

Directed Nickel-Catalyzed 1,2-Dialkylation of Alkenes

Joseph Derosa, Vincent A. van der Puyl, Van T. Tran, Mingyu Liu, **Keary Engle**

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A nickel-catalyzed conjunctive cross-coupling of non-conjugated alkenes, alkyl halides, and alkylzinc reagents is reported. Regioselectivity is controlled by chelation of a removable bidentate 8-aminoquinoline directing group. Under optimized conditions, a wide range of 1,2-dialkylated products can be accessed in moderate to excellent yields. To the best of our knowledge, this report represents the first example of three-component 1,2-dialkylation of non-conjugated alkenes to introduce differentiated alkyl fragments.

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Directed Nickel-Catalyzed 1,2-Dialkylolation of Alkenes

Joseph Derosa,^a Vincent A. van der Puyl,^a Van T. Tran,^a Mingyu Liu,^a Keary M. Engle^{*a}

A nickel-catalyzed conjunctive cross-coupling of non-conjugated alkenes, alkyl halides, and alkylzinc reagents is reported. Regioselectivity is controlled by chelation of a removable bidentate 8-aminoquinoline directing group. Under optimized conditions, a wide range of 1,2-dialkylated products can be accessed in moderate to excellent yields. To the best of our knowledge, this report represents the first example of three-component 1,2-dialkylolation of non-conjugated alkenes to introduce differentiated alkyl fragments.

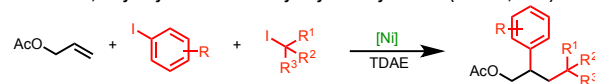
Introduction

Synthetic methods that enable expeditious access to carbogenic skeletons with high sp^3 character are a vital component of the synthetic toolkit, given the prevalence of such structures in natural products and their importance in modern drug discovery.¹ In the past several years, cross-coupling reactions² involving alkenes as conjunctive reagents have emerged as a powerful platform for forging two $C(sp^3)$ stereocenters in a single stroke.^{3–6} Orchestrating the elementary steps in conjunctive cross-coupling and controlling the regioselectivity, stereoselectivity, and 1,1-versus-1,2-selectivity in such transformations is challenging, and to address these issues, several approaches have been pursued, including intramolecular tethering of the alkene to one reaction partner,³ use of a conjugated alkene (e.g., styrenes, acrylates, and allenes),⁴ metalate rearrangements,⁵ and chelation control.⁶ These developments notwithstanding, existing methods typically require at least one $C(sp^2)$ reaction partner. A generally applicable, three-component “all-alkyl” conjunctive cross-coupling, capable of delivering differentiated alkyl fragments across an alkene, would be synthetically enabling but has not been developed to date.⁷ This is due not only to the aforementioned challenges with conjunctive cross-coupling but also to the inherent difficulties associated with $C(sp^3)$ – $C(sp^3)$ cross-coupling processes.^{8,9} In the present study we describe our efforts to bridge this gap through the development of a nickel-catalyzed three-component conjunctive cross-coupling of an alkyl organometallic nucleophile, an alkylhalide electrophile, and a non-conjugated alkene using a chelation control strategy.

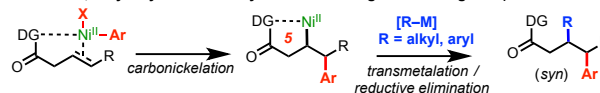
Several literature precedents of alkene 1,2-dicarbofunctionalization with alkyl reaction partners spoke to the viability of such a reaction but also illustrated challenges to be anticipated. Early work by Cardenas and coworkers demonstrated nickel-catalyzed intramolecular dialkylolation.⁹ Nevado and coworkers recently demonstrated that allyl acetate and related alkenes could react with tertiary alkyl iodides and aryl iodides in a nickel-catalyzed reductive conjunctive cross-coupling (Scheme 1A).⁶ Our group developed a 1,2-aryllalkylation reaction using aryl iodides and organozinc

reagents under nickel catalysis.^{6b} This reaction employed a removable bidentate directing group¹⁰ to control the regiochemical outcome through putative nickelacycle stabilization and to prevent otherwise rapid β -hydride (β -H) elimination (Scheme 1B).

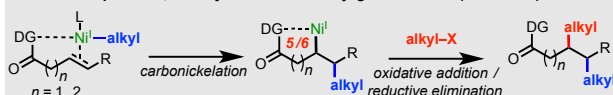
A. Reductive 1,2-aryllalkylation with tertiary alkyl and aryl halides (Nevado, 2017)



B. Directed 1,2-aryllalkylation with aryl iodides and organozinc reagents (Previous Work)



C. Three-component 1,2-dialkylolation of non-conjugated alkenes (This Work)



Scheme 1 Three-Component 1,2-Dicarbofunctionalization with $C(sp^3)$ Reaction Partners: Precedents and Current Work

The efficiency of our 1,2-aryllalkylation reaction prompted us to consider whether it would be possible to use alkyl halides and alkyl organometallic reagents with non-conjugated terminal and internal alkenes via chelation control (Scheme 1C). At the outset we recognized that successful realization of the proposed transformation would necessitate overcoming a series of obstacles, most notably the fact that alkylmetal species capable of undergoing β -H elimination are present in every step of the catalytic cycle. Additionally, with alkyl halide electrophiles it is known that single-electron oxidative addition pathways are sometimes preferred, particularly with first-row metals,^{8,9} which meant that there was potential for mechanistic divergence compared to our earlier work (Ni^I/Ni^{III} vs. Ni^0/Ni^{II}).

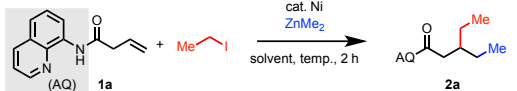
Results and discussion

To reduce this idea to practice, we began by exposing an alkenyl carbonyl compound **1a** to reaction conditions using iodoethane as the electrophile and dimethyl zinc as the nucleophile under nickel catalysis (Table 1). To suppress β -H elimination, we hypothesized that a strong, bidentate directing group would be beneficial. Given our group's previous success

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Electronic Supplementary Information (ESI) available.

in employing Daugulis's 8-aminoquinoline (AQ) directing group¹⁰ in 1,2-difunctionalization reactions,^{6b,11} we focused our efforts on this directing group.

Table 1 Optimization of 1,2-Dialkylation^a

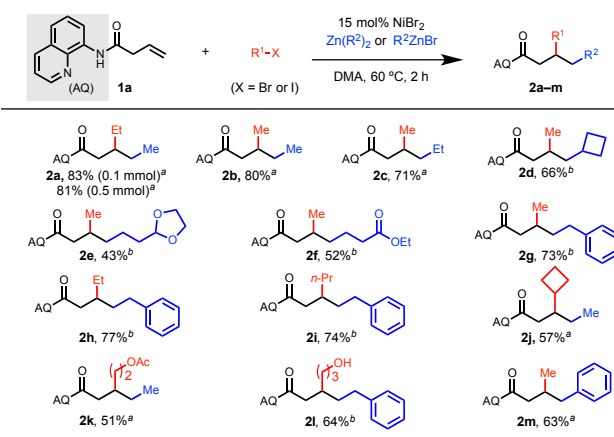


entry	cat. Ni	EtI (equiv)	ZnMe ₂ (equiv)	solvent (M)	temp. (°C)	yield (%) ^b
1	10% NiCl ₂ •glyme	2	2	DMA (0.5)	100	39
2	10% NiBr ₂	2	2	DMA (0.5)	100	37
3	10% NiCl ₂ •glyme	2	2	dioxane (0.5)	RT	n.d.
4	10% NiCl ₂ •glyme	2	2	DMF (0.5)	RT	13
5	10% NiCl ₂ •glyme	2	2	DMA (0.5)	RT	28
6	10% NiCl ₂ •glyme	2	2	DMA (0.1)	50	46
7	10% NiCl ₂ •glyme	2	2	DMA (0.2)	60	53
8	10% NiCl ₂ •glyme	4	4	DMA (0.2)	60	68
9	15% NiBr ₂	8	8	DMA (0.2)	60	81
10	15% NiBr ₂	8	6	DMA (0.2)	60	83

^a Reaction conditions: alkene (0.1 mmol), ZnMe₂ (1.2 M in toluene). ^b Yields determined by ¹H NMR analysis using CH₂Br₂ as internal standard; n.d. = not detected.

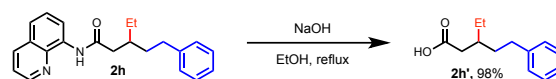
In a series of initial experiments, we were delighted to observe formation of the desired 1,2-dialkylated product **2a** in 39% yield with 10 mol% NiCl₂•glyme (entry 1). Interestingly, the product was determined to have electrophile incorporation at the β-position, opposite to that of our previously reported 1,2-arylalkylation methodology, suggestive of a different underlying mechanism. With NiCl₂•glyme as catalyst, the procedure could reliably be reproduced without the use of an inert atmosphere glovebox. We were also encouraged by the efficaciousness of a range of nickel(II) sources, including NiBr₂ which performed comparably to NiCl₂•glyme (entry 2). Interestingly, the reaction also resulted in 1,2-dimethylation as a byproduct in modest yield (24% by ¹H NMR, see Supporting Information). The reaction only proceeded in appreciable yield when polar aprotic solvents were used, so we opted to use DMA as the solvent for subsequent optimization. Through systematic screening, we were pleased to observe that the yield increased when the reaction was performed at concentrations lower than 0.5 M. With this change, the temperature could be decreased to 60 °C, and under these conditions, the desired product was formed in 53% yield. Next, we reasoned that the nucleophile and electrophile were being consumed through competitive two-component cross-coupling or homodimerization. Indeed, we observed a dramatic increase in yield proportional to the increase in equivalents of both electrophile and nucleophile that were used (entry 8). The reaction still provides >65% yield using 4 equivalents; however, we opted to utilize 6–8 equivalents of each component for the remainder of the study because they were inexpensive and commercially available (entries 9 and 10).

Table 2 Alkyl Nucleophile and Alkyl Electrophile Scope^{a-c}



^a Reaction conditions: alkene **1a** (0.1 mmol or 0.5 mmol), alkyl halide (8 equiv), dialkyl/diarylzinc (6 equiv), DMA, 60 °C, 2 h. ^b Organozinc bromide (8 equiv) in place of dialkyl/diarylzinc. ^c Percentages represent isolated yields.

With optimized conditions in hand, we first explored potential alkyl electrophiles and nucleophiles that were compatible in this 1,2-dialkylation reaction (Table 2).¹³ To our satisfaction, a wide range of primary alkyl electrophiles and nucleophiles were tolerated. By simply changing the identity of the nucleophilic and electrophilic components (*i.e.*, iodoethane/dimethylzinc to iodomethane/diethylzinc), both regioisomers could be synthesized in high yields (**2a** and **2c**). In general, secondary alkyl reaction partners did not perform well under the optimized conditions. Cyclobutyl coupling partners were an exception, however, and the corresponding difunctionalized products **2d** and **2j** could be obtained in high yields. Several synthetically useful functional groups were tolerated in this reaction, allowing for the installation of acetals, esters, and free alcohols in moderate to good yields (**2e**, **2f**, **2k**, and **2l**). Heterocycle-containing reaction partners were generally incompatible, which we hypothesize is due to catalyst coordination. Interestingly, 1,2-arylalkylation products could be accessed using diphenyl zinc (**2m**). Upon exposure to standard hydrolysis conditions, we found that the AQ auxiliary of a representative product could be unmasked to the corresponding carboxylic acid (Scheme 2).

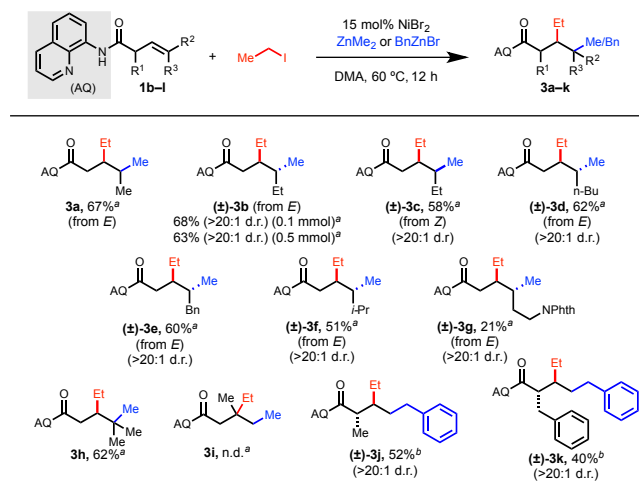


Scheme 2 Hydrolysis of AQ directing group.

Next, we examined internal and α-substituted terminal β,γ-unsaturated alkenes (Table 3). For these substrates, we elected to use iodoethane as the electrophile and dimethyl zinc or benzylzinc bromide as the nucleophile. Internal alkenes provided the desired *syn*-1,2-difunctionalized products in good yields and with high diastereomeric ratios (**3a–3g**). The relative

stereochemistry was determined by reacting representative internal alkene **1b** with diphenyl zinc and methyl iodide, yielding 1,2-arylation product reported in our previous methodology (see Supporting Information). Upon subjecting a trisubstituted alkene to the reactions conditions, we were pleased to discover that quaternary centers could be formed at the γ -position (**3h**). We questioned whether a 1,1-disubstituted alkene could react; however, the reaction did not proceed at all with this substrate (**3i**). We hypothesize that the putative chelation-stabilized alkylnickel intermediate is very sensitive to the proximal steric environment.

Table 3 β,γ -Alkene Substrate Scope^{a-c}

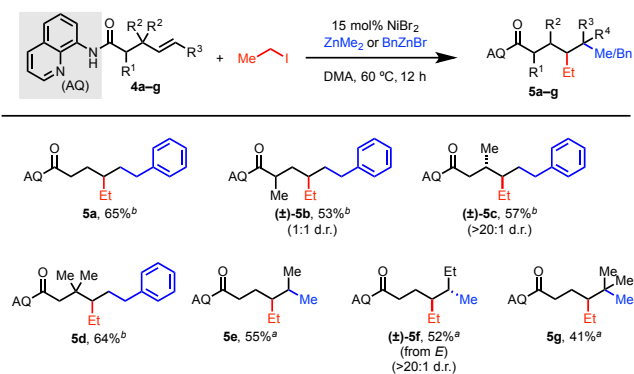


^a Reaction conditions: alkene **1b-l** (0.1 mmol or 0.5 mmol), iodoethane (8 equiv), dimethylzinc (8 equiv), DMA, 60 °C, 12 h. ^b Benzylzinc bromide (8 equiv) in place of dimethylzinc. ^c Percentages represent isolated yields.

To investigate the steric constraints of our optimized system, we subjected α -substituted substrates to the reaction conditions (**3j** and **3k**). More sterically bulky groups led to lower yields. In both successful cases, only a single diastereomer was detected.¹⁴

It is typically difficult to extend catalytic directed alkene functionalizations to substrates containing more distal functional groups due to the instability of the metalacycles that are six-membered or larger. Recently our group published a tridentate directing group strategy for the hydrofunctionalization of γ,δ -unsaturated alkenes; the tridentate directing group is thought to suppress β -H elimination in six-membered palladacycles.¹⁰

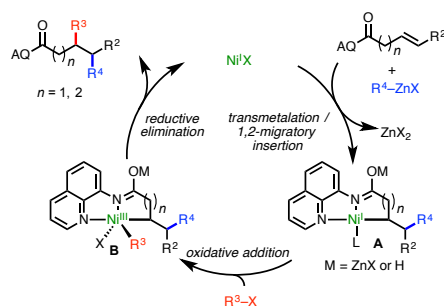
Table 4 γ,δ -Alkene Substrate Scope^{a-c}



^a Reaction conditions: alkene **4a-g** (0.1 mmol), iodoethane (8 equiv), dimethylzinc (8 equiv), DMA, 60 °C, 12 h. ^b Benzylzinc bromide (8 equiv) in place of dimethylzinc. ^c Percentages represent isolated yields.

An alternative strategy is to intercept the metalacycle in a rapid subsequent step, such that this downstream reaction can outcompete undesired β -H elimination. Given the unique reactivity patterns in this 1,2-dialkylation reaction, we thus questioned whether γ,δ -dialkylation would be feasible *via* a six-membered AQ-bound nickelacycle (Table 4). To this end, we employed a terminal γ,δ -unsaturated alkene substrate with iodoethane and benzylzinc bromide. Our standard reaction conditions delivered the desired product in 65% yield (**5a**), showcasing the ability of this transformation to introduce alkyl fragments at the γ - and δ -positions, which are challenging to functionalize using existing chemistry. We then introduced substituents at various positions to investigate the effects on diastereoselectivity. Interestingly, α -substituted starting materials gave the desired product, but with significantly diminished diastereoselectivity (**5b**). When the analogous β -substituted starting material was used, the desired product was delivered as a single diastereomer (**5c**).¹⁴ These results shed light on the influence of proximal substituents on competing nickelacycle formation pathways. Internal alkenes within this substrate class also reacted well to give dialkylated products (**5e** and **5f**). To our delight, the corresponding trisubstituted alkene also proved to be reactive, allowing formation of a quaternary center (**5g**). We further probed a representative δ,ϵ -unsaturated substrate but in this case could only detect isomerization byproducts.

Though a detailed mechanistic investigation of this transformation remains outside of the scope of the present manuscript, a plausible catalytic cycle consistent with experimental data is shown in Scheme 3. The cycle follows a Ni^I/Ni^{III} redox manifold, consistent with other alkyl-alkyl cross-coupling processes.^{3b,7d,7e,9h} Initially, a Ni^I catalyst undergoes a transmetalation/*syn*-1,2-migratory insertion sequence to yield putative nickelacycle **A**. This species is then intercepted by an alkyl halide *via* radical oxidative addition, forming Ni^{III} adduct **B**. A subsequent reductive elimination step delivers the desired 1,2-dialkylated product in a regioselective fashion and regenerates the active catalyst.



Scheme 3 Proposed catalytic cycle.

An alternative mechanism could also be envisioned in which oxidative addition of the alkyl halide occurs first, followed by *syn*-insertion to deliver the electrophile alkyl fragment proximal to the directing group and generate the 6- or 7-membered nickelacycle for substrates classes **1** and **4**, respectively. Though we have not conclusively ruled out this pathway at this stage, several observations stand counter to this mechanism. First, assuming this alternative pathway were operative, the observed regiochemical outcome when utilizing γ,δ -unsaturated alkenes (**4**) would indicate that the catalyst selectively forms a 7-membered alkyl nickelacycle in preference to a 6-membered alkyl nickelacycle, which is inconsistent with established trends in alkyl metalacycle formation.¹² Second, assuming the former point were true, it would stand to reason that δ,ϵ -unsaturated carbonyl compounds would also be compatible; however, in practice this substrate class was not tolerated. Third, formation of products such as **5g** following this alternative mechanism would require the intermediacy of a 7-membered tertiary-alkyl nickelacycle, a species that would be expected to be highly unstable.

As noted above, the present reaction delivers the opposite regiochemical outcome compared with previously reported conditions using a Ni(0) precatalyst and an aryl iodide electrophile,^{6b} potentially indicating mechanistic divergence in the two cases. Notably, Zhao and coworkers have also recently reported that the regiochemical outcome of nickel-catalyzed alkene 1,2-dicarbonylation reactions can be switched based on the identity of the electrophilic coupling partner.^{6c}

Conclusions

In conclusion, we have developed a three-component conjunctive coupling involving only alkyl components for β,γ - and γ,δ -difunctionalization of alkenyl carbonyl compounds. Using a removable directing group strategy, high regioselectivity and diastereoselectivity can be achieved, rendering this method a potentially powerful tool for rapidly assembling molecular complexity. Mechanistic studies are currently underway for determining the precise mechanism of nickel-catalyzed dicarbonylation and to expand the compatible electrophilic and nucleophilic coupling partners. These results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- 1 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
- 2 For reviews on transition-metal-catalyzed cross-coupling reactions, see: (a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062–5085; (b) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299–309.
- 3 V. B. Phapale, E. Buñuel, M. García-Iglesias and D. J. Cárdenas, *Angew. Chem. Int. Ed.*, 2007, **46**, 8790–8795.
- 4 For representative examples of conjunctive coupling using allenes, 1,3-dienes, styrenes, or acrylates, see: (a) T.-H. Huang, H.-M. Chang, M.-Y. Wu, and C.-H. Cheng, *J. Org. Chem.*, 2002, **67**, 99–105; (b) L. Liao, R. Jana, K. B. Urkalan and M. S. Sigman, *J. Am. Chem. Soc.*, 2011, **133**, 5784–5787; (c) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate and P. S. Baran, *Science*, 2016, **352**, 801–805; (d) K. M. Logan, K. B. Smith and M. K. Brown, *J. Am. Chem. Soc.*, 2015, **54**, 5228–5231. For a recent example of nickel-catalyzed reductive 1,2-dicarbonylation of conjugated alkenes and allylic alcohol derivatives, see: (e) A. García-Domínguez, Z. Li and C. Nevado, *J. Am. Chem. Soc.*, 2017, **139**, 6835–6838.
- 5 (a) L. Zhang, G. J. Lovinger, E. K. Edelstein, A. A. Szymaniak, M. P. Chierchia and J. P. Morken, *Science*, 2016, **351**, 70–74. For a recent example of Ni-catalyzed 1,2-dicarbonylation involving alkyl electrophiles via a metalate rearrangement, see: (b) G. A. Lovinger and J. P. Morken, *J. Am. Chem. Soc.*, 2017, **139**, 17293–17296.
- 6 (a) B. Shrestha, P. Basnet, R. K. Dhungana, S. KC, S. Thapa, J. M. Sears and R. Giri, *J. Am. Chem. Soc.*, 2017, **139**, 10653–10656; (b) J. Derosa, V. T. Tran, M. N. Boulous, J. S. Chen and K. M. Engle, *J. Am. Chem. Soc.*, 2017, **139**, 10657–10660; (c) W. Li, J. W. Boon and Y. Zhao, *Chem. Sci.*, 2018, **9**, 600–607. (d) S. Thapa, R. K. Dhungana, R. T. Magar, B. Shrestha, S. KC and R. Giri, *Chem. Sci.* 2018, DOI: 10.1039/C1037SC04351A.
- 7 Classical *vicinal*-difunctionalization reactions of α,β -unsaturated carbonyl compounds are a related class of reactions with well-established utility in organic synthesis. For selected reviews, see: (a) M. Suzuki and R. Noyori, in *Organocopper Reagents: A Practical Approach*; ed. R. J. K. Taylor, Oxford University Press, Oxford, 1994; ch. 9, pp 185–216; (b) R. J. K. Taylor, *Synthesis*, 1985, 364–392; (c) M. J. Chapdelaine and M. Hulce, *Org. React.*, 1990, **38**, 225–653; (d) M. Ihara and K. Fukumoto, *Angew. Chem. Int. Ed.*, 1993, **32**, 1010–1022.
- 8 For reviews on $C(sp^3)-C(sp^3)$ cross-coupling, see: (a) M. R. Netherton and G. C. Fu, *Adv. Synth. Catal.*, 2004, **346**, 1525–1532; (b) A. C. Frisch and M. Beller, *Angew. Chem. Int. Ed.*,

- 2005, **44**, 674–688; (c) A. Rudolph and M. Lautens, *Angew. Chem. Int. Ed.*, 2009, **48**, 2656–2670; (d) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417–1492; (e) X. Hu, *Chem. Sci.* 2011, **2**, 1867–1886.
- 9 For early examples of utilizing ancillary ligands to suppress β -hydride elimination in $C(sp^3)–C(sp^3)$ cross-coupling, see: (a) K. Tamao, Y. Kiso, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 9268–9269; (b) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158–163; (c) T. Katayama and M. Umeno, *Chem. Lett.*, 1991, **20**, 2073–2076. For representative examples of nickel-catalyzed $C(sp^3)–C(sp^3)$ cross-coupling, see: (d) A. E. Jensen and P. Knochel, *J. Org. Chem.*, 2002, **67**, 79–85; (e) J. Zhou and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 14726–14727; (f) J. Terao, H. Todo, H. Watanabe, A. Ikumi and N. Kambe, *Angew. Chem. Int. Ed.*, 2004, **43**, 6180–6182; (g) H. Gong, R. Sinisi and M. R. Gagne, *J. Am. Chem. Soc.*, 2007, **129**, 1908–1909. For a representative example of directed $C(sp^3)–C(sp^3)$ cross-coupling, see: (h) A. Wilsily, F. Tramutola, N. A. Owston and G. C. Fu, *J. Am. Chem. Soc.*, 2012, **134**, 5794.
- 10 For pioneering work on bidentate auxiliaries in Pd(II)-catalyzed C–H activation, see: (a) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155. For examples with Ni, see: (b) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 14952–14955; (c) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 898–901. For selected reviews, see: (d) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.*, 2013, **52**, 11726–11743; (e) O. Daugulis, J. Roane, and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064.
- 11 Z. Liu, T. Zeng, K. S. Yang and K. M. Engle, *J. Am. Chem. Soc.*, 2016, **138**, 15122–15125.
- 12 M. L. O'Duill, R. Matsuura, Y. Wang, J. L. Turnbull, J. A. Gurak, Jr., D.-W. Gao, G. Lu, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2017, **139**, 15576–15579.
- 13 In most cases, competitive 1,2-dialkylation with the nucleophile was also observed in 5–20% yield based on 1H NMR of the crude reaction mixture.
- 14 The relative configuration was assigned as *trans* by analogy to compounds prepared in Ref. 6b. The preference for *trans* product formation is believed to arise from more facile formation of the *trans* nickelacycle.

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SUPPORTING INFORMATION

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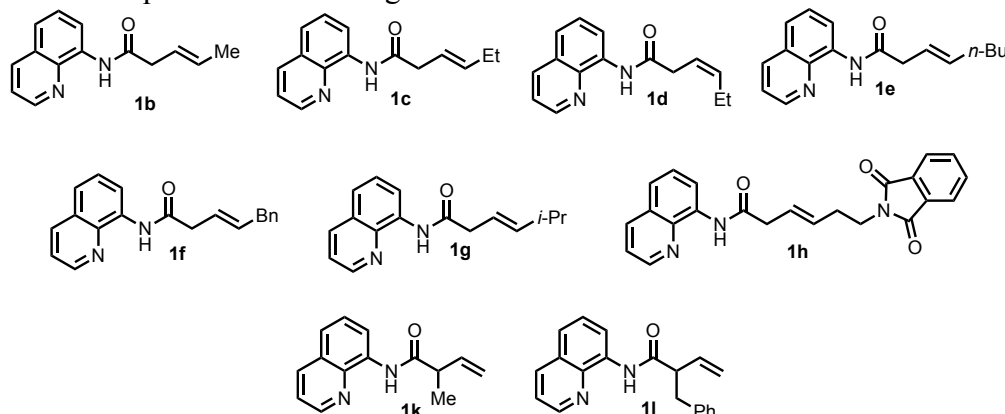
GENERAL INFORMATION

Unless otherwise noted, all materials were used as received from commercial sources without further purification. All aryl iodides, organozinc reagents, and solvents were purchased from MilliporeSigma, Alfa Aesar, Oakwood, and Combi-Blocks. Teflon-coated magnetic stir bars were soaked in concentrated nitric acid for at least 1 h, washed repeatedly with deionized water then acetone, and dried in an oven prior to use. In air- or moisture-sensitive reactions, anhydrous solvents from MilliporeSigma or from a Grubbs-type solvent purification system were used, and an inert atmosphere was maintained throughout the course of the reaction. ^1H and ^{13}C spectra were recorded with Bruker AV-400, DPX-500 and AV-600 instruments. Spectra were internally referenced to SiMe_4 or solvent signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, and m = multiplet. High-resolution mass spectra (HRMS) for new compounds were recorded on an Agilent LC/MSD TOF mass spectrometer.

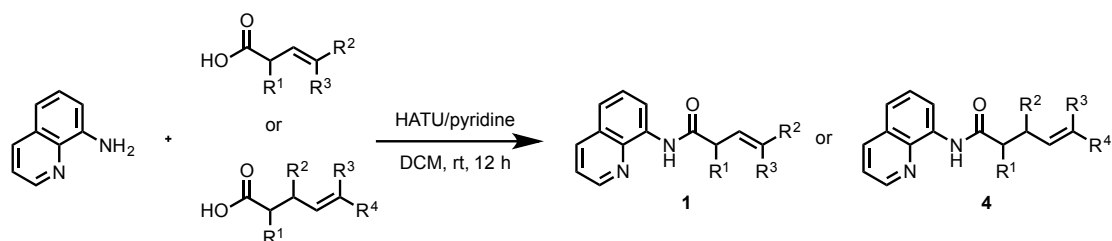
EXPERIMENTAL PROCEDURES

8-Aminoquinoline-Containing Alkene Substrate Synthesis

Table S1. 8-Aminoquinoline-containing alkene substrates **1b–h** and **1k–1l**.



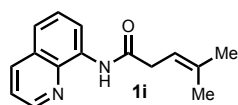
Alkene substrates **1b–h** and **1k–1l** were prepared according to literature methods.^{1,2}



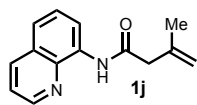
Scheme S1. Synthesis of alkene substrates using a general amide/ester coupling.

General Procedure for Amide Coupling: To a 50-mL flask equipped with a Teflon-coated stir bar was added alkenyl carboxylic acid (10 mmol, 1 equiv), 8-aminoquinoline (10 mmol, 1.0

equiv), HATU (11 mmol, 1.1 equiv), and dichloromethane (30 mL). After stirring at room temperature for 3 min, pyridine (20 mmol, 2 equiv) was added dropwise, and the reaction mixture was left to stir for 12 h. The reaction mixture was then washed with aq. NaHCO₃ (60 mL) and extracted with DCM (4 × 50 mL). The organic layers were combined, and the solvent was removed *in vacuo* to yield a yellow residue. Purification using column chromatography gave the pure product.

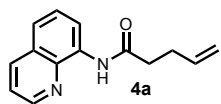


4-methyl-N-(quinolin-8-yl)pent-3-enamide (1i): A slurry of 2.94 g (60.0 mmol) NaCN in DMF (3.87 mL) was stirred at 0 °C as 1-bromo-3-methylbut-2-ene (50.0 mmol) was added slowly. The mixture was allowed to warm to room temperature and was then heated at 50 °C overnight. The reaction vessel was cooled to room temperature before extracting with pentane (3 × 50 mL). The organic layer was washed with brine, filtered over Na₂SO₄, and concentrated *in vacuo*. The corresponding 4-methylpent-3-enenitrile was carried on without purification and converted to 4-methylpent-enoic acid according to a literature procedure.³ The title compound was prepared from 4-methylpent-3-enoic acid (1.14 g, 10 mmol) and 8-aminoquinoline (1.44 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a brown oil (1.968 g, 82% yield). ¹H NMR (600 MHz, CDCl₃) δ 10.14 (s, 1H), 8.89–8.75 (m, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62–7.44 (m, 3H), 5.58 (tdt, *J* = 7.5, 2.9, 1.4 Hz, 1H), 3.37–3.26 (m, 2H), 1.93 (d, *J* = 1.4 Hz, 3H), 1.81 (d, *J* = 1.4 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 169.65, 147.75, 138.15, 137.71, 135.79, 134.07, 127.46, 126.95, 121.05, 120.93, 116.13, 115.82, 37.25, 25.37, 17.67; HRMS (ESI-TOF) Calc'd for C₁₅H₁₇N₂O⁺ [M+H]⁺ 241.1335, found 241.1339.

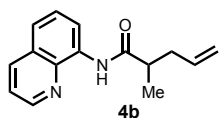


3-methyl-N-(quinolin-8-yl)but-3-enamide (1j): To a 50-mL Erlenmeyer flask equipped with a Teflon-coated magnetic stir bar were added chromium(VI) oxide (2.73 g, 2.7 M) and distilled water (4 mL). The reagent mixture was cooled to 0 °C, and concentrated sulfuric acid (2.3 mL) was added dropwise, thereby forming Jones reagent. The solution of Jones reagent was then diluted to a total volume of 10 mL with distilled water. To a 100-mL round-bottom flask equipped with a Teflon-coated magnetic stir bar were added 3-methyl-3-buten-1-ol (1 equiv) and acetone (30 mL). The reaction mixture was then cooled to 0 °C. Jones reagent was added slowly into the reaction mixture over a 30-min period. The reaction was maintained at 0 °C for an additional 2 h. After this time, the reaction mixture was quenched with EtOH (20 mL) while cooling. The reaction mixture was poured carefully into a separatory funnel containing water (30 mL) and extracted with DCM (2 × 30 mL). The combined organic extracts were dried with Na₂SO₄, filtered, and concentrated *in vacuo*. The crude carboxylic acid product was then carried on to the next step without further purification. The title compound was prepared from 3-methylbut-3-enoic acid (1.00 g, 10 mmol) and 8-aminoquinoline (1.44 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a yellow oil (1.781 g, 73% yield). ¹H NMR (600 MHz, CDCl₃) δ 10.09 (s, 1H), 8.87–8.76 (m, 2H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62–7.43 (m, 3H), 5.18–5.12 (m, 2H), 3.32 (d, *J* = 1.1 Hz, 2H), 1.95 (t, *J* = 1.1 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 168.69, 147.83, 139.40, 138.13,

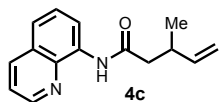
135.81, 134.00, 127.47, 126.91, 121.10, 121.07, 115.93, 115.47, 47.46, 22.09; **HRMS** (ESI-TOF) Calc'd for $C_{14}H_{15}N_2O^+$ $[M+H]^+$ 227.1179, found 227.1170.



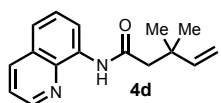
N-(quinolin-8-yl)pent-4-enamide (4a): The title compound was prepared from pent-4-enoic acid (1.00 g, 10 mmol) and 8-aminoquinoline (1.44 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a brown solid (2.011 g, 89% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.86–8.71 (m, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.56–7.48 (m, 2H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 5.94 (ddt, J = 16.7, 10.2, 6.4 Hz, 1H), 5.16 (dq, J = 17.1, 1.7 Hz, 1H), 5.05 (dq, J = 10.2, 1.4 Hz, 1H), 2.70–2.65 (m, 2H), 2.58 (tdd, J = 7.8, 5.7, 1.3 Hz, 2H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 170.94, 148.11, 138.34, 136.86, 136.37, 134.48, 127.94, 127.43, 121.58, 121.41, 116.46, 115.72, 37.33, 29.49; **HRMS** (ESI-TOF) Calc'd for $C_{14}H_{15}N_2O^+$ $[M+H]^+$ 227.1179, found 227.1179.



2-Methyl-N-(quinolin-8-yl)pent-4-enamide (4b): The title compound was prepared from 2-methyl-pent-4-enoic acid (1.14 g, 10 mmol) and 8-aminoquinoline (1.44 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a yellow oil (1.872 g, 78% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.88 (s, 1H), 9.13–8.59 (m, 2H), 8.16 (dd, J = 8.2, 1.7 Hz, 1H), 7.58–7.49 (m, 2H), 7.46 (dd, J = 8.2, 4.2 Hz, 1H), 6.03–5.76 (m, 1H), 5.15 (dq, J = 17.0, 1.6 Hz, 1H), 5.05 (ddt, J = 10.2, 2.0, 1.1 Hz, 1H), 2.70 (hept, J = 6.9 Hz, 1H), 2.64–2.51 (m, 1H), 2.46–2.23 (m, 1H), 1.35 (d, J = 6.9 Hz, 3H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 174.55, 148.13, 138.47, 136.35, 135.65, 134.52, 127.94, 127.45, 121.56, 121.37, 117.07, 116.48, 42.65, 38.45, 17.50; **HRMS** (ESI-TOF) Calc'd for $C_{15}H_{17}N_2O^+$ $[M+H]^+$ 241.1335, found 241.1334.

