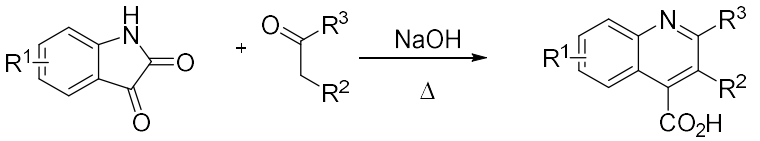
Reakcja Doebnera[37] to trzyskładnikowa synteza również pozwalająca na otrzymanie chinoliny, ale posiadającej podstawnik karboksylowy w pozycji 4. W reakcji reagują ze sobą anilina, aldehyd oraz kwas pirogronowy (Schemat 17).



Schemat 17 Synteza Doebnera

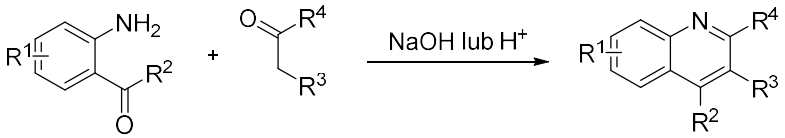
[33] M. Gaunt, C. Johansson, A. McNally, T. Vo *Drug Discov. Today* **2007**, *12*, 8. (b) J. Duan, P. Li *Catal. Sci. Technol*. **2014**, *4*, 311.
[34] A. Weyesa, E. Mulugeta *RSC Adv.* **2020**, *10*, 20784.
[35] Z. Skraup *Monatsh. Chem*. **1880**, *1,* 316.
[36] Y. Wu, L. Liu, H. Li, D. Wang, Y. Chen *J. Org. Chem***. 2006**, *71*, 6592.
[37] (a) O. Döbner *Liebigs Ann.* **1887**, *242,* 265. (b) H. Komatsu, T. Shigeyama, T. Sugimoto, H. Nishiyama *J. Org.Chem.* **2023**, *88*, 12816.

Do pochodnych chinoliny z grupą karbonylową w pozycji 4 prowadzi również synteza Pfitzingera.[38] W reakcji tej izatyna reaguje ze związkiem karbonylowym (Schemat 18).



Schemat 18 Synteza Pfitzingera

Wkrótce po opublikowaniu syntezy Skraupa, w 1882 roku opracowana została przez Friedländera kolejna fundamentalna synteza chinolin (Schemat 19).[39]

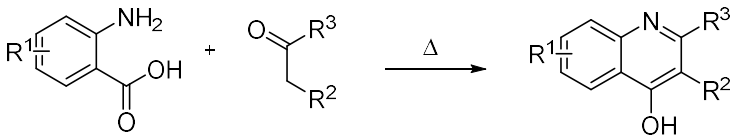


Schemat 19 Synteza Friedländera

Reakcja może być katalizowana zarówno kwasem jak i zasadą. Co interesujące, istnieją dwa konkurencyjne mechanizmy opisujące przebieg reakcji – różniące się kolejnością etapów – pierwszy zakłada możliwą reakcję aldolową, drugi utworzenie iminy – zasady Schiffa.

Modyfikacją metody Friedländera jest synteza opisana przez polskiego chemika Stefana Niementowskiego.[40] Odkrył on, że ogrzewanie kwasu antranilowego w obecności acetofenonu prowadzi do powstania 2-fenylo-4-hydroksychinoliny (Schemat 20). W reakcji mogą być również wykorzystane inne ketony oraz aldehydy.

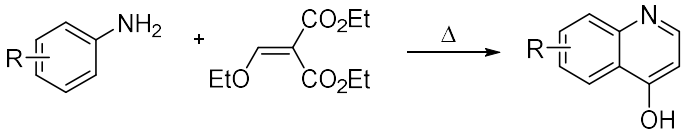
W przypadku reakcji Niementowskiego zakłada się, że najbardziej prawdopodobny przebieg reakcji jest poprzez utworzenie zasady Schiffa i następczej cyklizacji prowadzącej do powstania chinoliny.



Schemat 20 Synteza Niementowskiego

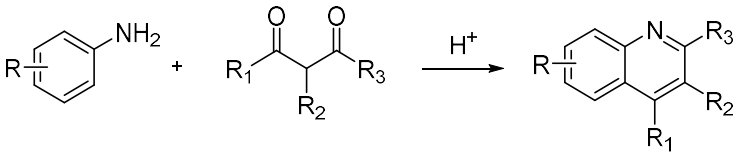
[38] (a) W. Pfitzinger *J. Prakt. Chem.* **1888**, *38*, 582. (b) Elghamry, Y. Al-Faiyz *Tetrahedron Lett.* **2016**, *57,* 110. (c) M.G-A. Shvekhgeimer *Chem. Heterocyc. Compd.* **2004**, *40*, 20.
[39] N. Anand, T. Chanda, S. Koley, S. Chowdhury, M. Sing *RSC Adv.* **2015**, *5*, 7654.
[40] (a) S. Niementowski *Chem. Ber.* **1905**, *38,* 2044. (b) R. Manske *Chem. Rev*. **1942**, *30*, 113.

Również metoda syntezy opracowana przez Gould-Jacoba[41] pozwala otrzymać pochodne 4-hydroksychinoliny (Schemat 21). Klasyczna reakcja opisana w 1939 roku jest oparta na kondensacji aniliny z pochodną kwasu malonowego, 2-(etoksymetyleno)malonianem dietylu. Podstawieniu ulega grupa etoksylowa, a następnie produkt pośredni pod wpływem temperatury ulega cyklizacji do pochodnej chinoliny. Ogrzewanie w warunkach kwasowych może prowadzić do dekarboksylacji pierwotnego produktu.



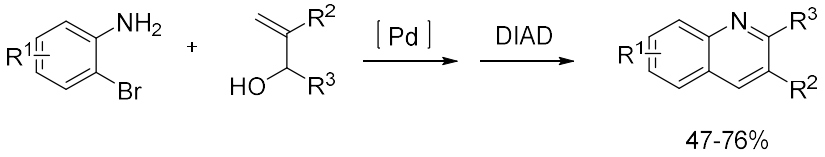
Schemat 21 Synteza Gould-Jacoba

W syntezie Combes'a anilina reaguje ze związkami 1,3-dikarbonylowymi (Schemat 22). W pierwszym etapie reakcji zachodzi kondensacja pomiędzy aminą aromatyczną oraz grupą karbonylową, w wyniku której powstaje zasada Schiffa. Następnie zachodzi wewnątrzcząsteczkowa substytucja elektrofilowa w pierścieniu aromatycznym.



Schemat 22 Synteza Combesa

O syntezie Larocka (Schemat 2)[6], było już powiedziane kilka słów w trakcie przedstawiania podstawowych metod otrzymywania indoli. *o*-Halogenoaniliny, które łatwo ulegają reakcji Hecka z alkinami mogą też reagować z alkoholami allilowymi.

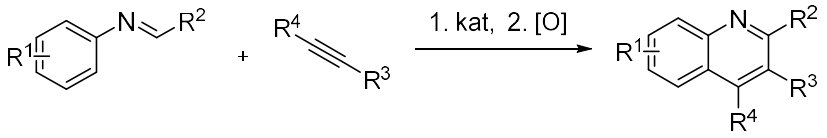


Schemat 23 Synteza chinolin opisana przez Larocka

[41] (a) T. Jennifer, B. Andrew, K. Stanislaw, W. Ying, C. Manwika, D. Stevan *J. Org. Chem*. **2017**, *82*, 1073. (b) R. Gould, W. Jacobs *J. Am. Chem. Soc.* **1939**, *61*, 2890.

Dodanie DIAD[42] (ester izopropylowy kwasu azodikarboksylowego) pozwala na odwodornienie produktu pośredniego otrzymanego w reakcji Larocka i otrzymanie chinoliny (Schemat 23).

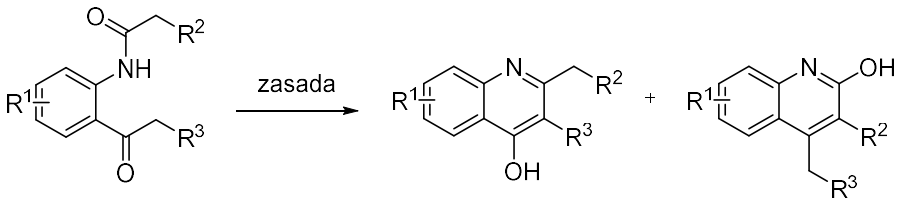
Synteza Povarova[43] opisana w 1963 roku oparta jest na cykloaddycji aromatycznej iminy i związku nienasyconego – alkenem lub alkinem. Imina powstaje w wyniku kondensacji aniliny z aldehydem.



Schemat 24 Synteza Povarova

Reakcję Povarova można sklasyfikować jako reakcję Dielsa-Aldera w której imina jest dienem a związek nienasycony dienofilem. Reakcje można prowadzić w układzie trójskładniowej mieszaniny otrzymując jako produkt chinolinę, ale dopiero po utlenieniu tetrahydrochinoliny powstającej pierwotnie (Schemat 24).[44]

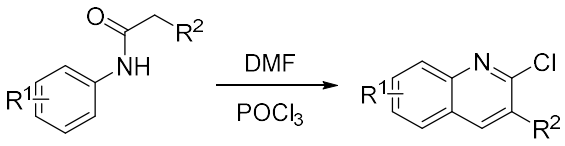
Cyklizacja Campsa[45] to reakcja chemiczna, podczas której *o*-(acyloamino)acetofenon pod wpływem zasady przekształca się w dwie różne hydroksychinoliny (Schemat 25). Proporcja produktów zależy od warunków reakcji i budowy substratów, ale w wielu przypadkach obserwuje się wysoką selektywność reakcji.



Schemat 25 Synteza Campsa

W syntezie Meth-Cohna[46] pochodne acetanilidu ulegają przekształceniu pod wpływem odczynnika Vilsmeiera (Schemat 26) do chinolin posiadających w pozycji 2 atom chloru.

[42] M. Stone *Org. Lett*. **2011**, *13*, 2326.
[43] (a) L. Povarov *Russ. Chem. Rev.* **1967**, *36*, 656. (b) W. de Paiva, Y. Rego, Â. de Fátima, S. Fernandes *Synthesis* **2022**, *54*, 3162.
[44] S. Kobayashi, H. Ishitani, S. Nagayama *Synthesis* **1995,** *9*, 1195.
[45] A. Fisyuk, A. Kostyuchenko, D. Goncharov *Russ. J. Org. Chem*. **2020**, *56*, 1649.
[46] O. Meth-Cohn, B. Narine *Tetrahedron Lett.*, **1978**, *19*, 2045.



Schemat 26 Synteza Meth-Cohna

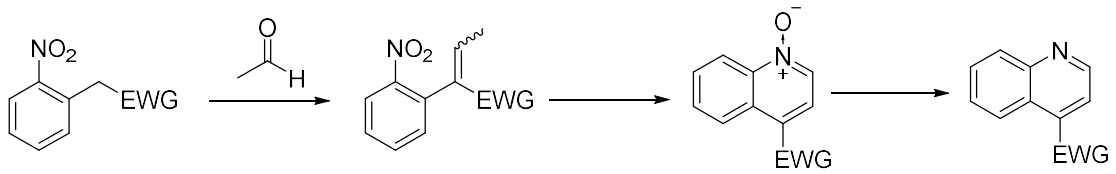
Pierwszy etap reakcji polega na formylowaniu Vilsmeiera-Haacka, drugi zaś na wewnątrz-cząsteczkowej substytucji elektrofilowej w pierścieniu aromatycznym (reakcja Friedla-Craftsa).

Związki heterocykliczne mają bardzo szeroki zakres zastosowań, a w szczególności pełnią ważną rolę w chemii medycznej. Z tego powodu intensywne badania nad syntezą związków heterocyklicznych prowadzone są od bardzo dawna. Pomimo przedstawienia we wstępie literaturowym jedynie podstawowych metod otrzymywania zaledwie trzech azotowych związków heterocyklicznych – zrobienie tego w sposób zwięzły było niezwykle trudne, a w sposób dokładny wręcz niemożliwe. W literaturze możemy znaleźć wiele przeglądów oraz książek opisujących chemię związków indolu, benzimidazolu oraz chinoliny. Obszerność dostępnej literatury poświęconej tej tematyce pokazuje jak ważna jest to dziedzina chemii – ile zostało już zrobione i jak dużo jeszcze przed nami.

4. Badania własne

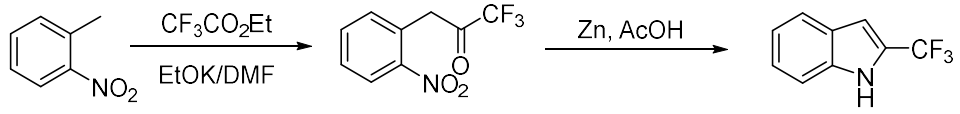
4.1. Chemiczna charakterystyka prezentowanych przemian

Synteza skumulowanych dwupierścieniowych układów heterocyklicznych w oparciu o *orto* podstawione pochodne nitrobenzenu polega na dobudowaniu pięcio- lub sześcioczłonowego pierścienia na bazie czterech atomów istniejących w nitrozwiązku, włączając grupę nitrową i węglowy lub azotowy podstawnik *orto*. Potrzebny jest do tego komponent spinający, zdolny utworzyć jedno- lub dwuatomowy mostek pomiędzy tymi centrami, oraz zdolność do reakcji chemicznej, w wyniku której mogą powstać nowe wiązania. Aby dana reakcja była możliwa do przeprowadzenia z wykorzystaniem nitrozwiązku kluczowe znaczenie ma niewątpliwie grupa nitrowa. Jej silnie elektronoakceptorowy charakter sprawia, że *orto* benzylowe centrum węglowe staje się podatne na działanie silnych zasad, a sama grupa nitrowa, jej centralny atom azotu, może być obiektem wewnątrzcząsteczkowego ataku nukleofilowego. Dodatkowa aktywacja pozycji benzylowej grupą electronoakceptorową (EWG) umożliwia skuteczne zastosowanie słabszych zasad. Ten schemat reaktywności został wykorzystany w syntezie pochodnych chinoliny posiadających podstawnik silnie electronoakceptorowy (EWG) w pozycji 4 (Schemat 27).



Schemat 27 Synteza pochodnej chinoliny posiadających podstawnik EWG w pozycji 4

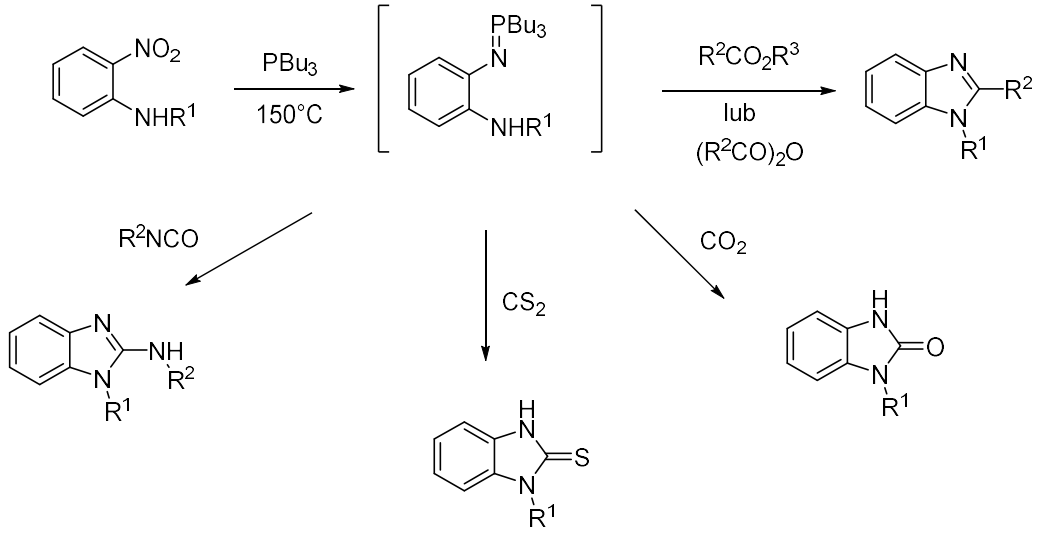
Nieco odmienny schemat został zastosowany w syntezie pochodnych 2-trójfluorometyloindolu, gdzie grupa nitrowa w pierwszym etapie aktywowała benzylowy atom węgla, w drugim zaś została zredukowana do grupy aminowej pełniącej rolę nukleofila (Schemat 28).



Schemat 28 Synteza 2-trifluorometyloindolu

Trzeci schemat (Schemat 29), zastosowany został w przekształceniach pochodnych *o*-nitroanilin, polega na początkowym przekształceniu grupy nitrowej w nukleofilowe centrum azotowe w postaci iminofosforanu, ugrupowania o charakterze aza-ylidu, a drugi etap wykorzystuje nukleofilowe

własności grupy *orto* aminowej. W ten sposób zostały zsyntezowane rozmaite pochodne 2-funkcjonalizowanych benzimidazoli.

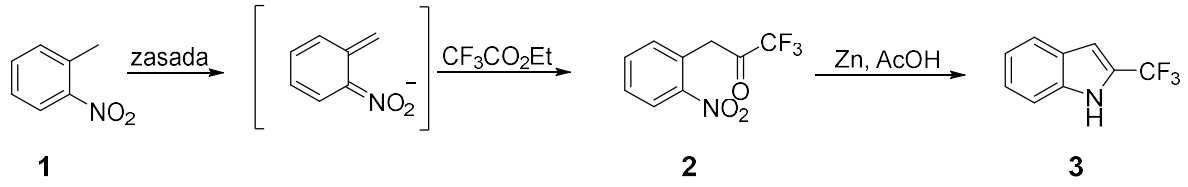


Schemat 29 Synteza pochodnych 2-funkcjonalizowanych benzimidazoli

4.2. Synteza 2-trifluorometyloindoli z odpowiednio podstawionych *o*-nitrotoluenów

Motyw strukturalny 2-trifluorometyloindolu jest licznie reprezentowany w związkach biologicznie czynnych. W literaturze można znaleźć szereg informacji na temat jak ważna jest struktura indolu w chemii medycznej[47] oraz w jak spektakularny sposób na właściwości biologiczne i medyczne może wpłynąć obecność grupy CF_3.[48]

Znanych jest szereg metod otrzymywania 2-CF_3-indoli,[49] jednak większość z nich jest złożona i wykorzystuje drogie reagenty (np. reagenty Togniego czy Umemoto) lub wymaga specjalnej aparatury (np. w przypadku reakcji prowadzonych w fotoreaktorach). Ponadto, większość nowoczesnych metod syntezy tych ważnych związków została opracowana lub jest skuteczna jedynie w bardzo małej skali laboratoryjnej (do kilkuset miligramów). Fakt ten budzi wątpliwości co do zastosowania metody w praktycznej syntezie wielogramowej, a tym bardziej w skali przemysłowej. Z tych powodów zdecydowano się na opracowanie efektywnej, tańszej oraz skalowanej metody otrzymywania 2-trifluorometyloindoli. Studia literaturowe pokazały, że do syntezy 2-trifluorometyloindoli nikt dotychczas nie wykorzystał reakcji typu Reisserta (lub Cleisena) bardzo prostej i ogólnej.



1 **2** **3**

Schemat 30 Synteza 2-trifluorometyloindolu z nitrotoluenu

[47] (a) R.J. Sundberg *The Chemistry of Indoles; Academic Press* **1970**. (b) G.W. Gribble *Heterocyclic Scaffolds II: Reactions and Applications of Indoles, In Top. Heterocycl. Chem* **2010**. (c) N.K. Kaushik, P. Attri, N. Kumar, Ch. Kim, A. Verma, E. Choi *Molecules* **2013**, *18*, 6620.

[48] (a) E.P. Gillis, K.J. Eastman, M.D. Hill, D.J. Donnelly, N.A. Meanwell *J. Med. Chem.* **2015**, *58,* 8315. (b) W.K. Hagmann *J. Med. Chem.* **2008**, *51*, 4359. (c) K. Müller, C. Faeh, F. Diederich *Science* **2007,** *317*, 1881.

[49] (a) V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, G. Haufe, V.G. Nenajdenko *Synthesis* **2009**, *23*, 3905. (b) Z. Wang, F. Ge, W. Wan, H. Jiang, J. Hao *J. Fluorine Chem.* **2007**, *128*, 1143. (c) K. Miyashita, K. Kondoh, K. Tsuchiya, H. Miyabe, T. Imanishi *J. Chem. Soc. Perkin Trans.* **1996**, *11,* 1261. (d) J. Pedroni, N. Cramer *Org. Lett.* **2016**, 18, 1932. (e) Z. Wang, T. Zhang, Q. Ma, W. Ni *Synthesis* **2014**, *46,* 3309. (f) Yamakawa, A.; Horino, Y. Jpn. Kokai Tokkyo Koho *JP 2008037760* **2008**. (g) X. Shi, X. Li, L. Ma, D. Shi *Catalysts* **2019**, *9*, 278. (h) J. Xie, Zh.-Q. Wang, G.-F Jiang *RSC Adv.* **2019**, *9*, 35098. (i) A. Miyazaki, R. Shimizu, H. Egami, M. Sodeoka *Hetrocycles* **2012**, *86*, 979. (j) R. Rey-Rodrigues, P. Retailleau, P. Bonnet, I. Gillaizeau *Chem.–Eur. J.* **2015**, *21*, 3572. (k) M.S. Wiehn, E.V. Vinogradova, A. Togni *J. Fluor. Chem.* **2010**, *131,* 951. (l) M. Yoshida, T. Yoshida, M. Kobayashi, N. Kamigata *J. Chem. Soc.* **1989,** *1*, 909. (m) W. J . Choi, S. Choi, K. Ohkubo, S. Fukuzumi, E.J. Cho, Y. You *Chem. Sci.* **2015**, *6*, 1454. (n) T. Kino, Y. Nagase, Y. Ohtsuka, K. Yamamoto, D. Uraguchi, K. Tokuhisa, T. Yamakawa *J. Fluorine Chem*. **2010**, *131*, 98.

W rezultacie zaproponowany został sposób polegający na acylowaniu anionu pochodnej *o*-nitrotoluenu trifluorooctanem etylu, z następczą reduktywną cyklizacją powstałego nitroketonu (Schemat 30). Atutem tej metody wydawała się być jej prostota oraz dostępność zastosowanych reagentów. W szczególności, reagentem dostarczającym grupę trifluorometylową w tej metodzie jest ester kwasu trifluorooctowego, bezpieczny w użyciu i jeden z najtańszych dostępnych źródeł grupy CF_3.

Opracowanie warunków reakcji

Pierwszym zadaniem w opracowaniu powyższej syntezy był dobór odpowiedniej zasady do wytworzenia nitrotoluenu, który następnie mógł zostać poddany reakcji acylowania.

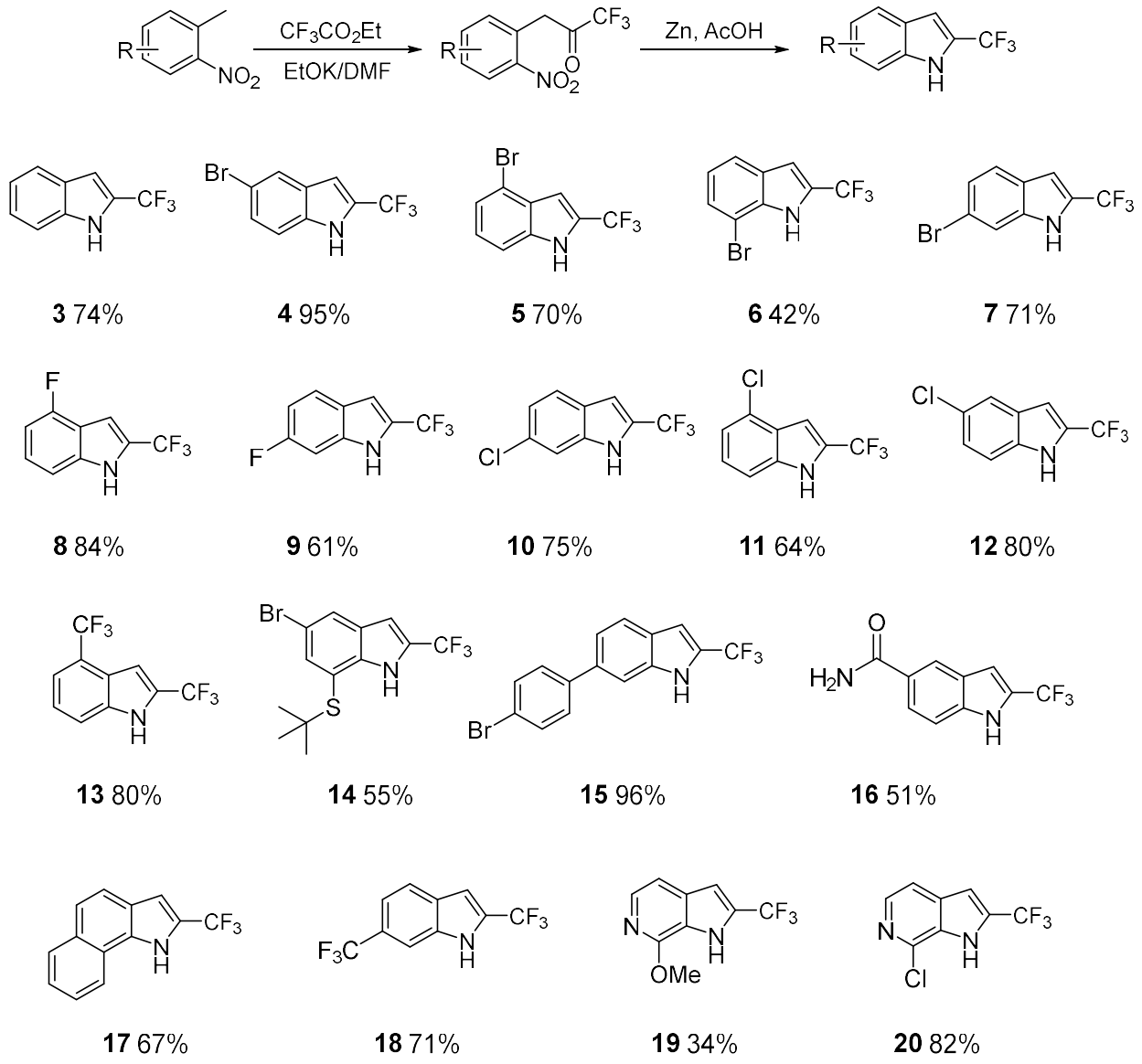
W literaturze opisane są przykłady deprotonowania *o*-nitrotoluenu przy pomocy zasad takich jak: wodorek sodu, wodorotlenek sodu, etanolan sodu lub *t*-butanolan potasu. Przydatność tych zasad w planowanej syntezie sprawdziłam na modelowej reakcji acylowania *o*-nitrotoluenu w różnych układach zasada/rozpuszczalnik.

Próby reakcji z użyciem *t*-butanolanu potasu w różnych rozpuszczalnikach (DMSO, THF oraz DMF) jak i wodorku sodu w DMF, prowadziły jedynie do śladowych ilości produktu **2**. Dopiero zastosowanie etanolanu potasu w DMF pozwoliło na otrzymanie produktu acylowania z wysoką wydajnością. Udało mi się również ustalić optymalny sposób prowadzenia reakcji polegający na tym, że do roztworu trifluorooctanu etylu w suchym DMF w temperaturze 0-50°C dodaje się w jednej porcji najpierw etanolan potasu a następnie nitrotoluen. W ten sposób można uniknąć powstawania produktu reakcji nitrotoluenu z jego anionem. Następnie mieszaninę pozostawia się do samoistnego ogrzania do temperatury pokojowej.

Kolejnym etapem był wybór odpowiedniego reagenta do reduktywnej cyklizacja związku **2** do produktu **3**. Naturalnym było zastosowanie w tym celu cynku w kwasie octowym, popularnego układu redukującego grupę nitrową i użytego w podobnym celu w klasycznej metodzie syntezy indoli Reisserta. Oprócz tego układu zbadałam możliwość zastosowania innych czynników redukujących takich jak Fe/NH_4Cl, $SnCl_2 \cdot H_2O/AcOH$ oraz $Na_2S_2O_4$. W porównawczych eksperymentach reakcja prowadzona w układzie Zn/AcOH dawała najwyższe wydajności i taki też układ został zastosowany w szerokim zakresie reakcji syntezy 2-trifluorometyloindoli. Dwuetapowa synteza prowadzona była z wykorzystaniem surowego, przejściowego produktu acylowania, bez jego izolacji i oczyszczania.

Zakres stosowalności metody

Opracowana metoda pozwoliła na otrzymanie szeregu podstawionych 2-trifluorometyloindoli z bardzo dobrymi wydajnościami (Schemat 31). Część z tych reakcji prowadzonych było w skali 100-250 mmoli, co pozwalało na otrzymanie w jednej reakcji kilkudziesięciu gramów produktu.

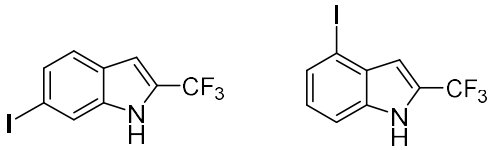


Schemat 31 Otrzymane pochodne 2-trifluorometyloindolu

W przypadku 5-bromo-2-nitrotoluenu udało się uzyskać wydajność nawet 95% reakcji przeprowadzonej w skali 100 mmoli. Jednocześnie, metoda wykazała pewną tolerancję na rodzaj podstawników w pierścieniu benzenowym i zarówno nitrotolueny podstawione chlorowcami jak i niektórymi grupami elektronoakceptorowymi (CN, CF_3) reagowały z wysoką wydajnością.

Zaobserwowane ograniczenia metody wynikają z wrażliwości podstawników na zasadowe warunki zastosowane w pierwszym etapie reakcji oraz na redukujący charakter etapu drugiego.

Reakcja 4-jodo i 6-jodo-2-nitrotoluenu przy zastosowaniu standardowego układu (Zn/AcOH) zachodziła z częściową redukcją jodu z cząsteczki produktu. Dysponując jedynie klasycznymi metodami rozdziału mieszaniny reakcyjnej rozdzielenie produktu głównego i ubocznego okazało się niemożliwe. Próba wykorzystania układów redukcyjnych opartych na chlorku cyny prowadziła do otrzymania jedynie hemiaminalu z niewielką wydajnością 36% a zastosowanie układu Fe/NH_4Cl okazało się nieskuteczne (Rysunek 4). Natomiast w obecności ditionianu sodowego w przypadku obu jodozwiązków powstał wyłącznie właściwy produkt (**21** oraz **22**), chociaż z nieco niższą wydajnością.



21 69% **22** 66%

Rysunek **4**

Ze względu na silne zasadowe środowisko reakcja nitrotoluenu zawierającego w pierścieniu grupę CN prowadziła do hydrolizy grupy cyjanowej do amidowej. Podstawniki w pierścieniu nitrotoluenu mają istotny wpływ na reaktywność danego związku w reakcji acylowania. 3-Metylo-2-nitrotoluen nie ulegał reakcji acylowania, gdyż jego kwasowość jest zbyt mała. Z drugiej strony, łatwo przeprowadzony w anion nitrotoluen podstawiony grupą SO_2Me, nie był wystarczająco nukleofilowy i w stosowanych warunkach nie reagował z trifluorooctanem etylu.

Podsumowanie

Niezależnie od pewnych ograniczeń, opracowana metoda pozwala na otrzymywanie szerokiej gamy podstawionych 2-trifluorometyloindoli w łagodnych warunkach, wykorzystując jedynie tanie, dostępne reagenty i bez wydzielenia produktów pośrednich. Wysokie wydajności i powtarzalne wyniki otrzymuje się prowadząc reakcje w skali wielogramowej, co jest cenną zaletą w perspektywie możliwości wykorzystania metody także do syntez wielkoskalowych.

Powyższe wyniki zostały opublikowane w pracy:

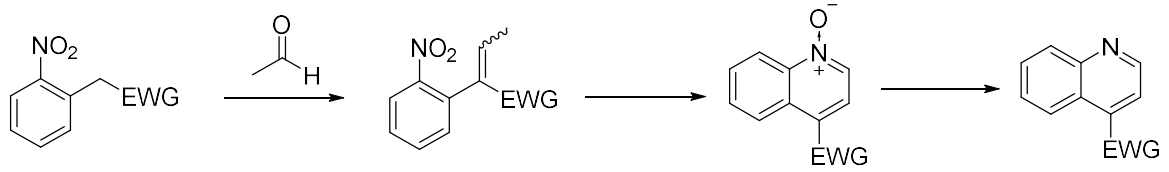
Magdalena Walewska-Królikiewicz, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel „Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes" *Tetrahedron Lett.* **2021**, *86*, 153515.

4.3. Synteza 4-EWG chinolin z aktywowanych pochodnych 2-nitrotoluenu

Szkielet chinoliny jest jednym z najważniejszych heterocyklicznych układów w chemii organicznej.[50] Różnie podstawione chinoliny, ich *N*-tlenki i podobne związki są ważnymi materiałami wyjściowymi w syntezie rozlicznych, bardziej złożonych cząsteczek o znanej lub przewidywanej aktywności biologiczna.[51] W szczególności dotyczy to chinolin posiadających podstawniki, które można modyfikować, przekształcać i w ten sposób rozszerzać zakres syntezy w stronę pożądanych struktur. Dlatego synteza takich związków powinna pozwolić na dostarczenie produktów w znacznych ilościach. Przegląd literatury wykazał niedostatek takich metod, a te opisane najczęściej wiązały się z użyciem kosztownych bądź niepożądanych reagentów i/lub warunków. Także prowadzone wcześniej i publikowane w Zespole VII prace nie dały zadowalających rezultatów ze względu na ich zakres, skalę i powtarzalność.[52]

Dwuetapowa synteza tlenków chinolin polegająca na kondensacji typu Knoevenagla aktywowanych pochodnych *o*-nitrotoluenu z aldehydem octowym, a następnie cyklokondensacji pod wpływem zasad, wymagała opracowania dla obu etapów warunków gwarantujących zadowalające wydajności procesu dla pochodnych nitrotoluenu aktywowanych różnymi grupami elektronoakceptorowymi (Schemat 32).

Chinoliny podstawione w pozycji 4 są w niewielkim stopniu opisane w literaturze.[53]



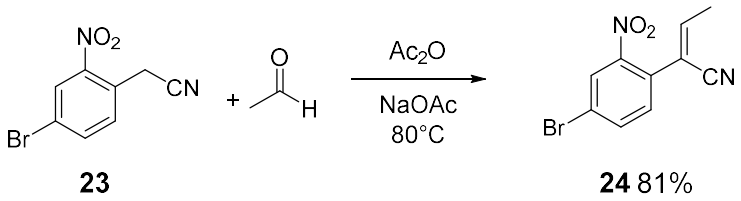
Schemat 32 Synteza pochodnej chinoliny posiadających podstawnik EWG w pozycji 4

Pierwszy etap syntezy jest oparty na kondensacji Knoevenagla. Obecność grupy elektronoakceptorowej pozwala na stabilizacje otrzymanego pod wpływem nawet słabej zasady

[50] (a) B.S. Matada, R. Pattanashettar, N.G. Yernale *Bioorg. Med. Chem.* **2021**, *32*, 115973. (b) O. Afzal, S. Kumar, M.R. Haider, M.R. Ali, R. Kumar, M. Jaggi, S. Bawa *Eur. J. Med. Chem.* **2015**, *97*, 871. (c) R.H. Manske *Chem. Rev.* **1942**, *30,* 113.
[51] (a) S. Sharma, K. Singh, S. Singh *Curr. Org. Synth*. **2023**, *20,* 606. (b) K. Singha, I. Habib, M. Hossain, *Chemistry Select* **2022**, *7,* e20220353. (c) V. Sharma, D.K. Mehta, R. Das *Mini-Rev. Med. Chem.* **2017**, *17*, 1557.
[52] (a) K. Anczkiewicz, M. Krolikiewicz, Z. Wrobel, K. Wojciechowski *Tetrahedron* **2015**, *71,* 3924. (b) Z. Wróbel, A. Kwast, M. Mąkosza *Synthesis* **1993**, *31*. (c) Z. Wrobel, M. Mąkosza *Tetrahedron* **1993**, 5315. (d) R. Bujok, Z. Wrobel, K. Wojciechowski *Tetrahedron Lett.* **2016**, *57,* 1014.
[53] (a) S.R. Banini, M.R. Turner, M.M. Cummings, B.C.G. Soderberg *Tetrahedron* **2011**, *67,* 3603. (b) F.N. Palmer, F. Lach, C. Poriel, A.G. Pepper, M.C. Bagley, A.M.Z. Slawin, Ch. Moody *J. Org. Biomol. Chem.* **2005**, *3,* 3805.

anionu oraz na przeprowadzenie reakcji addycji nukleofilowej. Produkt kondensacji można poddać cyklizacji do tlenku chinoliny. Osobnym zagadnieniem było znalezienie odpowiedniego sposobu redukcji tlenku chinoliny z zachowaniem grup 4-EWG.

Warunki kondensacji z aldehydem octowym wzorowane były na opisanej kondensacji Knoevenagla związków dikarboksylowych.[54] Aktywowane pochodne nitrotoluenu okazały się jednak za mało aktywne i opisany w literaturze bromek litu należało zastąpić mocniejszą zasadą. Próby wykorzystania w tym celu LiCl, Et_3N i DBU Były nieskuteczne. Dobre rezultaty zapewniło użycie NaOAc (Schemat 33).



23 **24** 81%

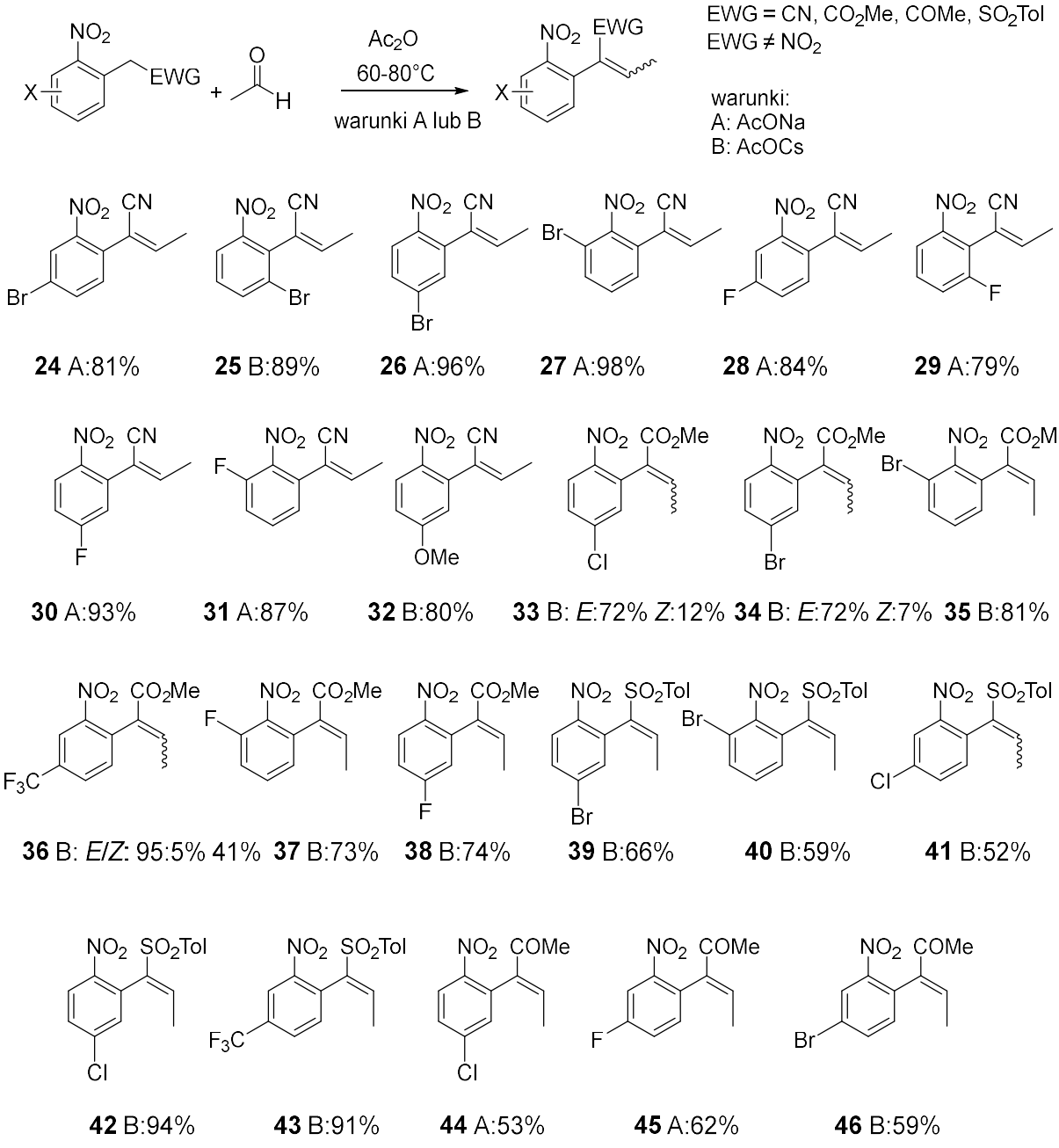
Schemat 33 Optymalizacja kondensacji Knoevenagla w pierwszym etapie syntezy

W tych warunkach została przeprowadzona synteza pochodnych 2-nitrostyrenu, w których rolę grupy aktywującej podwójne wiązanie pełniły, oprócz grupy cyjanowej, także sulfonowa, estrowa, karbonylowa oraz nitrowa (Schemat 34). W większości z nich produkty kondensacji powstawały z dobrą lub bardzo dobrą wydajnością. Jedynie reakcje α,2-dinitrotoluenu miały nieselektywny przebieg i prowadziły do złożonej mieszaniny produktów.

W niektórych przypadkach, gdy rezultat okazał się mało zadowalający znacznie lepsze wyniki zapewniało zastosowanie mocniejszej zasady – octanu cezu.

Geometria otrzymanych alkenów była zróżnicowana i silnie zdeterminowana wielkością aktywującej grupy funkcyjnej. Nienasycone nitryle tworzyły się wyłącznie w konfiguracji *Z*, sulfony w konfiguracji *E*, a estry jako mieszanina izomerów. Jak się okazało później na etapie cyklizacji konfiguracja tych związków nie odgrywała istotnej roli.

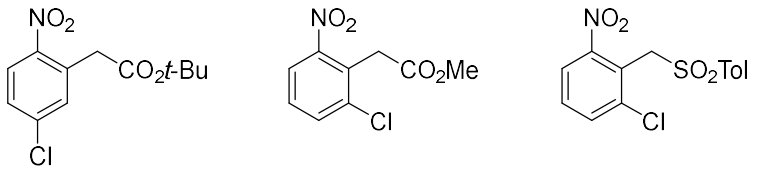
[54] M. Sylla, D. Joseph, E. Chevallier, C. Camara, F. Dumas *Synthesis* **2006**, *6*, 1045.



Schemat 34 Produkty kondensacji aktywowanych 2-nitrotoluenów z aldehydem octowym

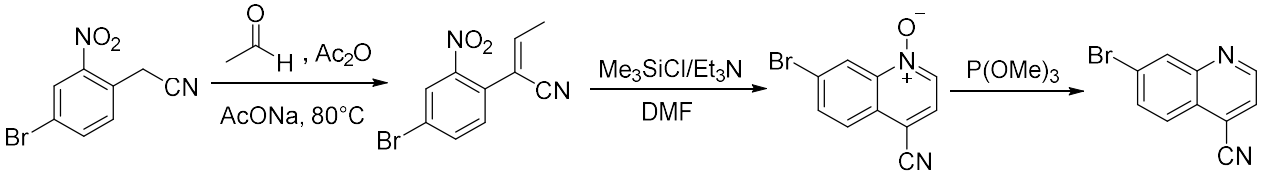
Ograniczenia reakcji, jakie zostały zaobserwowane, wynikały z zawady sterycznej występującej w rejonie tworzenia nowych wiązań. Produkt kondensacji nie powstał w reakcji dla związków aktywowanych grupą estrową i sulfonową, posiadających zatłoczenie w pozycji trzy w pierścieniu aromatycznym. Co ciekawe w przypadku analogicznego nitrylu wydajność otrzymanego produktu była bardzo wysoka. Również wielkość grupy estrowej wpływała negatywnie na przebieg reakcji

(Rysunek 5). Ester *t*-butylowy **47** nie dał spodziewanego produkt, podczas gdy zarówno analogiczny nitryl jak i ester metylowy reagowały z bardzo dobrą wydajnością.



47 **48** **49**

Rysunek 5 Substraty niereaktywne w reakcji kondensacji

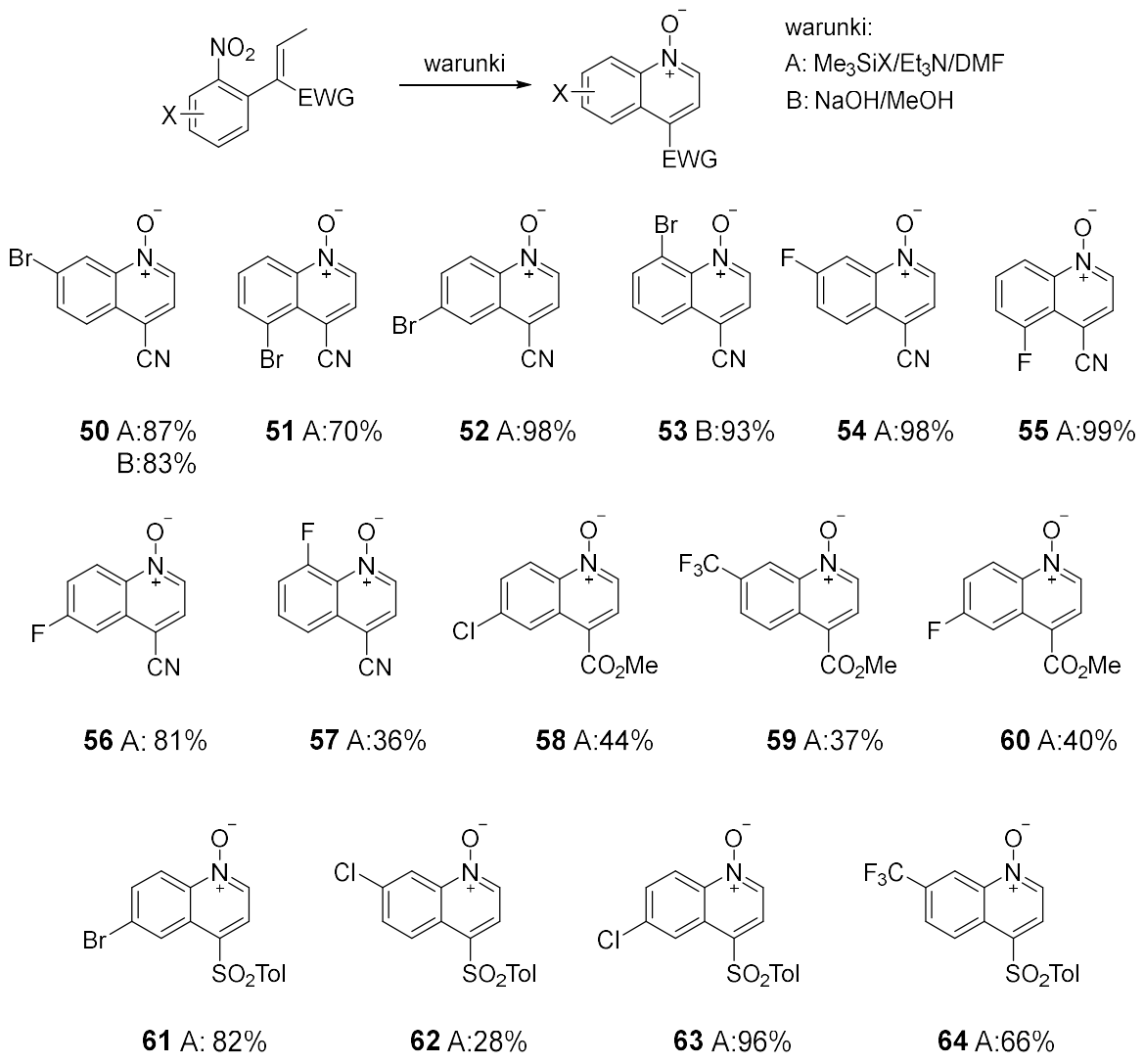


23 **24** 81% **50** 87% **70** 80%

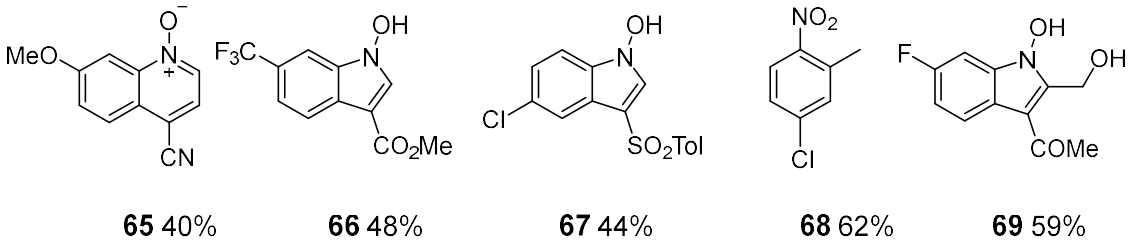
Schemat 35 Całkowita synteza modelowa o wydajności 56%

Na podstawie wcześniejszych prac, do etapu cyklizacji jako warunki najbardziej obiecujące, wybrane zostały Me_3SiCl/Et_3N i zasadowy NaOH/MeOH. Oba układy zostały sprawdzone w syntezie modelowej, zakończonej odtlenieniem otrzymanego tlenku chinoliny za pomocą $P(OMe)_3$ (Schemat 35).

Zebrane na Schemacie 36 wyniki zostały uzyskane w większości przy użyciu chlorku trimetylosililowego i trietyloaminy w DMF. Do cyklizacji estrów został jednak użyty bromek trimetylosililowy w HMPA, który zapewnił wyższe wydajności. W warunkach zasadowych cyklizacja nitryli przebiegała efektywnie, natomiast estry i sulfony dawały na ogół niepożądane produkty. Zostały one zidentyfikowane i został zaproponowany mechanizm ich powstawania. Produkt **65** powstał w reakcji cyklizacji bromonitrylu **24** z następczym podstawieniem atomu bromu przez jon metoksylowy.



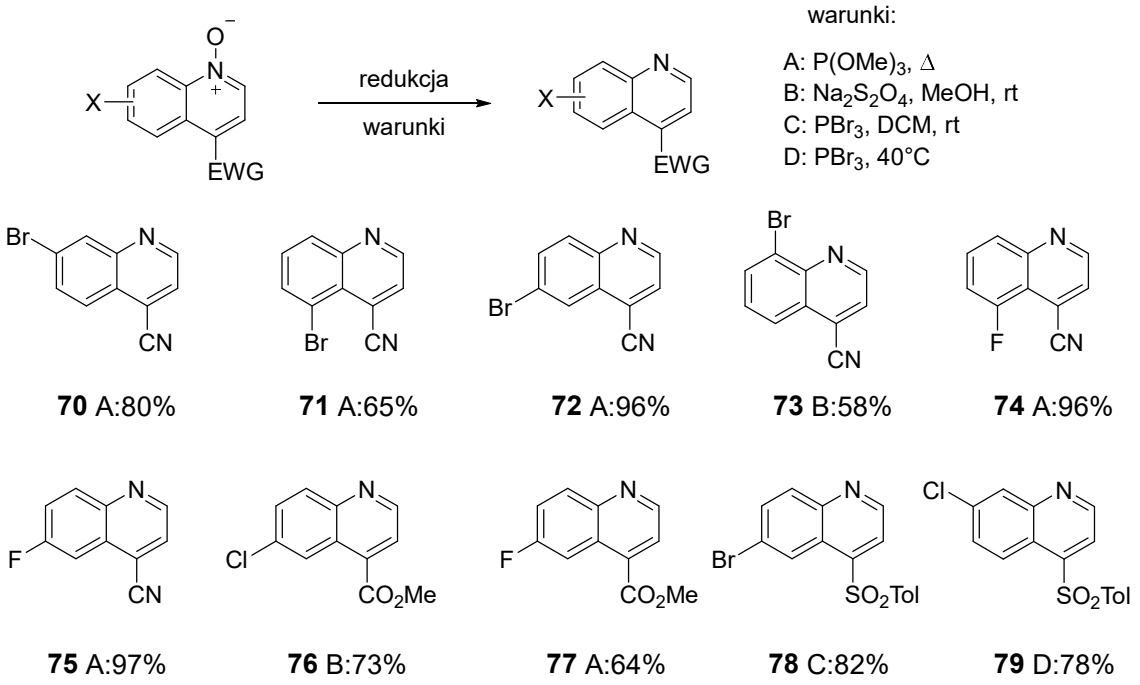
Schemat 36 Produkty cyklizacji do *N*-tlenków chinolin



Rysunek 6 Nieoczekiwane produkty cyklizacji w warunkach zasadowych

Do redukcji tlenków chinolin początkowo zastosowany został $P(OMe)_3$ w bardzo dużym nadmiarze jako czynnik redukujący oraz rozpuszczalnik. Sprawdził się w przypadku nitryli, także w skali wielogramowej (do 120 mmoli). Ditionian sodowy również dawał dobre rezultaty w redukcji nitryli

i estrów, jednak nie był odpowiedni dla sulfonów gdyż redukcji ulegała również grupa sulfonowa. Te związki udało się zredukować z zachowaniem grupy sulfonowej w łagodnych warunkach stosując PBr_3 w temperaturze pokojowej.



Schemat 37 Produkty redukcji tlenków chinolin do chinolin

Podsumowanie

Pomimo pewnych trudności udało się opracować bardzo praktyczną, eliminującą wykorzystanie metali ciężkich syntezę chinolin posiadających w pozycji 4 podstawniki wyciągające elektrony. Wykorzystanym substratem są łatwo dostępne i szeroko stosowane 2-nitrotolueny aktywowane obecnością podstawnika EWG w grupie metylowej. Dodatkowo, podobnie jak w przypadku przedstawionej w poprzednim rozdziale syntezy indolu, reakcje były prowadzone w skali wielogramowej.

Powyższe wyniki zostały opublikowane w pracy:

Magdalena Walewska-Królikiewicz, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel
*"*Comprehensive approach to the multigram, heavy-metal-free synthesis of 4-EWG-substituted quinoline derivatives" *Tetrahedron Lett.* **2023**, *146*, 133632.

4.4. Synteza 1,2-dipodstawionych benzimidazoli z *N*-arylo- i *N*-alkilo-2-nitroanilin

Większość klasycznych metod syntezy benzimidazoli, stosowanych z powodzeniem i rozwijanych do dziś, prowadzi do związków niepodstawionych na atomie azotu. W przypadku niesymetrycznego podstawienia pierścienia sześcioczłonowego łatwa tautomeryzacja powoduje powstawanie mieszanin izomerycznych produktów. Także następcze alkilowanie bądź arylowanie na atomie azotu nie jest regioselektywne. Z tego powodu zestaw metod syntezy bardziej złożonych, *N*-podstawionych benzimidazoli jest znacznie węższy.[55] Jednym z bardziej owocnych podejść jest wykorzystanie podstawionych na atomie azotu pochodnych 2-nitroanilin. Opisane w literaturze metody zaczynają się od redukcji grupy nitrowej do aminowej, co zwykle wiąże się z użyciem metali lub innych niewygodnych technik, a zróżnicowanie reaktywności między obydwoma grupami aminowymi nie zawsze gwarantują wysoką regioselektywność późniejszej cyklizacji.

W zespole VII IChO zaproponowano metodę polegającą na odtlenieniu grupy nitrowej przy pomocy związków fosforu(III) z utworzeniem na jej miejscu grupy iminofosforanowej, która następnie bierze udział w tworzeniu skondensowanego pierścienia heterocyklicznego. W ten sposób otrzymano szereg 1,2-dipodstawionych pochodnych benzimidazolu.

W swojej pracy postanowiłam wykorzystać zarówno wielokierunkową reaktywność (*o*-amino-arylo)iminofosforanów, jak i doświadczenie zdobyte na tym polu w zespole VII IChO w poprzednich latach, i rozszerzyć obszar zastosowań iminofosforanów w stronę użytecznych metod syntezy 1,2-dipodstawionych benzimidazoli. Prace te prowadzone były w dwóch kierunkach – opracowania praktycznej metody syntezy *N*-arylowych pochodnych 2-trifluorometylobenzimidazoli oraz podejście do syntezy 2-funkcjonalizowanych benzimidazoli podstawionych na atomie azotu grupą alkilową.

[55] L. Carvalho, E. Fernandes, M. Marques *Chem. Eur. J.* **2011**, *17*, 12544.

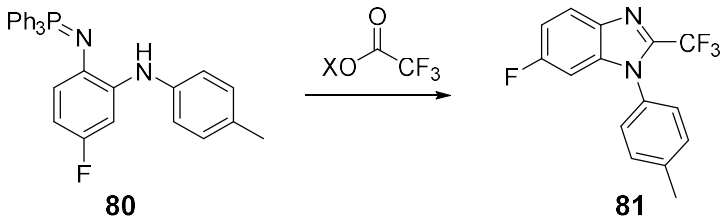
4.4.1. Synteza 1-arylo-2-trifluorometylobenzimidazoli z *o*-nitroanilin

Benzimidazol jest azotowym związkiem heterocyklicznym, którego pochodne mają szerokie zastosowanie w chemii biomedycznej. Biorąc pod uwagę wpływ grupy trifluorometylowej na własności struktur z nią związanych, połączenie benzimidazolu z grupą CF_3 wydaje się szczególnie ciekawe a w literaturze nie ma wielu opisanych metod pozwalających na osiągnięcie tego celu. Do syntezy pochodnych 2-trifluorometylowych została zaadaptowana wytyczona w ubiegłych latach metoda otrzymywania 2-(aryloamino)aryloiminofosforanów, a także ich reakcja z chlorkami kwasowymi prowadząca do 2-alkilowych pochodnych benzimidazolu.[56]

Wybór właściwych warunków reakcji

W celu realizacji celów niniejszych pracy wykorzystane zostały doświadczenia zdobyte w czasie wcześniejszych badań w zespole VII IChO PAN. Na ich podstawie potrzebne do badań *N*-aryloiminofosforany zostały otrzymane z *N*-arylo-2-nitroanilin i trifenylofosfiny.

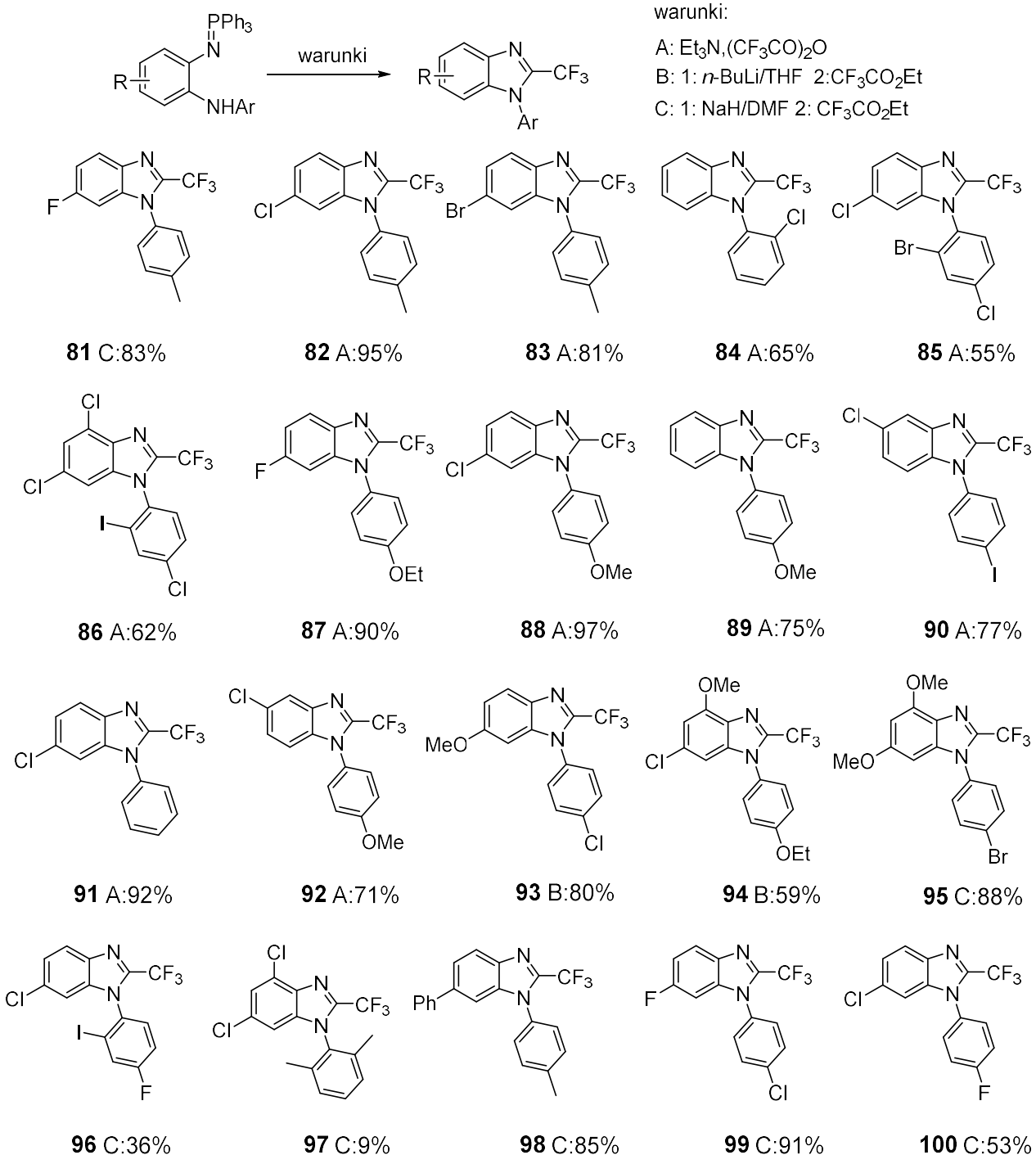
Tabela 1 Optymalizacja reakcji iminofosforanu z odpowiednim elektrofilem



80 **81**

Elektrofil X	Zasada	Rozpuszczalnik	Temp. [°C]/ Czas [h]	Wydajność [%]
Et	brak	MeCN	100/24	0
Et	EtOK	DMF	rt/24	0
Et	*t*-BuOK	DMF	rt/24	0
Et	n-BuLi	THF	-78 → rt/24	50
Et	NaH	DMF	60/3 → rt/24	83
Et	NaH	DMSO	60/3 → rt/24	ślady
Et	NaH	HMPA	50/3 → rt/24	67
CF_3CO	Et_3N	DCM	-78 → rt/24	63

[56] E. Łukasik, Z. Wróbel *ARKIVOC* **2016**, (iv), 67.



Schemat 38 Otrzymane pochodne 2-trifluorometylobenzimidazolu

Jako elektrofile zostały wybrane trifluorooctan etylu oraz bezwodnik trifluorooctowy. Optymalizacja warunków reakcji modelowej wykazała że najlepszymi warunkami dla przeprowadzenia reakcji

będzie użycie trifluorooctanu etylu wobec wodorku sodu w DMF. W tych warunkach otrzymałam szereg trifuorometylobenzimidazoli z bardzo dobrą wydajnością (Schemat 38).

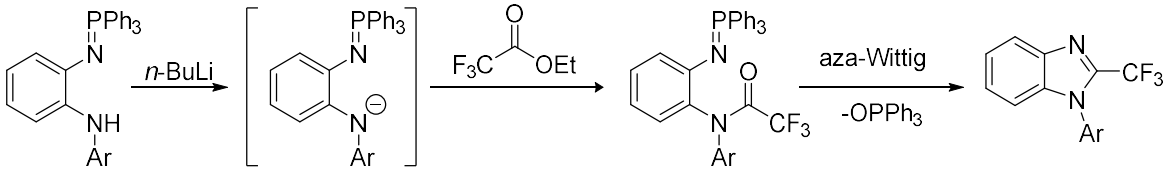
W trakcie sprawdzania zakresu stosowalności wybranej metody sporo wyników okazało się jednak niezadowalających. Z tego powodu dla związków które dawały niską wydajność sprawdzone zostały dodatkowo pozostałe możliwe warianty prowadzenia syntezy.

Dla związków zawierających w pozycji *orto* lub *para* podstawnik elektronodonorowy (OMe) trzeba było zastosować o wiele mocniejszą zasadę jaką jest *n*-BuLi (wariant B, Schemat 38) lub wodorek sodu (wariant C, Schemat 38), a w drugim etapie ester – trifluorooctan etylu. Dopiero przy zastosowaniu takich warunków można było uzyskać zadowalającą wydajność produktów.

Dobrych wydajności nie udało się otrzymać jedynie dla substratów zawierających podstawniki stwarzające znaczne zatłoczenie w okolicy centrum reakcji, czyli w pozycjach *orto* aromatycznego podstawnika przy atomie azotu.

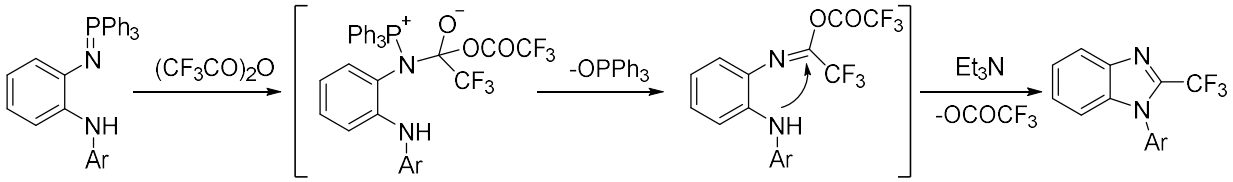
Mechanizm reakcji

W cząsteczce iminofosforanów stosowanych w badaniach znajdują się dwa centra nukleofilowe. Rozważania na temat przebiegu reakcji prowadzą do wniosku że w zależności od użytej zasady ma miejsce inny mechanizm reakcji (Schemat 39 oraz Schemat 40).



Schemat 39 Mechanizm reakcji z wykorzystaniem mocnej zasady

W przypadku wykorzystania mocnej zasady *n*-BuLi lub NaH następuje wygenerowanie anionu na atomie azotu aminowego który ulega reakcji acylowania, a następnie wewnątrzcząsteczkowej reakcji aza-Wittiga.



Schemat 40 Mechanizm cyklizacji z udziałem Et_3N oraz bezwodnika trifluorooctowego

Podsumowując, udało się opracować metodę syntezy 1-arylo-2-trifluorometylobenzimidazoli z *o*-nitroanilin. Zaproponowane wariantowe warunki reakcji pozwoliły na otrzymanie produktów w większości z bardzo dobrymi wydajnościami.

Powyższe wyniki zostały opublikowane w pracy:

Magdalena Walewska-Królikiewicz, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel

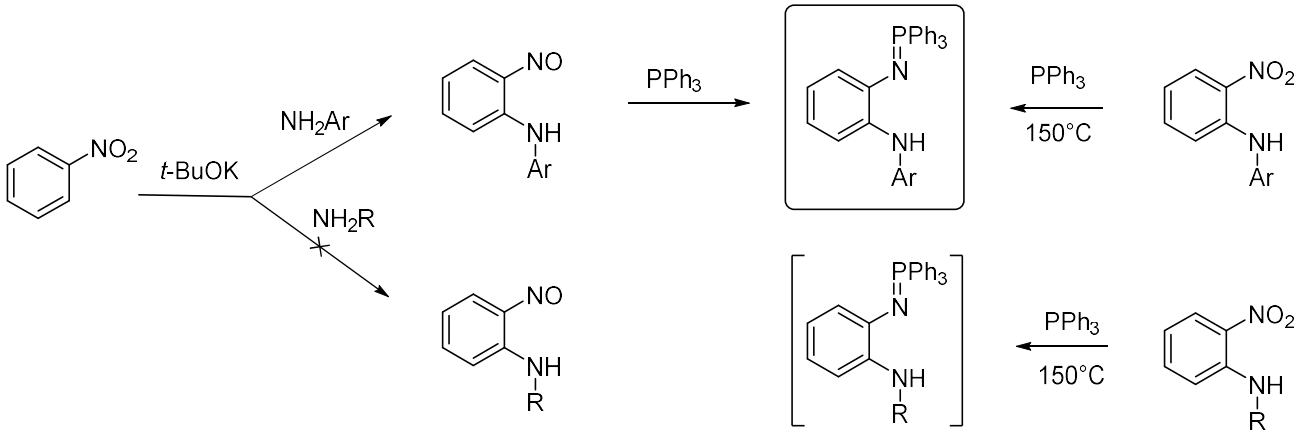
”(2-Aminoaryl)iminophosphoranes as Versatile Starting Materials for the Synthesis of

1-Aryl-2-trifluoromethylbenzimidazoles” *Synlett* **2022**, *33*, 1092.

4.4.2. Synteza 1-alkilo-2-funkcjonalizowanych benzimidazoli z *o*-nitroanilin

Literatura dotycząca aktywności biologicznej benzimidazoli pokazuje, że oprócz 1-arylowych lub 1-niepodstawionych pochodnych, te z grupą alkilową przy atomie azotu są licznie reprezentowane w chemii biomedycznej.[57]

Potrzeba opracowania praktycznej metody syntezy tytułowych związków istniała pomimo wytyczenia już wcześniej drogi prowadzącej do 1-arylowych pochodnych benzimidazolonu, benzimidazol-2-tionu, 2-aminobenzimidazolu i 2-alkilo(arylo)benzimidazolu.[58] Powód pierwszy, to ograniczone możliwości syntezy wyjściowych aryloiminofosforanów z grupą alkilową przy aminowym atomie azotu. Tradycyjna, łagodna i wydajna metoda, polegająca na reakcji *N*-alkilo-2-nitrozoanilin z fosfinami nie mogła być zastosowana ze względu na niedostępność takich nitrozoanilin, których nie udaje się otrzymać z odpowiednich nitrozwiazków i zdeprotonowanych amin alifatycznych. Jedyną metodą syntezy potrzebnych iminofosforanów z nitrozwiązków jest odtlenienie *N*-alkilo-2-nitroanilin w znacznie ostrzejszych warunkach. (Schemat 41).



Schemat 41 Sposoby otrzymywania N-podstawionych 2-aminoaryloiminofosforanów z nitroarenów.

Drugi powód, to stwierdzona na jednym przykładzie otrzymanego ze słabą wydajnością, iminofosforanu *N*-alkilowego jego nietrwałość i skłonność do rozkładu w procesie izolacji i oczyszczania. Fakt ten uniemożliwił stosowanie *N*-alkilowych iminofosforanów jako samodzielnych związków wyjściowych do dalszych syntez. Koniecznością było więc znalezienie

[57] (a) M. Alamgir, D.S.C. Black, N. Kumar *Top. Heterocycl. Chem.* **2007**, *9*, 87 (b) M. Tatsuta, M. Kataoka, K. Yasoshima, S. Sakakibara, Y. Shogase, M. Shimazaki, T. Yura, Y. Li, N. Yamamoto, J. Gupta, K. Urbahns, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2265.

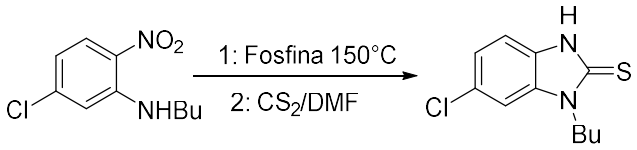
[58] (a) E. Łukasik, Z. Wróbel *Synlett* **2014**, *25*, 217. (b) E. Łukasik, Z. Wróbel *Heteroat. Chem.* **2016**, *27*, 372. (c) E. Łukasik, Z. Wróbel *Synthesis* **2016**, *48,* 1159. (d) E. Łukasik, Z. Wróbel *Synthesis* **2016**, *48,* 263. (e) E. Łukasik, Z. Wróbel *ARKIVOC* **2016**, *(iv),* 67.

najlepszego sposobu przekształcenia *N*-alkilo-2-nitroanilin w iminofosforany a następnie wykorzystanie ich *in situ* w następczych reakcjach cyklizacji.

Pierwszym krokiem był dobór związku fosforu(III) do reakcji tworzenia iminofosforanu. Wzorując się na wcześniejszych eksperymentach, przemianę modelowej *N*-butylo-5-chloro-2-nitroaniliny prowadziłam za pomocą nadmiaru związku fosforowego, bez rozpuszczalnika, w temperaturze 150°C. Z powodu nietrwałości, utworzony produkt był bez wydzielania wprowadzany w reakcję z dwusiarczkiem węgla, czego wynikiem było powstanie odpowiedniego benzimidazol-2-tionu. Wydajność tego produktu stanowiła porównawczą miarę efektywności pierwszego etapu.

Ze względu na niestabilność produktu pośredniego wybór fosfiny został dokonany na podstawie wydajności drugiego etapu reakcji modelowej (Tabela 2).

Tabela 2 Optymalizacja warunków pierwszego etapu reakcji



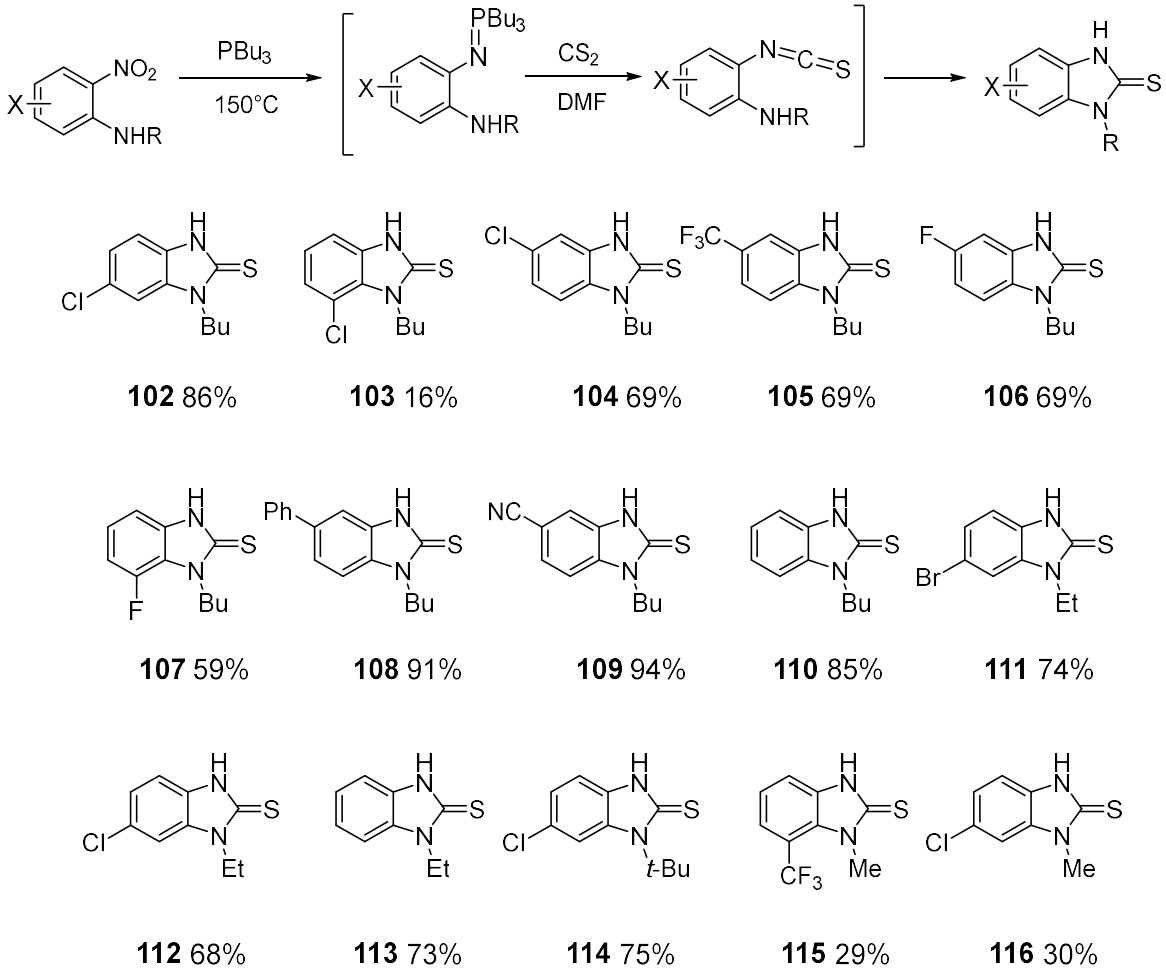
101 **102**

Fosfina	Eq	Wydajność [%]
$(Ph_2PCH_2)_2$	2	64
PPh_3	5	62
$P(OMe)_3$	5	50
PBu_3	5	74

Najwydajniejsza okazała się tributylofosfina i ona została użyta do wytworzenia przejściowych iminofosforanów, poddanych następnie reakcji z różnymi czynnikami elektrofilowymi w celu otrzymania podstawionych w pozycji 2-benzimidazoli.

Synteza benzimidazol-2-tionów oraz benzimidazol-2-onów

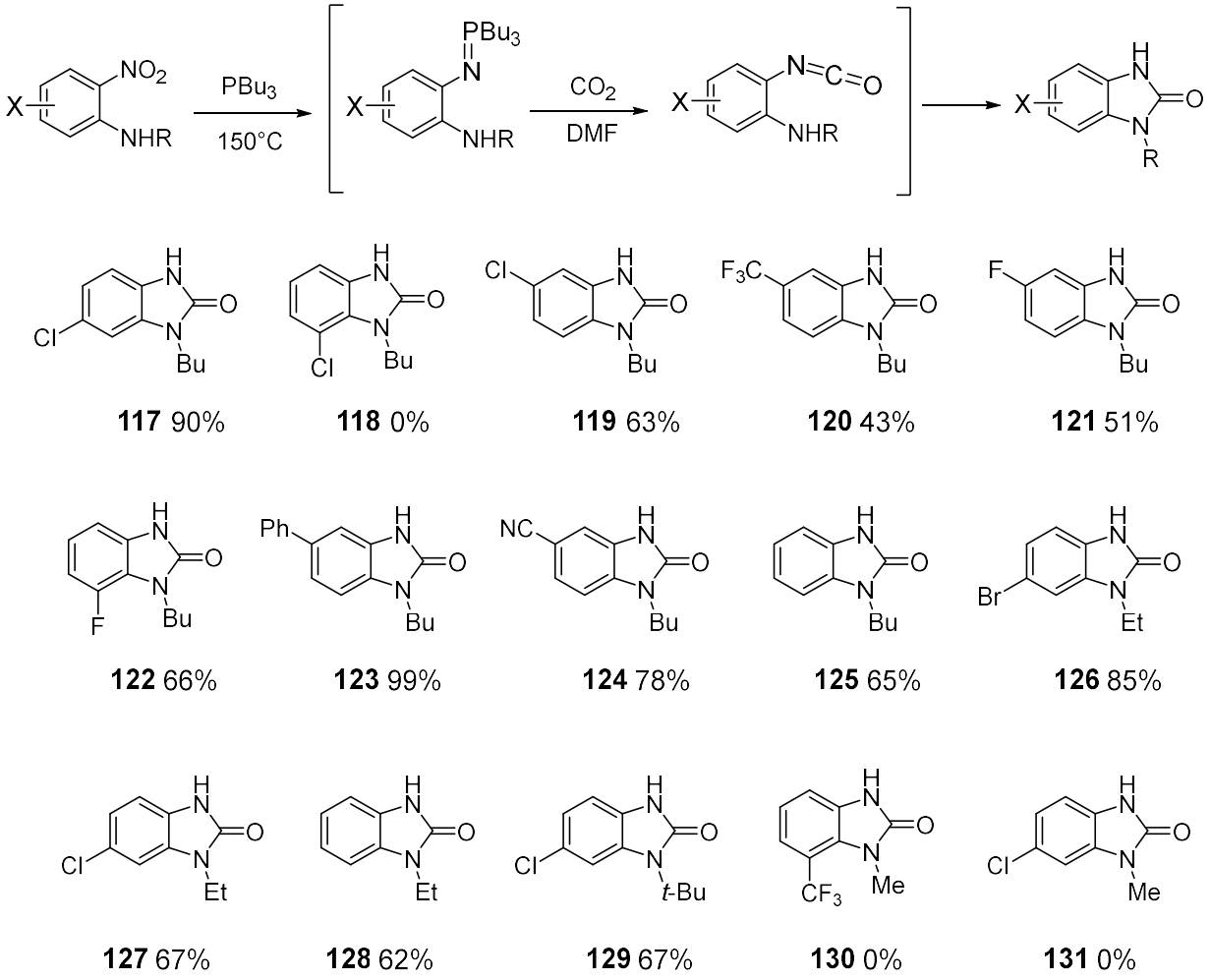
Benzimidazol-2-tiony otrzymałam w reakcji odpowiedniej nitroaniliny w dwuetapowej syntezie z wykorzystaniem disiarczku węgla (Schemat 42).



Schemat 42 Otrzymane pochodne benzimidazol-2-tionów

Wykorzystanie disiarczku węgla pozwoliło na otrzymanie szeregu produktów z dobrą wydajnością. Analogiczne reakcje zostały przeprowadzone z dwutlenkiem węgla (Schemat 43), wprowadzonym do środowiska reakcji w postaci rozdrobnionego suchego lodu w znacznym nadmiarze.

Warto zwrócić uwagę, że w przypadku niskiej wydajności reakcji z CS_2 analogiczna reakcja z CO_2 nie zaszła. Zakładamy, że wynika to z mniejszej reaktywności dwutlenku węgla.

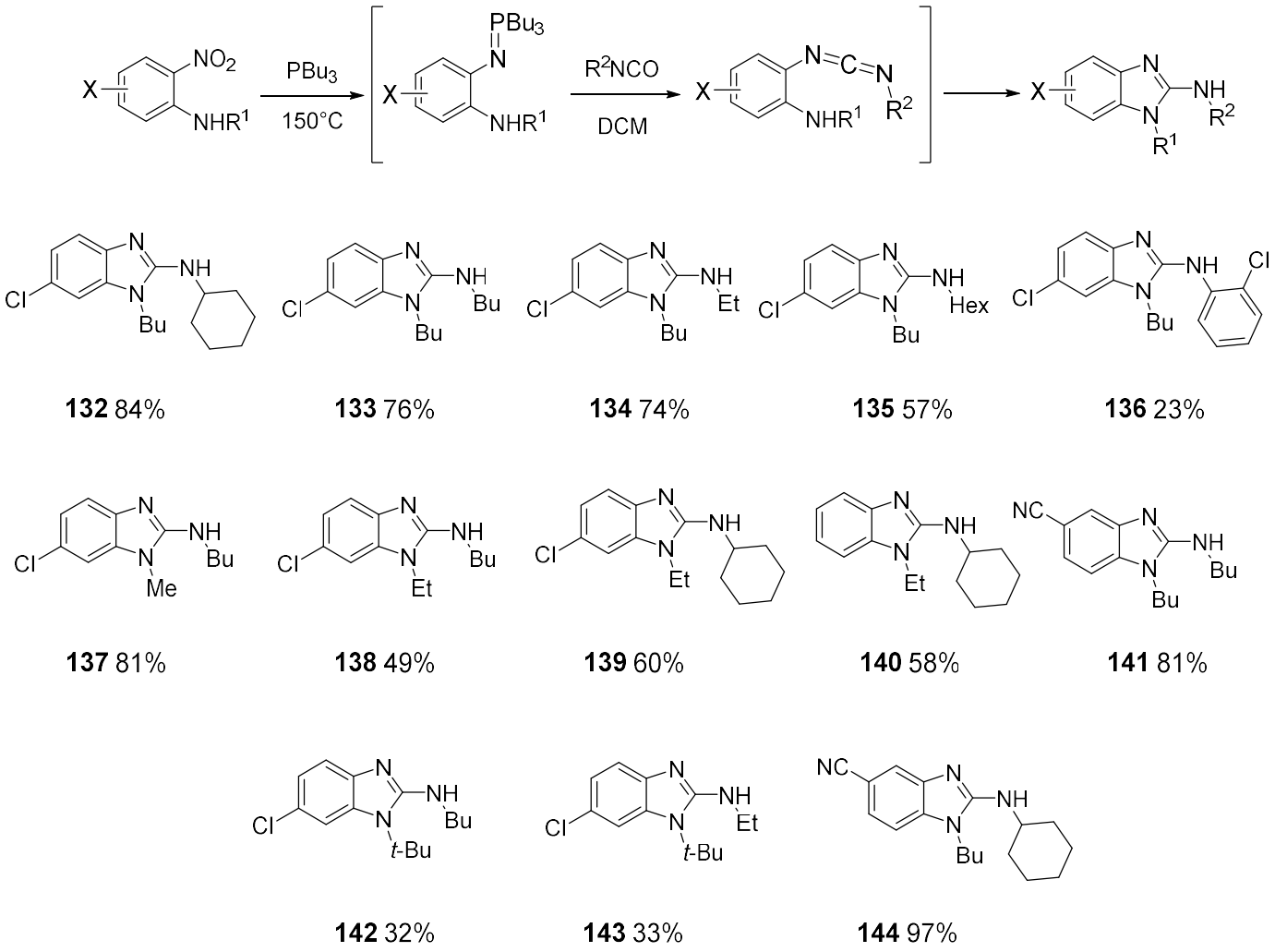


Schemat 43 Otrzymane pochodne benzimidazol-2-onów

Wielkość podstawnika alkilowego ma pozytywny wpływ na wydajność reakcji. Natomiast obecność dużych podstawników w pozycji *orto* do grupy alkiloaminowej wpływa na zmniejszenie wydajności reakcji. Próba przeprowadzenia reakcji z podstawnikiem w pozycji *orto* do grupy nitrowej w nitroanilinie (*N*-butylo-3-bromo-2-nitroanilina) nie pozwoliła na uzyskanie produktu.

Synteza 2-(alkiloamino)benzimidazoli

Po zadowalających rezultatach reakcji iminofosforanów z dwutlenkiem węgla oraz disiarczkiem węgla postanowiono sprawdzić przebieg reakcji z izocyjanianami. Reakcje wytworzonych *in situ* iminofosforanów z izocyjanianami prowadzone były w temperaturze pokojowej w DCM.

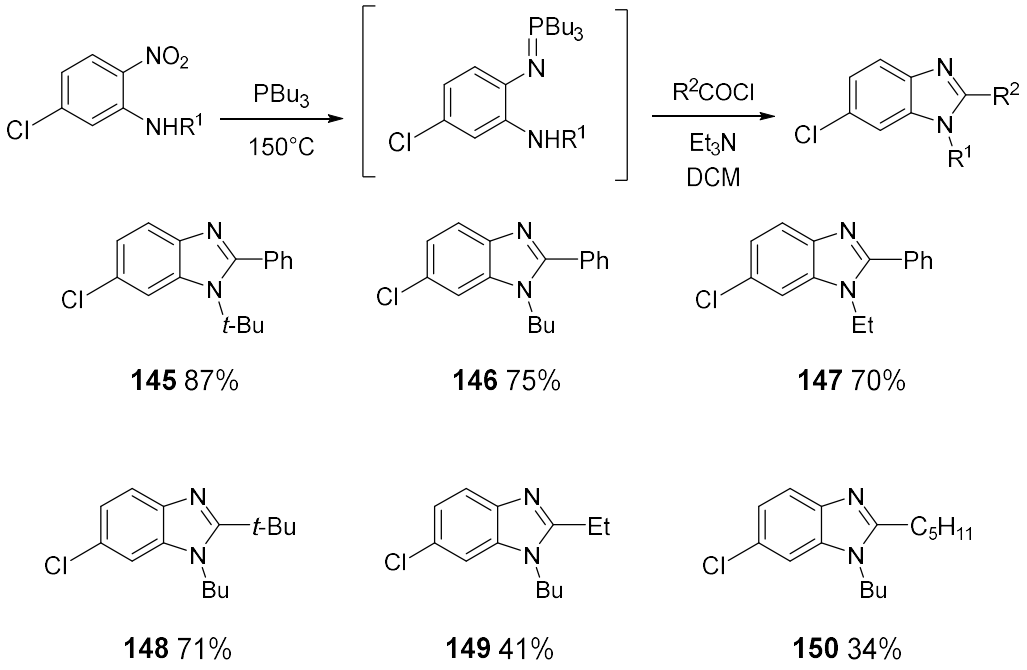


Schemat 44 Otrzymane pochodne 2-(alkiloamino)benzimidazoli

Większość produktów powstała z dobrą i bardzo dobrą wydajnością (49-97%, Schemat 44). Reakcja nie nakłada żadnych ograniczeń na rodzaj izocyjanianów alkilowych, jedynie podstawnik aromatyczny w izocyjanianie dał mało zadowalający rezultat (**136** - 23%). Można natomiast zaobserwować, że zatłoczenie przy atomie azotu anilinowego spowodowane obecnością rozgałęzionego podstawnika wyraźnie wpływa negatywnie na wydajność reakcji (**142** - 32% oraz **143**- 33%). Efekt ten nie był widoczny w reakcjach z CO_2 i CS_2 (produkty **129** - 67% oraz **114** - 75%).

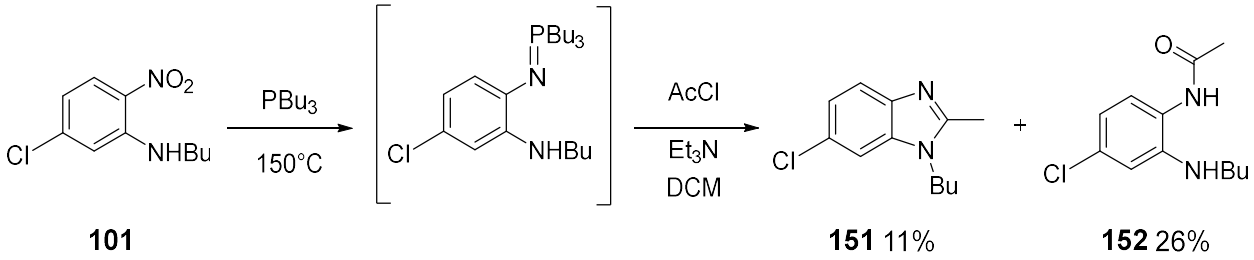
Synteza 1,2-dialkilobenzimidazoli

Wcześniejsze prace pokazały, że aryloiminofosforamny podstawione w pozycji *orto* grupą aryloaminową reagują z chlorkami kwasowymi tworząc 1-arylo-2-alkilobenzimidazole. W rozdziale 4.4.1 przedstawiłam też wyniki moich prac nad syntezą 1-arylo-2-trifluorometylobenzimidazoli z użyciem mocnej zasady i odpowiedniego estru. W dalszej kolejności podjęłam próby syntezy pochodnych 1,2-dialkilobenzimidazoli w reakcji związków karbonylowych z otrzymywanymi *in-situ* odpowiednimi iminofosforanami (Schemat 45).



Schemat 45 Otrzymane pochodne 1,2-dialkilobenzimidazoli

Reakcje z chlorkiem benzoilu pozwoliły na otrzymanie produktów z zadowalającą wydajnością. Analizując wpływ podstawnika alkilowego jego rozgałęzienie oraz wielkość można zauważyć wpływ tych czynników na wydajność reakcji. Z wyraźnie niższą wydajnością reagowały nierozgałęzione chlorki alkilowe. W przypadku chlorku acetylu powstawała mieszanina produktów (Schemat 46).

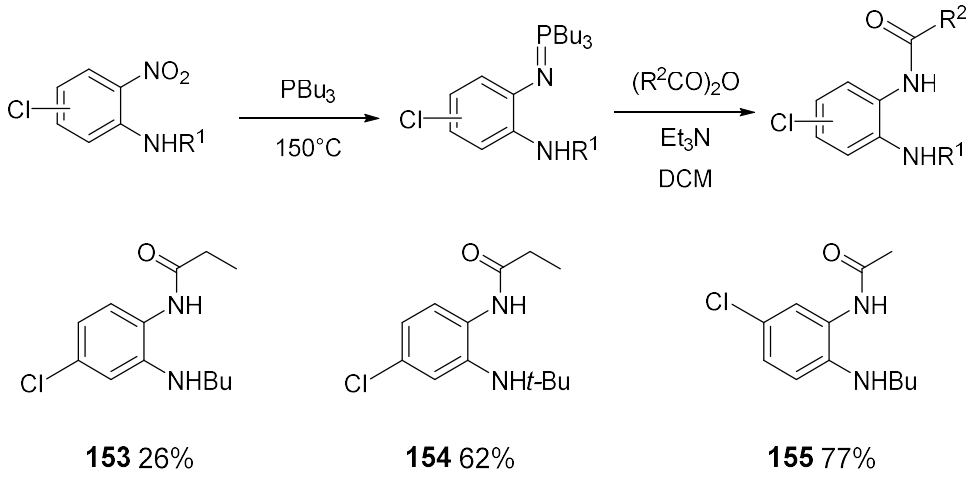


101 **151** 11% **152** 26%

Schemat 46 Reakcja z chlorkiem acetylu

Głównym produktem była *N*-acetylo-*o*-fenylenodiamina **152**. Zmiana proporcji reagentów, wydłużenie czasu reakcji oraz wykonanie próby w wyższej temperaturze nie przyniosła pożądanych rezultatów.

Przeprowadzona w tych samych warunkach reakcja z bezwodnikami kwasów alifatycznych pozwoliła jedynie na otrzymanie produktów *N*-acylowanych fenylenodiamin (Schemat 47).



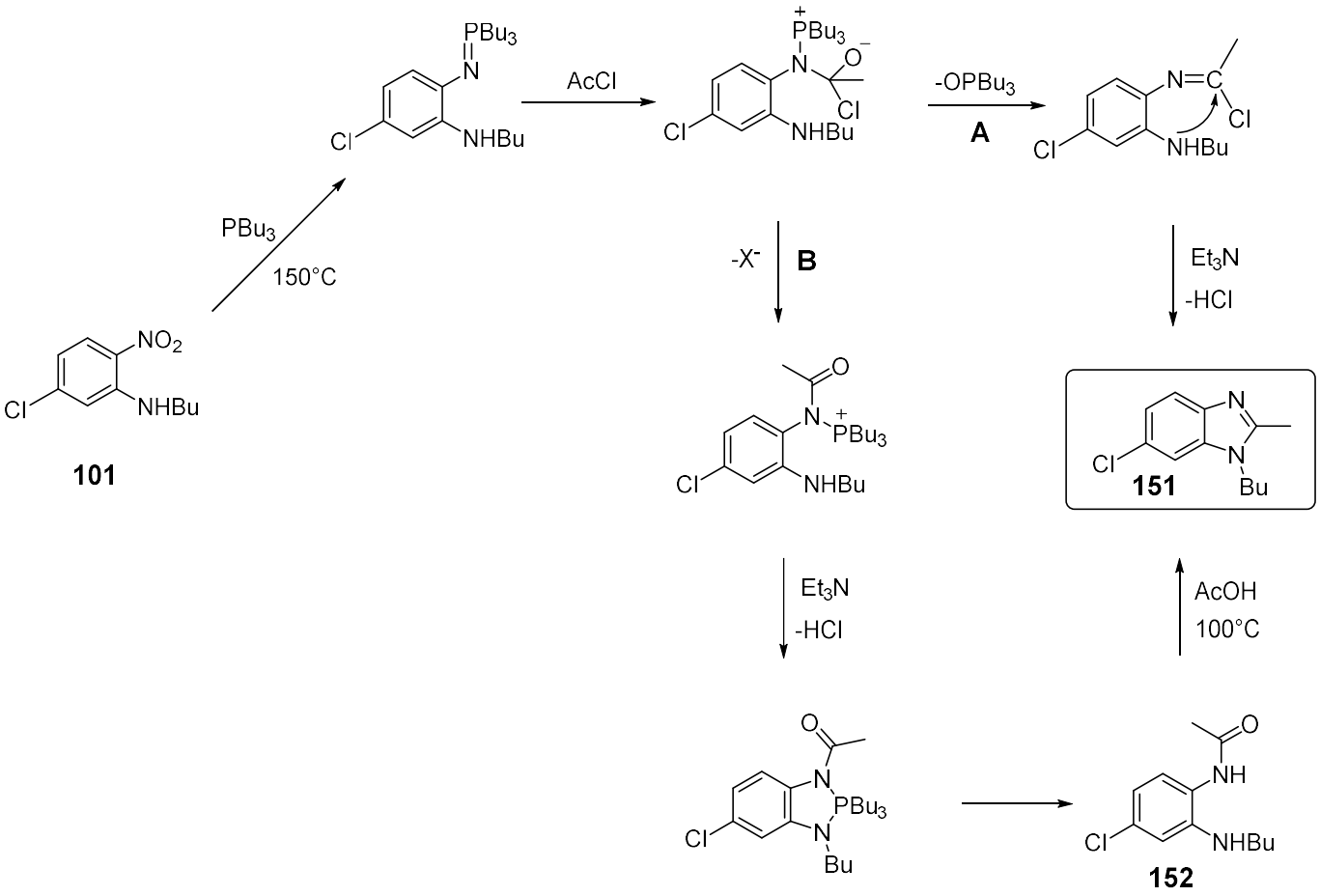
153 26% **154** 62% **155** 77%

Schemat 47 Otrzymane pochodne *N*-acylowanych fenylenodiamin

Jedyną możliwością otrzymania w większej ilości pożądanego produktu jest ogrzewanie surowej mieszaniny poreakcyjnej w kwasie octowym, gdyż spowoduje to cyklizację produktu ubocznego. Cyklizacja produktu *N*-acetylowanego **152** pod wpływem kwasu pozwoliła na otrzymanie produktu z 78% wydajnością.

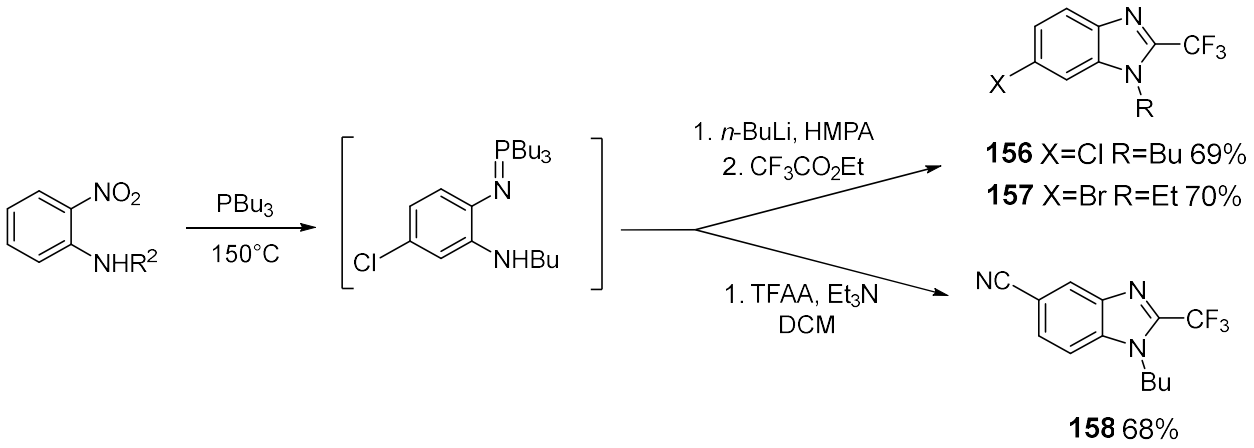
Konkurencyjne powstanie obu produktów może zostać wyjaśnione za pomocą następującego mechanizmu reakcji (Schemat 48). Produkt pośredni powstały w wyniku ataku nukleofilowego na węgiel karbonylowy (identyczna sytuacja ma miejsce w przypadku chlorku kwasowego jak i bezwodnika) może ulec dwóm różnym przekształceniom (A oraz B na schemacie 47) w zależności jaka grupa ulegnie eliminacji. Ścieżka A oparta na eliminacji tlenku fosfiny prowadzi do iminy,

której wewnątrzcząsteczkowa cyklizacja prowadzi do benzimidazolu. W przypadku ścieżki B produkt pośredni po odejściu jonu chlorkowego tworzy sól fosfoniową, której hydroliza w czasie przerobu poreakcyjnego prowadzi do niecyklicznego amidu.



Schemat 48 Mechanizm reakcji – wariant A oraz wariant B

Sprawdziłam również możliwość otrzymania ważnych pochodnych benzimidazolu z grupą 2-CF_3 i podstawnikiem alkilowym przy atomie azotu.



Schemat 49 Otrzymane pochodne benzimidazolu zawierające w pozycji 2 grupę CF_3

Zastosowane zostały oba warianty reakcji, skuteczne w reakcji pochodnych *N*-arylowych (rozdział 4.4.1), tj. cyklizacji iminofosforanu przy użyciu bezwodnika trifluorooctowego wobec trietyloaminy, oraz reakcja z trifluorooctanem etylu po deprotonowaniu iminofosforanu z użyciem BuLi (Schemat 49). Obie reakcje zakończyły się powodzeniem.

Mechanizm reakcji jest analogiczny do przedstawionego w rozdziale 4.2 dla iminofosforanów z podstawnikiem arylowym.

Podsumowanie

Otrzymane wyniki pozwalają na stwierdzenie, że *N*-[2-(alkilo-amino)phenylo]iminofosforany są ciekawymi i dogodnymi substratami w syntezie azotowych związków heterocyklicznych, w szczególności *N*-alkilobenzimidazoli.

Powyższe wyniki zostały opublikowane w pracy:

Magdalena Walewska-Królikiewicz, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel

„Synthesis of various 1-alkylbenzimidazole derivatives directly from 2-alkylaminonitroarenes via a two-steps, one-pot procedure” *J. Heterocycl. Chem.* **2024**, 1 DOI: 10.1002/jhet.4830

4.5. Podsumowanie

Przeprowadzone przeze mnie badania pozwoliły na opracowanie nowych, stosunkowo prostych i praktycznych metod syntezy związków heterocyklicznych opartych na szeroko znanych i ważnych szkieletach – indoli, benzimidazoli sfunkcjonalizowanych w pozycji 2 oraz chinolin podstawionych grupami elektronoakceptorowymi (EWG) w pozycji 4. Opracowana metodologia oparta jest na związkach łatwo dostępnych i prostych w użyciu, a dodatkowo zaproponowane reakcje można bez problemu przeprowadzić w dużej skali nie tracąc na efektywności procesu. Uzyskane wyniki dobitnie dowodzą potencjału, jaki w praktycznej syntezie azotowych związków heterocyklicznych mają nitroareny, a szczególnie ich *orto* funkcjonalizowane pochodne.

Pierwszym zadaniem było opracowanie syntezy 2-trifluorometyloindoli z odpowiedniego nitrotoluenu w warunkach zasadowych. Inspiracją do przeprowadzonych badań była znana od dawna reakcja Reisserta. Badania zakończyły się sukcesem, metoda okazała się efektywna i za jej pomocą otrzymałam szereg produktów z bardzo dobrymi wydajnościami.

W kolejnym etapie pracy zajęłam się rozszerzeniem metody syntezy pochodnych chinolin, posiadających w pozycji 4 grupy silnie elektronoakceptorowe. Wyjściowa metoda była znana, jednak ograniczona do wąskiego zakresu pochodnych cyjanowych. W trakcie moich prac, jej zakres udało się rozszerzyć dodatkowo na estry, związki karbonylowe i sulfony, pokonując przy tym specyficzne dla tych grup trudności, szczególnie na etapie redukcji odpowiednich tlenków chinolin. W wielu przypadkach opracowana trzyetapowa synteza okazała się bardzo wydajna, jednak szeroko zakrojone badania pozwoliły także na ujawnienie ograniczeń metody i mechanizmów procesów, które miały niekiedy miejsce, a których przebieg był nieoczekiwany.

Kolejnym celem było wykorzystanie iminofosforanów otrzymanych z *o*-nitroanilin w syntezie pochodnych benzimidazoli. W trakcie projektu zbadałam trwałość iminofosforanów w zależności od podstawnika przy atomie azotu. Potwierdziłam, że iminofosforany zawierające podstawnik alkilowy są nietrwałe i muszą być użyte *in situ*. Mimo nietrwałości okazały się użytecznymi substratami w syntezie benzimidazoli. W reakcji szeregu iminofosforanów (wygenerowanych *in situ* z nitroanilin) z elektrofilowymi czynnikami takimi jak disiarczek węgla, dwutlenek węgla, izocyjaniany alkilowe i arylowe) otrzymałam odpowiednie 2-funkcjonalizowane pochodne benzimidazolu.

Sprawdziłam również przebieg reakcji dla chlorków oraz bezwodników kwasowych, których przebieg nie był jednokierunkowy, tym niemniej udało się określić zakres wyjściowych związków, dla których reakcja zachodzi w stronę pożądanych 2-alkilo i 2-arylobenzimidazoli. Wyniki otrzymane w trakcie badań przedstawionych w tej pracy rozwijają klasyczne reakcje dodając im nowe możliwości zastosowania do efektywnej, skutecznej i taniej syntezy związków heterocyklicznych zdolnych do dalszej funkcjonalizacji w kierunku bardziej złożonych struktur o potencjalnych wartościowych własnościach. Wnoszą też wkład w lepszą znajomość niektórych elementarnych przemian leżących u podstaw opracowanych syntez, przebiegających niekiedy wielokierunkowo i ograniczonych ze strony zastosowanych substratów.

5. Streszczenie w języku polskim

Związki heterocykliczne zawierające w swojej strukturze atom azotu są bardzo ważnymi związkami, wiele z nich jest lekami ale ich rola nie sprowadza się jedynie do chemii biomedycznej. Z powodzeniem wykorzystywane są w wielu dziedzinach chemii i gałęziach przemysłu. W chemii organicznej możemy je spotkać jako substraty lub katalizatory wielu ważnych reakcji. Pomimo dostępnej ogromnej literatury na temat metod otrzymywania związków heterocyklicznych uważam, że ta ważna dziedzina wymaga dalszego wysiłku badawczego. Z tego powodu swoją uwagę skupiłam na opracowaniu nowych, wyróżniających się swoją prostotą i ekonomicznym podejściem syntez jednych z najważniejszych przedstawicieli związków heterocyklicznych jakimi są indole, benzimidazole oraz chinoliny. Aby tego dokonać skupiłam się na wykorzystaniu *orto* podstawionych pochodnych nitrobenzenu. W tym celu wykorzystałam łatwo dostępne i niedrogie *orto* podstawione pochodne nitrobenzenu, charakteryzujące się wielokierunkową reaktywnością.

Synteza 2-trifluorometyloindolu została zaplanowana w dwóch etapach i była inspirowana metodą Reisserta. Pierwszy etap polegał na acylowaniu grupy metylowej odpowiednio podstawionego *o*-nitrotoluenu w warunkach zasadowych, drugi zaś na reduktywnej cyklizacji produktu pośredniego z udziałem odpowiedniego reduktora (Zn/AcOH lub ditionian sodowy).

Otrzymanie chinolin podstawionych w pozycji 4 grupą elektronoakceptorową (EWG) było oparte na trzyetapowej syntezie polegającej na kondensacji typu Knoevenagla aktywowanych pochodnych *o*-nitrotoluenu z aldehydem octowym, cyklokondensacji i redukcji *N*-tlenku chinoliny do odpowiedniej chinoliny na ostatnim etapie syntezy. Powodzenie całkowitej syntezy – przy doborze warunków poszczególnych reakcji – miało miejsce dla pochodnych z grupa cyjanową, sulfonową i estrową. Nie powiodła się cyklizacja produktów kondensacji związków karbonylowych, a *o*-nitrotoluen aktywowany grupą nitrową nie dawał właściwego produktu już na etapie kondensacji Knoevenagla.

Trzecia koncepcja pozwalająca na otrzymanie szeregu pochodnych benzimidazoli została oparta na przekształceniach pochodnych *orto* nitroanilin. W pierwszym etapie pod wpływem fosfiny przekształceniu ulega grupa nitrowa w nukleofilowe centrum azotowe w postaci iminofosforanu który następnie jest poddawany reakcji z odpowiednim czynnikiem elektrofilowymi. W ten sposób zostały zsyntezowane rozmaite pochodne 2-funkcjonalizowanych benzimidazoli takie jak benzimidazolony, benzimidazol-tiony, 2-amino- 2-alkilo- i 2-arylobenzimidazole. Szczególna uwaga poświęcona została syntezie związków zawierających grupę 2-trifluorometylowa, a osobnym

zagadnieniem, które zostało pomyślnie rozwiązane była synteza 2-funkcjonalizowanych benzimidazoli z podstawnikiem alkilowym przy atomie azotu.

6. Streszczenie w języku angielskim / Abstract in English

Heterocyclic compounds containing a nitrogen atom in their structure are very important compounds. Many of them are drugs, but their role is not limited to biomedical chemistry. They are successfully used in many fields of chemistry and industry. In organic chemistry, we encounter them as substrates or catalysts for many important reactions. Despite the vast literature available on methods for obtaining heterocyclic compounds, I believe that this important field requires further research efforts. For this reason, I focused my attention on the development of new syntheses, distinguished by their simplicity and economic approach, of some of the most important representatives of heterocyclic compounds, such as indoles, benzimidazoles and quinolines. To achieve this, I focused on the use of ortho-substituted nitrobenzene derivatives. For this purpose, I used easily available and inexpensive ortho-substituted nitrobenzene derivatives, characterized by multidirectional reactivity.

The synthesis of 2-trifluoromethylindole was planned in two stages and was inspired by Reissert's method. The first step involved the acylation of the methyl group of an appropriately substituted *o*-nitrotoluene under basic conditions, while the second involved the reductive cyclization of the intermediate product using an appropriate reducing agent (Zn/AcOH or sodium dithionite).

The preparation of quinolines substituted in position 4 with an electron withdrawing group (EWG) was based on a three-step synthesis consisting of Knoevenagel-type condensation of activated *o*-nitrotoluene derivatives with acetaldehyde, cyclocondensation and reduction of quinoline *N*-oxide to the corresponding quinoline at the last stage of the synthesis. The complete synthesis was successful (with the selection of individual reaction conditions) for derivatives with cyano, sulfonate and ester groups. The cyclization of the condensation products of carbonyl compounds failed, and *o*-nitrotoluene activated with a nitro group did not give the proper product even at the Knoevenagel condensation stage.

The third concept allowing for the preparation of a number of benzimidazole derivatives was based on the transformation of *o*-nitroaniline derivatives. In the first stage, under the influence of phosphine, the nitro group is transformed into a nucleophilic nitrogen center in the form of an iminophosphate, which is then reacted with an appropriate electrophilic agent. In this way, various 2-functionalized benzimidazole derivatives have been synthesized, such as benzimidazolones, benzimidazolthiones, 2-amino-2-alkyl- and 2-arylbenzimidazoles. Particular attention was paid to the synthesis of compounds containing a 2-trifluoromethyl group. A separate problem that was

successfully solved was the synthesis of 2-functionalized benzimidazoles with an alkyl substituent at the nitrogen atom.

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Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes

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ABSTRACT

The acylation of 2-nitrotoluenes using ethyl trifluoroacetate, one of the least expensive sources of a trifluoromethyl group, produces intermediate 2-nitrobenzyl trifluoromethyl ketones which, without the need for isolation, are cyclized under the action of Zn/AcOH providing 2-(trifluoromethyl)indoles unsubstituted at the C3 position. The developed method avoids the use of expensive catalysts and harsh reaction conditions. The method is readily scalable without a significant decrease in performance upon going from 10- to 250-mmol scale.

Introduction

Among pharmaceutically interesting privileged motifs, both the indole groups [1] and fluoroalkyl groups [2] are of significant importance. Their potential increases greatly when they are placed in the same molecule, as this often leads to compounds with unique pharmacological properties [3]. Consequently, there is an increasing interest in the synthesis of biologically active structures containing fluorine for drug discovery, in which trifluoromethylated indoles play an important role.

Due to specific features of the trifluoromethyl group, not all general indole synthesis methods [4] can be used for their 2-trifluoromethyl derivatives [5]. In particular, the number of available methods is noticeably limited when the synthesis needs to be regioselective, and the desired 2-(trifluoromethyl)indole is unsubstituted at the C3 position (Scheme 1).

Well-established methods involve closure of the pyrrole ring on a suitably functionalized *o*-methylaniline bearing a trifluoromethyl group on the amino function (Scheme 1, path *a* [6] or path *b* [7]). Path *a* also includes palladium-catalyzed cyclization of the imidoyl chloride without its preceding bromination (X = H) [8]. 2–(Hydroxymethyl)anilines can be cyclized to 2-(trifluoromethyl)indoles in one-pot reactions promoted by $[Ph_3P^+\text{-}X]\ ^-CX_3$ *via in situ* formed imidoyl halide (path *c*) [9]. 2-(Trifluoromethyl)indoles can be prepared from 2-bromoaniline and 2-bromo-3,3,3-trifluoroprop-1-ene using palladium catalysis (path *d*) [10]. In the last decade, there has been increasing interest in the direct trifluoromethylation of indoles at the *C*2 position (Scheme 1, path *e*) using various trifluoromethylating reagents [11–14]. However, these reactions often suffer from a lack of regioselectivity, low yields, or require a blocked C3 position to achieve satisfactory yields [15]. Moreover, although they are presented as simple one-step reactions, they still require the synthesis of the appropriate indole core and the use of expensive reagents. Amongst popular methods employing trifluoromethylalkynyl starting arenes [16] or reagents [17–18], only one allows the preparation of 3-unsubstituted 2-(trifluoromethyl) indoles, although these are mainly *N*-sulfonylated [16].

None of the above-mentioned methods are general, and there are a lack of short, regioselective methods, avoiding the use of expensive reagents or catalysts. We believe that the procedure presented herein meets these conditions. It was developed based on our experiences in the synthesis of *N*-hydroxyindoles from substituted dinitrobenzenes [19], and was inspired by the Reissert indole synthesis [20]. This procedure makes the usually long and laborious [21] route from inexpensive nitroarenes to 2-(trifluoromethyl)indoles simpler and shorter.

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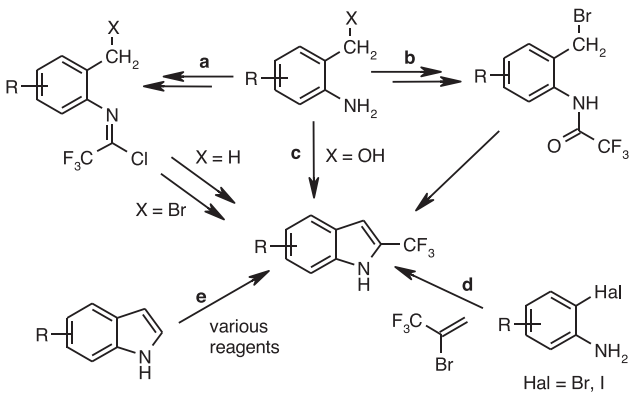


Scheme 1. Representative methods for the synthesis of 3-unsubstituted 2-(trifluoromethyl)indoles.

Results and discussion

The two-step reaction involves base-promoted functionalization of the methyl group of 2-nitrotoluenes **1** by acylation with ethyl trifluoroacetate, followed by reductive cyclization of nitrobenzyl ketones **2** leading directly to the corresponding 2-(trifluoromethyl)indoles **3** (Scheme 2).

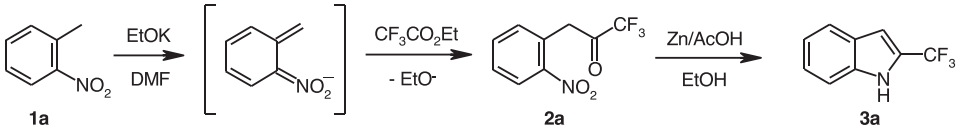
After short research, [22] reaction conditions were found which provided good yields of the desired 2-(trifluoromethyl)indoles. Accordingly, the trifluoroacetylation of 2-nitrotoluene with ethyl trifluoroacetate, carried out in EtOK/DMF at −50 °C to r.t., afforded the corresponding 2-nitrobenzyl trifluoromethyl ketone that, without isolation, was subjected to reductive cyclization in the presence of Zn in AcOH/EtOH. This procedure provided a number of 2-(trifluoromethyl)indoles **3**, mostly in satisfactory yields (Scheme 3). Only the reaction of 3-bromo-2-nitrotoluene (**1d**) was carried out in two stages, with intermediate isolation of the nitroketone **2d**, due to the need to separate it from by-products.

All the reactions were carried out on a multi-gram, preparative scale, up to 250 mmol in some cases. Notably, in the case of **3e** this short procedure gave twice the yield as that of the published, five-step synthesis [21]. Other reducing agents, such as $SnCl_2{\cdot}2H_2O$/EtOAc, Fe/NH_4Cl and $Na_2S_2O_2$, gave lower yields or resulted in incomplete reduction leading to *N*-hydroxyindoles instead of **3** [19]. On the other hand, sodium dithionite proved to be the reagent of choice for the reaction of iodine-substituted **1k** and **1l**. In these cases, the use of the other reducing agents gave the desired products contaminated with deiodinated indole **3a**, or only *N*-hydroxyindole **4** when $SnCl_2$ was used (Scheme 4). Although the content of the deiodinated by-product was never above 8%, its removal was exceptionally difficult by standard laboratory methods for compound separation.

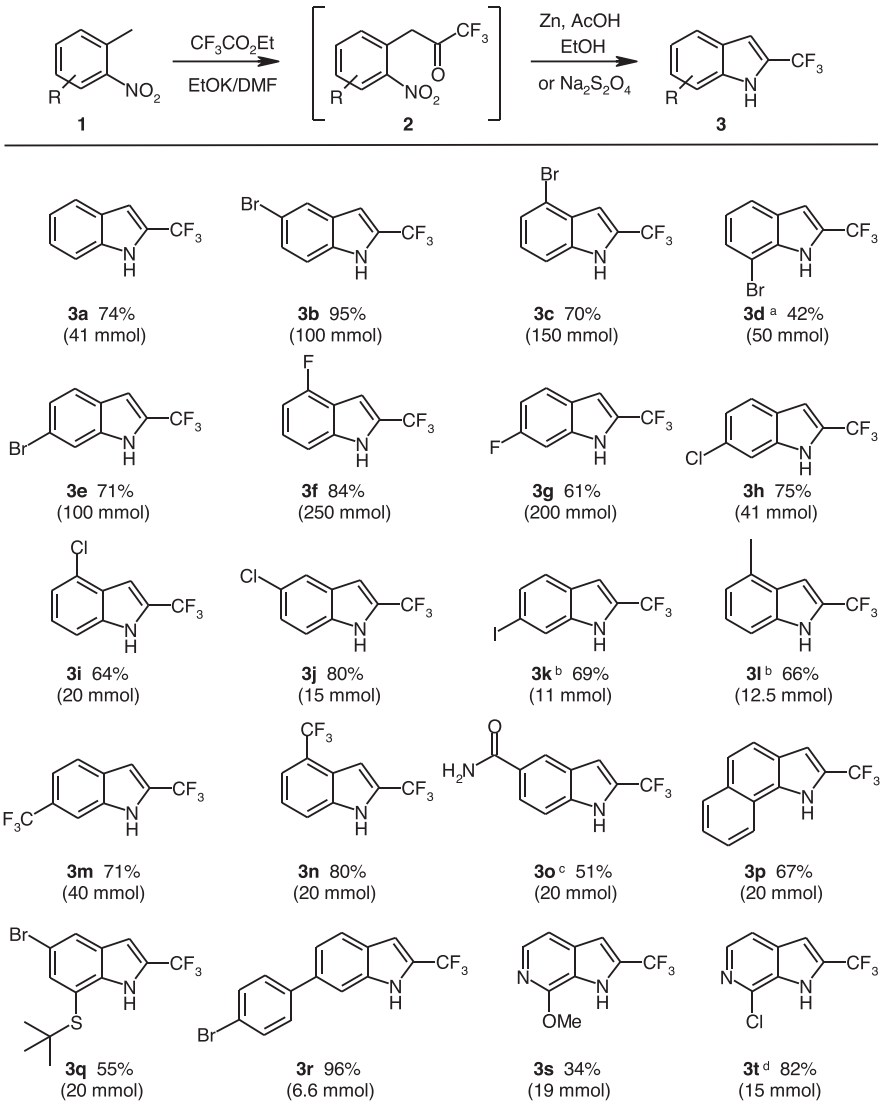
The reaction of **1t** gave comparable amounts of indole **3t** (33% yield) and cyclic hemiaminal **5** (49% yield) (Scheme 5). The outcome was reproducible, and extending the reaction time only slightly improved the product ratio. Quantitative dehydration of **5** of this mixture was achieved by stirring in glacial acetic acid for 72 h which resulted in an improved 82% yield of **3t**.

As expected, the use of EtOK in the trifluoroacetylation may affect some base-sensitive substituents in the starting nitrotoluene. Thus, the cyano substituent in 2-nitrotoluene **1o** was converted into an amide group, resulting in the formation of 2-(trifluoromethyl)-1*H*-indole-5-carboxamide (**3o**).

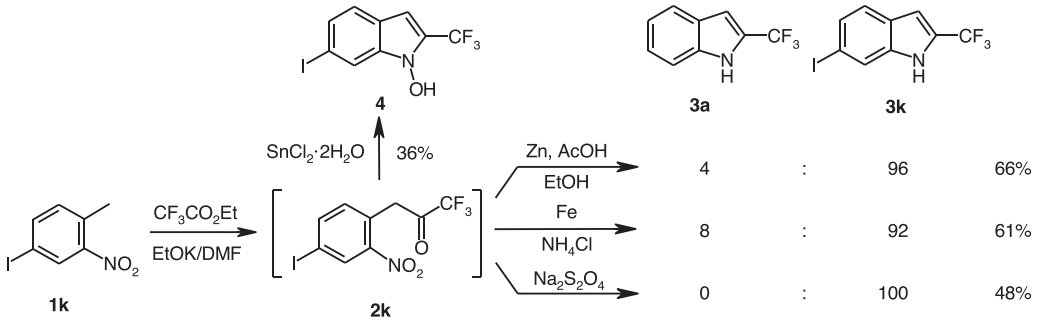
The trifluoroacetylation of **1** under basic conditions depends on both the acidity of the 2-nitrotoluenes and the reactivity of their anions (Fig. 1). The reactivity of nitrotoluenes appears to be the result of balancing the steric hindrance and electronic effects of the substituents. While 2-nitrotoluene **1u** did not undergo trifluoroacetylation, the *tert*-butylthio group (**1q**) gave a decent yield of indole (**3q**) (Scheme 2).



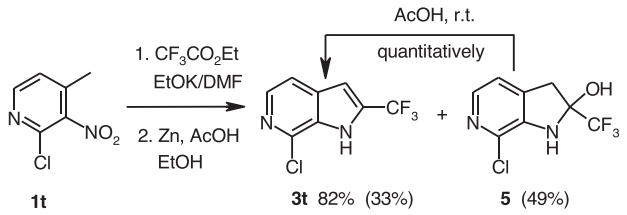
Scheme 2. Two-step synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes.



Scheme 3. Scope of 2-nitrotoluenes for the synthesis of 2-(trifluoromethyl)indoles, the reaction scale is specified in parentheses. Unless stated otherwise, the yields are for the reaction using Zn/AcOH in the second step. [a]Overall yield of the two-step procedure; [b] $Na_2S_2O_4$ was used as a reducing agent; [c] From 5-cyano-2-nitrotoluene (**1o**); [d] The yield after an additional acidic-promoted procedure (see further below).



Scheme 4. Comparison of reducing agents for the reaction of 4-iodo-2-nitrotoluene. Overall isolated yields from **1 k**. Product ratios taken from GC analyses.



Scheme 5. Improved procedure for the synthesis of **3 t**.

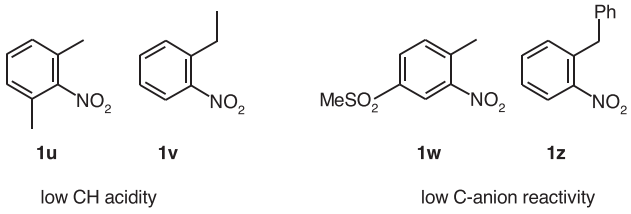


Fig. 1. Examples of 2-nitrotoluenes which were unreactive in the trtifluoroacetylation reaction.

At the opposite extreme, precursors of more stabilized carbanions (e.g. **1w** and **1z**) did not undergo acylation despite deprotonation of the starting nitrotoluene, which can be deduced from the observable color of the anion formation.

Conclusion

We have shown that the acylation of suitably acidic 2-nitrotoluenes by ethyl trifluoroacetate, one of the least expensive sources of a trifluoromethyl group, produces 2-nitrobenzyl trifluoromethyl ketone intermediates which, under the action of Zn/AcOH, undergo reductive cyclization providing 2-(trifluoromethyl)indoles unsubstituted at the C3 position. The developed method uses readily available starting nitroarenes and avoids expensive catalysts and harsh reaction conditions. Moreover, the method is usable up to a scale of 250 mmol.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153515. Detailed experimental procedures, analytical data and copies of ^1H and ^{13}C NMR spectra of the products (PDF).

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[22] The following reaction conditions were examined for the acylation but gave at most traces of **2a**: *t*-BuOK/DMF/-30 °C → rt, t-BuOK/DMSO/rt, NaH/DMF/rt, *t*-BuOK /THF/–50 °C → rt, and EtOK/THF/-50 °C → rt.

Supplementary Information

Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes

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General Remarks

Melting points were recorded in open capillary and are uncorrected. The ^{1}H and ^{13}C NMR spectra of all compounds studied were measured at temperature 298 K in $CDCl_3$ or deuterated dimethyl sulfoxide (DMSO-d_6) solutions with a Varian vnmrs-600 or Varian vnmrs-500 using tetramethylsilane (TMS) as the internal standard. Mass spectra (EI, 70 eV) were obtained on an AutoSpec Premier (Waters) spectrometer. For ESI+ and ESI- measurements, a Maldi SYNAPT G2-S HDMS (Waters) was used. Accurate mass measurements were obtained using magnetic sector mass analyzer (EI) or TOF analyzer (ESI). Silica gel Merck 60 (230-400 mesh) was used for column chromatography. GC analyses were performed on a Hewlett Packard HP6890 GC system with HP5 column and FID (carrier gas – helium). THF was distilled from sodium/benzophenone ketyl prior to use. DMF was dried over CaH_2, distilled and stored over molecular sieves. All commercial reagents were used without additional purification. Except for **1q** and **1r**, all starting 2-nitrotoluenes were commercially available.

Synthesis of 5-bromo-3-(*tert*-butylthio)-2-nitrotoluene (1q)

4-Bromo-2,6-difluoronitrobenzene (4.16 g, 17.4 mmol), diethyl malonate (3.5 mL, 20.9 g) and K_2CO_3 (7.2 g, 52 mmol) in dry DMSO (40 mL) were stirred at rt. for 24 h. The mixture was poured into cold water (300 mL) and conc. HCl (15 mL), followed by extraction with ethyl acetate (4×50 mL). The combined extracts were washed with diluted aqueous NaCl, dried (Na_2SO_4) and evaporated. The residue was dissolved in AcOH (60 mL) and conc. HCl (30 mL) and refluxed for 12 h. After cooling, the mixture was evaporated to dryness followed by drying in vacuo. The residue was dissolved in dry MeCN, Cu_2O (30 mg) was added and the mixture was stirred and refluxed for 12 h. After cooling, the mixture was filtered, the filtrate evaporated and chromatographed (hexane/ethyl acetate, 25:1) to give 2.51g (62% combined yield) of 5-bromo-1-fluoro-3-methyl-2-nitrobenzene as creamy crystals, mp 59-62 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H), 7.26-7.30 (m, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ = 17.6, 118.3 (q, J_{FC} = 22 Hz), 124.9 (q, J_{FC} = 10 Hz), 129.9 (q, J_{FC} = 4 Hz), 114.2, 134.6, 153.8 (q, J_{FC} = 262 Hz).

To a solution of the above compound (976 mg, 4.17 mmol) in DMF (10 mL) was added K_2CO_3 (1260 mg, 9.0 mmol) and *tert*-butyltiol (516 μL). The mixture was stirred at 100 °C for 2 days. After cooling, the mixture was poured into water (100 mL) and extracted with Et_2O (3×50 mL). The extract was washed with water (100 mL) and brine. After evaporation, the crude product was purified by column chromatography (SiO_2, hexane) to obtain **1q** as colorless liquid, 1.14 g (90%) yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.29 (s, 3H), 7.45 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 17.2, 31.2, 48.8, 122.6, 126.9, 131.5, 134.5, 138.3, 155.5; MS (EI) *m/z* 305 (0.1), 303 (0.1, $[M]^+$), 249 (20), 247 (19), 232 (9), 231 (9), 185 (14), 183 (14), 57 (100); Anal. Calcd for $C_{11}H_{14}BrNO_2S$: C, 43.43; H, 4.64; N, 4.60; S, 10.54. Found: C, 43.40; H, 4.49; N, 4.59; S, 10.25.

4-(4-Bromophenyl)-2-nitrotoluene (1r). Prepared from 4-chloro-2-nitrotoluene (2.57 g, 15 mmol) following the published general procedure.[1] Yield 2.40 g (55%), colorless crystals, mp 105-106 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.63 (s, 3H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.45-7.47 (m, 2H), 7.59-7.61 (m, 2H), 7.69 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.16 (d, *J* = 1.8 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 20.2, 122.6, 122.7, 128.4, 131.0, 132.2, 132.7, 133.4, 137.4, 139.1, 149.6; MS (EI) *m/z* 293 (52), 291 (53, $[M]^+$), 276 (51), 274 (51), 248 (32), 246 (35), 167 (57), 167 (57), 166 (55), 165 (100); HRMS (EI) *m/z* Calcd. for $C_{13}H_{10}{}^{79}BrNO_2$ $[M]^+$: 290.9895. Found: 290.9897.

Trifluoroacetylation of 2-nitrotoluenes 1. General procedure.

A solution of CF_3CO_2Et (11.9 g, 85 mmol) in dry DMF (60 mL) was cooled under Ar to -50 °C in a dry ice/acetone cooling bath. To the magnetically stirred mixture were successively added in one portion each, EtOK (2.15 g, 43 mmol) and 2-nitrotoluene **1** (20 mmol). The reaction mixture was left in the bath overnight allowing it to slowly reach room temperature. When the tlc control proved the reaction complete, the mixture was diluted with cold 10% HCl_{aq} (50 mL) and extracted with EtOAc (3×50 mL). The combined extracts were washed with water (3×60 mL) and dried with $MgSO_4$. After evaporation, the crude material [**2]** was subjected to the reductive cyclocondensation step.

Cyclocondensation of 2 by reduction with Zn/AcOH, procedure A

The crude product of the first step [**2**] was diluted with EtOH (70 mL) and AcOH (13 mL), the mixture was cooled to –50 °C and Zn powder (6.0 g) was added in one portion with stirring. The mixture was stirred overnight without cooling to slowly reach room temperature. After dilution with water (70 mL), the mixture was extracted with EtOAc (3×70 mL). The combined organic phase was dried ($MgSO_4$) and the solvent was removed under vacuum. It was then dissolved in MeOH (5 mL) and aqueous NH_3 (25%, 20 mL), and stirred at room temperature for 2-4 days to complete remove diethyl carbonate impurities. The mixture was diluted with water (50 mL) and extracted with EtOAc (3×70 mL). The combined organic phase was dried ($MgSO_4$) and the solvent was evaporated. If not stated otherwise the crude product was separated by column chromatography (SiO_2, hexane/EtOAc 4:1).

Cyclocondensation of 2k and 2l by reduction with $Na_2S_2O_4$, procedure B

The crude product of the first step (12.5 mmol) was diluted with THF (15 mL) and water (30 mL). To that mixture $Na_2S_2O_4$ (16.0 g, 93.1 mmol) was added and the mixture was stirred under reflux condenser at 70 °C for 2 h. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted with EtOAc (3×100 mL). After drying of the combined extracts, the solvent was evaporated and the residue was stirred with MeOH (5mL) and aqueous NH_3 (25%, 20 mL) then worked-up as in procedure A.

Cyclocondensation of 2l by reduction with Fe/NH_4Cl, procedure C

The crude product of the first step, obtained in a 12.5 mmol scale, was diluted with THF (10 mL), EtOH (20 mL) and water (10 mL). To that mixture, NH_4Cl (1.6 g) was added and the mixture was stirred at room temperature for 4 days, then filtered thru a Celite pad. The filtrate

was diluted with water (30 mL) and extracted with EtOAc (3×70 mL). The combined organic phase was dried ($MgSO_4$) and the solvent was removed under vacuum. The product was isolated by column chromatography (SiO_2, hexane/EtOAc 4:1).

Cyclocondensation of 2l by reduction with $SnCl_2$, procedure D

The crude product of the first step, obtained in a 12.5 mmol scale, was diluted with AcOH (60 mL) and EtOH (5 mL), and $SnCl_2 \cdot 2H_2O$ (10.3 g, 45.6 mmol) was added. The mixture was stirred at room temperature for 24 h then concentrated on a rotary evaporator, diluted with water (100 mL) and extracted with EtOAc (3×70 mL). The combined organic phase was dried ($MgSO_4$) and the solvent was removed under vacuum. The product was isolated by column chromatography (SiO_2, hexane/EtOAc 1:1) to obtain *N*-hydroxyindole **4**.

2-(Trifluoromethyl)-1*H*-indole (3a)[2,3]

Prepared from 2-nitrotoluene (**1a**, 4.72 mL, 41 mmol), scaled-up procedure A. Yield 5.6 g (74%), colorless crystals, mp 108-109 °C (lit.[4] mp 107-108 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.01 (s, 1H), 7.15 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H), 7.31 (ddd, J = 8.3, 7.1, 1.0 Hz, 1H), 7.51 (dd, J = 8.3, 0.9 Hz, 1H), 7.69 (d, 8.0 Hz, 1H), 12.26 (s, 1H); ^{13}C{^{1}H}NMR (150 MHz, DMSO-d_6) δ 103.5 (q, J_{FC} = 3.0 Hz), 112.8, 120.8, 122.0 (q, J_{FC} = 268.4 Hz), 122.1, 124.6, 125.3 (q, J_{FC} = 38 Hz), 126.4, 137.2; HRMS (ESI) *m/z* Calcd. for $C_9H_5F_3N$ [M-1]$^-$: 184.0374. Found: 184.0372.

5-Bromo-2-(trifluoromethyl)-1*H*-indole (3b)[5]

Prepared from 3-bromo-6-nitrotoluene (**1b**, 21.6 g, 100 mmol), scaled-up procedure A. Yield 25.6 g (95%), colorless crystals, mp 50-53 °C (lit.[5] mp 52-53 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (m, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.41 (dd, J = 8.7, 1.8 Hz, 1H), 7.82 (d, J = 1.8 Hz, 1H), 8.43 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 103.7 (q, J_{FC} = 3.5 Hz), 113.2, 114.3, 120.9 (q, J_{FC} = 268.2 Hz), 124.5, 126.9 (q, J_{FC} = 38.8 Hz), 127.9, 128.2, 134.7; HRMS (ESI) *m/z* Calcd. for $C_9H_4{}^{79}BrF_3N$ [M-1]$^-$: 261.9479. Found: 261.9483.

4-Bromo-2-(trifluoromethyl)-1*H*-indole (3c)

Prepared from 2-bromo-6-nitrotoluene (**1c**, 32.4 g, 150 mmol), scaled-up procedure A. Yield 27.6 g (70%), liquid, bp 80 °C/0.1 Torr. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.30 (dd, J = 8.6, 1.6 Hz, 1H), 7.535 (d, J = 8.6 Hz, 1H), 7.58 (br s, 1H), 8.36 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 104.4 (q, J_{FC} = 3Hz), 114.6, 118.4, 120.9 (q, J_{FC} = 268 Hz), 123.3, 124.1, 124.7, 125.4, 126.3 (q, J_{FC} = 39 Hz); HRMS (ESI) *m/z* Calcd. for $C_9H_4{}^{79}BrF_3N$ [M-1]$^-$: 261.9479. Found: 261.9478.

7-Bromo-2-(trifluoromethyl)-1*H*-indole (3d)

Prepared in two separate steps. **1-(3-Bromo-2-nitrophenyl)acetone (2d)** was prepared from 3-bromo-2-nitrotoluene (**1d**, 29 g, 134 mmol) following general procedure for trifluoroacetylation of **1** (see above). The crude product mixture was separated by column chromatography (SiO_2, hexane/EtOAc) Yield 19.0 g (50%), brownish crystals, mp 69-72 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (s, 2H), 7.29 (dd, J = 7.9, 1.1 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 7.71 (dd, J = 7.9, 1.1 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 39.4, 114.3, 115.4

(q, J_{FC} = 292.4 Hz), 125.4, 131.2, 131.7, 134.2, 186.2 (q, J_{FC} = 36.7 Hz); MS *m/z* 313 (42), 311 (43, $[M]^+$), 267 (36), 265 (37), 244 (55), 242 (55), 216 (84), 214 (86), 186 (72), 90 (100); HRMS (EI) *m/z* Calcd. for $C_9H_5{}^{79}BrF_3NO_3$ $[M]^+$: 310.9405. Found: 310.9407. The title compound was prepared from **2d** (19.0 g, 67 mmol), procedure A. Yield 15.1 g (85%, total yield from **1d** 42%), colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (m, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 8.52 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 105.0, 105.3 (q, J_{FC} = 3 Hz), 120.9 (q, J_{FC} = 268 Hz), 121.3, 122.3, 126.3 (q, J_{FC} = 40 Hz), 127.1, 127.5, 135.0; MS (EI) *m/z* 265 (98), 263 (100), 245 (49), 243 (50); HRMS (EI) *m/z* Calcd. for $C_9H_5{}^{79}BrF_3N$: 262.9557. Found: 262.9559.

6-Bromo-2-(trifluoromethyl)-1*H*-indole (3e) [5,6]

Prepared from 4-bromo-2-nitrotoluene (**1e**, 21.6 g, 100 mmol), scaled-up procedure A. Yield 18.7 g (71%), brown crystals, mp 42-43 °C (lit.[5] yellow liquid). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 7.31 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.60 (s, 1H), 8.36 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 104.4 (q, J_{FC} = 3.2 Hz), 114.7, 118.4, 120.9 (q, J_{FC} = 268.3 Hz), 123.3, 124.8, 125.5, 126.3 (q, J_{FC} = 38.9 Hz), 136.8; HRMS (ESI) *m/z* Calcd. for $C_9H_4{}^{79}BrF_3N$ $[M-1]^-$: 261.9479. Found: 261.9486.

4-Fluoro-2-(trifluoromethyl)-1*H*-indole (3f)[3]

Prepared from 2-fluoro-6-nitrotoluene (**1f**, 38.8 g, 250 mmol), scaled-up procedure A. Yield 42.7 g (84%), pale yellow liquid. (lit.[9] colorless oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 10.1, 7.8, 0.7 Hz, 1H), 7.03 (m, 1H, 7.20 (d, *J* = 8.2 Hz, 1H), 7.26 (td, *J* = 8.2, 5.0 Hz, 1H), 8.57 (br s, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 100.4 (q, J_{FC} = 3.0 Hz), 105.7 (d, J_{FC} = 17.8 Hz), 107.7 (d, J_{FC} = 3.9 Hz), 116.3 (d, J_{FC} = 22.3 Hz), 121 (q, J_{FC} = 268.6 Hz), 125.4 (d, J_{FC} = 7.3 Hz), 125.8 (d, J_{FC} = 39.1 Hz), 138.4, 157.5 (d, J_{FC} = 250.6 Hz); MS (EI) *m/z* 203 (100, $[M]^+$), 183 (81), 163 (24); HRMS (EI) *m/z* Calcd. for $C_9H_5F_4N$ $[M]^+$: 203.0358. Found: 203.0359.

6-Fluoro-2-(trifluoromethyl)-1*H*-indole (3g)[2,4,5]

Prepared from 4-fluoro-2-nitrotoluene (**1g**, 31.0 g, 200 mmol), scaled-up procedure A. Yield 25.2 g (62%), yellowish liquid (lit.[5] reddish brown liquid). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (m, 1H), 6.96 (ddd, *J* = 9.4, 8.8, 2.2 Hz, 1H), 7.05 (dd, *J* = 9.4, 2.2 Hz, 1H), 7.57 (dd, *J* = 8.8, 5.1 Hz, 1H), 8.30 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 97.8 (d, J_{FC} = 26.3 Hz), 104.4 (qd, J_{FC} = 3.5, 1.1 Hz), 110.5 (d, J_{FC} = 25.9 Hz), 121.0 (q, J_{FC} = 267.4 Hz), 123.2 (d, J_{FC} = 9.8 Hz), 124.2, 126.2 (J_{FC} = 39,4 Hz), 136.2 (d, 13.4 Hz), 161.2 (d, J_{FC} = 241.2 Hz); MS (EI) *m/z* 203 (100, $[M]^+$), 183 (75), 163 (25), 156 (13); HRMS (EI) *m/z* Calcd. for $C_9H_5F_4N$ $[M]^+$: 203.0358. Found: 203.0361.

6-Chloro-2-(trifluoromethyl)-1*H*-indole (3h)[2,4,5]

Prepared from 4-chloro-2-nitrotoluene (**1h**, 7.03 g, 41 mmol), scaled-up procedure A. Isolated by column chromatography (SiO_2, hexane/EtOAc 8:1 – 4:1). Yield 6.68 g (75%), pale yellow liquid. (lit.[5] reddish brown liquid). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (m, 1H), 7.17 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.43 (m, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 8.45 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 104.3 (q, J_{FC} = 3.5 Hz), 111.6, 120.9, (q, J_{FC} = 267.6 Hz), 122.2, 123.0,

125.1, 126.4 (q, J_{FC} = 39.3 Hz), 130.7, 136.4; MS (EI) *m/z* 221 (48), 219 (100, $[M]^+$), 199 (70), 164 (17); HRMS (EI) *m/z* Calcd. for $C_9H_5{}^{35}ClF_3N$ $[M]^+$: 219.0063. Found: 219.0067.

4-Chloro-2-(trifluoromethyl)-1*H*-indole (3i)[5]

Prepared from 2-chloro-6-nitrotoluene (**1i**, 3.43 g, 20 mmol), procedure A. Isolated by column chromatography (SiO_2, hexane/EtOAc 4:1). Yield 2.82 g (64%), brown oil (lit.[5] reddish brown liquid). ^1H NMR (500 MHz, $CDCl_3$) δ 7.04-7.06 (m, 1H), 7.19-7.26 (m, 2H), 7.31-7.34 (m, 1H), 8.51 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 103.0 (q, J_{FC} = 3.5 Hz), 110.3, 120.9, 120.9 (q, J_{FC} = 267.6 Hz), 125.4, 125.7, 126.2 (q, J_{FC} = 39.4 Hz), 127.4, 136.6; MS (EI) *m/z* 221 (42), 219 (100, $[M]^+$), 201 (29), 199 (63), 164 (29); HRMS (EI) *m/z* Calcd. for $C_9H_5F_3N{}^{35}Cl$ $[M]^+$: 219.0063. Found: 219.0068.

5-Chloro-2-(trifluoromethyl)-1*H*-indole (3j)[5]

Prepared from 2-chloro-6-nitrotoluene (**1j**, 2.57 g, 15 mmol), procedure A. Isolated by column chromatography (SiO_2, hexane/EtOAc 4:1). Yield 2.66 g (80%), colorless crystals, mp 60-62 °C (hexane/EtOAc) (lit.[5] yellow liquid). ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 7.28 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 1.9 Hz, 1H), 8.38 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 103.8 (q, J_{CF} = 3.5 Hz), 120.9 (q, J_{CF} = 267.6 Hz), 121.4, 125.3, 126.9, 127.0 (q, J_{CF} = 38.5 Hz), 127.6, 134.4; MS (EI) *m/z* 221 (46), 219 (100, $[M]^+$), 201 (35), 199 (64); HRMS (EI) *m/z* Calcd. for $C_9H_5{}^{35}ClF_3N$ $[M]^+$: 219.0063. Found:219.0069.

6-Iodo-2-(trifluoromethyl)-1*H*-indole (3k)

Prepared from 4-iodo-2-nitrotoluene (**1k**, 2.89 g, 11 mmol), procedure B. Yield 2.91 g (85%), colorless crystals mp 47-49 °C (DCM). ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 8.34, (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 89.0, 104.4 (q, J_{FC} = 3.5 Hz), 120.8, 120.9 (q, J_{FC} = 268.0 Hz), 123.6, 125.9, 126.1 (q, J_{FC} = 39.3 Hz), 130.2, 137.2; MS (EI) *m/z* 311 (100, $[M]^+$), 184 (43); HRMS (EI) *m/z* Calcd. for $C_9H_5F_3IN$ $[M]^+$: 310.9419. Found: 310.9421.

4-Iodo-2-(trifluoromethyl)-1*H*-indole (3l)

Prepared from 2-iodo-6-nitrotoluene (**1l**, 3,29 g, 12.5 mmol), procedure B. Yield 1.86 g (48%), creamy crystals, mp 59-60 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 6.89-6.91 (m, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 9.31 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 88.4, 107.9 (t, J_{FC} = 3.5 Hz), 111.7, 120.9 (t, J_{FC} = 268.2 Hz), 125.9 (t, J_{FC} = 39.3 Hz), 126.0, 130.8, 131.3, 134.9; MS (EI) *m/z* 311 (100), 184 (43); HRMS (EI) *m/z* Calcd. for $C_9H_5F_3IN$ $[M]^+$: 310.9419. Found: 310.9421.

2,6-Bis(trifluoromethyl)-1*H*-indole (3m)[3]

Prepared from 2-nitro-4-trifluoromethyltoluene (**1m**, 8.20 g, 40 mmol), scaled-up procedure A. Yield 7.16 g (71%), colorless solid, mp 49-51 °C (after quick distillation) (lit.[3] colorless wax). ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (m, 1H), 7.44 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.74 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 8.65 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 104.3 (q, J_{FC} = 3.5 Hz), 109.4 (q, J_{FC} = 4.6 Hz), 117.8 (q, J_{FC} = 3.5 Hz), 120.7 (q, J_{FC} = 268.2 Hz), 122.7, 124.6 (q, J_{FC} = 272.2 Hz), 127.0 (q, J_{FC} = 32.4 Hz), 128.3 (q, J_{FC} = 39.9 Hz), 128.8 (q,

J_{FC} = 1.2 Hz), 134.9; HRMS (ESI) *m/z* Calcd. for $C_{10}H_4F_6N$ [M-1]$^-$: 252.0248. Found: 252.0249.

2,4-Bis(trifluoromethyl)-1*H*-indole (3n)[3]

Prepared from 2-nitro-6-trifluoromethyltoluene (**1n**, 4.10 g, 20 mmol), procedure A. Yield 4.05 g (80%), colorless solid, mp 47-49 °C (lit.[3] yellow oil). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.40 (dd, *J* = 7.6, 8.3 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 8.65 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 103.05 (q, J_{FC} = 1.7 Hz), 103.07 (q, J_{FC} = 1.7 Hz), 115.5, 118.8 (q, J_{FC} = 4.6 Hz), 120.8 (q, J_{FC} = 268.2 Hz), 123.5 (q, J_{FC} = 32.9 Hz), 124.0, 124.4 (q, J_{FC} = 272.2 Hz), 124.1, 127.3 (q, J_{FC} = 39.3 Hz); MS (EI) *m/z* 253 (100, [M]$^+$), 233 (51), 183 (15); HRMS (EI) *m/z* Calcd. for $C_{10}H_5F_6N$ [M]$^+$: 253.0326. Found: 253.0329.

2-(Trifluoromethyl)-1*H*-indole-5-carboxamide (3o)

Prepared from 3-methyl-4-nitrobenzonitrile (**1o**, 3.24 g, 20 mmol), procedure A. Yield 2.39 g (51%), colorless solid, mp 150-152 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.11 (s, 1H), 7.19 (br s, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.82 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.92, br s, 1H), 8.26 (s, 1H), 12.46 (d, *J* = 1.4 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 104.7 (q, J_{FC} = 3 Hz), 112.3, 121.8 (q, J_{FC} = 267.3 Hz), 122.5, 124.3, 125.8, 126.4 (q, J_{FC} = 38.2 Hz), 127.4, 138.6, 168.8; MS (EI) *m/z* 228 (85, [M]$^+$), 212 (100), 184 (62); HRMS (EI) *m/z* Calcd. for $C_{10}H_7F_3N_2O$ [M]$^+$: 228.0510. Found: 228.0511.

2-(Trifluoromethyl)-1*H*-benzo[*g*]indole (3p)[3]

Prepared from 2-methyl-1-nitronaphthalene (**1p**, 3.82 g, 20.4 mmol), procedure A. Yield 3.30 g (69%), beige solid, mp 159-160 °C (lit.[3] yellow solid). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (m, 1H), 7.51 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.55-7.60 (m, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 9.09 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 105.8 (q, J_{FC} = 3.0 Hz), 119.6, 120.8, 121.4 (q, J_{FC} = 267.0 Hz), 121.5, 122.3, 122.9, 123.8 (q, J_{FC} = 38.9 Hz), 125.3, 126.1, 129.0, 131.51, 131.53; MS (EI) *m/z* 235 (100, [M]$^+$), 215 (57), 195 (13); HRMS (EI) *m/z* Calcd. for $C_{13}H_8F_3N$ [M]$^+$: 235.0609. Found: 235.0613.

5-Bromo-7-(*tert*-butylthio)-2-(trifluoromethyl)-1*H*-indole (3q)

Prepared from 5-bromo-3-(*tert*-butylthio)-2-nitrotoluene (**1q**, 6.2 g, 20.4 mmol), procedure A. Yield 3.94 g (55%), colorless solid, mp 57-58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9H), 6.89-6.90 (m, 1H), 7.59 (*J* = 1.8 Hz, 1H), 7.83 (*J* = 1.8 Hz, 1H), 8.84 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 31.2, 48.6, 104.1 (q, J_{FC} = 3.5 Hz), 113.7, 117.3, 120.7 (q, J_{FC} = 268.2 Hz), 125.6, 126.8 (q, J_{FC} = 39.3 Hz), 127.6, 136.1, 138.9; MS (EI) *m/z* 353 (16), 351 (16, [M]$^+$), 297 (87), 295 (86), 217 (13), 216 (39), 215 (27), 58 (100); HRMS (EI) *m/z* Calcd. for $C_{13}H_{13}{}^{79}BrF_3NS$ [M]$^+$: 350.9904. Found: 350.9908.

6-(4-Bromophenyl)-2-(trifluoromethyl)-1*H*-indole (3r)

Prepared from 4-(4-bromophenyl)-2-nitrotoluene (**1r**, 1.93 g, 6.63 mmol), scaled-down procedure A. Yield 2.16 g (96%), colorless crystals, mp 120-121 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 7.41 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48-7.51 (m, 2H), 7.56-7.60 (m, 3H), 7.74 (d, *J* = 8.4 Hz, 1H), 8.42 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 104.2 (q,

J_{FC} = 3.5 Hz), 109.9, 120.9, 121.2 (q, J_{FC} = 267.6 Hz), 121.4, 122.5, 126.1, 126.5 (q, J_{FC} = 39.3 Hz), 129.0, 131.9, 136.6, 137.1, 140.4; MS (EI) *m/z* 341 (99), 339 (100, $[M]^+$), 321 (28), 319 (27), 239 (22), 191 (29); HRMS (EI) *m/z* Calcd. for $C_{15}H_9{}^{79}BrF_3N$ $[M]^+$: 338.9870. Found: 338.9876.

7-Methoxy-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-c]pyridine (3s)

Prepared from 2-methoxy-4-methyl-3-nitropyridine (**1s**, 3.14 g, 19.0 mmol), procedure A. Isolated by column chromatography (SiO_2, hexane/EtOAc 4:1). Yield 1.33 g (32%) (col. hexane/EtOAc 3:1), pale beige crystals, mp 131-133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (s, 3H), 6.88 (s, 1H), 7.17 (d, *J* = 5.7 Hz, 1H), 7.84 (d, *J* = 5.7 Hz, 1H), 8.87 (br s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 53.3, 103.8 (q, J_{FC} = 2.9 Hz), 110.5, 120.7 (q, J_{FC} = 268.5 Hz), 121.6, 127.6 (q, J_{FC} = 39.3 Hz), 132.6, 136.6, 151.6; MS (EI) *m/z* 216 (100, $[M]^+$), 215 (84), 186 (62), 166 (41); HRMS (EI) *m/z* Calcd. for $C_9H_7F_3N_2O$ $[M]^+$: 216.0510. Found: 216.0514.

7-Chloro-2-(trifluoromethyl)-1*H*-pyrrolo[2,3-c]pyridine (3t)

Prepared from 2-chloro-4-methyl-3-nitropyridine (**1t**, 3.3 g, 15.0 mmol), procedure A, beside **5**. Isolated by column chromatography (SiO_2, hexane/EtOAc 9:1). Yield 1.08 g (33%). colorless crystals, mp 122-123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.01 (s, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 8.15 (d, *J* = 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 104.3 (q, J_{FC} = 3.0 Hz), 115.9, 120.3 (q, J_{FC} =269.0 Hz), 130.2 (q, J_{FC} = 40.1 Hz), 130.4, 133.2, 135.5, 138.9; MS (EI) *m/z* 222 (43), 220 (100, $[M]^+$), 200 (39), 184 (29), 165 (48); HRMS (EI) *m/z* Calcd. for $C_8H_4{}^{35}ClF_3N_2$ $[M]^+$: 220.0015. Found: 220.0009.

4-Iodo-2-(trifluoromethyl)-1*H*-indol-1-ol (4)

Prepared from 2-iodo-6-nitrotoluene (**1l**, 3,29 g, 12.5 mmol), procedure D. Isolated by column chromatography (SiO_2, hexane/EtOAc 1:1). Yield 1.47 g (36%), brown crystals, mp 47-49 °C (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 7.13-7.16 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 12.17 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 89.8, 102.2 (q, J_{FC} = 4.0 Hz), 110.1, 120.7 (q, J_{FC} = 268.2 Hz), 124.5 (q, J_{FC} = 38.1 Hz), 125.3, 126.7, 130.5, 134.5; MS (EI) *m/z* 327 (100, $[M]^+$), 311 (87), 310 (43), 183 (62); HRMS (EI) *m/z* Calcd. for $C_9H_5F_3INO$ $[M]^+$:$C_9H_5F_3INO$ $[M]^+$: 326.9368. Found: 326.9373.

7-Chloro-2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-2-ol (5)

Prepared from 2-chloro-4-methyl-3-nitropyridine (**1t**, 3.3 g, 15.0 mmol), procedure A, beside **3t**. Isolated by column chromatography (SiO_2, hexane/EtOAc 9:1).Yield g (1.75 g, 49%), pinkish crystals mp 98-101 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.18 (d, *J* = 18.3 Hz, 1H), 3.45 (d, *J* = 18.3 Hz, 1H), 7.18 (d, *J* = 4.6 Hz, 1H), 7.27 (s, 1H), 7.35 (s, 1H), 7.75 (d, *J* = 4.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 90.0 (q, J_{FC} = 31.8 Hz), 90.5 (q, J_{FC} = 32.5 Hz), 120.1, 124.4 (q, J_{FC} = 283.8 Hz), 130.2, 136.3, 139.8, 142.8; MS (EI) *m/z*. 240 (26), 238 (53, $[M]^+$), 171 (43), 169 (100), 132 (48); HRMS (EI) *m/z* Calcd. for $C_8H_6{}^{35}ClF_3N_2O$ $[M]^+$: 238.0121. Found: 238.0129.

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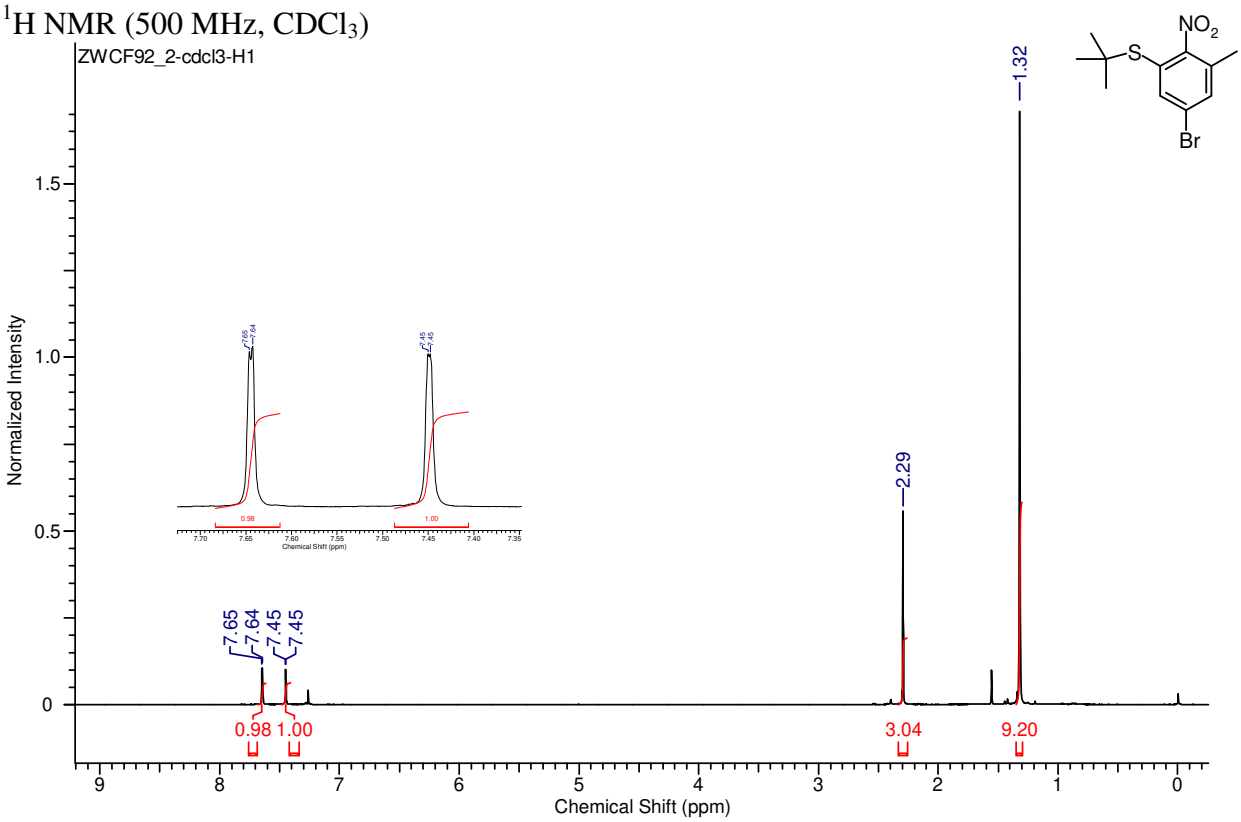
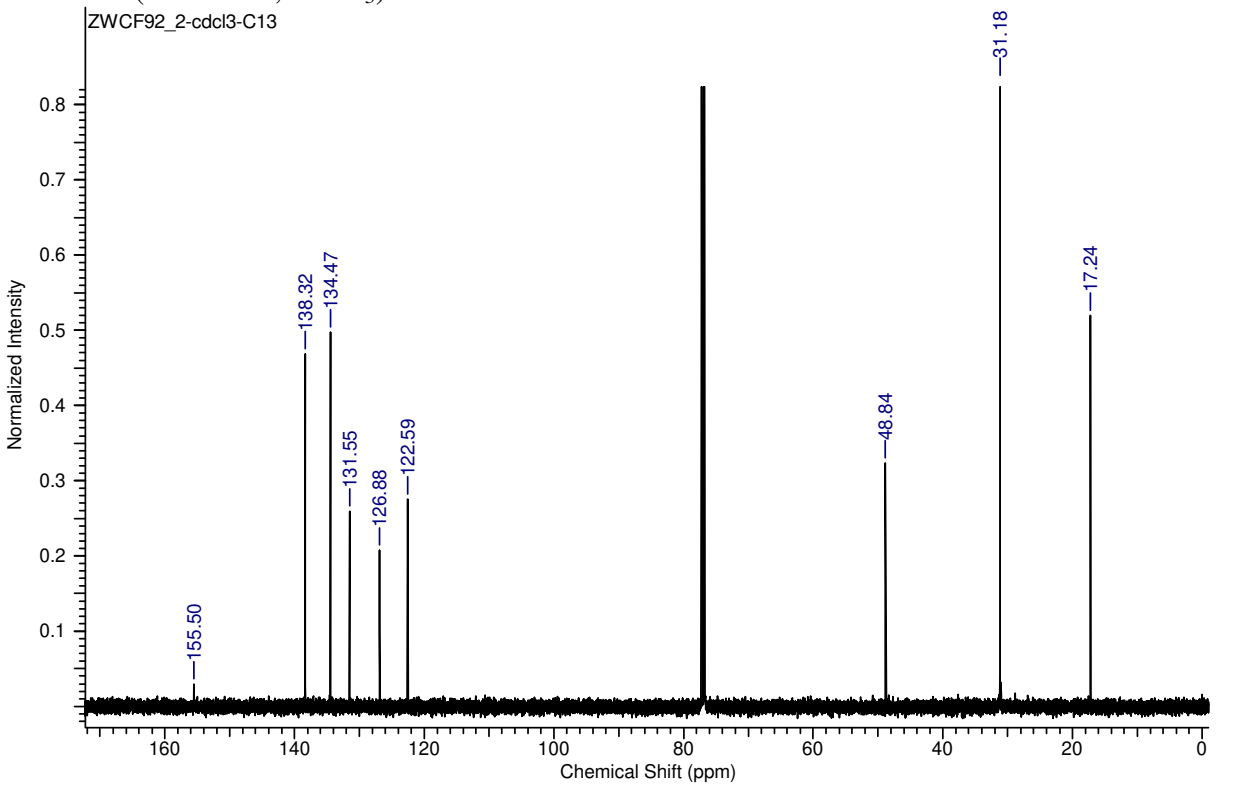
1q

^{1}H NMR (500 MHz, $CDCl_3$)

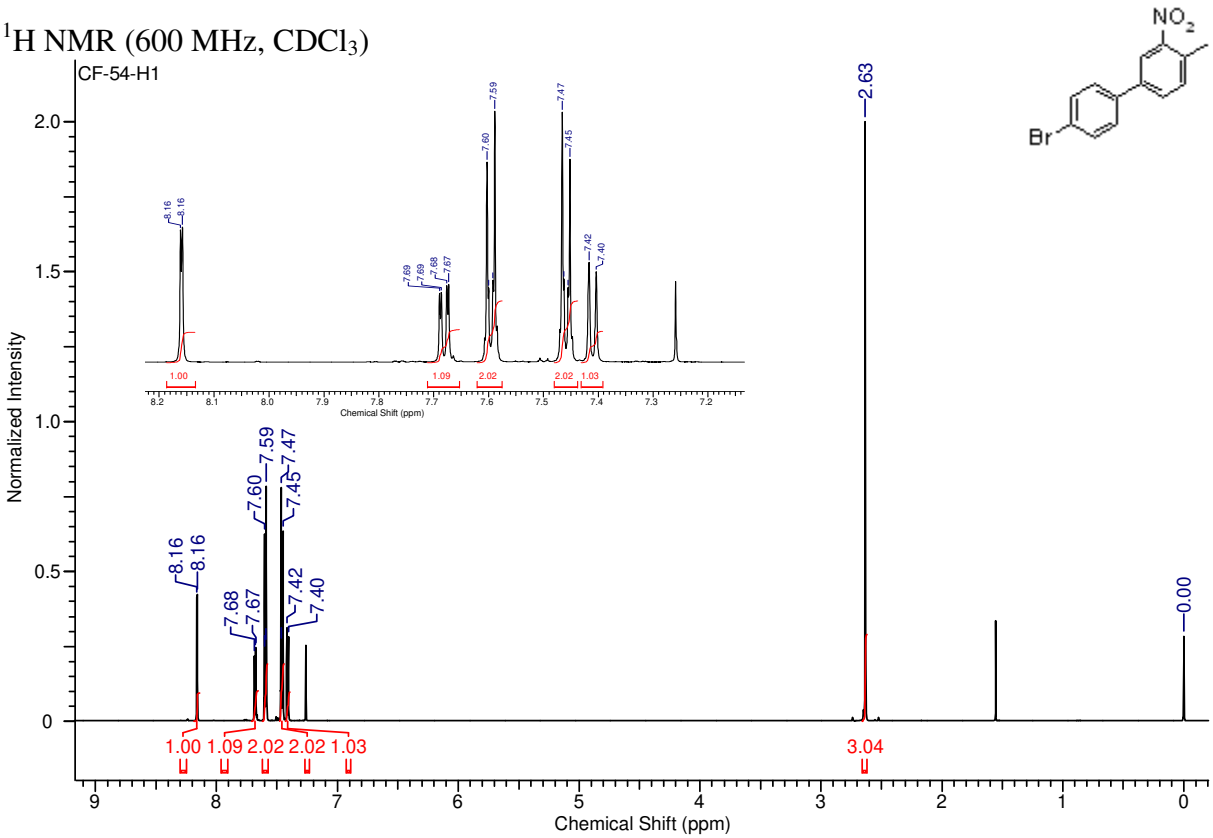


^{13}C NMR (125 MHz, $CDCl_3$)

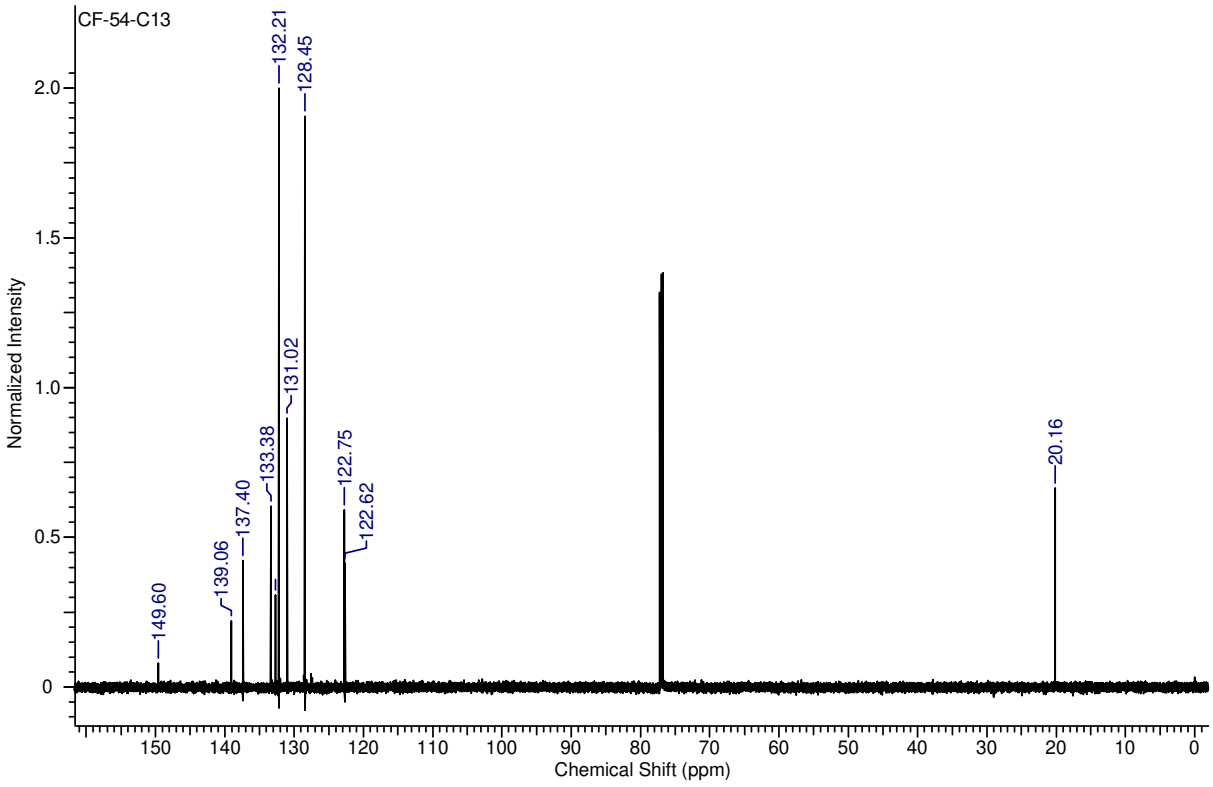


1r

^{1}H NMR (600 MHz, $CDCl_3$)

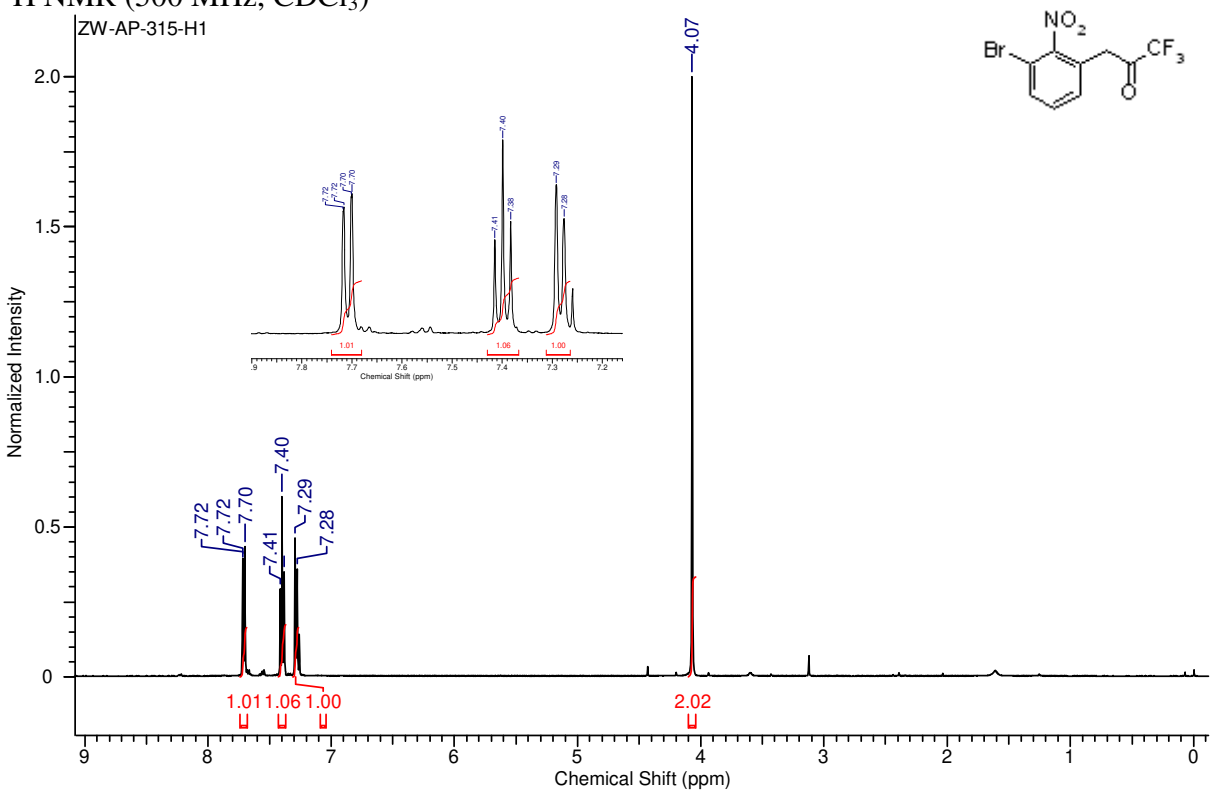


^{13}C NMR (150 MHz, $CDCl_3$)

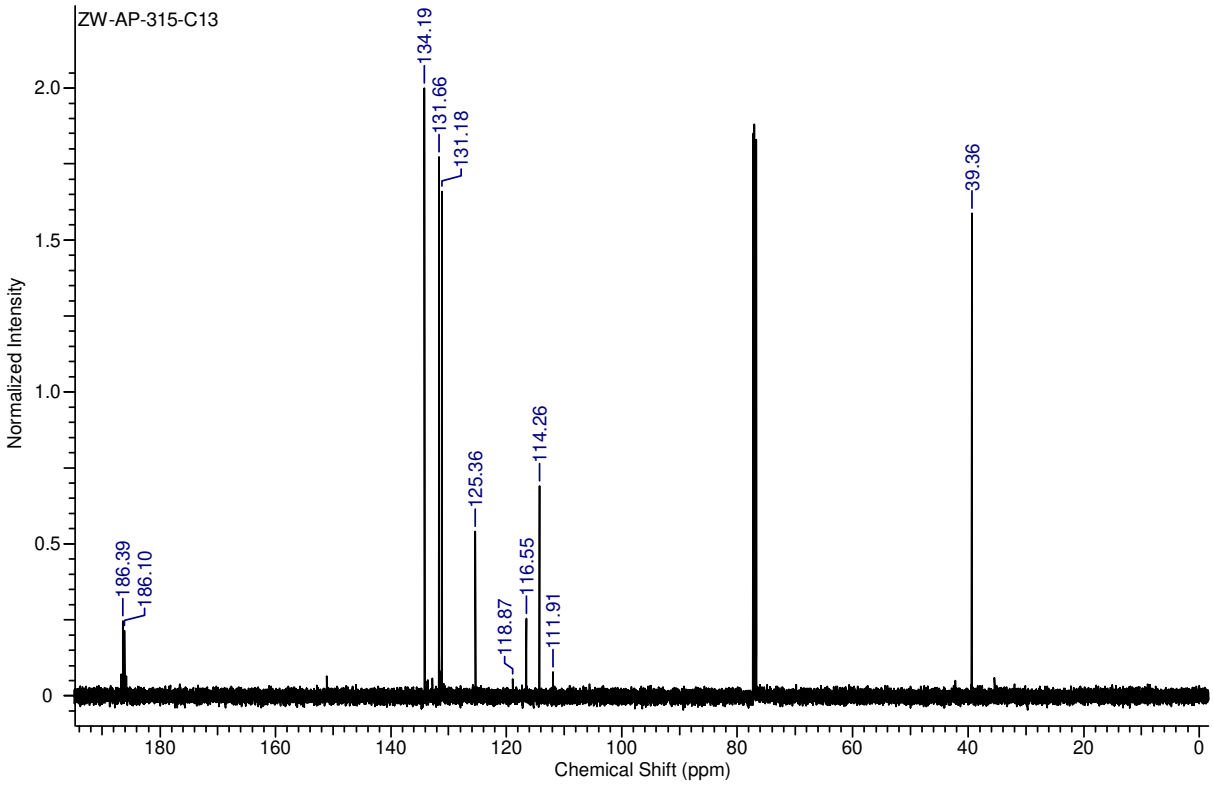


2d

^{1}H NMR (500 MHz, $CDCl_3$)

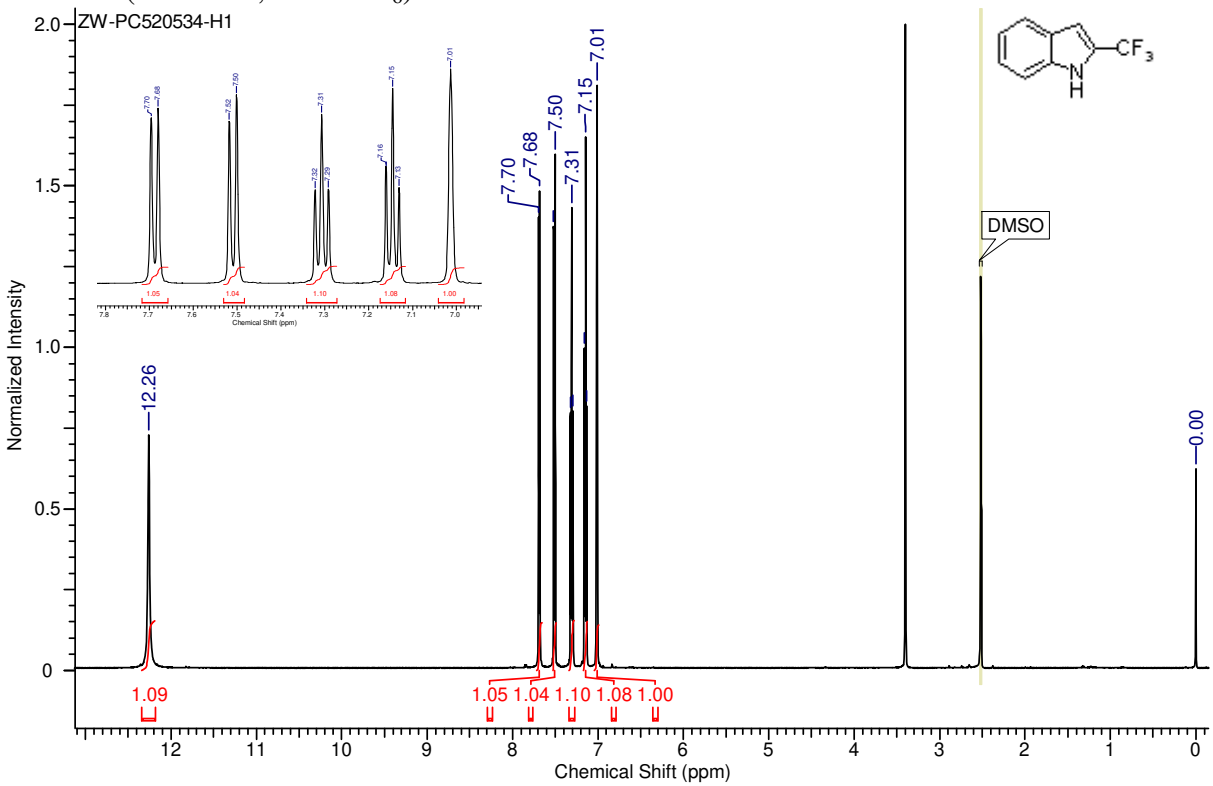


^{13}C NMR (125 MHz, $CDCl_3$)

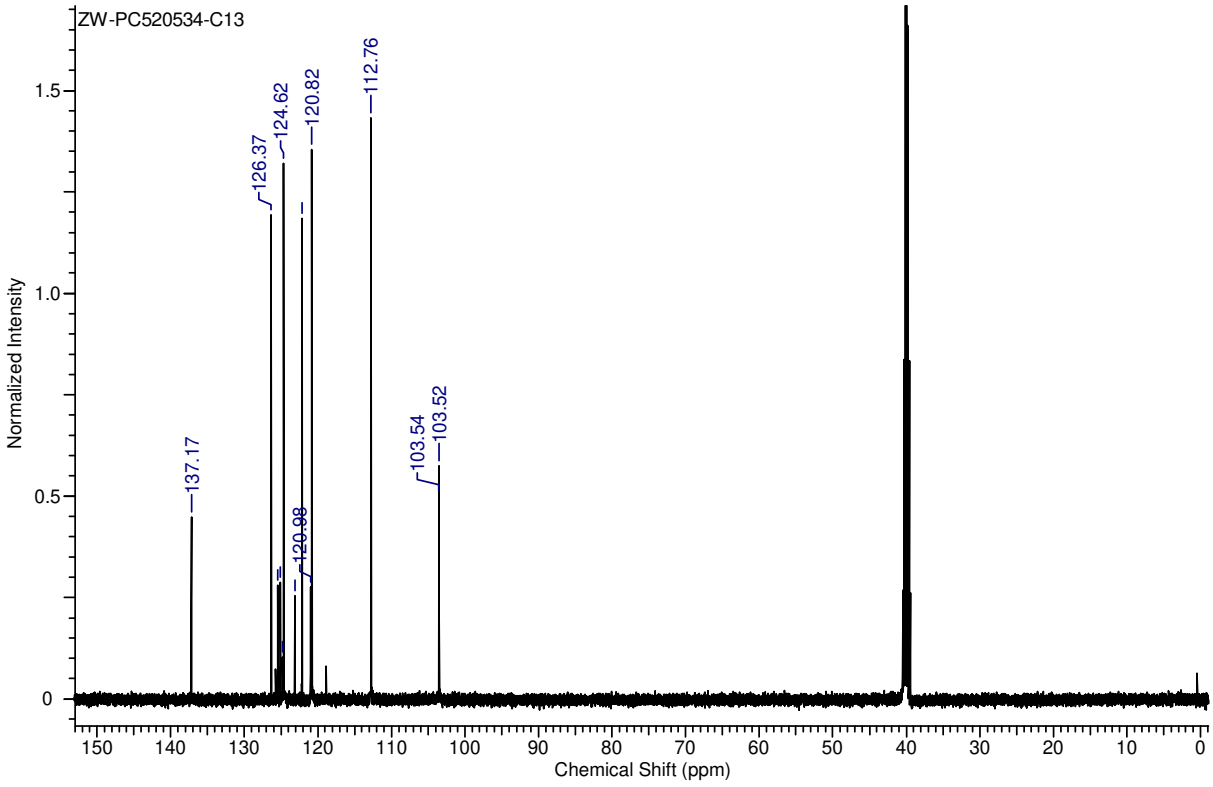


3a

^{1}H NMR (500 MHz, DMSO-d_6)

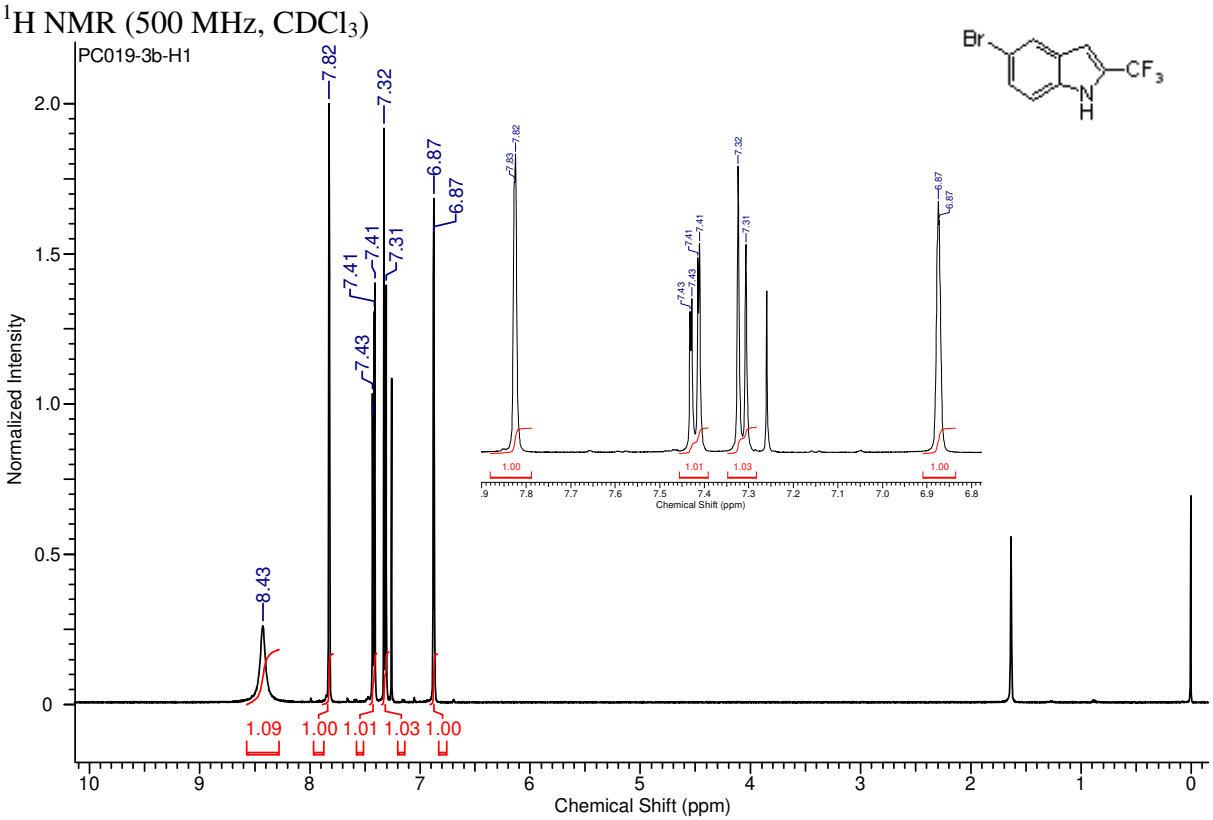


^{13}C NMR (125 MHz, DMSO-d_6)

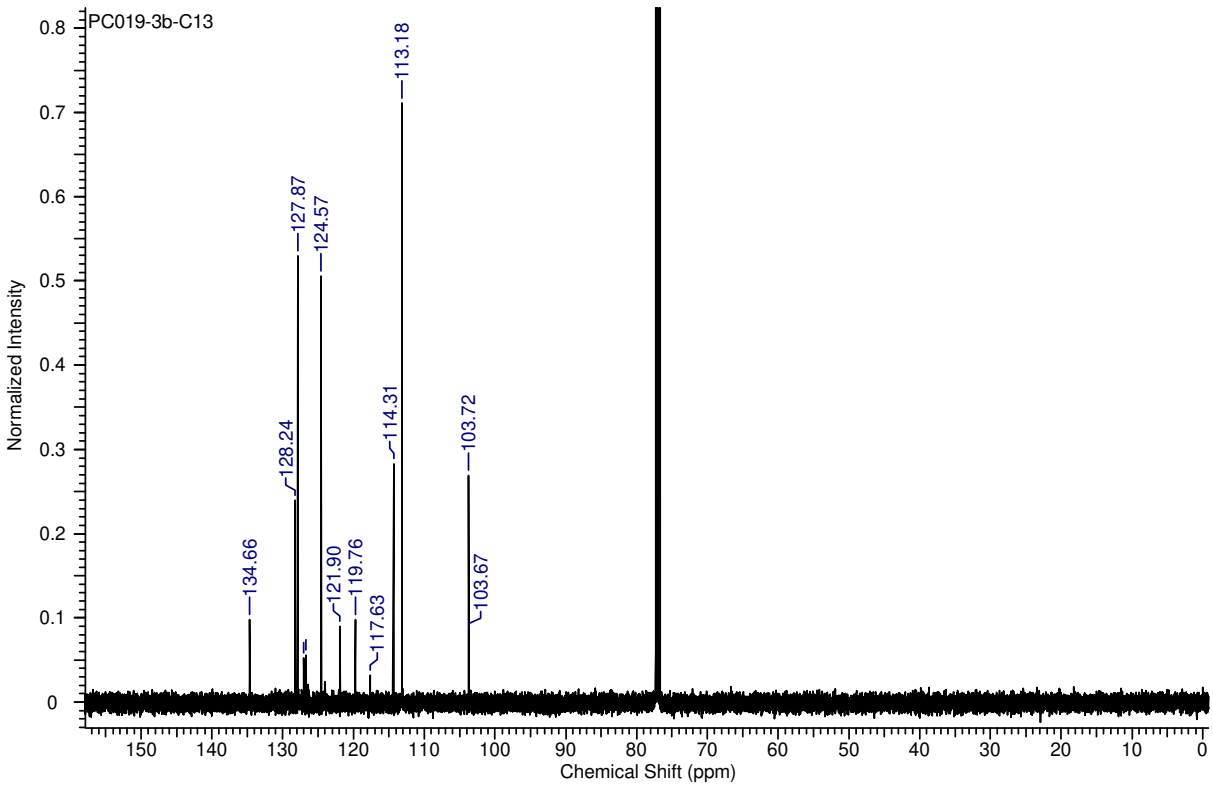


3b

^{1}H NMR (500 MHz, $CDCl_3$)

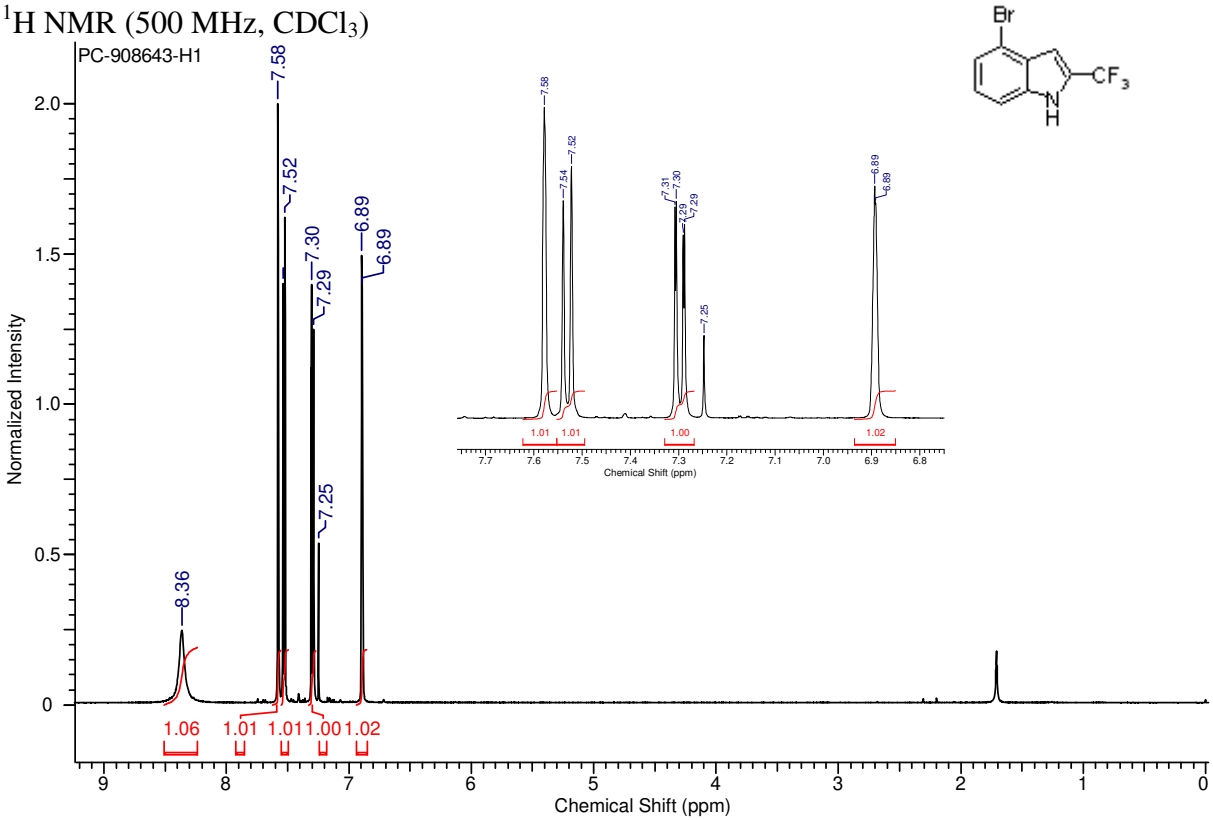


^{13}C NMR (125 MHz, $CDCl_3$)

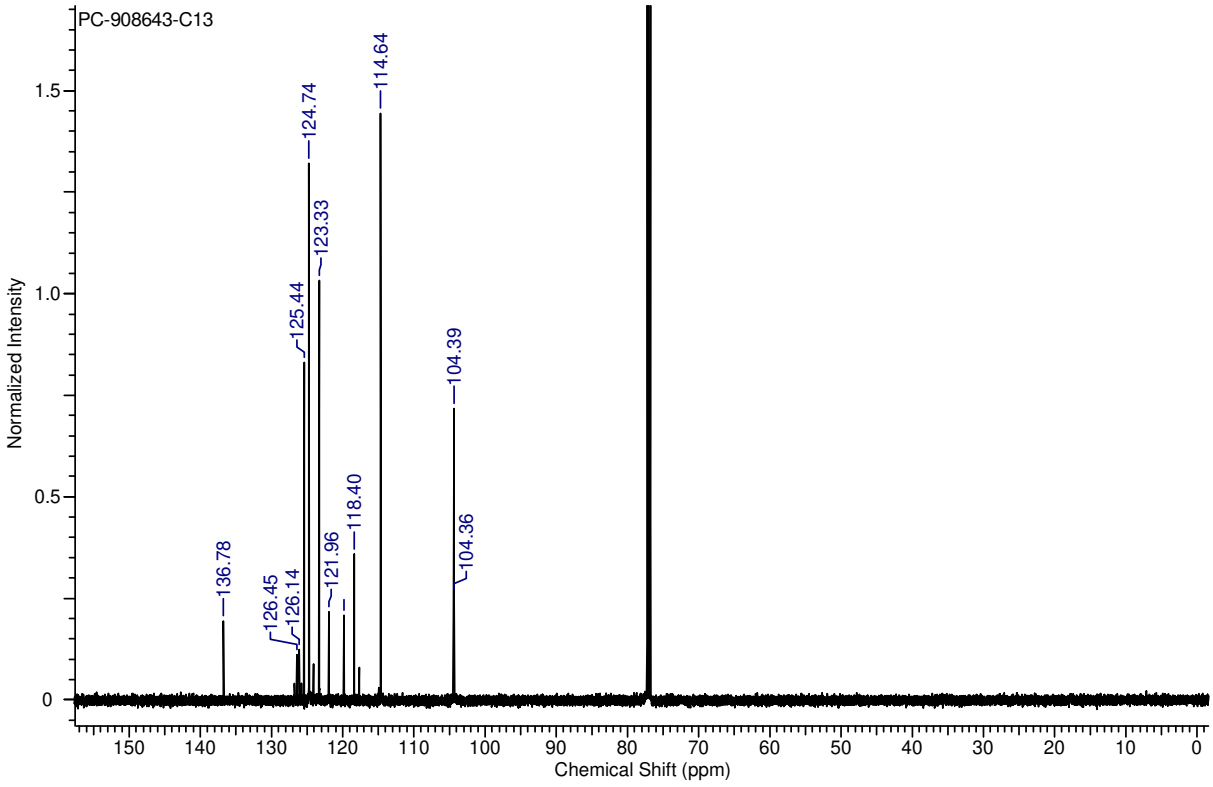


3c

^{1}H NMR (500 MHz, $CDCl_3$)

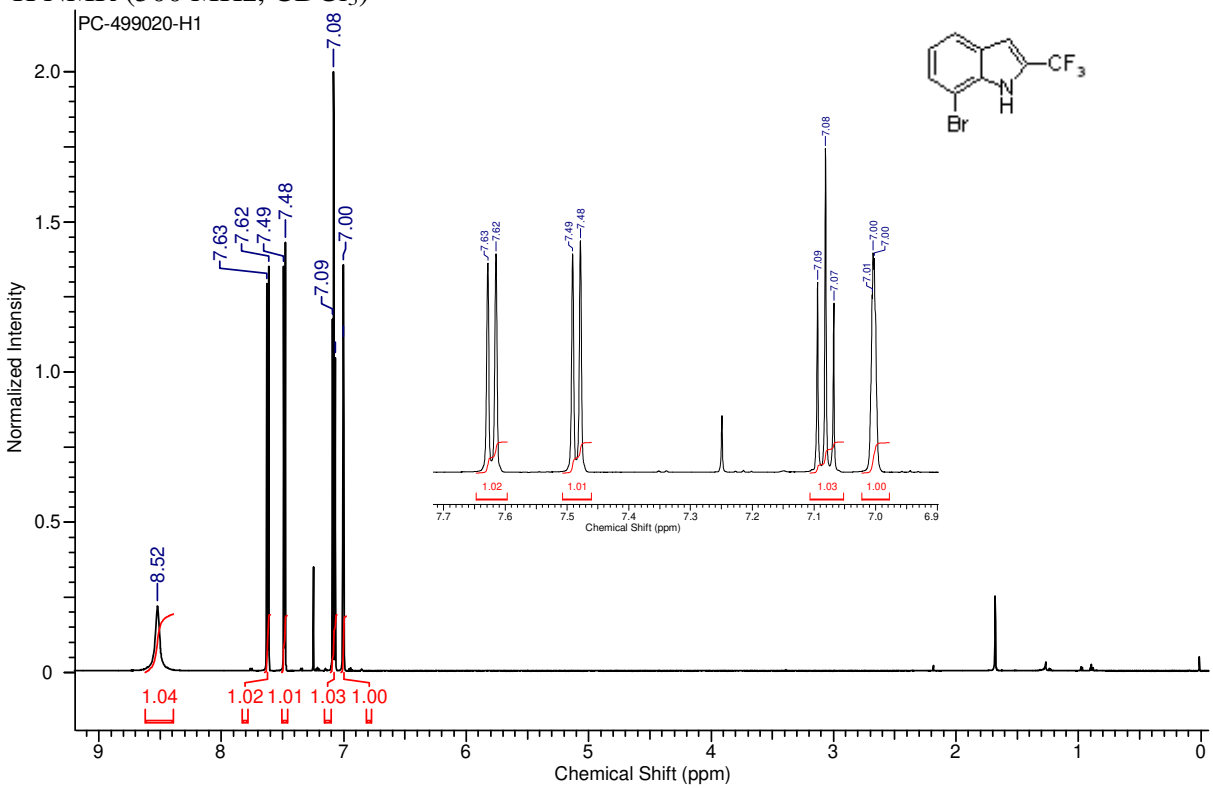


^{13}C NMR (125 MHz, $CDCl_3$)

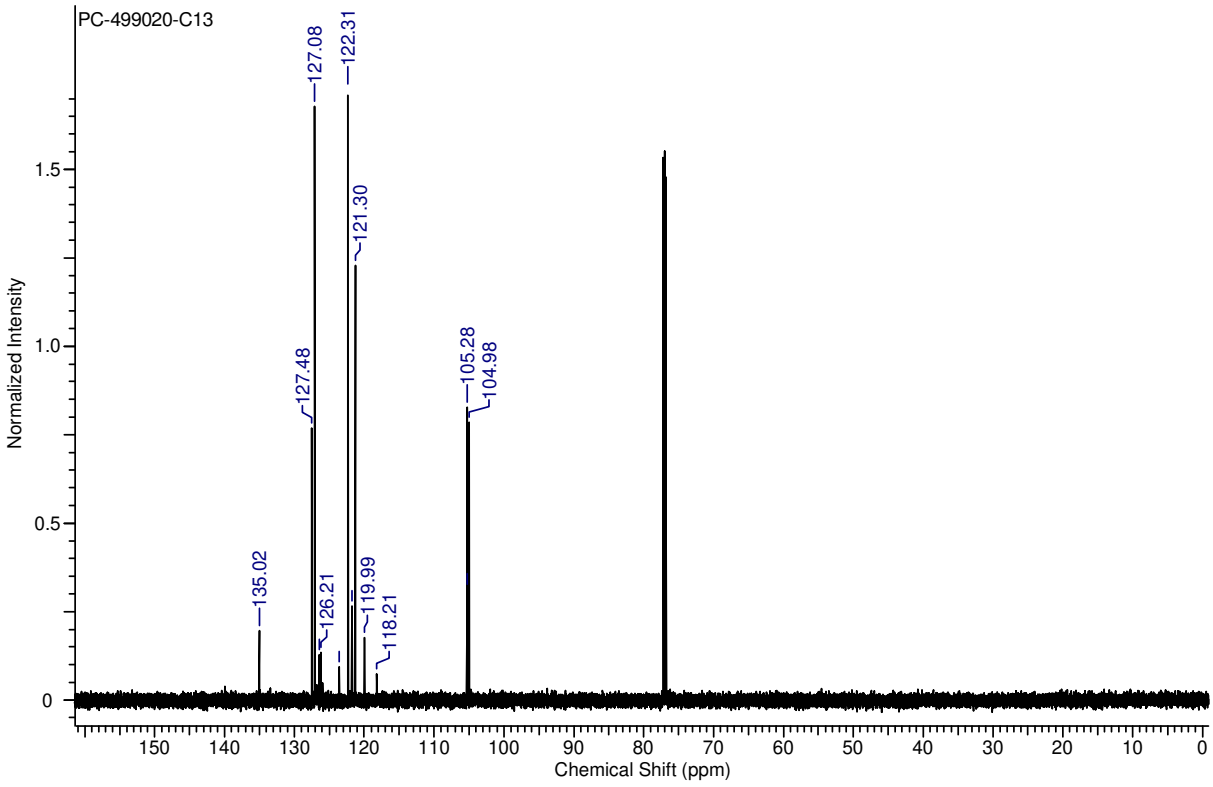


3d

^{1}H NMR (500 MHz, $CDCl_3$)

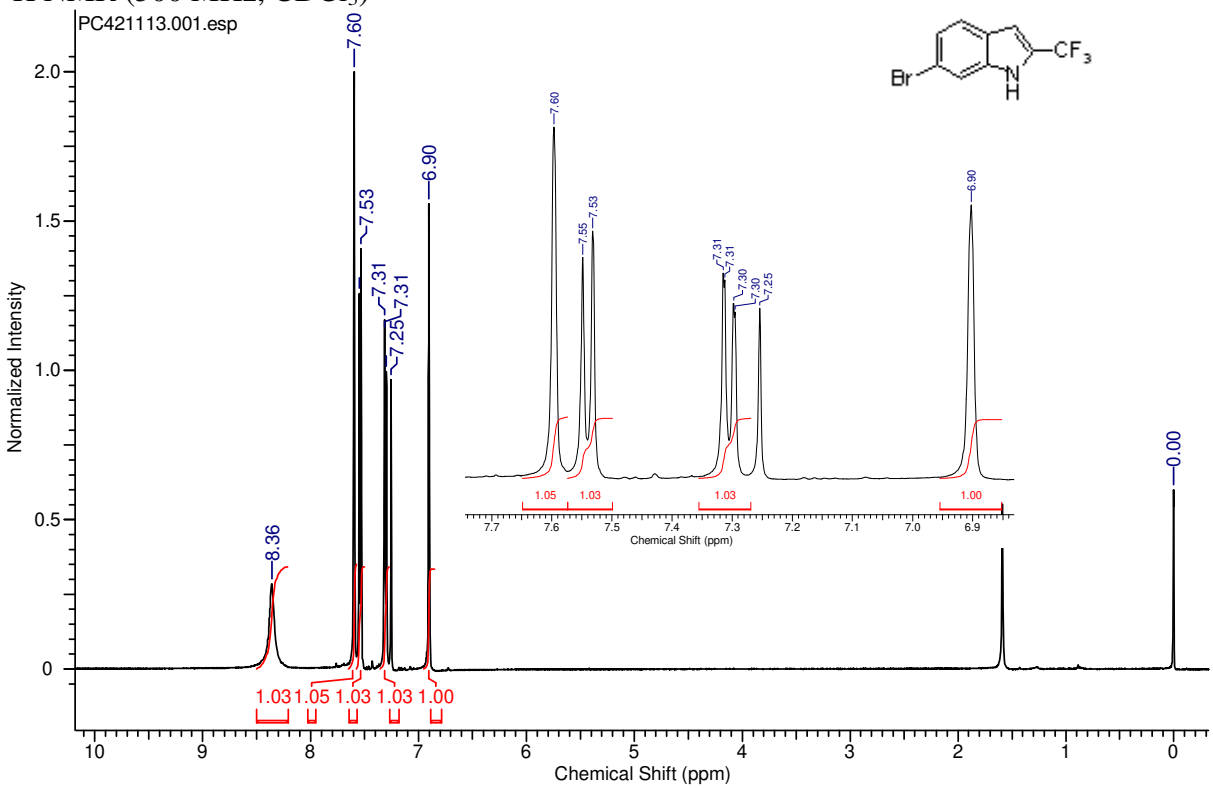


^{13}C NMR (125 MHz, $CDCl_3$)

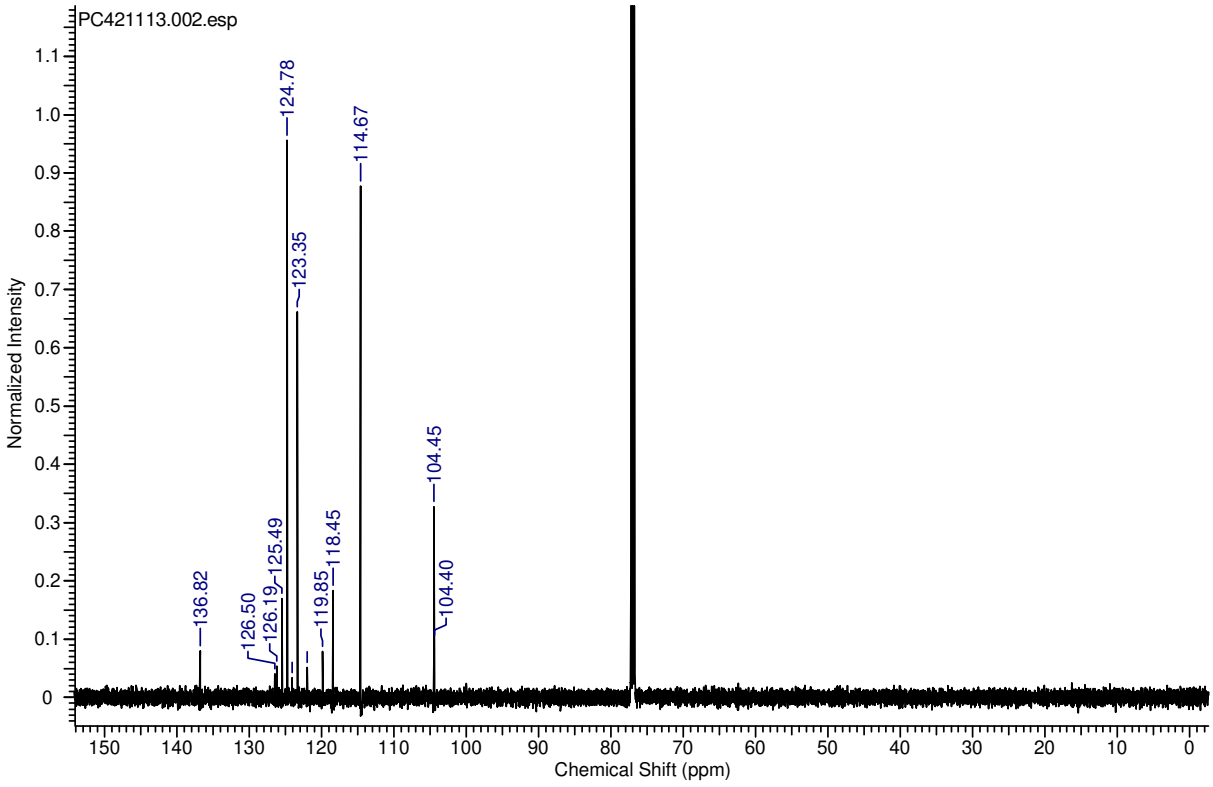


3e

^{1}H NMR (500 MHz, $CDCl_3$)

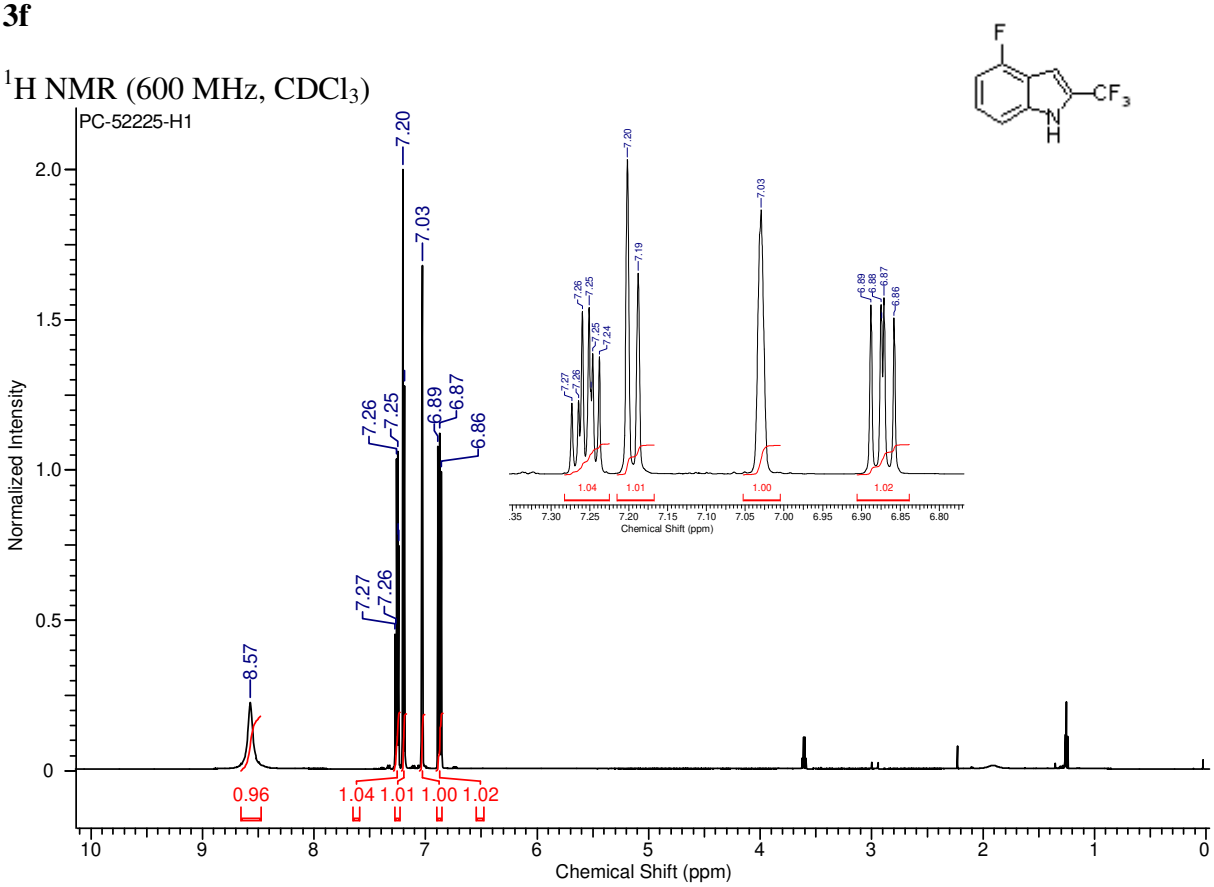


^{13}C NMR (125 MHz, $CDCl_3$)

