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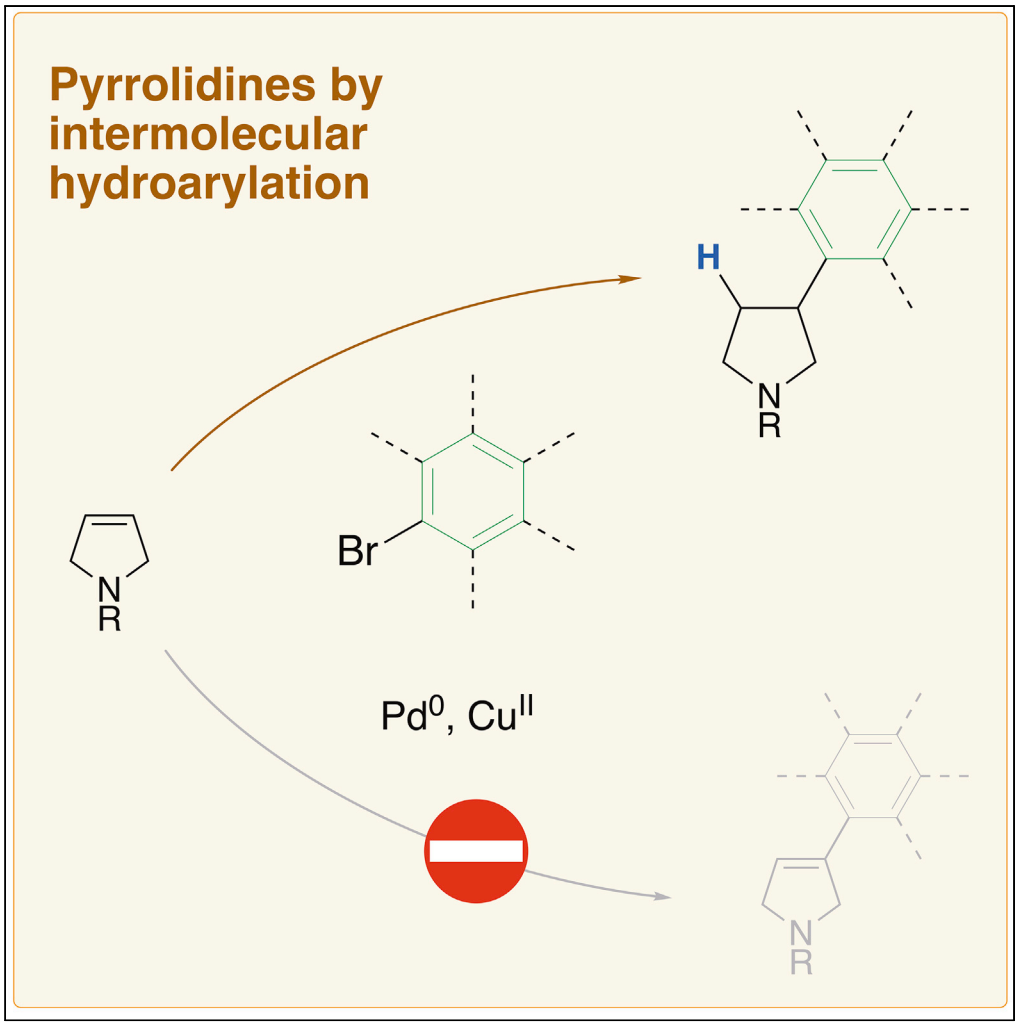

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HIGHLIGHTS

Pyrrolines undergo hydroarylation in palladium-catalyzed processes

The process allows facile catalytic entry to molecules with potent biological activity

The reaction has broad scope in arylating agents

Enables efficient manufacture of drug-like molecules from readily available precursors

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Synthesis of 3-Substituted Pyrrolidines via Palladium-Catalyzed Hydroarylation

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SUMMARY

Metal-catalyzed reactions have revolutionized synthetic chemistry, allowing access to unprecedented molecular architectures with powerful properties and activities. Nonetheless, some transformations remain sparse in number, or out of reach, even with the diverse modern catalytic chemical arsenal, including bimolecular alkene hydroarylation reactions. We report here a broad-scope, palladium-catalyzed pyrroline hydroarylation process that gives 3-aryl pyrrolidines, a class of small molecules with potency in a diverse range of biological scenarios. Thus, whereas N-acyl pyrrolines usually undergo palladium-catalyzed arylation to give alkene products, the corresponding reactions of N-alkyl pyrrolines deliver products of hydroarylation, pyrrolidines. The process has broad substrate scope and can be used to directly deliver drug-like molecules in a single step from readily available precursors.