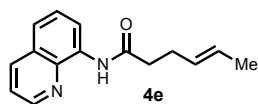


3-Methyl-N-(quinolin-8-yl)pent-4-enamide (4c): The title compound was prepared from 3-methyl-pent-4-enoic acid (1.14 g, 10 mmol) and 8-aminoquinoline (1.44 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a yellow oil (1.728 g, 72% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.80 (s, 1H), 9.05–8.59 (m, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.57–7.48 (m, 2H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 5.90 (ddd, J = 17.2, 10.3, 6.9 Hz, 1H), 5.13 (dt, J = 17.2, 1.4 Hz, 1H), 5.01 (dt, J = 10.4, 1.3 Hz, 1H), 2.99–2.85 (m, 1H), 2.62 (dd, J = 14.3, 7.1 Hz, 1H), 2.51 (dd, J = 14.3, 7.4 Hz, 1H), 1.17 (d, J = 6.8 Hz, 3H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 170.49, 148.11, 142.60, 138.35, 136.35, 134.48, 127.93, 127.43, 121.57, 121.40, 116.47, 113.61, 45.26, 34.83, 19.74; **HRMS** (ESI-TOF) Calc'd for $C_{15}H_{17}N_2O^+$ $[M+H]^+$ 241.1335, found 241.1331.

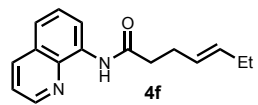


3,3-Dimethyl-N-(quinolin-8-yl)pent-4-enamide (4d): 3,3-Dimethylpent-4-enoic acid was prepared from methyl 3,3-dimethyl-pentenoate using a standard hydrolysis procedure. First, methyl 3,3-dimethyl-pentenoate (15 mmol, 1 equiv) was dissolved in a mixture of MeOH/THF/ H_2O (1:1:1, 1 M) and NaOH (30

mmol, 2 equiv) and stirred at reflux for 4 h. The crude reaction mixture was first extracted with EtOAc (3 × 20 mL), acidified with 2 M HCl, and extracted again with EtOAc (3 × 20 mL). The combined organic layers were concentrated *in vacuo*. The crude material was carried on to next step without further purification. The title compound was prepared from 3,3-dimethyl-pent-4-enoic acid (1.28 g, 10 mmol) and 8-aminoquinoline (1.00 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a yellow oil (2.032 g, 80% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.77 (s, 1H), 9.09–8.68 (m, 2H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.55–7.47 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.06 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.08 (d, *J* = 22.2 Hz, 1H), 5.05 (d, *J* = 16.2 Hz, 1H), 2.55 (s, 2H), 1.26 (s, 6H); **¹³C NMR** (150 MHz, CDCl₃) δ 169.91, 148.08, 146.90, 138.43, 136.28, 134.57, 127.92, 127.42, 121.52, 121.31, 116.41, 111.61, 51.17, 36.68, 27.07; **HRMS** (ESI-TOF) Calcd for C₁₆H₁₉N₂O⁺ [M+H]⁺ 255.1492, found 255.1490.

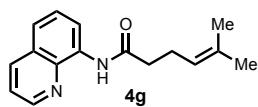


(*E*)-N-(quinolin-8-yl)hex-4-enamide (4e): (*E*)-Hex-4-enoic acid was prepared from (*E*)-hex-en-1-ol *via* Jones oxidation following an adapted literature procedure.⁴ To a 50-mL Erlenmeyer flask equipped with a Teflon-coated magnetic stir bar were added chromium(VI) oxide (2.73 g, 2.7 M) and distilled water (4 mL). The reagent mixture was cooled to 0 °C, and concentrated sulfuric acid (2.3 mL) was added dropwise, thereby forming Jones reagent. The solution of Jones reagent was then diluted to a total volume of 10 mL with distilled water. To a 100-mL round-bottom flask equipped with a Teflon-coated magnetic stir bar were added (*E*)-4-hexen-1-ol (1 equiv) and acetone (30 mL). The reaction mixture was then cooled to 0 °C. Jones reagent was added slowly into the reaction mixture over a 30-min period. The reaction was maintained at 0 °C for an additional 2 h. After this time, the reaction mixture was quenched with EtOH (20 mL) while cooling. The reaction mixture was poured carefully into a separatory funnel containing water (30 mL) and extracted with DCM (2 × 30 mL). The combined organic extracts were dried with Na₂SO₄, filtered, and concentrated *in vacuo*. The crude carboxylic acid product was then carried on to the next step without further purification. The title compound was prepared from (*E*)-hex-4-enoic acid (1.14 g, 10 mmol) and 8-aminoquinoline (1.00 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a brown solid (1.824 g, 76% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.82 (s, 1H), 8.80 (ddd, *J* = 8.9, 5.9, 1.6 Hz, 2H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.92–5.34 (m, 2H), 2.67–2.58 (m, 2H), 2.50 (tdd, *J* = 7.4, 5.8, 1.2 Hz, 2H), 1.69–1.63 (m, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.27, 148.09, 138.37, 136.35, 134.55, 129.34, 127.94, 127.45, 126.50, 121.56, 121.35, 116.46, 38.12, 28.50, 17.94; **HRMS** (ESI-TOF) Calcd for C₁₅H₁₇N₂O⁺ [M+H]⁺ 241.1335, found 241.1339.



(*E*)-N-(quinolin-8-yl)hept-4-enamide (4f): Ethyl (*E*)-hept-4-enoate was prepared from 1-penten-3-ol using a Claisen orthoester rearrangement procedure as previously described in the literature.⁵ Next, methyl (*E*)-hept-4-enoate (15 mmol, 1 equiv) was dissolved in a mixture of MeOH/THF/H₂O (1:1:1, 1M) and LiOH (30 mmol, 2 equiv) and stirred at room temperature for 4 h. The crude reaction mixture was first extracted with EtOAc (3 x 20 mL), acidified with 2M HCl, extracted again with EtOAc

(3 x 20 mL), and concentration *in vacuo*. The crude material was carried on to next step without further purification. The title compound was prepared from (*E*)-hept-4-enoic acid (1.28 g, 10 mmol) and 8-aminoquinoline (1.00 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a yellow oil (1.778 g, 70% yield). ¹H NMR (600 MHz, CDCl₃) δ 9.84 (s, 1H), 8.87–8.76 (m, 2H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.61–7.45 (m, 3H), 5.64 (dtt, *J* = 15.2, 6.1, 1.3 Hz, 1H), 5.54 (dtt, *J* = 14.9, 6.6, 1.5 Hz, 1H), 2.68–2.62 (m, 2H), 2.59–2.48 (m, 2H), 2.03 (ttt, *J* = 7.4, 6.2, 1.3 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.82, 147.62, 137.91, 135.88, 134.09, 133.20, 127.48, 126.99, 126.62, 121.09, 120.87, 115.98, 37.79, 28.06, 25.09, 13.29; HRMS (ESI-TOF) Calcd for C₁₆H₁₉N₂O⁺ [M+H]⁺ 255.1492, found 255.1496.



5-Methyl-N-(quinolin-8-yl)hex-4-enamide (4g): 5-Methylhex-4-enoic acid was prepared using a modified literature procedure.⁶ A mixture of 4-bromobutyric acid (8.38 g, 50 mmol, 1.0 equiv) and triphenylphosphine (13.11 g, 50 mmol, 1.0 equiv) was stirred at refluxed in MeCN (60 mL)

for 48 h. After this time period, the solvent was removed *in vacuo*. The residue was washed with CH₂Cl₂ (50 mL), filtered and washed again with CH₂Cl₂ (3 × 50 mL) to afford (3-carboxypropyl)triphenylphosphonium bromide. (3-Carboxypropyl)triphenylphosphonium bromide (924 mg, 2.16 mmol, 1.08 equiv) was suspended in THF (12 mL) at –20 °C. NaHMDS (2.16 mL, 4.32 mmol, 2.16 equiv) was added dropwise into the suspension, and the reaction mixture was stirred for 20 min. The reaction vessel was then cooled to –78 °C, and acetone (2.0 mmol, 1.0 equiv) was added. After 18 h, the solvent was removed *in vacuo*. H₂O (60 mL) was added to the residue, and the resulting mixture was extracted with diethyl ether (3 × 20 mL). The diethyl ether layers were discarded, and the aqueous layer was acidified using HCl (1 M). The acidified aqueous layer was further extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was carried on to the amide coupling without further purification. The title compound was prepared from (*E*)-hept-4-enoic acid (1.28 g, 10 mmol) and 8-aminoquinoline (1.00 g, 10 mmol) according to the general amide coupling procedure. Purification using silica gel column chromatography (2:1 hexane:EtOAc) gave the pure product as a yellow oil (1.778 g, % yield). ¹H NMR (600 MHz, CDCl₃) δ 9.82 (s, 1H), 8.82–8.78 (m, 2H), 8.16 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.23 (tq, *J* = 5.6, 1.5 Hz, 1H), 2.59 (dd, *J* = 7.9, 6.4 Hz, 2H), 2.51 (q, *J* = 7.4 Hz, 2H), 1.71 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.4 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.52, 148.07, 138.37, 136.34, 134.61, 133.46, 127.94, 127.46, 122.55, 121.54, 121.31, 116.44, 38.30, 25.74, 24.24, 17.80; HRMS (ESI-TOF) Calcd for C₁₆H₁₉N₂O⁺ [M+H]⁺ 255.1492, found 255.1498.

General Procedure for Dicarbofunctionalization of Alkenes

General Procedure A (with organozinc halides): To an 8-mL scintillation vial equipped with a Teflon-coated magnetic stir bar were added the alkene substrate (0.1 mmol), NiBr₂ (15 mol%), anhydrous DMA (0.5 mL), and alkyl electrophile (0.8 mmol). Next, the vial was equipped with a septum cap and organozinc halide (0.8 mmol) was added dropwise at room temperature. After addition was complete, the reaction vial was left to stir at 60 °C for 2–12 h. After the indicated reaction time, the vessel was allowed to cool to room temperature, and the reaction mixture was

diluted with 15 mL of aqueous HCl (1 M) and extracted with EtOAc (5×10 mL). The organic layers were combined, and the solvent was removed *in vacuo* to leave a yellow residue that afforded pure product after preparative thin layer chromatography (PTLC).

General Procedure B (with dialkylzinc): To an oven-dried 8-mL scintillation vial equipped with a Teflon-coated magnetic stir bar were added the alkene substrate (0.1 mmol or 0.5 mmol) and NiBr₂ (15 mol%). The vial was then equipped with a septum cap, which was pierced by a 20-gauge needle and introduced into an argon-filled glovebox antechamber. Once transferred inside the glovebox, anhydrous DMA (0.2 M), and the dialkylzinc reagent (6 or 8 equiv) were added. The vial was sealed with a screw-top septum cap, removed from the glovebox and alkyl halide (8 equiv) was added. (*Note:* If it is solid/high boiling, it can be added before the glovebox operation). The reaction vessel was placed in a heated stir plate at 60 °C for 2–12 h. After the indicated reaction time, the vessel was allowed to cool to room temperature, and the reaction mixture was diluted with 15 mL of aqueous HCl (1 M) and extracted with EtOAc (5×10 mL). The organic layers were combined, and the solvent was removed *in vacuo* to leave a yellow residue that afforded pure product after preparative thin layer chromatography (PTLC).

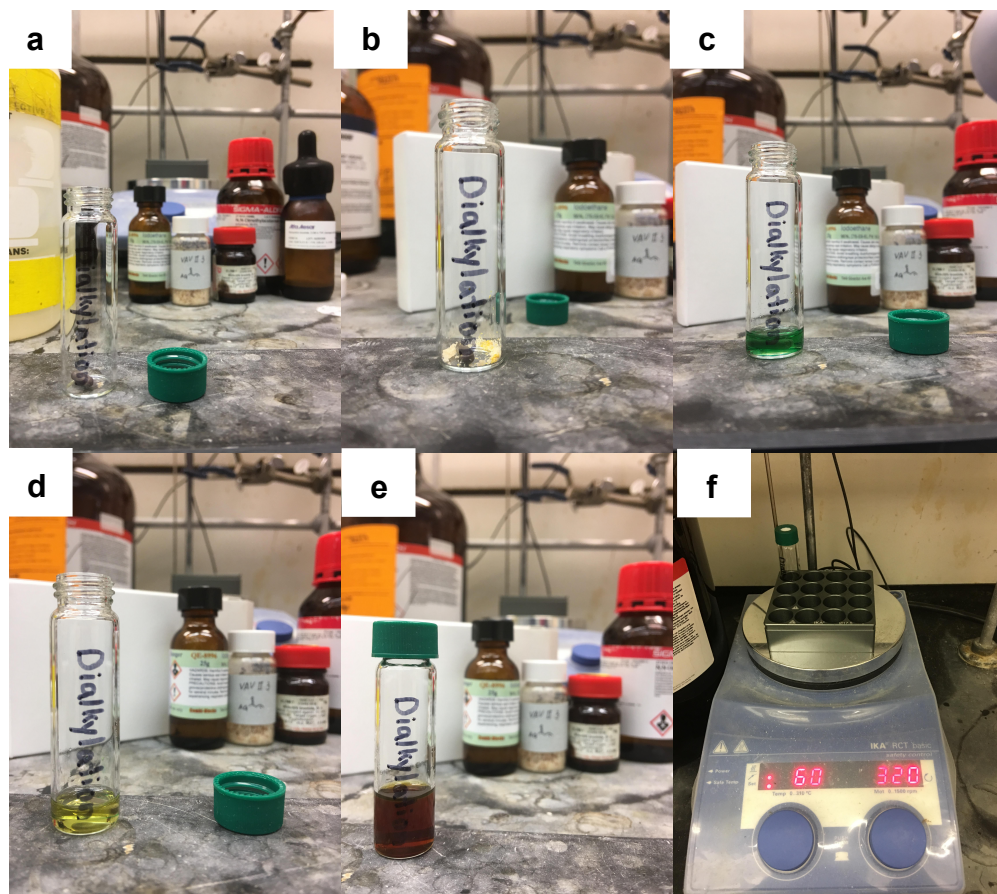
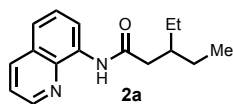
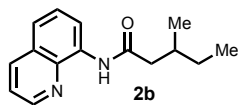


Figure S1. Photographic depiction of reaction setup following general procedure A. a) Standard reagents used outside glovebox. b) Reaction vial with alkene substrate and NiBr₂. c) Reaction vial with DMA (0.5 mL) added to solid components. d) Solution color change after addition of alkyl halide. e) Solution color change after addition of organozinc halide in THF. f) Reaction vial stirring at 60 °C.



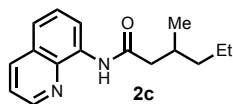
3-ethyl-*N*-(quinolin-8-yl)pentanamide (2a): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.6 mmol) according to General Procedure

A with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a yellow oil (21.2 mg, 83% yield). Additionally, the title compound was also prepared on larger scale from **1a** (106 mg, 0.5 mmol), iodoethane (624 mg, 4.0 mmol), and dimethylzinc (1.2 M in toluene, 3.0 mmol) according to General Procedure A with a reaction time of 2 h. Purification using silica gel column chromatography (1% EtOAc/Hexanes to 5% EtOAc/Hexanes, gradient) gave the pure product as a yellow oil (104 mg, 81% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.81 (s, 1H), 8.83–8.76 (m, 2H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.56–7.42 (m, 3H), 2.49 (d, *J* = 7.1 Hz, 2H), 1.97 (hept, *J* = 6.5 Hz, 1H), 1.46 (qdd, *J* = 7.3, 6.2, 5.0 Hz, 4H), 0.95 (t, *J* = 7.5 Hz, 6H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.76, 148.11, 138.35, 136.34, 134.60, 127.94, 127.46, 121.54, 121.28, 116.36, 42.60, 38.32, 25.80, 10.91; **HRMS** (ESI-TOF) Calc'd for C₁₆H₂₁N₂O⁺ [*M*+*H*]⁺ 257.1648, found 257.1650.



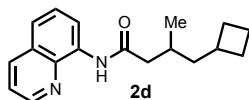
3-methyl-*N*-(quinolin-8-yl)pentanamide (2b): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodomethane (113 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.6 mmol) according to General

Procedure A with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (19.4 mg, 80% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.80 (s, 1H), 8.81 (dt, *J* = 6.1, 1.5 Hz, 2H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59–7.41 (m, 3H), 2.57 (dd, *J* = 14.2, 6.3 Hz, 1H), 2.35 (dd, *J* = 14.2, 8.2 Hz, 1H), 2.10 (h, *J* = 6.8 Hz, 1H), 1.55–1.47 (m, 1H), 1.39–1.28 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.50, 148.11, 138.35, 136.36, 134.57, 127.95, 127.46, 121.55, 121.31, 116.39, 45.67, 32.50, 29.49, 19.33, 11.41; **HRMS** (ESI-TOF) Calc'd for C₁₅H₁₉N₂O⁺ [*M*+*H*]⁺ 243.1492, found 243.1495.



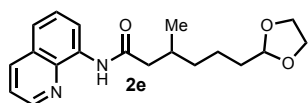
3-methyl-*N*-(quinolin-8-yl)hexanamide (2c): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodomethane (113 mg, 0.8 mmol), and diethylzinc (1.0 M in hexane, 0.6 mmol) according to General Procedure

A with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (18.2 mg, 71% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.79 (s, 1H), 8.84–8.75 (m, 2H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.57–7.42 (m, 3H), 2.56 (dd, *J* = 14.2, 6.2 Hz, 1H), 2.35 (dd, *J* = 14.2, 8.2 Hz, 1H), 2.23–2.13 (m, 1H), 1.50–1.40 (m, 2H), 1.40–1.31 (m, 1H), 1.31–1.24 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.47, 148.10, 138.35, 136.35, 134.57, 127.94, 127.46, 121.30, 116.39, 46.02, 39.13, 30.68, 20.13, 19.76, 14.23; **HRMS** (ESI-TOF) Calc'd for C₁₆H₂₁N₂O⁺ [*M*+*H*]⁺ 257.1648, found 257.1649.



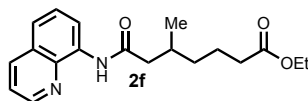
4-cyclobutyl-3-methyl-*N*-(quinolin-8-yl)butanamide (2d): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodomethane (113 mg, 0.8 mmol), and cyclobutylzinc bromide (0.5 M in THF, 0.8 mmol)

according to General Procedure B with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (18.6 mg, 66% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.80 (s, 1H), 8.86–8.80 (m, 2H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.60–7.42 (m, 3H), 2.55 (dd, *J* = 14.2, 6.2 Hz, 1H), 2.46 (hept, *J* = 7.9 Hz, 1H), 2.35 (dd, *J* = 14.2, 8.2 Hz, 1H), 2.22–2.13 (m, 1H), 2.13–2.04 (m, 2H), 1.88 (ddt, *J* = 10.9, 9.5, 8.4 Hz, 1H), 1.83–1.77 (m, 1H), 1.72–1.64 (m, 2H), 1.57 (dd, *J* = 7.9, 5.5 Hz, 1H), 1.42 (ddd, *J* = 13.4, 8.1, 7.0 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.39, 148.11, 138.36, 136.35, 134.57, 127.95, 127.46, 121.55, 121.30, 116.39, 46.10, 44.26, 34.16, 29.51, 29.22, 28.71, 19.92, 18.67; **HRMS** (ESI-TOF) Calc'd for C₁₈H₂₃N₂O⁺ [M+H]⁺ 283.1805, found 283.1809.



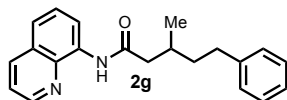
6-(1,3-dioxolan-2-yl)-3-methyl-N-(quinolin-8-yl)hexanamide (2e):

The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and 2-(1,3-dioxalan-2-yl)ethylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (14.1 mg, 43% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.81 (s, 1H), 8.82 (ddd, *J* = 9.0, 5.9, 1.6 Hz, 2H), 8.19 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.59–7.46 (m, 3H), 4.89 (t, *J* = 4.8 Hz, 1H), 4.01–3.94 (m, 2H), 3.89–3.84 (m, 2H), 2.60 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.38 (dd, *J* = 14.2, 8.2 Hz, 1H), 2.25–2.17 (m, 1H), 1.69 (ddd, *J* = 13.6, 8.9, 4.9 Hz, 2H), 1.54 (dddd, *J* = 21.4, 19.5, 8.7, 6.6 Hz, 3H), 1.40–1.34 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 170.82, 147.66, 137.89, 135.89, 134.08, 127.48, 126.98, 121.10, 120.87, 115.94, 104.08, 64.39, 45.39, 36.24, 33.56, 30.46, 21.03, 19.20; **HRMS** (ESI-TOF) Calc'd for C₁₉H₂₅N₂O₃⁺ [M+H]⁺ 329.1860, found 329.1861.



ethyl 5-methyl-7-oxo-7-(quinolin-8-ylamino)heptanoate (2f):

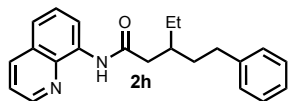
The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and 3-ethoxy-3-oxopropylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (17.0 mg, 52% yield). **¹H NMR** (600 MHz, CDCl₃) δ 10.18 (s, 1H), 9.22–9.15 (m, 2H), 8.55 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.97–7.81 (m, 3H), 4.51 (q, *J* = 7.1 Hz, 2H), 2.96 (dd, *J* = 14.3, 6.2 Hz, 1H), 2.80–2.66 (m, 3H), 2.63–2.55 (m, 1H), 2.19–2.05 (m, 2H), 1.89 (ddt, *J* = 13.2, 10.9, 5.4 Hz, 1H), 1.72 (dddd, *J* = 10.4, 8.0, 6.5, 3.8 Hz, 1H), 1.63 (t, *J* = 7.1 Hz, 3H), 1.46 (d, *J* = 6.6 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 173.67, 171.13, 148.14, 138.33, 136.36, 134.49, 127.93, 127.43, 121.58, 121.38, 116.42, 60.23, 45.72, 36.20, 34.44, 30.66, 22.46, 19.64, 14.24; **HRMS** (ESI-TOF) Calc'd for C₁₉H₂₅N₂O₃⁺ [M+H]⁺ 329.1860, found 329.1863.



3-methyl-5-phenyl-N-(quinolin-8-yl)pentanamide (2g):

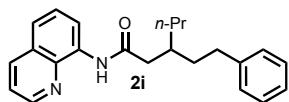
The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodomethane (113 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 2 h.

Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (23.2 mg, 73% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.79 (s, 1H), 8.81–8.66 (m, 2H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.61–7.39 (m, 3H), 7.27–7.23 (m, 2H), 7.21–7.18 (m, 2H), 7.18–7.13 (m, 1H), 2.74 (ddd, *J* = 13.7, 10.8, 5.6 Hz, 1H), 2.67 (ddd, *J* = 13.7, 10.6, 5.9 Hz, 1H), 2.62 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.40 (dd, *J* = 14.2, 8.2 Hz, 1H), 2.31–2.19 (m, 1H), 1.81 (ddt, *J* = 13.5, 11.2, 5.7 Hz, 1H), 1.64–1.57 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.11, 148.10, 142.43, 138.32, 136.35, 134.49, 128.34, 128.32, 127.93, 127.43, 125.69, 121.56, 121.37, 116.42, 45.82, 38.74, 33.47, 30.76, 19.76; **HRMS** (ESI-TOF) Calc'd for C₂₁H₂₃N₂O⁺ [M+H]⁺ 319.1805, found 319.1811.



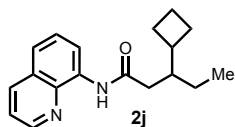
3-ethyl-5-phenyl-*N*-(quinolin-8-yl)pentanamide (2h): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 2 h.

Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (25.6 mg, 77% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.82 (s, 1H), 8.83–8.74 (m, 2H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.58–7.41 (m, 3H), 7.25–7.22 (m, 2H), 7.21–7.18 (m, 2H), 7.17–7.13 (m, 1H), 2.70 (dd, *J* = 9.6, 7.0 Hz, 2H), 2.56 (d, *J* = 7.0 Hz, 2H), 2.12 (hept, *J* = 6.5 Hz, 1H), 1.75 (tdd, *J* = 7.9, 6.5, 4.1 Hz, 2H), 1.58–1.50 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 171.38, 148.11, 142.59, 138.34, 136.35, 134.53, 128.34, 128.31, 127.94, 127.45, 125.66, 121.56, 121.35, 116.41, 42.77, 36.74, 35.40, 33.17, 26.26, 10.80; **HRMS** (ESI-TOF) Calc'd for C₂₂H₂₅N₂O⁺ [M+H]⁺ 333.1961, found 333.1964.



3-phenethyl-*N*-(quinolin-8-yl)hexanamide (2i): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), 1-bromopropane (98 mg, 0.8 mmol), benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 2 h. Purification using

preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (25.6 mg, 74% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.81 (s, 1H), 8.83–8.76 (m, 2H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.58–7.43 (m, 3H), 7.24 (d, *J* = 15.0 Hz, 2H), 7.21–7.17 (m, 2H), 7.17–7.11 (m, 1H), 2.74–2.65 (m, 2H), 2.56 (dd, *J* = 6.9, 1.6 Hz, 2H), 2.17 (h, *J* = 6.4 Hz, 1H), 1.78–1.70 (m, 2H), 1.51–1.37 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 171.35, 148.10, 142.58, 138.33, 136.34, 134.53, 128.34, 128.29, 127.44, 125.65, 121.56, 121.34, 116.41, 43.16, 36.14, 35.90, 35.19, 33.13, 19.75, 14.36; **HRMS** (ESI-TOF) Calc'd for C₂₃H₂₇N₂O⁺ [M+H]⁺ 347.2118, found 347.2118.

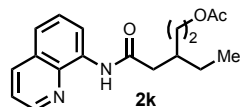


3-cyclobutyl-*N*-(quinolin-8-yl)pentanamide

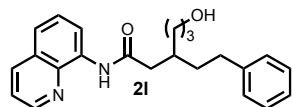
(2j): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), bromocyclobutane (108 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.6 mmol) according to General Procedure A with a reaction time of 2 h.

Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (16.1 mg, 57% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.82 (s, 1H), 8.87–8.77 (m, 2H), 8.18 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.60–7.44 (m, 3H), 2.46 (dd, *J* = 14.3, 5.9 Hz,

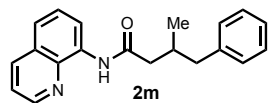
1H), 2.40 (dd, $J = 14.2, 7.5$ Hz, 1H), 2.37–2.26 (m, 1H), 2.10–2.03 (m, 2H), 2.00 (ddt, $J = 12.7, 10.4, 3.7$ Hz, 1H), 1.87–1.71 (m, 4H), 1.50 (dddd, $J = 15.0, 12.4, 6.9, 4.9$ Hz, 1H), 1.41–1.32 (m, 1H), 0.95 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.32, 147.66, 137.88, 135.88, 134.16, 127.48, 127.01, 121.08, 120.79, 115.88, 43.26, 39.99, 39.77, 27.27, 26.95, 23.83, 17.41, 10.46; **HRMS** (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}^+$ $[\text{M}+\text{H}]^+$ 283.1805, found 283.1808.



3-ethyl-5-oxo-5-(quinolin-8-ylamino)pentyl acetate (2k): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), 2-bromoethyl acetate (134 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.6 mmol) according to General Procedure A with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (4:1 hexane:EtOAc) gave the pure product as a colorless oil (16.9 mg, 51% yield). ^1H NMR (600 MHz, CDCl_3) δ 9.82 (s, 1H), 8.82–8.75 (m, 2H), 8.17 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.58–7.43 (m, 3H), 4.18 (qt, $J = 11.1, 6.9$ Hz, 2H), 2.61–2.50 (m, 2H), 2.17 (dq, $J = 14.4, 7.7, 7.1$ Hz, 1H), 2.03 (s, 3H), 1.78 (qd, $J = 6.9, 5.3$ Hz, 2H), 1.55–1.48 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.19, 170.93, 148.14, 138.31, 136.38, 134.45, 127.94, 127.44, 121.60, 121.44, 116.44, 62.63, 42.46, 34.04, 31.94, 26.29, 21.02, 10.80; **HRMS** (ESI-TOF) Calc'd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 315.1703, found 315.1708.

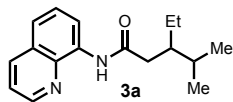


6-hydroxy-3-phenethyl-N-(quinolin-8-yl)hexanamide (2l): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), 1-3-bromo-1-propanol (111 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (3:1 hexane:EtOAc) gave the pure product as a colorless oil (23.2 mg, 64% yield). ^1H NMR (600 MHz, CDCl_3) δ 9.83 (s, 1H), 8.82–8.73 (m, 2H), 8.17 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.58–7.42 (m, 3H), 7.24 (dd, $J = 6.7, 1.3$ Hz, 2H), 7.21–7.18 (m, 2H), 7.17–7.13 (m, 1H), 3.67 (t, $J = 6.3$ Hz, 2H), 2.76–2.67 (m, 2H), 2.64 (dd, $J = 14.7, 6.2$ Hz, 1H), 2.55 (dd, $J = 14.6, 7.6$ Hz, 1H), 2.21 (dt, $J = 13.2, 6.4$ Hz, 1H), 1.80–1.72 (m, 2H), 1.70–1.63 (m, 2H), 1.56 (qd, $J = 6.7, 3.1$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.26, 148.16, 142.34, 138.31, 136.42, 134.39, 128.35, 128.34, 127.96, 127.44, 125.75, 121.60, 121.50, 116.57, 62.85, 42.84, 35.93, 34.69, 33.20, 29.85, 29.54; **HRMS** (ESI-TOF) Calc'd for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 363.2067, found 363.2070.

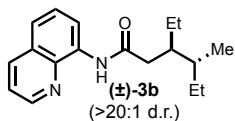


3-methyl-4-phenyl-N-(quinolin-8-yl)butanamide (2m): The title compound was prepared from **1a** (21.2 mg, 0.1 mmol), iodomethane (113 mg, 0.8 mmol), and diphenylzinc (122 mg, 0.6 mmol) according to General Procedure A with a reaction time of 2 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (19.1 mg, 63% yield). ^1H NMR (600 MHz, CDCl_3) δ 9.78 (s, 1H), 8.80 (t, $J = 6.9$ Hz, 2H), 8.15 (d, $J = 9.9$ Hz, 1H), 7.56–7.48 (m, 2H), 7.45 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.28 (t, $J = 7.5$ Hz, 2H), 7.25–7.17 (m, 3H), 2.79 (dd, $J = 13.4, 6.2$ Hz, 1H), 2.63–2.56 (m, 2H), 2.51 (ddp, $J = 14.3, 7.9, 6.4$ Hz, 1H), 2.38 (dd, $J = 14.2, 7.9$ Hz, 1H), 1.05 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.18, 148.24, 140.45, 138.45, 136.49, 134.62, 129.44, 128.39, 128.06, 127.56, 126.13, 121.70,

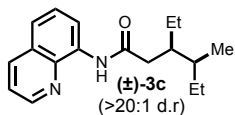
121.51, 116.56, 45.17, 43.22, 32.83, 19.77. Analytical data are consistent with previously published data.⁴



3-ethyl-4-methyl-N-(quinolin-8-yl)pentanamide (3a): The title compound was prepared from **1b** (22.6 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (18.1 mg, 67% yield). ¹H NMR (600 MHz, CDCl₃) δ 9.85 (s, 1H), 8.87–8.79 (m, 2H), 8.19 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.60–7.44 (m, 3H), 2.57 (dd, *J* = 14.6, 5.9 Hz, 1H), 2.41 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.00–1.93 (m, 1H), 1.91 (td, *J* = 6.8, 4.2 Hz, 1H), 1.55–1.46 (m, 1H), 1.41 (dt, *J* = 14.1, 7.2 Hz, 1H), 1.02–0.96 (m, 6H), 0.94 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.70, 147.65, 137.88, 135.88, 134.16, 127.48, 127.01, 121.08, 120.79, 115.89, 42.40, 39.19, 28.80, 23.29, 19.10, 18.18, 11.41; HRMS (ESI-TOF) Calc'd for C₁₇H₂₃N₂O⁺ [M+H]⁺ 271.1805, found 271.1806.

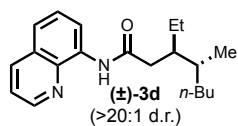


3-ethyl-4-methyl-N-(quinolin-8-yl)hexanamide (3b): The title compound was prepared from **1c** (24.0 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (19.3 mg, 68% yield). The title compound was also prepared on larger scale from **1c** (120.0 mg, 0.5 mmol), iodoethane (624 mg, 4.0 mmol), and dimethylzinc (1.2 M in toluene, 4.0 mmol) according to General Procedure A with a reaction time of 12 h. Purification using silica gel column chromatography (1% EtOAc/Hexanes to 5% EtOAc/Hexanes, gradient) gave the pure product as a colorless oil (89.5 mg, 63% yield). ¹H NMR (600 MHz, CDCl₃) δ 9.82 (s, 1H), 8.80 (ddd, *J* = 9.0, 5.9, 1.6 Hz, 2H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.58–7.42 (m, 3H), 2.54–2.42 (m, 2H), 2.02 (tdd, *J* = 12.2, 6.3, 3.6 Hz, 1H), 1.53–1.42 (m, 2H), 1.30 (dt, *J* = 13.6, 7.4 Hz, 1H), 1.20–1.10 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.91 (dd, *J* = 8.4, 7.0 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 172.09, 148.11, 138.35, 136.34, 134.63, 127.94, 127.47, 121.55, 121.25, 116.36, 41.75, 40.36, 36.65, 26.23, 22.83, 15.50, 12.30, 12.21; HRMS (ESI-TOF) Calc'd for C₁₈H₂₅N₂O⁺ [M+H]⁺ 285.1961, found 285.1964.

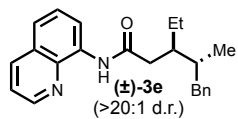


3-ethyl-4-methyl-N-(quinolin-8-yl)hexanamide (3c): The title compound was prepared from **1d** (24.0 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (16.5 mg, 58% yield). ¹H NMR (600 MHz, CDCl₃) δ 9.81 (s, 1H), 8.85–8.73 (m, 2H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.57–7.41 (m, 3H), 2.55 (dd, *J* = 14.6, 4.9 Hz, 1H), 2.29 (dd, *J* = 14.6, 8.8 Hz, 1H), 2.09–2.00 (m, 1H), 1.50–1.38 (m, 3H), 1.27–1.20 (m, 1H), 0.94 (td, *J* = 7.4, 2.2 Hz, 6H), 0.87 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.25, 148.10, 138.34, 136.34, 134.63, 127.94, 127.47, 121.55, 121.24, 116.33, 41.20, 39.17, 35.90, 27.07,

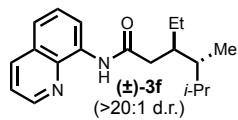
24.63, 14.73, 12.28, 12.00; **HRMS** (ESI-TOF) Calc'd for $C_{18}H_{25}N_2O^+$ $[M+H]^+$ 285.1961, found 285.1964.