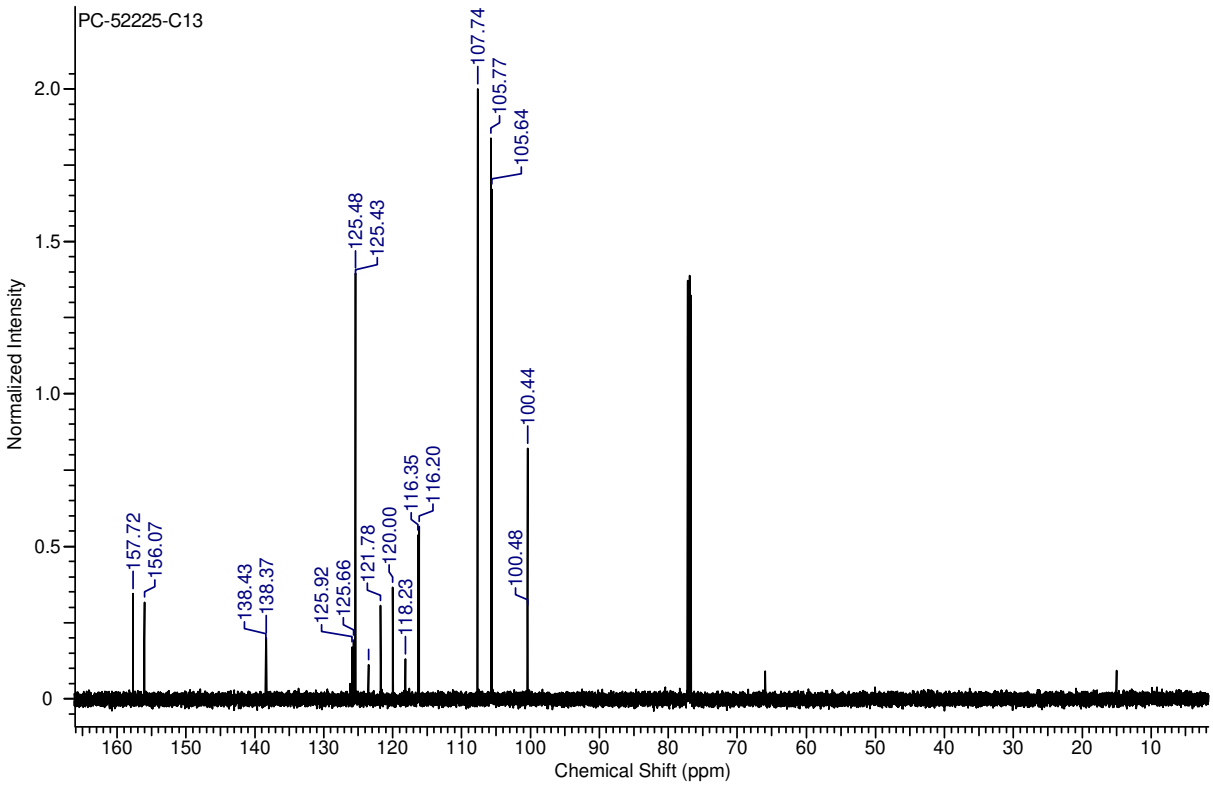


3f

^{1}H NMR (600 MHz, $CDCl_3$)

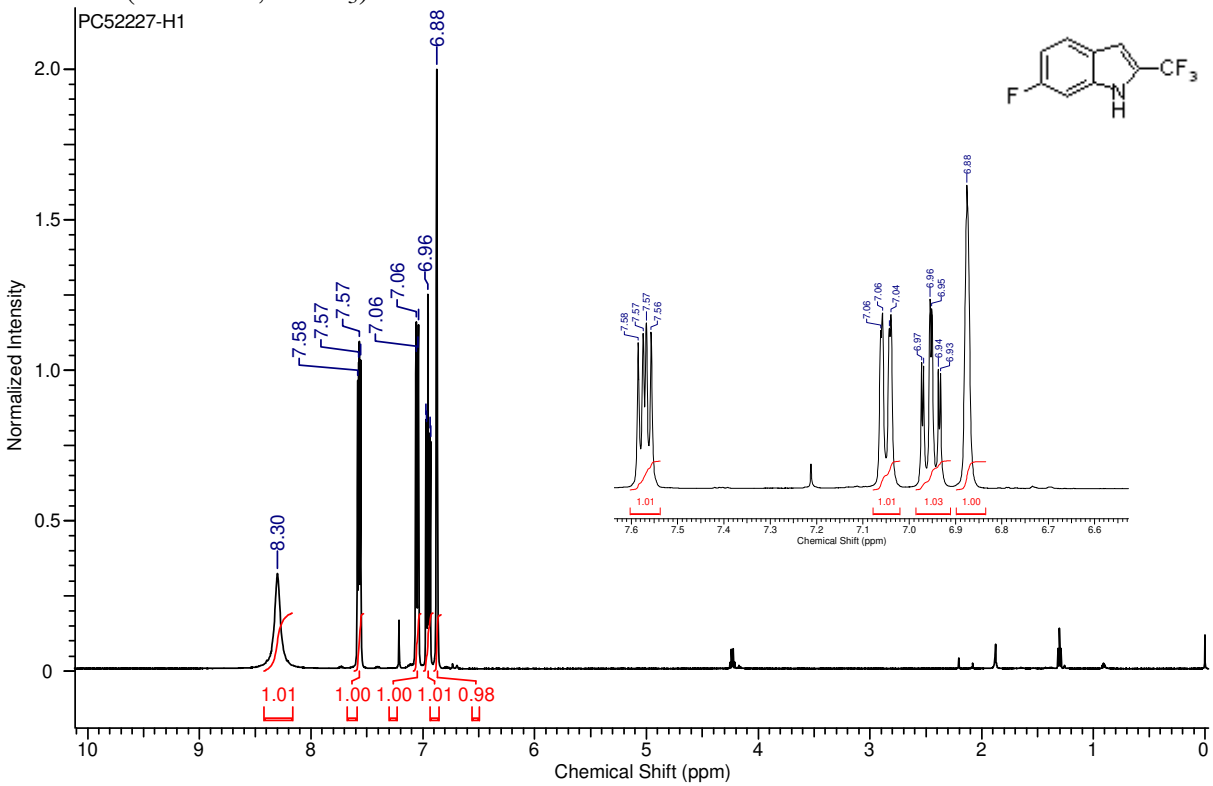


^{13}C NMR (150 MHz, $CDCl_3$)

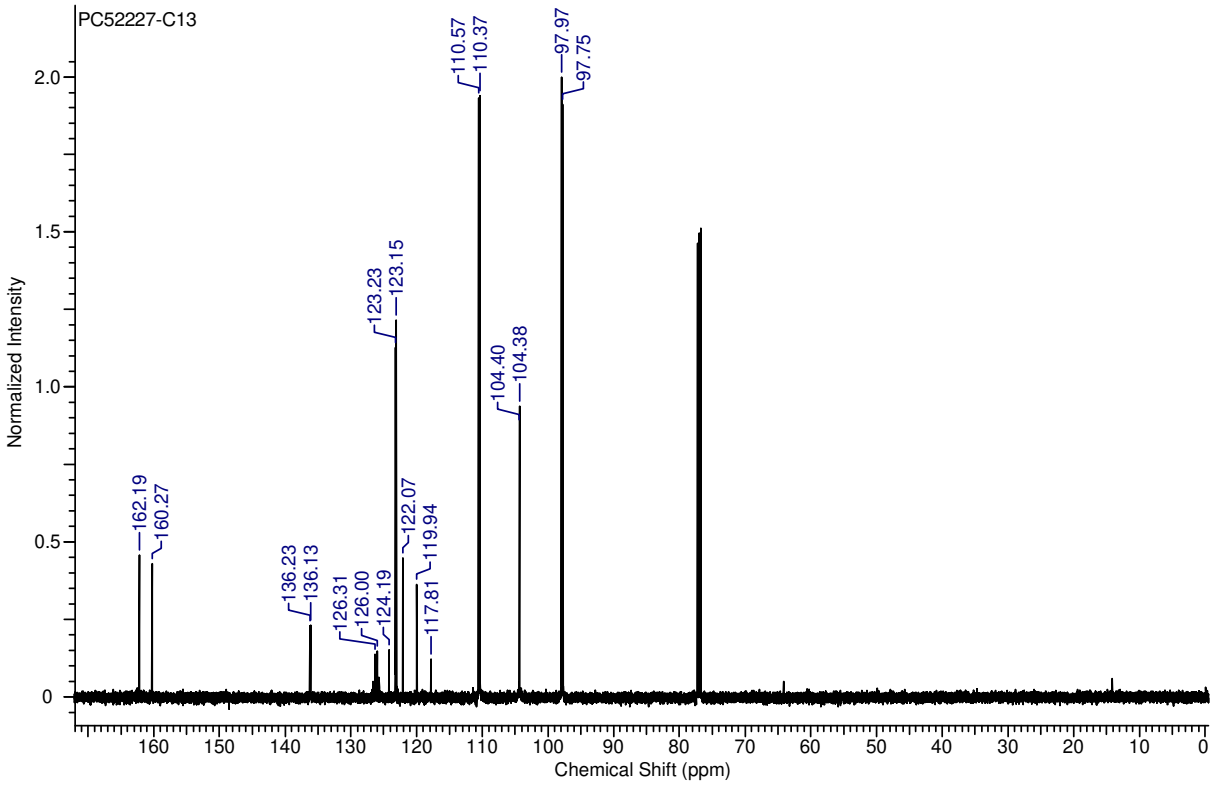


3g

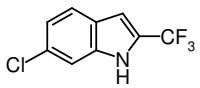
^{1}H NMR (500 MHz, $CDCl_3$)



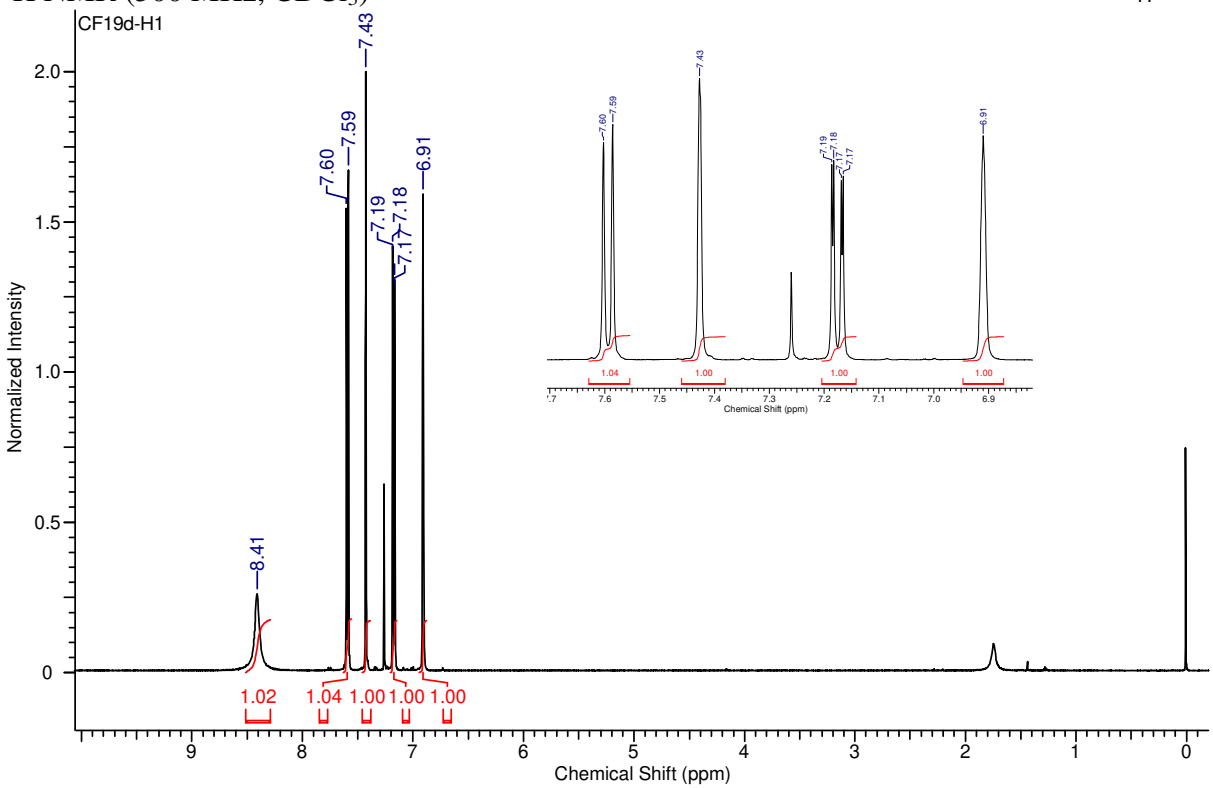
^{13}C NMR (125 MHz, $CDCl_3$)



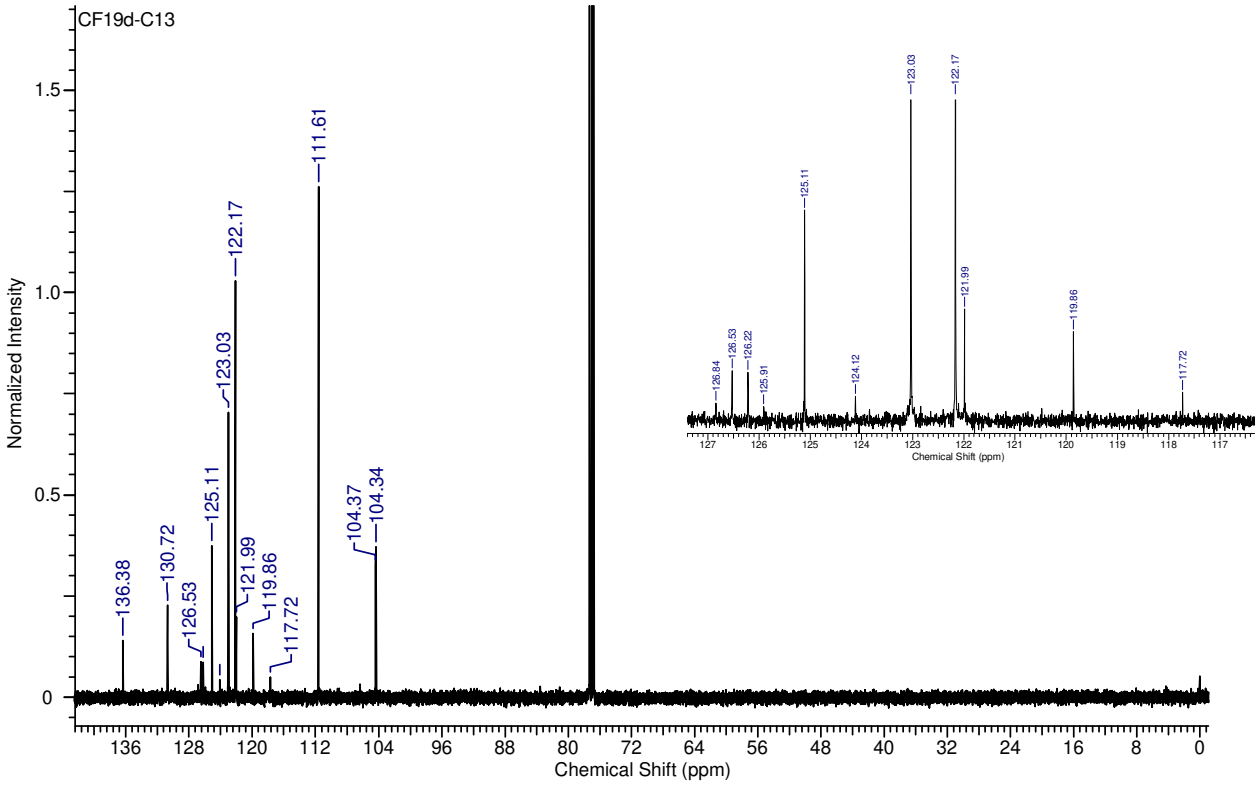
3h



^{1}H NMR (500 MHz, $CDCl_3$)

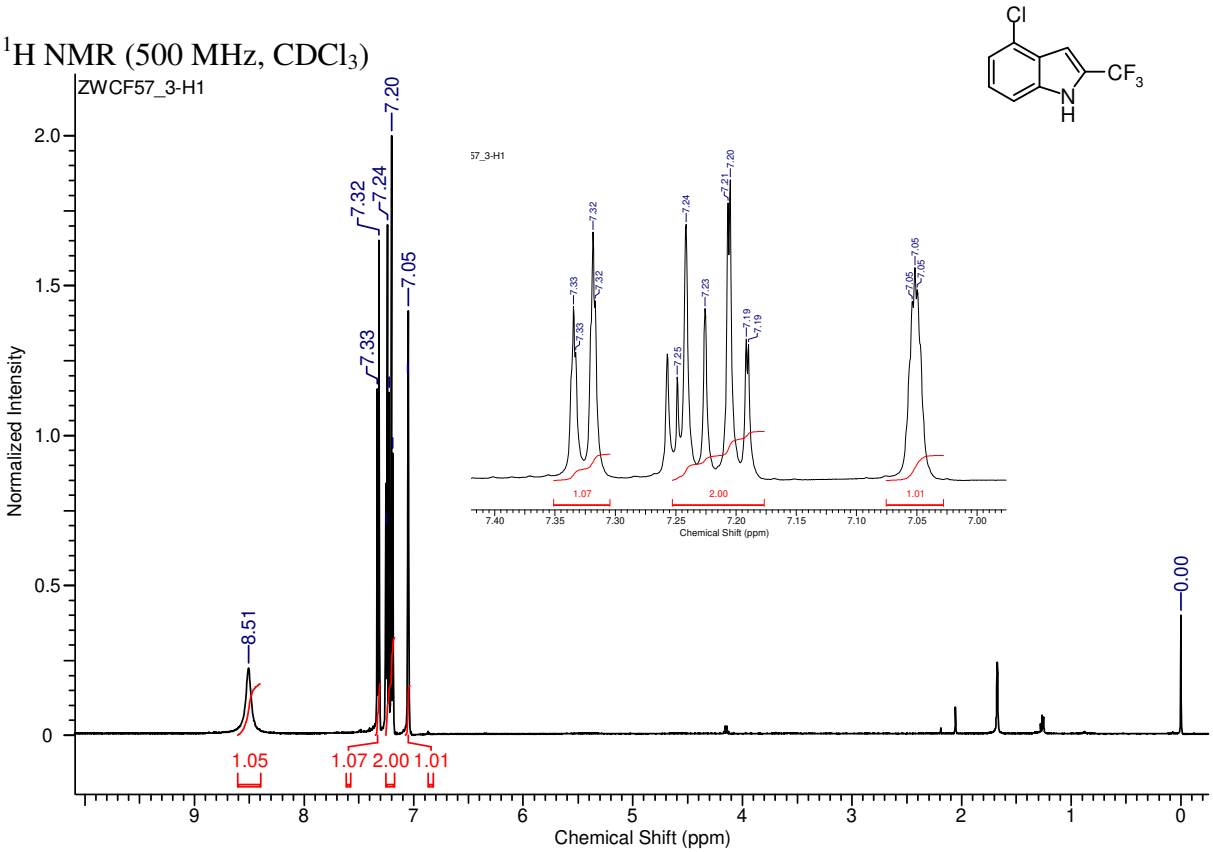


^{13}C NMR (125 MHz, $CDCl_3$)

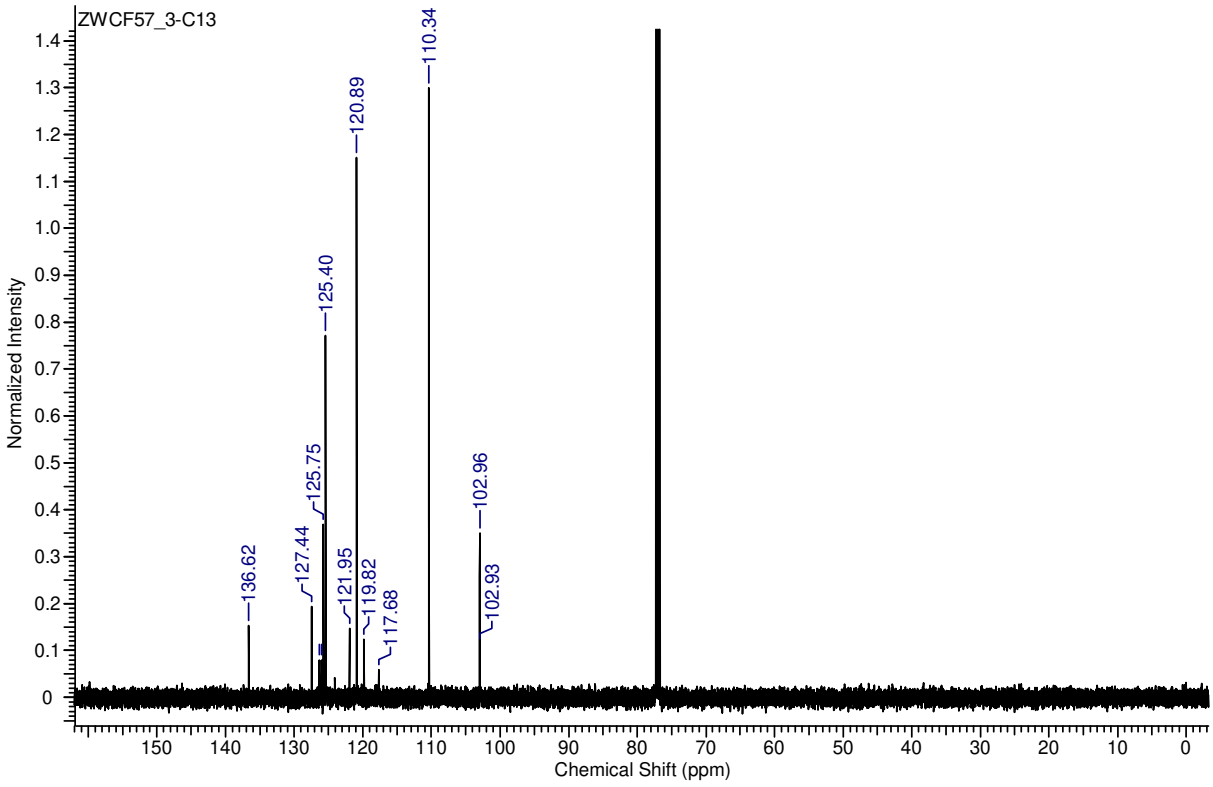


3i

^{1}H NMR (500 MHz, $CDCl_3$)

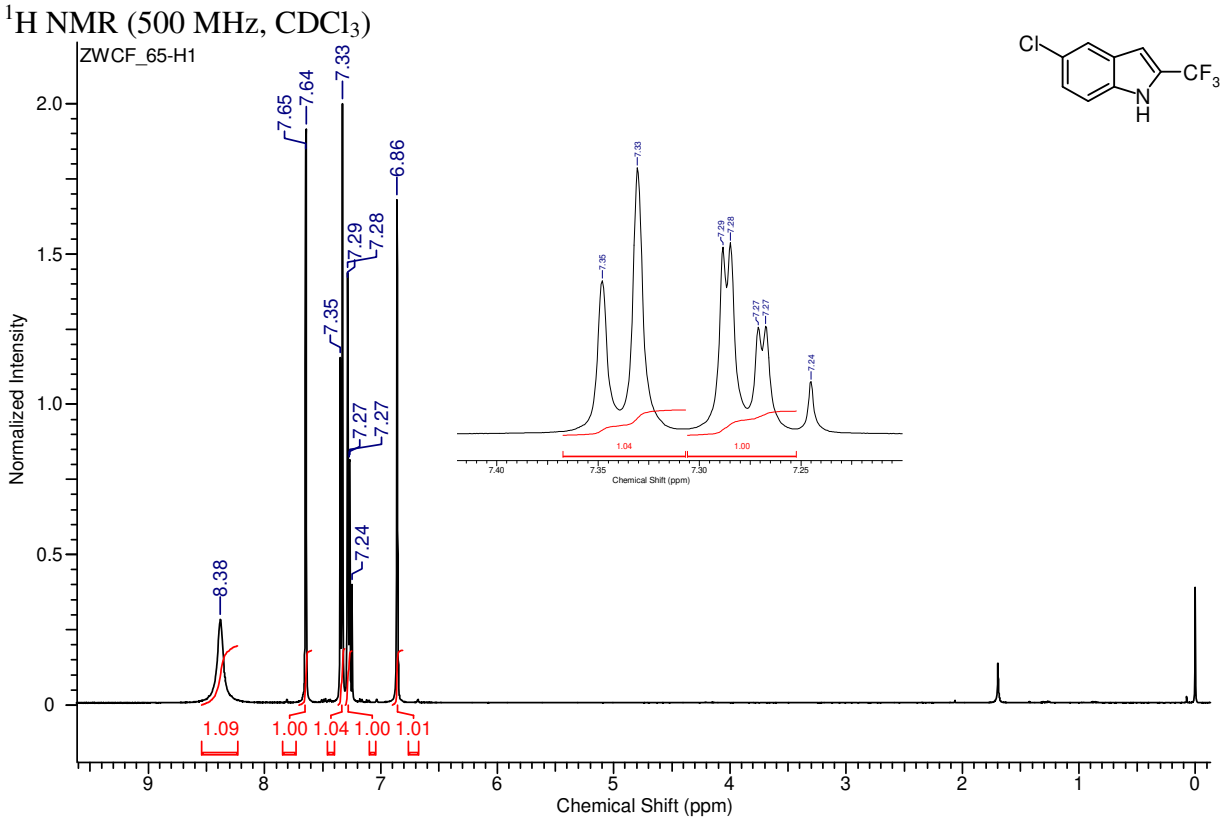


^{13}C NMR (125 MHz, $CDCl_3$)

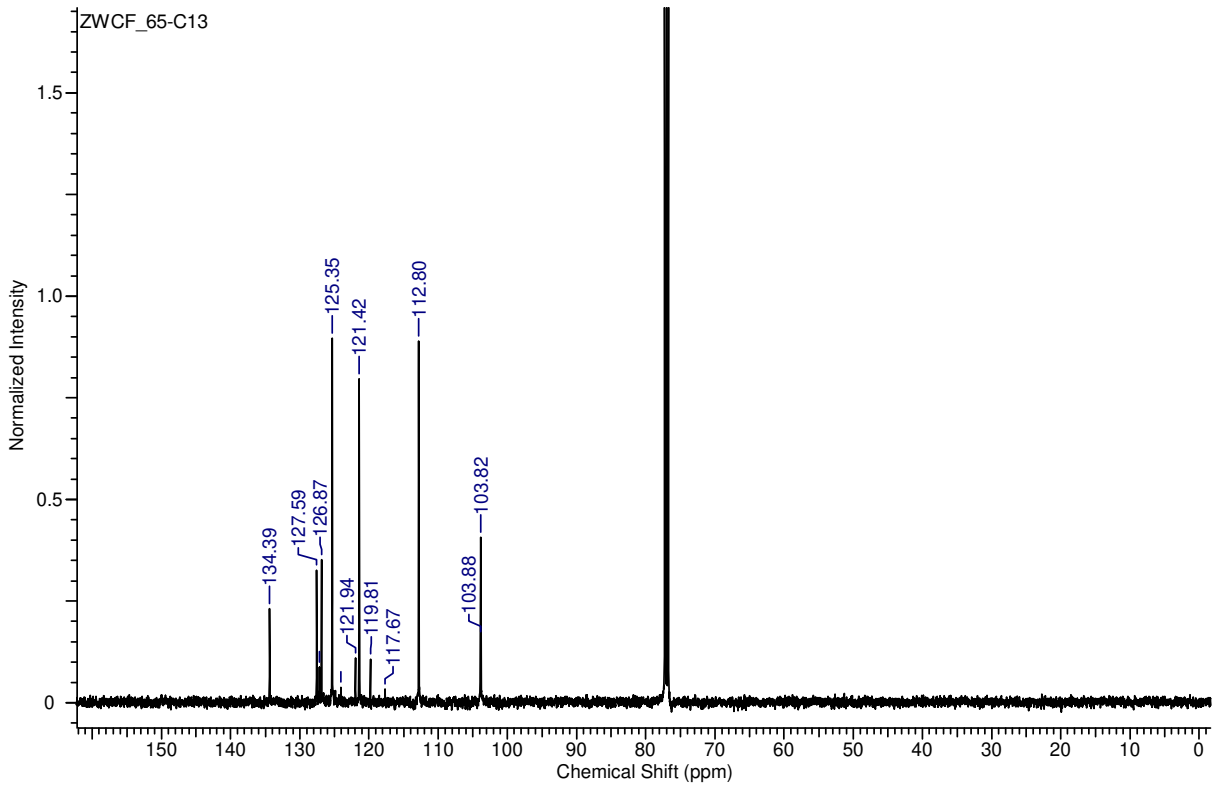


3j

^{1}H NMR (500 MHz, $CDCl_3$)

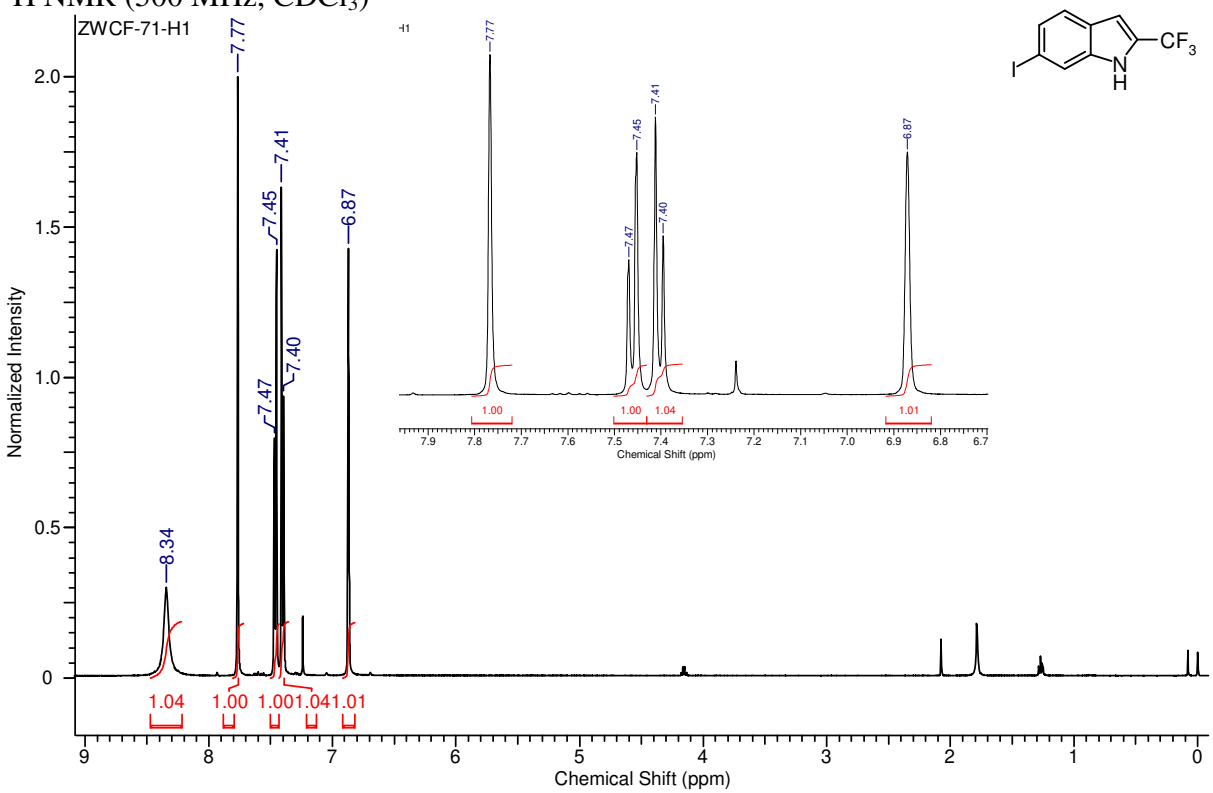


^{13}C NMR (125 MHz, $CDCl_3$)

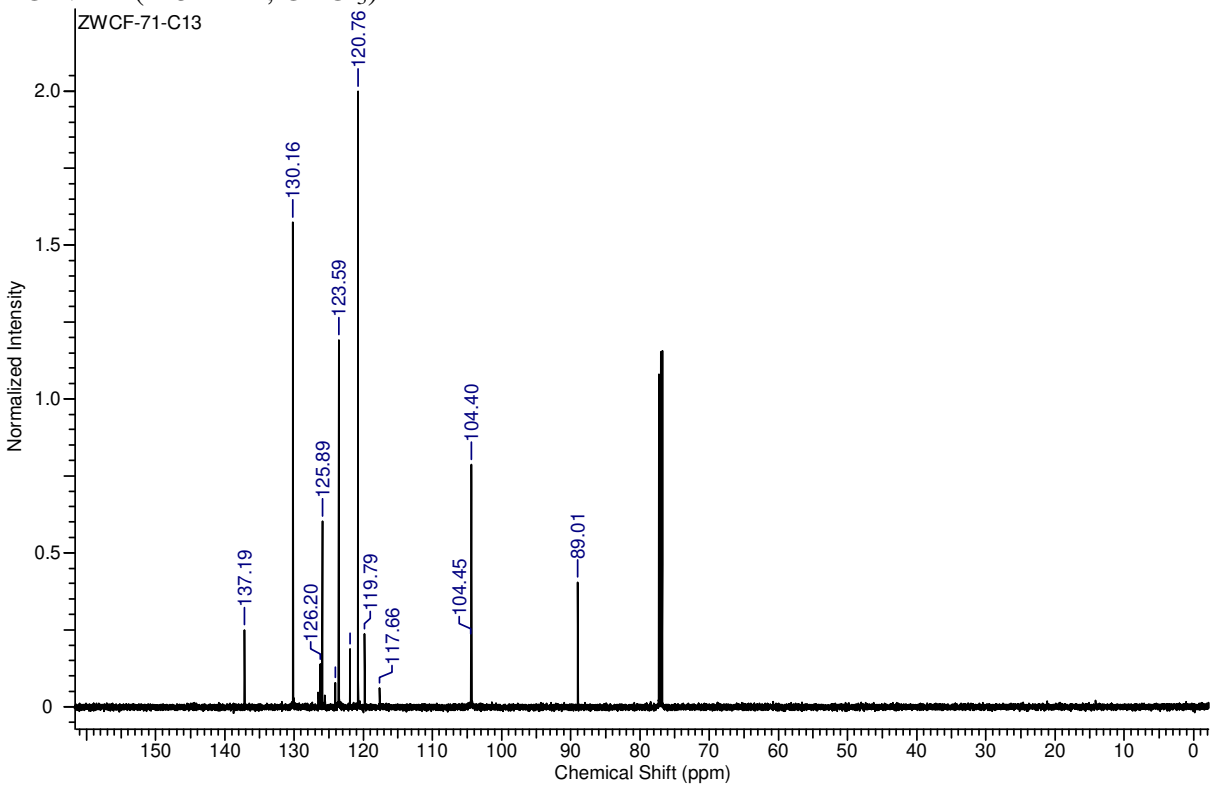


3k

^{1}H NMR (500 MHz, $CDCl_3$)

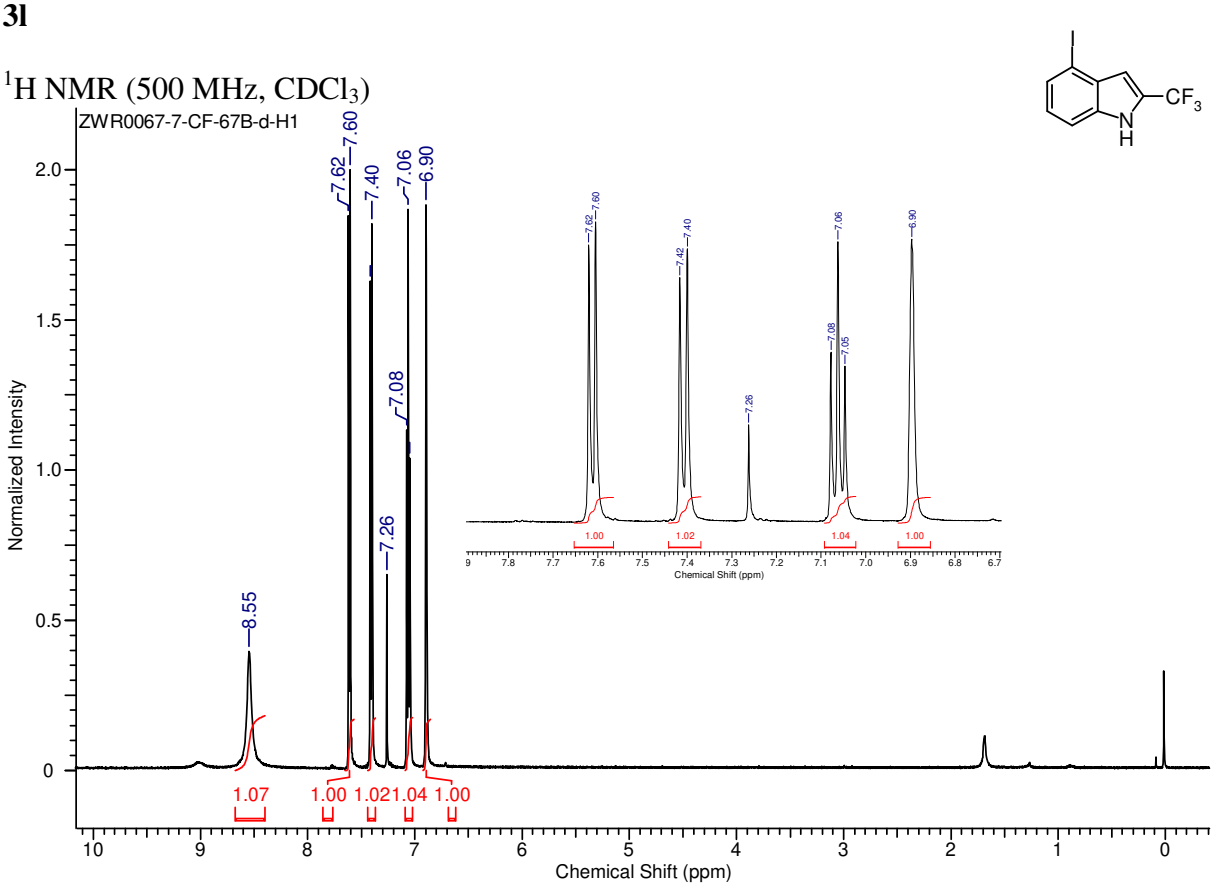


^{13}C NMR (125 MHz, $CDCl_3$)

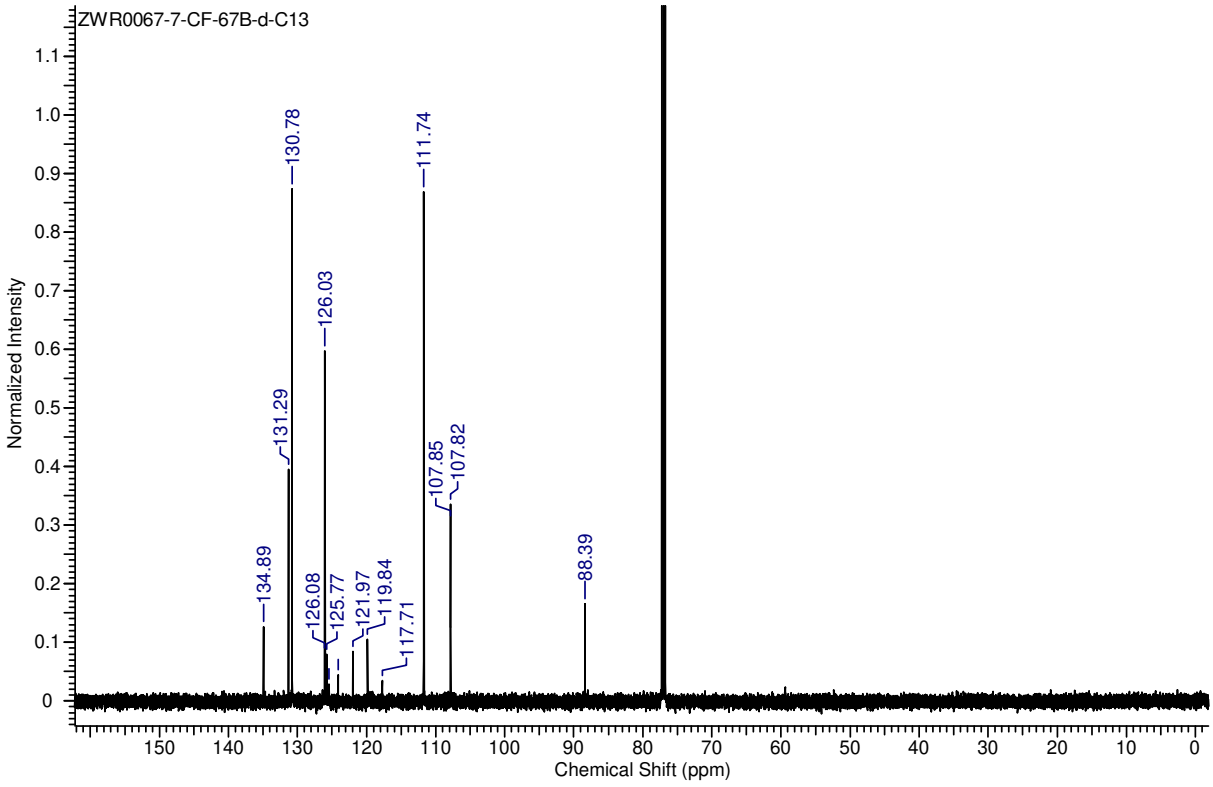


3l

^{1}H NMR (500 MHz, $CDCl_3$)

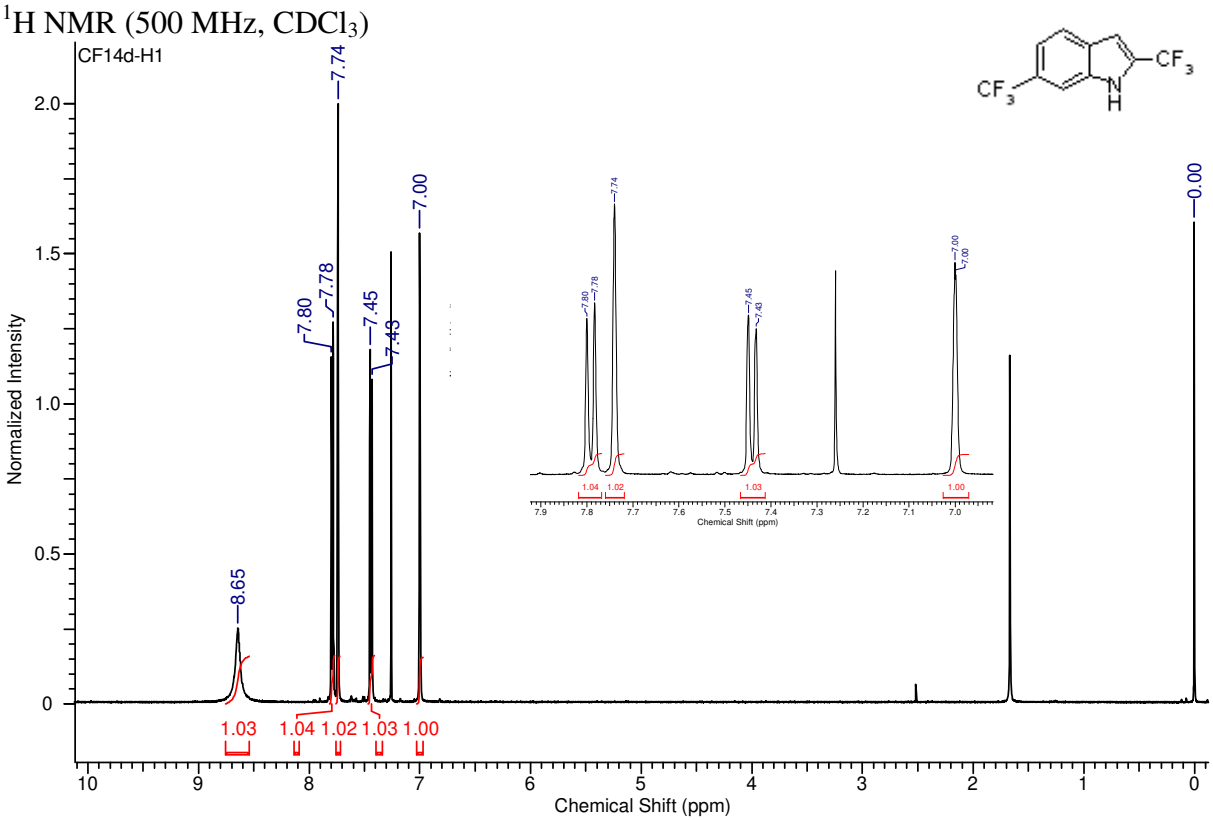


^{13}C NMR (125 MHz, $CDCl_3$)

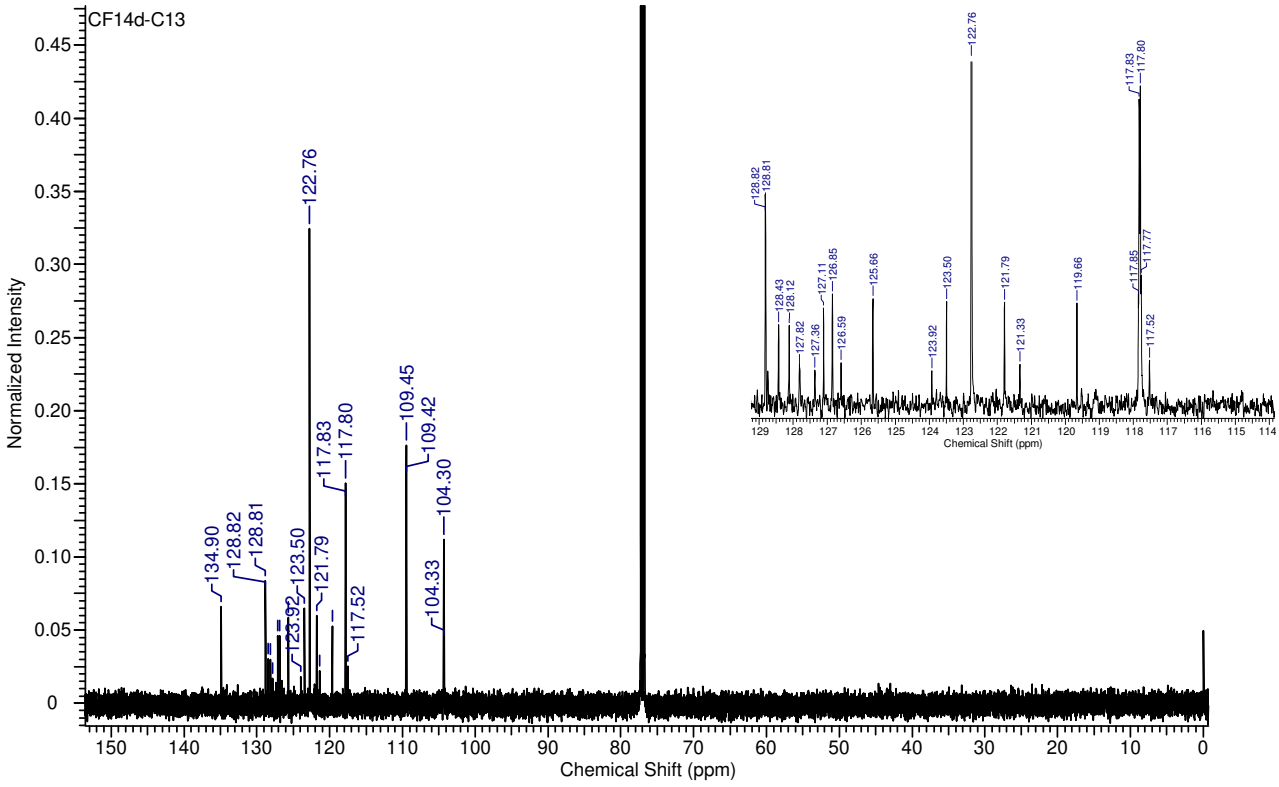


3m

^{1}H NMR (500 MHz, $CDCl_3$)

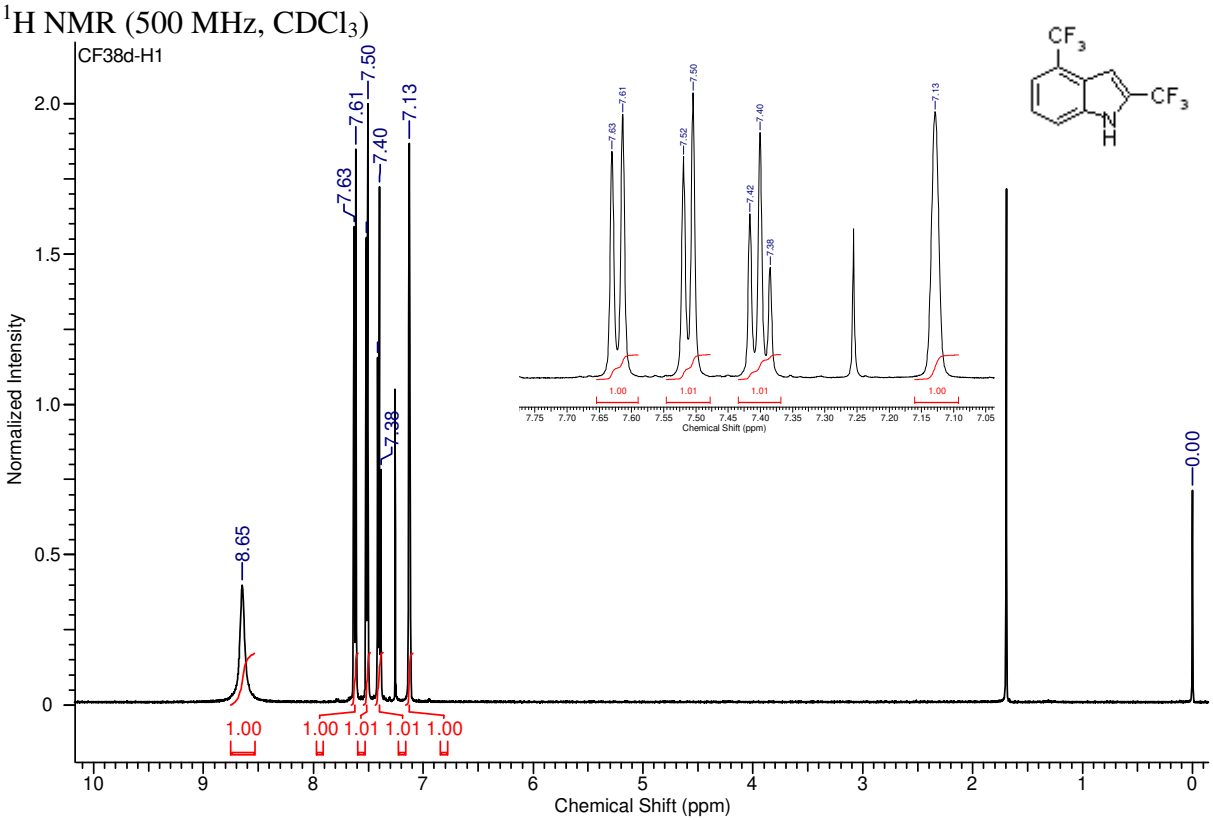


^{13}C NMR (125 MHz, $CDCl_3$)

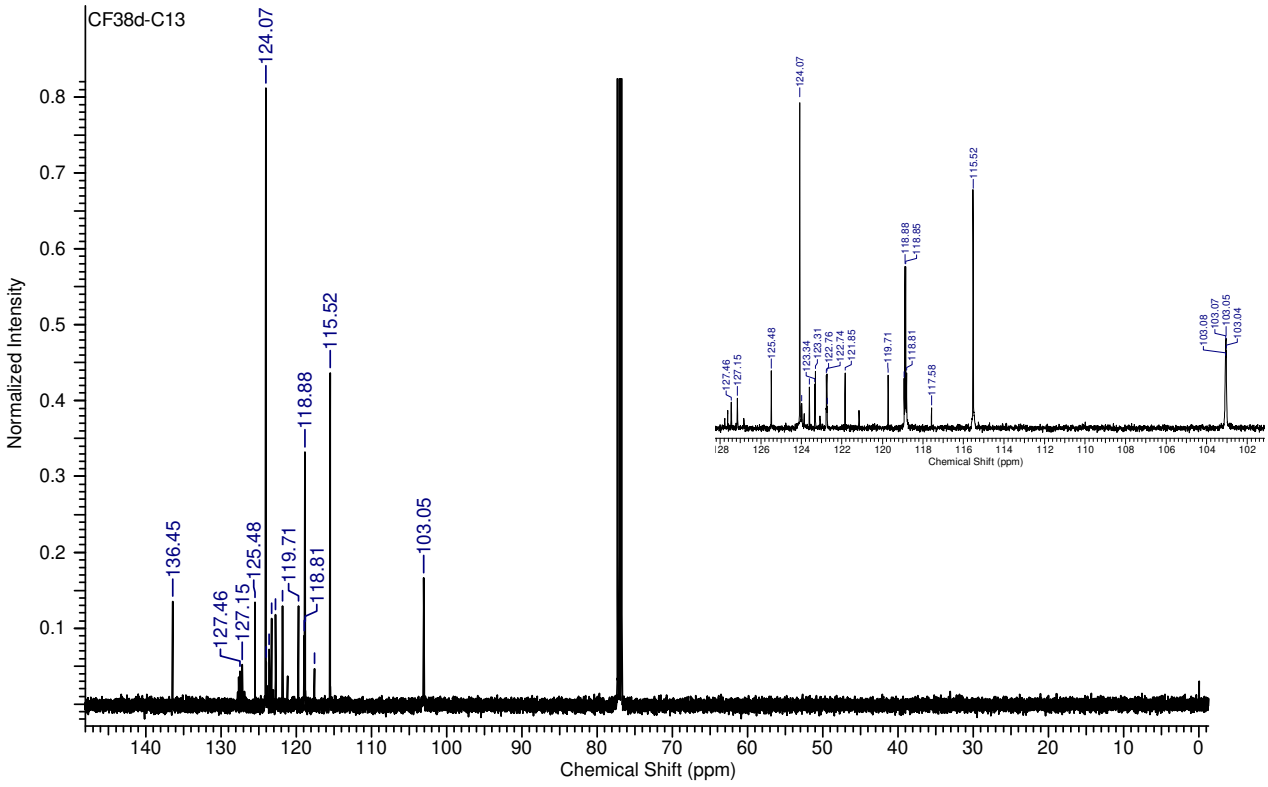


3n

^{1}H NMR (500 MHz, $CDCl_3$)

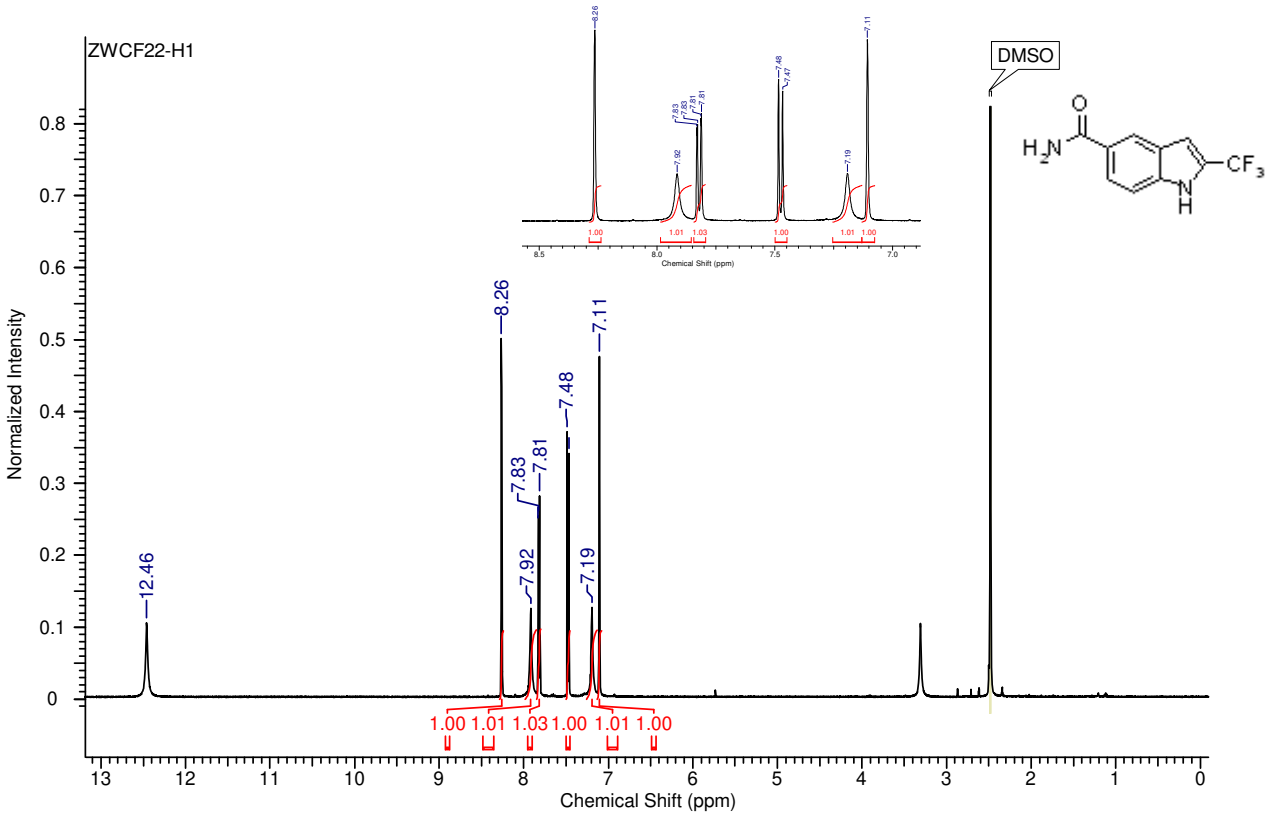


^{13}C NMR (125 MHz, $CDCl_3$)

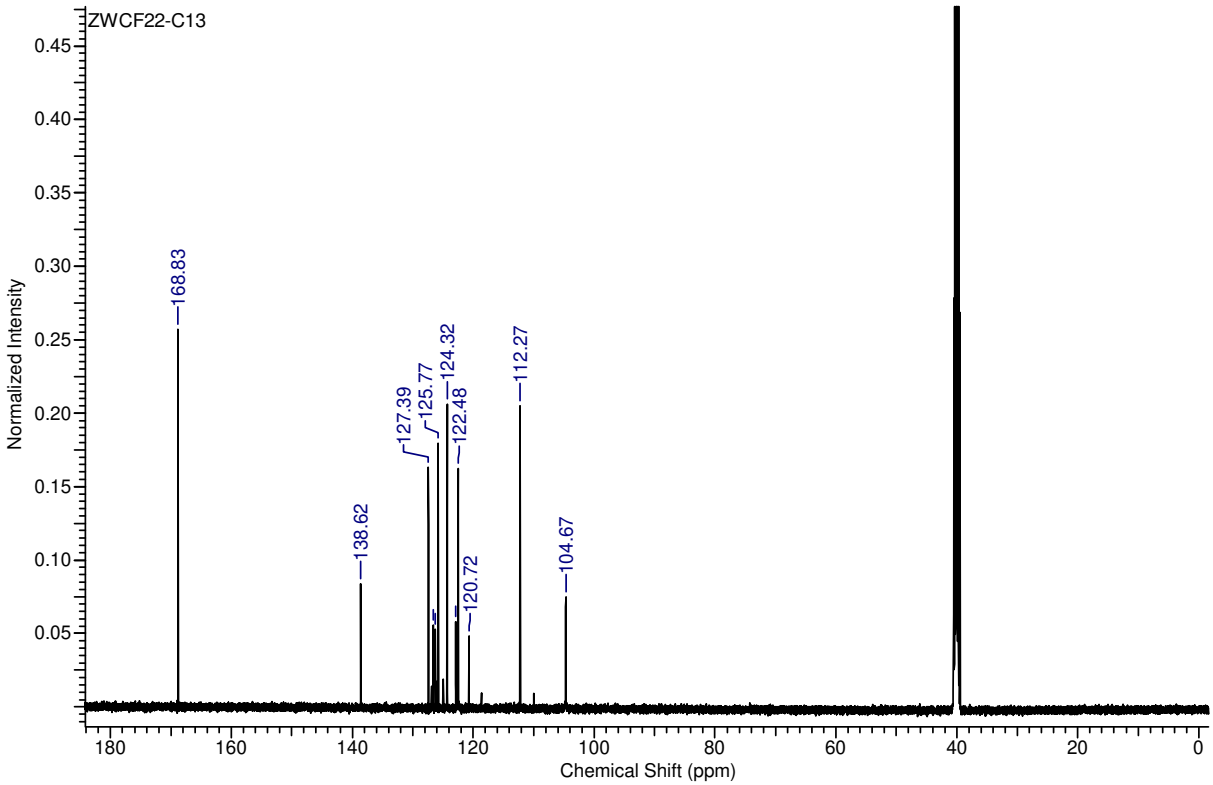


3o

^{1}H NMR (500 MHz, DMSO-d_6)

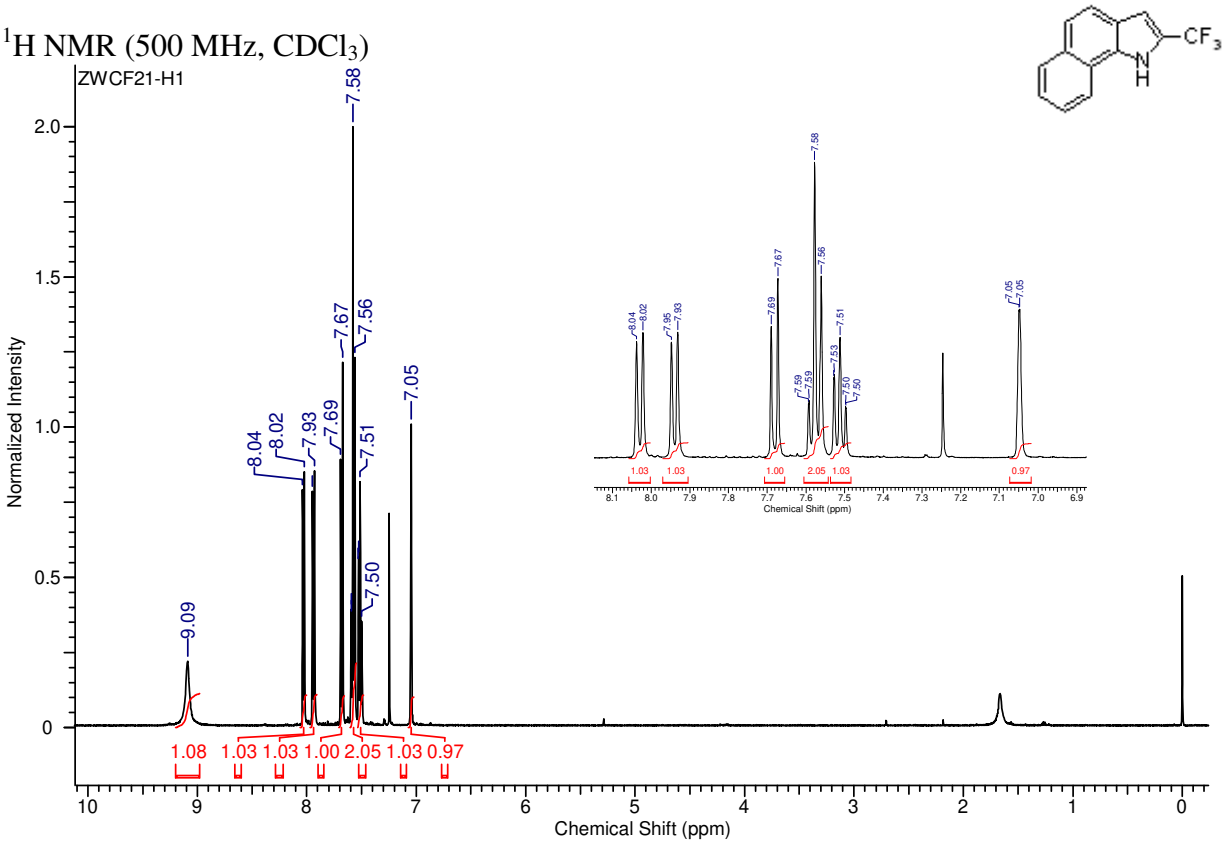


^{13}C NMR (125 MHz, DMSO-d_6)

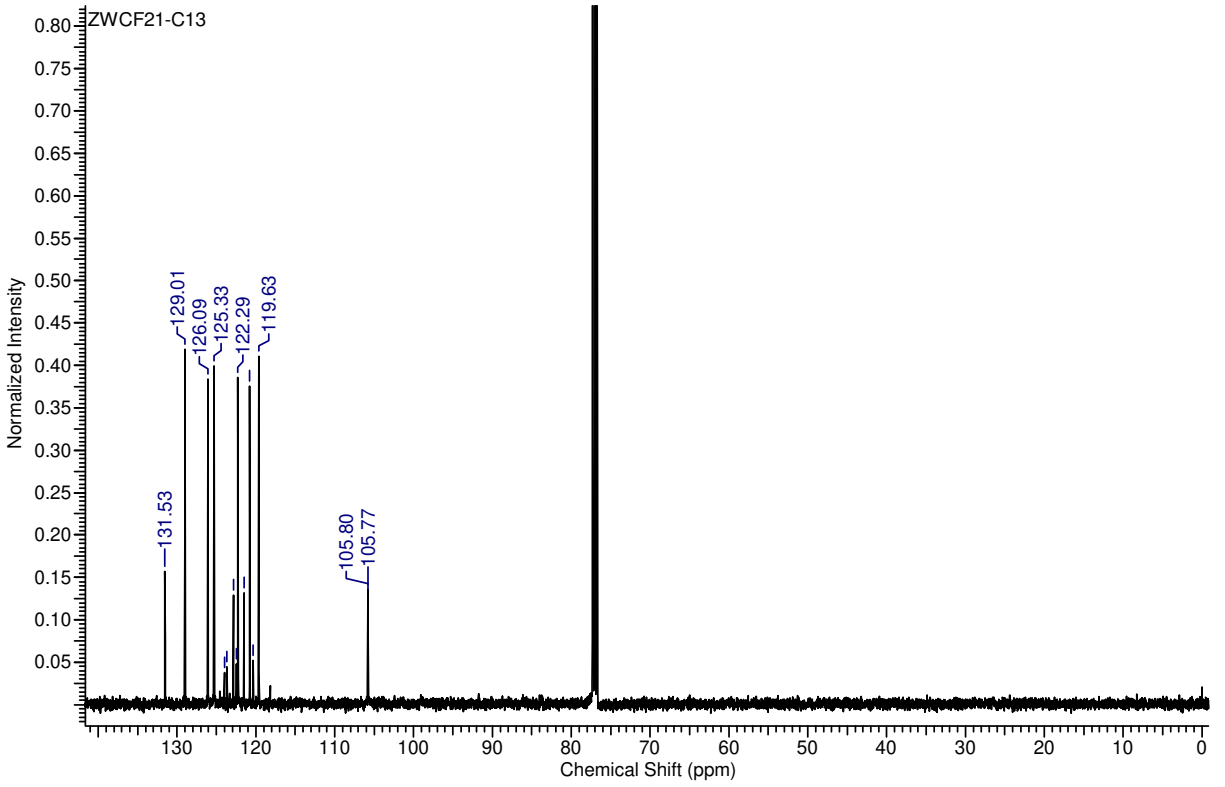


3p

^{1}H NMR (500 MHz, $CDCl_3$)

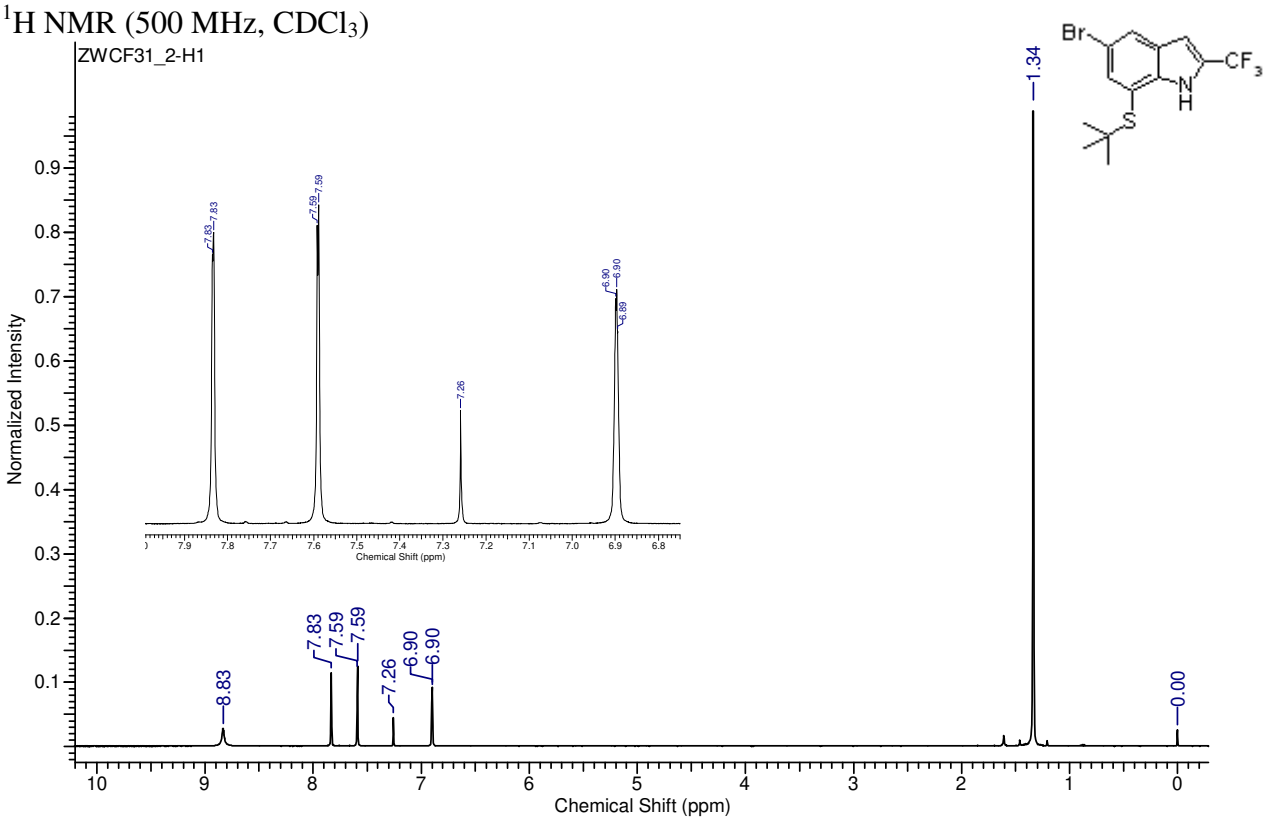


^{13}C NMR (125 MHz, $CDCl_3$)

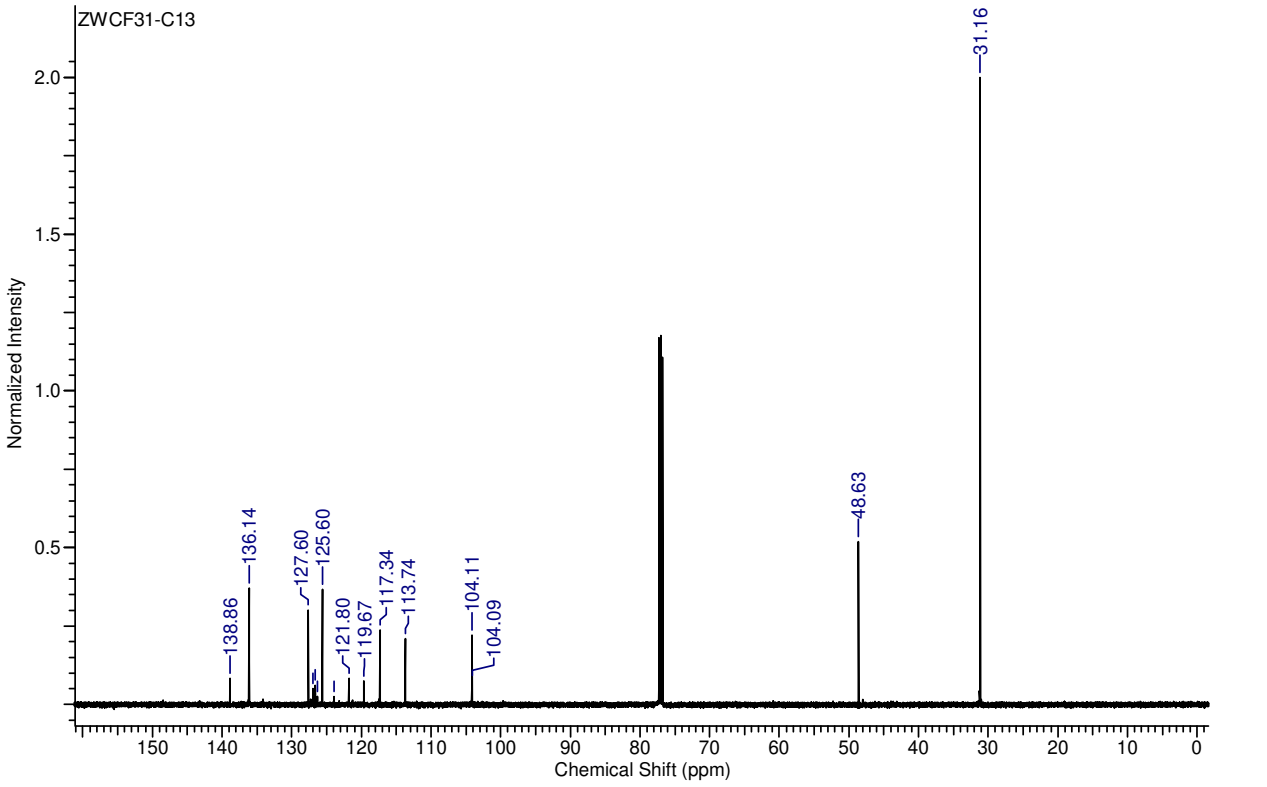


3q

^{1}H NMR (500 MHz, $CDCl_3$)

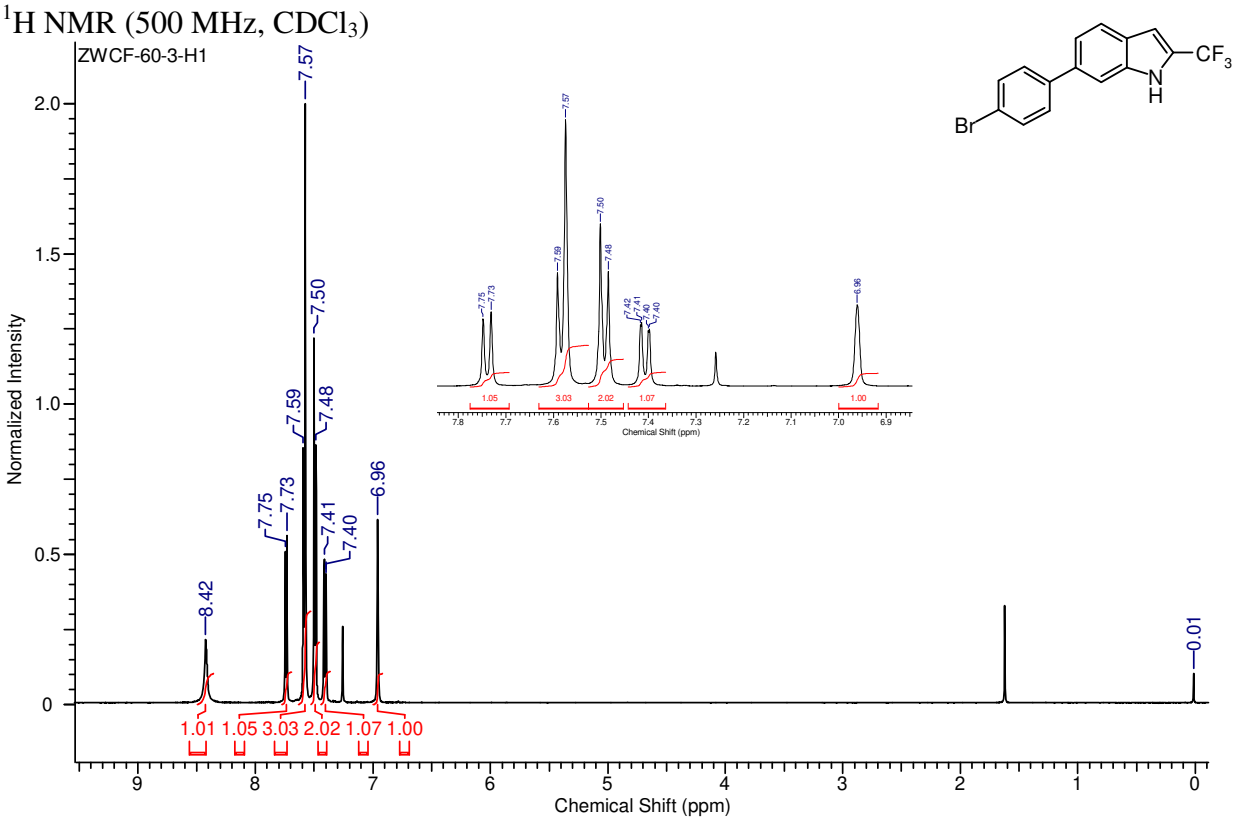


^{13}C NMR (125 MHz, $CDCl_3$)

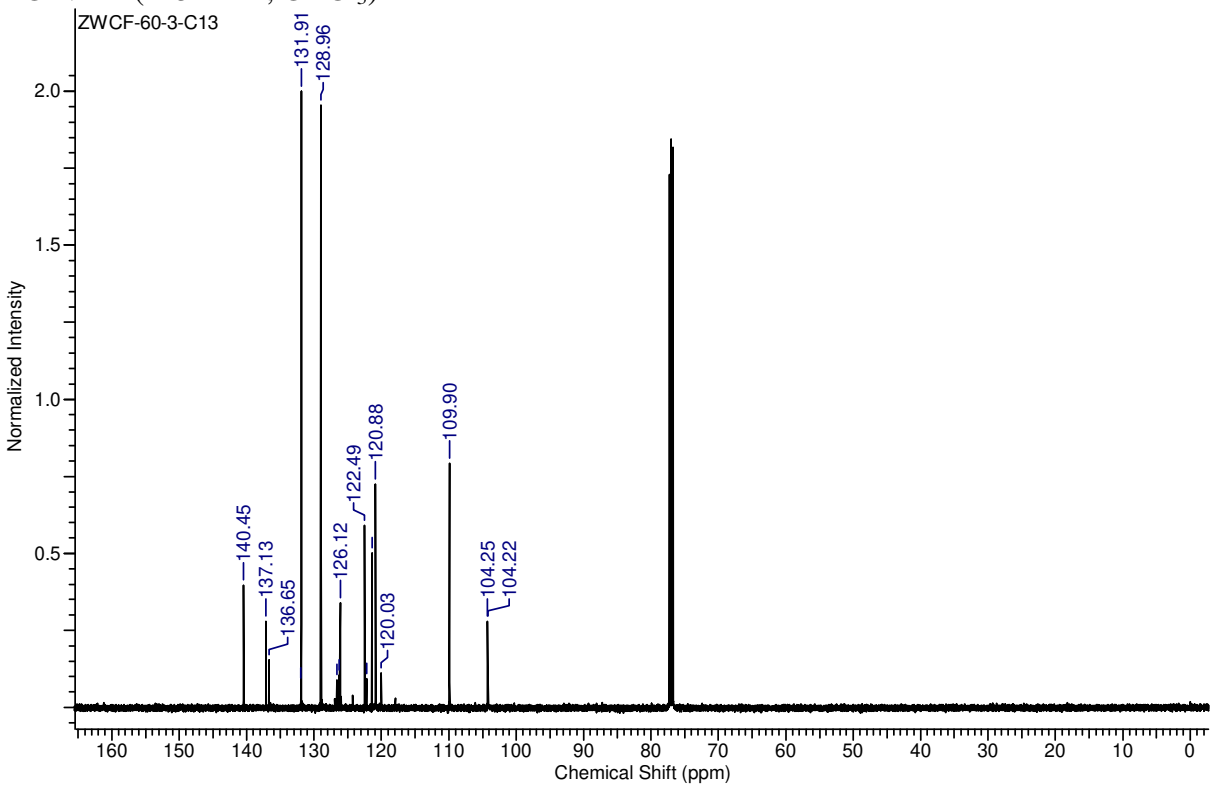


3r

^{1}H NMR (500 MHz, $CDCl_3$)

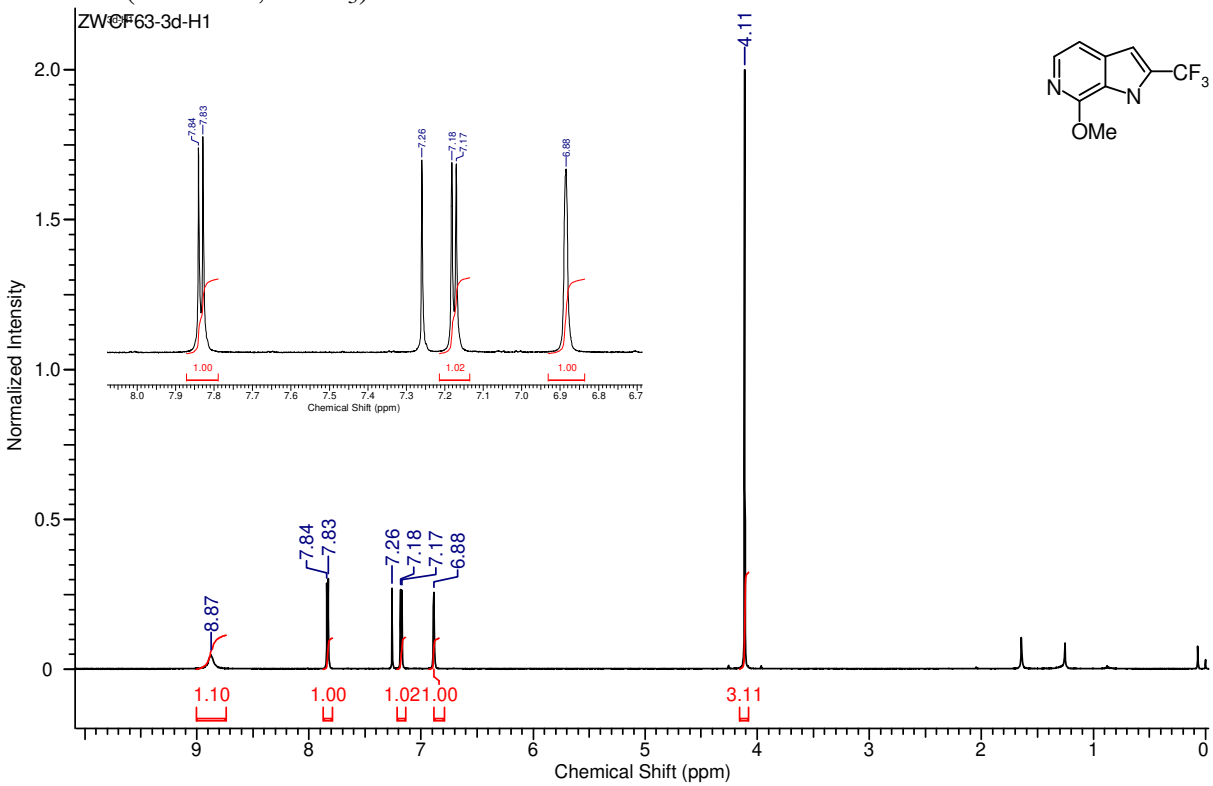


^{13}C NMR (125 MHz, $CDCl_3$)

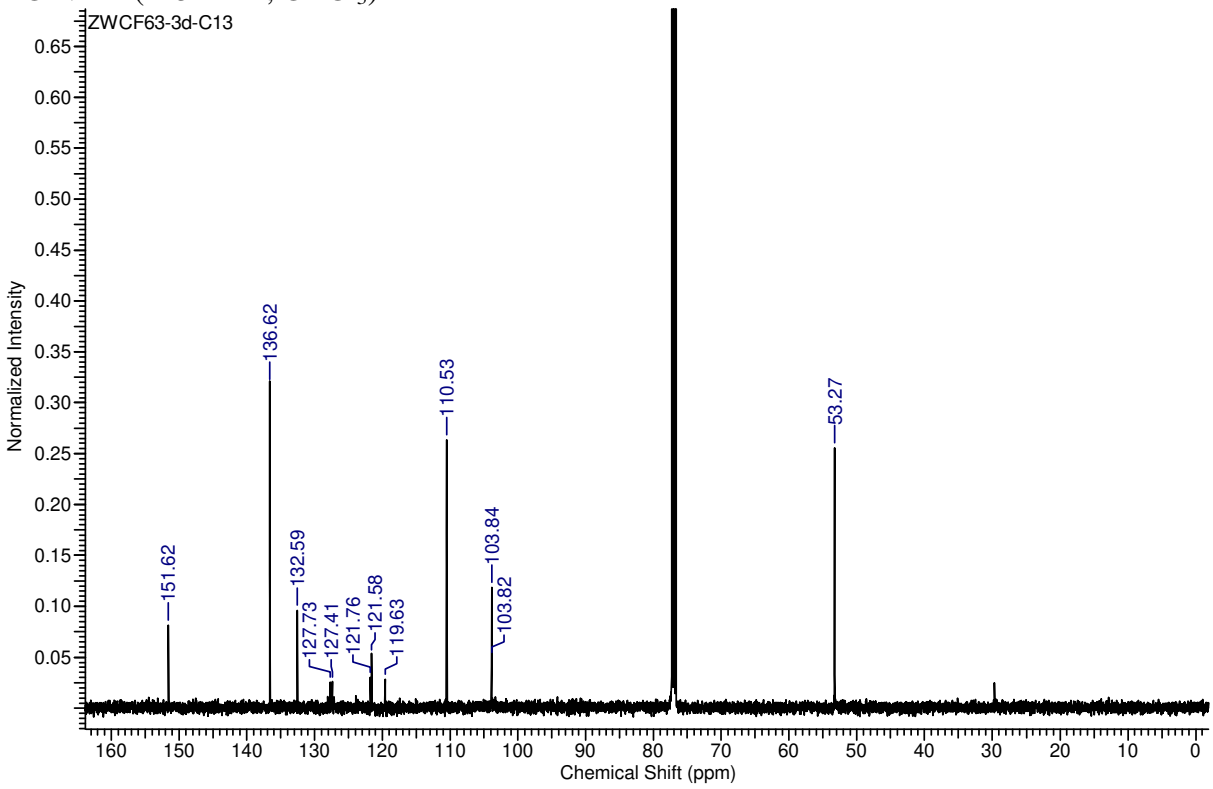


3s

^{1}H NMR (500 MHz, $CDCl_3$)

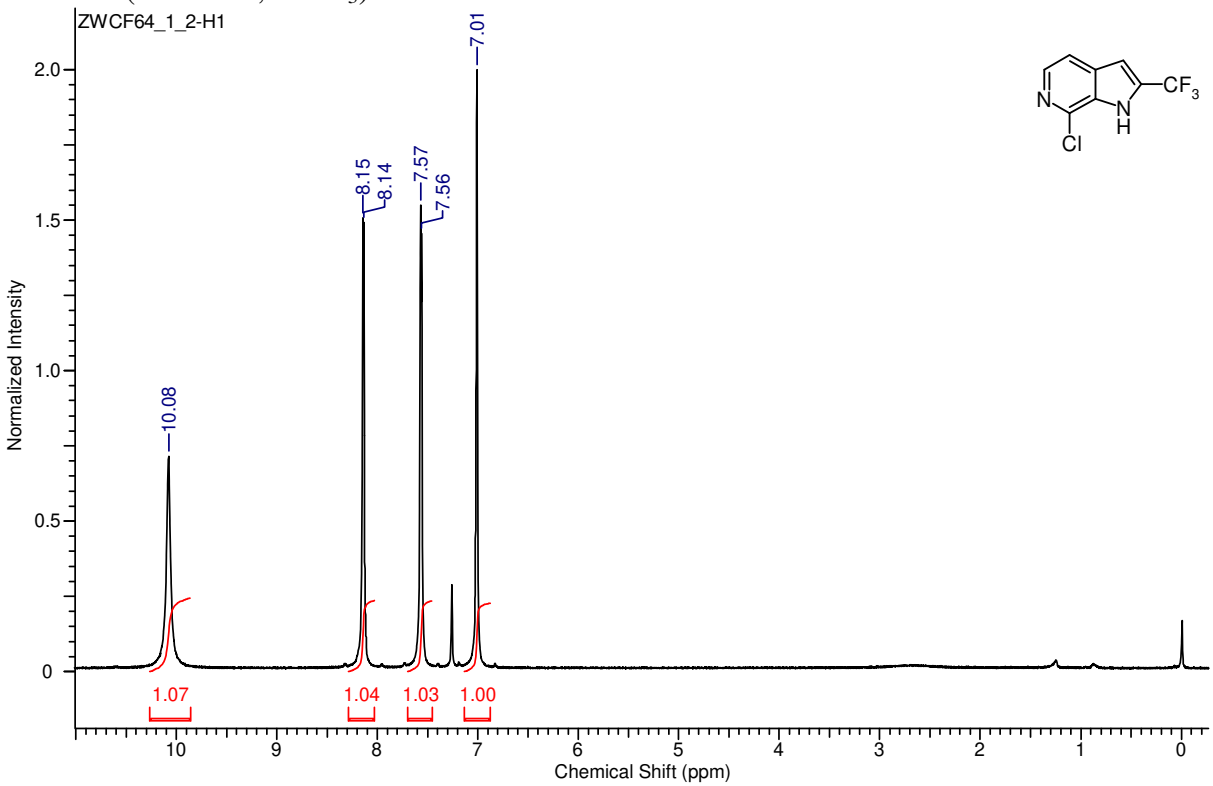


^{13}C NMR (125 MHz, $CDCl_3$)

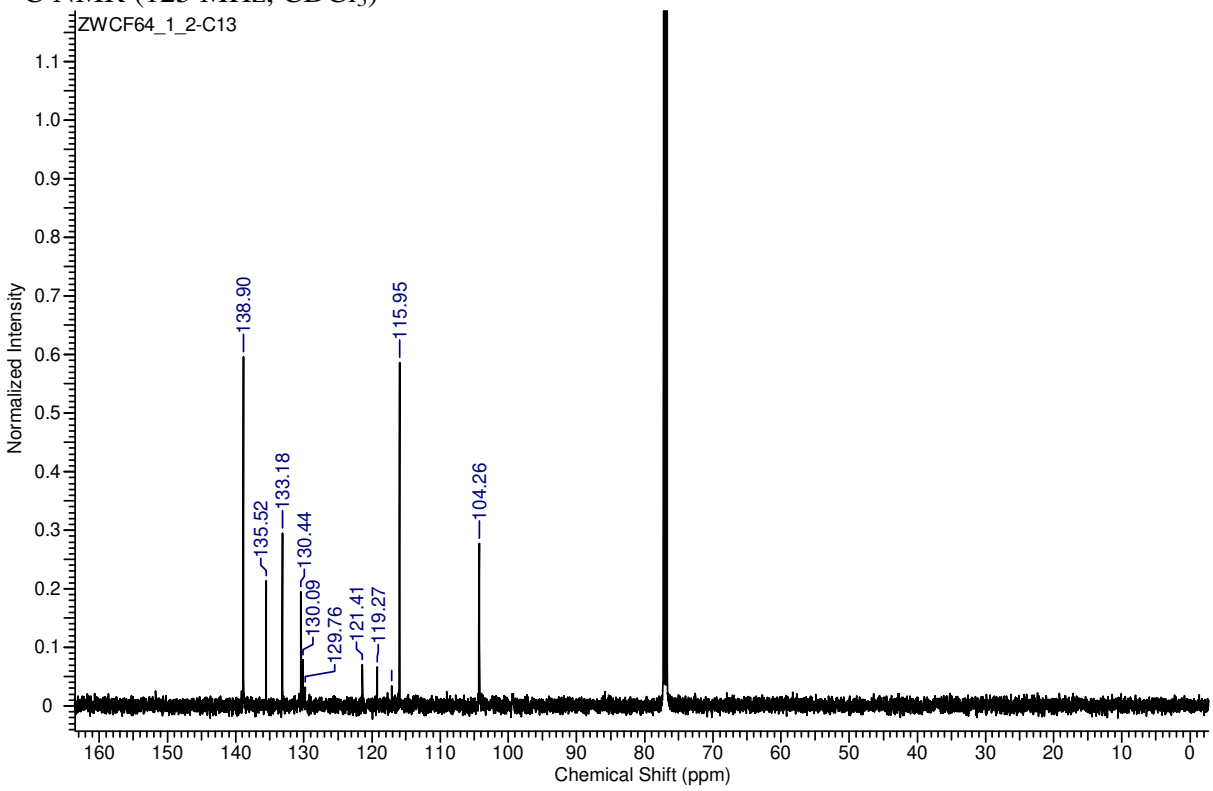


3t

^{1}H NMR (500 MHz, $CDCl_3$)

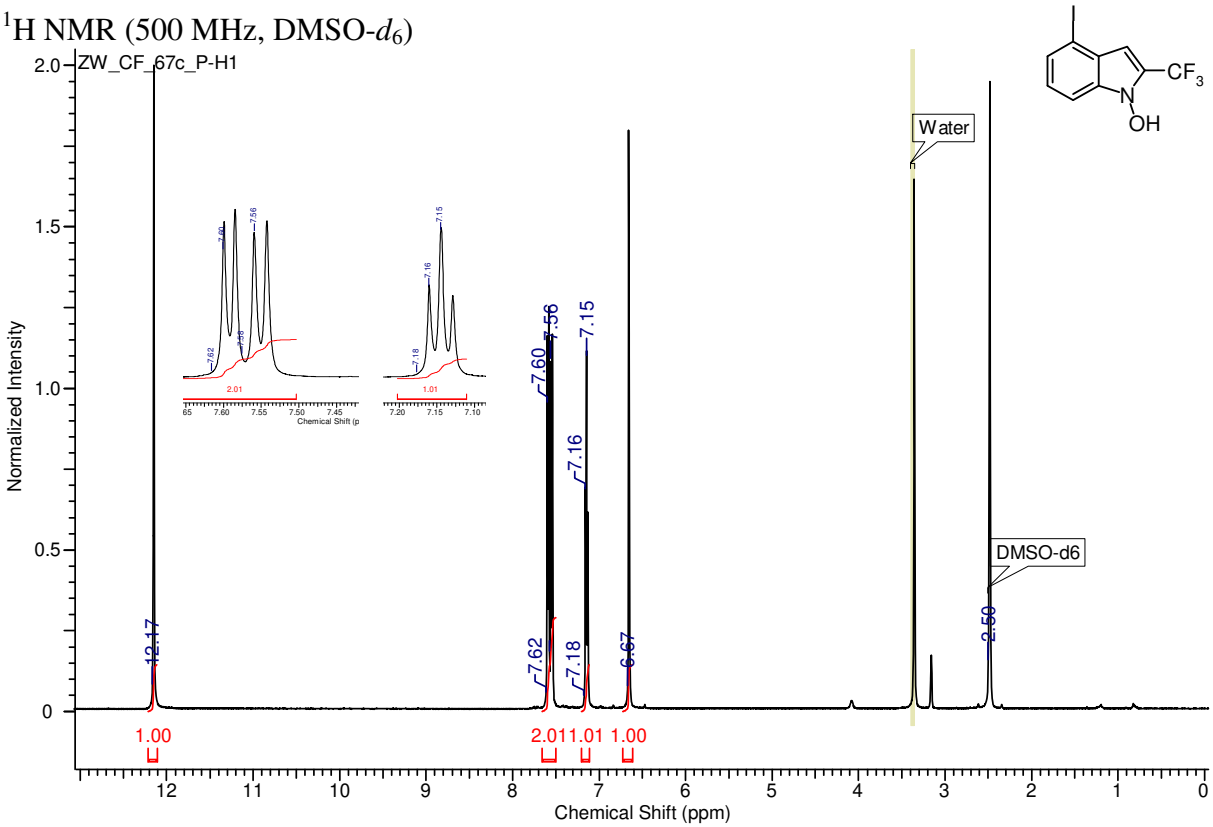


^{13}C NMR (125 MHz, $CDCl_3$)

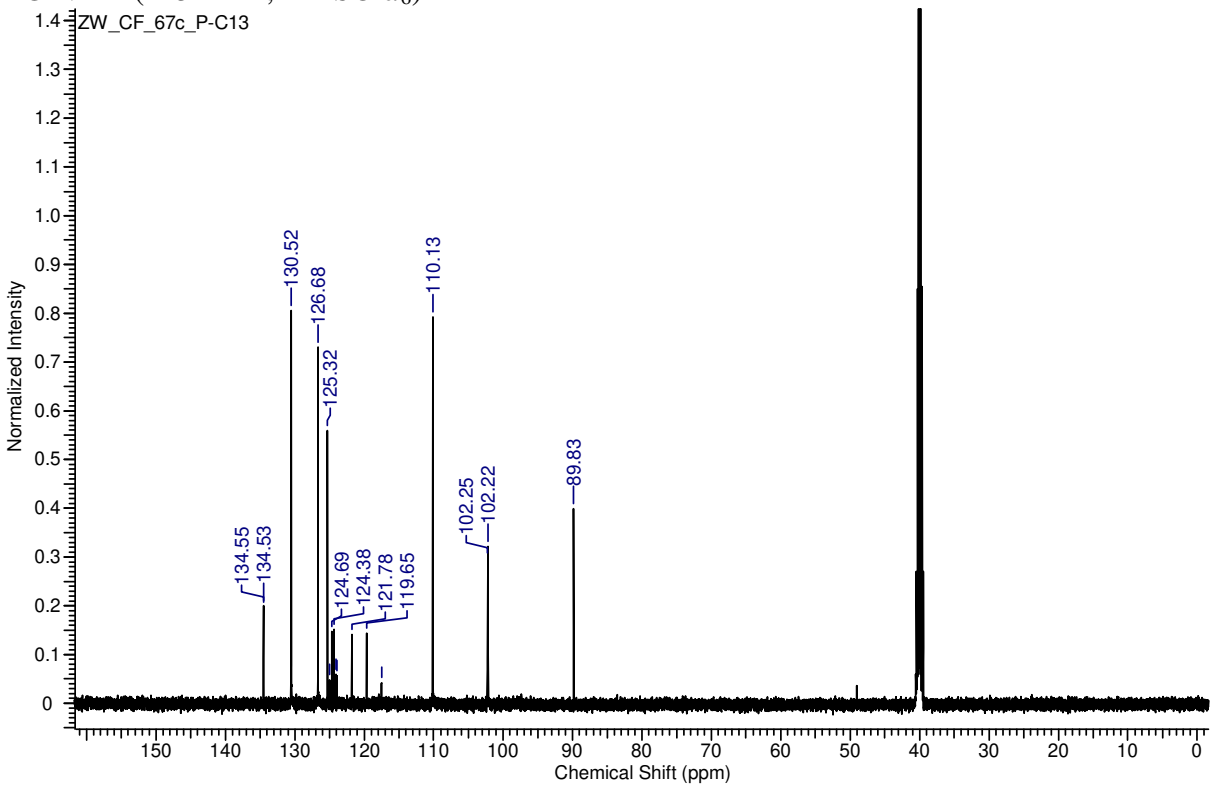


4

^{1}H NMR (500 MHz, DMSO-d_6)

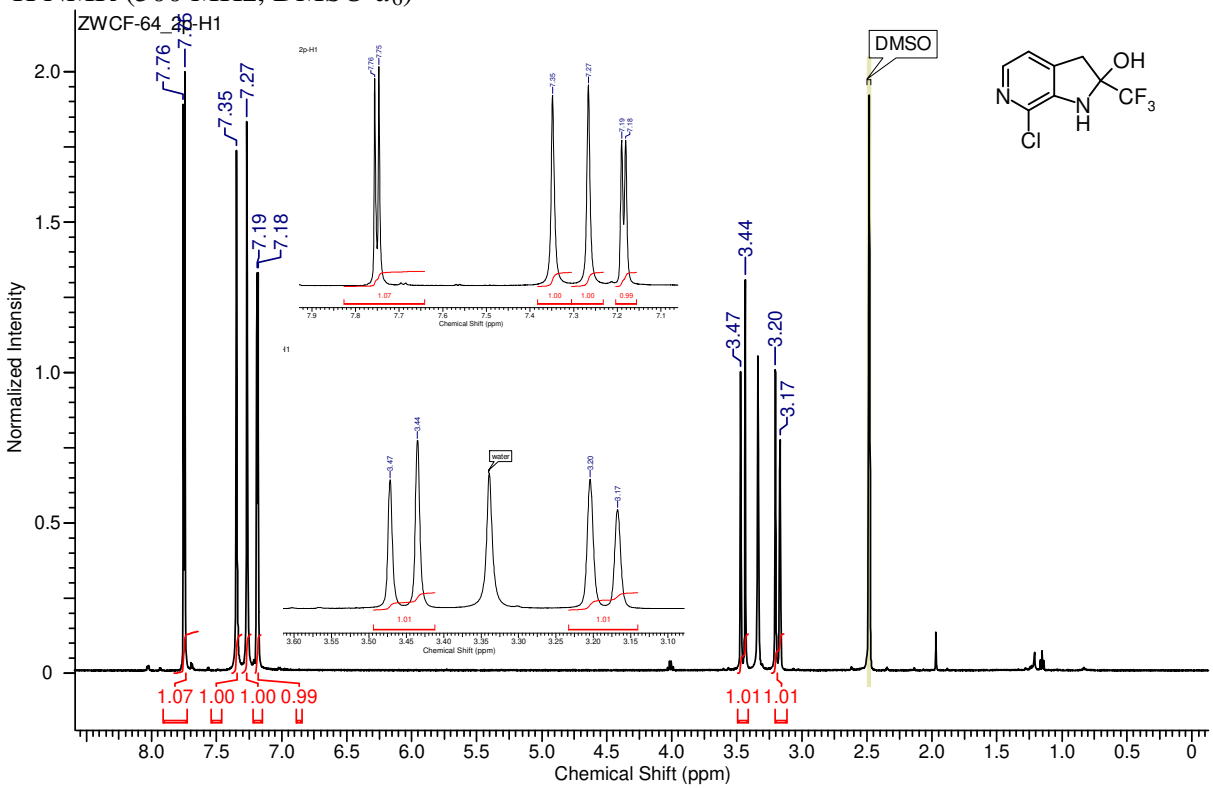


^{13}C NMR (125 MHz, DMSO-d_6)

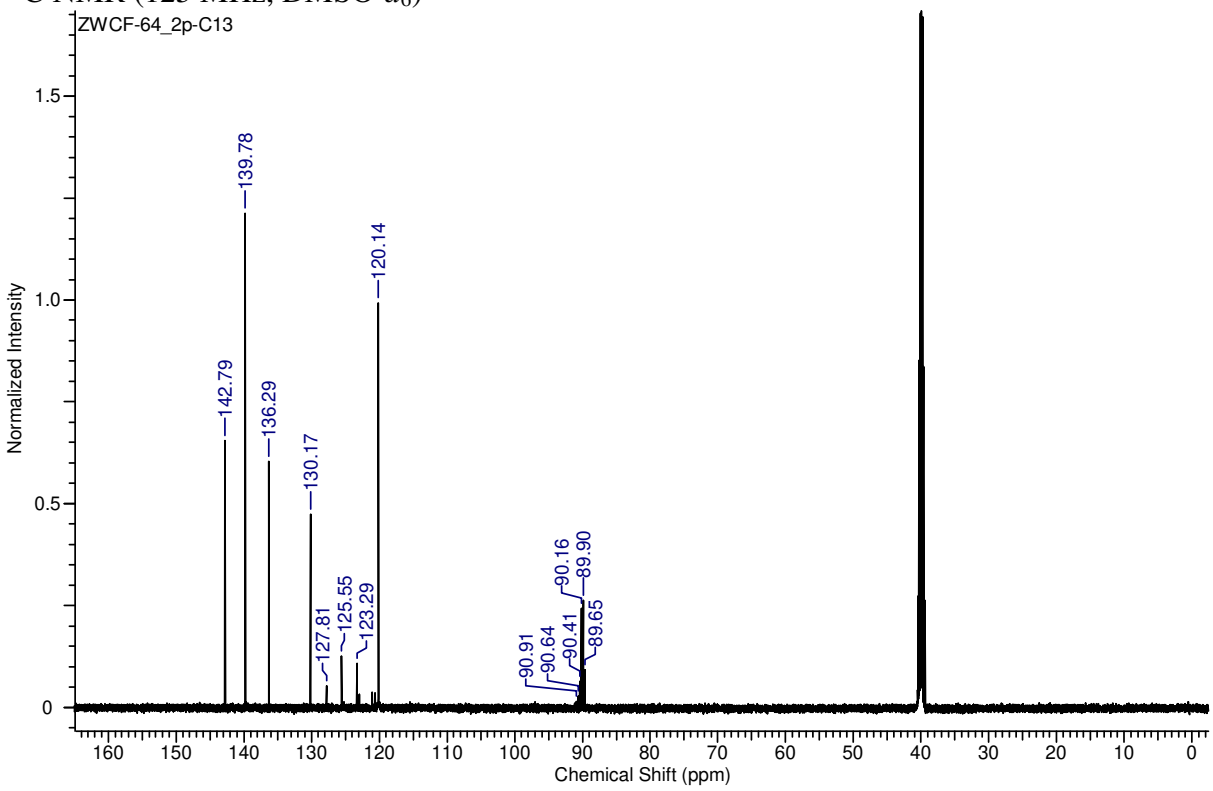


5

^{1}H NMR (500 MHz, DMSO-d_6)



^{13}C NMR (125 MHz, DMSO-d_6)



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Comprehensive approach to the multigram, heavy-metal-free synthesis of 4-EWG-substituted quinoline derivatives

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ABSTRACT

2-Nitrotoluenes activated by CN, SO_2Tol, CO_2R or COR groups condense under particular conditions with acetaldehyde in moderate to excellent yields. The unsaturated products are starting materials for cyclization furnishing quinoline oxides substituted with the above electron-withdrawing groups. Under relevant reaction conditions they can be reduced to the corresponding substituted quinolines. The protocol is suitable for multigram scale and extends the scope of the condensation step on non–CN–substituted 2-nitroarenes.

1. Introduction

The quinoline system is one of the most important backbones in organic chemistry [1]. Differently substituted quinolines, their *N*-oxides and similar bare compounds are important starting materials in the synthesis of various, more complex molecules of known or predicted biological activity [2]. In particular, this applies to quinolines having substituents that can be modified, further transformed and expanded towards the desired structures. Therefore, the synthesis of such compounds should be able to provide products in considerable amounts. Having to synthesize a series of 4-cyano quinoline derivatives on a multigram scale, we have found that the synthesis of various 4-substituted quinolines is poorly described in the literature. In our earlier work, the synthesis of 4-arylsulfonylquinolines from some nitroarenes and allyl sulfones was presented [3]. It was suitable for our goal as $ArSO_2$ group can be easily replaced by CN group, but it is not general and rather applicable to some specifically substituted products (Scheme 1, path a). Our two other methods for the synthesis of 4-CN quinolines from 2-cyanomethyl nitroarenes, by condensation with acetaldehyde followed by cyclization and reduction (path c) [4,5], or direct reaction with acrylonitrile (path d) [6], turned out to be somewhat tricky and reproducible only on a small, milligram scale. A palladium-catalyzed reaction, employing alkylidene derivatives of 2-nitroarylacetonitrile, leading directly to 4-cyanoquinolines, has been reported (path b) [7]. While it is an interesting method, especially from a mechanistic point of view, the reaction was demonstrated only on a very small scale. Moreover, the authors reported very poor reproducibility of the results of the essential condensation of nitroarylacetonitriles and related esters with acetic aldehyde [7]. Low yields of such transformation was also experienced by other authors using more complex reaction conditions [8].

2. Results and discussion

Considering all the above, we decided to reinvestigate our earlier route which was a two-stage process of quinoline construction and most promising in terms of practical synthetic scale. It consists of the Knoevenagel condensation of 2-cyanomethyl nitroarenes with acetaldehyde followed by a base- or chlorotrimethylsilane-promoted cyclization of the alkylidene intermediate (Scheme 1, path c, EWG = CN). 2-Nitrotoluenes activated in the methyl group by different EWG are suitable starting materials as they are sufficiently acidic for the use of weak bases and their anions are adequately reactive in nucleophilic condensations. Notably, they are easily available either commercially or by common reactions of nucleophilic substitution of hydrogen (VNS) or halogen ortho to the nitro group by appropriate active methylene compounds. In the model reaction of 4-bromo-2-nitrophenylacetonitrile (**1a**), some modifications of the reagents and procedures were tested for both steps leading to the quinoline oxide **3a** (Scheme 2). The final quinoline **4a** was intended to be obtained by separate deoxidation of **3a** [5]. This seemed more convenient than the one-step cyclization-reduction requiring the use of palladium complexes and CO under high pressure [7].

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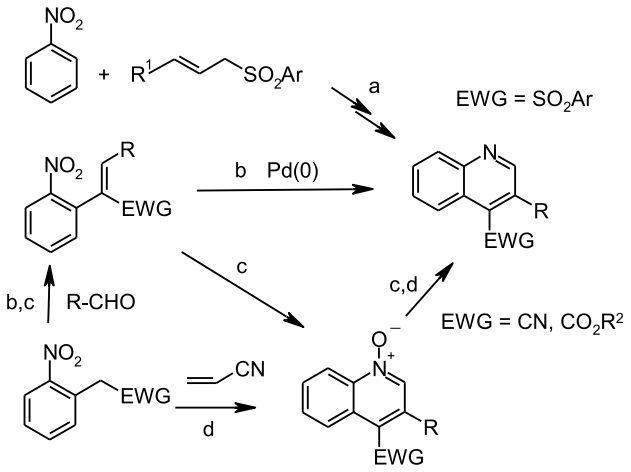


Scheme 1. Main routes from nitroarene derivatives to 4-EWG-substituted quinolines and their *N*-oxides; a: ref. 3; b: ref. 7; c: ref. 4 and 5; d: ref. 6.

Following the conditions for the Knoevenagel condensation, as reported by Dumas et al. [9], acetic anhydride was applied as dehydrating agent. However, LiBr that was used for promoting the condensation turned out to be ineffective in our model reaction due to the much lower acidity of **1** compared to malonates or similar dicarbonyl compounds [9]. After a brief search among bases (LiBr, LiCl, Et_3N, DBU, NaOAc), the latter was found to be a suitable one. The reaction was carried out on 1.0 mmol scale, with an excess of both acetaldehyde and Ac_2O, without any solvent for two days at 60–80 °C to provide the desired product **2a** almost quantitatively. However, in the reaction performed on a larger scale (starting from 20 g of **1a**) an isolated yield of 81% was achieved. For the cyclization reaction, both the methanolic solution of NaOH and chlorotrimethylsilane with Et_3N in DMF at room temperature proved to be successful conditions. The latter system was applied for the reaction performed on a multigram scale, giving 9.3 g of **3a** (87% isolated yield).

Having developed efficient and reliable procedures for the complete sequence of the reactions, we examined their scope regarding various substituents in the nitroaromatic ring, and attempted to expand the reactions to those that lead to quinolines substituted at C4 with different than CN electron-withdrawing groups such as CO_2R, COR, SO_2Ar and NO_2. Usually, the first attempt of the reaction was made using NaOAc, but if the result was unsatisfactory, the reaction was repeated with CsOAc and a better result was reported. Generally, for nitriles, NaOAc was efficient enough, whereas for esters and sulfones, CsOAc was substantially better. The results of the condensation step are shown in Scheme 3.

The reaction turned out to be general for the above-mentioned groups, except for the NO_2 group, for which a mixture of difficult-to-separate products was formed. The progress of the reaction was monitored by TLC, GC or ^{1}H NMR. Although the reaction was not optimized in individual cases (most of them were carried out according to the general procedure), it seems that in particular cases, it could be driven to completion by adding more acetaldehyde and Ac_2O during the reaction. For an illustrative example, see the synthesis of **2s** in the Experimental section. The reason is that in the slower reactions, acetaldehyde was consumed in a side reaction yielding the trimer. Even though it could be a source of acetaldehyde, we found that it did not participate in the condensation reaction under the reaction conditions.

The only limitation of this condensation appears to be due to steric hindrance in position 3 in the aromatic ring. Although insignificant for the linear CN group (**2b**, **2f**), it causes no reaction in the case of CO_2Me or SO_2Tol groups. This type of interaction can also be caused by a substituent larger than methyl ester group (Scheme 4).

The bulkiness of the EWG group also seems to determine the geometry of the alkene formed. While arylacetonitrile derivatives condensed to form *Z* isomers of the alkenes, other substituents like esters, ketones and sulfones gave unsaturated products predominantly in *E* configuration. Corresponding *Z* isomers were found in small or only trace amounts in the reaction of esters but were not even observed in the case of sulfone derivatives. The formation of an intermediate product, acetylated adduct of the carbanion to acetaldehyde, was observed in the ^{1}H NMR spectra of underreacted mixtures. In one case (**2s**), such a product (**2x**) was identified and isolated, although in very low yield. Since such an acylated aldol is incapable of retro addition, the final geometry seems to be controlled in the addition step of the nitrobenzyl anion to acetaldehyde. Thus, the favored anionic adduct becomes a precursor of the less sterically hindered final alkene. Geometry of the double bond in compounds **2** was determined by finding the similarity of their NMR spectra with those of comparable compounds for which geometry has been established and published. Especially informative in the ^{1}H NMR spectra were chemical shifts of the methyl group and of the adjacent proton which differ significantly in the opposite isomers [7,8].

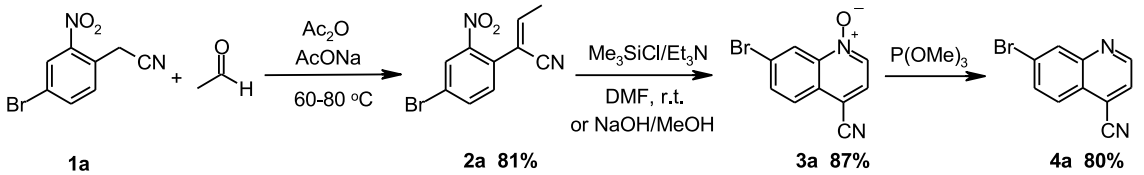
The cyclization of ethylidenes **2** to quinoline oxides **3** was initially carried out in the system described earlier [5], Me_3SiCl/Et_3N/DMF (Scheme 5, conditions A, X = Cl).

In the cases of nitriles, this system worked very well with one exception. Nitrile **2d** with bromine atom at position 6, instead of the expected quinoline N-oxide, gave a product of its subsequent rearrangement exclusively (Scheme 6). In the case of fluorine in place of bromine substituent, the desired reaction proceeded, albeit with moderate efficiency (**2h** → **3h**, 36% yield).

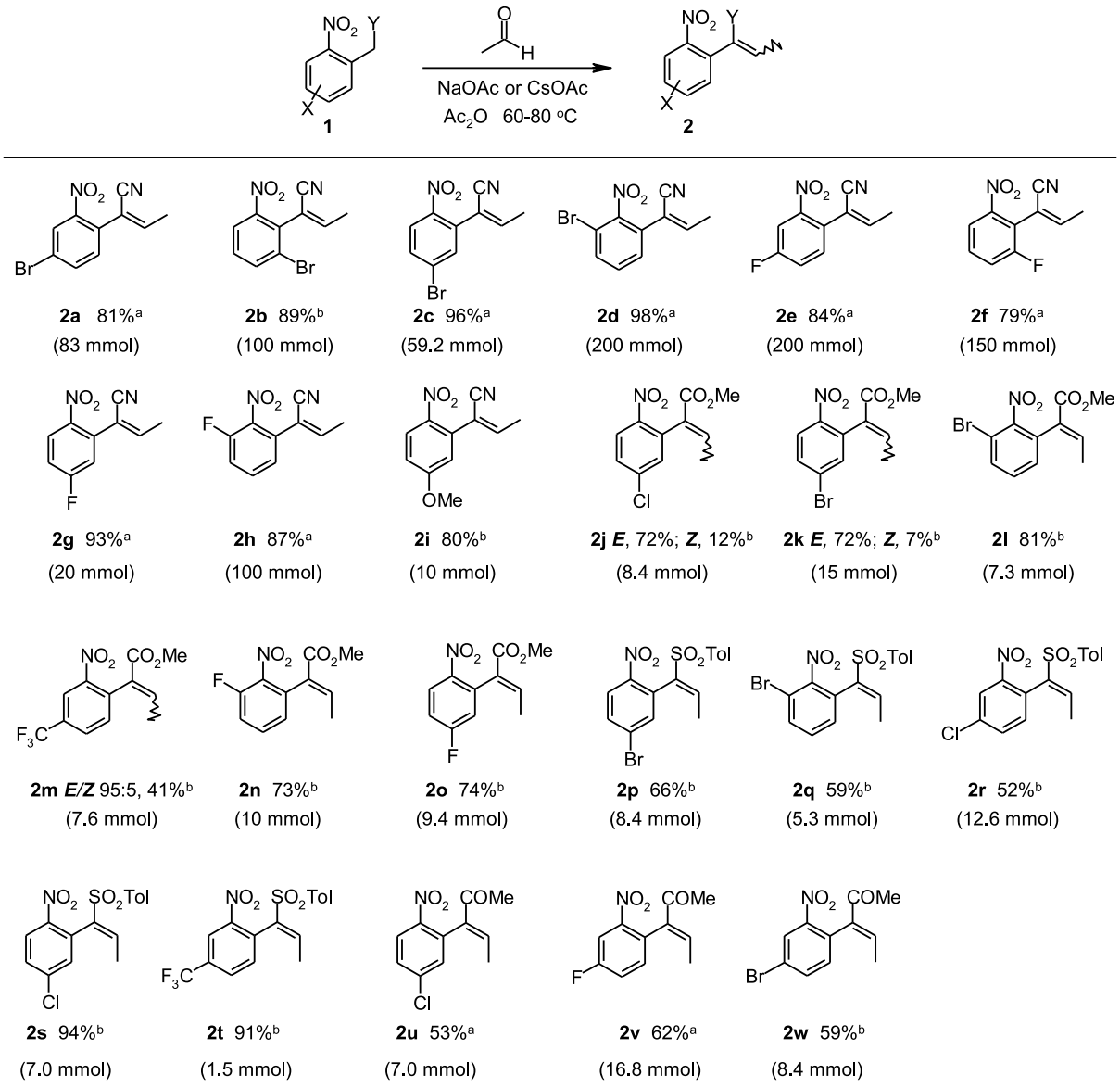
Most likely, the large substituent near the N–O group made it unstable, and thus increased susceptibility of the conversion of N-oxide to 2-hydroxyquinoline in the presence of Me_3SiCl, a transformation known while using acylating agents and Lewis acids. Esters cyclized less efficiently than nitriles. The use of HMPA instead of DMF improved the reactivity somewhat. Particularly, a more reactive Me_3SiBr instead of Me_3SiCl, in HMPA, led to higher yields.

Compound **2d** which did not transform into quinoline oxide under silylating conditions was successfully transformed into **3d** in high yield (93%) under basic NaOH/MeOH conditions [5]. Although this system was effective in some cases, a completely different course of the reaction took place in others (Scheme 7). Similar transformations occurred under more basic (KOMe/MeOH) conditions.

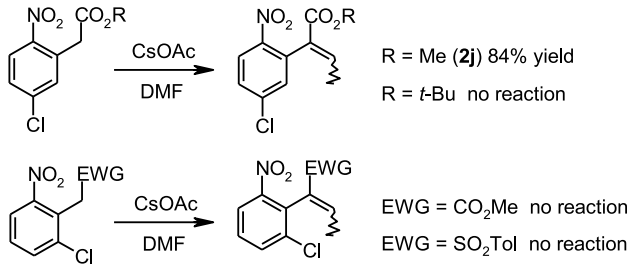
The occasional formation of *N*-hydroxyindoles and *N*-hydroxy-2-hydroxymethylindoles (similar to **6** and **8**, respectively) was reported and briefly discussed in our previous paper [5]. The mechanistic picture of the transformations involved in their formation still remain uncertain. Based on our results and the discussion published by Söderberg et al. on the results of similar cyclizations of nitrostyrenes carried out under reducing conditions [7]. a provisional mechanistic scheme can be



Scheme 2. Reaction sequence from 2-nitrobenzyl cyanides to 4-cyanoquinoline **4**. Given yields obtained in the multigram-scale experiments.



Scheme 3. Scope of the condensation reaction of **1.** [a] NaOAc; [b] CsOAc. Scale of the reaction (mmol of starting **1**) shown in brackets. In the typical reactions, for each 1.0 mmol of **1**, 2.0 mmol of sodium or cesium acetate, 0.5 mL of acetaldehyde and 0.7 mL of Ac_2O were used.

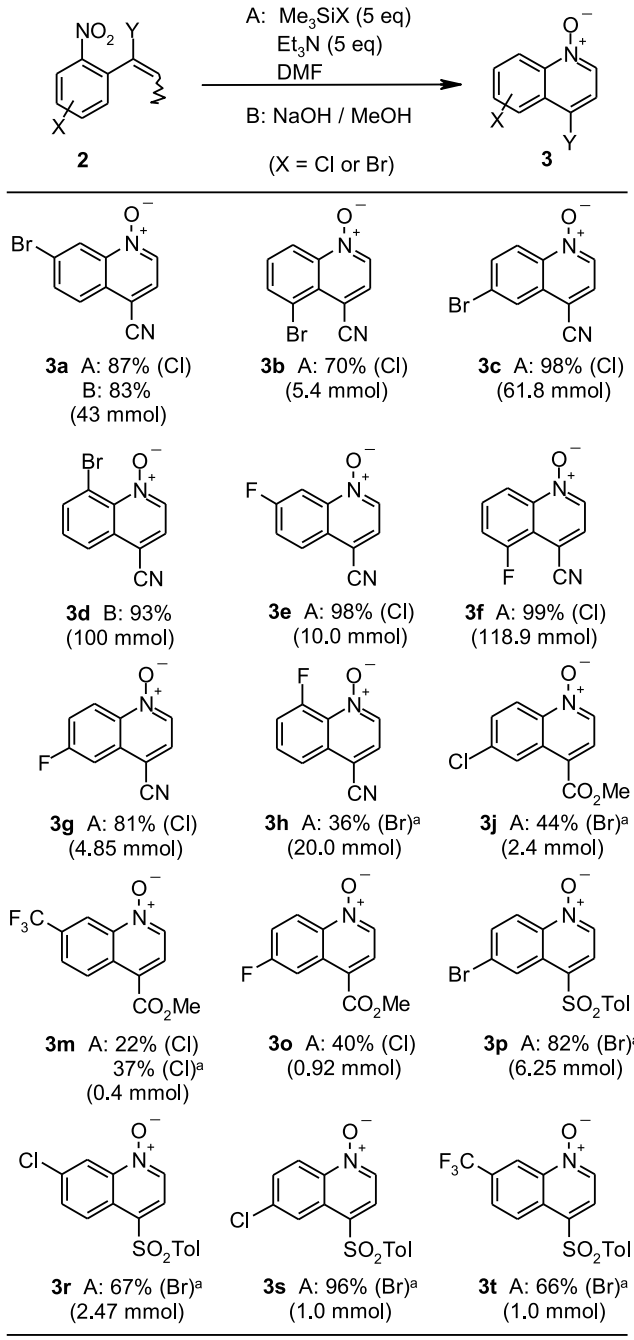


Scheme 4. Illustrative examples of steric hindrance in the formation of **2**.

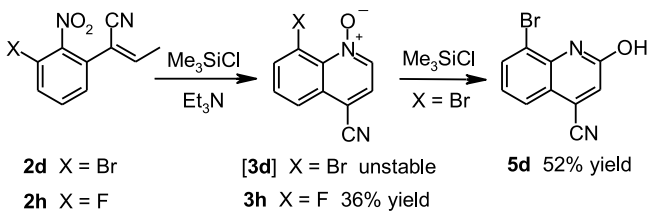
proposed (Scheme 8).

Deprotonation of nitrostyrenes **2** results in formation of mesomeric anion **9** which is believed to cyclize into seven-membered intermediate **10**, regardless of direction of electron movement indicated by the arrows in structure **9**. In our opinion, structure **A** is much more stable and both oxygen atoms are equally negatively charged. Thus, the addition of the carbanion to the oxygen atom of the nitro group (**9A** -> **10**), postulated by Söderberg, is less likely. Further steps of the reaction carried out without reducing agents may lead to N-hydroxy indoles **6** or **8** via common intermediate **12**. Strong support for the formation of **6** in this way, presented in our previous paper, was provided by the successful trapping of formaldehyde in a reaction that produced *N*-hydroxyindole without the hydroxymethyl group [5]. However, neither the results of this work nor those obtained previously [5] make it possible to predict or even explain observed results of the reactions of individual nitrostyrenes **2** (cf. **2m** → **6m** and **2v** → **8**). The only clear information drawn from our results is that nitrostyrenes **2** activated by CN group under basic conditions gave exclusively corresponding quinoline oxides (**3a** and **3d**). This observation is consistent with a different course of cyclization of nitrostyrenes activated with cyano and ester groups which was found in the reductive reactions carried out in the presence of palladium catalysts [7].

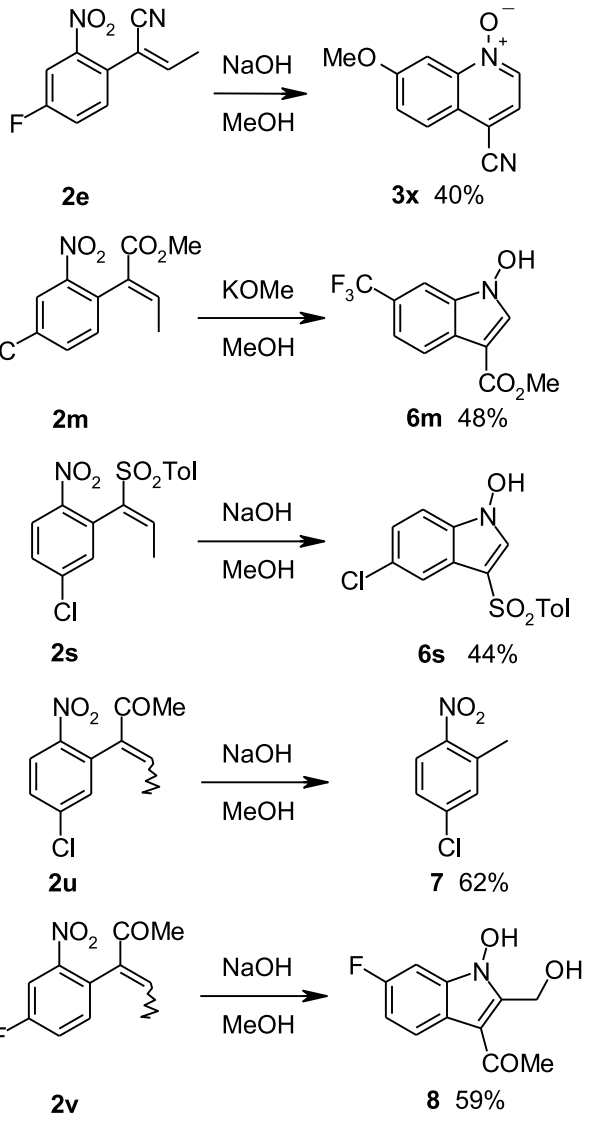
Rather unexpected formation of **7** could be explained by two



Scheme 5. Cyclization of **2**. Halogen atom X of Me_3SiX given in brackets. [a] HMPA was used instead of DMF. Scale of the reaction (mmol of starting **2**) shown in brackets.



Scheme 6. Transformation of **3** due to the bulkiness of the substituent at C8.

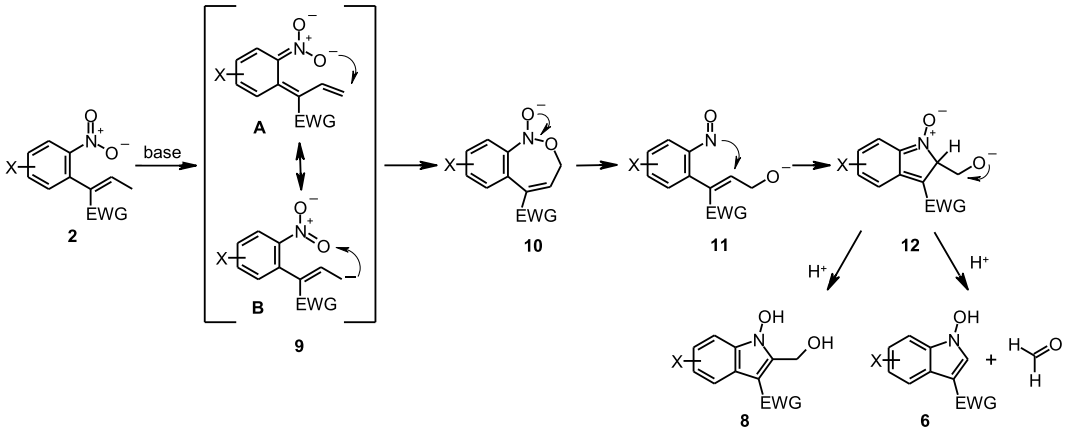


Scheme 7. Unusual products of the reactions carried out in basic systems.

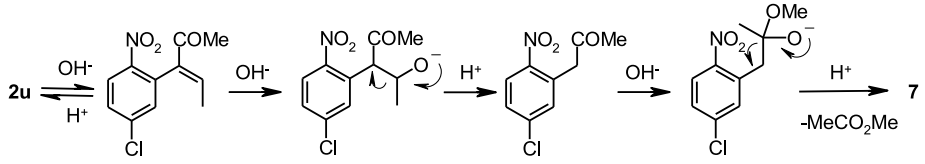
consecutive addition/elimination processes with C–C bond cleavage leading to the defunctionalized 2-nitrotoluene (Scheme 9).

Cyclization of unsaturated sulfones such as **2s** under basic conditions did not give expected quinoline derivatives (Scheme 7). Therefore, a few reaction systems based on silylating agents were tried and the best results were obtained using Me_3SiBr in HMPA (Scheme 10). However, under these conditions, analogously to the reaction of bromonitrile **2d**, the sulfone derivative with the expected sterically hindered **2q** reacted via unstable quinoline oxide **3q** to give the rearranged product, corresponding 2-hydroxyquinoline **5q** (25% yield). In the system containing Me_3SiCl, the alkylidene ketones **2u - 2w** were destroyed, while the use of NaOH/MeOH resulted in a different course of the reaction (Scheme 7). Consequently, the alkylidene ketones failed to give quinoxaline oxides.

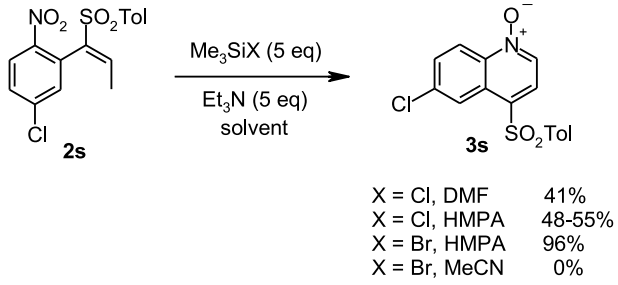
Deoxidation of oxides **3** seemed to be trivial. However, to obtain satisfactory results in all the tested reactions, numerous modifications of the basic system had to be undertaken (Scheme 11). Initially, for the deoxygenation of selected quinoline oxides, boiling $P(OMe)_3$ was used, and the procedure was found efficient for cyanoquinoline oxides **3a-c**, **3f** and **3g** which were reduced easily in the multigram-scale reactions (up to 120 mmol). Next, sodium dithionite was tried because of its friendlier properties and ease of reaction work-up and product isolation (procedure B). However, while this reagent was useful for the reduction of esters



Scheme 8. Possible way for the formation of indole derivatives **6** and **8**.



Scheme 9. Possible way of the formation of compound **7**.



Scheme 10. Efficiency of the sulfone **2s** cyclization in selected halosilane/solvent systems.

(**3j**, **3o**) and nitriles (**3d**, albeit less efficient than procedure A), it proved unsuitable for the sulfones **3p** and **3r** since it leads to the reduction of both the oxide function and the sulfone group. For the reduction of those quinoline oxides to be under as mild reaction conditions as possible, PBr_3 was used and was found to be effective even at room temperature.

In conclusion, a practical, metal-free synthesis of quinolines and their N-oxides equipped with some electron-withdrawing substituents was developed. Based on our experience and previous fragmentary investigations, it was adapted to an extended set of functional groups and multigram-scale requirements. Certain limitation reducing the scope of the particular steps of the synthesis were revealed, with the key being condensation of the starting 2-nitrobenzyl derivatives with acetic aldehyde and the subsequent cyclization of the unsaturated intermediates.

3. Experimental section

3.1. General remarks

Melting points were recorded in open capillary and are uncorrected. The ^1H and $^{13}C\{^1H\}$ NMR spectra of all compounds studied were measured at temperature 298 K in $CDCl_3$ or deuterated dimethyl sulfoxide (DMSO-d_6) solutions with a Varian vnmrs-600 or Varian vnmrs-500 using tetramethylsilane (TMS) as the internal standard. Mass spectra (EI, 70 eV) were obtained on an AutoSpec Premier (Waters) spectrometer. For ESI+ and ESI- measurements, a Maldi SYNAPT G2-S HDMS (Waters) was used. Accurate mass measurements were obtained using magnetic sector mass analyzer (EI) or TOF analyzer (ESI). Silica gel Merck 60 (230–400 mesh) was used for column chromatography. DMF was dried over CaH_2, distilled and stored over molecular sieves.

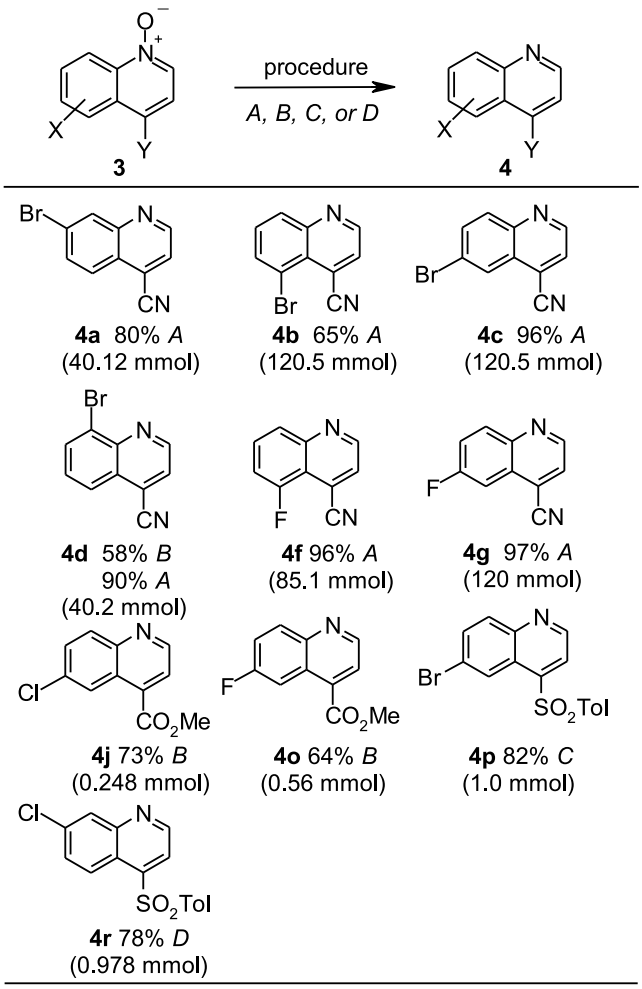
Starting nitro compounds **1a-d**, **1f** and **1g** were commercial. Compounds **1e** [10], **1h** [11], **1i,** [12] **1j** [13], **1k** [14], **1l** [15], **1m** [16], **1n** [17], **1o** [13], **1p,** [18] and **1u** [19] were obtained following the described literature procedures.

3.2. *General procedure for the synthesis of 2-nitrobenzyl tolyl sulfones 1q, 1r and 1t*

To a stirred solution of the appropriate 2-fluoro- or 2-chloronitroarene (20 mmol) and *t*-butyl [(4-methylphenyl)sulfonyl]acetate (5.4g, 20 mmol) in dry DMF (60 mL) were added K_2CO_3 (8.3 g) and the stirring was continued at room temperature until the reaction completion (tlc control). The crude ester was refluxed in a mixture of conc. HCl (25 mL) and AcOH (50 mL) until the gas evaluation ceased. The mixture was cooled to room temperature and poured into water (200 mL), then extracted with ethyl acetate (5 x 20 mL). The extract was dried, solvent evaporated and the product was isolated from the residue via column chromatography (SiO_2, ethyl acetate - hexane).

3.2.1. *1-Bromo-3-{[(4-methylphenyl)sulfonyl]methyl}-2-nitrobenzene (1q)*

Obtained from 8.8 g, 40 mmol of 1-bromo-3-fluoro-2-nitrobenzene. Yield 5.16 g (48%); Colorless crystals, mp: 148–151 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.36 (s, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.38 (t, $J = 8.0$ Hz, 1H), 7.55–7.59 (m, 3H), 7.69 (dd, $J = 8.0$, 0.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 21.7, 57.8, 113.9, 119.1, 123.0, 128.4, 130.0, 131.2, 131.8, 134.6, 134.7, 145.7. MS (EI) *m/z* 372 (0.4), 370 (0.4), 325 (4), 323 (4), 216 (59), 214 (61) 155 (58), 91 (100). HRMS (EI) *m/z* Calcd for $C_{14}H_{12}^{79}BrNO_4S$: 368.9670; Found: 368.9681.



Scheme 11. Procedures: *A*: $P(OMe)_3$ (excess), reflux; *B*: $Na_2S_2O_4$ (10 eq), MeOH, rt; *C*: PBr_3 (excess), DCM, rt; *D*: PBr_3 (excess, neat), 40 °C. Scale of the reaction (mmol of starting **3**) shown in brackets.

3.2.2. 4-Chloro-1-{[(4-methylphenyl)sulfonyl]methyl}-2-nitrobenzene (1r)

Obtained from 7.0 g, 40 mmol of 1,4-dichloro-2-nitrobenzene. Yield 11.3 g (87%); Colorless crystals, mp: 107–110 °C (lit [20]. 96–97 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.44 (s, 3H), 4.86 (s, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.59 (dd, J = 8.4, 2.2 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 58.0, 121.7, 125.6, 128.4, 130.0, 133.3, 134.8, 135.2, 136.0, 145.5, 149.6. MS (EI) *m/z* 325 (0.7), 293 (4), 172 (47), 170 (100), 155 (46), 112 (48), 91 (69). HRMS (EI) *m/z* Calcd for $C_{14}H_{12}^{35}ClNO_4S$: 325.0176; Found: 325.0178.

3.2.3. 1-{[(4-Methylphenyl)sulfonyl]methyl}-2-nitro-4-(trifluoromethyl) benzene (1t)

Obtained from 4.5 g, 20 mmol of 1-chloro-2-nitro-4-(trifluoromethyl)benzene. Yield 4.16 g (58%); Colorless crystals, mp: 133–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 5.20 (s, 2H), 7.40–7.42 (m, 2H), 7.55–7.57 (m, 2H), 7.63 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.37 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.5, 57.3, 122.9 (q, J_{FC} = 4.0 Hz), 123.2 (q, J_{FC} = 273.4 Hz), 127.7, 128.4, 130.2 (q, J_{FC} = 3.5 Hz), 130.4, 130.8 (q, J_{FC} = 33.5 Hz), 135.3, 136.2, 145.6, 150.0. MS (EI) *m/z* 359 (0.8, $[M]^+$), 204 (60), 155 (98), 91 (100). HRMS (EI) *m/z* Calcd for $C_{15}H_{12}F_3NO_4S$: 359.0439; Found: 359.0444.

3.3. Synthesis of 4-chloro-2-{[(4-methylphenyl)sulfonyl]methyl}-1-nitrobenzene (1s)

Compound **1s** was obtained from 4-nitrochlorobenzene (6.3 g, 40 mmol) and chloromethyl tolyl sulphone (8.2 g, 40 mmol), following the procedure, described for the analogous VNS reaction of chloromethyl phenyl sulphone [21]. Yield 9.12 g (70%); Creamy crystals, mp: 151–153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 5.09 (s, 2H), 7.40–7.42 (m, 2H), 7.51–7.53 (m, 2H), 7.44 (d, J = 2.3 Hz, 1H), 7.71 (dd, J = 8.7, 2.3 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.5, 57.2, 152.5, 127.7, 128.4, 130.3, 130.5, 134.4, 135.1, 138.2, 145.6, 148.3. HRMS (ESI) *m/z* Calcd for $C_{14}H_{12}^{35}ClNO_4SNa$: 348.0073; Found: 348.0078.

3.4. General procedure for the synthesis of 2-nitrobenzyl ketones 1v and 1w

The Dakin-West reaction: (2-Nitroaryl)acetic acid (53.3 mmol) was dissolved in Ac_2O (20 mL) and *N*-methylimidazole (1.0 mL) was added. The mixture was stirred at 40 °C for 10 days. The mixture was cooled to room temperature and poured into water (200 mL), then extracted with ethyl acetate (3 x 30 mL). The extract was dried, solvent evaporated and the product was isolated from the residue via column chromatography (SiO_2, ethyl acetate - hexane) to yield **1v** or **1w**.

3.4.1. 1-(4-Fluoro-2-nitrophenyl)acetone [22] (1v)

Obtained from 10.6 g, 53.3 mmol of (4-fluoro-2-nitrophenyl)acetic acid. Yield 6.38 g (61%); Pink crystals, mp: 60–62 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.10 (s, 2H), 7.24–7.27 (m, 1H), 7.31–7.34 (m, 1H), 7.86 (dd, J = 8.5, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 29.9, 47.9, 112.9 (d, J_{FC} = 26.6 Hz), 120.9 (d, J_{FC} = 21.4 Hz), 126.3 (d, J_{FC} = 4.0 Hz), 134.8 (d, J_{FC} = 8.1 Hz), 148.9, 161.3 (d, J_{FC} = 250.8 Hz), 203.2. MS (EI) *m/z* 198 (0.22 $[M+1]^+$), 155 (38), 138 (41), 110 (15), 107 (18),44 (100). HRMS (ESI) *m/z* Calcd for $C_9H_7FNO_3$ $[M-1]^-$: 196.0410; Found: 196.0412.

3.4.2. 1-(4-Bromo-2-nitrophenyl)acetone (1w)

Obtained from 9.7 g, 37.3 mmol of (4-bromo-2-nitrophenyl)acetic acid. Yield 5.44 g (57%); Creamy crystals, mp: 87–88 °C (lit [23]. 91–91.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 4.09 (s, 2H), 7.15 (d, J = 8.1 Hz, 1H), 7.71 (dd, J = 8.3, 2.0 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 30.0, 48.1, 121.5, 128.2, 129.2, 134.7, 136.5, 149.0, 202.8. MS (EI) *m/z* 258 (0.2, $[M+1]^+$), 217 (20), 215 (20), 200 (18), 198 (19), 44 (100). HRMS (ESI) *m/z* Calcd for $C_9H_7^{79}BrNO_3$ $[M-1]^-$: 255.9609; Found 255.9605.

3.5. Condensation of 1 with acetaldehyde. General procedure for the synthesis of 2

Nitro compound **1** (5.5 mmol), acetaldehyde (2.8 mL), Ac_2O (4.0 mL) and CsOAc (2.1 g, 11 mmol) or NaOAc (0.9 g, 11 mmol) were stirred at 55–75 °C for 3–14 days (amounts of the reagents and reaction conditions are given below for the particular compounds). After completion of the reaction, the mixture was cooled to room temperature and poured into cold water. The mixture was extracted with DCM (4 x 50 mL). The combined extract was washed with water, dried with Na_2SO_4 and the solvent evaporated. The residue was separated by column chromatography (SiO_2, ethyl acetate - hexane) to obtain the products. In the large-scale reactions, the major amount of the product was obtained after treating the crude product with hexane/EtOAc mixture and filtering the precipitate off. Additional amount of the product was isolated by column chromatography from the filtrate.

3.5.1. (2Z)-2-(4-Bromo-2-nitrophenyl)but-2-enenitrile (2a)

Obtained from 20.0 g, 83 mmol of **1a**, the reaction carried out at 60–75 °C for 2 days using NaOAc. Yield 17.9 g (81%); Brown crystals,

mp: 78–81 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.24 (d, J = 7.1 Hz, 3H), 6.58 (q, J = 7.1 Hz, 1H), 7.30, (d, J = 8.1 Hz, 1H), 7.80 (dd, J = 8.1, 2.0 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 17.9, 113.1, 114.5, 123.6, 128.1, 128.5, 132.8, 136.7, 147.5, 147.9. MS (EI) *m/z* 268 (22), 266 (23, $[M]^+$), 140 (68), 114 (56), 43 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7^{79}BrN_2O_2$: 265.9691; Found: 265.9684.

3.5.2. (2Z)-2-(2-Bromo-6-nitrophenyl)but-2-enenitrile (2b)

Obtained from 24.1 g, 100 mmol of **1b**, the reaction carried out at 65 °C for 4 days using CsOAc. Yield 23.7 g (89%); Pale yellow crystals, mp: 80–83 °C. ^{1}H NMR (600 MHz. $CDCl_3$): δ 2.12 (d, J = 7.1 Hz, 3H), 6.37 (q, J = 7.1 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 7.90 (d, J = 8.1 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz. $CDCl_3$): δ 17.7, 112.0, 114.3, 123.4, 126.4, 129.4, 130.9, 137.4, 148.7, 150.3. MS (EI) *m/z* 268 (39), 266 (36, $[M]^+$), 224 (37), 222 (35), 140 (83), 115 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7^{79}BrN_2O_2$: 265.9691; Found: 265.9684.

3.5.3. (2Z)-2-(5-Bromo-2-nitrophenyl)but-2-enenitrile (2c)

Obtained from 14.2 g, 59.2 mmol of **1c**, the reaction carried out at 60 °C for 3 days using NaOAc. Yield 16.5 g (96%); Beige crystals, mp: 80–83 °C (lit [4]. 68–78 °C). ^{1}H NMR (500 MHz. $CDCl_3$): δ 2.24 (d, J = 7.0 Hz, 3H), 6.63 (q, J = 7.0 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 8.7, 2.0 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 17.9, 113.0, 114.4, 126.5, 128.5, 131.4, 133.3, 134.7, 146.2, 147.9. MS (EI) *m/z* 268 (26), 266 (26, $[M]^+$), 140 (62), 115 (56), 114 (52), 44 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7^{79}BrN_2O_2$: 265.9691; Found: 256.9690.

3.5.4. (2Z)-2-(3-Bromo-2-nitrophenyl)but-2-enenitrile (2d)

Obtained from 48.2 g, 200 mmol of **1d**, in the reaction carried out at 60 °C for 3 days using NaOAc. Yield 52.4 g (98%); Pale yellow crystals, mp: 45–47 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 2.19 (d, J = 7.0 Hz, 3H), 6.68 (q, J = 7.0 Hz, 1H), 7.39–7.46 (m, 2H), 7.70 (dd, J = 8.1, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 18.3, 110.8, 114.0, 114.8, 128.3, 128.9, 131.3, 134.3, 149.8 (one signal invisible). MS (EI) *m/z* 268 (29), 266 (30, $[M]^+$), 224 (23), 222 (22), 140 (51), 115 (59), 43 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7^{79}BrN_2O_2$: 265.9691; Found: 265.9696.

3.5.5. (2Z)-2-(4-Fluoro-2-nitrophenyl)but-2-enenitrile (2e)

Obtained from 36.0 g, 200 mmol of **1e**, the reaction carried out at 60–65 °C for 4 days using NaOAc. Yield 34.6 g (84%); Colorless crystals, mp: 71–73 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 2.23 (d, J = 7.0 Hz, 3H), 6.55 (q, J = 7.0 Hz, 1H), 7.37–7.44 (m, 2H), 7.81 (dd, J = 7.8, 2.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 17.8, 112.9 (d, J_{FC} = 26.6 Hz), 113.1, 114.7, 121.0 (d, J_{FC} = 21.4 Hz), 126.0 (d, J_{FC} = 4.0 Hz), 133.4 (d, J_{FC} = 8.1 Hz), 147.3, 148.1, 162.2 (d, J_{FC} = 254.9 Hz). MS (EI) *m/z* 206 (29, $[M]^+$), 158 (33), 134 (43), 121 (22), 107 (32), 43 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7FN_2O_2$: 206.0492; Found: 206.0501.

3.5.6. (2Z)-2-(2-Fluoro-6-nitrophenyl)but-2-enenitrile (2f)

Obtained from 27.0 g, 150 mmol of **1f**, the reaction carried out at 60–65 °C for 2 days using NaOAc. Yield 24.47 g (79%); Creamy crystals, mp: 65–67 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.24 (d, J = 7.0 Hz, 3H), 6.55 (q, J = 7.0 Hz, 1H), 7.45 (t, J = 8.3 Hz, 1H), 7.57 (dd, J = 8.3, 5.7 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 17.9, 105.6, 114.6, 118.0 (d, J_{FC} = 19.1 Hz), 120.5 (d, J_{FC} = 3.5 Hz), 121.2 (d, J_{FC} = 23.1 HZ), 131.0 (d, J_{FC} = 9.2 Hz), 149.0, 149.9 (d, J_{FC} = 2.3 Hz), 160.0 (d, J_{FC} = 253.2 Hz). MS (EI) *m/z* 206 (35, $[M]^+$), 162 (23), 158 (26), 134 (62), 107 (39), 44 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7FN_2O_2$ $[M]^+$: 206.0492; Found: 206.0491.

3.5.7. (2Z)-2-(5-Fluoro-2-nitrophenyl)but-2-enenitrile (2g)

Obtained from 3.60 g, 20 mmol of **1g**, the reaction carried out at 60 °C for 1 day, using NaOAc. Yield 3.82 g (93%); Colorless crystals, mp: 88–90 °C (lit [5]. 76–79 °C). ^{1}H NMR (500 MHz. $CDCl_3$): δ 2.24 (d, J = 7.1 Hz, 3H), 6.63 (q, J = 7.1 Hz, 1H), 7.12 (dd, J = 8.3, 2.6 Hz, 1H), 7.24–7.28 (m, 1H), 8.15 (dd, J = 9.1, 4.9 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 17.8, 113.4 (d, J_{FC} = 1.2 Hz), 114.4, 117.1 (d, J_{FC} = 22.5 Hz), 119.0 (d, J_{FC} = 24.5 Hz), 128.0 (d, J_{FC} = 10.4 Hz), 123.7 (d, J_{FC} = 9.2 Hz), 143.6, 147.7, 164.6 (d, J_{FC} = 258.9 Hz). MS (EI) *m/z* 206 (37, $[M]^+$), 158 (34), 134 (65), 43 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7FN_2O_2$: 206.0492; Found: 206.0498.

3.5.8. (2Z)-2-(3-Fluoro-2-nitrophenyl)but-2-enenitrile (2h)

Obtained from 18.0 g, 100 mmol of **1h**, the reaction carried out at 60 °C for 4 days, using NaOAc. Yield 18.0 g (87%); Pale yellow crystals, mp: 41–43 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 2.21 (d, J = 7.0 Hz, 3H), 6.70 (q, J = 7.0 Hz, 1H), 7.27–7.33 (m, 2H), 7.57 (ddd, J = 8.2, 7.9, 5.2 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 18.2, 111.0 (d, J_{FC} = 2.9 Hz), 114.6, 117.9 (d, J_{FC} = 19.6 Hz), 125.4 (d, J_{FC} = 2.8 Hz), 129.1, 132.4 (d, J_{FC} = 8.7 Hz), 138.4, 149.5, 154.0 (d, J_{FC} = 260.1 Hz). MS (EI) *m/z* 206 (43, $[M]^+$), 162 (34), 134 (58), 121 (23), 107 (44), 44 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_7FN_2O_2$: 206.0492; Found: 206.0493.

3.5.9. (2Z)-2-(5-Methoxy-2-nitrophenyl)but-2-enenitrile (2i)

Obtained from 1.92 g, 10 mmol of **1i**, the reaction carried out at 60 °C for 13 days using CsOAc. Yield 1.74 g (80%); Beige crystals, mp: 100–101 °C (lit [5]. 98–100 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.21 (d, J = 7.0 Hz, 3H), 3.90 (s, 3H), 6.51 (q, J = 7.0 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.98 (dd, J = 9.1, 2.7 Hz, 1H), 8.14 (d, J = 9.1 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 17.7, 56.1, 114.3, 114.8, 114.9, 117.3, 127.8, 132.5, 140.4, 146.1, 163.5. MS (EI) *m/z* 218 (100, $[M]^+$), 175 (20), 149 (18), 131 (39), 120 (33). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}^{35}N_2O_3$: 218.0691; Found 218.0694.

3.5.10. Methyl (2E)-2-(5-chloro-2-nitrophenyl)but-2-enoate [2j(E)]

Obtained from 1.92 g, 8.4 mmol of **1i**, the reaction carried out at 60 °C for 2 days using CsOAc, separated from **2j(*Z*)**. Yield 1.55 g (72%); Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.73 (d, J = 7.1 Hz, 3H), 3.70 (s, 3H), 7.23 (q, J = 7.1 Hz, 1H), 7.25 (d, J = 2.3Hz, 1H), 7.49 (dd, J = 8.8 2.3 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 15.5, 52.2, 126.3, 129.0, 131.2, 132.4, 132.7, 139.5, 140.4, 146.8, 165.4. MS (EI) *m/z* 257 (4), 255 (15, $[M]^+$), 224 (27), 209 (46), 196 (81), 168 (51), 154 (46), 44 (100). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}^{35}ClNO_4$: 255.0298; Found: 255.0298.

3.5.11. Methyl (2Z)-2-(5-chloro-2-nitrophenyl)but-2-enoate [2j(Z)]

Obtained in the same reaction as **2j(*E*)**. Yield 254 mg (12%); Yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.30 (d, J = 7.1 Hz, 3H), 3.66 (s, 3H), 6.41 (q, J = 7.4 Hz, 21), 7.33 (d, J = 2.3 Hz, 1H), 7.44 (dd, J = 8.8 2.3 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 16.2, 51.6, 125.9, 128.6, 131.1, 132.4, 137.0, 139.7, 140.6, 146.1, 164.9. MS (EI) *m/z* 257 (2), 255 (6, $[M]^+$), 224 (26), 209 (50), 196 (90), 168 (57), 154 (54), 44 (100). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}^{35}ClNO_4$: 255.0298; Found: 255.0300.

3.5.12. Methyl (2E)-2-(5-bromo-2-nitrophenyl)but-2-enoate [2k(E)]

Obtained from 4.11 g, 15.0 mmol of **1k**, the reaction carried out at 65 °C for 3 days using CsOAc. Yield 3.24 g (72%); Pale yellow crystals, mp: 134–137 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.74 (d, J = 7.3 Hz, 3H), 3.70 (s, 3H), 7.24 (q, J = 7.3 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.7, 2.0 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.5, 55.2, 126.3, 128.0, 131.1, 132.0, 132.7, 135.3, 140.5, 147.3, 165.4. MS (EI) *m/z* 301 (3), 299 (3, $[M]^+$), 270 (14), 268 (14), 255 (39), 253 (37), 242 (59), 240 (64), 133 (82), 117 (89), 43 (100). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}^{79}BrNO_4$: 298.9793; Found: 298.9790.

3.5.13. Methyl (2Z)-2-(5-bromo-2-nitrophenyl)but-2-enoate [2k(Z)]

Obtained as above and separated from **2k(*E*)**. Yield 403 mg (7%); Colorless crystals, mp: 82–84 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 2.30 (d, J = 7.3 Hz, 3H), 3.66 (s, 3H), 6.42 (q, J = 7.3 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.61 (dd, J = 8.7, 2.1 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H). ^{13}C{^{1}H}

NMR (125 MHz. $CDCl_3$): δ 16.2, 51.6, 125.9, 128.2, 131.0, 131.6, 135.3, 137.0, 143.6, 146.6, 164.8. MS (EI) *m/z* 301 (9), 299 (9, $[M]^+$), 270 (30), 268 (31), 255 (62), 253 (60), 242 (81), 240 (86), 133 (89), 117 (100). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}^{79}BrNO_4$: 298.9793; Found: 298.9807.

3.5.14. Methyl (2E)-2-(3-bromo-2-nitrophenyl)but-2-enoate (2l)

Obtained from 2.0 g, 7.3 mmol of **1l**, the reaction carried out at 60 °C for 4 days using CsOAc. Yield 1.77 g (81%); Colorless crystals, mp: 97–99 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.69 (d, $J = 7.2$ Hz, 3H), 3.72 (s, 3H), 7.20 (dd, $J = 7.7$, 1.0 Hz, 1H), 7.29 (q, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 8.0$ Hz, 1H), 7.68 (dd, $J = 8.0$, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.7, 52.2, 113.2, 129.1, 130.46, 130.48, 131.0, 133.4, 144.6, 150.9, 165.3. MS (EI) *m/z* 301 (1), 299 (1, $[M]^+$), 270 (21), 268 (22), 242 (78), 240 (82), 214 (55), 212 (65), 133 (94), 117 (100). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}^{79}BrNO_4$: 298.9793; Found: 298.9802.

3.5.15. Methyl 2-[2-nitro-4-(trifluoromethyl)phenyl]but-2-enoate E/Z 94:6 (2m)

Obtained from 2.0 g, 7.6 mmol of **1m**, the reaction carried out at 60–65 °C for 5 days using CsOAc. Yield 874 mg (41%); Colorless crystals, mp: 189–192 °C. ^{1}H NMR (500 MHz. $CDCl_3$) (*E*): δ 1.72 (d, $J = 7.3$ Hz, 3H), 3.68 (s, 3H), 7.26 (q, $J = 7.3$ Hz, 1H), 7.42 (d, $J = 7.8$ Hz, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 8.39 (s, 1H); (*Z*): δ 2.31 (d, $J = 7.3$ Hz, 3H), 3.64 (s, 3H), 6.44 (q, $J = 7.3$ Hz, 1H), 7.48 (d, $J = 7.8$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 8.30 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$) (*E*): δ 15.4, 52.2, 122.1 (q, $J_{FC} = 4.0$ Hz), 122.6 (q, $J_{FC} = 272.8$ Hz), 129.6 (q, $J_{FC} = 3.5$ Hz), 131.1, 131.5 (q, $J_{FC} = 34.1$ Hz), 133.6, 134.5 (q, $J_{FC} = 1.2$ Hz), 140.9, 148.5, 165.1; (*Z*) the only recognizable signals: δ 16.2, 51.6. MS (EI) *m/z* 289 (5, $[M]^+$), 270 (14), 258 (32), 230 (73), 214 (41), 202 (55), 44 (100). HRMS (EI) *m/z* Calcd for $C_{12}H_{10}F_3NO_4$: 289.0562; Found: 289.0572.

3.5.16. Methyl (2E)-2-(3-fluoro-2-nitrophenyl)but-2-enoate (2n)

Obtained from 2.1 g, 10.0 mmol of **1n**, the reaction carried out at 60 °C for 5 days using CsOAc. Yield 1.74 g (73%); Flesh-colored crystals, mp: 201–203 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.72 (d, $J = 7.3$ Hz, 3H), 3.72 (s, 3H), 7.04 (d, $J = 7.7$ Hz, 1H), 7.26–7.31 (m, 2H), 7.51–7.55 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.6, 52.2, 116.9 (d, $J_{FC} = 18.9$ Hz), 127.0 (d, $J_{FC} = 4.0$ Hz), 129.4 (d, $J_{FC} = 2.0$ Hz), 131.5, 132.2 (d, $J_{FC} = 9.0$ Hz), 139.2 (d, $J_{FC} = 10.0$ Hz), 143.5, 154.3 (d, $J_{FC} = 260.3$ Hz), 165.3. MS (EI) *m/z* 239 (39, $[M]^+$), 208 (38), 182 (26), 167 (100) 152 (57). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}FNO_4$: 239.0594; Found: 239.0587.

3.5.17. Methyl (2E)-2-(5-fluoro-2-nitrophenyl)but-2-enoate (2o)

Obtained from 2.0 g, 9.4 mmol of **1o**, the reaction carried out at 60 °C for 4 days using CsOAc. Yield 1.66 g (74%); Colorless crystals, mp: 178–180 °C.^{1}H NMR (500 MHz. $CDCl_3$): δ 1.74 (d, $J = 7.2$ Hz, 3H), 3.71 (s, 3H), 6.97 (dd, $J = 8.3$, 2.8 Hz, 1H), 7.19–7.25 (m, 2H), 8.22 (dd, $J = 9.0$, 5.1 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.4, 52.2, 115.8 (d, $J_{FC} = 23.1$ Hz), 119.4 (d, $J_{FC} = 23.7$ Hz), 127.6 (d, $J_{FC} = 10.4$ Hz), 131.5 (d, $J_{FC} = 1.2$ Hz), 134.1 (d, $J_{FC} = 9.2$ Hz), 140.1, 144.6, 164.5 (d, $J_{FC} = 257.8$ Hz), 165.3. MS (EI) *m/z* 239 (13, $[M]^+$), 208 (28), 164 (32), 152 (56), 109 (90). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}FNO_4$: 239.0594; Found: 239.0599.

3.5.18. (1E)-1-(5-Bromo-2-nitrophenyl)prop-1-enyl 4-methylphenyl sulfone (2p)

Obtained from 3.11 g, 8.42 mmol of **1p**, the reaction carried out at 60 °C for 5 days using CsOAc. Yield 2.22 g (66%); Colorless crystals, mp: 142–143 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.74 (d, $J = 7.1$ Hz, 3H), 2.42 (s, 3H), 7.22–7.23 (m, 2H), 7.29 (q, $J = 7.1$ Hz, 1H), 7.36 (d, $J = 2.2$ Hz, 1H), 7.44–7.46 (m, 2H), 7.68 (dd, $J = 8.7$, 2.2 Hz, 1H), 7.81 (d, $J = 8.7$ Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.6, 21.6, 126.0, 127.3, 127.5, 128.6, 129.7, 133.3, 134.9, 136.3, 139.0, 140.6, 144.9, 148.0. MS (EI) *m/z* 242 (98), 240 (100), 170 (35), 168 (37), 117 (96). HRMS (ESI) *m/z* Calcd for $C_{16}H_{14}^{79}BrNNaO_4S$ $[M+Na]^+$: 417.9725; Found: 417.9728.

3.5.19. (1E)-1-(3-Bromo-2-nitrophenyl)prop-1-enyl 4-methylphenyl sulfone (2q)

Obtained from 1.96 g, 5.3 mmol of **1q**, the reaction carried out at 60 °C for 4 days using CsOAc. Yield 1.24 g (59%); Pale brown crystals, mp: 127–130 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.75 (d, $J = 7.3$ Hz, 3H), 2.43 (s, 3H), 7.24–7.26 (m, 2H), 7.29 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.33–7.38 (m, 2H), 7.47–7.49 (m, 2H), 7.71 (dd, $J = 8.0$, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 16.2, 21.7, 113.5, 125.4, 128.7, 129.8, 130.9, 131.9, 134.9, 135.1, 138.2, 143.1, 144.9, 150.9. MS (EI) *m/z* 396 (0.2, $[M+H]^+$), 142 (78), 240 (79), 170 (38), 168 (36), 117 (100). HRMS (EI) *m/z* Calcd for $C_{16}H_{15}^{79}BrNO_4S$: 395.9905; Found: 395.9893.

3.5.20. (1E)-1-(4-Chloro-2-nitrophenyl)prop-1-enyl 4-methylphenyl sulfone (2r)

Obtained from 4.10 g, 12.6 mmol of **1r**, in the reaction carried out at 60 °C for 5 days using CsOAc. Yield 2.31 g (52%); Colorless crystals, mp: 124–126 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.75 (d, $J = 7.1$ Hz, 3H), 2.42 (s, 3H), 7.19 (d, $J = 8.3$ Hz, 1H), 7.24 (d, $J = 8.1$ Hz, 2H), 7.33 (q, $J = 7.1$ Hz, 1H), 7.45 (q, $J = 8.3$ Hz, 2H), 7.58 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.94 (d, $J = 2.1$ Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.5, 21.6, 123.8, 124.9, 128.5, 129.7, 133.0, 134.7, 135.1, 136.3, 139.0, 140.7, 144.8, 149.6. Anal. Calcd for $C_{16}H_{14}ClNO_4S$: C, 54.63; H, 4.01; N, 3.98; Cl, 10.17; S, 9.11; Found: C, 54.49; H, 3.98; N, 3.84; Cl, 10.17; S, 9.05.

3.5.21. (1E)-1-(5-Chloro-2-nitrophenyl)prop-1-enyl 4-methylphenyl sulfone (2s)

Obtained from 2.29 g, 7.03 mmol of **1s**, the reaction carried out at 75 °C for 4 days using CsOAc. Double the amount of anhydride was used and an additional three times after each reaction day the initial amount of acetaldehyde was added. Yield 2.33 g (94%); Pale brown crystals, mp: 106–109 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.75 (d, $J = 7.1$ Hz, 3H), 2.41 (s, 3H), 7.19 (d, $J = 2.3$ Hz, 1H), 7.23 (d, $J = 8.2$ Hz, 2H), 7.30 (q, $J = 7.1$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.51 (dd, $J = 8.8$, 2.3 Hz, 1H), 7.89 (d, $J = 8.8$ Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.5, 21.6, 126.0, 127.3, 128.6, 129.7, 130.3, 133.4, 135.0, 139.1, 139.2, 140.5, 144.7, 147.5. MS (EI) *m/z* 352 (1, $[M+H]^+$), 198 (46), 196 (100). Anal. Calcd for $C_{16}H_{14}ClNO_4S$: C, 54.63; H, 4.01; N, 3.98; Cl, 10.17; S, 9.11; Found: C, 54.22; H, 3.94; N, 3.88; Cl, 10.33; S, 9.07.

3.5.22. 1-{(1E)-1-[(4-methylphenyl)sulfonyl]prop-1-enyl}-2-nitro-4-(trifluoromethyl)benzene (2t)

Obtained from 540 mg, 1.5 mmol of **1t**, the reaction carried out at 60 °C for 4 days using CsOAc. Yield 525 mg (91%); Pale yellow crystals, mp: 136–138 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.74 (d, $J = 7.1$ Hz, 3H), 2.42 (s, 3H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.35 (q, $J = 7.1$ Hz, 1H), 7.42–7.46 (m, 3H), 7.85 (dd, $J = 8.0$, 1.8 Hz, 1H), 8.18 (d, $J = 1.8$ Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.6, 21.6, 121.9 (q, $J_{FC} = 3.5$ Hz), 122.5 (q, $J_{FC} = 273.4$ Hz), 128.5, 129.3 (q, $J_{FC} = 2.9$ Hz), 129.8, 132.7 (q, $J_{FC} = 34.7$ Hz), 133.0 (q, $J_{FC} = 34.1$ Hz), 134.8, 134.9, 139.0, 141.0, 145.0, 149.3. MS (EI) *m/z* 386 (0.6, $[M+H]^+$), 230 (100), 158 (54), 145 (47), 91 (55). HRMS (EI) *m/z* Calcd for $C_{17}H_{15}F_3NO_4S$ $[M+H]^+$: 386.0674; Found: 386.0668.

3.5.23. (3E)-3-(5-Chloro-2-nitrophenyl)pent-3-en-2-one (2u)

Obtained from 1.49 g, 7.0 mmol of **1u**, the reaction carried out at 60 °C for 5 days using NaOAc. After 3 days of the reaction an excess of acetaldehyde (30%) and 2.0 mL of the anhydride were added and the reaction was continued for additional two days. Yield 807 mg (53%); Colorless crystals, mp: 167–169 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.76 (d, $J = 7.1$ Hz, 3H), 2.42 (s, 3H), 7.03 (q, $J = 7.1$ Hz, 1H), 7.18 (d, $J = 2.2$ Hz, 1H), 7.49 (dd, $J = 8.8$, 2.2 Hz, 1H), 8.10 (d, $J = 8.8$ Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.9, 26.0, 126.2, 128.9, 132.2, 133.2, 139.4,

139.6, 141.3, 146.8, 196.5. MS (EI) *m/z* 240 (2, $[M+H]^+$), 197 (17), 193 (19), 182 (14), 180 (24), 117 (20), 43 (100). HRMS (EI) *m/z* Calcd for $C_{11}H_{11}^{35}ClNO_3$ $[M+H]^+$: 240.0427; Found: 240.0431.

3.5.24. (3E)-3-(4-Fluoro-2-nitrophenyl)pent-3-en-2-one (2v)

Obtained from 3.32 g, 16.8 mmol of **1v**, the reaction carried out at 60 °C for 30 days using NaOAc. Yield 2.32 g (62%); Yellow oil. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.74 (d, J = 7.1 Hz, 3H), 2.40 (s, 3H), 7.02 (q, J = 7.1 Hz 1H), 7.17 (dd, J = 8.6, 5.6 Hz, 1H), 7.36 (td, J = 8.6, 2.5 Hz, 1H), 7.85 (dd, J = 8.6, 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 15.9, 26.0, 112.4 (d, J_{FC} = 26.6 Hz), 120.6 (d, J_{FC} = 21.4 Hz), 127.3 (d, J_{FC} = 4.0 Hz), 133.8 (d, J_{FC} = 7.5 Hz), 139.5, 141.3, 149.0 (d, J_{FC} = 8.1 Hz), 161.6 (d, J_{FC} = 252.0 Hz), 196.8. MS (EI) *m/z* 224 (4, $[M+H]^+$), 181 (11), 164 (27), 152 (12), 138 (20), 133 (23), 44 (100). HRMS (EI) *m/z* Calcd for $C_{11}H_{11}FNO_3$ $[M+H]^+$: 224.0723; Found: 224.0722.

3.5.25. (3E)-3-(4-Bromo-2-nitrophenyl)pent-3-en-2-one (2w)

Obtained from 2.17 g, 8.42 mmol of **1w**, the reaction carried out at 60 °C for 2 days using CsOAc. Yield 1.42 g (59%); Orange oil. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.74 (d, J = 7.1 Hz, 3H), 2.40 (s, 3H), 7.02 (q, J = 7.1 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.75 (dd, J = 8.2, 1.9 Hz, 1H), 8.26 (d, J = 1.9 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 16.0, 26.0, 122.1, 127.8, 130.2, 133.6, 136.3, 139.5, 141.3.196.6. HRMS (ESI) *m/z* Calcd for $C_{11}H_{11}^{79}BrNO_3$ $[M+H]^+$: 283.9922; Found: 283.9921.

3.5.26. 2-(5-Chloro-2-nitrophenyl)-1-methyl-2-[(4-methylphenyl) sulfonyl]ethyl acetate (2x)

Isolated as a side product from the reaction of **1s**, described for **2s** (see above). Yield 14 mg (0.5%); Colorless crystals, mp: 196–198 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 1.20 (d, J = 6.4 Hz, 3H), 1.85 (s, 3H), 2.41 (s, 3H), 5.63 (d, J = 8.6 Hz, 1H), 5.76–5.83 (m, 1H), 7.27–7.29 (m, 2H), 7.47 (dd, J = 8.8, 2.2 Hz, 1H), 7.60–7.63 (m, 2H), 7.81 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 18.4, 20.9, 21.6, 66.0, 68.8, 126.6, 127.3, 128.4, 129.8, 130.1, 130.9, 136.1, 139.7, 145.2, 148.9, 169.4. MS (EI) *m/z* 412 (0.2, $[M+H]^+$), 256 (17), 196 (36), 180 (20), 91 (36), 44 (100). HRMS (ESI) *m/z* Calcd for $C_{18}H_{18}^{35}ClNNaO_6S$ $[M+Na]^+$: 434.0441; Found: 434.0438.

3.6. General procedures for the cyclization of 2 at a 1.0-mmol scale. Synthesis of quinoline oxides 3

3.6.1. Procedure A

A solution of **2** (1.0 mmol) in dry DMF or HMPA (3 mL) was treated with Me_3SiCl or Me_3SiBr (5 mmol) followed by the addition of Et_3N (5 mmol, 0.70 mL) during stirring at room temperature. The reaction was continued until completion (tlc control). The mixture was poured into aq. HCl (50 mL), extracted with ethyl acetate (5 x 20 mL), the extract was dried, and solvent evaporated. The product was isolated from the residue by column chromatography (SiO_2, ethyl acetate - hexane) or, partially, by simple crystallization.

3.6.2. Procedure B

Nitrotoluene derivative **2** (1.0 mmol) was dissolved (or suspended) in methanol (3 mL) and treated with methanolic NaOH (or KOMe in the case of **2m**) (1.0 mL of a 1 M soln.). The mixture was stirred at room temperature until the substrate was consumed (2 min–3 h, tlc control). After acidic work-up and extraction with ethyl acetate (5 x 20 mL) the product was isolated by column chromatography (ethyl acetate - hexane 1:2 to 1:1).

For both procedures: In the large-scale reactions the major amount of the product was obtained after treating the crude product with hexane/EtOAc mixture and filtering the precipitate off. Additional amount of the product was isolated from the filtrate by column chromatography.

3.6.3. 7-Bromoquinoline-4-carbonitrile-1-oxide (3a)

Obtained from 9.3 g, 43 mmol of **2a,** procedure A (Me_3SiCl/DMF). Yield 9.3 g (87%); Brown crystals, mp: 216–217 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 7.68 (d, J = 6.5 Hz, 1H), 6.93 (dd, J = 8.8, 1.9 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.48 (d, J = 6.5 Hz, 1H), 8.91 (d, J = 1.9 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 105.9, 115.0, 123.0, 126.2, 126.7, 127.2, 127.8, 134.7, 135.5, 142.6. MS (EI) *m/z* 250 (91), 248 (91, $[M]^+$), 232 (16), 170 (14), 153 (29), 141 (80), 114 (100). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2O$: 247.9585; Found: 247.9589.

3.6.4. 5-Bromoquinoline-4-carbonitrile-1-oxide (3b)

Obtained from 1.17 g, 5.43 mmol of **2b**, procedure A (Me_3SiCl/DMF). Yield 0.94 g (70%); Brown crystals, mp: 179–182 °C (lit [6]. 197–201 °C). ^{1}H NMR (500 MHz. $CDCl_3$): δ 7.65 (dd, J = 8.9, 7.6 Hz, 1H), 7.79 (d, J = 6.6 Hz, 1H), 8.06 (dd, J = 7.6, 1.1 Hz, 1H), 8.49 (d, J = 6.6 Hz, 1H), 8.77 (dd, J = 8.9, 1.1 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 105.9, 117.0, 120.2, 120.4, 127.2, 130.6, 131.3, 134.7, 137.0, 144.1. MS (EI) *m/z* 250 (98), 248 (100, $[M]^+$), 169 (30), 153 (23), 141 (54), 114 (67). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2O$: 247.9585; Found: 247.9588.

3.6.5. 6-Bromoquinoline-4-carbonitrile-1-oxide (3c)

Obtained from 16.5 g, 61.8 mmol of **2c**, procedure A (Me_3SiCl/DMF). Yield 15.4 g (98%); Orange crystals, mp: 202–203 °C (lit [4]. 227–229 °C). ^{1}H NMR (600 MHz. $CDCl_3$): δ 7.68 (d, J = 6.4 Hz, 1H), 7.93 (dd, J = 9.3, 1.9 Hz, 1H), 8.37 (d, J = 1.9 Hz, 1H), 8.47 (d, J = 6.4 Hz, 1H), 8.58 (d, J = 9.3 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz. $CDCl_3$): δ 104.8, 115.0, 122.1, 126.3, 127.1, 128.1, 130.1, 135.0, 135.2, 141.1. MS (EI) *m/z* 250 (98), 248 (100, $[M]^+$), 234 (28), 232 (29), 153 (37), 141 (86). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2O$: 247.9585; Found: 247.9584.

3.6.6. 8-Bromoquinoline-4-carbonitrile-1-oxide (3d)

Obtained from 26.7 g, 100 mmol of **2d**, procedure B (NaOH/MeOH). Yield 23.2 g (93%); Beige crystals, mp: 221–222 °C dec. ^{1}H NMR (500 MHz. DMSO-d_6): δ 7.77 (t, J = 7.9 Hz, 1H), 8.17–8.23 (m, 3H), 8.71 (d, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. DMSO-d_6): δ 105.1, 112.8, 116.4, 126.5, 128.6, 131.6, 132.0, 138.1, 139.03, 139.07. MS (EI) *m/z* 250 (99), 248 (100, $[M]^+$), 234 (28), 232 (29), 220 (47), 153 (24), 141 (91), 114 (81). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2O$: 247.9585; Found: 247.9591.

3.6.7. 7-Fluoroquinoline-4-carbonitrile-1-oxide (3e)

Obtained from 2.06 g, 10 mmol of **2e**, procedure A (Me_3SiCl/DMF). Yield 1.84 g (98%); Beige crystals, mp: 208–211 °C. ^{1}H NMR (500 MHz. $CDCl_3$): δ 7.61–7.66 (m, 2H), 8.25 (dd, J = 9.1, 5.4 Hz, 1H), 8.40 (dd, J = 9.1, 2.5 Hz, 1H), 8.52 (d, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz. $CDCl_3$): δ 105.8 (d, J_{FC} = 26.9 Hz), 105.9, 115.2, 121.5 (d, J_{FC} = 25.9 Hz), 125.3 (d, J_{FC} = 3.0 Hz), 126.0 (d, J_{FC} = 2.0 Hz), 128.7 (d, J_{FC} = 9.0 Hz), 135.5, 164.3 (d, J_{FC} = 257.3 Hz), 165.4. MS (EI) *m/z* 188 (100, $[M]^+$), 172 (22), 160 (21), 133 (81). HRMS (EI) *m/z* Calcd for $C_{10}H_5FN_2O$: 188.0386; Found: 188.0387.

3.6.8. 5-Fluoroquinoline-4-carbonitrile-1-oxide (3f)

Obtained from 24.5 g, 118.9 mmol of **2f**, procedure A (Me_3SiCl/DMF). Yield 22.1 g (99%); Beige crystals, mp: 195–196 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.53 (m, 1H), 7.70 (d, J = 6.5 Hz, 1H), 7.78–7.82 (m, 1H), 8.50 (d, J = 6.5 Hz, 1H), 8.53 (d, J = 8.8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 101.0, 115.7 (d, J_{FC} = 19.6 Hz), 116.0, 116.3 (d, J_{FC} = 4.6 HZ), 120.0 (d, J_{FC} = 16.2 Hz), 128.1, 131.4 (d, J_{FC} = 8.7 Hz), 135.3, 143.2, 157.3 (d, J_{FC} = 259.5 Hz). MS (EI) *m/z* 188 (100, $[M]^+$), 172 (40), 160 (27), 145 (18), 133 (42). HRMS (EI) *m/z* Calcd for $C_{10}H_5FN_2O$: 188.0386; Found: 188.0385.

3.6.9. 6-Fluoroquinoline-4-carbonitrile-1-oxide (3g)

Obtained from 1.0 g, 4.85 mmol of **2g**, procedure A (Me_3SiCl/DMF). Yield 913 mg (81%); Beige crystals, mp: 178–181 °C (lit [5]. 176–181 °C). ^{1}H NMR (500 MHz. $CDCl_3$): δ 7.60 (ddd, J = 9.8, 7.7, 2.6 Hz, 1H), 7.68 (d, J = 6.2 Hz, 1H), 7.85 (dd, J = 8.4, 2.6 Hz, 1H), 8.45 (d, J = 6.2

Hz, 1H), 8.75 (dd, $J = 9.8$, 5.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 105.4 (d, $J_{FC} = 5.2$ Hz), 110.2 (d, $J_{FC} = 24.8$ Hz), 115.0, 121.6 (d, $J_{FC} = 26.0$ Hz), 123.6 (d, $J_{FC} = 9.2$ Hz), 127.3, 130.7 (d, $J_{FC} = 10.4$ Hz), 134.5, 139.4, 163.2 (d, $J_{FC} = 256.6$ Hz). MS (EI) *m/z* 188 (100, $[M]^+$), 172 (24), 160 (41), 133 (81). HRMS (EI) *m/z* Calcd for $C_{10}H_5FN_2O$: 188.0386; Found: 188.0390.

3.6.10. 8-Fluoroquinoline-4-carbonitrile-1-oxide (3h)

Obtained from 4.12 g, 20.0 mmol of **2h**, procedure A (Me_3SiBr/HMPA). Yield 1.35 g (36%); Orange crystals, mp: 180–205 °C (dec). ^1H NMR (600 MHz. DMSO-d_6): δ 7.68–7.72 (m, 1H), 7.86–7.90 (m, 1H), 7.91–7.95 (m, 1H), 8.13 (d, $J = 6.5$ Hz, 1H), 8.61 (d, $J = 6.5$ Hz, 1H). $^{13}C\{^1H\}$ NMR (150 MHz. DMSO-d_6): δ 103.9 (d, $J_{FC} = 4.0$ Hz), 115.8, 117.5 (d, $J_{FC} = 21.4$ Hz), 121.7 (d, $J_{FC} = 5.8$ Hz), 128.5, 131.4, 131.6 (d, $J_{FC} = 8.7$ Hz), 132.2, 137.9, 154.1 (d, $J_{FC} = 263.6$ Hz).MS (EI) *m/z* 188 (100), 172 (16), 160 (21), 133 (51). HRMS (EI) *m/z* Calcd for $C_{10}H_5FN_2O$: 188.0386; Found: 188.0384.

3.6.11. Methyl 6-chloroquinoline-4-carboxylate-1-oxide (3j)

Obtained from 631 mg, 2.44 mmol of **2j**, procedure A (Me_3SiBr/HMPA). Yield 261 mg (44%); Pinkish powder, mp: 197–198 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 4.00 (s, 3H), 7.69 (dd, $J = 9.3$, 2.1 Hz, 1H), 8.01 (d, $J = 6.5$ Hz, 1H), 8.45 (d, $J = 6.5$ Hz, 1H), 8.67 (dd, $J = 9.3$, 2.1 Hz, 1H), 9.11 (d. $J = 2.1$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 52.7, 121.5, 121.6, 125.5, 125.9, 129.1, 131.2, 134.4, 137.1, 140.8, 164.6. MS (EI) *m/z* 239 (37), 237 (100, $[M]^+$), 206 (70), 150 (19). HRMS (EI) *m/z* Calcd for $C_{11}H_8^{35}ClNO_3$: 237.0193; Found: 237.0197.

3.6.12. Methyl 7-(trifluoromethyl)quinoline-4-carboxylate-1-oxide (3m)

Obtained from 115 mg, 0.4 mmol of **2m**, procedure A (Me_3SiCl/HMPA). Yield 40 mg (37%); Red crystals, mp: 101–103 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 4.03 (s, 3H), 7.91 (dd, $J = 9.0$, 1.4 Hz, 1H), 8.12 (d, $J = 6.5$ Hz, 1H), 8.55 (d, $J = 6.5$ Hz, 1H), 9.06 (s, 1H), 9.26 (d, $J = 9.0$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 52.8, 118.0 (q, $J_{FC} = 4.56$ Hz), 122.3, 123.3 (q, $J_{FC} = 272.8$ Hz), 125.9 (q, $J_{FC} = 3.4$ Hz), 126.3, 128.4, 130.1 (q, $J_{FC} = 1.1$ Hz), 132.1 (q, $J_{FC} = 33.5$ Hz), 135.2, 141.8, 164.5. MS (EI) *m/z* 271 (100, $[M]^+$), 240 (84), 212 (20), 184 (22). HRMS (EI) *m/z* Calcd for $C_{12}H_8F_3NO_3$: 271.0456; Found: 271.0449.

3.6.13. Methyl 6-fluoroquinoline-4-carboxylate-1-oxide (3o)

Obtained from 220 mg, 0.92 mmol of **2o**, procedure A (Me_3SiCl/DMF). Yield 81.3 mg (40%); Colorless crystals, mp: 178–180 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 4.01 (s, 3H), 7.53 (ddd, $J = 9.8$, 7.1, 2.6 Hz, 1H), 8.05 (d, $J = 6.4$ Hz, 1H), 8.45 (d, $J = 6.4$ Hz, 1H), 8.75–8.82 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 52.7, 111.3 (d, $J_{FC} = 26.1$ Hz), 120.3 (d, $J_{FC} = 26.0$ Hz), 121.9 (d, $J_{FC} = 5.8$ Hz), 122.8 (d, $J_{FC} = 9.8$ Hz), 125.6, 129.9 (d, $J_{FC} = 11.6$ Hz), 133.8, 139.5, 163 (d, $J_{FC} = 252.0$ Hz), 164.7. MS (EI) *m/z* 221 (100), 190 (72), 162 (29), 134 (33), 107 (23). HRMS (EI) *m/z* Calcd for $C_{11}H_8FNO_3$: 221.0488; Found: 221.0489.

3.6.14. 6-Bromo-4-tosylquinoline-1-oxide (3p)

Obtained from 6.25 mmol, 2.47 g of **2p**, procedure A (Me_3SiBr/HMPA). Yield 1.93 g (82%); Pale beige crystals, mp: 170–171 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.32–7.36 (m, 2H), 7.82 (dd, $J = 9.3$, 2.0 Hz, 1H), 7.83–7.86 (m, 2H), 8.15 (d, $J = 6.6$ Hz, 1H), 8.51 (d, $J = 6.6$ Hz, 1H), 8.55 (d, $J = 9.3$ Hz, 1H), 8.84 (d, $J = 2.0$ Hz, 1H. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 21.6, 122.2, 124.4, 125.8, 126.4, 127.6, 127.7, 130.3, 131.7, 134.3, 134.4, 137.1, 141.3, 145.4. MS (EI) *m/z* 379 (37), 377 (36, $[M]^+$), 218 (23), 139 (100). HRMS (EI) *m/z* Calcd for $C_{16}H_{12}^{79}BrNO_3S$: 376.9721; Found: 376.9727.

3.6.15. 7-Chloro-4-[(4-methylphenyl)sulfonyl]quinoline-1-oxide (3r)

Obtained from 868 mg, 2.47 mmol of **2r**, procedure A (Me_3SiBr/HMPA). Yield 553 mg (67%); Colorless crystals, mp: 210–212 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 2.34 (s, 3H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.89 (dd, $J = 9.2$, 2.3 Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 2H), 8.20 (d, $J = 6.6$ Hz, 1H), 8.53 (d, $J = 2.3$ Hz, 1H), 8.55 (d, $J = 9.2$ Hz, 1H), 8.78 (d, $J = 6.6$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. DMSO-d_6): δ 21.5, 119.6, 123.7, 125.3, 127.4, 127.9, 130.8, 131.5, 131.9, 136.1, 136.7, 137.4, 142.6, 145.7. MS (EI) *m/z* 335 (26), 333 (55, $[M]^+$), 218 (21), 139 (100). HRMS (EI) *m/z* Calcd for $C_{16}H_{12}^{35}ClNO_3S$: 333.0226; Found: 333.0232.

3.6.16. 6-Chloro-4-[(4-methylphenyl)sulfonyl]quinoline-1-oxide (3s)

Obtained from 352 mg, 1.0 mmol of **2s**, procedure A (Me_3SiBr/HMPA). Yield 320 mg (96%); Beige crystals, mp: 229–232 °C. ^1H NMR (500 MHz. DMSO-d_6): δ 2.37 (s, 3H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.92 (dd, $J = 9.1$, 2.2 Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 2H), 8.24 (d, $J = 6.5$ Hz, 1H), 8.55 (d, $J = 2.2$ Hz, 1H), 8.58 (d, $J = 9.1$ Hz, 1H), 8.81 (d, $J = 6.5$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. DMSO-d_6): δ 21.0, 119.1, 123.2, 124.9, 127.0, 127.5, 130.3, 131.0, 131.4, 135.6, 136.3, 137.0, 142.2, 145.2. MS (EI) *m/z* 335 (28), 333 (54, $[M]^+$), 218 (33), 139 (100). HRMS (EI) *m/z* Calcd for $C_{16}H_{12}^{35}ClNO_3S$: 333.0226; Found: 333.0211.

3.6.17. 4-[(4-Methylphenyl)sulfonyl]-7-(trifluoromethyl)quinoline-1-oxide (3t)

Obtained from 385 mg, 1.0 mmol of **2t**, procedure A (Me_3SiBr/HMPA). Yield 241 mg (66%); Colorless crystals, mp: 189–192 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.33–7.35 (m, 2H), 7.85–7.87 (m, 2H), 7.90 (dd, $J = 9.0$, 1.8 Hz, 1H), 8.27 (d, $J = 6.6$ Hz, 1H), 8.60 (d, $J = 6.6$ Hz, 1H), 8.82 (d, $J = 9.0$ Hz, 1H), 9.02 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 21.6, 118.6 (q, $J_{FC} = 4.6$ Hz), 123.0 (q, $J_{FC} = 272.8$ Hz), 125.3, 126.3 (q, $J_{FC} = 3.4$ Hz), 126.8, 127.1, 127.7, 130.2, 132.59, 132.61 (q, $J_{FC} = 34.1$ Hz), 135.0, 137.1, 142.1, 145.5. MS (EI) *m/z* 367 (50, $[M]^+$), 139 (100), 91 (25). HRMS (EI) *m/z* Calcd for $C_{17}H_{12}F_3NO_3S$: 367.0490 Found: 367.0508.

3.6.18. 7-Methoxyquinoline-4-carbonitrile-1-oxide (3x)

Obtained from 4.12 g, 20 mmol of **2e**, procedure B (NaOH/MeOH). Yield 1.62 g (40%); Pale yellow crystals, mp: 216–219 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 4.03 (s, 3H), 7.45 (dd, $J = 9.1$, 2.3 Hz, 1H), 7.53 (d, $J = 6.3$ Hz, 1H), 8.03 (d, $J = 2.3$ Hz, 1H), 8.07 (d, $J = 9.1$ Hz, 1H), 8.50 (d, $J = 6.3$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 56.2, 98.7, 106.0, 115.5, 123.1, 125.0, 124.2, 127.1, 135.2, 143.6, 162.8. MS (EI) *m/z* 200 (100, $[M]^+$), 170 (44), 155 (35), 153 (58). HRMS (EI) *m/z* Calcd for $C_{11}H_8N_2O_2$: 200.0586; Found: 200.0586.

3.6.19. 8-Bromo-2-hydroxyquinoline-4-carbonitrile (5d)

Obtained from 2.67 g, 10 mmol of **2d**, procedure A (Me_3SiCl/DMF). Yield 1.30g (52%); Colorless crystals, mp: 263–267 °C. ^1H NMR (500 MHz. DMSO-d_6): δ 7.30 (t, $J = 7.8$ Hz, 1H), 7.43 (s, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 11.23 (br s, 1H). $^{13}C\{^1H\}$ NMR not recorded due to extremely low solubility of **5d** in standard solvents. MS (EI) *m/z* 250 (99), 248 (100, $[M]^+$), 222 (47), 220 (47), 141 (54), 140 (27), 114 (68). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2O$: 247.9585; Found: 247.9580.

3.6.20. 8-Bromo-4-[(4-methylphenyl)sulfonyl]quinolin-2-ol (5q)

Obtained from 264 mg, 0.67 mmol of **2q**, procedure A (Me_3SiBr/HMPA). Yield 62 mg (25%); Pale pink crystals, mp: 219–221 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 2.44 (s, 3H), 7.14 (t, $J = 8.2$ Hz, 1H), 7.27 (s, 1H), 7.36–7.39 (m, 2H), 7.76 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.86–7.89 (m, 2H), 8.39 (dd, $J = 8.2$, 1.2 Hz, 1H), 9.21 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 21.7, 109.7, 115.2, 123.9, 125.1, 125.7, 128.5, 130.3, 134.8, 135.2, 136.1, 146.0, 150.1, 159.8. MS (EI) *m/z* 379 (100), 377 (97, $[M]^+$), 314 (23), 312 (23), 234 (28), 115 (49), 91 (82). HRMS (EI) *m/z* Calcd for $C_{16}H_{12}^{79}BrNO_3S$: 376.9721; Found: 376.9722.

3.6.21. Methyl 1-hydroxy-6-trifluoromethyl-1H-indole-3-carboxylate (6m)

Obtained from 723 mg, 2.5 mmol of **2m**, procedure B (KOMe/MeOH). Yield 310 mg (48%); Colorless crystals, mp: 152–154 °C (EtOAc/hexane). ^1H NMR (500 MHz, DMSO-d_6): δ 3.81 (s, 3H), 7.51 (d,

$J = 8.6$ Hz, 1H), 7.80 (s, 1H), 8.19 (d, $J = 8.6$ Hz, 1H), 8.42 (s, 1H), 12.34 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. DMSO-d_6): δ 51.0, 101.3, 106.9 (q, $J_{FC} = 4.6$ Hz), 118.0 (q, $J_{FC} = 3.5$ Hz), 121.6, 123.3 (q, $J_{FC} = 31.8$ Hz), 124.7 (q, $J_{FC} = 1.1$ Hz), 124.8 (q, $J_{FC} = 271.7$ Hz), 132.4, 133.4, 163.8. MS (EI) *m/z* 259 (100, $[M]^+$), 228 (94). HRMS (EI) *m/z* Calcd for $C_{11}H_8F_3NO_3$: 259.0456; Found: 259.0464.

*3.6.22. 5-Chloro-3-[(4-methylphenyl)sulfonyl]-1H-indol-1-ol **(6s)***

Obtained from 493 mg, 1.4 mmol of **2s**, procedure B (NaOH/MeOH). Yield 201 mg (44%); Colorless crystals, mp: 218–220 °C. ^1H NMR (600 MHz. DMSO-d_6): δ 2.29 (s, 3H), 7.29 (d, $J = 8.7$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.51 (d, $J = 8.7$ Hz, 1H), 7.75 (s, 1H), 7.85 (d, $J = 8.0$ Hz, 2H), 8.44 (s, 1H), 12.35 (br s, 1H). $^{13}C\{^1H\}$ NMR (150 MHz. DMSO-d_6): δ 21.4, 109.7, 112.2, 118.1, 121.1, 124.2, 126.7, 127.5, 130.3, 131.4, 132.5, 140.8, 143.8. MS (EI) *m/z* 323 (47), 321 (100, $[M]^+$), 307 (18), 305 (48), 240 (30), 166 (30), 139 (35). HRMS (EI) *m/z* Calcd for $C_{15}H_{12}^{35}ClNO_3S$: 321.0226; Found: 321.0222.

*3.6.23. 1-[6-Fluoro-1-hydroxy-2-(hydroxymethyl)-1H-indol-3-yl] ethanone **(8)***

Obtained from 446 mg, 2.0 mmol of **2v**, procedure B (NaOH/MeOH). Yield 265 mg (59%); Creamy crystals, mp: not measured due to gradual decomposition. ^1H NMR (500 MHz, DMSO-d_6): δ 2.63 (s, 3H), 4.90 (s, 2H), 5.46 (br s, 1H), 7.05–7.10 (m, 1H), 7.24 (d, $J = 8.6$ Hz, 1H), 8.17 (dd, $J = 8.6$, 5.14 Hz, 1H), 11.889 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 30.0, 51.8, 95.3 (d, $J_{FC} = 25.6$ Hz), 109.3, 110.6 (d, $J_{FC} = 23.7$ Hz), 118.4, 123.0 (d, $J_{FC} = 9.8$ Hz), 132.9 (d, $J_{FC} = 12.1$ Hz), 143.1, 159.3 (d, $J_{FC} = 238.1$ Hz), 193.3. MS (EI) *m/z* 193 (100, $[M - CH_2O]^+$), 178 (96), 161 (32), 133 (27). HRMS (EI) *m/z* Calcd for $C_{11}H_{10}FNO_3Na$: 246.0542; Found: 246.0539.

3.7. Procedures for deoxidation of quinoline oxides 3

3.7.1. Procedure A. Typical multigram-scale example

7-Bromoquinoline-4-carbonitrile-1-oxide (**3a**) (10.0 g, 40.1 mmol) was refluxed in $P(OMe)_3$ (250 mL) (or heated to specified temperature) for 2 h, then the volatile material was evaporated. The major amount of the product was obtained after treating the crude product with hexane/EtOAc mixture and filtering the precipitate off. Additional amount of the product was isolated from the filtrate by column chromatography (SiO_2, EtOAc/hexane). Combined yield 7.45 g (80%) of **4a**.

3.7.2. Procedure B. Typical example

Quinoline oxide **3** (1.0 mmol) and $Na_2S_2O_4$ (10 mmol) were stirred in MeOH (30 mL) at rt for the time specified. The mixture was poured into water and extracted with DCM (3 x 50 mL). The combined extracts were dried with Na_2SO_4 and the solvent evaporated. The product was isolated by column chromatography (SiO_2, EtOAc/hexane).

3.7.3. Procedure C

6-Bromo-4-methylquinoline-1-oxide (**3p**) (378 mg, 1.0 mmol) dissolved in DCM (10 mL) was cooled to −70 °C, PBr_3 (1.0 mL) was added and the mixture was allowed to warm to room temperature. After that, the mixture was poured into cold water, the organic layer was separated and the water layer was extracted with DCM (3 x 20 mL). Combined extracts were dried with Na_2SO_4 and the solvent evaporated. Quinoline **4p** (296 mg, 82%) was isolated by column chromatography (SiO_2, EtOAc/hexane).

3.7.4. Procedure D

7-Chloro-4-[(4-methylphenyl)sulfonyl]quinoline-1-oxide (**3r**) (326 mg, 0.978 mmol) was mixed with PBr_3 (5.0 mL) while cooled with water bath. The mixture was then heated to 40 °C for 10 min, poured into cold water and extracted with DCM (3 x 20 mL). Combined extracts were dried with Na_2SO_4 and the solvent evaporated. The product **4r** (243 mg, 78%) was isolated by column chromatography (SiO_2, EtOAc/hexane).

*3.7.5. 7-Bromoquinoline-4-carbonitrile **(4a)***

Obtained from 10.0 g, 40.12 mmol of **3a**, procedure A; Yield 7.45 g (80%); Brownish crystals, mp: 167–168 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 7.74 (d, $J = 4.4$ Hz, 1H), 7.85 (dd, $J = 8.8$, 1.8 Hz, 1H), 8.07 (d, $J = 8.8$ Hz, 1H), 8.40 (d, $J = 1.8$ Hz, 1H), 9.05 (d, $J = 4.4$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 115.1, 118.8, 124.4, 124.9, 125.6, 126.2, 132.7, 132.8, 148.6, 150.5. MS (EI) *m/z* 234 (99), 232 (100, $[M]^+$), 153 (73), 126 (28). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2$: 231.9636; Found 231.9630.

*3.7.6. 5-Bromoquinoline-4-carbonitrile **(4b)***

Obtained from 30.0 g, 120.5 mmol of **3b**, procedure A at 80–90 °C; Yield 18.2 g (65%); Brownish crystals, mp: 148–149 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 7.66 (dd, $J = 8.5$, 7.6 Hz, 1H), 7.89 (d, $J = 4.4$ Hz. 1H), 7.99 (dd, $J = 7.6$, 1.1 Hz, 1H), 8.18 (dd, $J = 8.5$, 1.1 Hz, 1H), 9.01 (d, $J = 4.4$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 117.1, 118.70, 118.74, 124.1, 129.9, 130.94, 130.95, 134.93, 149.6, 149.8. MS (EI) *m/z* 234 (99), 232 (100, $[M]^+$), 153 (97), 126 (53). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2$: 231.9636; Found 231.9647.

*3.7.7. 6-Bromoquinoline-4-carbonitrile [24] **(4c)***

Obtained from 30.0 g, 120.5 mmol of **3c**, procedure A at 100 °C; Yield 27.0 g (96%); Brownish crystals, mp: 171–173 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 7.75 (d, $J = 4.4$ Hz, 1H), 7.93 (dd, $J = 9.0$, 2.1 Hz, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 8.36 (d, $J = 2.1$ Hz, 1H), 9.05 (d, $J = 4.4$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 115.0, 117.7, 123.9, 125.5, 126.8, 127.2, 132.0, 146.8, 149.7. MS (EI) *m/z* 234 (99), 232 (100, $[M]^+$), 153 (72), 126 (46). HRMS (EI) *m/z* Calcd for $C_{10}H_5^{79}BrN_2$: 231.9636; Found 231.9642.

*3.7.9. 5-Fluoroquinoline-4-carbonitrile **(4f)***

Obtained from 16.0 g, 85.1 mmol of **3f**, procedure A at 100 °C; Yield 14.1 g (96%); Orange crystals, mp: 165–166 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 7.24 ($J = 10.1$, 8.4 Hz, 1H), 7.77–7.83 (m, 2H), 8.04 (d, $J = 8.4$ Hz, 1H), 9.06 ($J = 4.3$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 113.3 (d, $J_{FC} = 1.5$ Hz), 114.1 (d, $J_{FC} = 12.1$ Hz) 116.30 (d, $J_{FC} = 12.1$ Hz), 116.32, 126.6 (d, $J_{FC} = 4.6$ Hz), 127.0, 130.7 (d, $J_{FC} = 8.7$ Hz), 149.2, 150.2 (d, $J_{FC} = 1.1$ Hz), 156.6 (d, $J_{FC} = 258.9$ Hz). MS (EI) *m/z* 172 (100, $[M]^+$), 145 (30). HRMS (EI) *m/z* Calcd for $C_{10}H_5FN_2$: 172.0437; Found 172.0438.

*3.7.10. 6-Fluoroquinoline-4-carbonitrile **(4g)***

Obtained from 22.5 g, 120 mmol of **3g**, procedure A at 100 °C; Yield 20.1 g (97%); Beige solid, mp: 126–128 °C (dec). ^1H NMR (500 MHz. $CDCl_3$): δ 7.64 (td, $J = 9.3$, 2.7 Hz, 1H), 7.76 (d, $J = 4.4$ Hz, 1H), 7.83 (dd, $J = 8.4$, 2.7 Hz, 1H), 8.23 (dd, $J = 9.3$, 5.2 Hz, 1H), 9.01 (d, $J = 4.4$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 108.7 (d, $J_{FC} = 24.3$ Hz), 115.1, 118.2 (d, $J_{FC} = 5.8$ Hz), 121.7 (d, $J_{FC} = 25.4$ Hz), 125.4, 126.9 (d, $J_{FC} = 10.4$ Hz), 133.2 (d, $J_{FC} = 9.8$ Hz), 145.3, 148.7 (d, $J_{FC} = 2.9$ Hz), 162.0 (d, $J_{FC} = 253.7$ Hz). MS (EI) *m/z* 172 (100, $[M]^+$), 145 (35). HRMS (EI) *m/z* Calcd for $C_{10}H_5FN_2$: 172.0437; Found 172.0439.

*3.7.11. Methyl 6-chloroquinoline-4-carboxylate [25] **(4j)***

Obtained from 59.0 mg, 0.248 mmol of **3j**, procedure B, 24 h; Yield 40.0 mg (73%); Colorless crystals, mp: 79–81 °C (lit [25]. mp: 79.5 °C). ^1H NMR (500 MHz. $CDCl_3$): δ 4.06 (s, 3H), 7.72 (dd, $J = 9.0$, 2.2 Hz, 1H), 7.96 (d, $J = 4.3$ Hz, 1H), 8.11 (d, $J = 9.0$ Hz, 1H), 8.87 (d, $J = 2.2$ Hz, 1H), 9.01 (d, $J = 4.3$ Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 52.9, 123.1, 124.7, 125.7, 130.8, 131.6, 133.7, 134.5, 147.6, 149.9, 166.1. MS (EI) *m/z* 223 (40), 221 (100, $[M]^+$), 190 (70), 162 (71). HRMS (EI) *m/z* Calcd for $C_{11}H_8^{35}ClNO_2$: 221.0244; Found 221.0243.

*3.7.12. Methyl 6-fluoroquinoline-4-carboxylate **(4o)***

Obtained from 125 mg, 0.56 mmol of **3o**, procedure B, 7 days; Yield 73.0 mg (64%); Pale beige crystals, mp: 59–60 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 4.03 (s, 3H), 7.53 (ddd, $J = 9.3$, 7.8, 2.9 Hz, 1H), 7.96 (d, $J =$

4.3 Hz, 1H), 8.16 (dd, J = 9.3, 5.6 Hz, 1H), 8.52 (dd, J = 10.8, 2.9 Hz, 1H), 8.97 (d, J = 4.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 52.8, 109.6 (d, J_{FC} = 24.8 Hz), 120.1 (d, J_{FC} = 26.0 Hz), 123.1, 126.1 (d, J_{FC} = 11.0 Hz), 132.5 (d, J_{FC} = 9.2 Hz), 133.8 (d, J_{FC} = 6.4 Hz), 146.4 (d, J_{FC} = 1.2 Hz), 148.9 (d, J_{FC} = 2.9 Hz), 161.6 (d, J_{FC} = 249.1 Hz), 166.2. MS (EI) *m/z* 205 (100, $[M]^+$), 174 (80), 146 (90), 119 (27), 99 (18). HRMS (EI) *m/z* Calcd for $C_{11}H_8FNO_2$: 205.0539; Found 205.0546.

*3.7.13. 6-Bromo-4-[(4-methylphenyl)sulfonyl]quinoline [26] (**4p**)*

Obtained from 378 mg, 1.0 mmol of **3p**, procedure C. Yield 296 mg (82%); Colorless crystals, mp: 186–188 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 2.40 (s, 3H), 7.32,7.35 (m, 2H), 7.83 (dd, J = 9.0, 2.1 Hz, 1H), 7.86–7.89 (m, 2H), 8.03 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 4.4 Hz, 1H), 8.85 (d, J = 2.1 Hz, 1H), 9.08 (d, J = 4.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 21.6, 121.7, 123.2, 123.4, 126.7, 128.1, 130.2, 132.1, 134.0, 136.8, 144.4, 145.4, 148.0, 150.0. MS (EI) *m/z* 363 (25), 361 (24, $[M]^+$), 299 (17), 297 (18), 218 (100). HRMS (EI) *m/z* Calcd for $C_{16}H_{12}^{79}BrNO_2S$: 360.9772; Found 360.9781.

*3.7.14. 7-Chloro-4-[(4-methylphenyl)sulfonyl]quinoline, [26,27](**4r**)*

Obtained from 326 mg, 0.978 mmol of **3r**, procedure C. Yield 43 mg (78%); Colorless solid, mp: 155–157 °C. ^1H NMR (500 MHz. $CDCl_3$): δ 2.40 (s. 3H), 7.31–7.34 (m, 2H), 7.60 (dd, J = 9.2, 2.1 Hz, 1H), 7.85–7.88 (m, 2H), 8.10 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.64 (d, J = 9.2 Hz, 1H), 9.10 (d, J = 4.4 Hz. 1H). $^{13}C\{^1H\}$ NMR (125 MHz. $CDCl_3$): δ 21.6, 120.5, 121.0, 125.6, 128.0, 129.4, 129.7, 130.1, 136.5, 136.9, 145.4, 145.5, 149.9, 150.8. MS (EI) *m/z* 319 (34), 317 (85, $[M]^+$), 248 (27), 218 (100), 139 (58). HRMS (EI) *m/z* Calcd for $C_{16}H_{12}^{35}ClNO_2S$ 317.0277; Found: 317.0278.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2023.133632.

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Supplementary Information

Comprehensive approach to the multigram, heavy-metal-free synthesis of 4-EWG-substituted quinoline derivatives

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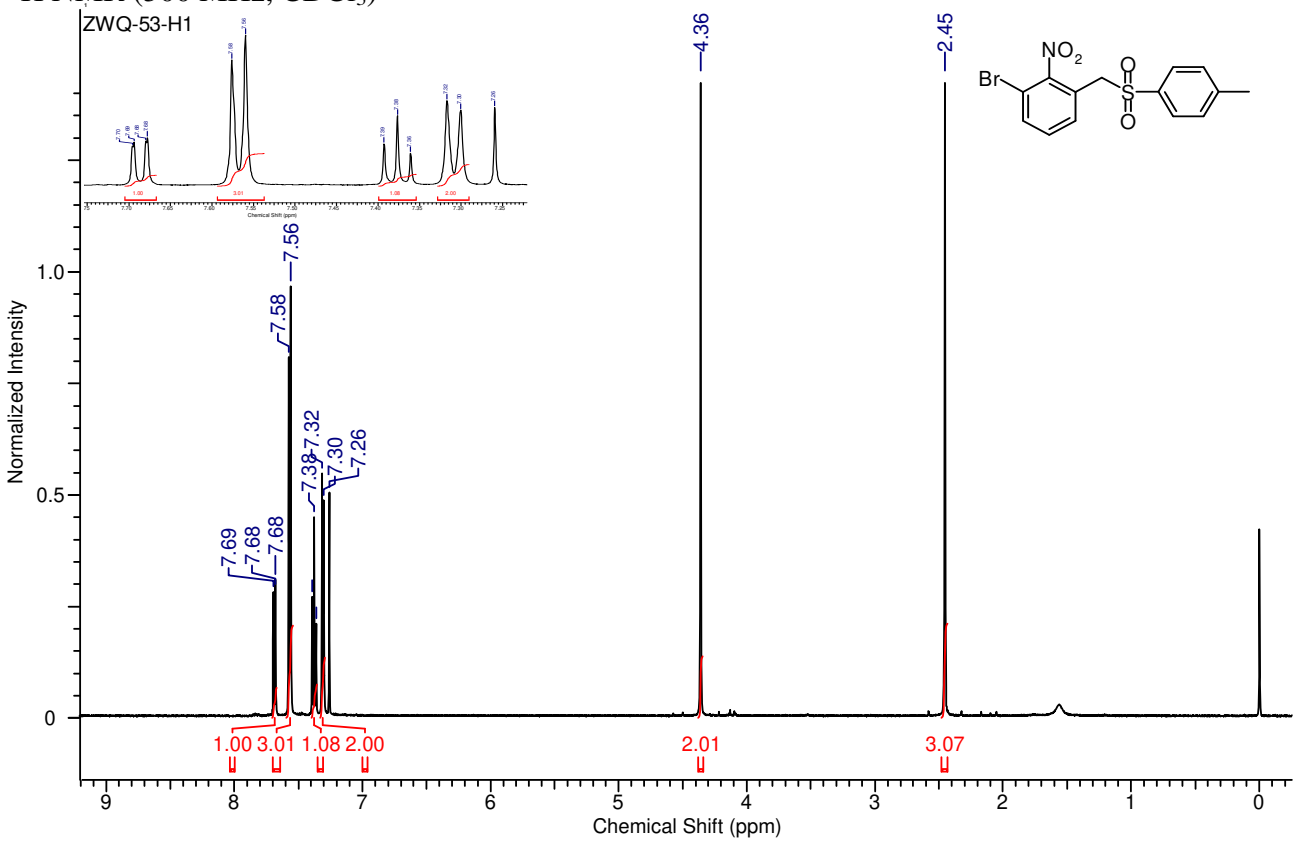
E-mail: zbigniew.wrobel@icho.edu.pl.

