

Title	Hydrogenation and other palladium mediated transformations for the construction of important molecular frameworks
Authors	Kehoe, Roberta A.
Publication date	2024
Original Citation	Kehoe, R. A. 2024. Hydrogenation and other palladium mediated transformations for the construction of important molecular frameworks. PhD Thesis, University College Cork.
Type of publication	Doctoral thesis
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Download date	2026-08-29 19:31:21
Item downloaded from	https://hdl.handle.net/10468/16384

Hydrogenation and other Palladium Mediated Transformations for the Construction of Important Molecular Frameworks



University College Cork

Coláiste na hOllscoile Corcaigh

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Thesis presented for the degree of

Doctor of Philosophy

to National University of Ireland, Cork.

School of Chemistry

Supervisor: Dr. Gerard P. McGlacken

Head of School: Prof. Anita Maguire

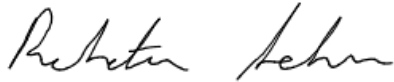
March 2024

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.



Roberta Kehoe

27-March-2024

Date

Acknowledgements

Firstly, I would like to thank my supervisor Dr. Ger McGlacken for his mentorship and guidance throughout my PhD journey. I appreciate that you were never further than an email away when I had questions and needed insight. Your understanding of the importance to encourage and maintain group morale and friendship really helped the difficult PhD journey, especially after the pandemic. I would also like to thank the Science Foundation Ireland (grant number SFI/12/IP/1315) and the Synthesis and Solid State Pharmaceutical Centre (SSPC) (SFI/12/RC/2275, SFI/12/RC/2275_P2 and SFI/21/FFP-A/8784) for funding this research in addition to the Higher Education Authority for providing extra funding due to Covid-19 related delays.

This research would have truly been impossible without the kind assistance of the UCC technical staff. Dr. Lorraine Bateman, Dr. Dan McCarthy and Dr. Denis Lynch, thank you all for your invaluable NMR assistance. Denis, I will forever be grateful for your patience, insights, and unrelenting willingness to help people, be it chemistry related questions or the 300/400 MHz constantly having issues. Thank you to Dr. Florence McCarthy and again Denis Lynch for mass spec services, we cannot do it without you. Sincere thanks to Dr. Francis Harrington for the use of his centrifuge...I promise this is the last time! The Kane building would not be the same without Dr. Tom O'Mahony keeping everything together, Denis Duggan and Tina Kent for providing great store services and keeping everyone's spirits high. Imelda Power, thank you for unrelentingly tracking down the last chemical I needed that went missing, you very much facilitated the completion of my PhD. To Dr. Ian O'Connor, Dr. Trevor Carey and the late Derry Kearney, thank you for everything you have done and always been up for a chat and laughs.

I am very lucky to have met so many wonderful people during my research. The GMG group, Mark, Eimear, Dave, Amy, Aobha, Emma A, Marie-Clara, Conor, Muireann, Ella, Ben, Si-Lok, Emma F, James, Geoffrey, Kishore and more recently, Aidan, thank you all for your support, friendship, wisdom, kindness, and humour. It was a pleasure working alongside you and I apologise for not always being the tidiest! To all the other 'Organics', thank you all for making the PhD experience so much more enjoyable, between birthday cake, dressing up for Halloween, trips to Sicilian Delights and days/nights out, I am very grateful for this time. To the UCC alumni who I first met long-long ago during my Masters; Thomas, Aaran, Dan, Ryan, Kevin O'S, Tim and Louise, those are some of my fondest memories of the Kane and thank you for encouraging me to pursue further research. To Davy Jones, who has bookended my PhD. From the very start you were there to break the back on all my projects before you left for Scotland. I cannot express in words how grateful and appreciative I am for your help from start to finish of my research. You're

back in UCC now, though for me it's like you never left as you have always made yourself available for the many questions I've had over the years. Not only are you an otherworldly chemist, but you are also an incredible friend. Although I've told you a thousand times, I'll tell you once more, thank you so much for all your help and friendship.

To my housemates and best friends, you started this journey with me and you're finishing it with me. Ellie, Pa, Kev, Niall and Heather, you all know how much harder this would have been without you guys. Coming home each day to friends has been such a privilege and thank you all for keeping me smiling even on the tough days. Same applies to my other besties, tag rugby and badminton friends, you guys kept me more sane than you know. To Eoin, you had the incredible gift of distracting me from my PhD worries. You ensured I kept the work/life balance through the many concerts, trips and walks around the Lough. I would have gone cracked otherwise. Thank you for being there and being such an antagonist! Let's have an Irish coffee to celebrate.

To my family, words can't express my gratitude for all you have done for me. Mam and Dad, from doing a washing load for me to providing financial assistance, you've been there for me no matter what I needed, big or small. Thank you for encouraging me and tolerating my curiosity... even if they were such 'Robyn' things to do. To my brother and sister, I couldn't have asked for better siblings, and I appreciate and love you guys very much. To my extended family, I am so lucky to have such kind and enthusiastic people around me, you've all been incredible support. My thanks would not be complete without mention of my four-legged friends, Minnie, Rollo, Kimi and Momsy. You guys were the best therapists a PhD student could ask for.

Abstract

This thesis is presented as a thesis by publication and includes two peer-reviewed published chapters and a third chapter to be submitted, pending external nanoparticle analysis. The numbering of the compounds, schemes and figures are unchanged and are as per the published manuscripts. Therefore, compound, figure and scheme numbering etc. is independent for each chapter. This work mostly describes the use of palladium catalysts in hydrogenation reactions to form molecular structures of interest in pharmaceuticals and medicine.

Chapter 2

Building molecular complexity usually requires numerous synthetic steps, isolations, and purifications. In addition, many reagents/solvents can be required, and the processes can take a lot of time. Designing one-pot tandem reaction methods is an environmentally friendly approach to building complexity which negates the need for intermediate isolation/purification and saves on time and costs. In this chapter, a one-pot Mizoroki-Heck/direct arylation/hydrogenation sequence was developed to access biologically significant alkylated benzofuroquinolines, benzofuropyridines and dibenzofurans. This one-pot method combines three mechanistically distinct palladium-catalysed reactions from a single pre-catalyst without the need for exogenous ligands and inorganic base. A library of novel compounds was synthesised, including a deuterated derivative, and some green metric calculations were carried out.

Chapter 3

Extended aromatic systems exhibit an associated 2D character which is often not conducive to clinical success. Compounds with more 3D (sp^3) character often progress further in clinical studies. Introducing this '3-dimensionality' at a late-stage allows for initial access to the unparalleled scope and broad applicability of sp^2 - sp^2 cross-coupling which is then followed by hydrogenation to add a third dimension. This work describes the use of simple hydrogenation reagents and conditions to selectively reduce tetracyclic benzofuroquinolines, incorporating more sp^3 character into the target compounds at 'late stage'. Deuterium was also incorporated to form deuterated derivatives. Additionally, the deuteration provided some interesting insights into the source of the deuterium/hydrogen in this reaction. The role of the oxygen atom in benzofuroquinoline was also explored.

Chapter 4

The Z-alkene motif is ubiquitous in chemistry and is found across pharmaceutical, agricultural and materials industries. The selective formation of Z-alkenes by

hydrogenation methods remains a challenge, as isomerisation to the *E*-alkene can occur in addition to over-reduction to the respective alkane. The widely used Lindlar's catalyst facilitates the selective hydrogenation of alkynes to *Z*-alkenes. However, there are many problems associated with the use of this catalyst. The use of ligand stabilised nanoparticles can facilitate the formation of *Z*-alkenes with low catalytic loadings and increased reproducibility. This chapter describes the development and use of ligand stabilised palladium-dodecanethiolate nanoparticles for the semi-hydrogenation of alkynes to form *Z*-selective alkenes. These nanoparticles also facilitate the introduction of deuterium into the alkene bond while maintaining selectivity and excellent deuterium incorporation.

For my parents, Joan and Robert

*...even when we find not what we seek, we find something as well worth
seeking as what we missed.*

— Robert Boyle

Knowledge once gained casts a light beyond its immediate boundaries.

— John Tyndall

Abbreviations

AcOH	Acetic acid
ADME	Absorption, distribution, metabolism and excretion
aq.	Aqueous
Ar	Aryl / Aromatic
atm.	Atmospheres
ATR	Attenuated total reflectance
Br	Bromine
br s	Broad singlet (spectral)
C	Carbon
¹³ C NMR	Carbon nuclear magnetic resonance
<i>ca.</i>	<i>circa</i>
calcd.	Calculated
CCDC	Cambridge Crystallographic Data Centre
CDCl ₃	Deuterated chloroform
<i>cf.</i>	confer (compare)
CMD	Concerted Metalation Deprotonation
Co	Cobalt
conc.	Concentration
conv.	Conversion
CPME	Cyclopentyl methyl ether
CSA	Camphorsulfonic acid
d	Doublet (spectral)
D	Deuterium
D ₂	Deuterium gas
DA	Dodecylamine
DCI	Deuterium chloride
DCM	Dichloromethane
dd	Doublet of doublets (spectral)
ddd	Doublet of doublet of doublets (spectral)
DEPT	Distortionless enhancement of polarisation transfer
DMA	Dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO- <i>d</i> ₆	Deuterated dimethyl sulfoxide
dt	Doublet of triplets (spectral)
DT	Dodecanethiol(ate)
<i>e.g.</i>	For example
EDG	Electron-donating group
eq.	Equivalents
equiv.	Equivalents
ESI	Electrospray Ionisation / Electronic supplementary information
Et	Ethyl
etc.	<i>et cetera</i>
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron-withdrawing group
FDA	Food and Drug Administration
¹⁹ F NMR	Fluorine nuclear magnetic resonance
g	gram(s)
h	Hour
H	Hydrogen

H ₂	Hydrogen gas
¹ H NMR	Proton nuclear magnetic resonance
Het	Hetero
HFIP	Hexafluoroisopropanol
HMBC	Heteronuclear multiple bond correlation
hr	Hour(s)
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
ICP	Inductively coupled plasma
<i>i</i> PrOH	Isopropyl alcohol
IR	Infrared
<i>J</i>	NMR coupling constant, in Hz
K ₂ PdCl ₄	Potassium tetrachloropalladate
lit.	Literature
LRMS	Low resolution mass spectrometry
m	Milli (10 ⁻³) / Multiplet (spectral)
M	Molarity, moles per litre
Me	Methyl
2-MeTHF	2-Methyl tetrahydrofuran
mg	Milligram
MHz	Megahertz
mL	Millilitre
mmol	Millimole
mol	Mole
mol%	Mole percent
m.p.	Melting point
MsOH	Methanesulfonic acid
MW	Molecular weight
m/z	Mass-to-charge ratio
N	Nitrogen
NaBH ₄	Sodium borohydride
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NP	Nanoparticle(s)
NSAID	Non-steroidal anti-inflammatory drug
Pd	Palladium
Pd/C	Palladium-on-carbon
Ph	Phenyl
POCl ₃	Phosphoryl chloride
ppm	Parts per million
Pt	Platinum
PTFE	Polytetrafluoroethylene
q	Quartet (spectral)
Ref	Reference
RET	Rearranged during transfection
Rh	Rhodium
Ru	Ruthenium
r.t.	Room temperature
S	Sulfur
S _E Ar	Electrophilic aromatic substitution
SI	Supplementary information
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
s	Singlet (spectral)
t	Triplet (spectral)
TEM	Transmission electron microscopy
Temp.	Temperature
TFA	Trifluoroacetic acid
TOF/Tof	Time-of-flight
UV	Ultraviolet (Spectroscopy)
wt%	Concentration, weight percentage
Zn	Zinc
μ	Micro (10^{-6})
μg	Microgram
δ	Delta
°C	Degrees Celsius

Overview

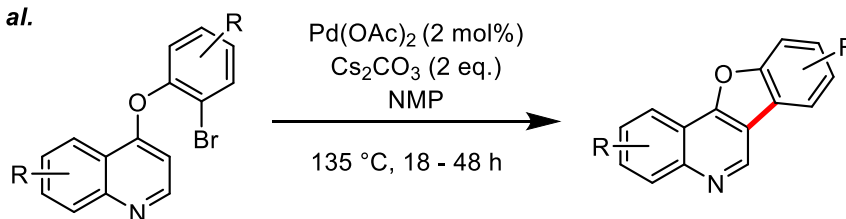
The aim of this thesis is to develop facile novel methodologies to access important chemical building blocks and biologically relevant compounds through palladium catalysed hydrogenation and other reactions. Hydrogenation reactions involve the addition of hydrogen atoms to unsaturated molecules to form fully saturated or partially saturated compounds. Hydrogenation is one of the most versatile transformations and is used across multiple disciplines of chemistry (pharmaceutical, agrochemical, petrochemical etc.). Hydrogenation reactions account for approximately 20% of all chemical processes.^[1] This high percentage is owed to the high versatility and applicability of the hydrogenation reaction to multiple functionalities. Despite the overall hydrogenation reaction being exothermic, the requirement for a high activation energy prevents it from taking place without the use of a catalyst.^[2] In this thesis, each of the three research chapters presented use a palladium catalyst to facilitate a hydrogenation reaction, however the palladium (pre)catalyst is usually different, as are the substrates.

Aims and Objectives

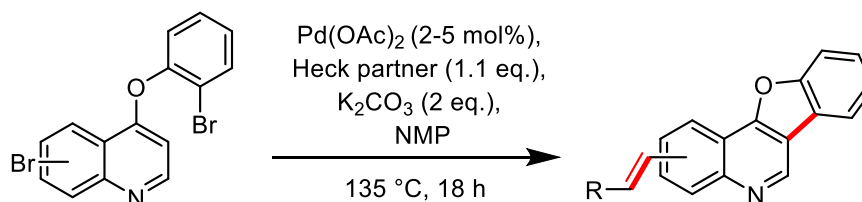
The primary aim of **Chapter 2** was to develop a novel 3-step one-pot methodology to achieve alkylated benzofuroquinolines. This work develops upon previously published work in the McGlacken group to form benzofuroquinoline scaffolds.^[3] Initial optimisation for building the benzofuroquinoline scaffold was undertaken by Shanahan *et al.* using a bromophenol and 4-chloroquinoline to form a phenoxyquinoline intermediate, which is then ring closed *via* direct arylation.^[3a] Shanahan's work was developed upon by Hickey *et al.* after discovering addition of a second bromine to the scaffold inhibited benzofuroquinoline formation.^[3b] It was hypothesised that the palladium catalyst approached a catalytic 'dead end' upon insertion into the less sterically hindered non-ring closing C–Br bond. In order to liberate the palladium catalyst from the non-productive C–Br bond, a coupling partner was inserted (Mizoroki-Heck or Suzuki), and formation of the furan ring was restored. (**Scheme AO1**).

Scheme AO1. Previous work published by the McGlacken group.^[3]

Shanahan *et al.*



Hickey *et al.*

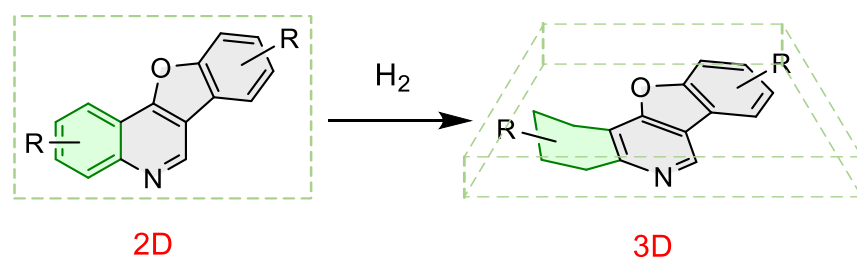


Building upon this work, the objectives of **Chapter 2** were to:

- Incorporate a third step in the previous one-pot cross-coupling/C–H functionalisation reaction using hydrogenation.
- Find a greener and less toxic solvent than *N*-methyl-pyrrolidone (NMP) as this solvent is regarded a Substance of Very High Concern (SVHC) as per the European Chemicals Agency.^[4]
- Determine whether this methodology can be applied to various scaffolds.
- Incorporate deuterium into our final compound after hydrogenation optimisation.
- Compare the new procedure to the current state-of-the-art Mizoroki-Heck/direct arylation/hydrogenation sequence^[5] through green metric calculations.

Chapter 3 takes a different look at the hydrogenation of benzofuroquinoline scaffolds (**Scheme AO2**). Inspiration came after reading interesting articles in the literature about ‘Escaping from Flatland’. The articles presented the idea of transforming once planar molecules into more ‘3-dimensional’ scaffolds^[6] with the rationale being that introducing more saturation into drug candidates can lead to greater clinical success.

Scheme AO2. General transformation for the reduction of the benzofuroquinoline scaffold. Image adapted from Kehoe *et al.*^[7]

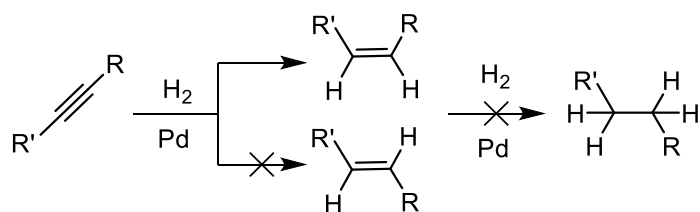


The objectives of **Chapter 3** were to:

- Find simple conditions that selectively break the aromaticity of our benzofuroquinoline scaffolds to form more saturated and, therefore, more ‘3-dimensional’ core structures.
- Determine the robustness of the reaction by using various substituted benzofuroquinoline substrates.
- Incorporate deuterium into the scaffold through reduction of the aromatic system to form deuterated ‘3-dimensional’ structures.
- Undertake some initial mechanistic investigations to determine the importance of the benzofuro- heteroatom in the selectivity of this reduction.
- Investigate the source of the reducing hydrogen.

Chapter 4 investigates a different aspect of palladium catalysed selective hydrogenation. The aim of this chapter was to apply ligand stabilised palladium nanoparticles in the semi-hydrogenation of alkynes (**Scheme AO3**). The semi-hydrogenation of alkynes involves reducing the alkyne sp bond to the corresponding alkene sp^2 bond without overreduction to the alkane sp^3 bond. In addition to the chemoselective issue of forming an alkene bond without over-reduction to the alkane, an additional stereoselective issue arises in that either *Z*- or *E*-alkene isomers can form.

Scheme A03. General transformation for the semi-hydrogenation of alkynes to Z-alkenes



The objectives of **Chapter 4** were to:

- Investigate the selective formation of Z-alkenes by semi-hydrogenation using ligand stabilised palladium-dodecylamine (Pd-N) nanoparticles.
- Investigate the selective formation of Z-alkenes by semi-hydrogenation using ligand stabilised palladium-dodecanethiolate (Pd-S) nanoparticles.
- Determine whether an inverted selectivity from Z-alkenes to E-alkenes could be achieved.
- Incorporate deuterium into the newly formed alkene bond and still maintain high Z-alkene selectivity with minimal alkane formation.

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Chapter 1

Introduction

I looked for it because I thought it should exist.

– *Harold Urey on the discovery of deuterium*

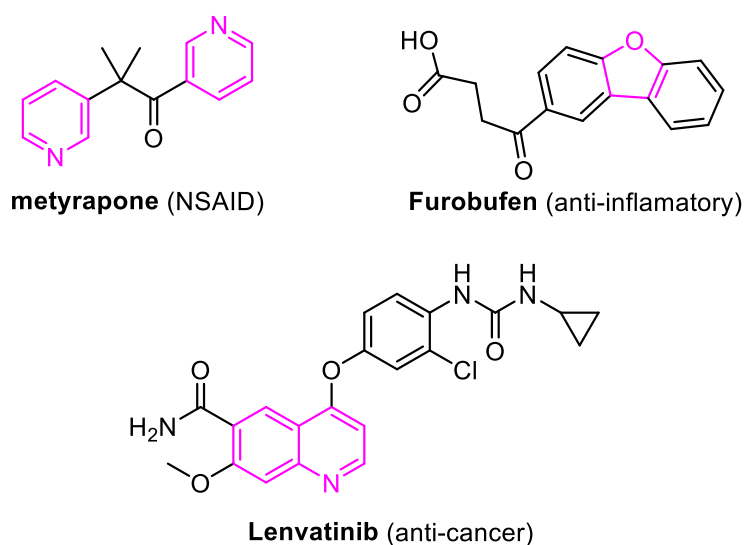
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1 Benzofuroquinoline Starting Materials

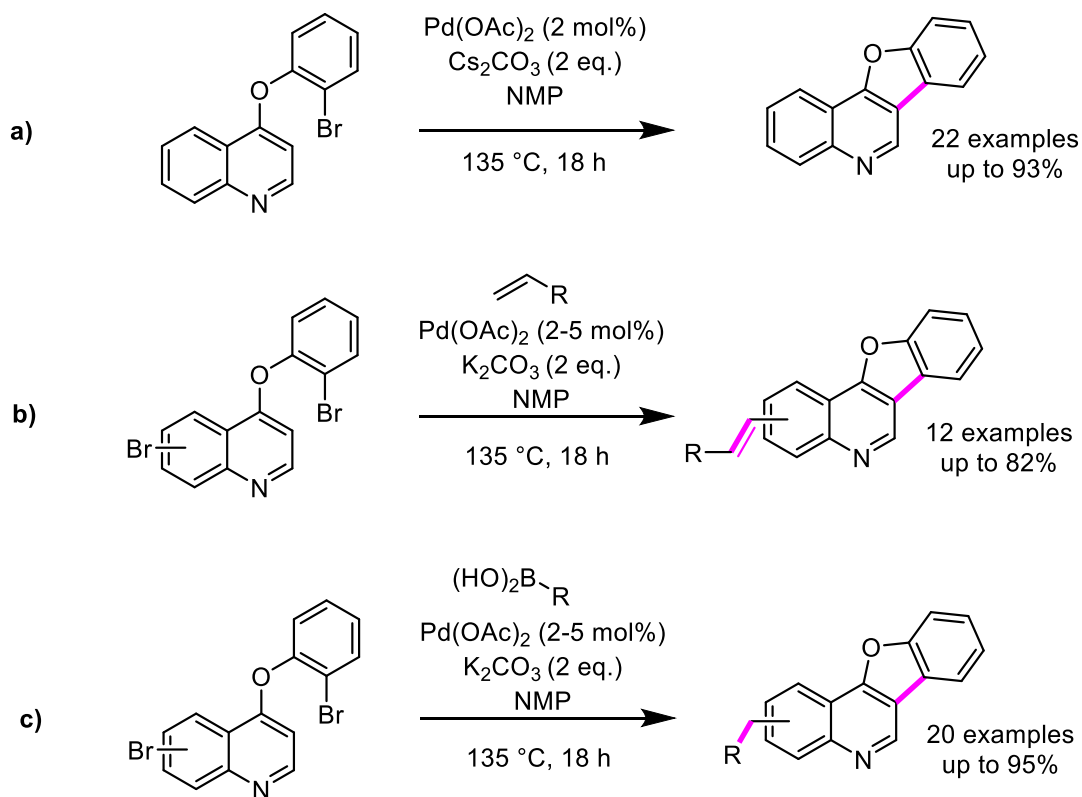
Previous work undertaken in the McGlacken group focuses on the synthesis and construction of (hetero)aromatic backbones of biological significance. Of particular interest to the group are oxygen and nitrogen containing heteroaromatics such as furan and pyridine containing systems. Pyridine, quinoline and furan ring systems are the 2nd, 22nd and 25th most frequently observed of the 351 ring systems present in FDA-approved small molecule drugs respectively (**Figure I1**).^[1] Research into novel methodologies for the construction of these frameworks is of vital importance for the continued discovery of new biologically active compounds.

Figure I1. Examples of pyridine, furan and quinoline containing drugs.



Previously in the McGlacken group, benzofuroquinoline scaffolds have been developed which combines both a quinoline and benzofuran ring. First, Shanahan *et al.* constructed the benzofuroquinoline motif by developing a direct arylation methodology from a bromophenoxy quinoline intermediate (**Scheme I1**).^[2] During the optimisation process of this work, it was noted that the direct arylation reaction did not proceed when a second bromine atom was present on the bromophenoxy quinoline substrate. This led to further investigations by Hickey and Shanahan *et al.* which led to a theory that the catalyst was coming to a 'dead-end' at the non-constructive bromine site. They found that upon addition of coupling partner; i) a cross-coupling reaction took place and ii) the liberated catalyst was then able to undertake the direct arylation bond-forming process. This work was duly reported as one-pot cross-coupling/direct arylation methodology for the formation of substituted benzofuroquinolines *via* the addition of a Suzuki or Mizoroki-Heck coupling partner (**Scheme I1**).^[3] They also report on how quinoline can act as a ligand to the palladium and act as a pre-catalyst in this reaction.^[3]

Scheme I1. Previous work in the McGlacken group on benzofuroquinoline scaffolds. a) Shanahan *et al.* (2018),^[2] b) Mizoroki-Heck examples, Shanahan and Hickey *et al.* (2020),^[3] c) Suzuki-Miyaura examples, Shanahan and Hickey *et al.* (2020).^[3]



The work in this thesis further develops upon this reported work by the incorporation of a third step in the one-pot process *via* hydrogenation of a Mizoroki-Heck intermediate. Further developments are made to the methodology to omit the need for NMP as solvent and the need for added base.

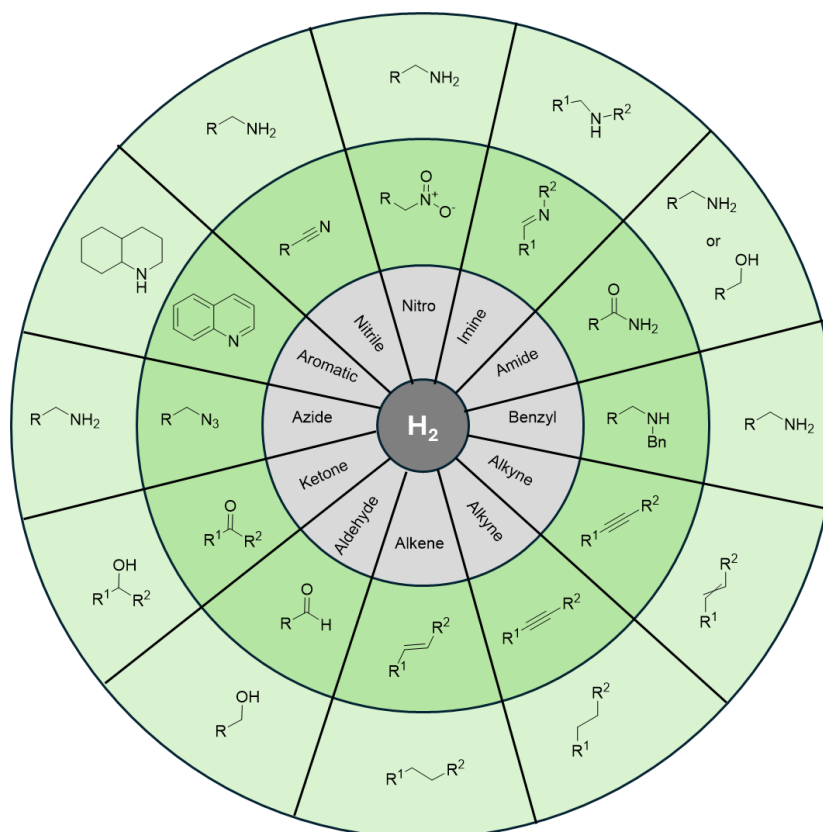
2 Hydrogenation

The Nobel Prize in Chemistry was awarded to French Chemist Paul Sabatier in 1912 (along with Victor Grignard) for his contributions to the field of hydrogenation chemistry. Initial experiments, undertaken with Senderens, involved adding a steady stream of ethylene and hydrogen gas over nickel metal at 300 °C. Ethane gas evolved, indicating that the hydrogenation of ethylene was successful. Their work extended to show the hydrogenation of benzene to cyclohexane, nitriles to amines, aldehydes and ketones to alcohols and carbon monoxide and carbon dioxide to methane, amongst other transformations.^[4]

The hydrogenation reaction, since then, has been greatly developed and can be applied to many different motifs for different purposes such as reduction, deprotection and functional group transformation (**Figure I2**).^[5] Progress has also been made in the

metallic source of catalyst that can be used in hydrogenations such as cobalt, iron, copper, iridium, rhodium, ruthenium, platinum and palladium.^[5] Due to the wide applicability and versatility of the hydrogenation reaction, 20 – 25% of all FDA approved

Figure I2. Examples of hydrogenation reaction transformations. Darker green: substrate, lighter green: product.



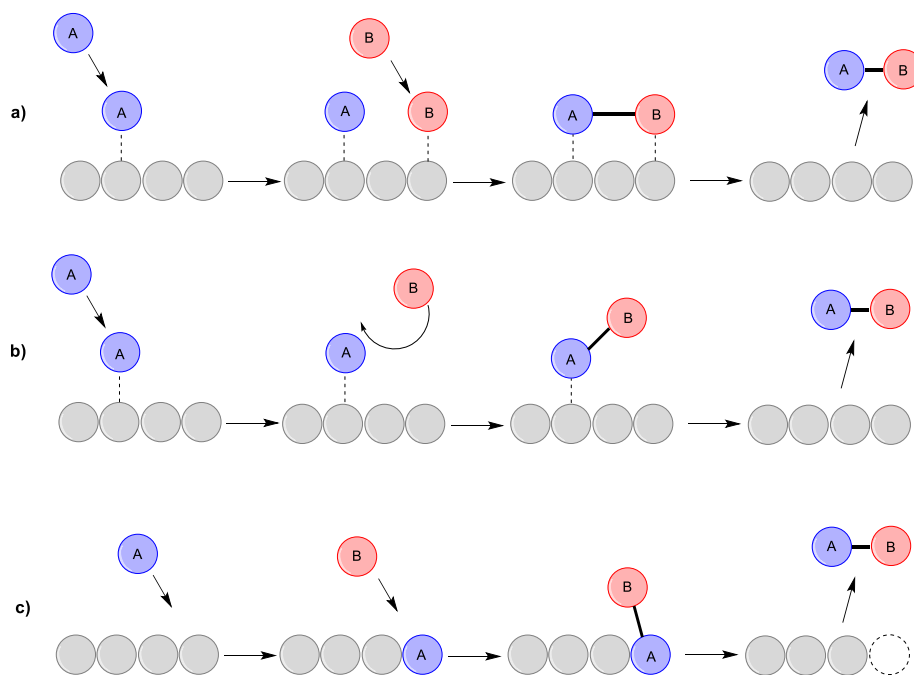
drugs on the market contain at least one hydrogenation step in their synthesis.^[6] Although homogeneous hydrogenation catalysts exist,^[7] industry mainly utilises heterogeneous catalysts due to their lower cost, broad applicability and their ease of removal from reaction mixtures.^[5] The hydrogenation reaction is also applied to the synthesis of fatty acids and vitamins,^[8] and the petrochemical industry.^[9]

2.1 Hydrogenation Mechanism

It is generally accepted that there are three main mechanisms of hydrogen reduction on a (heterogeneous) surface, namely; a) Langmuir-Hinshelwood mechanism, b) Eley-Rideal mechanism and c) Mars-Van Krevelen mechanism.^[10] The Langmuir-Hinshelwood mechanism follows the principle that all reagents adsorb to the catalyst surface, react together, and then leave the surface as a newly bound species (**Figure I3, a**).^[11] The Eley-Rideal mechanism is followed when one reagent binds to the surface, a second reagent approaches the adsorbed substrate and reacts, without itself being

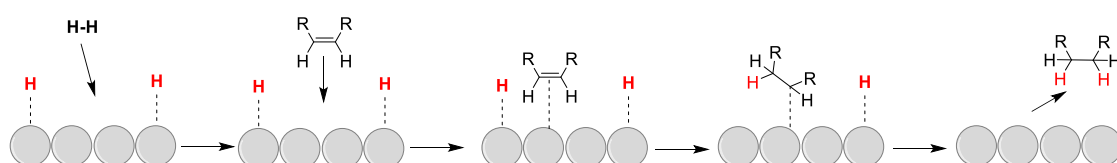
adsorbed. The newly formed species then leaves the surface (**Figure I3, b**).^[12] The Mars-Van Krevelen mechanism describes when a substrate adsorbs to the surface and reacts with an atom in the surface lattice, e.g. oxygen, and the newly formed species leaves the surface, leaving a gap in the lattice surface which can later be repopulated (**Figure I3, c**).^[13]

Figure I3. Schematic representation of surface Mechanisms. a) Langmuir-Hinshelwood, b) Eley-Rideal, c) Mars-Van Krevelen.



For heterogeneous hydrogenation catalysis, a Horiuti-Polanyi mechanism is reported which is a type of Langmuir-Hinshelwood mechanism and is the most commonly accepted mechanism for the hydrogenation reaction.^[14] In the context of this thesis, the hydrogenation of an alkene is described. The mechanism consists of three fundamental steps: a) adsorption of the hydrogen and alkene substrates, b) uptake of hydrogen from the catalyst surface into the unsaturated bond and c) reductive elimination of the newly formed alkane (**Figure I4**).^[15] Typically, the two hydrogen atoms are added *syn* to the double bond (added to the same face), however, some substrates and catalysts, as well as certain reaction conditions (e.g., temperature, and hydrogen pressure) can cause *anti*-addition to occur (where H is added to opposite sides of the face).^[5]

Figure I4. Schematic of Horiuti-Polanyi mechanism for the hydrogenation of an alkene.

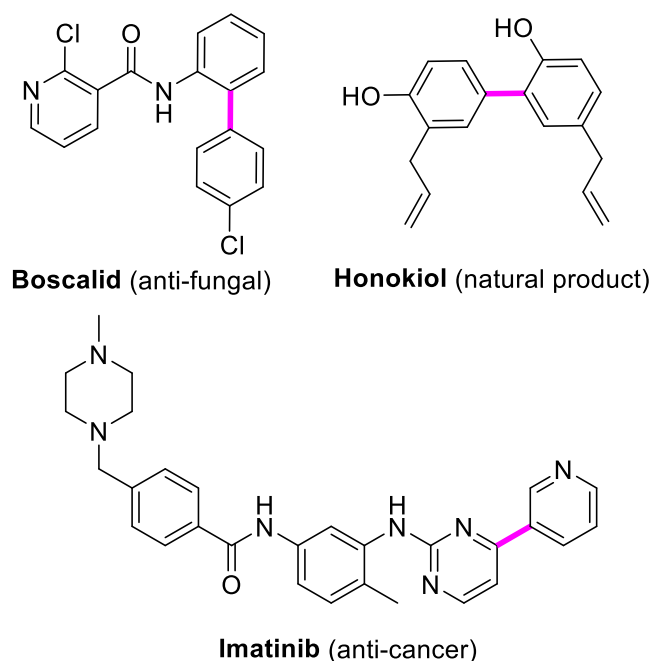


Deuterium gas can also be used as a replacement for hydrogen gas for the formation of deuterated compounds and isomerisation of the alkene can also occur. More on deuteration and isomerisation is described below under the ‘Semi-Hydrogenation Mechanism’ section.

3 Aryl-Aryl Bond Formation

Connecting two or more (hetero)aryl groups by the formation of new carbon-carbon bonds is one of the most important chemical transformations in organic synthesis. The biaryl motif is an omni-present substructure in medicinal chemistry and therefore poses an essential synthetic target. Anti-cancer compound Imatinib, natural product Honokiol and anti-fungal agrichemical Boscalid are all examples of biaryl containing compounds (**Figure I5**).

Figure I5. Important biaryl structural motif in pharmaceutical, natural and agrichemical products.

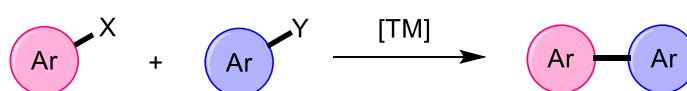


In 1901, Ullmann demonstrated that using stoichiometric quantities of copper could facilitate the reductive coupling of haloarenes to form symmetric biaryls.^[16] Since this initial finding, many cross-coupling methodologies have been developed, following from this work.^[17] Particularly, carbon-carbon bond forming chemistry began to significantly develop in the 1970's with the emergence of cross-coupling reactions.^[18] Awarded the Nobel Prize in Chemistry in 2010 for their work in this field, Heck,^[19] Negishi^[20] and Suzuki^[21] utilised palladium metal as a catalyst to form a new carbon-carbon bonds using an aryl-halide and an alkene, an organo-zinc reagent and a boronic acid respectively. Other cross-coupling methodology is also available using alkynes and copper^[22], organo-

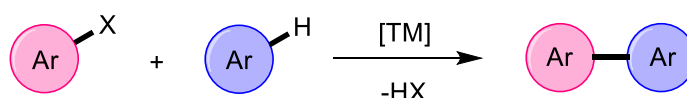
tin reagents^[23] and organo-magnesium reagents,^[24] amongst others. Typically, cross-coupling reactions involve the use of two 'pre-activated' reagents which usually take the form of an organo-halide with an organo-metallic reagent (**Figure I6**). Although high selectivity and high yields are obtained *via* these conventional methods, they suffer from some inherent drawbacks. The need to pre-functionalise both cross-coupling partners often results in the synthesis of non-commercially available reagents which leads to inefficiencies in time, cost, waste and atom economy. Additionally, unfavourable quantities of stoichiometric metallic waste formed during the coupling reaction and the evolution of inevitable by-products leads to further post-reaction inefficiencies.

Figure I6. Methodologies for aryl-aryl bond formation.

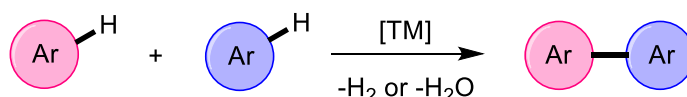
Traditional Cross-Coupling



Single C-H Activation Direct Arylation



Double C-H Activation Direct Arylation



X = halide or pseudohalide, Y = B(OR)₃ (Suzuki), ZnXR (Negishi), SnR₃ (Stille), TM = transition metal catalyst.

3.1 Direct Arylation

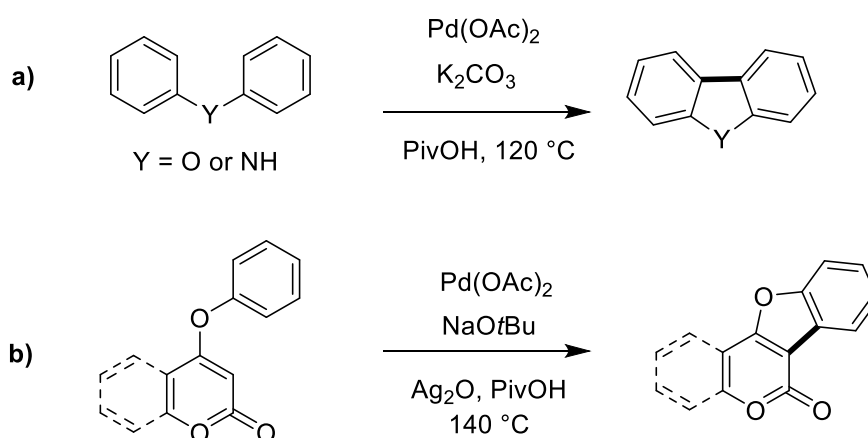
To address the associated issues with traditional cross coupling, in more recent years, focus has been shifted towards coupling that involves just one or *no* pre-functionalised aryl partners (**Figure I6**). This is termed single or double direct arylation respectively. Direct arylation involves both a C–H activation and a C–H functionalisation step to form the new carbon-carbon bond. Usually, C–H activation is the mechanistic step associated with the breaking of the C–H bond (and subsequent formation of the new C–Pd bond). The term C–H functionalisation is the overall exchange of a H (C–H) with a new group (C–R). Due to direct arylation protocols that avoid the installation of activating groups, the quantity of associated waste is reduced.^[25] The development of novel direct arylation

methodologies are on the 'Wanted List' of top pharmaceutical companies for the formation of new molecular entities.^[26]

The most atom-economical direct arylation method is termed double C–H activation and ideally the waste products are typically H₂ or H₂O. This methodology is advantageous due to reduction of by-product formation and low number of reaction steps. However, double C–H activation can be difficult to achieve for a variety of reasons such as poor selectivity (due to multiple C–H bonds having similar bond dissociation energies) and the inherent chemical inertness of many C–H bonds (due to low polarisability).^[27]

Relevant to the structures in this work, in 2008, Fagnou and co-workers published the synthesis of dibenzofurans and carbazoles *via* double C–H activation of diarylethers and diarylamines (**Scheme I2, a**).^[28] The McGlacken group developed a route to polycyclic pyrones and coumarins by intramolecular double C–H coupling of phenoxy-substituted substrates (**Scheme I2, b**).^[29]

Scheme I2. Palladium-catalysed intramolecular double C–H activation direct arylation a) Fagnou, 2008^[28]
b) McGlacken, 2016.^[29]

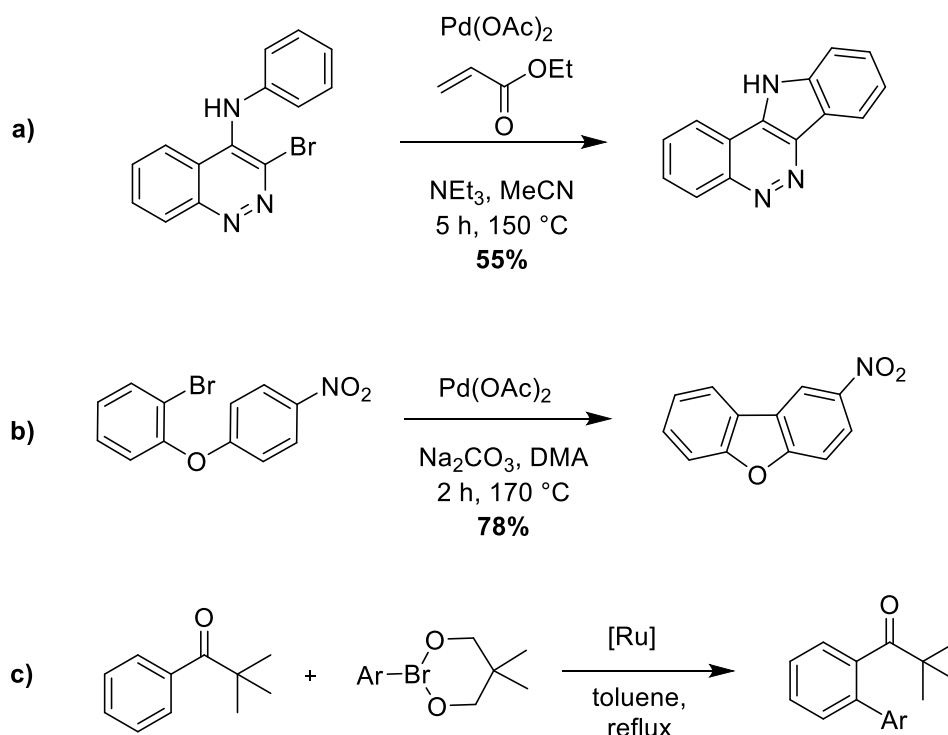


In order to achieve a greater library of direct arylation compounds, a chemical compromise is made in the form of single C–H activation methodology. In this case, one precursor is pre-functionalised (usually with a halide) which is still more environmentally benign than traditional cross-coupling techniques with the added benefit of having more control over reaction selectivity than double C–H activation.

An early example of particular structural relevance to this work is the findings by Ames and co-workers first published in 1982.^[30] Ames and co-workers described an unexpected side reaction when attempting to undertake a Heck reaction with bromocinnolines.^[30–31] They uncovered the formation of a direct arylation product instead of the anticipated Heck product to afford the formation of a 5-membered ring (**Scheme**

I3, a). A second report by Ames and co-workers in 1983 describes the direct arylation of diphenylethers to form dibenzofuran motifs *via* direct arylation (**Scheme I3, b**). Miura and Chatani, in 2003, published an intermolecular ruthenium-catalysed ortho-arylation of aromatic ketones with arylboronates which represented the first example of the catalytic coupling of C–H bonds with organometallic reagents *via* oxidative addition.^[32]

Scheme I3. Palladium-catalysed intra/inter-molecular direct arylation by Ames and coworkers. a) Ames, 1982.^[30] b) Ames, 1983.^[31a] c) Miura and Chatani, 2003.^[32]



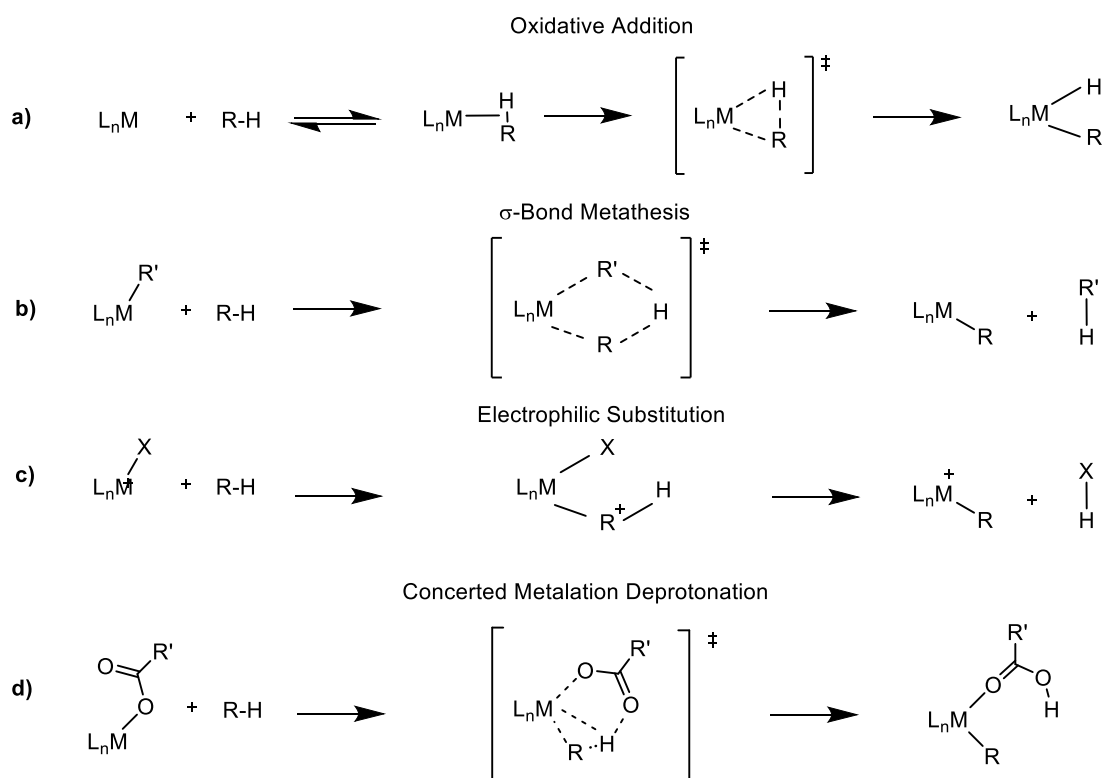
3.2 Direct Arylation Mechanism

Customarily, three unique mechanisms are mainly considered for C–H bond activations, specifically, a) oxidative addition with late transition metals, b) σ -bond metathesis with early transition metals, c) electrophilic aromatic substitution (S_EAr), and d) concerted metalation deprotonation (when carboxylate/carbonate base is present) (**Scheme I4**).^[33]

The mechanism can change depending on the substrate, solvent, base, ligand and additive. It was initially speculated that a S_EAr mechanism was followed when a carbonate/carboxylate base was used. However, much computational and mechanistic work has been undertaken which led to a proposed alternate Concerted Metalation Deprotonation (CMD) mechanism is at play.^[25a, 33d, 34] Typically, S_EAr mechanisms require electron rich aryls to undergo reaction, however it was noted by Fagnou^[35] and Echavarren^[34a] independently that, C–H bond functionalisation was not significantly affected by the electronic nature of the substrate, which is uncharacteristic of a S_EAr

pathway. This suggested to them that an alternative mechanism is possible that does not rely on electron rich aryls. In fact, Fagnou subjected an electron rich and an electron poor substrate to his reaction conditions and found that the electron rich substrate was marginally more favoured.^[35] The same selectivity was observed by Echavarren which indicates a possible alternative mechanism is followed. A larger bias toward electron poor substrates would be expected in the case of an S_EAr mechanism (**Figure I7**).^[34a, 36]

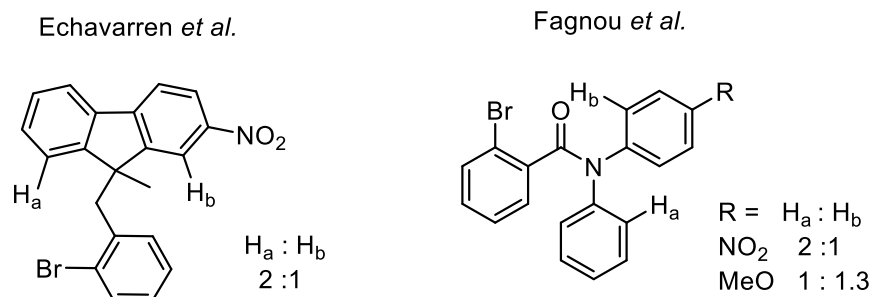
Scheme I4. Proposed C–H bond metalation mechanisms (adapted from Ackermann, 2011).^[33e]



Large Kinetic Isotope Effects (KIEs) that were also obtained from intramolecular competition experiments indicated that the C–H bond cleavage step is kinetically significant. This is in support of the CMD mechanism as breaking of the C–H bond is not part of the rate determining step for S_EAr mediated reactions. The rate determining step of S_EAr is the formation of the palladium-substrate σ -complex which is not significantly affected by the hydrogen/deuterium atom involved. The cleavage of the C–H or C–D bond in the CMD mechanism, however, is directly involved in the rate determining step. These factors lead to an alternative, concerted metalation deprotonation mechanism to be proposed which has since been confirmed using computational and other methods (**Scheme I4, d**).^[28, 33d, 34b, 34c, 35, 36b, 37] It was suspected and then computationally affirmed that the carbonate or carboxylate base plays a vital role in the mechanism.^[33d] As can be seen in **Scheme I4, d**, a 6-membered intermediate was elucidated as part of the CMD step in which the base plays a fundamental role. As the name suggests, there is a

concerted step in which the carbonate/carboxylate base deprotonates the C–H proton while, concurrently, the palladium is metalating to the C–H carbon. This, in effect, cleaves the C–H bond to form a new C–Pd bond which can then undergo functionalisation to product.

Figure I7. Competition experiments between electron-poor and electron-rich aryls.



4 One-Pot Reactions

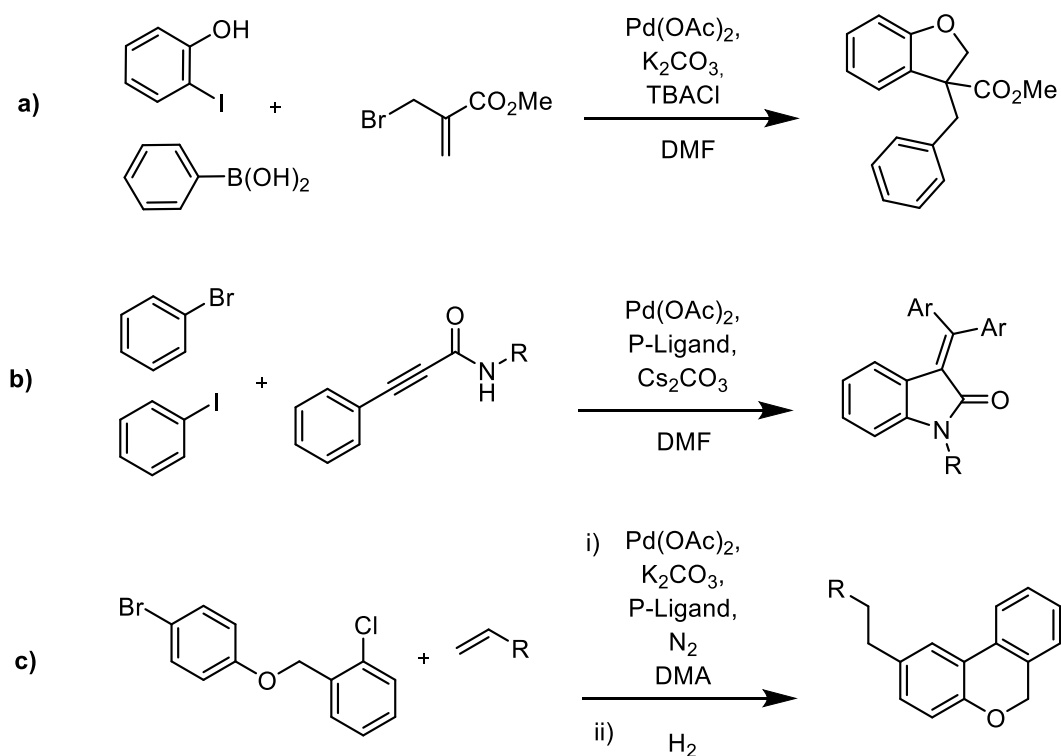
A one-pot reaction is a reaction sequence in which all reagents are input into a single reaction vessel and undergo a series of reaction steps to produce the target compound. One-pot reactions are an efficient and environmentally economical processes that can be used to make biologically important scaffolds for the pharmaceutical and fine chemicals industry.^[38] This ‘all-in-one-pot’ methodology reduces the amount of labour involved, reduces interaction with harmful intermediates, reduces the quantity of waste produced, reduces the cost involved in the production of the compound and the amount of time it takes to get the product.^[39] As idealistic as it sounds, achieving a one-pot synergistic process has some major challenges and is therefore not applicable to all processes.

Designing these methodologies such that there is reagent, solvent, temperature and by-product compatibility can be a huge roadblock in terms of developing reaction cohesion and appreciable yields. Use of catalysts can be an added challenge as the dynamic nature of the catalyst can have either a promoting or deleterious effect on subsequent reactions and by-products.^[40]

Of particular relevance to this thesis are one-pot process that involve the use of a single pre-catalyst that ultimately catalyses more than two mechanistically distinct reaction steps. There are some examples of catalysts that catalyse more than two steps in a one-pot synthesis. In one case, Lamaty and co-workers undertake a allylation/carbopalladation/Suzuki cross-coupling using a palladium catalyst, iodophenol, bromo acrylate and a boronic acid (**Scheme I5, a**).^[41] Zhu and coworkers demonstrate a intermolecular *N*-arylation/intermolecular carbopalladation/C–H activation/C–C bond

formation sequence using a palladium catalyst that undergoes three distinct catalytic pathways (**Scheme I5, b**).^[42] The most relevant example to this work is the one-pot Mizoroki-Heck/direct arylation/hydrogenation sequence undertaken by Fagnou and co-workers in 2006 using a single palladium pre-catalyst.^[43] He describes the formation of a benzochromene using palladium acetate, potassium carbonate, a phosphine ligand, degassed dimethylacetamide under nitrogen atmosphere. The mixture is let stir at 130 °C for 24 hours which is then followed by insertion of a hydrogen balloon to facilitate the third step in the sequence. Fagnou's work serves as the state-of-the-art for the one-pot sequence we propose for the work in this thesis (**Scheme I5, c**). The work described in **Chapter 2** of this thesis focuses on a one-pot Mizoroki-Heck/direct arylation/hydrogenation sequence for the construction of biologically important benzofuroquinolines. This work develops upon the work previously undertaken in the group (see above) and the work of Fagnou and co-workers in 2006.^[2-3, 43]

Scheme I5. Examples of Pd-catalysed one-pot reactions with three distinct catalytic steps.



4.1 Ligand-Free One-Pot Reactions

Typically, palladium catalysed cross couplings use phosphorus-based ligands to aid the catalytic cycle. In 'ligand free' systems, deactivation of Pd(0) generally occurs by the formation of palladium aggregates, often termed palladium black. The phosphine ligands aid in keeping the palladium in the desired oxidation state, help stabilise palladium species, alter catalyst reactivity and are useful in aiding ligation/de-ligation of the

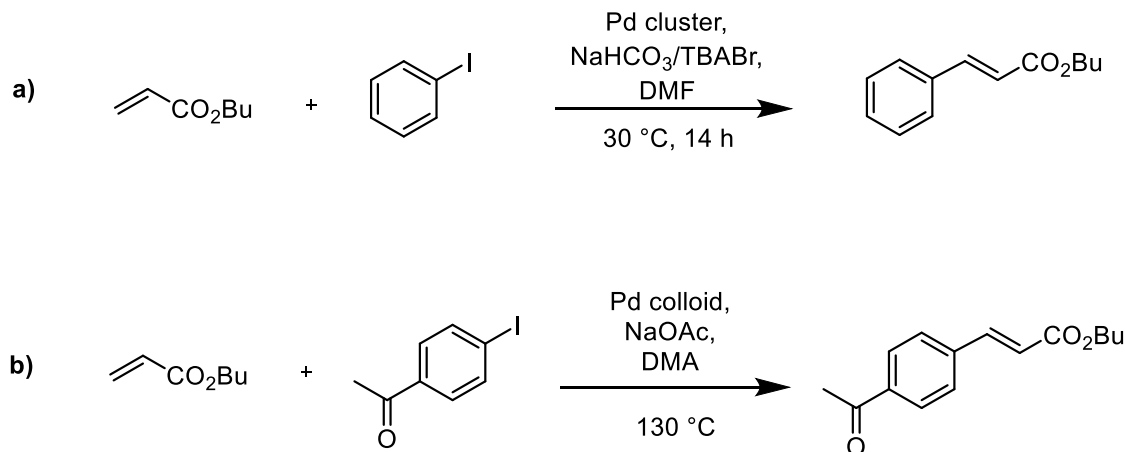
substrates/products.^[19c] Phosphine ligands, however, can be expensive and sensitive to air, and difficult to separate from products, therefore many protocols are being developed to circumvent the need for these added ligands.^[44]

Pioneering ligand-free conditions were developed by Jeffery and co-workers upon discovery that tetraalkylammonium salts could be used in replacement for phosphine ligands.^[45] It is thought that the ammonium salts work well in these reactions because; i) they have solid-liquid phase-transfer properties and can aid in solubilising solid salts such as sodium or potassium acetates which are scarcely soluble in many solvents, ii) they can act as a liquid-liquid phase-transfer agent for reactions in which one substrate may be soluble and another not, iii) the halide or acetate counter-ion in the salt can be promoters to increase the rates of some catalytic steps such as oxidative addition,^[46] iv) it can act as a stabilising additive to increase the lifetime of under-ligated Pd(0) species. This aspect is crucial for phosphine-free systems. Jeffery and co-workers speculated that the quaternary ammonium salts act as palladium stabilisers which can form *in situ* generated nanoparticles when using palladium acetate as pre-catalyst. The quaternary ammonium salt stabilised nanoparticles prevent the metal from aggregating which encourages reaction turnover. Such is the importance of this finding of this application of quaternary ammonium salts, much literature on the Heck reaction refer to these conditions as 'Jeffery conditions'.

Due to the emergence of new technology, Reetz and Maase and co-workers demonstrated *via* experimentation with *in situ* transmission electron spectroscopy (TEM) the spontaneous formation of tetraoctylammonium acetate stabilised palladium nanoparticles from palladium acetate, as Jeffery had speculated years previously.^[47] It was reported that they had a mean diameter of 2.0 nm to 2.5 nm. They also investigated their Heck reaction using styrene and bromobenzene with a palladium pre-catalyst, sodium acetate as base and NMP as solvent. It is known that the coordinating solvent (NMP) can help form Pd nanoparticles, which is speculated to aid the one-pot methodologies previously reported from the McGlacken group, as mentioned above.^[2-3, 47d, 48] Reetz and co-workers took periodic samples of the aforementioned reaction mixture and found the presence of palladium nanoparticles.^[47c, 49] Similarly, they studied Jeffery's conditions for the presence of palladium nanoparticles formed during the reaction of ethyl acrylate, iodobenzene, sodium acetate and a tetrabutylammonium bromide salt with a palladium catalyst in DMF. Nanoparticles of average diameter 1.6 nm were detected which is in agreement with known literature that chemical reduction of transition metal salts in the presence of ammonium salts leads to stabilised colloids.^[49-50] Reetz and Beller have also independently demonstrated that pre-formed quaternary

ammonium salt stabilised colloids are catalytically active in cross-coupling reactions (**Scheme I6**).^[51]

Scheme I6. a) Reetz^[51a] and b) Beller^[51b] demonstrating quaternary ammonium palladium colloids used in cross coupling reactions.

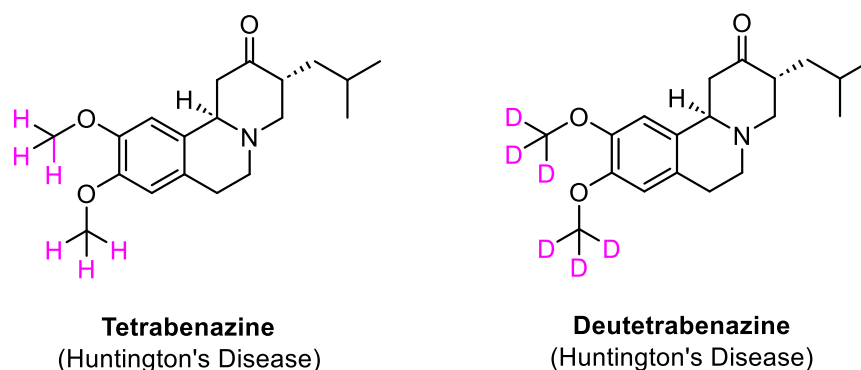


5 Deuterium in Medicinal Compounds

An additional neutron in a hydrogen atom forms its heavier isotope, deuterium. Despite this subtle structural modification, it is known that exchanging a hydrogen for a deuterium atom in drugs induces effects in pharmacokinetics, pharmacodynamics, solubility and toxicity profiles of deuterated drugs as compared to their non-deuterated analogues.^[52]

Bioisosteres are chemical substituents or groups with similar physical or chemical properties which produce broadly similar biological properties in the same chemical compound. Introducing deuterium in place of hydrogen is one of the simplest examples of a bioisostere. The inclusion of deuterium into market drugs has flourished in recent years since the first FDA approved deuterated drug, deutetrabenazine was approved for Huntington's disease in 2017 (**Figure I8**).^[53] This deuterated analogue of tetrabenazine demonstrated a far superior pharmacokinetic profile which allowed a significant reduction in both dose and dosing frequency, highlighting the difference that bioisosteres can impart.^[53] It was noted that tetrabenazine resulted in the reduction of serotonin production in patients, therefore its administration was highly restricted. Tetrabenazine is also metabolised rapidly to an inactive metabolite which resulted in the need for frequent drug administration and higher doses required. Deutetrabenazine incorporates deuterium at the metabolic 'soft spots' and therefore the drug is metabolised more slowly which increased patients to more active drug. This allows for lower dose drugs to be administered less frequently.^[54]

Figure 18. Structure of tetrabenazine and deutetabenazine.



The two isotopes are often very similar in terms of physiochemical properties with deuterium displaying a lower lipophilicity ($\Delta \log P_{\text{oct}} -0.006$), different pK_a values (can be higher or lower compound dependant) and C–D bond length being shorter than that of C–H by 0.005 Å. The greatest difference is the increase weight of deuterium which causes a reduced vibrational frequency compared to that of C–H. This results in a greater activation energy of the C–D bond, and hence slower cleavage, resulting it in being more stable than a C–H bond.^[55] This effect is described by the deuterium Kinetic Isotope Effect (KIE, k_H/k_D).^[56] KIEs can be capitalised upon by chemists to improve overall drug profiles due to the associated slower rate of bond cleavage caused by the heavier isotope.

Deuteration has become a very useful tool for researchers in the drug discovery process.^[57] Deuterium is a stable isotope which allows for it to be incorporated into drugs and compounds without any special handling. Its mass can be differentiated from hydrogen by mass spectrometry which allows it to be used to identify, monitor and comprehend biological and chemical processes.^[58] Deuterated compounds can be used to understand the metabolic pathway of the respective compounds by being able to track the isotope in biological systems. As it is a safe isotope for humans, this is a useful tool for medicinal chemists to exploit.^[59]

More than half of all drugs on the market are metabolised by CYP450 enzymes.^[60] Metabolism by this pathway is associated with many drawbacks such as formation of unstable or toxic metabolites or saturation of the enzyme which can lead to harmful drug-drug interactions. Therefore, an approach undertaken by medicinal chemists is the replacement of more labile hydrogen with deuterium which, based on the KIE, can mitigate the P450 metabolism and diminish its disadvantages when replaced at a C–H cleavage site.^[61] It is noted, however, that blocking a natural metabolic pathway may

induce 'metabolic switching' in which a different pathway is induced which may also result in undesired side-effects.^[62]

Thus, although the use of deuterium in drugs appears promising and has an exciting future ahead, it does present some shortcomings. Although the difference in lipophilicity between hydrogen and deuterium atoms is negligible, when multiple deuterium atoms are present the additive effect might lead to significant lipophilicity differences and rate of absorbances.^[63] It is also challenging to add deuterium selectively to target sites in molecules as it is possible that there are many C–H bonds with similar reactivity. Additionally, the extent of deuteration can also be a difficult challenge to overcome as achieving high deuterium incorporation can be difficult. It is typically desirable for the site to contain a high deuterium level incorporation (>98%).^[57] However, with the emergence of more and more deuterated precursors and starting materials available for purchase, in addition to novel methodologies to incorporate deuterium, the importance of new deuterated drugs can be explored more easily and rapidly than ever before. Work developed in this thesis demonstrates the incorporation of deuterium into molecules of interest to the pharmaceutical and fine chemicals industry. High levels of deuterium are incorporated in conjunction with novel methodologies to achieve these deuterated structures.

6 'Escaping from Flatland'

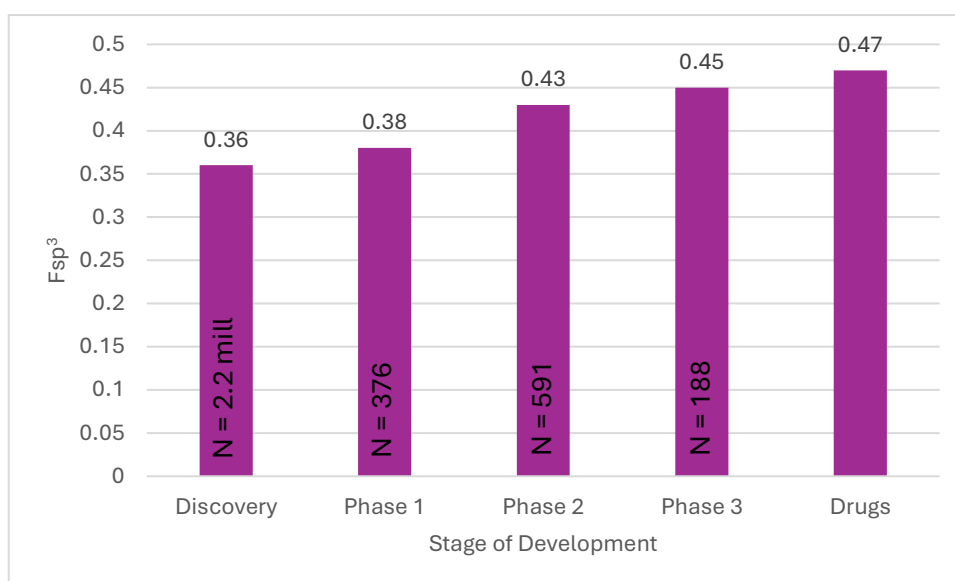
The pharmaceutical industry is facing many challenges currently, and one is the attrition rates of discovery compounds in clinical trials.^[64] Although access to more drug candidates has been facilitated through cross-coupling type of reactions, clinical success of new drugs has not risen in response.^[64-65] Pioneering work by Lovering and co-workers in 2009 endeavoured to determine the relationship between the level of saturation in a drug molecule and its success through clinical trials.^[66] Since the early 2000's, diversity oriented synthesis has emerged with the purpose to build more diverse and architecturally more complex drug candidates.^[67] These compounds will be more natural product-like and/or more amenable to exploring further into and impacting different areas of chemical and biological space.

Lovering and co-workers acknowledge that Lipinski's rule of five, and other more modern molecule descriptors such as polar surface area and number of rotatable bonds, are also important when designing and characterising a successful drug candidate.^[68] However, they noted that the level of complexity of a molecule is not captured by these criteria in terms of saturation and chiral centres. To quantify the level of complexity in a molecule by means of saturation, they devised a descriptor called 'fractional sp^3 character' which

was the number of sp^3 hybridised carbons over the total number of carbons in the molecule (F_{sp^3} = number sp^3 carbons / total number of carbons).

They analysed the data from the GVK BIO database and dictated that the clinical phase reported for a compound is the highest phase the compound reached.^[66] They found a positive correlation between the level of complexity (level of saturation and presence of chiral centres) and the success of a compound progressing from drug discovery phase to clinical trials to drugs with the average F_{sp^3} of drug candidates of 0.47 (**Figure I9**).

Figure I9. Graph adapted from Lovering, 2009 showing relationship between drug candidate F_{sp^3} character and their progress through clinical trials.^[66]



In a subsequent follow-up paper in 2013, Lovering investigated the level of F_{sp^3} character and off-target effects.^[69] This is an important angle to address, as toxicity is the main cause for failure of drug candidates to progress through clinical trials.^[70] Lovering subjects discovery compounds at Pfizer to a panel of biological assays to analyse and polypharmacology or off-target activity. The analysis suggested that the three-dimensionality that complexity imparts may result in less toxicity as it better complements the spatial subtleties of target proteins due to higher selectivity. It was found that increased complexity led to both a reduction in promiscuity and inhibition of cytochrome P450 enzymes. This is in agreement with a study by Greene and Wang which states that molecules with higher specificity and selectivity are expected to demonstrate lower toxicity due to them having less off-target activity.^[71]

Due to their unique properties and stability, aromatic compounds have been the focus of a rich area of research for pharmaceutical drug design. Commonly, the formation of extended aromatic systems is executed through the use of well-established cross-coupling reactions such as Sonogashira, Suzuki-Miyaura, Mizoroki-Heck reactions and

many more.^[72] Although access to more drug candidates has been facilitated through these type of reactions, clinical success of new drugs has not risen in response.^[64-65] The synthesis of saturated (hetero)aromatic ring systems is not trivial as evidenced by the ten-fold reduction of fractional sp^3 character of drugs from 1959 and 2009.^[73] This aligns with the emergence with cross-coupling reactions to form planar compounds.

6.1 Aromatic Ring-Count

In a complimentary study to Loverings work, Ritchie and co-workers in 2009 discussed the detrimental effect of high aromatic ring count in successful drug design.^[74] The outcome of the study revealed that oral drug candidates with fewer aromatic rings had a higher probability to be developed into drugs and, in addition, greater than three aromatic rings in a candidate was associated with poorer developability and therefore, greater attrition in development. The study also addressed the effect of aromatic ring count on parameters such as LogP, solubility and cytochrome inhibition (**Figure I10**).

Figure I10. A summary of the data from Ritchie and co-workers study, 2009.^[74] Green shading represents increased developability, and red shading represents decreased developability.

Number of aromatic rings	1	2	3	4	5
clogP	1.9	2.9	3.7	4.4	5.1
LogD _{7.4}	1.3	2.1	2.4	2.7	2.9
Serum albumin binding (%)	78	88	93	96	96
Aqueous solubility (ug/ml)	100	79	57	36	28
P450 3A4 inhibition (pIC ₅₀)	4.7	4.9	5.2	5.4	5.6
hERG inhibition (pIC ₅₀)	5.2	5.6	5.7	5.7	5.5

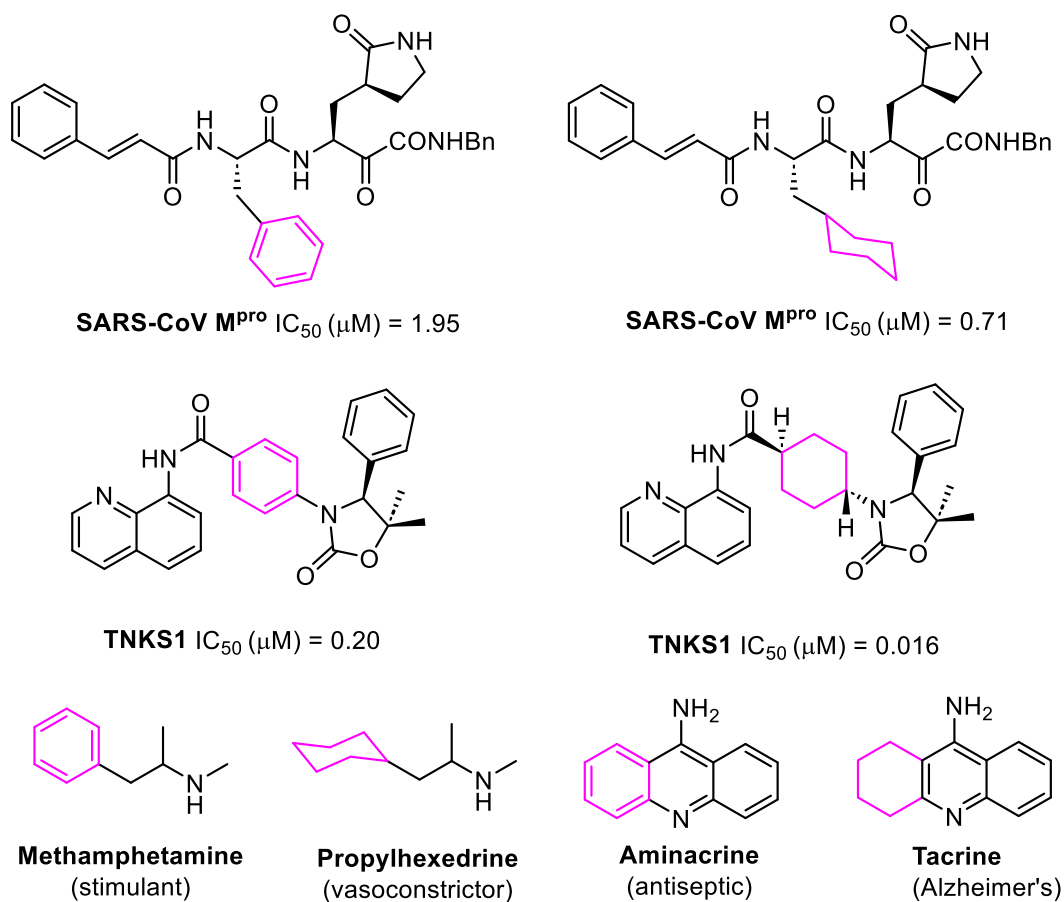
Expanding upon this study, Ritchie and co-workers undertook a second study that gave further insights into aromatic rings in compound developability by addressing rings as carbocycles and heterocycles.^[75] The study showed that aromatic carbocycles were more detrimental to compound developability than heteroaromatics and concluded that is more advisable not only to limit the number of overall aromatic rings in a molecule but also to replace aromatic carbocycles with heterocyclic congeners where possible.

For these reasons, it is important to introduce more complexity into compounds quantified by increased saturation and limiting the number of aromatic substituents in drug candidates. Developing new methodologies that allows for the inclusion of these features at a 'late-stage' is vital for the continued success of diverse clinical candidates. A potentially facile way to incorporate more sp^3 character into (hetero)cyclic systems is through hydrogenation. By breaking the aromaticity of the molecule through hydrogenation, more complexity is added without a significant increase in molecular weight.

6.2 Late-Stage Functionalisation

A recent study by Glorius and colleagues addresses the dramatic difference in activity that non-planar compounds express relative to their planar congeners and describes the 'late-stage' saturation of drug molecules.^[76] Highlighting the difference a small structural change can make, the aliphatic cyclohexane SARS-CoV M^{pro} inhibitor is more than twice as active as its aromatic congener (**Figure I11**).^[77] Similarly, differing saturation between TNKS1 congener inhibitors displayed differing potencies.^[78]

Figure I11. Examples of how saturation can improve drug activity and the application of the drug.



Additionally, many on-market drugs have a similar congener with some saturated ring systems, that display very different medicinal applications. As examples, methamphetamine is a controlled substance due to its stimulant properties, while its non-aromatic analogue, propylhexedrine, is a topical medicine for vasoconstriction.^[79] The topical antiseptic, aminacrine has a partially saturated analogue, tacrine, which is an approved medicine to treat Alzheimer's disease (**Figure I11**).^[80] As mentioned previously, there are various problems associated with a high level of aromaticity in compounds, including poor solubility in aqueous media, high lipophilicity and decreased protein

binding.^[74-75] Therefore, it is imperative that more work is carried out towards the development of protocols for the synthesis of saturated compounds. Some of the work outlined in this thesis addresses this facet of chemistry through 'late-stage' hydrogenation of planar aromatic compounds to give tetracyclic benzofuroquinoline scaffolds. The starting materials are easily accessed through well-established sp^2 - sp^2 bond forming chemistry.

7 Reduction of Aromatic Systems

The hydrogenation of aromatic compounds is a key transformation in organic synthesis that allows access to more structurally complex compounds. The first aromatic ring was hydrogenated in 1912 by Willstätter and Hatt^[81] and since then, a wealth of knowledge in the area of aromatic and heteroaromatic hydrogenations has been conducted, highlighted by numerous reviews in this area.^[7, 82] Synthesis of moderately complex aliphatic rings is often difficult and can be an inefficient process involving numerous steps.^[82f] It is for this reason that there is a high level of interest in developing new methodologies to access these type of structures in a more step-efficient fashion. Additionally, there are a vast number of structural permutations of aromatic substrates available due to highly efficient cross-coupling methodologies in the organic chemists arsenal.

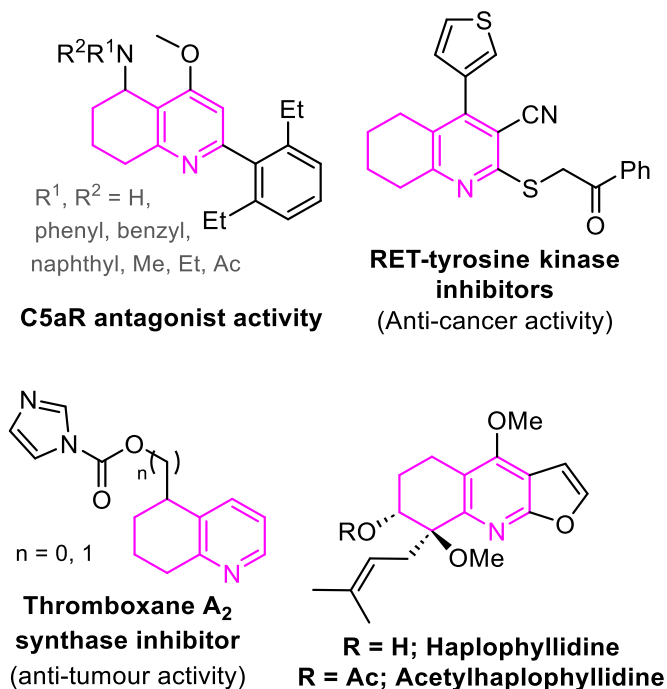
Due to the stability of aromatic compounds, usually harsh reaction conditions are required to overcome the kinetic barrier of hydrogenation due to the loss of aromaticity.^[83] Reported work in this area mainly focuses on metal catalysts (Pt,^[84] Ru,^[85] and Rh^[86]) and usually requires strongly acidic solvent, high pressures and/or high temperatures. Although homogeneous catalysts for hydrogenation reactions are reported,^[7] the main focus for this thesis is on heterogeneous catalysts. Homogeneous catalysts are advantageous in that they are specific, have a defined structure and can be used in very small quantities. Heterogeneous catalysts on the other hand are often cheaper, can be more easily removed from reaction mixtures, and are usually easier to handle. Palladium-on-carbon (Pd/C) is a commercially available heterogeneous catalyst with demonstrated hydrogenation abilities across numerous moieties and functional groups.^[87]

8 Hydrogenation of Quinoline

The reduced quinoline motif, tetrahydroquinoline, is a very common pharmacophore and is found in many biologically active natural products and pharmacologically relevant therapeutics.^[88] Reduction of quinoline can occur at the heterocycle, the carbocycle or at both these rings, to form decahydroquinoline.^[89] The importance of carbocycle reduction is highlighted by their many applications such as C5a receptor antagonist agents,^[90] RET

tyrosine kinase inhibitors,^[91] Thromboxane A₂ synthase inhibitors^[92] and natural products Haplophyllidine and Acetylhaplophyllidine (**Figure I12**)^[93] among others.

Figure I12. Partially hydrogenated quinolines in bioactive compounds and natural products.

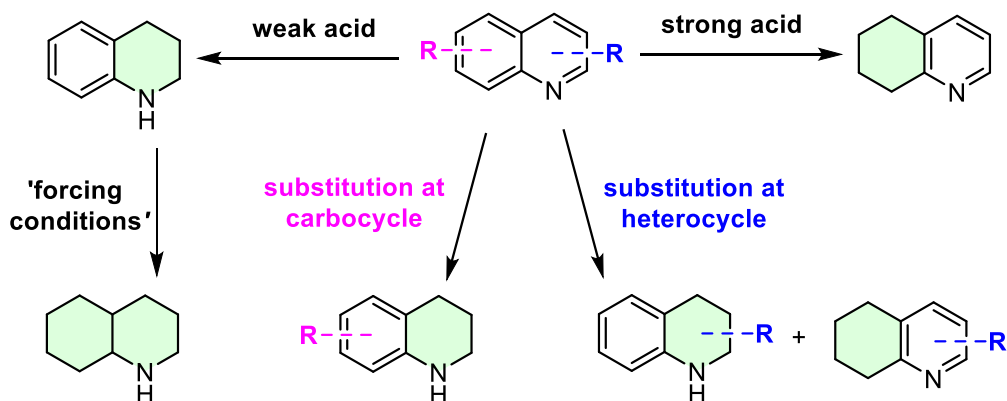


8.1 Selective Quinoline Reduction

As mentioned above, reduction of quinoline can occur at the heterocycle, the carbocycle or full reduction of both these rings to form decahydroquinoline.^[89] Finding conditions to selectively reduce the target ring without over reduction to undesired side-products is a difficult challenge. One might consider the difficulty of using a heterogenous catalyst to hydrogenate quinoline due to the availability of the nitrogen lone pair to bind to the catalytic surface and act as a poison.^[5] It is specifically for this reason that quinoline is added to catalysts such as Lindlar's catalyst to reduce the catalytically active surface sites.^[94] It is often for this purpose that acidic medium is used in the hydrogenation of nitrogen containing species in order to protonate the nitrogen and therefore block such undesired binding. Additionally, the protonated ring can then lay flat against the catalytic surface and may be more prone to hydrogenation.^[95] Hydrogenation of the heterocyclic ring is more prevalent in the literature and may be due to the reduced aromaticity of the pyridine ring.^[89, 96] In general, under weakly acidic conditions (e.g. AcOH), quinolines are reduced preferentially at the heterocyclic ring but if the reaction time is prolonged or more rigorous reaction conditions are used, both rings can become reduced (**Scheme I7**).^[5, 84f, 97] On the other hand, in strongly acidic pH, reduction of the carbocycle is induced.^[84a-e]

It is possible that increased protonation of the quinoline allows for this to happen, however the exact mechanism behind this observation is not yet elucidated.

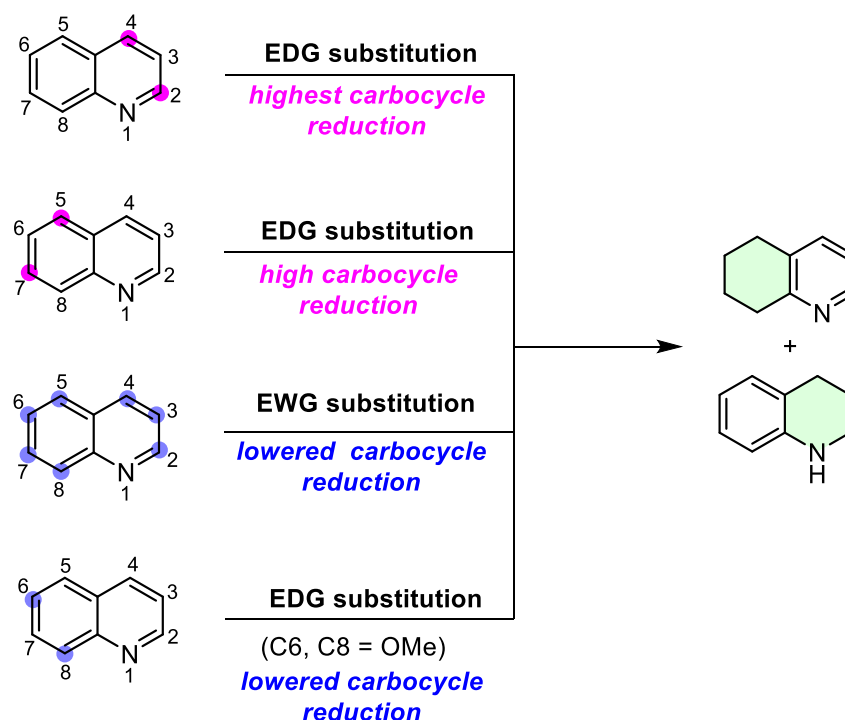
Scheme 17. General outline of the factors influencing product outcome for the hydrogenation of quinoline. Adapted from Lowrys thesis.^[98]



Canonical work by Vierhapper and Hönel investigated the effect of substitution patterns on the selectivity of quinoline hydrogenation.^[84c-e] The data they collected indicated that reduction is more favoured at the carbocycle when the quinoline nitrogen is more basic or, in other words, has more electron density. In addition, substitution at the carbocycle encouraged more heterocycle reduction, whereas substitution at the heterocycle encouraged more carbocycle reduction. This may be due to steric hinderance for hydrogenation at the substituted ring in addition to electronic effects.

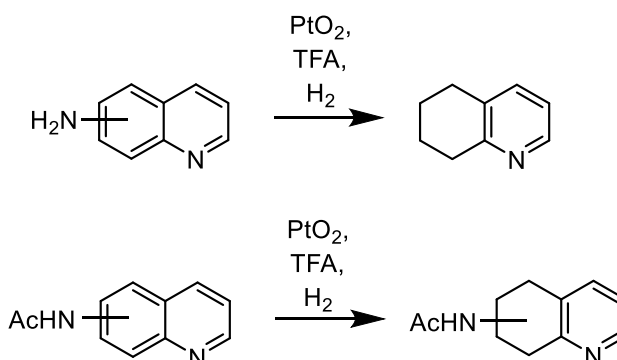
There were some outliers in terms of these trends. For example, in the presence of substituents on the C6 or C8 position, a reduction in the proportion of carbocyclic-reduced quinoline is observed. In the case of the electron donating methoxy group at C6, very little carbocycle was hydrogenated. Substitution at C6 with methyl, *tert*-butyl or *isopropyl* did not have a great effect on yield when compared to unsubstituted quinoline. Lower levels of carbocycle reduction were also observed for C8 methoxy substituted quinoline when compared to methyl, *tert*-butyl and *iso*-propyl groups. The strongly electron-withdrawing trifluoromethyl group reduces the amount of carbocycle reduction due to the withdrawal of electron density from the quinoline nitrogen. Electron donating group substitution at the quinoline C2, C4, C5 and C7 results in a large increase in basicity due to the resonance structures adding electron density to the quinoline nitrogen. Particularly, the presence of the electron-donating groups on the heterocyclic ring has a greater effect than those on the carbocycle. Therefore, substitution at the C2 and C4 positions has the greatest effect on the nitrogen basicity than C5 and C7 (**Figure I13**).^[99]

Figure I13. General quinoline substitution trends on the effect of hydrogenation selectivity.



Skupinska *et al.* also undertook selectivity investigations which complimented the work by Vierhapper and Hönel.^[84f] They also found that steric and electronic factors were at play in terms of selectivity. They reported that substitution on the heterocyclic ring of quinolines resulted in more carbocycle reduction, and that reduction of the carbocycle diminished upon substitution on the carbocycle. Electron donating groups on the heterocycle were reported to show complete selectivity for carbocycle reduction, whereas the presence of electron withdrawing groups on the heterocycle showed some formation of heterocycle reduction also. In this work they also found that hydrogenolysis of the amino group occurred under the reaction conditions resulting in an unsubstituted product (**Scheme I8**). To circumvent this issue, the amine was protected using an acetamido-group which was later removed post-hydrogenation to leave the amine intact.

Scheme I8. Hydrodeamination and protection with acetamido-group.^[84f]

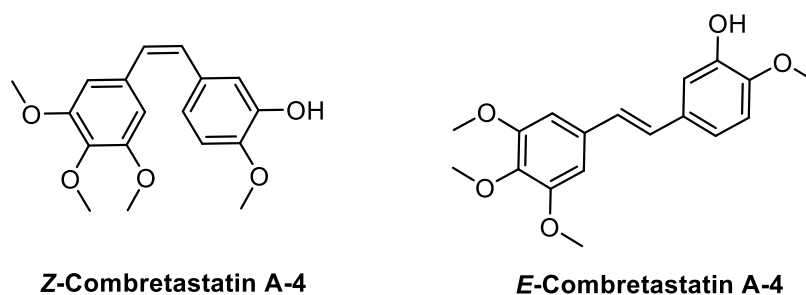


9 Partial-Hydrogenation

Partial-hydrogenation is a type of hydrogenation that, in our case, refers to reduction of alkynes to alkenes. This is a very useful transformation with many applications. The challenge in this instance is two-fold; i) accessing the alkene without over-hydrogenation to the alkane and ii) selectively forming the desired *Z*- or *E*-alkene isomer.^[100] As a vital transformation for the production of both bulk and fine chemicals, a selective-hydrogenation of alkynes methodology must balance catalytic and substrate activity versus chemo and stereoselectivity.^[8, 101] These selective hydrogenation reactions typically involve a heterogeneous catalyst, similar to most hydrogenations. It is for this reason that selective hydrogenation is not straightforward hydrogenation and specialist catalysts are often needed.

The isomeric form of an alkene, namely *Z*- and *E*-, is a significant factor in determining the biological activity of a molecule. For example, Combretastatin A-4 is a stilbene analogue that exhibits anti-cancer activity.^[102] In *Z*-configuration, the drug demonstrates nanomolar cytotoxicity. Conversely, the *E*-isomer of Combretastatin A-4 exhibits much lower potency and inhibits cell growth in the micromolar concentration (**Figure I14**).^[102b, 103] Stereoselective access to either isomer, therefore, is a key component of alkene synthesis.

Figure I14. Structure of *Z*-Combretastatin A-4 and *E*-Combretastatin A-4.

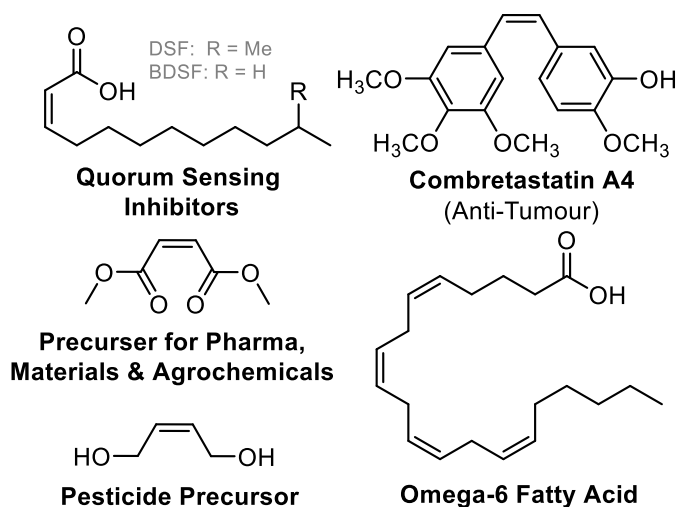


The *Z*-alkene moiety is ubiquitous in chemistry^[101-102, 104] and is present in both simple and complex molecules such as quorum sensing inhibitors^[105], prostaglandins^[106] and pharmaceutically relevant compounds (**Figure I15**).^[103, 107]

The current challenges are obtaining *Z*-alkenes with high stereo- and chemo-selectivity. The state-of-the-art in achieving these *Z*-alkenes, other than olefination-type chemistry, is the semi-hydrogenation of alkynes using a poisoned palladium catalyst such as Lindlar's catalyst.^[108] The Pd catalyst is treated with lead and quinoline which act as catalytic poisons^[94a, 109] to reduce the formation of the over-hydrogenated product. The

lead modifier slows the formation of hydrides and encourages the binding of the alkyne over the alkene (thermodynamic factor).^[94]

Figure I15. Examples of industrially relevant Z-alkenes.



Quinoline serves to be a binding competitor with the alkene to the palladium site *via* the nitrogen lone pair, hence reducing the amount of over-hydrogenation.^[94b] The requirement for both lead and quinoline as catalyst modifiers are drawbacks of this conventional catalytic system, in addition to batch variability,^[110] reproducibility^[111] and selectivity issues.^[94a, 109d] Several Pd catalyst design methods have been established to address some of these issues with Lindlar's catalyst. One strategy, is to form Pd nanocatalyst alloys with other metals,^[112] and/or alloys with light elements.^[113] Another is the formation of ordered Pd nanoparticles.^[100, 114]

10 Nanoparticles

Nanoparticles are very small materials (1 – 100 nm) which are often used as metallic catalysts.^[115] Working at the interface of homo- and heterogeneous catalysis, they have unique physical and chemical properties due to their small size and large surface area. Nanoparticles are suitable for many applications such as coatings, sensors, diagnostics, display technologies, energy storage and most applicable to this work, catalysis.^[115] Due to the many categories of nanoparticles available, this introduction will focus on ligand stabilised nanoparticles as catalysts in semi-hydrogenation reactions.

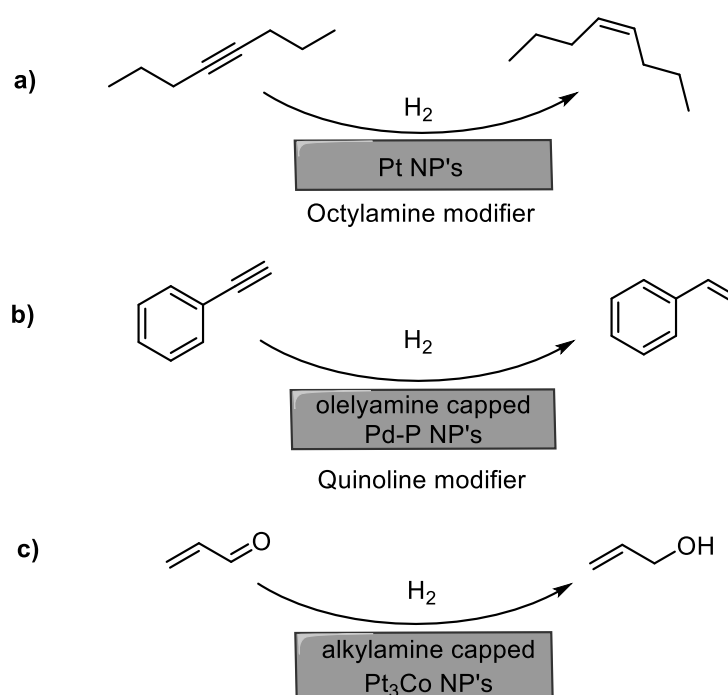
It has been known for some time that particle size is of paramount importance in catalysis.^[116] Nanoparticles afford a very large surface to volume ratio in addition to a large number of catalytically available surface atoms depending on particle size. Nanoparticles not bound to a solid support are said to be unsupported and can be stabilised by organic ligands.^[117] These ligand-capped nanoparticles can be dissolved or

suspended in a solvent, promoting even surface chemistry which encourages higher selectivity.^[118] The choice of capping ligand also has a decisive role in altering the chemical activity and selectivity of the catalytic process. The focus of this work is on thiol and amine-based ligand-stabilised palladium nanoparticles. There is some precedent in the literature for the use of these type of ligands to execute semi-hydrogenation reactions which is discussed in the subsequent paragraphs.^[100, 114]

10.1 Alkylamine Ligands

Alkylamine ligands have been used as additives/ligands to modify (semi)hydrogenation reactions (**Scheme I9**).^[119] Shevchenko and co-workers studied alkylamines as additives with Pt and CoPt₃ nanoparticles in the semi-hydrogenation of 4-octyne.^[120] They found that adding an octylamine ligand to the nanoparticle mixture increased the selectivity (80% Z-selectivity) of their hydrogenation for the alkene intermediate and minimised overreduction to the alkane. Zhao used oleylamine capped Pd nanoparticles in conjunction with a quinoline modifier to tune the reactivity of phenylacetylene to selectively form styrene with 93% selectivity for the alkene.^[121] A very low catalytic loading of 0.13 mol% was used. Wu and co-workers developed alkylamine capped platinum/cobalt nanoparticles to selectively hydrogenate an allyl aldehyde (acrolein) to an allyl alcohol.^[119c]

Scheme I9. Examples of literature precedent for the use of alkylamine ligands in semi-hydrogenation reactions. a) Shevchenko *et al.*, 2012,^[120b] b) Zhao, 2016,^[121] c) Wu *et al.*, 2012.^[119c]



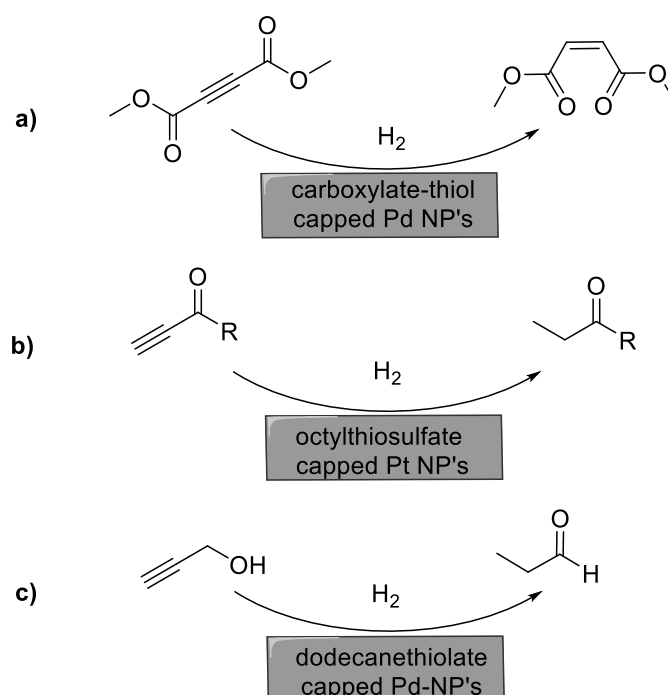
They used long chain amines and hypothesised that the long alkyl chains blocked the alkene from adsorbing to the catalyst surface, which provided the selectivity for this reaction. A low catalytic loading of 0.6 mol% was used and 95% selectivity was achieved.

10.2 Alkylthiol Ligands

The use of thiolate ligands in conjunction with palladium nanoparticles for hydrogenation reactions has been reported in the literature.^[113d, 119a, 119b, 122] The catalytic activity of thiolate-covered palladium is somewhat surprising as sulfur-containing species usually act as poisons to the palladium surface.^[123] In one particular case, Chen and co-workers installed carboxylate-thiol ligands into a palladium nanostructure for the semi-hydrogenation of dimethyl acetylenedicarboxylate (DMAD), on a graphene oxide support (**Scheme I10**).^[124] Good *Z:E* selectivity was reported, however, high catalytic loadings were used and over-hydrogenation to the alkane product was a significant issue. San *et al.* used octylthiosulfate as a capping ligand for platinum nanoparticles for the semi-hydrogenation of activated terminal alkynes.^[125]

Scheme I10. Examples of literature precedent for the use of thiol ligands in semi-hydrogenation reactions.

a) Chen *et al.*, 2017,^[124] b) San *et al.*, 2017,^[125] c) Gavia *et al.*, 2013.^[126]



Although conversions of up to 100% were achieved, a high catalytic loading of 5 mol% was required and their methodology was only applied to terminal alkynes. Gavia *et al.* described the use of palladium-dodecanethiolate nanoparticles to facilitate propargyl alcohol isomerisation to saturated carbonyl analogues.^[126] This transformation is facilitated by thermodynamically-driven isomerisation of the allyl alcohol product to the

more stable carbonyl form, thus preventing isolation of the desired alkene. It is possible that, overtime, dynamic surface restructuring occurs with sulfur-based nanoparticles. Ligands/substrates adsorb and desorb from the surface of the catalyst during the reaction period which has an effect on the reaction kinetics and product outcome.^[127] It is known that thiol adsorption to the reactive Pd surface can induce the C–S bond cleavage of alkylthiol adsorbates.^[128] The resulting sulfur atoms can partially passivate the palladium surface and can generate significant changes in the electronic properties of the metal.^[127e, 129] This changing of the nanoparticle surface can alter the reactivity of the nanoparticle over time.

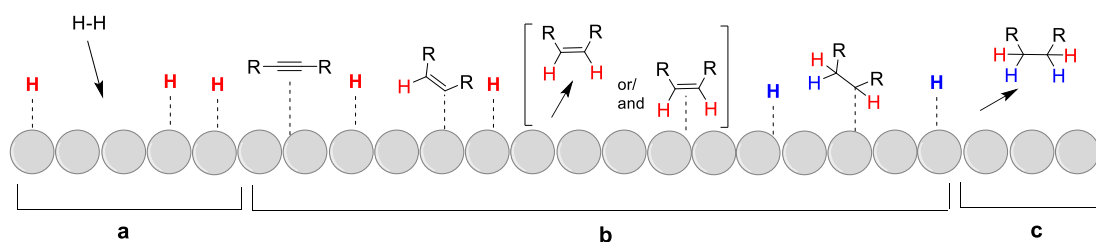
11 Semi-Hydrogenation Mechanism

The semi-hydrogenation of alkynes by nanoparticles follows the Horiuti-Polanyi mechanism, similar to as described above, except both the alkyne and alkene substrates compete for hydrogenation. One of the keys to a successful semi-hydrogenation set-up is to bias the catalyst towards alkyne adsorption and hydrogenation and for the alkene be free to leave the surface to prevent over-hydrogenation.^{[130] [131]}

Similar to as described at the beginning of the introduction, the first step of the mechanism is activation of dihydrogen which can be classified as homolytic dissociation and heterolytic cleavage.^[132] The homolytic dissociation of hydrogen gas generally occurs on the surface of group VIII group elements such as Pt^[133] and Pd.^[134] These metals can accommodate the s electrons from dihydrogen in their d orbitals. Back-bonding from these d-orbitals into σ -antibonding orbitals allows for the bonds in dihydrogen to homolytically cleave.^[135] It is a known phenomenon that hydrides can migrate below the surface atoms into the bulk layer and form a high-energy subsurface hydride. It is these hydrides that are known to contribute to over-hydrogenation products which is detrimental to selectivity.^[132, 136]

The alkyne then binds to the palladium metal surface and uptakes a hydrogen atom at C1 and forms a σ -bond with a palladium atom at C2. Then C2 can uptake a hydrogen atom to give an alkene. This alkene can then remain π -bonded to the palladium surface or dissociate from the surface. The alkene and alkyne can now be in competition for active sites on the metal surface. Subsequently, more alkyne substrate can bind to the surface and reduce to form the target alkene or the newly formed alkene can bind and reduce to form the over-hydrogenated alkane product (**Figure I16**).^[137] This is an example of where the competition for selectivity takes effect.^[100, 138] If the alkene stays bound to the surface or if it desorbs and then re-adsorbs, it can potentially over-hydrogenate to the alkane.

Figure I16. Mechanism for the semi-hydrogenation of alkynes. Section b is a reversible process.



11.1 Isomerisation and Deuteration

Isomerisation at the alkene can also occur as adsorption, desorption and readsorption can occur at the surface (**Figure I16, section b** and **Figure I17**). This sequence can cause exchange of hydrogen (or deuterium) atoms that are on the metal surface. The addition of the first hydrogen (or deuterium) atom to the alkene allows for free-rotation to occur due to the single-bond intermediate. The intermediate can then lose a hydrogen atom to reform the alkene but could now represent an alternative isomer. This process can be repeated a number of times which can result in poor selectivity and is reversible. In the case of deuterium gas, this reversibility can lead to multiple deuterium–hydrogen (D–H) exchanges which can result in higher or lower than expected deuterium incorporation (**Figure I18**).^[130-131]

Figure I17. Isomerisation of *Z*-alkene to *E*-alkene.

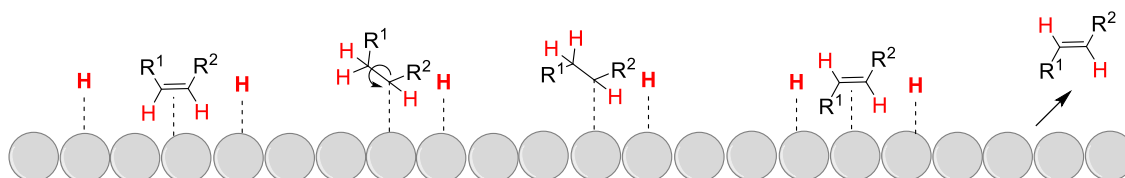
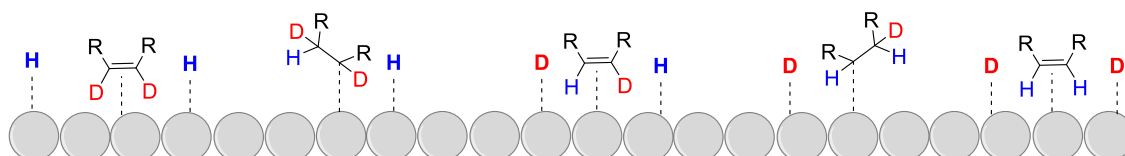


Figure I18. Deuterium-Hydrogen exchange mechanism.



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To learn is not to know; there are the learners and the learned.

Memory makes one, philosophy the others.

– *Alexandre Dumas, The Count of Monte Cristo*

The more you know, the more you know you don't know.

– *Aristotle*

Chapter 2

A phosphine free, inorganic base free, one-pot tandem Mizoroki-Heck olefination/ direct arylation/ hydrogenation sequence, to give multicyclic alkylated heteroarenes.

Preface

This chapter has been peer reviewed and is published in RSC Green Chemistry (DOI: 10.1039/d3gc01403g). I am first author on this publication, and I undertook drafting of the manuscript, assembly of the SI and most experimental work. Dr. Mark Light undertook all XRD analysis.

Abstract

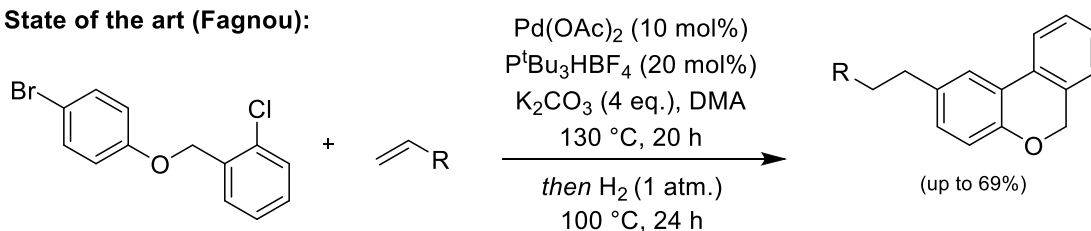
One-pot processes which facilitate a number of tandem reactions, represent an environmentally friendly approach to building molecular complexity. In addition, there are significant cost and time saving benefits. However, unearthing multiple reactions that display substrate, reagent and solvent compatibility across two or more reactions, is not straightforward. This is even more pronounced when using catalysts, which by their nature, are present in small amounts and thus susceptible to poisoning. Herein we describe a phosphine-free, inorganic base free, no added (inorganic) base, multi-step, one-pot reaction sequence which enables the rapid synthesis of complex, medically relevant heterocycles in excellent yields. This Pd-catalysed approach combines Heck olefination, C–H activation, and hydrogenation, and the same pre-catalyst is involved in the three mechanistically distinct processes. Quinolines as substrates are used in the main, but we also provide a neat extension to pyridines and simple aryl substrates. Deuterium (D₂) incorporation can be facilitated through use of the COware apparatus in the Heck step. Favourable mass productivity (MP), environmental impact factor (EF), solvent intensity (SI) and process mass intensity (PMI) values are reported. While the motivation to avoid problematic additives (inorganic base and P-ligands) and problematic solvent (DMA and NMP) was driven by a green agenda, the removal of reaction inputs in the context of one-pot strategies might also serve to reduce the bad actors and improve yields in one-pot processes.

Introduction

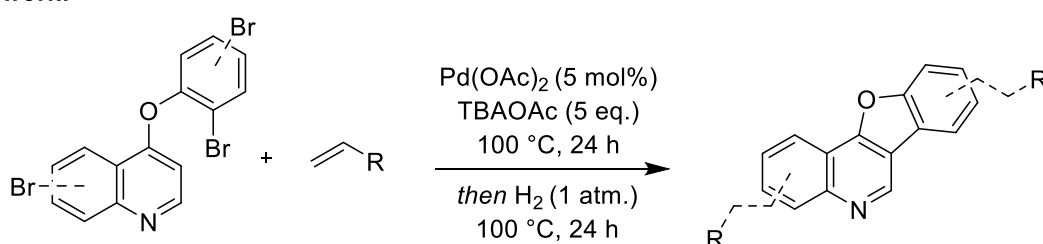
The design of one-pot, multi-step reaction sequences is highly desirable in the context of green organic synthesis, as molecular complexity is rapidly achieved, whilst avoiding wasteful isolation and purification of reaction intermediates.^[1] Achieving substrate, reagent and solvent compatibility across two or more reactions is not straightforward and, thus, unearthing multiple compatible reactions, which work together in a single medium, is very challenging. This problem is even more pronounced when considering transition metal-catalysed reactions, as catalytic performance can be dramatically influenced by the various reaction inputs and outputs. This presents a barrier to the

optimisation of multi-step, one-pot processes as the structure of the initial catalyst is not static, and changes over the course of one or more steps due to interactions with intermediates and by-products. Consequently, individual reaction optimisation is less applicable and due regard must be given to the potential role of other upstream or downstream reaction components. Auto-tandem catalysis is defined as a domino reaction process in which one catalyst promotes two or more fundamentally distinct chemical transformations in a single reactor.^[2] There has been tremendous progress in the development of Pd-catalysed auto-tandem processes, in a bid to develop greener synthetic methods. A key feature of this approach is that Pd acts as the catalyst in two sequential, one-pot reactions.^[3] Interestingly, extending this concept to the development of processes with three or more mechanistically distinct Pd-catalysed reactions has proven challenging and examples are sparse in the literature.^[4]

State of the art (Fagnou):



This work:



✓ No added phosphine ligand ✓ TBAOAc as base and reaction medium ✓ 21 examples (up to 83%)

Scheme 1 Comparison to previous work from a green perspective.

Fagnou and co-workers previously reported a rare example of a three-reaction process, wherein a series of benzochromenes were prepared in good yields (**Scheme 1**). While this exquisite example demonstrates the power of auto-tandem catalysis, there is clear potential for further green chemistry improvement and expansion.

Quinolines, pyridines and furans represent important molecule classes in medicinal and natural product chemistry.^[5] Core quinoline, pyridine and furan motifs are the 22nd, 2nd and 25th most abundant of the 351 ring systems present in FDA-approved drugs respectively.^[6] Direct arylation *via* C—H activation of these moieties has received significant attention in recent years, as the protocol avoids the introduction of activating groups, and the associated waste. Direct arylation *via* C—H activation also facilitates the introduction of new aryl groups which could be difficult using traditional (Het)Ar-(Het)Ar

bond forming processes such as the Suzuki-Miyaura and Stille reactions.^[7] This is especially the case with intramolecular reactions, where the installation of halides and boronic acids (or stannanes) onto a single substrate is often difficult.

We posited that intramolecular direct arylation of quinolines could be coupled with a Mizoroki-Heck alkenylation and a hydrogenation in a one-pot sequence to give decorated tri- and tetra-cyclic quinolines with a built-in benzofuran. However, we were also aware that the quinoline nitrogen atom can ligate Pd^[8a] and thus effect a synergistic or deleterious effect on any of the three Pd-mediated process.^[8] In any case, we were keen to apply a 'bottom-up' green chemistry approach to develop tricyclic alkylated heterocycles, bearing key functionalities relevant to medicinal chemistry.

We set ourselves the specific challenges of **1)** minimising catalyst loading **2)** eliminating the need for a P-ligand **3)** avoiding the use of toxic solvents such as DMA and NMP and **4)** carrying out the reactions in air. Herein we describe the successful execution of these goals (**Scheme 1**). We expand the substrate scope from quinolinyl to pyridinyl and simple aryl ethers. Also, for the first time in these types of processes, we introduce deuterium *via* reduction of the Heck products using the COware apparatus (which circumvents the difficulty in accessing D₂ gas). Finally, some initial investigation of the catalytic species required for each step is presented.

Results and Discussion

Optimisation Study

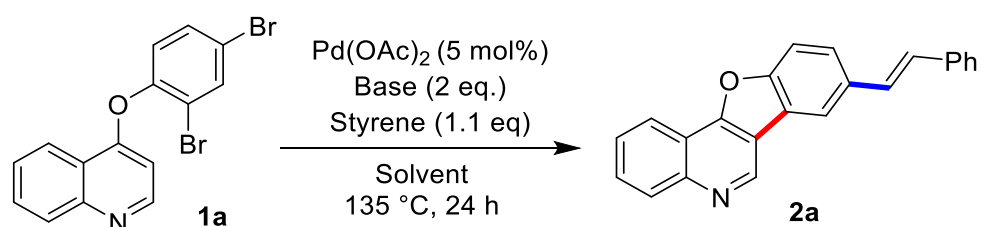
A one-pot method is previously described in our group forming benzofuroquinoline products by a two-step Mizoroki-Heck/ direct arylation reaction in *N*-methylpyrrolidone (NMP) as solvent.^[8c, 9] We first determined whether the previously reported conditions supported the hydrogenation of the resultant alkene from the Mizoroki-Heck step. After successfully determining that the reduction of the alkene was viable in the one-pot process, our next goal was to optimise the palladium content in the reaction.

Using both NMP and 1,4-dioxane it was found that 5 mol% Pd(OAc)₂ was sufficient to achieve full conversion to our alkene intermediate **2a**. In previously published work in the group, 2 mol% was enough to facilitate some reactions.^[8c] However, we discovered that, although 2 mol% Pd was enough to perform the first two steps, the hydrogenation step was sluggish and, therefore, 5 mol% was required for the third step incorporation.

We then revisited our previously reported one-pot, two-step methodology again, with a view toward obviating the need for *N*-methylpyrrolidone (NMP) as solvent.^[8c, 9] We began our optimisation efforts with a number of more desirable solvents (**Table 1** and supporting

information for further information).^[10] Initially, we found that 1,4-dioxane gave rise to moderate conversion (**Table 1, entry 1**), which was improved slightly through the addition of 18-crown-6 as an additive (**Table 1, entry 2**). Jeffery and co-workers have previously shown that the use of quaternary ammonium salts as additives in Pd-catalysed olefination reactions led to superior reaction performance.^[11]

Table 1: Optimisation of Heck olefination reaction.



Entry	Solvent	Additive	Base	Conversion ^a
1	1,4-Dioxane	--	K ₂ CO ₃	65%
2	1,4-Dioxane	18-crown-6	K ₂ CO ₃	73%
3	1,4-Dioxane	TBACl	K ₂ CO ₃	100% (80%)
4	1,4-Dioxane	TBACl	--	15%
5	1,4-Dioxane	TBACl	NaOAc	77%
6	1,4-Dioxane	TBAOAc	K ₂ CO ₃	98% (79%)
7	1,4-Dioxane	TBAOAc	--	84%
8^b	1,4-Dioxane	TBAOAc	--	98% (77%)
9^b	EtOAc	TBAOAc	--	100%
10^b	CPME	TBAOAc	--	98% (78%)
11^b	Cyrene	TBAOAc	--	98%
12^b	H ₂ O	TBAOAc	--	88%
13	DMA	--	K ₂ CO ₃	92%
14	Sulfolane	--	K ₂ CO ₃	80%
15	DMF	--	K ₂ CO ₃	87%
16	Cyrene	--	K ₂ CO ₃	60%
17	2-Me THF	--	K ₂ CO ₃	64%
18	Isopropyl acetate	--	K ₂ CO ₃	64%
19	N-Butyl-pyrrolidone	--	K ₂ CO ₃	93%
20	CPME	--	K ₂ CO ₃	56%

^aConversion to product **3a** determined by ¹H NMR analysis, isolated yields following chromatographic purification in parentheses; ^b3.00 eq. TBAOAc used.

Gratifyingly, the use of tetrabutylammonium chloride (TBACl) in 2.00 equivalents in place of 18-crown-6 resulted in near quantitative formation of olefin **2a** (**Table 1, entry 3**).

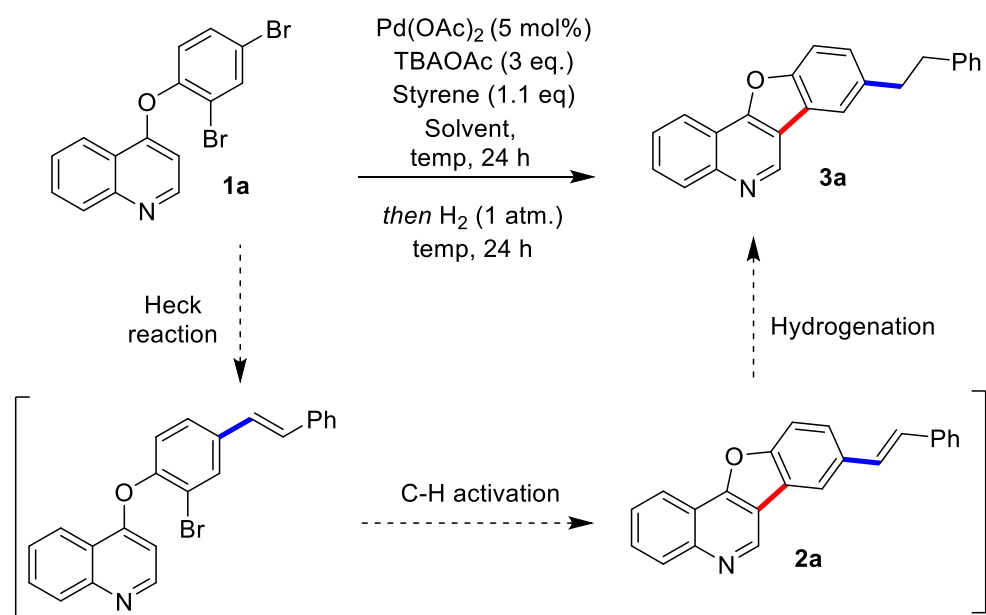
Conducting the reaction in the absence of base or using NaOAc in place of K_2CO_3 gave lower conversion (**Table 1, entry 4—5**). We also explored the use of tetrabutylammonium acetate (TBAOAc).^[12] Exchanging TBAOAc for TBACl resulted in similarly excellent results (**Table 1, entry 6 cf. Table 1, entry 3**). Encouraged by this initial result, we wondered whether TBAOAc could also act as the base for the reaction and replace K_2CO_3 . We knew the acetate ion could act as base from previously tried NaOAc, which gave 77% conversion to the target compound (**Table 1, entry 5**). Using TBAOAc in the absence of K_2CO_3 , these conditions gave rise to **2a** in good conversion (**Table 1, entry 7**), which was then rendered quantitative on increasing the equivalents of TBAOAc from 2.00 to 3.00 (**Table 1, entry 8**).

Although preferable to NMP, 1,4-dioxane is still not an ideal solvent for this transformation from a green chemistry perspective. To our delight, the use of TBAOAc enabled this chemistry to proceed in several more desirable solvents, including EtOAc, CPME, Cyrene and water with 3.00 equivalents (**Table 1, entry 9—12** and supporting information for further information). Other solvents used are described in **entries 12—20**.

With optimised conditions for the first two steps in hand, we next turned our attention to finding compatible conditions for the subsequent reduction step (**Table 2**). Alkene reduction with molecular hydrogen is ideal from a green chemistry perspective.^[13]

Although conducting the reaction in CPME, Cyrene, EtOAc and 2-MeTHF typically led to excellent conversions to olefin **2a**, elevated temperatures were generally required to achieve quantitative hydrogenation (**Table 2, entry 1—8**). Furthermore, Cyrene appeared to polymerise during the course of the reaction, thus proving problematic.^[14] As TBAOAc melts at approximately 100 °C, we wondered whether molten TBAOAc could act as both base for the first two reactions and a reaction medium for the hydrogenation step. Indeed, quantitative formation of reduced product **3a** was recorded using TBAOAc at both 135 °C and 100 °C (**Table 2, entry 9—10**).

Table 2: Optimisation of three-step one-pot sequence.



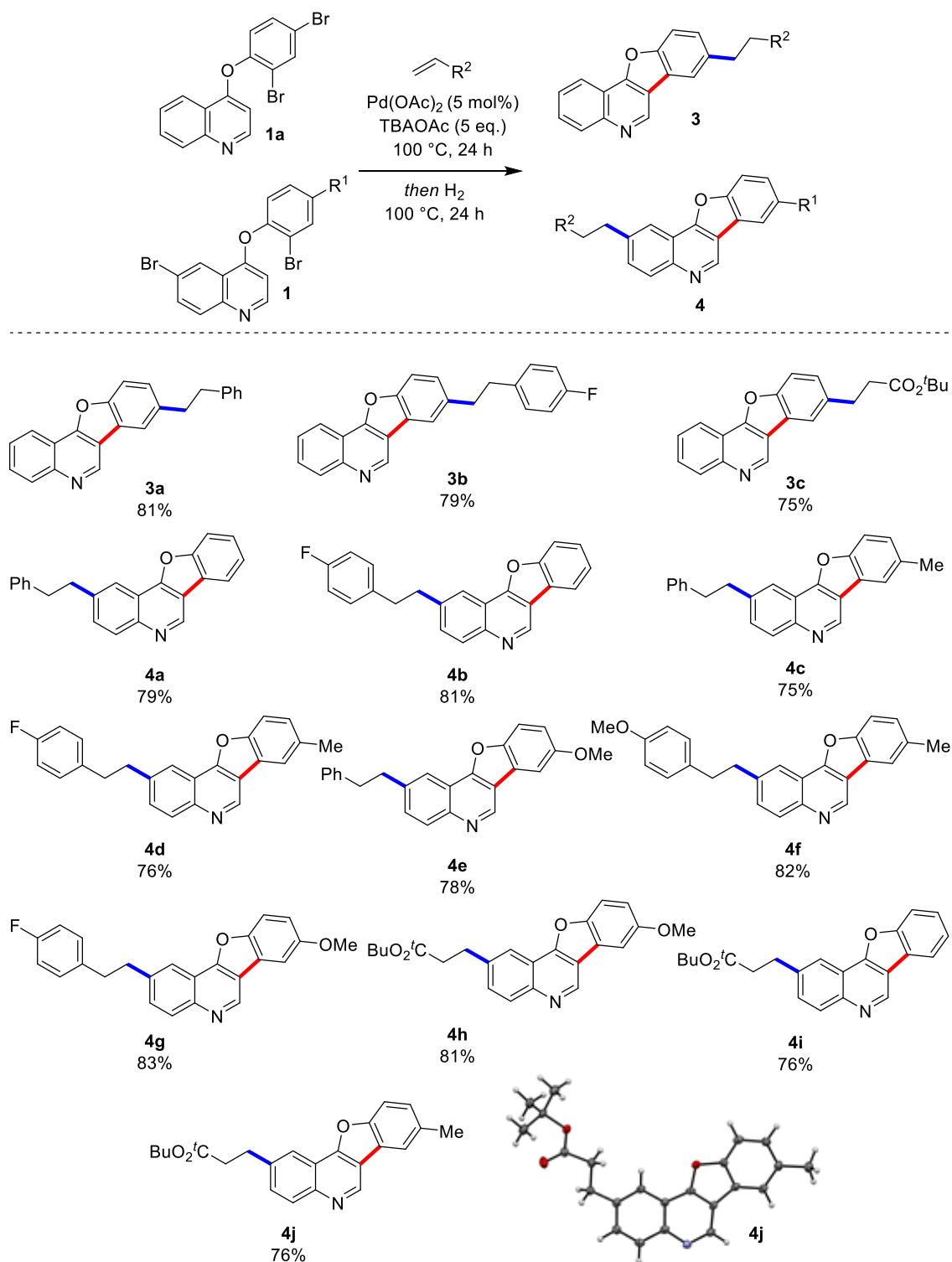
Entry	Solvent	Temperature	Conversion to 2a ^a	Conversion to 3a ^a
1	CPME	90 °C	28%	n.d.
2	CPME	110 °C	98%	100%
3	Cyrene	100 °C	74%	n.d.
4	Cyrene	135 °C	98%	100%
5	EtOAc	60 °C	n.d.	n.d.
6 ^b	EtOAc	90 °C	100%	n.a.
7	2-MeTHF	70 °C	14%	n.d.
8	2-MeTHF	90 °C	100%	50%
9 ^c	--	135 °C	100%	100%
10 ^c	--	100 °C	100%	100%

^aConversion to products 2a and 3a determined by ¹H NMR analysis from starting material 1a, ^bn.a. = not applicable: EtOAc did not support the hydrogenation step ^c5.00 eq. TBAOAc used as reaction medium; n.d. = not determined.

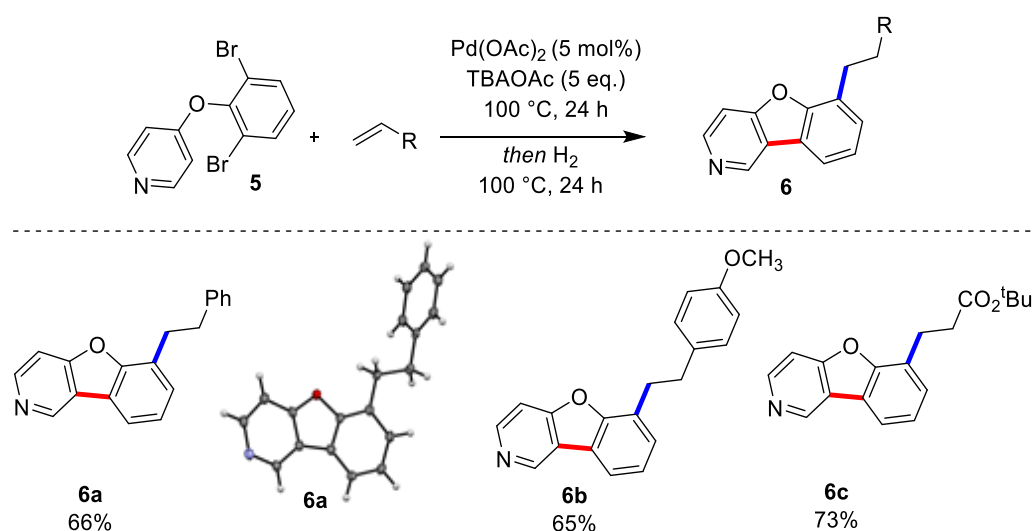
Substrate Scope

We then extended the scope of our optimised conditions to include several phenoxyquinoline substrates (**Scheme 2**). The products, prepared through our three-step, one-pot process were isolated in excellent yields following purification by column chromatography. The scope was established by varying the precursors for the Heck reaction. The reaction worked well irrespective of whether the aryl bromide Heck partner

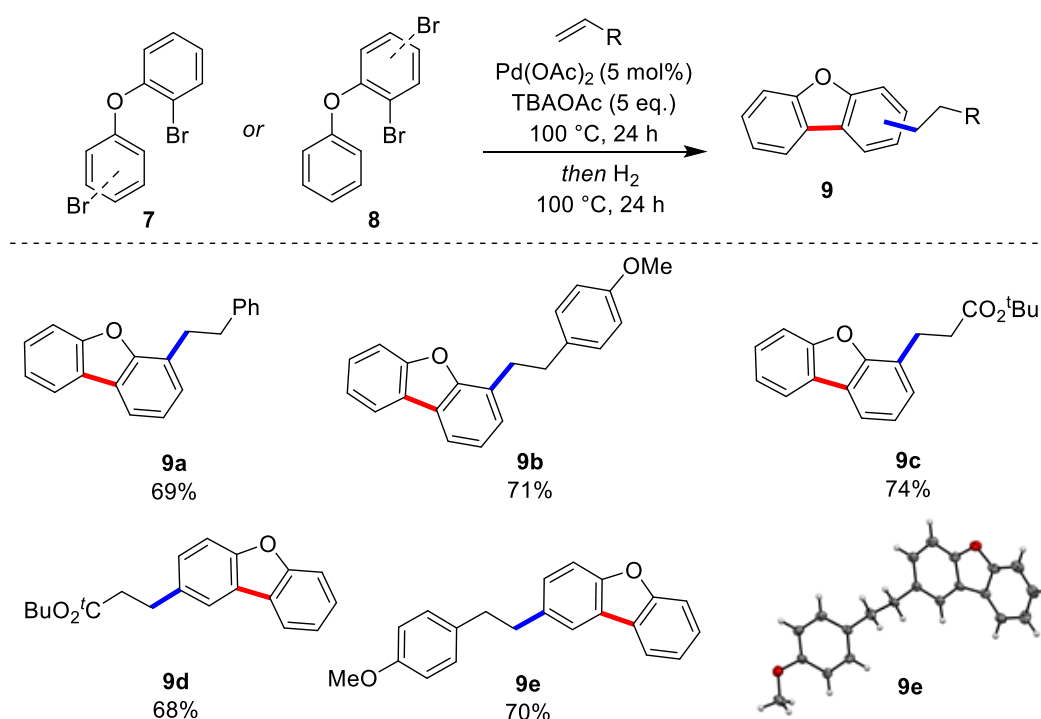
was on the pendant phenoxy- ring or the quinoline core. Both electron-rich and electron-poor olefin coupling partners were also well-tolerated.



Scheme 2 Scope of phenoxyquinoline substrates.



Scheme 3 Scope of phenoxy pyridine substrates.



Scheme 4 Scope of diarylether substrates.

Pyridines are often difficult substrates in direct arylation reactions.^[9] However, their prevalence in biologically active compounds^[6] prompted us to submit a series of phenoxy pyridines to our optimal conditions (**Scheme 3**). We were pleased that both electron-rich and electron poor olefins were compatible with the Heck-hydrogenation sequence, giving novel benzofuropyridines **6a–6c** in good yields. Finally, we were interested in exploring the synthesis of benzofurans *via* this approach (**Scheme 4**). Benzofuran derivatives are ubiquitous in bioactive molecules and have well-established uses as antimicrobial and anticancer chemotherapeutics.^[15] This class of substrates also

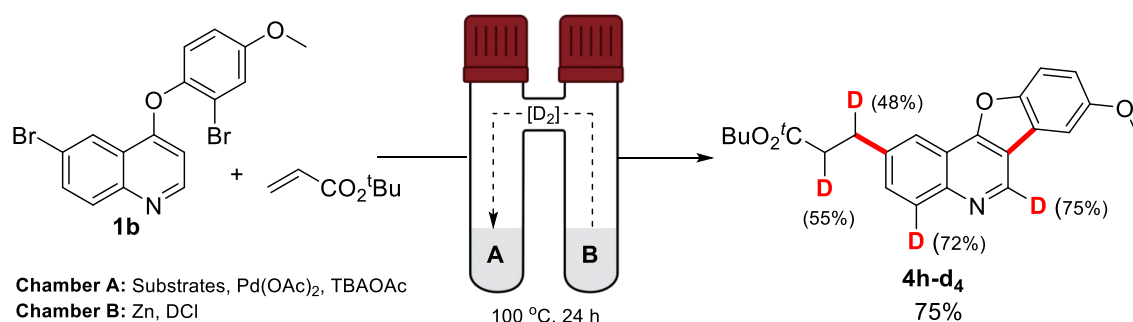
constitutes an interesting extension as they do not possess a coordinating nitrogen atom. The reaction worked well with diaryl ether substrates (**9a–9e**).^[16]

Deuterium Incorporation and Mechanistic Studies

In a bid to better understand the underlying mechanistic processes which were operative in this complex transformation, we undertook a series of mechanistic studies.

Deuterium Incorporation

Incorporating deuterium into target molecules has many important applications in the context of mechanistic studies (e.g., kinetic isotope effects), but also by enhancing metabolic stability and pharmacokinetics, aiding ADME studies, bettering toxicity profiles in drugs and creating new chemical entities of commercial importance.^[17] To facilitate easy access to D₂ for this study, we used the 'COWare' apparatus developed by Skrydstrup (**Scheme 5**).^[18] This apparatus connects two chambers by a glass bridge which facilitates *ex situ* gas generation. Here D₂ was generated (by addition of DCl to zinc) and successfully incorporated into the final structure **4h-d₄** by addition across the double bond. The ability to isotopically label these densely functionalised molecules at a late stage in their preparation demonstrates the medicinal chemistry potential of this approach. Interestingly, some incorporation of D was observed at other locations on the quinoline, which might provide a rich avenue of further research.



Scheme 5 Deuterium incorporation using COWare apparatus.

Sequence of the Direct Arylation and Olefination Reactions

Initially, we were curious whether the direct arylation and Heck reactions took place concurrently or sequentially. ¹H NMR analysis of the reaction between dibromoquinoline **1b** and styrene, under the optimised conditions, revealed that the Heck reaction was significantly faster than the direct arylation reaction. This result suggests that oxidative addition to the less hindered quinoline Ar–Br bond is favoured over oxidative addition at the phenoxy Ar–Br. Indeed, we have previously observed a similar trend in reactivity

when studying tandem Suzuki-Miyaura/ C–H activation reactions on phenoxyquinoline substrates.^[8a]

Probing the Catalytic Species in the Hydrogenation Reaction

During the Heck olefination/C–H activation process, we observed the formation of palladium black, and we were interested to determine the speciation of Pd during the hydrogenation step. We considered it most likely that heterogeneous or soluble nanoparticulate Pd, formed *in situ*, was catalysing the hydrogenation reaction.^[3e, 19] To discern the impact of soluble Pd sources, we undertook a filtration test. Initially, we performed the first two reaction steps (Heck and C–H activation) using a dibromoquinoline and styrene as per our established reaction conditions (see supplementary material for more information). However, before inserting the hydrogen balloon, we filtered the reaction mixture through a 2 µm PTFE syringe filter and placed the filtrate back into a clean reaction vial. The reaction mixture was then purged with hydrogen and allowed to stir for a further 24 hours at 100 °C. As the reaction mixture was rid of visible aggregates of palladium, it appeared as a brown homogenous solution. Complete conversion to the hydrogenated product was observed by ¹H NMR spectroscopy. Thus, interestingly, it appears that soluble Pd nanoparticles are active catalysts in the hydrogenation reaction.^[19]

Possible Mechanistic Pathway

It is clear from the optimised reaction conditions that there is no obvious reducing agent to achieve the active Pd(0) species from the Pd(II) pre-catalyst. However, as discussed in the introduction and above, it is known that tetraalkylammonium salts can form *in situ* palladium nanoparticles from palladium pre-catalysts which are catalytically active in cross-coupling reactions.^[11b-d, 20] It is also possible that Pd(0) is formed through a Wacker type process by the use of tributylamine as a reducing agent.^[21] Tributylamine could be formed by the decomposition of tetraalkylammonium salts. It has been reported that ammonium salts can degrade *via* a Hofmann type elimination^[22] or anti-Menshutkin elimination to form tributylamine as a by-product.^[22b, 23] Now that Pd(0) is available, the Mizorokuchi-Heck catalytic cycle can commence (we know this is the first step in the product formation due to NMR data). The direct arylation mechanism may then occur, going through the 6-membered CMD intermediate due to the presence of a carboxylate base.^[24] It is not suspected that an S_EAr mechanism is followed primarily as both electron rich and electron deficient substrates are tolerated (although it is possible that more than one mechanism is operational).^[25] The final hydrogenation step may be facilitated by the *in situ* palladium nanoparticles, the palladium black formed or by another unknown

catalytic form in the mixture.^[4b] It is expected that the Horiuti-Polanyi mechanism is followed for the hydrogenation process. Evidence of this is shown by the full hydrogenation of the alkene, however less than 100% deuterium has been incorporated across the bond. This highlights a mechanistic reversibility which is observed in the Horiuti-Polanyi mechanism.^[26]

Analysis of Green Chemistry Metrics

Finally, as we set ourselves the challenge to design a 'bottom-up' green chemistry approach to the polycyclic alkylated heterocycles in this study, we turned to calculating green metrics to evaluate the greenness of our reaction versus the current state-of-the-art reported by Fagnou (**Scheme 1**).^[4b] The metrics were determined as per previously reported calculations by Ma *et al.*^[27] Analysis was conducted on atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency (RME), optimum efficiency (OE), process mass intensity (PMI), E-factor (EF), solvent intensity (SI) and water intensity (WI) (**Figure 1** and see supporting information for the definition of the metrics and methodology).

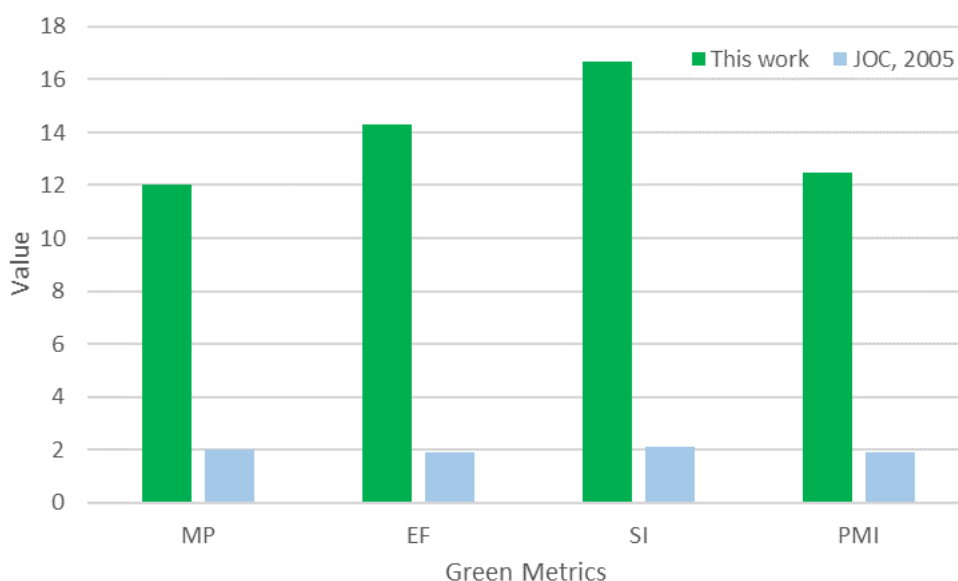


Figure 1 Quantitative comparison of green chemistry metrics for this work and previous work by Fagnou.^[4b] For illustration purposes, EF, SI and PMI values were inverted and multiplied by 100 (calculation can be found in SI).

As shown in **Figure 1**, our process constitutes a significant green chemistry improvement under these metrics due to our system not requiring an ancillary phosphine ligand, added base and excess solvent. For comparison, in green metric calculations, we input our quinoline substrate with Fagnou's conditions and input Fagnou's chromene substrate

into our new conditions. Both metrics show the more favourable greenness of our conditions (see supporting information).

The MP of the average one-pot values of 12% is six times higher than that of Fagnou's process, which has a value of just 2%. MP is an important metric that indicates the level of resource consumption as it includes all benign and non-benign reagents such as catalysts, base and solvent.

Conclusions

Achieving substrate, ligand and solvent compatibility across three mechanistically distinct catalytic reactions is challenging. In the methodology described here, no P-ligand or inorganic base is added, with TBAOAc acting as both ionic liquid and base. Decorated tri- and tetra-cyclic alkylated heteroarenes are conveniently and rapidly formed. Our new methodology greatly improves on the current state-of-the-art and demonstrates superior green chemistry values across many of the key metrics.

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**A phosphine free, inorganic base free, one-pot tandem Mizoroki-Heck olefination/
direct arylation/ hydrogenation sequence, to give muticyclic alkylated
heteroarenes**

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Experimental

Solvents and reagents were used as obtained from commercial sources and without purification. Tetrabutylammonium acetate was sourced from Sigma Aldrich. Melting points were measured in a Thomas Hoover Capillary Melting Point apparatus. Infrared spectra were measured on a Perkin Elmer Spectrum Two spectrometer, using universal ATR sampling accessories. Column chromatography was carried out using 60 Å (35–70 µm) silica. Both DCM:EtOAc and cyclohexane:EtOAc (a greener alternative) have been shown to be effective as eluent for purification methods. Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). The developed plates were visualized under UV light.

High-resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier TOF LC-MS instrument in University College Cork. Samples were run in electrospray ionization (ESI) mode using 50% acetonitrile/water containing 0.1% formic acid as an eluent; samples were made up at a concentration of *ca.* 1 mg mL⁻¹. Acquisitions were internally calibrated using sodium formate clusters. Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer (QAA1202) in electron spray ionisation mode (ESI) using acetonitrile:water (1:1) containing 0.1% formic acid as eluent.

Nuclear magnetic resonance (NMR) samples were run in deuterated chloroform (CDCl₃). ¹H NMR (600 MHz), ¹H NMR (500 MHz), ¹H NMR (400 MHz), and ¹H NMR (300 MHz) spectra were recorded on Bruker Avance III 600, Bruker Avance 500, Bruker Avance 400, and Bruker Avance III 300 NMR spectrometers, respectively, in proton-coupled mode using tetramethylsilane (TMS) as the internal standard. ¹³C NMR (150.9 MHz), ¹³C NMR (125 MHz), ¹³C NMR (100 MHz), and ¹³C NMR (75.5 MHz) spectra were recorded on Bruker Avance III 600, Bruker Avance 500, Bruker Avance 400, and Bruker Avance III 300 NMR spectrometers, respectively, in proton-decoupled mode at 300 K using TMS as the internal standard. All spectra were assigned with the aid of DEPT (Distortionless Enhancement by Polarisation Transfer) experiments run in DEPT-90, DEPT-135 and DEPT-q modes and COSY (correlated spectroscopy). Specific assignments were made using HSQC (Heteronuclear Single Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Correlation) experiments. All spectroscopic data for known compounds is in agreement with those previously reported unless otherwise stated. ¹⁹F NMR (282 MHz) spectra were recorded on a Bruker Avance III 300 NMR spectrometer in proton-decoupled mode at 300 K. All spectra were run at University College Cork. Chemical shifts (δ) are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz). Splitting

patterns in ^1H NMR spectra are designated as follows: s (singlet), br s (broad singlet), d (doublet), br d (broad doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), td (triplet of doublets), q (quartet), quin (quintet), and m (multiplet).

The COware apparatus was purchased from Sigma Aldrich and the hydrogen pressure was estimated using $PV = nRT$ formula by using the quantity of hydrogen generated. It is worth noting that a 20 mL COware apparatus was used for these experiments. The COware apparatus has two chambers that are connected by a glass bridge, allowing for *ex situ* gas to be generated in one chamber which can then interact with the reaction mixture in the second chamber (**Figure 1S**). These can be annotated as chamber 'A' and chamber 'B'.

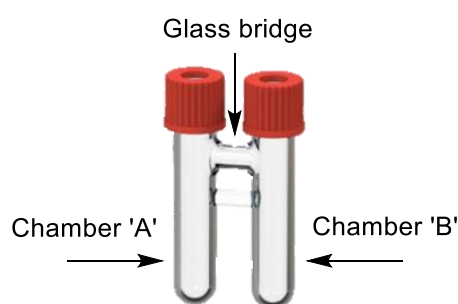


Figure 1S: COware apparatus and set-up.

General Procedure 1: Synthesis of phenoxyquinoline starting materials

A mixture of the 4-chloroquinoline substrate (1 eq.), the phenol (3.5 eq.) and NaOH (1.5 eq., crushed pellets) was stirred at 120 °C until TLC analysis indicated the reaction was complete (2 – 24 hours). The reaction mixture was cooled to room temperature and 10% aqueous NaOH (10 mL) was added and stirred for 30 min. The aqueous layer was extracted with DCM (3 × 15 mL). The organic layers were combined and washed with 6M NaOH (3 × 15 mL), water (10 mL) and brine (10 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. Impure products were purified by column chromatography over silica gel using cyclohexane:EtOAc (100:0 - 70:30) or DCM:EtOAc (100:0 - 97:3). The substrate 6-bromo-4-(2-bromo-4-methoxyphenoxy)quinoline **1b** was columned in DCM (100%), followed by a wash of diethyl ether (5 mL).

General Procedure 2: One-pot reaction conditions

To a screw capped vial was added the quinoline/pyridine/diaryl ether substrate (1 eq.), heck coupling partner (1.1 eq.), $\text{Pd}(\text{OAc})_2$ (5 mol%) and tetrabutylammonium acetate (5 eq.) which was stirred at 100 °C for 24 hours. The reaction mixture was then purged with hydrogen gas and stirred under a hydrogen atmosphere for a further 24 hours at

100 °C. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography. The benzofuroquinoline and benzofuopyridine products **3**, **4** and **6** eluted in DCM:EtOAc (100:0 – 95:5) or cyclohexane:EtOAc (100:0 – 70:30). The dibenzofuran products **9** eluted in hexane:DCM (100:0 – 80:20) or cyclohexane:EtOAc (100:0 – 90:10).

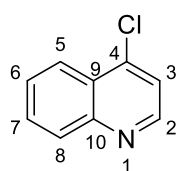
General Procedure 3: Synthesis of deuterated benzofuroquinoline

Generating D₂ at 3 atm.

To chamber 'A' of the COware^[1] apparatus was put the benzofuroquinoline substrate (1 eq.), Heck coupling partner (1.1 eq.), Pd(OAc)₂ (5 mol%) and tetrabutylammonium acetate (5 eq.). To the second chamber 'B' was added Zinc powder (3.65 eq.). Chamber 'A' was placed into an oil bath and was stirred at 100 °C for 24 hours. DCI (4M, 7.3 eq.) was added *via* syringe to chamber 'B' which initiated the D₂ formation and reaction was let stir at 100 °C for a further 24 hours. The crude product was purified by silica gel column chromatography and eluted in a gradient cyclohexane:EtOAc (100:0 – 70:30) or DCM:EtOAc (100:0 – 95:5).

Synthesis of 4-chloroquinoline:

4-Chloroquinoline S1

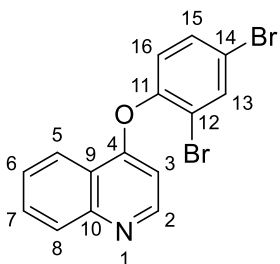


A mixture of 4-quinolinol (2.00 g, 13.78 mmol) and phosphoryl chloride (6.40 mL, 68.9 mmol) was stirred at 120 °C for 16 hours. The crude mixture was poured onto ice and neutralised with solid sodium bicarbonate. The neutralised aqueous mix was extracted with DCM (3 × 15 mL). The organic layers were combined and washed with aqueous sodium bicarbonate (3 × 15 mL), water (15 mL) and brine (15 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to yield the final product. Yellow solid, 80% yield (1.80 g); m.p. 27 – 28 °C (lit. 26 – 28 °C)^[2]; IR ν_{max} /cm⁻¹: 2460 (C-H stretch), 1619 (aromatic C=C stretch), 1383 (C=N stretch), 760 (C-Cl stretch); ¹H NMR (300 MHz, CDCl₃) δ = 8.79 (d, 1H, *J* 4.6 Hz, H-**2**), 8.25 (dd, 1H, *J* 8.4, 1.0 Hz, H-**5**), 8.14 (dd, 1H, *J* 8.4, 0.6 Hz, H-**8**), 7.79 (ddd, 1H, *J* 8.4, 6.9, 1.4 Hz, H-**7**), 7.66 (ddd, 1H, *J* 8.4, 6.9, 1.4 Hz, H-**6**), 7.50 (d, 1H, *J* 4.6 Hz, H-**3**) ppm; ¹³C NMR (75.5 MHz, CDCl₃) δ = 149.8 (CH-**2**), 149.1 (qC-**10**), 142.6 (qC-**4**), 130.4 (CH-**7**), 129.8 (CH-**8**), 127.6 (CH-**6**), 126.5 (qC-**9**), 124.1 (CH-**5**), 121.2 (CH-**3**) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₉H₇Cl³⁵N: 164.0267; found: 164.0261.

Synthesis of phenoxyquinoline substrates as per General Procedure 1

4-(2,4-dibromobenzyl)quinoline 1a

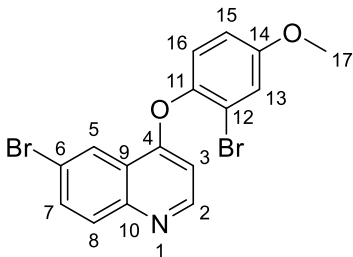
Synthesis of substrate **1a** as per general procedure 1 using 4-chloroquinoline **S1** (1.00 g, 6.14 mmol), 2,4-dibromophenol (5.41 g, 21.48 mmol) and NaOH (0.37 g, 9.21 mmol).



White solid, 95% yield, (2.21 g); m.p. 123 – 125 °C (lit: 125 – 126 °C)^[3]; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3033 (aromatic C-H stretch), 1594 (C=N stretch), 1563 (aromatic C=C stretch), 1373, 1232 (ether C-O stretch), 677 (C-Br stretch); ¹H NMR (300 MHz, CDCl₃) δ = 8.69 (d, 1H, *J* 5.1 Hz, H-2), 8.38 (dd, 1H, *J* 8.4 Hz, 0.9 Hz, H-5), 8.12 (d, 1H, *J* 8.4 Hz, H-8), 7.88 (d, 1H, *J* 2.3 Hz, H-13), 7.79 (ddd, 1H, *J* 8.4, 6.9, 1.4, H-7), 7.62 (ddd, 1H, *J* 8.3, 7.0, 1.3 Hz, H-6), 7.54 (dd, 1H, *J* 8.6, 2.3 Hz, H-15), 7.12 (d, 1H, *J* 8.6 Hz, H-16), 6.43 (d, 1H, *J* 5.1 Hz, H-3) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = 160.3 (qC-4), 150.9 (CH-2), 150.6 (qC-11), 149.8 (qC-10), 136.6 (CH-13), 132.3 (CH-15), 130.4 (CH-7), 129.2 (CH-8), 126.5 (CH-6), 124.2 (CH-16), 121.7 (CH-5), 120.9 (qC-9), 119.3 (qC-14), 117.3 (qC-12), 103.8 (CH-3) ppm; LRMS *m/z* (ESI+) 378, 380, 372 [(M+H)⁺, 100%].

6-Bromo-4-(2-bromo-4-methoxyphenoxy)quinoline 1b

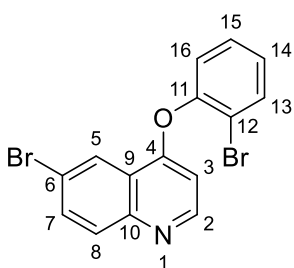
Synthesis of substrate **1b** as per general procedure 1 using 6-bromo-4-chloroquinoline (0.80 g, 3.30 mmol, 1 eq.), with an additional 2 eq. of 4-methoxyphenol (3.30 g, 16.49 mmol, 5 eq.) and NaOH (0.20 g, 4.95 mmol, 1.5 eq.).



White solid, 25% yield (336 mg); m.p. 122 – 124 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3008 (aromatic C-H stretch), 1589 (C=N stretch), 1565 (aromatic C=C stretch), 1349, 1267, 1202 (ether C-O stretch), 673 (C-Br stretch); ¹H NMR (300 MHz, CDCl₃) δ = 8.65 (d, 1H, *J* 5.2 Hz, H-2), 8.58 (d, 1H, *J* 2.2 Hz, H-5), 7.96 (d, 1H, *J* 9.0 Hz, H-8), 7.82 (dd, 1H, *J* 9.0, 2.2 Hz, H-7), 7.24 (d, 1H, *J* 2.9 Hz, H-13), 7.16 (d, 1H, *J* 8.9 Hz, H-16), 6.95 (dd, 1H, *J* 8.9, 2.9 Hz, H-15), 6.39 (d, 1H, *J* 5.2 Hz, H-3), 3.85 (s, 3H, C(17)-H₃) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = 160.3 (qC-4), 158.0 (qC-14), 151.4 (CH-2), 148.3 (qC-10), 144.1 (qC-11), 133.6 (CH-7), 130.8 (CH-8), 124.3 (CH-5), 123.7 (CH-16), 122.1 (qC-9), 120.2 (qC-6), 119.0 (CH-13), 116.6 (qC-12), 115.0 (CH-15), 103.8 (CH-3), 55.9 (CH₃-17) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₆H₁₂Br⁷⁹₂NO₂: 407.9229; found: 407.9227.

6-Bromo-4-(2-bromophenoxy)quinoline 1c

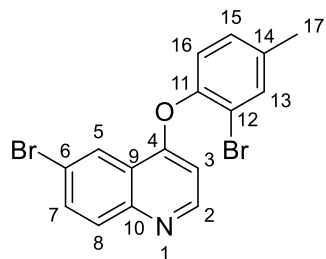
Synthesis of substrate **1c** as per general procedure 1 using 6-Bromo-4-chloroquinoline (1.00 g, 4.12 mmol), 2-bromophenol (2.49 g, 14.43 mmol) and NaOH (0.25 g, 6.19 mmol).



Off-white solid, 88% yield (2.03 g); m.p. 92 – 94 °C (lit. 97 – 98 °C)^[3]; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3070 (aromatic C-H stretch), 1589 (C=N stretch), 1560 (aromatic C=C stretch), 1348, 1223 (ether C-O stretch), 658 (C-Br stretch); ¹H NMR (400 MHz, CDCl₃) δ = 8.67 (d, 1H, *J* 5.1 Hz, H-2), 8.60 (d, 1H, *J* 2.1 Hz, H-5), 8.02 (d, 2H, *J* 9.0 Hz, H-8), 7.86 (dd, 1H, *J* 9.0, 2.2 Hz, H-7), 7.72 – 7.76 (m, 1H, H-13), 7.45 (ddd, 1H, *J* 8.8, 7.4, 1.4 Hz, H-15), 7.21 – 7.28 (m, 2H, H-14, H-16), 6.42 (d, 1H, *J* 5.1 Hz, H-3) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 160.2 (qC-4), 151.0 (CH-2), 150.6 (qC-11), 147.8 (qC-10), 134.4 (CH-13), 134.0 (CH-7), 130.5 (CH-8), 129.4 (CH-15), 127.7 (CH-14), 124.4 (CH-5), 123.3 (CH-16), 122.1 (qC-9), 120.6 (qC-6), 116.3 (qC-12), 104.2 (CH-3) ppm; LRMS *m/z* (ESI+) 378, 380, 372 [(M+H)⁺, 100%].

6-Bromo-4-(2-bromo-4-methylphenoxy)quinoline 1d

Synthesis of substrate **1d** as per general procedure 1 using 6-Bromo-4-chloroquinoline (1.00 g, 4.12 mmol), 4-bromo-2-methylphenol (2.70 g, 14.43 mmol) and NaOH (0.25 g, 6.19 mmol).

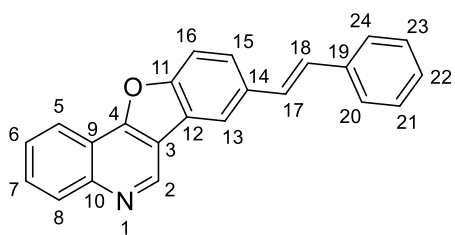


Light-brown solid, 88% yield (1.42 g); m.p. 94 – 95 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2964 (aromatic C-H stretch), 2922 (methyl C-H stretch), 1587 (C=N stretch), 1563 (aromatic C=C stretch), 1351, 1205 (ether C-O stretch), 670 (C-Br stretch); ¹H NMR (300 MHz, CDCl₃) δ = 8.65 (d, 1H, *J* 5.1 Hz, H-2), 8.58 (d, 1H, *J* 2.2, H-5), 7.96 (d, 1H, *J* 9.0 Hz, H-8), 7.83 (dd, 1H, *J* 9.0, 2.2 Hz, H-7), 7.54 (d, 1H, *J* 2.0 Hz, H-13), 7.22 (ddd, 1H, *J* 8.2, 2.0, 0.6 Hz, H-16), 7.11 (d, 1H, *J* 8.2 Hz, H-15), 6.40 (d, 1H, *J* 5.1 Hz, H-3), 2.41 (s, 3H, C(17)-H₃) ppm; ¹³C NMR (150.9 MHz, CDCl₃) δ = 160.1 (qC-4), 151.3 (CH-2), 148.3 (qC-11), 148.2 (qC-10), 137.9 (qC-14), 134.6 (CH-13), 133.7 (CH-7), 130.8 (CH-8), 129.9 (CH-16), 124.4 (CH-5), 122.9 (CH-15), 122.1 (qC-9), 120.3 (qC-6), 115.9 (qC-12), 104.0 (CH-3), 20.7 (CH₃-17) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₆H₁₂Br⁷⁹₂NO: 391.9280; found: 391.9278.

Synthesis of Direct-Arylation/Mizoroki-Heck Intermediate

(E)-8-Styrylbenzofuro[3,2-c]quinoline 2a

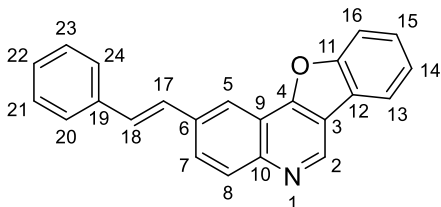
To a screw capped vial was added the quinoline substrate **1a** (200.0 mg, 0.53 mmol), styrene (66 μ L, 0.58 mmol), Pd(OAc)₂ (5.92 mg, 5 mol%) and tetrabutylammonium acetate (795.4 mg, 2.64 mmol) which was stirred at 100 °C for 24 hours. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5).



Off-white solid, 86% yield (146 mg); m.p. 202 – 204 °C (lit: 200 – 203 °C)^[3]; IR ν_{max} /cm⁻¹: 1651 (*trans* alkene C=C stretch), 1597 (C=N stretch), 1568 (aromatic C=C stretch), 1327, 1195 (ether C-O stretch); ¹H NMR (300 MHz, CDCl₃) δ = 9.50 (s, 1H, (H-2), 8.39 (dd, 1H, *J* 8.1, 1.3 Hz, H-5), 8.27 (d, 1H, *J* 8.5 Hz, H-8), 8.19 (s, 1H, H-13), 7.63 – 7.83 (m, 4H, H-6, H-7, H-15, H-16), 7.52 – 7.61 (m, 2H, H-20, H-24), 7.14 – 7.44 (m, 5H, H-17, H-18, H-21, H-22, H-23) ppm; ¹³C NMR (75.5 MHz, CDCl₃) δ = 158.0 (qC-4), 155.6 (qC-11), 147.5 (qC-10), 144.4 (CH-2), 137.2 (qC-19), 133.9 (qC-14), 129.9 (CH-8), 129.4 (CH-7), 128.9 (CH-18), 128.8 (2 $\times$ CH-21, CH-24), 128.1 (CH-17), 127.1 (CH-6), 126.5 (2 $\times$ CH-20, CH-24), 126.0 (CH-15), 123.3 (qC-12), 120.8 (CH-5), 118.2 (CH-13), 117.2 (qC-9), 116.2 (qC-3), 112.2 (CH-16) ppm; LRMS *m/z* (ESI+) 322 [(M+H)⁺, 100%].

(E)-2-Styrylbenzofuro[3,2-c]quinoline 2b

To a screw capped vial was added the quinoline substrate **1c** (200.0 mg, 0.53 mmol), styrene (66 μ L, 0.58 mmol), Pd(OAc)₂ (5.92 mg, 5 mol%) and tetrabutylammonium acetate (795.4 mg, 2.64 mmol) which was stirred at 100 °C for 24 hours. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5).



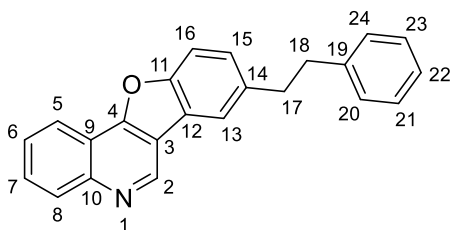
White solid, 88% yield (149 mg); m.p. 202 – 204 °C (lit: 201 – 202 °C)^[3]; IR ν_{max} /cm⁻¹: 1666 (*trans* alkene C=C stretch), 1650 (C=N stretch), 1560 (aromatic C=C stretch), 1375, 1180 (ether C-O stretch); ¹H NMR (300 MHz, CDCl₃) δ : 9.41 (s, 1H, H-2), 8.39 (d, 1H, *J* 1.8 Hz, H-5), 8.22 (d, 1H, *J* 8.9 Hz, H-8), 8.07 (dd, 1H, *J* 7.6, 0.8 Hz, H-13), 7.98 (dd, 1H, *J* 8.9, 2.0 Hz, H-7), 7.76 (d, 1H, *J* 8.1 Hz, H-16), 7.66–7.22 (m, 9H, H-14, H-15, H-17, H-18, H-20, H-21, H-22, H-23, H-24) ppm; ¹³C NMR (75.5 MHz, CDCl₃) δ : 157.4 (qC-4), 156.0 (qC-11), 147.0 (qC-10), 143.9 CH-2, 137.0

(qC-**19**), 136.1 (qC-**6**), 130.6 CH-**18**), 130.1 CH-**8**), 128.8 (2 × CH-**21**, CH-**23**), 128.1 (CH-**22**), 127.8 (CH-**17**), 127.3 (CH-**15**), 127.2 (CH-**7**), 126.8 (2 × CH-**20**, CH-**24**), 124.1 (CH-**14**), 122.7 (qC-**12**), 120.7 (CH-**13**), 118.6 (CH-**5**), 117.4 (qC-**9**), 116.7 (qC-**3**), 112.1 (CH-**16**) ppm; HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd. for $C_{23}H_{16}NO$: 322.1226; found: 322.1223.

One-Pot Products as per General Procedure 2

8-Phenethylbenzofuro[3,2-c]quinoline **3a**

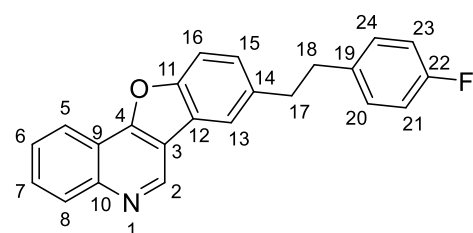
Synthesis of product **3a** as per general procedure 2 using **1a** (100 mg, 0.26 mmol), $Pd(OAc)_2$ (2.96 mg, 5 mol%), TBAOAc (398 mg, 1.32 mmol), styrene (33.0 μ L, 0.29 mmol) and one hydrogen balloon.



White solid, 81% yield (69 mg); m.p. 129 – 131 °C; IR ν_{max}/cm^{-1} : 2925 (alkyl C-H stretch), 1600 (C=N stretch), 1567 (aromatic C=C stretch), 1341, 1193 (ether C-O stretch); 1H NMR (500 MHz, $CDCl_3$): δ = 9.46 (s, 1H, H-**2**), 8.40 (d, 1H, J 8.1 Hz, H-**5**), 8.30 (d, 1H, J 8.1 Hz, H-**8**), 7.87 (d, 1H, J 1.2 Hz, H-**13**), 7.75 – 7.80 (m, 1H, H-**7**), 7.68 (t, 1H, J 8.1 Hz, H-**6**), 7.63 (d, 1H, J 8.4 Hz, H-**16**), 7.33 (dd, 1H, J 8.4, 1.7 Hz, H-**15**), 7.18 – 7.31 (m, 5H, H-**20**, H-**21**, H-**22**, H-**23**, H-**24**), 2.99 – 3.17 (m, 4H, C(**17**)- H_2 , C(**18**)- H_2) ppm; ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 157.8 (qC-**4**), 154.6 (qC-**11**), 147.1 (qC-**10**), 144.3 (CH-**2**), 141.4 (qC-**19**), 137.8 (qC-**14**), 129.7 (CH-**8**), 129.3 (CH-**7**), 128.5 (2 × CH-**20**, CH-**24**), 128.4 (2 × CH-**21**, CH-**23**), 128.0 (CH-**15**), 127.0 (CH-**6**), 126.1 (CH-**22**), 122.7 (qC-**12**), 120.8 (CH-**5**), 120.1 (CH-**13**), 117.3 (qC-**9**), 116.4 (qC-**3**), 111.7 (CH-**16**), 38.5 (CH₂-**17**), 37.9 (CH₂-**18**) ppm; HRMS (ESI-TOF) m/z : $[M+H]^+$ calcd. for $C_{23}H_{18}NO$: 324.1383, found: 324.1385.

8-(4-Fluorophenethyl)benzofuro[3,2-c]quinoline **3b**

Synthesis of product **3b** as per general procedure 2 using **1a** (100 mg, 0.26 mmol), $Pd(OAc)_2$ (2.96 mg, 5 mol%), TBAOAc (398 mg, 1.32 mmol), 4-fluorostyrene (33.6 μ L, 0.29 mmol) and one hydrogen balloon.

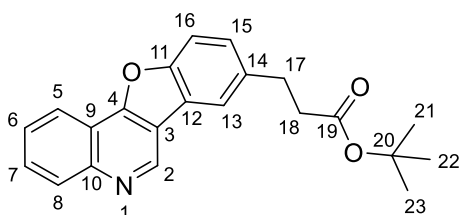


White solid, 79% yield (71 mg); m.p. 162 – 163 °C; IR ν_{max}/cm^{-1} : 2919 (aromatic C-H stretch), 1603 (C=N stretch), 1565 (aromatic C=C stretch), 1320, 1213 (ether C-O stretch), 1050 (C-F stretch); 1H NMR (600 MHz, $CDCl_3$): δ = 9.48 (br s, 1H, H-**2**), 8.42 (br d, 1H, J 6.1 Hz, H-**5**), 8.31 (br d, 1H, J 6.1 Hz, H-**8**), 7.86 (s, 1H, H-

13), 7.80 (t, 1H, J 7.0 Hz, H-7), 7.70 (t, 1H, J 7.0 Hz, H-6), 7.64 (d, 1H, J 8.3 Hz, H-16), 7.30 (dd, 1H, J 8.3, 1.3 Hz, H-15), 7.13 (m, 2H, H-20, H-24), 6.97 (m, 2H, H-21, H-23), 2.97 – 3.13 (m, 4H, C(17)-H₂, C(18)-H₂) ppm; ¹³C NMR (150.9 MHz, CDCl₃): δ = 161.4 (d, $^1J_{(C,F)}$ = 244 Hz, C(22)-F), 157.9 (qC-4), 154.7 (qC-11), 146.9 (qC-10), 144.0 (CH-2), 137.6 (qC-14), 136.9 (d, $^4J_{(C,F)}$ = 3 Hz, qC-19), 129.9 (d, $^3J_{(C,F)}$ = 8 Hz, 2 $\times$ CH-20, CH-24), 129.5 (2 $\times$ CH-7, CH-8), 128.0 (CH-15), 127.2 (CH-6), 122.7 (qC-12), 120.9 (CH-5), 120.2 (CH-13), 117.3 (qC-9), 116.4 (qC-3), 115.1 (d, $^2J_{(C,F)}$ = 21 Hz, 2 $\times$ CH-21, CH-23), 111.8 (CH-16), 38.0 (CH₂-17), 37.6 (CH₂-18) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ = – 117.3 ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₂₃H₁₇FNO: 342.1289; found: 342.1298.

***tert*-Butyl 3-(benzofuro[3,2-*c*]quinolin-8-yl)propanoate 3c**

Synthesis of product **3c** as per general procedure 2 using **1a** (100 mg, 0.26 mmol), Pd(OAc)₂ (2.96 mg, 5 mol%), TBAOAc (398 mg, 1.32 mmol), *tert*-butylacrylate (42.0 μ L, 0.29 mmol) and one hydrogen balloon.