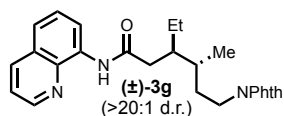
3-ethyl-4-methyl-N-(quinolin-8-yl)octanamide (3d): The title compound was prepared from **1e** (26.8 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (19.3 mg, 62% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.80 (ddd, J = 9.0, 5.9, 1.6 Hz, 2H), 8.16 (dd, J = 8.2, 1.7 Hz, 1H), 7.58–7.42 (m, 3H), 2.57–2.39 (m, 2H), 2.04–1.95 (m, 1H), 1.65 (s, 1H), 1.49 (dq, J = 14.9, 7.5, 5.4 Hz, 1H), 1.44–1.18 (m, 7H), 1.17–1.07 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); **¹³C NMR** (125 MHz, $CDCl_3$) δ 172.11, 148.10, 138.35, 136.34, 134.63, 127.94, 127.48, 121.54, 121.24, 116.35, 42.00, 40.31, 34.70, 33.21, 30.03, 23.04, 22.90, 16.08, 14.15, 12.25; **HRMS** (ESI-TOF) Calc'd for $C_{20}H_{29}N_2O^+$ $[M+H]^+$ 313.2274, found 313.2279.



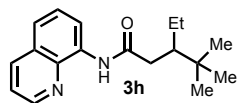
3-ethyl-4-methyl-5-phenyl-N-(quinolin-8-yl)pentanamide (3e): The title compound was prepared from **1f** (30.2 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (20.7 mg, 60% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.83–8.75 (m, 2H), 8.16 (dd, J = 8.2, 1.7 Hz, 1H), 7.63–7.43 (m, 3H), 7.22 (dd, J = 8.1, 7.0 Hz, 2H), 7.16–7.10 (m, 3H), 2.82 (dd, J = 13.3, 4.6 Hz, 1H), 2.60 (dd, J = 14.6, 6.6 Hz, 1H), 2.52 (dd, J = 14.6, 7.4 Hz, 1H), 2.37–2.27 (m, 1H), 2.11–2.06 (m, 1H), 2.06–2.01 (m, 1H), 1.67–1.58 (m, 1H), 1.42 (dt, J = 13.9, 7.4 Hz, 1H), 1.01 (t, J = 7.4 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); **¹³C NMR** (125 MHz, $CDCl_3$) δ 171.75, 148.12, 141.49, 138.33, 136.34, 134.58, 129.06, 128.18, 128.16, 127.94, 127.46, 125.65, 121.55, 121.30, 116.37, 41.92, 40.33, 39.92, 37.08, 23.23, 15.62, 12.19; **HRMS** (ESI-TOF) Calc'd for $C_{23}H_{27}N_2O^+$ $[M+H]^+$ 347.2118, found 347.2120.



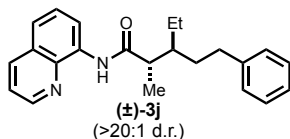
3-ethyl-4,5-dimethyl-N-(quinolin-8-yl)hexanamide (3f): The title compound was prepared from **1g** (25.4 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (15.2 mg, 51% yield). **¹H NMR** (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.80 (ddd, J = 9.0, 5.9, 1.5 Hz, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.57–7.41 (m, 3H), 2.61 (dd, J = 14.7, 6.2 Hz, 1H), 2.48 (dd, J = 14.7, 8.0 Hz, 1H), 2.24–2.13 (m, 1H), 1.63 (dq, J = 13.6, 6.8 Hz, 1H), 1.54 (dq, J = 14.0, 7.6, 3.4 Hz, 1H), 1.33 (pd, J = 7.2, 4.6 Hz, 1H), 1.27–1.17 (m, 1H), 0.99–0.94 (m, 6H), 0.86 (dd, J = 6.8, 6.0 Hz, 6H); **¹³C NMR** (125 MHz, $CDCl_3$) δ 171.93, 148.09, 138.32, 136.32, 134.60, 127.91, 127.45, 121.54, 121.22, 116.33, 41.68, 41.10, 38.90, 30.21, 21.86, 21.63, 19.92, 11.93, 11.76; **HRMS** (ESI-TOF) Calc'd for $C_{19}H_{27}N_2O^+$ $[M+H]^+$ 299.2118, found 299.2119.



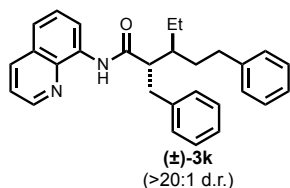
6-(1,3-dioxoisindolin-2-yl)-3-ethyl-4-methyl-*N*-(quinolin-8-yl)hexanamide (3g): The title compound was prepared from **1h** (38.5 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (9.0 mg, 21% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.80 (s, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.72 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.80 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.68 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.54–7.40 (m, 3H), 3.78–3.68 (m, 2H), 2.53 (dd, *J* = 14.7, 6.4 Hz, 1H), 2.43 (dd, *J* = 14.7, 7.6 Hz, 1H), 2.05 (s, 1H), 1.85 (dtd, *J* = 12.7, 8.2, 4.1 Hz, 1H), 1.78 (ddt, *J* = 10.3, 7.2, 3.7 Hz, 1H), 1.47 (ddd, *J* = 15.1, 7.6, 6.1 Hz, 2H), 1.35 (dq, *J* = 14.3, 7.5 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.55, 168.37, 148.14, 138.32, 136.31, 134.52, 133.79, 132.16, 127.91, 127.42, 123.11, 121.56, 121.29, 116.37, 41.85, 39.99, 36.71, 32.46, 32.12, 23.09, 15.95, 12.18; **HRMS** (ESI-TOF) Calc'd for C₂₆H₂₈N₃O₃⁺ [M+H]⁺ 430.2125, found 430.2131.



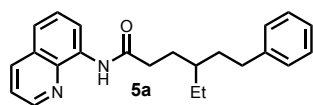
3-ethyl-4,4-dimethyl-*N*-(quinolin-8-yl)pentanamide (3h): The title compound was prepared from **1i** (24.0 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (17.6 mg, 62% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.83 (s, 1H), 8.87–8.75 (m, 2H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.58–7.42 (m, 3H), 2.69 (dd, *J* = 15.3, 4.7 Hz, 1H), 2.32 (dd, *J* = 15.4, 7.1 Hz, 1H), 1.86 (dddd, *J* = 9.2, 7.0, 4.7, 3.2 Hz, 1H), 1.70 (dq, *J* = 13.8, 7.6, 3.2 Hz, 1H), 1.18 (ddt, *J* = 14.4, 9.2, 7.3 Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.96 (s, 9H); **¹³C NMR** (150 MHz, CDCl₃) δ 172.53, 148.09, 138.35, 136.35, 134.74, 127.95, 127.49, 121.54, 121.17, 116.29, 46.85, 39.66, 33.72, 27.67, 23.99, 13.55; **HRMS** (ESI-TOF) Calc'd for C₁₈H₂₅N₂O⁺ [M+H]⁺ 285.1961, found 285.1965.



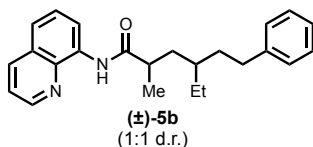
3-ethyl-2-methyl-5-phenyl-*N*-(quinolin-8-yl)pentanamide (3j): The title compound was prepared from **1k** (22.6 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (18.0 mg, 52% yield). **¹H NMR** (600 MHz, CDCl₃) δ 9.89 (s, 1H), 8.85–8.70 (m, 2H), 8.16 (ddd, *J* = 8.2, 3.3, 1.7 Hz, 1H), 7.60–7.40 (m, 3H), 7.23–7.15 (m, 4H), 7.13–7.08 (m, 1H), 2.70 (t, *J* = 6.9 Hz, 1H), 2.68–2.58 (m, 2H), 1.89–1.83 (m, 2H), 1.70–1.63 (m, 1H), 1.55–1.51 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 174.98, 148.14, 142.65, 138.50, 136.32, 134.57, 128.30, 128.27, 127.95, 127.46, 125.63, 121.54, 121.27, 116.39, 44.95, 42.36, 32.92, 31.51, 23.97, 14.08, 11.46; **HRMS** (ESI-TOF) Calc'd for C₂₃H₂₇N₂O⁺ [M+H]⁺ 347.2118, found 347.2120.



2-benzyl-3-ethyl-5-phenyl-*N*-(quinolin-8-yl)pentanamide (3k): The title compound was prepared from **11** (30.2 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (16.9 mg, 40% yield). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.61 (s, 1H), 8.80–8.65 (m, 2H), 8.16–8.06 (m, 1H), 7.53–7.35 (m, 3H), 7.26–7.22 (m, 3H), 7.19 (ddd, $J = 11.3, 8.0, 5.9$ Hz, 5H), 7.16–7.04 (m, 2H), 3.16 (dd, $J = 13.6, 10.1$ Hz, 1H), 2.94 (dd, $J = 13.6, 4.4$ Hz, 1H), 2.86 (ddd, $J = 10.2, 5.9, 4.4$ Hz, 1H), 2.70 (dddd, $J = 31.6, 13.2, 10.4, 5.5$ Hz, 2H), 1.96 (ddt, $J = 13.5, 11.1, 5.4$ Hz, 1H), 1.91–1.66 (m, 3H), 1.49 (dt, $J = 14.4, 7.3$ Hz, 1H), 0.99 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 172.98, 148.01, 142.43, 140.30, 138.34, 136.19, 134.33, 128.92, 128.39, 128.37, 128.31, 127.84, 127.36, 126.07, 125.71, 121.47, 121.26, 116.38, 53.54, 42.13, 35.57, 33.12, 32.13, 23.70, 11.75; **HRMS** (ESI-TOF) Calc'd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}^+$ $[\text{M}+\text{H}]^+$ 423.2431, found 423.2431.

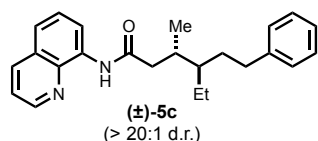


4-ethyl-6-phenyl-*N*-(quinolin-8-yl)hexanamide (5a): The title compound was prepared from **4a** (22.6 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (22.5 mg, 65% yield). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.81 (s, 1H), 8.86–8.75 (m, 2H), 8.16 (dt, $J = 8.3, 2.2$ Hz, 1H), 7.58–7.40 (m, 3H), 7.25 (d, $J = 1.7$ Hz, 3H), 7.21–7.14 (m, 3H), 2.68–2.60 (m, 2H), 2.60–2.53 (m, 2H), 1.90–1.83 (m, 2H), 1.70–1.62 (m, 2H), 1.51–1.42 (m, 3H), 0.93 (t, $J = 7.3$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 172.01, 148.10, 142.90, 138.34, 136.37, 134.57, 129.19, 128.34, 128.30, 127.47, 125.62, 121.57, 121.32, 116.40, 38.25, 35.55, 34.99, 33.08, 28.74, 25.52, 10.66; **HRMS** (ESI-TOF) Calc'd for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}^+$ $[\text{M}+\text{H}]^+$ 347.2118, found 347.2119.



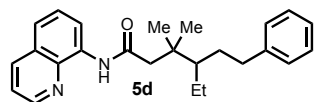
4-ethyl-2-methyl-6-phenyl-*N*-(quinolin-8-yl)hexanamide (5b): The title compound was prepared from **4b** (24.0 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the product as a colorless oil (19.1 mg, 53% yield). This product was isolated as an inseparable 1:1 mixture of diastereomers. The reported d.r. was determined by $^1\text{H NMR}$ analysis; d.r. values for the crude reaction mixture and purified product were identical. The ensuing analytical data represents both diastereomers. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.87 (s, 1H), 8.80 (ddt, $J = 5.6, 3.7, 1.7$ Hz, 2H), 8.17 (dt, $J = 8.3, 1.8$ Hz, 1H), 7.59–7.41 (m, 3H), 7.25–7.08 (m, 5H), 2.70 (dp, $J = 14.0, 6.8, 6.2$ Hz, 1H), 2.60 (dt, $J = 10.1, 6.8$ Hz, 2H), 1.90 (dt, $J = 16.6, 8.4$ Hz, 1H), 1.73–1.58 (m, 2H), 1.53–1.39 (m, 4H), 1.32 (dd, $J = 6.8, 2.2$ Hz, 3H), 0.90 (q, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 148.14, 142.99, 138.47, 136.35, 136.33, 134.59, 128.35, 128.31, 128.24, 128.20, 127.94, 127.46, 125.56, 125.51, 121.56, 121.30, 116.46, 40.75,

40.59, 38.35, 38.31, 36.47, 36.45, 35.25, 35.12, 33.01, 32.84, 25.79, 25.73, 18.60, 18.53, 10.42, 10.40; **HRMS** (ESI-TOF) Calc'd for $C_{24}H_{29}N_2O^+$ $[M+H]^+$ 361.2274, found 361.2274.



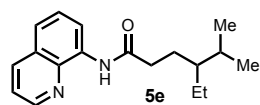
4-ethyl-3-methyl-6-phenyl-N-(quinolin-8-yl)hexanamide (5c): The title compound was prepared from **4c** (24.0 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 12 h.

Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (20.5 mg, 57% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.80 (dq, J = 5.6, 1.9, 1.5 Hz, 2H), 8.16 (dd, J = 8.2, 1.7 Hz, 1H), 7.56–7.43 (m, 3H), 7.27–7.24 (m, 2H), 7.23–7.19 (m, 2H), 7.18–7.12 (m, 1H), 2.70 (ddd, J = 13.6, 10.9, 5.5 Hz, 1H), 2.65–2.58 (m, 1H), 2.57 (dd, J = 14.0, 5.3 Hz, 1H), 2.47–2.40 (m, 1H), 2.37–2.29 (m, 1H), 1.68 (dddd, J = 13.6, 10.8, 5.9, 4.7 Hz, 1H), 1.53 (dddd, J = 13.5, 10.7, 7.9, 5.5 Hz, 1H), 1.43 (pd, J = 7.1, 2.2 Hz, 2H), 1.38–1.30 (m, 1H), 1.03–0.91 (m, 6H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.59, 148.11, 142.98, 138.33, 136.35, 134.54, 128.37, 128.29, 127.94, 127.45, 125.64, 121.57, 121.33, 116.39, 43.76, 43.08, 34.31, 32.20, 31.88, 23.69, 15.65, 12.21; **HRMS** (ESI-TOF) Calc'd for $C_{24}H_{29}N_2O^+$ $[M+H]^+$ 361.2274, found 361.2271.



4-ethyl-3,3-dimethyl-6-phenyl-N-(quinolin-8-yl)hexanamide (5d):

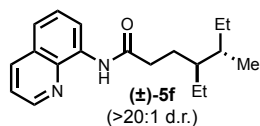
The title compound was prepared from **4d** (25.4 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and benzylzinc bromide (0.5 M in THF, 0.8 mmol) according to General Procedure B with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (23.9 mg, 64% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.84–8.77 (m, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.57–7.40 (m, 3H), 7.26 (d, J = 4.2 Hz, 2H), 7.22–7.15 (m, 3H), 2.74 (ddd, J = 13.5, 11.8, 5.2 Hz, 1H), 2.61 (ddd, J = 13.5, 11.4, 5.6 Hz, 1H), 2.47 (d, J = 2.4 Hz, 2H), 1.89 (dddd, J = 14.4, 11.7, 5.7, 2.9 Hz, 1H), 1.77–1.68 (m, 1H), 1.46 (dddd, J = 13.7, 11.8, 7.1, 5.3 Hz, 1H), 1.29 (qd, J = 6.7, 6.0, 2.7 Hz, 2H), 1.14 (d, J = 2.5 Hz, 6H), 1.03 (t, J = 7.3 Hz, 3H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 170.83, 148.11, 143.08, 138.37, 136.31, 134.56, 128.35, 128.30, 127.93, 127.43, 125.68, 121.54, 121.27, 116.32, 49.32, 48.58, 37.66, 36.50, 33.50, 25.33, 25.29, 23.91, 14.35; **HRMS** (ESI-TOF) Calc'd for $C_{25}H_{31}N_2O^+$ $[M+H]^+$ 375.2431, found 375.2432.



3-ethyl-2-methyl-5-phenyl-N-(quinolin-8-yl)pentanamide (5e):

The title compound was prepared from **4e** (24.0 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (15.6 mg, 55% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.84–8.74 (m, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.59–7.40 (m, 3H), 2.66–2.46 (m, 2H), 1.95–1.59 (m, 3H), 1.47–1.35 (m, 1H), 1.35–1.23 (m, 2H), 1.21–1.11 (m, 1H), 0.95–0.85 (m, 9H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 172.21, 148.09, 138.35, 136.36, 134.61, 127.94, 127.47, 121.55, 121.27, 116.38,

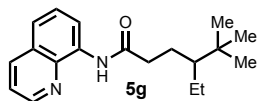
45.16, 36.51, 28.89, 25.90, 22.74, 19.35, 19.12, 12.01; **HRMS** (ESI-TOF) Calc'd for $C_{18}H_{25}N_2O^+$ $[M+H]^+$ 285.1961, found 285.1965.



4-ethyl-5-methyl-N-(quinolin-8-yl)heptanamide

(5f): The title compound was prepared from **4f** (25.4 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h.

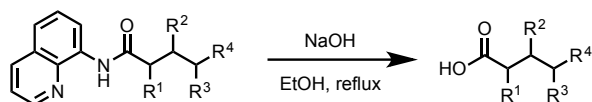
Purification using preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (15.5 mg, 52% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.86–8.78 (m, 2H), 8.19 (dd, J = 8.2, 1.7 Hz, 1H), 7.62–7.45 (m, 3H), 2.66–2.52 (m, 2H), 1.82 (qdt, J = 13.7, 9.4, 6.6 Hz, 2H), 1.57–1.48 (m, 1H), 1.48–1.35 (m, 2H), 1.33–1.26 (m, 1H), 1.25–1.16 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.93–0.90 (m, 3H), 0.88 (d, J = 6.9 Hz, 3H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.73, 147.62, 137.90, 135.90, 134.15, 127.48, 127.01, 121.09, 120.80, 115.93, 43.23, 36.15, 35.59, 26.09, 21.74, 14.69, 11.98, 11.87; **HRMS** (ESI-TOF) Calc'd for $C_{19}H_{27}N_2O^+$ $[M+H]^+$ 299.2118, found 299.2119.



4-ethyl-5,5-dimethyl-N-(quinolin-8-yl)hexanamide (5g): The title compound was prepared from **4g** (26.8 mg, 0.1 mmol), iodoethane (137 mg, 0.8 mmol), and dimethylzinc (1.2 M in toluene, 0.8 mmol) according to General Procedure A with a reaction time of 12 h. Purification using

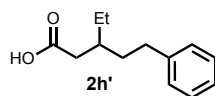
preparative thin layer chromatography (PTLC) (9:1 hexane:EtOAc) gave the pure product as a colorless oil (12.2 mg, 41% yield). **¹H NMR** (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.85–8.76 (m, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.59–7.40 (m, 3H), 2.69 (ddd, J = 15.2, 10.0, 5.3 Hz, 1H), 2.45 (ddd, J = 14.7, 9.6, 6.5 Hz, 1H), 2.13 (dddd, J = 12.8, 9.5, 6.5, 2.4 Hz, 1H), 1.40 (dddd, J = 13.2, 10.9, 9.7, 5.3 Hz, 1H), 1.34–1.22 (m, 3H), 0.92 (d, J = 14.6 Hz, 12H); **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.75, 147.63, 137.89, 135.91, 134.14, 127.49, 127.01, 121.10, 120.83, 115.95, 42.28, 36.91, 32.75, 29.24, 27.20, 26.86, 13.62; **HRMS** (ESI-TOF) Calc'd for $C_{19}H_{27}N_2O^+$ $[M+H]^+$ 299.2118, found 299.2121.

General Procedure for Removal of 8-Aminoquinoline Directing Group



Scheme S2. Amide hydrolysis to remove 8-aminoquinoline directing group.

General Procedure for Hydrolysis of Directing Group: The 8-aminoquinoline directing group was removed by adapting a literature procedure.⁷ To a flame-dried 20-mL sealed vessel equipped with a Teflon-coated magnetic stir bar was added dicarbofunctionalized product (0.1 mmol), NaOH (1.5 mmol, 15 equiv), and 0.4 mL of EtOH. The resulting mixture was stirred at 130 °C for 16 h. At this time, the reaction mixture was allowed to cool to room temperature, diluted with 50 mL of EtOAc and washed with HCl (1 M, 3 × 4 mL). The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo* to give pure hydrolysis free acid product.



3-ethyl-5-phenylpentanoic acid (2h'): The title compound was prepared from **2h** (33.2 mg, 0.1 mmol) using the general directing group hydrolysis procedure. Following a straightforward work-up, the product was obtained as a brown oil (20.1 mg, 98% yield). ^1H NMR (600 MHz, CDCl_3) δ 7.30–7.26 (m, 2H), 7.20–7.15 (m, 3H), 2.62 (t, J = 8.2 Hz, 2H), 2.36 (d, J = 7.0 Hz, 2H), 1.90 (hept, J = 6.5 Hz, 1H), 1.70–1.60 (m, 2H), 1.51–1.39 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 141.91, 127.89, 127.84, 125.30, 37.65, 35.62, 34.80, 32.54, 25.67, 10.22.

Optimization Table with Dimethylated Byproduct

Table S2. Optimization table (as shown in Table 1) with demethylated byproduct yields.^{a,b}

entry	cat. Ni	EtI (equiv)	ZnMe ₂ (equiv)	solvent (M)	temp. (°C)	yield 2a (%) ^b	yield 2a' (%) ^b
1	10% NiCl ₂ •glyme	2	2	DMA (0.5)	100	39	24
2	10% NiBr ₂	2	2	DMA (0.5)	100	37	18
3	10% NiCl ₂ •glyme	2	2	dioxane (0.5)	RT	n.d.	n.d.
4	10% NiCl ₂ •glyme	2	2	DMF (0.5)	RT	13	5
5	10% NiCl ₂ •glyme	2	2	DMA (0.5)	RT	28	17
6	10% NiCl ₂ •glyme	2	2	DMA (0.1)	50	46	26
7	10% NiCl ₂ •glyme	2	2	DMA (0.2)	60	53	13
8	10% NiCl ₂ •glyme	4	4	DMA (0.2)	60	68	14
9	15% NiBr ₂	8	8	DMA (0.2)	60	81	17
10	15% NiBr ₂	8	6	DMA (0.2)	60	83	12

^aReaction conditions: alkene (0.1 mmol), ZnMe₂ (1.2 M in toluene). ^bYields determined by ^1H NMR analysis using CH₂Br₂ as internal standard; n.d. = not detected.

Determination of Relative Stereochemistry for Internal Substrates

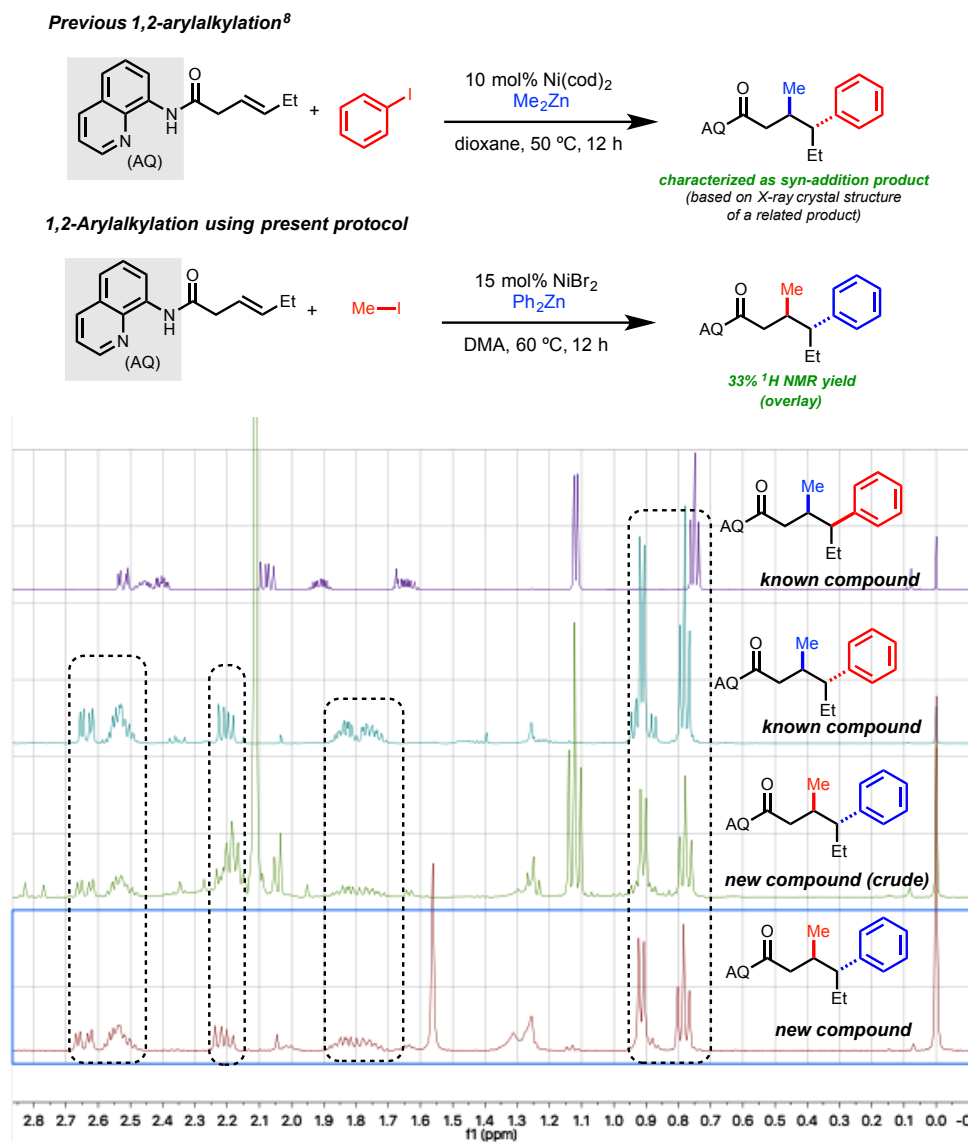
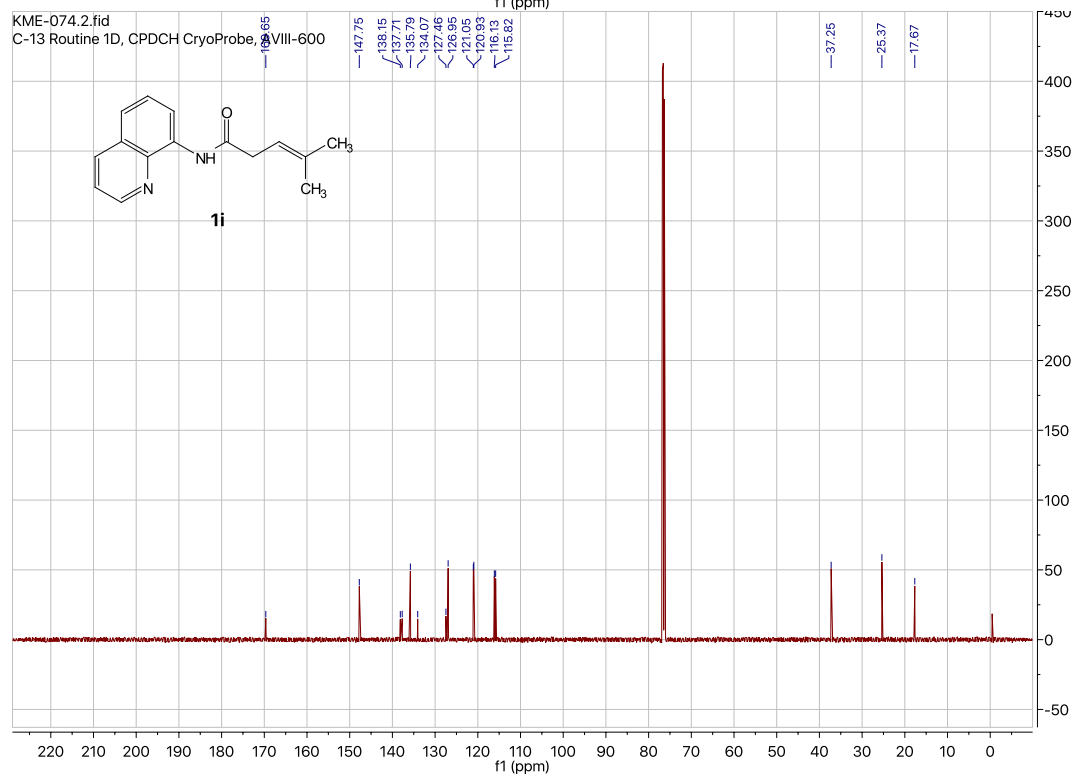
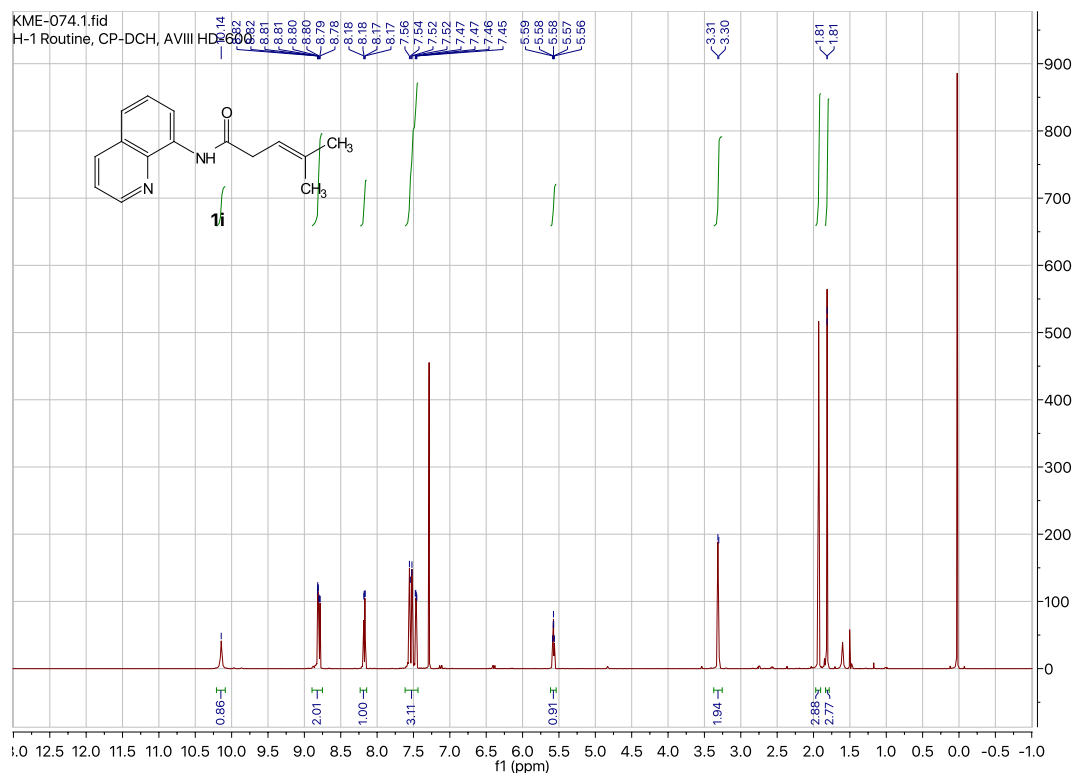


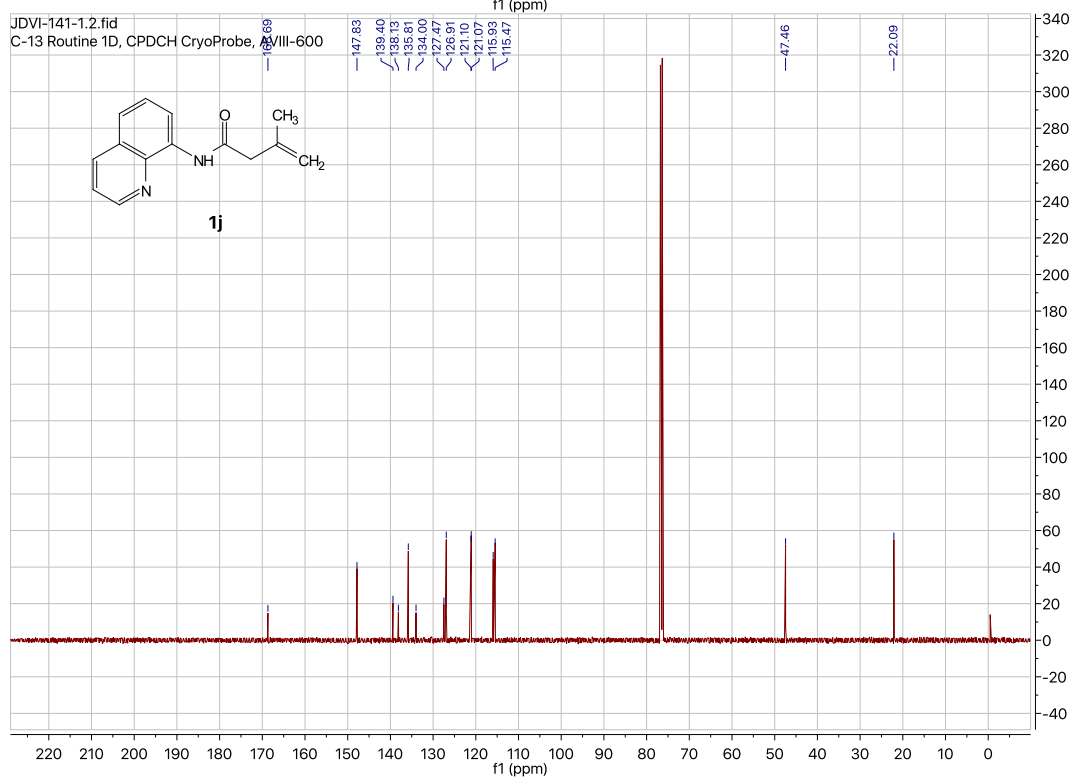
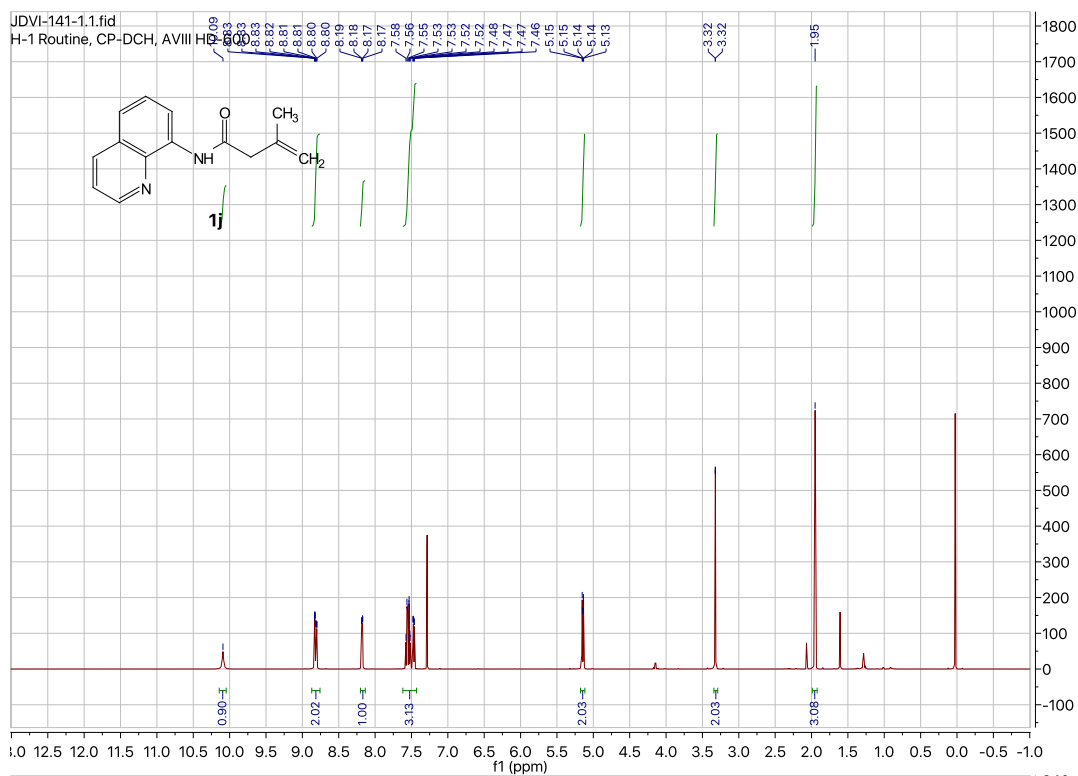
Figure S2. Comparison of a previously characterized diastereomer under previous literature conditions and an adapted synthesis of the same diastereomer using current conditions.