CONTENTS:

1q

^{1}H NMR (500 MHz, $CDCl_3$)



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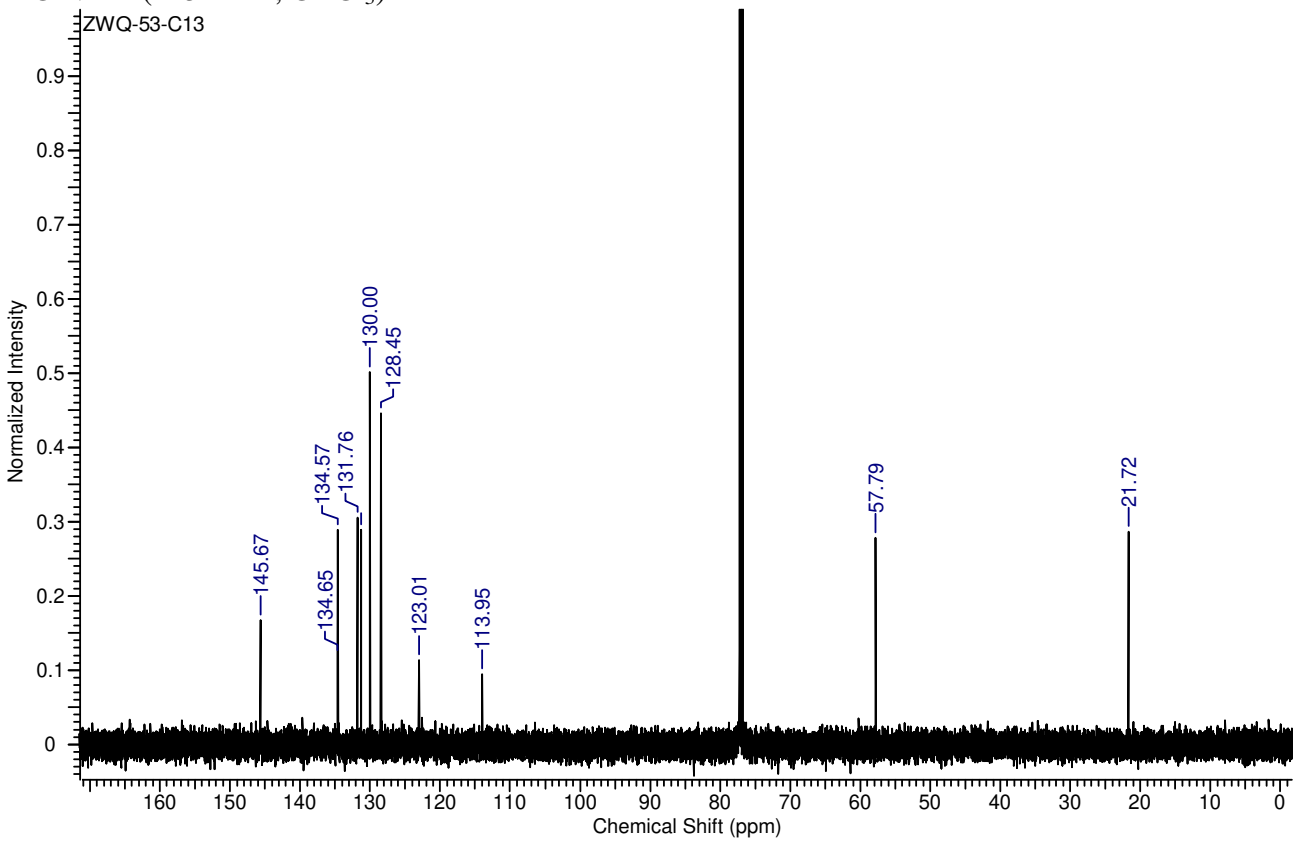

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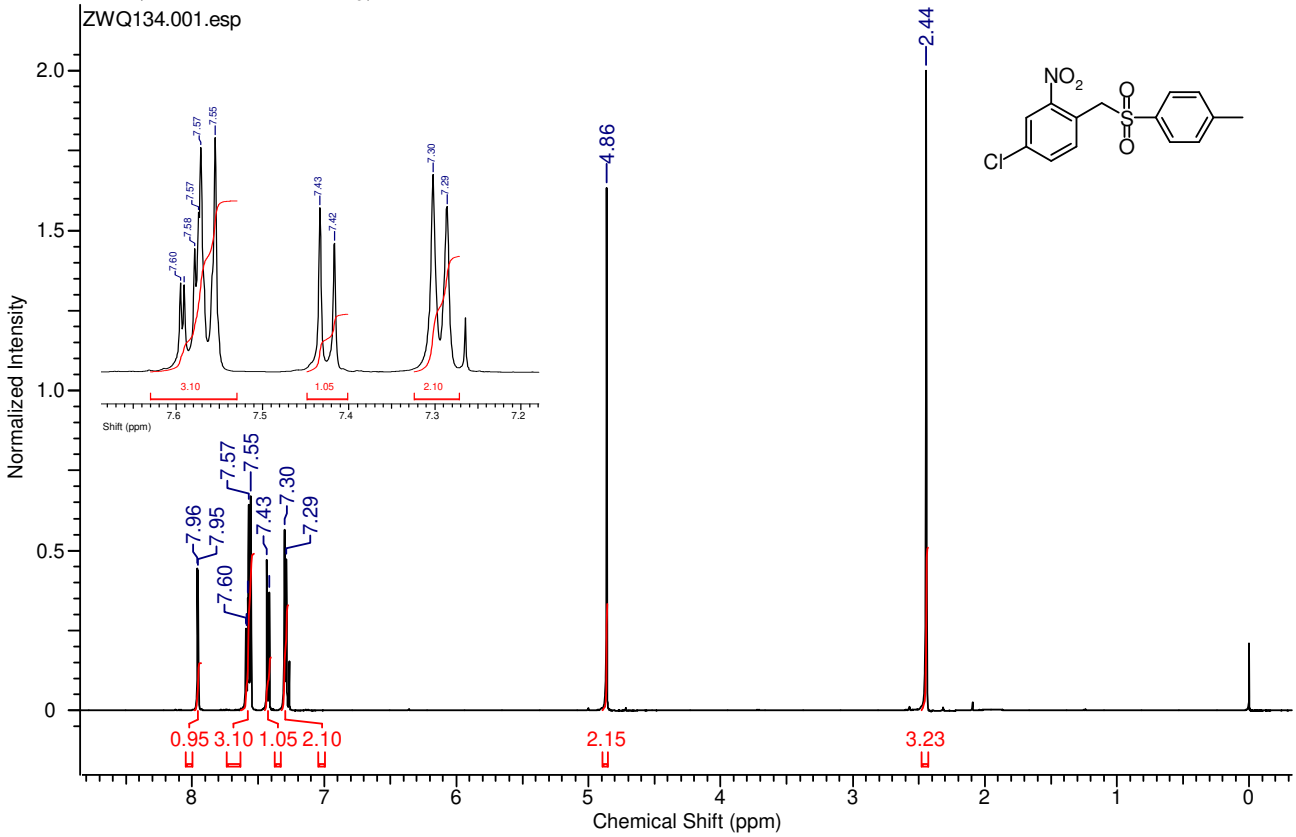

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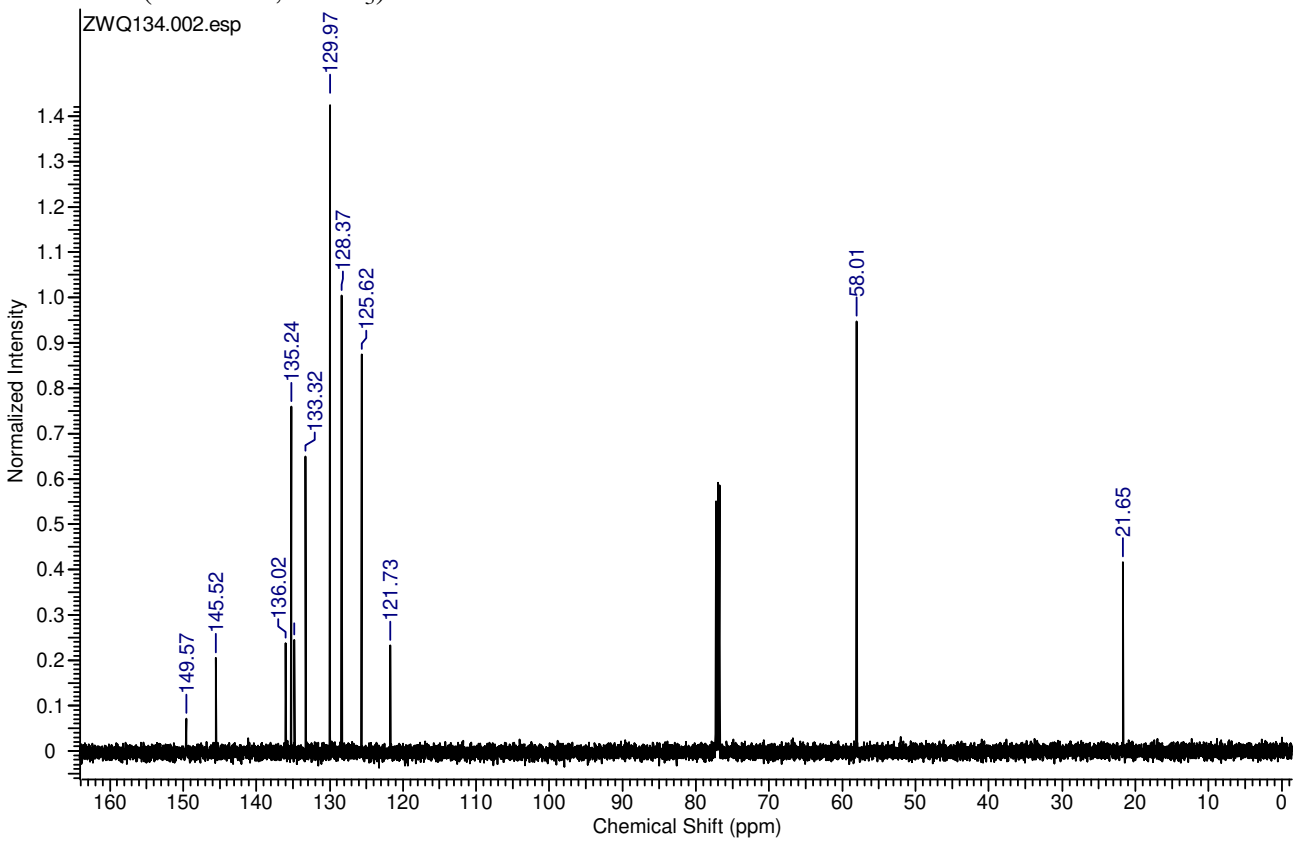

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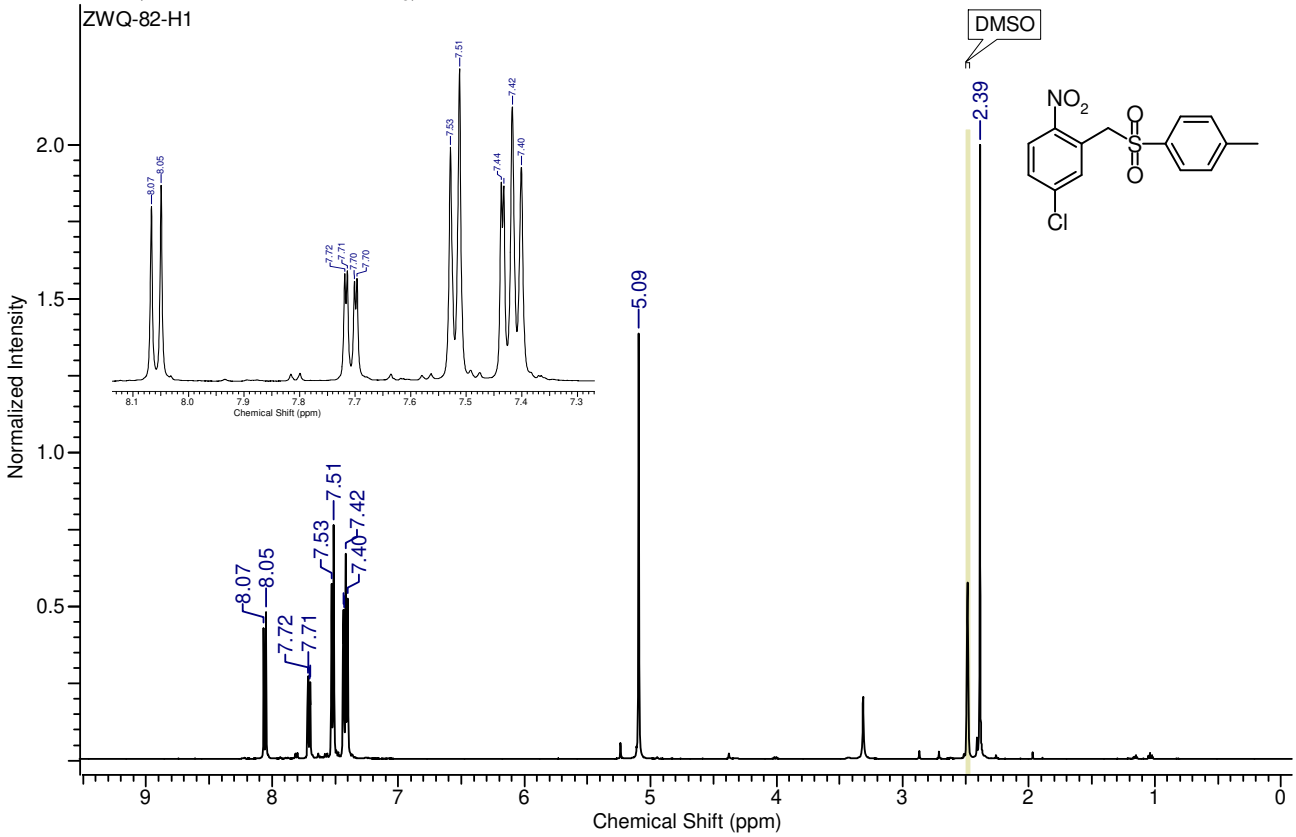

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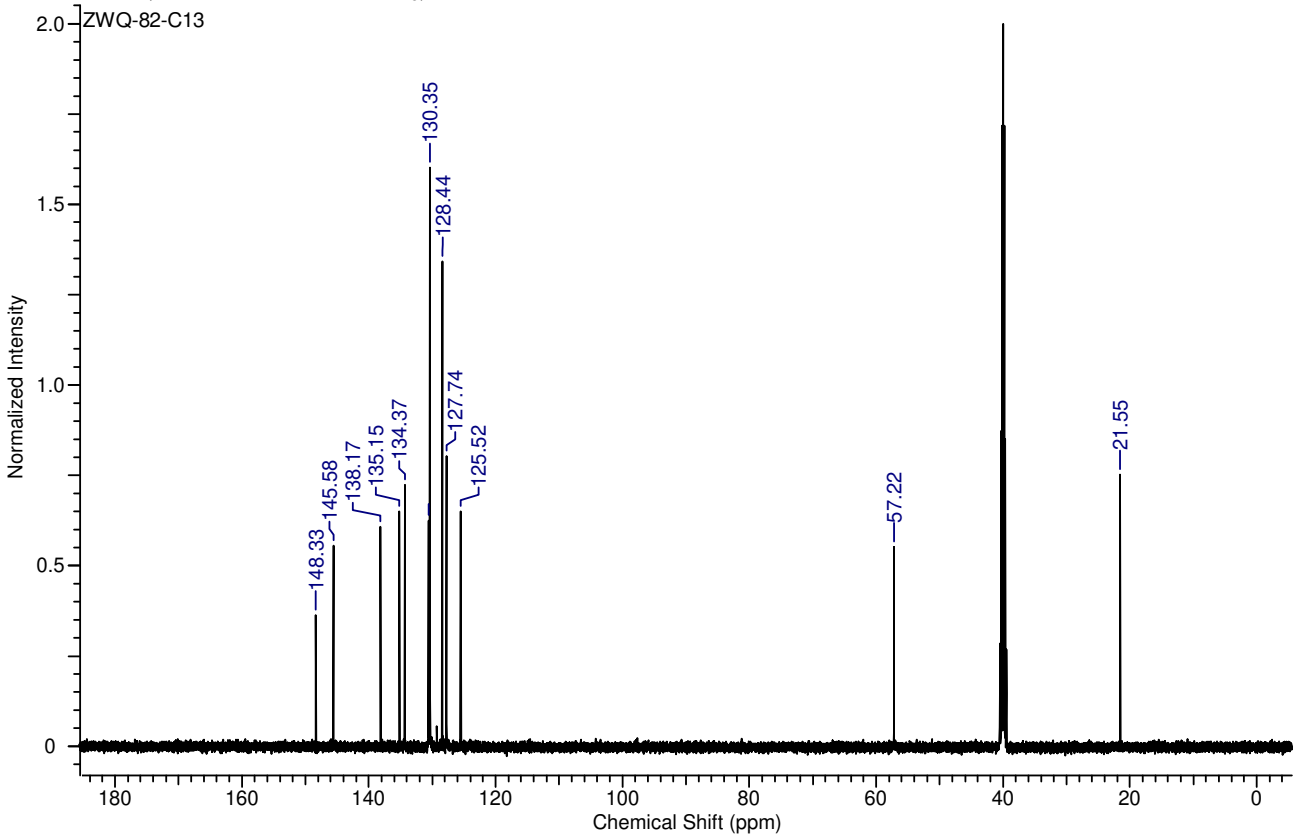

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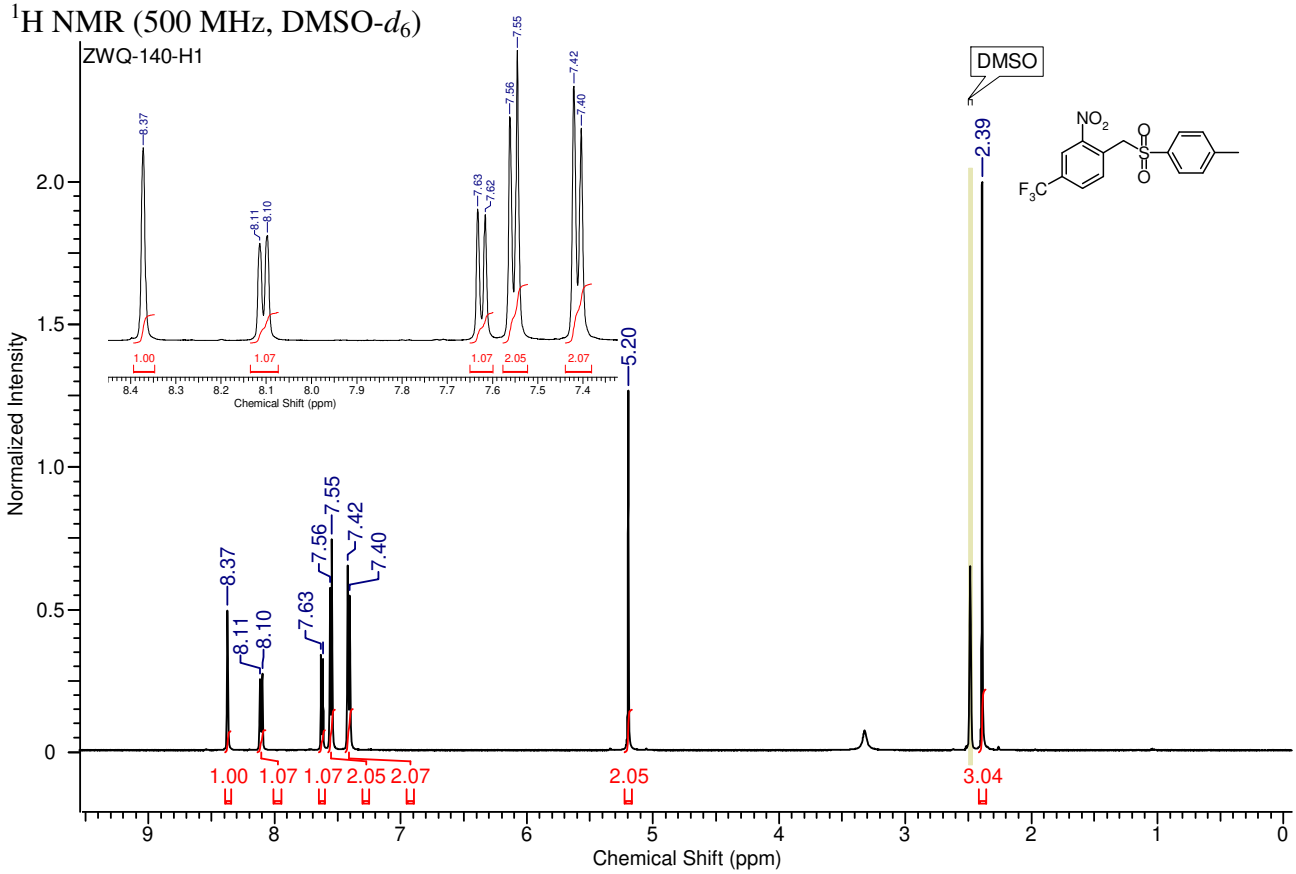

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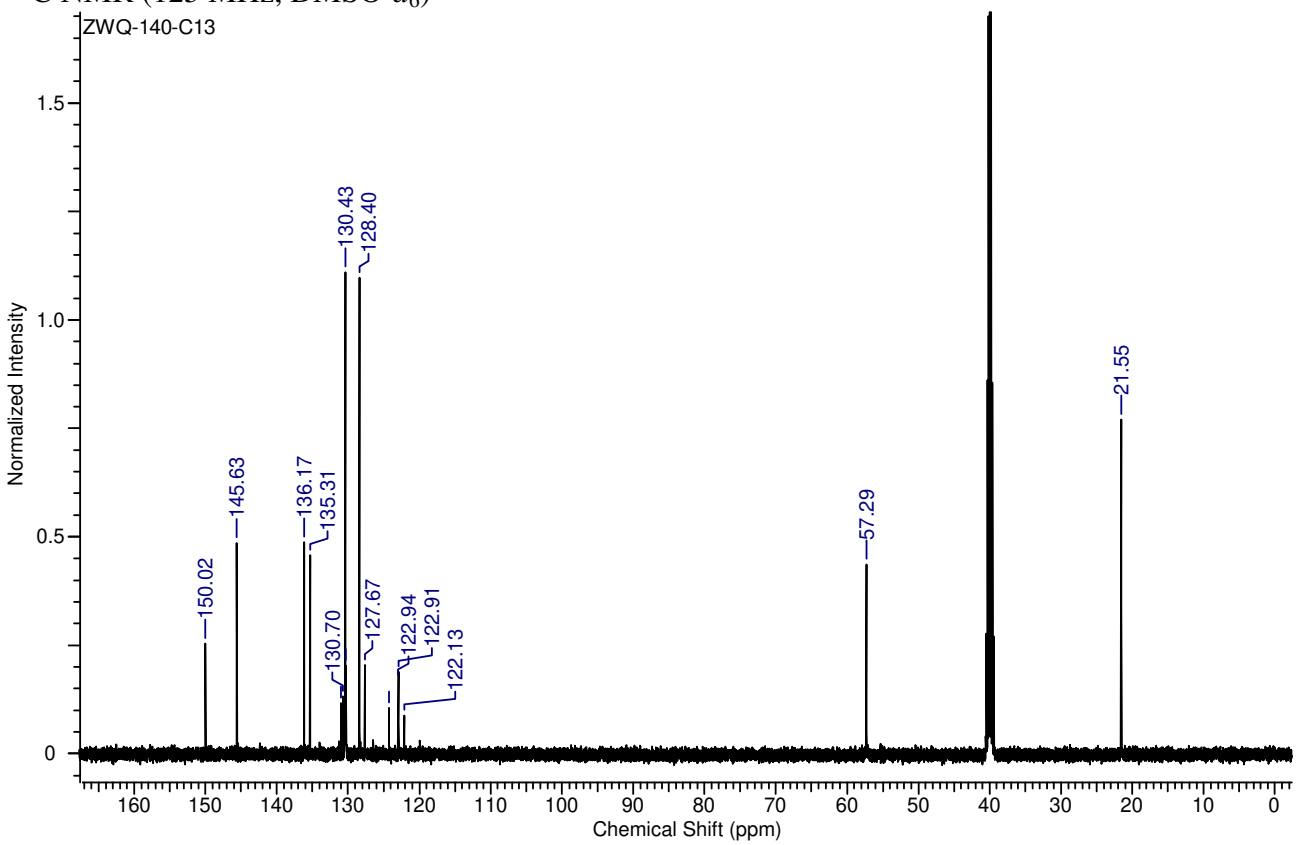

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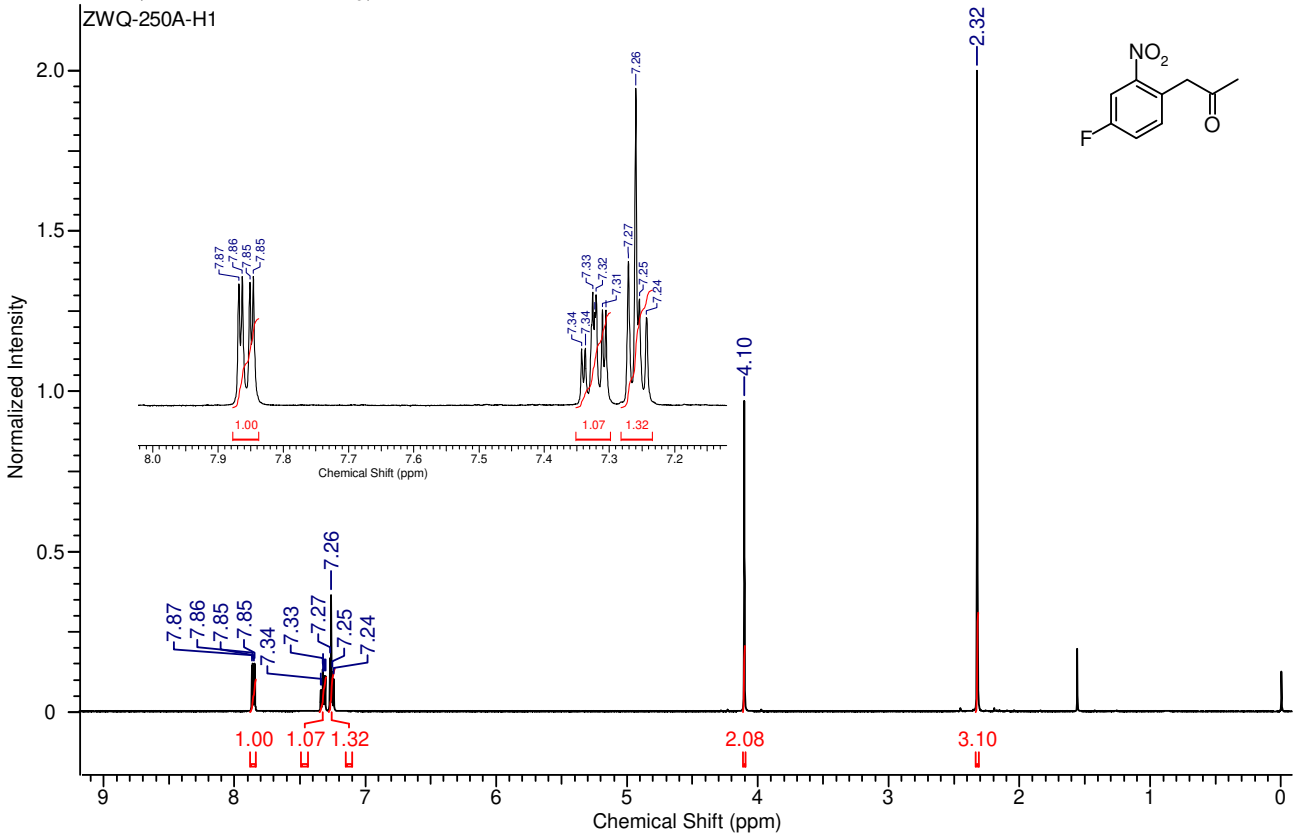

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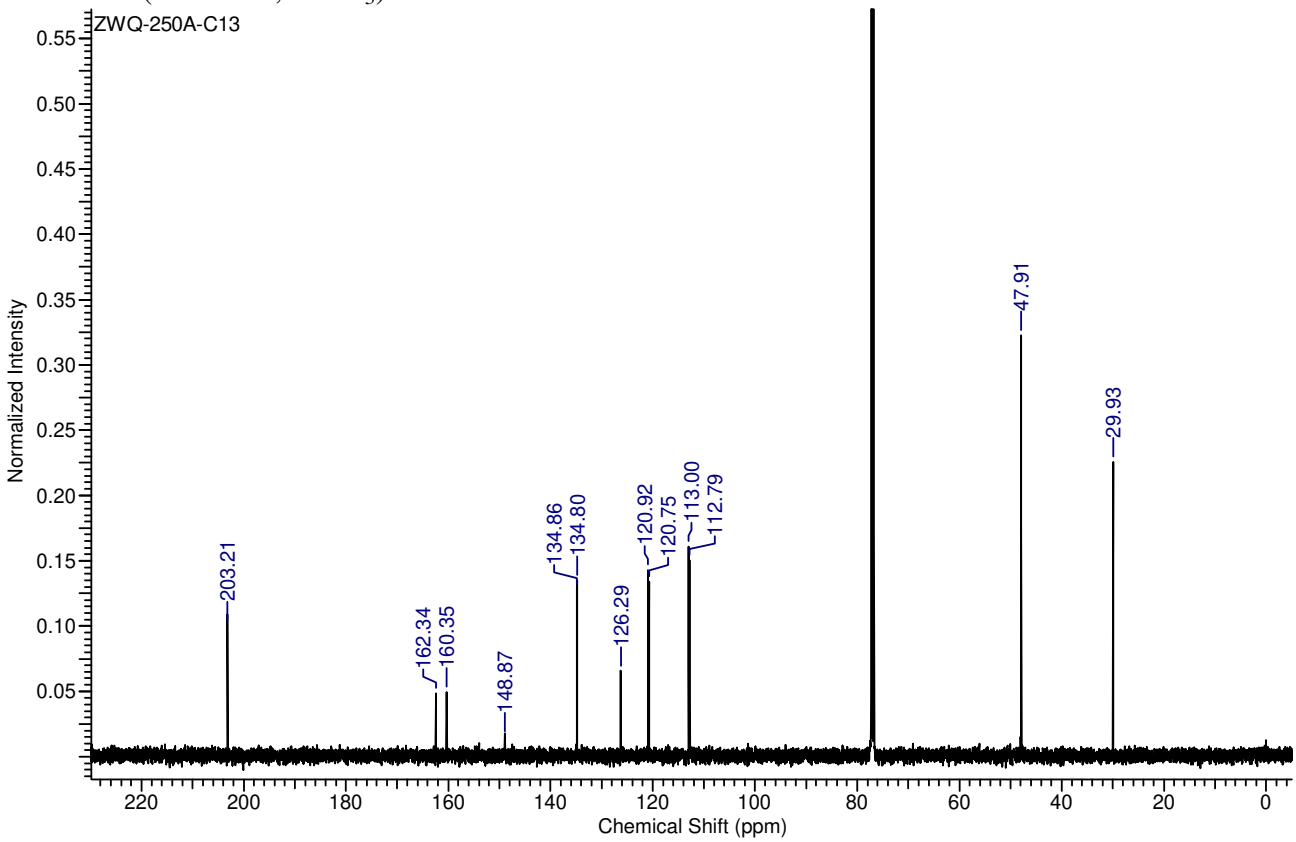

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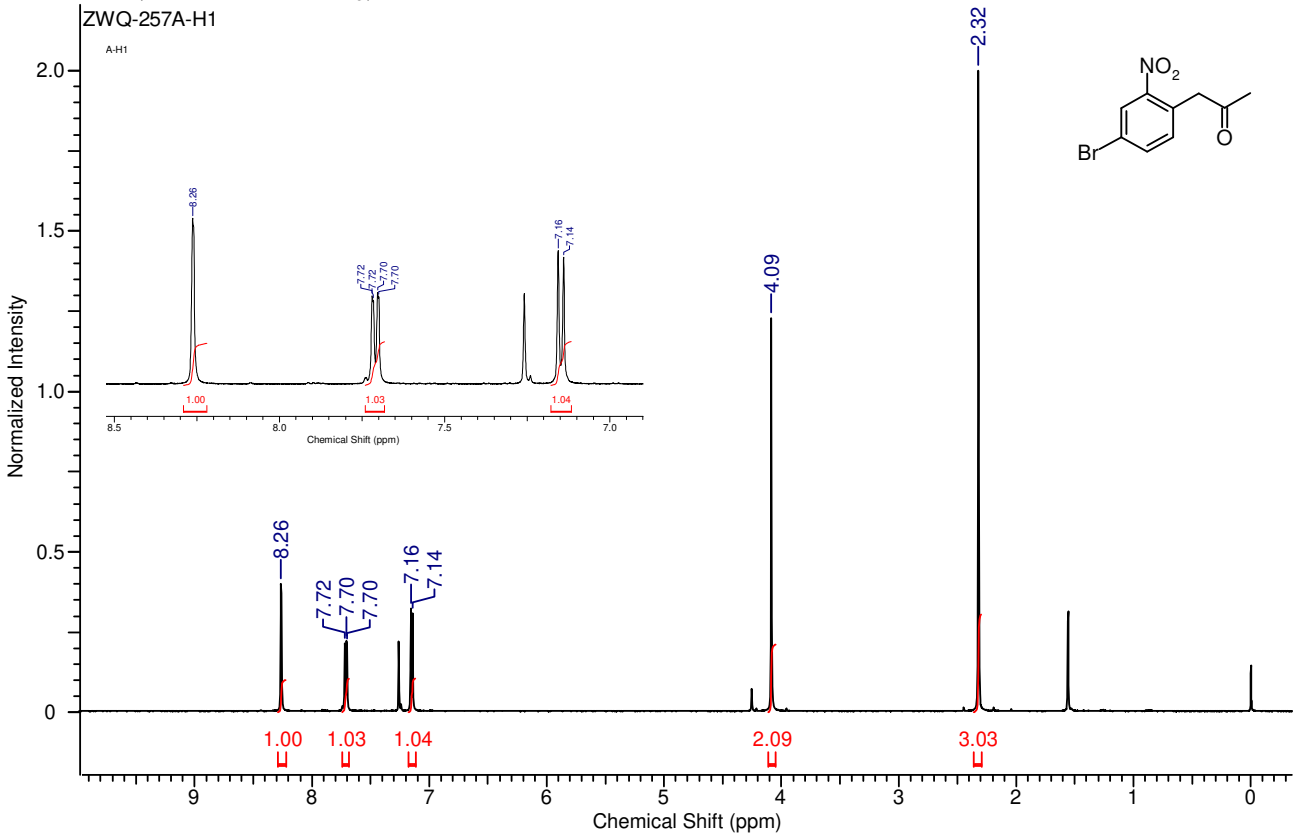

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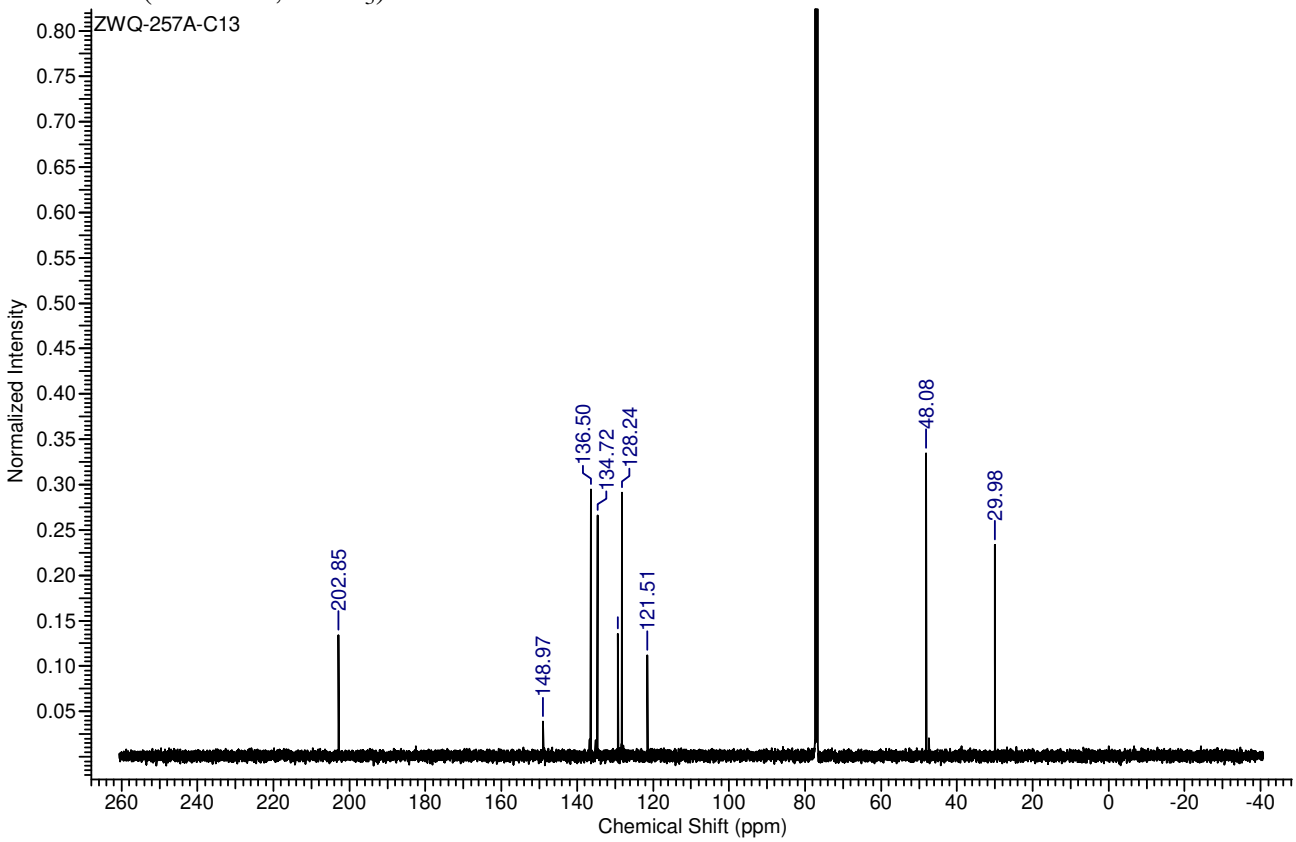

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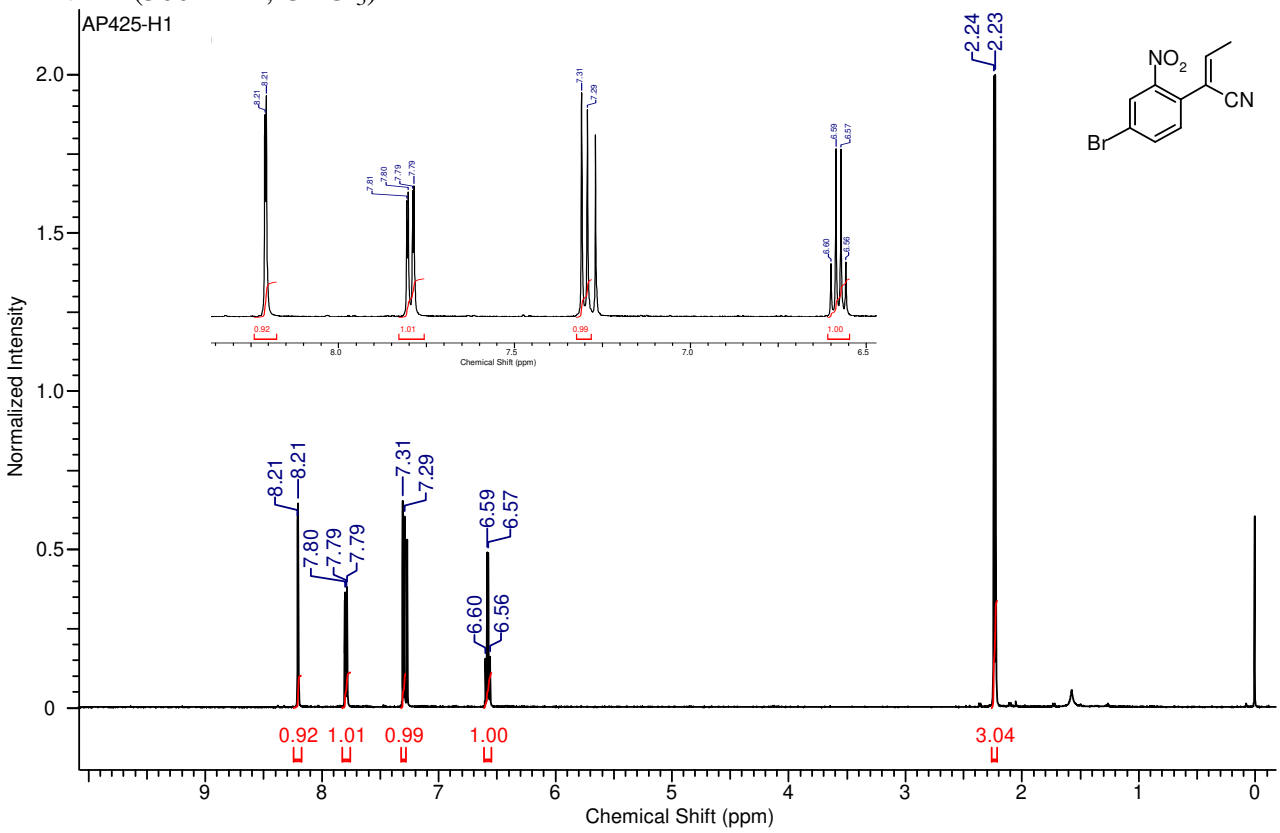

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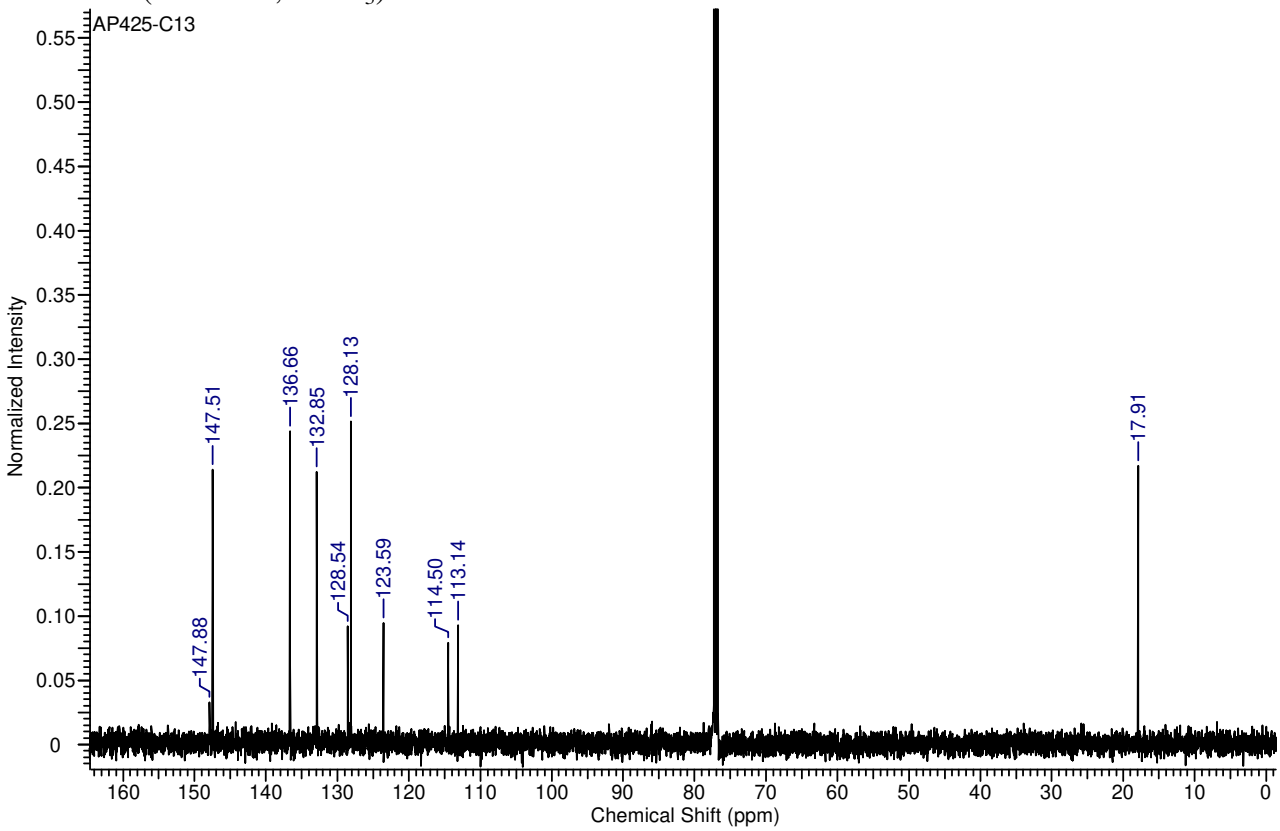

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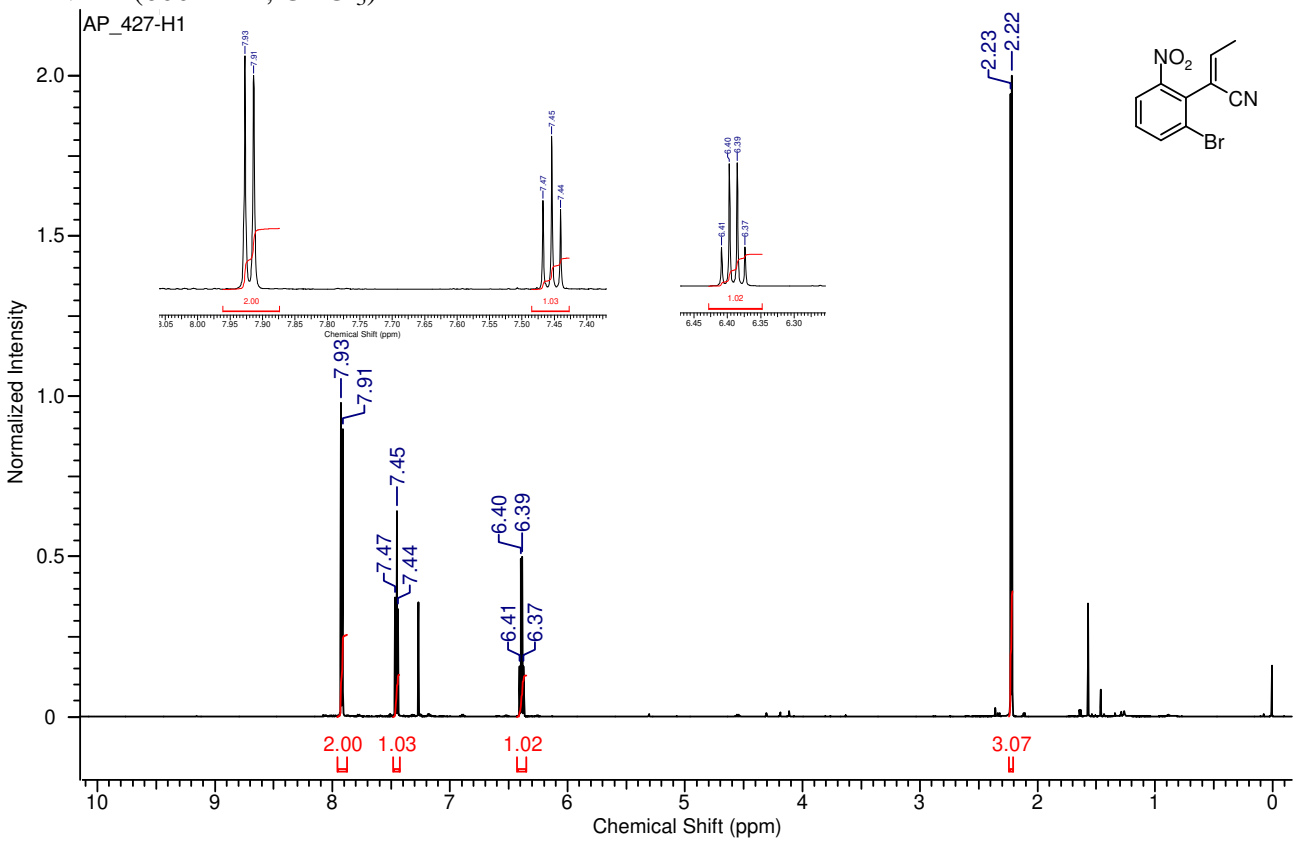

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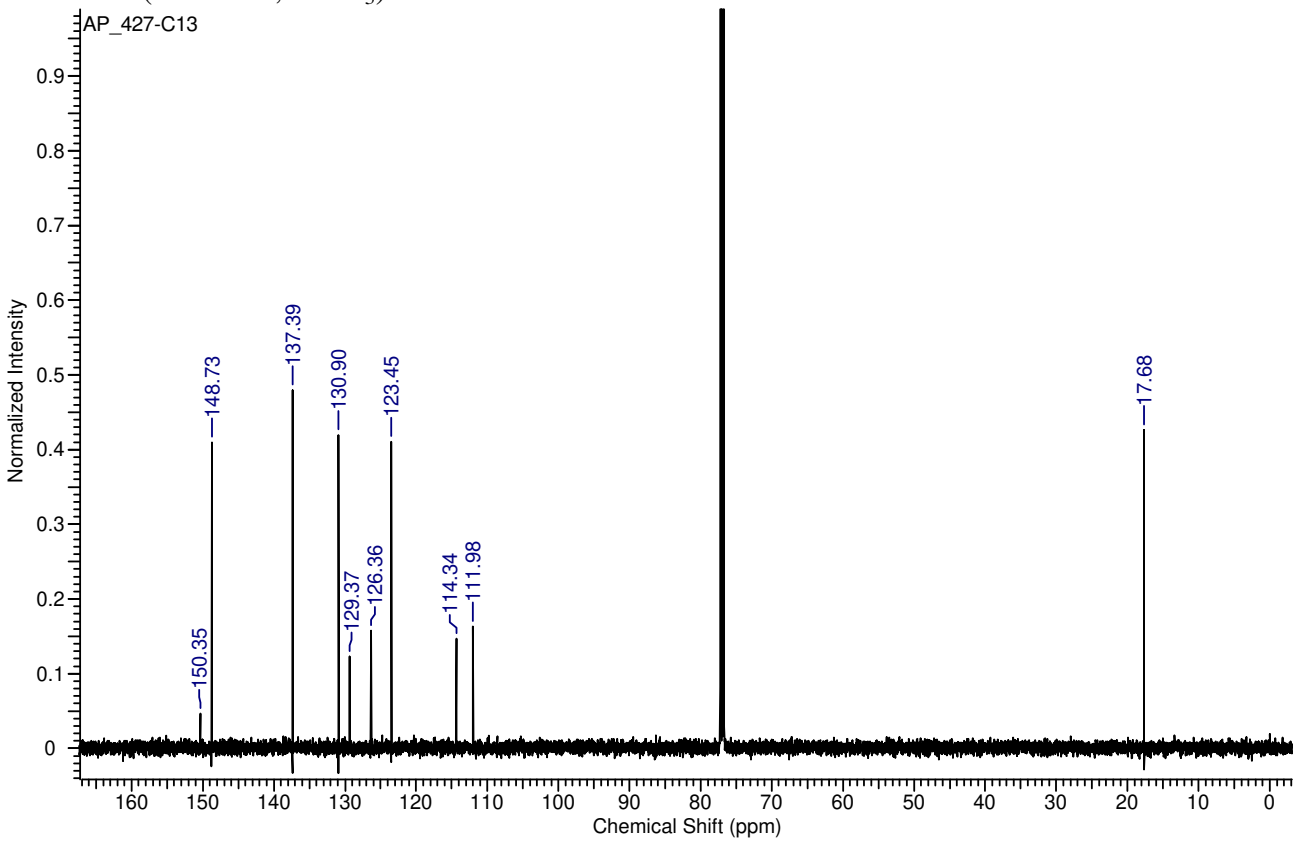

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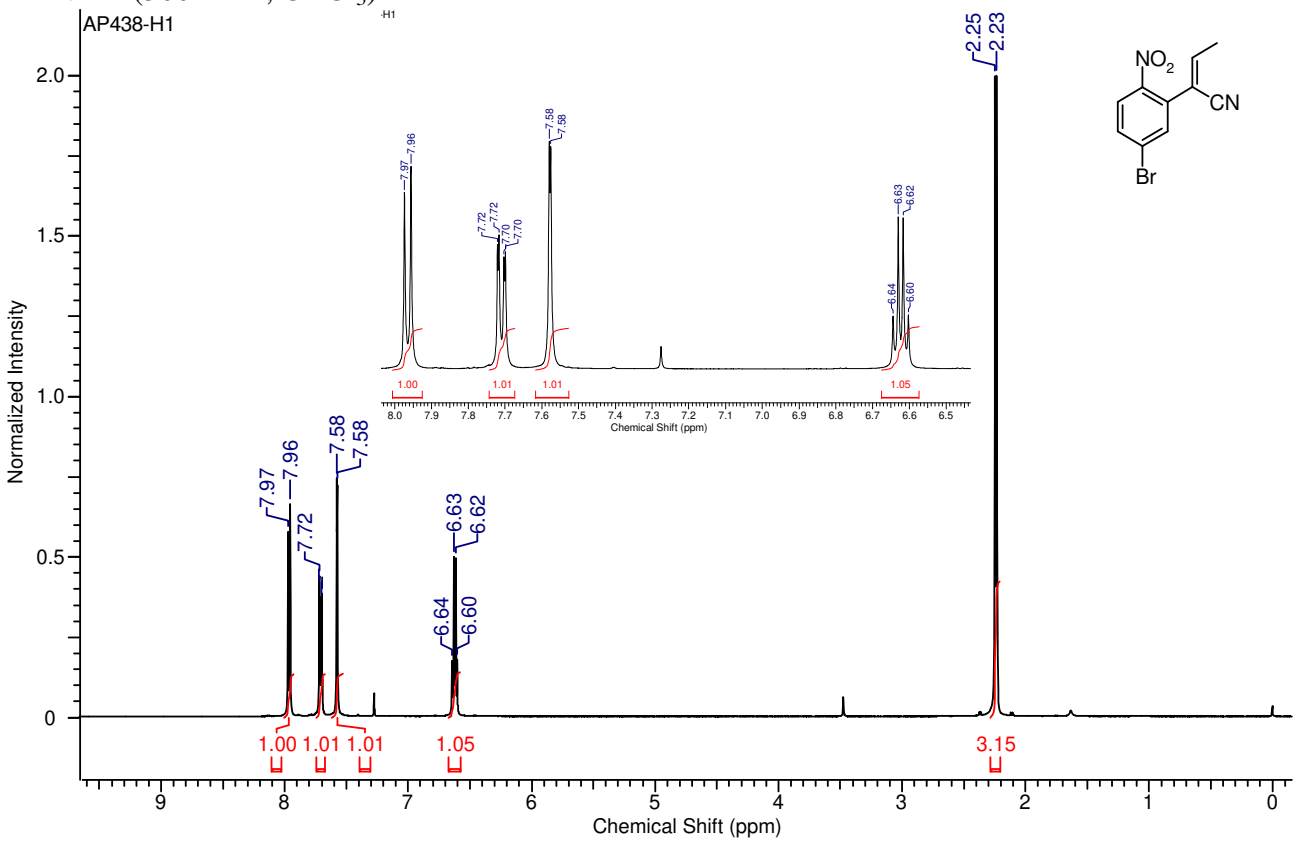

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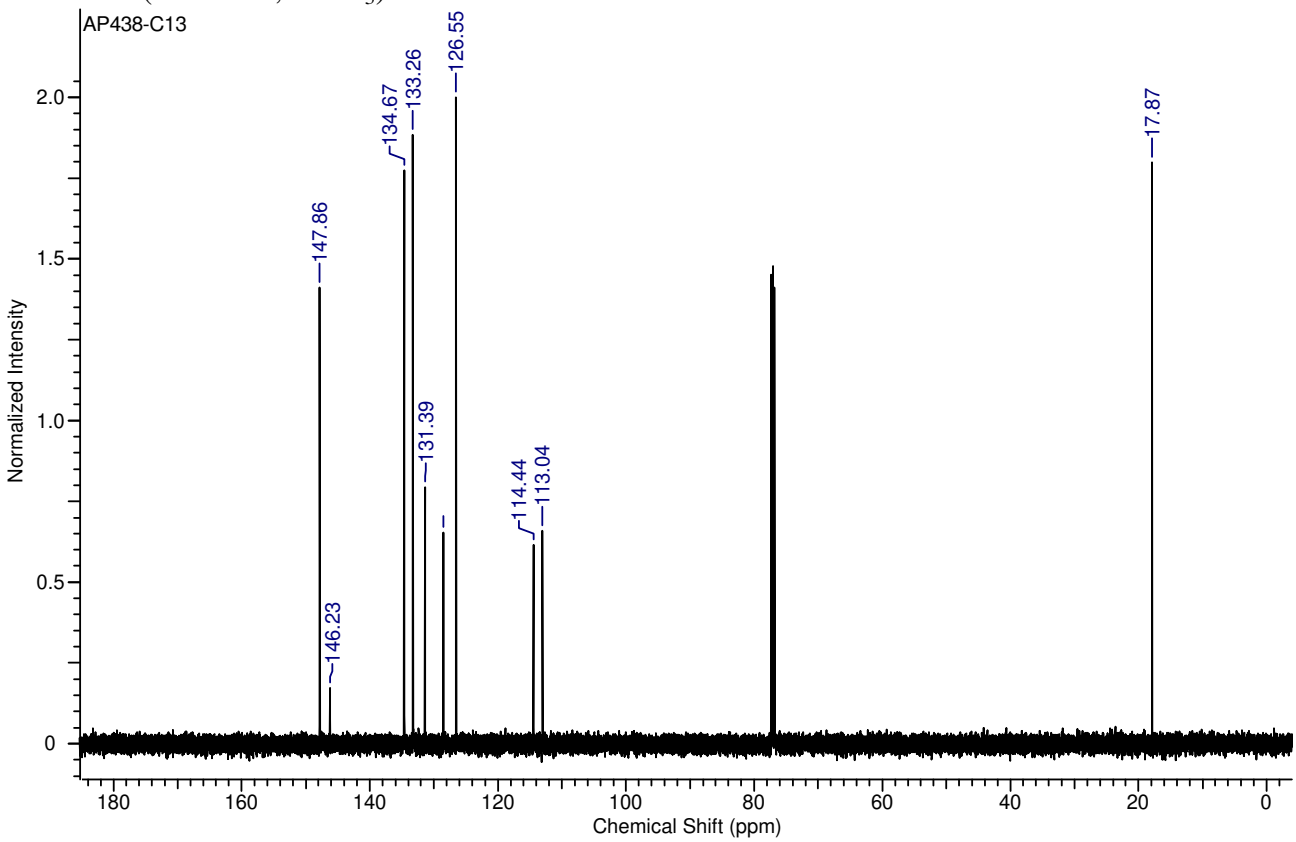

2d

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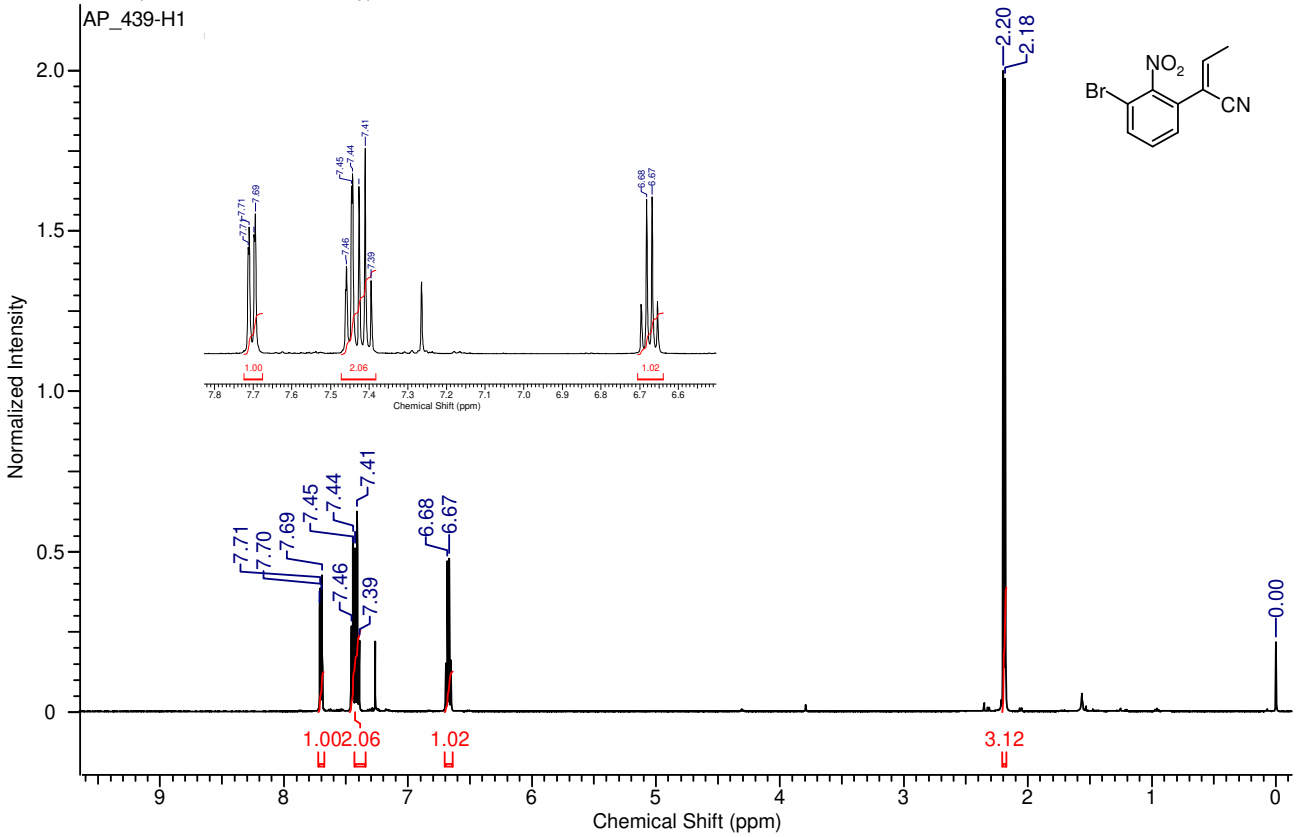

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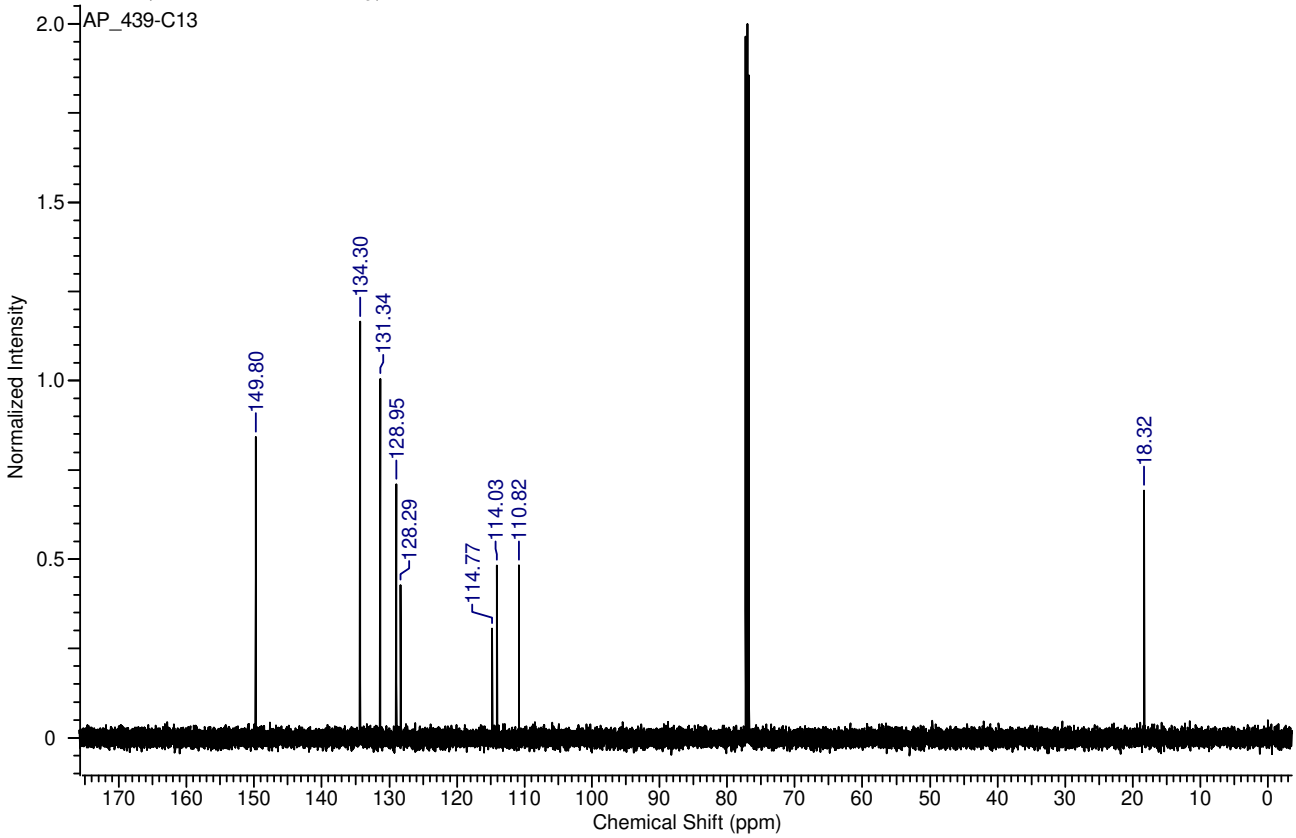

2e

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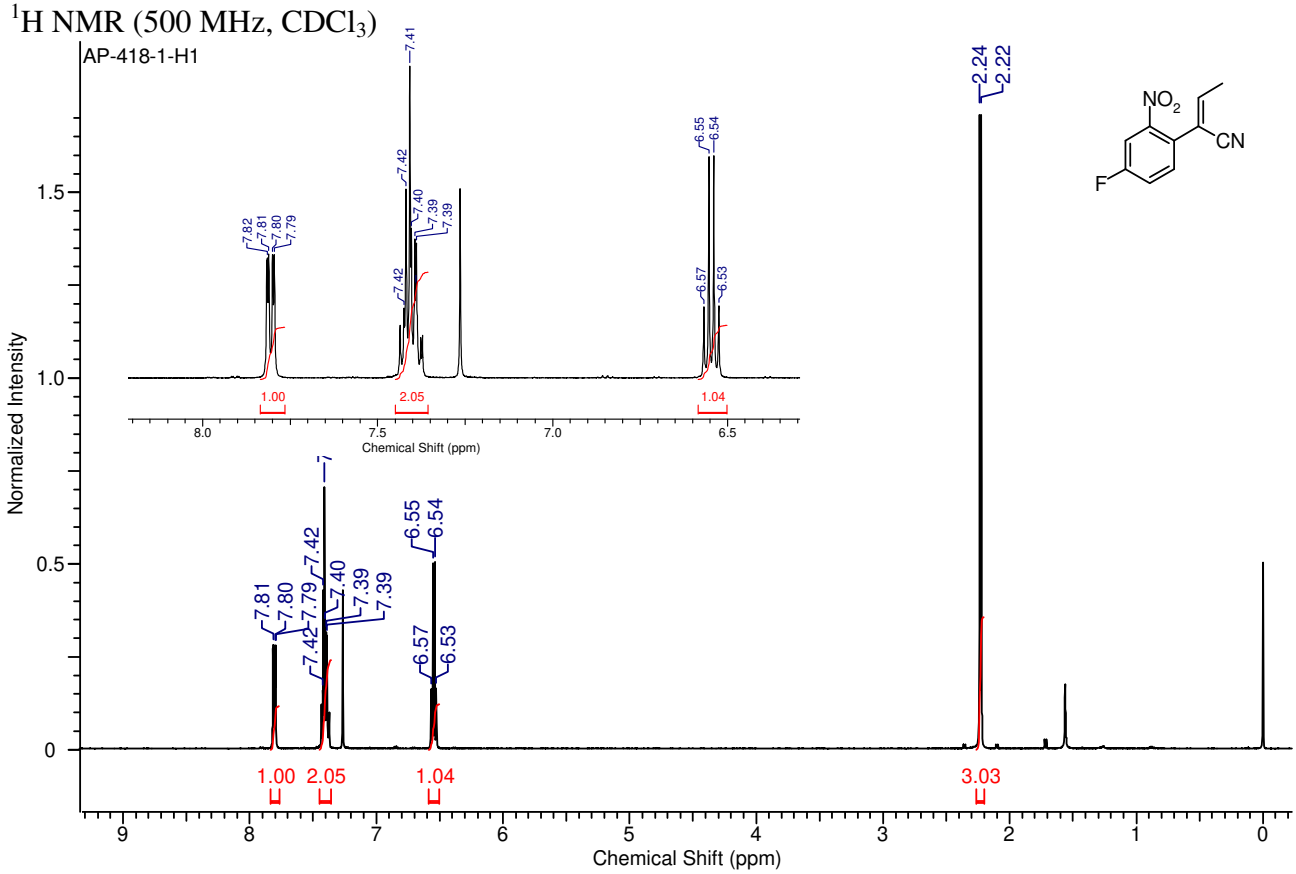

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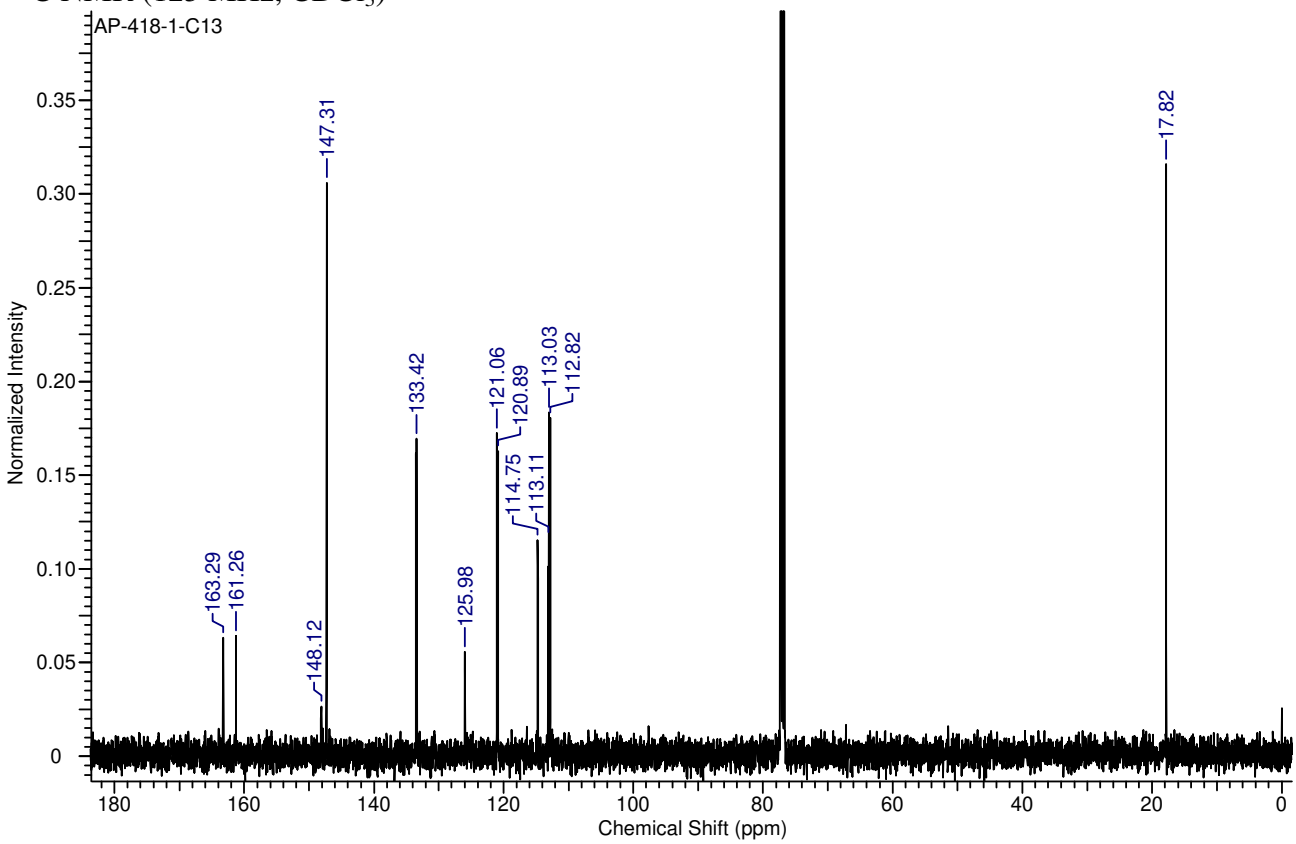

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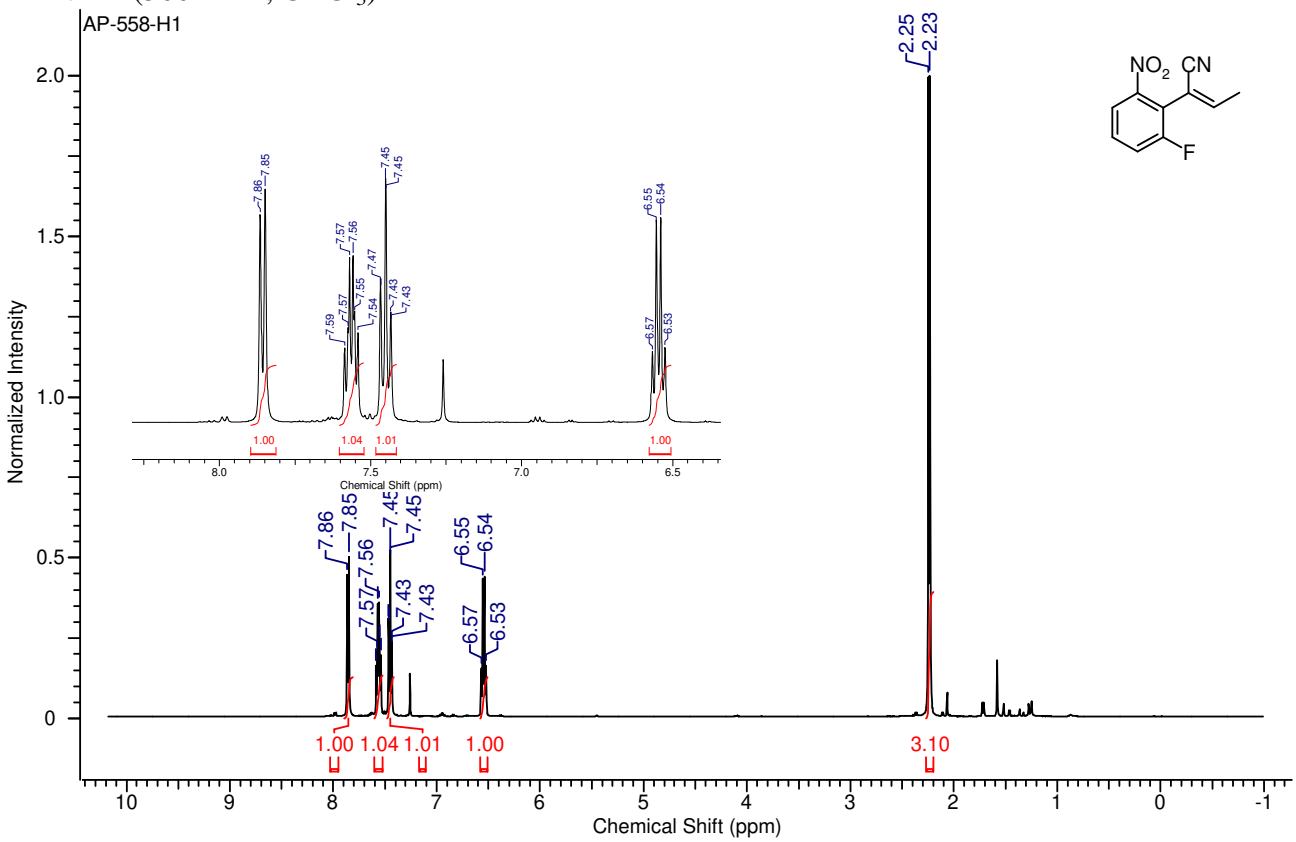

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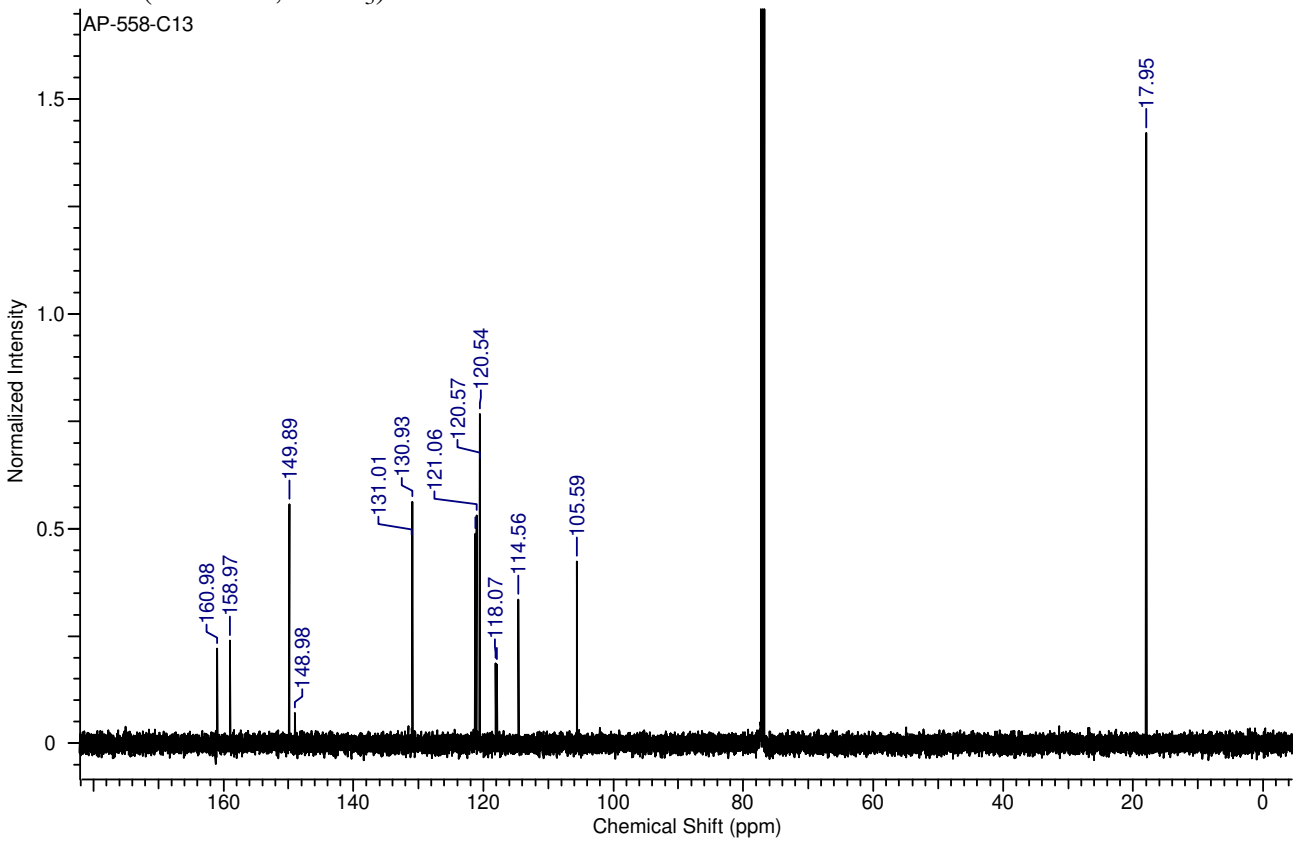

2g

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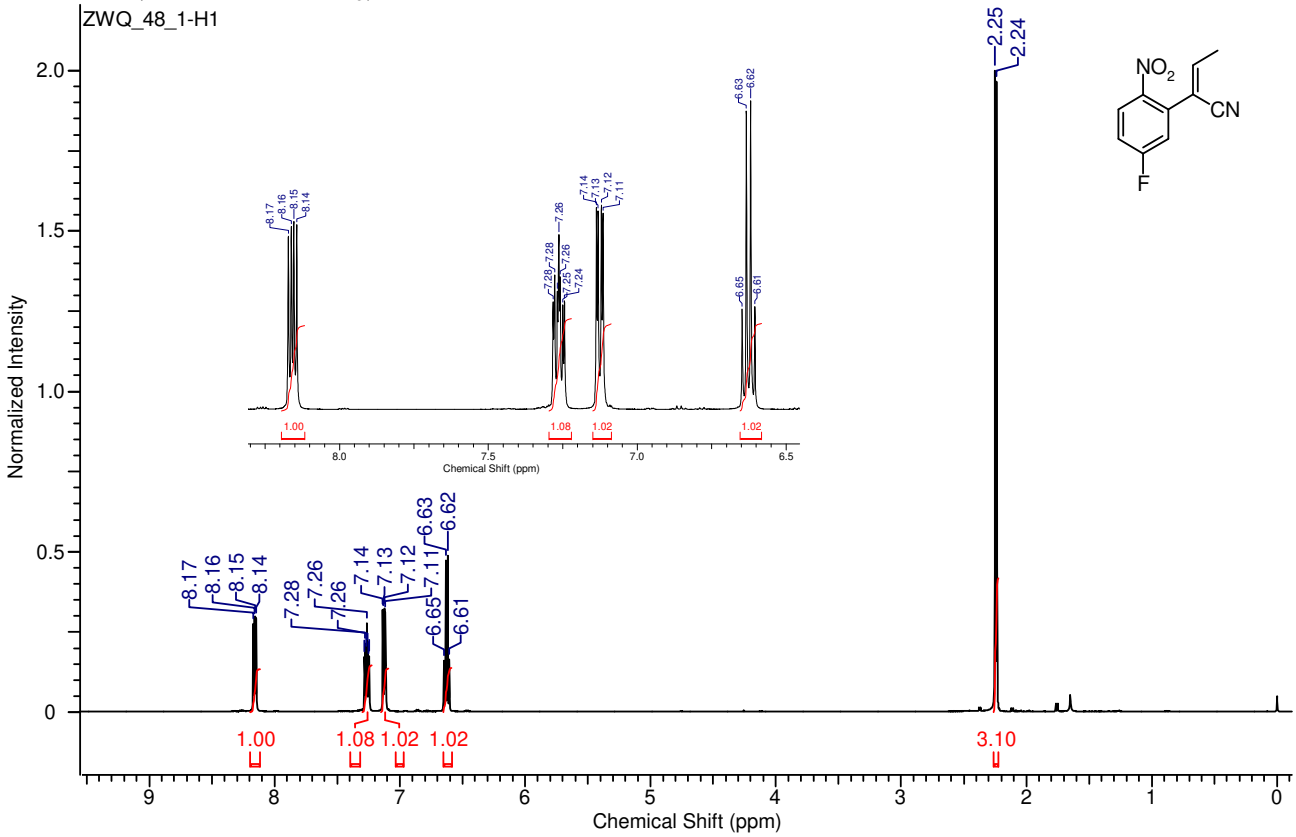

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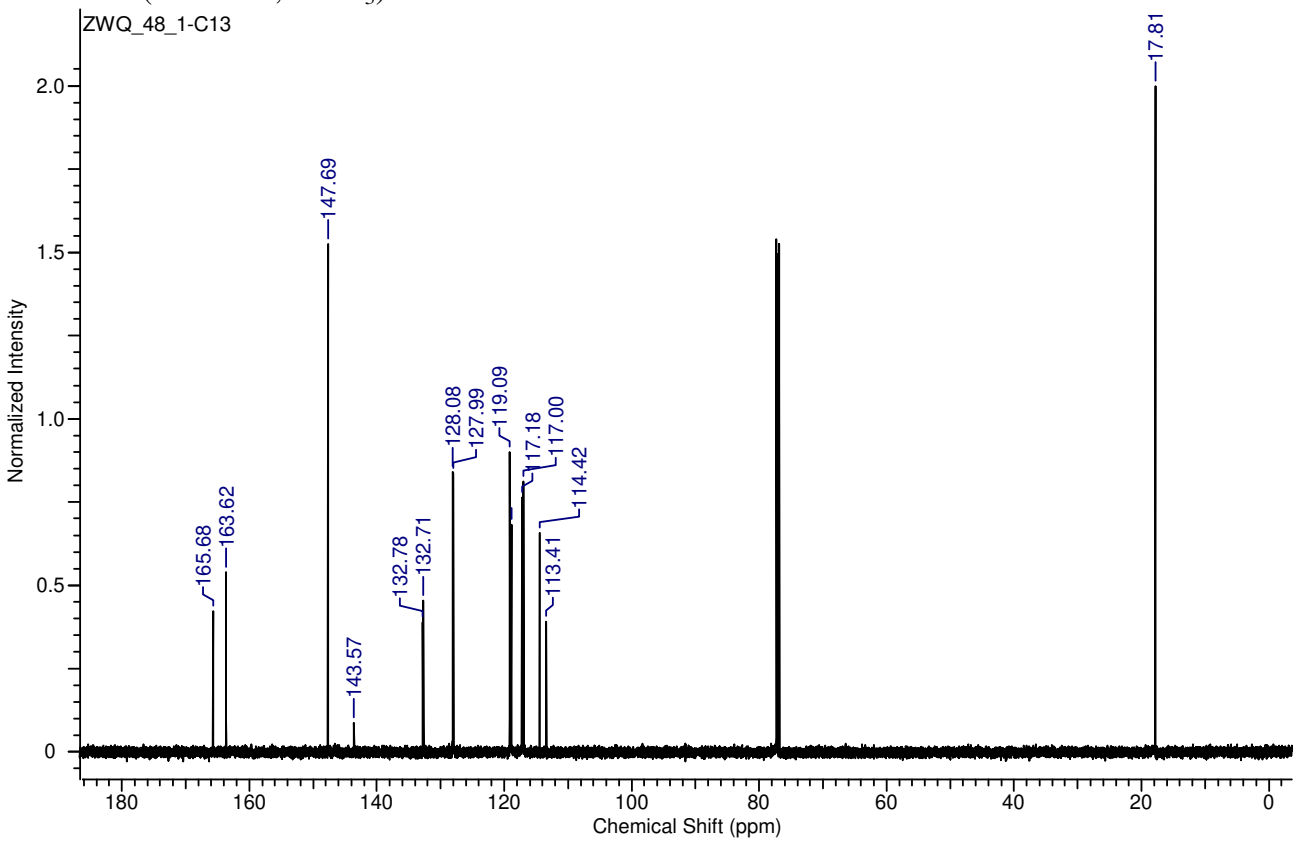

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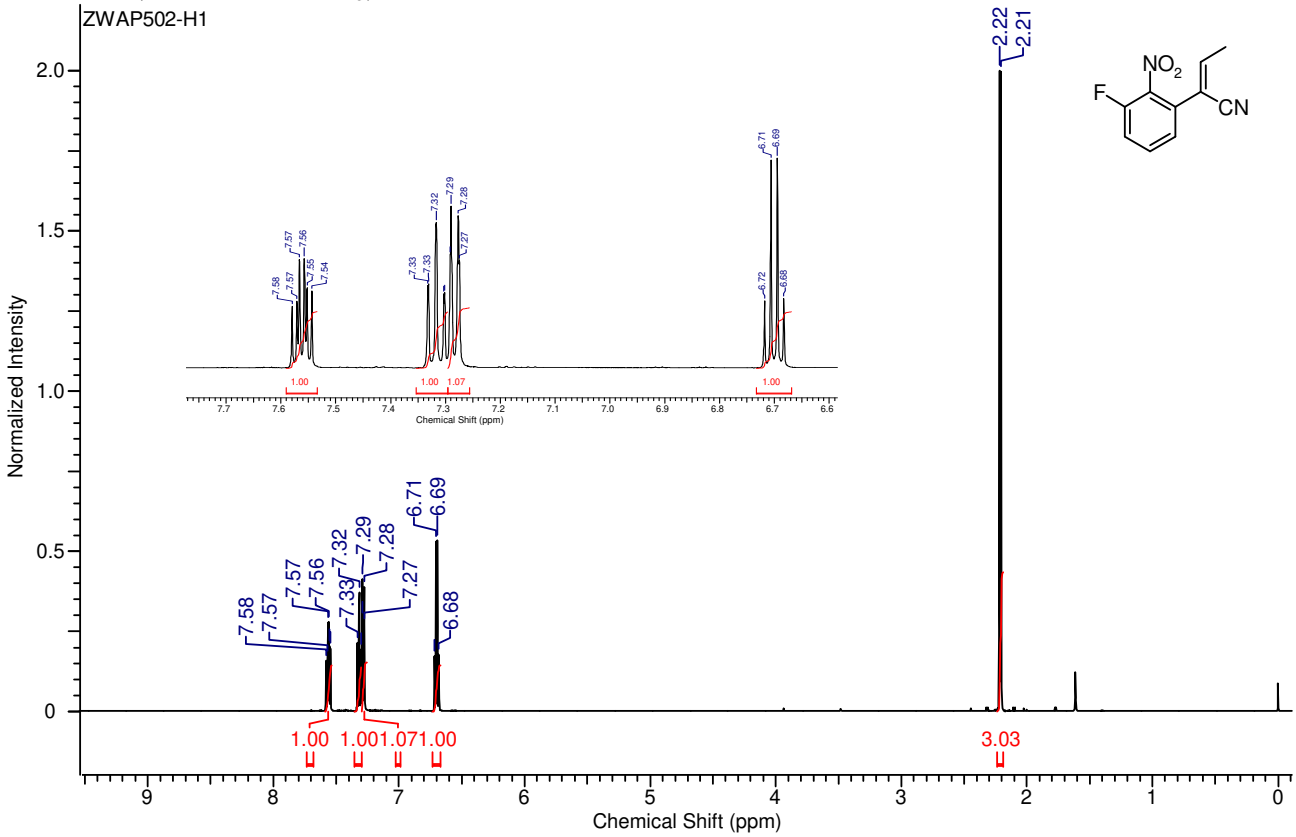

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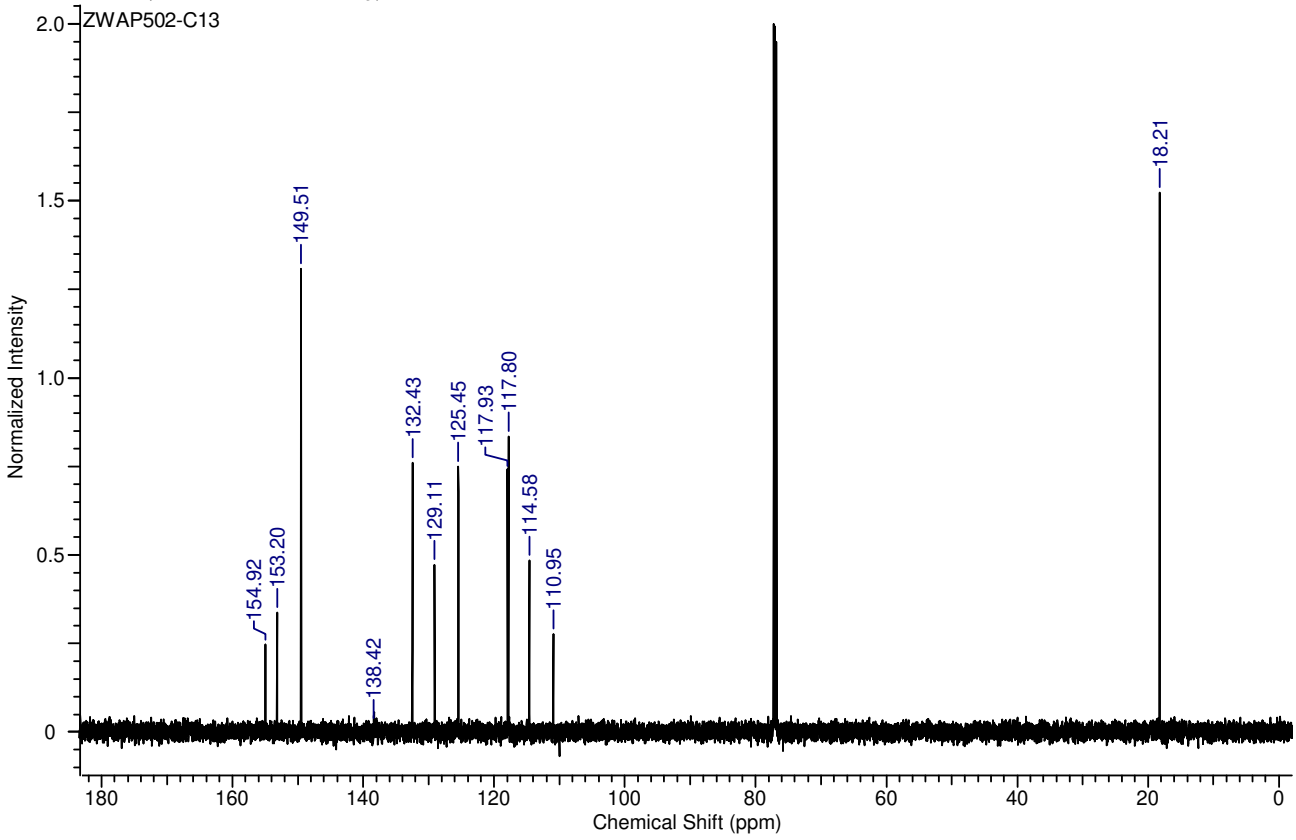

2i

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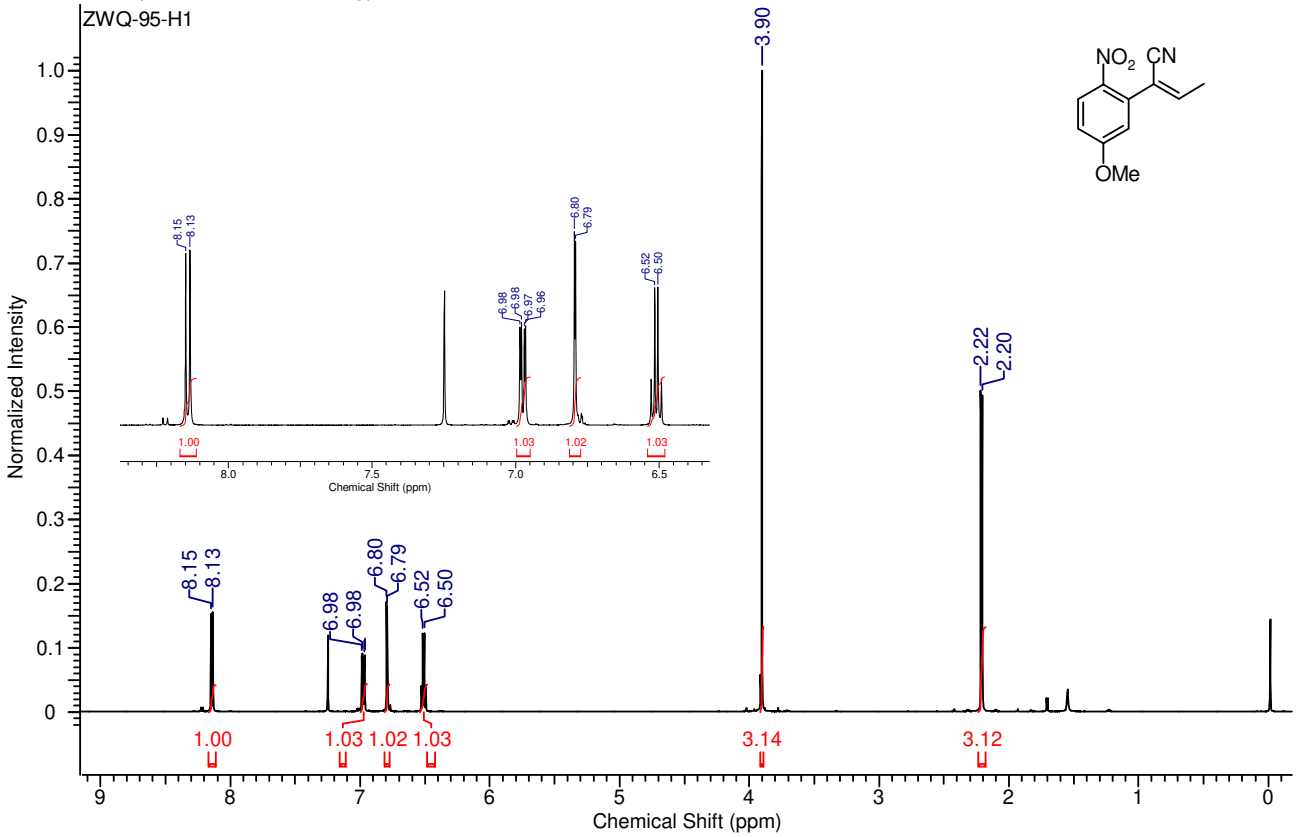

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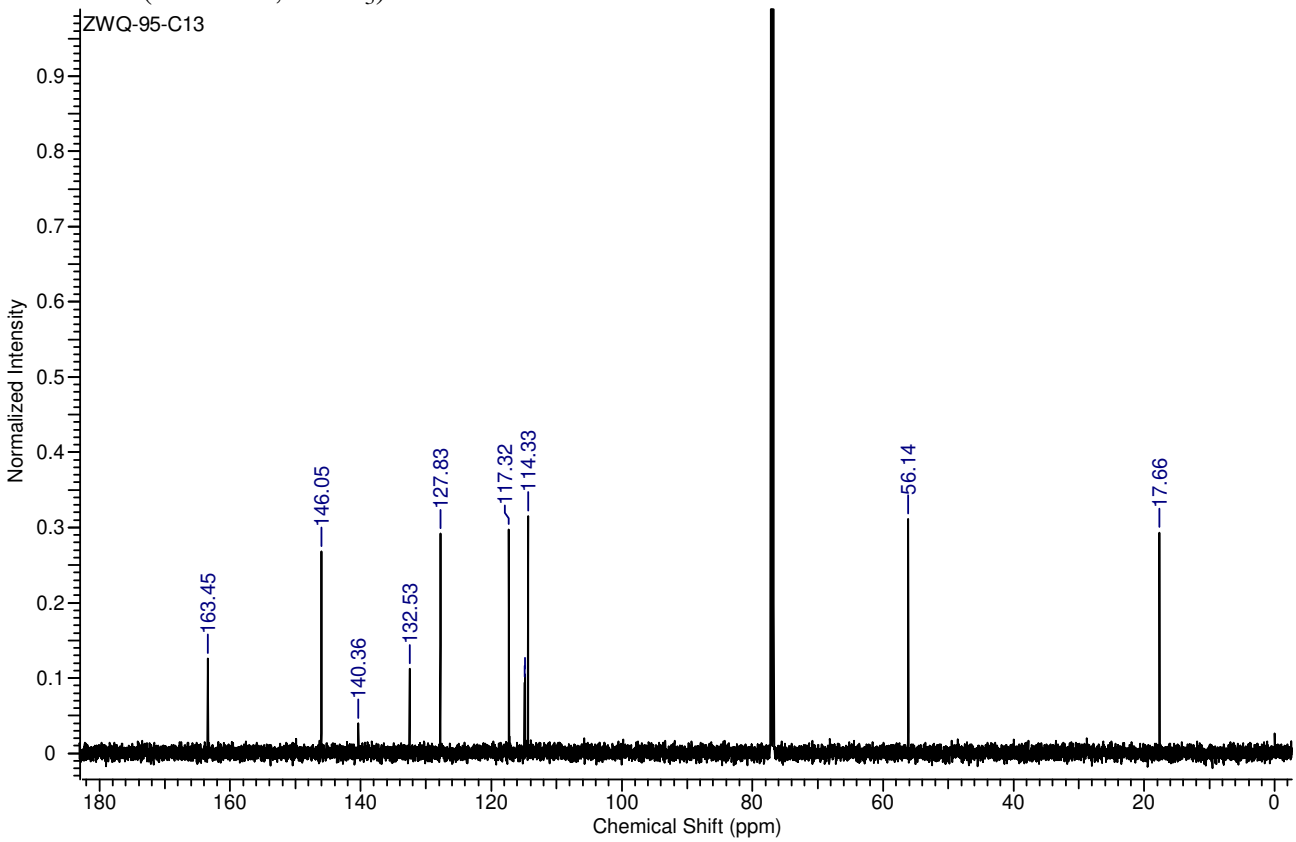

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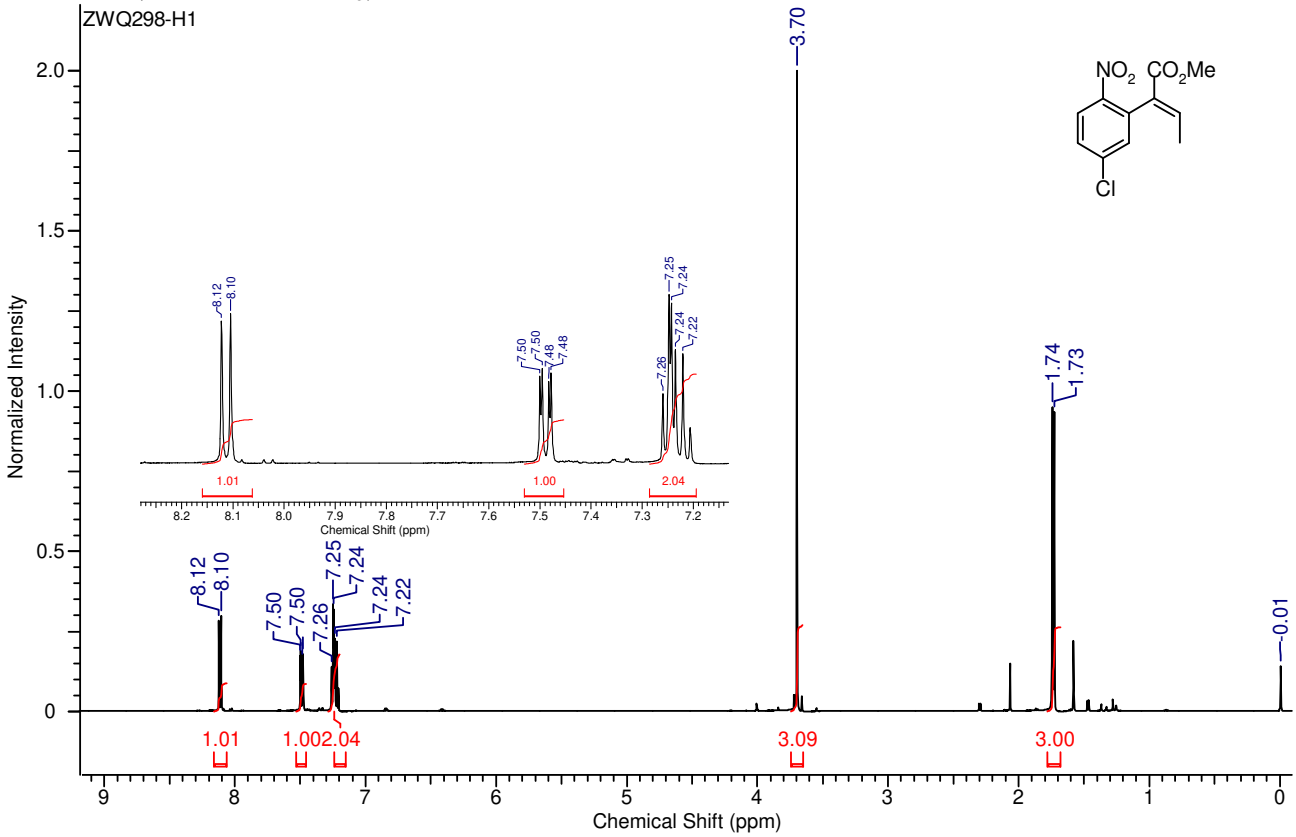

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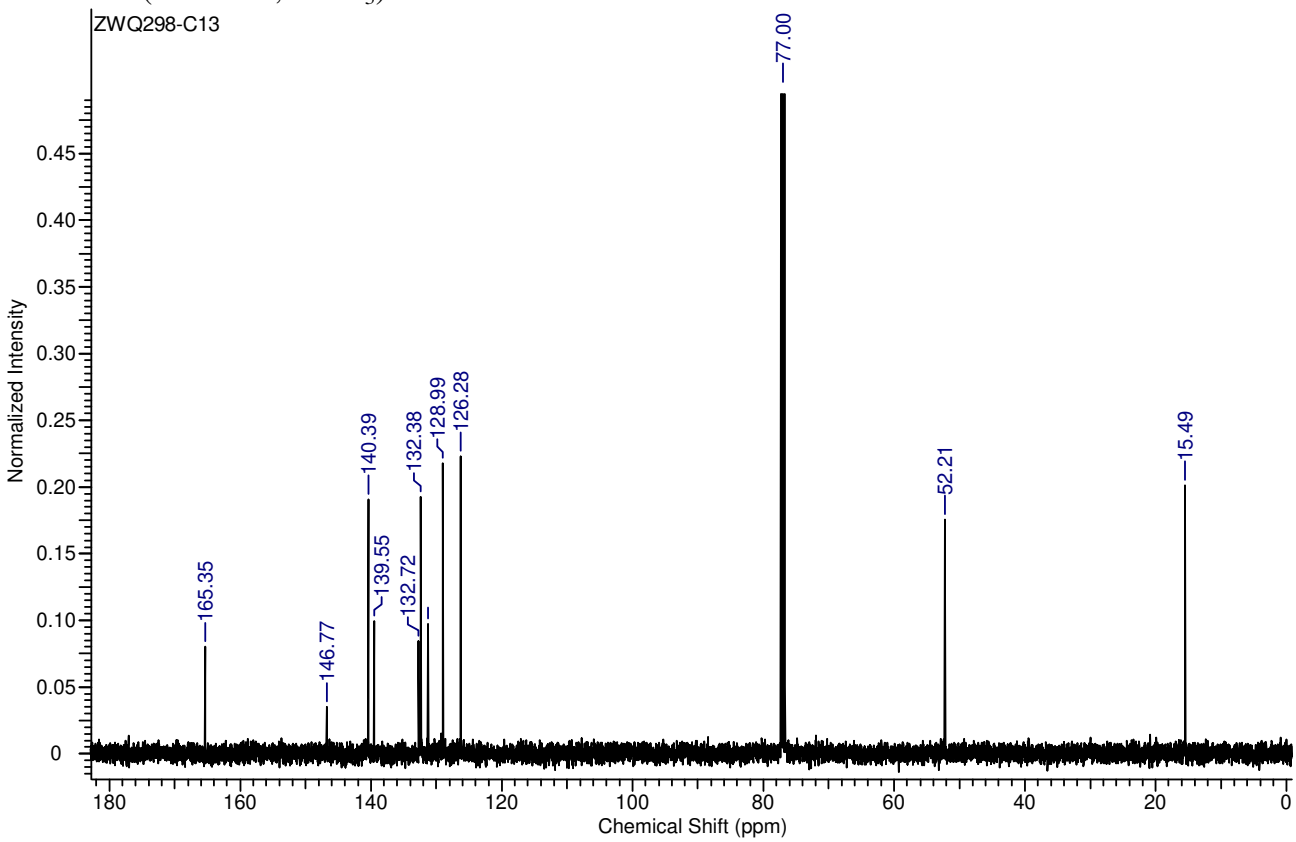

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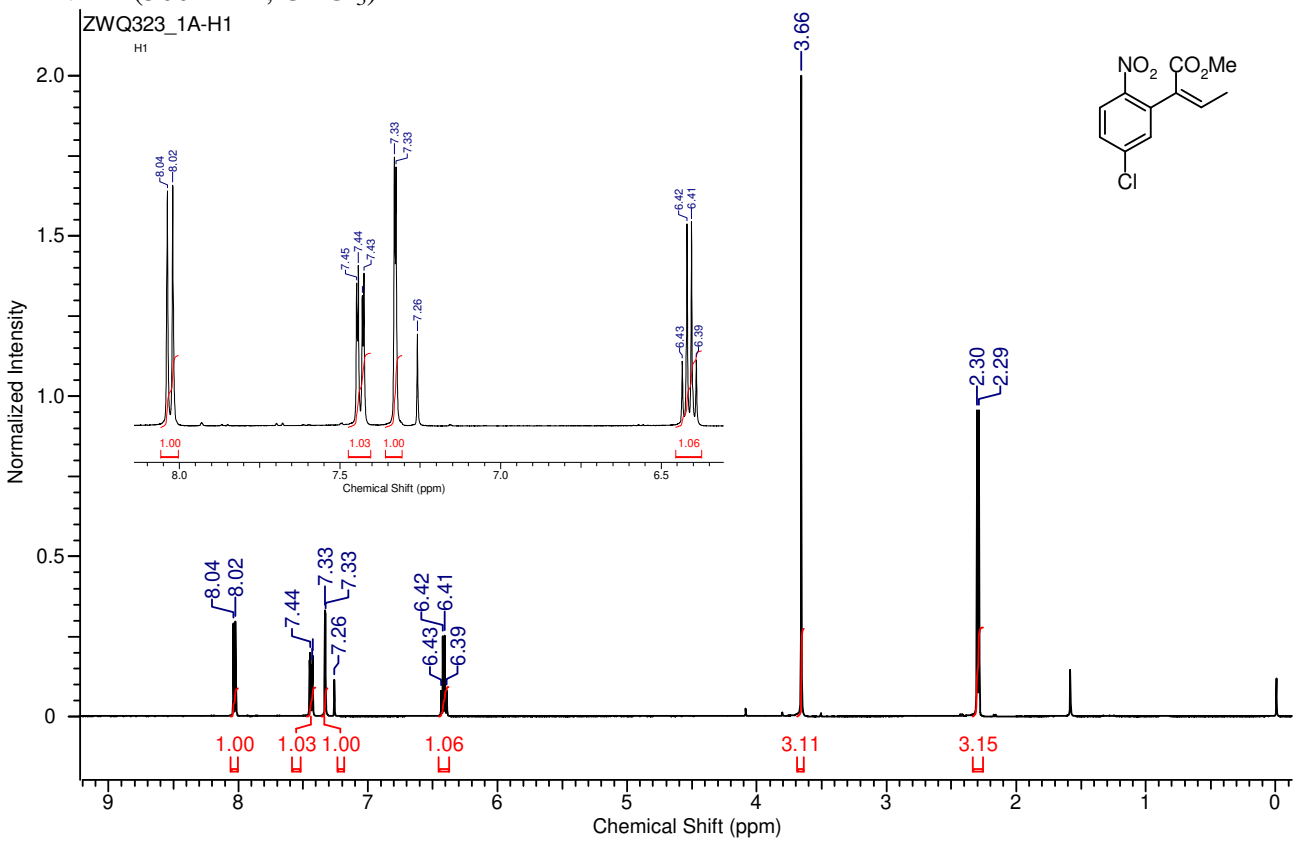

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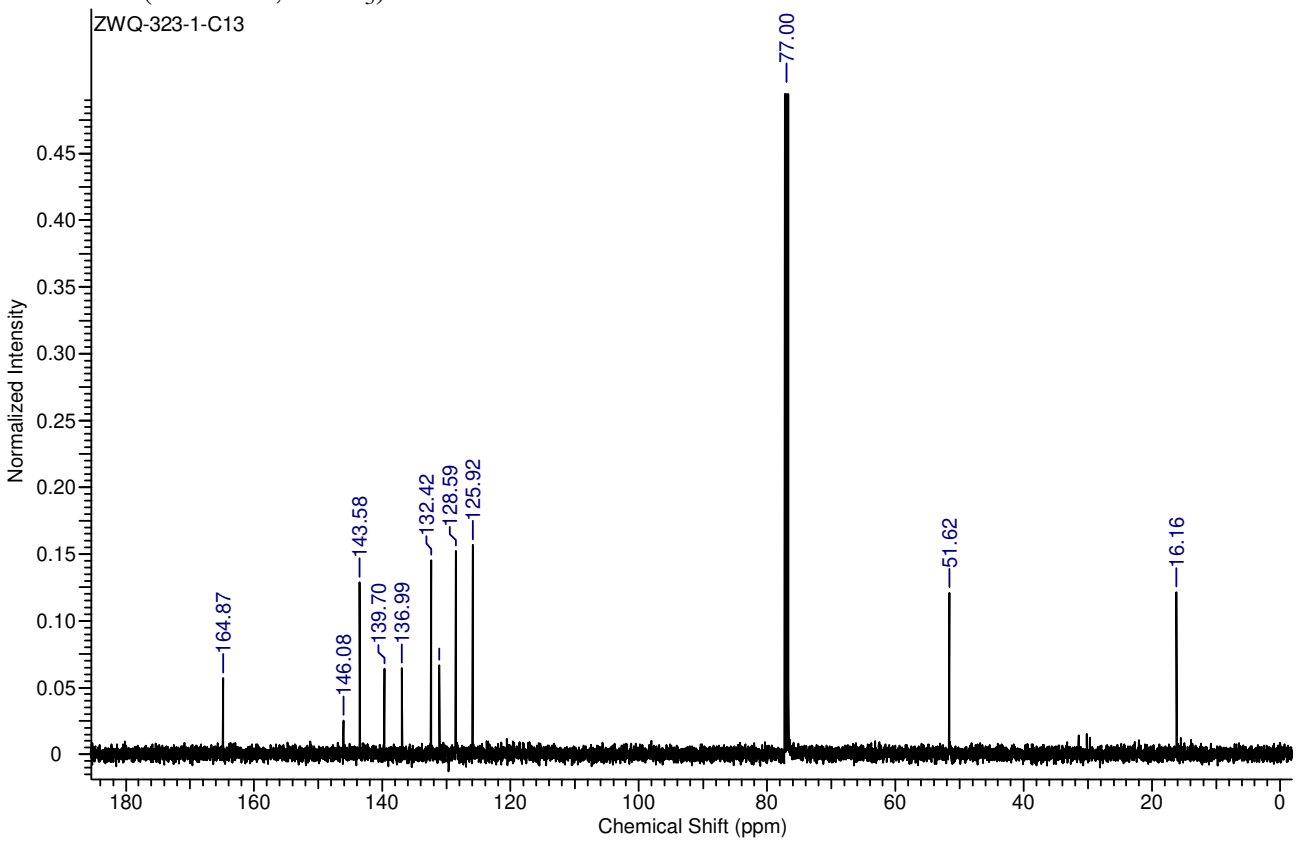

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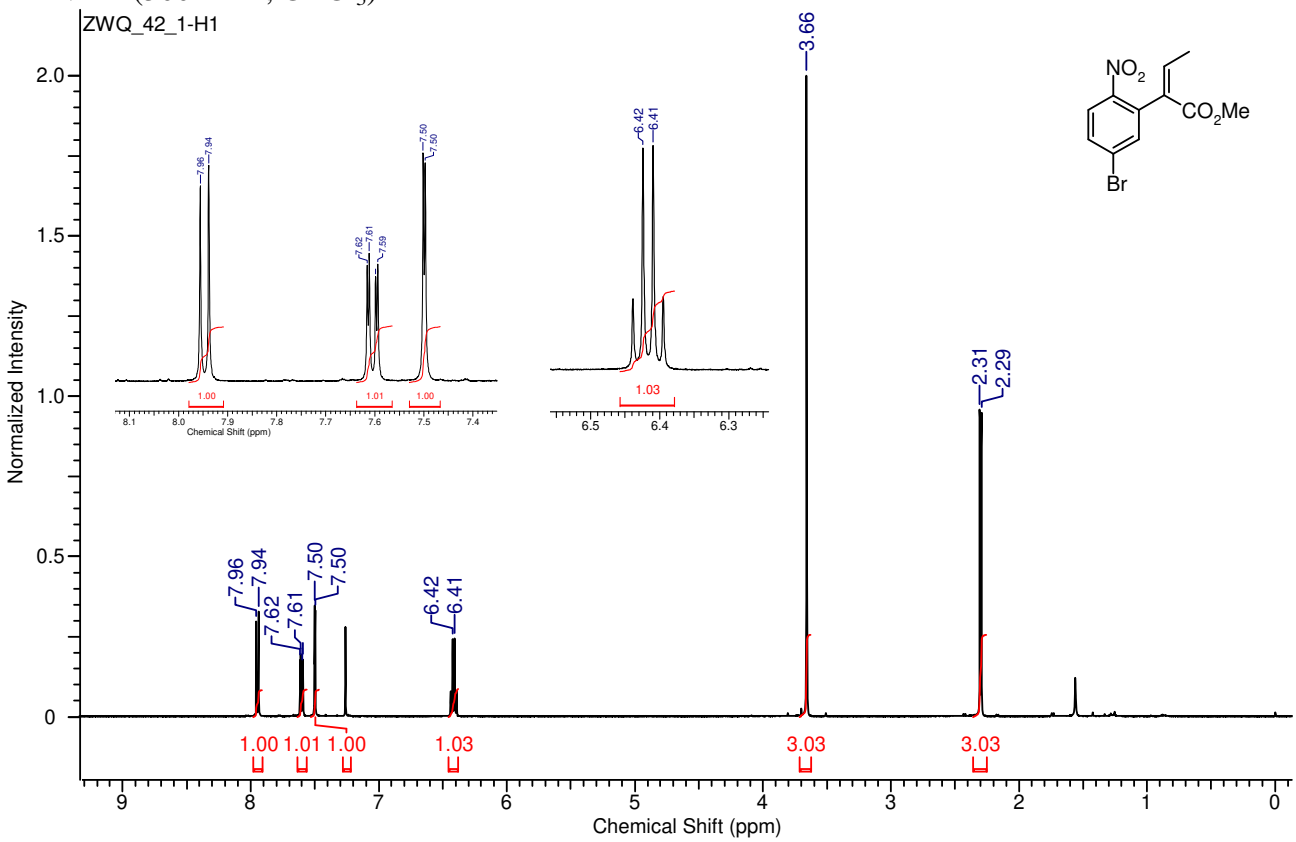

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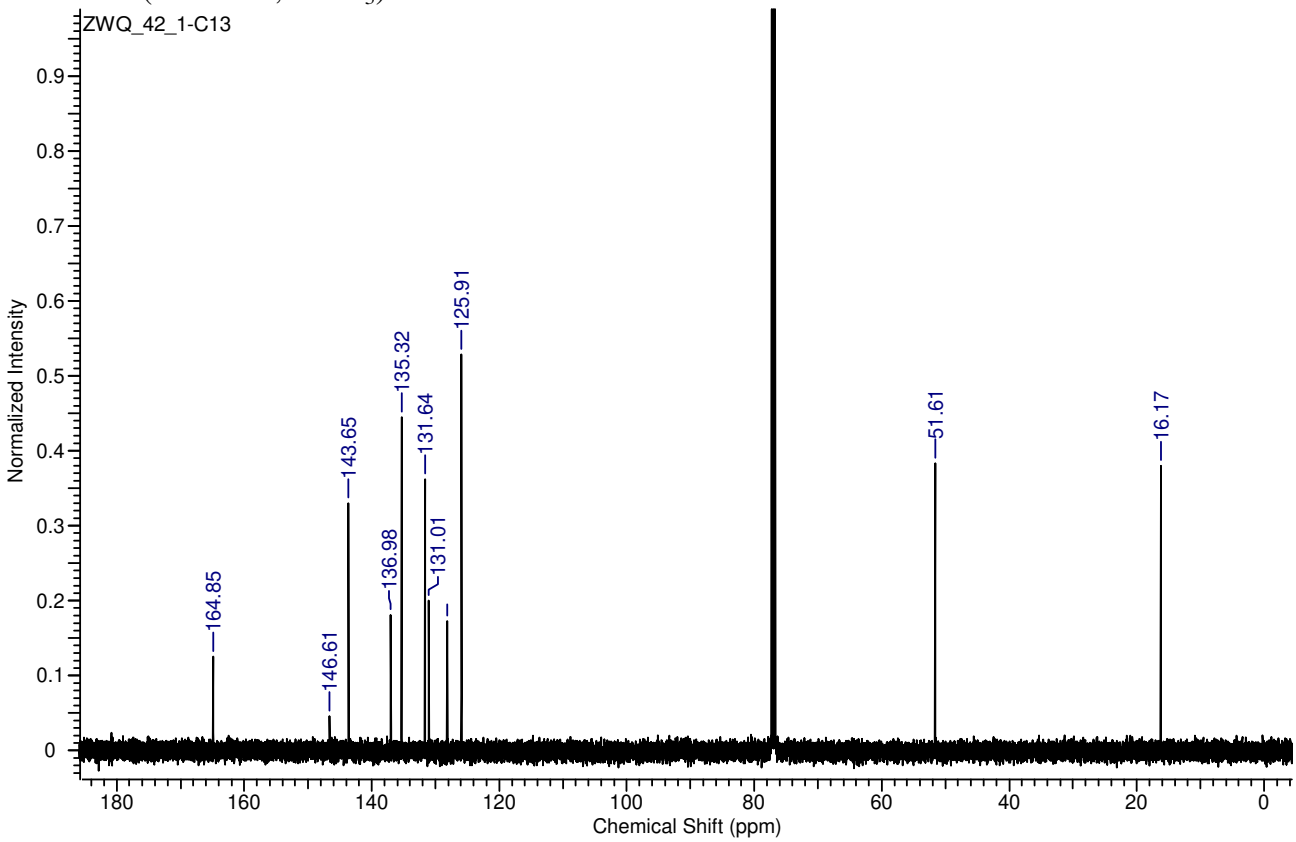

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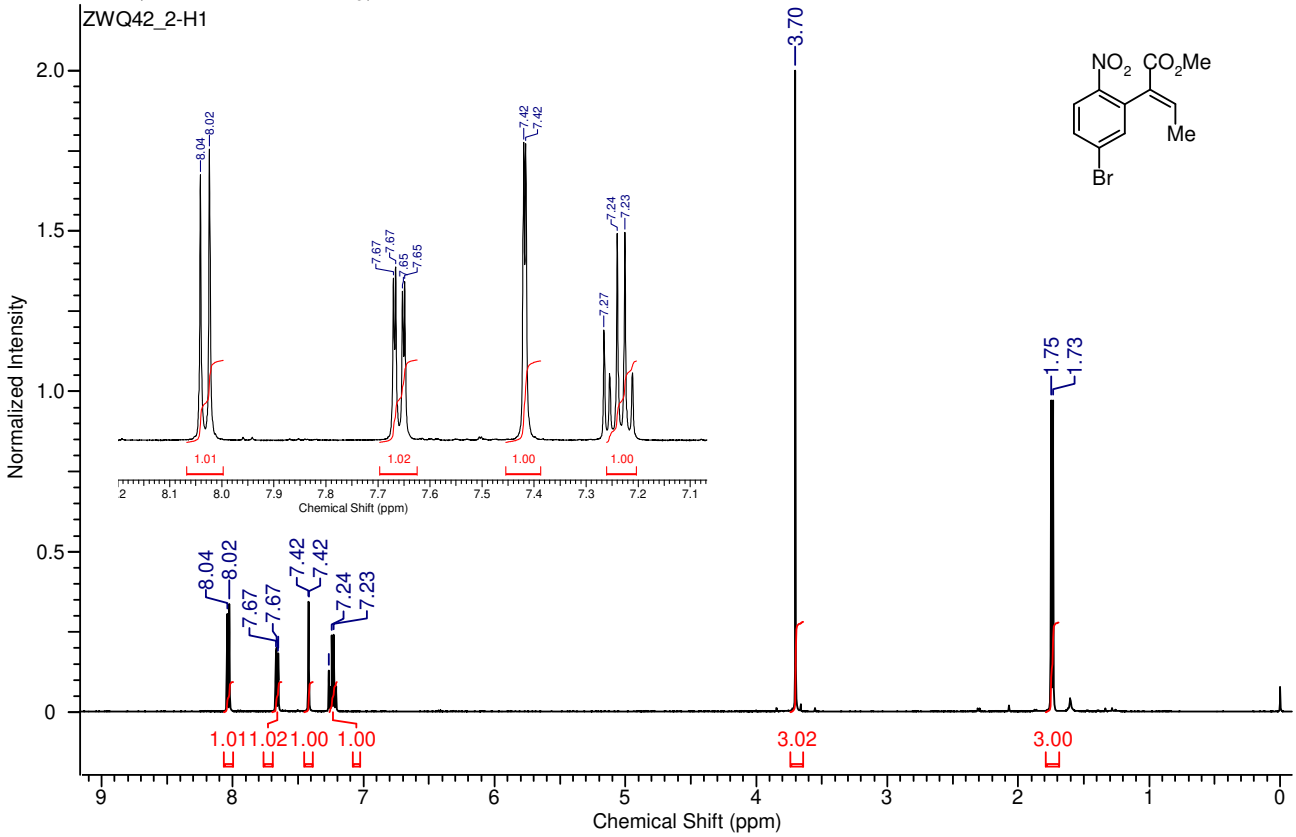

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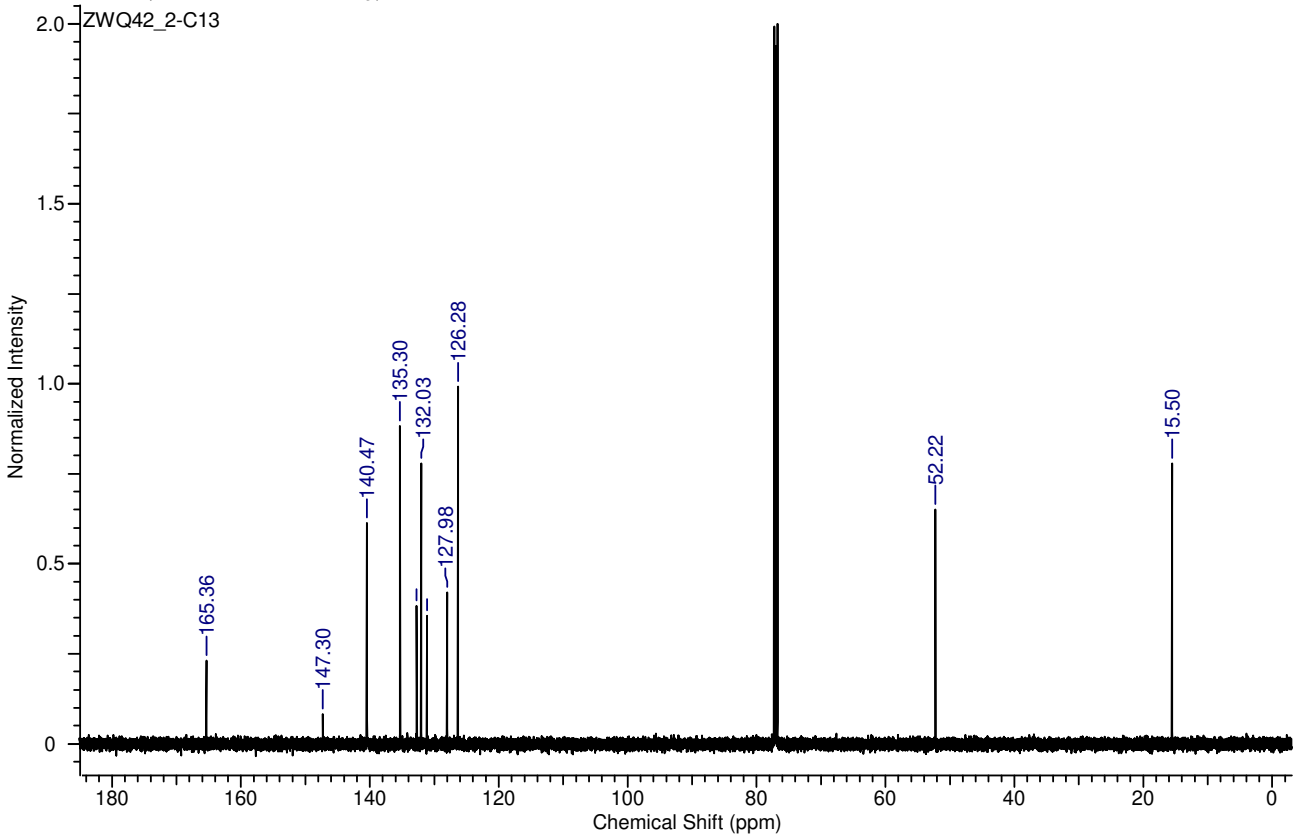
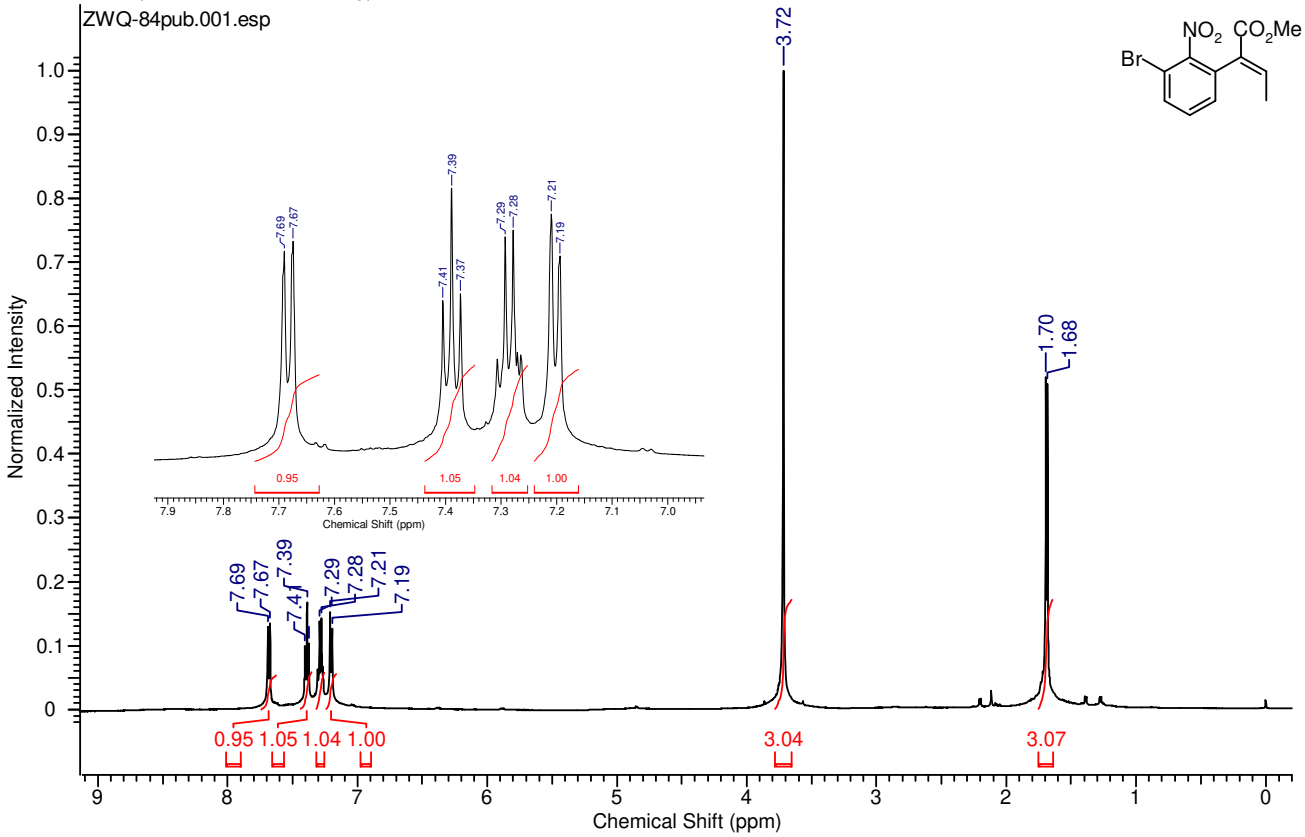
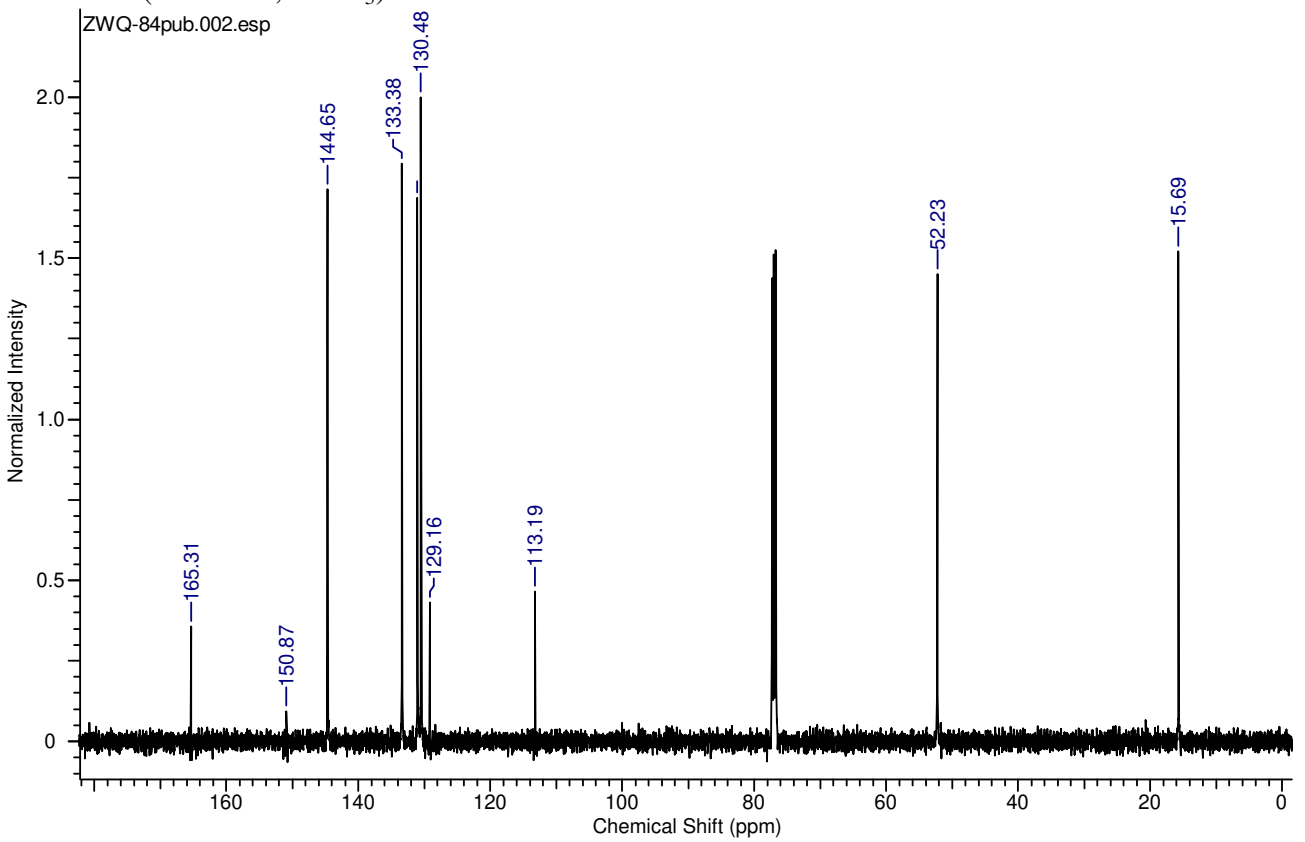


2l

^{1}H NMR (500 MHz, $CDCl_3$)

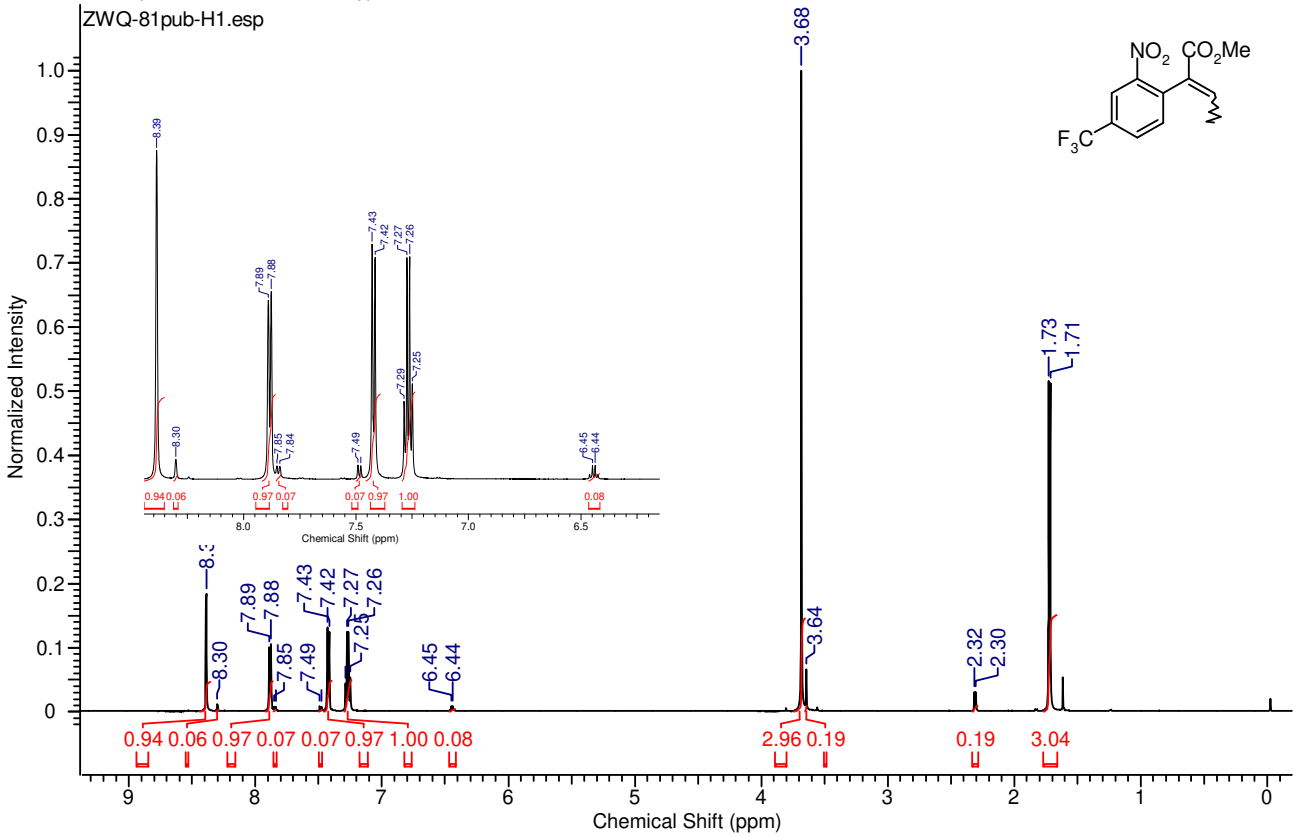


^{13}C NMR (125 MHz, $CDCl_3$)

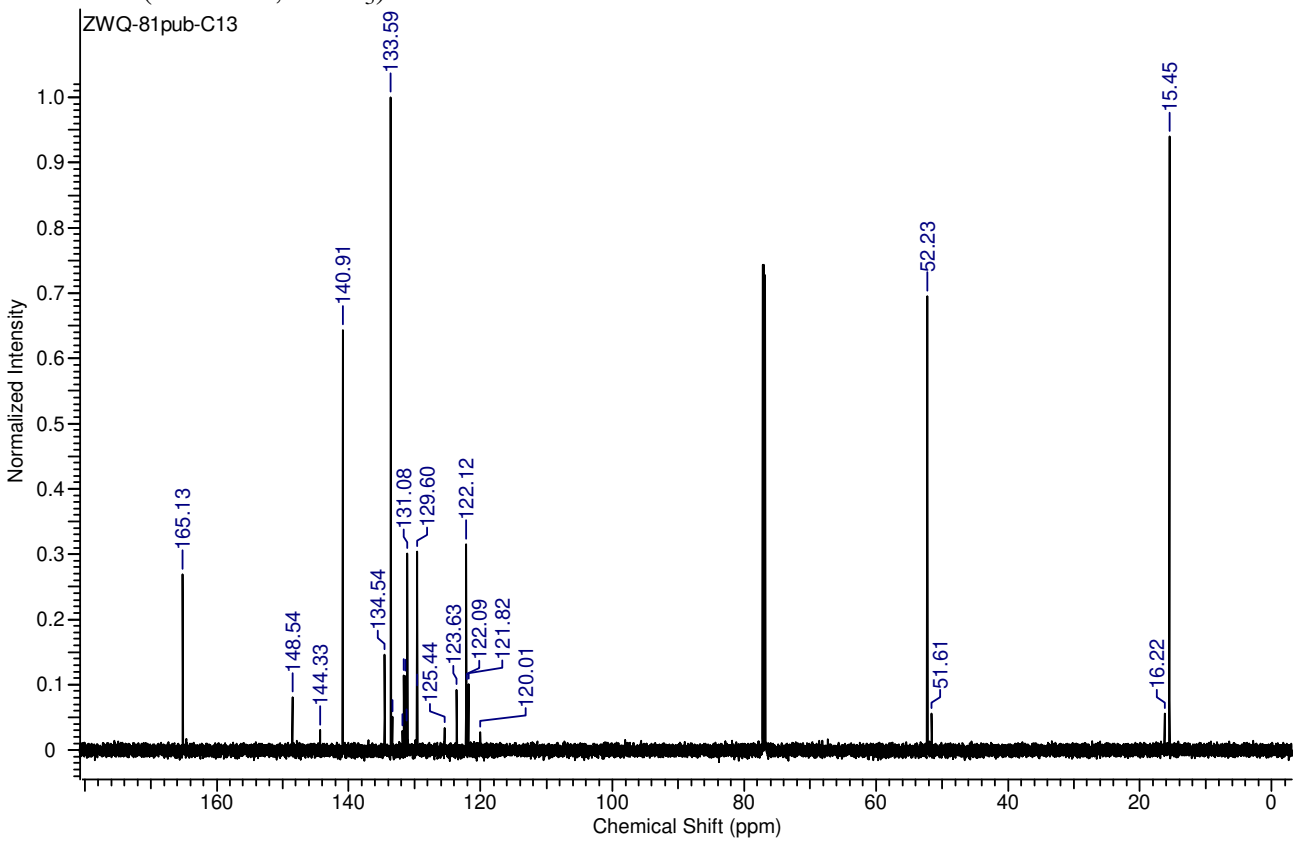


2m *E/Z* 94:6

^{1}H NMR (600 MHz, $CDCl_3$)

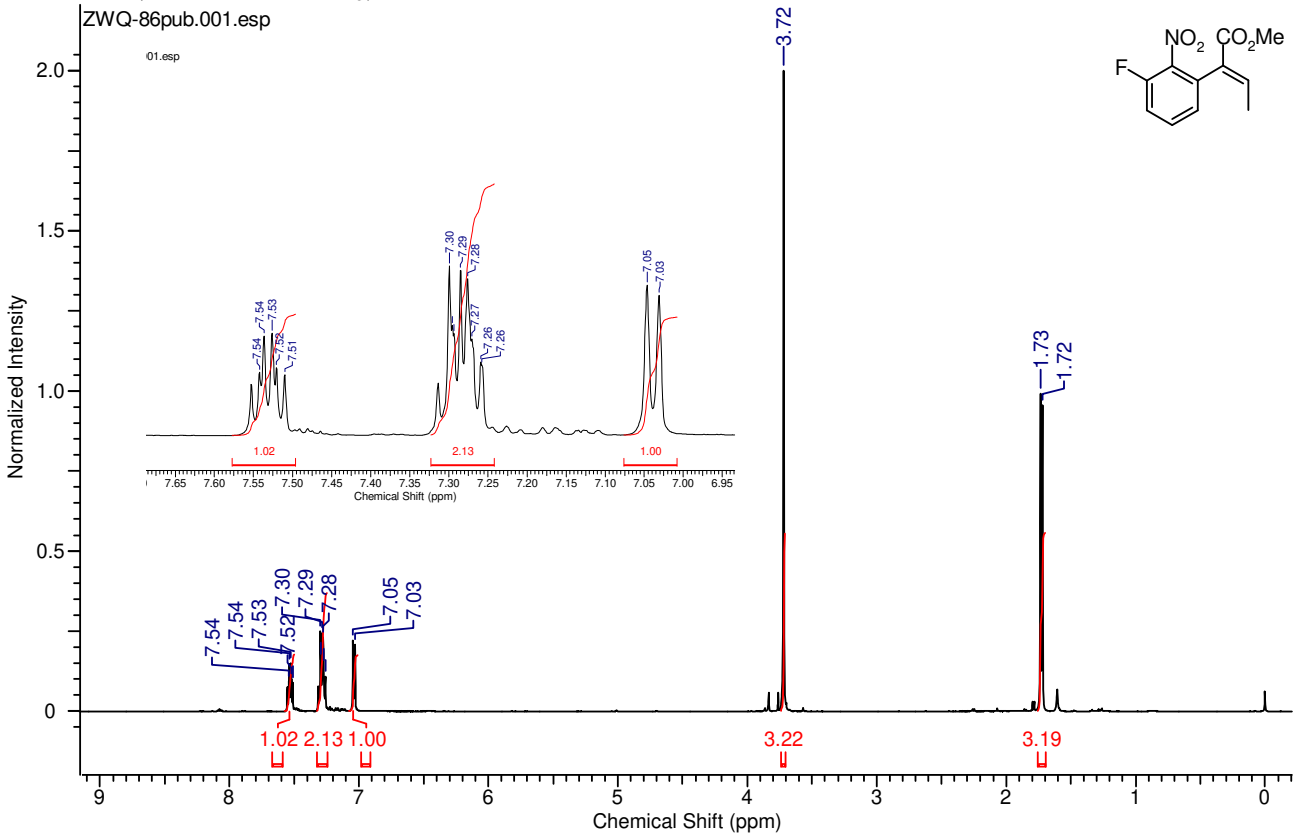


^{13}C NMR (150 MHz, $CDCl_3$)

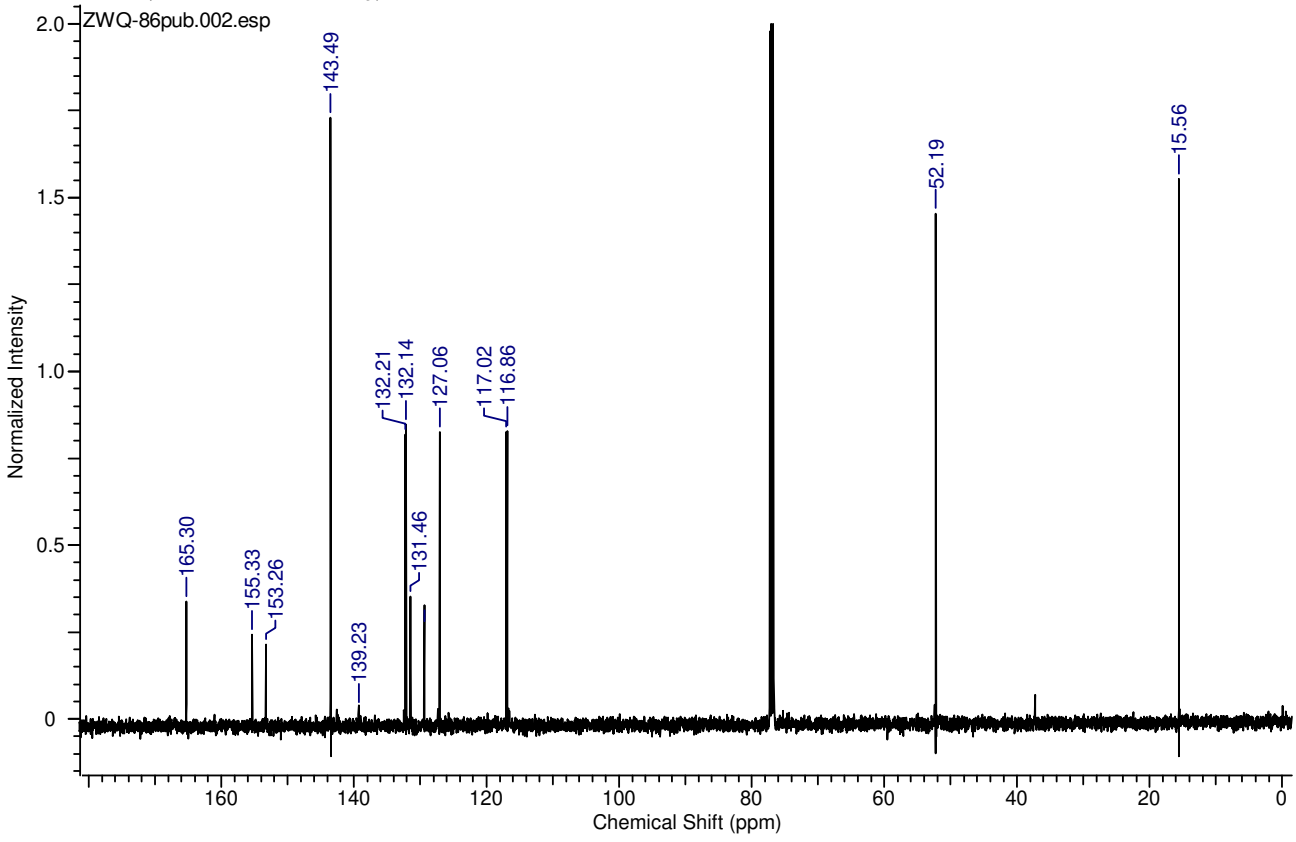


2n

^{1}H NMR (500 MHz, $CDCl_3$)

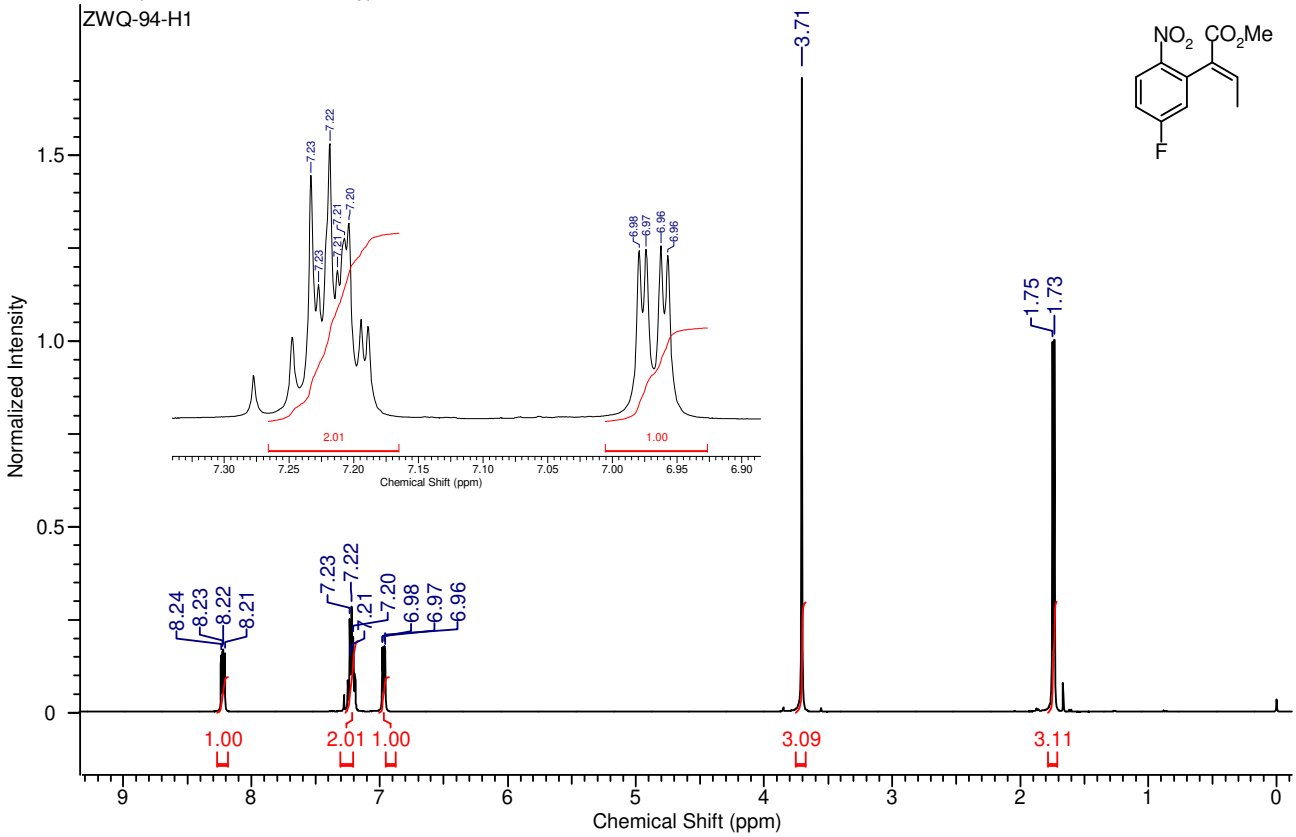


^{13}C NMR (125 MHz, $CDCl_3$)

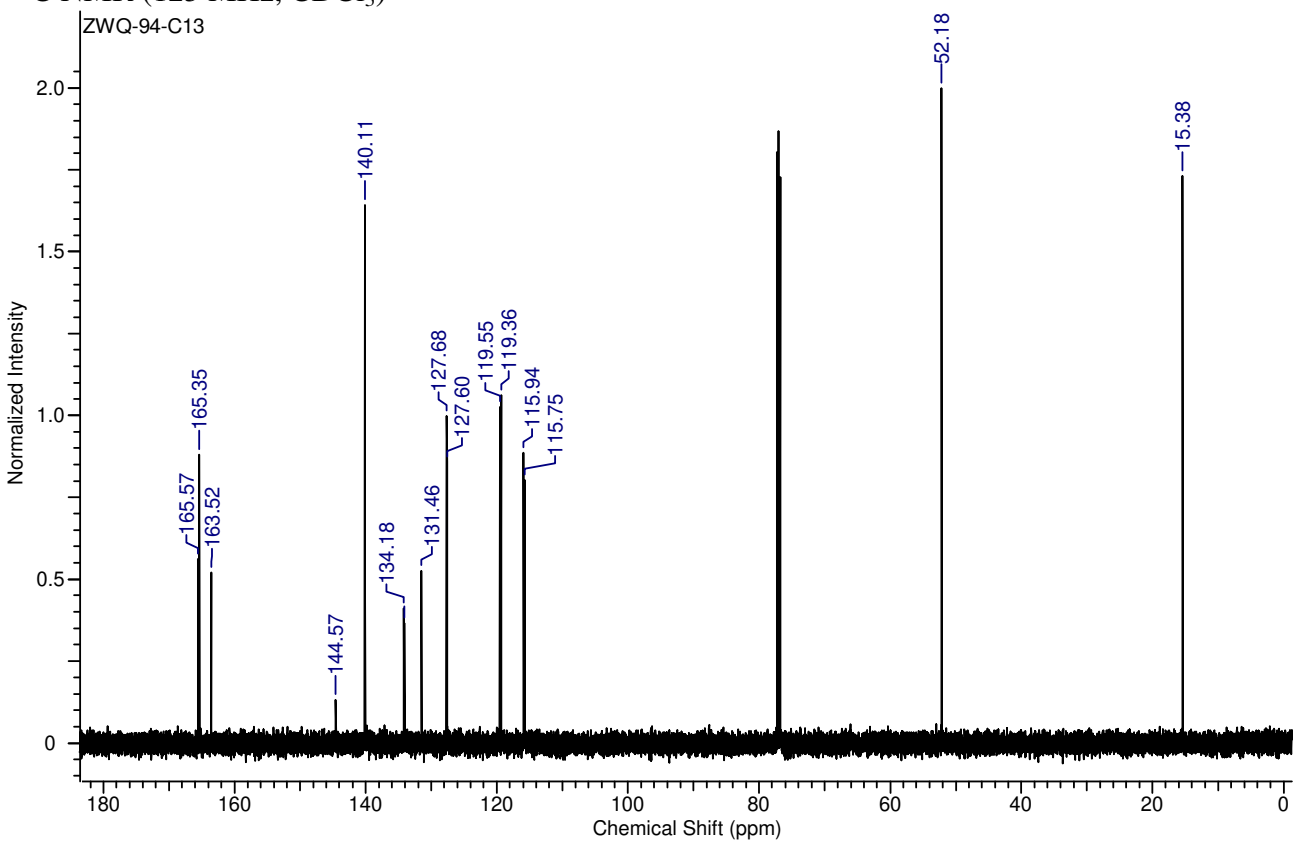


2o

^{1}H NMR (500 MHz, $CDCl_3$)

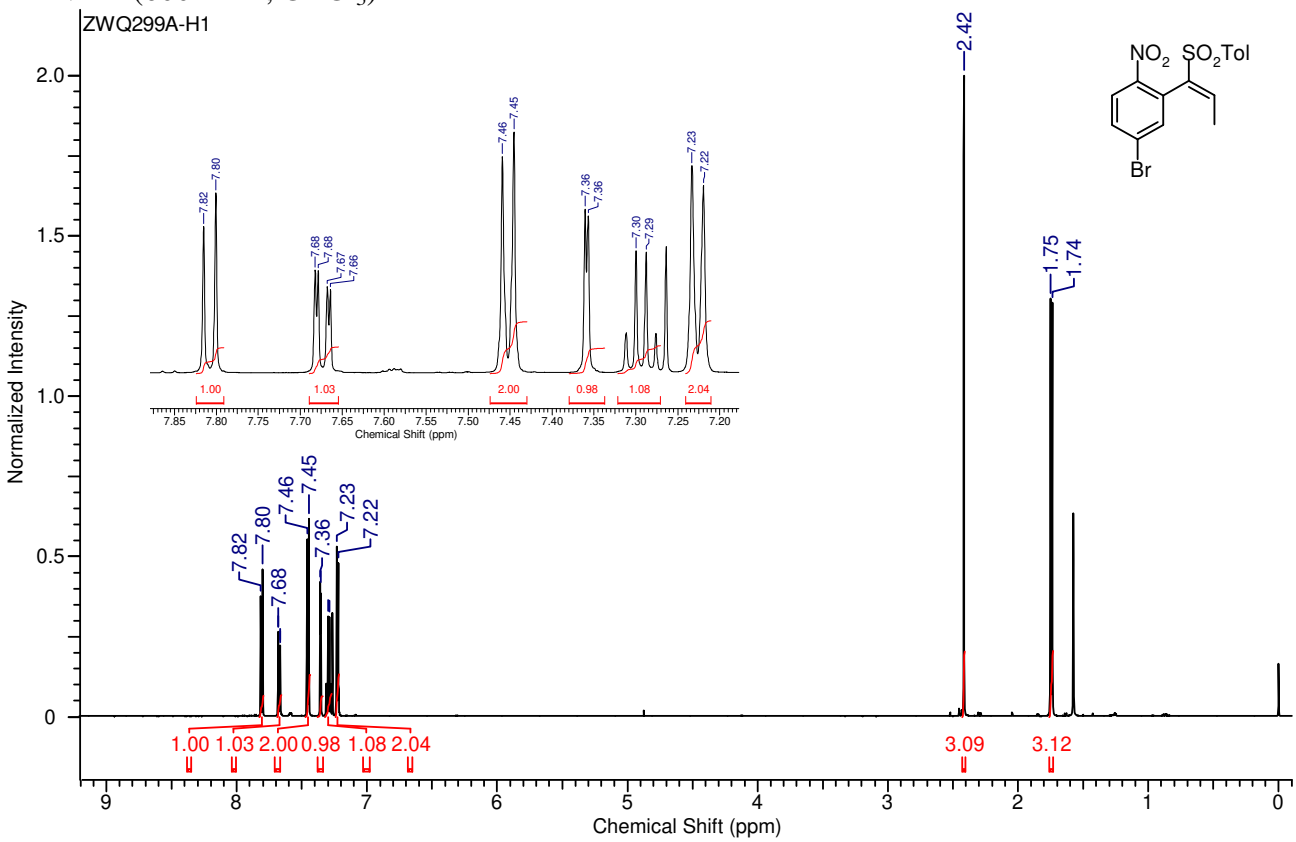


^{13}C NMR (125 MHz, $CDCl_3$)

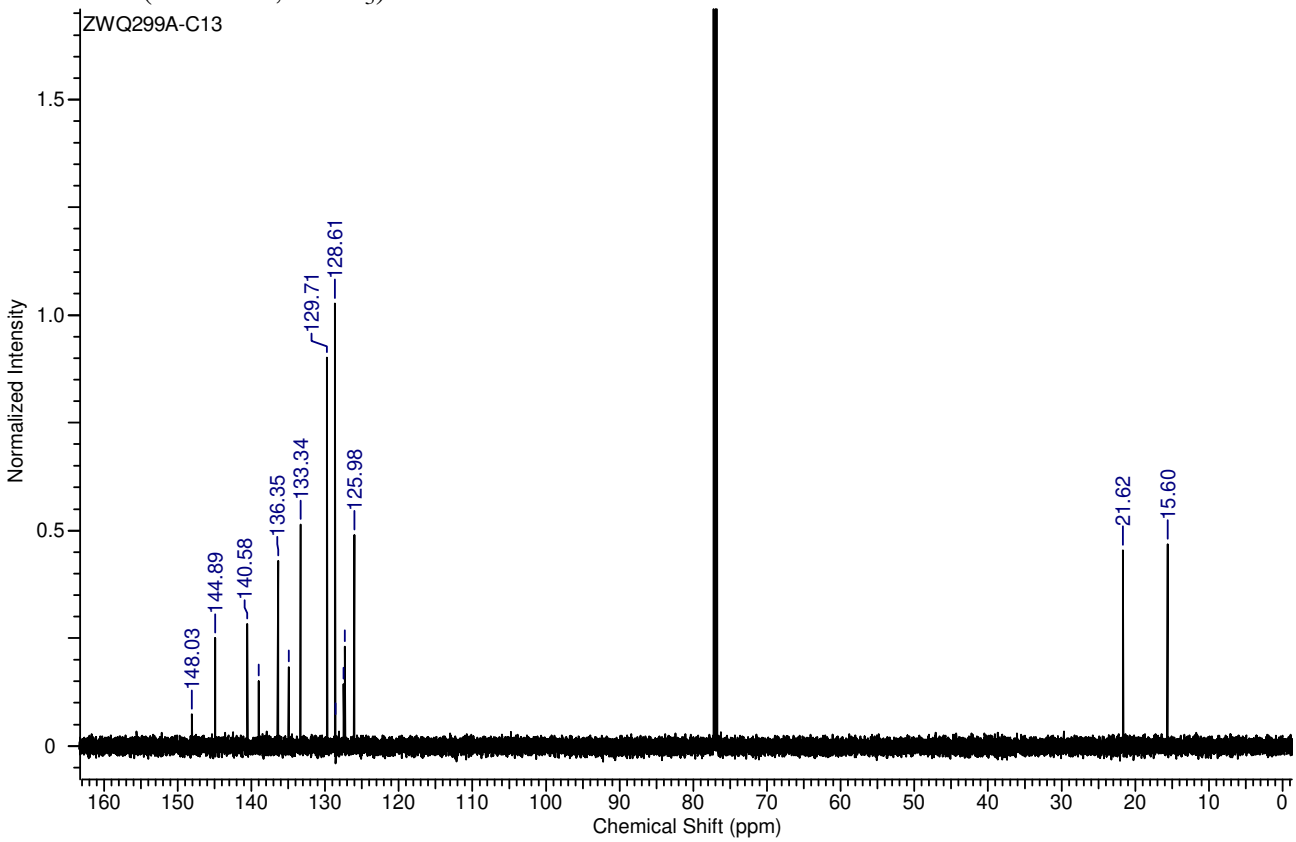


2p

^{1}H NMR (600 MHz, $CDCl_3$)

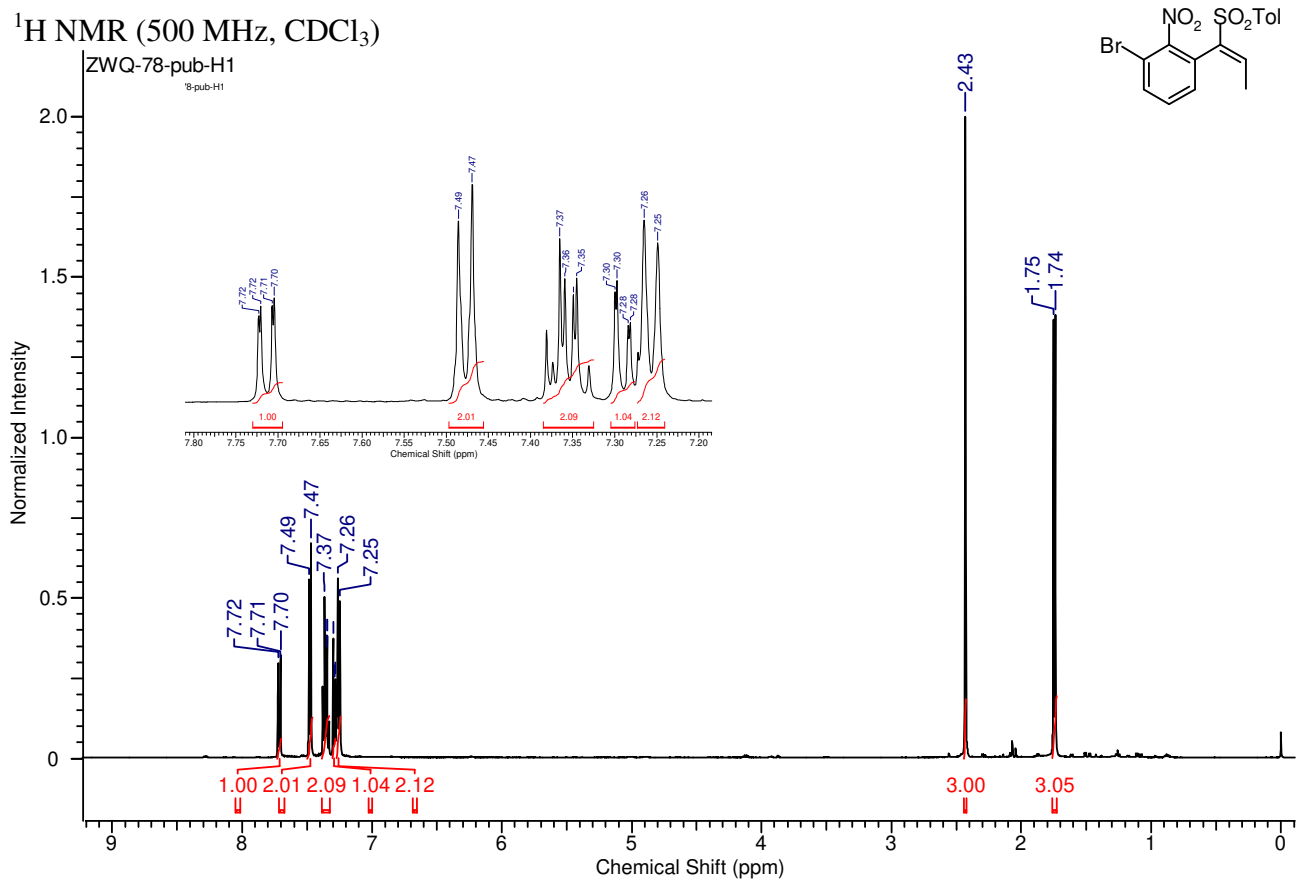


^{13}C NMR (150 MHz, $CDCl_3$)

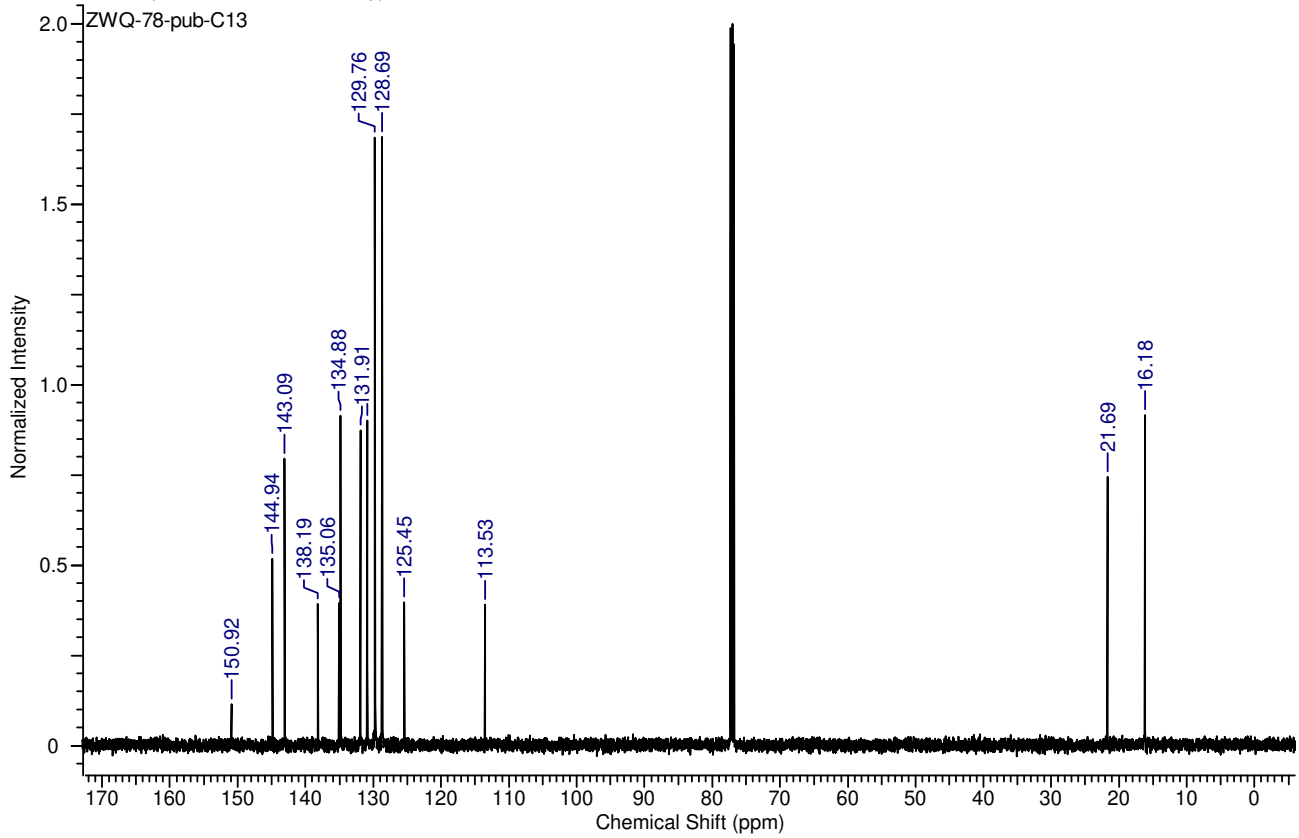


2q

^{1}H NMR (500 MHz, $CDCl_3$)

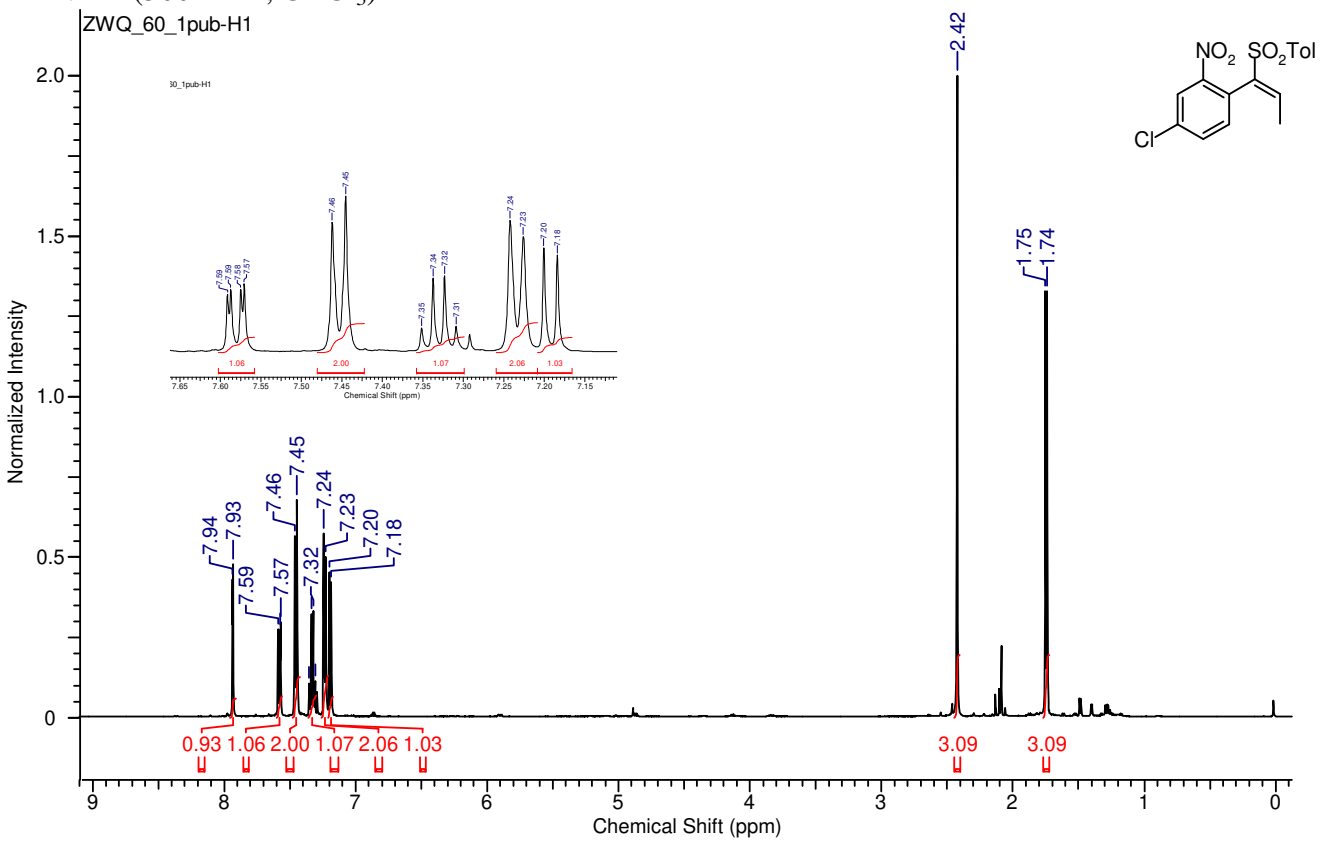


^{13}C NMR (125 MHz, $CDCl_3$)

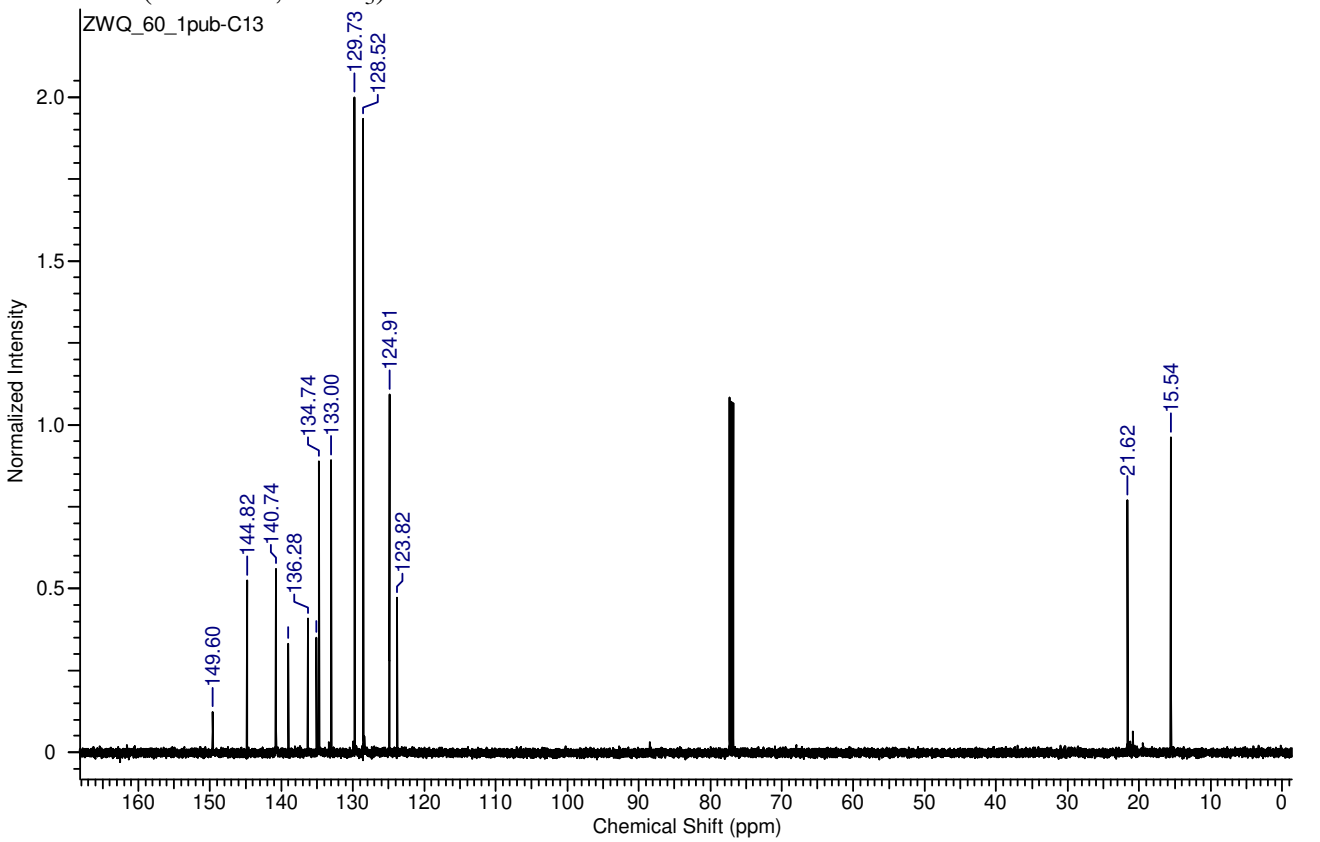


2r

^{1}H NMR (500 MHz, $CDCl_3$)

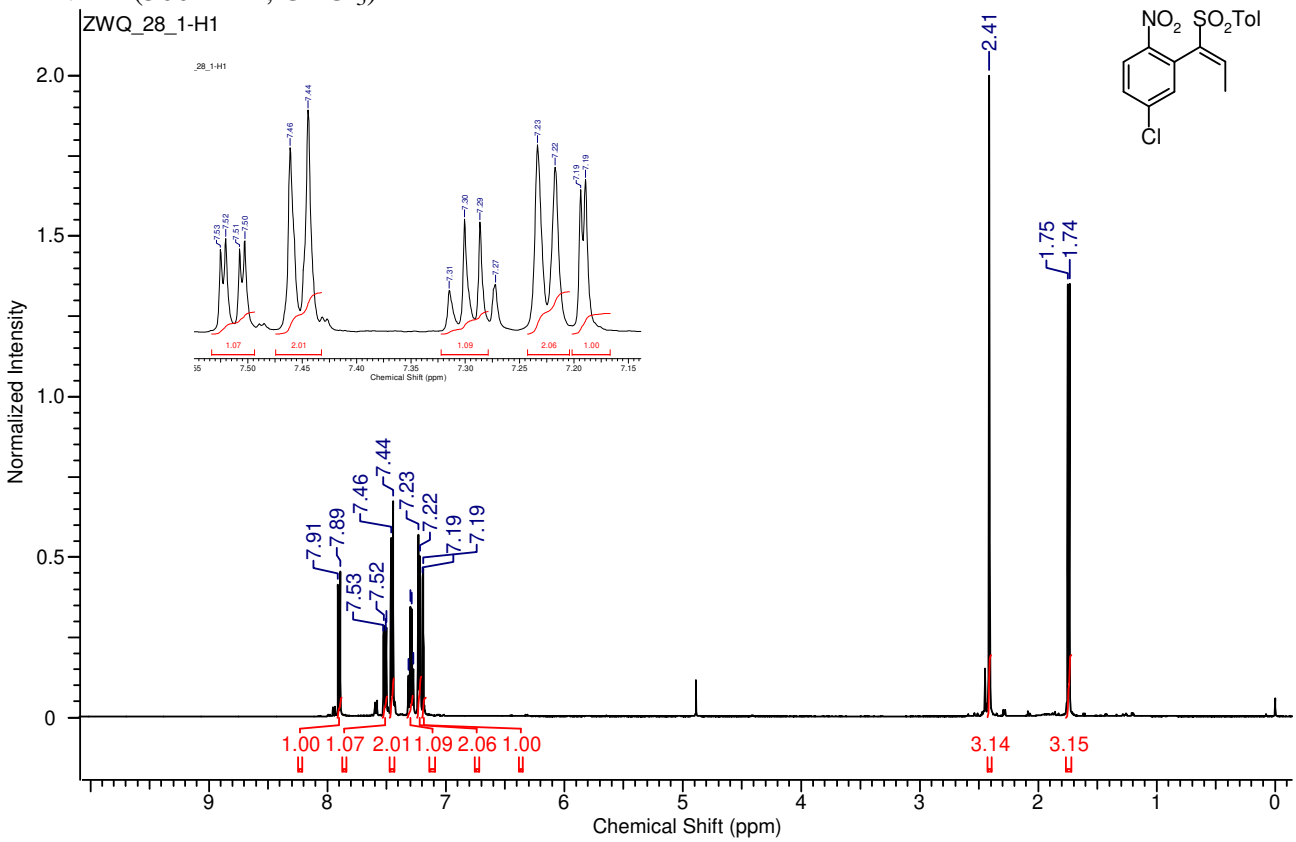


^{13}C NMR (125 MHz, $CDCl_3$)

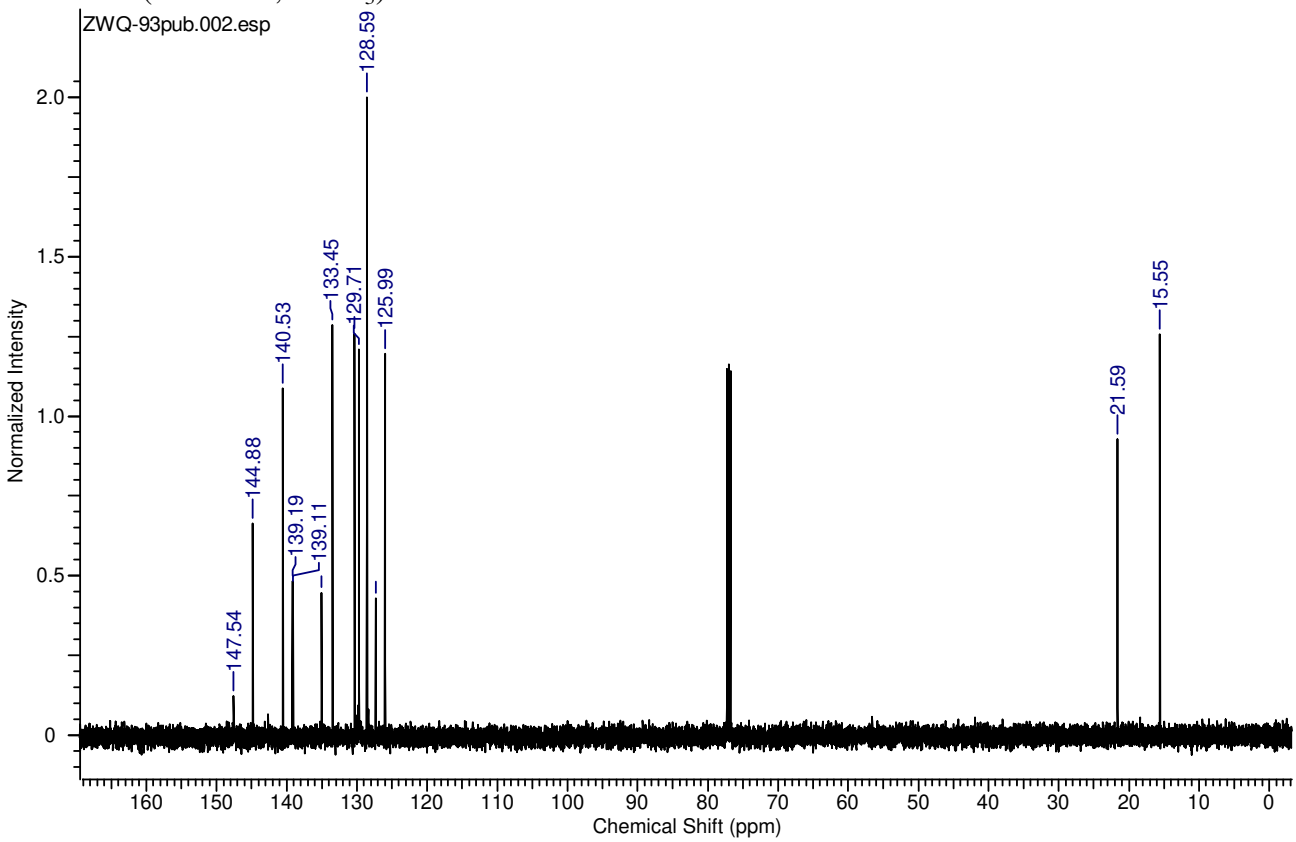


2s

^{1}H NMR (500 MHz, $CDCl_3$)

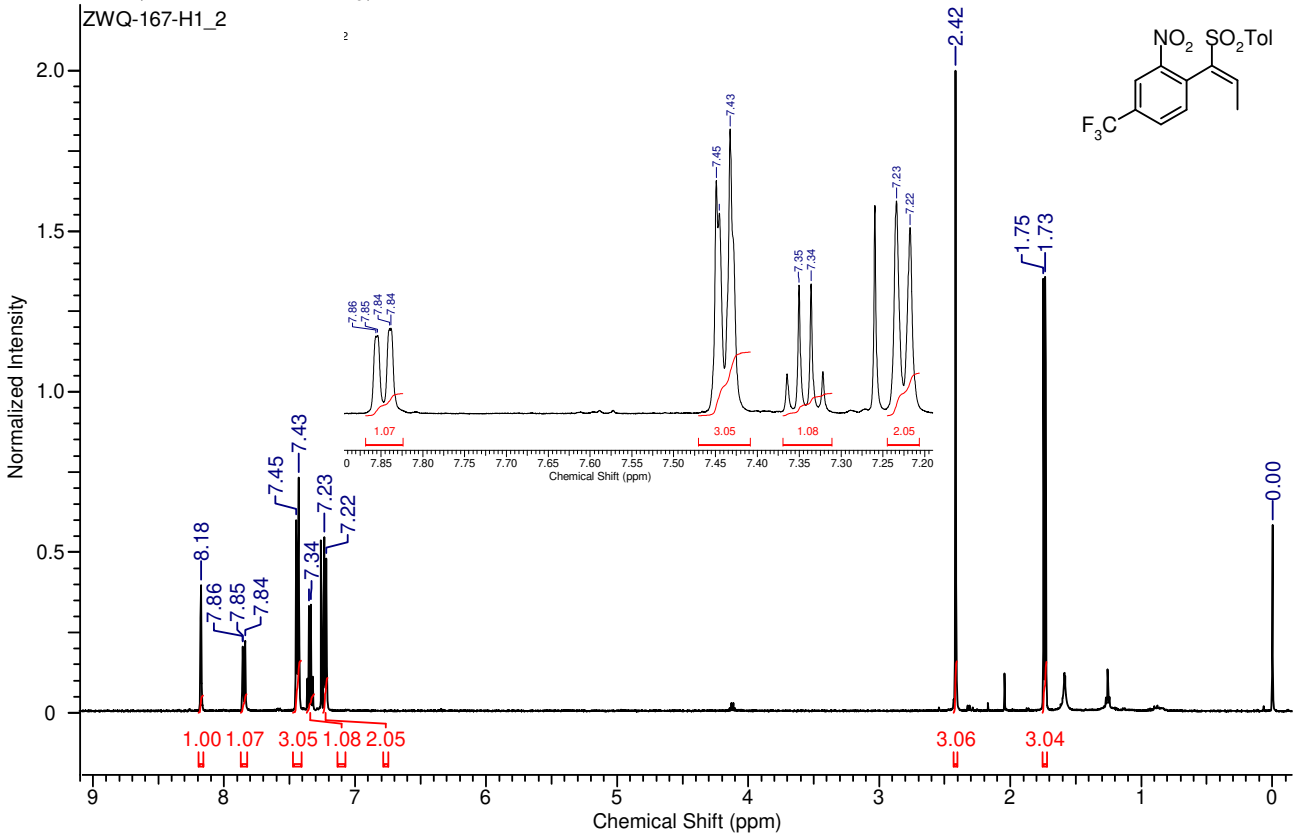


^{13}C NMR (125 MHz, $CDCl_3$)

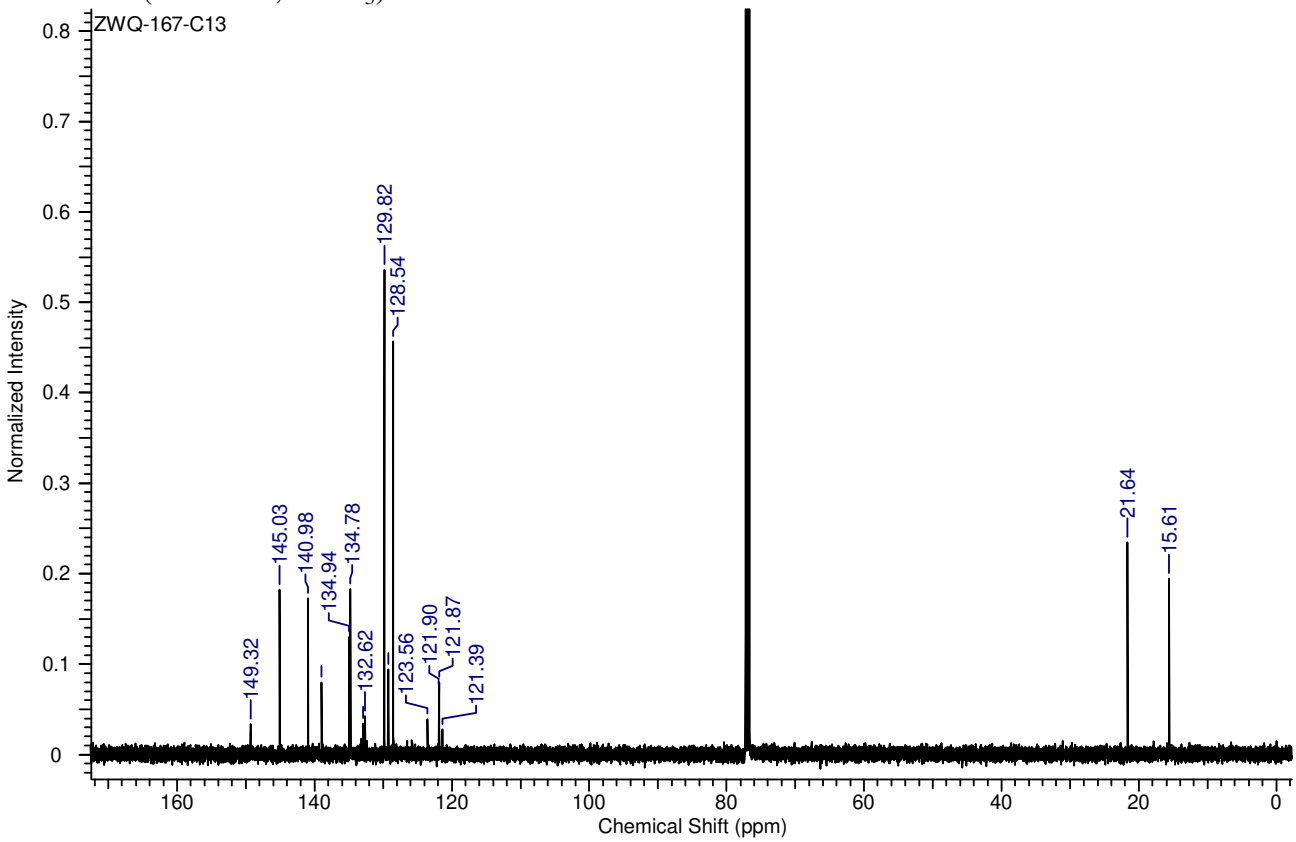


2t

^{1}H NMR (500 MHz, $CDCl_3$)

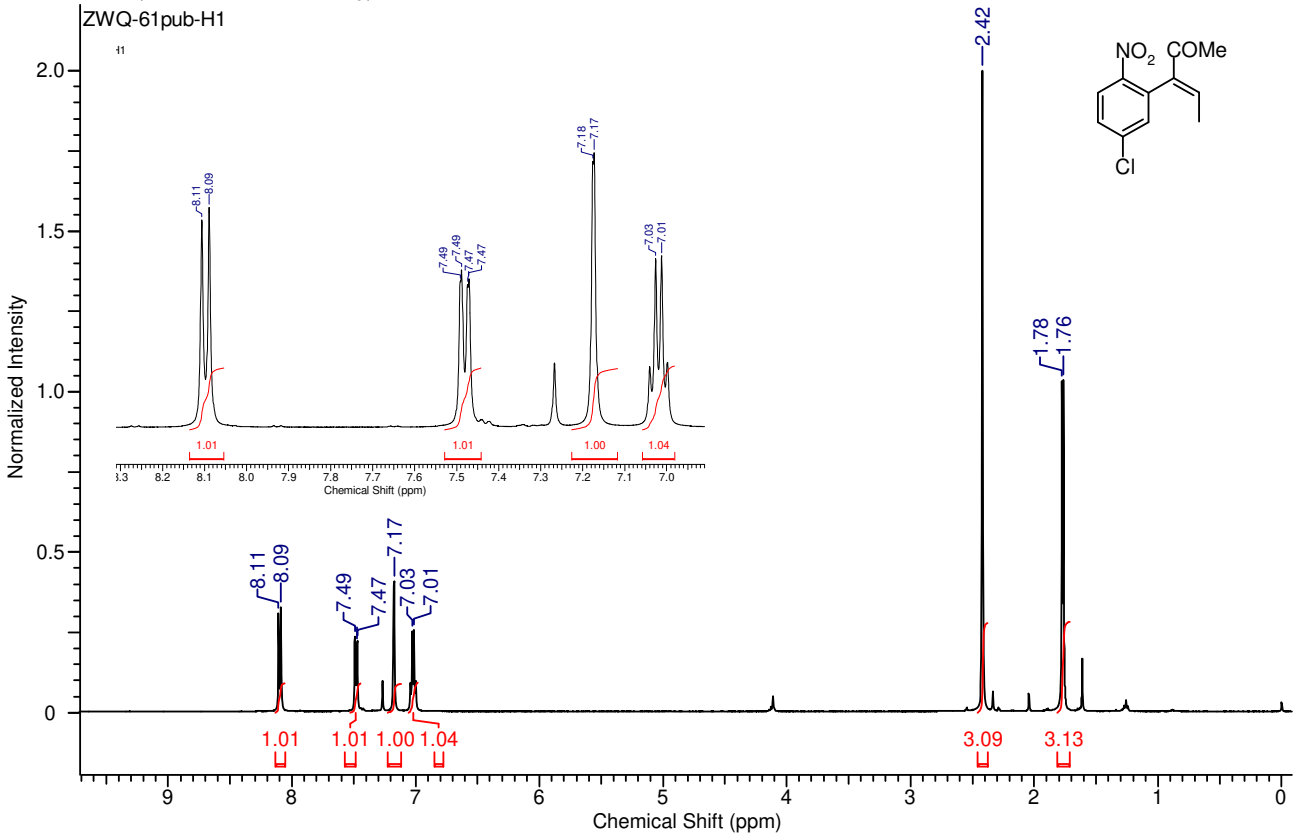


^{13}C NMR (125 MHz, $CDCl_3$)

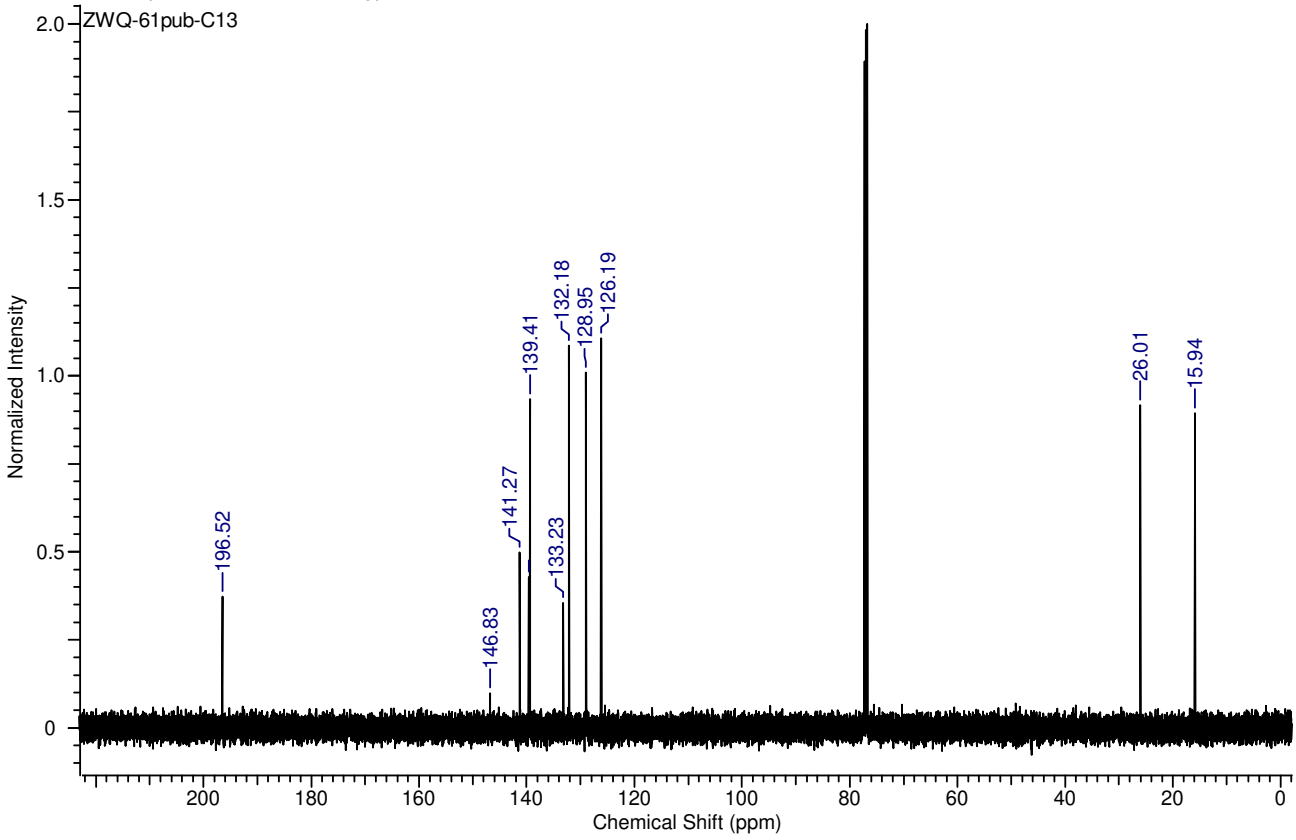


2u

^{1}H NMR (500 MHz, $CDCl_3$)

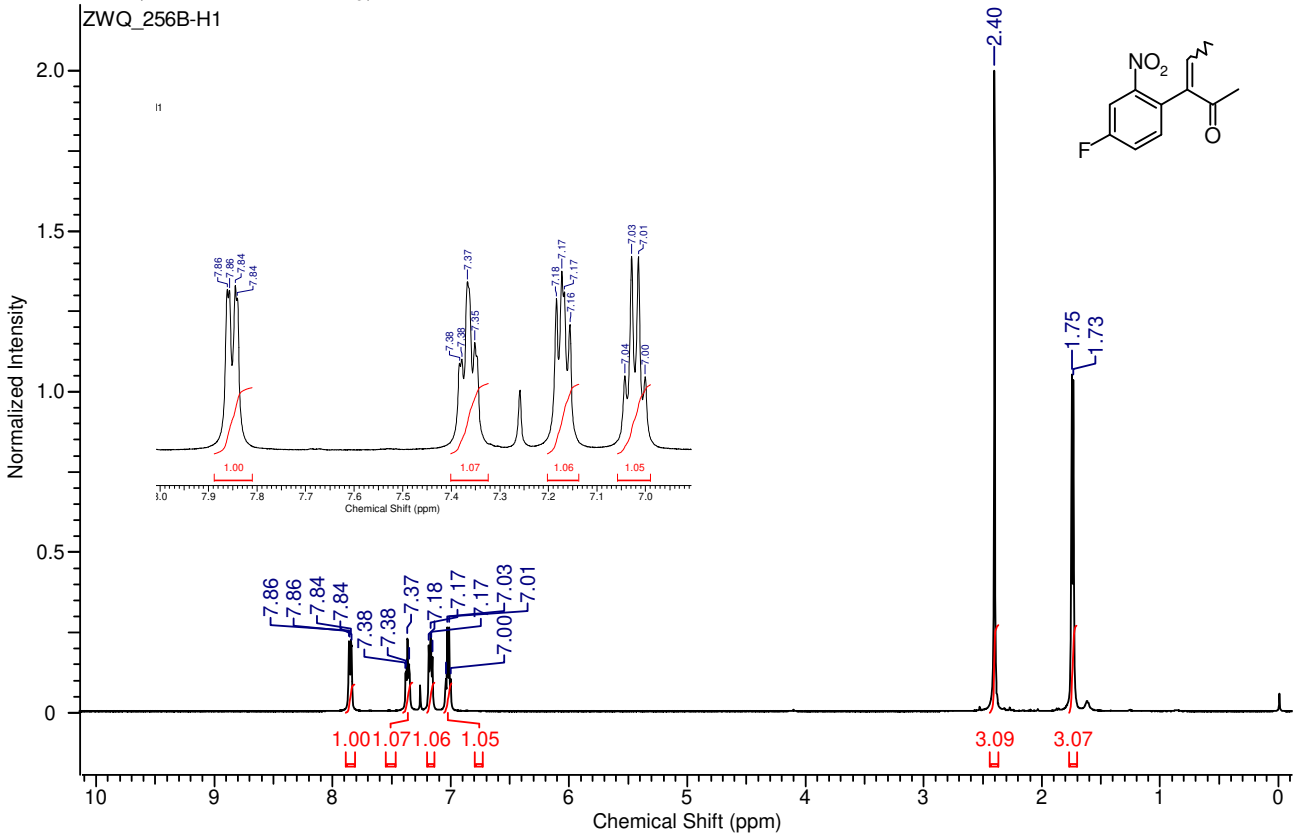


^{13}C NMR (125 MHz, $CDCl_3$)

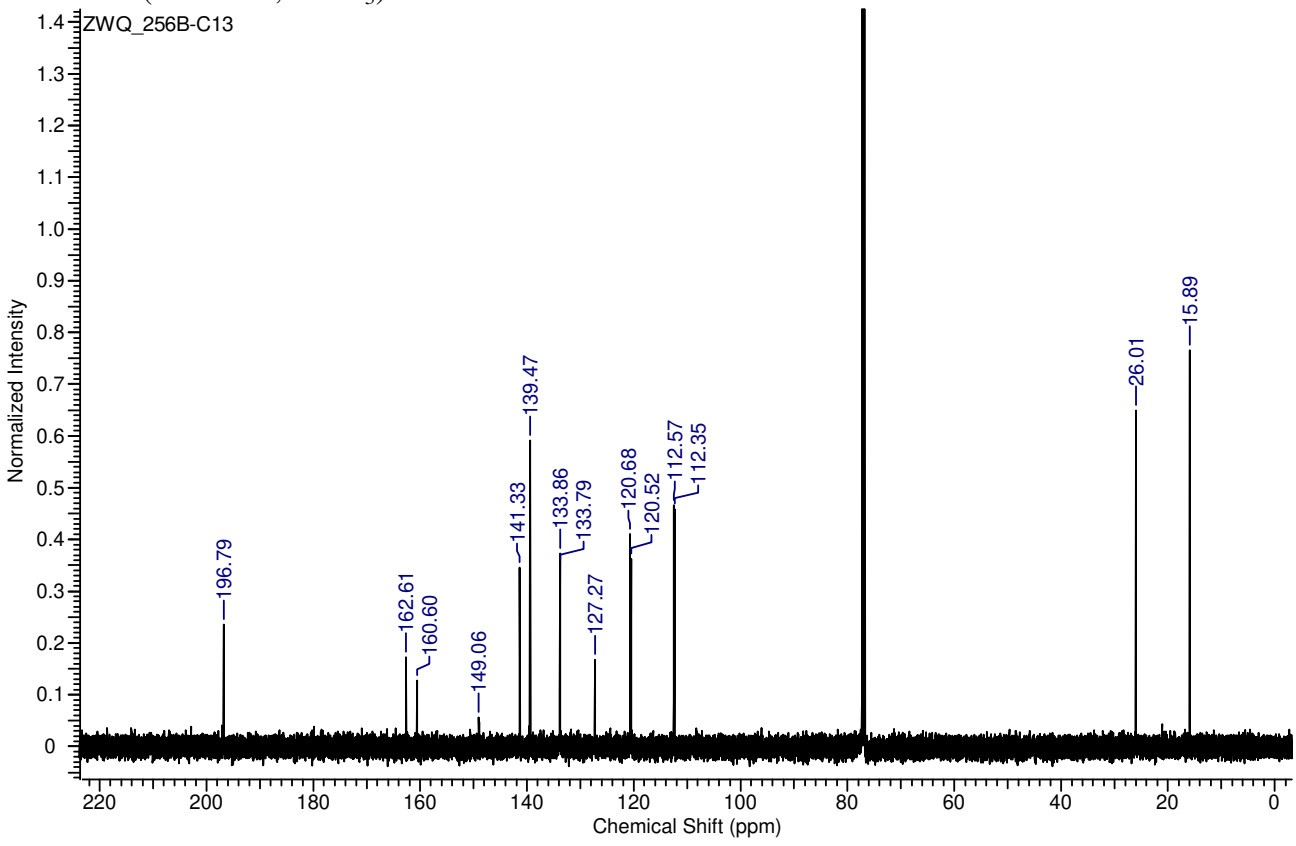


2v

^{1}H NMR (500 MHz, $CDCl_3$)