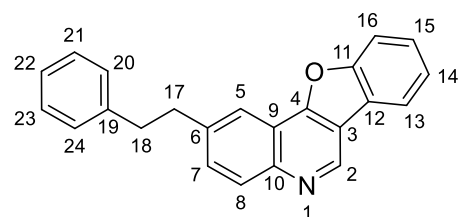
White solid, 75% yield (69 mg); m.p. 105 – 106 °C;

IR $\nu_{\max}/\text{cm}^{-1}$: 2973 (alkyl C-H stretch), 1716 (ester C=O stretch), 1565 (C=N stretch), 1478 (aromatic C=C stretch), 1367, 1204 (ether C-O stretch), 1140 (ester C-O stretch); ¹H NMR (300 MHz, CDCl₃): δ

= 9.48 (s, 1H, H-2), 8.42 (dd, 1H, J 8.2, 0.9 Hz, H-5), 8.32 (d, 1H, J 8.2 Hz, H-8), 7.94 (d, 1H, J 1.4 Hz, H-13), 7.77 – 7.85 (m, 1H, H-7), 7.70 – 7.75 (m, 1H, H-6), 7.67 (d, 1H, J 8.7 Hz, H-16), 7.40 (dd, 1H, J 8.7, 1.8 Hz, H-15), 3.13 (t, 2H, J 7.7 Hz, C(17)-H₂), 2.66 (t, 2H, J 7.7 Hz, C(18)-H₂), 1.42 (s, 9H, 3 $\times$ C(21)-H₃, C(22)-H₃, C(23)-H₃) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 172.0 (qC-19), 158.1 (qC-4), 154.8 (qC-11), 146.7 (qC-10), 143.8 (CH-2), 137.2 (qC-14), 129.6 (CH-7), 129.3 (CH-8), 128.0 (CH-15), 127.3 (CH-6), 122.7 (qC-12), 120.9 (CH-5), 120.2 (CH-13), 117.3 (qC-9), 116.4 (qC-3), 111.9 (CH-16), 80.6 (qC-20), 37.5 (CH₂-18), 31.1 (CH₂-17), 28.1 (3 $\times$ CH₃-21, CH₃-22, CH₃-23) ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₂₂H₂₂NO₃: 348.1594; found: 348.1598.

2-Phenethylbenzofuro[3,2-*c*]quinoline 4a

Synthesis of product **4a** as per general procedure 2 using **1c** (100 mg, 0.26 mmol), Pd(OAc)₂ (2.96 mg, 5 mol%), TBAOAc (398 mg, 1.32 mmol), styrene (33.0 μ L, 0.29 mmol) and one hydrogen balloon.



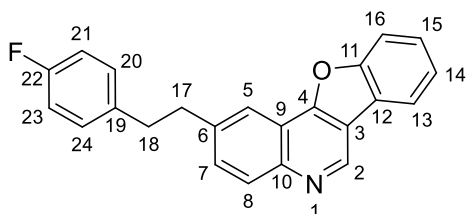
White solid, 79% yield (67 mg); m.p. 112 – 113 °C;

IR $\nu_{\max}/\text{cm}^{-1}$: 3023 (aromatic C-H stretch), 2922 (alkyl C-H stretch), 1589 (C=N stretch), 1562

(aromatic C=C stretch), 1370, 1188 (ether C-O stretch); ^1H NMR (500 MHz, CDCl_3): δ = 9.42 (br s, 1H, H-2), 8.15 – 8.21 (m, 2H, H-5, H-8), 8.06 (d, 1H, J 7.7 Hz, H-13), 7.72 (d, 1H, J 7.7 Hz, H-16), 7.60 (dd, 1H, J 8.5, 1.4 Hz, H-7), 7.52 (t, 1H, J 7.7 Hz, H-15), 7.45 (t, 1H, J 7.7 Hz, H-14), 7.17 – 7.32 (m, 5H, H-20, H-21, H-22, H-23, H-24), 3.03 – 3.24 (m, 4H, C(17)- H_2 , C(18)- H_2) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 157.3 (qC-4), 156.0 (qC-11), 146.1 (qC-10), 143.5 (CH-2), 141.3 (qC-6), 141.0 (qC-19), 130.9 (CH-7), 129.6 (CH-8), 128.5 (4 $\times$ CH-20, CH-21, CH-23, CH-24), 127.2 (CH-15), 126.1 (CH-22), 124.1 (CH-14), 122.8 (qC-12), 120.6 (CH-13), 119.3 (CH-5), 117.1 (qC-9), 116.4 (qC-3), 112.1 (CH-16), 38.1 (CH₂-17), 37.7 (CH₂-18) ppm; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{18}\text{NO}$: 324.1383; found: 324.1390.

2-(4-Fluorophenethyl)benzofuro[3,2-c]quinoline 4b

Synthesis of product **4b** as per general procedure 2 using **1c** (100 mg, 0.26 mmol), $\text{Pd}(\text{OAc})_2$ (2.96 mg, 5 mol%), TBAOAc (398 mg, 1.32 mmol), 4-fluorostyrene (33.6 μL , 0.29 mmol) and one hydrogen balloon.

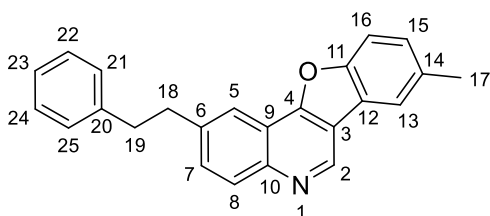


White solid, 81% yield (73 mg); m.p. 130 – 131 $^{\circ}\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3038 (aromatic C-H stretch), 2923 (alkyl C-H stretch), 1598 (C=N stretch), 1564 (aromatic C=C stretch), 1346, 1218 (ether C-O stretch), 1014 (C-F stretch); ^1H NMR (500

MHz, CDCl_3): δ = 9.45 (br s, 1H, H-2), 8.22 (d, 1H, J 8.5 Hz, H-8), 8.16 (s, 1H, H-5), 8.08 (d, 1H, J 7.2 Hz, H-13), 7.74 (d, 1H, J 8.3 Hz, H-16), 7.59 (dd, 1H, J 8.5, 1.7 Hz, H-7), 7.52 – 7.56 (m, 1H, H-15), 7.45 – 7.49 (m, 1H, H-14), 7.12 – 7.17 (m, 2H, H-20, H-24), 6.94 – 6.99 (m, 2H, H-21, H-23), 3.02 – 3.21 (m, 4H, C(17)- H_2 , C(18)- H_2); ^{13}C NMR (125 MHz, CDCl_3): δ = 161.4 (d, $^1J_{\text{C,F}}$ = 244 Hz, C(22)-F), 157.4 (qC-4), 156.0 (qC-11), 145.8 (qC-10), 143.4 (CH-2), 140.8 (qC-6), 136.7 (d, $^4J_{\text{C,F}}$ = 3 Hz, qC-19), 130.9 (CH-7), 129.9 (d, $^3J_{\text{C,F}}$ = 8 Hz, 2 $\times$ CH-20, CH-24), 129.5 (CH-8), 127.3 (CH-15), 124.2 (CH-14), 122.7 (qC-12), 120.7 (CH-13), 119.4 (CH-5), 117.0 (qC-9), 116.4 (qC-3), 115.2 (d, $^2J_{\text{C,F}}$ = 21 Hz, 2 $\times$ CH-21, CH-23), 112.1 (CH-16), 38.1 (CH₂-18), 36.8 (CH₂-17) ppm; ^{19}F NMR (282 MHz, CDCl_3): δ = -117.2 ppm; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{17}\text{FNO}$: 342.1289; found: 342.1294.

8-Methyl-2-phenethylbenzofuro[3,2-c]quinoline **4c**

Synthesis of product **4c** as per general procedure 2 using **1d** (100 mg, 0.25 mmol), Pd(OAc)₂ (2.86 mg, 5 mol%), TBAOAc (383.5 mg, 1.27 mmol), styrene (32.0 μ L, 0.28 mmol) and one hydrogen balloon.

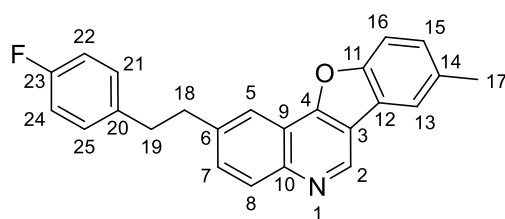


White solid; 75% (64 mg); m.p. 157 – 158 °C, IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3026 (aromatic C-H stretch), 2920 (alkyl C-H stretch), 2857 (methyl C-H stretch), 1593 (C=N stretch), 1565 (aromatic C=C stretch), 1325, 1188 (ether C-O stretch); ¹H

NMR (500 MHz, CDCl₃): δ = 9.39 (s, 1H, H-2), 8.09 – 8.25 (m, 2H, H-5, H-8), 7.85 (s, 1H, H-13), 7.60 (d, 1H, *J* 8.4 Hz, H-16), 7.16 – 7.36 (m, 6H, H-15, H-21, H-22, H-23, H-24, H-25), 3.03 – 3.25 (m, 4H, H-18, H-19), 2.55 (s, 3H, C(17)-H₃) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 157.6 (qC-4), 154.4 (qC-11), 145.8 (qC-10), 143.4 (CH-2), 141.3 (qC-20), 141.0 (qC-6), 133.8 (qC-14), 130.9 (CH-7), 129.4 (CH-8), 128.5 (3 $\times$ CH-22, CH-23, CH-24), 128.4 (CH-15), 126.1 (2 $\times$ CH-21, CH-25), 122.7 (qC-12), 120.6 (CH-13), 119.3 (CH-5), 117.2 (qC-9), 116.4 (qC-3), 111.6 (CH-16), 38.1 (CH₂-18), 37.7 (CH₂-19), 21.5 (CH₃-17) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₄H₂₀NO₂: 338.1539; found: 338.1544.

2-(4-Fluorophenethyl)-8-methylbenzofuro[3,2-c]quinoline **4d**

Synthesis of product **4d** as per general procedure 2 using **1d** (100 mg, 0.25 mmol), Pd(OAc)₂ (2.86 mg, 5 mol%), TBAOAc (383.5 mg, 1.27 mmol), 4-fluorostyrene (33.4 μ L, 0.28 mmol) and one hydrogen balloon.



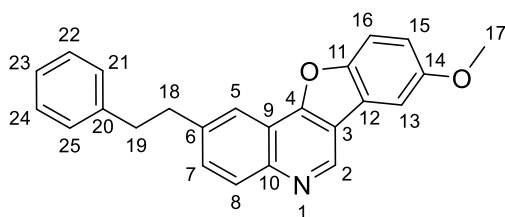
White solid; 76% yield (68 mg); m.p. 151 – 153 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2921 (alkyl C-H stretch), 2855 (methyl C-H stretch), 1597 (C=N stretch), 1565 (aromatic C=C stretch), 1324, 1218 (ether C-O stretch), 1185 (C-F stretch); ¹H NMR (300

MHz, CDCl₃): δ = 9.38 (s, 1H, H-2), 8.17 (d, 1H, *J* 8.7 Hz, H-8), 8.12 (s, 1H, H-5), 7.84 (s, 1H, H-13), 7.58 (d, 1H, *J* 8.4 Hz, H-16), 7.56 (dd, 1H, *J* 8.7, 1.9 Hz, H-7), 7.31 (dd, 1H, *J* 8.4, 1.3 Hz, H-15), 7.11-7.16 (m, 2H, H-21, H-25), 6.93 – 6.98 (m, 2H, H-22, H-24), 3.10 (m, 4H, H-18, H-19), 2.53 (s, 3H, C(17)-H₃) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 161.4 (d, ¹*J*_(C,F) = 248 Hz, C(23)-F), 157.5 (qC-4), 154.4 (qC-11), 145.9 (qC-10), 143.4 (CH-2), 140.6 (qC-6), 136.8 (d, ⁴*J*_(C,F) = 3 Hz qC-20), 133.8 (qC-14), 130.7 (CH-7), 129.8 (d, ³*J*_(C,F) = 8 Hz, 2 $\times$ CH-21, CH-25), 129.5 (CH-8), 128.4 (CH-15), 122.7 (qC-12), 120.6 (CH-13), 119.4 (CH-5), 117.2 (qC-9), 116.4 (qC-3), 115.2 (d, ²*J*_(C,F) = 22 Hz, 2 $\times$ CH-22,

CH-**24**), 111.6 (CH-**16**), 38.1 (CH₂-**18**), 36.8 (CH₂-**19**), 21.4 (CH₃-**17**) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ = -117.2 ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₄H₁₉FNO: 356.1445; found: 356.1447.

8-Methoxy-2-phenethylbenzofuro[3,2-c]quinoline **4e**

Synthesis of product **4e** as per general procedure 2 using **1b** (100 mg, 0.24 mmol), Pd(OAc)₂ (2.74 mg, 5 mol%), TBAOAc (369 mg, 1.22 mmol), styrene (31.0 μL, 0.27 mmol) and one hydrogen balloon.

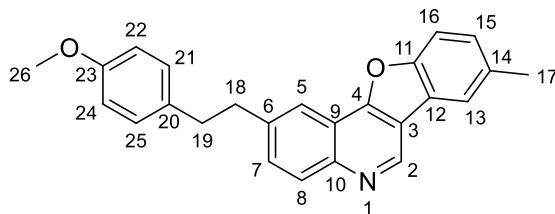


White solid, 78% yield (68 mg), m.p. 152 – 153; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3030 (aromatic C-H stretch), 2920 (alkyl C-H stretch), 2830 (methoxy C-H stretch), 1594 (C=N stretch), 1568 (aromatic C=C stretch), 1319, 1267,

1228 (ether C-O stretch); ¹H NMR (400 MHz, CDCl₃): δ = 9.41 (s, 1H, H-**2**), 8.21 (d, 1H, *J* 8.7 Hz, H-**8**), 8.17 (s, 1H, H-**5**), 7.63 (d, 1H, *J* 9.0 Hz, H-**16**, overlapping with H-**7**), 7.62 (dd, 1H, *J* 8.4, 1.8 Hz, H-**7**, overlapping with H-**16**), 7.52 (d, 1H, *J* 2.5 Hz, H-**13**), 7.19 – 7.34 (m, 5H, H-**21**, H-**22**, H-**23**, H-**24**, H-**25**), 7.12 (dd, 1H, *J* 9.0 Hz, 2.5, H-**15**), 3.95 (s, 3H, C(**17**)-H₃), 3.05 – 3.25 (m, 4H, C(**18**)-H₂, C(**19**)-H₂) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 158.2 (qC-**4**), 156.9 (qC-**11**), 150.7 (qC-**14**), 145.4 (qC-**10**), 143.1 (CH-**2**), 141.2 (2 × qC-**6**, qC-**20**), 131.1 (CH-**7**), 129.1 (CH-**8**), 128.5 (3 × CH-**22**, CH-**23**, CH-**24**), 126.2 (2 × CH-**21**, CH-**25**), 123.2 (qC-**12**), 119.4 (CH-**5**), 117.2 (qC-**9**), 116.7 (qC-**3**), 115.7 (CH-**15**), 112.7 (CH-**16**), 103.3 (CH-**13**), 56.1 (CH₃-**17**), 38.1 (CH₂-**18**), 37.7 (CH₂-**19**) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₄H₂₀NO₂: 354.1489; found: 354.1489.

2-(4-Methoxyphenethyl)-8-methylbenzofuro[3,2-c]quinoline **4f**

Synthesis of product **4f** as per general procedure 2 using **1d** (100 mg, 0.25 mmol), Pd(OAc)₂ (2.86 mg, 5 mol%), TBAOAc (383.5 mg, 1.27 mmol), 4-methoxystyrene (37.2 μL, 0.28 mmol) and one hydrogen balloon.



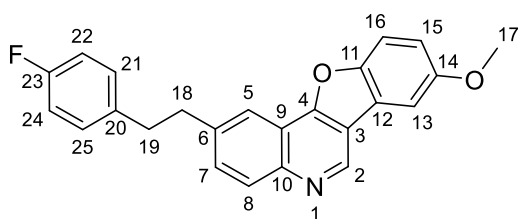
White solid; 82% yield (77 mg); m.p. 156 – 158 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2960 (alkyl C-H stretch), 2875 (methyl C-H stretch), 2837 (methoxy C-H stretch), 1611 (C=N stretch), 1563 (aromatic C=C stretch), 1367, 1187,

1175 (ether C-O stretch); ¹H NMR (300 MHz, CDCl₃): δ = 9.41 (s, 1H, H-**2**), 8.19 (d, 1H, H-**8**, overlapping with H-**5**), 8.18 (s, 1H, H-**5**, overlapping with H-**8**), 7.90 (s, 1H, H-**13**), 7.62 (d, 1H, *J* 8.4, H-**16**, overlapping with H-**7**), 7.60 (d, 1H, H-**7**, overlapping with H-**16**), 7.35 (dd, 1H, *J* 8.4, 1.5, H-**15**), 7.10 – 7.16 (m, 2H, H-**21**, H-**25**), 6.80 – 6.86 (m, 2H, H-

22, H-**24**), 3.79 (s, 3H, C(**26**)-H₃), 3.01 – 3.20 (m, 4H, H-**19**, H-**18**), 2.56 (s, 3H, C(**17**)-H₃) ppm; ¹³C NMR (150.9 MHz, CDCl₃): δ = 157.9 (qC-**23**), 157.6 (qC-**4**), 154.4 (qC-**11**), 145.7 (qC-**10**), 143.3 (CH-**2**), 141.1 (qC-**6**), 133.9 (qC-**14**), 133.3 (qC-**20**), 131.0 (CH-**7**), 129.4 (2 × CH-**21**, CH-**25**), 129.3 (CH-**8**), 128.4 (CH-**15**), 122.7 (qC-**12**), 120.6 (CH-**13**), 119.4 (CH-**5**), 117.2 (qC-**9**), 116.4 (qC-**3**), 113.8 (2 × CH-**22**, CH-**24**), 111.6 (CH-**16**), 55.3 (CH₃-**26**), 38.3 (CH₂-**18**), 36.8 (CH₂-**19**), 21.5 (CH₃-**17**) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₅H₂₂NO₂: 368.1645; found: 368.1656.

2-(4-Fluorophenethyl)-8-methoxybenzofuro[3,2-c]quinoline **4g**

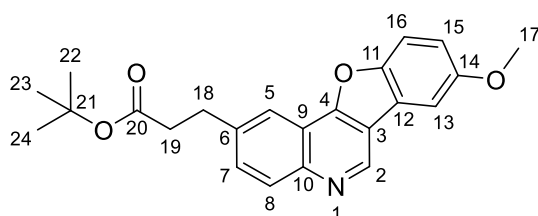
Synthesis of product **4g** as per general procedure 2 using **1b** (100 mg, 0.24 mmol), Pd(OAc)₂ (2.74 mg, 5 mol%), TBAOAc (369 mg, 1.22 mmol), 4-fluorostyrene (32.9 μL, 0.27 mmol) and one hydrogen balloon.



White solid, 83% yield (75 mg); m.p. 170 – 171 °C; IR *v*_{max}/cm⁻¹: 2944 (alkyl C-H stretch), 2861 (methoxy C-H stretch), 1600 (C=N stretch), 1565 (aromatic C=C stretch), 1368, 1245, 1219 (ether C-O stretch), 1049 (C-F stretch); ¹H NMR (500 MHz, CDCl₃): δ = 9.38 (s, 1H, H-**2**), 8.15 (d, 1H, *J* 8.6 Hz, H-**8**), 8.11 (s, 1H, H-**5**), 7.60 (d, 1H, *J* 9.0 Hz, H-**16**), 7.56 (dd, 1H, *J* 8.6, 1.8 Hz, H-**7**), 7.50 (d, 1H, *J* 2.6 Hz, H-**13**), 7.12 – 7.17 (m, 2H, H-**21**, H-**25**), 7.10 (dd, 1H, *J* 9.0, 2.6 Hz, H-**15**), 6.93 – 6.99 (m, 2H, H-**22**, H-**24**), 3.94 (s, 3H, C(**17**)-H₃), 3.01 – 3.19 (m, 4H, H-**18**, H-**19**) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 161.4 (d, ¹*J*_(C,F) = 244 Hz, C(**23**)-F), 157.9 (qC-**4**), 156.9 (qC-**11**), 150.7 (qC-**14**), 146.1 (qC-**10**), 143.6 (CH-**2**), 140.5 (qC-**6**), 136.8 (d, ⁴*J*_(C,F) = 3 Hz, qC-**20**), 130.7 (CH-**7**), 129.8 (d, ³*J*_(C,F) = 8 Hz, CH-**21**, CH-**25**), 129.8 (CH-**8**), 123.3 (qC-**12**), 119.3 (CH-**5**), 117.2 (qC-**9**), 116.7 (qC-**3**), 115.5 (CH-**15**), 115.2 (d, ²*J*_(C,F) = 22 Hz, CH-**22**, CH-**24**), 112.6 (CH-**16**), 103.4 (CH-**13**), 56.1 (CH₃-**17**), 38.1 (CH₂-**18**), 36.8 (CH₂-**19**) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ = -117.2 ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₄H₁₉FNO₂: 372.1399; found: 372.1394.

tert*-Butyl 3-(8-methoxybenzofuro[3,2-*c*]quinolin-2-yl)propanoate **4h*

Synthesis of product **4h** as per general procedure 2 using **1b** (100 mg, 0.24 mmol), Pd(OAc)₂ (2.74 mg, 5 mol%), TBAOAc (369 mg, 1.22 mmol), *tert*-butylacrylate (39.4 μ L, 0.27 mmol) and one hydrogen balloon.

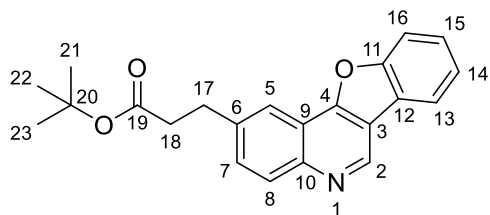


White solid, 81% yield (75 mg); m.p. 119 – 120 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2981 (alkyl C-H stretch), 2830 (methoxy C-H stretch), 1717 (ester C=O stretch), 1594 (C=N stretch), 1567 (aromatic C=C stretch), 1367, 1205

(ether C-O stretch), 1147 (ester C-O stretch), 1028 (ether C-O stretch); ¹H NMR (500 MHz, CDCl₃): δ = 9.37 (s, 1H, H-2), 8.13 – 8.21 (m, 2H, H-5, H-8), 7.63 (d, 1H, *J* 7.2 Hz, H-7), 7.60 (d, 1H, *J* 9.0 Hz, H-16), 7.46 (d, 1H, *J* 2.5 Hz, H-13), 7.09 (dd, 1H, *J* 9.0, 2.5 Hz, H-15), 3.93 (s, 3H, C(17)-H₃), 3.18 (t, 2H, *J* 7.7 Hz, H-18), 2.71 (t, 2H, *J* 7.7 Hz, H-19), 1.43 (s, 9H, 3 $\times$ C(22)-H₃, C(23)-H₃, C(24)-H₃) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 171.9 (qC-20), 157.9 (qC-4), 156.8 (qC-11), 150.7 (qC-14), 146.1 (qC-10), 143.5 (CH-2), 139.9 (qC-6), 130.5 (CH-7), 129.8 (CH-8), 123.3 (qC-12), 119.3 (CH-5), 117.2 (qC-9), 116.7 (qC-3), 115.5 (CH-15), 112.6 (CH-16), 103.3 (CH-13), 80.6 (qC-21), 56.0 (CH₃-17), 36.7 (CH₂-19), 31.2 (CH₂-18), 28.1 (3 $\times$ CH₃-22, CH₃-23, CH₃-24) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₃H₂₄NO₄: 378.1700; found: 378.1703.

tert*-Butyl 3-(benzofuro[3,2-*c*]quinolin-2-yl)propanoate **4i*

Synthesis of product **4i** as per general procedure 2 using **1c** (100 mg, 0.26 mmol), Pd(OAc)₂ (2.96 mg, 5 mol%), TBAOAc (398 mg, 1.32 mmol), *tert*-butylacrylate (42.0 μ L, 0.29 mmol) and one hydrogen balloon.



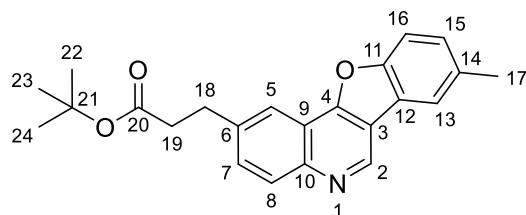
White solid, 76% yield (DCM:EtOAc, 70 mg), 73% yield (cyclohexane:EtOAc, 67 mg); m.p. 109 – 110 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2923 (alkyl C-H stretch), 1728 (ester C=O stretch), 1599 (C=N stretch), 1462 (aromatic C=C stretch), 1368,

1270 (ether C-O stretch), 1150 (ester C-O stretch); ¹H NMR (500 MHz, CDCl₃): δ = 9.43 (s, 1H, H-2), 8.16 – 8.24 (m, 2H, H-5, H-8), 8.10 (dd, 1H, *J* 7.7, 0.6 Hz, H-13), 7.72 (d, 1H, *J* 8.4 Hz, H-16), 7.64 (br d, 1H, *J* 6.8 Hz, H-7), 7.50 – 7.54 (m, 1H, H-15), 7.42 – 7.47 (m, 1H, H-14), 3.19 (t, 2H, *J* 7.8 Hz, C(17)-H₂), 2.72 (t, 2H, *J* 7.8 Hz, C(18)-H₂), 1.43 (s, 9H, C(21)-H₃, C(22)-H₃, C(23)-H₃) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 171.9 (qC-19), 157.3 (qC-4), 156.0 (qC-11), 146.0 (qC-10), 143.5 (CH-2), 140.1 (qC-6), 130.7 (CH-7), 129.6 (CH-8), 127.3 (CH-15), 124.1 (CH-14), 122.7 (qC-12), 120.6 (CH-13), 119.3 (CH-

5), 117.1 (qC-9), 116.5 (qC-3), 112.1 (CH-16), 80.6 (qC-20), 36.7 (CH₂-18), 31.2 (CH₂-17), 28.1 (3 × CH₃-21, CH₃-22, CH₃-23) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₂H₂₂NO₃: 348.1594; found: 348.1585.

***tert*-Butyl 3-(8-methylbenzofuro[3,2-*c*]quinolin-2-yl)propanoate 4j**

Synthesis of product **4j** as per general procedure 2 using **1d** (100 mg, 0.25 mmol), Pd(OAc)₂ (2.86 mg, 5 mol%), TBAOAc (383.5 mg, 1.27 mmol), *tert*-butylacrylate (41.0 μL, 0.28 mmol) and one hydrogen balloon.

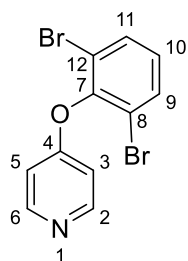


White solid; 76% yield (70 mg); m.p. 115 – 116 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2962 (alkyl C-H stretch), 2873 (methyl C-H stretch), 1731 (ester C=O stretch), 1594 (C=N stretch), 1567 (aromatic C=C stretch), 1302, 1255 (ether C-O stretch),

1190 (ester C-O stretch); ¹H NMR (500 MHz, CDCl₃): δ = 9.39 (s, 1H, H-2), 8.20 (s, 1H, H-5), 8.18 (d, 1H, *J* 8.5 Hz, H-8), 7.86 (s, 1H, H-13), 7.63 (dd, 1H, *J* 8.5, 1.8 Hz, H-7), 7.60 (d, 1H, *J* 8.4 Hz, H-16), 7.33 (dd, 1H, *J* 8.4, 1.2 Hz, H-15), 3.19 (t, 1H, *J* 7.7 Hz, H-18), 2.71 (t, 1H, *J* 7.7 Hz, H-19), 2.55 (s, 3H, C(17)-H₃), 1.43 (s, 9H, C(22)-H₃, C(23)-H₃, C(24)-H₃); ¹³C NMR (125 MHz, CDCl₃): δ = 172.0 (qC-20), 157.5 (qC-4), 154.4 (qC-11), 146.1 (CH-10), 143.6 (CH-2), 140.0 (qC-6), 133.8 (qC-14), 130.5 (CH-7), 129.7 (CH-8), 128.4 (CH-15), 122.7 (qC-12), 120.5 (CH-13), 119.3 (CH-5), 117.2 (qC-9), 116.4 (qC-3), 111.6 (CH-16), 80.6 (qC-21), 36.8 (CH₂-19), 31.2 (CH₂-18), 28.1 (3 × CH₃-22, CH₃-23, CH₃-24), 21.4 (CH₃-17) ppm; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₂₃H₂₄NO₃: 362.1751; found: 362.1757.

Synthesis of Phenenoxyppyridine Starting Material

4-(2,6-Dibromophenoxy)pyridine 5



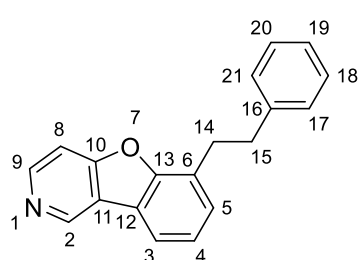
A mixture of 4-chloropyridine hydrochloride (1.0 g, 6.67 mmol) and 2,6-dibromophenol (5.8 g, 23.3 mmol) were stirred 130 °C 24 hours. The reaction mixture was cooled to room temperature and 10% aqueous NaOH (10 mL) was added and stirred for 30 min. The aqueous layer was extracted with DCM (3 × 15 mL). The organic layers were combined and washed with 6M NaOH (3 × 15 mL), water (10 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was recrystallised from cyclohexane if necessary. White solid, 46% yield (1.01 g); m.p. 92 – 93 °C (lit: 91 – 93 °C)^[3]; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 1578 (C=N stretch), 1257, 1202 (ether C-O stretch), 667 (C-Br stretch); ¹H NMR (300 MHz, CDCl₃) δ = 8.49 (d, 2H, *J* 5.2 Hz, H-2, H-6), 7.63

(d, 2H, J 8.1 Hz, H-9, H-11), 7.07 (t, 1H, J 8.1 Hz, H-10), 6.72 – 6.77 (m, 2H, H-3, H-5) ppm; ^{13}C NMR (75.5 MHz, CDCl_3) δ = 162.5 (qC-4), 151.5 (2 $\times$ CH-2, CH-6), 147.7 (qC-7), 133.1 (2 $\times$ CH-9, CH-11), 128.3 (CH-10), 118.3 (2 $\times$ qC-8, qC-12), 110.8 (2 $\times$ CH-3, CH-5) ppm; LRMS m/z (ESI+) 328, 330, 332 $[(\text{M}+\text{H})^+$, 100%].

One-Pot Pyridine Products

6-Phenethylbenzofuro[3,2-*c*]pyridine 6a

Synthesis of product **6a** as per general procedure 2 using **5** (100 mg, 0.30 mmol), $\text{Pd}(\text{OAc})_2$ (3.41 mg, 5 mol%), TBAOAc (458.2 mg, 1.51 mmol), styrene (38.3 μL , 0.33 mmol) and one hydrogen balloon.

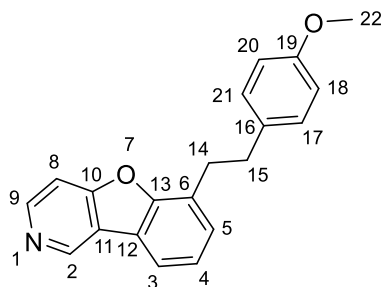


Colourless oil, 66% yield (55 mg); IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3022 (aromatic C-H stretch), 2921 (alkyl C-H stretch), 1599 (C=N stretch), 1494 (aromatic C=C stretch), 1346, 1244 (ether C-O stretch); ^1H NMR (600 MHz, CDCl_3): δ = 9.35 (br s, 1H, H-2), 8.75 (br s, 1H, H-9), 7.87 (dd, 1H, J 7.4, 1.0 Hz, H-4), 7.57 (br s, 1H, H-8), 7.17 – 7.35 (m, 7H, H-

3, H-5, H-17, H-18, H-19, H-20, H-21), 3.05 – 3.32 (m, 4H, C(14)- H_2 , C(15)- H_2) ppm; ^{13}C NMR (150.9 MHz, CDCl_3): δ = 160.8 (qC-10), 154.5 (qC-13), 146.8 (CH-9), 143.2 (CH-2), 141.3 (qC-16), 128.6 (CH-5), 128.5 (CH-17, CH-21), 128.4 (CH-18, CH-20), 126.2 (qC-6), 126.1 (CH-19), 124.0 (CH-3), 121.3 (2 $\times$ qC-11, qC-12), 118.9 (CH-4), 108.0 (CH-8), 36.1 (CH₂-15), 31.9 (CH₂-14) ppm; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{16}\text{NO}$: 273.1274; found: 273.1286.

6-(4-Methoxyphenethyl)benzofuro[3,2-*c*]pyridine 6b

Synthesis of product **6b** as per general procedure 2 using **5** (100 mg, 0.30 mmol), $\text{Pd}(\text{OAc})_2$ (3.41 mg, 5 mol%), TBAOAc (458.2 mg, 1.51 mmol), 4-methoxystyrene (44.5 μL , 0.33 mmol) and one hydrogen balloon.



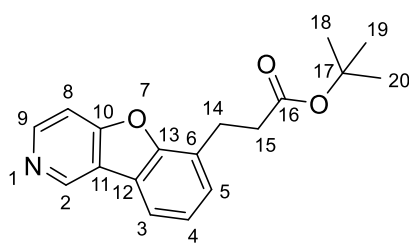
Colourless oil, 65% yield (60 mg); IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3031 (aromatic C-H stretch), 2925 (alkyl C-H stretch), 2855 (methoxy C-H stretch), 1594 (C=N stretch), 1575 (aromatic C=C stretch), 1340, 1243 (ether C-O stretch); ^1H NMR (600 MHz, CDCl_3): δ = 9.27 (br s, 1H, H-2), 8.67 (br s, 1H, H-9), 8.87 (dd, 1H, J 7.3, 1.7 Hz, H-4), 7.53 (br

d, 1H, J 3.9 Hz, H-9), 7.26 – 7.36 (m, 2H, H-3, H-5), 7.10 – 7.16 (m, 2H, H-17, H-21), 6.82 (m, 2H, H-18, H-20), 3.78 (s, 3H, C(22)- H_3), 2.97 – 3.31 (m, 4H, C(14)- H_2 , C(15)- H_2) ppm; ^{13}C NMR (150.9 MHz, CDCl_3): δ = 160.8 (qC-19), 157.9 (qC-10), 154.5 (qC-

13), 147.1 (CH-**9**), 143.5 (CH-**2**), 133.5 (qC-**16**), 129.4 (2 × CH-**17**, CH-**21**), 128.6 (CH-**5**), 126.2 (qC-**6**), 123.9 (CH-**3**), 122.1 (qC-**11**), 121.2 (CH-**12**), 118.8 (CH-**4**), 113.8 (2 × CH-**18**, CH-**19**), 107.6 (CH-**8**), 55.3 (CH₃-**22**), 35.2 (CH₂-**15**), 32.2 (CH₂-**14**) ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₂₀H₁₈NO₂: 304.1332; found: 304.1336.

tert*-Butyl 3-(benzofuro[3,2-*c*]pyridin-6-yl)propanoate **6c*

Synthesis of product **6c** as per general procedure 2 using **5** (100 mg, 0.30 mmol), Pd(OAc)₂ (3.41 mg, 5 mol%), TBAOAc (458.2 mg, 1.51 mmol), *tert*-butylacrylate (49.0 μL, 0.33 mmol) and one hydrogen balloon.

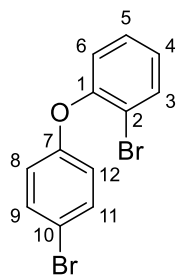


Colourless oil, 73% yield (66 mg); IR $\nu_{\max}/\text{cm}^{-1}$: 2976 (alkyl C-H stretch), 1724 (ester C=O stretch), 1593 (C=N stretch), 1575 (aromatic C=C stretch), 1367, 1209 (ether C-O stretch), 1145 (ester C-O stretch); ¹H NMR (600 MHz, CDCl₃): δ = 9.24 (s, 1H, H-**2**), 8.65

(d, 1H, J 5.9 Hz, H-**9**), 7.88 (dd, 1H, J 6.9, 2.1 Hz, H-**4**), 7.54 (dd, 1H, J 5.7, 0.8 Hz, H-**8**), 7.31 – 7.40 (m, 2H, H-**3**, H-**5**), 3.28 (t, 2H, J 7.6 Hz, C(**14**)-H₂), 2.74 (t, 2H, J 7.6 Hz, C(**15**)-H₂), 1.41 (s, 9H, C(**18**)-H₃, C(**19**)-H₃, C(**20**)-H₃) ppm; ¹³C NMR (150.9 MHz, CDCl₃): δ = 172.0 (qC-**16**), 160.9 (qC-**10**), 154.5 (qC-**13**), 147.0 (CH-**9**), 143.4 (CH-**2**), 128.6 (CH-**5**), 125.2 (qC-**6**), 124.1 (CH-**3**), 122.0 (qC-**11**), 121.3 (qC-**12**), 119.2 (CH-**4**), 107.7 (CH-**8**), 80.6 (qC-**17**), 35.3 (CH₂-**15**), 28.1 (3 × CH₃-**18**, CH₃-**19**, CH₃-**20**), 25.4 (CH₂-**14**) ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₁₈H₂₀NO₃: 298.1438; found: 298.1436.

Synthesis of Diaryl Ether Starting Materials

1-Bromo-2-(4-bromophenoxy)benzene **7**

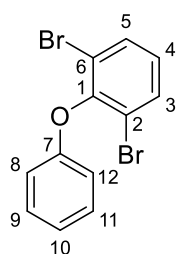


A mixture of 2-bromophenol (361.8 mg, 2.1 mmol), 4-bromophenylboronic acid (840.0, 4.18 mmol), Cu(OAc)₂ (363.0 mg, 2.0 mmol), Et₃N (1.4 mL, 10 mmol), 3 Å molecular sieves (250 mg) was added to DCM (20 mL) and stirred at room temperature for 72 hours. The reaction mixture was diluted with hexane, filtered through celite, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel and eluted with hexane (100%).

Colourless oil, 48% yield (332 mg); IR $\nu_{\max}/\text{cm}^{-1}$: 3065 (aromatic C-H stretch), 1575 (aromatic C=C stretch), 1232, 1163 (ether C-O stretch), 659 (C-Br stretch); ¹H NMR (300 MHz, CDCl₃) δ = 7.63 (dd, 1H, J 7.9, 1.5 Hz, H-**3**), 7.38 – 7.45 (m, 2H, H-**9**, H-**11**), 7.27 (td, 1H, J 8.0, 8.0, 1.6 Hz, H-**5**), 7.04 (td, 1H, J 8.0, 8.0, 1.6 Hz, H-**4**), 6.97 (dd, 1H,

J 8.1, 1.4, H-6), 6.79 – 6.85 (m, 2H, H-8, H-12) ppm; ^{13}C NMR (75.5 MHz, CDCl_3): δ = 156.3 (qC-7), 153.1 (qC-1), 134.1 (CH-3), 132.8 (2 $\times$ CH-9, CH-11), 128.9 (CH-5), 125.7 (CH-4), 121.1 (CH-6), 119.6 (CH-8), 115.8 (CH-10), 115.3 (CH-2) ppm; LRMS m/z (ESI+) 329 [(M+H) $^+$, 10%].

1,3-Dibromo-2-phenoxybenzene **8**



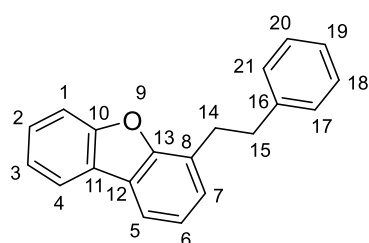
To a solution of 2,6-dibromophenol (600 mg, 2.38 mmol) in THF (21 mL) at 0 °C was added $t\text{BuOK}$ (354 mg, 2.62 mmol) and stirred for 15 min. The iodonium salt (1.05 g, 2.86 mmol) was added to the mixture and was let stir at room temperature for five days. The solvent was then removed *in vacuo* and water (15 mL) was added. The aqueous phase was extracted with DCM (3 $\times$ 15 mL) and the organic layers were combined. The organic layers were washed with water (3 $\times$ 15 mL) and brine (15 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*.

Light brown solid, 38% yield (299 mg); m.p. 55 – 57 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3072 (aromatic C-H stretch), 1589 (aromatic C=C stretch), 1242, 1194 (ether C-O stretch), 686 (C-Br stretch); ^1H NMR (300 MHz, CDCl_3) δ = 7.60 (d, 2H, J 8.0 Hz, H-3, H-5), 7.23 – 7.34 (m, 2H, H-9, H-11), 6.97 – 7.08 (m, 2H, H-4, H-10), 6.77 – 6.84 (m, 2H, H-8, H-12) ppm; ^{13}C NMR (75.5 MHz, CDCl_3): δ = 156.5 (qC-7), 149.2 (qC-1), 133.1 (2 $\times$ CH-3, CH-5), 129.7 (CH-9, CH-11), 127.4 (CH-4), 122.5 (CH-10), 119.0 (2 $\times$ CH-2, CH-6), 115.1 (CH-8, CH-12) ppm; LRMS m/z (ESI+) 327 [(M-H) $^-$, 55%].

One-Pot Diaryl Ether Products

4-Phenethyldibenzo[*b,d*]furan **9a**

Synthesis of product **9a** as per general procedure 2 using **8** (100.0 mg, 0.30 mmol), $\text{Pd}(\text{OAc})_2$ (3.42 mg, 5 mol%), TBAOAc (459.6 mg, 1.52 mmol), styrene (39.0 μL , 0.34 mmol) and one hydrogen balloon.

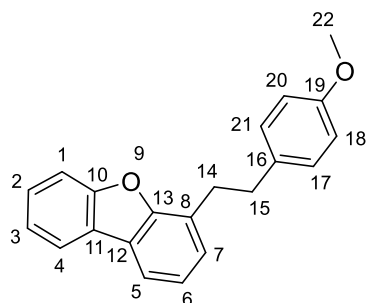


White solid, 69% (57 mg); m.p. 51 – 53 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3028 (aromatic C-H stretch), 2923 (alkyl C-H stretch), 1586 (aromatic C=C stretch) 1182 (ether C-O stretch); ^1H NMR (300 MHz, CDCl_3): δ = 7.93 (dd, 1H, J 0.7 Hz, H-12), 7.79 (dd, 1H, J 6.7, 2.2 Hz, H-6), 7.58 (d, 1H, J 8.2 Hz, H-1), 7.41 – 7.48 (m, 1H, H-2), 7.14 – 7.37 (m, 8H, H-3, H-5, H-7, H-17, H-18, H-19, H-20, H-21), 3.05 – 3.33 (m, 4H, C(14)- H_2 , C(15)- H_2) ppm; ^{13}C NMR (150.9 MHz, CDCl_3): δ = 156.0 (qC-10), 154.7 (qC-13), 141.8 (qC-16), 128.5 (2 $\times$ CH-17, CH-21), 128.3 (2 $\times$ CH-18, CH-20), 127.3 (CH-7), 126.9 (CH-2), 126.0 (CH-19), 125.7 (qC-8), 124.5 (qC-

12), 123.9 (qC-**11**), 122.7 (CH-**5**), 122.6 (CH-**3**), 120.7 (CH-**4**), 118.4 (CH-**6**), 111.7 (CH-**1**), 36.1 (CH₂-**15**), 32.0 (CH₂-**14**) ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₂₀H₁₇O: 273.1274; found: 273.1262.

4-(4-Methoxyphenethyl)dibenzo[*b,d*]furan **9b**

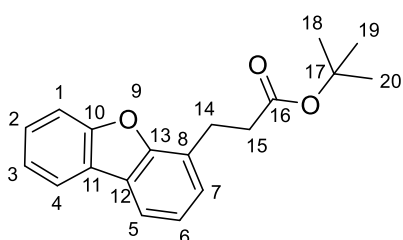
Synthesis of product **9b** as per general procedure 2 using **8** (100.0 mg, 0.30 mmol), Pd(OAc)₂ (3.42 mg, 5 mol%), TBAOAc (459.6 mg, 1.52 mmol), 4-methoxystyrene (45.2 μL, 0.34 mmol) and one hydrogen balloon.



White solid, 71% yield (65 mg); m.p. 78 – 80 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3026 (aromatic C-H stretch), 2910 (alkyl C-H stretch), 2833 (methoxy C-H stretch), 1510 (aromatic C=C stretch), 1303, 1241, 1180 (ether C-O stretch); ¹H NMR (300 MHz, CDCl₃): δ = 7.94 (ddd, 1H, J 7.6, 1.2, 0.6 Hz, H-**7**), 7.79 (dd, 1H, J 7.0, 1.9 Hz, H-**6**), 7.59 (d, 1H, J 8.2 Hz, H-**1**), 7.41 – 7.48 (m, 1H, H-**2**), 7.29 – 7.36 (m, 1H, H-**3**), 7.20 – 7.25 (m, 2H, H-**5**, H-**7**), 7.16 (m, 2H, H-**17**, H-**21**), 6.79 – 6.86 (m, 2H, H-**18**, H-**20**), 3.78 (s, 3H, C(**22**)-H₃), 2.99 – 3.29 (m, 4H, C(**14**)-H₂, C(**15**)-H₂) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = 157.9 (qC-**19**), 156.1 (qC-**10**), 154.8 (qC-**13**), 133.9 (qC-**16**), 129.4 (2 × CH-**17**, CH-**21**), 127.4 (CH-**7**), 126.9 (CH-**2**), 125.9 (qC-**8**), 124.6 (qC-**11**), 123.9 (qC-**12**), 122.7 (CH-**5**), 122.6 (CH-**3**), 120.7 (CH-**4**), 118.4 (CH-**6**), 113.8 (2 × CH-**18**, CH-**20**), 111.7 (CH-**1**), 55.3 (CH₃-**22**), 35.2 (CH₂-**15**), 32.3 (CH₂-**14**) ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₂₁H₁₉O₂: 303.1380; found: 303.1393.

tert-Butyl 3-(dibenzo[*b,d*]furan-4-yl)propanoate **9c**

Synthesis of product **9c** as per general procedure 2 using **8** (100.0 mg, 0.30 mmol), Pd(OAc)₂ (3.48 mg, 5 mol%), TBAOAc (459.6 mg, 1.52 mmol), *tert*-butylacrylate (49.1 μL, 0.34 mmol) and one hydrogen balloon.

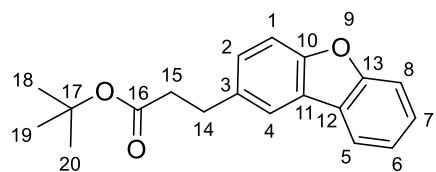


Colourless oil, 74% yield (67 mg), IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2976 (alkyl C-H stretch), 1724 (ester C=O stretch), 1587 (aromatic C=C stretch), 1350, 1184 (ether C-O stretch), 1144 (ester C-O stretch); ¹H NMR (300 MHz, CDCl₃): δ = 7.92 (dd, 1H, J 7.8, 0.6 Hz, H-**4**), 7.79 (dd, 1H, J 7.1, 1.7 Hz, H-**6**), 7.58 (d, 1H, J 8.2 Hz, H-**1**), 7.44 (m, 1H, H-**2**), 7.21 – 7.35 (m, 3H, H-**3**, H-**5**, H-**7**), 3.27 (t, 2H, J 7.7 Hz, C(**14**)-H₂), 2.74 (t, 2H, J 7.7 Hz, C(**15**)-H₂), 1.41 (s, 9H, C(**18**)-H₃, C(**19**)-H₃, C(**20**)-H₃) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = 172.3 (qC-**16**), 156.0 (qC-**10**), 154.7 (qC-**13**), 131.4 (qC-**8**), 127.3 (CH-**7**), 127.0 (CH-**2**), 124.8 (qC-**12**), 124.5 (qC-**11**), 122.8 (CH-**5**), 122.6 (CH-**3**), 120.7 (CH-**4**), 118.7 (CH-**6**),

111.7 (CH-1), 80.4 (qC-17), 35.5 (CH₂-15), 28.1 (3 × CH₃-18, CH₃-19, CH₃-20), 25.6 (CH₂-14) ppm; HRMS (ESI-TOF) *m/z*: [M+Na⁺]: [C₁₉H₂₀O₃][Na]⁺: 319.1305; found: 319.1306.

***tert*-Butyl 3-(dibenzo[*b,d*]furan-2-yl)propanoate 9d**

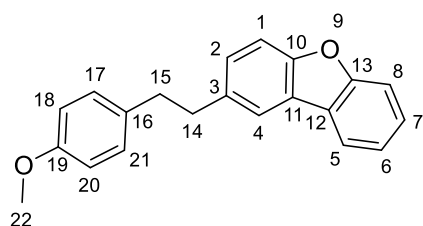
Synthesis of product **9d** as per general procedure 2 using **8** (100.0 mg, 0.30 mmol), Pd(OAc)₂ (3.48 mg, 5 mol%), TBAOAc (459.6 mg, 1.52 mmol), *tert*-butylacrylate (49.1 μL, 0.34 mmol) and one hydrogen balloon.



Colourless oil, 68% yield (61 mg); IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2976 (alkyl C-H stretch), 1724 (ester C=O stretch), 1366, 1194 (ether C-O stretch), 1141 (ester C-O stretch); ¹H NMR (300 MHz, CDCl₃): δ = 7.91 (dd, 1H, *J* 7.6, 0.7 Hz, H-5), 7.78 (d, 1H, *J* 1.3 Hz, H-4), 7.55 (d, 1H, *J* 8.2, H-8), 7.40 – 7.49 (m, 2H, H-1, H-7), 7.27 – 7.36 (m, 2H, H-2, H-6), 3.07 (t, 2H, *J* 7.7 Hz, C(14)-H₂), 2.62 (t, 2H, *J* 7.7 Hz, C(15)-H₂), 1.42 (s, 9H, 3 × C(18)-H₃, C(19)-H₃, C(20)-H₃) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = 172.2 (qC-16), 156.6 (qC-13), 154.9 (qC-10), 135.3 (qC-3), 127.6 (CH-2), 127.0 (CH-7), 124.3 (qC-11), 124.2 (qC-12), 122.6 (CH-6), 120.5 (CH-5), 120.1 (CH-4), 111.7 (CH-8), 111.4 (CH-1), 80.4 (qC-17), 37.7 (CH₂-15), 31.1 (CH₂-14), 28.1 (3 × CH₃-18, CH₃-19, CH₃-20); HRMS (ESI-TOF) *m/z*: [M+Na⁺]: [C₁₉H₂₀O₃][Na]⁺: 319.1307; found: 319.1305.

2-(4-Methoxyphenethyl)dibenzo[*b,d*]furan 9e

Synthesis of product **9e** as per general procedure 2 using **8** (100.0 mg, 0.30 mmol), Pd(OAc)₂ (3.48 mg, 5 mol%), TBAOAc (459.6 mg, 1.52 mmol), *tert*-butylacrylate (45.1 μL, 0.34 mmol) and one hydrogen balloon.

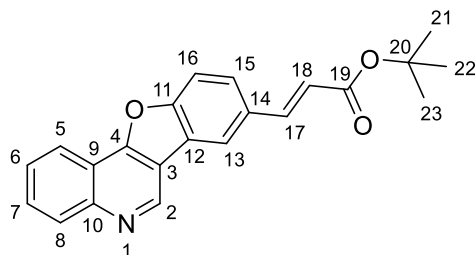


Colourless oil, 65% yield (DCM:EtOAc, 60 mg), 70% (cyclohexane:EtOAc, 65 mg); IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3039 (aromatic C-H stretch), 2857 (alkyl C-H stretch), 2839 (methoxy C-H stretch), 1510 (aromatic C=C stretch), 1300, 1244, 1175 (ether C-O stretch); ¹H NMR (300 MHz, CDCl₃): δ = 7.92 (ddd, 1H, *J* 7.6, 1.3, 0.6 Hz, H-5), 7.73 (dd, 1H, *J* 1.8, 0.4 Hz, H-4), 7.55 (ddd, 1H, *J* 8.1, 1.0, 0.7 Hz, H-8), 7.40 – 7.48 (m, 2H, H-1, H-7), 7.34 (dd, 1H, *J* 7.6, 1.0 Hz, H-6), 7.22 – 7.26 (m, 1H, H-2), 7.07 – 7.14 (m, 2H, H-17, H-21), 6.79 – 6.86 (m, 2H, H-18, H-20), 3.79 (s, 3H, C(22)-H₃), 2.89 – 3.10 (m, 4H, C(14)-H₂, C(15)-H₂) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = 157.9 (qC-19), 156.5 (qC-13), 154.8 (qC-10), 136.4 (qC-3), 133.8 (qC-16), 129.4 (2 × CH-17, CH-21), 127.8 (CH-2), 127.0 (CH-7), 124.3 (qC-11), 124.2 (qC-12), 122.5 (CH-6), 120.6 (CH-5), 120.2 (CH-

4), 113.8 (2 × CH-**18**, CH-**20**), 111.6 (CH-**8**), 111.2 (CH-**1**), 55.3 (CH₃-**22**), 38.1 (CH₂-**14**), 37.6 (CH₂-**15**) ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₂₁H₁₉O₂: 303.1016; found: 303.1011.

tert*-Butyl (*E*)-3-(benzofuro[3,2-*c*]quinolin-8-yl)acrylate **S2*

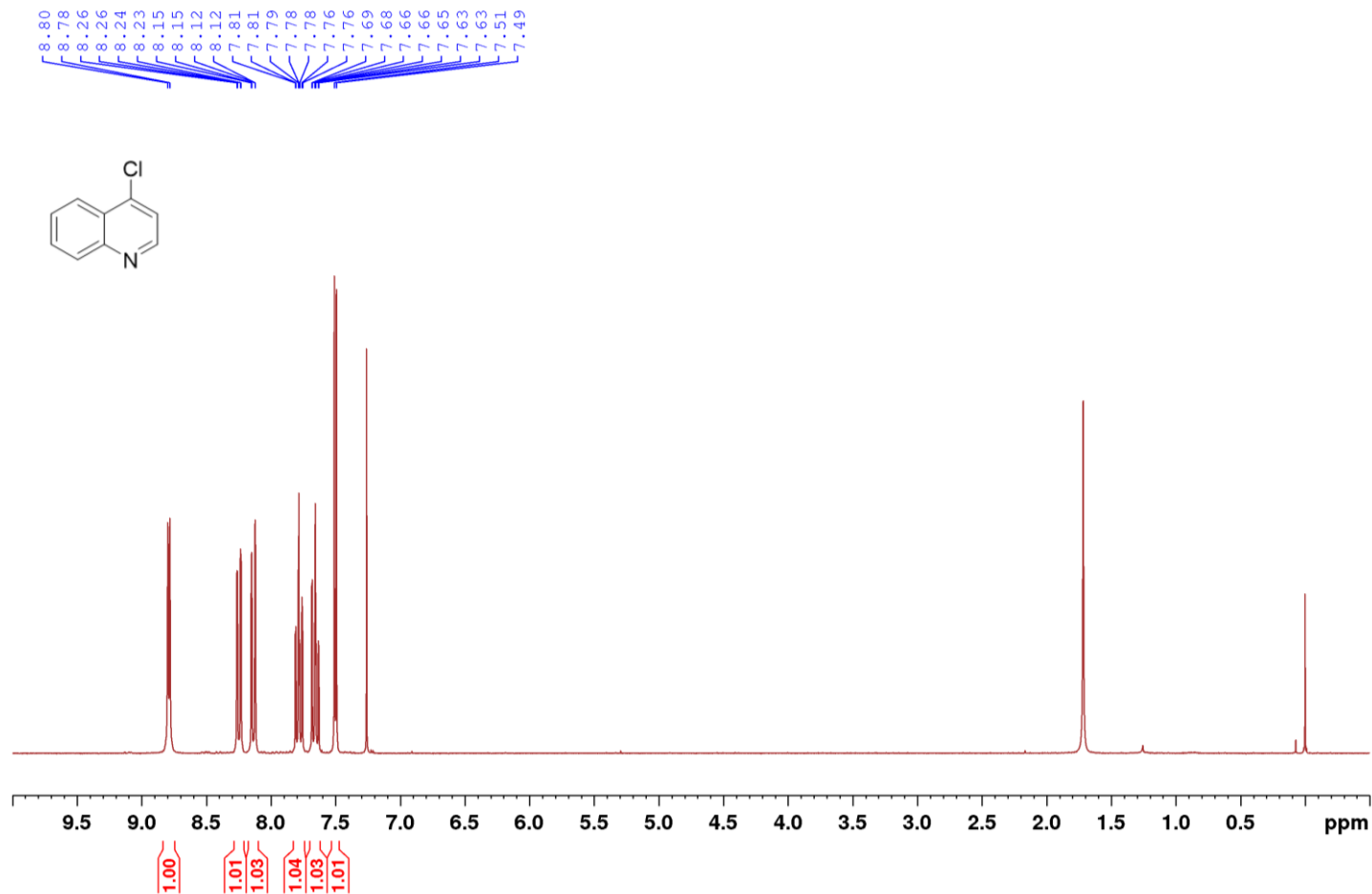
Synthesis of product **S2** as per general procedure 1 using **1a** (1.00 g, 2.64 mmol), Pd(OAc)₂ (29.6 mg, 5 mol%), TBAOAc (3.97 g, 13.19 mmol), *tert*-butylacrylate (425 μL, 2.90 mmol) and hydrogen balloons.

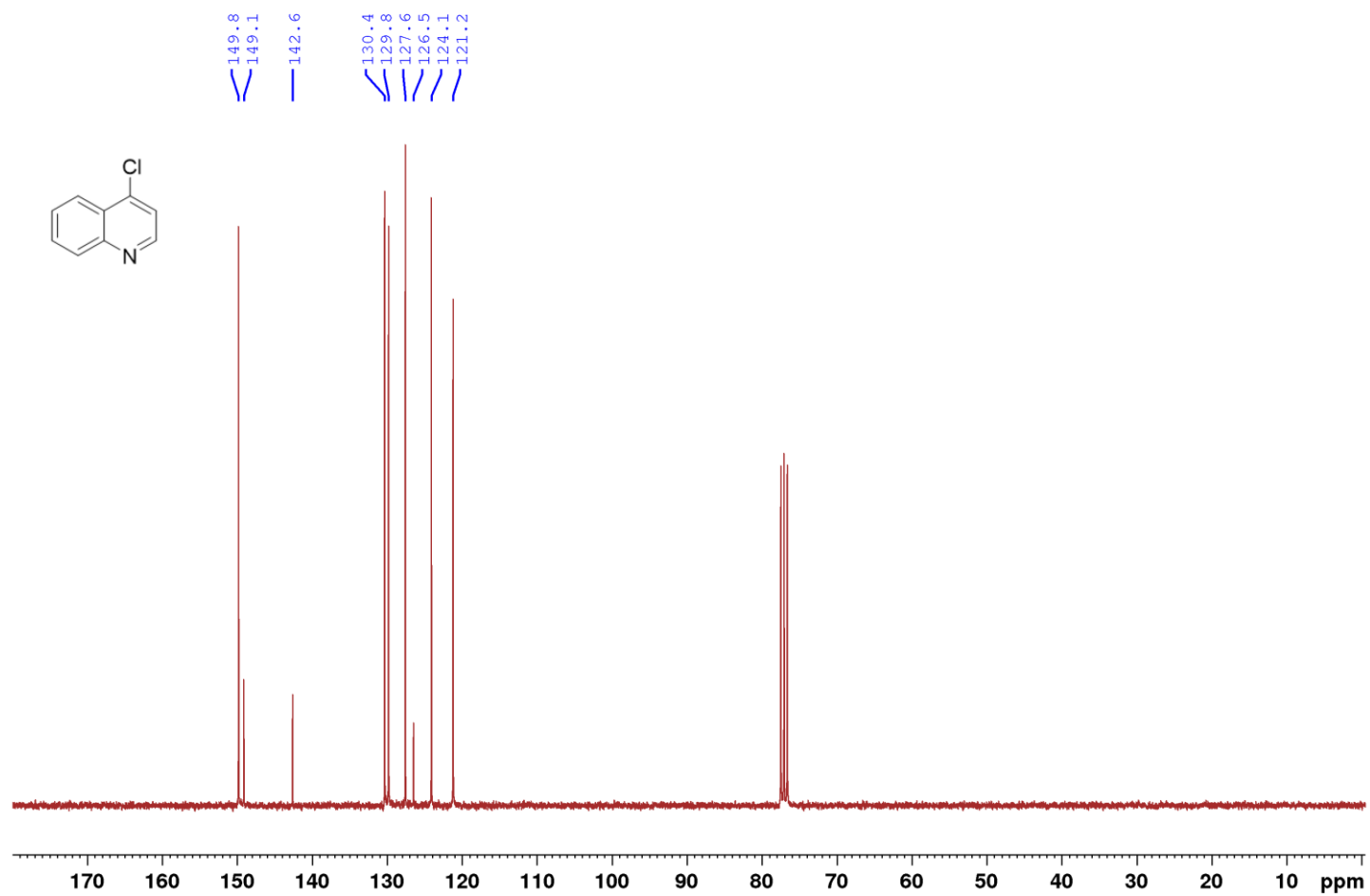


White solid, 88% yield (802 mg); m.p. 155 – 157 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 1704 (ester C=O stretch), 1668 (trans alkene C=C stretch), 1599 (C=N stretch), 1565 (aromatic C=C stretch), 1337, 1208 (ether C-O stretch), 1149 (ester C-O stretch); ¹H NMR (300 MHz, CDCl₃): δ = 9.45 (s, 1H, H-**2**), 8.36 (dd, 1H, J 8.1, 1.1 Hz, H-**5**), 8.25 (d, 1H, J 8.4, H-**8**), 8.17 (s, 1H, H-**13**), 7.83–7.62 (m, 5H, H-**6**, H-**7**, H-**15**, H-**16**, H-**17**), 6.47 (d, 1H, J 15.9 Hz, H-**18**), 1.58 (s, 9H, C(**21**)-H₃, C(**22**)-H₃, C(**23**)-H₃) ppm; ¹³C NMR (75.5 MHz, CDCl₃): δ = : 166.2 (qC-**19**), 158.2 (qC-**4**), 156.7 (qC-**11**), 147.7 (qC-**10**), 144.3 (CH-**2**), 143.0 (CH-**17**), 131.2 (qC-**14**), 130.0 (CH-**8**), 129.6 (CH-**7**), 127.24 (CH-**6**), 127.21 (CH-**15**), 123.5 (qC-**12**), 120.8 (CH-**5**), 120.3 (CH-**18**), 120.2 (CH-**13**), 117.1 (qC-**9**), 115.9 (qC-**3**), 112.5 (CH-**16**), 80.7 (qC-**20**), 28.2 (× 3 CH₃-**21**, CH₃-**22**, CH₃-**23**) ppm; HRMS (ESI-TOF) m/z : [M+H]⁺ calcd. for C₂₂H₂₀NO₃: 346.1438; found: 346.1430.

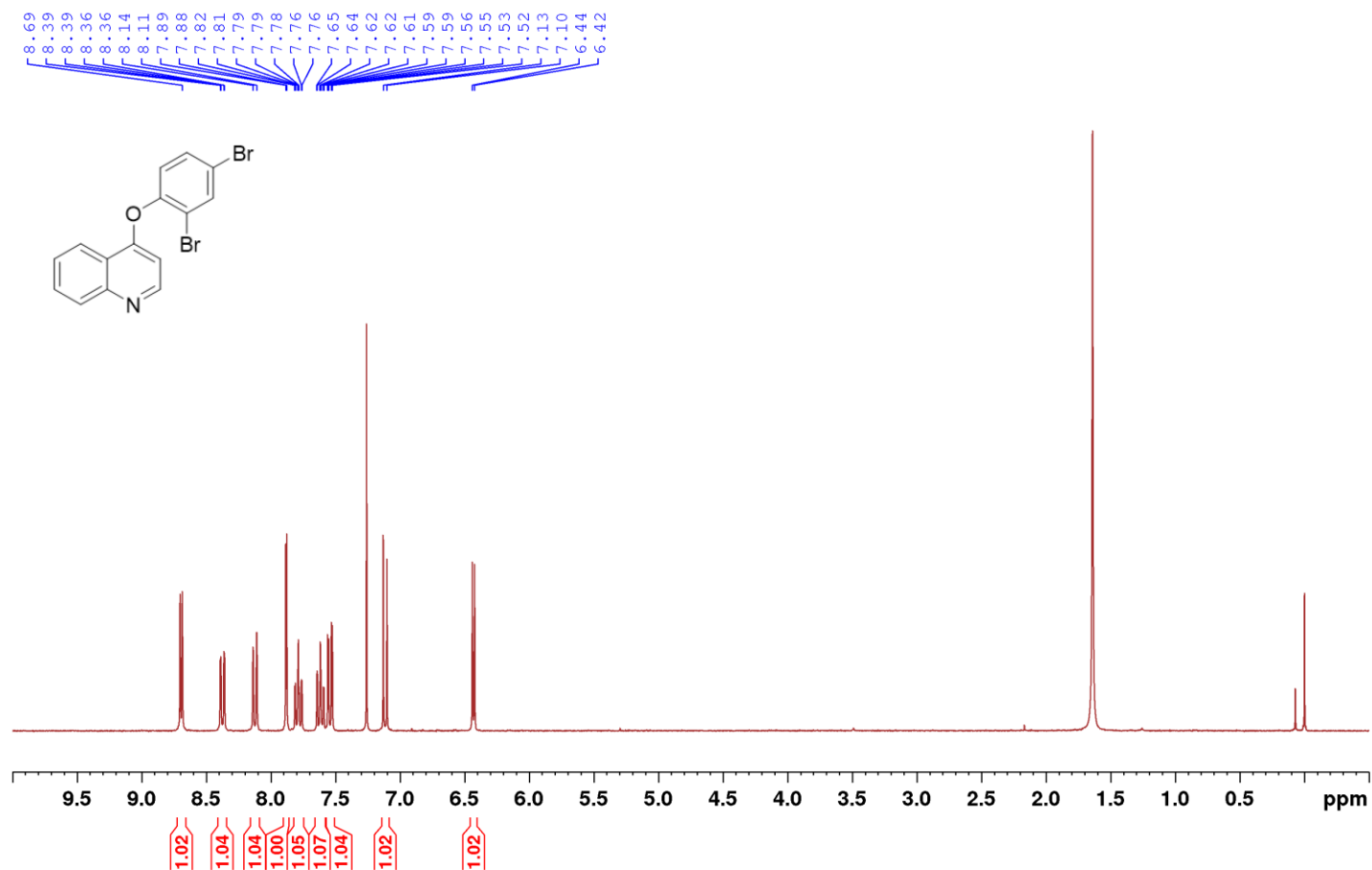
^1H NMR, ^{13}C and ^{19}F NMR Spectra

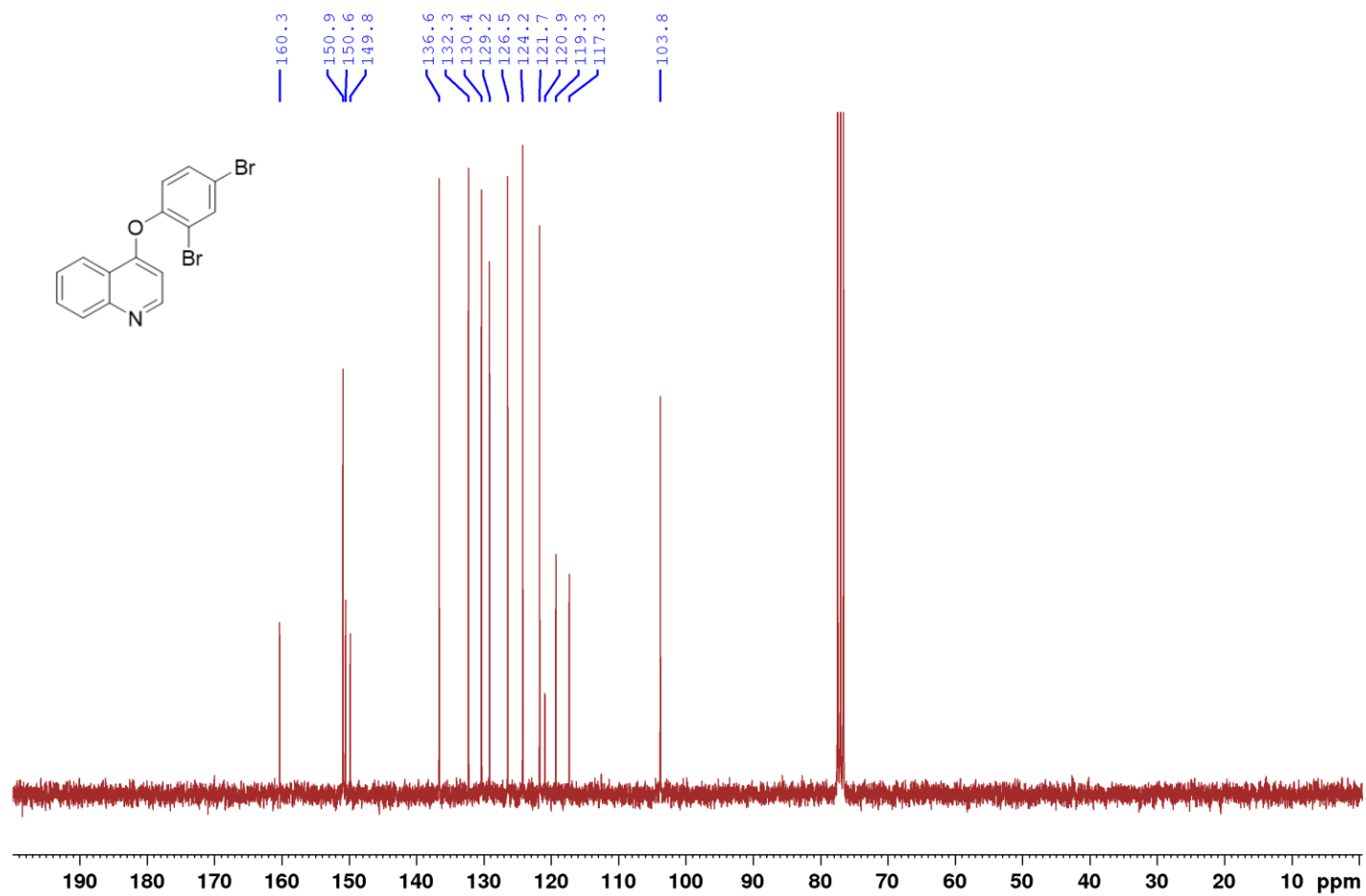
4-Chloroquinoline S1



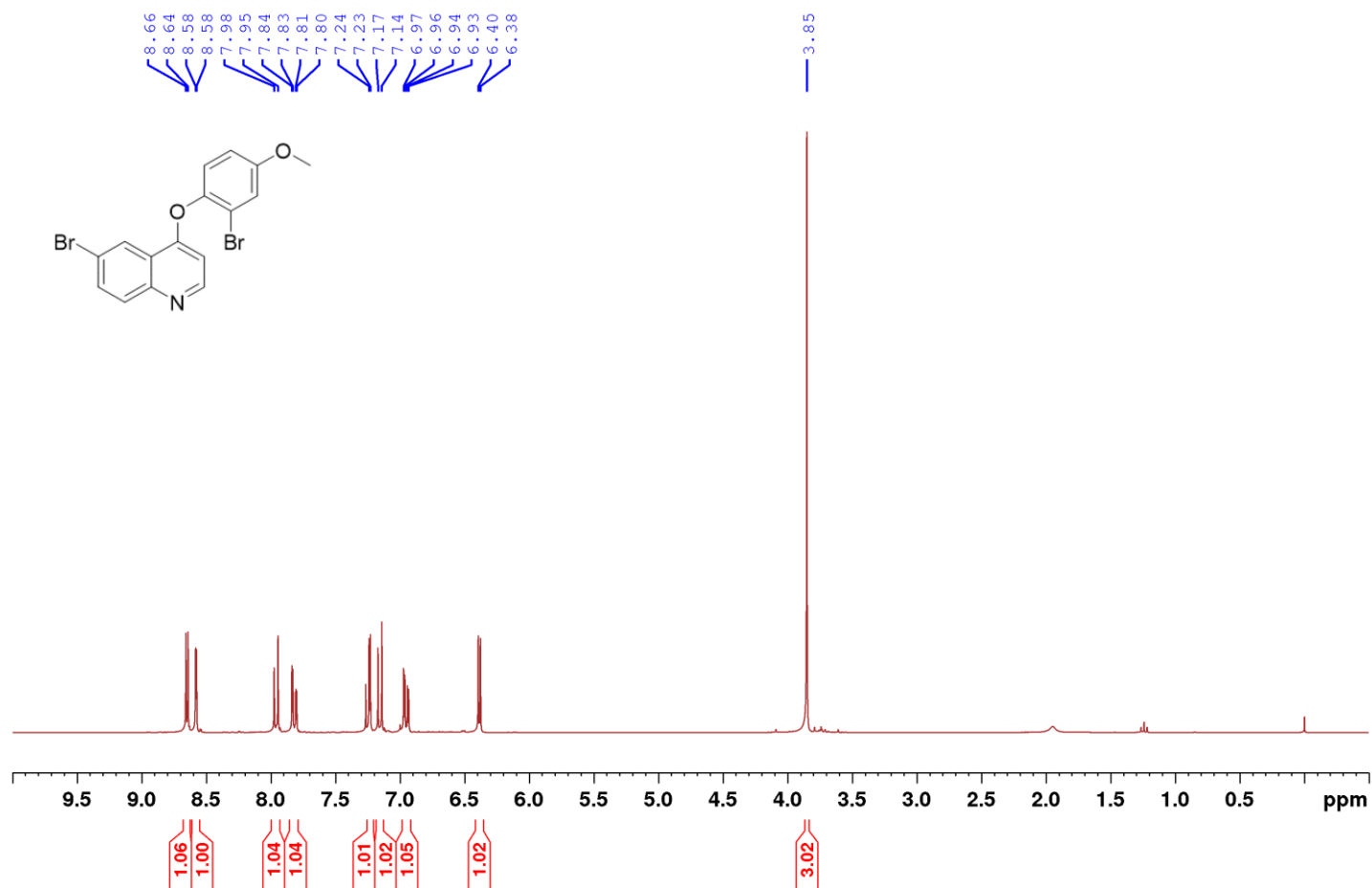


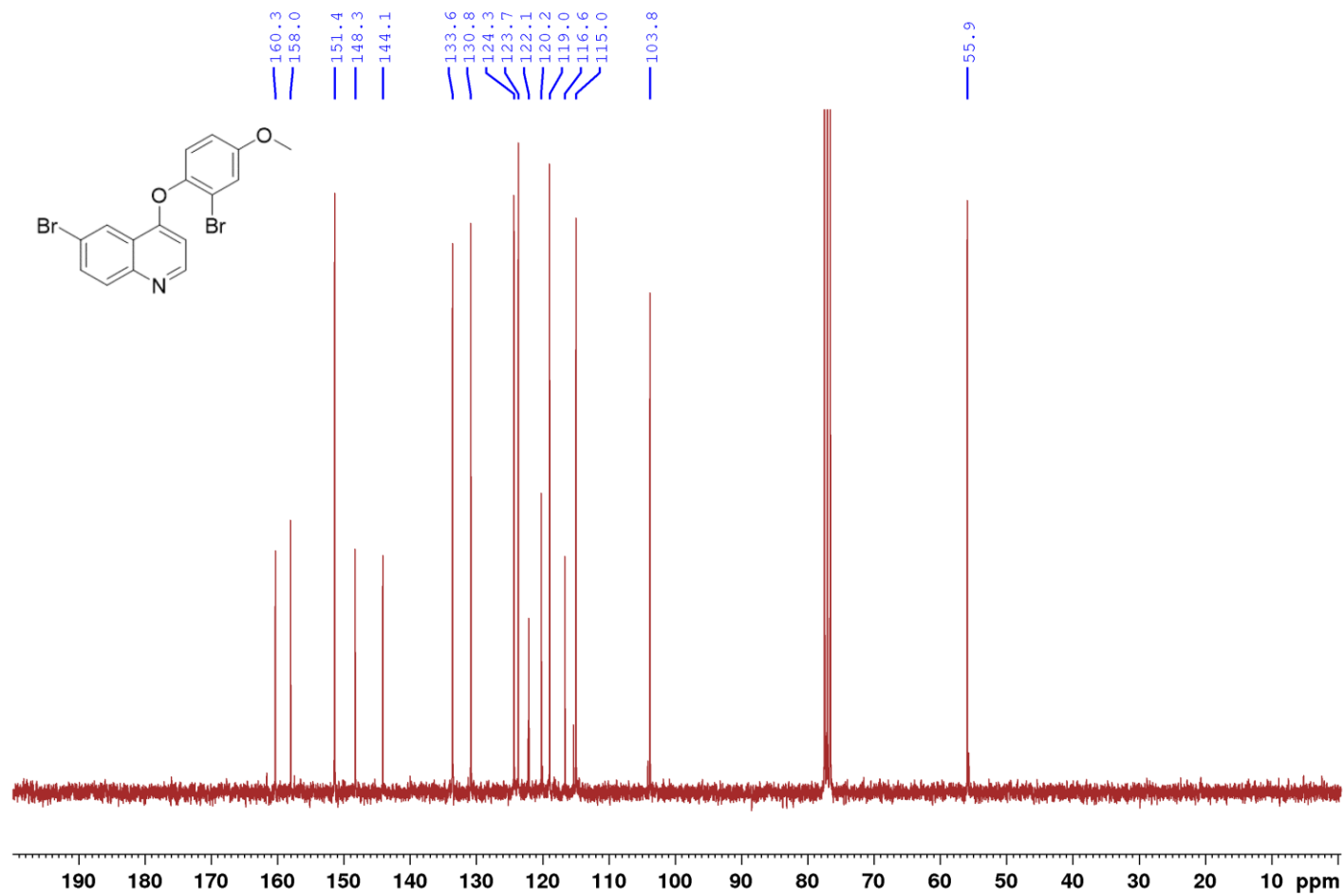
4-(2,4-Dibromophenoxy)quinoline 1a



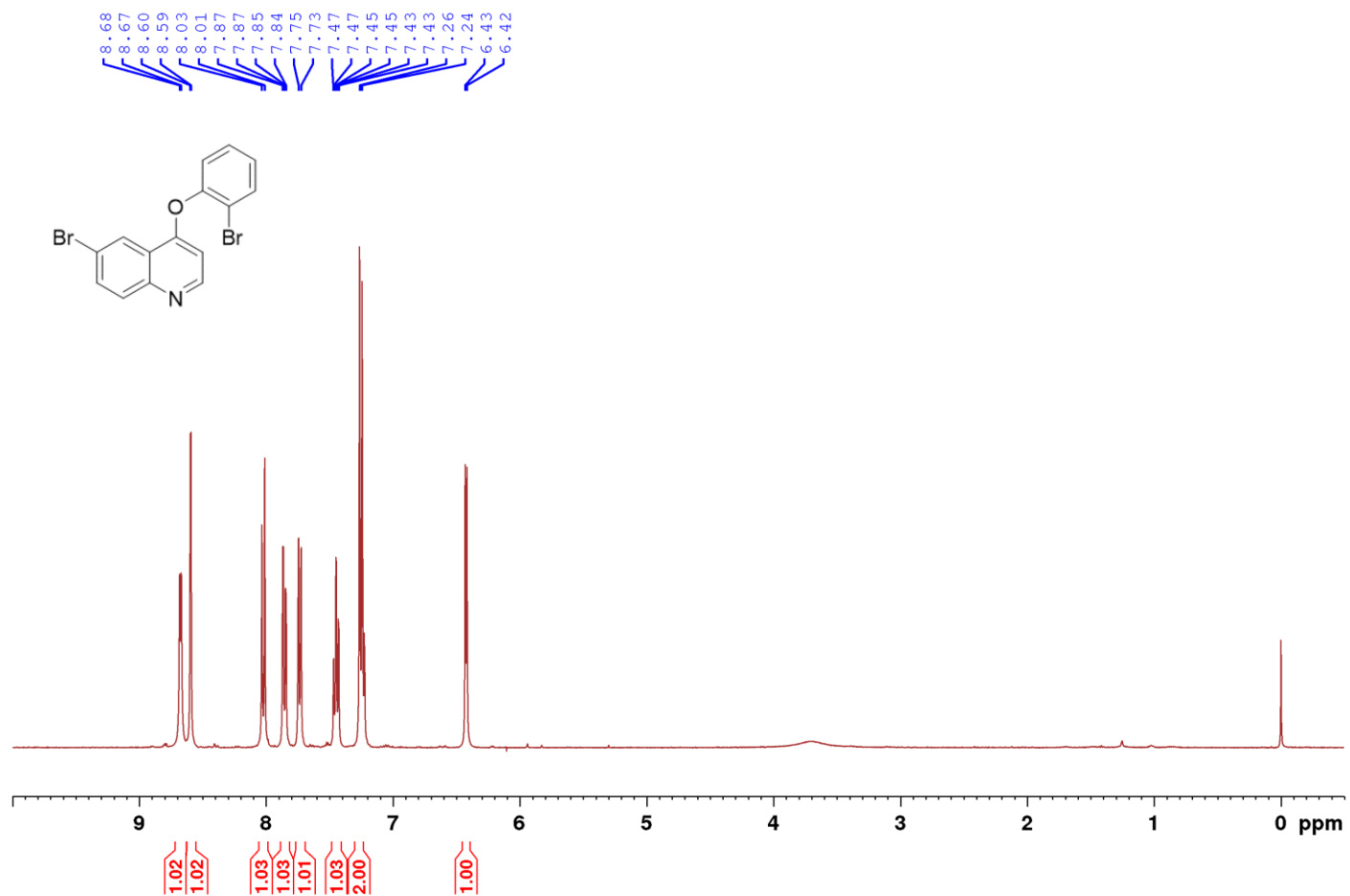


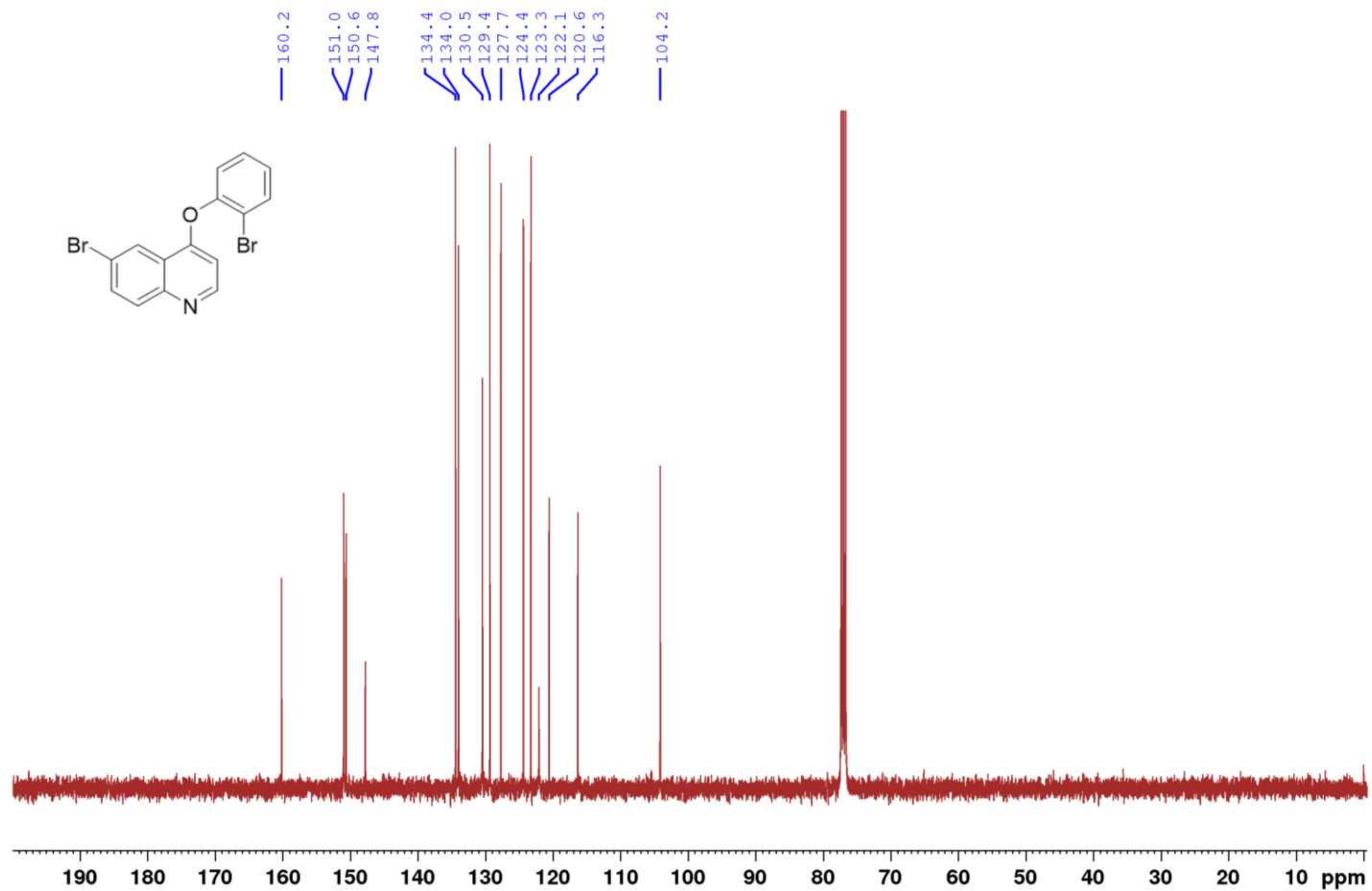
6-Bromo-4-(2-bromo-4-methoxyphenoxy)quinoline 1b



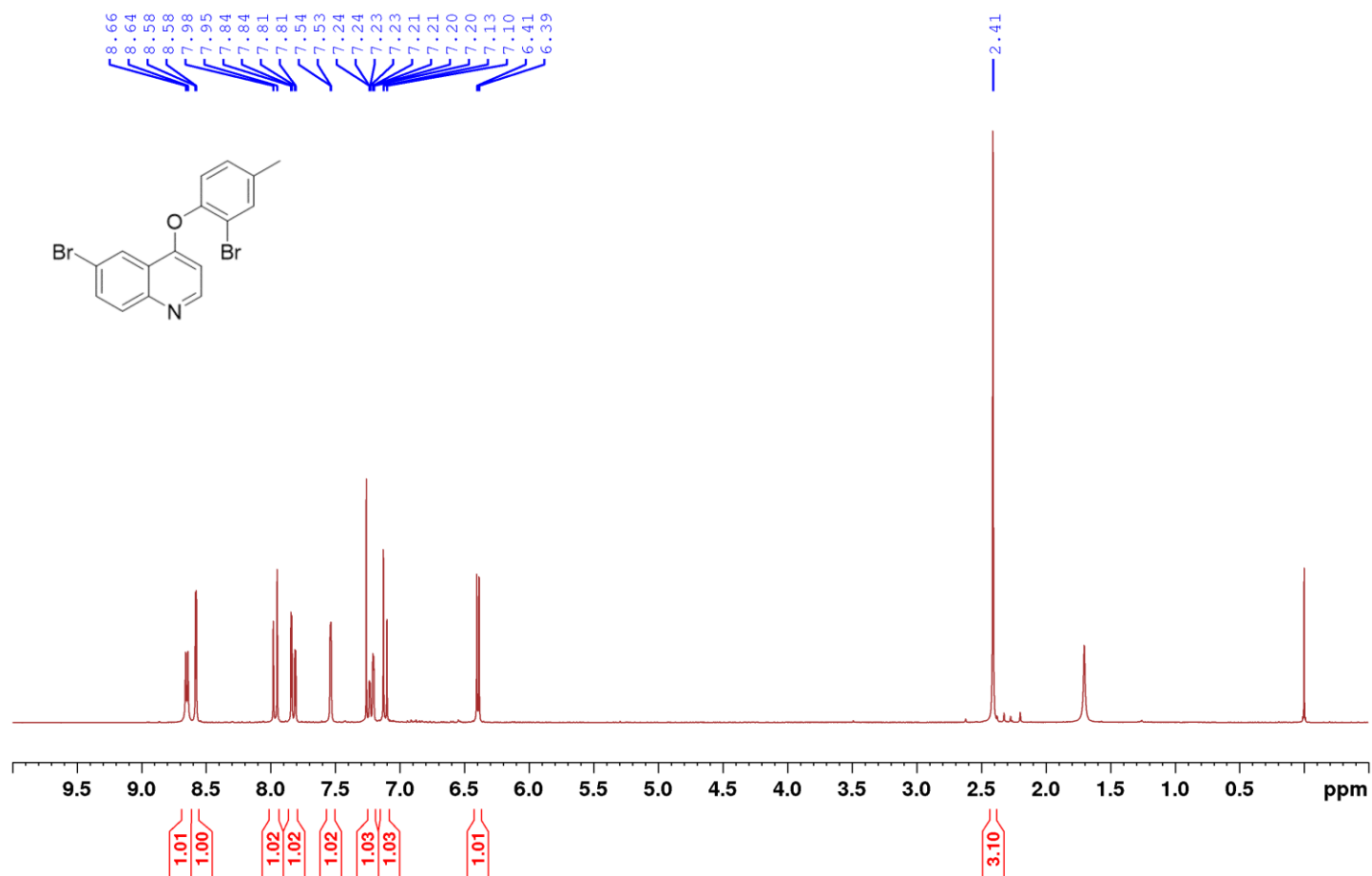


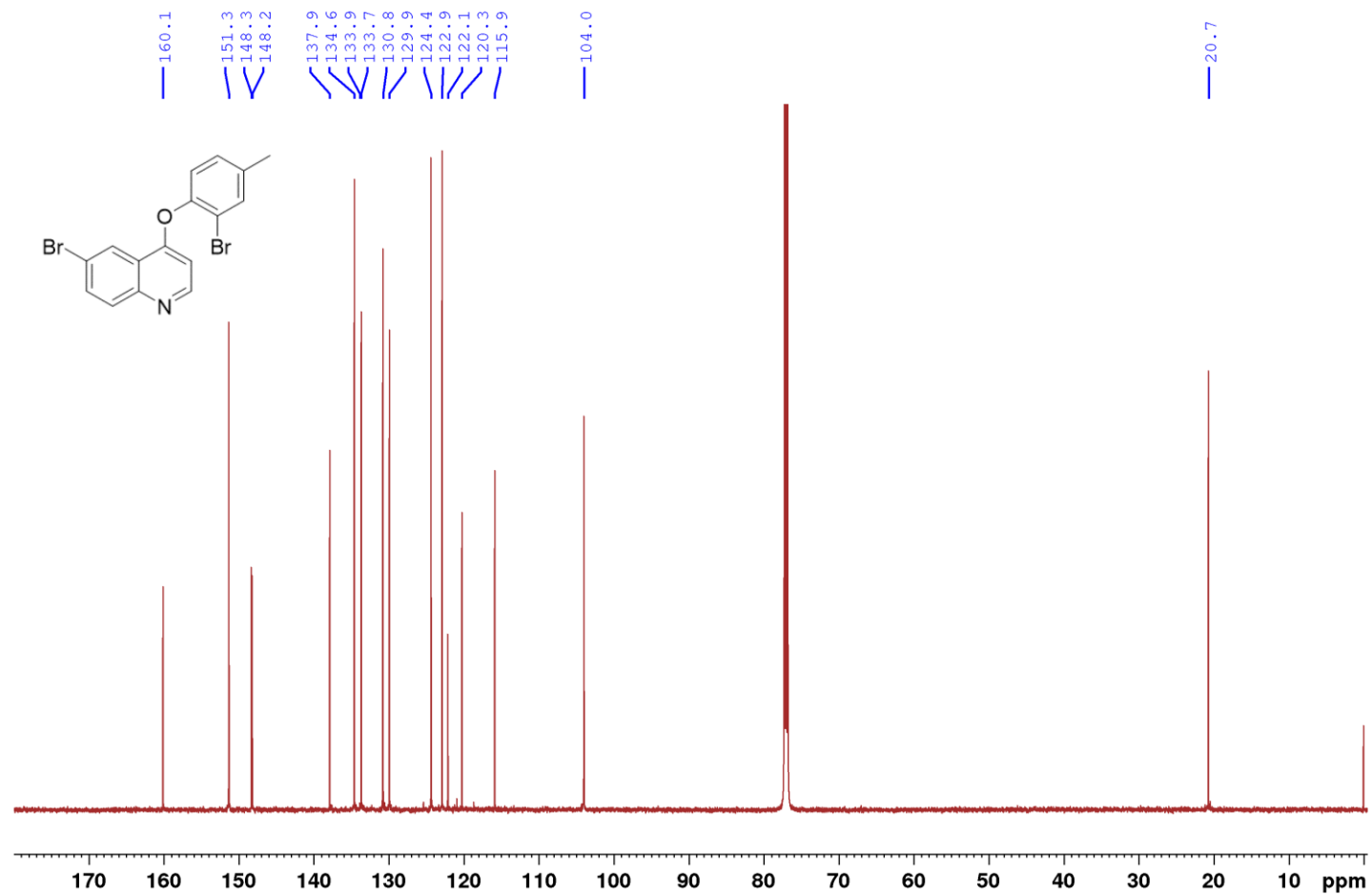
6-Bromo-4-(2-bromophenoxy)quinoline 1c



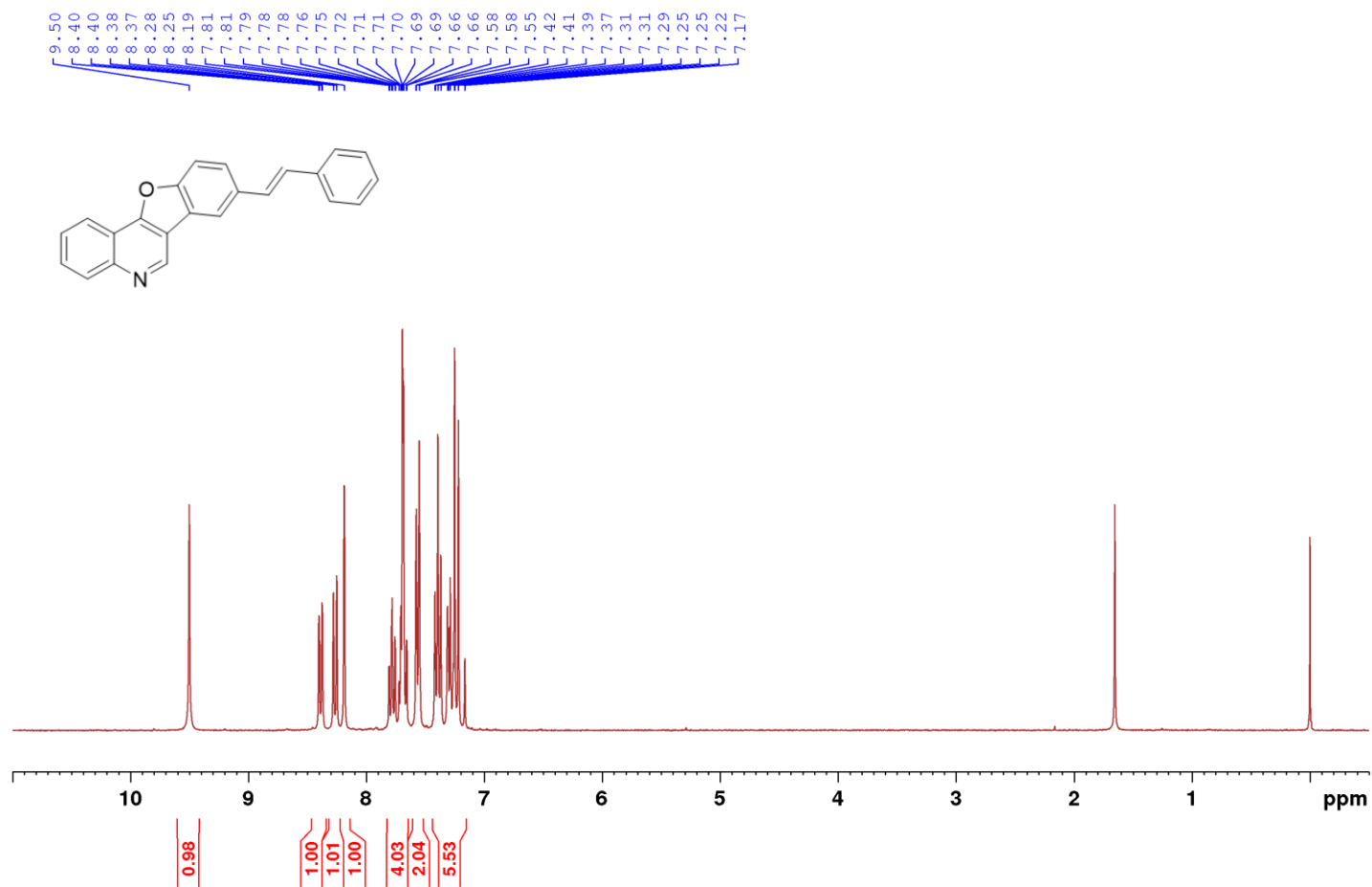


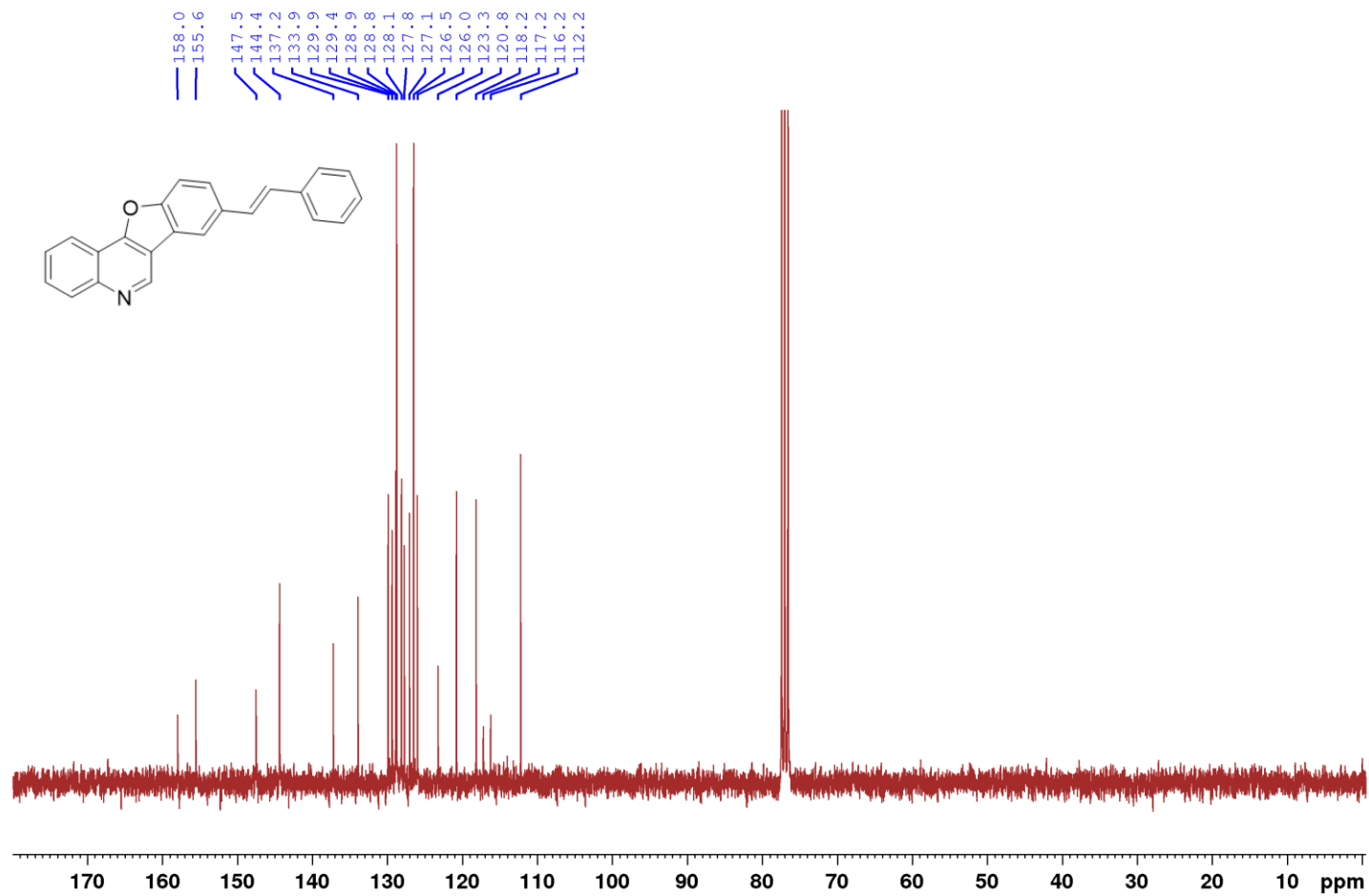
6-Bromo-4-(2-bromo-4-methylphenoxy)quinoline 1d



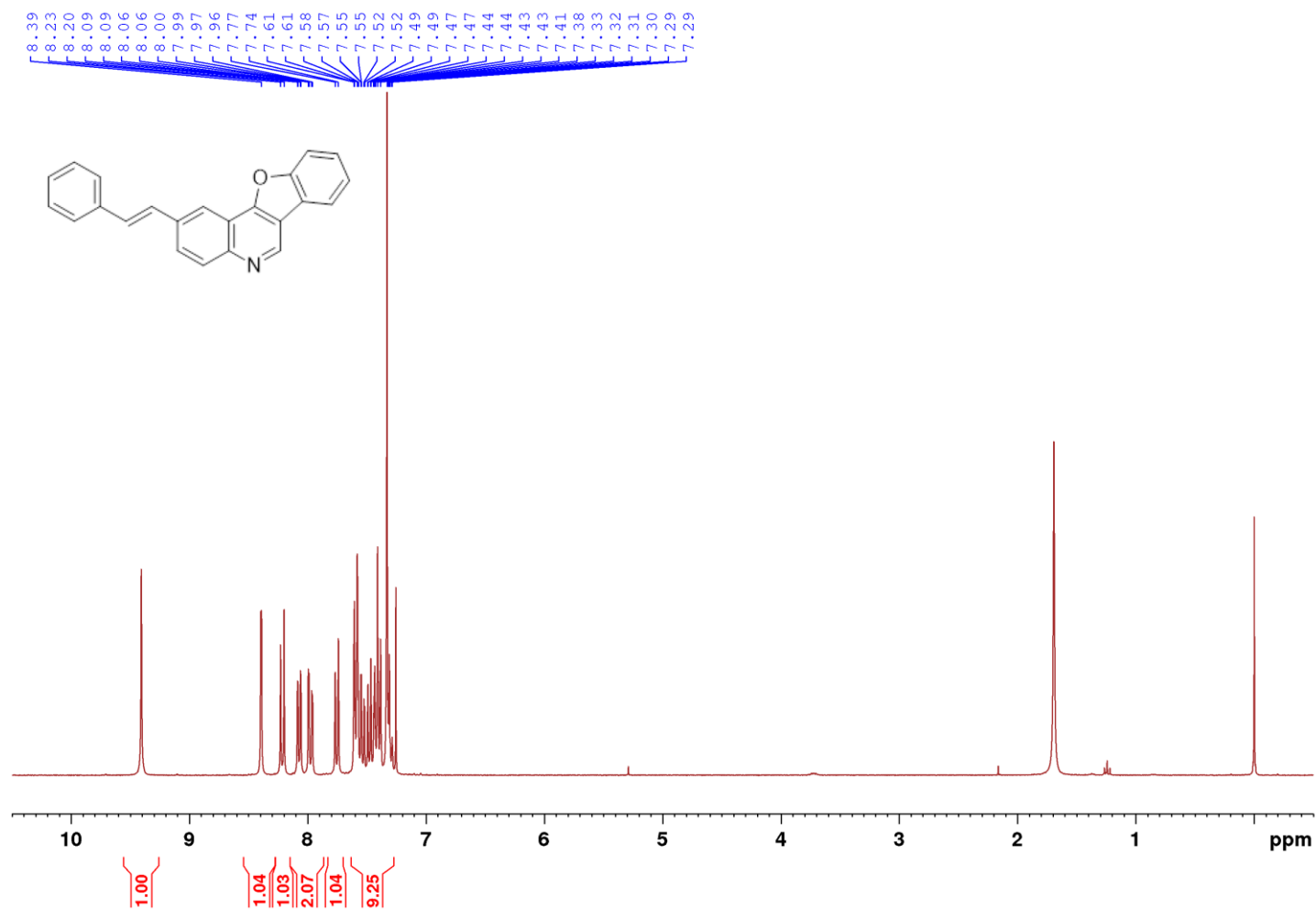


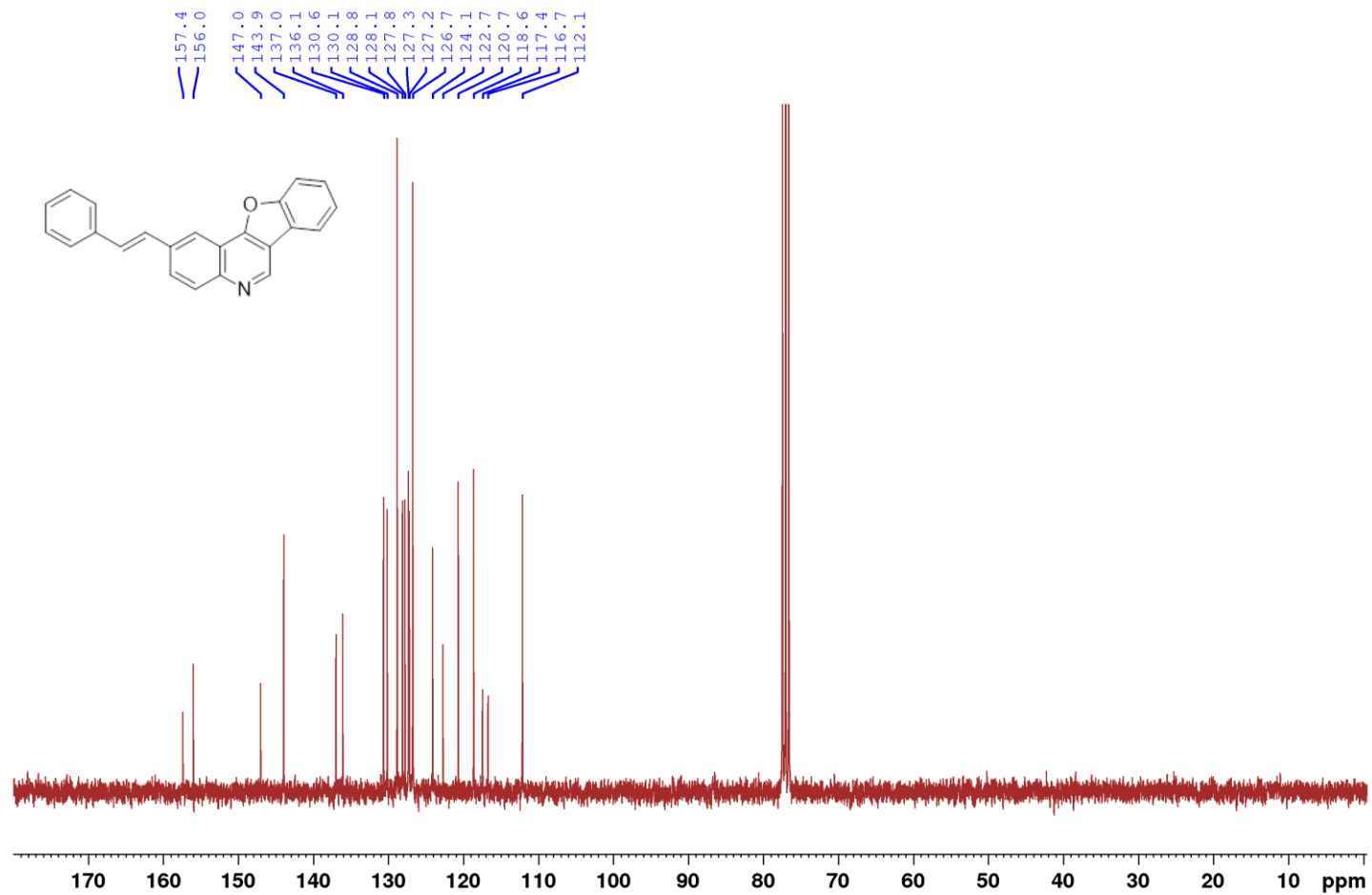
(E)-8-Styrylbenzofuro[3,2-c]quinoline 2a



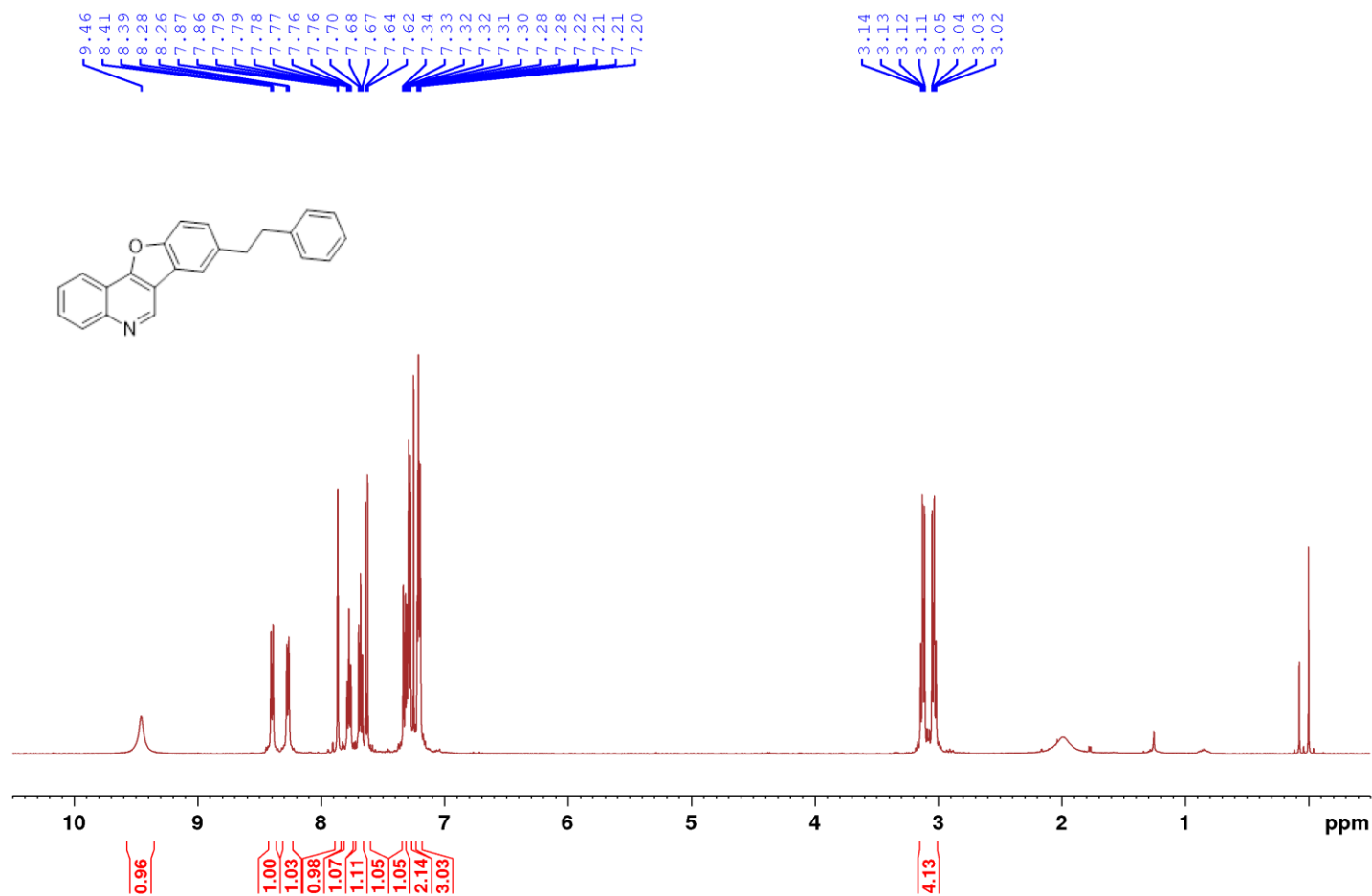


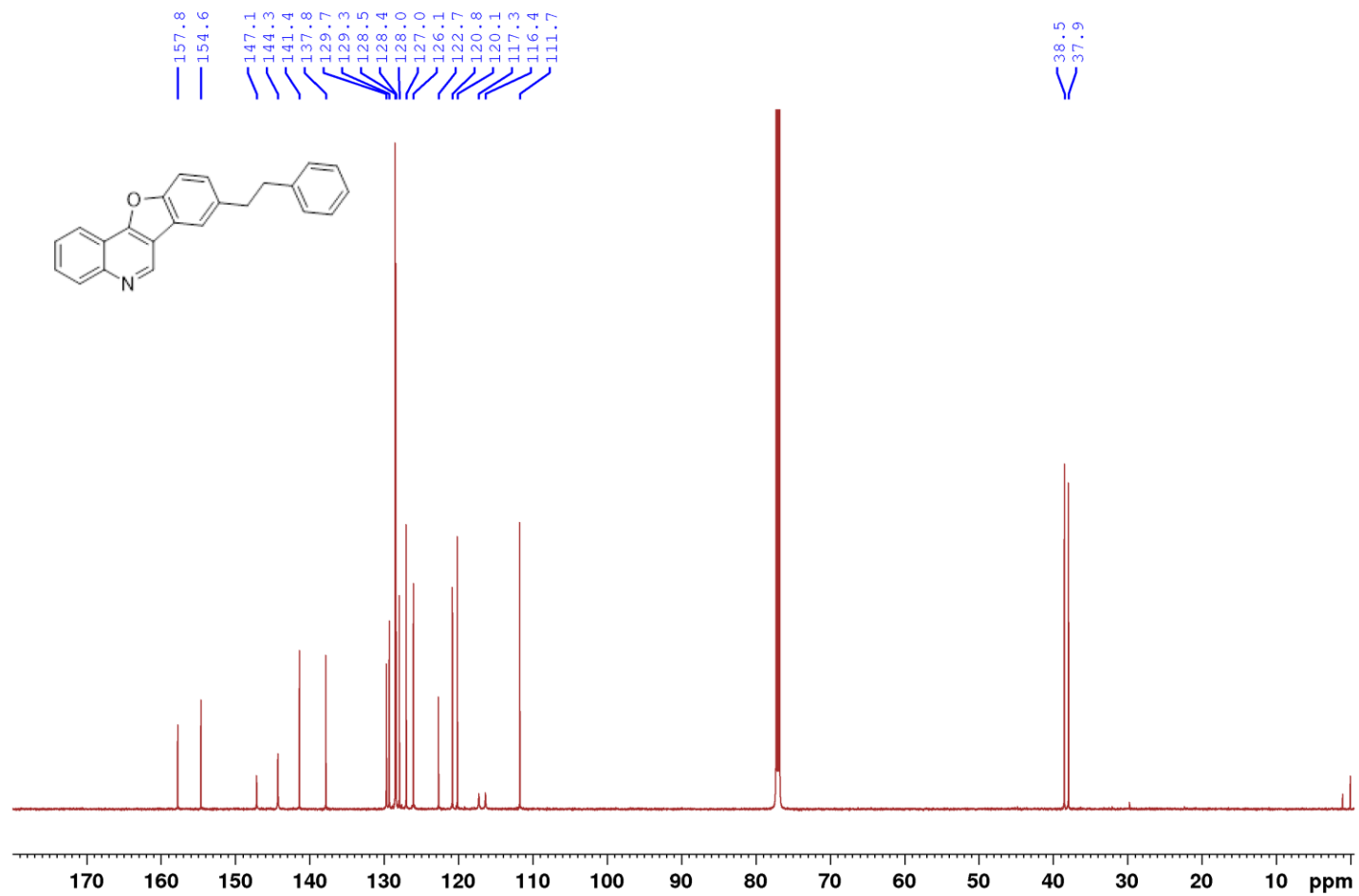
(E)-2-Styrylbenzofuro[3,2-c]quinoline 2b



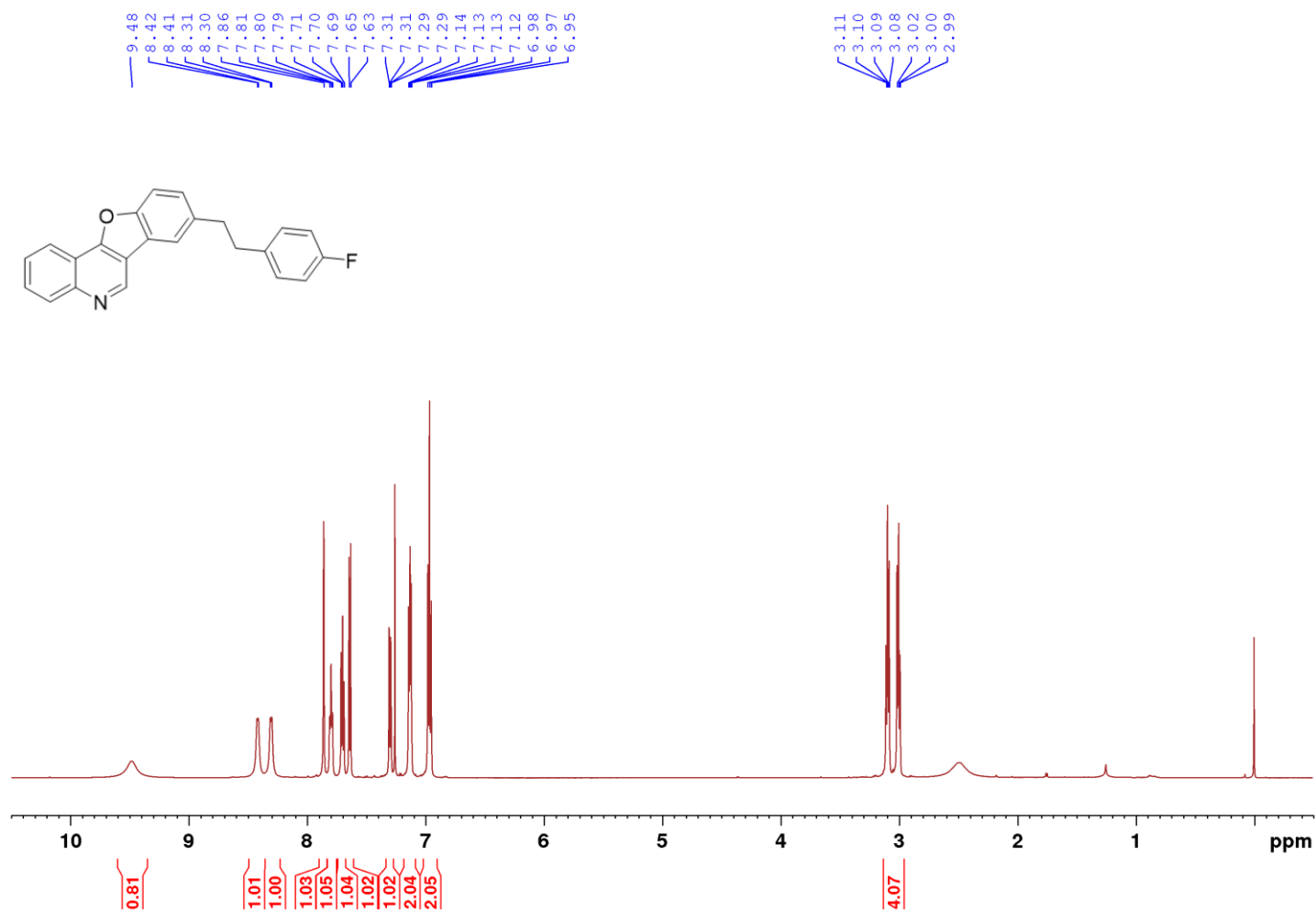


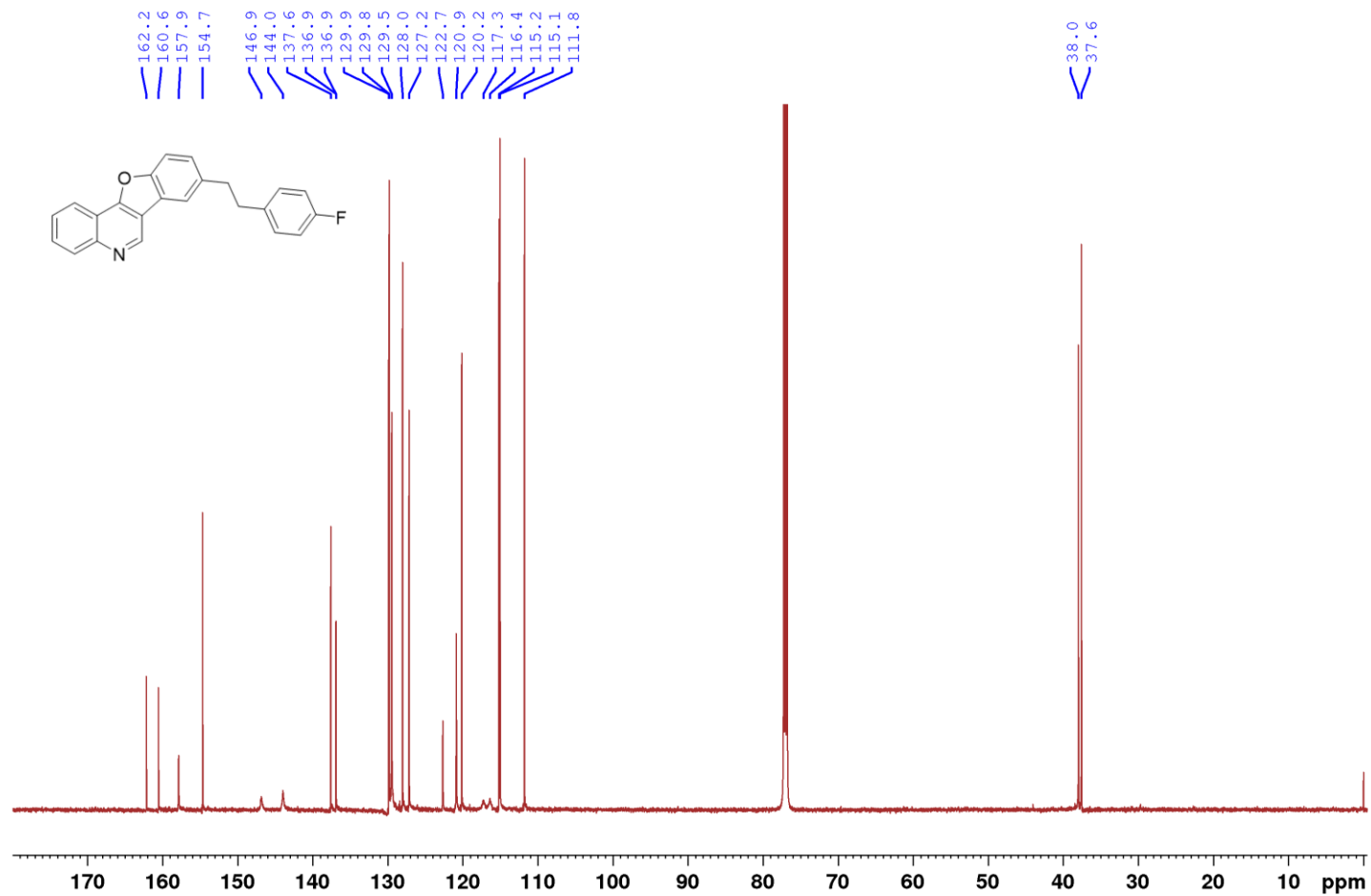
8-Phenethylbenzofuro[3,2-c]quinoline 3a

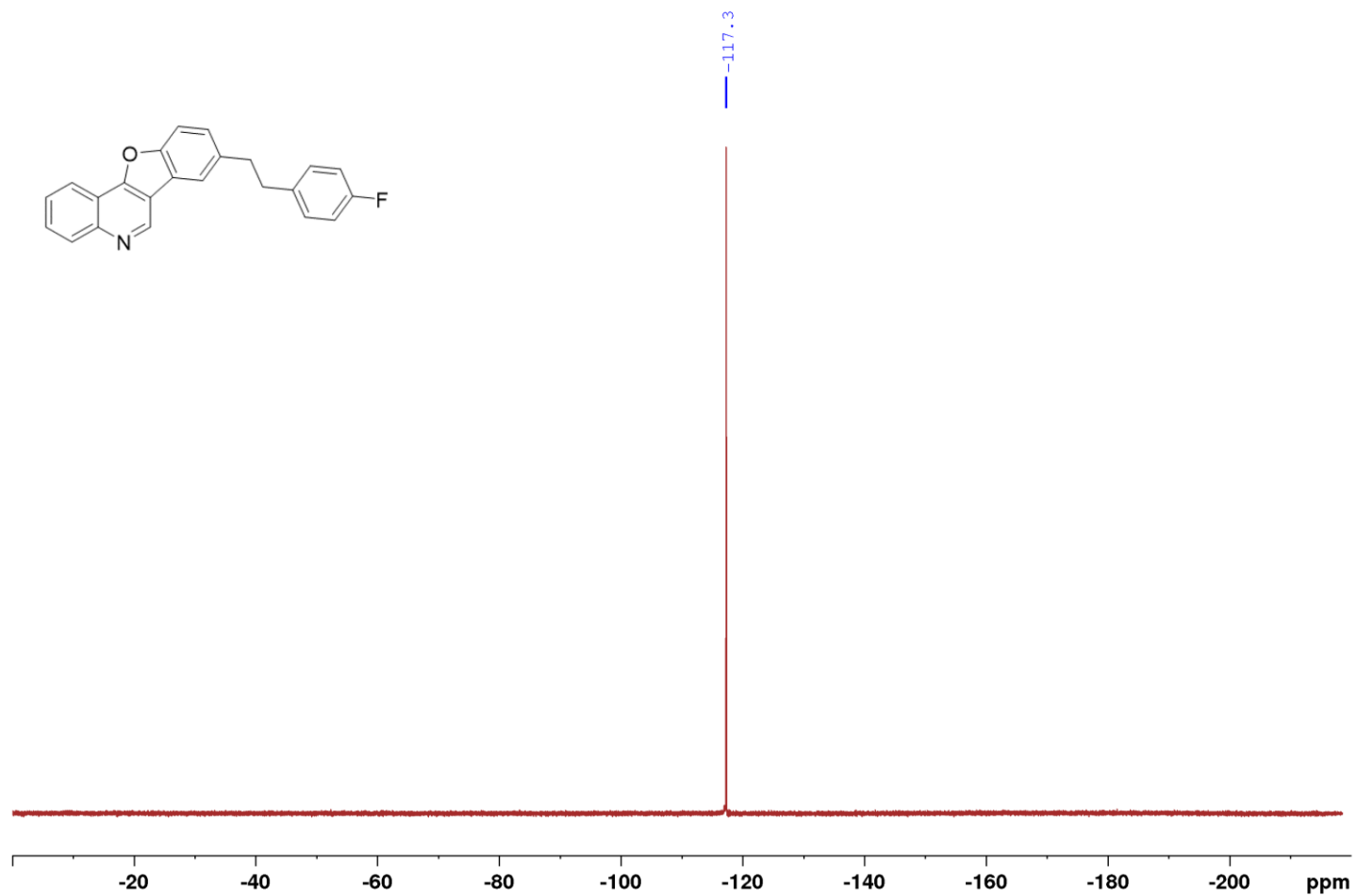




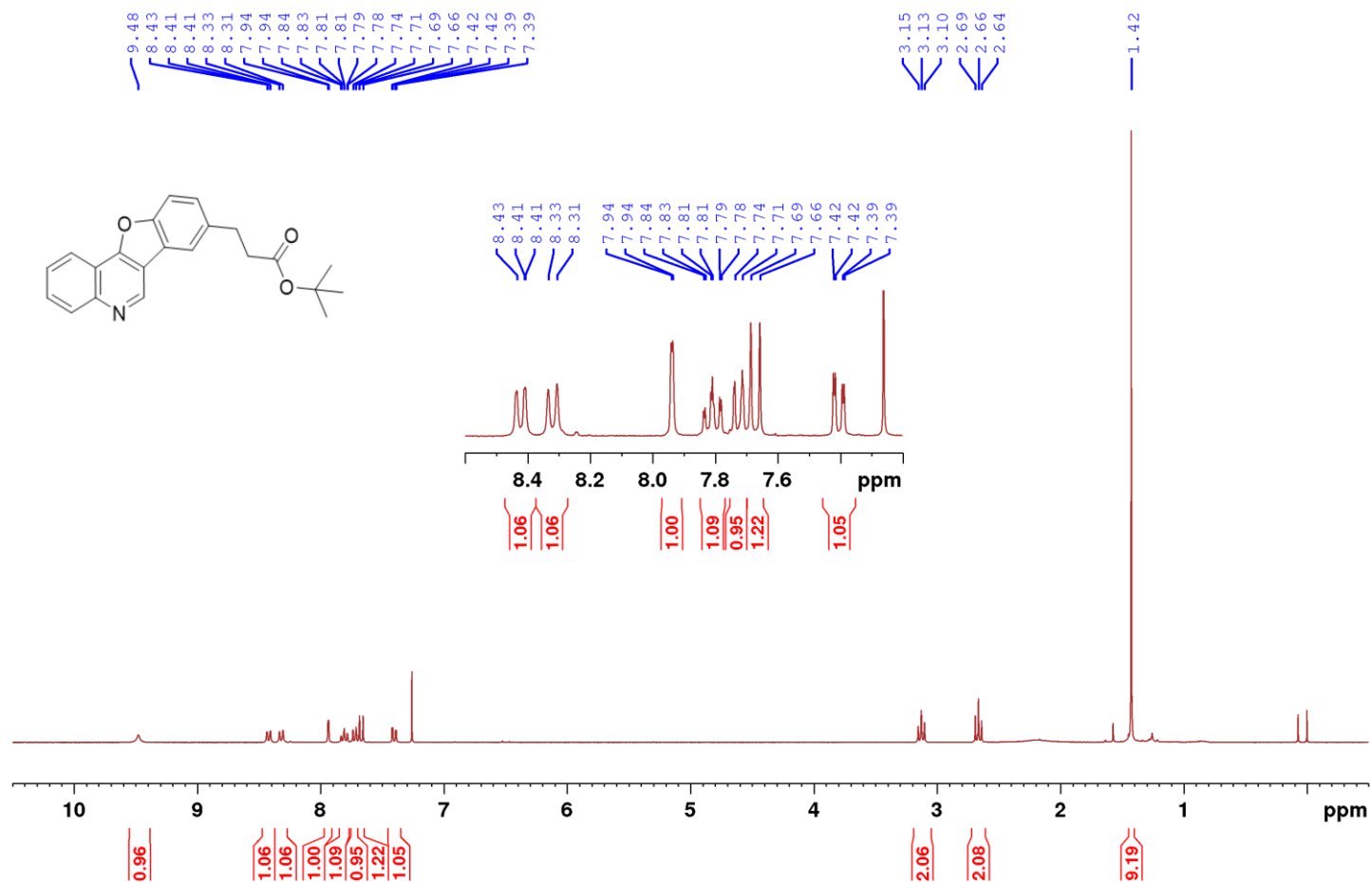
8-(4-Fluorophenethyl)benzofuro[3,2-c]quinoline 3b

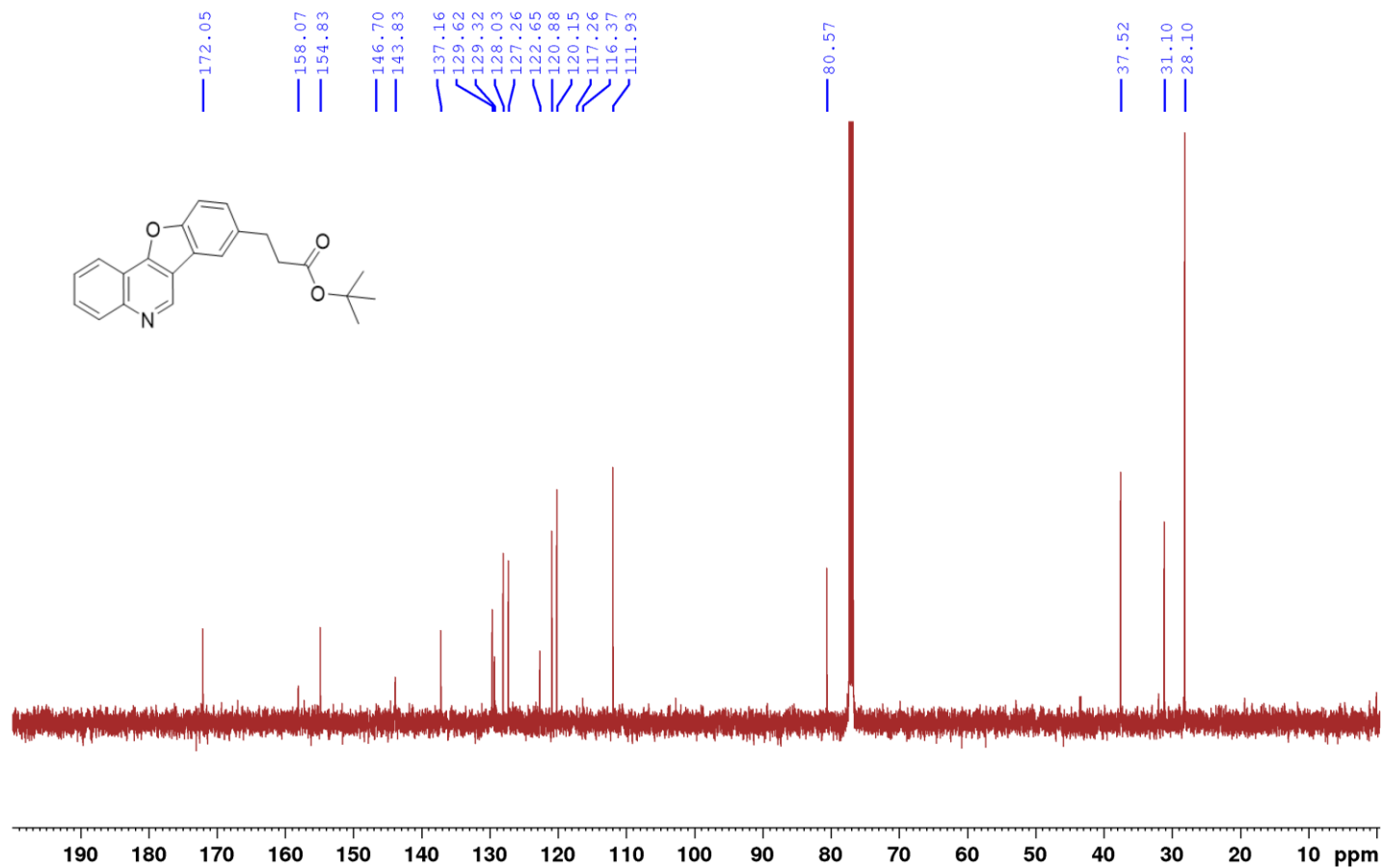




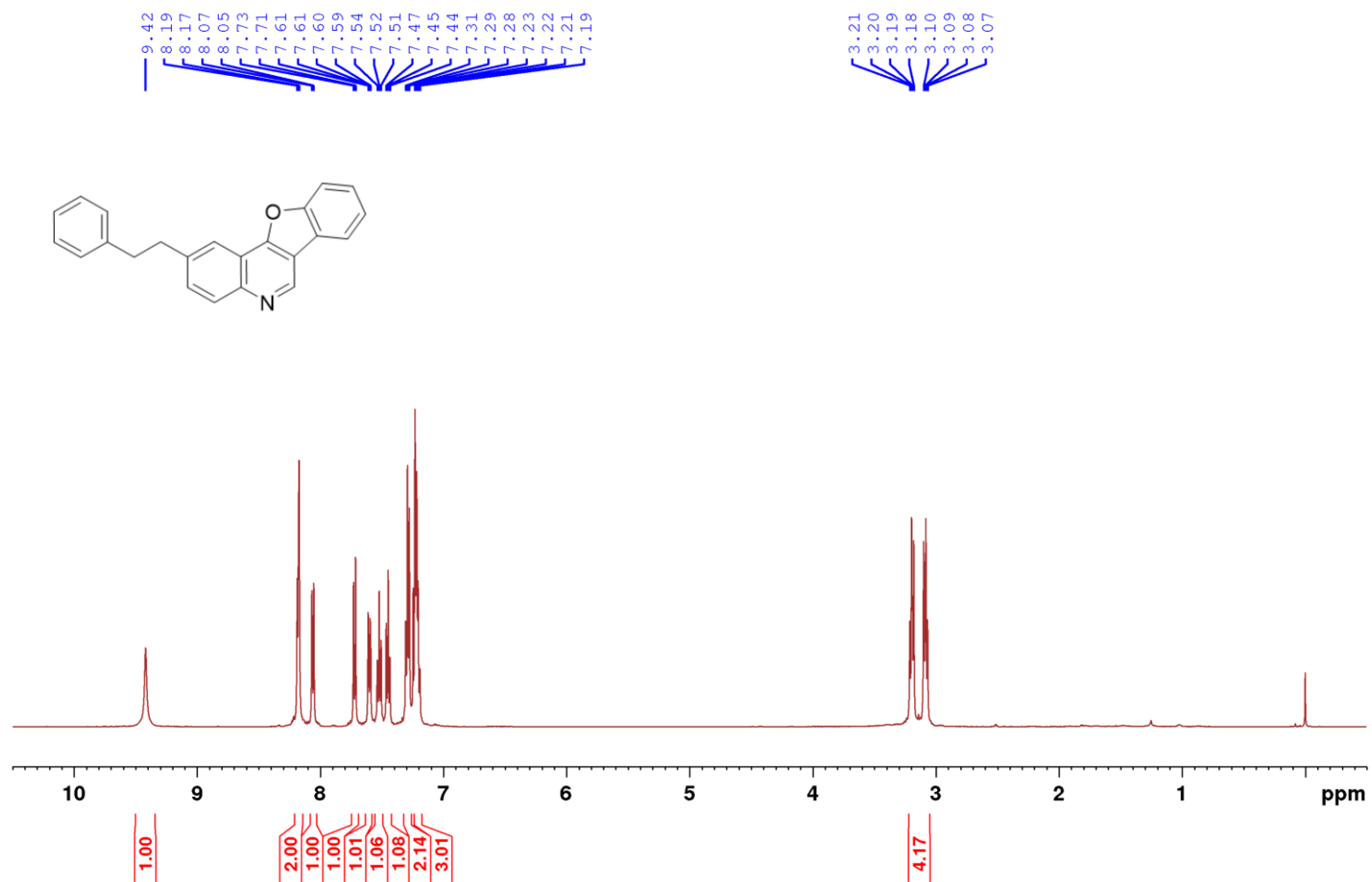


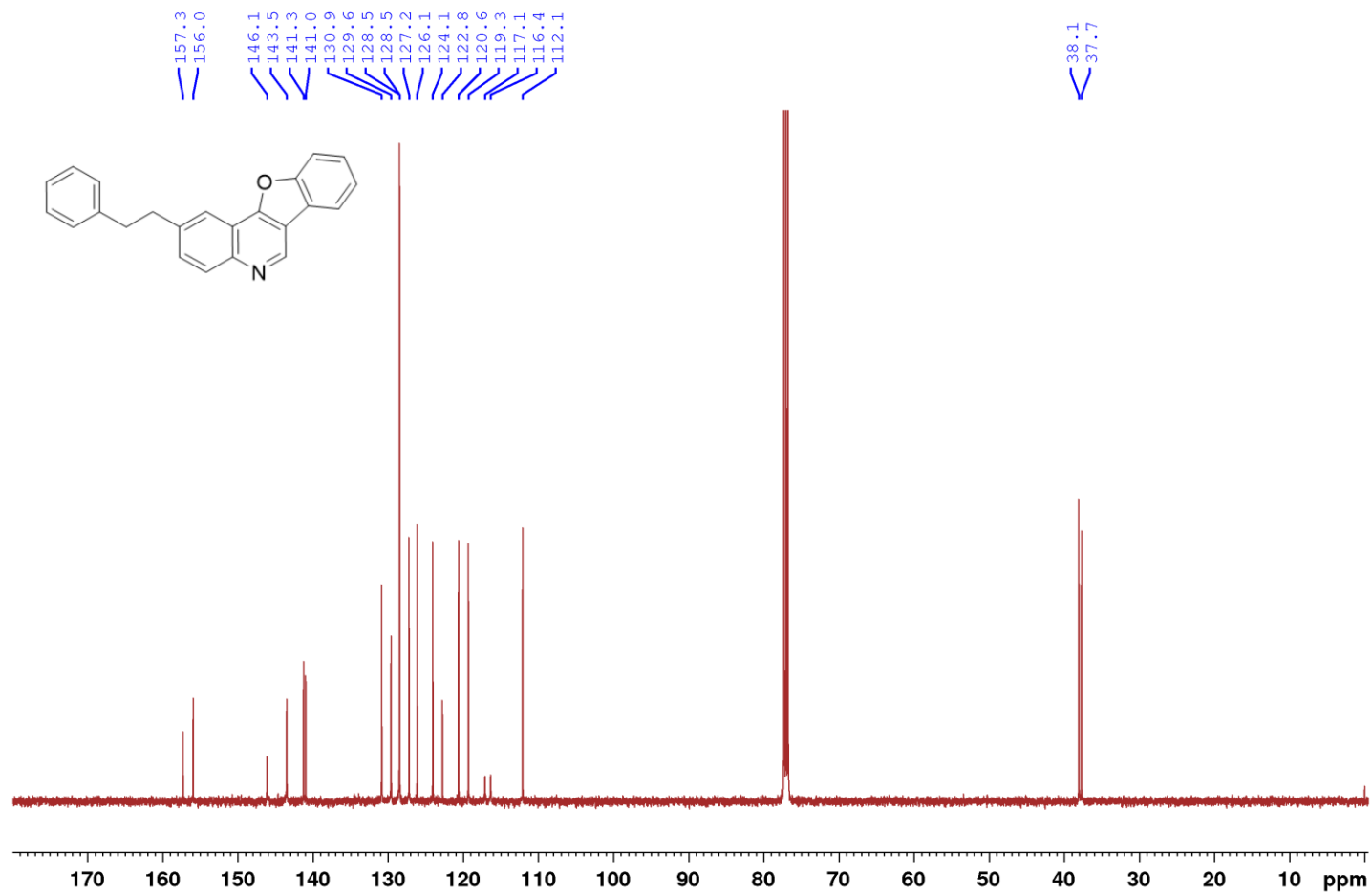
***tert*-Butyl 3-(benzofuro[3,2-*c*]quinolin-8-yl)propanoate 3c**



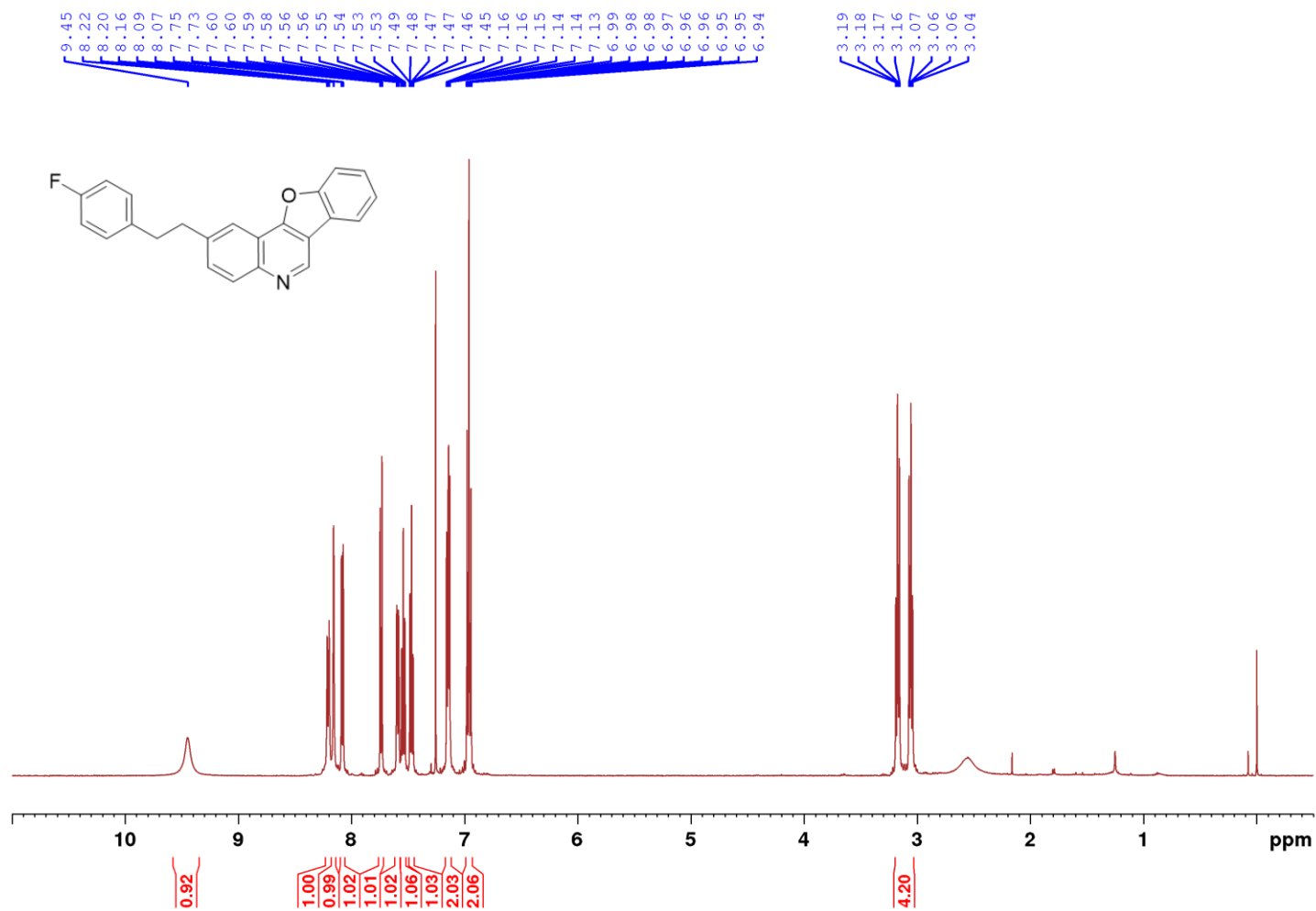


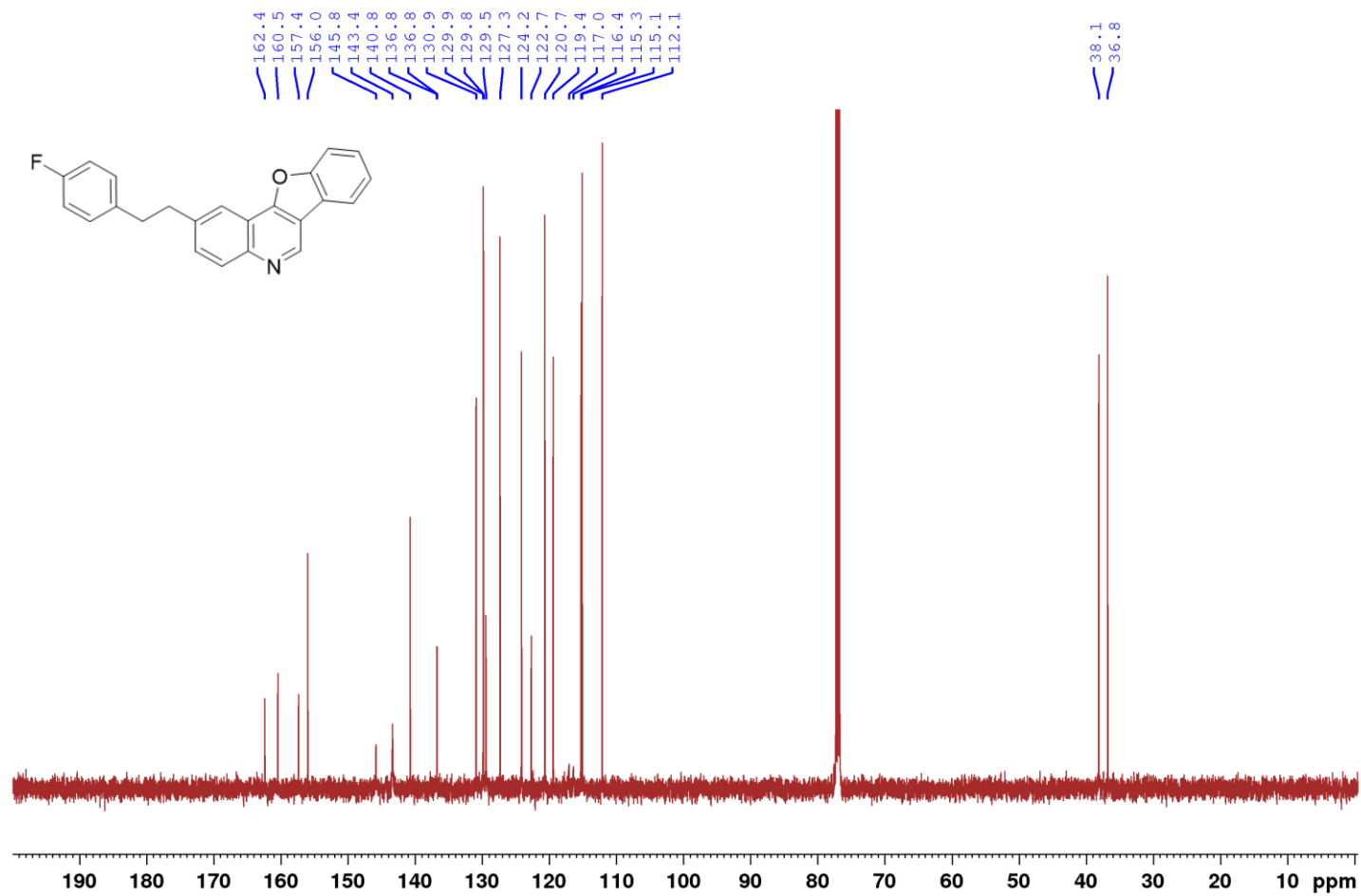
2-Phenethylbenzofuro[3,2-c]quinoline 4a

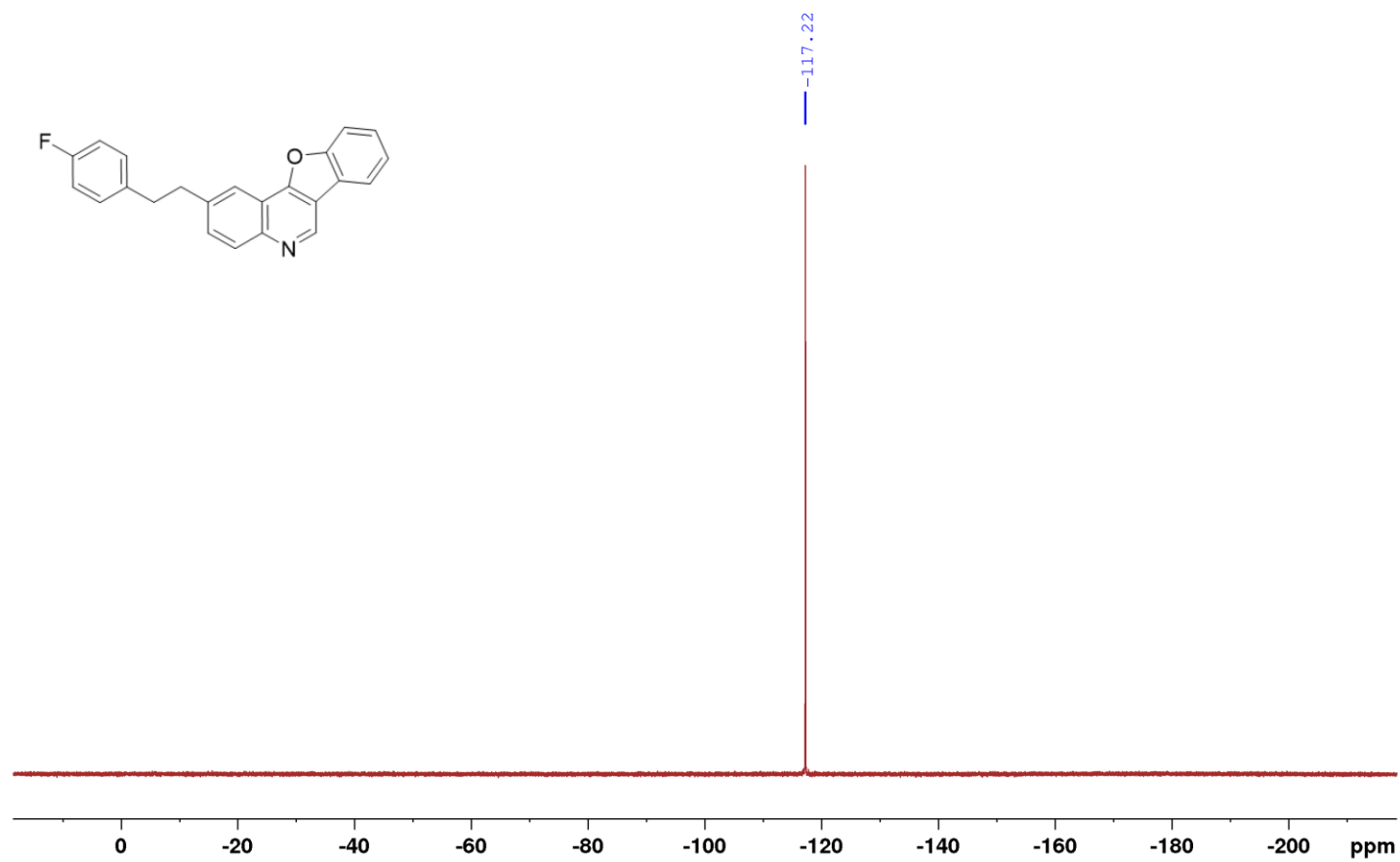




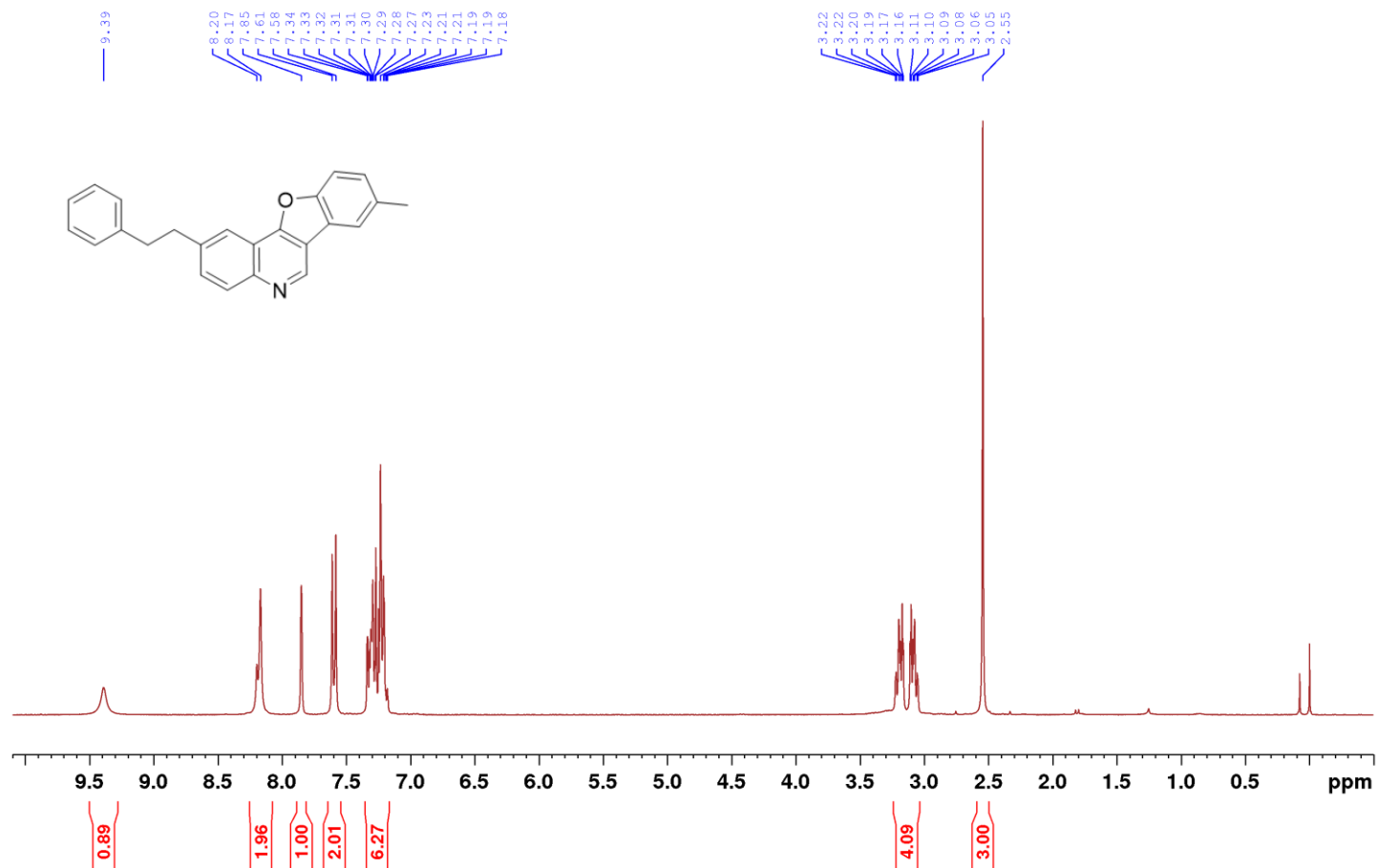
2-(4-Fluorophenethyl)benzofuro[3,2-c]quinoline 4b

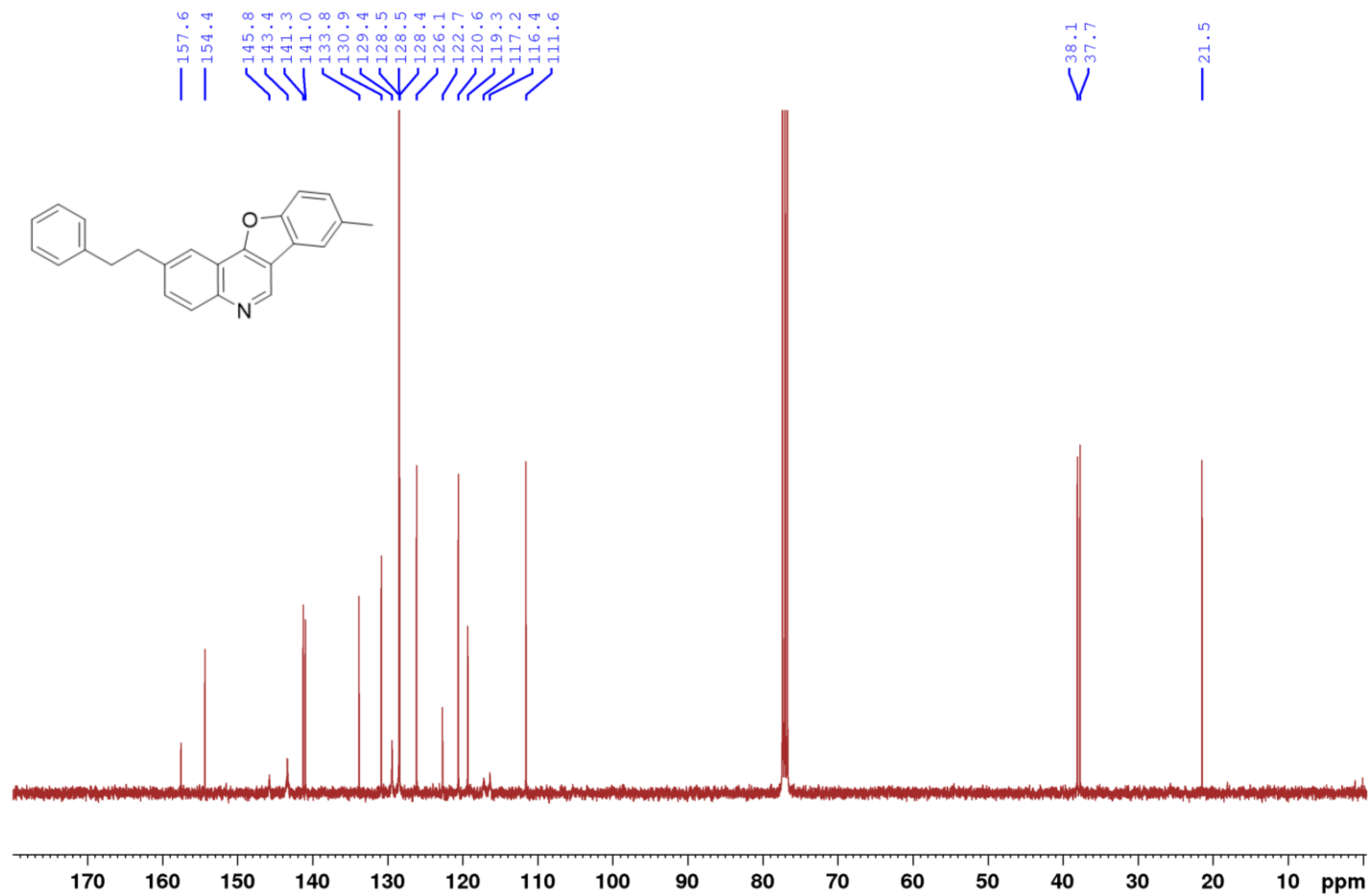




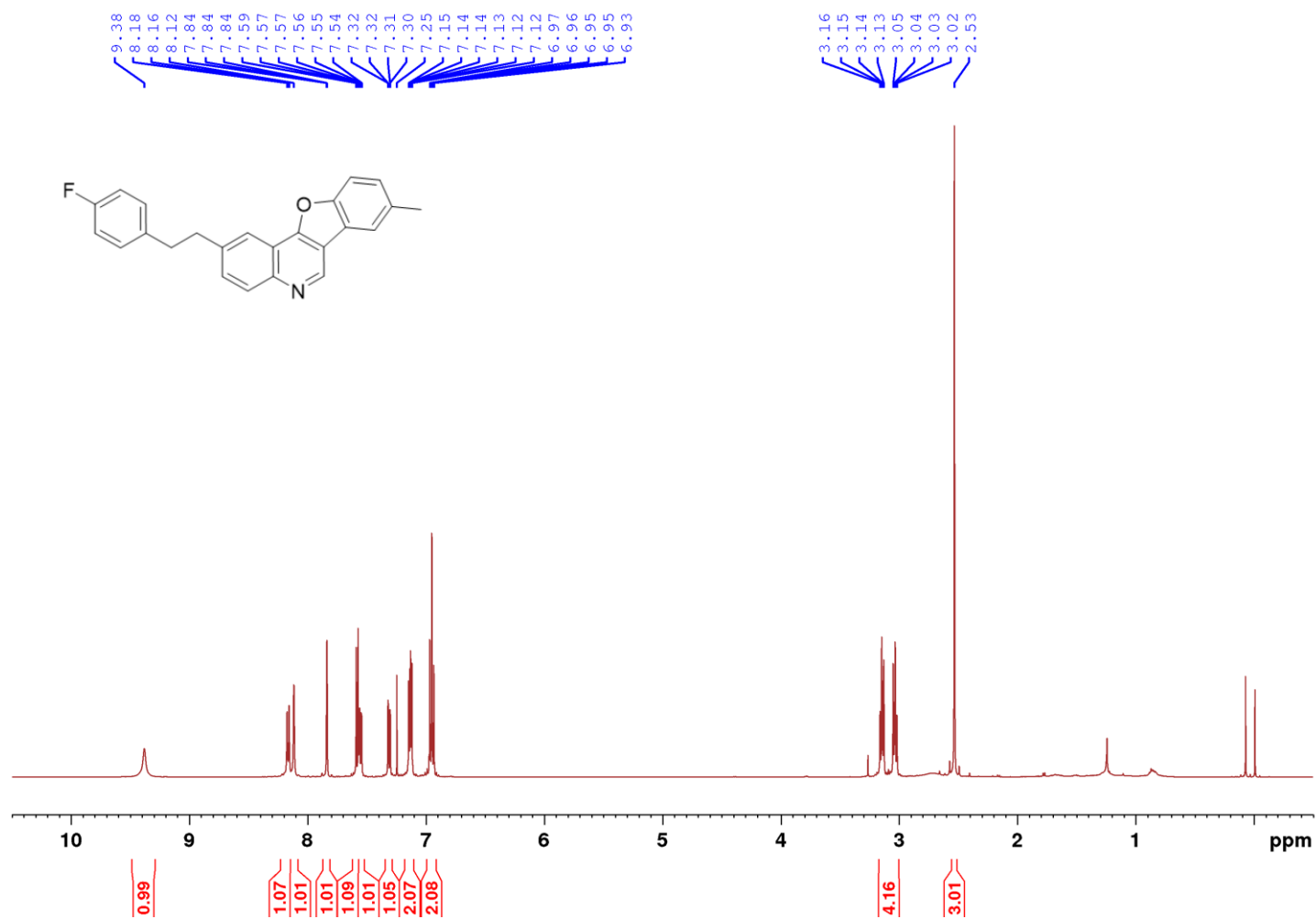


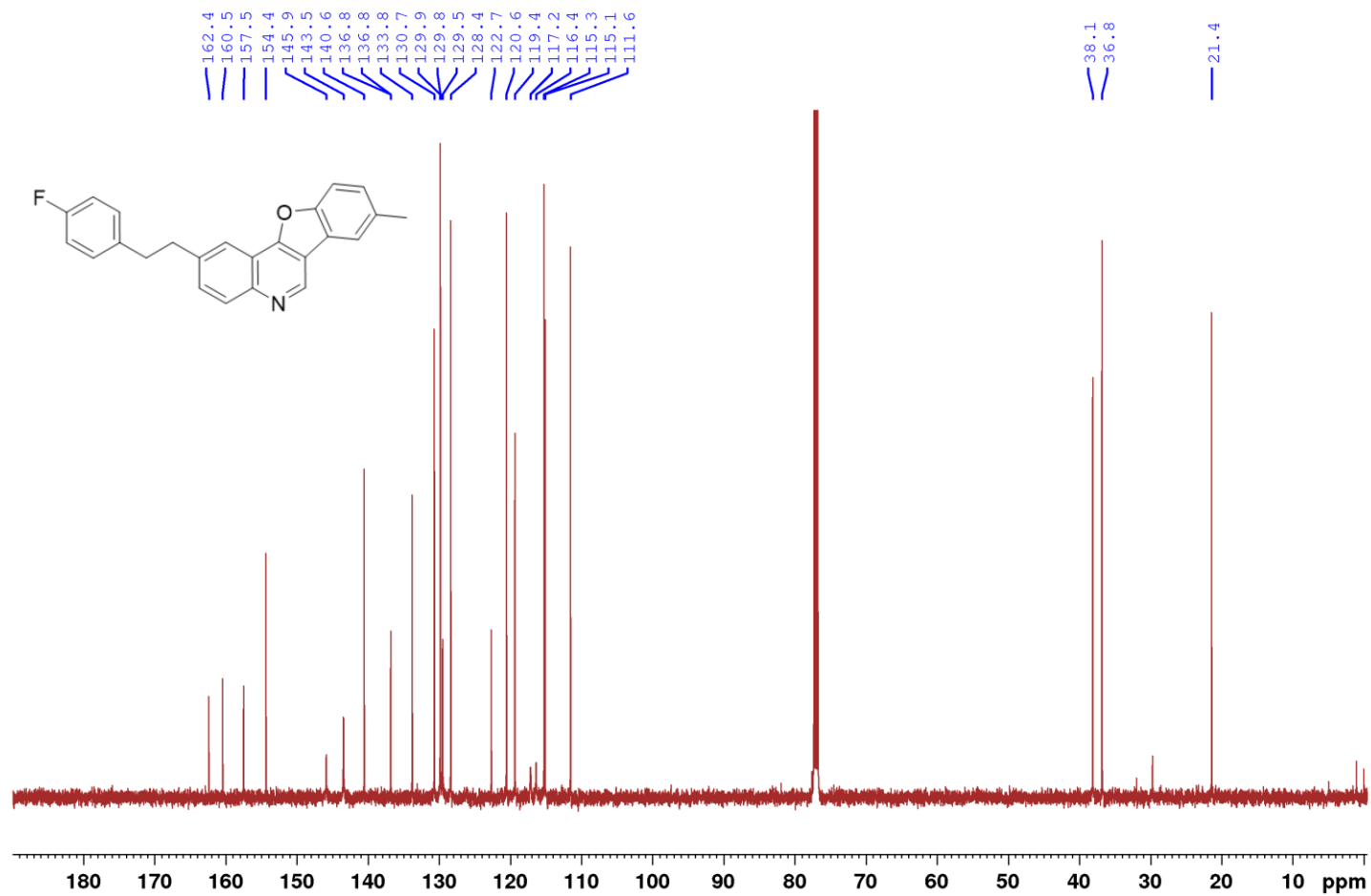
8-Methyl-2-phenethylbenzofuro[3,2-c]quinoline 4c