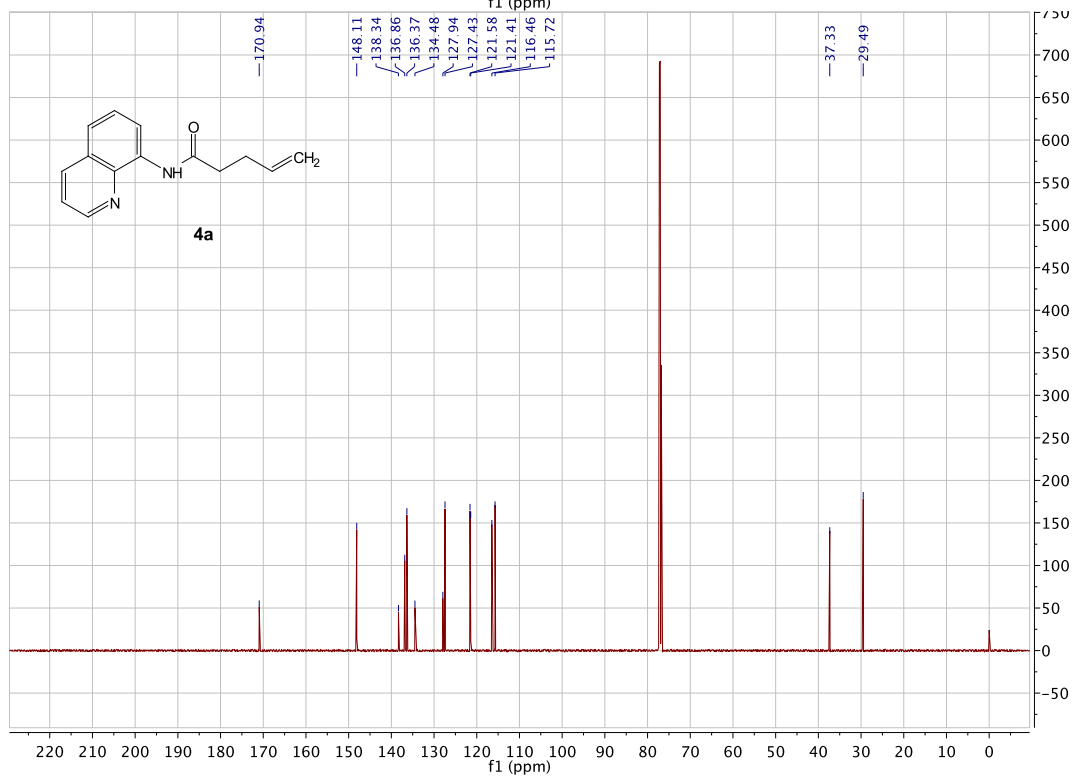
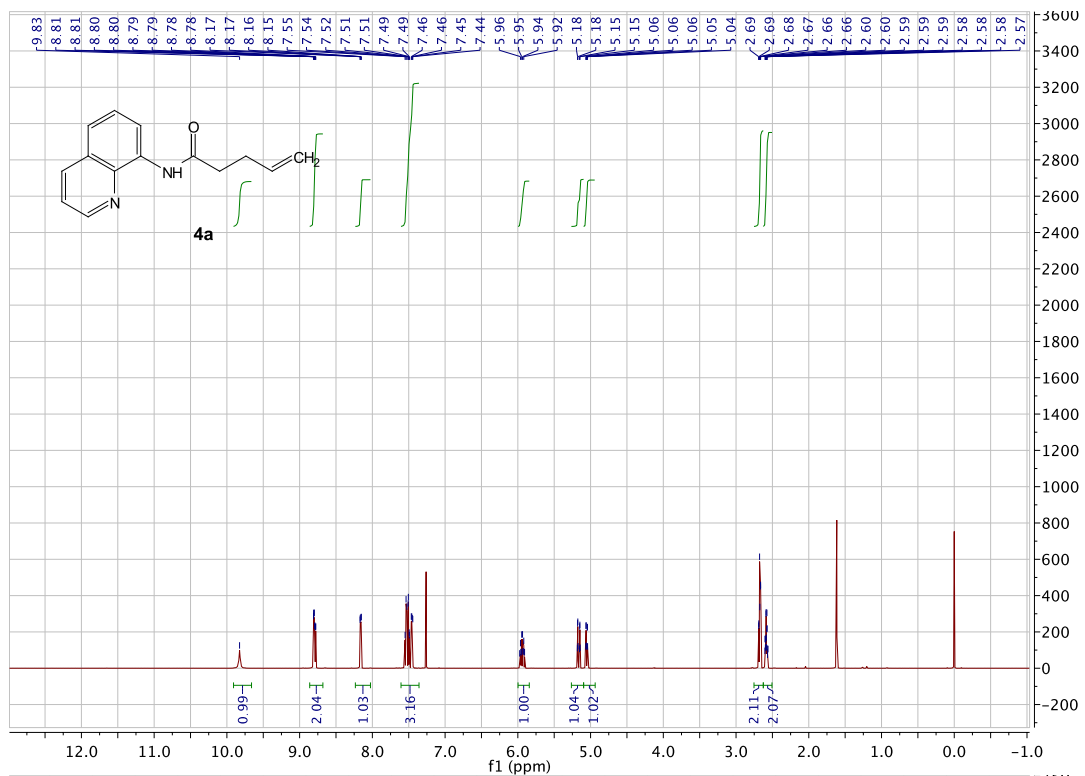
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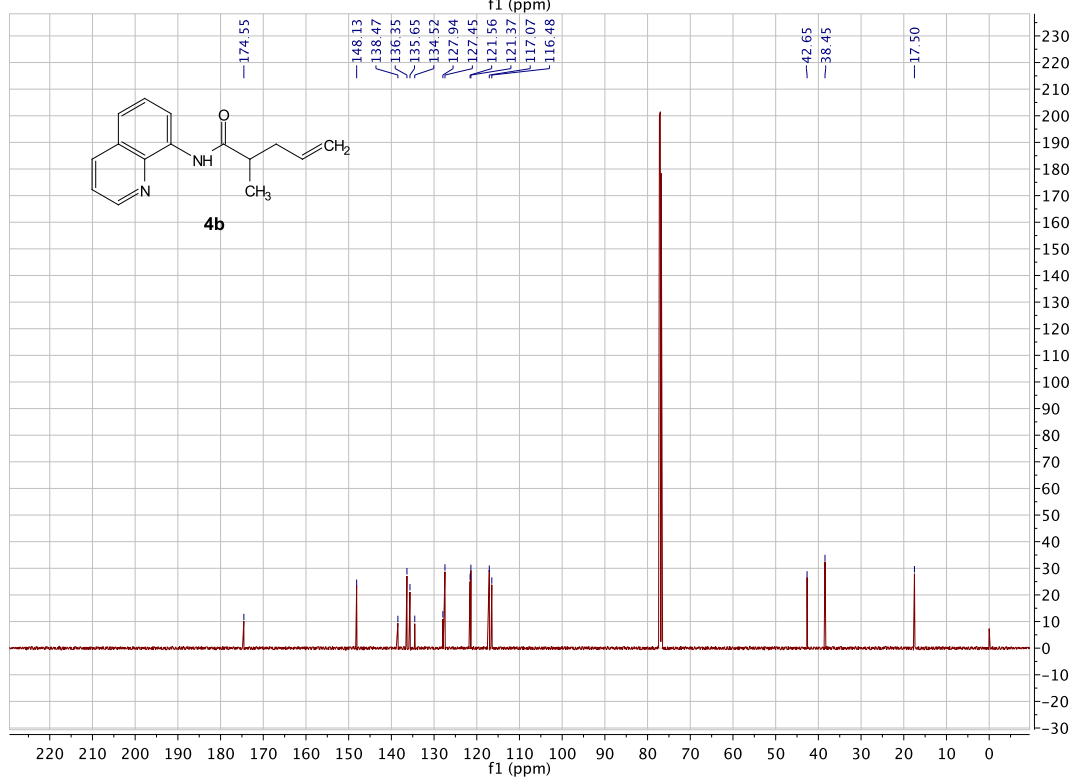
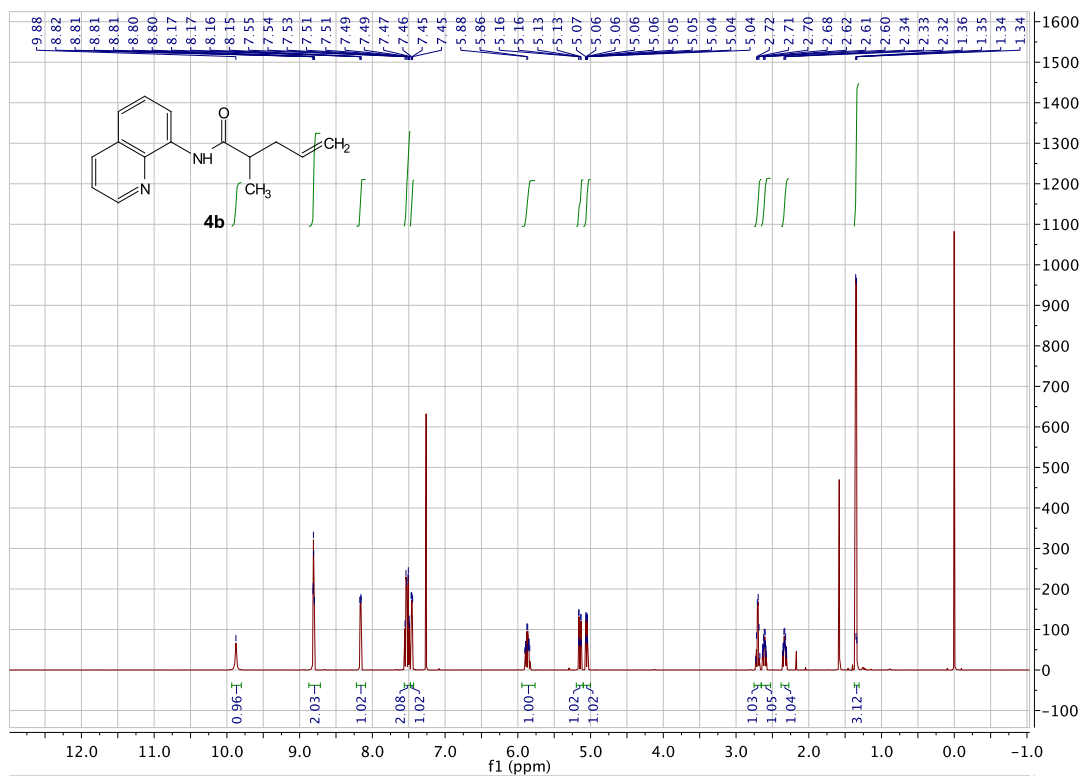
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- (2) K. S. Yang, J. A. Gurak, Jr., Z. Liu and K. M. Engle, *J. Am. Chem. Soc.* 2016, **138**, 14705–14712.
- (3) D. E. Cane, G. Yang, R. M. Coates, H. J. Pyun and T. M. Hohn, *J. Org. Chem.* 1992, **57**, 3454–3462.
- (4) B. H. Toder, S. J. Branca and A. B. Smith, *J. Am. Chem. Soc.* 1981, **103**, 1996–2008.
- (5) R. N. Shakhmaev, A. U. Ishbaeva and I. S. Shayakhmetova, *Russ. J. Gen. Chem.* 2009, **79**, 1171–1174.
- (6) C. K. Tan, L. Zhou and Y.-Y. Yeung, *Org. Lett.* 2011, **13**, 2738–2741.
- (7) J. Roane and O. Daugulis, *J. Am. Chem. Soc.* 2016, **138**, 4601–4607.
- (8) J. Derosa, V. T. Tran, M. N. Boulous, J. S. Chen and K. M. Engle, *J. Am. Chem. Soc.* 2017, **139**, 10657–10660.

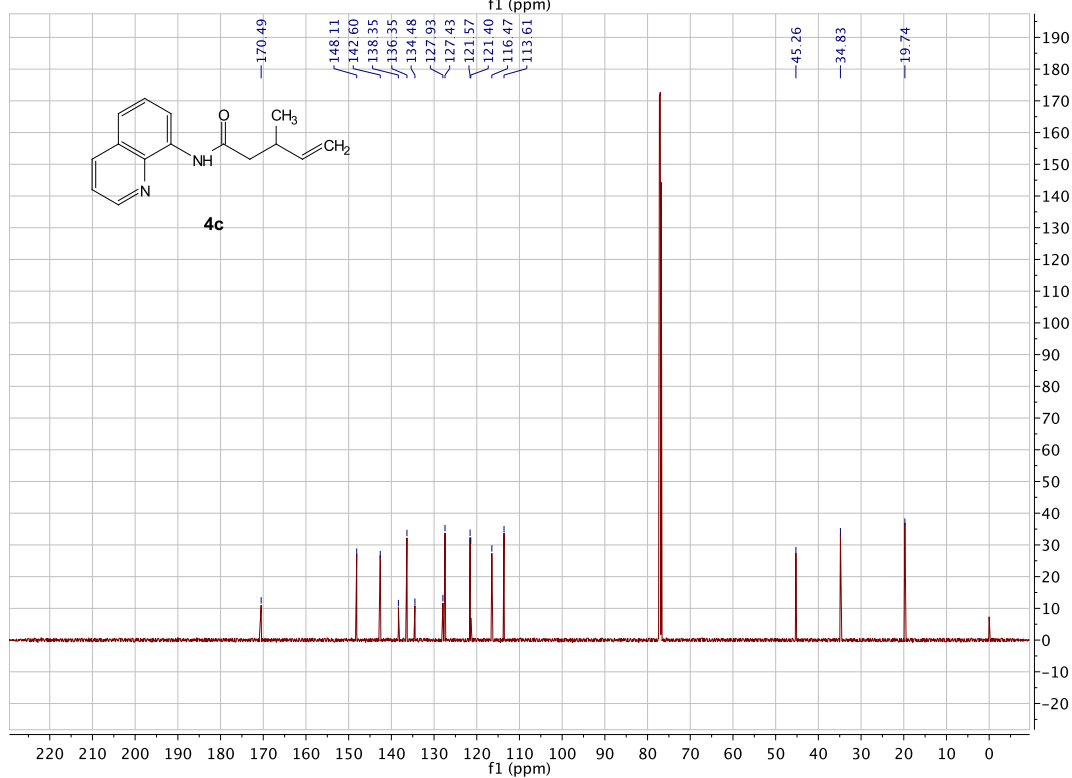
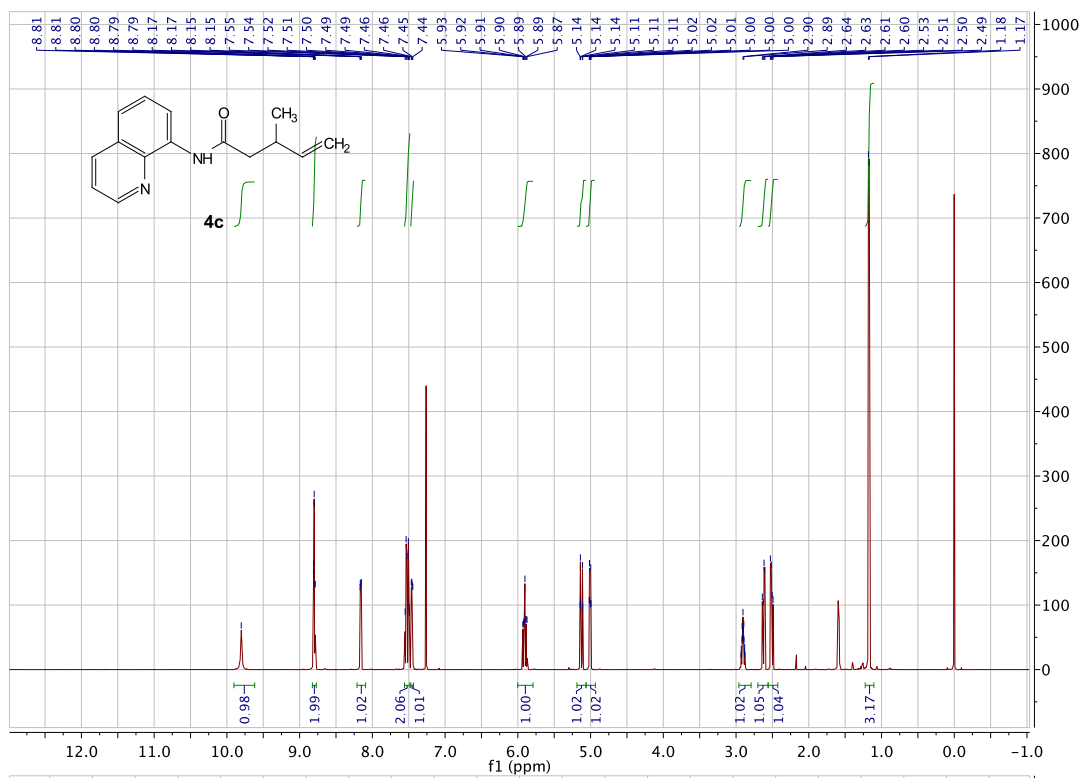
NMR SPECTRA

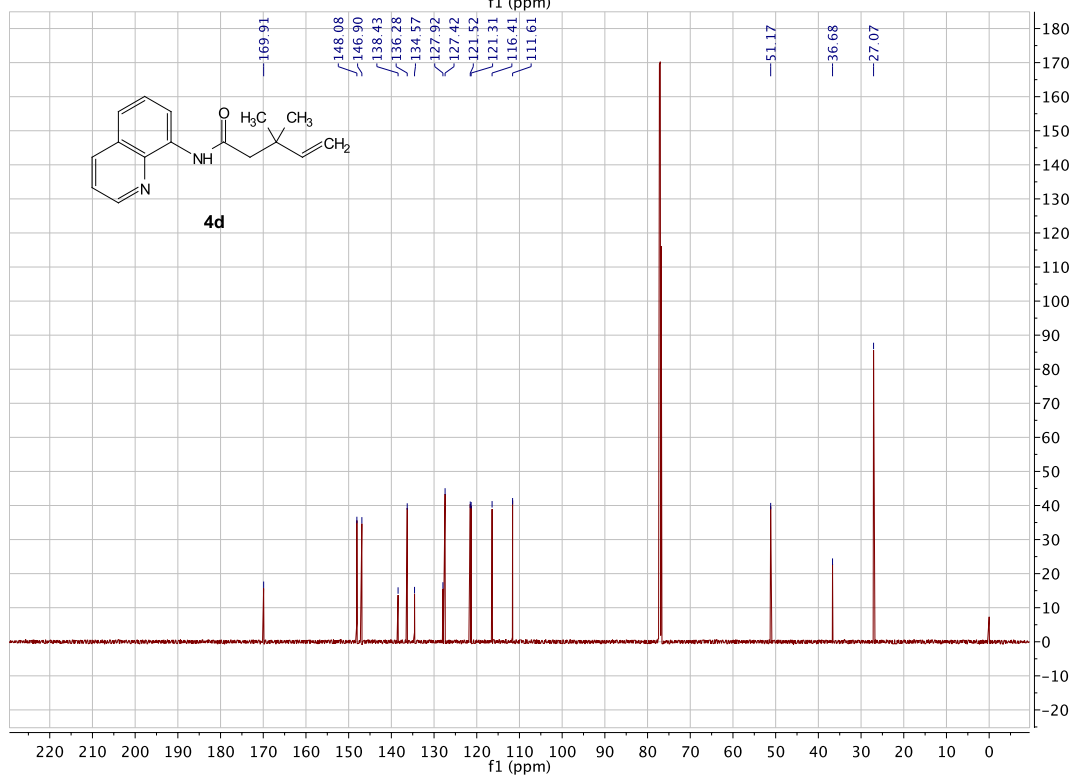
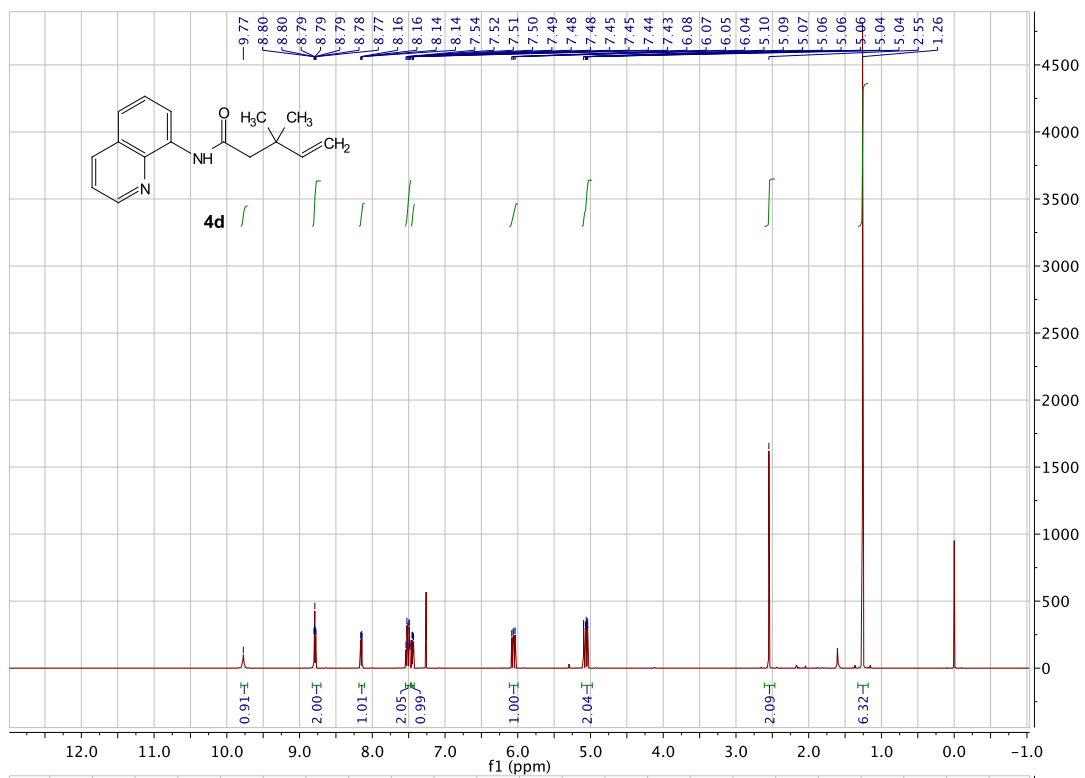


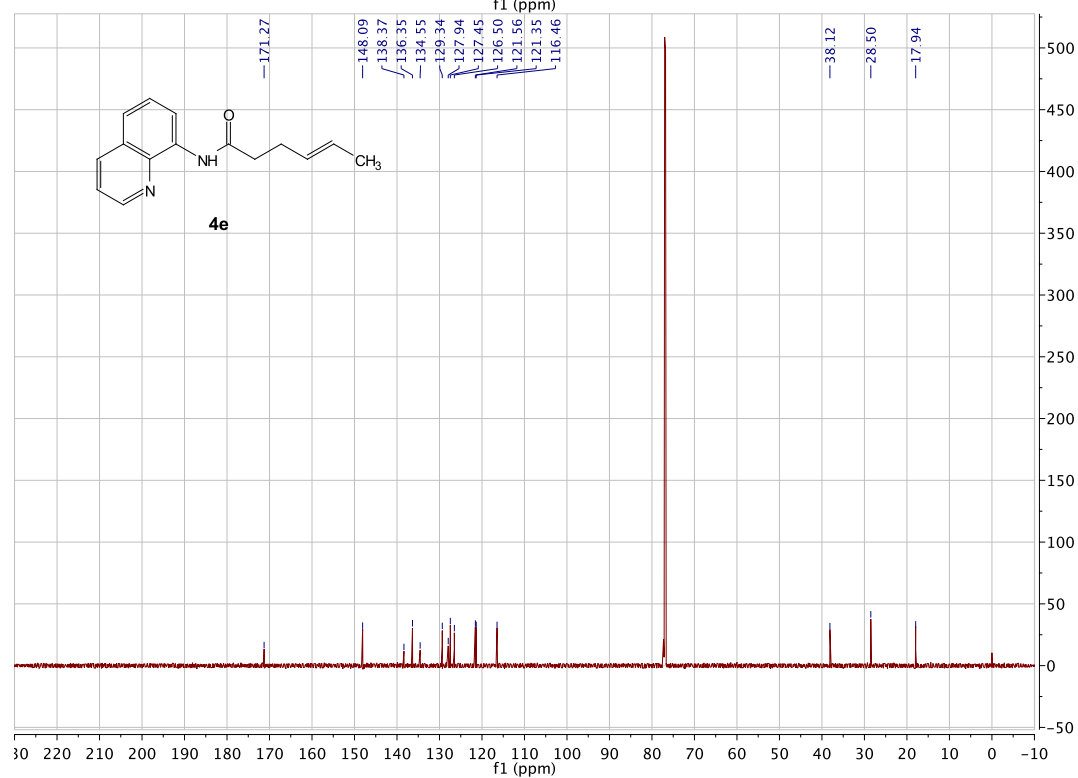
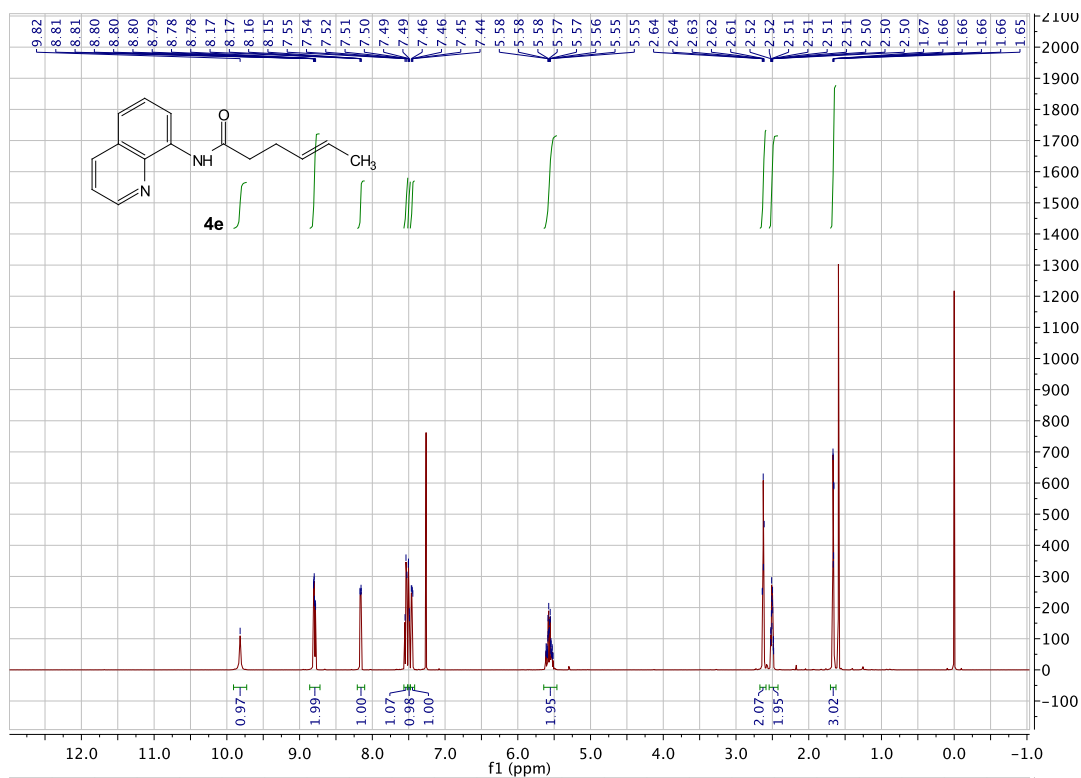


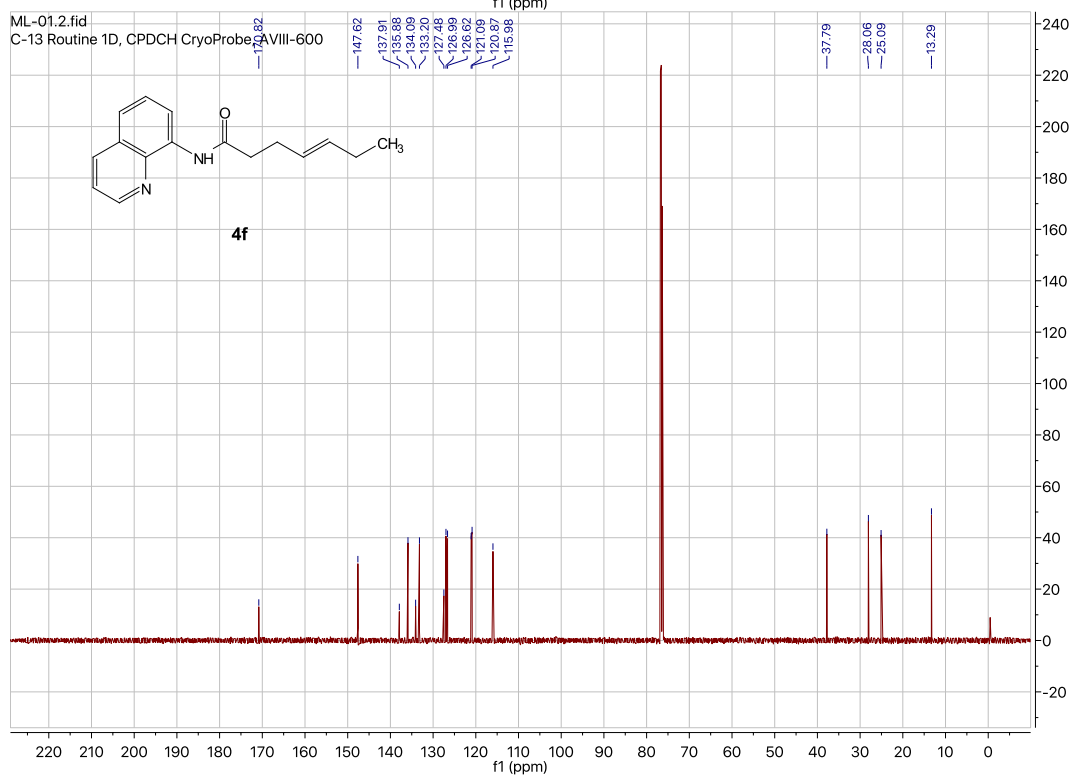
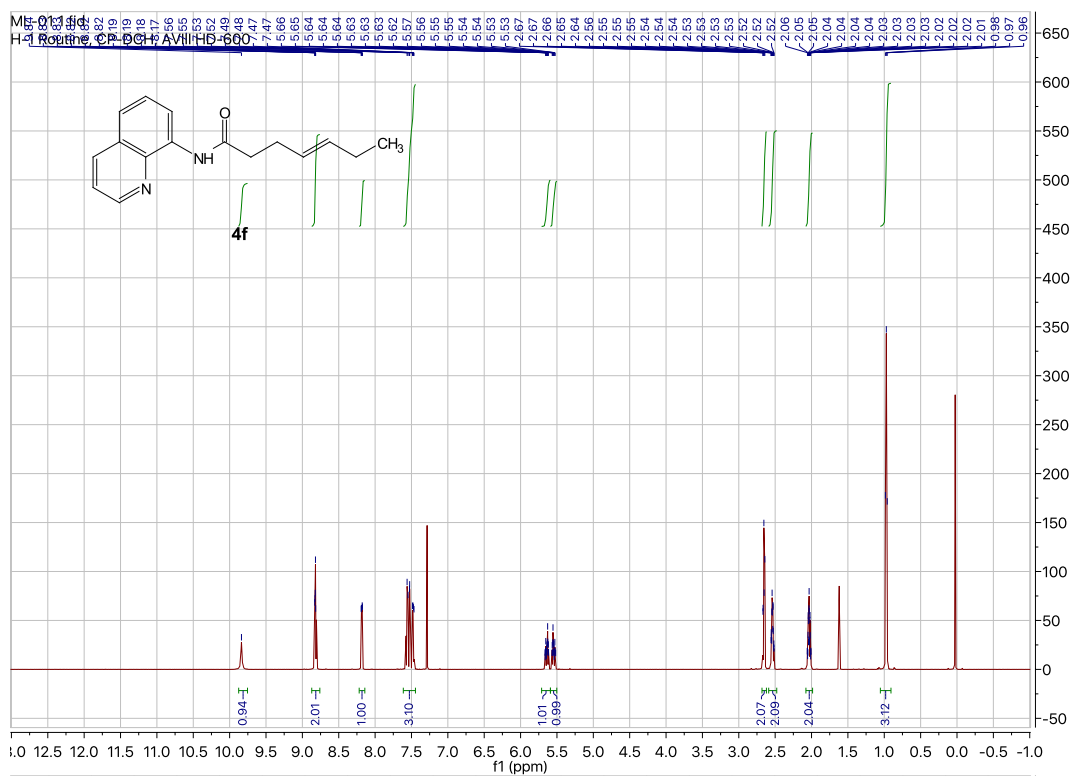