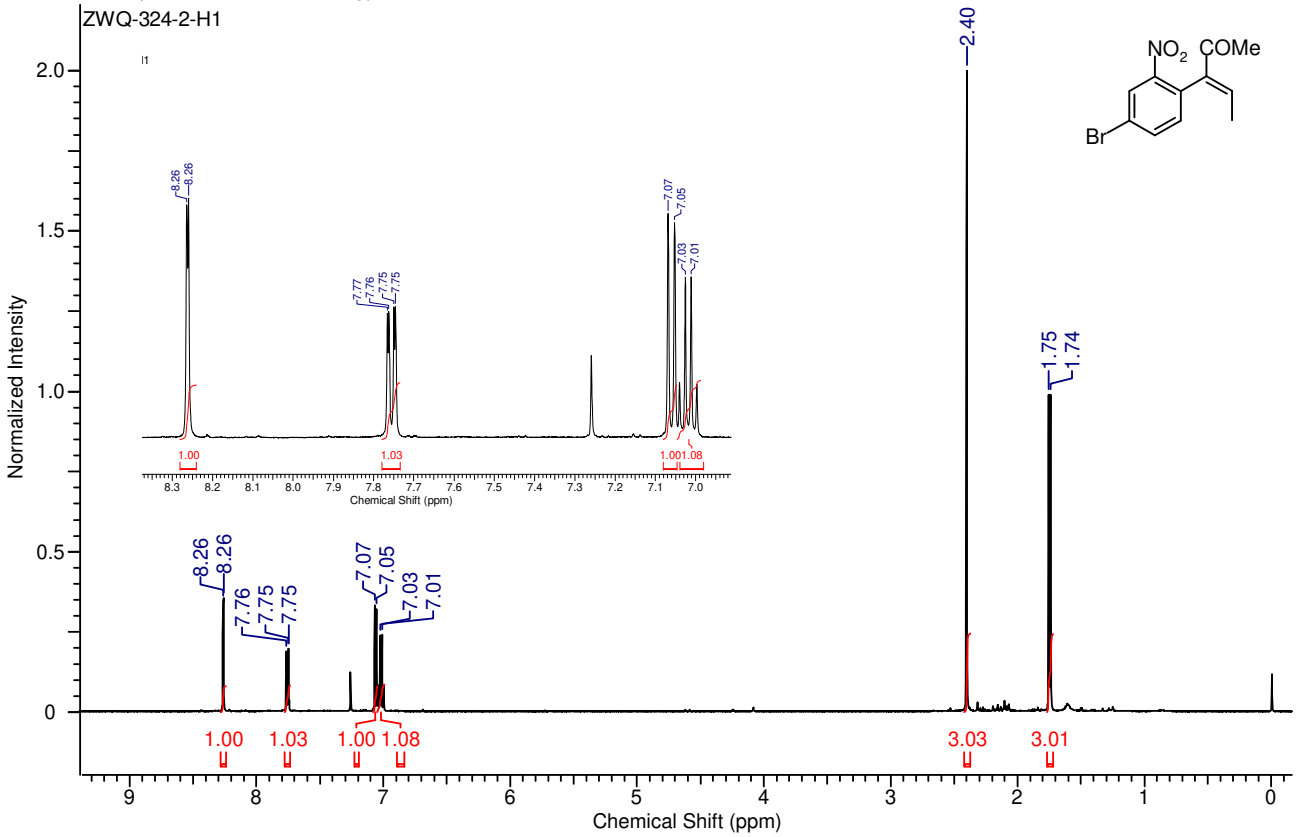


^{13}C NMR (125 MHz, $CDCl_3$)

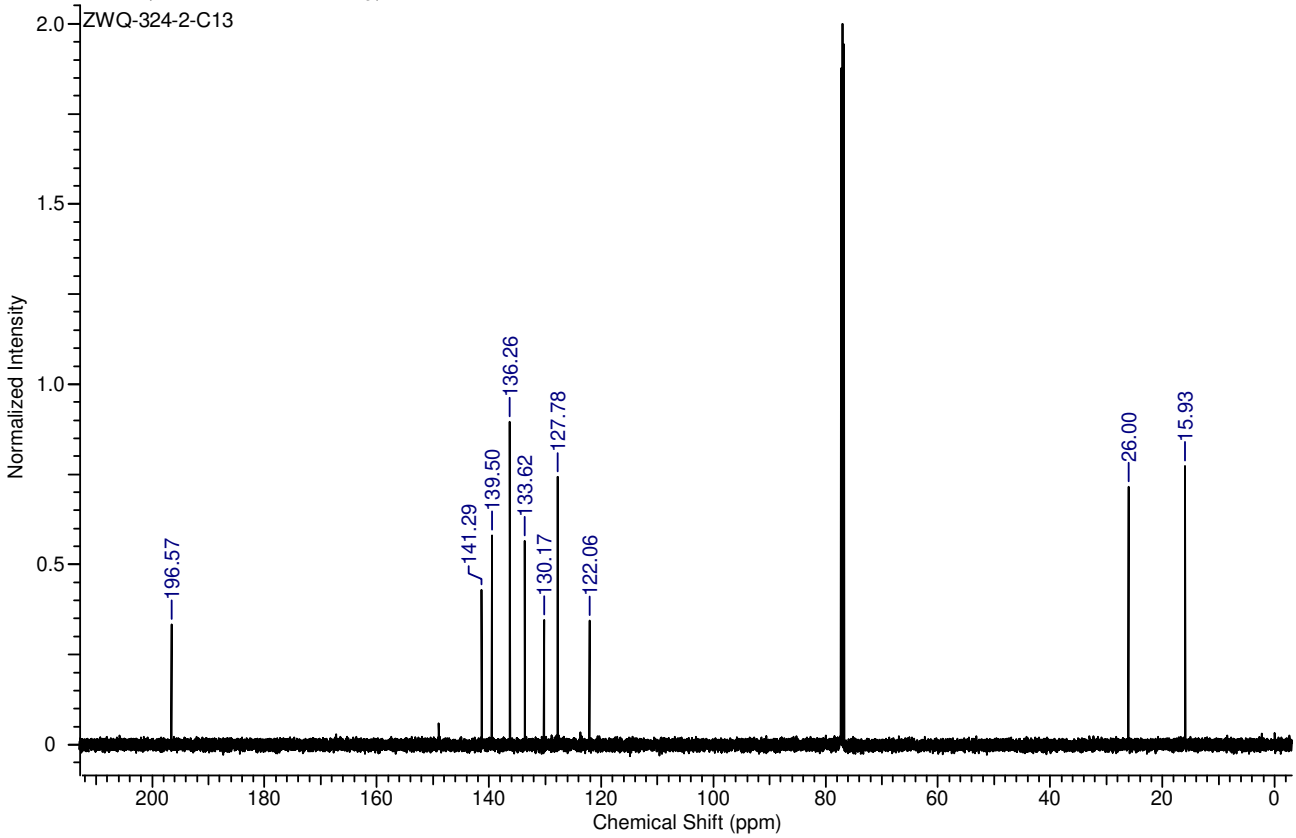


2w

^{1}H NMR (500 MHz, $CDCl_3$)

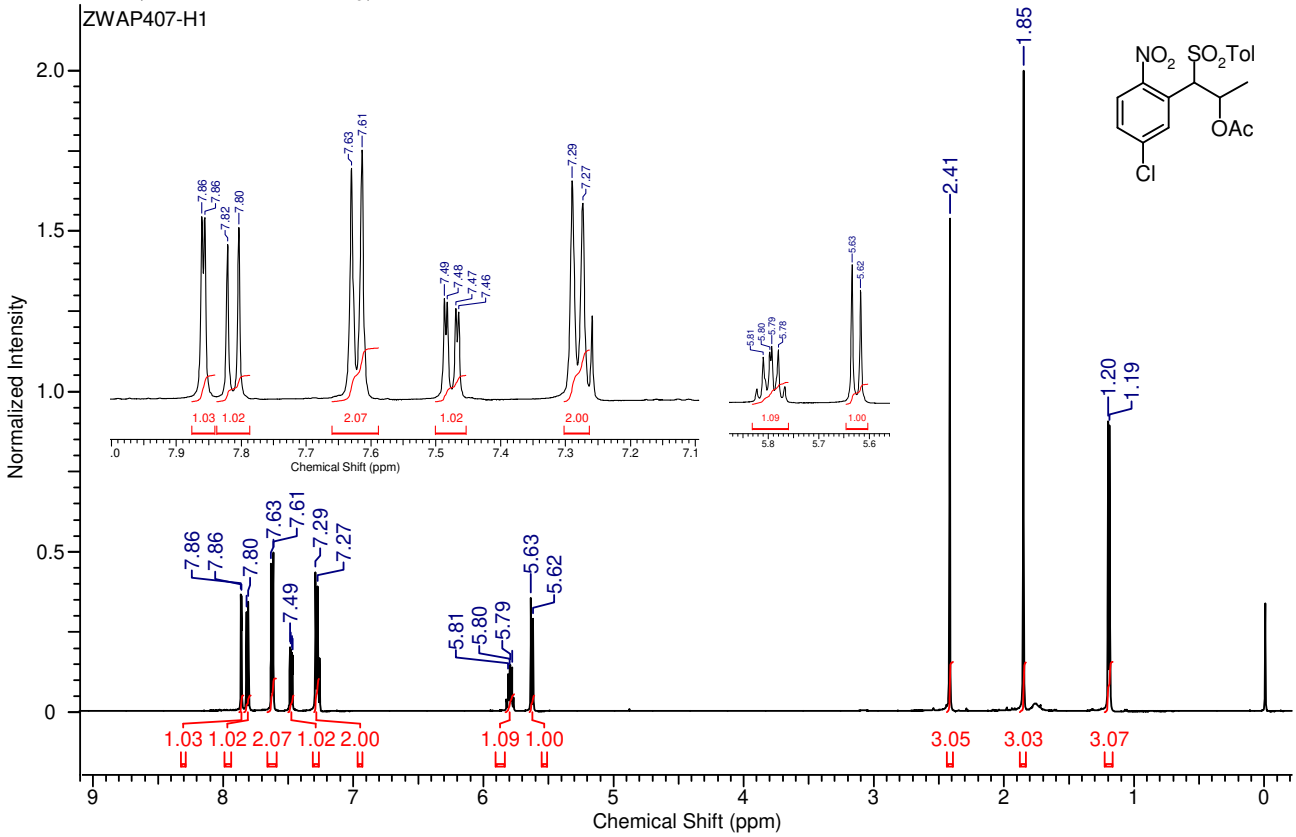


^{13}C NMR (125 MHz, $CDCl_3$)

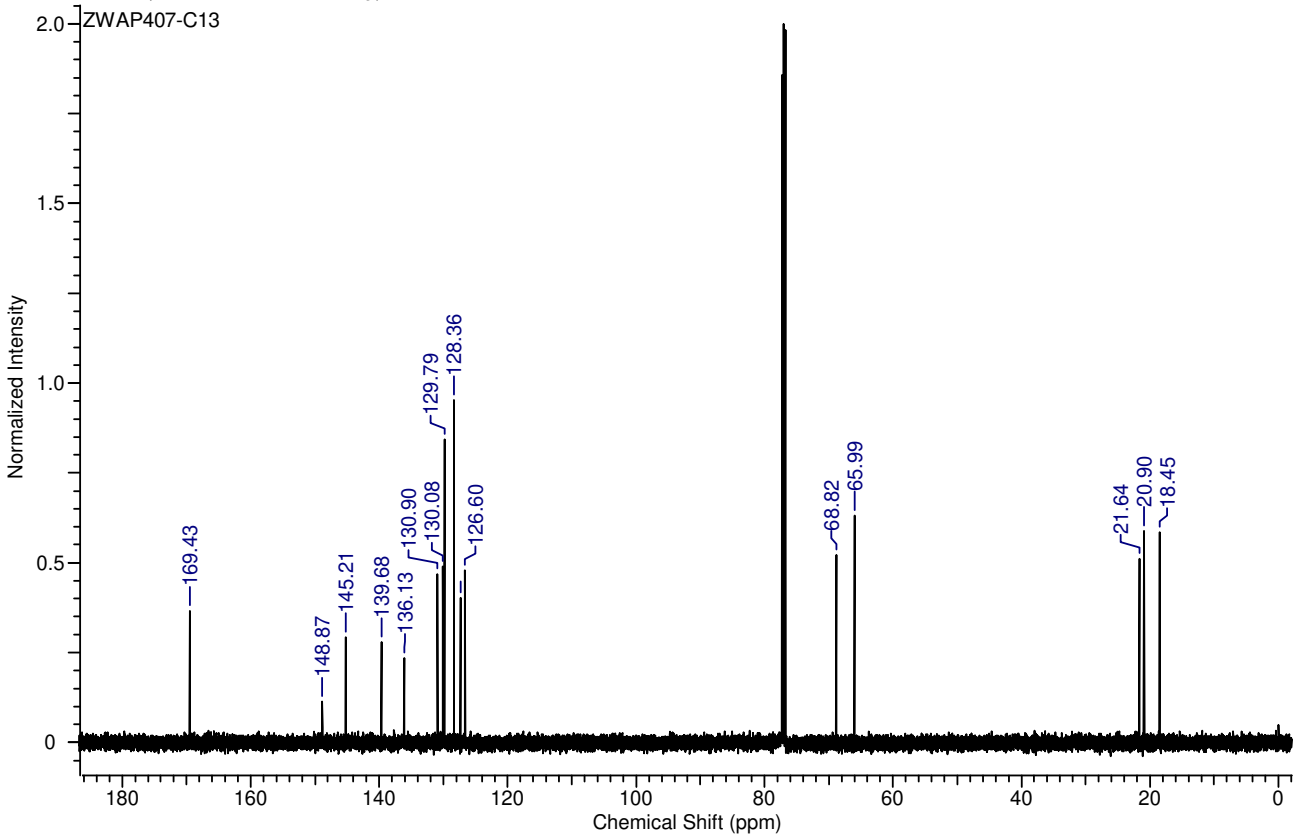


2x

^{1}H NMR (500 MHz, $CDCl_3$)

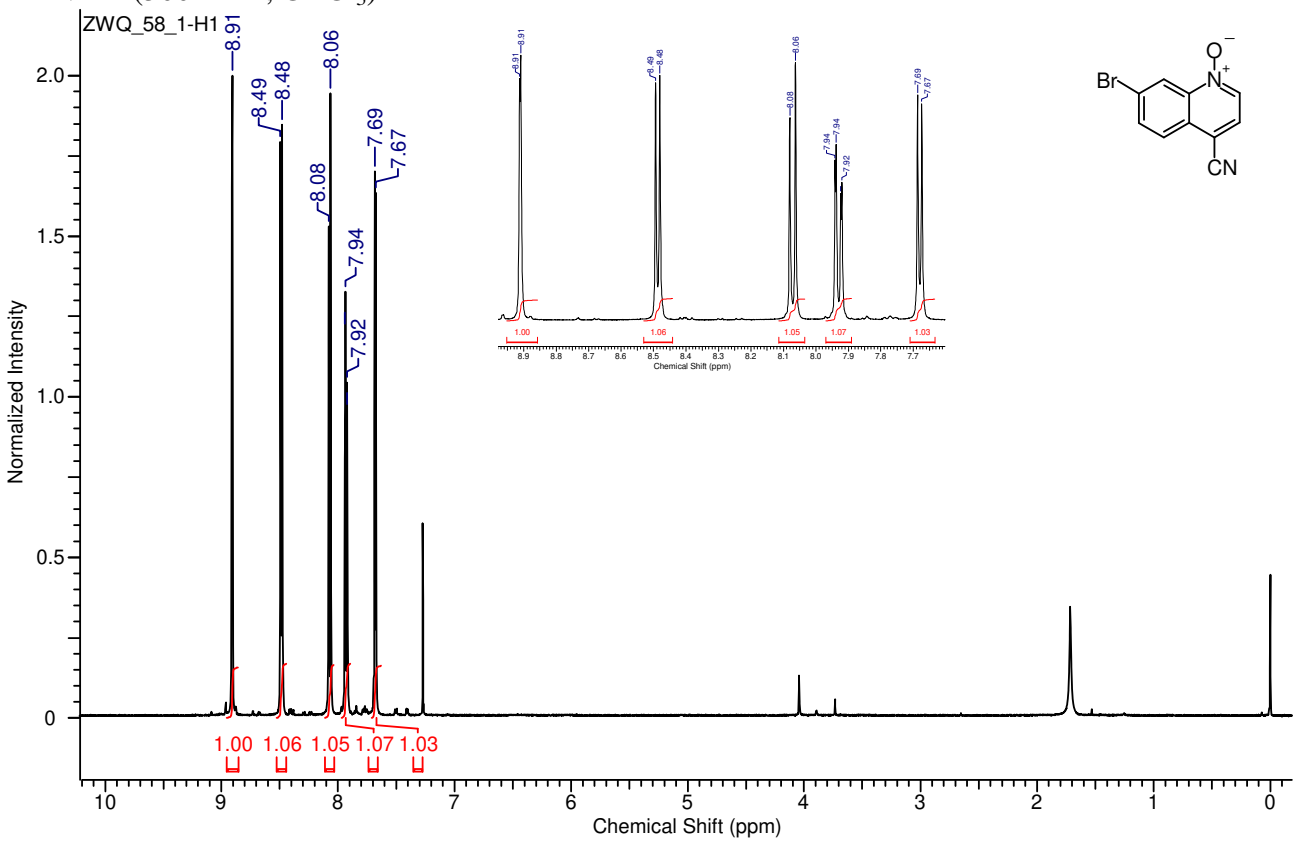


^{13}C NMR (125 MHz, $CDCl_3$)

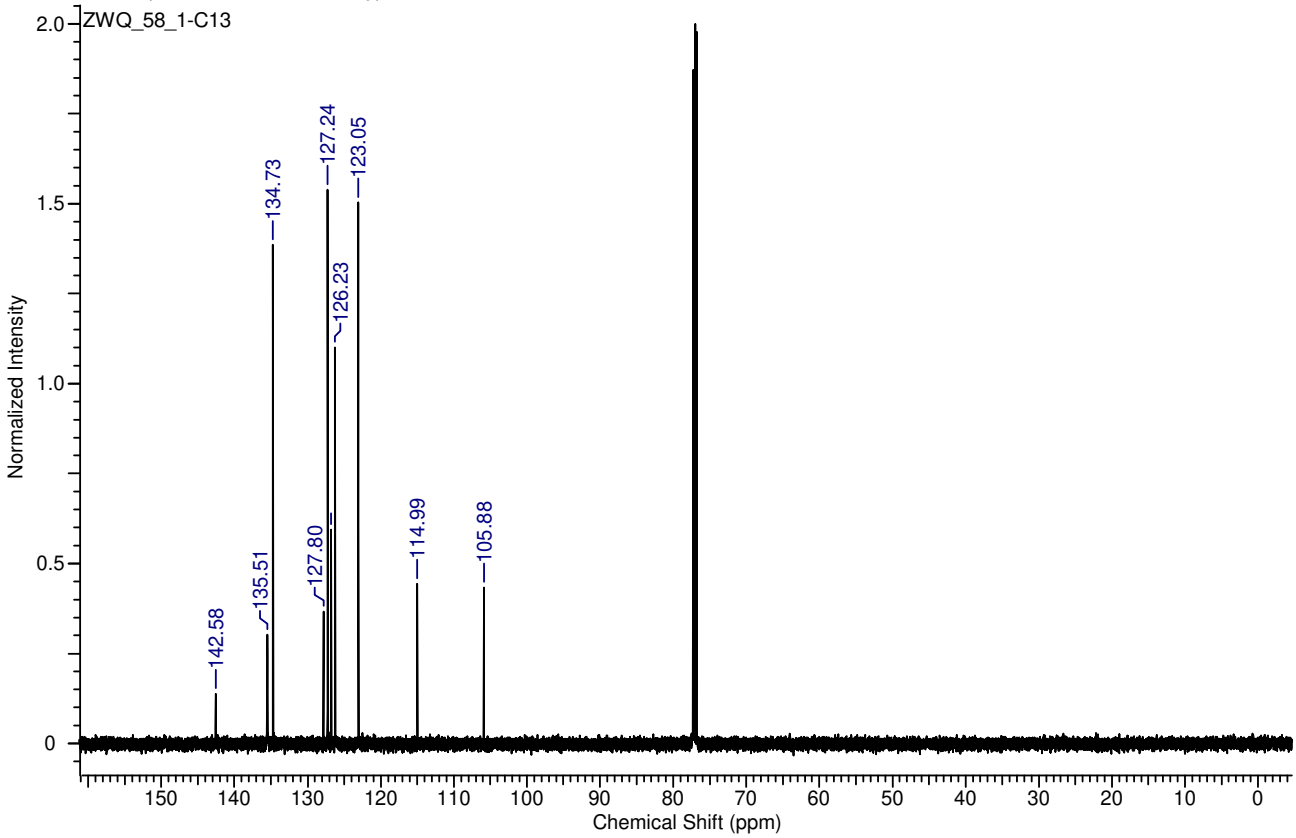


3a

^{1}H NMR (500 MHz, $CDCl_3$)

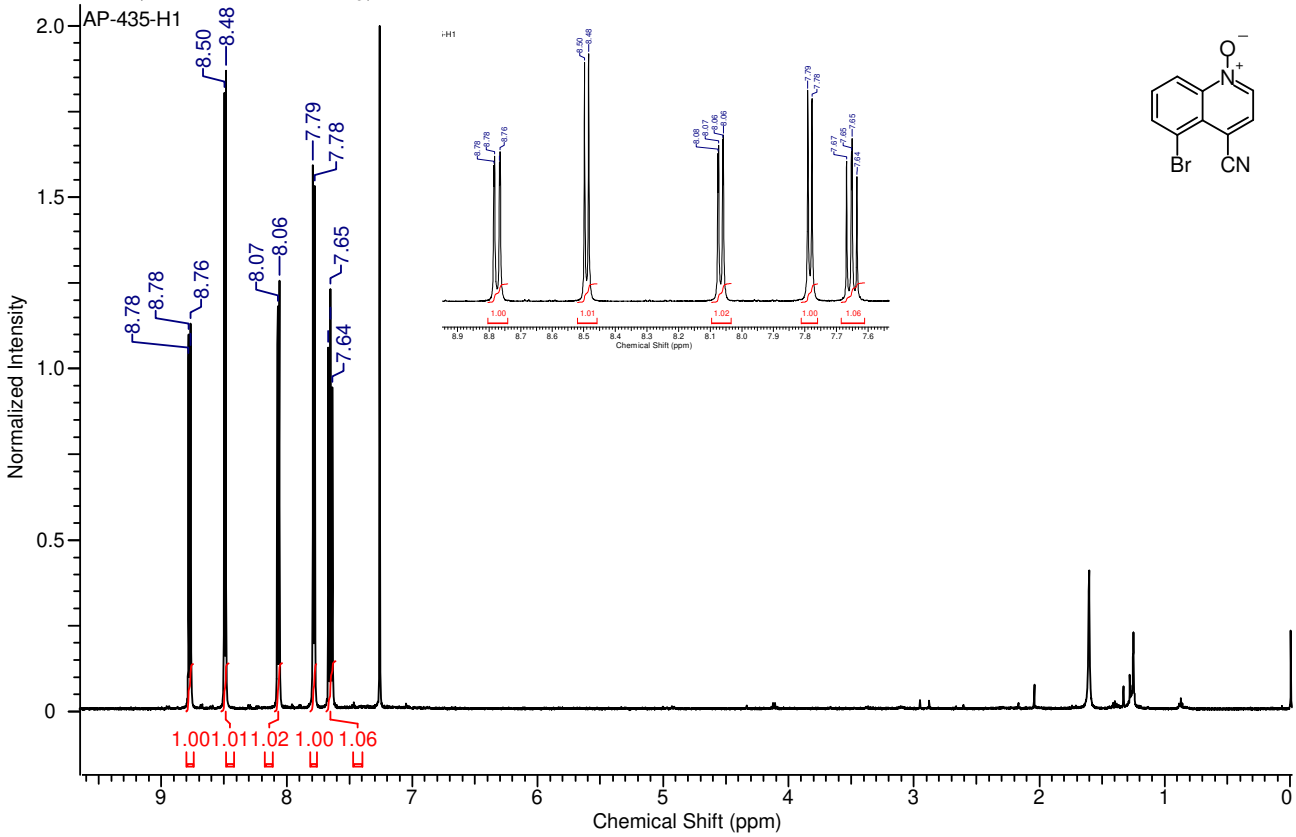


^{13}C NMR (125 MHz, $CDCl_3$)

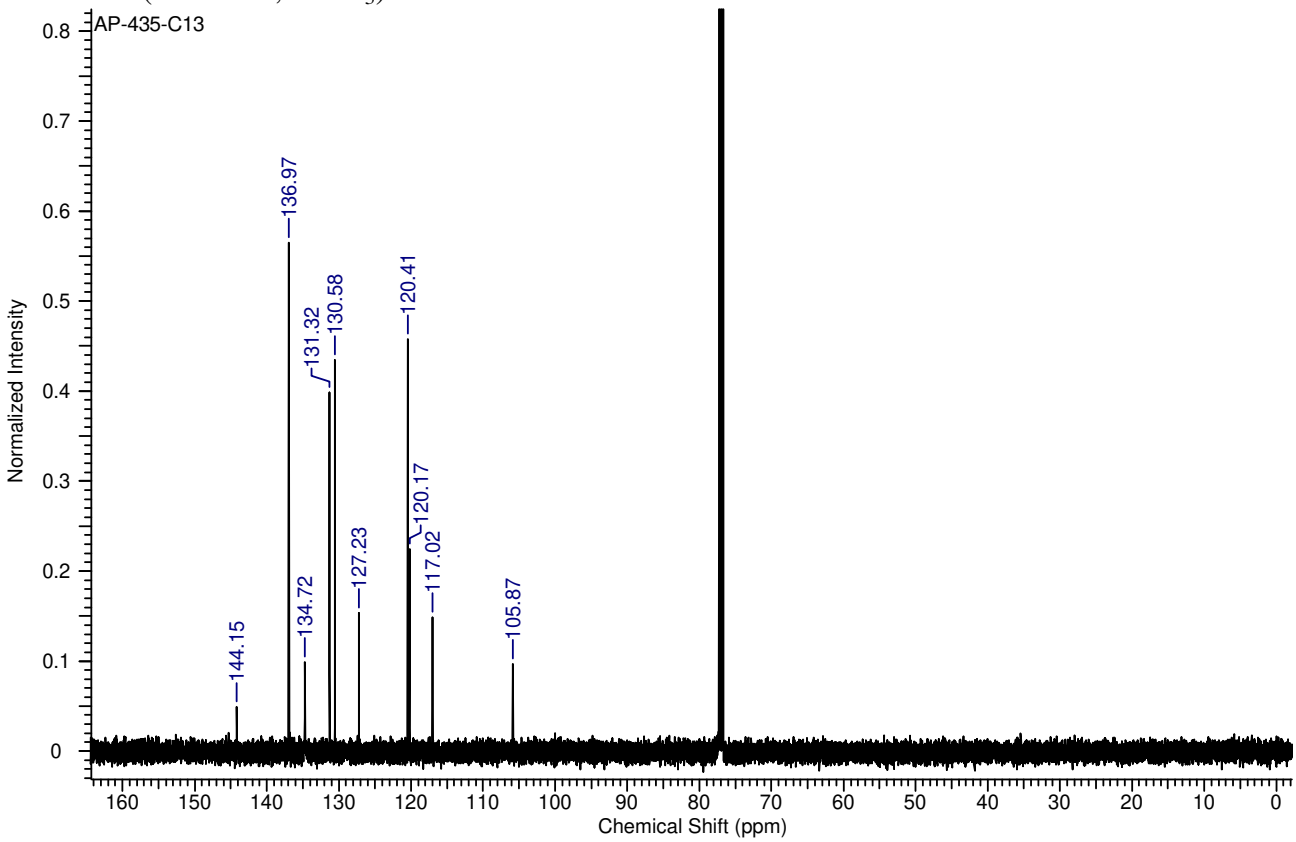


3b

^{1}H NMR (500 MHz, $CDCl_3$)

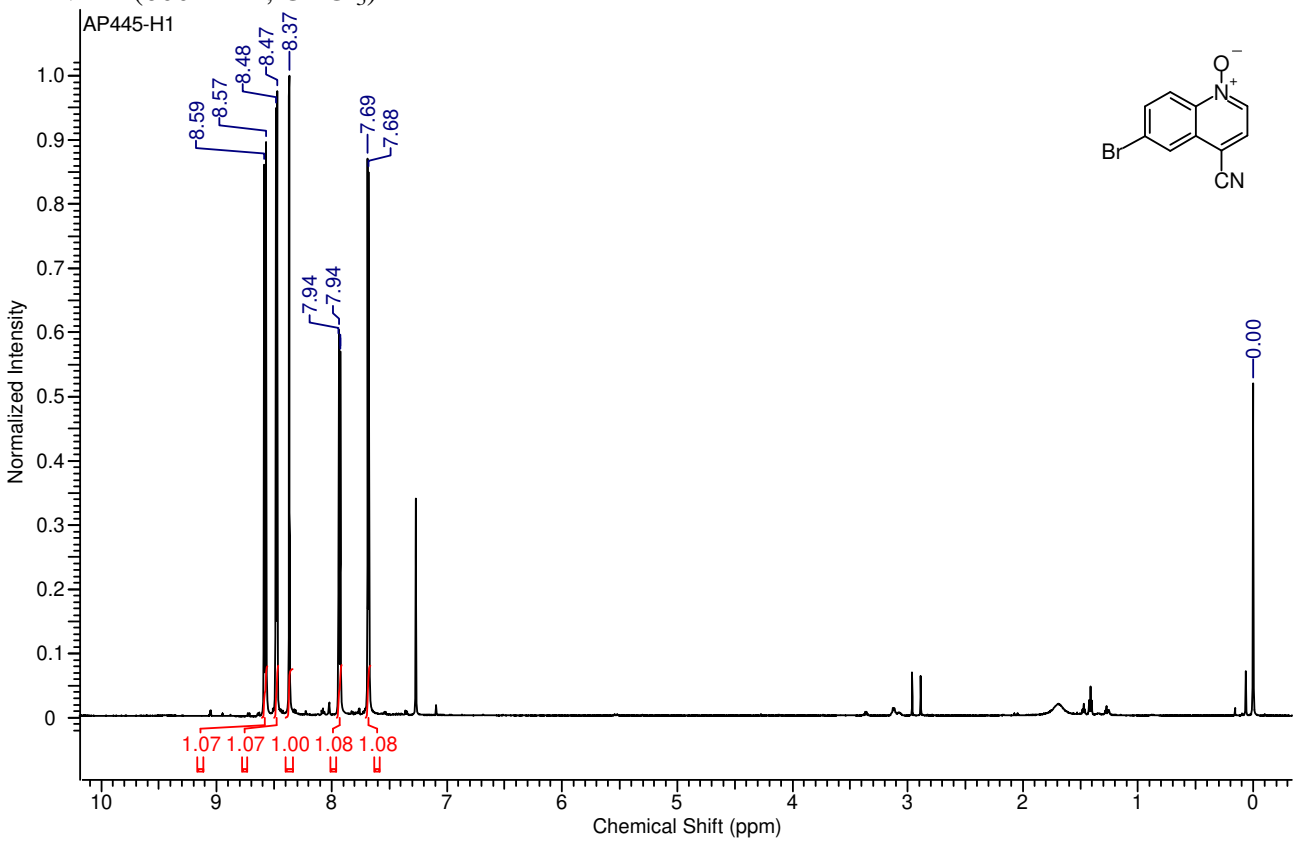


^{13}C NMR (125 MHz, $CDCl_3$)

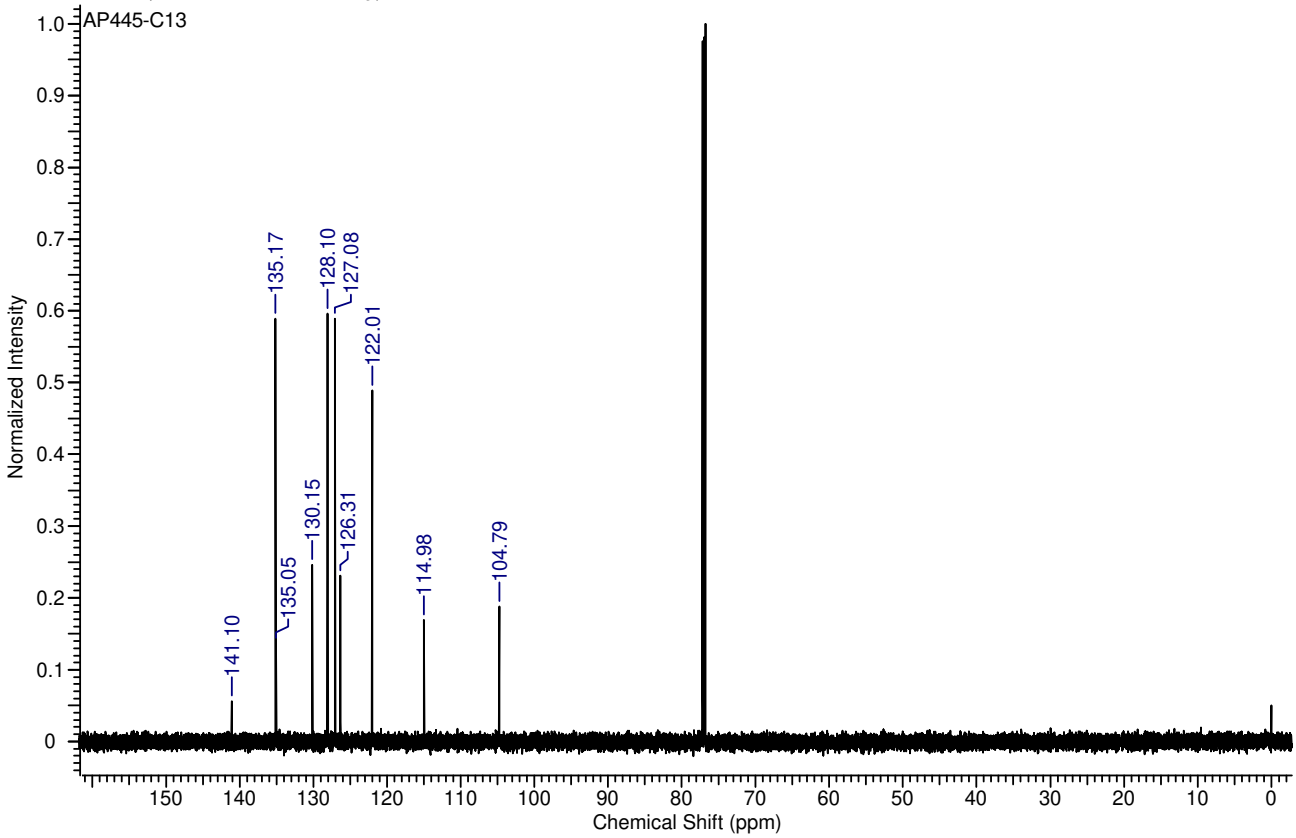


3c

^{1}H NMR (600 MHz, $CDCl_3$)

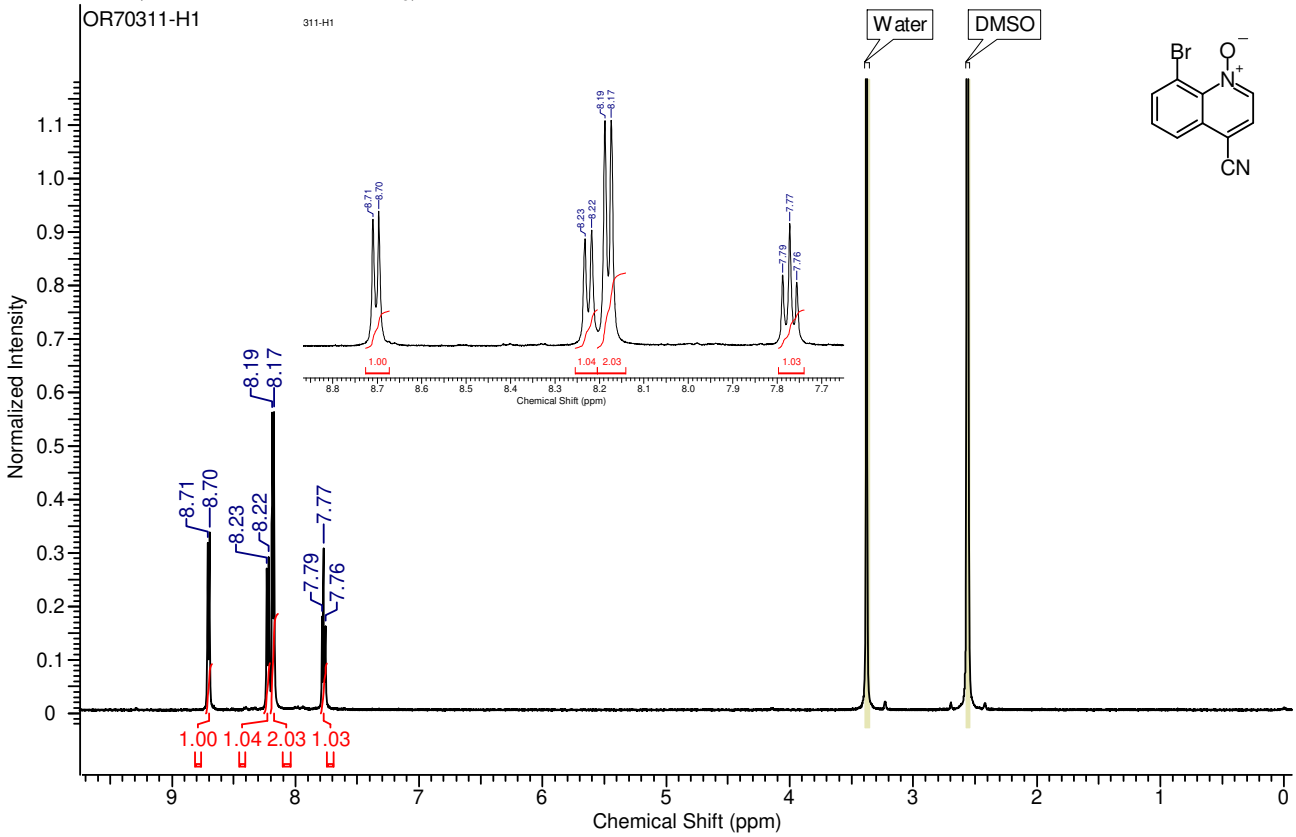


^{13}C NMR (150 MHz, $CDCl_3$)

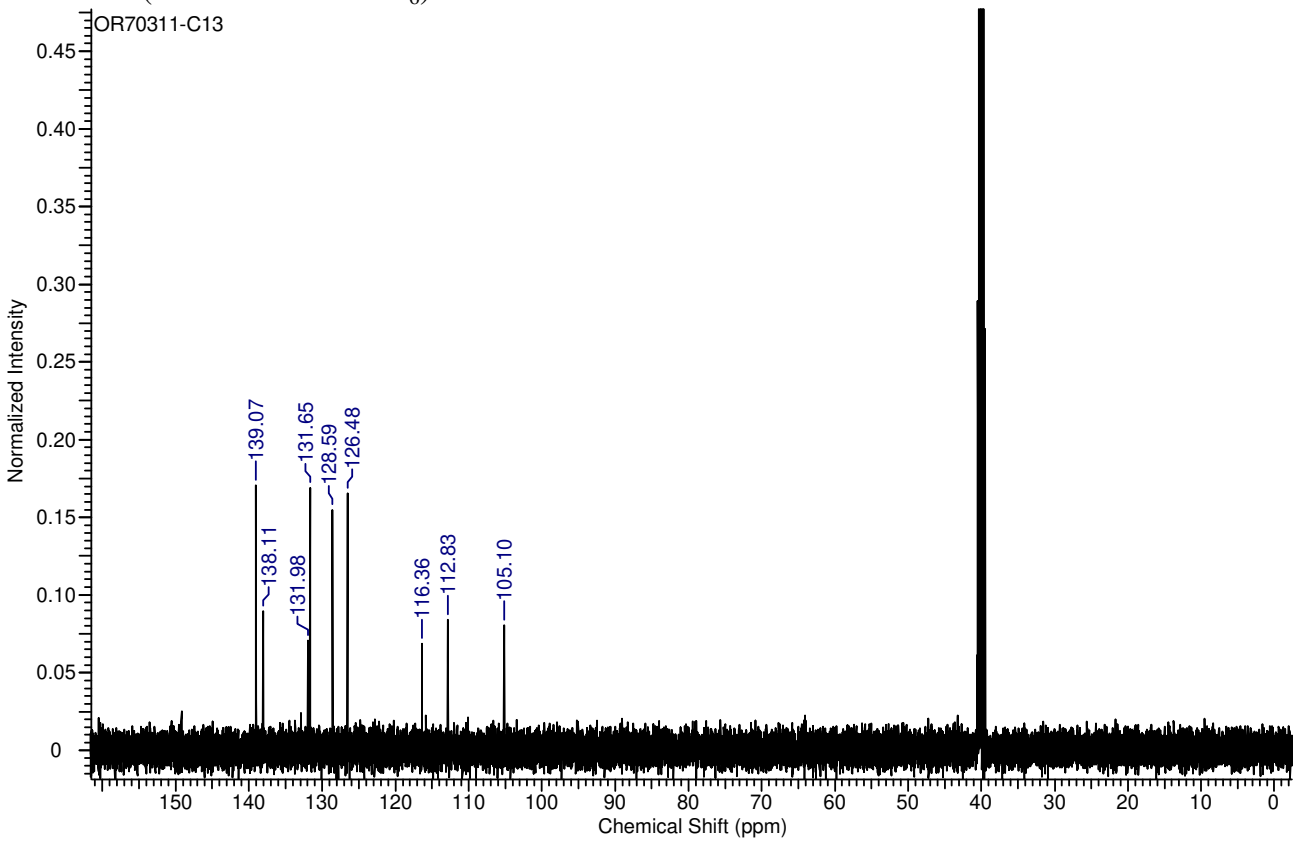


3d

^{1}H NMR (500 MHz, DMSO-d_6)

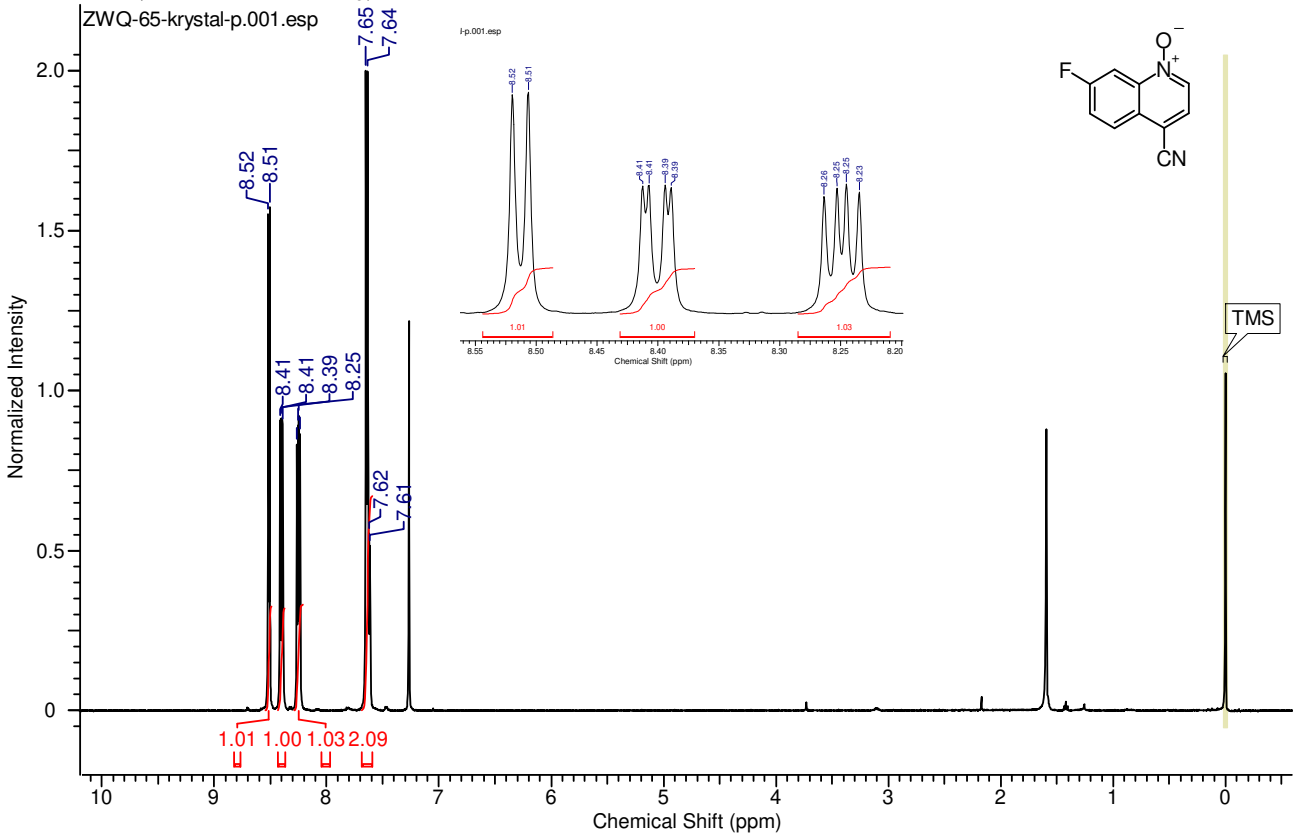


^{13}C NMR (125 MHz. DMSO-d_6)

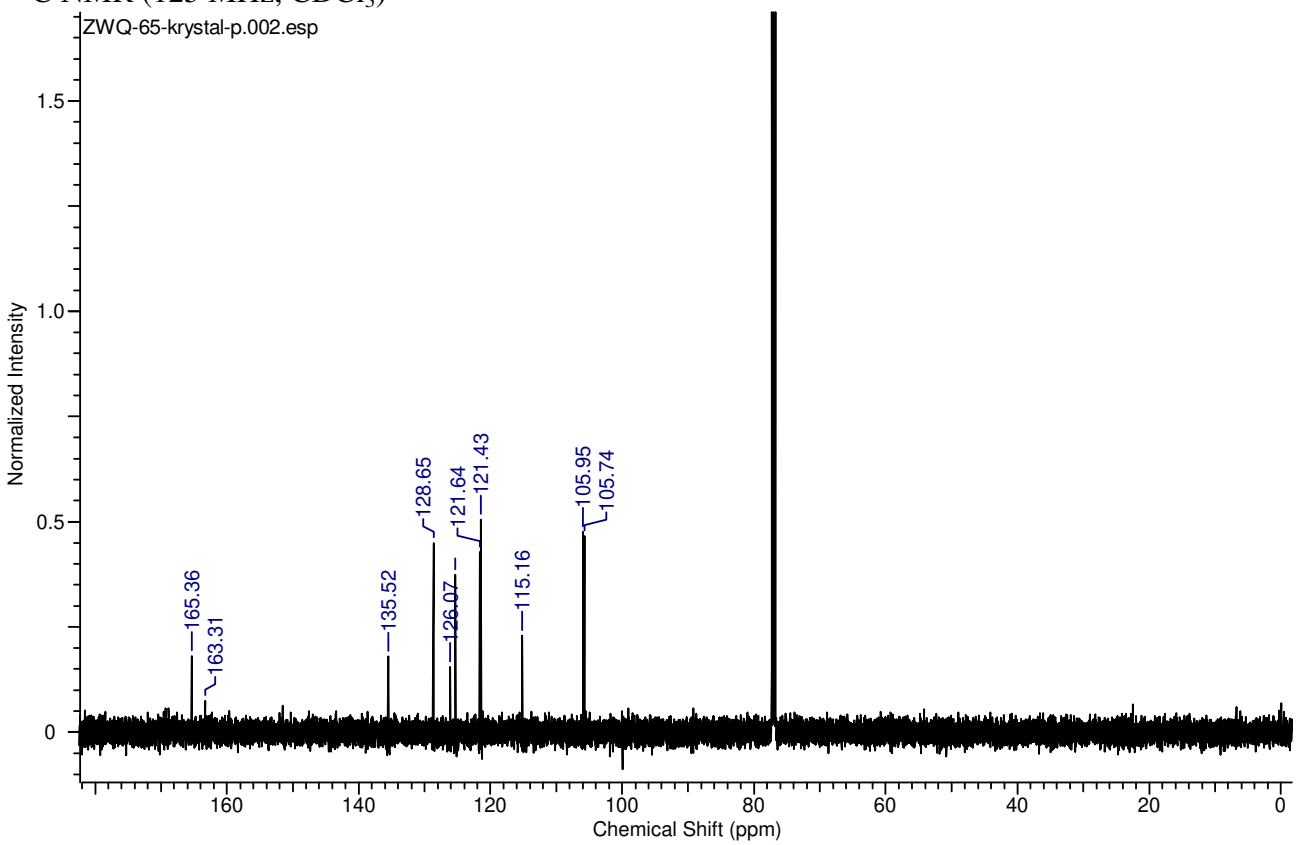


3e

^{1}H NMR (500 MHz, $CDCl_3$)

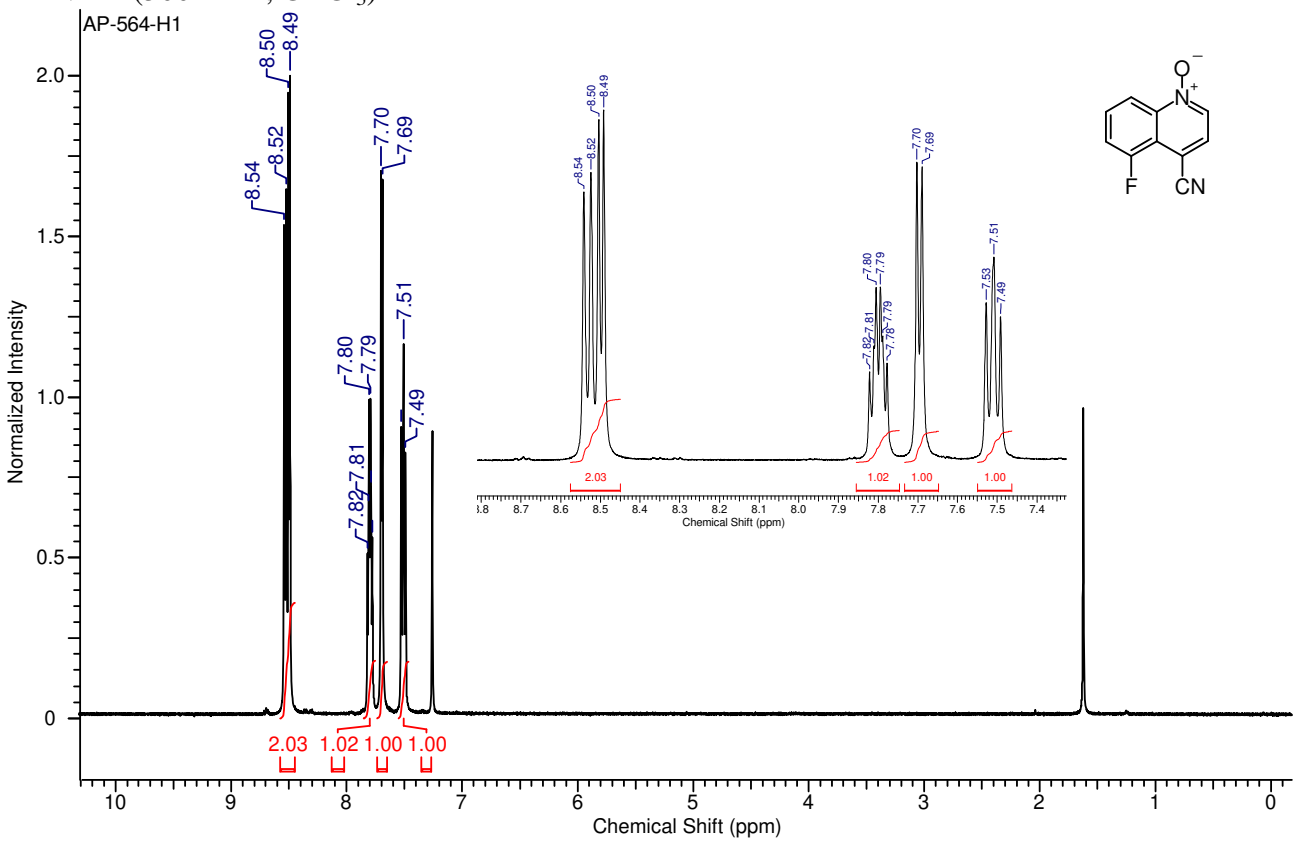


^{13}C NMR (125 MHz, $CDCl_3$)

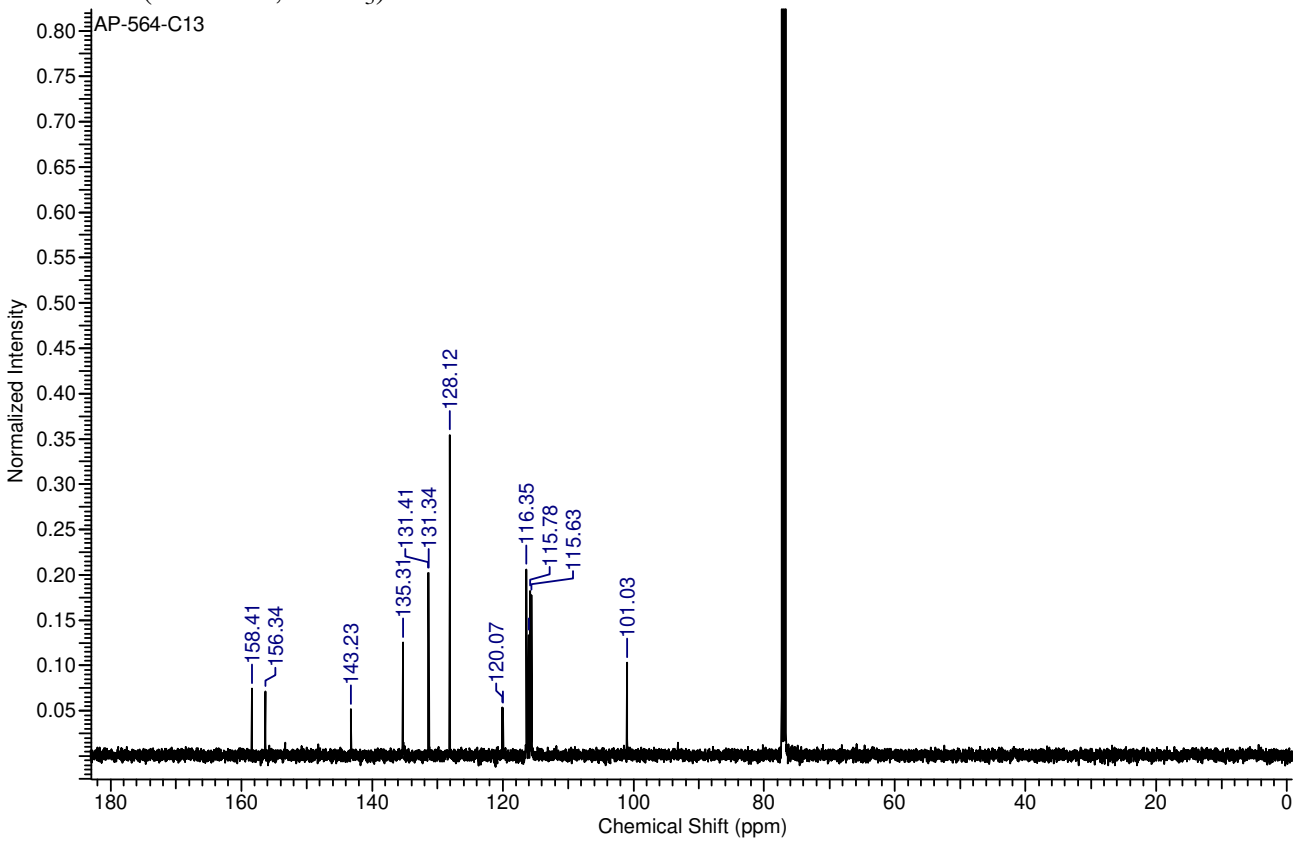


3f

^{1}H NMR (500 MHz, $CDCl_3$)

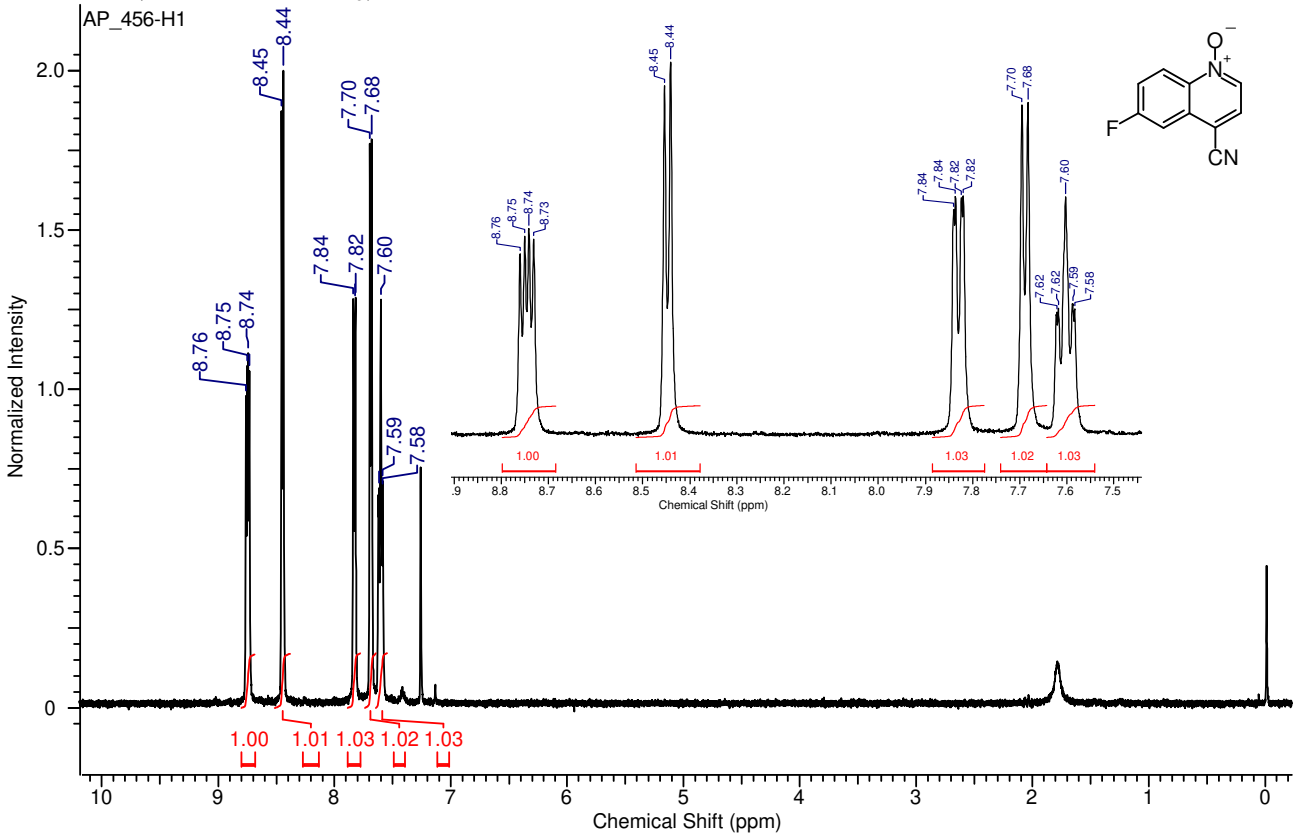


^{13}C NMR (125 MHz, $CDCl_3$)

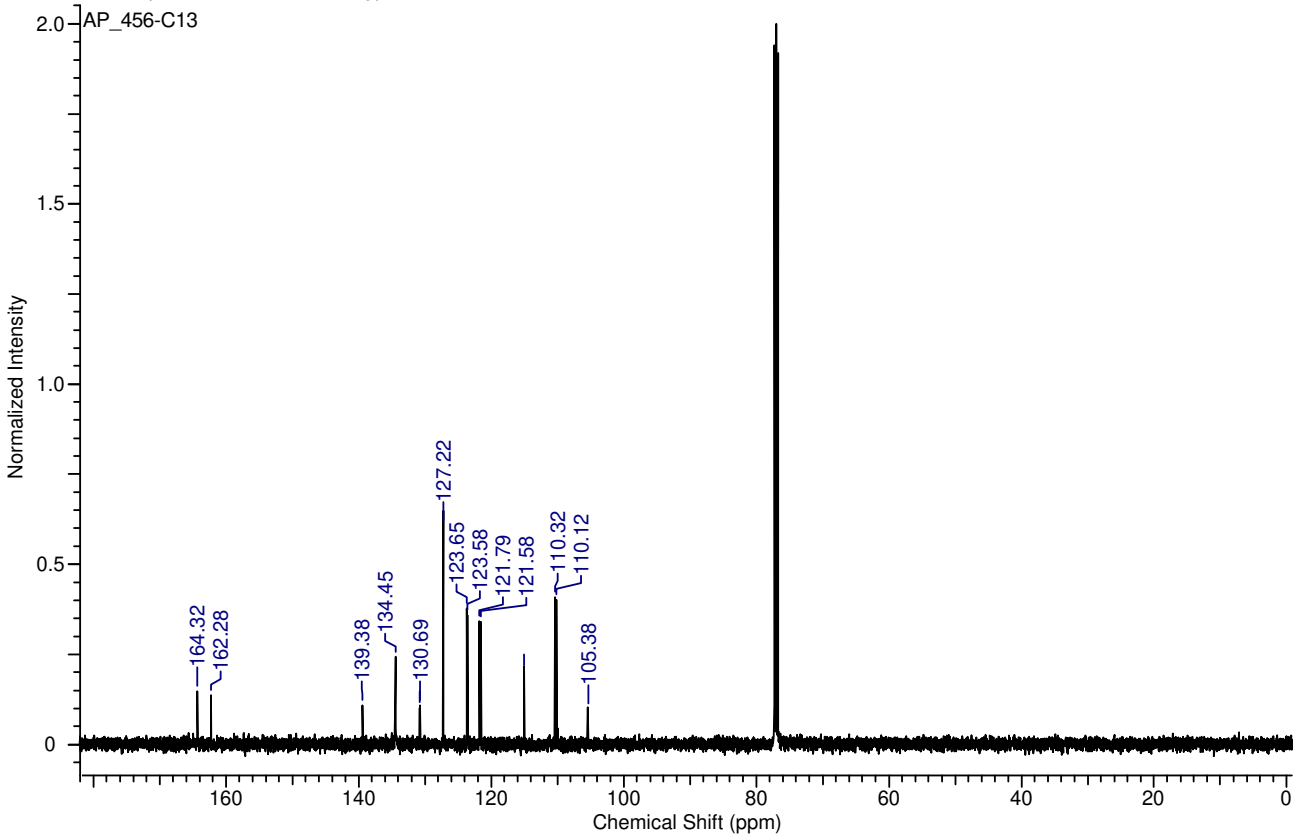


3g

^{1}H NMR (500 MHz, $CDCl_3$)

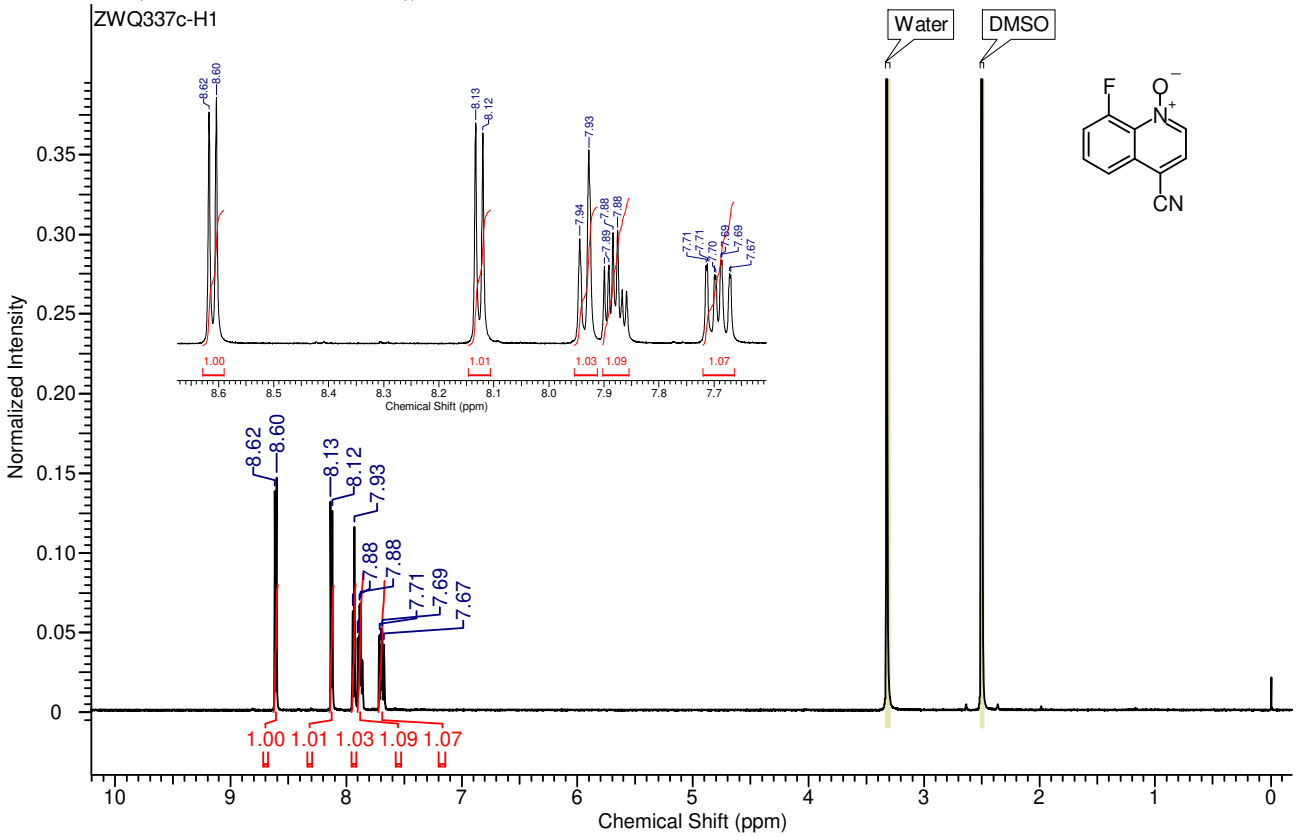


^{13}C NMR (125 MHz, $CDCl_3$)

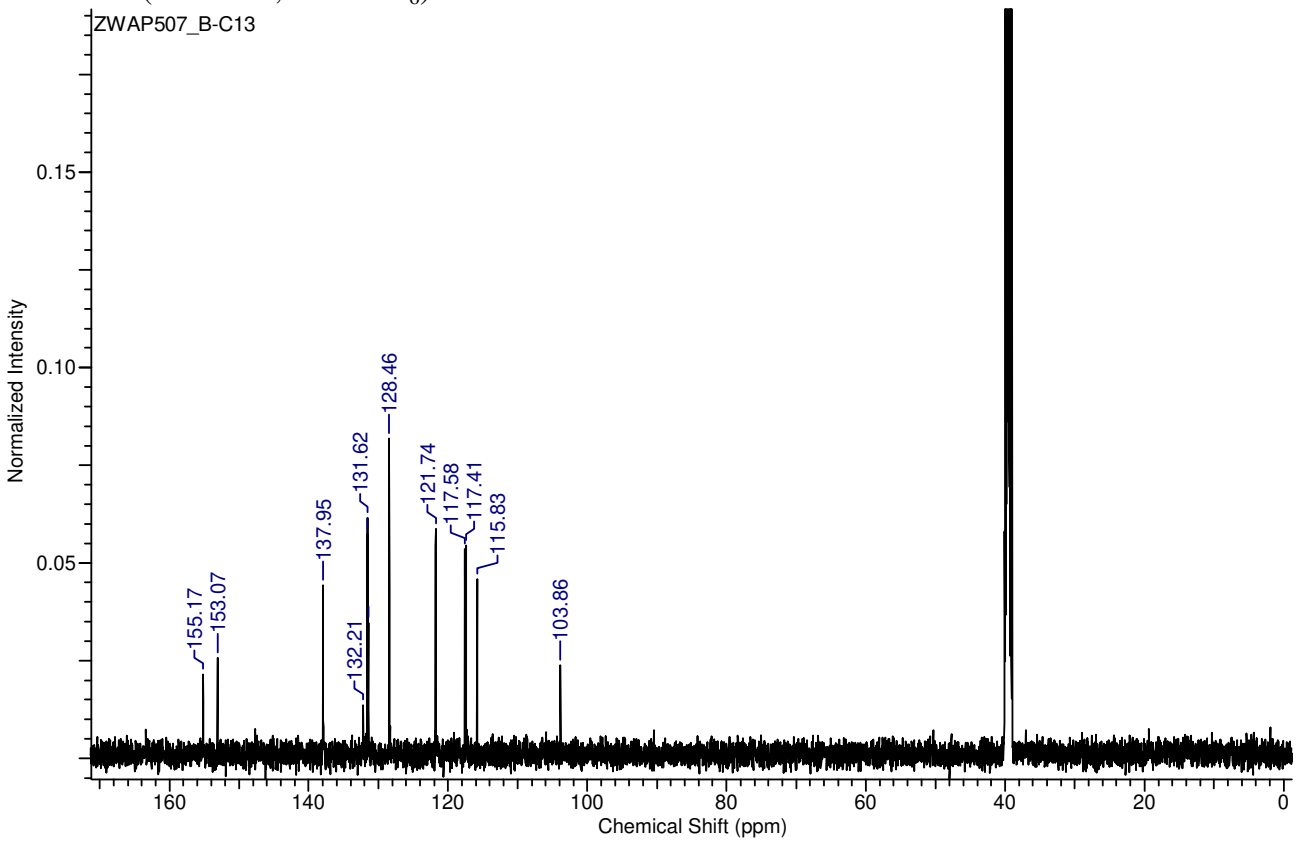


3h

^{1}H NMR (500 MHz, DMSO-d_6)

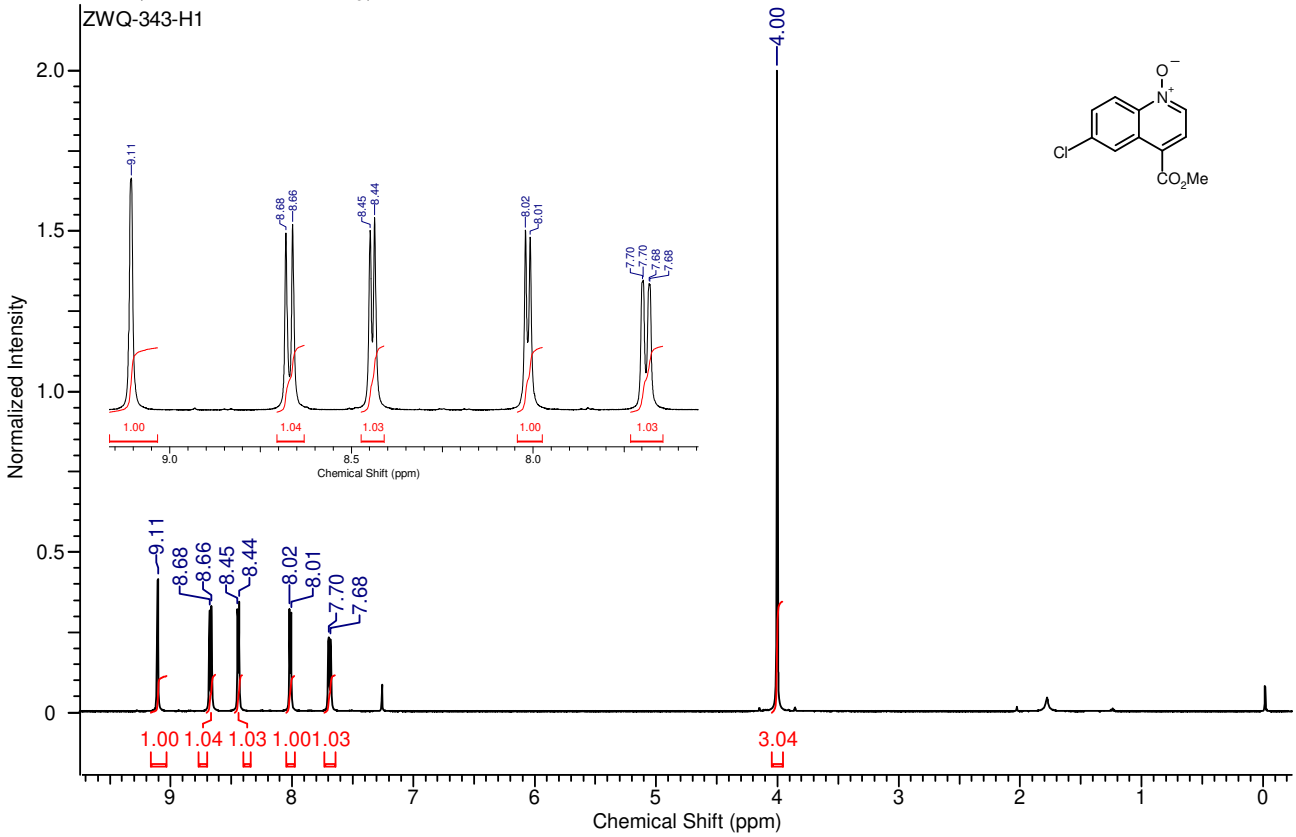


^{13}C NMR (125 MHz, DMSO-d_6)

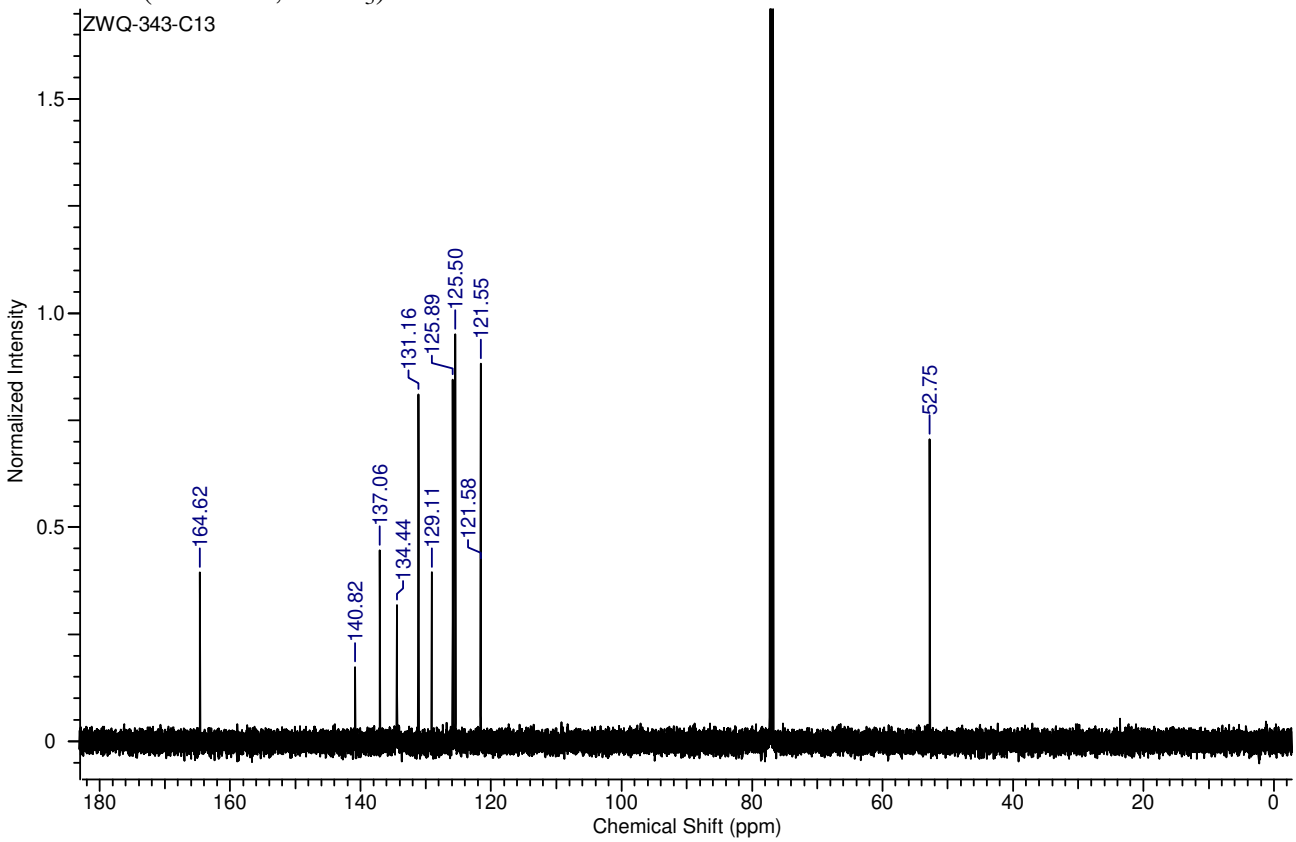


3j

^{1}H NMR (500 MHz, $CDCl_3$)

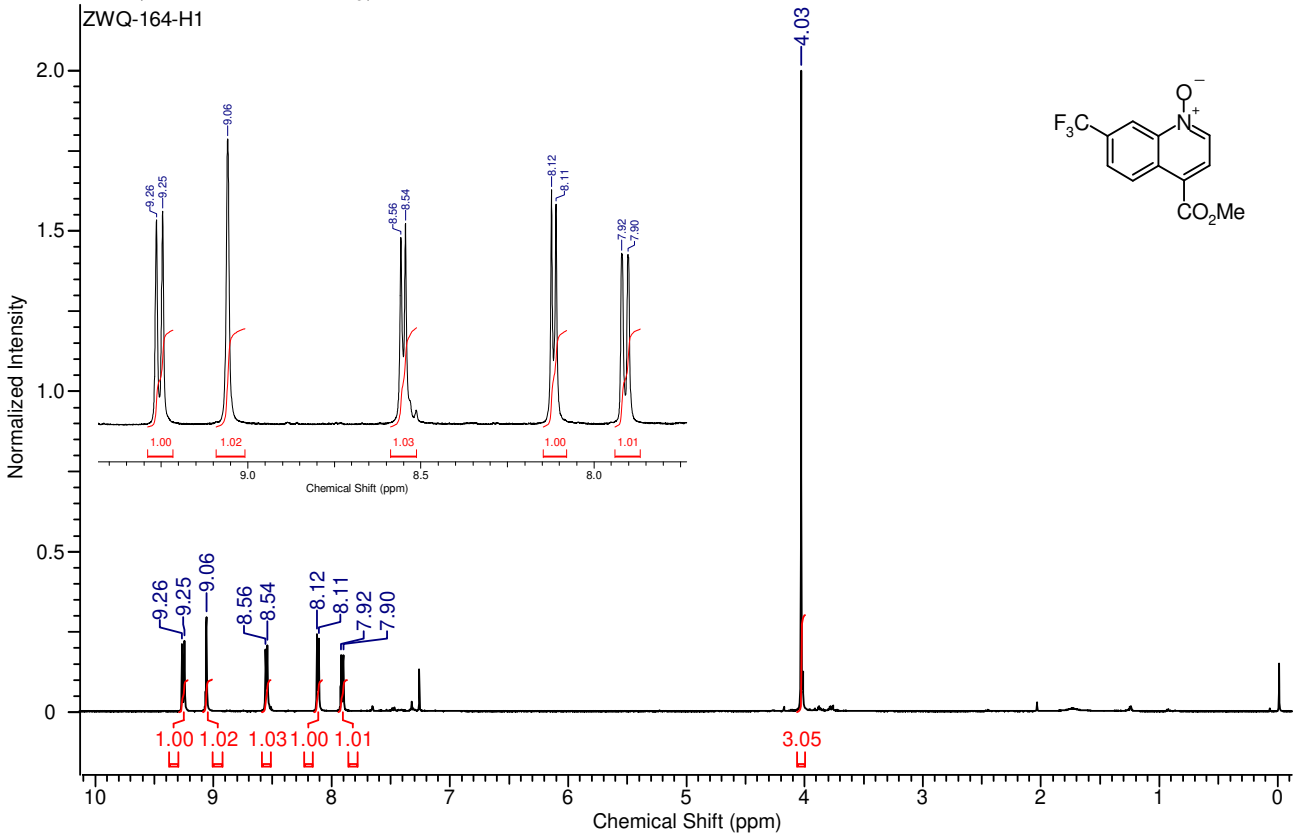


^{13}C NMR (125 MHz, $CDCl_3$)

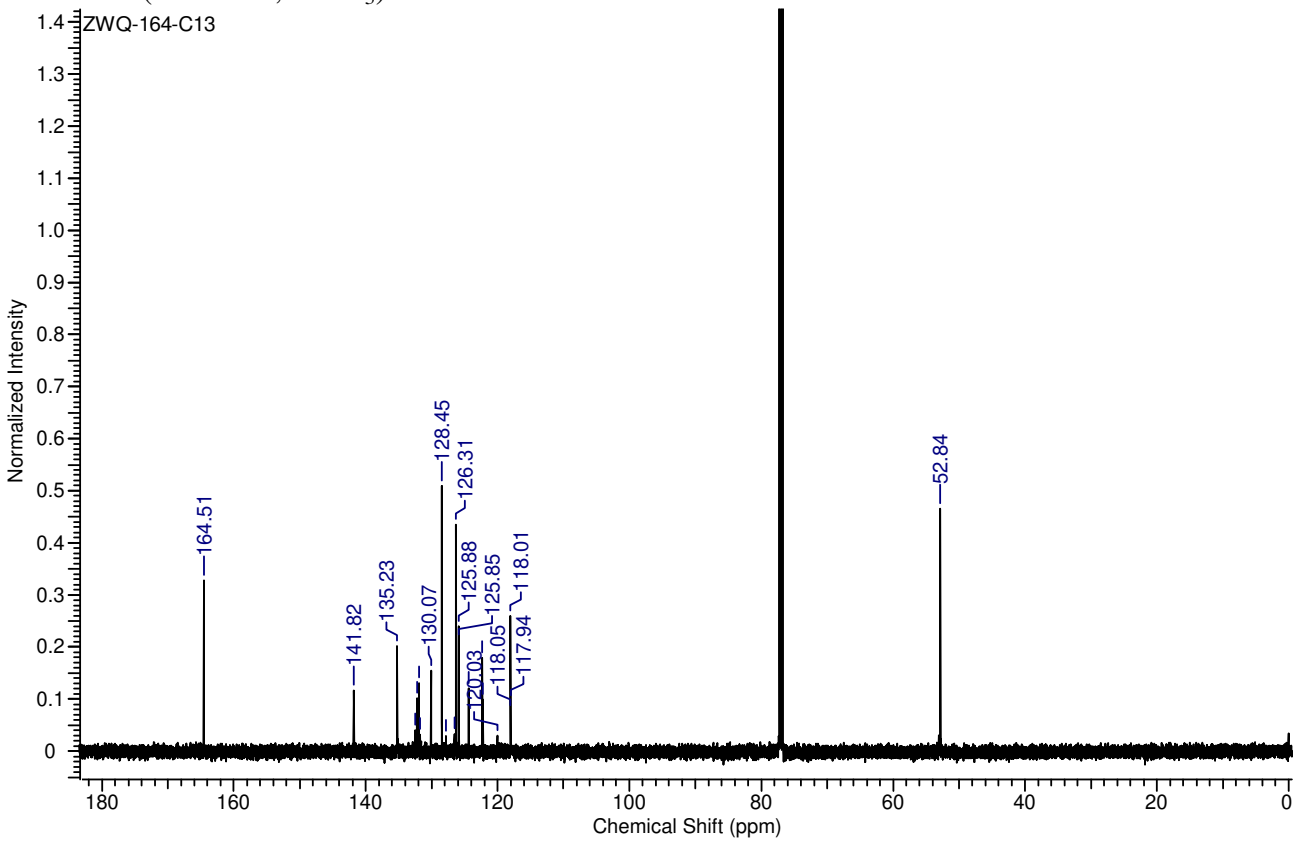


3m

^{1}H NMR (500 MHz, $CDCl_3$)

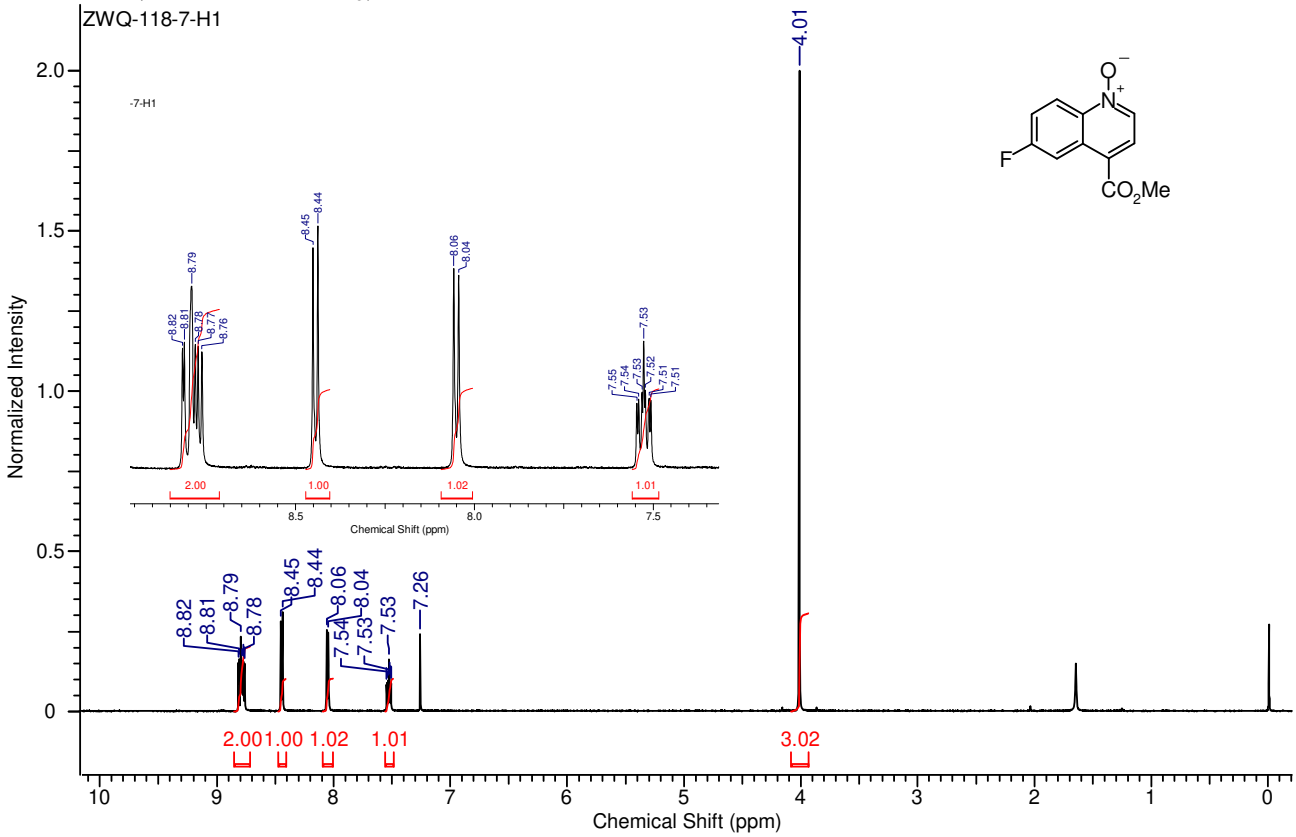


^{13}C NMR (125 MHz, $CDCl_3$)

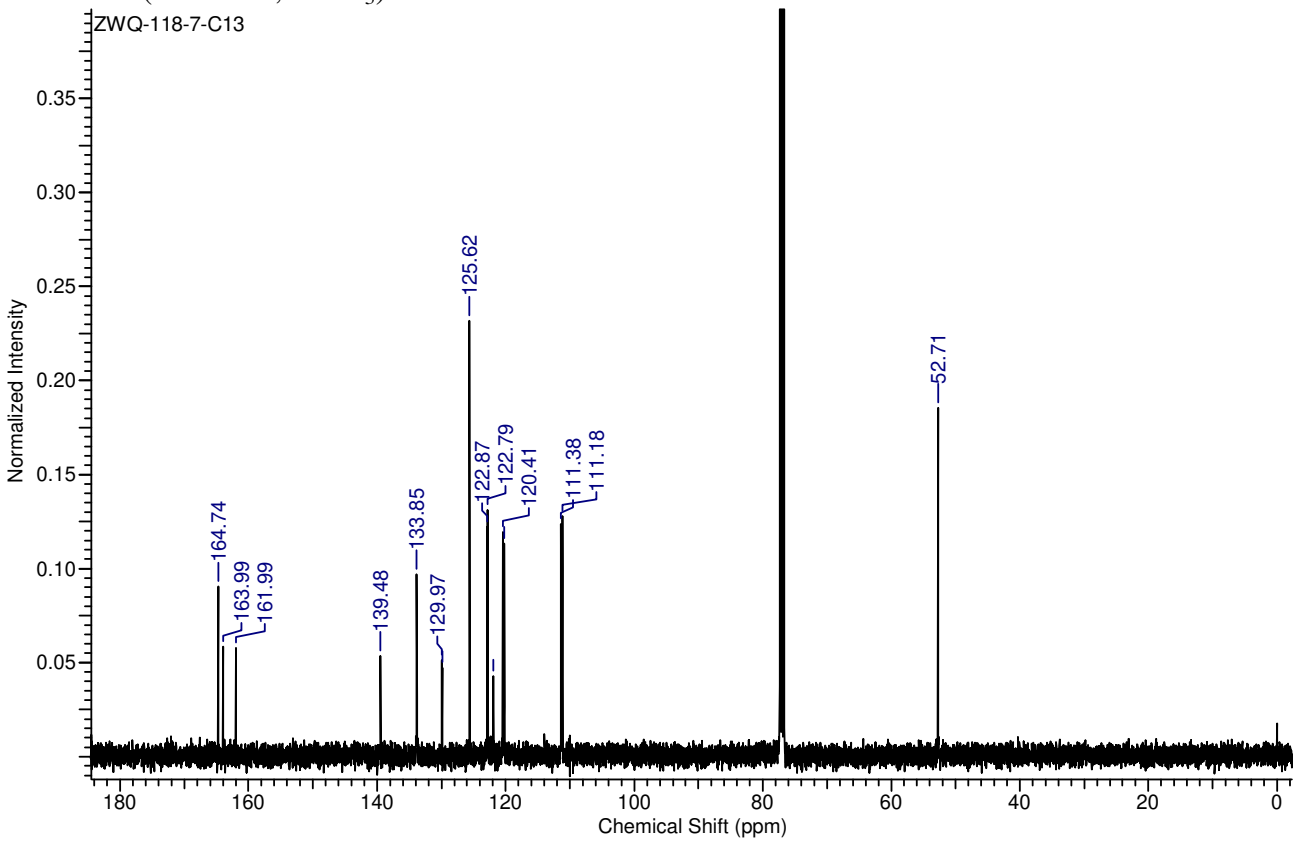


3o

^{1}H NMR (500 MHz, $CDCl_3$)



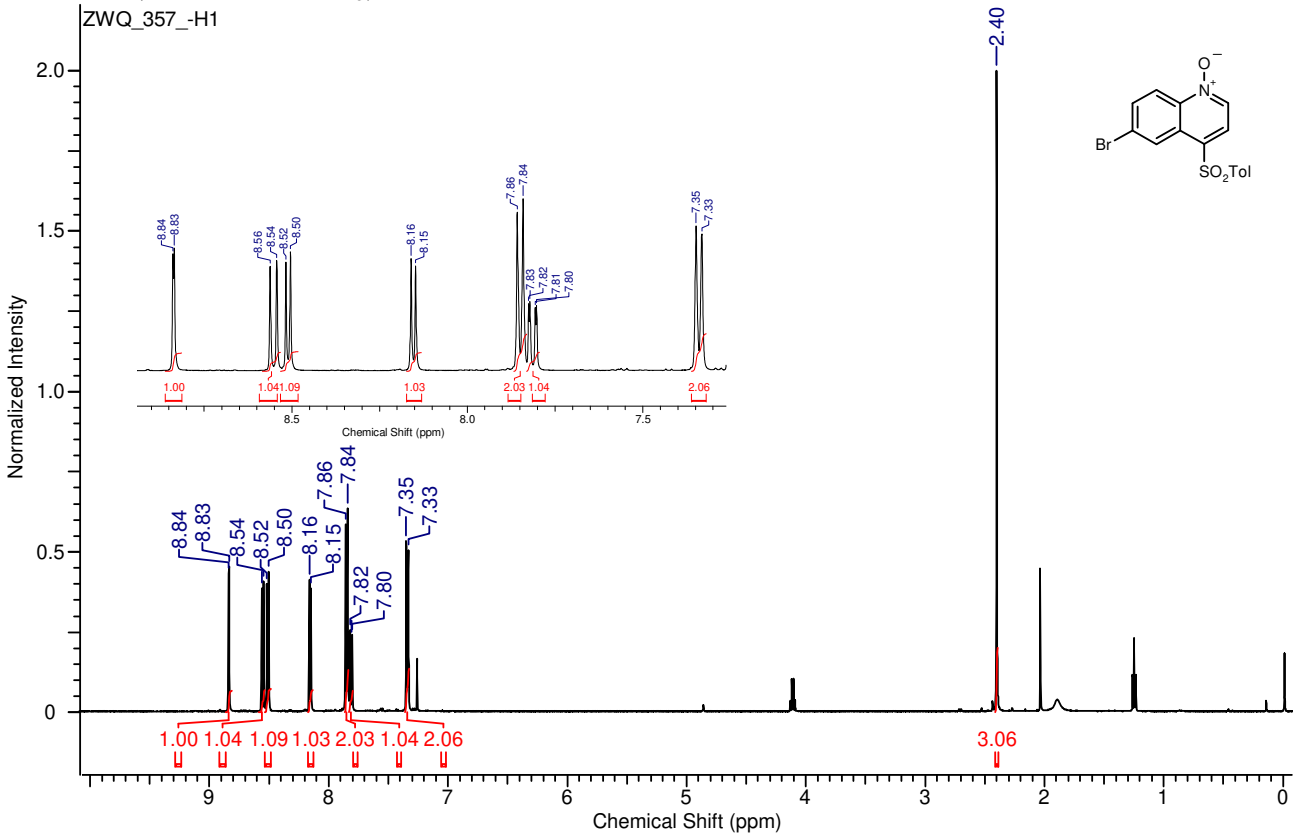
^{13}C NMR (125 MHz, $CDCl_3$)



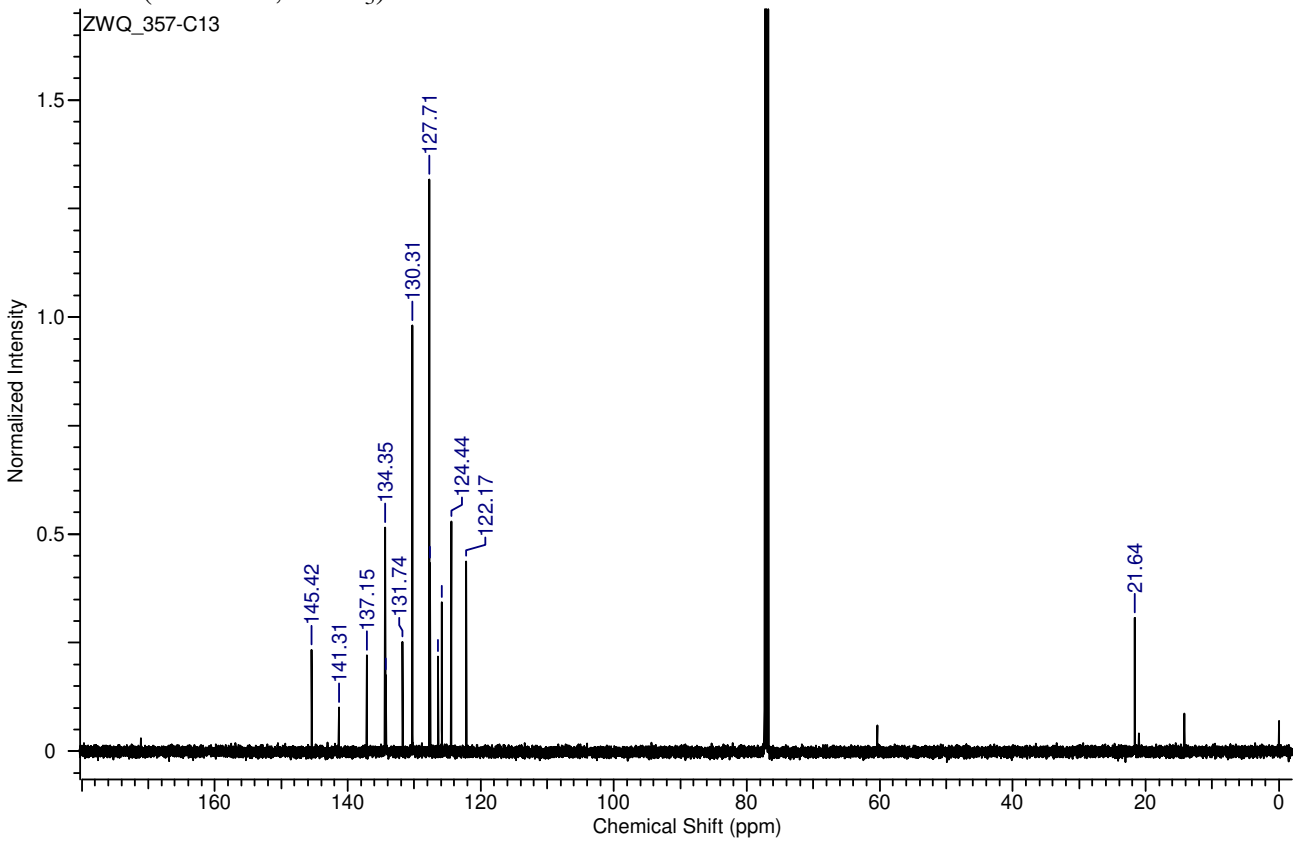
31 Q ox 3p [superfluous signals are derived from residual, non-removable ethyl acetate]

3p

^{1}H NMR (500 MHz, $CDCl_3$)

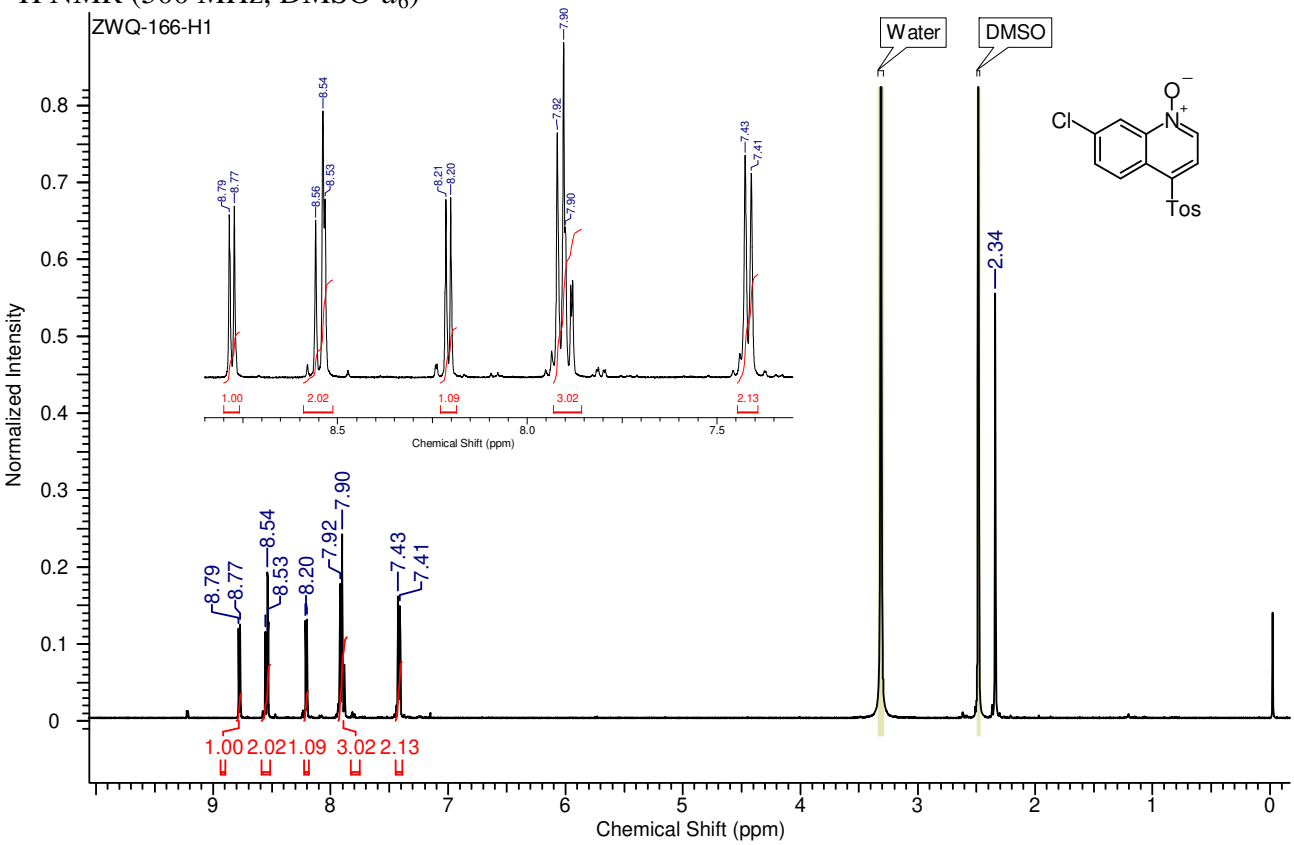


^{13}C NMR (125 MHz, $CDCl_3$)

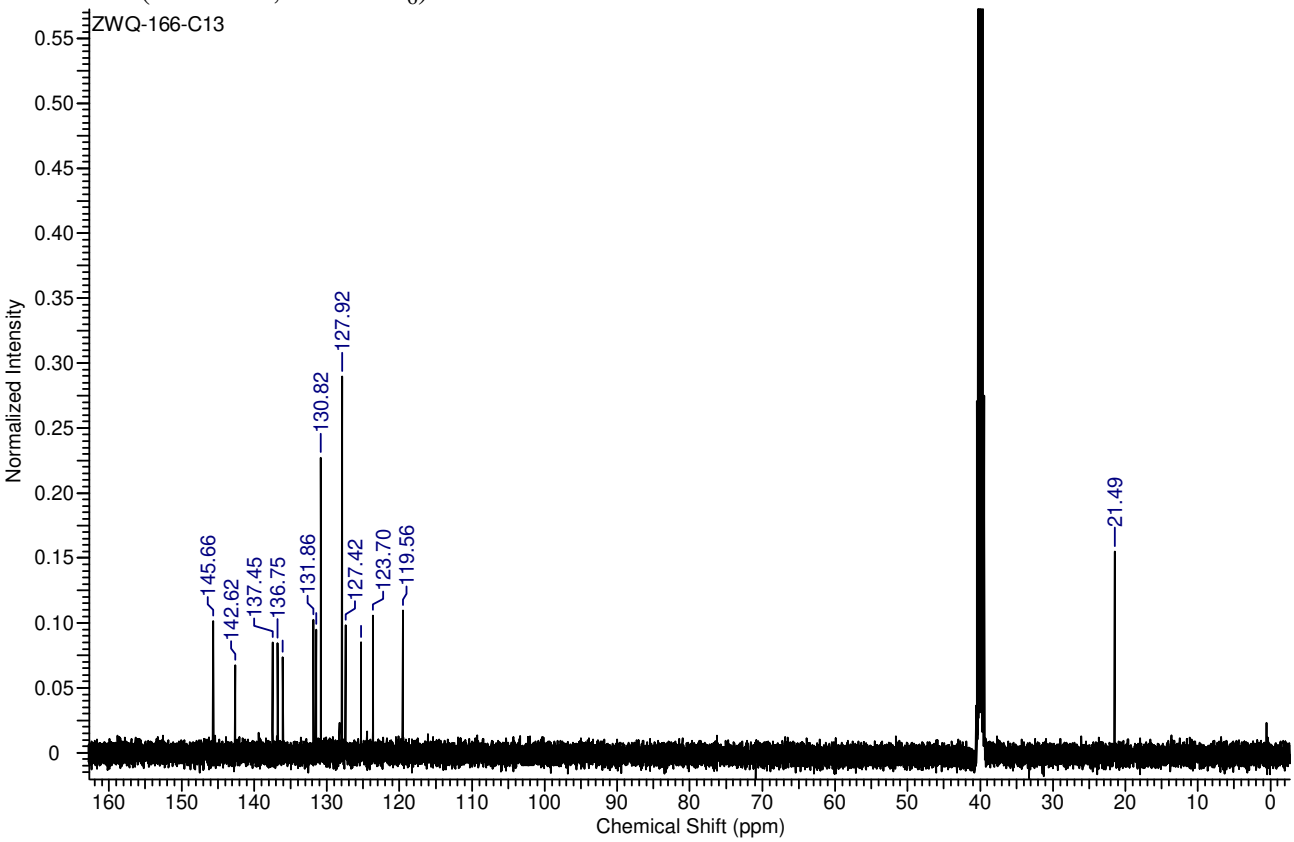


3r

^{1}H NMR (500 MHz, DMSO-d_6)

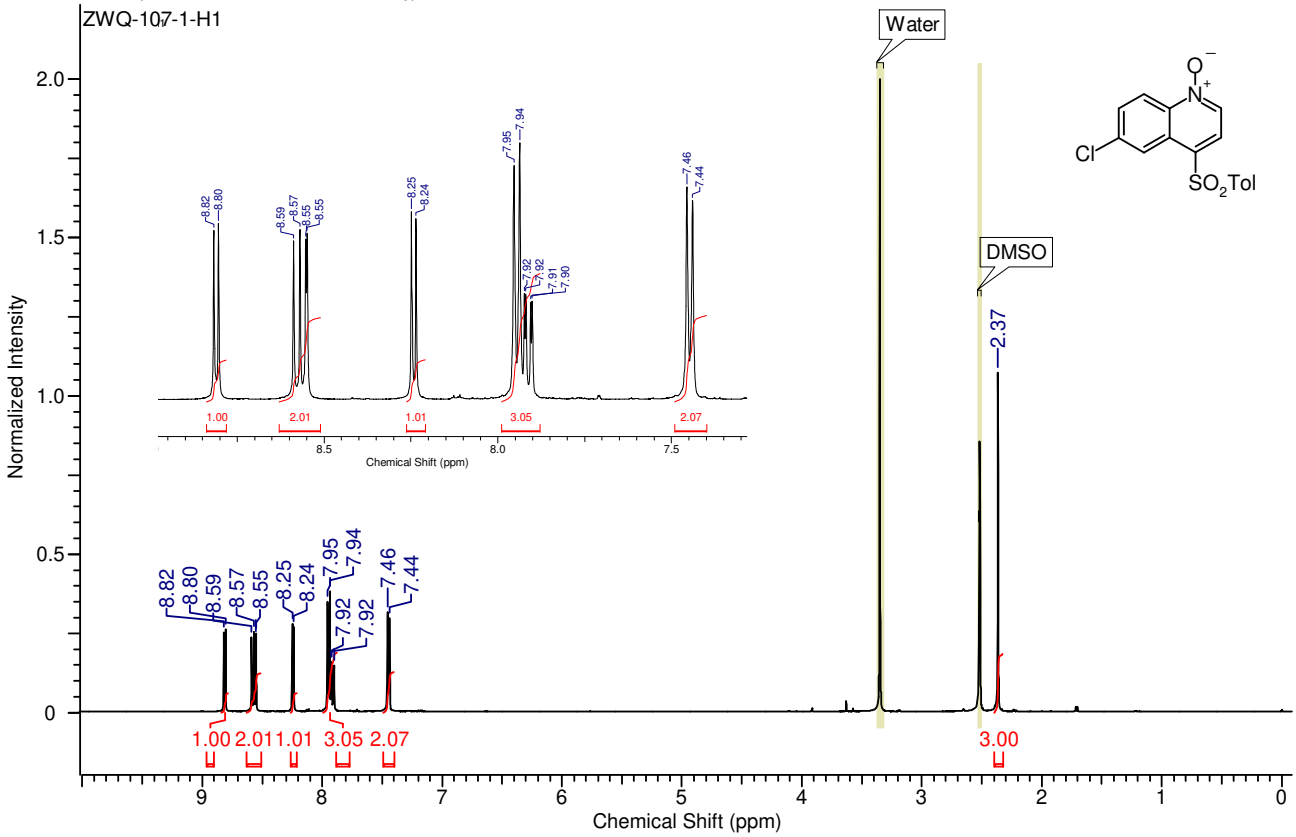


^{13}C NMR (125 MHz, DMSO-d_6)

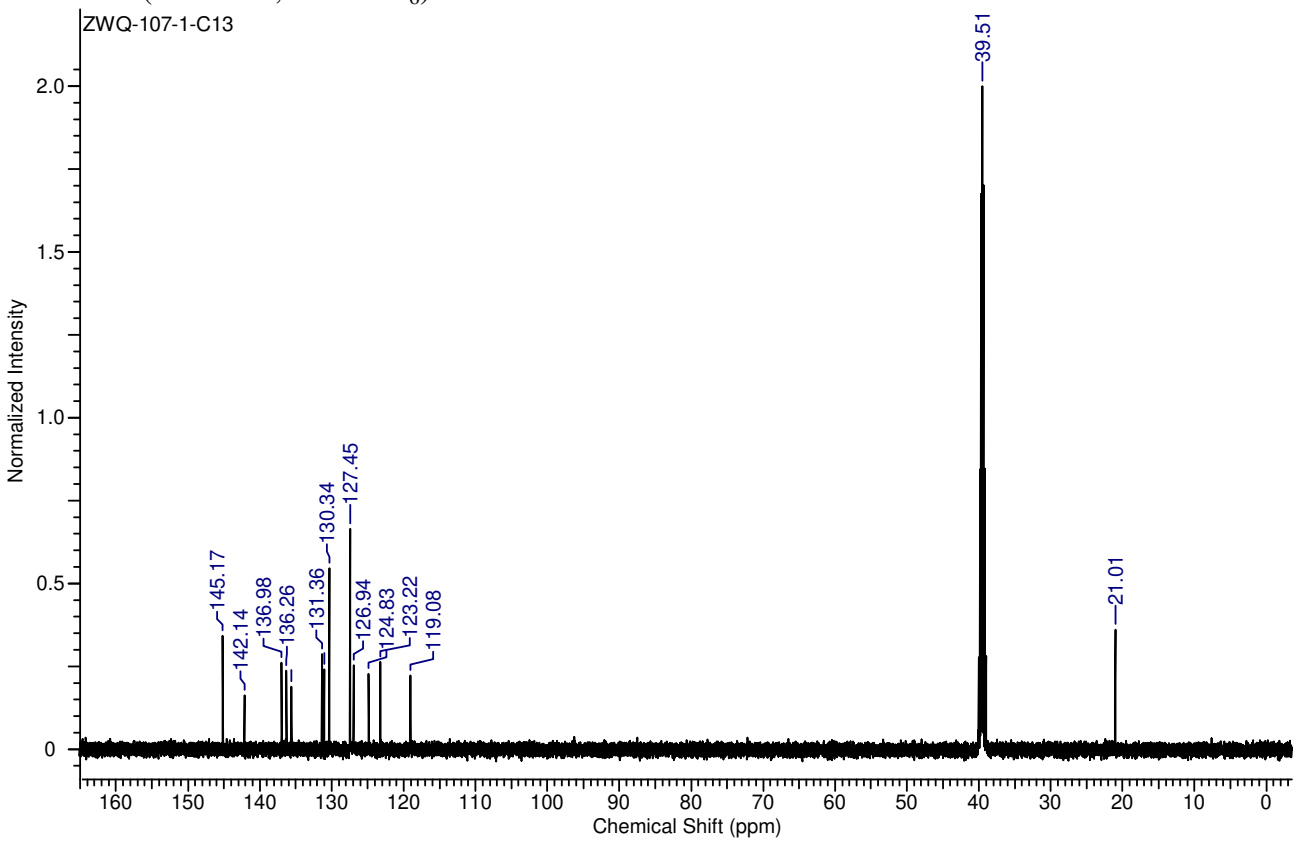


3s (DMSO) alternative

^{1}H NMR (500 MHz, DMSO-d_6)

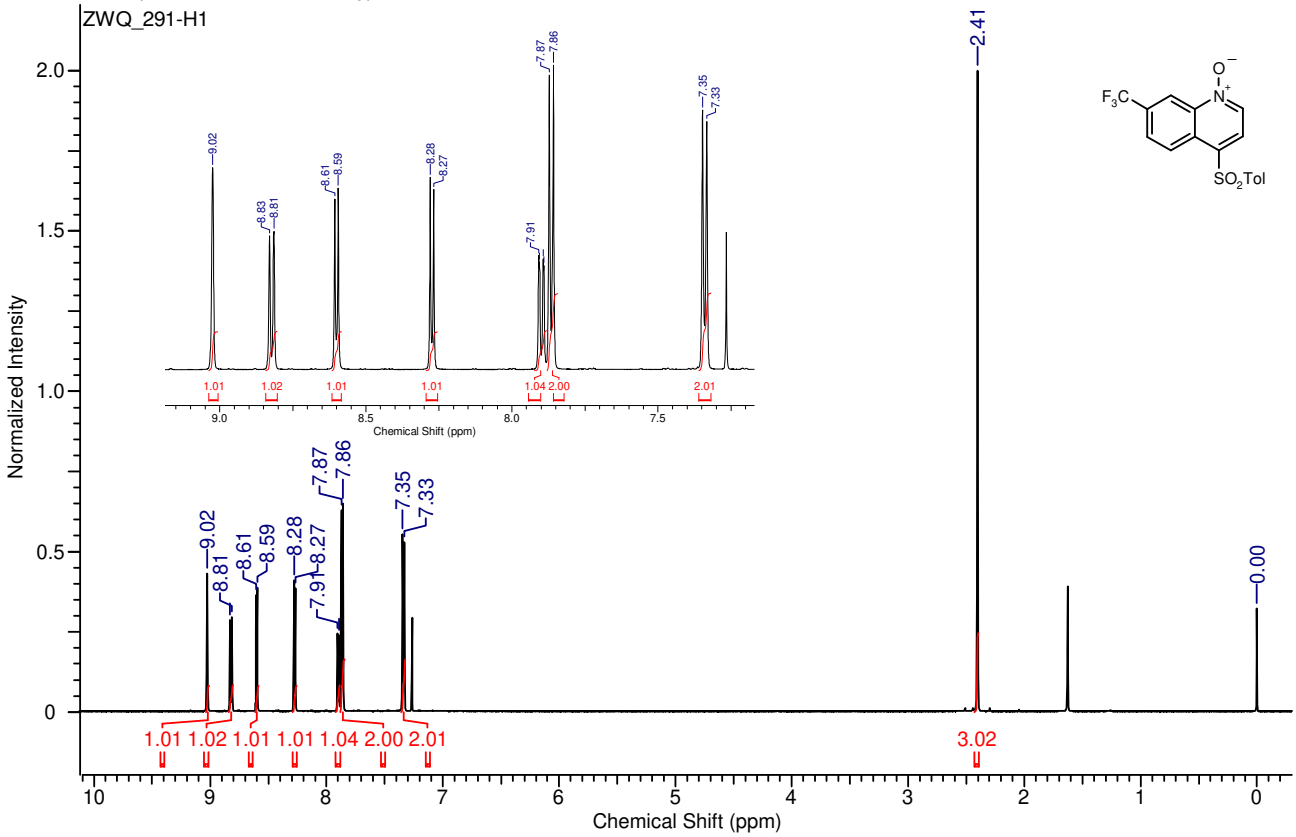


^{13}C NMR (125 MHz, DMSO-d_6)

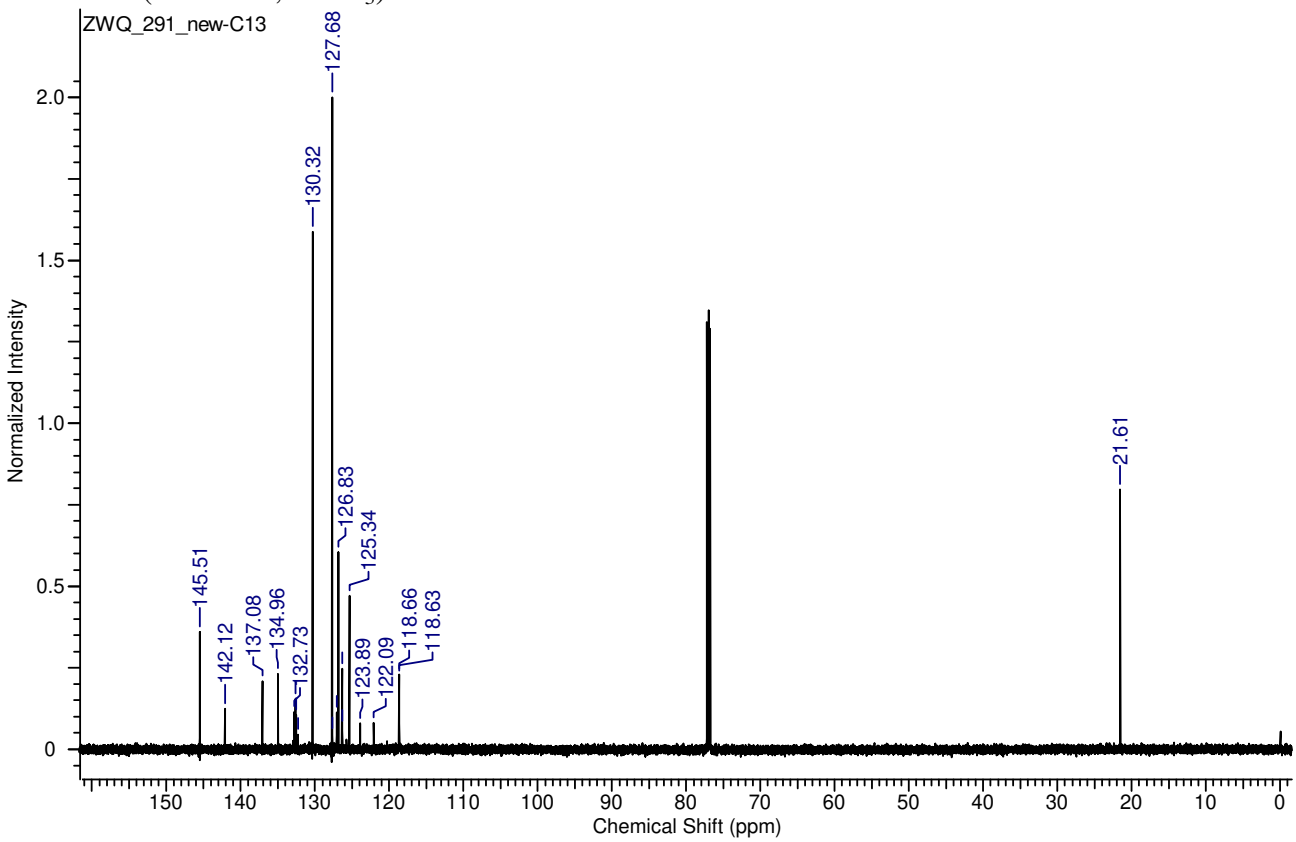


3t

^{1}H NMR (600 MHz, $CDCl_3$)

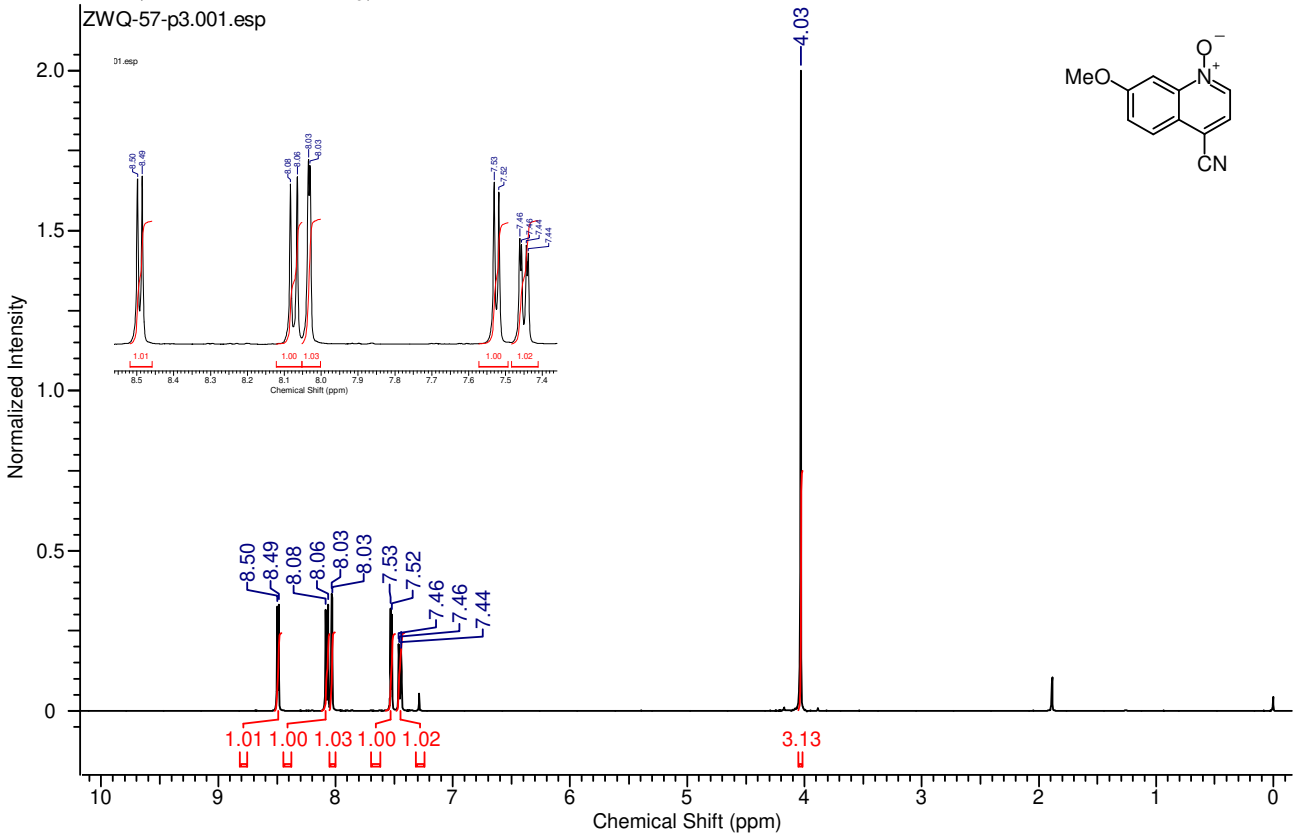


^{13}C NMR (150 MHz, $CDCl_3$)

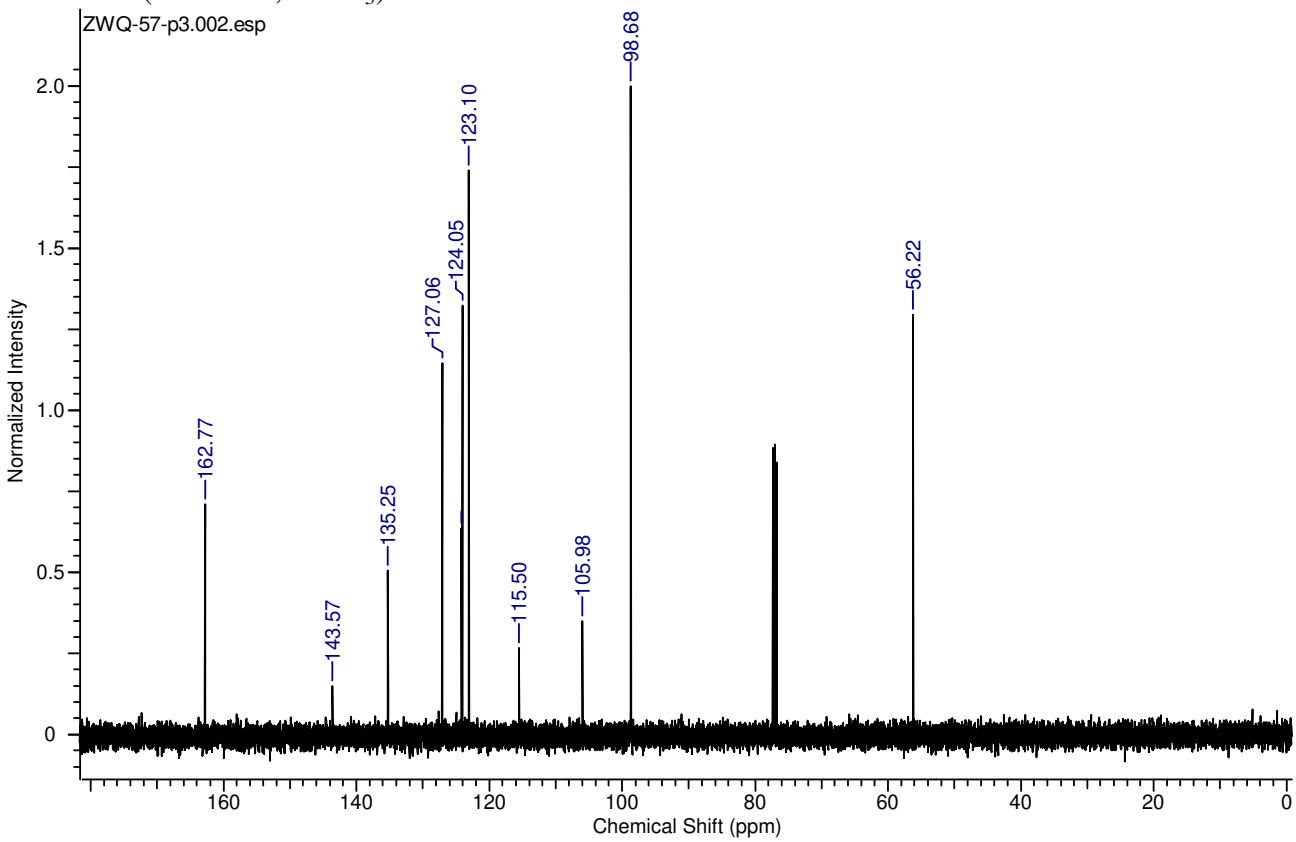


3x

^{1}H NMR (500 MHz, $CDCl_3$)

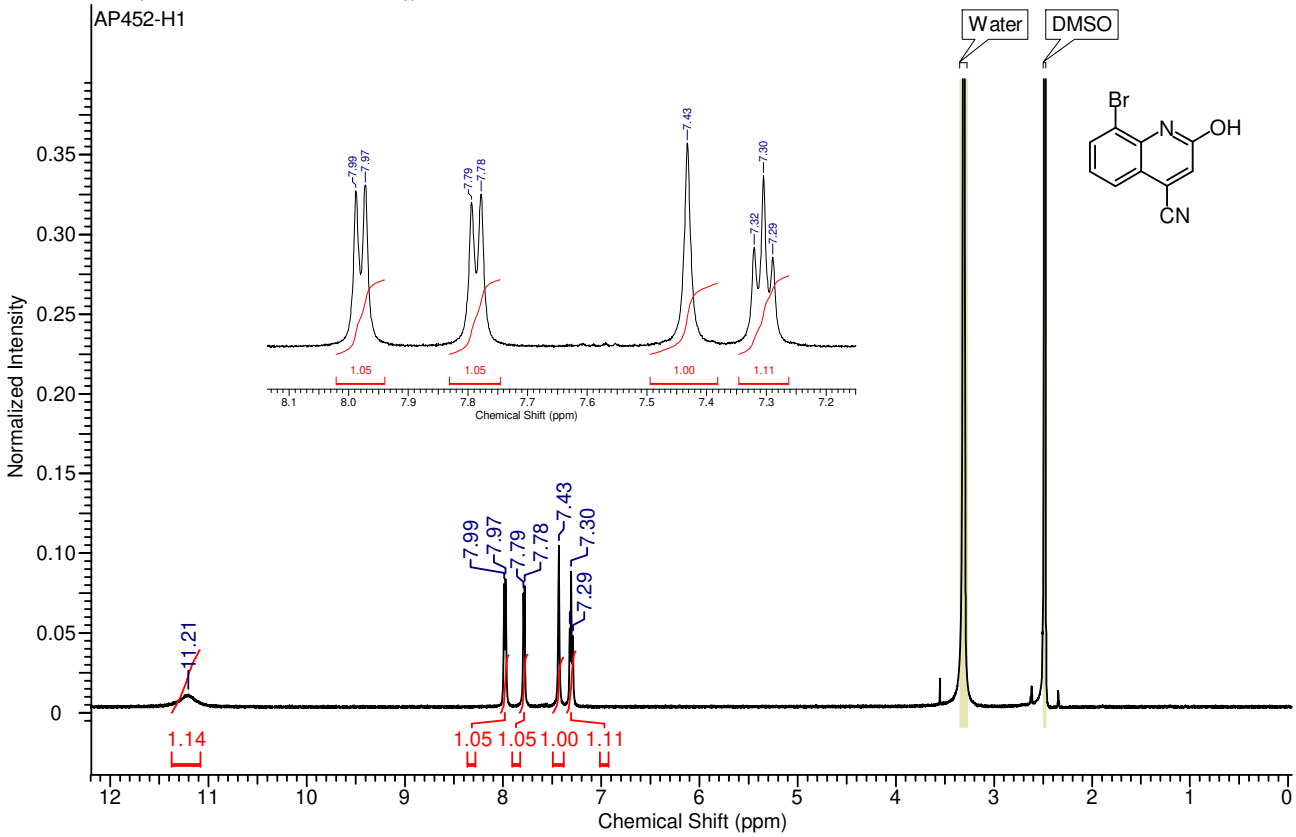


^{13}C NMR (125 MHz, $CDCl_3$)



5d

^{1}H NMR (500 MHz, DMSO-d_6)

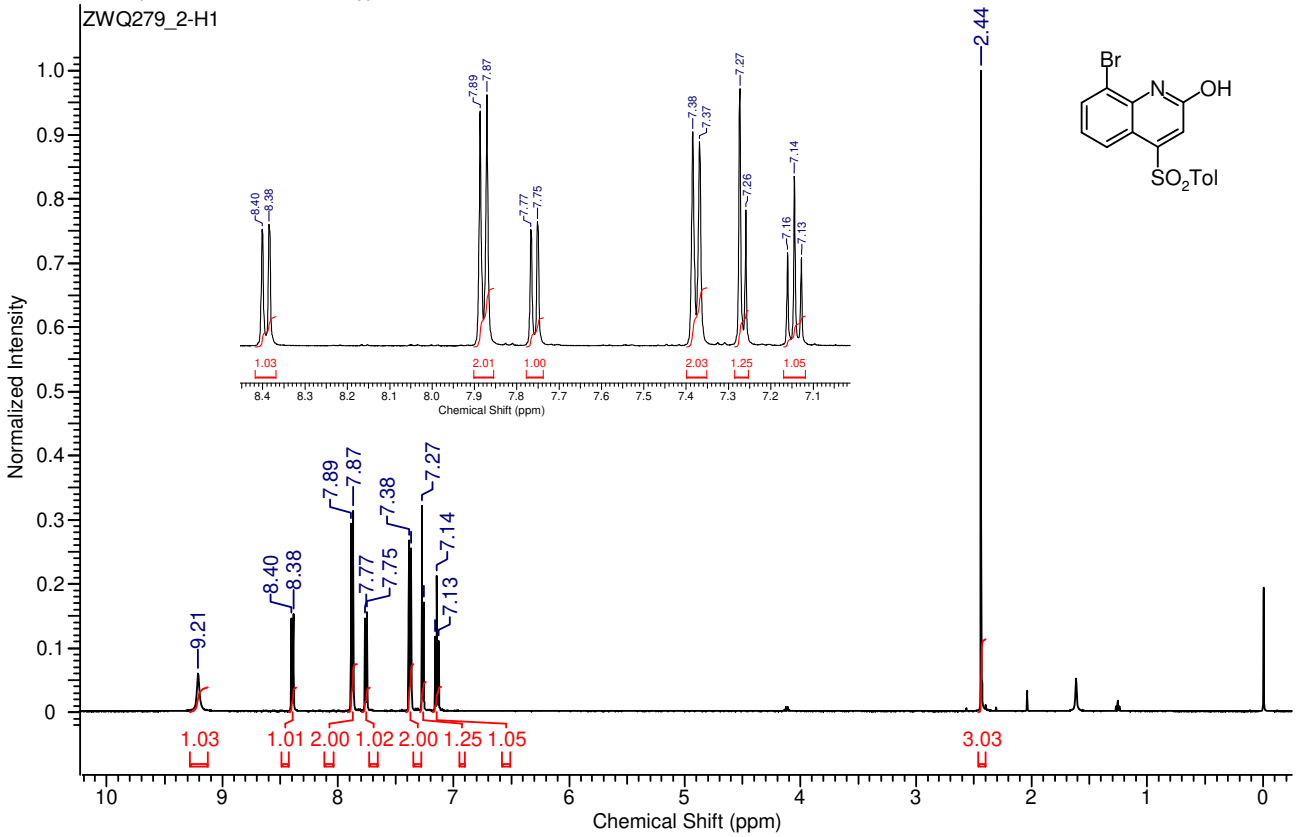


^{13}C NMR (125 MHz, DMSO-d_6)

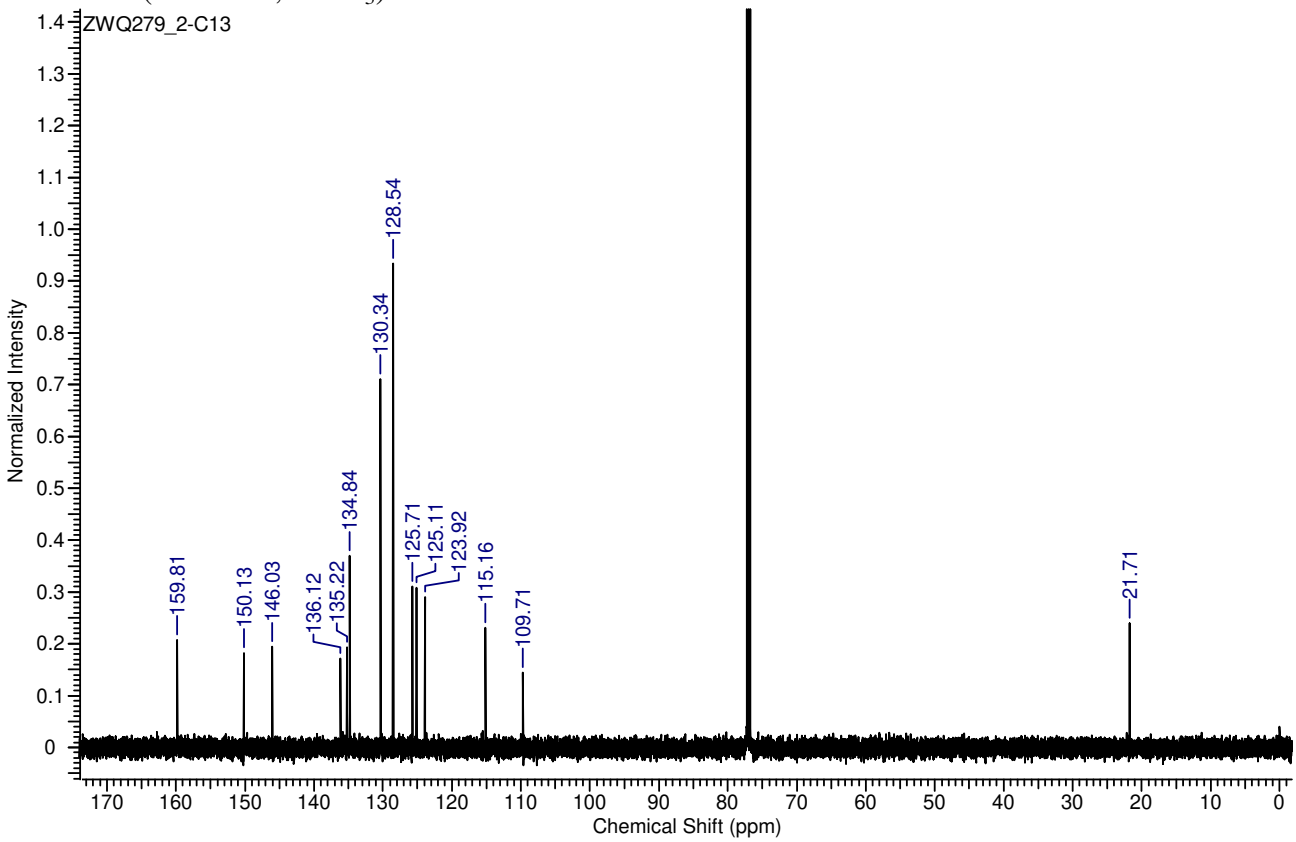
Not recorded due to extremely low solubility of **5d** in standard solvents.

5q

^{1}H NMR (500 MHz, $CDCl_3$)

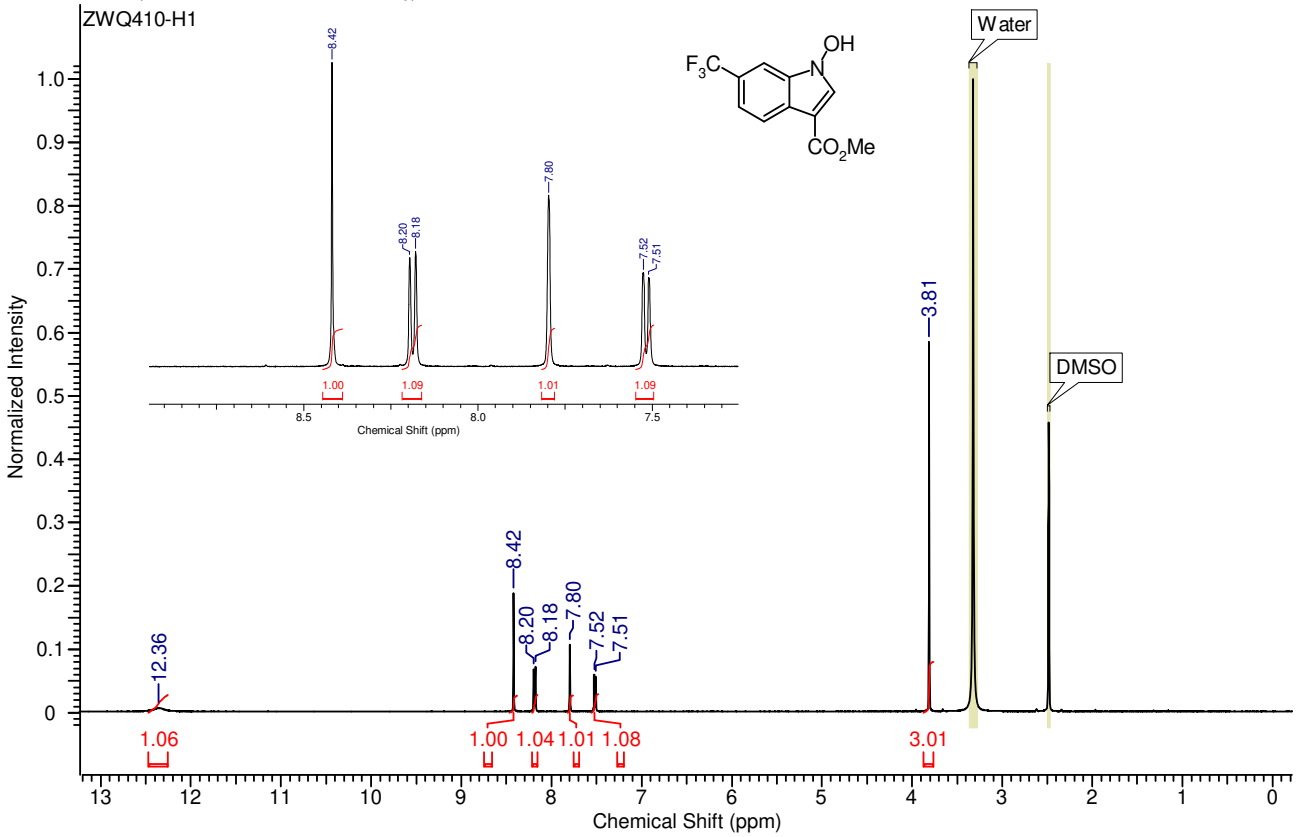


^{13}C NMR (125 MHz, $CDCl_3$)

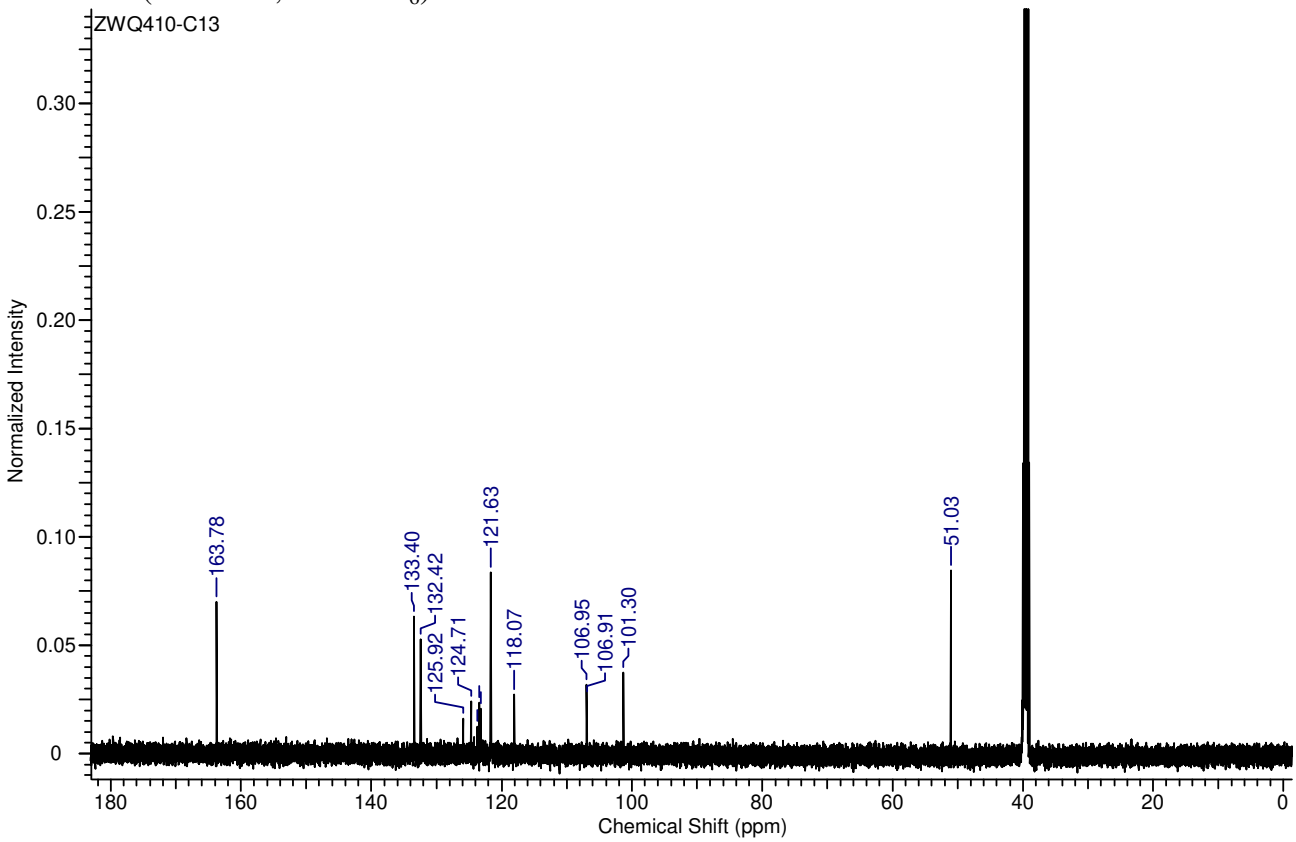


6m

^{1}H NMR (500 MHz, DMSO-d_6)

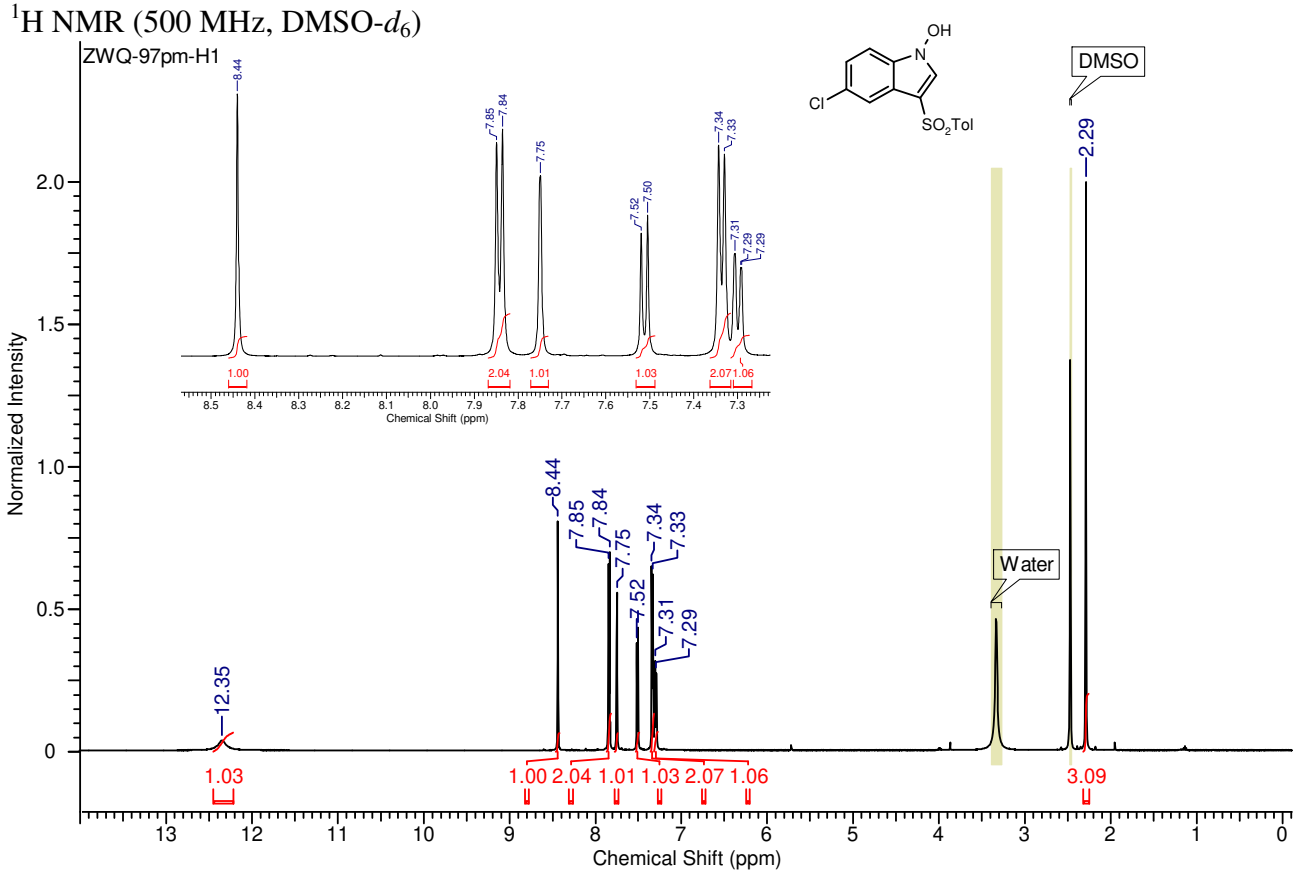


^{13}C NMR (125 MHz, DMSO-d_6)

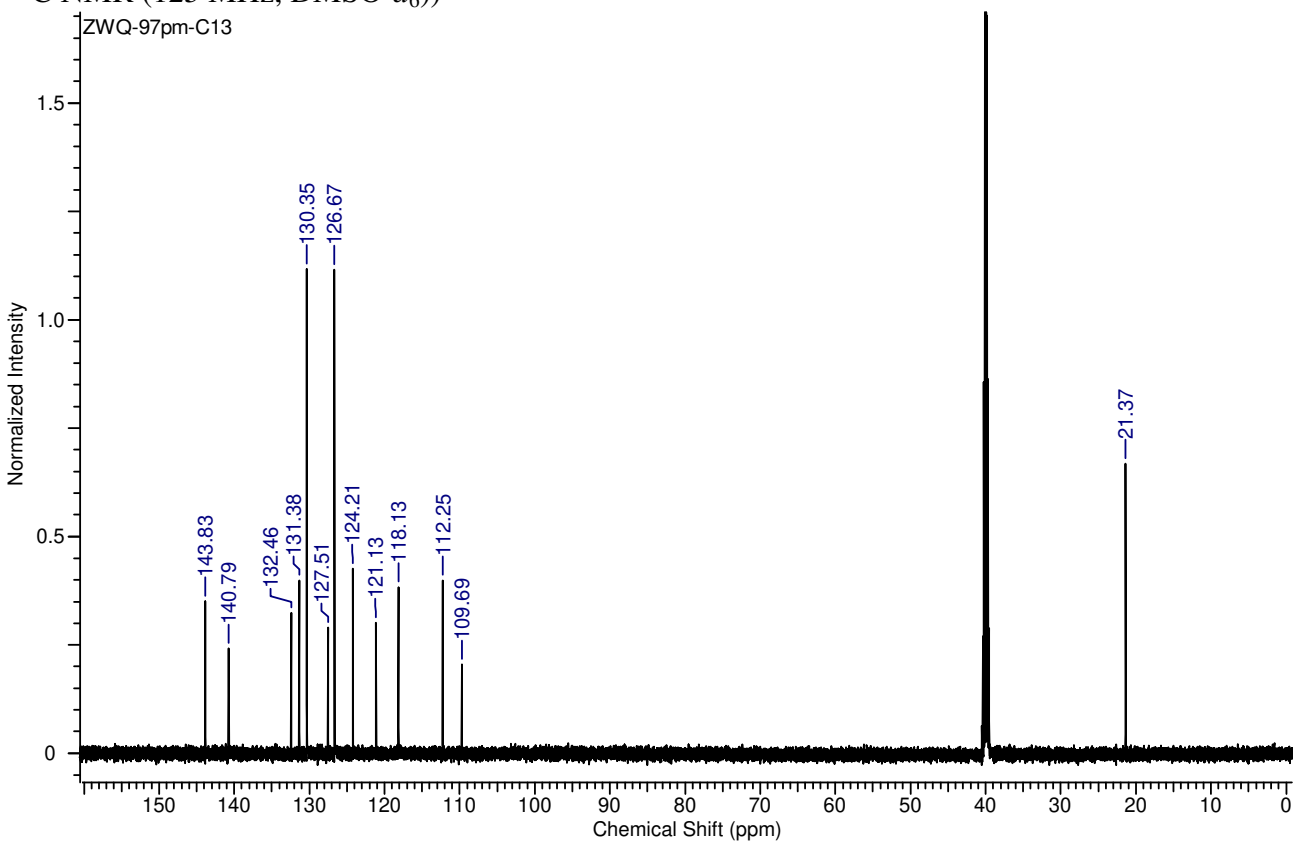


6s

^{1}H NMR (500 MHz, DMSO-d_6)

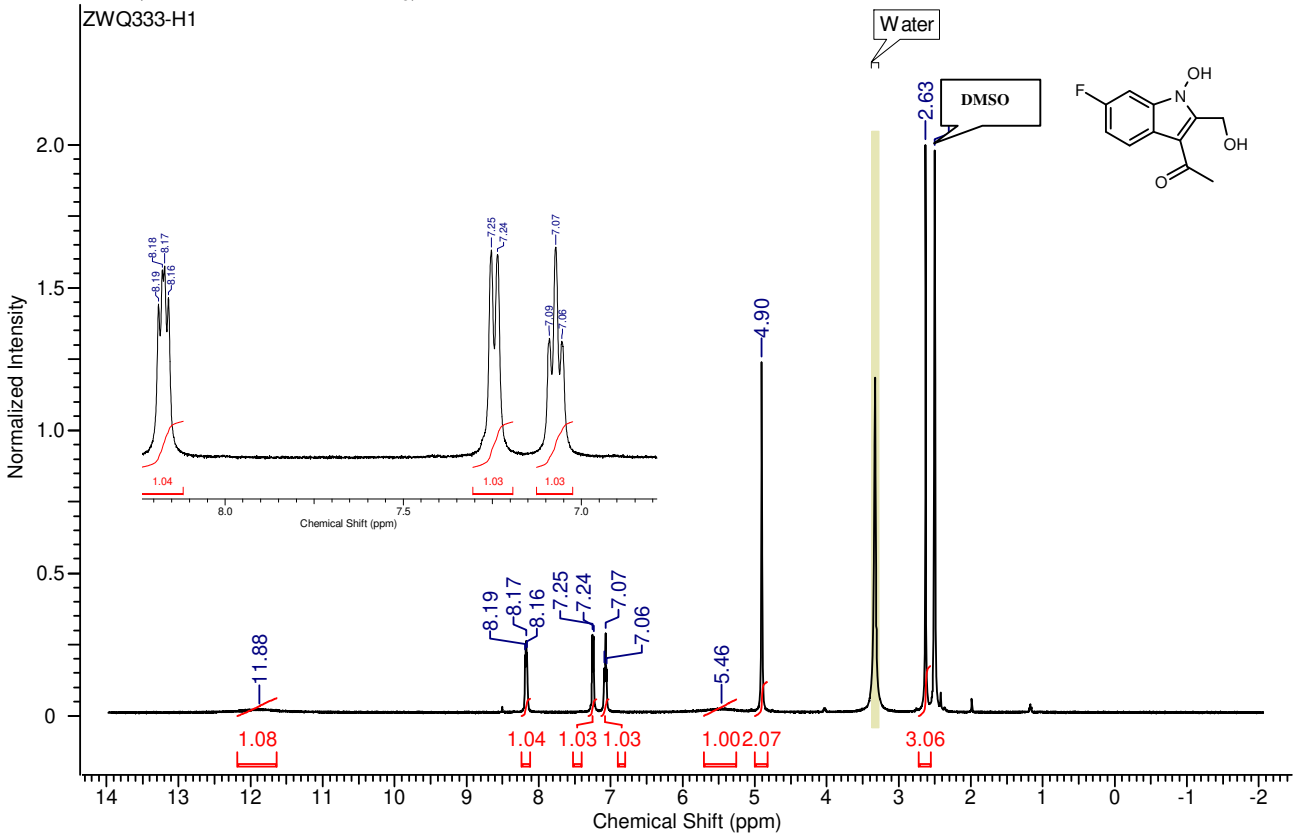


^{13}C NMR (125 MHz, DMSO-d_6))

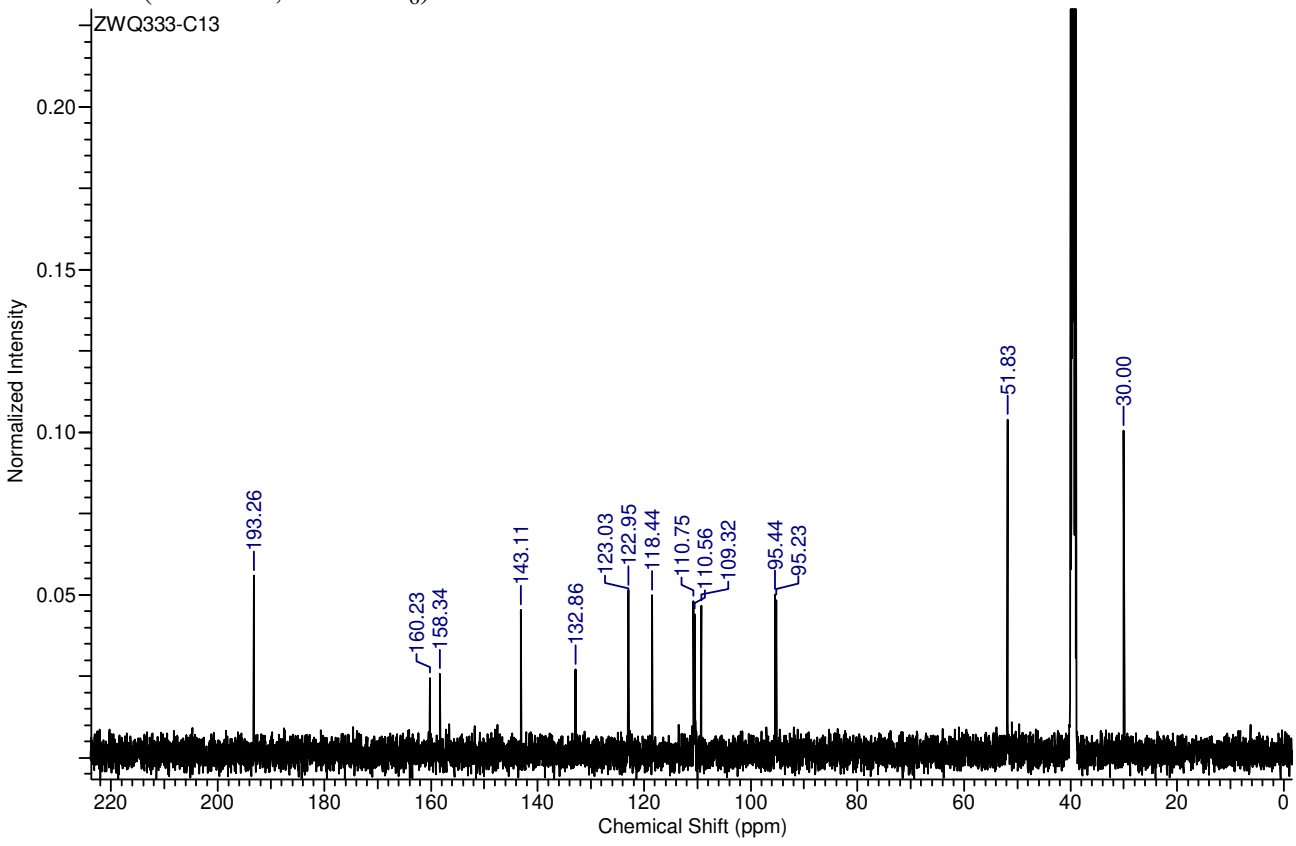


8

^{1}H NMR (500 MHz, DMSO-d_6)

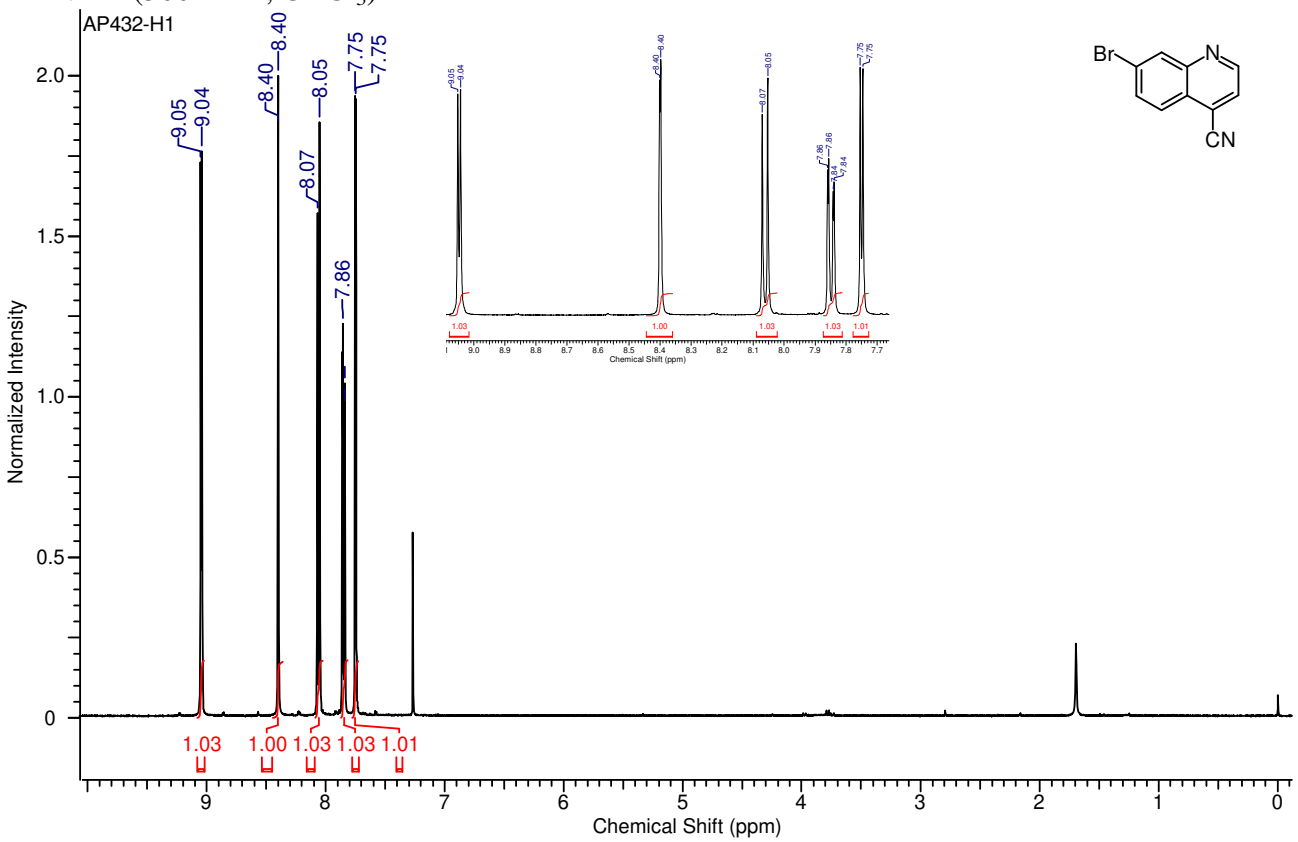


^{13}C NMR (125 MHz, DMSO-d_6)

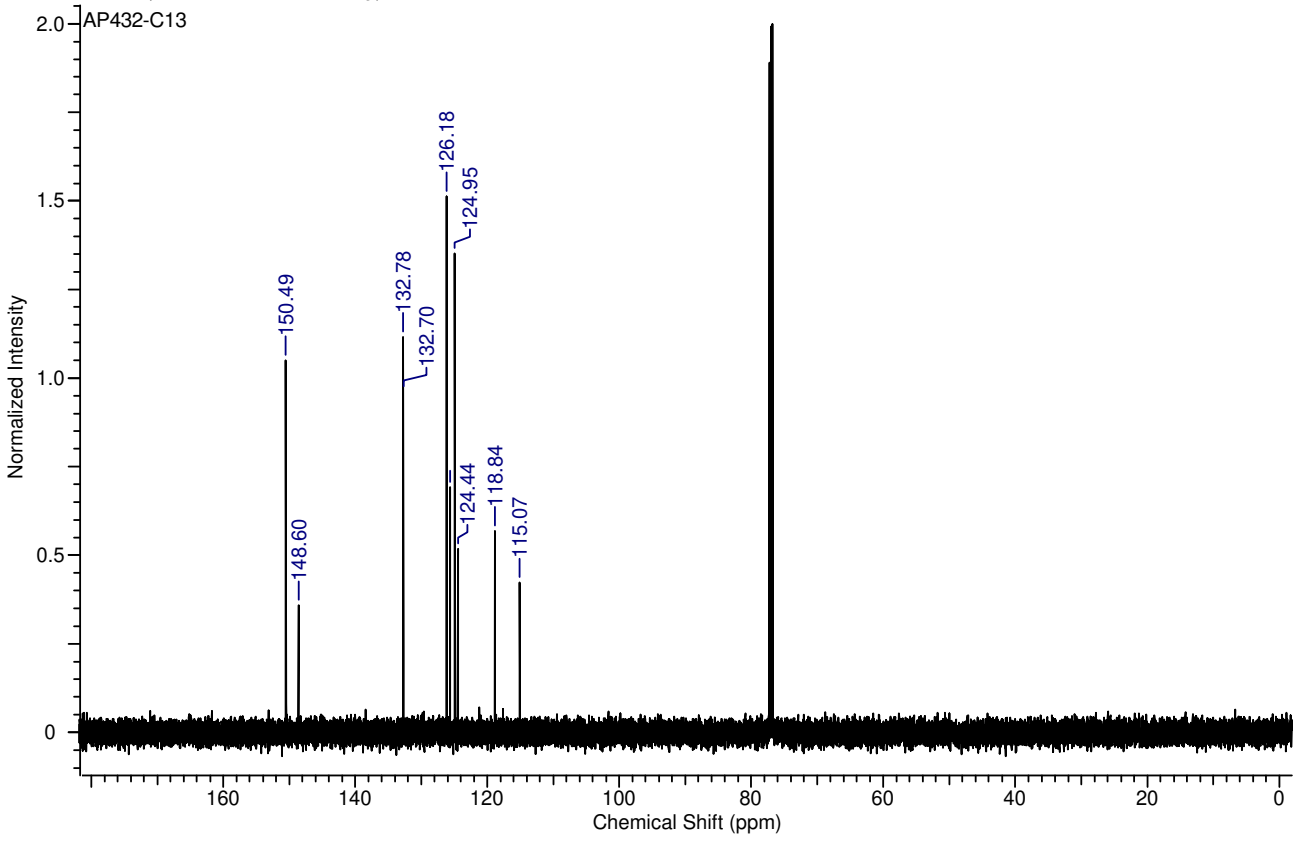


4a

^{1}H NMR (500 MHz, $CDCl_3$)

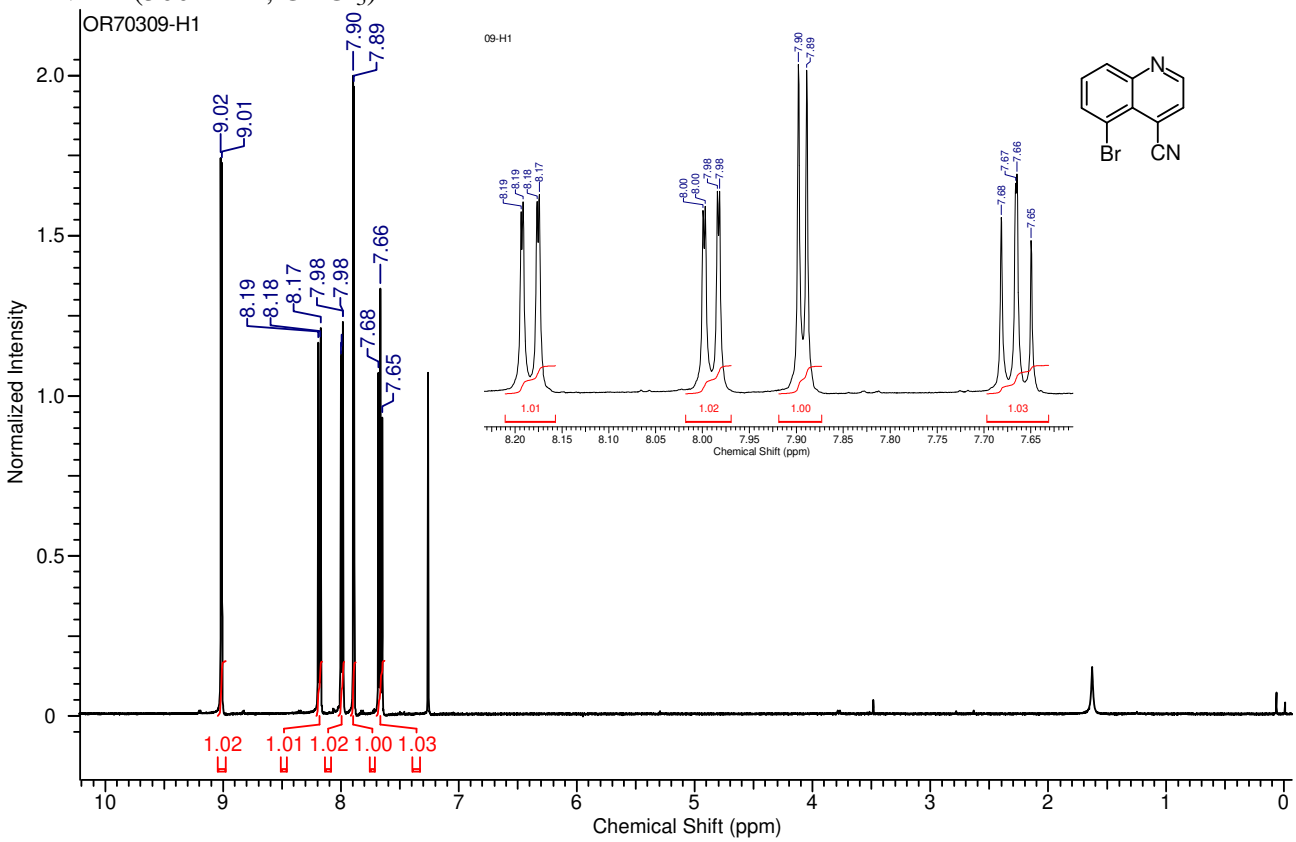


^{13}C NMR (125 MHz, $CDCl_3$)

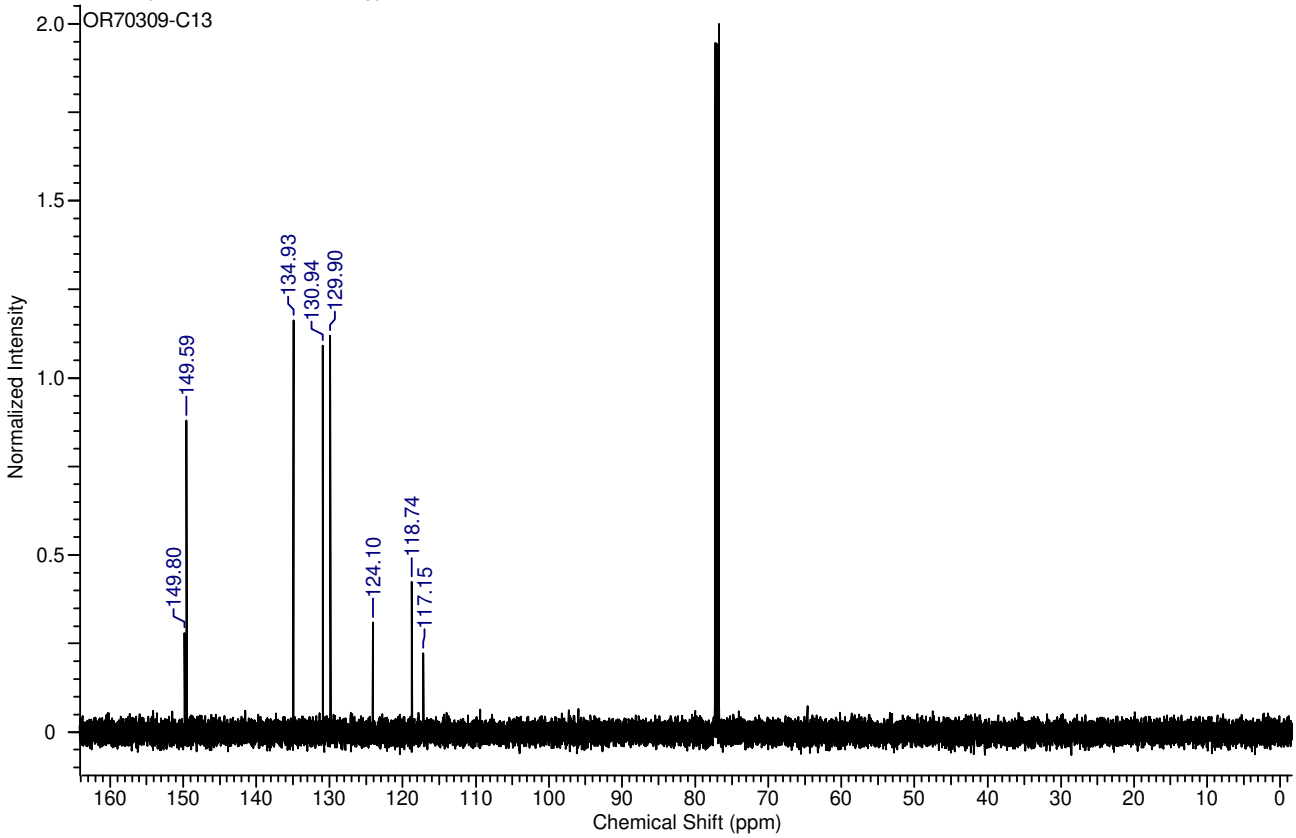


4b

^{1}H NMR (500 MHz, $CDCl_3$)

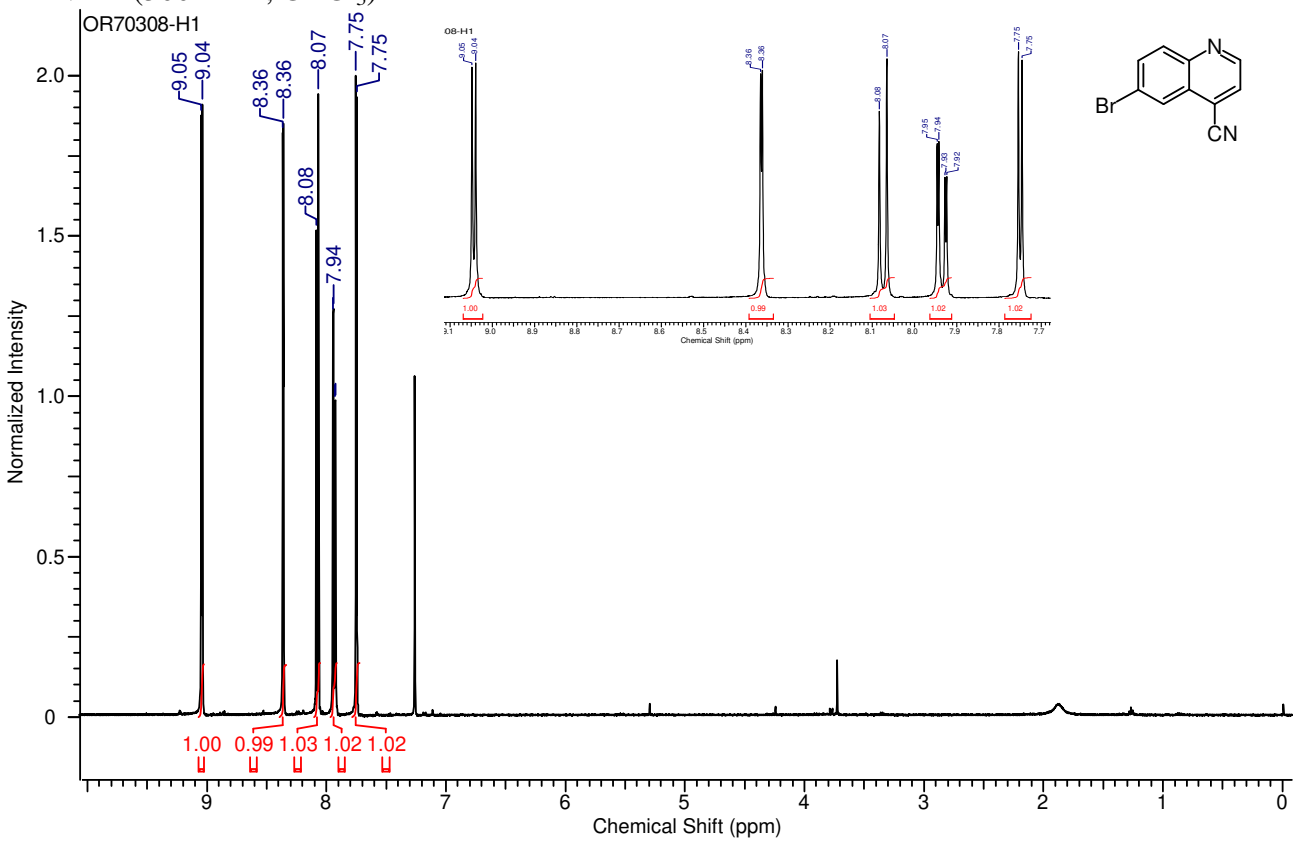


^{13}C NMR (125 MHz, $CDCl_3$)

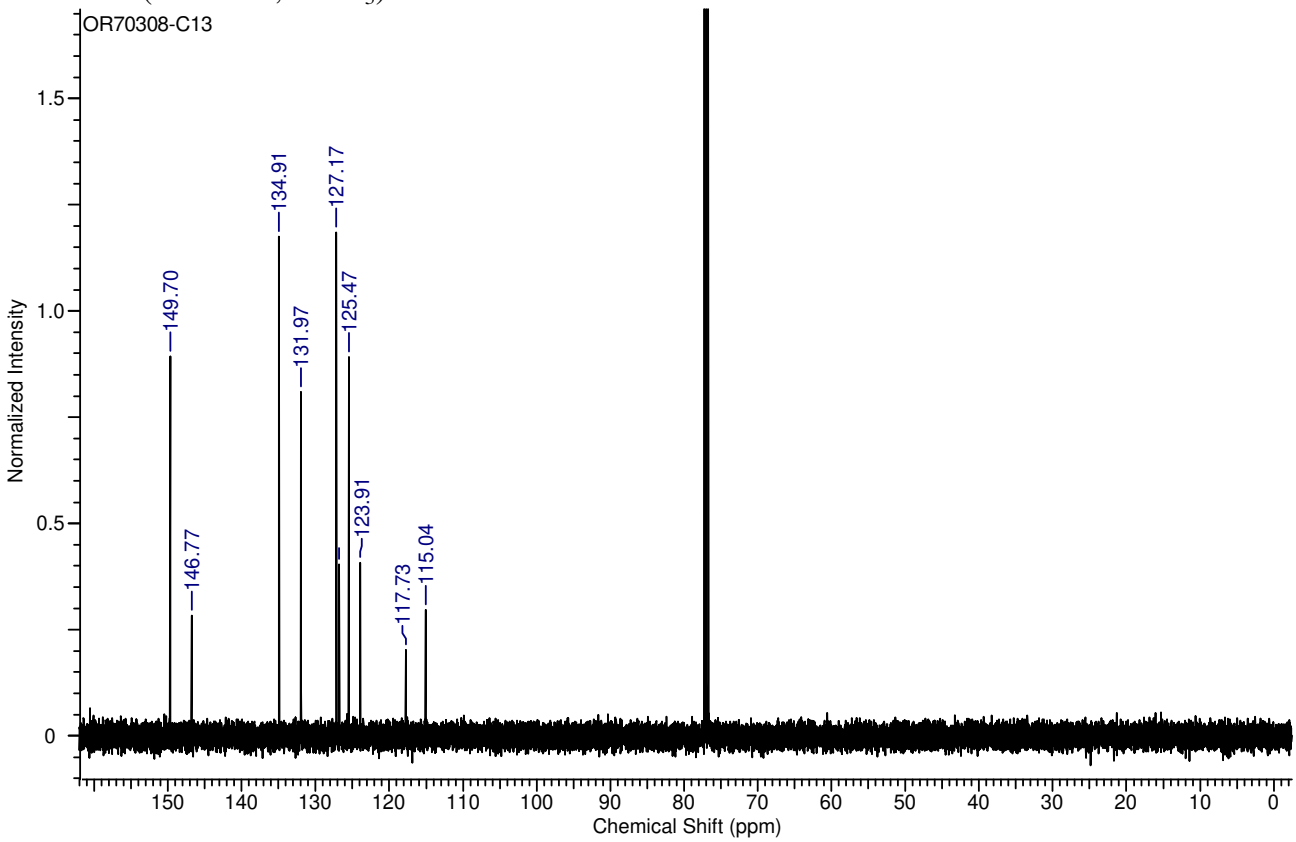


4c

^{1}H NMR (500 MHz, $CDCl_3$)

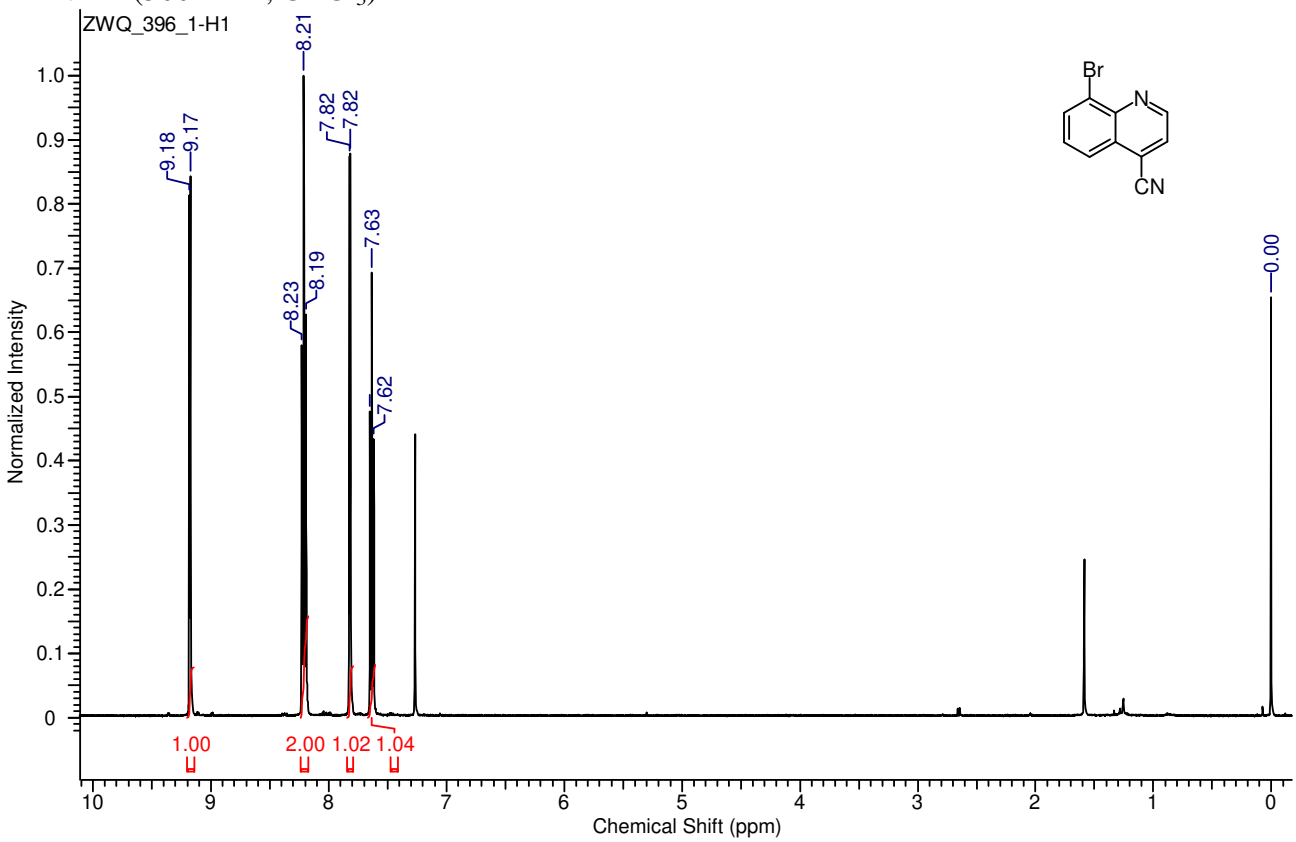


^{13}C NMR (125 MHz, $CDCl_3$)

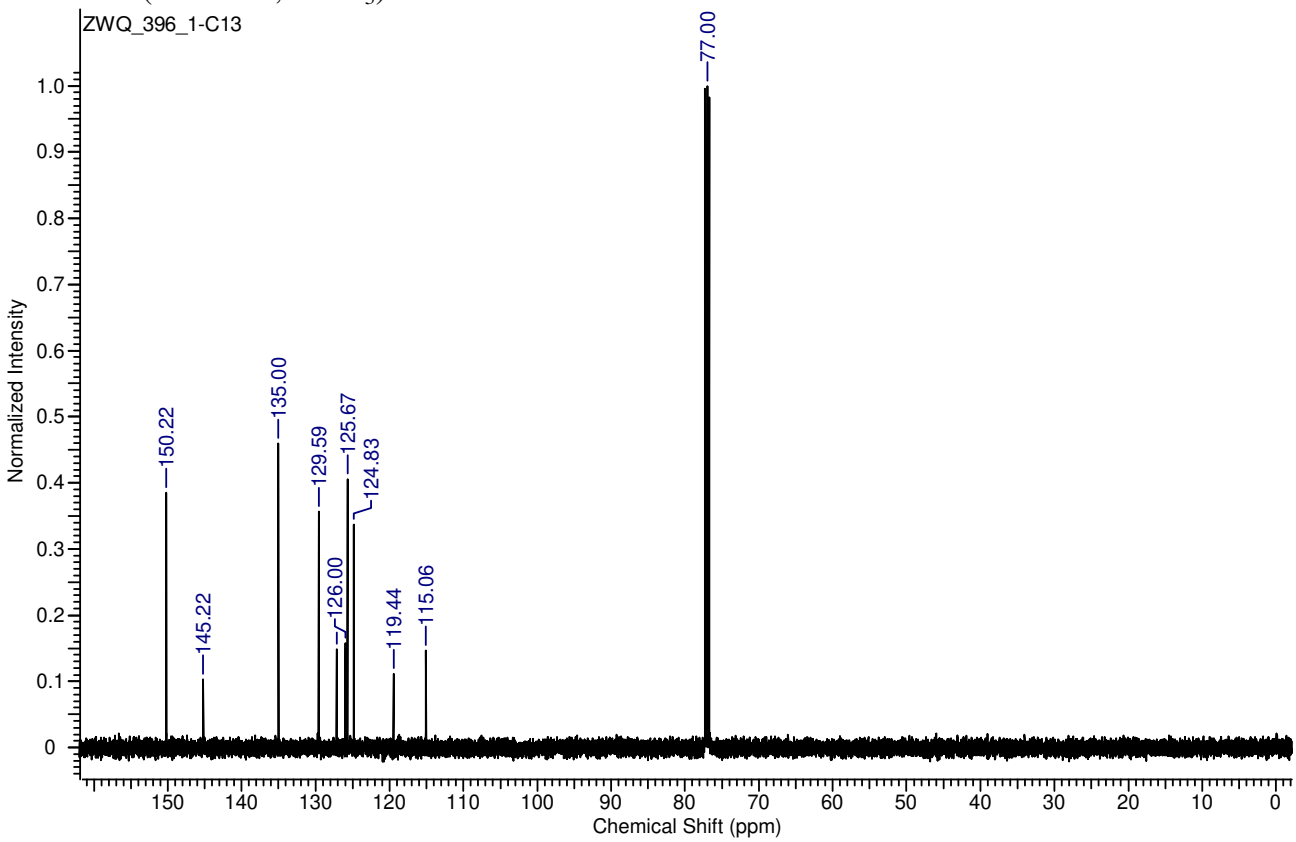


4d

^{1}H NMR (500 MHz, $CDCl_3$)

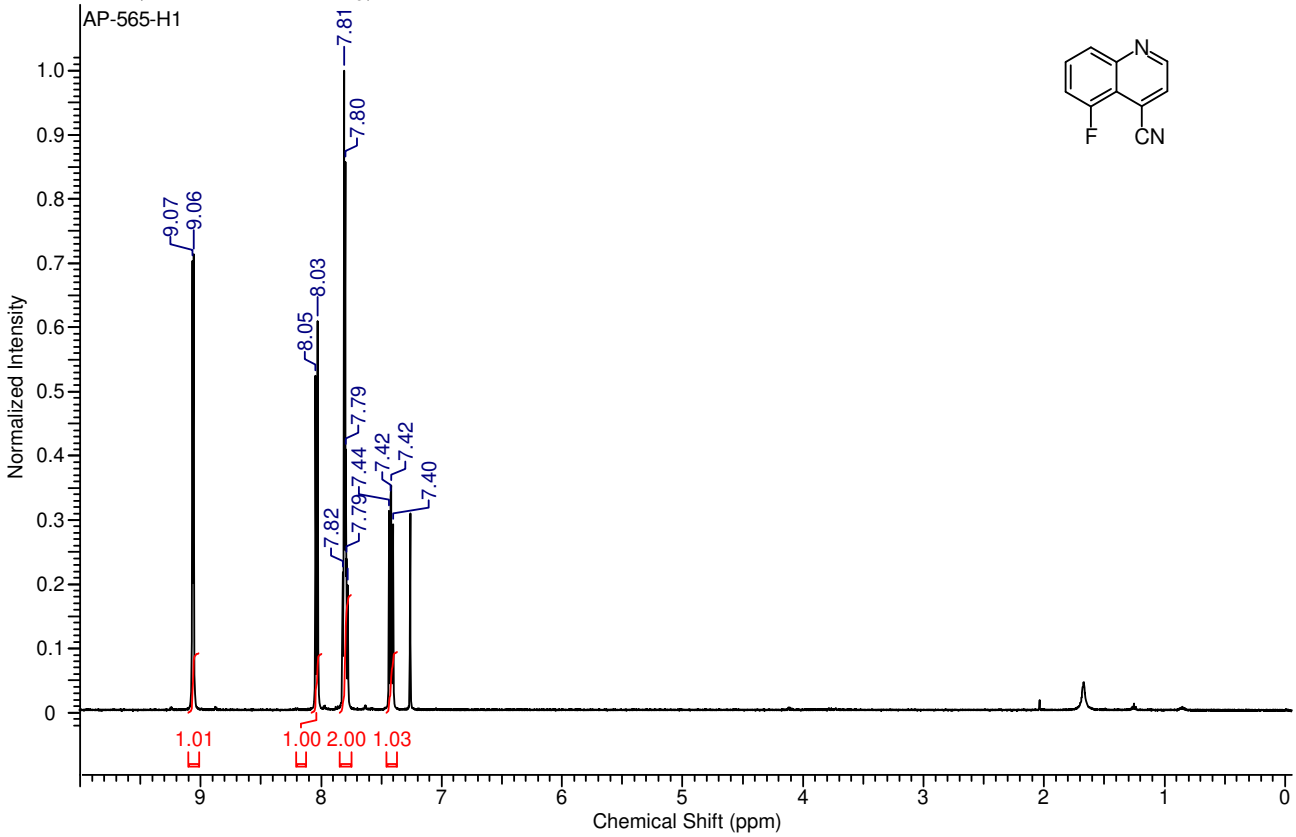


^{13}C NMR (125 MHz, $CDCl_3$)

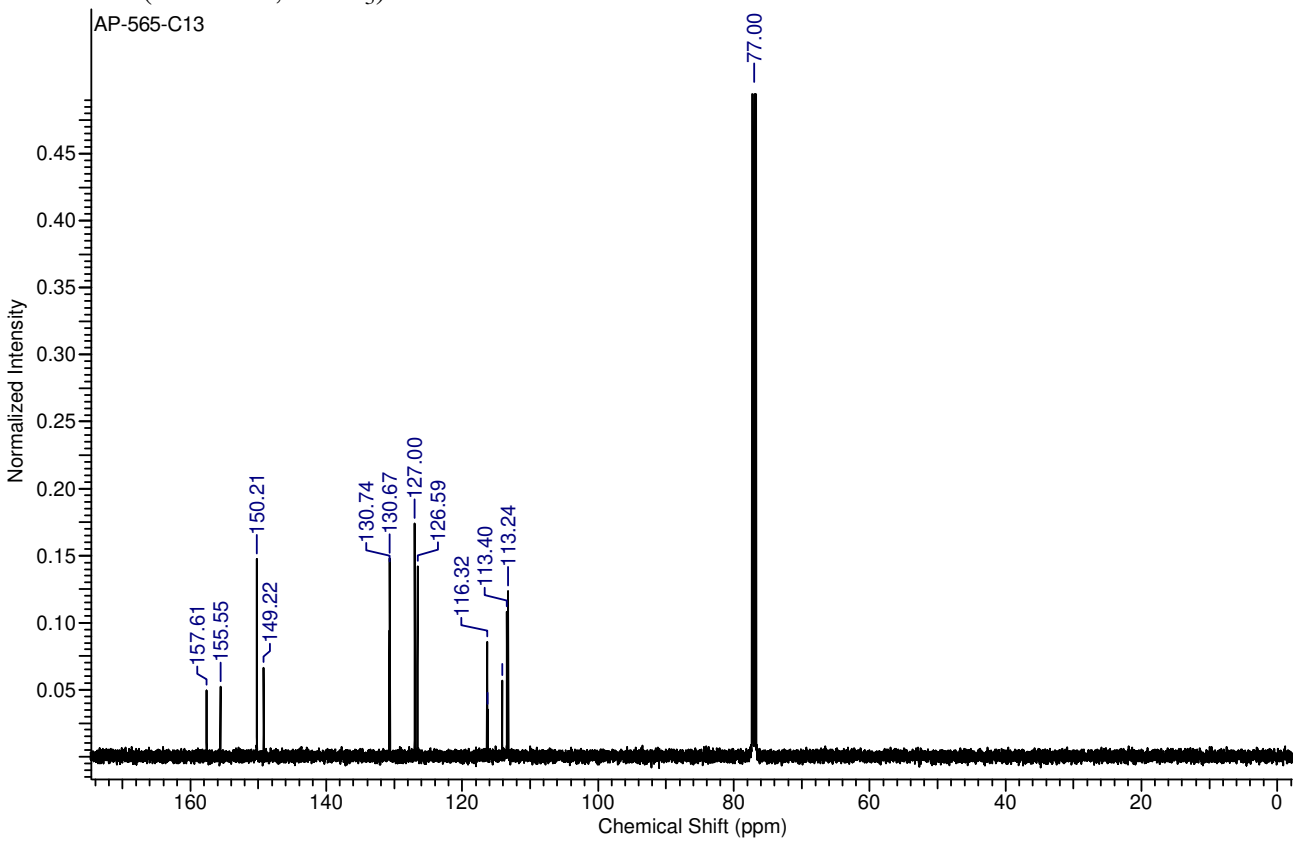


4f

^{1}H NMR (500 MHz, $CDCl_3$)

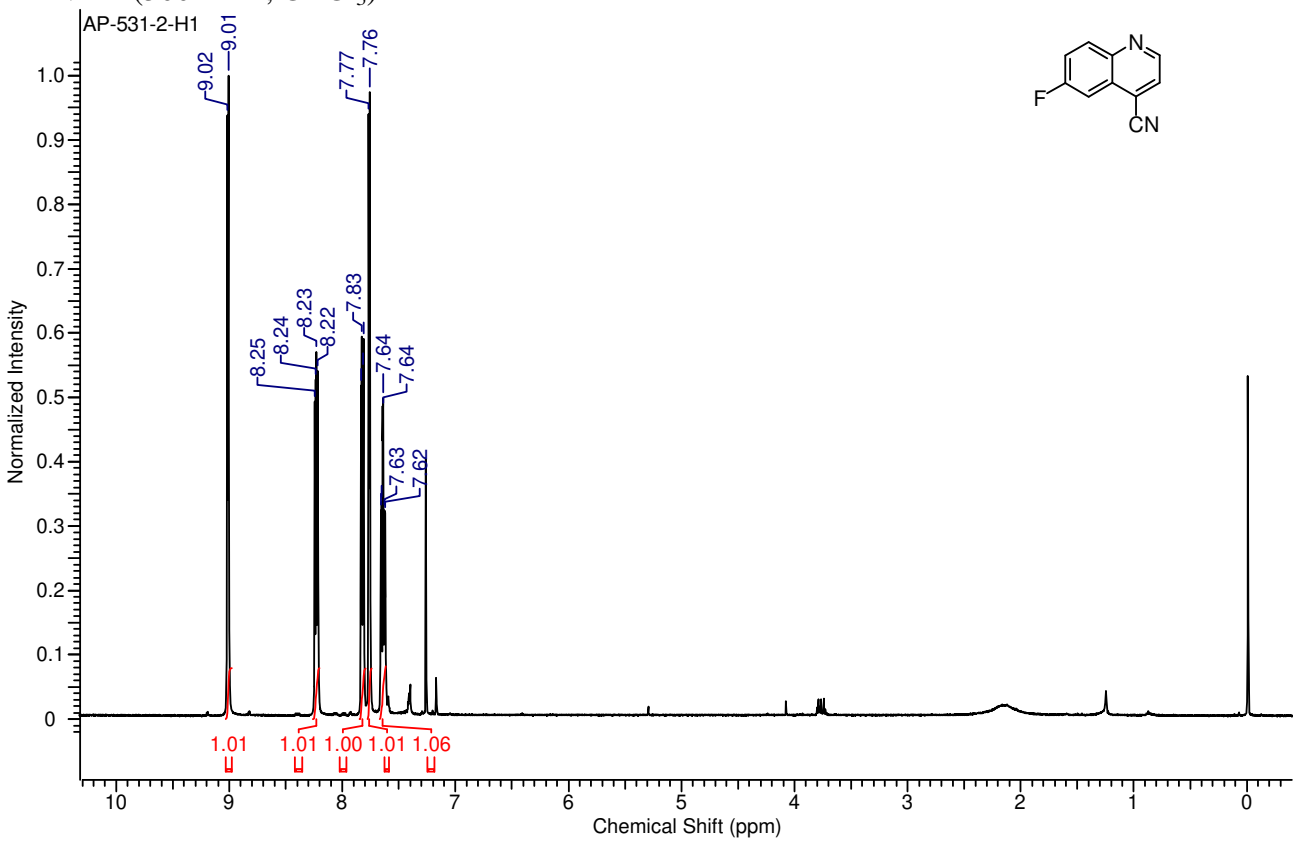


^{13}C NMR (125 MHz, $CDCl_3$)

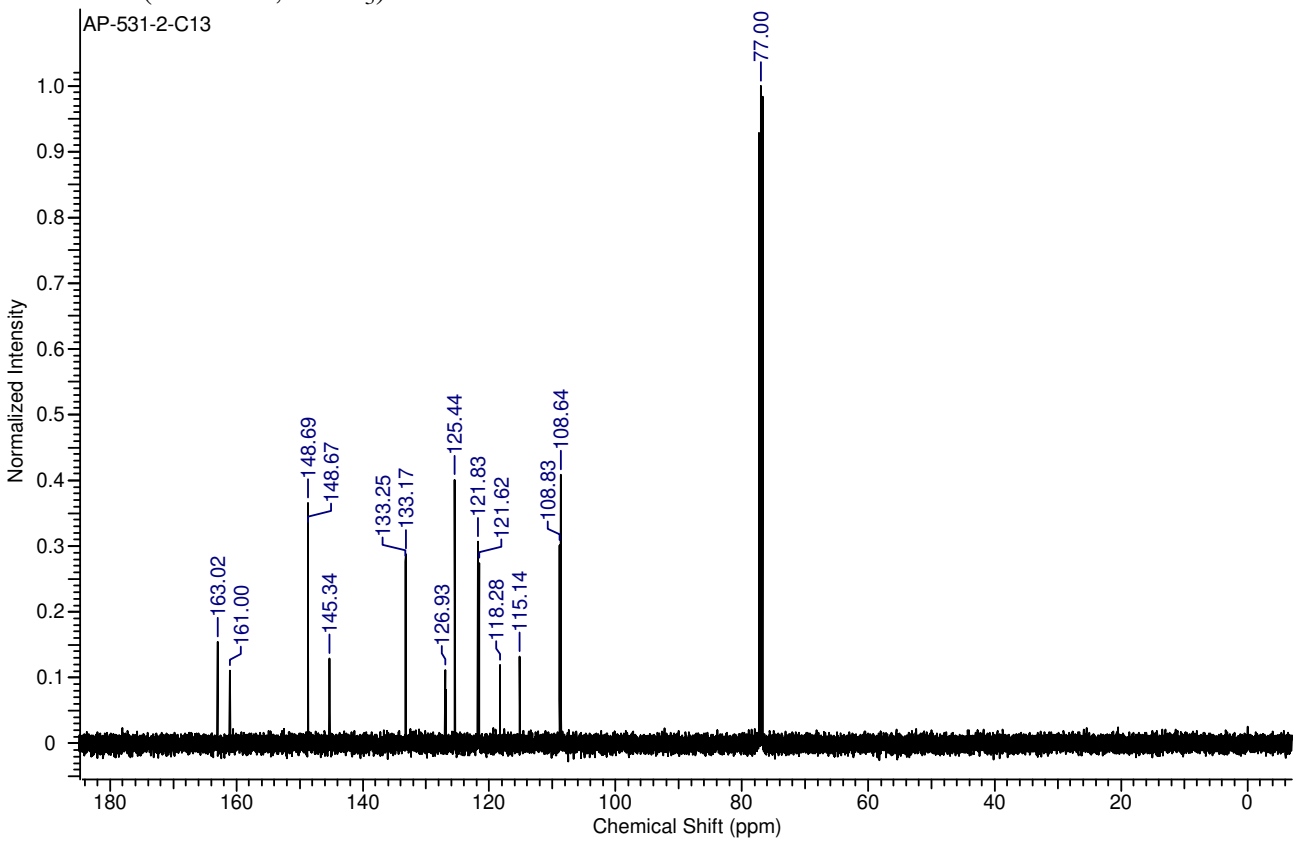


4g

^{1}H NMR (500 MHz, $CDCl_3$)

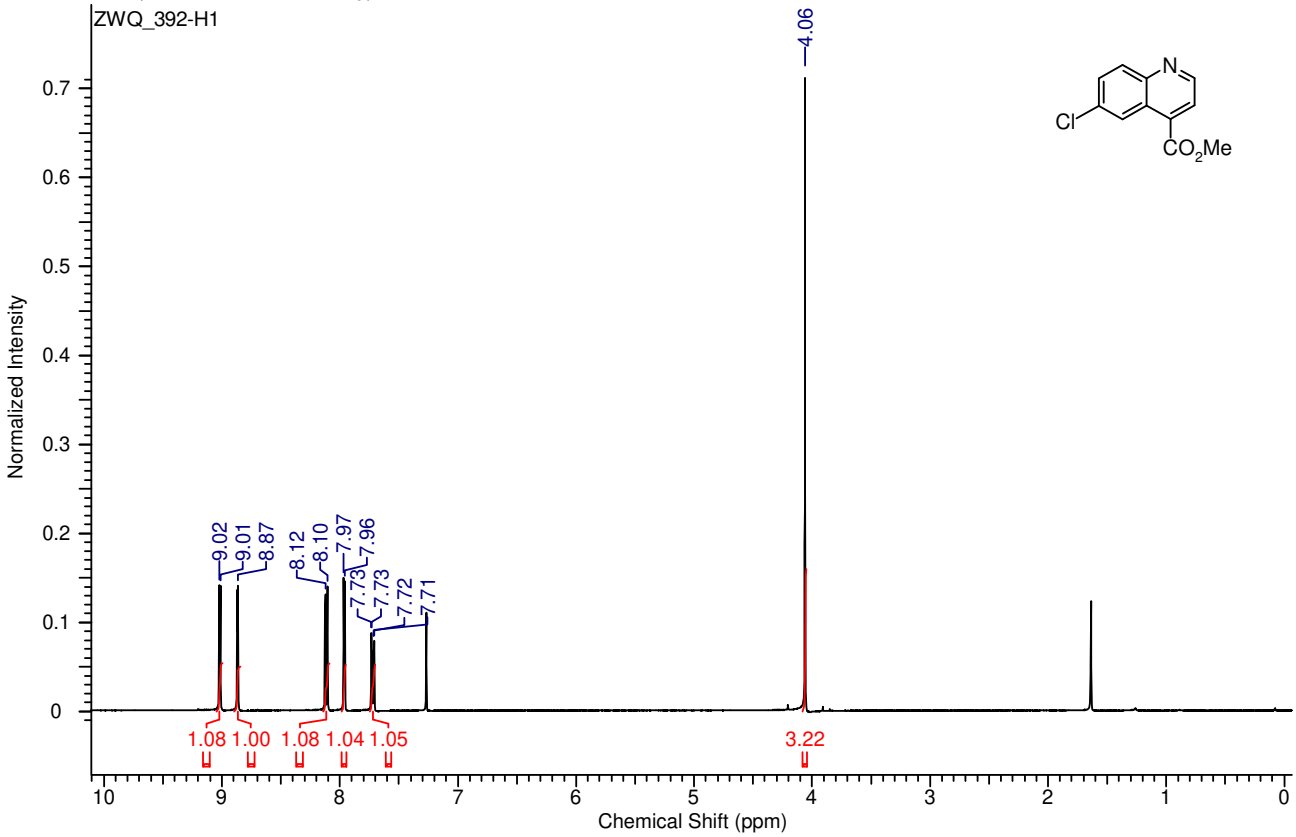


^{13}C NMR (125 MHz, $CDCl_3$)

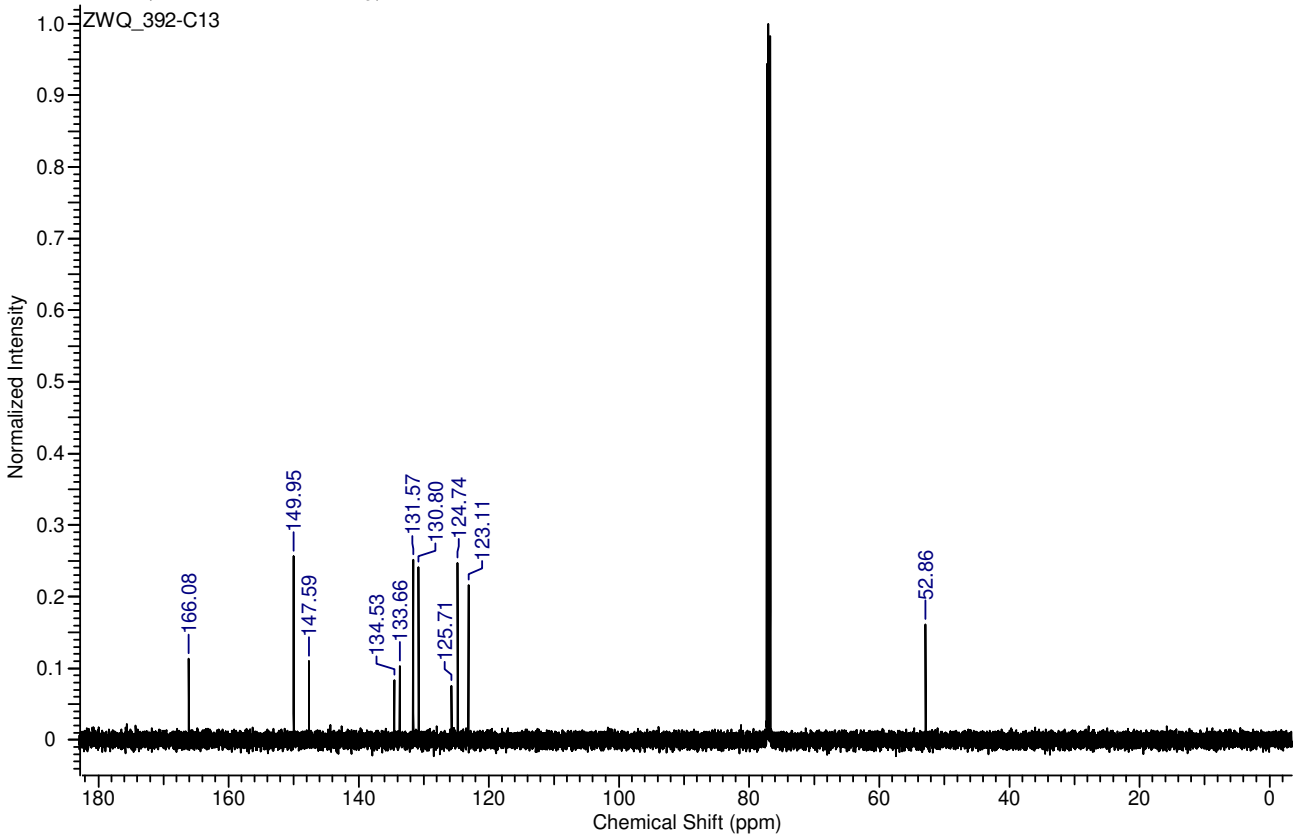


4j

^{1}H NMR (500 MHz, $CDCl_3$)

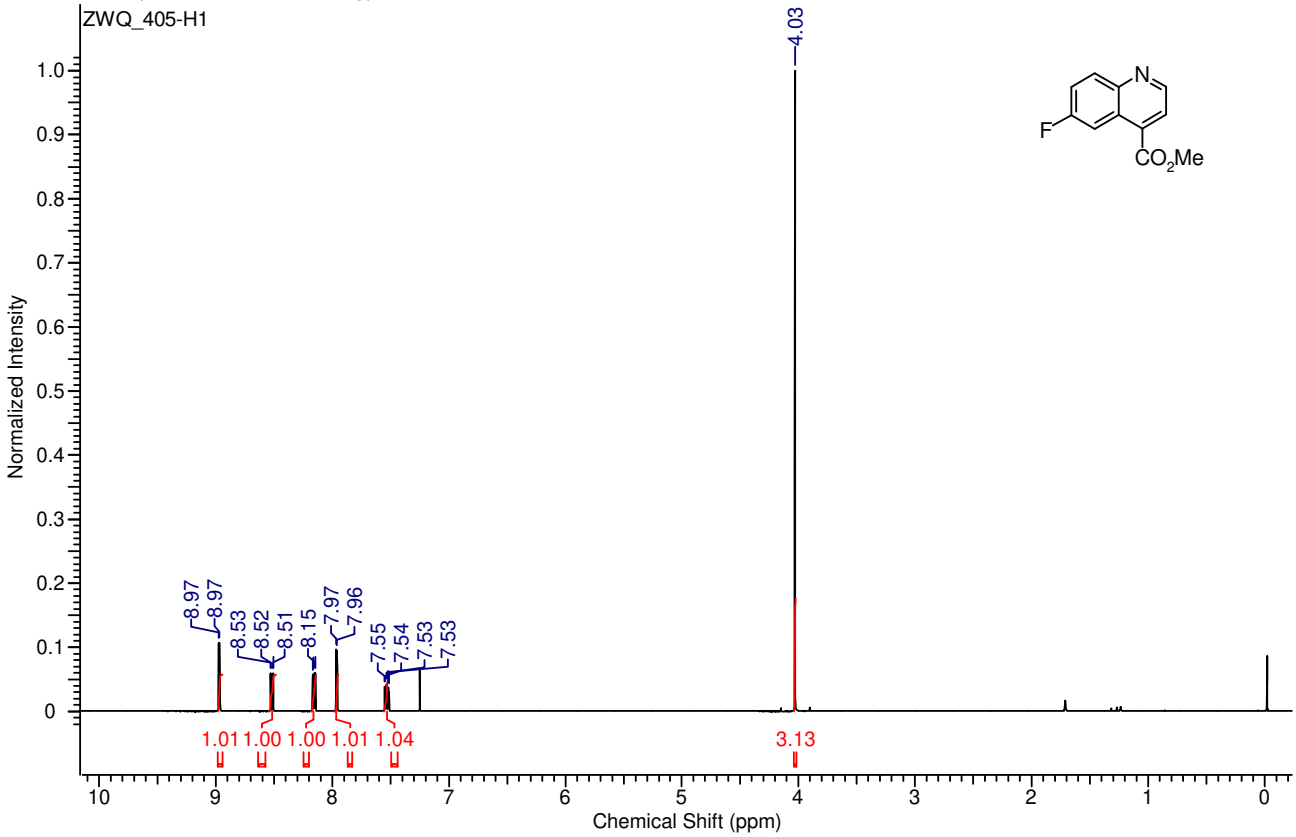


^{13}C NMR (125 MHz, $CDCl_3$)

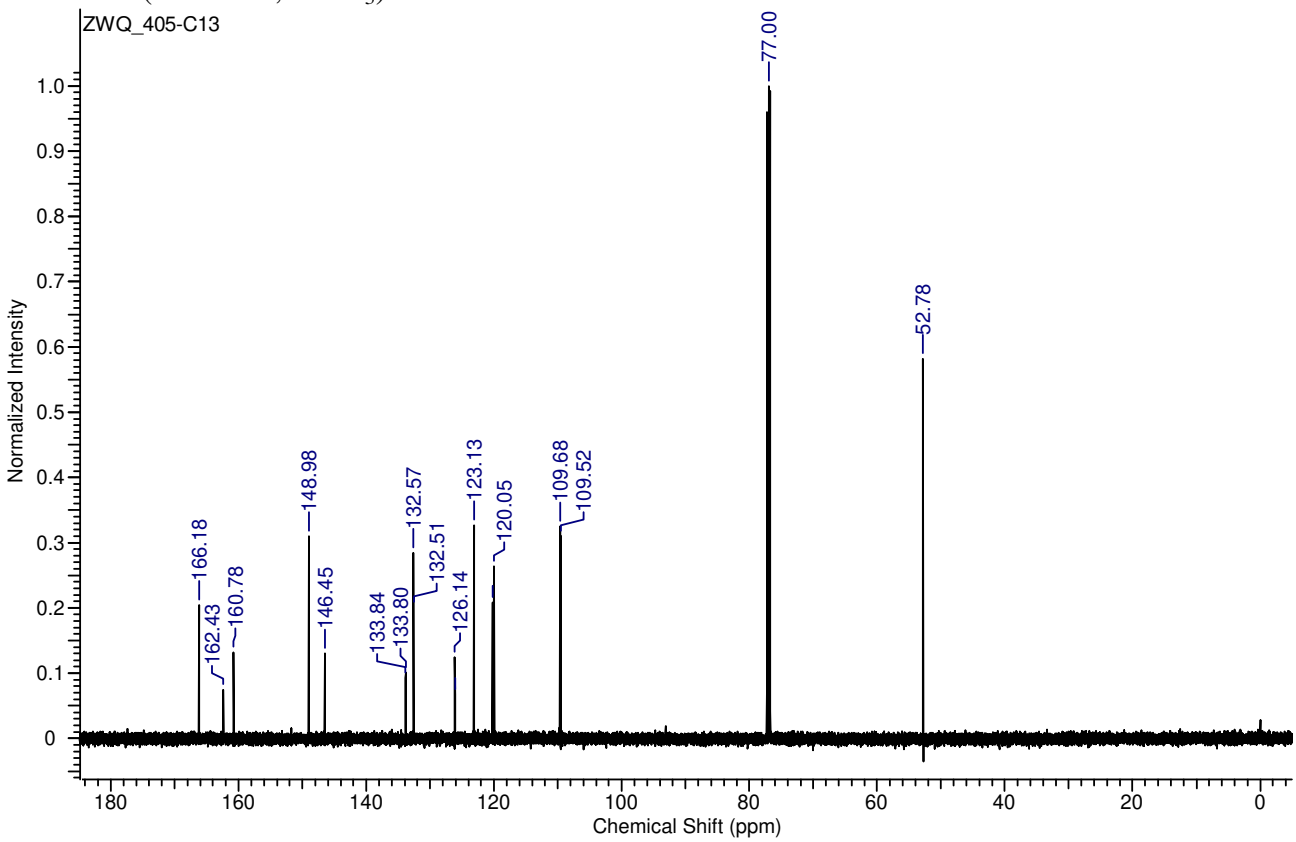


4o

^{1}H NMR (600 MHz, $CDCl_3$)

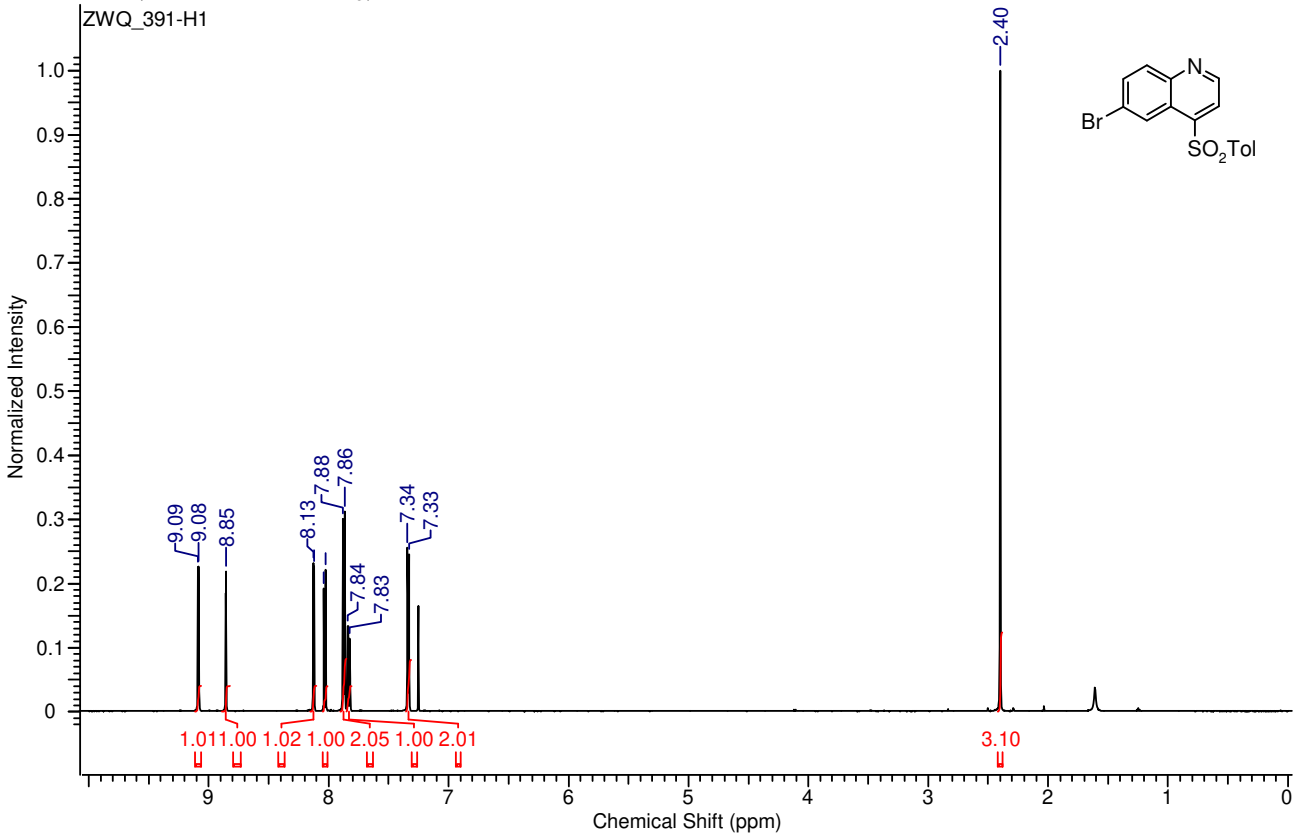


^{13}C NMR (150 MHz, $CDCl_3$)

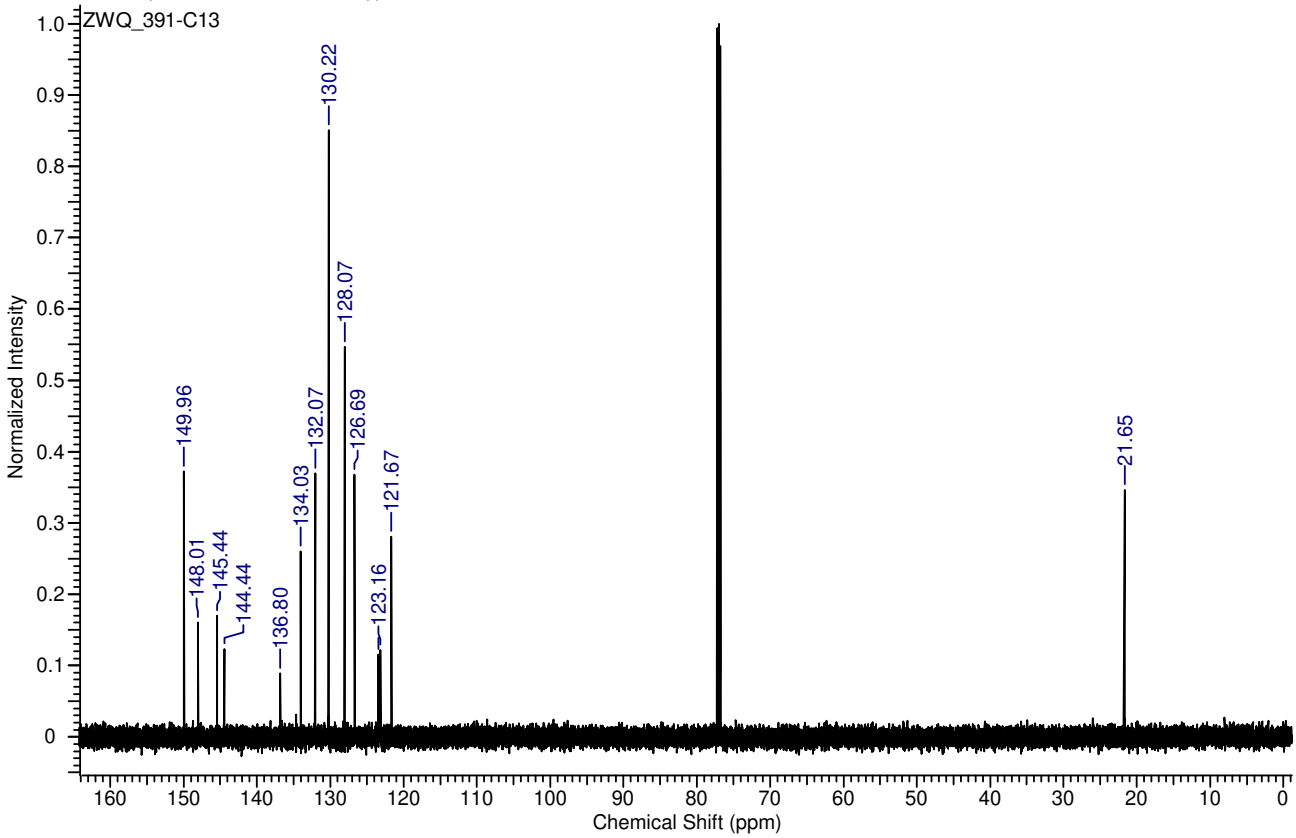


4p

^{1}H NMR (500 MHz, $CDCl_3$)

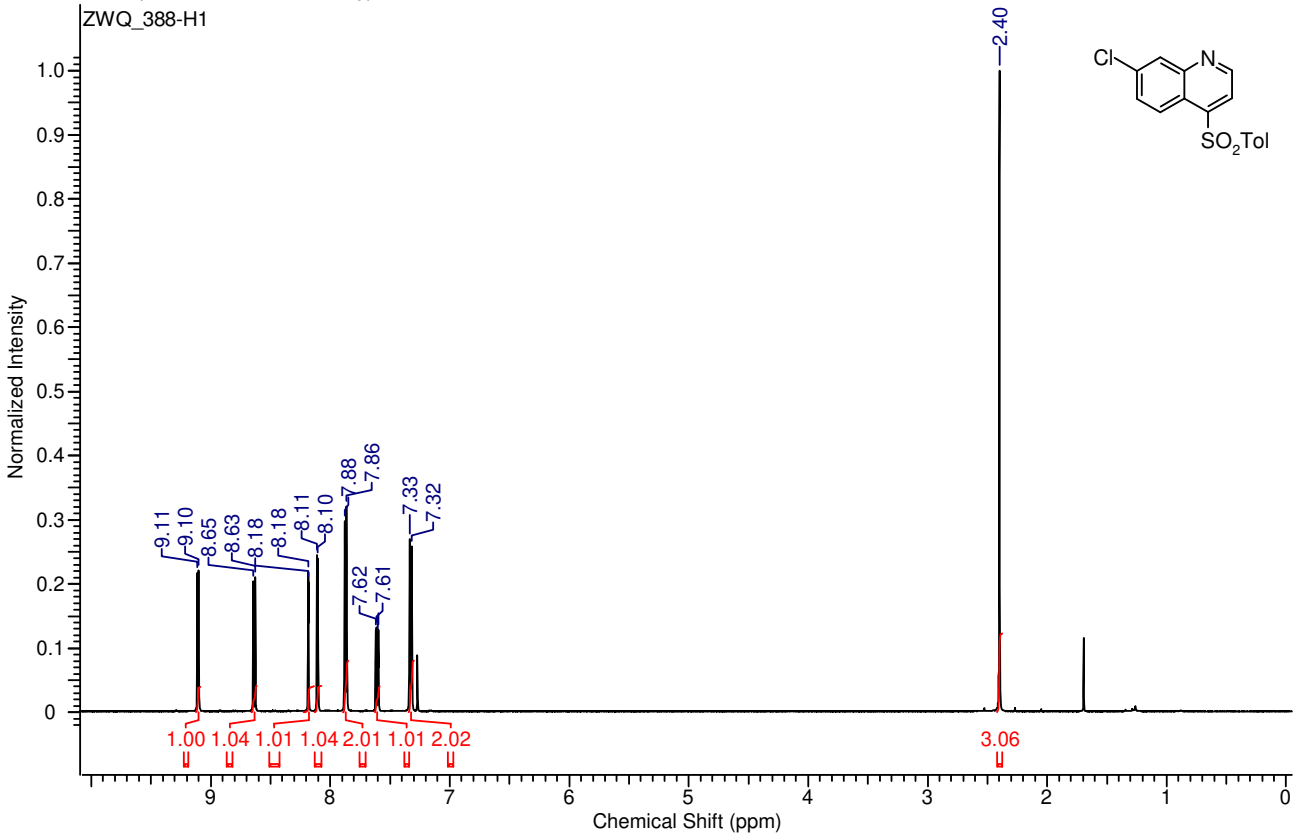


^{13}C NMR (125 MHz, $CDCl_3$)

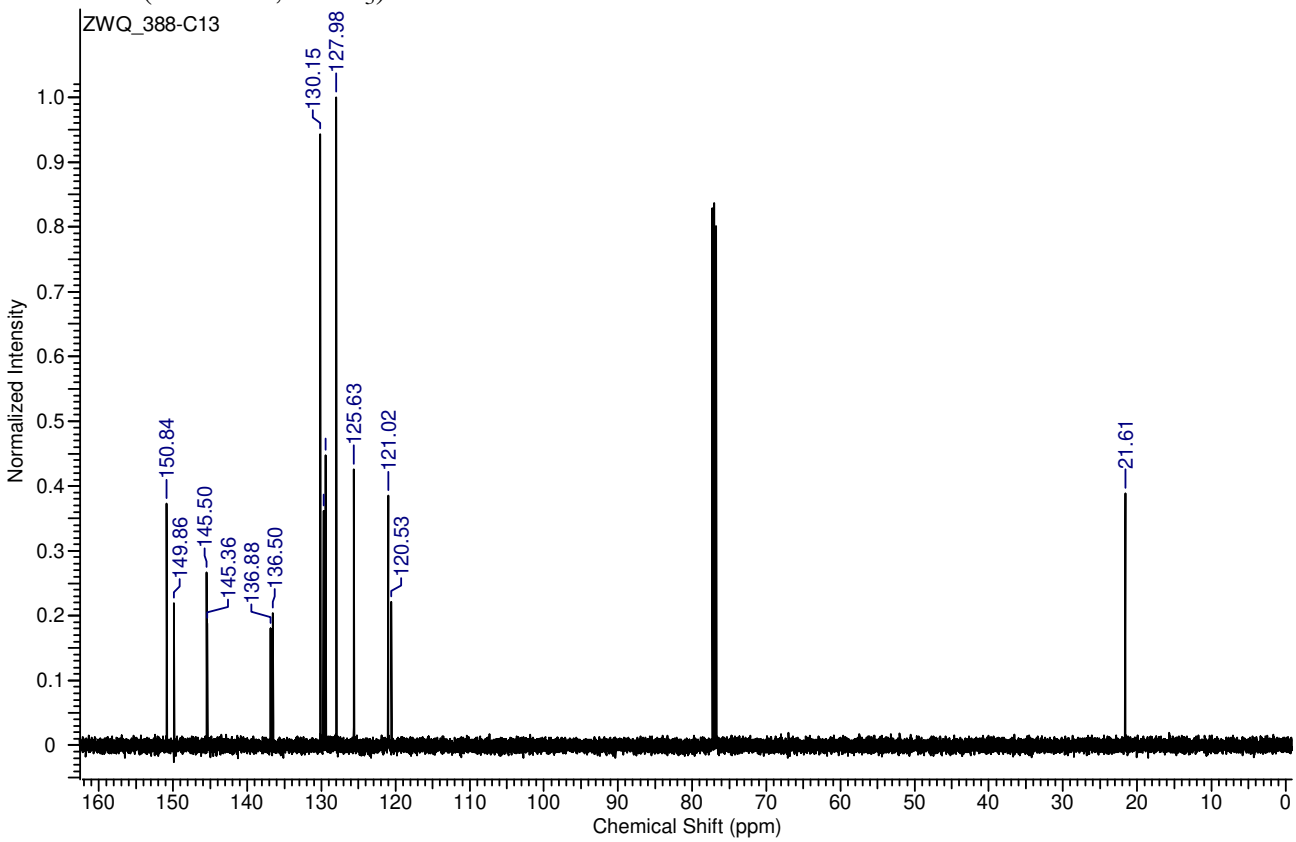


4r

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)



Synlett M. Walewska-Królikiewicz et al. Letter

(2-Aminoaryl)iminophosphoranes as Versatile Starting Materials for the Synthesis of 1-Aryl-2-trifluoromethylbenzimidazoles

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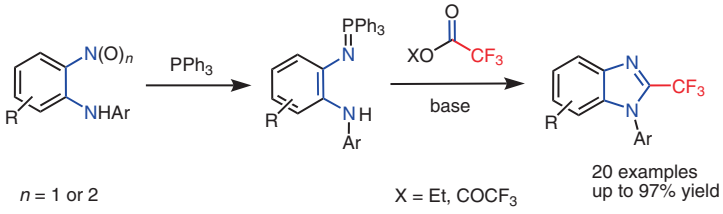
zbigniew.wrobel@icho.edu.pl
[b] Monmouth University, 400 Cedar Ave, West Long Branch, NJ 07764, USA



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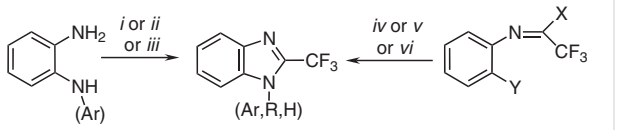
Abstract A new route to 2-(trifluoromethyl)benzimidazoles is described which involves the condensation of (2-arylamino)iminophosphoranes with trifluoroacetyl esters or trifluoroacetic anhydride. The method allows the synthesis of the title compounds from simple nitroarenes without the use of separate reduction steps and metallic reagents or expensive catalysts.