INTRODUCTION

Small molecules with saturated and unsaturated heterocyclic cores are ubiquitous in biochemistry, and much attention has been paid to the manufacture of such structures in academia and industry. Nitrogen-containing saturated rings are particularly privileged structures in biology, and there has therefore been intense interest in the design and use of these heterocycles as drug-like molecules: ca. 60% of the currently US Food and Drug Administration-approved small molecule drugs contain such a motif (Vitaku, et al., 2014). Within the N-heterocycle-containing drug library, the pyrrolidine motif is a very frequently seen structure, and these five-membered rings are widely used in drug discovery, with even relatively simple pyrrolidines often possessing great potency (Figure 1).

Methods to deliver functionalized pyrrolidines directly by catalytic processes are relatively scarce, with the majority of reported methods involving ring-construction, rather than peripheral modification of intact pyrrolidines. In addition, certain classes of substituted pyrrolidines lend themselves rather more favorably to ring modification than others: thus, although there have been elegant efforts for both non-catalytic (Kerrick and Beak, 1991; Beak et al., 1994; Gelardi et al., 2013; Jain et al., 2017) and catalytic (Chatani et al., 2000; Shaw et al., 2016) conversion of unsubstituted pyrrolidines to 2-substituted derivatives, there are a few methods that efficiently deliver 3-substituted pyrrolidines, a structural class with diverse biological activity (Hutton et al., 2014; Wong et al., 2012; Wang et al., 2018; Holechek et al., 2018; Grandel et al., n.d. WO, 2007118899A1; Drescher et al., n.d. WO, 2006040182A1; Sonesson et al., 1997). For the latter compounds, there is usually a requirement for a directing group (Affron and Bull 2016; Feng et al., 2015; Mondal et al., 2016) or N-protection, which limits direct access to structurally simple bioactive N–H or N-alkyl pyrrolidines (such as bioactive N-propyl compounds, Figure 1B).

The Mizoroki-Heck (MH) reaction (Braese and de Meijere, 2014; Oestreich, 2009) was one of the earliest reported method (Mizoroki et al., 1971; Heck and Nolley, 1972) to execute direct, substoichiometric catalytic modification of simple alkenes; for cycloalkenes, the MH reaction proceeds by overall functionalization of an sp^3—rather than an sp^2—CH bond, due to the stereoelectronic control for β-hydride elimination in the key palladium(II) intermediates **1** (Figure 2A). In addition to the parent cycloalkene systems, the reaction can be applied to 2,3-dihydropyrans (Mata et al., 2007; Wu and Zhou, 2014) (**2**, X=O) and the analogous N-carbamoyl pyrrolines (Sonesson et al., 1996; Carpes and Correia, 2002; Montes de Oca and Correia, 2003; Garcia et al., 2005; Peixoto da Silva et al., 2007; Finelli et al., 2015) (**2**, X=N–C[O]R) (Figure 2), but the reactions can be unpredictable (cf. Figures 2A and 2B). MH reactions of N–H or N-alkyl azacycloalkenes can be further complicated by competing oxidation processes, and there are few reports of effective MH reactions for this class of substrate; the fact that many biologically active piperidines and pyrrolidines have this substitution pattern is a drastic limitation to the method. In addition, higher N-alkyl analogs (which can possess enhanced activity (Ekenstam et al., 1957; Figure 1B) are difficult to access directly using existing MH

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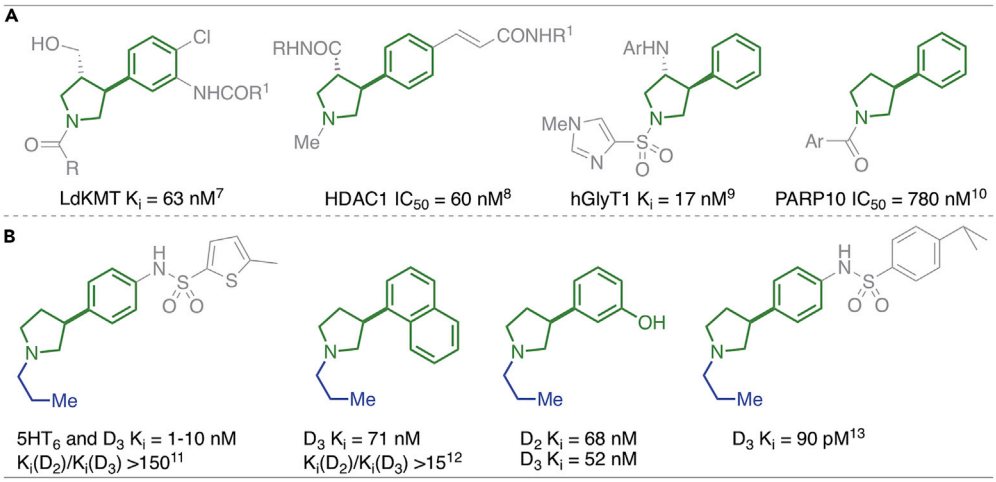