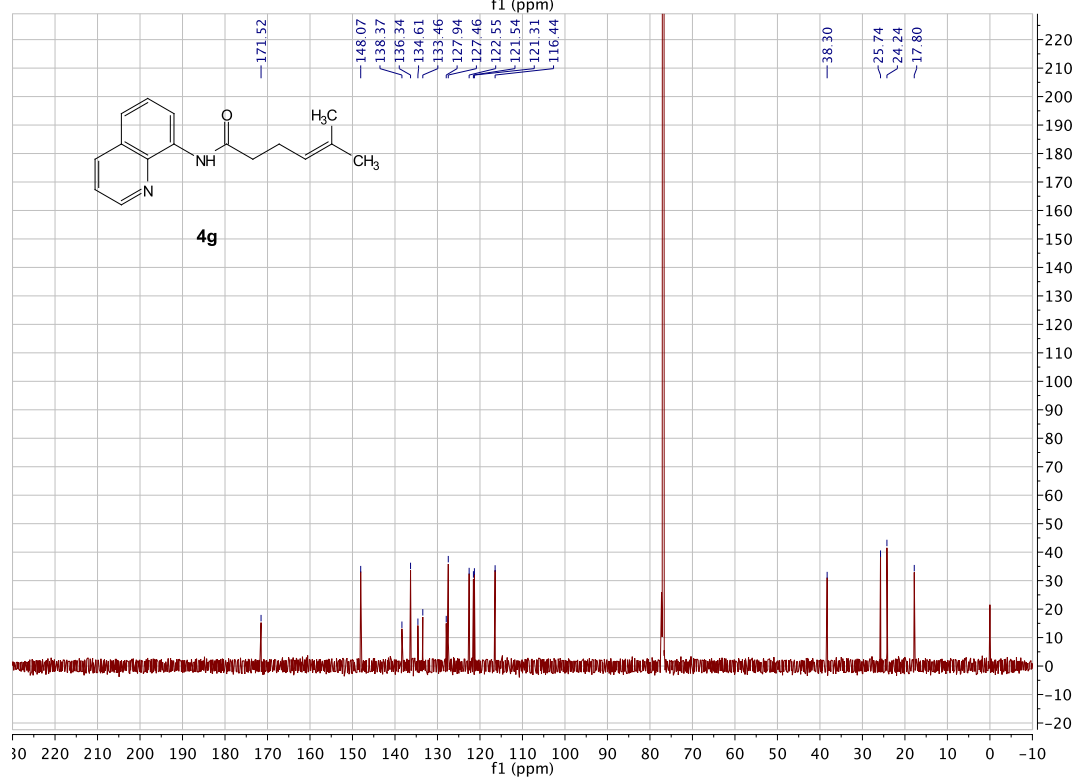
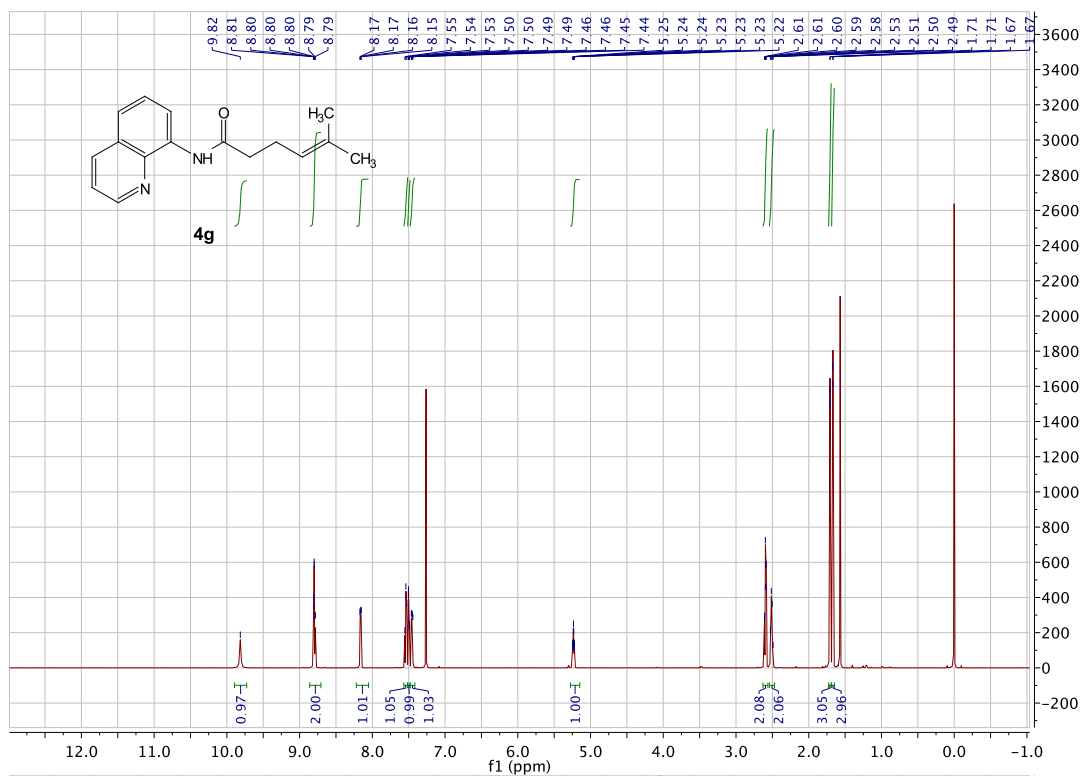


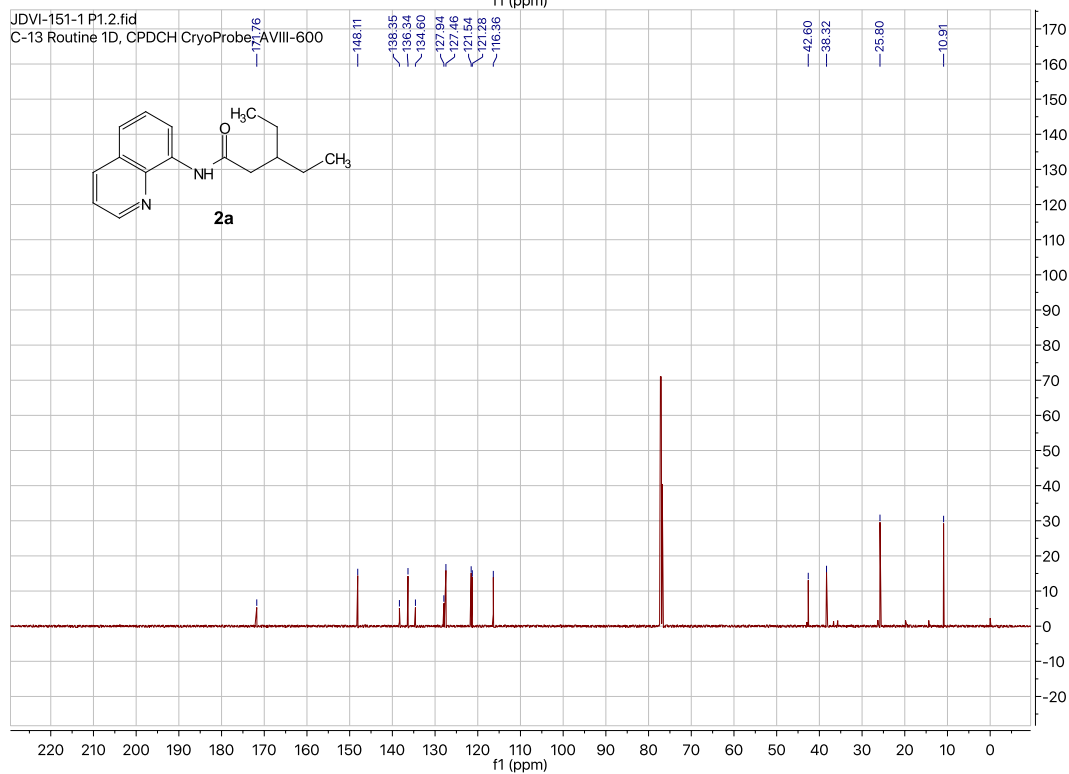
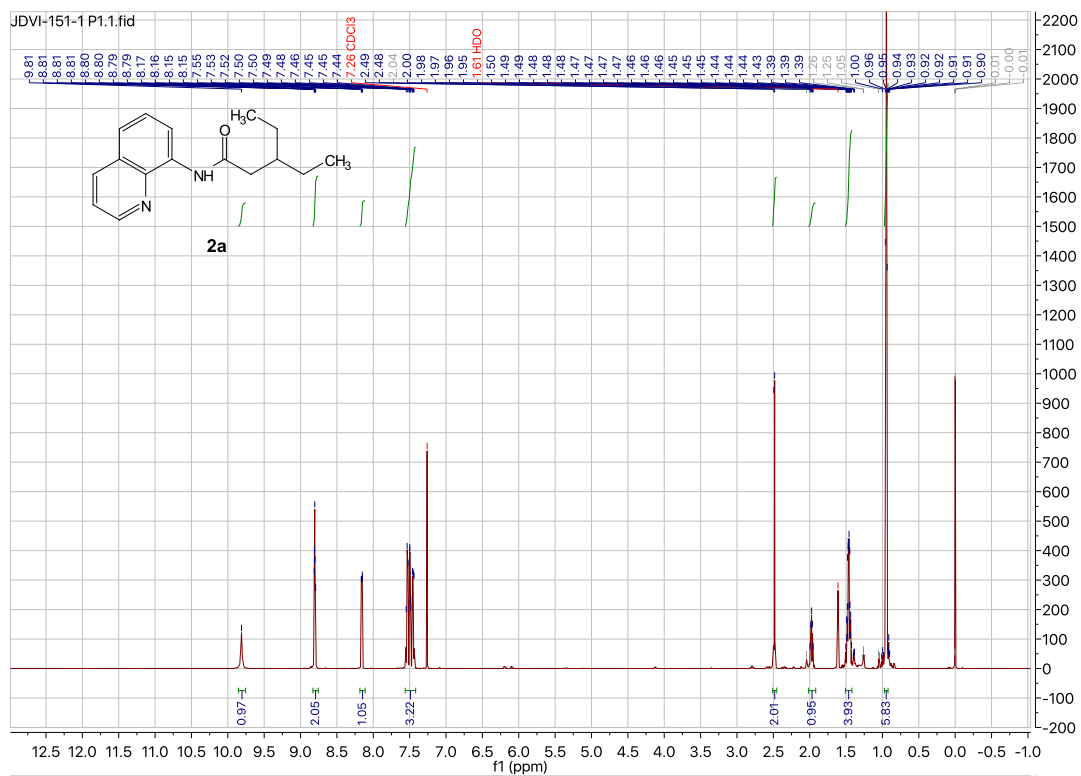


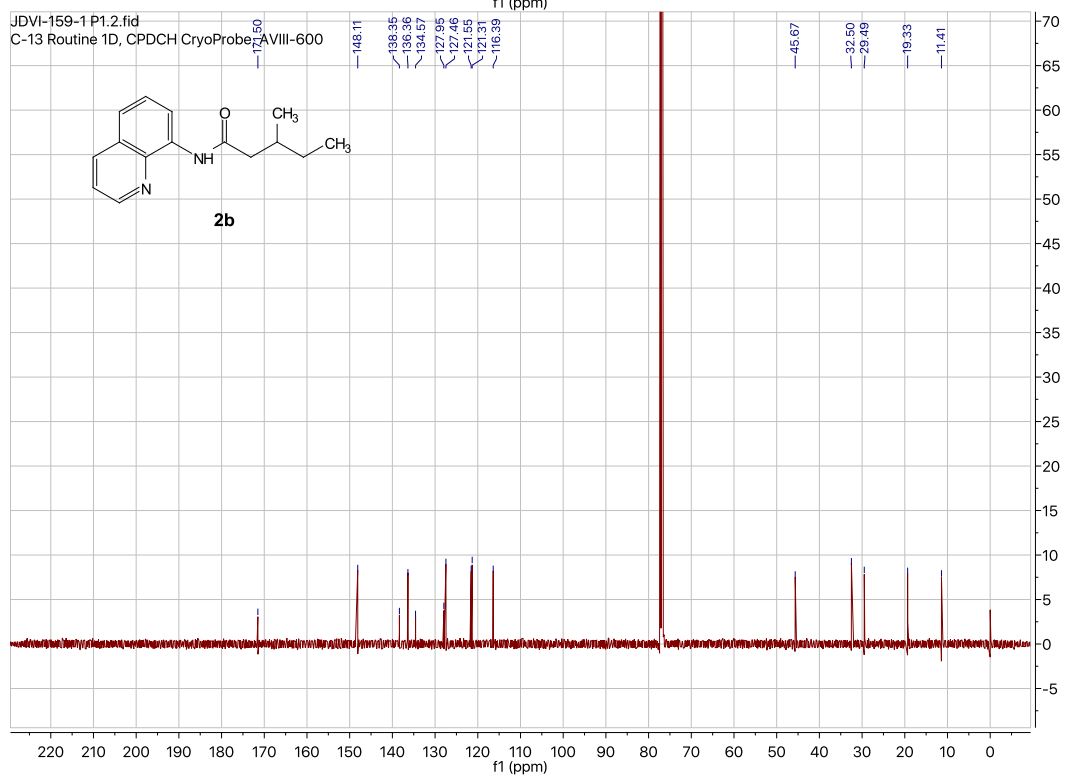
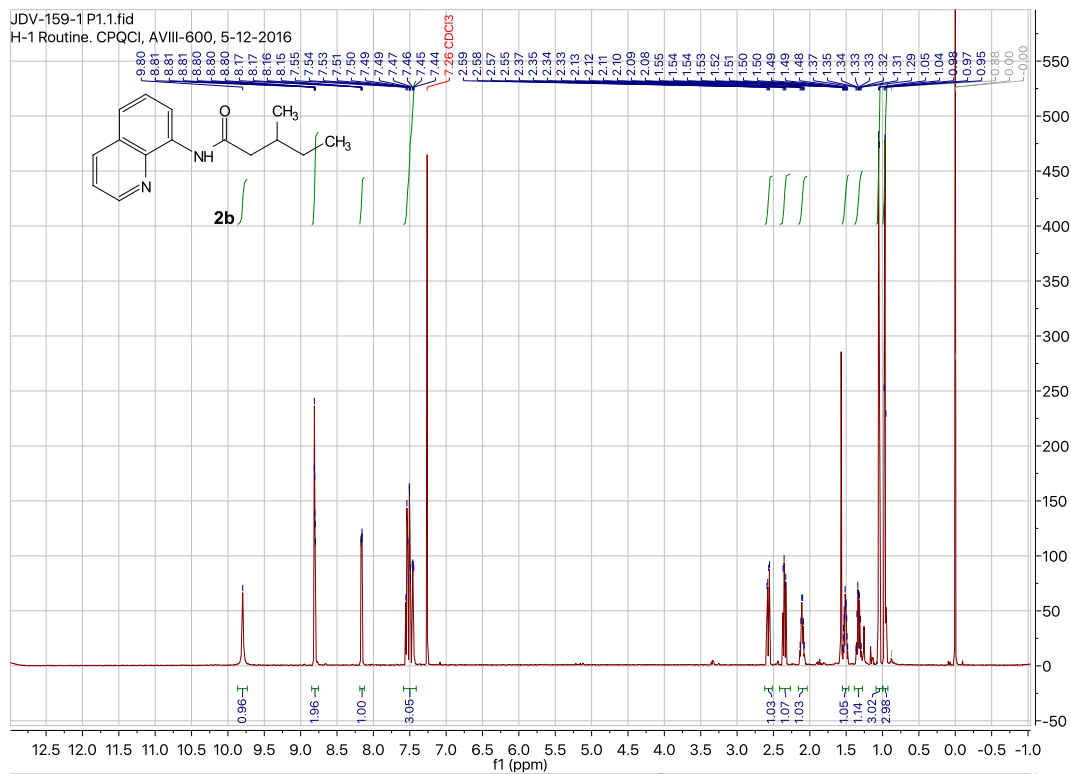


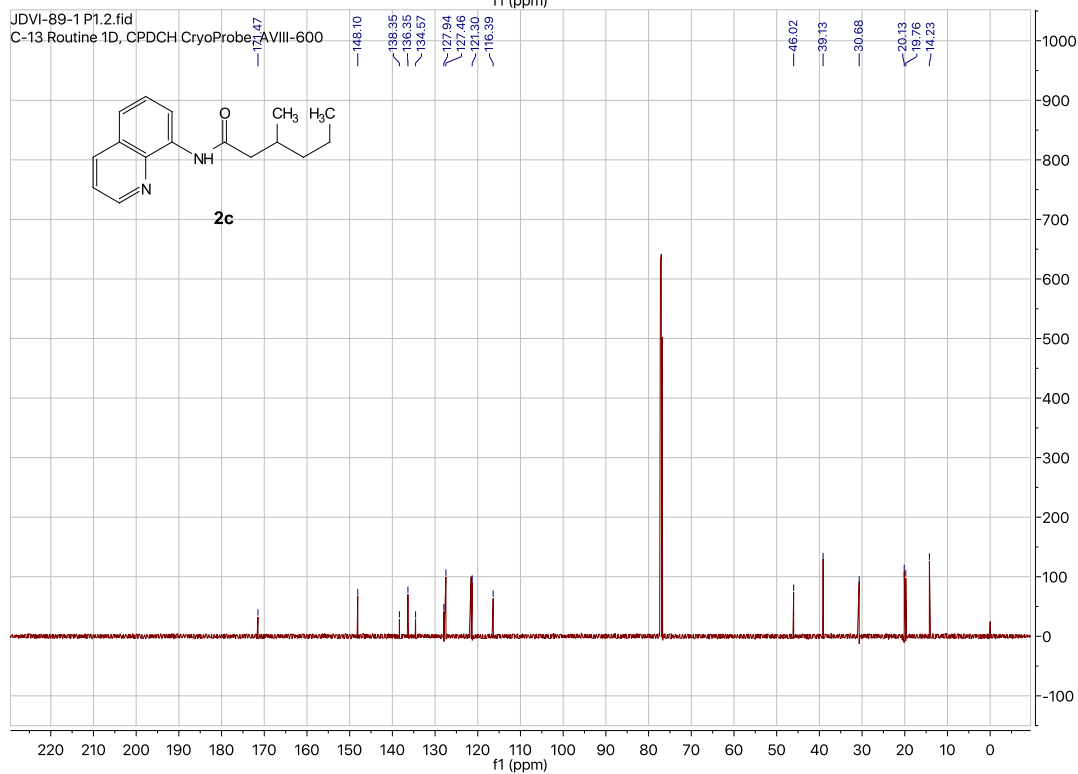
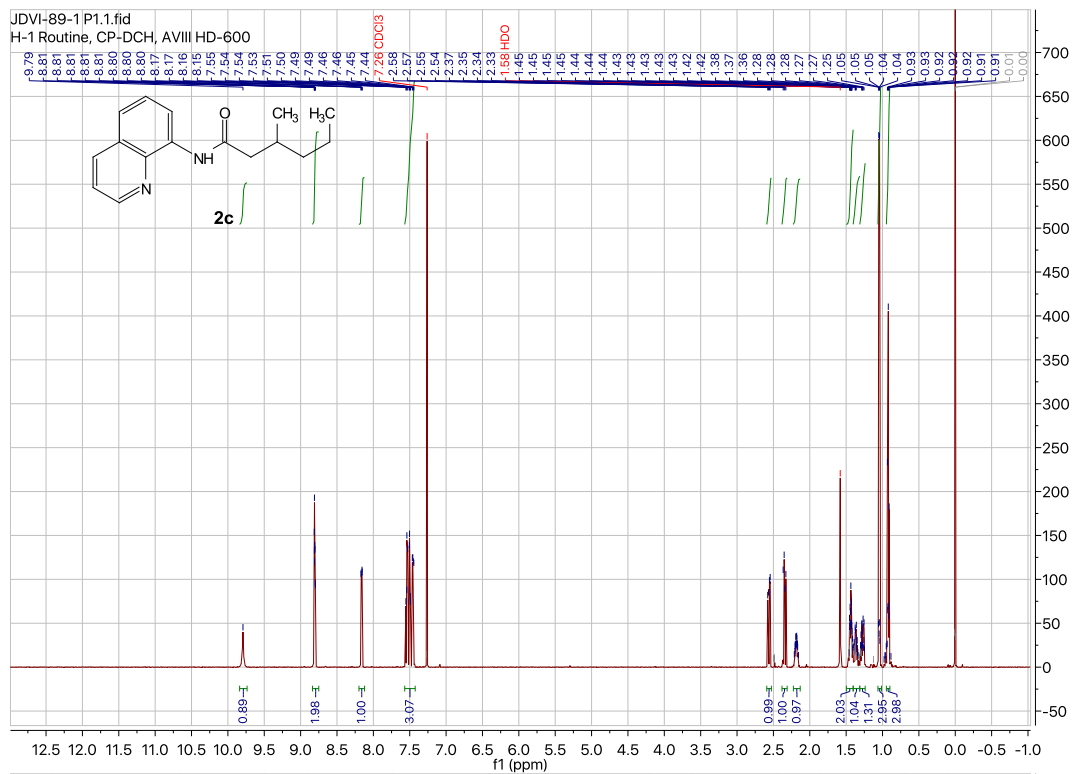


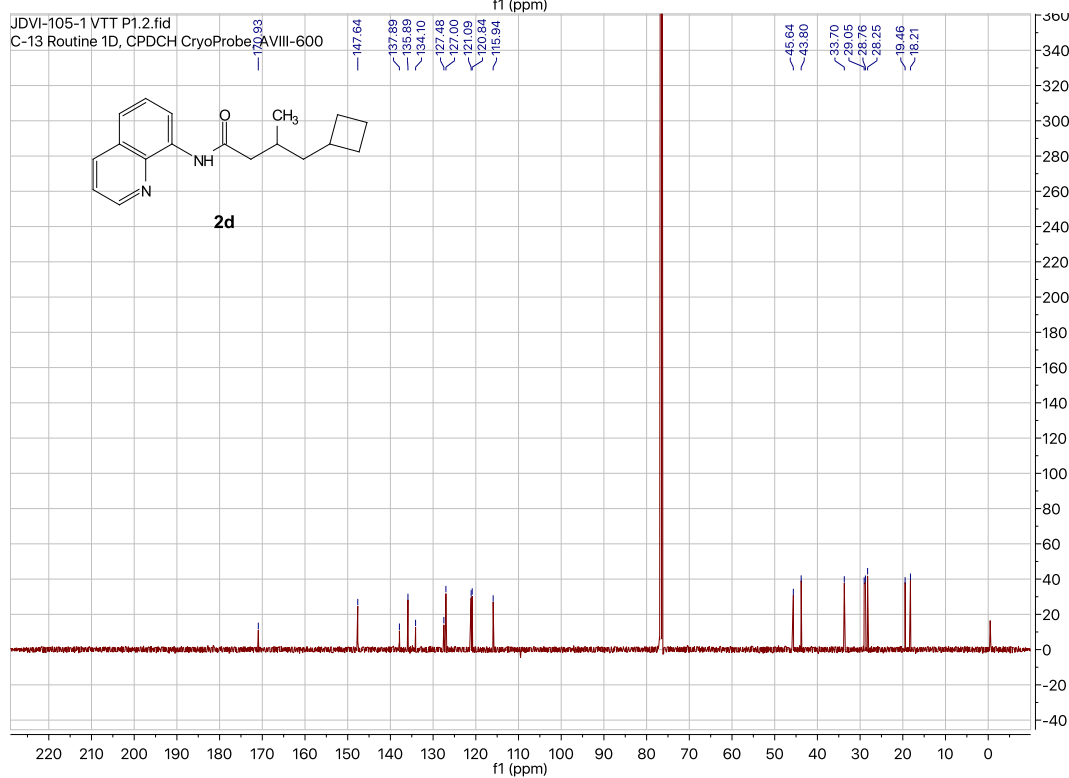
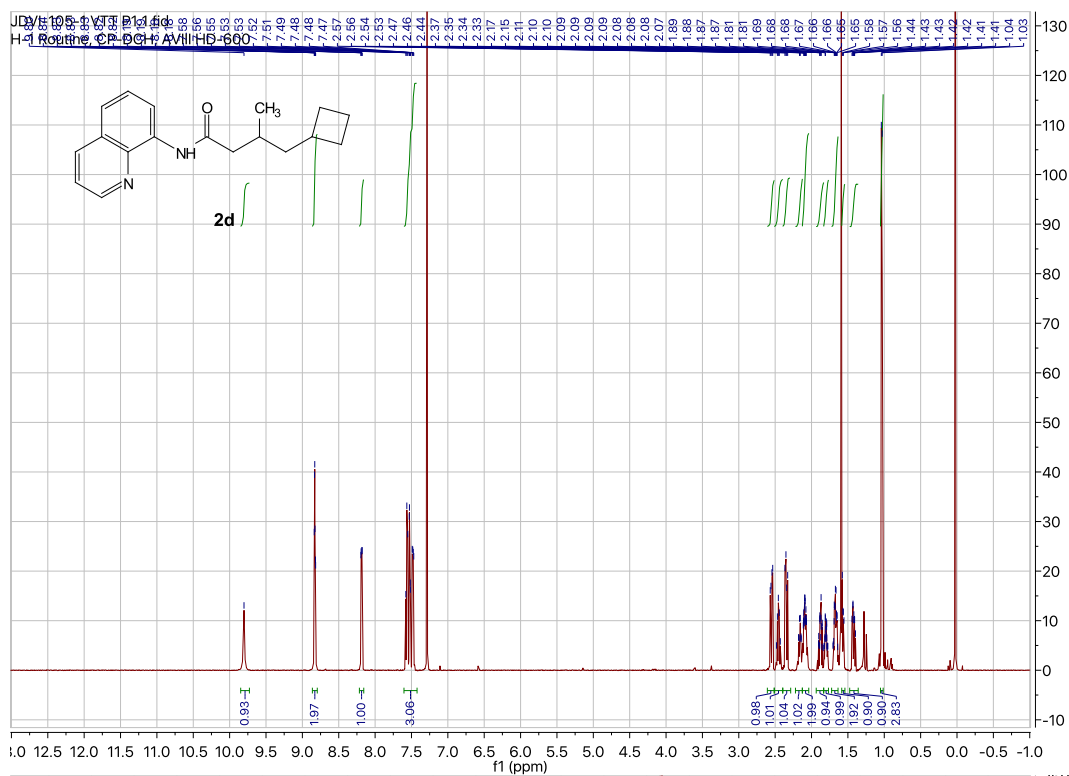


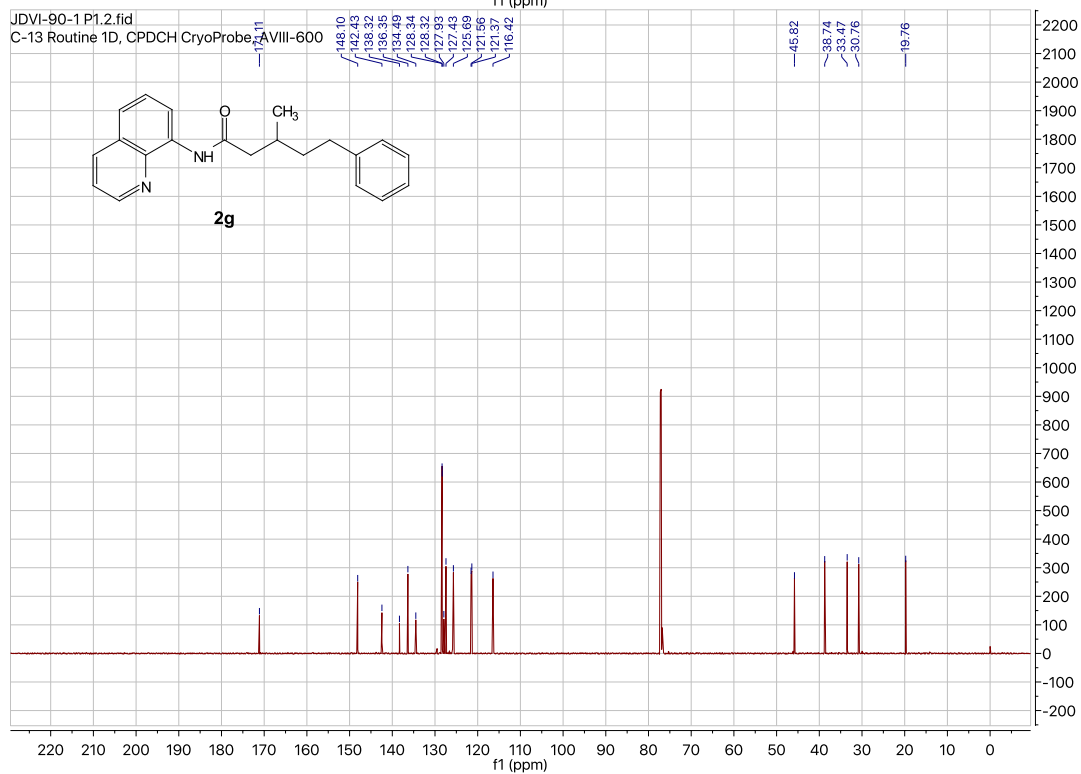
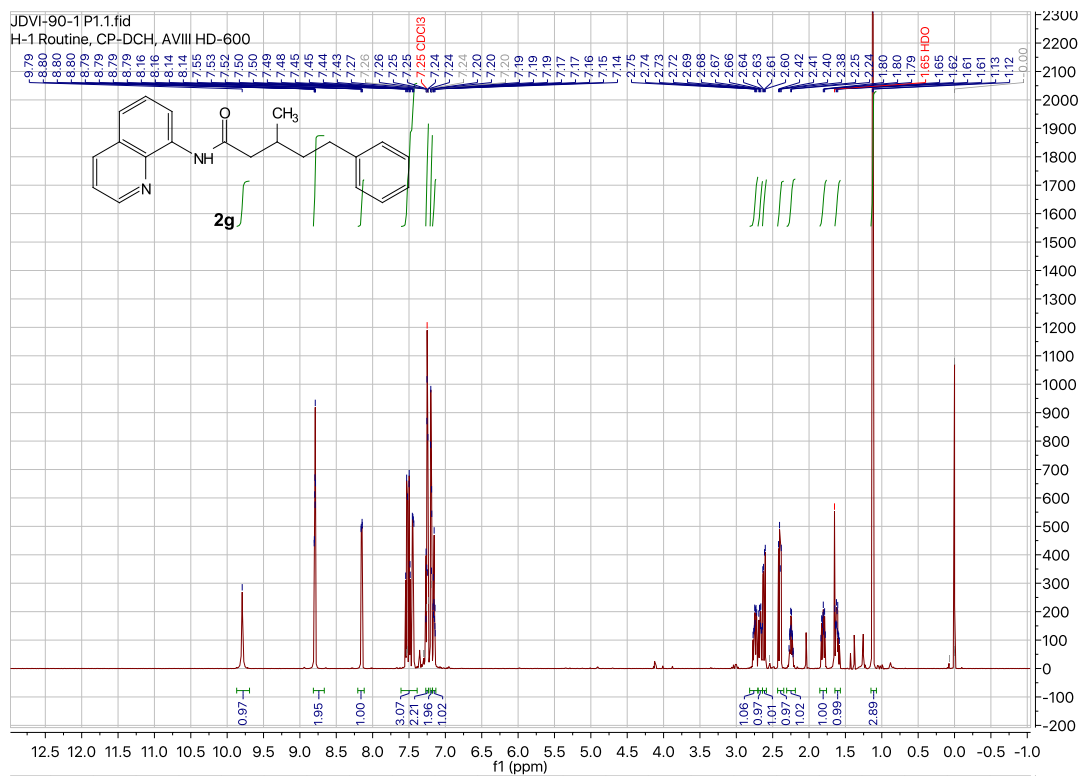


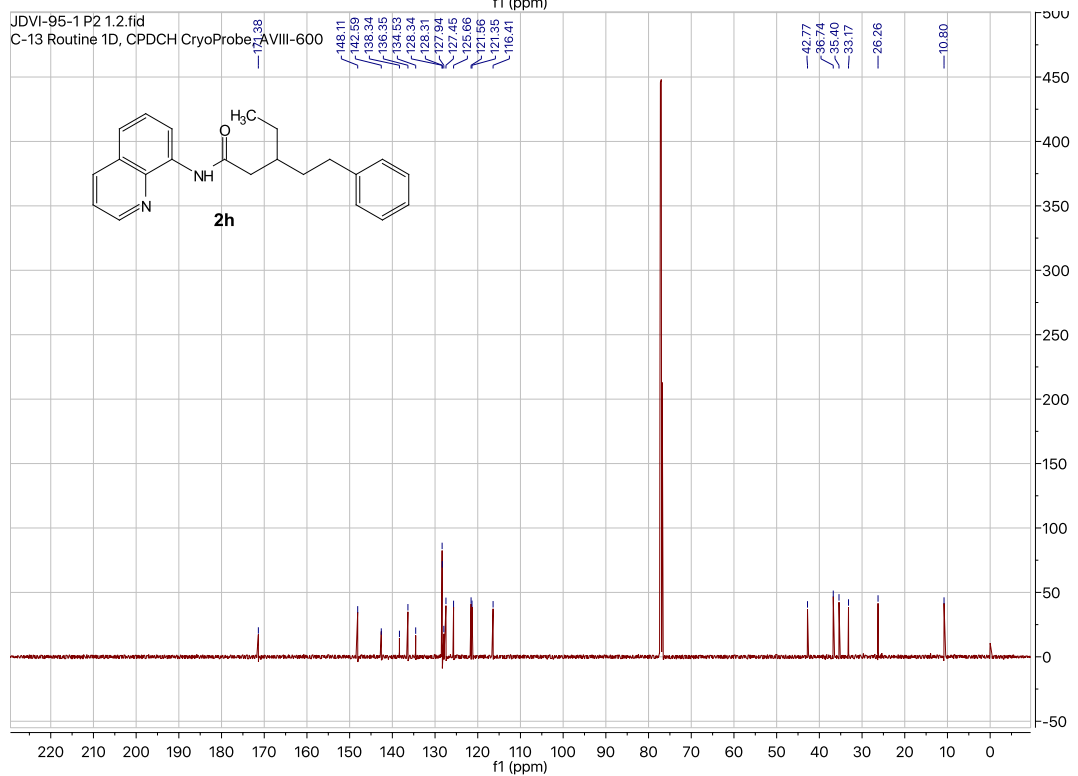
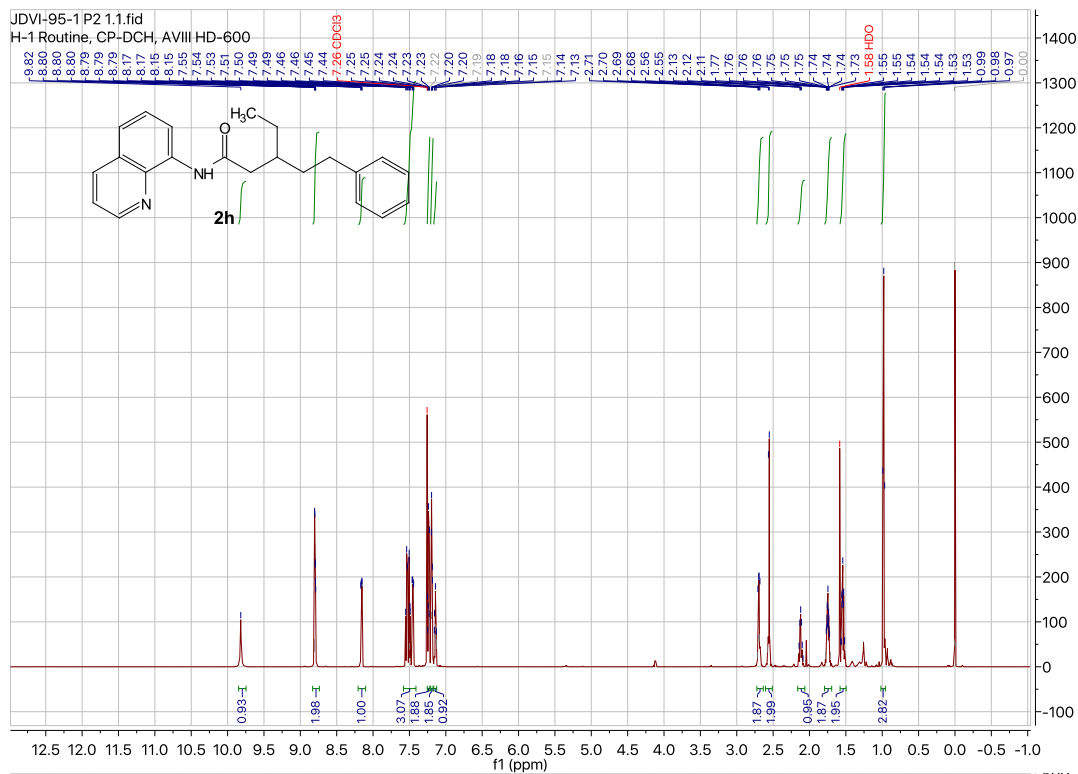