Key words cyclization, condensation, heterocycles, annulation, benzimidazoles

Aryliminophosphoranes (also known as phosphazenes and phosphine imides) exhibit ylide-like reactivity which can be employed for the construction of various nitrogen structures,[1] frequently via aza-Wittig reaction. Amine group located in the *ortho* position of the aromatic ring allows cyclization reactions, giving rise to various fused heterocyclic systems. In 2014, we described the efficient formation of 2-(arylamino)iminophosphoranes in the reaction of 2-nitrosodiarylamines with triphenylphosphine,[2a] and the complementary method starting from 2-nitroanilines was developed somewhat later.[2b] These compounds turned out to be versatile starting materials in the synthesis of a variety of nitrogen heterocycles like benzimidazoles,[2a,3] triazoles,[4] benzimidazol-2-ones,[5a] benzimidazol-2-thiones,[5b] and benzazepines.[3]

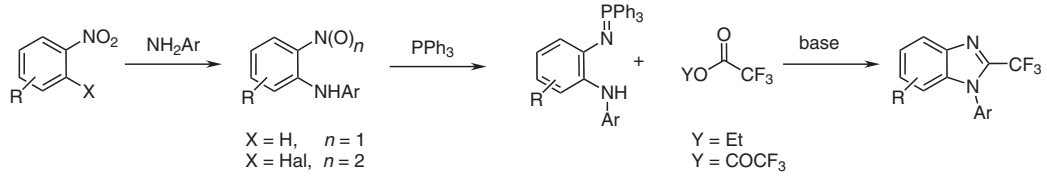
In all those cases, the iminophosphoranes can be considered as an alternative to the *ortho*-phenylenediamine derivatives, commonly used as starting materials in the syntheses of condensed nitrogen heterocycles. Unfortunately, arylenediamines are compounds that are inconvenient to store, handle, and purify. Therefore, they are usually used immediately after their preparation, which may be impractical in certain cases. Moreover, there are numerous problems in the synthesis of arylenediamines when more complex, regioselectively substituted compounds are required. Unless the desired N-substituted derivatives are commercially available, their synthesis requires *ortho*-halogenated nitroarenes while these halogens are wasted in the substitution process. The subsequent reduction introduces metal reductants or catalysts, thus the synthetic methods based on arylenediamines become both relatively expensive and not environmentally friendly. Nevertheless, among several methods known for the synthesis of 2-(trifluoromethyl)benzimidazoles the most frequently used are those based on arylenediamines (Scheme 1).[6] Other methods involve trifluoromethylimidoyl[7] or trifluoromethylacetamido[8] derivatives of 2-haloarylamines both as starting materials or intermediates. 2-(Trifluoromethyl)benzimidazoles were also obtained in the reductive cyclization of 2-nitroaniline derivatives[9] and by direct, oxidative trifluoromethylation of benzimidazoles.[10]



Scheme 1 Common methods for the synthesis of 2-(trifluoromethyl)benzimidazoles. *Reagents and conditions*: i) TFA, Δ; ii) TFA, PPh_3/CCl_4; iii) $CF_3COCH_2COCF_3$, $Fe(OTf)_3$; iv) $ArNH_2$, CuX, X = Cl, Y = I; v) CuX, X = OH, Y = ArNH; vi) Pd(II), BINAP, X = ArNH, Y = Br.

Due to the high value of both the benzimidazole scaffold[11] and the fluorine-containing groups[12] in pharmacological chemistry, there is still great interest in the development of useful synthetic methods in this field.

In this work we present 2-(arylamino)phenyliminophosphoranes as convenient and stable equivalents of 2-arylarylenediamines in the synthesis of the title compounds (Scheme 2). The method is intended for the synthe-

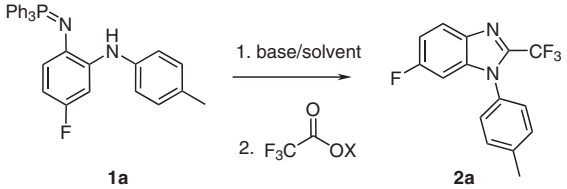


Scheme 2 Proposed synthetic path from simple nitroarenes to 2-(trifluoromethyl)benzimidazoles

sis of N-aryl-substituted benzimidazoles, hence it enriches the selection of methods that can be used for this purpose.[6f,j,7,9a]

Although the first steps of Scheme 2 had been developed previously, it was necessary to find convenient reaction conditions for the condensation of 2-(arylamino)phenyliminophosphates with trifluoroacetyl reagents followed by five-membered ring closure. For that goal, a model cyclocondensation of iminophosphorane **1a**, resulting in the formation of 2-trifluoromethylimidazole **2a**, was performed under selected reaction conditions (Table 1). Although our previous studies were successful in the use of acid chlorides to form 3-substituted benzimidazoles from (2-arylamino)aryliminophosphates,[3] the use of trifluoroacetyl chloride, needed for our present goal, was rejected due to its physicochemical properties and high toxicity.

Table 1 Optimization of the Model Cyclocondensation of **1a**



1a **2a**

Entry	X	Base	Solvent	Temp (°C)/time (h)	Yield (%)[a]
1	Et	none	MeCN	100/24	0
2	Et	none	xylenes	150/24	21
3	Et	EtOK	DMF	r.t./24	0
4	Et	*t*-BuOK	DMF	r.t./24	0
5	Et	*n*-BuLi	THF	–78 to r.t./24	50
6	Et	NaH	DMF	60/3 then r.t./24	78–83
7	Et	NaH	DMSO	60/3 then r.t./24	trace
8	Et	NaH	HMPA	50/3 then r.t./24	67
9	CF_3CO	Et_3N	DCM	–78 to r.t./24	63

[a] Isolated yield.

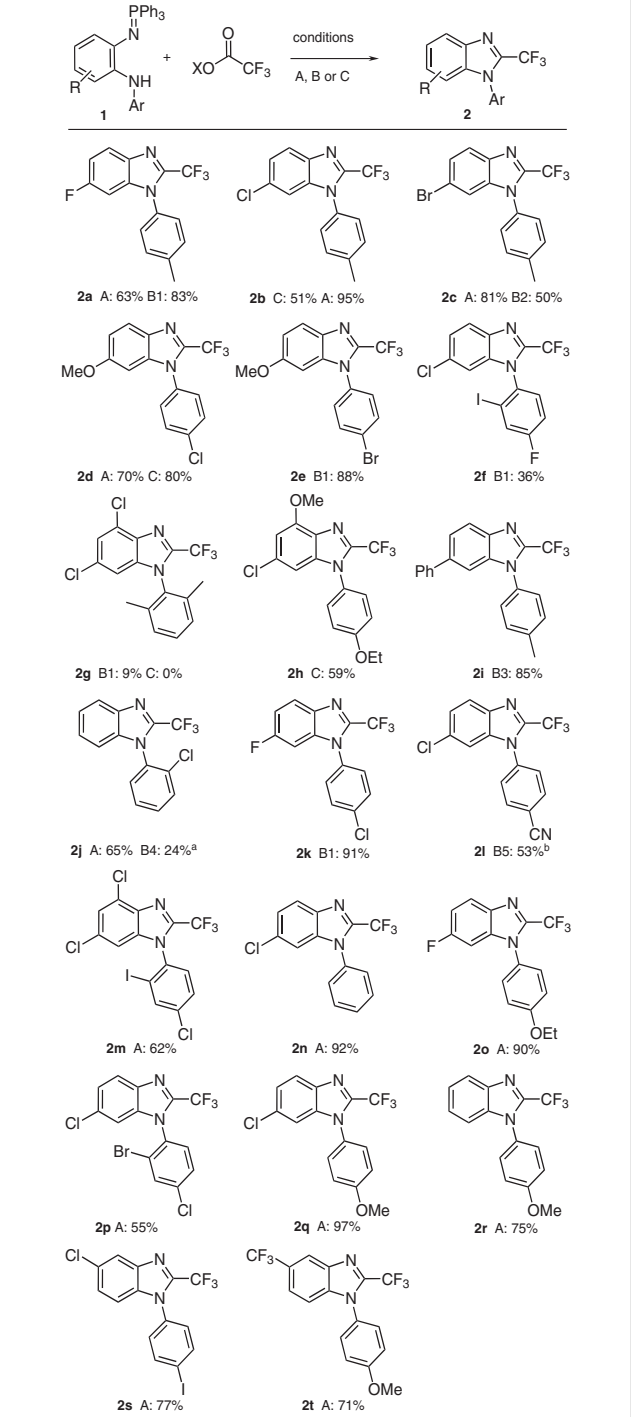
The screening of the reaction conditions allowed rejection of those under which the reaction did not occur, or where the yields were very low. The highest reproducible results were achieved under conditions shown in entry 6 (Table 1) when NaH in DMF was used for deprotonation of **1**. Thus, quantitatively generated anion was then condensed with ethyl trifluoroacetate at room temperature. These conditions were applied for the reaction of some other iminophosphoranes. We found, however, that in numerous cases the achieved results were unsatisfactory, and other reaction conditions were more suitable. Apparently, the chosen model reaction was not sufficiently representative.

Moreover, the iminophoshoranes **1** selected for the reagent screening are substituted and polysubstituted with various groups at different positions in both aromatic rings. Consequently, they vary in their reactivity noticeably on all steps of the process. The results presented in Scheme 3 were obtained under a choice of reaction conditions.[13]

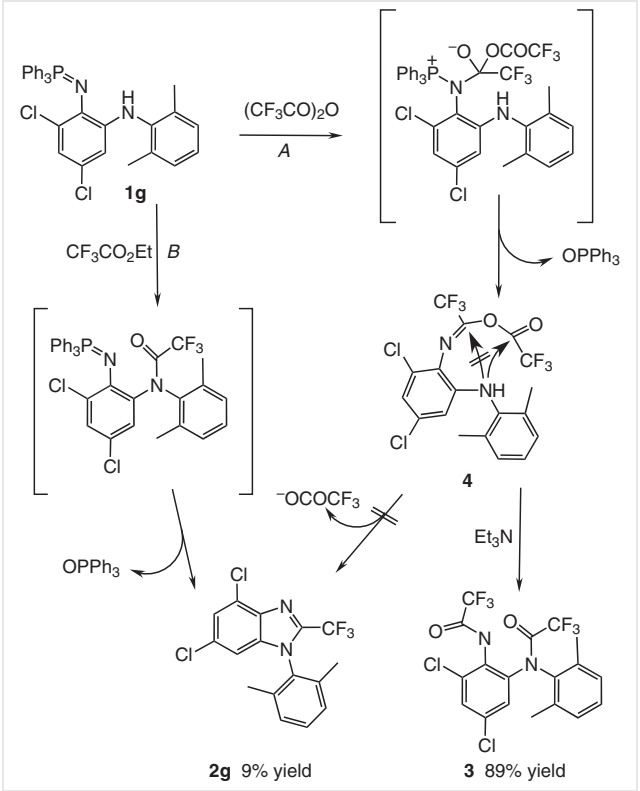
Contrary to the model reaction, reactions of several iminophosphoranes occurred more efficiently when trifluoroacetic anhydride was applied under very mild basic conditions (Scheme 3, conditions *A*). However, these conditions were not the best in all cases. Relatively less acidic iminophosphoranes reacted better when stronger bases were used. Although the reaction tolerated both electron-withdrawing and electron-donating substituents, steric hindrances caused by large *ortho* substituents in one or both aromatic rings considerably lowered the resulting yields regardless of the reaction conditions. In the particular case of iminophosphorane **1g**, the desired reaction practically failed under conditions *C*. When carried out under conditions *B* at higher temperature for a longer time, it gave only very low yields of **2g**. On the contrary, under conditions *A* the reaction led smoothly to the formation of **3** in 89% yield (Scheme 4).[14] The structure of **3** was difficult to determine even based on extended NMR techniques but was unambiguously resolved by single-crystal X-ray analysis (Figure 1). Isolation of that compound sheds light on the reaction mechanism which appears to vary depending on the reaction conditions.

Acylation of iminophosphoranes **1** with ethyl trifluoroacetate requires their deprotonation with the formation of active nitrogen anion. This is accomplished using strong bases such as NaH or *n*-BuLi.

Trifluoroacetylation of the nitrogen anion leads to a trifluoroacetamide which condenses intramolecularly with the nitrogen ylide via *aza*-Wittig process. In the case of **1g** the central nitrogen anion is relatively crowded, hence difficult to access and react. The reaction of **1** with trifluoroacetic anhydride in the presence of a weak base occurs differently. Nucleophilic reactivity of the nitrogen ylide appears



Scheme 3 Substrate scope of iminophosphoranes **1**. *Reagents and conditions*: A: X = CF_3CO, Et_3N/DCM, −70 °C to r.t.; B1–B5: X = OEt, NaH/DMF, 25–75 °C then r.t. overnight (see ref. 13 for details); C: X = Et, *n*-BuLi/THF, −70 °C, 25 min then r.t. overnight. [a] 65% of Ph_3P were isolated. [b] Additionally, a product of ethylation of the aniline nitrogen of iminophosphorane **1l** was isolated in 24% yield (see the Supporting Information for details).



Scheme 4 Simplified mechanistic scheme of the formation of compounds **2g** and **3** under conditions B and A, respectively.

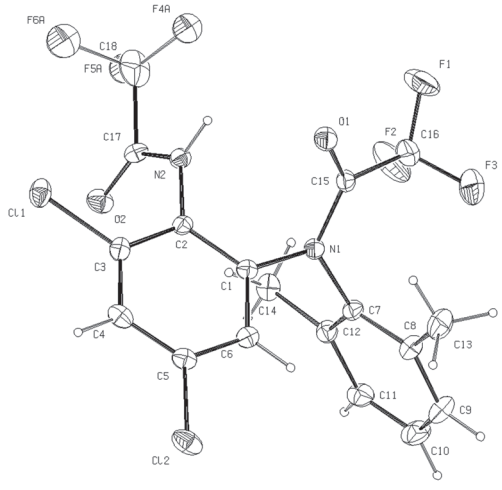


Figure 1 ORTEP structure of compound **3**[15]

to be high enough to react with the anhydride, with the elimination of triphenylphosphine oxide (*aza*-Wittig condensation). In the case of **4**, further cyclization leading to benzimidazole **2** via the five-membered intermediate does not occur. Instead, intramolecular trifluoroacetylation of

the diarylamine nitrogen leads to the final product **3**. Favored formation of a seven-membered intermediate versus a five-membered intermediate is not common but may be caused by some steric reasons. Apparently, due to the two *ortho* methyl substituents, the intramolecular acylation process (**4** → **2g**) seems to be sterically hindered. It is reasonable to assume that reactions of other iminophosphoranes **1** with trifluoroacetic anhydride under conditions *A* proceeded in the same way but, with the last step not being restricted, they provided respective benzimidazoles **2**.

It is noteworthy that in this process trifluoroacetic anhydride plays a double role as an acylating agent. Considering the yield of **3** (89%) and only 10% excess of trifluoroacetic anhydride over **1g** used in the reaction (*Procedure A*), it is obvious that the second acylation must occur intramolecularly, with the same anhydride molecule. Otherwise, the second acylation, involving diarylamine nitrogen, should be much faster than the initial acylation of the N-ylide. This, however, would lead to the formation of **2g** similarly to the reaction carried out under conditions *B*.

In summary, we have demonstrated that (2-arylaminoaryl)iminophosphoranes, easily obtained by a two-step synthesis from nitroarenes and anilines, are convenient starting materials for efficient cyclocondensation with trifluoroacetic anhydride or ethyl trifluoroacetate, affording a wide assortment of 1-aryl-2-(trifluoromethyl)benzimidazoles in good to excellent yields. The reaction is compatible with polysubstituted substrates except for some exceptionally crowded cases.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0041-1737489.

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(13) **General Procedures for the Synthesis of 2(Trifluoromethyl)benzimidazoles 2**
Procedure A: Iminophosphorane **1** (3 mmol) was dissolved in dry DCM (15 mL) under nitrogen, and Et_3N (480 μL, 3.6 mmol) was added. The mixture was cooled in a dry ice bath, and trifluoroacetic anhydride (600 μL, 3.3 mmol) was added. The cooling bath was removed, and the mixture was stirred at r.t. overnight. The mixture was poured into cold water (100 mL), extracted with DCM (3 × 50 mL), dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was then separated by column chromatography (silica gel, hexane/EtOAc) to obtain pure product **2**.
Procedure B: Iminophosphorane **1** (3 mmol) was dissolved in dry DMF (10 mL). NaH (150 mg, 3.6 mmol, 60% suspension in mineral oil) was added, and the mixture was stirred at r.t. for 20 min. The reaction was then carried out at the temperature and

time indicated in Scheme 3 as *B1*: 60 °C/3 h; *B2*: 60 °C/5 h; *B3*: 70 °C/3 h; *B4*: 75 °C/2 h; *B5*: r.t./1 h. After the evolution of H_2 ceased, the mixture was cooled to r.t., and an excess of CF_3CO_2Et (1.5 mL) was added. The mixture was stirred at r.t. overnight. The reaction mixture was poured into sat. NH_4Cl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with water and dried with Na_2SO_4. The solvent was then evaporated, and the residue was purified by column chromatography (silica gel, hexane/EtOAc) to obtain pure product **2**.
Procedure C: Iminophosphorane **1** (3 mmol) was dissolved under N_2 in freshly distilled dry THF (20 mL), and the mixture was cooled to –78 °C. *n*-BuLi (2.2 mL, 3.6 mmol, 1.6 M in hexane) was added followed by addition of HMPA (3 mL). The mixture was stirred at –78 °C for 20 min, and an excess of CF_3CO_2Et (1.5 mL) was added. The cooling bath was removed, and the mixture was stirred at r.t. overnight. The reaction mixture was poured into sat. NH_4Cl (100 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with water and dried with Na_2SO_4. The solvent was then evaporated, and the residue was separated by column chromatography (silica gel, hexane/EtOAc) to obtain pure product.

6-Fluoro-1-(4-methylphenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (**2a**)

Procedure B1; yield 443 mg (83%); yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 6.82 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.14 (ddd, *J* = 9.1, 9.1, 2.4 Hz, 1 H), 7.27–7.30 (m, 2 H), 7.37–7.39 (m, 2 H), 7.86 (dd, *J* = 9.1, 4.6 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.3, 97.7 (d, J_{FC} = 27.7 Hz), 113.0 (d, J_{FC} = 26.0 Hz), 118.6 (q, J_{FC} = 271.7 Hz), 122.5 (d, J_{FC} = 9.8 Hz), 127.0, 130.5, 131.4, 137.0, 137.6 (d, J_{FC} = 13.2 Hz), 144.4, 141.5 (q, J_{FC} = 37.6 Hz), 161.3 (d, J_{FC} = 243.9 Hz). MS (EI): m/z = 294 (100) $[M]^+$, 225 (16), 91 (20). HRMS (EI): m/z calcd for $C_{15}H_{10}F_4N_2$ $[M]^+$: 294.0780; found: 294.0775.

(14) ***N*-{2,4-Dichloro-6-[(2,6-dimethylphenyl)(trifluoroacetyl)amino]phenyl}-2,2,2-trifluoroacetamide (3)**

Procedure A; yield 1.26 g (89%); colorless crystals, mp 149–151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (s, 6 H), 6.71 (d, *J* = 2.1 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.53 (d, *J* = 2.1 Hz, 1 H), 7.66 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9, 115.6 (q, J_{FC} = 287.8 Hz), 115.7 (q, J_{FC} = 288.4, Hz), 123.4, 125.7, 129.5, 129.6, 130.6, 135.3, 135.5, 135.7, 137.0, 137.8, 154.5 (q, J_{FC} = 38.1 Hz), 158.4 (q, J_{FC} = 37.6 Hz). MS (EI): m/z = 474 (68), 472 (100) $[M]^+$, 405 (98), 403 (66), 339 (48), 264 (32), 261 (46), 105 (62). HRMS (EI): m/z calcd for $C_{18}H_{12}{}^{35}Cl_2F_6N_2O_2$ $[M]^+$: 472.0180; found: 472.0175.

(15) CCDC 2160756 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

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Supporting Information

(2-Aminoaryl)iminophosphoranes as Versatile Starting Materials for the Synthesis of 1-Aryl-2 trifluoromethylbenzimidazoles

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CONTENTS:

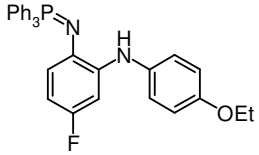
General Remarks

Melting points were recorded in open capillary and are uncorrected. The ^{1}H and ^{13}C NMR spectra of all compounds studied were measured at temperature 298 K in $CDCl_3$ or deuterated dimethyl sulfoxide (DMSO-d_6) solutions with a Varian vnmrs-600 or Varian vnmrs-500 using tetramethylsilane (TMS) as the internal standard. Mass spectra (EI, 70 eV) were obtained on an AutoSpec Premier (Waters) spectrometer. Accurate mass measurements were obtained using magnetic sector mass analyzer (EI). Silica gel Merck 60 (230-400 mesh) was used for column chromatography. THF was distilled from sodium/benzophenone ketyl prior to use. DMF was dried over CaH_2, distilled and stored over molecular sieves. All commercial reagents were used without additional purification.

Except for **1f**, **1g**, **1m**, **1o**, **1s** and **1t** the starting (2-aminoaryl)iminophosphoranes were obtained according to the previously published procedures.[1-6]

Synthesis of (2-aminoaryl)iminophosphoranes 1f, 1g, 1m and 1o. Representative procedure.[2]

To a stirred suspension of PPh_3 (3.93 mg, 15.0 mmol) in dry MeCN (50 mL) solid *N*-(4-ethoxyphenyl)-4-fluoro-2-nitrosoaniline[7] (1.56 g, 6.0 mmol) was added portionwise during 30 minutes with external cooling with cold water, and the mixture was stirred at room temperature overnight. The solid precipitated was filtered off, the filtrate was concentrated under vacuum and chromatographed using hexane-ethyl acetate mixtures (8:1 to 2:1) to obtain sufficiently pure iminophosphorane **1o**.



Iminophosphorane 1o

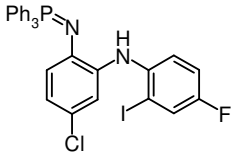
Yield 7.82 g (99%); Pale green crystals, mp 174-177 °C.

^{1}H NMR (600 MHz, DMSO-d_6) δ = 1.29 (t, *J* = 7.0 Hz, 3H), 3.96 (q, *J* = 7.0 Hz, 2H), 6.01 (td, *J* = 8.5, 3.0 Hz, 1H), 6.15 (ddd, *J* = 8.5, 5.8, 1.4 Hz, 1H), 6.61 (dt, *J* = 11.2, 2.8 Hz, 1H), 6.87-6.90 (m, 2H), 7.47 (br s, 1H), 7.53-7.55 (m, 6H), 7.59-7.62 (m, 3H), 7.72-7.76 (m, 6H).

^{13}C NMR (150 MHz, DMSO-d_6) δ = 15.2, 63.6, 98.0 (d, *J* = 27.2 Hz), 102.9 (d, *J* = 21.4 Hz), 115.7, 118.3 (dd, *J* = 9.2, 8.5 Hz), 121.9, 129.4 (d, *J* = 11.6 Hz), 130.5 (d, *J* = 99.4 Hz), 132.5 (d, *J* = 9.8 Hz), 132.55, 134.4 (d, *J* = 1.7 Hz), 135.9, 140.2 (dd, *J* = 11.6, 9.4 Hz), 154.0, 155.3 (d, *J* = 230.6 Hz).

MS (EI) *m/z* 506 (100, $[M]^+$), 477 (49), 262 (22).

HRMS (EI) *m/z* Calcd. for $C_{32}H_{28}FN_2OP$ $[M]^+$: 506.1923. Found: 506.1920.



Iminophosphorane 1f

Obtained from *N*-(4-fluoro-2-iodophenyl)-4-chloro-2-nitrosoaniline[8] (3.05 g, 8.1 mmol). Yield 4.43 g (88%); Brown crystals, mp 190-192 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.25 (d, *J* = 8.2 Hz, 1H), 6.38 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.89-6.91 (m, 1H), 7.20 (dt, *J* = 8.2, 2.5 Hz, 1H), 7.37 (dd, *J* = 8.6, 5.3 Hz, 1H), 7.53-7.57 (m, 6H), 7.58-7.62 (m, 3H), 7.69 (s, 1H), 7.73 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.76-7.80 (m, 6H).

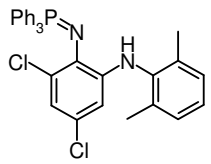
^{13}C NMR (125 MHz, DMSO-d_6) δ = 91.5 (d, *J* = 8.1 Hz), 111.8, 116.3 (d, *J* = 22.0 Hz), 118.3 (d, *J* = 8.1 Hz), 119.2, 121.1, 126.1 (d, *J* = 24.3 Hz), 129.5 (d, *J* = 11.6 Hz), 129.8 (d, *J* = 100.0 Hz), 132.6 (d, *J* = 9.8 Hz), 132.8 (d, *J* = 2.3 Hz), 138.3, 138.4, 138.5, 140.1 (d, *J* = 1.7 Hz), 156.6 (d, *J* = 242.2 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ = -121.84.

^{31}P NMR (202 MHz, $CDCl_3$) δ = 7.202.

MS (EI) *m/z* 624 (44), 622 (100, $[M]^+$), 496 (36), 262 (58), 233 (27).

HRMS (EI) *m/z* Calcd. for $C_{30}H_{22}{}^{35}ClFIN_2P$ $[M]^+$: 622.0238. Found: 622.0217.



Iminophosphorane 1g

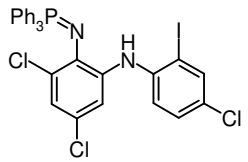
Obtained from *N*-(2,6-dimethylphenyl)-3,5-dichloro-2-nitrosoaniline[9] (5.90 g, 20 mmol). Yield 10.1 g (93%); Colorless crystals, mp 153-155 °C.

^{1}H NMR (600 MHz, DMSO-d_6) δ = 1.89 (s, 6H), 5.60 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.33 (s, 1H), 6.48 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.01-7.03 (m, 1H), 7.05-7.07 (m, 2H), 7.49-7.53 (m, 6H), 7.55-7.59 (m, 3H), 7.64-7.69 (m, 6H).

^{13}C NMR (150 MHz, DMSO-d_6) δ = 18.1, 107.0, 116.7 (d, J_{PC} = 2.9 Hz), 122.8 (d, J_{PC} = 2.9 Hz), 126.3, 127.4 (d, J_{PC} = 7.0 Hz), 128.9, 129.3 (d, J_{PC} = 12.1 Hz), 132.0 (d, J_{PC} = 101.7 Hz), 132.2 (d, J_{PC} = 9.2 Hz), 132.4 (d, J_{PC} = 2.9 Hz), 133.2 (d, J_{PC} = 1.9 Hz), 135.3, 138.1, 144.0(d, J_{PC} = 9.2 Hz).

MS (EI) *m/z* 542 (36), 540 (53, $[M]^+$), 278 (100), 262 (62), 183 (62).

HRMS (EI) *m/z* Calcd. for $C_{32}H_{27}{}^{35}Cl_2N_2P$ $[M]^+$: 540.1289. Found: 540.1292



Iminophosphorane 1m

N-(4-Chloro-2-iodophenyl)-3,5-dichloro-2-nitrosoaniline was obtained from 2,4-dichloronitrobenzene (3.07 g,16.0 mmol) and 4-chloro-2-iodoaniline (4.05 g, 16.0 mmol) following the published general procedure.[8]

Yield: 4.19 g (61%); mp 133-134 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.65 (d, *J* = 2.1 Hz, 1H), 7.12 (d, *J* = 2.1 Hz. 1H), 7.23-7.26 (m, 1H), 7.41 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 12.2 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 96.8, 113.7, 120.1, 127.5, 129.8, 132.8, 133.8, 137.0, 139.6, 144.8, 147.2, 150.9.

MS (EI) *m/z* 428 (2), 426 (2, $[M]^+$), 408 (5), 301 (98), 299 (100), 236 (39), 234 (36).

HRMS (EI) *m/z* Calcd. for $C_{12}H_6{}^{35}Cl_3IN_2O$ $[M]^+$: 425.8590. Found: 425.8596.

Iminophosphorane **1m** was obtained from the above nitrosoaniline (3.69 g, 8.6 mmol). Yield 5.36 g (92%); Colorless crystals, mp 179-181 °C.

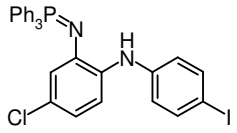
^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.71 (d, *J* = 2.1 Hz, 1H), 6.83-6.85 (m, 2H), 7.05 (d, *J* = 8.6 Hz, 1H), 7.14 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.37-7.45 (m, 6H), 7.45-7.49 (m, 3H), 7.64-7.69 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 90.9, 111.9, 119.0, 120.7 (d, J_{PC} = 2.3 Hz), 123.1 (d, J_{PC} = 2.9 Hz), 126.3, 128.2 (d, J_{PC} = 6.9 Hz), 128.5 (d, J_{PC} = 12.1 Hz), 128.8, 131.6 (d, J_{PC} = 2.9 Hz), 131.9 (d, J_{PC} = 102.9 Hz), 132.4 (d, J_{PC} = 9.8 Hz), 135.4 (d, J_{PC} = 1.6 Hz), 138.4, 139.9 (d, J_{PC} = 11.6 Hz), 142.1.

MS (EI) *m/z* 674 (80), 672 (80, $[M]^+$), 622 (60), 263 (61), 262 (100).

HRMS (EI) *m/z* Calcd. for $C_{30}H_{21}{}^{35}Cl_3IN_2{}^{31}P$ $[M]^+$: 671.9553 Found: 671.9533.

Synthesis of 2-(arylamino) iminophosphoranes 1 from 2-nitrodiarylamines. General procedure:[5]
To a solid 2-nitrodiarylamine (1 equiv.) was added Ph_3P (5 equiv.) and the mixture was heated up to melt, then it was stirred at 150 °C for 12 h. After cooling down, the crude mixture was chromatographed using hexane–EtOAc gradient eluent (9:1–2:1) to isolate sufficiently pure product **1**.



Iminophosphorane 1s

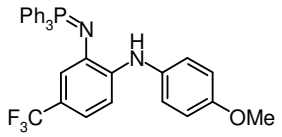
Obtained from *N*-(4-chloro-2-nitrophenyl)-4-iodoaniline (6.74 g, 18 mmol). Yield 7.18 g (66%); Colorless crystals, mp 150-152 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.38-6.39 (m, 1H), 6.60 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.93-6.95 (m, 2H), 7.13 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.40 (s, 1H), 6.45-6.54 (m, 8H), 6.55-7.00 (m, 3H), 7.70-7.75 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 80.9, 114.1, 117.1, 117.9, 119.4, 124.1, 128.8, (d, J_{CP} = 12.1 Hz), 129.9 (d, J_{CP} = 100.6 Hz), 132.1 (d, J_{CP} = 2.9 Hz), 132.4 (d, J_{CP} = 9.8 Hz), 135.5 (d, J_{CP} = 19.6 Hz), 137.9, 141.0, 143.6.

MS (EI) *m/z* 604 (100, $[M]^+$), 478 (20), 262 (60), 183 (55).

HRMS (EI) *m/z* Calcd. for $C_{30}H_{23}{}^{35}ClIN_2P$ $[M]^+$: 604.0332. Found: 604.0331.



Iminophosphorane 1t

Obtained from *N*-[2-nitro-4-(trifluoromethyl) phenyl]-4-methoxyaniline (4.68 g, 15 mmol). Yield 5.77 g (71%); Pale pink crystals, mp 152-153 °C.

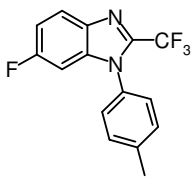
^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.83 (s, 3H), 6.56 (s, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.90-6.94 (m, 2H), 7.00 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.21-7.24 (m, 2H), 7.48-7.60 (m, 10H), 7.75-7.81 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.6, 108.8, 114.6, 115.1 (q, J_{FC} = 4.4 Hz), 118.8 (q, J_{FC} = 31.2 Hz), 123.1, 124.0, 125.1 (q, J_{FC} = 270.5 Hz), 128.8 (d, J_{CP} = 12.1 Hz), 130.2 (d, J_{CP} = 100.1 Hz), 132.1 (d, J_{CP} = 2.9 Hz), 132.5 (d, J_{CP} = 9.8 Hz), 135.7, 137.5, 142.8 (d, J_{FC} = 19.6 Hz), 155.2.

MS (EI) *m/z* 542 (100, $[M]^+$), 527 (32), 262 (24).

HRMS (EI) *m/z* Calcd. for $C_{32}H_{26}F_3N_2OP$ $[M]^+$: 542.1735. Found: 542.1726.

Analytical data for 2-trifluoromethylbenzimidazoles 2b-t.



6-Chloro-1-(4-methylphenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2b)

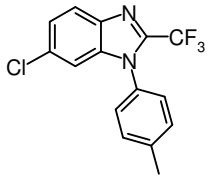
Procedure A: 885 mg (95%); Brown crystals, mp 70-73 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.49 (s, 3H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.27-7.30 (m, 2H), 7.36 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.38-7-41 (m, 2H), 7.84 (d, *J* = 8.7 Hz. 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3, 111.3, 118.6 (q, J_{FC} = 271.7 Hz), 122.4, 124.9, 127.0, 130.5, 131.2, 131.7, 137.9, 139.2, 140.5, 141.8 (q, J_{FC} = 38.7 Hz).

MS (EI) *m/z* 312 (42), 310 (100, $[M]^+$), 91 (25).

HRMS (EI) *m/z* Calcd. for $C_{15}H_{10}{}^{35}ClF_3N_2$ $[M]^+$: 310.0485. Found: 310.0483.



6-Bromo-1-(4-methylphenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2c)

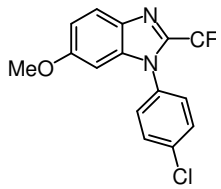
Procedure B2: Yield 533 mg (50%); Brick-red crystals, mp 101-103 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.49 (s, 3H), 7.27-7.29 (m, 2H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.37-7.40 (m, 2H), 7.50 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3, 114.3, 118.6 (q, J_{FC} = 272.2 Hz), 119.2, 122.7, 117.1, 127.6, 130.5, 131.2, 138.2, 139.6, 140.5, 141.6 (q, J_{FC} = 38.7 Hz).

MS (EI) *m/z* 356 (99), 354 (100, $[M]^+$), 206 (14), 205 (14), 91 (28).

HRMS (EI) *m/z* Calcd. for $C_{15}H_{10}{}^{79}BrF_3N_2$ $[M]^+$: 353.997. Found: 353.9977.



1-(4-Chlorophenyl)-6-methoxy-2-(trifluoromethyl)-1*H*-benzimidazole (2d)

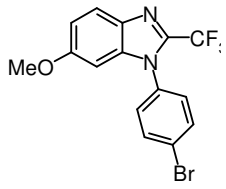
Procedure C: Yield 784 mg (80%); Procedure A: 685 mg (70%); Pale pink crystals, mp 152-155 °C (lit.[10] mp 152-154 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.77 (s, 3H), 6.49 (d, *J* = 2.3 Hz, 1H), 7.03 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.35-7.39 (m, 2H), 7.55-7.59 (m, 2H), 7.79 (d, *J* = 9.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.8, 93.0, 114.6, 118.7 (q, J_{FC} = 271.7 Hz), 122.2, 128.8, 130.2, 133.0, 135.0, 136.1, 137.9, 139.7 (q, J_{FC} = 38.5 Hz), 159.0.

MS (EI) *m/z* 328 (43), 326 (100, $[M]^+$), 311 (31), 276 (10).

HRMS (EI) *m/z* Calcd. for $C_{15}H_{10}{}^{35}ClF_3N_2O$ $[M]^+$: 326.0434. Found: 326.0423.



1-(4-Bromophenyl)-6-methoxy-2-(trifluoromethyl)-1*H*-benzimidazole (2e)

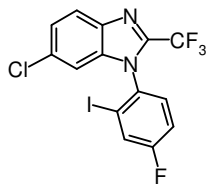
Procedure B1: Yield 981 mg (88%); Colorless crystals, mp 139-141 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.78 (s, 3H), 6.49 (d, *J* = 2.3 Hz, 1H), 7.04 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.29-7.32 (m, 2H), 7.72-7.75 (m, 2H), 7.79 (d, *J* = 8.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.8, 93.0, 114.7, 118.7 (q, J_{FC} = 271.4 Hz), 122.2, 124.1, 129.1, 133.2, 133.5, 135.0, 137.8, 139.5, 149.4 (q, J_{FC} = 38.7 Hz).

MS (EI) *m/z* 372 (99), 370 (100, $[M]^+$), 357 (32), 355 (33), 276 (28), 248 (29).

HRMS (EI) *m/z* Calcd. for $C_{15}H_{10}{}^{79}BrF_3N_2O$ $[M]^+$: 369.9929. Found: 369.9931.



6-Chloro-1-(4-fluoro-2-iodophenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2f)

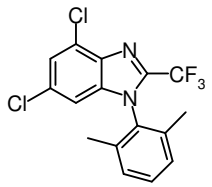
Procedure B1: Yield 477 mg (36%); Coral-red crystals, mp 150-153 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.00 (dd, *J* = 1.3, 0.6 Hz, 1H), 7.30 (ddd, *J* = 8.7, 7.6, 2.8 Hz, 1H), 7.41 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.43 (dd, *J* = 8.7, 5.0 Hz, 1H), 7.78 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 98.1 (d, J_{FC} = 8.7 Hz), 111.2, 116.8 (d, J_{FC} = 22.5 Hz), 118.2 (q, J_{FC} = 272.2 Hz), 122.7, 125.3, 127.5 (d, J_{FC} = 24,8 Hz), 130.4 (d, J_{FC} = 9.2 Hz), 132.3, 133.1 (d, J_{FC} = 3.5 Hz), 136.6, 139.2, 140.1 (d, J_{FC} = 39.2 Hz), 161.8, 163.5.

MS (EI) *m/z* 442 (37), 440 (100, $[M]^+$), 314 (65).

HRMS (EI) *m/z* Calcd. for $C_{14}H_6{}^{35}ClF_4IN_2$ $[M]^+$: 439.9200. Found: 439.9199.



4,6-Dichloro-1-(2,6-dimethylphenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2g)

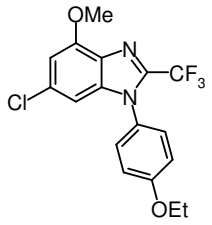
Procedure B1: Yield 97 mg (9**%**); Colorless crystals, mp 125-128 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.92 (s, 6H), 6.87 (d, *J* = 1.7 Hz, 1H), 7.24-7.27 (m, 2H), 7.39-7.42 (m, 1H), 7.45 (d, *J* = 1.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.1, 109.5, 118.2 (q, J_{FC} = 272.2 Hz), 124.9, 127.4, 130.0, 130.6, 131.5, 132.0, 136.6, 136.7, 137.4, 141.9 (q, J_{FC} = 39.3 Hz).

MS (EI) *m/z* 360 (64), 358 (100, $[M]^+$), 291 (36), 289 (60), 254 (30).

HRMS (EI) *m/z* Calcd. for $C_{16}H_{11}{}^{35}Cl_2F_3N_2$ $[M]^+$: 358.0251. Found: 358.0253.



6-Chloro-1-(4-ethoxyphenyl)-4-methoxy-2-(trifluoromethyl)-1*H*-benzimidazole (2h)

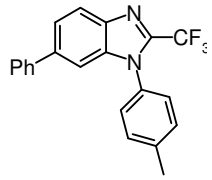
Procedure C: Yield 655 mg (59%); Colorless crystals, mp 138-141 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.47 (t, *J* = 7.1 Hz, 3H), 4.04 (s, 3H), 4.11 (q, *J* = 7.1 Hz, 2H), 6.71 (d, *J* = 1.6 Hz, 1H), 6.75 (d, *J* = 1.6 Hz, 1H), 7.01-7.04 (m, 2H), 7.26-7.30 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.7, 56.2, 63.9, 103.8, 105.6, 115.3, 118.5 (q, J_{FC} = 272.2 Hz), 126.2, 128.5, 130.0, 132.3, 139.0, 140.4 (q, J_{FC} = 38.7 Hz), 152.5, 160.1.

MS (EI) *m/z* 372 (38), 370 (100, $[M]^+$), 341 (64), 326 (68), 311 (19).

HRMS (EI) *m/z* Calcd. for $C_{17}H_{14}{}^{35}ClF_3N_2O_2$ $[M]^+$: 370.0696. Found: 370.0686.



1-(4-Methylphenyl)-6-phenyl-2-(trifluoromethyl)-1*H*-benzimidazole (2i)

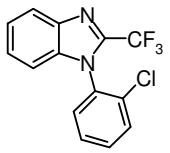
Procedure B3: Yield 897 mg (85%); Orange crystals, mp 116-118 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.49 (s, 3H), 7.30-7.35 (m, 4H), 7.38-7.43 (m, 4H), 7.54-7.55 (m, 2H), 7.65 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3, 109.5, 118.8 (q, J_{FC} = 272.2 Hz), 121.5, 123.9, 127.2, 127.47, 127.51, 128.8, 130.4, 131.7, 137.9, 139.6, 140.1, 140.2, 141.0, 141.3 (q, J_{FC} = 38.1 Hz).

MS (EI) *m/z* 352 (100, $[M]^+$), 166 (12), 91 (9).

HRMS (EI) *m/z* Calcd. for $C_{21}H_{15}F_3N_2$ $[M]^+$: 352.1187. Found: 352. 1176.



1-(2-Chlorophenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2j)

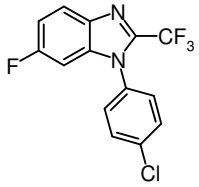
Procedure A: Yield 578 mg (65%); Yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.00-7.02 (m, 1H), 7.38-7.44 (m, 2H), 7.45-7.51 (m, 2H), 7.54-7.58 (m, 1H), 7.64-7.66 (m, 1H), 7.95-7.98 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 111.0, 118.6 (q, J_{FC} = 272.2 Hz), 127.6, 124.1, 126.0, 128.0, 130.1, 130.7, 131.6, 132.1, 133.2, 136.4, 140.70, 140.70 (q, J_{FC} = 38.7 Hz)

MS (EI) *m/z* 298 (34), 296 (100, $[M]^+$), 261 (25), 192 (22).

HRMS (EI) *m/z* Calcd. for $C_{14}H_8{}^{35}ClF_3N_2$ $[M]^+$: 296.0328. Found: 296.0339.



1-(4-Chlorophenyl)-6-fluoro-2-(trifluoromethyl)-1*H*-benzimidazole (2k)

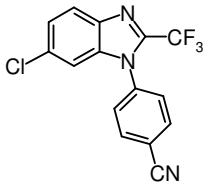
Procedure B1: Yield 860 mg (91%); Orange crystals, mp 75-79 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.81 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.16 (dt, *J* = 9.0, 2.5 Hz, 1H), 7.34-7.38 (m, 2H), 7.57-7.59 (m, 2H), 7.87 (dd, *J* = 9.0, 4.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 97.5 (d, J_{FC} = 28.3 Hz), 113.3 (d, J_{FC} = 25.4 Hz), 118.5 (q, J_{FC} = 271.7 Hz), 122.8 (d, J_{FC} = 10.4 Hz), 128.6, 130.3, 132.5, 136.4, 137.1, 137.3 (d, J_{FC} = 14.4 Hz), 141.3 (qd, J_{FC} = 39.3, 3.5 Hz), 161.4 (d, J_{FC} = 245.1 Hz).

MS (EI) *m/z* 316 (37), 314 (100, $[M]^+$), 210 (22).

HRMS (EI) *m/z* Calcd. for $C_{14}H_7{}^{35}ClF_4N_2$ $[M]^+$: 314.0234. Found: 314.0246.



4-[6-Chloro-2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]benzonitrile (2l)

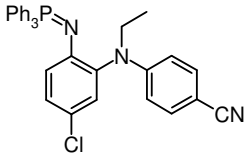
Procedure B5: Yield 510 mg (53%); Pale pink crystals, mp 143-145 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.13 (d, *J* = 1.6 Hz, 1H), 7.40 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.57-7.60 (m, 2H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.92-7.95 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 110.8, 114.6, 117.2, 118.4 (q, J_{FC} = 272.2 Hz), 122.8, 125.6, 128.3, 132.5, 134.0, 137.0, 137.8, 139.3, 141.1 (q, J_{FC} = 39.3 Hz).

MS (EI) *m/z* 323 (36), 321 (100, $[M]^+$).

HRMS (EI) *m/z* Calcd. for $C_{15}H_7{}^{35}ClF_3N_3$ $[M]^+$: 321.0281. Found: 321.0279.



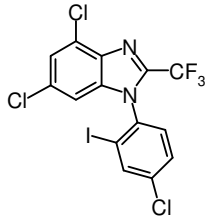
5-Chloro-1-*N*-(4-cyanophenyl)-1-*N*-ethyl-2-*N*-(triphenyl-λ5-phosphanylidene)benzene-1,2-diamine was isolated in addition to **2l** from the reaction.

Procedure B5: Yield 520 mg (24%); Colorless crystals, mp 192-195 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ =.1.21 (t, *J* = 7.1 Hz, 3H), 3.77 (q, *J* = 7.1 Hz, 2H), 7.45 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.53-6.56 (m, 2H), 6.81 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.09 (t, *J* = 2.7 Hz, 1H), 7.28-7.31 (m, 2H), 7.35-7.39 (m, 6H), 7.46-7.52 (m, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ =.12.7, 46.5, 96.7, 112.5, 121.2 (d, J_{PC} = 14.4 Hz), 123.0 (d, J_{PC} = 10.4 Hz), 127.3, 128.6 (d, J_{PC} = 12.1 Hz), 129.8, 130.4 (d, J_{PC} = 100.0 Hz), 131.8 (d, J_{PC} = 2.9 Hz), 132.2 (d, J_{PC} = 9.8 Hz), 132.9, 138.6 (d, J_{PC} = 22.5 Hz), 147.0, 151.6.

HRMS (EI) *m/z* Calcd. for $C_{33}H_{27}{}^{35}ClN_3{}^{31}P$ $[M]^+$: 531.1631 Found: 531.1628.



4,6-Dichloro-1-(4-chloro-2-iodophenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2m)

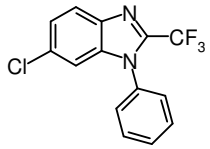
Procedure A: Yield 915 mg (62%); Colorless crystals, mp. 81-83 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.91 (d, *J* = 1.7 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 7.58 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.06 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 98.1, 110.1, 118.0 (q, J_{FC} = 272.8 Hz), 125.1, 127.6, 129.9, 130.1, 132.4, 135.2, 136.9, 137.1, 137.7, 139.9, 141.4 (q, J_{FC} = 39.3 Hz).

MS (EI) *m/z* 494 (37), 492 (98), 490 (100, $[M]^+$), 330 (24), 328 (36), 198 (26).

HRMS (EI) *m/z* Calcd. for $C_{14}H_5{}^{35}Cl_3F_3IN_2$ $[M]^+$: 489.8515. Found: 489.8505.



6-Chloro-2-1-phenyl-(trifluoromethyl)-1*H*-benzimidazole (2n)

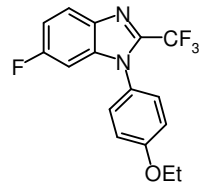
Procedure A: Yield 820 mg (92%); Pale pink crystals, mp 157-160 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.13 (dd, *J* = 1.9, 0.5 Hz, 1H), 7.35 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.38-7.41 (m, 2H), 7.55-7.60 (m, 3H), 7.83 (dd, *J* = 8.8, 0.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 111.2, 118.4 (q, J_{FC} = 272.2 Hz), 122.4, 125.0, 127.3, 129.9, 130.2, 131.8, 133.9, 137.1, 139.2, 141.5 (q, J_{FC} = 38.7 Hz).

MS (EI) *m/z* 298 (47), 296 (100, $[M]^+$), 192 (16).

HRMS (EI) *m/z* Calcd. for $C_{14}H_8{}^{35}ClF_3N_2$ $[M]^+$: 296.0328. Found: 296.0328.



1-(4-Ethoxyphenyl)-6-fluoro-2-(trifluoromethyl)-1*H*-benzimidazole (2o)

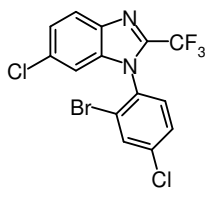
Procedure A: Yield 875 mg (90%); Yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.46 (t, *J* = 7.0 Hz, 3H), 4.11 (q, *J* = 7.0 Hz, 2H), 6.80 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.02-7.05 (m, 2H), 7.11 (dt, *J* = 9.0, 2.5 Hz, 1H), 7.27-7.30 (m, 2H), 7.83 (dd, *J* = 9.0, 4.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.7, 63.9, 97.7 (d, J_{FC} = 37.7 Hz), 113.0 (d, J_{FC} = 25.4 Hz), 115.4, 118.6 (q, J_{FC} = 272.2 Hz), 122.5 (d, J_{FC} = 10.4 Hz), 126.2, 128.4, 137.0, 137.8 (d, J_{FC} = 14.4 Hz), 141.7 (q, J_{FC} = 38.3 Hz), 160.1, 161.3 (d, J_{FC} = 244.5 Hz).

MS (EI) *m/z* 324 (100, $[M]^+$), 296 (97), 227 (26).

HRMS (EI) *m/z* Calcd. for $C_{16}H_{12}F_4N_2O$ $[M]^+$: 324.0886. Found: 324.0870.



1-(2-Bromo-4-chlorophenyl)-6-chloro-2-(trifluoromethyl)-1H-benzimidazole (2p)

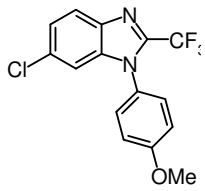
Procedure A: Yield 681 mg (55%); Pale yellow crystals, mp 157-160 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.01 (d, *J* = 1.7 Hz, 1H), 7.39 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.84 (d, *J* = 2.2 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 111.0, 118.3 (q, J_{FC} = 272.2 Hz), 122.7, 123.6, 125.4, 129.1, 130.7, 131.9, 132.3, 133.8, 136.4, 137.7, 139.2, 141.2 (q, J_{FC} = 39.3 Hz).

MS (EI) *m/z* 412 (54), 410 (100, $[M]^+$), 408 (71), 294 (26).

HRMS (EI) *m/z* Calcd. for $C_{14}H_6{}^{79}Br^{35}Cl_2F_3N_2$ $[M]^+$: 407.9043. Found: 407.9057.



6-Chloro-1-(4-methoxyhenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2q)

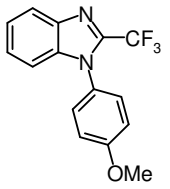
Procedure A: Yield 950 mg (97%); Pale purple crystals, mp 112-115 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.90 (s, 3H), 7.04-7.09 (m, 2H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.29-7.32 (m, 2H), 7.35 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.6, 111.2, 115.0, 118.6 (q, J_{FC} = 272.7 Hz), 122.3, 124.9, 126.2, 128.6, 131.7, 138.1, 139.2, 141.8 (q, J_{FC} = 38.1 Hz), 160.7.

MS (EI) *m/z* 328 (25), 330 (100, $[M]^+$).

HRMS (EI) *m/z* Calcd. for $C_{15}H_{10}{}^{35}ClF_3N_2O$ $[M]^+$: 326.0434. Found: 326.0437.



1-(4-Methoxyhenyl)-2-(trifluoromethyl)-1*H*-benzimidazole (2r)

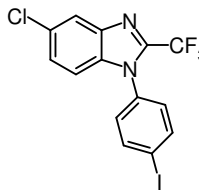
Procedure A: Yield 658 mg (75%); Colorless crystals, mp 87-89 °C (lit.[10] mp 84-88 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.89 (s, 3H), 7.04-7.06 (m, 2H), 7.12-7.14 (m, 1H), 7.31-7.33 (m, 2H), 7.34-7.39 (m, 2H), 7.90-7.92 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.6, 111.2, 114.8, 118.8 (q, J_{FC} = 272.7 Hz), 121.3, 123.9, 125.7, 126.8, 128.6, 137.5, 140.6, 141.1 (q, J_{FC} = 38.1 Hz), 160.5.

MS (EI) *m/z* 292 (100, $[M]^+$), 277 (12), 249 (10).

HRMS (EI) *m/z* Calcd. for $C_{15}H_{11}F_3N_2O$ $[M]^+$: 292.0823. Found: 292.0815.



5-Chloro-1-(4-iodophenyl)-2-trifluoromethyl)-1*H*-benzimidazole (2s)

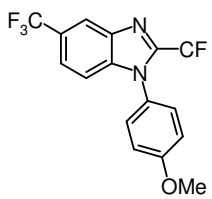
Procedure A: Yield 975 mg (77%); Pink crystals, mp 151-153 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.08 (d, *J* = 8.7 Hz, 1H), 7.16-7.18 (m, 2H), 7.37 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.93-7.95 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 96.1, 111.9, 118.5 (q, J_{FC} = 272.2 Hz), 121.2, 126.8, 129.0, 130.0, 133.7, 135.5, 139.3, 141.4, 141.7 (q, J_{FC} = 39.3 Hz).

MS (EI) *m/z* 424 (37), 422 (100, $[M]^+$), 260 (37).

HRMS (EI) *m/z* Calcd. for $C_{14}H_7{}^{35}ClF_3IN_2$ $[M]^+$: 421.9295. Found: 421.9282.



1-(4-Methoxyphenyl)-2,5-bis(trifluoromethyl)-1*H*-benzimidazole (2t)

Procedure A: Yield 766 mg (71%); Yellow crystals, mp 77-79 °C .

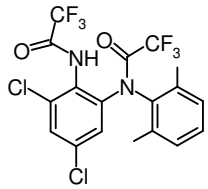
^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.92 (s, 3H), 7.08-7.10 (m, 2H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.31-7.34 (m, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 8.21 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.6, 112.0, 115.1, 118.5 (q, J_{FC} = 272.2 Hz),

119.3 (q, J_{FC} = 4.6 Hz), 122.5 (q, J_{FC} = 3.5 Hz), 124.1 (q, J_{FC} =271.7 Hz), 126.1, 126.6 (q, J_{FC} = 32.9 Hz), 128.5, 139.3, 140.0, 143.0 (q, J_{FC} = 38.7 Hz), 160.8.

MS (EI) *m/z* 360 (100, $[M]^+$), 317 (12), 291 (15), 222 (30).

HRMS (EI) *m/z* Calcd. for $C_{16}H_{10}F_6N_2O$ $[M]^+$: 360.0697. Found: 360.0703.



_N_-{2,4-Dichloro-6-[(2,6-dimethylphenyl)(trifluoroacetyl)amino]phenyl}-2,2,2-trifluoroacetamide (3)

Procedure A: Yield 1.26 g (89%); Colorless crystals, mp 149-151 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.15 (s, 6H), 6.71 (d, *J* = 2.1 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 2.1 Hz, 1H), 7.66 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.9, 115.6 (q, J_{FC} = 287.8 Hz), 115.7 (q, J_{FC} = 288.4, Hz), 123.4, 125.7, 129.5, 129.6, 130.6, 135.3, 135.5, 135.7, 137.0, 137.8, 154.5 (q, J_{FC} = 38.1 Hz), 158.4 (q, J_{FC} = 37.6 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ = -70.40, -75.96.

MS (EI) *m/z* 474 (68), 472 (100, $[M]^+$), 405 (98), 403 (66), 339 (48), 264 (32), 261 (46), 105 (62).

HRMS (EI) *m/z* Calcd. for $C_{18}H_{12}{}^{35}Cl_2F_6N_2O_2$ $[M]^+$: 472.0180. Found: 472.0175.

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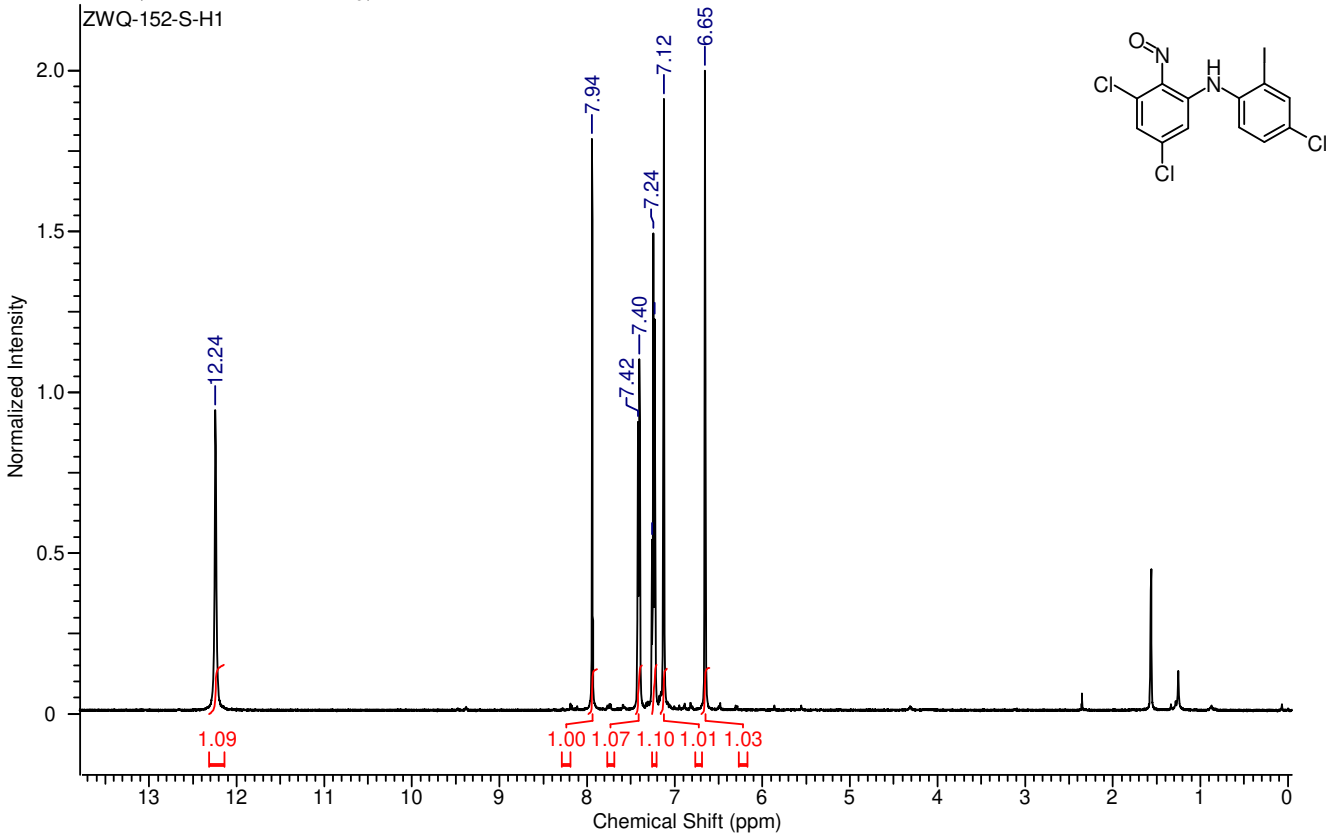
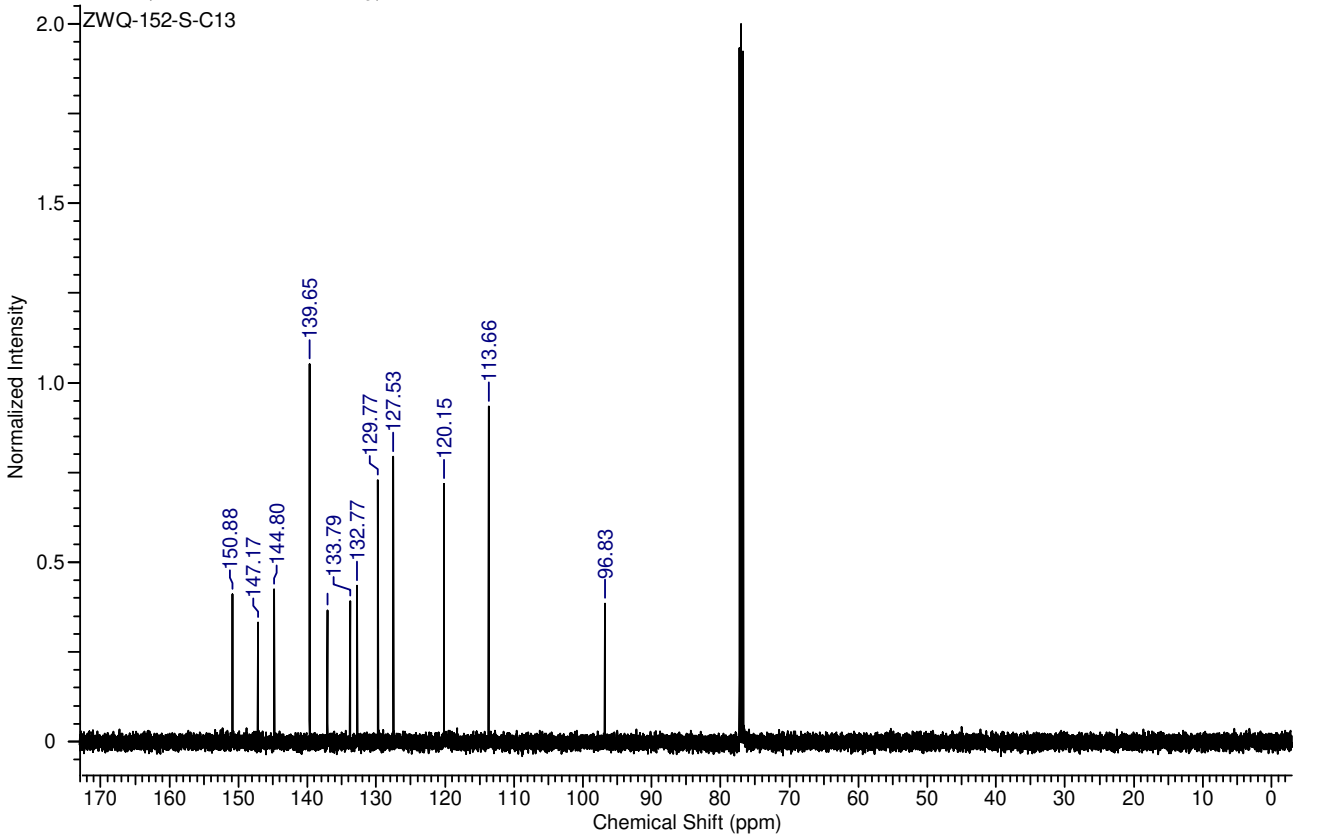
***N*-(4-Chloro-2-iodophenyl)-3,5-dichloro-2-nitrosoaniline**

^{1}H NMR (500 MHz, $CDCl_3$)

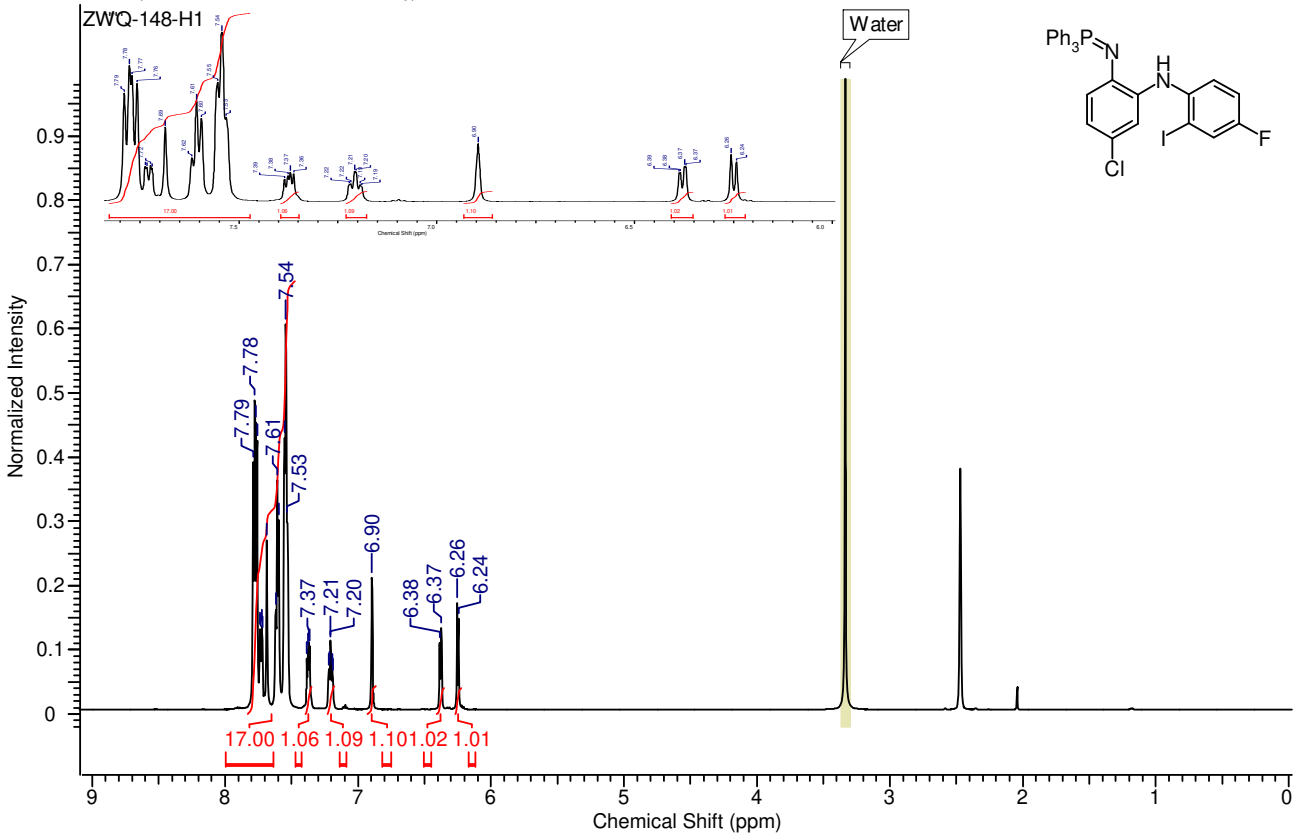


^{13}C NMR (125 MHz, $CDCl_3$)

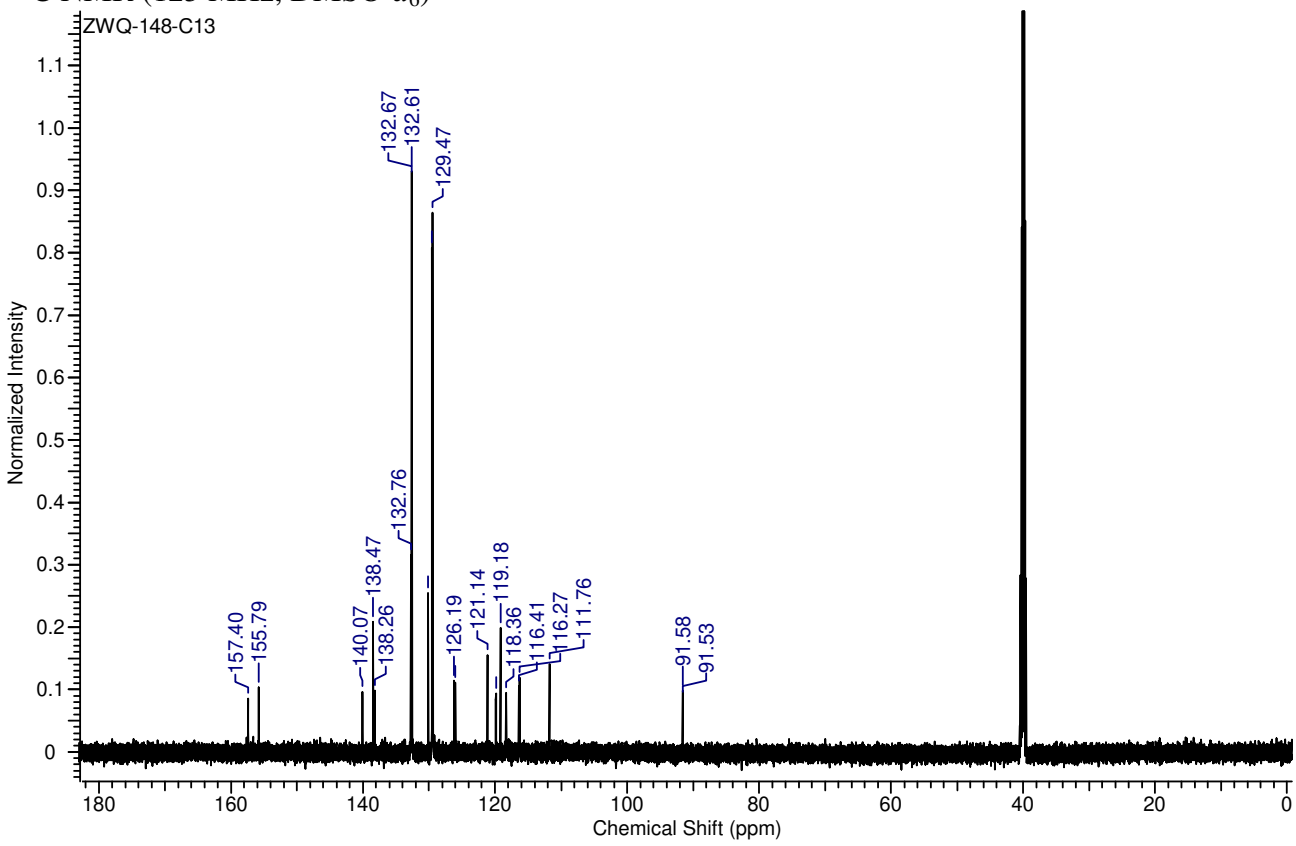


1f

^{1}H NMR (500 MHz, DMSO-d_6)

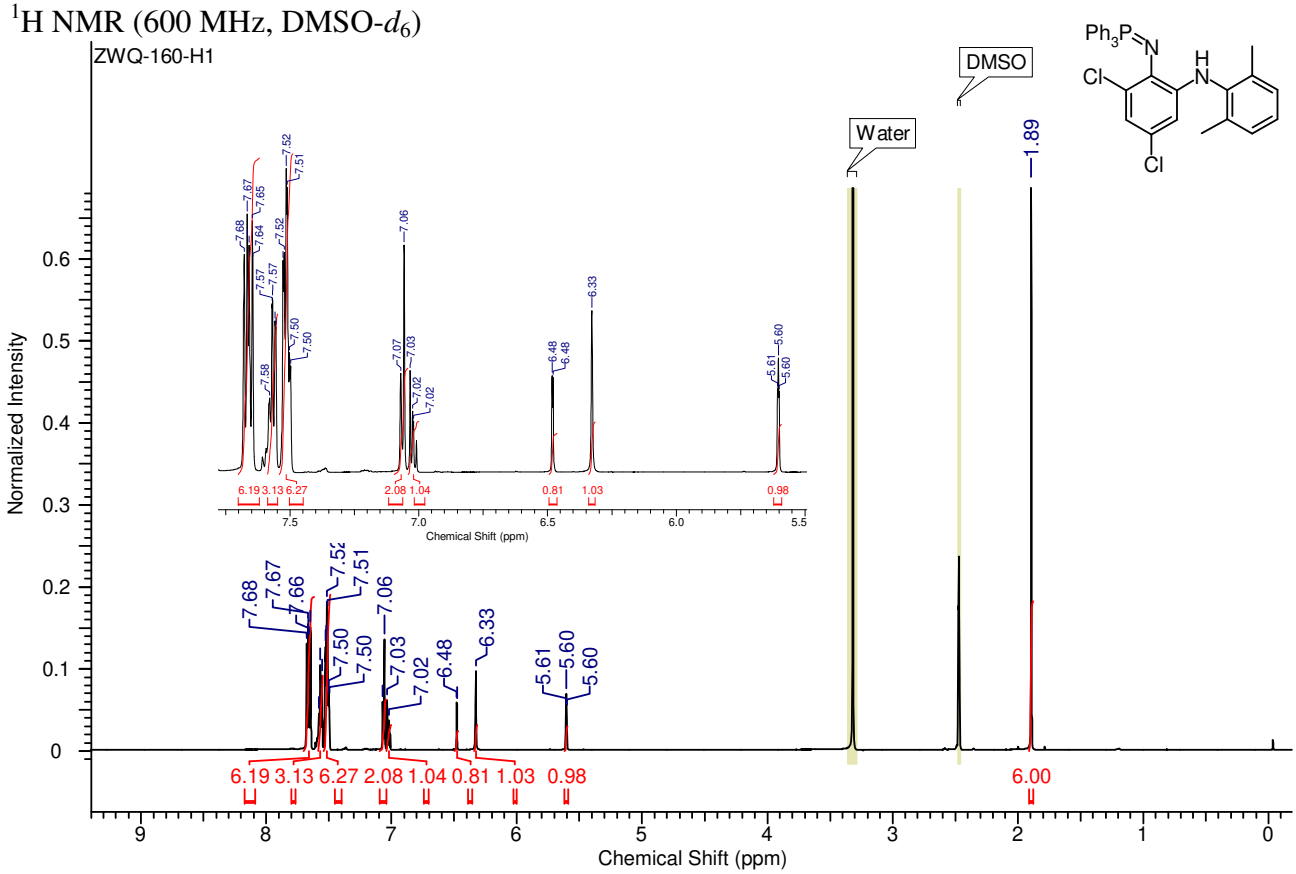


^{13}C NMR (125 MHz, DMSO-d_6)

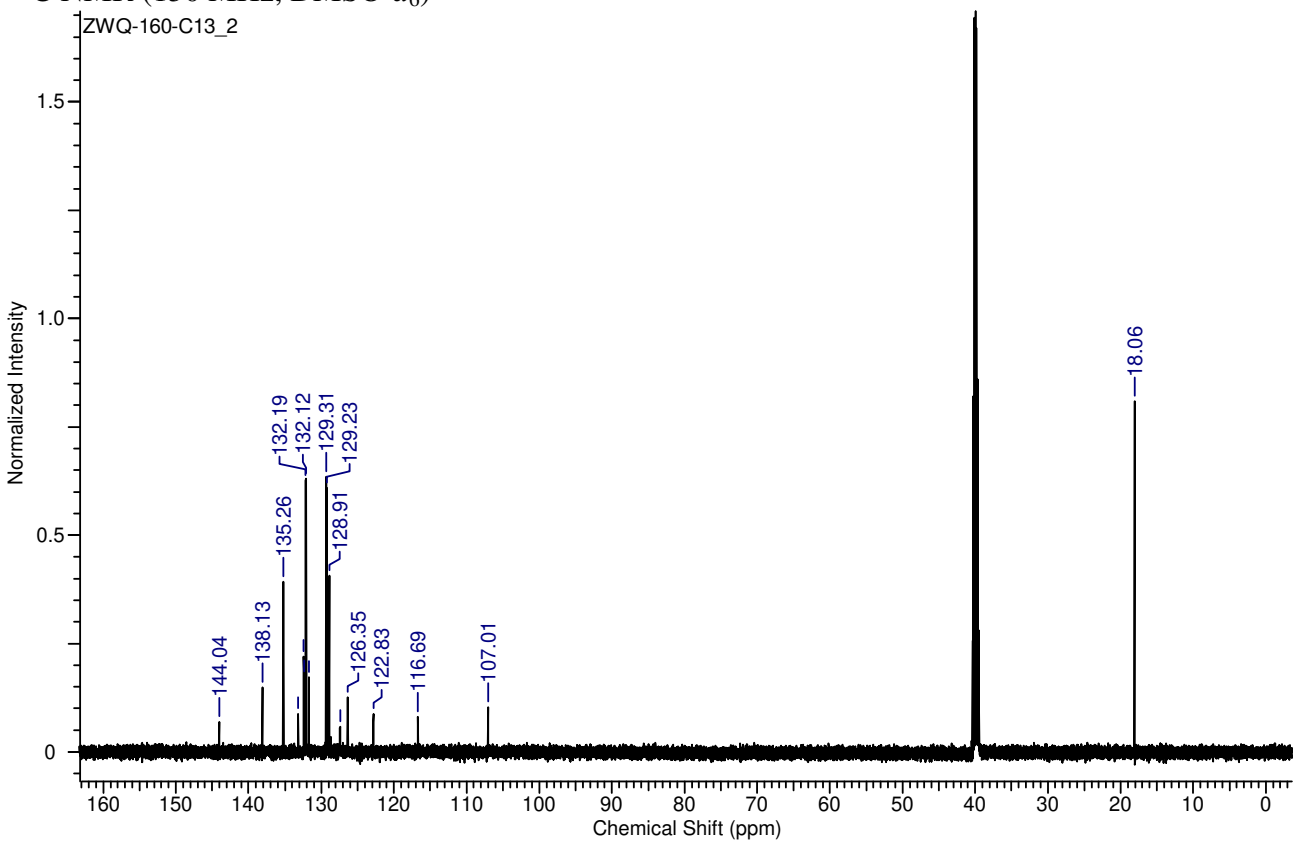


1g

^{1}H NMR (600 MHz, DMSO-d_6)

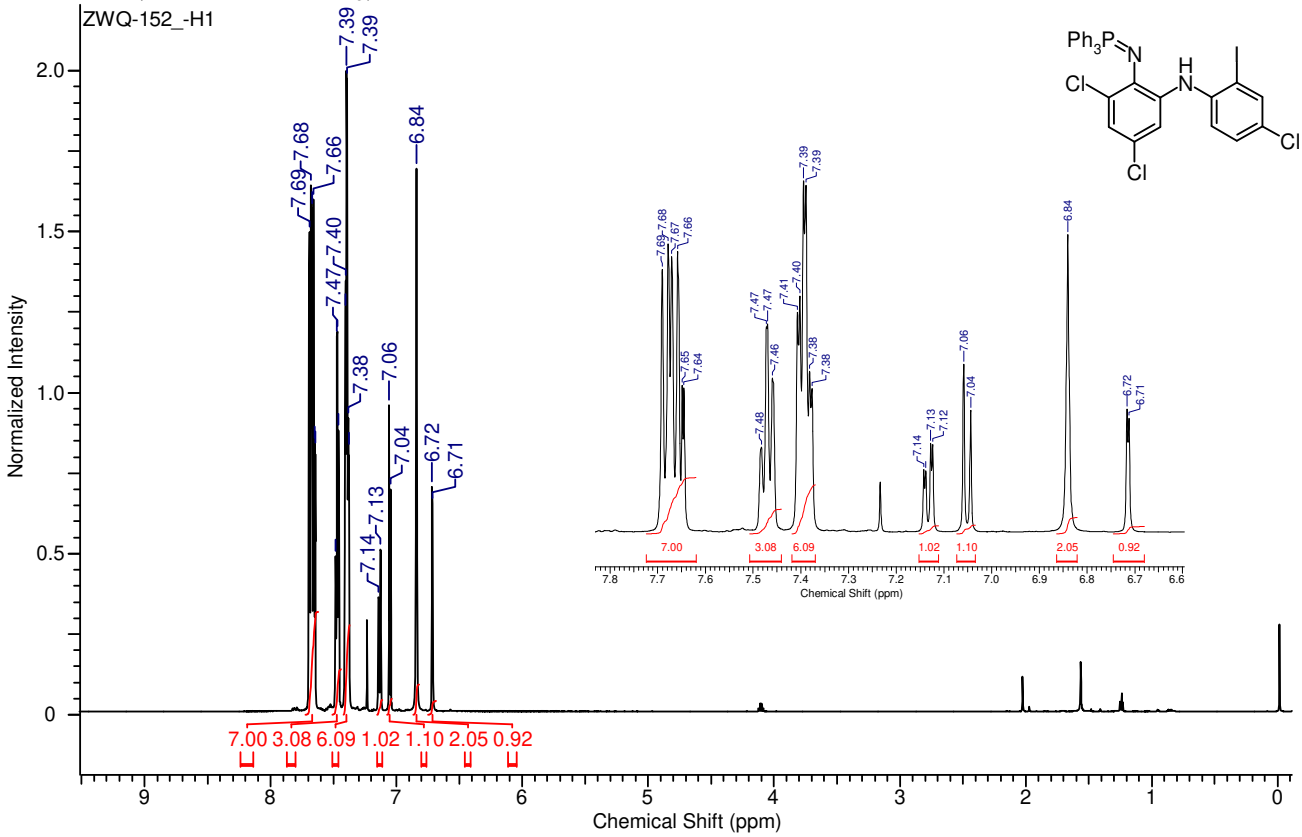


^{13}C NMR (150 MHz, DMSO-d_6)

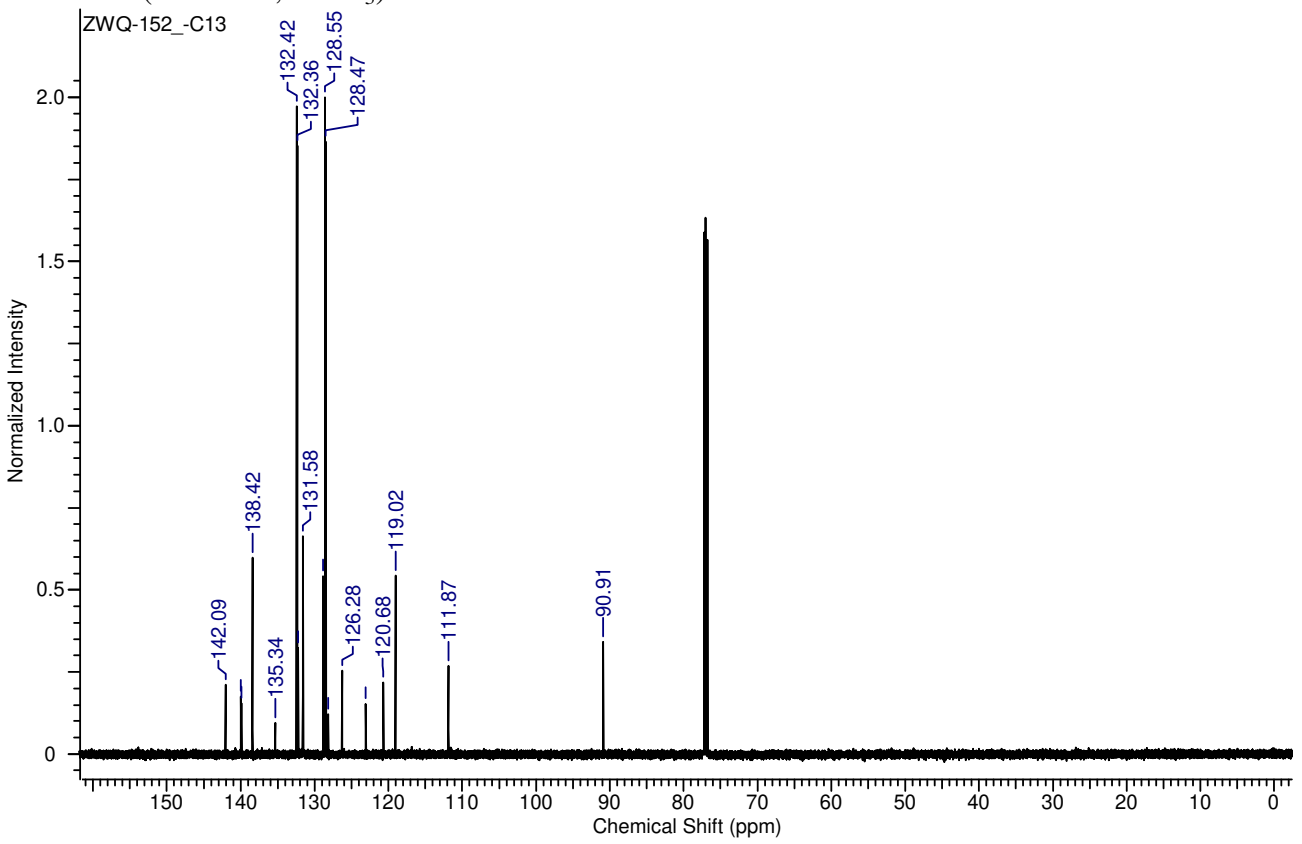


1m

^{1}H NMR (500 MHz, $CDCl_3$)

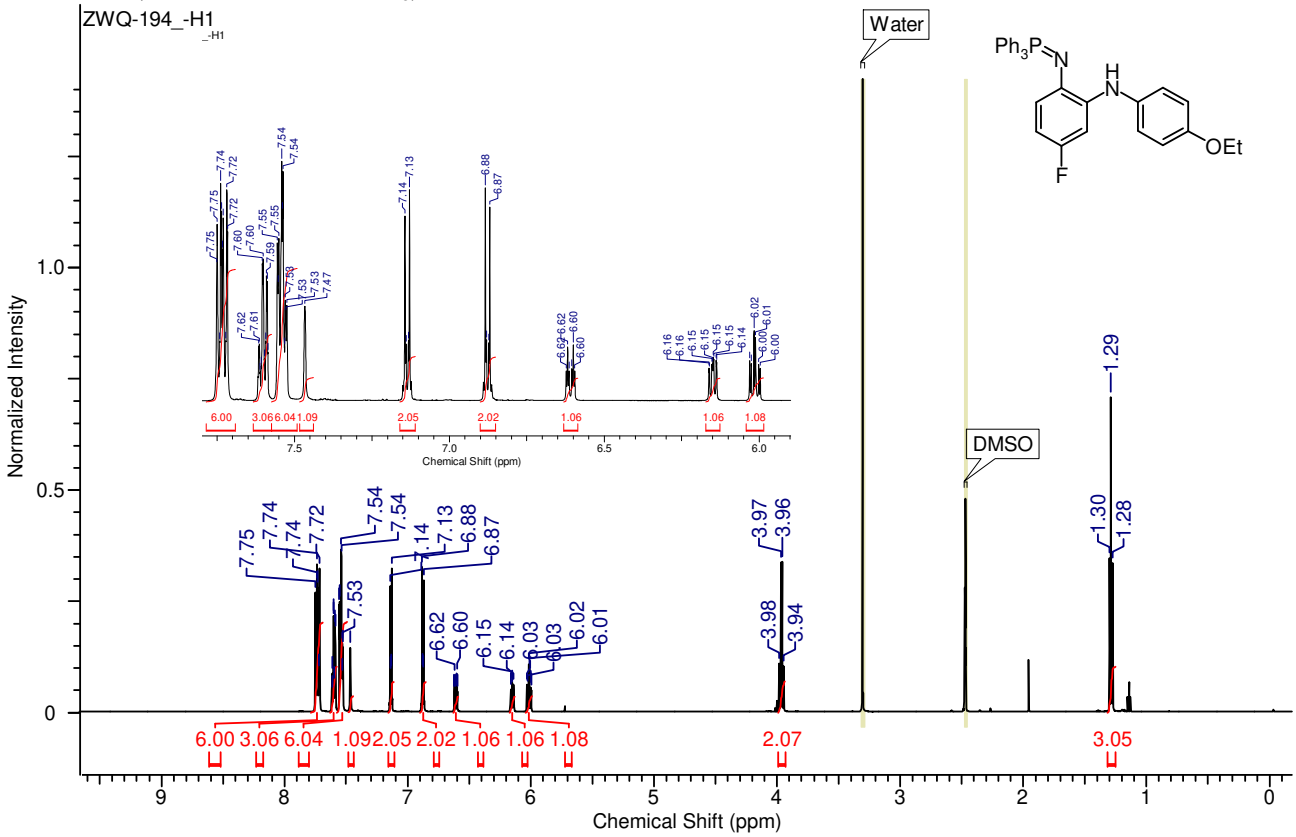


^{13}C NMR (125 MHz, $CDCl_3$)

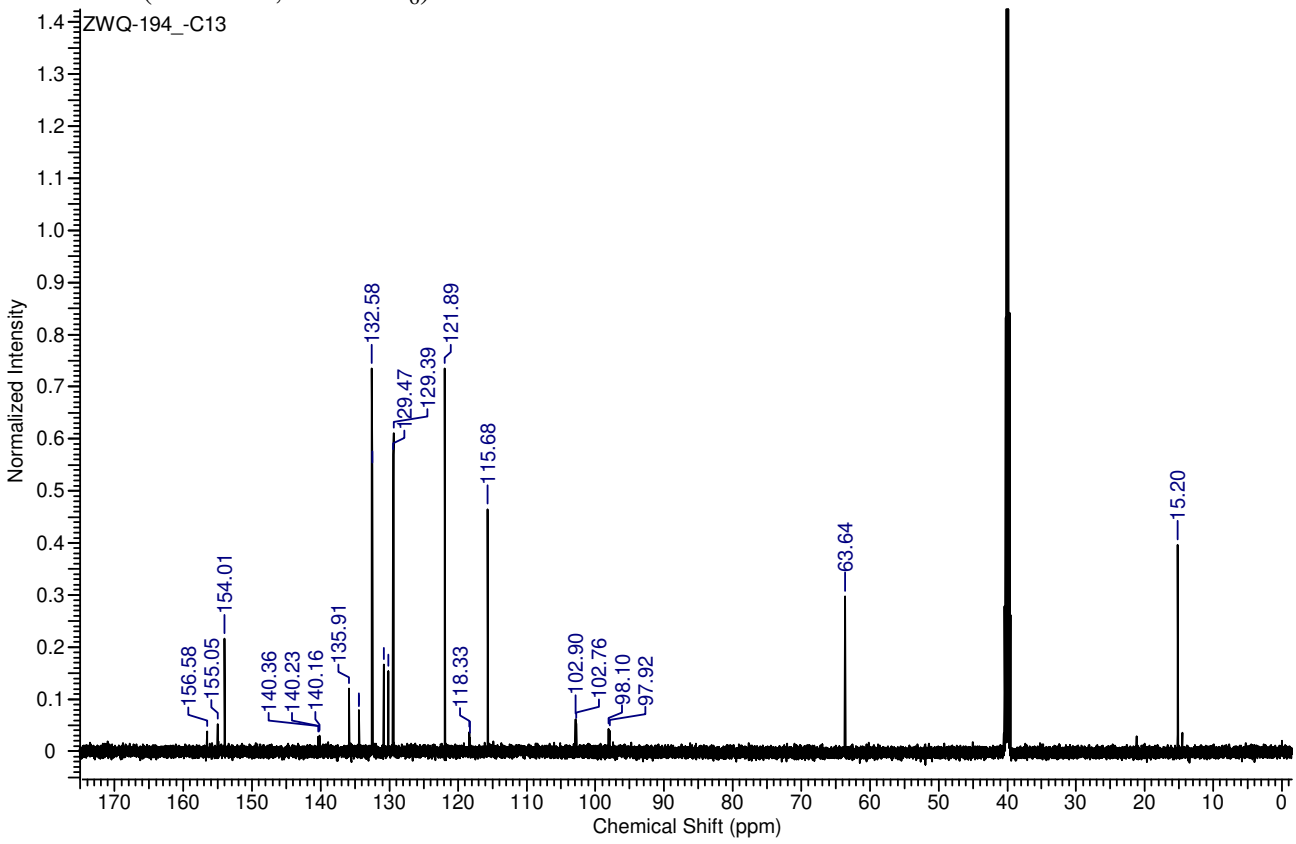


1o

^{1}H NMR (600 MHz, DMSO-d_6)

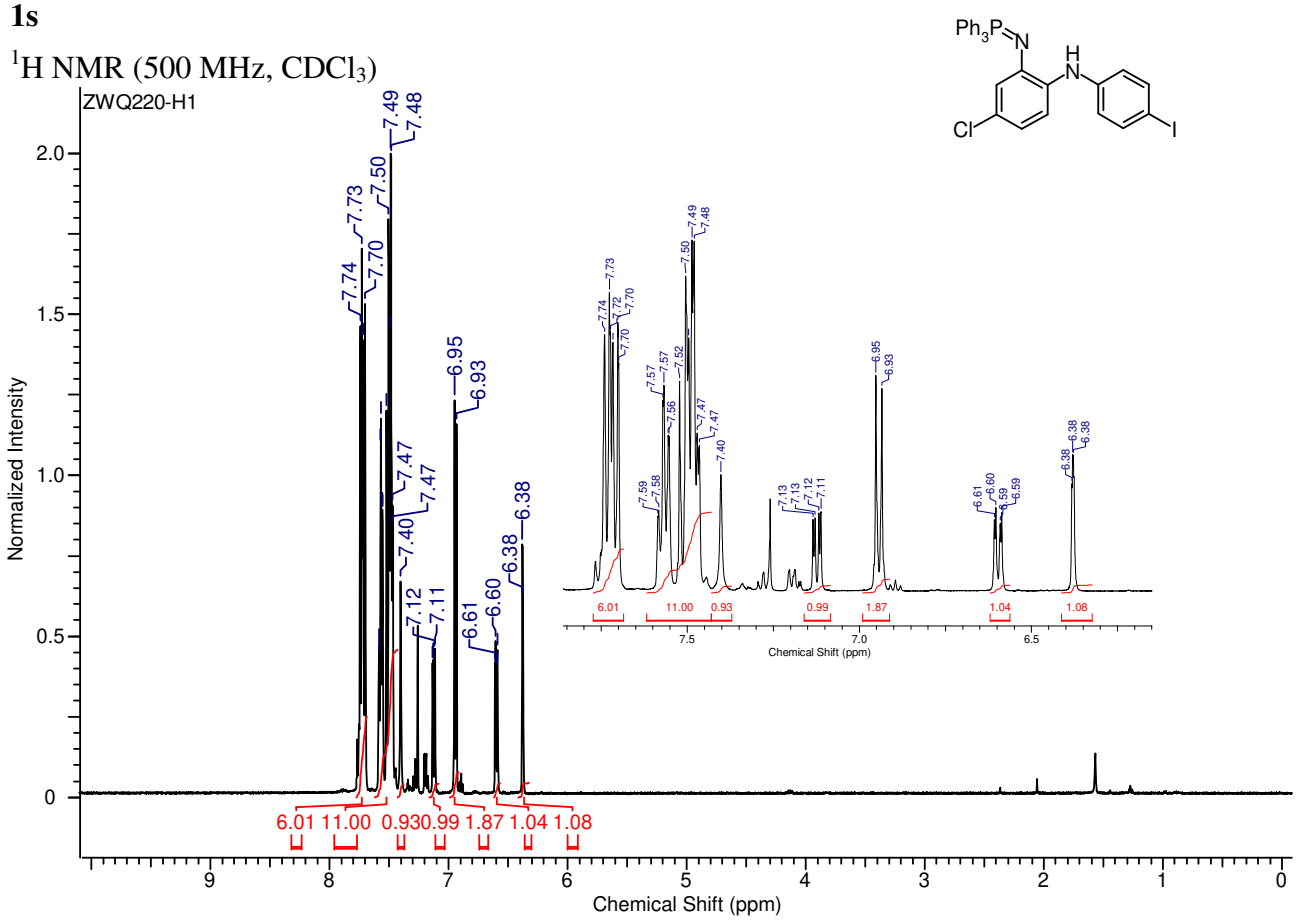


^{13}C NMR (150 MHz, DMSO-d_6)

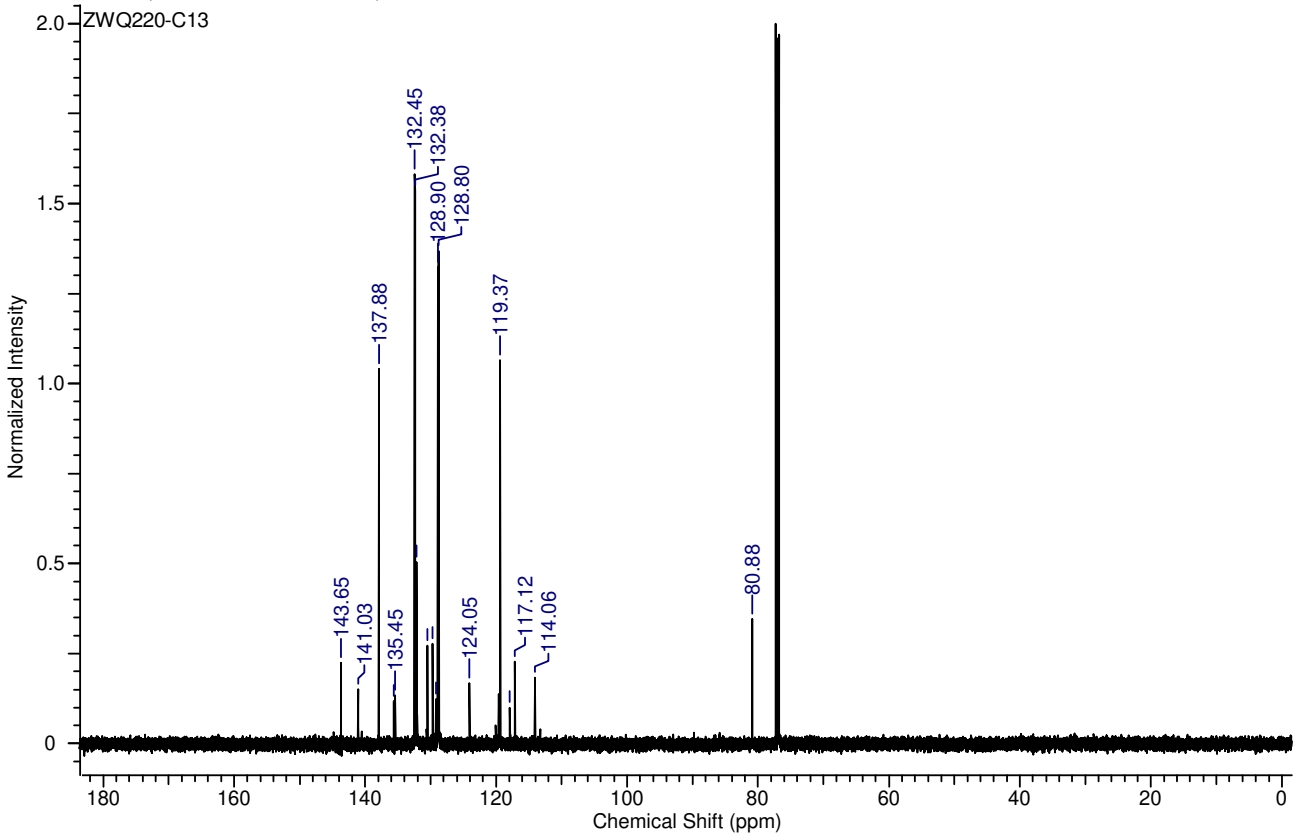


1s

^{1}H NMR (500 MHz, $CDCl_3$)

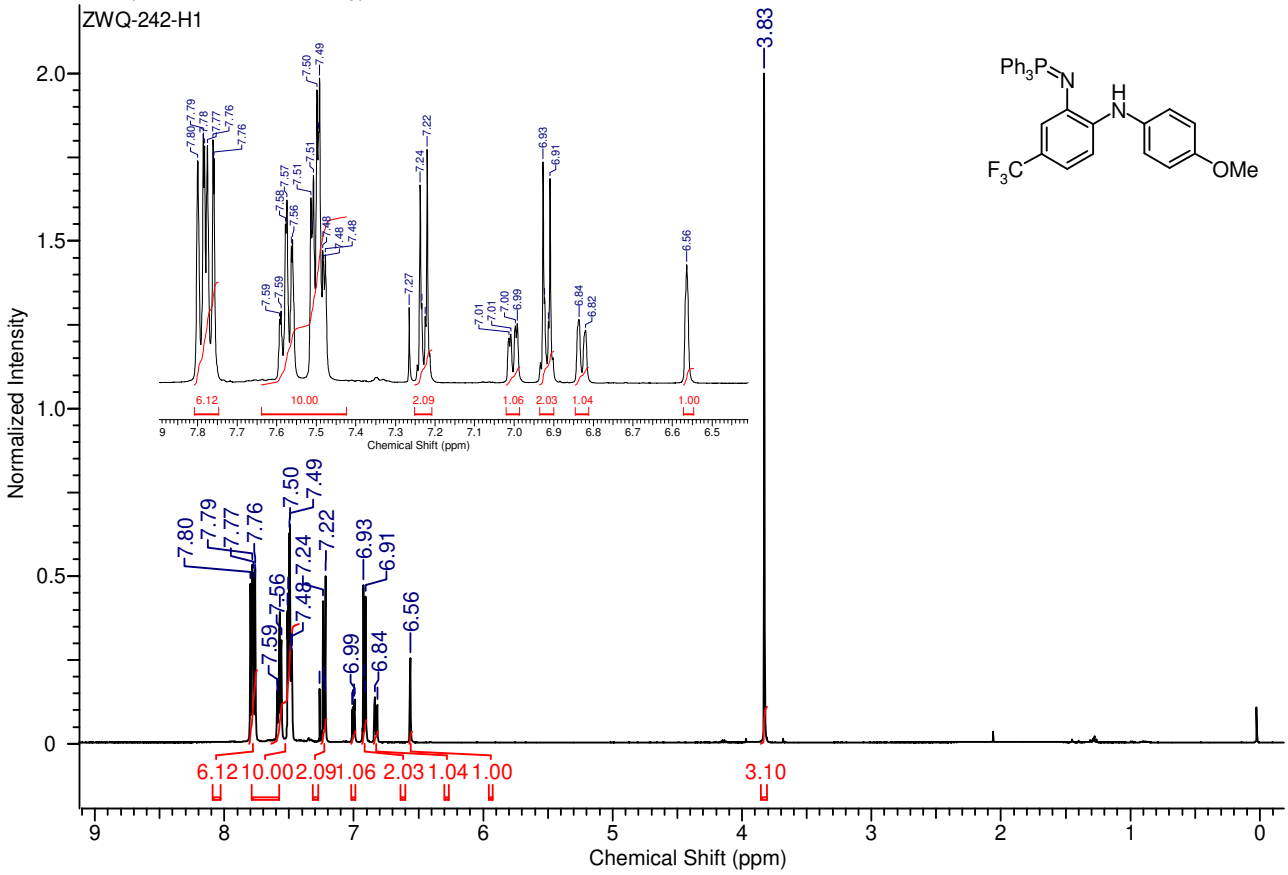


^{13}C NMR (125 MHz, $CDCl_3$)

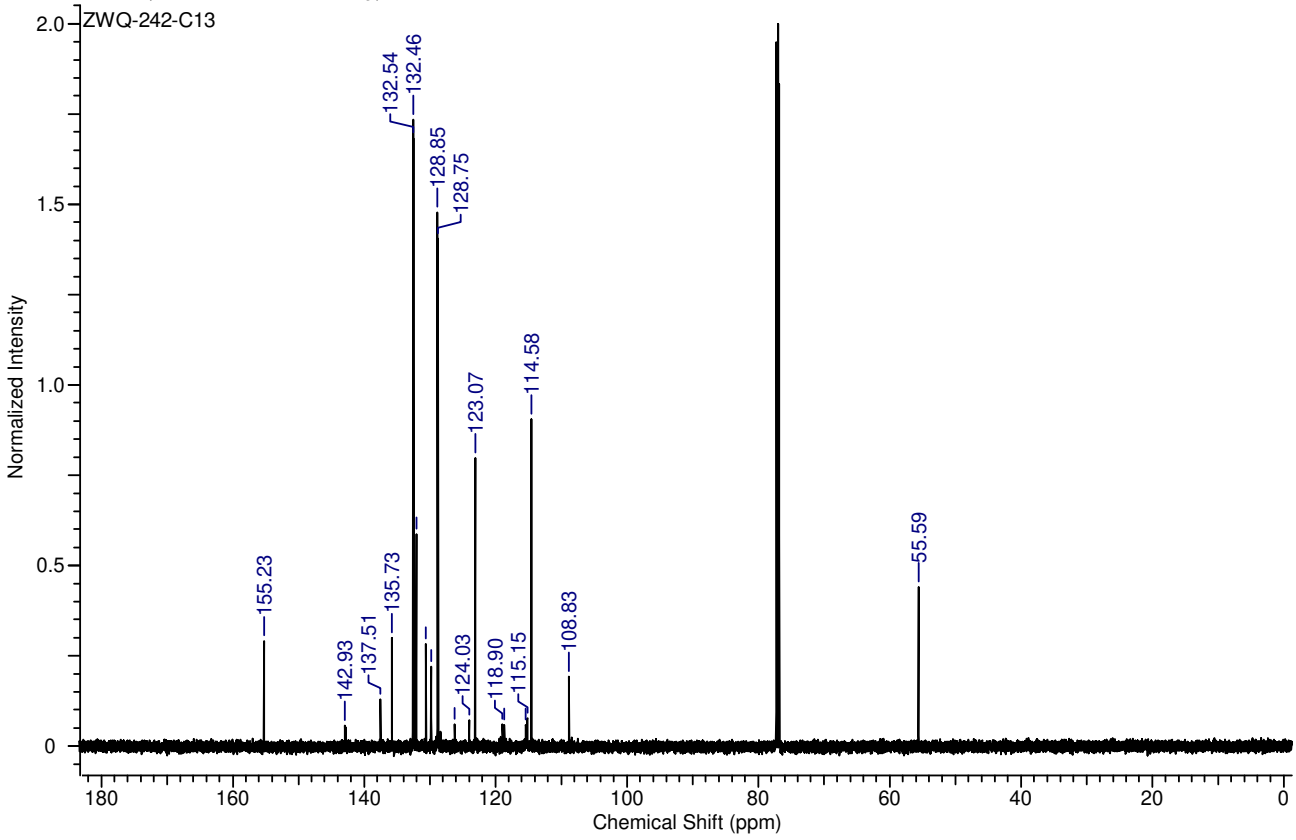


1t

^{1}H NMR (500 MHz, $CDCl_3$)

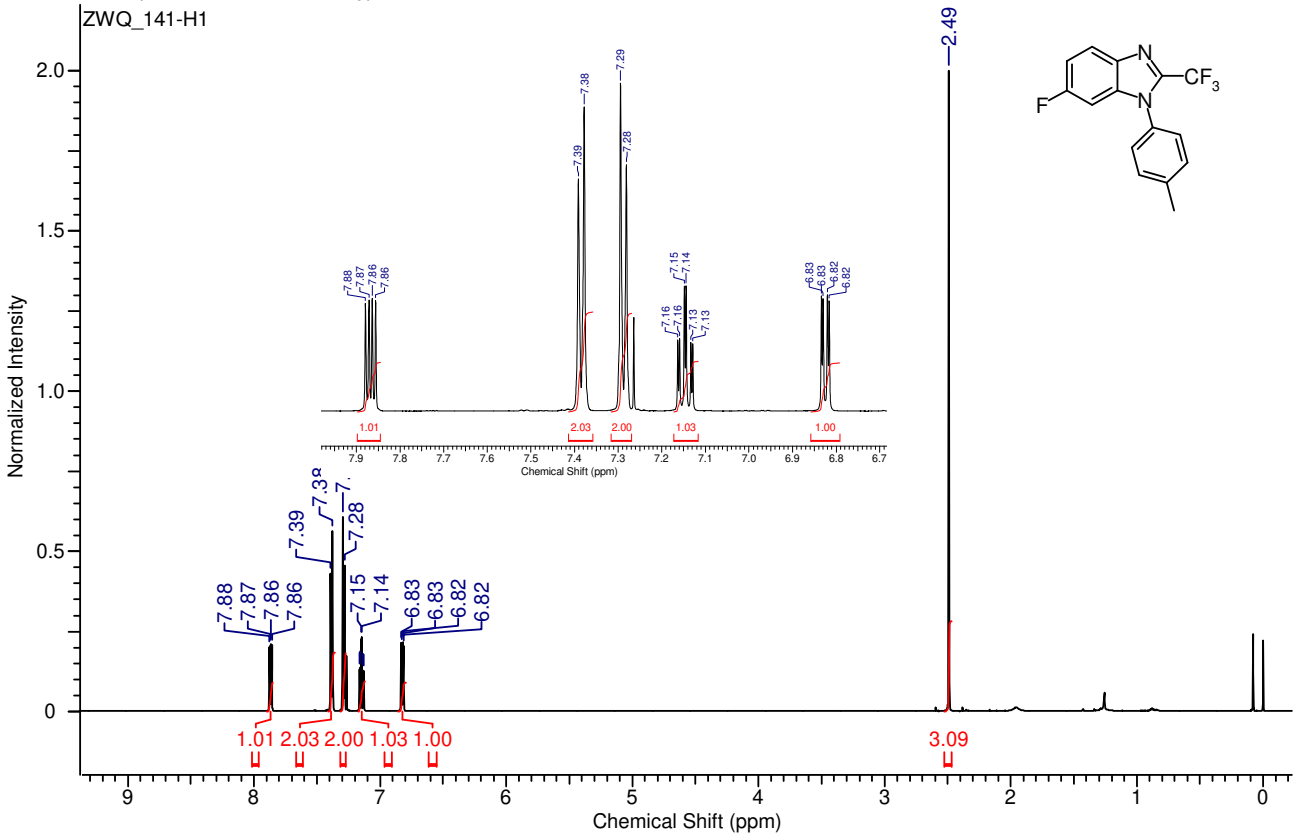


^{13}C NMR (125 MHz, $CDCl_3$)

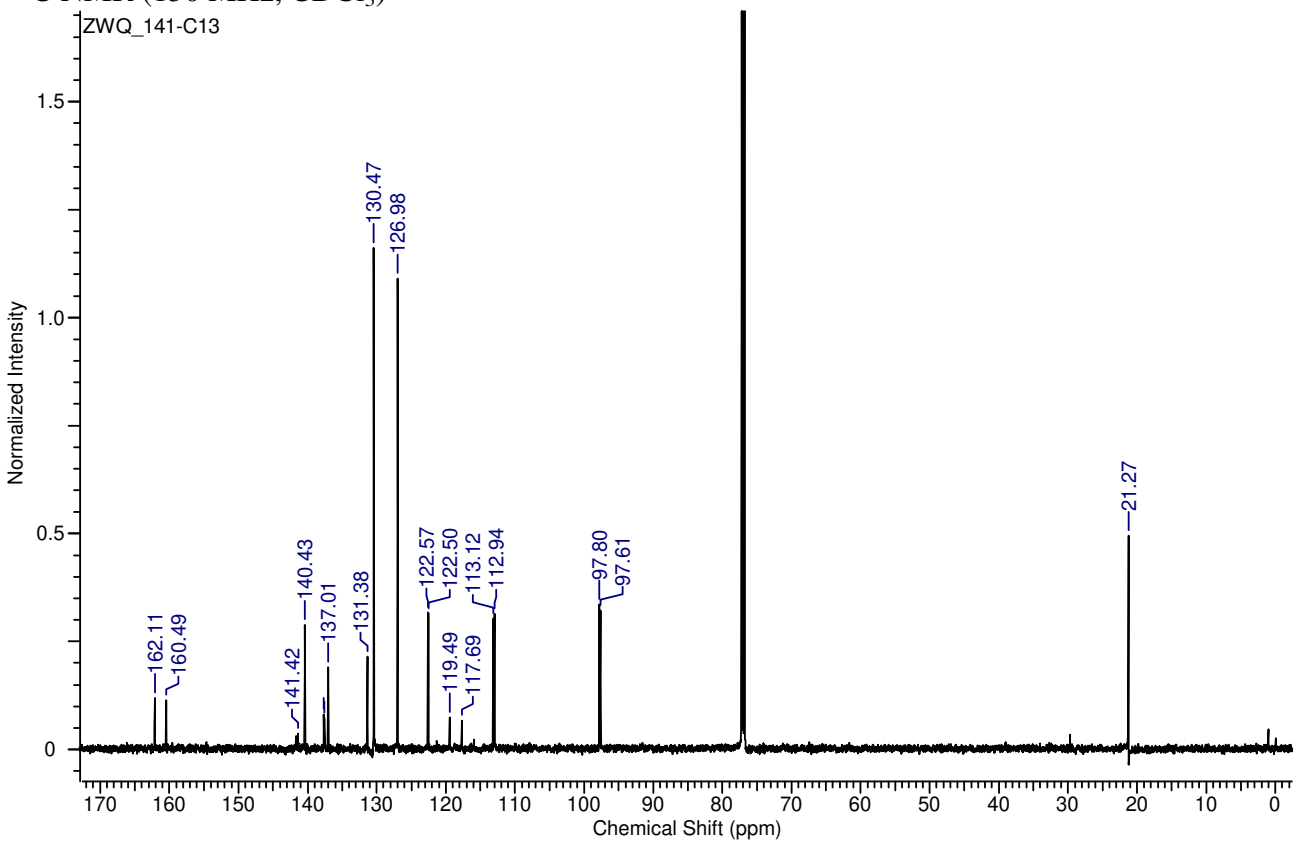


2a

^{1}H NMR (600 MHz, $CDCl_3$)

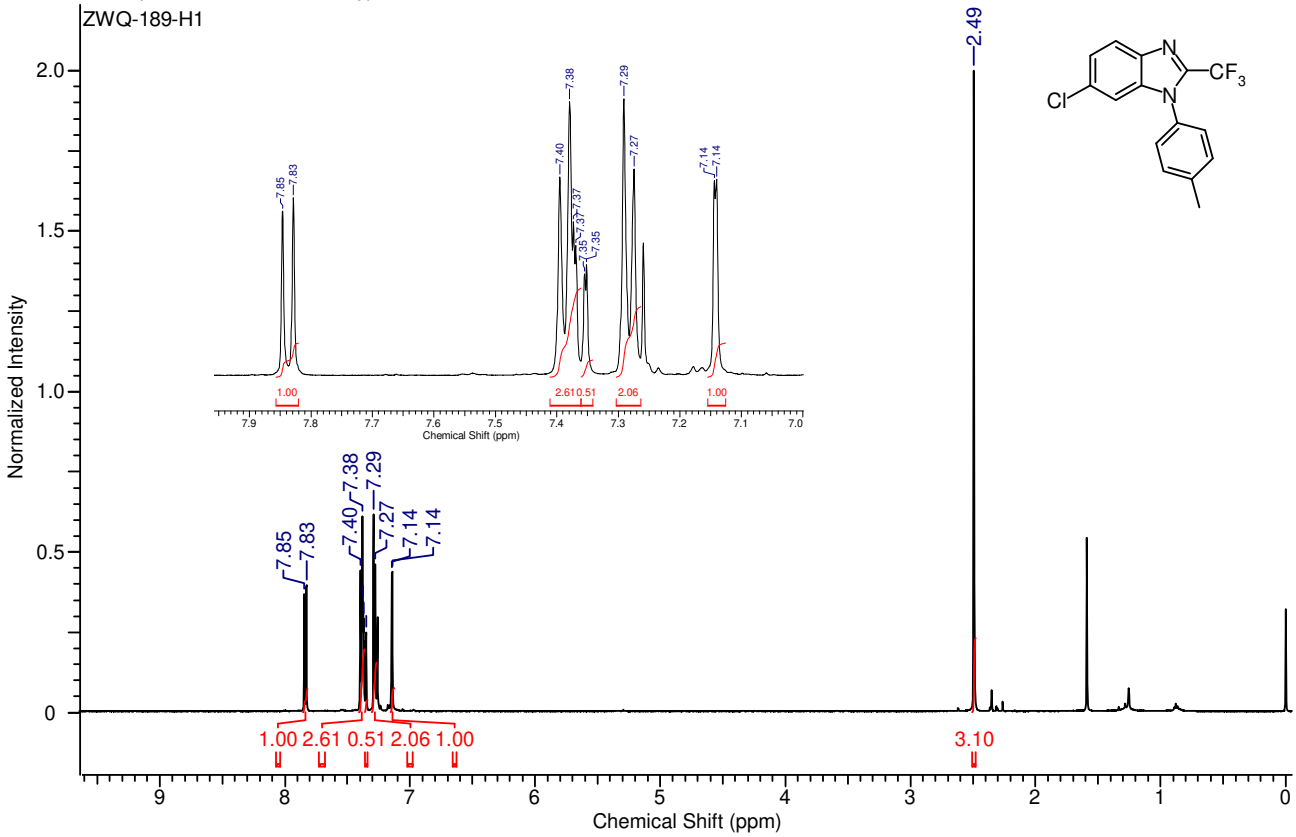


^{13}C NMR (150 MHz, $CDCl_3$)

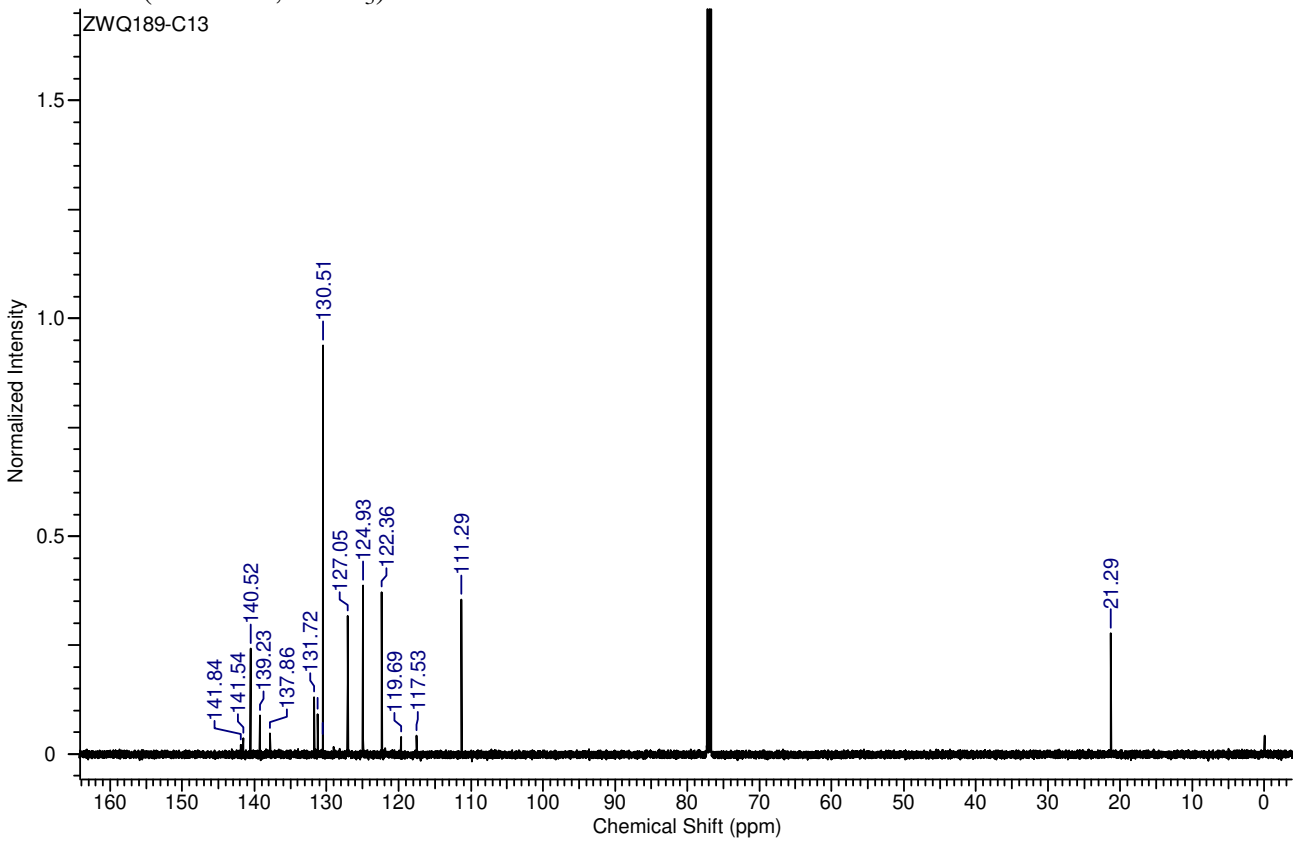


2b

^{1}H NMR (500 MHz, $CDCl_3$)

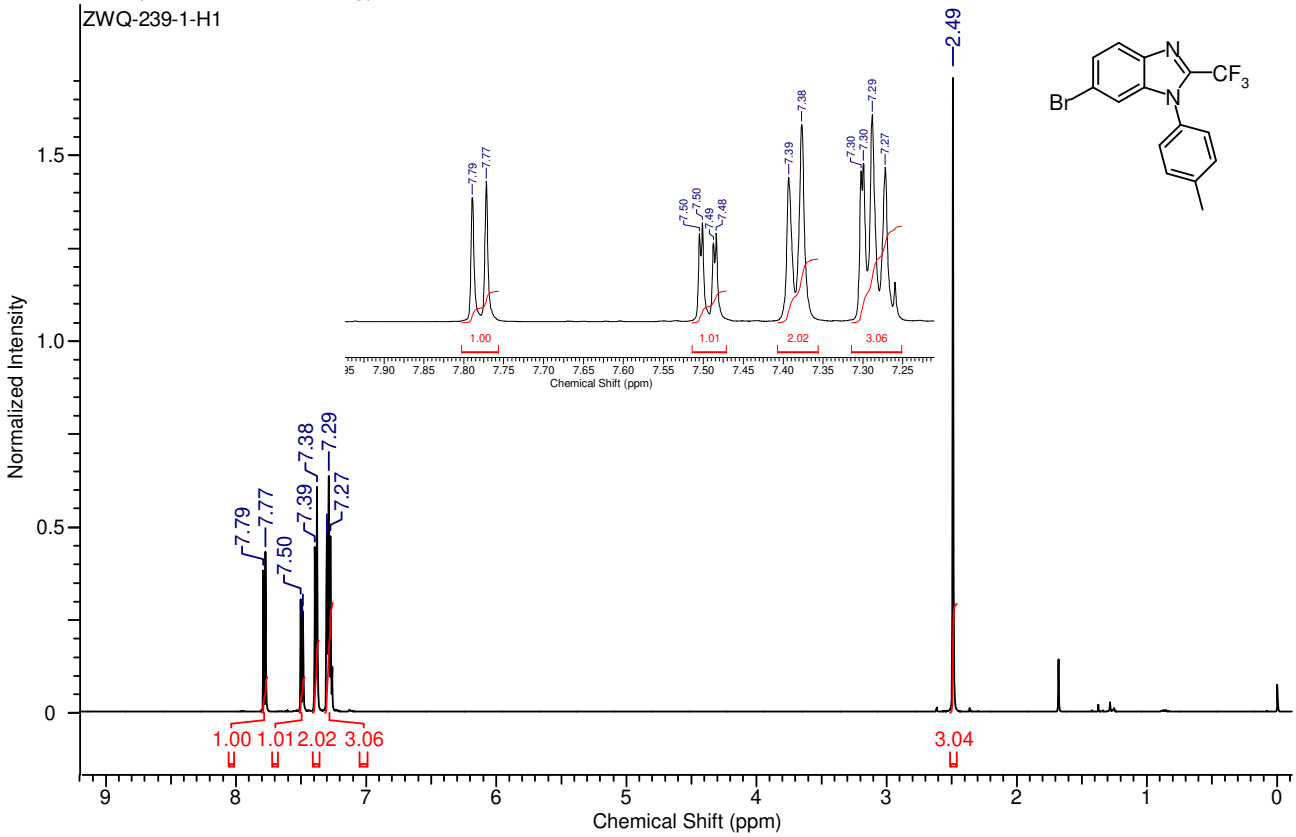


^{13}C NMR (125 MHz, $CDCl_3$)

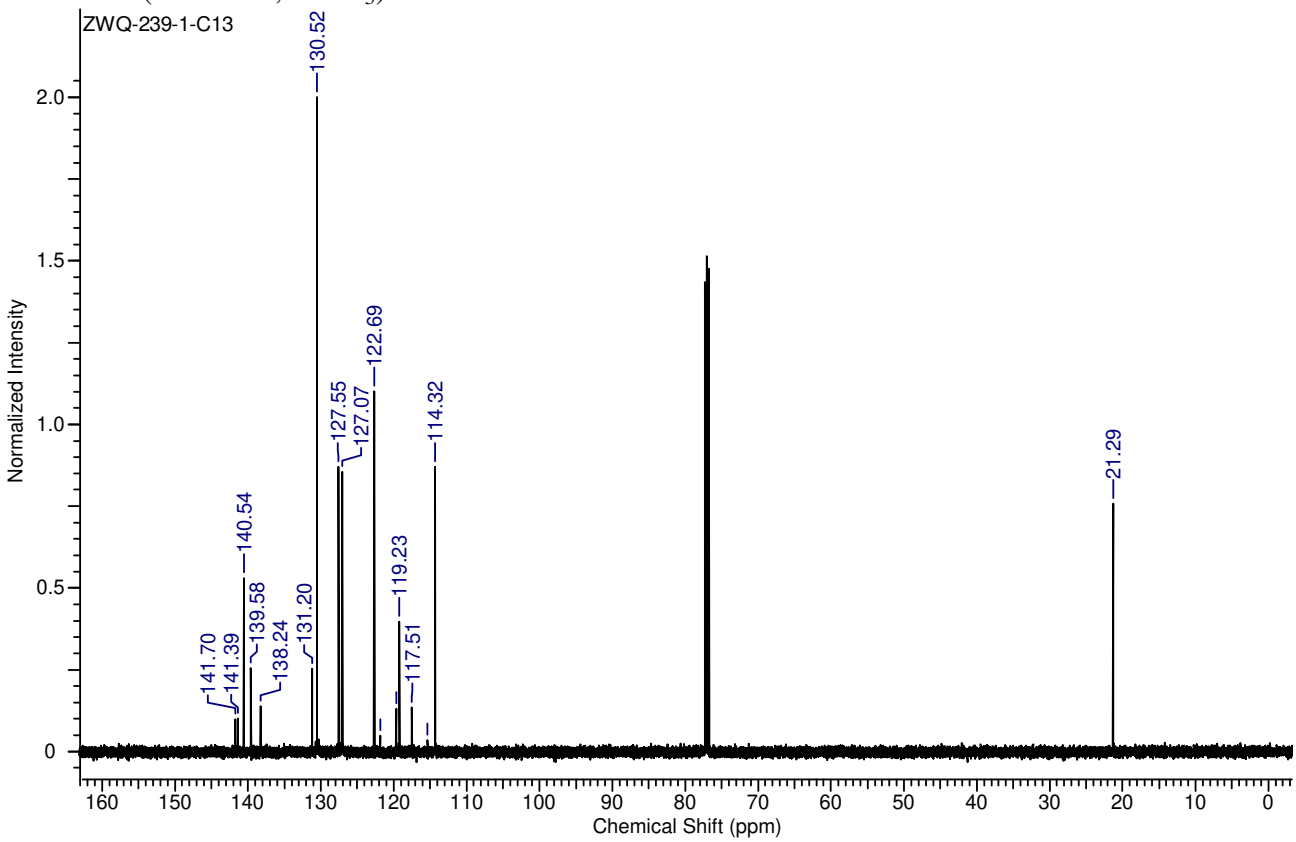


2c

^{1}H NMR (500 MHz, $CDCl_3$)

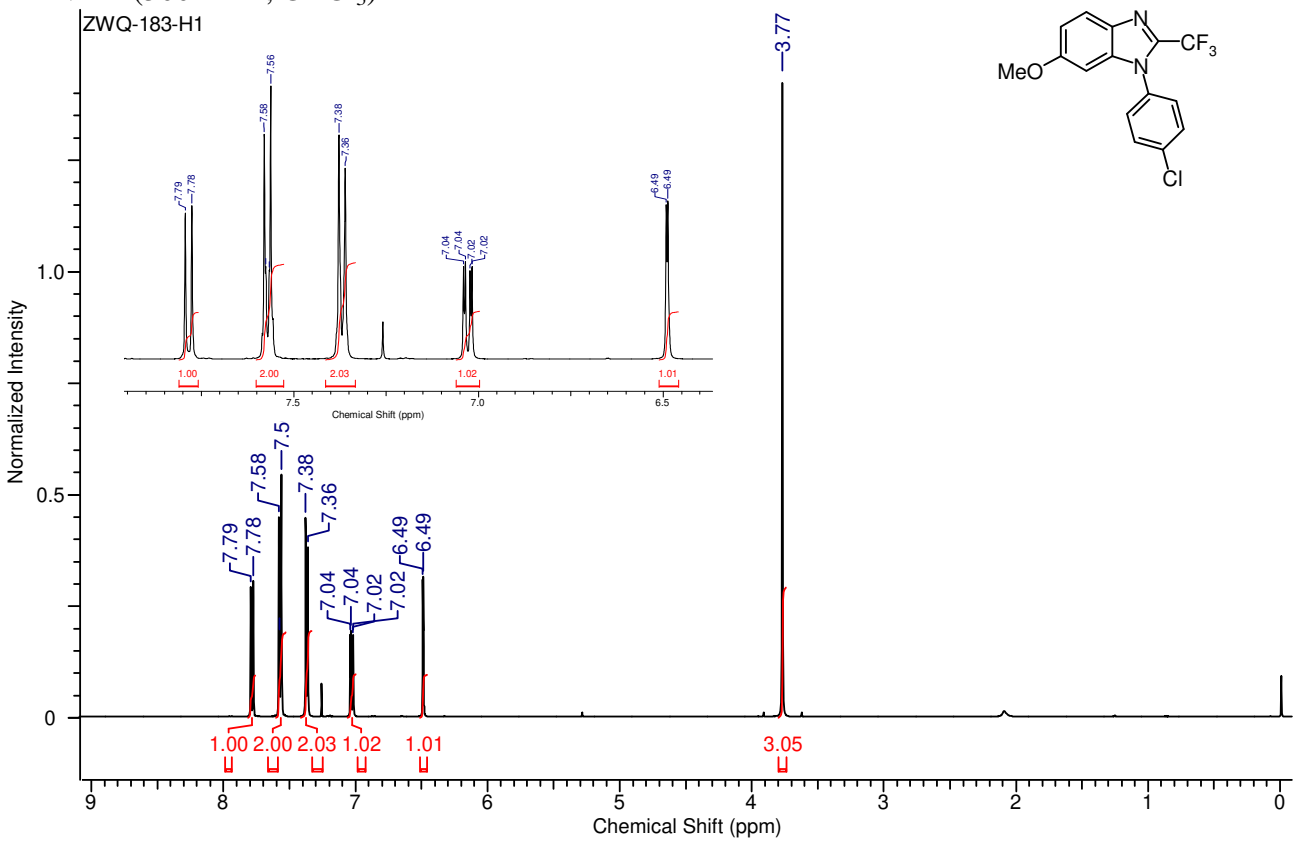


^{13}C NMR (125 MHz, $CDCl_3$)

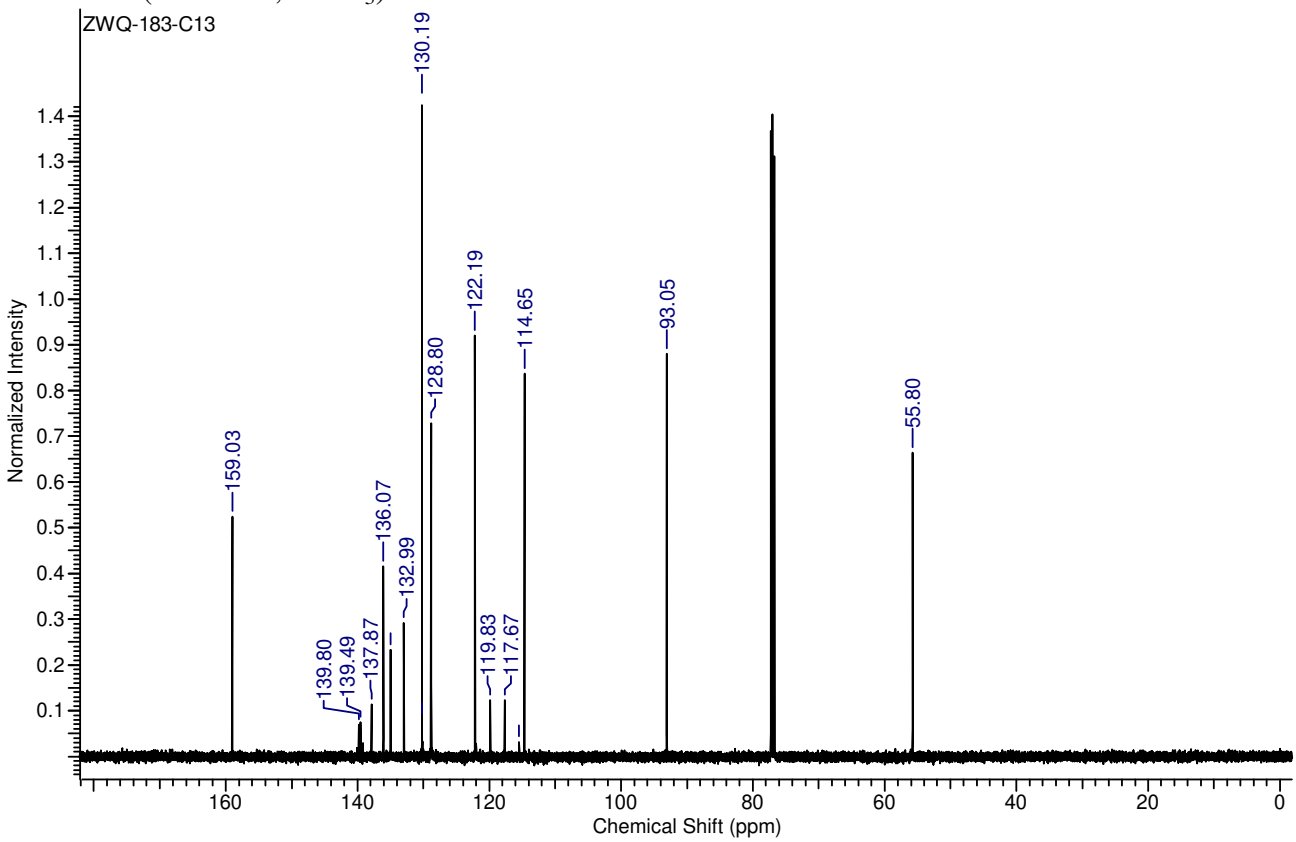


2d

^{1}H NMR (500 MHz, $CDCl_3$)

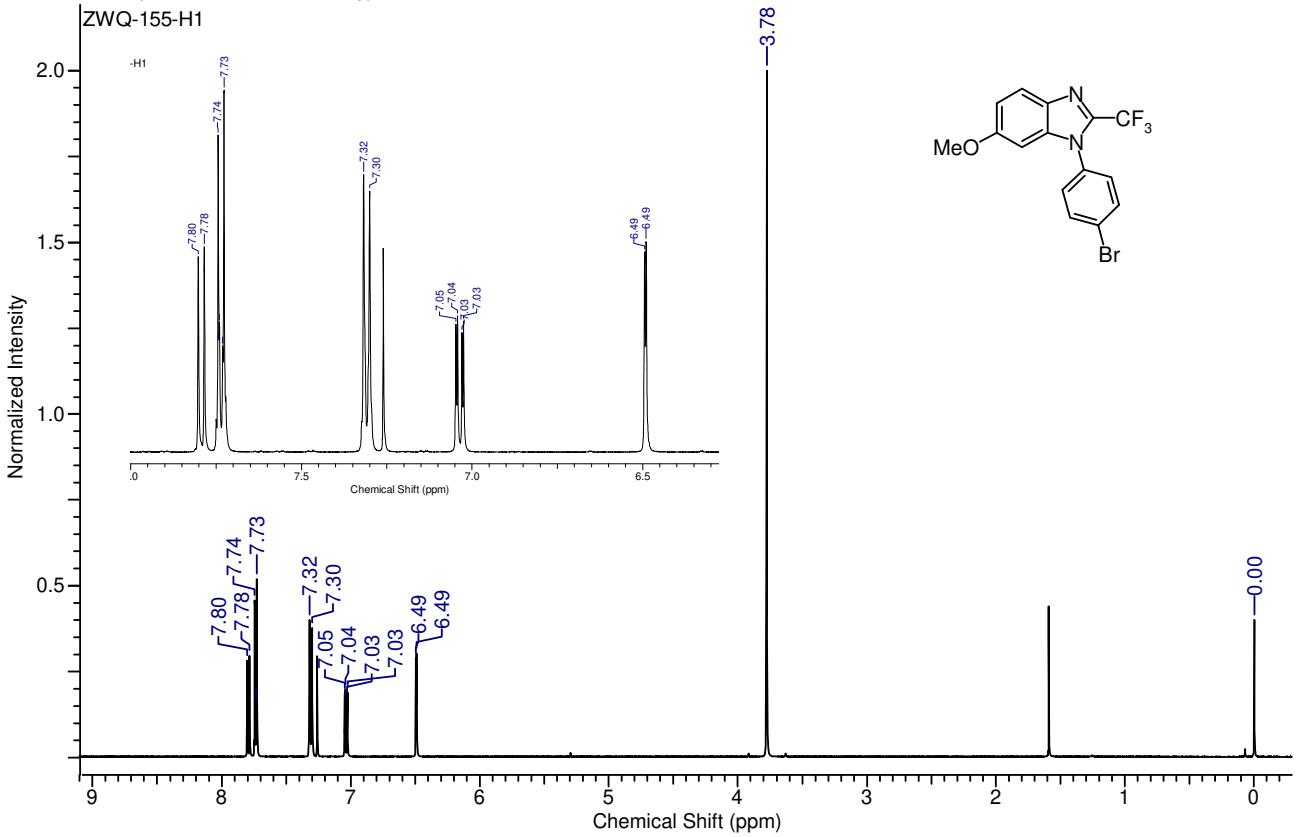


^{13}C NMR (125 MHz, $CDCl_3$)

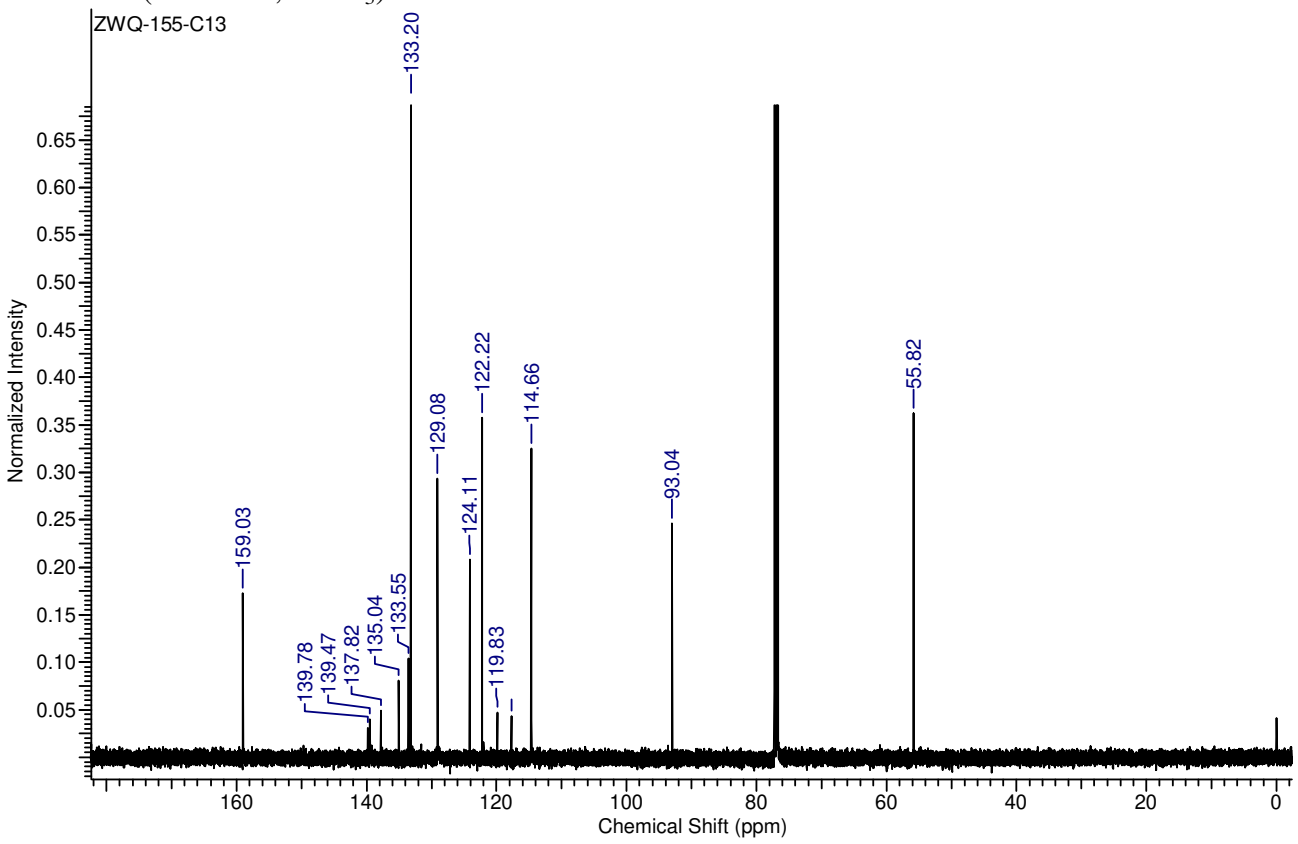


2e

^{1}H NMR (500 MHz, $CDCl_3$)

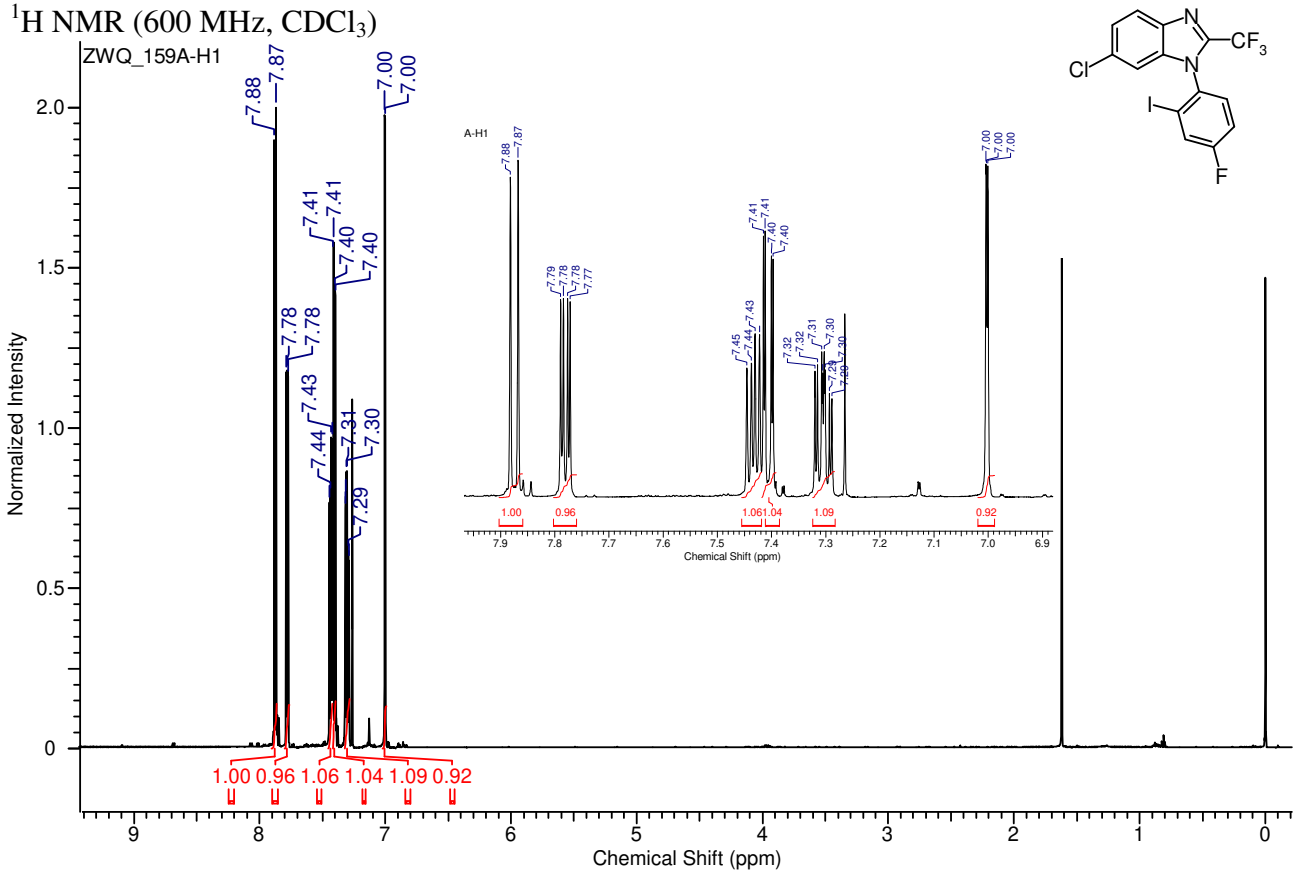


^{13}C NMR (125 MHz, $CDCl_3$)

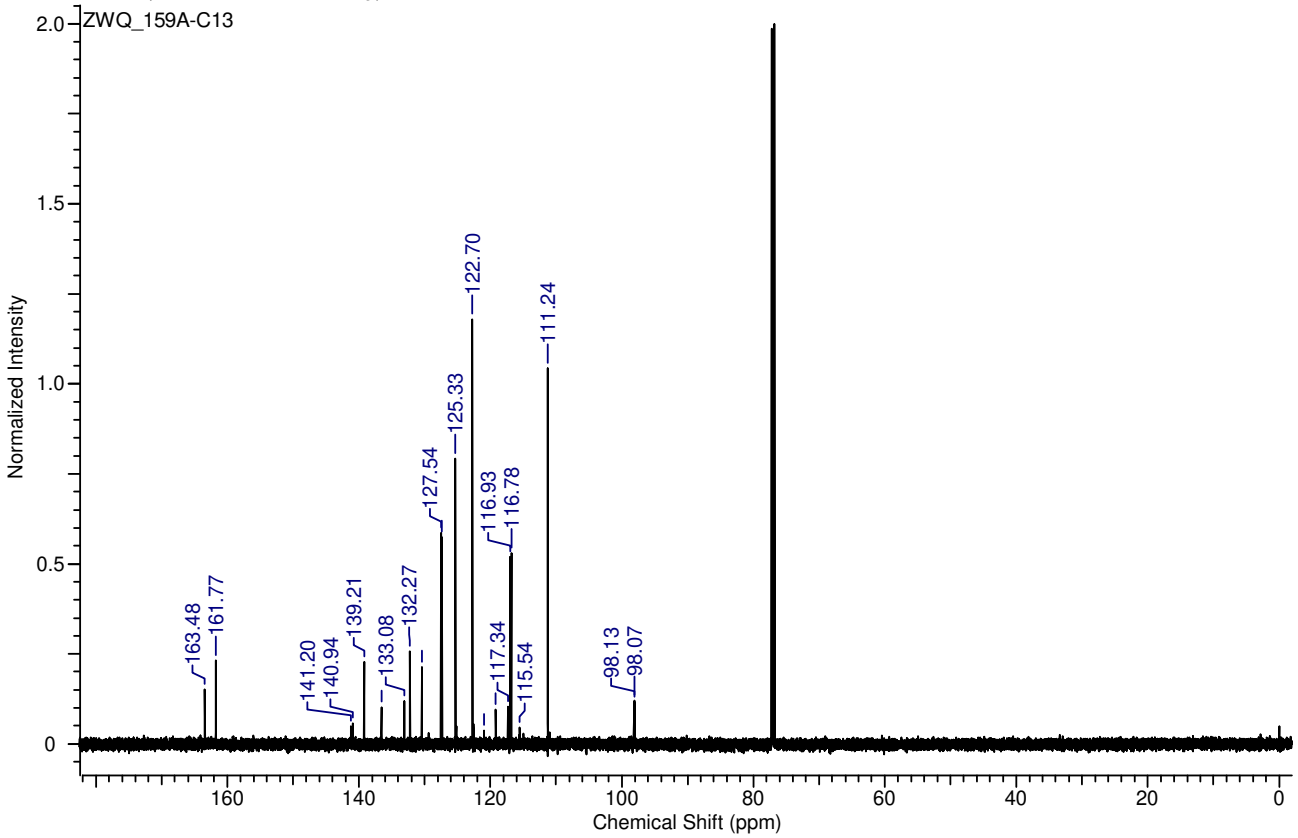


2f

^{1}H NMR (600 MHz, $CDCl_3$)

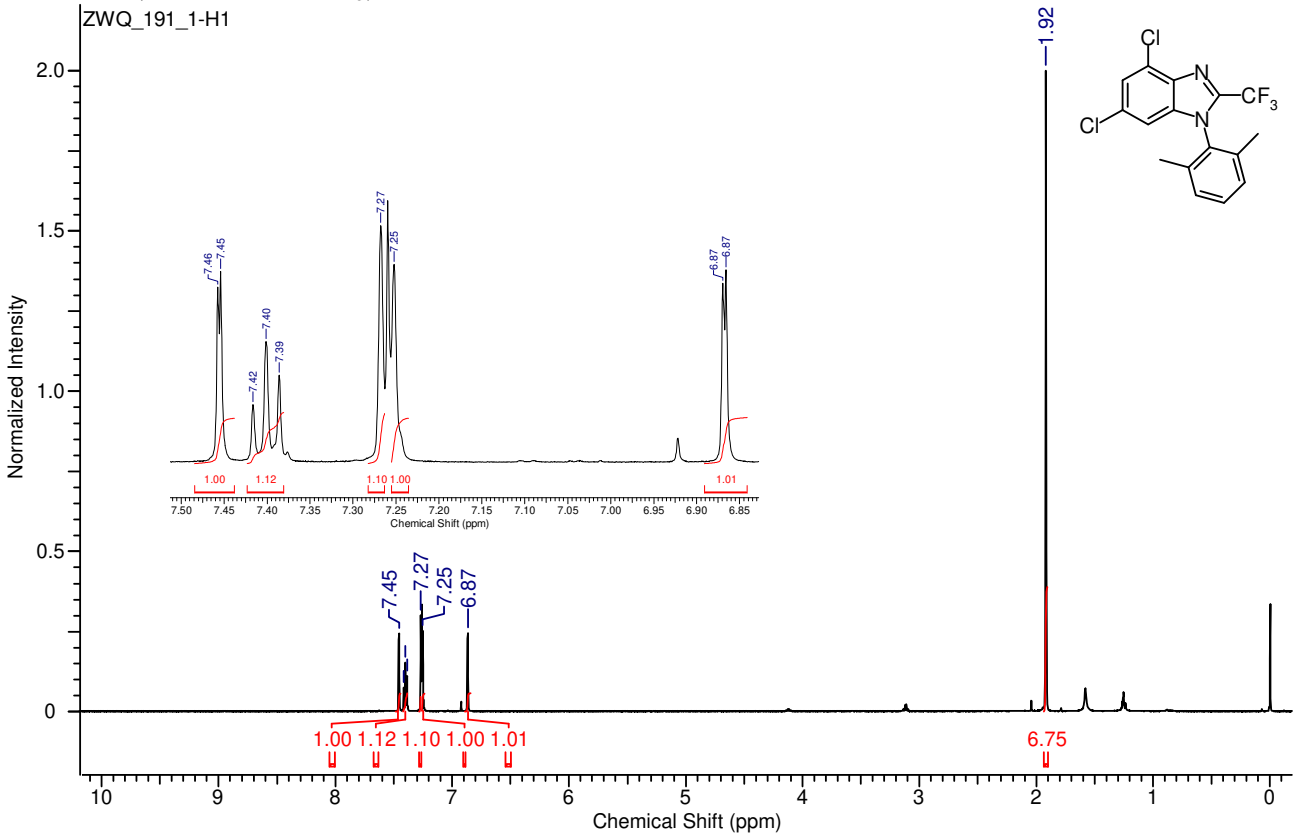


^{13}C NMR (150 MHz, $CDCl_3$)

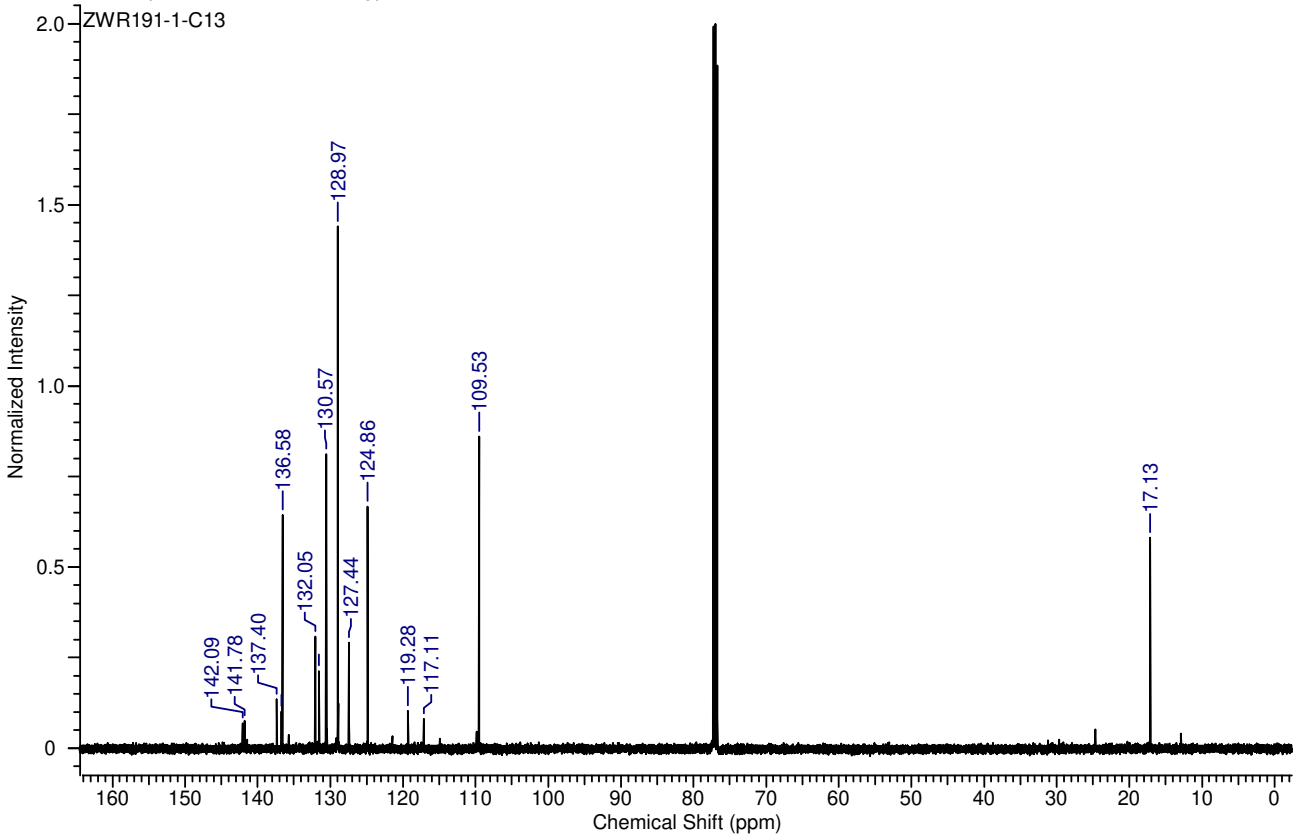


2g

^{1}H NMR (500 MHz, $CDCl_3$)

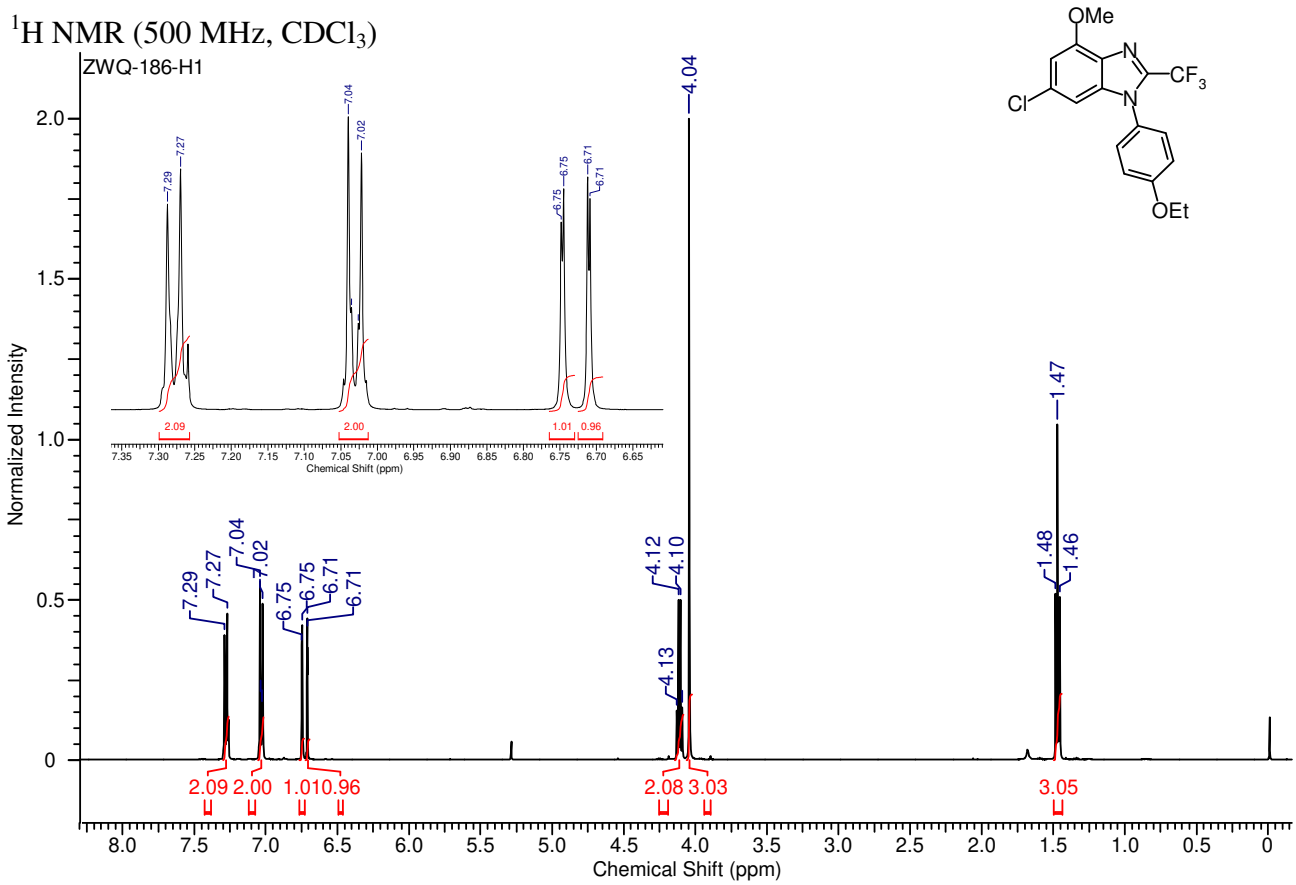


^{13}C NMR (125 MHz, $CDCl_3$)

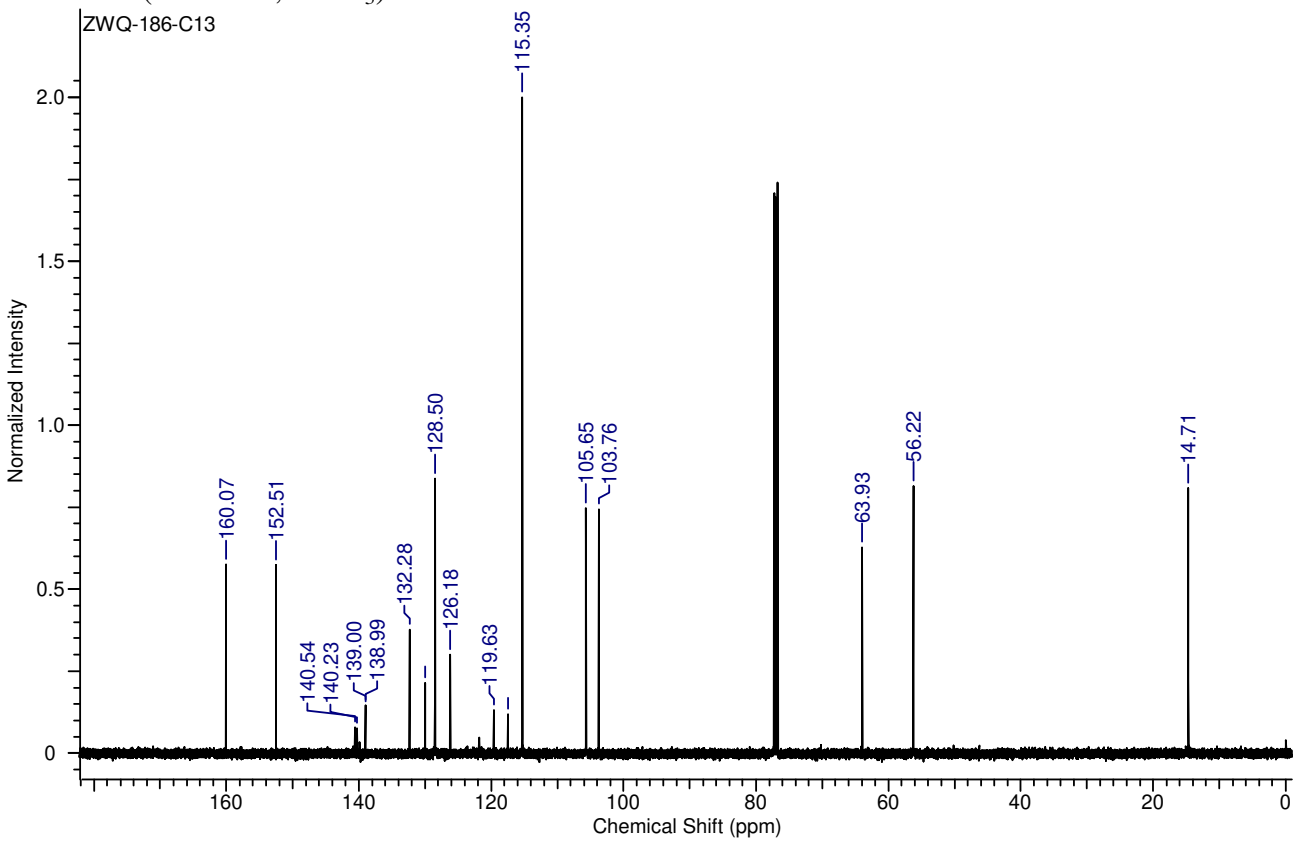


2h

^{1}H NMR (500 MHz, $CDCl_3$)

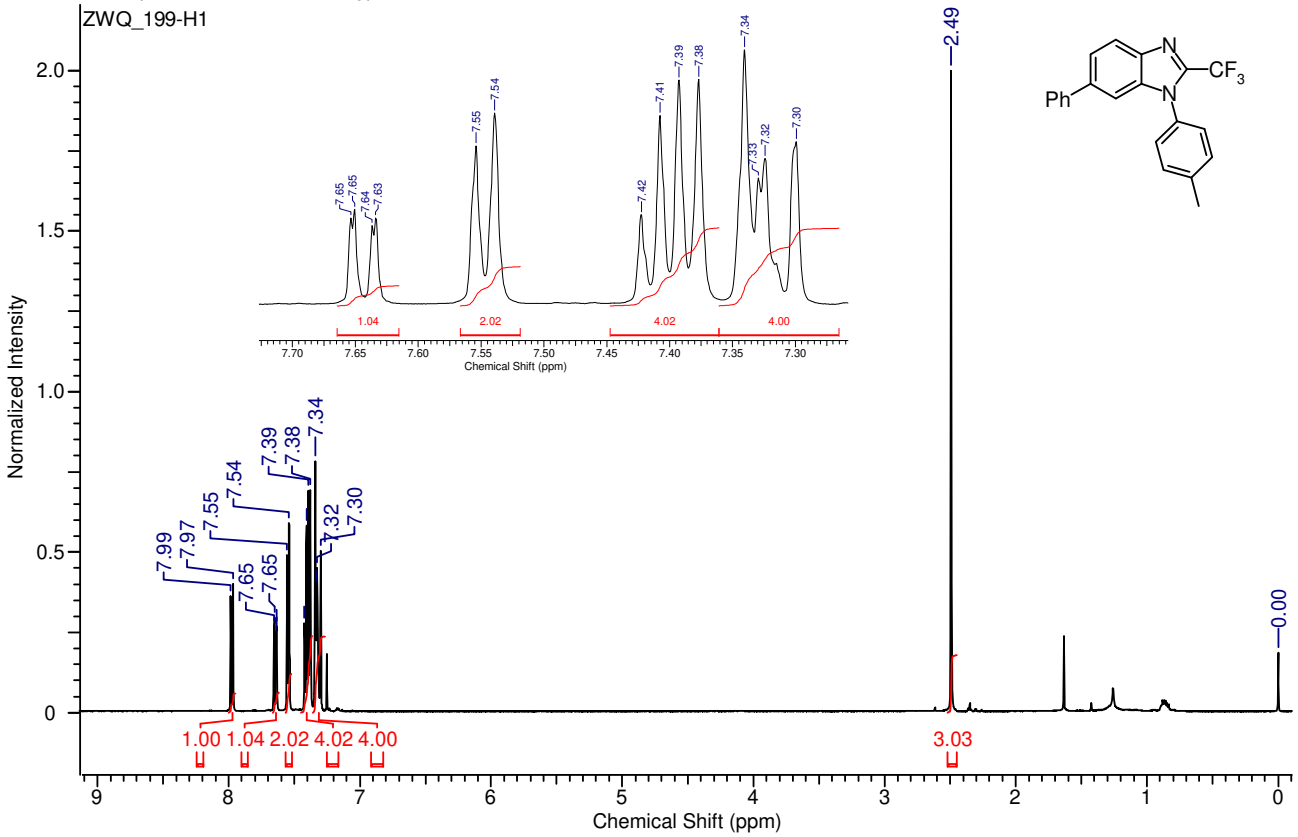


^{13}C NMR (125 MHz, $CDCl_3$)

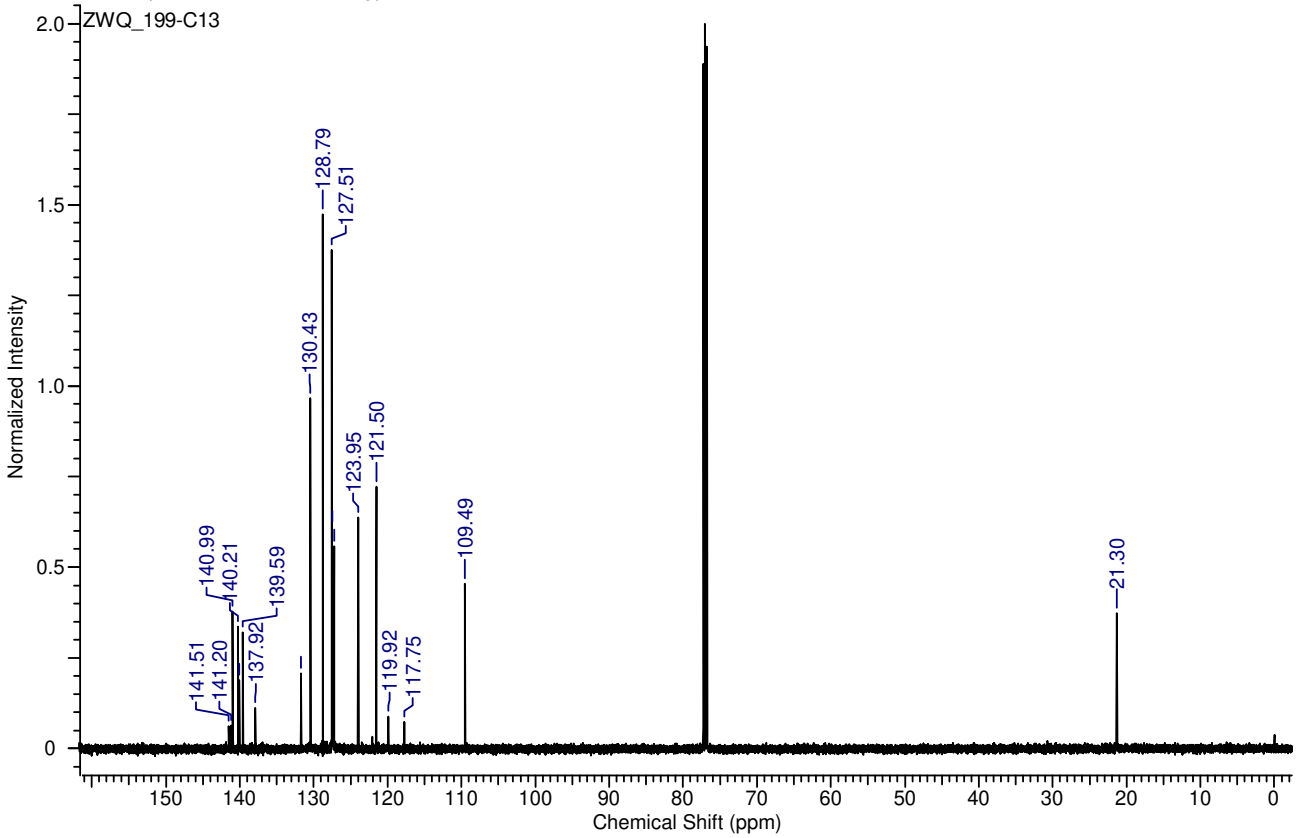


2i

^{1}H NMR (500 MHz, $CDCl_3$)

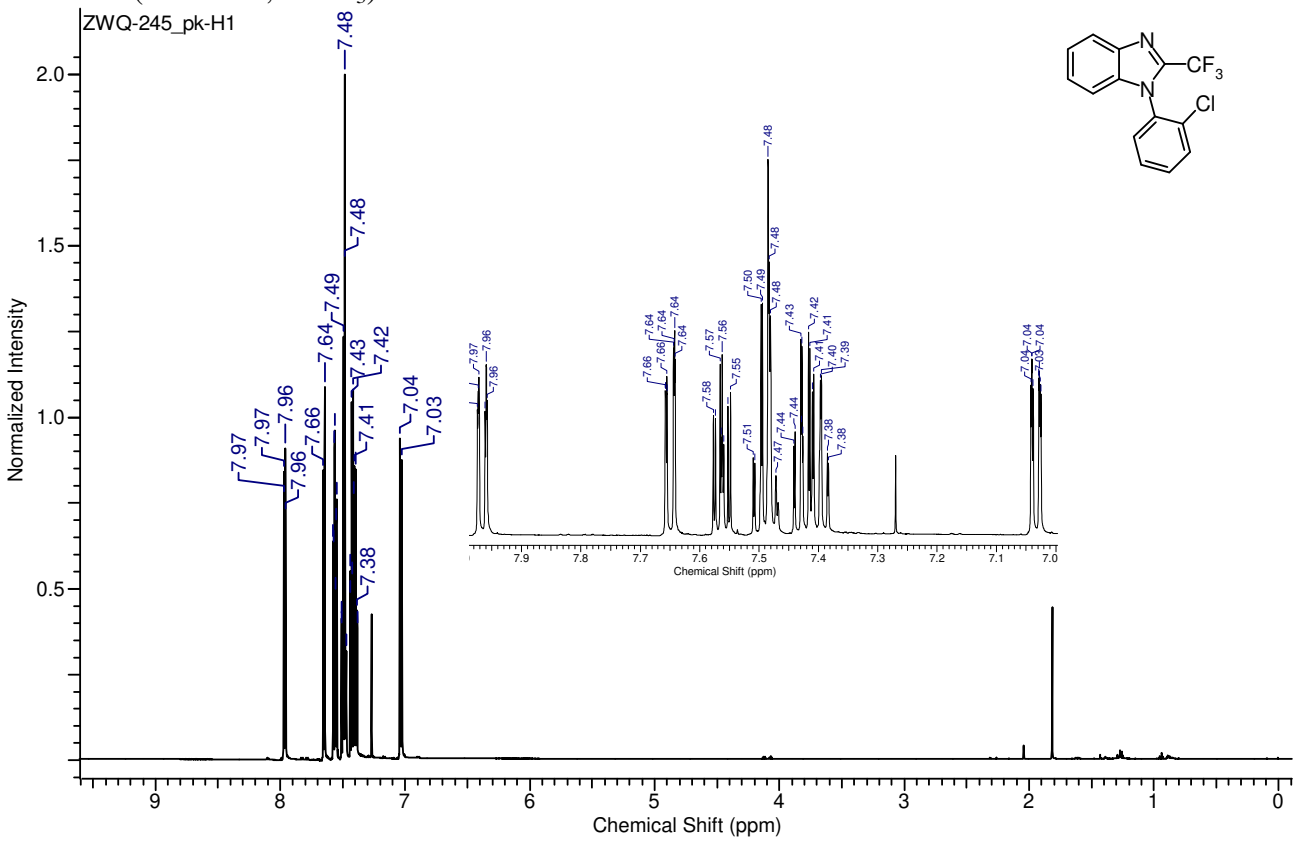


^{13}C NMR (125 MHz, $CDCl_3$)

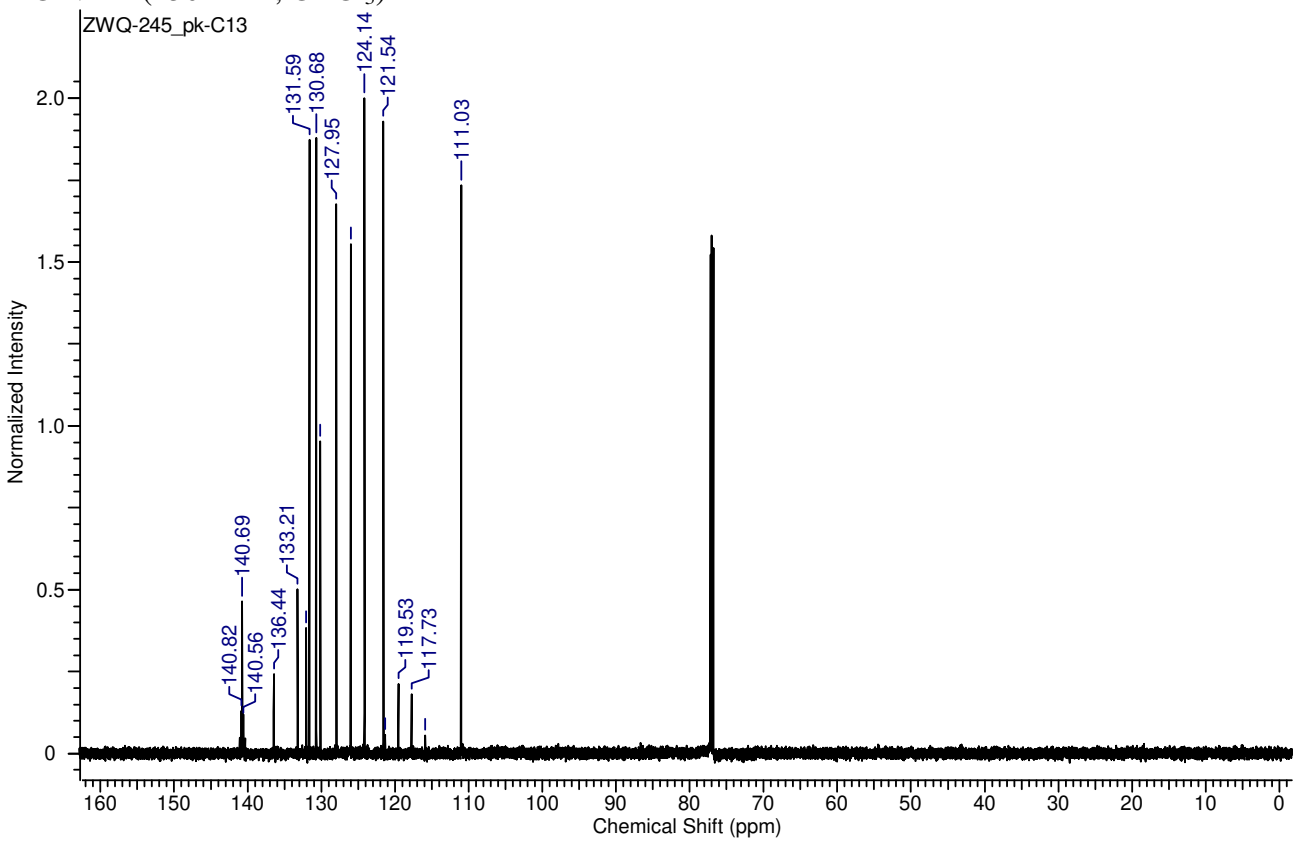


2j

^{1}H NMR (600 MHz, $CDCl_3$)

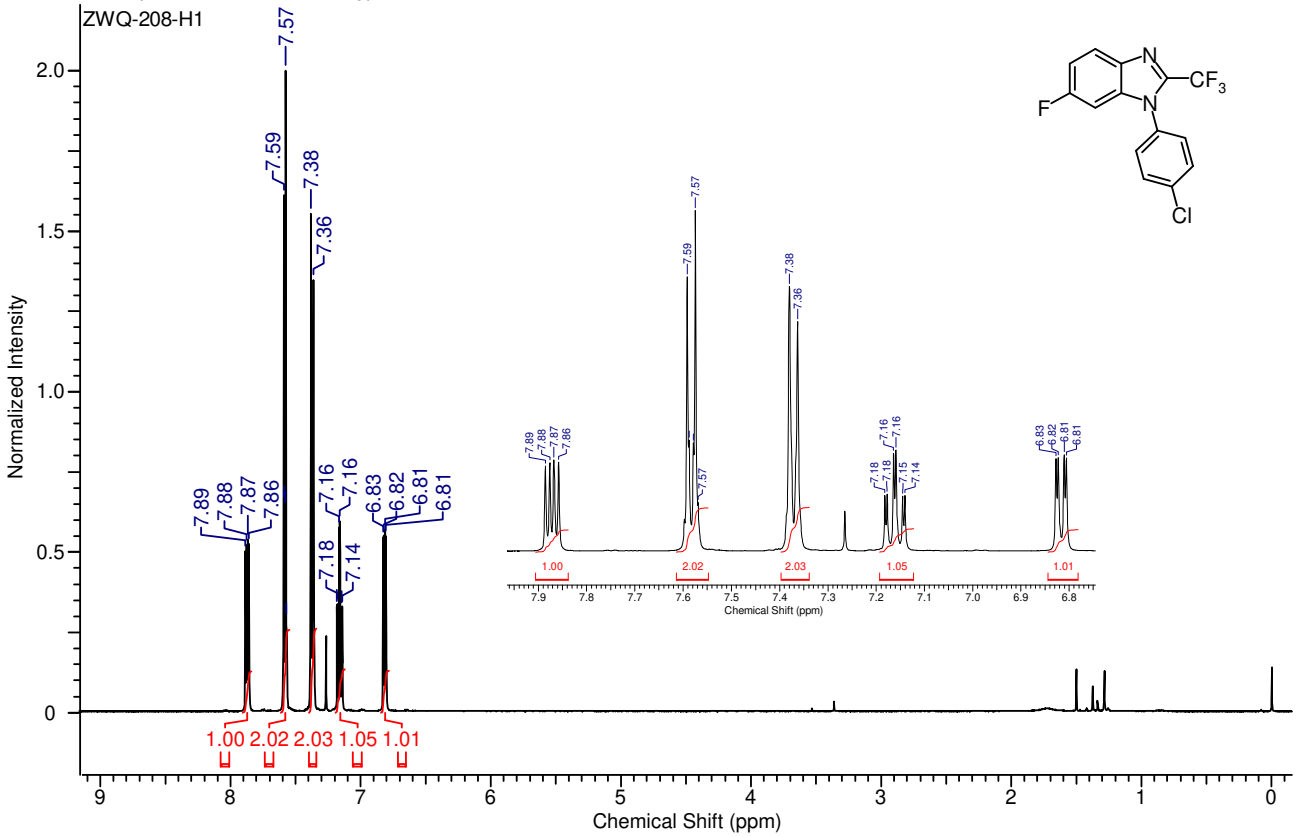


^{13}C NMR (150 MHz, $CDCl_3$)

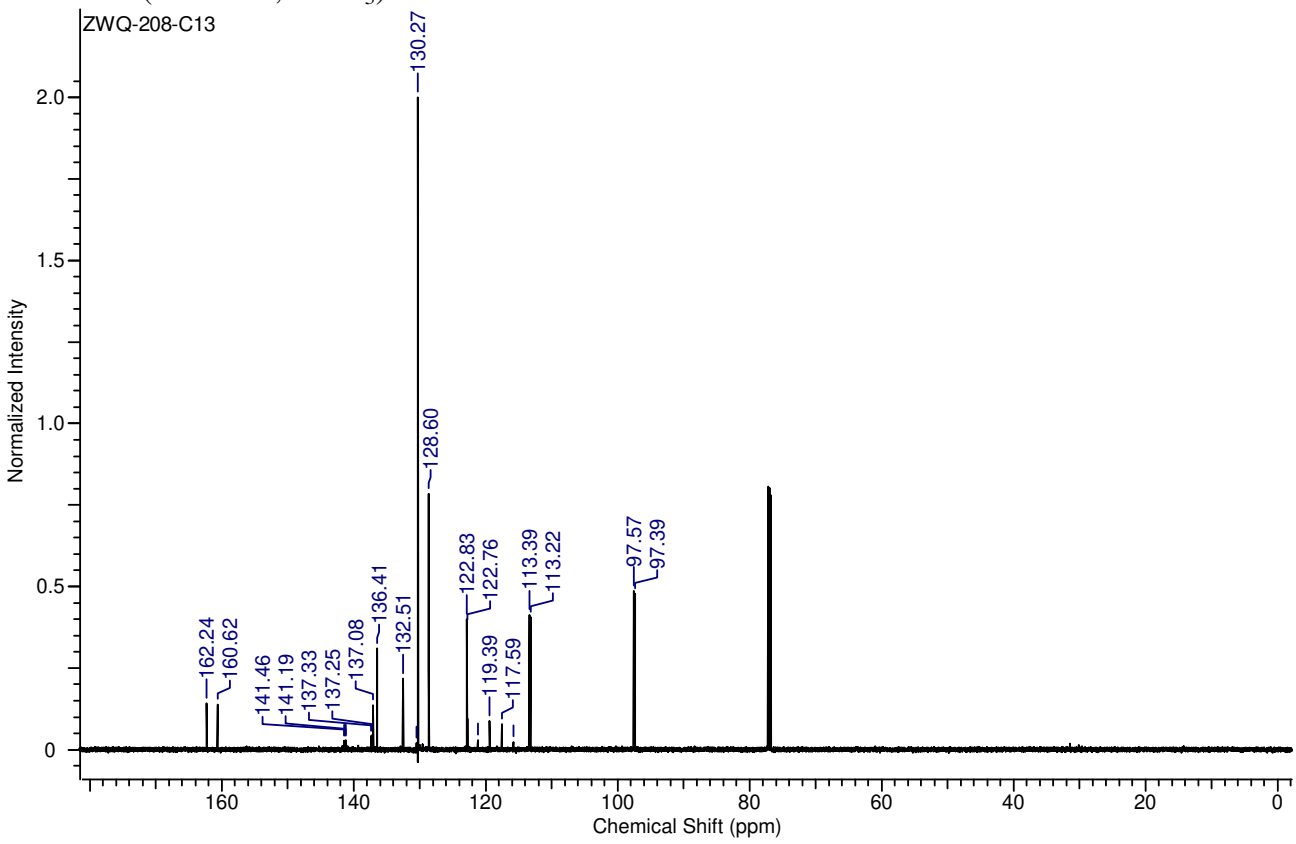


2k

^{1}H NMR (500 MHz, $CDCl_3$)

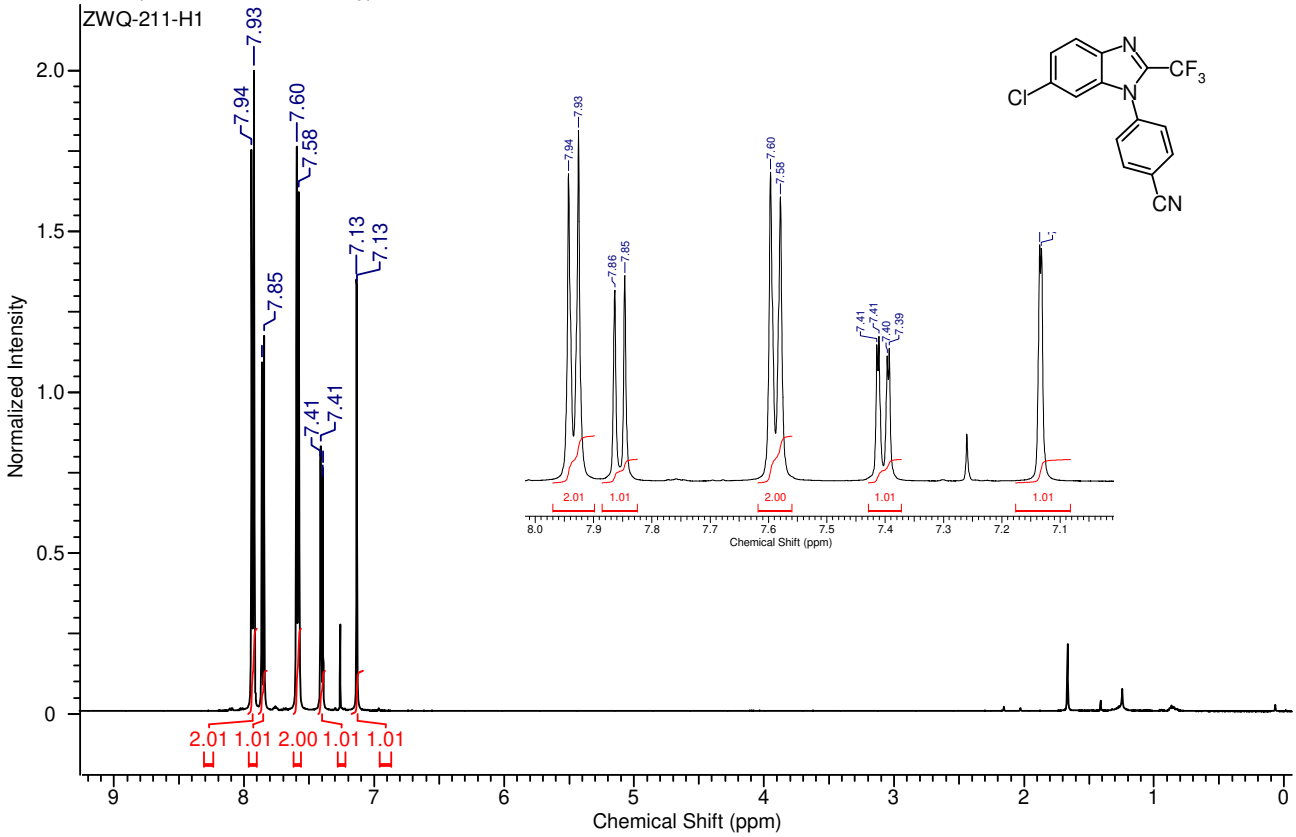


^{13}C NMR (125 MHz, $CDCl_3$)

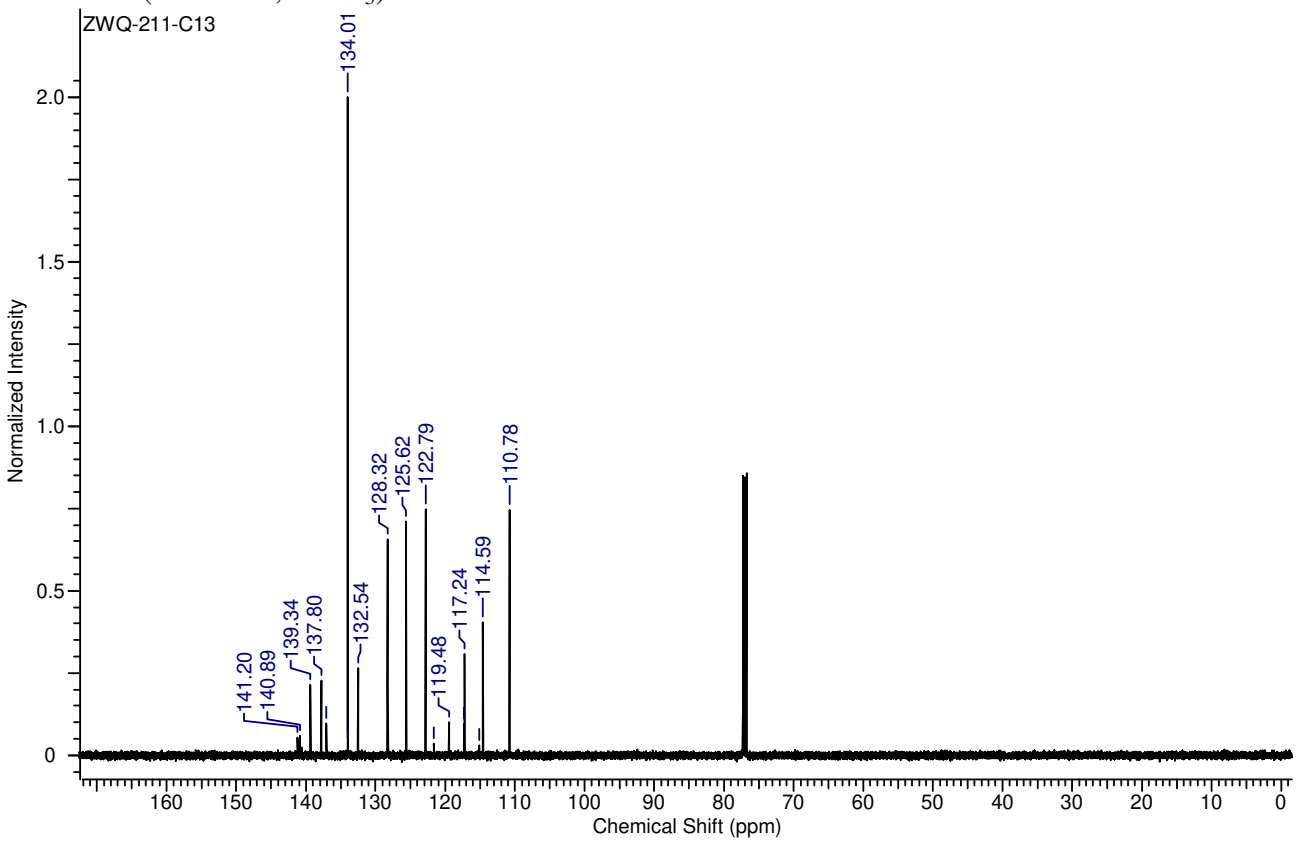


2l

^{1}H NMR (500 MHz, $CDCl_3$)