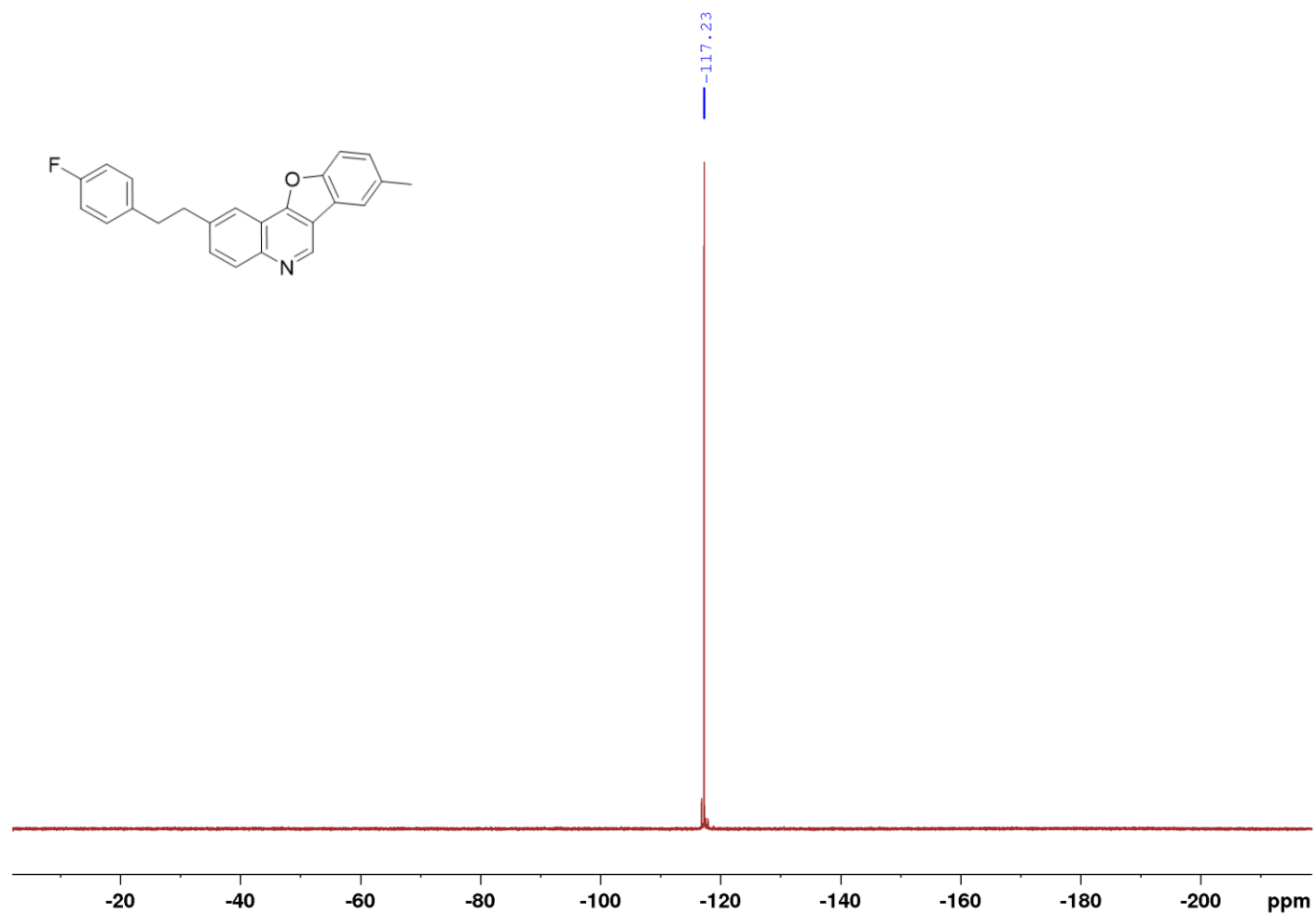




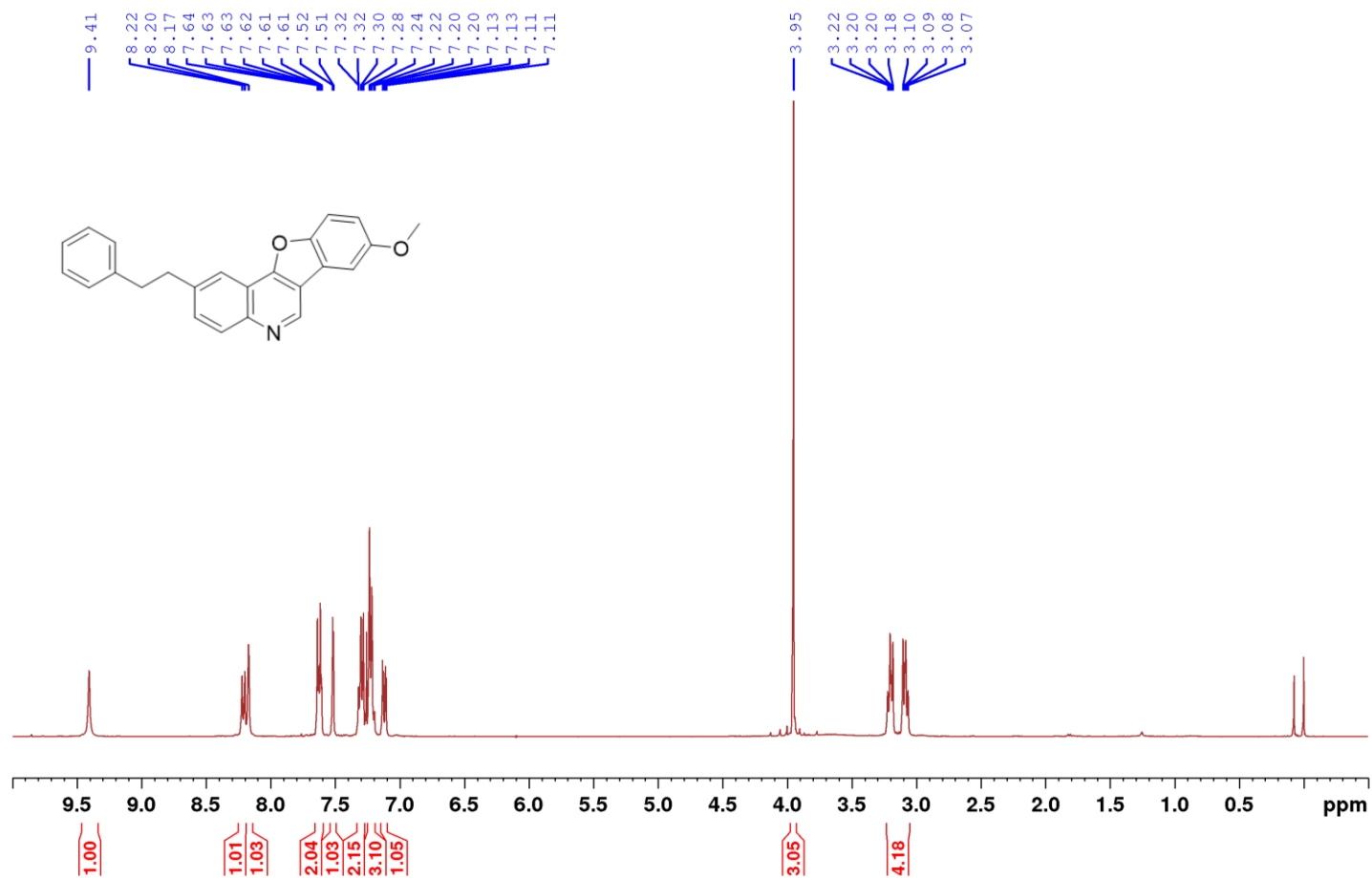
2-(4-Fluorophenethyl)-8-methylbenzofuro[3,2-c]quinoline 4d

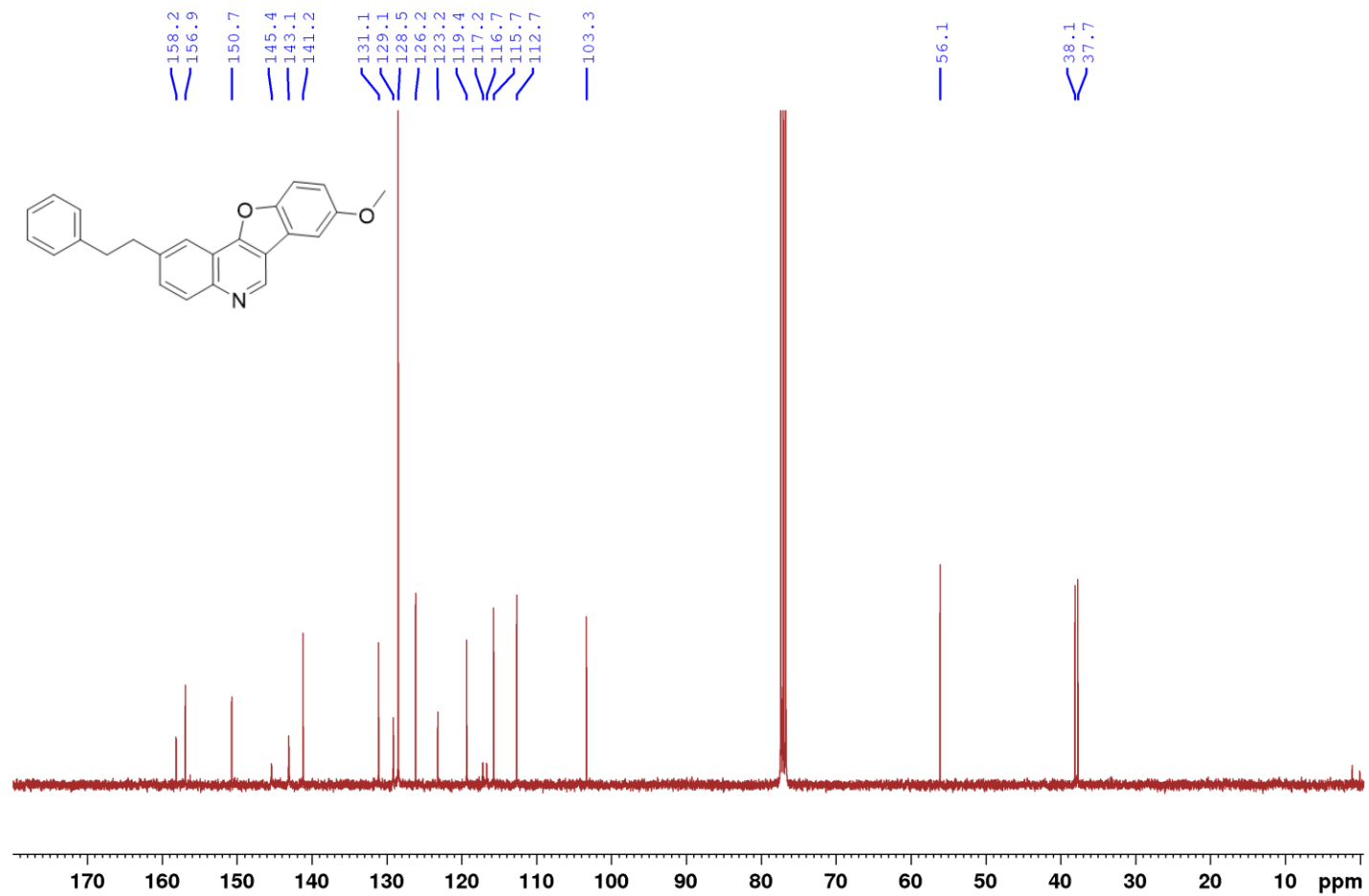




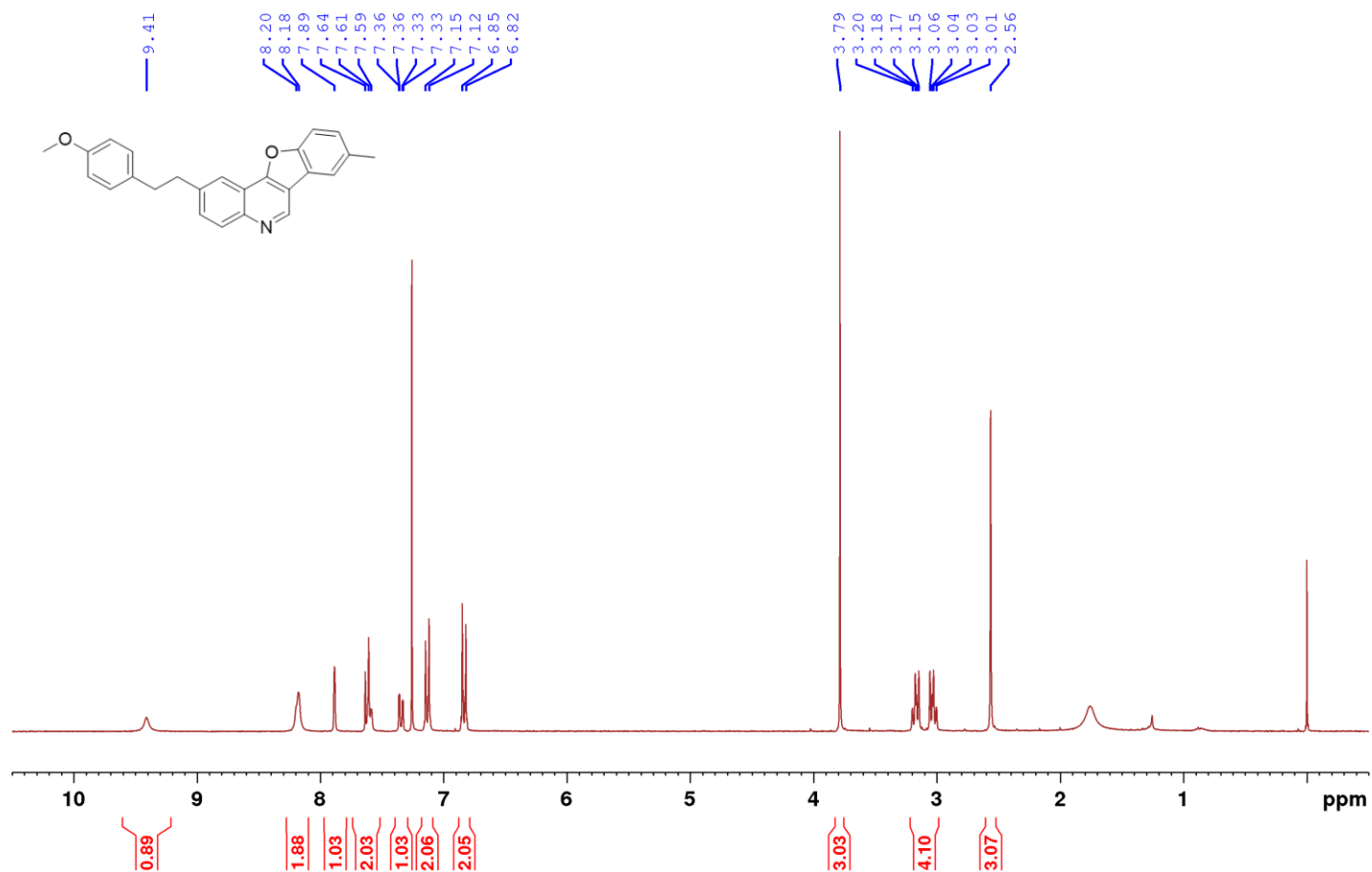


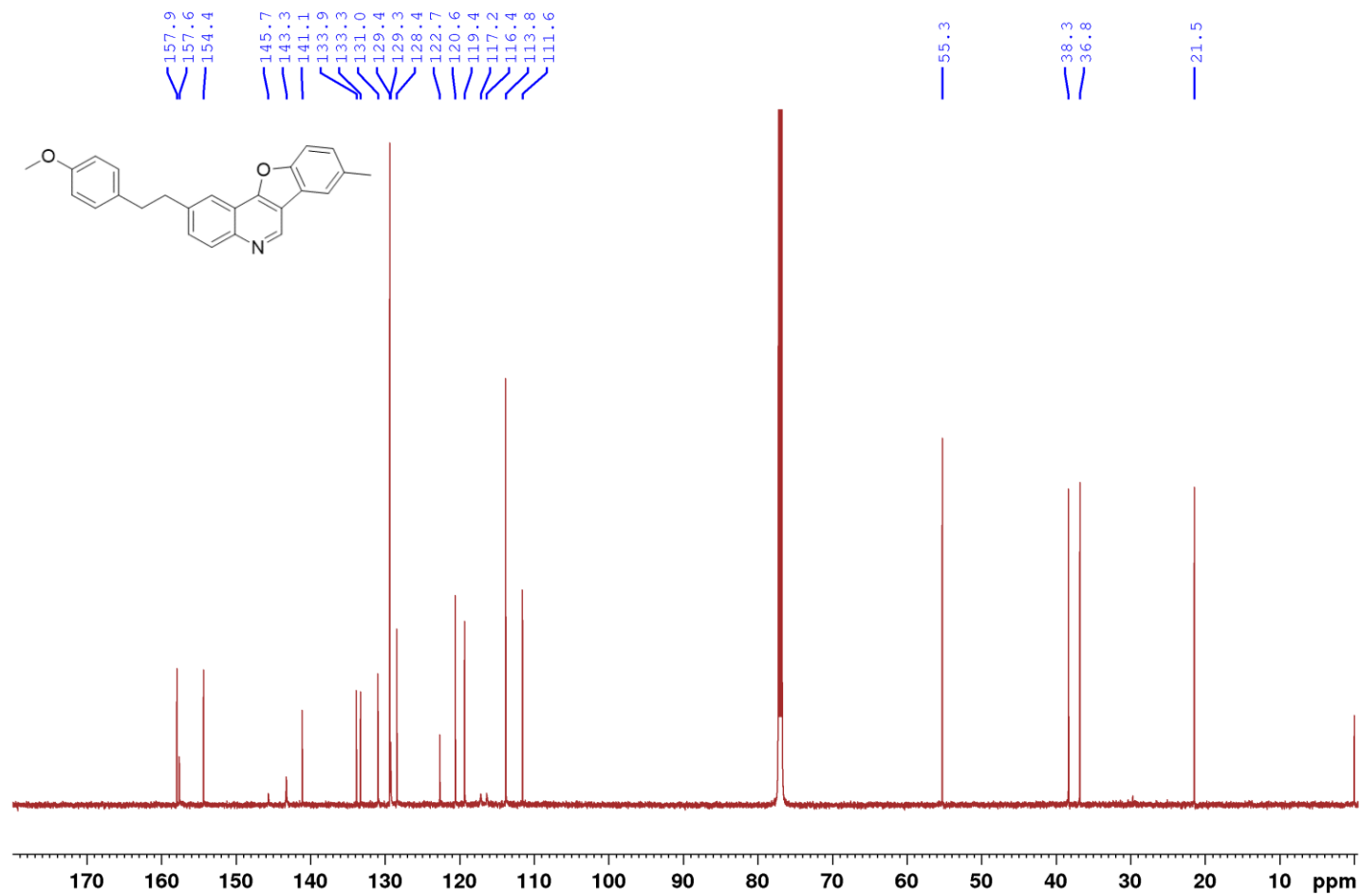
8-Methoxy-2-phenethylbenzofuro[3,2-c]quinoline 4e



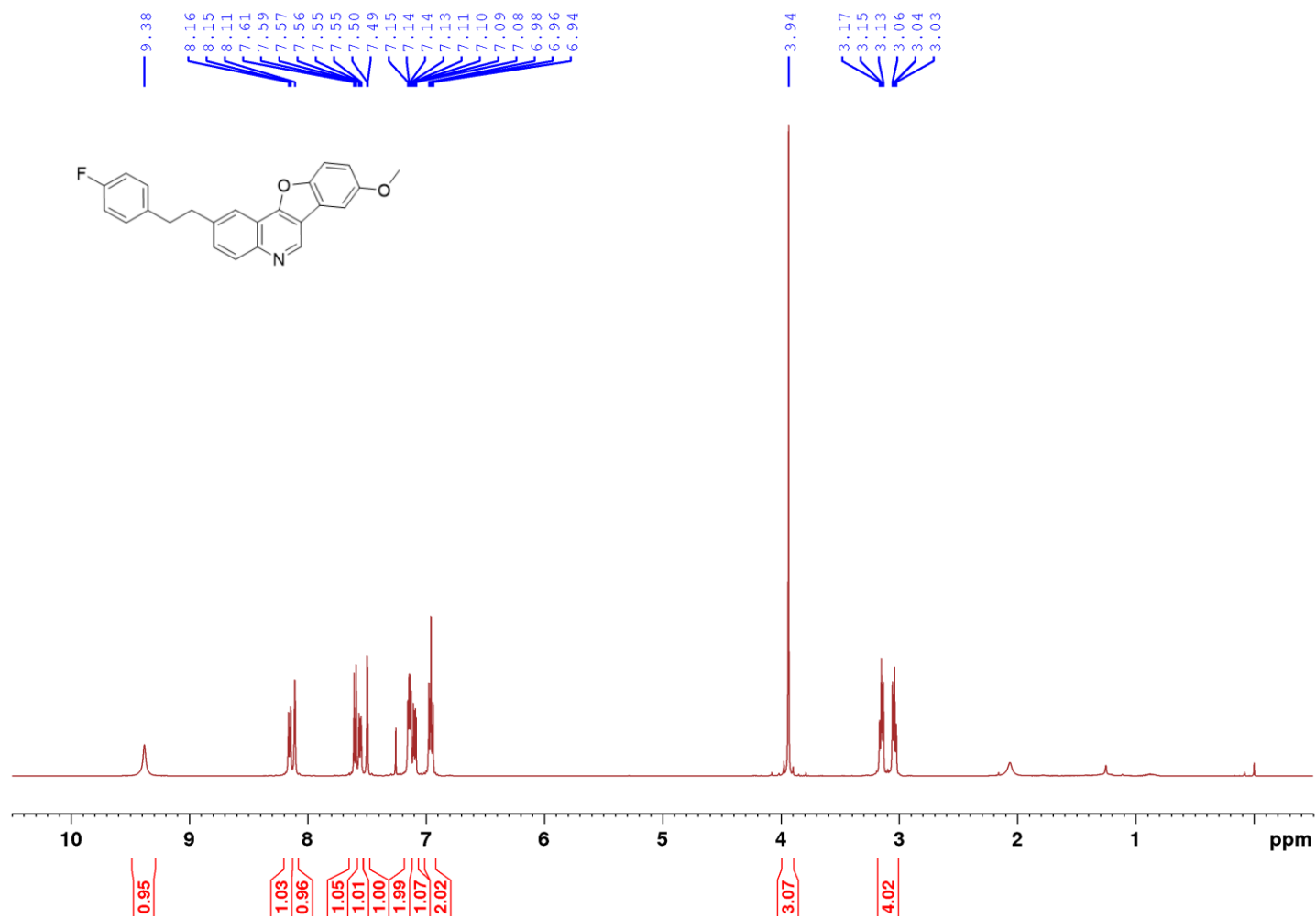


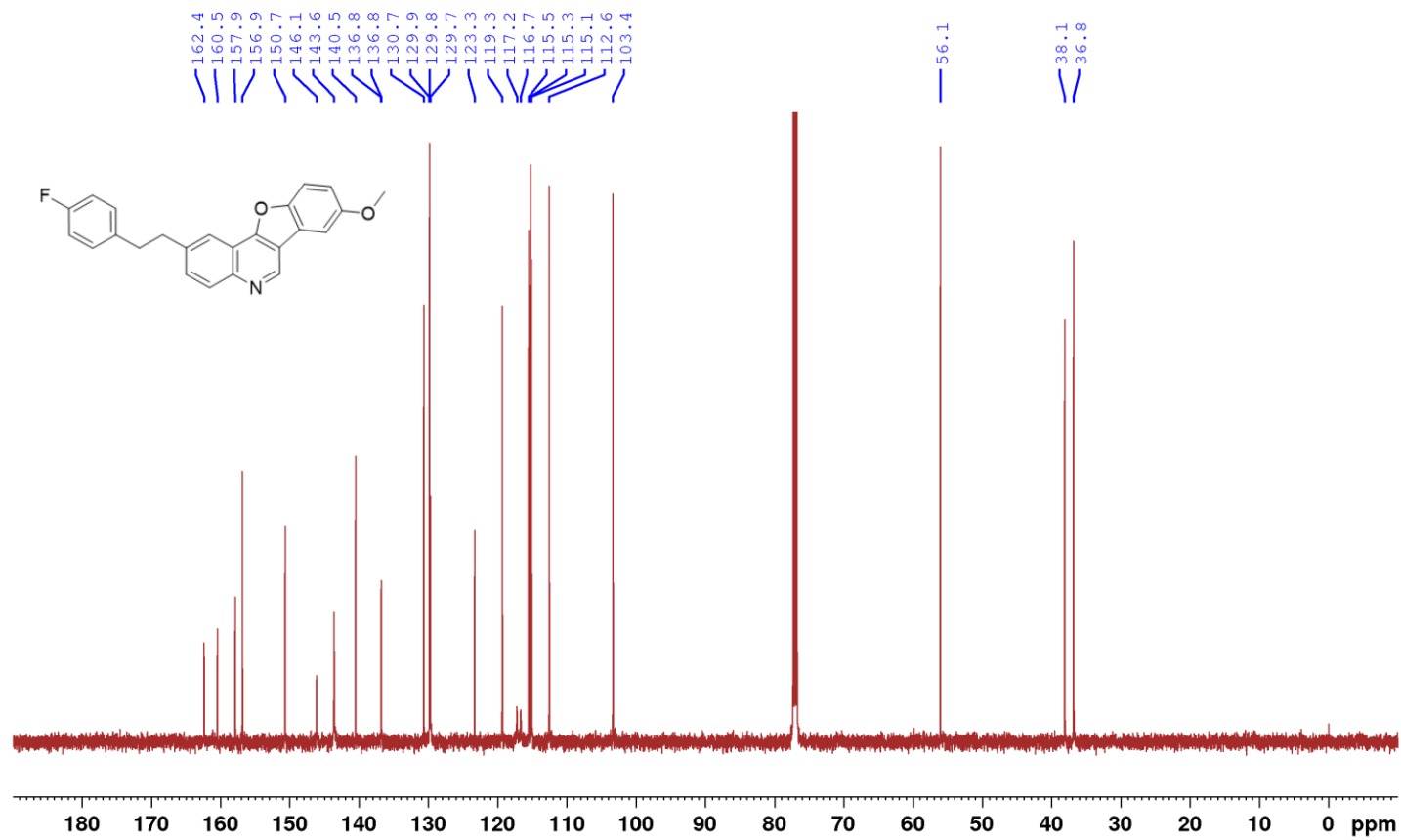
2-(4-Methoxyphenethyl)-8-methylbenzofuro[3,2-c]quinoline 4f

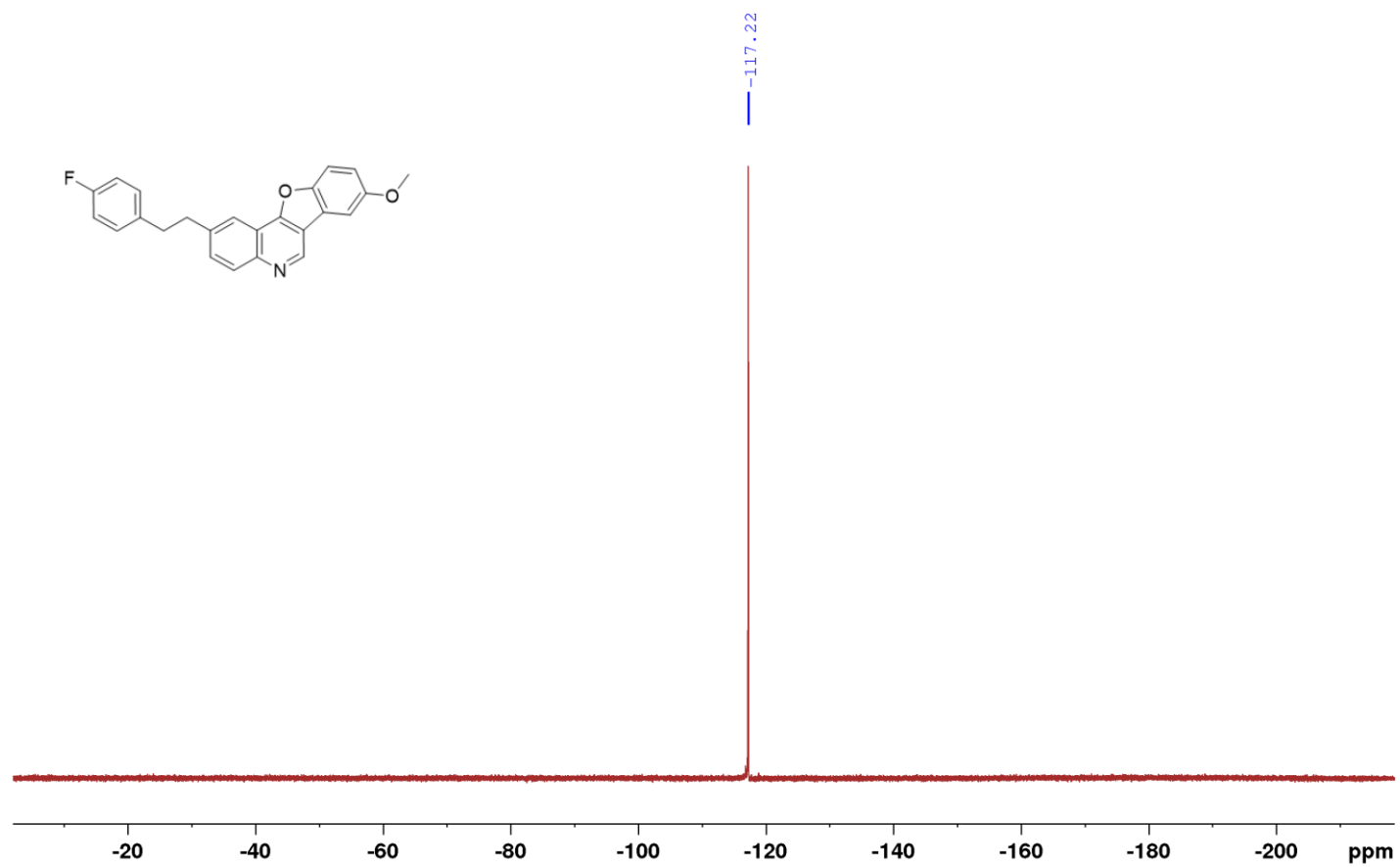




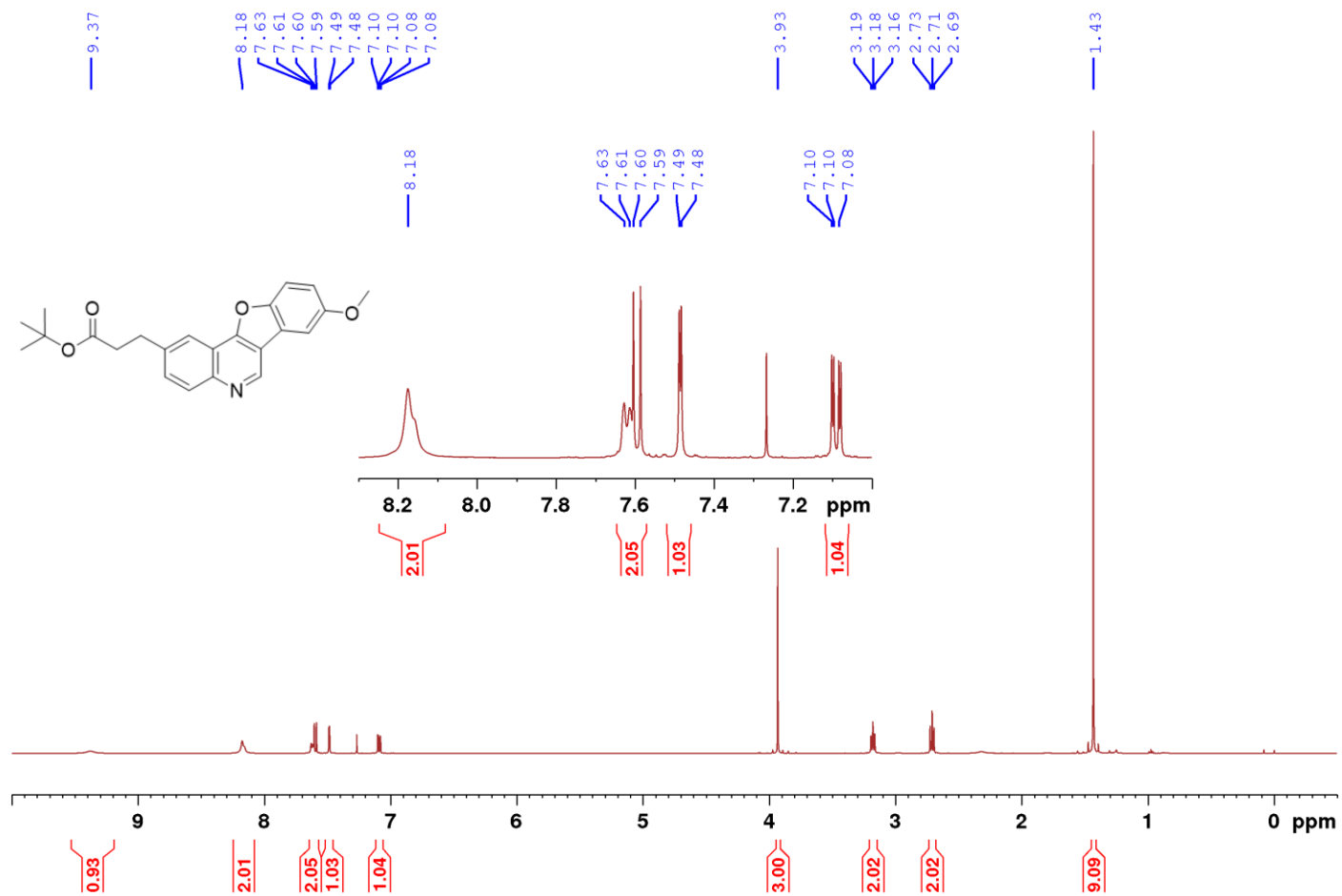
2-(4-Fluorophenethyl)-8-methoxybenzofuro[3,2-c]quinoline 4g

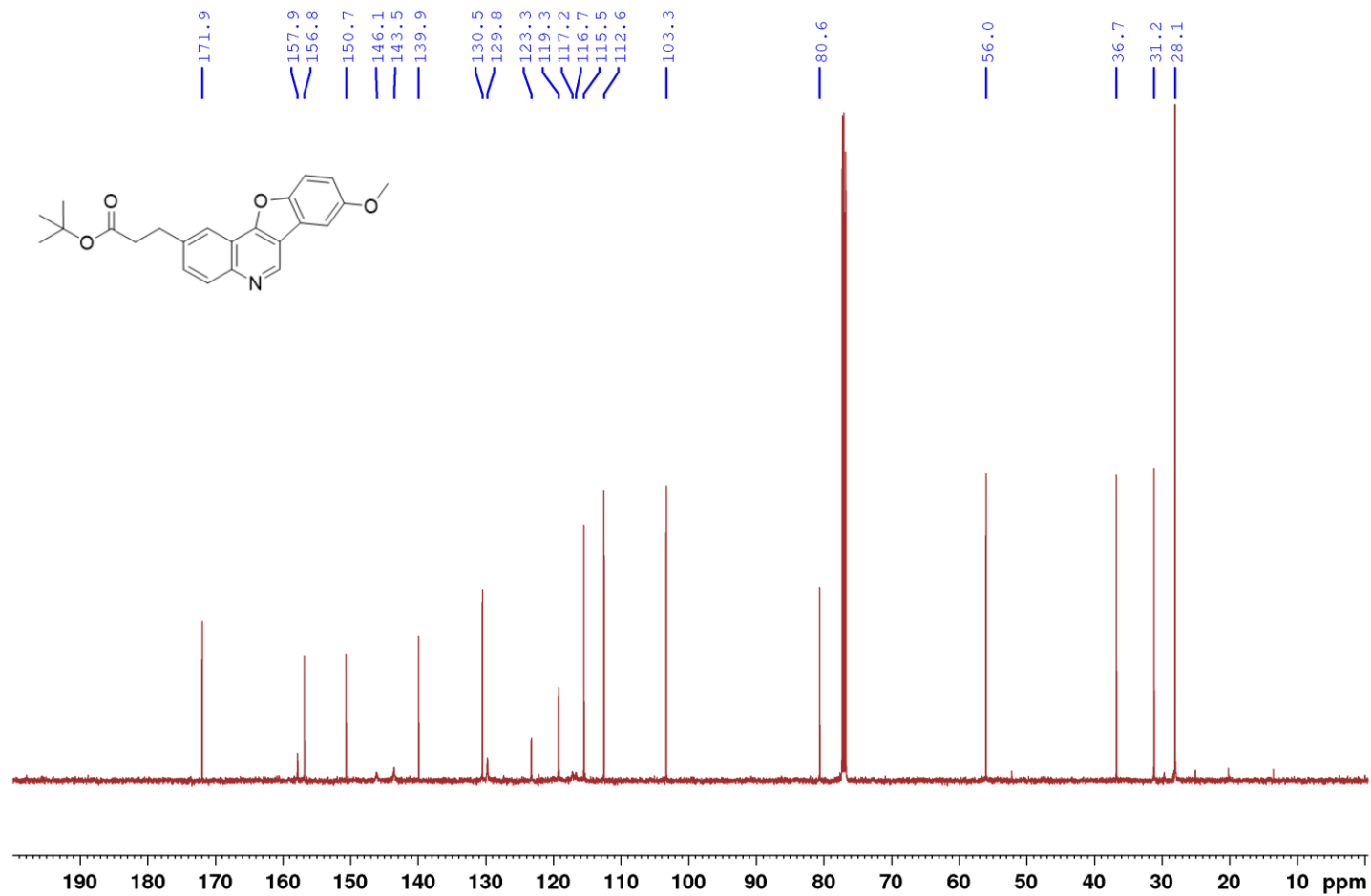




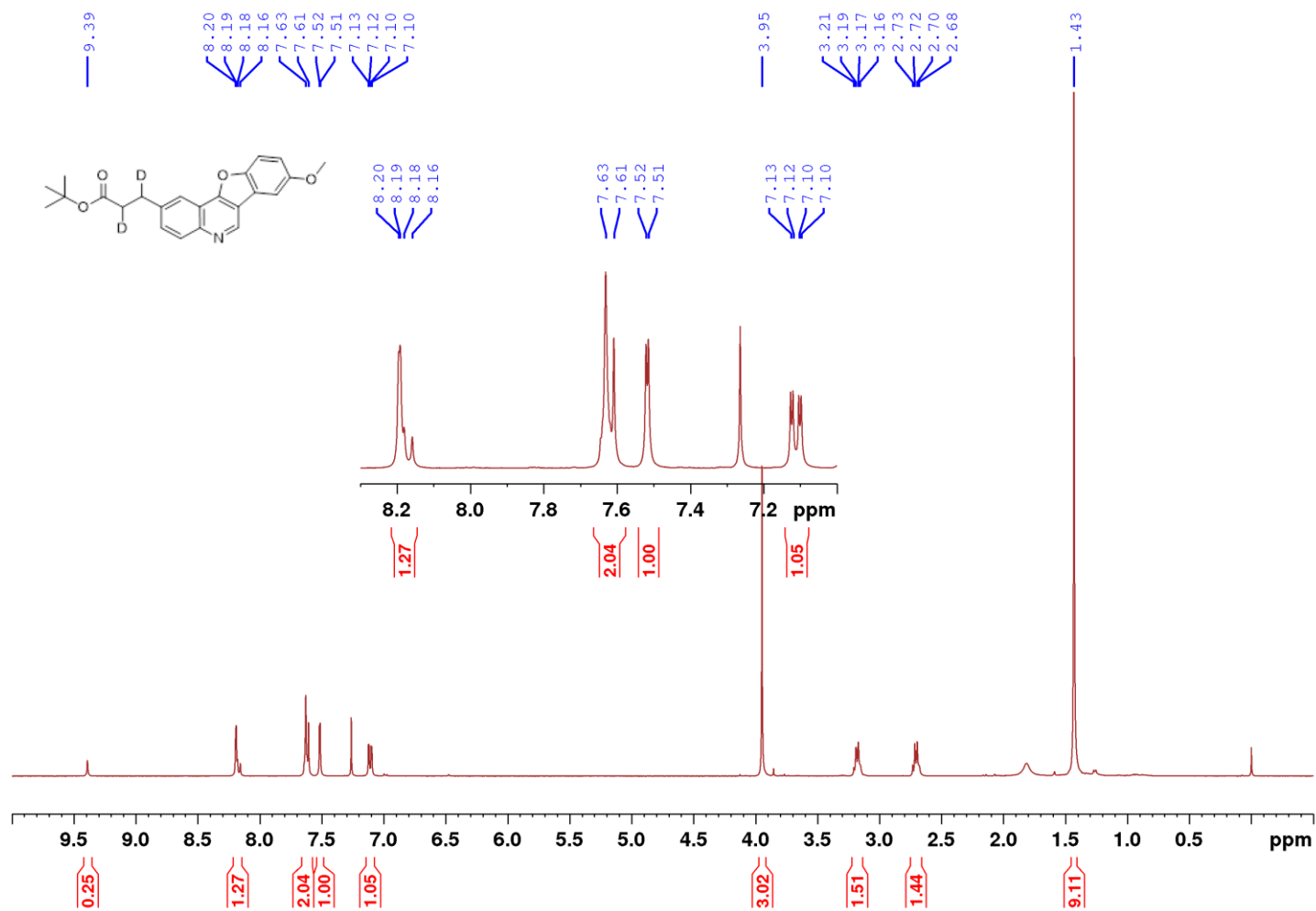


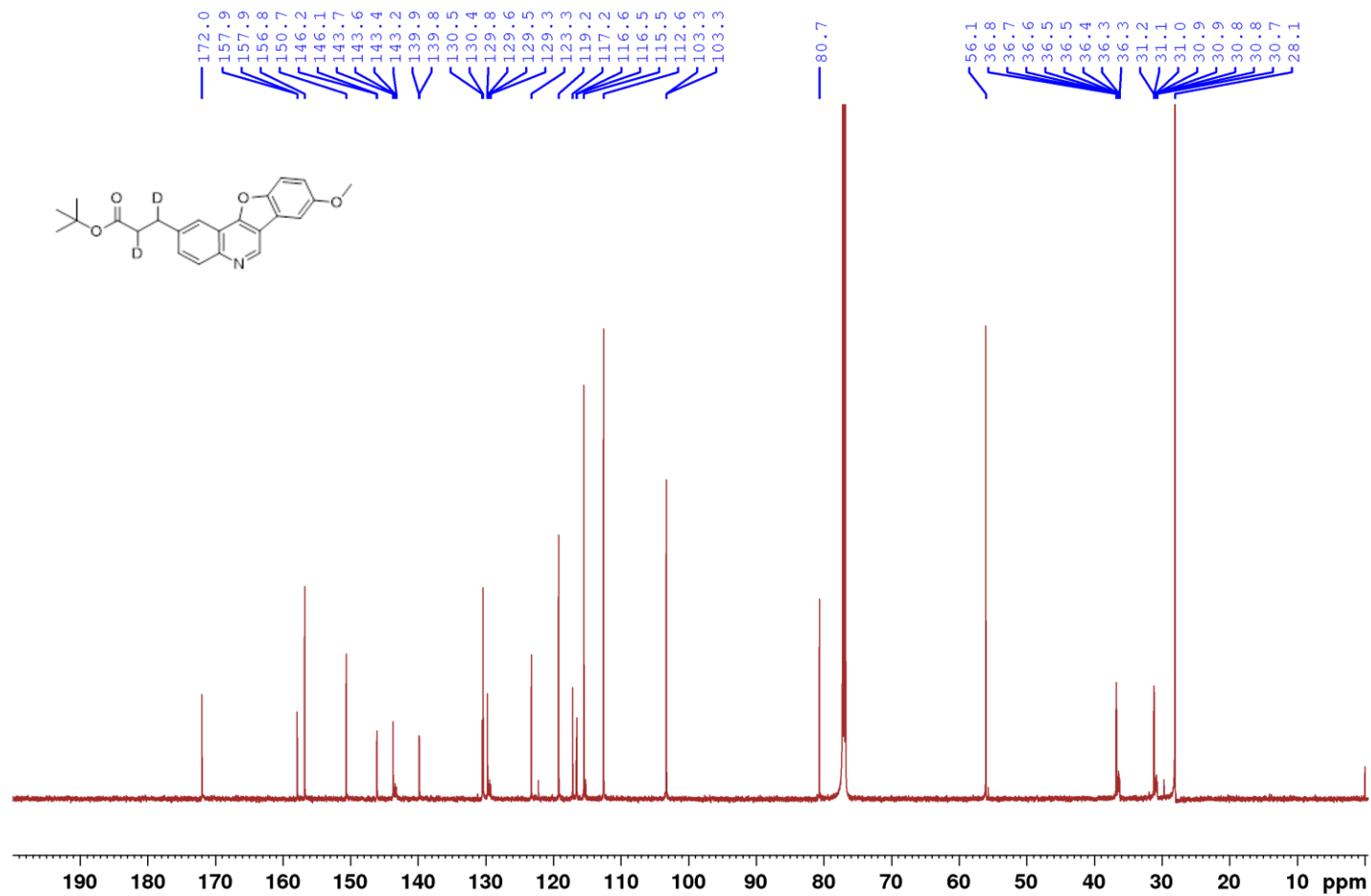
***tert*-Butyl 3-(8-methoxybenzofuro[3,2-*c*]quinolin-2-yl)propanoate 4h**



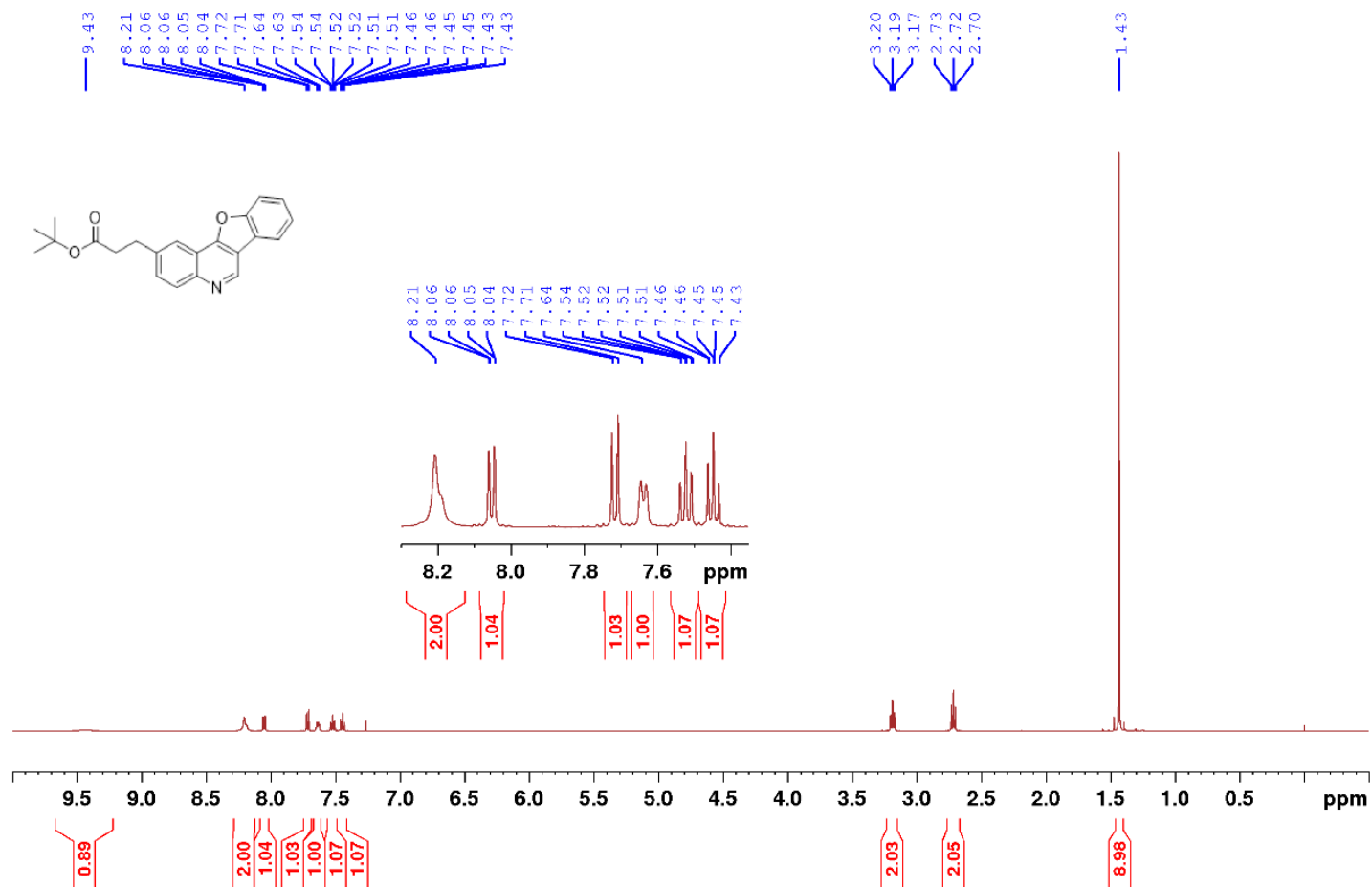


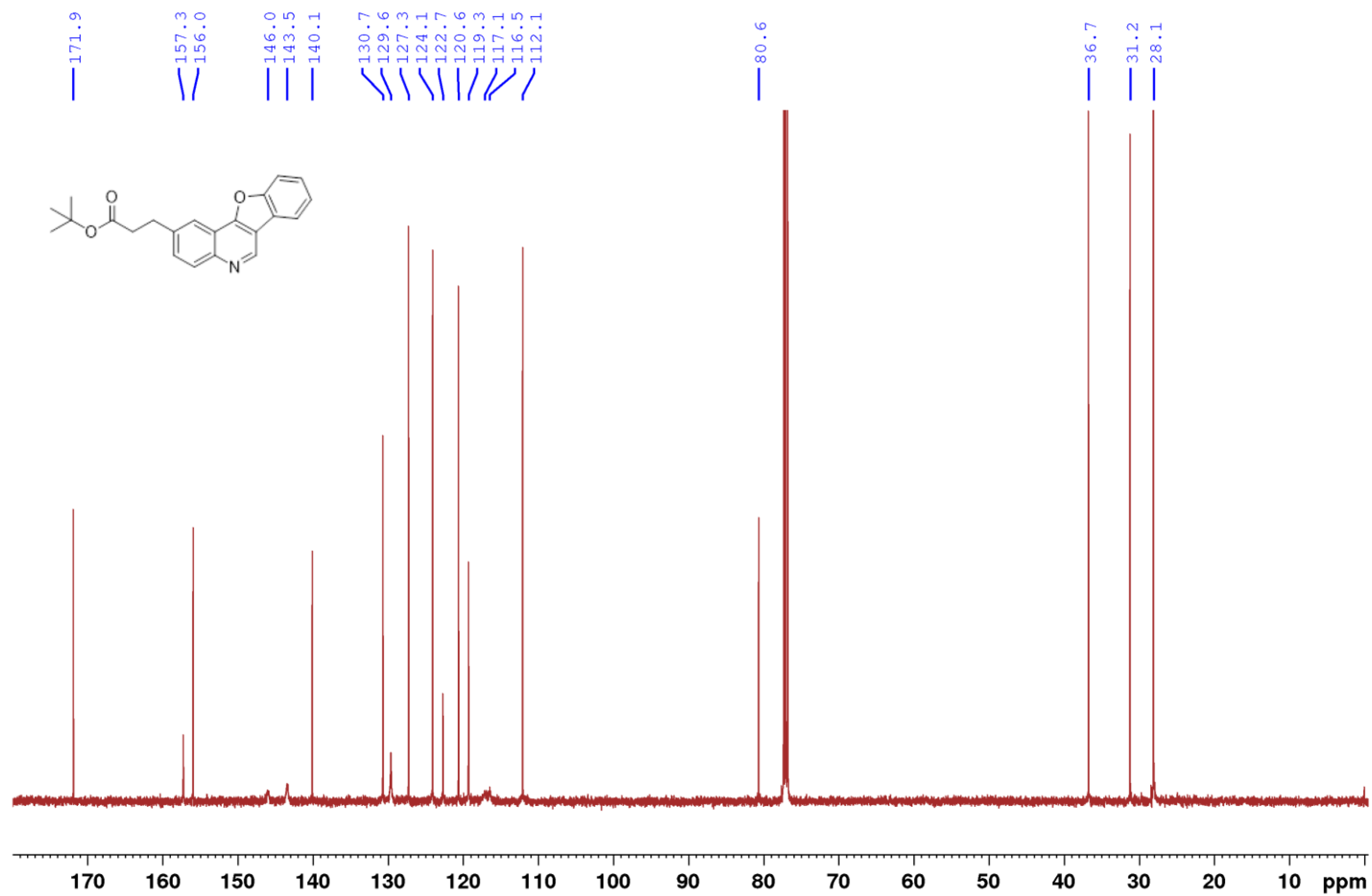
tert-butyl (3R)-3-(8-methoxybenzofuro[3,2-c]quinolin-2-yl-4,6-d2)propanoate-2,3-d2 4h-d₄



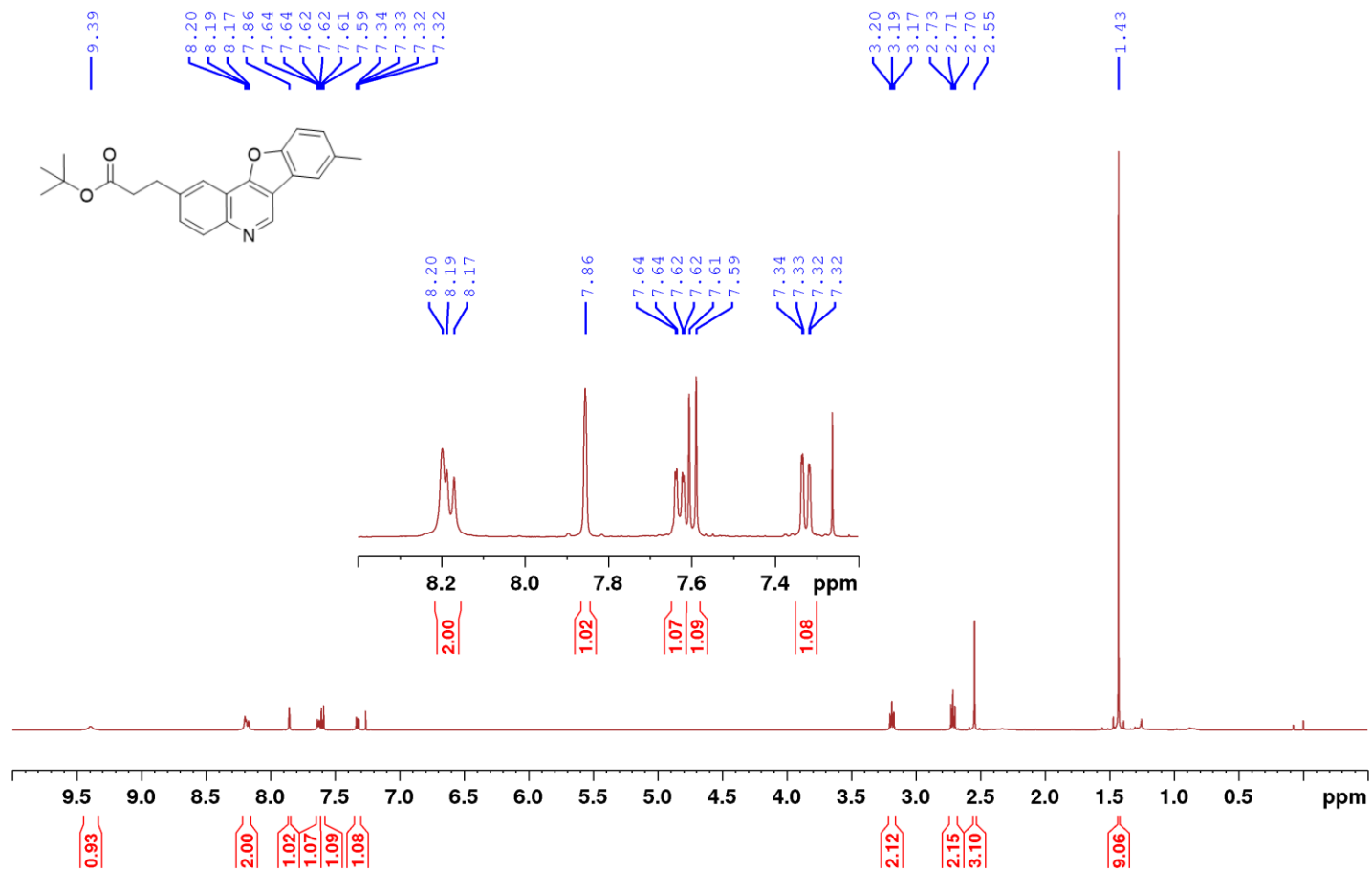


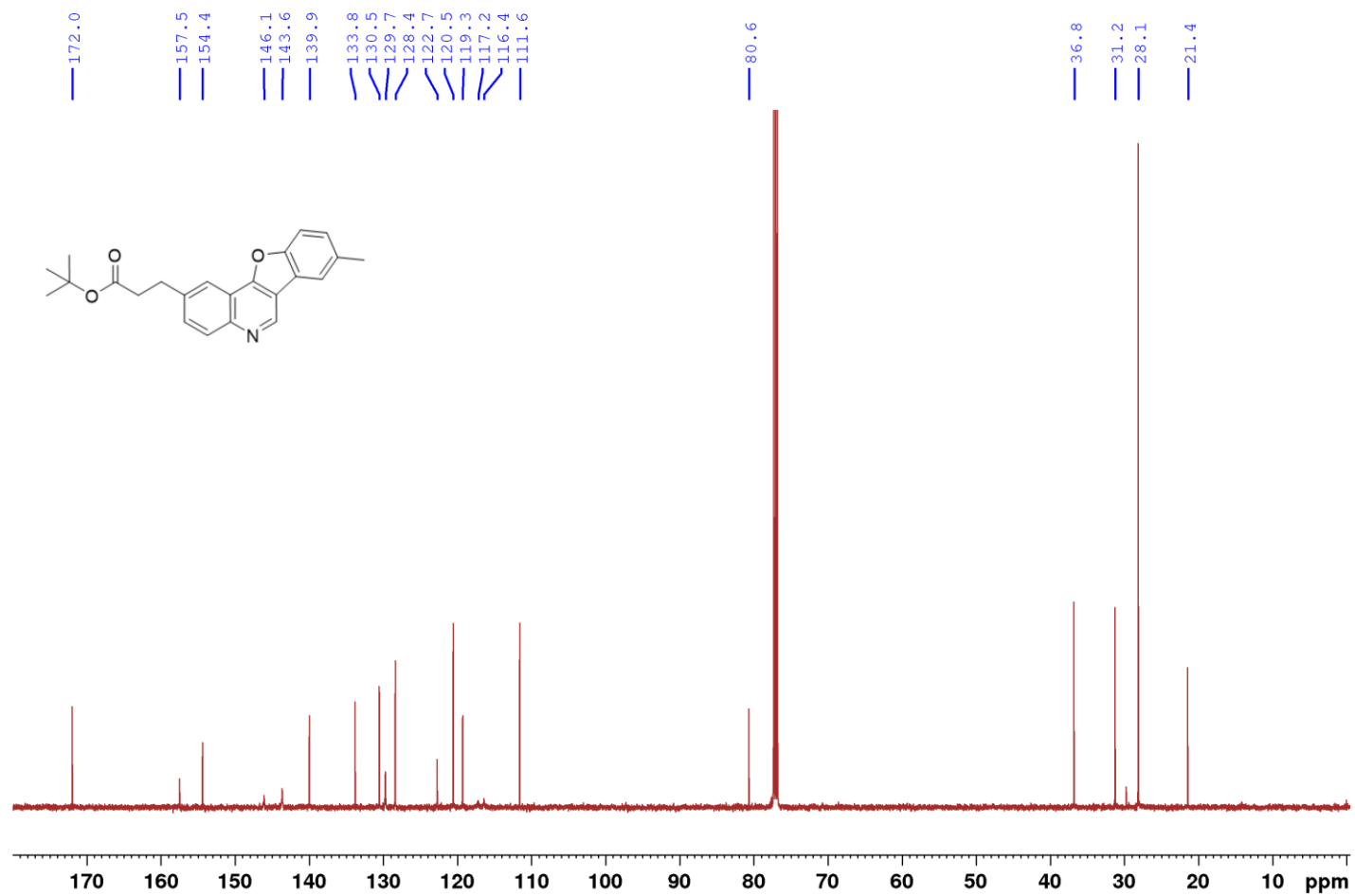
***tert*-Butyl 3-(benzofuro[3,2-*c*]quinolin-2-yl)propanoate 4i**



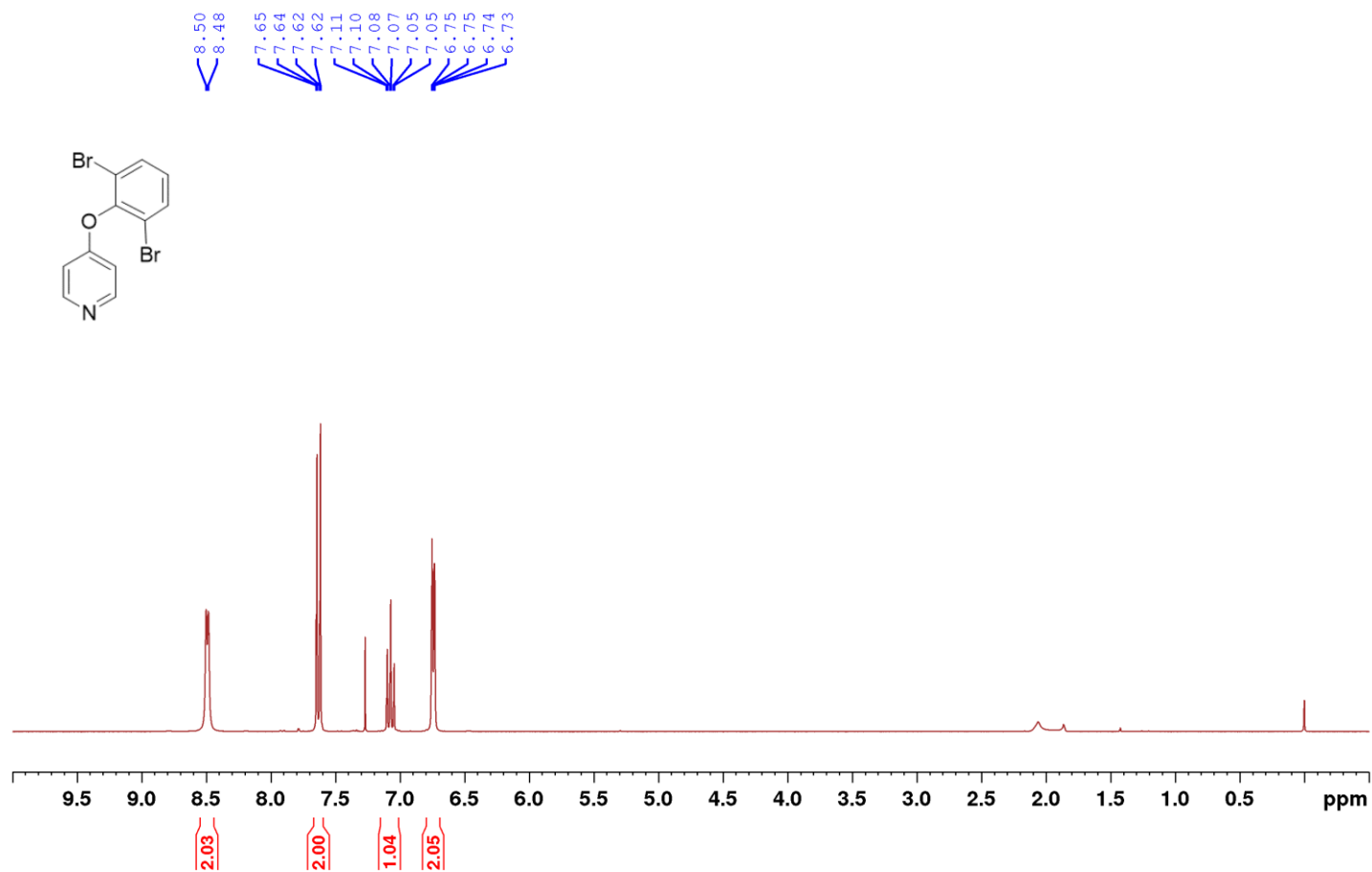


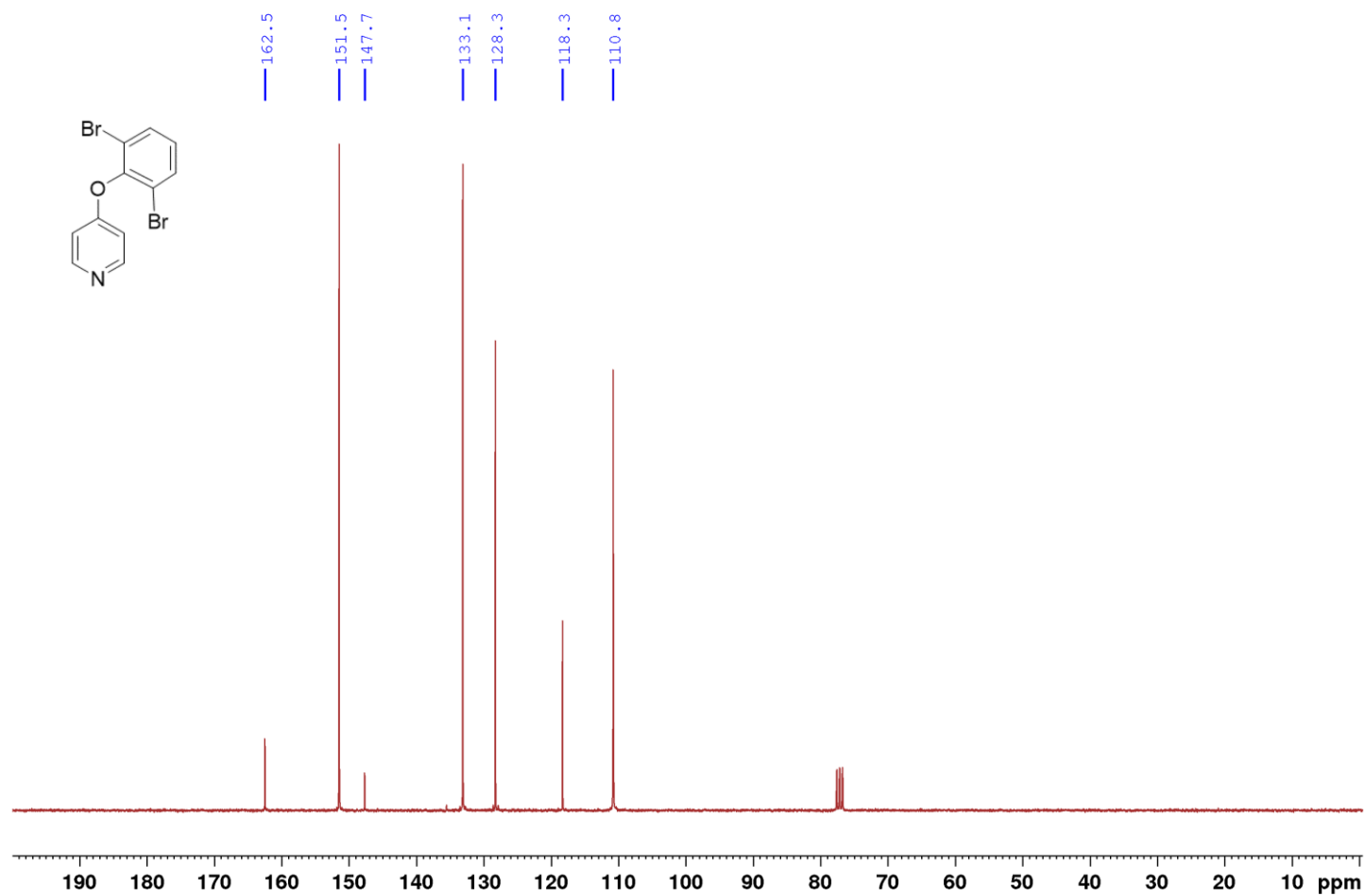
***tert*-Butyl 3-(8-methylbenzofuro[3,2-*c*]quinolin-2-yl)propanoate 4j**



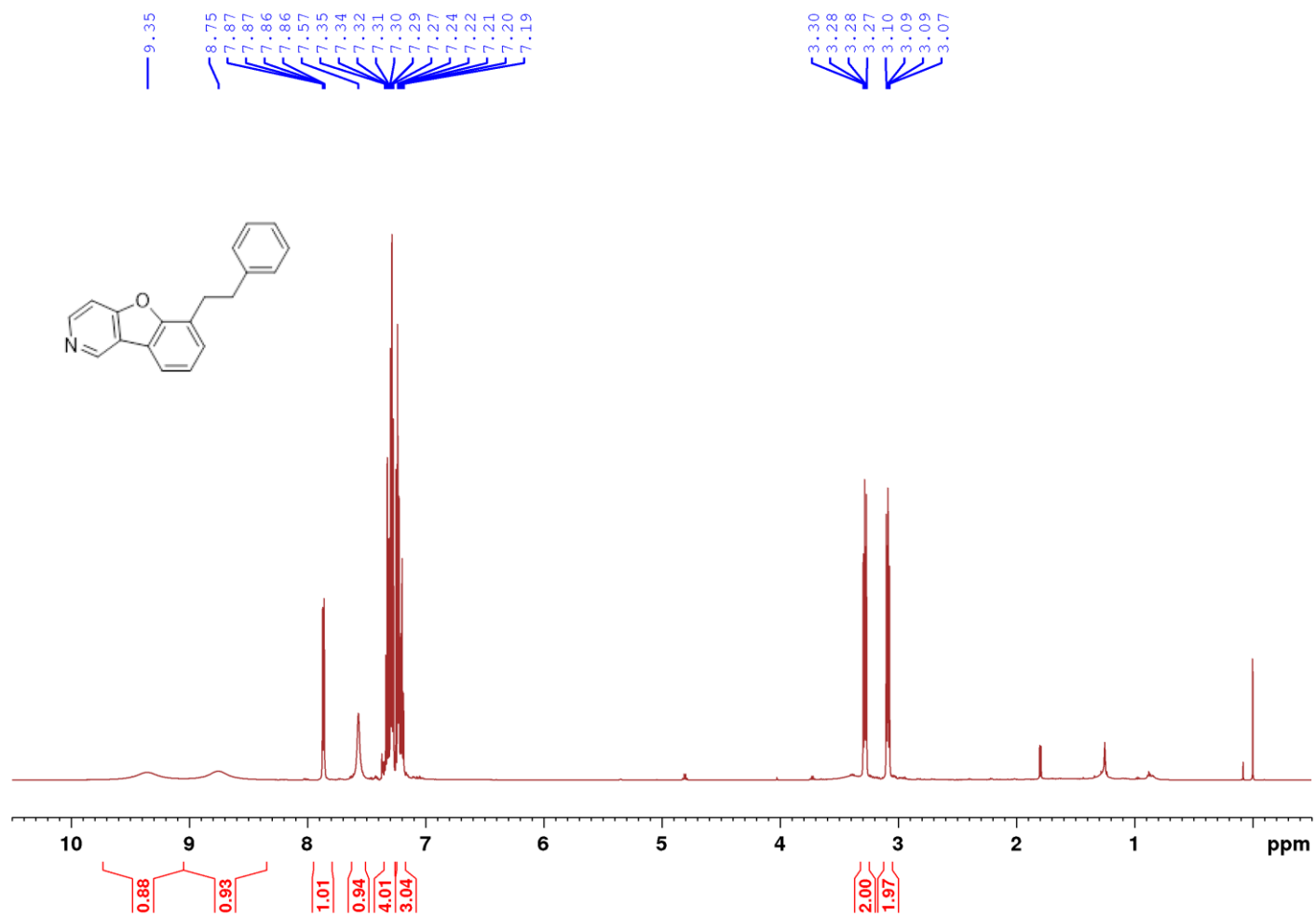


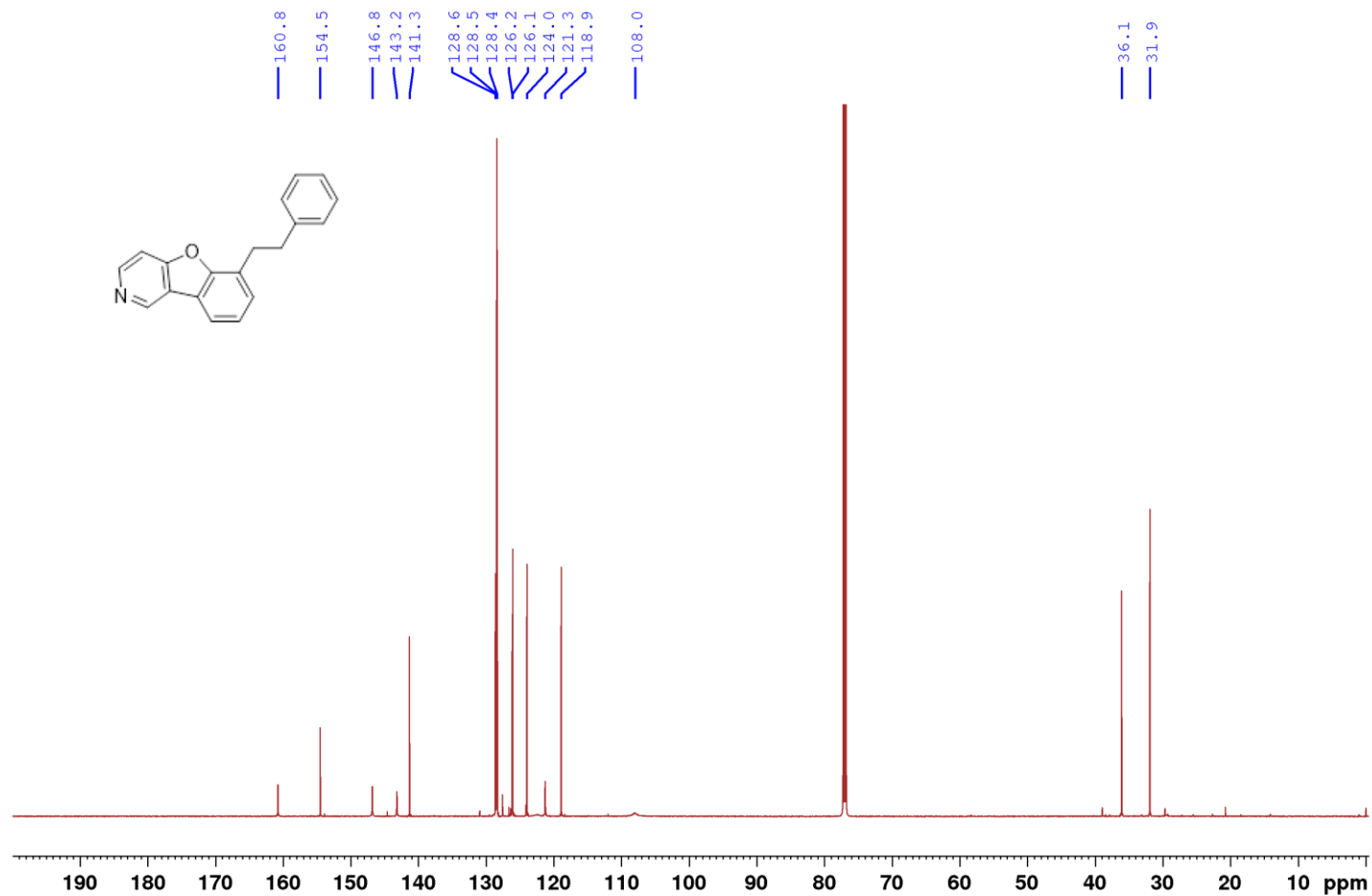
4-(2,6-Dibromophenoxy)pyridine 5



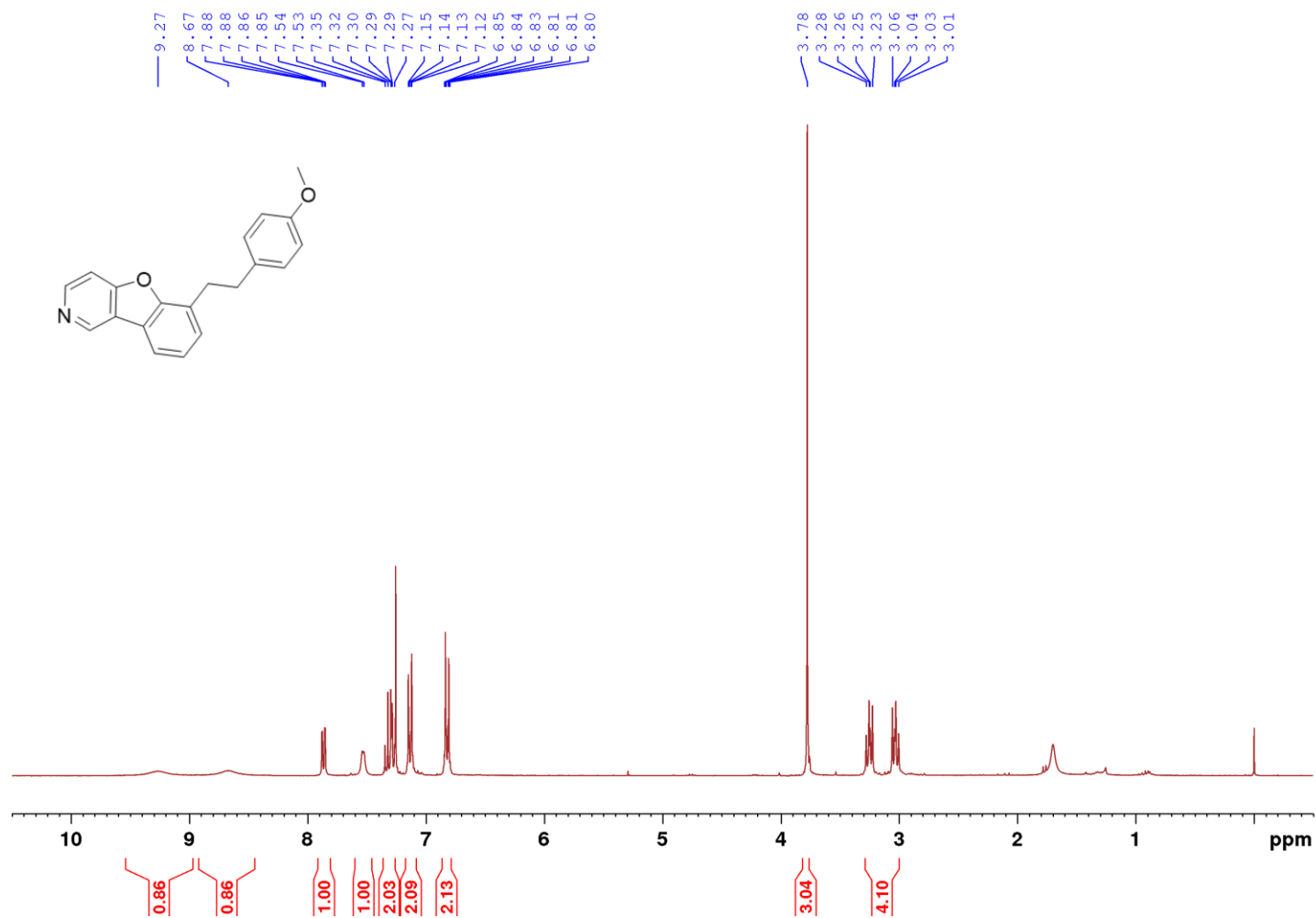


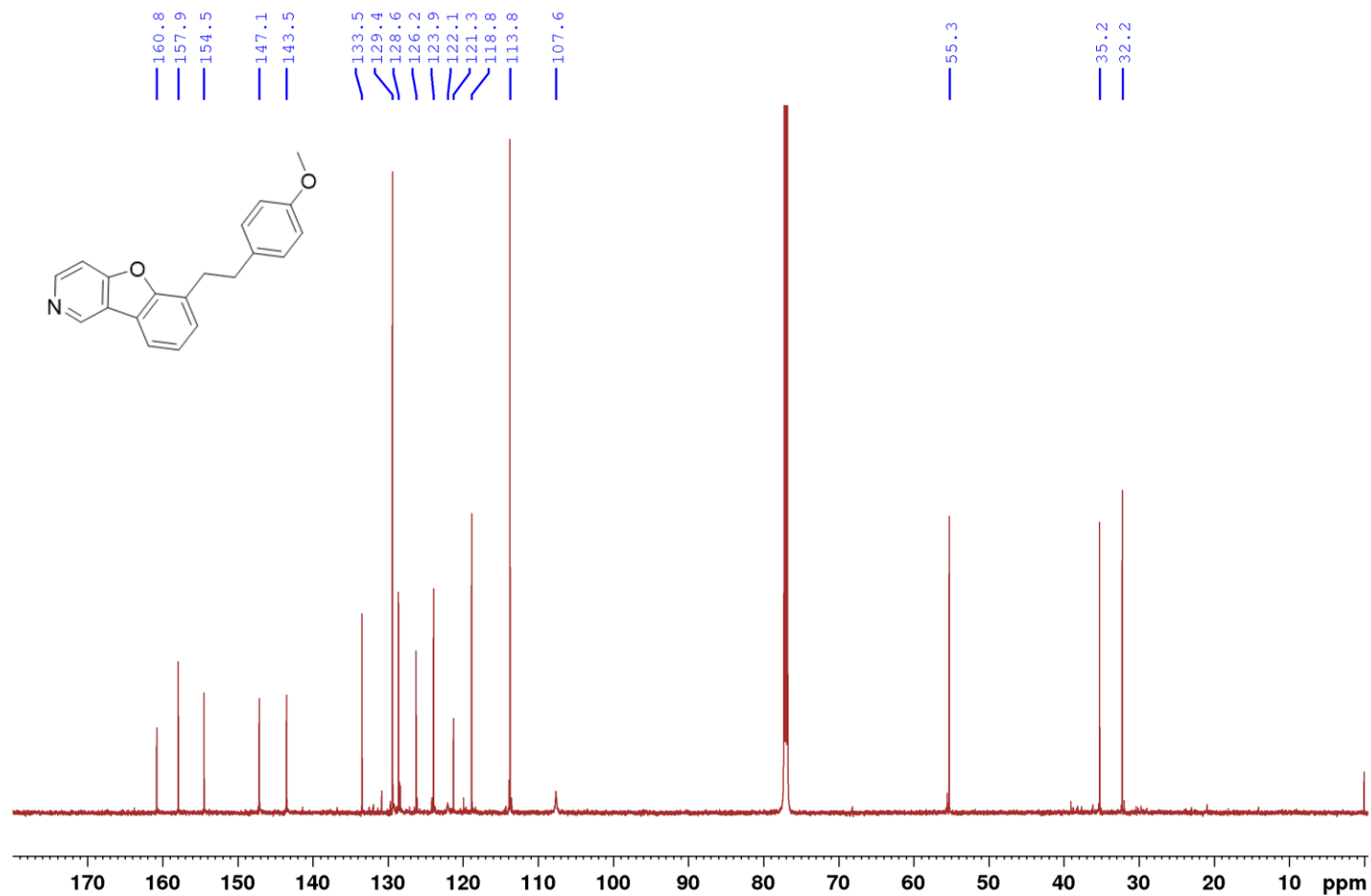
6-phenethylbenzofuro[3,2-c]pyridine 6a



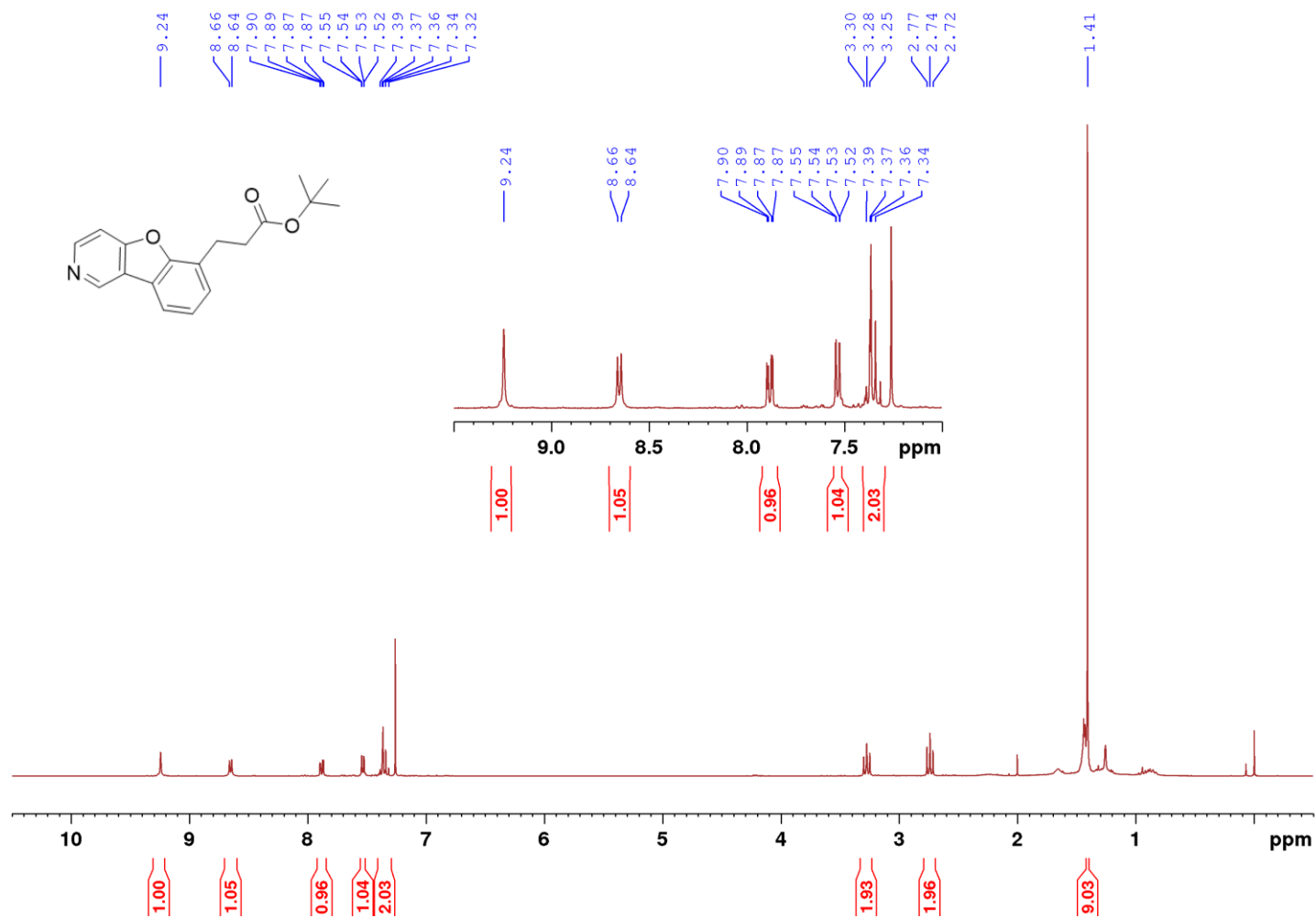


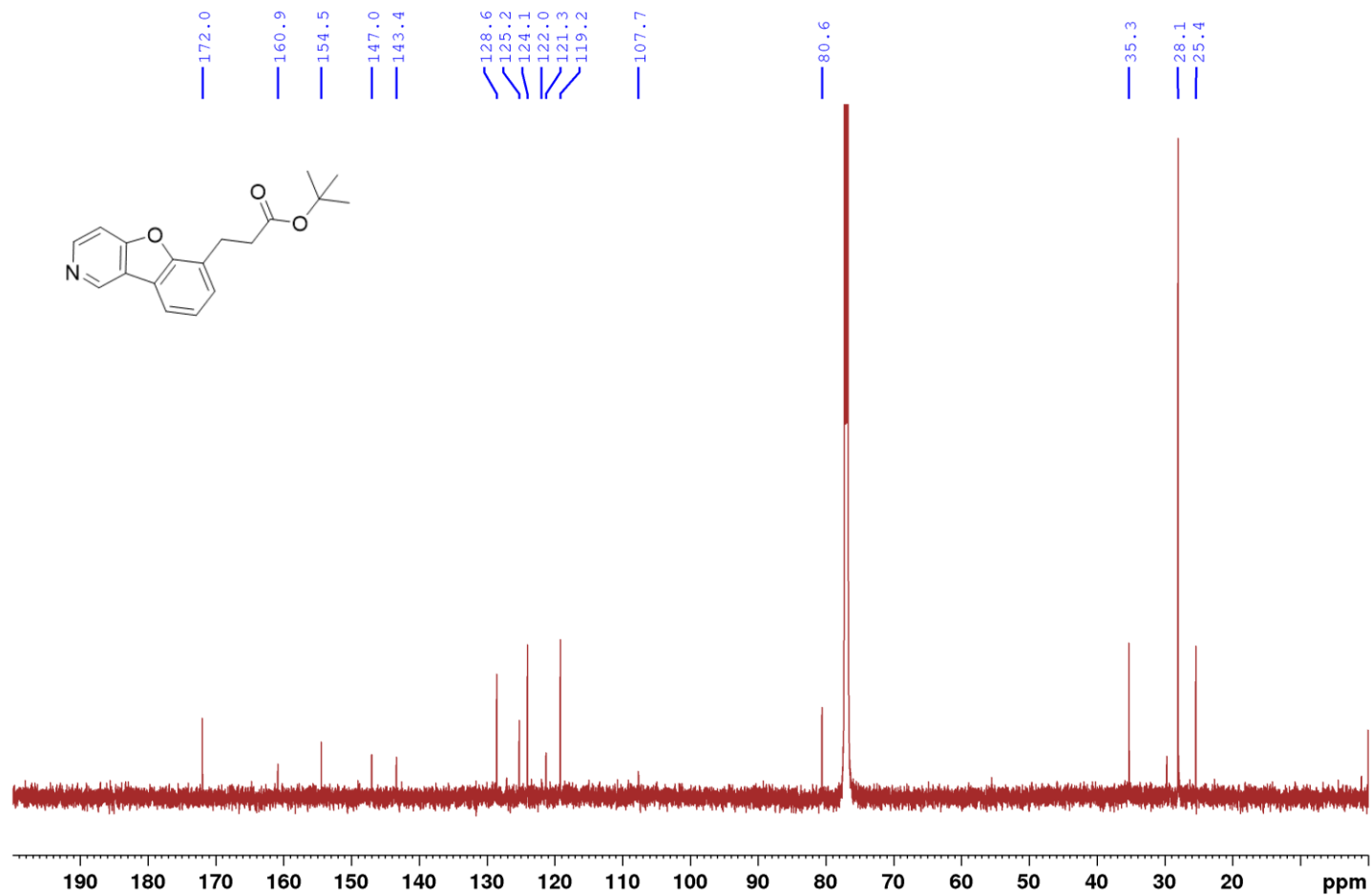
6-(4-Methoxyphenethyl)benzofuro[3,2-c]pyridine 6b



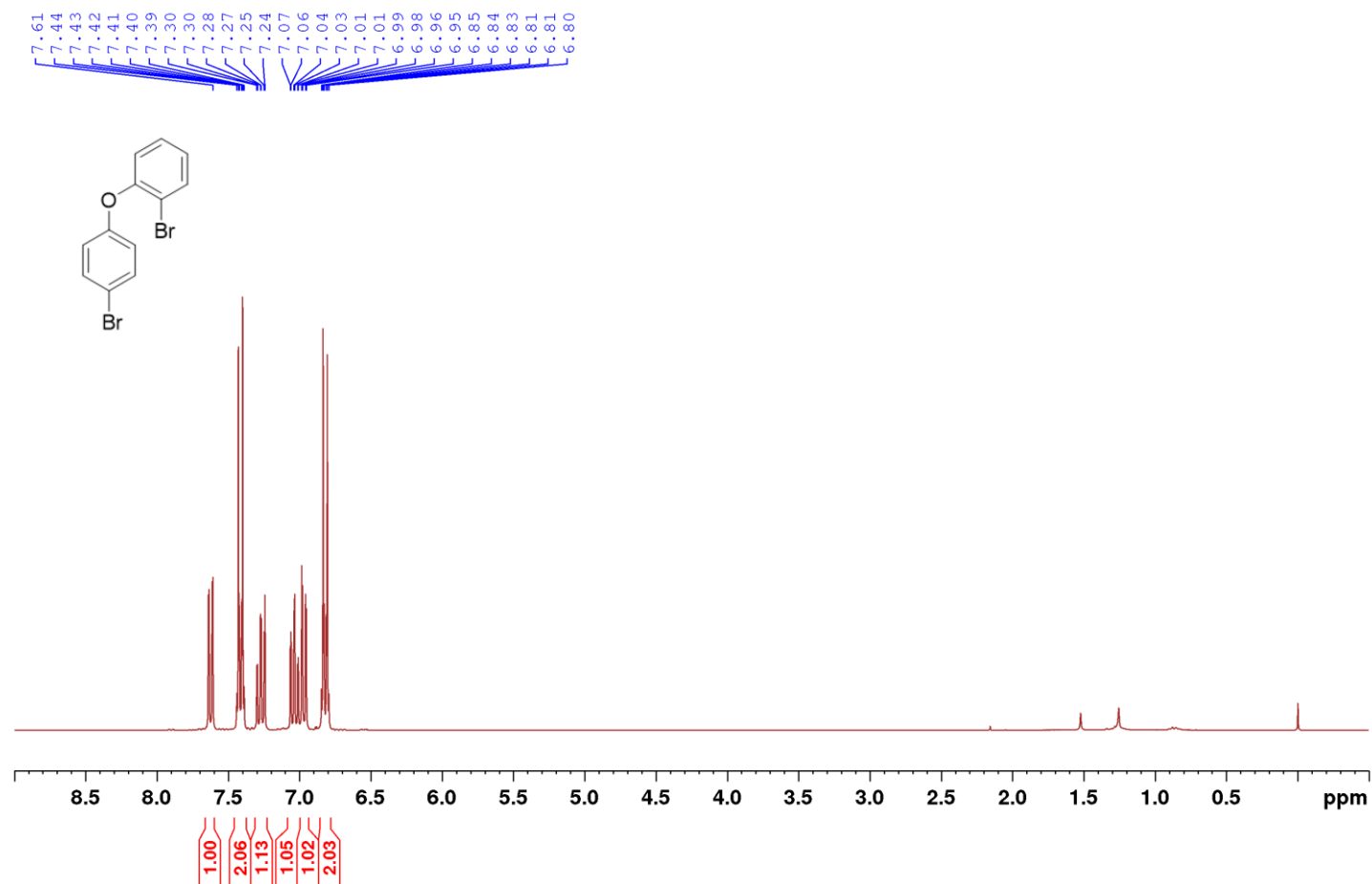


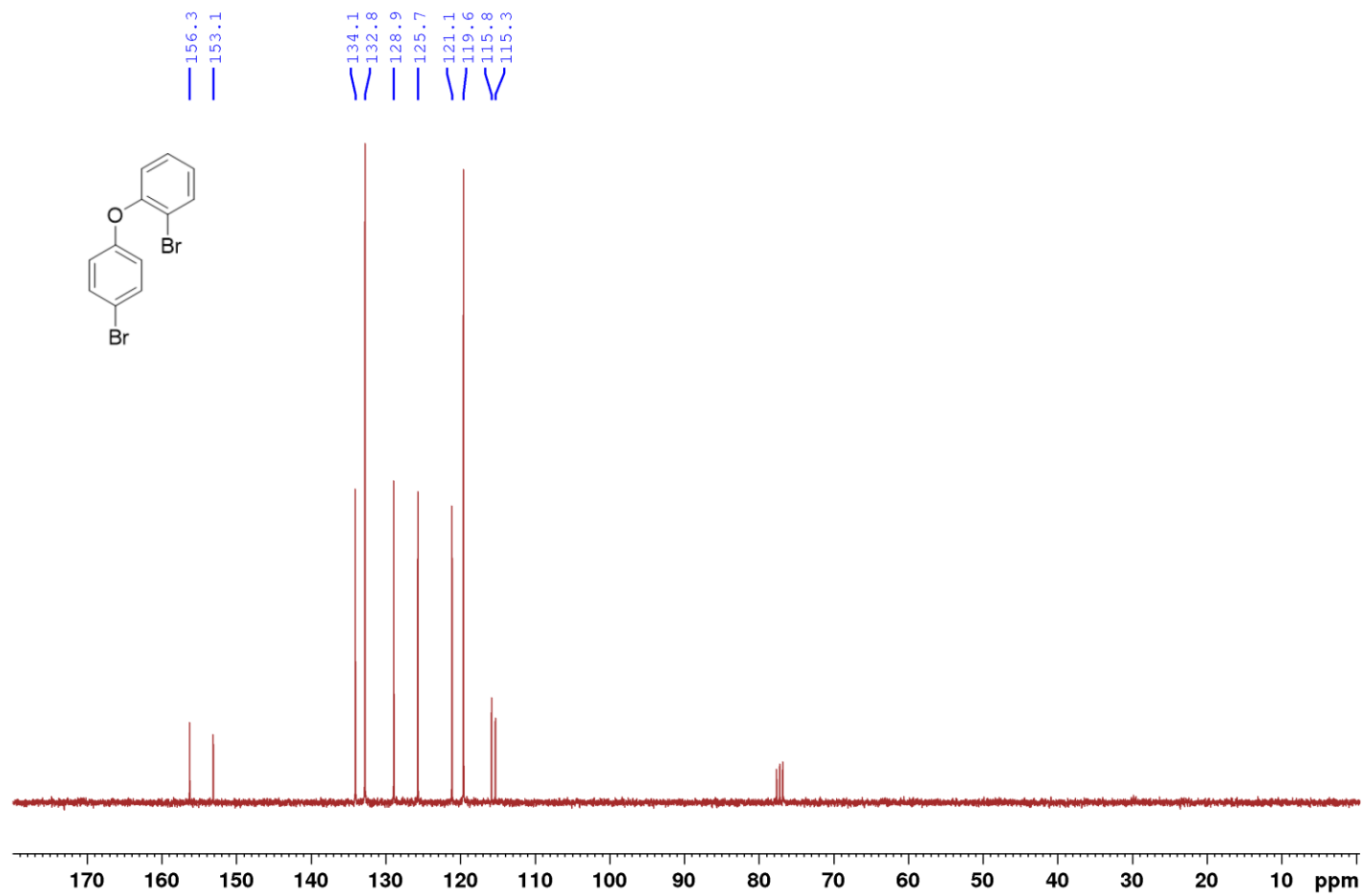
***tert*-Butyl 3-(benzofuro[3,2-*c*]pyridin-6-yl)propanoate 6c**



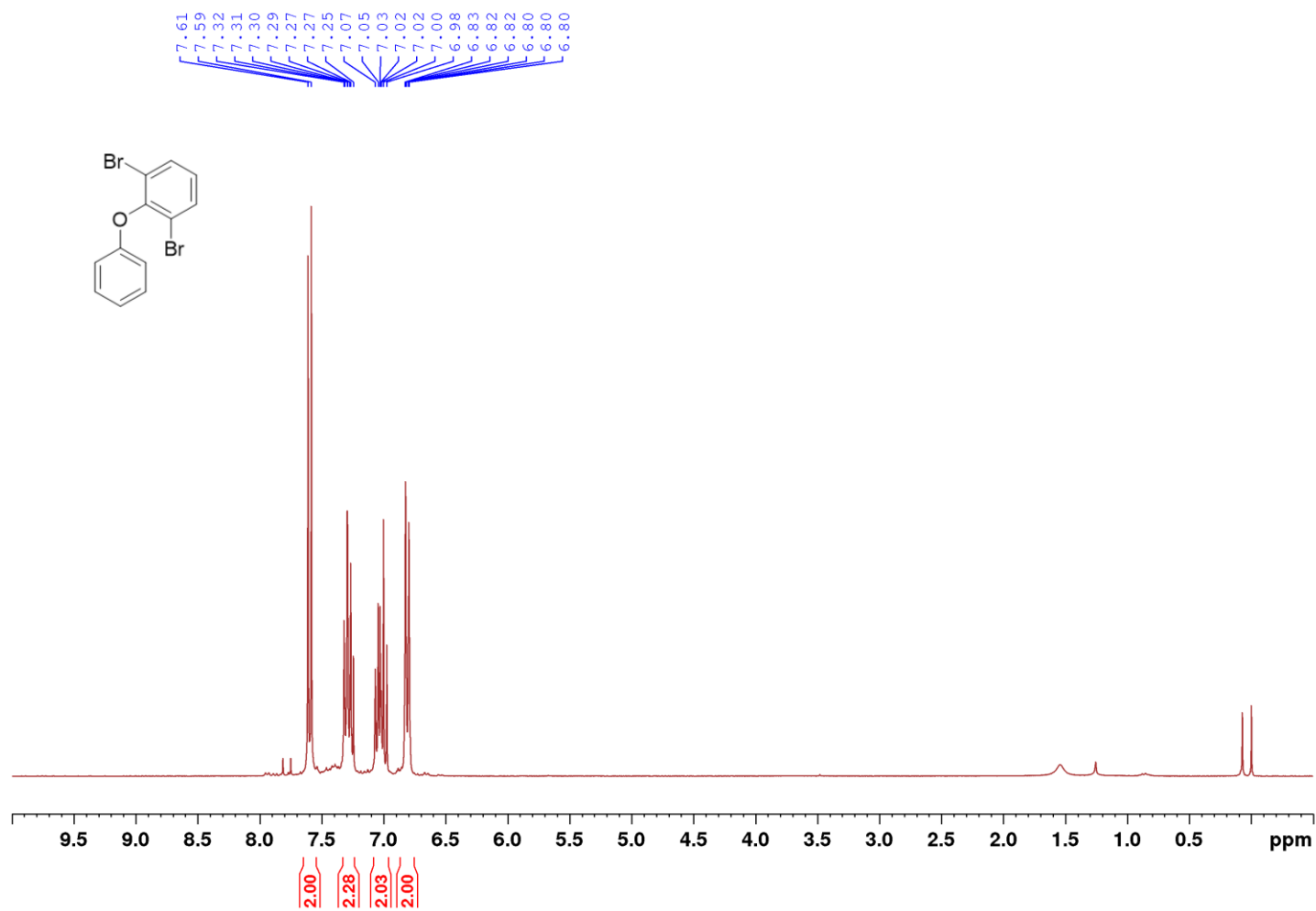


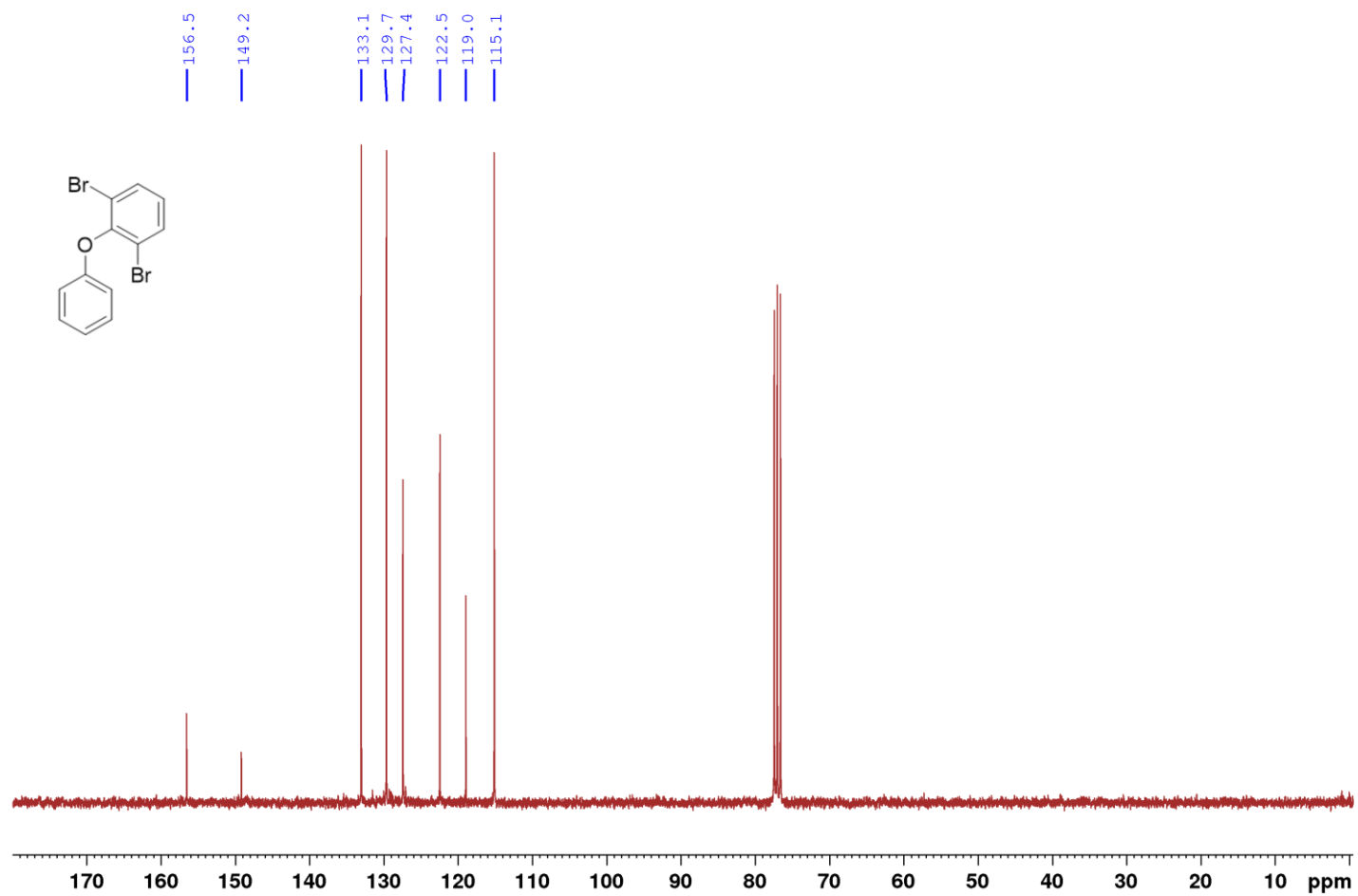
1-Bromo-2-(4-bromophenoxy)benzene 7



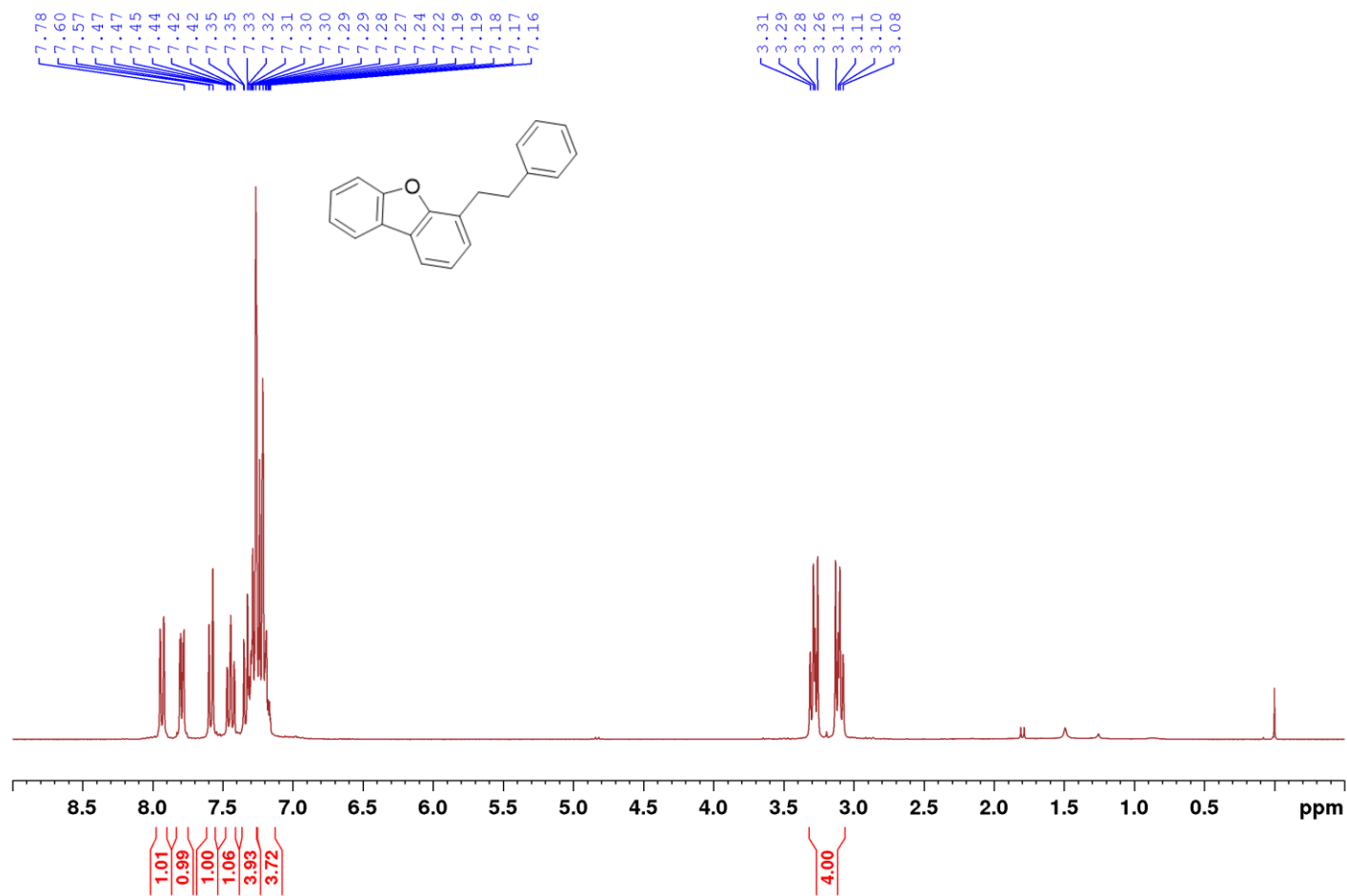


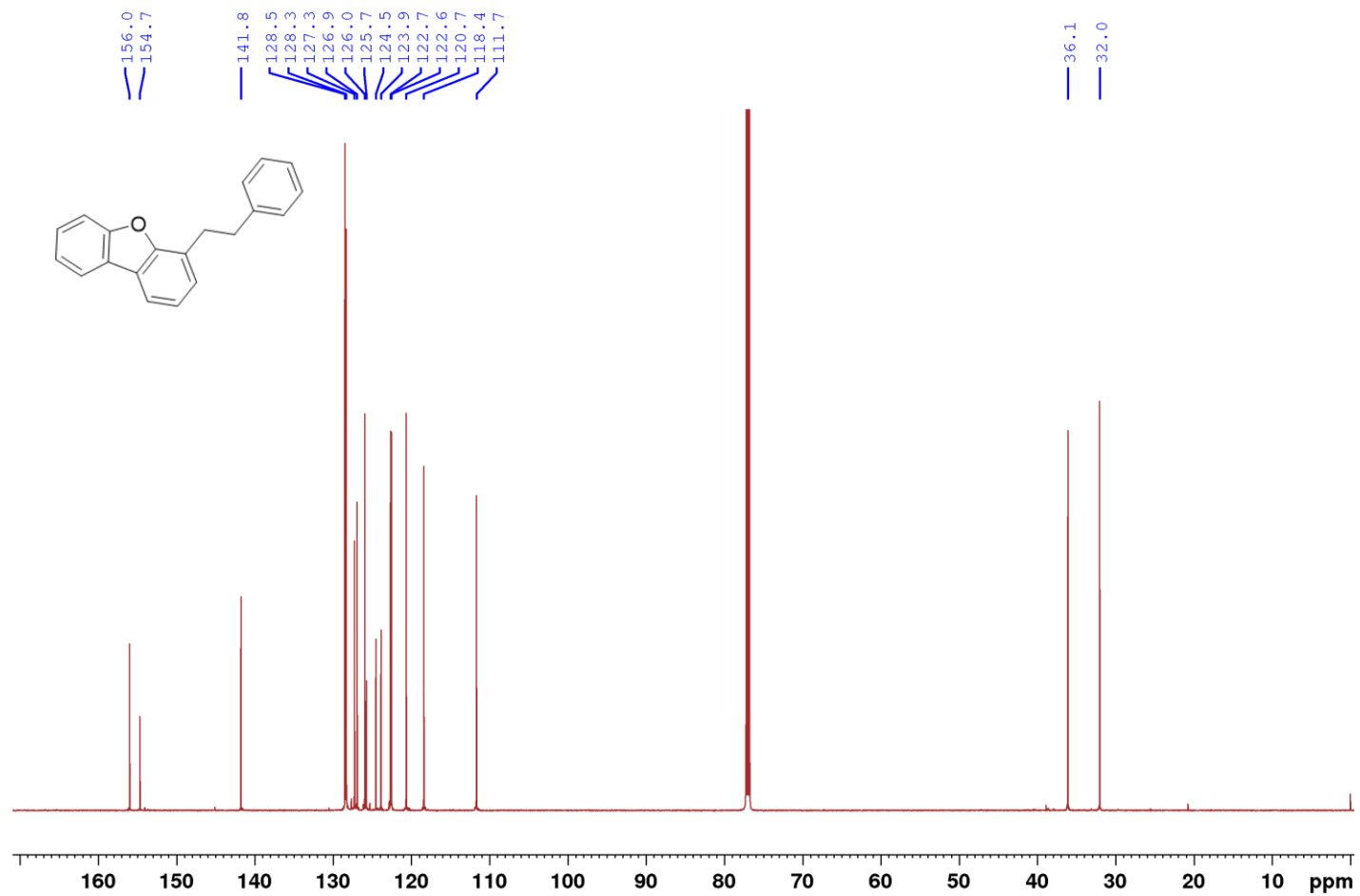
1,3-Dibromo-2-phenoxybenzene 8



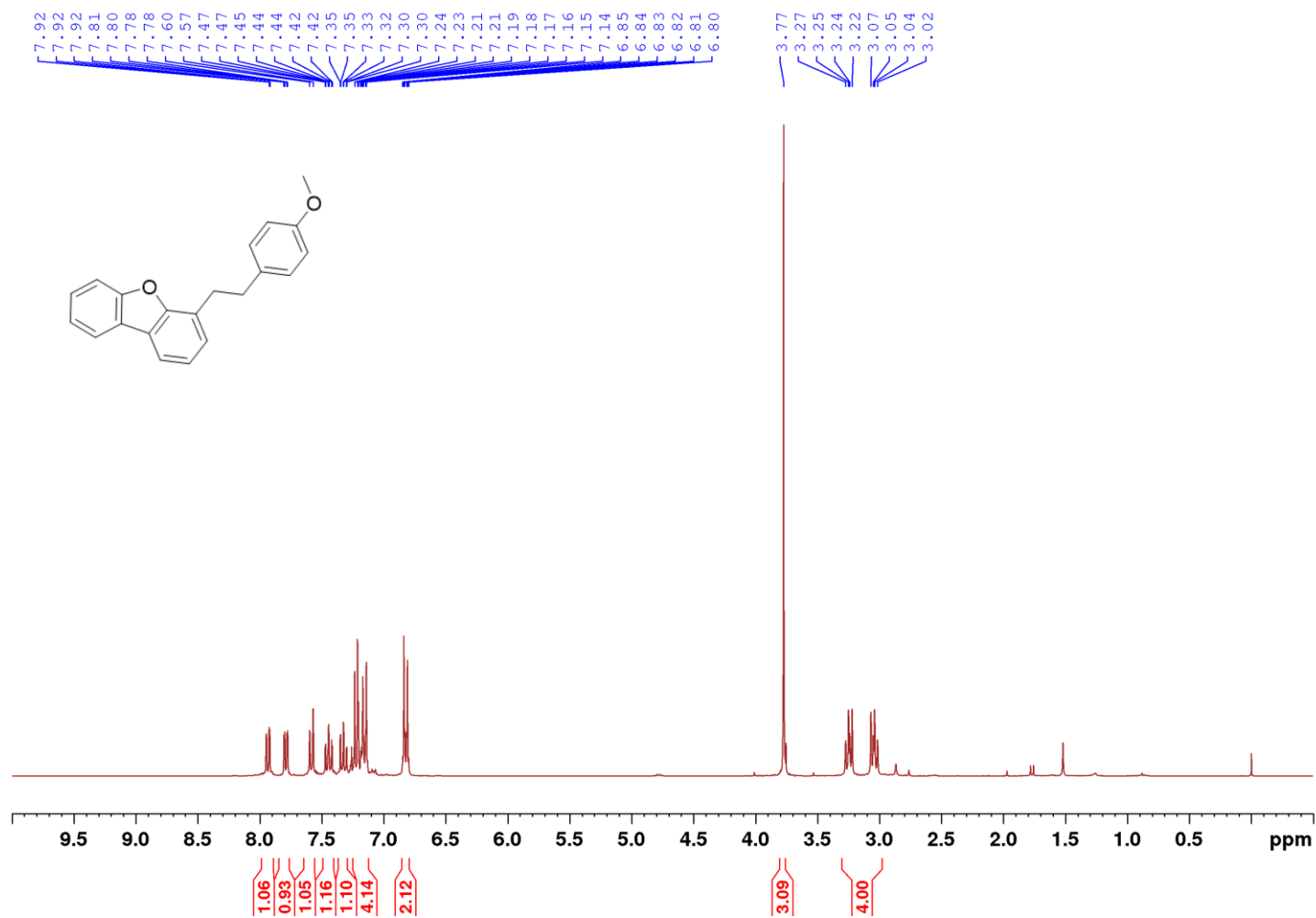


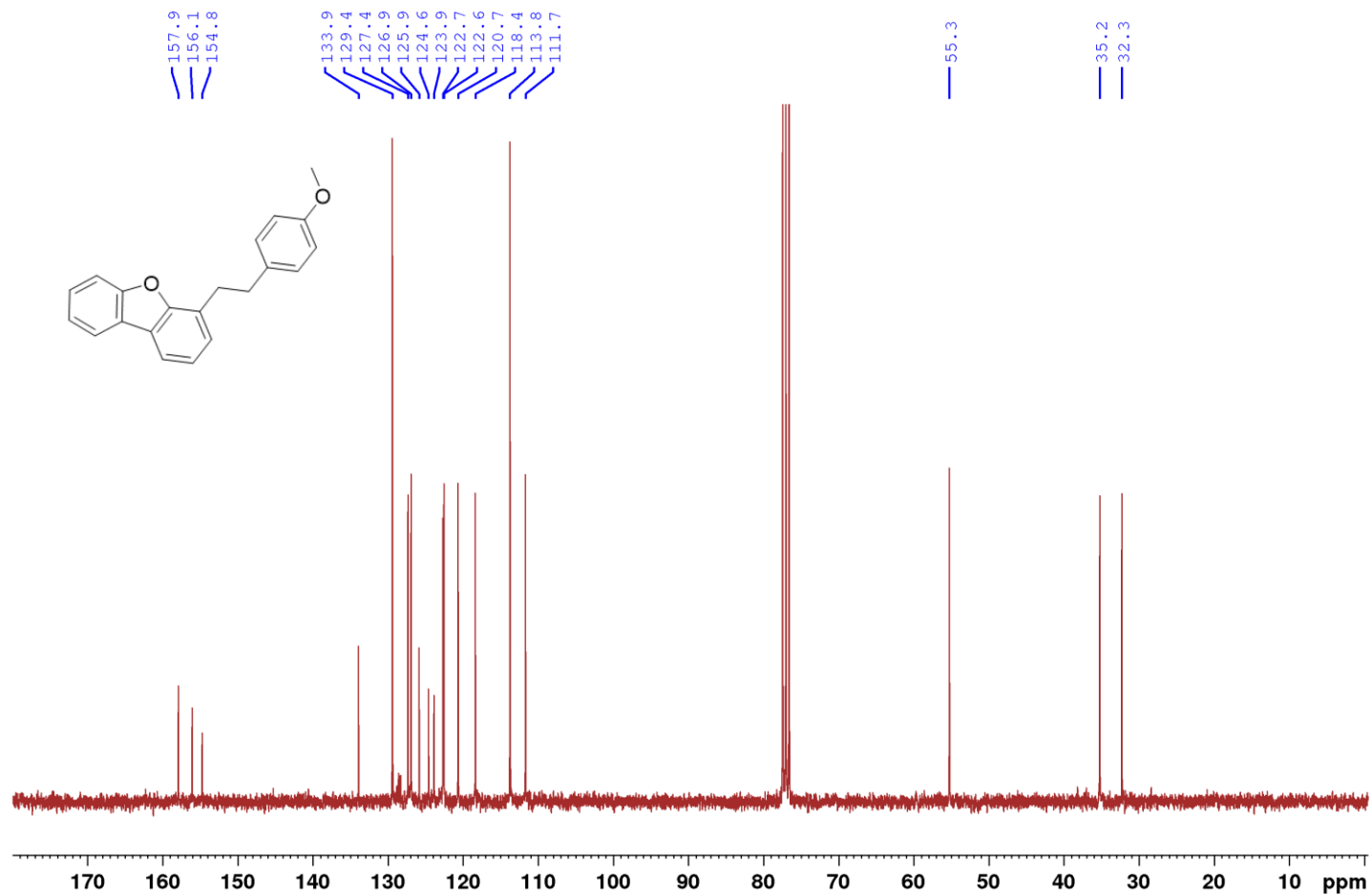
4-phenethyldibenzo[*b,d*]furan 9a



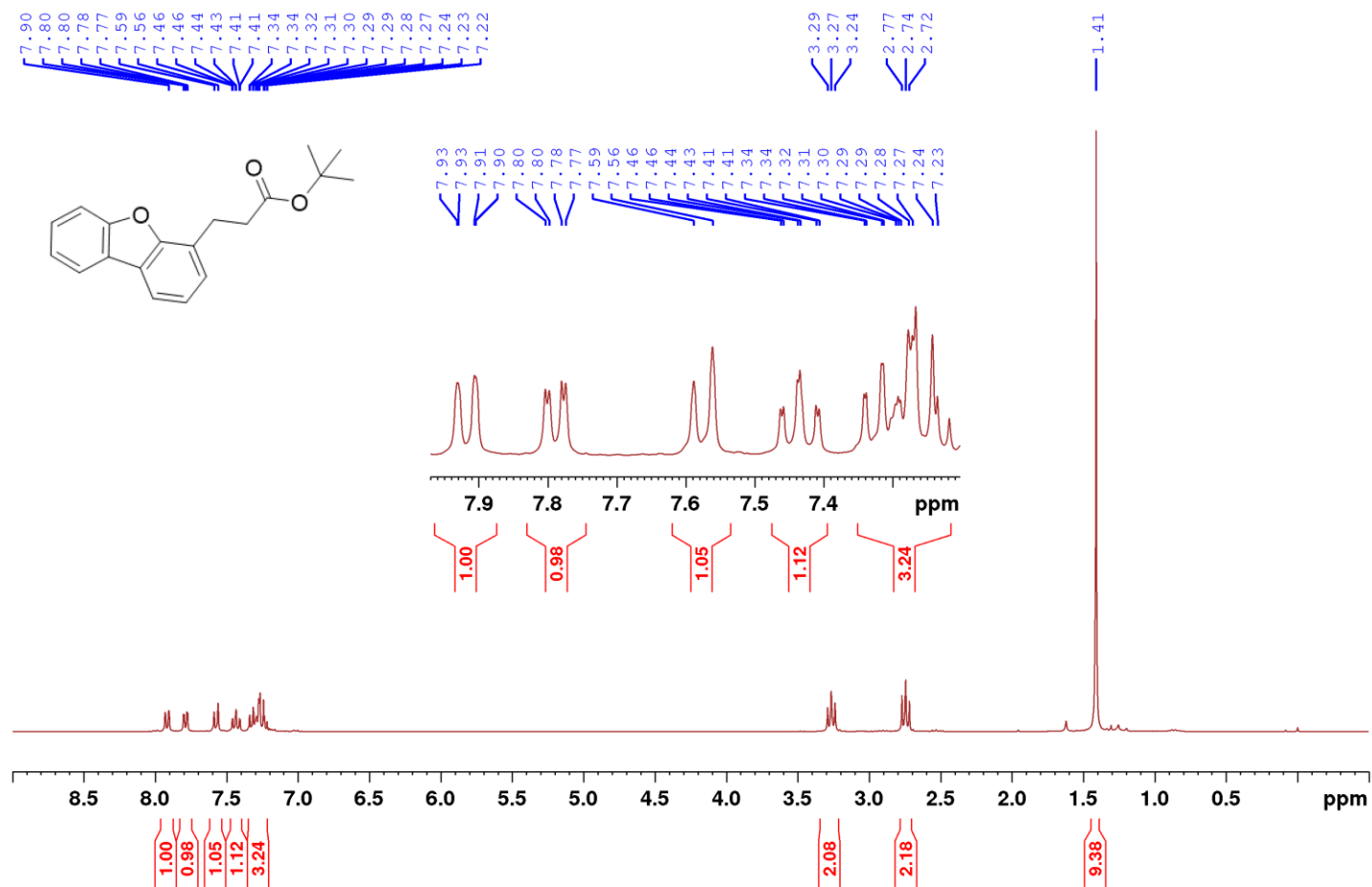


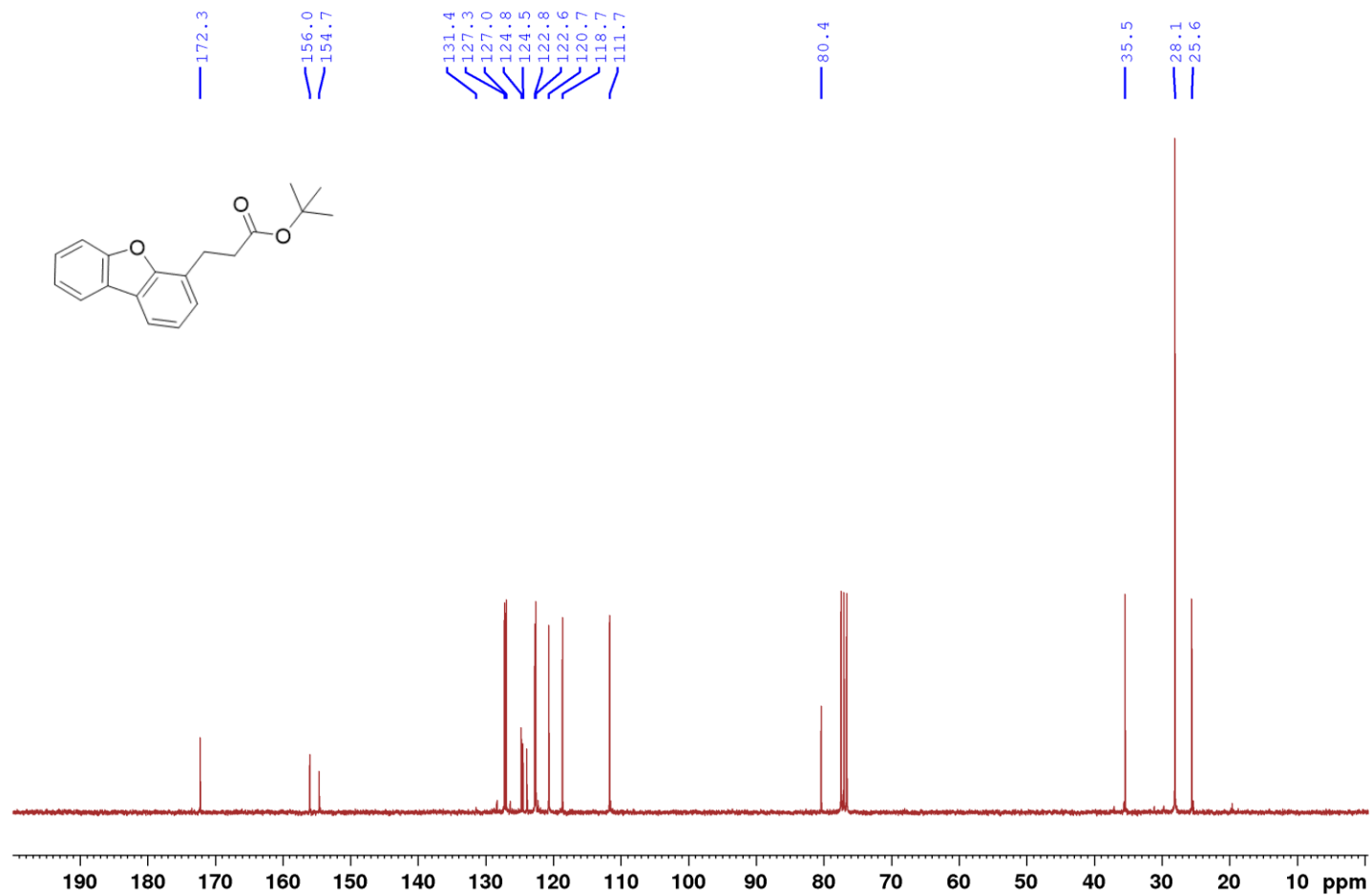
4-(4-Methoxyphenethyl)dibenzo[*b,d*]furan 9b



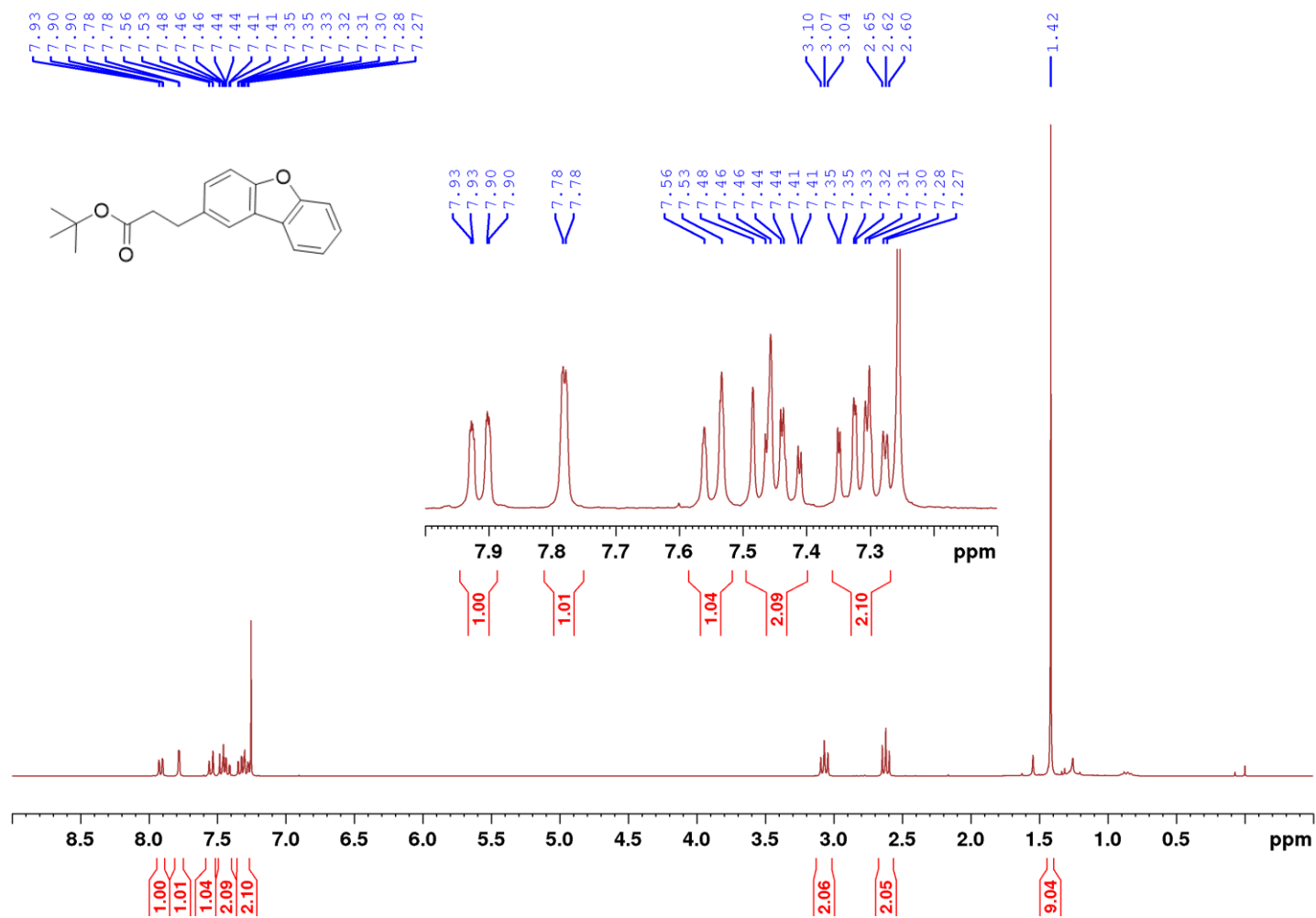


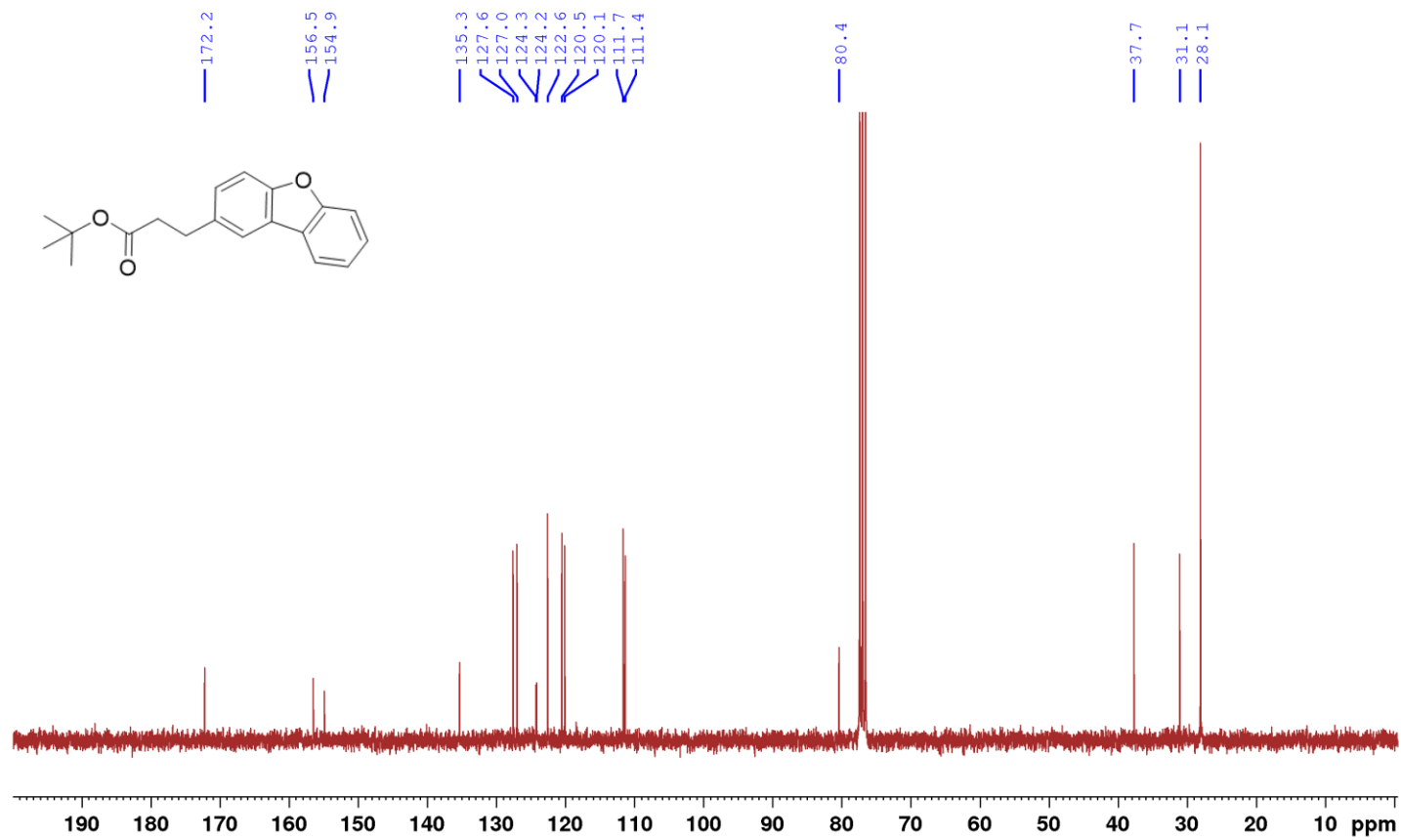
***tert*-Butyl 3-(dibenzo[*b,d*]furan-4-yl)propanoate 9c**



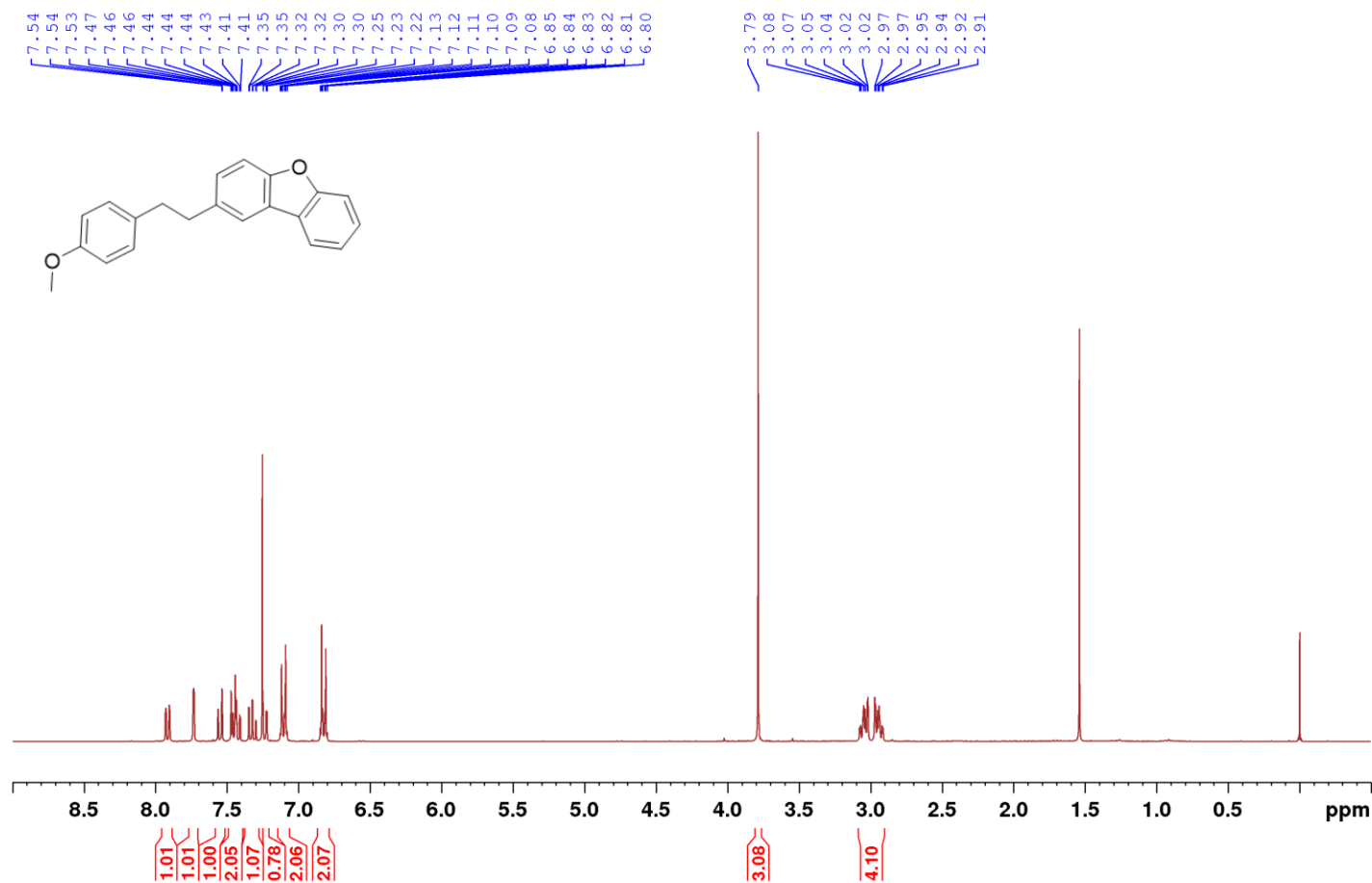


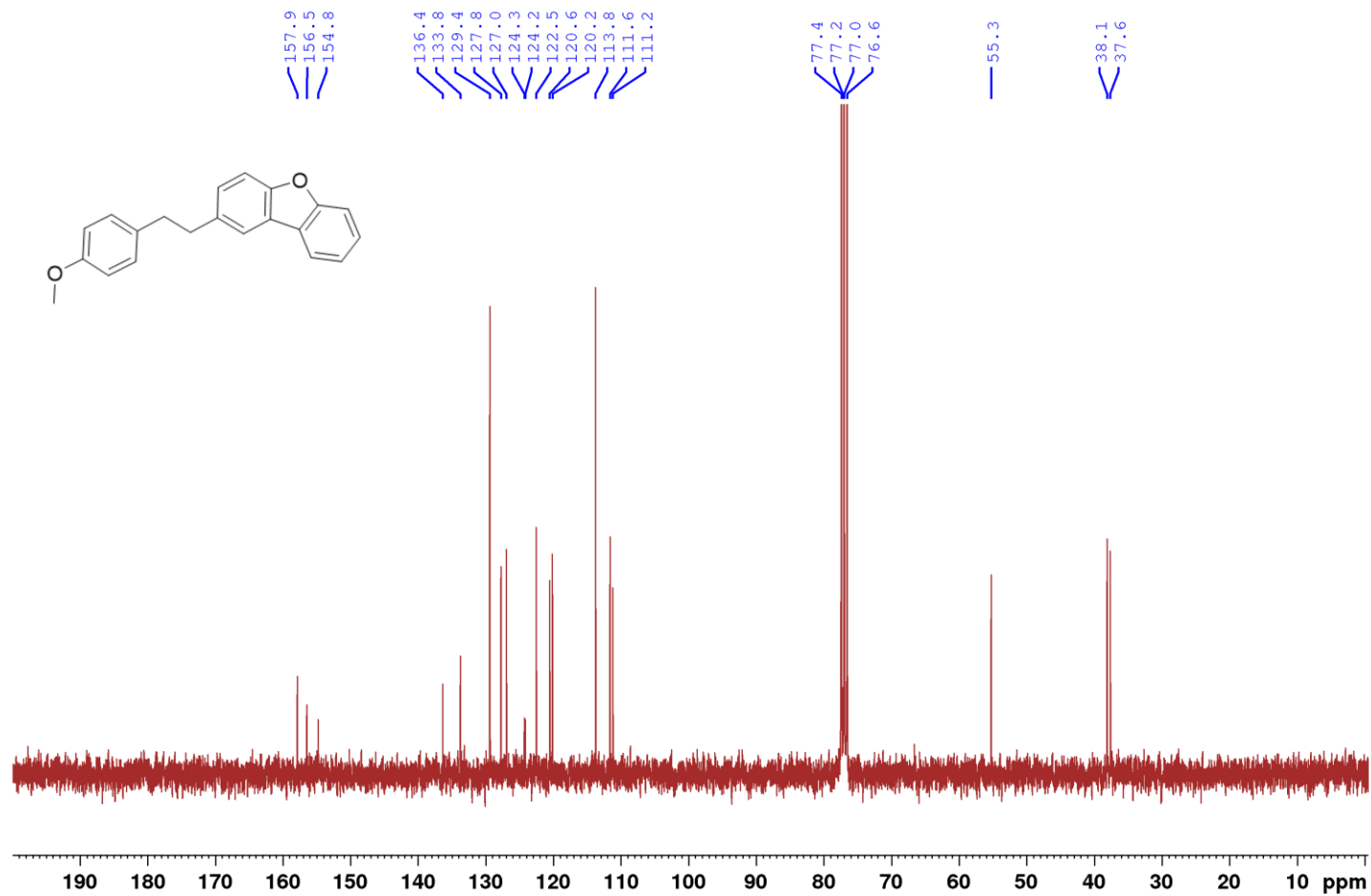
***tert*-Butyl 3-(dibenzo[*b,d*]furan-2-yl)propanoate 9d**



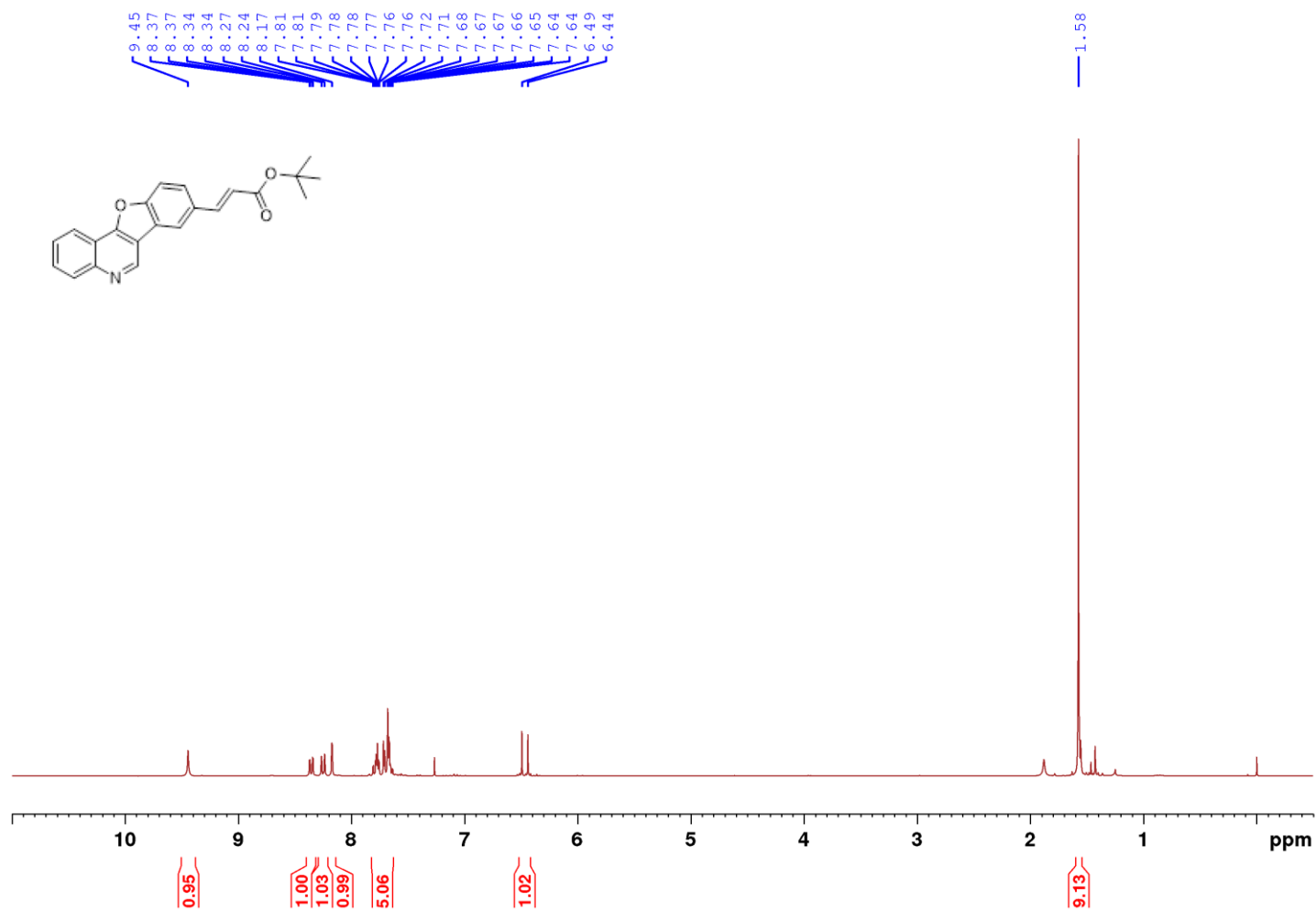


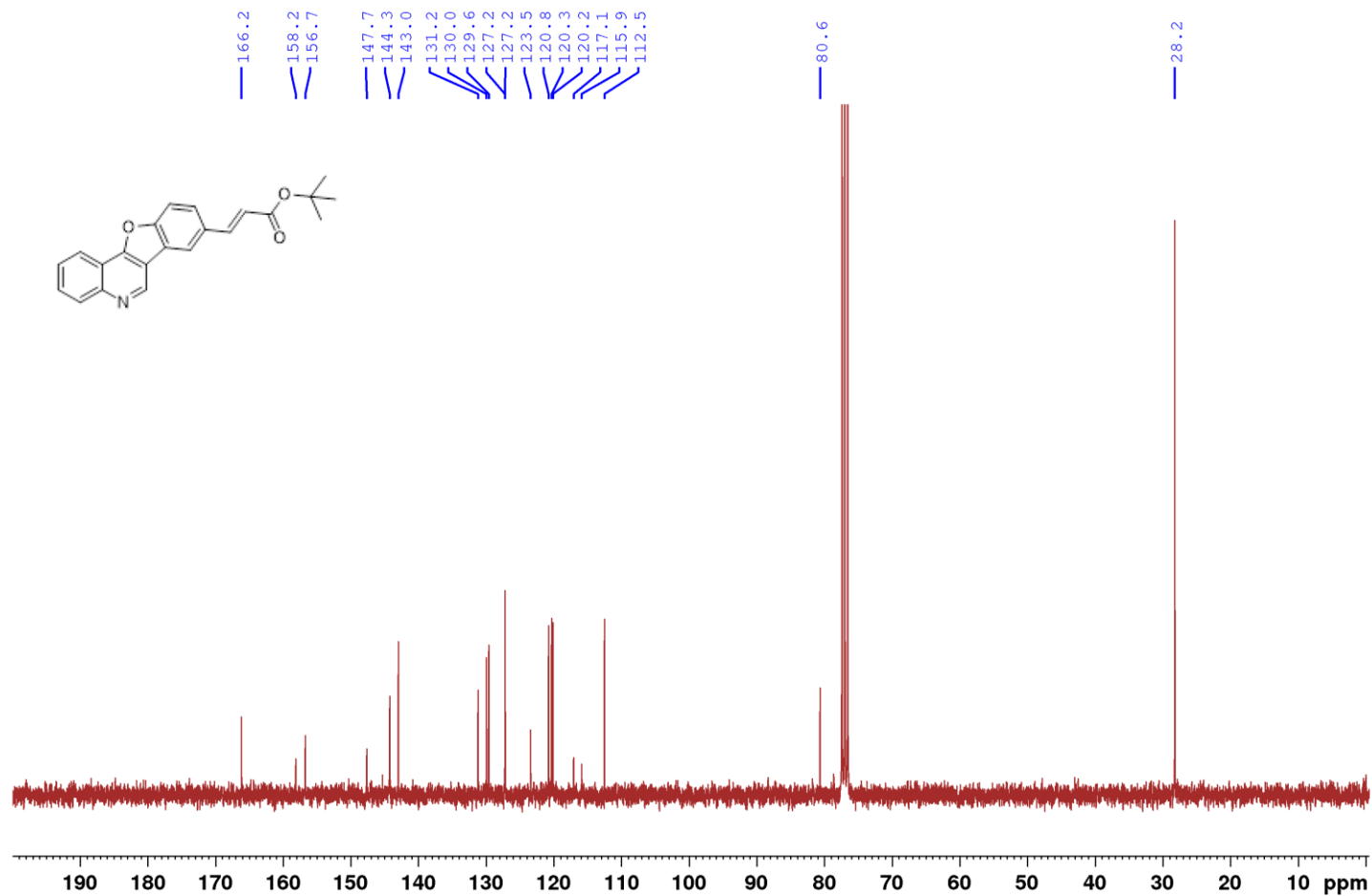
2-(4-Methoxyphenethyl)dibenzo[*b,d*]furan 9e





***tert*-Butyl (*E*)-3-(benzofuro[3,2-*c*]quinolin-8-yl)acrylate S2**





X-Ray Crystallography Methods

This work was undertaken by Dr. Mark Light at the University of Southampton. Single crystals were obtained from a saturated solution of methanol by slow evaporation. A suitable crystal was selected and mounted on a **MITIGEN** holder with silicon oil. Data were collected using a ROD, Synergy Custom system, **HyPix** diffractometer equipped with an Oxford Cryosystems low-temperature device operating at a steady temperature of $T = 100(2)$ K. Data were measured using ω scans with Cu K_α radiation. The diffraction pattern was indexed and the total number of runs, and images was based on the strategy calculation from the program **CrysAlisPro** 1.171.41.93a (Rigaku OD, 2020). A multi-scan absorption correction was performed using CrysAlisPro 1.171.41.93a^[4]. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient of these materials is obtained at $\lambda = 1.54184\text{\AA}$.

The structures were solved, and the space group determined by the **ShelXT**^[5] structure solution program using dual methods and by using and by using **Olex2**^[6] as the graphical interface. These models were refined by full matrix least squares minimisation on F^2 version 2016/6 of **ShelXL**^[7]. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

_exptl_absorpt_process_details: CrysAlisPro 1.171.41.93a^[4] using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

Crystal Data

There is a single molecule in the asymmetric unit for compounds **3a**, **3b**, **3c**, **4d**, **4h**, **4j** and **6a** which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

There is a single molecule in the asymmetric unit for compounds **9a**, which is represented by the reported sum formula. In other words: Z is 2 and Z' is 1.

For compound **9e**, the value of Z' is 2. This means that there are two independent molecules in the asymmetric unit.

Table 1S: X-ray diffraction collection data and refinement details.

Compound	3a	3b	3c	4d	4h	4j	6a	9a	9e
Formula	C ₂₃ H ₁₇ NO	C ₂₃ H ₁₆ FNO	C ₂₂ H ₂₁ NO ₃	C ₂₄ H ₁₈ FNO	C ₂₃ H ₂₃ NO ₄	C ₂₃ H ₂₃ NO ₃	C ₁₉ H ₁₅ NO	C ₂₀ H ₁₆ O	C ₂₁ H ₁₈ O ₂
D_{calc}/g cm⁻³	1.320	1.382	1.326	1.374	1.327	1.296	1.321	1.268	1.291
m/mm⁻¹	0.628	0.745	0.707	0.732	0.735	0.086	0.639	0.592	0.645
Formula Weight	323.38	341.37	347.40	355.39	377.42	361.42	273.32	272.33	302.35
Colour	clear colourless	clear colourless	clear colourless	clear colourless	clear colourless	clear colourless	clear colourless	clear colourless	clear colourless
Shape	needle-shaped	irregular-shaped	block-shaped	plate-shaped	block-shaped	prism-shaped	block-shaped	plate-shaped	plate-shaped
Size/mm³	0.24×0.05×0.02	0.28×0.05×0.03	0.12×0.10×0.06	0.19×0.18×0.03	0.12×0.09×0.05	0.09×0.02×0.01	0.39×0.06×0.04	0.18×0.11×0.02	0.30×0.10×0.06
T/K	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
Crystal System	monoclinic	orthorhombic	monoclinic	monoclinic	orthorhombic	monoclinic	monoclinic	triclinic	monoclinic
Flack Parameter	-	-0.10(7)	-	-	-0.16(8)	-	-	-	-
Hoofit Parameter	-	-0.10(7)	-	-	-0.11(7)	-	-	-	-
Space Group	P2 ₁ /c	Pna2 ₁	P2 ₁ /c	P2 ₁ /n	P2 ₁ 2 ₁ 2 ₁	P2 ₁ /c	P2 ₁ /c	P-1	P2 ₁ /c
a/Å	4.80750(10)	12.4459(2)	19.3497(7)	5.6809(2)	5.40640(10)	12.0444(9)	13.1980(2)	6.3822(4)	7.6458(2)
b/Å	27.2149(4)	27.6090(4)	7.1784(2)	13.8095(5)	9.64370(10)	5.6218(3)	5.61880(10)	10.2110(8)	6.14330(10)
c/Å	12.4496(2)	4.77340(10)	12.8947(5)	21.8999(9)	36.2282(5)	27.7622(17)	18.6771(3)	11.3886(12)	66.279(2)
a/°	90	90	90	90	90	90	90	84.533(7)	90
b/°	92.5230(10)	90	103.665(4)	91.229(3)	90	99.864(7)	97.2680(10)	89.069(7)	91.529(2)
g/°	90	90	90	90	90	90	90	74.931(6)	90
V/Å³	1627.27(5)	1640.23(5)	1740.37(11)	1717.66(11)	1888.86(5)	1852.0(2)	1373.91(4)	713.37(11)	3112.05(13)
Z	4	4	4	4	4	4	4	2	8
Z'	1	1	1	1	1	1	1	1	2
Wavelength/Å	1.54184	1.54184	1.54184	1.54184	1.54184	0.71073	1.54184	1.54184	1.54184
Radiation type	Cu K _α	Cu K _α	Cu K _α	Cu K _α	Cu K _α	Mo K _α	Cu K _α	Cu K _α	Cu K _α
Q_{min}^h	3.248	3.201	4.704	3.784	4.745	3.919	3.376	3.899	3.335
Q_{max}^h	76.365	76.759	76.710	76.633	76.382	30.328	74.889	66.473	66.497
Measured Refl's.	15653	15030	10678	3518	18320	12007	19810	5814	30515
Indep't Refl's	3254	2914	3488	3518	3778	4623	2774	2417	5621
Refl's I≥2 s(I)	2923	2791	2955	3311	3609	2595	2494	2067	5280
R_{int}	0.0347	0.0310	0.0296	.	0.0385	0.0616	0.1188	0.0579	0.1228
Parameters	226	235	239	245	257	248	190	190	418
Restraints	0	1	0	0	0	0	0	0	372
Largest Peak	0.177	0.154	0.332	0.670	0.135	0.246	0.308	0.566	0.617
Deepest Hole	-0.219	-0.194	-0.225	-0.720	-0.192	-0.292	-0.415	-0.479	-0.585
GooF	1.062	1.065	1.096	1.091	1.029	0.992	1.025	1.171	1.090
wR₂ (all data)	0.0957	0.0794	0.1443	0.4329	0.0751	0.1166	0.1564	0.3906	0.3493
wR₂	0.0932	0.0786	0.1391	0.4312	0.0739	0.0972	0.1520	0.3868	0.3480
R₁ (all data)	0.0454	0.0313	0.0509	0.1488	0.0311	0.1270	0.0607	0.1453	0.1323
R₁	0.0402	0.0299	0.0446	0.1448	0.0293	0.0530	0.0564	0.1351	0.1298

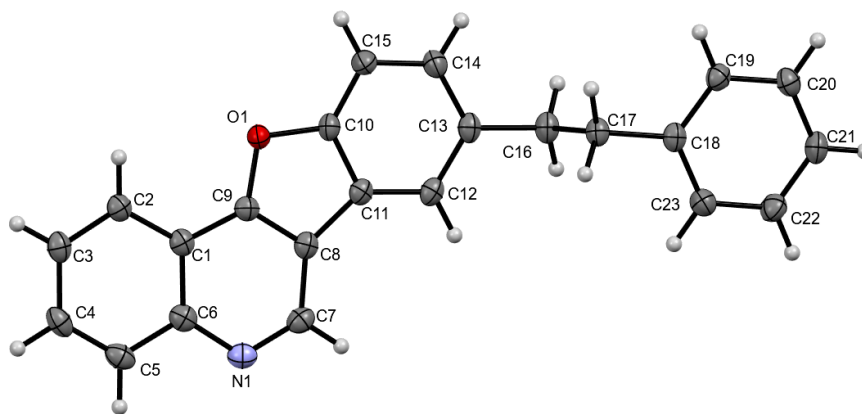


Figure 2S: Thermal ellipsoid of compound **3a** drawn at the 50% probability level.

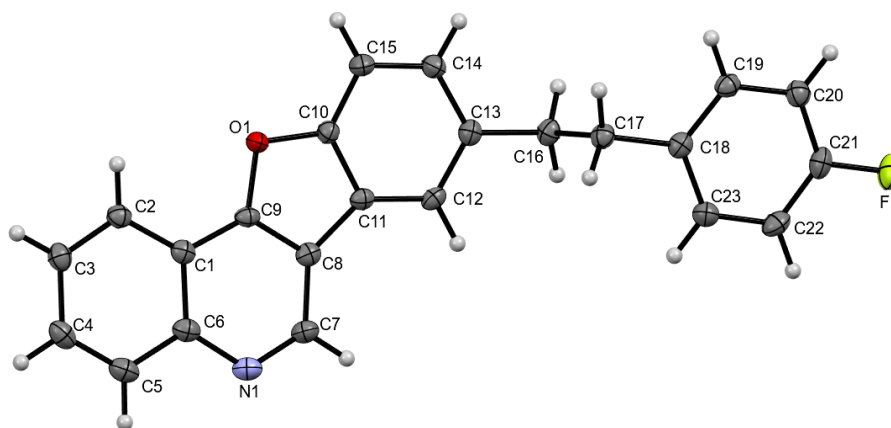


Figure 3S: Thermal ellipsoid of compound **3b** drawn at the 50% probability level.

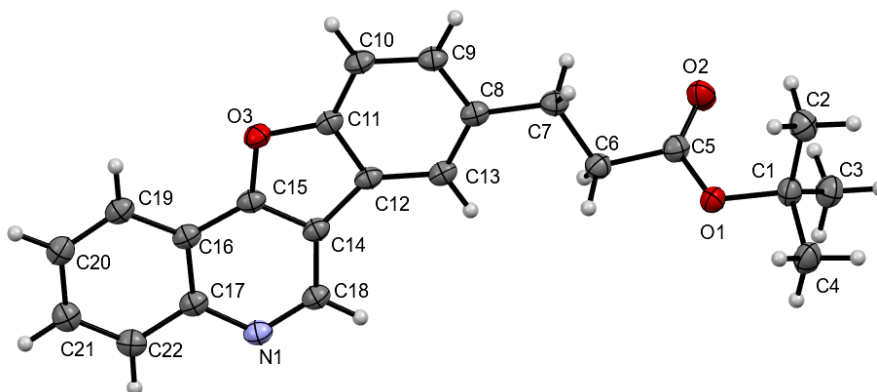


Figure 4S: Thermal ellipsoid of compound **3c** drawn at the 50% probability level.

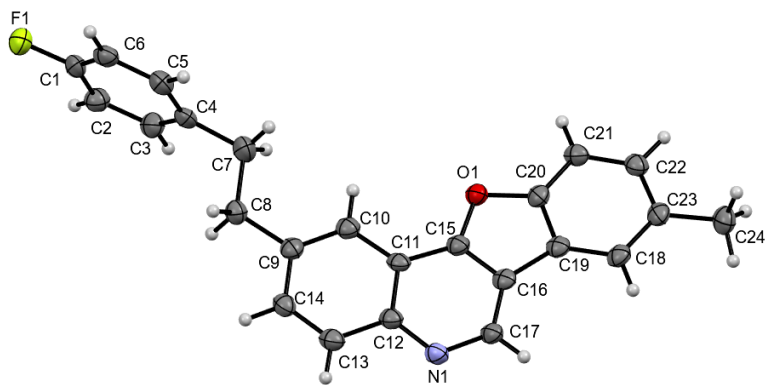


Figure 5S: Thermal ellipsoid of compound **4d** drawn at the 50% probability level.

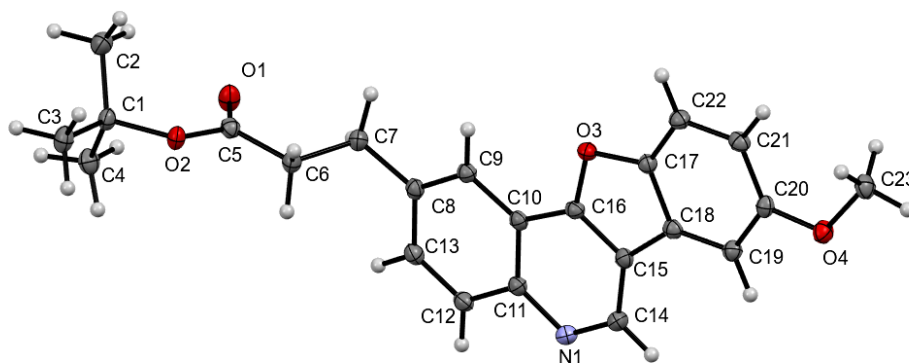


Figure 6S: Thermal ellipsoid of compound **4h** drawn at the 50% probability level.

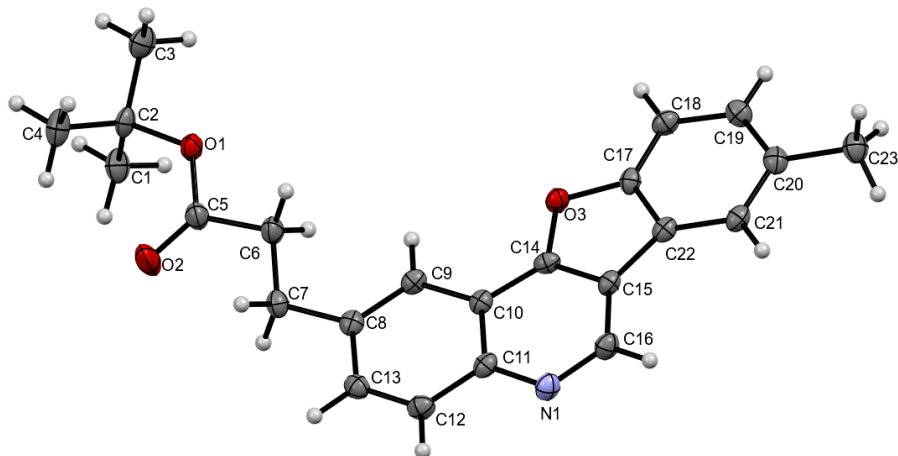


Figure 7S: Thermal ellipsoid of compound **4j** drawn at the 50% probability level.

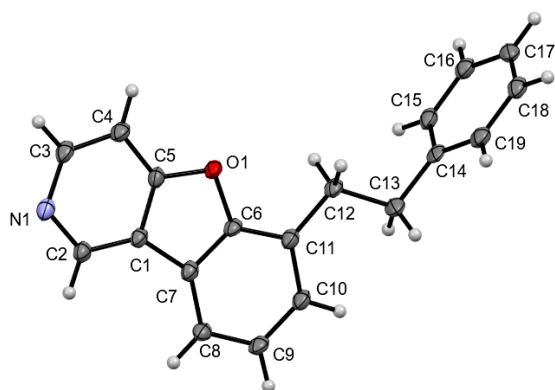


Figure 8S: Thermal ellipsoid of compound **6a** drawn at the 50% probability level.

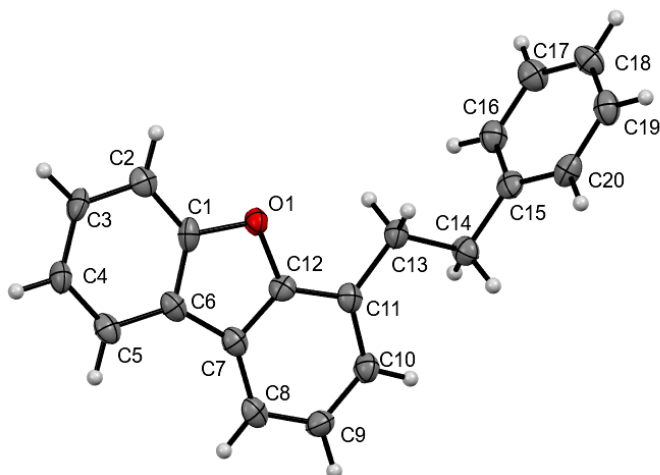


Figure 9S: Thermal ellipsoid of compound **9a** drawn at the 50% probability level.