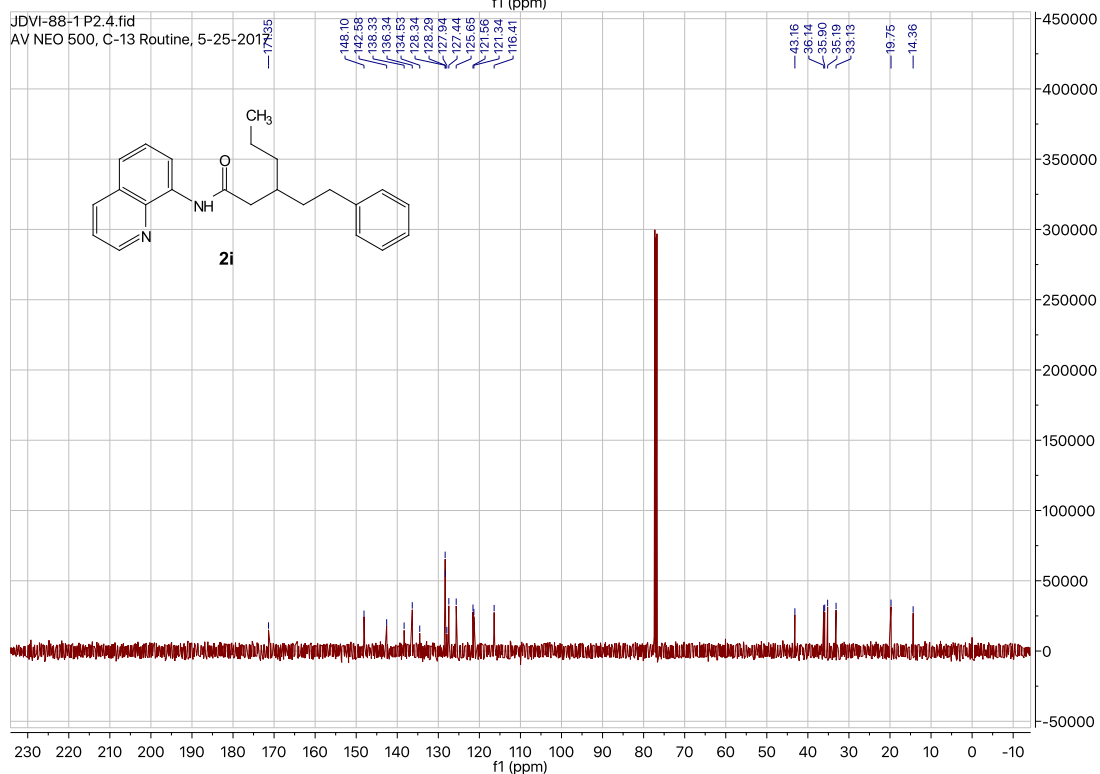
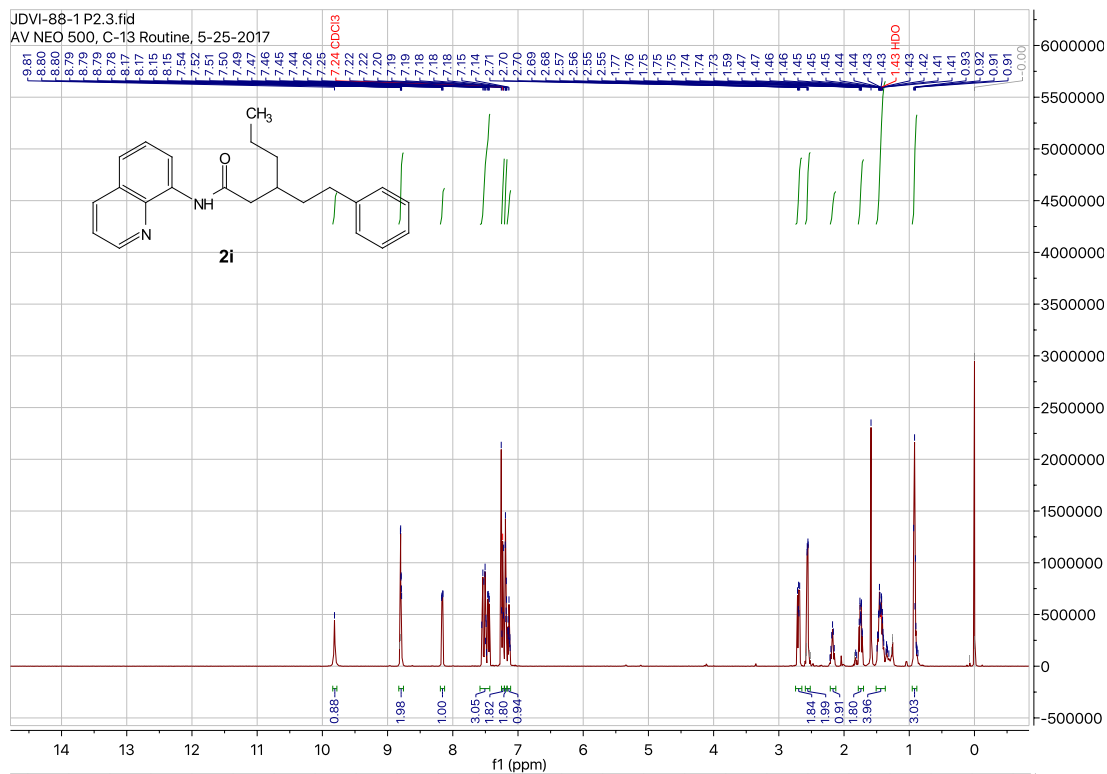


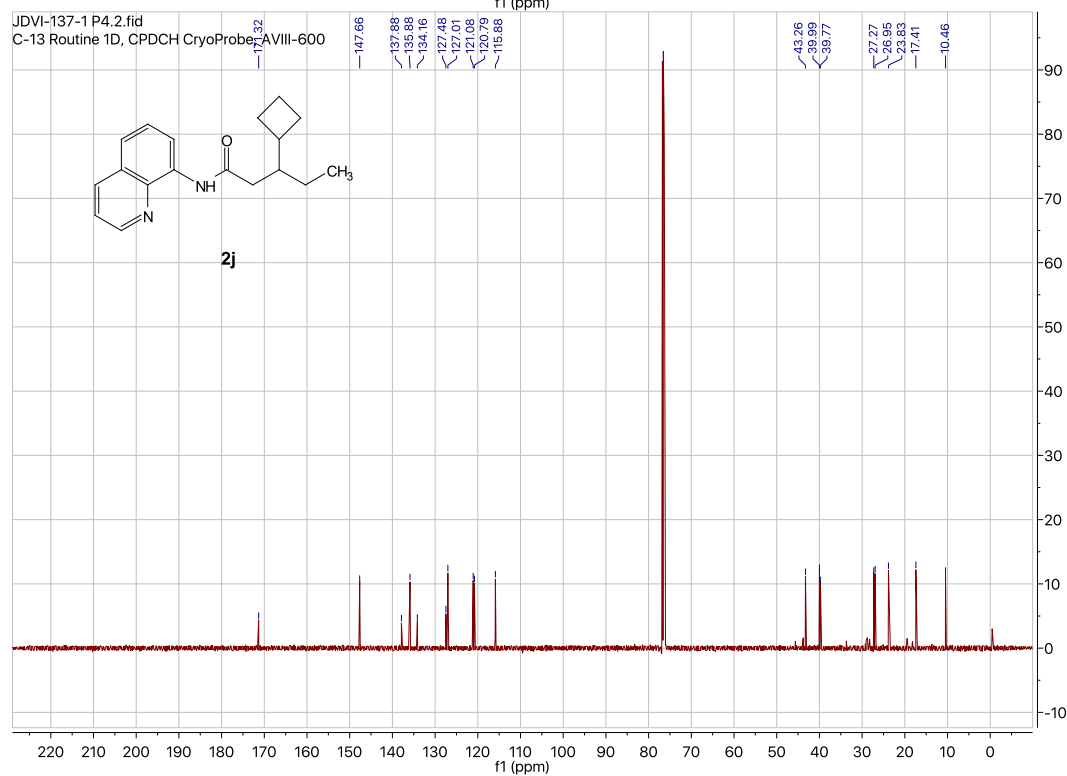
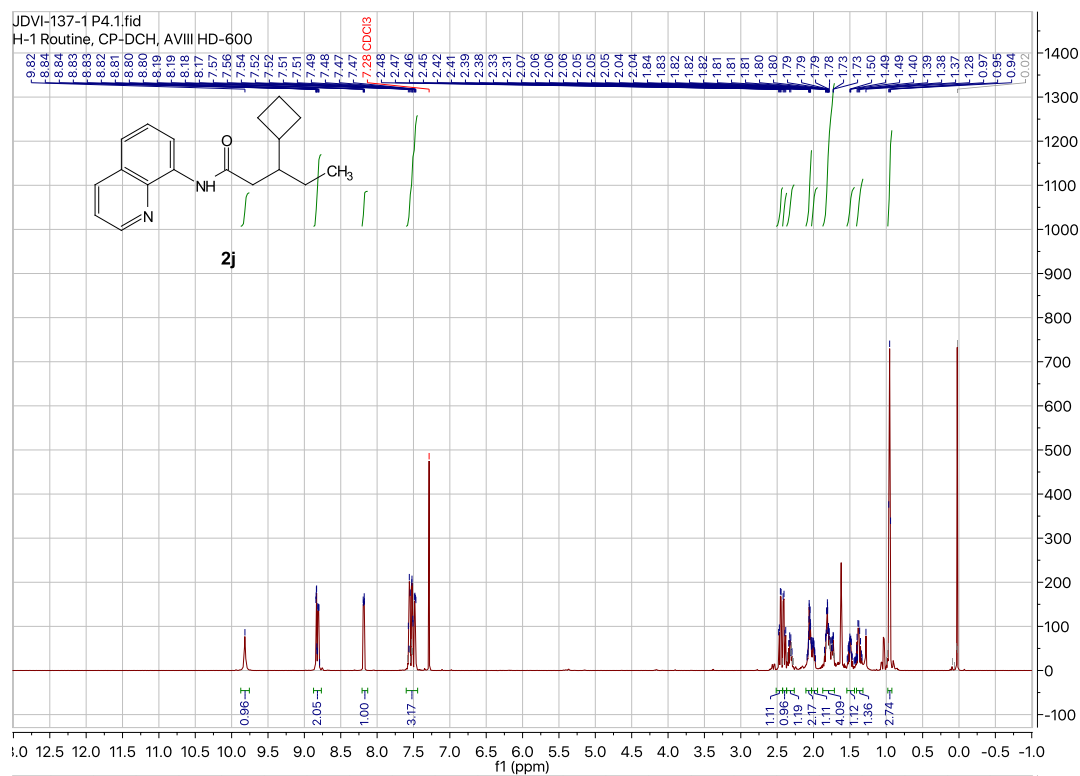


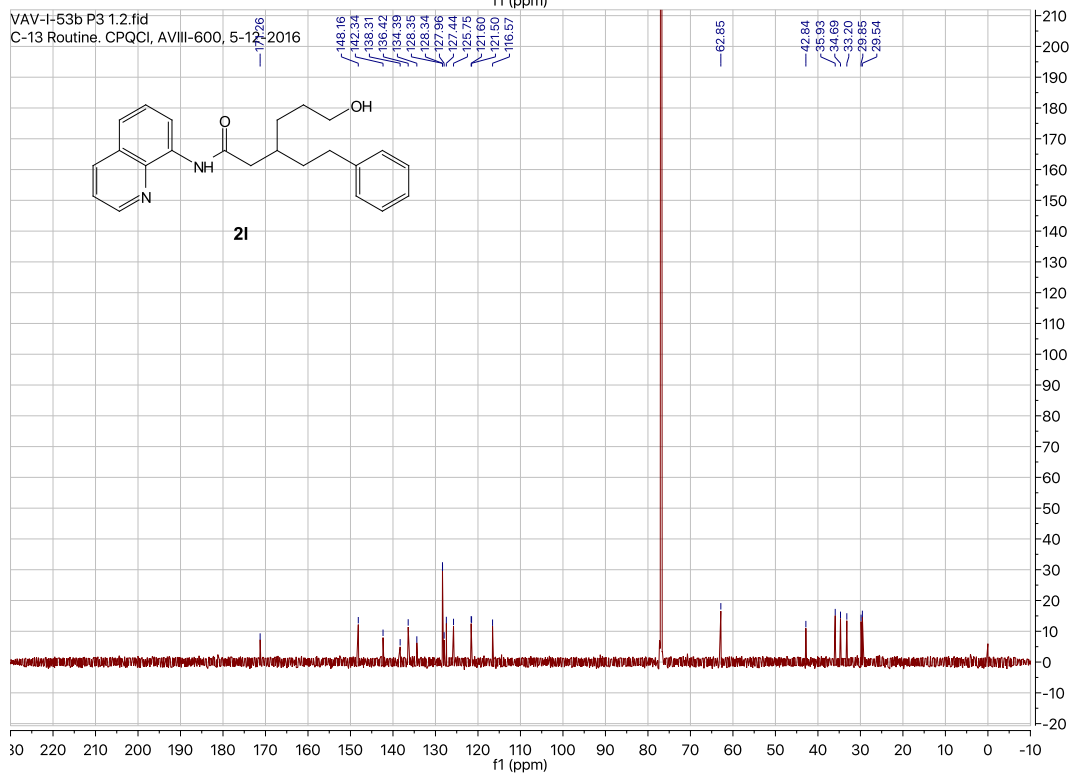
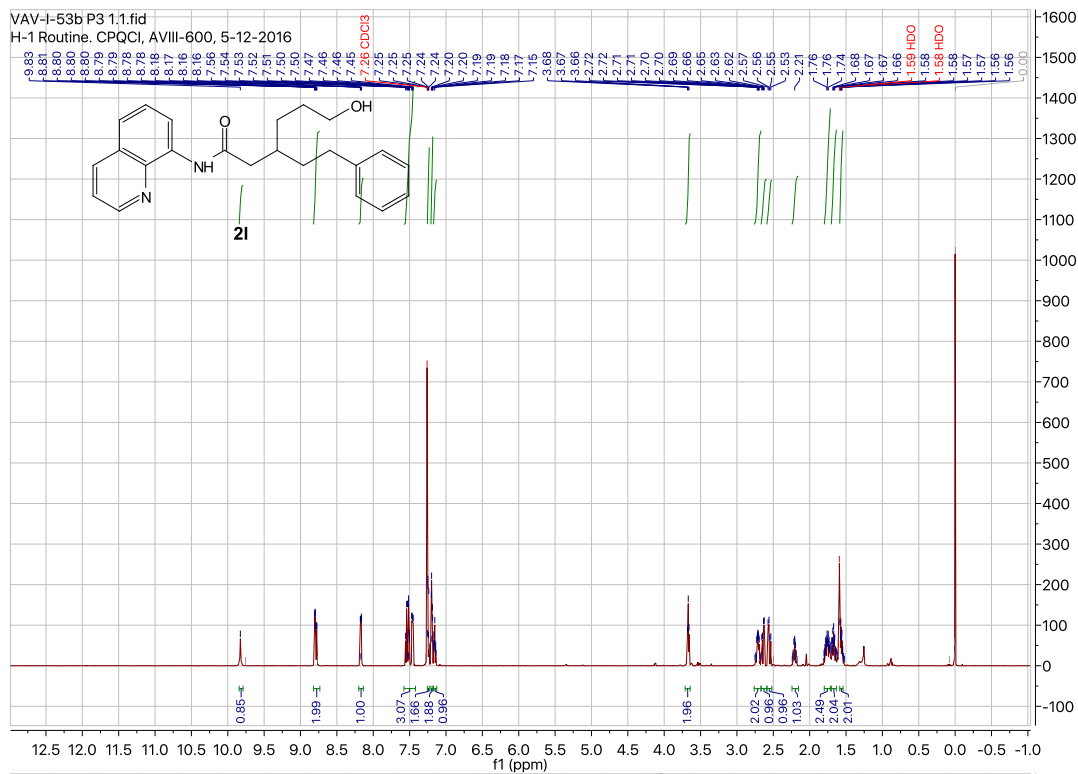


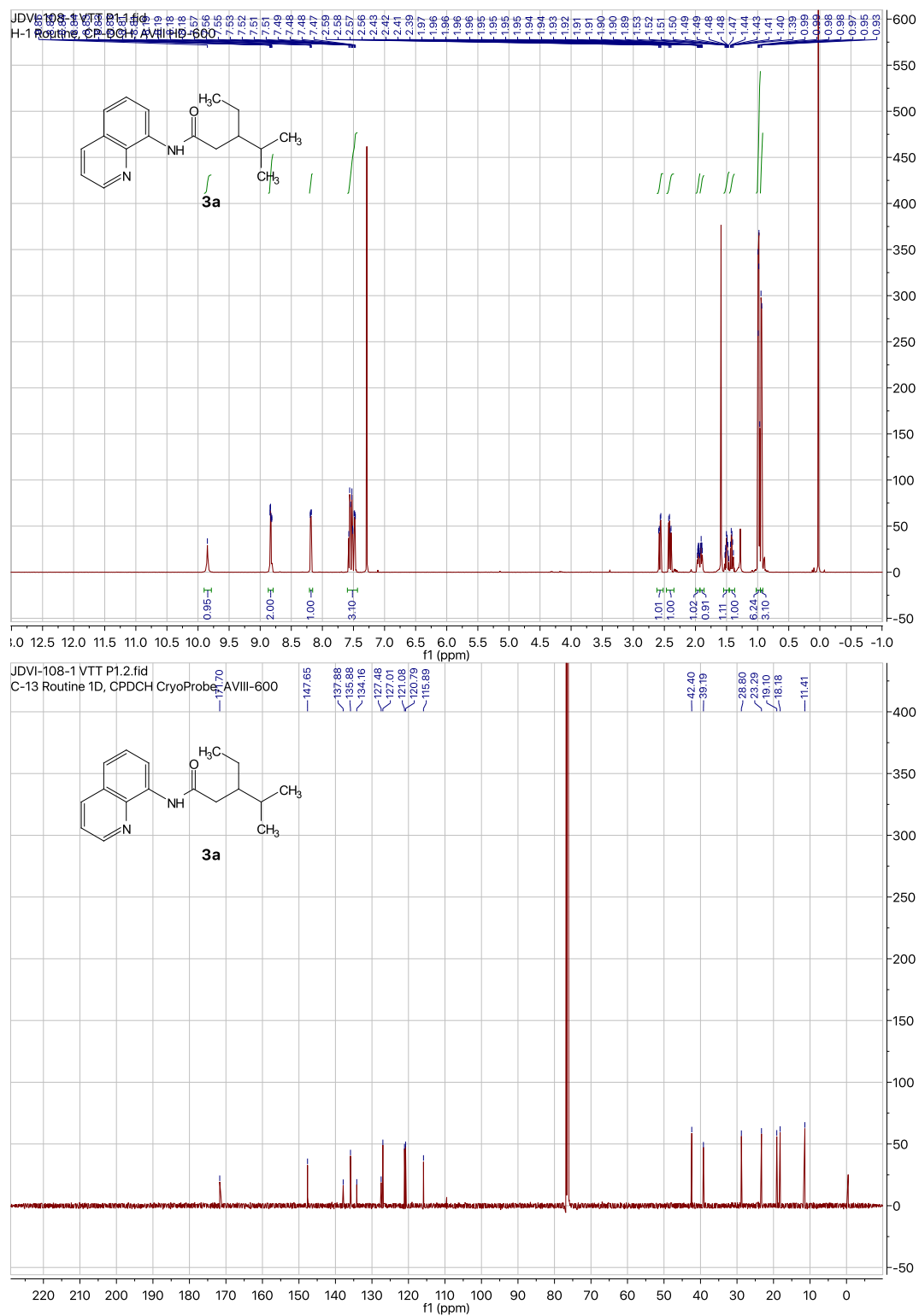


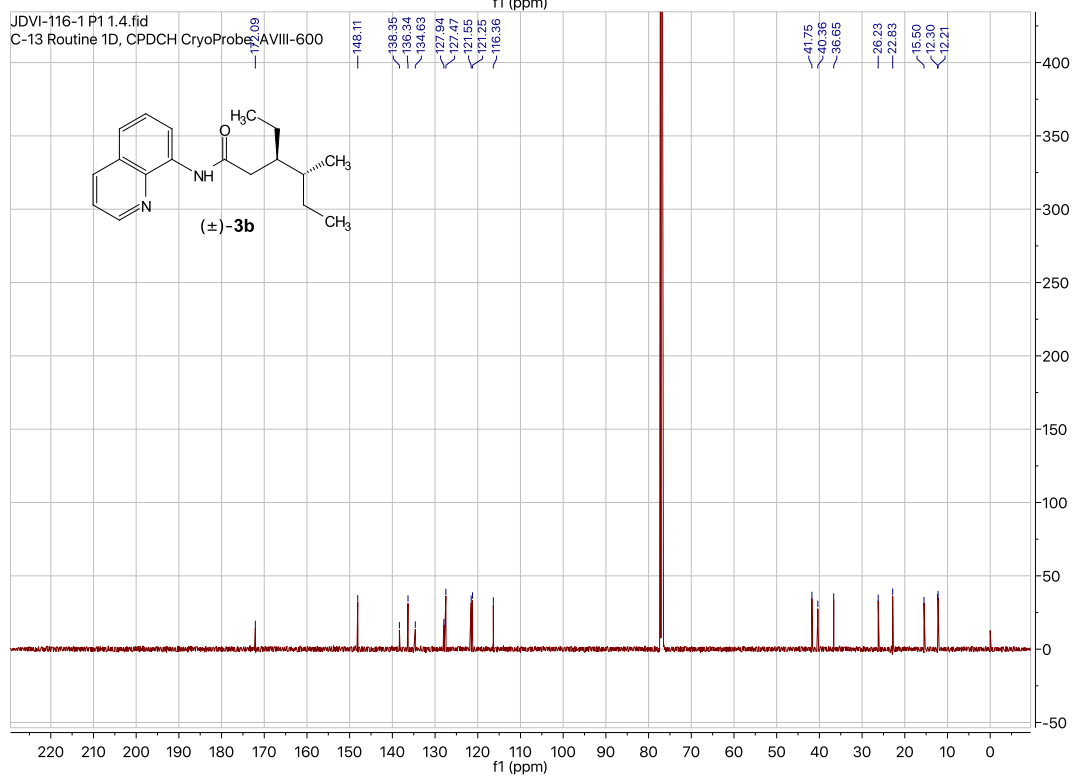
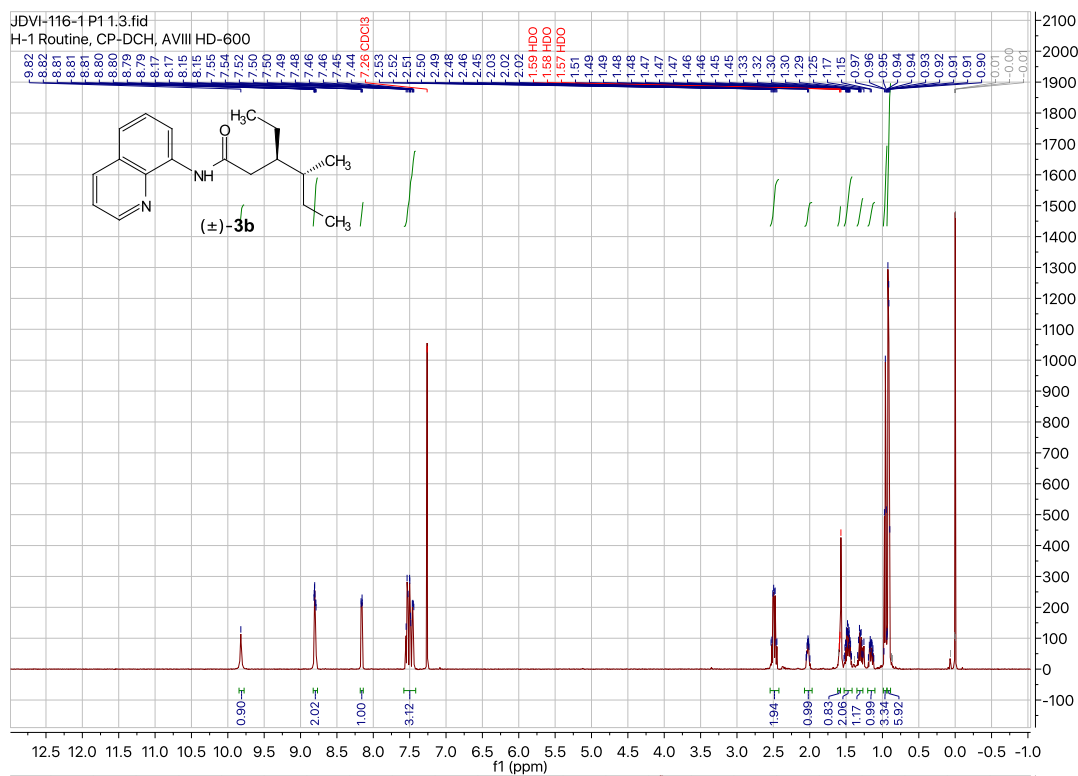


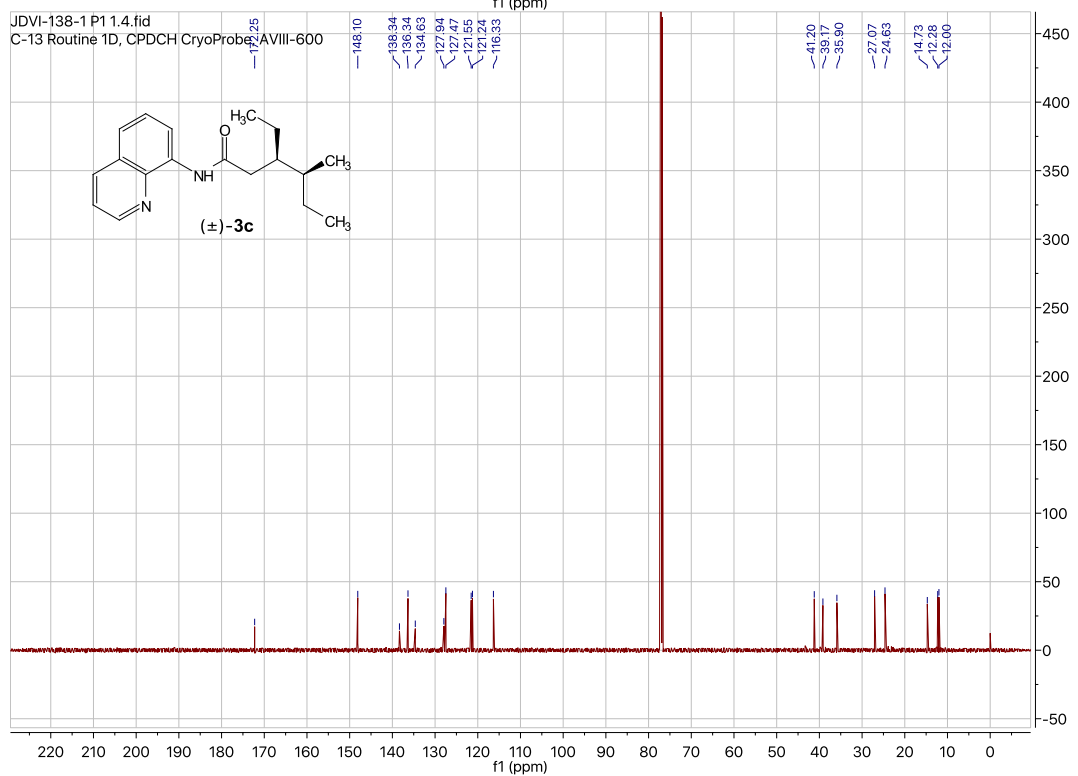
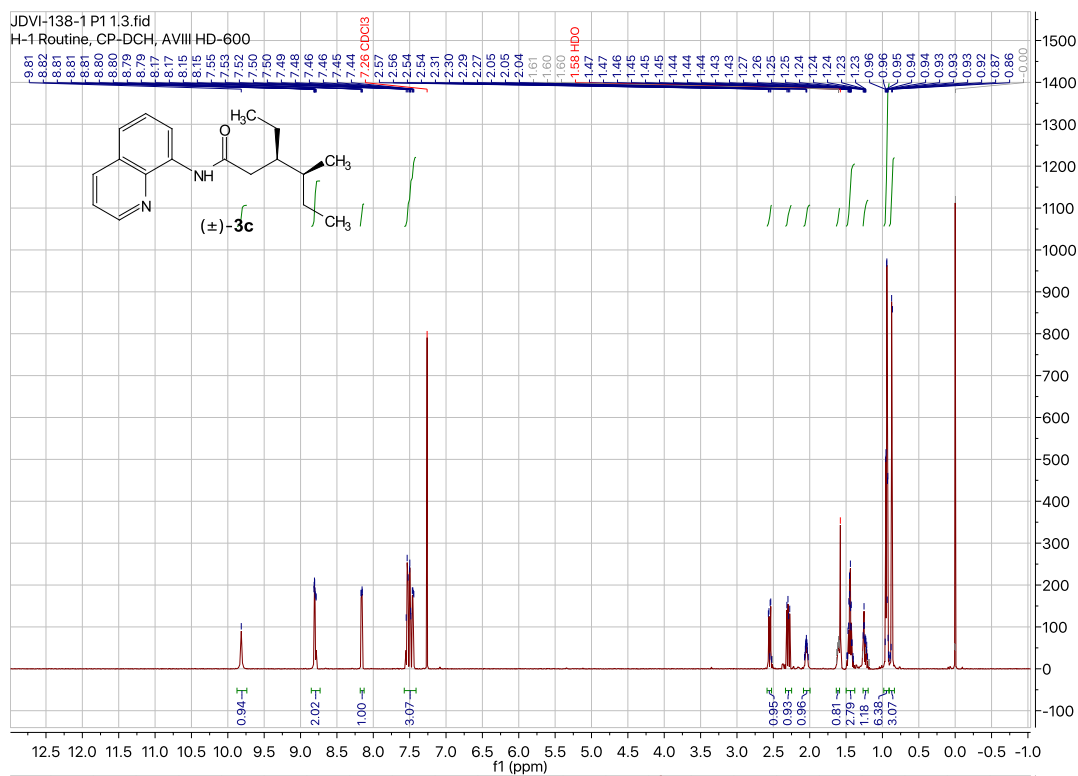


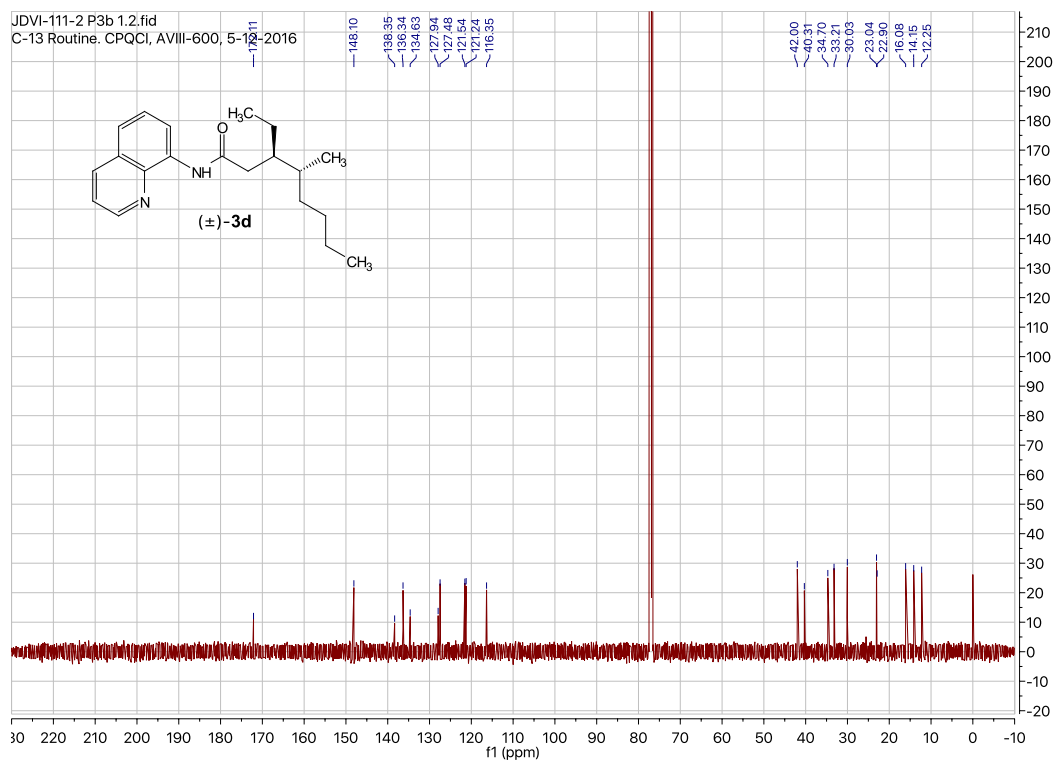
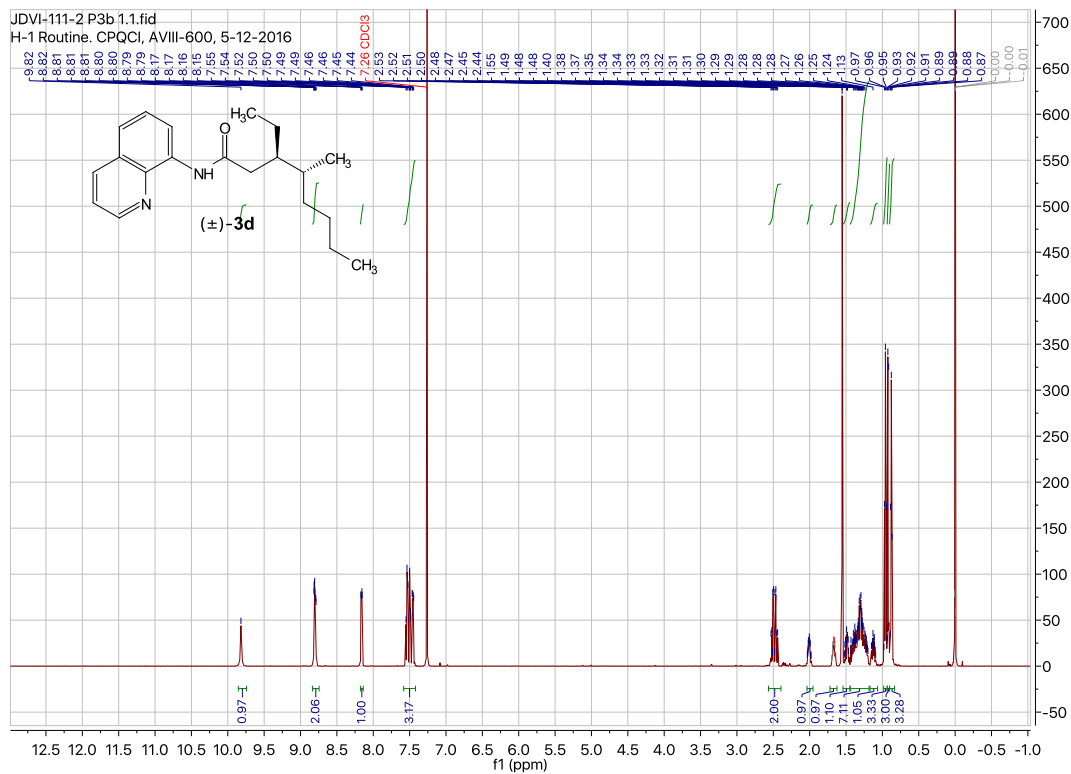