Figure 1. Saturated Five-Membered Nitrogen Heterocycles

(A) 3-Aryl pyrrolidines are privileged structures, exhibiting powerful effects in a diverse range of biological scenarios, such as leishmaniasis, histone deacetylation, neurotransmission, and gene transcription.

(B) 1-Propyl-3-aryl pyrrolidines are potent and selective ligands for serotonin and dopamine receptors.

methodology, often requiring deacylation-alkylation strategies. We recently reported (Sweeney et al., 2018) conditions to effect the MH reaction of 1-propyl tetrahydropyridine in an improved, gram-scale, protecting-group-free route to the drug molecule preclamol (3-PPP, **4**) (Figure 2C). The observed regiochemistry was ascribed to the intermediacy of a chelated palladium complex **5**.

In theory, interception of **1** and **5** by a hydride source could lead to saturated products, rather than alkenes; in practice, such hydroarylation reactions (Beletskaya and Cheprakov, 2000; Namyslo et al., 2010) are

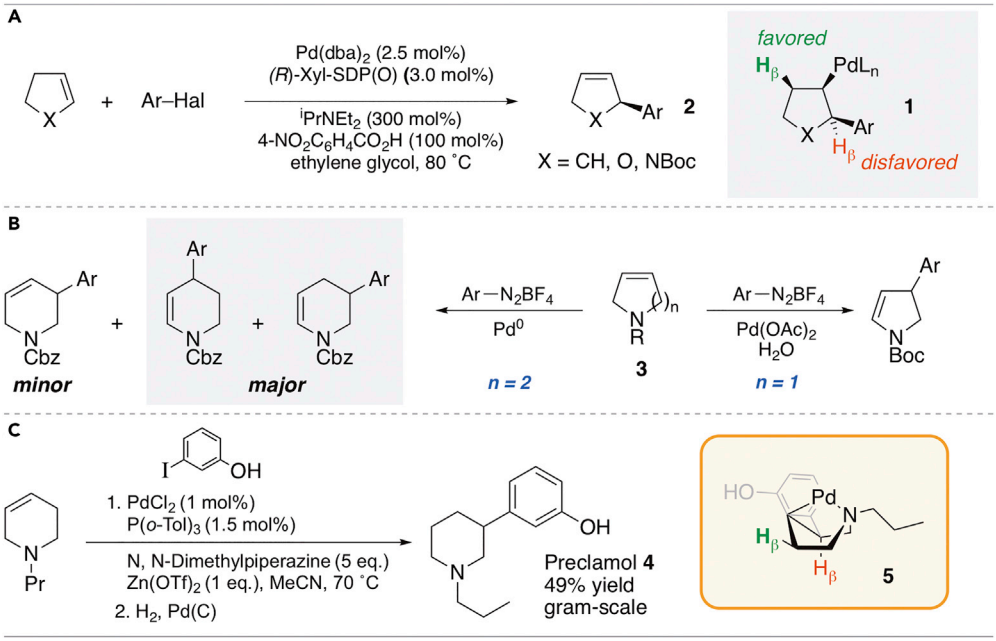


Figure 2. Mizoroki-Heck Arylation of Unsaturated Heterocycles Proceeds by Overall sp3-Functionalization

(A) Carba- and heterocycloalkene MH arylation favors allylic functionalization, controlled by β-hydride accessibility.

(B) Mizoroki-Heck-Matsuda arylations of N-acyl pyrrolines and tetrahydropyridines often give mixtures of products.

(C) MH arylations of N-alkyl tetrahydropyridines are controlled by chelation.