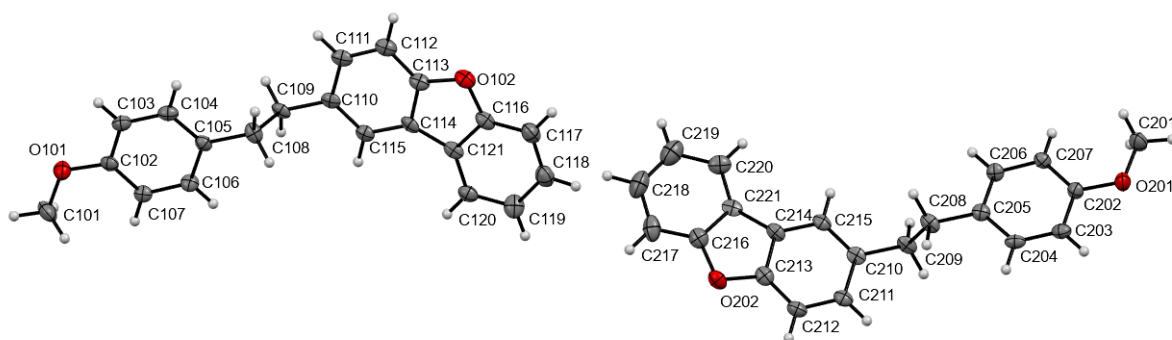


Figure 10S: Thermal ellipsoids of compound **9e** drawn at the 50% probability level.

Calculation of Green Metrics

The following formulae were used to calculate the following; atom economy (AE), atom efficiency (AEf), Carbon efficiency (CE), reaction mass efficiency (RME), optimum efficiency (OE), process mass intensity (PMI), mass productivity (MP), E-factor, solvent intensity (SI) and water intensity (WI).^[8] For RME calculation, neither catalyst nor solvent is included in this calculation. For the calculations including hydrogen gas, it assumed that 1 eq. of H₂ was incorporated into the final product for these calculations. When solving metrics that include solvent, it assumed that all 5 eq. of TBAOAc is used as solvent in these calculations.

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$AEf = AE \times \text{yield}\%$$

$$CE = \frac{\text{amount of carbon in the product}}{\text{total carbon present in reactants}} \times 100$$

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$OE = \frac{RME}{AE} \times 100$$

$$PMI = \frac{\text{total mass of input material in the whole process}}{\text{mass of product}}$$

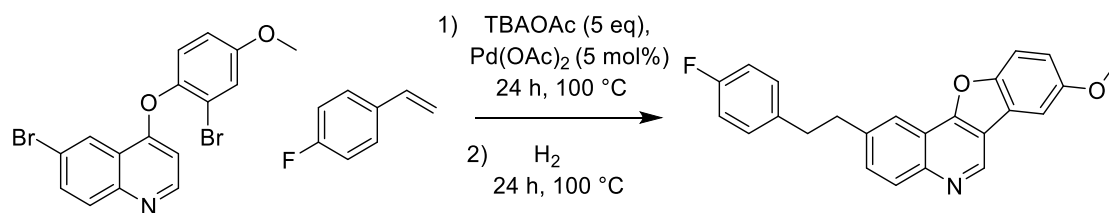
$$MP = \frac{1}{PMI} \times 100$$

$$E \text{ Factor} = PMI - 1$$

$$SI = \frac{\text{total mass of solvents exclud. water in whole process}}{\text{mass of product}}$$

$$WI = \frac{\text{total mass of water used in the whole process}}{\text{mass of product}}$$

Green metrics for 2-(4-fluorophenethyl)-8-methoxybenzofuro[3,2-c]quinoline **4g**



1b, MW 409.08 g/mol MW 122.14 g/mol

4g, MW 371.41 g/mol

Materials used for metrics calculations: 6-bromo-4-(2-bromo-4-methoxyphenoxy)quinoline **1b** (100.00 mg, 0.244 mmol), 4-fluorostyrene (33.00 mg, 0.269 mmol), tetrabutylammonium acetate (369.00 mg, 1.22 mmol), Pd(OAc)₂ (2.74 mg, 0.0122 mmol), hydrogen gas (0.40 mg, 0.202 mmol), 2-(4-fluorophenethyl)-8-methoxybenzofuro[3,2-c]quinoline **4g** (75.00 mg, 0.202 mmol, 83% yield).

$$AE \text{ } \mathbf{4g} = \frac{371.41}{409.08 + 122.14 + 2.016} \times 100 = 70$$

$$AEf \text{ } \mathbf{4g} = 70 \times 83\% = 58$$

$$CE \text{ } \mathbf{4g} = \frac{(24 \times 0.202)}{(16 \times 0.244) + (8 \times 0.269)} \times 100 = 80$$

$$RME \text{ } \mathbf{4g} = \frac{75}{100 + 33 + 0.4} \times 100 = 56$$

$$OE \text{ } \mathbf{4g} = \frac{56}{70} \times 100 = 80$$

$$PMI \text{ } \mathbf{4g} = \frac{100 + 33 + 0.4 + 2.74 + 369}{75} = 7$$

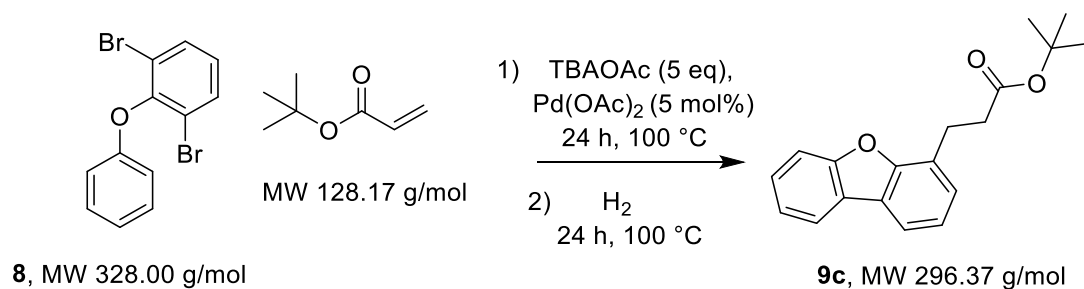
$$MP \text{ } \mathbf{4g} = \frac{1}{7} \times 100 = 14$$

$$E \text{ Factor } \mathbf{4g} = 7 - 1 = 6$$

$$SI \text{ } \mathbf{4g} = \frac{369}{75} = 5$$

$$WI \text{ } \mathbf{4g} = \frac{0}{75} = 0$$

Green metrics for *tert*-butyl 3-(dibenzo[*b,d*]furan-4-yl)propanoate **9c**



Materials used for metrics calculations: 1,3-dibromo-2-phenoxybenzene **8** (100.00 mg, 0.300 mmol), *tert*-butyl acrylate (43.60 mg, 0.340 mmol), tetrabutylammonium acetate (460.00 mg, 1.500 mmol), Pd(OAc)₂ (3.40 mg, 0.0150 mmol), hydrogen gas (0.43 mg, 0.213 mmol), *tert*-butyl 3-(dibenzo[*b,d*]furan-4-yl)propanoate **9c** (67 mg, 0.213 mmol, 74% yield).

$$AE \text{ 9c} = \frac{296.37}{328.00 + 128.17 + 2.016} \times 100 = 65$$

$$AEf \text{ 9c} = 65 \times 74\% = 48$$

$$CE \text{ 9c} = \frac{(19 \times 0.213)}{(12 \times 0.300) + (7 \times 0.340)} \times 100 = 68$$

$$RME \text{ 9c} = \frac{67}{100 + 43.6 + 0.43} \times 100 = 47$$

$$OE \text{ 9c} = \frac{47}{65} \times 100 = 72$$

$$PMI \text{ 9c} = \frac{100 + 43.6 + 0.43 + 3.40 + 460}{67} = 9$$

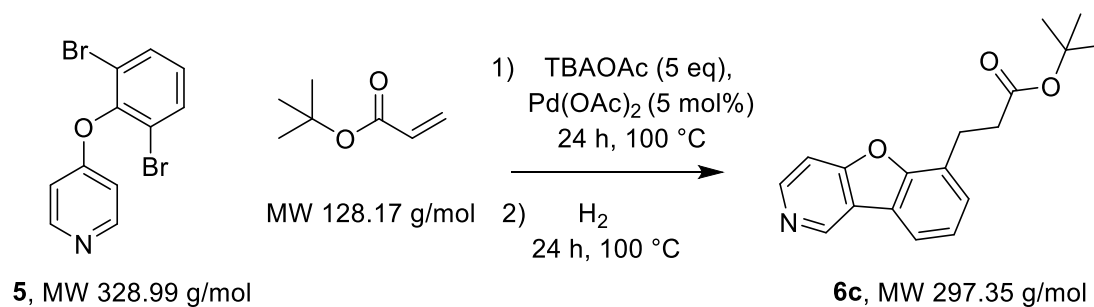
$$MP \text{ 9c} = \frac{1}{9} \times 100 = 11$$

$$E \text{ Factor 9c} = 9 - 1 = 8$$

$$SI \text{ 9c} = \frac{460}{67} = 7$$

$$WI \text{ 9c} = \frac{0}{67} = 0$$

Green metrics for *tert*-butyl-3-(benzofuro[3,2-*c*]pyridin-6-yl)propanoate **6c**



Materials used for metrics calculations: 4-(2,6-dibromophenoxy)pyridine **5** (100.00 mg, 0.304 mmol), *tert*-butyl acrylate (42.90 mg, 0.334 mmol), tetrabutylammonium acetate (458.00 mg, 1.520 mmol), Pd(OAc)₂ (3.41 mg, 0.015 mmol), hydrogen gas (0.45 mg, 0.222 mmol), *tert*-butyl-3-(benzofuro[3,2-*c*]pyridin-6-yl)propanoate **6c** (66 mg, 0.222 mmol, 73% yield).

$$AE \text{ 6c} = \frac{297.35}{328.99 + 128.17 + 2.016} \times 100 = 66$$

$$AEf \text{ 6c} = 66 \times 73\% = 48$$

$$CE \text{ 6c} = \frac{(18 \times 0.222)}{(11 \times 0.304) + (7 \times 0.334)} \times 100 = 70$$

$$RME \text{ 6c} = \frac{66}{100 + 42.9 + 0.45} \times 100 = 46$$

$$OE \text{ 6c} = \frac{46}{66} \times 100 = 69$$

$$PMI \text{ 6c} = \frac{100 + 42.9 + 0.45 + 3.41 + 458}{66} = 9$$

$$MP \text{ 6c} = \frac{1}{9} \times 100 = 11$$

$$E \text{ Factor 6c} = 9 - 1 = 8$$

$$SI \text{ 6c} = \frac{458}{66} = 7$$

$$WI \text{ 6c} = \frac{0}{67} = 0$$

Average metrics for our one-pot Mizoroki-Heck/direct arylation/hydrogenation reaction:

$$AE = \frac{70 + 65 + 66}{3} = 67$$

$$AEf = \frac{58 + 48 + 48}{3} = 51$$

$$CE = \frac{80 + 68 + 70}{3} = 73$$

$$RME = \frac{56 + 47 + 46}{3} = 50$$

$$OE = \frac{80 + 72 + 69}{3} = 73$$

$$PMI = \frac{7 + 9 + 9}{3} = 8$$

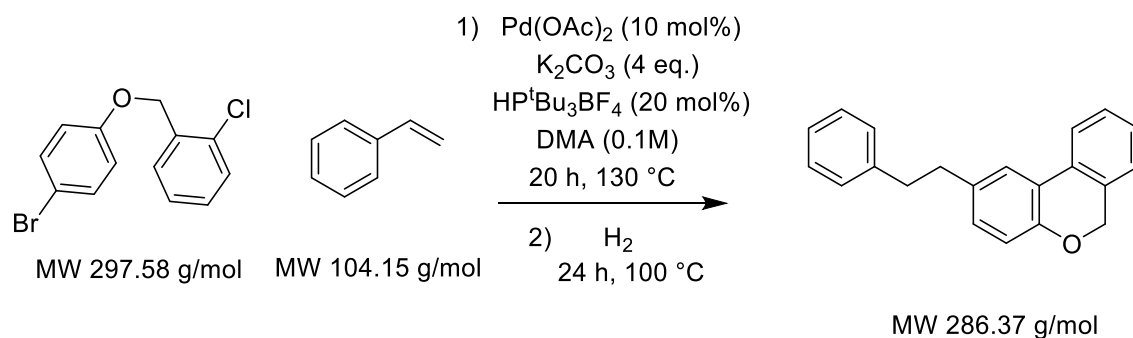
$$MP = \frac{14 + 11 + 11}{3} = 12$$

$$E \text{ Factor} = \frac{6 + 8 + 8}{3} = 7$$

$$SI = \frac{5 + 7 + 7}{3} = 6$$

$$WI = \frac{0 + 0 + 0}{3} = 0$$

Green metrics for Fagnou et al. compound 2-Phenethyl-6H-benzo[c]chromene^[9]



Reagents used for metrics calculations: 1-(2-chlorobenzoyloxy)-4-bromobenzene (106.0 mg, 0.36 mmol), potassium carbonate (197.0 mg, 1.43 mmol), $\text{Pd}(\text{OAc})_2$ (8.0 mg, 0.036 mmol), styrene (36.0 mg, 0.36 mmol), $\text{HP}(t\text{-Bu})_3\text{BF}_4$ (26.0 mg, 0.071 mmol), hydrogen gas (0.5 mg, 0.248 mmol), dimethylacetamide (3384 mg, 3.6 mL) and 2-phenethyl-6H-benzo[c]chromene (71.0 mg, 0.248 mmol, 69%).

$$AE = \frac{286.37}{297.58 + 104.15 + 2.016} \times 100 = 71$$

$$AEf = 71 \times 69\% = 49$$

$$CE = \frac{(21 \times 0.248)}{(13 \times 0.36) + (8 \times 0.36)} \times 100 = 69$$

$$RME = \frac{71}{106.0 + 36.0 + 0.5} \times 100 = 50$$

$$OE = \frac{50}{71} \times 100 = 70$$

$$PMI = \frac{106.0 + 36.0 + 0.5 + 8.0 + 26.0 + 197.0 + 3384.0}{71} = 53$$

$$MP = \frac{1}{53} \times 100 = 2$$

$$E \text{ Factor} = 53 - 1 = 52$$

$$SI = \frac{3384}{71} = 48$$

$$WI = \frac{0}{71} = 0$$

Table 2S: Green metrics (AE, AEf, CE, RME, OE, PMI, MP, EF, SI, WI)

Entry	4g	9c	6c	Average of 4g,9c and 6c	chromene (Fagnou)
Best yield%	83	74	73	77	69
AE (%)	70	65	66	67	71
AEf (%)	58	48	58	51	49
CE (%)	8	68	70	73	69
RME (%)	56	47	46	50	50
OE (%)	80	72	69	73	70
PMI (g g⁻¹)	7	9	9	8	53
MP (%)	14	11	11	12	2
EF (g g⁻¹)	6	8	8	7	52
SI (g g⁻¹)	5	7	7	6	48
WI (g g⁻¹)	0	0	0	0	0

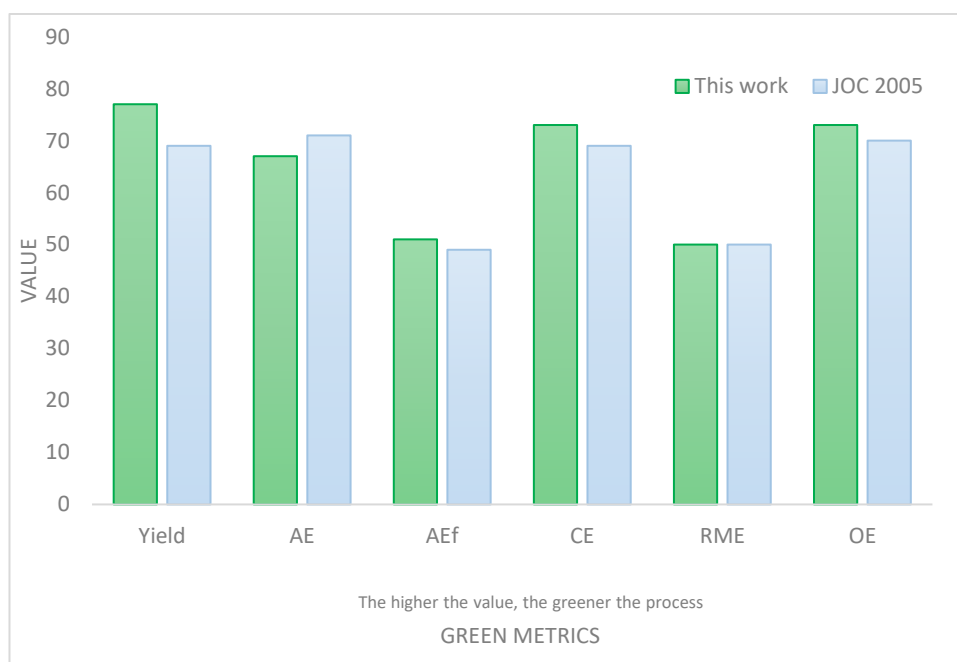
Graph 1S: Additional Green Metrics analysis in relation to **Figure 1** in main manuscript for our one-pot average and the current state of the art.^[9]

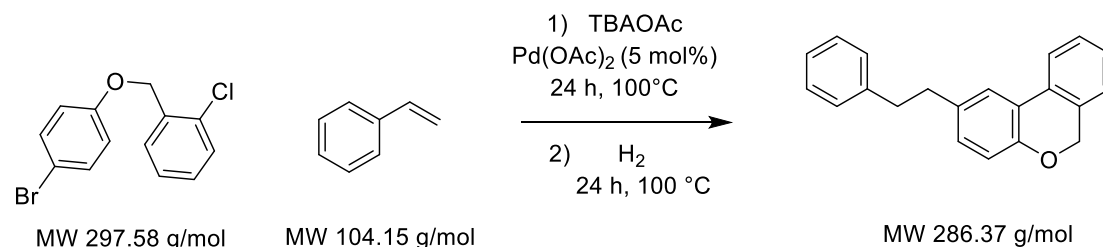
Table 3S: Calculation for inverse of EF, SI and PMI as per **Graph 1** in main manuscript

Green Metric	As calculated		1/calculation		Multiply by 100	
	Ours	Fagnou	Ours	Fagnou	Ours	Fagnou
MP	12	2	N/A	N/A	N/A	N/A
EF	7	52	0.1429	0.0192	14.29	1.92
SI	6	48	0.1667	0.0208	16.66	2.08
PMI	8	53	0.1250	0.0189	12.5	1.89

Comparison of Fagnou's Substrate to Our Substrate:

Fagnou's substrate using our conditions.

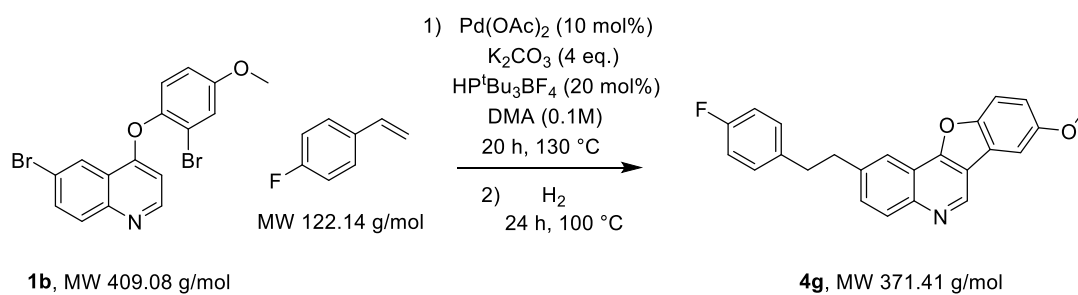
Table 4S: Fagnou's substrate using our conditions.



Material	MW (g/mol)	mmol	Weight (mg)	Yield %	Carbons
1-(2-Chlorobenzyl)-4-bromobenzene	297.58	0.336	100.00		13
TBAOAc	301.5	1.680	506.59		
4-FluoroStyrene	122.14	0.370	45.15		8
Pd(OAc) ₂	224.5	0.017	3.77		
2-Phenethyl-6H-benzo[c]chromene	286.37	0.279	79.90	83	21
H ₂	2.016	0.279	0.56		

Green Metric	Value
AE	67.90
AEf	48.99
CE	68.88
RME	54.83
OE	80.75
PMI	8.21
MP	12.18
EF	7.21
SI	6.34
WI	0.00

Table 5S: Our substrate using Fagnou's conditions.



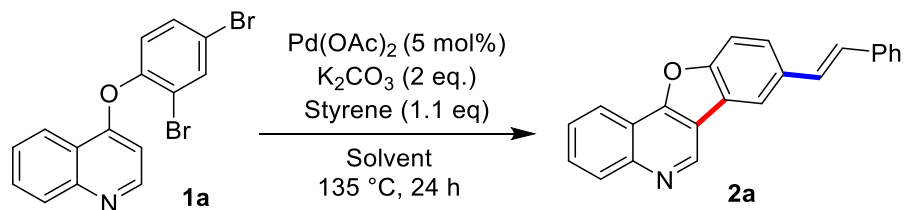
	MW		Weight		
Material	(g/mol)	mmol	(mg)	Yield %	Carbons
1b	409.08	0.36	147.27		16
4-Fluorostyrene	122.14	0.36	43.97		8
$\text{Pd}(\text{OAc})_2$	224.5	0.036	8.08		
K_2CO_3	138.2	1.43	197.63		
$\text{HP}^t\text{Bu}_3\text{BF}_4$	290.13	0.071	26		
DMA	87.12	0.36	3384		
H_2	2.016	0.248	0.50		
4g	371.41	0.248	92.11	69	24

Green Metric	Value
AE	69.65
AEf	38.17
CE	68.89
RME	48.04
OE	68.95
PMI	41.34
MP	2.42
EF	40.34
SI	36.74
WI	0

Note: Green metrics for scale-up reaction can be found in Section 5, Table 8S below.

Additional Solvents Used in Optimisation Scope

Table 6S: Additional solvents used in optimisation scope.



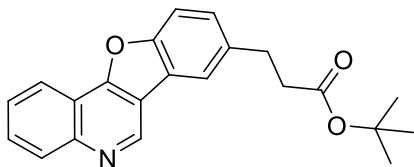
Entry	Solvent	Conversion to 2a ^a
1	DMA	92%
2	DMF	87%
3	Sulfolane	80%
4	2-Me THF	64%
5	1,4-Dioxane	65%
6	Toluene	60%
7	<i>N</i> -methyl pyridone	90%
8	<i>N</i> -benzyl pyrrolidone	90%
9	<i>N</i> -butyl pyrrolidone	93%
10	Ethylene Carbonate	0%
11	CPME	56%
12	Cyrene	60%

^a Conversion to product **2a** from substrate **1a** determined by ¹H NMR analysis.

Scale up Reaction Experimental Data

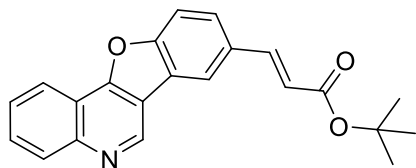
Procedure for Atmospheric Pressure Scale-Up Reaction

Gram scale reaction for benzofuroquinoline **3c**.



To a Schlenk flask was added the quinoline substrate **1a** (1.00 g, 2.64 mmol, 1 eq), *tert*-butylacrylate (0.425 mL, 2.90 mmol, 1.1 eq.), Pd(OAc)₂ (0.030 g, 0.132 mmol, 5 mol%) and tetrabutylammonium acetate (3.98 g, 13.19 mmol, 5 eq.) which was stirred at 100 °C for 24 hours. 1-Butanol (4 mL) was then added, and the reaction was purged with hydrogen and let stir under an atmosphere of hydrogen at 100 °C for 30 hours. A second loading of Pd(OAc)₂ (5 mol%) was added and the reaction was stirred under a H₂ atmosphere for a further 8 hours at 100 °C. This was followed by a second addition of 1-butanol (30 mL) which was let stir under H₂ for another 8 hours at 100 °C. The reaction solvent was removed under reduced pressure, dried on a hi-vac line for 24 hours and an NMR yield was taken with trimethoxybenzene as internal standard. (NMR yield: 45%)

Procedure for Elevated Hydrogen Pressure Scale-Up Reaction



To a Schlenk flask was added the phenoxyquinoline substrate (1.00 g, 2.64 mmol, 1 eq.), *tert*-butylacrylate (0.425 mL, 2.90 mmol, 1.1 eq.), Pd(OAc)₂ (0.030 g, 0.132 g, 5 mol%) and tetrabutylammonium acetate (3.97 g, 13.19 mmol, 5 eq.) which was stirred at 100 °C for 24 hours. The reaction mixture was then transferred to a hydrogenation crucible (**Table 7S**, run 2 and 3, 1-butanol (8 mL) was added) and heated to 100 °C. The pressure of hydrogen was adjusted to preference and the reaction was monitored by ¹H NMR. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography. The benzofuroquinoline intermediate **2S** eluted in cyclohexane:EtOAc (100:0 – 70:30).

Results

We undertook a gram scale reaction and were pleased to find that the Mizoroki-Heck and C–H activation reactions proceeded very cleanly (99% conversion, 88% isolated yield). However, the hydrogenation step was more sluggish (initially as per General Procedure 2). It was necessary to add solvent to the reaction mixture at the hydrogenation step, presumably to aid in the solubility of hydrogen gas. 1-Butanol (4 mL) was added to the mixture at the hydrogenation step, however the hydrogenation did not exceed 42% conversion even after extended reaction time (30 hours). A second addition

of Pd(OAc)₂ (5 mol%) was added, and stirred for a further 8 hours, however, no increase in product was observed. In a final effort, additional 1-butanol (30 mL) was added, however, a total of 45% NMR yield was obtained of the target compound in addition to some degradation of material. We tried some more forcing conditions to achieve full conversion to the target reduced compound. We subjected our alkene intermediate to hydrogen pressures as high as 4 bar at 100 °C, however no conversion to our reduced product was detected (see **Table 7S**).

Table 7S: Scale-up pressure hydrogenation conditions.

Run	Time h (total h)	1-Butanol (mL)	Pressure (bar)	Temp (°C)	Conversion
1	2	0	3	100	SP & SM
	+1 (3)	0	3	100	SP & SM
	+1 (4)	0	4	100	SP & SM
2	3	8	1.5	50	SM
	+1 (4)	8	2.5	50	SM
	+3 (7)	8	3.5	50	SM
3	3	8	2.5	100	SM
	+3 (6)	8	3.5	100	SM

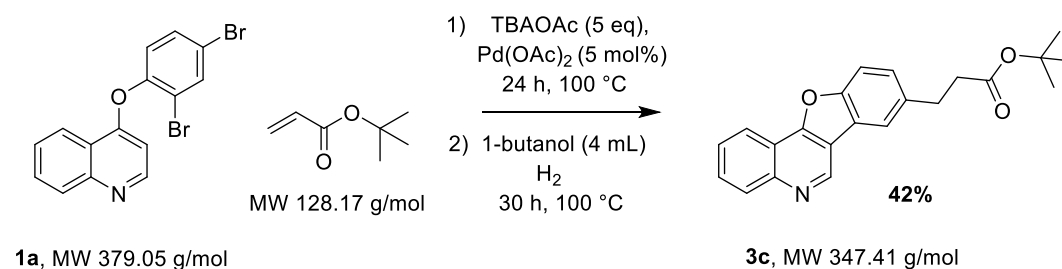
SP = Side Products, SM = Starting Material, '+' indicates additional run time

It is known that high pressure hydrogenations are fraught with challenges and many examples of 'working' reactions encounter difficulties at larger scale.^[10] Jones *et al.* highlights an inherent difficulty in scaled up hydrogenation reactions in that the mixing rates of the three phases can be poor.^[10b] Some catalytic systems had to change completely based on attempts to scale-up. Merck, in their synthesis of MK-677, had to develop a new methodology for their scale-up reduction from using Pd/BaSO₄ catalyst with sulphur compounds on lab scale to Pd/C catalyst combined with HCl scavengers for large-scale.^[10a] Wagner *et al.* found that undesired side product formation was observed on large scale hydrogenation of 3,4,5-trimethoxybenzoic acid chloride. The group found that side-product trimethoxytoluene was formed in addition to water. In addition, the acyl chloride decomposed mainly to the acid that precipitated out from the solvent.^[11] Poh *et al.* scaled up the hydrogenation of graphene to graphane. Previously reported methods describe the successful reduction of minute quantities of material. In order to scale-up the process, the group had to develop a completely new methodology to achieve their desired scale.^[10c] Additionally, if it is indeed the case that *in situ*-formed palladium nanoparticles are the surface on which the hydrogenation takes place, a great paper by Khanuja *et al.* describe the effects that temperature and pressure have on palladium

nanoparticles. This would indeed change the reactivity of the nanoparticles and possibly rendering them ineffective at the pressures we tried. They describe that Pd–H interaction is strongly influenced by the temperature and pressure dependences of physisorption, chemisorption, and diffusion. They also show hydrogen induced degradation in crystalline quality and temperature induced lattice disorder.^[12] Based on the (non-exhaustive) information, the scale up of the hydrogenation step would require a non-trivial amount of additional optimisation.

Green Metric calculations for the scale up reaction performed at atmospheric pressure.

Table 8S: Scale up reaction at atmospheric pressure at 42% yield.



Material	MW (g/mol)	Mol	Weight (g)	Yield %	carbons
1a	379.05	2.64	1.00		15
TBAOAc	301.5	13.19	3.97		
<i>t</i> -butyl- acrylate	128.17	2.90	0.37		7
Pd(OAc) ₂	224.5	0.13	0.030		
3c	347.41	1.11	0.38	42	22
H ₂	2.016	1.11	2.23		
1-butanol	74.12	43.71	3.24		

Green Metric	Scale-up Value	Fagnou's substrate/Fagnous Conditions Values	Our substrate/Fagnous conditions Values	% Difference 'A' ^a	% Difference 'B' ^a
AE	68	71	60	-4%	13%
Aef	29	49	38	-51%	-27%
CE	41	69	69	-51%	-51%
RME	11	50	48	-128%	-125%
OE	16	70	69	-126%	-125%
PMI	20	53	41	90%	69%
MP	5	2	2	86%	86%
EF	19	52	40	93%	71%
SI	10	48	37	131%	115%
WI	0	0	0	0%	0%

'A' = percent difference of Scale-up vs Fagnou's substrate using Fagnou's state-of-the-art conditions; 'B' = percent difference of Scale-up vs our substrate using Fagnou's state-of-the-art conditions; ^a A negative percent difference indicates a less favourable outcome for our scaled-up process vs Fagnou's process.

A green metric analysis was carried out for our scaled-up process (2.64 mmol) versus the current state-of-the-art. The metrics show, that although the scale-up yield was just

42%, the PMI, MP, EF, and SI have scored better than Fagnou's original small scale (0.36 mmol). Of note the solvent intensity is still less than that of Fagnou's by ~100% and used a green solvent instead of the current DMA. The PMI, MP, and EF describe the overall efficiency of the process encompassing all reagents, both benign and non-benign, and therefore provides a good picture of the overall greenness of a process. There is a downfall in some green metric values such as RME and OE, however these metrics omit important factors such as catalyst, ligands and solvent. It can be seen from these calculations that, although our scale-up process is still un-optimised, our overall process produces better green metrics than the current state of the art in addition to not requiring higher Pd loading, additional ligand and harmful solvents.

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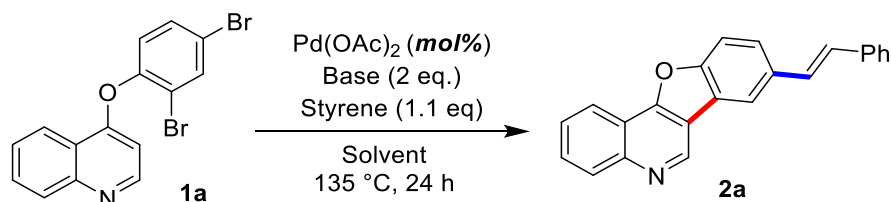
Unpublished Work and Further Discussion for Chapter 2

In addition to the work undertaken in the main manuscript and the supplementary information, non-published experiments were undertaken during the course of this project. The additional experiments that were undertaken are briefly outlined below.

Solvent Scope

In addition to the published conditions to find a replacement for NMP as solvent, several additional reaction conditions were attempted using various solvents outlined in **Table UW1**. Literature precedent prompted the use of *N*-methyl morpholine^[1] and Cyrene^[2] in addition to the already mentioned solvents in the main manuscript and the SI.

Table UW1. Additional solvents for the one-pot reaction.



Entry	Solvent(s)	Pd(OAc) ₂ (mol%)	Base	% conversion ^[a]
1	NMP	1	K ₂ CO ₃	85
2	NMP	2	K ₂ CO ₃	88
3	NMP	5	K ₂ CO ₃	100
4	H ₂ O	5	K ₂ CO ₃	0
5	H ₂ O:NMP (1:1)	5	K ₂ CO ₃	2
6	1,4-Dioxane	1	K ₂ CO ₃	0
7	1,4-Dioxane	2	K ₂ CO ₃	51
8	NMP:1,4-Dioxane (1:10)	5	K ₂ CO ₃	35
9	NMP:1,4-Dioxane (1:1)	5	K ₂ CO ₃	79
10	Dioxane: 18-C-6	5	K ₂ CO ₃	73
11	Dioxane: PVP	5	K ₂ CO ₃	52
12	1,4-Dioxane:DA	5	K ₂ CO ₃	60
13	DMF (anhydrous)	5	K ₂ CO ₃	90
14	Cyrene	5	TEA	26
15	Cyrene	5	DABCO	18
16	Cyrene	5	DBU	33
17	2-Methyl THF:DA	5	K ₂ CO ₃	69
18	Isopropyl acetate	5	K ₂ CO ₃	64
19	Isopropyl acetate: DA	5	K ₂ CO ₃	70
20	pyridine	5	K ₂ CO ₃	60
21	pyrrolidine	5	K ₂ CO ₃	0
22	<i>N</i> -methyl morpholine	5	K ₂ CO ₃	71

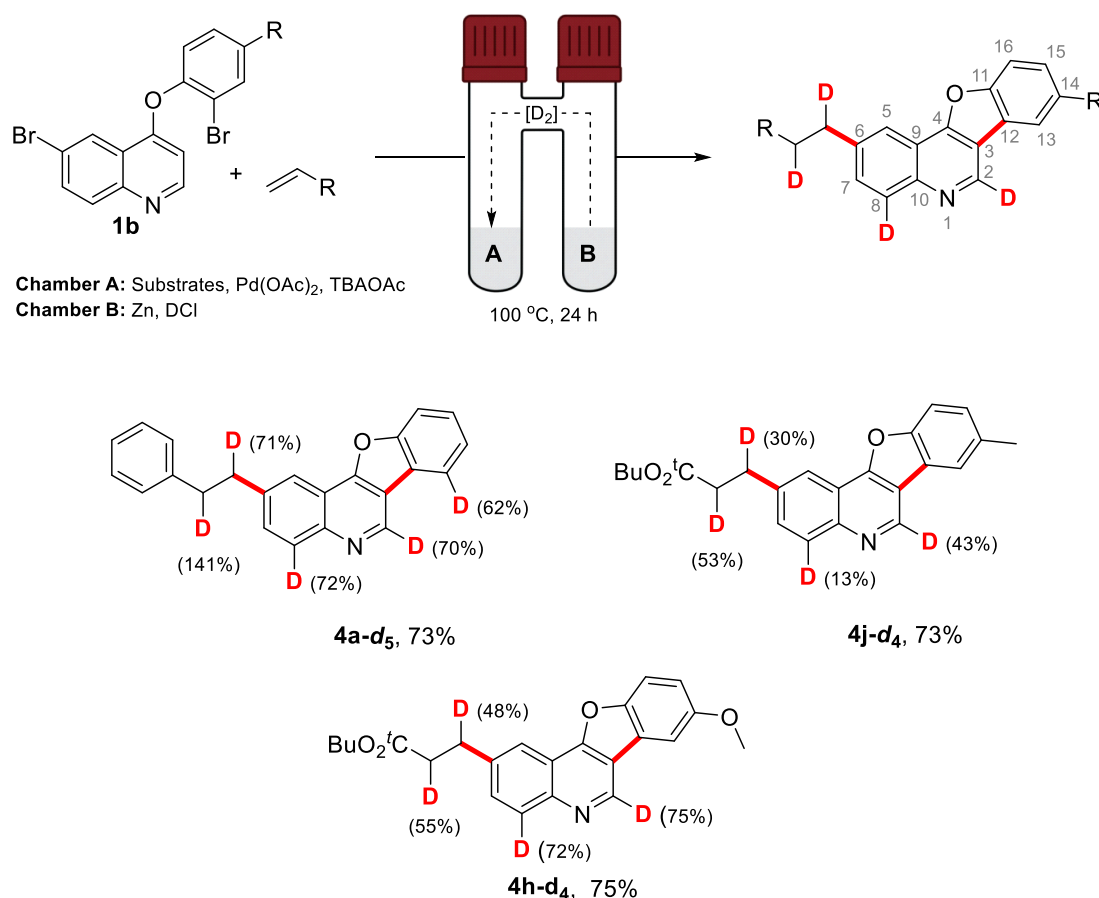
^[a] All conversions to **2a** were determined using ¹H NMR analysis. DA: dodecylamine; PVP: polyvinylpyrrolidone

Due to the propensity of Cyrene to undergo a self-Aldol reaction in the presence of base, a few different bases were tried (**entries 14 – 16**) to see if any were compatible with the solvent under these conditions.^[2a, 3] From **Chapter 4** it is known that adding dodecylamine to a palladium nanoparticle reaction mixture that it aided the catalytic turnover. It was speculated that if dodecylamine was added to the reaction, it could possibly act as a palladium ligand and keep the catalyst active for longer (**entries 12, 17** and **19**). Unfortunately adding the ligand made no marked effect. Adding in additional ligands such as dodecylamine (DA) or polyvinyl pyrrolidone (PVP) to various solvents was also tried (both in 0.01 mmol), rationalising that they might stabilise any palladium nanoparticles that are formed *in situ*.

Additional Deuteration Experiments:

We also utilised the COware apparatus for the deuteration of two additional substrates **4a-d₅** and **4j-d₄**. The procedure followed is as described in the **Chapter 2 SI** - general procedure 3 (**Scheme UW1**).

Scheme UW1: Additional deuteration experiments using the COware apparatus.



Isolated yields shown. Deuterium incorporation was determined by ¹H and ²H NMR.

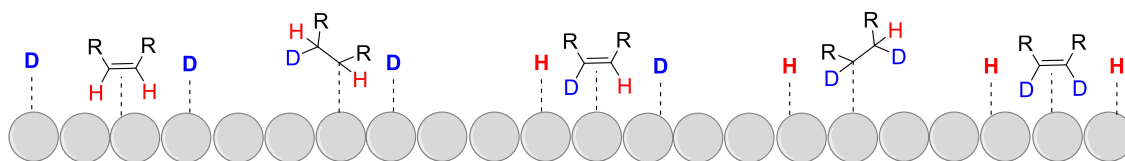
It is clear that there is C–H activation across more than one site in these type of substrates with multiple sites of deuteration. There is additional C–H activation in the C13 position for **4a-d₅** structure. This may be due to more steric freedom as compared to the C14 substituted **4j-d₄** and **4h-d₄**. It is possible that the additional deuteration is observed on the ‘nitrogen side’ of the benzofuroquinoline scaffold due to the perpendicular binding of the quinoline nitrogen on the surface of the catalyst.^[4] It is possible that there is hydrogen-deuterium exchange at the C2 and C8 sites due to the close proximity of those hydrogens to the catalytic surface. As for the C13 site, which is further away from the surface, it is possible that palladium ring walking is occurring.

Ring-walking (chain-walking) has been defined as a process in which discrete alkyl–metal species undergo an iterative sequence of 1,2- or 1,3-hydride shifts along a single hydrocarbon chain. Palladium ring-walking occurs when the palladium catalyst stays bound to the π -system, then moves to another electrophilic position, and undertakes an additional transformation rather than leaving the π -system^[5] This phenomenon makes it possible for reactions to occur at other sites on conjugated systems, and allows for the development of remote functionalisation. It is known that ring-walking can occur for cross-coupling reactions,^[5a, 6] and is also very important in polymer synthesis.^[7] It is possible that this process is responsible for the additional C–D incorporation in our benzofuroquinolines (particularly the more remote C13).

The Minisci reaction allows for the direct functionalisation of electron deficient heteroaromatic rings with radicals.^[8] In the case of the benzofuroquinoline scaffold, the electrophilic site, C2, could be susceptible to radical attack at this position due to the electronegative adjacent nitrogen atom. Although no reports of a Minisci-type reaction using hydrogen or deuterium gas have been reported, it may be possible that a generated deuterium (or hydrogen) radical could attack the C2 site which would cause additional deuteration.

Interestingly, over-deuteration is observed in compound **4a-d₅** at C18 and under-deuteration is observed at C17. This indicates that the deuteration/hydrogenation mechanism is reversible and this is described by the Horiuti-Polanyi mechanism (**Figure UW1**).^[9] When the reverse reaction takes place (in which an atom, hydrogen or deuterium, is placed back on the surface), there is a good chance that a hydrogen atom will transfer to palladium, rather than a deuterium. In fact, the forward and reverse motion must occur multiple times to explain the various structures and percentage incorporations observed. Eventually the alkane undergoes an irreversible reductive elimination with varying quantities of deuterium and/or hydrogen atoms attached, resulting in over- and/or under-deuteration.

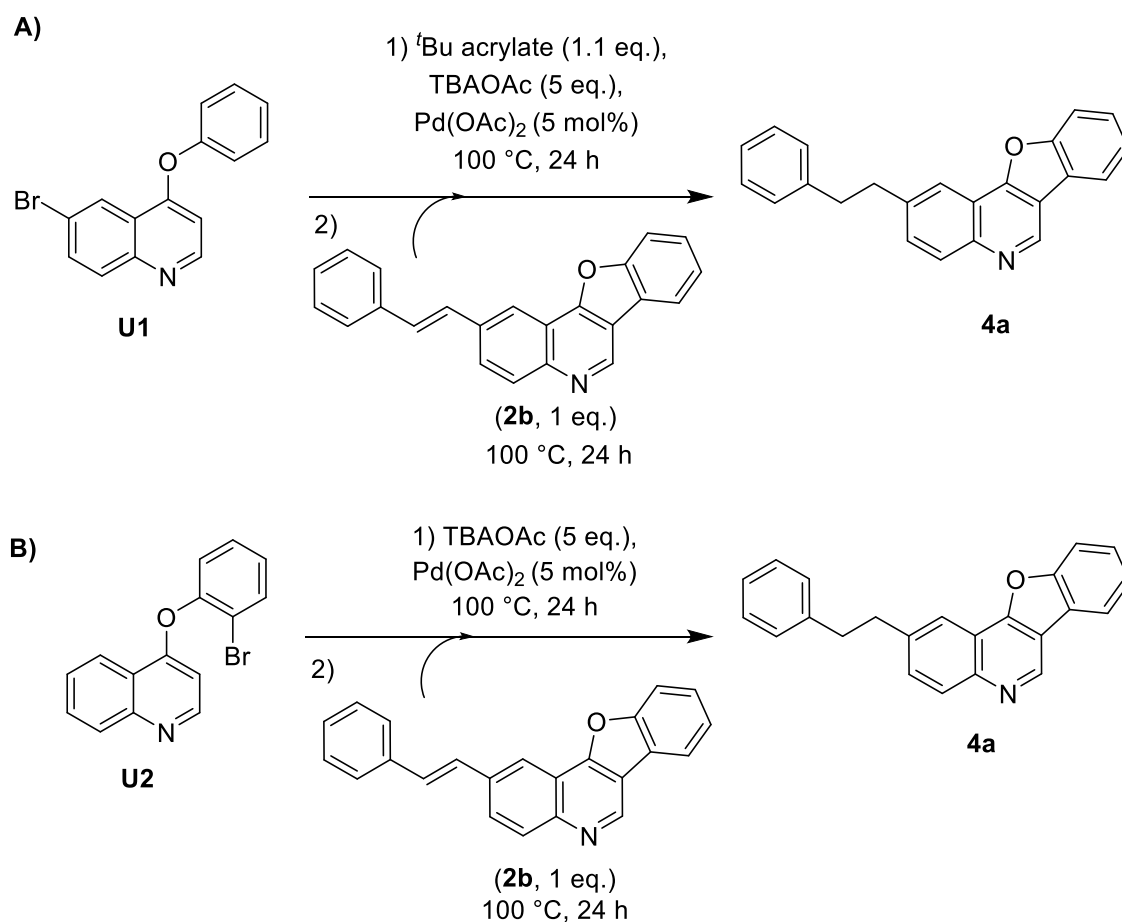
Figure UW1. Reversible hydrogen-deuterium exchange mechanism.



Probing the Catalytic Species in the Hydrogenation Reaction

As $\text{Pd}(\text{OAc})_2$ is the pre-catalytic source that enables each of these transformations, we were interested in gleaning an insight into the Pd catalyst speciation and first looked at the hydrogenation step. The first test involved carrying out a Mizoroki-Heck reaction (only) and then determining if the hydrogenation step would work (**Scheme UW2**). After the Mizoroki-Heck reaction of **U1**, the substrate **2b** was added and it did get reduced to product **4a**. This indicates that an active hydrogenation catalytic species is formed after the Mizoroki-Heck step. Additionally, a similar experiment was carried out using a direct arylation reaction (only) using **U2**. Again, the Pd species after the direct arylation step was effective in catalysing the hydrogenation of **2b** to **4a**.

Scheme UW2. Insight into hydrogenation catalytic species.

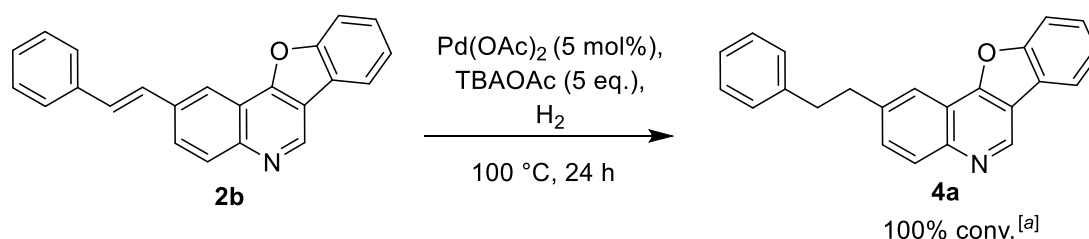


A) Heck only reaction followed by input of **2a**. B) Direct arylation only reaction followed by input of **2a**.

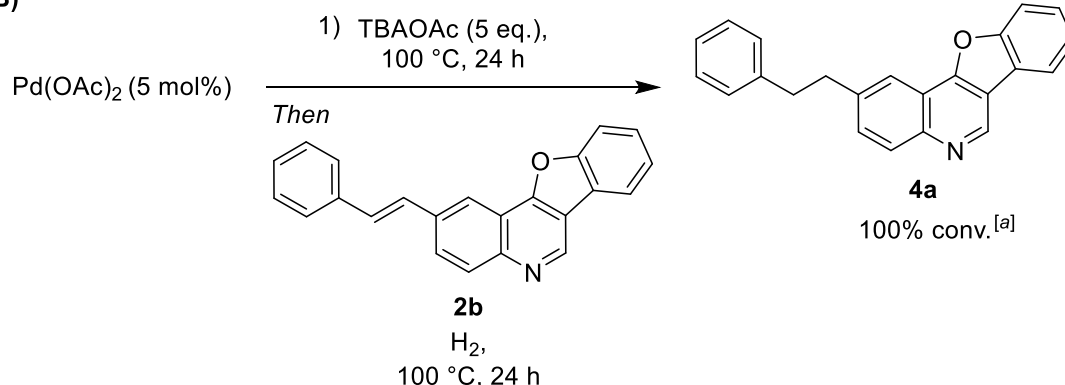
We then wished to discern if the $\text{Pd}(\text{OAc})_2$ could facilitate the hydrogenation step. Thus, following these reactions, our inquiry turned to $\text{Pd}(\text{OAc})_2$ as a potential hydrogenation mediator. Both $\text{Pd}(\text{OAc})_2$ and substrate **2b** were added at the beginning of the reaction under hydrogenation conditions with a H_2 balloon (**Scheme UW3, A**). In parallel, a second reaction was set-up in which pre-treated $\text{Pd}(\text{OAc})_2$ (heated at 100 °C for 24 hours) was present and then substrate **2b** was added (**Scheme UW3, B**).

Scheme UW3. Suitability of heat-treated vs untreated $\text{Pd}(\text{OAc})_2$ in facilitating the hydrogenation reaction.

A)



B)



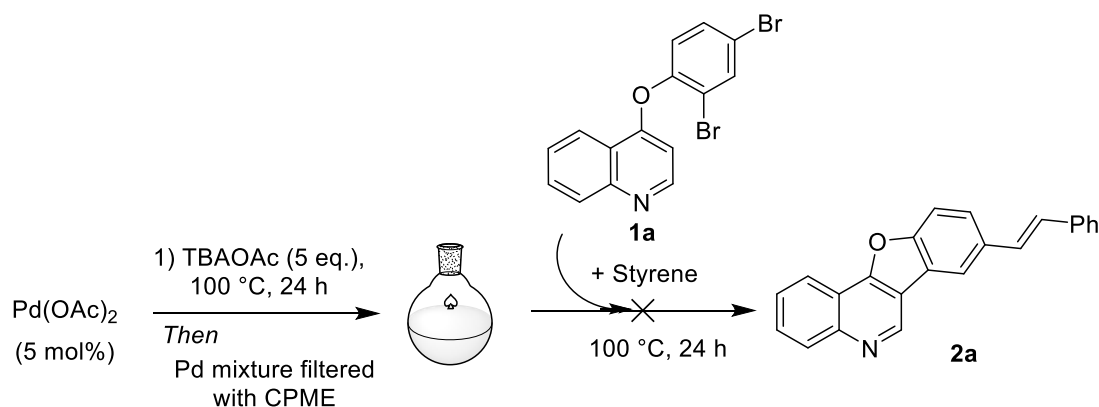
A) $\text{Pd}(\text{OAc})_2$ not heated before substrate **2b** was added **B)** $\text{Pd}(\text{OAc})_2$ heated at 100 °C for 24 hours before substrate **2b** was added.

It was found that 'pre-treatment' of the $\text{Pd}(\text{OAc})_2$ in reaction 'B' was not necessary for the complete hydrogenation of intermediate **2b**. It appeared that sufficient degradation of $\text{Pd}(\text{OAc})_2$ was occurring in reaction 'A' to allow for hydrogenation of the substrate.

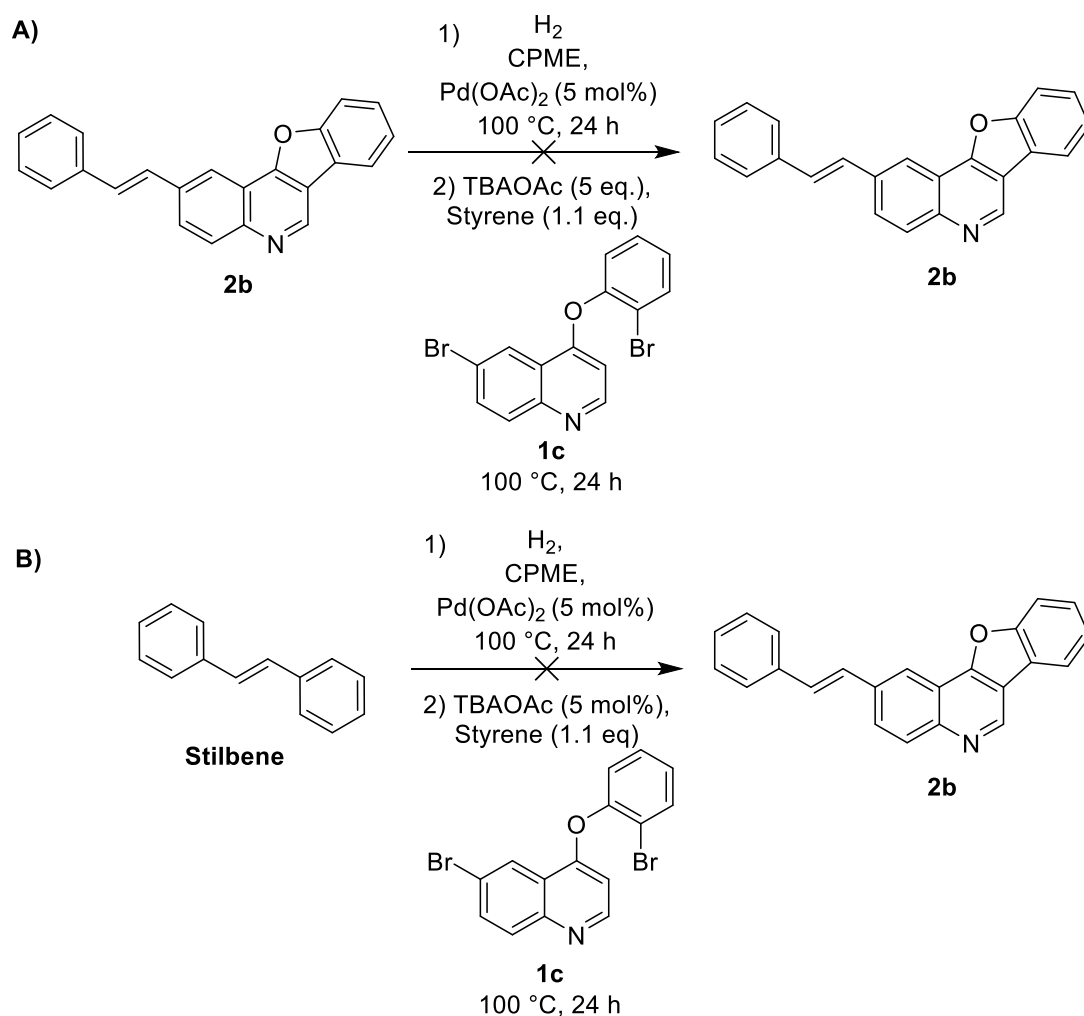
Finally, we were curious to know whether a soluble Pd species, independently generated, could perform a Mizoroki-Heck/direct arylation reaction. Thus, a mixture of $\text{Pd}(\text{OAc})_2$ and TBAOAc was heated for 24 hours at 100 °C. The mixture was then filtered through a 2µm PTFE syringe filter (with CPME) and placed into a clean reaction vial (**Scheme UW4**). To the palladium mixture was added phenoxyquinoline **1a** and styrene and was let stir at 100 °C for 24 hours. No product **3a** was observed, with just starting materials remaining suggesting that the catalytic species that is not captured by the

filtration system is not catalytically active for the Mizoroki-Heck or direct arylation reaction sequence. This uncaptured catalyst is active, however, for the hydrogenation, as mentioned in the main manuscript.

Scheme UW4. Filtered palladium species after heating and filtering for the Mizoroki-Heck/direct arylation.



Scheme UW5. Palladium reactivity after hydrogenation step for Mizoroki-Heck/direct arylation.



A) Palladium reactivity after hydrogenation of **2b** and **B)** palladium reactivity after hydrogenation of stilbene.

We then investigated if a soluble Pd species, *after performing a hydrogenation*, could facilitate the Mizoroki-Heck/direct arylation steps. Thus, we performed hydrogenation on both phenoxyquinoline **2b** and stilbene (**Scheme UW 5**). This was to determine whether the catalytic species after hydrogenation in our system using our substrates behaved differently to a generic hydrogenation.

Both stilbene and **2b** were subjected to our hydrogenation conditions and after 24 hours, it was found that for both conditions **A** and **B**, full hydrogenation of initial **2a** and stilbene was observed. Phenoxyquinoline **1c** was loaded into each reaction mixture in addition to styrene to initiate the one-pot sequence. However, analysis after a further 24 hours found that only ~14% of the Mizoroki-Heck product was observed for both systems with no direct arylation observed. This suggests that the nature of the catalyst after the hydrogenation step, independent of substrate, is not compatible with the one-pot Mizoroki-Heck/direct arylation transformation.

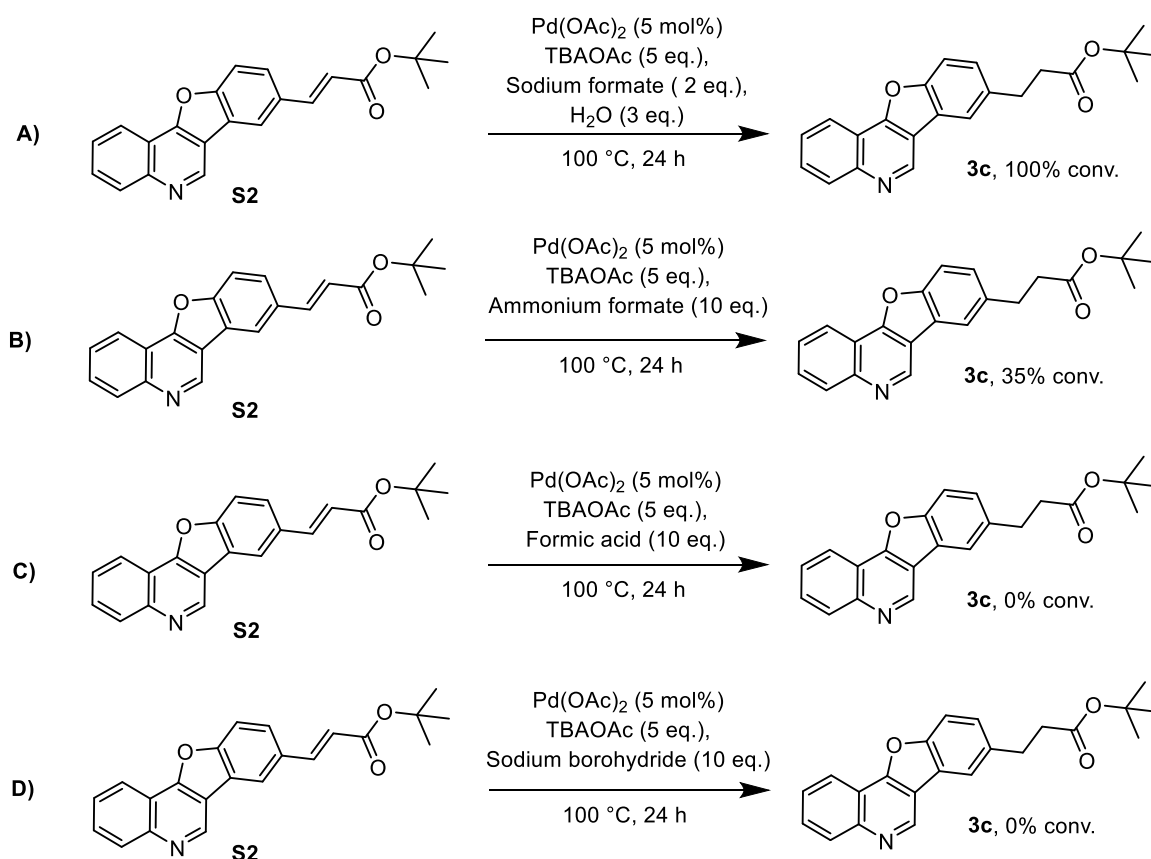
In summary, these findings indicate that Pd(OAc)₂, heated Pd(OAc)₂, and the catalytic species after a Mizoroki-Heck (only) and a direct arylation (only) facilitate the hydrogenation step given 24 hours at 100 °C. This indicates that the hydrogenation catalyst is not necessarily a catalytic by-product of the initial Mizoroki-Heck/ direct arylation steps. Additionally, the Mizoroki-Heck/ direct arylation steps are not supported by heated, and then filtered Pd(OAc)₂, nor post-hydrogenation catalytic species given 24 hours at 100 °C.

Transfer Hydrogenation

We investigated a number of conditions which are synonymous with palladium catalysed transfer hydrogenations using the following reagents; 1) ammonium formate, 2) sodium formate, 3) formic acid and 4) sodium borohydride.^[10]

Initially we investigated transfer hydrogenation on the Heck intermediate **S2** to test the viability of this approach on a 100 mg scale (0.26 mmol) and had the most success with sodium formate (2 eq, 100% conv.) followed by ammonium formate (10 eq, 35% conv.) (**Scheme UW6**). We then undertook our one-pot procedure using sodium formate at gram scale and unfortunately only trace formation of the reduced product **3c** was detected. Even though we managed to demonstrate the viability of the transfer hydrogenation going from Heck intermediate **S2** to product **3c**, these conditions were incompatible with the three step, one-pot procedure.

Scheme UW6. Transfer Hydrogenation reaction conditions.

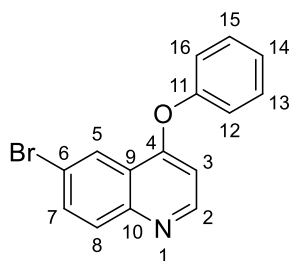


All conversions are based upon ^1H NMR analysis.

Unpublished Compound Characterisation

6-Bromo-4-phenoxyquinoline **U1**

Synthesis of substrate **U1** as per Chapter 2 - general procedure 1 using 6-bromo-4-chloroquinoline (0.500 g, 2.07 mmol), phenol (0.682 g, 7.24 mmol) and NaOH (0.124 g, 3.11 mmol).



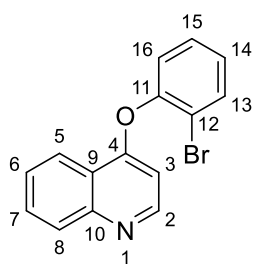
Off-white solid; 80% yield (0.498 g); m.p. 85 – 87 °C (lit: 84 – 86 °C)^[11]; IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3398 (C-H stretch), 1569 (aromatic C=C stretch), 1488 (aromatic C=C stretch), 1354 (C=N stretch), 1214 (ether C-O stretch), 660 (C-Br stretch); ^1H NMR (300 MHz, CDCl_3) δ = 8.67 (d, 1H, J 5.2 Hz, H-2), 8.54 (d, 1H, J 2.3 Hz, H-5), 7.95 (d, 1H, J 9.0 Hz, H-8), 7.81 (dd, 1H, J 9.0,

2.3 Hz, H-7), 7.43 – 7.52 (m, 2H, H-13, H-15), 7.7 – 7.35 (m, 1H, H-14), 7.15 – 7.22 (m, 2H, H-12, H-16), 6.55 (d, 1H, J 5.2 Hz, H-3) ppm; ^{13}C NMR (75.5 MHz, CDCl_3) δ = 161.0 (qC-4), 154.0 (qC-11), 151.5 (CH-2), 148.3 (qC-10), 133.6 (CH-7), 130.9 (CH-8), 130.4 (2 × CH-13, CH-15), 125.9 (CH-14), 124.3 (CH-5), 122.6 (qC-9), 121.1 (CH-12, CH-16),

120.2 (qC-6), 104.7 (CH-3) ppm; HRMS (ESI-TOF) m/z : $[M+H]^+$: $C_{15}H_{11}BrNO$: 300.0024; found: 300.0014.

4-(2-Bromophenoxy)quinoline **U2**

Synthesis of substrate **U2** as per Chapter 2 - general procedure 1 in SI using 4-chloroquinoline (1.0 g, 6.12 mmol), 2-bromophenol (3.71 g, 21.4 mmol) and NaOH (0.367 g, 9.2 mmol). Characterised as per compound **S11** in Chapter 2.



Yellow solid; 85% yield (1.72 g); m.p. 63 – 65 °C (lit: 62 – 64 °C)^[12]; IR $\nu_{\max}/\text{cm}^{-1}$: 3433 (C-H stretch), 1592 (aromatic C=C stretch), 1307 (C=N stretch), 1230 (C-O stretch), 659 (C-Br stretch); ^1H NMR (300 MHz, CDCl_3) δ = 8.67 (d, 1H, J 5.2 Hz, H-2), 8.42 (dd, 1H, J 8.3, 0.9 Hz, H-5), 8.12 (d, 1H, J 8.3 Hz, H-8), 7.68 – 7.80 (m, 2H, H-7, H-13), 7.60 (ddd, 1H, J 8.2, 6.9, 1.1 Hz, H-6), 7.36 – 7.44 (m, 1H, H-15), 7.15 – 7.25 (m, 2H, H-16, H-14), 6.41 (d, 1H, J 5.2 Hz, H-3) ppm; ^{13}C NMR (75.5 MHz, CDCl_3) δ = 160.7 (qC-4), 151.2 (qC-11), 151.0 (CH-2), 149.8 (qC-10), 134.3 (CH-13), 130.2 (CH-7), 129.2 (CH-15), 129.1 (CH-8), 127.3 (CH-14), 126.3 (CH-6), 123.2 (CH-16), 121.9 (CH-5), 121.1 (qC-9), 116.3 (qC-12), 103.7 (CH-3) ppm; HRMS (ESI-TOF) m/z : $[M+H]^+$: $C_{15}H_{11}BrNO$: 300.0024; found: 300.0017.

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You'll learn things you never knew, you never knew.

— *Colours of the Wind, Pocahontas*

If it's not Here, that means it's out There.

— *Winnie the Pooh, A.A Milne*

Chapter 3

Regioselective partial hydrogenation and deuteration of
tetracyclic (hetero)aromatic systems using a simple
heterogeneous catalyst

Preface

This chapter has been peer-reviewed and is published in Chemistry – A European Journal (doi.org/10.1002/chem.202400102). I am co-first author on this publication with Dr. Amy Lowry. I undertook the majority of the work and assembled, drafted and edited the manuscript and assembled the SI. Amy synthesised and characterised the following compounds: phenoxyquinolines **S13**, **S14**, **S15**, **S16**, **S24**, **S25** and **S26**; benzofuroquinolines **1b**, **1c**, **1d**, **1f**, **1g**, **S3**, **S4** and **S5**; and final products **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2k**, **2l**, **2o**, **4a**, **4b** and **4d** and grew any corresponding crystals (in addition to **6b**). Amy also performed the **1a** vs **1c** competition experiment (in SI). She also found that MsOH could be used to convert **1a** to **2a** and she undertook all hydrodehalogenation reactions (in SI) except for compounds **1m**, **1n** and **S2**. I performed all other experimental work except for X-ray crystallography which was undertaken by Dr. Mark Light. For the purposes of this thesis, the formatting of the paper and the SI has been maintained, however, the proton and carbon assignments have been added into the SI.

Abstract

The introduction of added ‘3-dimensionality’ through late-stage functionalisation of extended (hetero)aromatic systems is a powerful synthetic approach. The abundance of starting materials and cross-coupling methodologies to access the precursors allows for highly diverse products. Subsequent selective partial reduction can alter the core structure in a manner of interest to medicinal chemists. Herein, we describe the precise, partial reduction of polycyclic heteroaromatic systems using a simple heterogeneous catalyst. The approach can be extended to introduce deuterium (again at late-stage). Excellent yields can be obtained using simple reaction conditions.

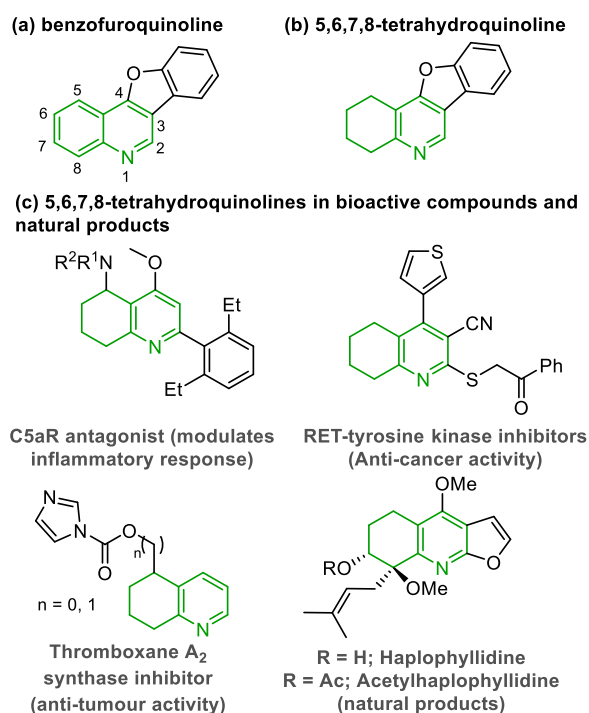
Introduction

Aromatic and extended aromatic compounds play a key role in many disciplines of chemistry, and have provided a molecular framework for pharmaceutical drug design in particular.^[1] At least partially as a consequence of the success of catalytic C(*sp*²)–C(*sp*²) cross-coupling methodologies, there has been a predominant trend in drug design strategies (over several decades) to focus on rather planar compounds.^[2] However, the associated 2D character of extended aromatic compounds is often not conducive to clinical success,^[3] where 3D character is advantageous.^[4] Indeed, molecules exhibiting greater levels of *sp*³ character progress further through clinical trials (a trend attributed mainly to greater selectivity and solubility)^[5] and many of the top selling pharmaceutical drugs contain saturated carbo- and/or heterocyclic ring systems.^[4]

Uncovering new methodologies to form less planar, novel drug candidates is essential for the continued success of medicines through clinical trials. A highly attractive approach that can enable synthetic access to compounds with a high degree of 3D character while harnessing the unparalleled scope and broad applicability of sp^2 - sp^2 cross-coupling reactions is to introduce 3D character through hydrogenation of aromatic compounds. As will be demonstrated below, this approach enables selective modification of highly functionalised planar aromatic compounds, and thus is highly suitable for late-stage modification of complex planar compounds of the type that are frequently encountered as precursors (or final products) in the latter stages of syntheses of pharmaceutical compounds.

Quinolines, pyridines and furans represent critically important molecule classes in medicinal and natural product chemistry.^[6] The partially reduced quinoline motif, tetrahydroquinoline, is also a common pharmacophore and is found in many natural products and pharmacologically relevant therapeutics (**Figure 1c**).^[7] Benzofuroquinolines (see **Figure 1a**) are biologically significant compounds in which quinoline and benzofuran systems are fused together in a planar tetracyclic aromatic system.^[8]

Figure 1. (a) Fused quinoline (green) and benzofuran (black) rings to form the benzofuroquinoline scaffold; (b) carbocyclic reduced tetrahydroquinoline; (c) selected examples of reduced carbocyclic quinolines in bioactive compounds and natural products.



In the research described herein, we focused on generation of derivatives of these planar compounds containing significant additional 3D character (see **Figure 1b**), since non-planar derivatives (containing a higher proportion of sp^3 centres) of fully aromatic bi-, tri- and tetracyclic rings systems frequently possess very different biological activity to their planar, fully aromatic analogues.^[9]

Conditions have been reported under which simple quinolines undergo hydrogenation at either (i) the heterocyclic ring, (ii) the carbocyclic ring, or (iii) both rings.^[10] However, these conditions are typically harsh, requiring high pressures and temperatures, and the reactions often suffer from issues with selectivity (i.e., competitive reduction of heterocyclic and carbocyclic rings).^[11] Chemoselective reduction of the carbocyclic ring in these systems is rare, emphasising the urgency for novel methodologies to access these core structures^[10a, 12] and there is limited work in general on the selective reduction of polycyclic aromatic compounds.^[13] Selective reduction of the heterocyclic or carbocyclic ring systems in bicyclic compounds mainly utilises specialised homogeneous Pt,^[13a, 14] Ru,^[15] and Rh^[16] catalysis and requires harsh conditions such as strongly acidic solvent, high pressures and/or high temperatures. Although there have been significant advances in homogeneous hydrogenation catalysis,^[17] heterogeneous catalysis is still at the forefront in industrial processes due to easier handling, separation and potential recyclability of the catalyst. In particular, Pd/C is a simple and accessible heterogeneous catalyst.^[18]

There are few examples of quinolines undergoing selective hydrogenation using Pd/C using atmospheric hydrogen pressure currently in the literature. Shelke and co-workers selectively reduce the carbocyclic ring in a hydrofuroquinoline derivative using Pd/C (10 mol%), H₂ (atm.) in EtOAc at room temperature for 5 days.^[19] In 2016, Comins used Pd/C (12 mol%), H₂ (atm.), Li₂CO₃ (1.2 eq.) in EtOH at room temperature for 5 days to also yield the reduced carbocycle of the respective 4-methoxyquinoline.^[20] Recently, Tanaka and Usuki subjected unsubstituted quinoline to Pd/C (10 ml%), H₂ (atm.), AcOH at room temperature for 15 hours and achieved hydrogenation of both the carbo- and heterocycle of quinoline to form decahydroquinoline.^[18d]

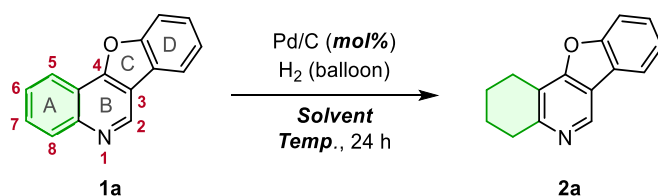
The work described here involves the highly selective partial dearomatisation of benzofuroquinolines using the widely available, simple Pd/C catalyst. Importantly, we also introduce deuterium into the carbocyclic ring through *ex situ* D₂ formation. Our deuterium-based experiments also revealed a surprising insight into the mechanistic pathway.

Results and Discussion

Optimisation Studies

We began our optimisation using unsubstituted benzofuroquinoline **1a**. We observed that tetrahydrobenzofuroquinoline **2a** could be formed from **1a** in very high yield using Pd/C (10 mol%) and H₂ (balloon) in AcOH after stirring at room temperature for 24 hours (**Table 1**, entry 1). Reduction of the amount of catalyst (to 5 mol%) also allowed for full conversion at 50 °C (entry 2). Further lowering of catalyst led to reduced amount of product (entries 3 and 4). Using hexafluoroisopropanol ($pK_a = 9.3$ in H₂O)^[21] as solvent instead of AcOH ($pK_a = 4.72$ in H₂O)^[22] resulted in just 9% conversion from **1a** to **2a** (entry 5). Use of trifluoroacetic acid ($pK_a = -0.3$ in H₂O)^[22b] also led to selective reduction of the A-ring of **1a** in excellent yield (entry 6).

Table 1. Initial optimisation of reaction conditions.



Entry	Pd/C (mol%)	Solvent	Temp. (°C)	% Conversion ^[a] (Isolated) ^[b]
1	10	AcOH	r.t.	100 (96)
2	5	AcOH	50	100 (94)
3	2	AcOH	80	75
4	2	AcOH	r.t.	5
5	10	HFIP	r.t.	9
6	10	TFA	r.t.	100 (95)

^[a] Conversion determined using ¹H NMR analysis of **1a** and **2a**. ^[b] Isolated yield in parentheses. HFIP: hexafluoroisopropanol, TFA: trifluoroacetic acid, r.t.: room temperature.

Substrate Scope

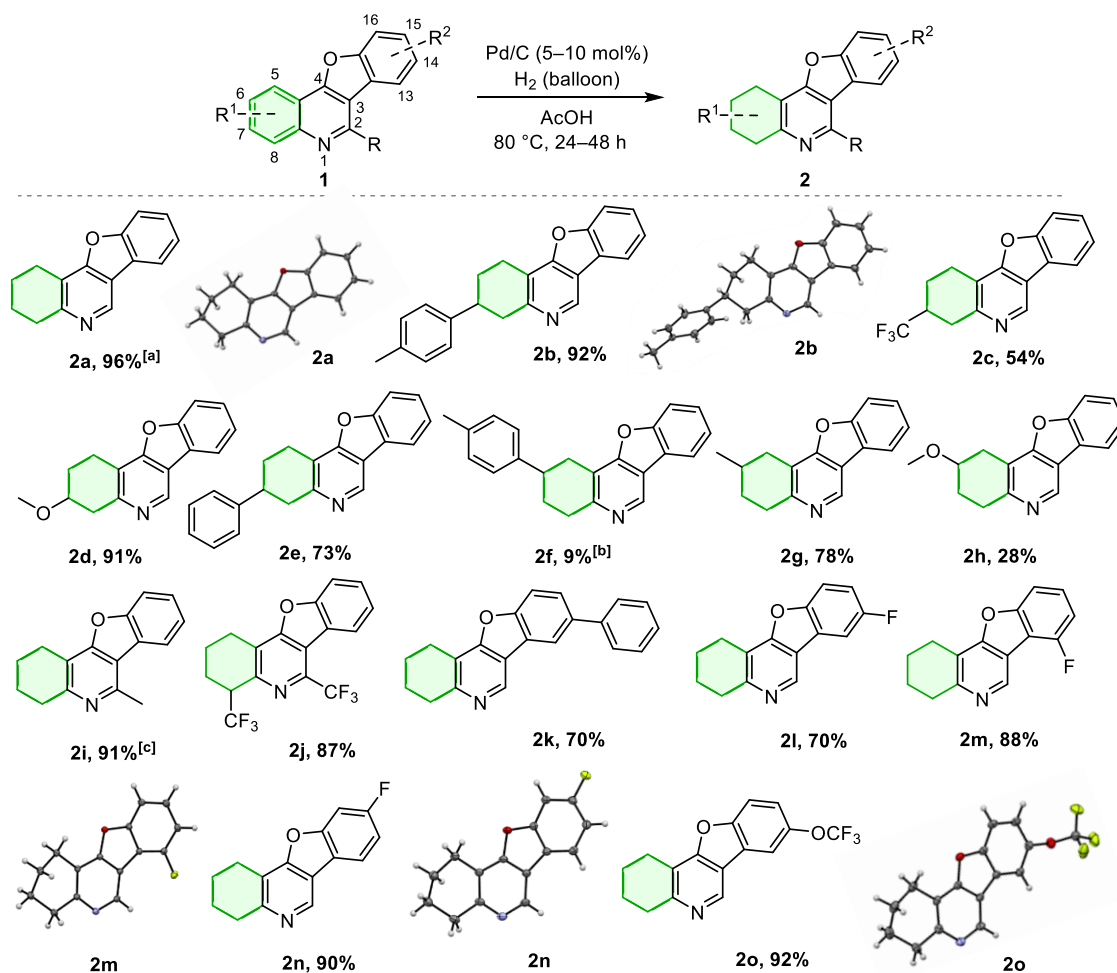
Based on our success in the selective reduction of the A-ring of benzofuroquinoline **1a**^[23] to **2a** (**Table 1**), we adopted 5 mol% Pd/C, 50 °C, and 24 hour reaction time in AcOH solvent (under a H₂ atmosphere provided through a balloon) as our standard conditions.

These conditions were applied in the selective reductions of a diverse array of substituted benzofuroquinolines. Substitution at C-7 of the benzofuroquinoline skeleton did not hinder product formation and selectively reduced products **2b–e** were obtained from the

corresponding fully aromatic compounds (**1b–e**) in moderate to excellent yields (54–92%) (**Scheme 1**). 2-Methylbenzofuroquinoline **1i** required elevated temperature and extended time for full reduction of the A-ring. However, an excellent yield (91%) of **2i** was obtained.

Products bearing substituents at the C-6 position were, in some cases, formed in lowered yields (**2f**, **2h**). However, 6-methyl-substituted product **2g** was produced in a yield of 78%. The effect of C-8 substitution on the efficacy of selective A-ring hydrogenation was investigated through examination of the conversion of **1j** (incorporating the 2,8-bis(trifluoromethyl) quinoline motif commonly present in anti-malarial compounds)^[24] to **2j**. Pleasingly, **2j** was isolated in 87% yield.

Scheme 1. Substrate scope with substitution on the A-ring, B-ring and D-ring.

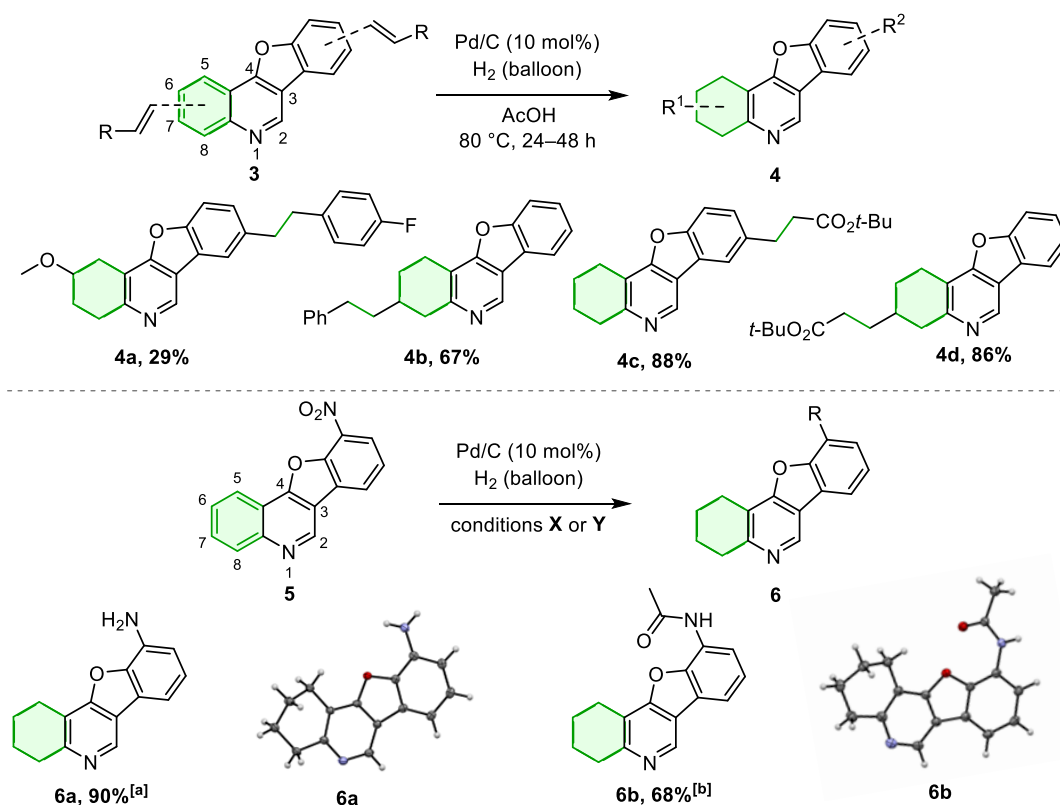


^[a] Pd/C (5 mol%), 50 °C, 24 h. ^[b] Pd/C (10 mol%), 100 °C, 72 h. ^[c] Pd/C (10 mol%), 100 °C, 48 h.

D-ring substituted products **2k–o** were also obtained in good to excellent yields (68–92%). In several cases (**2a**, **2b**, **2m**, **2n**, **2p**, **3e** and **3f**), the structures of the products were verified by obtaining X-ray crystal structures of the crystalline products.

Next, substrates with olefin pendant groups (easily installed via a Heck-Mizoroki reaction)^[23c] could have both the carbocyclic ring and the alkene functional group of the starting material reduced (**Scheme 2**), conveniently yielding alkylated products (**4a–4d**) in yields of 29–88% (again, the presence of a methoxy substituent at the 6-position resulted in a low yield for **4a** – cf. compound **2h** in **Scheme 1**). Additionally, we were pleased to find that the acid-labile *tert*-butyl esters in products **4c** and **4d** were retained. Next, the concomitant reduction of a nitro group in substrate **5** was investigated under our standard conditions. Surprisingly, a mixture of the amine product **6a** (ca. 56%) and *N*-acetylated product **6b** (ca. 44%) was observed initially. To achieve selective amine formation, we revisited alternative acids. Pleasingly, we found that using 3 equivalents of methanesulfonic acid (MsOH, $pK_a = -2.6$ in H_2O)^[22] in *i*PrOH allowed for selective formation of **6a** in 90% yield.

Scheme 2. Extended Scope of Selectively Reduced Substituted Benzofuroquinolines.



Conditions **X**: MsOH (2M, 3 eq.) in *i*PrOH, $80\text{ }^{\circ}C$, 24 h. Conditions **Y**: AcOH, $80\text{ }^{\circ}C$, 72 h. ^[a] Used conditions **X**. ^[b] Used conditions **Y**.

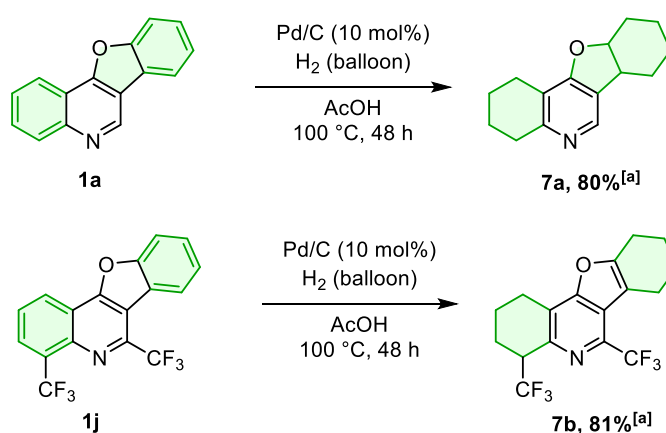
Selective hydrogenation of **1a** was also undertaken on larger (5 mmol, 1.10 g) scale, and gave an isolated yield of **2a** of 91% (using Pd/C (5 mol%), AcOH, H_2 , 24 h, $50\text{ }^{\circ}C$).

Finally, when the substrates **1a** and **1j** were subjected to extended reaction times, yields of 80% and 81% of **7a** and **7b** respectively, could be obtained (see **Scheme 3**).

Interestingly, reduction of three of the four rings in tetracycle **1a**, was observed, leaving the pyridine ring untouched, whereas with the bis-trifluoro compound **1j**, two of the four rings were reduced. For reference, hydrogenation of C-2-methylated compound **1i** under the same conditions resulted in reduction of the A-ring only, i.e., in formation of compound **2i** (see **Scheme 1**). Multi-ring reduction products **7a** and **7b** represent new heterocyclic cores and will be the subject of future work.

Some competition studies (see SI for details) show that substitution of the A-ring leads to reduced reactivity relative to **1a**. Bias then appears to favour electron donating groups, with **2d** formation outcompeting **2c**, for example (see SI for details).

Scheme 3. Highly unusual selectivity; double ring reduction products.



^[a] Isolated yields.

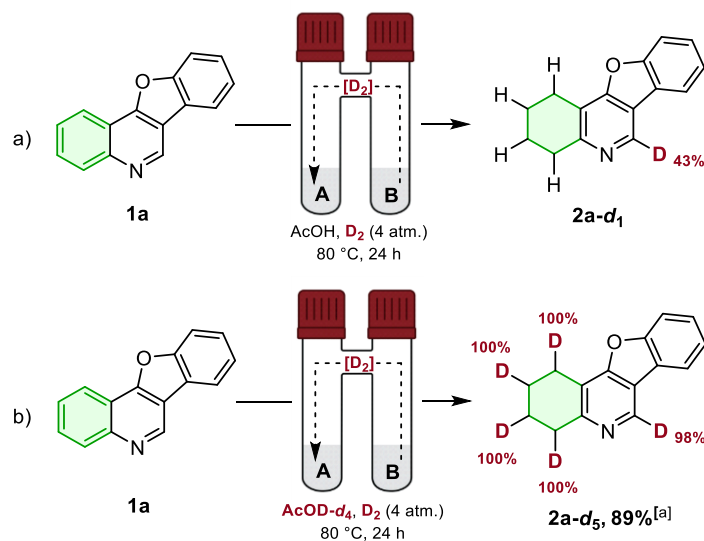
Deuterium incorporation

Deuterated compounds have many important applications, and are extensively used in studies of reaction mechanisms and pharmacokinetics.^[25] Additionally, in 2017, the first deuterium containing drug, deutetrabenazine, was approved by the FDA.^[26] The difficulty in accessing D₂ gas directly, can in some cases be circumvented by using the 'COware' apparatus, which allows for *ex-situ* gas generation (**Scheme 4** and SI).^[27] In our case, using DCl and Zn metal to generate D₂ gas, we observed full reduction *but no deuterium incorporation* into the A-ring (**Scheme 4a**). The source of hydrogen was unclear to us. However when AcOD-*d*₄ was used in conjunction with D₂, full incorporation of deuterium was observed (**Scheme 4b**)^[28] In the latter case, 98% deuterium incorporation was also observed at the C-2 position (**Scheme 4b**).

A control experiment in which compound **1a** was dissolved in AcOH in the absence of D₂ gas (i.e. no Zn, but in which DCl was present in the COware apparatus) resulted in no formation of **2a** or **2a-d_x** (i.e., no reduction whatsoever), indicating that the presence of H₂ or D₂ gas is essential for the reduction process to occur even if the H or D atoms

supplied by the gas are not incorporated into the structure of the reduced compound. This finding will provide the basis for future work.

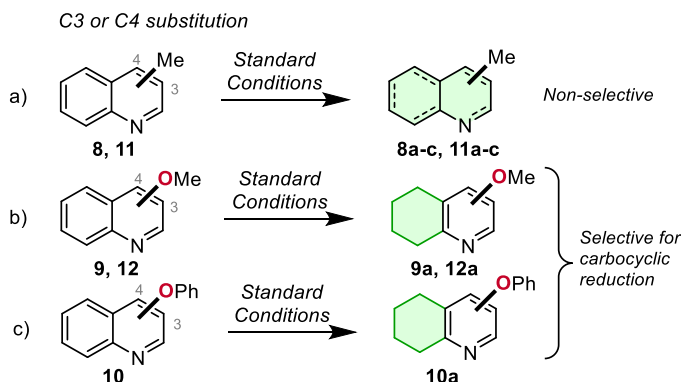
Scheme 4. Deuterium incorporation using COWare apparatus.



^[a] Isolated yield.

To gain an insight into the structural requirements for selective carbocyclic reduction, several carefully chosen substituted quinolines were subjected to the optimised hydrogenation conditions (**Scheme 5**). In reactions of quinolines bearing a methyl or phenyl group substituent at the 3- or 4-position, little or no selectivity was exhibited between hydrogenation of the carbocyclic ring and the heteroaromatic ring (**Scheme 5a**). In contrast, reactions of 3- or 4-methoxy or phenoxy-substituted quinolines exhibited exclusive carbocyclic ring hydrogenation (**Scheme 5b** and **5c**, see SI for conversions and more details). This indicates that a more electron rich heterocyclic ring or improved nitrogen basicity impacts the selectivity of this reaction.

Scheme 5. Requirements for selective carbocyclic reduction.



Standard Conditions: Pd/C (5 mol%), AcOH, H₂ (balloon), 50 °C, 24 h.

Mechanistic Insight

As discussed in the introduction, both the pH environment and quinoline substitution have an effect on the selectivity outcome of the hydrogenation.^[14b-e, 18d] In the case of the benzofuroquinoline scaffold, it has been determined through our experimentation that acidic solvent is required. However, the selectivity remains the same whether for strong acid (e.g. TFA) or weak acid (e.g. AcOH) is used. The A-ring substitution of quinoline had a more dramatic effect on reaction outcome, especially at C6 and C8 positions. We observed depreciated conversion for C6 and C8 positions with electron-donating group substitution. This lowered amount of hydrogenation at the carbocyclic ring at with substitution at C6 and C8 has also been reported in the literature for quinoline scaffolds, which remains true for our benzofuroquinoline scaffold.^[13a, 14a-e] These observations are in addition to our separate experimental work on substituting the heterocycle to determine selectivity (**Scheme 5**)

Although, the 6-methyl substituted product **2g** was obtained in excellent yield (78%), the 6-methoxy **2h**, 6-tolyl **2f** substrates were formed in much lower yields of just 28% and 9% respectively, even after extended reaction times (**Scheme 1**). Additionally, the C8 position was substituted with electron-donating methoxy group (as mentioned above) and was subjected to our hydrogenation conditions. Interestingly, this position was even more sluggish to react with a small maximum observed conversion of 10% as judged by NMR analysis. These results are surprising as it has been suggested that increasing the electron density on the heterocyclic ring induces more carbocycle reduction. In this case, one might anticipate a faster conversion to the reduced compound, however, the opposite effect is observed. It could be considered that other factors such as sterics are involved, however the 8-CF₃ substituted substrate **2j** (albeit electron-withdrawing) was reduced without issue. It is possible that the additional 2-CF₃ for this substrate **2j** plays a part in the reduction, however, it is an interesting observation.

It is also speculated that the CMD mechanism is at play for the direct arylation in the construction of the benzofuroquinoline substrates. This is, once again, due to the fact that conversion to the products does not appear to depend on the electronics of the substrate.^[29] For example, 7-CF₃ benzofuroquinoline **1c** and 7-MeO benzofuroquinoline **1d** were both isolated in excellent yields (86% and 91% respectively) which indicates no electronic bias for electron rich systems for the S_EAr mechanism. Additionally, the 6,7-dimethoxy benzofuroquinoline **U9** (see unpublished work) was not formed, which is a very electron rich system. When the electron density is depreciated, as in 6,7-dimethyl benzofuroquinoline **U11**, the direct arylation occurs (86% isolated yield, see unpublished work). This shows that di-substitution is supported, however, more electron rich systems

are not. This suggests a possible alternative mechanism to S_EAr (such as CMD) is in effect, however, more investigations would need to be undertaken to define the exact mechanism.

Conclusions

Uncovering practical methodologies to effect small (yet significant) changes to the core structure of medicinally important compounds has recently gained traction, due to the urgent need for increased clinical success of drug candidates.^[3d] With this type of approach (recently termed molecular editing),^[30] selectivity is the key. In the work described here, the selective hydrogenation of substituted benzofuroquinolines was demonstrated, using a simple, highly accessible heterogeneous catalyst. This methodology demonstrates a great strategy for late-stage modification of complex heteroaromatic structures of the type that appear widely in existing, highly planar pharmaceutical compounds, thus providing straightforward access to analogues with a high degree of 3-dimensionality. In addition, deuterium could be introduced very conveniently through *ex-situ* D₂ formation. Finally, the 'O' at the 4-position in these substrates helps control selectivity.

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Supplementary Information for Chapter 3:

**Regioselective partial hydrogenation and deuteration of tetracyclic
(hetero)aromatic systems using a simple heterogeneous catalyst**

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General Experimental Details

Solvents and reagents were used as obtained from commercial sources and without purification. Tetrabutylammonium acetate was sourced from Sigma Aldrich. Infrared spectra were obtained for novel compounds and were measured on a Perkin Elmer Spectrum Two spectrometer, using universal ATR sampling accessories. Column chromatography was carried out using 60 Å (35–70 µm) silica. Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). The developed plates were visualized under UV light. High-resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier time of flight (TOF) LC-MS instrument in University College Cork. Samples were run in electrospray ionization (ESI) mode using 50% acetonitrile/water containing 0.1% formic acid as an eluent; samples were made up at a concentration of ca. 1 mg mL⁻¹. Acquisitions were internally calibrated using sodium formate clusters. Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer (QAA1202) in electrospray positive ionisation mode (ESI+) using acetonitrile:water (1:1) containing 0.1% formic acid as eluent. Nuclear magnetic resonance (NMR) samples were run using deuterated chloroform (CDCl₃) as solvent unless otherwise stated. ¹H NMR (600 MHz), ¹H NMR (500 MHz), ¹H NMR (400 MHz), and ¹H NMR (300 MHz) spectra were recorded on Bruker Avance III 600, Bruker Avance 500, Bruker Avance 400, and Bruker Avance III 300 NMR spectrometers, respectively, in proton-coupled mode using tetramethylsilane (TMS) as the internal standard. Signal assignments were supported by COSY (correlation spectroscopy) or HMBC (Heteronuclear Multiple-Bond Correlation spectroscopy) NMR spectroscopic experiments where necessary. ¹³C NMR (150 MHz), ¹³C NMR (125 MHz), ¹³C NMR (100 MHz), and ¹³C NMR (75 MHz) spectra were recorded on Bruker Avance III 600, Bruker Avance 500, Bruker Avance 400, and Bruker Avance III 300 NMR spectrometers, respectively, in proton-decoupled mode at 300 K using TMS as the internal standard. All spectra were assigned with the aid of DEPT (Distortionless Enhancement by Polarisation Transfer) experiments run in DEPT-90, DEPT-135 and DEPT-q modes when necessary. Specific assignments were made using HSQC (Heteronuclear Single Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Correlation) NMR spectroscopic experiments. All spectroscopic data for known compounds is in agreement with those previously reported unless otherwise stated. ¹⁹F NMR (282 MHz), ¹⁹F NMR (376 MHz) and ¹⁹F NMR (471 MHz) spectra were recorded on a Bruker Avance III 300 NMR spectrometer, Bruker Avance 400, and Bruker Avance 500 in proton-decoupled mode at 300 K. All spectra were run at University College Cork. Chemical shifts (δ) are expressed as parts per million (ppm), positive shift being

downfield from TMS; coupling constants (J) are expressed in hertz (Hz). Splitting patterns in ^1H NMR spectra are designated as follows: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), td (triplet of doublets), q (quartet), quin (quintet), and m (multiplet). Melting points were measured in a Thomas Hoover Capillary Melting Point apparatus and are uncorrected. The COware apparatus was purchased from Sigma Aldrich and the hydrogen pressure was estimated using the $PV = nRT$ formula by using the quantity of hydrogen generated. It is worth noting that a 20 mL COware apparatus was used for these experiments. The COware apparatus has two chambers that are connected by a glass bridge, allowing for *ex situ* gas to be generated in one chamber which can then interact with the reaction mixture in the second chamber Warning: pressurised reaction vessel (**Figure 1S**). These can be annotated as chamber 'A' and chamber 'B'.

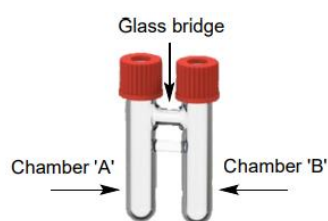


Figure 1S. COware apparatus and set-up.

The procedure followed to synthesise the benzofuroquinoline substrates depended on availability of starting materials at the time (see General Procedures below). Benzofuroquinoline substrates **1e**, **1k**, **1l**, **1o**, **3a** and **S1** (**Figure 2s**) were synthesised during previous work in the group (see reported procedures) and were provided as starting materials for this work.^[1]

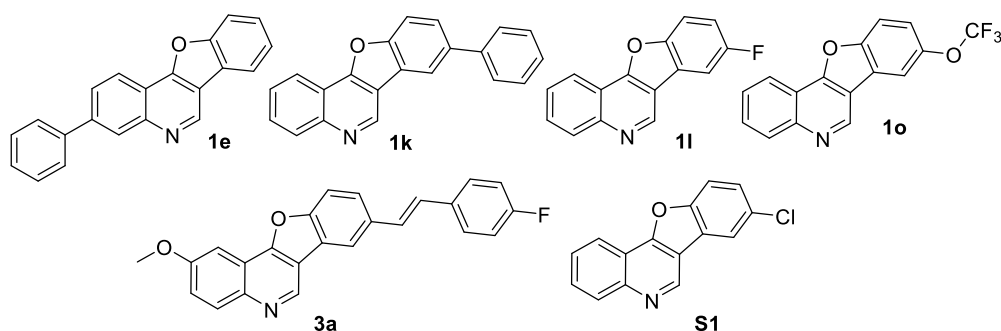


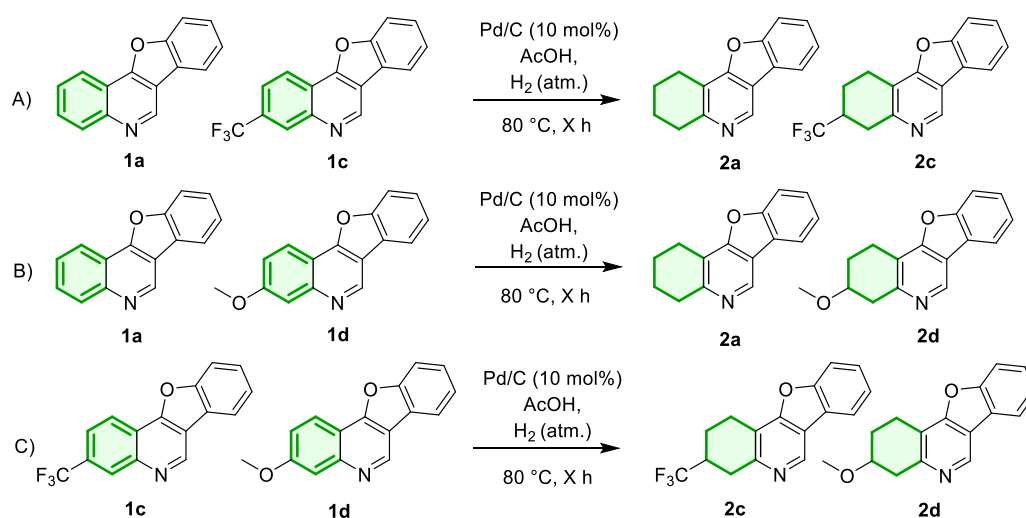
Figure 2S. Benzofuroquinoline substrates **1e**, **1k**, **1l**, **1o**, **3a** and **S1**.

Additional Experiments:

Competition Experiments (See substrate scope in main manuscript)

A series of competition experiments were carried out to determine the effect of electron withdrawing or electron donating groups on the rate of reaction (in comparison to unsubstituted benzofuroquinoline) (**Table 1S**). Comparing **1c** and **1d** to **1a**, it was found that **1a** reduced faster on both occasions.

Table 1S: Competition experiments between unsubstituted, electron-withdrawing and electron donating group containing benzofuroquinolines.

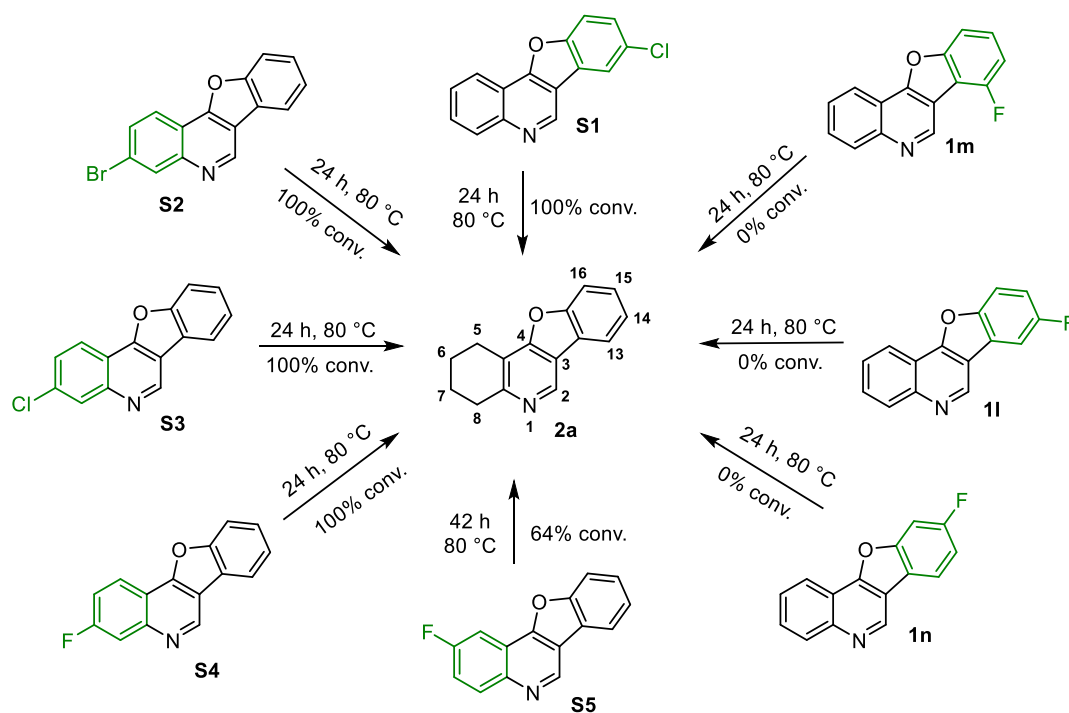


Reaction	4 h (conv. %) ^[a]		24 h (conv. %) ^[a]	
A	2a	2c	2a	2c
	100	5	100	48
B	2a	2d	2a	2d
	100	15	100	85
C	2c	2d	2c	2d
	6	17	48	87

^[a] Conversion determined by ¹H NMR analysis at both 4 hours and 24 hours.

Additionally, **1c** had a slower reaction rate than **1d**. These results indicate that the rate of the hydrogenation reaction is reduced with substitution and is reduced more by the presence of the electron withdrawing substituents, in comparison to the electron donating group at the 7-position.

Hydrodehalogenation (See substrate scope in main manuscript)



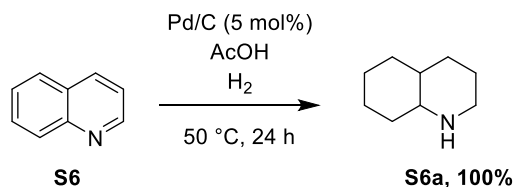
Scheme 1S: Hydrodehalogenation of chlorine, bromine and fluorine substituents on the A- and D-ring of benzofuroquinoline under the standard reaction conditions. Reaction conditions: 10 mol% Pd/C, H₂ (balloon), AcOH. All conversions determined using ¹H NMR analysis.

Reactions were undertaken as per general procedure 5. Full hydrodehalogenation to unsubstituted benzofuroquinoline **2a** is observed for 7-bromobenzofuroquinoline **S2**, 7-chlorobenzofuroquinoline **S3** and 7-fluorobenzofuroquinoline **S4** (**Scheme 1S**). For **S5**, only 65% conversion to the A-ring reduced, defluorinated **2a** was observed, with the remaining reaction mixture being starting **S5**. D-ring substitution was more robust towards hydrodefluorination (see **1l**, **1m**, **1n**), however the chlorine atom was fully cleaved in **S1**.

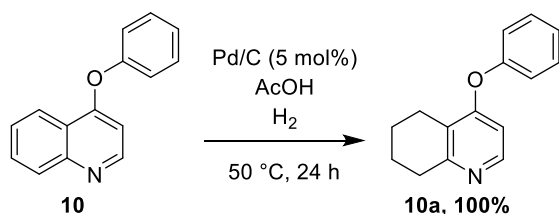
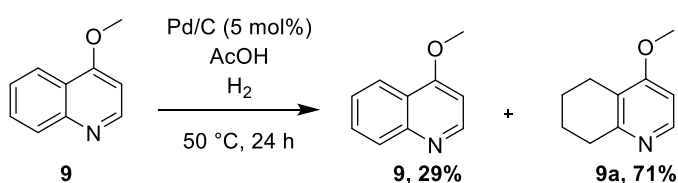
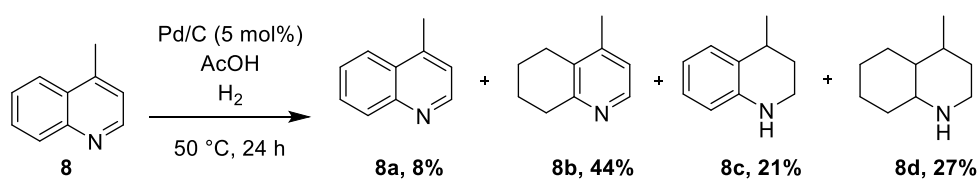
Hydrogenation of Substituted Quinolines (See scheme 5 in main manuscript)

All reactions were carried out as per general procedure 5. All percentages are conversions from the respective quinoline starting material. All conversions were determined using ^1H NMR analysis of starting materials and products.

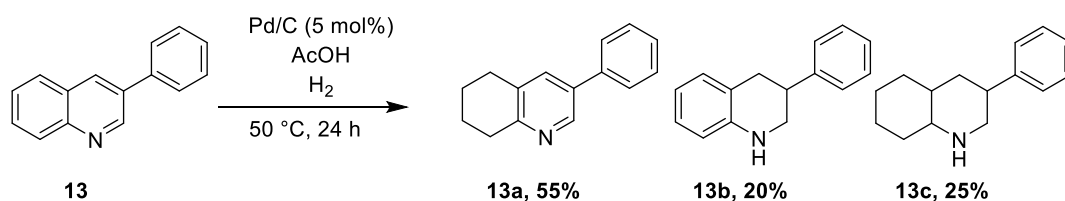
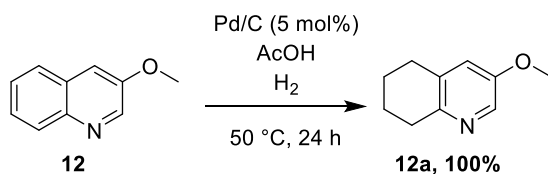
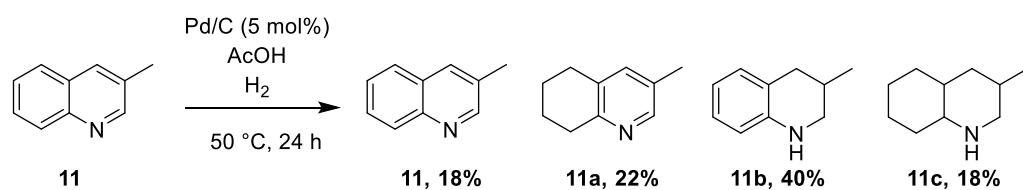
Unsubstituted quinoline



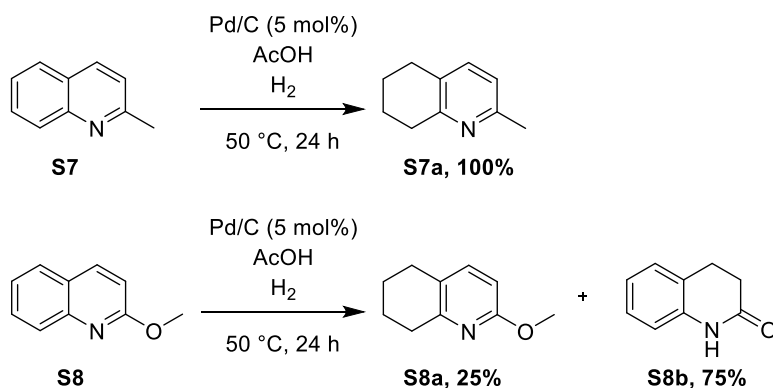
C-4 substituted quinolines



C-3 substituted quinolines



C-2 substituted quinolines

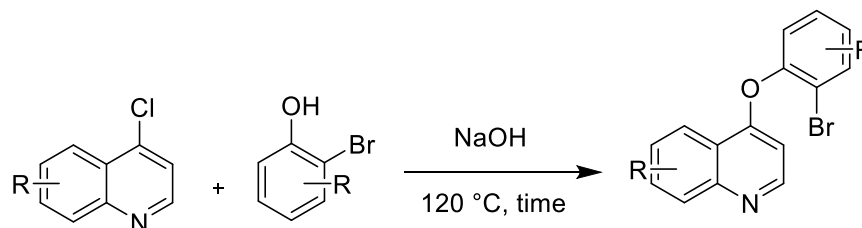


Scheme 2S: Mechanistic Insights: Expansion on products formed from the hydrogenation of C-2, C-3 and C-4 substituted quinolines.

In addition to the C-4 and C-3 positions discussed in the main manuscript, the C-2 position was also investigated. Reactions were undertaken with C-2 substituted **S7** and **S8** as per general procedure 5. In this case, both quinolines showed reduction at both hetero- and carbocycle reduction although only one contains an oxygen heteroatom. This may be due to strenuous conditions required to reduce the heterocyclic ring with C-2 substitution. The reduction of **S8** gave a mixture of reduced carbocycle **S8a** and reduced cyclic amide **S8b** while retaining the aromatic carbocyclic ring.

General Procedures

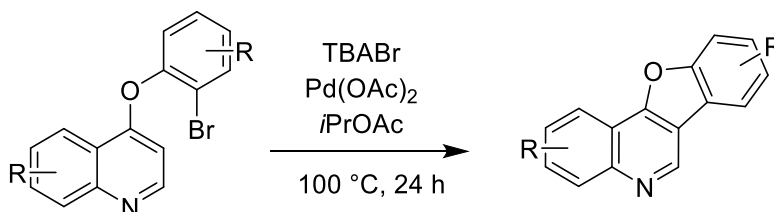
General Procedure 1: Synthesis of phenoxyquinoline starting materials



A mixture of the 4-chloroquinoline substrate (1 eq.), the phenol (3.5 eq.) and NaOH (1.5 eq., crushed pellets) was stirred at 120 °C until TLC analysis indicated the reaction was complete (2 – 24 hours). The reaction mixture was cooled to room temperature and 10% aqueous NaOH was added and stirred for 30 min. The aqueous layer was extracted with DCM. The organic layers were combined and washed with 6M NaOH, water and brine, dried over MgSO₄, filtered, and concentrated in vacuo. Impure products were purified by column chromatography over silica gel using cyclohexane:EtOAc (100:0 – 70:30) or DCM:EtOAc (100:0 – 97:3).

General Procedure 2: Synthesis of benzofuroquinolines using tetrabutylammonium bromide ^[2]

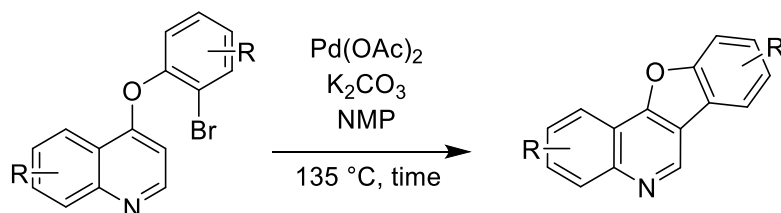
The procedure followed to synthesise the benzofuroquinoline substrates depended on availability of starting materials at the time.



To a screw capped vial was added the phenoxyquinoline substrate (1 eq.), Pd(OAc)₂ (5 mol%), tetrabutylammonium bromide (2 eq.), K₂CO₃ (2 eq) in isopropyl acetate (1.5 mL/mmol) which was stirred at 100 °C for 24 hours. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5).

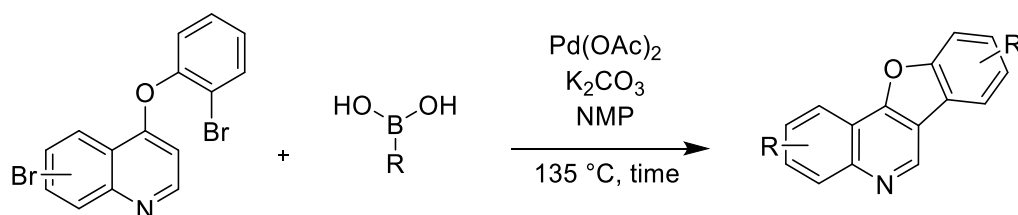
General Procedure 3: Synthesis of benzofuroquinolines using NMP ^[1a]

The procedure followed to synthesise the benzofuroquinoline substrates depended on availability of starting materials at the time.



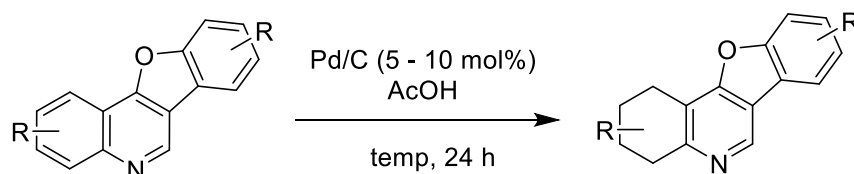
To a screw capped vial was added the phenoxyquinoline substrate (1 eq.), $\text{Pd}(\text{OAc})_2$ (5 mol%), K_2CO_3 (2 eq.) in NMP (1.5 mL/ mmol) which was stirred at $135\text{ }^\circ\text{C}$ and monitored by ^1H NMR. Upon reaction completion, the crude reaction mixture was filtered through celite, concentrated *in vacuo* and then loaded onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5).

General Procedure 4: Synthesis of benzofuroquinolines with Suzuki coupling using NMP ^[1b]



To a screw capped vial was added the di-brominated phenoxyquinoline substrate (1 eq.), $\text{Pd}(\text{OAc})_2$ (5 mol%), K_2CO_3 (2 eq.), boronic acid (1.1 eq) in NMP (1.5 mL/ mmol) which was stirred at $135\text{ }^\circ\text{C}$ and monitored by ^1H NMR. Upon reaction completion, the crude reaction mixture was filtered through celite, concentrated *in vacuo* and then loaded onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5).

General Procedure 5: Hydrogenation of benzofuroquinolines



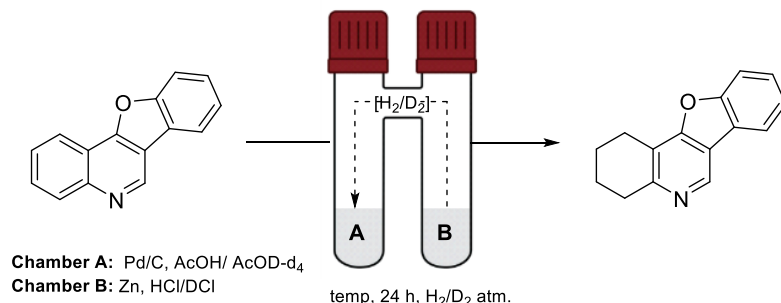
The benzofuroquinoline substrate (1 eq.) and Pd/C (10 wt%, 10 mol% [unless otherwise stated]) was added to the reaction tube, in acetic acid (6 mL/mmol). The reaction tube was sealed with a rubber septum and purged with N_2 before purging with H_2 *via* balloon

and needle. The reaction was stirred under a H₂ atmosphere and heated to the desired temperature for 24 hours (unless otherwise stated). The reaction mixture was diluted with DCM and filtered through Celite. Water was added, and the filtrate was neutralised with solid NaHCO₃. The aqueous phase was then extracted with DCM and the combined organic phases were washed with sat. NaHCO₃, water, and brine, then dried over MgSO₄, filtered, and concentrated *in vacuo* to give the product. When necessary, chromatographic purification was carried out by flash column chromatography in DCM/EtOAc (100:0 – 95:5) or DCM/MeOH (100:0 – 98:2).

Deuteration experiments

General Procedure 6: Synthesis of deuterated benzofuroquinoline

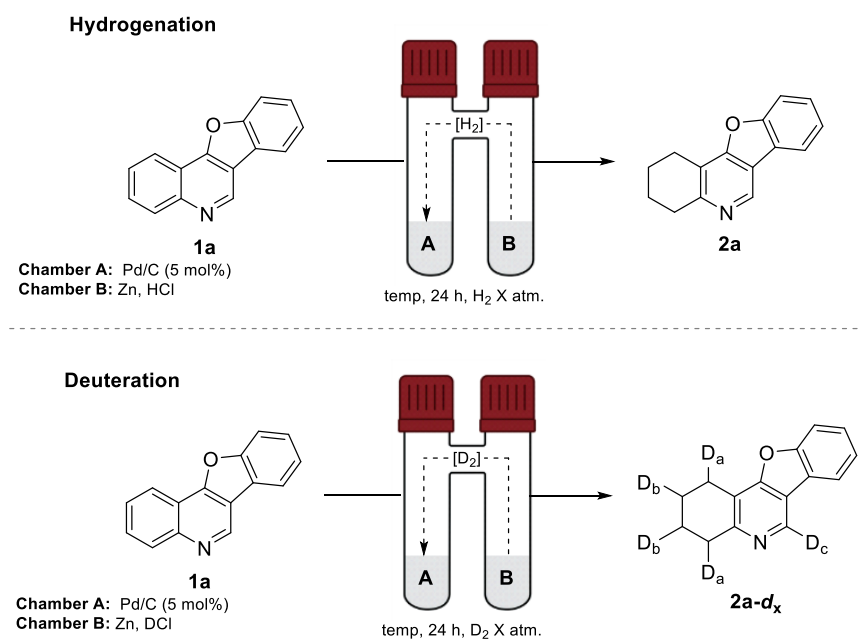
- Generating D₂ at 4 atm.



To chamber 'A' of the COware^[3] apparatus was put the benzofuroquinoline substrate (1 eq.), Pd/C (10 %wt, 5 mol%) and AcOH/AcOD-*d*₄. To the second chamber 'B' was added zinc powder (6.8 eq.). Chamber 'A' was placed into an oil bath at 80 °C and HCl/DCl (4M, 13.6 eq.) was added via syringe to chamber 'B' which initiated the D₂ formation and reaction was let stir at 80 °C for 24 hours. The reaction mixture was diluted with DCM and filtered through Celite. Water was added, and the filtrate was neutralised with solid NaHCO₃. The aqueous phase was then extracted with DCM and the combined organic phases were washed with NaHCO₃, water, and brine, then dried over MgSO₄, filtered, and concentrated *in vacuo* to give the product. Chromatographic purification was carried out by flash column chromatography in DCM/EtOAc (100:0 – 97:3).

Optimisation of COware Apparatus (See Scheme 4 in main manuscript)

Reactions were carried out as per general procedure 6. Initial use of the COware involved optimising hydrogenation conditions of benzofuroquinoline **1a** using HCl and Zn to form H₂ gas (**Table 2S**, entries 1 – 3). It was found that an increase from 50 °C to 80 °C was necessary to achieve full reduction to **2a** in the COware apparatus at 4 atm. HCl was then replaced with DCl to generate D₂ gas and form the deuterated products **2a-d_x** (entries 4 – 6).

Table 2S: Optimisation of hydrogenation and deuteration in COware apparatus.

Entry	Temp °C	Pressure Atm.	Gas source	Solvent	Zn	Conv. to 2a/2a-d _x % ^[a]	D ₂ incorp ^[b]		
Hydrogenation									
1	50	3	HCl	AcOH	Yes	40	NA		
2	50	4	HCl	AcOH	Yes	60	NA		
3	80	4	HCl	AcOH	Yes	100	NA		
Deuteration							Da	Db	Dc
4	80	4	DCl	AcOH	Yes	99	0	0	43
5	80	4	DCl	AcOD-d ₄	Yes	100	100	100	98
6	80	4	HCl	AcOD-d ₄	Yes	100	68	50	46
7	80	4	DCl	AcOH	No	0	NA	NA	NA

^[a]Conversion determined using ¹H NMR analysis of **1a** and **2a/2a-d_x**.^[b] Deuterium incorporation was determined by ¹H NMR analysis.

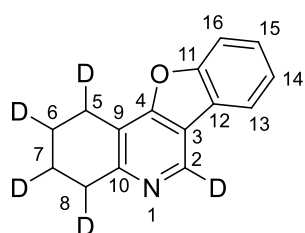
Using DCl and Zn to generate D₂ gas, we observed full reduction of the A-ring in AcOH at 80 °C. However, unexpectedly, deuterium incorporation was *only* observed at the C-2 position (labelled D_c) with 43% incorporation. There was no deuterium incorporation on the newly reduced carbocyclic ring (entry 4). To investigate further, we carried out the same reaction using AcOD-d₄ and found near full incorporation of deuterium (**2a-d₅**: D_a, 100%; D_b, 100%, D_c 98%), in 94% isolated yield (entry 5). We then wondered if replacing D₂ gas with H₂ gas, and AcOD-d₄ as solvent, would maintain full deuterium incorporation in the carbocyclic ring. These conditions led to partial deuterium incorporation across each site (D_a, 68%; D_b, 50%, D_c 46%) (entry 6). This tells us that both the solvent and

the gas are important sources of hydrogens/deuteriums this reaction. No reduction takes place in the absence of H₂ or D₂ gas in the COware apparatus (entry 7).

Characterisation of Deuterated benzofuroquinoline

1,2,3,4-Tetrahydrobenzofuro[3,2-c]quinoline-1,2,3,4,6-d₅ (2a-d₅)

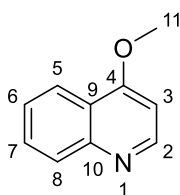
Synthesis of substrate **2a-d₅** as per general procedure 6 using **1a** (0.050 g, 0.23 mmol), Pd/C (12.2 mg, 0.023 mmol), AcOD-d₄ (1.10 mL) in chamber A and Zn (0.102 g, 1.56 mmol, 6.8 eq.) and DCI (4M, 0.78 mL, 3.12 mmol, 13.6 eq.) in chamber B.



White solid; 89% (0.046 g); **m.p.** 146 – 148 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2961, 2926, 2851, 1558, 1392, 1191, 1011; **¹H NMR (300 MHz, CDCl₃)** δ = 8.90 (s, 1H, H-2), 7.89 (dd, 1H, *J* = 0.8, 7.5, H-13), 7.51 (d, 1H, *J* = 8.2 Hz, H-16), 7.40 (td, 1H, *J* = 1.4, 7.5 Hz, H-15), 7.36 (td, 1H, *J* = 1.0, 7.5 Hz, H-14), 3.03 – 2.90 (m, 2H, H-5, H-8), 1.93 – 1.78 (m, 2H, H-6, H-7) ppm; **²H NMR (500 MHz, CHCl₃ + CDCl₃)** δ = 8.89 (br s, D-2), 2.93 (br s, D-5, D-8) 1.81 (br s, D-5, D-6) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 160.1 (qC-4), 156.0 (qC-11), 155.6 (qC-10), 139.6 (t, *J_D* = 28 Hz, CH/D-2), 127.4 (CH-15), 123.6 (CH-14), 122.4 (qC-12), 121.0 (CH-13), 118.6 (qC-3), 116.8 (qC-9), 111.8 (CH-16), 32.0 (t, *J_D* = 20 Hz, C(5)-H/D), 22.5 (t, *J_D* = 20 Hz, C(6)-H/D), 21.8 (t, *J_D* = 20 Hz, C(8)-H/D), 22.0 (t, *J_D* = 20 Hz, C(7)-H/D) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. For [C₁₅H₉D₅NO]⁺: 229.1384; found: 229.1381.

Synthesis of Quinolines

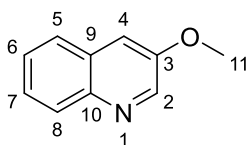
4-Methoxyquinoline (**9**)^[4]



To MeOH (10 mL) at 0 °C was added sodium metal (0.500 g, 45.0 mmol, 15 eq.) and let stir until the sodium metal was consumed. To the resulting sodium methanolate was added 4-chloroquinoline (0.500 g, 3.06 mmol, 1eq.) in MeOH (5 mL) and the mixture was heated to 80 °C and let stir for 16 hours. The reaction was cooled to 0 °C and water was added and then extracted with Et₂O. The organic layer was washed with water and brine, dried over MgSO₄ and evaporated under vacuum. The crude mixture was purified by column chromatography in Et₂O (100%) to yield **9**.

Light brown oil; 81% (0.317 g); **¹H NMR (400 MHz, CDCl₃)** δ = 8.72 (d, 1H, *J* = 5.2 Hz, H-2), 8.18 (d, 1H, *J* = 8.4 Hz, H-5), 8.04 (d, 1H, *J* = 8.4 Hz, H-8), 7.68 (overlapping ddd, 1H, *J* = 1.2, 7.0, 8.4 Hz, H-7), 7.48 (overlapping ddd, 1H, *J* = 0.7, 7.0, 8.2 Hz, H-6), 6.68 (d, 1H, *J* = 5.2 Hz, H-3), 3.99 (s, 3H, CH₃-11) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 162.3 (qC-4), 151.3 (CH-2), 149.1 (qC-10), 129.7 (CH-7), 128.8 (CH-8), 125.6 (CH-6), 121.8 (CH-5), 121.4 (qC-9), 100.0 (CH-3), 55.6 (C(11)-H₃) ppm; **HRMS** (ESI-TOF positive mode) *m/z*: [M + H]⁺ calcd. for: [C₁₀H₁₀NO]⁺: 160.0757; found: 160.0760.

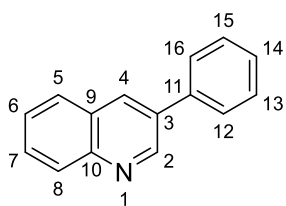
3-Methoxyquinoline (**12**)^[5]



To MeOH (7 mL) at 0 °C was added sodium metal (0.500 g, 45.0 mmol, 18.8 eq.) and was let stir until the sodium metal as consumed. To the sodium methanolate solution was added 3-bromoquinoline (0.500 g, 2.40 mmol, 1 eq.) in dimethylformamide (5 mL) and copper iodide (23 mg, 0.12 mmol, 5 mol%). The mixture was refluxed at 180 °C for 48 h. The reaction was then cooled to 0 °C and water was added and the mixture was extracted with Et₂O. The organic layer was washed with water and brine, dried over MgSO₄ and evaporated under vacuum. The crude mixture was purified by column chromatography in Et₂O (100%) to yield **12**.

Colourless oil; 45% (0.173 g); **¹H NMR (500 MHz, CDCl₃)** δ = 8.68 (d, 1H, *J* = 2.9 Hz, H-2), 8.04 (ddd, 1H, *J* = 0.8, 1.5, 8.3 Hz, H-8), 7.73 (dd, 1H, *J* = 1.5, 8.0 Hz, H-5), 7.55 (ddd, 1H, *J* = 1.5, 6.8, 8.3 Hz, H-7), 7.50 (ddd, 1H, *J* = 1.5, 7.0, 8.3 Hz, H-6), 7.37 (d, 1H, *J* = 2.9 Hz, H-4), 3.94 (s, 3H, CH₃-11) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 153.1 (qC-3), 144.6 (CH-2), 143.5 (qC-10), 129.2 (CH-8), 128.8 (qC-9), 127.1 (CH-6), 126.7 (one of CH-5 or CH-7), 126.6 (one of CH-5 or CH-7), 112.2 (CH-4), 55.5 (C(11)-H₃) ppm; **HRMS** (ESI-TOF positive mode) *m/z*: [M + H]⁺ calcd. for: [C₁₀H₁₀NO]⁺: 160.0757; found: 160.0756.

3-Phenylquinoline (13)

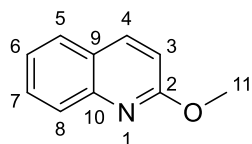


To a mixture of degassed THF (8 mL) and water (8 mL) was added 3-bromoquinoline (1.0 g, 4.81 mmol, 1 eq.), phenyl boronic acid (0.665 g, 5.29, 1.1 eq.), K_2CO_3 (1.33 g, 9.62 mmol, 2 eq.) and $Pd(PPh_3)_4$ (0.556 g, 0.481 mmol, 10 mol %). The reaction mixture was heated to 80 °C and stirred for 24 hours.

The cooled reaction mixture was purified by column chromatography in DCM (100%) to yield **13**.

Light brown solid; 82% (0.820 g); **m.p.** 49 - 51 °C (lit. m.p. 50 – 51 °C)^[6]; **1H NMR (400 MHz, $CDCl_3$)** δ = 9.19 (d, 1H, J = 2.2 Hz, H-2), 8.29 (d, 1H, J = 2.0 Hz, H-4), 8.14 (d, 1H, J = 8.6 Hz, H-8), 7.87 (d, 1H, J = 8.3 Hz, H-5), 7.66 – 7.76 (m, 3H, H-7, H-12, H-16), 7.61 – 7.48 (m, 3H, H-6, H-13, H-15), 7.43 (t, 1H, J = 7.4 Hz, H-14) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 150.0 (CH-2), 147.4 (qC-10), 137.9 (qC-11), 133.9 (qC-3), 133.2 (CH-4), 129.4 (CH-7), 129.3 (CH-8), 129.2 (2 $\times$ CH-13, CH-15), 128.1 (CH-14), 128.04 (qC-9), 128.01 (CH-5), 127.4 (2 $\times$ CH-12, CH-16), 127.0 (CH-7) ppm; **HRMS** (ESI-TOF positive mode) m/z : $[M + H]^+$ calcd. for: $[C_{15}H_{12}N]^+$: 206.0964; found: 206.0966.

2-Methoxyquinoline (S8)^[7]

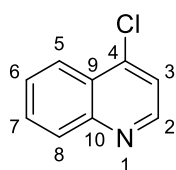


To MeOH (10 mL) at 0 °C was added sodium metal (0.500 g, 45.0 mmol, 15 eq.) and let stir until the sodium metal was consumed. To the resulting sodium methanolate was added 2-chloroquinoline (0.500 g, 3.06 mmol, 1 eq) and the mixture was heated to 80 °C

and let stir for 16 hours. Water was added to the mixture and was extracted with Et_2O . The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated under vacuum. The crude mixture was purified by column chromatography in Et_2O (100%) to yield **S8**.

Colourless oil; 83% (0.404 g); **1H NMR (500 MHz, $CDCl_3$)** δ = 7.85 (d, 1H, J = 8.9 Hz, H-4), 7.77 (d, 1H, J = 8.5 Hz, H-8), 7.59 (dd, 1H, J = 1.3, 8.0 Hz, H-5), 7.51 (ddd, 1H, J = 1.5, 7.0, 8.4 Hz, H-7), 7.26 (ddd, 1H, J = 1.2, 7.0, 8.1 Hz, H-6), 6.79 (d, 1H, J = 8.9 Hz, H-3), 3.98 (s, 3H, CH_3 -11) ppm; **^{13}C NMR (125 MHz, $CDCl_3$)** δ = 162.4 (qC-2), 146.6 (qC-10), 138.6 (CH-4), 129.5 (CH-7), 127.4 (CH-5), 127.3 (CH-8), 125.1 (qC-9), 124.0 (CH-6), 113.1 (CH-3), 53.4 (C(11)-H₃) ppm; **HRMS** (ESI-TOF positive mode) m/z : $[M + H]^+$ calcd. for: $[C_{10}H_{10}NO]^+$: 160.0757; found: 160.0755.

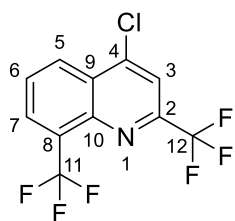
4-Chloroquinoline (**S9**)^[8]



A mixture of 4-quinolinol (2.00 g, 13.8 mmol, 1 eq.) and phosphoryl chloride (6.40 mL, 69.0 mmol, 5 eq.) was stirred at 110 °C for 4 hours. The crude mixture was poured onto ice and neutralised with solid sodium bicarbonate. The neutralised aqueous mix was extracted with DCM. The organic layers were combined and washed with aqueous sodium bicarbonate, water, and brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to yield the final product **S9**.

Yellow solid, 80% (1.80 g); **m.p.** 27 – 28 °C (lit. m.p. 27 – 28 °C)^[2]; **¹H NMR (300 MHz, CDCl₃)** δ = 8.79 (d, 1H, *J* = 4.6 Hz, H-2), 8.25 (dd, 1H, *J* = 1.0, 8.4 Hz, H-5), 8.14 (dd, 1H, *J* = 0.6, 8.4 Hz, H-8), 7.79 (ddd, 1H, *J* = 1.4, 6.9, 8.4 Hz, H-7), 7.66 (ddd, 1H, *J* = 1.4, 6.9, 8.4 Hz, H-6), 7.50 (d, 1H, *J* = 4.6 Hz, H-3) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 149.8 (CH-2), 149.1 (qC-10), 142.6 (qC-4), 130.4 (CH-7), 129.8 (CH-8), 127.6 (CH-6), 126.5 (qC-9), 124.1 (CH-5), 121.2 (CH-3) ppm; **HRMS** (ESI-TOF positive mode) *m/z*: [M+H]⁺ calcd. for: [C₉H₇Cl³⁵N]⁺: 164.0267; found: 164.0261.

4-Chloro-2,8-bis(trifluoromethyl)quinoline (**S10**)^[9]



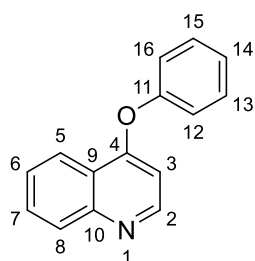
A mixture of 2,8-bis(trifluoromethyl)-4-quinolinol (1.50 g, 6.88 mmol, 1 eq.) and phosphoryl chloride (3.21 mL, 34.38 mmol, 5 eq.) was stirred at 110 °C for 4 hours. The crude mixture was poured onto ice and neutralised with solid sodium bicarbonate. The neutralised aqueous mix was extracted with DCM. The organic layers were combined and washed with aqueous sodium bicarbonate, water, and brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to yield the final product **S10**.

Off-white solid; 75% (1.53 g); **m.p.** 47 – 49 °C (lit. m.p. 49 – 51 °C)^[9]; **¹H NMR (500 MHz, CDCl₃)** δ = 8.50 (dd, 1H, *J* = 1.0, 8.4 Hz, H-5), 8.23 (d, 1H, *J* = 8.4 Hz, H-7), 7.92 (s, 1H, H-3), 7.83 (t, 1H, *J* = 8.0 Hz, H-6) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 148.3 (q, *J*_(C, F) = 36 Hz, qC-2), 145.0 (qC-4), 144.3 (qC-10), 130.1 (q, *J*_(C, F) = 5 Hz, CH-7), 129.3 (q, *J*_(C, F) = 31 Hz, qC-8), 128.4 (CH-5), 128.3 (CH-6), 127.5 (qC-9), 123.2 (q, *J*_(C, F) = 275 Hz, qC-11), 120.6 (q, *J*_(C, F) = 275 Hz, qC-12), 118.2 (q, *J*_(C, F) = 2 Hz, CH-3) ppm; **¹⁹F NMR (471 MHz, CDCl₃)** δ = –60.3 (CF₃), –68.0 (CF₃) ppm; **HRMS** (ESI-TOF positive mode) *m/z*: [M + H]⁺ calcd. for: [C₁₁H₅Cl³⁵F₆N]⁺: 300.0009; found: 300.0007.

Synthesis of Phenoxyquinoline Intermediates

4-phenoxyquinoline (**10**)

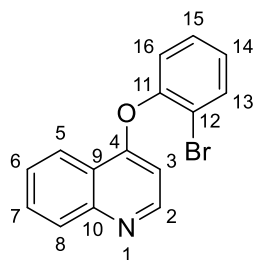
Synthesis of substrate **10** as per general procedure 1 using 4-chloroquinoline **S9** (0.500 g, 3.06 mmol), phenol (1.0 g, 10.7 mmol) and NaOH (0.184 g, 4.59 mmol).



Orange oil; 90% (0.609 g); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.65 (d, 1H, J = 5.2 Hz, H-2), 8.36 (dd, 1H, J = 1.1, 8.3 Hz, H-5), 8.10 (d, 1H, J = 8.5 Hz, H-8), 7.73 (overlapping ddd, 1H, J = 1.5, 6.9, 8.5 Hz, H-7), 7.55 (overlapping ddd, 1H, J = 1.2, 6.9, 8.2 Hz, H-6), 7.40 – 7.48 (m, 2H, H-13, H-15), 7.23 – 7.31 (m, 1H, H-14), 7.14 – 7.20 (m, 2H, H-12, H-16), 6.53 (d, 1H, J = 5.2 Hz, H-3) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 161.9 (qC-4), 154.4 (qC-11), 151.1 (CH-2), 149.8 (qC-10), 130.3 (2 $\times$ CH-13, CH-15), 130.1 (CH-7), 129.1 (CH-8), 126.1 (CH-6), 125.6 (CH-14), 121.8 (CH-5), 121.5 (qC-9), 121.1 (2 $\times$ CH-12, CH-16), 104.4 (CH-3) ppm; **LRMS**: m/z (ESI+): 222 [(M + H) $^+$, 100%].

4-(2-Bromophenoxy)quinoline (**S11**)

Synthesis of substrate **S11** as per general procedure 1 using 4-chloroquinoline **S9** (1.0 g, 6.12 mmol), 2-bromophenol (3.71 g, 21.4 mmol) and NaOH (0.367 g, 9.2 mmol).

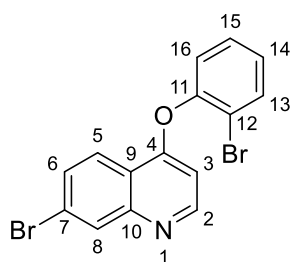


Off-white solid; 85% (1.56 g); **m.p.** 63 – 64 $^{\circ}\text{C}$ (lit. **m.p.** 62 – 64 $^{\circ}\text{C}$)^[1a]; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.67 (d, 1H, J = 5.1 Hz, H-2), 8.42 (dd, 1H, J = 1.2, 8.4 Hz, H-5), 8.12 (d, 1H, J = 8.4 Hz, H-8), 7.77 (overlapping ddd, 1H, J = 1.5, 6.8, 8.4 Hz, H-7), 7.71 (dd, 1H, J = 1.5, 8.0 Hz, H-13), 7.60 (overlapping ddd, 1H, J = 1.2, 7.0, 8.2 Hz, H-6), 7.40 (ddd, 1H, J = 1.5, 7.4, 8.2 Hz, H-15), 7.15 – 7.25 (m, 2H, H-14, H-16), 6.41 (d, 1H, J = 5.1 Hz, H-3) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 160.7 (qC-4), 151.2 (qC-11), 151.0 (CH-2), 149.8 (qC-10), 134.3 (CH-13), 130.2 (CH-7), 129.2 (CH-15), 129.1 (CH-8), 127.3 (CH-14), 126.3 (CH-6), 123.2 (CH-16), 121.9 (CH-5), 121.1 (qC-9), 116.3 (qC-12), 103.7 (CH-3) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H] $^+$ calcd. for $[\text{C}_{15}\text{H}_{11}\text{Br}^{79}\text{NO}]^+$: 300.0019; found: 300.0016.

7-Bromo-4-(2-bromophenoxy)quinoline (**S12**)

Synthesis of substrate **S12** as per general procedure 1 using 4-chloro-7-bromoquinoline (0.291 g, 1.19 mmol), 2-bromophenol (0.720 g, 4.17 mmol) and NaOH (0.714 g, 1.79 mmol).

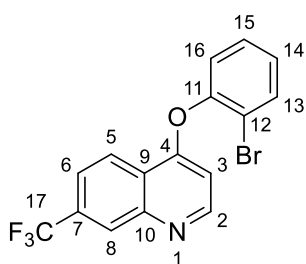
Brown solid; 90% (0.409 g); **m.p.** 72 – 73 $^{\circ}\text{C}$ (lit. **m.p.** 73 – 74 $^{\circ}\text{C}$)^[1b]; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.65 (d, 1H, J = 5.2 Hz, H-2), 8.29 (s, 1H, H-8, overlapping with doublet from



H-5), 8.28 (d, 1H, $J = 7.5$ Hz, H-5, overlapping with singlet from H-8), 7.71 (dd, 1H, $J = 1.5, 8.0$ Hz, H-6), 7.68 (dd, 1H, $J = 2.0, 8.9$ Hz, H-13), 7.42 (ddd, 1H, $J = 1.5, 7.5, 8.9$ Hz, H-15), 7.19 – 7.26 (m, 2H, H-14, H-16), 6.40 (d, 1H, $J = 5.2$ Hz, H-3) ppm; ^{13}C NMR (125 MHz, CDCl_3) $\delta = 160.8$ (qC-4), 152.1 (CH-2), 150.8 (qC-11), 150.5 (qC-10), 134.4 (CH-13), 131.4 (CH-8), 129.8 (CH-6), 129.3 (CH-15), 127.5 (CH-14), 124.6 (qC-7), 123.5 (CH-5), 123.3 (CH-16), 119.7 (qC-9), 116.3 (qC-12), 103.9 (CH-3) ppm; HRMS (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{15}\text{H}_{10}\text{Br}^{79}\text{NO}]^+$: 377.9129; found: 377.9119.

4-(2-Bromophenoxy)-7-(trifluoromethyl)quinoline (S13)

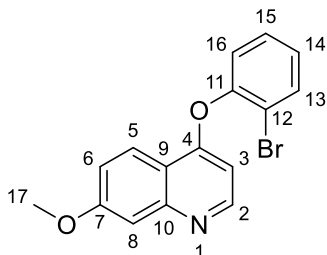
Synthesis of substrate **S13** as per general procedure 1 using 4-chloro-7-trifluoromethylquinoline (1.06 g, 4.58 mmol), 2-bromophenol (2.77 g, 16.03 mmol) and NaOH (0.275 g, 6.87 mmol).



Orange viscous oil; 85% (1.44 g); ^1H NMR (400 MHz, CDCl_3) $\delta = 8.75$ (d, 1H, $J = 5.1$ Hz, H-2), 8.55 (d, 1H, $J = 8.7$ Hz, H-5), 8.42 (s, 1H, H-8), 7.77 (dd, 1H, $J = 1.2, 8.7$ Hz, H-6), 7.72 (dd, 1H, $J = 1.3, 8.0$ Hz, H-13), 7.47–7.38 (m, 1H, H-15), 7.31–7.17 (m, 2H, H-14, H-16), 6.50 (d, 1H, $J = 5.1$ Hz, H-3) ppm; ^{13}C NMR (101 MHz, CDCl_3) $\delta = 160.7$ (qC-4), 152.5 (CH-2), 150.7 (qC-11), 148.9 (qC-10), 134.5 (CH-13), 132.1 (q, $^2J_{\text{C,F}} = 33$ Hz, qC-7), 129.4 (CH-15), 127.8 (CH-14), 127.0 (q, $^3J_{\text{C,F}} = 4$ Hz, CH-8), 124.0 (q, $^1J_{\text{C,F}} = 273$ Hz, qC-17), 123.5 (CH-5), 123.4 (CH-16), 122.7 (qC-9), 122.0 (q, $^3J_{\text{C,F}} = 3$ Hz, CH-6), 116.4 (qC-12), 105.06 (CH-3) ppm; ^{19}F NMR (376 MHz, CDCl_3) $\delta = -62.7$ (CF_3 -17) ppm; HRMS (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{16}\text{H}_{10}\text{Br}^{79}\text{F}_3\text{NO}]^+$: 367.9892; found: 367.9895.

4-(2-Bromophenoxy)-7-methoxyquinoline (S14)

Synthesis of substrate **S14** as per general procedure 1 using 4-chloro-7-methoxyquinoline (0.950 g, 14.9 mmol), 2-bromophenol (9.02 g, 9.02 mmol) and NaOH (0.294 g, 7.36 mmol).

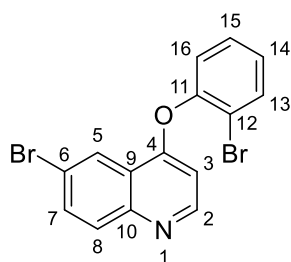


Brown solid; 94% (0.153 g); m.p. 101 – 102 °C (lit. m.p. 99 – 100 °C)^[1a]; ^1H NMR (300 MHz, CDCl_3) $\delta = 8.59$ (d, 1H, $J = 5.2$ Hz, H-2), 8.29 (d, 1H, $J = 9.2$ Hz, H-5), 7.71 (dd, 1H, $J = 1.5, 8.0$ Hz, H-13), 7.45–7.36 (m, 2H, H-8, H-15), 7.28–7.15 (m, 3H, H-6, H-14, H-16), 6.29 (d, 1H, $J = 5.2$ Hz, H-3), 3.97 (s, 3H, CH_3 -17) ppm; ^{13}C NMR (75 MHz, CDCl_3) $\delta = 161.5$ (qC-7), 160.8 (qC-4), 151.9 (qC-10), 151.6 (CH-2), 151.3 (qC-11), 134.4 (CH-13), 129.2 (CH-15), 127.3 (CH-14), 123.3

(CH-16), 123.2 (CH-5), 119.3 (CH-6), 116.4 (qC-12), 115.9 (qC-9), 107.4 (CH-8), 102.5 (CH-3), 55.6 (C(17)-H₃) ppm; **LRMS**: m/z (ESI⁺): 330 [(M + H)⁺, 100%].

6-Bromo-4-(2-bromophenoxy)quinoline (S15)

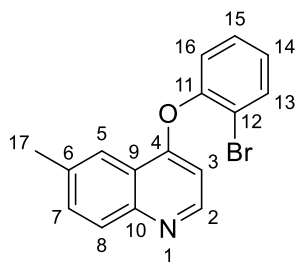
Synthesis of substrate **S15** as per general procedure 1 using 4-chloro-6-bromoquinoline (0.804 g, 3.32 mmol), 2-bromophenol (2.01 g, 11.62 mmol) and NaOH (0.199 g, 4.97 mmol).



Orange solid; 97% (1.21 g); **m.p.** 95 – 97 °C (lit. m.p. 97 – 98 °C)^[1b]; **¹H NMR (400 MHz, CDCl₃)** δ = 8.67 (br s, 1H, H-2), 8.58 (d, 1H, J = 2.1 Hz, H-5), 7.97 (d, 1H, J = 9.0 Hz, H-8), 7.83 (dd, 1H, J = 2.1, 9.0 Hz, H-7), 7.75–7.71 (m, 1H, H-13), 7.46–7.40 (m, 1H, H-15), 7.28–7.20 (m, 2H, H-14, H-16), 6.40 (d, 1H, J = 5.1 Hz, H-3) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 160.0 (qC-4), 151.5 (CH-2), 150.9 (qC-11), 148.5 (qC-10), 134.5 (CH-13), 133.8 (CH-7), 131.0 (CH-8), 129.4 (CH-15), 127.7 (CH-14), 124.5 (CH-5), 123.4 (CH-16), 122.3 (qC-9), 120.5 (qC-6), 116.5 (qC-12), 104.3 (CH-3) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₅H₁₀Br⁷⁹₂NO]⁺: 377.9124; found: 377.9122.

4-(2-Bromophenoxy)-6-methylquinoline (S16)

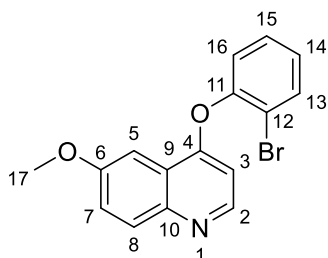
Synthesis of substrate **S16** as per general procedure 1 using 4-chloro-6-methylquinoline (0.469 g, 2.64 mmol), 2-bromophenol (1.60 g, 9.24 mmol) and NaOH (0.166 g, 4.15 mmol).



Yellow viscous oil; 84% (0.694 g); **¹H NMR (300 MHz, CDCl₃)** δ = 8.61 (d, 1H, J = 4.6 Hz, H-2), 8.18 (s, 1H, H-5), 8.00 (d, 1H, J = 8.6 Hz, H-8), 7.72 (dd, 1H, J = 1.6, 7.9 Hz, H-13), 7.60 (dd, 1H, J = 2.0, 8.6 Hz, H-7), 7.41 (ddd, 1H, J = 1.6, 7.3, 8.1 Hz, H-15), 7.24–7.14 (m, 2H, H-14, H-16), 6.37 (d, 1H, J = 5.1 Hz, H-3), 2.59 (s, 3H, CH₃-17) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 160.4 (qC-4), 151.42 (qC-11), 150.2 (CH-2), 148.6 (qC-10), 136.4 (qC-6), 134.4 (CH-13), 132.6 (CH-7), 129.3 (CH-15), 129.0 (CH-8), 127.3 (CH-14), 123.3 (CH-16), 121.1 (qC-9), 120.7 (CH-5), 116.5 (qC-12), 104.0 (CH-3), 22.0 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₆H₁₃Br⁷⁹NO]⁺: 314.0175; found: 314.0177.

4-(2-Bromophenoxy)-6-methoxyquinoline (S17)

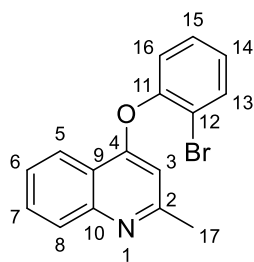
Synthesis of substrate **S17** as per general procedure 1 using 4-chloro-6-methoxyquinoline (1.75 g, 9.03 mmol), 2-bromophenol (7.82 g, 45.2 mmol) and NaOH (0.540 g, 13.5 mmol).



Brown oil; 91% (2.70 g); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.54 (d, 1H, J = 5.1 Hz, H-2), 8.01 (d, 1H, J = 9.2 Hz, H-8), 7.72 (dd, 1H, J = 1.5, 8.0 Hz, H-13), 7.64 (d, 1H, J = 2.8 Hz, H-5), 7.45–7.38 (m, 2H, H-7, H-15), 7.26–7.16 (m, 2H, H-14, H-16), 6.40 (d, 1H, J = 5.1 Hz, H-3), 3.98 (s, 3H, CH_3 -17) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ = 159.8 (qC-4), 157.9 (qC-6), 151.4 (qC-11), 148.5 (CH-2), 146.0 (qC-10), 134.4 (CH-13), 130.8 (CH-8), 129.3 (CH-15), 127.3 (CH-14), 123.3 (CH-16), 123.0 (CH-7), 121.9 (qC-9), 116.5 (qC-12), 104.3 (CH-3), 99.5 (CH-5), 55.8 (C(17)-H₃) ppm; **LRMS**: m/z (ESI⁺): 330, [(M + H)⁺, 100%].

4-(2-Bromophenoxy)-2-methylquinoline (S18)

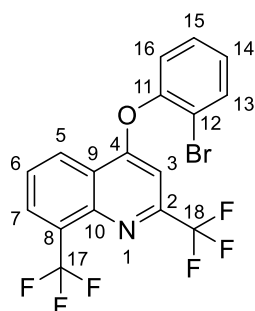
Synthesis of substrate **S18** as per general procedure 1 using 4-chloro-2-methylquinoline (0.500 g, 2.81 mmol), 2-bromophenol (1.70 g, 9.85 mmol) and NaOH (0.169 g, 4.20 mmol).



Off-white solid; 79% (0.667 g); **m.p.** 94 – 96 °C (lit. m.p. 98 – 101 °C)^[1a]; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 8.34 (d, 1H, J = 8.5 Hz, H-5), 8.02 (d, 1H, J = 8.5 Hz, H-8), 7.68 – 7.77 (m, 2H, H-7, H-13), 7.53 (t, 1H, J = 7.5 Hz, H-6), 7.42 (t, 1H, J = 8.1 Hz, H-15), 7.17 – 7.25 (m, 2H, H-14, H-16), 6.28 (s, 1H, H-3), 2.59 (s, 1H, CH_3 -17) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 160.8 (qC-4), 159.9 (qC-2), 151.3 (qC-11), 149.4 (qC-10), 134.3 (CH-13), 130.2 (CH-7), 129.1 (CH-15), 128.3 (CH-8), 127.1 (CH-14), 125.4 (CH-6), 123.2 (CH-16), 121.7 (CH-5), 119.5 (qC-9), 116.3 (qC-12), 104.2 (CH-3), 25.7 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₆H₁₃Br⁷⁹NO]⁺: 314.0175; found: 314.0183.

4-(2-Bromophenoxy)-2,8-bis(trifluoromethyl)quinoline (S19)

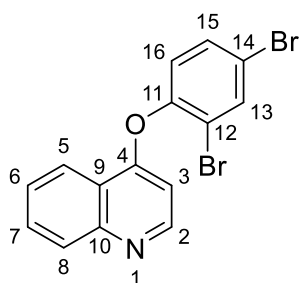
Synthesis of substrate **S19** as per general procedure 1 using quinoline **S10** (1.40 g, 4.67 mmol), 2-bromophenol (4.04 g, 23.4 mmol) and NaOH (0.280 g, 7 mmol).



White solid; 59% (1.20 g); **m.p.** 77 – 79 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2982, 2867, 1591, 1313, 1238, 1133, 1108, 708; **^1H NMR (500 MHz, CDCl_3)** δ = 8.70 (dd, 1H, J = 0.8, 8.4 Hz, H-5), 8.22 (d, 1H, J = 7.4 Hz, H-7), 7.80 – 7.74 (m, 2H, H-6, H-13), 7.49 (dt, 1H, J = 1.6, 7.8 Hz, H-15), 7.32 – 7.27 (m, 2H, H-14, H-16), 6.75 (s, 1H, H-3) ppm; **^{13}C NMR (600 MHz, CDCl_3)** δ = 162.3 (qC-4), 150.1 (qC-10), 149.5 (q, $^2J_{\text{C}, \text{F}}$ = 35 Hz, qC-2), 145.1 (qC-11), 134.7 (CH-13), 129.8 (q, $^3J_{\text{C}, \text{F}}$ = 6 Hz, CH-7), 129.6 (CH-15), 128.6 (q, $^2J_{\text{C}, \text{F}}$ = 28 Hz, qC-8), 128.3 (CH-14), 126.8 (CH-6), 126.3 (CH-5), 123.5 (q, $^1J_{\text{C}, \text{F}}$ = 274 Hz, C(17)-F₃), 123.2 (CH-16), 121.9 (qC-9) 120.9 (q, $^1J_{\text{C}, \text{F}}$ = 275 Hz, C(18)-F₃), 116.1 (qC-12), 100.1 (q, $^3J_{\text{C}, \text{F}}$ = 2 Hz, CH-3) ppm; **^{19}F NMR (282 MHz, CDCl_3)** δ = -60.4 (CF₃), -68.1 (CF₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₇H₉Br⁷⁹F₆NO]⁺: 435.9766; found: 439.9765.

4-(2,4-dibromophenoxy)quinoline (S20)

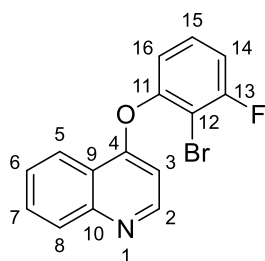
Synthesis of substrate **S20** as per general procedure 1 using 4-chloroquinoline **S9** (1.00 g, 6.14 mmol), 2,4-dibromophenol (5.41 g, 21.48 mmol) and NaOH (0.37 g, 9.21 mmol).



White solid; 95%, (2.21 g); **m.p.** 123 – 125 °C (lit: 125 – 126 °C)^[1b] **^1H NMR (300 MHz, CDCl_3)** δ = 8.69 (d, 1H, J = 5.1 Hz, H-2), 8.38 (dd, 1H, J = 0.9, 8.4 Hz, H-5), 8.12 (d, 1H, J = 8.4 Hz, H-8), 7.88 (d, 1H, J = 2.3 Hz, H-13), 7.79 (ddd, 1H, J = 1.3, 7.0, 8.4 Hz, H-7), 7.62 (ddd, 1H, J = 1.3, 7.0, 8.4 Hz, H-6), 7.54 (dd, 1H, J = 2.3, 8.6 Hz, H-15), 7.12 (d, 1H, J = 8.6 Hz, H-16), 6.43 (d, 1H, J = 5.1 Hz, H-3) ppm; **^{13}C NMR (75 MHz, CDCl_3)** δ = 160.3 (qC-4), 150.9 (CH-2), 150.6 (qC-11), 149.8 (qC-10), 136.6 (CH-13), 132.3 (CH-15), 130.4 (CH-7), 129.2 (CH-8), 126.5 (CH-6), 124.2 (CH-16), 121.7 (CH-5), 120.9 (qC-9), 119.3 (qC-14), 117.3 (qC-12), 103.8 (CH-3) ppm; **LRMS** m/z (ESI+) 378, 380, 372 [(M+H)⁺, 100%].

4-(2-Bromo-3-fluorophenoxy)quinoline (S21)

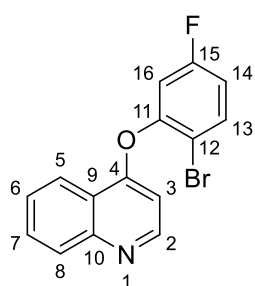
Synthesis of substrate **S21** as per general procedure 1 using 4-chloroquinoline **S9** (1.20 g, 7.33 mmol), 2-bromo-3-fluorophenol (5.0 g, 25.7 mmol) and NaOH (0.440 g, 11.0 mmol).



Green oil; 95% (2.22 g); IR $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3071, 1501, 1460, 1306, 1237, 1097, 699; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.70 (d, 1H, J = 5.2 Hz, H-2), 8.38 (dd, 1H, J = 1.5, 8.4 Hz, H-5), 8.12 (d, 1H, J = 8.4 Hz, H-8), 7.78 (overlapping ddd, 1H, J = 1.5, 6.9, 8.4 Hz, H-7), 7.61 (overlapping ddd, 1H, J = 1.1, 6.9, 8.2 Hz, H-6), 7.37 (overlapping dt, 1H, J = 6.0, 8.2 Hz, H-15), 7.10 (td, 1H, J = 1.4, 8.2 Hz, H-14), 7.03 (dt, 1H, J = 1.4, 8.2 Hz, H-16), 6.46 (d, 1H, J = 5.2 Hz, H-3) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 160.6 (d, $^1J_{\text{C,F}}$ = 250 Hz, qC-13), 160.3 (qC-4), 152.8 (d, $^3J_{\text{C,F}}$ = 3 Hz, qC-11), 151.0 (CH-2), 149.9 (qC-10), 130.3 (CH-7), 129.2 (CH-8), 129.1 (CH-15), 126.5 (CH-6), 121.7 (CH-5), 121.0 (qC-9), 118.2 (d, $^4J_{\text{C,F}}$ = 3 Hz, CH-16), 113.6 (d, $^2J_{\text{C,F}}$ = 22 Hz, CH-14), 104.6 (d, $^2J_{\text{C,F}}$ = 23 Hz, qC-12), 104.1 (CH-3) ppm; $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ = -103.3 (CF-13) ppm; HRMS (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{15}\text{H}_{10}\text{Br}^{79}\text{FNO}]^+$: 317.9924; found: 317.9921.

4-(2-Bromo-5-fluorophenoxy)quinoline (S22)

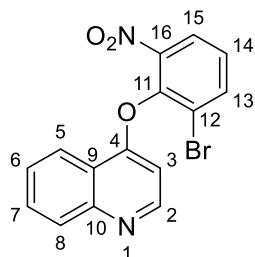
Synthesis of substrate **S22** as per general procedure 1 using 4-chloroquinoline **S9** (0.700 g, 4.27 mmol), 2-bromo-5-fluorophenol (2.86 g, 15.0 mmol) and NaOH (0.264 g, 6.60 mmol).



White solid; 90% (1.26 g); m.p. 71 – 73 °C (lit. m.p. 77 – 78 °C)^[1a]; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.72 (d, 1H, J = 5.2 Hz, H-2), 8.36 (dd, 1H, J = 0.9, 8.4 Hz, H-5), 8.13 (d, 1H, J = 8.4 Hz, H-8), 7.79 (overlapping ddd, 1H, J = 1.5, 6.9, 8.4 Hz, H-7), 7.56 – 7.72 (m, 2H, H-6, H-13), 6.91 – 7.02 (m, 2H, H-14, H-16), 6.49 (d, 1H, J = 5.2 Hz, H-3) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 162.4 (d, $^1J_{\text{C,F}}$ = 250 Hz, qC-15), 160.1 (qC-4), 152.1 (d, $^3J_{\text{C,F}}$ = 11 Hz, qC-11), 151.0 (CH-2), 149.9 (qC-10), 134.8 (d, $^3J_{\text{C,F}}$ = 9 Hz, CH-13), 130.4 (CH-7), 129.2 (CH-8), 126.5 (CH-6), 121.7 (CH-5), 121.0 (qC-9), 114.5 (d, $^2J_{\text{C,F}}$ = 22 Hz, CH-14), 110.8 (d, $^2J_{\text{C,F}}$ = 25 Hz, CH-16), 110.7 (qC-12), 104.2 (CH-3) ppm; $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ = -111.0 (CF-15) ppm; HRMS (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{15}\text{H}_{10}\text{Br}^{79}\text{FNO}]^+$: 317.9924; found: 317.9922.

4-(2-Bromo-6-nitrophenoxy)quinoline (S23)

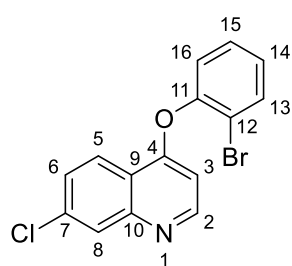
Synthesis of substrate **S23** as per general procedure 1 with the addition of 1,2-dichlorobenzene as solvent and stirred at 150 °C for 3 days. From 4-chloroquinoline **S9** (1.0 g, 6.11 mmol), 2-bromo-6-nitrophenol (0.666 g, 30.6 mmol) and NaOH (0.367 g, 9.16 mmol).



White solid; 85% (1.80 g); **m.p.** 107 – 109 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3058, 2894, 1564, 1535, 1306, 1254, 1231, 715; **¹H NMR (300 MHz, CDCl₃)** δ = 8.69 (d, 1H, J = 5.2 Hz, H-2), 8.39 (dd, 1H, J = 1.4 Hz, 8.4 Hz, H-5), 8.13 (d, 1H, J = 8.4 Hz, H-8), 8.05 (dd, 1H, J = 1.6, 8.3 Hz, H-15), 7.97 (dd, 1H, J = 1.6, 8.3 Hz, H-13), 7.80 (overlapping ddd, 1H, J = 1.6, 6.9, 8.3 Hz, H-7), 7.63 (overlapping ddd, 1H, J = 1.4, 6.9, 8.4 Hz, H-6), 7.39 (t, 1H, J = 8.3 Hz, H-14), 6.35 (d, 1H, J = 5.2 Hz, H-3) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 159.5 (qC-4), 150.7 (CH-2), 149.9 (qC-10), 144.5 (qC-16), 144.4 (qC-11), 138.7 (CH-13), 130.4 (CH-7), 129.1 (CH-8), 127.5 (CH-14), 126.6 (CH-6), 125.2 (CH-15), 121.8 (CH-5), 120.4 (qC-9), 120.0 (qC-12), 102.9 (CH-3) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[M + H]^+$ calcd. for $[\text{C}_{15}\text{H}_{10}\text{Br}^{79}\text{N}_2\text{O}_3]^+$: 344.9870; found: 344.9868.

4-(2-Bromophenoxy)-7-chloroquinoline (S24)

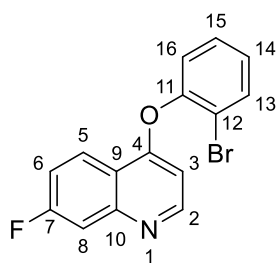
Synthesis of substrate **S24** as per general procedure 1 using 4,7-dichloroquinoline (3.01 g, 15.1 mmol), 2-bromophenol (9.14 g, 52.9 mmol) and NaOH (0.910 g, 22.8 mmol).



Yellow solid; 97% (4.91 g); **m.p.** 70 – 73 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2981, 1614, 1590, 1562, 1487, 1469, 1419, 1377, 1302, 1262, 1220, 1099, 1052, 1033, 1013, 858; **¹H NMR (400 MHz, CDCl₃)** δ = 8.66 (d, 1H, J = 4.5 Hz, H-2), 8.35 (d, 1H, J = 8.9 Hz, H-5), 8.10 (d, 1H, J = 1.9 Hz, H-8), 7.71 (dd, 1H, J = 1.4, 8.0 Hz, H-13), 7.54 (dd, 1H, J = 1.9, 8.9 Hz, H-6), 7.44–7.39 (m, 1H, H-15), 7.26–7.18 (m, 2H, H-14, H-16), 6.39 (d, 1H, J = 5.2 Hz, H-3) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 160.8 (qC-4), 152.3 (CH-2), 150.9 (qC-11), 150.3 (qC-10), 136.3 (qC-7), 134.5 (CH-13), 129.3 (CH-15), 128.2 (CH-8), 127.6 (CH-14), 127.3 (CH-6), 123.5 (CH-5), 123.3 (CH-16), 119.5 (qC-9), 116.4 (qC-12), 103.9 (CH-3) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[M + H]^+$ calcd. for $[\text{C}_{15}\text{H}_{10}\text{Br}^{79}\text{Cl}^{35}\text{NO}]^+$: 333.9629; found: 333.9626.

4-(2-Bromophenoxy)-6-fluoroquinoline (S25)

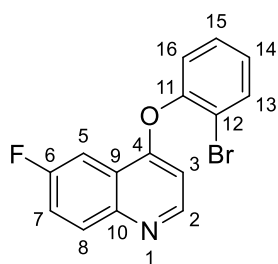
Synthesis of substrate **S25** as per general procedure 1 using 4-chloro-7-fluoroquinoline (0.525 g, 2.89 mmol), 2-bromophenol (1.75 g, 10.11 mmol) and NaOH (0.173 g, 4.34 mmol).



Orange solid; 91% (0.835 g); **m.p.** 77 – 79 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2981–2844, 1629, 1571, 1508, 1469, 1427, 1379, 1308, 1224, 1135, 1051, 875, 780, 741; **¹H NMR (300 MHz, CDCl₃)** δ = 8.66 (d, 1H, J = 5.2 Hz, H-2), 8.43 (dd, 1H, J = 6.1, 9.2 Hz, H-5), 7.76–7.70 (m, 2H, H-8, H-13), 7.47–7.34 (m, 2H, H-6, H-15), 7.28–7.18 (m, 2H, H-14, H-16), 6.37 (d, 1H, J = 5.2 Hz, H-3) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 163.8 (d, $^1J_{\text{C,F}}$ = 251 Hz, qC-7), 161.0 (d, $^5J_{\text{C,F}}$ = 1 Hz, qC-4), 152.5 (CH-2), 151.2 (d, $^3J_{\text{C,F}}$ = 13 Hz, qC-10), 151.0 (qC-11), 134.5 (CH-13), 129.4 (CH-15), 127.6 (CH-14), 124.5 (d, $^3J_{\text{C,F}}$ = 10 Hz, CH-5), 123.4 (CH-16), 118.1 (d, $^4J_{\text{C,F}}$ = 1 Hz, qC-9), 116.7 (d, $^2J_{\text{C,F}}$ = 25 Hz, CH-6), 116.5 (qC-12), 113.0 (d, $^2J_{\text{C,F}}$ = 21 Hz, CH-8), 103.3 (d, $^6J_{\text{C,F}}$ = 2 Hz, CH-3) ppm; **¹⁹F NMR (282 MHz, CDCl₃)** δ = –108.9 (CF-7) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₅H₁₀Br⁷⁹FNO]⁺: 317.9924; found: 317.9929.

4-(2-Bromophenoxy)-6-fluoroquinoline (S26)

Synthesis of substrate **S26** as per general procedure 1 using 4-chloro-6-fluoroquinoline (0.262 g, 1.44 mmol), 2-bromophenol (0.872 g, 5.04 mmol) and NaOH (0.086 g, 2.16 mmol).