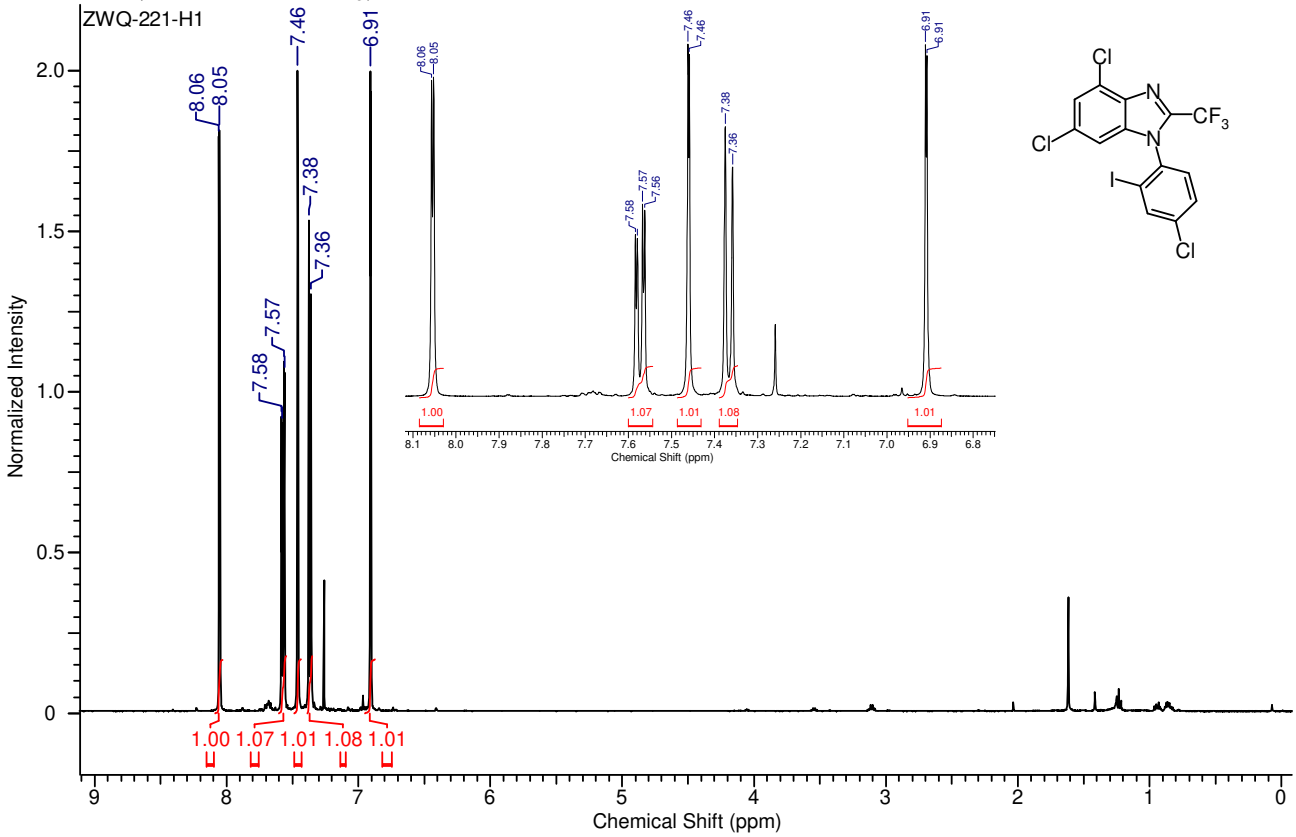


^{13}C NMR (125 MHz, $CDCl_3$)

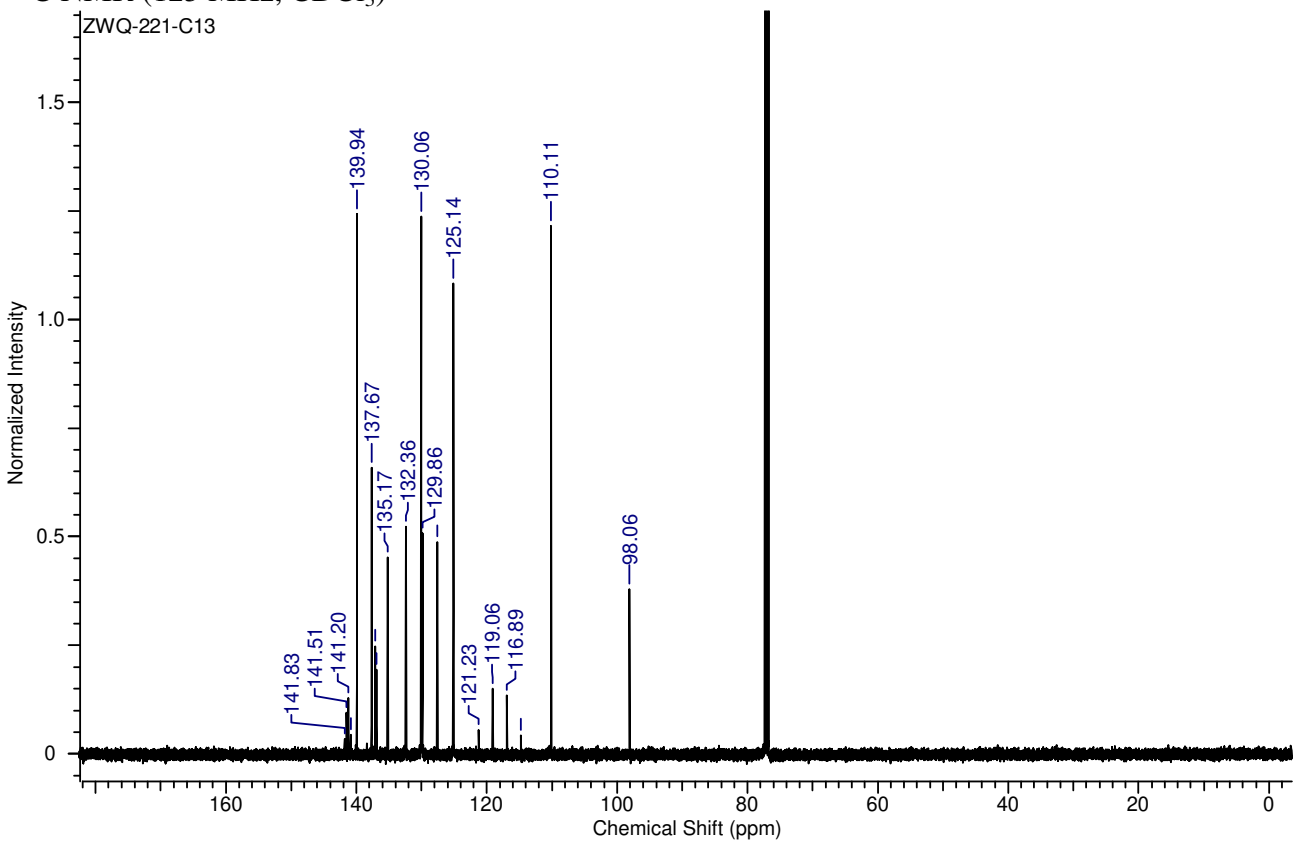


2m

^{1}H NMR (500 MHz, $CDCl_3$)

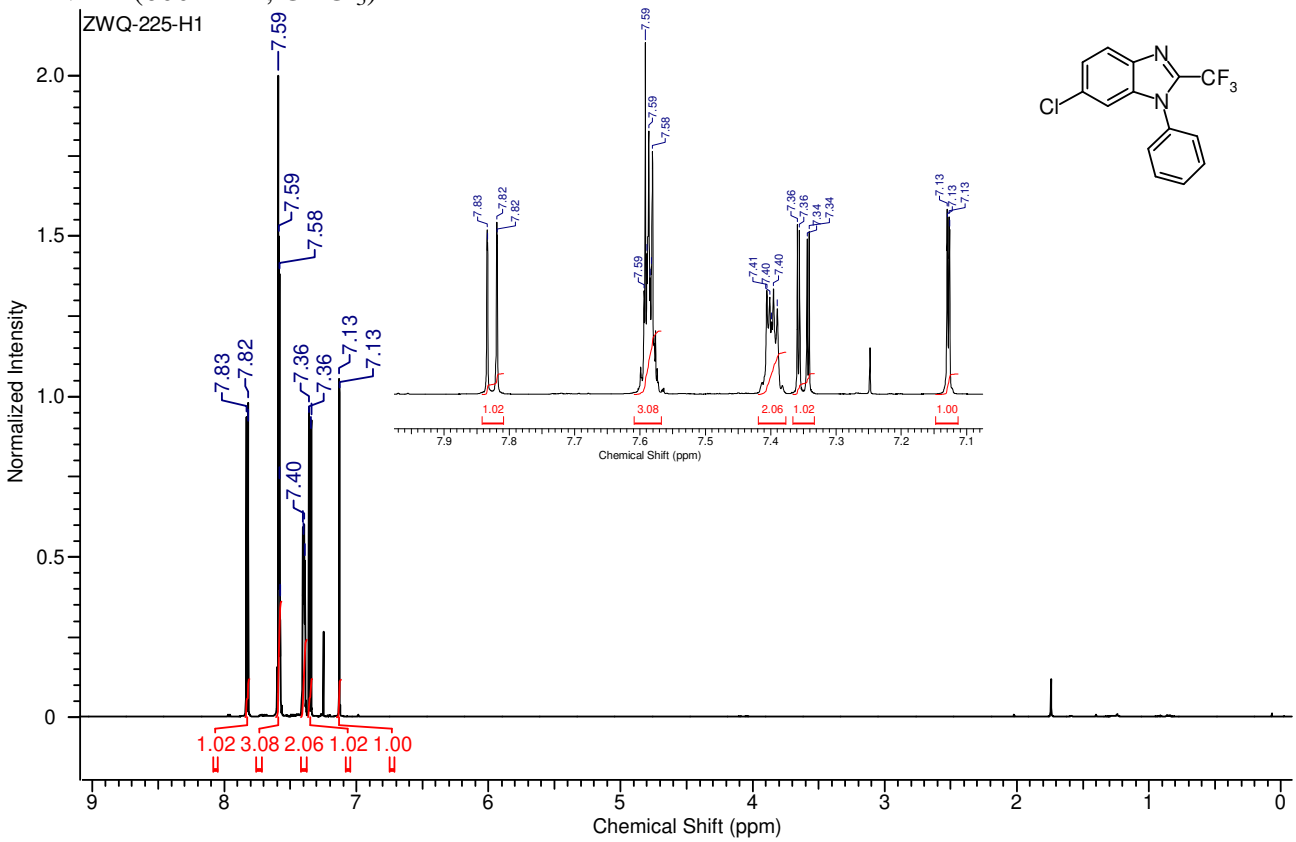


^{13}C NMR (125 MHz, $CDCl_3$)

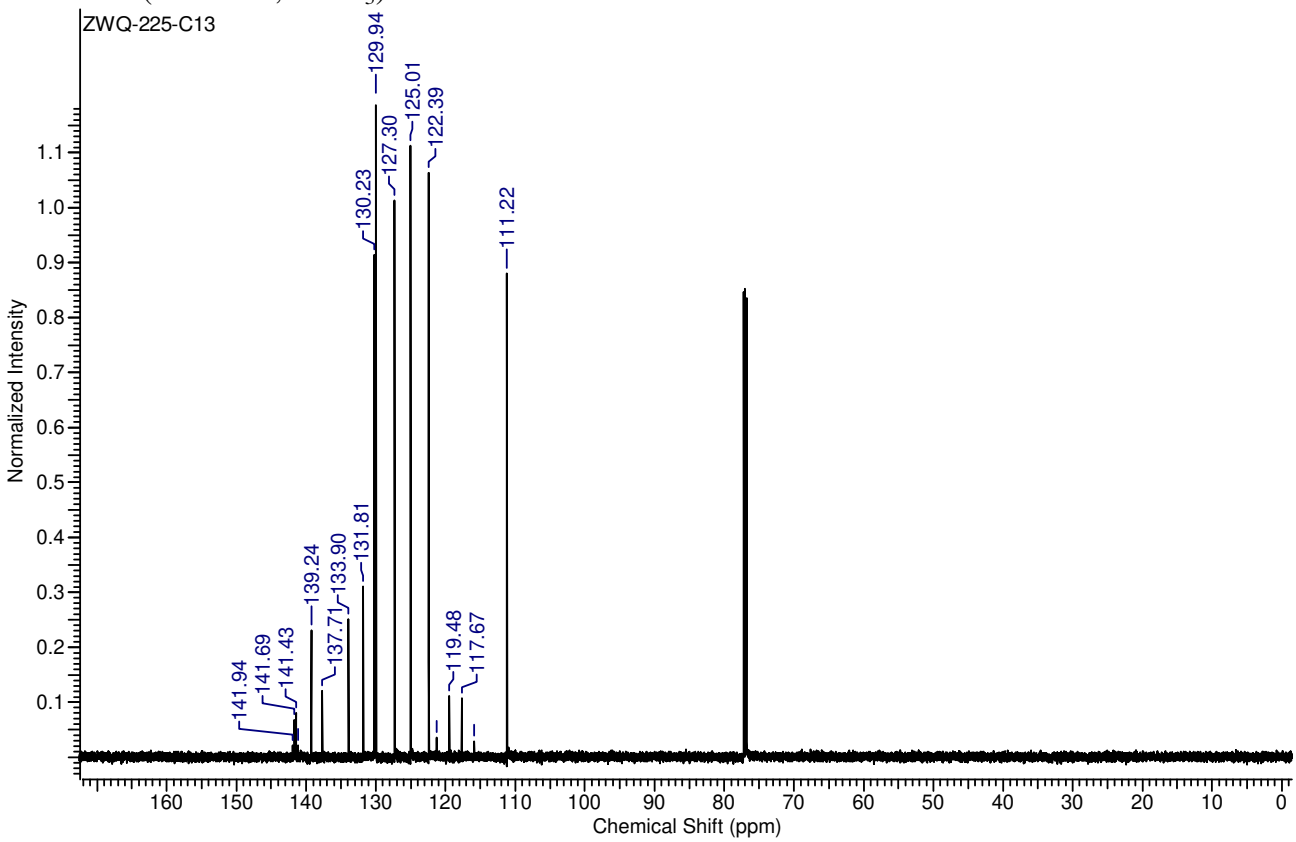


2n

^{1}H NMR (600 MHz, $CDCl_3$)

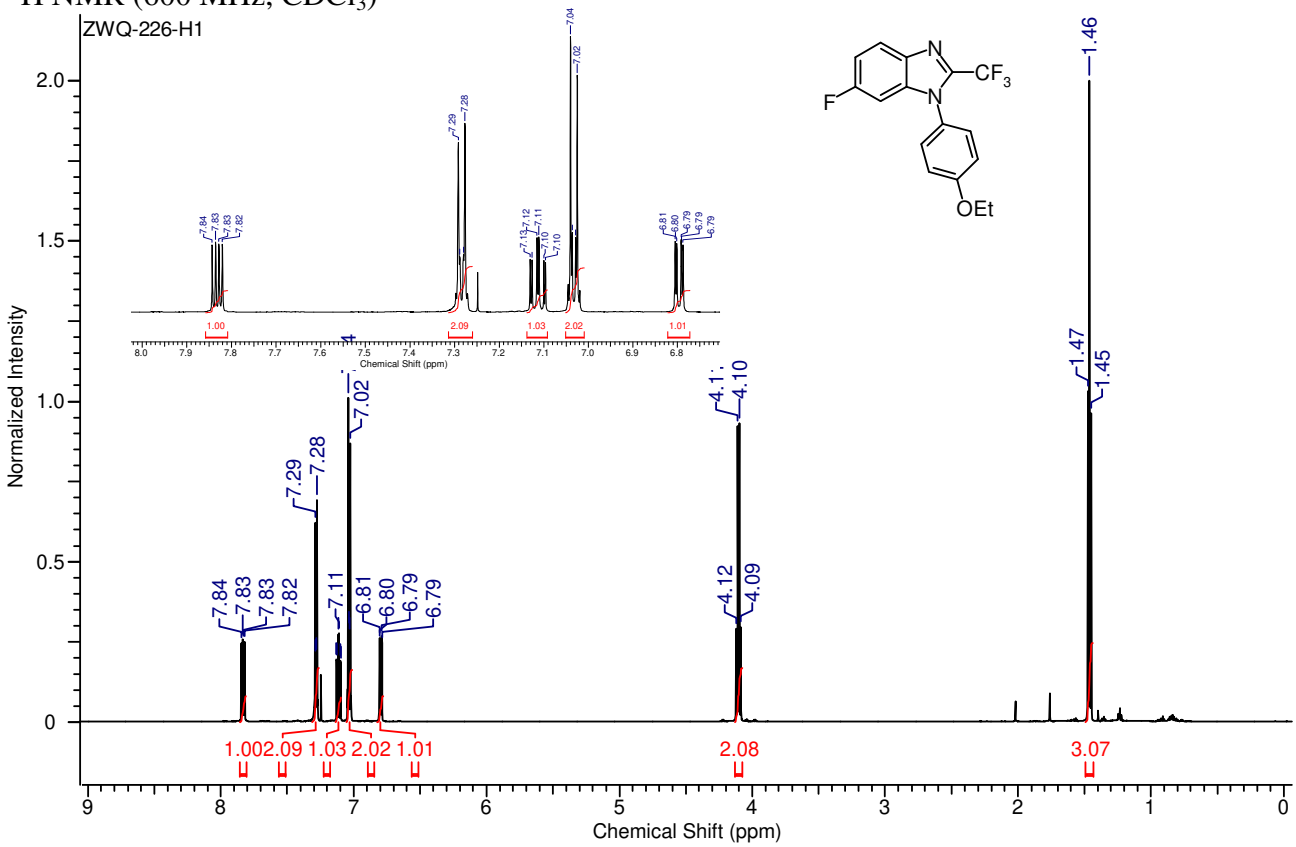


^{13}C NMR (150 MHz, $CDCl_3$)

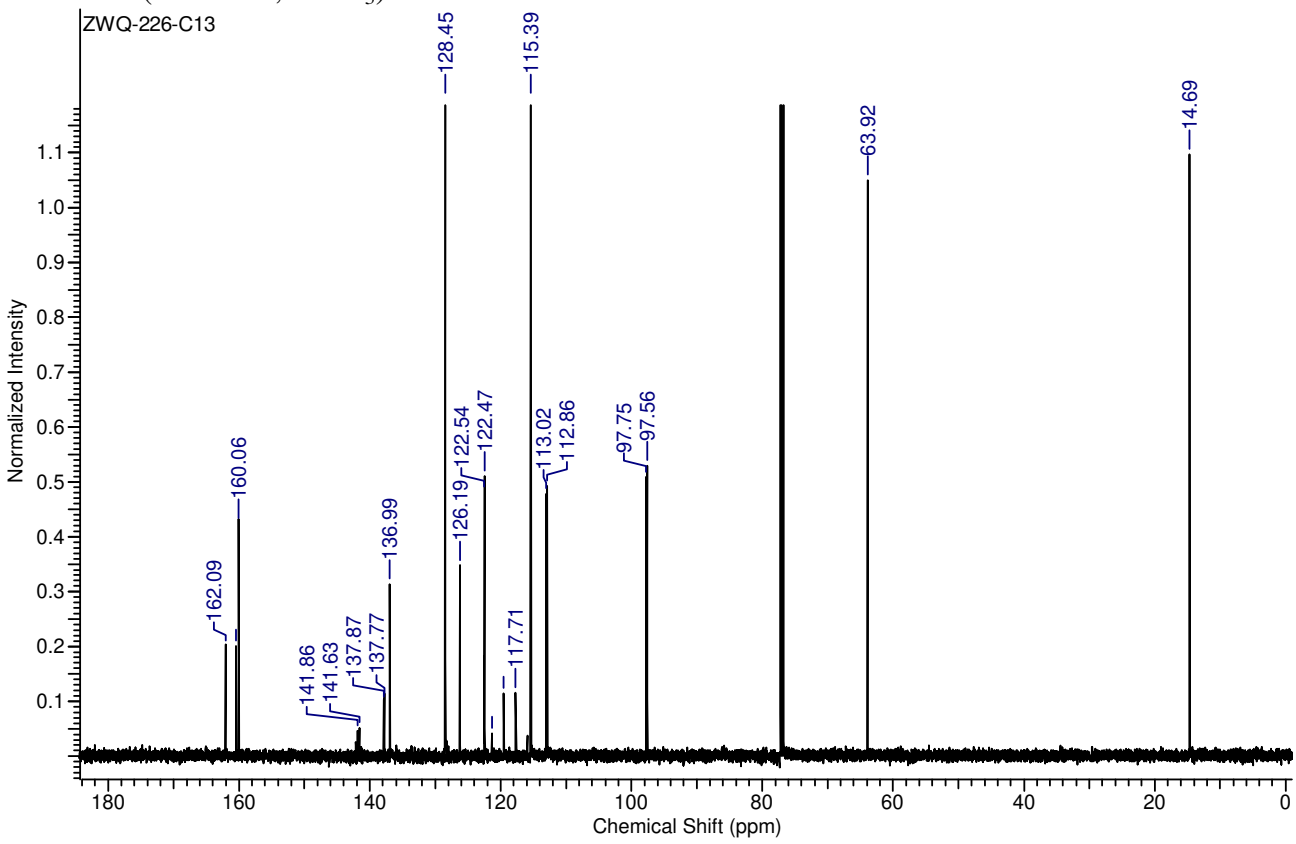


2o

^{1}H NMR (600 MHz, $CDCl_3$)

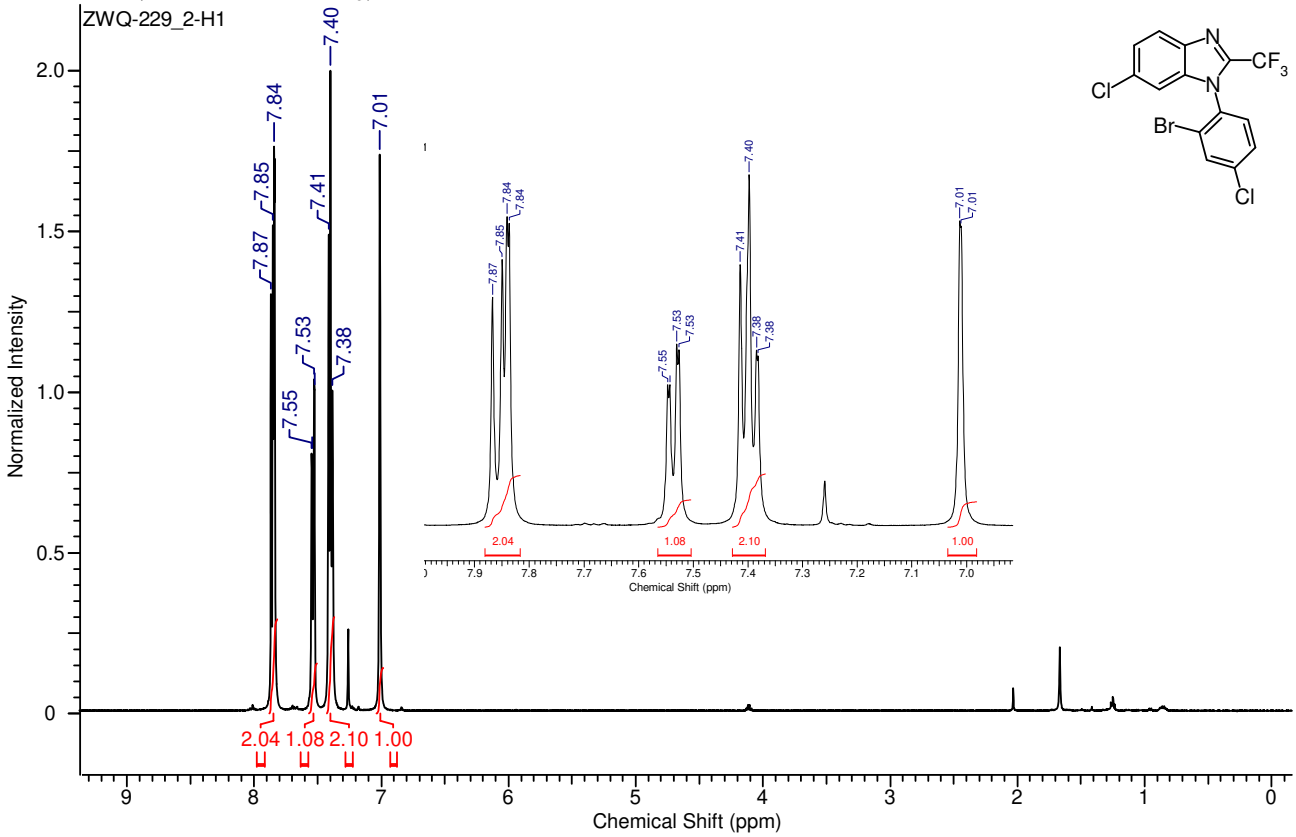


^{13}C NMR (150 MHz, $CDCl_3$)

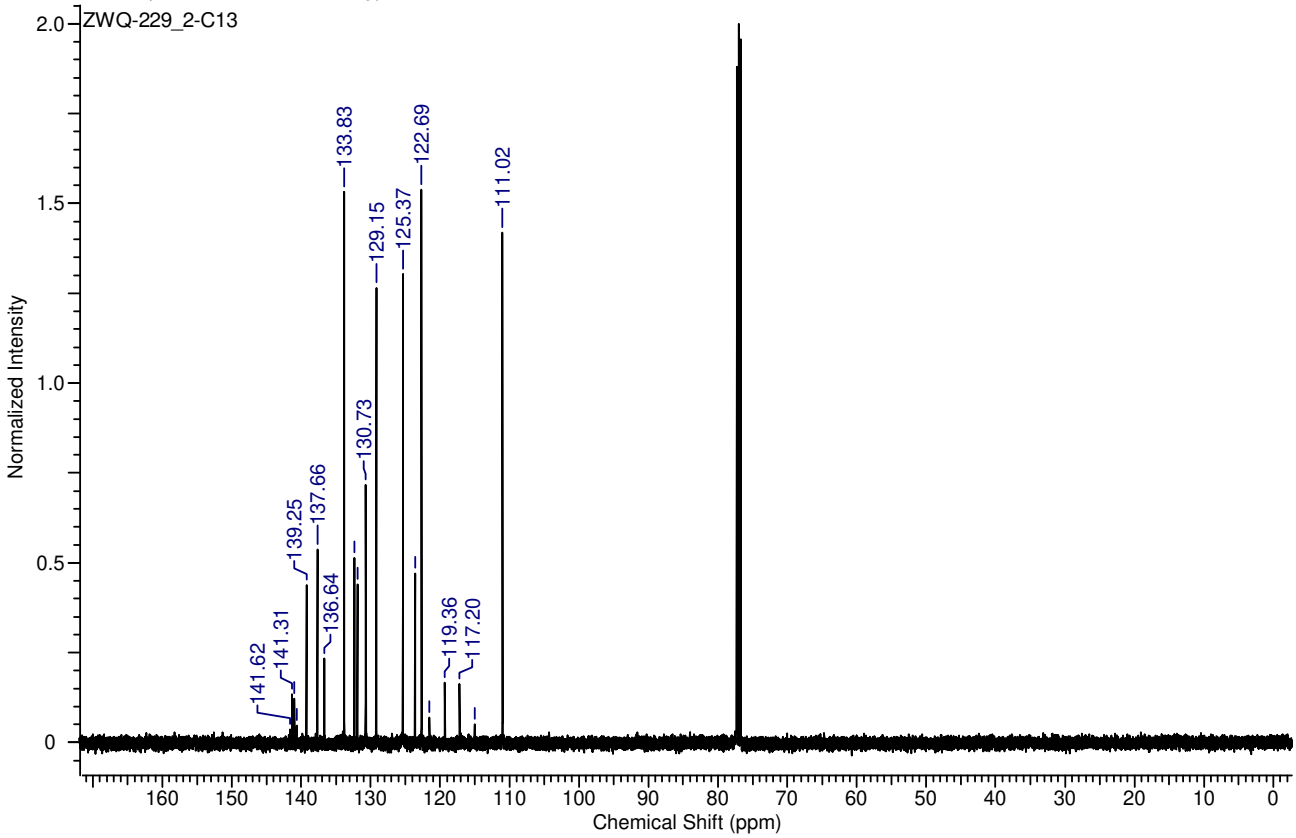


2p

^{1}H NMR (500 MHz, $CDCl_3$)

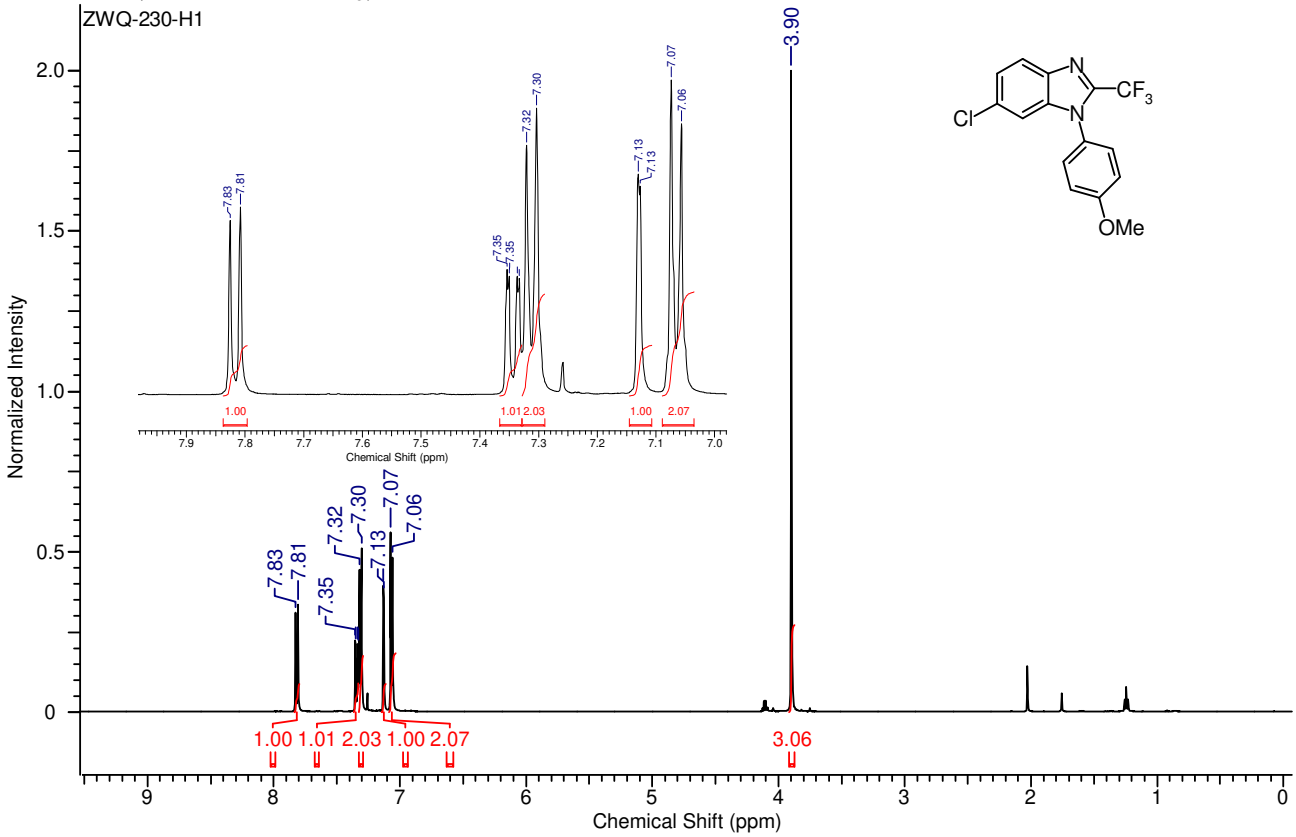


^{13}C NMR (125 MHz, $CDCl_3$)

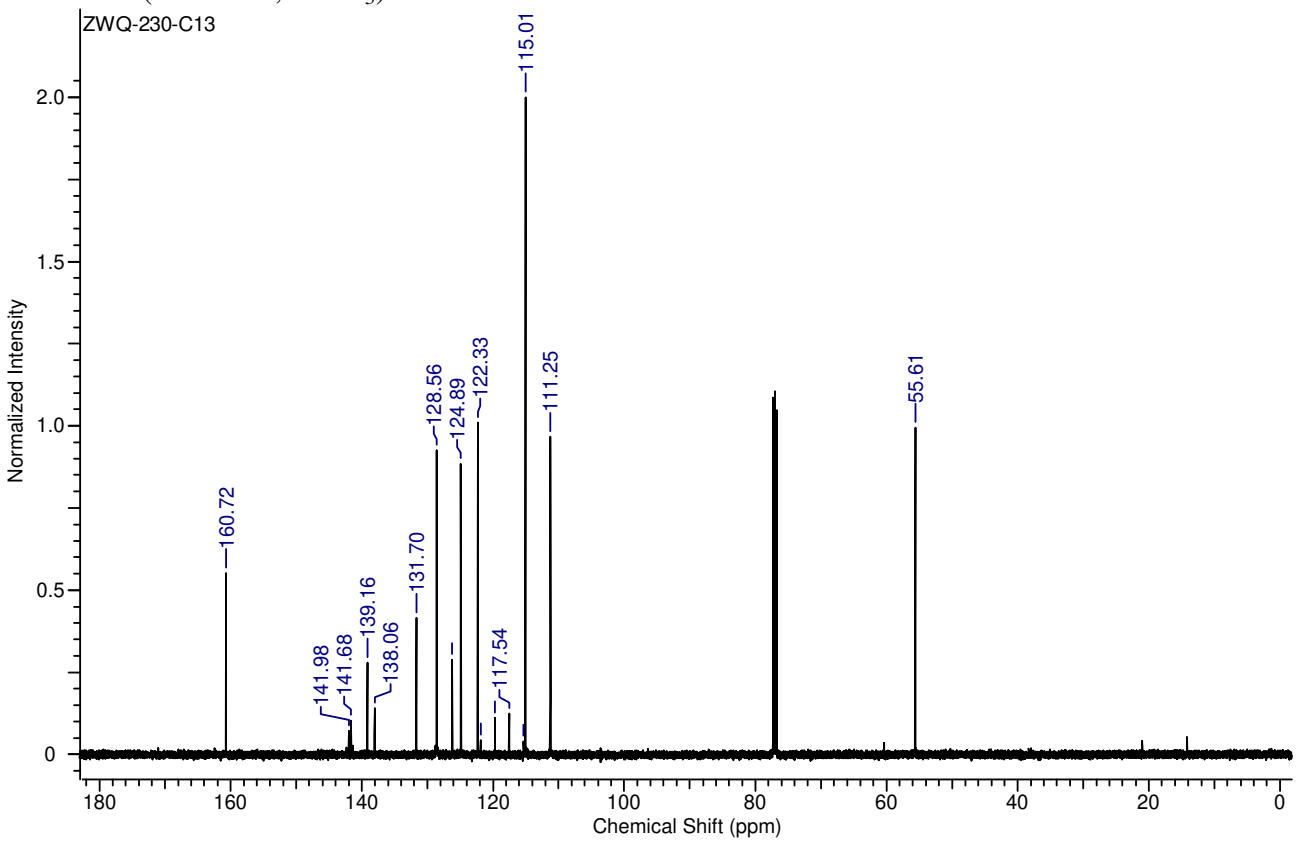


2q

^{1}H NMR (500 MHz, $CDCl_3$)

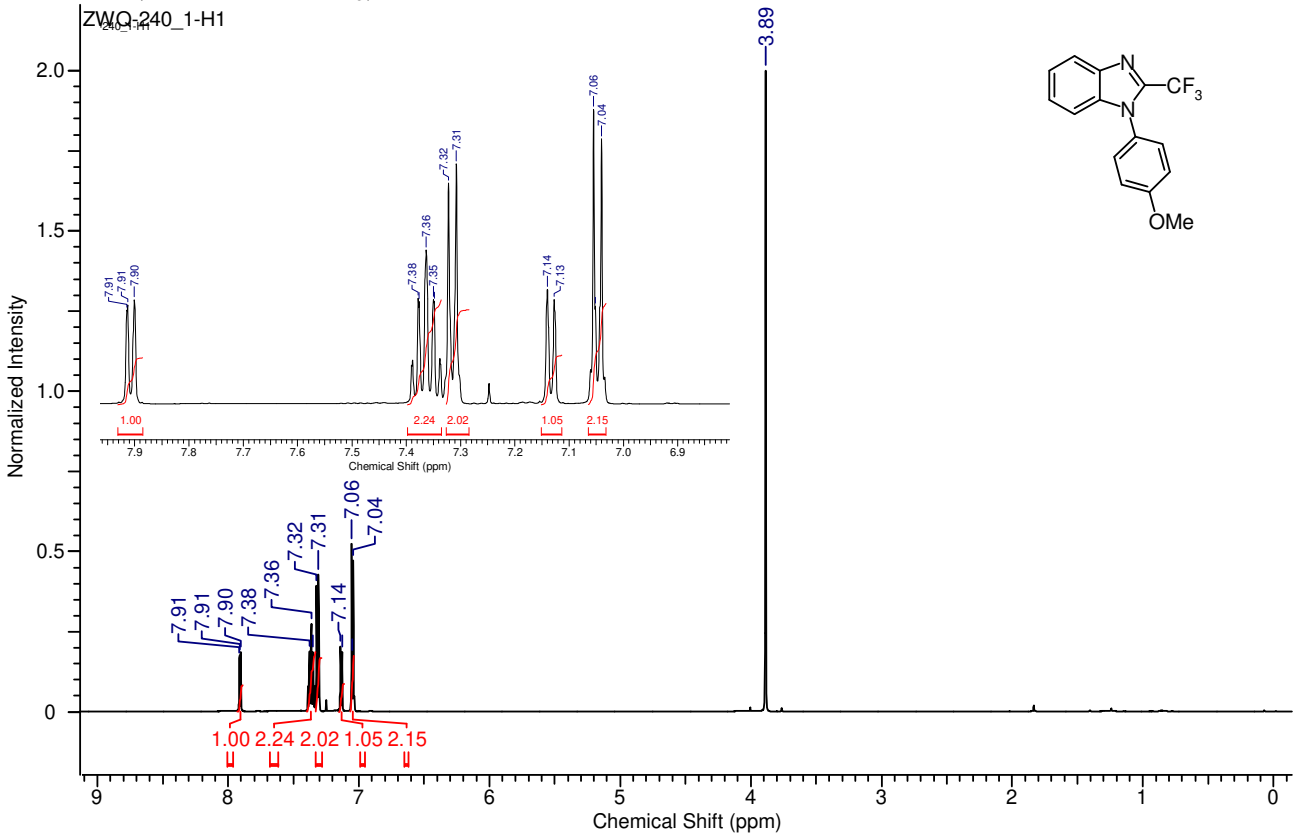


^{13}C NMR (125 MHz, $CDCl_3$)

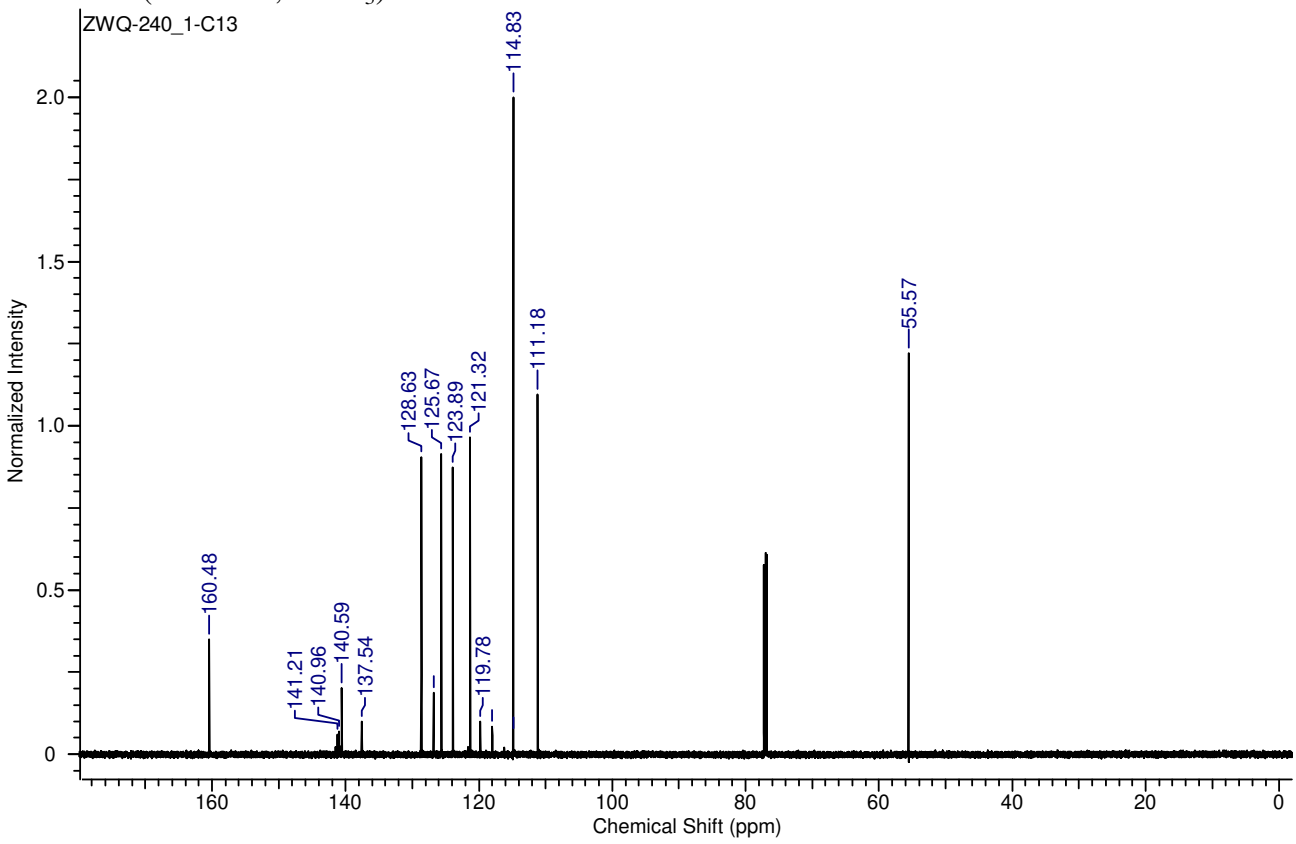


2r

^{1}H NMR (500 MHz, $CDCl_3$)

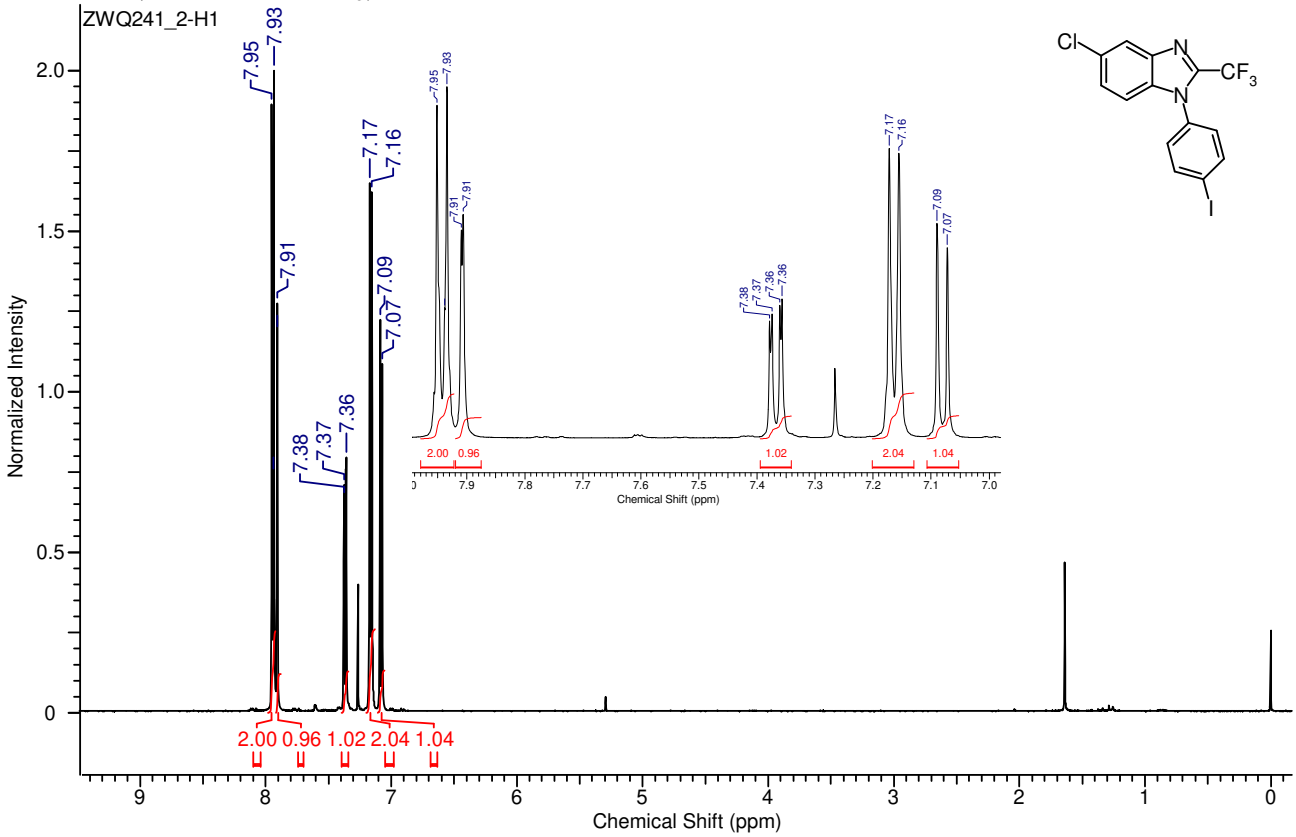


^{13}C NMR (125 MHz, $CDCl_3$)

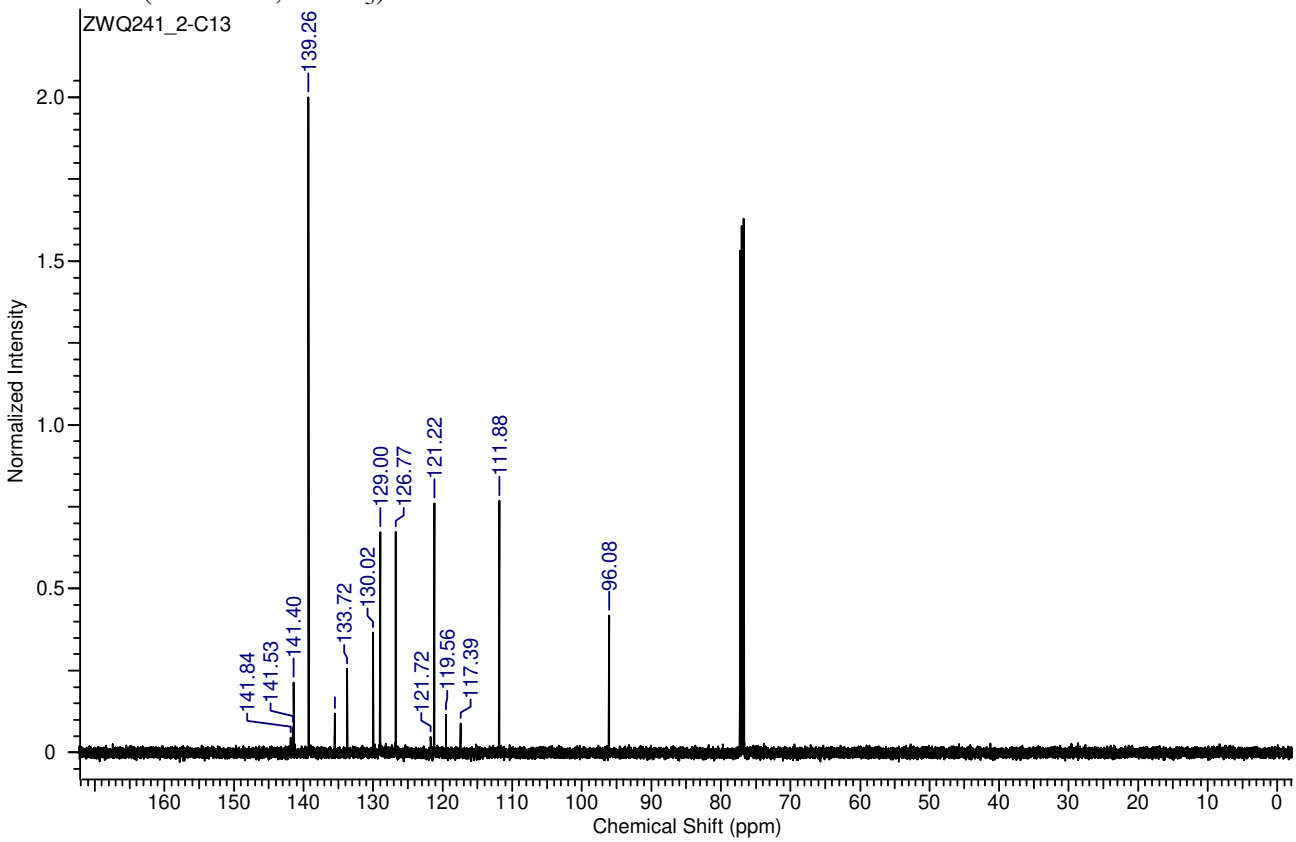


2s

^{1}H NMR (500 MHz, $CDCl_3$)

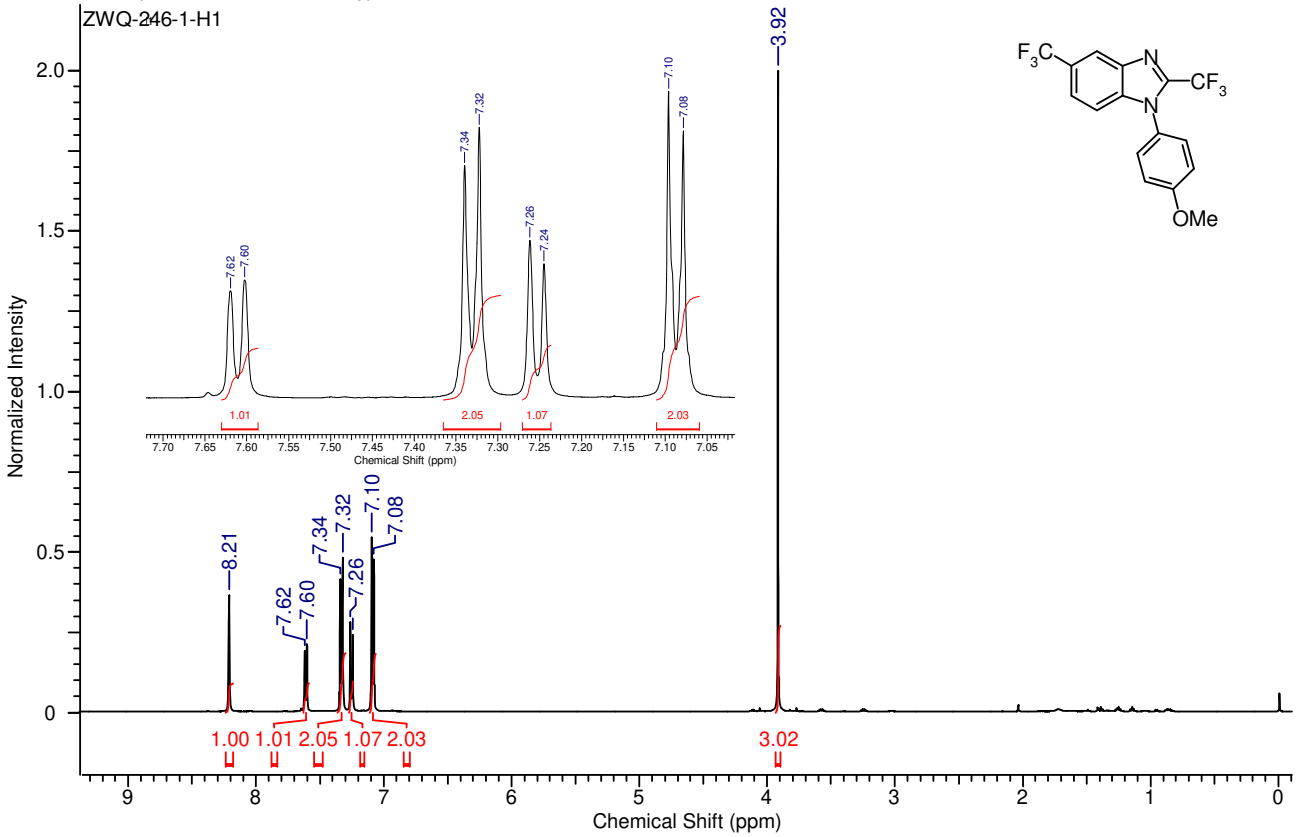


^{13}C NMR (125 MHz, $CDCl_3$)

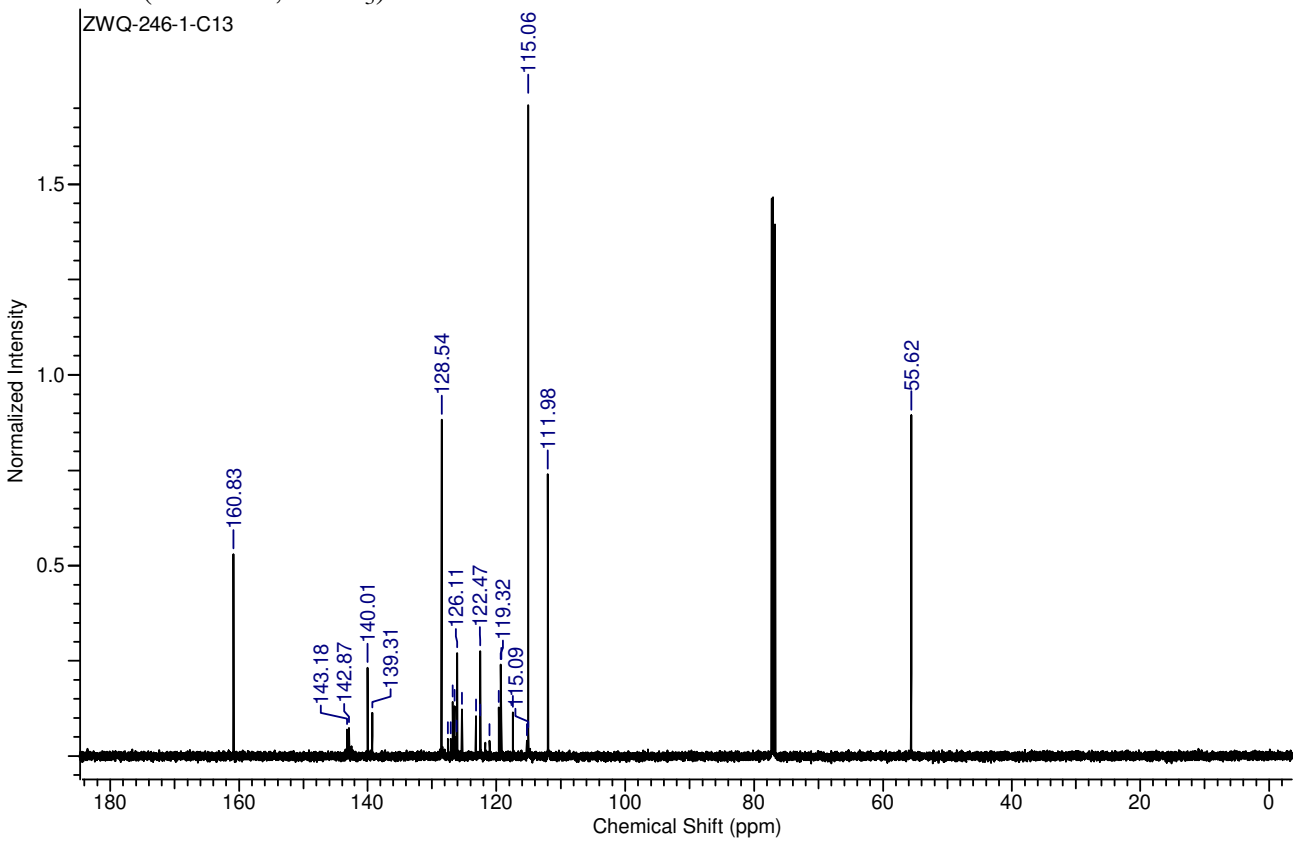


2t

^{1}H NMR (500 MHz, $CDCl_3$)

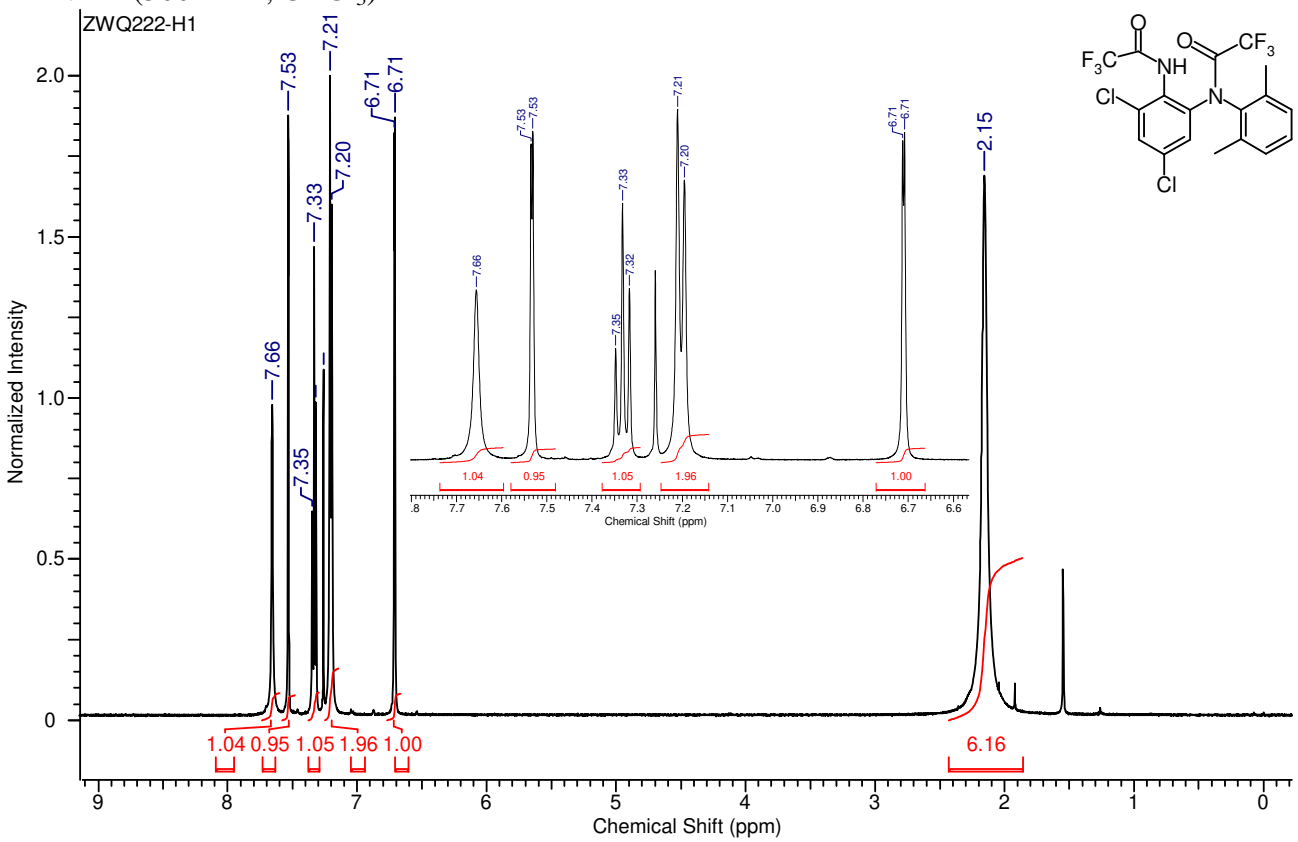


^{13}C NMR (125 MHz, $CDCl_3$)

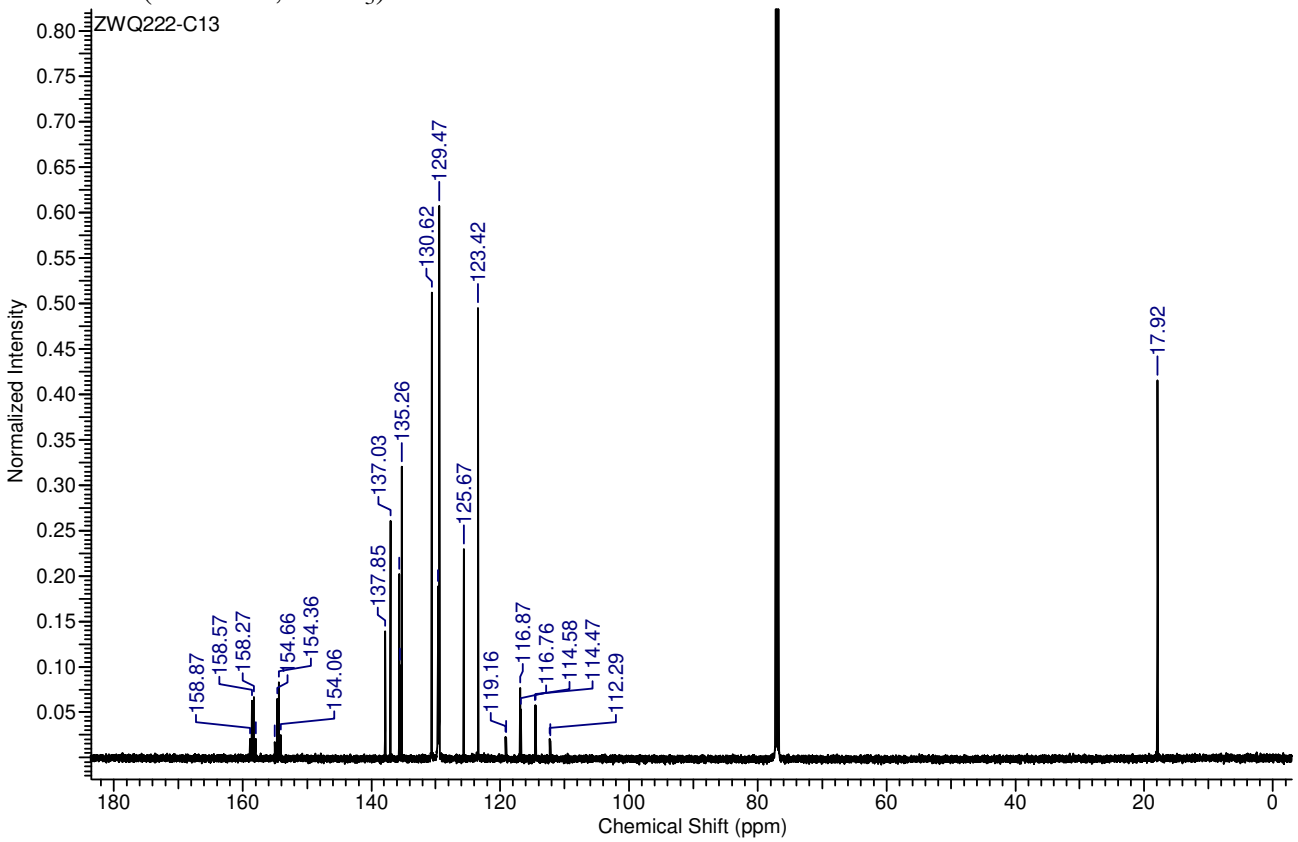


3

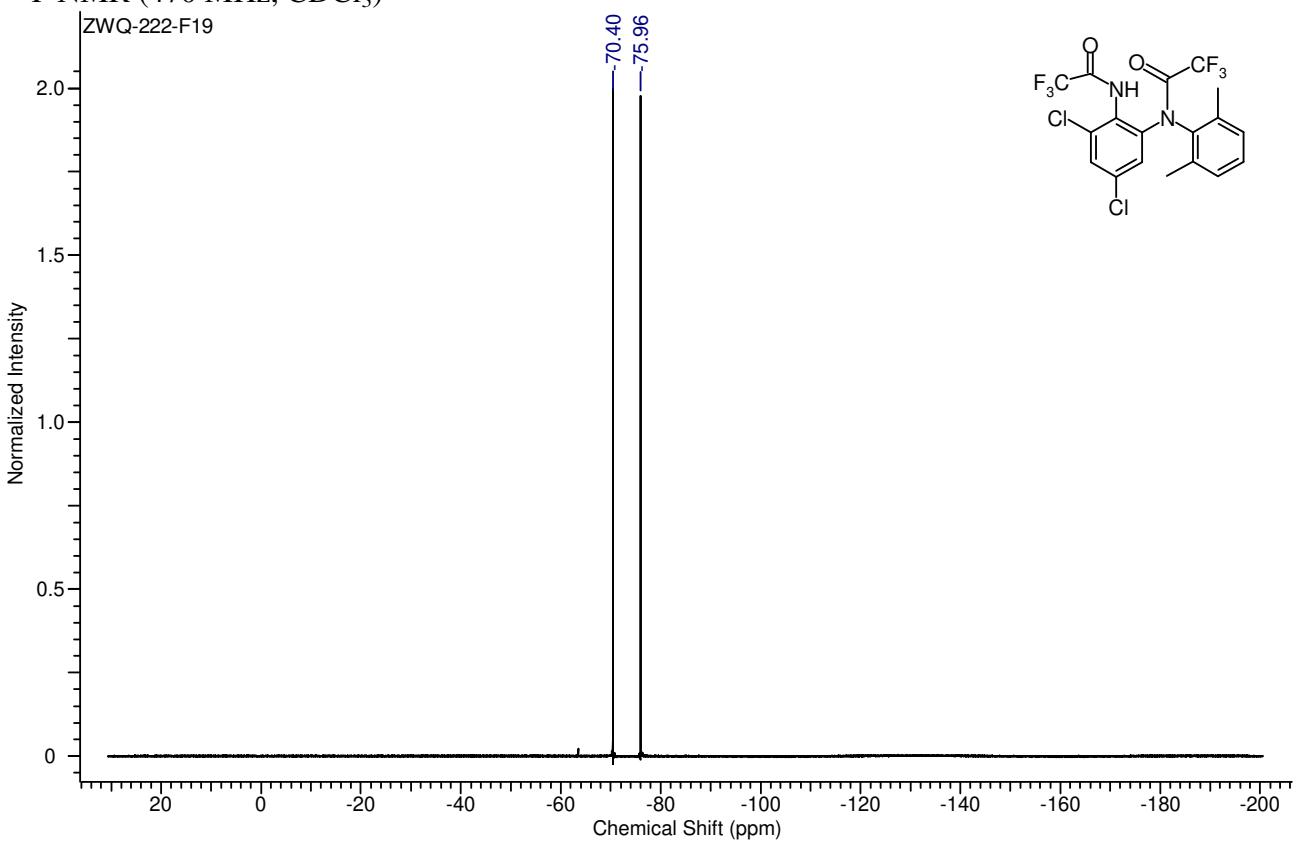
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

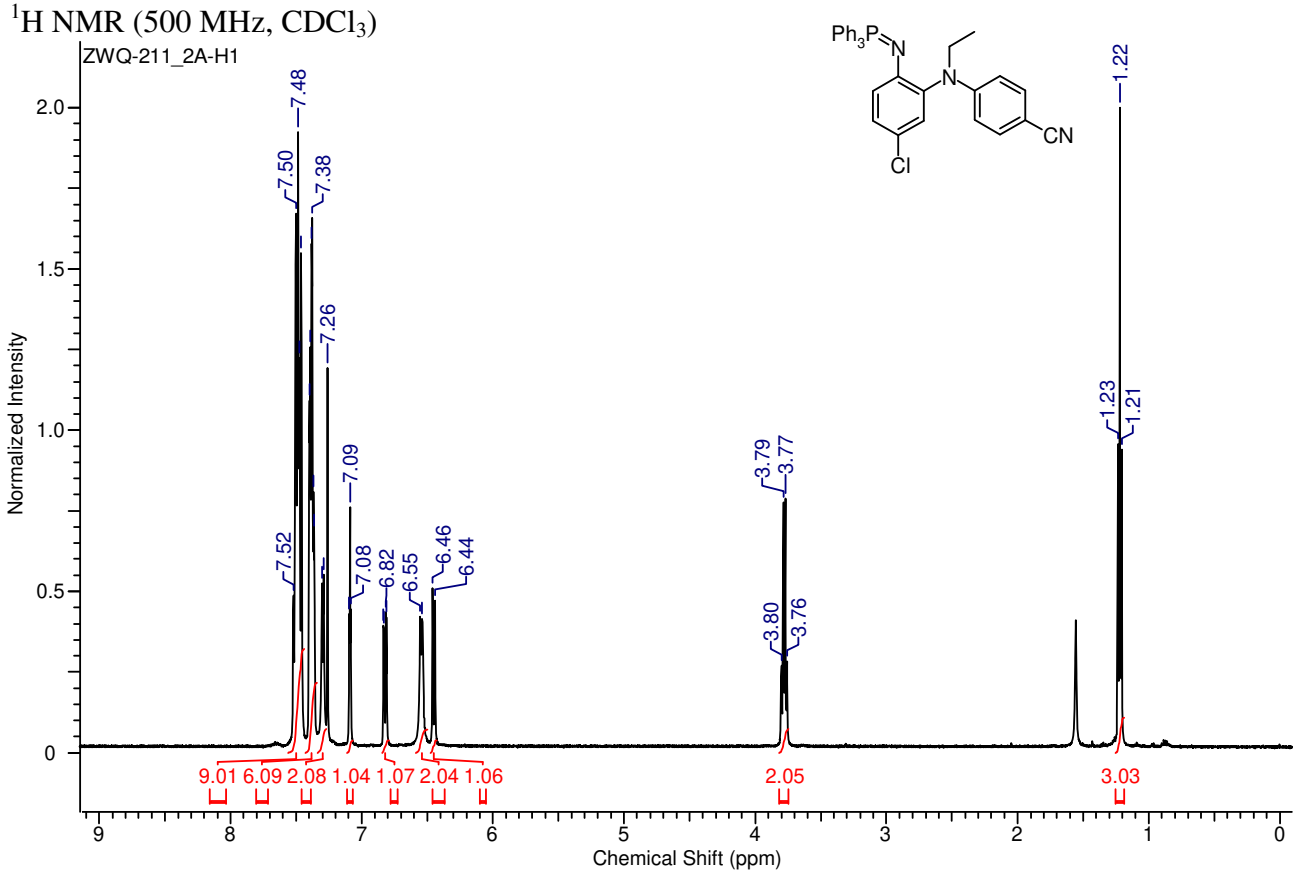


^{19}F NMR (470 MHz, $CDCl_3$)

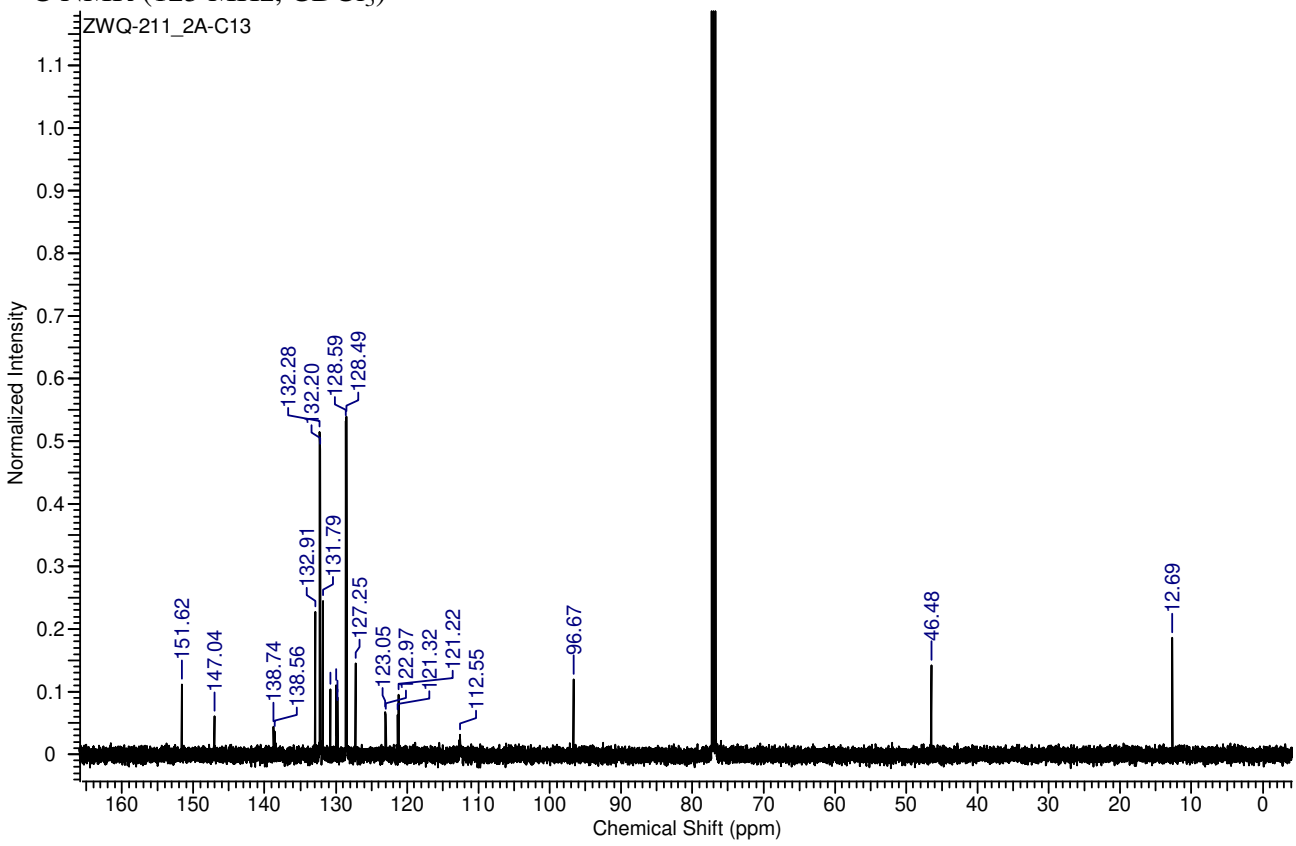


5-Chloro-1-*N*-(4-cyanophenyl)-1-*N*-ethyl-2-*N*-(triphenyl-λ5-phosphanylidene)benzene-1,2-diamine

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)



Computing details for compund 3

Data collection: Bruker *APEX2*; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXL2014* (Sheldrick, 2014); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2014); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: PublCIF [Westrip, S. P. (2010). *J. Apply. Cryst.*, **43**, 920-925].

Crystal data

$C_{18}H_{12}Cl_2F_6N_2O_2$	$F(000)$ = 1904
M_r = 473.20	D_x = 1.530 Mg m^{-3}
Monoclinic, $P2_1/n$	Cu $K\alpha$ radiation, λ = 1.54178 Å
a = 12.5870 (5) Å	Cell parameters from 2960 reflections
b = 25.8834 (9) Å	θ = 3.4–68.6°
c = 13.2647 (5) Å	μ = 3.52 mm^{-1}
β = 108.079 (3)°	T = 296 K
V = 4108.2 (3) Å^3	Needle, colorless
Z = 8	0.23 × 0.13 × 0.10 mm

Data collection

Bruker APEX-II CCD diffractometer	7046 independent reflections
Radiation source: fine-focus sealed tube	2960 reflections with $I > 2\sigma(I)$
Graphite monochromator	R_{int} = 0.142
ϕ and ω scans	θ_{max} = 68.6°, θ_{min} = 3.4°
Absorption correction: numerical *SADABS*	h = -15→14
T_{min} = 0.493, T_{max} = 0.722	k = -31→31
42730 measured reflections	l = -14→14

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.087	Hydrogen site location: inferred from neighbouring sites
$wR(F^2)$ = 0.237	H-atom parameters constrained
S = 1.00	$w = 1/[\sigma^2(F_o^2) + (0.0899P)^2 + 5.1186P]$ where $P = (F_o^2 + 2F_c^2)/3$
7046 reflections	$(\Delta/\sigma)_{max}$ = 0.005
543 parameters	$\Delta\rangle_{max}$ = 0.52 e Å^{-3}
6 restraints	$\Delta\rangle_{min}$ = -0.41 e Å^{-3}

Special details

Experimental. Crystal selected for X-ray experiment was small needle with dimensions 0.234 mm x 0.127 mm x 0.099 mm

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell

parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Disorder on fluor atoms

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²) for (3)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
Cl1	0.66562 (16)	0.51007 (8)	1.05411 (15)	0.0845 (6)	
Cl2	1.10616 (18)	0.47697 (8)	1.16604 (16)	0.0964 (7)	
Cl3	1.05619 (13)	0.55807 (8)	0.38561 (14)	0.0732 (6)	
Cl4	0.75799 (17)	0.40499 (7)	0.32972 (17)	0.0884 (7)	
F1	0.8539 (6)	0.77880 (19)	1.1084 (6)	0.157 (3)	
F2	0.8784 (7)	0.7553 (2)	0.9672 (5)	0.170 (3)	
F3	1.0117 (6)	0.7686 (2)	1.0985 (6)	0.173 (3)	
F4A	0.5606 (9)	0.6851 (4)	0.9629 (8)	0.114 (4)*	0.521 (11)
F4B	0.5195 (9)	0.6624 (5)	0.9753 (8)	0.100 (4)*	0.479 (11)
F5A	0.5073 (10)	0.6611 (4)	0.8020 (8)	0.114 (4)*	0.521 (11)
F5B	0.5873 (11)	0.6970 (5)	0.8583 (11)	0.159 (6)*	0.479 (11)
F6A	0.4626 (10)	0.6135 (4)	0.9137 (10)	0.151 (6)*	0.521 (11)
F6B	0.4669 (11)	0.6367 (5)	0.8169 (11)	0.145 (6)*	0.479 (11)
F7	0.5794 (6)	0.7198 (2)	0.2430 (5)	0.162 (3)	
F8	0.5803 (6)	0.6935 (2)	0.3865 (5)	0.164 (3)	
F9	0.4548 (5)	0.6735 (2)	0.2564 (7)	0.211 (4)	
F10	0.9074 (6)	0.7274 (2)	0.4005 (6)	0.177 (3)	
F11	1.0542 (6)	0.7056 (3)	0.4942 (14)	0.338 (9)	
F12	0.9436 (12)	0.7244 (3)	0.5517 (7)	0.299 (8)	
O1	0.8632 (4)	0.68468 (18)	1.1705 (4)	0.0765 (14)	
O2	0.6574 (4)	0.5836 (2)	0.8468 (4)	0.0814 (15)	
O3	0.6739 (4)	0.63813 (18)	0.2069 (4)	0.0691 (13)	
O4	0.9458 (4)	0.62013 (19)	0.5577 (4)	0.0741 (14)	
N1	0.9449 (4)	0.6561 (2)	1.0509 (4)	0.0549 (13)	
N2	0.7224 (4)	0.6180 (2)	1.0133 (4)	0.0586 (14)	
H2	0.7120	0.6423	1.0532	0.070*	
N3	0.6421 (4)	0.59377 (19)	0.3416 (4)	0.0469 (12)	
N4	0.8673 (4)	0.62733 (19)	0.3792 (4)	0.0566 (14)	
H4A	0.8491	0.6483	0.3263	0.068*	
C1	0.9220 (5)	0.6028 (2)	1.0696 (5)	0.0525 (16)	
C2	0.8139 (5)	0.5849 (3)	1.0511 (5)	0.0513 (16)	
C3	0.7989 (6)	0.5327 (3)	1.0715 (5)	0.0611 (18)	
C4	0.8881 (7)	0.4992 (3)	1.1054 (5)	0.070 (2)	
H4	0.8766	0.4644	1.1166	0.084*	
C5	0.9932 (6)	0.5177 (3)	1.1222 (5)	0.0652 (19)	
C6	1.0119 (5)	0.5689 (3)	1.1040 (5)	0.0579 (17)	
H6	1.0843	0.5808	1.1147	0.069*	

C7	1.0306 (5)	0.6649 (2)	0.9997 (6)	0.0573 (17)
C8	1.1401 (6)	0.6728 (3)	1.0641 (6)	0.074 (2)
C9	1.2206 (6)	0.6760 (3)	1.0128 (8)	0.095 (3)
H9	1.2948	0.6812	1.0528	0.114*
C10	1.1940 (8)	0.6718 (3)	0.9051 (9)	0.103 (3)
H10	1.2500	0.6738	0.8732	0.124*
C11	1.0876 (8)	0.6649 (3)	0.8453 (7)	0.080 (2)
H11	1.0714	0.6621	0.7722	0.096*
C12	1.0007 (6)	0.6616 (3)	0.8890 (6)	0.0630 (18)
C13	1.1728 (6)	0.6771 (4)	1.1828 (7)	0.106 (3)
H13A	1.1074	0.6741	1.2050	0.159*
H13B	1.2076	0.7099	1.2047	0.159*
H13C	1.2243	0.6499	1.2145	0.159*
C14	0.8816 (6)	0.6571 (3)	0.8204 (6)	0.078 (2)
H14A	0.8460	0.6903	0.8146	0.118*
H14B	0.8431	0.6329	0.8515	0.118*
H14C	0.8793	0.6453	0.7512	0.118*
C15	0.9066 (5)	0.6932 (3)	1.1019 (6)	0.0617 (18)
C16	0.9122 (9)	0.7490 (3)	1.0691 (10)	0.098 (3)
C17	0.6509 (6)	0.6122 (3)	0.9154 (7)	0.067 (2)
C18	0.5454 (11)	0.6493 (5)	0.8966 (8)	0.141 (4)
C21	0.7288 (5)	0.5570 (2)	0.3451 (5)	0.0487 (15)
C22	0.8390 (5)	0.5743 (2)	0.3636 (5)	0.0485 (15)
C23	0.9209 (5)	0.5379 (3)	0.3665 (5)	0.0548 (17)
C24	0.8976 (5)	0.4854 (3)	0.3567 (5)	0.0568 (17)
H24	0.9537	0.4614	0.3600	0.068*
C25	0.7897 (6)	0.4697 (2)	0.3419 (5)	0.0591 (18)
C26	0.7051 (5)	0.5050 (2)	0.3352 (5)	0.0578 (17)
H26	0.6322	0.4936	0.3239	0.069*
C27	0.5530 (5)	0.5789 (2)	0.3851 (5)	0.0511 (16)
C28	0.4532 (5)	0.5614 (3)	0.3154 (6)	0.0628 (18)
C29	0.3685 (6)	0.5507 (3)	0.3591 (7)	0.077 (2)
H29	0.3002	0.5388	0.3148	0.093*
C30	0.3816 (7)	0.5568 (3)	0.4637 (7)	0.091 (3)
H30	0.3227	0.5498	0.4900	0.109*
C31	0.4825 (7)	0.5734 (3)	0.5305 (6)	0.079 (2)
H31	0.4915	0.5773	0.6023	0.095*
C32	0.5719 (5)	0.5844 (3)	0.4927 (6)	0.0625 (18)
C33	0.4333 (6)	0.5534 (3)	0.1979 (5)	0.083 (2)
H33A	0.4105	0.5854	0.1611	0.125*
H33B	0.3757	0.5280	0.1716	0.125*
H33C	0.5010	0.5416	0.1866	0.125*
C34	0.6809 (6)	0.6025 (3)	0.5675 (5)	0.084 (2)
H34A	0.6995	0.6356	0.5448	0.126*

H34B	0.7385	0.5781	0.5681	0.126*
H34C	0.6748	0.6055	0.6376	0.126*
C35	0.6281 (5)	0.6341 (3)	0.2738 (5)	0.0545 (17)
C36	0.5597 (7)	0.6799 (3)	0.2900 (8)	0.082 (2)
C37	0.9225 (6)	0.6448 (3)	0.4769 (7)	0.0631 (19)
C38	0.9498 (10)	0.7009 (4)	0.4771 (9)	0.108 (3)

Atomic displacement parameters (Å^2) for (3)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.0934 (14)	0.0951 (14)	0.0709 (13)	-0.0336 (11)	0.0341 (11)	-0.0093 (11)
Cl2	0.1140 (17)	0.0839 (14)	0.0742 (14)	0.0385 (12)	0.0044 (12)	-0.0032 (11)
Cl3	0.0507 (10)	0.1054 (14)	0.0639 (12)	-0.0009 (9)	0.0185 (9)	-0.0002 (10)
Cl4	0.1005 (15)	0.0628 (11)	0.1043 (17)	-0.0009 (10)	0.0353 (13)	-0.0170 (11)
F1	0.224 (6)	0.071 (3)	0.235 (7)	0.026 (4)	0.157 (6)	0.002 (4)
F2	0.315 (9)	0.074 (4)	0.117 (5)	0.024 (4)	0.063 (6)	0.020 (4)
F3	0.161 (6)	0.088 (4)	0.281 (9)	-0.042 (4)	0.083 (6)	-0.014 (5)
F7	0.238 (7)	0.085 (4)	0.211 (7)	0.053 (4)	0.142 (6)	0.053 (4)
F8	0.271 (8)	0.120 (5)	0.117 (5)	0.093 (5)	0.083 (5)	-0.008 (4)
F9	0.066 (4)	0.116 (5)	0.413 (13)	0.028 (3)	0.019 (5)	-0.034 (6)
F10	0.256 (8)	0.076 (4)	0.132 (5)	-0.062 (4)	-0.036 (5)	0.024 (4)
F11	0.114 (6)	0.095 (5)	0.77 (3)	-0.032 (4)	0.089 (10)	0.052 (10)
F12	0.63 (2)	0.099 (5)	0.122 (6)	-0.086 (9)	0.049 (9)	-0.042 (5)
O1	0.090 (3)	0.083 (3)	0.068 (3)	-0.015 (3)	0.041 (3)	-0.018 (3)
O2	0.090 (4)	0.093 (4)	0.058 (3)	0.008 (3)	0.017 (3)	-0.016 (3)
O3	0.068 (3)	0.087 (3)	0.057 (3)	0.004 (2)	0.026 (3)	0.017 (3)
O4	0.084 (4)	0.076 (3)	0.056 (3)	0.005 (3)	0.013 (3)	-0.003 (3)
N1	0.059 (3)	0.058 (3)	0.051 (4)	-0.004 (3)	0.022 (3)	-0.003 (3)
N2	0.053 (3)	0.072 (4)	0.051 (4)	0.001 (3)	0.015 (3)	-0.012 (3)
N3	0.044 (3)	0.056 (3)	0.042 (3)	0.005 (2)	0.015 (3)	0.006 (3)
N4	0.057 (3)	0.056 (3)	0.052 (4)	-0.006 (3)	0.012 (3)	0.005 (3)
C1	0.056 (4)	0.058 (4)	0.044 (4)	0.004 (3)	0.015 (3)	0.000 (3)
C2	0.050 (4)	0.063 (4)	0.044 (4)	-0.003 (3)	0.019 (3)	-0.007 (3)
C3	0.069 (5)	0.074 (5)	0.043 (4)	-0.015 (4)	0.023 (4)	-0.007 (4)
C4	0.102 (6)	0.062 (5)	0.050 (5)	0.009 (5)	0.028 (5)	0.002 (4)
C5	0.073 (5)	0.071 (5)	0.050 (5)	0.012 (4)	0.017 (4)	0.000 (4)
C6	0.057 (4)	0.076 (5)	0.038 (4)	0.002 (4)	0.012 (3)	-0.001 (4)
C7	0.056 (4)	0.063 (4)	0.059 (5)	-0.004 (3)	0.027 (4)	0.001 (4)
C8	0.056 (5)	0.088 (5)	0.075 (6)	-0.007 (4)	0.017 (4)	0.008 (4)
C9	0.057 (5)	0.124 (7)	0.106 (8)	-0.016 (5)	0.028 (5)	0.009 (6)
C10	0.094 (7)	0.119 (8)	0.120 (9)	-0.001 (6)	0.067 (7)	0.009 (7)
C11	0.098 (6)	0.079 (5)	0.080 (6)	0.006 (5)	0.052 (6)	0.011 (4)
C12	0.069 (5)	0.064 (4)	0.062 (5)	-0.007 (4)	0.027 (4)	0.000 (4)
C13	0.073 (6)	0.138 (8)	0.092 (7)	-0.020 (5)	0.003 (5)	-0.005 (6)
C14	0.084 (6)	0.078 (5)	0.067 (5)	-0.006 (4)	0.015 (5)	0.010 (4)

C15	0.065 (4)	0.062 (4)	0.063 (5)	-0.016 (4)	0.028 (4)	-0.015 (4)
C16	0.107 (8)	0.067 (6)	0.128 (9)	-0.008 (5)	0.047 (7)	-0.005 (6)
C17	0.048 (4)	0.077 (5)	0.075 (6)	0.010 (4)	0.019 (5)	0.004 (5)
C18	0.177 (12)	0.167 (11)	0.065 (7)	-0.033 (10)	0.019 (8)	-0.050 (8)
C21	0.053 (4)	0.054 (4)	0.040 (4)	0.004 (3)	0.016 (3)	-0.004 (3)
C22	0.053 (4)	0.057 (4)	0.039 (4)	-0.005 (3)	0.020 (3)	0.001 (3)
C23	0.050 (4)	0.074 (5)	0.040 (4)	0.004 (3)	0.014 (3)	0.002 (3)
C24	0.060 (4)	0.070 (5)	0.041 (4)	0.010 (4)	0.018 (4)	-0.001 (4)
C25	0.076 (5)	0.052 (4)	0.052 (5)	0.000 (4)	0.023 (4)	-0.004 (3)
C26	0.066 (4)	0.060 (4)	0.053 (4)	-0.004 (4)	0.026 (4)	-0.011 (4)
C27	0.052 (4)	0.060 (4)	0.048 (5)	-0.002 (3)	0.025 (3)	-0.001 (3)
C28	0.057 (4)	0.071 (5)	0.062 (5)	-0.008 (4)	0.020 (4)	-0.005 (4)
C29	0.049 (4)	0.109 (6)	0.072 (6)	-0.016 (4)	0.016 (4)	0.009 (5)
C30	0.068 (6)	0.129 (7)	0.087 (7)	-0.005 (5)	0.041 (5)	0.017 (6)
C31	0.075 (5)	0.121 (7)	0.051 (5)	0.006 (5)	0.033 (5)	0.008 (5)
C32	0.056 (4)	0.082 (5)	0.048 (5)	0.000 (4)	0.016 (4)	0.004 (4)
C33	0.076 (5)	0.112 (6)	0.053 (5)	-0.009 (5)	0.008 (4)	-0.015 (5)
C34	0.076 (5)	0.121 (7)	0.053 (5)	0.000 (5)	0.018 (4)	-0.005 (5)
C35	0.053 (4)	0.068 (5)	0.041 (4)	0.000 (3)	0.011 (3)	0.002 (4)
C36	0.087 (6)	0.067 (5)	0.101 (7)	0.016 (5)	0.044 (6)	0.012 (5)
C37	0.059 (5)	0.061 (5)	0.063 (6)	-0.006 (4)	0.010 (4)	-0.005 (4)
C38	0.134 (9)	0.091 (7)	0.081 (8)	-0.059 (7)	0.007 (7)	-0.011 (6)

Geometric parameters (Å, º) for (3)

Cl1—C3	1.724 (7)	C8—C9	1.387 (10)
Cl2—C5	1.721 (7)	C8—C13	1.503 (10)
Cl3—C23	1.723 (6)	C9—C10	1.366 (11)
Cl4—C25	1.717 (6)	C9—H9	0.9300
F1—C16	1.282 (9)	C10—C11	1.340 (11)
F2—C16	1.295 (11)	C10—H10	0.9300
F3—C16	1.295 (10)	C11—C12	1.391 (9)
F4A—C18	1.252 (13)	C11—H11	0.9300
F4B—C18	1.234 (13)	C12—C14	1.497 (9)
F5A—C18	1.234 (13)	C13—H13A	0.9600
F5B—C18	1.492 (16)	C13—H13B	0.9600
F6A—C18	1.464 (15)	C13—H13C	0.9600
F6B—C18	1.246 (14)	C14—H14A	0.9600
F7—C36	1.271 (8)	C14—H14B	0.9600
F8—C36	1.275 (9)	C14—H14C	0.9600
F9—C36	1.266 (9)	C15—C16	1.515 (11)
F10—C38	1.205 (10)	C17—C18	1.594 (13)
F11—C38	1.269 (11)	C21—C26	1.378 (8)
F12—C38	1.185 (12)	C21—C22	1.404 (8)
O1—C15	1.217 (7)	C22—C23	1.388 (8)

O2—C17	1.196 (8)	C23—C24	1.388 (8)
O3—C35	1.204 (7)	C24—C25	1.373 (8)
O4—C37	1.203 (8)	C24—H24	0.9300
N1—C15	1.348 (8)	C25—C26	1.385 (8)
N1—C1	1.445 (7)	C26—H26	0.9300
N1—C7	1.460 (7)	C27—C32	1.380 (8)
N2—C17	1.339 (9)	C27—C28	1.386 (8)
N2—C2	1.397 (7)	C28—C29	1.390 (9)
N2—H2	0.8600	C28—C33	1.514 (9)
N3—C35	1.353 (7)	C29—C30	1.355 (10)
N3—C21	1.438 (7)	C29—H29	0.9300
N3—C27	1.463 (7)	C30—C31	1.372 (10)
N4—C37	1.344 (8)	C30—H30	0.9300
N4—C22	1.418 (7)	C31—C32	1.395 (9)
N4—H4A	0.8600	C31—H31	0.9300
C1—C2	1.385 (8)	C32—C34	1.498 (9)
C1—C6	1.392 (8)	C33—H33A	0.9600
C2—C3	1.403 (9)	C33—H33B	0.9600
C3—C4	1.379 (9)	C33—H33C	0.9600
C4—C5	1.359 (9)	C34—H34A	0.9600
C4—H4	0.9300	C34—H34B	0.9600
C5—C6	1.380 (9)	C34—H34C	0.9600
C6—H6	0.9300	C35—C36	1.518 (10)
C7—C12	1.400 (9)	C37—C38	1.493 (11)
C7—C8	1.394 (9)		

C15—N1—C1	118.3 (5)	F4A—C18—F6A	108.7 (11)
C15—N1—C7	123.6 (5)	F6B—C18—F5B	101.4 (12)
C1—N1—C7	116.3 (5)	F4B—C18—F5B	105.9 (11)
C17—N2—C2	120.8 (6)	F5A—C18—C17	110.5 (10)
C17—N2—H2	119.6	F6B—C18—C17	112.3 (11)
C2—N2—H2	119.6	F4B—C18—C17	117.3 (10)
C35—N3—C21	118.2 (5)	F4A—C18—C17	113.5 (10)
C35—N3—C27	120.5 (5)	F6A—C18—C17	101.1 (10)
C21—N3—C27	118.7 (5)	F5B—C18—C17	100.8 (10)
C37—N4—C22	119.8 (5)	C26—C21—C22	120.0 (6)
C37—N4—H4A	120.1	C26—C21—N3	120.2 (5)
C22—N4—H4A	120.1	C22—C21—N3	119.7 (5)
C2—C1—C6	120.1 (6)	C23—C22—C21	118.3 (6)
C2—C1—N1	121.7 (6)	C23—C22—N4	120.2 (5)
C6—C1—N1	118.2 (6)	C21—C22—N4	121.5 (5)
C1—C2—N2	120.9 (6)	C22—C23—C24	121.9 (6)
C1—C2—C3	118.1 (6)	C22—C23—Cl3	119.3 (5)
N2—C2—C3	121.0 (6)	C24—C23—Cl3	118.8 (5)

C4—C3—C2	121.6 (6)	C25—C24—C23	118.3 (6)
C4—C3—Cl1	119.4 (6)	C25—C24—H24	120.8
C2—C3—Cl1	119.0 (6)	C23—C24—H24	120.8
C5—C4—C3	118.9 (7)	C24—C25—C26	121.4 (6)
C5—C4—H4	120.6	C24—C25—Cl4	119.5 (5)
C3—C4—H4	120.6	C26—C25—Cl4	119.1 (5)
C4—C5—C6	121.4 (7)	C25—C26—C21	120.0 (6)
C4—C5—Cl2	119.9 (6)	C25—C26—H26	120.0
C6—C5—Cl2	118.7 (6)	C21—C26—H26	120.0
C5—C6—C1	119.8 (6)	C32—C27—C28	123.6 (6)
C5—C6—H6	120.1	C32—C27—N3	118.4 (6)
C1—C6—H6	120.1	C28—C27—N3	118.0 (6)
C12—C7—C8	123.0 (6)	C27—C28—C29	116.2 (7)
C12—C7—N1	118.8 (6)	C27—C28—C33	124.0 (6)
C8—C7—N1	118.1 (6)	C29—C28—C33	119.9 (7)
C9—C8—C7	116.2 (7)	C30—C29—C28	122.5 (7)
C9—C8—C13	120.3 (7)	C30—C29—H29	118.7
C7—C8—C13	123.4 (7)	C28—C29—H29	118.7
C10—C9—C8	121.9 (8)	C29—C30—C31	119.5 (7)
C10—C9—H9	119.0	C29—C30—H30	120.3
C8—C9—H9	119.0	C31—C30—H30	120.3
C11—C10—C9	120.4 (8)	C30—C31—C32	121.3 (7)
C11—C10—H10	119.8	C30—C31—H31	119.3
C9—C10—H10	119.8	C32—C31—H31	119.3
C10—C11—C12	122.1 (8)	C27—C32—C31	116.8 (7)
C10—C11—H11	118.9	C27—C32—C34	123.0 (6)
C12—C11—H11	118.9	C31—C32—C34	120.1 (7)
C7—C12—C11	116.3 (7)	C28—C33—H33A	109.5
C7—C12—C14	122.3 (6)	C28—C33—H33B	109.5
C11—C12—C14	121.3 (7)	H33A—C33—H33B	109.5
C8—C13—H13A	109.5	C28—C33—H33C	109.5
C8—C13—H13B	109.5	H33A—C33—H33C	109.5
H13A—C13—H13B	109.5	H33B—C33—H33C	109.5
C8—C13—H13C	109.5	C32—C34—H34A	109.5
H13A—C13—H13C	109.5	C32—C34—H34B	109.5
H13B—C13—H13C	109.5	H34A—C34—H34B	109.5
C12—C14—H14A	109.5	C32—C34—H34C	109.5
C12—C14—H14B	109.5	H34A—C34—H34C	109.5
H14A—C14—H14B	109.5	H34B—C34—H34C	109.5
C12—C14—H14C	109.5	O3—C35—N3	124.4 (6)
H14A—C14—H14C	109.5	O3—C35—C36	117.3 (7)
H14B—C14—H14C	109.5	N3—C35—C36	118.0 (6)
O1—C15—N1	123.9 (6)	F7—C36—F9	105.9 (8)
O1—C15—C16	117.4 (7)	F7—C36—F8	104.9 (8)

N1—C15—C16	118.7 (7)	F9—C36—F8	104.7 (8)
F3—C16—F1	105.3 (9)	F7—C36—C35	111.1 (7)
F3—C16—F2	103.8 (9)	F9—C36—C35	115.1 (8)
F1—C16—F2	107.8 (9)	F8—C36—C35	114.3 (7)
F3—C16—C15	114.4 (9)	O4—C37—N4	126.2 (7)
F1—C16—C15	111.9 (8)	O4—C37—C38	121.5 (8)
F2—C16—C15	113.0 (8)	N4—C37—C38	112.3 (8)
O2—C17—N2	128.5 (7)	F12—C38—F10	106.6 (12)
O2—C17—C18	120.3 (8)	F12—C38—F11	97.7 (11)
N2—C17—C18	111.2 (7)	F10—C38—F11	105.0 (11)
F6B—C18—F4B	116.2 (13)	F12—C38—C37	115.2 (10)
F5A—C18—F4A	117.2 (13)	F10—C38—C37	120.8 (9)
F5A—C18—F6A	104.1 (10)	F11—C38—C37	108.7 (10)

C15—N1—C1—C2	57.1 (8)	N2—C17—C18—F6A	-99.3 (8)
C7—N1—C1—C2	-137.7 (6)	O2—C17—C18—F5B	-92.9 (10)
C15—N1—C1—C6	-124.7 (6)	N2—C17—C18—F5B	87.9 (9)
C7—N1—C1—C6	40.5 (8)	C35—N3—C21—C26	-128.4 (6)
C6—C1—C2—N2	-177.9 (5)	C27—N3—C21—C26	33.6 (8)
N1—C1—C2—N2	0.2 (9)	C35—N3—C21—C22	54.4 (7)
C6—C1—C2—C3	2.1 (9)	C27—N3—C21—C22	-143.6 (6)
N1—C1—C2—C3	-179.8 (5)	C26—C21—C22—C23	2.9 (9)
C17—N2—C2—C1	111.9 (7)	N3—C21—C22—C23	-180.0 (5)
C17—N2—C2—C3	-68.1 (8)	C26—C21—C22—N4	-177.0 (6)
C1—C2—C3—C4	-2.2 (9)	N3—C21—C22—N4	0.2 (8)
N2—C2—C3—C4	177.7 (6)	C37—N4—C22—C23	-74.0 (8)
C1—C2—C3—Cl1	177.5 (4)	C37—N4—C22—C21	105.9 (7)
N2—C2—C3—Cl1	-2.5 (8)	C21—C22—C23—C24	-3.0 (9)
C2—C3—C4—C5	1.8 (10)	N4—C22—C23—C24	176.8 (6)
Cl1—C3—C4—C5	-177.9 (5)	C21—C22—C23—Cl3	178.3 (4)
C3—C4—C5—C6	-1.3 (10)	N4—C22—C23—Cl3	-1.8 (8)
C3—C4—C5—Cl2	179.2 (5)	C22—C23—C24—C25	1.1 (9)
C4—C5—C6—C1	1.1 (10)	Cl3—C23—C24—C25	179.8 (5)
Cl2—C5—C6—C1	-179.3 (5)	C23—C24—C25—C26	1.0 (9)
C2—C1—C6—C5	-1.6 (9)	C23—C24—C25—Cl4	-179.9 (5)
N1—C1—C6—C5	-179.7 (6)	C24—C25—C26—C21	-1.1 (10)
C15—N1—C7—C12	-112.6 (7)	Cl4—C25—C26—C21	179.8 (5)
C1—N1—C7—C12	83.1 (7)	C22—C21—C26—C25	-0.9 (9)
C15—N1—C7—C8	71.5 (8)	N3—C21—C26—C25	-178.0 (5)
C1—N1—C7—C8	-92.8 (7)	C35—N3—C27—C32	-114.3 (7)

C12—C7—C8—C9	-1.7 (11)	C21—N3—C27—C32	84.1 (7)
N1—C7—C8—C9	174.0 (6)	C35—N3—C27—C28	64.0 (8)
C12—C7—C8—C13	179.1 (7)	C21—N3—C27—C28	-97.6 (7)
N1—C7—C8—C13	-5.2 (10)	C32—C27—C28—C29	2.1 (10)
C7—C8—C9—C10	0.2 (12)	N3—C27—C28—C29	-176.2 (6)
C13—C8—C9—C10	179.4 (8)	C32—C27—C28—C33	-177.6 (7)
C8—C9—C10—C11	0.7 (14)	N3—C27—C28—C33	4.1 (10)
C9—C10—C11—C12	0.0 (13)	C27—C28—C29—C30	-0.1 (11)
C8—C7—C12—C11	2.3 (10)	C33—C28—C29—C30	179.6 (7)
N1—C7—C12—C11	-173.4 (6)	C28—C29—C30—C31	-1.1 (13)
C8—C7—C12—C14	-175.2 (6)	C29—C30—C31—C32	0.4 (13)
N1—C7—C12—C14	9.1 (9)	C28—C27—C32—C31	-2.7 (10)
C10—C11—C12—C7	-1.4 (11)	N3—C27—C32—C31	175.5 (6)
C10—C11—C12—C14	176.2 (8)	C28—C27—C32—C34	178.9 (7)
C1—N1—C15—O1	7.4 (10)	N3—C27—C32—C34	-2.9 (10)
C7—N1—C15—O1	-156.7 (6)	C30—C31—C32—C27	1.4 (11)
C1—N1—C15—C16	-169.5 (7)	C30—C31—C32—C34	179.9 (7)
C7—N1—C15—C16	26.5 (10)	C21—N3—C35—O3	9.6 (9)
O1—C15—C16—F3	109.7 (10)	C27—N3—C35—O3	-152.1 (6)
N1—C15—C16—F3	-73.2 (11)	C21—N3—C35—C36	-163.9 (6)
O1—C15—C16—F1	-9.9 (13)	C27—N3—C35—C36	34.4 (9)
N1—C15—C16—F1	167.1 (8)	O3—C35—C36—F7	-12.8 (11)
O1—C15—C16—F2	-131.8 (9)	N3—C35—C36—F7	161.2 (7)
N1—C15—C16—F2	45.3 (11)	O3—C35—C36—F9	107.6 (9)
C2—N2—C17—O2	-6.8 (11)	N3—C35—C36—F9	-78.5 (10)
C2—N2—C17—C18	172.3 (7)	O3—C35—C36—F8	-131.2 (8)
O2—C17—C18—F5A	-30.0 (15)	N3—C35—C36—F8	42.8 (10)
N2—C17—C18—F5A	150.8 (10)	C22—N4—C37—O4	-5.3 (10)
O2—C17—C18—F6B	14.3 (16)	C22—N4—C37—C38	177.2 (7)
N2—C17—C18—F6B	-164.9 (11)	O4—C37—C38—F12	-34.8 (16)
O2—C17—C18—F4B	152.8 (11)	N4—C37—C38—F12	142.9 (12)
N2—C17—C18—F4B	-26.4 (14)	O4—C37—C38—F10	-165.1 (10)
O2—C17—C18—F4A	-164.0 (10)	N4—C37—C38—F10	12.6 (15)
N2—C17—C18—F4A	16.8 (14)	O4—C37—C38—F11	73.6 (15)
O2—C17—C18—F6A	79.8 (10)	N4—C37—C38—F11	-108.7 (12)

Hydrogen-bond geometry (Å, º) for (3)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
N2—H2···O1	0.86	2.32	2.859 (7)	121
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
N4—H4*A*···O1^{ii}	0.86	2.33	3.128 (7)	155
N2—H2···O3^{iii}	0.86	2.24	2.866 (7)	130
N2—H2···O1	0.86	2.32	2.859 (7)	121
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
N2—H2···O1	0.86	2.32	2.859 (7)	121
N2—H2···F4*A*	0.86	2.21	2.602 (12)	108
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
N2—H2···O1	0.86	2.32	2.859 (7)	121
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
N4—H4*A*···O1^{ii}	0.86	2.33	3.128 (7)	155
N2—H2···O3^{iii}	0.86	2.24	2.866 (7)	130
N2—H2···O1	0.86	2.32	2.859 (7)	121
N2—H2···O1	0.86	2.32	2.859 (7)	121
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N2—H2···O1	0.86	2.32	2.859 (7)	121
N2—H2···O3^{iii}	0.86	2.24	2.866 (7)	130
N4—H4*A*···O1^{ii}	0.86	2.33	3.128 (7)	155
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N2—H2···O1	0.86	2.32	2.859 (7)	121
N2—H2···O3^{iii}	0.86	2.24	2.866 (7)	130
N4—H4*A*···O1^{ii}	0.86	2.33	3.128 (7)	155
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148
N2—H2···O1	0.86	2.32	2.859 (7)	121
N4—H4*A*···O3	0.86	2.30	2.788 (7)	117
C24—H24···O4^{i}	0.93	2.53	3.353 (8)	148

Symmetry codes: (i) -*x*+2, -*y*+1, -*z*+1; (ii) *x*, *y*, *z*-1; (iii) *x*, *y*, *z*+1.

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RESEARCH ARTICLE

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Synthesis of various 1-alkylbenzimidazole derivatives directly from 2-alkylaminonitroarenes via a two-step, one-pot procedure

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Abstract

N-Alkyl-2-nitroanilines deoxygenated with tributylphosphine form intermediate 2-(alkylamino)aryliminophosphoranes, which were subjected, without isolation, to various cyclocondensation reactions with CS_2, CO_2, alkyl isocyanates, acyl chlorides, anhydrides, or esters. A simple, convenient, one-pot procedure provided derivatives of unsymmetrically substituted 1-alkylbenzimidazoles functionalized at C2 in good to excellent yields. The method does not require the use of metals, sensitive catalysts, or pressure.

1 | INTRODUCTION

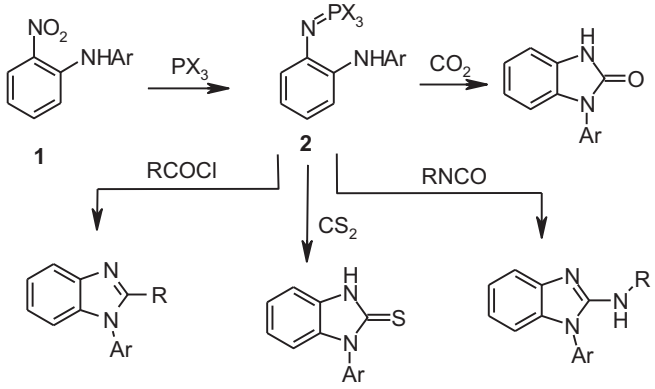
Diversely substituted benzimidazoles are fragments of important structures of biologically active compounds and existing or considered pharmaceutical products [1, 2]. In recent years, we have presented a convenient approach to their synthesis from simple nitroarenes via 2-arylaminoiminophosphoranes. The method allowed the synthesis of diverse 2-substituted benzimidazoles such as 2-amino or 2-alkylbenzimidazoles, 2-benzimidazolones, and the corresponding 2-thiones (Scheme 1) [3–7].

However, the developed method was limited to N-aryl products. The reason was that 2-aminonitrosoarenes, a convenient source of iminophosphoranes, could be readily obtained by nucleophilic substitution of the *ortho* hydrogen (S_N^H) in nitroarenes with arylamines in the presence of strong bases. However, this reaction did not proceed in the case of alkylamines. Thus, 2-(alkylamino) aryliminophosphoranes were not available using this method. Further research showed that 2-(arylamino)aryliminophosphoranes can be obtained from appropriate 2-arylaminonitroarenes in a reductive process caused by trivalent phosphorus compounds [8]. Now, we decided to examine whether this approach may also be suitable for N-alkyl derivatives to open a new way for the synthesis of 1-alkylbenzimidazoles. This seemed worthy of investigation because the literature on the biological activity of benzimidazoles shows that, apart from 1-unsubstituted derivatives, those with an alkyl or aralkyl group on the nitrogen atom are clearly more represented than those substituted with any aryl group [1]. In the particular case of 2-thiobenzimidazole **D** (Figure 1), a direct comparison of compounds differing in the substituent at N-1 showed a much stronger activity of N-alkyl than N-aryl derivatives [9].

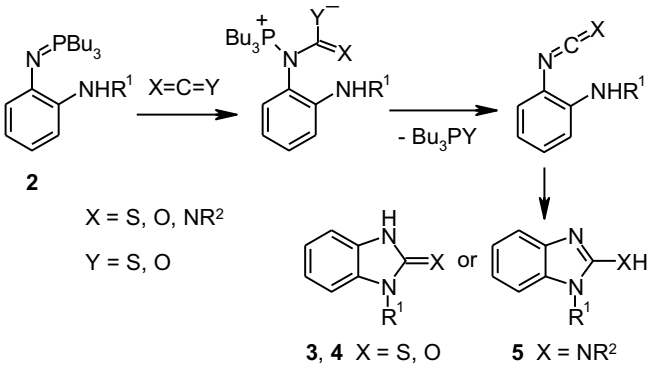
2 | RESULTS AND DISCUSSION

The success of the projected method relies on the efficient deoxygenation of the nitro group in 2-alkylaminonitroarenes **1** by phosphorous (III) compounds, leading to the formation of the corresponding iminophosphoranes **2**.

Our initial approach was to obtain (2-alkylamino)aryliminophosphoranes by deoxygenation of the corresponding *N*-alkyl-2-nitroanilines with triphenyl or tributylphosphines,



SCHEME 1 Formation of *N*-[2-(arylamino)phenyl] iminophosphoranes (**2**) [8] and their use for the synthesis of 1-arylbenzimidazole derivatives, as described previously [3–7].



SCHEME 2 General scheme for the use of iminophosphoranes in the synthesis of 2-functionalized N-alkyl benzimidazoles **3**, **4**, and **5**.

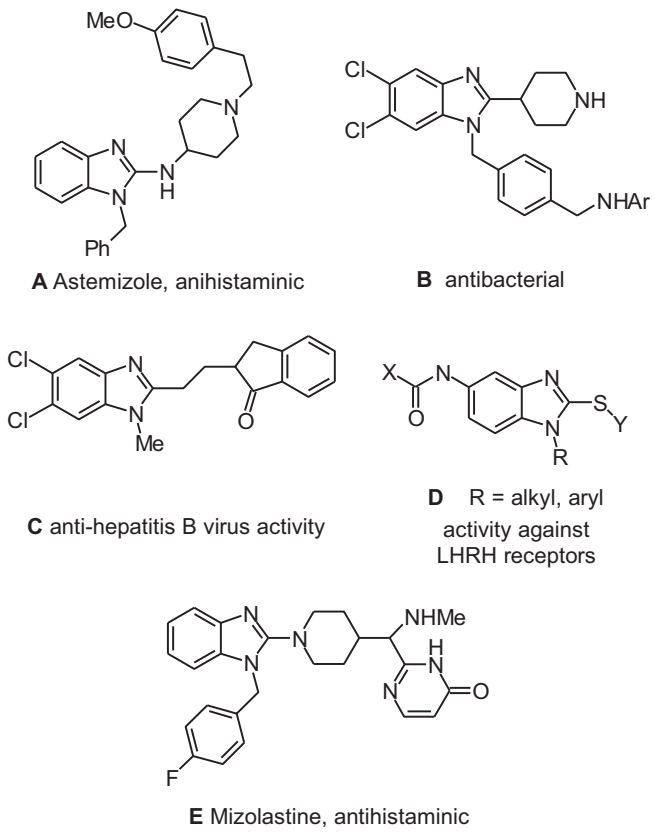
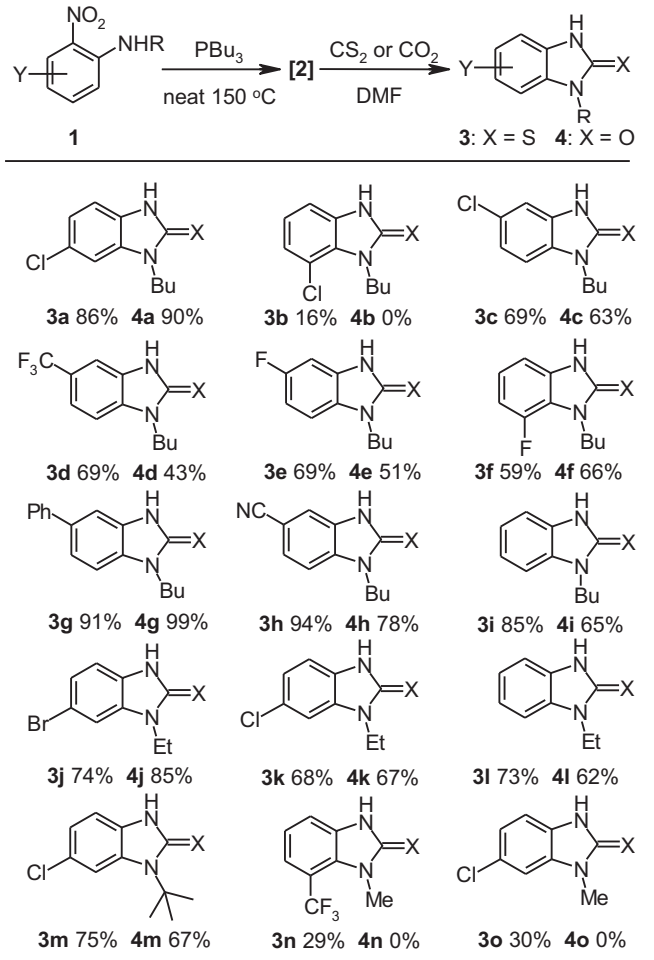


FIGURE 1 Illustrative examples of benzimidazoles showing pharmacological activity.



SCHEME 3 Cyclocondensation of intermediate **2** with CS_2 and CO_2. Total isolated yields based on **1** are given.

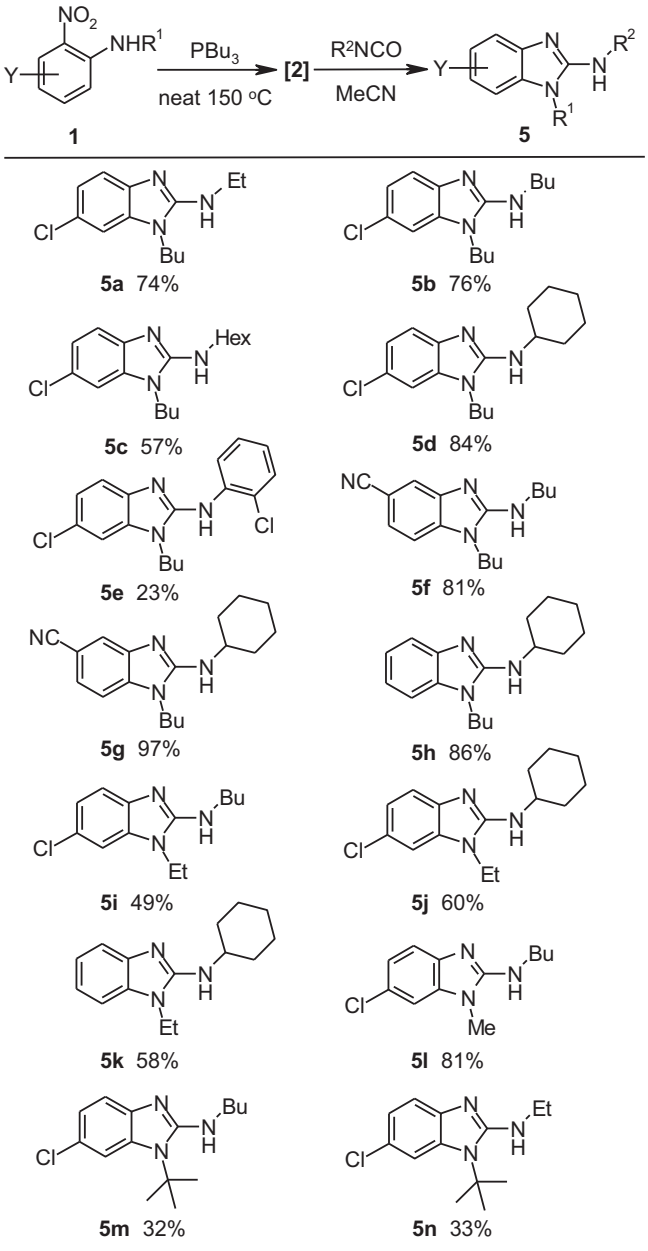
since two examples of target iminophosphoranes have been obtained previously [8]. The reactions of the model *N*-butyl-*N*-(5-chloro-2-nitrophenyl)amine (**1a**) with PPh_3 and PBu_3, carried out under previously described conditions [8], were successful, but the relevant products (**2a** and **2b**, respectively) were found to be unstable and difficult to isolate in pure form. The yield of the crude product was rather low (ca. 34% in both cases) and decreased with each subsequent purification attempt. Thus, they were identified based on high resolution mass spectrometry (HRMS) measurements and the NMR spectra of the crude compounds. The projected syntheses of benzimidazoles were decided to be performed

without the isolation of the intermediate iminophosphoranes. Based on our previous experiments, the heating of an excess of PBu_3 at 150°C in an ampoule for 24 h was chosen as the reaction condition. The formation of **2** was observed by thin layer chromatography (TLC), but the intermediate was not isolated. Instead, the crude product was subjected to further transformations without purification. This procedure was found as a convenient alternative for the usual two-step procedure in the synthesis of dibenzodiazepine derivatives via (2-arylamino)aryliminophosphoranes [10]. It also turned out to be right in this case, as the final results obtained from **1a** (i.e., **3a** and **4a**) were much better than might be predicted on the basis of the combined yield of the two-step reaction via the isolated iminophosphoranes **2** (Scheme 2).

It is noteworthy that the formation of **2** from appropriate nitroarenes is believed to occur via deoxygenation of the nitro group, leading to the intermediate nitrene, which reacts with trialkylphosphine to give the final iminophosphorane. However, when an alkyl group is attached to the *ortho*-amine nitrogen, alternative processes take place, the major one being the insertion of the nitrene to the C–H bond of the alkyl group, leading to benzimidazole system [8]. This process was previously found in the reactions of tertiary *ortho*-nitroanilines N-substituted with an aryl and a methyl group, but in the case described here, reactions of secondary *N*-alkyl-2-nitroanilines, it was not observed.

The results of cyclocondensation of **2** with CS_2 and CO_2 (compounds **3** and **4**, respectively) are presented in Scheme 3. While most of the yields are good or at least satisfactory, there are a number of results, which call for explanation. The most striking observation is that in the case where thiobenzimidazoles are formed in low yields (15–30% from **1b**, **1n**, and **1o**), the corresponding benzimidazolones are not formed at all. This must be due to the lower reactivity and availability of gaseous CO_2 compared to CS_2, as the formation of iminophosphorane intermediates in both reactions is believed to be equally effective. Another observation is the interesting structure-dependence of the reaction yields when the reactions of **1a**, **1k**, and **1o** are compared. The starting nitroanilines differ only in N-alkyl groups, and the yields of the reactions increase along with the size of the alkyl. The effect may be related to the privileged conformation of the alkylamino group that is most suitable for the cyclization step as well.

Low yields in the reactions of **1b** and **1o**, which are substituted *ortho* to the alkylamino group, may support this explanation because those substituents (but not the small fluorine in **1f**) force the N-alkyl group to be arranged in a way that makes the cyclization difficult. An even more pronounced steric effect was observed for the large substituent *ortho* to the nitro group (position 3 in **1**), manifested by unsuccessful reactions of *N*-butyl-3-bromo-2-nitroaniline derived iminophosphorane with both CS_2 and CO_2.



SCHEME 4 Cyclocondensation of intermediate **2** with isocyanates. Total isolated yields based on **1** are given.

The synthesis of 1-alkyl-2-aminobenzimidazoles **5** was performed following the procedure applied previously [3] to the reactions of isolated (2-arylamino)aryliminophosphoranes with alkyl- and aryl isocyanates. The reaction initially leads to carbodiimides, susceptible to further conversions [11]. In this case, intramolecular addition of the nucleophilic *ortho*-amine function leads to the 2-aminobenzimidazole framework. The in situ reaction of intermediate **2** with alkyl isocyanates

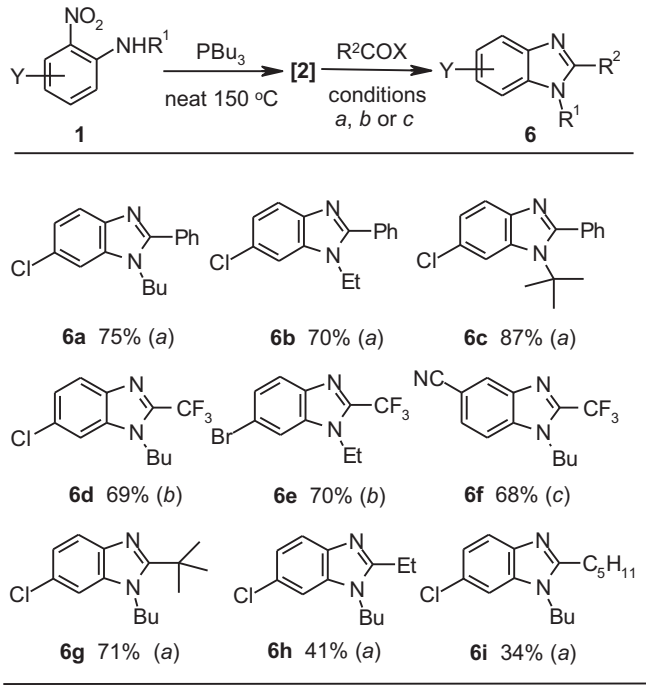
proceeded smoothly in a dichloromethane solution at room temperature, furnishing the expected products mostly in good yields (Scheme 4).

The presented procedure is much simpler and shorter than commonly used methods for synthesizing 2-aminobenzimidazoles, unsymmetrically substituted at five and/or six positions. Synthesis of such compounds, also prepared from N-substituted *ortho*-nitroanilines, involves more steps, including reduction of the nitro group requiring the use of metals in catalytic (Pd and Pt) or over-stoichiometric (Zn, Sn, and Fe) amounts [12].

Phenyliminophosphoranes, possessing an *ortho*-arylamino group are also known to react with some acid chlorides to form 2-alkyl- or 2-arylbenzimidazoles [4].

Thus, we tried to cyclize N-alkyl *ortho*-aminoaryliminophosphoranes **2** with various derivatives of carboxylic acids, including chlorides, anhydrides, and esters. Again, they were generated from appropriate N-alkyl *ortho*-nitroanilines and without isolation, treated with a carboxylic derivative and suitable base (Scheme 5).

The reactions of **1** with aromatic acid chlorides, represented by benzoil chloride, occurred selectively and efficiently (**6a–c**). Also, trifluoroacetic anhydride gave the desired products satisfactorily (**6d–f**). Reactions of chlorides and anhydrides of aliphatic carboxylic acids were more problematic. While certain acid chlorides gave benzimidazoles in moderate yields (**6g–i**), the reactions of acetyl chloride led to a mixture of benzimidazole **6j**



SCHEME 5 Reaction conditions (in parentheses): *a* X = Cl, Et_3N, DCM, r.t.; *b* i) n-BuLi/HMPA, −78°C, ii) CF_3CO_2Et, −78°C → r.t.; *c* X = CF_3CO_2, Et_3N, DCM, r.t.

and N-acetylated arylenediamine **7a**, both in low yields (Scheme 6).

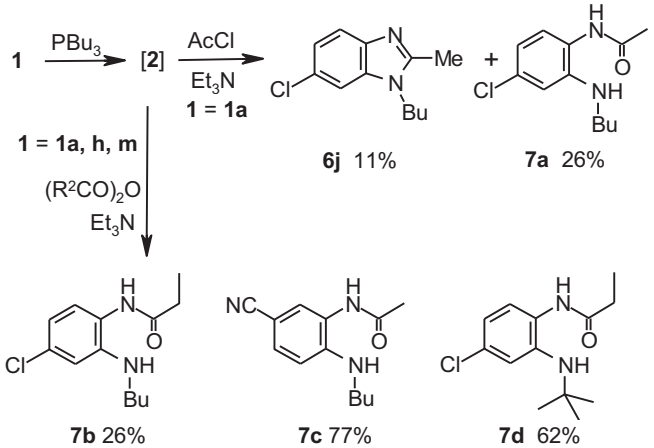
The compounds were isolated from the reaction mixtures using a standard aqueous work-up procedure and column chromatography. In separate experiments, neither a prolonged, 48 h reaction at room temperature nor a 2-day refluxing of the reaction mixture in dichloromethane (DCM) changed the ratio **7a**:**6j** (as measured by the gas chromatography (GC) of the crude product mixtures). Thus, compound **7a** seems to be a product of hydrolysis: a side product rather than an uncyclized intermediate.

Acetyl and propionyl anhydrides reacted with iminophosphoranes, generated from **1a**, **1h**, and **1m**, furnishing only *N*-acylarylenediamines **7b**, **7c**, and **7d**, respectively, in reasonable yields.

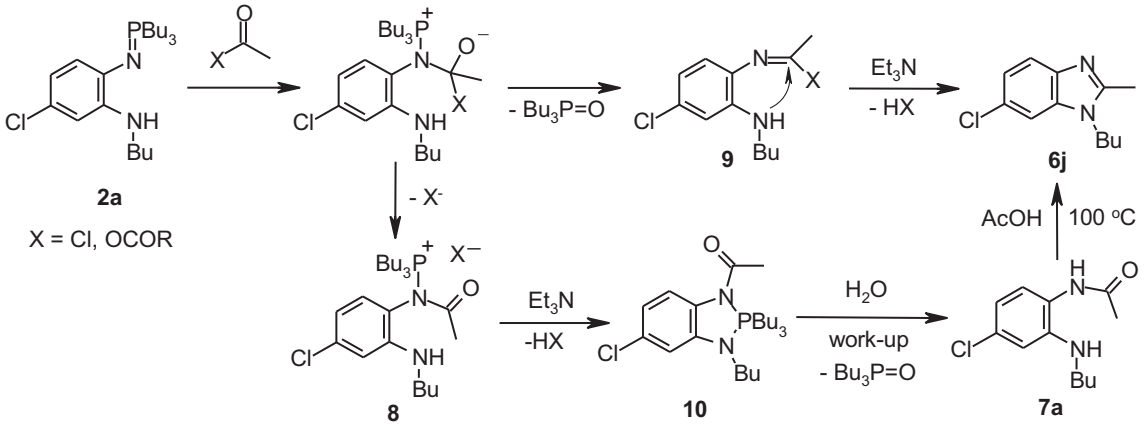
Two possible pathways of the reaction can be considered (Scheme 7). From the same initial adduct, two intermediates, phosphonium salt **8** and imine **9**, can be formed by the elimination of X^- or phosphine oxide, respectively. While very active imidoyl chloride **9** can easily cyclize to imidazole ring, iminophosphonium chloride **8** forms diazaphosphole [13] **10**, which is unable to form **6** but hydrolyzes during work-up, giving **7** as an isolable final product.

Since several factors are involved in the competing processes, predicting the course of a specific reaction and product distribution may be difficult without conducting much broader, focused investigations.

From the synthetic point of view, it is beneficial that the undesired compounds **7**, formed as major or side products, can easily be converted into the expected benzimidazoles, albeit in an additional reaction step. It was shown that **7a**, when subjected to the classical cyclization conditions (AcOH at 100°C, 48 h), furnished **6j** in 78% yield.



SCHEME 6 Formation of *N*-acylphenylenediamines.



SCHEME 7 Exemplified, proposed formation of the observed products **6j** and **7a**.

A strong base used in the reaction conditions *b* (Scheme 5 forced the generation of the carbanionic center on the amine nitrogen atom and its acylation with weaker electrophiles such as esters. This process, followed by aza-Wittig cyclization, can also provide benzimidazole **6** (e.g., formation of **6f**). However, this path is restricted to reactions promoted with strong bases. The formation of **7** under the weak basic conditions proves that the neutral amine nitrogen cannot compete with the ylide nitrogen in reactions with electrophiles. This is in accordance with a suggested course of related reactions described in the literature [14].

3 | CONCLUSION

A synthetic path, leading from *ortho*-nitroanilines to 2-functionalized benzimidazoles, was examined and applied for N-alkyl derivatives. The two-step, one-pot procedure involves the intermediate formation of iminophosphorane, which was subjected to cyclocondensation reactions with CS_2, CO_2, alkyl isocyanates, acyl chlorides, anhydrides, or esters. It was shown that *N*-alkylbenzimidazolones, benzimidazole-2-thiones, 2-alkylamino- and 2-alkylbenzimidazoles can be obtained in satisfactory yields. The method extends a synthetic approach previously developed for N-aryl- or N-alkylbenzimidazole systems, broadly represented among more complex, biologically active compounds.

4 | EXPERIMENTAL SECTION

4.1 | General information

Melting points were recorded in open capillary and are uncorrected. The ^{1}H and ^{13}C NMR spectra of all compounds studied were measured at temperature 298 K in $CDCl_3$ or deuterated dimethyl sulfoxide (DMSO-d_6) solutions with a Varian vnmrs-600 or Varian vnmrs-500 using tetramethylsilane (TMS) as the internal standard. Mass spectra (electron impact [EI], 70 eV) were obtained on an AutoSpec Premier (Waters) spectrometer. For positive and negative electrospray ionization (ESI+ and ESI−) measurements, a Maldi SYNAPT G2-S HDMS (Waters) was used. Accurate mass measurements were obtained using magnetic sector mass analyzer (EI) or turnover frequency analyzer (ESI). Silica gel Merck 60 (230–400 mesh) was used for column chromatography. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl prior to use. Dimethylformamide (DMF) was dried over CaH_2, distilled, and stored over molecular sieves. All commercial reagents were used without additional purification.

The following nitroanilines were obtained according to the published procedures: **1a** [15], **1b** [15], **1c** [12f], **1d** [16], **1j** [17], **1 k** [18], and **1o** [12d]. Nitroanilines **1i** and **1l** were commercial. Preparation of **1e–h**, **1m**, and **1n** and their analytical data are described in Supporting Information.

4.2 | General procedure for the synthesis of 2-(alkylamino) phenyliminophosphoranes 2

An ampoule, equipped with a Teflon stopcock, was filled with nitroaniline **1** (2.0 mmol) and *n*-Bu_3P (2.4 mL) and heated at 150°C for 24 h. After the reaction was complete, the mixture was cooled to room temperature and used directly in the next reaction step.

4.3 | General procedure for the synthesis of benzimidazole-thiones 3

A mixture containing particular iminophosphorane **2**, obtained according to the general procedure, was diluted

with dry DMF (10 mL), cooled with an ice bath, and CS_2 (2.2 mmol, 0.14 mL) was added in one portion. The reaction flask was stoppered, the cooling bath was removed, and the mixture was stirred at room temperature. After the reaction was complete (1–2 days, monitored by TLC), the reaction mixture was poured into water (100 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with water (3 × 50 mL), dried over Na_2SO_4 and the volatile material was evaporated in a vacuum (an aspirator, then an oil pump). The residue was purified by column chromatography (SiO_2, hexane/EtOAc 8:1 to 4:1 or to 1:1 if needed). An analytically pure samples of the products were obtained by recrystallization from ethyl acetate-hexane.

4.3.1 | 1-Butyl-6-chloro-1,3-dihydro-2*H*-benzimidazole-2-thione (**3a**)

Yield 413 mg (86%); beige solid, mp 185–197°C. ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.89$ (t, $J = 7.4$ Hz, 1H), 1.27–1.35 (m, 2H), 1.61–1.68 (m, 2H), 3.30 (br s, 1H), 4.18 (t, $J = 7.4$ Hz, 2H), 7.14 (d, $J = 8.4$ Hz, 1H), 7.18 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.57 (d, $J = 1.7$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.7$, 19.3, 29.5, 42.9, 109.5, 110.6, 122.6, 126.8, 129.6, 133.5, 169.1. MS (EI) m/z 242 (31), 240 (77, $[M]^+$), 207 (87), 184 (100). HRMS (EI) m/z calcd. for $C_{11}H_{13}{}^{35}ClN_2S$: 240.0488; found: 240.0486.

4.3.2 | 1-Butyl-7-chloro-1,3-dihydro-2*H*-benzimidazole-2-thione (**3b**)

Yield (16%); flesh-colored solid, mp 118–120°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.01$ (t, $J = 7.4$ Hz, 3H), 1.46–1.54 (m, 2H), 1.79–1.88 (m, 2H), 4.61–4.66 (m, 2H), 7.11 (t, $J = 7.8$ Hz, 1H), 7.17 (d, $J = 7.8$, 1H), 7.22 (t, $J = 7.8$ Hz, 1H), 12.11 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.8$, 19.9, 31.8, 45.5, 108.9, 115.6, 123.9, 124.6, 128.8, 132.7, 168.6. MS (EI) m/z 242 (15), 240 (42, $[M]^+$), 207, (52), 186 (37), 184 (100). HRMS (EI) m/z calcd. for $C_{11}H_{13}{}^{35}ClN_2S$: 240.0488; found: 240.0478.

4.3.3 | 1-Butyl-5-chloro-1,3-dihydro-2*H*-benzimidazole-2-thione (**3c**)

Yield 332 mg (69%); red oil. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.99$ (t, $J = 7.3$ Hz, 3H), 1.42–1.49 (m, 2H), 1.77–1.85 (m, 2H), 4.26 (t, $J = 7.6$ Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 1H), 7.08 (d, $J = 8.3$ Hz, 1H), 7.18 (dd, $J = 8.3$, 1.8 Hz, 1H), 7.31 (d, $J = 1.8$ Hz, 1H), 12.00 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.1, 30.0, 44.2, 109.8, 110.4, 123.0, 129.1, 131.3, 131.4, 168.4. MS (EI) m/z 242 (20), 240 (56), 209 (26), 207 (76), 184 (100). HRMS (EI) m/z calcd. for $C_{11}H_{13}{}^{35}ClN_2S$: 240.0488; found: 240.0482.

4.3.4 | 1-Butyl-5-(trifluoromethyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (**3d**)

Yield 378 mg (69%); beige crystals, mp 131–134°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.00$ (t, $J = 7.4$ Hz, 3H), 1.42–1.50 (m, 2H), 1.81–1.88 (m, 2H), 4.32 (t, $J = 7.4$ Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 1H), 7.54 (s, 1H), 11.96 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.1, 30.0, 44.3, 107.4 (q, $J_{FC} = 4.0$ Hz), 109.2, 120.1 (q, $J_{FC} = 4.0$ Hz), 124.1 (q, $J_{FC} = 272.2$ Hz), 125.7 (q, $J_{FC} = 32.9$ Hz), 130.4, 135.9, 169.9. MS (EI) m/z 274 (59, $[M]^+$), 241 (86), 232 (32), 218 (100). HRMS (EI) m/z calcd. for $C_{12}H_{13}F_3N_2S$: 274.0752; found: 274.0750.

4.3.5 | 1-Butyl-5-fluoro-1,3-dihydro-2*H*-benzimidazole-2-thione (**3e**)

Yield 309 mg (69%); beige crystals, mp 101–103°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.99$ (t, $J = 7.2$ Hz, 3H), 1.42–1.50 (m, 2H), 1.79–1.85 (m, 2H), 4.27 (t, $J = 7.6$ Hz, 2H), 6.95 (ddd, $J = 9.4$, 8.7, 2.3 Hz, 1H), 7.04 (dd, $J = 8.1$, 2.3 Hz, 1H), 7.08 (dd, $J = 8.7$, 4.3 Hz, 1H), 12.1 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.1, 30.0, 44.2, 97.9 (d, $J_{FC} = 27.7$ Hz), 109.5 (d, $J_{FC} = 9.8$ Hz), 110.1 (d, $J_{FC} = 24.8$ Hz), 129.1 (d, $J_{FC} = 1.1$ Hz), 131.1 (d, $J_{FC} = 12.7$ Hz), 159.7 (d, $J_{FC} = 241.6$ Hz), 168.3. MS (EI) m/z 224 (76, $[M]^+$), 191 (74), 182 (29), 168 (100). HRMS (EI) m/z calcd. for $C_{11}H_{13}FN_2S$: 224.0783; found: 224.0777.

4.3.6 | 1-Butyl-7-fluoro-1,3-dihydro-2*H*-benzimidazole-2-thione (**3f**)

Yield 266 mg (59%); colorless crystals, mp 100–103°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.99$ (t, $J = 7.4$ Hz, 1H), 1.43–1.51 (m, 2H), 1.79–1.88 (m, 2H), 4.42 (t, $J = 7.4$ Hz, 2H), 6.90–6.95 (m, 1H), 7.09–7.14 (m, 2H), 12.18 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 19.8, 31.2 (d, $J_{FC} = 1.7$ Hz), 46.1, 106.4 (d, $J_{FC} = 4.0$ Hz), 109.6 (d, $J_{FC} = 17.9$ Hz), 120.8 (d, $J_{FC} = 13.3$ Hz), 123.8 (d, $J_{FC} = 7.5$ Hz), 133.2 (d, $J_{FC} = 6.9$ Hz), 147.1 (d, $J_{FC} = 246.2$ Hz), 168.1. MS (EI) m/z 224 (48, $[M]^+$), 191 (50), 182 (15), 181 (13), 168 (100). HRMS (EI) m/z calcd. for $C_{11}H_{13}FN_2S$: 224.0783; found: 224.0786.

4.3.7 | 1-Butyl-5-phenyl-1,3-dihydro-2*H*-benzimidazole-2-thione (**3g**)

Yield 513 mg (91%); colorless crystals, mp 158–161°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.01$ (t, $J = 7.3$ Hz, 1H), 1.45–1.53 (m, 2H), 1.84–1.90 (m, 2H), 4.32 (t, $J = 7.3$ Hz, 2H), 7.21–7.23 (m, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.42–7.46 (m, 3H), 7.49–7.50 (m, 1H), 7.56–7.58 (m, 2H), 11.86 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.8$, 20.1, 30.1, 44.1, 108.7, 109.3, 122.2, 127.2, 127.3, 128.8, 131.2, 132.2, 137.1, 140.6, 168.0. MS (EI) m/z 282 (96, $[M]^+$), 249 (100), 240 (49), 226 (97) HRMS (EI) m/z calcd. for $C_{17}H_{18}N_2S$: 282.1191; found: 282.1189.

4.3.8 | 1-Butyl-2-thioxo-2,3-dihydro-1*H*-benzimidazole-5-carbonitrile (**3h**)

Yield 436 mg (94%); beige crystals, mp 219–222°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.99$ (t, $J = 7.4$ Hz, 1H), 1.42–1.48 (m, 2H), 1.78–1.85 (m, 2H), 4.29 (t, $J = 7.4$ Hz, 2H), 7.24 (d, $J = 8.3$ Hz, 1H), 7.52 (dd, $J = 8.3$, 1.3 Hz, 1H), 7.57 (d, $J = 1.3$ Hz, 1H). The NH signal too broad to be noticed. ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.1, 29.9, 44.4, 106.5, 109.7, 113.7, 118.7, 127.3, 130.6, 135.7, 170.2. MS (EI) m/z 231 (58, $[M]^+$), 198 (81), 175 (100). HRMS (EI) m/z calcd. for $C_{12}H_{13}N_3S$: 231.0830; found: 231.0828.

4.3.9 | 1-Butyl-1,3-dihydro-2*H*-benzimidazole-2-thione (**3i**)

Yield 351 mg (85%); beige solid, mp 116–119°C (Ref. [19] mp 91–93°C). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.98$ (t, $J = 7.5$ Hz, 1H), 1.42–1.50 (m, 2H), 1.80–1.86 (m, 2H), 4.29 (t, $J = 7.5$ Hz, 2H), 7.15–7.23 (m, 3H), 7.28–7.31 (m, 1H), 11.85 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.8$, 20.1, 30.0, 44.0, 109.1, 110.2, 122.7, 123.2, 130.6, 132.7, 167.6. MS (EI) m/z 206 (85, $[M]^+$), 173 (84), 164 (37), 150 (100). HRMS (EI) m/z calcd. for $C_{11}H_{14}N_2S$: 206.0878; found: 206.0875.

4.3.10 | 6-Bromo-1-ethyl-1,3-dihydro-2*H*-benzimidazole-2-thione (**3j**)

Yield 380 mg (74%); creamy crystals, mp 199–201°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.41$ (t, $J = 7.3$ Hz, 3H), 4.31 (q, $J = 7.3$ Hz, 2H), 7.15–7.18 (m, 1H), 7.31–7.34 (m, 2H), 11 94 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.0$, 39.2, 111.3, 112.1, 116.0, 126.3, 129.7, 133.4, 167.9. MS (EI) m/z 258 (97), 256 (100), 230 (49), 228 (49), 149 (20). HRMS (EI) m/z calcd. for $C_9H_9{}^{79}BrN_2S$: 255.9670; found: 255.9668.

4.3.11 | 6-Chloro-1-ethyl-1,3-dihydro-2*H*-benzimidazole-2-thione (**3k**)

Yield 288 mg (68%); creamy crystals, mp 207–210°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.41$ (t, $J = 7.4$ Hz, 3H), 4.31 (q, $J = 7.3$ Hz, 2H), 7.16–7.23 (m, 3H), 1187 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.0$, 39.3, 109.3, 110.9, 123.5, 128.8, 129.3, 133.1, 168.1. MS (EI) m/z 214 (34), 212 (94, $[M]^+$), 186 (36), 184 (100). HRMS (EI) m/z calcd. for $C_9H_9{}^{35}ClN_2S$: 212.0175; found: 212.0181.

4.3.12 | Ethyl-1,3-dihydro-2*H*-benzimidazole-2-tione (**3l**)

Yield 260 mg (73%); colorless crystals, mp 169–171°C (Ref. [20] mp 161.5–162°C). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.41$ (t, $J = 7.3$ Hz, 1H), 4.36 (q, $J = 7.3$ Hz, 2H), 7.16–7.23 (m, 3H), 7.29–7.32 (m, 1H), 11.86 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.0$, 39.0, 109.0, 110.3, 122.7, 123.2, 130.7, 132.2, 167.2. MS (EI) m/z 178 (100, $[M]^+$), 150 (94). HRMS (EI) m/z calcd. for $C_9H_{10}N_2S$: 178.0565; found: 178.0570.

4.3.13 | 1-*tert*-Butyl-6-chloro-1,3-dihydro-2*H*-benzimidazole-2-thione (**3m**)

Yield 360 mg (75%); beige solid, mp 216–218°C. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 2.07$ (s, 9H), 7.15 (dd, $J = 8.5$, 1.7 Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 1H), 7.69 (d, $J = 1.7$ Hz, 1H), 12.1 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 29.9$, 63.2, 110.5, 113.9, 123.0, 127.9, 130.1, 134.1, 168.6. MS (EI) m/z 240 (17, $[M]^+$), 186 (36), 184 (100). HRMS (EI) m/z calcd. for $C_{11}H_{13}{}^{35}ClN_2S$: 240.0488; found: 240.0486.

4.3.14 | 1-Methyl-7-(trifluoromethyl)-1,3-dihydro-2*H*-benzimidazole-2-thione (**3n**)

Yield 135 mg (29%); colorless crystals, mp 219–222°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 3.98$ (q, $J = 2.0$ Hz, 3H), 7.29 (t, $J = 8.1$ Hz, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 7.55 (d, $J = 8.1$ Hz, 1H), 11.86 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 33.4$, 113.2 (q, $J_{FC} = 33.5$ Hz), 113.9, 121.0 (q, $J_{FC} = 5.8$ Hz), 122.7, 123.2 (q, $J_{FC} = 271.7$ Hz), 129.7, 132.0, 170.3. MS (EI) m/z 232 (100, $[M]^+$), 199 (40).

HRMS (EI) m/z calcd. for $C_9H_7F_3N_2S$: 232.0282; found: 232.0287.

4.3.15 | 6-Chloro-1-methyl-1,3-dihydro-2*H*-benzimidazole-2-thione (**3o**)

Yield [21] 119 mg (30%); beige solid, mp 278–280°C. ^{1}H NMR (600 MHz, DMSO-d_6) $\delta = 3.61$ (s, 3H), 7.13 (d, $J = 8.3$ Hz, 1H), 7.17 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.51 (d, $J = 1.9$ Hz, 1H), 12.9 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) $\delta = 30.2$, 109.6, 110.5, 122.6, 126.7, 129.6, 134.1, 169.6. MS (EI) m/z 200 (39), 198 (100, $[M]^+$), 165 (36). HRMS (EI) m/z calcd. for $C_8H_7{}^{35}ClN_2S$: 198.0018; found: 198.0025.

4.4 | General procedure for the synthesis of benzimidazole-2-thiones 4

Iminophosphorane **2**, obtained according to the general procedure (see above), was diluted with dry DMF (10 mL), placed in a glass ampoule equipped with a Teflon stopcock, cooled to ca. −65°C, and solid CO_2 (a large excess of crushed dry ice, ca. 1 g) was added in one portion. The reaction vessel was tightened, the cooling bath was removed, and the mixture was stirred at room temperature for 1–2 days (monitored by TLC). After the reaction was completed, it was processed as described in the synthesis of **3**.

4.4.1 | 1-Butyl-6-chloro-1,3-dihydro-2*H*-benzimidazol-2-one (**4a**)

Yield 403 mg (90%); beige crystals, mp 120–123°C (Ref. [22] mp 120–121°C). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.98$ (t, $J = 7.3$ Hz, 1H), 1.39–1.45 (m, 2H), 1.72–1.78 (m, 2H), 3.86 (t, $J = 7.3$ Hz, 2H), 6.98–6.99 (m, 1H), 7.02–7.06 (m, 2H), 10.77 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.0, 30.3, 40.8, 108.2, 110.4, 121.3, 126.69, 126.70, 131.1, 150.0. MS (EI) m/z 226 (35), 224 (90, $[M]^+$), 207 (30), 184 (22), 183 (32), 182 (64), 181 (68), 168 (100), 153 (47). HRMS (EI) m/z calcd. for $C_{11}H_{13}{}^{35}ClN_2O$: 224.0716; found: 224.0723.

4.4.2 | 1-Butyl-5-chloro-1,3-dihydro-2*H*-benzimidazol-2-one (**4c**)

Yield 283 mg (63%); colorless crystals, mp 145–147°C (Ref. [5] mp 141–143°C). ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 0.95$ (t, $J = 7.4$ Hz, 3H), 1.36–1.42 (m, 2H), 1.70–1.75 (m, 2H), 3.85 (t, $J = 7.4$ Hz, 2H), 6.67 (d, $J = 8.3$ Hz, 1H), 7.03 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.13 (d, $J = 1.9$ Hz, 1H), 10.79 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 13.7$, 20.0, 30.4, 40.8, 108.5, 110.1, 121.1, 126.9, 128.93, 128.95, 155.9. MS (EI) m/z 226 (24), 224 (77, $[M]^+$), 207 (23), 183 (27), 181 (77), 170 (32), 168 (100), 153 (36). HRMS (EI) m/z calcd. for $C_{11}H_{13}{}^{35}ClN_2O$: 224.0716; found: 224.0719.

4.4.3 | 1-Butyl-5-(trifluoromethyl)-1,3-dihydro-2*H*-benzimidazol-2-one (**4d**)

Yield 222 mg (43%); colorless crystals, mp 134–136°C (Ref. [23] mp 115–116°C). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.97$ (t, $J = 7.3$ Hz, 1H), 1.38–1.46 (m, 2H), 1.73–1.80 (m, 2H), 3.92 (t, $J = 7.3$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 1H), 7.41 (s, 1H), 11.13 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.6$, 20.0, 30.4, 40.9, 107.0 (q, $J_{FC} = 4.0$ Hz), 107.6, 118.6 (q, $J_{FC} = 4.0$ Hz), 124.5 (q, $J_{FC} = 271.1$ Hz), 123.8 (q, $J_{FC} = 32.9$ Hz), 128.1, 132.8 (q, $J_{FC} = 1.1$ Hz), 156.2. MS (EI) m/z 258 (65, $[M]^+$), 241 (25), 216 (62), 215 (69), 202 (100), 187 (34). HRMS (EI) m/z calcd. for $C_{12}H_{13}F_3N_2O$: 258.0980; found: 258.0980.

4.4.4 | 1-Butyl-5-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (**4e**)

Yield 213 mg (51%); brownish crystals, mp 113–115°C (Ref. [3] mp 111–112°C). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.96$ (t, $J = 7.4$ Hz, 1H), 1.37–1.45 (m, 2H), 1.70–1.77 (m, 2H), 3.87 (t, $J = 7.4$ Hz, 2H), 6.76–6.80 (m, 1H), 6.86–6.92 (m, 2H), 10.98 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.1, 30.4, 40.7, 98.0 (d, $J_{FC} = 28.3$ Hz), 107.5 (d, $J_{FC} = 24.3$ Hz), 107.9 (d, $J_{FC} = 9.2$ Hz), 126.4 (d, $J_{FC} = 1.7$ Hz), 128.7 (d, $J_{FC} = 12.7$ Hz), 156.3, 158.7 (d, $J_{FC} = 237.6$ Hz). MS (EI) m/z 208 (94, $[M]^+$), 191 (24), 166 (60), 165 (95), 152 (100), 137 (41), 124 (27). HRMS (EI) m/z calcd. for $C_{11}H_{13}FN_2O$: 208.1012; found: 208.1021.

4.4.5 | 1-Butyl-7-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (**4f**)

Yield 275 mg (66%); brownish crystals, mp 147–150°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.96$ (t, $J = 7.3$ Hz, 1H), 1.38–1.46 (m, 2H), 1.72–1.80 (m, 2H), 4.01 (t, $J = 7.3$ Hz, 2H), 6.78–6.82 (m, 1H), 6.92–6.99 (m, 2H), 11.03 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 19.8, 31.8, 42.4, 106.0 (d, $J_{FC} = 2.9$ Hz), 108.5 (d, $J_{FC} = 18.5$ Hz), 117.6 (d, $J_{FC} = 12.7$ Hz), 121.6 (d, $J_{FC} = 6.9$ Hz), 130.7 (d, $J_{FC} = 7.5$ Hz), 147.3 (d, $J_{FC} = 242.2$ Hz), 155.8. MS

(EI) m/z 208 (73, $[M]^+$), 191 (21), 166 (45), 165 (88), 152 (100), 137 (27). HRMS (EI) m/z calcd. for $C_{11}H_{13}FN_2O$: 208.1012; found: 208.1014.

4.4.6 | 1-Butyl-5-phenyl-1,3-dihydro-2*H*-benzimidazol-2-one (**4g**)

Yield 527 mg (99%); beige crystals, mp 128–130°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.99$ (t, $J = 7.3$ Hz, 1H), 1.40–1.48 (m, 2H), 1.76–1.83 (m, 2H), 3.94 (t, $J = 7.3$ Hz, 2H), 7.04–7.06 (m, 1H), 7.30–7.34 (m, 2H), 7.38–7.40 (m, 1H), 7.40–7.44 (m, 2H), 7.56–7.58 (m, 2H), 10.53 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.8$, 20.1, 30.6, 40.8, 108.0, 108.5, 120.3, 126.8, 127.0, 128.7, 128.71, 129.8, 135.1, 141.3, 156.0. MS (EI) m/z 266 (100, $[M]^+$), 223 (45), 210 (53), 195 (25). HRMS (EI) m/z calcd. for $C_{17}H_{18}N_2O$: 266.1419; found: 266.1409.

4.4.7 | 1-Methyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carbonitrile (**4h**)

Yield 385 mg (89%); beige crystals, mp 158–161°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.96$ (t, $J = 7.3$ Hz, 1H), 1.36–1.40 (m, 2H), 1.71–1.78 (m, 2H), 3.91 (t, $J = 7.3$ Hz, 2H), 7.04–7.06 (m, 1H), 7.38–7.40 (m, 2H), 11.00 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.6$, 20.0, 30.3, 40.9, 104.3, 108.2, 112.8, 119.4, 126.2, 128.2, 133.6, 155.8. MS (EI) m/z 215 (77, $[M]^+$), 198 (24), 173 (66), 172 (66), 159 (100), 144 (34). HRMS (EI) m/z calcd. for $C_{12}H_{13}N_3O$: 215.10.59; found: 215.1058.

4.4.8 | 1-Butyl-1,3-dihydro-2*H*-benzimidazol-2-one (**4i**)

Yield 247 mg (65%); beige crystals, mp 104–107°C (Ref. [24] mp 98–100°C). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.97$ (t, $J = 7.4$ Hz, 1H), 1.39–1.46 (m, 2H), 1.73–1.80 (m, 2H), 3.90 (t, $J = 7.4$ Hz, 2H), 6.98–7.01 (m, 1H), 7.04–7.10 (m, 2H), 7.11–7.14 (m, 1H), 10.13 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.1, 30.5, 40.6, 107.8, 109.7, 121.1, 121.3, 128.1, 130.4, 155.8. MS (EI) m/z 190 (100, $[M]^+$), 147 (35), 134 (30), 119 (23). HRMS (EI) m/z calcd. for $C_{11}H_{14}N_2O$: 190.1106; found: 190.1099.

4.4.9 | 6-Bromo-1-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (**4j**)

Yield 410 mg (85%); beige powder, mp 183–185°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.35$ (t, $J = 7.3$ Hz, 3H), 3.91 (q, $J = 7.3$ Hz, 2H), 7.00 (d, $J = 8.3$ Hz, 1H), 7.13 (d, $J = 1.8$ Hz, 1H), 7.18 (dd, $J = 8.3$, 1.8 Hz, 1H), 10.7 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.6$, 35.8, 110.9, 111.0, 113.8, 124.2, 127.2, 131.1, 155.5. MS (EI) m/z 242 (98), 240 (100, $[M]^+$), 227 (42), 243 (45), 214 (35), 212 (36). HRMS (EI) m/z calcd. for $C_9H_9{}^{79}BrN_2O$: 239.9898; found: 239.9899.

4.4.10 | 6-Chloro-1-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (**4k**)

Yield 263 mg (67%); beige crystals, mp 192–195°C (Ref. [25] 190–191°C). ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.35$ (t, $J = 7.3$ Hz, 3H), 3.91 (q, $J = 7.3$ Hz, 2H), 6.98–6.99 (m, 1H), 7.02–7.03 (m, 2H), 10.7 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 13.5$, 35.8, 108.1, 110.5, 121.4, 126.7, 126.8, 130.8, 155.7. MS (EI) m/z 198 (30), 196 (100, $[M]^+$), 181 (54), 168 (41), 153 (23). HRMS (EI) m/z calcd. for $C_9H_9{}^{35}ClN_2O$: 196.0403; found: 196.0405.

4.4.11 | 1-Ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (**4l**)

Yield 182 mg (56%); orange solid, mp 120–122°C (Ref. [26] 117–118°C). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.17$ (t, $J = 7.3$ Hz, 3H), 3.79 (q, $J = 7.3$ Hz, 3H), 6.93–7.00 (m, 3H), 7.08 (d, $J = 7.1$ Hz, 1H), 10.77 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.4$, 34.6, 107.5, 108.7, 120.4, 120.6, 128.3, 129.8, 153.9. MS (EI) m/z 162 (100, $[M]^+$), 147 (67), 134 (37), 119 (27). HRMS (EI) m/z calcd. for $C_9H_{10}N_2O$: 162.0793; found: 162.0799.

4.4.12 | 1-*tert*-Butyl-6-chloro-1,3-dihydro-2*H*-benzimidazol-2-one (**4m**)

Yield 300 mg (67%); pink crystals, mp 190–193°C. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.80$ (s, 9H), 6.99 (d, $J = 8.4$ Hz, 1H), 7.01 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.39 (d, $J = 1.7$ Hz, 1H), 10.44 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 29.3$, 58.6, 109.9, 112.2, 120.8, 125.9, 127.2, 131.0, 156.0. MS (EI) m/z 226 (3), 224 (11, $[M]^+$), 170 (32), 168 (100). HRMS (EI) m/z calcd. for $C_{11}H_{13}{}^{35}ClN_2O$: 224.0716; found: 224.0714.

4.5 | General procedure for the synthesis of benzimidazol-2-amines 5

Iminophosphorane **2**, obtained according to the general procedure (see above), was diluted with dry MeCN

(10 mL), cooled with ice bath, and an appropriate isocyanate (3.0 mmol) was added in one portion. The reaction flask was stoppered, the cooling bath was removed, and the mixture was stirred overnight at room temperature. After completion (monitored by TLC), the reaction was proceeded according to the work-up described in the procedure for the synthesis of **3**.

4.5.1 | 1-Butyl-6-chloro-*N*-ethyl-1*H*-benzimidazol-2-amine (**5a**)

Yield 372 mg (74%); colorless crystals, mp 149–151°C (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.86$ (t, $J = 7.3$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.23–1.30 (m, 2H), 1.50–1.57 (m, 2H), 3.35–3.40 (m, 2H), 3.92 (t, $J = 7.3$ Hz, 2H), 6.70 (t, $J = 5.4$ Hz, 1H), 6.90 (dd, $J = 8.3$, 2.0 Hz, 1H), 7.12 (d, $J = 8.3$ Hz, 1H), 7.21 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.7$, 15.0, 19.3, 30.5, 37.2, 41.0, 107.4, 115.5, 119.8, 122.2, 135.6, 141.6, 155.3. MS (EI) m/z 253 (33), 251 (100), 222 (30), 181 (43), 167 (47). HRMS (EI) m/z calcd. for $C_{13}H_{18}{}^{35}ClN_3$: 251.1189; found: 251.1187.

4.5.2 | *N*,1-Dibutyl-6-chloro-1*H*-benzimidazol-2-amine (**5b**)

Yield 425 mg (76%); colorless solid, mp 179–182°C (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta =$ o.84–0.91 (m, 6H), 1.24–1.38 (m, 4H), 1.50–1.60 (m, 4H), 3.31–3.35 (m, overlapped with water), 3.93 (t, $J = 7.2$ Hz, 2H), 6.69 (t, $J = 5.4$ Hz, 1H),6.90 (dd, $J = 8.3$, 1.7 Hz, 1H), 7.11 (d, $J = 8.3$ Hz, 1H), 7.20 (d, $J = 1.7$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.7$, 13.8, 19.3, 19.6, 30.5, 31.3, 41.0, 42.1, 107.3, 115.5, 119.8, 122.2, 135.6, 141.6, 155.3. MS (EI) m/z 281 (20), 279 (61, $[M]^+$), 236 (35), 208 (60), 181 (100), 167 (63). HRMS (EI) m/z calcd. for $C_{15}H_{22}{}^{35}ClN_3$: 279.1502; found: 279.1496.

4.5.3 | 6-Chloro-*N*-hexyl-1-methyl-1*H*-benzimidazol-2-amine (**5c**)

Yield 350 mg (57%); creamy crystals, mp 156–159°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.85$–0.90 (m, 3H), 0.96 (t, $J = 7.3$ Hz, 3H), 1.26–1.42 (m, 8H), 1.65–1.74 (m, 4H), 5.50–3.55 (m, 2H), 3.83 (t, $J = 7.3$ Hz, 2H), 4.49 (br s, 1H), 7.02 (d, $J = 2.0$ Hz, 1H), 7.05 (dd, $J = 8.3$, 2.0 Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 14.0, 20.2, 22.5, 26.6, 29.8, 30.9, 31.5, 42.3, 43.6, 107.5, 116.6, 121.3, 124.9, 135.0, 140.2, 154.2. MS (EI) m/z 309 (70), 307 (70, $[M]^+$), 278 (44), 228 (88), 199 (46), 185 (56), 181 (72), 44 (100). HRMS (EI) m/z calcd. for $C_{17}H_{26}{}^{35}ClN_3$: 307.1815; found: 307.1807.

4.5.4 | 1-Butyl-6-chloro-*N*-cyclohexyl-1*H*-benzimidazol-2-amine (**5d**)

Yield 513 mg (84%); colorless solid, mp 184–186°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.93$ (t, $J = 7.3$ Hz, 3H), 1.15–1.45 (m, 6H), 1.61–1.75 (m, 5H), 2.09–2.16 (m, 2H), 3.77 (t, $J = 7.3$ Hz, 2H), 3.88–3.96 (m, 1H), 4.12 (br s, 1H), 6.98 (d, $J = 1.8$ Hz, 1H), 7.01 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.7$, 20.1, 24.8, 25.6, 30.8, 33.8, 42.0, 51.7, 107.3, 116.5, 121.1, 124.5, 135.0, 140.8, 153.6. MS (EI) m/z 307 (19), 305 (57, $[M]^+$), 223 (29), 207 (29), 183 (33), 181 (100), 167 (92). HRMS (EI) m/z calcd. for $C_{17}H_{24}{}^{35}ClN_3$: 305.1659; found: 305.1656.

4.5.5 | 1-Butyl-6-chloro-*N*-(2-chlorophenyl)-1*H*-benzimidazol-2-amine (**5e**)

Yield 153 mg (23%); yellow solid, mp 175–178°C. ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.00$ (t, $J = 7.5$ Hz, 3H), 1.42–1.48 (m, 2H), 1.81–1.87 (m, 2H), 4.03 (t, $J = 7.5$ Hz, 2H), 6.98 (ddd, $J = 8.0$, 7.3, 1.5 Hz, 1H), 7.13–7.17 (m, 2H), 7.34 (ddd, $J = 8.4$, 7.3, 1.5 Hz, 1H), 7.38–7.40 (m, 1H), 7.49 (d, $J = 8.4$ Hz, 1H). 8.55 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 13.7$, 20.3, 31.1, 42.9, 108.2, 118.4, 118.9, 121.3, 122.1, 122.6, 126.4, 128.1, 128.9, 134.2, 136.0, 140.1, 149.0. MS (EI) m/z 335 (54), 333 (83, $[M]^+$), 298 (100), 242 (64). HRMS (EI) m/z calcd. for $C_{17}H_{17}{}^{35}Cl_2N_3$: 333.0800; found: 333.0801.

4.5.6 | 1-Butyl-2-(butylamino)-1*H*-benzimidazole-5-carbonitrile (**5f**)

Yield 438 mg (81%); pale pink crystals, mp 171–173°C. (EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.85$ (t, $J = 7.5$ Hz, 3H), 0.89 (t, $J = 7.5$ Hz, 3H), 1.20–1.27 (m, 2H), 1.29–1.37 (m, 2H), 1.52–1.60 (m, 4H), 3.35 (q, $J = 6.0$ Hz, 2H), 3.99 (t, $J = 7.2$ Hz, 2H), 6.97 (t, $J = 5.5$ Hz, 1H), 7.27 (s, 2H), 7. 53 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.6$, 13.7, 19.3, 19.5, 30.4, 31.2, 41.1, 42.1, 101.8, 108.1, 117.8, 120.7, 122.5, 138.2, 142.8, 156.2. MS (EI) m/z 270 (65, $[M]^+$), 227 (39), 199 (65), 172 (100), 158 (59). HRMS (EI) m/z calcd. for $C_{16}H_{22}N_4$: 270.1844; found: 270.1847.

4.5.7 | 1-Butyl-2-(cyclohexylamino)-1*H*-benzimidazole-5-carbonitrile (**5g**)

Yield 575 mg (97%); colorless crystals, mp 160–163°C (EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.85$ (t, $J = 7.5$ Hz, 3H), 1.10–1.34 (m, 7H), 1.51–1.61 (m, 3H), 1.68–1.76 (m, 2H), 1.91–2.00 (m, 2H), 3.68–3.77 (m, 1H), 4.01 (t, $J = 7.2$ Hz, 2H), 6.68 (d, $J = 7.8$ Hz, 1H), 7.27 (s, 2H), 7.54 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.6$, 19.2, 15.0, 25.4, 30.4, 32.7, 41.0, 51.7, 101.8, 108.2, 117.8, 120.7, 122.5, 138.1, 142.6, 155.5. MS (EI) m/z 296 (44, $[M]^+$), 214 (30), 198 (26), 172 (100), 158 (92). HRMS (EI) m/z calcd. for $C_{18}H_{24}N_4$: 296.2001; found: 296.2002.

4.5.8 | 1-Butyl-*N*-cyclohexyl-*1H*-benzimidazol-2-amine (**5h**)

Yield 466 mg (86%); beige solid, mp 117–119°C. ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.87$ (t, $J = 7.3$ Hz, 3H), 1.11–1.36 (m, 8H), 1.53–1.62 (m, 2H), 1.71–1.75 (m, 2H), 1.95–2.02 (m, 2H), 3.68–3.76 (m, 1 H), 3.95 (t, $J = 7.2$ Hz, 2H), 6.25 (d, $J = 7.8$ Hz, 1H), 6.84 (t, $J = 7.6$ Hz, 1H), 6.90 (t, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 7.6$ Hz, 1H), 7.15 (d, $J = 7.6$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.7$, 19.3, 25.0, 25.5, 30.5, 32.9, 40.7, 51.4, 107.2, 114.7, 117.9, 119.9, 134.5, 142.7, 153.9. MS (EI) m/z 271 (53), 189 (29), 173 (30), 147 (100), 133 (90). HRMS (EI) m/z calcd. for $C_{17}H_{25}N_3$: 271.2048; found: 271.2057.

4.5.9 | *N*-Butyl-6-chloro-1-ethyl-1*H*-benzimidazol-2-amine (**5i**)

Yield 314 mg (73%); colorless crystals, mp 182–184°C. (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.84$ (t, $J = 7.5$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H), 1.30 (sext, $J = 7.5$ Hz, 2H), 1.52 (quint. $J = 7.2$ Hz, 2H), 3.29 (q, $J = 5.9$ Hz, 2H), 3.94 (q, $J = 7.2$ Hz, 2H), 6.74–6.76 (m, 1H), 6.90 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.18 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.8$, 19.6, 31.3, 36.0, 42.1, 107.2, 115.5, 119.8, 122.2, 135.1, 141.8, 155.1 (one aliphatic signal invisible). MS (EI) m/z 253 (36), 251 (100, $[M]^+$), 208 (60), 195 (42), 181 (56), 167 (99). HRMS (EI) m/z calcd. for $C_{13}H_{18}{}^{35}ClN_3$: 251.1189; found: 215.1193.

4.5.10 | 6-Chloro-*N*-cyclohexyl-1-ethyl-1*H*-benzimidazol-2-amine (**5j**)

Yield 333 mg (60%); pale yellow solid, mp 174–176°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.16$–1.28 (m, 3H), 1.32 (t, $J = 7.5$ Hz, 3H), 1.42–1.50 (m, 2H), 1.62–1.68 (m, 1H), 1.71–1.78 (m, 2H), 2.12–2.18 (m, 2H), 3.84 (q, $J = 7.5$ Hz, 2H), 3.88–4.01 (m, 2H), 7.01 (d, $J = 1.8$ Hz, 1H), 7.03 (dd, $J = 8.3$, 1.8 Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.8$, 24.9, 25.6, 33.9, 36.8, 51.7, 107.2, 116.7, 121.1, 124.5, 134.6, 141.2, 153.4. MS (EI) m/z 279 (19), 277 (58, $[M]^+$), 195 (82), 167 (100). HRMS (EI) m/z calcd. for $C_{15}H_{20}{}^{35}ClN_3$: 277.1346; found: 277.1349.

4.5.11 | *N*-Cyclohexyl-1-ethyl-1*H*-benzimidazol-2-amine (**5k**)

Yield 283 mg (58%); colorless solid, mp 139–142°C (EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.14$ (t, $J = 7.1$ Hz, 3H), 1.23–1.38 (m, 4H), 1.58–1.64 (m, 1H), 1.68–1.76 (m, 2H), 1.95–1.20 (m, 2H), 3.65–3.73 (m, 1H), 3.99 (q, J – 7.1 H, 2H), 6.29 (d, $J = 7.9$ Hz, 1H), 6.82–6.92 (m, 2H), 7.09 (d, $J = 7.1$ Hz, 1H), 7.15 (d, $J = 7.3$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.8$, 25.0, 25.5, 32.9, 35.8, 51.4, 107.0, 114.7, 118.0, 120.0, 134.0, 142.8, 153.6. MS (EI) m/z 243 (75, $[M]^+$), 161 (80), 133 (100). HRMS (EI) m/z calcd. for $C_{15}H_{21}N_3$: 243.1735; found: 243.1730.

4.5.12 | 6-Chloro-*N*,1-dimethyl-1*H*-benzimidazol-2-amine (**5l**)

Yield 384 mg (81%); beige solid, mp 164–167°C. ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H), 1.30–1.38 (m, 2H), 1.53–1.60 (m, 2H), 3.29–3.33 (m, 2H), 3.45 (s, 3H), 6.70 (t, $J = 5.3$ Hz, 1H), 6.90 (dd, $J = 8.3$, 1.5 Hz, 1H), 7.11 (d, $J = 8.3$ Hz, 1H), 7.20 (d, $J = 1.3$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.8$, 19.6, 28.3, 31.3, 42.2, 107.2, 115.5, 119.8, 122.2, 136.2, 141.6, 155.9. MS (EI) m/z 239 (32), 237 (84, $[M]^+$), 208 (28), 197 (24), 196 (37), 195 (70), 194 (85), 181 (100). HRMS (EI) m/z calcd. for $C_{12}H_{16}{}^{35}ClN_3$: 237.1033; found: 237.1039.

4.5.13 | *N*-Butyl-1-*tert*-butyl-6-chloro-1*H*-benzimidazol-2-amine (**5m**)

Yield 179 mg (32%); beige solid, mp 95–98°C (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.89$ (t, $J = 7.5$ Hz, 3H), 1.28–1.36 (m, 2H), 1.55–1.61 (m, 2H), 1.71 (s, 9H), 3.33–3.37 (m, 2H), 5.90 (t, $J = 5.4$ Hz, 1H), 6.91 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.8$, 19.7, 29.6, 31.1, 43.1, 57.5, 111.7, 115.9, 119.7, 121.8, 135.0, 141.8, 155.6. MS (EI) m/z 335 (54), 333 (83, $[M]^+$), 298 (100), 242 (64). HRMS (EI) m/z calcd. for $C_{15}H_{22}{}^{35}ClN_3$: 279.1502; found: 279.1501.

4.5.14 | 1-*tert*-Butyl-6-chloro-*N*-ethyl-1*H*-benzimidazol-2-amine (**5n**)

Yield 166 mg (33%); flesh-colored solid, mp 121–124°C. ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.16$ (t, $J = 7.1$ Hz, 3H), 1.71 (s, 9H), 3.36–3.42 (m, 2H), 5.95 (t, $J = 5.4$ Hz, 1H), 6.92, (dd, $J = 8.3$, 2.0 Hz, 1H), 7.14 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 15.0$, 29.6, 38.1, 57.5, 111.8, 115.9, 119.7, 121.8, 135.0, 141.8, 155.5. MS (EI) m/z 253 (20), 251 (63, $[M]^+$), 195 (72), 180 (940), 167 (100), 152 (45). HRMS (EI) m/z calcd. for $C_{13}H_{18}{}^{35}ClN_3$: 251.1189; found: 251.1192.

4.6 | Procedures for the reactions of intermediate 2 with acid chlorides and anhydrides

Iminophosphorane **2**, obtained according to the general procedure (see above), was diluted with DCM (10 mL), cooled with ice bath, and an appropriate acid chloride (4.0 mmol) or anhydride (3.0 mmol) along with Et_3N (2.2 mmol) were added to this solution. The cooling bath was removed and the mixture was stirred at room temperature for 24 h (for acid chlorides) or 48 h (for anhydrides). When the reaction was complete, it was proceeded according to the work-up described for the synthesis of **3**.

4.6.1 | 1-Butyl-6-chloro-2-phenyl-1*H*-benzimidazole (**6a**)

Yield 426 mg (75%); colorless crystals, mp 94–97°C (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.70$ (t, $J = 7.3$ Hz, 3H), 1.06–1.11 (m, 2H), 1.55–1.60 (m, 2H), 4.26 (t, $J = 7.3$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.52–7.56 (m, 3H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.72–7.74 (m, 2H), 7.80 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.2$, 19.1, 31.1, 43.9, 110.9, 120.4, 122.2, 126.9, 128.8, 129.1, 129.8, 130.1, 136.4, 141.3, 154.1. MS (EI) m/z 286 (40), 284 (100, $[M]^+$), 257 (7), 255 (22), 243 (26), 241 (75), 228 (24). HRMS (EI) m/z calcd. for $C_{17}H_{17}{}^{35}ClN_2$: 284.1080; found: 284.1077.

4.6.2 | 6-Chloro-1-ethyl-2-phenyl-1*H*-benzimidazole (**6b**)

Yield 359 mg (70%); colorless crystals, mp 135–138°C (hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.1.45$ (t, $J = 7.2$ Hz, 3H), 4.24 (q, $J = 7.2$ Hz, 2H), 7.26–7.28 (m, 1H), 7.41 (s, 1H), 7.51–7.53 (m, 3H), 7.69–7.75 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 15.14$, 39.7, 110.0, 120.7, 123.1, 128.4, 128.8, 129.1, 129.9, 130.0, 135.9, 141.6, 154.2. MS (EI) m/z 258 (33), 257 (36), 256 (100, $[M]^+$), 255 (62), 241 (30), 228 (30). HRMS (EI) m/z calcd. for $C_{15}H_{13}{}^{35}ClN_2$: 265.0767; found: 256.0770.

4.6.3 | 1-*tert*-Butyl-6-chloro-2-phenyl-1*H*-benzimidazole (**6c**)

Yield [27] 495 mg (87%); pale yellow crystals, mp 141–143°C (hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.60$ (s, 9H), 7.25 (dd, $J = 8.5$, 1.7 Hz, 1H), 7.41–7.46 (m, 5H), 7.69 (d, $J = 8.5$ Hz, 1H), 7.72 (d, $J = 1.7$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 31.4$, 59.4, 114.6, 120.8, 122.6, 127.7, 127.9, 129.3, 129.6, 135.1, 135.3, 141.6, 154.3. MS (EI) m/z 286 (7), 284 (22, $[M]^+$), 230 (49), 228 (100). HRMS (EI) m/z calcd. for $C_{17}H_{17}{}^{35}ClN_2$: 284.1080; found: 284.1079.

4.6.4 | 1-Butyl-2-(trifluoromethyl)-1*H*-benzimidazole-5-carbonitrile (**6f**)

Yield 363 mg (68%); pale yellow crystals, mp 88–90°C (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.87$ (t, $J = 7.2$ Hz, 3H), 1.28–1.36 (m, 2H), 1.70–177 (m, 2H), 4.41 (t, $J = 7.6$ Hz, 2H), 7.84 (dd, $J = 8.7$, 1.1 Hz, 1H), 8.03 (d, $J = 8.7$ Hz, 1H), 8.42–8.43 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.4$, 19.3, 31.6, 45.0, 106.1, 113.8, 118.7 (q, $J_{FC} = 271.7$ Hz), 119.1, 126.4, 128.1, 138.1, 139.8, 141.9 (q, $J_{FC} = 38.1$ Hz). MS (EI) m/z 267 (90, $[M]^+$), 225 (45), 224 (100), 211 (23), 198 (26), 156 (35). HRMS (EI) m/z calcd. for $C_{13}H_{12}F_3N_3$: 267.0983; found: 267.0979.

4.6.5 | 1-Butyl-2-tert-butyl-6-chloro-1*H*-benzimidazole (**6g**)

Yield 375 mg (71%); yellowish oil. ^{1}H NMR (600 MHz, DMSO-d_6) $\delta = 0.92$ (t, $J = 7.4$ Hz, 3H), 1.40–1.46 (m, 2H), 1.42 (s, 9H), 1.64–1.69 (m, 2H), 4.24–4.27 (m, 2H), 7.11 (dd. $J = 8.4$, 1.9 Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.58 (d, $J = 1.9$ Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) $\delta = 13.6$, 19.4, 29.3, 31.4, 33.9, 44.7, 110.1, 119.9, 121.4, 126.3, 137.0, 140.1, 161.1. MS (EI) m/z 266 (33), 254 (100, $[M]^+$), 251 (31), 235 (95), 237 (27), 235 (86), 207 (51), 193 (64), 166 (42). HRMS (EI) m/z calcd. for $C_{15}H_{21}{}^{35}ClN_2$: 264.1393; found.264.1394.

4.6.6 | 1-Butyl-6-chloro-2-ethyl-1*H*-benzimidazole (**6h**)

Yield 193 mg (41%); brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.86$ (t, $J = 7.4$ Hz, 3H), 1.24–1.30 (m, 2H), 1.30 (t, $J = 7.4$ Hz, 3H), 1.59–1.64 (m, 2H), 2.82 (q, $J = 7.4$ Hz, 2H), 4.12 (t, $J = 7.4$ Hz, 2H), 7.11 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 1.9$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 11.4$, 13.6, 19.4, 19.9, 31.4, 42.6, 109.9, 119.5, 121.2, 125.9, 135.9, 141.0, 157.1. MS (EI) m/z 238 (48), 236 (99, $[M]^+$), 209 (49), 207 (100), 193 (84), 179 (56), 165 (34). HRMS (EI) m/z calcd. for $C_{13}H_{17}{}^{35}ClN_2$: 236.1080; found: 236.1082.

4.6.7 | 1-Butyl-6-chloro-2-pentyl-1*H*-benzimidazole (**6i**)

Yield 199 mg (34%); yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.85$–0.90 (m, 6H), 1.25–1.38 (m, 6H), 1.58–1.66 (m, 2H), 1.73–1.81 (m, 2H), 2.80 (t, $J = 7.6$ Hz, 2H), 4.14 (t, $J = 7.6$ Hz, 2H), 7.12 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 1.9$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.6$, 13.8, 19.4, 21.9, 26.3, 26.5, 30.9, 31.5, 42.7, 109.9, 119.5, 121.3, 125.9, 135.8, 141.1, 156.1. MS (EI) m/z 280 (12), 278 (39, $[M]^+$), 235 (60), 207 (92), 180 (100), 166 (75). HRMS (EI) m/z calcd. for $C_{16}H_{23}{}^{35}ClN_2$: 278.1550; found: 278.1547.

4.6.8 | 1-Butyl-6-chloro-2-methyl-1*H*-benzimidazole (**6j**)

Yield 49 mg (11%); colorless crystals, mp 164–167°C (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.86$ (t, $J = 7.3$ Hz, 3H), 1.24–1.30 (m, 2H), 1.60–1.66 (m, 2H), 2.49 (s, 3H), 4.13 (t, $J = 7.3$ Hz, 2H), 7.11 (dd, $J = 8.6$, 2.0 H, 1H), 7.47 (d, $J = 8.6$ Hz, 1H), 7.62 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.5$, 13.6, 19.4, 31.1, 42.9, 109.9, 119.3, 121.3, 125.9, 135.9, 141.0, 152.9. MS (EI) m/z 224 (22), 222 (67, $\{M\}^+$), 181 (28), 179 (100). HRMS (EI) m/z calcd. for $C_{12}H_{15}{}^{35}ClN_2$: 222.0924; found: 222.0917.

4.6.9 | *N*-[2-(Butylamino)-4-chlorophenyl] acetamide (**7a**)

Yield 125 mg (26%); colorless crystals, mp 114–117°C (hexane). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H), 7.32–7.38 (m, 2H), 1.49–1.54 (m, 2H), 2.01 (s, 3H), 3.00 (q, $J = 7.3$ Hz, 2H), 5.13 (t, $J = 5.3$ Hz, 1H), 6.52 (dd, $J = 8.2$, 2.2 Hz, 1H), 6.54 (d, $J = 2.2$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 9.06 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.8$, 19.8, 23.3, 30.6, 42.5, 109.8, 114.5, 122.3, 127.0, 130.5, 143.8, 168.7. MS (EI) m/z 242 (13), 240 (39, $[M]^+$), 223 (12), 199 (21), 197 (64), 157 (31), 155 (100). HRMS (EI) m/z calcd. for $C_{12}H_{17}{}^{35}ClN_2O$: 240.1029; found: 240.1028.

4.6.10 | *N*-[2-(Butylamino)-4-chlorophenyl] propanamide (**7b**)

Yield 133 mg (26%); colorless solid, mp 144–146°C. ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.90$ (t, $J = 7.3$ Hz, 3H), 1.06 (t, $J = 7.5$ Hz, 3H), 1.33–141 (m, 2H), 1.49–1.56 (m, 2H), 2.32 (q, $J = 7.5$ Hz, 2H), 2.99–3.04 (m, 2H), 5.07–5.10 (m, 1H), 6.53–6.56 (m, 2H), 7.13 (d, $J = 8.2$ Hz, 1H), 9.01 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 9.8$, 13.8, 19.7, 28.9, 30.6, 42.5, 109.9, 114.6, 122.3, 126.9, 130.4, 143.8, 172.4. MS (EI) m/z 256 (12), 254 (38, $[M]^+$), 225 (26), 211 (42), 155 (100). HRMS (EI) m/z calcd. for $C_{13}H_{19}{}^{35}ClN_2O$: 254.1186; found: 254.1193.

4.6.11 | *N*-[2-(Butylamino)-5-cyanophenyl] acetanamide (**7c**)

Yield 356 mg (77%); colorless solid, mp 145–147°C. ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H), 1.31–1.38 (m, 2H), 1.49–1.56 (m, 2H), 2.04 (s, 3H), 3.09–3.13 (m, 2H), 5.89 (t, $J = 5.1$ Hz, 1H), 6.67 (d, $J = 8.6$ Hz, 1H), 7.38 (dd, $J = 8.6$, 1.5 Hz, 1H), 7.49 (d, $J = 1.5$ Hz, 1H), 9.12 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 13.7$, 19.7, 23.4, 30.4, 42.1, 95.1, 110.2, 120.1, 123.0, 129.0, 130.8, 146.2, 169.0. MS (EI) m/z 231 (33, $[M]^+$), 188 (52), 146 (100). HRMS (EI) m/z calcd. for $C_{13}H_{17}N_3O$: 231.1372; found: 231.1367.

4.6.12 | *N*-[2-(*tert*-Butylamino)-4-chlorophenyl]propanamide (**7d**)

Yield 315 mg (62%); colorless crystals, mp 112–115°C. (hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 1.07$ (t, $J = 7.4$ Hz, 3H), 1.27 (s, 9H), 2.30 (q, $J = 7.4$ Hz, 2H), 4.42 (br s, 1H), 6.63 (dd, $J = 8.3$, 2.2 H, 1H), 6.81 (d, $J = 2.2$ Hz, 1H), 7.12 (d, $J = 8.3$ Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 9.9$, 28.9, 29.2, 50.9, 114.8, 116.1, 124.8, 127.5, 129.8, 142.2, 172.5. MS (EI) m/z 256 (15), 254 (46, $[M]^+$), 241 (31), 239 (96), 185 (29), 183 (96), 142 (100). HRMS (EI) m/z calcd. for $C_{13}H_{19}{}^{35}ClN_2O$: 254.1186; found: 254.0.1183.

4.7 | Procedure for the reactions of intermediate 2 with ethyl trifluoroacetate

A mixture containing particular iminophosphorane **2**, obtained according to the general procedure, was dissolved under N_2 in freshly distilled dry THF (15 mL). The mixture was cooled to −78°C. *n*-BuLi (1.5 mL, 2.4 mmol, 1.6 M in hexane) was added followed by addition of hexamethylphosphoramide (2 mL). The mixture was stirred at −78°C for 20 min, and an excess of CF_3CO_2Et (1.5 mL) was added. The cooling bath was removed, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into sat. NH_4Cl (100 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with water and dried with Na_2SO_4. The solvent was then evaporated, and the residue was separated by column chromatography (SiO_2, hexane/EtOAc) to obtain a pure product.

4.7.1 | 1-Butyl-6-chloro-2-(trifluoromethyl)-1*H*-benzimidazole (**6d**)

Yield 381 mg (69%); yellow crystals, mp 97–100°C. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.99$ (t, $J = 7.4$ Hz, 1H), 1.40–1.47 (m, 2H), 1.81–1.87 (m, 2H), 4.25 (t, $J = 7.4$ Hz, 2H), 7.32 (dd, $J = 8.8$, 1.8 Hz, 1H), 7.43 (d, $J = 1.8$ Hz, 1H), 7.77 (d, $J = 8.8$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 13.5$, 20.0, 31.9, 45.2 (q, $J_{FC} = 1.7$ Hz), 110.6, 118.9 (q, $J_{FC} = 271.1$ Hz), 122.6, 124.5, 131.2, 135.9 (q, $J_{FC} = 1.1$ Hz), 139.7, 141.2 (q, $J_{FC} = 38.7$ Hz). MS (EI) *m*/*z* 278 (32), 276 (100, $[M]^+$), 233 (70), 220 (45), 200 (22), 165 (41). HRMS (EI) *m*/*z* calcd. for $C_{12}H_{12}{}^{35}ClF_3N_2$: 276.0641; found: 276.0647.

4.7.2 | 6-Bromo-1-ethyl-2-trifluoromethyl-1*H*-benzimidazole (**6e**)

Yield 410 mg (70%); yellow crystals, mp 112–114°C (hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.34$ (t. $J = 7.1$ Hz, 3H), 4.42 (q, $J = 7.1$ Hz, 2H), 7.50 (dd, $J = 8.7$, 1.7 Hz, 1H), 7.76 (d, $J = 8.7$ Hz, 1H), 8.15 (d, $J = 1.7$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 15.1$, 40.0, 114.7, 118.0, 118.83 (q, $J_{FC} = 271.3$ Hz), 122.6, 126.8, 136.1, 139.5, 139.8 (q, $J_{FC} = 38.1$ Hz). MS (EI) *m*/*z* 294 (99), 292 (100, $[M]^+$), 279 (47), 277 (48), 246 (22), 244 (22), 189 (44). HRMS (EI) *m*/*z* calcd. for $C_{10}H_8{}^{79}BrF_3N_2$: 291.9823; found: 291.9817.

ACKNOWLEDGMENTS

This work was financed by a subvention from the Institute of Organic Chemistry, Polish Academy of Sciences.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Supporting Information

Synthesis of various 1-alkylbenzimidazole derivatives directly from 2-alkylaminonitroarenes via a two-step, one-pot procedure.

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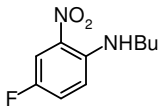
CONTENTS:

General remarks

Melting points were recorded in open capillary and are uncorrected. The ^{1}H and ^{13}C NMR spectra of all compounds studied were measured at temperature 298 K in $CDCl_3$ or deuterated dimethyl sulfoxide (DMSO-d_6) solutions with a Varian vnmrs-600 or Varian vnmrs-500 using tetramethylsilane (TMS) as the internal standard. Mass spectra (EI, 70 eV) were obtained on an AutoSpec Premier (Waters) spectrometer. For ESI+ and ESI- measurements a Maldi SYNAPT G2-S HDMS (Waters) was used. Accurate mass measurements were obtained using magnetic sector mass analyzer (EI) or TOF analyzer (ESI). Silica gel Merck 60 (230-400 mesh) was used for column chromatography. THF was distilled from sodium/benzophenone ketyl prior to use. DMF was dried over CaH_2, distilled and stored over molecular sieves. All commercial reagents were used without additional purification.

General procedure for the synthesis of *N*-alkyl-2-nitroanilines 1

A mixture of appropriate 2-chloro- or 2-fluoro- nitro compound (20 mmol) was added portionwise to the amine (0.2 mol, neat or as a 33% water solution in the case of $MeNH_2$) and the mixture was stirred at room temperature until the starting material was consumed (determined by TLC, 8-48 h). The reaction mixture was diluted with water (200 mL) and extracted with DCM (3 x 100 mL). The combined organic solution was washed with water (3 x 200 mL), dried with Na_2SO_4 and evaporated. Most of the products were further used without purification. When it was necessary, product was purified by column chromatography using hexanes/ethyl acetate mixture as eluent.



N-Butyl-4-fluoro-2-nitroaniline (**1e**)

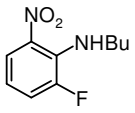
Yield 3.05 g (72%); Red oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.98 (t, *J* = 7.3 Hz, 3H), 1.43-1.51 (m, 2H), 1.68-1.74 (m, 2H), 3.26-3.30 (m, 2H), 6.83 (dd, *J* = 9.4, 4.5 Hz, 1H), 7.21-7.26 (m, 1H), 7.87 (dd, *J* = 9.4, 3.1 Hz, 1H), 7.93 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.7, 20.2, 31.0, 43.0, 111.9 (d, J_{FC} = 26.0 Hz), 115.0 (d, J_{FC} = 6.9 Hz), 125.0 (d, J_{FC} = 23.7 Hz), 130.4 (d, J_{FC} = 9.2 Hz), 142.8, 152.2 (d, J_{FC} = 238.1 Hz).

MS (EI) *m/z* 212 (37, $[M]^+$), 169 (100), 122 (19), 111 (26).

HRMS (EI) *m/z* Calcd. for $C_{10}H_{13}FN_2O_2$: 212.0961; Found 212.0962.



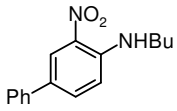
N-Butyl-2-fluoro-6-nitroaniline (**1f**)
Yield 3.45 g (81%); orange oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.96 (t, *J* = 7.3 Hz, 3H), 1.44-1.51 (m, 2H), 1.67-1.73 (m, 2H), 3.55-3.60 (m, 2H), 6.55 (ddd *J* = 8.7, 7.8, 4.6 Hz, 1H), 7.15 (ddd *J* = 13.9, 7.8, 1.6 Hz, 1H), 7.82 (br s, 1H), 7.93, 7.96 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.7, 19.9, 32.9, 45.9 (d, J_{FC} = 12.7 Hz), 114.0 (d, J_{FC} = 8.1 Hz), 121.8 (d, J_{FC} = 20.8 Hz), 122.5 (d, J_{FC} = 2.9 Hz), 134.6 (d, J_{FC} = 6.9 Hz), 136.9 (d, J_{FC} = 12.1 Hz), 152.7 (d, J_{FC} = 245.1 Hz).

MS (EI) *m/z* 212 (40, $[M]^+$), 169 (100), 122 (20), 111 (30).

HRMS (EI) *m/z* Calcd. for $C_{10}H_{13}FN_2O_2$: 212.0961; Found 212.0956.



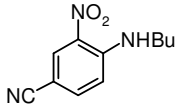
N-Butyl-*N*-(3-nitro-1,1'-biphenyl-4-yl)amine (**1g**)
Yield 4.32 g (80%); red solid, mp 75-77 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.02 (t, *J* = 7.3 Hz, 3H), 1.48-1.55 (m, 2H), 1.72-1.78 (m, 2H), 3.33-3.37 (m, 2H), 6.94 (d, *J* = 9.0 Hz, 1H), 7.32-7.35 (m, 1H), 7.42-7.45 (m, 2H), 7.55-7.57 (m, 2H), 7.72 (dd, *J* = 9.0, 2.2 Hz, 1H), 8.1 (br s, 1H), 8.44 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.7, 20.2, 31.0, 42.8, 114.3, 124.4, 126.1, 127.0, 128.2, 128.9, 131.8, 134.9, 138.8, 144.8.

MS (EI) *m/z* 270 (73, $[M]^+$), 227 (100), 152 (26).

HRMS (EI) *m/z* Calcd. for $C_{16}H_{18}N_2O_2$: 270.13.68; Found 270.1368.



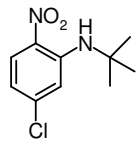
4-(Butylamino)-3-nitrobenzonitrile (**1h**)
Yield 4.30 g (98%); yellow crystals, mp 73-76 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.98 (t, *J* = 7.3 Hz, 3H), 1.43-1.51 (m, 2H), 1.70-1.76 (m, 2H), 3.33-3.37 (m, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 7.58 (dd, *J* = 9.0, 1.8 Hz, 1H), 8.38 (br s, 1H), 8.46 (d, *J* = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.6, 20.0, 30.6, 42.9, 97.7, 114.8, 117.9, 131.1, 132.1, 137.5, 147.1.

MS (EI) *m/z* 219 (32,$[M]^+$), 176 (100), 118 (24).

HRMS (EI) *m/z* Calcd. for $C_{11}H_{13}N_3O_2$: 219.1008; Found 219.1008.



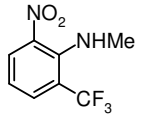
N-(*tert*-Butyl)-5-chloro-2-nitroaniline (**1m**)
Yield 3.25 g (71%); orange crystals, mp 99-101 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.50 (s, 9H), 6.55 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 8.42 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 29.6, 51.9, 115.1, 115.2, 128.7, 131.0, 141.8, 145.1.

MS (EI) *m/z* 230 (13), 228 (38), 215 (36), 213 (100, $[M]^+$), 174 (22), 172 (66).

HRMS (EI) *m/z* Calcd. for $C_{10}H_{13}{}^{35}ClN_2O_2$: 228.0666; Found 228.0669.



N-Methyl-2-nitro-6-(trifluoromethyl)aniline (**1n**)

Yield 3.34 g (76%); red oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.03 (q, *J* = 1.7 Hz, 3H), 6.79 (t, *J* = 7.7 Hz, 1H), 7.04 (br s, 1H), 7.78 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.4 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 33.8, 115.4, 118.0 (q, J_{FC} = 31.2 Hz), 123.8 (q, J_{FC} = 272.8 Hz), 130.7 (q, J_{FC} = 1.2 Hz), 134.0 (q, J_{FC} = 6.4 Hz), 137.6, 144.5 (q, J_{FC} = 1.2 Hz),

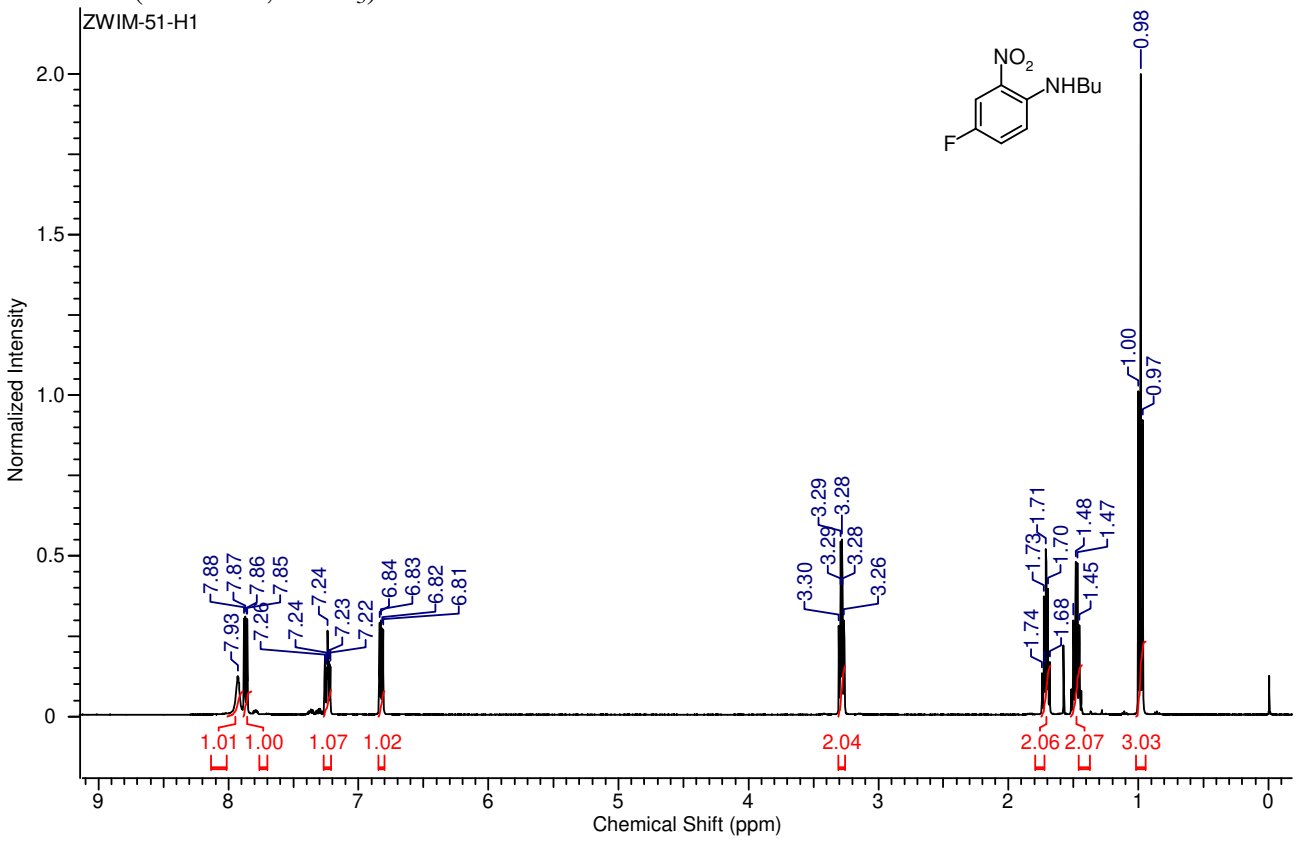
MS (EI) *m/z* 220 (73, $[M]^+$), 182 (32), 167 (26), 145 (47), 127 (100), 105 (52).

HRMS (EI) *m/z* Calcd. for $C_8H_7F_3N_2O$: 220.0460; Found 220.0471.