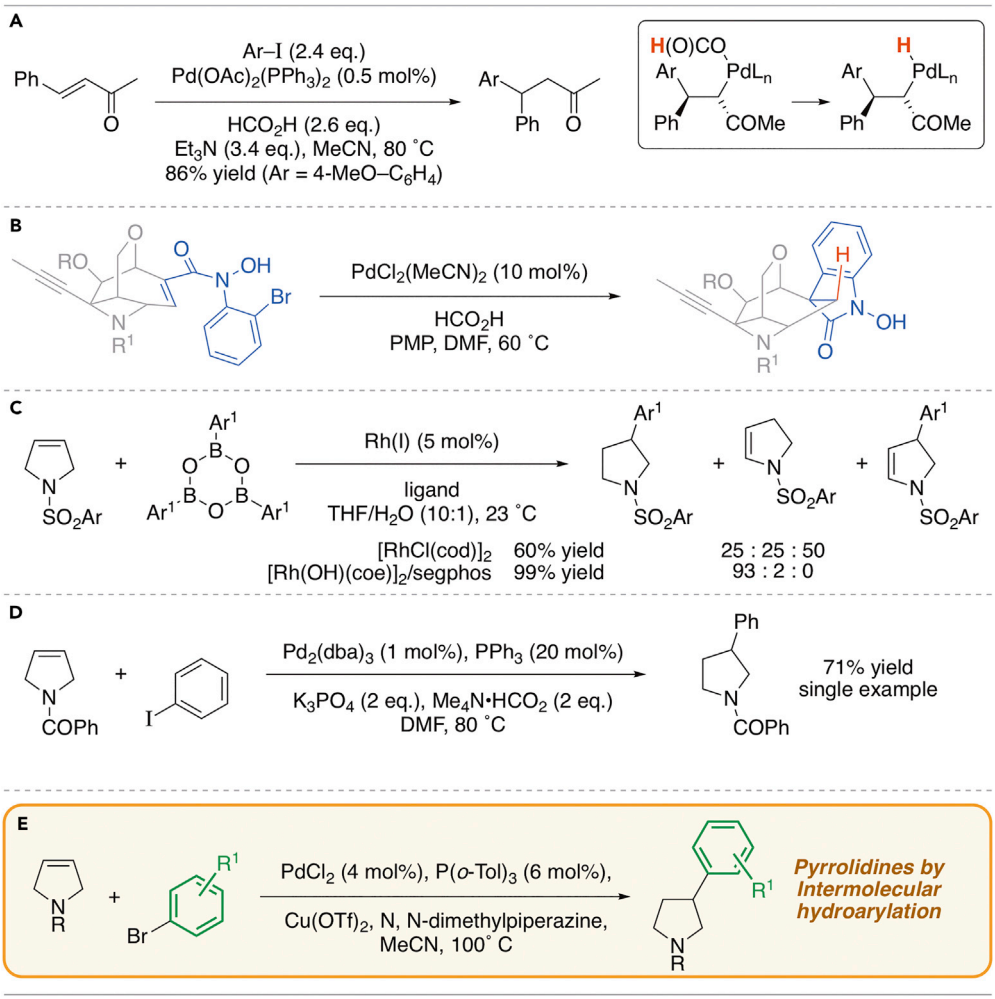


Figure 3. Reductive Mizoroki-Heck Processes Are Rare, and Confined to a Small Number of Reaction Types

(A) Conjugate-type additions.

(B) Intramolecular.

(C) Rh-catalyzed pyrroline hydroarylation.

(D) N-acylpyrroline reductive MH.

(E) This work: reductive Mizoroki-Heck reaction—palladium-catalyzed hydroarylation of pyrrolines.

narrowly confined to conjugate-like additions (Figure 3A) (Cacchi and Arcadi, 1983), constrained alkenes (Larock and Johnson, 1989; Bai et al., 1996), and intramolecular processes (Figure 3B) (Larock and Babu, 1987; Burns et al., 1988; Kong et al., 2017; Diethelm and Carreira, 2015). Although a rhodium-catalyzed process has been reported (Figure 3C) (So et al., 2013), to date, only one intermolecular palladium-catalyzed hydroarylation reaction to give pyrrolidines has been described (Figure 3D) (Gurak and Engle, 2018); we report here a novel, broad-scope, palladium-catalyzed hydroarylation process (Figure 3E), directly furnishing 3-substituted pyrrolidines efficiently.