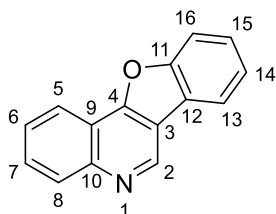


Orange solid; 78% (0.358 g); **m.p.** 81 – 83 °C (lit. m.p. 75 – 79 °C)^[1a]; **¹H NMR (300 MHz, CDCl₃)** δ = 8.64 (br s, 1H, H-2), 8.11 (dd, 1H, J = 5.2, 9.3 Hz, H-8), 8.01 (dd, 1H, J = 2.8, 9.3 Hz, H-5), 7.73 (dd, 1H, J = 1.4, 7.9 Hz, H-13), 7.54 (ddd, 1H, J = 2.8, 8.3, 9.2 Hz, H-7), 7.47–7.39 (m, 1H, H-15), 7.27–7.17 (m, 2H, H-14, H-16), 6.42 (d, 1H, J = 5.0 Hz, H-3) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 160.6 (d, $^1J_{\text{C,F}}$ = 248 Hz, qC-6), 160.4 (d, $^4J_{\text{C,F}}$ = 5 Hz, qC-4), 151.0 (qC-11), 150.4 (d, $^6J_{\text{C,F}}$ = 1 Hz, CH-2), 147.0 (qC-10), 134.5 (CH-13), 131.8 (d, $^3J_{\text{C,F}}$ = 9 Hz, CH-8), 129.38 (CH-15), 127.6 (CH-14), 123.4 (CH-16), 121.9 (d, $^3J_{\text{C,F}}$ = 11 Hz, qC-9), 120.5 (d, $^2J_{\text{C,F}}$ = 26 Hz, CH-7), 116.5 (qC-12), 105.8 (d, $^2J_{\text{C,F}}$ = 24 Hz, CH-5), 104.2 (CH-3) ppm; **¹⁹F NMR (282 MHz, CDCl₃)** δ = –112.7 (CF-6) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₅H₁₀Br⁷⁹FNO]⁺: 317.9924; found: 317.9925.

Synthesis of Benzofuroquinolines

Benzofuro[3,2-*c*]quinoline (1a)

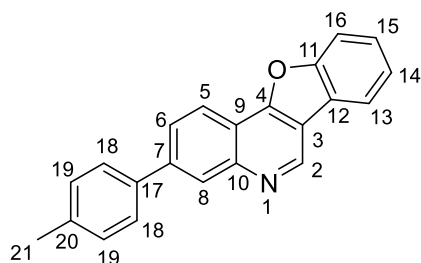
Synthesis of substrate **1a** as per general procedure 2 using **S11** (1.0 g, 3.33 mmol), TBABr (2.15 g, 6.66 mmol), Pd(OAc)₂ (0.037 g, 5 mol%), K₂CO₃ (0.921 g, 6.66 mmol) and *i*PrOAc (5 mL).



Off-white solid; 88% yield (1.42 g); **m.p.** 133 – 135 °C; (lit. m.p. 132 – 135 °C)^[1a]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.46 (br s, 1H, H-2), 8.38 (d, 1H, *J* = 7.6 Hz, H-5), 8.25 (d, 1H, *J* = 8.8 Hz, H-8), 8.06 (d, 1H, *J* = 7.6 Hz, H-13), 7.62 – 7.82 (m, 3H, H-6, H-7, H-16), 7.40 – 7.56 (m, 2H, H-14, H-15) ppm; **¹³C NMR (151 MHz, CDCl₃)** δ = 157.5 (qC-4), 156.0 (qC-11), 147.4 (qC-10), 144.4 (CH-2), 129.9 (CH-8), 129.3 (CH-7), 127.2 (CH-15), 127.0 (CH-6), 124.0 (CH-14), 122.7 (qC-12), 120.8 (CH-5), 120.6 (CH-13), 117.2 (qC-9), 116.3 (qC-3), 112.1 (CH-16) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₁₀NO]⁺: 220.0757; found: 220.0763.

3-(*p*-Tolyl)benzofuro[3,2-*c*]quinoline (1b)

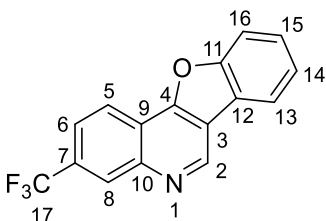
Synthesis of substrate **1b** as per general procedure 4 using **S12** (0.617 g, 1.63 mmol), Pd(OAc)₂ (0.018 g, 0.082 mmol), *p*-tolylboronic acid (0.244 g, 1.80 mmol), K₂CO₃ (0.450 g, 3.26 mmol) in NMP (2.44 mL).



Pale-yellow solid; 73% yield (0.366 g); **m.p.** 205 – 207 °C (lit. m.p. 200 – 202 °C)^[1b]; **¹H NMR (400 MHz, CDCl₃)** δ = 9.49 (s, 1H, H-2), 8.47 (d, 1H, *J* = 1.6 Hz, H-8), 8.44 (d, 1H, *J* = 8.5 Hz, H-5), 8.08 (dd, 1H, *J* = 0.7, 7.6 Hz, H-13), 7.94 (dd, 1H, *J* = 1.6, 8.5 Hz, H-6), 7.75 (d, 1H, *J* = 8.0 Hz, H-16), 7.69 (d, 2H, *J* = 8.0 Hz, H-18), 7.56–7.51 (m, 1H, H-15), 7.47 (td, 1H, *J* = 0.9, 7.6 Hz, H-14), 7.33 (d, 2H, *J* = 8.0 Hz, H-19), 2.44 (s, 3H, CH₃-21) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 157.6 (qC-4), 156.1 (qC-11), 148.0 (qC-10), 144.9 (CH-2), 142.2 (qC-8), 138.0 (qC-17), 137.5 (qC-20), 129.9 (2 × C, CH-19), 127.4 (2 × C, CH-18), 127.3 (CH-8), 127.3 (CH-15), 126.6 (CH-6), 124.2 (CH-14), 122.9 (qC-12), 121.3 (CH-5), 120.7 (CH-13), 116.3 (qC-3), 116.0 (qC-9), 112.2 (CH-16), 21.3 (C(21)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₂H₁₆NO]⁺: 310.1226; found: 310.1229.

3-(Trifluoromethyl)benzofuro[3,2-c]quinoline (1c)

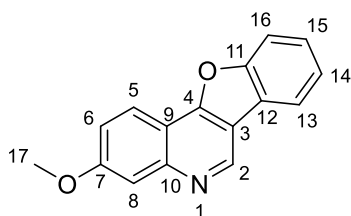
Synthesis of substrate **1c** as per general procedure 3 using **S13** (1.34 g, 3.63 mmol), Pd(OAc)₂ (0.041 g, 0.182 mmol), K₂CO₃ (1.00 g, 7.27 mmol) in NMP (5.50 mL).



Pale-yellow solid; 91% yield (0.951 g); **m.p.** 182 – 184 °C (lit. m.p. 182 – 185 °C)^[10]; **¹H NMR (400 MHz, CDCl₃)** δ = 9.57 (s, 1H, H-2), 8.56 (s, 1H, H-8), 8.51 (d, 1H, *J* = 8.6 Hz, H-5), 8.14–8.08 (m, 1H, H-13), 7.87 (dd, 1H, *J* = 1.6, 8.6 Hz, H-6), 7.78 (d, 1H, *J* = 8.3 Hz, H-16), 7.63–7.57 (m, 1H, H-15), 7.51 (td, 1H, *J* = 1.0, 7.5 Hz, H-14) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 156.8 (qC-4), 156.3 (qC-11), 146.3 (qC-10), 145.8 (CH-2), 131.1 (q, ²*J*_(C, F) = 33 Hz, qC-7), 128.1 (CH-15), 127.8 (q, ³*J*_(C, F) = 4 Hz, CH-8), 124.6 (CH-14), 124.1 (q, ¹*J*_(C, F) = 272 Hz, CF₃-17), 122.8 (q, ³*J*_(C, F) = 3 Hz, CH-6), 122.3 (qC-12), 122.1 (CH-5), 121.0 (CH-13), 118.9 (qC-9), 117.9 (qC-3), 112.4 (CH-16) ppm; **¹⁹F NMR (376 MHz, CDCl₃)** δ = –62.51 (CF₃-17) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₉F₃NO]⁺: 288.0631; found: 288.0630.

3-Methoxybenzofuro[3,2-c]quinoline (1d)

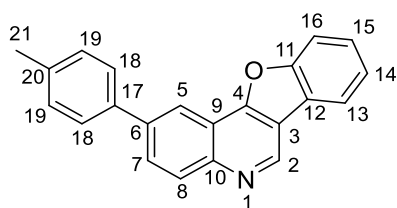
Synthesis of substrate **1d** as per general procedure 3 using **S14** (0.797 g, 2.41 mmol), Pd(OAc)₂ (0.028 g, 0.125 mmol), K₂CO₃ (0.671 g, 4.86 mmol) in NMP (3.62 mL).



Off-white solid; 86% yield (0.520 g); **m.p.** 150 – 151 °C (lit. m.p. 146 – 147 °C)^[1a]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.34 (s, 1H, H-2), 8.21 (d, 1H, *J* = 9.0 Hz, H-5), 7.98 (dd, 1H, *J* = 1.0, 7.5 Hz, H-13), 7.66 (d, 1H, *J* = 7.7 Hz, H-16), 7.55 (d, 1H, *J* = 2.5 Hz, H-8), 7.50–7.37 (m, 2H, H-14, H-15), 7.29 (dd, 1H, *J* = 2.5, 9.0 Hz, H-6), 3.96 (s, 3H, CH₃-17) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 160.8 (qC-7), 157.9 (qC-4), 155.9 (qC-11), 149.4 (qC-10), 144.7 (CH-2), 126.9 (CH-15), 124.1 (CH-14), 123.0 (qC-12), 122.0 (CH-5), 120.4 (CH-13), 119.9 (CH-6), 115.1 (qC-3), 112.1 (CH-16), 111.8 (CH-9), 108.5 (CH-8), 55.7 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₁₂NO₂]⁺: 250.0863; found: 250.0866.

2-(*p*-Tolyl)benzofuro[3,2-c]quinoline (1f)

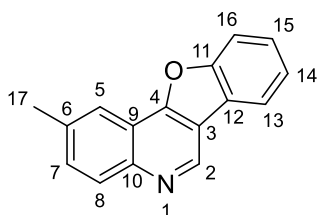
Synthesis of substrate **1f** as per general procedure 4 using **S15** (1.06 g, 2.79 mmol), Pd(OAc)₂ (0.031 g, 0.138 mmol), *p*-tolylboronic acid (0.417 g, 3.07 mmol), K₂CO₃ (0.771 g, 5.57 mmol) in NMP (4.20 mL).



Off-white solid; 22% yield (0.188 g); **m.p.** 180 – 182 °C (lit. m.p. 183 – 185 °C)^[1b]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.47 (s, 1H, H-2), 8.59 (d, 1H, J = 2.0 Hz, H-5), 8.31 (d, 1H, J = 8.8 Hz, H-8), 8.11 (d, 1H, J = 7.4 Hz, H-13), 8.04 (dd, 1H, J = 2.0, 8.8 Hz, H-7), 7.80–7.69 (m, 3H, H-16, H-18), 7.60–7.44 (m, 2H, H-14, H-15), 7.34 (d, 2H, J = 7.9 Hz, H-19), 2.45 (s, 3H, CH₃-21) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 157.7 (qC-4), 156.1 (qC-11), 146.7 (qC-10), 144.2 (CH-2), 139.8 (qC-6), 138.0 (qC-20), 137.3 (qC-17), 130.3 (CH-8), 129.9 (2 $\times$ C, CH-19), 128.9 (CH-7), 127.5 (2 $\times$ C, CH-18), 127.4 (CH-15), 124.2 (CH-14), 122.9 (qC-12), 120.8 (CH-13), 118.1 (CH-5), 117.5 (qC-9), 116.7 (qC-3), 112.2 (CH-16), 21.3 (C(21)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₂₂H₁₆NO]⁺: 310.1226; found: 310.1225.

2-Methylbenzofuro[3,2-c]quinoline (1g)

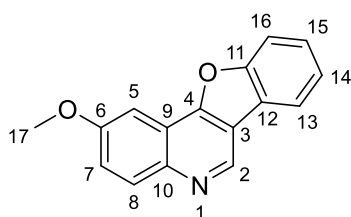
Synthesis of substrate **1g** as per general procedure 3 using **S16** (0.670 g, 2.13 mmol), Pd(OAc)₂ (0.024 g, 0.109 mmol), K₂CO₃ (0.589 g, 4.27 mmol) in NMP (3.30 mL).



Off-white solid; 79% yield (0.392 g); **m.p.** 159 – 160 °C (lit. m.p. 157 – 159 °C)^[10]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.38 (s, 1H, H-2), 8.15–8.10 (m, 2H, H-5, H-8), 8.04 (d, 1H, J = 7.5 Hz, H-13), 7.70 (d, 1H, J = 8.1 Hz, H-16), 7.60–7.39 (m, 3H, H-7, H-14, H-15), 2.60 (s, 3H, CH₃-17) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 157.2 (qC-4), 156.0 (qC-11), 146.1 (qC-10), 143.5 (CH-2), 137.2 (qC-6), 131.6 (CH-7), 129.7 (CH-8), 127.2 (CH-15), 124.1 (CH-14), 122.9 (qC-12), 120.7 (CH-13), 119.8 (CH-5), 117.2 (qC-9), 116.4 (qC-3), 112.2 (CH-16), 21.9 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₆H₁₂NO]⁺: 234.0913; found: 234.0915.

2-Methoxybenzofuro[3,2-c]quinoline (1h)

Synthesis of substrate **1h** as per general procedure 2 using **S17** (1.0 , 3.03 mmol), TBABr (1.95 g, 6.06 mmol), Pd(OAc)₂ (0.034 g, 5 mol%), K₂CO₃ (0.838 g, 6.06 mmol) and *i*PrOAc (4.5 mL).

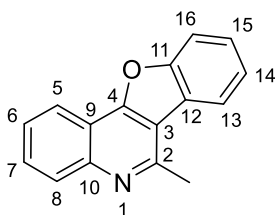


White solid; 83% yield (0.094 g); **m.p.** 151 – 153 °C (lit. m.p. 150 – 152 °C)^[1a]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.31 (s, 1H, H-2), 8.13 (d, 1H, J = 9.2 Hz, H-8), 8.05 (d, 1H, J = 7.5 Hz, H-13), 7.71 (d, 1H, J = 8.1 Hz, H-16), 7.61–7.34 (m, 4H, H-5, H-7, H-14, H-15), 4.01 (s, 3H, CH₃-17) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 158.4 (qC-6), 157.0 (qC-4), 156.0 (qC-11), 143.5 (qC-10),

141.8 (CH-2), 131.5 (CH-8), 127.3 (CH-15), 124.1 (CH-14), 123.0 (qC-12), 121.9 (CH-7), 120.8 (CH-13), 118.0 (qC-9), 116.6 (qC-3), 112.1 (CH-16), 98.8 (CH-5), 55.9 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₁₂NO₂]⁺: 250.0863; found: 250.0860.

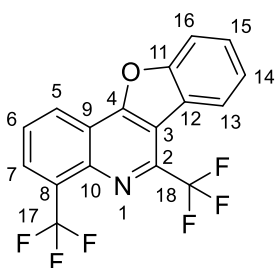
6-Methylbenzofuro[3,2-c]quinoline (1i)

Synthesis of substrate **1i** as per general procedure 2 using **S18** (0.200 g, 0.636 mmol), TBABr (0.409 g, 1.27 mmol), Pd(OAc)₂ (0.007 g, 5 mol%), K₂CO₃ (0.176 g, 1.27 mmol) and *i*PrOAc (0.95 mL).



Off-white solid; 91% yield (0.271 g); **m.p.** 128 – 130 °C (lit. m.p. 132 – 134 °C)^[1a]; **¹H NMR (300 MHz, CDCl₃)** δ = 8.38 (d, 1H, *J* = 8.0 Hz, H-5), 8.18 (d, 1H, *J* = 8.4 Hz, H-8), 8.09 (d, 1H, *J* = 7.6 Hz, H-13), 7.71 – 7.80 (m, 2H, H-7, H-16), 7.63 (t, 1H, *J* = 7.5 Hz, H-6), 7.54 (dt, 1H, *J* = 1.2, 7.5 Hz, H-15, overlapping with H-14), 7.48 (t, 1H, *J* = 7.5 Hz, H-14, overlapping with H-15), 3.15 (s, 3H, CH₃-17) ppm; **¹³C NMR (150.9 MHz, CDCl₃)** δ = 157.4 (qC-4), 155.9 (qC-11), 154.8 (qC-2), 146.9 (qC-10), 129.4 (CH-7), 128.9 (CH-8), 126.8 (CH-15), 126.1 (CH-6), 124.0 (CH-14), 123.5 (qC-12), 121.8 (CH-13), 120.7 (CH-5), 116.2 (qC-9), 115.4 (qC-3), 112.1 (CH-16), 24.3 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₁₂NO]⁺: 234.0913; found: 234.0916.

4,6-Bis(trifluoromethyl)benzofuro[3,2-c]quinoline (1j)

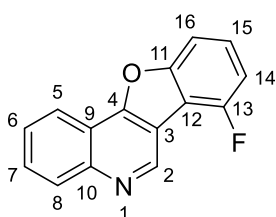


Synthesis of substrate **1j** as per general procedure 2 using **S19** (1.20 g, 2.75 mmol), TBABr (1.77 g, 5.50 mmol), Pd(OAc)₂ (0.031 g, 5 mol%), K₂CO₃ (0.760 g, 5.50 mmol) and *i*PrOAc (4.1 mL).
White solid; 64% (0.626 g); **m.p.** 164 – 165 °C; **IR** $\tilde{\nu}_{\text{max}}$ cm⁻¹: 2922, 2855, 1579, 1429, 1305, 1125, 1105, 964, 746; **¹H NMR (300 MHz, CDCl₃)** δ = 8.66 (d, 1H, *J* = 6.4 Hz, H-13), 8.26 (d, 1H, *J* = 7.8 Hz, H-6), 8.20 (d, 1H, *J* = 7.4 Hz, H-7), 7.90 – 7.75 (m, 2H, H-15, H-16), 7.64 (dt, 1H, *J* = 1.2, 7.4 Hz, H-5), 7.54 (dt, 1H, *J* = 0.9, 7.8 Hz, H-14) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 158.5 (qC-11), 156.1 (qC-4), 142.1 (d, ²*J*_(C, F) = 38 Hz, qC-8), 141.2 (qC-3), 129.2 (²*J*_(C, F) = 30 Hz, qC-2), 128.7 (CH-5), 128.5 (d, ³*J*_(C, F) = 6 Hz, CH-7), 127.5 (CH-13), 125.1 (CH-15), 124.9 (CH-14), 123.5 (q, ¹*J*_(C, F) = 275 Hz, qC(17)-F₃), 123.3 (q, ⁴*J*_(C, F) = 4 Hz, CH-6), 121.4 (q, ¹*J*_(C, F) = 275 Hz, qC(18)-F₃), 120.2 (qC-12), 118.2 (qC-9), 113.9 (qC-10), 112.1 (CH-16) ppm; **¹⁹F NMR (282 MHz, CDCl₃)** δ = -60.4 (CF₃), -67.6 (CF₃) ppm; **HRMS**

(ESI-TOF; positive mode) m/z : $[M + H]^+$ calcd. for: $[C_{17}H_8F_6NO]^+$; 356.0505; found: 356.0507.

7-Fluorobenzofuro[3,2-c]quinoline (1m)

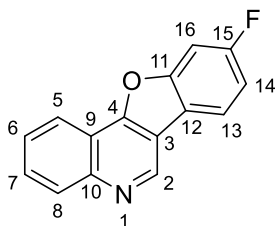
Synthesis of substrate **1m** as per general procedure 2 using **S21** (1.0 g, 3.14 mmol), TBABr (2.03 g, 6.29 mmol), $Pd(OAc)_2$ (0.035 g, 5 mol%), K_2CO_3 (0.869 g, 6.29 mmol) and *i*PrOAc (4.7 mL).



White solid; 91% yield (0.679 g); **m.p.** 153 – 155 °C; **IR** $\tilde{\nu}_{max}/cm^{-1}$: 2973, 1509, 1441, 1344, 1171, 1018; **1H NMR (300 MHz, $CDCl_3$)** δ = 9.53 (s, 1H, H-2), 8.38 (dd, 1H, J = 1.2, 8.2 Hz, H-5), 8.28 (d, 1H, J = 8.5 Hz, H-8), 7.80 (overlapping ddd, 1H, J = 1.5, 7.0, 8.5 Hz, H-7), 7.70 (overlapping ddd, 1H, J = 1.0, 7.1, 8.2 Hz, H-6), 7.54 (dd, 1H, J = 0.8, 8.5 Hz, H-16), 7.48 (overlapping dt, 1H, J = 5.1, 7.9 Hz, H-15), 7.17 (overlapping ddd, 1H, J = 1.0, 7.9, 9.0 Hz, H-14) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 157.2 (d, $^1J_{(C,F)} = 250$ Hz, qC-13), 157.4 (d, $^3J_{(C,F)} = 10$ Hz, qC-11), 157.1 (qC-4), 147.4 (qC-10), 145.4 (d, $^4J_{(C,F)} = 2$ Hz, CH-2), 130.0 (CH-8), 129.6 (CH-7), 127.9 (d, $^3J_{(C,F)} = 8$ Hz, CH-15), 127.2 (CH-6), 120.8 (CH-5), 116.8 (qC-9), 114.2 (qC-3), 112.0 (d, $^2J_{(C,F)} = 22$ Hz, qC-12), 110.3 (d, $^2J_{(C,F)} = 20$ Hz, CH-14), 108.1 (d, $^4J_{(C,F)} = 4$ Hz, CH-16) ppm; **^{19}F NMR (282 MHz, $CDCl_3$)** δ = -116.5 (CF-13) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[M + H]^+$ calcd. for: $[C_{15}H_9FNO]^+$; 238.0663; found: 238.0663.

9-Fluorobenzofuro[3,2-c]quinoline (1n)

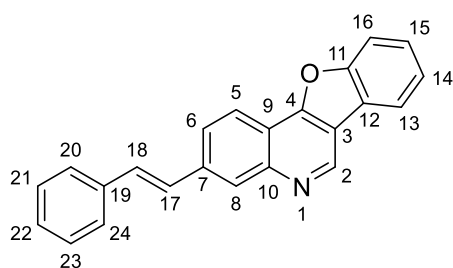
Synthesis of substrate **1n** as per general procedure 2 using **S22** (0.200 g, 0.629 mmol), TBABr (0.406 g, 1.26 mmol), $Pd(OAc)_2$ (0.007 g, 5 mol%), K_2CO_3 (0.174 g, 1.26 mmol) and *i*PrOAc (0.94 mL).



White solid; 93% yield (0.555 g); **m.p.** 134 – 136 °C **1H NMR (300 MHz, $CDCl_3$)** δ = 9.46 (s, 1H, H-2), 8.40 (d, 1H, J = 8.1 Hz, H-5), 8.27 (d, 1H, J = 8.4 Hz, H-8), 8.03 (overlapping dd, 1H, J = 5.4, 8.6, H-13), 7.80 (ddd, 1H, J = 1.5, 7.0, 8.4 Hz, H-7), 7.71 (t, 1H, J = 7.8 Hz, H-6), 7.48 (dd, 1H, J = 2.2, 8.6 Hz, H-16), 7.24 (dt, 1H, J = 2.2, 9.1 Hz, H-14) ppm; **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 161.2 (d, $^1J_{(C,F)} = 247$ Hz, qC-15), 157.1 (d, $^5J_{(C,F)} = 2$ Hz, qC-4), 155.2 (d, $^3J_{(C,F)} = 13$ Hz, qC-11), 146.2 (qC-10), 143.0 (CH-2), 128.9 (CH-8), 128.3 (CH-7), 126.2 (CH-6), 120.1 (d, $^3J_{(C,F)} = 10$ Hz, CH-13), 119.6 (CH-5), 118.0 (d, $^4J_{(C,F)} = 2$ Hz, qC-12), 116.0 (qC-9), 114.8 (qC-3), 111.3 (d, $^2J_{(C,F)} = 24$ Hz, CH-14), 99.3 (d, $^2J_{(C,F)} = 27$ Hz, CH-16) ppm; **^{19}F NMR (282 MHz, $CDCl_3$)** δ = -112.2 (CF-13) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[M + H]^+$ calcd. for $[C_{15}H_9FNO]^+$: 238.0663; found: 238.0662.

(E)-3-Styrylbenzofuro[3,2-c]quinoline (3b) ^[2]

To a screw capped vial was added the quinoline **S12** substrate (0.114 g, 0.30 mmol, 1 eq.), styrene (0.04 mL, 0.33 mmol, 1.1 eq.), Pd(OAc)₂ (3.4 mg, 5 mol%) and tetrabutylammonium acetate (0.484 g, 1.5 mmol, 5 eq.) which was stirred at 100 °C for 24 hours. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5) to yield **3b**.

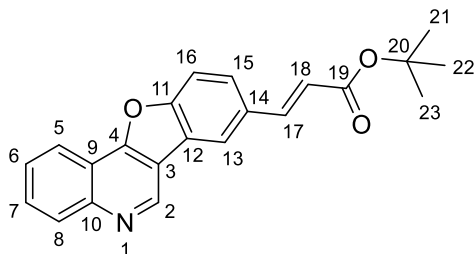


Off-white solid; 75% (0.072 g); **m.p.** 178 – 180 °C (lit. **m.p.** 179 – 182 °C)^[1b]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.46 (s, 1H, H-2), 8.36 (d, 1H, *J* = 8.6 Hz, H-5), 8.27 (d, 1H, *J* = 1.4 Hz, H-8), 8.07 (dd, 1H, *J* = 0.9, 7.5 Hz, H-13), 7.91 (dd, 1H, *J* = 1.4, 8.6 Hz, H-6), 7.74 (d, 1H, *J* = 7.9 Hz, H-16), 7.65–

7.20 (m, 9H, H-14, H-15, H-17, H-18, H-20, H-21, H-22, H-23, H-24) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 157.4 (qC-4), 156.1 (qC-11), 147.9 (qC-10), 144.8 (CH-2), 138.5 (qC-7), 137.0 (qC-19), 130.7 (CH-18), 128.8 (2 × CH, CH-21, CH-22), 128.1 (2 × CH, CH-17, CH-22), 128.0 (CH-8), 127.2 (CH-15), 126.8 (2 × CH, CH-20, CH-24), 124.9 (CH-6), 124.1 (CH-14), 122.7 (qC-12), 121.1 (CH-5), 120.6 (CH-13), 116.3 (2 × qC, qC-3, qC-9), 112.1 (CH-16) ppm; **HRMS** (ESI-TOF positive mode) *m/z*: [M+H]⁺ calcd. for [C₂₃H₁₆NO]⁺: 322.1226; found: 322.1227.

tert-Butyl (E)-3-(benzofuro[3,2-c]quinolin-8-yl)acrylate (3c)^[2]

To a screw capped vial was added the quinoline **S20** substrate (0.076 g, 0.20 mmol, 1 eq.), *tert*-butylacrylate (0.08 mL, 0.55 mmol, 1.1 eq.), Pd(OAc)₂ (2.2 mg, 5 mol%) and tetrabutylammonium acetate (0.322g, 1.0 mmol, 5 eq.) which was stirred at 100 °C for 24 hours. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5) to yield **3c**.



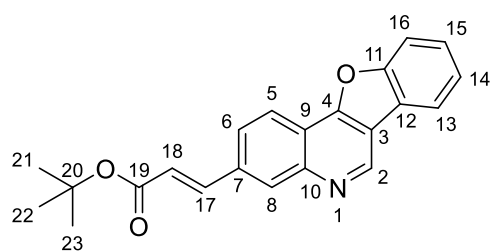
White solid, 88% yield (0.802 g); **m.p.** 155 – 157 °C (lit. **m.p.** 157 – 158 °C)^[1b]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.45 (s, 1H, H-2), 8.36 (dd, 1H, *J* = 1.1, 8.1 Hz, H-5), 8.25 (d, 1H, *J* = 8.4 Hz, H-8), 8.17 (s, 1H, H-13), 7.83–7.62 (m, 5H, H-6, H-

7, H-15, H-16, H-17), 6.47 (d, 1H, *J* = 15.9 Hz, H-18), 1.58 (s, 9H, CH₃-21, CH₃-22, CH₃-23) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 166.2 (qC-19), 158.2 (qC-4), 156.7 (qC-11), 147.7 (qC-10), 144.3 (CH-2), 143.0 (CH-17), 131.2 (qC-14), 130.0 (CH-8), 129.6 (CH-7), 127.24 (CH-6), 127.21 (CH-15), 123.5 (qC-12), 120.8 (CH-5), 120.3 (CH-18), 120.2 (CH-13), 117.1 (qC-9), 115.9 (qC-3), 112.5 (CH-16), 80.7 (qC-20), 28.2 (3 × CH₃, C(21)-

H₃, C(**22**)-H₃, C(**23**)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M+H]⁺ calcd. for [C₂₂H₂₀NO₃]⁺: 346.1438; found: 346.1430.

***tert*-Butyl (*E*)-3-(benzofuro[3,2-*c*]quinolin-3-yl)acrylate (**3d**)^[2]**

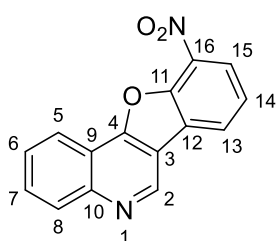
To a screw capped vial was added the quinoline **S12** substrate (0.190 mg, 0.50 mmol, 1 eq.), *tert*-butylacrylate (0.08 mL, 0.55 mmol, 1.1 eq.), Pd(OAc)₂ (2.2 mg, 5 mol%) and tetrabutylammonium acetate (0.806 g, 2.5 mmol, 5 eq.) which was stirred at 100 °C for 24 hours. The crude reaction mixture was loaded directly onto silica gel for purification by column chromatography and eluted in DCM:EtOAc (100:0 – 95:5) to yield **3c**.



White solid; 79% (0.137 g); **m.p.** 165 – 166 °C (lit. *m.p.* 164 – 165);^[1b] **¹H NMR (300 MHz, CDCl₃)** δ = 9.49 (s, 1H, H-**2**), 8.55–8.24 (m, 2H, H-**5**, H-**8**), 8.09 (dd, 1H, *J* = 0.8, 7.6 Hz, H-**13**), 7.93–7.69 (m, 3H, H-**6**, H-**16**, H-**17**), 7.64–7.35 (m, 2H, H-**14**, H-**15**), 6.58 (d, 1H, *J* = 16.0 Hz, H-**18**), 1.58 (s, 9H, H-**21**, H-**22**, H-**23**) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 166.0 (qC-**19**), 157.1 (qC-**4**), 156.2 (qC-**11**), 147.4 (qC-**10**), 145.1 (CH-**2**), 142.8 (CH-**17**), 135.6 (qC-**7**), 130.7 (CH-**8**), 127.6 (CH-**15**), 125.1 (CH-**6**), 124.3 (CH-**14**), 122.5 (qC-**12**), 122.0 (CH-**18**), 121.5 (CH-**5**), 120.8 (CH-**13**), 117.7 (qC-**9**), 117.1 (qC-**3**), 112.2 (CH-**16**), 80.9 (qC-**20**), 28.2 (3 × CH₃, C(**21**)-H₃, C(**22**)-H₃, C(**23**)-H₃) ppm; **LRMS** *m/z* (ESI+) 346 [(M+H)⁺, 100%].

10-Nitrobenzofuro[3,2-*c*]quinoline (5**)**

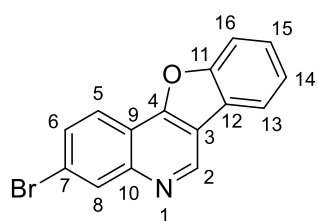
Synthesis of substrate **5** as per general procedure 2 using **S23** (0.500 g, 1.45 mmol), TBABr (0.935 g, 2.90 mmol), Pd(OAc)₂ (16.3 mg, 5 mol%), K₂CO₃ (0.401 g, 2.90 mmol) and *i*PrOAc (2.2 mL).



White solid; 91% yield (0.701 g); **m.p.** 255 – 257 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3086, 2922, 1561, 1519, 1341, 1284, 1227, 1192; **¹H NMR (500 MHz, CDCl₃)** δ = 9.53 (s, 1H, H-**2**), 8.57 (ddd, 1H, *J* = 0.6, 1.4, 8.2 Hz, H-**5**), 8.41 (dd, 1H, *J* = 1.1, 7.8 Hz, H-**15**), 8.37 (dd, 1H, *J* = 1.1, 8.2 Hz, H-**13**), 8.31 (d, 1H, *J* = 8.5 Hz, H-**8**), 7.87 (overlapping ddd, 1H, *J* = 1.4, 7.0, 8.5 Hz, H-**7**), 7.78 (overlapping ddd, 1H, *J* = 1.1, 7.0, 8.2 Hz, H-**6**), 7.63 (dd, 1H, *J* = 7.8 Hz, H-**14**) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 158.6 (qC-**4**), 148.1 (qC-**16**), 148.0 (qC-**10**), 143.8 (CH-**2**), 134.6 (qC-**11**), 130.4 (CH-**7**), 129.9 (CH-**8**), 127.8 (CH-**6**), 126.9 (CH-**15**), 126.8 (qC-**12**), 124.2 (CH-**14**), 123.1 (CH-**13**), 121.2 (CH-**5**), 116.7 (qC-**9**), 114.7 (qC-**3**) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₉N₂O₃]⁺; 265.0608; found: 265.0605.

3-Bromobenzofuro[3,2-c]quinoline (**S2**)

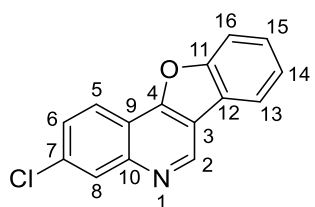
A 15 mL Schlenk was flame-dried and cooled to r.t. under vacuum. The Schlenk was refilled with nitrogen and **S12** (0.030 g, 0.08 mmol, 1.0 equiv.), QPhos (5.6 mg, 0.008 mmol, 10 mol%), Pd(QPhos)₂ (6.1 mg, 0.004 mmol, 5 mol%) and K₂CO₃ (0.022 g, 0.16 mmol, 2.0 equiv.) were added and the Schlenk placed under vacuum once more for ~10 min. The Schlenk was evacuated and refilled with nitrogen three times and distilled 1,4-dioxane (0.5 mL) was added *via* septum. The Schlenk was sealed, and the resulting mixture stirred at 125 °C for 24 h. The cooled reaction mixture was diluted with DCM, filtered through a short plug of Celite, rinsed with DCM and the filtrate concentrated under reduced pressure. Purification *via* column chromatography (DCM;EtOAc 100:0 – 99:1) yielded **S2**.



White solid; 30% (0.070 g); **m.p.** 165 – 166 °C (lit. m.p. 166 – 167 °C)^[1b]; **IR** $\tilde{\nu}_{\text{max}}$ **cm**⁻¹: 1615, 1559, 1273, 1101, 755; **¹H NMR (500 MHz, CDCl₃)** δ = 9.46 (s, 1H, H-2), 8.44 (d, 1H, *J* = 1.8 Hz, H-8), 8.26 (d, 1H, *J* = 8.7 Hz, H-5), 8.08 (d, 1H, *J* = 7.7 Hz, H-13), 7.77 (dd, 1H, *J* = 1.9, 8.7 Hz, H-6), 7.74 (d, 1H, *J* = 8.2 Hz, H-16), 7.56 (overlapping ddd, 1H, *J* = 1.3, 7.3, 8.5 Hz, H-15), 7.48 (ddd, 1H, *J* = 0.9, 7.7, 8.4 Hz, H-14) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 157.3 (qC-4), 156.0 (qC-11), 147.9 (qC-10), 145.4 (CH-2), 132.3 (CH-8), 130.5 (CH-6), 127.6 (CH-15), 124.3 (CH-14), 123.4 (qC-7), 122.4 (qC-12), 122.1 (CH-5), 120.7 (CH-13), 116.7 (qC-3), 115.8 (qC-9), 112.2 (CH-16) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₉Br⁷⁹NO]⁺: 297.9862; found: 297.9859.

3-Chlorobenzofuro[3,2-c]quinoline (**S3**)

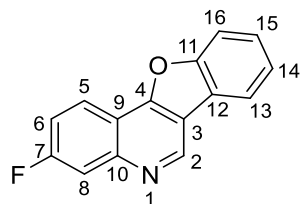
Synthesis of substrate **S3** as per general procedure 3 using **S24** (0.407 g, 1.22 mmol), Pd(OAc)₂ (13.9 mg, 0.0619 mmol), K₂CO₃ (0.340 g, 2.46 mmol) in NMP (1.82 mL).



Pale yellow solid; 80% (0.247 g); **m.p.** = 149 – 151 °C (lit. m.p. 155 – 157 °C)^[1a]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.45 (s, 1H, H-2), 8.31 (d, 1H, *J* = 8.8 Hz, H-5), 8.24 (d, 1H, *J* = 1.9 Hz, H-8), 8.07 (dd, 1H, *J* = 0.8, 7.6 Hz, H-13), 7.73 (d, 1H, *J* = 8.2 Hz, H-16), 7.63 (dd, 1H, *J* = 1.9, 8.8 Hz, H-6), 7.58–7.52 (m, 1H, H-15), 7.47 (td, 1H, *J* = 1.0, 7.5 Hz, H-14) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 157.3 (qC-4), 156.1 (qC-11), 147.8 (qC-10), 145.5 (CH-2), 135.3 (qC-7), 129.1 (CH-8), 128.0 (CH-6), 127.6 (CH-15), 124.4 (CH-14), 122.5 (qC-12), 122.2 (CH-5), 120.8 (CH-13), 116.7 (qC-3), 115.6 (qC-9), 112.3 (CH-16) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₉Cl³⁵NO]⁺: 254.0367; found: 254.0361.

3-Fluorobenzofuro[3,2-c]quinoline (**S4**)

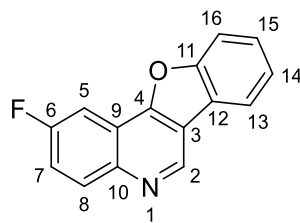
Synthesis of substrate **S4** as per general procedure 3 using **S25** (0.746 g, 2.35 mmol), Pd(OAc)₂ (26.8 mg, 0.119 mmol), K₂CO₃ (0.649 g, 4.70 mmol) in NMP (3.50 mL).



Off-white solid; 77% (0.427 g); **m.p.** 149 – 151 °C (lit. m.p. 150 – 151 °C)^[11]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.46 (s, 1H, H-2), 8.39 (dd, 1H, *J* = 6.0, 9.1 Hz, H-5), 8.07 (ddd, 1H, *J* = 0.6, 1.5, 7.5, H-13), 7.89 (dd, 1H, *J* = 2.5, 10.3 Hz, H-8), 7.75–7.71 (m, 1H, H-16), 7.58–7.43 (m, 3H, H-6, H-14, H-15) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 163.1 (d, ¹*J*_(C,F) = 250 Hz, qC-F), 157.5 (qC-4), 155.9 (qC-11), 148.5 (d, ³*J*_(C,F) = 12.5 Hz, qC-10), 145.6 (CH-2), 127.4 (CH-15), 124.3 (CH-14), 123.0 (d, ³*J*_(C,F) = 10 Hz, CH-5), 122.5 (qC-12), 120.7 (CH-13), 117.3 (d, ²*J*_(C,F) = 26 Hz, CH-6), 116.0 (d, ⁶*J*_(C,F) = 2 Hz, qC-3), 114.1 (qC-9), 114.0 (d, ²*J*_(C,F) = 21 Hz, CH-8), 112.2 (CH-16) ppm; **¹⁹F NMR (282 MHz, CDCl₃)** δ = –109.3 (CF-7) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₉FNO]⁺: 238.0663; found: 238.0665.

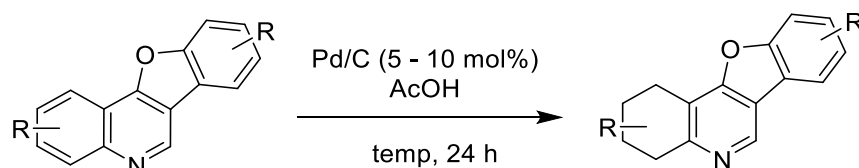
2-Fluorobenzofuro[3,2-c]quinoline (**S5**)

Synthesis of substrate **S5** as per general procedure 3 using **S26** (0.319 g, 1.00 mmol), Pd(OAc)₂ (11.2 mg, 0.0501 mmol), Cs₂CO₃ (0.652 g, 2.00 mmol) in NMP (1.50 mL). Cs₂CO₃ used in place of K₂CO₃.



Off-white solid; 86% (0.205 g); **m.p.** 149 – 151 °C (lit. m.p. 146–148 °C)^[1a]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.39 (s, 1H, H-2), 8.23 (dd, 1H, *J* = 5.2, 9.2 Hz, H-8), 8.05 (d, 1H, *J* = 7.5 Hz, H-13), 7.94 (dd, 1H, *J* = 2.8, 8.6 Hz, H-5), 7.71 (d, 1H, *J* = 8.2 Hz, H-16), 7.57–7.42 (m, 3H, H-7, H-14, H-15) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 160.9 (d, ¹*J*_(C-F) = 249 Hz, qC-F), 157.1 (d, ⁴*J*_(C-F) = 5 Hz, qC-4), 156.1 (qC-11), 144.5 (qC-10), 143.7 (d, ⁶*J*_(C-F) = 3 Hz, CH-2), 132.6 (d, ³*J*_(C-F) = 9 Hz, CH-8), 127.7 (CH-15), 124.3 (CH-14), 122.6 (qC-12), 120.9 (CH-13), 119.3 (d, ²*J*_(C-F) = 26 Hz, CH-7), 117.9 (d, ³*J*_(C-F) = 11 Hz, qC-9), 116.9 (qC-3), 112.3 (CH-16), 104.8 (d, ²*J*_(C-F) = 24 Hz, CH-5) ppm; **¹⁹F NMR (282 MHz, CDCl₃)** δ = –111.5 (CF) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₉FNO]⁺: 238.0663; found: 238.0672.

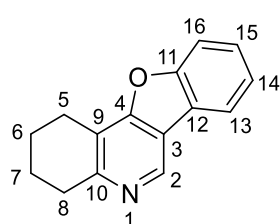
Synthesis of Reduced Products



Note: reactions were carried out for a reaction time of 24 hours unless otherwise stated.

1,2,3,4-Tetrahydrobenzofuro[3,2-c]quinoline (**2a**)

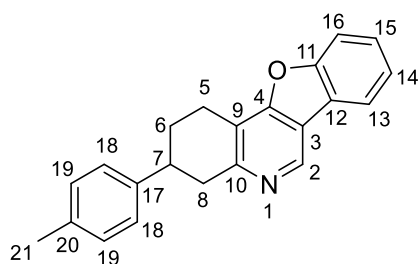
Synthesis of substrate **2a** as per general procedure 5 using **1a** (0.050 g, 0.23 mmol), Pd/C (12.1 mg, 0.011 mmol, 5 mol%), AcOH (1.10 mL) and H₂ balloon at 50 °C.



White solid; 96% (0.049 g); **m.p.** 151 – 152 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2936, 1600, 1570, 1462, 1446, 1410, 1192, 1123, 849, 760; **¹H NMR (300 MHz, CDCl₃)** δ = 8.96 (s, 1H, H-2), 7.94 (d, 1H, J = 7.5, H-13), 7.57 (d, 1H, J = 8.2 Hz, H-16), 7.50–7.42 (m, 1H, H-15), 7.36 (td, 1H, J = 1.0, 7.5 Hz, H-14), 3.05 (m, 4H, CH₂-5, CH₂-8), 2.05–1.86 (m, 4H, CH₂-6, CH₂-7) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 160.1 (qC-4), 156.1 (qC-11), 155.8 (qC-10), 140.1 (CH-2), 127.5 (CH-15), 123.6 (CH-14), 122.5 (qC-12), 121.0 (CH-13), 118.8 (qC-3), 116.9 (qC-9), 111.9 (CH-16), 32.6 (C(5)-H₂), 23.2 (C(6)-H₂), 22.4 (C(8)-H₂), 22.0 (C(7)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₅H₁₄NO]⁺: 224.2070; found: 224.1068.

3-(*p*-Tolyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (**2b**)

Synthesis of substrate **2b** as per general procedure 5 using **1b** (0.062 g, 0.20 mmol), Pd/C (21 mg, 0.020 mmol), AcOH (1.20 mL) and H₂ balloon at 80 °C for 30 hours.

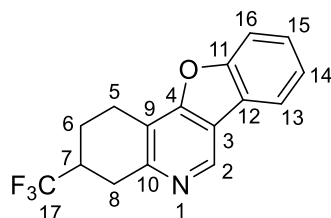


Pale-yellow solid; 92% (0.058 g), **m.p.** 128 – 132 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2927, 1574, 1513, 1444, 1192, 1020, 822, 753; **¹H NMR (400 MHz, CDCl₃)** δ = 9.02 (s, 1H, H-2), 7.98 (d, 1H, J = 7.5 Hz, H-13), 7.60 (d, 1H, J = 8.2 Hz, H-16), 7.52–7.45 (m, 1H, H-15), 7.39 (t, 1H, J = 7.5 Hz, H-14), 7.21 (d, 2H, J = 8.0 Hz, H-18), 7.16 (d, 2H, J = 8.0 Hz, H-19), 3.43–3.00 (m, 5H, CH₂-5, CH₂-8, CH-7), 2.35 (s, 3H, CH₃-21), 2.32–2.25 (m, 1H, one of CH₂-6), 2.08–1.94 (m, 1H, one of CH₂-6) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 160.1 (qC-4), 156.2 (qC-11), 155.5 (qC-10), 142.7 (qC-17), 140.4 (CH-2), 136.1 (qC-20), 129.4 (2 × CH-19), 127.7 (CH-15), 126.9 (2 × CH-18), 123.8 (CH-14), 122.5 (qC-12), 121.1 (CH-13), 119.0 (qC-3), 116.3 (qC-9), 112.0 (CH-16), 40.2 (C(5)-H₂),

40.1 (CH-7), 29.4 (C(6)-H₂), 22.5 (C(8)-H₂), 21.1 (C(21)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₂H₂₀NO]⁺: 314.1539; found: 314.1543.

3-(Trifluoromethyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2c)

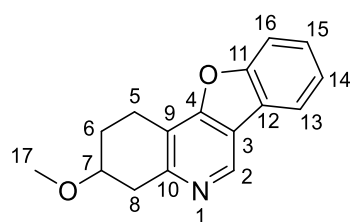
Synthesis of substrate **2c** as per general procedure 5 using **1c** (0.115 g, 0.40 mmol), Pd/C (43 mg, 0.040 mmol), AcOH (2.40 mL) and H₂ balloon at 80 °C for 30 hours.



White solid; 54% (0.063 g); **m.p.** 158 – 159 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2936, 1576, 1450, 1417, 1391, 1277, 1252, 1160, 1118, 1055, 1004, 770, 753; **¹H NMR (300 MHz, CDCl₃)** δ = 9.03 (s, 1H, H-2), 7.99 (d, 1H, *J* = 7.6 Hz, H-13), 7.61 (d, 1H, *J* = 8.2 Hz, H-16), 7.55–7.45 (m, 1H, H-15), 7.40 (td, 1H, *J* = 0.9, 7.6 Hz, H-14), 3.43–3.31 (two overlapping doublets, 2H, *J* = 4.5, 17.3 Hz, one of CH₂-5 and one of CH₂-8), 3.19–2.90 (m, 2H, one of CH₂-5 and one of CH₂-8), 2.75–2.58 (m, 1H, H-7), 2.43–2.31 (m, 1H, one of CH₂-6), 1.93–1.75 (m, 1H, one of CH₂-6) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 159.8 (qC-4), 156.2 (qC-11), 152.3 (qC-10), 141.0 (CH-2), 128.0 (CH-15), 127.6 (q, ¹*J*_(C, F) = 278 Hz, CF₃-17), 124.0 (CH-14), 122.2 (qC-12), 121.2 (CH-13), 119.4 (qC-3), 115.6 (qC-9), 112.1 (CH-16), 39.5 (q, ²*J*_(C, F) = 28 Hz, CH-7), 31.4 (q, ³*J*_(C, F) = 3 Hz, C(8)-H₂), 21.3 C(5)-H₂), 21.1 (q, ³*J*_(C, F) = 3 Hz, C(6)-H₂) ppm; **¹⁹F NMR (376 MHz, CDCl₃)** δ = – 62.5 (C-F₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₁₃F₃NO]⁺: 292.0932; found: 292.0944.

3-Methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2d)

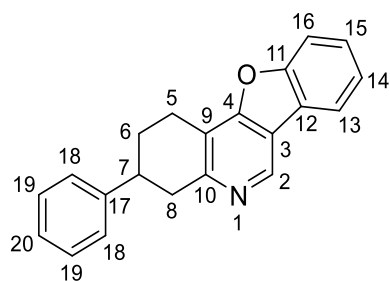
Synthesis of substrate **2d** as per general procedure 5 using **1d** (0.050 g, 0.20 mmol), Pd/C (21 mg, 0.020 mmol), AcOH (1.20 mL) and H₂ balloon at 80 °C.



Pale-yellow oil; 91% (0.046 g); **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2929, 1603, 1574, 1445, 1192, 1101, 750; **¹H NMR (400 MHz, CDCl₃)** δ = 9.00 (s, 1H, H-2), 7.96 (d, 1H, *J* = 7.4 Hz, H-13), 7.59 (d, 1H, *J* = 8.2 Hz, H-16), 7.48 (t, 1H, *J* = 7.7 Hz, H-15), 7.38 (t, 1H, *J* = 7.4 Hz, H-14), 3.91–3.84 (m, 1H, H-7), 3.47 (s, 3H, CH₃-17), 3.45–2.99 (m, 4H, CH₂-5, CH₂-8), 2.17–1.81 (m, 2H, CH₂-6) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 159.8 (qC-4), 156.2 (qC-11), 153.2 (qC-10), 140.7 (CH-2), 127.8 (CH-15), 123.8 (CH-14), 122.3 (qC-12), 121.1 (CH-13), 119.2 (qC-3), 116.2 (qC-9), 112.0 (CH-16), 75.2 (CH-7), 56.2 (C(17)-H₃), 37.9 (C(8)-H₂), 26.3 (C(6)-H₂), 19.1 (C(5)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₁₆NO₂]⁺: 254.1176; found: 254.1173.

3-Phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2e)

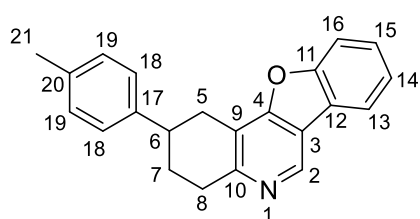
Synthesis of substrate **2e** as per general procedure 5 using **1e** (0.037 g, 0.12 mmol), Pd/C (13 mg, 0.012 mmol), AcOH (0.75 mL) and H₂ balloon at 80 °C for 30 hours.



Off-white solid; 73% (0.023 g); **m.p.** 133 – 135 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2923, 1599, 1572, 1444, 1411, 1191, 1017, 745, 700; **¹H NMR (400 MHz, CDCl₃)** δ = 9.01 (s, 1H, H-2), 7.97 (d, 1H, *J* = 7.6 Hz, H-13), 7.59 (d, 1H, *J* = 8.2 Hz, H-16), 7.47 (t, 1H, *J* = 7.8 Hz, H-15), 7.41–7.30 (m, 5H, H-14, H-18, H-19), 7.25 (t, 1H, *J* = 6.9 Hz, H-20), 3.46 – 3.00 (m, 5H, CH₂-5, CH-7, CH₂-8), 2.34–2.26 (m, 1H, one of CH₂-6), 2.10–1.96 (m, 1H, one of CH₂-6) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 160.1 (qC-4), 156.2 (qC-11), 155.4 (qC-10), 145.7 (qC-17), 140.5 (CH-2), 128.7 (2 × CH-19), 127.7 (CH-15), 127.0 (2 × CH-18), 126.5 (CH-20), 123.8 (CH-14), 122.4 (qC-12), 121.1 (CH-13), 119.0 (qC-3), 116.2 (qC-9), 112.0 (CH-16), 40.5 (CH-7), 40.1 (C(5)-H₂), 29.3 (C(6)-H₂), 22.5 (C(8)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₁H₁₈NO]⁺: 300.1383; found: 300.1389.

2-(*p*-Tolyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2f)

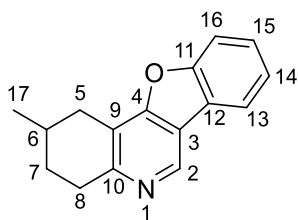
Synthesis of substrate **2f** as per general procedure 5 using **1f** (0.078 g, 0.25 mmol), Pd/C (27 mg, 0.025 mmol), AcOH (1.50 mL) and H₂ balloon at 100 °C for 72 hours.



Pale-yellow solid; 9% (0.007 g); **m.p.** 58 – 60 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2924, 1605, 1572, 1445, 1192, 1122, 748; **¹H NMR (600 MHz, CDCl₃)** δ = 9.05 (s, 1H, H-2), 8.00 (d, 1H, *J* = 7.4 Hz, H-13), 7.58 (d, 1H, *J* = 8.1 Hz, H-16), 7.49 (t, 1H, *J* = 7.7 Hz, H-15), 7.41 (t, 1H, *J* = 7.4 Hz, H-14), 7.24 (d, 2H, *J* = 7.8 Hz, H-18), 7.18 (d, 2H, *J* = 7.8 Hz, H-19), 3.55–3.42 (m, 1H, one of CH₂-5), 3.36–3.18 (m, 2H, CH₂-8), 3.17–3.03 (m, 2H, CH-6 and one of CH₂-5), 2.37 (s, 3H, CH₃-21), 2.37–2.30 (m, 1H, one of CH₂-7), 2.18–2.10 (m, 1H, one of CH₂-7) ppm; **¹³C NMR (151 MHz, CDCl₃)** δ = 160.1 (qC-4), 156.2 (qC-11), 154.9 (qC-10), 142.6 (qC-17), 139.8 (CH-2), 136.2 (qC-20), 129.5 (2 × CH-19), 127.9 (CH-15), 126.9 (2 × CH-18), 123.9 (CH-14), 122.3 (qC-12), 121.2 (CH-13), 118.7 (qC-3), 116.9 (qC-9), 112.1 (CH-16), 39.1 (CH-6), 32.7 (C(8)-H₂), 30.5 (C(7)-H₂ or C(5)-H₂), 30.3 (C(7)-H₂ or C(5)-H₂), 21.2 (C(21)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₂H₂₀NO]⁺: 314.1539; found: 314.1540.

2-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2g)

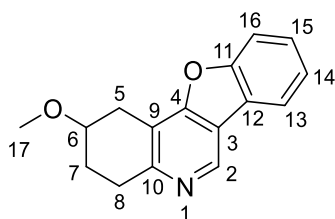
Synthesis of substrate **2g** as per general procedure 5 using **1g** (0.047 g, 0.20 mmol), Pd/C (22 mg, 0.020 mmol), AcOH (1.20 mL) and H₂ balloon at 80 °C.



Off-white solid; 78% (0.037 g); **m.p.** 97 – 99 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2925, 1606, 1572, 1446, 1192, 1122, 996, 864, 835, 748; **¹H NMR (500 MHz, CDCl₃)** δ = 8.98 (s, 1H, H-2), 7.96 (ddd, 1H, J = 0.6, 1.3, 7.7 Hz, H-13), 7.60–7.57 (m, 1H, H-16), 7.49–7.45 (m, 1H, H-15), 7.38 (td, 1H, J = 1.0, 7.6 Hz, H-14), 3.25 (dd, 1H, J = 4.3, 16.8 Hz, one of CH₂-5), 3.17 (ddd, 1H, J = 3.4, 5.4, 17.6 Hz, one of CH₂-8), 3.12–3.03 (m, 1H, one of CH₂-8), 2.57 (dd, 1H, J = 10.3, 16.8 Hz, one of CH₂-5), 2.10–1.97 (m, 2H, CH-6 and one of CH₂-7), 1.62 (dtd, J = 5.6, 11.0, 12.8 Hz, one of CH₂-7), 1.19 (d, 3H, J = 6.6 Hz, CH₃-17) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 160.1 (qC-4), 156.1 (qC-11), 155.5 (qC-10), 140.1 (CH-2), 127.6 (CH-15), 123.7 (CH-14), 122.5 (qC-12), 121.1 (CH-13), 118.8 (qC-3), 116.6 (qC-9), 112.0 (CH-16), 32.3 (C(8)-H₂), 31.4 (C(7)-H₂), 30.7 (C(5)-H₂), 28.3 (CH-6), 21.8 (C(17)-H₃), ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₆H₁₆NO]⁺: 238.1226; found: 238.1232.

2-Methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2h)

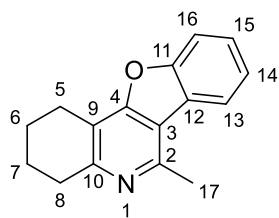
Synthesis of substrate **2h** as per general procedure 5 using **1h** (0.051 g, 0.20 mmol), Pd/C (22 mg, 0.020 mmol), AcOH (1.20 mL) and H₂ balloon at 80 °C.



Yellow oil; 28% (0.014 g); **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2928, 1604, 1572, 1445, 1343, 1191, 1100, 960, 880, 835, 749; **¹H NMR (600 MHz, CDCl₃)** δ = 8.99 (s, 1H, H-2), 7.97 (d, 1H, J = 7.6 Hz, H-13), 7.60 (d, 1H, J = 8.2 Hz, H-16), 7.48 (t, 1H, J = 7.6 Hz, H-15), 7.39 (t, 1H, J = 7.6 Hz, H-14), 3.88–3.83 (m, 1H, CH-6), 3.49 (s, 3H, CH₃-17), 3.35 (dd, 1H, J = 4.5, 16.8 Hz, 1H, one of CH₂-5), 3.28–3.21 (m, 1H, one of CH₂-8), 3.15–3.05 (m, 2H, one of CH₂-5 and CH₂-8), 2.21–2.09 (m, 2H, CH₂-7) ppm; **¹³C NMR (151 MHz, CDCl₃)** δ = 160.4 (qC-4), 156.1 (qC-11), 154.7 (qC-10), 140.4 (CH-2), 127.7 (CH-15), 123.8 (CH-14), 122.4 (qC-12), 121.1 (CH-13), 119.0 (qC-3), 114.3 (qC-9), 112.0 (CH-16), 74.1 (CH-6), 56.2 (C(17)-H₃), 29.4 (C(8)-H₂), 28.1 (C(5)-H₂), 27.4 (C(7)-H₂), ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₆H₁₆NO₂]⁺: 254.1176; found: 254.1177.

6-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2i)

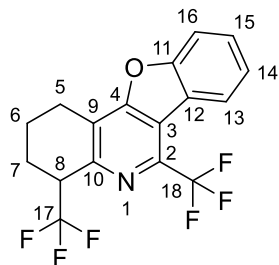
Synthesis of substrate **2i** as per general procedure 5 using **1i** (0.050 g, 0.21 mmol), Pd/C (24.3 mg, 0.023 mmol, 10 mol%), AcOH (1.10 mL) and H₂ balloon at 100 °C for 48 h.



White solid; 91% (0.041 g); **m.p.** 81 – 83 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2941, 2918, 2853, 1578, 1443, 1197, 1076; **¹H NMR (500 MHz, CDCl₃)** δ = 7.96 (dd, 1H, *J* = 0.7, 7.7 Hz, H-**13**), 7.57 (ddd, 1H, *J* = 0.7, 0.9, 8.2 Hz, H-**16**), 7.50–7.42 (ddd, 1H, *J* = 1.3, 7.4, 8.2 Hz, H-**15**), 7.36 (dt, 1H, *J* = 1.0, 7.6 Hz, H-**14**), 3.02 (m, 4H, CH₂-**5**, CH₂-**8**), 2.92 (s, 3H, CH₃-**17**), 2.01–1.88 (m, 4H, CH₂-**6**, CH₂-**7**) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 160.1 (qC-**4**), 155.9 (qC-**11**), 154.7 (qC-**10**), 150.3 (qC-**2**), 126.8 (CH-**15**), 123.5 (CH-**14**), 123.3 (qC-**12**), 121.9 (CH-**13**), 116.7 (qC-**3**), 114.4 (qC-**9**), 111.7 (CH-**16**), 32.4 (C(**5**)-H₂), 23.2 (C(**6**)-H₂), 22.8 (C(**17**)-H₃), 22.1 (C(**8**)-H₂), 22.0 (C(**7**)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₁₆NO]⁺: 238.1226; found: 238.1227.

4,6-Bis(trifluoromethyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2j)

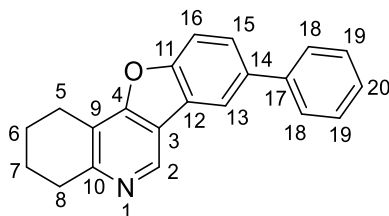
Synthesis of substrate **2j** as per general procedure 5 using **1j** (0.050 g, 0.14 mmol), Pd/C (15.0 mg, 0.014 mmol), AcOH (1.10 mL) and H₂ balloon at 80 °C.



White solid; 87% (0.044 mg); **m.p.** 150 – 152 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2958, 2927, 1570, 1470, 1237, 1173, 1113, 1098; **¹H NMR (500 MHz, CDCl₃)** δ = 8.19 (dd, 1H, *J* = 0.8, 8.0 Hz, H-**13**), 7.67 (ddd, 1H, *J* = 0.8, 1.0, 8.3 Hz, H-**16**), 7.60 (overlapping ddd, 1H, *J* = 1.3, 7.3, 8.3 Hz, H-**15**), 7.47 (overlapping ddd, 1H, *J* = 1.0, 7.3, 8.1 Hz, H-**14**), 3.94 – 3.84 (m, 1H, H-**8**), 3.25 (dt, 1H, *J* = 5.6, 18.0 Hz, one of H₂-**5**), 3.13 (dt, 1H, *J* = 7.3, 17.5, one of H₂-**5**), 2.40 – 2.31 (m, 1H, one of H₂-**7**), 2.23 – 2.12 (m, 2H, one of H₂-**6** and one of H₂-**7**), 2.01 – 1.92 (m, 1H, one from H₂-**6**) ppm; **¹³C NMR (157 MHz, CDCl₃)** δ = 159.7 (qC-**4**), 155.5 (qC-**11**), 145.6 (qC-**10**), 137.6 (q, ²*J*_(C,F) = 38 Hz, qC-**2**), 128.3 (CH-**15**), 125.6 (q, ¹*J*_(C,F) = 280 Hz, C(**17**)-F₃), 123.5 (CH-**14**), 123.0 (q, ⁵*J*_(C,F) = 4 Hz, CH-**13**), 121.2 (qC-**12**), 120.8 (q, ¹*J*_(C,F) = 175 Hz, C(**18**)-F₃), 118.8 (qC-**9**), 116.6 (qC-**3**), 111.0 (CH-**16**), 43.2 (q, ²*J*_(C,F) = 26 Hz, C-**8**), 22.0 (q, ³*J*_(C,F) = 2 Hz, C(**7**)-H₂), 20.1 (C(**5**)-H₂), 16.9 (C(**6**)-H₂) ppm; **¹⁹F NMR (471 MHz, CDCl₃)** δ = –66.3 (CF₃), –66.4 (CF₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₇H₁₂F₆NO]⁺: 360.0818; found: 360.0819.

8-Phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2k)

Synthesis of substrate **2k** as per general procedure 5 using **1k** (0.070 g, 0.24 mmol), Pd/C (25 mg, 0.024 mmol), AcOH (1.40 mL) and H₂ balloon at 80 °C.

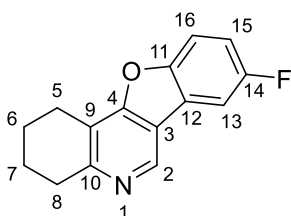


White solid; 70% (0.050 g); **m.p.** 116 – 118 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2927, 1635, 1567, 1470, 1410, 1195, 1069, 1033, 767, 701; **¹H NMR (400 MHz, CDCl₃)** δ = 9.00 (s, 1H, H-2), 8.12 (d, 1H, *J* = 1.4 Hz, H-13), 7.69–7.58 (m, 4H, H-15, H-16, H-18), 7.46 (t, 2H, *J* = 7.4 Hz, H-19),

7.36 (t, 1H, *J* = 7.4 Hz, H-20), 3.17–3.00 (m, 4H, CH₂-5, CH₂-8), 2.05–1.88 (m, 4H, CH₂-6, CH₂-7) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 160.6 (qC-4), 156.0 (qC-10), 155.6 (qC-11), 141.0 (qC-17), 140.1 (CH-2), 137.4 (qC-14), 129.0 (2 × CH-19), 127.5 (2 × CH-18), 127.4 (CH-20), 127.0 (CH-15), 123.0 (qC-12), 119.5 (CH-13), 118.8 (qC-3), 117.0 (qC-9), 112.0 (CH-16), 32.6 (C(5)-H₂), 23.2 (C(6)-H₂), 22.4 (C(8)-H₂), 22.0 (C(7)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₁H₁₈NO]⁺: 300.1383; found: 300.1392.

14-Fluoro-5,6,7,8-tetrahydrobenzofuro[3,2-c]quinoline (2l)

Synthesis of substrate **2l** as per general procedure 5 using **1l** (0.050 g, 0.21 mmol), Pd/C (22.4 mg, 0.021 mmol), AcOH (1.10 mL) and H₂ balloon at 80 °C.

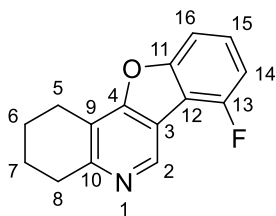


White solid; 70% (0.047 g); **m.p.** = 141 – 144 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2935, 1635, 1599, 1573, 1476, 1423, 1343, 1168, 1156, 1115, 1091, 897, 862, 816, 798; **¹H NMR (400 MHz, CDCl₃)** δ = 8.92 (s, 1H, H-2), 7.58 (dd, 1H, *J* = 2.6, 8.0 Hz, H-13), 7.48 (dd, 1H, *J* = 4.0, 9.0 Hz, H-16), 7.15 (td, 1H, *J* = 2.6, 9.0 Hz, H-15), 3.06

(t, 2H, *J* = 6.1 Hz, CH₂-8), 3.01 (t, 2H, *J* = 6.1 Hz, CH₂-5), 2.03–1.87 (m, 4H, CH₂-6, CH₂-7) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 161.0 (qC-4), 159.5 (d, ¹*J*_(C, F) = 241 Hz, qCF), 156.4 (qC-10), 152.1 (qC-11), 140.3 (CH-2), 123.5 (d, ³*J*_(C, F) = 10 Hz, qC-12), 118.6 (d, ⁴*J*_(C, F) = 2 Hz, qC-3), 117.1 (qC-9), 114.8 (d, ²*J*_(C, F) = 26 Hz, CH-15), 112.6 (d, ³*J*_(C, F) = 9 Hz, CH-16), 107.2 (d, ²*J*_(C, F) = 26 Hz, CH-13), 32.6 (C(5)-H₂), 23.1 (C(6)-H₂), 22.3 (C(8)-H₂), 21.9 (C(7)-H₂) ppm; **¹⁹F NMR (376 MHz, CDCl₃)** δ = –119.1 (C-F) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₁₃FNO]⁺: 242.0976; found: 242.0985.

7-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2m)

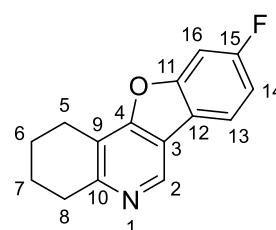
Synthesis of substrate **2m** as per general procedure 5 using **1m** (0.050 g, 0.21 mmol), Pd/C (22.4 mg, 0.021 mmol), AcOH (1.10 mL) and H₂ balloon at 80 °C.



White solid; 88% (0.045 g); **m.p.** 108 – 110 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2929, 2860, 1570, 1492, 1243, 1222, 1015; **¹H NMR (300 MHz, CDCl₃)** δ = 9.03 (s, 1H, H-**2**), 7.44 – 7.36 (m, 2H, H-**15**, H-**16**), 7.08 (overlapping ddd, 1H, J = 1.0, 7.9, 9.0 Hz, H-**14**), 3.11 – 3.01 (m, 4H, H-**5**, H-**8**), 2.05 – 1.89 (m, 4H, H-**6**, H-**7**) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 159.6 (qC-**4**), 157.4 (d, $^1J_{\text{C,F}}$ = 250 Hz, qC-**13**), 157.4 (d, $^3J_{\text{C,F}}$ = 9 Hz, qC-**11**), 156.1 (qC-**10**), 141.5 (d, $^4J_{\text{C,F}}$ = 3 Hz, CH-**2**), 128.1 (d, $^3J_{\text{C,F}}$ = 8 Hz, CH-**15**), 116.7 (qC-**9**), 116.3 (d, $^3J_{\text{C,F}}$ = 3 Hz, qC-**3**), 111.5 (d, $^2J_{\text{C,F}}$ = 23 Hz, qC-**12**), 109.9 (d, $^2J_{\text{C,F}}$ = 19 Hz, CH-**14**), 107.8 (d, $^4J_{\text{C,F}}$ = 4 Hz, CH-**16**), 32.5 (C(**5**)-H₂), 23.0 (C(**6**)-H₂), 22.2 (C(**8**)-H₂), 21.8 (C(**7**)-H₂) ppm; **¹⁹F NMR (282 MHz, CDCl₃)** δ = –115.9 (C-F) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₅H₁₃FNO]⁺: 242.0976; found: 242.0974.

9-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2n)

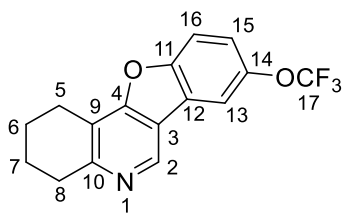
Synthesis of substrate **2n** as per general procedure 5 using **1n** (0.050 g, 0.21 mmol), Pd/C (22.4 mg, 0.021 mmol), AcOH (1.10 mL) and H₂ balloon at 80 °C.



White solid; 90% (0.046 g); **m.p.** 129 – 131 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2922, 2851, 1571, 1408, 1120, 1091, 1026; **¹H NMR (300 MHz, CDCl₃)** δ = 8.94 (s, 1H, H-**2**), 7.89 (dd, 1H, J = 5.4, 8.6 Hz, H-**13**), 7.30 (dd, 1H, J = 2.3, 8.6 Hz, H-**14**), 7.12 (ddd, 1H, J = 2.3, 8.6, 9.3 Hz, H-**16**), 3.11 – 2.99 (m, 4H, CH₂-**5**, CH₂-**8**), 2.5 – 1.85 (m, 4H, CH₂-**6**, CH₂-**7**) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 162.4 (d, $^1J_{\text{C,F}}$ = 244 Hz, qC-**15**), 160.7 (qC-**4**), 156.3 (d, $^3J_{\text{C,F}}$ = 13 Hz, qC-**11**), 155.5 (qC-**10**), 139.6 (CH-**2**), 121.4 (d, $^3J_{\text{C,F}}$ = 10 Hz, CH-**13**), 118.7 (d, $^4J_{\text{C,F}}$ = 2 Hz, qC-**12**), 118.1 (qC-**3**), 116.8 (qC-**9**), 111.6 (d, $^2J_{\text{C,F}}$ = 24 Hz, CH-**16**), 100.0 (d, $^2J_{\text{C,F}}$ = 28 Hz, CH-**14**), 32.4 (C(**5**)-H₂), 23.1 (C(**6**)-H₂), 22.2 (C(**8**)-H₂), 21.9 (C(**7**)-H₂) ppm; **¹⁹F NMR (282 MHz, CDCl₃)** δ = –112.2 (C-F) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. For [C₁₅H₁₃FNO]⁺: 242.0976; found: 242.0972.

8-(Trifluoromethoxy)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (2o)

Synthesis of substrate **2o** as per general procedure 5 using **1o** (0.085 g, 0.28 mmol), Pd/C (30 mg, 0.028 mmol), AcOH (1.70 mL) and H₂ balloon at 80 °C.

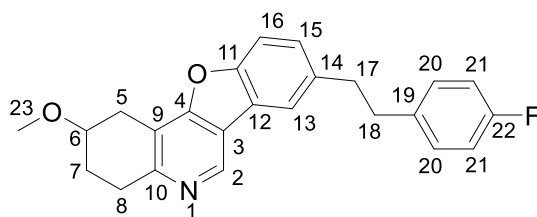


Off-white solid; 92% (0.080 g); **m.p.** 116 – 118 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2942, 1635, 1576, 1462, 1434, 1252, 1197, 1153; **¹H NMR (400 MHz, CDCl₃)** δ = 8.96 (s, 1H, H-2), 7.80 (s, 1H, H-13), 7.56 (d, 1H, J = 8.9 Hz, H-16), 7.32 (dd, 1H, J = 1.3, 8.9 Hz, H-15), 3.08 (t, 2H, J = 6.2 Hz, CH₂-8), 3.04

(t, 2H, J = 6.2 Hz, CH₂-5), 2.04–1.88 (m, 4H, CH₂-6, CH₂-7) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 161.0 (qC-4), 156.8 (qC-10), 154.0 (qC-11), 145.4 (q, $^2J_{\text{C,F}}$ = 2 Hz, qC-14), 140.4 (CH-2), 123.6 (qC-12), 120.9 (CH-15), 120.7 (q, $^1J_{\text{C,F}}$ = 257 Hz, C(17)-F₃), 118.2 (qC-3), 117.2 (qC-9), 113.9 (CH-13), 112.7 (CH-16), 32.6 (C(5)-H₂), 23.1 (C(6)-H₂), 22.3 (C(8)-H₂), 21.9 (C(7)-H₂) ppm; **¹⁹F NMR (376 MHz, CDCl₃)** δ = –58.2 (CF₃-17) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₁₆H₁₃F₃NO₂]⁺: 308.0893; found: 308.0905.

8-(4-fluorophenethyl)-2-methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (4a)

Synthesis of substrate **4a** as per general procedure 5 using **3a** (0.075 g, 0.20 mmol), Pd/C (22 mg, 0.020 mmol), AcOH (1.20 mL) and H₂ balloon at 80 °C. ¹H NMR analysis showed a mixture of **4a** (7% conversion) and only alkene reduction (93% reduction). Isolated alkene-reduced substrate (0.030 g, 0.081 mmol, 1 eq.) was resubmitted with Pd/C (13 mg, 0.012 mmol, 15 mol%) in AcOH (0.60 mL) as per general procedure 5 at 80 °C for 48 hours. The product was then purified by preparative thin layer chromatography (DCM/EtOAc 1:1 + 1% NEt₃).



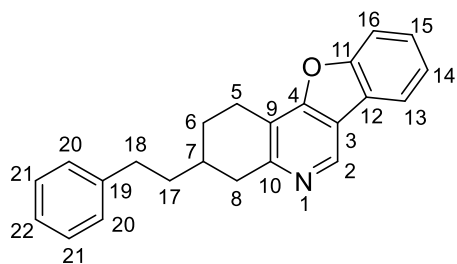
Colourless oil; 29% (0.009 g); **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2927, 1638, 1575, 1509, 1480, 1433, 1220, 1192, 1103, 825, 752; **¹H NMR (500 MHz, CDCl₃)** δ = 8.96 (s, 1H, H-2), 7.74 (d, 1H, J = 1.7 Hz, H-13), 7.48 (d, 1H, J = 8.4 Hz, H-

16), 7.23 (dd, 1H, J = 1.7, 8.4 Hz, H-15), 7.13–7.08 (m, 2H, H-20), 6.95 (t, 2H, J = 8.7, H-21), 3.88–3.81 (m, 1H, CH-6), 3.48 (s, 3H, CH₃-23), 3.34 (dd, 1H, J = 4.8, 16.9 Hz, one of CH₂-5), 3.24 (m, 1H, one of CH₂-8), 3.12–3.03 (m, 4H, one of CH₂-5, one of CH₂-8, and CH₂-17), 3.00–2.95 (m, 2H, CH₂-18), 2.22–2.09 (m, 2H, CH₂-7) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 161.5 (d, $^1J_{\text{C,F}}$ = 244 Hz, qC-22), 160.8 (qC-4), 154.8 (qC-10 or qC-11), 154.7 (qC-10 or qC-11), 140.4 (CH-2), 137.2 (qC-14), 137.1 (qC-19), 130.0 (d, $^3J_{\text{C,F}}$ = 8 Hz, 2 × CH-20), 128.3 (CH-15), 122.5 (qC-12), 120.7 (CH-13), 119.0 (qC-3), 115.3

(d, $^2J_{(C,F)} = 21$ Hz, $2 \times$ CH-**21**), 114.3 (qC-**9**), 111.7 (CH-**16**), 74.2 (CH-**6**), 56.2 (C(**23**)-H₃), 38.1 (C(**17**)-H₂), 37.7 (C(**18**)-H₂), 29.5 (C(**8**)-H₂), 28.2 (C(**5**)-H₂), 27.5 (C(**7**)-H₂) ppm; **¹⁹F NMR (376 MHz, CDCl₃)** $\delta = -117.4$ (CF) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₂₄H₂₃FNO₂]⁺: 376.1707; found: 376.1706.

3-Phenethyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline (4b)

Synthesis of substrate **4b** as per general procedure 5 using **3b** (0.078 g, 0.24 mmol), Pd/C (26 mg, 0.024 mmol), AcOH (1.50 mL) and H₂ balloon for 30 hours.



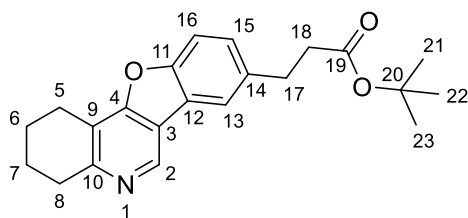
Off-white solid; 67% (0.053 g); **m.p.** 114 – 118 °C;

IR $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2921, 1602, 1573, 1427, 1343, 1195, 1016, 919, 747, 696; **¹H NMR (400 MHz, CDCl₃)** $\delta = 8.99$ (s, 1H, H-**2**), 7.95 (d, 1H, $J = 7.4$ Hz, H-**13**), 7.58 (d, 1H, $J = 8.0$ Hz, H-**16**), 7.46 (t, 1H, $J = 7.4$ Hz, H-**15**), 7.37 (t, 1H, $J = 7.4$ Hz, H-**14**), 7.32–7.16

(m, 5H, H-**20**, H-**21**, H-**22**), 3.34–3.12 (m, 2H, one of CH₂-**5** and one of CH₂-**8**), 3.01–2.87 (m, 1H, one of CH₂-**5**), 2.84–2.71 (m, 3H, CH₂-**18** and one of CH₂-**8**), 2.21–1.16 (m, 5H, CH₂-**17**, CH₂-**6** and H-**7**) ppm; **¹³C NMR (101 MHz, CDCl₃)** $\delta = 160.1$ (qC-**4**), 156.1 (qC-**11**), 155.4 (qC-**10**), 142.6 (qC-**19**), 140.3 (CH-**2**), 128.5 (4 $\times$ CH-**20** and CH-**21**), 127.6 (CH-**15**), 125.9 (CH-**22**), 123.7 (CH-**14**), 122.5 (qC-**12**), 121.1 (CH-**13**), 118.9 (qC-**3**), 116.6 (qC-**9**), 112.0 (CH-**16**), 39.1 (C(**8**)-H₂), 38.2 (C(**17**)-H₂), 33.9 (CH-**7**), 33.3 (C(**18**)-H₂), 28.2 (C(**6**)-H₂), 22.0 (C(**5**)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. for [C₂₃H₂₂NO]⁺: 328.1696; found: 328.1683.

tert-Butyl 3-(1,2,3,4-tetrahydrobenzofuro[3,2-c]quinolin-8-yl)propanoate (4c)

Synthesis of substrate **4c** as per general procedure 5 using **3c** (0.050 g, 0.20 mmol), Pd/C (21.7 mg, 0.020 mmol), AcOH (1.10 mL) and H₂ balloon at 80 °C.



White solid; 88% (0.54 mg); **m.p.** 58 – 60 °C; **IR**

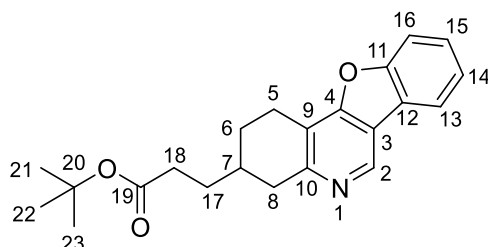
$\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3071, 3018, 1620, 1568, 1501, 1392, 1238, 1159; **¹H NMR (300 MHz, CDCl₃)** $\delta = 8.88$ (s, 1H, H-**2**), 7.73 (d, 1H, $J = 1.7$ Hz, H-**13**), 7.41 (d, 1H, $J = 8.5$ Hz, H-**16**), 7.23 (dd, 1H, $J = 1.7$,

8.5 Hz, H-**15**), 3.06 – 2.92 (m, 6H, CH₂-**5**, CH₂-**8**, CH₂-**17**), 2.55 (t, 2H, $J = 7.7$ Hz, CH₂-**18**), 1.98 – 1.78 (m, 4H, CH₂-**6**, CH₂-**7**), 1.34 (s, 9H, CH₃-**21**, CH₃-**22**, CH₃-**23**) ppm; **¹³C NMR (125 MHz, CDCl₃)** $\delta = 171.1$ (qC-**19**), 159.3 (qC-**4**), 154.5 (qC-**11**), 153.7 (qC-**10**), 138.9 (CH-**2**), 135.3 (qC-**14**), 126.9 (CH-**15**), 121.4 (qC-**12**), 119.4 (CH-**13**), 117.6 (qC-**3**), 115.8 (qC-**9**), 110.5 (CH-**16**), 79.5 (qC-**20**), 36.5 (C(**18**)-H₂), 31.4 (C(**5**)-H₂), 30.0 (C(**17**)-H₂), 27.1 (3 $\times$ C(**21**)-H₃, C(**22**)-H₃, C(**23**)-H₃), 22.1 (C(**6**)-H₂), 21.2 (C(**8**)-H₂), 20.9

(C(7)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₂H₂₆NO₃]⁺: 352.1913; found: 352.1911.

tert-Butyl 3-(1,2,3,4-tetrahydrobenzofuro[3,2-c]quinolin-3-yl)propanoate (4d)

Synthesis of substrate **4d** as per general procedure 5 using **3d** (0.057 g, 0.17 mmol), Pd/C (18 mg, 0.017 mmol), AcOH (1.0 mL) and H₂ balloon for 30 hours.

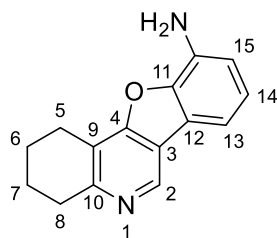


White solid; 86% (0.050 g); **m.p.** 91 – 94 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2926, 1724, 1573, 1445, 1366, 1190, 1141, 1017, 747; **¹H NMR (400 MHz, CDCl₃)** δ = 8.98 (s, 1H, H-2), 7.96 (d, 1H, *J* = 7.5 Hz, H-13), 7.58 (d, 1H, *J* = 8.2 Hz, H-16), 7.47 (t, 1H, *J* = 7.5 Hz, H-15), 7.38 (t, 1H, *J* =

7.5 Hz, H-14), 3.28–3.18 (m, 2H, one of CH₂-5 and one of CH₂-8), 3.03–2.88 (m, 1H, one of CH₂-5), 2.70 (dd, 1H, *J* = 10.4, 17.2 Hz, one of CH₂-8), 2.39 (t, 2H, *J* = 7.7 Hz, CH₂-18), 2.16–2.07 (m, 1H, one of CH₂-6), 1.99–1.91 (m, 1H, CH-7), 1.81–1.74 (m, 2H, CH₂-17), 1.59–1.49 (m, 1H, one of CH₂-6), 1.46 (s, 9H, CH₃-21, CH₃-22, CH₃-23) ppm; **¹³C NMR (101 MHz, CDCl₃)** δ = 173.2 (qC-19), 160.0 (qC-4), 156.1 (qC-11), 155.1 (qC-10), 140.3 (CH-2), 127.6 (CH-15), 123.7 (CH-14), 122.4 (qC-12), 121.0 (CH-13), 118.9 (qC-3), 116.5 (qC-9), 112.0 (CH-16), 80.4 (qC-20), 38.9 (C(8)-H₂), 33.9 (CH-7), 33.2 (C(18)-H₂), 31.4 (C(17)-H₂), 28.3 (3 × C(21)-H₃, C(22)-H₃, C(23)-H₃), 27.9 (C(6)-H₂), 21.9 (C(5)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₂H₂₆NO₃]⁺: 352.1907; found: 352.1921.

1,2,3,4-Tetrahydrobenzofuro[3,2-c]quinolin-10-amine (6a)

Synthesis of substrate **6a** as per general procedure 5. AcOH was replaced with MsOH (2M, 0.57 mL, 1.14 mmol, 3 eq.) in *i*PrOH (2.2 mL). From **5** (0.100 g, 0.38 mmol), Pd/C (40.2 mg, 0.038mmol) and H₂ balloon at 80 °C.

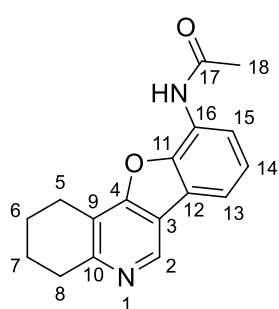


White solid; 90% (0.081 g); **m.p.** 202 – 204 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3320, 3197, 2932, 1641, 1575, 1500, 1444, 1425, 1323, 1187, 1163, 1071, 893, 783, 753, 730; **¹H NMR (500 MHz, CDCl₃)** δ = 8.94 (s, 1H, H-2), 7.36 (dd, 1H, *J* = 1.0, 7.7 Hz, H-13), 7.18 (t, 1H, *J* = 7.7 Hz, H-14), 6.83 (dd, 1H, *J* = 1.0, 7.7 Hz, H-15), 4.07 (br s, 2H, NH₂), 3.02 – 3.10 (m, 4H, CH₂-5, CH₂-8), 1.90 – 2.02 (m, 4H, CH₂-6, CH₂-7) ppm; **¹³C NMR (125 MHz, CDCl₃)** δ = 159.8 (qC-4), 155.3 (qC-10), 144.6 (qC-11), 140.3 (CH-2), 132.0 (qC-16), 124.4 (CH-14), 122.8 (qC-12), 119.4 (qC-3), 116.8 (qC-9), 113.4 (CH-15), 110.6 (CH-13), 32.4 (C(5)-H₂), 23.1 (C(6)-H₂), 22.3

(C(8)-H₂), 21.9 (C(7)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₁₅N₂O]⁺: 239.1179; found: 239.1186.

***N*-(1,2,3,4-Tetrahydrobenzofuro[3,2-*c*]quinolin-10-yl)acetamide (6b)**

Synthesis of substrate **6b** as per general procedure 5 using **5** (100 g, 0.38 mmol), Pd/C (40.2 mg, 0.038 mmol), AcOH (2.20 mL) and H₂ balloon at 80 °C for 72 h.

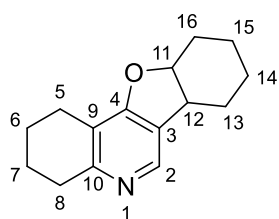


White solid; 68% (0.072 g); **m.p.** 233 – 234 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3228, 2930, 1669, 1574, 1542, 1433, 1418, 1402, 1277, 1194, 1075, 792, 741, 734; **¹H NMR (600 MHz, CDCl₃)** δ = 8.97 (s, 1H, H-2), 8.34 (d, 1H *J* = 7.6 Hz, H-13), 7.80 (br s, 1H, NH), 7.67 (d, 1H, *J* = 7.3 Hz, H-15), 7.35 (t, 1H, *J* = 7.6 Hz, H-14), 3.11–3.02 (m, 4H, CH₂-5, CH₂-8), 2.34 (s, 3H, CH₃-18), 1.99 (d, 2H, *J* = 4.9 Hz, CH₂-7), 1.93 (d, 2H, *J* = 4.9 Hz, CH₂-6) ppm; **¹³C NMR (151 MHz, CDCl₃)** δ = 168.6 (q(C=O)-17), 159.7 (qC-4), 156.1 (qC-10), 145.3 (qC-11), 140.4 (CH-2), 124.5 (CH-14), 123.9 (qC-16), 122.7 (qC-12), 119.0 (qC-3), 118.8 (CH-13), 116.9 (qC-9), 116.1 (CH-15), 32.5 (C(5)-H₂), 24.9 (C(18)-H₃), 23.1 (C(6)-H₂), 22.5 (C(8)-H₂), 21.9 (C(7)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₇H₁₇N₂O₂]⁺: 281.1285; found: 281.1297.

Synthesis of Extended Reduction Products:

1,2,3,4,6b,7,8,9,10,10a-Decahydrobenzofuro[3,2-*c*]quinoline (7a)

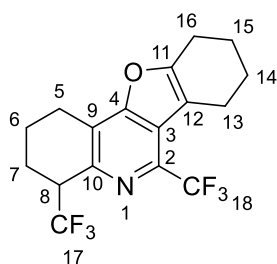
Synthesis of substrate **7a** as per general procedure 5 using **1a** (0.050 g, 0.23 mmol), Pd/C (22.4 mg, 0.023 mmol), AcOH (1.10 mL) and H₂ balloon with elevated temperature of 100 °C and reaction time of 48 hours.



White solid; 80% (0.042 g); **m.p.** 87 – 89 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2930, 2857, 1617, 1579, 1458, 1288, 1070, 937, 907; **¹H NMR (600 MHz, CDCl₃)** δ = 8.06 (s, 1H, H-2), 4.73 (dt, *J* = 5.1, 7.0 Hz, 1H, H-11), 3.25 (q, *J* = 7.1 Hz, 1H, H-12), 2.86 (t, *J* = 6.3 Hz, 2H, H₂-8), 2.64 (t, *J* = 6.3 Hz, 2H, H₂-5), 2.02–1.94 (m, 1H, one of H₂-16), 1.91–1.75 (m, 6H, H₂-6, H₂-7, one of H₂-13 and one of H₂-16), 1.55–1.47 (m, 4H, one of H₂-13, one of H₂-14, and H₂-15), 1.40–1.32 (m, 1H, one of H₂-14) ppm; **¹³C NMR (151 MHz, CDCl₃)** δ = 164.7 (qC-4), 157.5 (qC-10), 141.4 (CH-2), 126.7 (qC-3), 115.9 (qC-9), 84.2 (CH-11), 38.7 (CH-12), 32.5 (C(8)-H₂), 28.2 (C(13)-H₂), 27.5 (C(16)-H₂), 23.2 (C(6)-H₂ or C(7)-H₂), 22.4 (C(5)-H₂), 22.2 (C(6)-H₂ or C(7)-H₂), 21.7 (C(14)-H₂), 20.3 (C(15)-H₂) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₂₀NO]⁺: 230.1539; found: 230.1551.

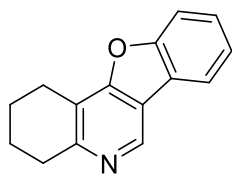
4,6-Bis(trifluoromethyl)-1,2,3,4,6b,7,8,9,10,10a-decahydrobenzofuro[3,2-c]quinoline (**7b**)

Synthesis of substrate **7b** as per general procedure 5 using **1j** (0.050 g, 0.14 mmol), Pd/C (15.0 mg, 0.014 mmol), AcOH (1.10 mL) and H₂ balloon with elevated temperature of 100 °C and reaction time of 48 hours.



White solid; 81% (0.041 mg); **m.p.** 106 – 108 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2953, 2856, 1626, 1462, 1242, 1163, 1111, 1040; **¹H NMR (600 MHz, CDCl₃)** δ = 3.82 (m, 1H, H-**8**), 3.11 (dt, 1H, J = 5.5 Hz, one of H₂-**5**), 3.00 (dt, 1H, J = 7.7 Hz, one of H₂-**5**), 2.82 – 2.77 (m, 2H, H₂-**16**), 2.74 (t, 2H, J = 5.8 Hz, H₂-**13**), 2.34 – 2.26 (m, 1H, one of H₂-**7**), 2.15 – 2.04 (m, 2H, one of H₂-**6** and one of H₂-**7**), 1.97 – 1.92 (m, 2H, H₂-**15**), 1.91 – 1.83 (m, 3H, one of H₂-**6** and H₂-**14**) ppm; **¹³C NMR (151 MHz, CDCl₃)** δ = 158.9 (qC-**4**), 157.4 (qC-**11**), 142.6 (qC-**10**), 136.8 (q, $^2J_{\text{C,F}}$ = 37 Hz, qC-**2**), 126.8 (q, $^1J_{\text{C,F}}$ = 282 Hz, C(**17**)-F₃), 121.9 (qC-**9**), 121.8 (q, $^1J_{\text{C,F}}$ = 272 Hz, C(**18**)-F₃), 121.2 (qC-**3**), 111.4 (qC-**12**), 43.9 (q, $^2J_{\text{C,F}}$ = 25 Hz, C-**8**), 23.7 (C(**16**)-H₂), 23.2 (q, $^3J_{\text{C,F}}$ = 2 Hz, C(**7**)-H₂), 22.6 (C(**14**)-H₂), 22.2 (C(**15**)-H₂), 21.7 (C(**5**)-H₂), 21.6 (q, $^5J_{\text{C,F}}$ = 4 Hz, C(**13**)-H₂), 18.0 (C(**6**)-H₂) ppm; **¹⁹F NMR (471 MHz, CDCl₃)** δ = –63.5 (CF₃), –66.6 (CF₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : [M + H]⁺ calcd. For [C₁₇H₁₆F₆NO]⁺: 364.1131; found: 364.1138.

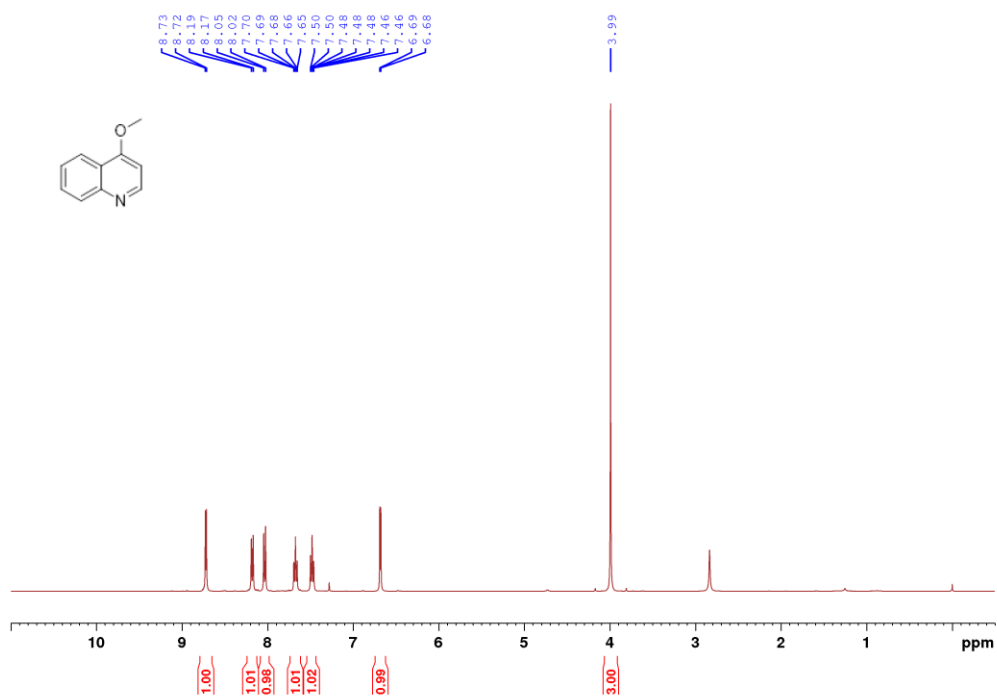
Scale up Synthesis of **2a**



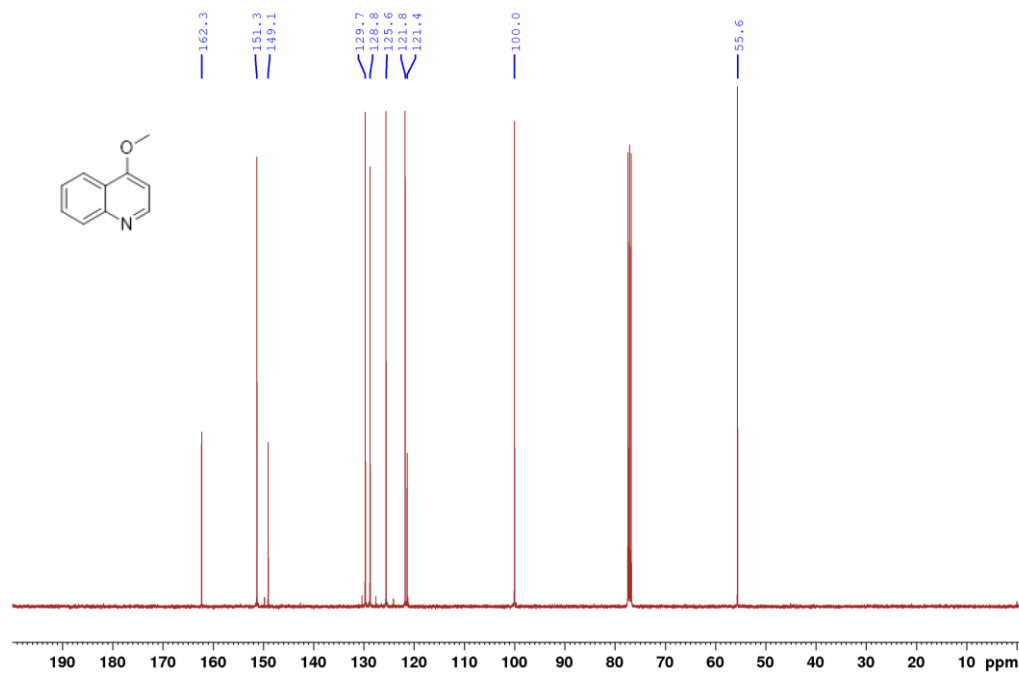
The scale up synthesis of **2a** was performed as per general procedure 5 using **1a** (1.10 g, 5.01 mmol), Pd/C (267 mg, 0.025 mmol, 5 mol%), AcOH (16.0 mL) and H₂ balloon in a 50 mL schlenk flask at 50 °C. yield: 91% (1.02 g) characterised as per **2a** above.

NMR Spectra of Substituted Quinolines

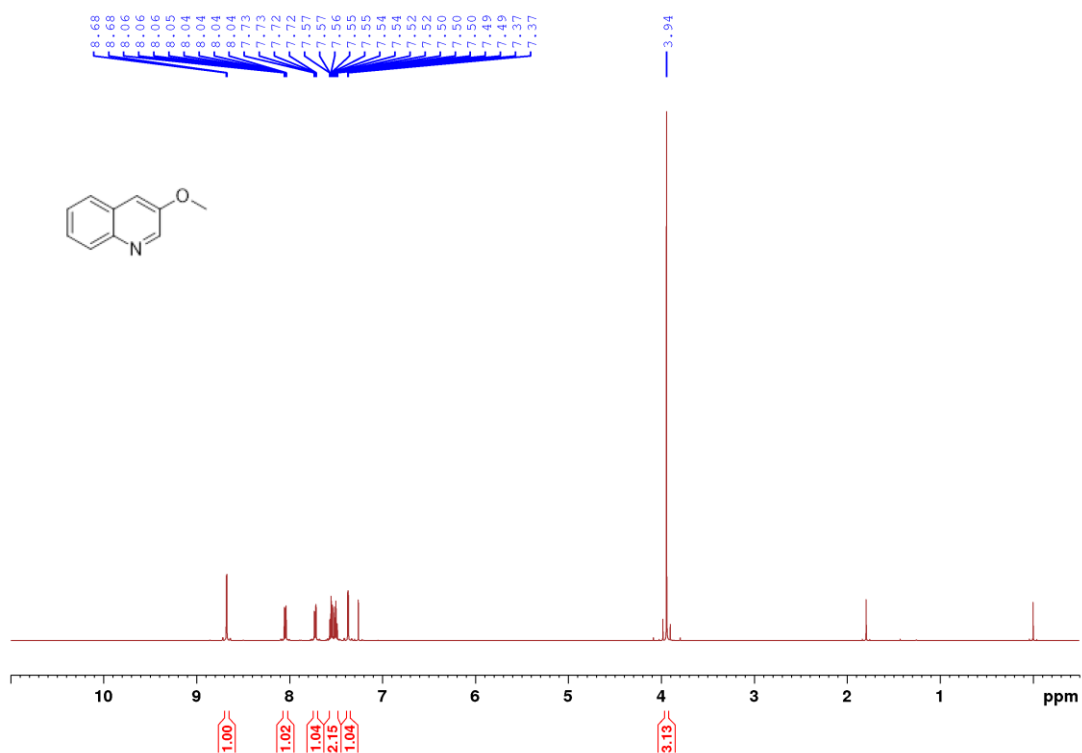
4-Methoxyquinoline ^1H NMR, 400 MHz, CDCl_3 (9)



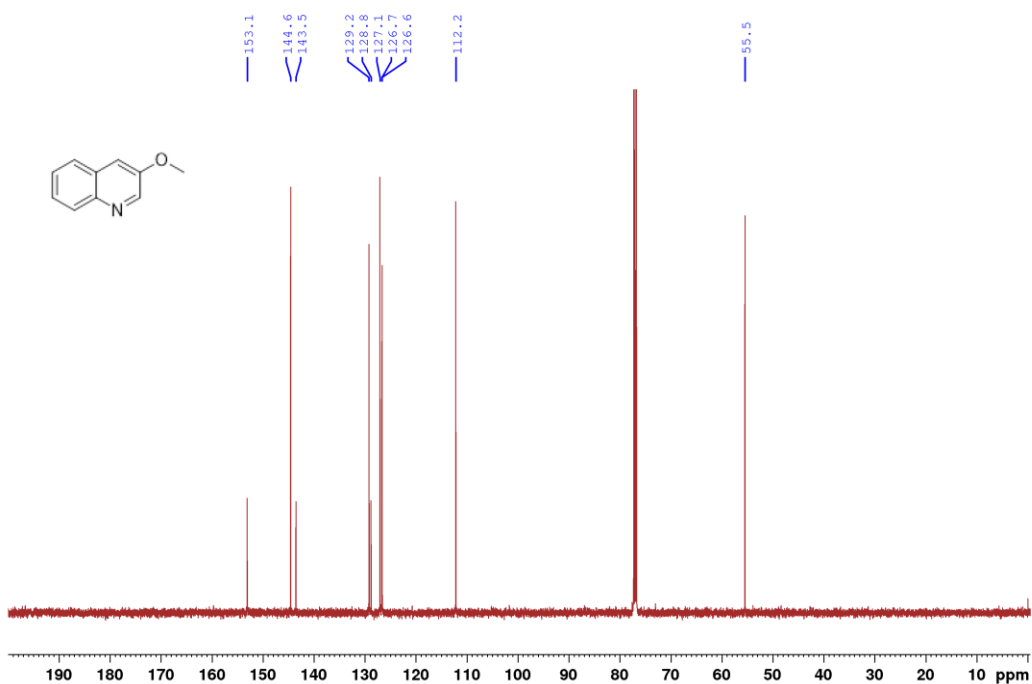
4-Methoxyquinoline ^{13}C NMR, 75 MHz, CDCl_3 (9)



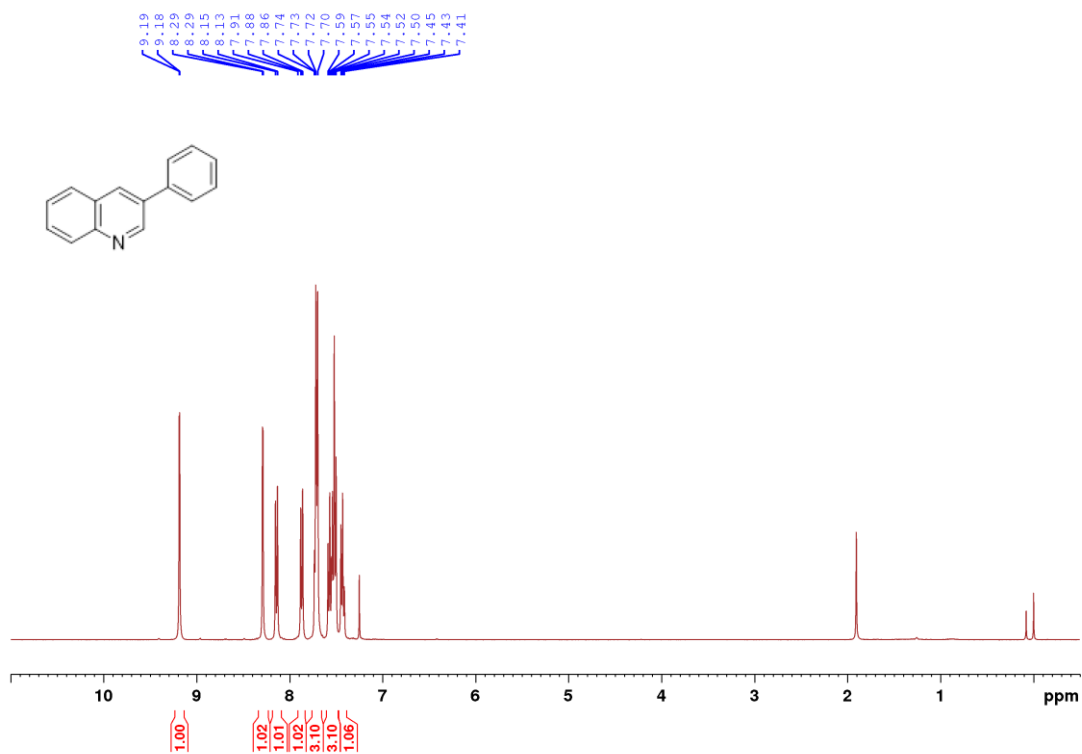
3-Methoxyquinoline ^1H NMR, 500 MHz, CDCl_3 (12)



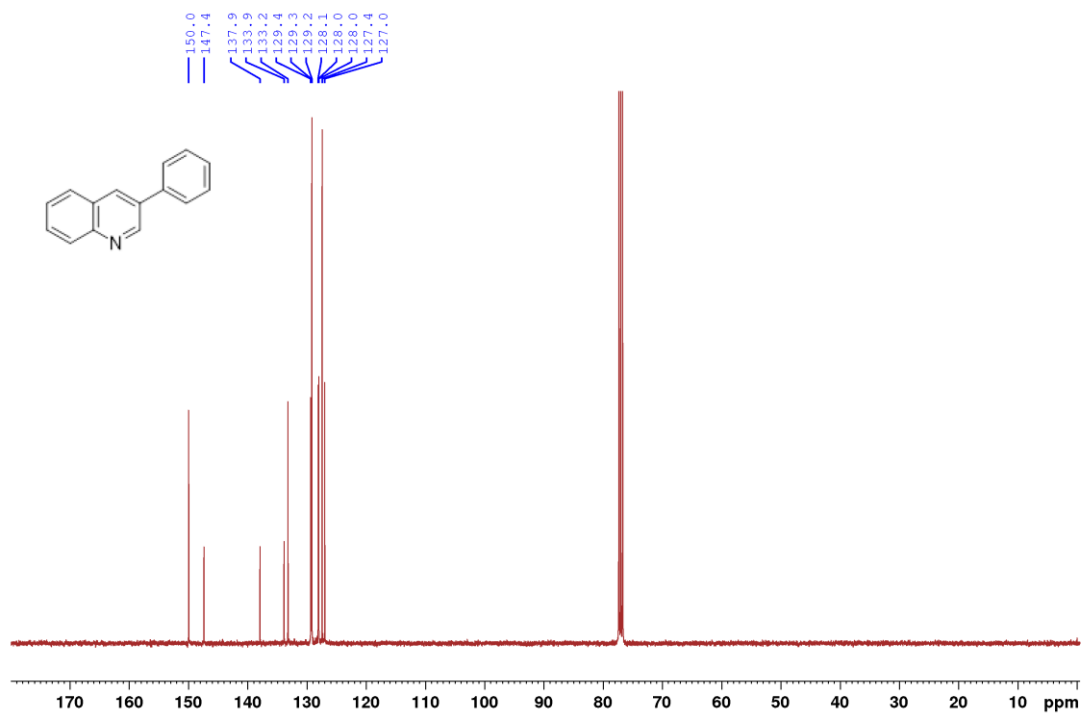
3-Methoxyquinoline ^{13}C NMR, 125 MHz, CDCl_3 (12)



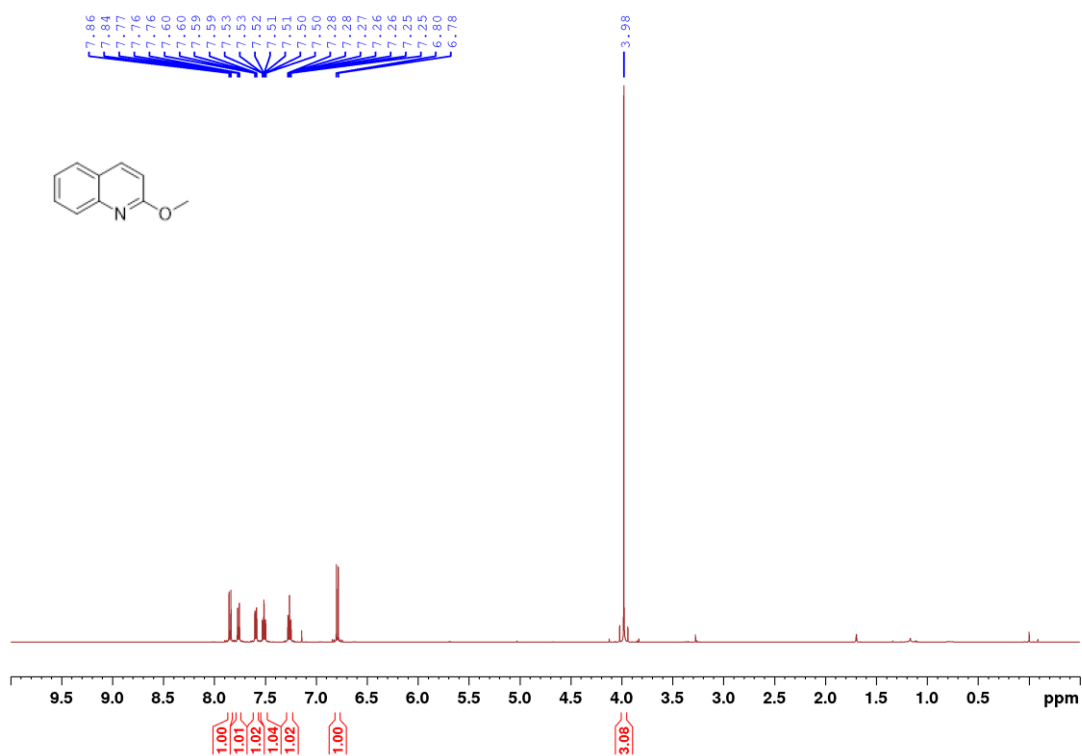
3-Phenylquinoline ^1H NMR, 400 MHz, CDCl_3 (13)



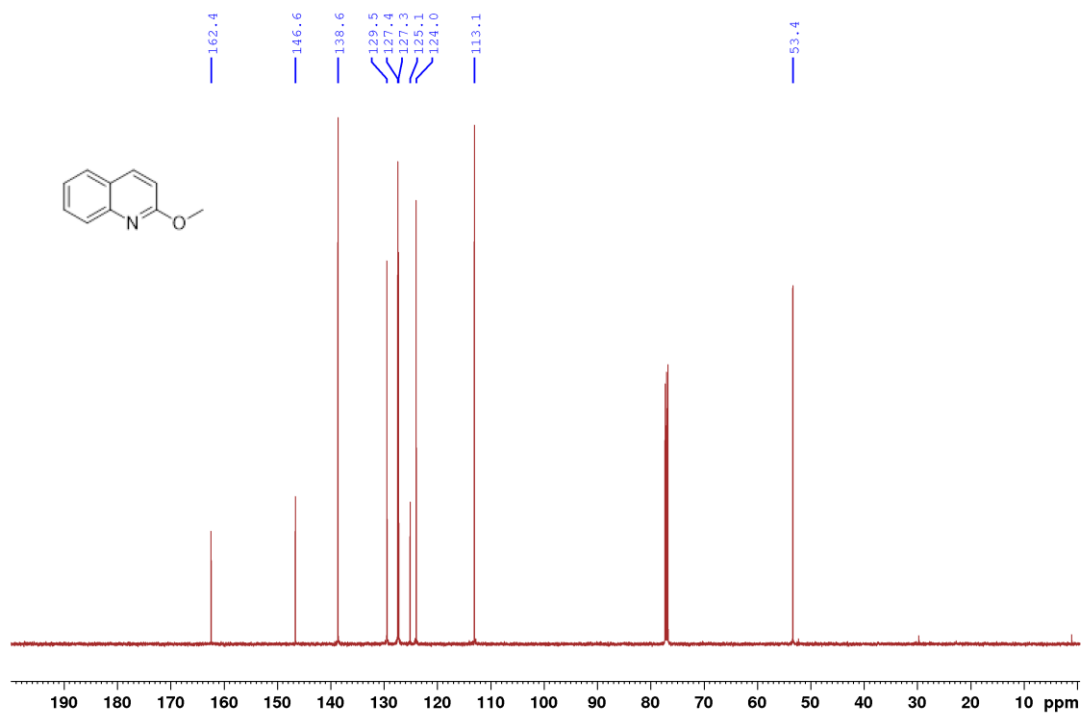
3-Phenylquinoline ^{13}C NMR, 75 MHz, CDCl_3 (13)



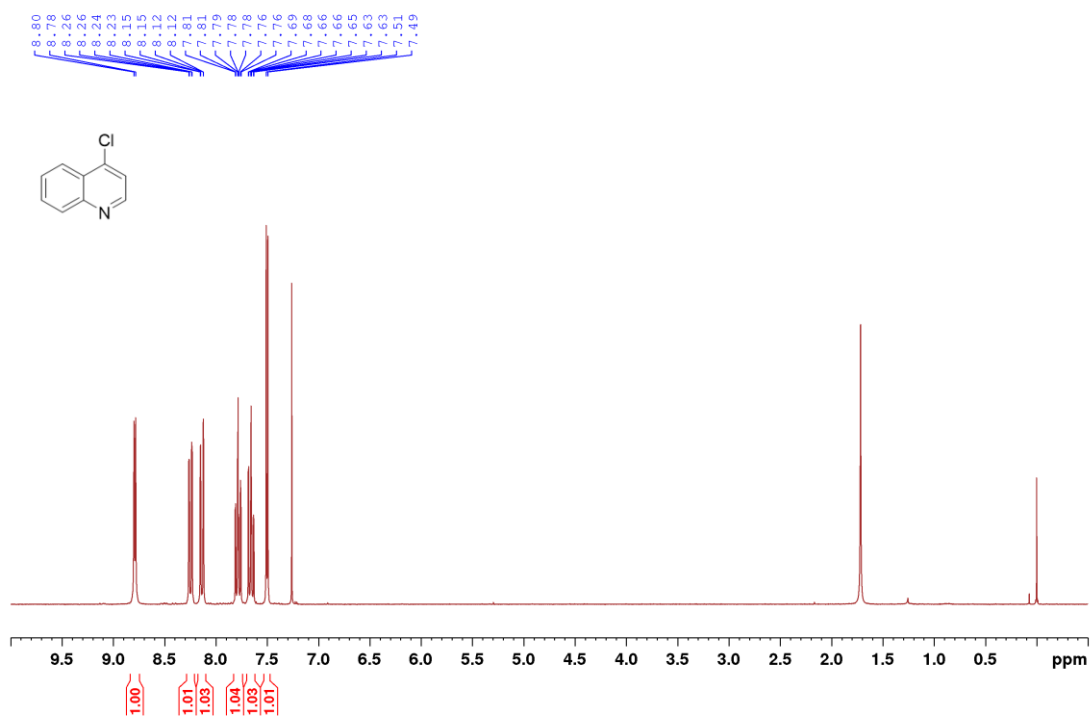
2-Methoxyquinoline ^1H NMR, 500 MHz, CDCl_3 (S8)



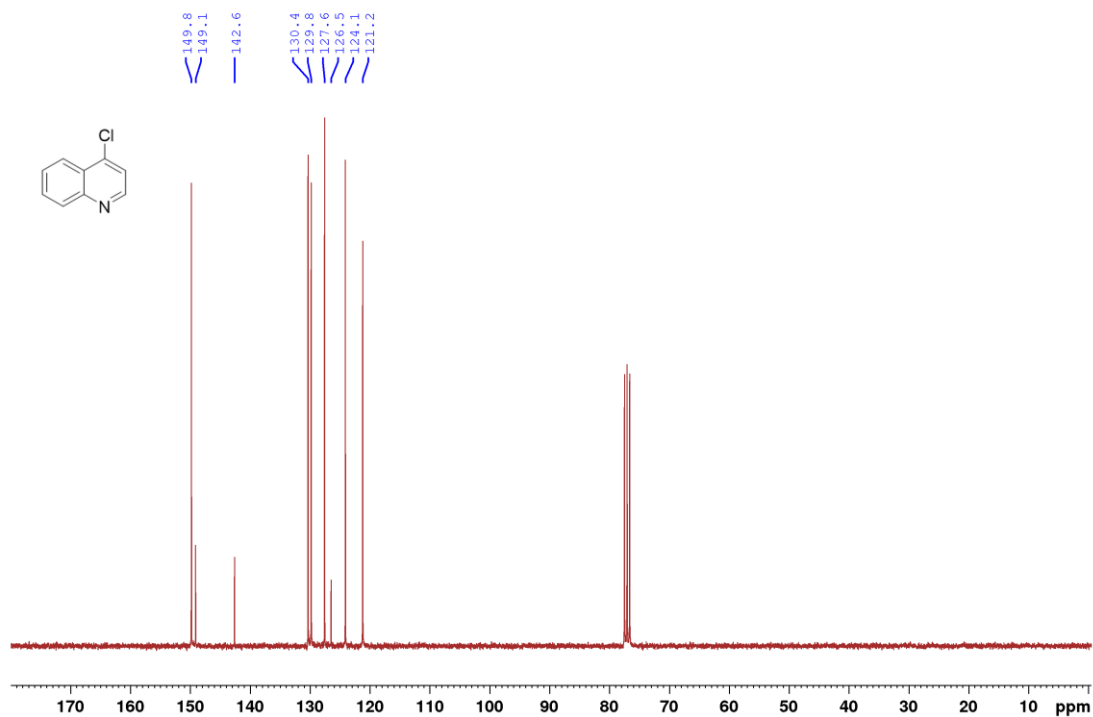
2-Methoxyquinoline ^{13}C NMR, 125 MHz, CDCl_3 (S8)



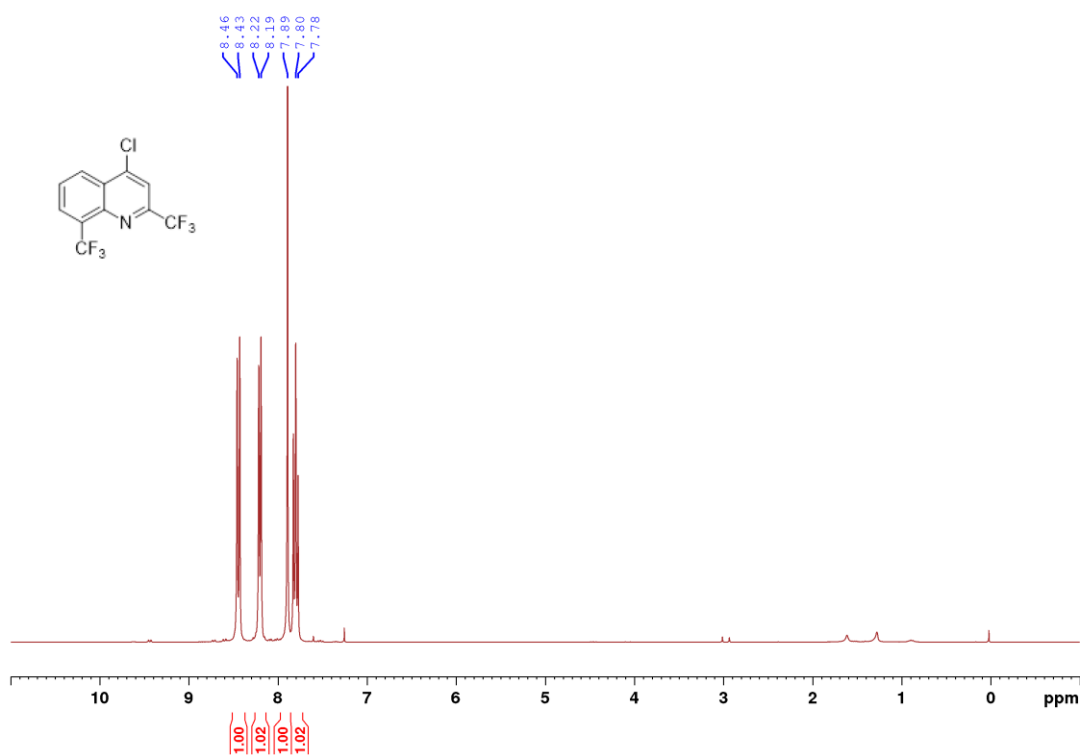
4-Chloroquinoline ^1H NMR, 300 MHz, CDCl_3 (S9)



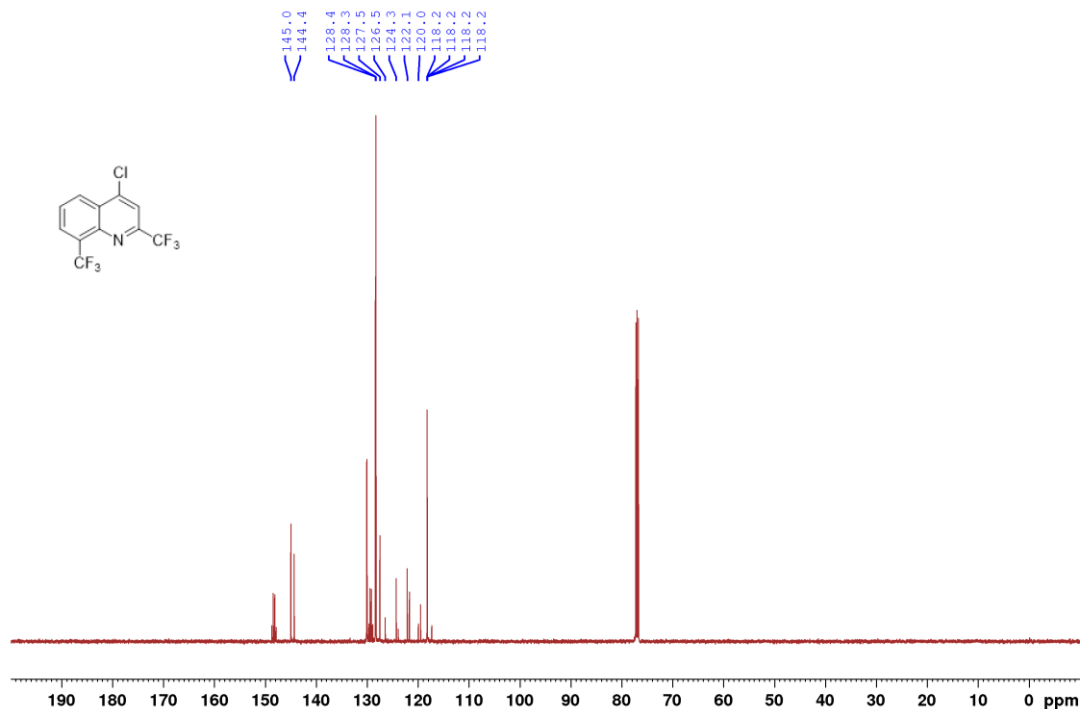
4-Chloroquinoline ^{13}C NMR, 75 MHz, CDCl_3 (S9)



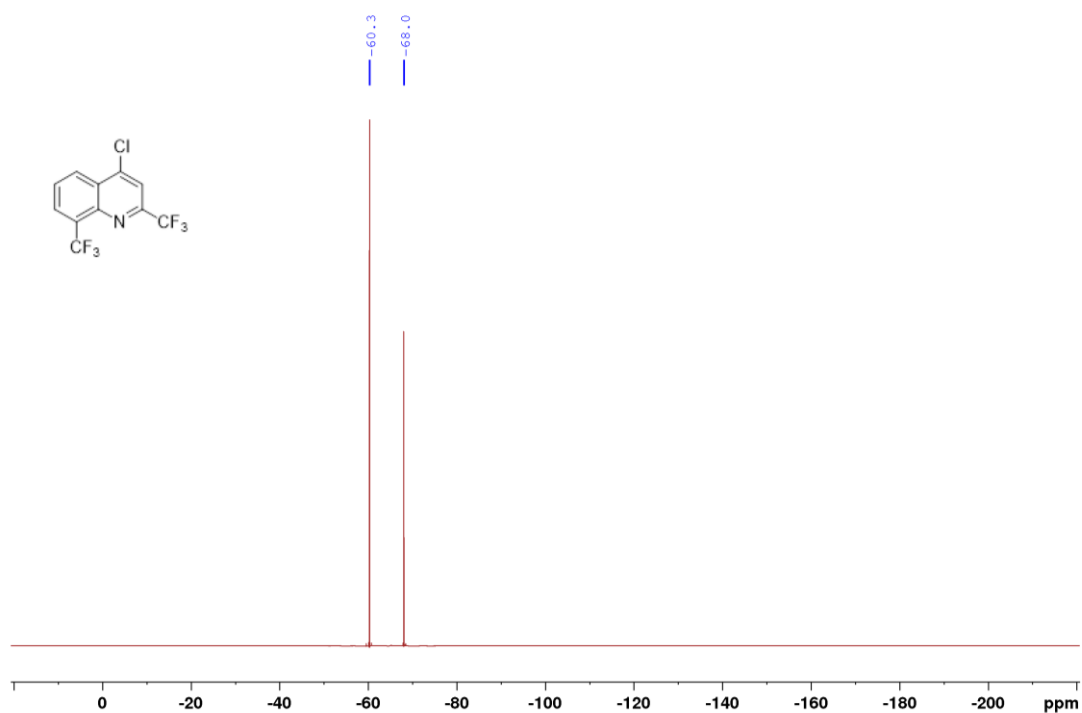
4-Chloro-2,8-bis(trifluoromethyl)quinoline ^1H NMR, 500 MHz, CDCl_3 (S10)



4-Chloro-2,8-bis(trifluoromethyl)quinoline ^{13}C NMR, 125 MHz, CDCl_3 (S10)

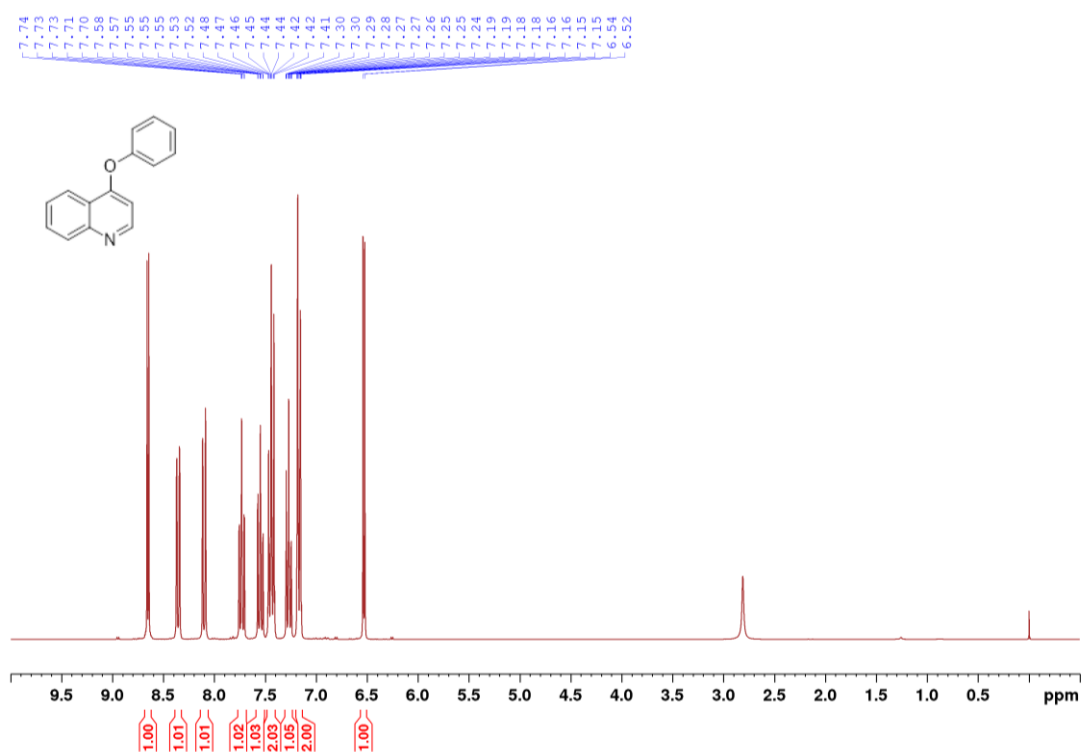


4-Chloro-2,8-bis(trifluoromethyl)quinoline ^{19}F NMR, 471 MHz, CDCl_3 (S10)

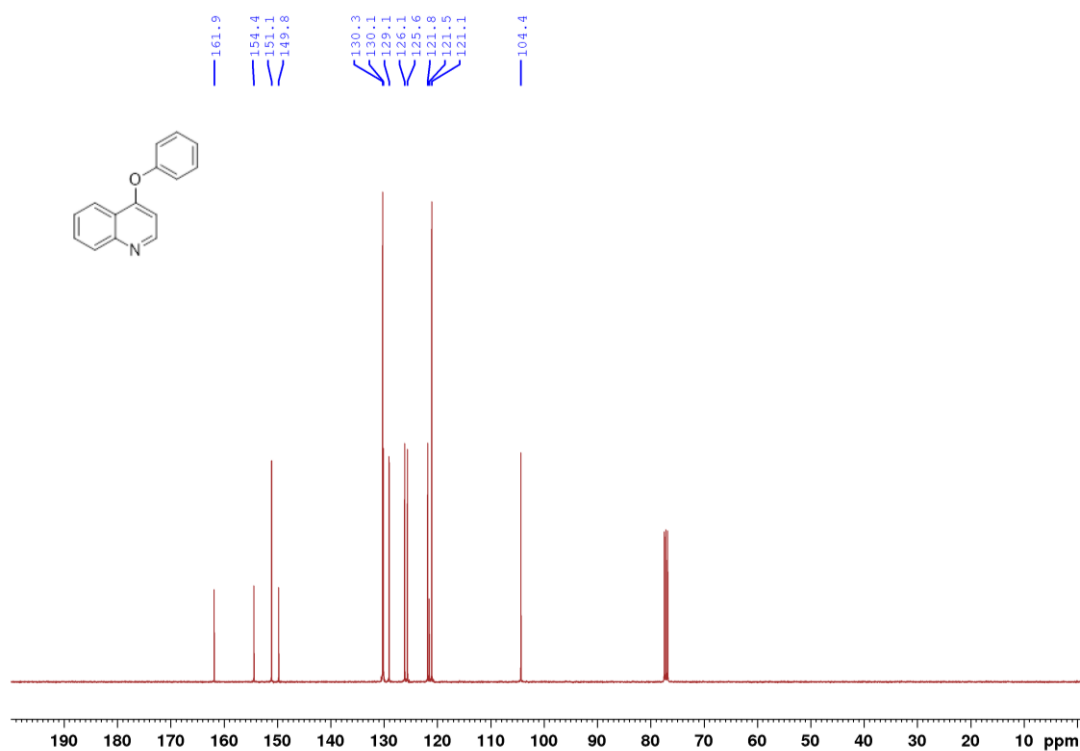


NMR Spectra of Phenoxyquinolines

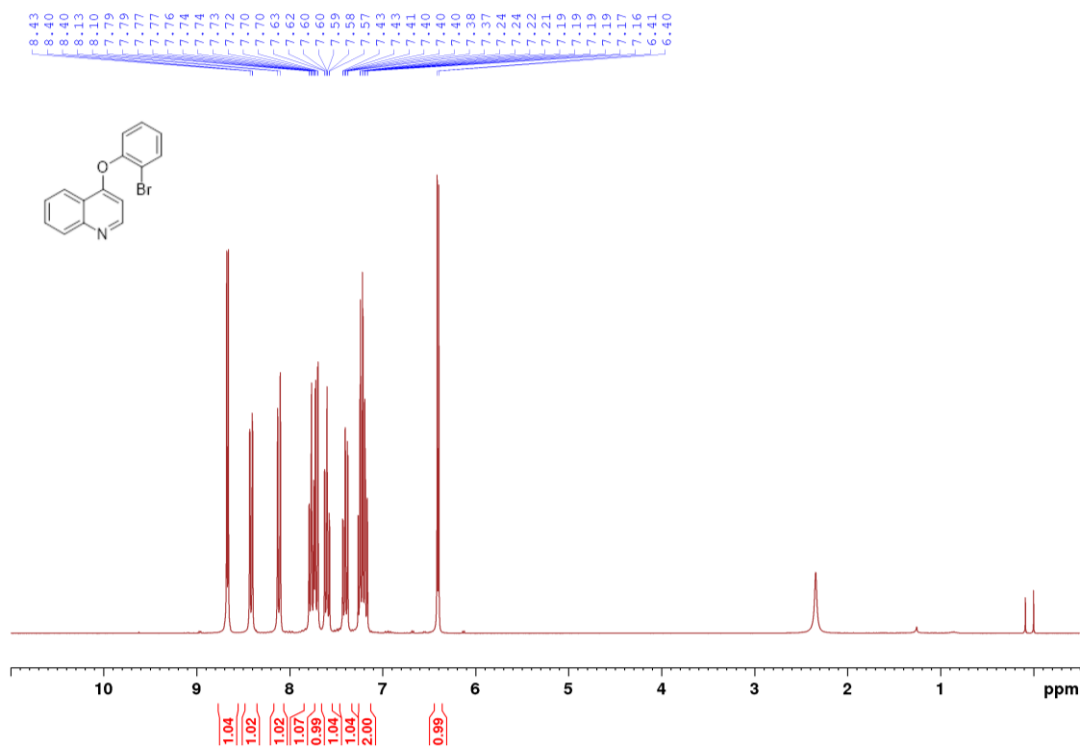
4-Phenoxyquinoline ^1H NMR, 500 MHz, CDCl_3 (10)



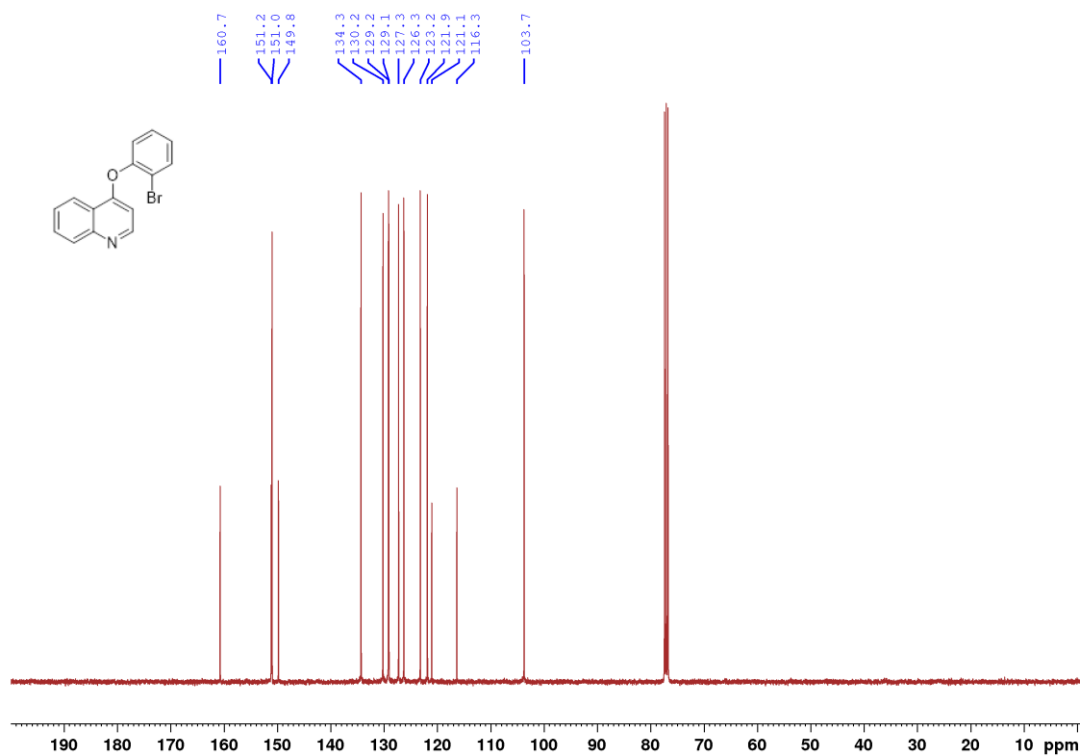
4-Phenoxyquinoline ^{13}C NMR, 125 MHz, CDCl_3 (10)



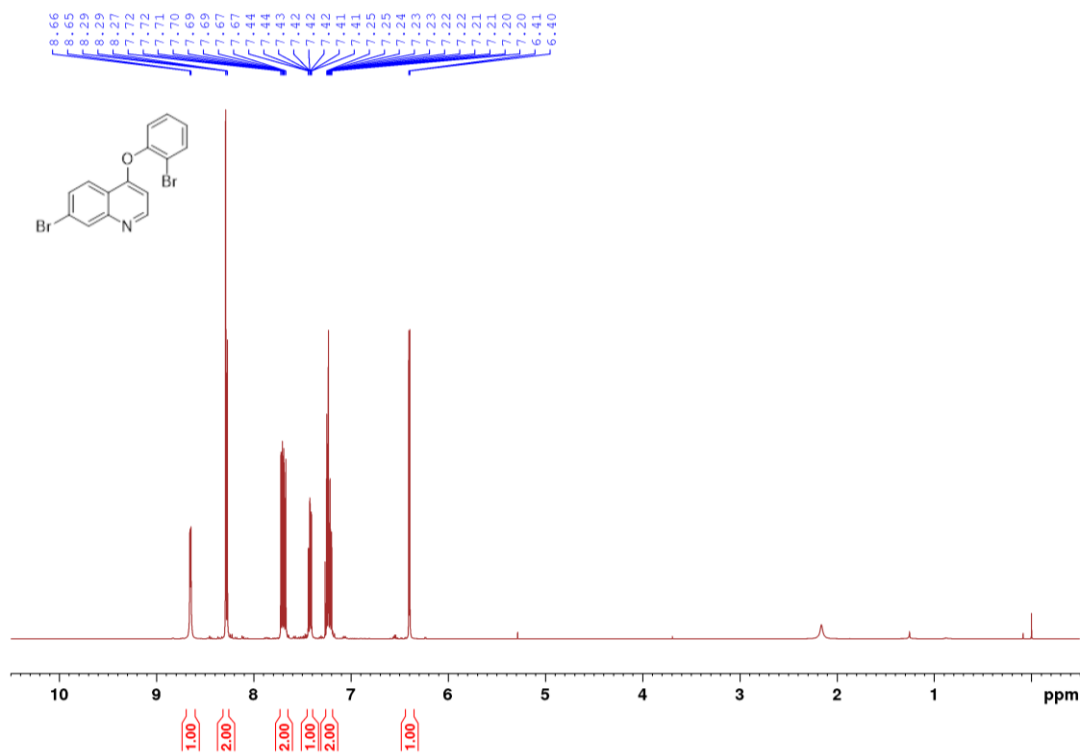
4-(2-Bromophenoxy)quinoline ^1H NMR, 500 MHz, CDCl_3 (S11)



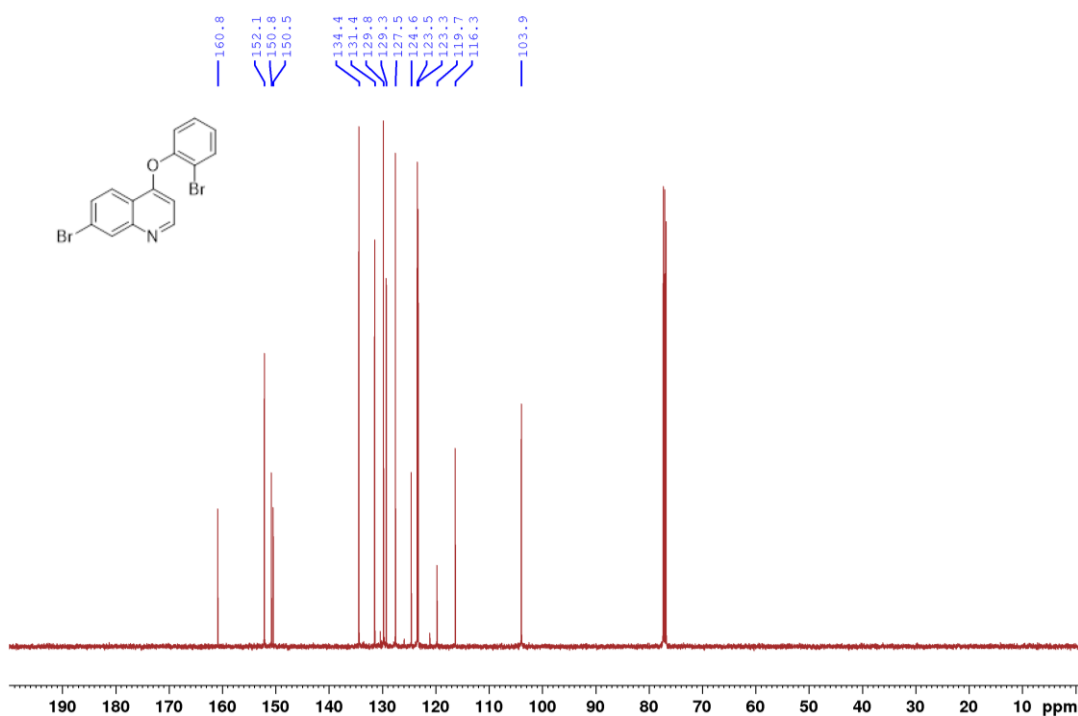
4-(2-Bromophenoxy)quinoline ^{13}C NMR, 125 MHz, CDCl_3 (S11)



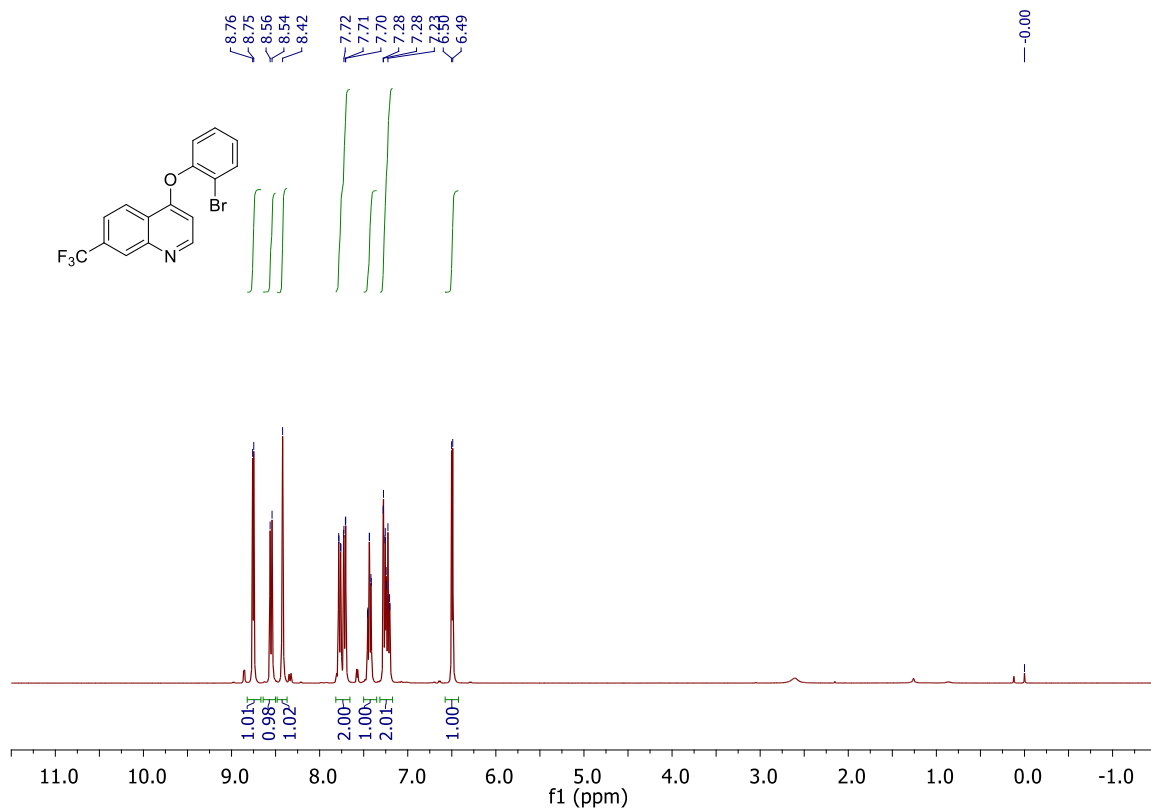
7-Bromo-4-(2-bromophenoxy)quinoline ^1H NMR, 500 MHz, CDCl_3 (S12)



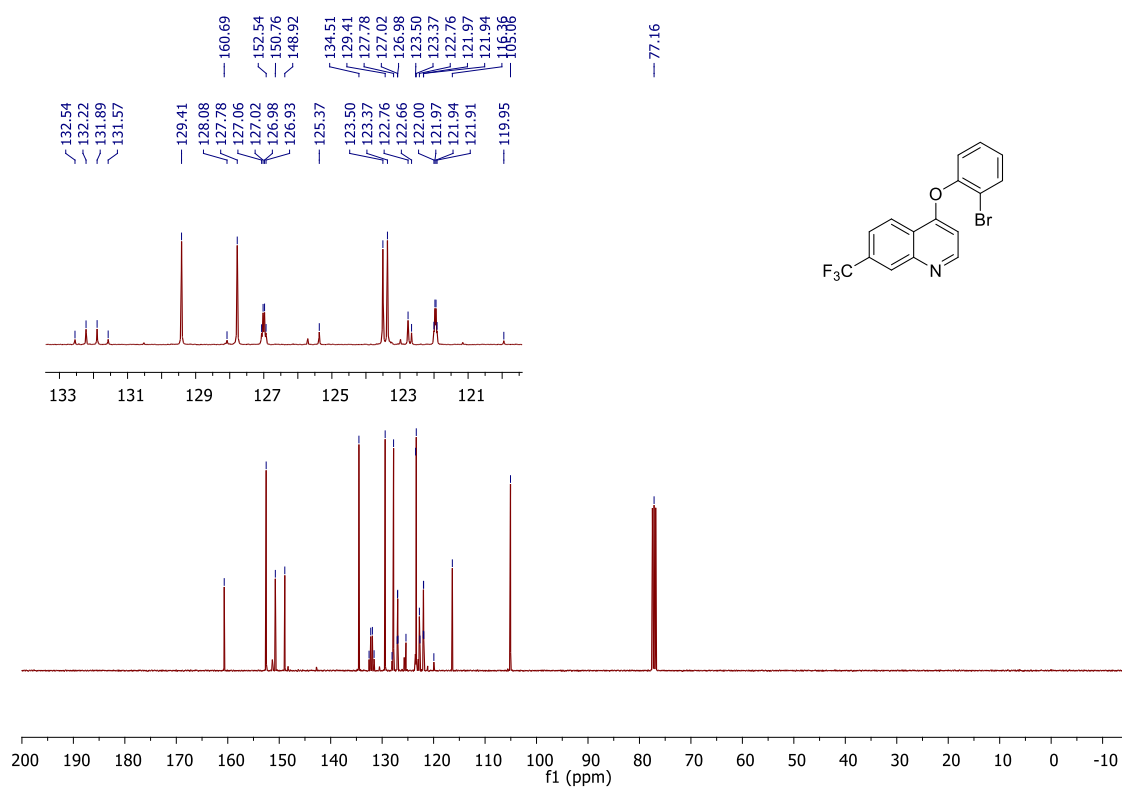
7-Bromo-4-(2-bromophenoxy)quinoline ^{13}C NMR, 125 MHz, CDCl_3 (S12)



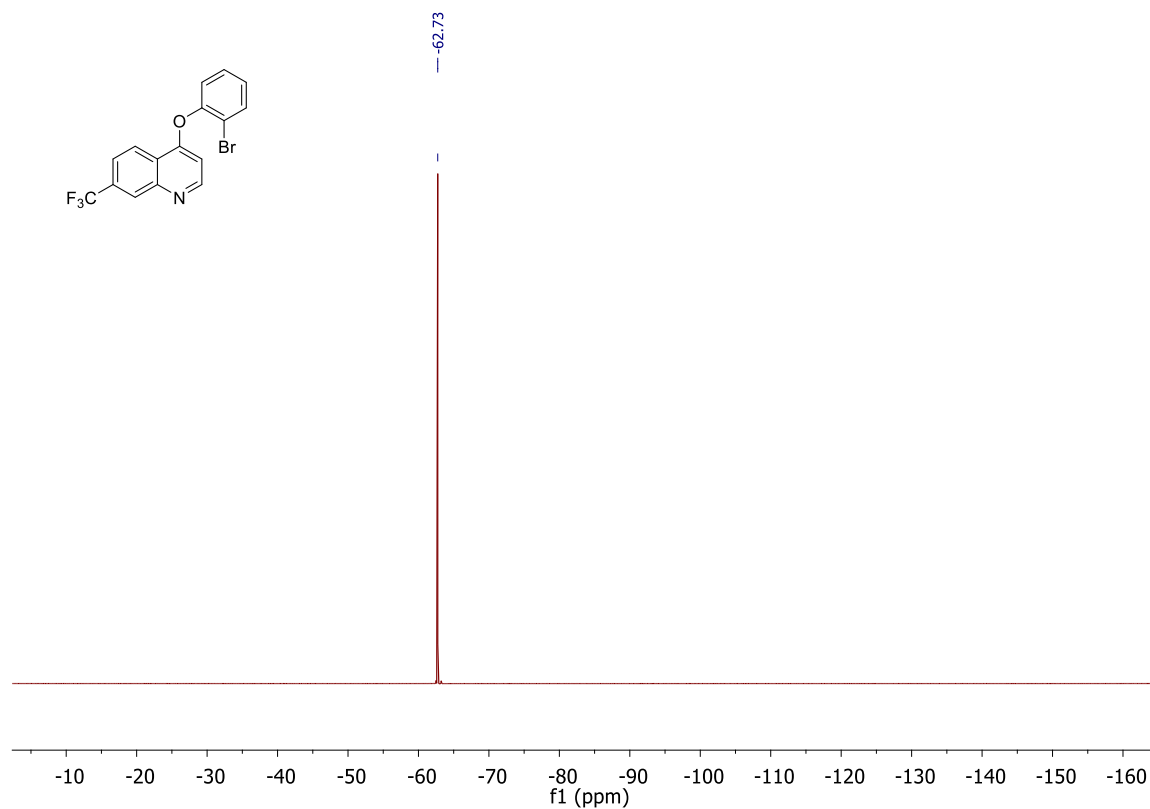
4-(2-Bromophenoxy)-7-(trifluoromethyl)quinoline ^1H NMR, 400 MHz, CDCl_3 (S13)



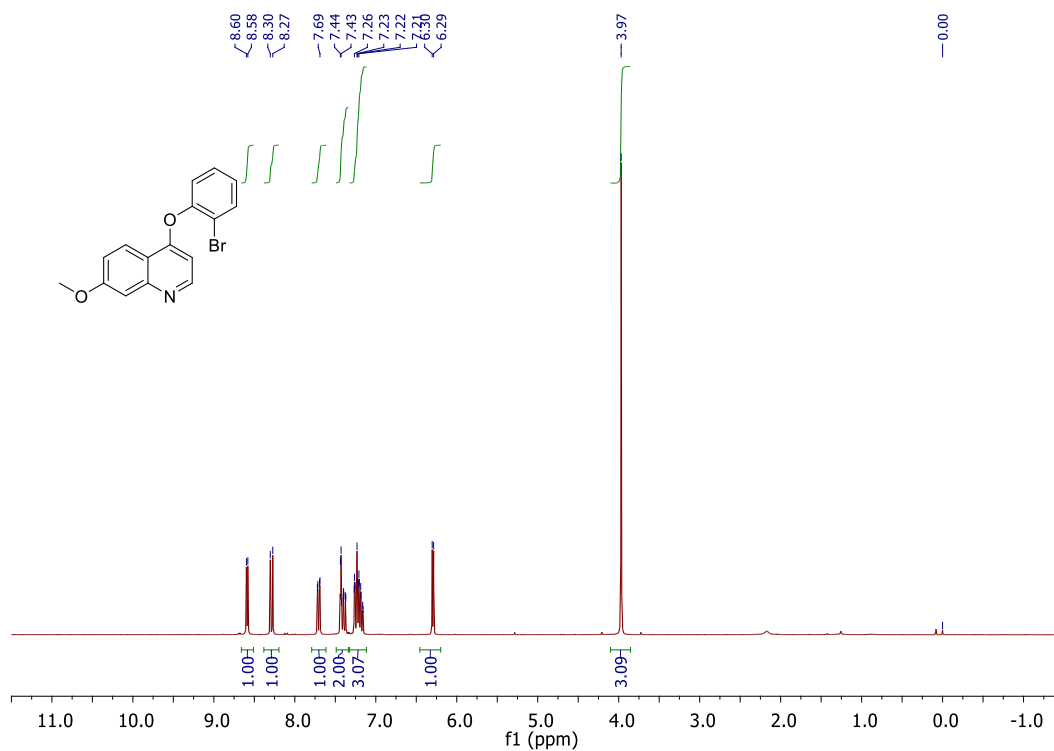
4-(2-Bromophenoxy)-7-(trifluoromethyl)quinoline ^{13}C NMR, 100 MHz, CDCl_3 (S13)



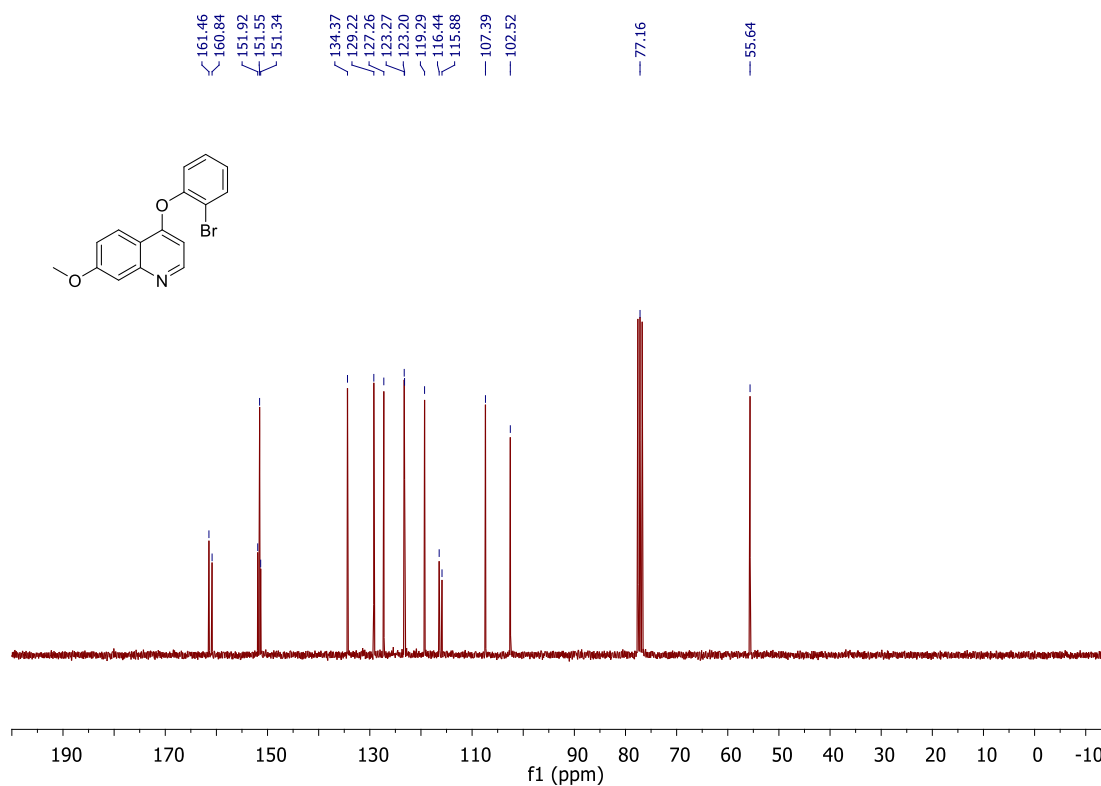
4-(2-Bromophenoxy)-7-(trifluoromethyl)quinoline ^{19}F NMR, 376 MHz, CDCl_3 (S13)



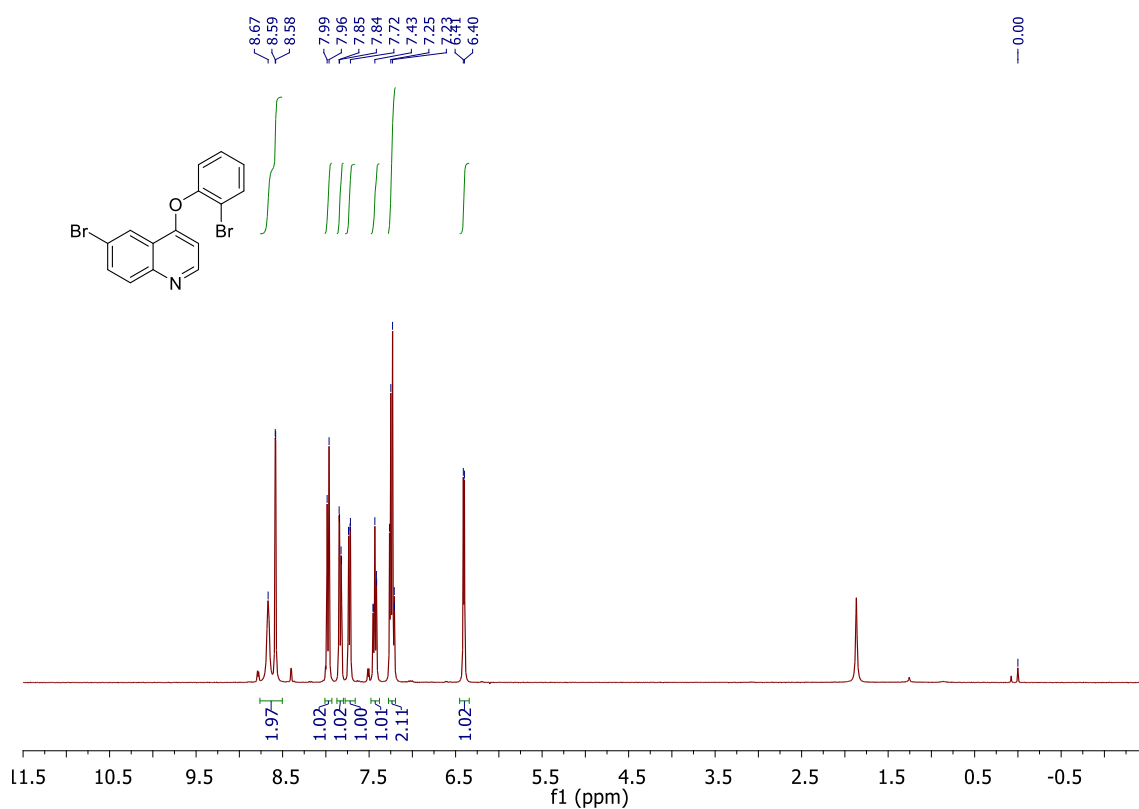
4-(2-Bromophenoxy)-7-methoxyquinoline ^1H NMR, 300 MHz, CDCl_3 (S14)



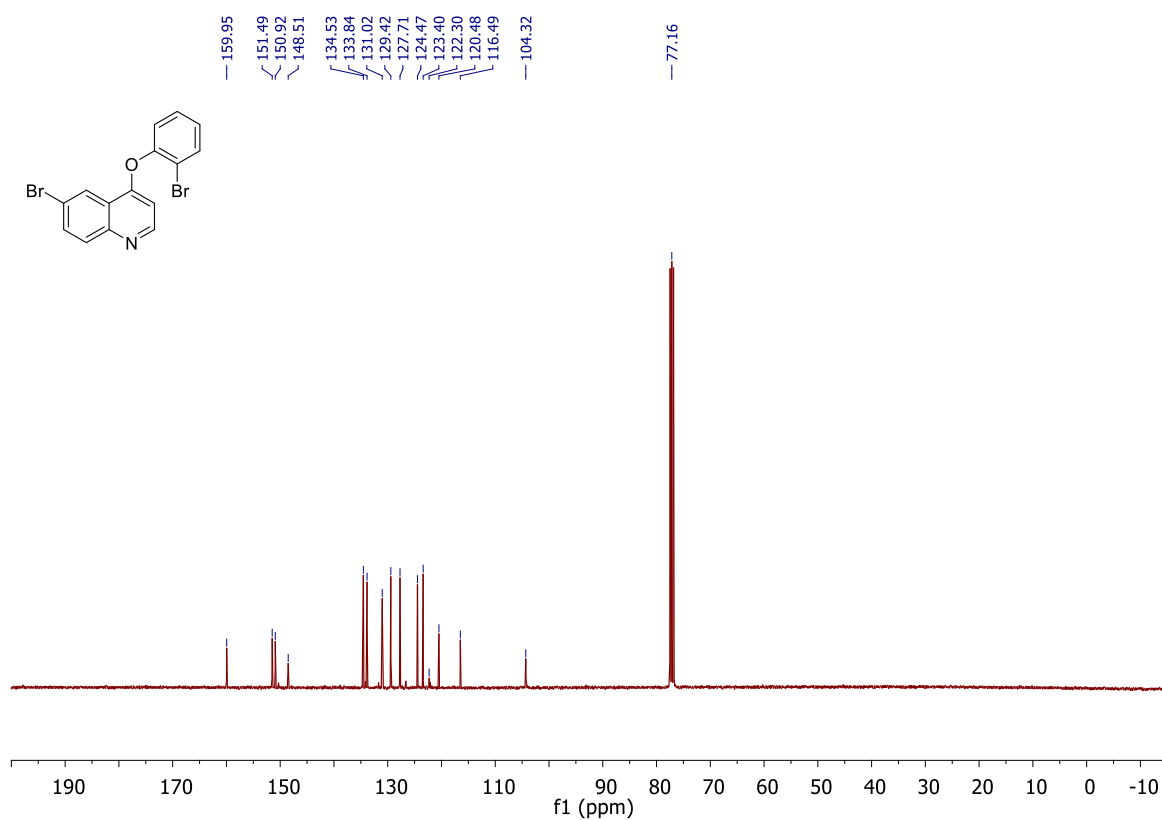
4-(2-Bromophenoxy)-7-methoxyquinoline ^{13}C NMR, 75 MHz, CDCl_3 (S14)



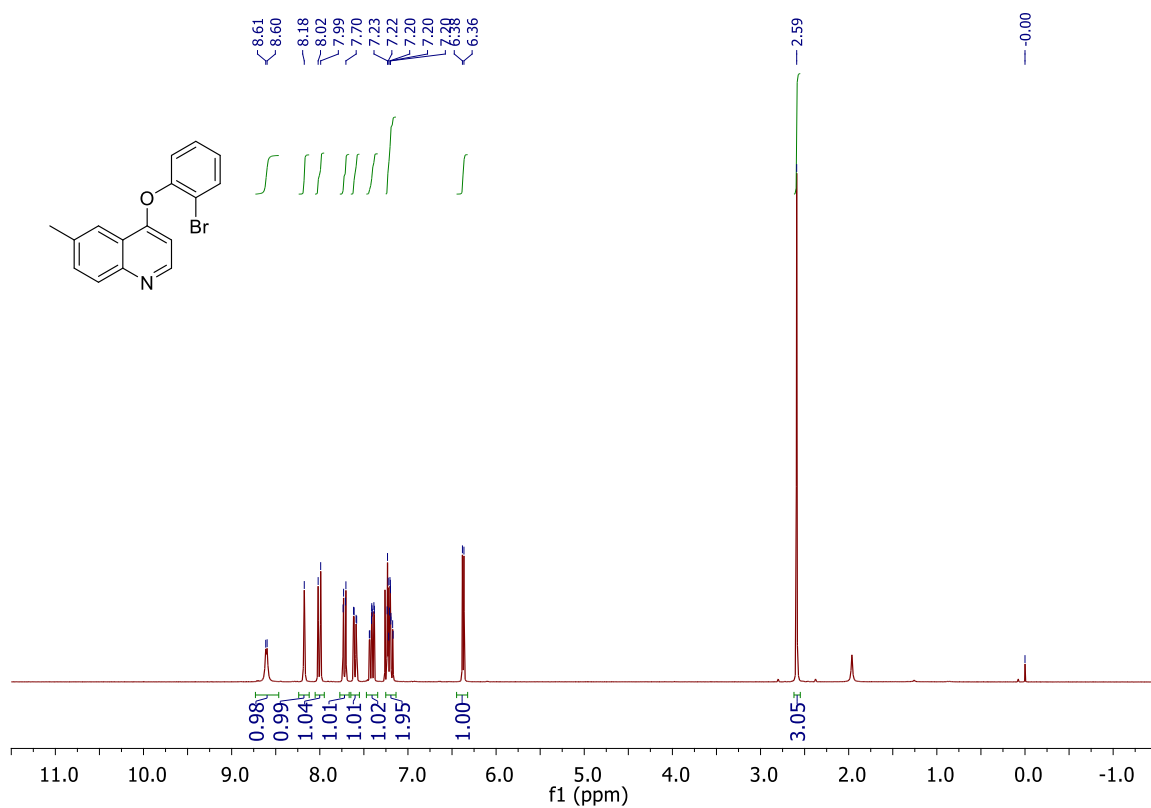
6-Bromo-4-(2-bromophenoxy)quinoline ^1H NMR, 400 MHz, CDCl_3 (S15)



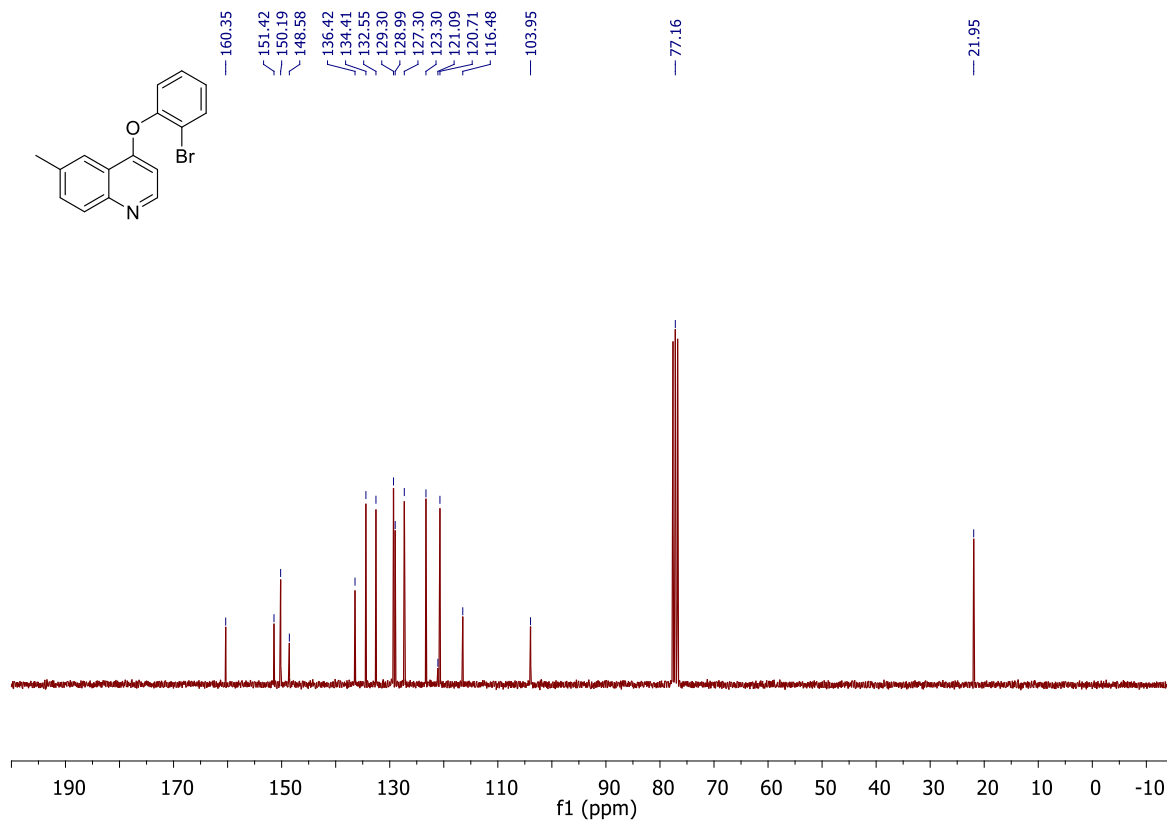
6-Bromo-4-(2-bromophenoxy)quinoline ^{13}C NMR, 100 MHz, CDCl_3 (S15)