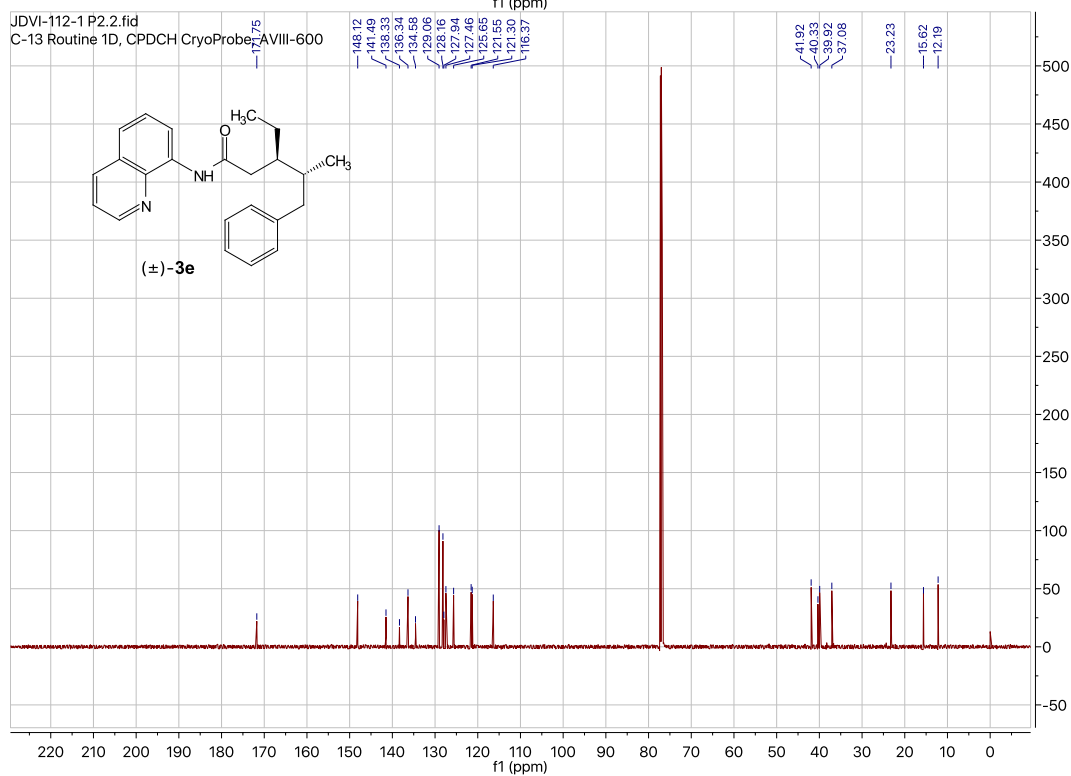
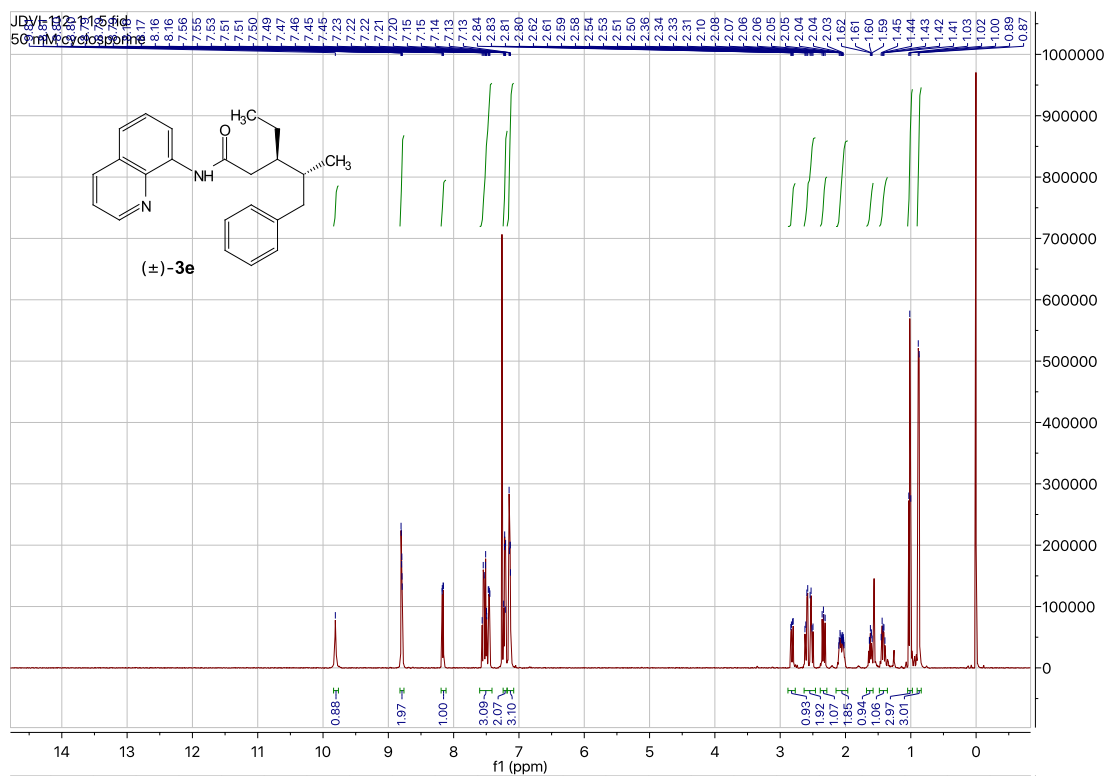


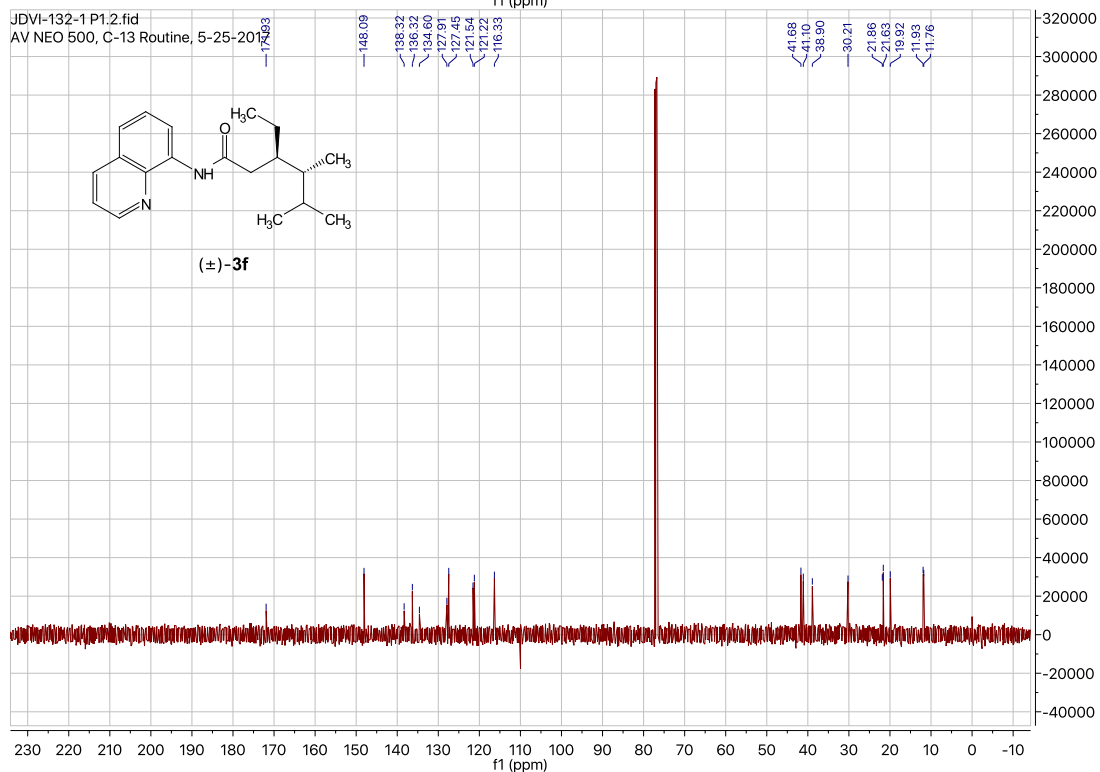
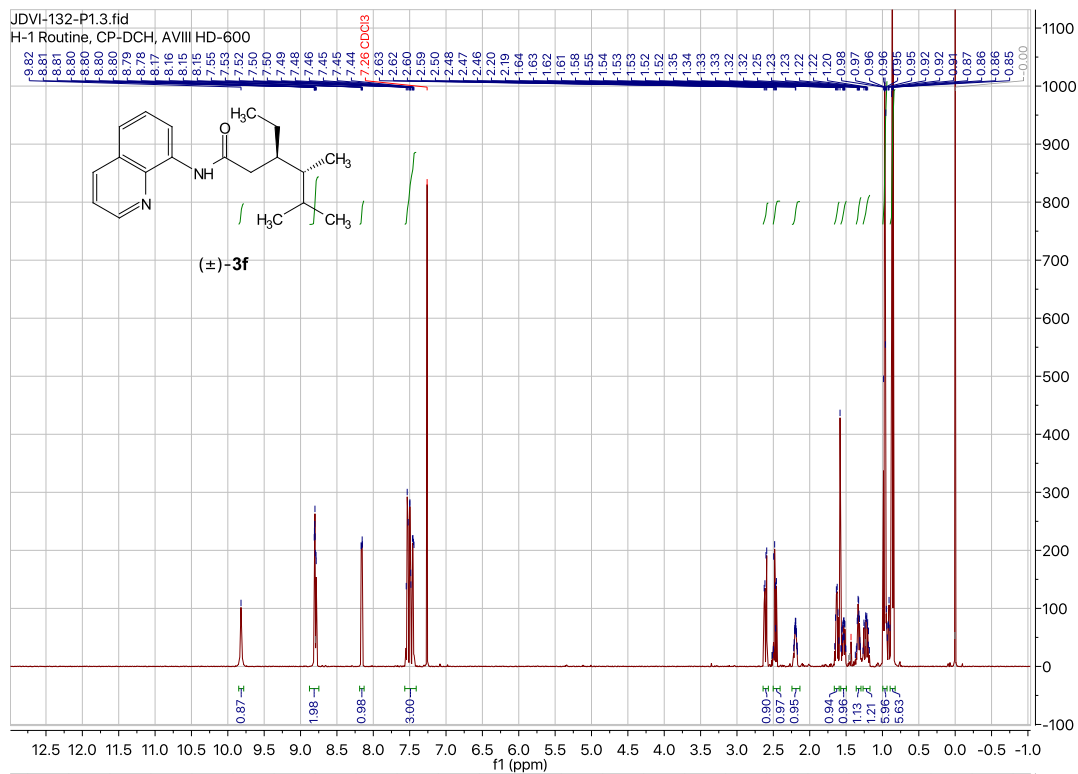


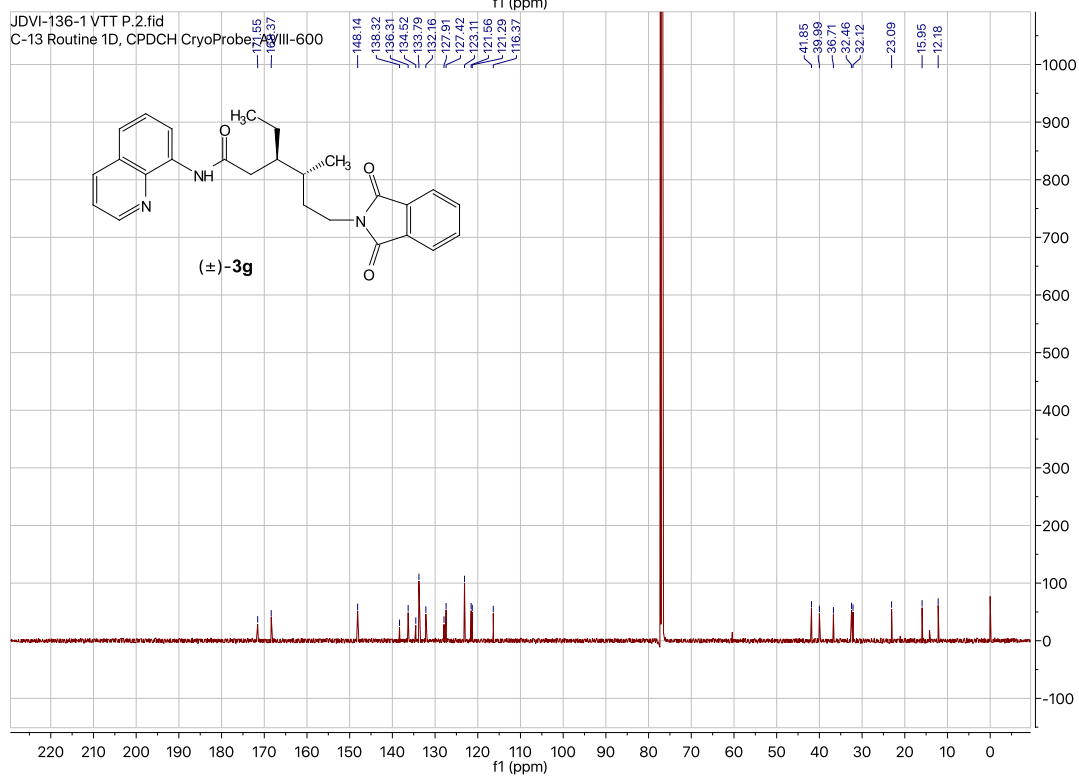
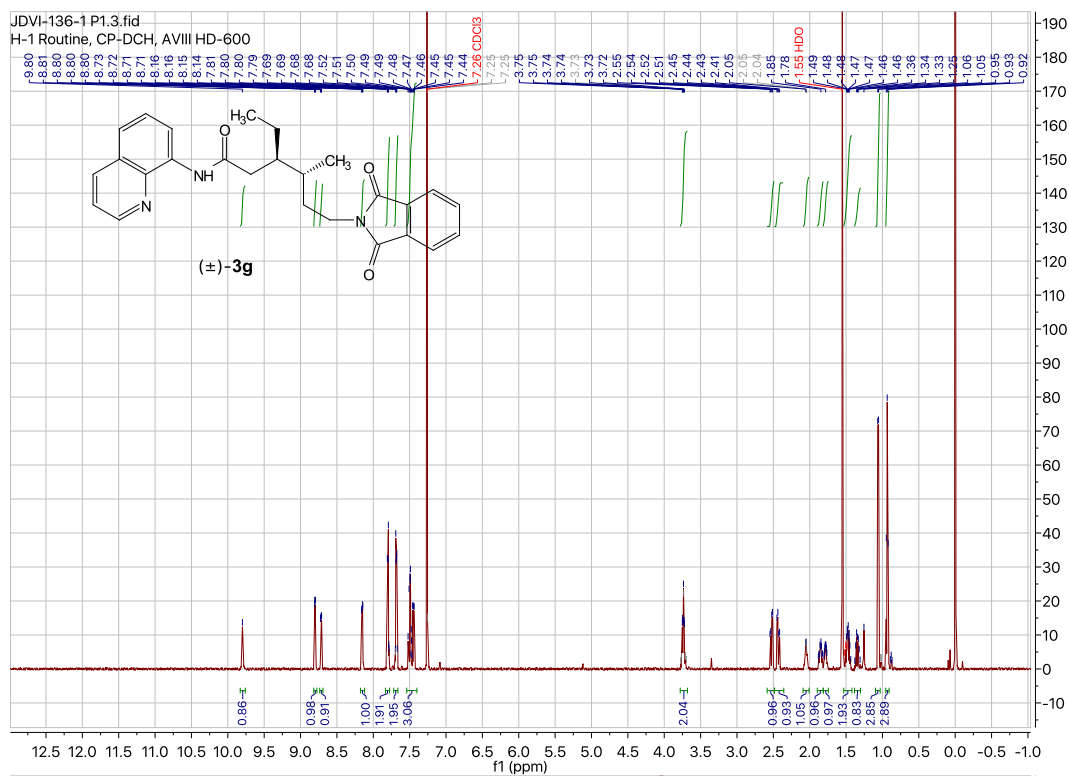


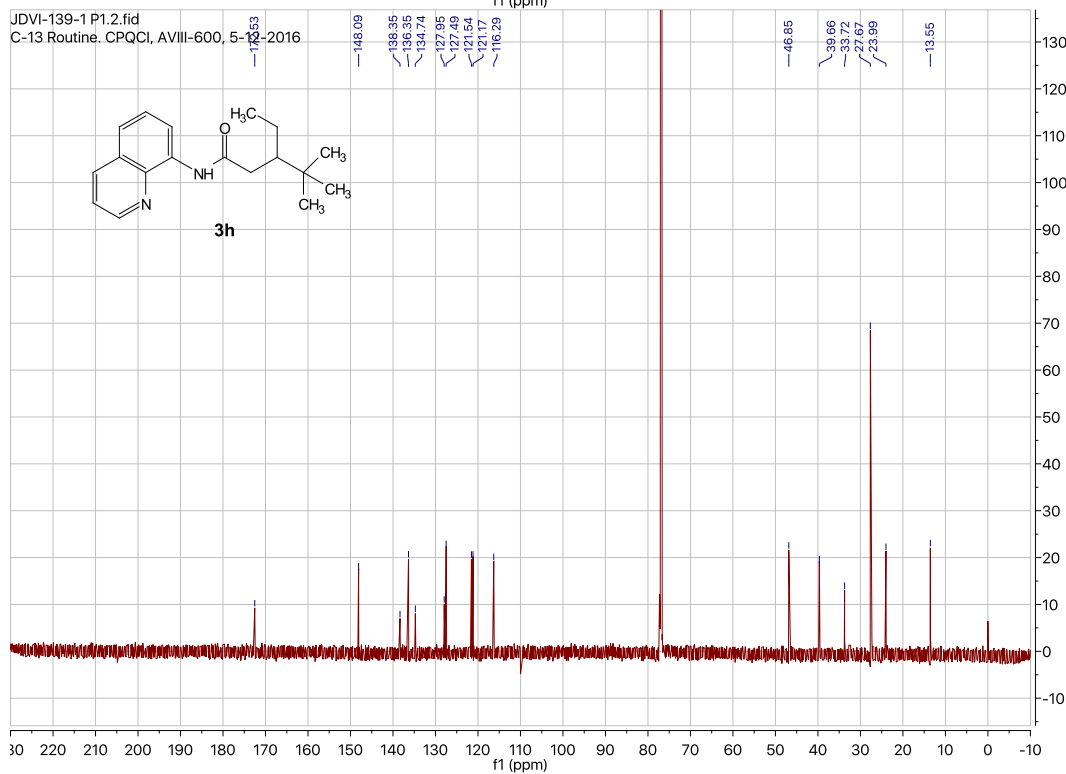
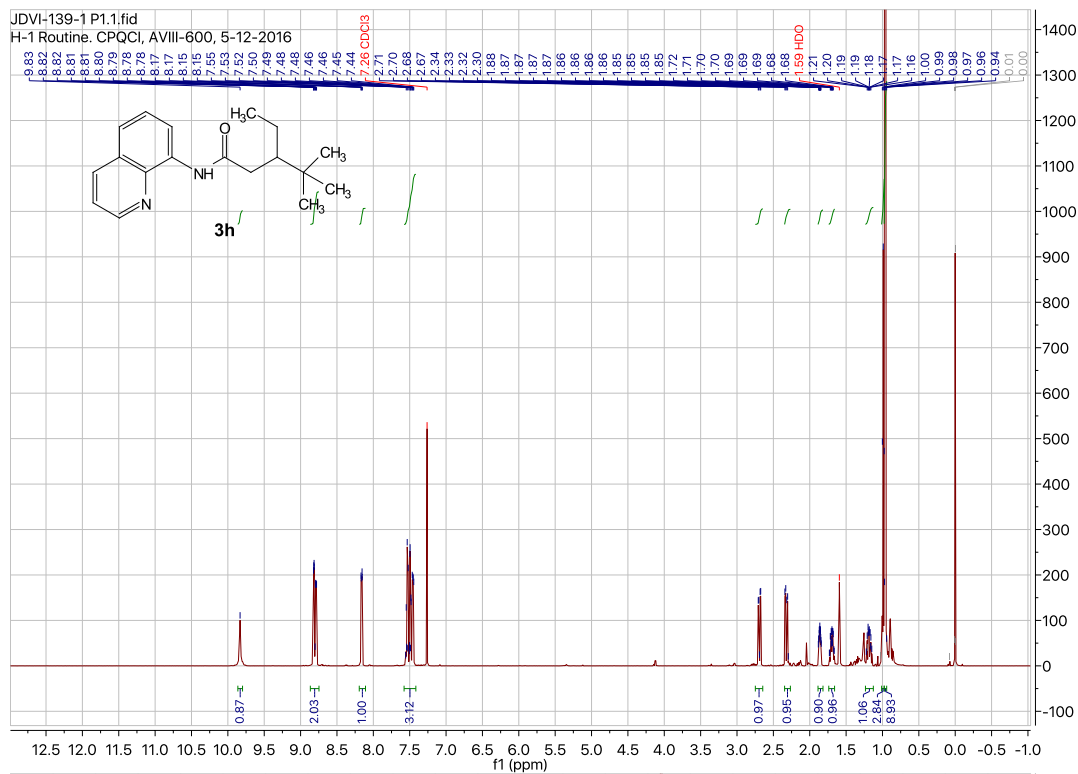


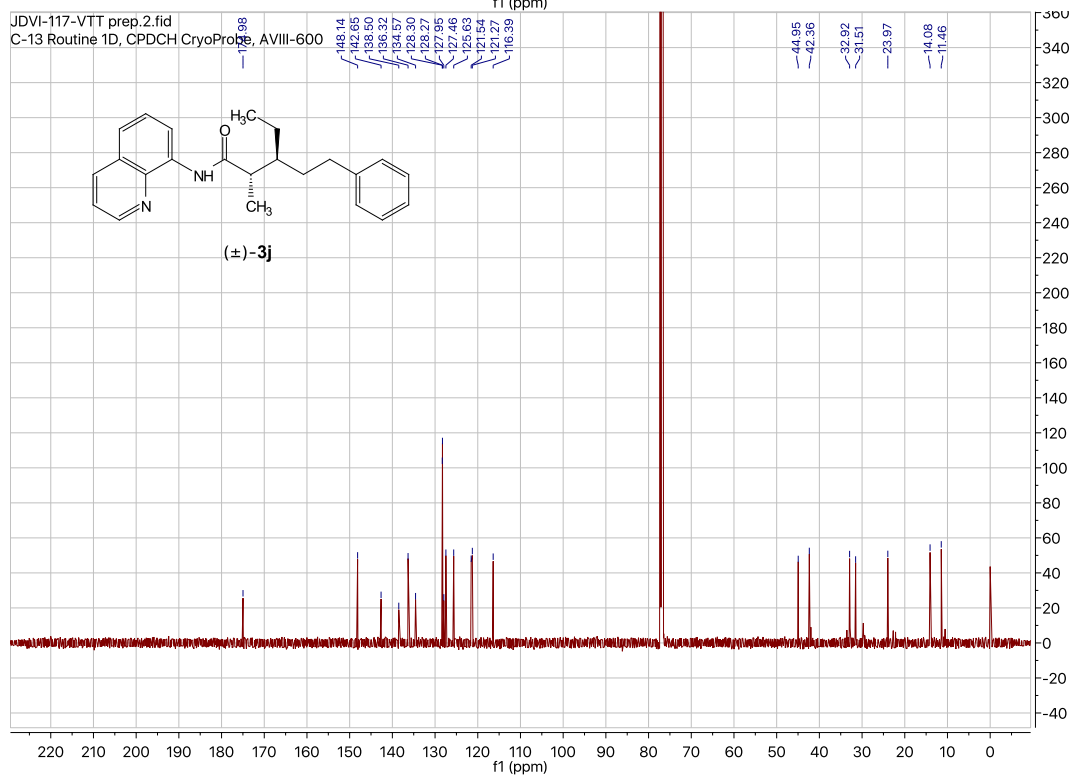
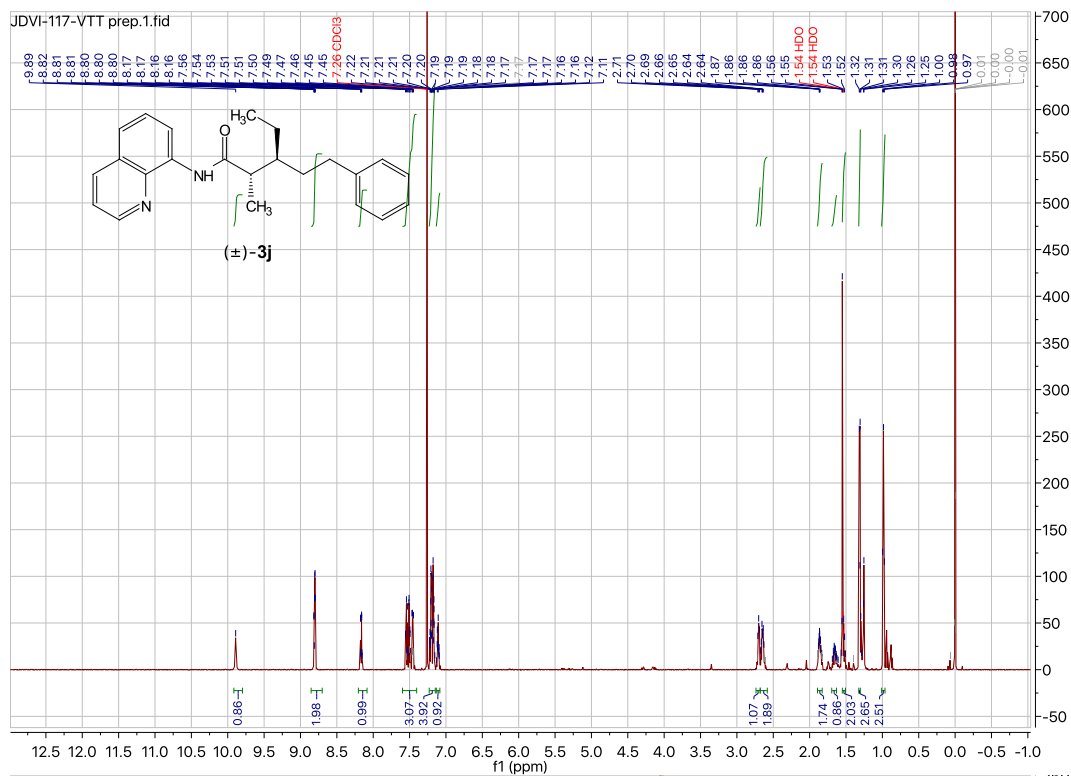


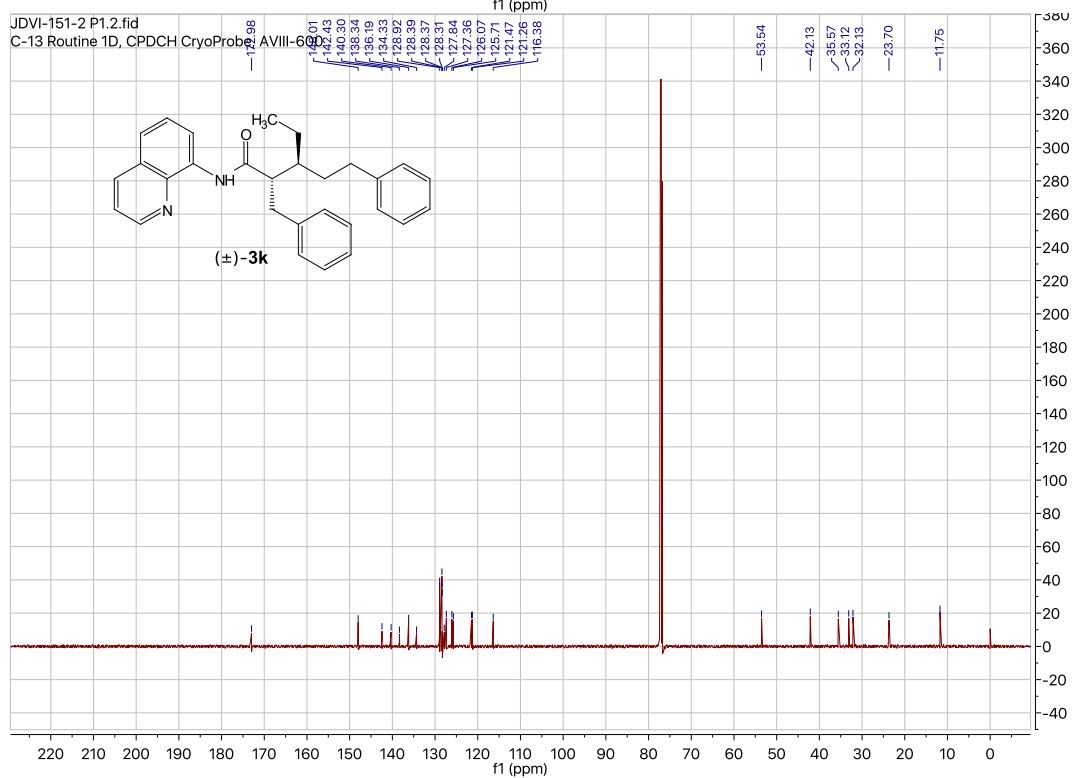
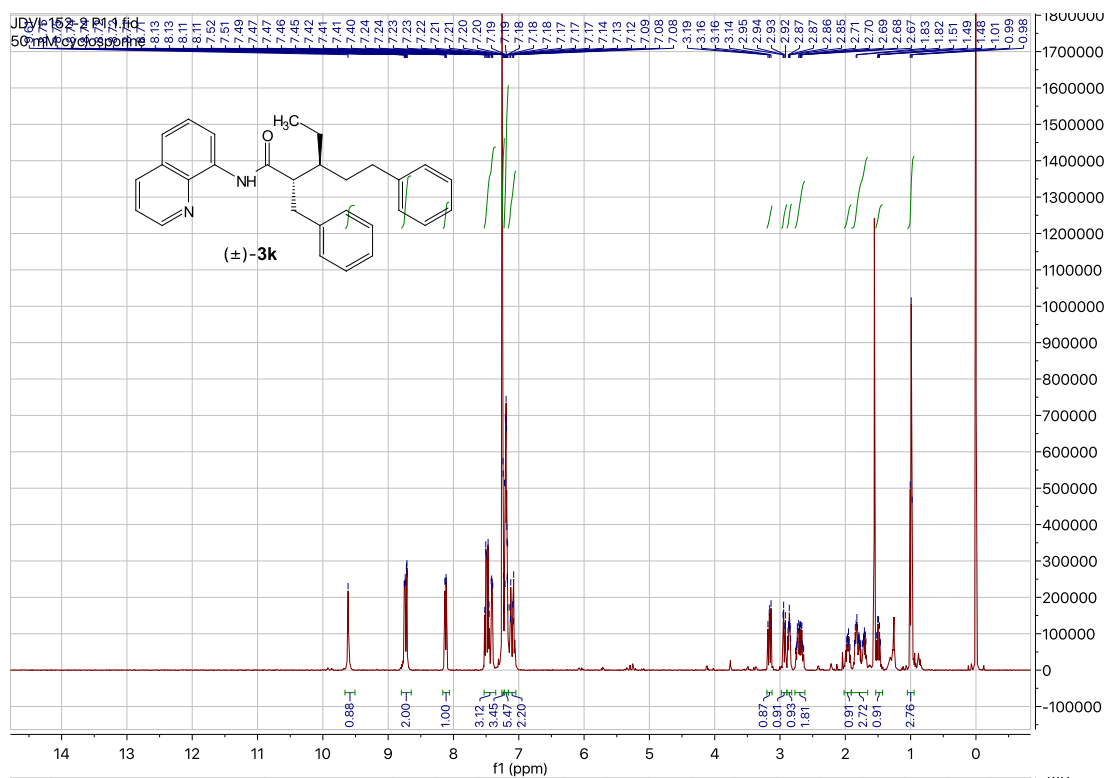