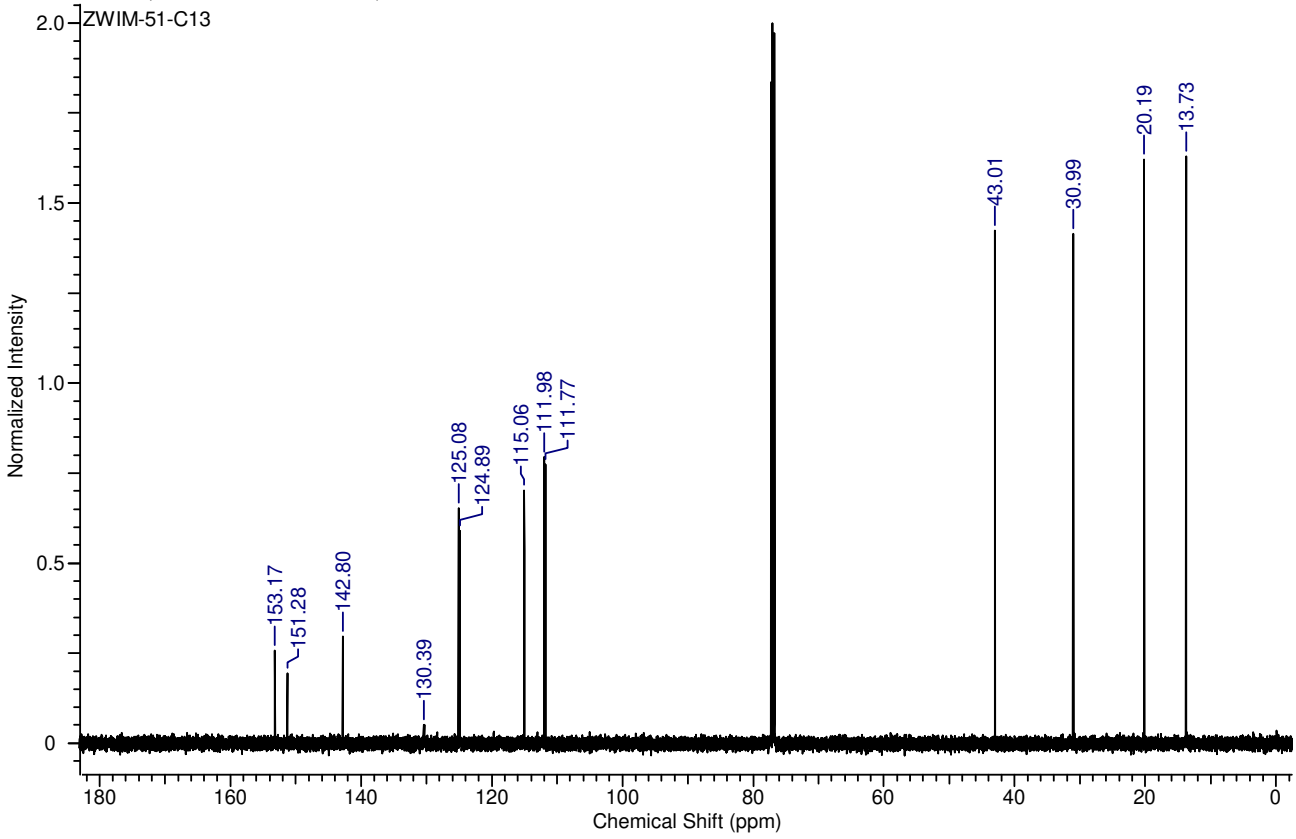
Starting 2-nitroanilines

1e

^{1}H NMR (500 MHz, $CDCl_3$)

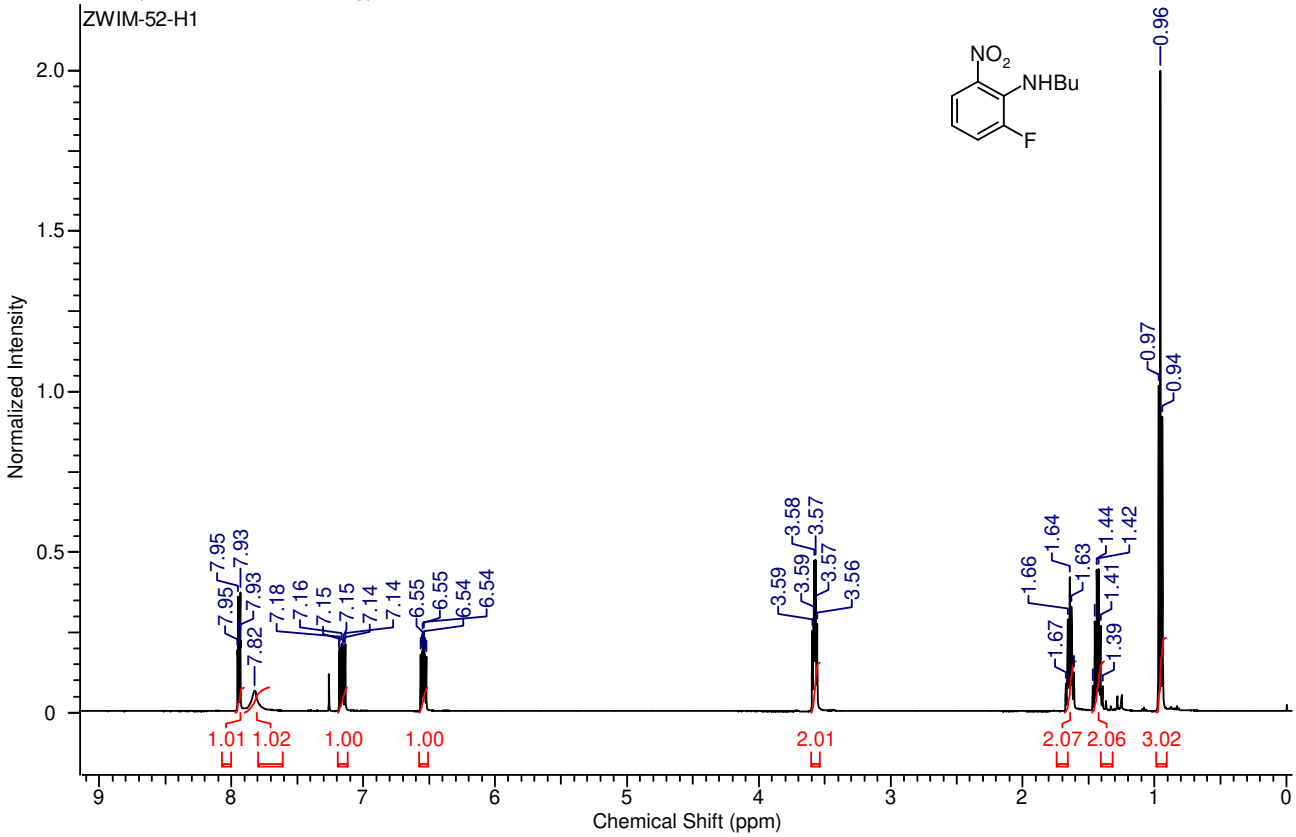


^{13}C NMR (125 MHz, $CDCl_3$)

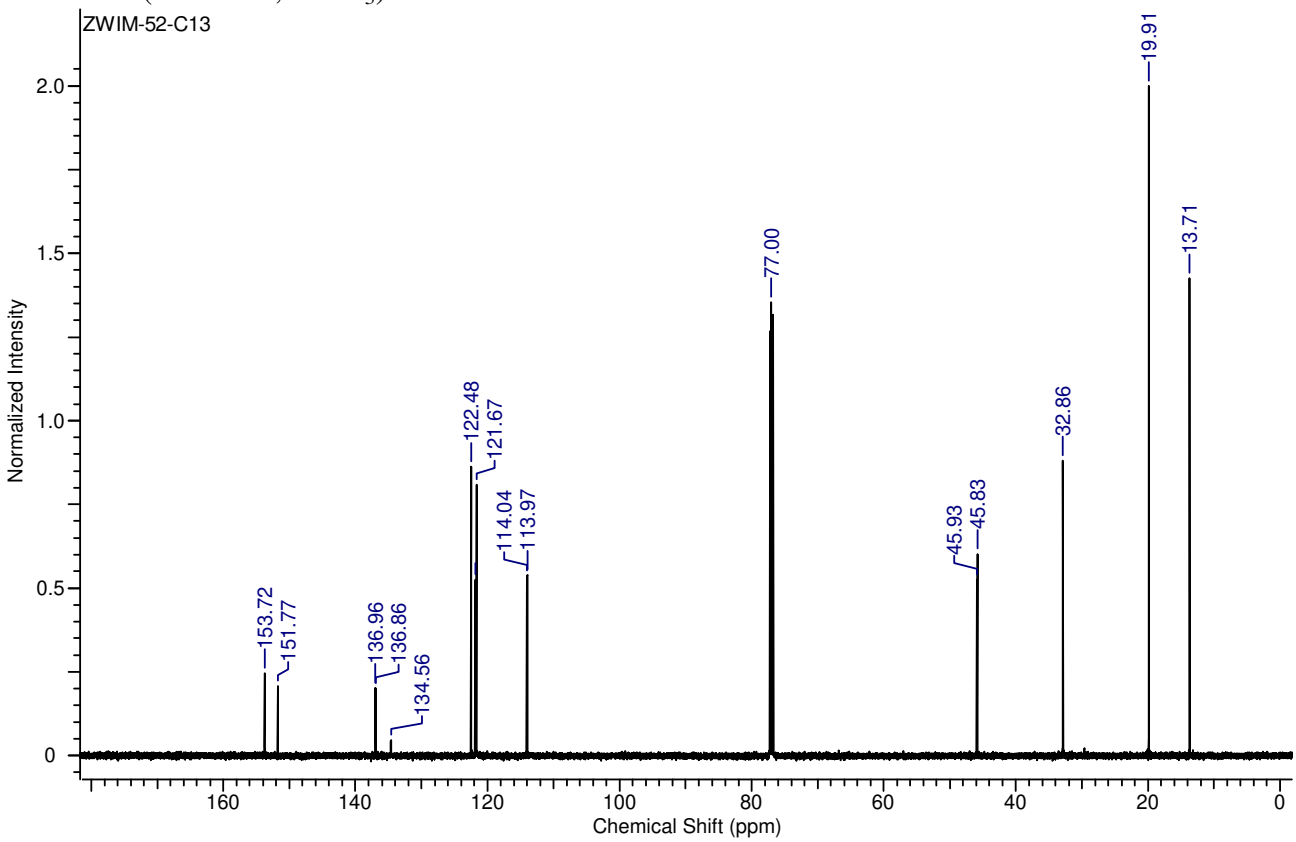


1f

^{1}H NMR (500 MHz, $CDCl_3$)

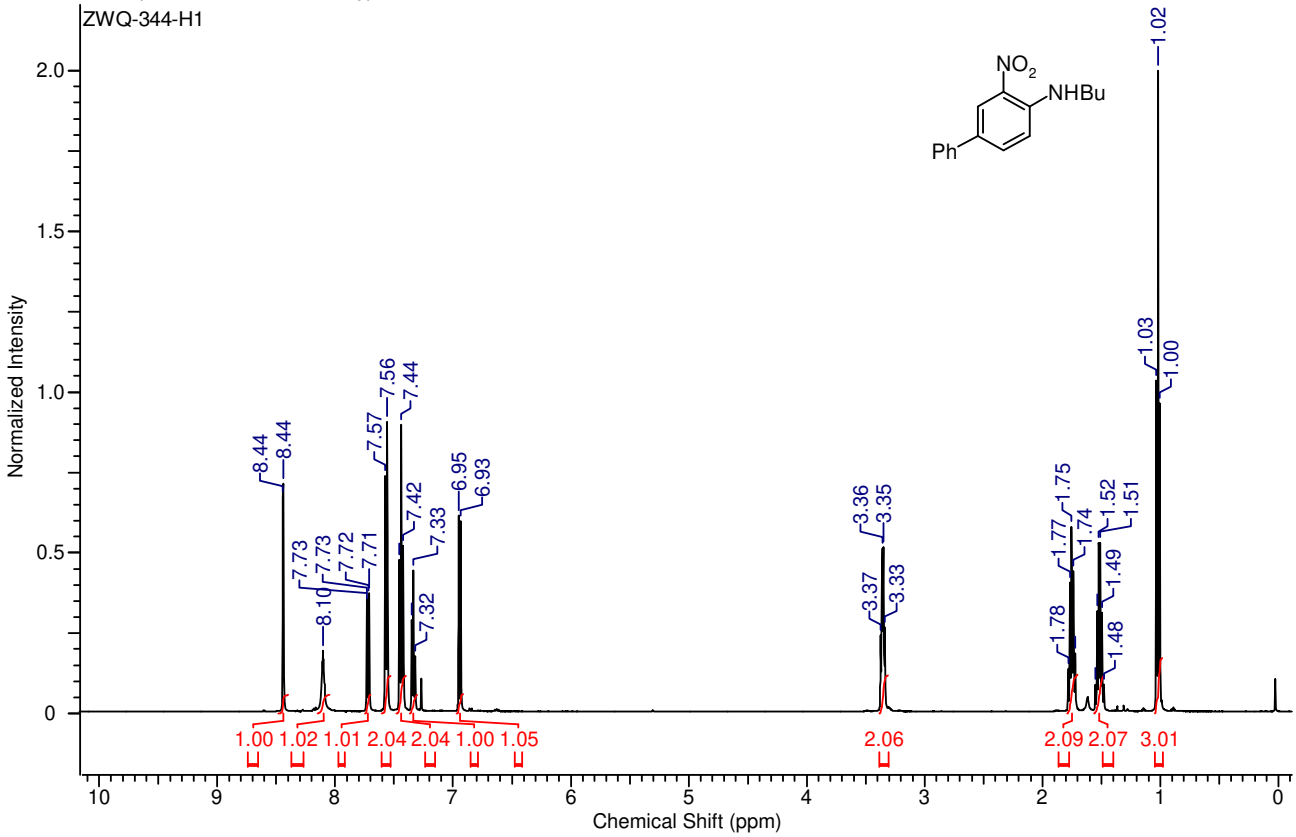


^{13}C NMR (125 MHz, $CDCl_3$)

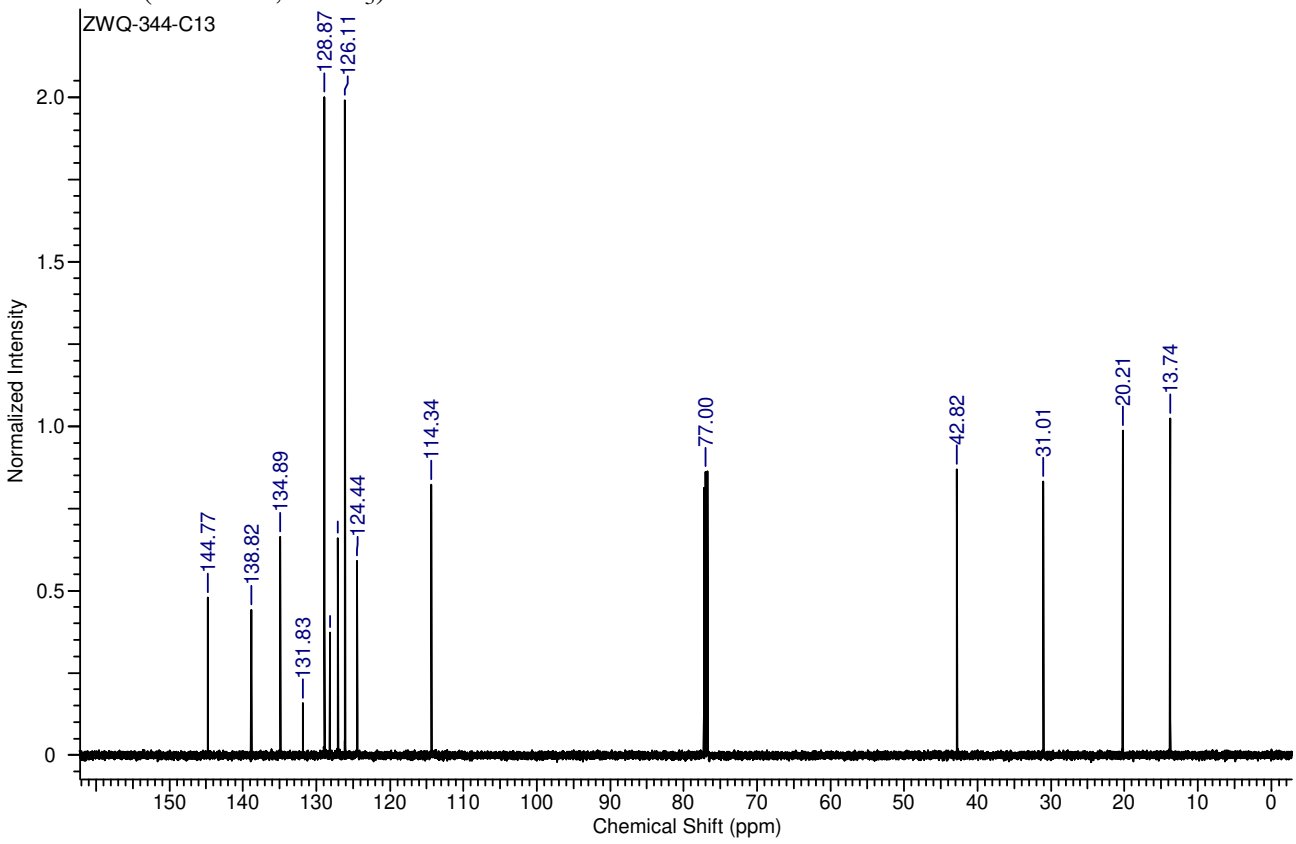


1g

^{1}H NMR (500 MHz, $CDCl_3$)

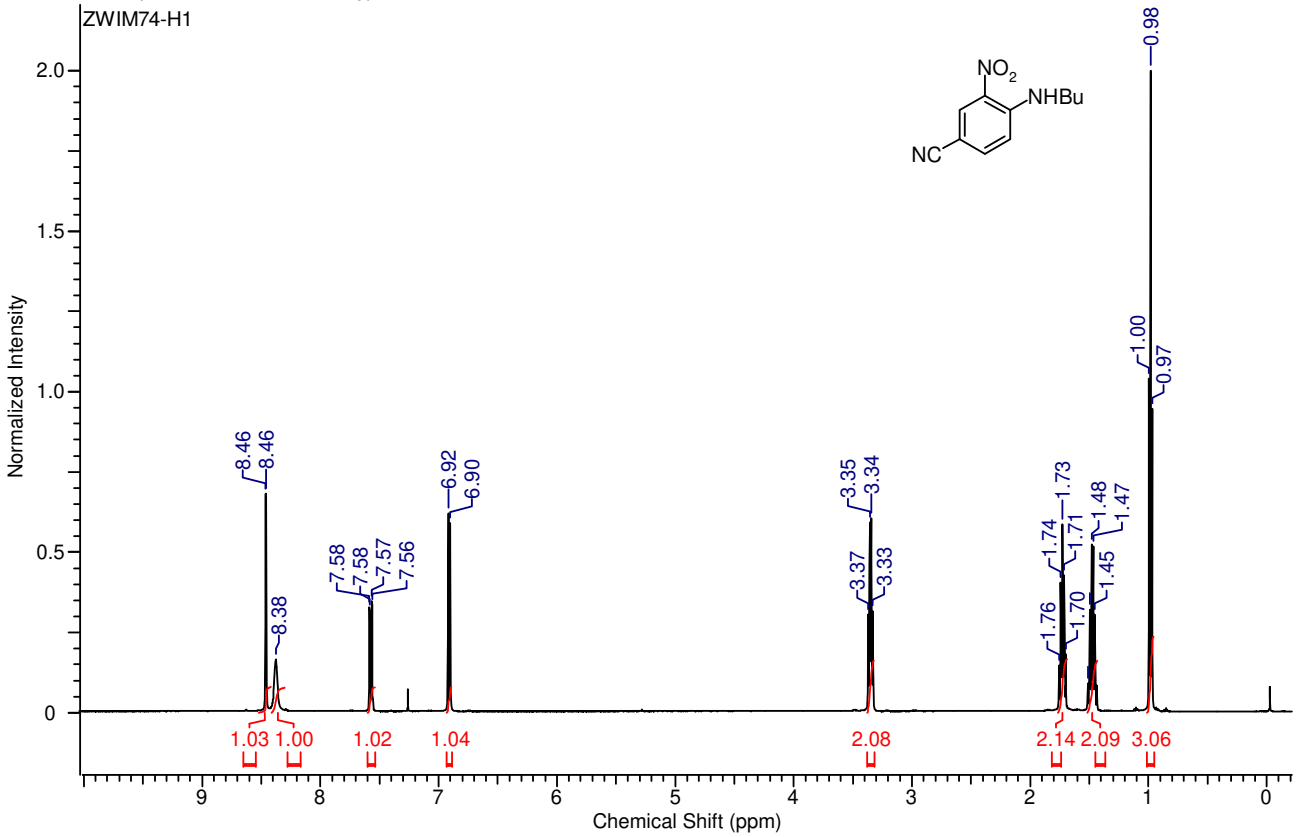


^{13}C NMR (125 MHz, $CDCl_3$)

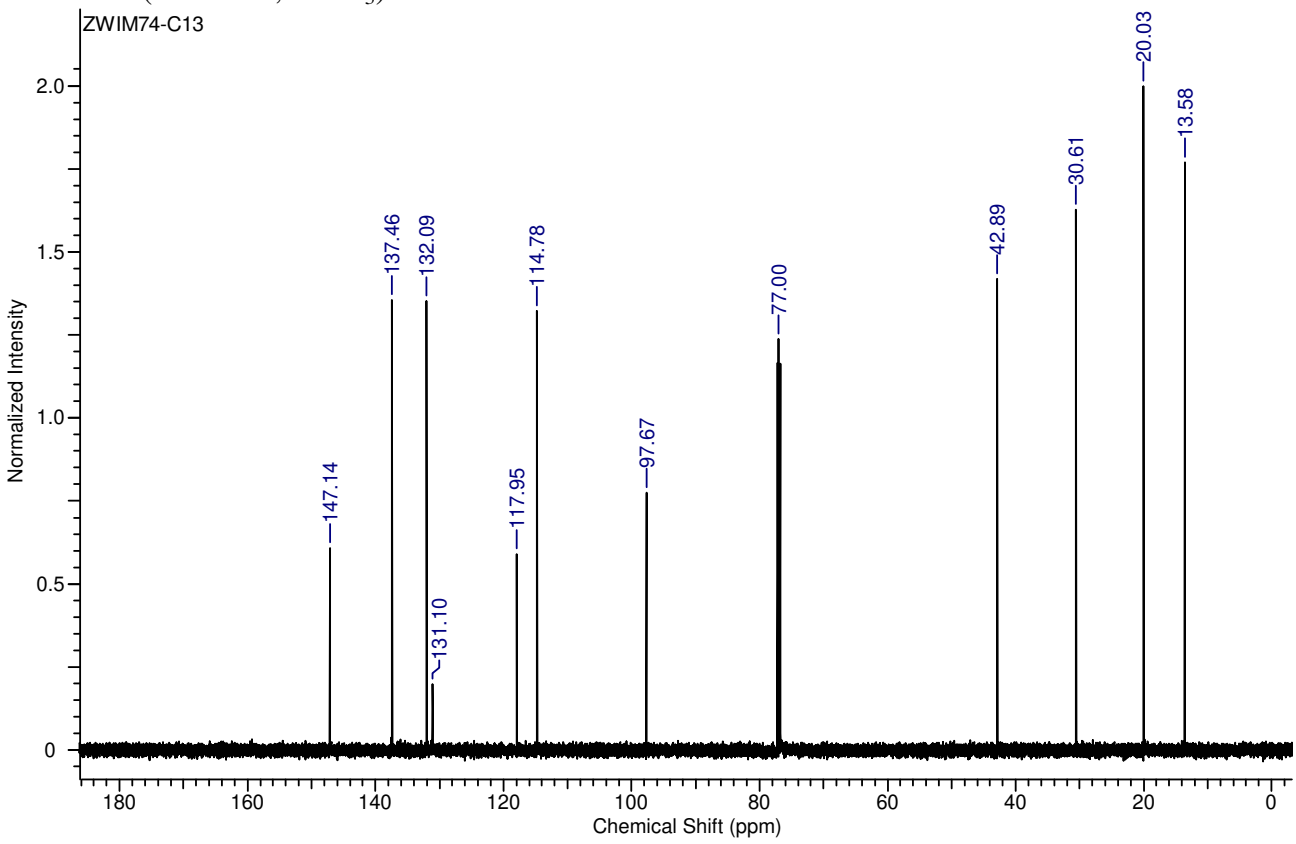


1h

^{1}H NMR (500 MHz, $CDCl_3$)

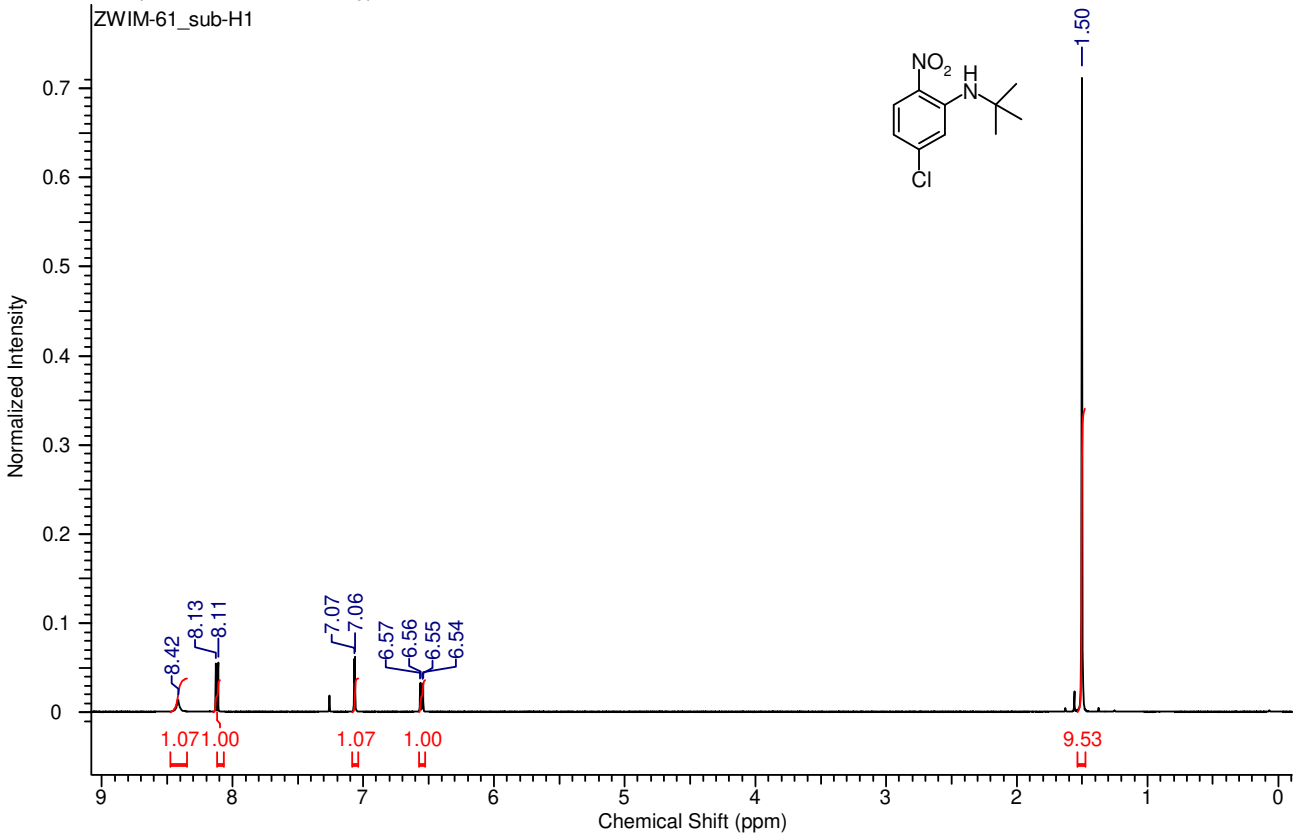


^{13}C NMR (125 MHz, $CDCl_3$)

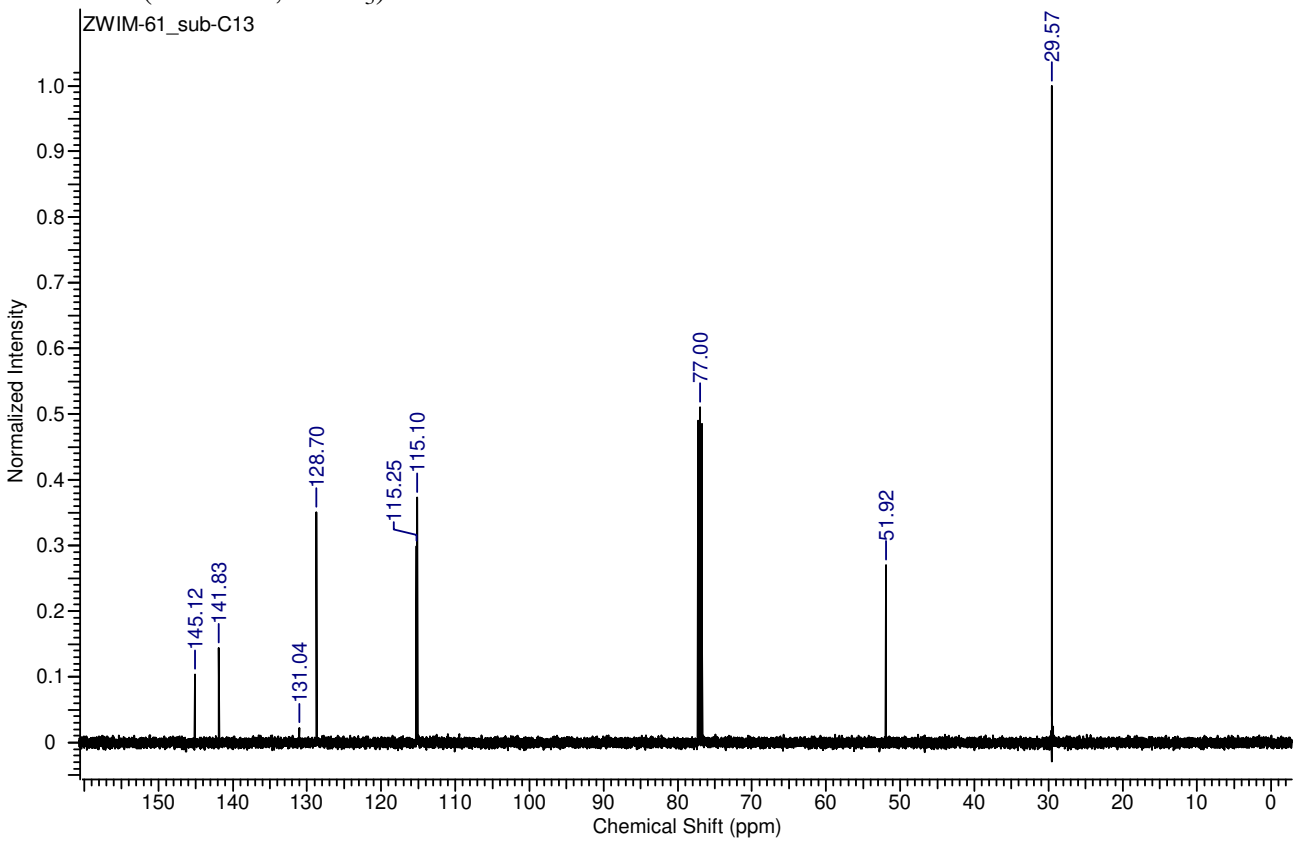


1m

^{1}H NMR (500 MHz, $CDCl_3$)

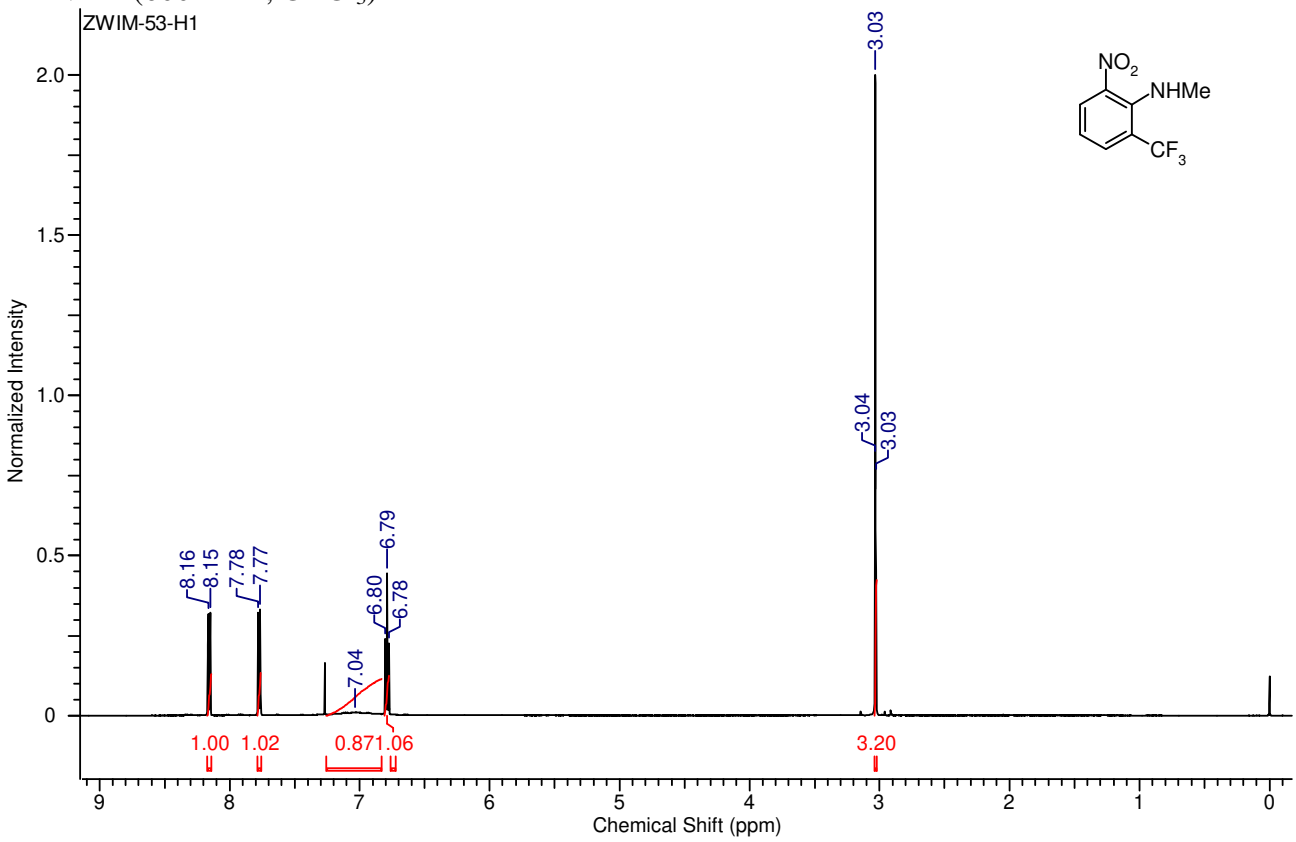


^{13}C NMR (125 MHz, $CDCl_3$)

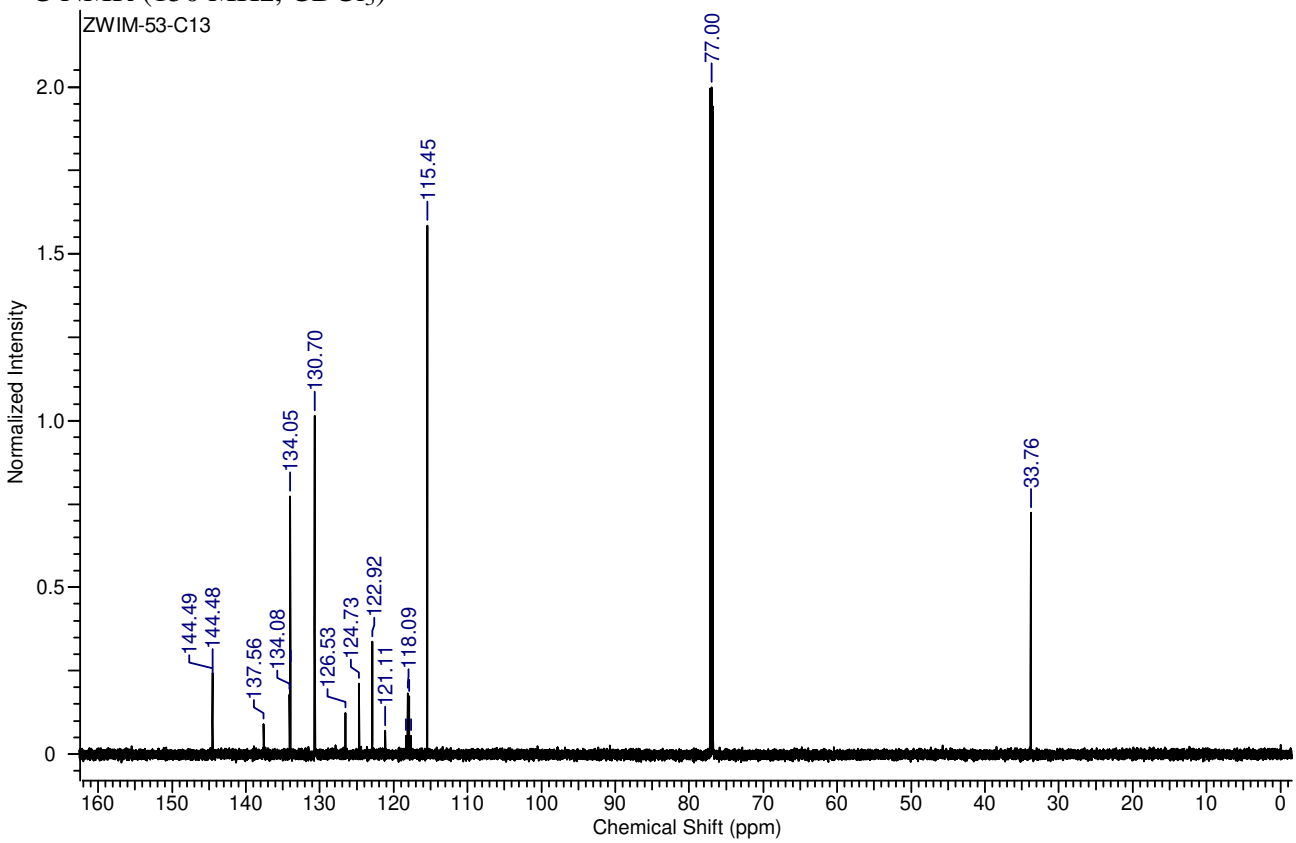


1n

^{1}H NMR (600 MHz, $CDCl_3$)



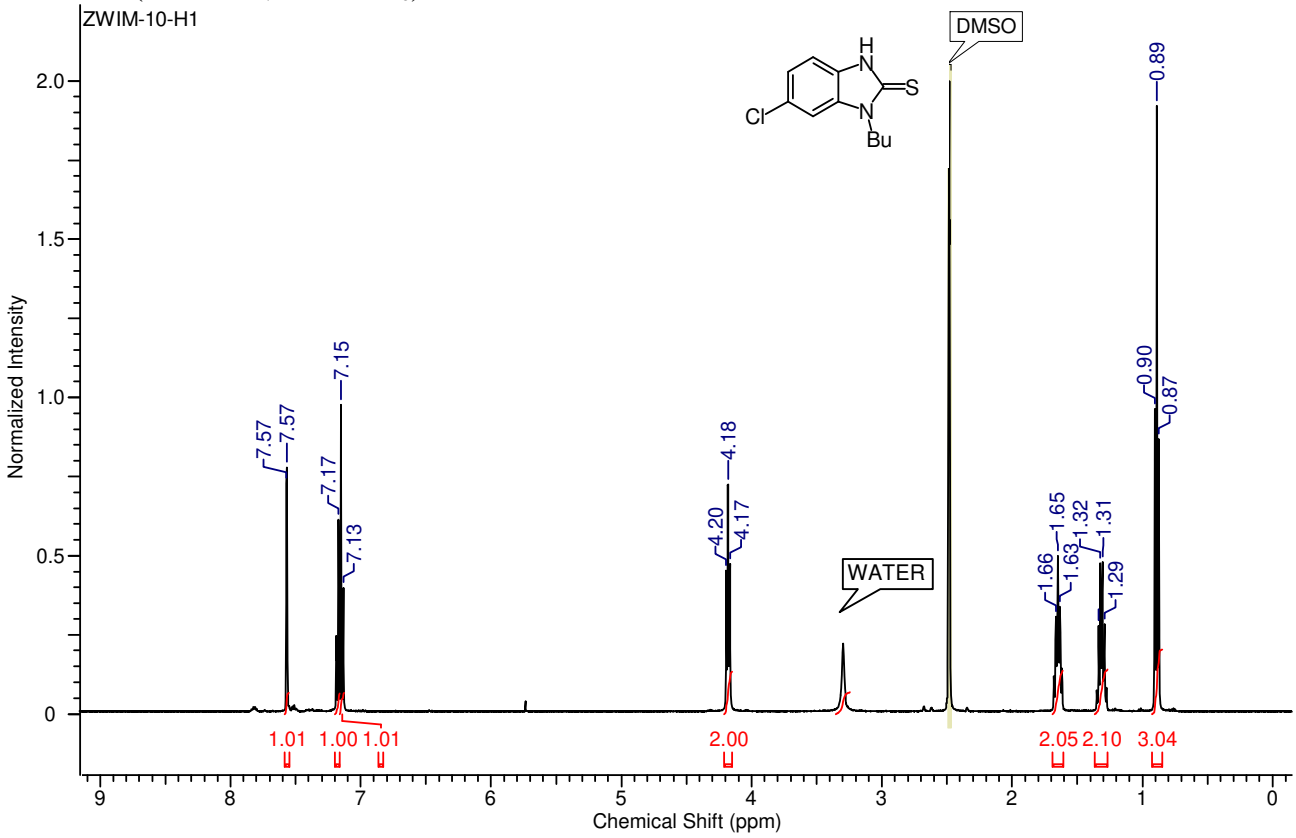
^{13}C NMR (150 MHz, $CDCl_3$)



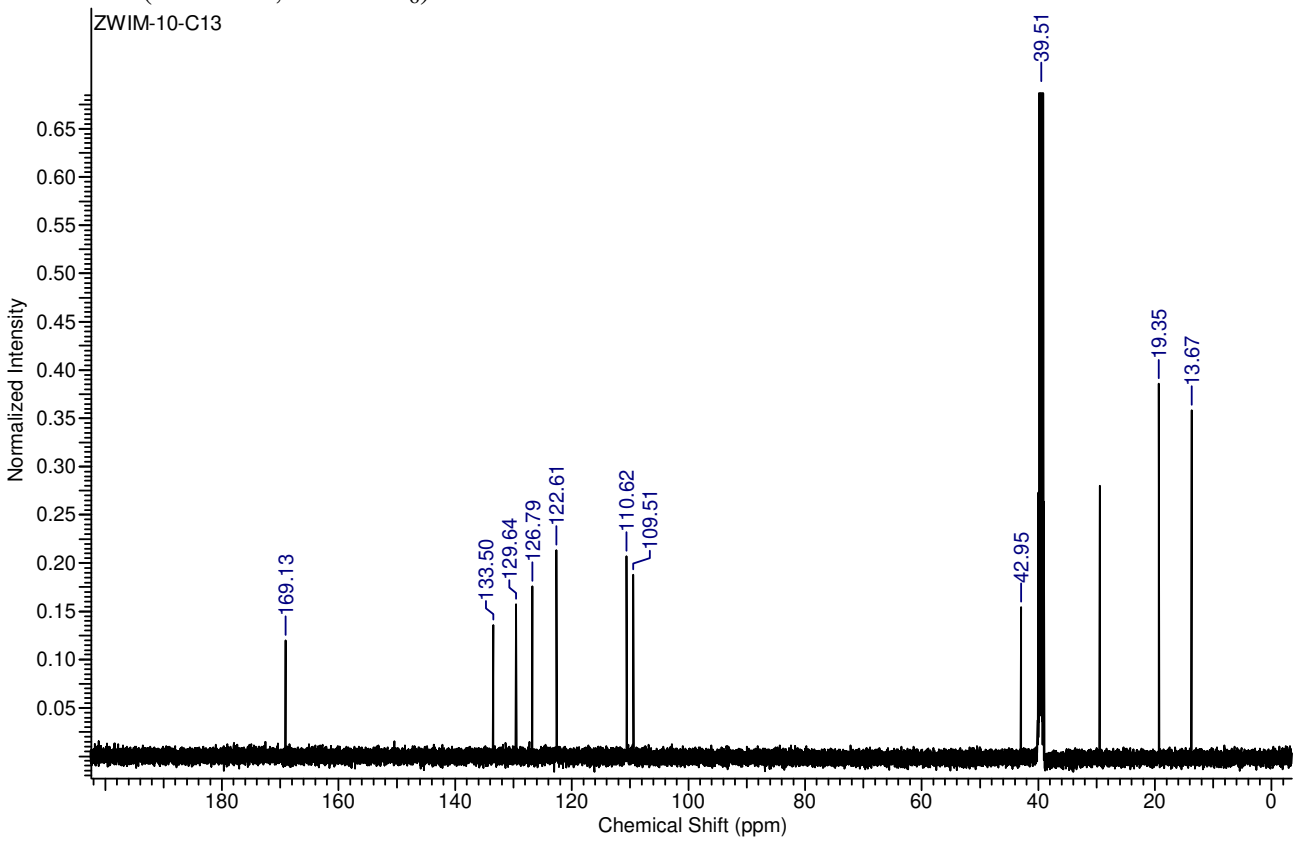
***N*-alkyl-benzimidazole-thiones 3**

3a

^{1}H NMR (500 MHz, DMSO-d_6)

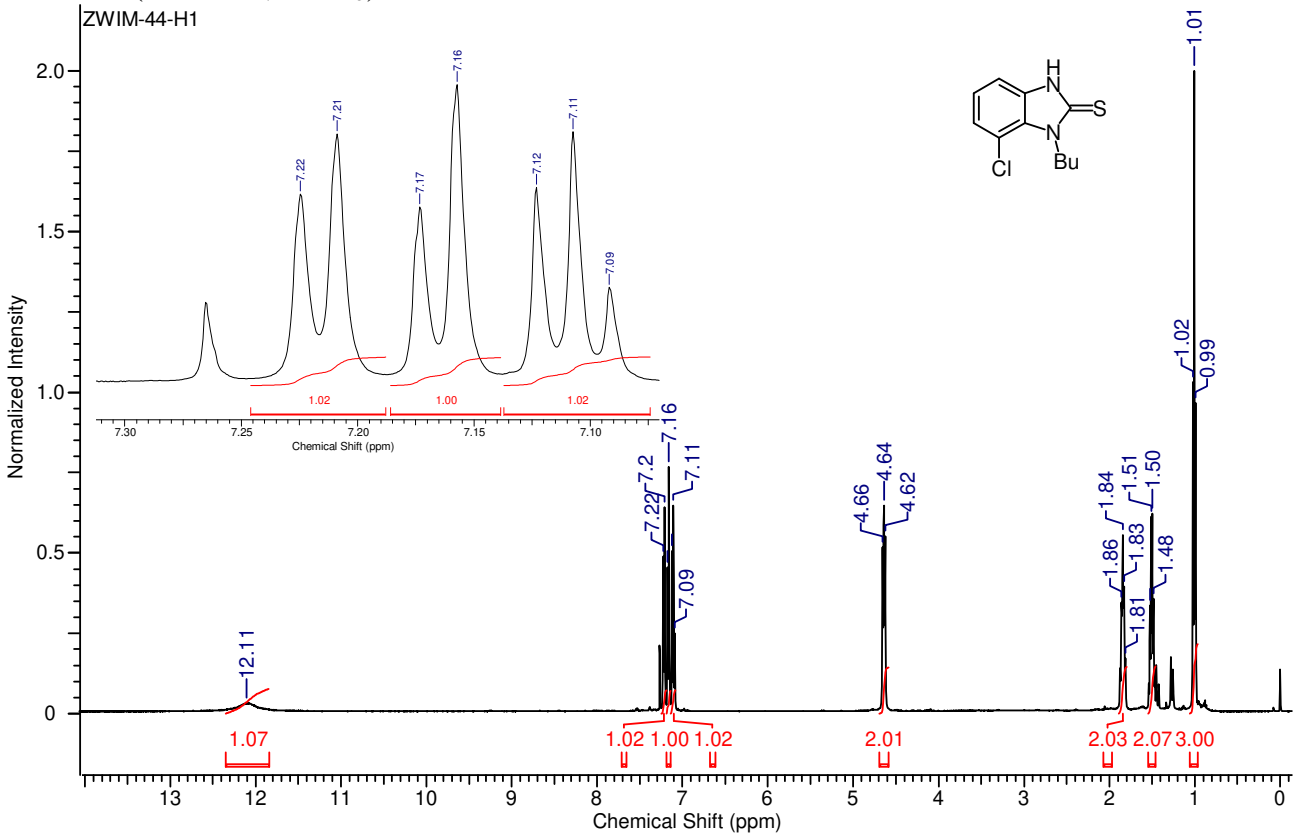


^{13}C NMR (125 MHz, DMSO-d_6)

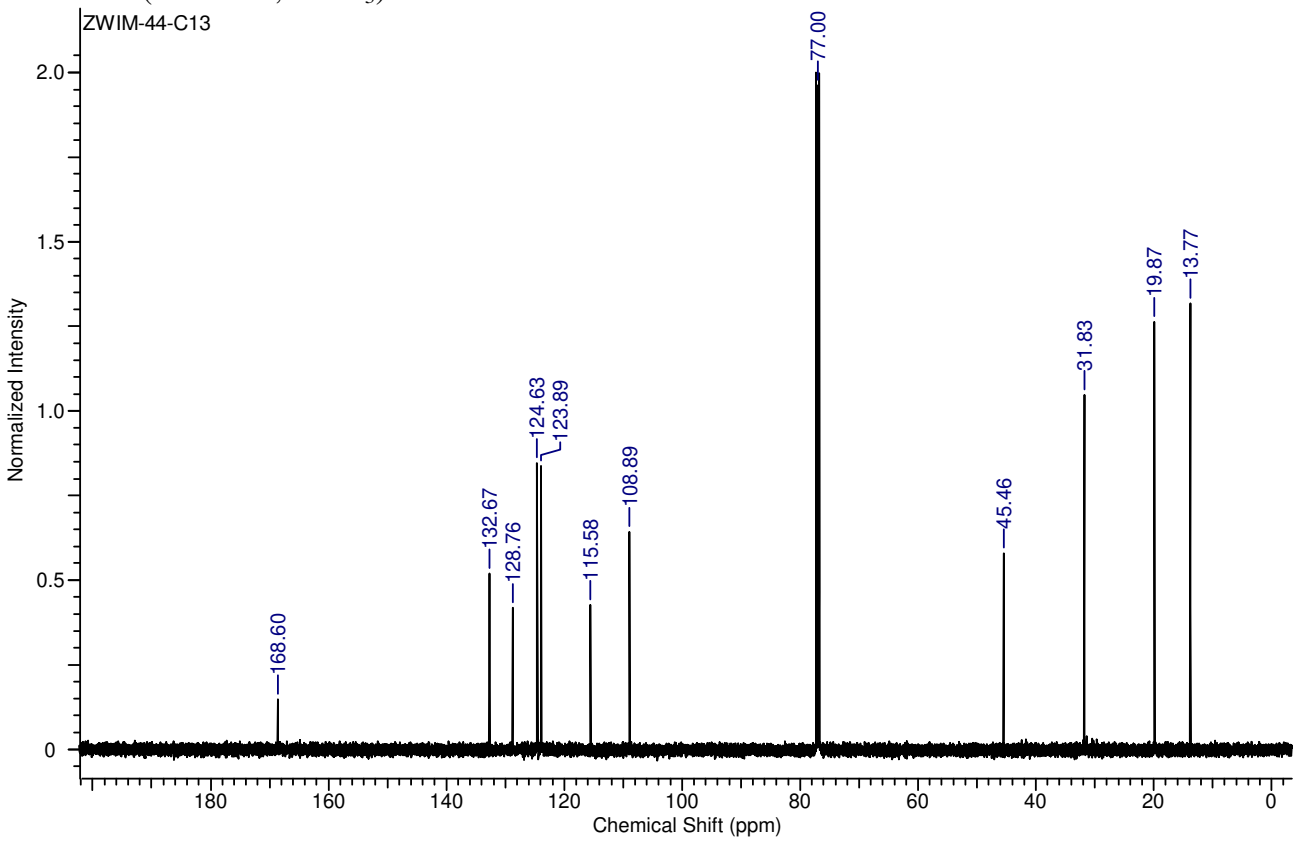


3b

^{1}H NMR (500 MHz, $CDCl_3$)

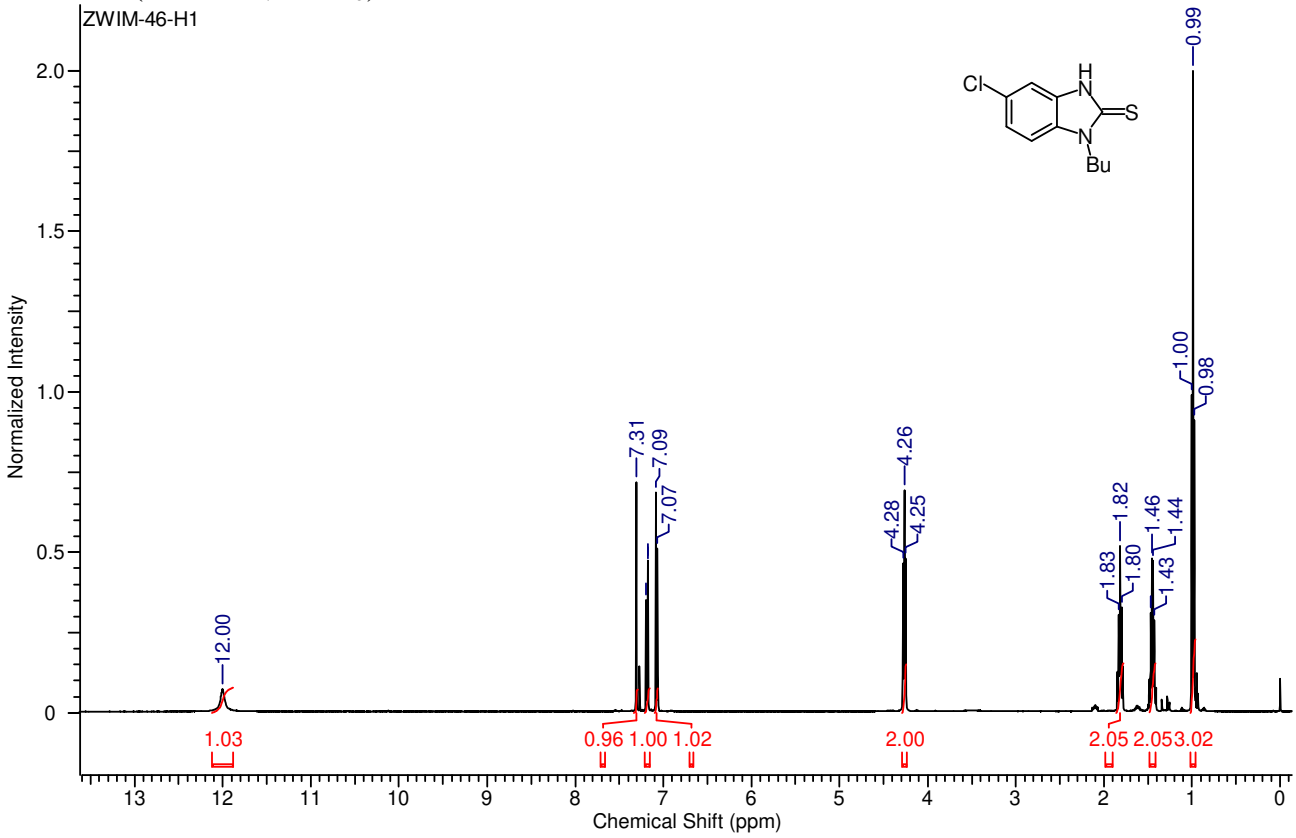


^{13}C NMR (125 MHz, $CDCl_3$)

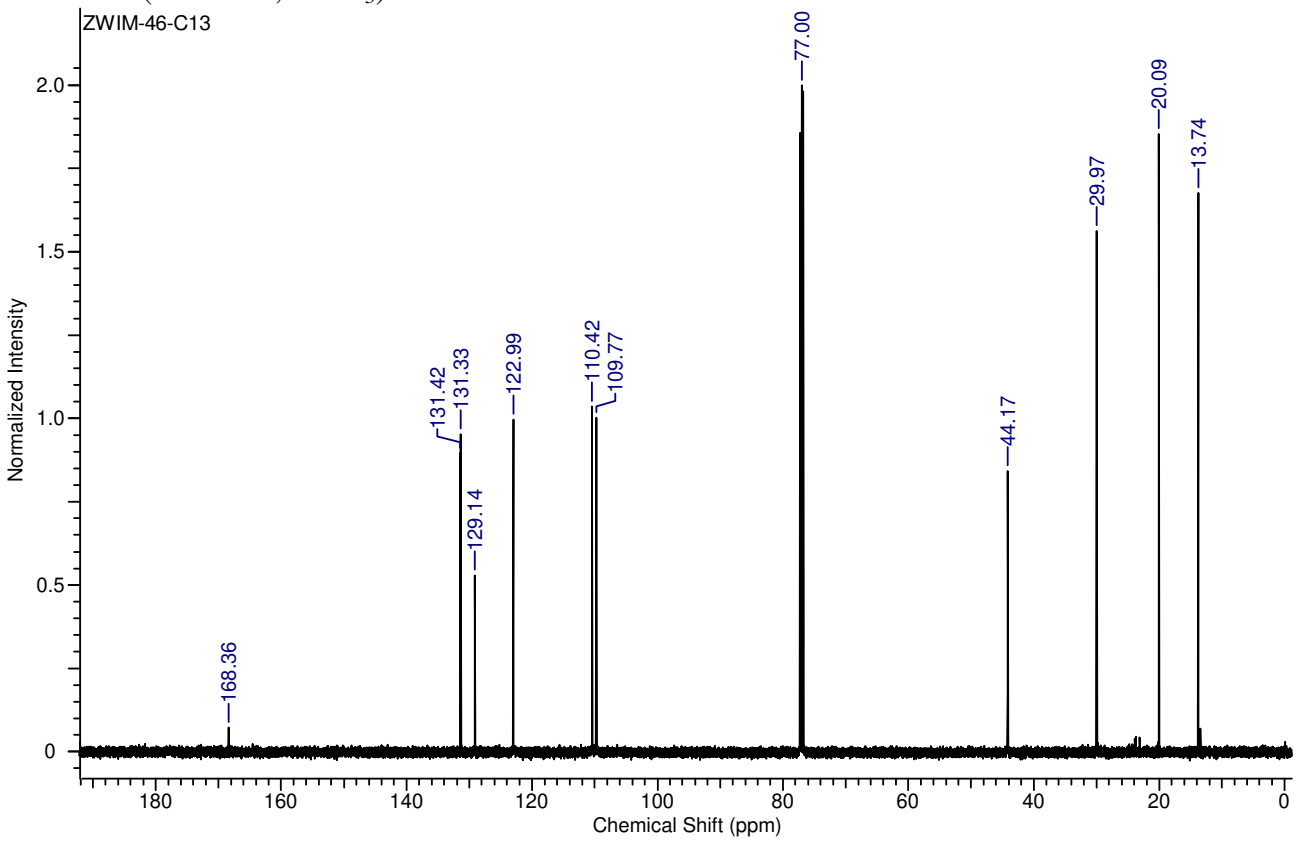


3c

^{1}H NMR (500 MHz, $CDCl_3$)

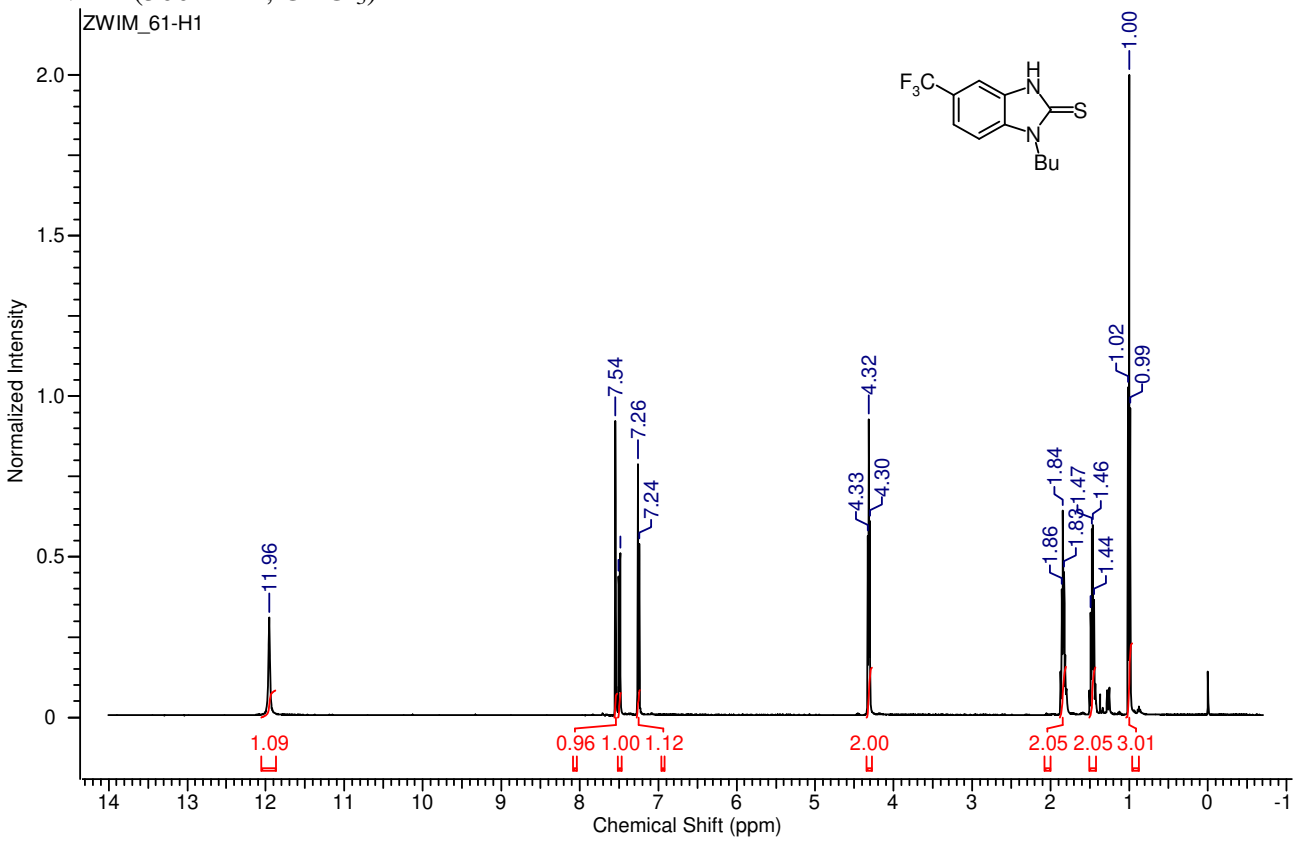


^{13}C NMR (125 MHz, $CDCl_3$)

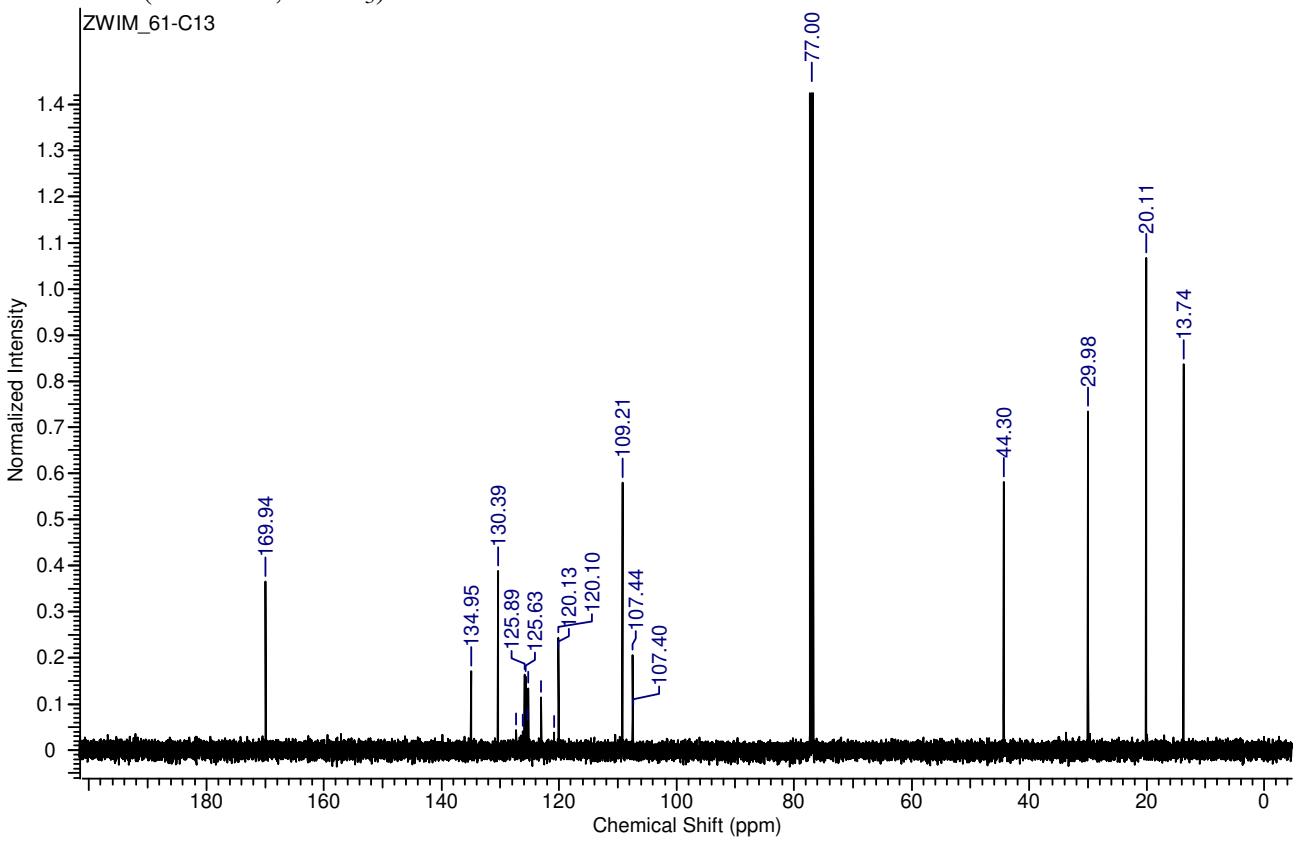


3d

^{1}H NMR (500 MHz, $CDCl_3$)

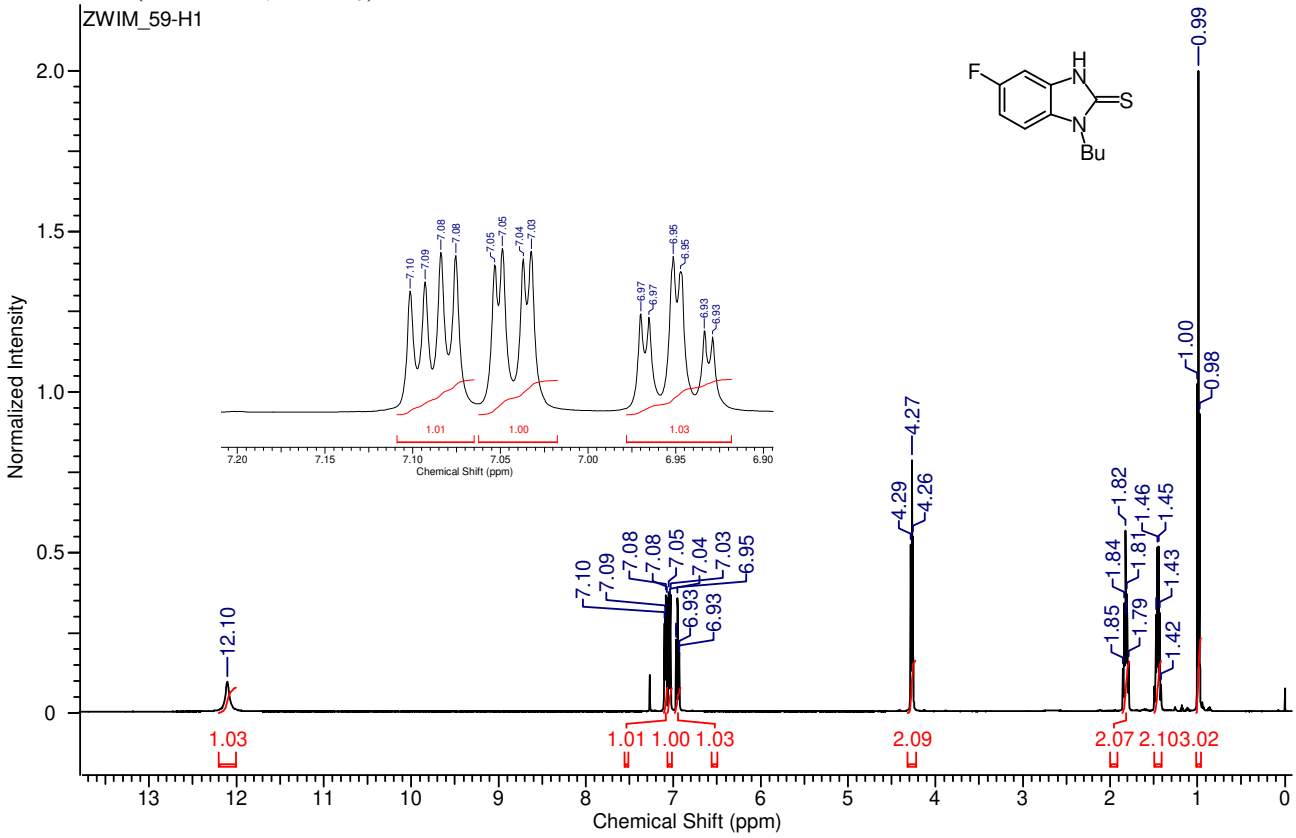


^{13}C NMR (125 MHz, $CDCl_3$)

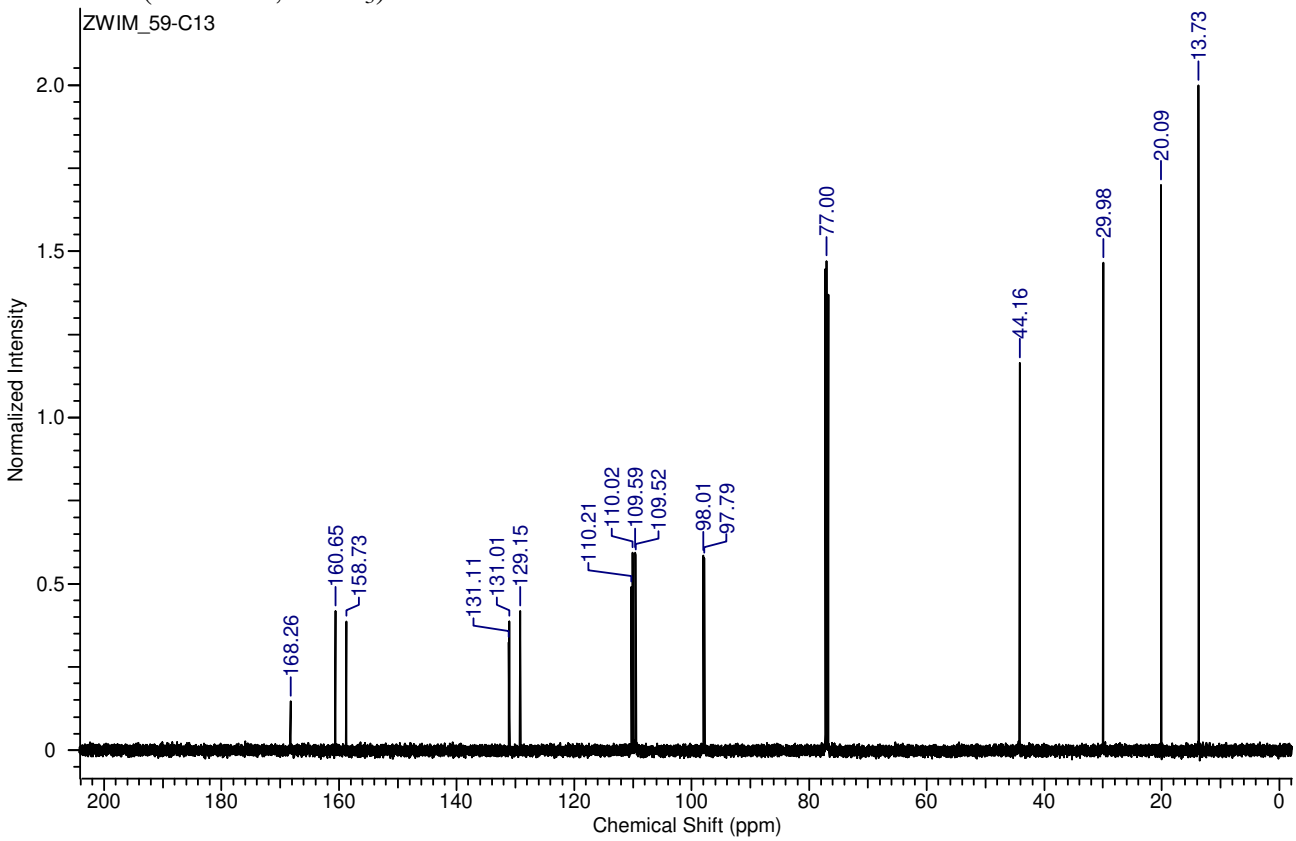


3e

^{1}H NMR (500 MHz, $CDCl_3$)

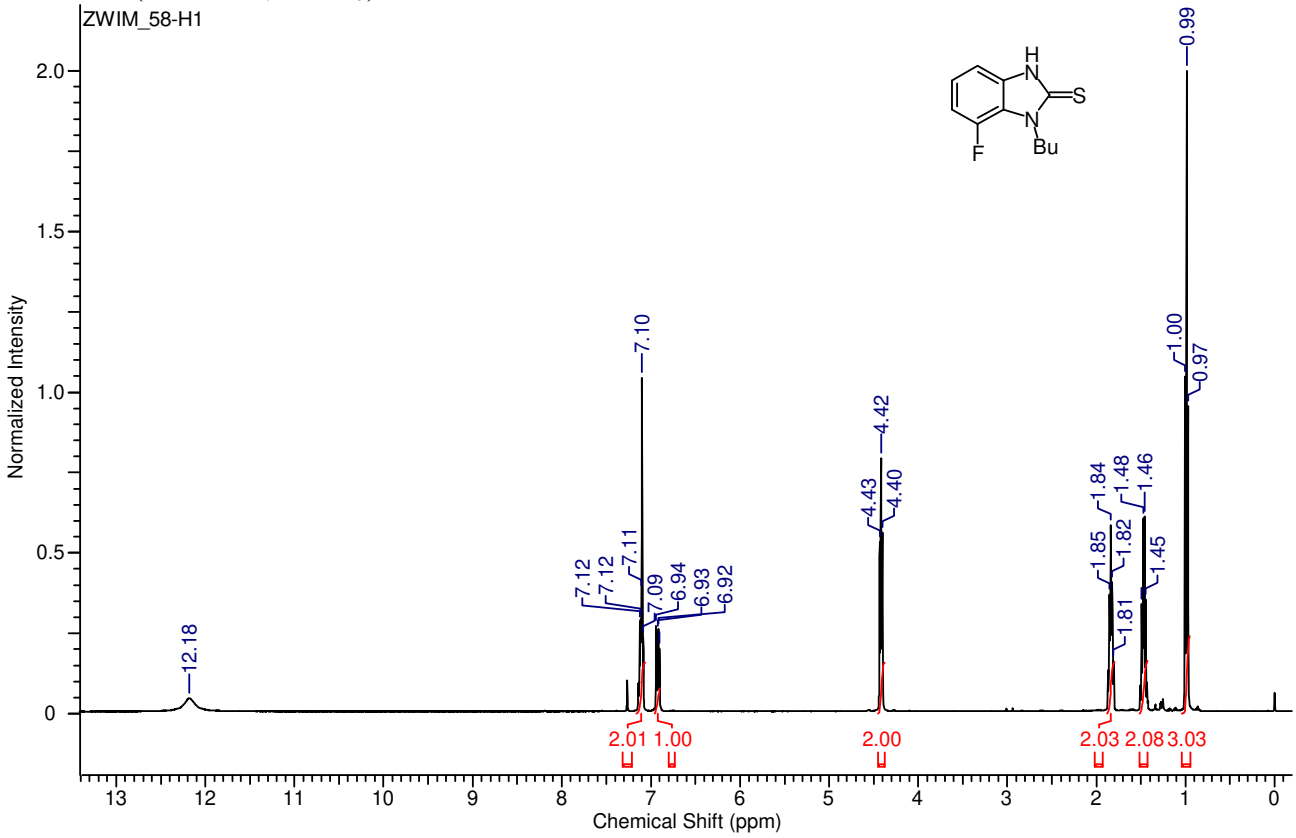


^{13}C NMR (125 MHz, $CDCl_3$)

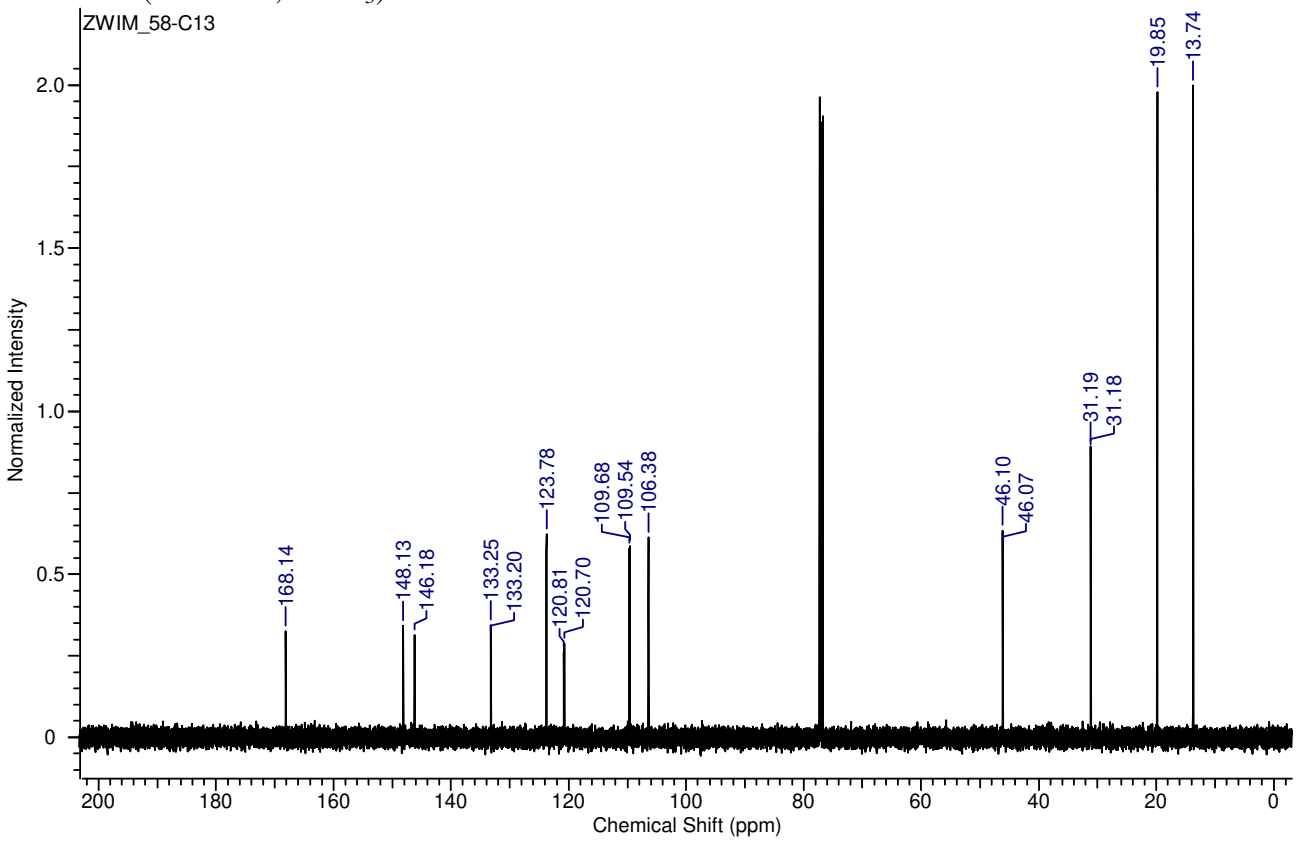


3f

^{1}H NMR (500 MHz, $CDCl_3$)

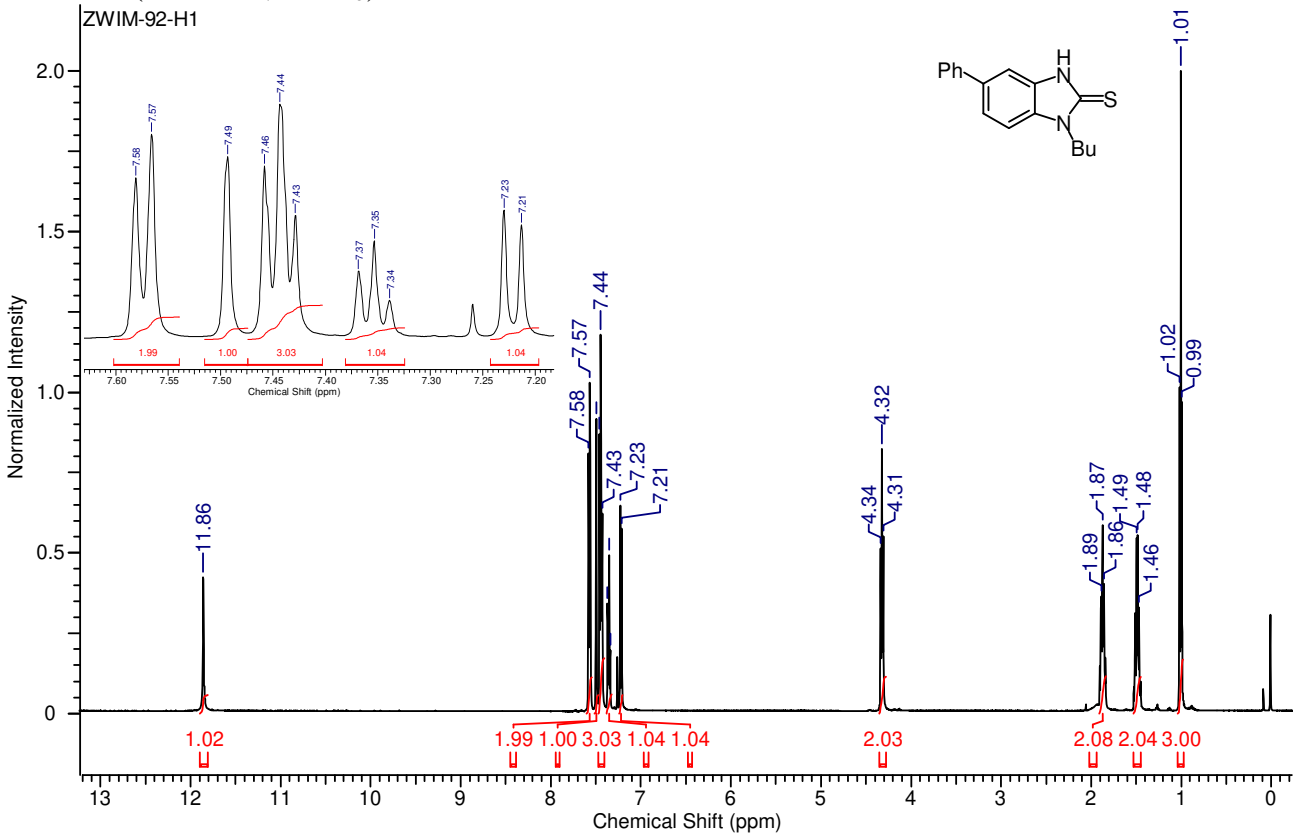


^{13}C NMR (125 MHz, $CDCl_3$)

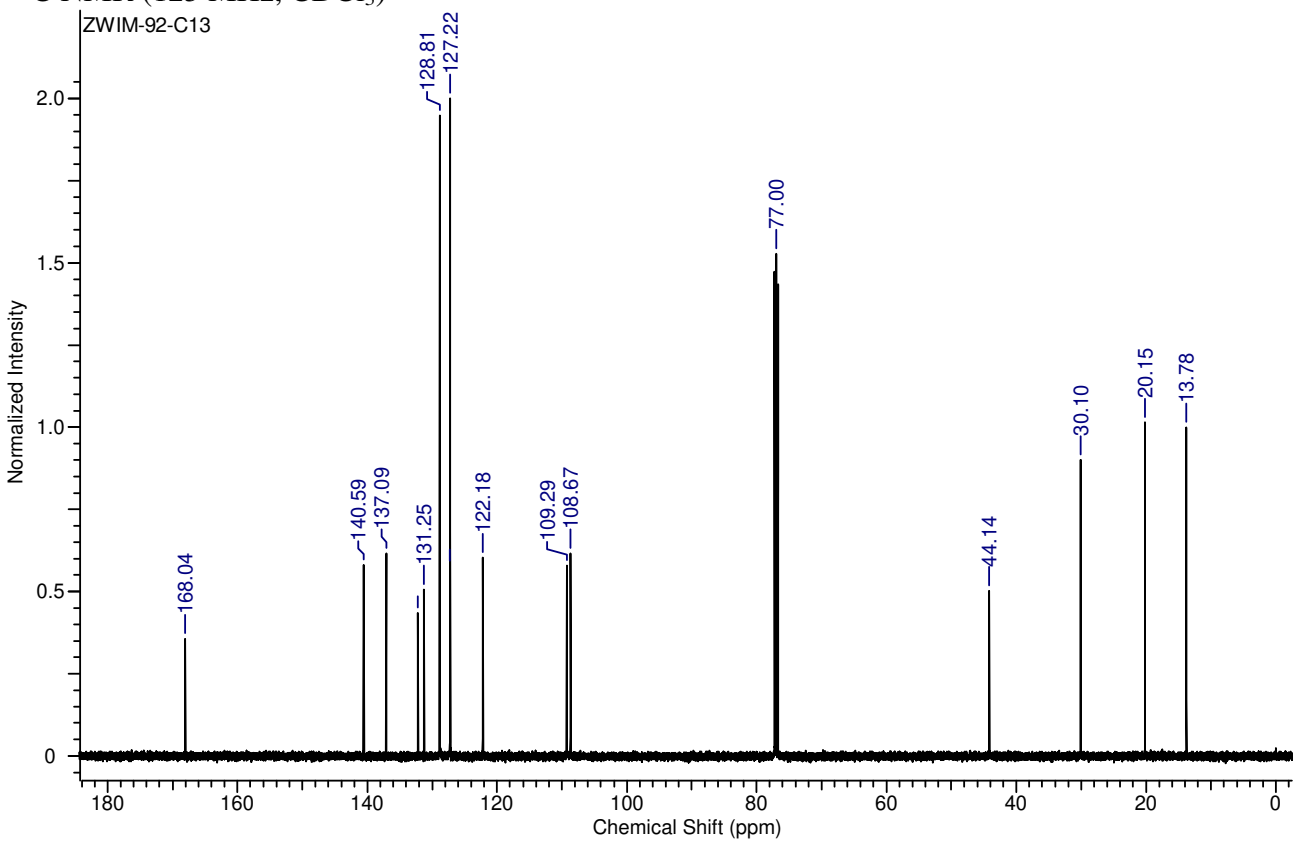


3g

^{1}H NMR (500 MHz, $CDCl_3$)

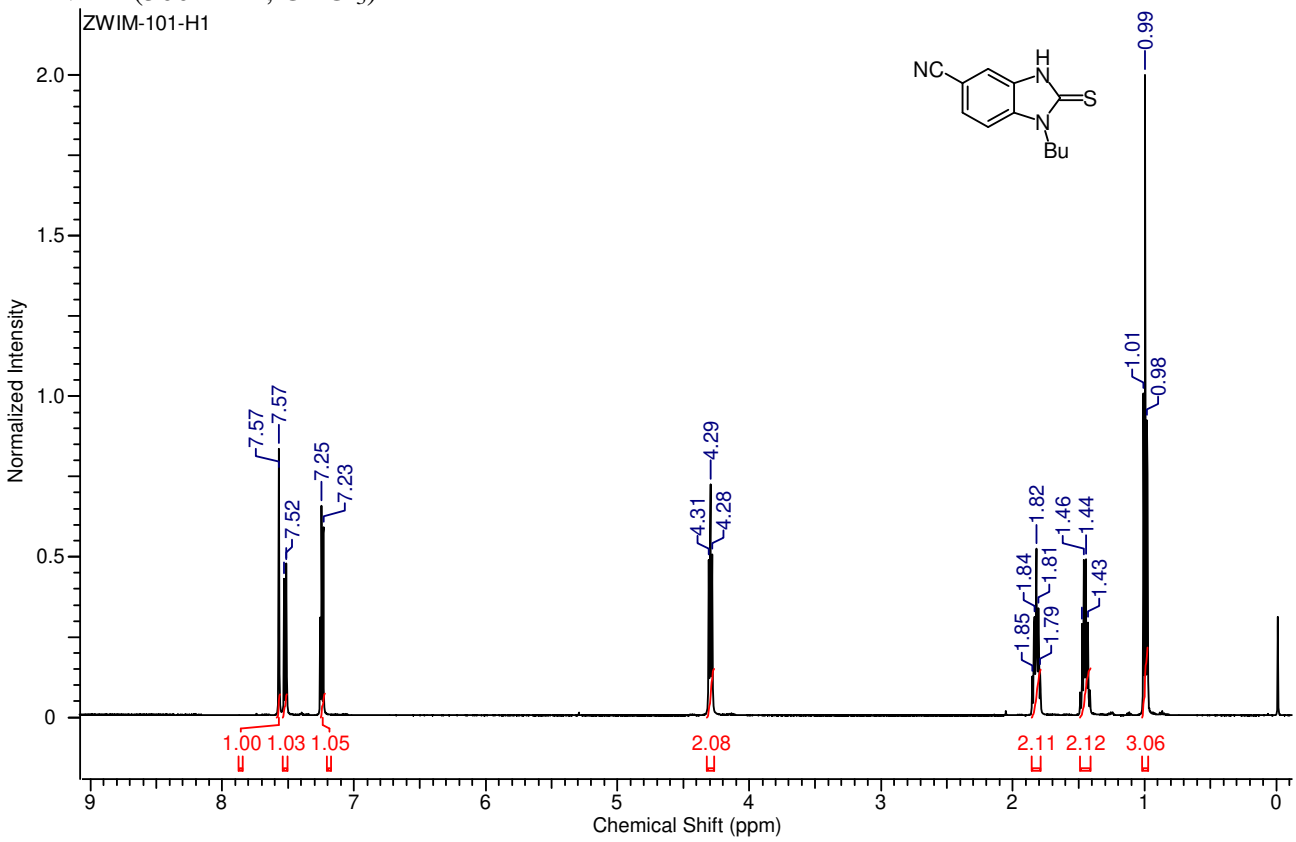


^{13}C NMR (125 MHz, $CDCl_3$)

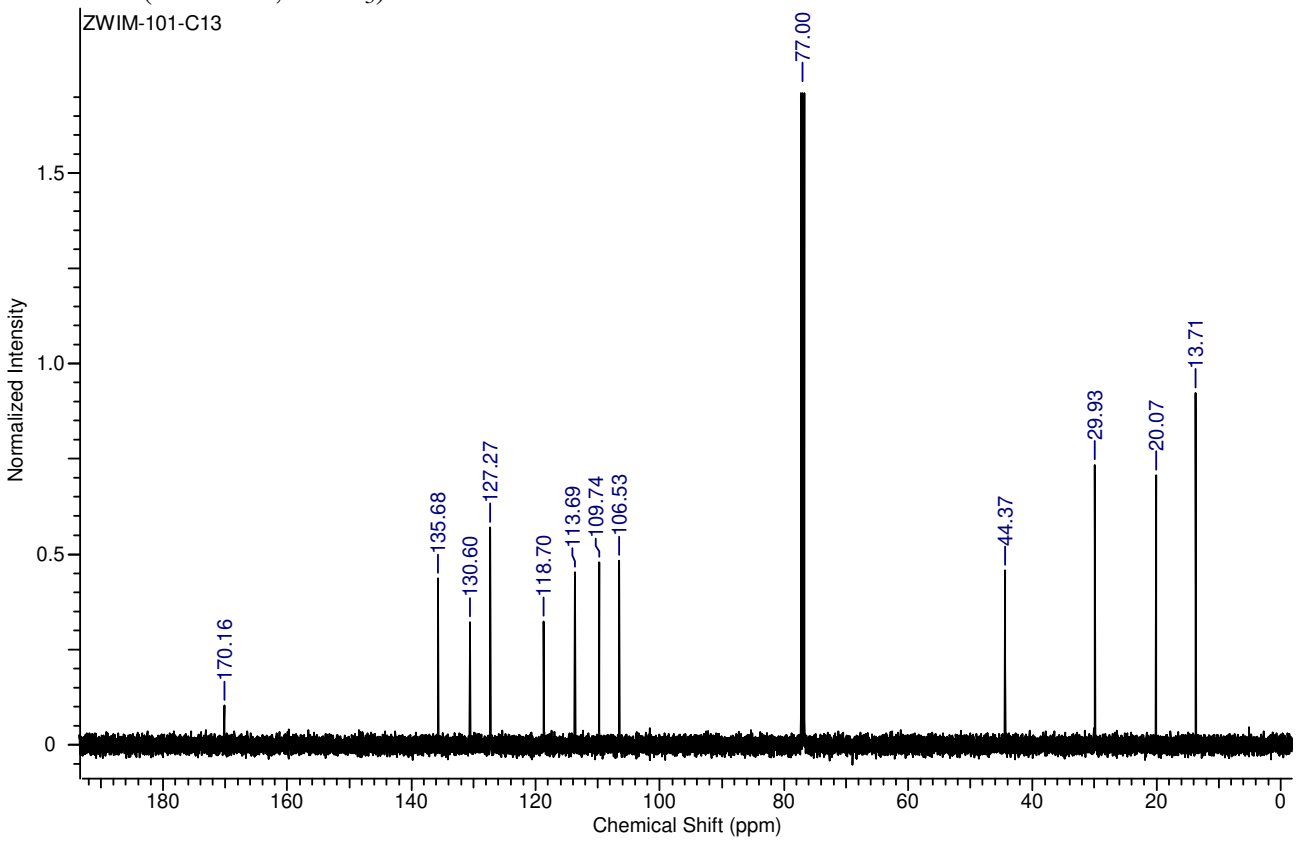


3h

^{1}H NMR (500 MHz, $CDCl_3$)

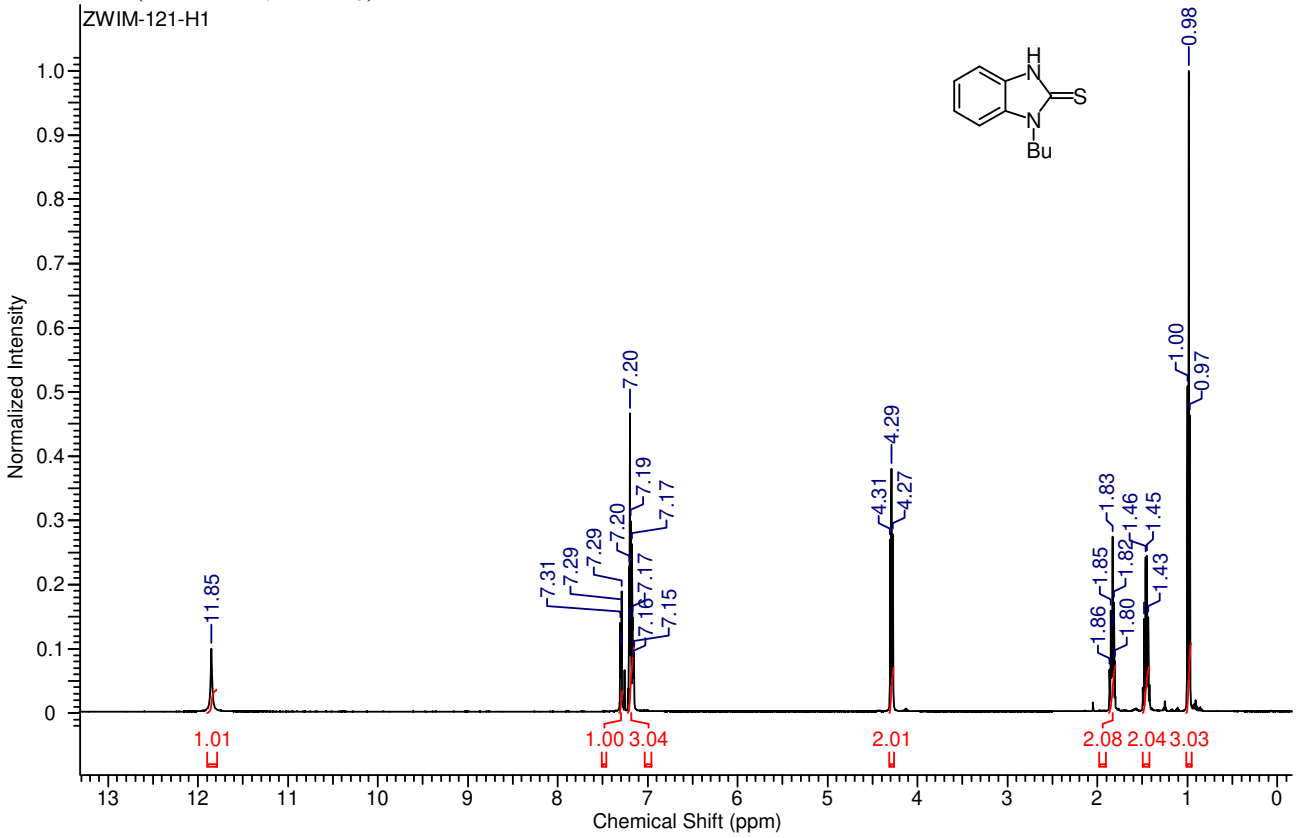


^{13}C NMR (125 MHz, $CDCl_3$)

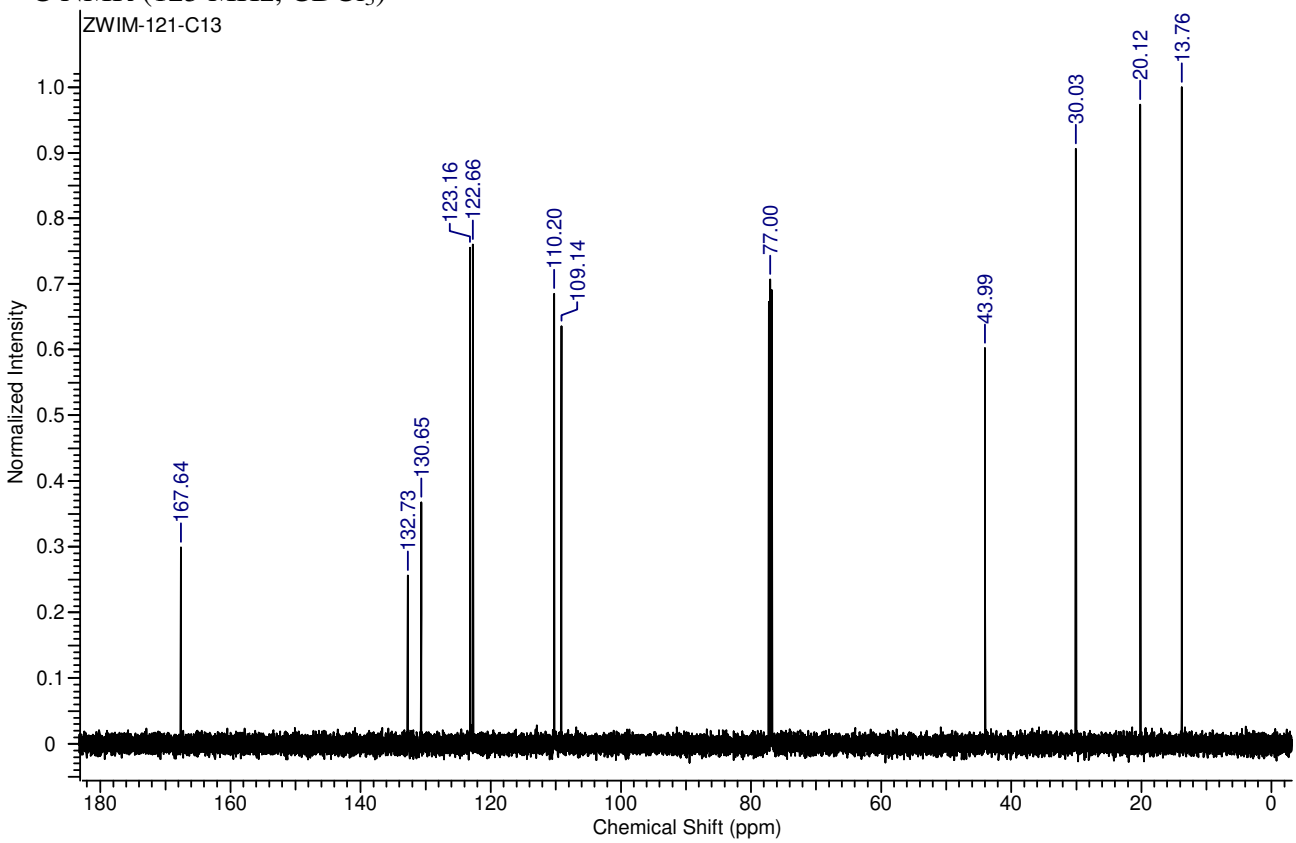


3i

^{1}H NMR (500 MHz, $CDCl_3$)

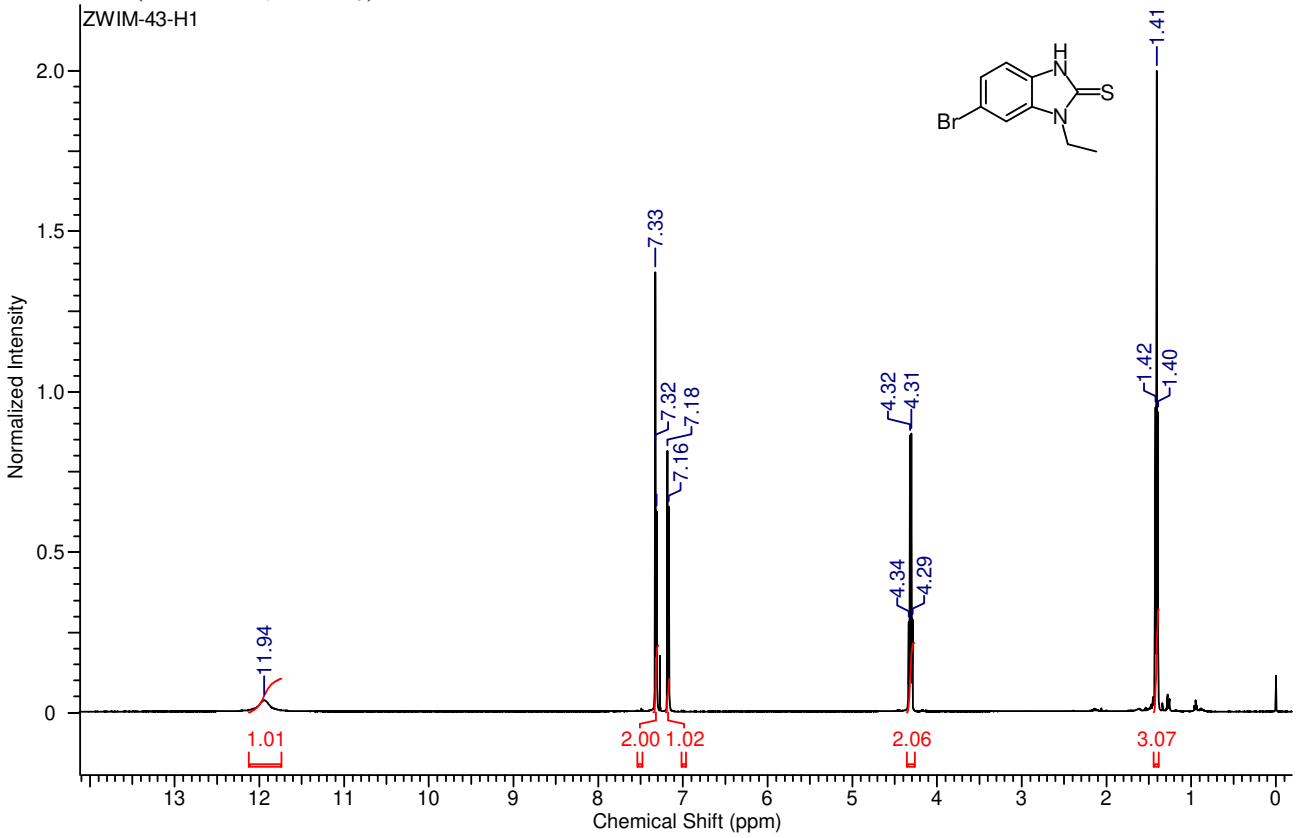


^{13}C NMR (125 MHz, $CDCl_3$)

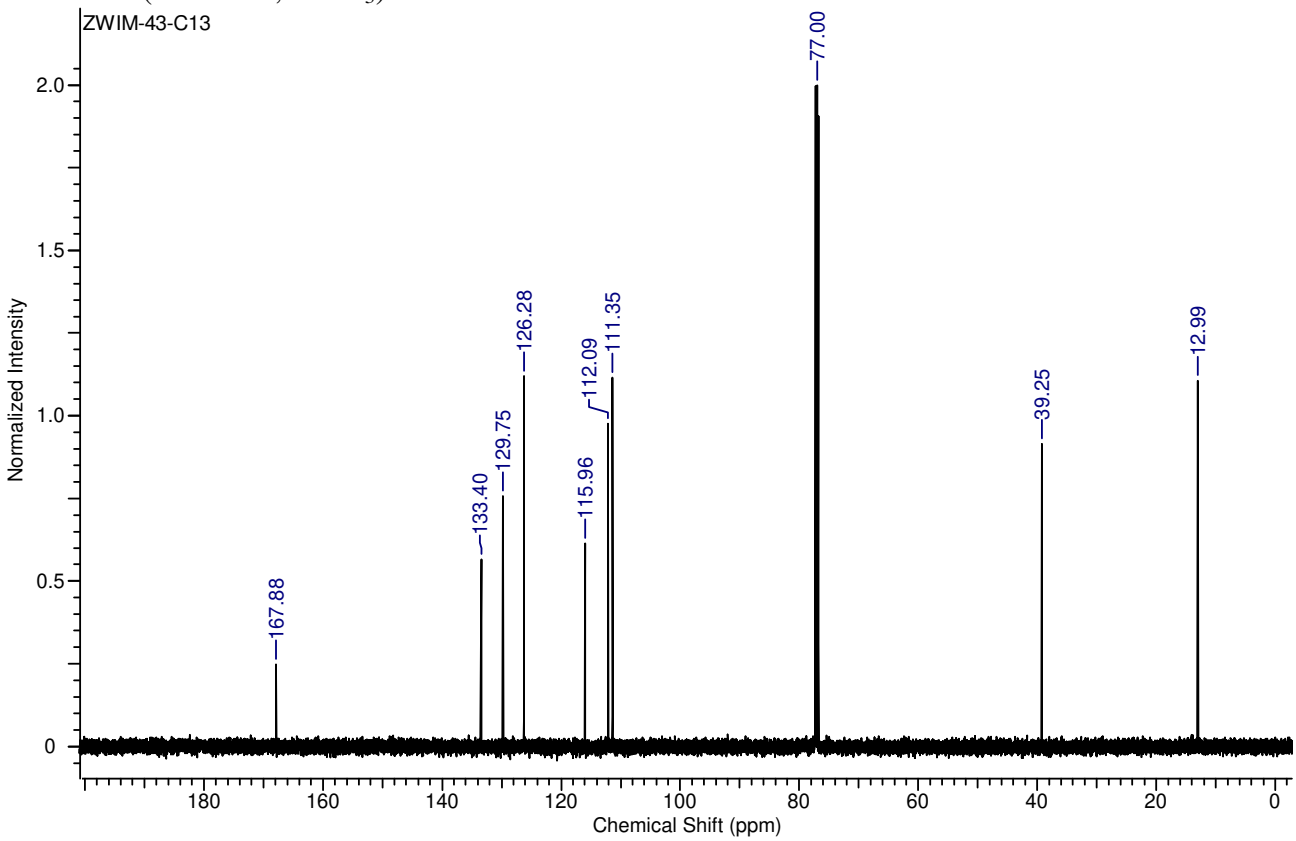


3j

^{1}H NMR (500 MHz, $CDCl_3$)

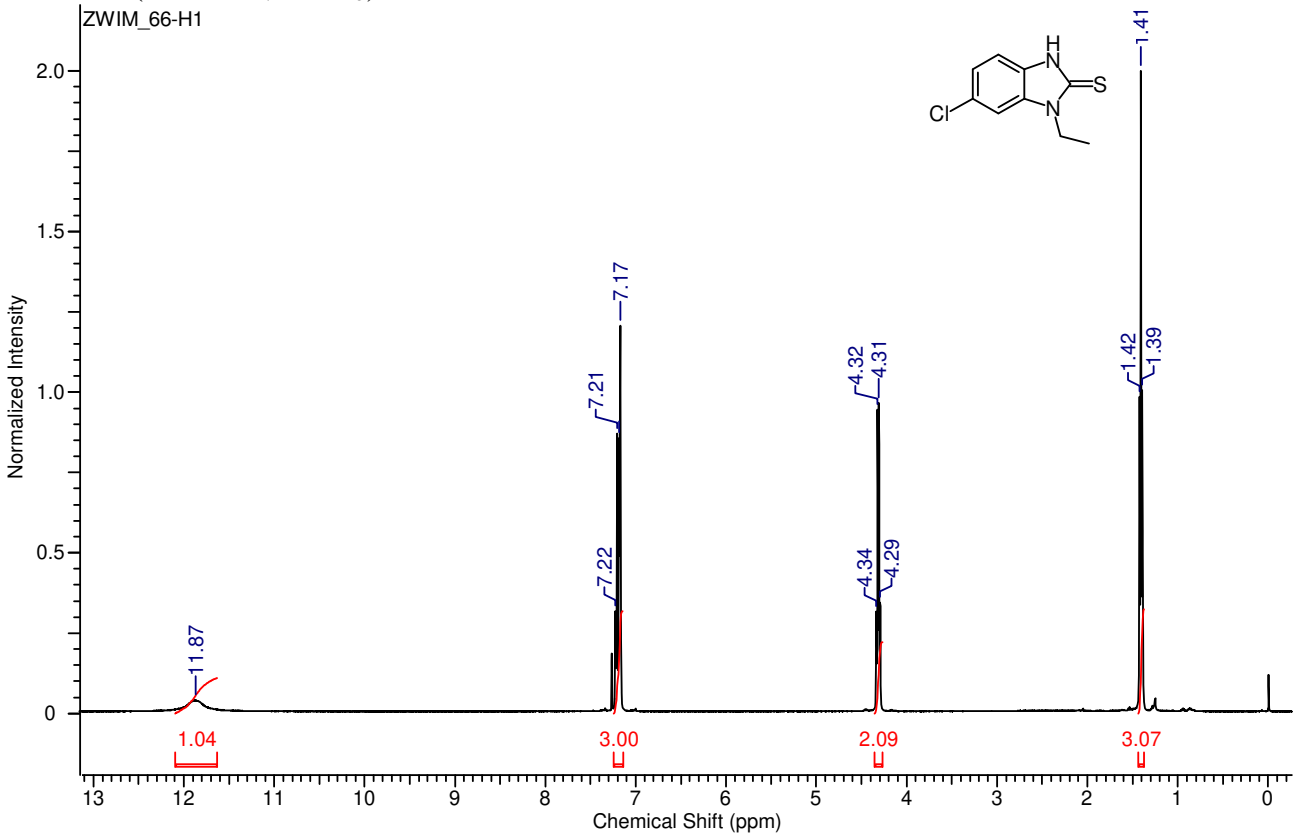


^{13}C NMR (125 MHz, $CDCl_3$)

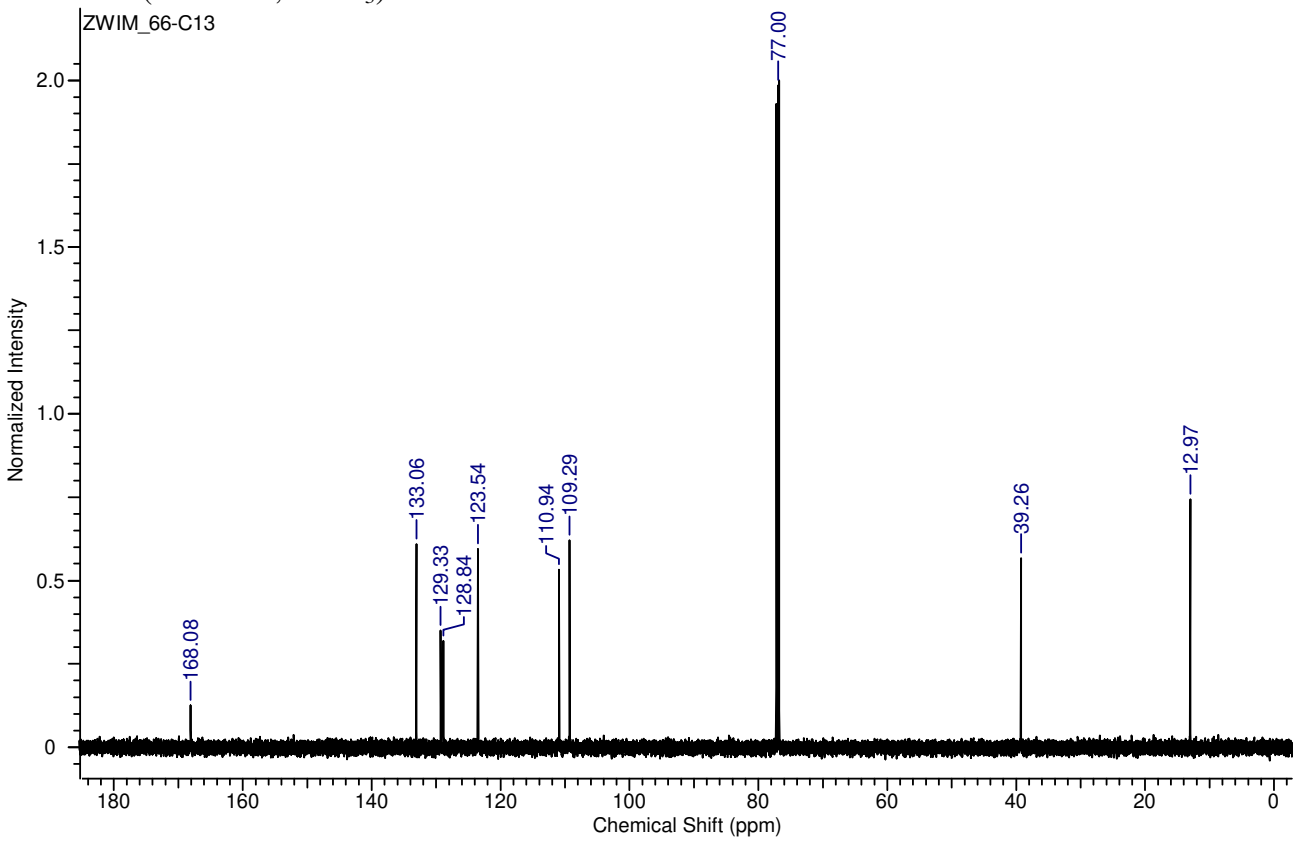


3k

^{1}H NMR (500 MHz, $CDCl_3$)

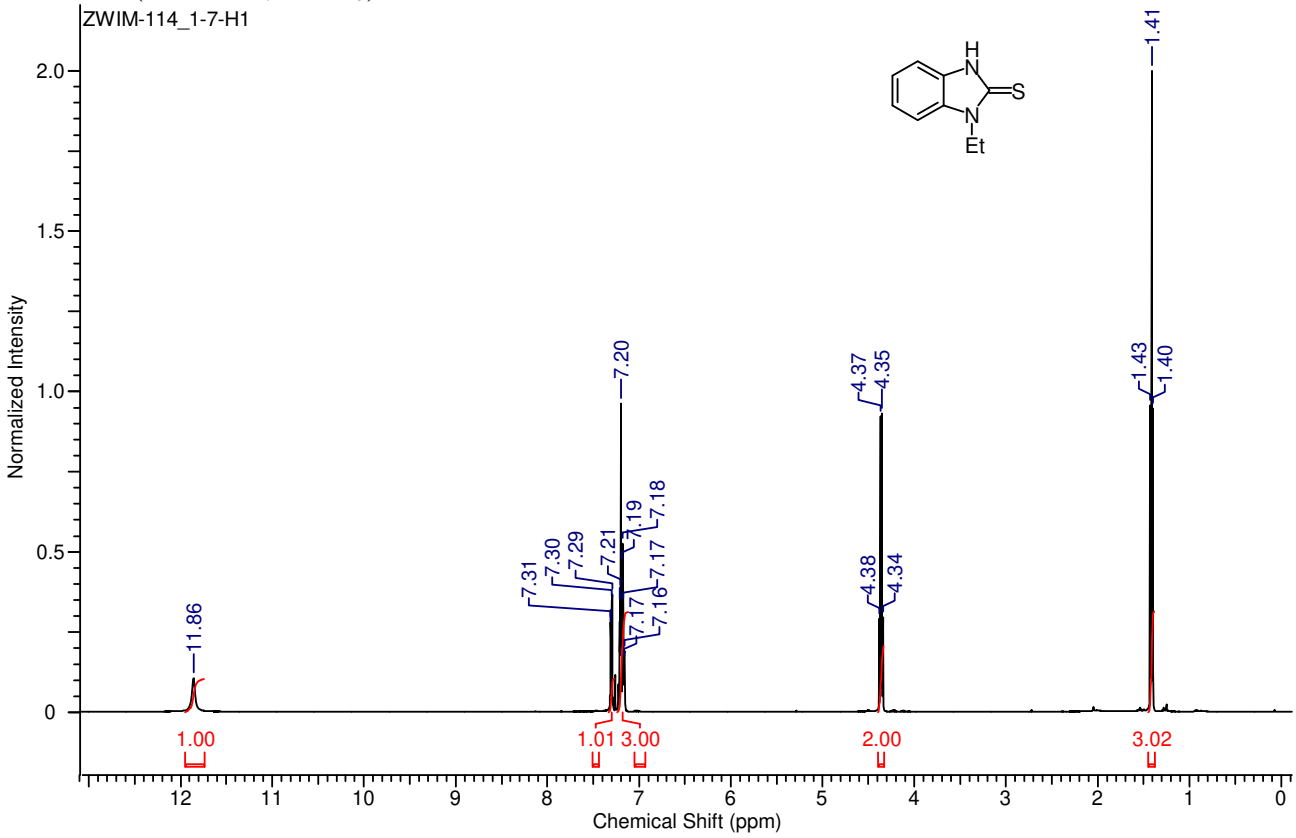


^{13}C NMR (125 MHz, $CDCl_3$)

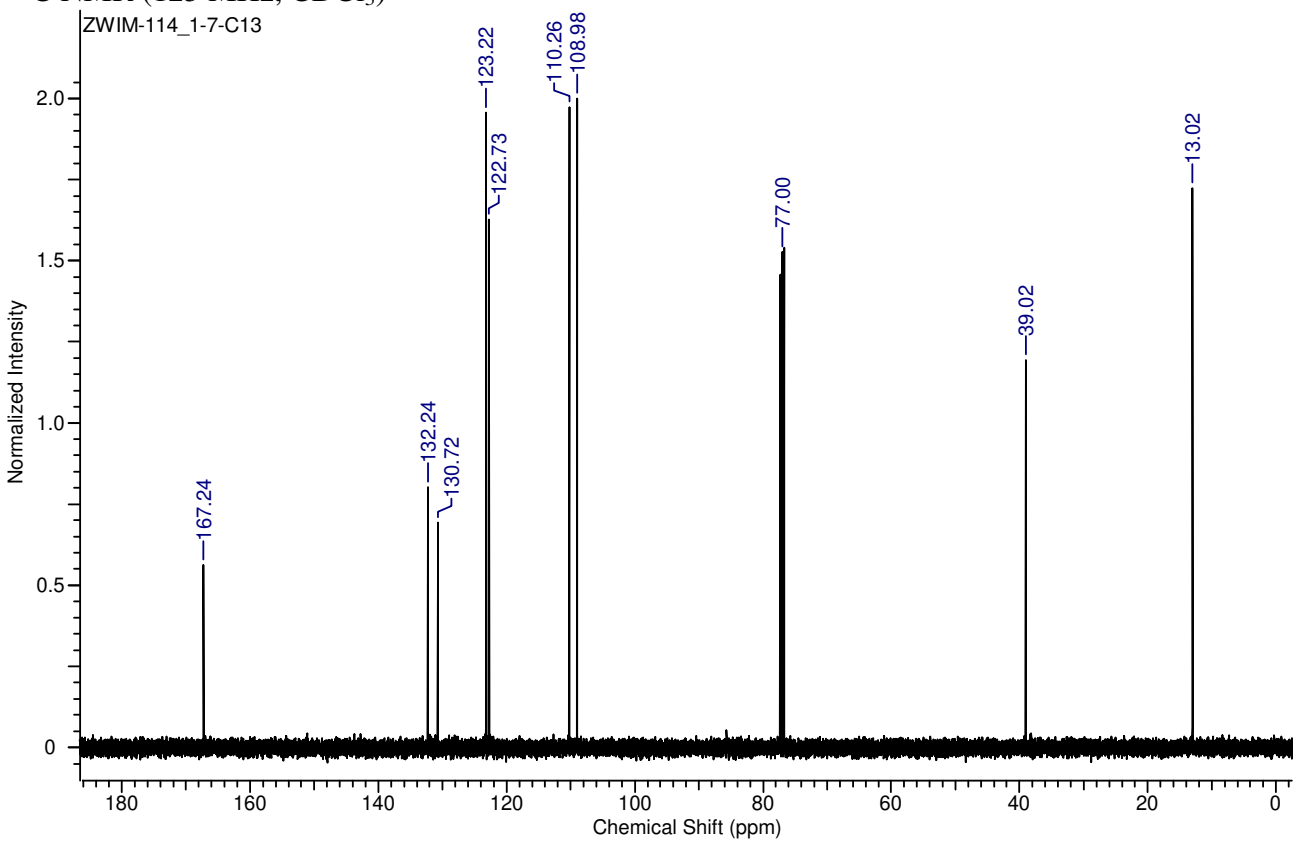


3l

^{1}H NMR (500 MHz, $CDCl_3$)

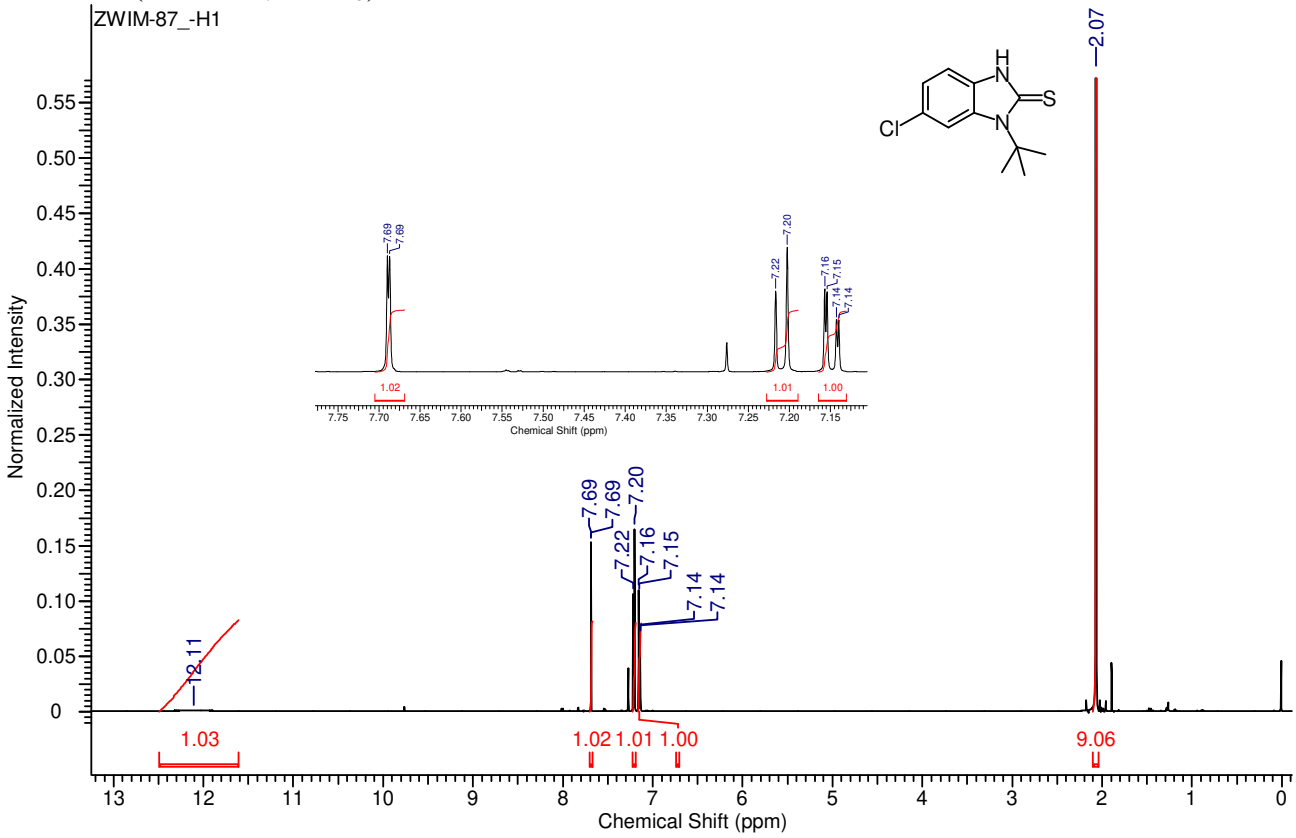


^{13}C NMR (125 MHz, $CDCl_3$)

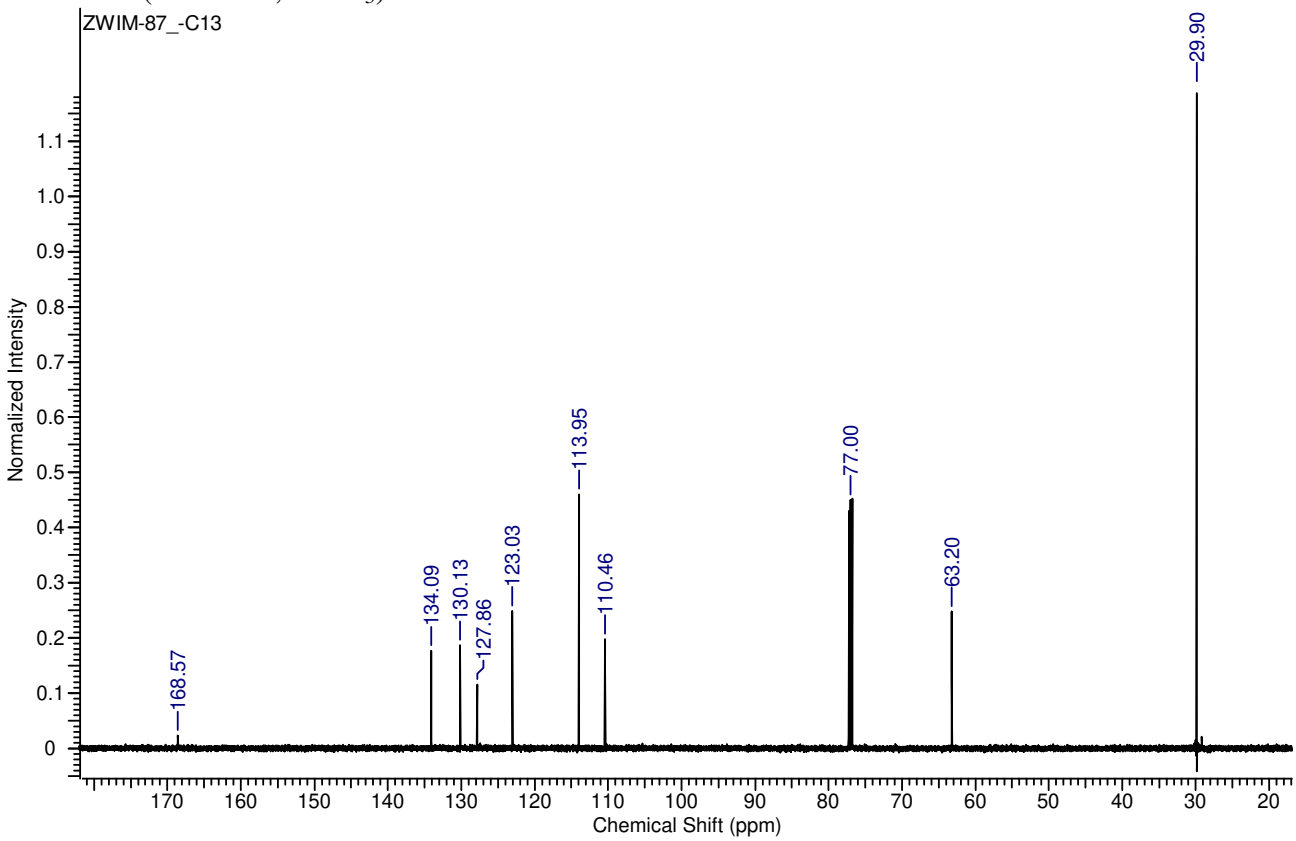


3m

^{1}H NMR (600 MHz, $CDCl_3$)

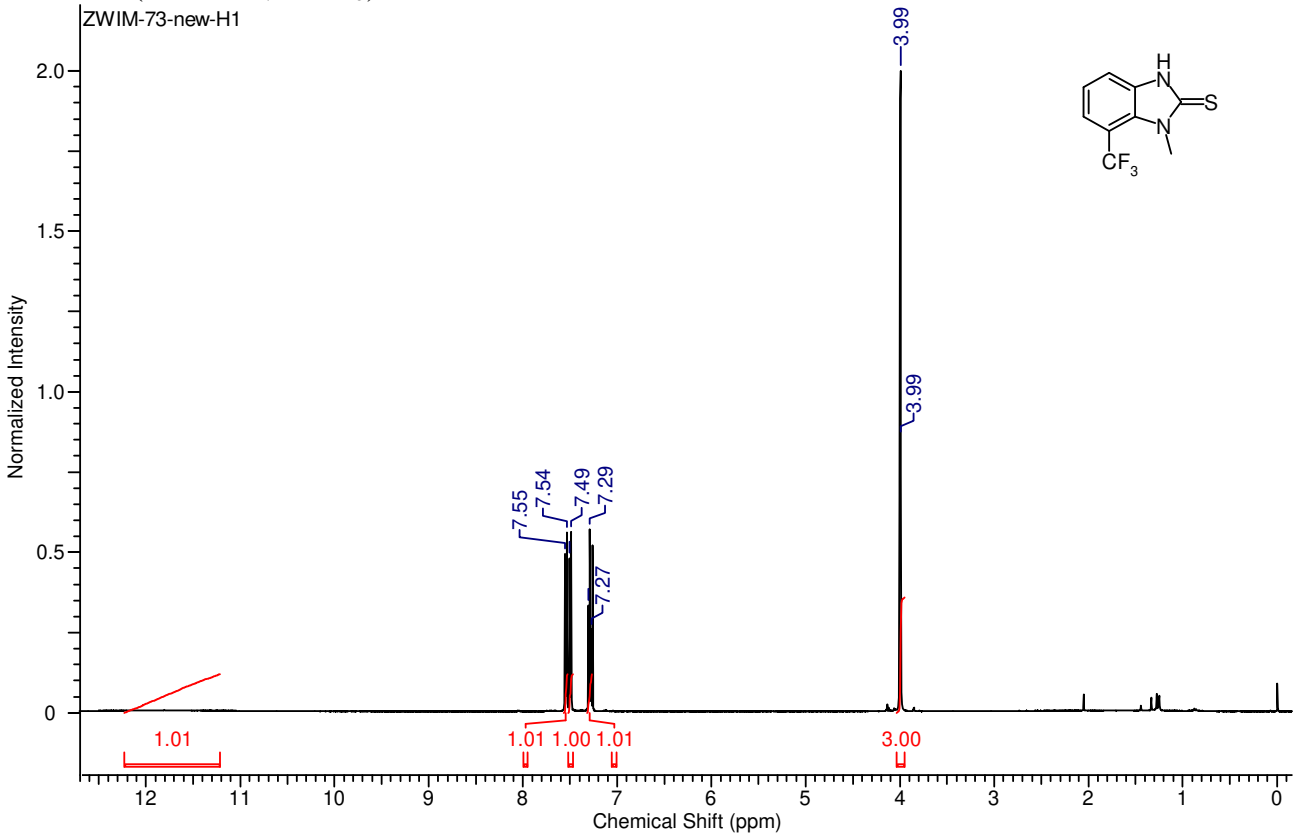


^{13}C NMR (150 MHz, $CDCl_3$)

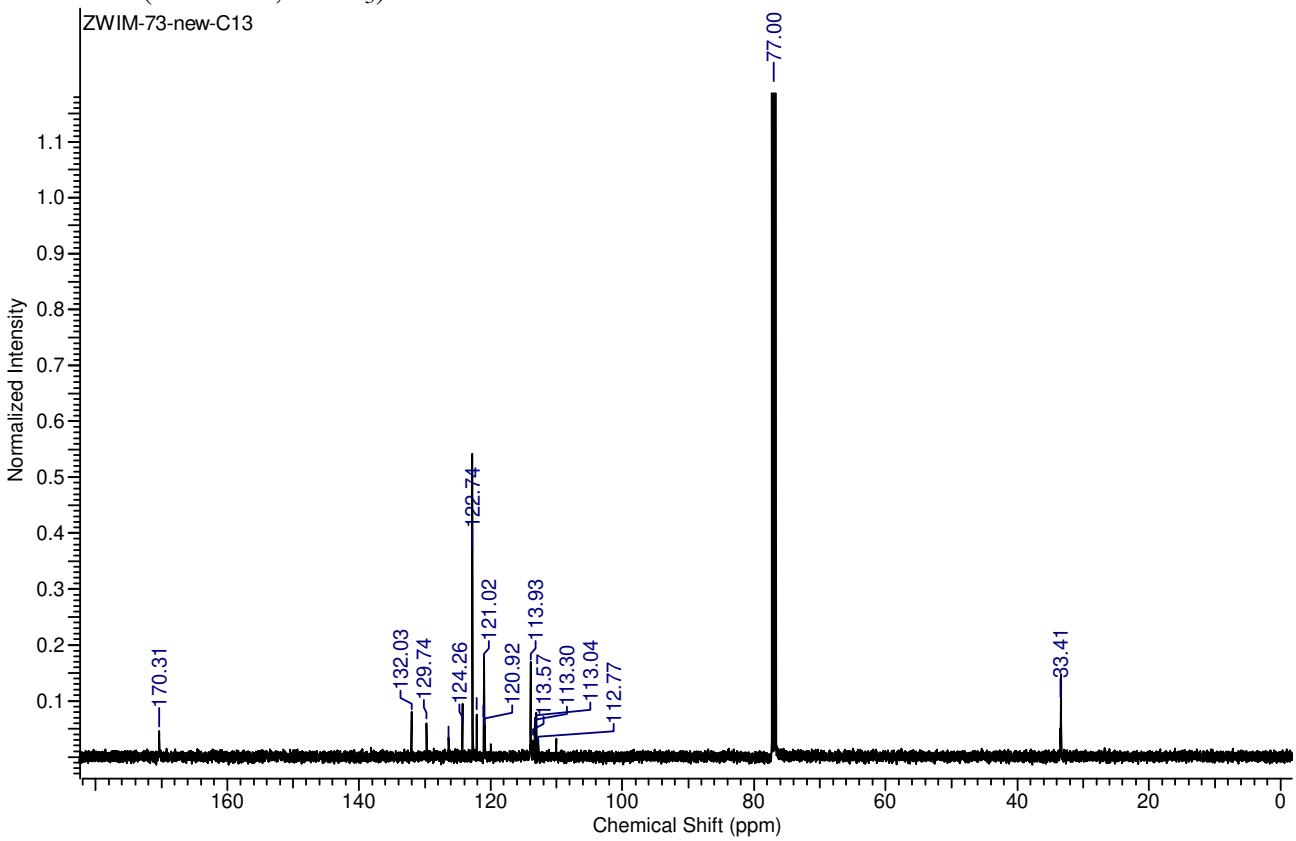


3n

^{1}H NMR (600 MHz, $CDCl_3$)

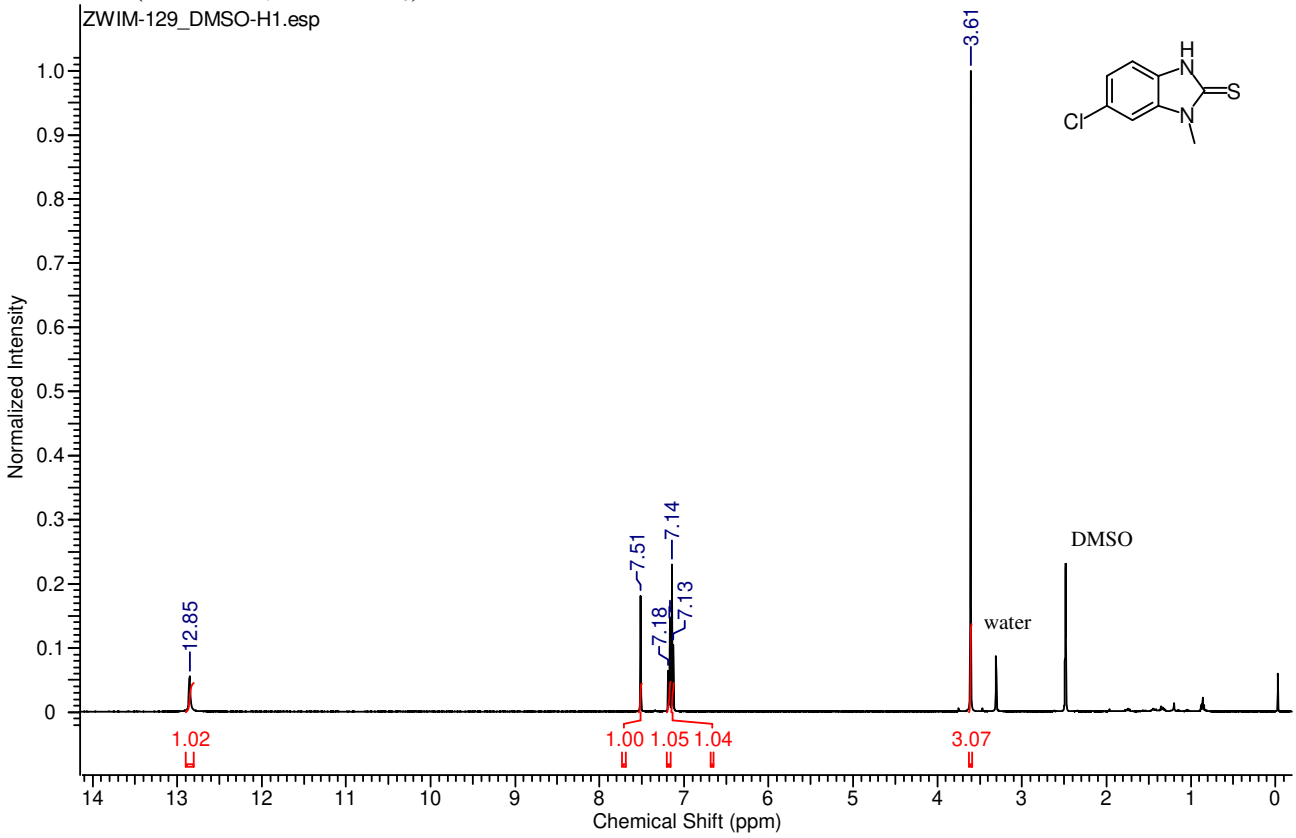


^{13}C NMR (150 MHz, $CDCl_3$)

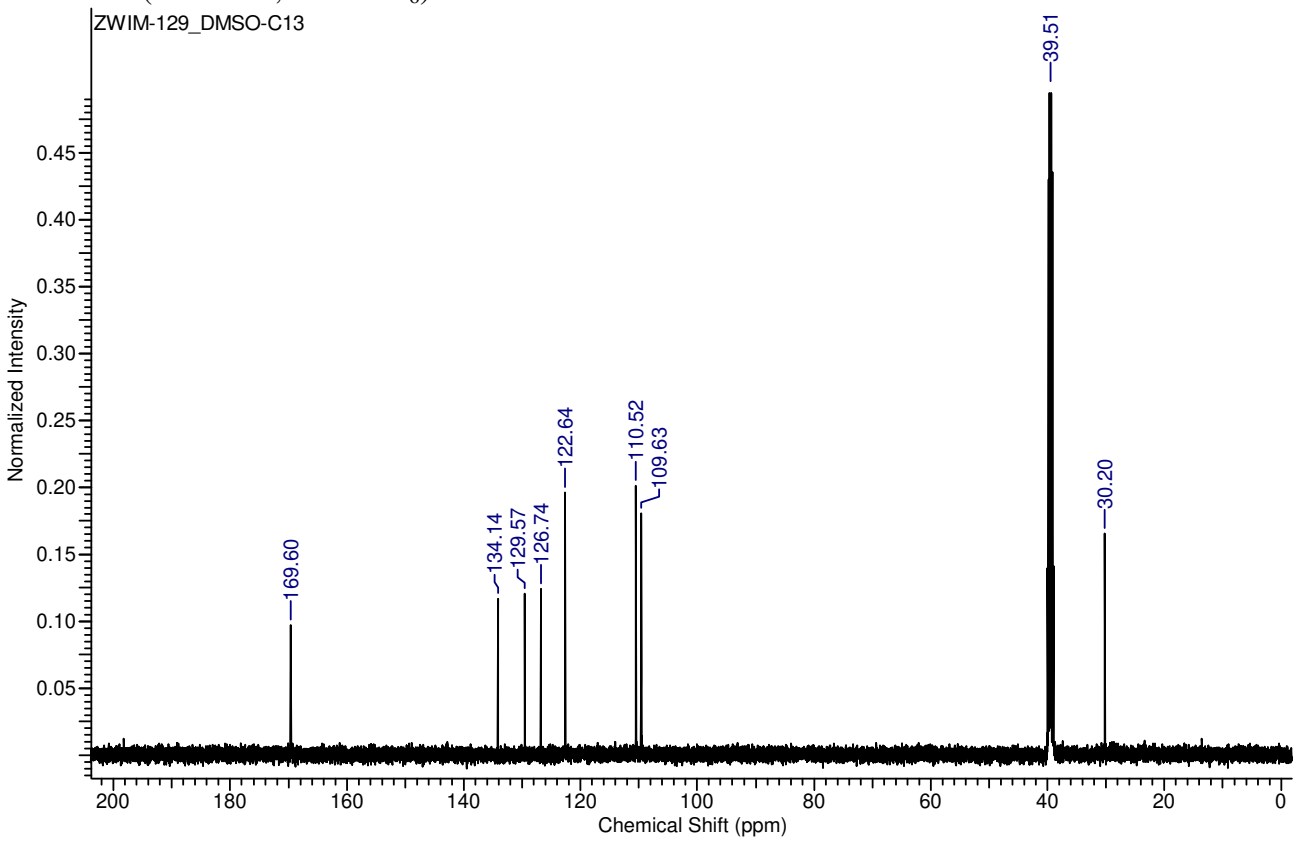


3o

^{1}H NMR (600 MHz, DMSO-d_6)

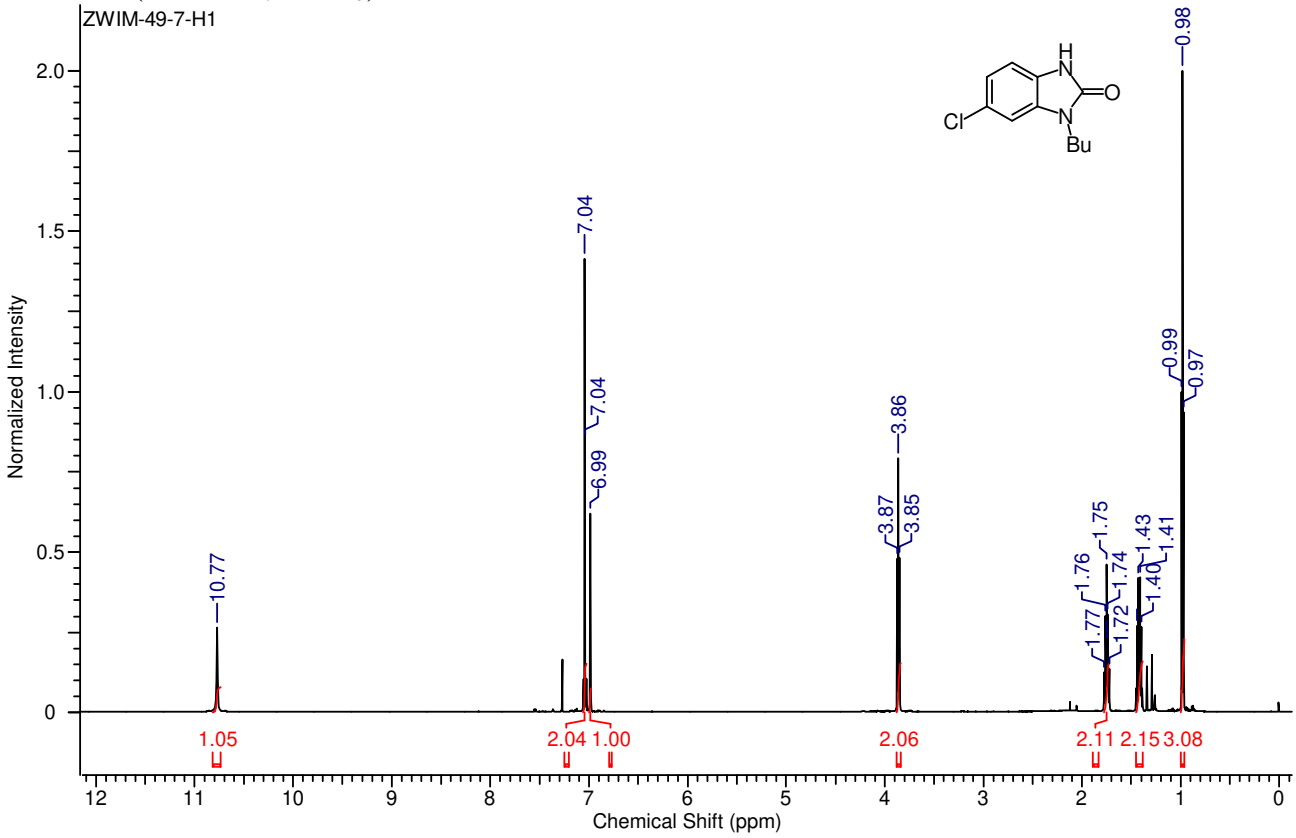


^{13}C NMR (150 MHz, DMSO-d_6)

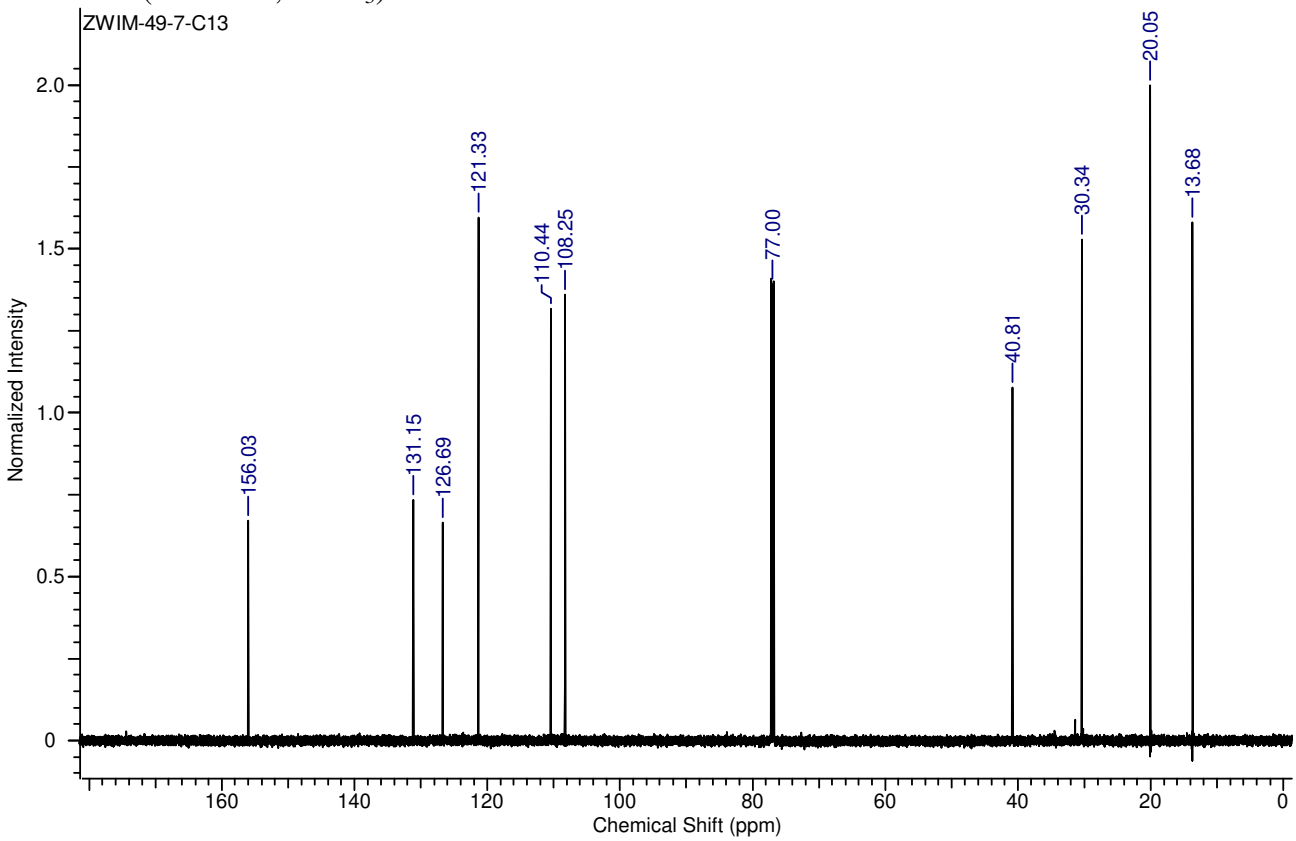


4a

^{1}H NMR (600 MHz, $CDCl_3$)

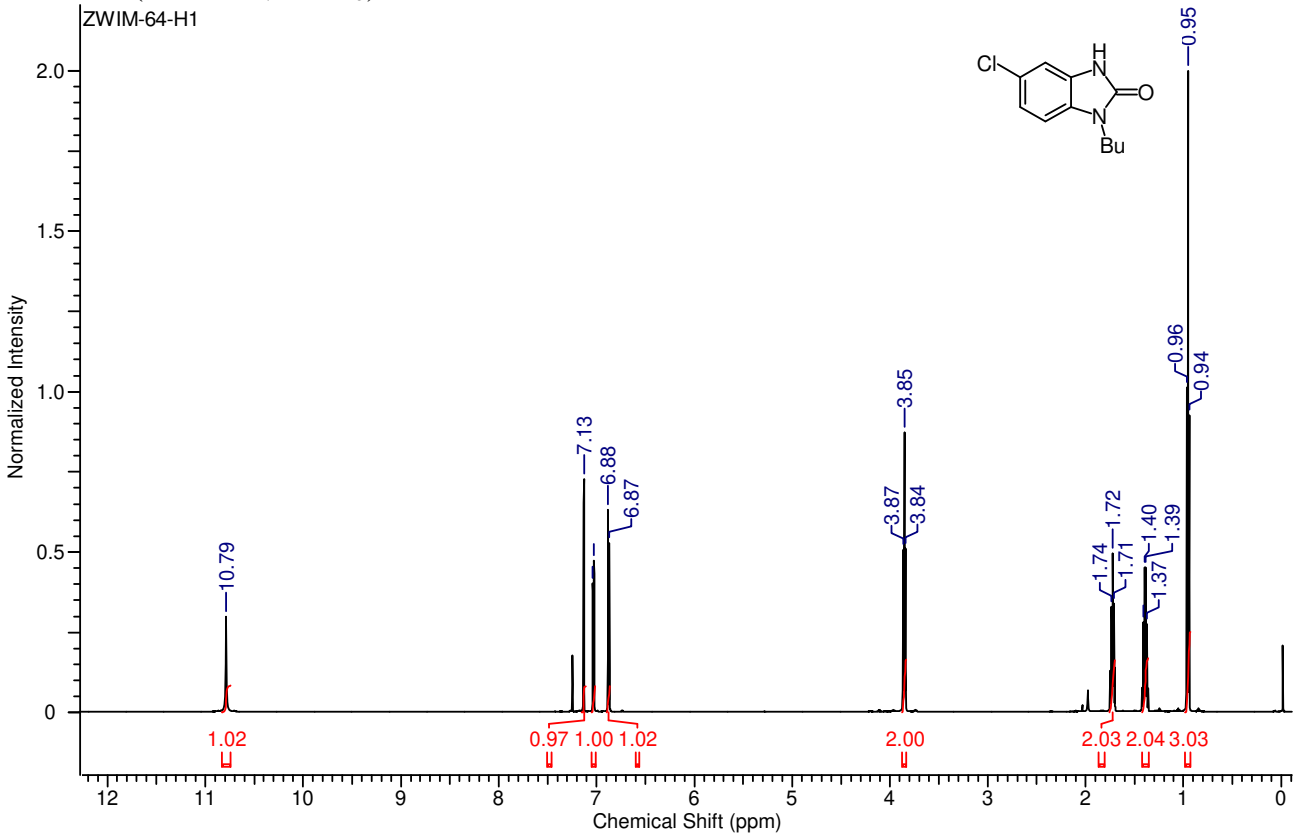


^{13}C NMR (150 MHz, $CDCl_3$)

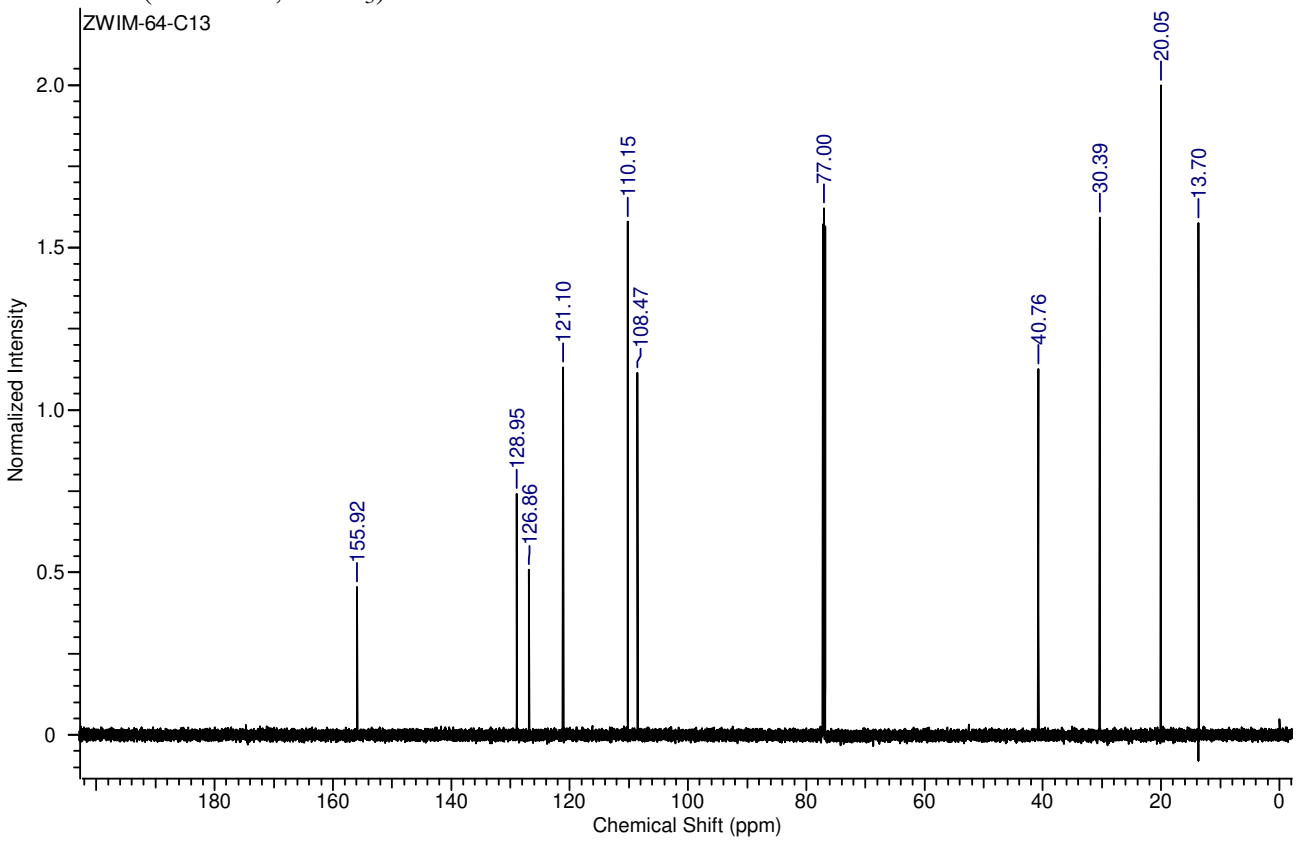


4c

^{1}H NMR (600 MHz, $CDCl_3$)

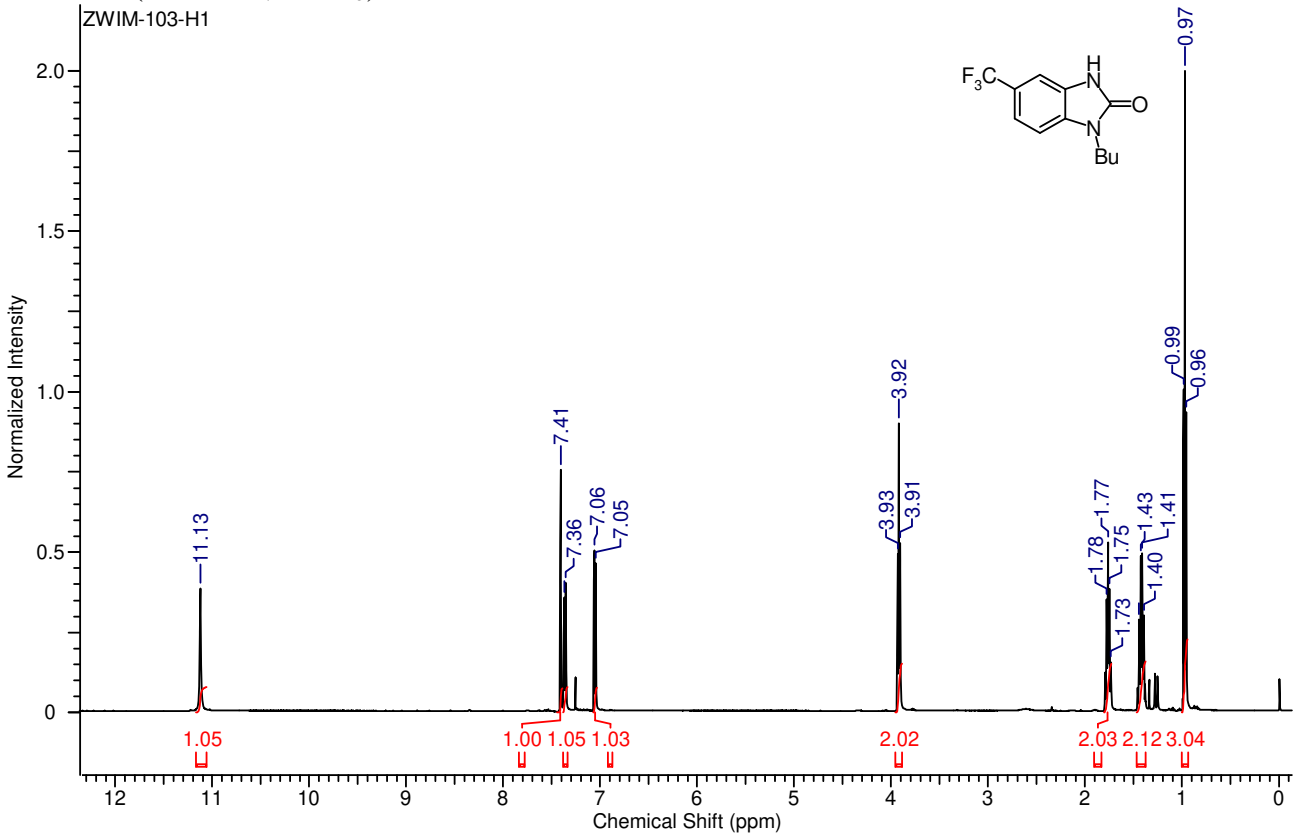


^{13}C NMR (150 MHz, $CDCl_3$)

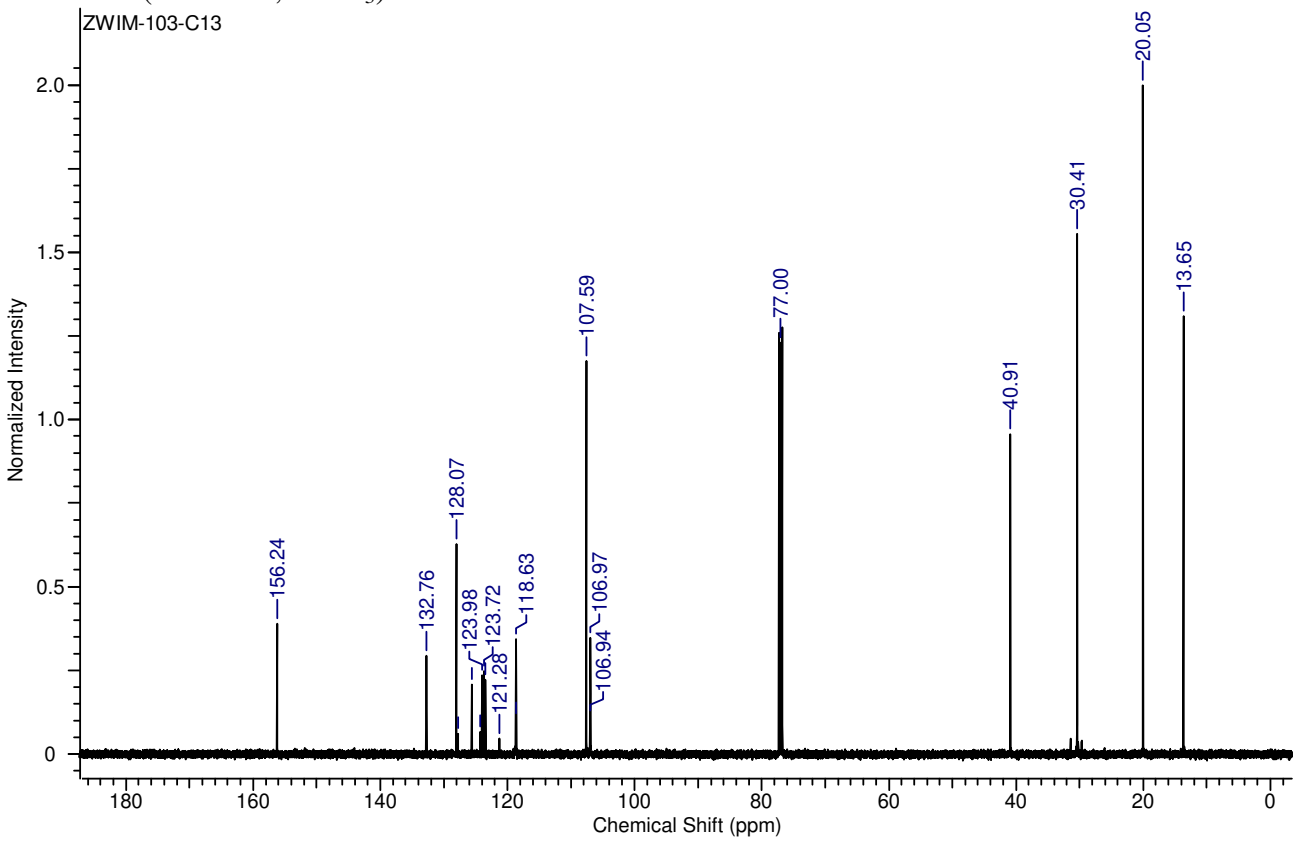


4d

^{1}H NMR (500 MHz, $CDCl_3$)

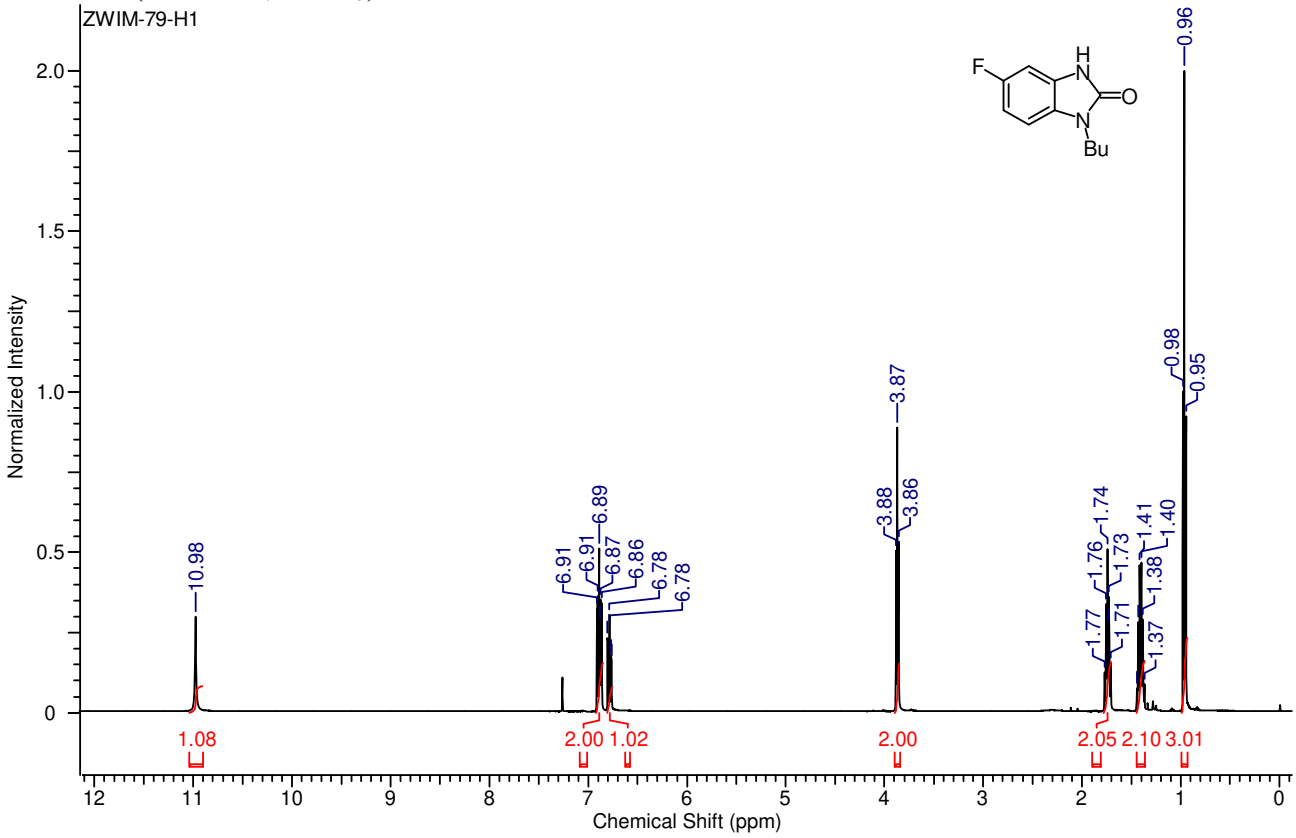


^{13}C NMR (125 MHz, $CDCl_3$)

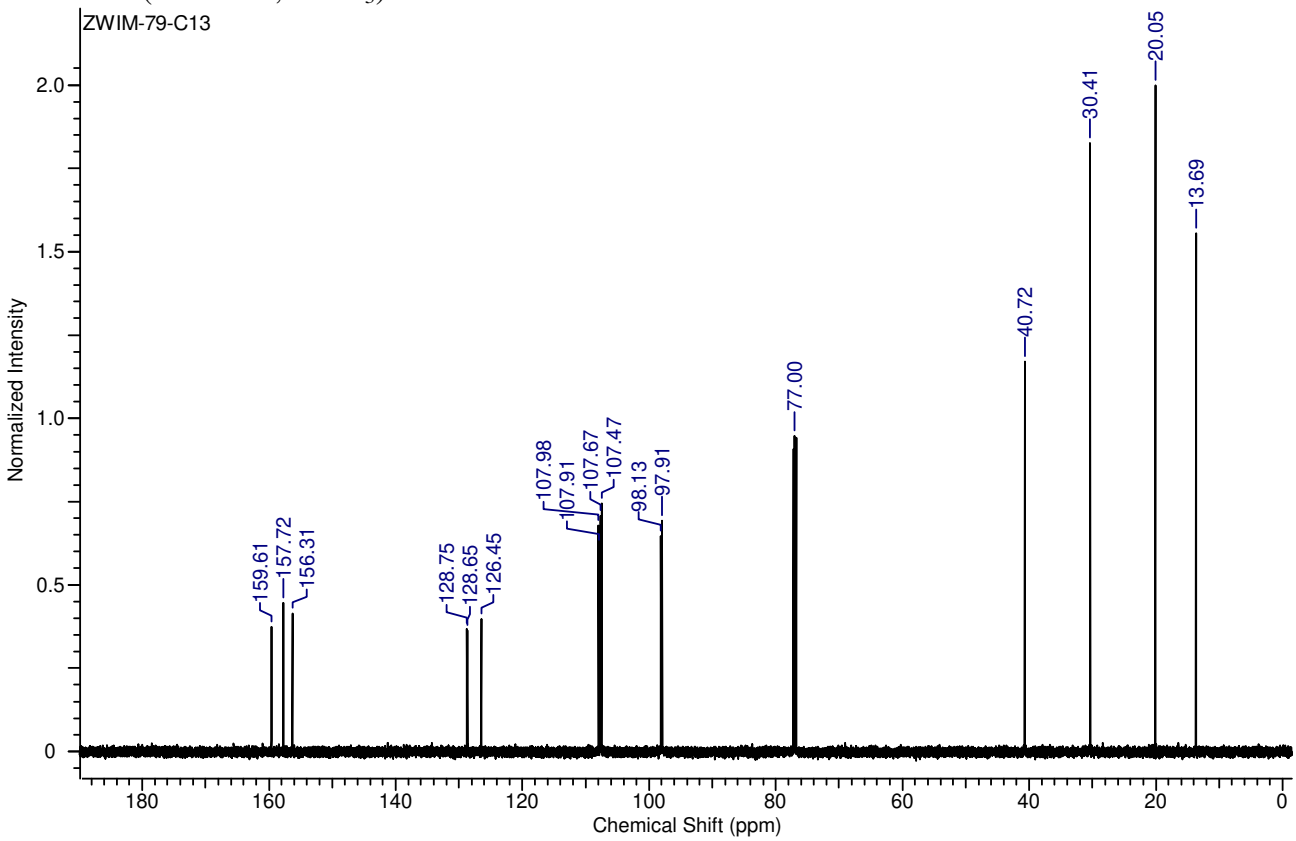


4e

^{1}H NMR (500 MHz, $CDCl_3$)

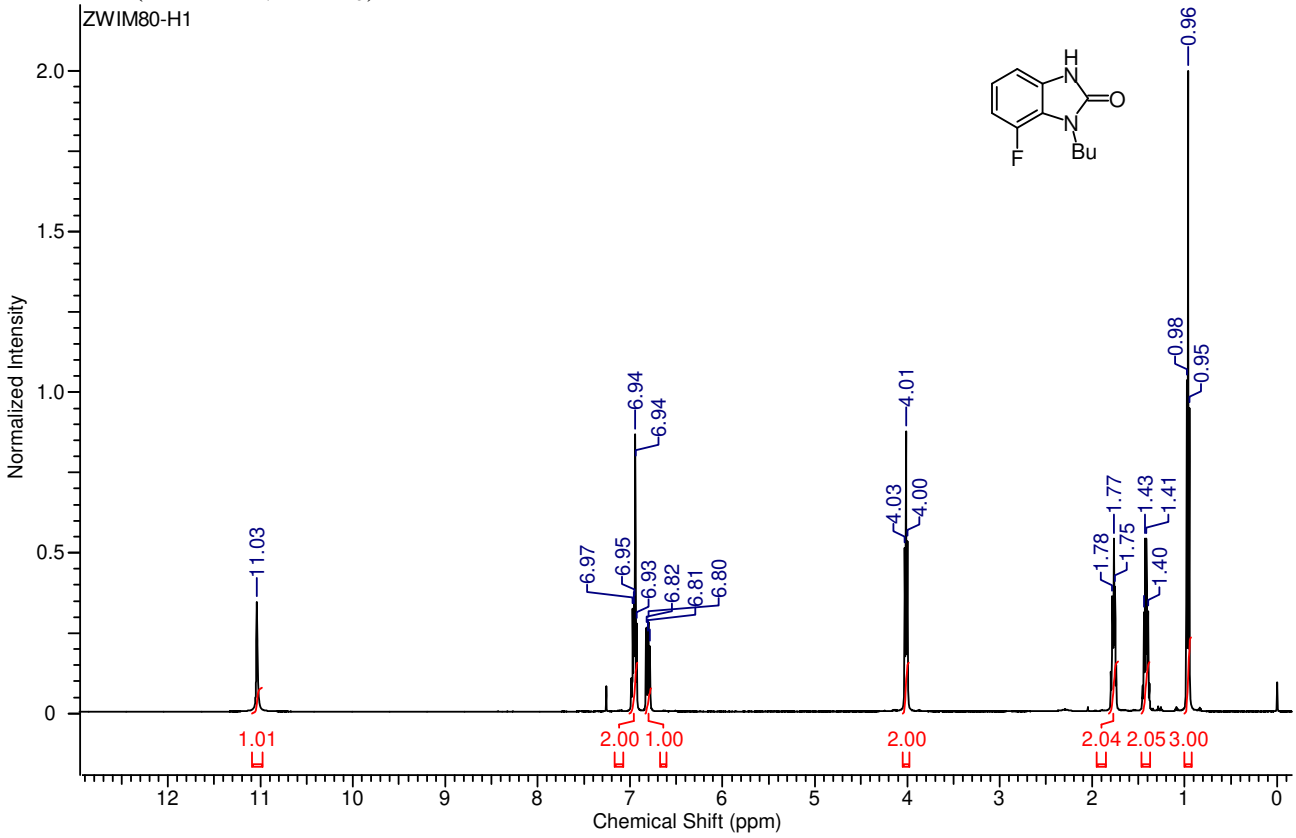


^{13}C NMR (125 MHz, $CDCl_3$)

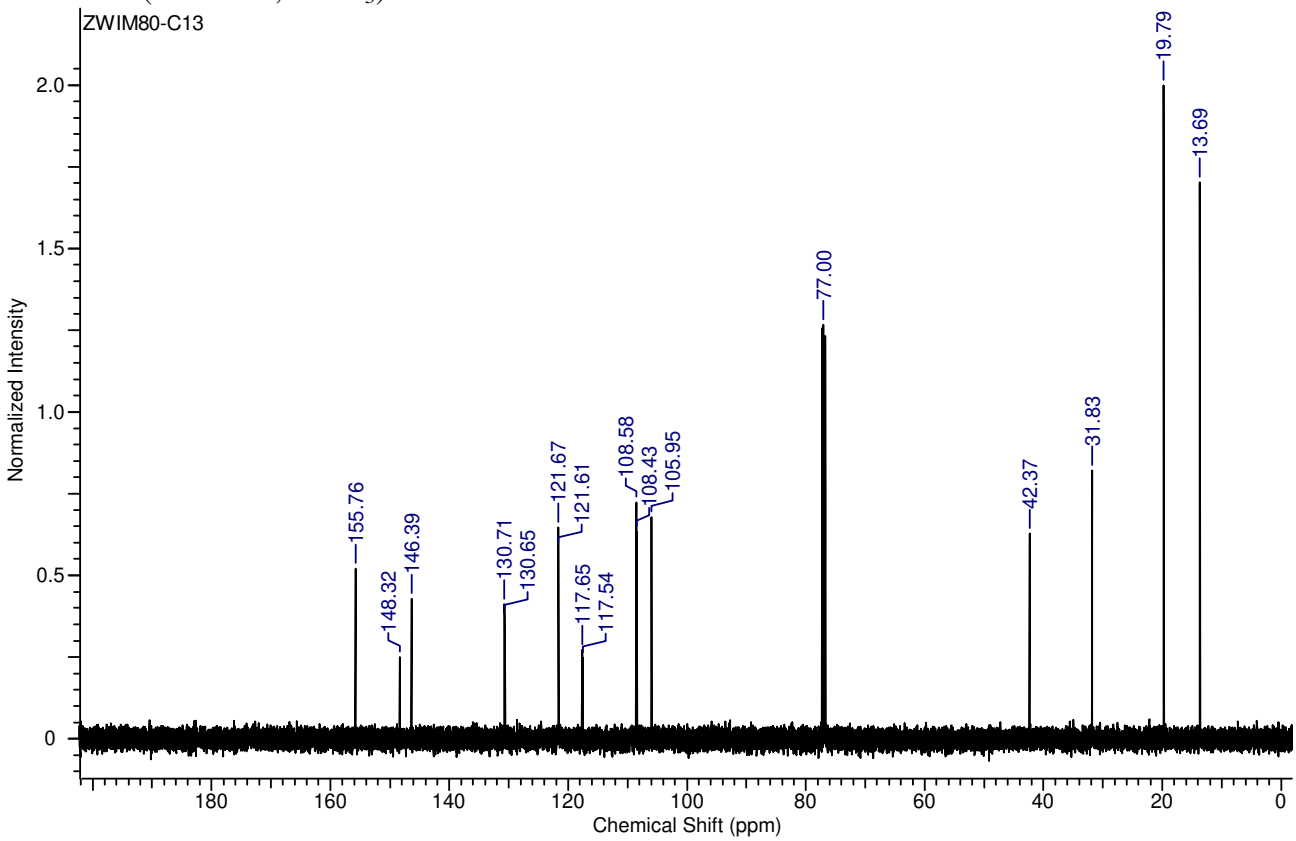


4f

^{1}H NMR (500 MHz, $CDCl_3$)

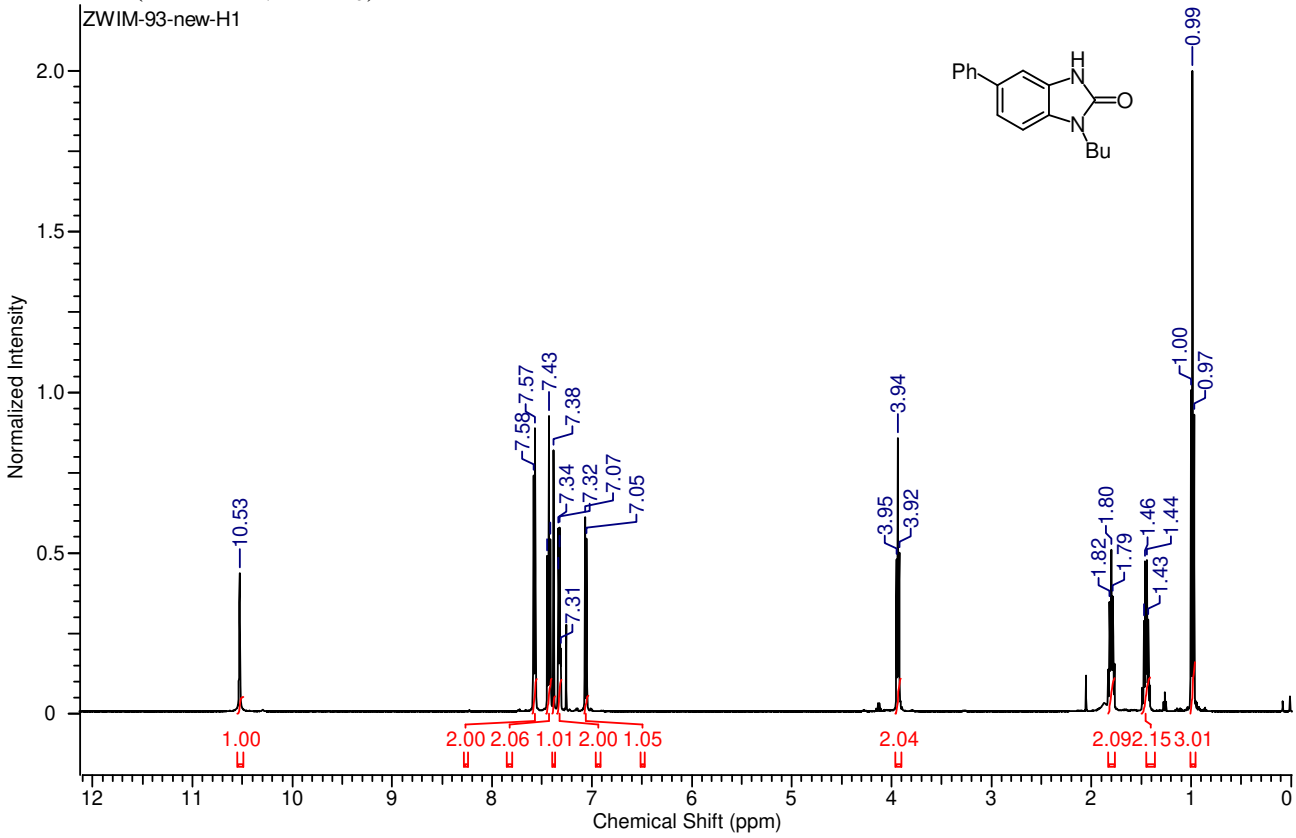


^{13}C NMR (125 MHz, $CDCl_3$)

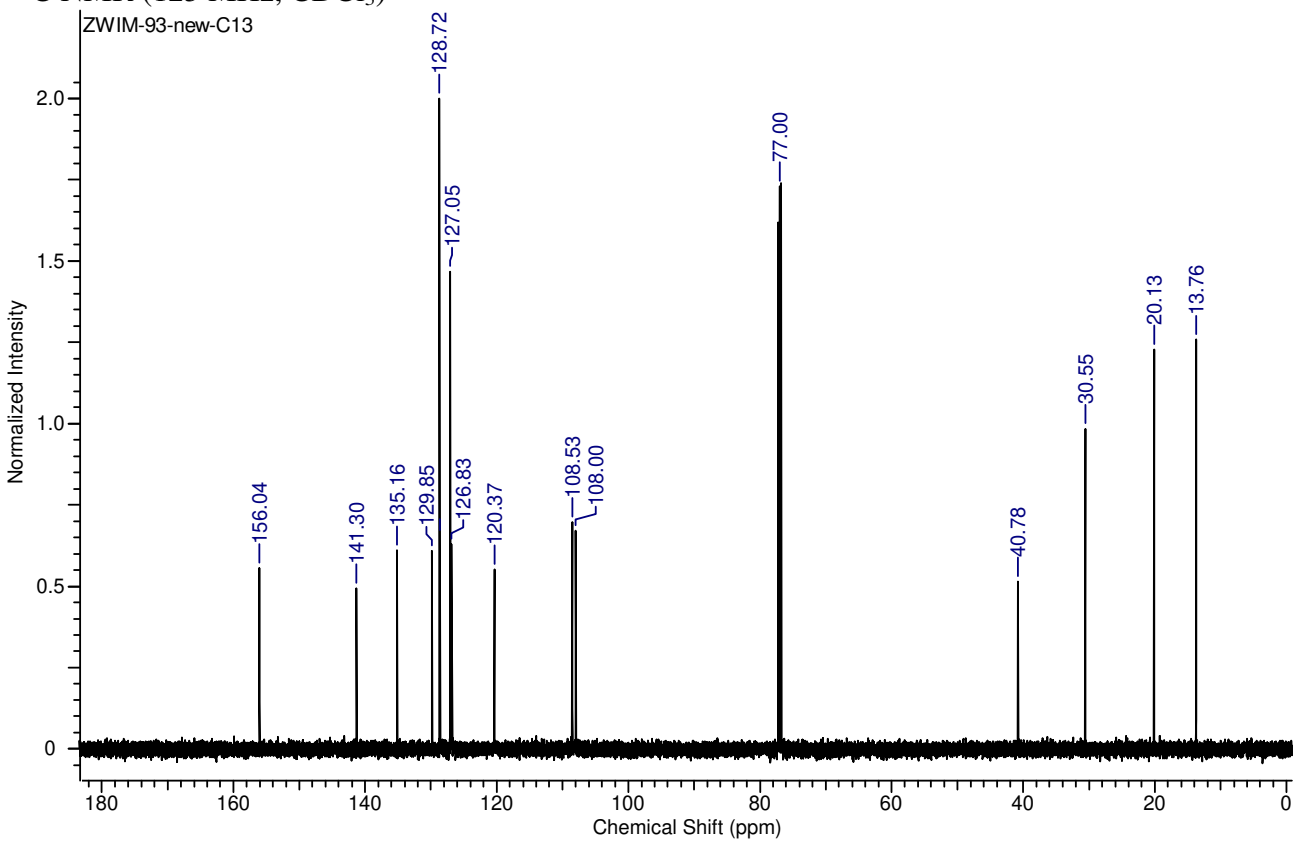


4g

^{1}H NMR (500 MHz, $CDCl_3$)

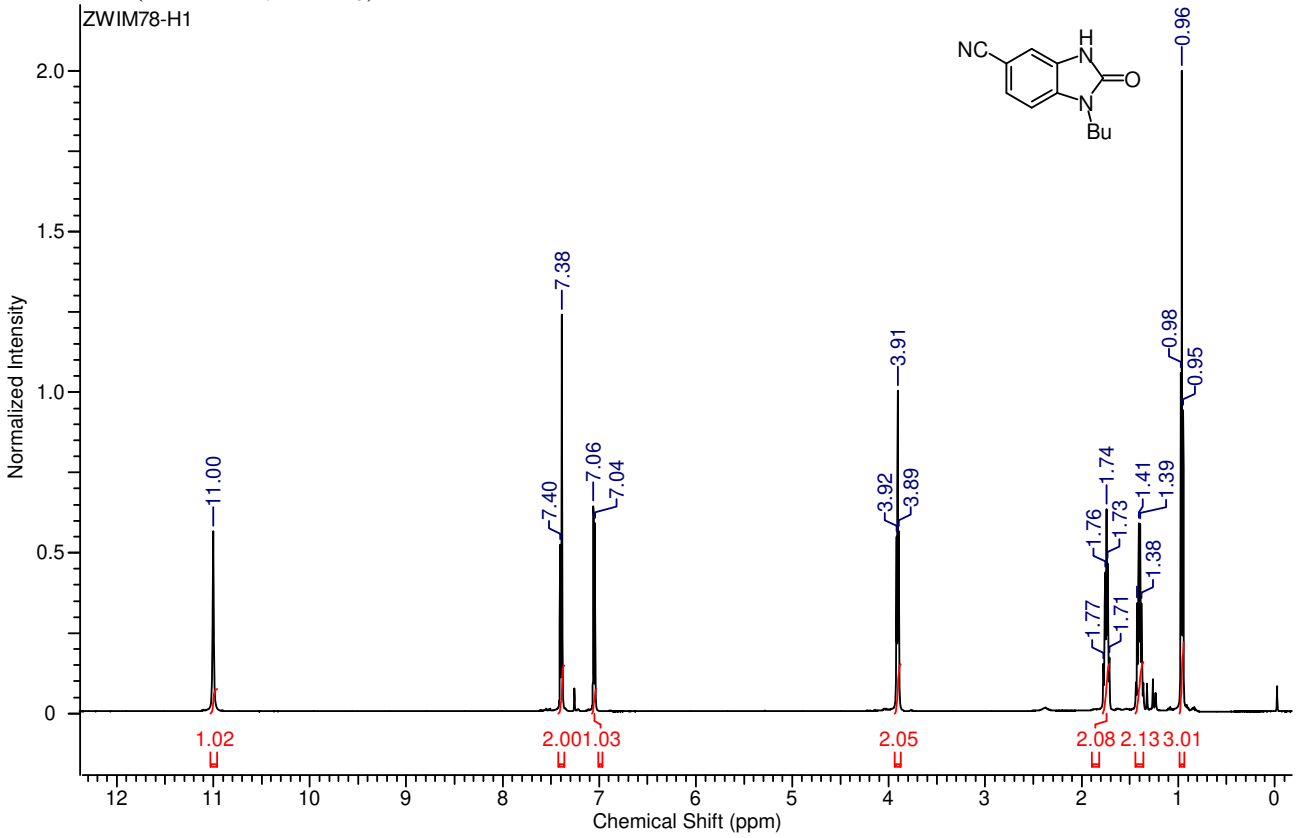


^{13}C NMR (125 MHz, $CDCl_3$)

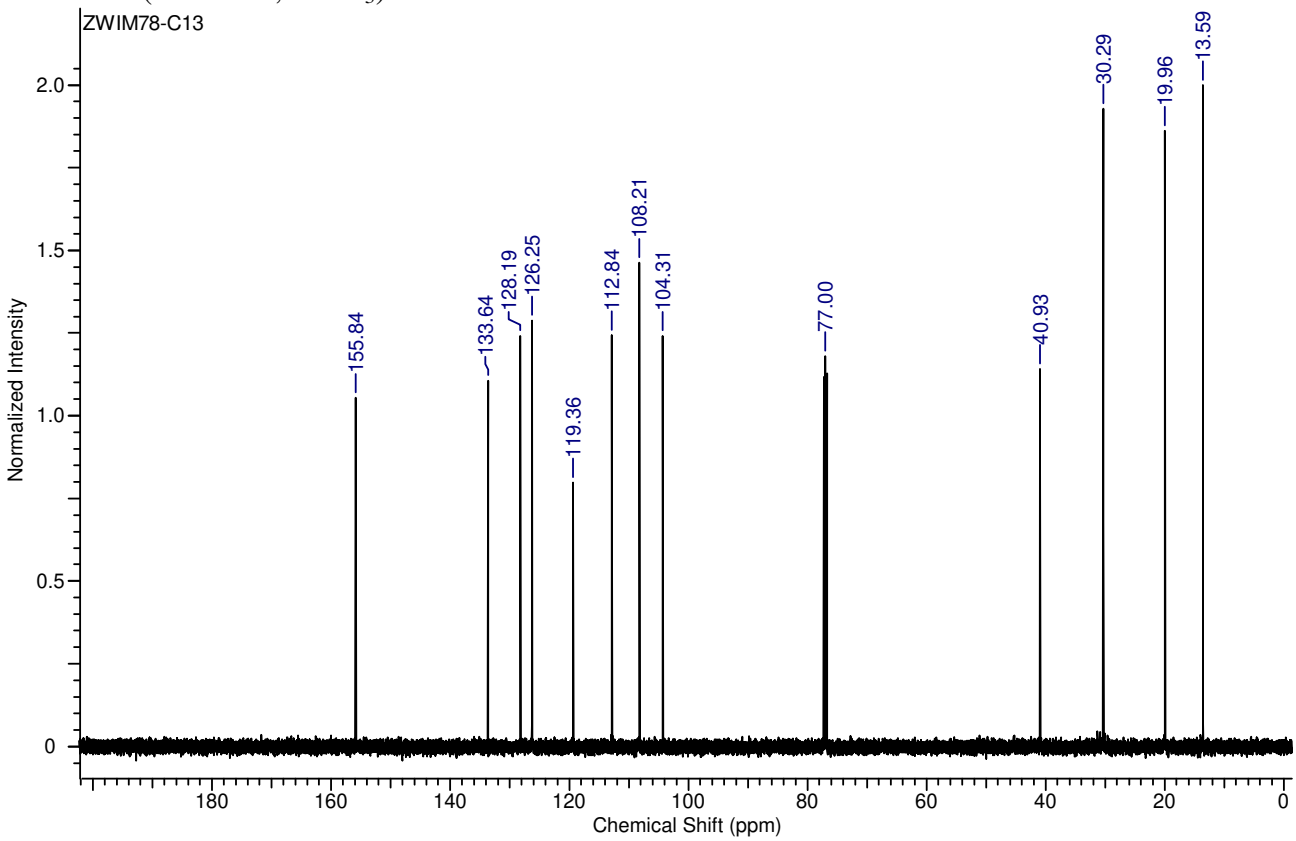


4h

^{1}H NMR (500 MHz, $CDCl_3$)

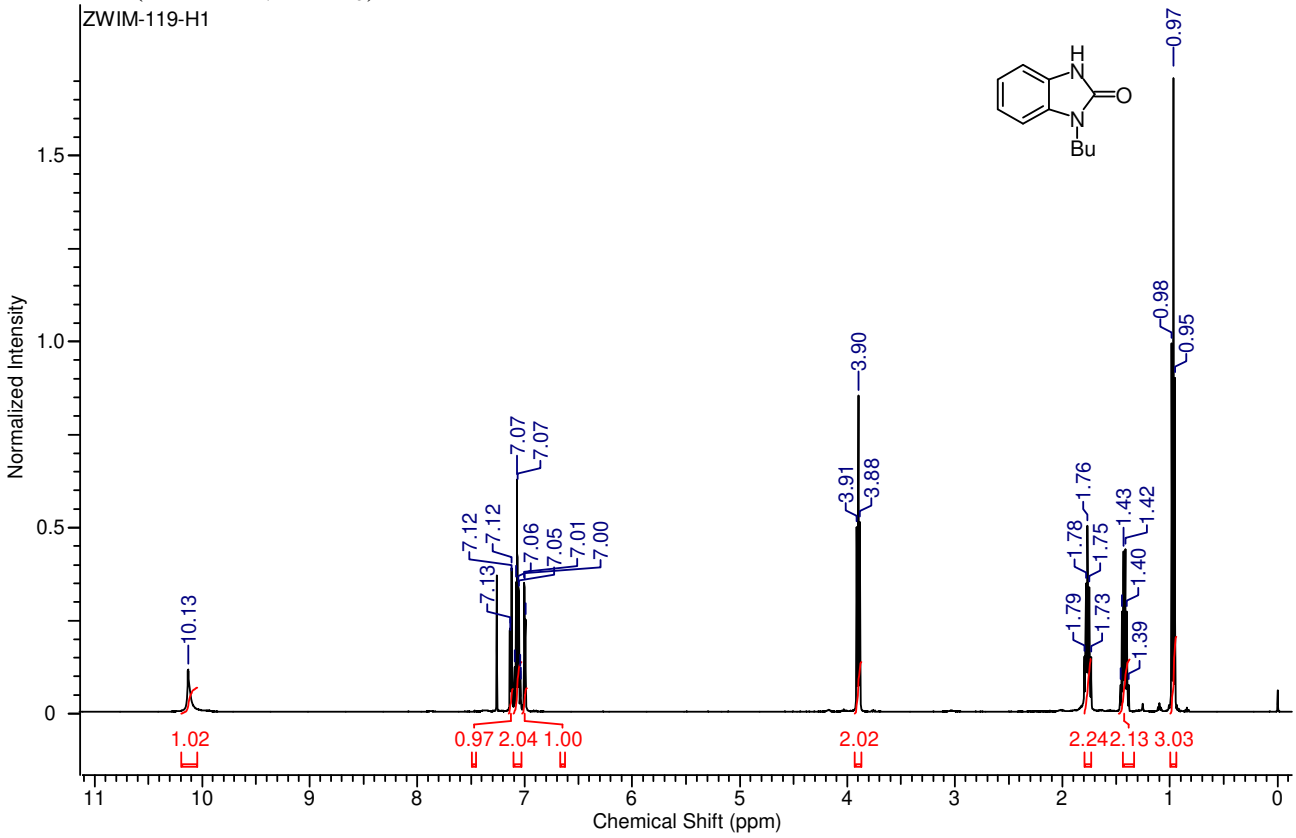


^{13}C NMR (125 MHz, $CDCl_3$)

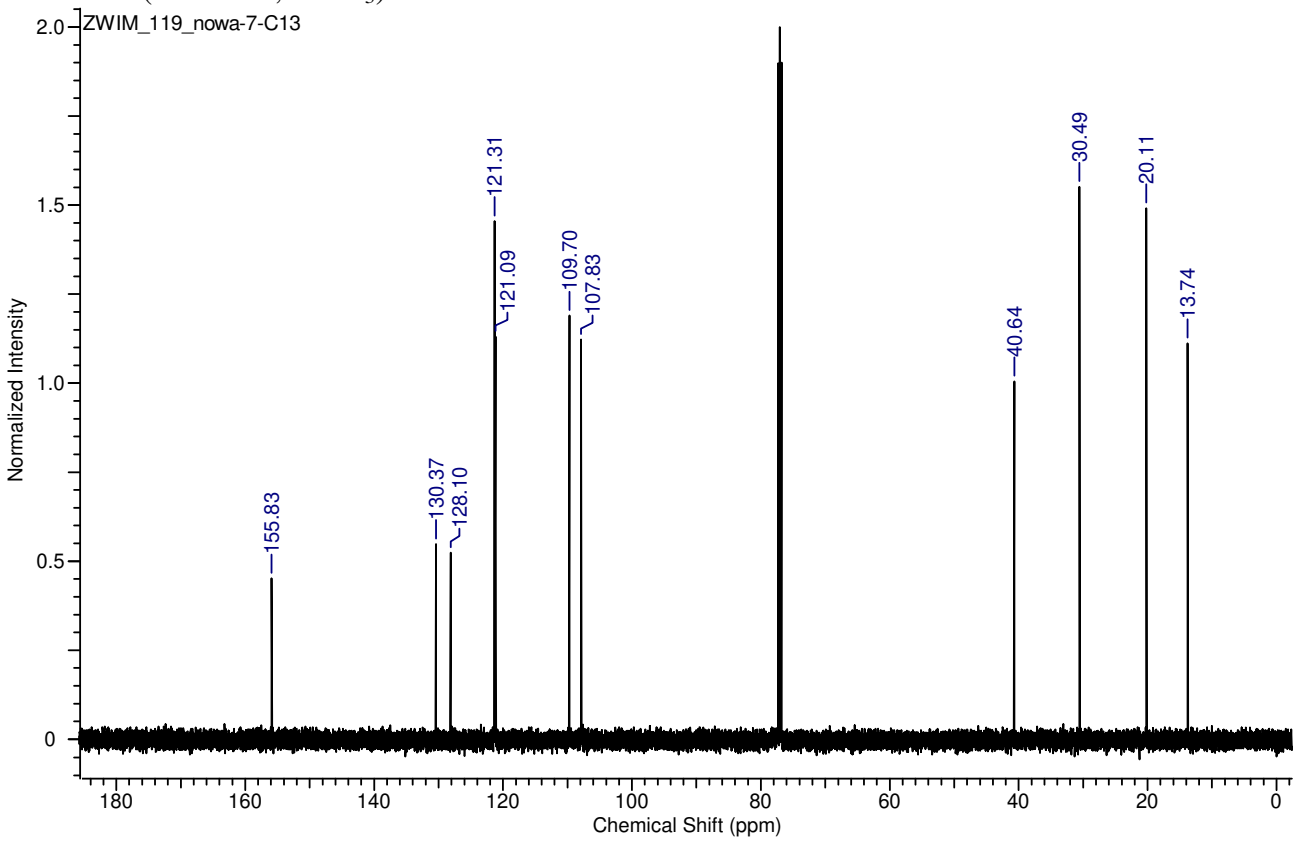


4i

^{1}H NMR (500 MHz, $CDCl_3$)

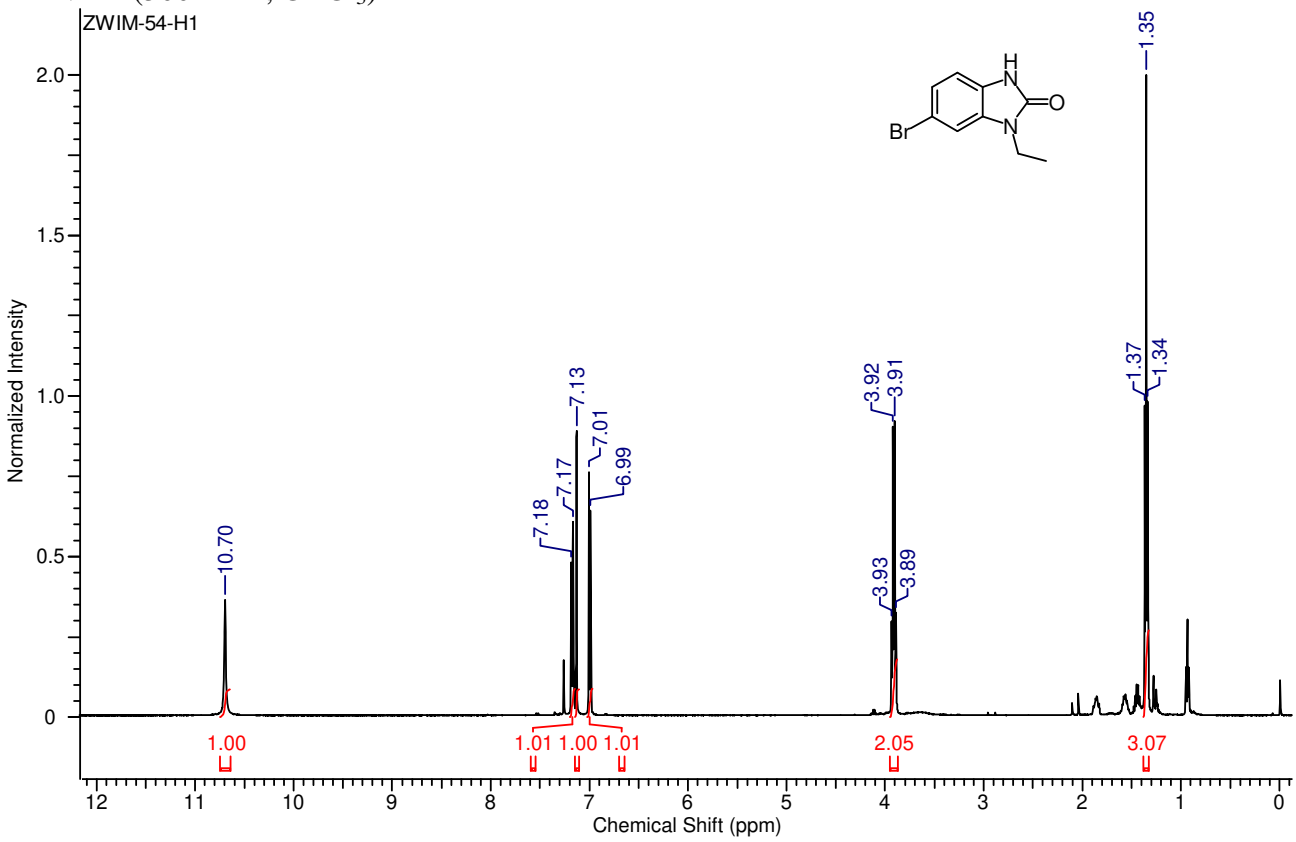


^{13}C NMR (125 MHz, $CDCl_3$)

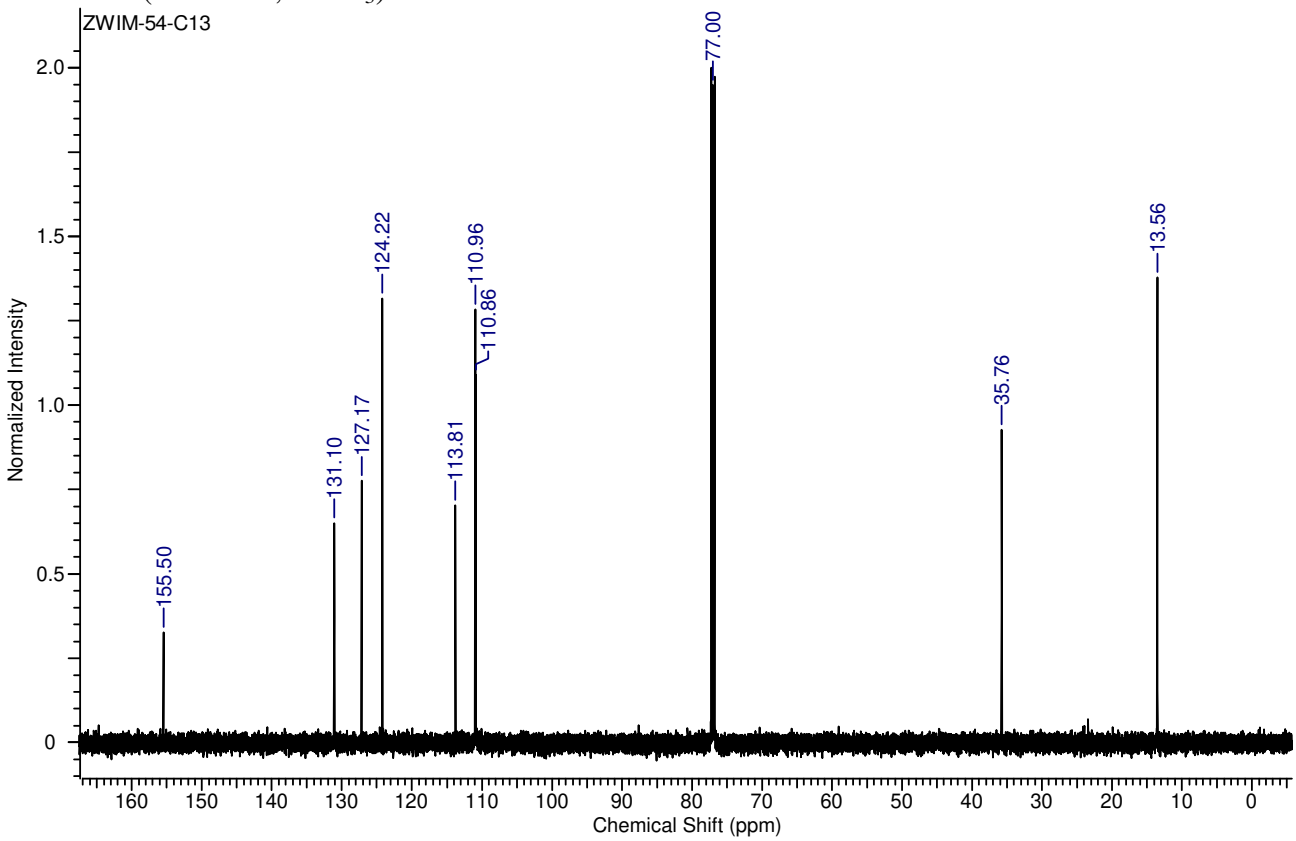


4j

^{1}H NMR (500 MHz, $CDCl_3$)

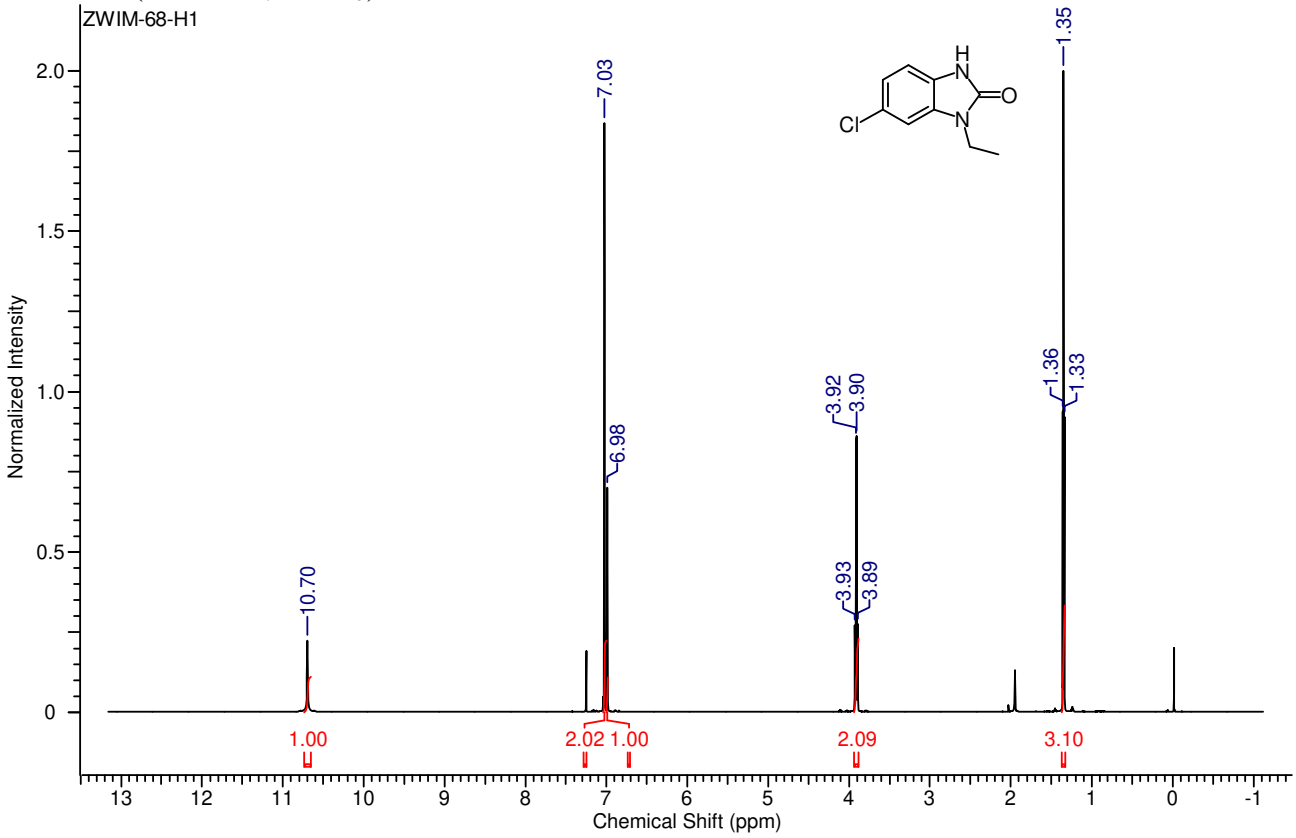


^{13}C NMR (125 MHz, $CDCl_3$)

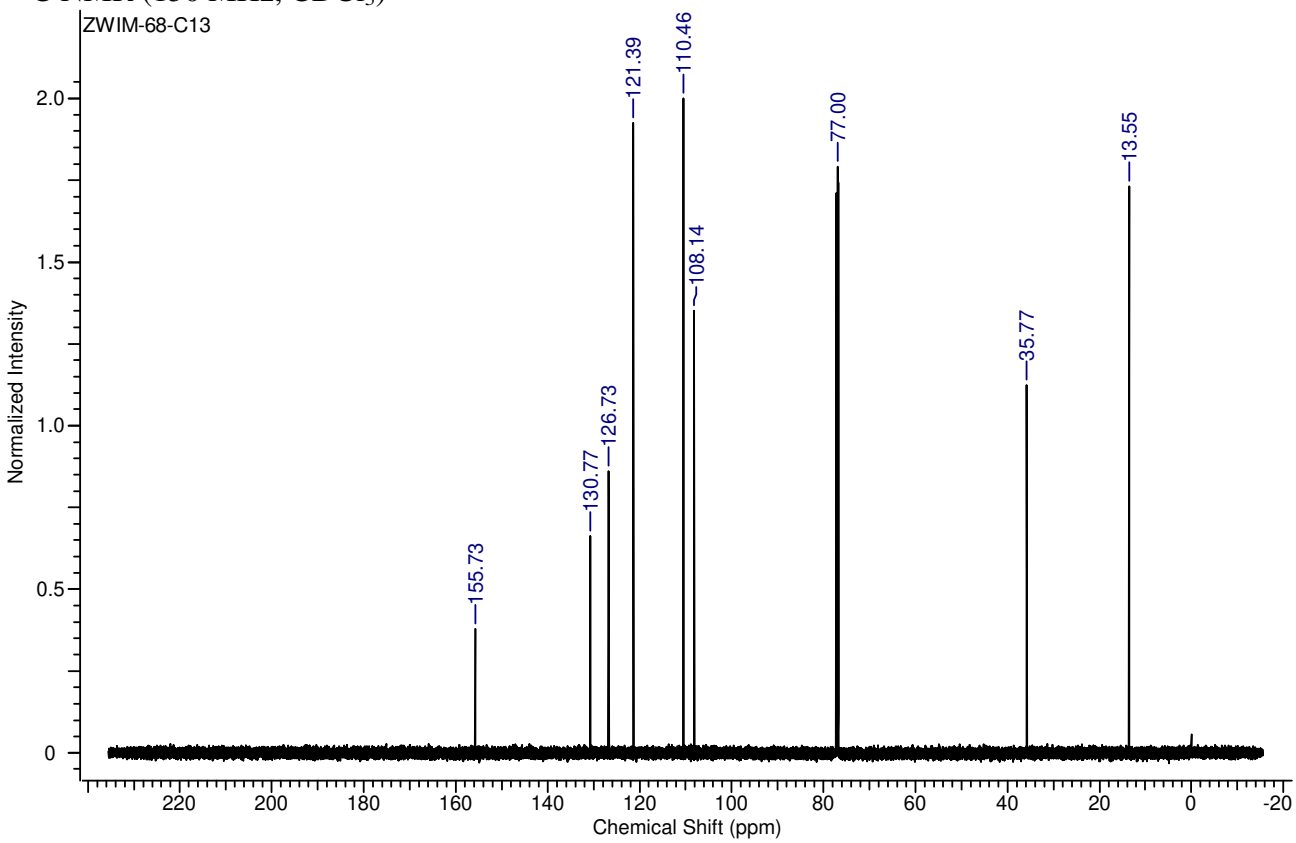


4k

^{1}H NMR (600 MHz, $CDCl_3$)

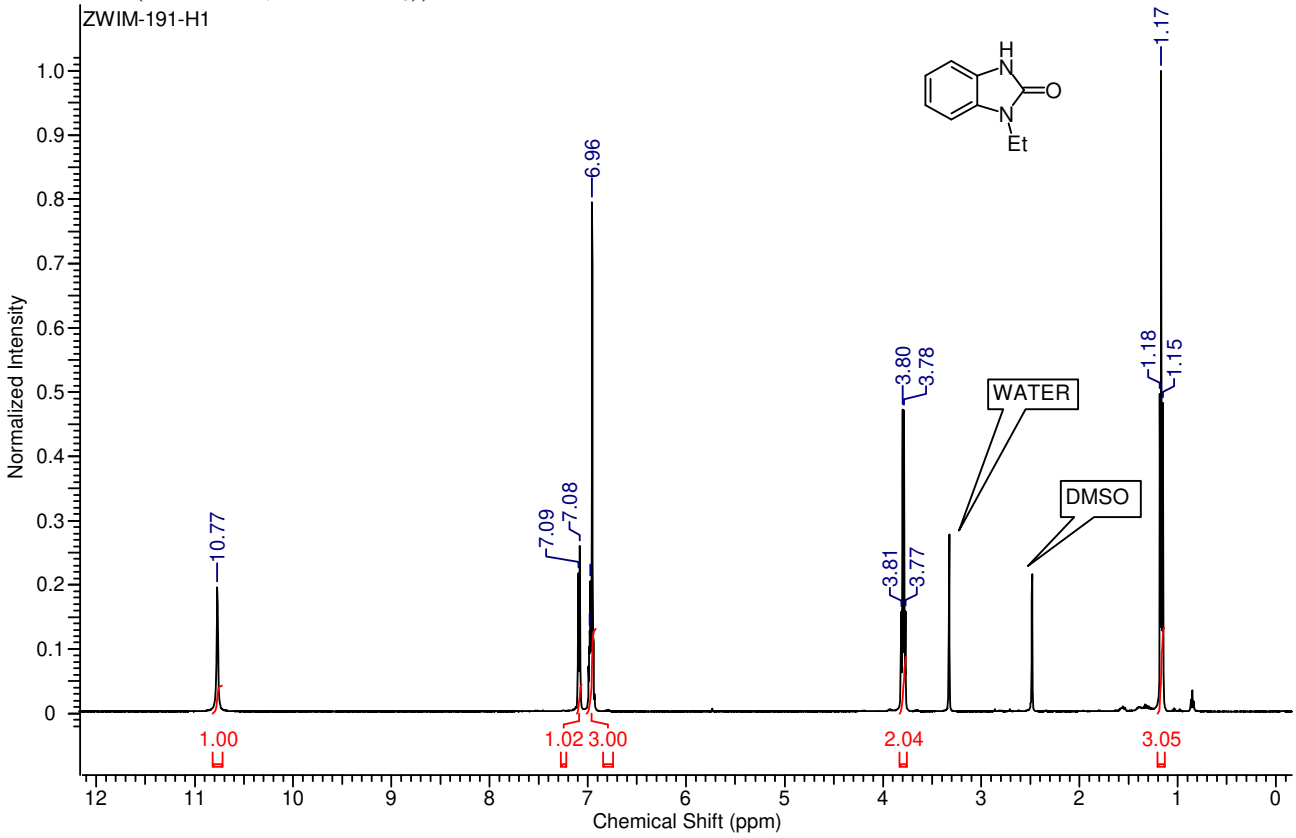


^{13}C NMR (150 MHz, $CDCl_3$)