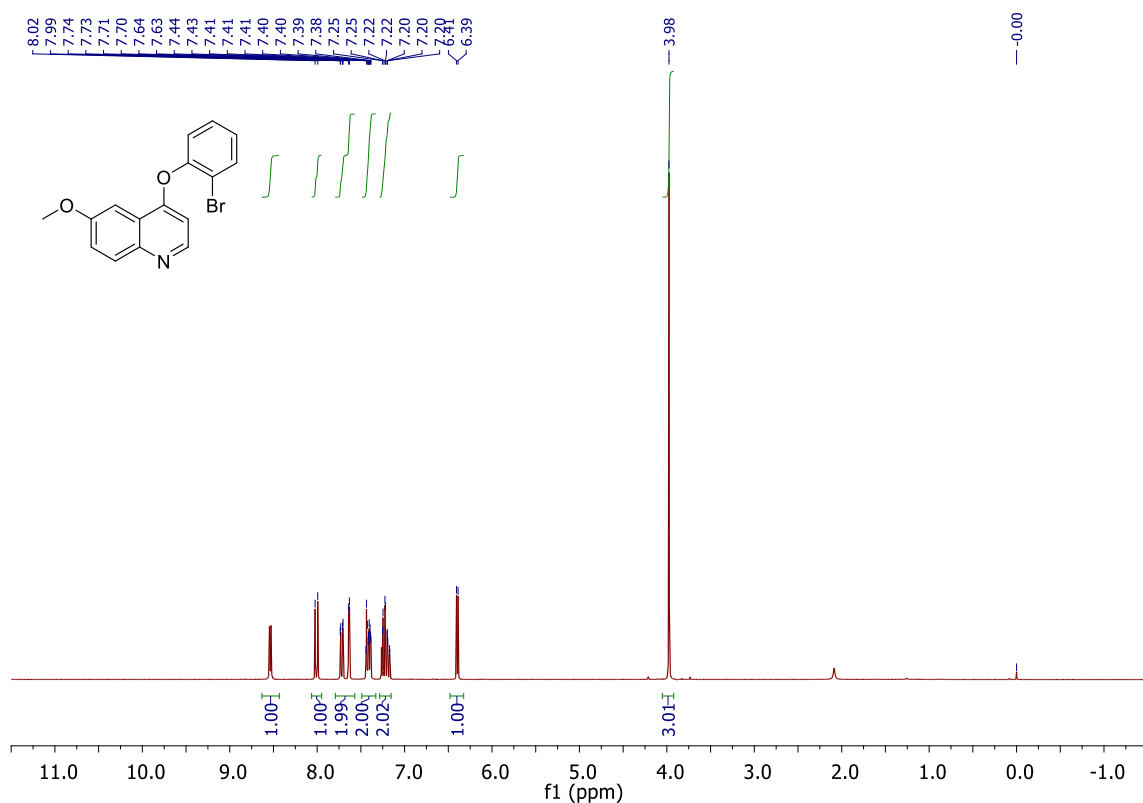
4-(2-Bromophenoxy)-6-methylquinoline ^1H NMR, 300 MHz, CDCl_3 (S16)



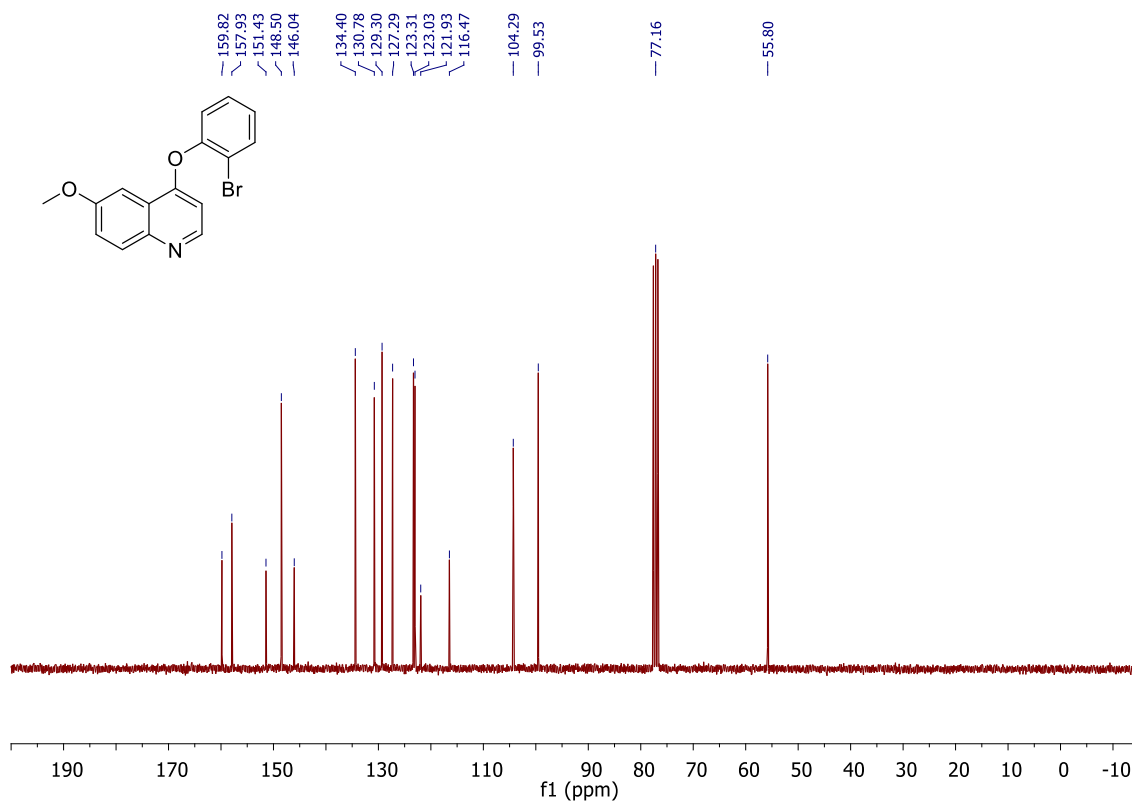
4-(2-Bromophenoxy)-6-methylquinoline ^{13}C NMR, 75 MHz, CDCl_3 (S16)



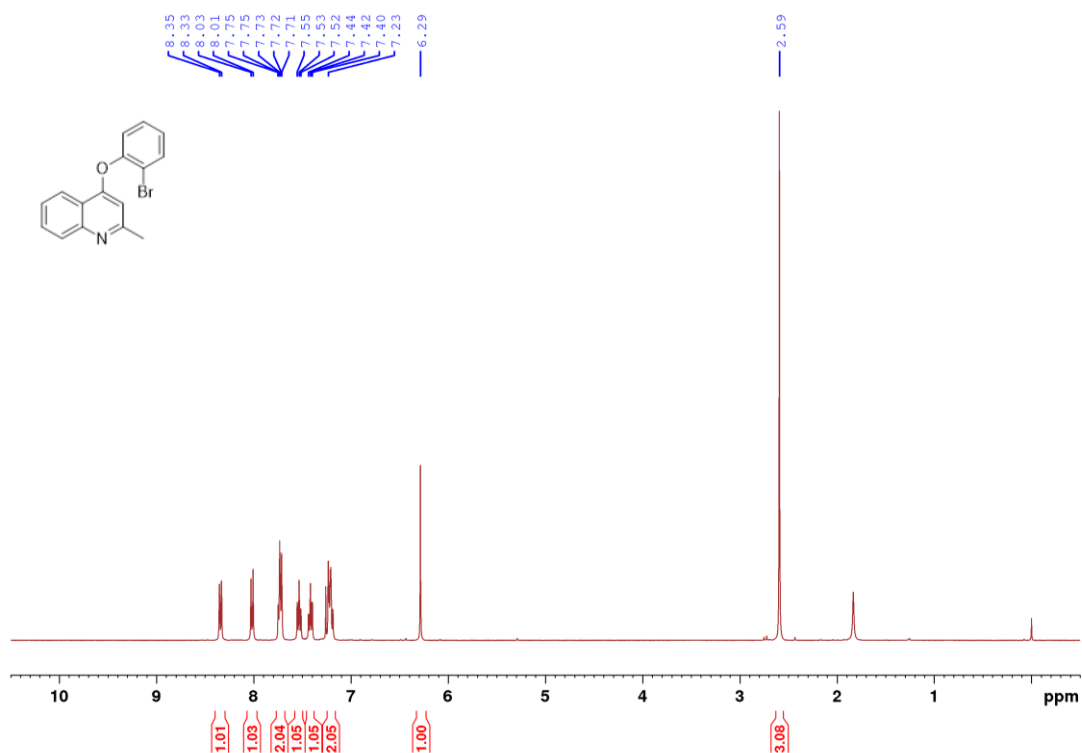
4-(2-Bromophenoxy)-6-methoxyquinoline ^1H NMR, 300 MHz, CDCl_3 (S17)



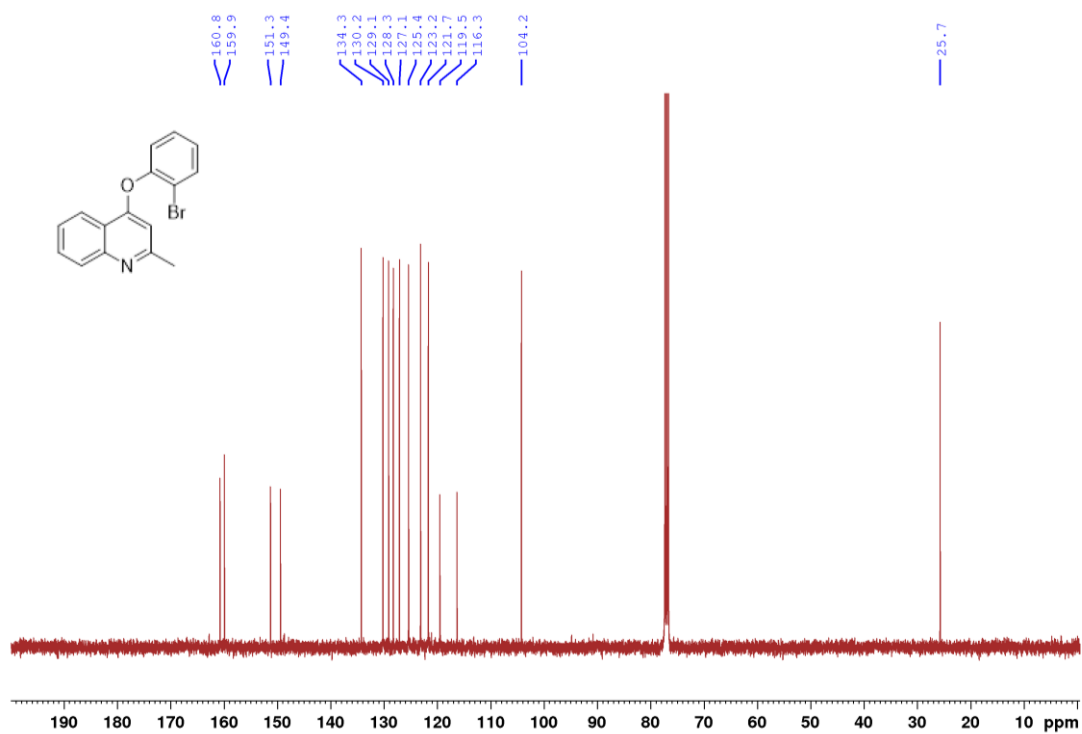
4-(2-Bromophenoxy)-6-methoxyquinoline ^{13}C NMR, 75 MHz, CDCl_3 (S17)



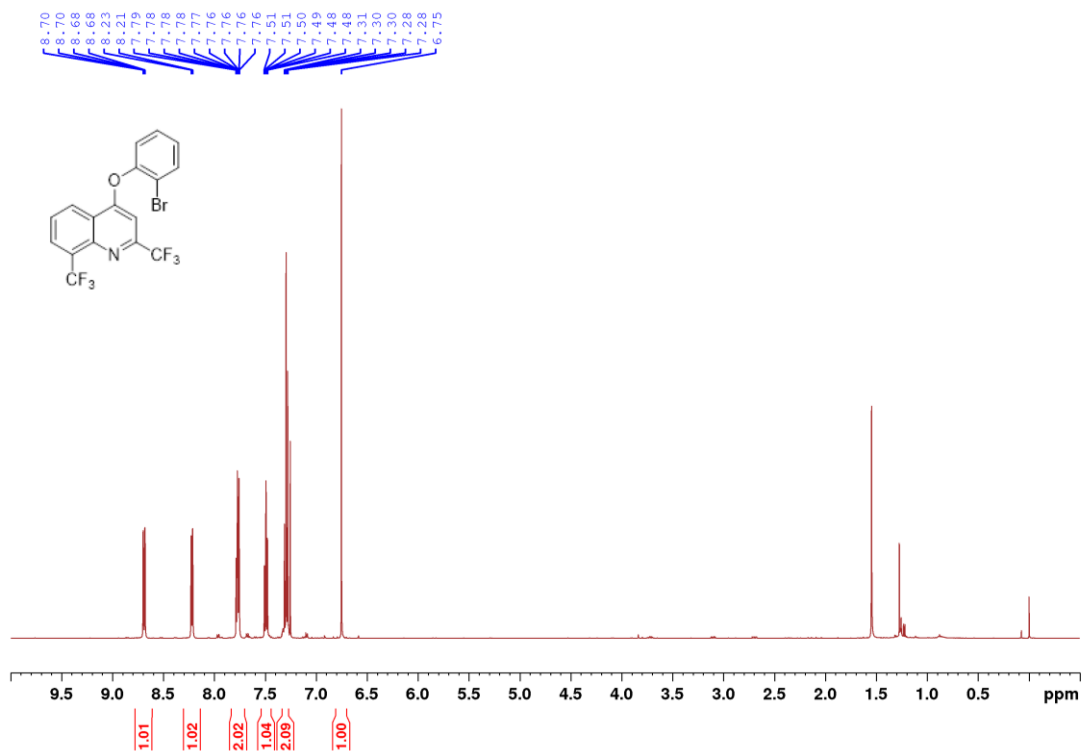
4-(2-Bromophenoxy)-2-methylquinoline ^1H NMR, 500 MHz, CDCl_3 (S18)



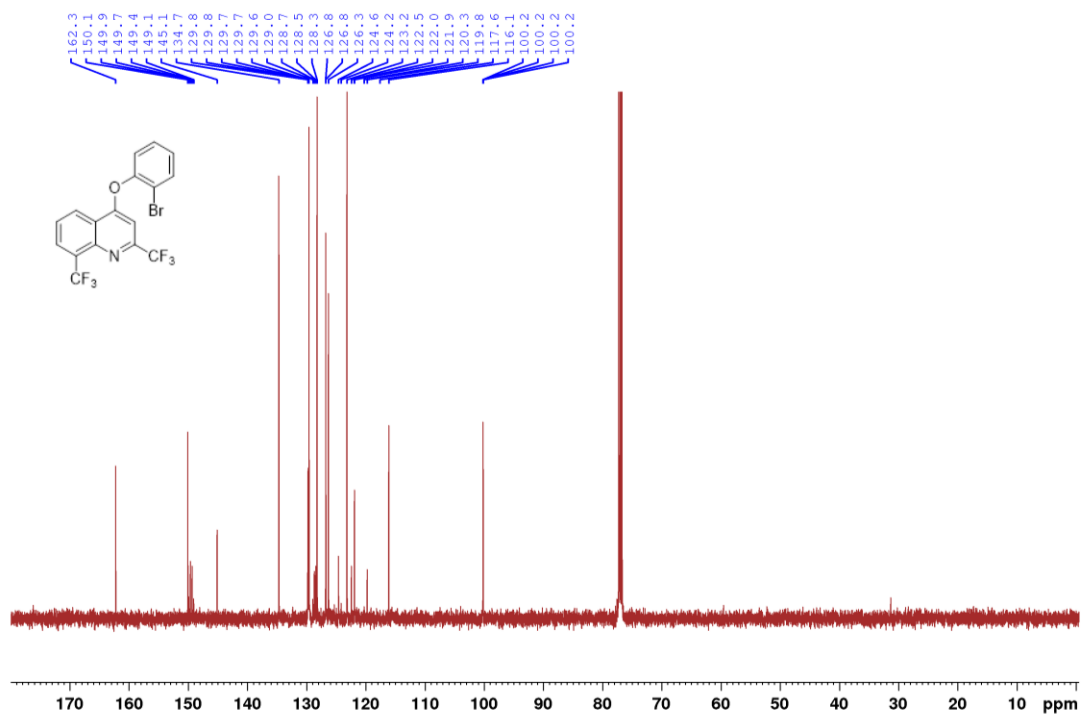
4-(2-Bromophenoxy)-2-methylquinoline ^{13}C NMR, 125 MHz, CDCl_3 (S18)



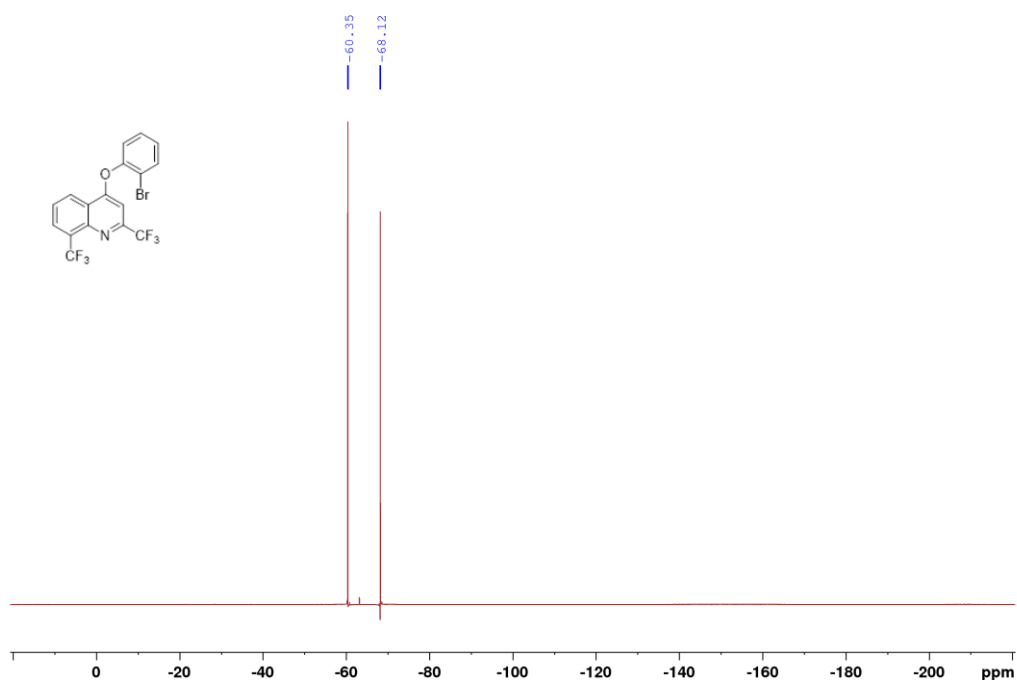
4-(2-Bromophenoxy)-2,8-bis(trifluoromethyl)quinoline ¹H NMR, 500 MHz, CDCl₃ (S19)



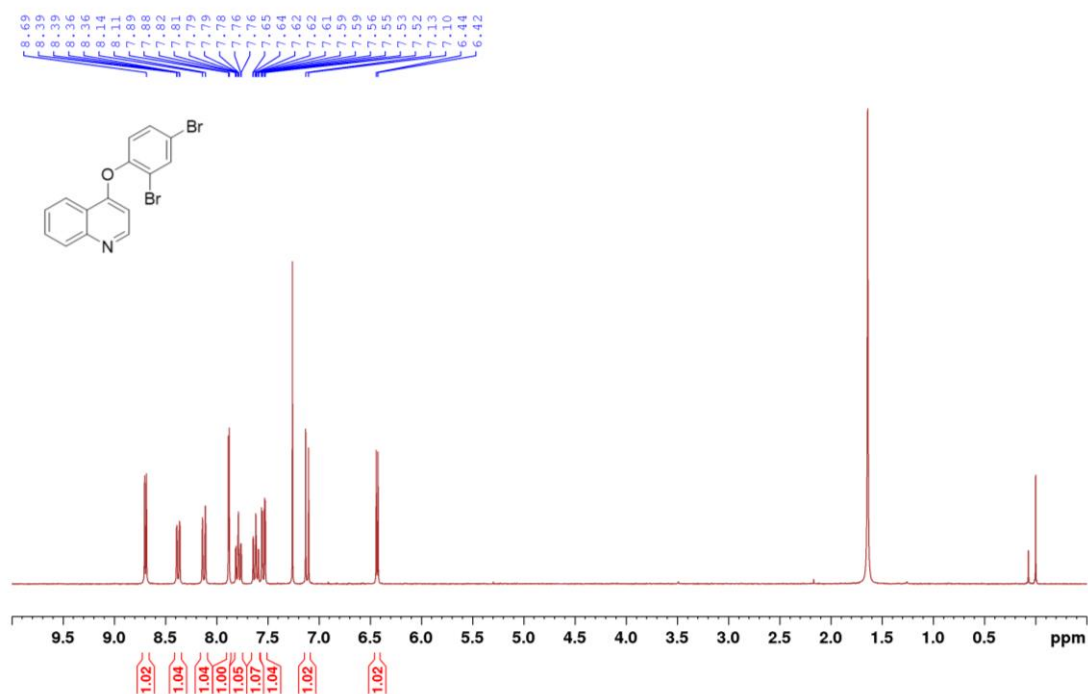
4-(2-Bromophenoxy)-2,8-bis(trifluoromethyl)quinoline ¹³C NMR, 125 MHz, CDCl₃ (S19)



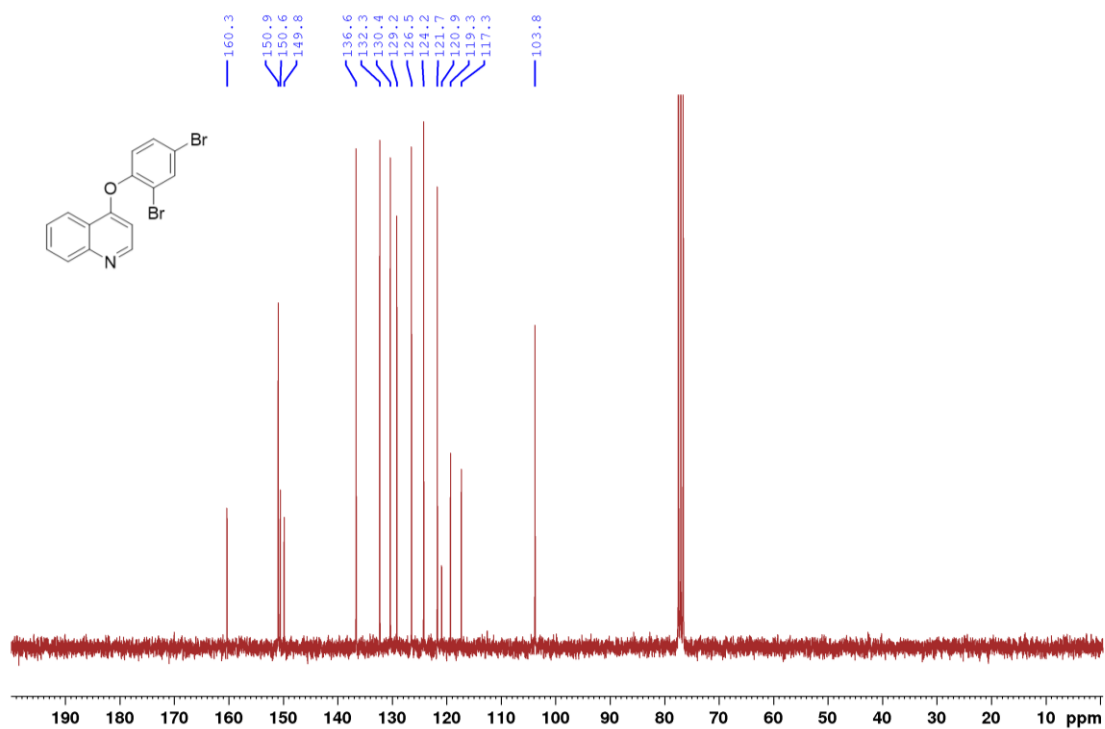
4-(2-Bromophenoxy)-2,8-bis(trifluoromethyl)quinoline ^{19}F NMR, 282 MHz, CDCl_3 (S19)



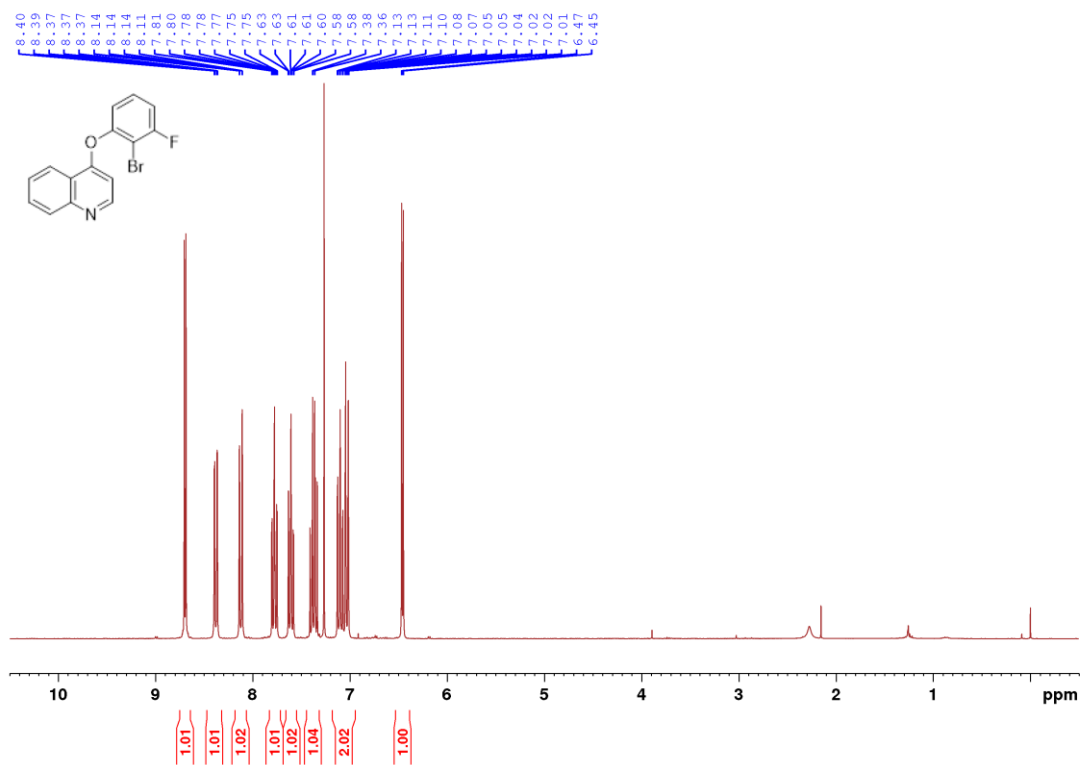
4-(2,4-Dibromobenzyl)quinoline ^1H NMR, 300 MHz, CDCl_3 (S20)



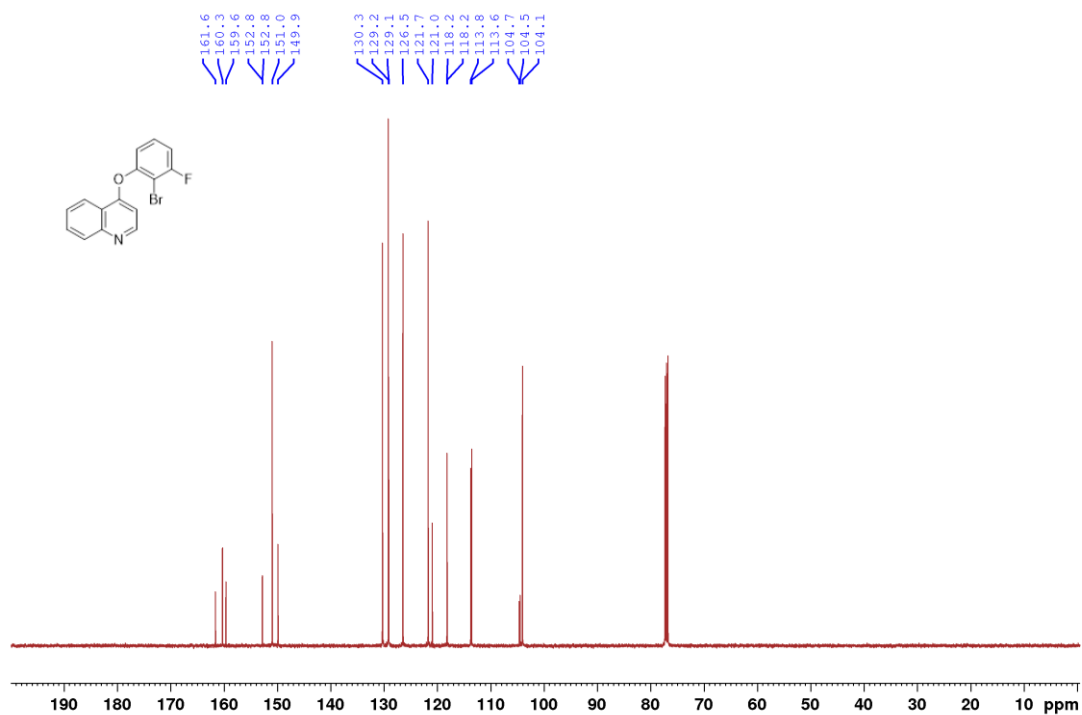
4-(2,4-Dibromobenzyl)quinoline ^{13}C NMR, 75 MHz, CDCl_3 (S20)



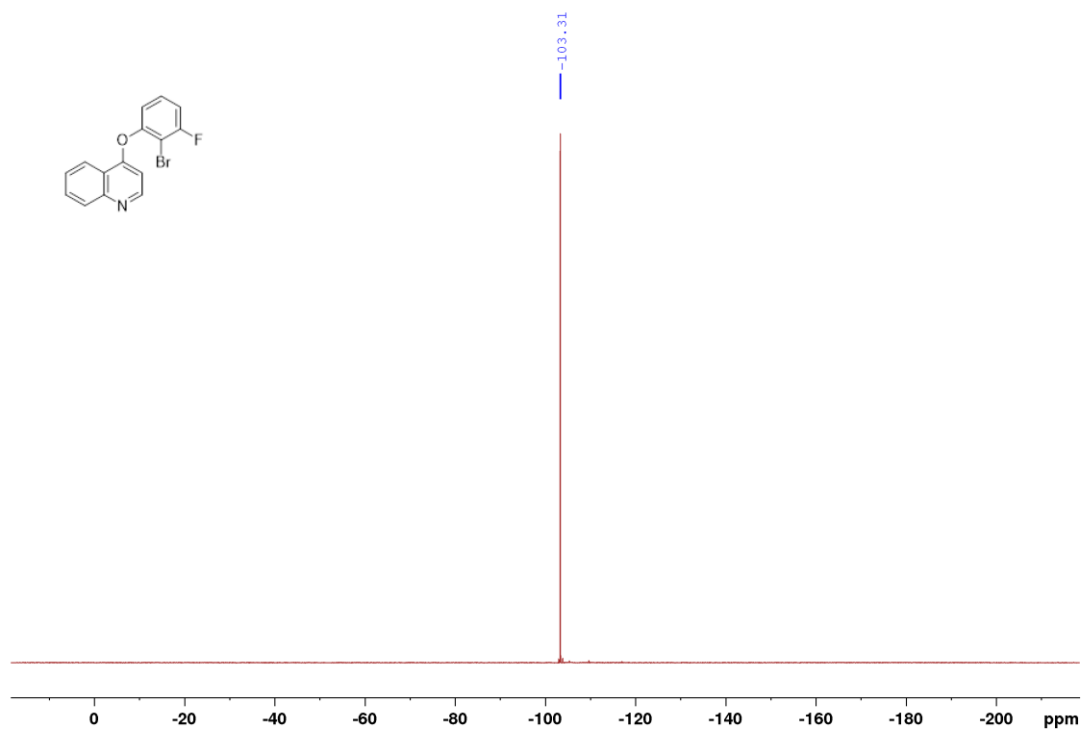
4-(2-Bromo-3-fluorophenoxy)quinoline ^1H NMR, 300 MHz, CDCl_3 (S21)



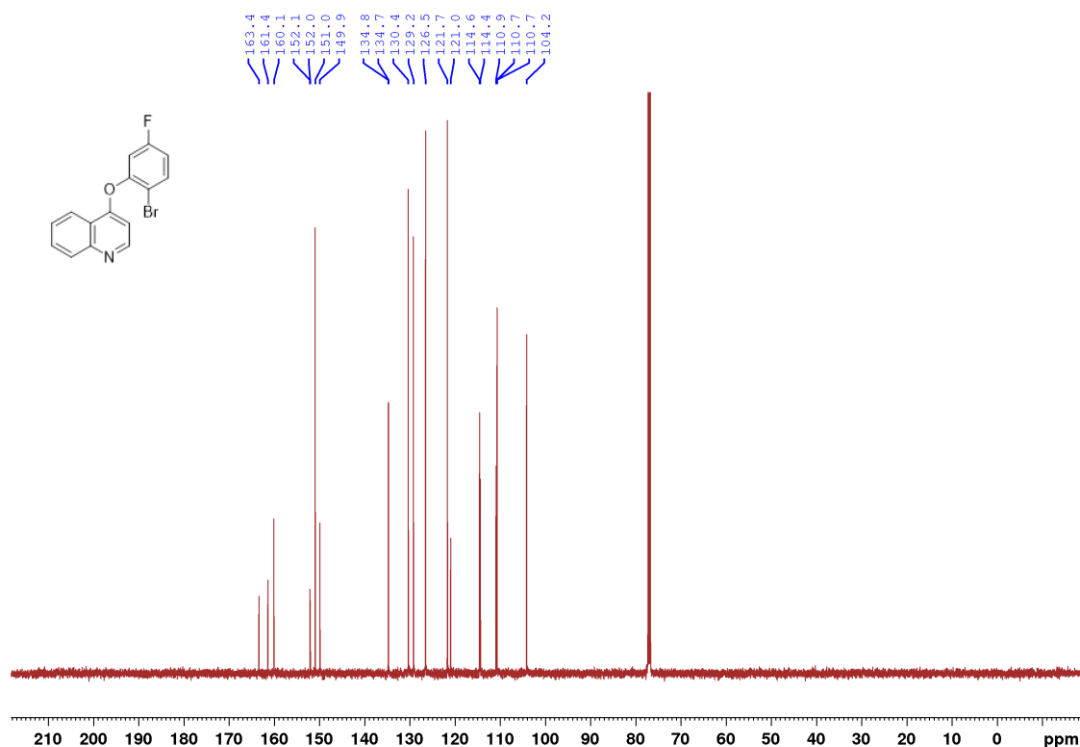
4-(2-Bromo-3-fluorophenoxy)quinoline ^{13}C NMR, 125 MHz, CDCl_3 (S21)



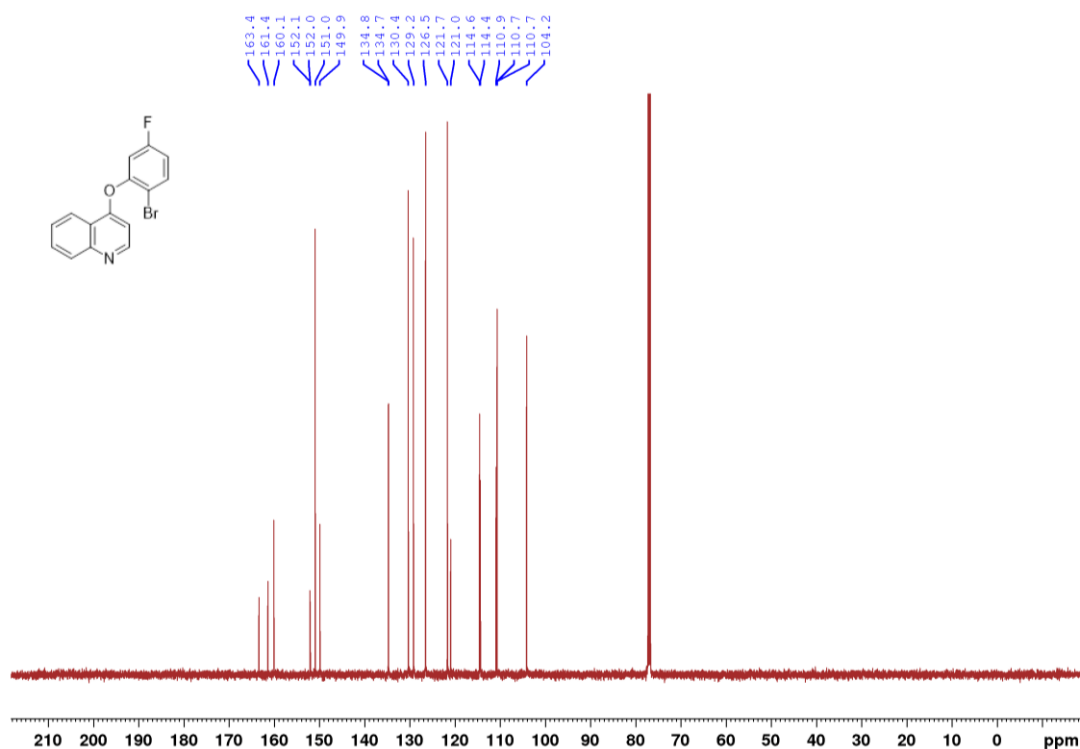
4-(2-Bromo-3-fluorophenoxy)quinoline ^{19}F NMR, 282 MHz, CDCl_3 (S21)



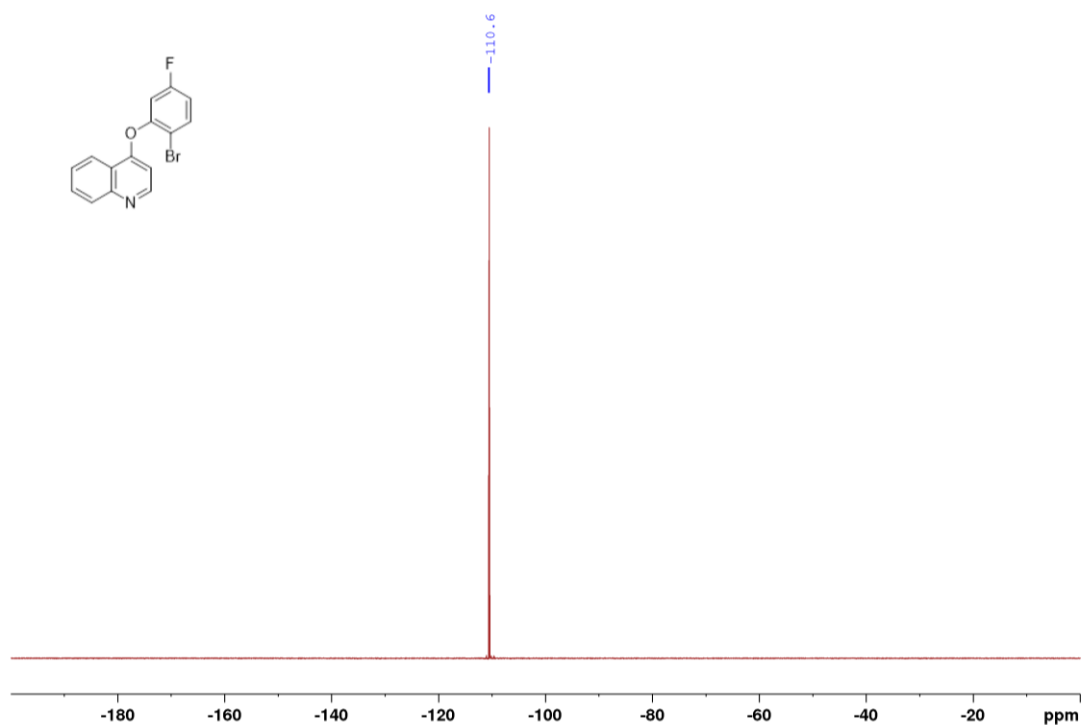
4-(2-Bromo-5-fluorophenoxy)quinoline ^1H NMR, 500 MHz, CDCl_3 (S22)



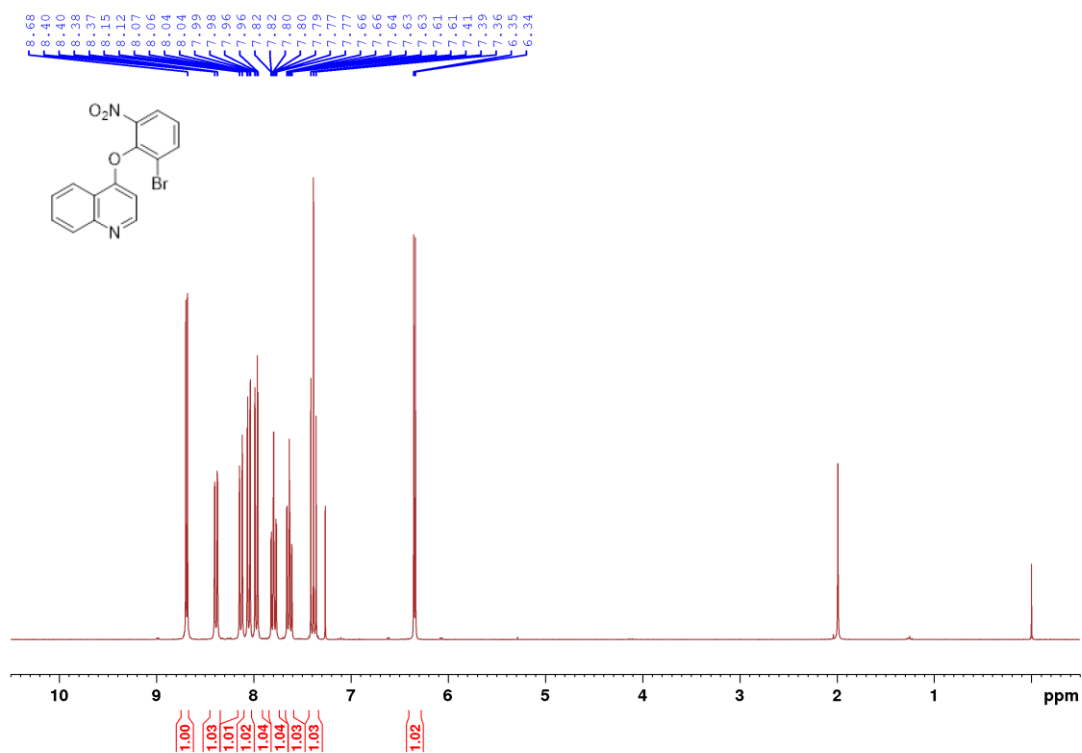
4-(2-Bromo-5-fluorophenoxy)quinoline ^{13}C NMR, 125 MHz, CDCl_3 (S22)



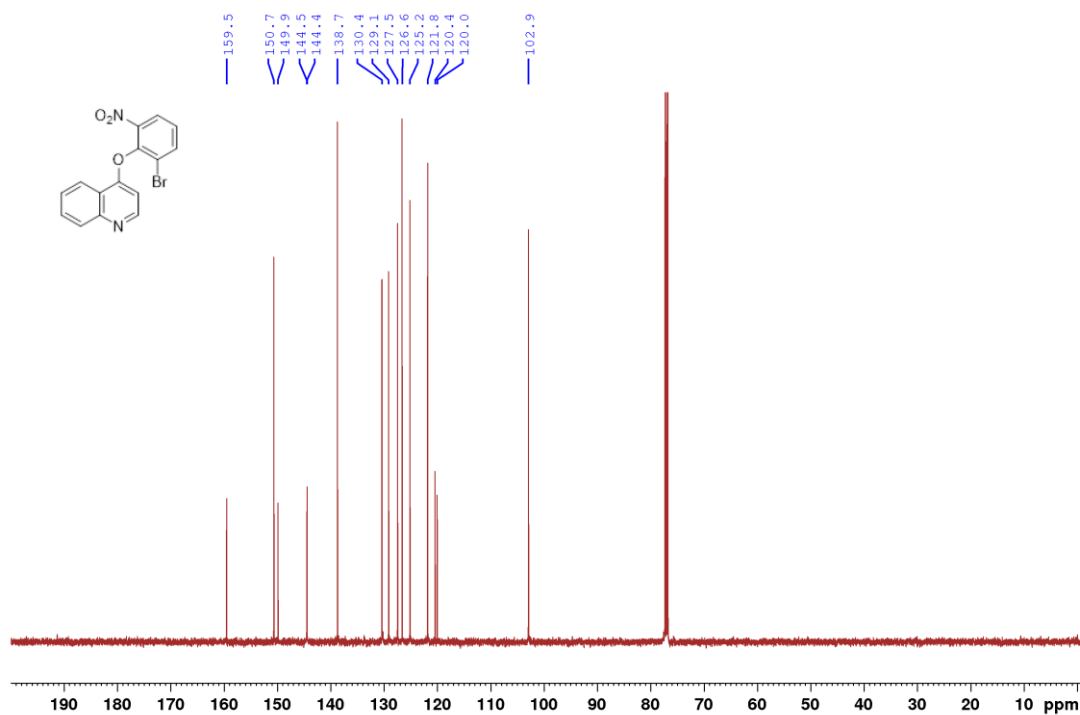
4-(2-Bromo-5-fluorophenoxy)quinoline ^{19}F NMR, 282 MHz, CDCl_3 (S22)



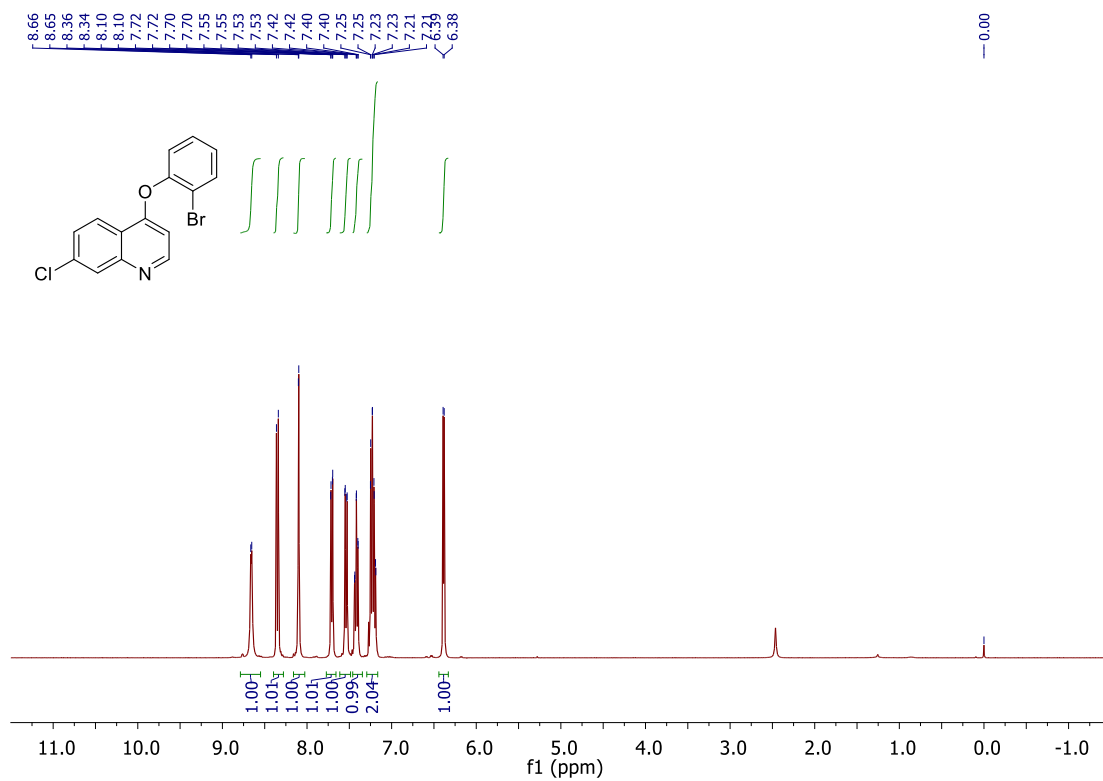
4-(2-Bromo-6-nitrophenoxy)quinoline ^1H NMR, 500 MHz, CDCl_3 (S23)



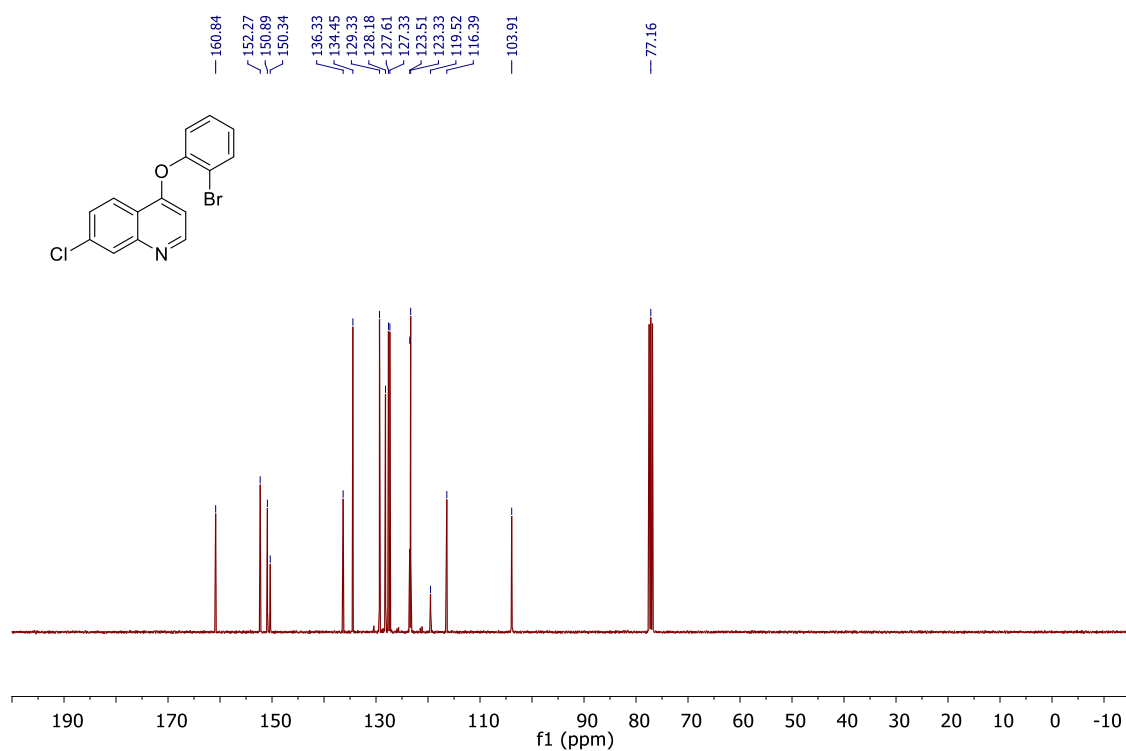
4-(2-Bromo-6-nitrophenoxy)quinoline ^{13}C NMR, 125 MHz, CDCl_3 (S23)



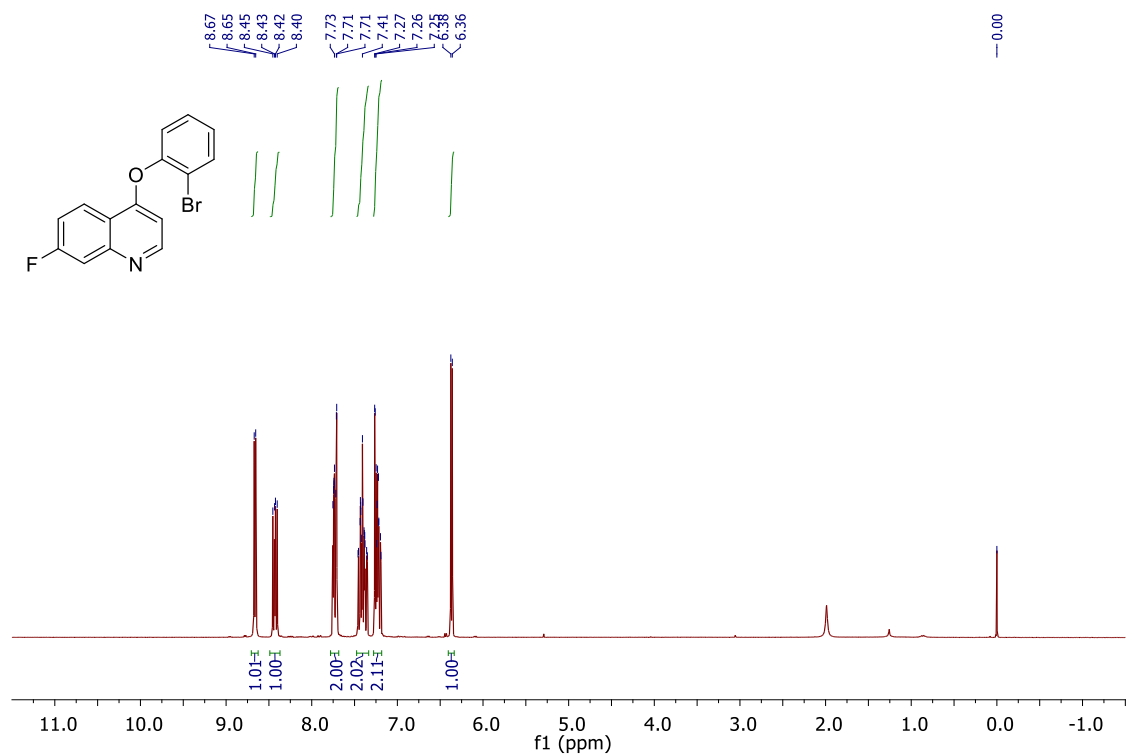
4-(2-Bromophenoxy)-7-chloroquinoline ^1H NMR, 400 MHz, CDCl_3 (S24)



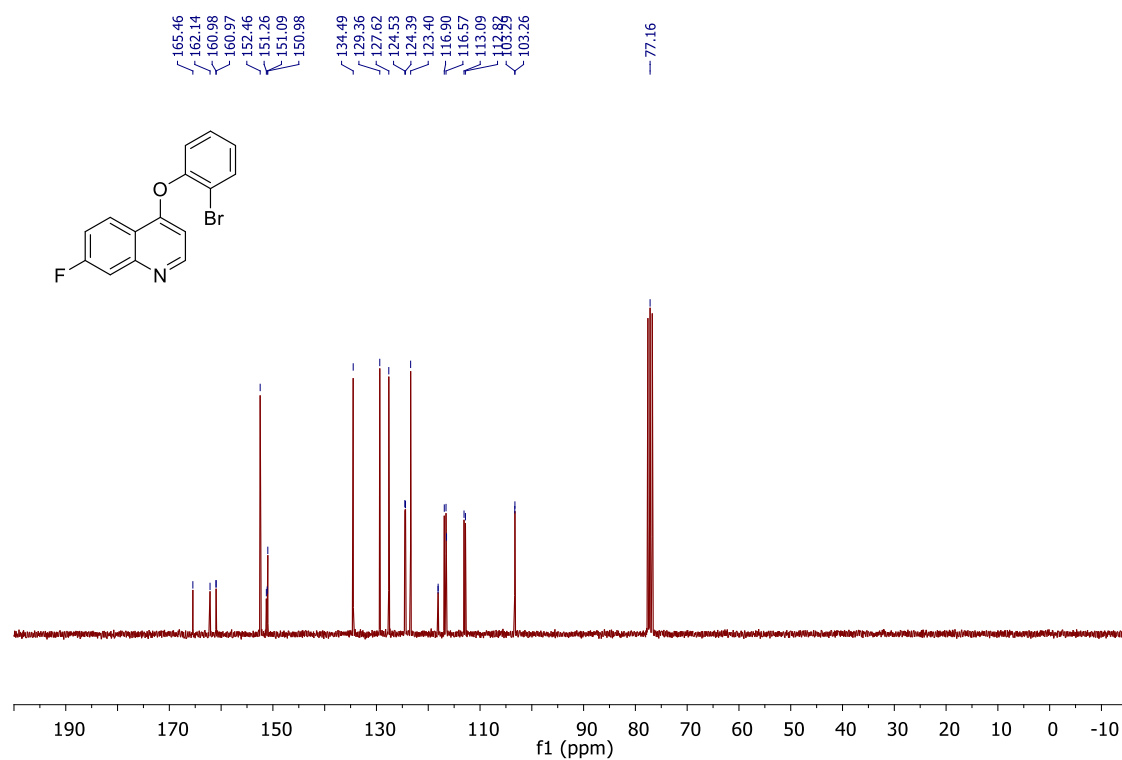
4-(2-Bromophenoxy)-7-chloroquinoline ^{13}C NMR, 100 MHz, CDCl_3 (S24)



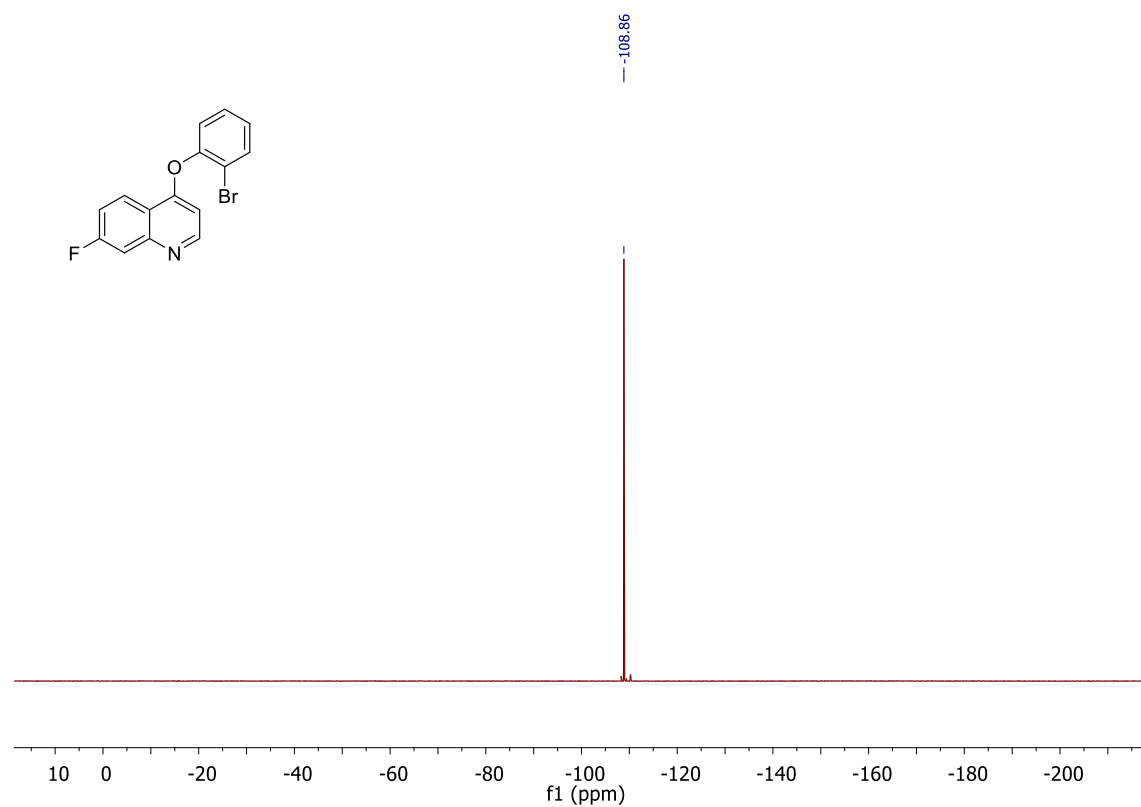
4-(2-Bromophenoxy)-6-fluoroquinoline ^1H NMR, 300 MHz, CDCl_3 (S25)



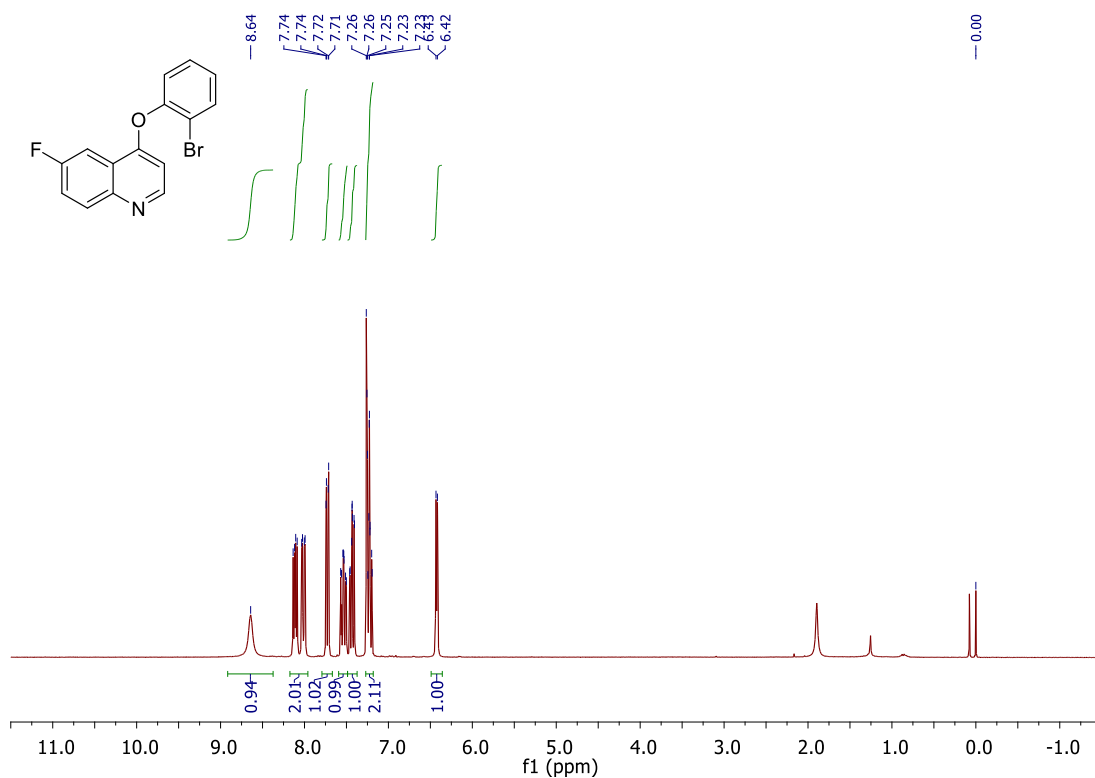
4-(2-Bromophenoxy)-6-fluoroquinoline ^{13}C NMR, 75 MHz, CDCl_3 (S25)



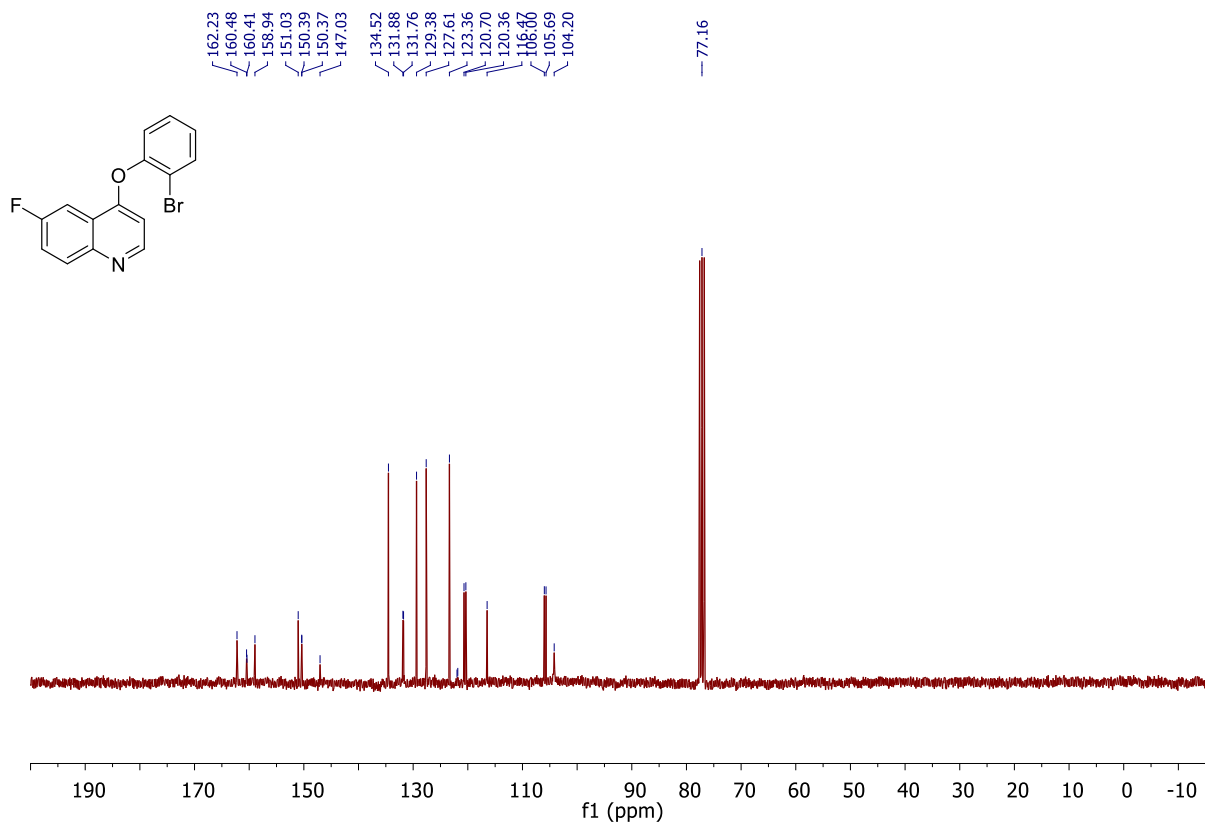
4-(2-Bromophenoxy)-6-fluoroquinoline ^{19}F NMR, 282 MHz, CDCl_3 (S25)



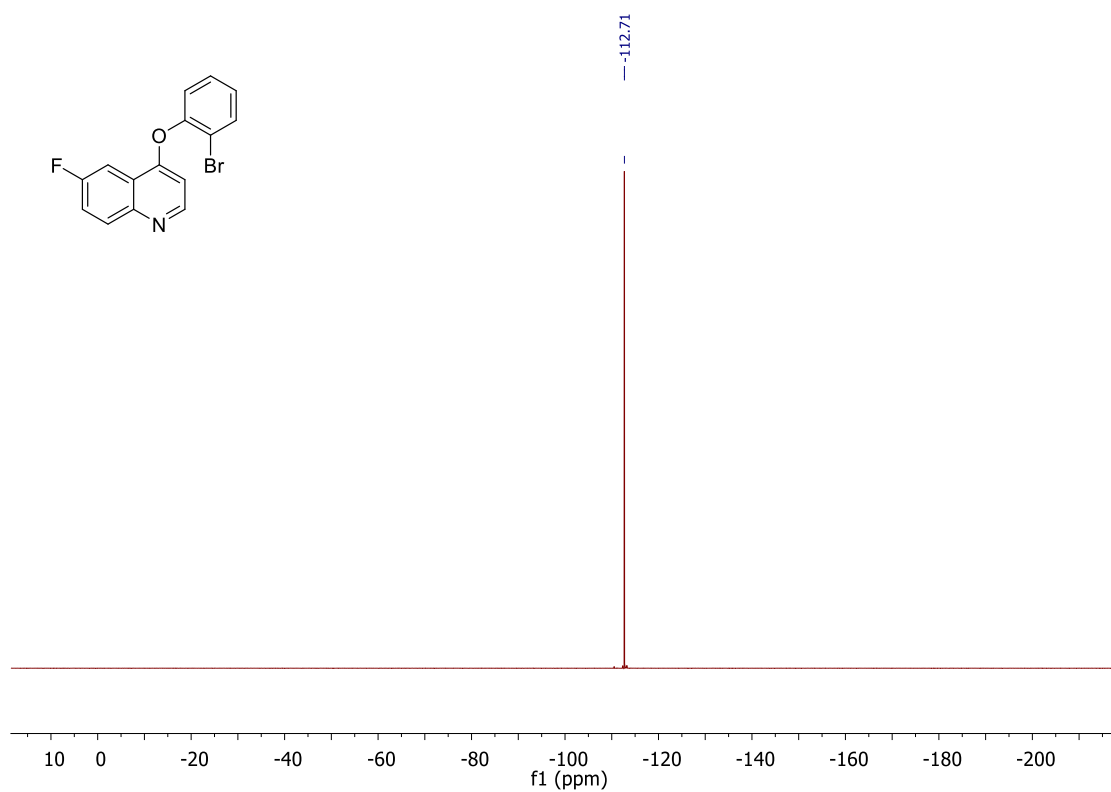
4-(2-Bromophenoxy)-6-fluoroquinoline ¹H NMR, 300 MHz, CDCl₃ (S26)



4-(2-Bromophenoxy)-6-fluoroquinoline ¹³C NMR, 75 MHz, CDCl₃ (S26)

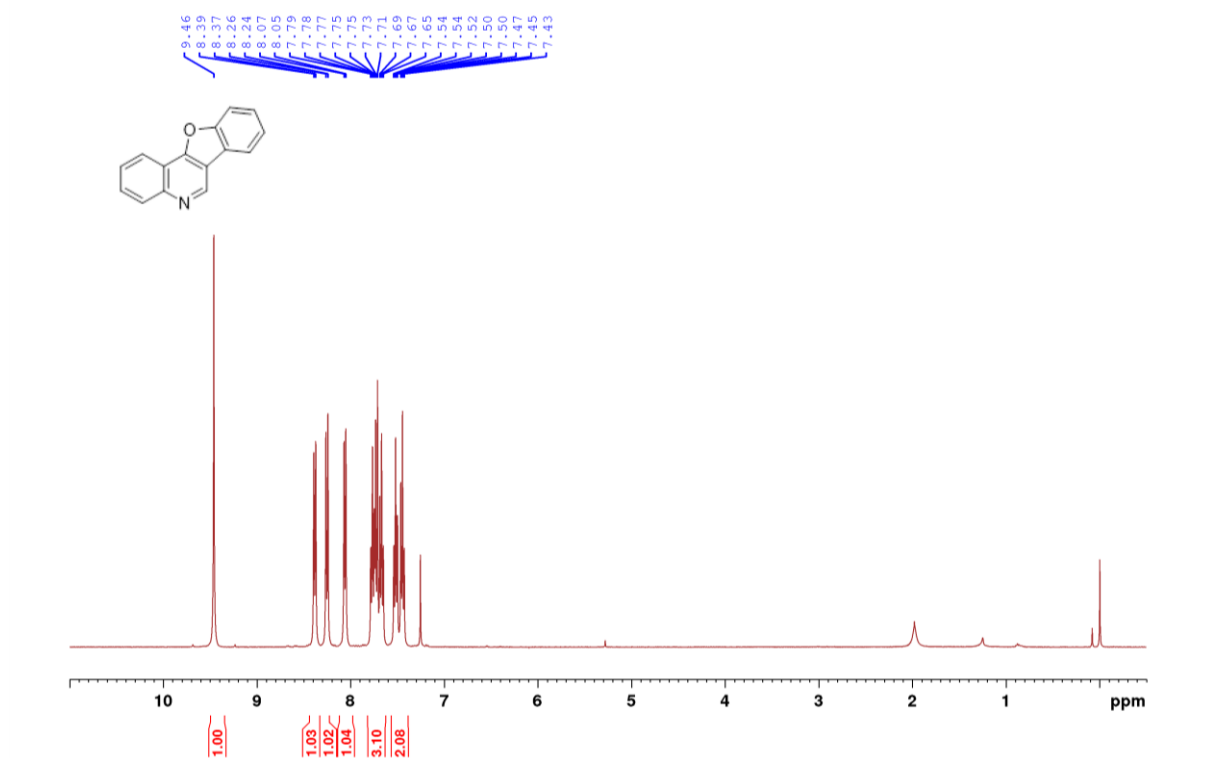


4-(2-Bromophenoxy)-6-fluoroquinoline ^{19}F NMR, 282 MHz, CDCl_3 (S26)

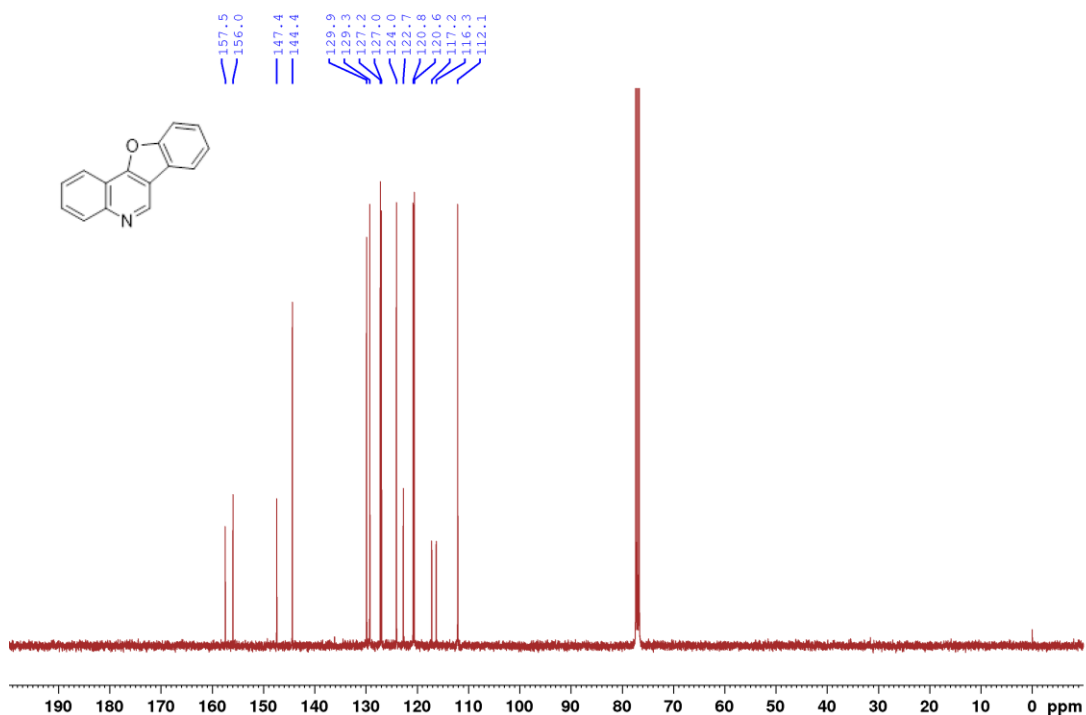


NMR Spectra of Benzofuroquinolines

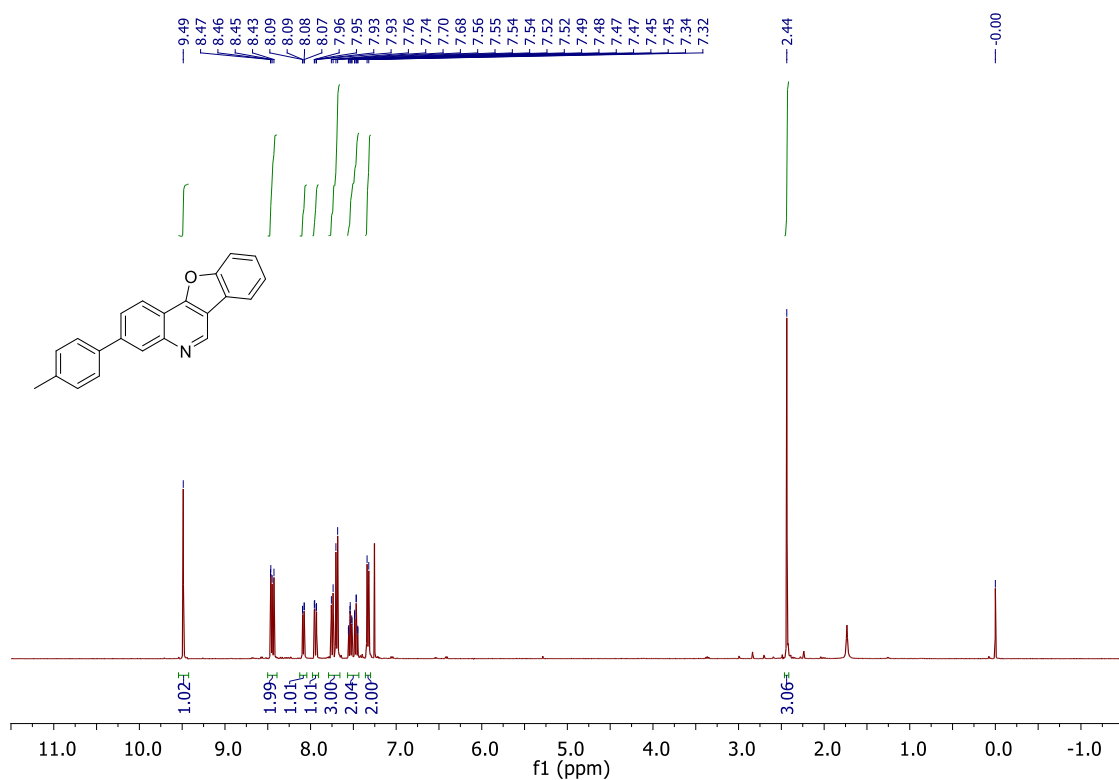
Benzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (1a)



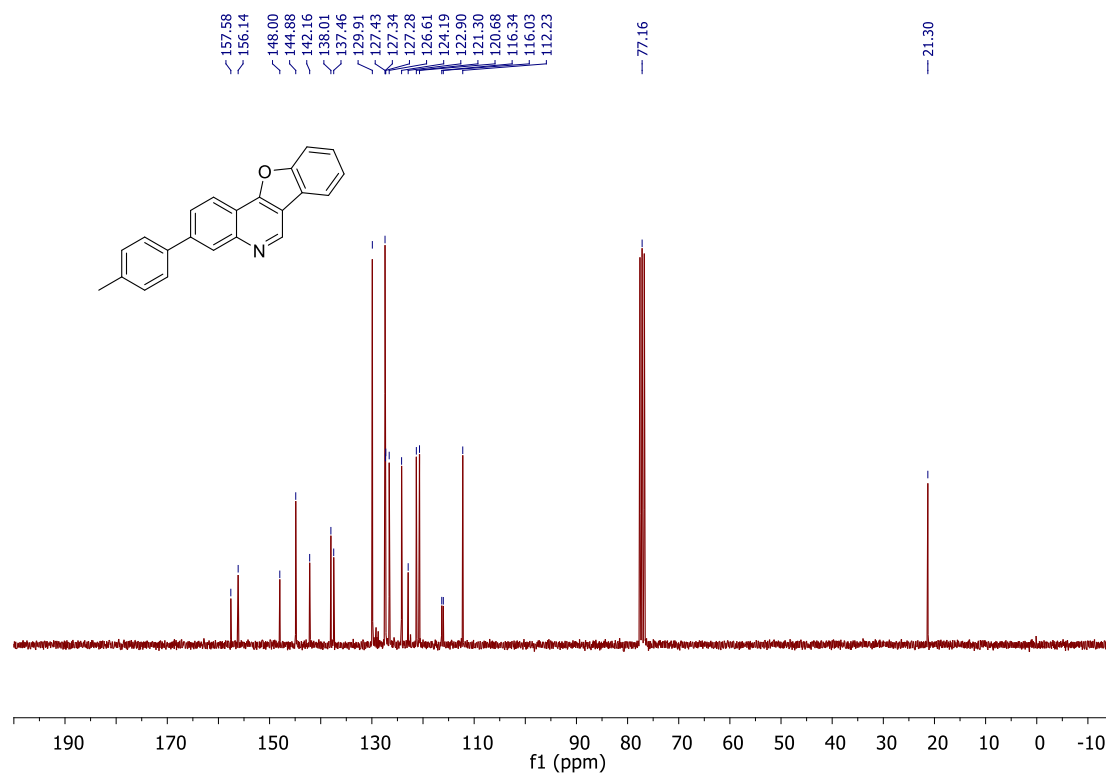
Benzofuro[3,2-c]quinoline ^{13}C NMR, 150 MHz, CDCl_3 (1a)



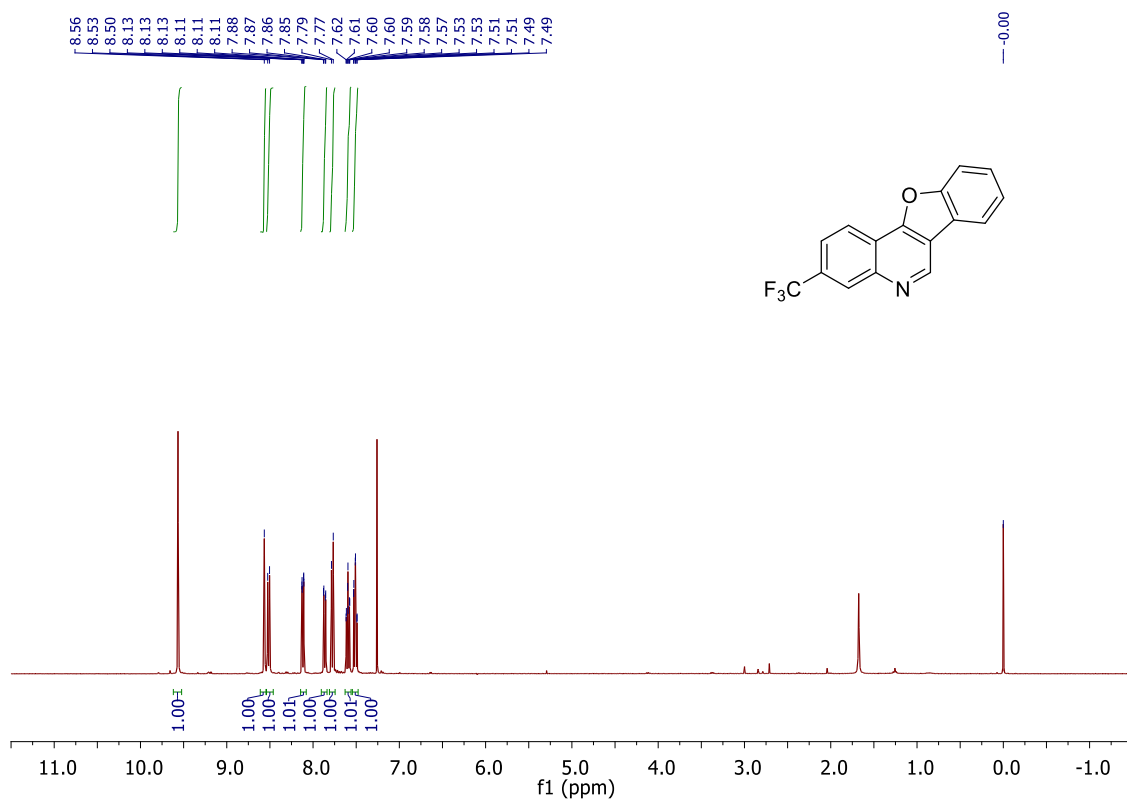
3-(*p*-Tolyl)benzofuro[3,2-c]quinoline ^1H NMR, 400 MHz, CDCl_3 (1b)



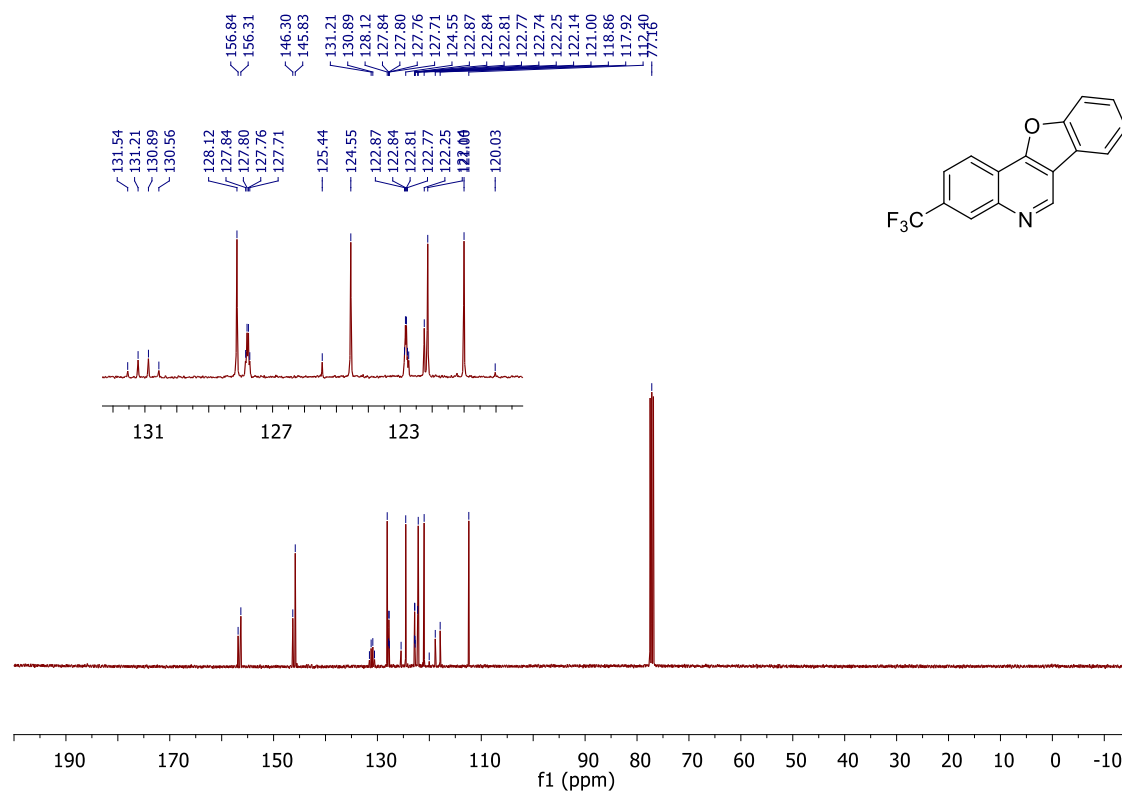
3-(*p*-Tolyl)benzofuro[3,2-*c*]quinoline ¹³C NMR, 100 MHz, CDCl₃ (1b)



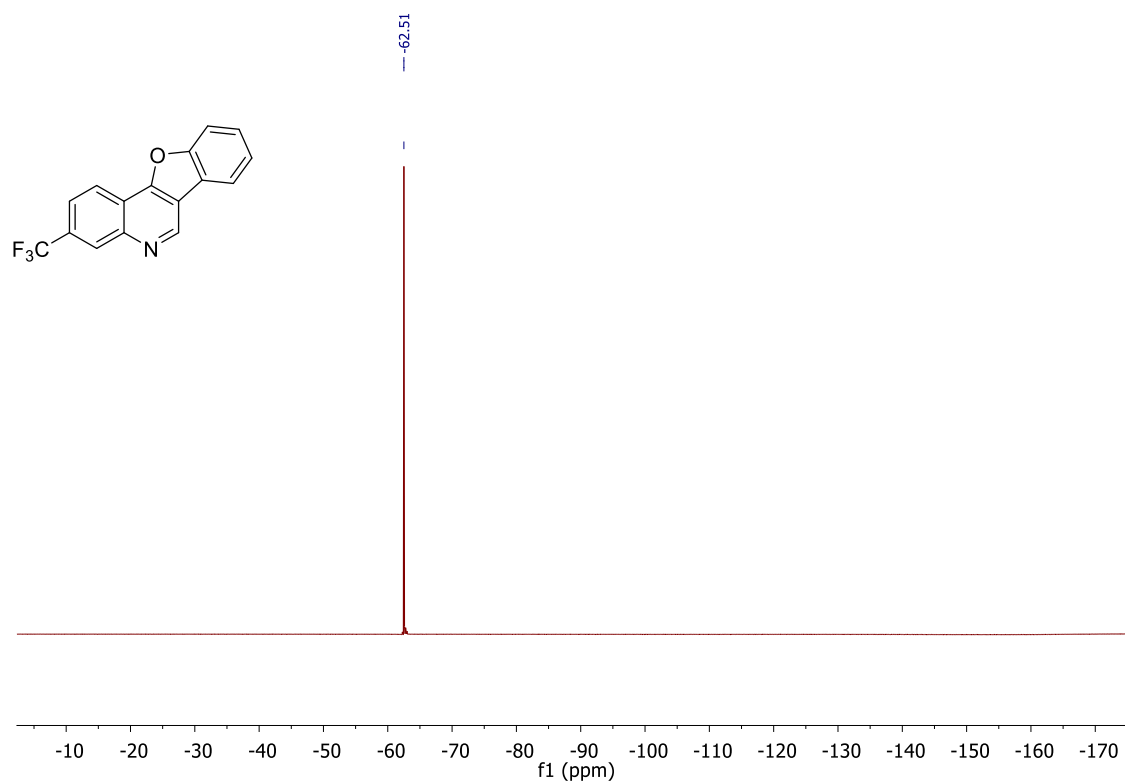
3-(Trifluoromethyl)benzofuro[3,2-*c*]quinoline ¹H NMR, 400 MHz, CDCl₃ (1c)



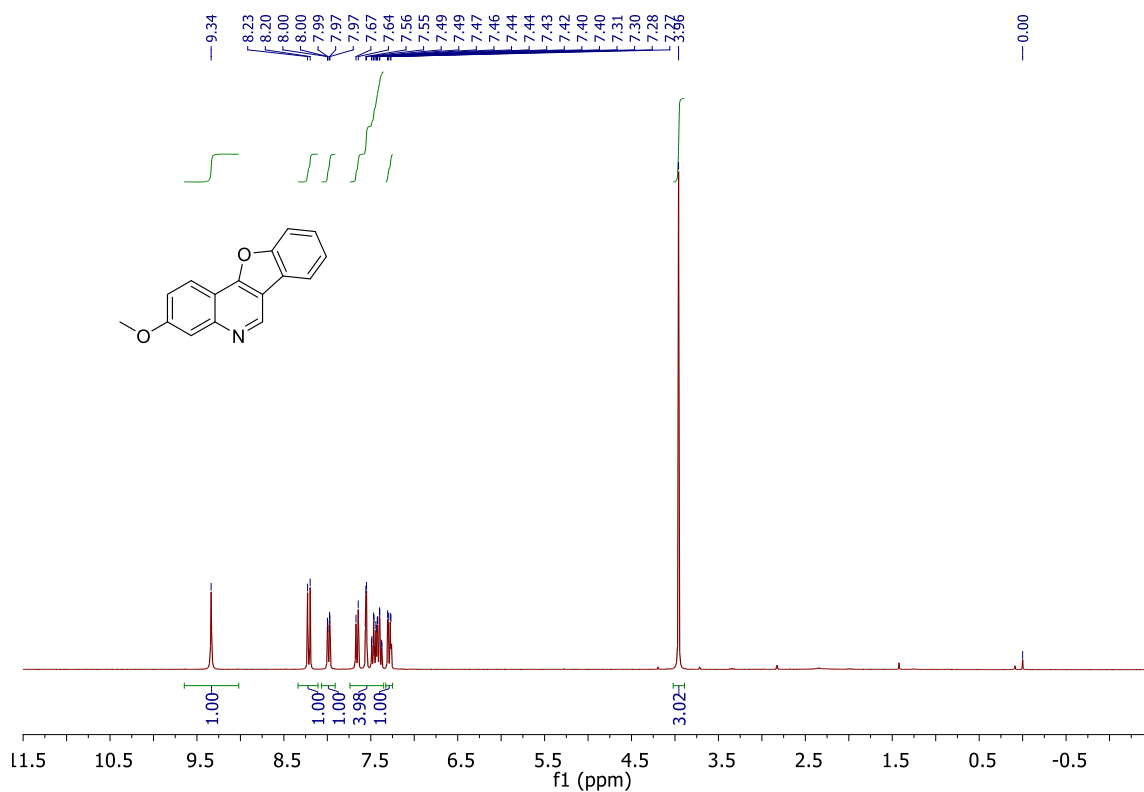
3-(Trifluoromethyl)benzofuro[3,2-c]quinoline ^{13}C NMR, 100 MHz, CDCl_3 (1c)



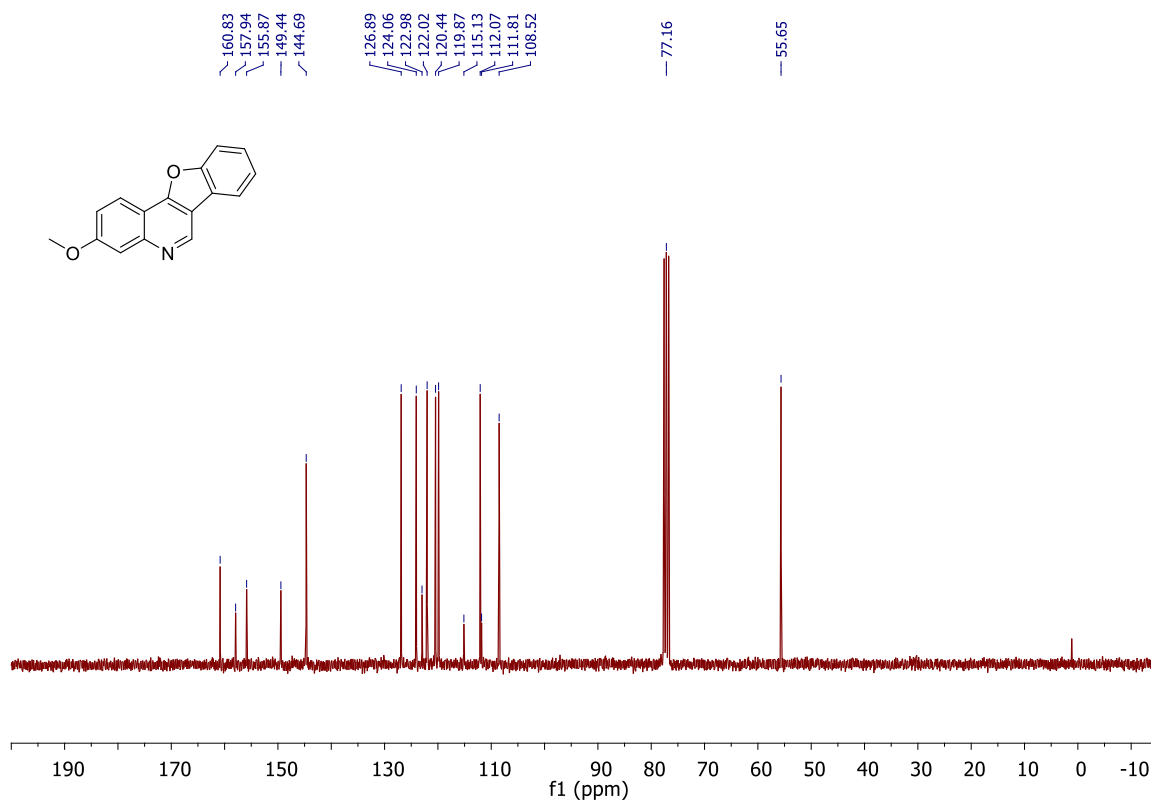
3-(Trifluoromethyl)benzofuro[3,2-c]quinoline ^{19}F NMR, 376 MHz, CDCl_3 (1c)



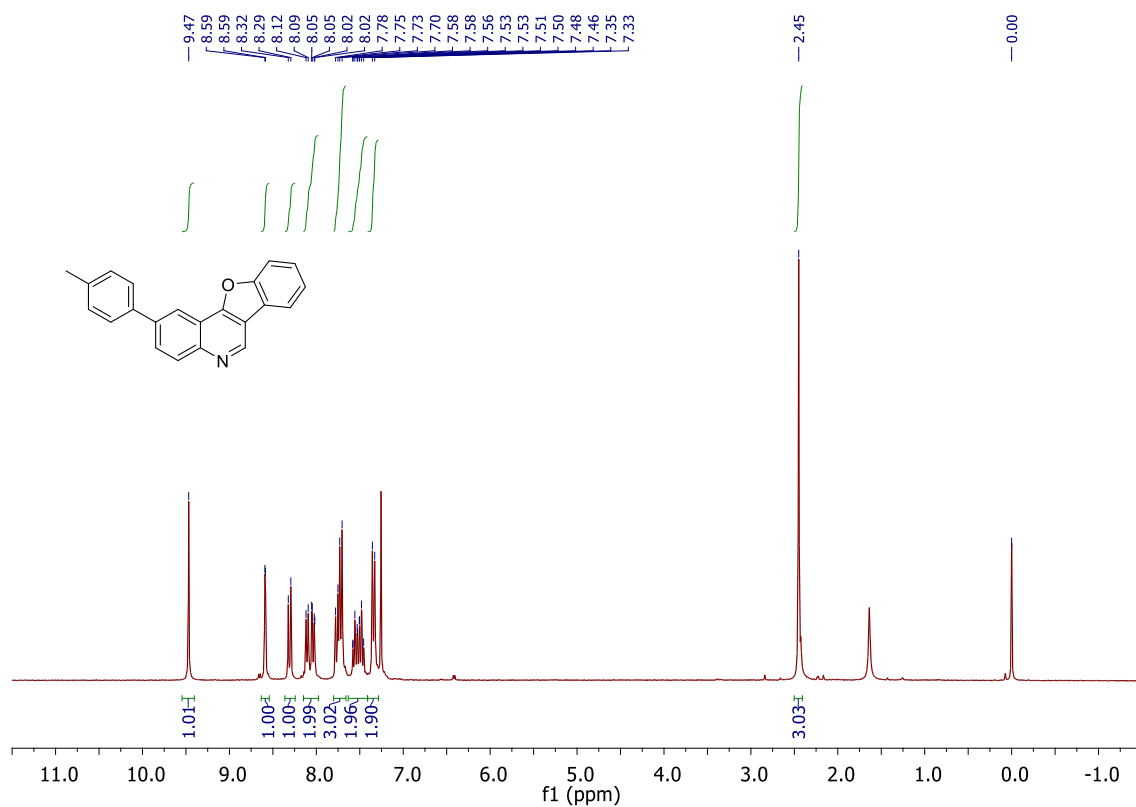
3-Methoxybenzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (1d)



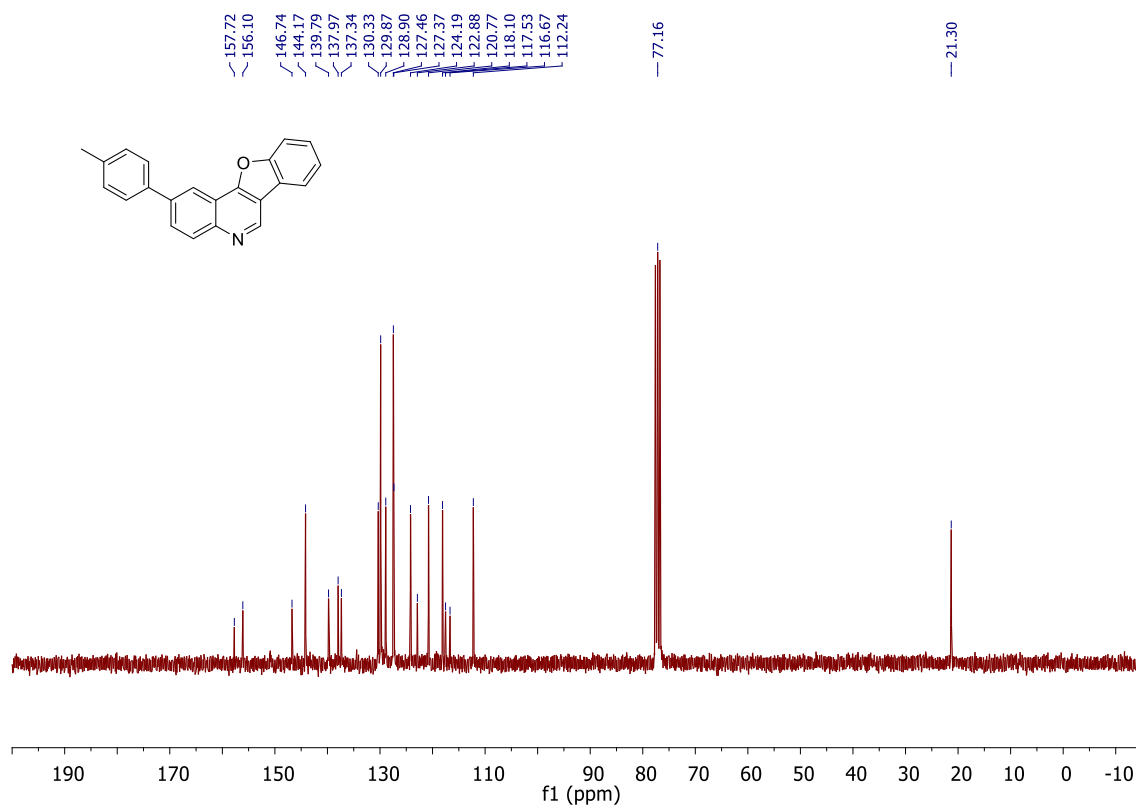
3-Methoxybenzofuro[3,2-c]quinoline ^{13}C NMR, 75 MHz, CDCl_3 (1d)



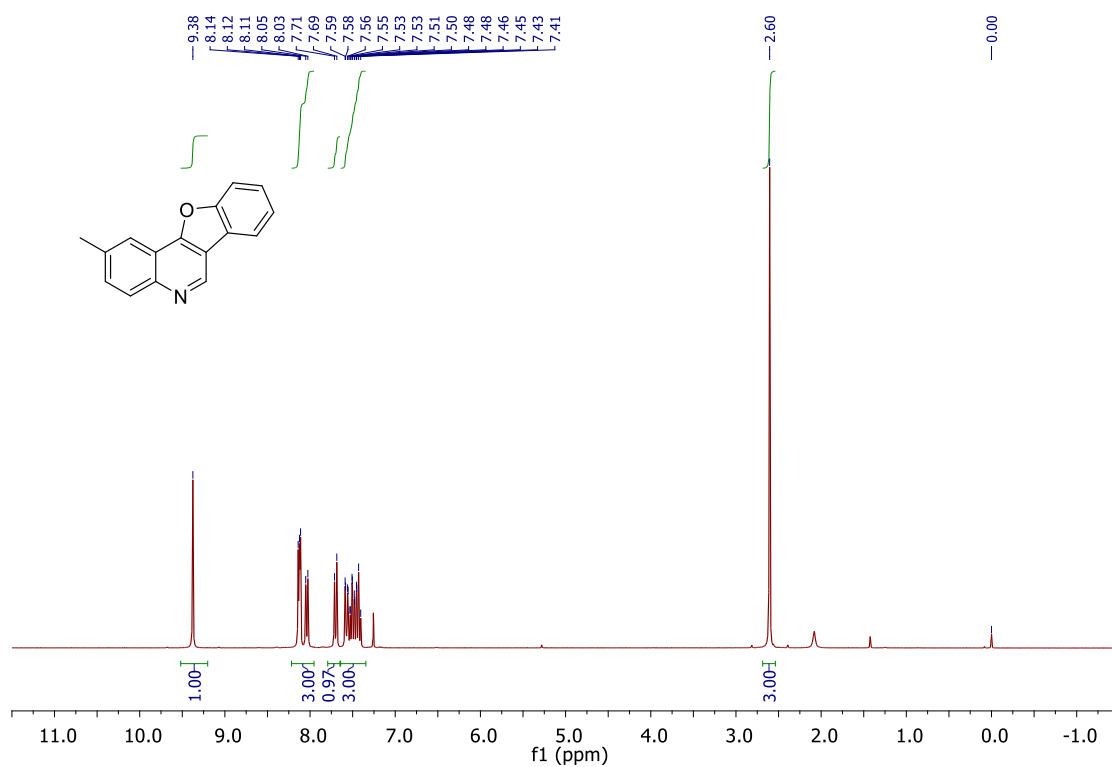
2-(*p*-Tolyl)benzofuro[3,2-*c*]quinoline ¹H NMR, 300 MHz, CDCl₃ (1f)



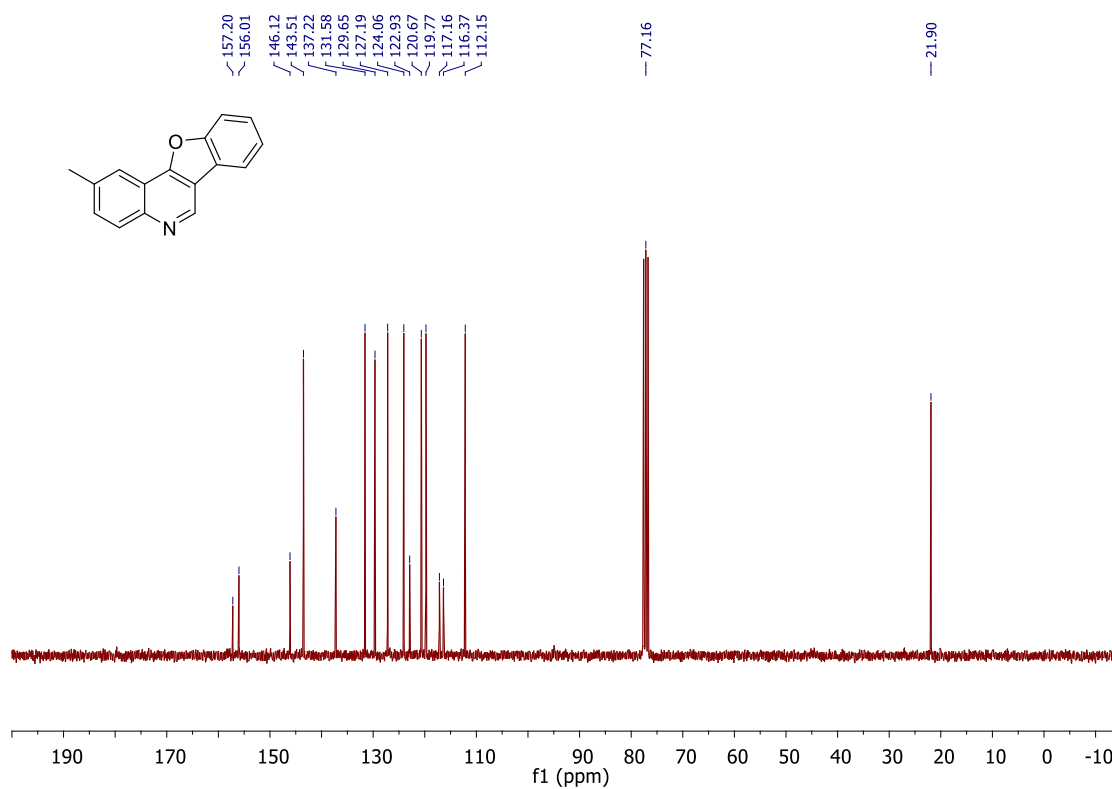
2-(*p*-Tolyl)benzofuro[3,2-*c*]quinoline ¹³C NMR, 75 MHz, CDCl₃ (1f)



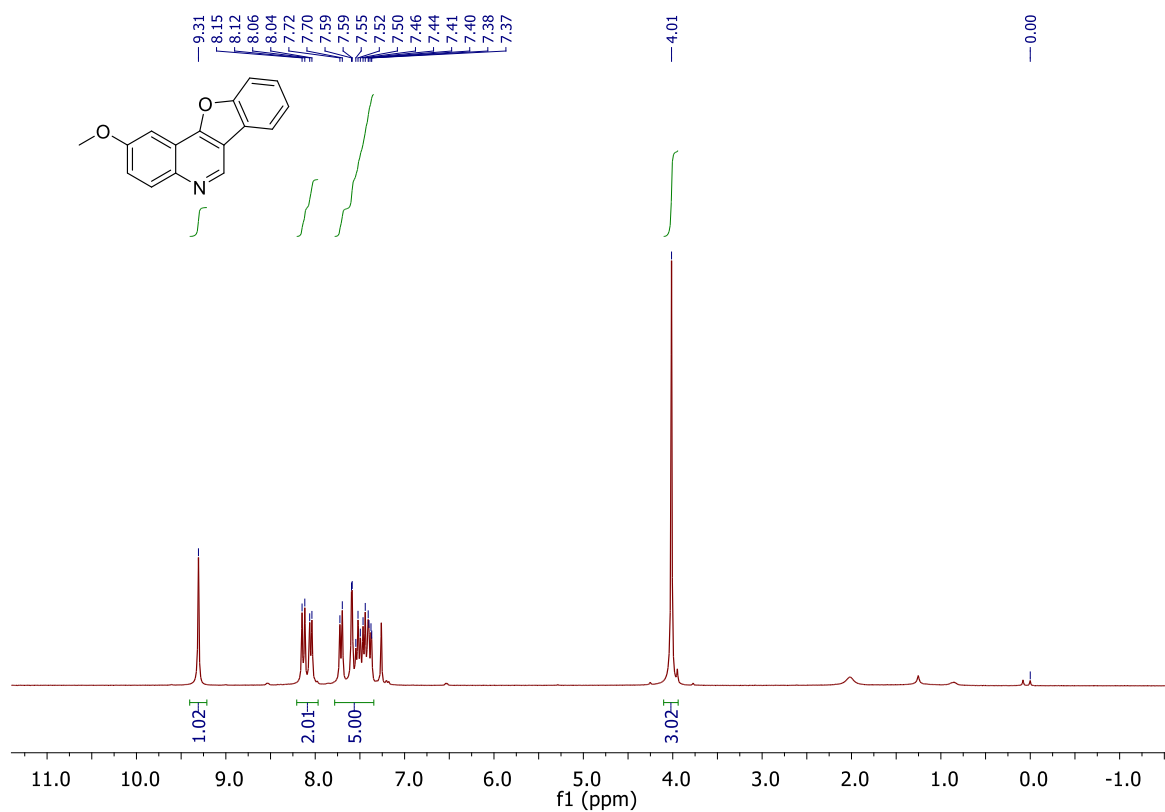
2-Methylbenzofuro[3,2-c]quinoline¹H NMR, 300 MHz, CDCl₃ (1g)



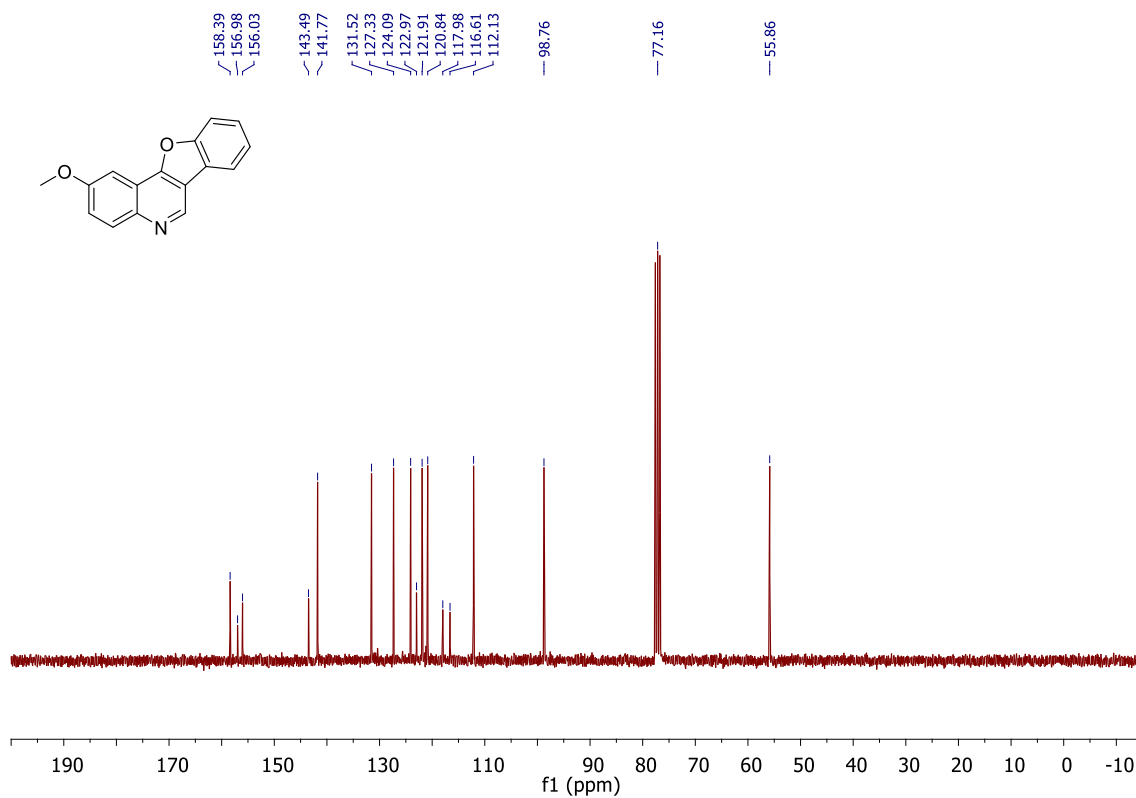
2-Methylbenzofuro[3,2-c]quinoline¹³C NMR, 75 MHz, CDCl₃ (1g)



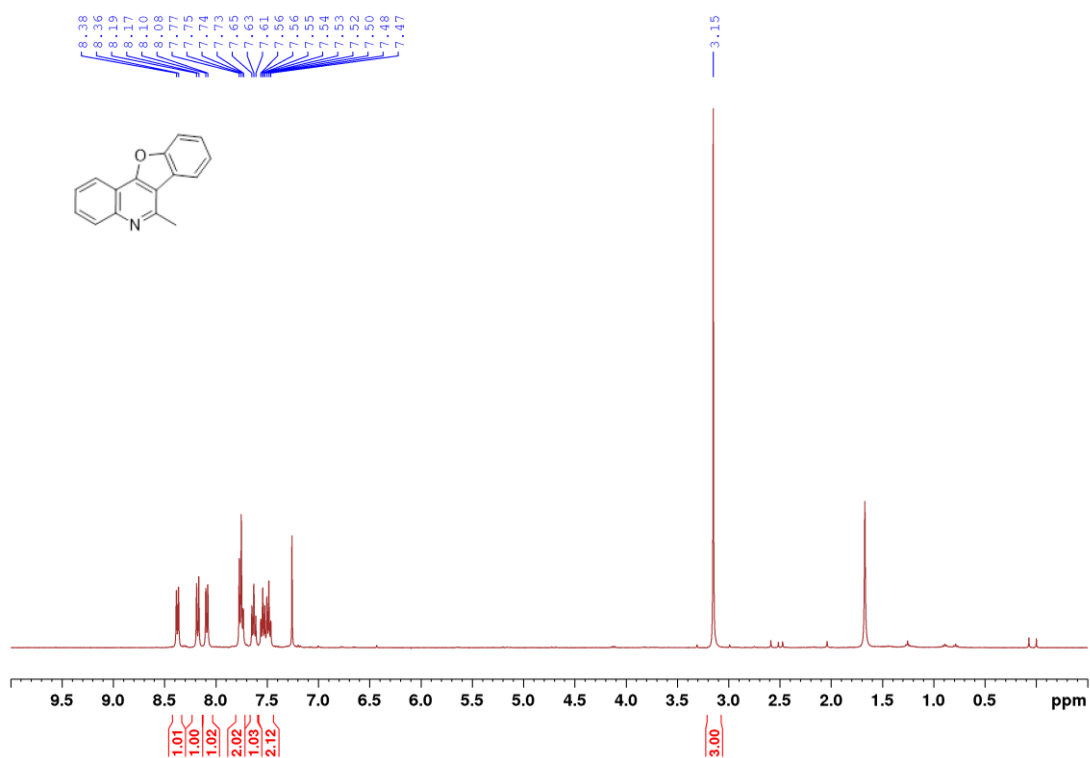
2-Methoxybenzofuro[3,2-c]quinoline ¹H NMR, 300 MHz, CDCl₃ (1h)



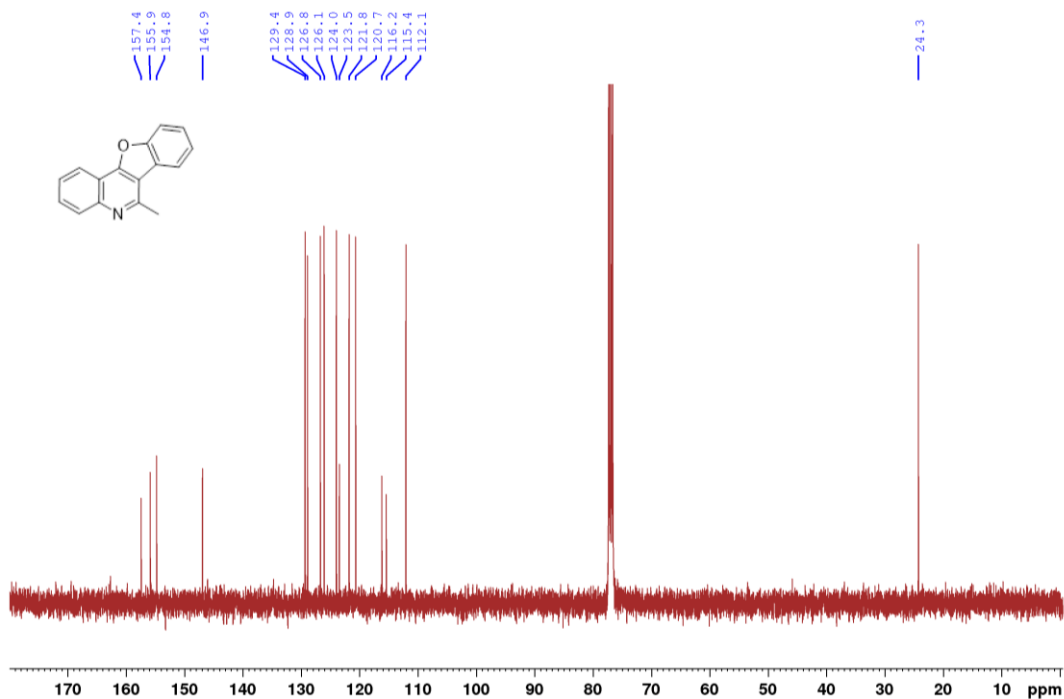
2-Methoxybenzofuro[3,2-c]quinoline ¹³C NMR, 75 MHz, CDCl₃ (1h)



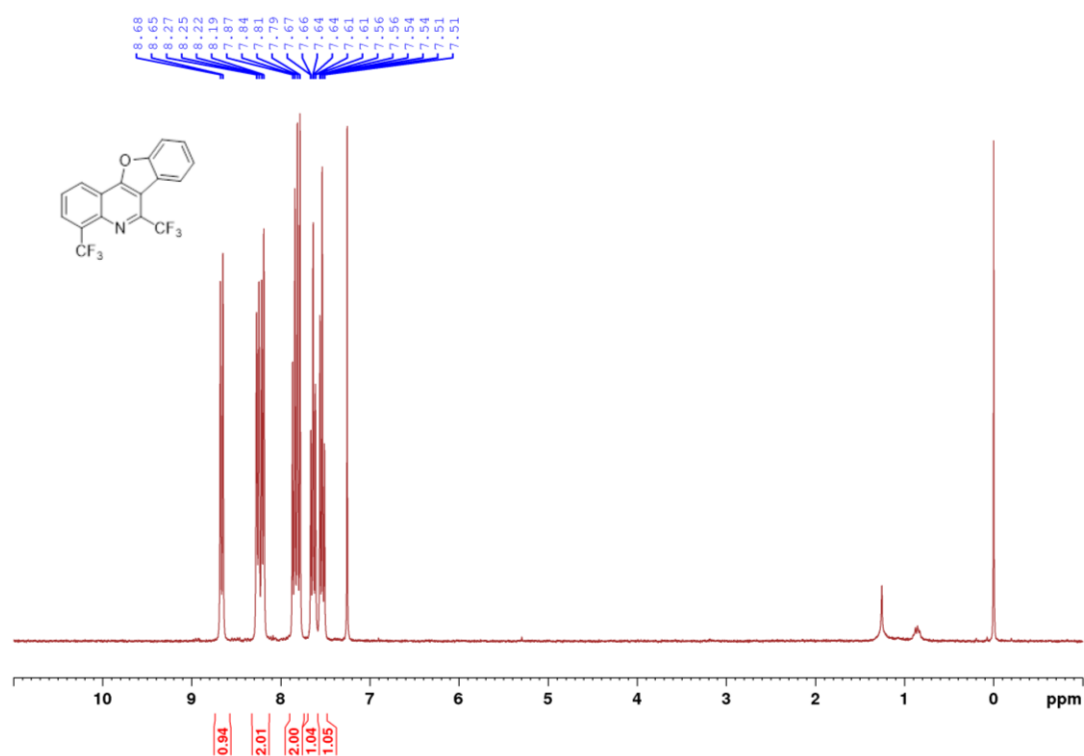
6-Methylbenzofuro[3,2-c]quinoline ^1H NMR, 500 MHz, CDCl_3 (1i)



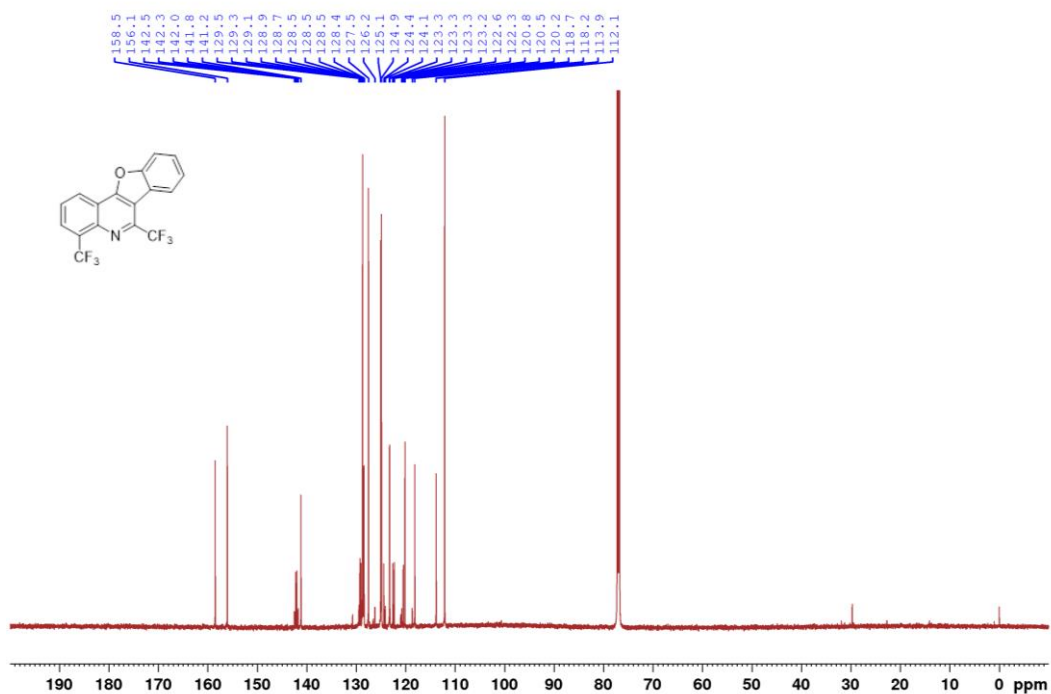
6-Methylbenzofuro[3,2-c]quinoline ^{13}C NMR, 150 MHz, CDCl_3 (1i)



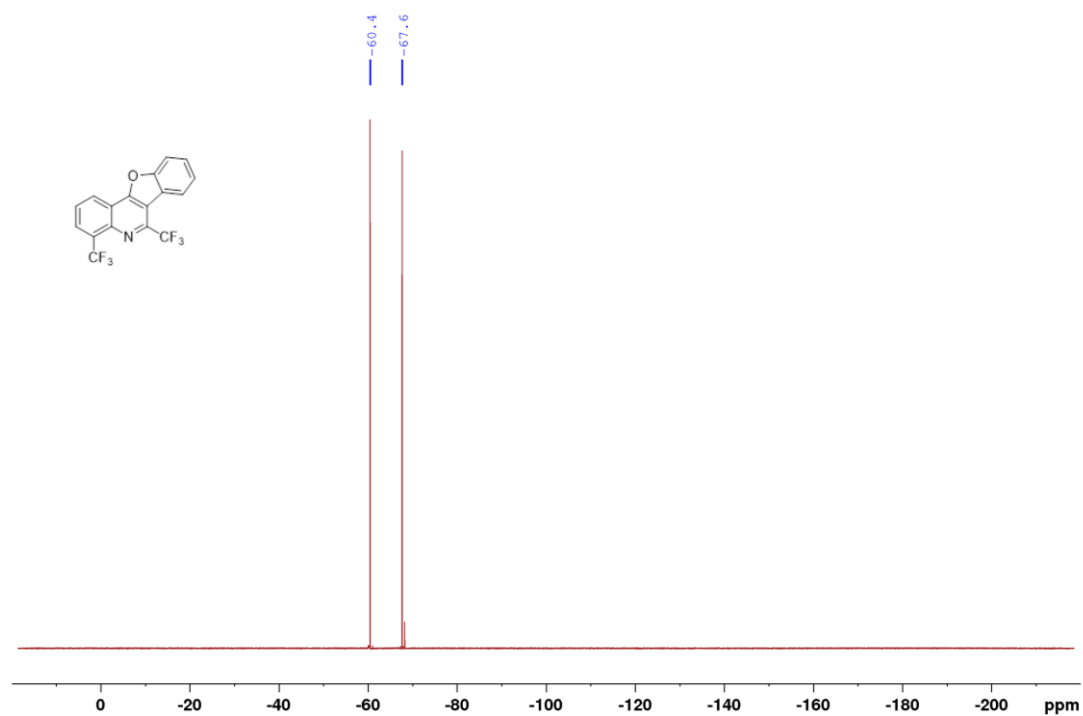
4,6-Bis(Trifluoromethyl)benzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (1j)



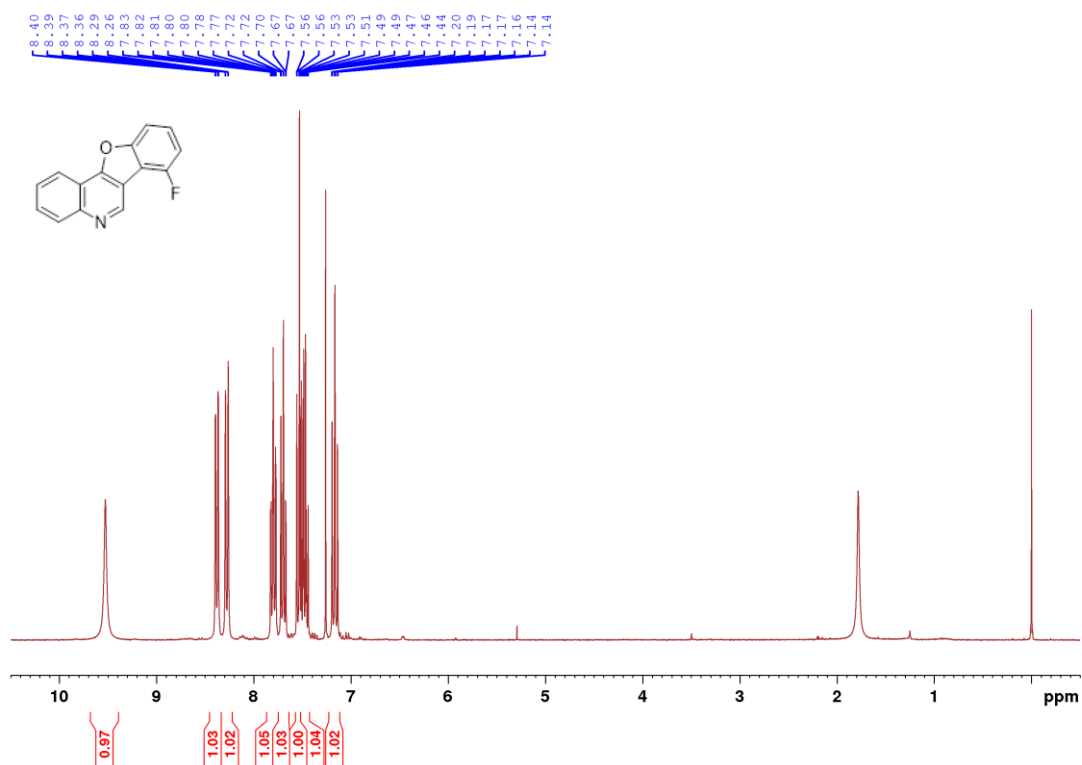
4,6-Bis(trifluoromethyl)benzofuro[3,2-c]quinoline ^{13}C NMR, 125 MHz, CDCl_3 (1j)



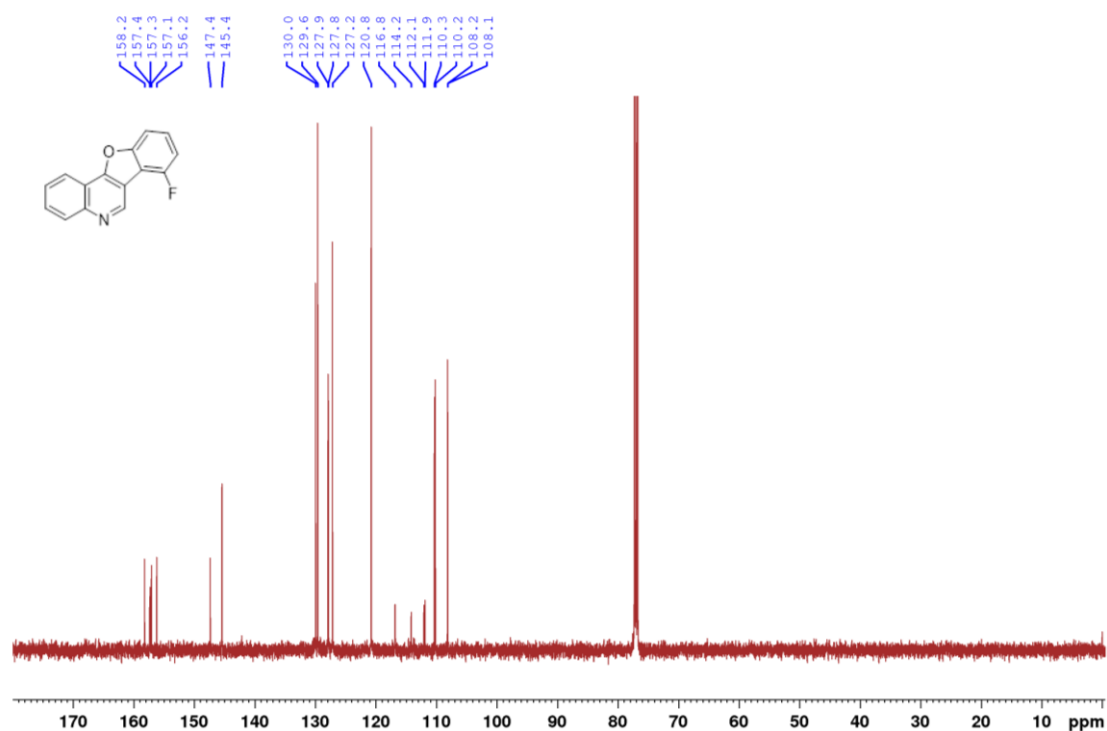
4,6-Bis(Trifluoromethyl)benzofuro[3,2-c]quinoline ^{19}F NMR, 282 MHz, CDCl_3 (1j)



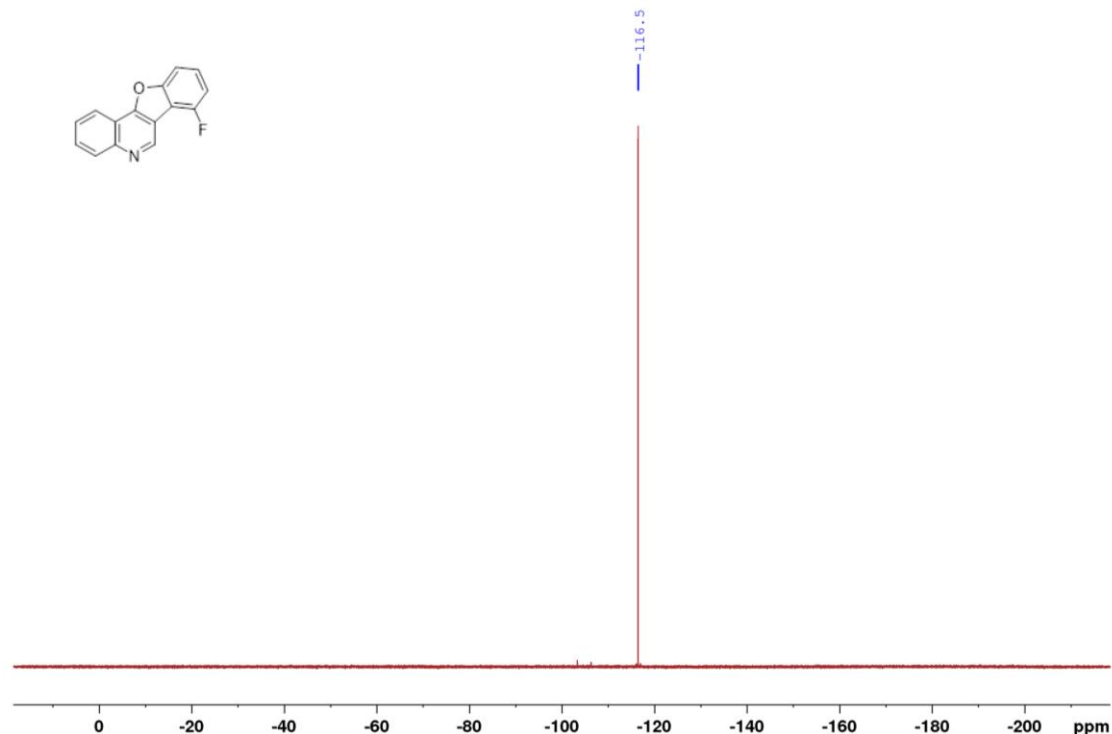
7-Fluorobenzofuro[3,2-c]quinoline ^1H NMR, 500 MHz, CDCl_3 (1m)



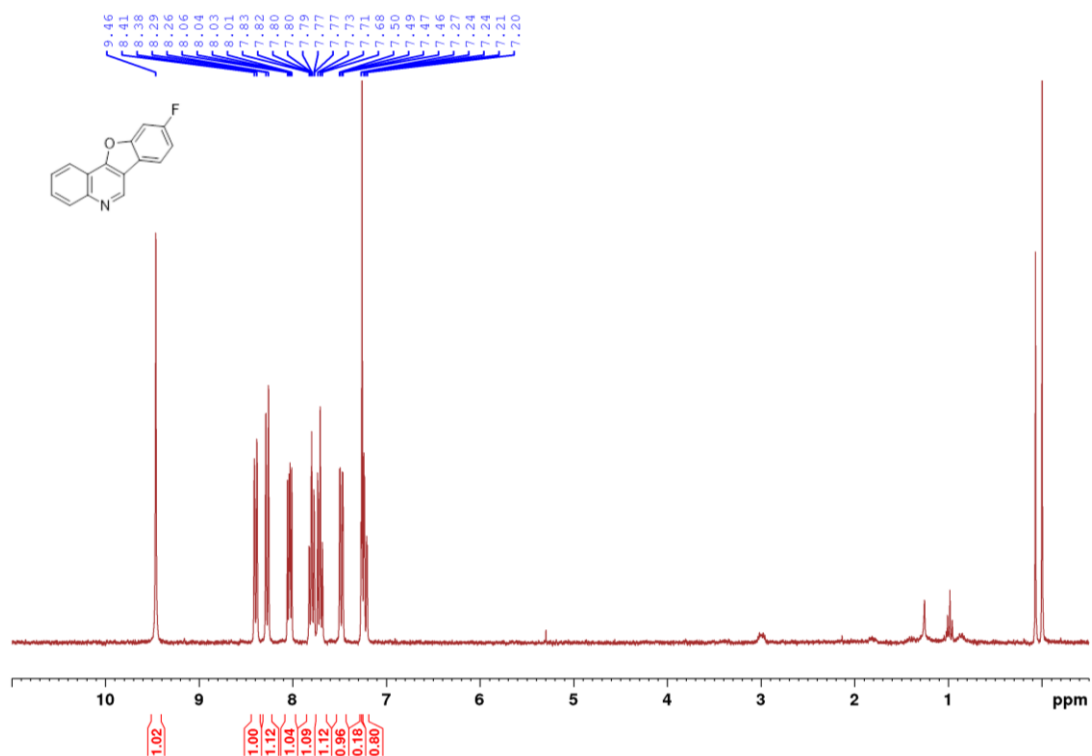
7-Fluorobenzofuro[3,2-c]quinoline ^{13}C NMR, 125 MHz, CDCl_3 (1m)



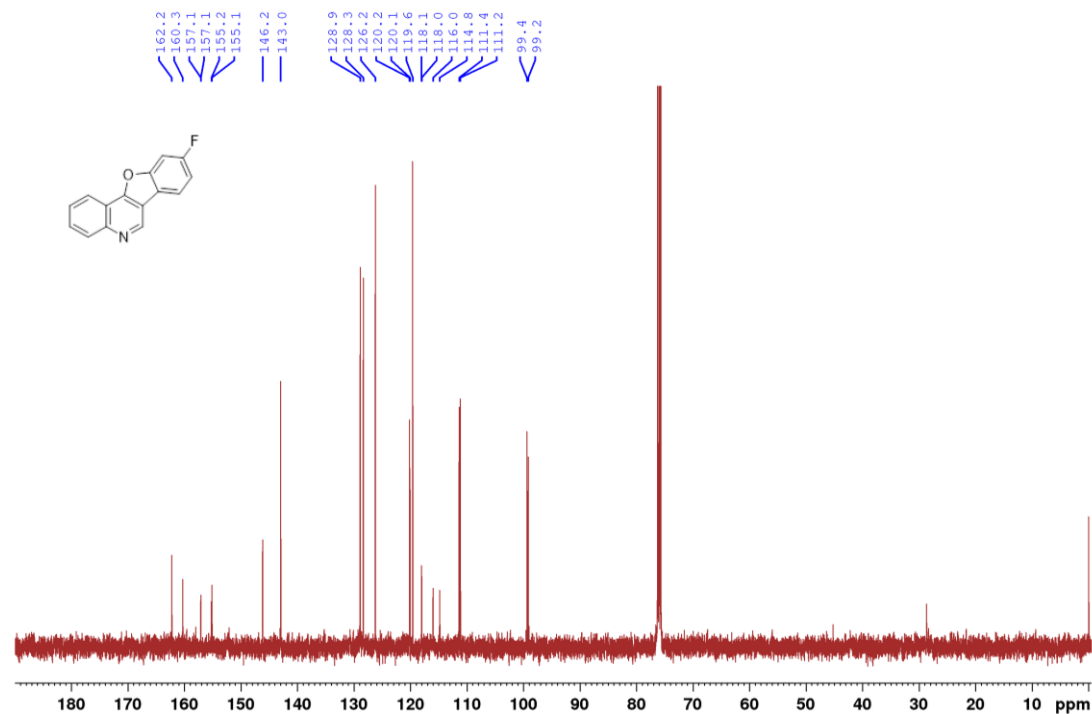
7-Fluorobenzofuro[3,2-c]quinoline ^{19}F NMR, 282 MHz, CDCl_3 (1m)



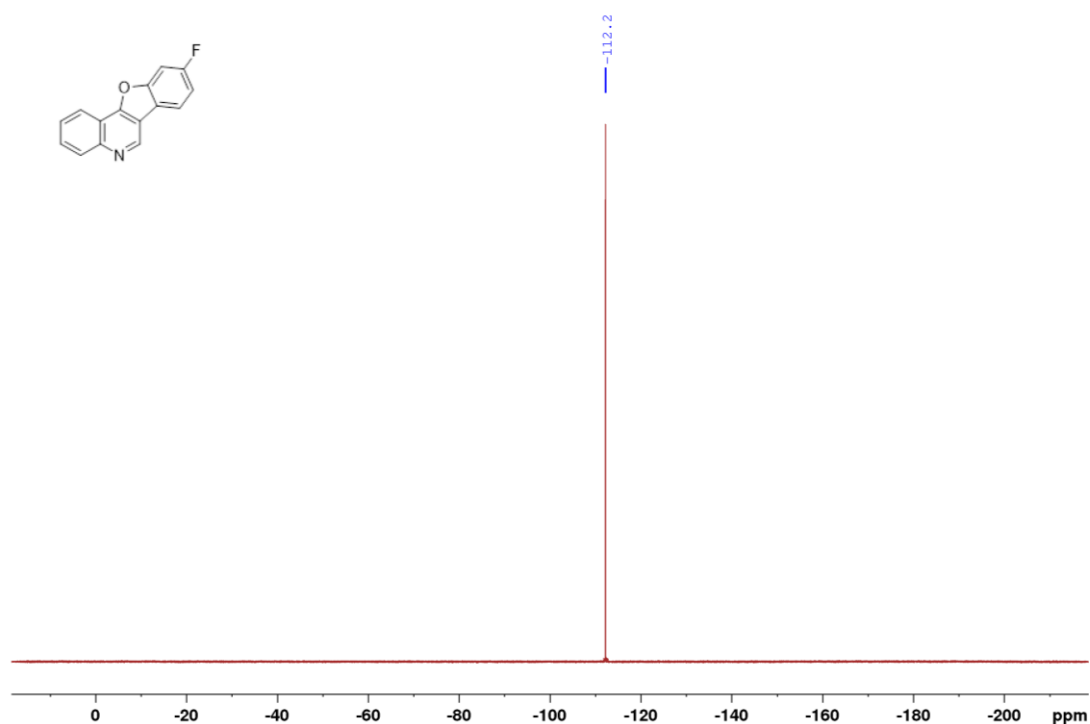
9-Fluorobenzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (1n)



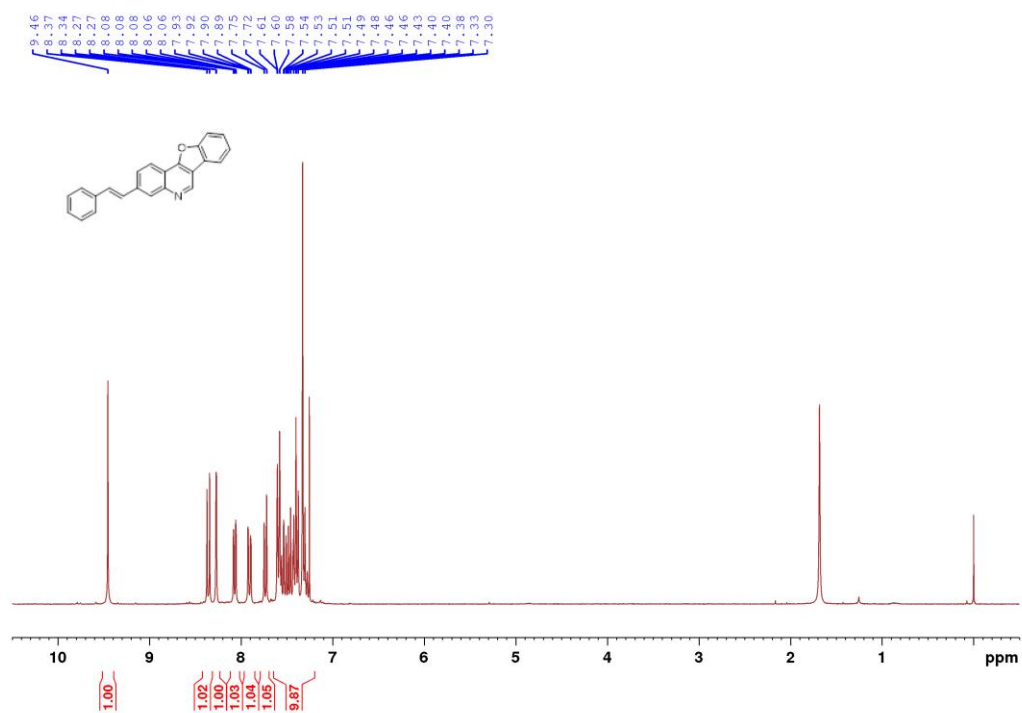
9-Fluorobenzofuro[3,2-c]quinoline ^{13}C NMR, 150 MHz, CDCl_3 (1n)



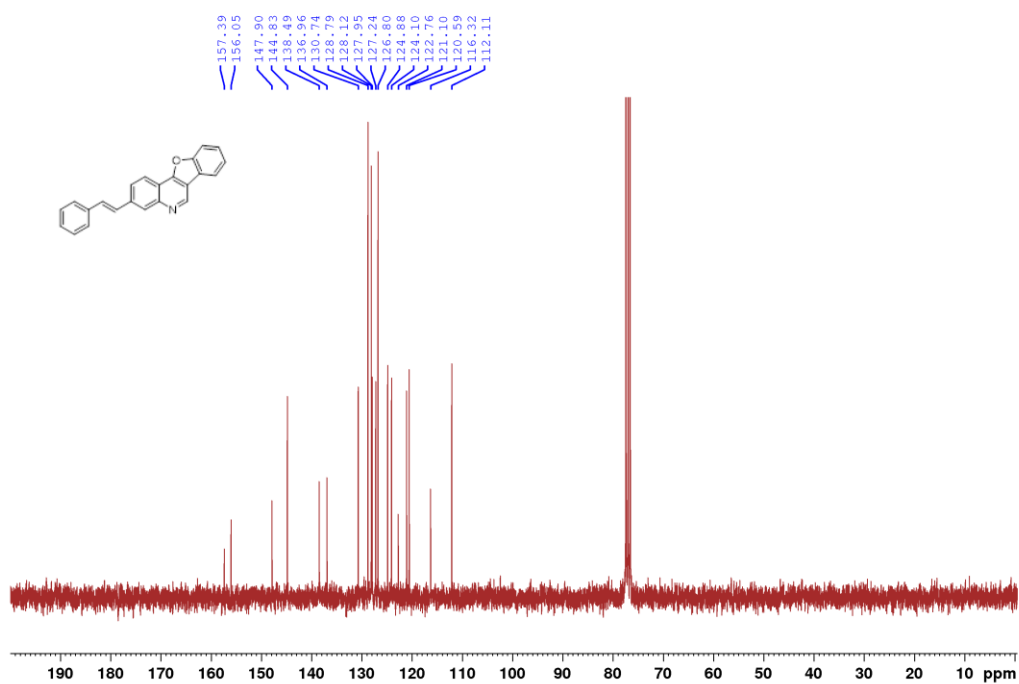
9-Fluorobenzofuro[3,2-c]quinoline ^{19}F NMR, 282 MHz, CDCl_3 (1n)



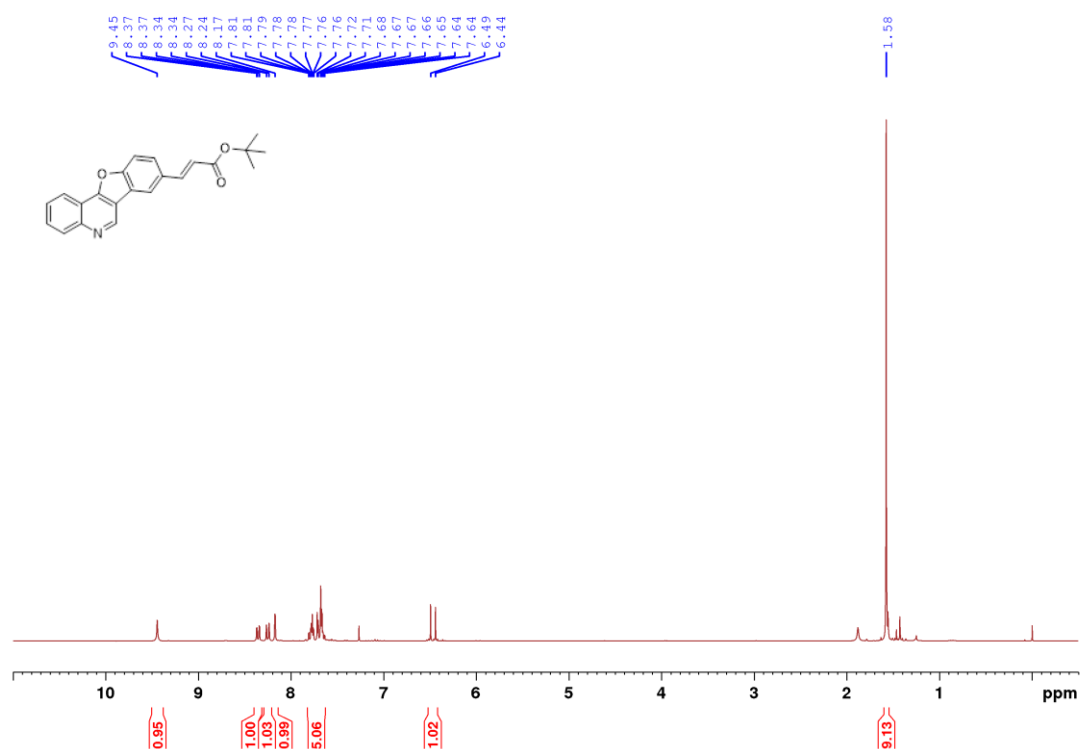
(E)-3-Styrylbenzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (3b)



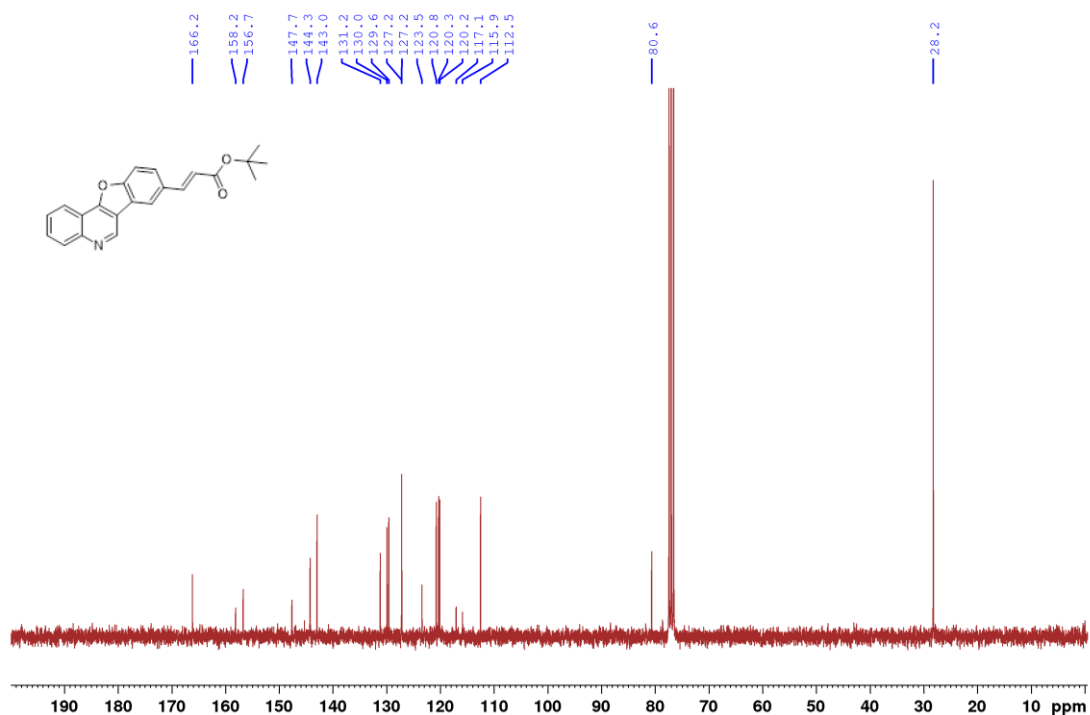
(E)-3-Styrylbenzofuro[3,2-c]quinoline ^{13}C NMR, 75 MHz, CDCl_3 (3b)



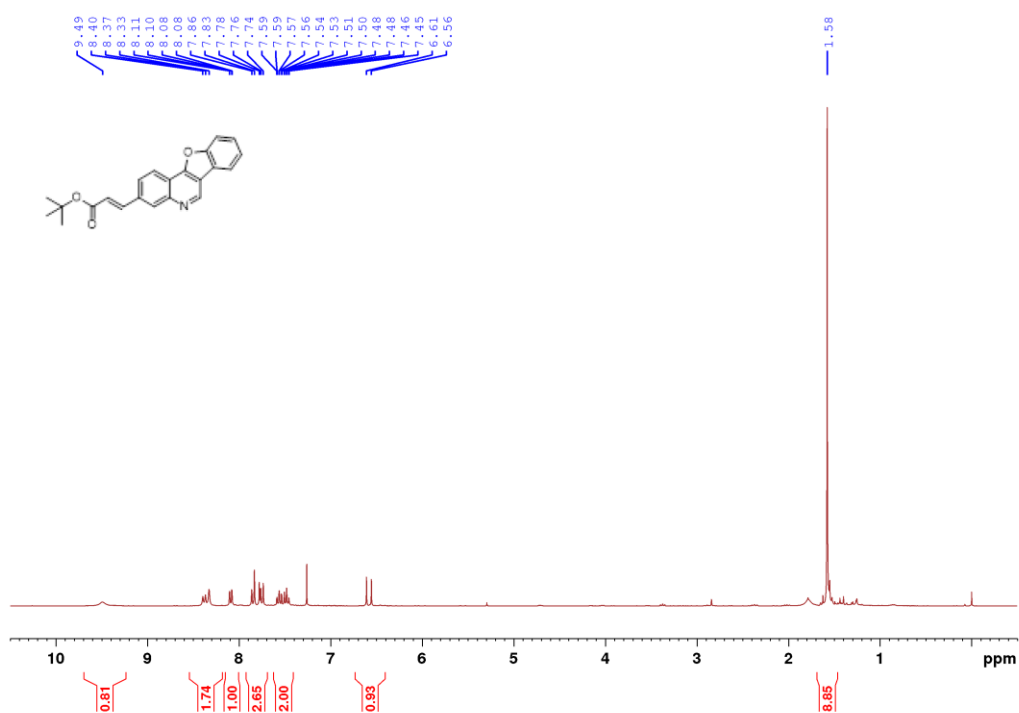
***tert*-Butyl (E)-3-(benzofuro[3,2-c]quinolin-8-yl)acrylate ^1H NMR, 300 MHz, CDCl_3 (3c)**



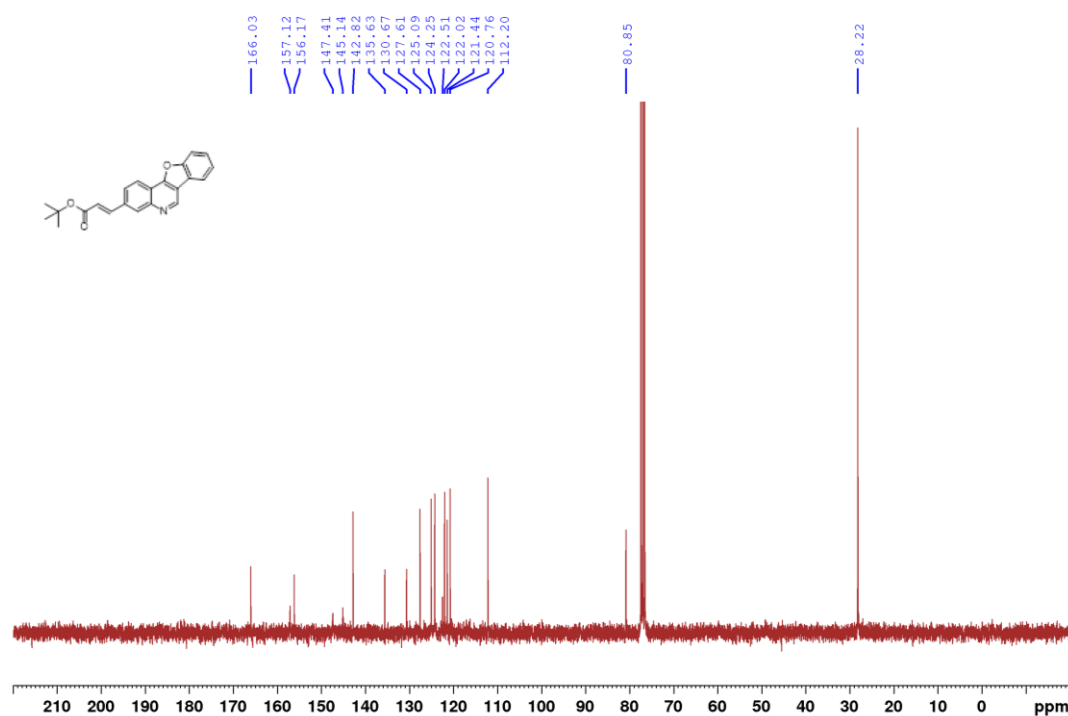
***tert*-Butyl (*E*)-3-(benzofuro[3,2-*c*]quinolin-8-yl)acrylate ¹³C NMR, 75 MHz, CDCl₃ (3c)**



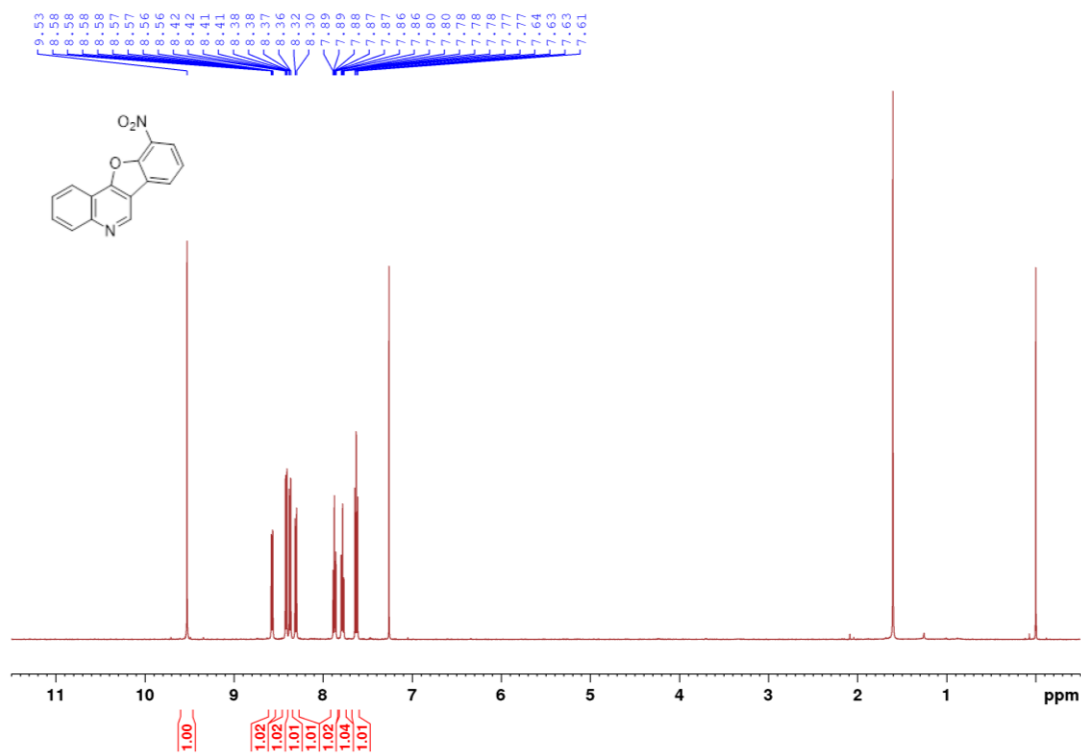
***tert*-Butyl-(*E*)-3-(benzofuro[3,2-*c*]quinolin-3-yl)acrylate ¹H NMR, 300 MHz, CDCl₃ (3d)**



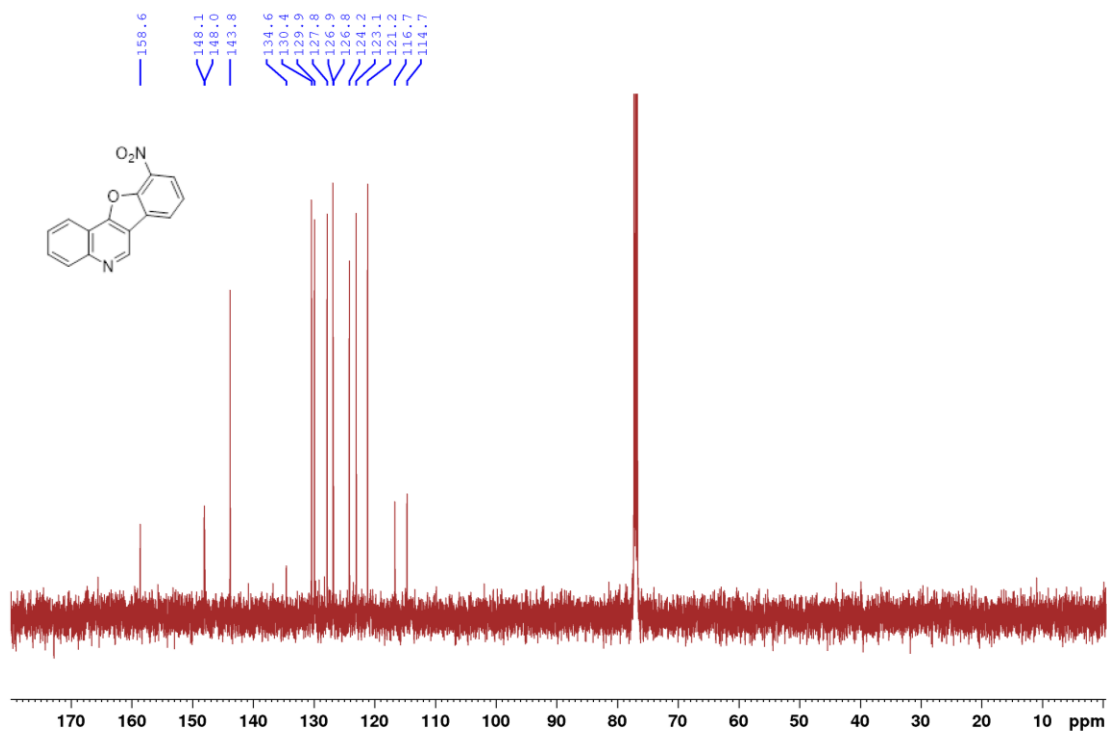
***tert*-Butyl-(*E*)-3-(benzofuro[3,2-*c*]quinolin-3-yl)acrylate ¹³C NMR, 75 MHz, CDCl₃ (3d)**



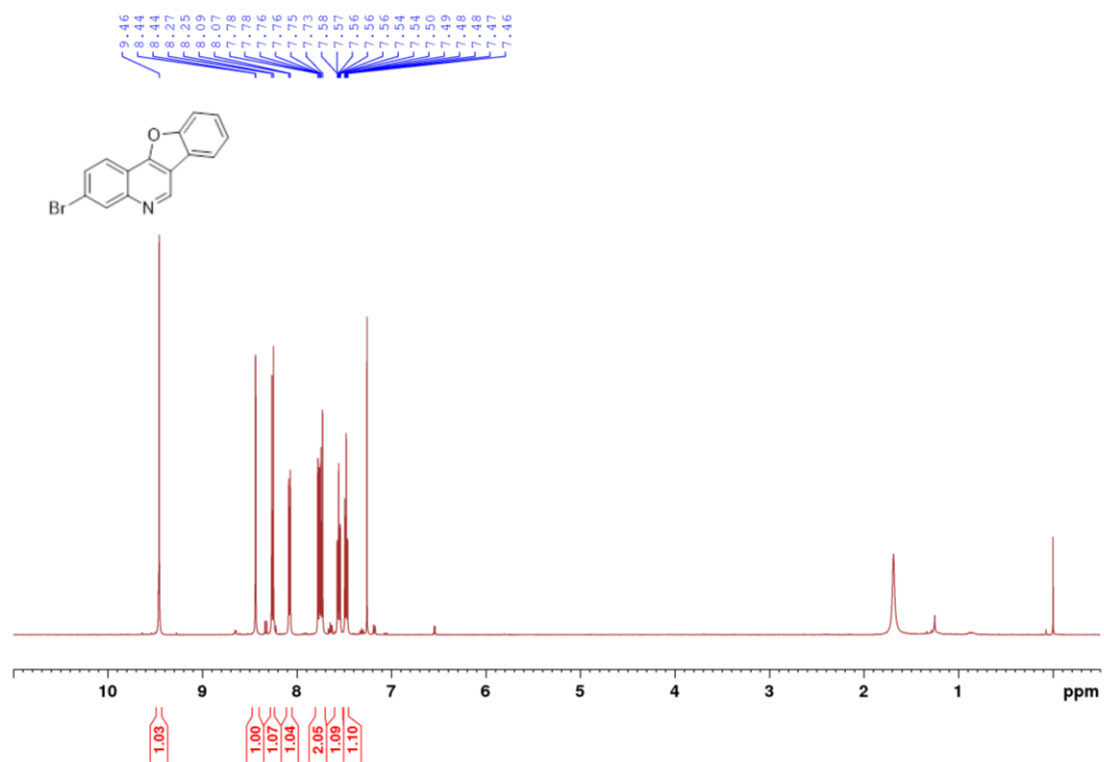
10-Nitrobenzofuro[3,2-*c*]quinoline ¹H NMR, 500 MHz, CDCl₃ (5)



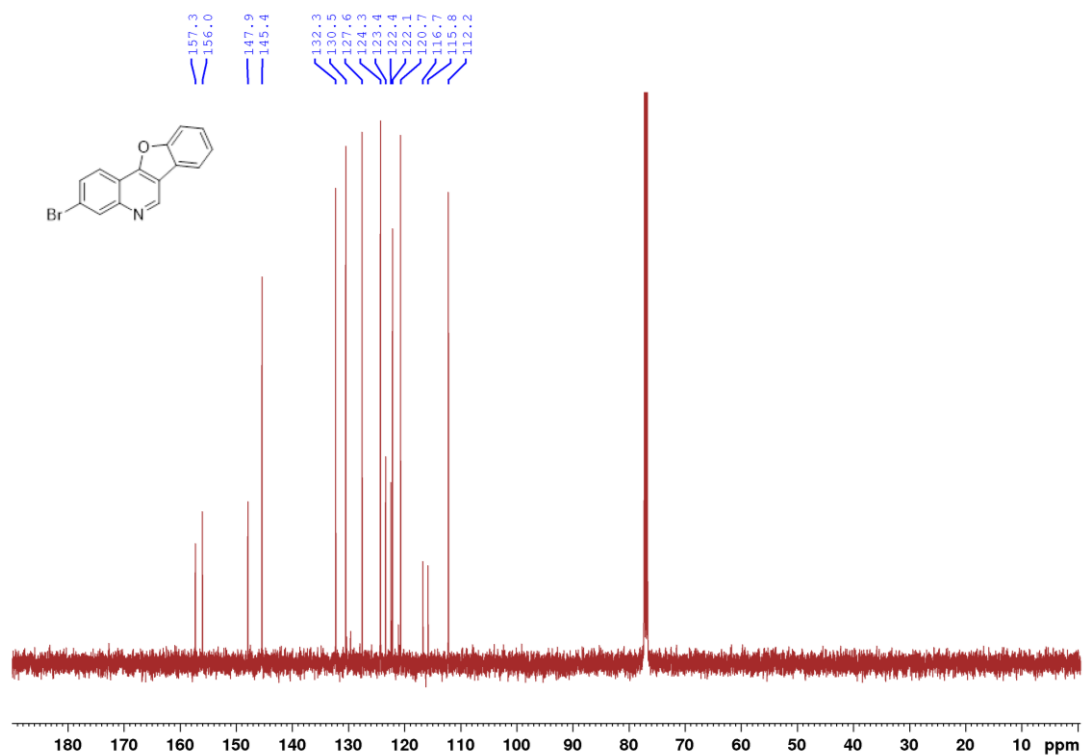
10-Nitrobenzofuro[3,2-c]quinoline ^{13}C NMR, 125 MHz, CDCl_3 (5)