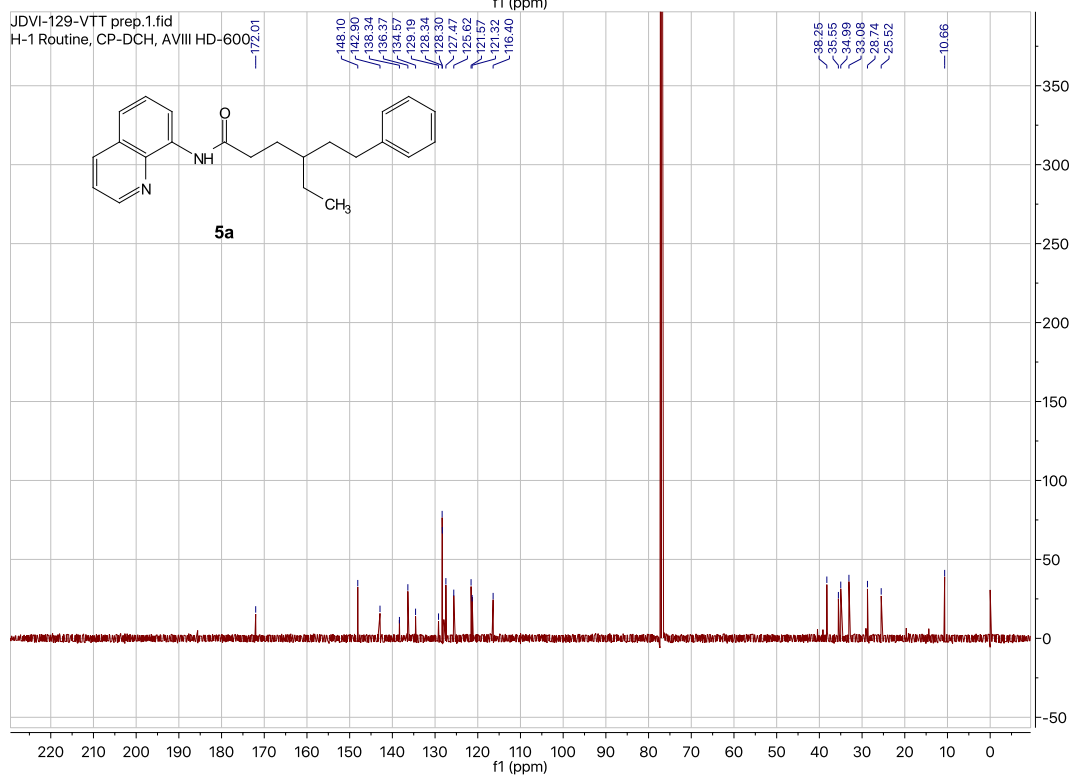
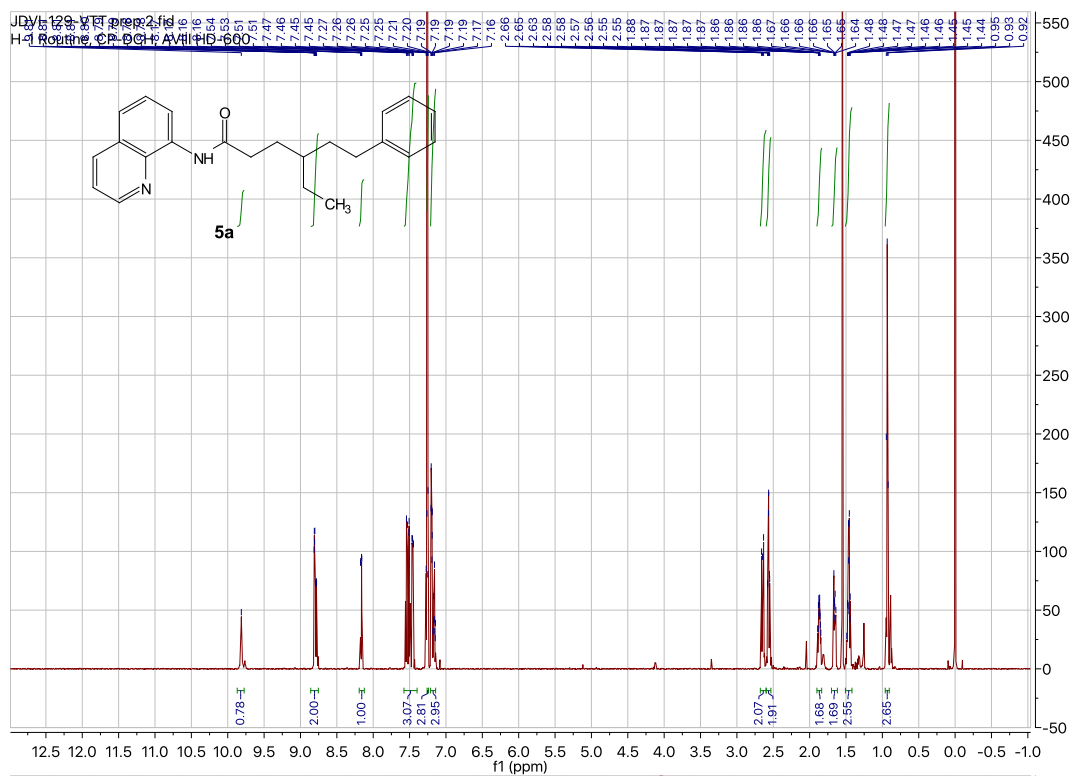


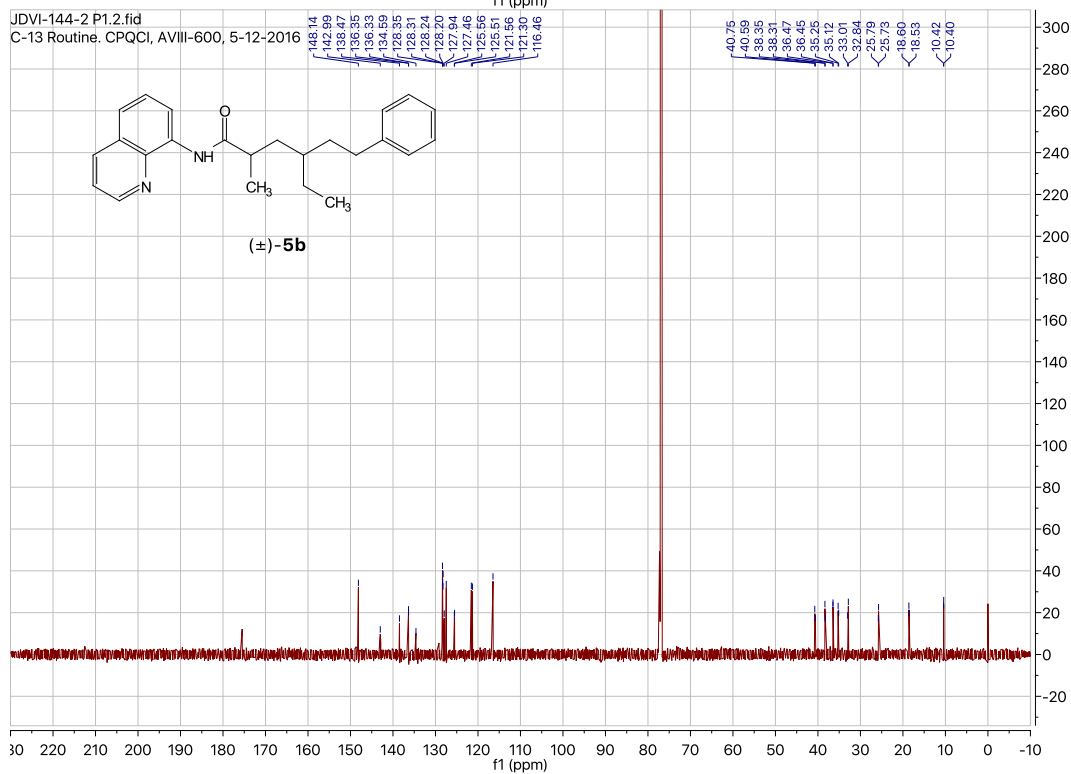
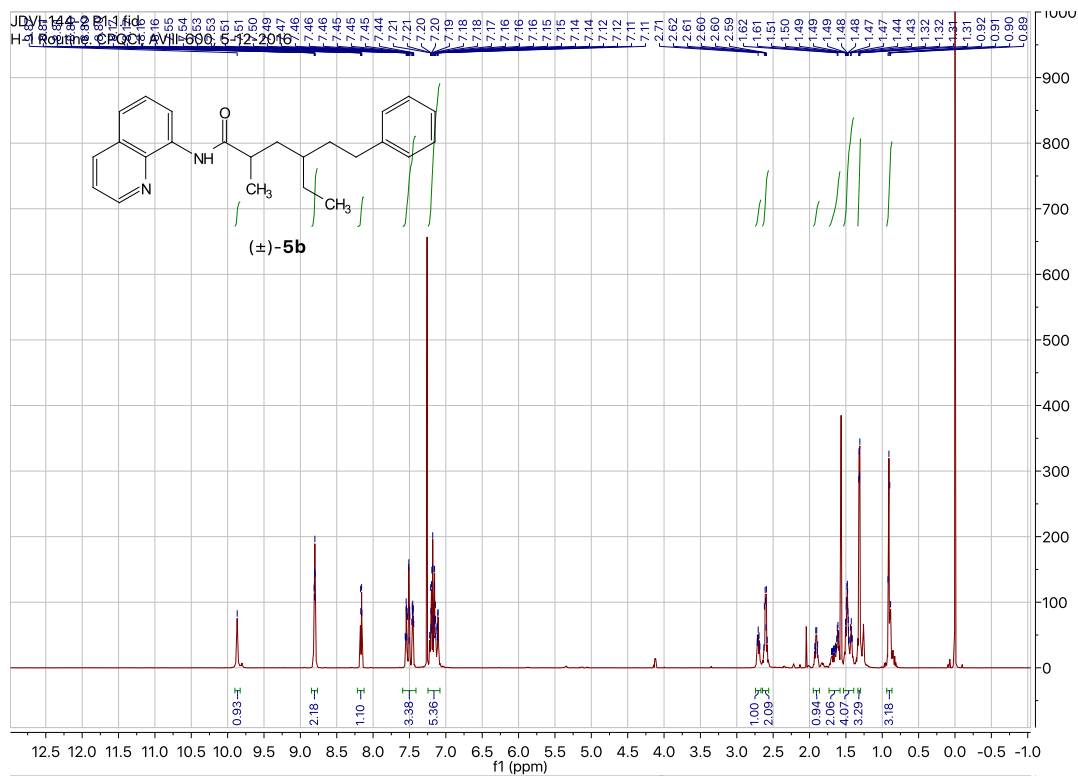


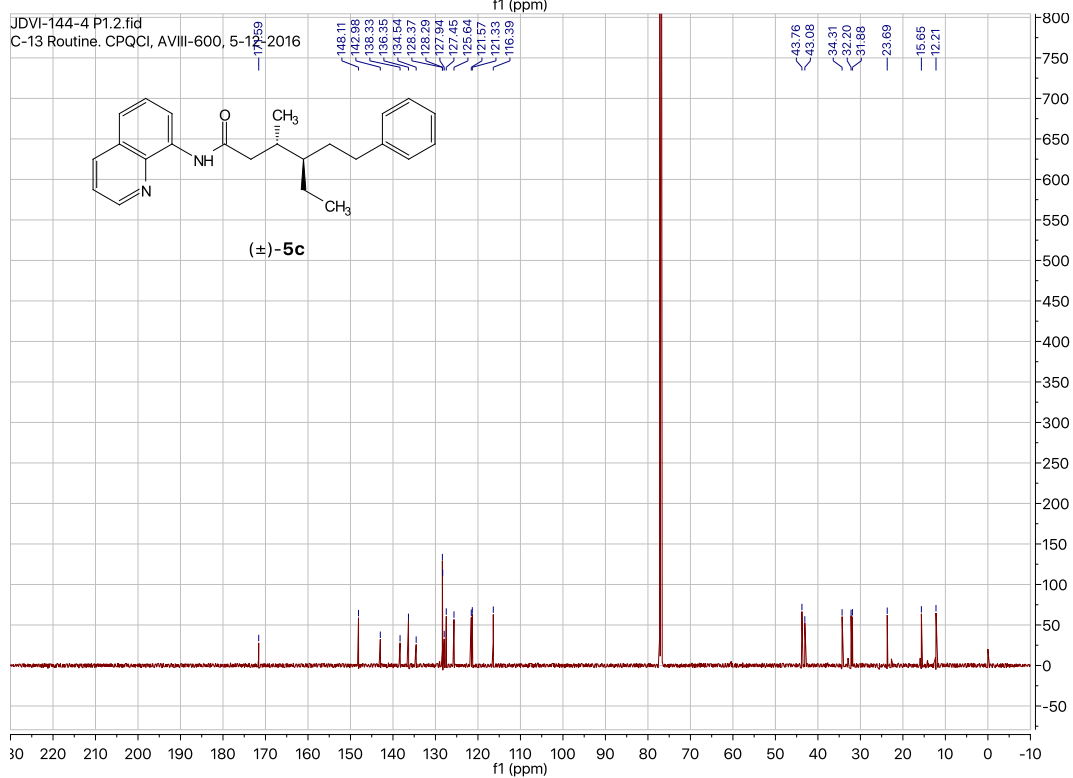
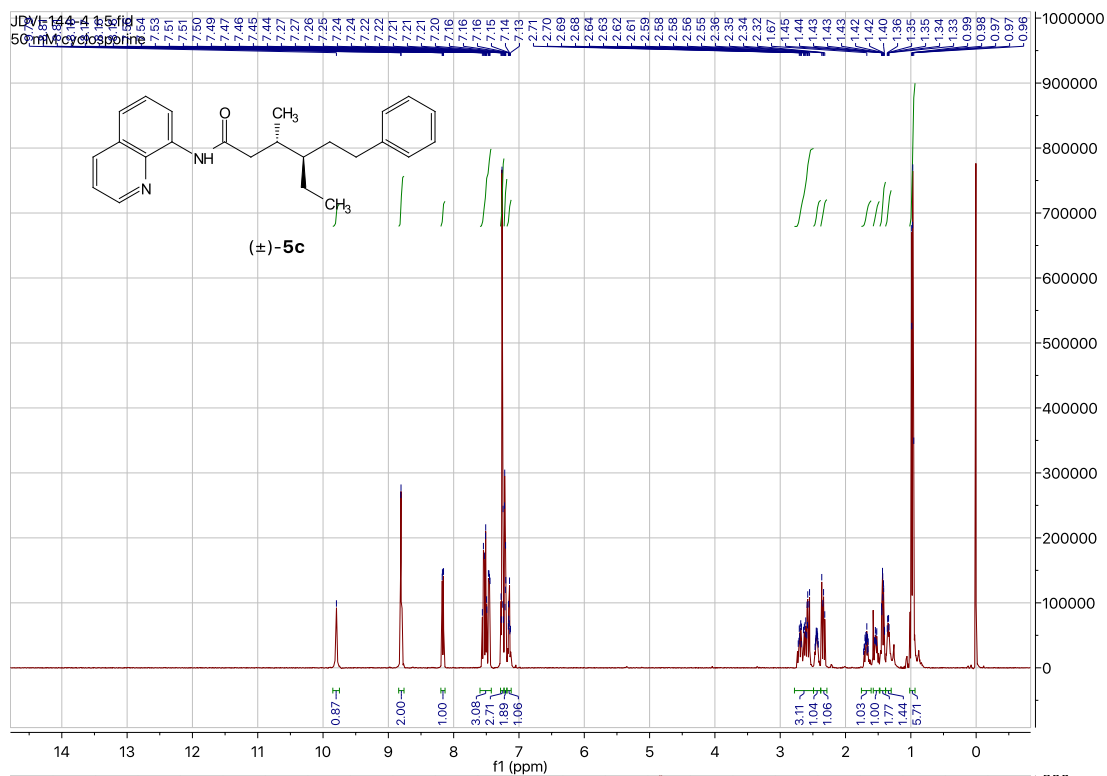


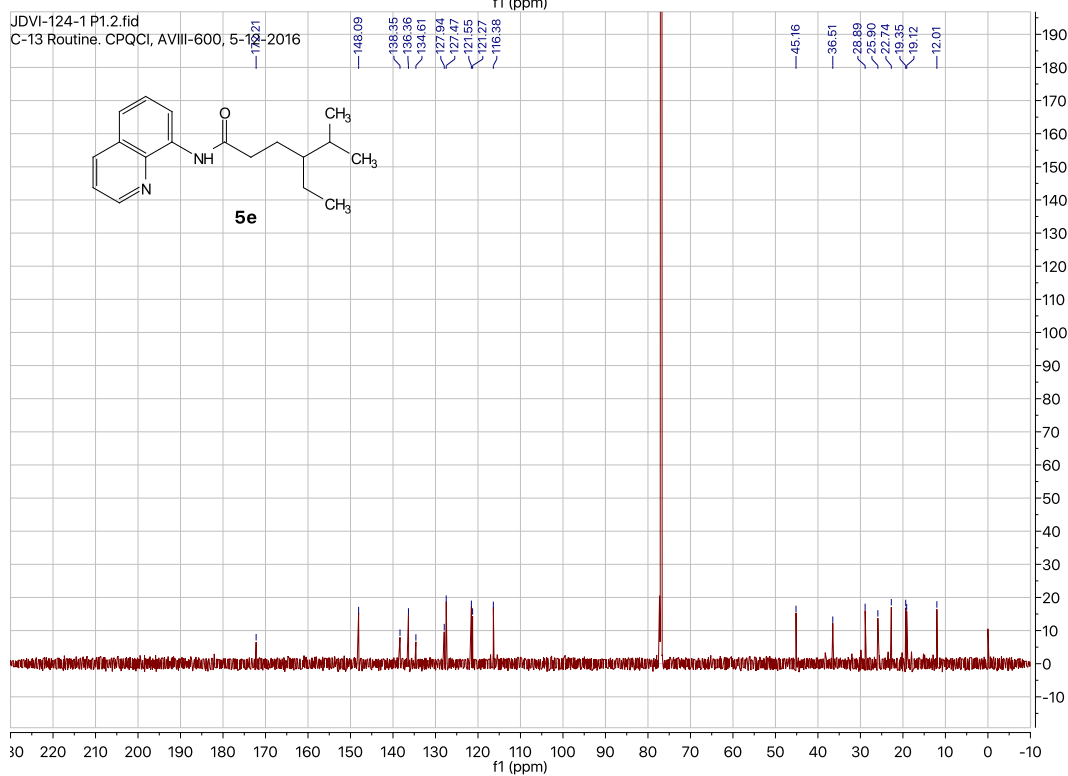
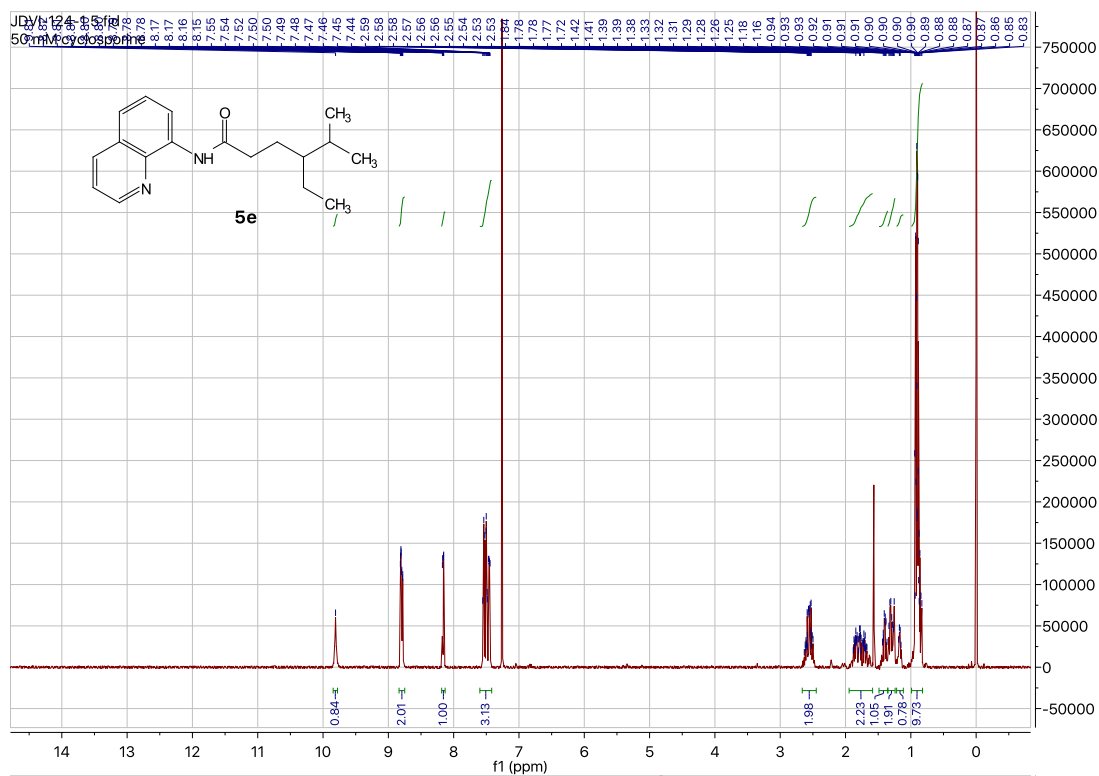


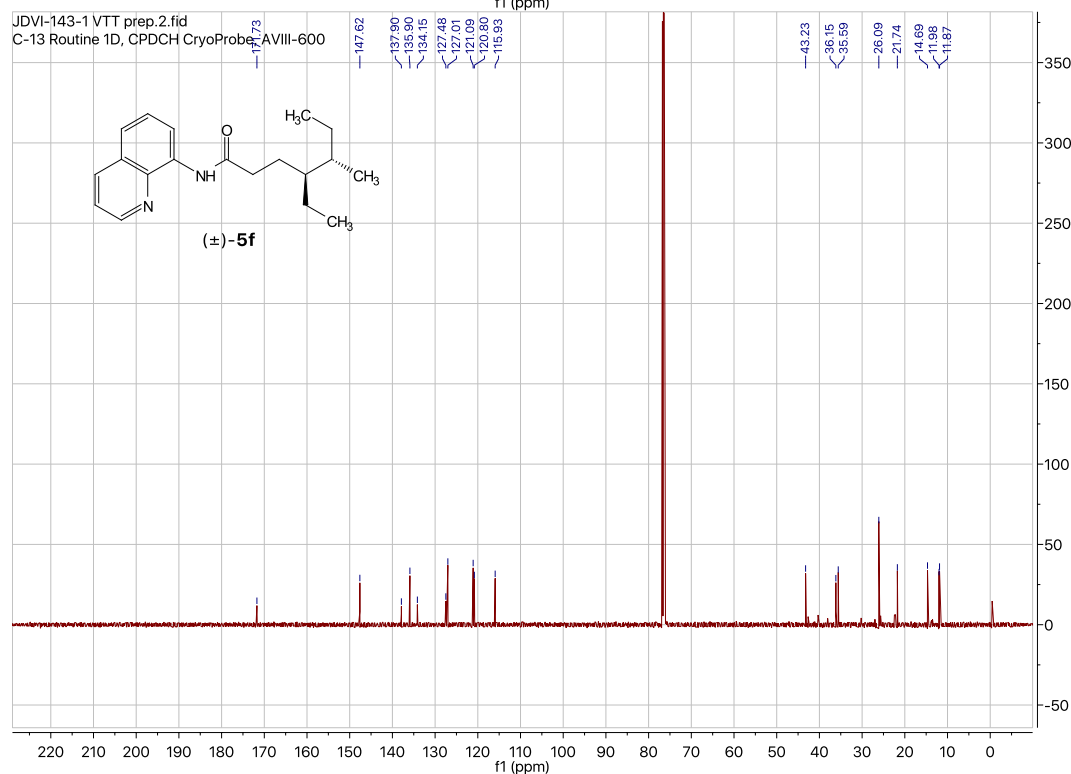
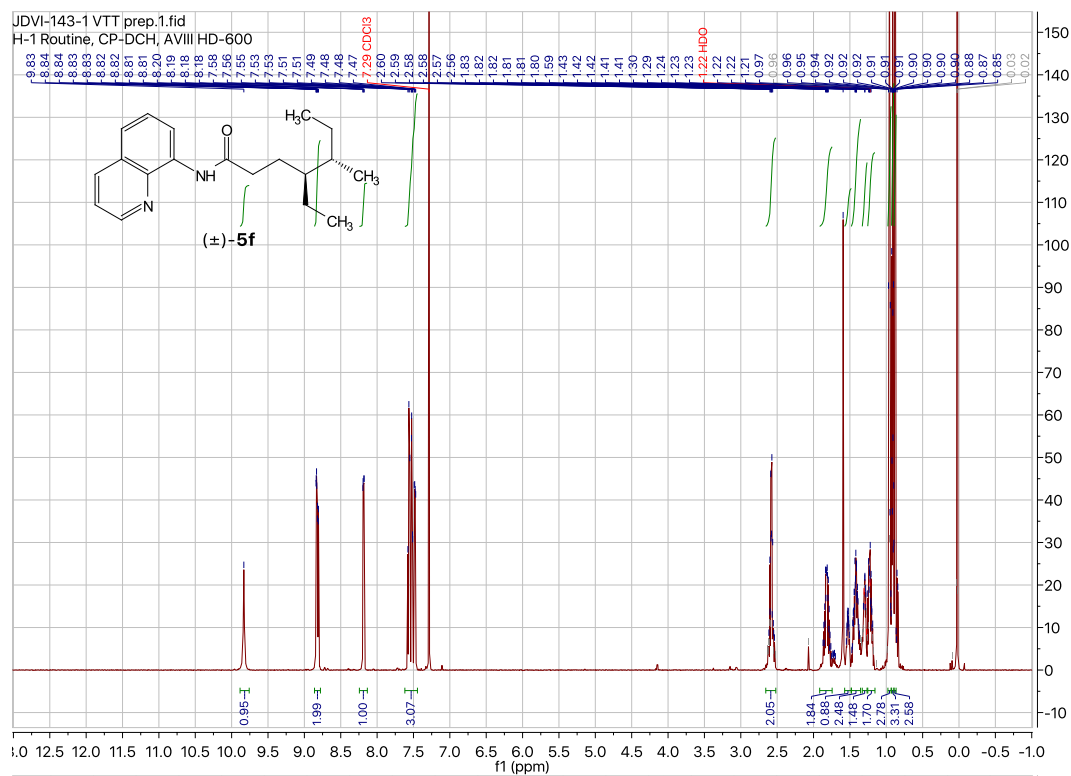


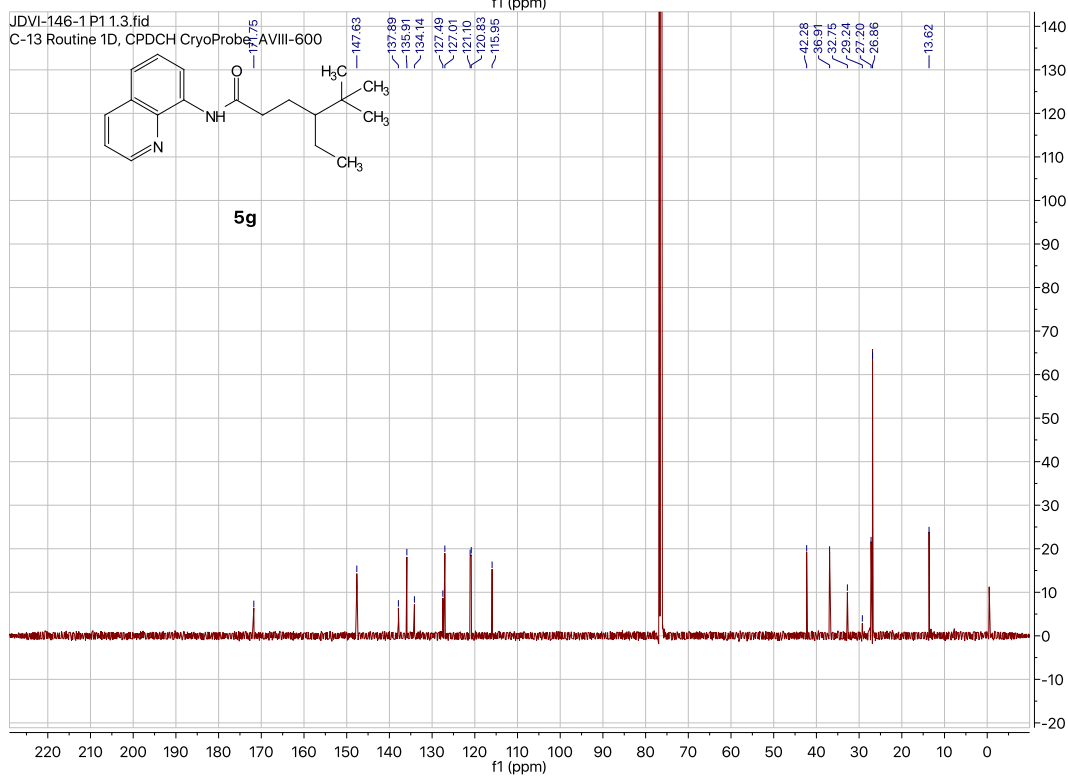
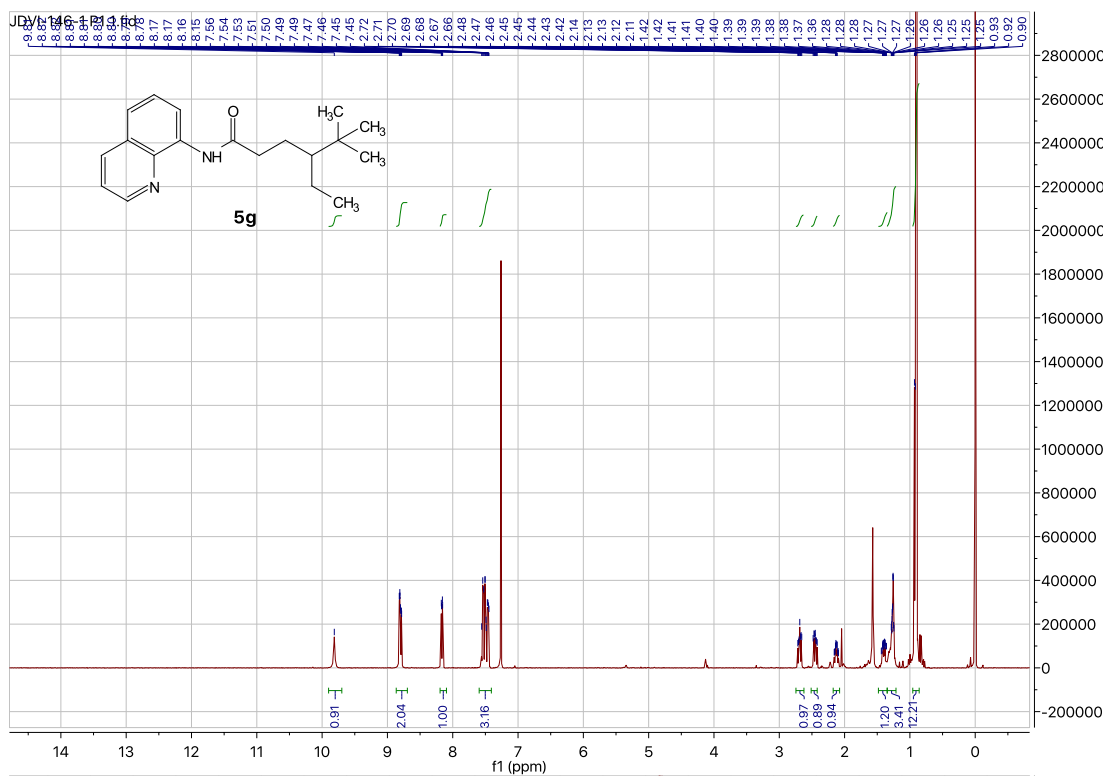


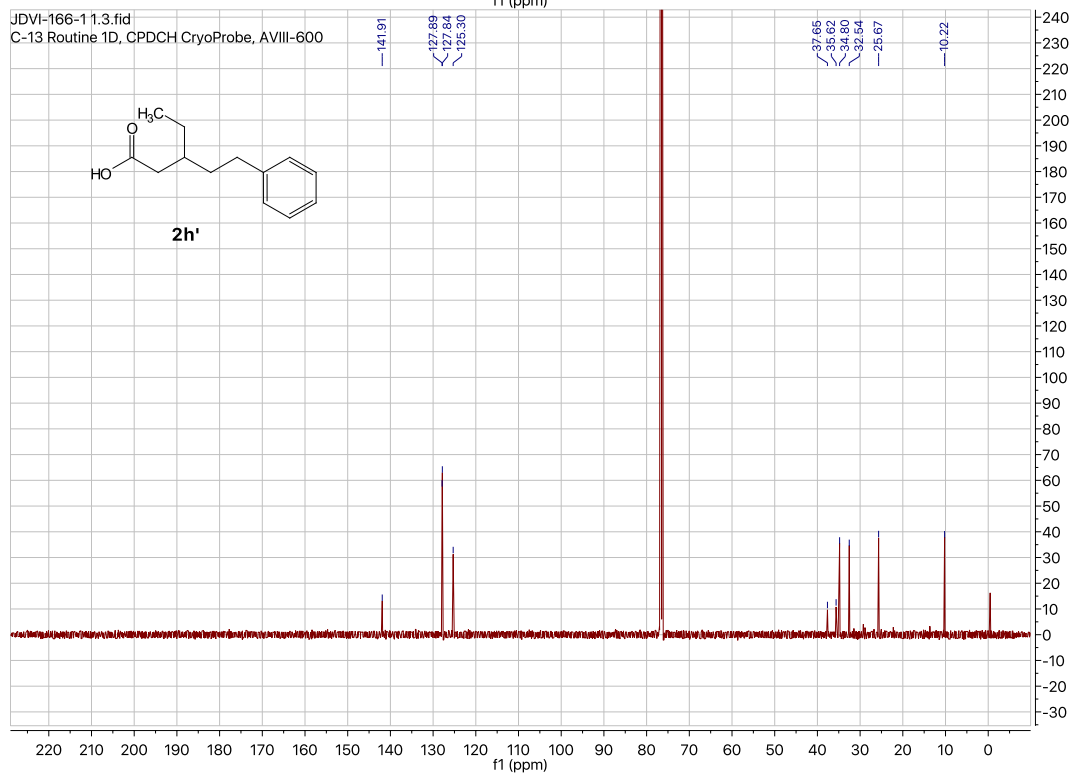
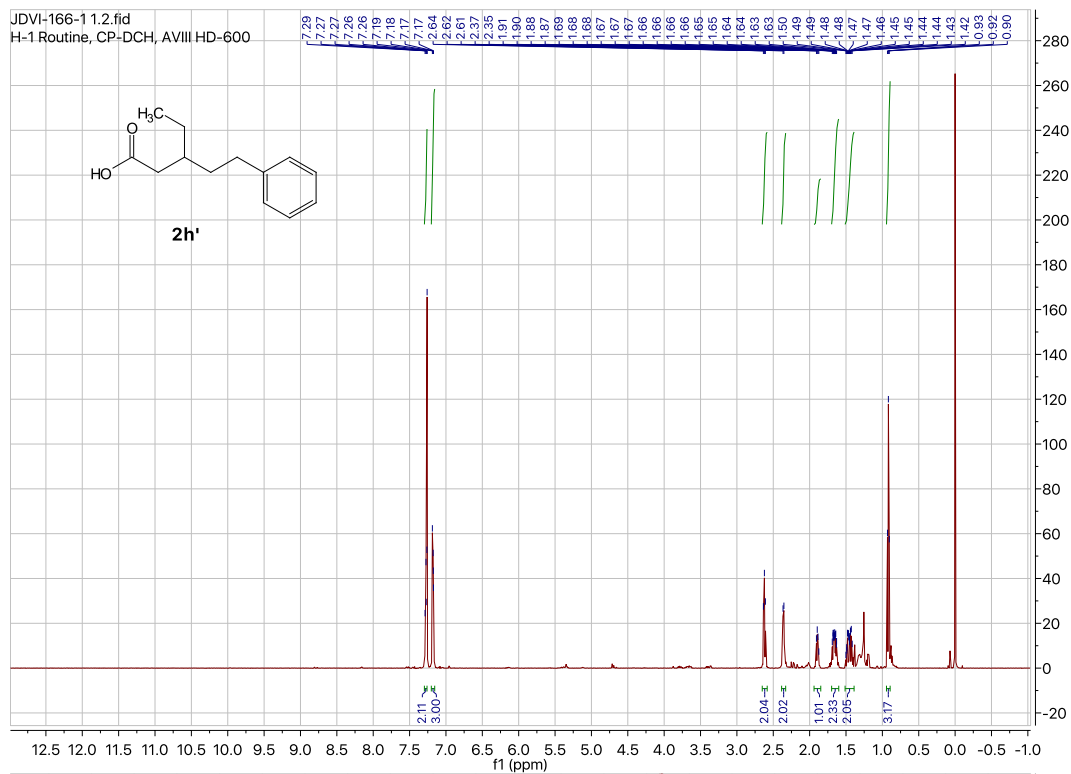












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