RESULTS AND DISCUSSION

During the course of the optimization of the route to preclamol shown in Figure 2C, it became clear that redox side reactions were significant competitors to the desired arylation process; in addition to the monoarylated product, hydroarylated product **6** was also obtained in ca. 3% yield (Figure 4A). We supposed that the hydride necessary to deliver **6** originated in the substrate (present in excess), leading to dihydropyridiniums **7**, reactive species notorious for their propensity for side reaction (such as dimerization [Baldwin et al., 1998]), and we deduced that this would explain the relatively low yields of MH products compared

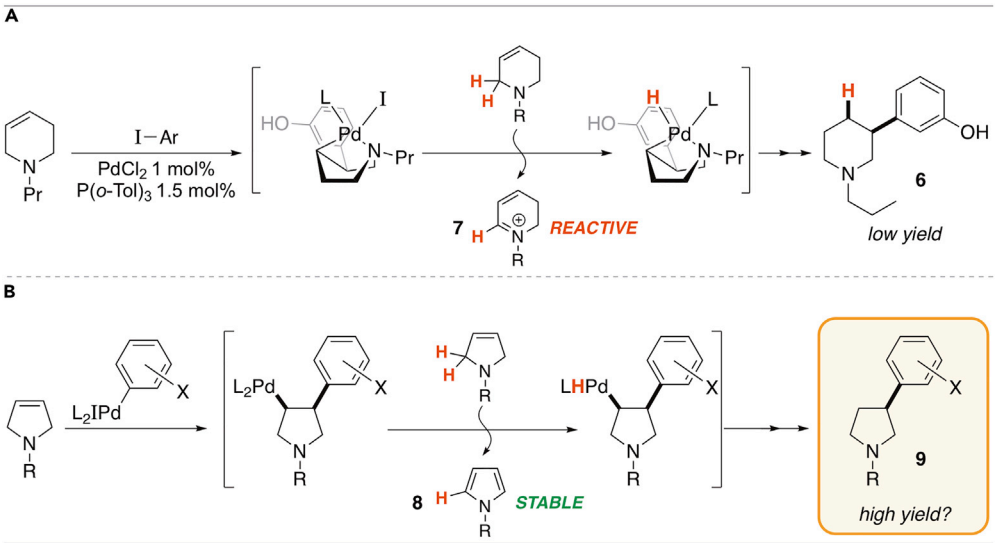


Figure 4. Hijacking Redox Side Reactions to Deliver an Efficient Alkene Hydroarylation Reaction

(A) Tetrahydropyridine MH reaction: redox processes are deleterious.

(B) Pyrroline MH reaction: harnessing pyrrole stability to favor hydroarylation.

with the parent cycloalkenes. Based on this analysis, we proposed that reaction of the lower homolog, pyrroline, should proceed more efficiently, since the analogous oxidized by-product (pyrrole **8**, Figure 4B) would be stable and therefore would neither initiate nor participate in further side reactions. If this were the case, we assumed that the latter reaction would cleanly deliver hydroarylated product (pyrrolidine **9**) rather than the traditional olefinic product.

We were, therefore, gratified to observe that reaction of pyrroline **10** with iodide **11** under the MH conditions previously identified in the tetrahydropyridine series gave pyrrolidine **9a** as the only coupled product (Figure 5 yields calculated using ^{19}F nmr); N-propylpyrrole was also obtained, in approximately equal yield, confirming the hydride source to be the excess substrate and validating the original hypothesis.

Encouraged by the first-pass reaction, we next undertook a screening study (key data given in Table 1), which indicated conditions using bromide **12** as substrate with 4 mol% loading of Pd catalyst (entry 11) as being optimal, when considering stoichiometry, reaction time, and yield.

Traditional silver(I) additives delivered low yield of coupled product (entry 1), but the use of $Zn(OTf)_2$ was productive (entries 3 and 5), though less efficient than $Cu(OTf)_2$ (cf. entries 2 and 3, and entries 4 and 5), although only protodehalogenation was observed (in 97% yield) when no additive was present (entry 7); these data indicate that the additive is acting as a Lewis acid (vide infra).

Having identified an efficient and practical protocol, we next moved to examine the scope of the process and were gratified to observe that a diverse range of aryl bromides underwent the reductive MH reaction, delivering 3-substituted pyrrolidines **9a–9t** generally in good yields (Figure 6). The process was also applicable to N-benzylpyrroline, giving the synthetically tractable pyrrolidines **13a** and **13b**.