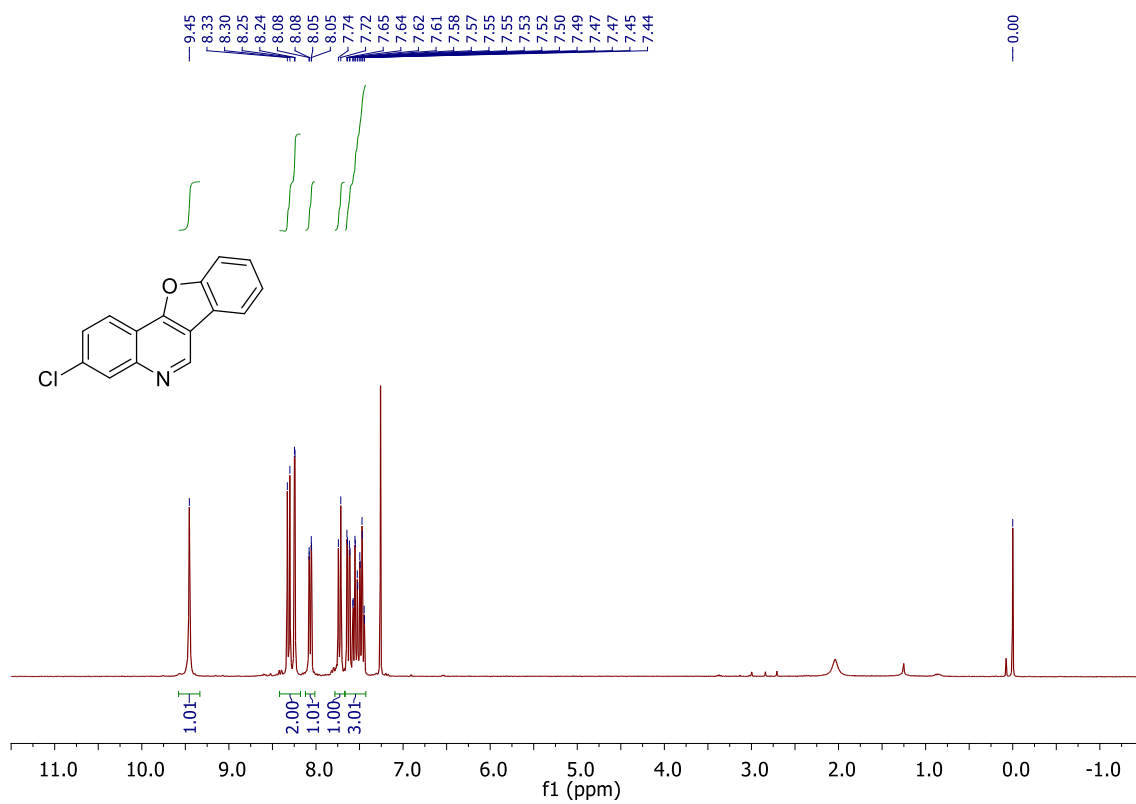
3-Bromobenzofuro[3,2-c]quinoline ^1H NMR, 500 MHz, CDCl_3 (S2)



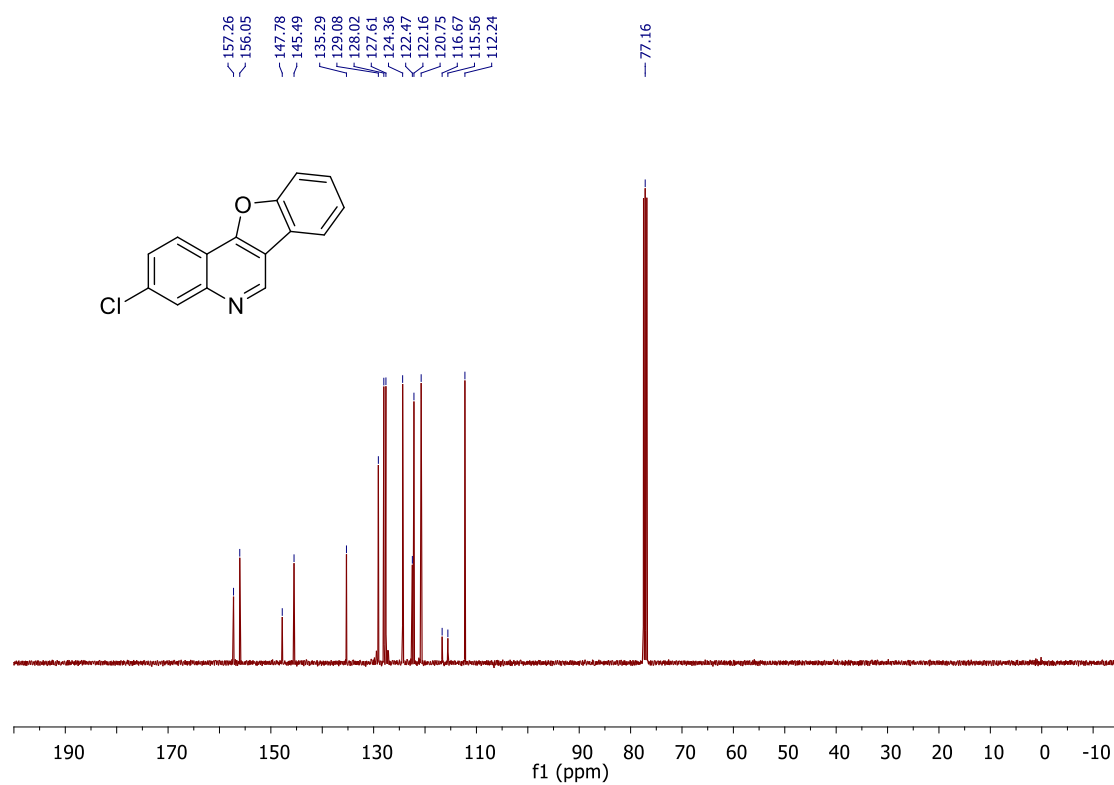
3-Bromobenzofuro[3,2-c]quinoline ^{13}C NMR, 125 MHz, CDCl_3 (S2)



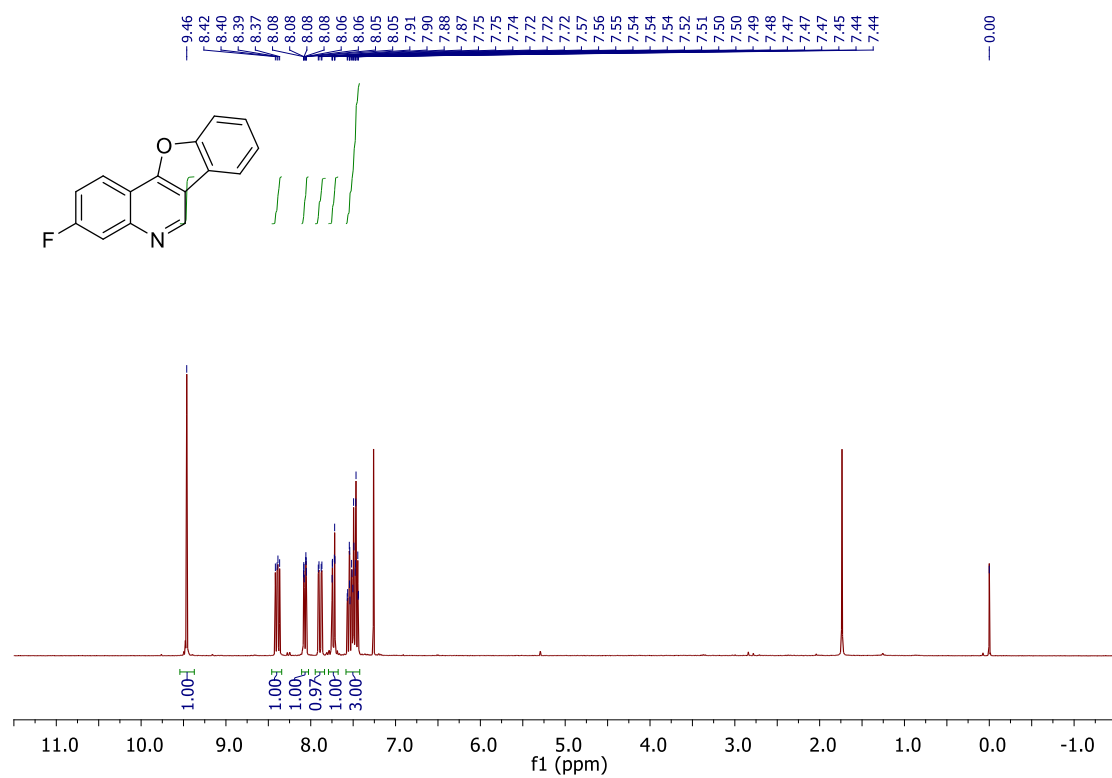
3-Chlorobenzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (S3)



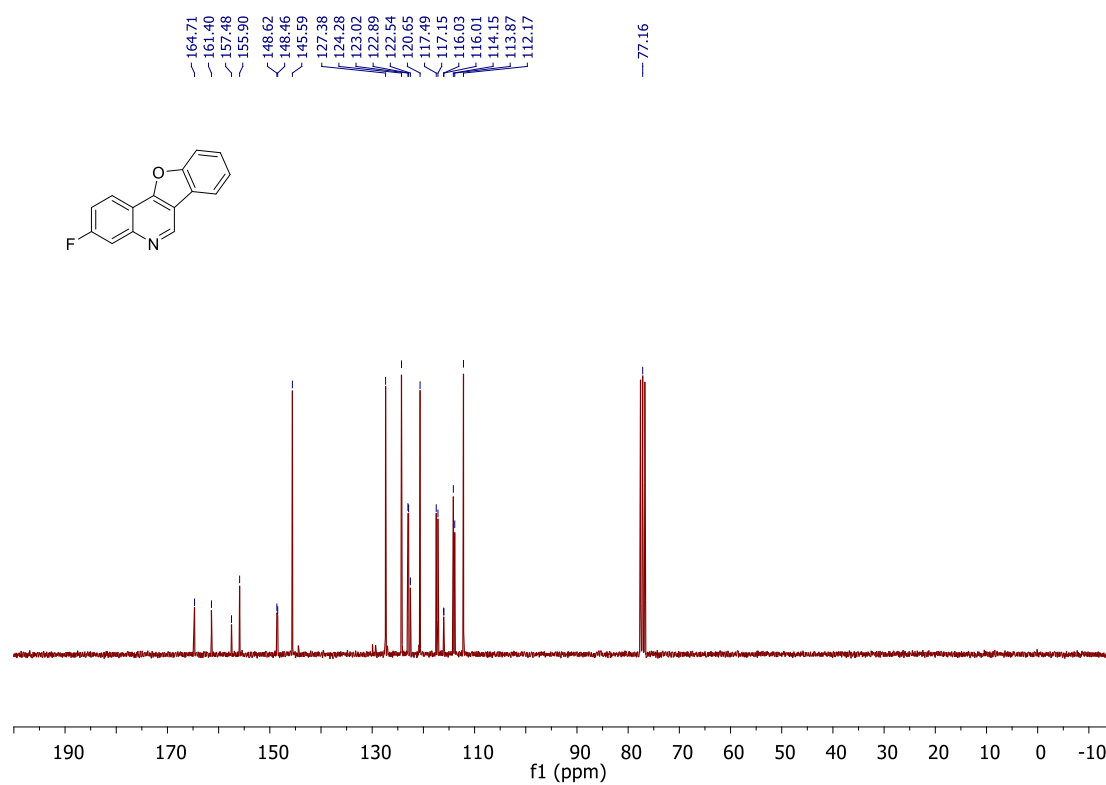
3-Chlorobenzofuro[3,2-c]quinoline ^{13}C NMR, 100 MHz, CDCl_3 (S3)



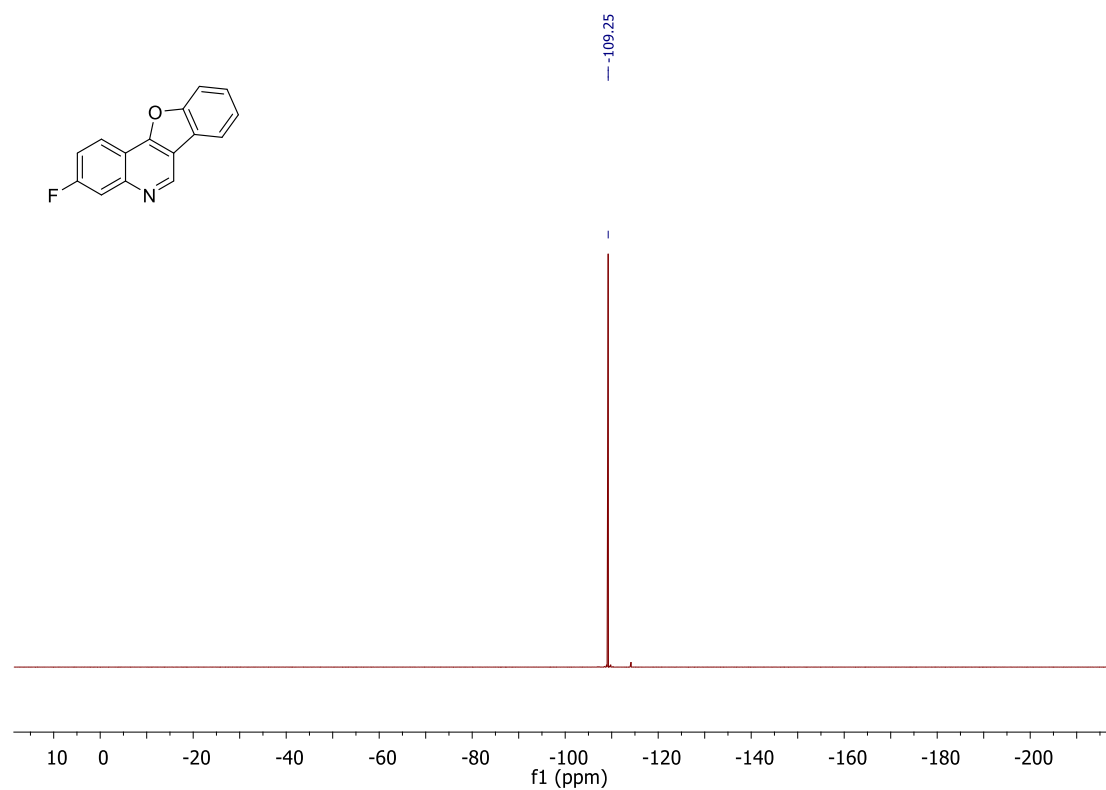
3-Fluorobenzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (S4)



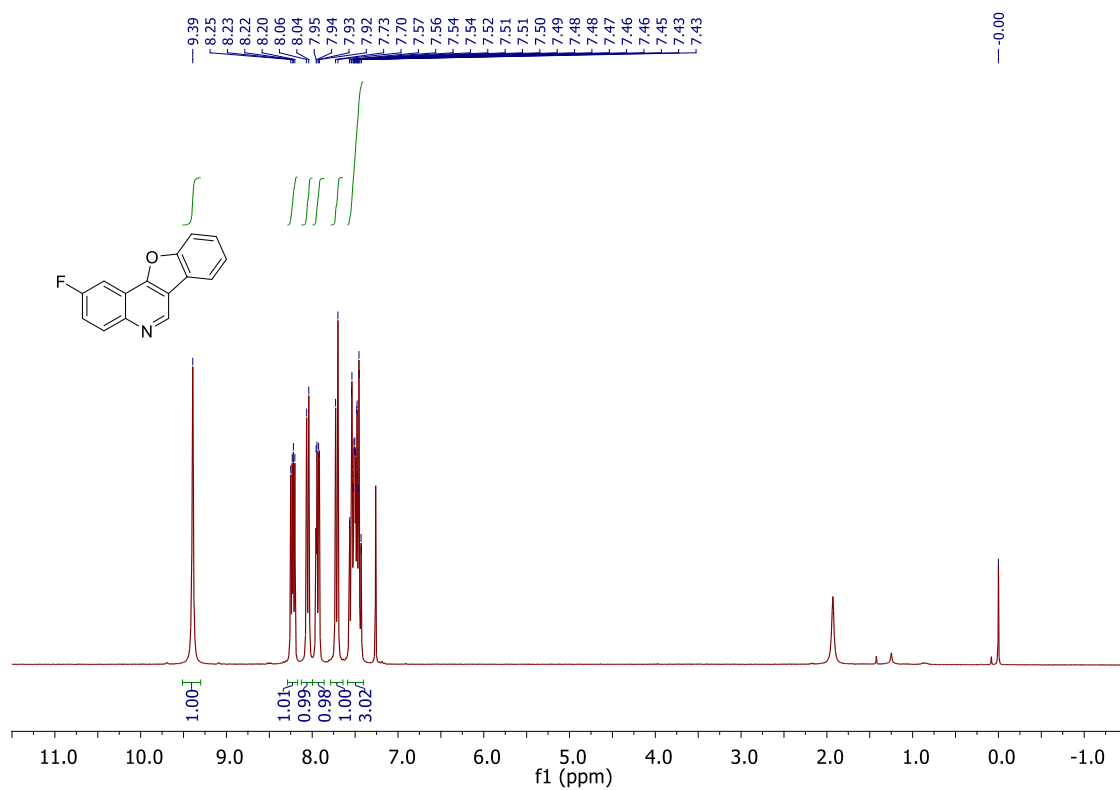
3-Fluorobenzofuro[3,2-c]quinoline ^{13}C NMR, 75 MHz, CDCl_3 (S4)



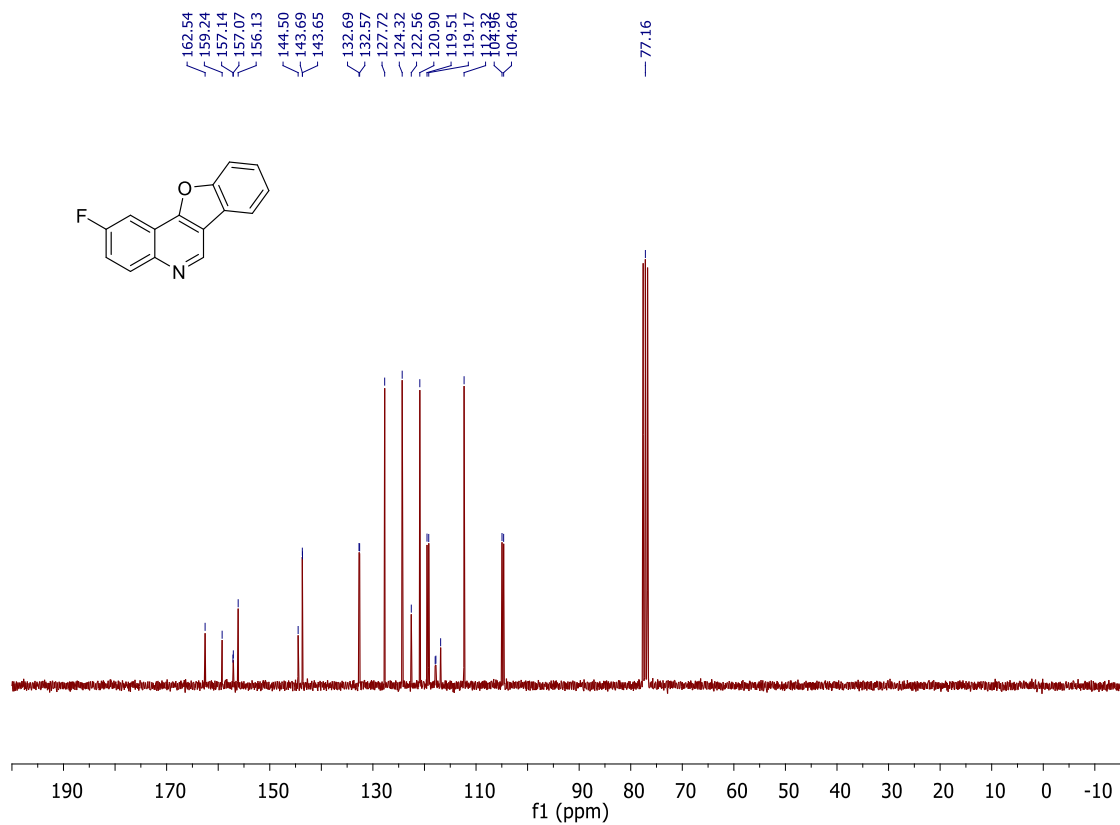
3-Fluorobenzofuro[3,2-c]quinoline ^{19}F NMR, 282 MHz, CDCl_3 (S4)



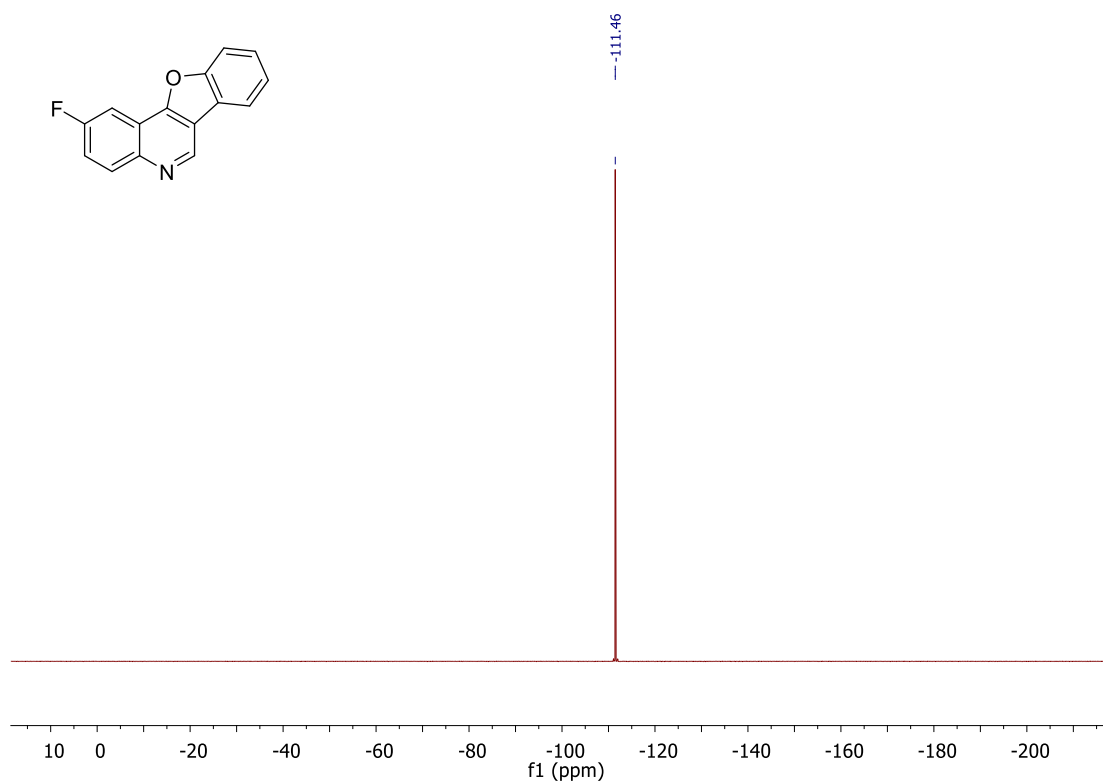
2-Fluorobenzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (S5)



2-Fluorobenzofuro[3,2-c]quinoline ^{13}C NMR, 75 MHz, CDCl_3 (S5)

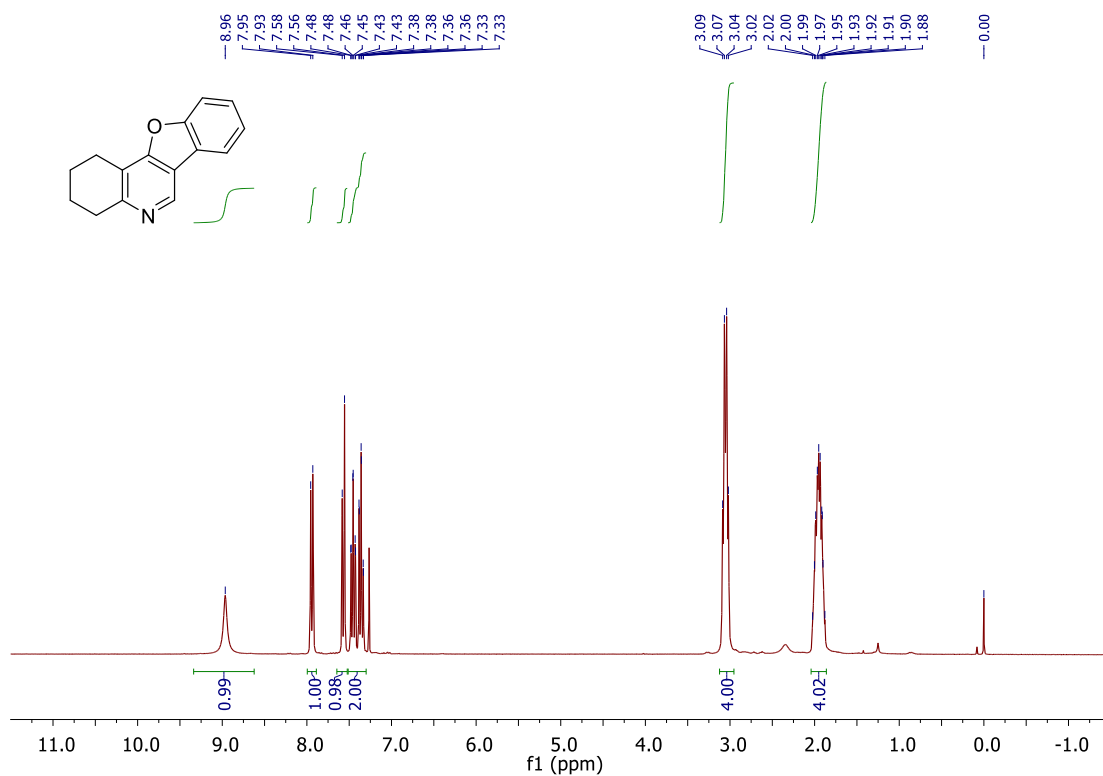


2-Fluorobenzofuro[3,2-c]quinoline ^{19}F NMR, 282 MHz, CDCl_3 (S5)

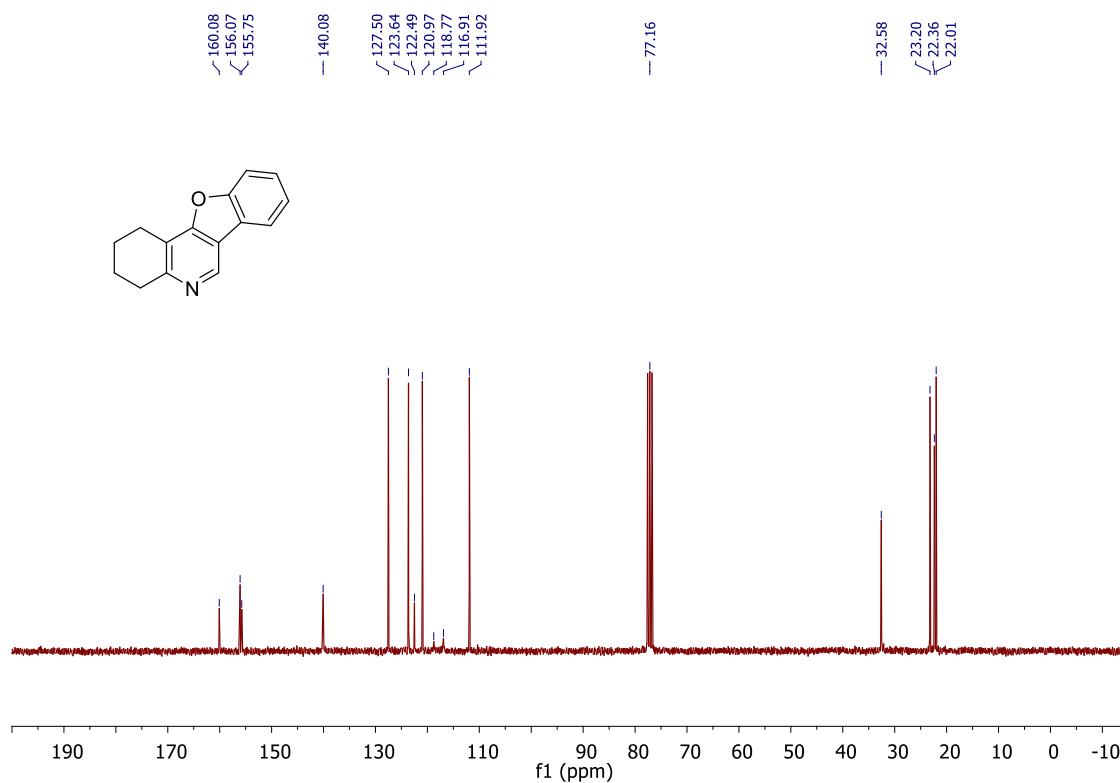


NMR Spectra of Reduced Products

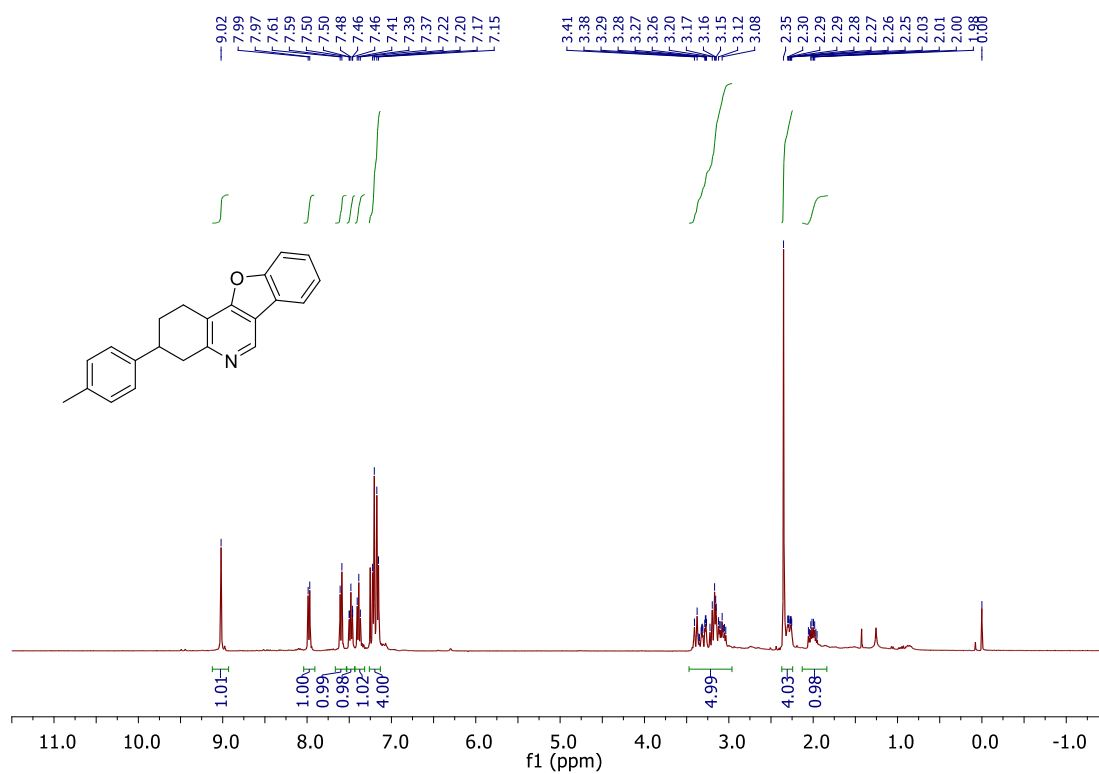
1,2,3,4-Tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 300 MHz, CDCl_3 (2a)



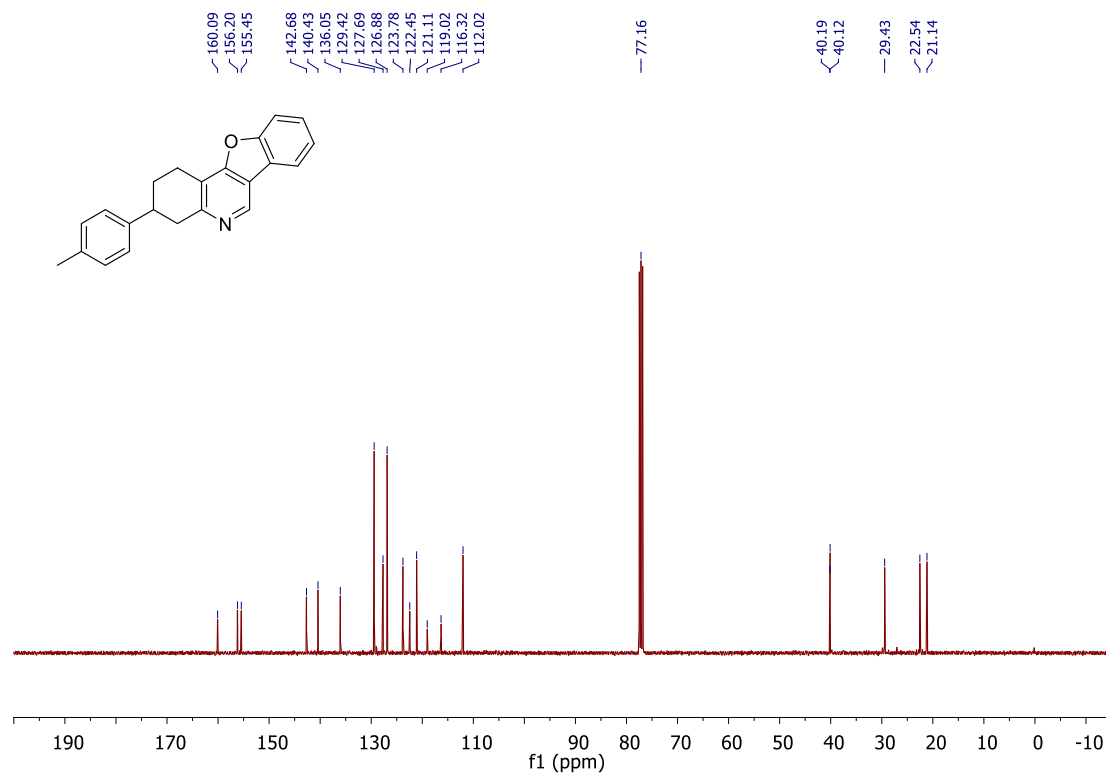
1,2,3,4-Tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 75 MHz, CDCl_3 (2a)



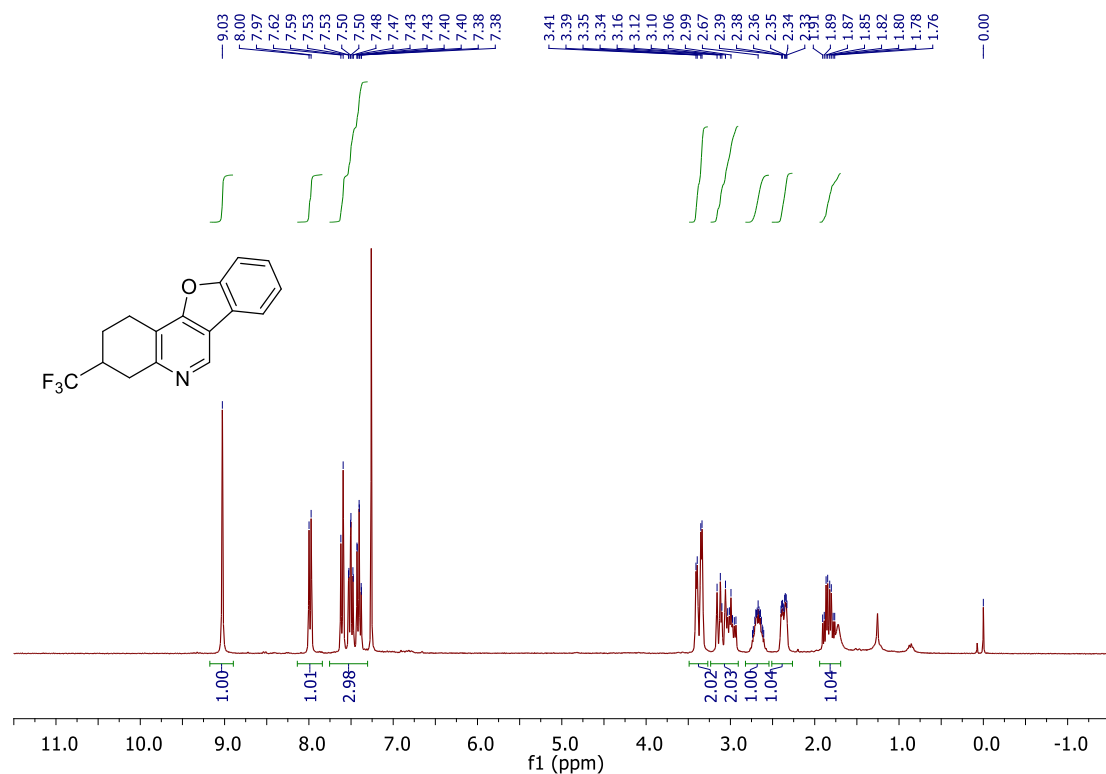
3-(*p*-Tolyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 400 MHz, CDCl_3 (2b)



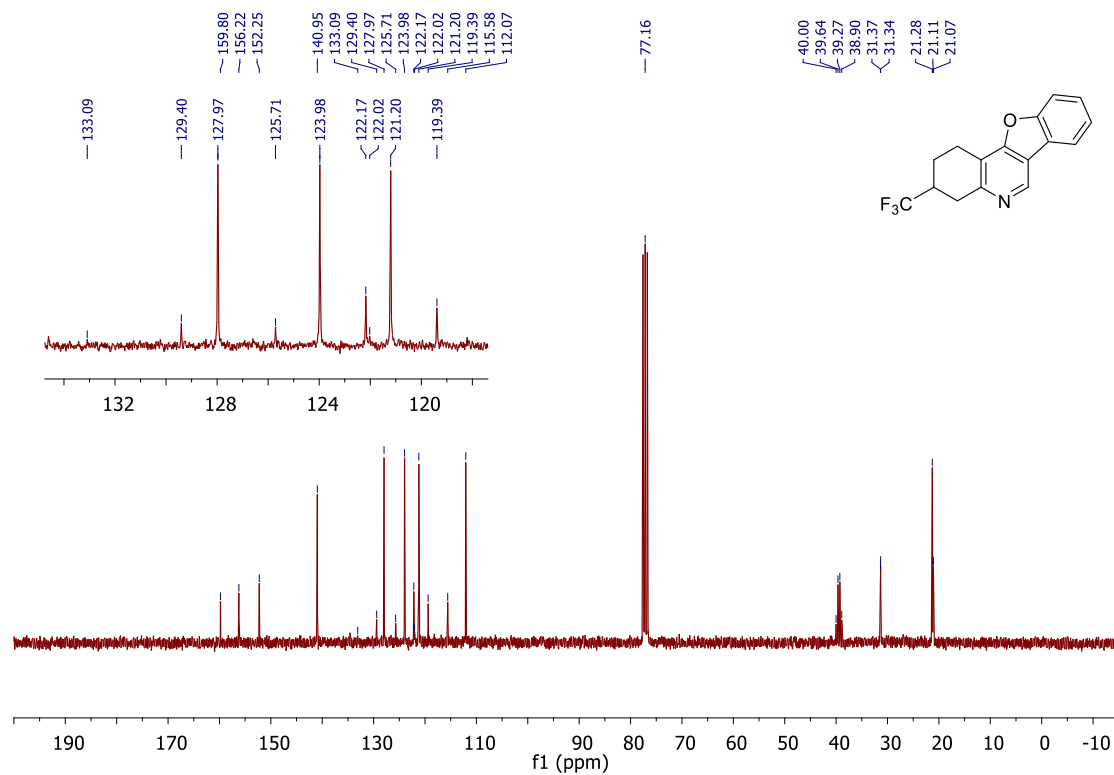
3-(*p*-Tolyl)-1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinoline ¹³C NMR, 100 MHz, CDCl₃ (2b)



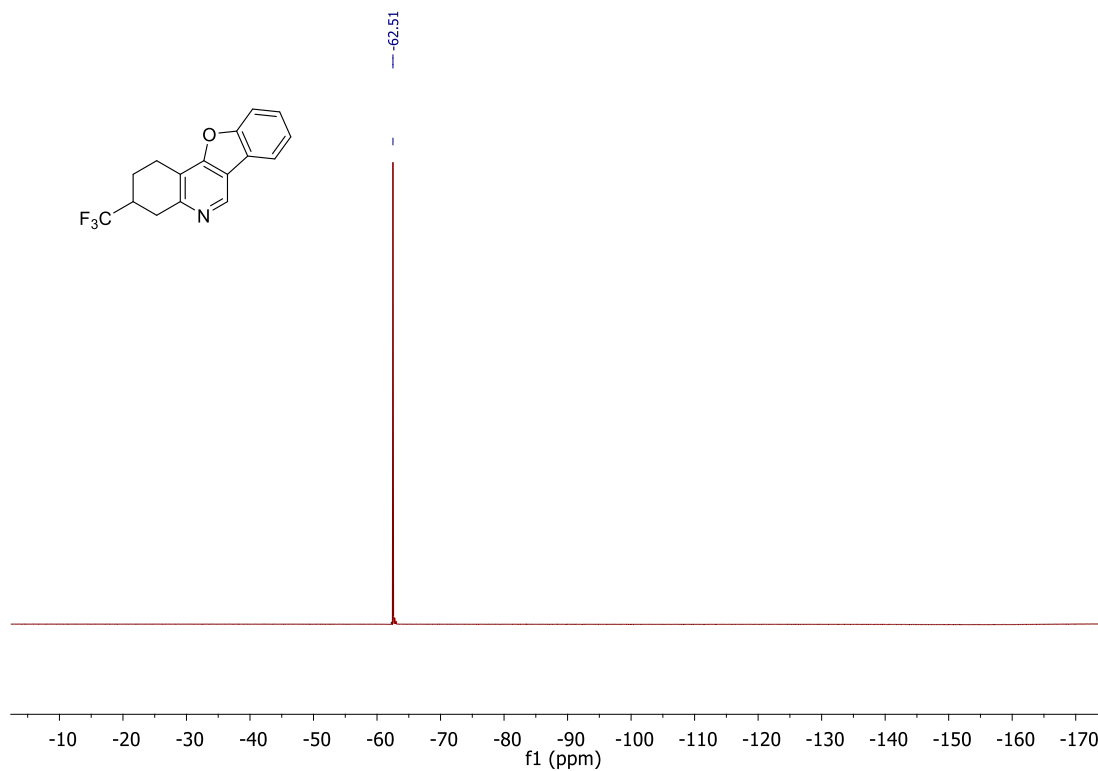
3-(Trifluoromethyl)-1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinoline ¹H NMR, 300 MHz, CDCl₃ (2c)



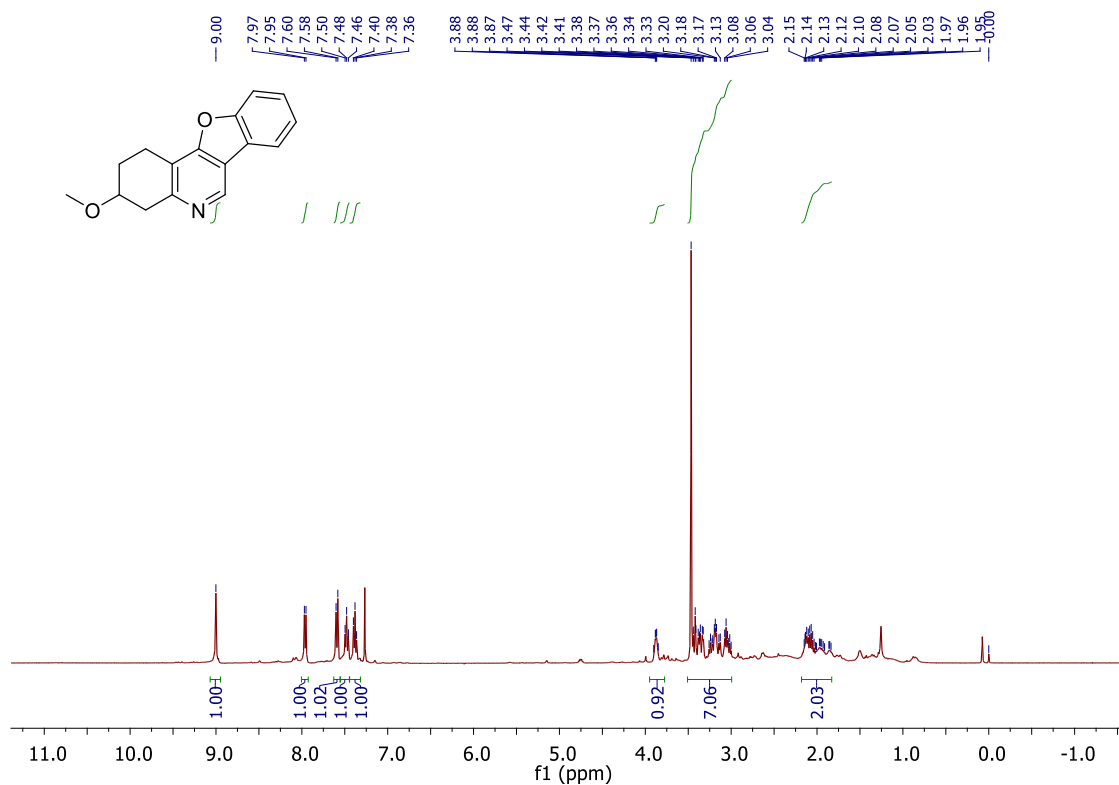
3-(Trifluoromethyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 75 MHz, CDCl_3 (2c)



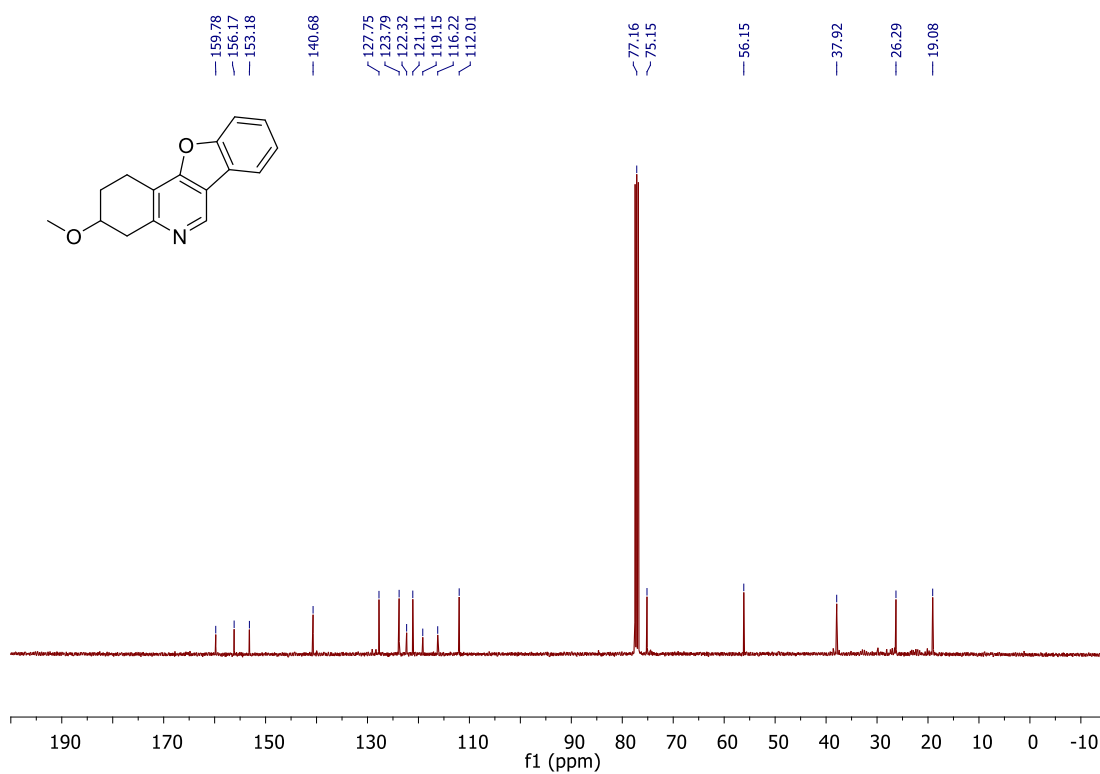
3-(Trifluoromethyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{19}F NMR, 376 MHz, CDCl_3 (2c)



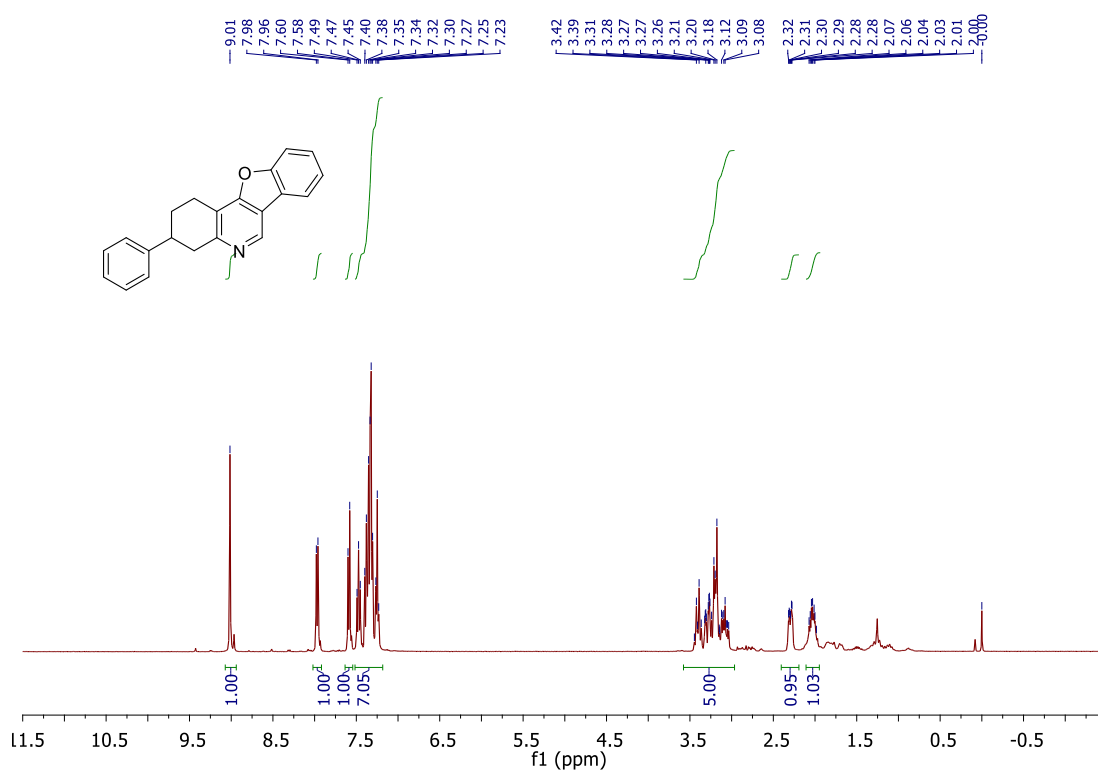
3-Methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹H NMR, 400 MHz, CDCl₃ (2d)



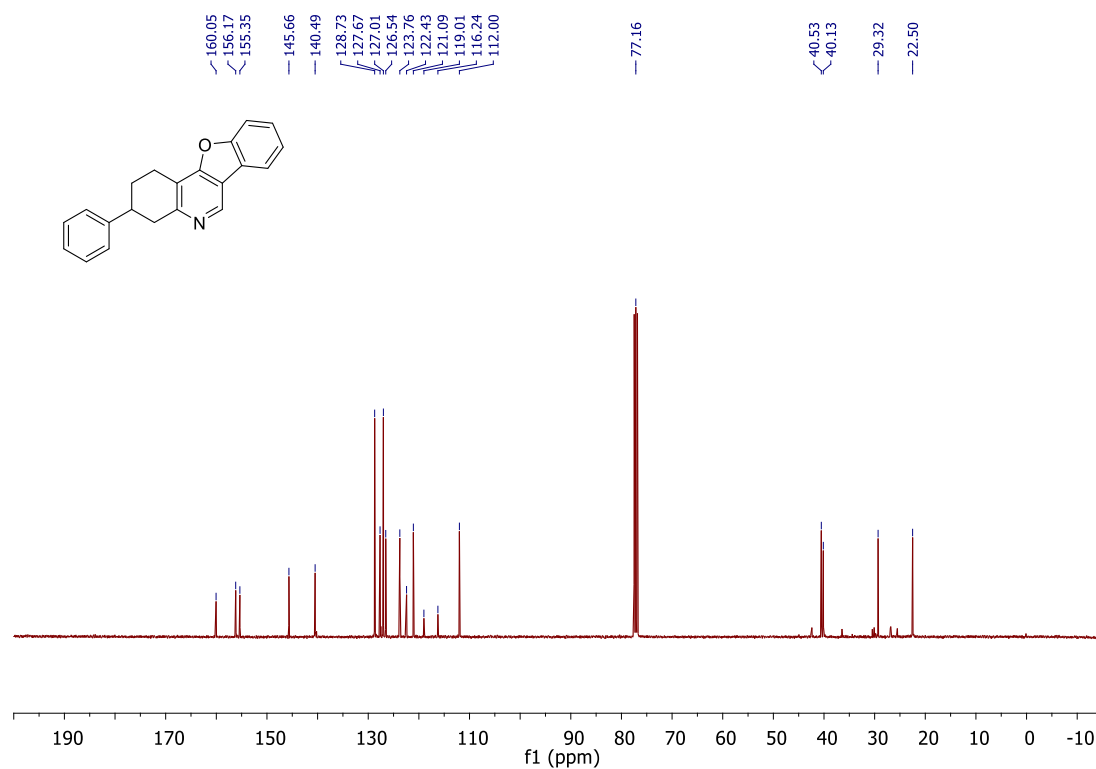
3-Methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹³C NMR, 100 MHz, CDCl₃ (2d)



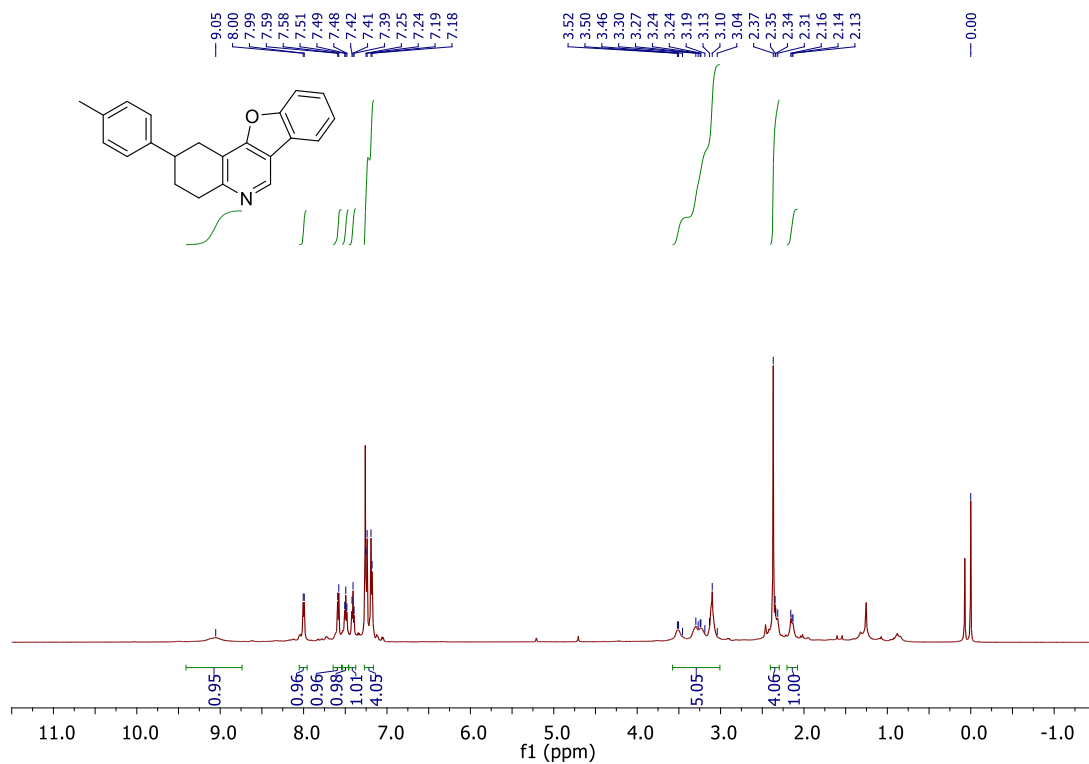
3-Phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 400 MHz, CDCl_3 (2e)



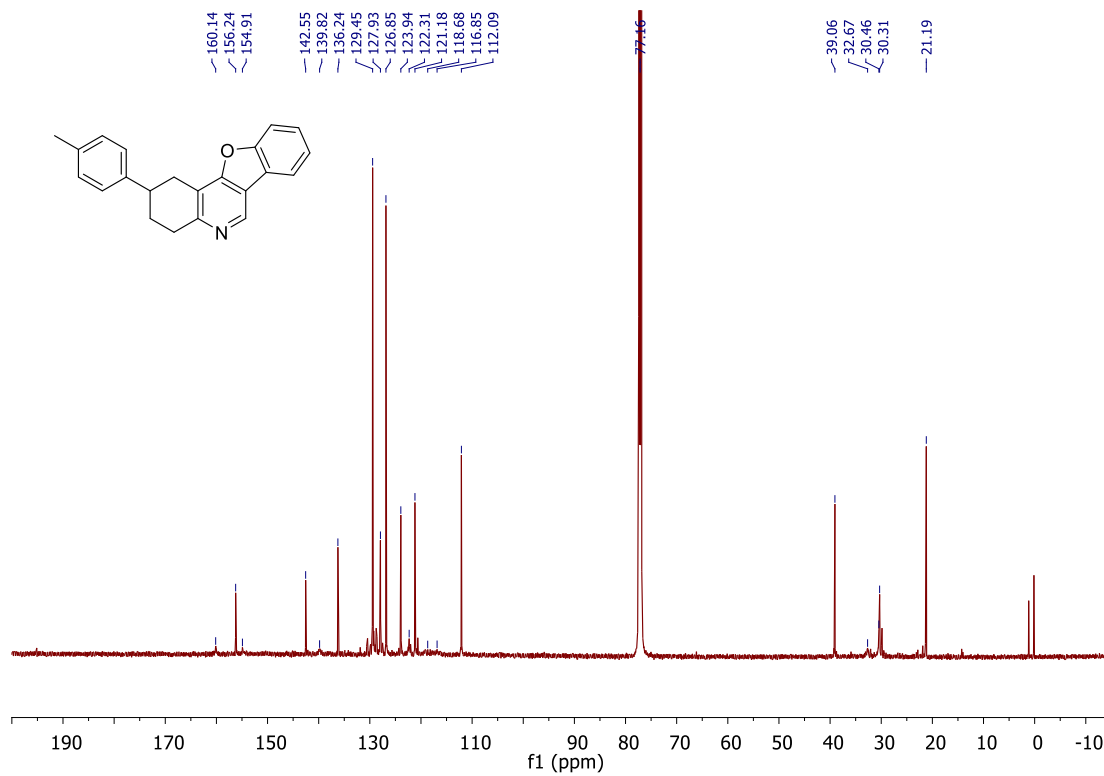
3-Phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 100 MHz, CDCl_3 (2e)



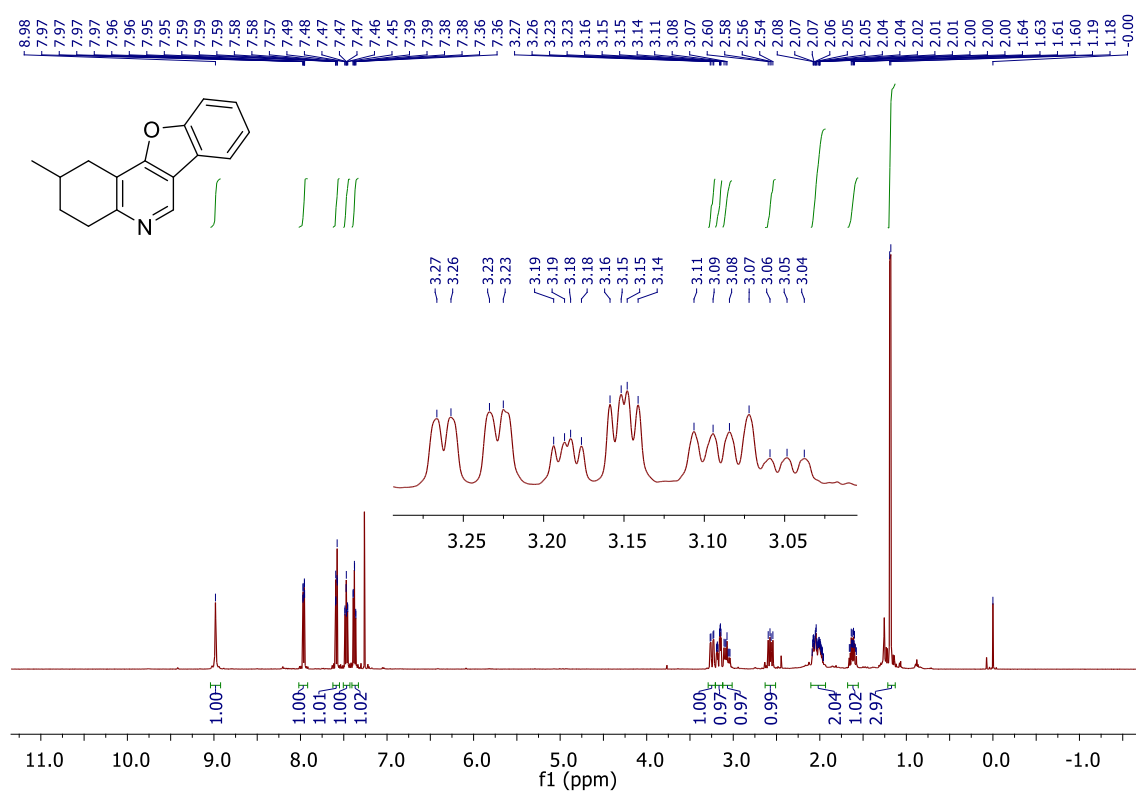
2-(*p*-Tolyl)-1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinoline ¹H NMR, 600 MHz, CDCl₃ (2f)



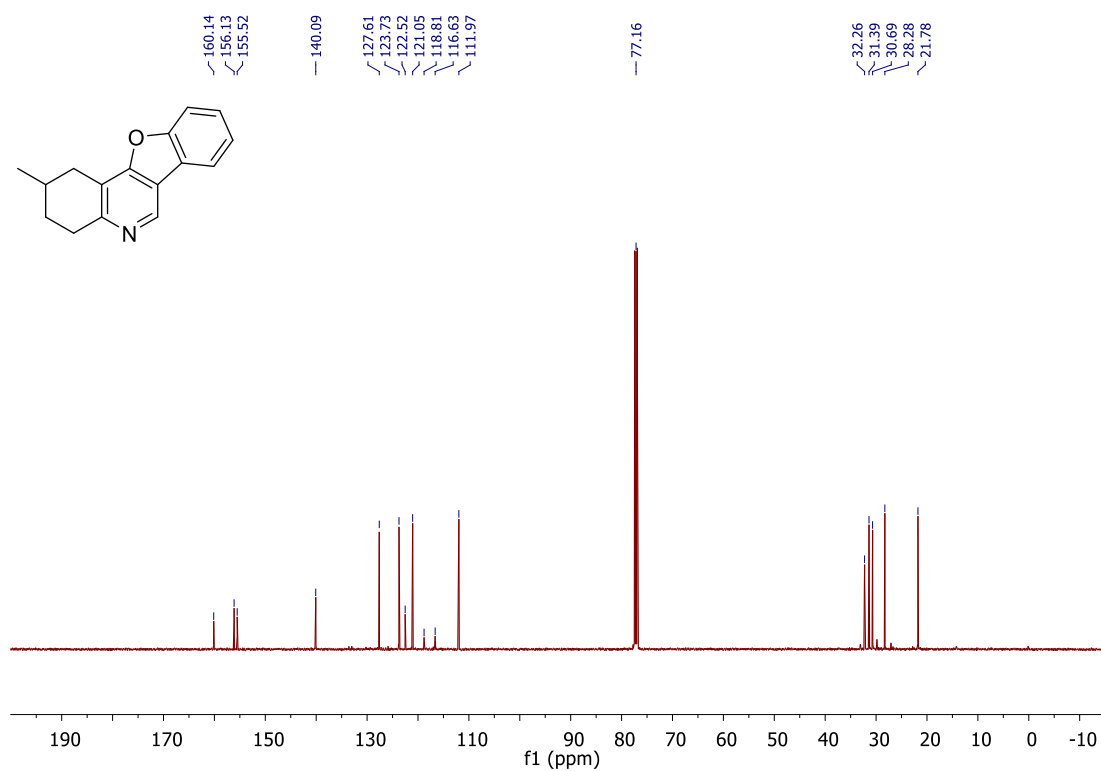
2-(*p*-Tolyl)-1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinoline ¹³C NMR, 150 MHz, CDCl₃ (2f)



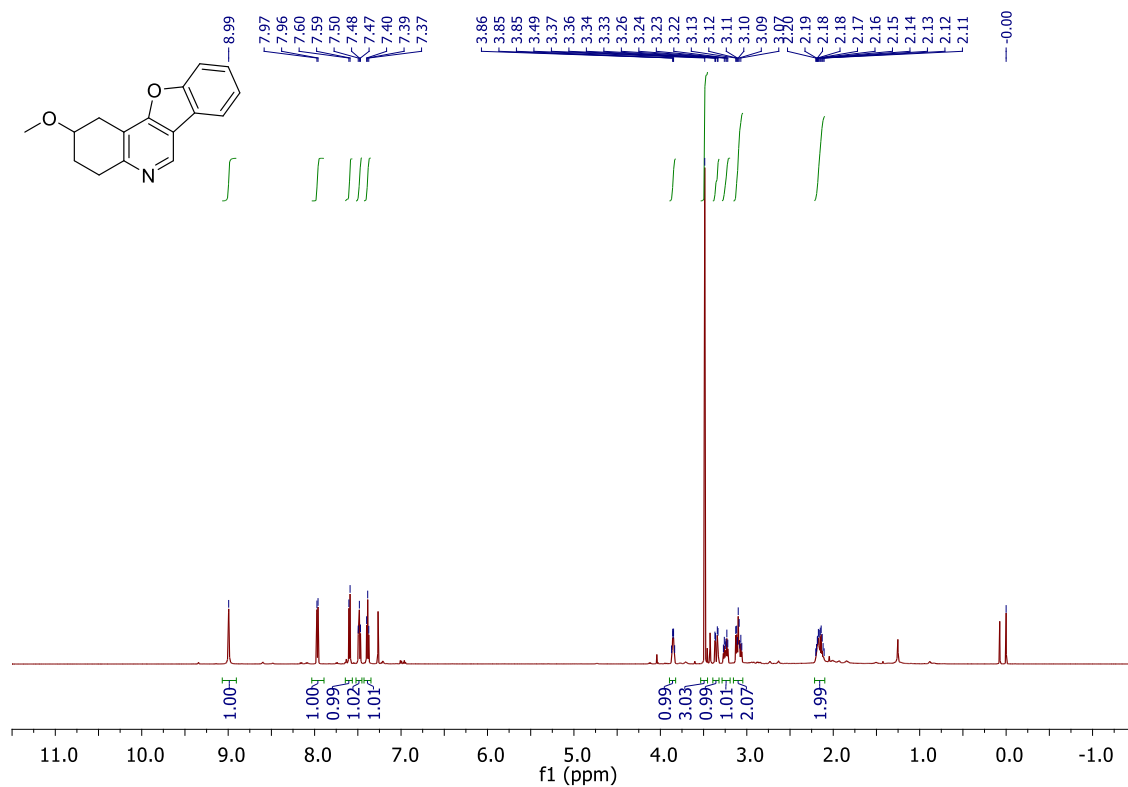
2-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 500 MHz, CDCl_3 (2g)



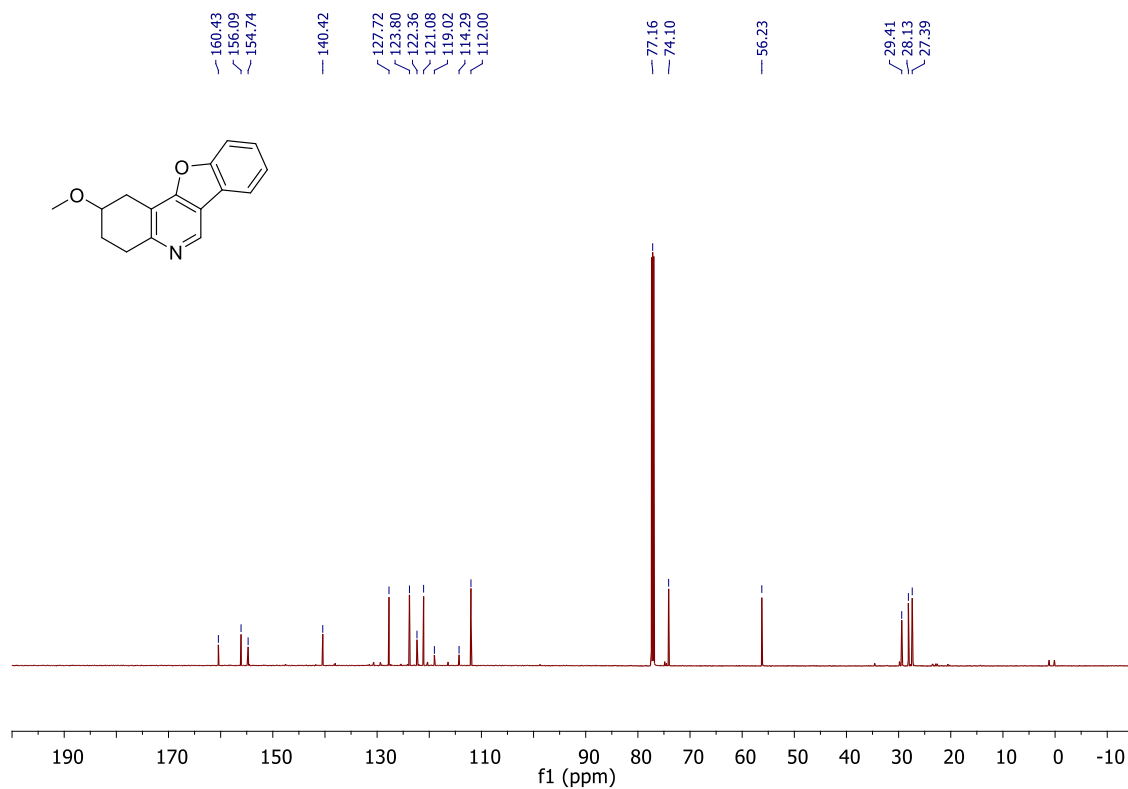
2-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 125 MHz, CDCl_3 (2g)



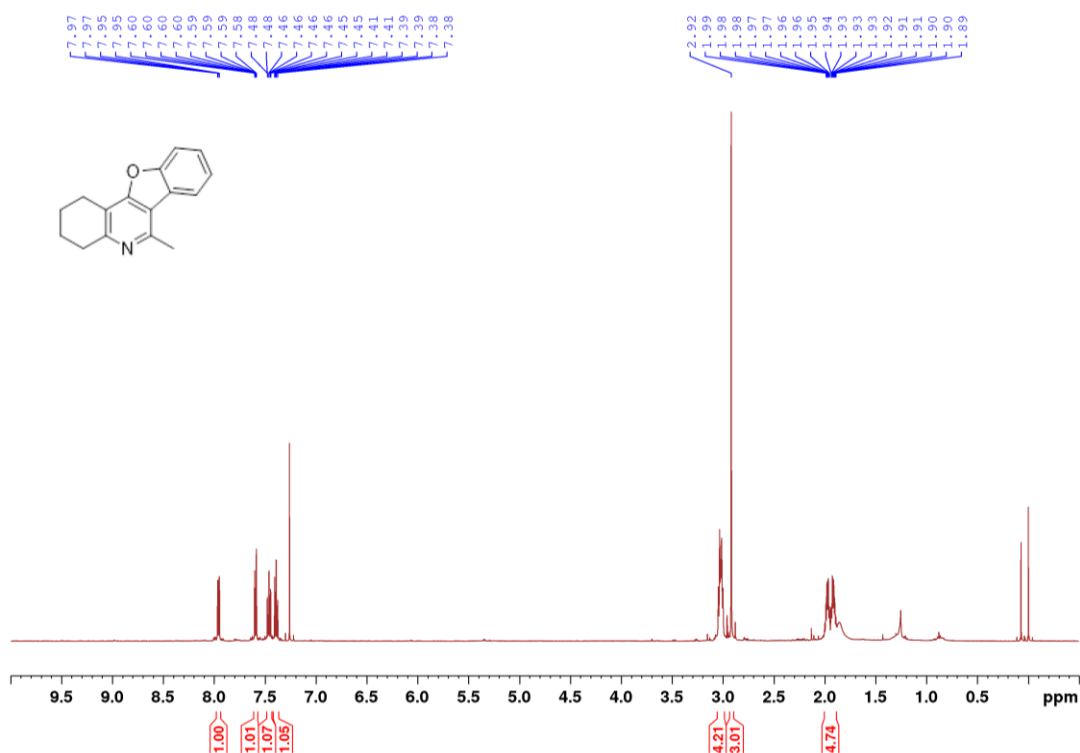
2-Methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹H NMR, 600 MHz, CDCl₃ (2h)



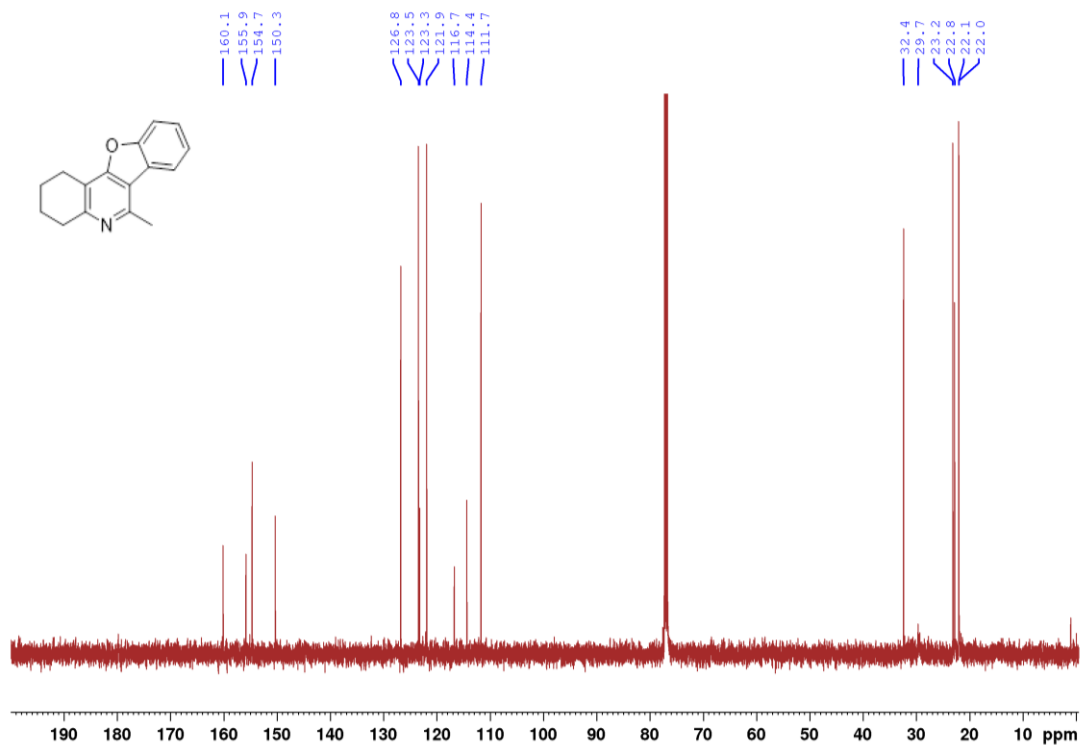
2-Methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹³C NMR, 150 MHz, CDCl₃ (2h)



6-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 500 MHz, CDCl_3 (2i)



6-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 125 MHz, CDCl_3 (2i)



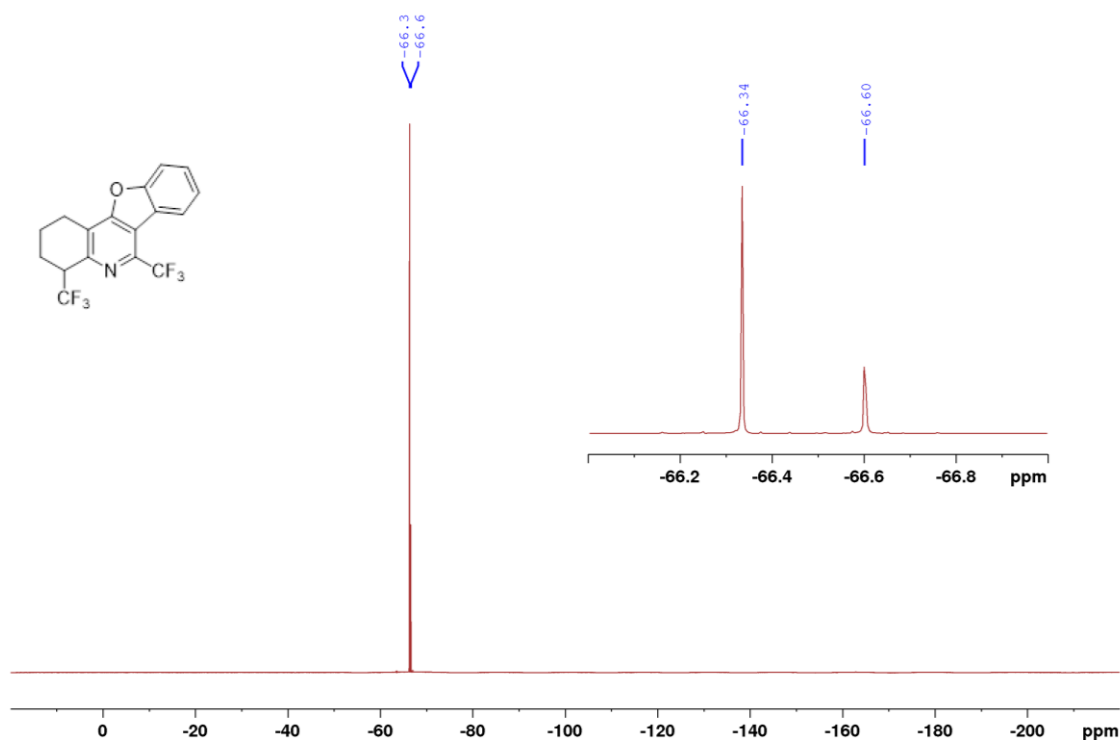
[illegible]

Chemical structure: Cc1ccc2c(c1)c(c3ccccc3O2)C(F)(F)F

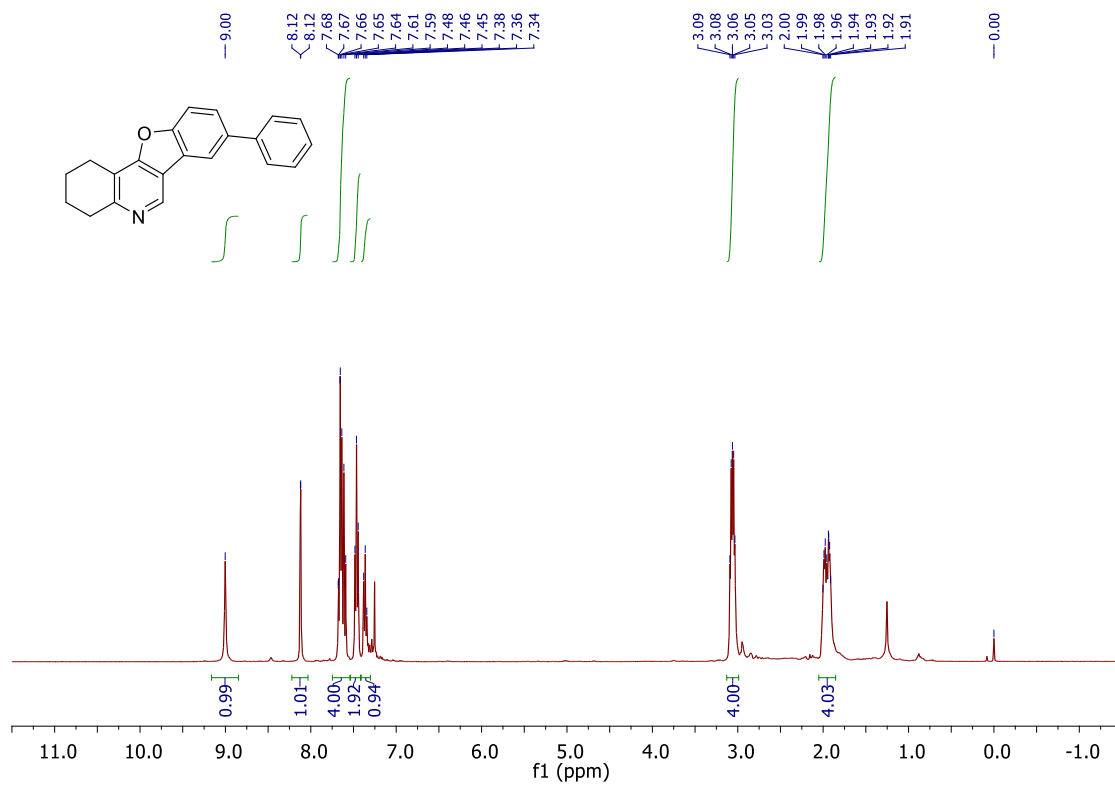
¹³C NMR peaks (ppm):

- 159.7, 155.5, 145.8, 138.0, 137.8, 137.5, 137.3, 136.9, 136.5, 136.3, 132.7, 124.7, 123.5, 123.0, 123.0, 123.0, 123.0, 122.8, 121.7, 121.2, 119.9, 118.8, 116.6, 111.0
- 43.4, 43.2, 43.1, 42.9
- 22.0, 22.0, 22.0, 22.0, 20.9, 16.9

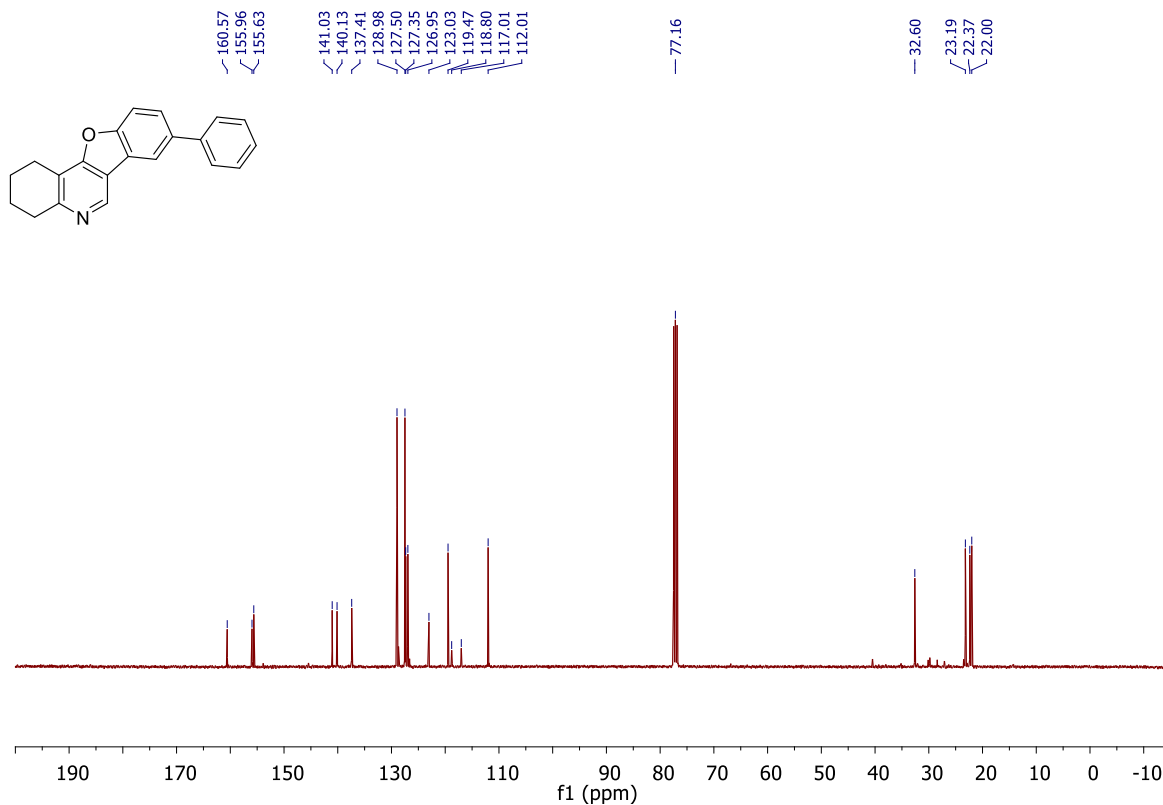
4,6-Bis(trifluoromethyl)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{19}F NMR, 471 MHz, CDCl_3 (2j)



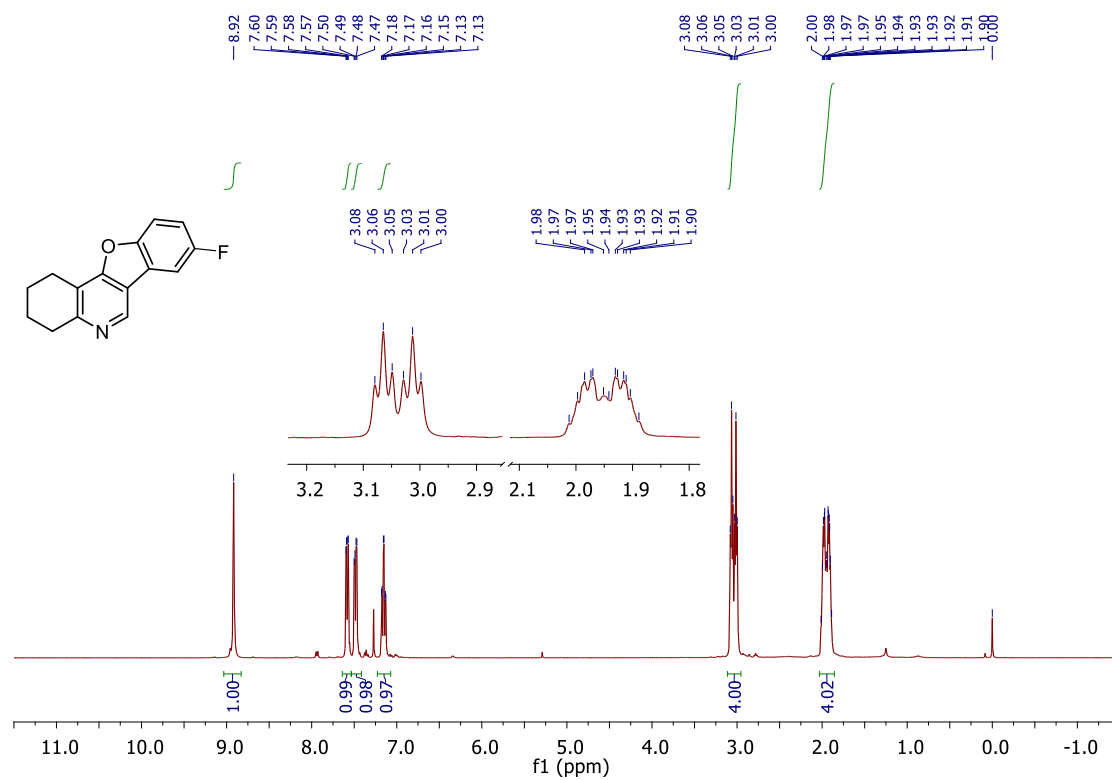
8-Phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 400 MHz, CDCl_3 (2k)



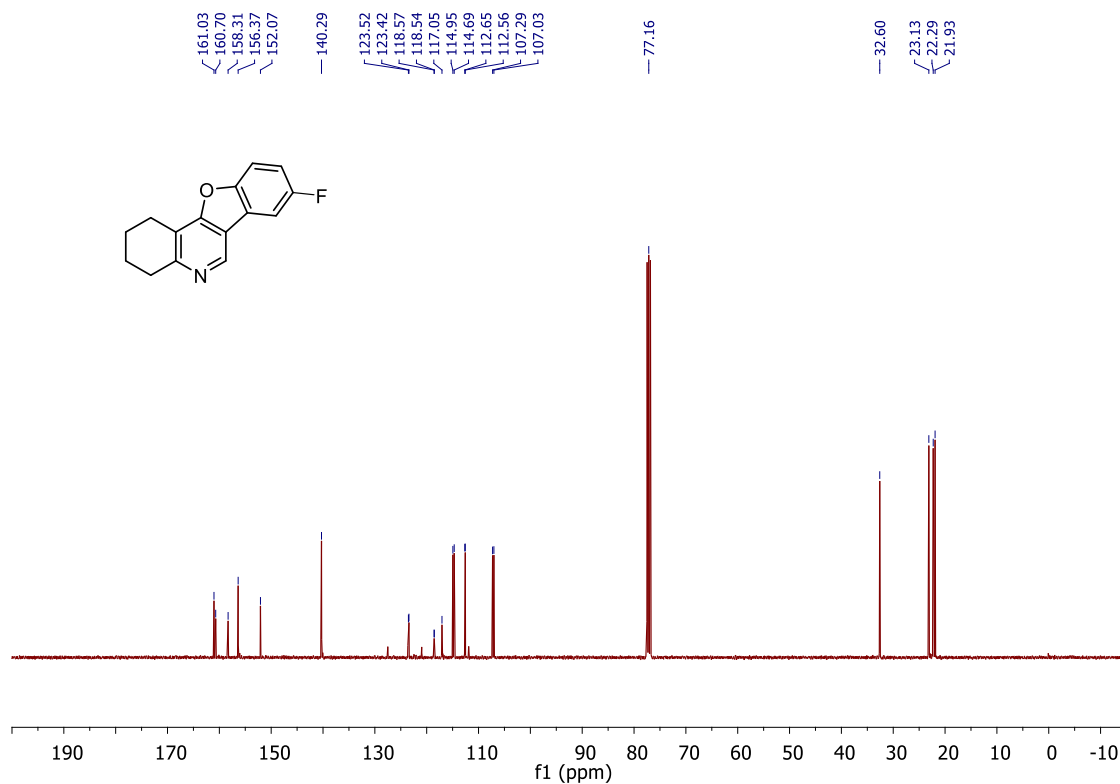
8-Phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 100 MHz, CDCl_3 (2k)



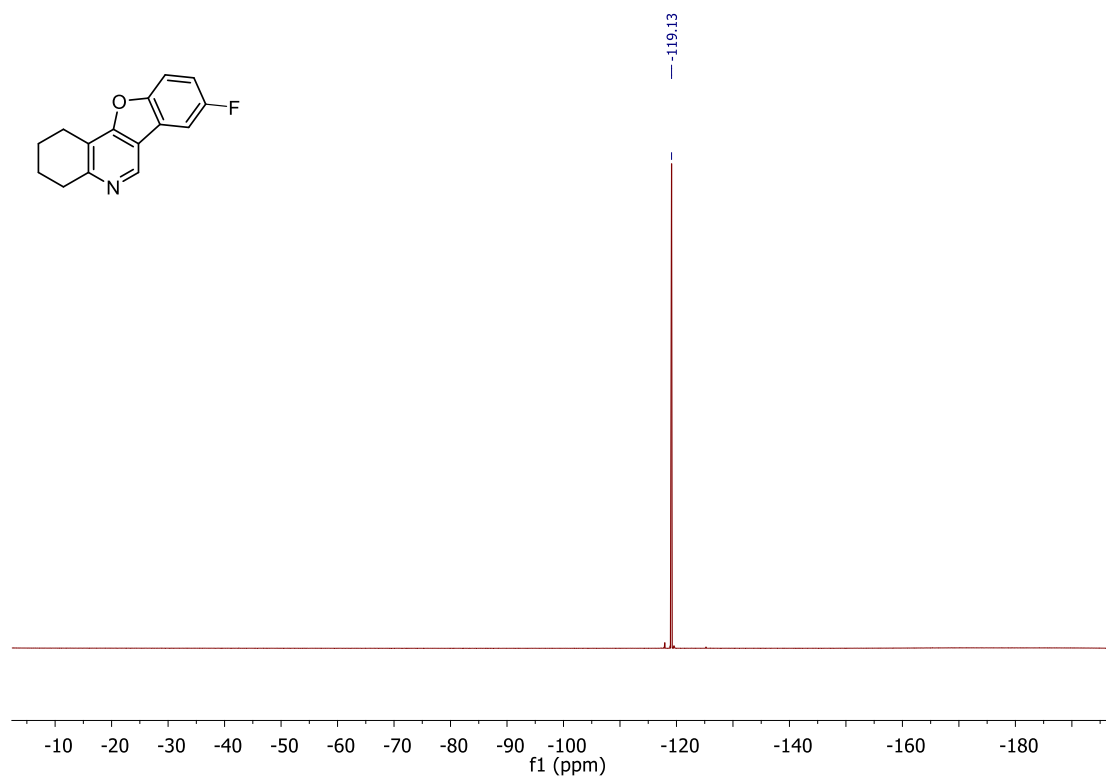
14-Fluoro-5,6,7,8-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 400 MHz, CDCl_3 (2l)



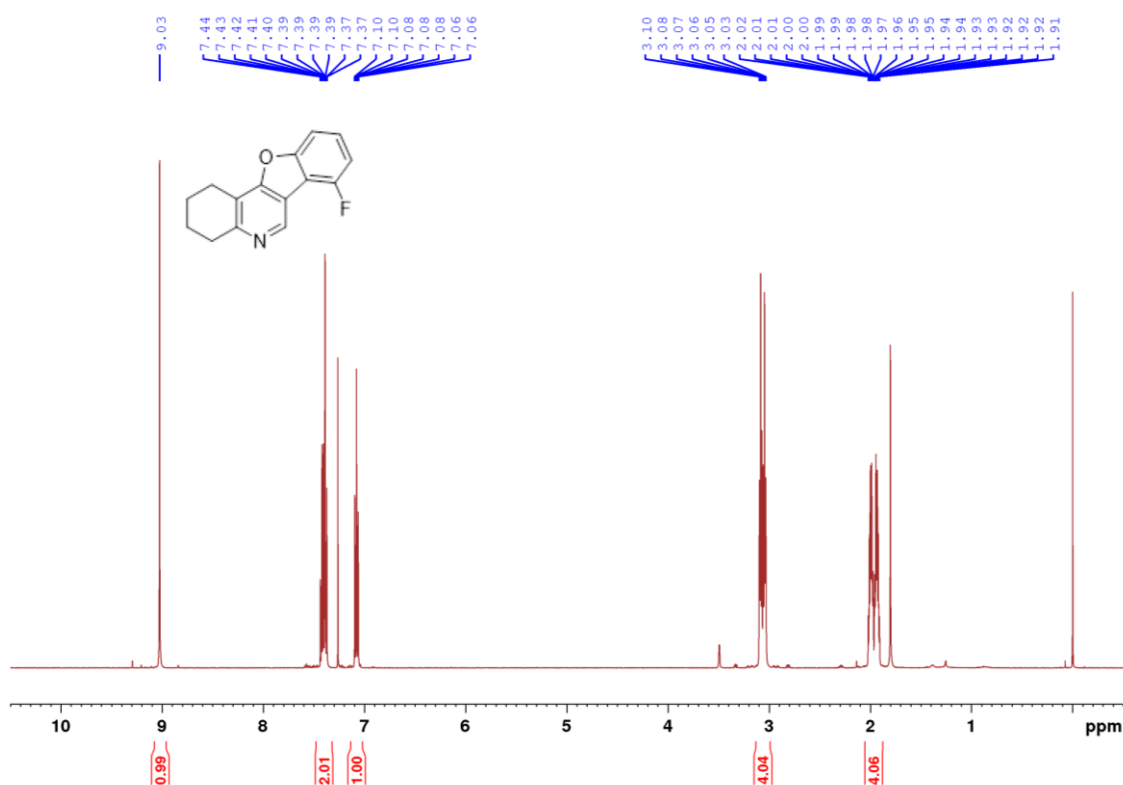
14-Fluoro-5,6,7,8-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 100 MHz, CDCl_3 (2l)



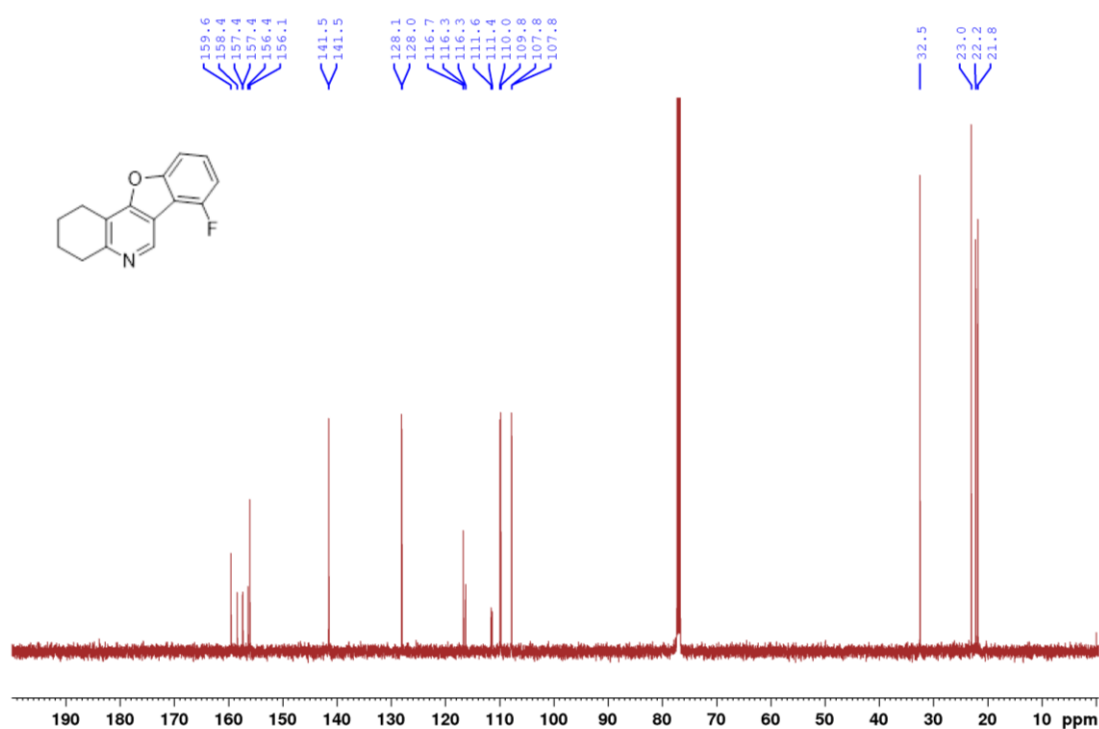
14-Fluoro-5,6,7,8-tetrahydrobenzofuro[3,2-c]quinoline ^{19}F NMR, 376 MHz, CDCl_3 (2l)



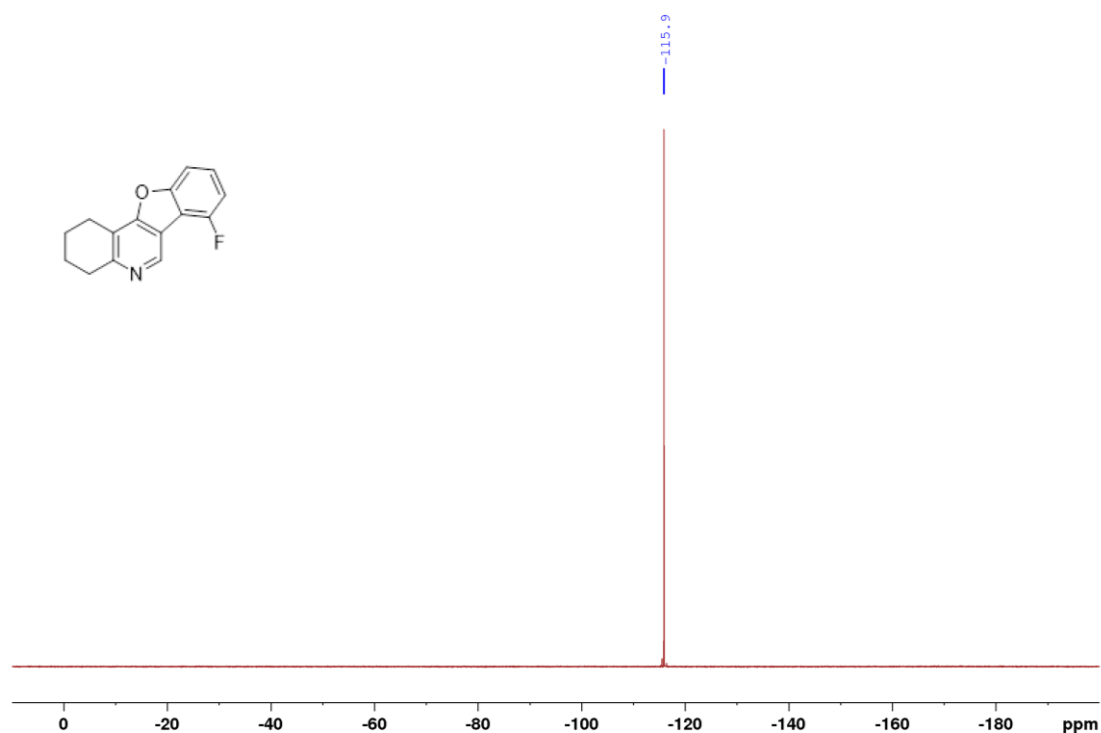
7-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹H NMR, 500 MHz, CDCl₃ (2m)



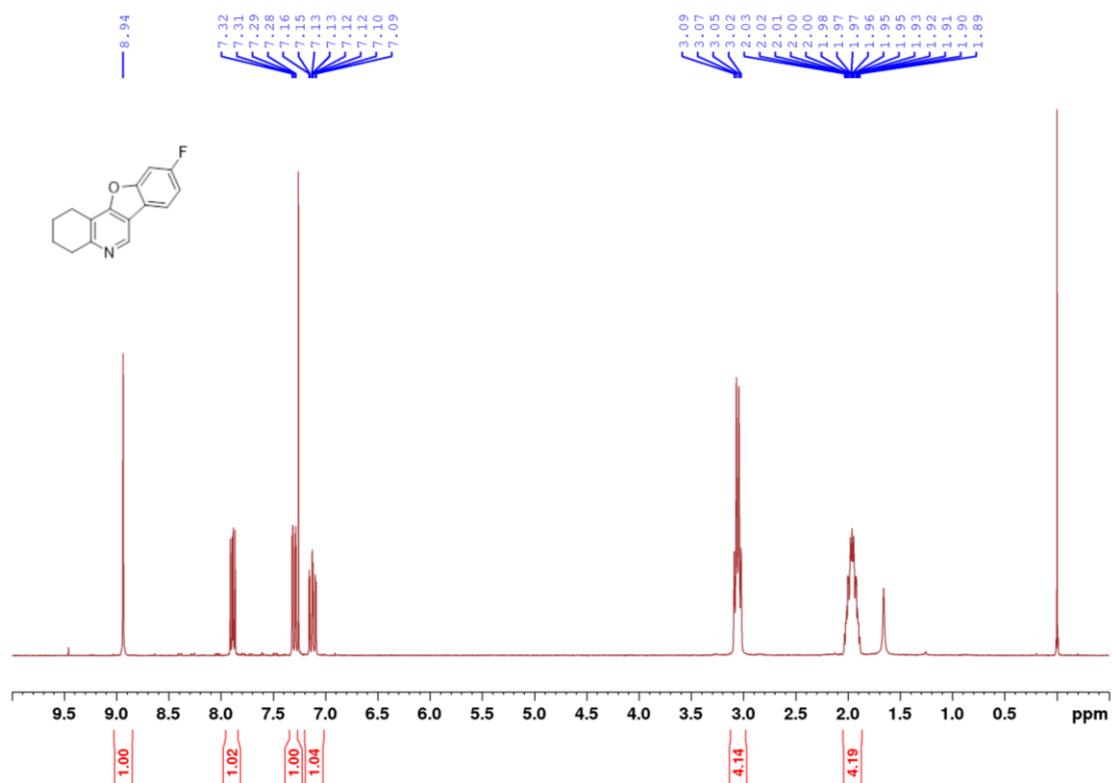
7-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹³C NMR, 125 MHz, CDCl₃ (2m)



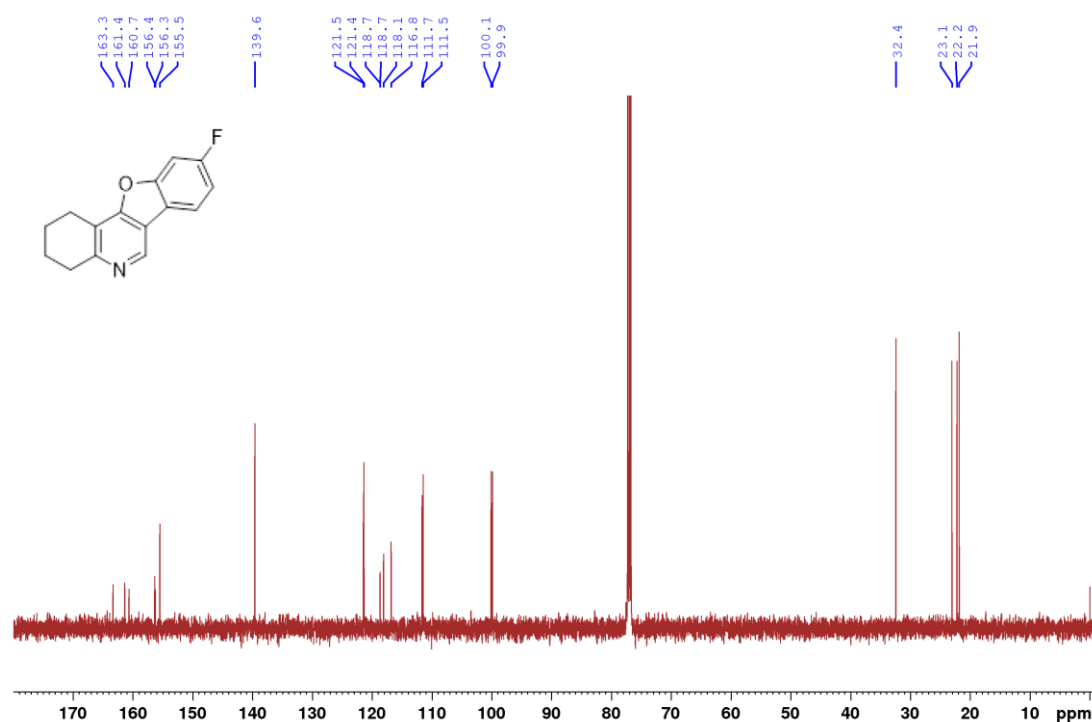
7-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{19}F NMR, 282 MHz, CDCl_3 (2m)



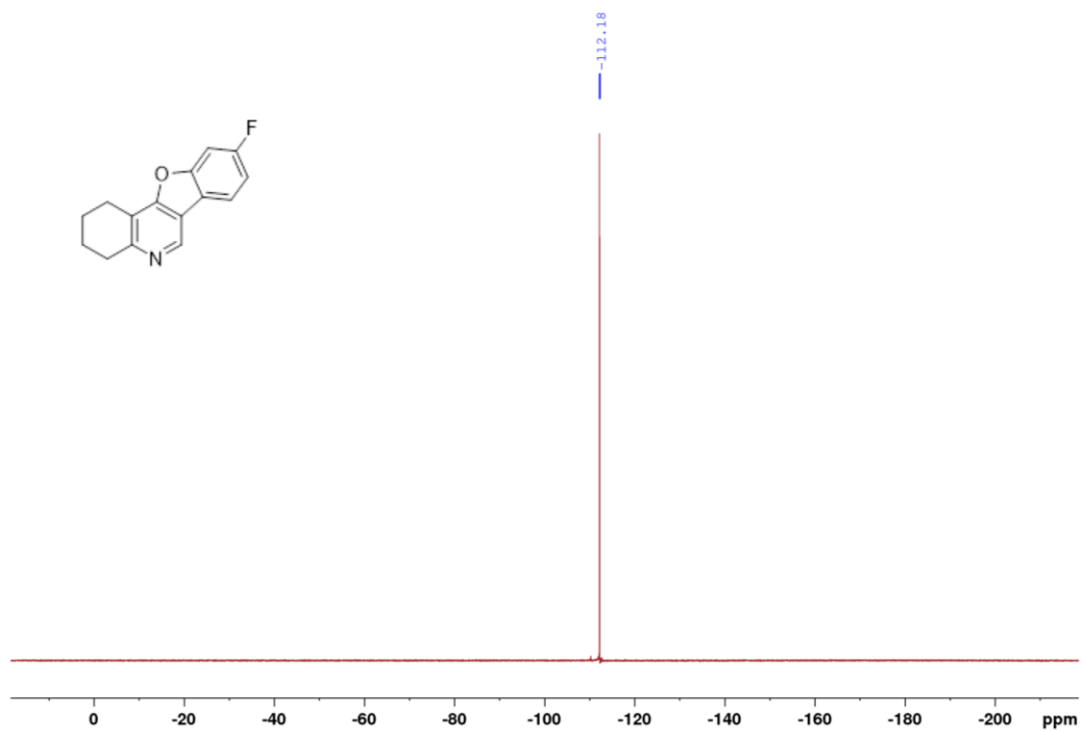
9-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 500 MHz, CDCl_3 (2n)



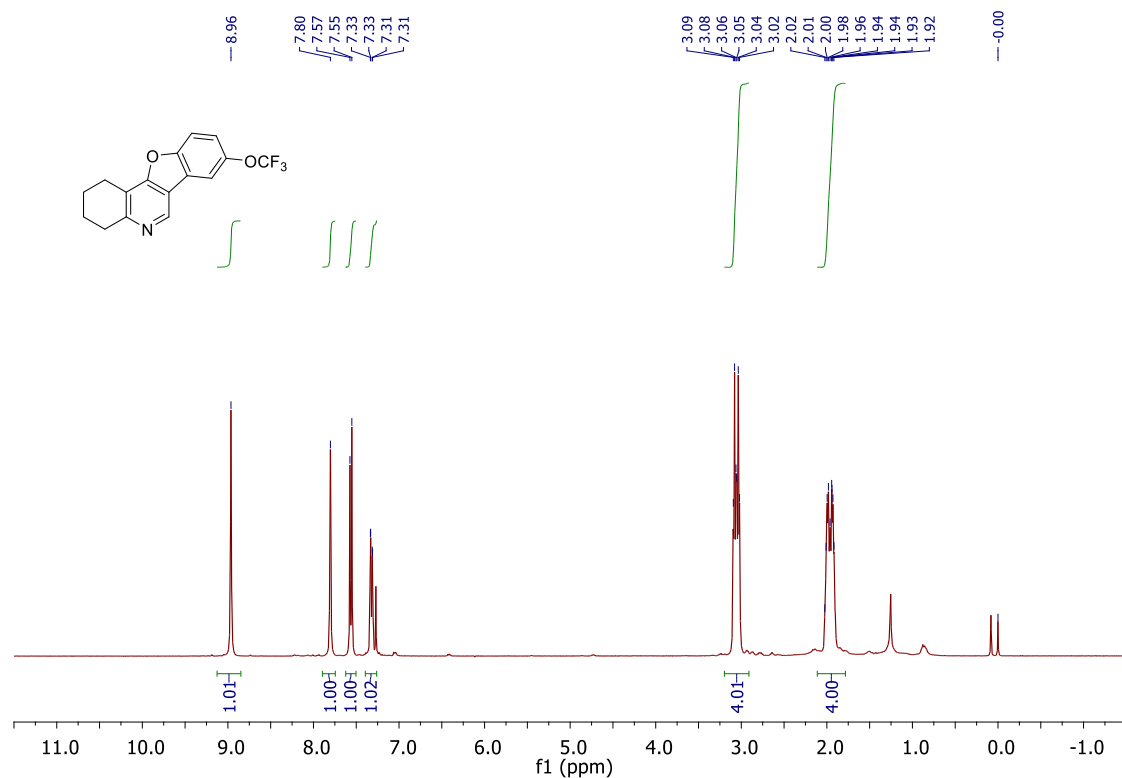
9-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 125 MHz, CDCl_3 (2n)



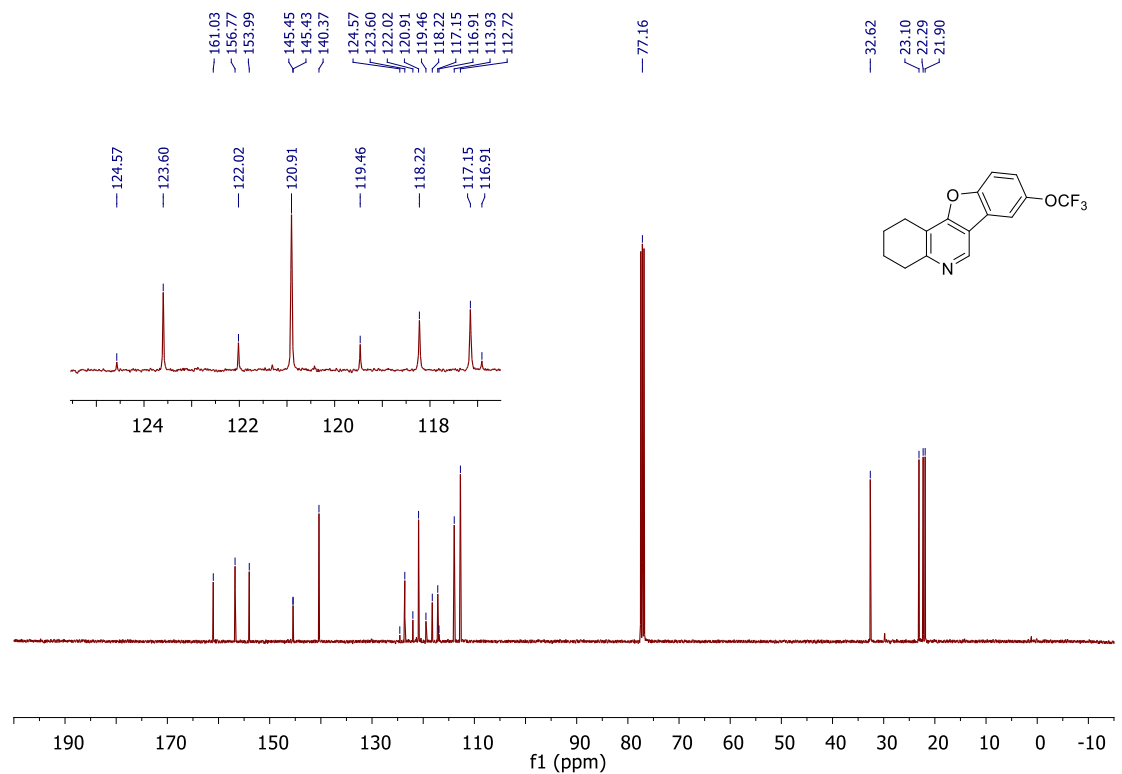
9-Fluoro-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{19}F NMR, 282 MHz, CDCl_3 (2n)



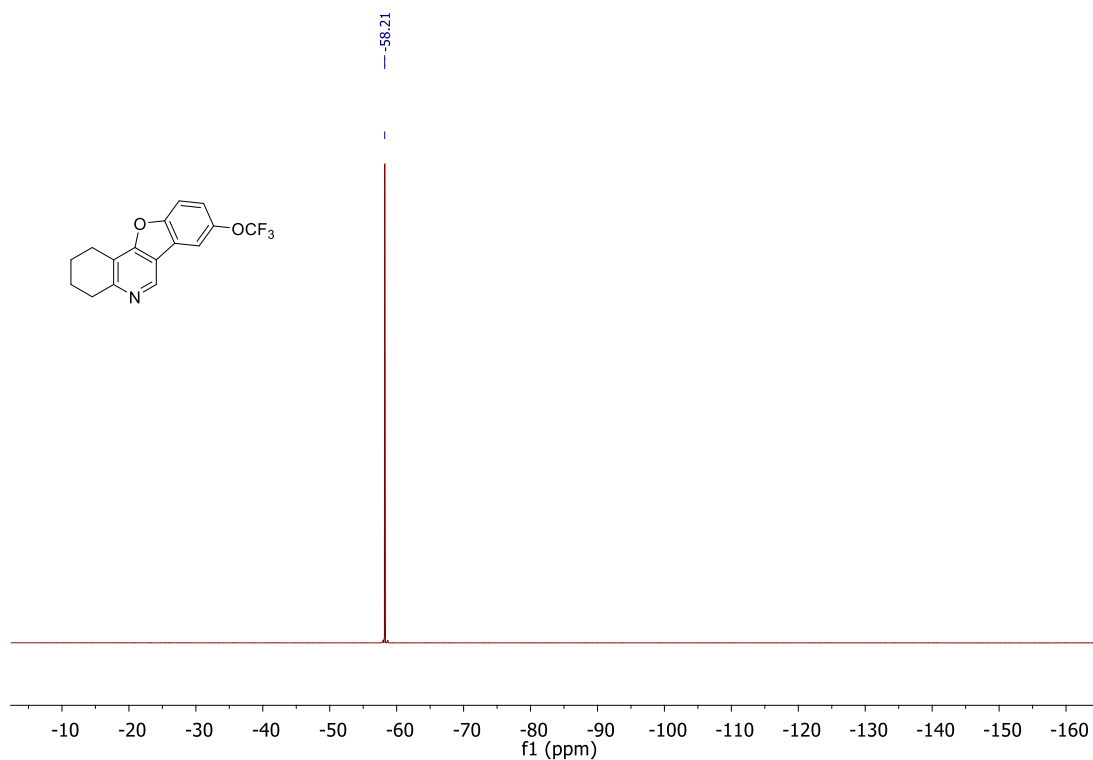
8-(Trifluoromethoxy)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 400 MHz, CDCl_3 (2o)



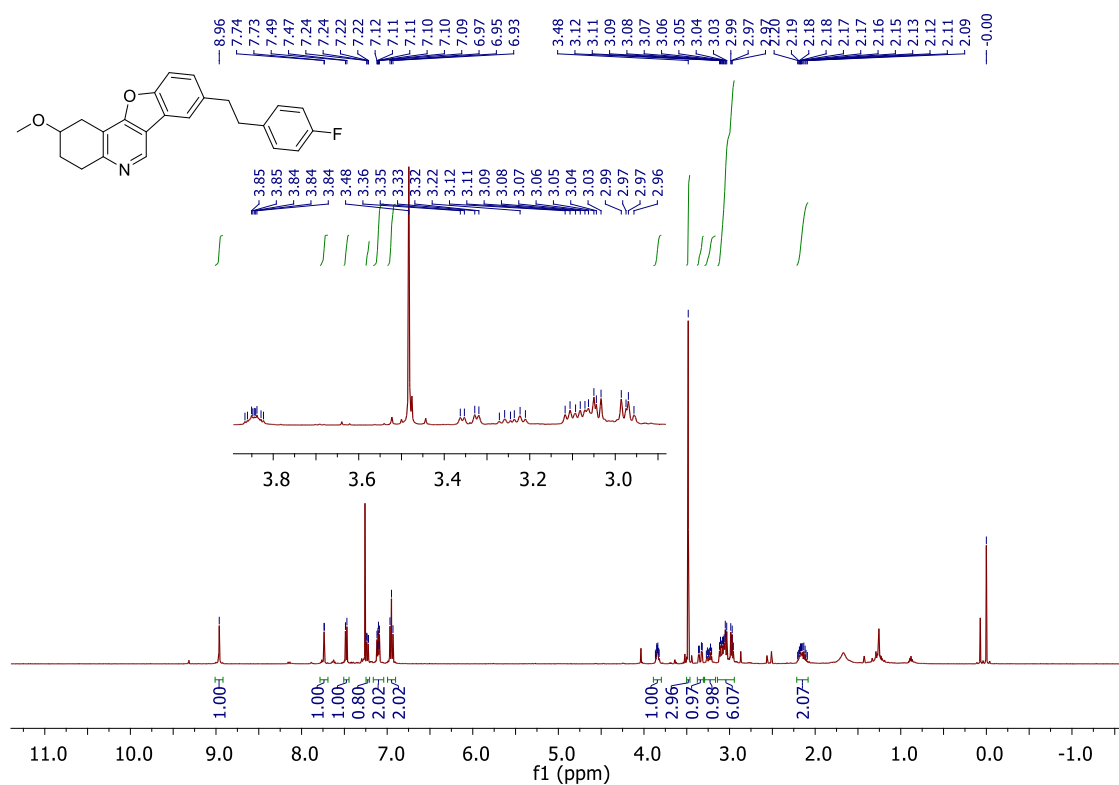
8-(Trifluoromethoxy)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{13}C NMR, 100 MHz, CDCl_3 (2o)



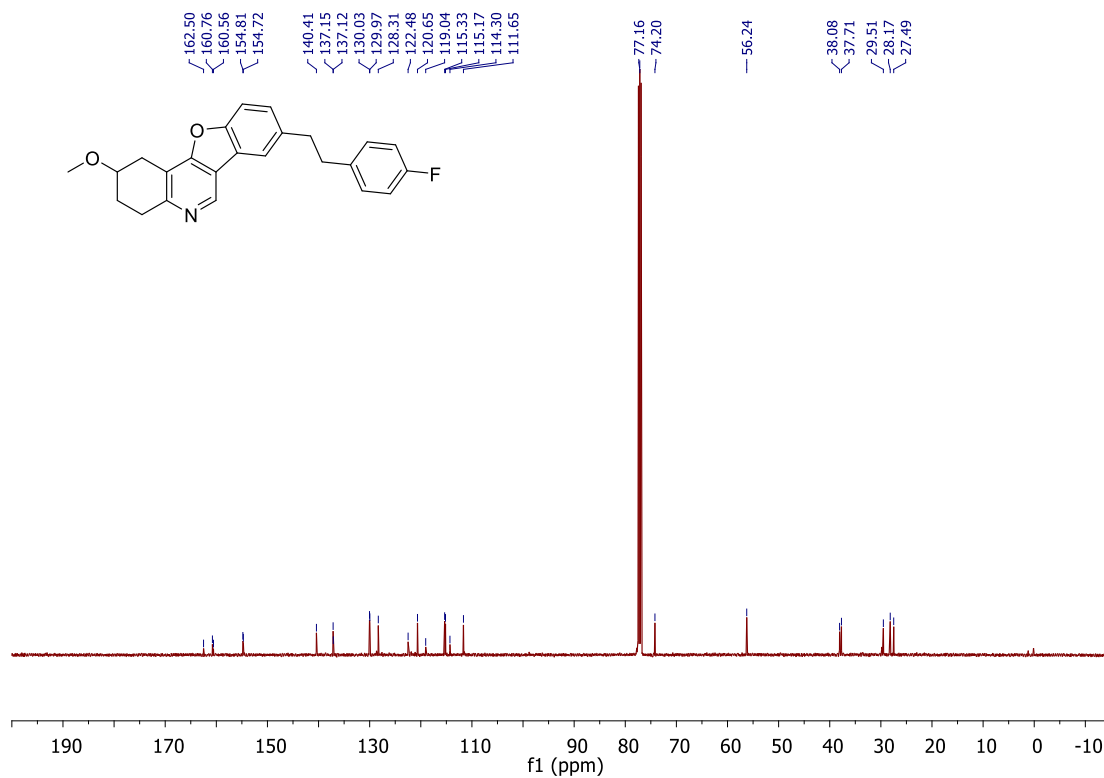
8-(Trifluoromethoxy)-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^{19}F NMR, 376 MHz, CDCl_3 (2o)



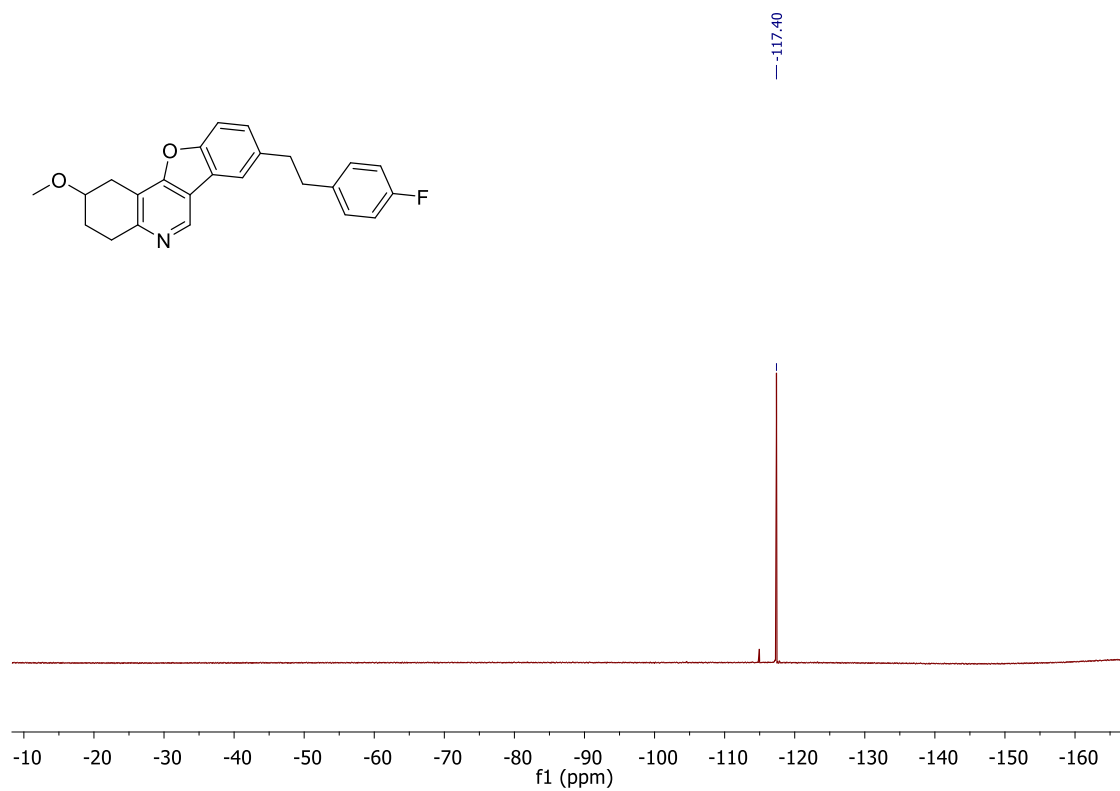
8-(4-fluorophenethyl)-2-methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ^1H NMR, 500 MHz, CDCl_3 (4a)



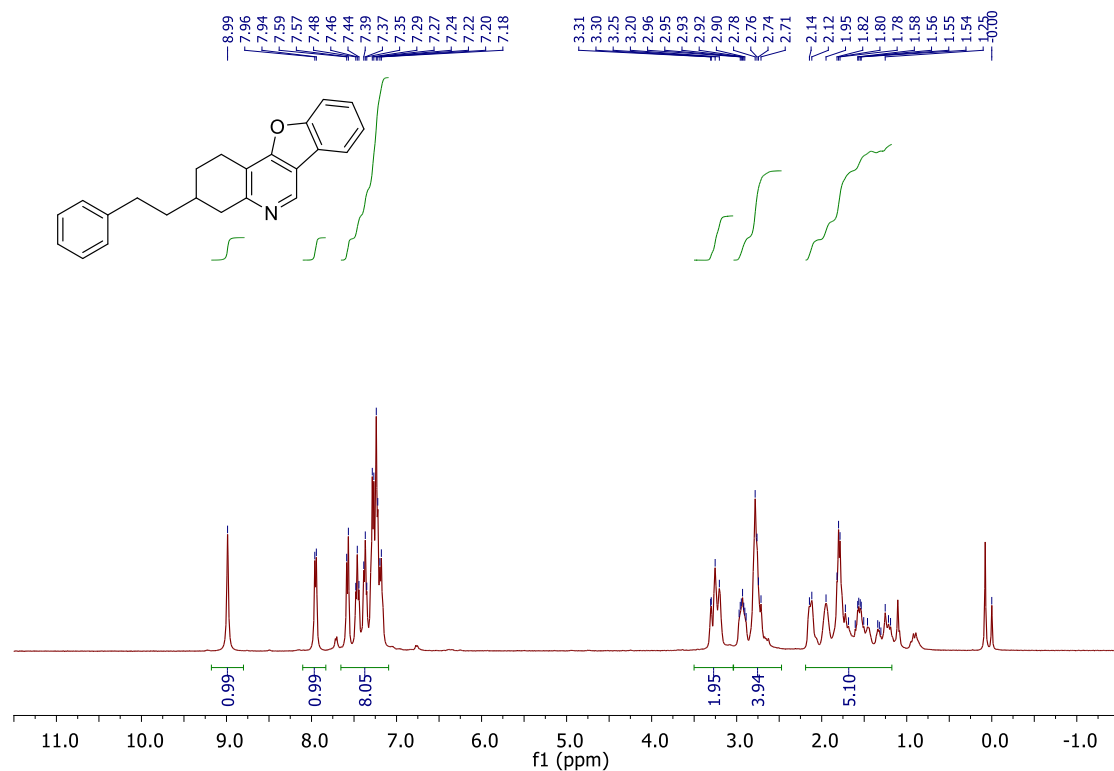
8-(4-fluorophenethyl)-2-methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹³C NMR, 125 MHz, CDCl₃ (4a)



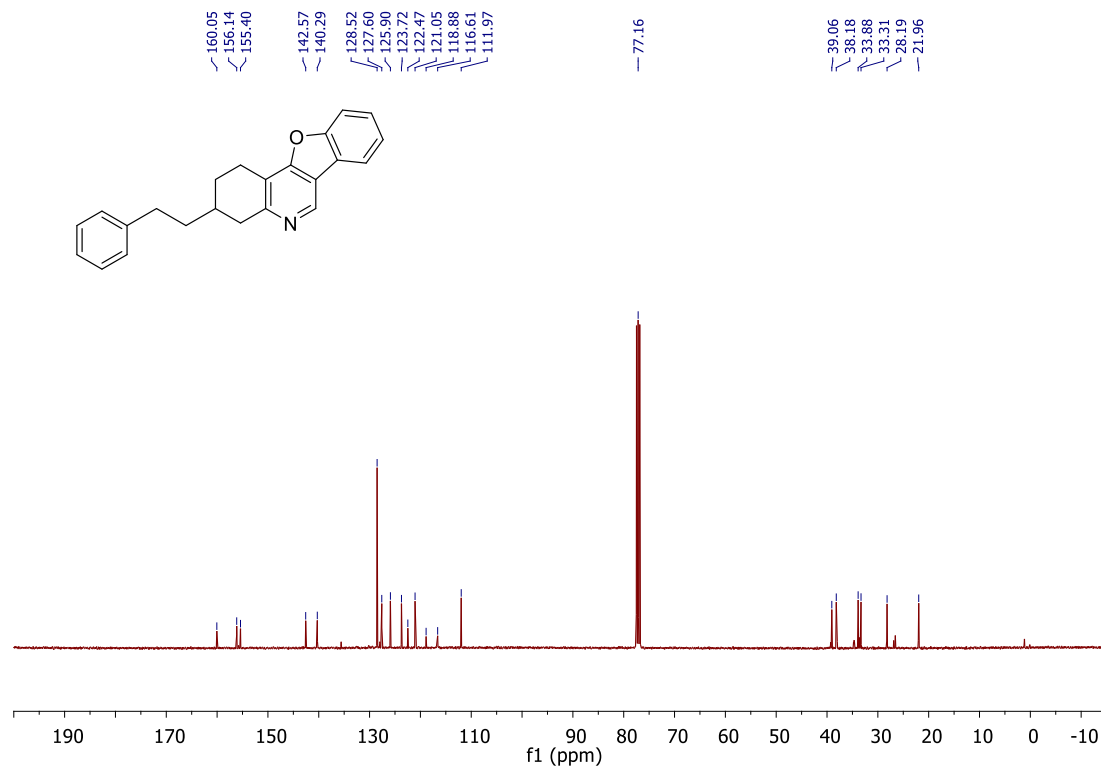
8-(4-Fluorophenethyl)-2-methoxy-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹⁹F NMR, 376 MHz, CDCl₃ (4a)



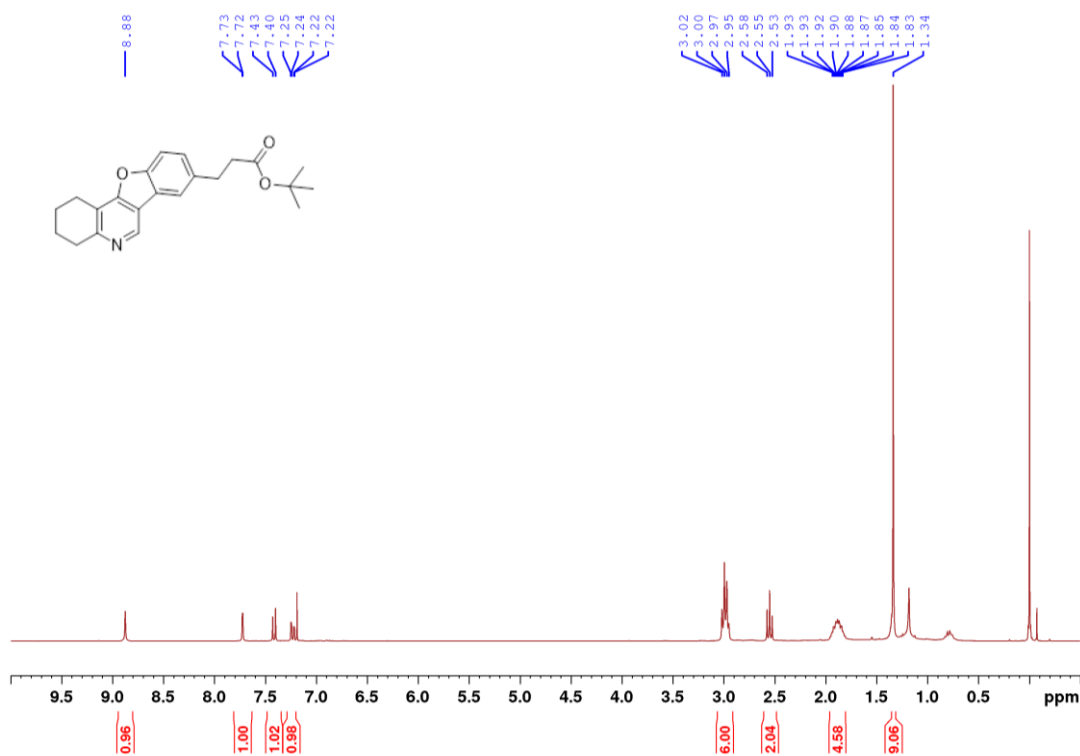
**3-Phenethyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹H NMR, 400 MHz, CDCl₃
(4b)**



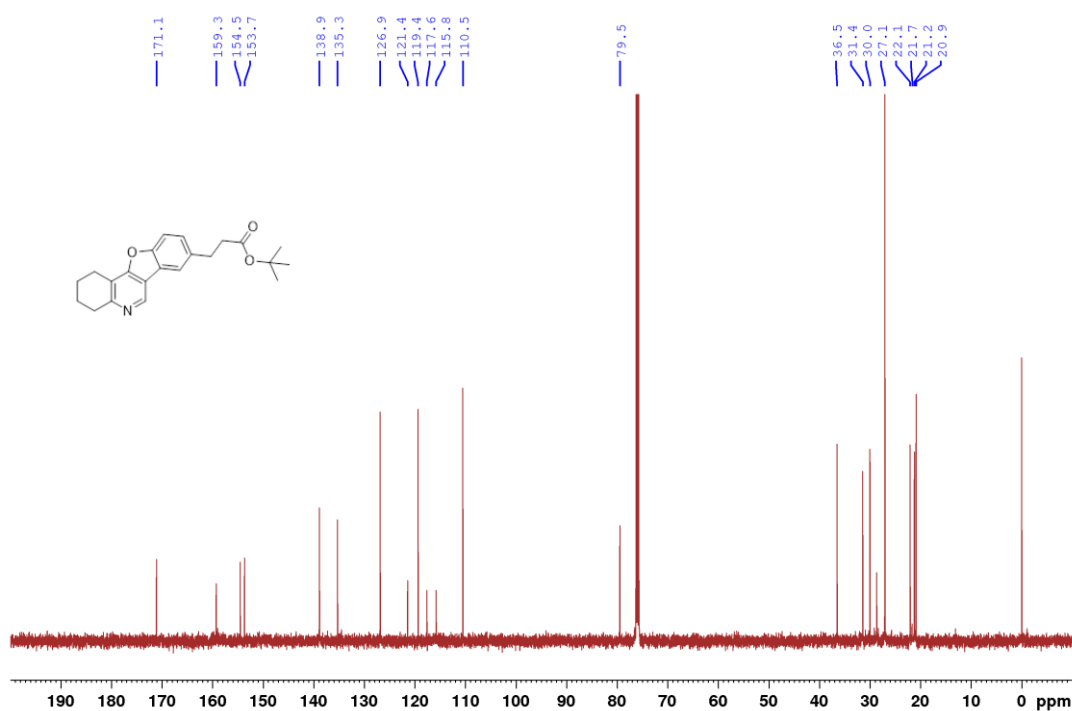
**3-Phenethyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]quinoline ¹³C NMR, 100 MHz, CDCl₃
(4b)**



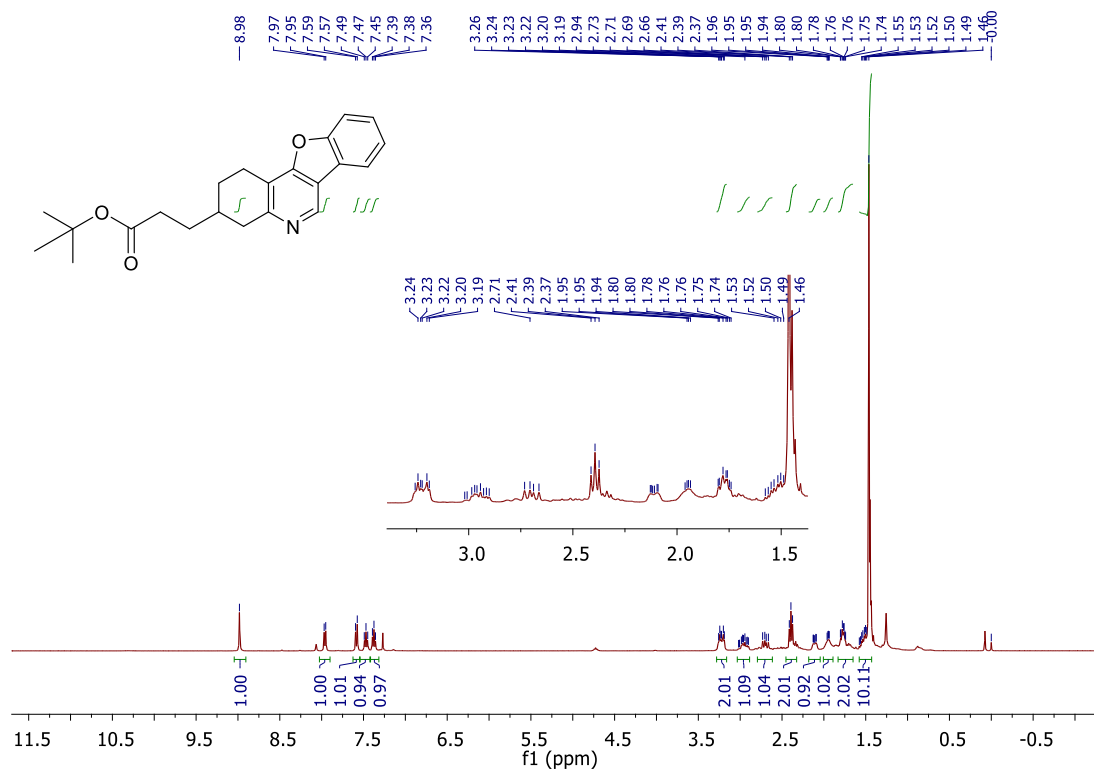
***tert*-Butyl-3-(1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinolin-8-yl)propanoate** ¹H NMR, 300 MHz, CDCl₃ (4c)



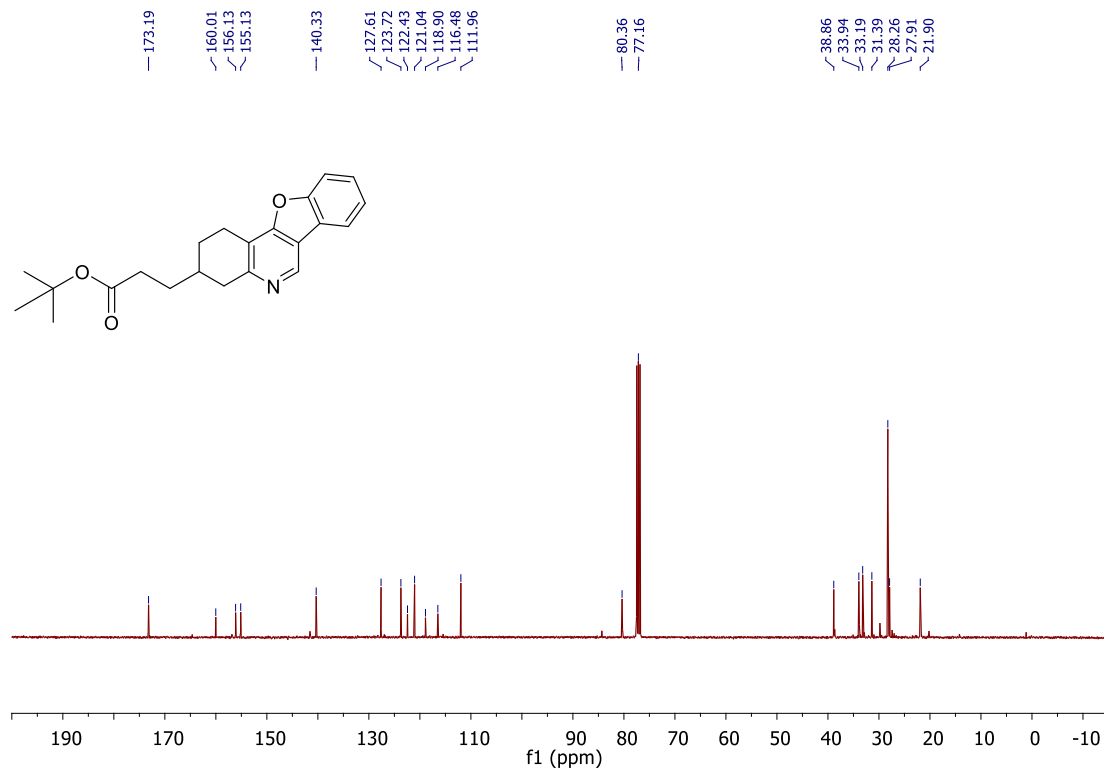
***tert*-Butyl-3-(1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinolin-8-yl)propanoate** ¹³C NMR, 125 MHz, CDCl₃ (4c)



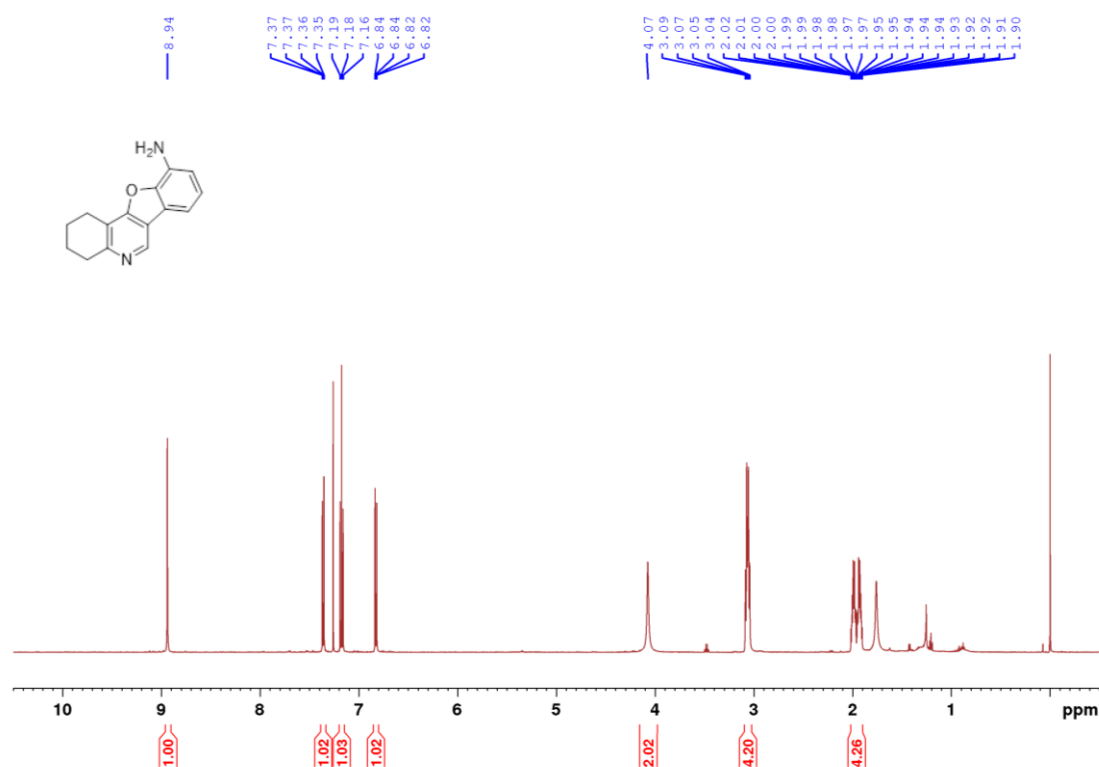
***tert*-Butyl 3-(1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinolin-3-yl)propanoate ¹H NMR, 400 MHz, CDCl₃ (4d)**



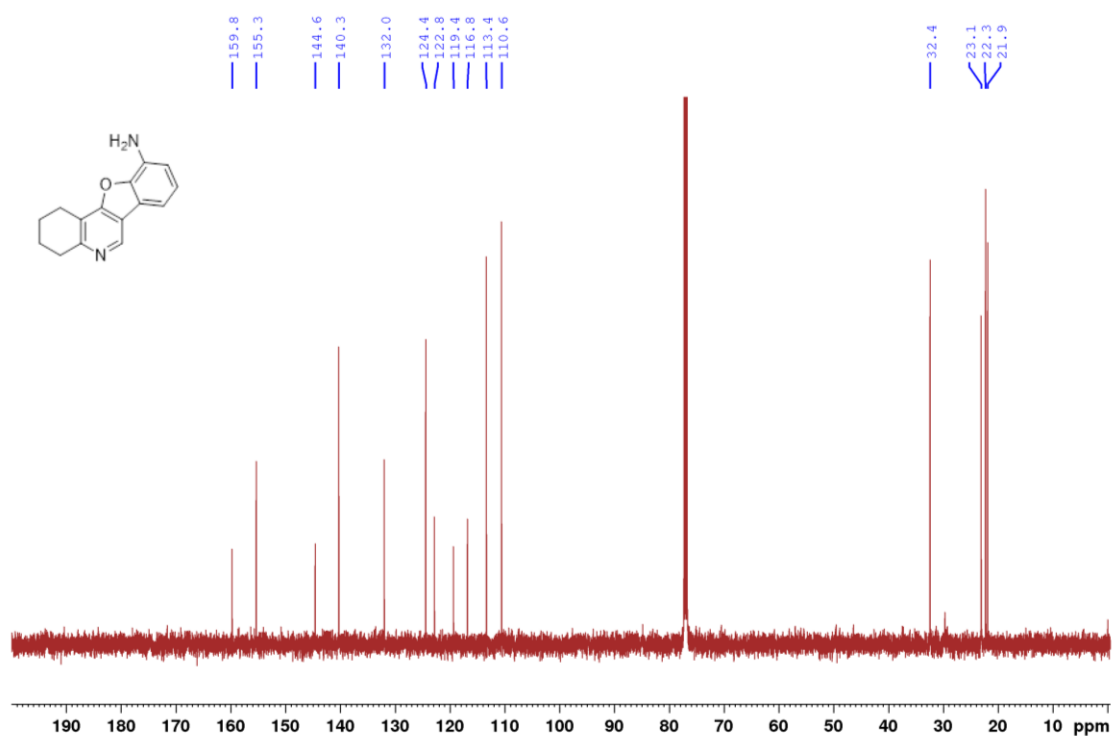
***tert*-Butyl 3-(1,2,3,4-tetrahydrobenzofuro[3,2-*c*]quinolin-3-yl)propanoate ¹³C NMR, 100 MHz, CDCl₃ (4d)**



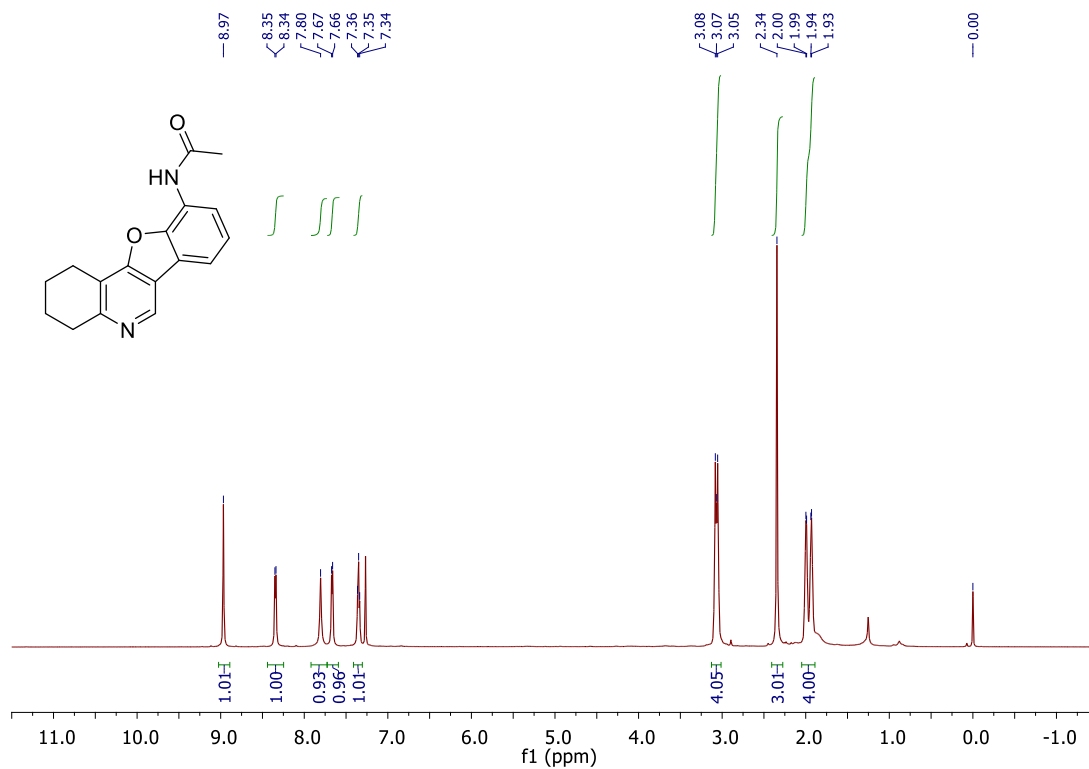
1,2,3,4-Tetrahydrobenzofuro[3,2-c]quinolin-10-amine ^1H NMR, 500 MHz, CDCl_3 (6a)



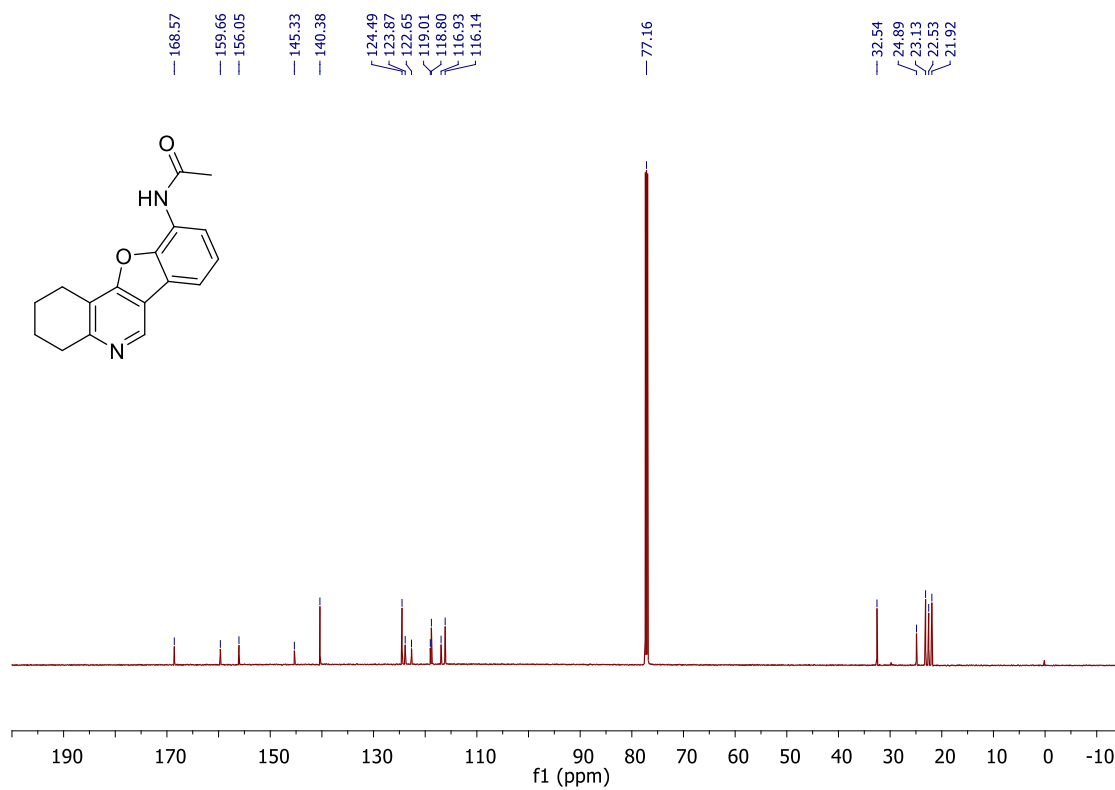
1,2,3,4-Tetrahydrobenzofuro[3,2-c]quinolin-10-amine ^{13}C NMR, 125 MHz, CDCl_3 (6a)



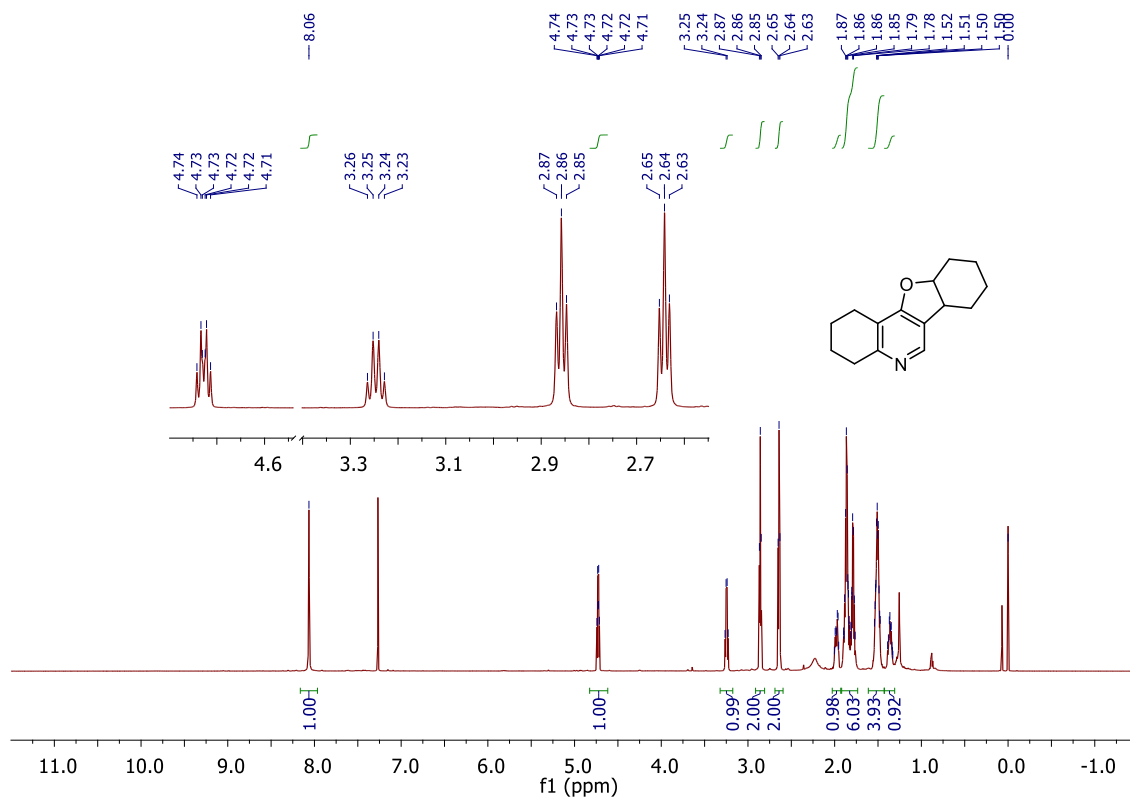
***N*-(1,2,3,4-Tetrahydrobenzofuro[3,2-*c*]quinolin-10-yl)acetamide ¹H NMR, 600 MHz, CDCl₃ (6b)**



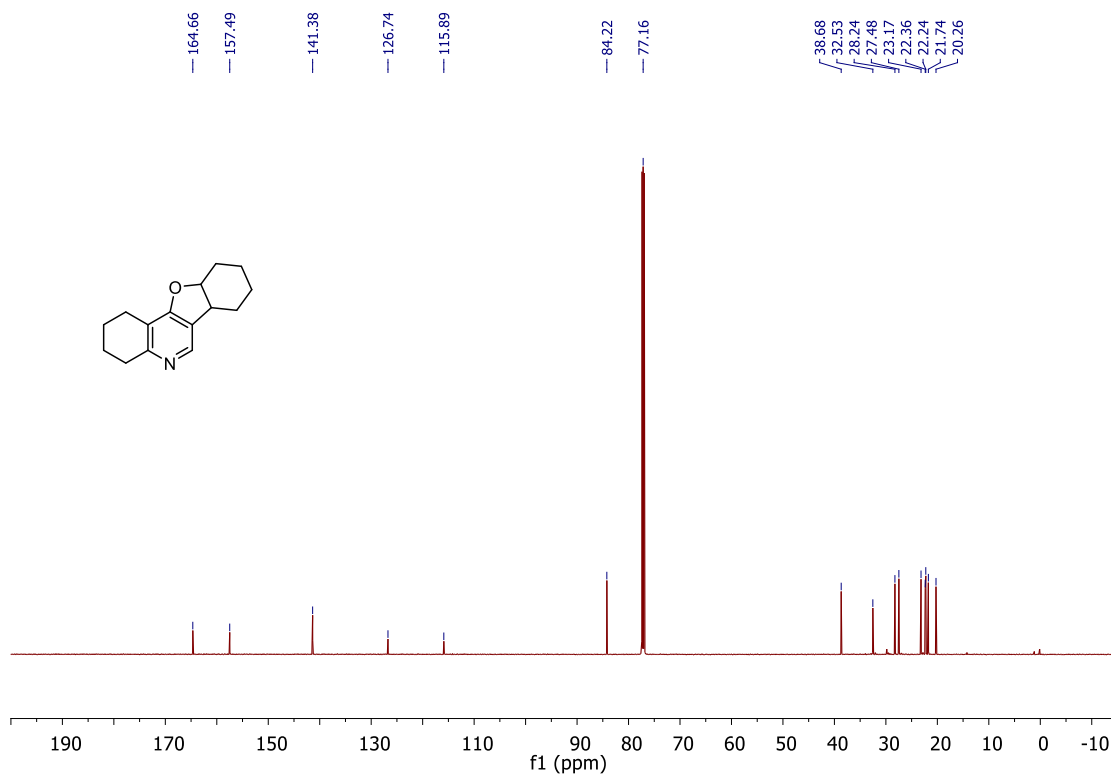
***N*-(1,2,3,4-Tetrahydrobenzofuro[3,2-*c*]quinolin-10-yl)acetamide ¹³C NMR, 150 MHz, CDCl₃ (6b)**



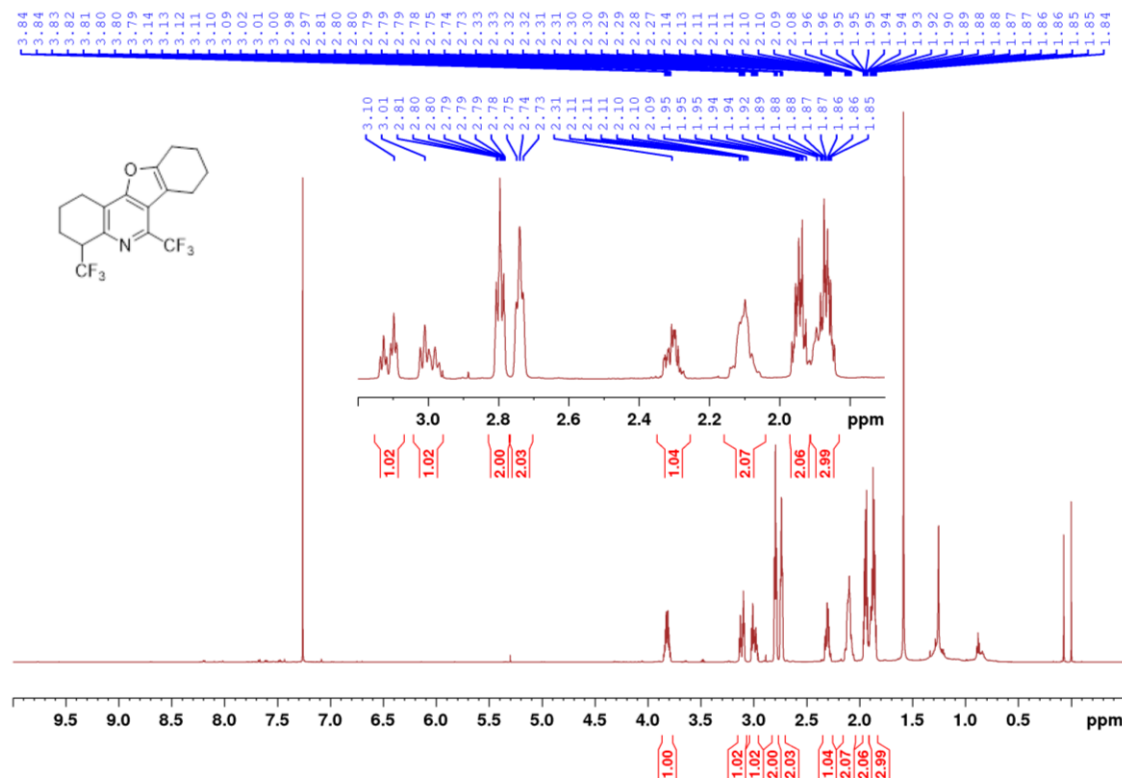
1,2,3,4,6b,7,8,9,10,10a-Decahydrobenzofuro[3,2-c]quinoline ¹H NMR, 600 MHz, CDCl₃ (7a)



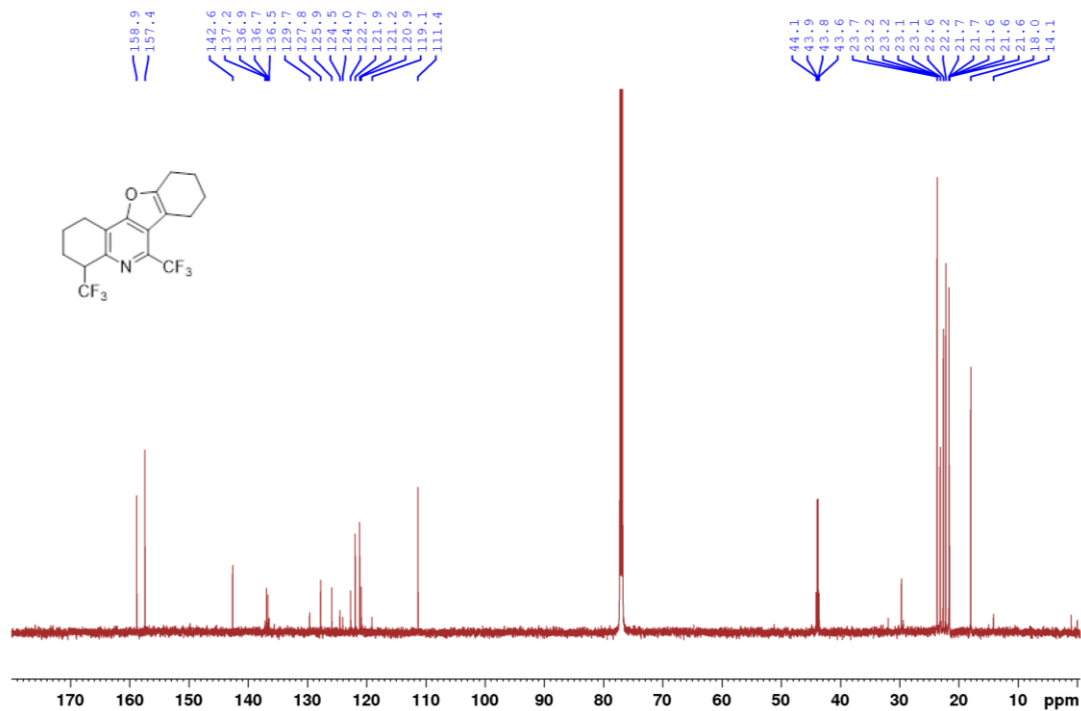
1,2,3,4,6b,7,8,9,10,10a-Decahydrobenzofuro[3,2-c]quinoline ¹³C NMR, 150 MHz, CDCl₃ (7a)



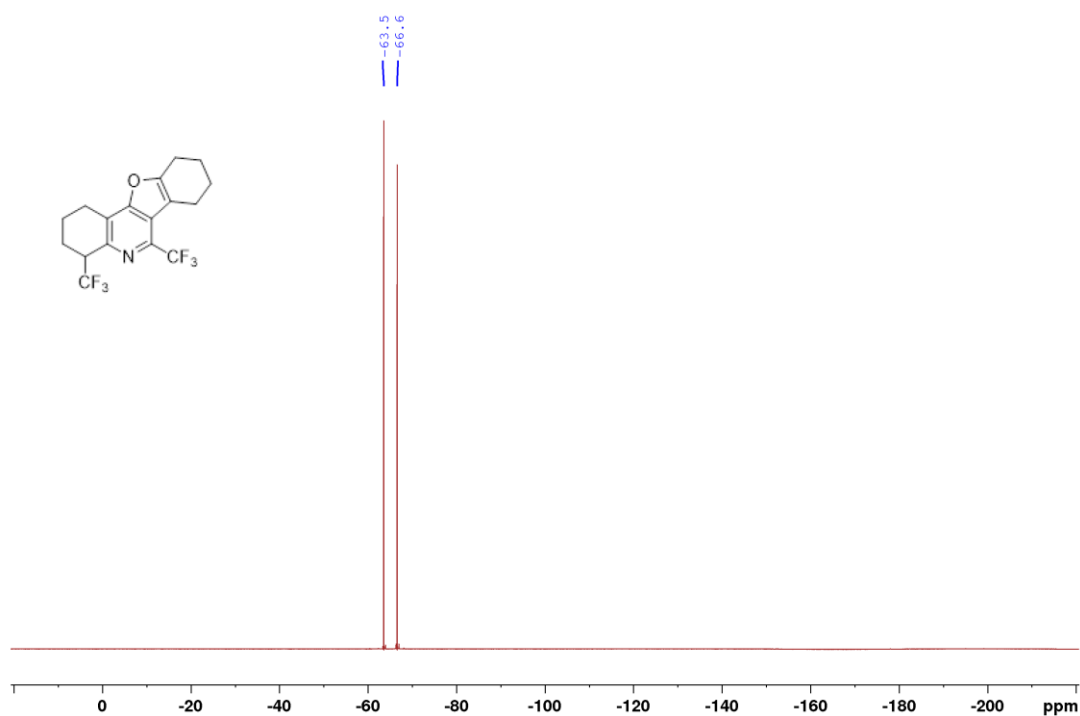
4,6-Bis(trifluoromethyl)-1,2,3,4,6b,7,8,9,10,10a-decahydrobenzofuro[3,2-c]quinoline ¹H NMR, 600 MHz, CDCl₃ (7b)



4,6-Bis(trifluoromethyl)-1,2,3,4,6b,7,8,9,10,10a-decahydrobenzofuro[3,2-c]quinoline ¹³C NMR, 150 MHz, CDCl₃ (7b)



4,6-Bis(trifluoromethyl)-1,2,3,4,6b,7,8,9,10,10a-decahydrobenzofuro[3,2-c]quinoline ¹⁹F NMR, 471 MHz, CDCl₃ (7b)



X-Ray Crystallography Methods

This work was undertaken by Dr. Mark Light at the University of Southampton. Single crystals were obtained from a saturated solution of methanol or DCM by slow evaporation. A suitable crystal was selected on mounted on a **MITIGEN** holder with silicon oil. Data were collected using a ROD, Synergy Custom system, **HyPix** diffractometer equipped with an Oxford Cryosystems low temperature device operating at a steady temperature of $T = 100(2)$ K. Data were measured using w scans with Cu K_α /Mo K_α radiation. The diffraction pattern was indexed and the total number of runs, and images was based on the strategy calculation from the program **CrysAlisPro** 1.171.41.93a (Rigaku OD, 2022). A multi-scan absorption correction was performed using CrysAlisPro 1.171.41.93a.^[12] Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient of these materials is obtained at $\lambda = 1.54184\text{\AA}$.