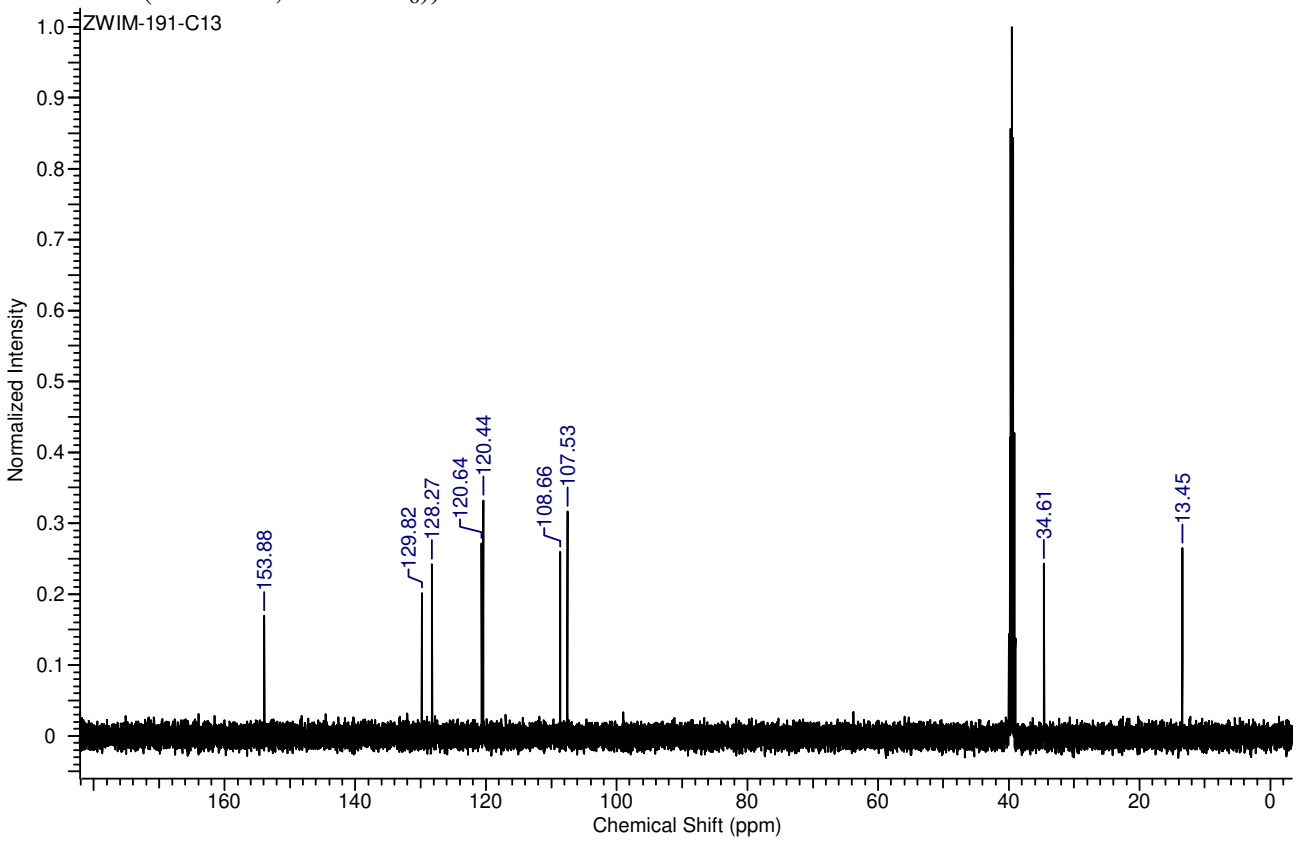


4l

^{1}H NMR (500 MHz, DMSO-d_6))

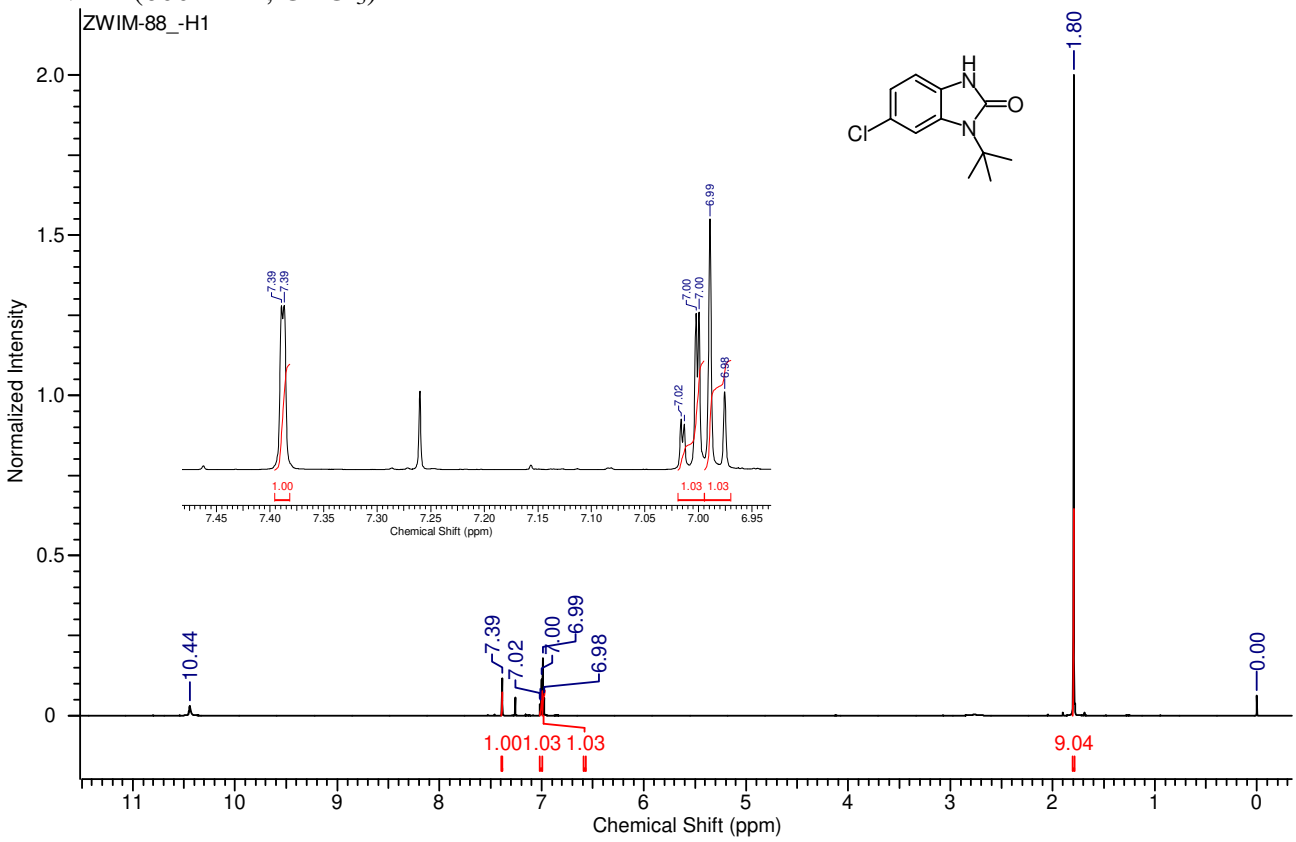


^{13}C NMR (125 MHz, DMSO-d_6))

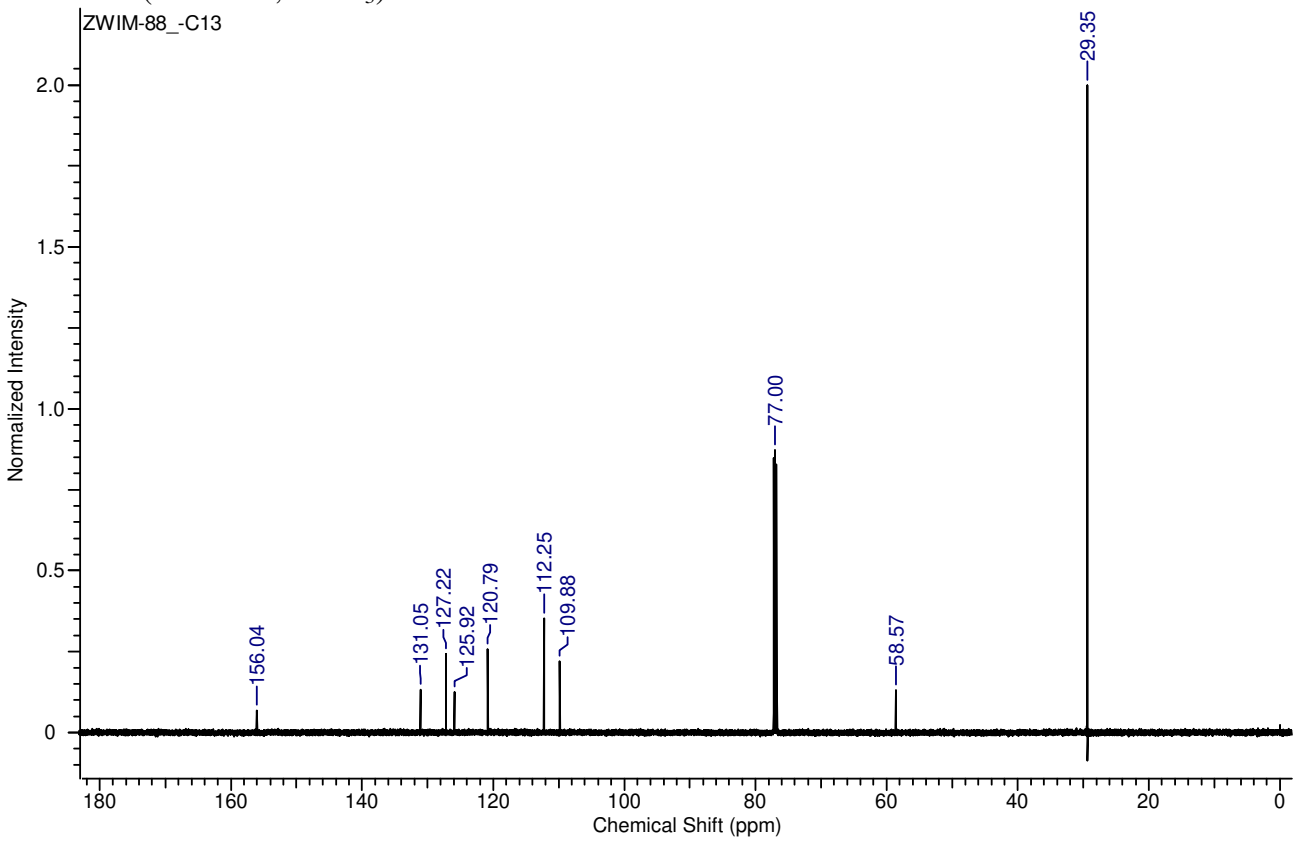


4m

^{1}H NMR (600 MHz, $CDCl_3$)



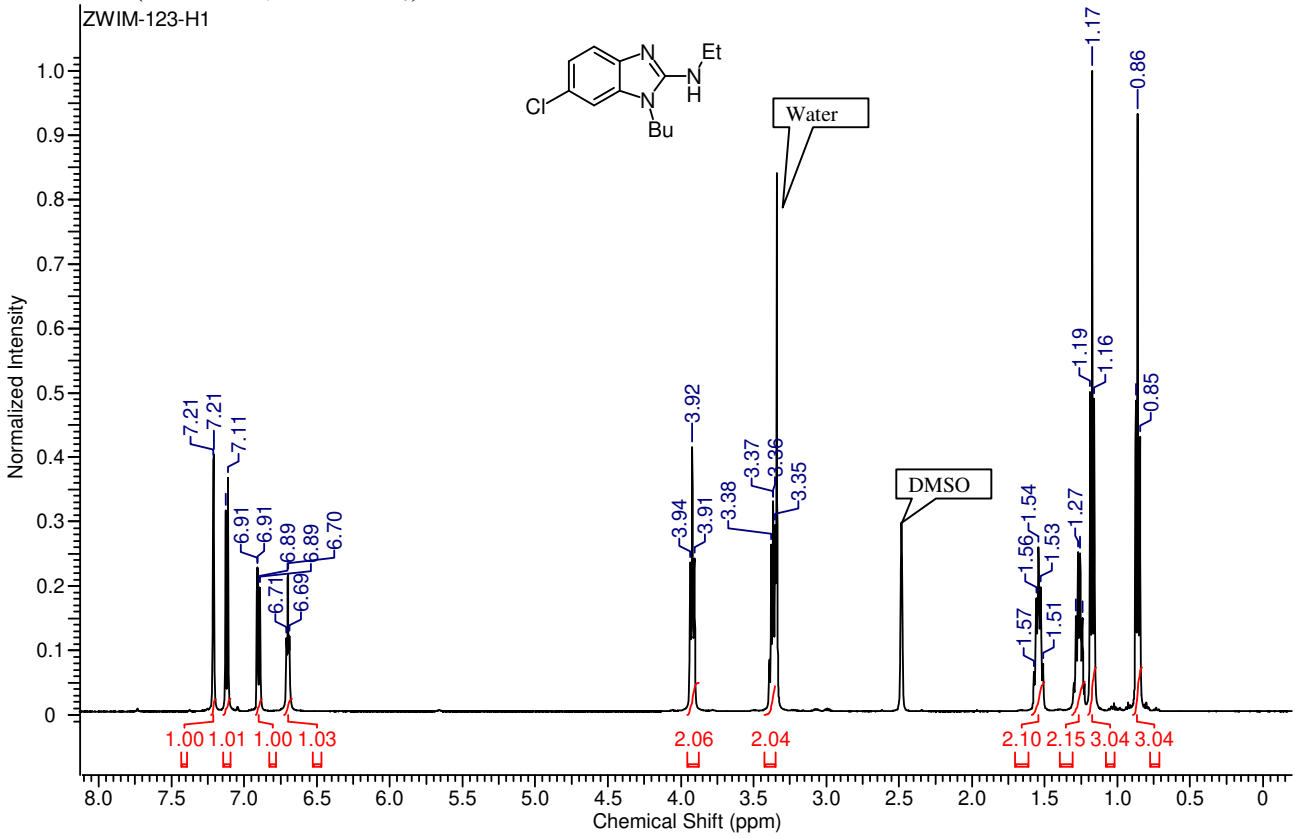
^{13}C NMR (150 MHz, $CDCl_3$)



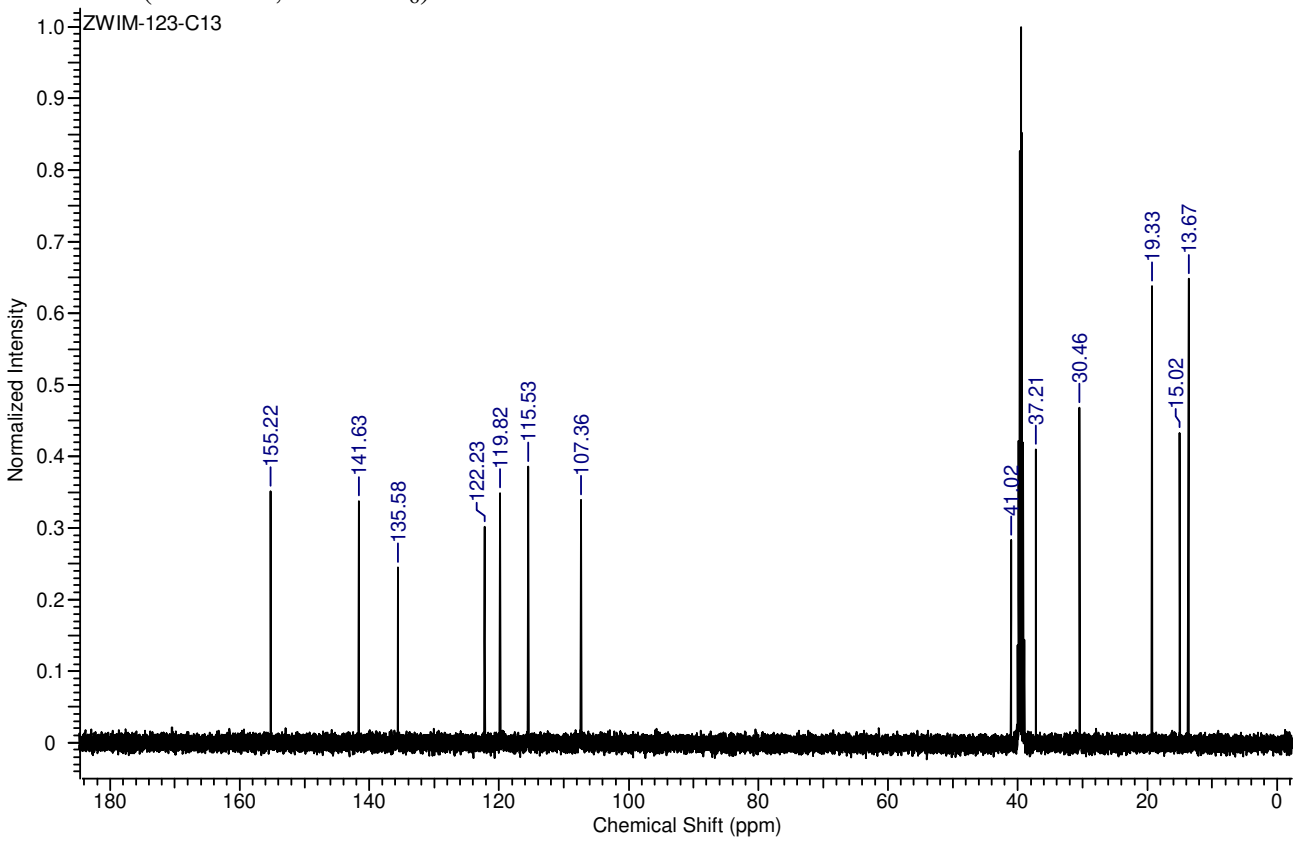
***N*-Alkyl-2-aminobenzimidazoles 5**

5a

^{1}H NMR (500 MHz, DMSO-d_6)

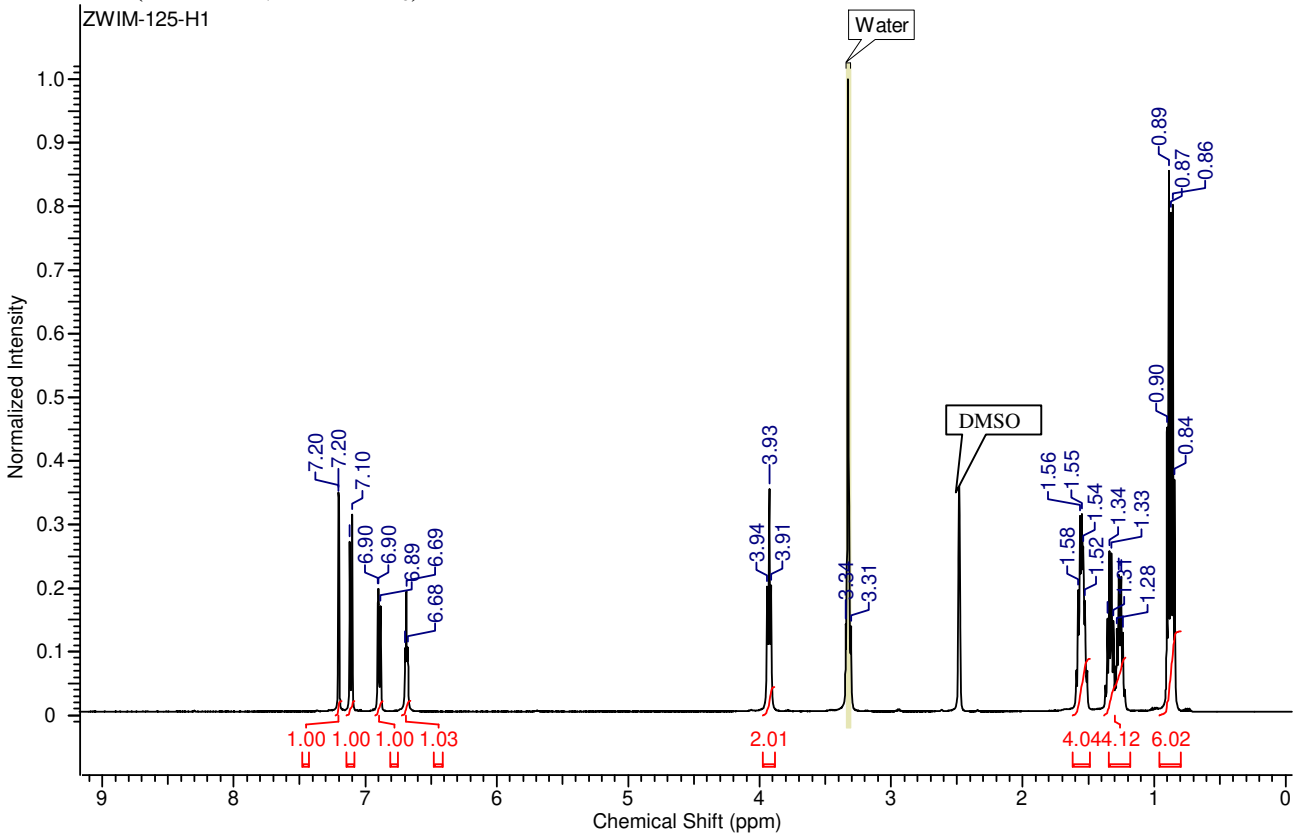


^{13}C NMR (125 MHz, DMSO-d_6)

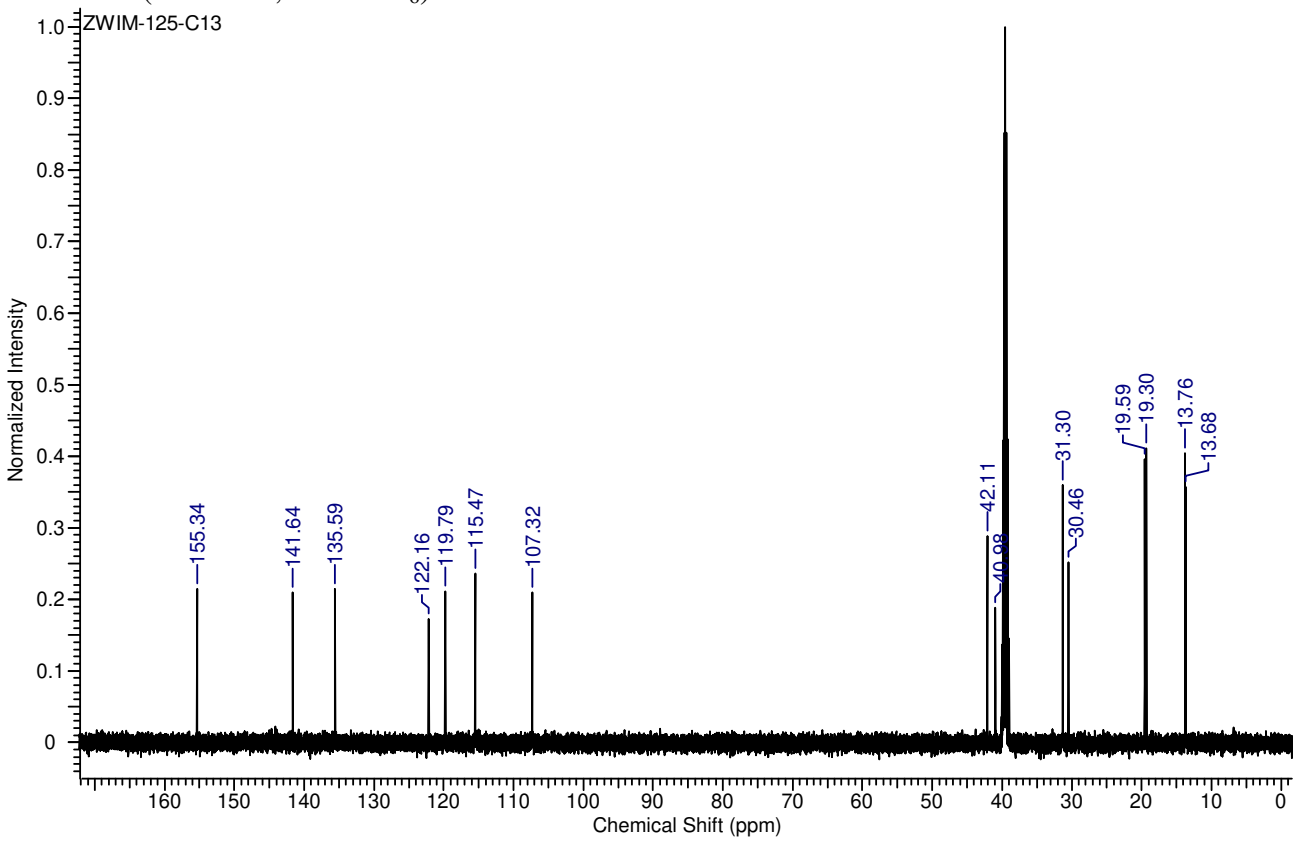


5b

^{1}H NMR (500 MHz, DMSO-d_6)

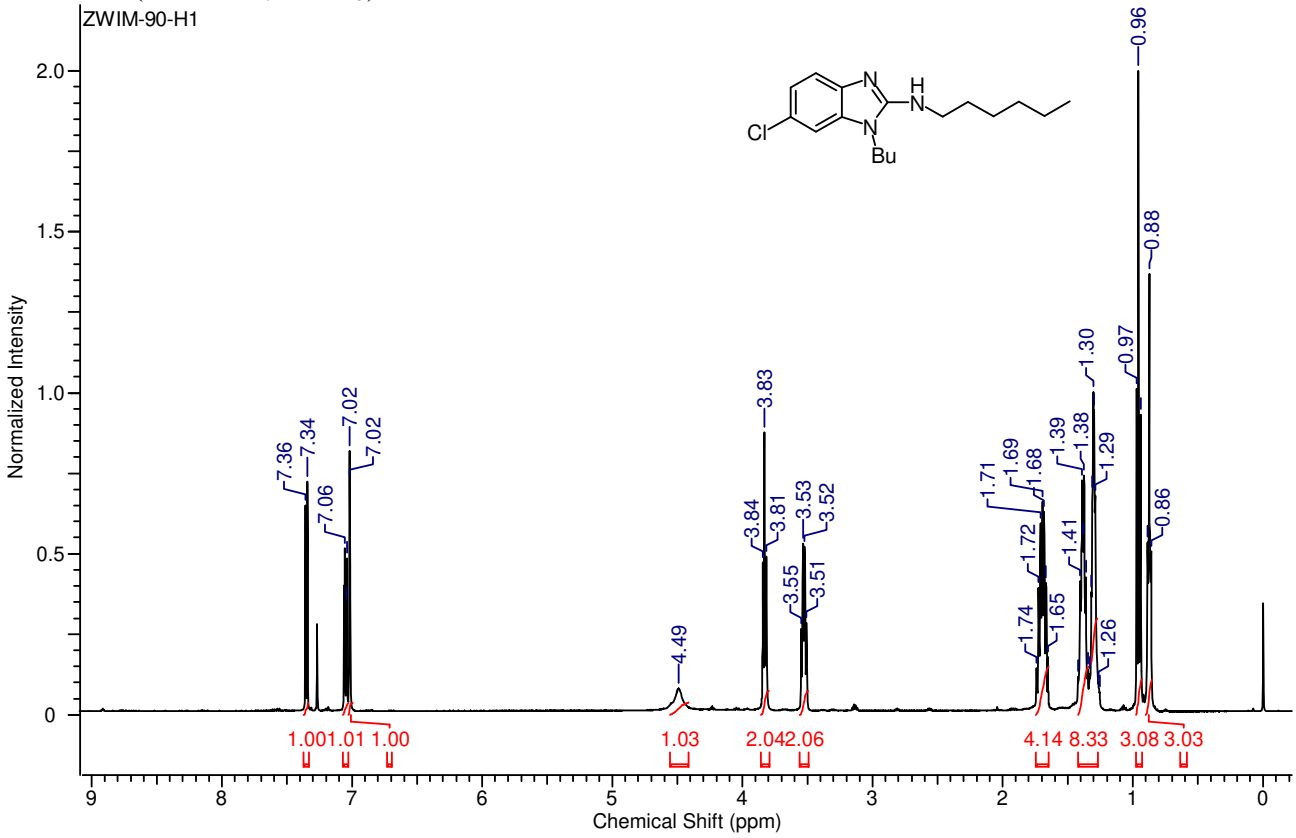


^{13}C NMR (125 MHz, DMSO-d_6)

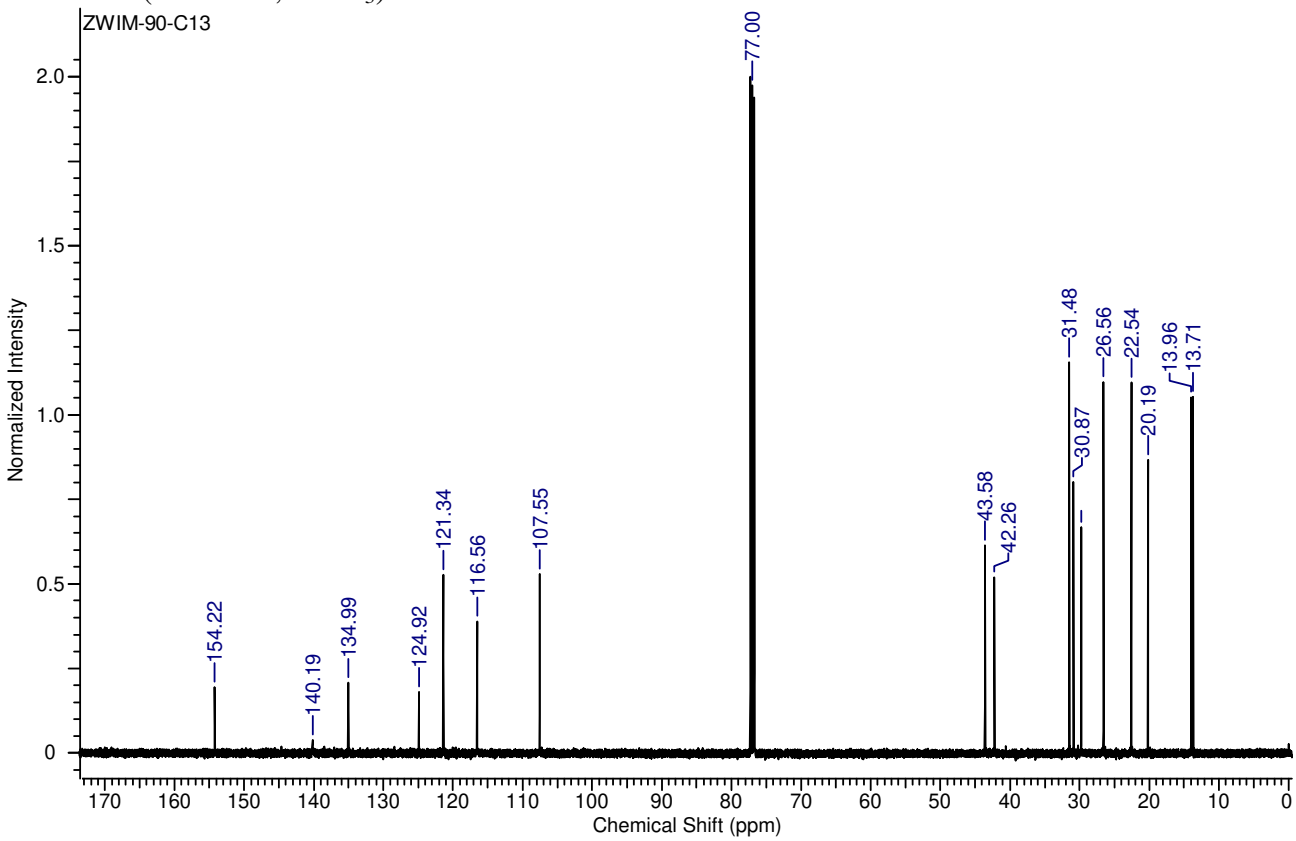


5c

^{1}H NMR (500 MHz, $CDCl_3$)

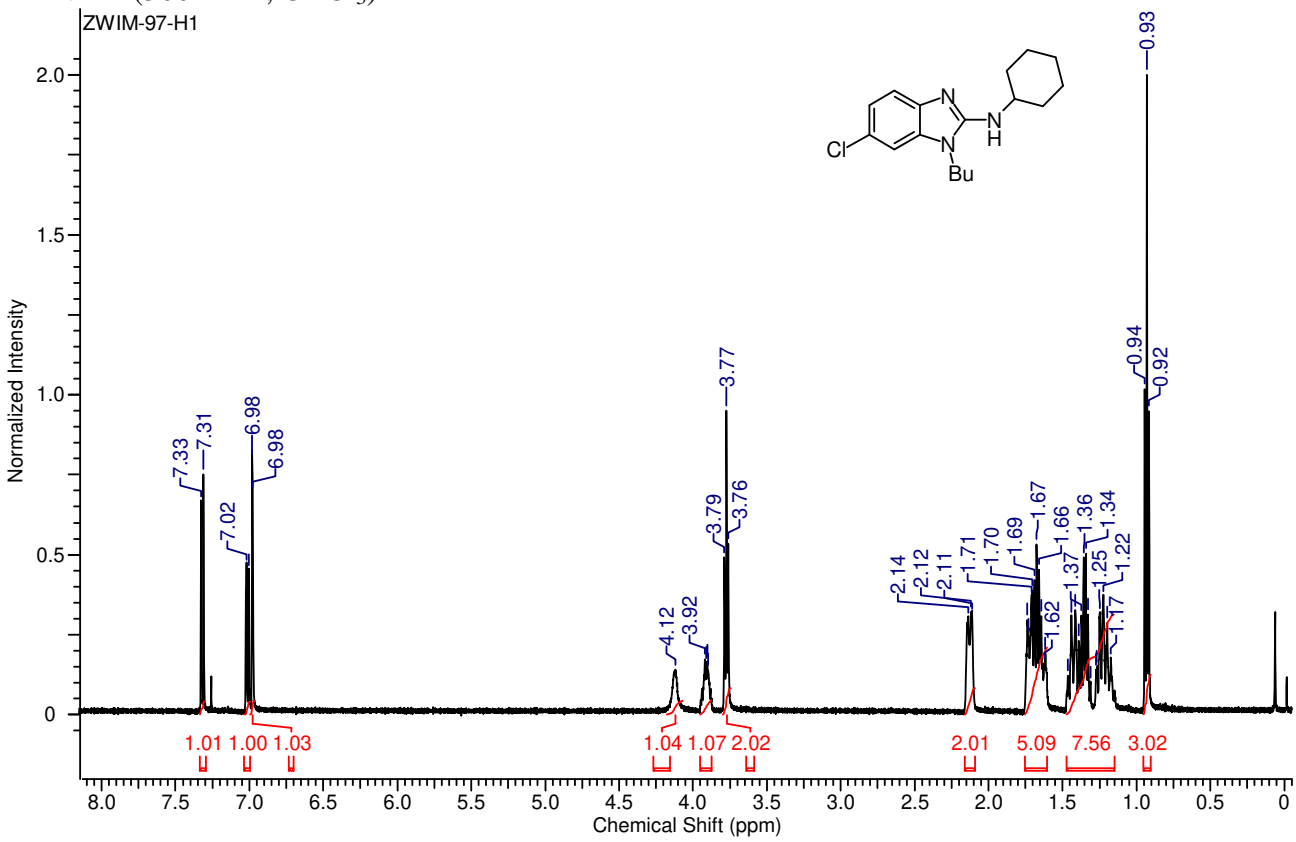


^{13}C NMR (125 MHz, $CDCl_3$)

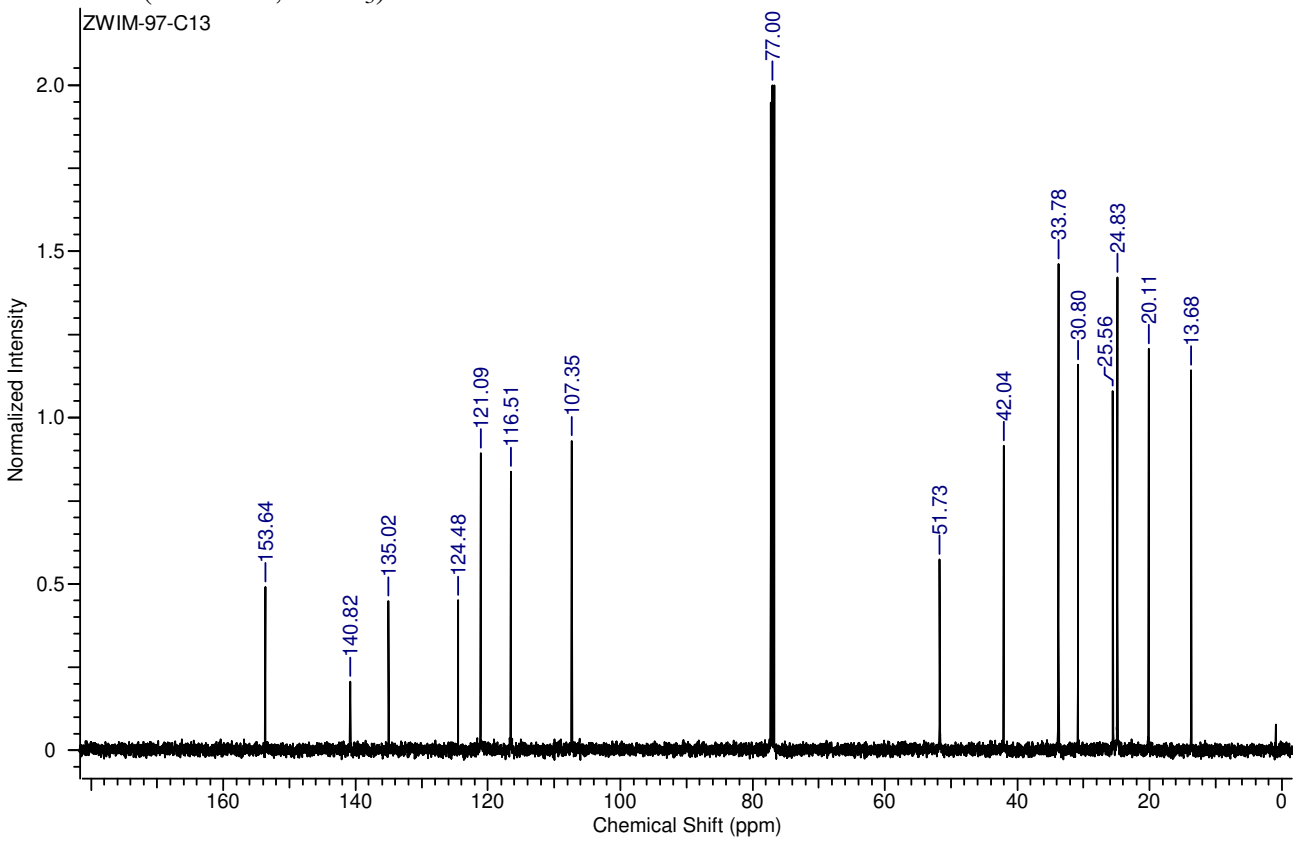


5d

^{1}H NMR (500 MHz, $CDCl_3$)

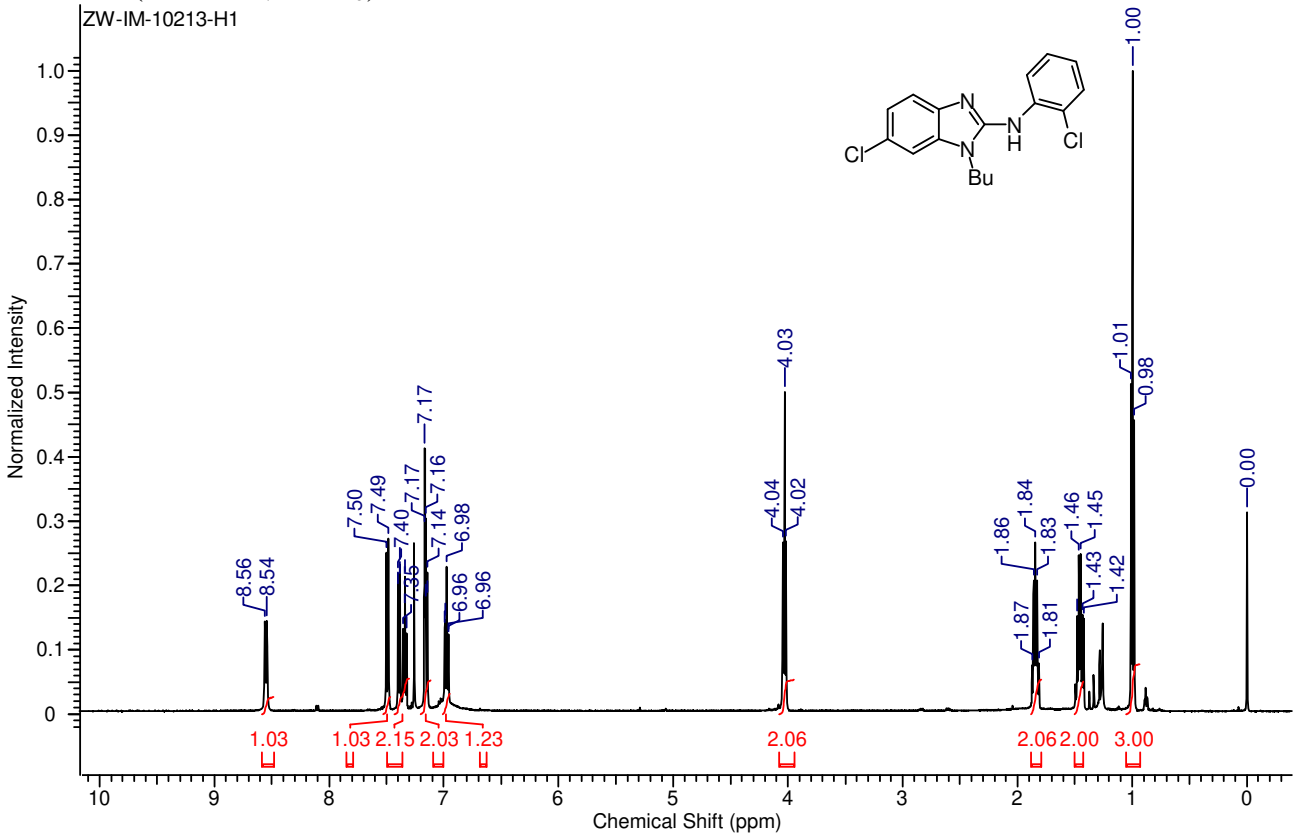


^{13}C NMR (125 MHz, $CDCl_3$)

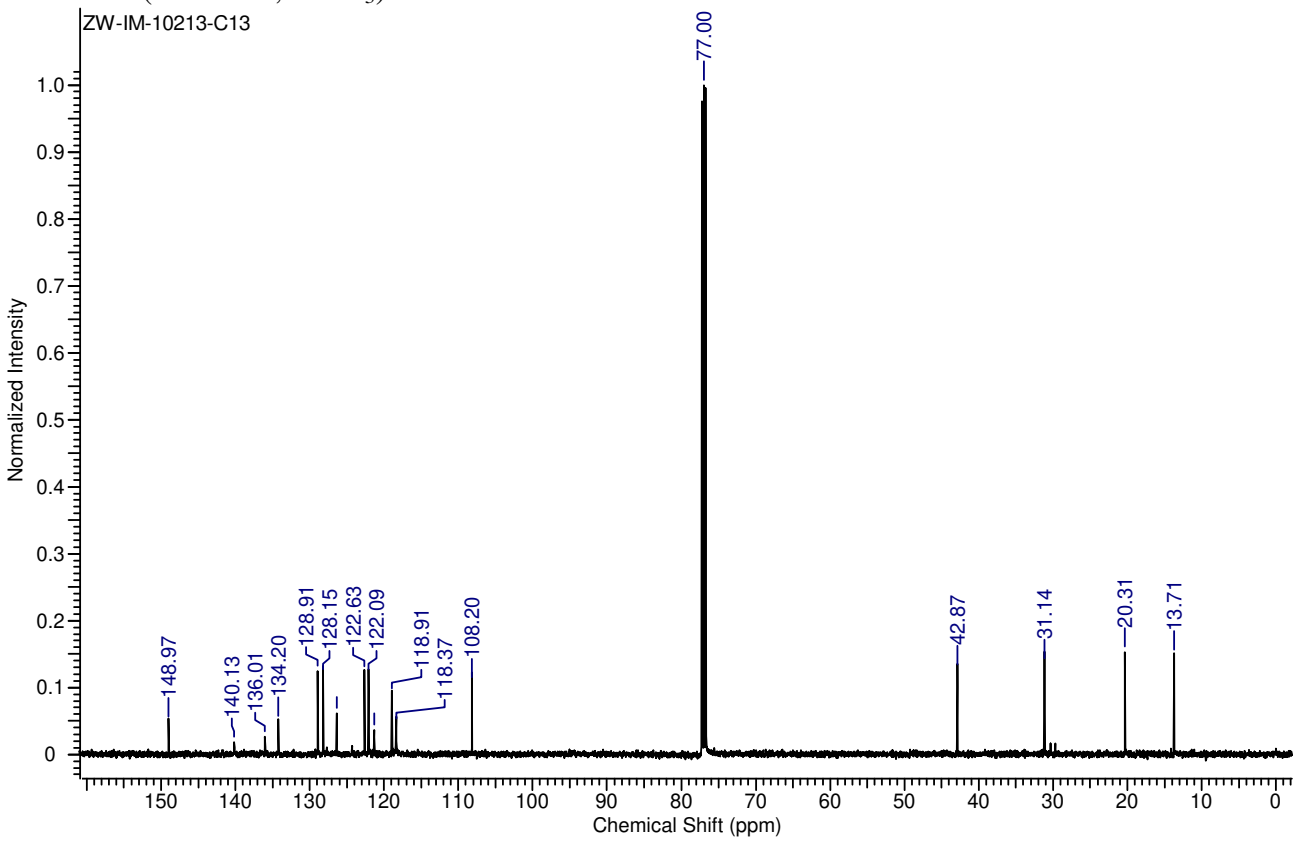


5e

^{1}H NMR (600 MHz, $CDCl_3$)

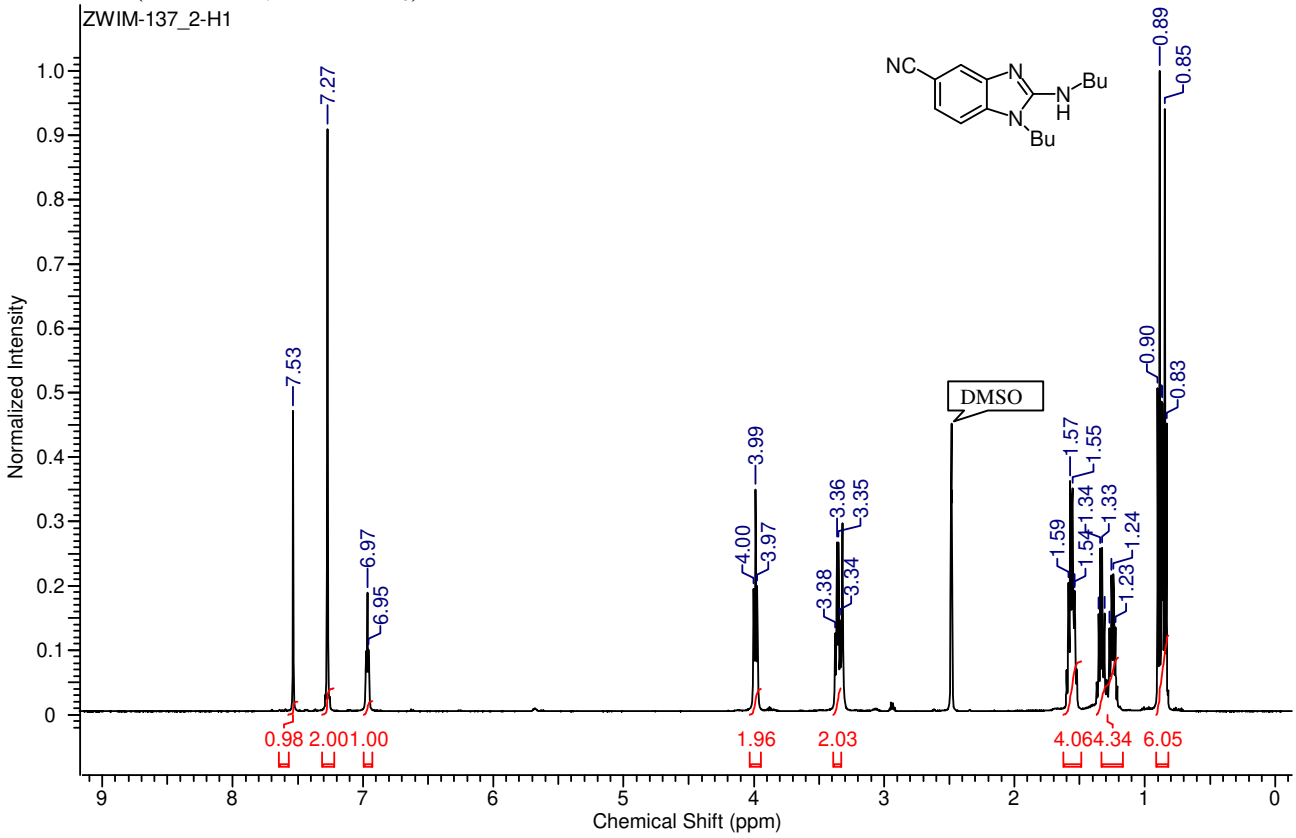


^{13}C NMR (150 MHz, $CDCl_3$)

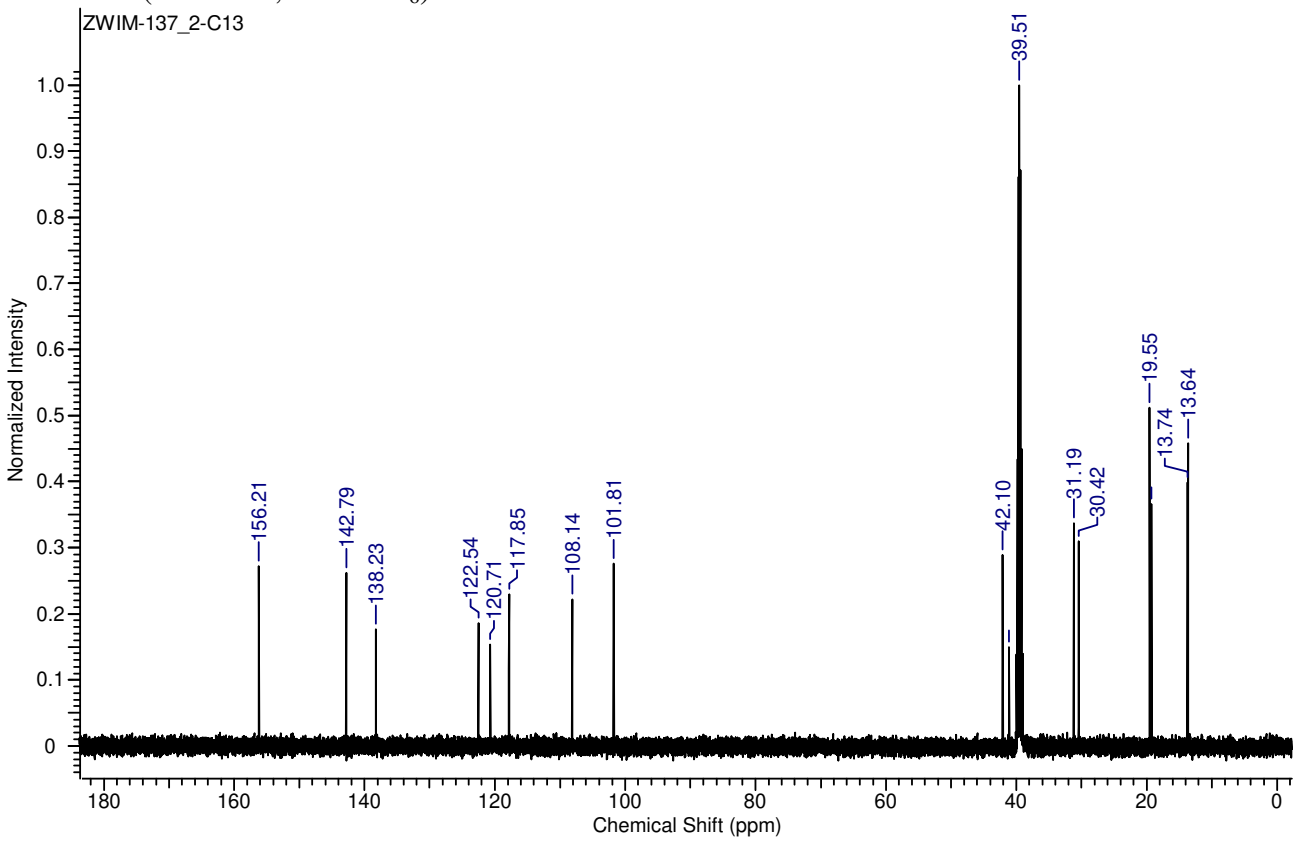


5f

^{1}H NMR (500 MHz, DMSO-d_6)

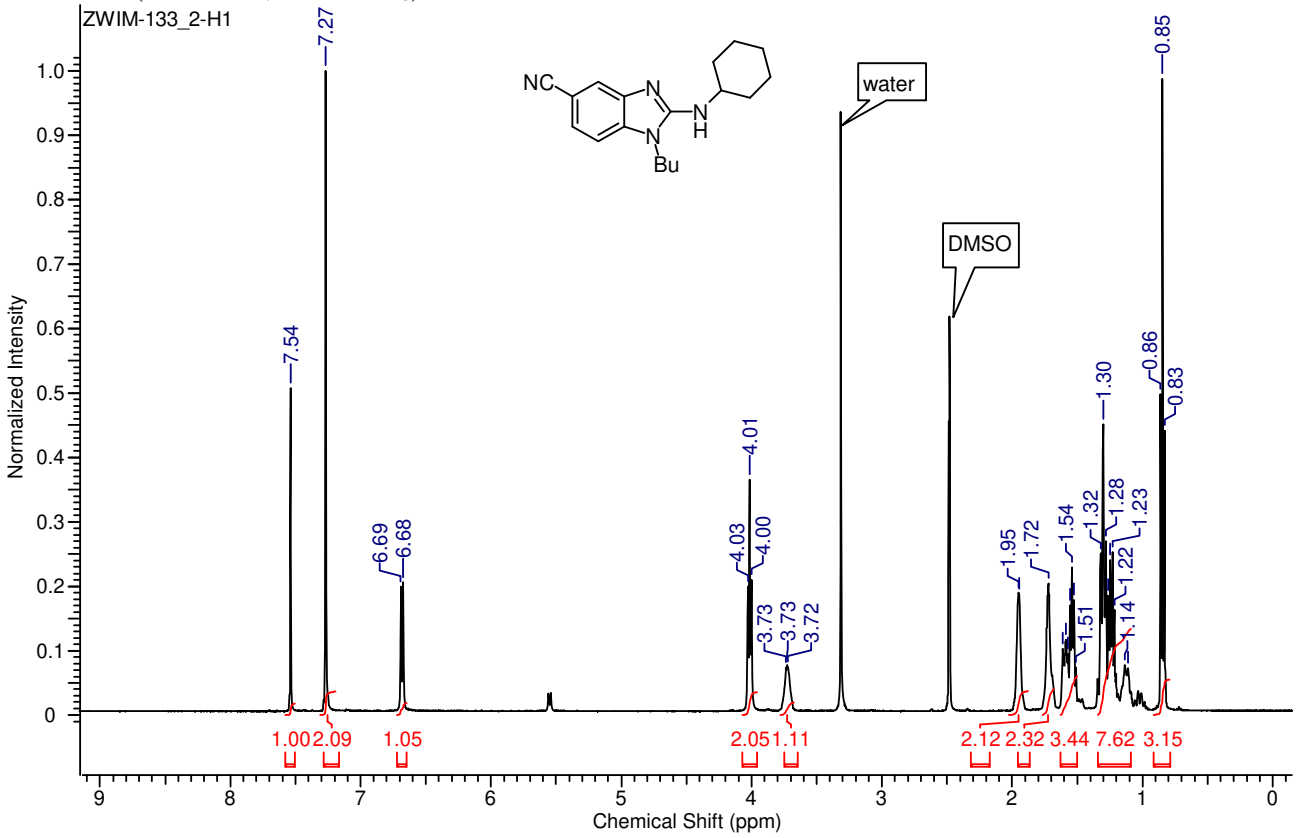


^{13}C NMR (125 MHz, DMSO-d_6)

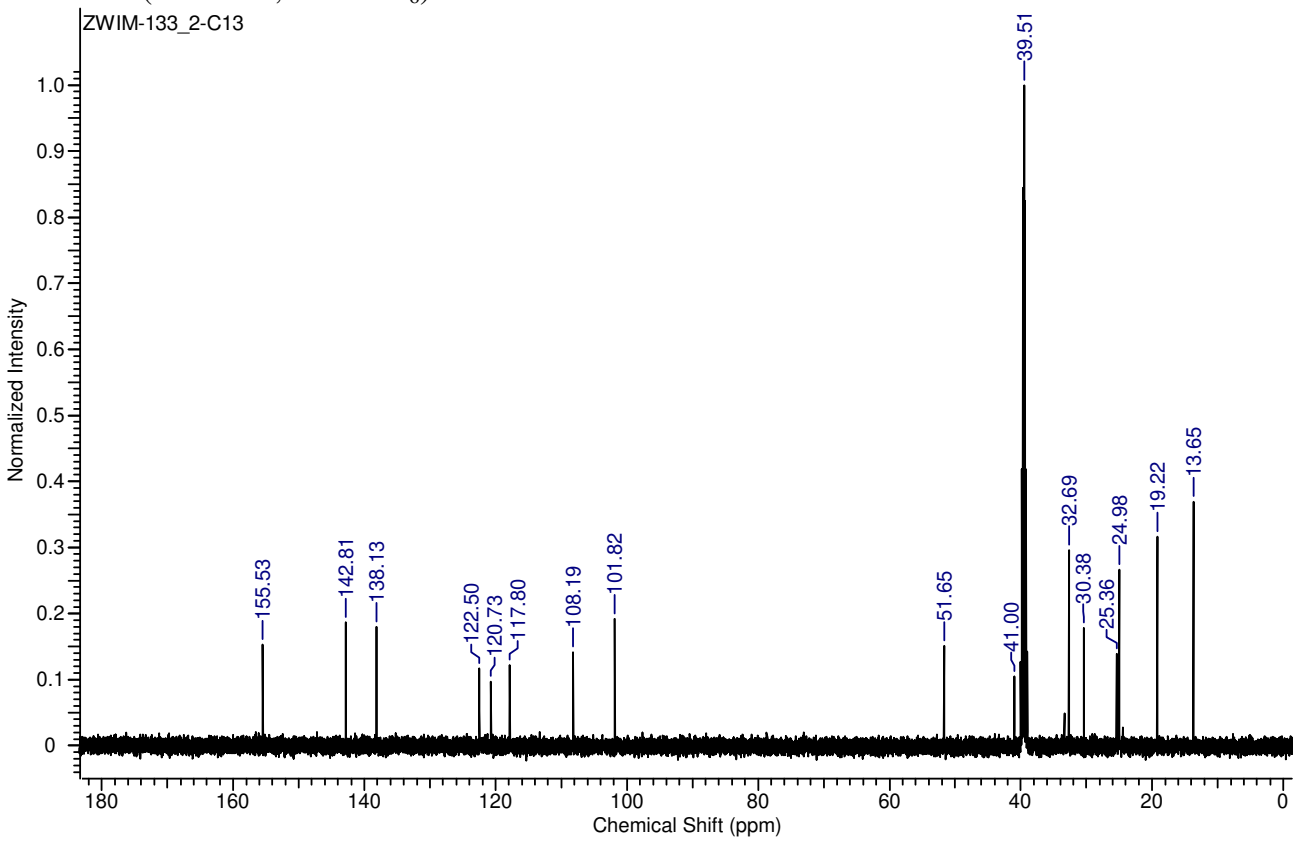


5g

^{1}H NMR (500 MHz, DMSO-d_6)

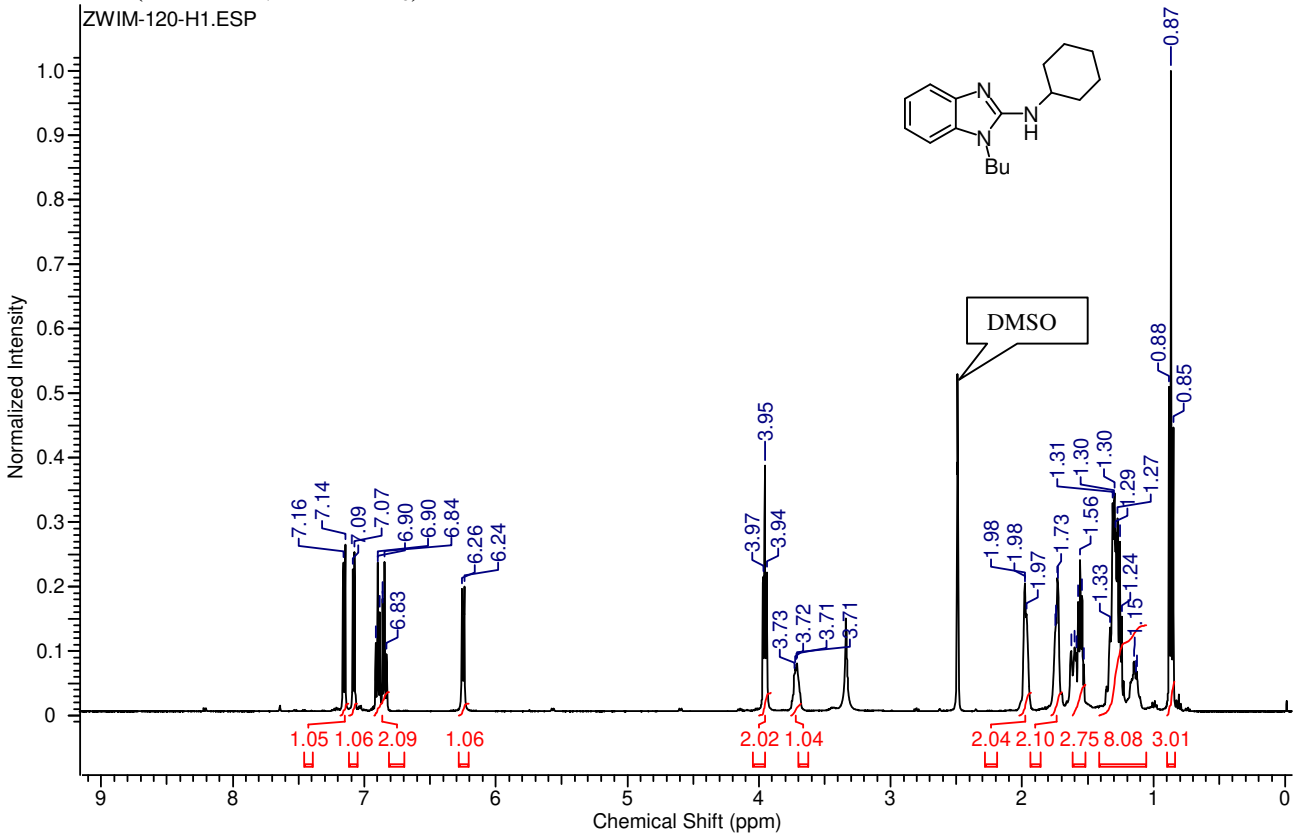


^{13}C NMR (125 MHz, DMSO-d_6)

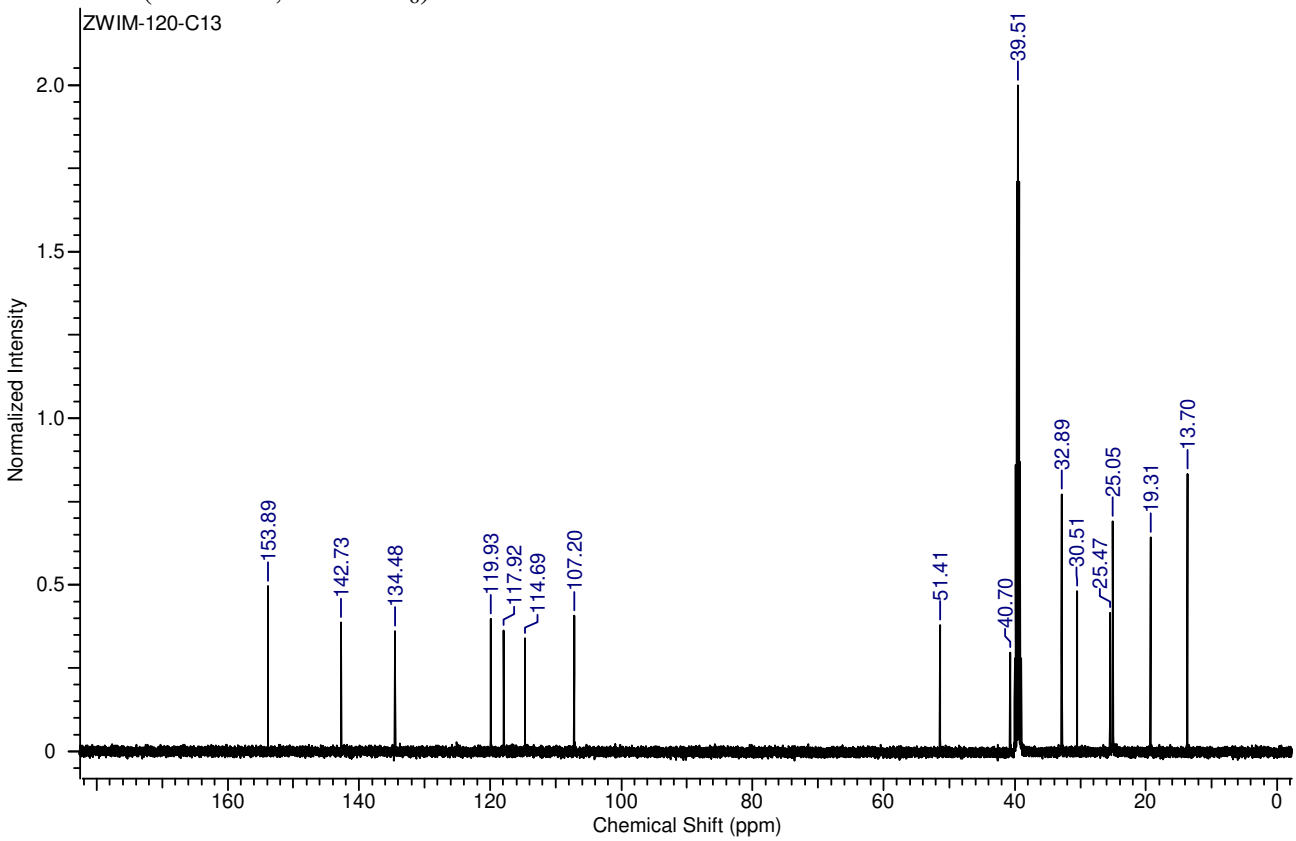


5h

^{1}H NMR (500 MHz, DMSO-d_6)

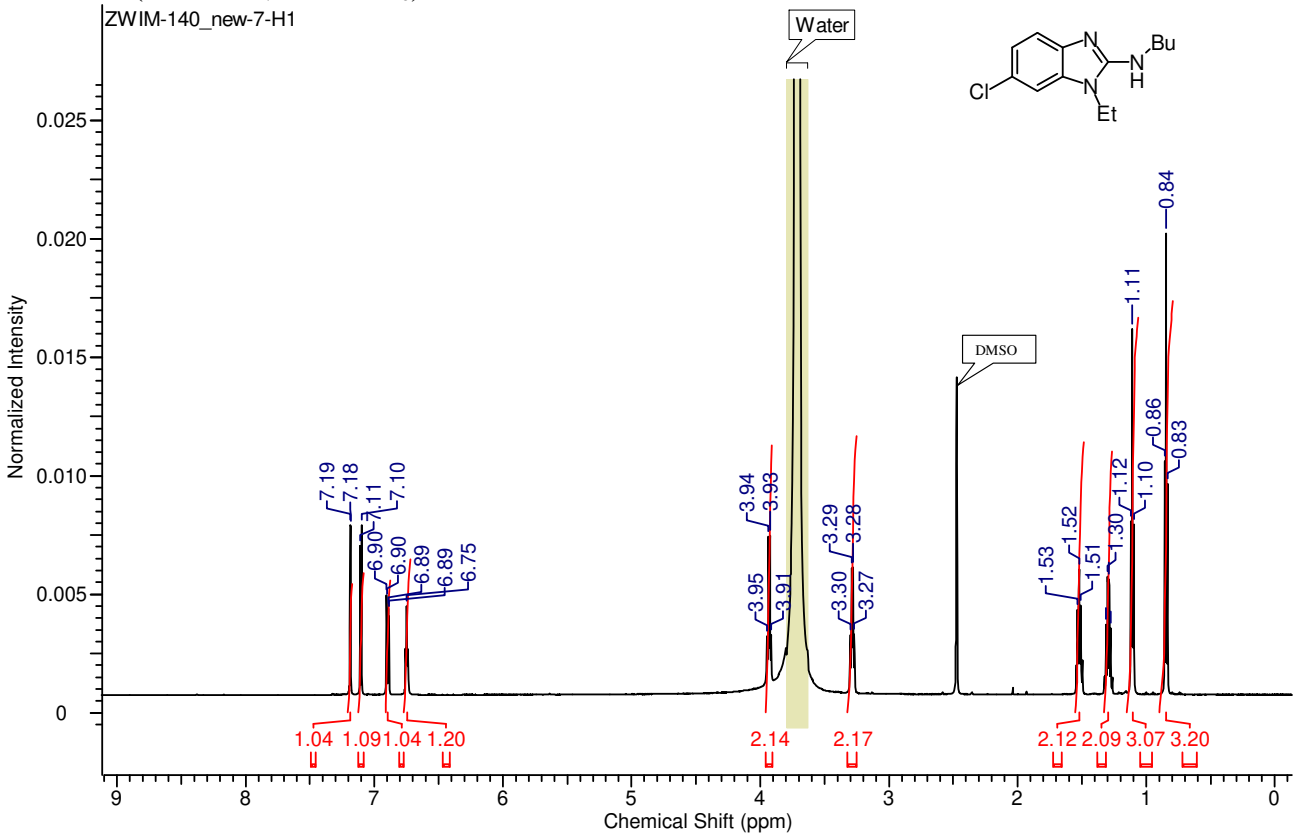


^{13}C NMR (125 MHz, DMSO-d_6)

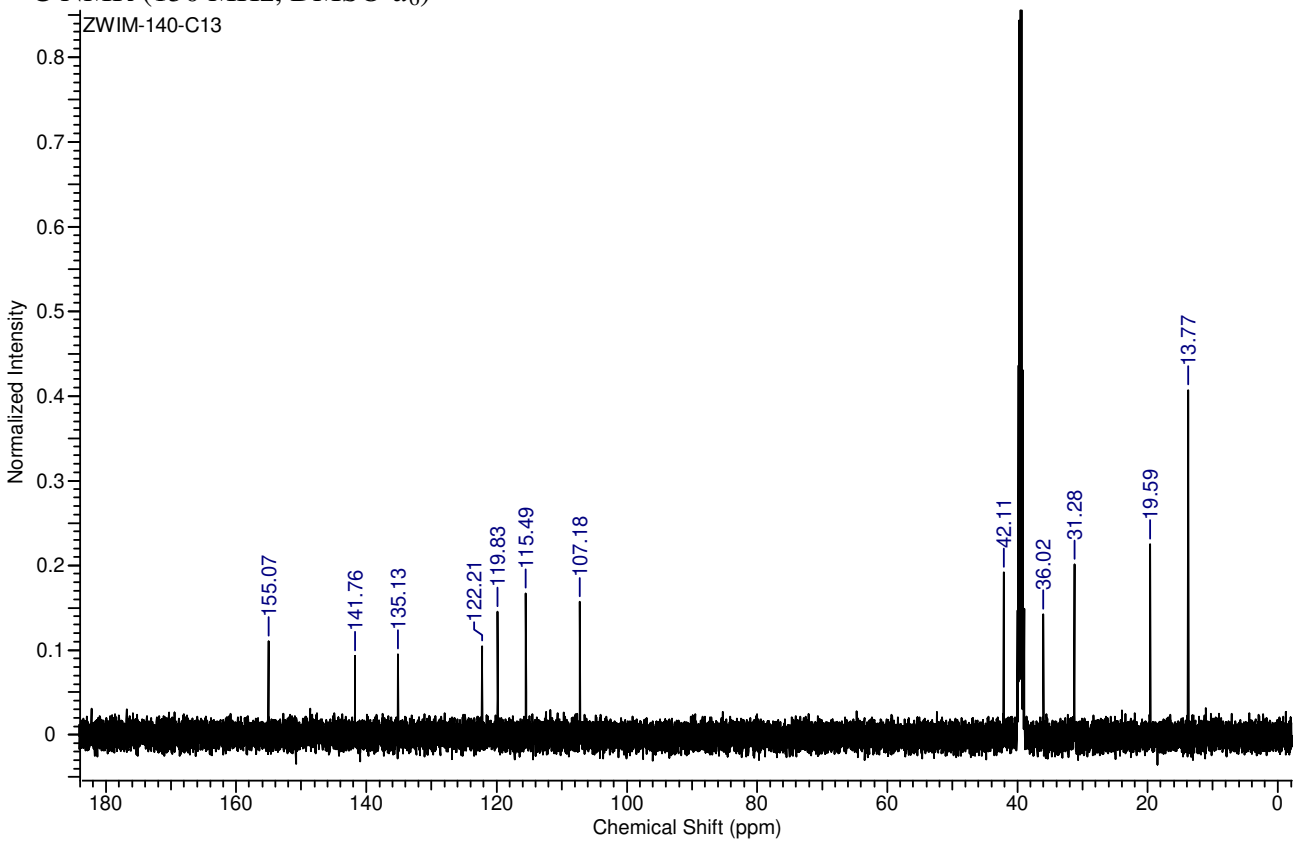


5i

^{1}H NMR (600 MHz, DMSO-d_6)

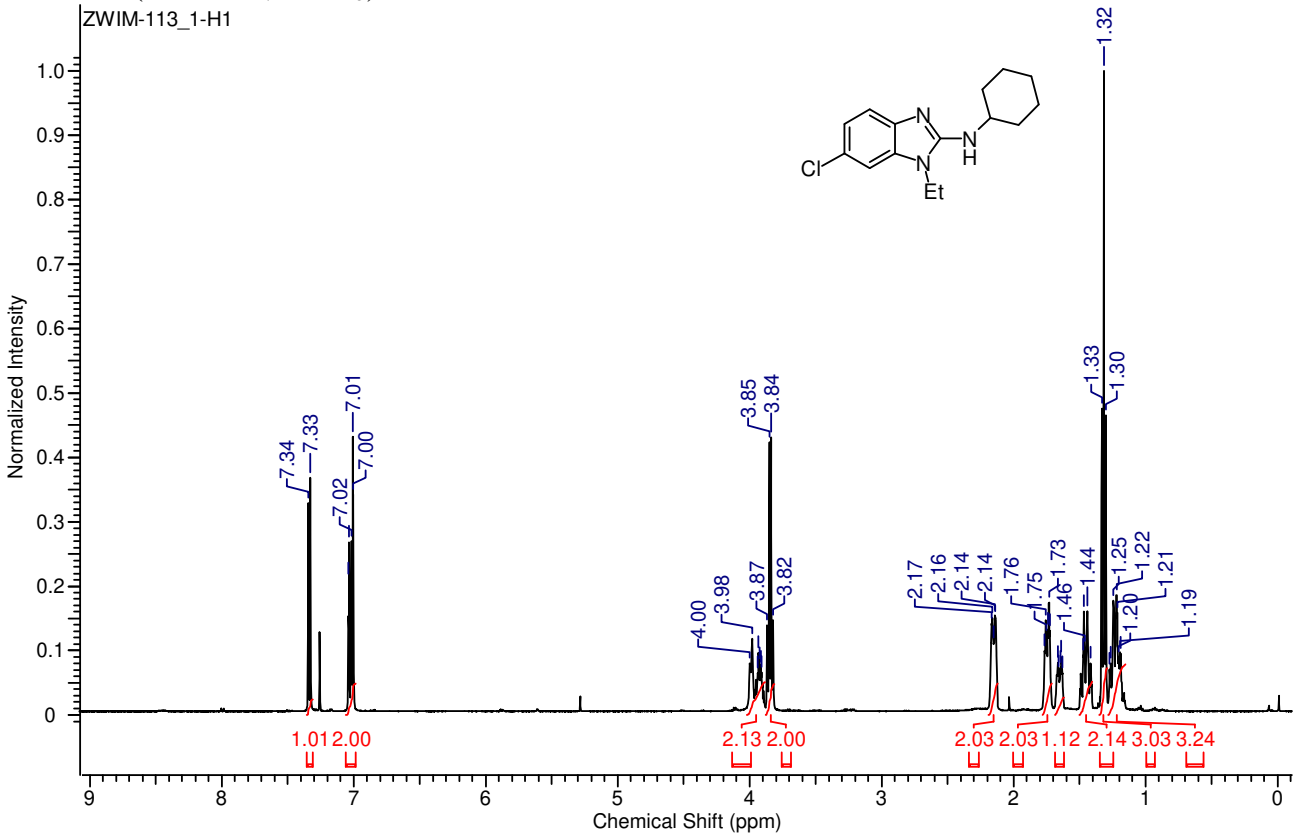


^{13}C NMR (150 MHz, DMSO-d_6)

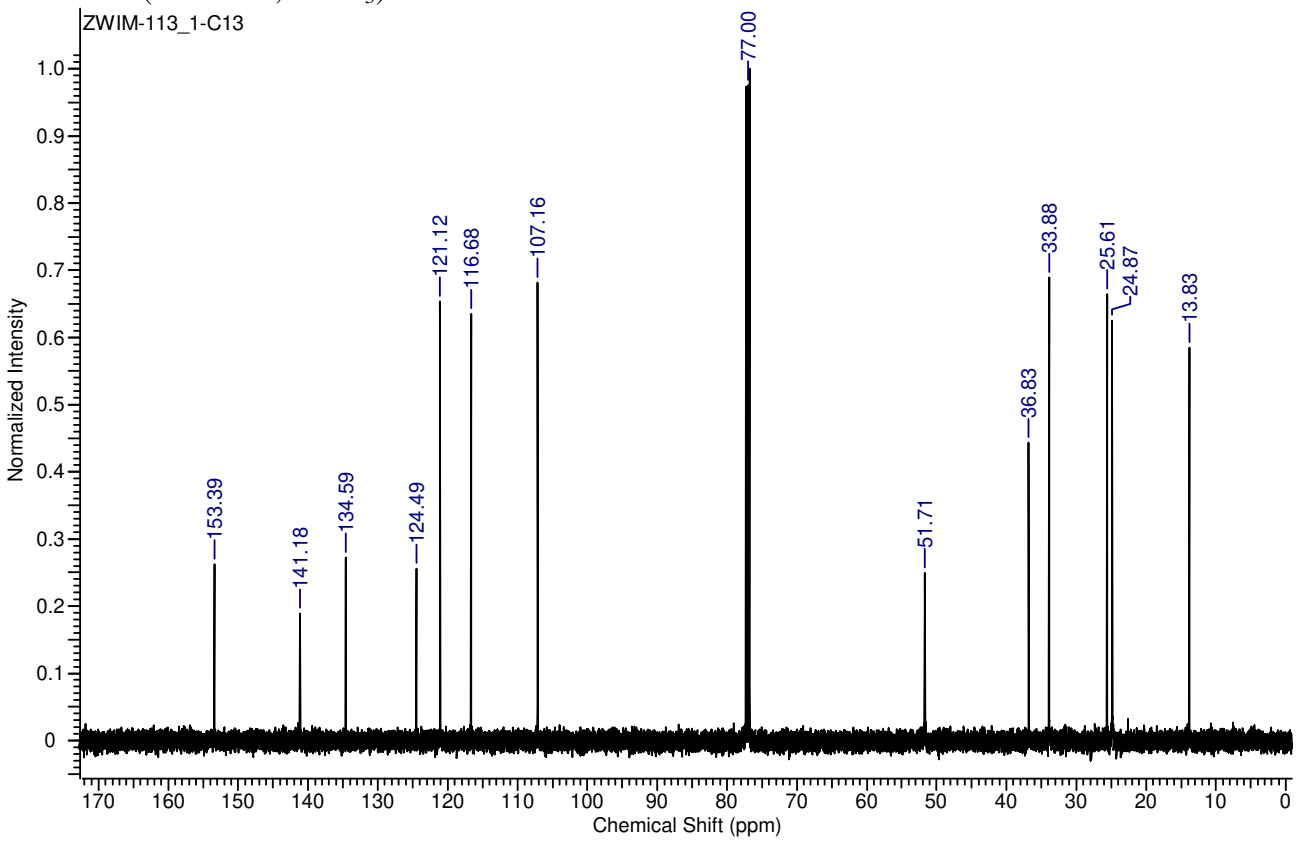


5j

^{1}H NMR (500 MHz, $CDCl_3$)

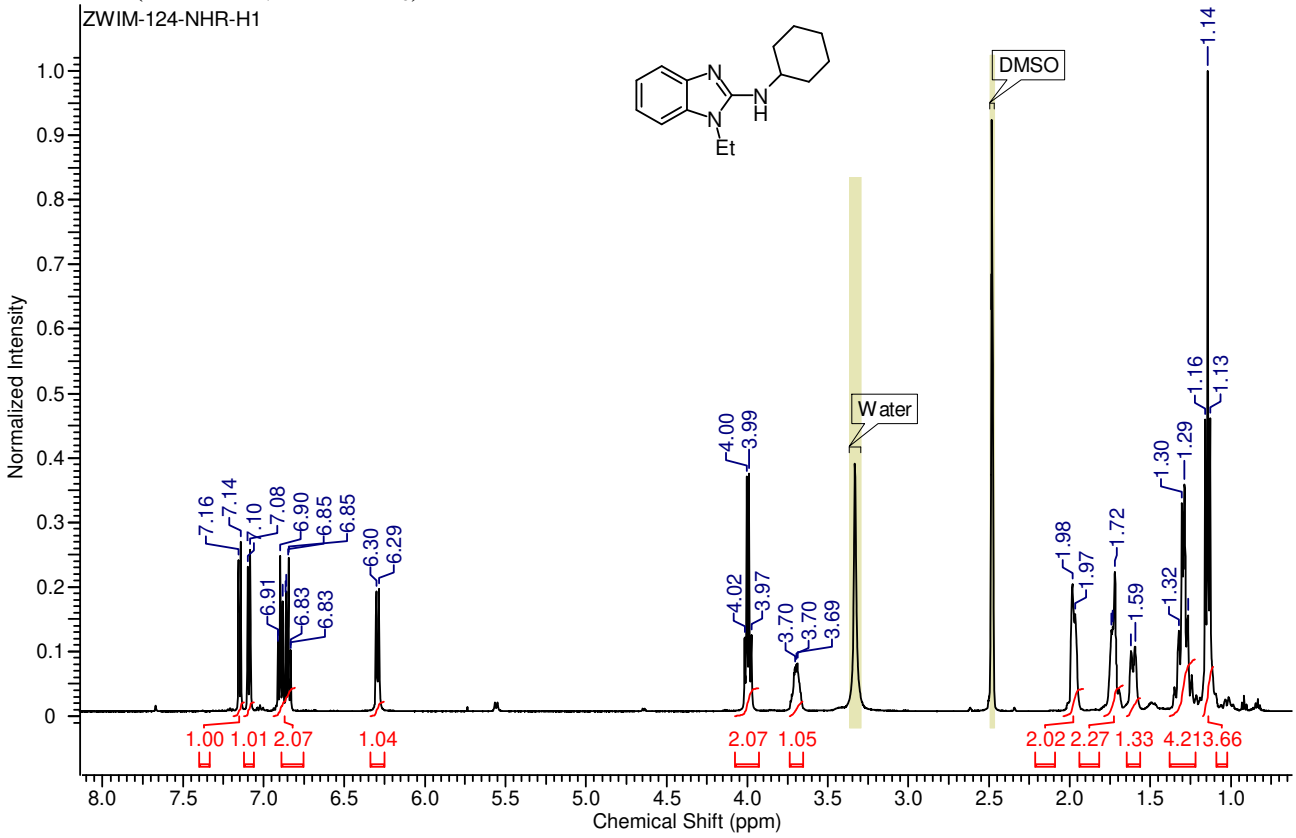


^{13}C NMR (125 MHz, $CDCl_3$)

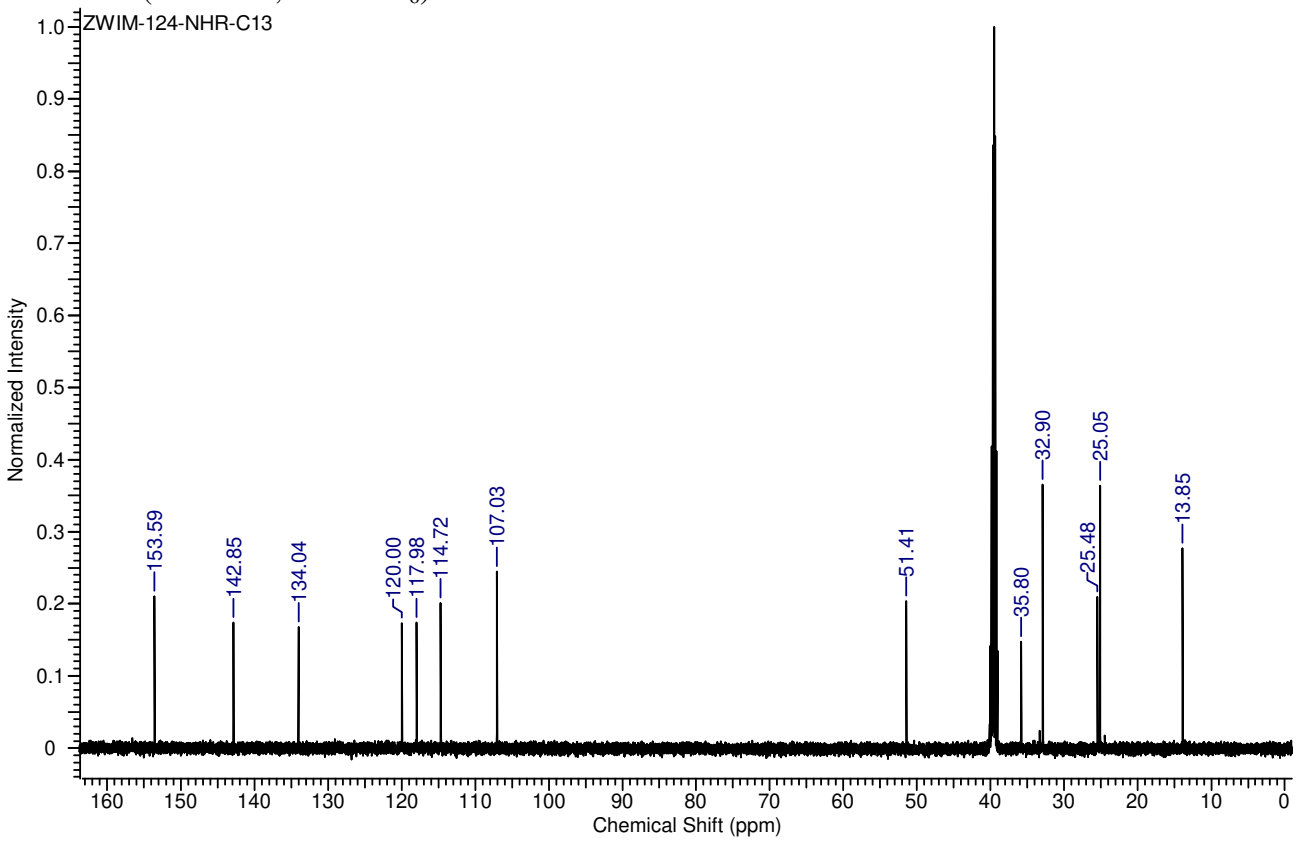


5k

^{1}H NMR (500 MHz, DMSO-d_6)

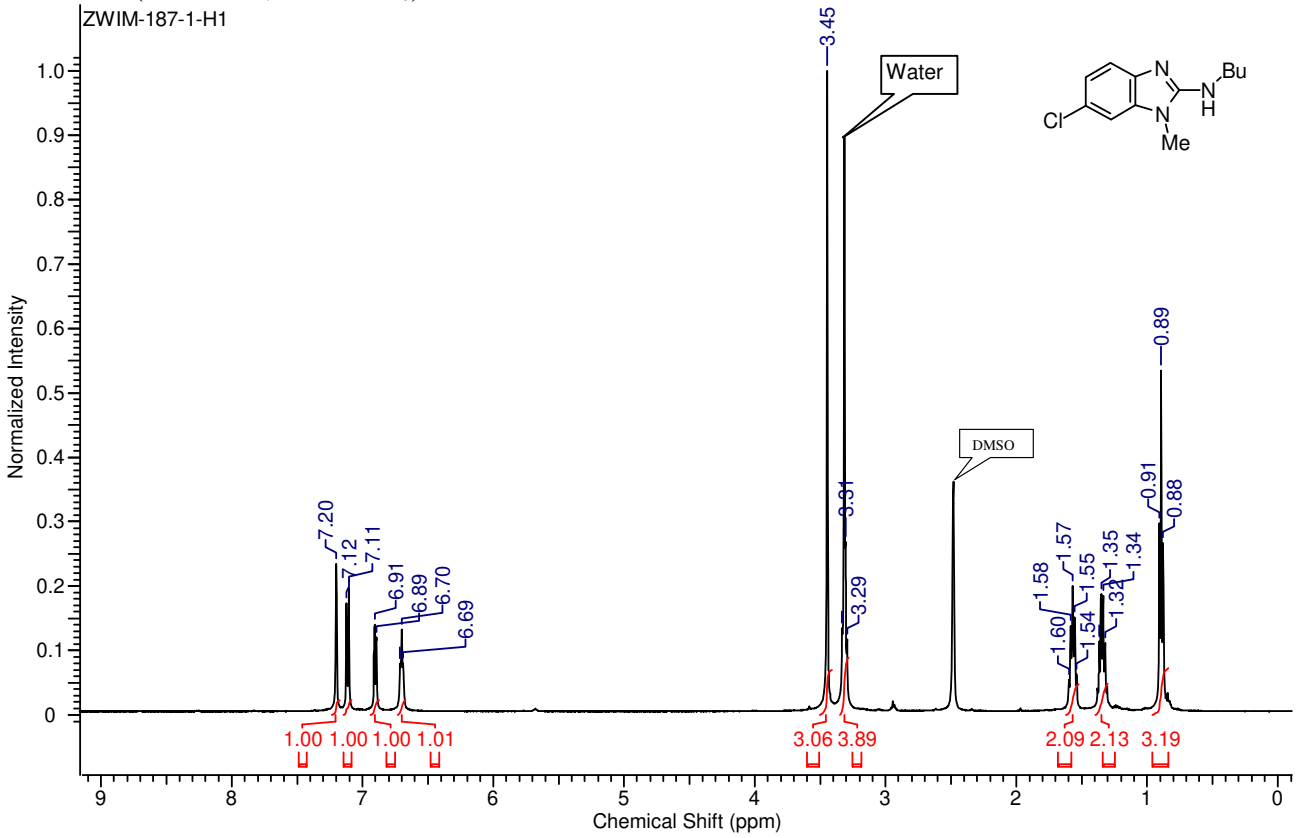


^{13}C NMR (125 MHz, DMSO-d_6)

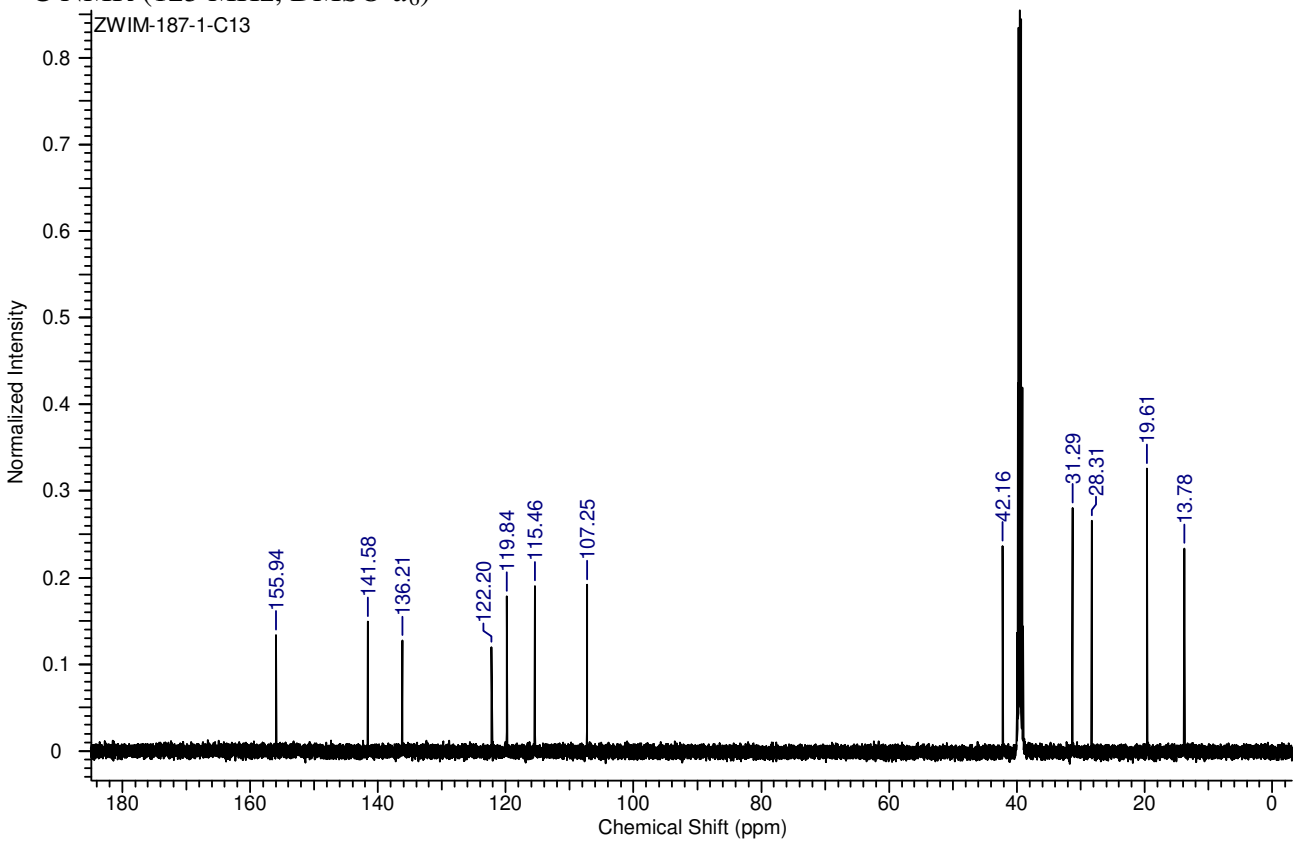


5l

^{1}H NMR (500 MHz, DMSO-d_6)

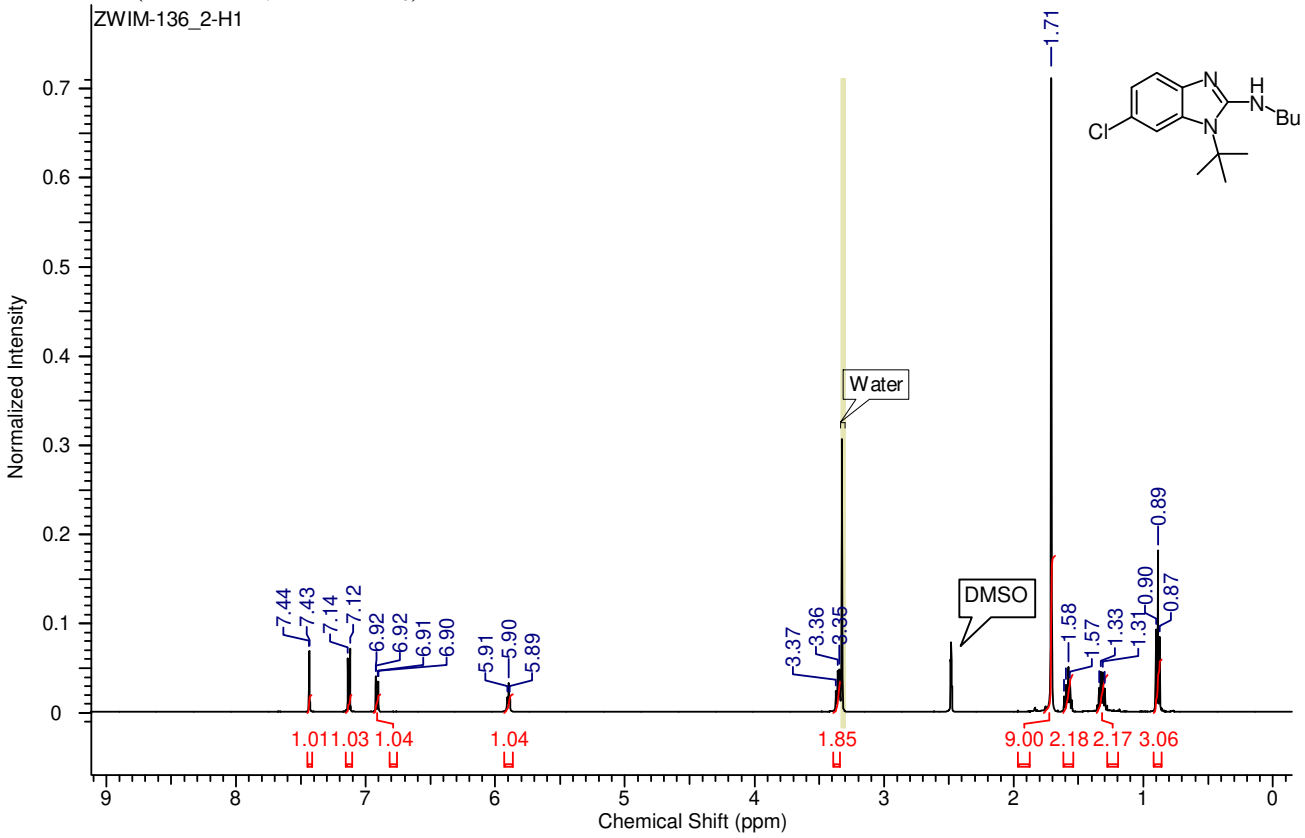


^{13}C NMR (125 MHz, DMSO-d_6)

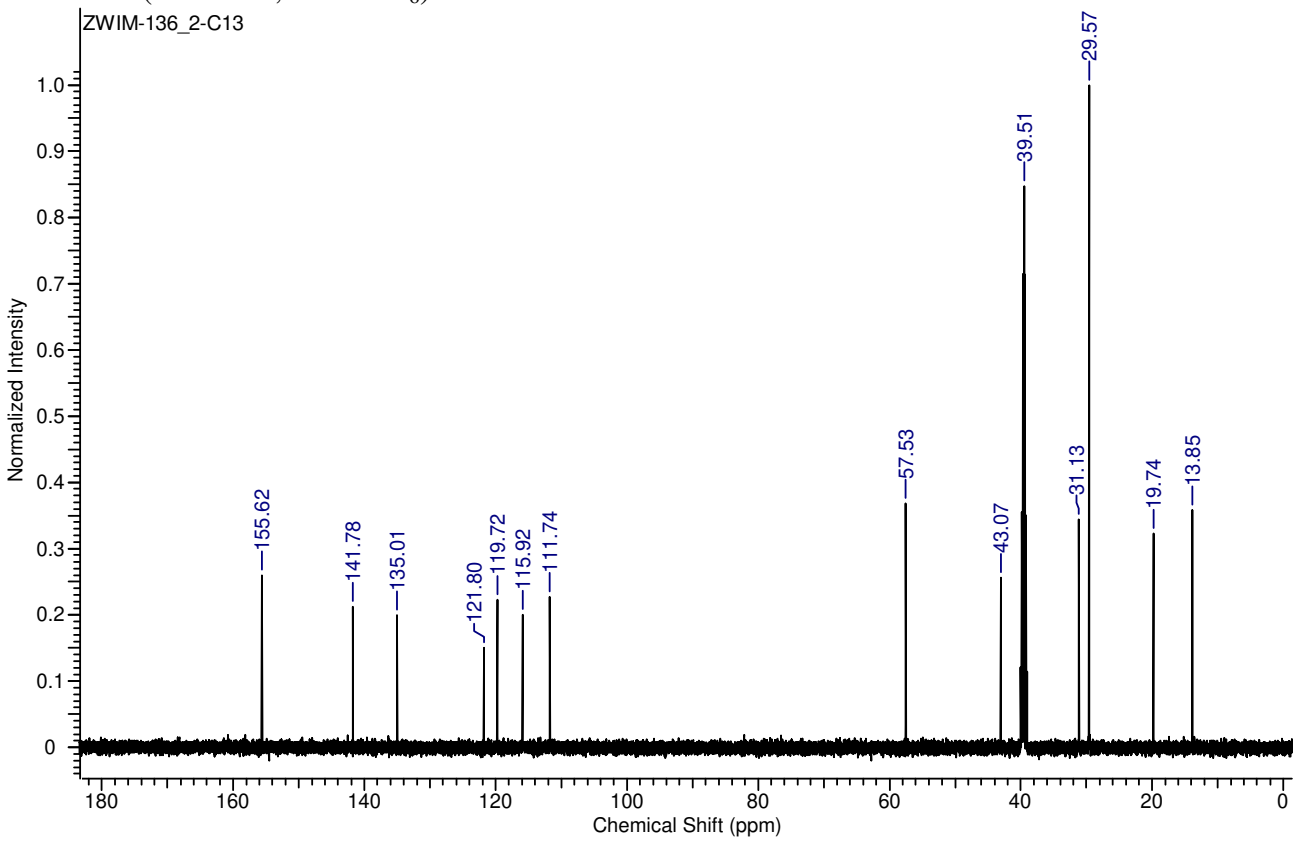


5m

^{1}H NMR (500 MHz, DMSO-d_6)

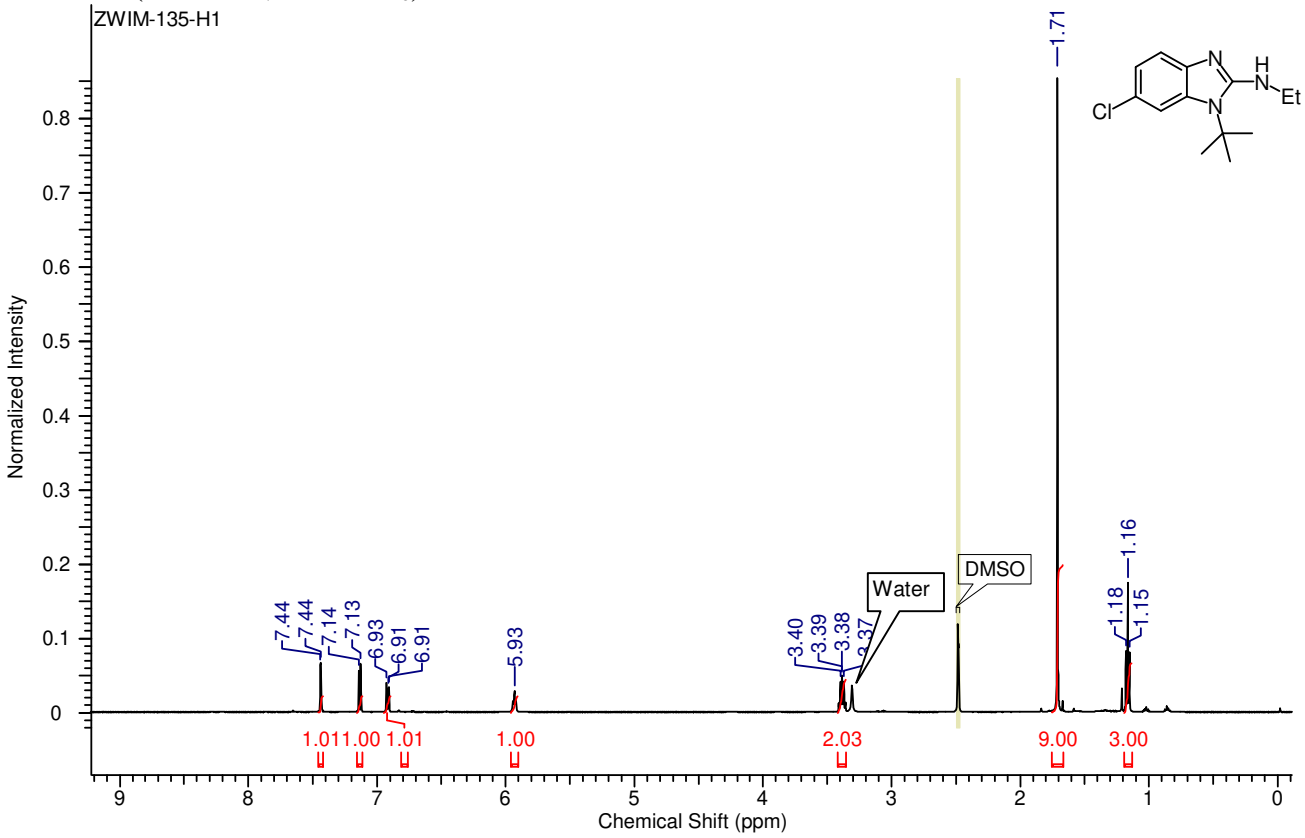


^{13}C NMR (125 MHz, DMSO-d_6)

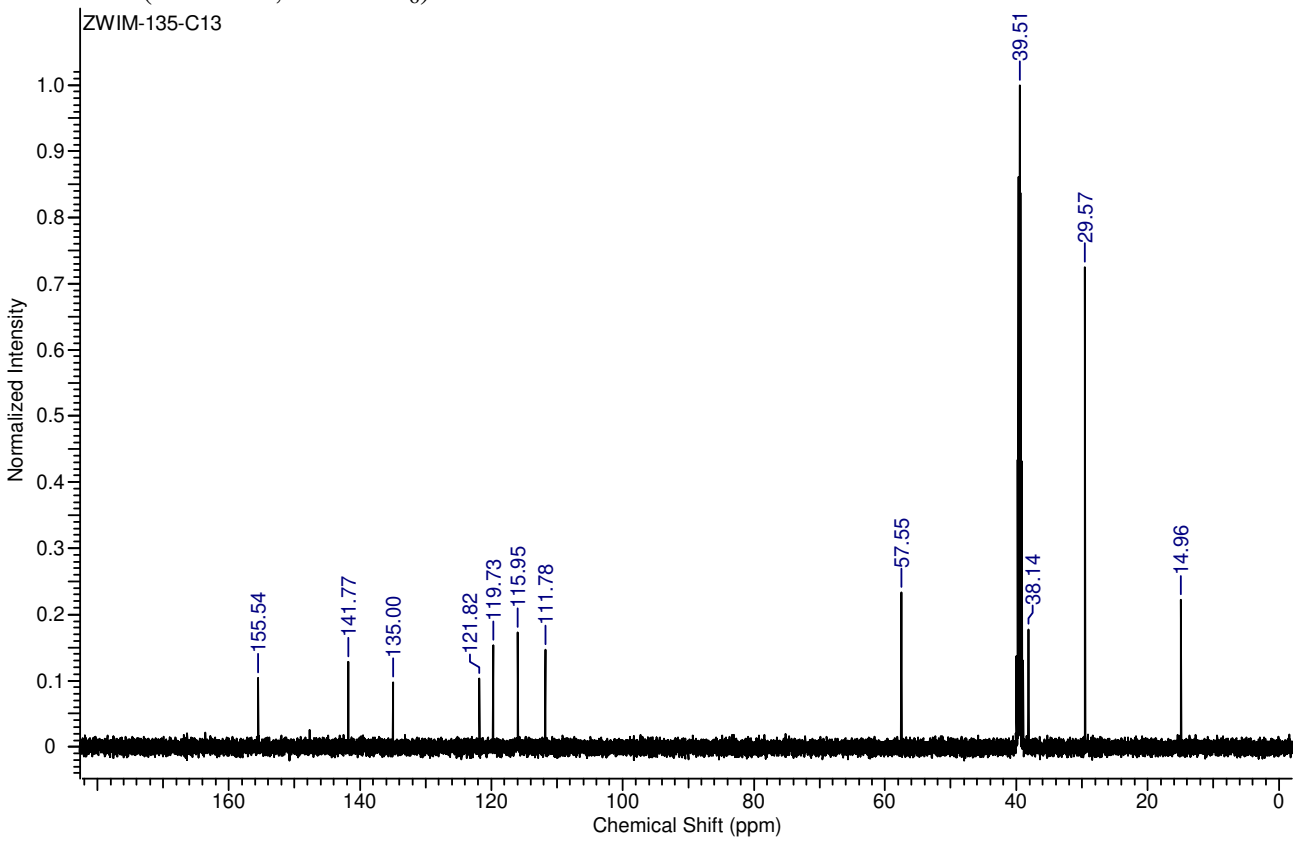


5n

^{1}H NMR (500 MHz, DMSO-d_6)



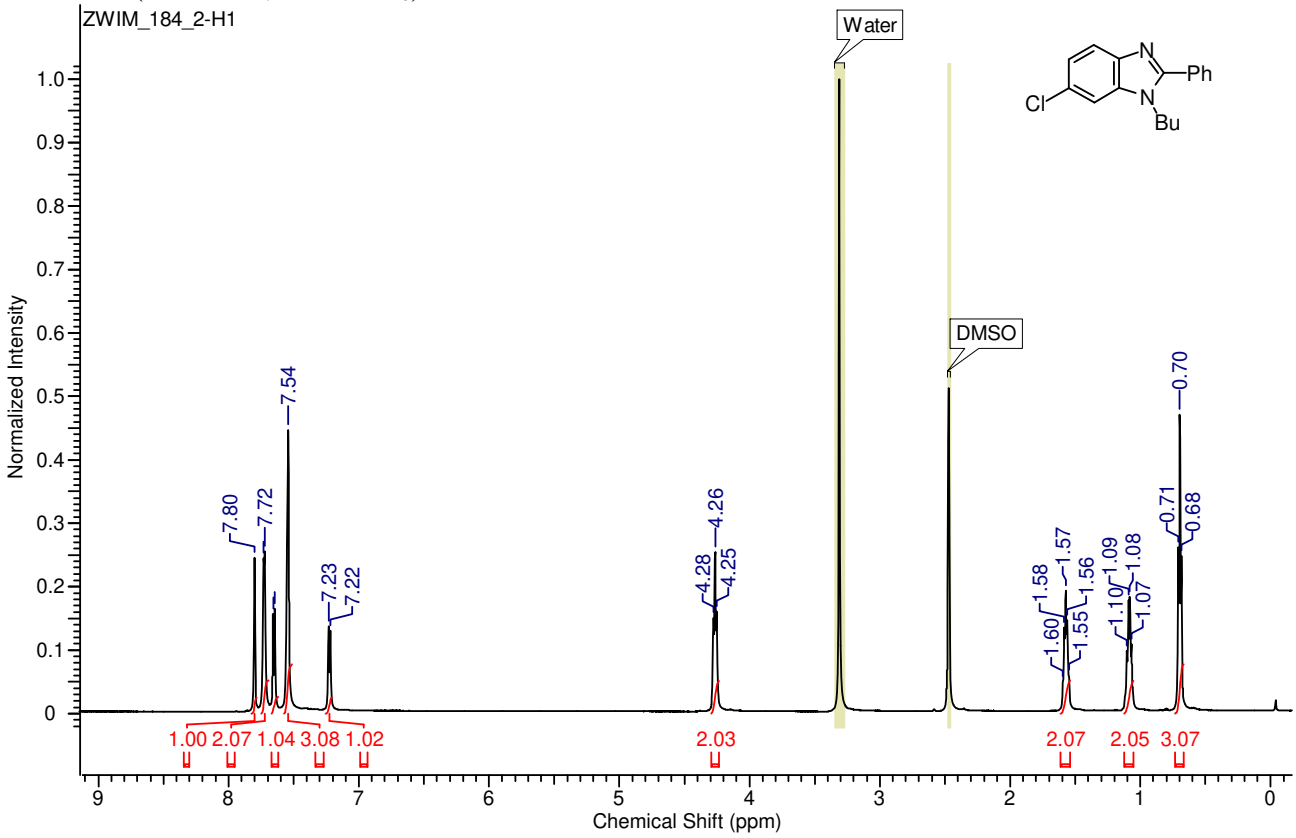
^{13}C NMR (125 MHz, DMSO-d_6)



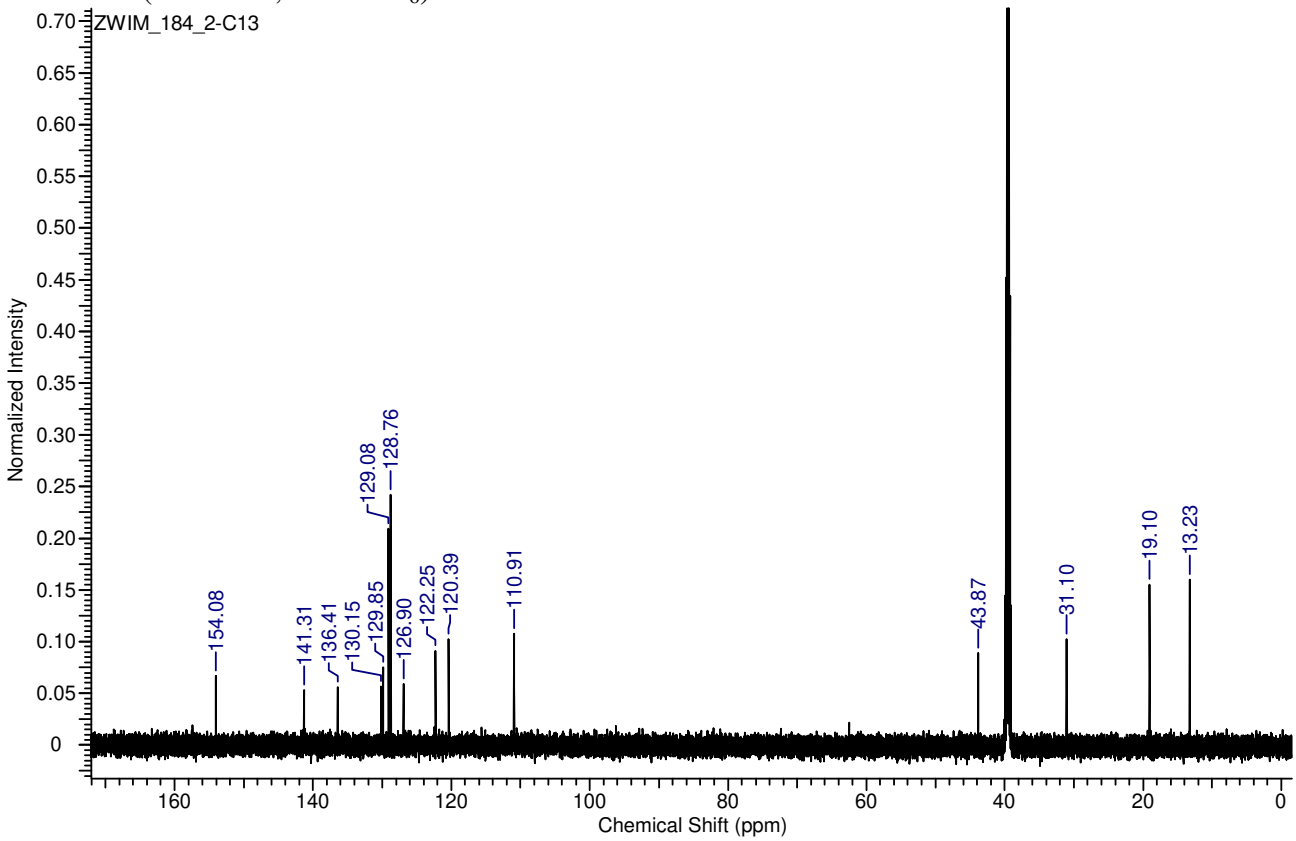
***N*-Alkyl-2-alkilo/arylo-benzimidazoles 6**

6a

^{1}H NMR (500 MHz, DMSO-d_6)

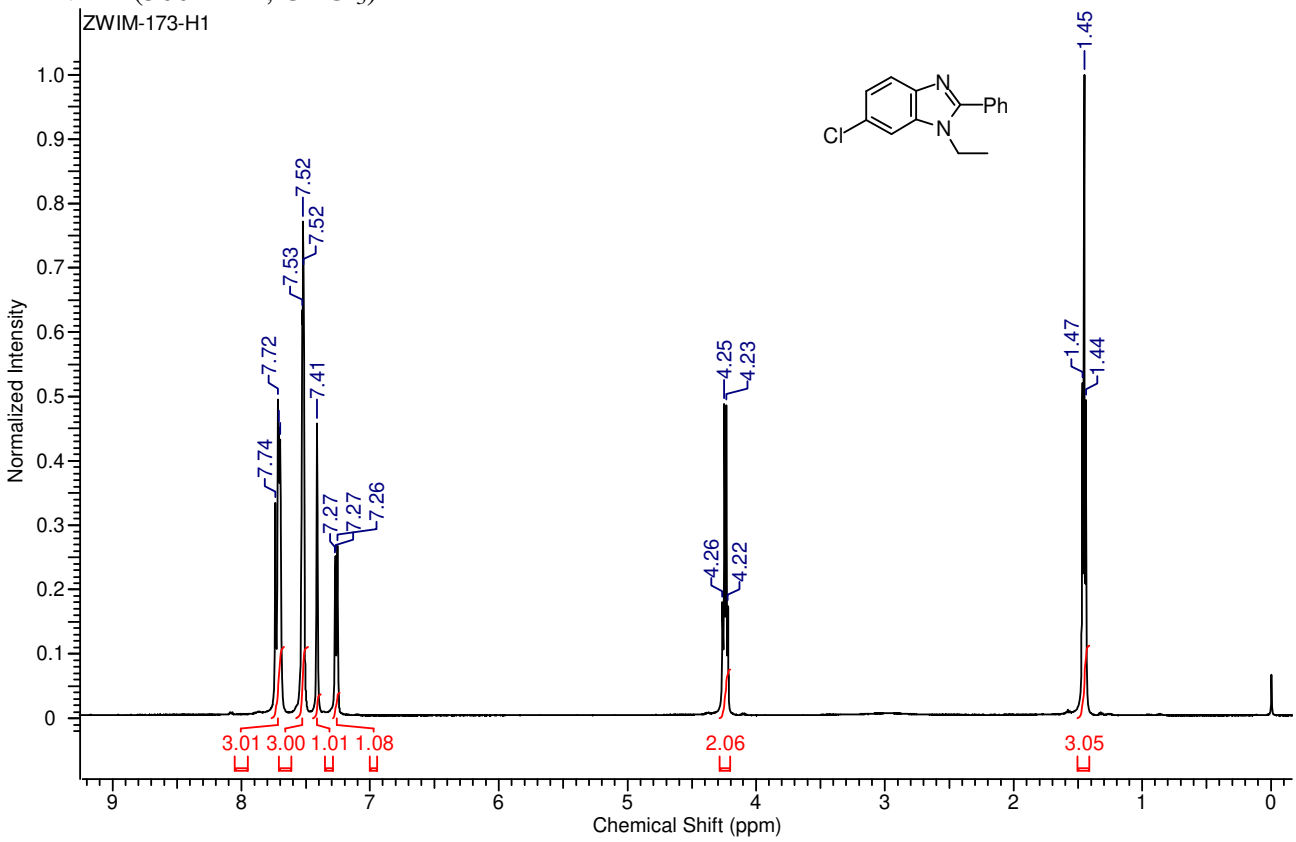


^{13}C NMR (125 MHz, DMSO-d_6)

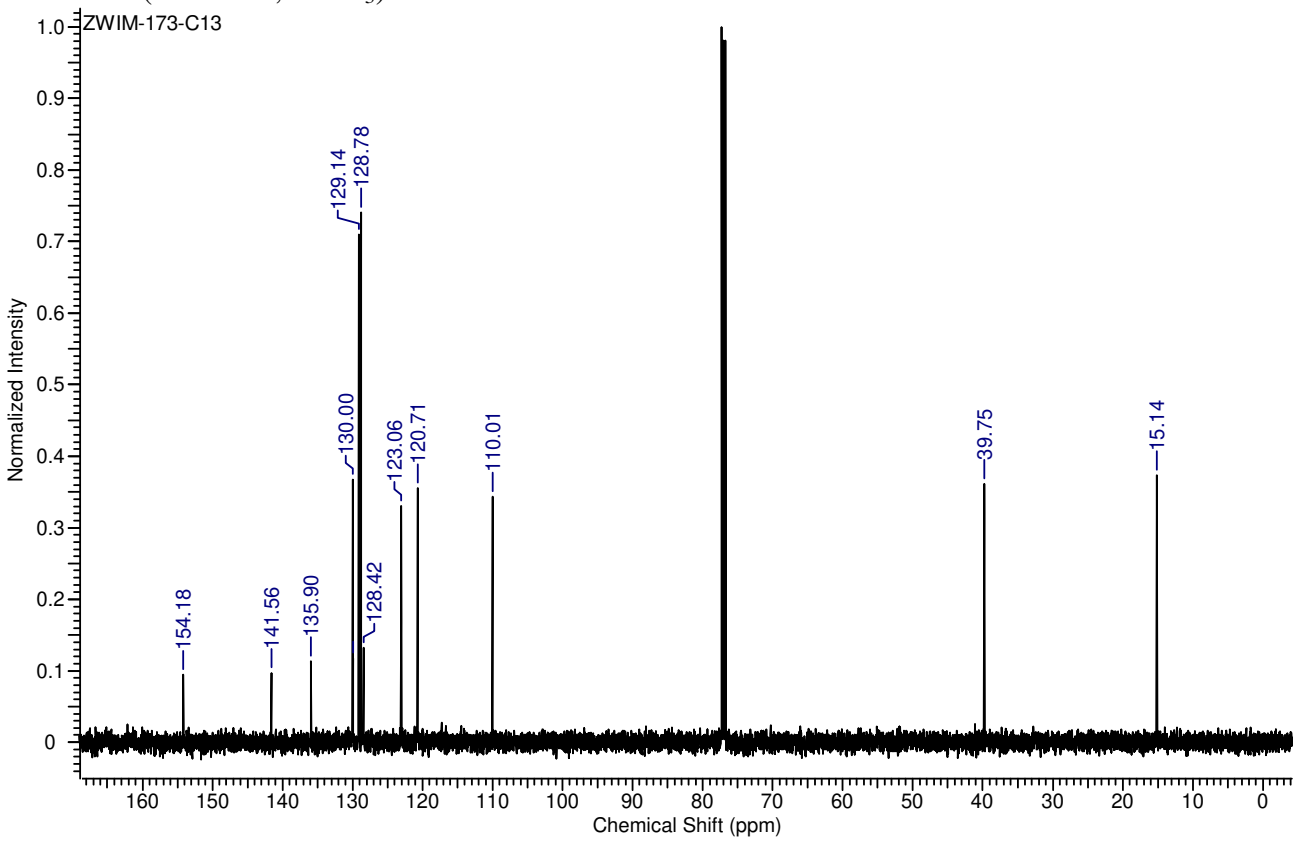


6b

^{1}H NMR (500 MHz, $CDCl_3$)

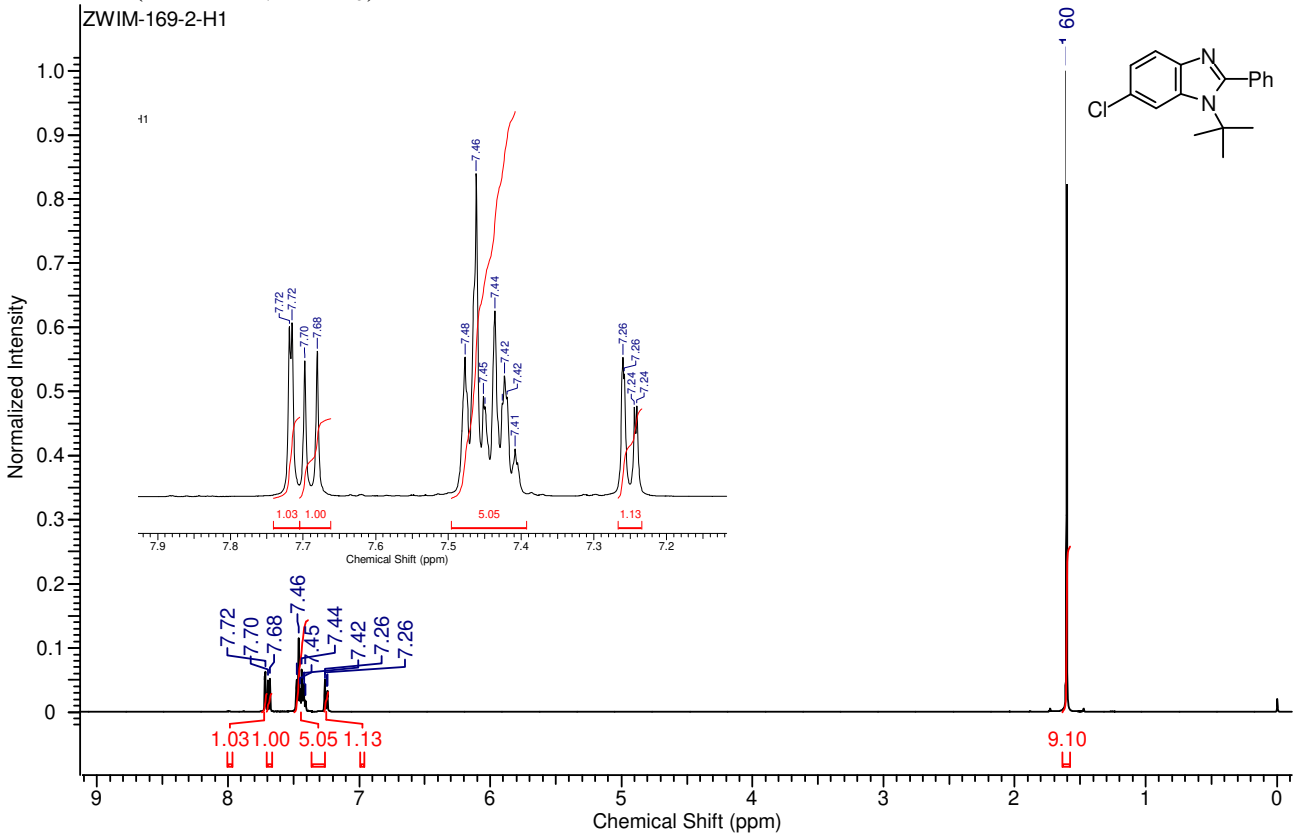


^{13}C NMR (125 MHz, $CDCl_3$)

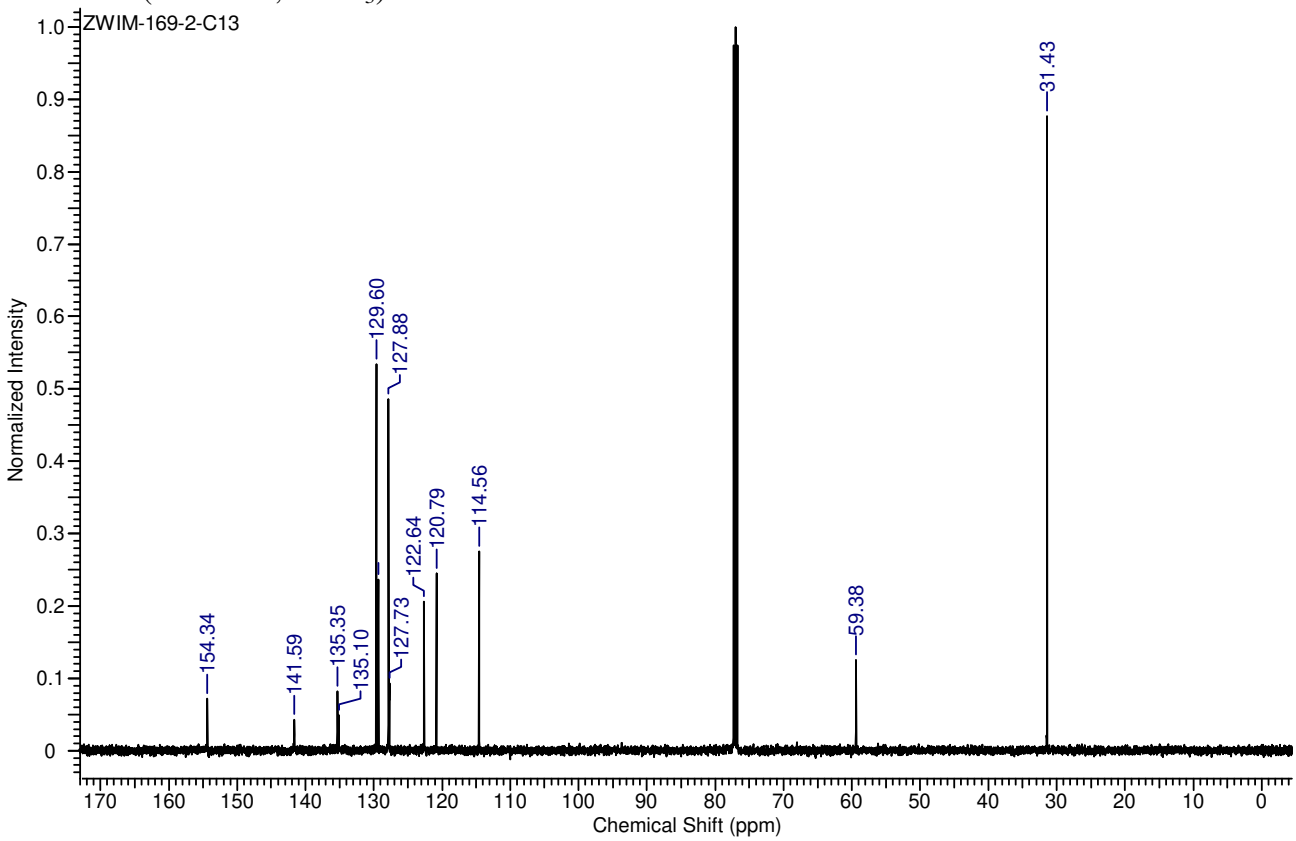


6c

^{1}H NMR (500 MHz, $CDCl_3$)

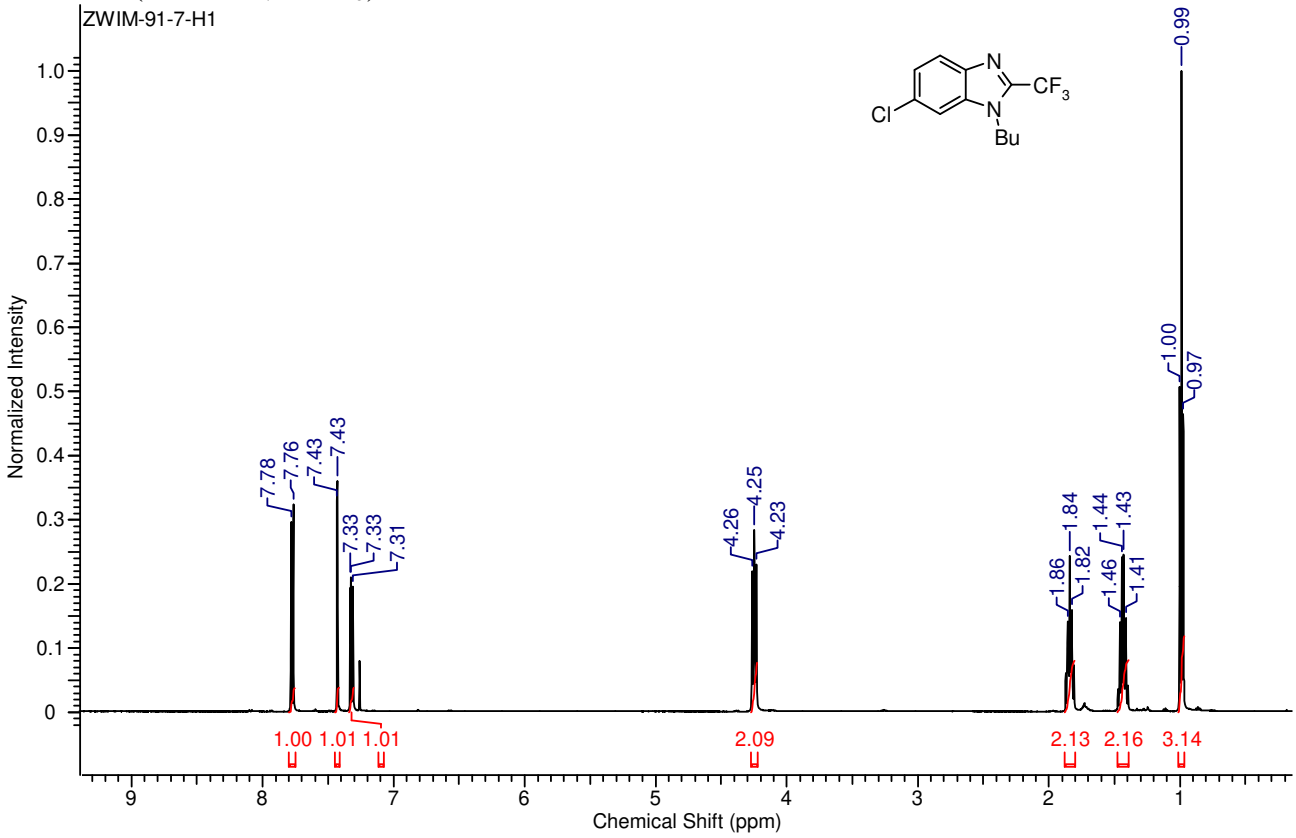


^{13}C NMR (125 MHz, $CDCl_3$)

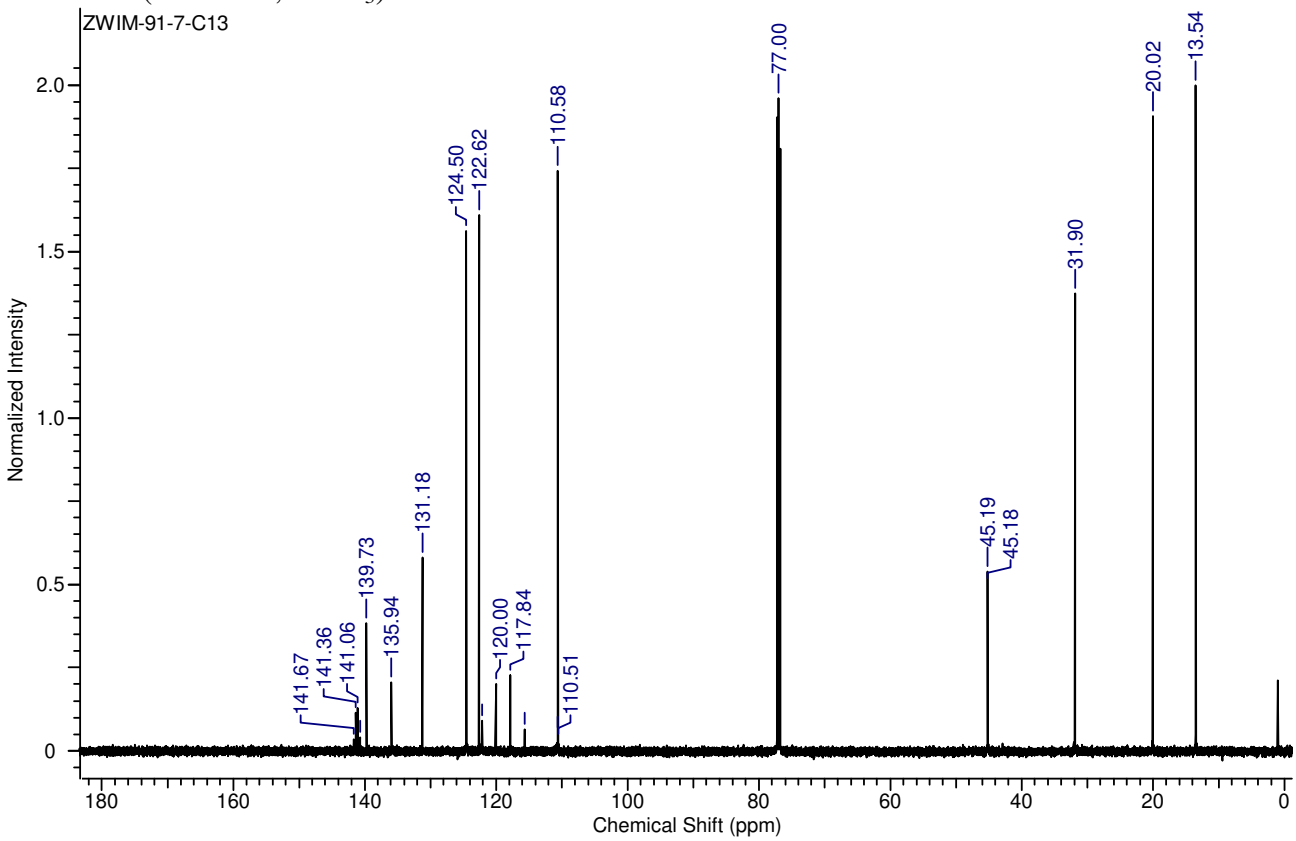


6d

^{1}H NMR (500 MHz, $CDCl_3$)

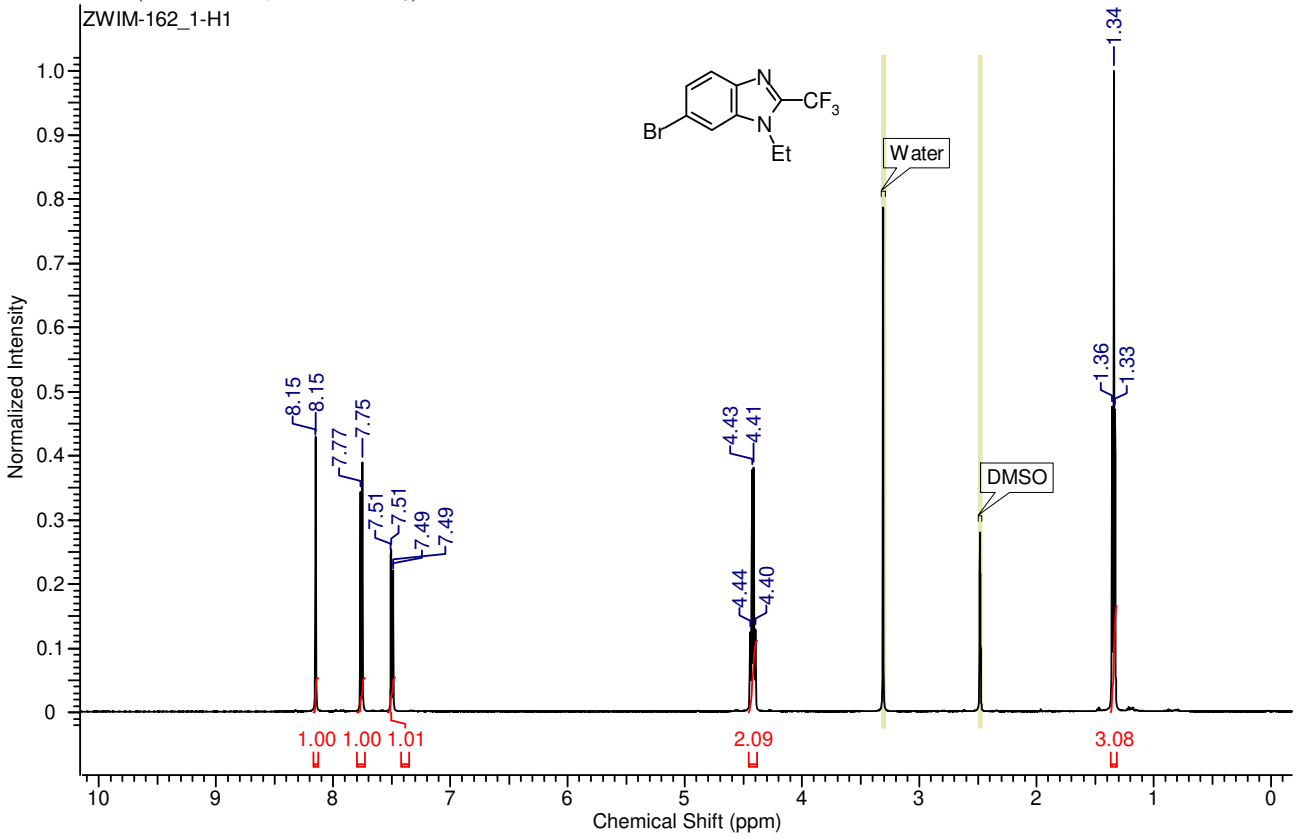


^{13}C NMR (125 MHz, $CDCl_3$)

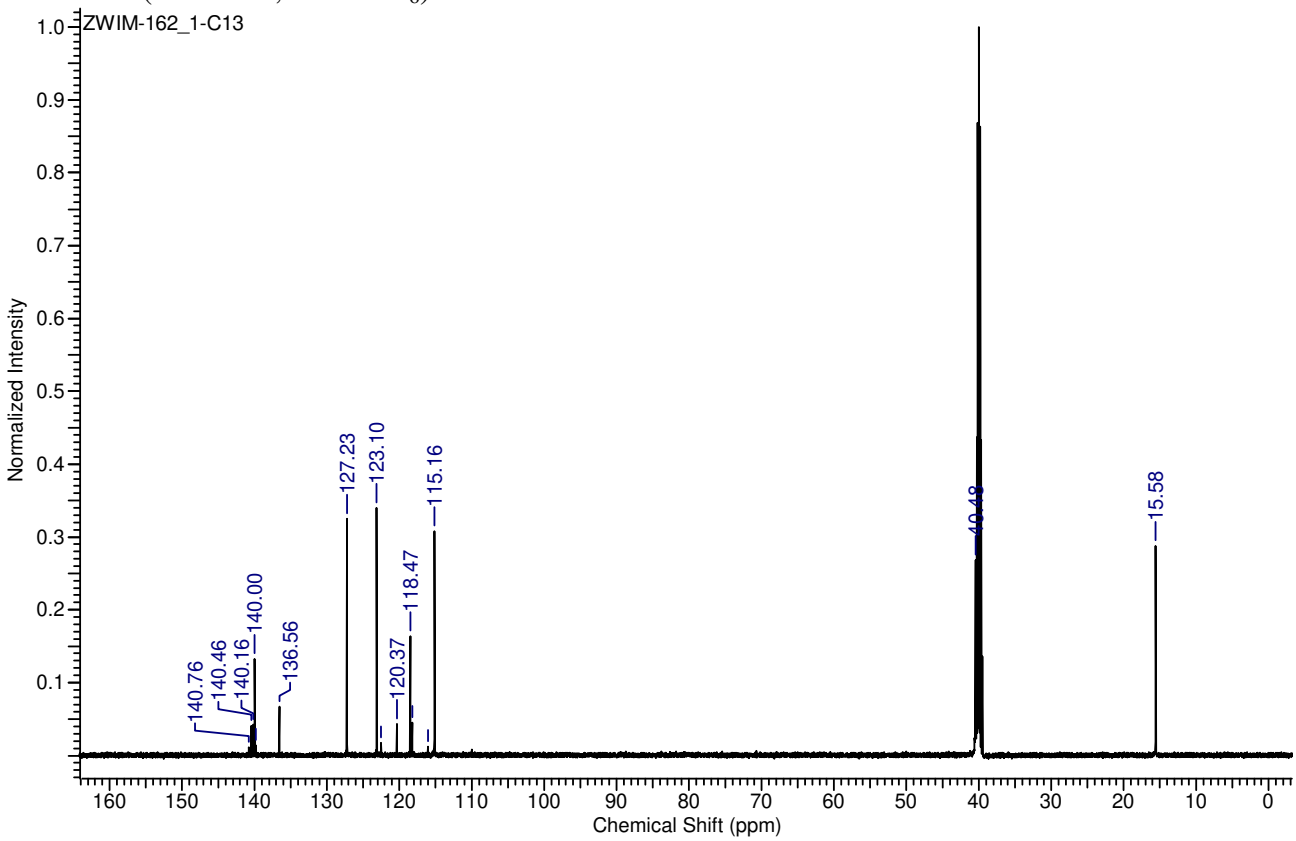


6e

^{1}H NMR (500 MHz, DMSO-d_6)

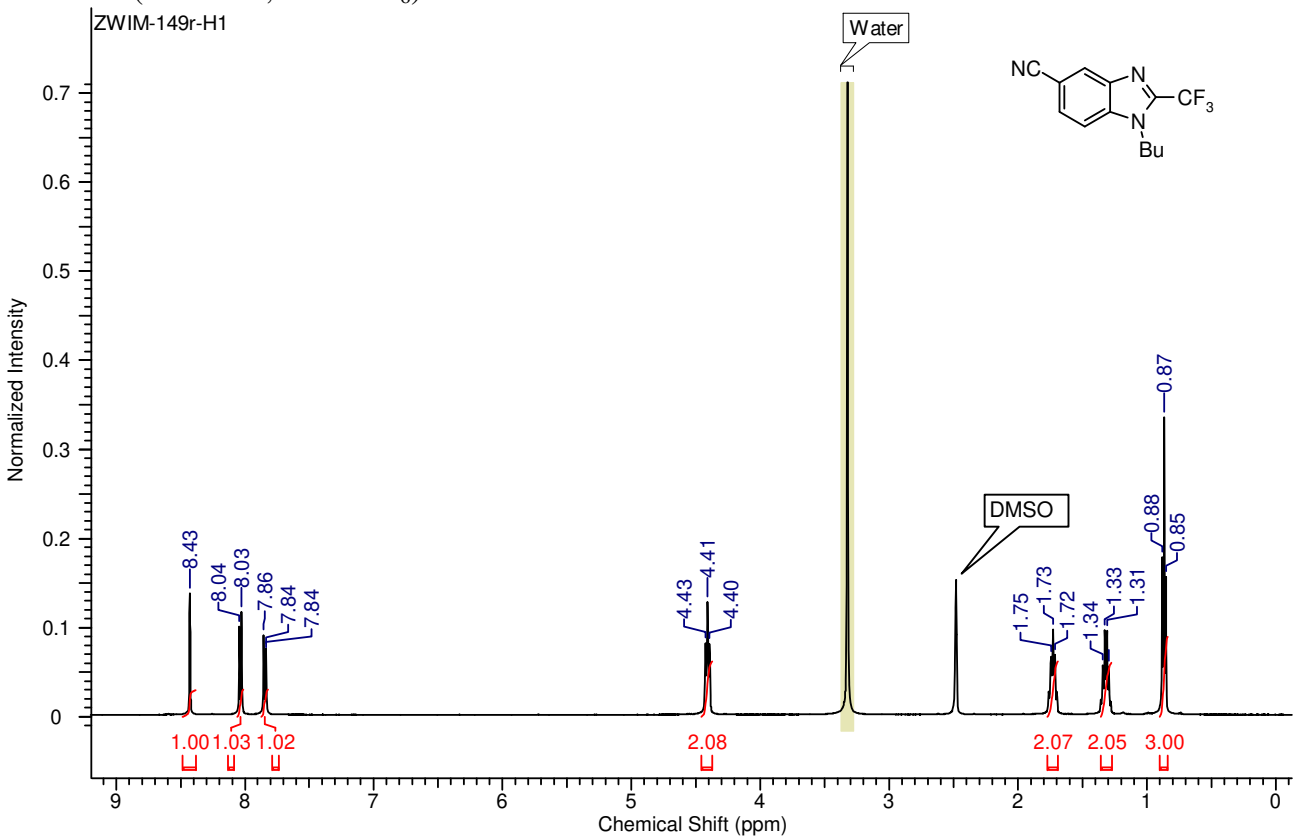


^{13}C NMR (125 MHz, DMSO-d_6)

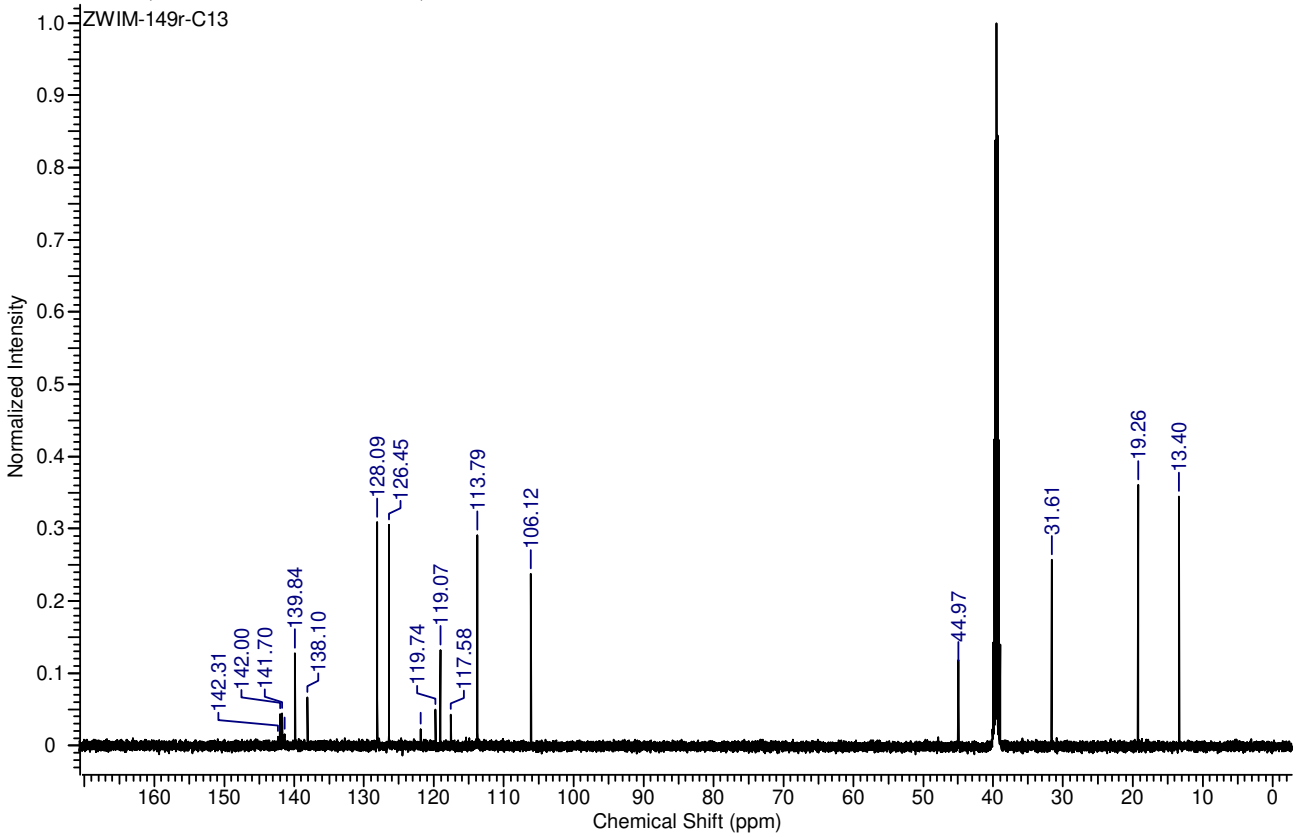


6f

^{1}H NMR (500 MHz, DMSO-d_6)

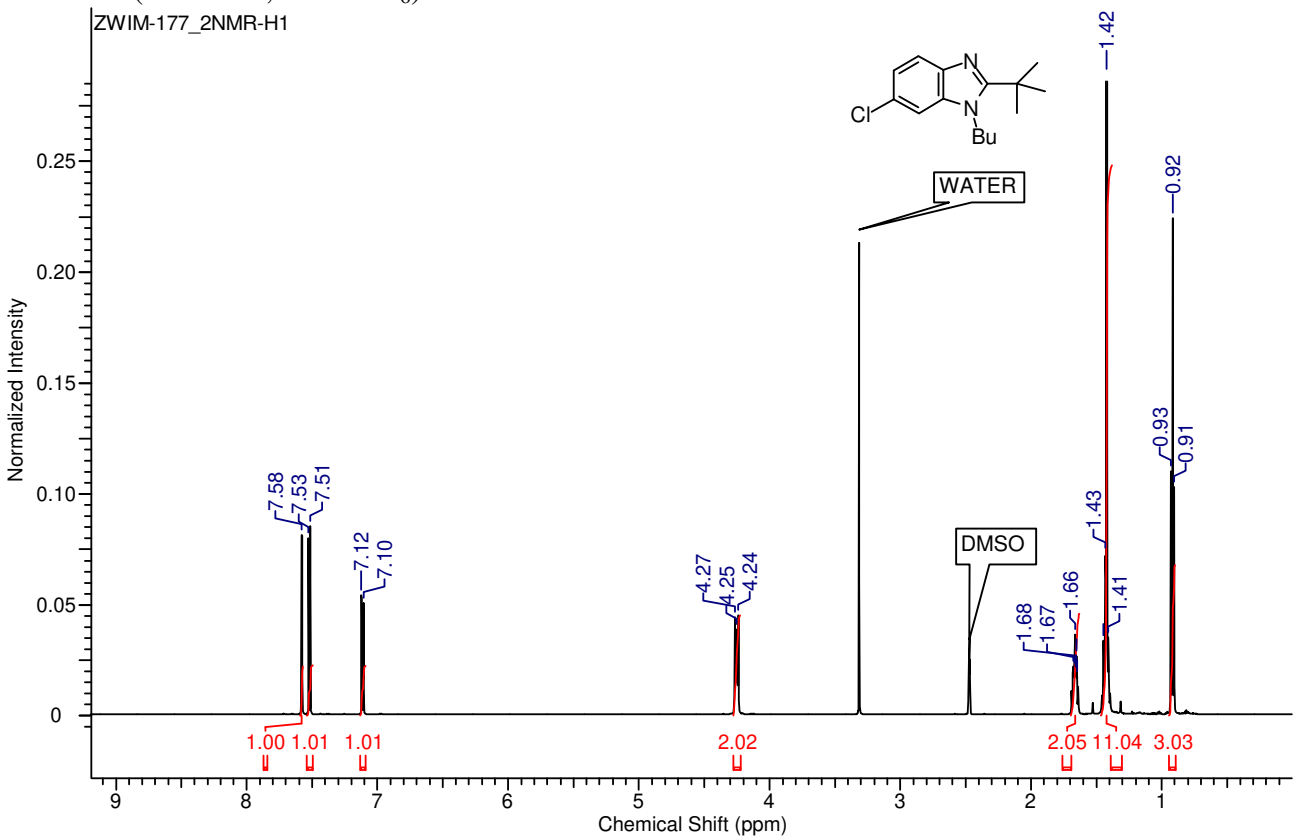


^{13}C NMR (125 MHz, DMSO-d_6)

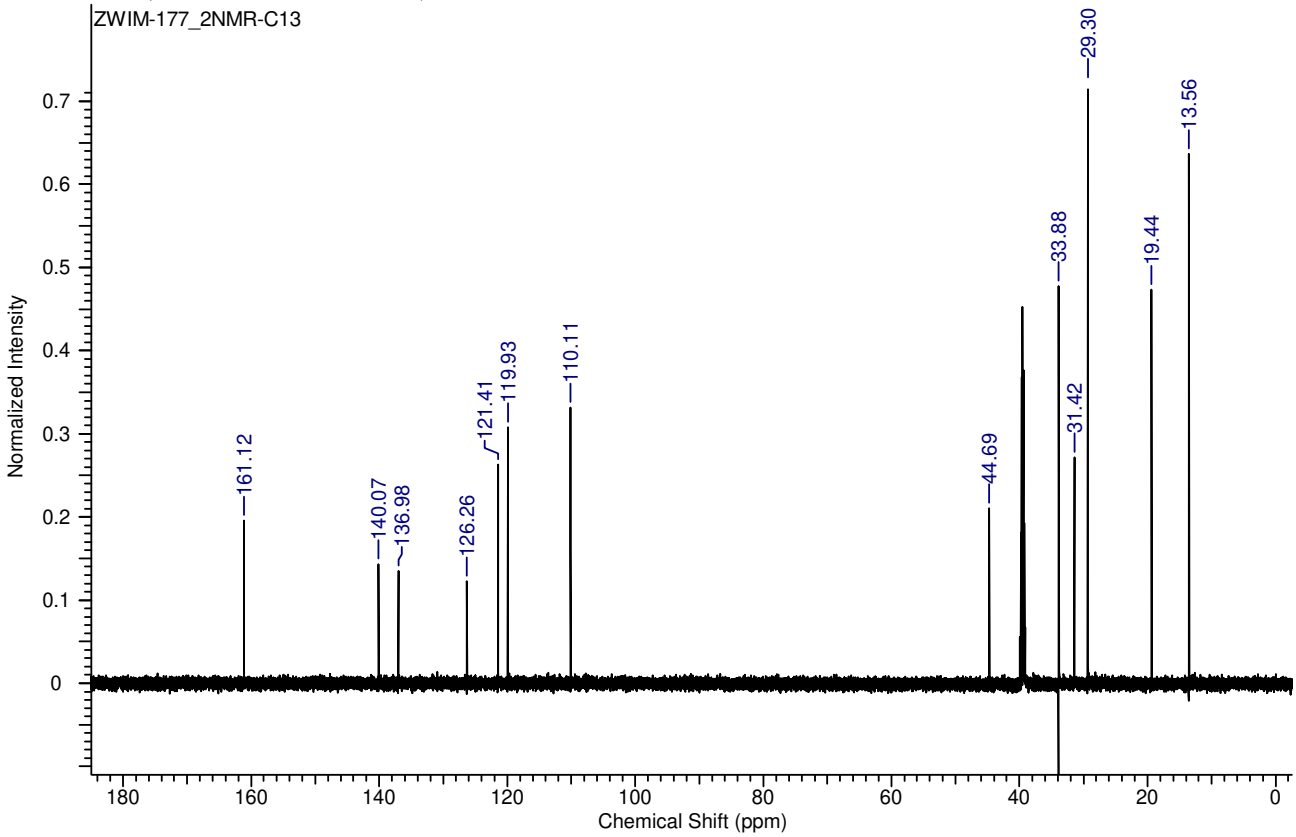


6g

^{1}H NMR (600 MHz, DMSO-d_6)

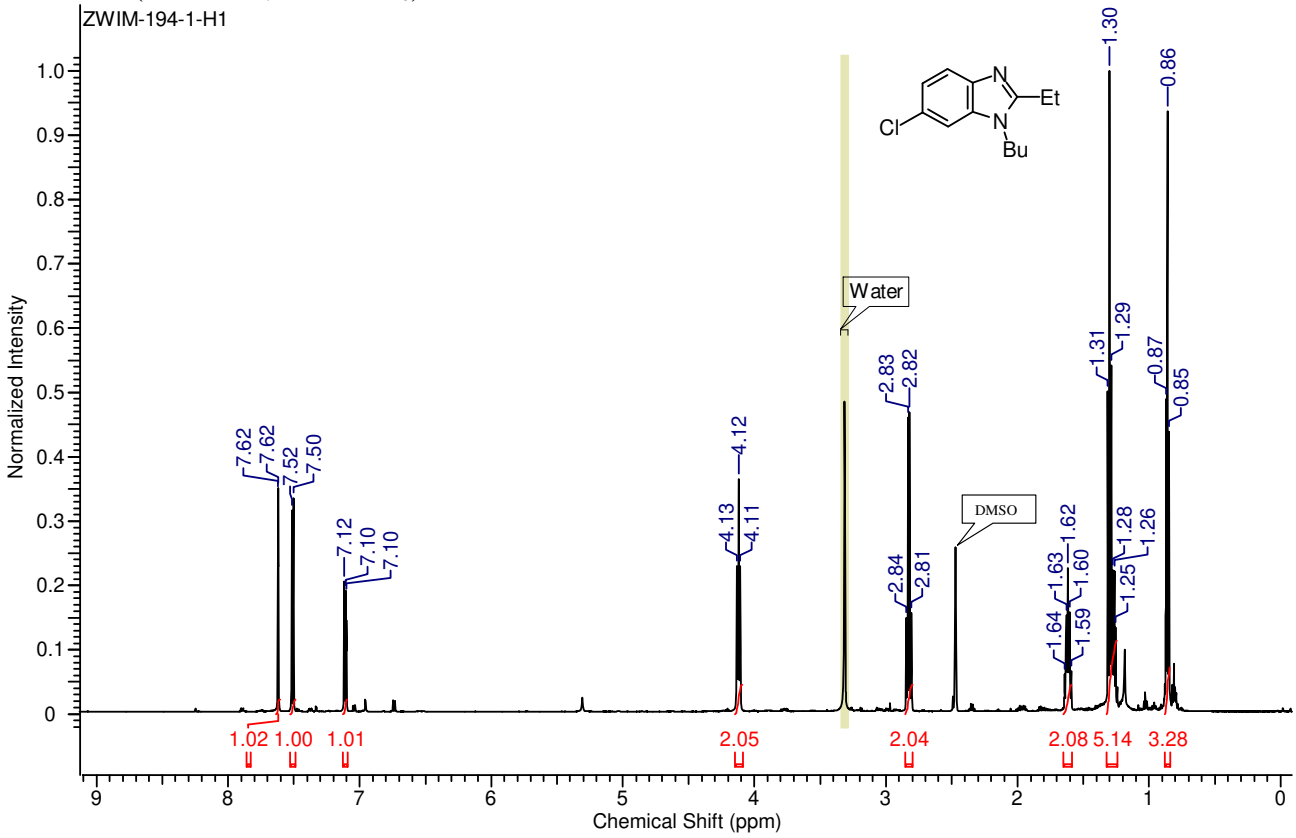


^{13}C NMR (150 MHz, DMSO-d_6)

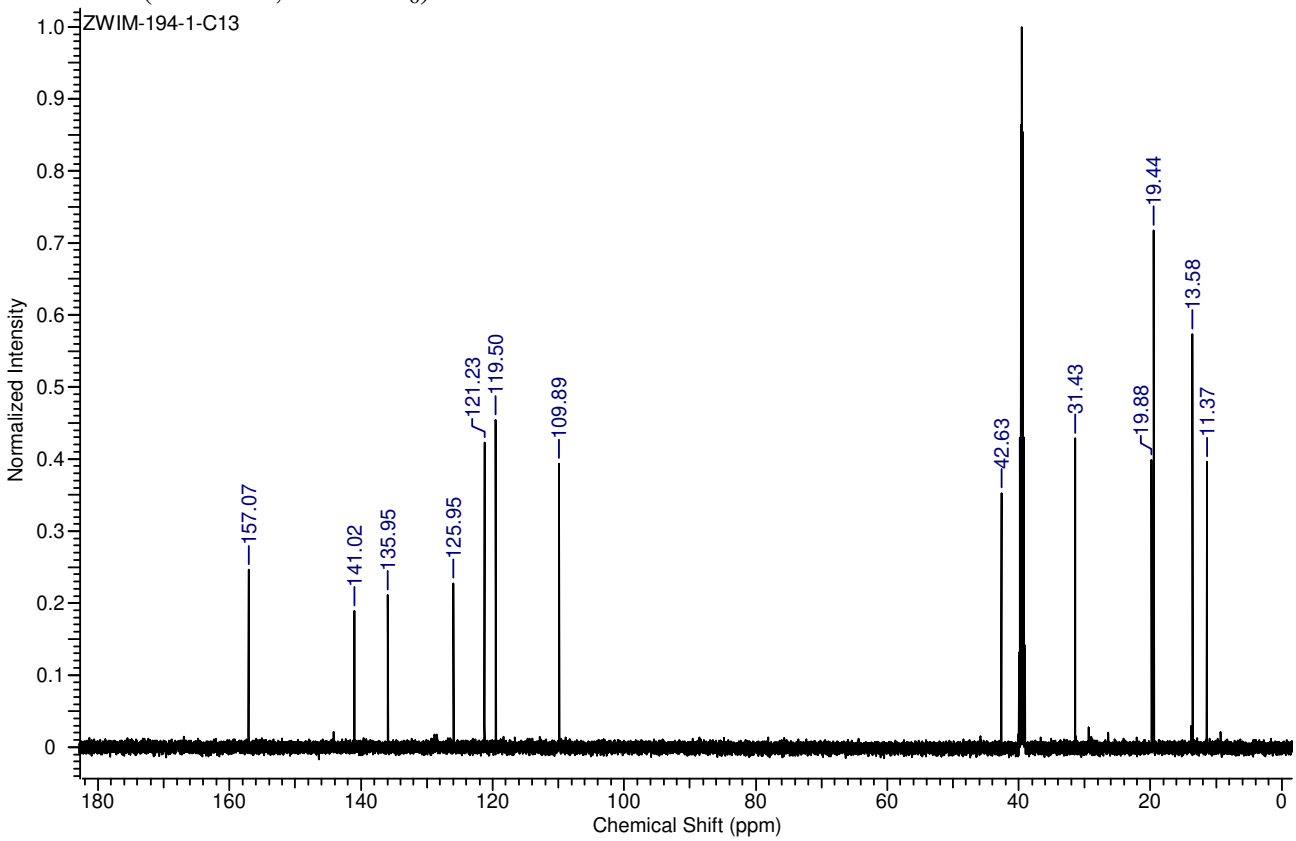


6h

^{1}H NMR (600 MHz, DMSO-d_6)

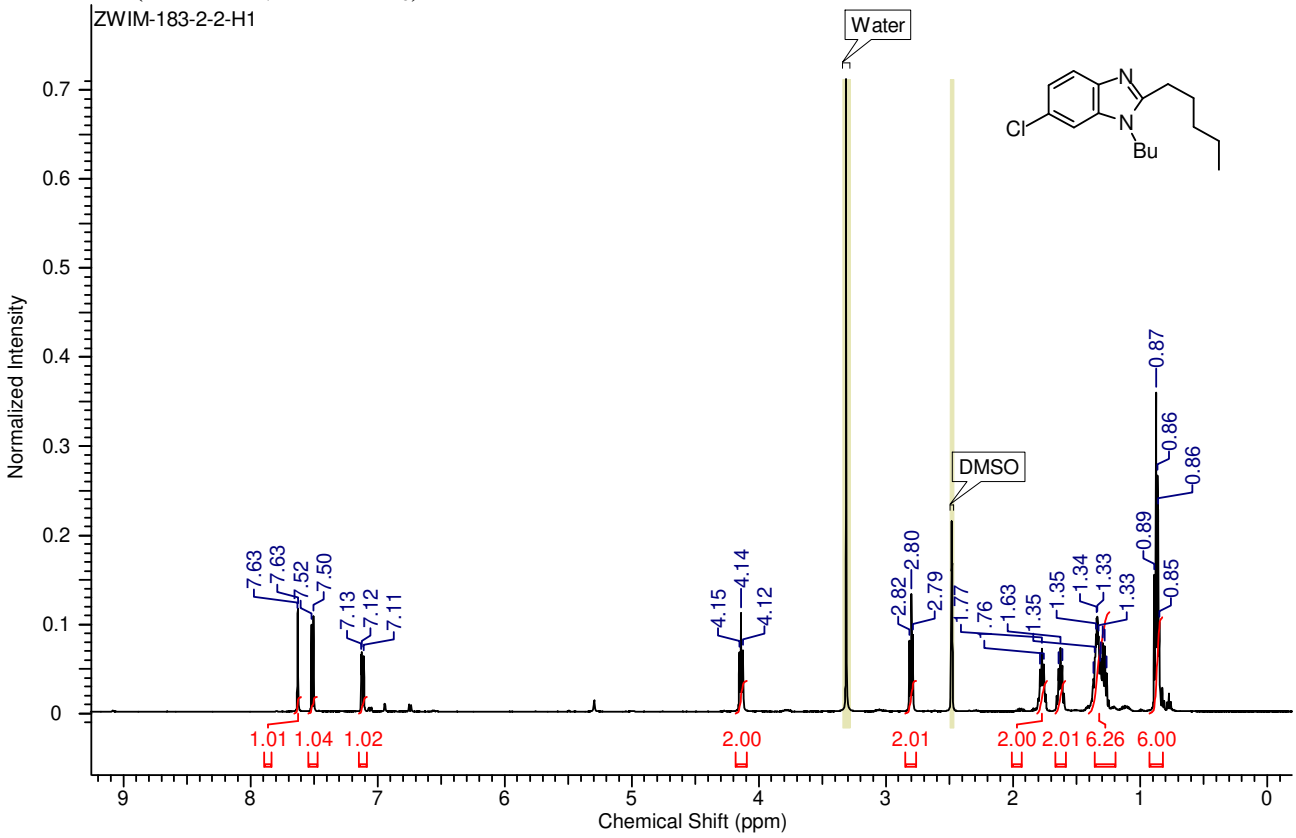


^{13}C NMR (150 MHz, DMSO-d_6)

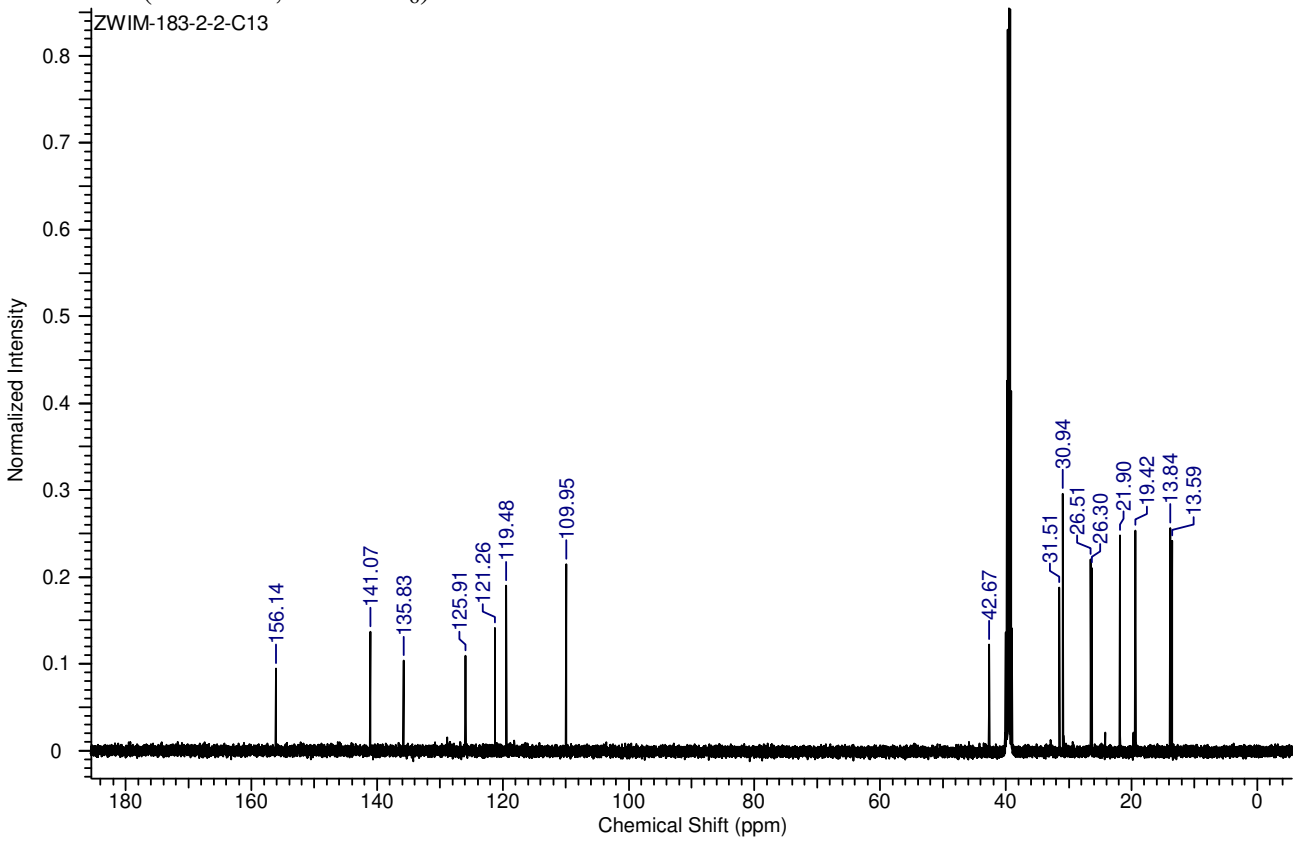


6i

^{1}H NMR (500 MHz, DMSO-d_6)

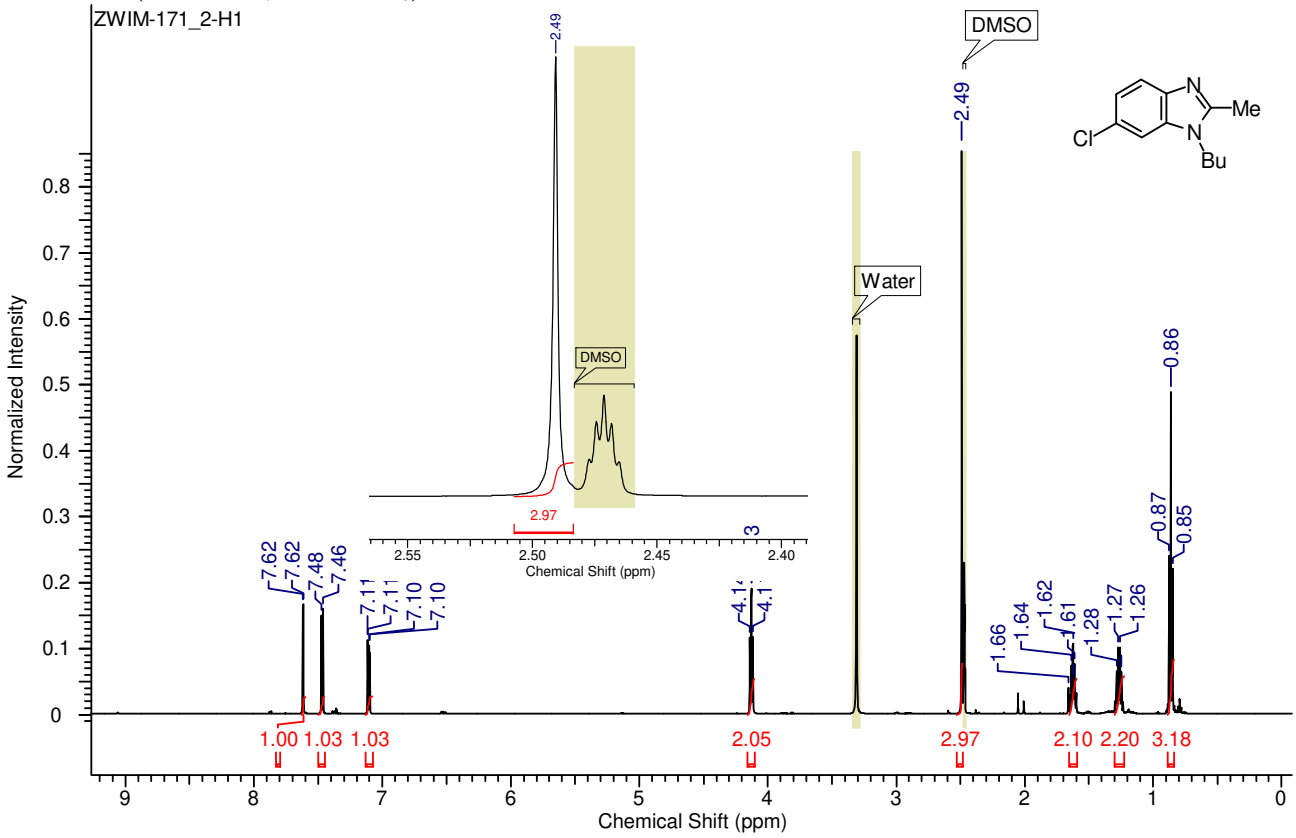


^{13}C NMR (125 MHz, DMSO-d_6)

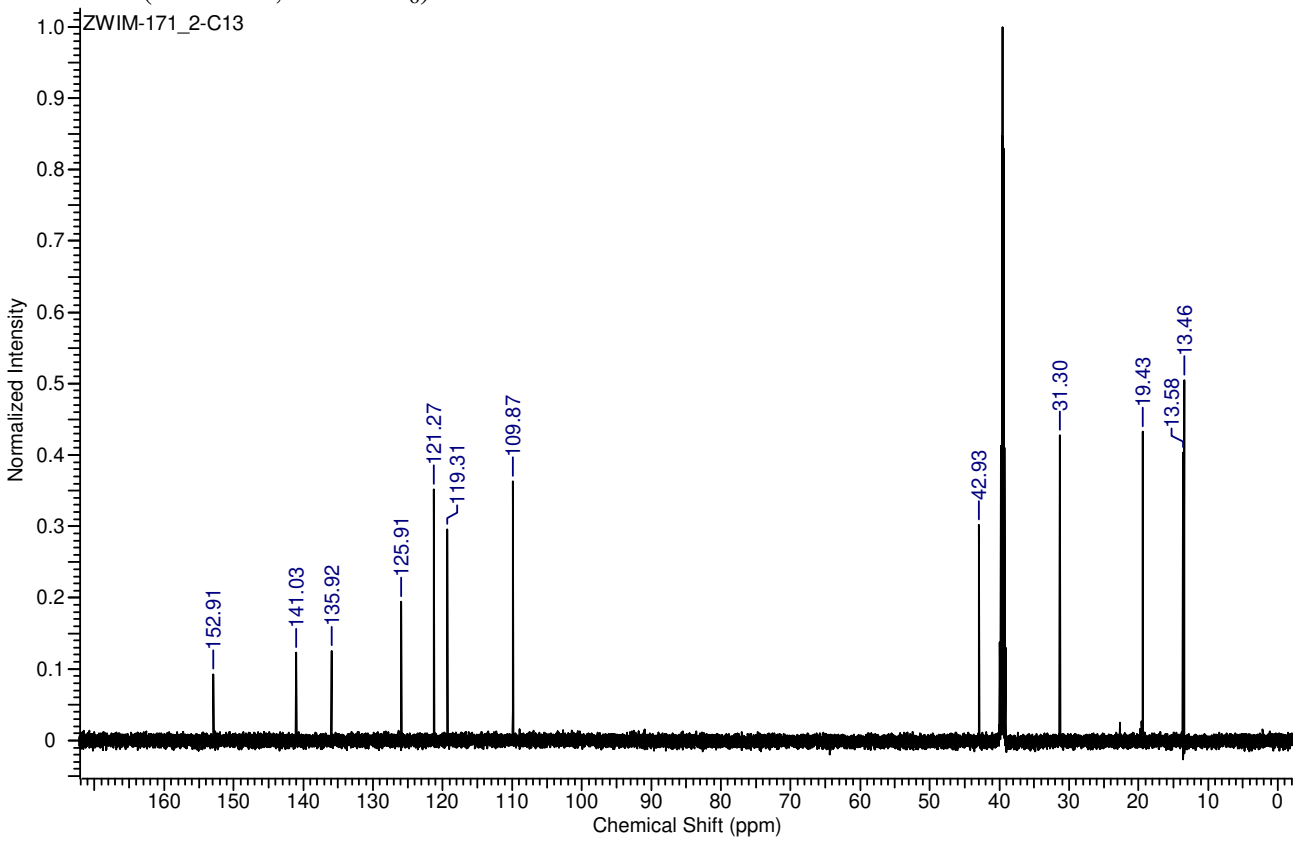


6j

^{1}H NMR (600 MHz, DMSO-d_6)



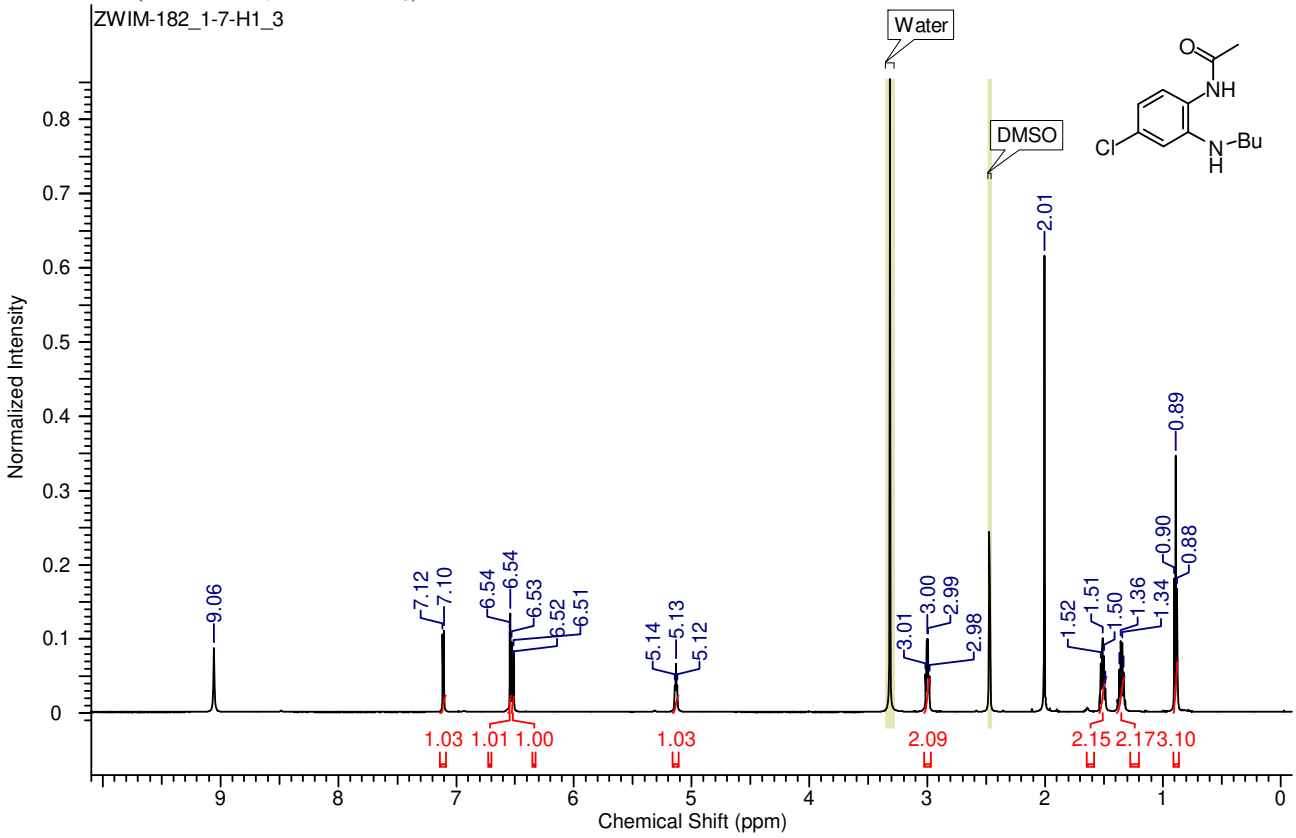
^{13}C NMR (150 MHz, DMSO-d_6)



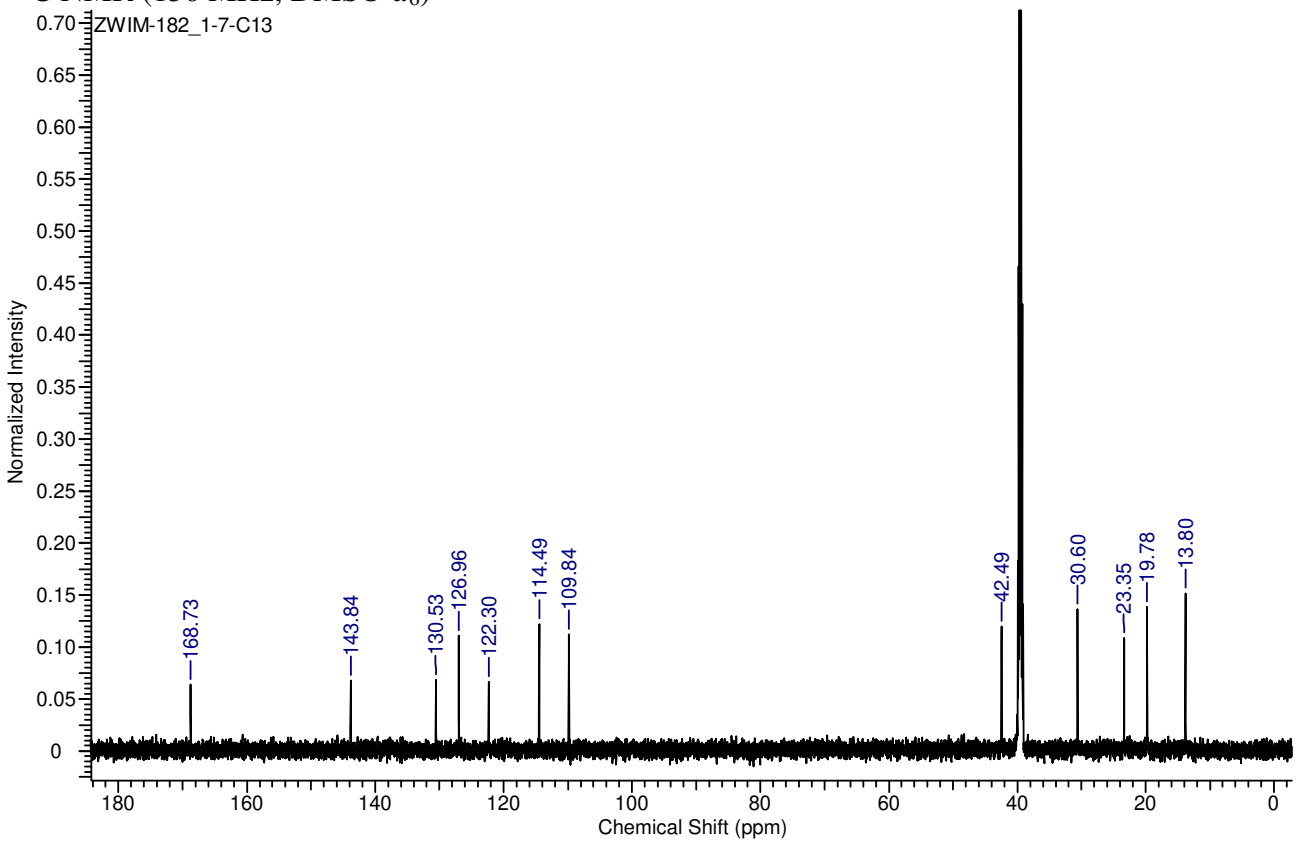
***N*-Alkyl-*N'*-acyl-*o*-phenylenediamines 7**

7a

^{1}H NMR (600 MHz, DMSO-d_6)

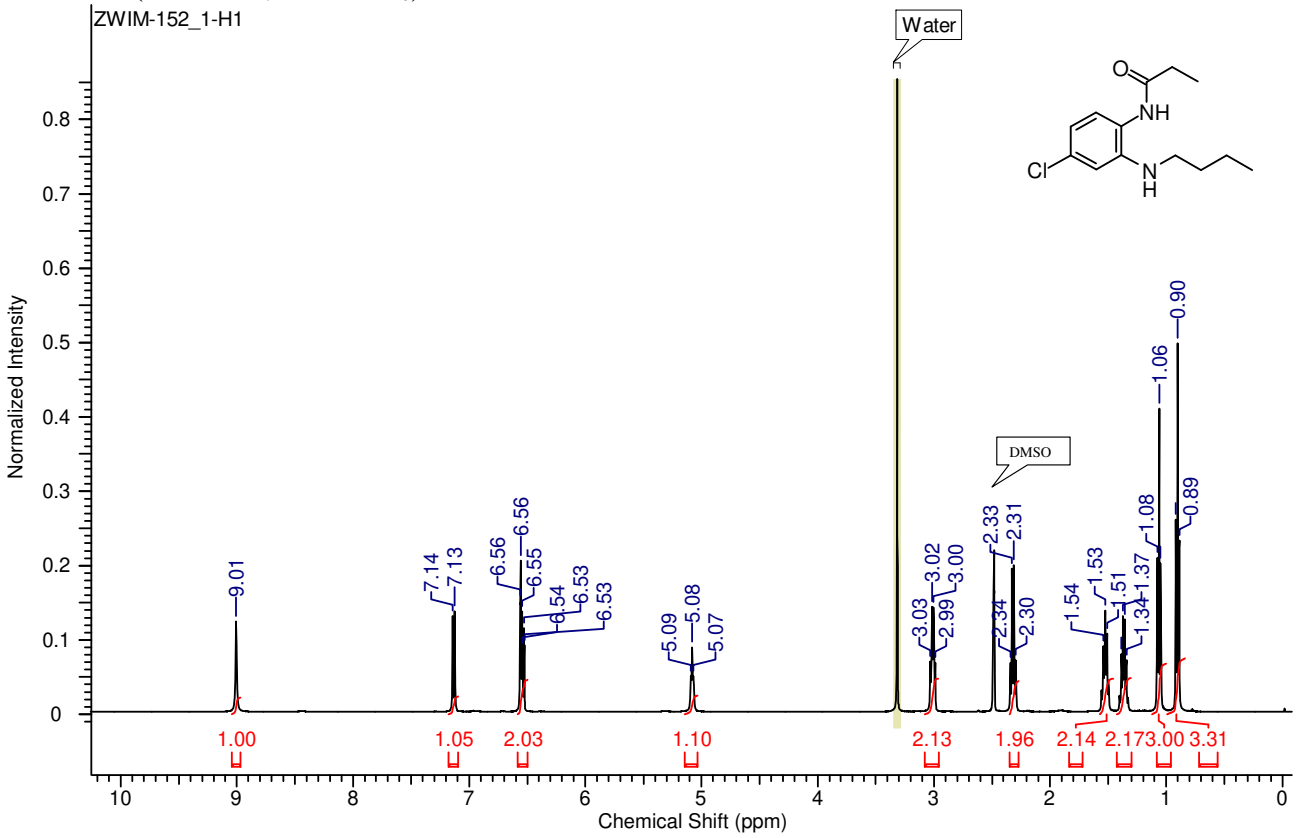


^{13}C NMR (150 MHz, DMSO-d_6)

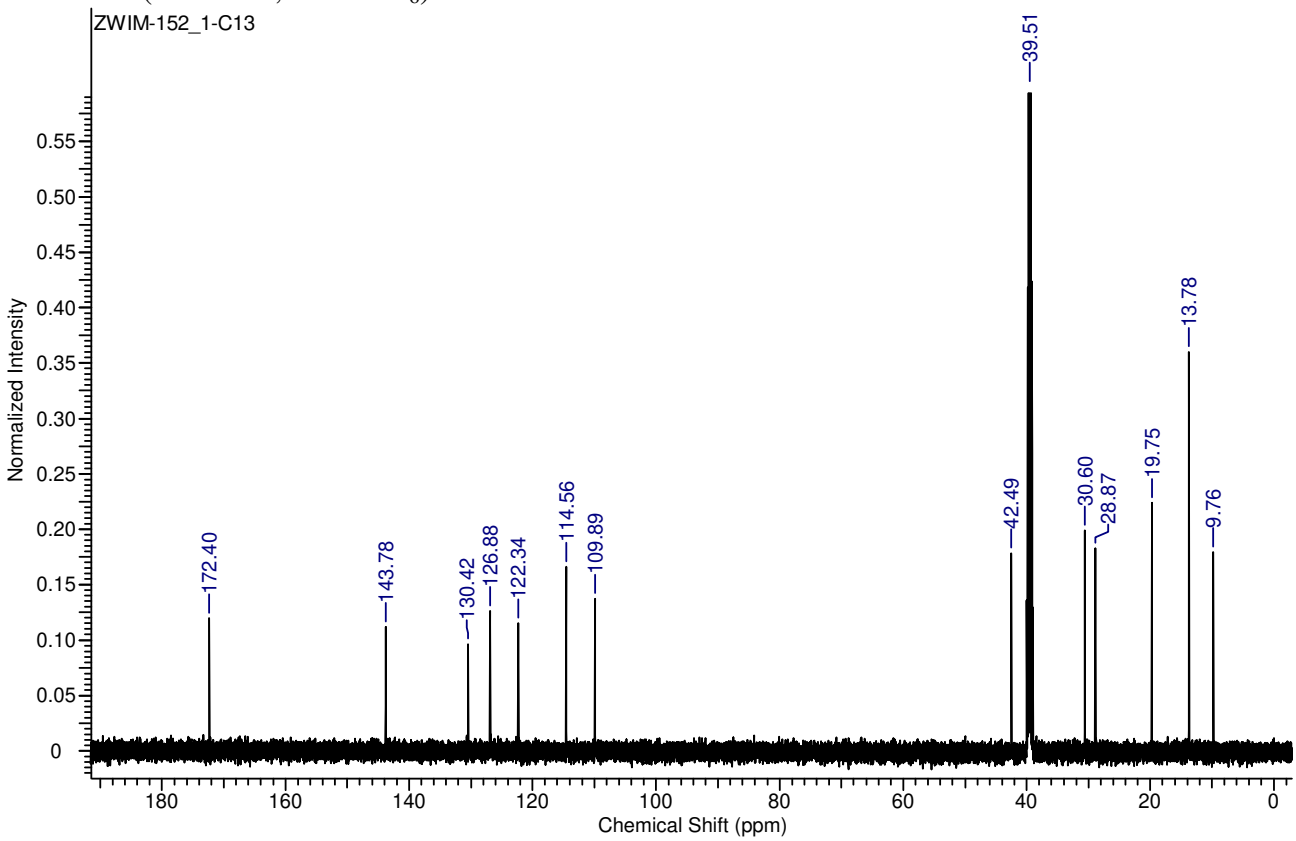


7b

^{1}H NMR (500 MHz, DMSO-d_6)

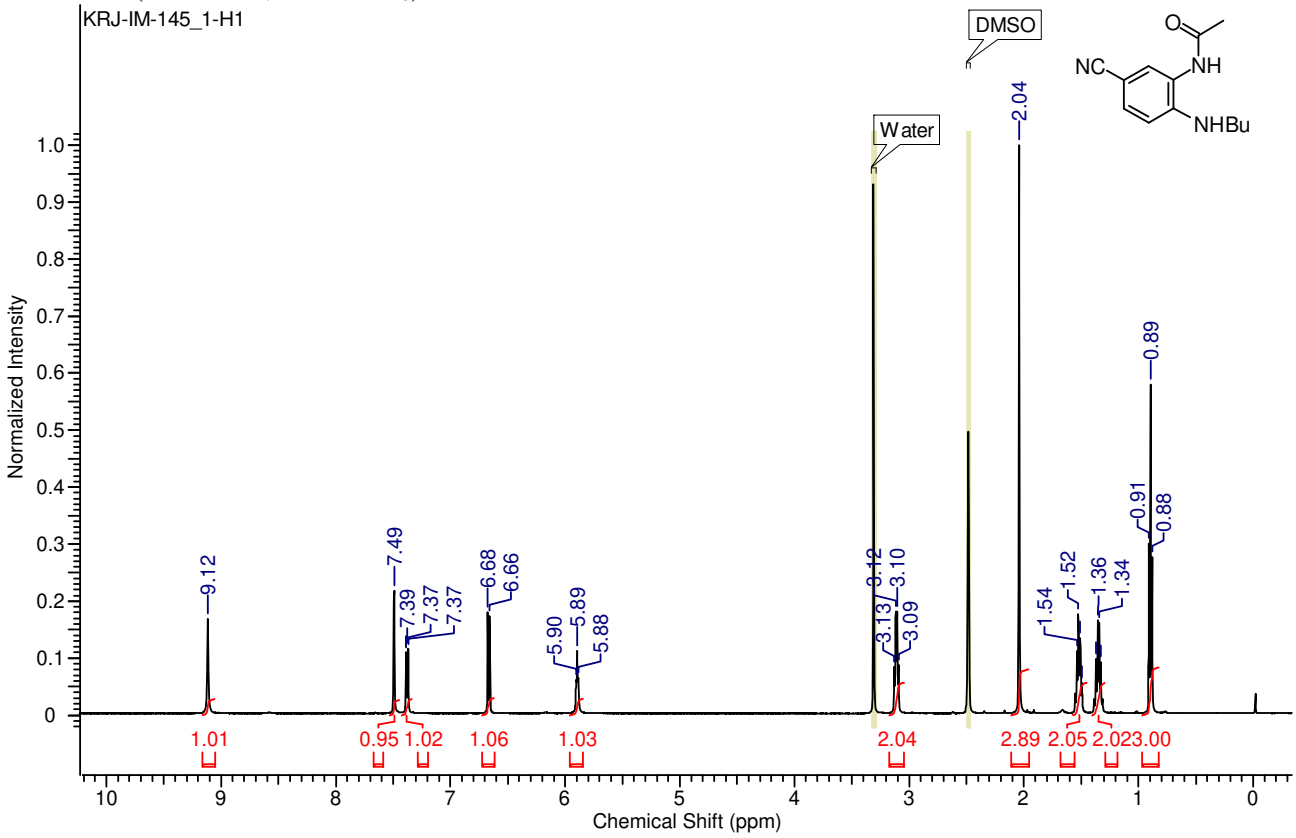


^{13}C NMR (125 MHz, DMSO-d_6)

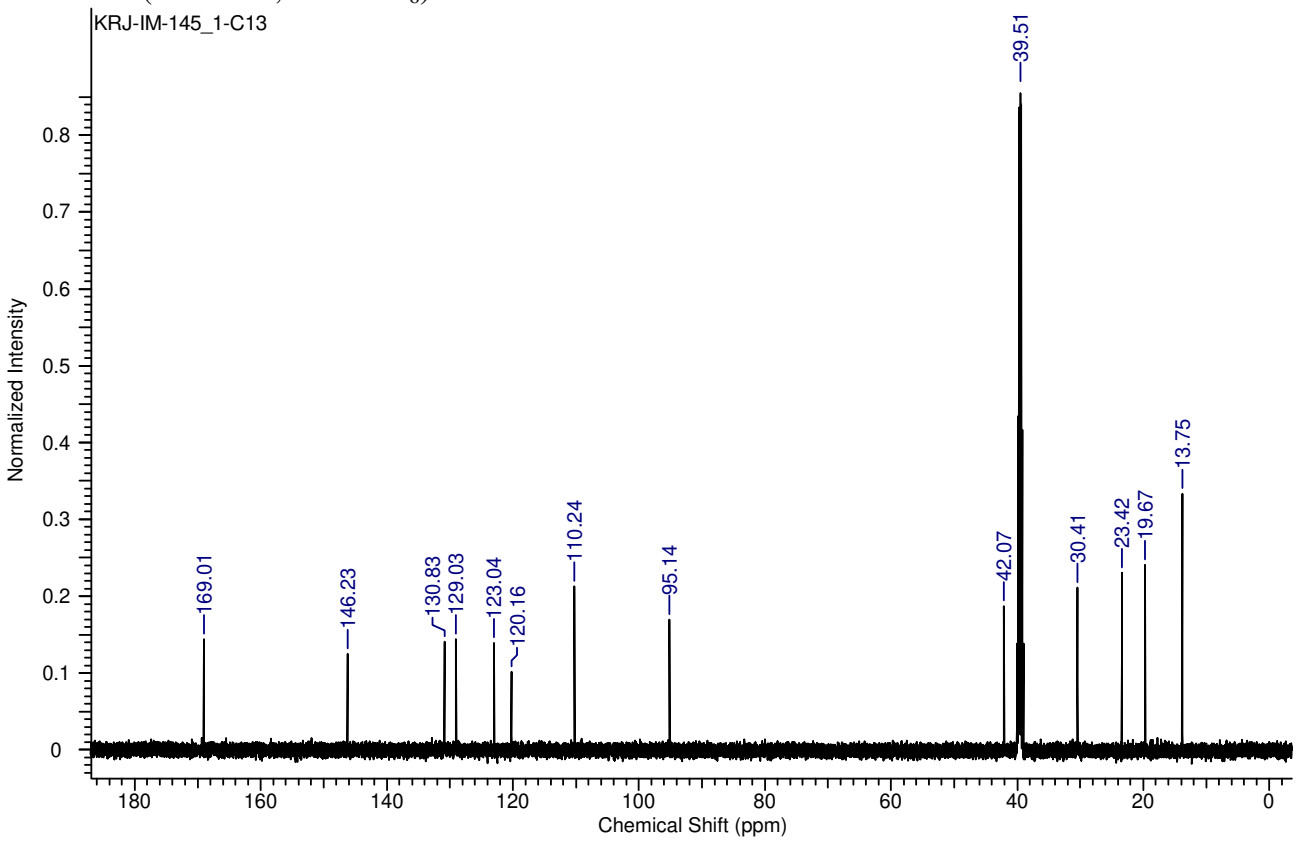


7c

^{1}H NMR (500 MHz, DMSO-d_6)

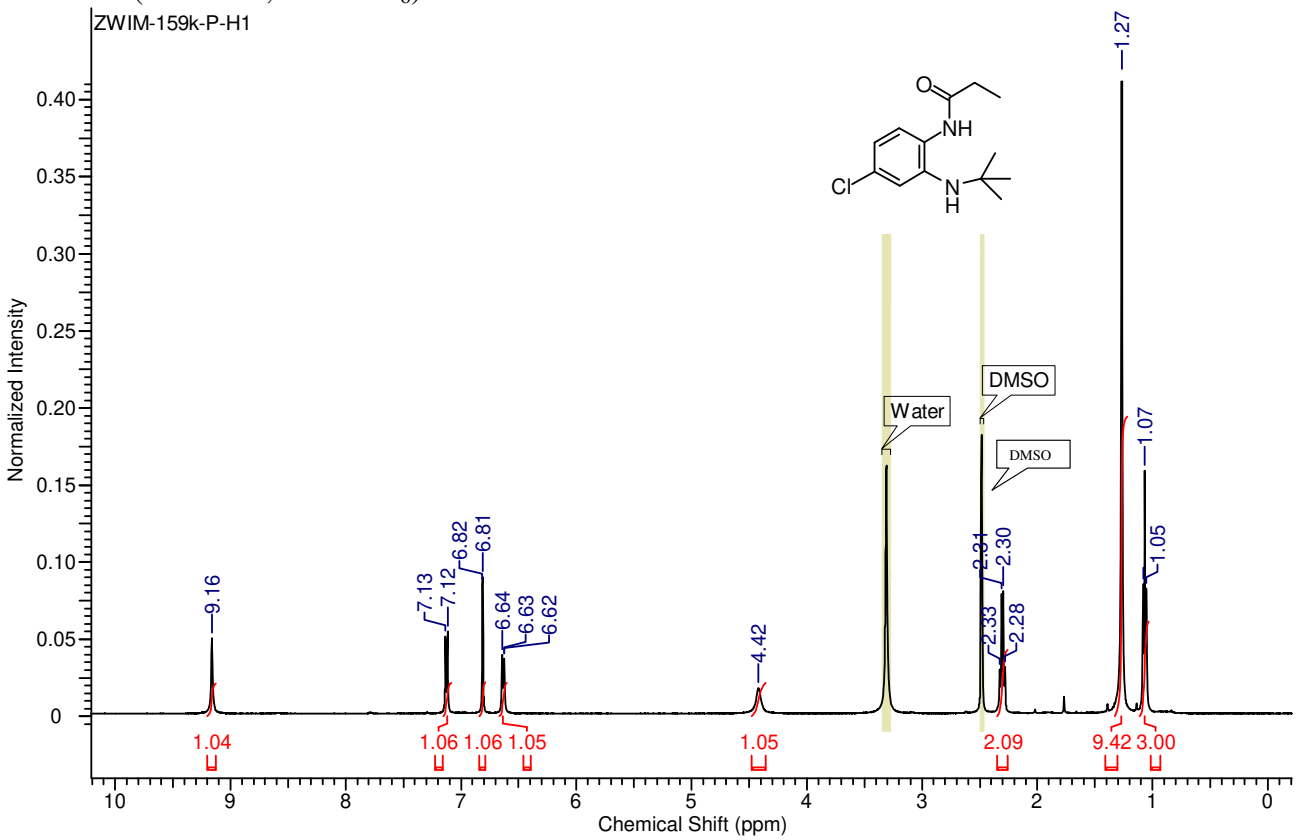


^{13}C NMR (125 MHz, DMSO-d_6)

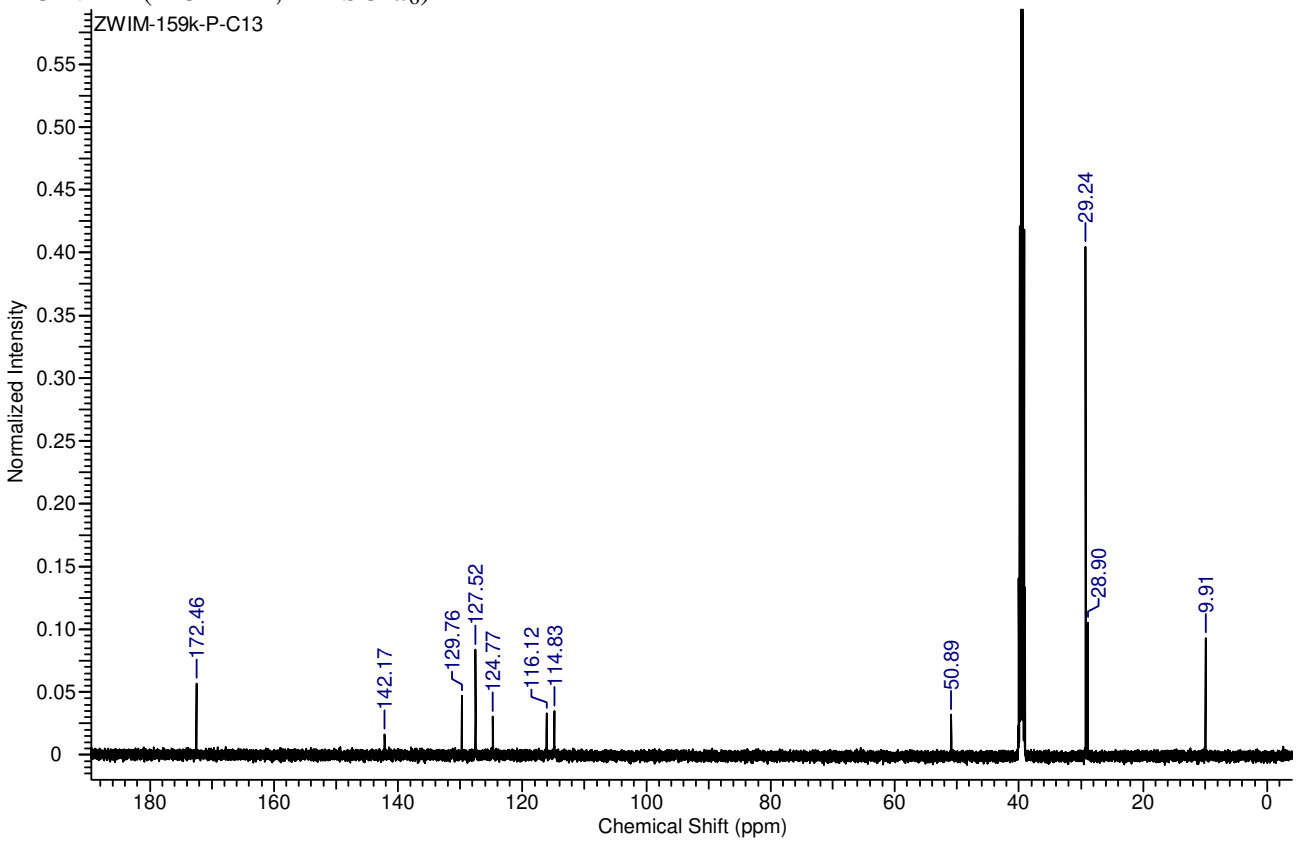


7d

^{1}H NMR (500 MHz, DMSO-d_6)



^{13}C NMR (125 MHz, DMSO-d_6)



OŚWIADCZENIA WSPÓŁAUTORÓW PUBLIKACJI

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Kierownik zespołu VII
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01-224 Warszawa

Instytut Chemii Organicznej
Polskiej Akademii Nauk

Oświadczam, że mój wkład w postanie niniejszej publikacji polegał na:

- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes *Tetrahedron Lett.* **2021**, *86*, 153515.

- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel (2-Aminoaryl)iminophosphoranes as Versatile Starting Materials for the Synthesis of 1-Aryl-2-trifluoromethylbenzimidazoles *Synlett* **2022**, *33*, 1092.

- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel Comprehensive approach to the multigram, heavy-metal-free synthesis of 4-EWG-substituted quinoline derivatives *Tetrahedron Lett.* **2023**, *146*, 133632.

- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel Synthesis of various 1-alkylbenzimidazole derivatives directly from 2-alkylaminonitroarenes via a two-steps, one-pot procedure *J. Heterocycl. Chem.* **2024** DOI: 10.1002/jhet.4830

Propozycja badań, wykonanie kilka eksperymentów, dyskusja merytoryczna

Zbigniew Wróbel

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Oświadczam, że mój wkład w powstanie niżej wymienionych czterech publikacji polegał na doradztwie metodologicznym, dyskusji zagadnień mechanistycznych, opracowywaniu wyników doświadczalnych i pomocy w redagowaniu artykułów.

- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes *Tetrahedron Lett.* **2021**, *86*, 153515.
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7.05.2024

AKwast

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West Long Branch, NJ 07764, USA

I declare that my contribution to these publications consisted of substantive discussion, editing the works, and improving the language.

- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes *Tetrahedron Lett.* **2021**, *86*, 153515.

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Oświadczam, że mój wkład w powstanie tych publikacji polegał na merytorycznej dyskusji, redagowaniu prac i doskonaleniu języka.

Bogdan Wilk 07 May 2024

Bogdan Wilk, Ph.D.

mgr Magdalena Walewska-Królikiewicz

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Oświadczam, że mój wkład w powstanie niniejszych publikacji polegał na:

Syntezie substratów oraz produktów, optymalizacji reakcji modelowych, przygotowaniu związków do analiz NMR oraz MS, pomiarach temperatur topnienia oraz dyskusji mechanistycznych, metodologicznych oraz koncepcyjnych.

- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel „Two-step, regioselective, multigram-scale synthesis of 2-(trifluoromethyl)indoles from 2-nitrotoluenes", *Tetrahedron Lett.* **2021**, 86, 153515

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- **Magdalena Walewska-Królikiewicz**, Bogdan Wilk, Andrzej Kwast, Zbigniew Wróbel Comprehensive approach to the multigram, heavy-metal-free synthesis of 4-EWG-substituted quinoline derivatives, *Tetrahedron Letter* **2023**, 146, 133632

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Magdalena Walewska-Królikiewicz

potwierdzam Zbigniew Wróbel