The structures were solved, and the space group determined by the **ShelXT**^[13] structure solution program using dual methods and by using and by using **Olex2**^[14] as the graphical interface. These models were refined by full matrix least squares minimisation on F^2 version 2016/6 of **ShelXL**.^[15] All nonhydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

_exptl_absorpt_process_details: CrysAlisPro 1.171.41.93a^[12] using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

Crystal Data

There is a single molecule in the asymmetric unit for compounds **2a**, **2m** and **6b** which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

There is a single molecule in the asymmetric unit for compounds **2n**, which is represented by the reported sum formula. In other words: Z is 2 and Z' is 1.

For compound **2b** and **2o**, the value of Z' is 4. This means that there are four independent molecules in the asymmetric unit.

For **6a**, the value of Z is 2 and the value of Z' is 0.5. This means that only half of the formula unit is present in the asymmetric unit, with the other half consisting of symmetry equivalent atoms.

CCDC

X-ray crystallographic data for compounds **2a** [CCDC 2115483], **2b** [CCDC 2288736], **2m** [CCDC 2304121], **2n** [CCDC 2267614], **2o** [CCDC 2288587], **6a** [CCDC 2298734], **6b** [CCDC 2267627].

Table 3S: X-ray-crystallographic data

Compound	2a	2b	2m	2n	2o	6a	6b
Formula	C ₁₅ H ₁₃ NO	C ₂₂ H ₁₉ NO	C ₁₅ H ₁₂ FNO	C ₁₅ H ₁₂ FNO	C ₁₆ H ₁₂ F ₃ NO ₂	C ₃₀ H ₃₀ N ₄ O ₃	C ₁₇ H ₁₆ N ₂ O ₂
Moiety Formula	-	-	-	-	-	2(C ₁₅ H ₁₄ N ₂ O), H ₂ O	-
D_{calc}/cm^{-3}	1.391	1.299	1.470	1.448	1.516	1.362	1.381
m/mm^{-1}	0.087	0.079	0.104	0.102	0.128	0.089	0.740
Formula Weight	223.26	313.38	241.26	241.26	307.27	494.58	280.32
Colour	clear colourless	clear colourless	clear light yellow	clear colourless	clear colourless	Clear colourless	clear colourless
Shape	block-shaped	block-shaped	prism-shaped	prism-shaped	plate-shaped	plate-shaped	plate-shaped
Size/mm ³	0.24×0.07×0.07	0.32×0.27×0.21	0.39×0.33×0.18	0.34×0.25×0.08	0.31×0.16×0.05	0.25×0.12×0.08	0.35×0.08×0.05
T/K	100(2)	100(2)	100(2)	100.00(10)	100(2)	100(2)	100(2)
Crystal System	monoclinic	monoclinic	monoclinic	triclinic	triclinic	orthorhombic	orthorhombic
Flack Parameter	-	0.16(18)	-	-	-	-0.2(3)	-0.02(11)
Hooft Parameter	-	0.12(17)	-	-	-	-0.1(3)	0.04(8)
Space Group	$P2_1/n$	Cc	$P2_1/n$	$P-1$	$P-1$	$P2_12_12$	$Pca2_1$
$a/\text{\AA}$	6.3620(2)	18.4541(3)	6.47150(10)	6.4065(2)	8.31680(10)	19.8325(5)	16.0017(2)
$b/\text{\AA}$	13.7876(4)	10.4924(2)	13.8628(2)	8.1840(2)	12.97700(10)	12.1409(3)	9.58830(10)
$c/\text{\AA}$	12.2250(3)	33.1638(5)	12.2344(2)	11.1469(4)	25.7022(3)	5.00950(10)	8.78600(10)
a°	90	90	90	80.146(2)	92.3890(10)	90	90
b°	96.314(2)	93.1390(10)	96.8270(10)	73.974(3)	93.2610(10)	90	90
g°	90	90	90	86.980(2)	103.1990(10)	90	90
$V/\text{\AA}^3$	1065.83(5)	6411.80(19)	1089.80(3)	553.43(3)	2692.04(5)	1206.21(5)	1348.03(3)
Z	4	16	4	2	8	2	4
Z'	1	4	1	1	4	0.5	1
Wavelength/ $\text{\AA}$	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073	1.54184
Radiation type	Mo K α	Mo K α	Mo K α	Mo K α	Mo K α	Mo K α	Cu K α
Q_{min}°	2.234	2.211	2.229	1.927	1.839	1.967	4.612
Q_{max}°	28.497	30.491	33.624	28.494	36.209	32.271	76.799
Measured Refl's.	16387	70366	35257	44256	222974	17067	12298

Indep't Refl's	2708	16238	3981	2798	24401	3691	2201
Refl's I≥2 σ(I)	2375	15124	3679	2519	16973	3493	2165
R_{int}	0.0483	0.0207	0.0218	0.0825	0.0524	0.0250	0.0250
Parameters	154	901	163	163	800	180	195
Restraints	0	40	0	0	5	0	1
Largest Peak	0.357	0.654	0.525	0.359	0.615	0.347	0.167
Deepest Hole	-0.236	-0.403	-0.238	-0.243	-0.335	-0.183	-0.188
Goof	1.071	1.020	1.082	1.089	1.016	1.035	1.036
wR_2 (all data)	0.1069	0.1163	0.1024	0.1159	0.1396	0.0884	0.0709
wR_2	0.1038	0.1140	0.1006	0.1128	0.1245	0.0868	0.0706
R_1 (all data)	0.0435	0.0485	0.0367	0.0444	0.0809	0.0346	0.0273
R_1	0.0385	0.0446	0.0346	0.0407	0.0490	0.0327	0.0268

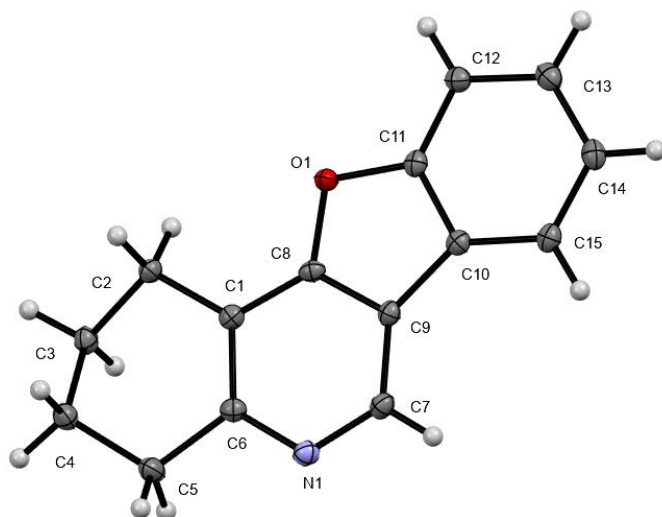


Figure 3S: Thermal ellipsoid of compound **2a** drawn at the 50% probability level.

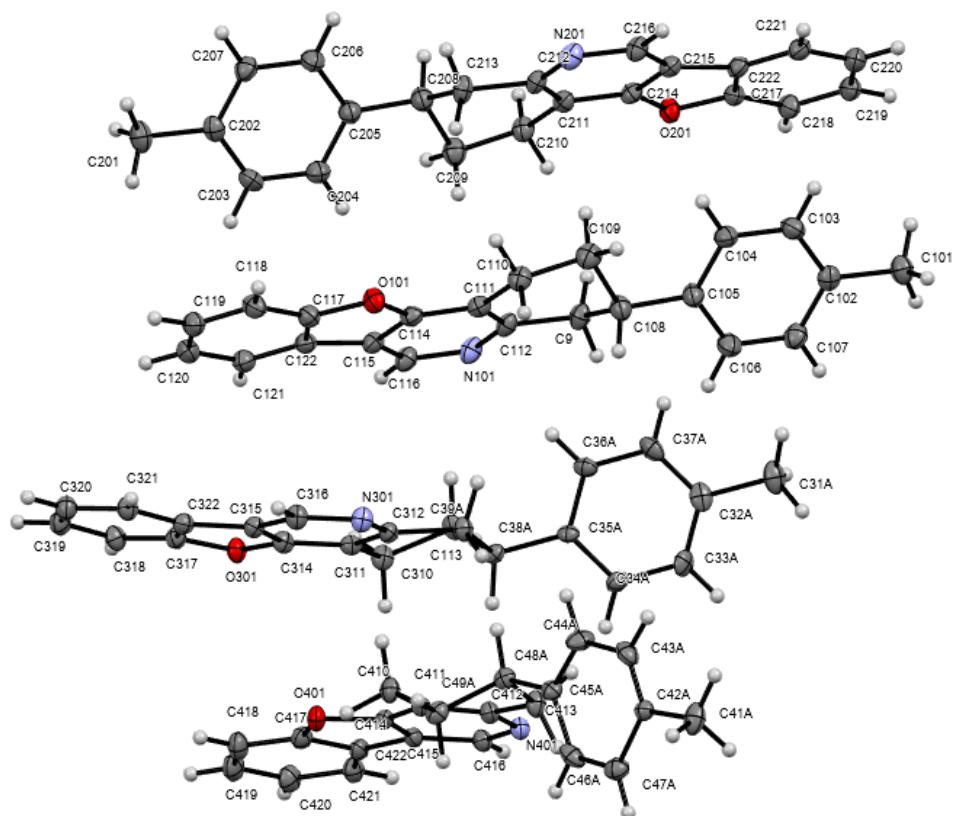


Figure 4S: Thermal ellipsoids of compound **2b** drawn at the 50% probability level.

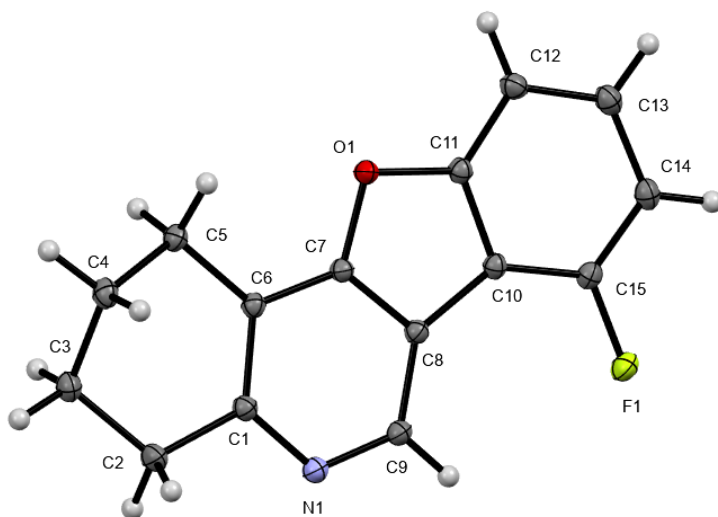


Figure 5S: Thermal ellipsoids of compound **2m** drawn at the 50% probability level.

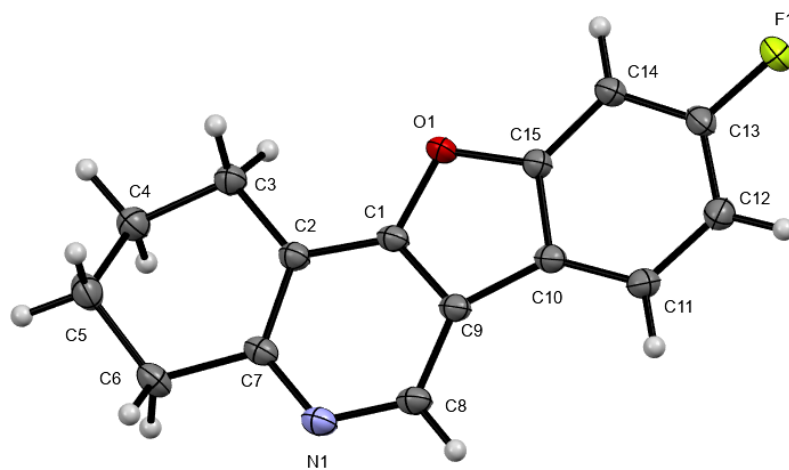


Figure 6S: Thermal ellipsoid of compound **2n** drawn at the 50% probability level.

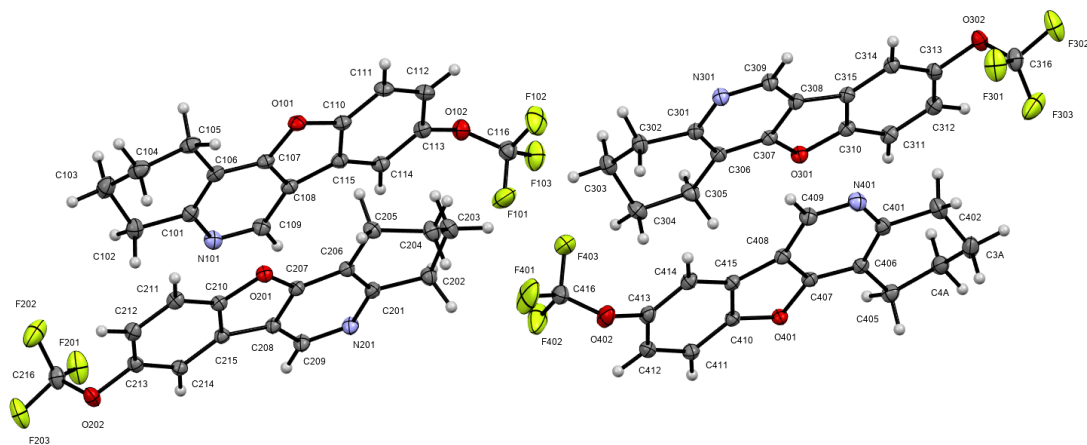


Figure 7S: Thermal ellipsoids of compound **2o** drawn at the 50% probability level.

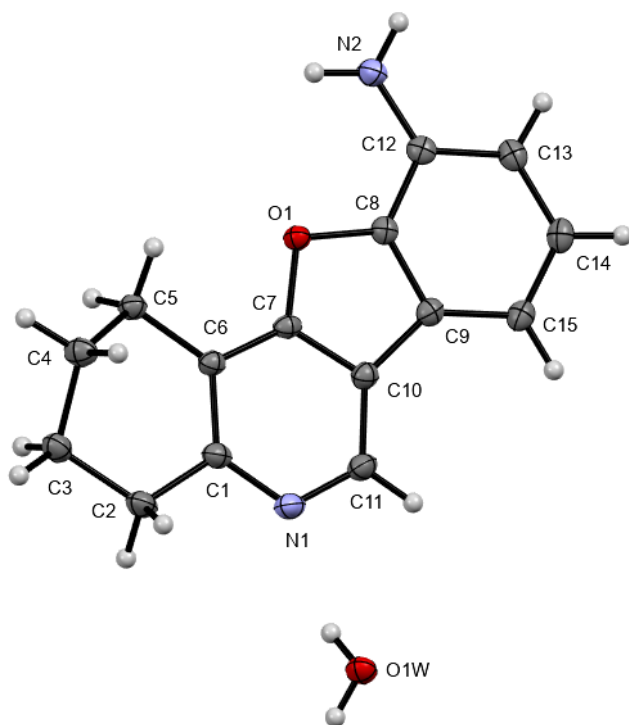


Figure 8S: Thermal ellipsoid of compound **6a** drawn at the 50% probability level.

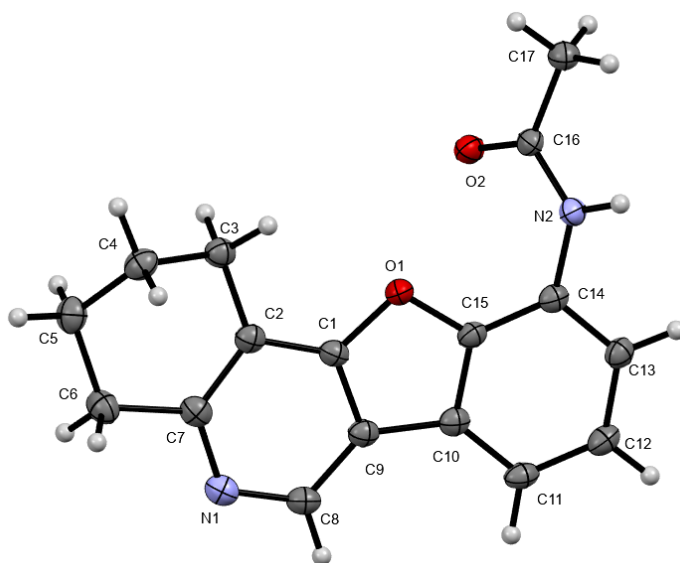


Figure 9S: Thermal ellipsoid of compound **6b** drawn at the 50% probability level.

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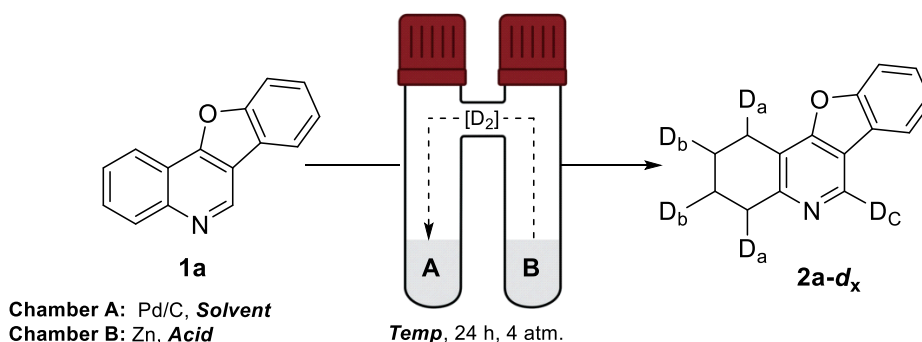
Unpublished Work and Further Discussion for Chapter 3

In addition to the work undertaken in the main manuscript and the supplementary information, some further unpublished experiments were undertaken during the course of this project. The additional experiments that were undertaken are briefly outlined below.

Deuteration Experiments

In addition to the deuteration results found in the SI (**SI**, **Table 2S**), additional investigations were also conducted to evaluate the importance of the deuterated solvent as the source of the reducing deuterium. **Table UW1** contains **entries 1 – 4** which are taken from **Table 2S** in the SI but also contains additional **entries 5 – 8** which simulate **entry 3** but outside the COware apparatus. These reactions were undertaken in a vial and septum set-up. This was to use H₂ gas directly and omit any possible interference from the HCl and zinc.

Table UW1. Additional deuteration experiments.



Entry	Temp °C	Source Pd/C	Atm.	gas source	Solvent	Zn	Conv (%) ^[a]	Deuteration (%) ^[b]		
								D _a	D _b	D _c
1	80	SA	4	DCI	AcOH	yes	99	0	0	43
2	80	SA	4	DCI	AcOH- <i>d</i> ₄	yes	100	100	100	98
3	80	SA	4	HCl	AcOH- <i>d</i> ₄	yes	100	68	50	46
4	80	SA	4	DCI	AcOH	No	0	N/A	N/A	N/A
5 ^[c]	50	SA	N/A	H ₂	AcOH- <i>d</i> ₄	N/A	100	52	43	55
6 ^[c]	50	Strem	N/A	H ₂	AcOH- <i>d</i> ₄	N/A	98	45	40	79
7 ^[c]	50	TCI	N/A	H ₂	AcOH- <i>d</i> ₄	N/A	100	45	45	85
8 ^[c]	50	Alfa Aesar	N/A	H ₂	AcOH- <i>d</i> ₄	N/A	96	50	55	84

^[a] All conversions are to **2a-d_x** and were determined by ¹H NMR analysis. ^[b] Degree of deuteration for **2a-d_x** was determined by ¹H NMR analysis. ^[c] These experiments were carried out in a black cap vial with septum. SA = Sigma Aldrich.

It is seen when deuterated solvent AcOD- d_4 is used in conjunction with H_2 gas (**entries 3 and 5 – 8**), a mixture of hydrogen and deuterium is incorporated into the molecule. This unexpected finding was repeated with different sources of Pd/C to determine it wasn't a batch-specific phenomenon (**entries 5 – 8**). Each source was found to have a similar outcome of approximately 50% incorporation of deuterium in the A-ring and the C-2 position.

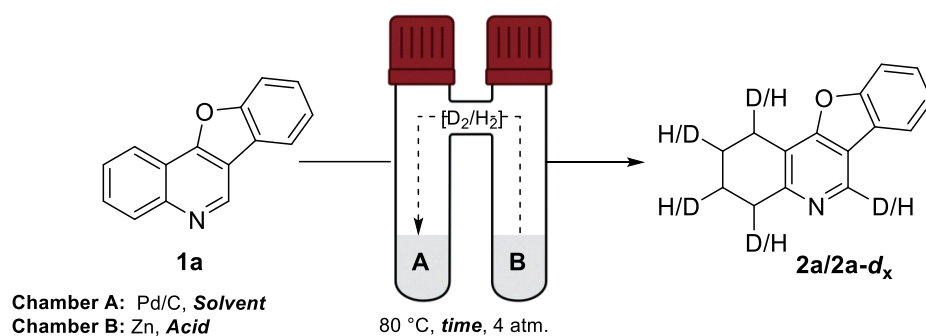
These results are possibly explained due to the preference of Pd/C surface to form a Pd-H bond over Pd-D due to a deuterium isotope effect.^[1] When D_2 gas is generated, it forms a Pd-D bond. Therefore, we postulate that the acidic protons in the large excess of AcOH exchanges the Pd-D for Pd-H, which is much more readily used for hydrogenation than Pd-D. Therefore, when D_2 gas is used with AcOH, there is no incorporation of deuterium at D_a and D_b . When H_2 is used with AcOH- d_4 , there is a ~50% uptake due to the large excess of Pd-D present. When both D_2 and AcOH- d_4 is used, full deuterium incorporation is observed. The exchange of the C-2 proton for a C-2 deuteron was expected for the benzofuroquinolines as a similar result was observed in previously reported work.^[2] This C-H activation at the C-2 position could lead to an interesting path of further research.

We then attempted to capture the rate of hydrogenation versus deuteration by setting up parallel COware experiments. One set-up was for hydrogenation and the other for deuteration (**Table UW2**). We did this experiment to determine whether the rate of hydrogenation was significantly faster than that of deuteration as this would suggest that the Pd-H species would be more rapidly up-taken than the Pd-D species. However, our result was inconclusive and therefore, more work needs to be done to elucidate this mechanism.

Pre-Protonation of the Quinoline

It was determined that acidic conditions were necessary for the hydrogenation of the benzofuroquinolines (as the hydrogenation was not supported by MeOH, EtOH, *i*PrOH or HFIP alone). We were interested to elucidate whether pre-protonated quinoline would undergo the reduction in non-acidic solvents. The benzofuroquinoline hydrochloride **U1** was obtained by stirring the benzofuroquinoline **1a** in HCl (3 M in CPME, 22 eq.) for 3 days (**Scheme UW1**).

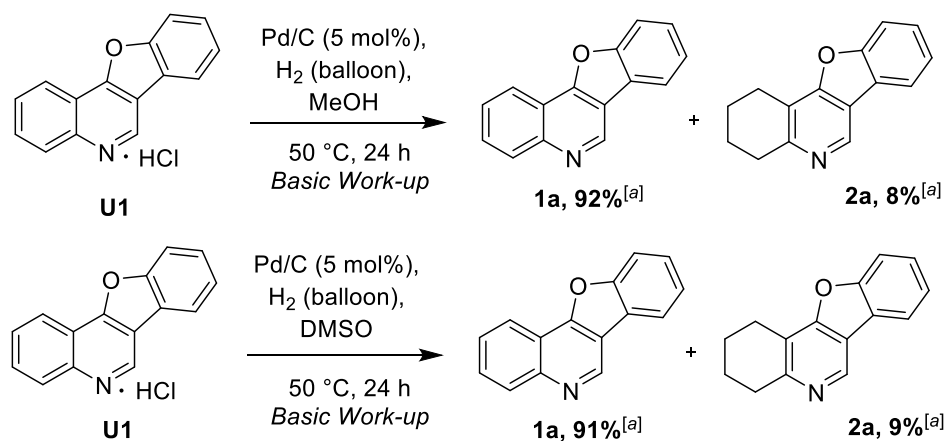
Table UW2. Attempts to capture the rate of hydrogenation vs deuteration into compound **1a**.



Entry	Time (h)	Solvent	Acid	Conv (%) ^[a]
1	10 min	AcOH	HCl	0
2	10 min	AcOD-d ₄	DCI	0
3	1	AcOH	HCl	3
4	1	AcOD-d ₄	DCI	0
5	4	AcOH	HCl	39
6	4	AcOD-d ₄	DCI	40
7	6	AcOH	HCl	45
8	6	AcOD-d ₄	DCI	40

^[a] All conversions were to **2a** or **2a-d_x** and were determined by ¹H NMR analysis.

Scheme UW1. Pre-protonated benzofuroquinoline undergoing hydrogenation conditions in non-acidic solvent.



^[a] All conversions were determined by ¹H NMR analysis.

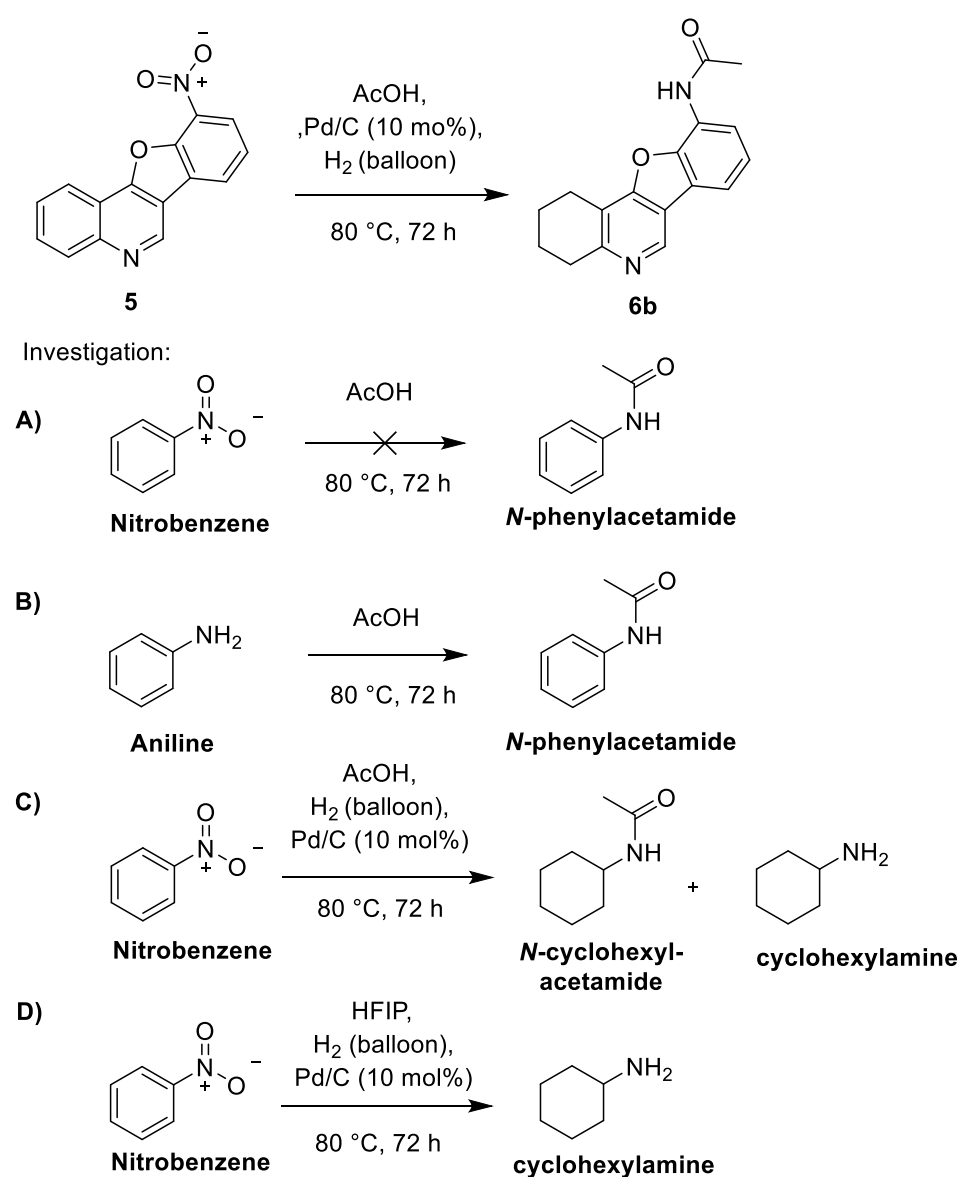
Pre-protonation of the substrate had the same outcome as that of the non-protonated substrate **1a** in non-acidic solvent. Approximately 9% of the benzofuroquinoline was reduced to **2a** indicating that pre-protonation does not assist the hydrogenation in non-acidic solvents. It was postulated that the chloride counterion does not accurately reflect

our reaction conditions, therefore, the acetate and the trifluoroacetate salt was attempted to be made, however no product was furnished.

Nitro to Amine to Amide Investigation

Upon discovering that nitro-containing substrates underwent amide formation in the presence of acetic acid, we were curious to determine whether hydrogen and Pd/C was necessary for this transformation. We set-up parallel experiments in which nitrobenzene and aniline were stirred in acetic acid (only) for 72 hours at 80 °C (mimicking our optimised conditions for compound **6b**) (**Scheme UW2**).

Scheme UW2. Investigation into the amide formation from the nitro-group.

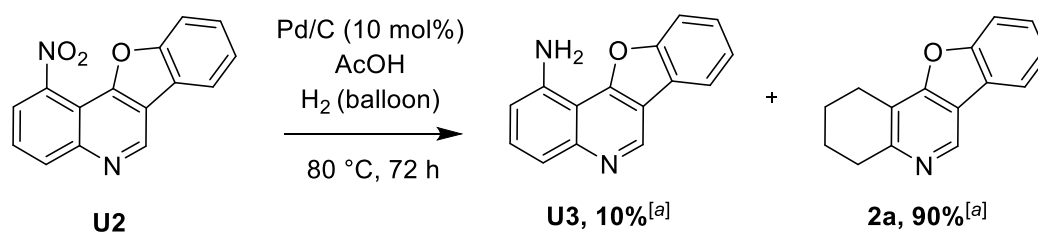


Products were determined by ¹H NMR analysis and compared to those published in the literature.^[3]

Nitrobenzene remained unchanged, however aniline reacted with the acetic acid to form *N*-phenylacetamide (**Scheme UW2, A and B**). Following this, another two reactions were set-up in which nitrobenzene was input into the optimised conditions with Pd/C and H₂ using AcOH as solvent in one and HFIP as solvent in the other (**Scheme UW2, C and D**). In acidic conditions (AcOH) the nitrobenzene undergoes hydrogenation to the amine which then undergoes amide formation (we know it doesn't go directly from nitrobenzene to the amide from the above experiment). Additionally, the benzene ring in nitrobenzene reduces to cyclohexane forming both *N*-cyclohexylacetamide and cyclohexylamine in 50:50 mixture (**C**). Nitrobenzene in HFIP with Pd/C and H₂ forms cyclohexylamine in 100% conversion (**D**). This tells us that the nitro group must undergo hydrogenation to the amine in order to achieve the amide and secondly, that the amine can undergo amide formation without Pd/C or H₂. A similar result was observed by Skupinska and co-workers in the hydrogenation of amino-quinoline.^[4] They found that the amine was cleaved upon hydrogenation. They therefore protected the amine before hydrogenation with an acetamido-group which was then deprotected to leave the reduced amino-quinoline intact.

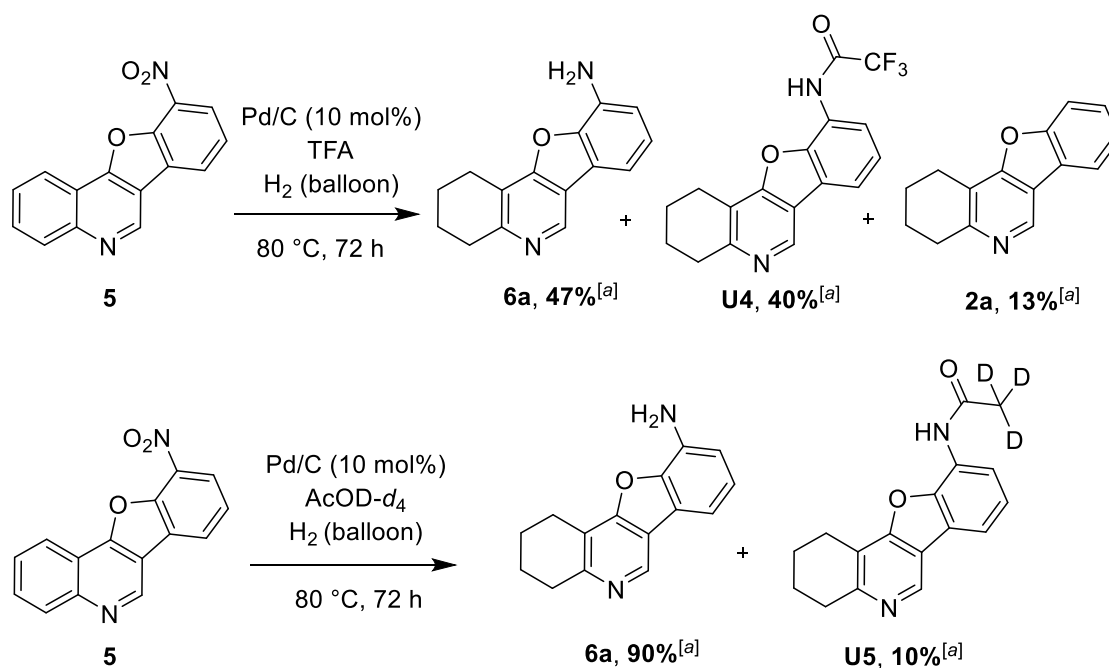
In addition to C-16 nitro-substituted substrate **5**, the C-5 position was also investigated with the nitro group. As the 5-position is one of our only non-investigated sites on the benzofuroquinoline scaffold, we wanted to probe this site. Unfortunately, however, the only readily available 4-chloroquinoline with C-5 substitution was a nitro-group. Accessing a reduced C-5 substituted product presented some issues. The nitro group at C-5 in **U2** underwent hydrogenation to the amine to form **U3** and then subsequent deamination to the unsubstituted product **2a** (**Scheme UW3**). At no point was the A-ring reduced amine product detected, indicating that either the amine is removed before A-ring reduction, or it is removed concomitantly with A-ring reduction. This rendered us unable to access the C-5 position for this publication, although the amine intermediate **U3** could be converted to a more robust group in the future to form a new substrate at C-5. Considering that acOH proved a good reagent for amide formation in these reaction conditions, and that the reaction is viable in TFA also (**Table 1**, main manuscript), it was speculated whether TFA or deuterated acetic acid (AcOH-*d*₄) would also work to form amide products **U4** and **U5** (**Scheme UW4**). Unfortunately, a mixture of products was observed for the use of TFA as the solvent/reagent, with some deamination observed also and therefore **U4** was not isolated. The reaction was slow for AcOH-*d*₄ and was not pursued further.

Scheme UW3. C-5 nitro-substituted benzofuroquinoline.



^[a] Conversions were determined by ¹H NMR analysis.

Scheme UW4. Use of TFA and AcOD-*d*₄ as solvent and reagent to form amide products.

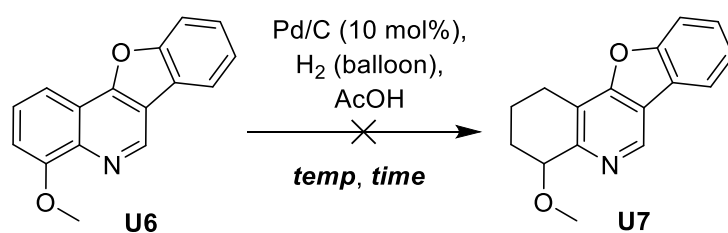


^[a] Conversions were determined by ¹H NMR analysis.

8-Methoxy benzofuroquinoline

In addition to the C-8 substituted trifluoromethyl substrate **1j**, the C-8 position was also substituted with a methoxy group. However, this substrate did not get reduced at the A-ring in appreciable yields. Mostly starting material **U6** remained with ~3% product **U7** even after higher temperatures and longer reaction times. Similar to the C-6 position, perhaps, the C-8 position with electron donating groups also prove to be slow at reducing. Similar to the C-5 position, C-8 substituted quinoline starting materials were in short supply and therefore require further investigation.

Table UW3. Attempts to optimise benzofuroquinoline **U6**.



Entry	Time (h)	Temp (°C)	Conversion to U7 (%) ^[a]
1	24	80	1
2	24	100	2
3	48	100	7
4	72	100	10

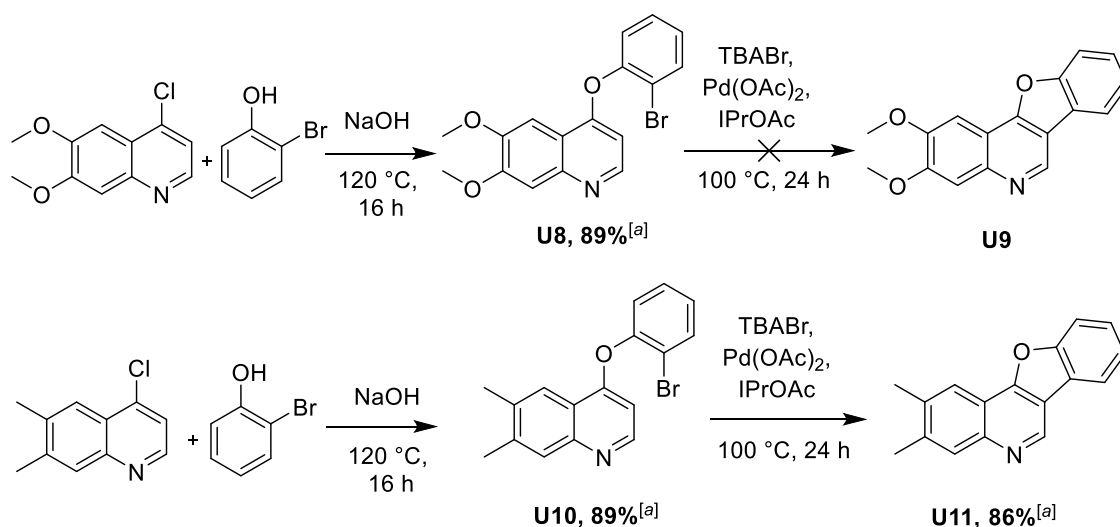
^[a] Conversions were determined by ¹H NMR analysis.

Disubstituted Benzofuroquinolines

Although the disubstituted work was mostly undertaken by Dr. Amy Lowry, initial investigations were undertaken by myself before handing over to Amy. Firstly, dimethoxy substituted phenoxy quinoline **U8** was synthesised as per general procedure 1 in the corresponding SI. Difficulty was encountered for the ring-closing step to form the benzofuroquinoline starting material **U9** (**Scheme UW5**). A dimethyl substrate was then attempted through initial phenoxyquinoline formation **U10** as per general procedure 1, followed by ring closing as per general procedure 2. Success was found in forming substrate **U11** with 86% yield.

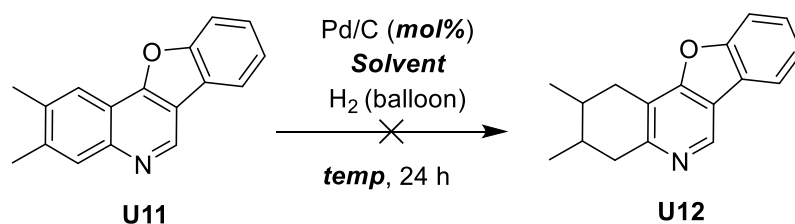
Initial attempts were made to reduce the dimethyl substituted **U11** using our optimised conditions to **U12**. Unfortunately, no A-ring reduction was observed using these conditions. The reduction of the disubstituted products was then handed to Dr. Amy Lowry to continue investigating.

Scheme UW5. Synthesis of disubstituted products.



^[a]Yields shown are isolated yields after purification.

Table UW4. Optimisation attempts for the reduction of dimethyl benzofuroquinoline **U11**.



Entry	Pd/C (mol%)	Solvent	Temp (°C)	Conv. to U12 (%) ^[a]
1	5	AcOH	50	0
2	5	AcOH	80	0
3	7	AcOH	80	0
4	5	TFA	80	0

^[a] Conversions were determined by ¹H NMR analysis.

Alternate Sources.

Catalyst

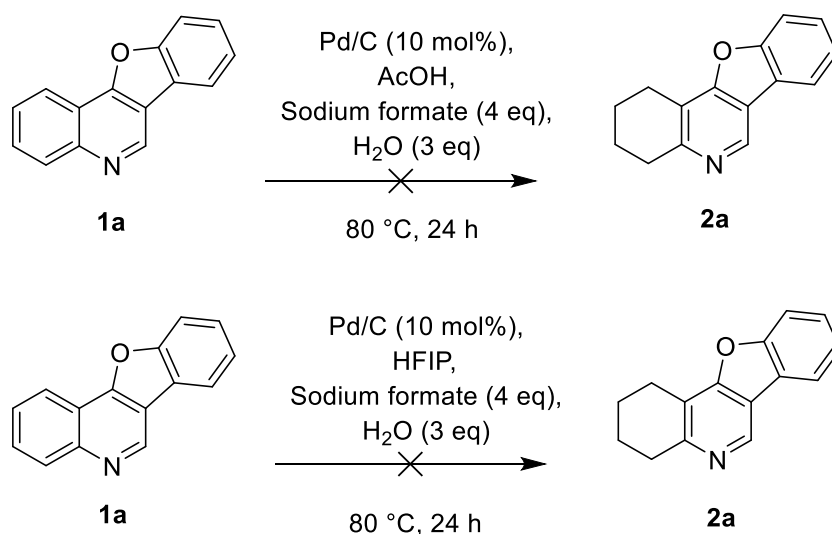
Instead of relying on the need for commercial Pd/C, we investigated whether we could simulate our own catalyst using Pd(OAc)₂ and charcoal. This was done by adding in both the Pd(OAc)₂ (10 mol%, 10 wt% of charcoal) and the charcoal into the reaction mixture in place of Pd/C. Under otherwise standard reaction conditions, pleasingly, we formed 54% of unsubstituted compound **2a** from **1a** in 24 hours and 100% of compound **2a** in 48 hours. The extra time needed for complete hydrogenation may be due to the need for Pd(OAc)₂ to degrade and/or change to the active form of the catalyst. As this method

was not as practical as commercial Pd/C we did not continue with the Pd(OAc)₂/charcoal conditions.

Transfer Hydrogenation

Another popular method for hydrogenation in the literature is transfer hydrogenation^[5] which does not use gaseous H₂ as hydrogen source. Transfer hydrogenation was attempted using sodium formate (conditions adapted from **Chapter 2**) in both acidic and non-acidic conditions. Unfortunately, no reduced product **2a** was observed.

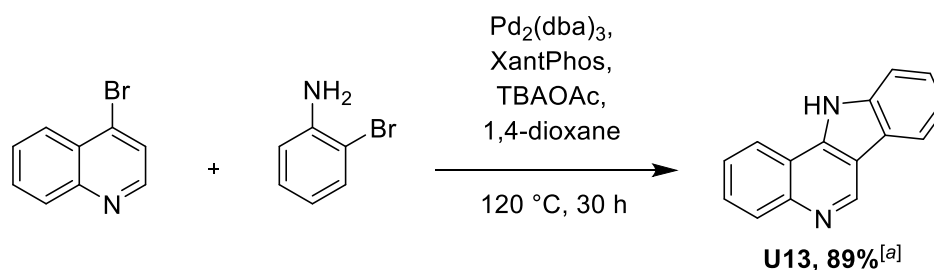
Scheme UW6. Transfer hydrogenation attempts using AcOH and HFIP.



Indoloquinoline Scaffold

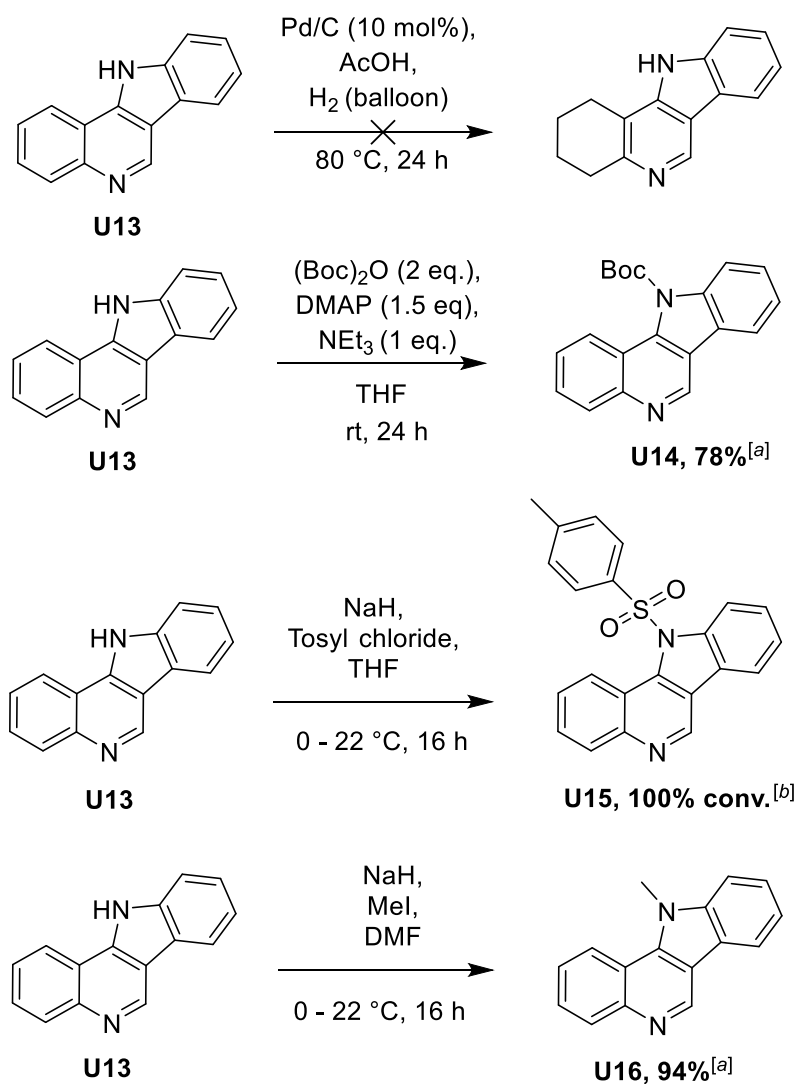
In addition to benzofuroquinoline substrates, we also applied our reducing conditions to the indoloquinoline scaffold **U13**. The indoloquinoline scaffold was synthesised as per currently unpublished conditions highlighted in **Scheme UW7**. This methodology is currently being developed within the McGlacken group.

Scheme UW7. Synthesis of iodoquinoline by one-pot Buchwald-Hartwig reaction.



^[a] Yield shown is isolated yield.

Scheme UW8. Reactions with indoloquinoline **U13** scaffold.



^[a] Yields shown are isolated yields after purification. ^[b] **U15** was formed in 100% conversion from **U13**, however the tosyl group was cleaved during column chromatography.

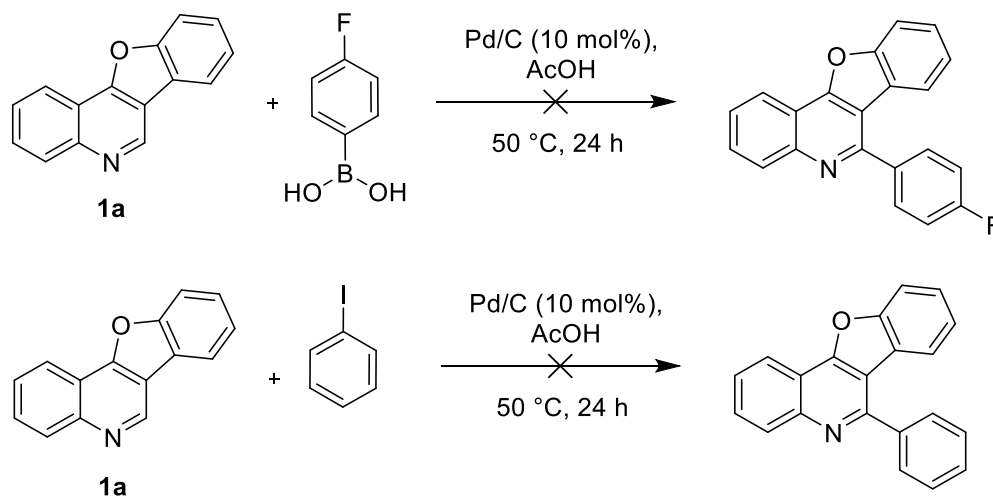
Under standard conditions (Pd/C (10 mol%), AcOH, H₂ (balloon) at 80 °C), no reduction of **U13** took place. From there, we decided to block the indole N–H with a protecting group. We installed a Boc, tosyl and a methyl group (**Scheme UW8**) however, no reduction took place under the same conditions as **U13**.

It was speculated whether higher pressures would be necessary to achieve hydrogenation of the indoloquinoline. Methylated substrate **U16** was subjected to a Parr hydrogenator at 35 psi (2.4 atm.) at room temperature for 5 hours. No reduction had occurred, so we determined the indoloquinoline scaffold incompatible with our reduction conditions.

Additional C–H activation

From our deuteration experiments in both **Chapter 2** and **3**, additional C–H activation was observed at the C-2 position of the benzofuroquinoline scaffold. This led to some initial attempts of undertaking C–H functionalisation reactions. A generic Suzuki reaction was attempted using Pd/C as catalyst in AcOH (**Scheme UW8**) in addition to a direct arylation with an aryl iodide. No formation of new products was detected by ^1H NMR.

Scheme UW9. Additional C–H activation reactions.

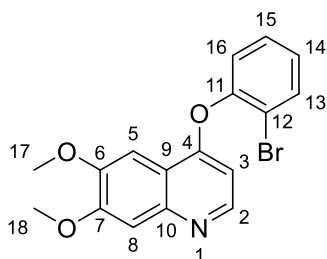


Unpublished Compound Characterisation

Phenoxyquinolines

4-(2-Bromophenoxy)-6,7-dimethoxyquinoline U8

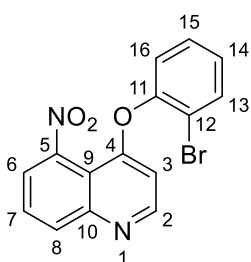
From 4-chloro-6,7-dimethoxyquinoline (0.500 g, 2.24 mmol), 2-bromophenol (0.83 mL, 7.83 mmol) and crushed NaOH pellets (0.134 g, 3.35 mmol) as per general procedure 1 outlined in Chapter 3 SI.



Sticky orange semi-solid; 89% (0.721 g); **m.p.** 87 – 87 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3320, 3175, 2930, 1595, 1623, 1467, 1350, 1120, 845, 777; **^1H NMR (300 MHz, CDCl_3)** δ = 8.49 (d, 1H, J = 4.8 Hz, H-2), 7.61 (s, 1H, H-5), 7.50 (s, 1H, H-8), 7.73 (dd, 1H, J = 1.4, 8.0 Hz, H-13), 7.44–7.37 (m, 1H, H-15), 7.25–7.15 (m, 2H, H-14, H-16), 6.36 (d, 1H, J = 4.8 Hz, H-3), 4.07 (s, 6H, CH_3 -17, CH_3 -18) ppm; **^{13}C NMR (75 MHz, CDCl_3)** δ = 159.9 (qC-4), 153.3 (qC-7), 151.2 (qC-11), 149.9 (qC-6), 148.1 (CH-2), 146.3 (qC-10), 134.3 (CH-13), 129.2 (CH-15), 128.6 (CH-8), 127.2 (CH-14), 123.2 (CH-16), 116.3 (C(Br)-12), 115.8 (qC-9), 107.4 (CH-8), 103.0 (CH-3), 99.6 (CH-5), 56.2 (C(18)-H₃ and C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{17}\text{H}_{15}\text{BrNO}_3]^+$: 360.0230; found: 360.0225.

4-(2-Bromophenoxy)-5-nitroquinoline U17

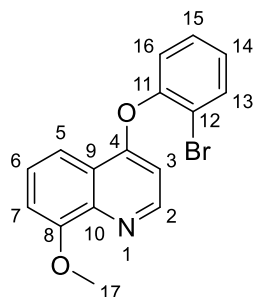
From 4-chloro-5-nitroquinoline (0.500 g, 2.40 mmol), 2-bromophenol (0.88 mL, 8.39 mmol) and crushed NaOH pellets (0.144 g, 3.60 mmol) as per general procedure 1 outlined in Chapter 3 SI.



Pale yellow solid; 65% (1.076 g); **m.p.** 126 – 128 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3085, 3060, 2623, 1579, 1559, 1305, 1268, 1216, 714; **^1H NMR (500 MHz, CDCl_3)** δ = 8.77 (d, 1H, J = 5.2 Hz, H-2), 8.28 (dd, 1H, J = 1.1, 8.6 Hz, H-6), 7.79 (dd, 1H, J = 7.5, 8.5 Hz, H-7), 7.68 – 7.72 (m, 2H, H-8, H-13), 7.39 – 7.44 (m, 1H, H-15), 7.19 – 7.25 (m, 2H, H-14, H-16), 6.56 (d, 1H, J = 5.2 Hz, H-3) ppm; **^{13}C NMR (125 MHz, CDCl_3)** δ = 158.8 (qC-4), 152.5 (CH-2), 150.2 (qC-11), 150.1 (qC-5), 146.3 (qC-10), 134.4 (CH-13), 132.7 (CH-6), 129.4 (CH-15), 128.7 (CH-7), 127.9 (CH-14), 123.1 (CH-16), 121.1 (CH-8), 116.2 (qC-12), 112.5 (qC-9), 106.2 (CH-3) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{15}\text{H}_{10}\text{BrN}_2\text{O}_3]^+$: 344.9870; found: 344.9865.

4-(2-Bromophenoxy)-8-methoxyquinoline U18

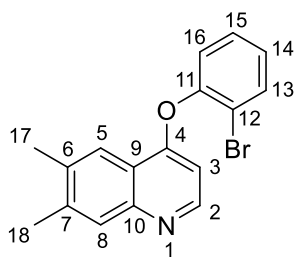
From 4-chloro-8-methoxyquinoline (3.00 g, 15.49 mmol), 2-bromophenol (8.10 mL, 77.46 mmol) and crushed NaOH pellets (0.929 g, 23.24 mmol) as per general procedure 1 outlined in Chapter 3 SI.



Brown oil; 97% (4.97 g); **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2957, 2839, 2594, 1302, 1257, 1224, 658; **^1H NMR (300 MHz, CDCl_3)** δ = 8.69 (d, 1H, J = 5.1 Hz, H-2) 7.97 (dd, 1H, J = 1.1, 8.4 Hz, H-7), 7.71 (dd, 1H, J = 1.5, 8.0 Hz, H-13), 7.52 (t, 1H, J = 8.0 Hz, H-6), 7.40 (ddd, 1H, J = 1.5, 7.5, 8.0 Hz, H-15), 7.23 (dd, 1H, J = 1.5, 8.0 Hz, H-16), 7.19 (ddd, 1H, J = 1.5, 7.5, 8.0 Hz, H-14), 7.12 (dd, 1H, J = 1.0, 7.8 Hz, H-5), 6.45 (d, 1H, J = 5.1 Hz, H-3), 4.10 (s, 3H, CH_3 -17) ppm; **^{13}C NMR (125 MHz, CDCl_3)** δ = 160.6 (qC-4), 155.3 (qC-8), 151.2 (qC-11), 149.8 (CH-2), 141.8 (qC-10), 134.3 (CH-13), 129.2 (CH-15), 127.2 (CH-14), 126.4 (CH-6), 123.1 (CH-16), 122.1 (qC-9), 116.3 (qC-12), 113.5 (CH-7), 108.4 (CH-5), 104.5 (CH-3), 56.0 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{16}\text{H}_{13}\text{BrNO}_2]^+$: 330.01242; found: 330.0123.

4-(2-Bromophenoxy)-6,7-dimethylquinoline U10

From 4-chloro-6,7-dimethylquinoline (0.400 g, 2.09 mmol), 2-bromophenol (0.847 mL, 7.26 mmol) and crushed NaOH pellets (0.126 g, 3.13 mmol) as per general procedure 1 outlined in Chapter 3 SI.

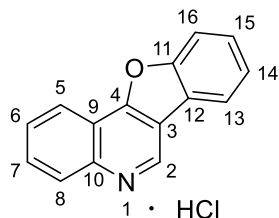


Orange solid; 89% (0.612 g); **m.p.** 121 – 123 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2981–2826, 1562, 1465, 1439, 1346, 1262, 1223, 1052, 1033, 1014, 878, 759; **^1H NMR (300 MHz, CDCl_3)** δ = 8.57 (d, 1H, J = 5.1 Hz, H-2), 8.13 (s, 1H, H-5), 7.86 (s, 1H, H-8), 7.71 (dd, 1H, J = 1.4, 7.9 Hz, H-13), 7.44–7.37 (m, 1H, H-15), 7.25–7.15 (m, 2H, H-14, H-16), 6.32 (d, 1H, J = 5.1 Hz, H-3), 2.50 (s, 6H, CH_3 -17 and CH_3 -18) ppm; **^{13}C NMR (75 MHz, CDCl_3)** δ = 160.2 (qC-4), 151.4 (qC-11), 150.1 (CH-2), 149.1 (qC-10), 140.5 (qC-7), 136.3 (qC-6), 134.3 (CH-13), 129.2 (CH-15), 128.6 (CH-8), 127.1 (CH-14), 123.2 (CH-16), 121.0 (CH-5), 119.5 (qC-9), 116.4 (qC(Br)-12), 103.3 (CH-3), 20.5 (C(18)-H₃), 20.3 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) m/z : $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{17}\text{H}_{15}\text{BrNO}]^+$: 328.0332; found: 328.0339.

Benzofuroquinolines

Benzofuro[3,2-c]quinolin-5-ium chloride **U1**

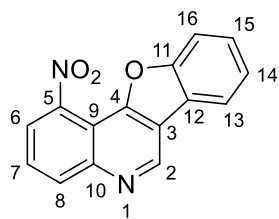
1a (0.150 mg, 0.68 mmol, 1 eq.) was dissolved in CPME (3.00 mL) and HCl in CPME was added (3 M, 5.0 mL, 15 mmol, 22 eq.) and stirred at room temperature for 3 days. The reaction mixture was filtered and washed with CPME (10 mL) to yield **U1**.



White solid; 74% (0.129 g); **m.p.** >250 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3013, 2971, 2377, 2049, 1939, 1645, 1584, 1409, 1183, 1062, 747, 564, 437; **¹H NMR (300 MHz, MeOD-*d*₄)** δ = 9.92 (s, 1H, H-2), 8.59 (ddd, 1H, *J* = 0.6, 1.4, 8.4 Hz, H-5), 8.27 (m, 2H, H-8, H-13), 8.10 (ddd, 1H, *J* = 1.4, 7.1, 8.4 Hz, H-7), 7.99 (ddd, 1H, *J* = 1.0, 7.1, 8.4 Hz, H-6), 7.86 (d, 1H, *J* = 8.4 Hz, H-16), 7.67 (ddd, 1H, *J* = 1.4, 7.4, 8.4 Hz, H-15), 7.56 (ddd, 1H, *J* = 1.0, 7.4, 7.9 Hz, H-13) ppm; **¹³C NMR (75 MHz, MeOD-*d*₄)** δ = 161.2 (qC-4), 157.1 (qC-11), 140.6 (CH-2), 138.2 (qC-10), 133.8 (CH-7), 130.0 (CH-6), 129.8 (CH-15), 125.7 (CH-14), 121.9 (CH-5), 121.8 (CH-8), 121.2 (CH-13), 120.7 (qC-12), 117.3 (qC-3), 116.5 (qC-9), 112.3 (CH-16) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₁₀NO]⁺: 220.0757; found: 220.0761.

1-Nitrobenzofuro[3,2-c]quinoline **U2**

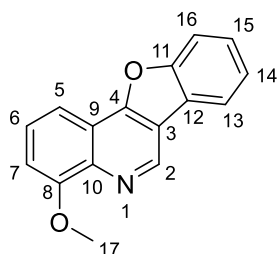
Synthesis of substrate **U2** as per general procedure 2 in Chapter 3 SI using **U17** (1.00 g, 2.90 mmol), Pd(OAc)₂ (0.0325 g, 0.145 mmol), TBABr (1.87 g, 5.80 mmol), K₂CO₃ (0.800 g, 5.80 mmol) in *i*PrOAc (3 mL).



White solid; 85% (0.650 g); **m.p.** 198 – 200 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3077, 2877, 1556, 1526, 1362, 1321, 1228, 1195; **¹H NMR (500 MHz, CDCl₃)** δ = 9.57 (s, 1H, H-2), 8.46 (dd, 1H, *J* = 1.1, 8.5 Hz, H-8), 8.10 (ddd, 1H, *J* = 0.6, 1.3, 7.8 Hz, H-13), 7.99 (dd, 1H, *J* = 1.1, 7.6 Hz, H-6), 7.79 (dd, 1H, *J* = 7.6, 8.5 Hz, H-7), 7.73 (d, 1H, *J* = 8.4 Hz, H-16), 7.58 (overlapping ddd, 1H, *J* = 1.3, 7.3, 8.4 Hz, H-15), 7.48 (dd, 1H, *J* = 1.0, 7.8 Hz, H-14) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 156.1 (qC-4), 153.5 (qC-11), 147.3 (qC-10), 146.1 (CH-2), 144.8 (qC-5), 134.4 (CH-8), 128.5 (CH-15), 127.3 (CH-7), 124.6 (CH-14), 122.4 (CH-6), 121.2 (qC-12), 120.7 (CH-13), 119.1 (qC-9), 112.7 (CH-16), 109.7 (qC-3) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for: [C₁₅H₉N₂O₃]⁺; 265.0608 found: 265.0609.

4-methoxybenzofuro[3,2-c]quinoline U6

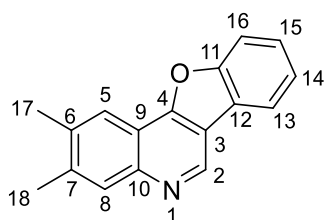
Synthesis of substrate **U6** as per general procedure 2 in Chapter 3 SI using **U18** (2.00 g, 6.06 mmol), Pd(OAc)₂ (0.068 g, 0.303 mmol), TBABr (3.90 g, 12.11 mmol), K₂CO₃ (1.670 g, 12.11 mmol) in *i*PrOAc (3 mL) and stirred at 100 °C for 3 days.



Yellow solid; 59% (0.890 g); **m.p.** 200 – 201 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 3359, 3256, 1587, 1517, 1397, 1263, 1035, 754; **¹H NMR (500 MHz, CDCl₃)** δ = 9.49 (s, 1H, H-2), 8.10 (ddd, 1H, *J* = 0.6, 1.2, 7.5 Hz, H-13), 7.98 (dd, 1H, *J* = 1.1 8.2 Hz, H-5), 7.74 (ddd, 1H, *J* = 0.6, 1.2, 8.2 Hz, H-16), 7.61 (t, 1H, *J* = 8.2 Hz, H-6), 7.54 (ddd, 1H, *J* = 1.2, 7.5, 8.2 Hz, H-15), 7.46 (dd, 1H, *J* = 1.1, 8.2, H-14), 7.14 (dd, 1H, *J* = 1.1, 7.8 Hz, H-7), 4.15 (s, 3H, CH₃-17) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 157.5 (qC-4), 156.0 (qC-11), 155.9 (qC-8), 143.0 (qC-9), 139.0 (qC-10), 127.4 (CH-6), 127.3 (CH-15), 124.0 (CH-14), 122.7 (qC-11), 120.8 (qC-12), 118.2 (qC-9), 117.0 (qC-3), 112.6 (CH-5), 112.1 (CH-16), 107.9 (CH-7), 56.1 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₆H₁₂NO₂]⁺: 250.0863; found: 250.0863.

2,3-Dimethylbenzofuro[3,2-c]quinoline U11

Synthesis of substrate **U11** as per general procedure 2 in Chapter 3 SI using **U10** (0.200 g, 0.609 mmol), Pd(OAc)₂ (0.0065 g, 0.030 mmol), TBABr (0.393 g, 1.22 mmol) and K₂CO₃ (0.168 g, 1.22 mmol) in *i*PrOAc (1.0 mL).

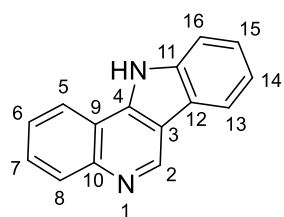


Off white solid; 92% (0.307 g); **m.p.** 152 – 154 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2981–2826, 1641, 1559, 1455, 1347, 1191, 1055, 1033, 743; **¹H NMR (300 MHz, CDCl₃)** δ = 9.35 (s, 1H, H-2), 8.09 (s, 1H, H-5), 8.03 (dd, 1H, *J* = 1.0, 7.5 Hz, H-13), 7.99 (s, 1H, H-8), 7.69 (d, 1H, *J* = 7.7 Hz, H-16), 7.49 (td, 1H, *J* = 1.5, 7.8 Hz, H-15), 7.42 (td, 1H, *J* = 1.1, 7.5 Hz, H-14), 2.51 (s, 3H, CH₃-17 or CH₃-18), 2.49 (s, 3H, CH₃-17 or CH₃-18) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 157.2 (qC-4), 156.0 (qC-11), 146.8 (qC-10), 143.5 (CH-2), 139.7 (qC-7), 137.2 (qC-6), 129.4 (CH-8), 127.0 (CH-15), 124.0 (CH-14), 123.1 (qC-12), 120.6 (CH-13), 120.2 (CH-5), 115.8 (qC-3), 115.5 (qC-9), 112.1 (CH-16), 20.7 (C(18)-H₃), 20.4 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₇H₁₄NO]⁺: 248.1070; found: 248.1066.

Indoloquinolines

11H-Indolo[3,2-c]quinoline U13

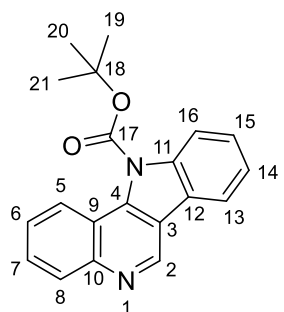
4-Bromoquinoline (0.208 g, 1.0 mmol, 1 eq.), 2-bromoaniline (0.189 g, 1.1 mmol, 1.1 eq.), Pd₂(dba)₃ (0.0458 g, 0.05 mmol, 5 mol%), Xantphos (0.0349 g, 0.06 mmol, 6 mol%) and TBAOAc (0.603 g, 2.0 mmol, 2 eq.) were dissolved in 1,4-dioxane (2 mL) in a black cap vial and stirred at 120 °C for 30 hours. The crude reaction material was filtered through celite and loaded onto silica gel for column chromatography and eluted in MeOH in DCM (100:0 – 98:2) to yield **U13**.



Tan solid; 89% yield (0.169 g); **m.p.** > 250 °C (lit. m.p. 333 – 336 °C)^[6]; **¹H NMR (300 MHz, DMSO-*d*₆)** δ = 13.22 (br s, 1H, N-H), 9.79 (s, 1H, H-2), 8.64 (dd, 1H, *J* = 1.0, 8.2 Hz, H-5), 8.39 (d, 1H, *J* = 7.8 Hz, H-13), 8.21 (d, 1H, *J* = 8.2 Hz, H-8), 7.75 – 7.93 (m, 3H, H-6, H-7, H-16), 7.59 (t, 1H, *J* = 7.5 Hz, H-15), 7.44 (t, 1H, *J* = 7.5 Hz, H-14) ppm; **¹³C NMR (151 MHz, DMSO-*d*₆)** δ = 142.0 (qC-10), 141.6 (CH-2), 140.6 (qC-4), 139.3 (qC-11), 129.9 (CH-8), 126.9 (CH-7), 126.7 (CH-6), 125.4 (CH-15), 122.8 (CH-5), 121.9 (qC-12), 121.7 (CH-14), 120.7 (CH-13), 116.4 (qC-9), 114.1 (qC-3), 112.4 (CH-16) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₁₅H₁₁N₂]⁺: 219.0917; found: 219.0914.

tert-Butyl-11H-indolo[3,2-c]quinoline-11-carboxylate U14

To **U13** (0.040 g, 0.183 mmol, 1 eq.) dissolved in THF (4 mL) in a round bottom flask, was added DMAP (0.034 g, 0.275 mmol, 1.5 eq.), NEt₃ (0.13 mL, 0.183 mmol, 1 eq.) and (Boc)₂O (0.080 g, 0.366 mmol, 2 eq.). The mixture was stirred at rt for 24 hours and was purified by silica gel column chromatography and eluted slowly in DCM:MeOH (100:0 – 99:1) to yield **U14**.

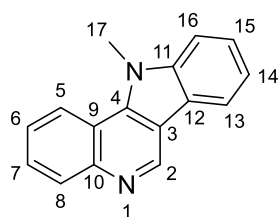


White solid; 78% yield (0.045 g); **m.p.** 83 – 85 °C; **IR** $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$: 2913, 2853, 1741, 1565, 1462, 1304, 1221, 1067; **¹H NMR (300 MHz, CDCl₃)** δ = 9.53 (s, 1H, H-2), 8.47 (d, 1H, *J* = 8.5 Hz, H-5), 8.26 (d, 1H, *J* = 8.5 Hz, H-8), 8.19 (d, 1H, *J* = 8.3 Hz, H-16), 8.15 (d, 1H, *J* = 7.8 Hz, H-13), 7.72 (t, 1H, *J* = 7.6 Hz, H-7), 7.61 (t, 1H, *J* = 7.6 Hz, H-6), 7.54 (t, 1H, *J* = 7.8 Hz, H-15), 7.47 (t, 1H, *J* = 7.8 Hz, H-14), 1.77 (s, 9H, CH₃-19, CH₃-20, CH₃-21) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 151.0 (qC-17), 147.9 (qC-10), 143.7 (CH-2), 139.9 (qC-4), 139.6 (qC-11), 130.4 (CH-8), 128.3 (CH-7), 127.2 (CH-15), 125.6 (CH-6), 125.0 (CH-5), 124.1 (qC-12), 123.9 (CH-14), 119.6 (CH-13), 118.9 (qC-3), 118.8 (qC-9), 115.3 (CH-16),

85.7 (qC-18), 28.2 (3 × CH₃, C(19)-H₃, C(20)-H₃, C(21)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for [C₂₀H₁₉N₂O₂]⁺: 319.1441; found: 319.1439.

11-Methyl-11H-indolo[3,2-c]quinoline **U16**

U13 (0.120 g, 0.590 mmol, 1 eq.) in DMF (1.5 mL) was cooled to 0 °C and NaH (0.066 g, 1.65 mmol, 3 eq.) and was let stir for 2 hours at 0 °C. MeI (0.038 mL, 0.605 mmol, 1.1 eq.) was added and the mixture was let warm to rt and stirred for 16 hours. Water was added slowly and a yellow solid precipitated and was isolated by filtration. A recrystallisation of the solid from MeOH yielded **U16**.



Yellow solid; 92% yield (0.120 g); **m.p.** 140 – 142 °C (lit. m.p. 145 – 146 °C)^[7]; **¹H NMR (300 MHz, CDCl₃)** δ = 9.50 (s, 1H, H-2), 8.56 (dd, 1H, *J* = 1.2, 8.4 Hz, H-5), 8.29 (dd, 1H, *J* = 1.2, 8.4 Hz, H-8), 8.20 (dt, 1H, *J* = 0.9, 7.8 Hz, H-13), 7.71 (overlapping ddd, 1H, *J* = 1.4, 6.9, 8.4 Hz, H-7), 7.59 (overlapping ddd, 1H, *J* = 1.4, 6.9, 8.4 Hz, H-6), 7.52 – 7.56 (m, 2H, H-15, H-16), 7.35 – 7.42 (m, 1H, H-14), 4.31 (s, 3H, CH₃-17) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ = 146.9 (qC-10), 144.4 (CH-2), 140.5 (qC-11), 139.8 (qC-4), 130.7 (CH-8), 127.6 (CH-7), 125.6 (CH-15), 125.5 (CH-6), 121.8 (CH-5), 121.7 (qC-12), 121.1 (CH-14), 119.8 (CH-13), 118.3 (qC-9), 115.1 (qC-3), 109.4 (CH-16), 33.4 (C(17)-H₃) ppm; **HRMS** (ESI-TOF; positive mode) *m/z*: [M + H]⁺ calcd. for: [C₁₆H₁₃N₂]⁺; 233.1073; found: 233.1073.

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Take the pieces and build them skywards.

—Machines, Biffy Clyro

Chapter 4

The semi-hydrogenation and deuteration of alkynes by ligand stabilised palladium-dodecylamine and palladium-dodecanethiolate nanoparticles.

Preface

This chapter will be ready for journal submission upon full analysis of the Pd-S nanoparticles. An original batch of Pd-S nanoparticles was prepared and characterised (by TEM) by Dr Éadaoin Casey and the Materials Chemistry and Analysis Group at UCC. The original batch of catalyst was tested in alkyne reductions by me. The more recent batches of catalyst were prepared by me. The batches prepared by me showed similar selectivity to the original batch, but slightly higher reactivity. The catalyst batches prepared by me will be thoroughly analysed before submission of the journal paper. ICP was undertaken by Niraj Patil in University of Limerick. I undertook all the other experimental work, and the manuscript and SI was prepared by me except for the nanoparticle analysis and characterisation.

Abstract

The semi-hydrogenation of alkynes to selectively access alkenes is a crucial transformation across many disciplines of chemistry. Achieving high stereo- and chemoselectivity for this reaction is a huge challenge, however, which must be overcome. This work describes, for the first time, the use of palladium-dodecanethiolate nanoparticles for semi-hydrogenation of alkynes with very low catalytic loading at atmospheric pressure of hydrogen. Excellent selectivity is observed for the *Z*-alkene. 'Semi-deuteration' is also undertaken with excellent deuterium incorporation without loss of *Z*-alkene selectivity.

Introduction

Selective semi-hydrogenation of alkynes to alkenes is of key importance in the synthesis of natural products, pharmaceuticals and fine chemicals.^[1] Palladium is one of the most widely used metals for hydrogenation (using H₂) reactions.^[2] However, unmodified palladium catalysts can lead to over-reduction to alkanes and/or poor *E/Z* selectivity in the olefin product.^[3]

Traditionally, the use of Lindlar's catalyst, which consists of deactivated palladium supported on CaCO₃ or BaCO₃, along with added quinoline and lead (Pb), has been the method of choice for semi-hydrogenation of alkynes^[4]. Despite the obvious drawbacks (toxic lead^[5], other exogenous poisons^[5-6] and use of large quantities of inorganic support), Lindlar's catalyst has maintained widespread use in industry.^[7] Furthermore, owing to the varying methods of catalyst production, there are significant issues with reproducibility^[8] and batch-to-batch variability.^[9]

Several Pd catalyst design methods have been established to address some of these issues with Lindlar's catalyst. One strategy, is to form Pd nanocatalyst alloys with other metals,^[1e, 2d-f, 2n, 3, 10] and/or alloys with light elements.^[2i, 11] Another is the formation of ordered Pd nanostructures.^[12] In one particular case, Chen and co-workers installed carboxylate-thiol ligands into a palladium nanostructure for the semi-hydrogenation of dimethyl acetylenedicarboxylate (DMAD), on a graphene oxide support system.^[13] Good *Z:E* selectivity was reported, however, high catalytic loadings were used and over-hydrogenation to the alkane product was a significant issue.

Another strategy involves the formation of ligand stabilised Pd nanoparticles through coordinating atoms such as N, S, or P.^[14] The choice of the coordinating capping ligand has a decisive role in altering the chemical activity and selectivity of the catalytic process. Organic ligands can reversibly bind to the Pd surface, modify the active sites, and alter the relative adsorption strength of alkyne/alkene.^[15]

The use of thiol(ate) ligands in conjunction with both supported and unsupported palladium nanoparticles for hydrogenation reactions has been reported, and proved effective for palladium catalysts.^[11c, 16] These describe the use of sulfur or thiols to modify palladium for the hydrogenation of epoxides, furfural, alkynes, allyl alcohols and alkenes. Huang and co-workers found that a thiolate ligand additive was most efficient in facilitating selective hydrogenation when added to Lindlar and Pd/C catalysts.^[17]

Gavia *et al.* describe the use of palladium-dodecanethiolate nanoparticles to facilitate propargyl alcohol isomerisation to saturated carbonyl analogues.^[18] The catalytic activity of thiolate-covered palladium is surprising since sulfur-containing species usually act as poisons for palladium active sites.^[19]

To date there is no alkylthiol stabilised palladium nanoparticle for the semi-hydrogenation of alkynes that can be used in very low catalytic loadings while maintaining high selectivity. Herein we describe a catalytic system based on Pd nanoparticles, stabilised with amine or thiol ligands. Both catalysts proved capable in the selective partial hydrogenation of alkynes to *Z*-alkenes. The methodology addresses many of the problematic aspects of using Lindlar's catalyst. Additionally, we demonstrate that the palladium-dodecanethiolate nanoparticles can be used to introduce deuterium into the *Z*-alkene products with very high deuterium incorporation (93% D).

Results and Discussion

Optimisation of Pd-N nanoparticles

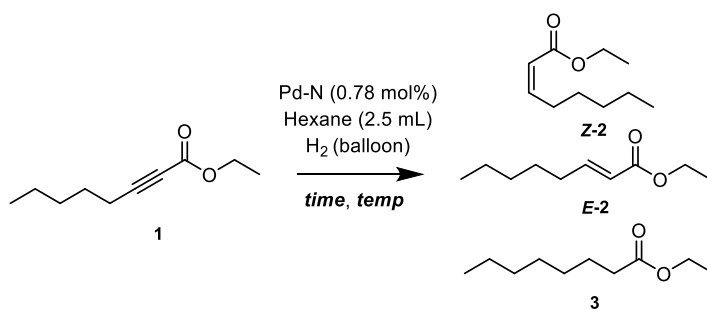
Our preliminary work began with the use of palladium-dodecylamine (Pd-N) nanoparticles (NP's) for the hydrogenation of alkynes to alkenes. The nanoparticles were synthesised as per procedure by Casey *et al* adapted from Moreno *et al*.^[16d, 20] The Pd-N NP's have a well-defined spherical shape with a mean diameter of 2.5 nm and were dispersed in toluene (**Figure 1**). We chose ethyl-2-octynoate **1** as a suitable substrate as it forms the basic structure of a number of important compounds such as quorum sensing inhibitors,^[21] fatty acid derivatives,^[22] and food/fragrance related compounds.^[23]

The general reaction set-up involved mixing the substrate, solvent, and nanoparticle mixture in a vial before addition to a Schlenk flask. The hydrogen atmosphere was introduced using a balloon. Initially, a temperature of 50 °C, over 10 minutes, resulted in some undesired *E*-isomer **E-2** and overreduction to alkane **3** (**Table 1, entry 1**). Unreacted alkyne **1** was observed over shorter reaction time at both room temperature and 0 °C (**entries 2 and 3**). These results indicate highly active nanoparticles toward hydrogenation (even at 0 °C). Optimised conditions were found by stirring at room temperature for 1.5 hours and full consumption of the alkyne **1** under atmospheric pressure of H₂ with 0.78 mol% Pd-N (**entry 4**) was achieved. Over reduction to the alkane function **3** was low at 5% and the *Z:E* selectivity of alkenes **Z-2** and **E-2** was 94:6.

Despite promising initial results, we noticed Pd aggregation was occurring after approximately 30 minutes, which coincided with decreased turnover (and selectivity).^[16c, 16d] Interestingly, spiking the reaction mixture with additional dodecylamine ligand restored Pd solubility and catalytic activity. However, selectivity was lost (see SI for details).

To help extend the lifetime of our catalyst, we turned our attention to less labile thiol-derived Pd nanoparticles,^[17, 24] specifically Pd-dodecanethiol nanoparticles (Pd-S NP's).

Table 1. Optimisation table for the semi-hydrogenation of ethyl-2-octynoate **1** using Pd-N NP's.

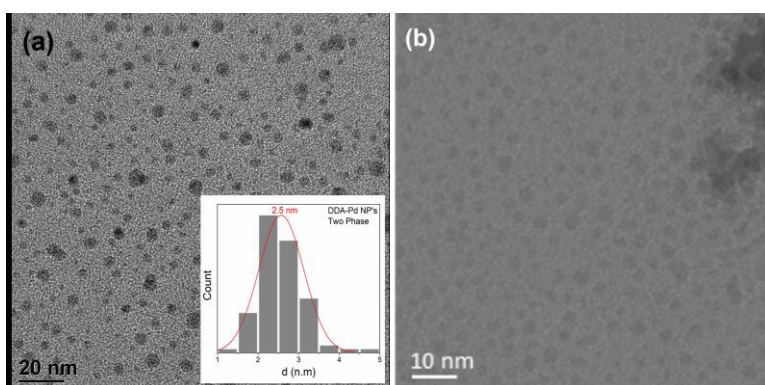


Entry	Pd-N mol%	Temp (°C)	Time (min)	Composition (%) ^[a]					Yield ^[b]
				1	Z-2	E-2	3		
1	0.78	50	10	0	68	17	15	-	
2	0.78	rt	10	11	81	4	4	-	
3	0.78	0	10	13	86	1	0	-	
4	0.78	rt	90	0	89	6	5	95%	

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis. ^[b] Isolated yield of mixture after column chromatography.

Following a method by Fornasiero and co-workers,^[25] we conveniently prepared Pd-S nanoparticles. As we await full analysis on our nanoparticles, for the purposes of this thesis, data from previously published Pd-S nanoparticles made by Casey *et al.* have been provided (**Figure 1**). Casey *et al.* found the Pd-S nanoparticles to be spherical in shape and have a mean diameter of 2.7 nm and were dispersed in THF.

Figure 1. TEM images of a) Pd-N nanoparticles with particle distribution curve and b) Pd-S nanoparticles.



Images obtained and adapted from Casey's PhD thesis.^[20]

Optimisation of Pd-S nanoparticles

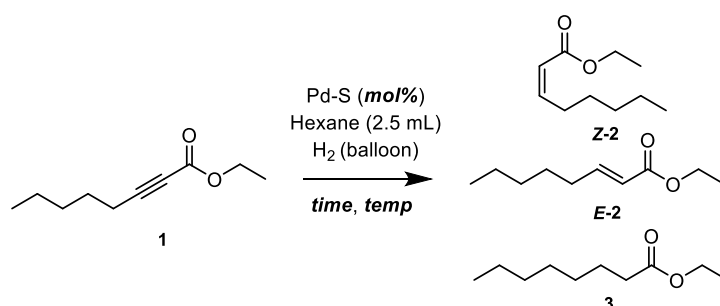
Again, we tested the Pd-S nanoparticles on ethyl-2-octynoate **1**. Our initial reaction (**Table 2, entry 1**) showed that the Pd-S catalyst was less reactive than the amine

analogue (Pd-N). However, with slight modification of the reaction conditions (increased time 0.5 to 1.5 hours), excellent chemoselectivity was observed, and only small quantities of over-reduced alkane **3** were formed, even at full consumption of alkyne **1** (**entry 2**). Further extension of the reaction time (3 hours) led to diminished selectivity (**entry 3**).

Lowering the concentration of nanoparticles showed positive effects on the selectivity of the reaction (**entries 4 and 5**). When maintaining all other reaction conditions, but reducing the temperature by 10 °C, the consumption of the alkyne **1** is dramatically reduced (**entry 6**). Selectivity for **Z-2** could be increased by lowering the reaction temperature to 40 °C and extending the reaction time to 3 hours (**entry 7**). Optimised conditions were found to be Pd-S (0.08 mol%), H₂ (balloon) at 40 °C stirring for 3 h. Using these conditions, the isomers were formed in 95:5 **Z-2**:**E-2** with just 2% alkane **3** formation, at full consumption of the alkyne **1** (**entry 7**).

The nanoparticles were prepared several times and maintained their reactivity and selectivity across each batch, addressing one of the major issues associated with Lindlar's catalyst.

Table 2. Optimisation table for the semi-hydrogenation of ethyl-2-octynoate **1** using Pd-S NP's.



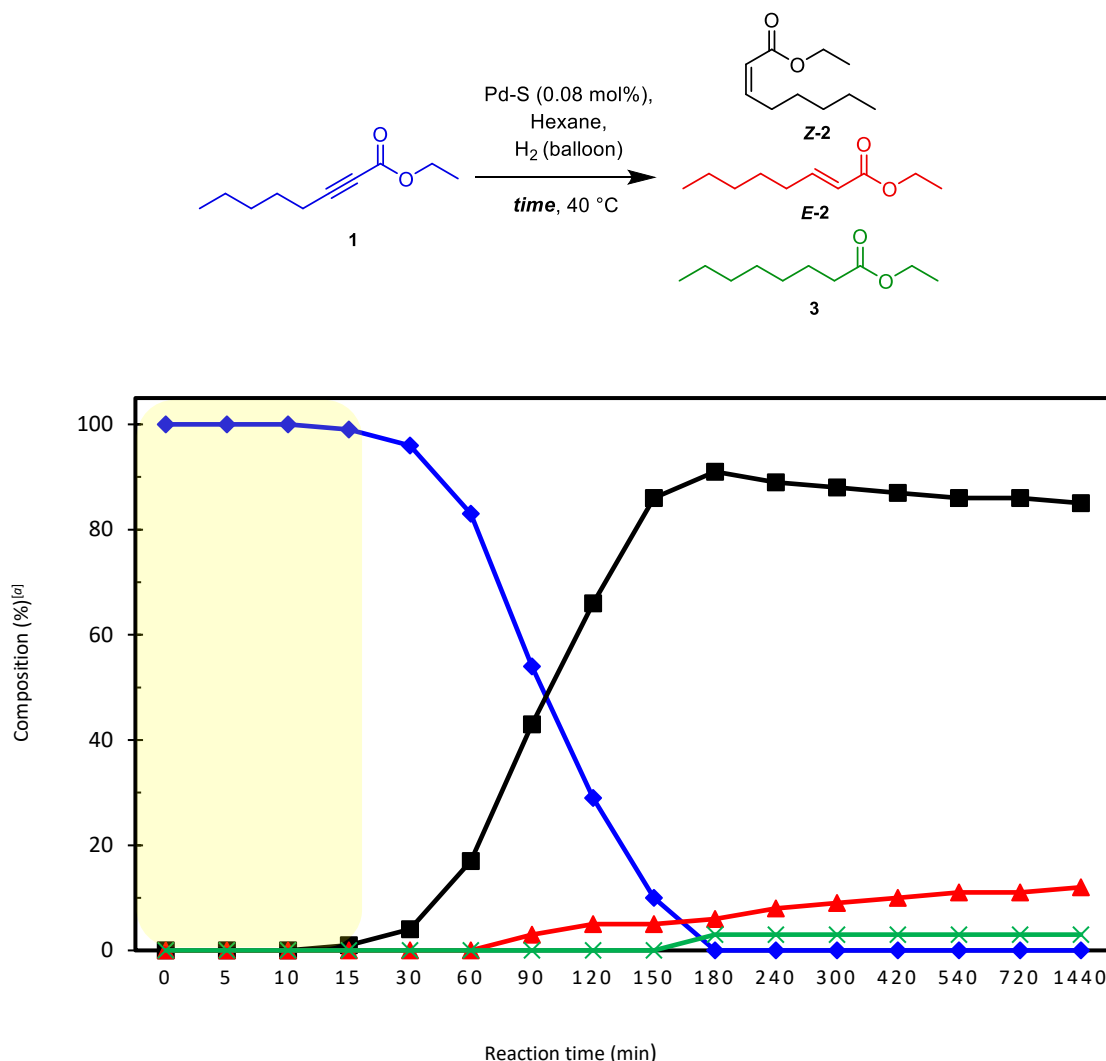
Entry	Pd-S mol%	Temp (°C)	Time (h)	Composition (%) ^[a]				Yield ^[b]
				1	Z-2	E-2	3	
1	0.16	50	0.5	63	35	2	0	-
2	0.16	50	1.5	0	91	7	2	90%
3	0.16	50	3	0	81	15	4	-
4	0.08	50	1.5	0	92	5	3	92%
5	0.08	50	3	0	89	9	2	88%
6	0.08	40	1.5	51	46	3	0	-
7	0.08	40	3	0	93	5	2	93%

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis. ^[b] Isolated yield of mixture after column chromatography.

Reaction monitoring

Monitoring of the reduction of ethyl-2-octynoate **1** with the Pd-S NP catalyst revealed an initial induction (lag) period (**Graph 1**) common with heterogeneous catalysts (often related to the time required for ligand desorption and/or rearrangement).^[26] After approximately 30 minutes, we observed a dramatic increase in the formation of hydrogenated products. Initially, strong preference for the *Z*-alkene **Z-2** is observed, although prolonged reaction times lead to some isomerisation to the more thermodynamically stable *E*-alkene **E-2**, along with some over-reduction to alkane **1**.

Graph 1. Concentration of products over time for the hydrogenation of ethyl-2-octynoate **1** using Pd-S NP's.



^[a] The composition of the reaction mixture was determined by ¹H NMR analysis. Useful time markers: 180 min = 3 hours, 420 min = 7 hours, 1440 min = 24 hours. (◆) ethyl-2-octynoate **1**, (■) Z-ethyl-2-octenoate **Z-2**, (▲) E-ethyl-2-octenoate **E-2**, (X) ethyl octanoate **3**. The yellow box indicates the initial induction time captured by reaction monitoring.

There is a steady consumption of alkyne **1** between 30 and 150 minutes which corresponds to almost total *Z*-isomer **Z-2** formation. At 180 min (3 hours), we see slow formation of the *E*-isomer **E-2**. Alkane **3** formation is observed at 3 hours and is maintained at approximately 3% until completion of monitoring (at 24 hours).

Noting the apparent *Z* to *E* conversion over time, we could completely switch selectivity for the *E*-olefin (**Z-2:E-2**, 19:81) using increased Pd loading (0.64 mol%). Interestingly, at this level of Pd loading, there is no induction period observed (see SI for details).

Deuteration using *ex situ* D₂ formation

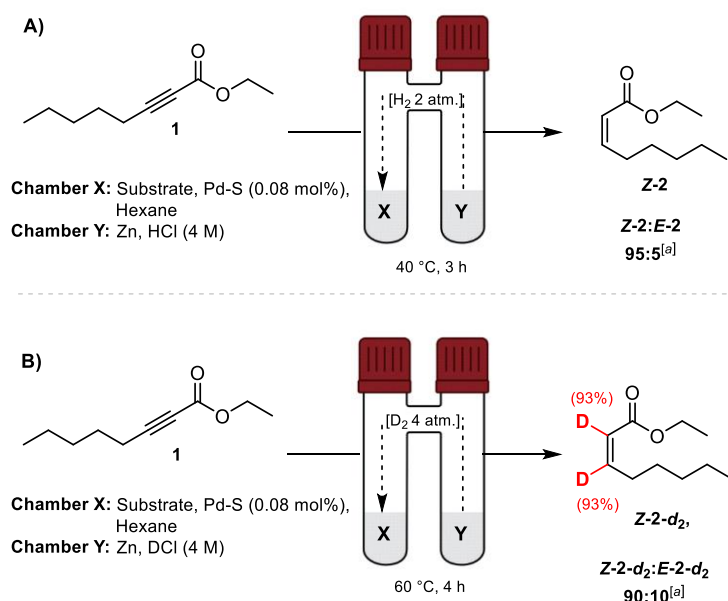
Deuterated compounds have been extensively used for many different applications including mechanism elucidation (kinetic isotope effect), pharmacokinetic studies and metabolic stability enhancement.^[27] More recently, deuterium containing drugs have been approved by the FDA as new active pharmaceutical ingredients in medicines.^[28]

The widespread use of H₂ in reductions, could, in theory, be conveniently mirrored by the use of D₂. However, issues and cost associated with tanked D₂ gas almost completely negate its use. Recently, however, the use of Skrudstry's COware apparatus^[29] has been shown to allow the introduction of deuterium conveniently through the generation of D₂ gas *ex situ*.^[30] We envisaged that the introduction of deuterium into newly formed olefins would be of tremendous use in the formation of labelled olefins.

Firstly, we optimised addition of H₂ to alkyne **1** using the COware apparatus (using DCI and Zn). We achieved a ratio of alkenes **Z-2** and **E-2** of *Z:E* 95:5 with small amounts of unreacted alkyne **1** and alkane **3** remaining (**Scheme 1** and SI for more details). An increased (theoretical) pressure appeared to be required for the deuterium analogue, but nevertheless, and pleasingly, an excellent level (93%) of deuterium was incorporated into the *Z*-olefin (with a *Z:E* ratio of 90:10).

This is clearly a highly efficient methodology for deuteration of alkynes and a rare case of deuterium incorporation into olefins in this manner. For reference, one study undertaken by Lu and co-workers used tanked D₂ gas over a Pd-nanopore structure in the partial reduction of an alkyne. They obtained a 1:1 ratio of H:D in their product olefin.^[31]

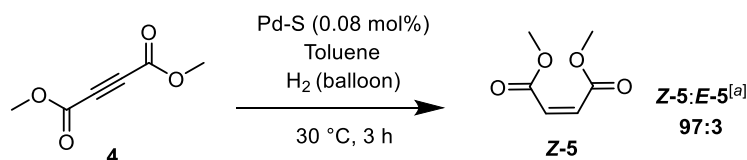
Scheme 1. A) Hydrogenation and B) Deuteration of ethyl-2-octynoate **1 using COWare apparatus.**



^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

Finally, we chose to extend the methodology to dimethyl acetylenedicarboxylate (DMAD, **4**). The *Z*-isomer of DMAD (dimethyl maleate, **Z-5**) is used as a key pharmaceutical, agricultural and materials intermediate.^[32] We found that that this substrate also displayed very good selectivity with 97:3 **Z-5:E-5** ratio (with 6% alkane **6**).

Scheme 2. Semi-hydrogenation of DMAD **4 with Pd-S NP's.**



^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

Conclusion

This work demonstrates the effective *Z*-selective alkyne reduction using dodecanehtiolate supported palladium nanoparticles. The nanoparticles display a number of advantages over Lindlar's catalyst and do not require an inorganic support or poisons (Pb). They are easily prepared and consistent batch-to-batch. Over-reduction to the alkane is minimal and excellent *Z*:*E* selectivity is observed. Excellent deuterium incorporation to produce valuable labelled olefins is demonstrated with minimal overreduction to the alkyne, even at increased pressure.

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Supplementary Information for Chapter 4:

The semi-hydrogenation and deuteration of alkynes by ligand stabilised palladium-dodecylamine and palladium-dodecanethiolate nanoparticles

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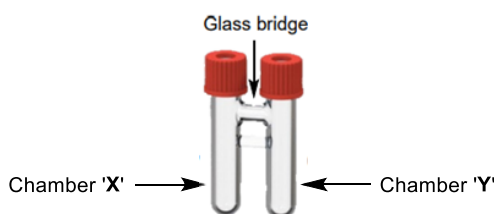
General Considerations

Solvents and reagents were used as obtained from suppliers and without further purification unless otherwise stated.

Column chromatography was carried out using 60 Å (35–70 µm) silica. NMR spectra were run in CDCl₃ using TMS as the internal standard at 25 °C. ¹H NMR (300 MHz) were recorded on a Bruker Avance 300 NMR spectrometer. Chemical shifts (δ) are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz). Splitting patterns in ¹H NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), ddt (doublet of doublet of triplets), t (triplet), q (quartet), m (multiplet). All spectroscopic data for known compounds was in agreement with those previously reported unless otherwise stated.

The COware apparatus was purchased from Sigma Aldrich and the hydrogen pressure was estimated using the $PV = nRT$ formula. It is worth noting that a 20 mL COware apparatus was used for these experiments. The COware apparatus has two chambers that are connected by a glass bridge, allowing for *ex situ* gas to be generated in one chamber which can then interact with the reaction mixture in the second chamber. Warning: pressurised reaction vessel (**Figure 1SI**). These can be annotated as chamber 'X' and chamber 'Y'.

Figure 1SI. COware apparatus and set-up.



Assignment of Ratios:

Synthesis of Pd-N Nanoparticles^[1]

As per Casey's PhD thesis.^[1]

Synthesis of Pd-S Nanoparticles^[2]

To K₂PdCl₄ (20 mg, 0.06 mmol) dissolved in water (2 mL), was added THF (11 mL) followed by dodecanethiol (6.0 mg, 0.03 mmol) in THF (1 mL) and was stirred at room temperature for 5 minutes. An aqueous solution (1 mL) of NaBH₄ (23.2 mg, 0.6 mmol) was added dropwise over 30 seconds resulting in a black suspension and was stirred for

a further 5 minutes at room temperature. The reaction mixture was added to a centrifuge vial and washed with water (16 mL × 3), MeOH (16 mL × 3) and acetone (16 mL × 3) at 3000 rpm with sonication between each wash. The nanoparticle pellet was solubilised in THF and transferred to a round bottom flask and the solvent removed *in vacuo* and placed on a high vacuum line for 16 hours. The resulting dried nanoparticles were weighed and then redistributed in THF (10 mL) and sonicated for 10 minutes to yield a black solution.

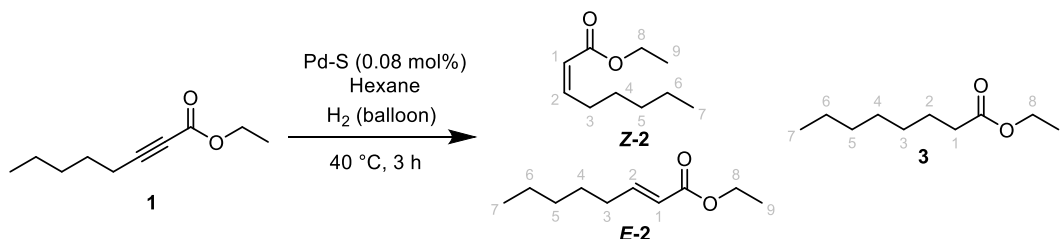
General Procedure 1: Semi-Hydrogenation of Alkynes

To a Schlenk flask was added alkyne (0.5 mmol), Pd-S (0.1 mL, 0.08 mol%)/Pd-N (0.1 mL, 0.78 mol%) and hexane (2.5 mL). The flask was evacuated and refilled three times with hydrogen gas from a balloon, shook gently and then stirred vigorously for the designated time and temperature. The reaction mixture was filtered through a PTFE 2 µm filter and transferred to a round bottom flask and the solvent removed *in vacuo* to leave the crude reaction mixture. Selected mixtures were purified by column chromatography on silica gel and weighed to obtain a yield.

Compound Characterisation

Ethyl-2-octynoate

From ethyl-2-octynoate **1** (0.085 g, 0.5 mmol), Pd-S NP's (0.1 mL, 0.08 mol%) in hexane (2.5 mL) and stirred for 3 hours at 40 °C as per general procedure 1.



¹H NMR (300 MHz, CDCl₃) of crude reaction mixture of semi-hydrogenation products:

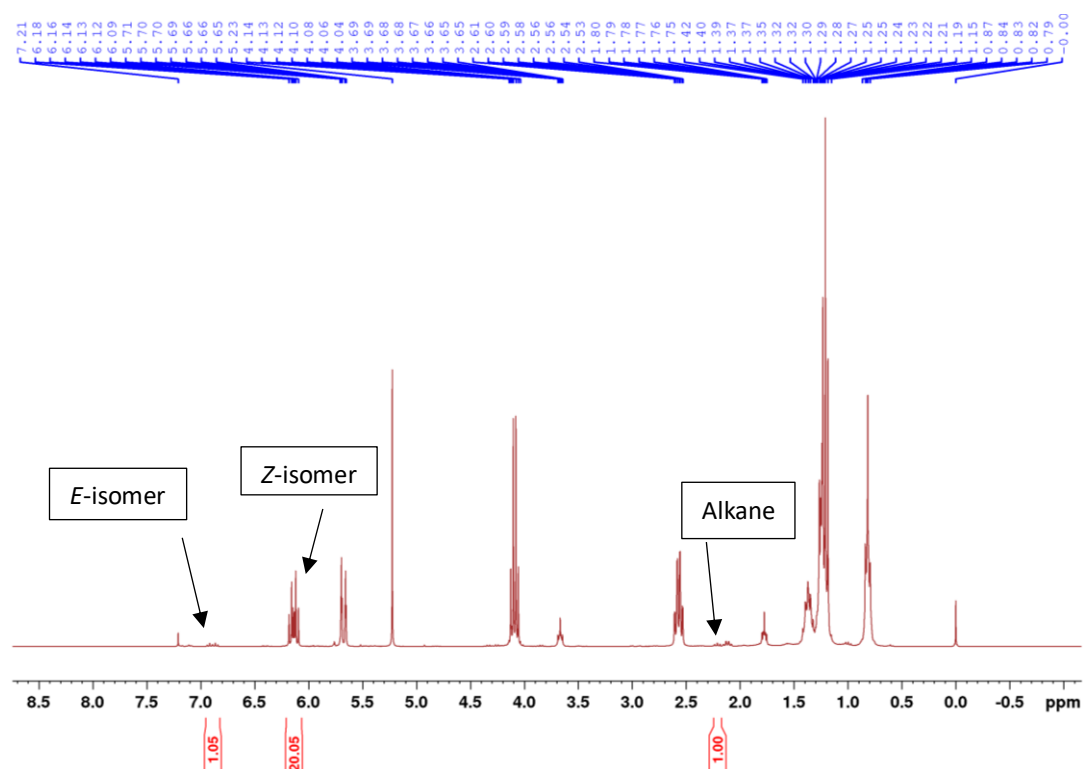
Assigned to (See **Figure 2SI**):

Z-Ethyl-2-octenoate (**Z-2**): δ = 6.13 (dt, 1H, J = 7.5, 11.5 Hz, H-**2**), 5.67 (dt, 1H, J = 1.7, 11.5 Hz, H-**1**), 4.08 (q, 2H, J = 7.1 Hz, overlapping with *E*-isomer and alkane, H₂-**8**), 2.57 (dq, 2H, J = 1.7, 7.4 Hz, H₂-**3**), 1.45 – 1.31 (m, overlapping with *E*-isomer, 3H, H₃-**9**), 1.20 (t, 6H, J = 7.1 Hz, H₂-**4**, H₂-**5**, H₂-**6**), 0.86 – 0.78 (m, overlapping with *E*-isomer, 3H, H₃-**7**) ppm.

E-Ethyl-2-octenoate (**E-2**): δ = 6.88 (dt, 1H, J = 7.0, 15.6 Hz, H-**2**), 5.73 (dt, 1H, J = 1.5, 15.6 Hz, H-**1**), 4.08 (q, 2H, J = 7.2 Hz, overlapping with *Z*-isomer and alkane, H₂-**8**), 2.11 (dq, 2H, J = 1.6, 7.1 Hz, H₂-**3**), 1.31 – 1.45 (m, overlapping with *Z*-isomer, 3H, H₃-**9**), 1.60 – 1.28 (m, overlapping with *Z*-isomer, 6H, H₂-**4**, H₂-**5**, H₂-**6**), 0.86 – 0.78 (m, overlapping with *Z*-isomer, 3H, H₃-**7**) ppm.

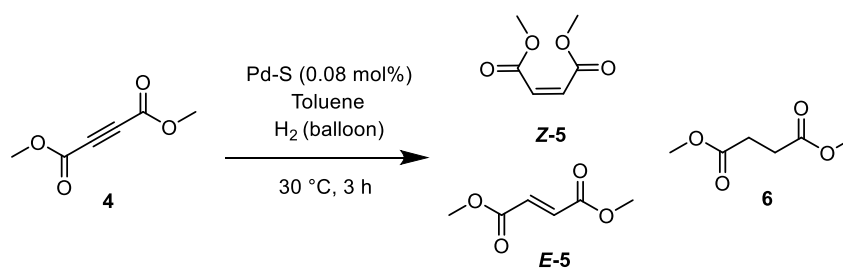
Ethyl octanoate (**3**): δ = 4.14–4.00 (m, overlapping with *Z*- and *E*-isomers, 2H, H₂-**8**), 2.21 (t, 2H, J = 7.7 Hz, H₂-**1**), 1.60 – 1.50 (m, 2H, H₂-**2**), 1.27 – 1.15 (m, 11H, H₂-**4**, H₂-**5**, H₂-**6**, H₃-**9**), 0.86 – 0.76 (m, 3H, H₃-**7**) ppm.

Figure 2SI. Representative example of ^1H NMR analysis of semi-hydrogenation products of ethyl-2-octynoate **1**. ^1H NMR 300 MHz, CDCl_3 .



Dimethyl acetylenedicarboxylate (DMAD, **4)**

From dimethyl acetylenedicarboxylate **4** (0.071 g, 0.5 mmol), Pd-S (0.1 mL, 0.08 mol%) in toluene (2.5 mL) and stirred for 3 hours at 30 °C as per general procedure 1.



^1H NMR (300 MHz, CDCl_3) of crude reaction mixture of semi-hydrogenation products:

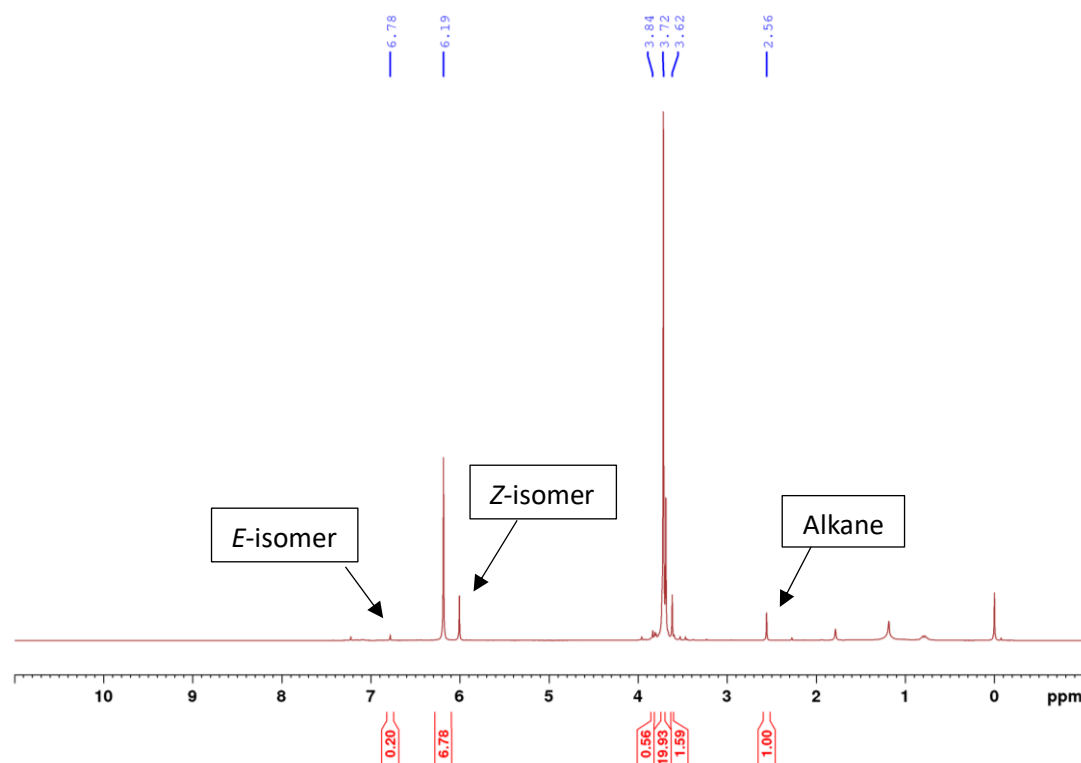
Assigned to (See **Figure 3SI**):

Z-Dimethyl maleate (**Z-5**): δ = 6.19 (s, 2H, 2 $\times$ alkene CH), 3.72 (s, 6H, 2 $\times$ CH_3) ppm.

E-Dimethyl fumarate (**E-5**): δ = 6.78 (s, 2H, 2 $\times$ alkene CH), 3.84 (s, 6H, 2 $\times$ CH_3) ppm.

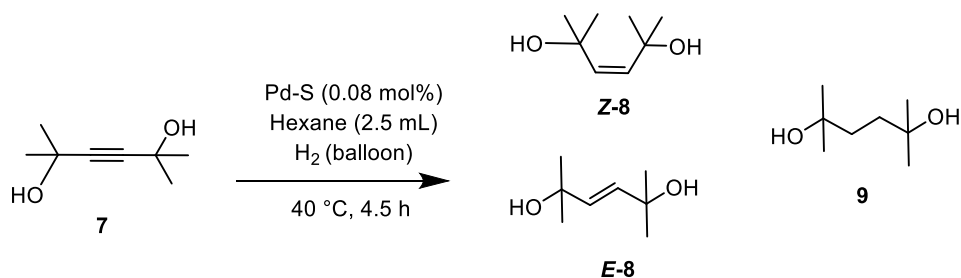
Dimethyl succinate (**6**) δ = 3.62 (s, 6H, 2 $\times$ CH_3), 2.56 (s, 4H, 2 $\times$ CH_2) ppm.

Figure 3SI. Representative example of ^1H NMR analysis of the semi-hydrogenation products of DMAD **4**. 1,3,5-trimethoxybenzene present as internal standard (6.08 ppm and 3.88 ppm). ^1H NMR 300 MHz, CDCl_3 .



2,5-Dimethyl-3-hexyne-2,5-diol **7**

From 2,5-dimethyl-3-hexyne-2,5-diol **7** (0.071 g, 0.5 mmol), Pd-S NP's (0.1 mL, 0.08 mol%) in hexane (2.5 mL) and stirred for 4.5 hours at 40 °C as per general procedure 1.



^1H NMR (300 MHz, CDCl_3) of crude reaction mixture of semi-hydrogenation products:

Assigned to (See **Figure 4SI**):

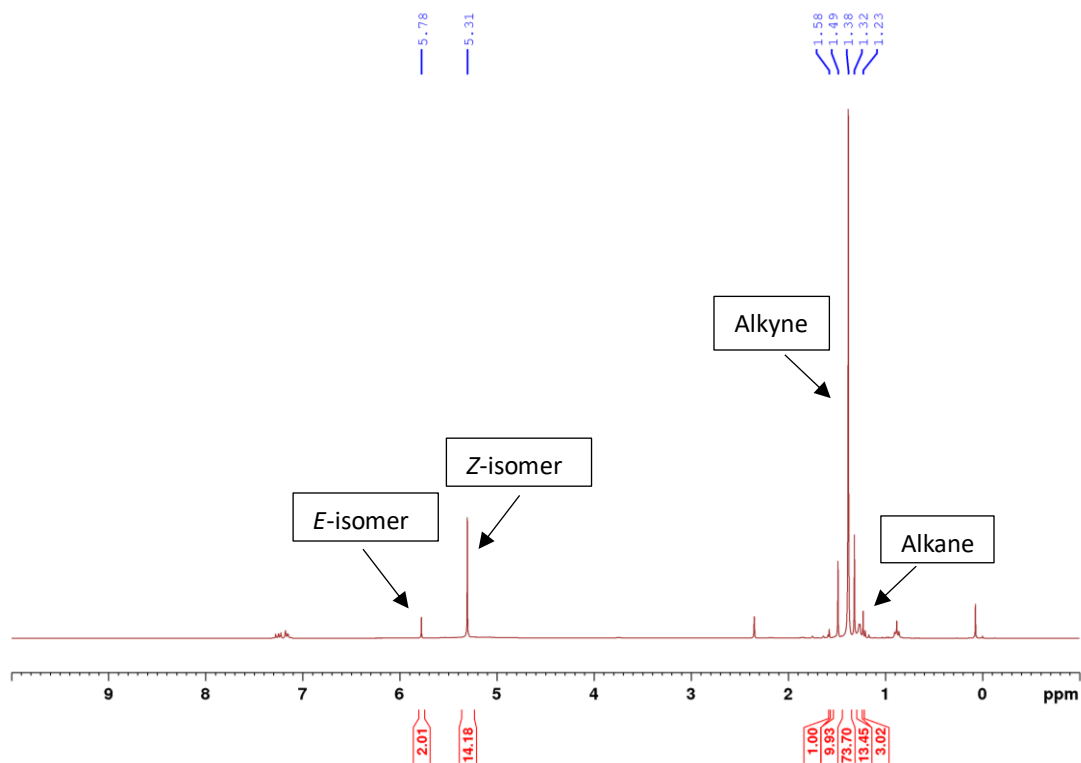
2,5-Dimethyl-3-hexyne-2,5-diol (**7**): $\delta = 1.49$ (s, 12H, 4 $\times$ CH_3) ppm.

Z-2,5-Dimethyl-3-hexene-2,5-diol (**Z-8**): $\delta = 5.31$ (s, 2H, 2 $\times$ alkene CH), 1.38 (s, 12H, 4 $\times$ CH_3) ppm.

E-2,5-Dimethyl-3-hexene-2,5-diol (**E-8**): $\delta = 5.78$ (s, 2H, 2 $\times$ alkene CH), 1.32 (s, 12H, 4 $\times$ CH_3) ppm.

2,5-Dimethylhexane-2,5-diol (**9**): $\delta = 1.58$ (s, 4H), 1.23 (s, 12H) ppm.

Figure 4SI. Representative example of ^1H NMR analysis of the semi-hydrogenation products of 2,5-dimethyl-3-hexyne-2,5-diol **7**. ^1H NMR 300 MHz, CDCl_3 .



Monitoring Reactions (see main manuscript - Graph 1 and SI - Graph 1SI)

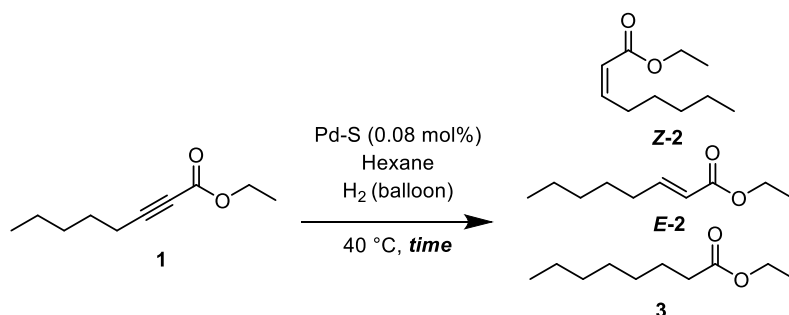
General Procedure 2: Reaction Monitoring Experiment

To a Schlenk flask was added ethyl-2-octynoate **1** (1 mmol), Pd-S NP's (0.2 mL, 0.08 mol% / 1.6 mL, 0.64 mol%) and hexane (5 mL). The flask was evacuated and refilled three times with hydrogen gas from a balloon, shook gently and then stirred vigorously at 40 °C. Samples of the reaction mixture were removed *via* syringe periodically (see Tables 1SI and 2SI) and analysed by ¹H NMR. Separate control experiments were set up and analysed by ¹H NMR at 3 hours, 12 hours, and 24 hours for each reaction.

Ethyl-2-octynoate by Pd-S NP's (0.08 mol%)

As per general procedure 2 for Pd-S (0.08 mol%).

Table 1SI: Ratio assignments of alkyne **1**, Z-alkene **Z-2**, E-alkene **E-2** and alkane **3** for the reaction monitoring of ethyl-2-octynoate **1** for 24 hours at 0.08 mol% Pd-S NP's.



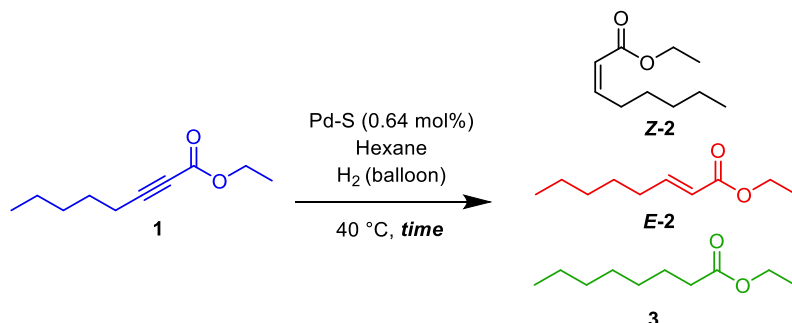
Time min (h)	Composition (%) ^[a]			
	1	Z-2	E-2	3
0	100	0	0	0
5	100	0	0	0
10	100	0	0	0
15	99	1	0	0
30	96	4	0	0
60 (1)	83	17	0	0
90	54	43	3	0
120 (2)	29	66	5	0
150	10	86	5	0
180 (3)	0	91	6	3
Control at 180 (3)	0	93	5	2
240 (4)	0	89	8	3
300 (5)	0	88	9	3
420 (7)	0	87	10	3
540 (9)	0	86	11	3
720 (12)	0	86	11	3
Control at 720 (12)	0	90	7	3
1440 (24)	0	85	12	3
Control at 1440 (24)	0	91	6	3

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

Ethyl-2-octynoate by Pd-S NP's (0.64 mol%)

As per general procedure 2 for Pd-S (0.64 mol%).

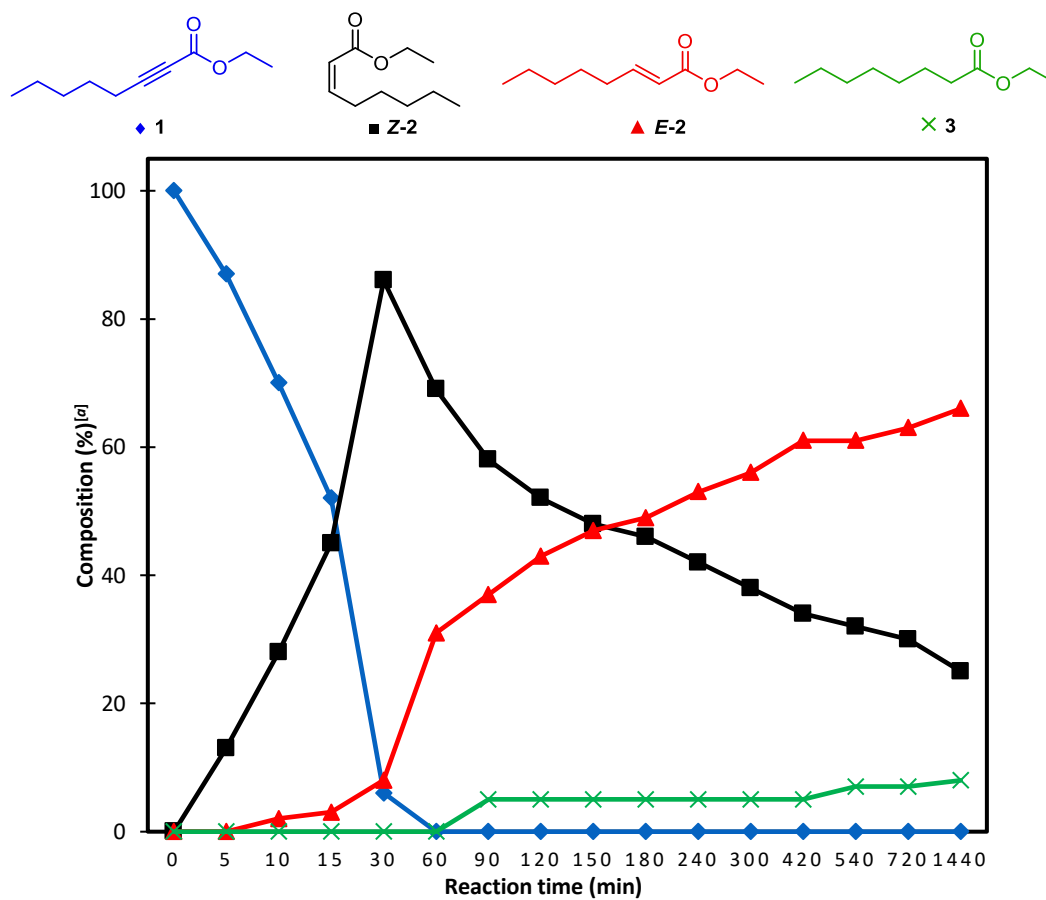
Table 2SI: Ratio assignments of alkyne **1**, Z-alkene **Z-2**, E-alkene **E-2** and alkane **3** for the reaction monitoring of ethyl-2-octynoate **1** for 24 hours at 0.64 mol% Pd-S NP's.



Time min (h)	Composition (%)			
	1	Z-2	E-2	3
0	100	0	0	0
5	87	13	0	0
10	70	28	2	0
15	52	45	3	0
30	6	86	8	0
60 (1)	0	69	31	0
90	0	58	37	5
120 (2)	0	52	43	5
150	0	48	47	5
180 (3)	0	46	49	5
Control at 180 (3)	0	48	47	5
240 (4)	0	42	53	5
300 (5)	0	38	56	5
420 (7)	0	34	61	5
540 (9)	0	32	61	7
720 (12)	0	30	63	7
Control at 720 (12)	0	28	66	6
1440 (24)	0	25	66	8
Control at 1440 (24)	0	17	73	10

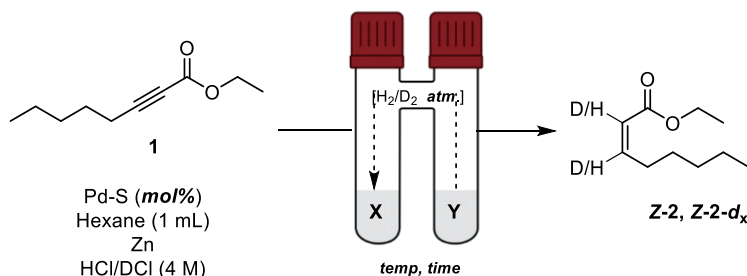
^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

Graph 1SI: Concentration of products over time for the semi-hydrogenation of ethyl-2-octynoate **1** using Pd-S NP's 0.64 mol%.



^[a] The reaction was monitored by periodic sampling and ¹H NMR analysis. (♦) ethyl-2-octynoate **1**, (■) Z-ethyl-2-octenoate **Z-2**, (▲) E-ethyl-2-octenoate **E-2**, (×) ethyl octanoate **3**.

Semi-Hydrogenation/Deuteration Using the COware Apparatus^[3]

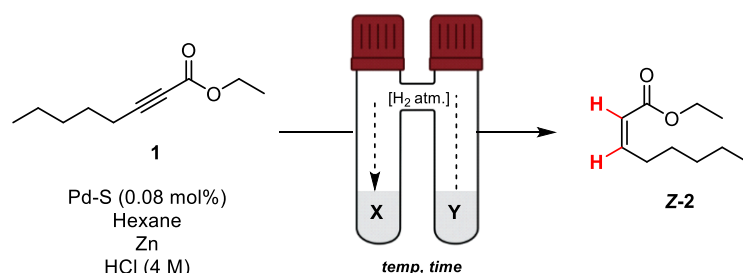


General Procedure 3: For gas pressure of 2 atm.: To the reaction chamber (labelled **X**) of the COware apparatus was added ethyl-2-octynoate **1** (0.085 g, 0.5 mmol), Pd-S NP's (0.1 mL, 0.08 mol%) and hexane (1 mL). To the generation chamber (labelled **Y**) was added Zn powder (0.049 g, 0.75 mmol) and both chambers were sealed with the septa and caps. HCl (for hydrogenation, 4 M, 0.38 mL, 1.5 mmol) or DCI (for deuteration, 4 M, 0.38 mL, 1.5 mmol) was added *via* syringe through the septum into the generation chamber **Y**, initiating the production of gas. The reaction mixture was stirred at the desired temperature for the designated time. Then the contents of the reaction chamber were filtered through a PTFE 2 µm filter and transferred to a round bottom flask and the solvent removed *in vacuo* to leave the crude reaction mixture. Quantities of Zn and HCl/DCI were adapted as per desired gas pressure.

Optimisation Data for Semi-Hydrogenation Using COware for Hydrogen Incorporation

As per general procedure 3 for hydrogenation.

Table 3SI: Optimisation table for the hydrogenation of ethyl-2-octynoate **1** using COware apparatus. (See main manuscript)



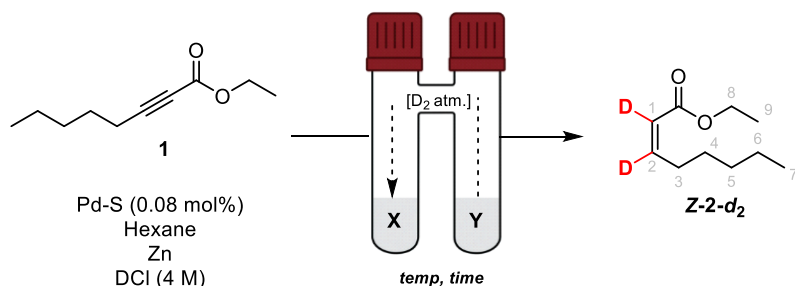
Entry	Pd-S (mol%)	Atm.	Equiv. H ₂	Temp (°C)	Time (h)	Composition (%) ^[a]			
						1	Z-2	E-2	3
1	0.08	2	3.1	40	2	61	37	2	0
2	0.08	2	3.1	40	3	1.5	92	5	1.5

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

Optimisation Data for Semi-Hydrogenation Using COware for Deuterium Incorporation

As per general procedure 3 for deuteration.

Table 4SI. Optimisation table for the deuteration of ethyl-2-octynoate **1** using COware apparatus. (See main manuscript)



Entry	Pd-S (mol%)	Atm.	Equiv. D ₂	Temp (°C)	Time (h)	Composition (%) ^[a]			
						1	Z-2-d₂	E-2-d₂	3-d₄
1	0.08	3	4.7	40	3	61	39	trace	0
2	0.08	4	6.2	40	3	82	18	trace	0
3	0.16	4	5.9	60	3	0	65	31	4
4	0.08	4	5.9	60	3	17	77	6	0
5	0.08	4	5.9	60	4	0	90	10	trace
6	0.08	2.6	3.8	60	4	20	75	5	0

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

¹H and ²H NMR Spectra for Deuterated Ethyl-2-octenoate **1**

¹H NMR Analysis (300 MHz, CDCl₃, see **Figure 5SI**):

Z-Ethyl-2-octenoate-d_x (**Z-2-d_x**): δ = 6.20 – 6.15 (m, depreciated signal, H-**2**), 5.76 – 5.73 (m, depreciated signal, H-**1**), 4.14 (q, 2H, *J* = 7.1 Hz, overlapping with *E*-isomer, H₂-**8**), 2.64 (t, 2H, *J* = 7.7 Hz, H₂-**3**), 1.50 – 1.21 (m, overlapping with *E*-isomer, 9H, H₂-**4**, H₂-**5**, H₂-**5**, H₃-**9**), 0.93 – 0.83 (m, overlapping with *E*-isomer, 3H, H₃-**7**) ppm.

E-Ethyl-2-octenoate-d_x (**E-2-d_x**): δ = 7.00 – 6.90 (m, 1H, H-**2**), 5.82 – 5.79 (m, 1H, H-**1**), 4.14 (q, 2H, *J* = 7.1 Hz, overlapping with *Z*-isomer, H₂-**8**), 2.18 (t, 2H, *J* = 7.1 Hz, H₂-**3**), 1.51 – 1.21 (m, overlapping with *Z*-isomer, 9H, H₂-**4**, H₂-**5**, H₂-**5**, H₃-**9**), 0.93 – 0.83 (m, overlapping with *Z*-isomer, 3H, H₃-**7**) ppm.

^2H NMR Analysis (500 MHz, $\text{CDCl}_3/\text{CHCl}_3$, see **Figure 6SI**):

Z-Ethyl-2-octenoate- d_2 (**Z-2- d_2**): δ = 6.23 (br s, 1D, D-2), 5.76 (br s, 1D, overlapping with *E*-isomer, D-1) ppm.

E-Ethyl-2-octenoate- d_2 (**E-2- d_2**): δ = 6.97 (br s, 1D, D-2), 5.76 (br s, 1D, overlapping with *Z*-isomer, D-1) ppm.

Ethyl octanoate- d_4 (**3- d_4**): δ = 2.23 (br s, 2D, D-1), 1.55 (br s, 2D, D-2) ppm.

Figure 5SI. ^1H NMR spectrum of deuterated ethyl-2-octenoate. ^1H NMR 300 MHz, CDCl_3 .

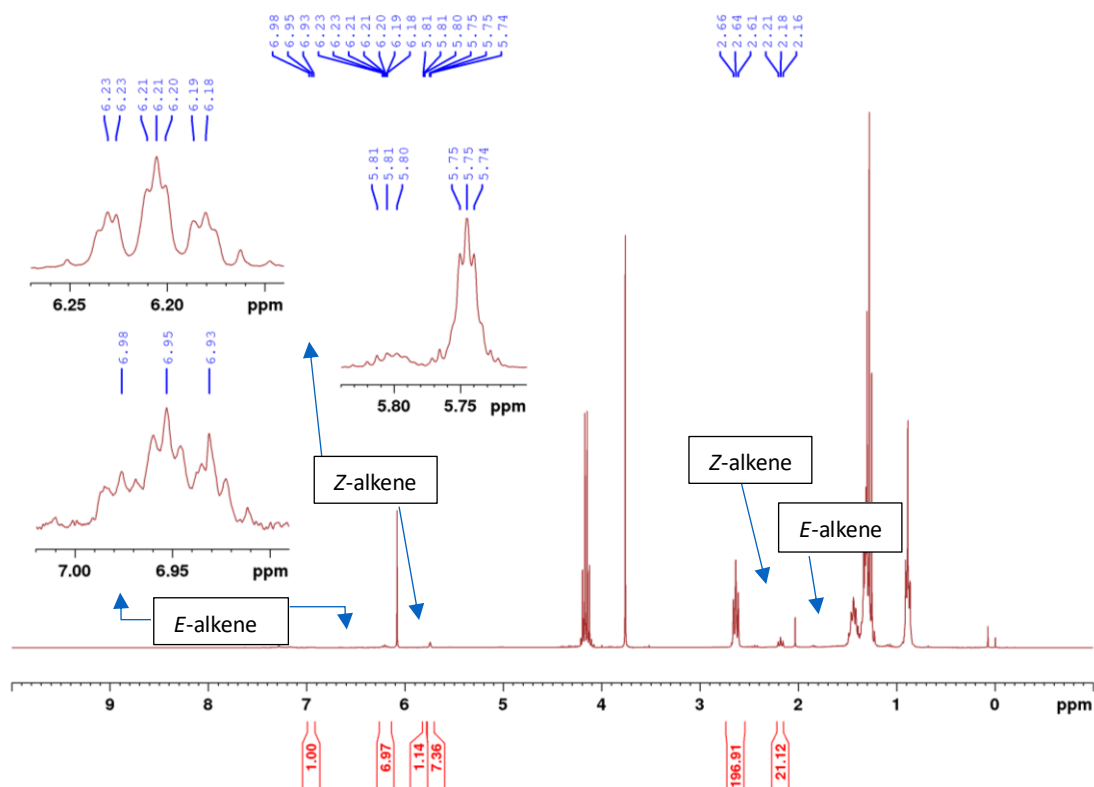
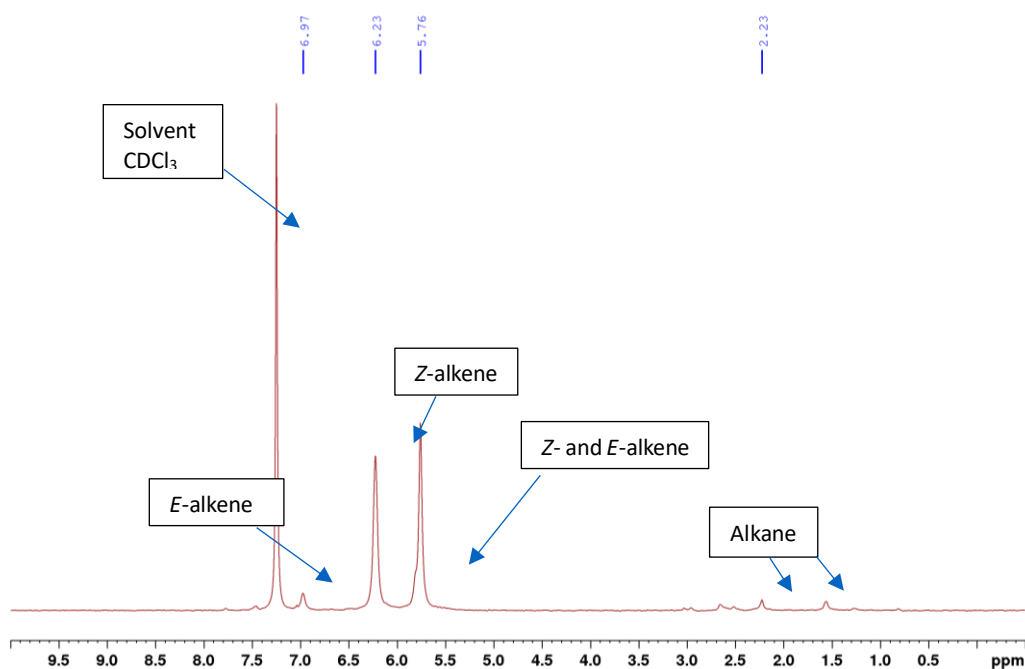


Figure 6S1. ^2H NMR spectrum of deuterated ethyl-2-octenoate. ^2H NMR 500 MHz, $\text{CHCl}_3 + \text{CDCl}_3$.



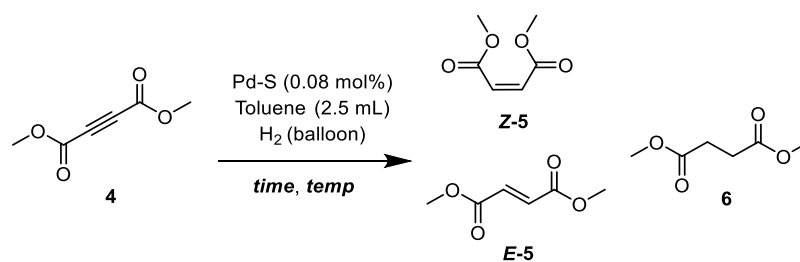
Calculation for Percentage Deuterium Incorporation

Percentage deuterium incorporation was calculated from the deuterated Z-alkene signal at 6.21 ppm and non-deuterated alkyl Z-alkene signal at 2.64 ppm. The relative ratios of these peaks are 1.00:14.13. The sum of these integrals is 15.13. Therefore, the total amount of deuterium in the alkene is 14.13 divided by 15.13 which is 93%.

Optimisation of DMAD and 2,5-Dimethyl-3-hexyne-2,5-diol

Semi-Hydrogenation of DMAD 4

From DMAD **4** (0.071 g, 0.5 mmol), in toluene (2.5 mL), Pd-S (0.1 mL, 0.08 mol%) as per general procedure 1.

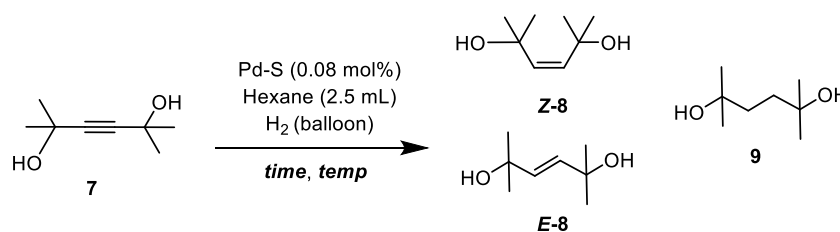
Table 5SI. Optimisation data for the semi-hydrogenation of DMAD **4**.

Entry	Pd-S (mol%)	Temp (°C)	Time (h)	Composition (%) ^[a]			
				4	Z-5	E-5	6
1	0.08	40	1.5	5	88	4	3
2	0.08	40	2	0	84	5	11
3	0.08	40	2.5	0	83	6	11
4	0.08	30	2.5	0	91	3	6
5	0.08	30	3	0	85	6	9

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

Semi-Hydrogenation of 2,5-Dimethyl-3-hexyne-2,5-diol 7

From 2,5-dimethyl-3-hexyne-2,5-diol **7** (0.071 g, 0.5 mmol), in hexane (2.5 mL), Pd-S (0.1 mL, 0.08 mol%) as per general procedure 1.

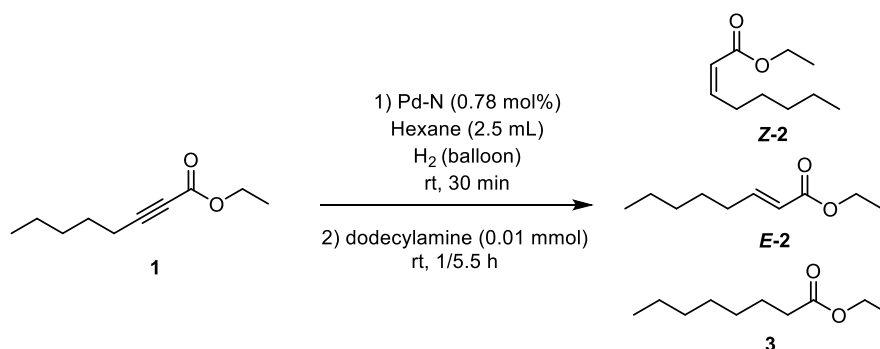
Table 6SI. Optimisation data for the semi-hydrogenation of 2,5-dimethyl-3-hexyne-2,5-diol **7**.

Entry	Pd-S (mol%)	Temp (°C)	Time (h)	Composition (%) ^[a]			
				7	Z-8	E-8	9
1	0.08	40	2.5	62	34	3	0
2	0.08	40	2.5	40	53	7	0
3	0.08	40	4.5	10	75	14	1
4	1.32	40	4.5	33	50	11	6

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

Procedure for Spiking Reaction Mixture with Dodecylamine After Aggregation (See Pd-N NP optimisation in main manuscript)

Table 7SI. Results from resuspension of catalyst upon addition of additional dodecylamine ligand to aggregated catalyst.



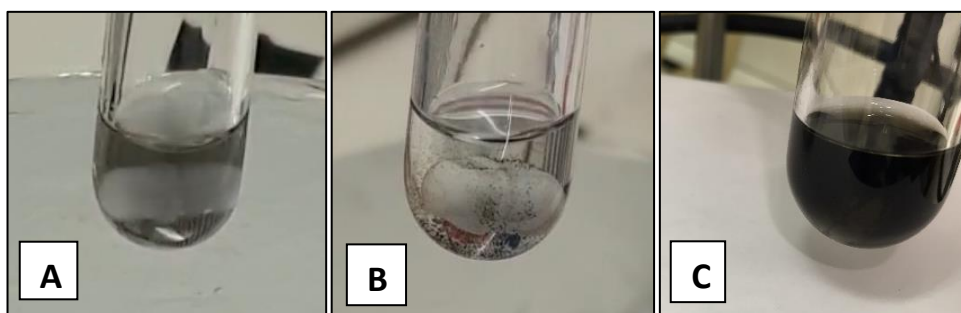
Entry	Dodecylamine (0.01 mmol)	Total Duration (h)	Composition (%) ^[a]			
			1	Z-2	E-2	3
1	Yes	1.5	0	50	15	35
2	No	1.5	0	89	6	5
3	Yes	6	0	9	12	79
4	No	6	0	88	6	6

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

To a Schlenk flask was added ethyl-2-octynoate **1** (0.5 mmol), Pd-N (0.1 mL, 0.78 mol%) and hexane (2.5 mL). The flask was evacuated and refilled three times with hydrogen gas from a balloon, shook gently and then stirred vigorously for 30 minutes at room temperature. An aliquot of dodecylamine (0.01 mmol) in toluene (1 mL) was added to the reaction mixture and stirred at room temperature for a further 1 hour/ 5.5 hours. The reaction mixture was filtered through a PTFE 2 µm filter and transferred to a round bottom flask and the solvent removed *in vacuo* to leave the crude reaction mixture.

The longer reaction time was to exaggerate any effect the spiking may have on the reaction mixture. It appears that hydrogenation activity is restored, however it was unselective with 79% of the mixture being alkane **3** (Table 7SI, entry 3 and Figure 7SI).

Figure 7SI. Images of catalyst aggregation and resuspension.



A) Pd-N catalyst before reaction initiation **B)** aggregated catalyst, **C)** Resuspended catalyst upon addition of dodecylamine ligand to aggregated catalyst.

Materials Analysis:

All analysis for Pd-N and Pd-S nanoparticles are as per Casey's PhD thesis unless otherwise stated.^[1] ICP analysis for Pd-S was undertaken in the University of Limerick and it was found that our Pd-S nanoparticles had 31% Pd content.

Mol% Calculation Pd-S NP's

Total weight of nanoparticles synthesised (dried): 13.2 mg

Dissolved catalyst: 13.2 mg dissolved in 10 mL THF solvent

Dissolved catalyst: 0.132 mg in 0.1 mL used in reaction

mmol substrate: 0.5 mmol

Pd content as per ICP data: 31% constitution

Atomic weight Pd: 106.42 g/mol

Calculation:

mg to g: $0.132 \text{ mg} \div 1000 = 0.000132 \text{ g Pd in } 0.1 \text{ mL}$

% g Pd: $0.000132 \times 0.31 = 0.000041 \text{ g}$

Mol Pd: $0.000041 \text{ g} \div 106.42 = 3.85 \times 10^{-7} \text{ mol}$

mmol Pd: $3.85 \times 10^{-7} \text{ mol} \times 1000 = 0.00038 \text{ mmol}$

Mol% catalyst = (moles of catalyst $\times$ 100) $\div$ (moles of catalyst + mole of limiting reagent)

Mol% catalyst = $(0.00038 \times 100) \div (0.00038 + 0.5)$

Mol% catalyst = 0.08 mol% Pd in 0.1 mL catalyst.

Note Since Initial Submission

Since initial submission of this thesis in March, we have since received analytical data on the nanoparticle catalyst. Unfortunately, further analysis will be required to determine the nature of the catalyst to confirm the [Pd] content.

References

- [1] É. Casey, PhD Thesis, University College Cork, **2022**.
- [2] M. Cargnello, N. L. Wieder, P. Canton, T. Montini, G. Giambastiani, A. Benedetti, R. J. Gorte, P. Fornasiero, *Chem. Mater.* **2011**, 23, 3961-3969.
- [3] S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res.* **2016**, 49, 594-605.

Unpublished Work and Further Discussion for Chapter 4

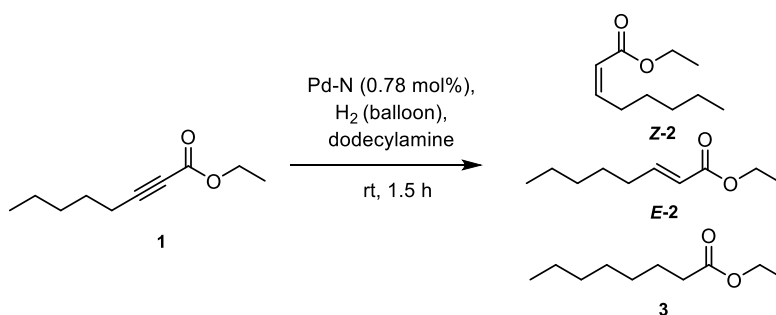
In addition to the work undertaken in the main manuscript and the supplementary information, some further non-published experiments were undertaken during the course of this project. The additional experiments that were undertaken are outlined below.

Dodecylamine Nanoparticles

Spiking Reaction Mixture with Dodecylamine Ligand

As mentioned in the main manuscript, hydrogenation activity of the Pd-N NP's after aggregation could be reestablished after addition of more dodecylamine ligand (albeit unselective hydrogenation). Following this, it was questioned what effect adding the ligand at the *start* of the reaction may have. For this experiment, an aliquot of 0.1 mL of varying concentrations were added to the original optimised reaction conditions (**Table UW1**).

Table UW1. Addition of dodecylamine ligand at the start of the reaction.



Entry	Dodecylamine (mmol)	Composition (%) ^[a]			
		1	Z-2	E-2	3
1	0.01	0	6	10	84
2	0.001	0	66	6	28
3	0.0001	0	86	7	7
4	N/A	0	89	6	5

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

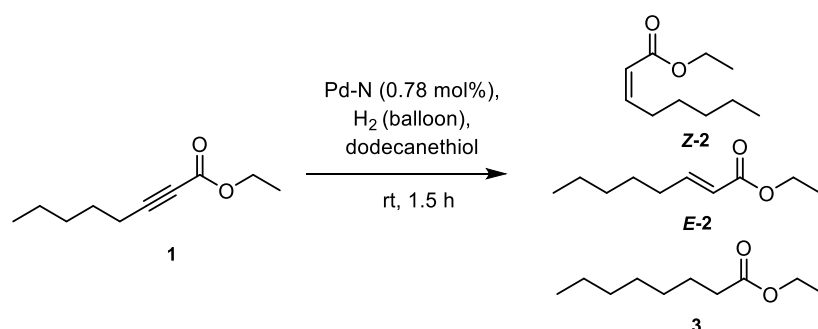
From the results in **Table UW1**, the addition of extra dodecylamine ligand increases the reactivity of the nanoparticles. This is possibly due to additional available ligand stabilising the nanoparticles which allows for more reactivity. When no additional ligand is added (**entry 4**), there is 89% Z-alkene **Z-2** present at full consumption of the alkyne **1**. Upon increasing the concentration of the ligand, the selectivity of the reaction decreases. Interestingly, the concentration of **E-2** does not seem to be greatly affected

by the concentration of added ligand. This suggests that it is the *Z*-alkene that is more susceptible to over-reduction than the *E*-alkene and that the *Z*-alkene does not readily isomerise to the *E*-alkene.

Spiking Reaction Mixture with Dodecanethiol Ligand

Following these results, the dodecylamine ligand additive was replaced with stronger binding dodecanethiol to determine the reactivity impact (**Table UW2**).^[1]

Table UW2. Addition of dodecanethiol ligand at the start of the reaction.



Entry	Dodecanethiol (mmol)	Temp (°C)	Composition (%) ^[a]			
			1	Z-2	E-2	3
1	0.01	rt	100	0	0	0
2	0.001	rt	0	69	5	26
3	0.0001	rt	7	83	6	4
4	N/A	rt	0	89	6	5
5	0.01	50	100	0	0	0

^[a] The composition of the reaction mixture was determined by ¹H NMR analysis.

At the highest concentration of dodecanethiol (**entry 1**), no hydrogenation occurs with just **1** remaining after 1.5 hours. It is possible that the stronger palladium–sulfur interaction displaces many of the dodecylamine ligands, and rendering the Pd 'over-ligated' and thus the substrate cannot compete for the Pd surface.^[2] Of note, no observed aggregation occurred under these conditions. As the concentration of dodecanethiol ligand decreases (**entry 2**), some reactivity of the nanoparticles restored. There is much observed alkane **3** under these conditions and is possibly due to lack of nanoparticle aggregation. Additionally, the concentration of ligand could be at the concentration in which it adds stability to the nanoparticle without blocking too much of the nanoparticle surface, allowing for substrate adsorption. At the lowest concentration of dodecanethiol (**entry 3**), aggregation was observed after 1 hour (longer than the usual ~30-minute

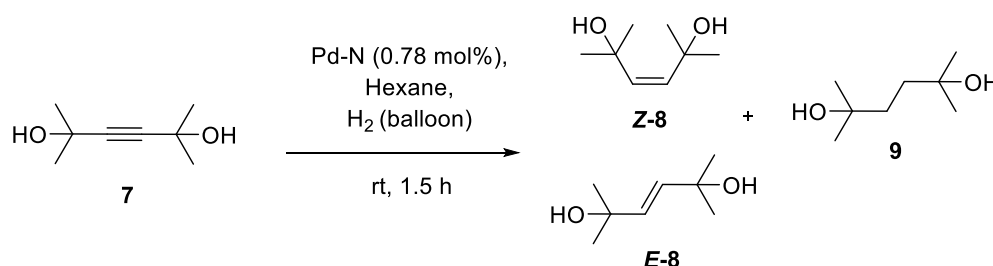
mark). This indicates that the dodecanethiol ligand aids in keeping the nanoparticles from aggregating. Although the nanoparticles did aggregate, there is still some alkyne **1** remaining demonstrating that the dodecanethiol ligands slow the reaction down.

From the main manuscript, it is known that the Pd-S nanoparticles require heat in order to facilitate the hydrogenation reaction. The experiment was tried again with the highest concentration of dodecanethiol added (**entry 5**), however, this time the reaction temperature was increased to 50 °C to see whether any activity would be observed. Even at the elevated temperature, only alkyne **1** was remaining. The addition of the dodecanethiol ligands halts or slows the reactivity down which is the opposite effect to the addition of dodecylamine ligands as discussed above. This may be attributed to the dodecanethiol ligands being more strongly ligated to the palladium core and therefore changing the reactivity of the nanoparticle.

Additional Substrate

A small number of substrates were tested with the dodecylamine nanoparticles to form the respective Z-alkene.

Scheme UW1. Semi hydrogenation of 2,5-dimethyl-3-hexyne-2,5-diol **7**.



Diol **7** was subjected to the standard reaction conditions of 1.5 hour stirring at room temperature (**Scheme UW1**). The diol **7** was completely insoluble in hexane, however, it still reacted to give **Z-8:E-8** 83:17 and 6% alkane **9**. It was decided to reduce the reaction time as the nanoparticles appeared to reduce this substrate more quickly than the ester **1**. It was found that the selectivity at 0 °C was the best with a selectivity of 98:2 **Z-8:E-8** with 4% alkane formation at full consumption of the alkyne. Its possible that hydrogen bonding between the two hydroxyl groups in the *cis* orientation aids in the high Z-alkene selectivity.

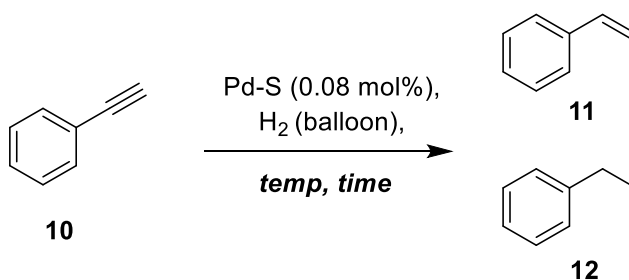
At this point in the project, focus was shifted to Pd-S nanoparticles and further investigations were ceased for Pd-N NP's.

Terminal alkynes

In addition to internal alkynes, we wanted to investigate whether our nanoparticle system would be suitable for the formation of terminal alkenes from terminal alkynes without over reduction to the alkane, akin to the work by Zhao.^[3]

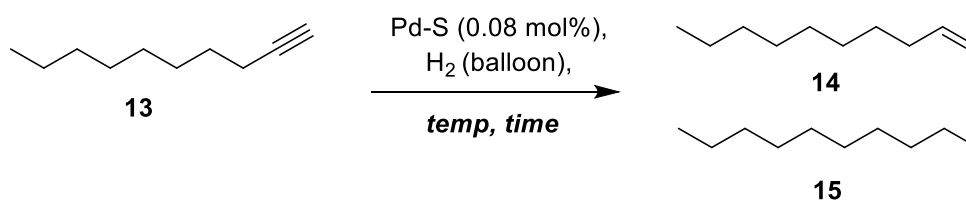
Terminal alkynes phenylacetylene **10** and 1-decyne **13** were subjected to Pd-DT nanoparticles as described in **Table UW3** and **Table UW4**.

Table UW3. Semi-hydrogenation of phenylacetylene.



Entry	Temp (°C)	Time (h)	Alkyne %	Alkene %	Alkane %
1	40	2.5	0	61	39
2	40	1	1	82	17
3	40	40 min	9	80	11

Table UW4. Semi-hydrogenation of 1-decyne.



Entry	Temp (°C)	Time (h)	Alkyne %	Alkene %	Alkane %
1	40	1	25	0	75
2	40	0.5	30	0	70
3	40	2	20	0	80

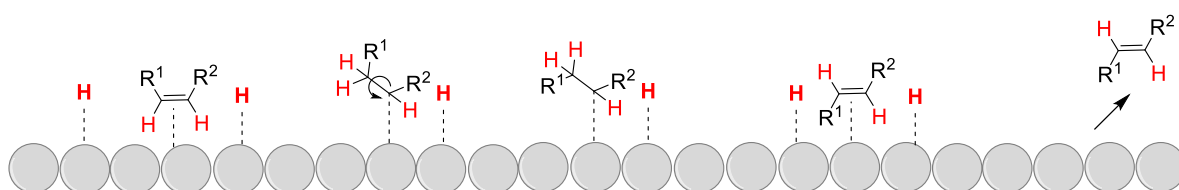
It can be seen from the above data that terminal alkynes do not exhibit the same selectivity as internal alkynes do in this system. It is possible that the terminal alkyne/alkene is adsorbing more strongly to the surface of the nanoparticle and therefore more prone to over reduction. Additionally, there is less steric bulk around the reactive

The fatty acid derivative, stearolic acid **17**, was also subjected to the reaction conditions (**Table UW5**, entries 7 – 10). Under extended reaction conditions (5 – 6 hours) some reactivity was observed, however the resulting mixture gave a complex ^1H and ^{13}C NMR spectra, indicating that the reaction was not selective, therefore, this substrate was no longer pursued. The unactivated alkynes, particularly substrates **7** and **16** indicate that selectivity can still be observed for the *Z*-alkene, however the reactions react slower (possibly due to hydrogen bonding). Little alkane is observed for these substrates. The unactivated stearolic acid has the added difficulty of access of the alkyne to the active surface of the nanoparticle. It is possible that the long alkyl chains block surface adsorption and additionally, it is possible that we are observing some alkyne/alkene chain walking due to the complicated nature of the resulting NMR spectra.^[4]

Mechanistic Insight

The semi-hydrogenation of alkynes follows the Horiuti-Polanyi mechanism, and this is evidenced by the isomerisation observed of our alkene products.^[4] A mixture of *Z* and *E*-alkenes are obtained using our optimised conditions with palladium nanoparticles, be they dodecanethiol or dodecylamine stabilised. This is due to the reversible mechanistic step in the Horiuti-Polanyi process which involves a rotatable single bond intermediate (**Figure UW1**). Upon hydrogenation from the alkyne, it is known that *syn*-addition occurs, resulting in an initial kinetic product, the *Z*-alkene.^[5] However, the *Z*-alkene (either still adsorbed to the surface, or desorbed and the re-adsorbed) can then isomerise to the thermodynamic product, the *E*-alkene. In order for this to happen; i) a rotatable bond must form *via* the addition of a hydrogen atom, ii) the bond must rotate to the opposite orientation and iii) a hydrogen atom must be lost back to the surface to reform the alkene.^[4-6] This causes the inversion of stereochemistry. It is possible that the alkene can also reform the alkyne by losing two hydrogen atoms to the surface as this process is also reversible. An irreversible loss of the over-reduced alkane product terminates any further activity of that particular molecule. Therefore, minimising the reversibility (and hence increasing the chance of isomerisation) is a crucial controlling factor in the outcome of reaction stereochemistry. Minimising alkene adsorption time, additionally, is a key aspect to controlling chemoselectivity which also poses challenges.

Figure UW1. Isomerisation of *Z*-alkene to *E*-alkene



It is also interesting that, although isomerisation is observed, the percent deuterium incorporation remains quite high at 93%. This is a pleasing result and may be attributed to the simple reaction conditions of substrate, catalyst, solvent and gas. It was also pleasing to see, that even at elevated pressures, there were minimal negative effects in terms of reaction selectivity and need for modified reaction conditions. It has been reported that undertaking hydrogenation reactions at elevated pressures can affect the catalyst morphology and reactivity and, therefore, selectivity.^[7]

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*"I have an apple that thinks it's a pear. And a bun that thinks it's a cat. And
a lettuce that thinks it's a lettuce"*

"It's a clever lettuce then"

"Hardly, why would anything clever think it's a lettuce?"

"Even if it is a lettuce?"

*"Especially then, bad enough to be a lettuce. How awful to think you are
one too."*

— Patrick Rothfuss, adapted from 'The Wise Man's Fear'

Chapter 5

Conclusions and Future Work

Conclusions

In **Chapter 2** of this thesis, a novel three-step one-pot Mizoroki-Heck/direct arylation/hydrogenation sequence was developed. It was found that neat tetrabutylammonium acetate facilitated the three-reaction sequence, replacing reprotoxic NMP, that had been used previously. The TBAOAc also negated the need for added base acting as both the solvent and base in this reaction. The hydrogenation reaction could be undertaken at atmospheric hydrogen pressure using a balloon set up. These reaction conditions facilitated a varied scope of core structures, namely, benzofuroquinoline, quinoline and dibenzofuran scaffolds to furnish over 20 novel compounds. The targets were synthesised in good to excellent yields. Three deuterated examples were also formed. In these cases, the COware apparatus was used to form D₂ gas *ex-situ* using DCl and Zn powder. Green metrics were carried out to compare our new-found conditions to the state-of-the-art. The calculations show a marked improvement across most metrics, as our conditions use less solvent, ligand, base and catalyst.

Investigations were conducted into the active palladium species facilitating the reaction sequence. When at 100 °C, Pd(OAc)₂ facilitates; 1) the initial two steps in the sequence and 2) an independent hydrogenation. However, the Pd species formed after; 1) heating then filtering Pd(OAc)₂ and 2) the hydrogenation step, does not allow the Mizoroki-Heck/direct arylation reaction to proceed. Additionally, after a Mizoroki-Heck (only) and direct arylation (only), the resulting Pd species allows the hydrogenation to take place.

It was found that transfer hydrogenation reagent, sodium formate, when used as a replacement for hydrogen gas, facilitated the reduction of the alkene bond on the alkene-benzofuroquinoline intermediate. However, when used in the one-pot protocol, the three-step reaction was not facilitated.

This work was published in RSC 'Green Chemistry'.^[1]

In **Chapter 3** of this thesis, a simple methodology was established to install 'late-stage' 3D character into planar multicyclic heteroarenes. The pi network of benzofuroquinolines was disrupted upon reduction. The conditions included Pd/C, AcOH and hydrogen gas at atmospheric pressure to selectively reduce the quinoline benzene ring ('A-ring') in the tetracyclic scaffold. This methodology was applied to substituted analogues and 23 novel compounds were produced in good to excellent yields. It was found that MsOH (3 eq.) could be used with *i*PrOH, to replace AcOH as solvent. As AcOH was found to form amides when using nitro substrates, the amine could be accessed using the MsOH and *i*PrOH method. Under slightly more forcing conditions (higher catalytic loading and temperature) both the quinoline and benzofuran benzene rings could be reduced to form

further '3-dimensional' structures. Deuterium was also incorporated using the COware apparatus with excellent yield and selectivity. Hydrodehalogenation was observed for some substrates. For example, chlorine was cleaved, independent of its position on the ring scaffold. Fluorine was cleaved when on the A-ring and partial cleavage was observed when it was present elsewhere on the structure (benzofuran). It was also uncovered that the oxygen heteroatom at the C3 or C4 position affected the selectivity of the quinoline ring reduction. When the oxygen atom was attached to C3 or C4 (as a methoxy or phenoxy substituent), the carbocycle in quinoline was primarily reduced. When the oxygen atom was absent, the heterocycle was mostly reduced, or a mixture of products was formed.

It was found that when a nitro group was present at the C5 position, under our standard reaction procedure, reduction from the nitro to the amine was found in addition to amine-cleaved A-ring reduced compound. Both TFA and AcOD- d_4 were also used as amide forming reagents, however a mixture of products and slow reactivity was obtained respectively in these cases. A C8-methoxy substituted substrate was also found to be sluggish to undergo reduction (even more-so than the C6 methoxy substrate). A benzofuroquinoline with 6,7-dimethyl substitution was subjected to our standard conditions, however, no reduction was observed even after extended reaction times and higher temperatures. A second substrate scaffold, indoloquinoline, was also subjected to the reduction conditions, however no hydrogenation was observed.

This work was published in 'Chemistry – A European Journal'.^[2]

Ligand stabilised palladium nanoparticles for the semi-hydrogenation of alkynes was investigated in **Chapter 4**, primarily on ethyl-2-octynoate. The current go-to for the formation of *Z*-alkenes from alkynes involves Lindlar's catalyst. However, there are many associated issues with this catalyst that need to be addressed. This chapter investigated the use of dodecylamine and dodecanethiol stabilised Pd nanoparticles for the semi-hydrogenation to alkenes. One of the main issues with semi-hydrogenation is the stereoselectivity of the resulting alkene. Despite this issue, palladium-dodecylamine (Pd-N) nanoparticles gave good *Z:E* selectivity of 94:6 using [Pd-N] 0.78 mol%. The second main issue pertaining to semi-hydrogenation is chemoselectivity, as over-reduction to the alkane is possible. Pleasingly, the Pd-N nanoparticles, under optimised conditions, only gave 5% alkane in the mixture. The Pd-N nanoparticles possessed observable aggregation after ~30 minutes which slowed and then halted all hydrogenation activity. It was speculated that the nanoparticle selectivity could be related to catalyst degradation. Interestingly, upon the addition of ligand at the point of nanoparticle

aggregation, the catalyst was resuspended, and hydrogenation activity resumed, however it was unselective.

Additionally, it was found that inputting additional dodecylamine ligand (of varying concentrations) at the beginning of a Pd-N catalysed reaction decreased the selectivity of the reaction and led to significant over-reduction to the alkane. Interestingly, the concentration of the *E*-alkene was not greatly impacted by the additional ligand (staying at around 8%) indicating that the *Z*-alkene over-reduces much more readily. Addition of the stronger binding dodecanethiol ligand at the beginning of a Pd-N catalysed reaction was also investigated. At all concentrations of added ligand, slower alkyne consumption was observed (than when no ligand was added). Due to the aggregation issue with Pd-N nanoparticles, focus was shifted to the more strongly binding ligand, dodecanethiol, and palladium-dodecanethiol (Pd-S) nanoparticles were synthesised.

Pd-S nanoparticles also resulted in good *E:Z* ratios of 95:5 (at [Pd-S] 0.08 mol%) without the issue of aggregation. A higher temperature and slightly longer reaction time was required for Pd-S nanoparticles (compared to Pd-N nanoparticles), most likely due to the stronger palladium–sulfur interaction. Minimal over-reduction to the alkane was also observed using Pd-S nanoparticles. Reaction progress was monitored by ¹H NMR, and revealed an initial induction period when using Pd-S nanoparticles of ~30 minutes. Upon 8-fold increase of the catalytic loading of [Pd-S] to 0.64 mol%, an inversion of selectivity from the *Z*- to the *E*-isomer is observed. Initially, the alkyne is rapidly consumed and forms the *Z*-isomer, which then rapidly isomerises to the *E*-isomer resulting in a *Z:E* ratio of 19:89. Further levels of *E*-formation could not be achieved, as after 24 hours, the Pd nanoparticles had aggregated. Similar to **Chapter 2** and **3**, deuteration was also undertaken as part of this Chapter. Excellent D-incorporation was observed (93%), a good *Z:E* ratio was maintained (at 90:10) and only a trace amount of alkane was present post-reaction.

Future Work

As described in **Chapter 2**, it was determined that the Mizoroki-Heck/direct arylation sequence worked with 100% conversion to the alkene intermediate at a larger scale (1.00 g, 2.64 mmol). However, our attempts to incorporate a hydrogenation step at larger scale failed. Future work would be to determine the limitation to this hydrogenation step and to uncover conditions that facilitate the hydrogenation step on a larger scale.

The work described in **Chapter 2** resulted in more than 20 novel, alkylated benzofuroquinolines, benzofuopyridines and dibenzofurans. As these scaffolds are of biological significance, they will be tested as part of an ongoing collaboration in UCC

testing for activity against for *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The compounds will also be sent to CO-ADD in Australia for further anti-microbial testing. More specifically, the difference in biological activity between the fully aromatic compounds and those with added 3D character will be investigated.

During the course of the deuteration experiments, additional C–H functionalisation was observed at the C2 position of the tetracyclic quinolines (with almost 100% deuterium incorporation). It could be a future research avenue to explore the functionalisation at the C2 position of these quinolines.

Future work within the group to continue this project could involve trying to replace palladium metal with an alternative, more benign metal/catalyst. Manganese has been reported to be effective in cross-coupling reactions^[3] and has also shown success in C–H activation.^[4] Additionally, earth-abundant iron, copper, cobalt and nickel have also been used for C–H activation processes with much promise.^[5] The challenge would be developing the third hydrogenation step into the sequence using these metals. However, it would be interesting to begin investigations using these metals for the initial C–H functionalisation and cross-coupling reactions to start. Perhaps a transfer-hydrogenation could be incorporated to facilitate the final step.^[6]

The work outlined in **Chapter 3** furnished more than 20 novel compounds that will undergo the same biological analysis as the compounds described in **Chapter 2**. The biological activity of these compounds will be of particular interest as we will be comparing the outcome for the planar substrate versus their non-planar products. As discussed in the introduction, the activity can vary dramatically with small structural changes.^[7] This will glean insight into the relationship between substrate shape and relative microbe inhibition or upregulation. Another interesting result will be the effect that the deuterated substrate has on the microbes.^[8] In this instance, the planar **1a**, non-planar **2a** and deuterated unsubstituted substrate **2a-d₅** will be compared and any differences in activity will be investigated.

Of high interest is the source of the hydrogen/deuterium that is used in the reduction step described in **Chapter 3**. The deuteration experiments revealed that the H/D installed in the final products could originate from both the gas and the solvent. It would be interesting to try the reactions again using TFA and TFA-*d*₁ to see if a stronger acid has a different outcome in terms of deuterium incorporation. The obtention of ~50% deuterium incorporation when using AcOD-*d*₄ and H₂ gas was an unexpected result and further examination of this reaction, and the associated mechanism is warranted.

A major goal of this work is to carry out this process in an asymmetric fashion. While asymmetric reactions using heterogeneous catalysis is rare, there are some recent reports in this space.^[9]

The nanoparticles discussed in **Chapter 4** demonstrate some interesting reactivities for the semi-hydrogenation of alkynes. Isomerisation experiments could be undertaken to confirm the mechanism of reaction isomerisation i.e., is the *Z*-alkene readsorbing on the surface and isomerising to the *E*-alkene or is another mechanism at play. These experiments could be facilitated using the alkene and D₂ gas. Secondly, it would be of interest to test the Pd-S nanoparticles for reduction of S-containing compounds. S-Containing compounds are known to be very problematic for Pd-catalysed reactions.^[10] However, a strongly binding S-ligand could out-compete S-binding from the substrate, and thus facilitate reduction. Finally, as stated earlier, analysis of the Pd-S nanoparticles (prepared by me) is required before publication.

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Theories cannot claim to be indestructible. They are only the plough which the ploughman uses to draw his furrow and which he has every right to discard for another one, of improved design, after the harvest.

— *Paul Sabatier, Nobel Lecture, 1912*