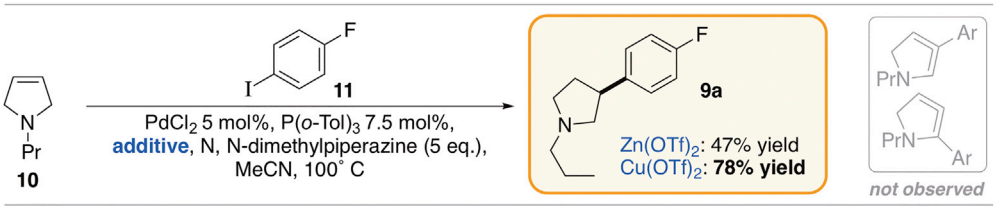
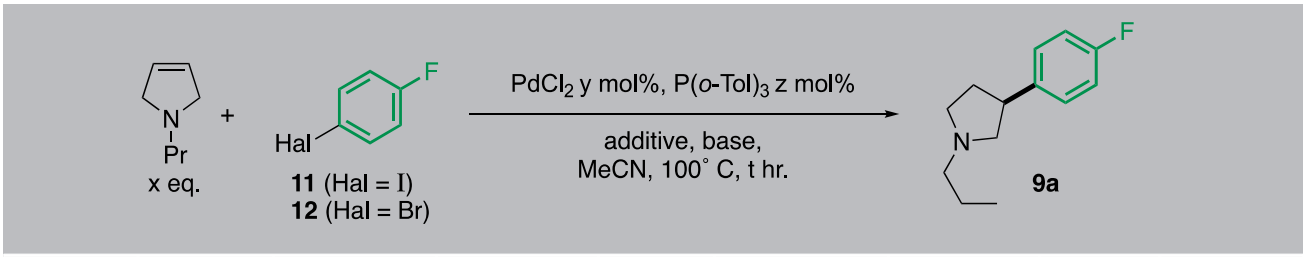


Figure 5. N-Alkyl Pyrroline Arylation: an Efficient Bimolecular Reductive Mizoroki-Heck Reaction



Entry	x/Eq.	y/mol %	z/mol %	Hal	Additive[a]	Base[b]	t/hr	Yield (%)[c]
1	4	5	5	I	$AgNO_3$	DABCO	17	20
2	4	5	7.5	I	$Cu(OTf)_2$	DMpip[d]	17	78
3	4	5	7.5	I	$Zn(OTf)_2$	DMpip	17	47[e]
4	4	5	7.5	Br	$Cu(OTf)_2$	DMpip	17	77
5	4	5	7.5	Br	$Zn(OTf)_2$	DMpip	17	32[f]
6	3	1	1.5	Br	$Cu(OTf)_2$	DMpip	17	62
7	3	5	7.5	Br	None	DMpip	20	0[g]
8	3	1	1.5	Br	$Cu(OTf)_2$	DMpip	90	71
9	3	2	3	Br	$Cu(OTf)_2$	DMpip	26	71
10	3	3	4.5	Br	$Cu(OTf)_2$	DMpip	26	78[h]
11	3	4	6	Br	$Cu(OTf)_2$	DMpip	17	77[i]
12	3	5	7.5	Br	$Cu(OTf)_2$	DMpip	17	80
13	2.5	3	4.5	Br	$Cu(OTf)_2$	DMpip	26	75
14	2.5	5	7.5	Br	$Cu(OTf)_2$	DMpip	26	76

Table 1. Optimization of Reaction Conditions

DABCO = 1,4-diazabicyclo[2.2.2]octane.

[a]1 equivalent.

[b]5 equivalents.

[c]Estimated from ^{19}F NMR.

[d]N, N-Dimethylpiperazine.

[e]Fluorobenzene obtained in 26% yield.

[f]Fluorobenzene obtained in 61% yield.

[g]Fluorobenzene obtained in 97% yield.

[h]97% conversion.

[i]100% conversion.

The power of this method is exemplified in the preparation of nanomolar dopamine antagonist **9k**, which is accessed in one step using the protocol described above, compared with the multi-step process, which is the only previously described synthetic strategy to obtain **9k** (Figure 7).

With regard to the precise mechanism in play, it is not unreasonable to assume that an intermediate such as cationic complex **14** (Figure 8) is involved (although isolation of complex 14 remains elusive, the importance of N-coordination to this process was confirmed by the use of N-sulfonyl pyrrolines under the reaction conditions, whereupon the only products obtained were 3-aryl 2-pyrrolines): **14** (formed by ligand exchange of halide for pyrroline, promoted by $Cu(OTf)_2$ [Anson et al., 2006; Fang et al., 2014]) can rapidly be converted to palladium hydride **15** (generating pyrrole **8** as by-product), which reductively eliminates the hydroarylated product and returns the catalyst to the cycle.

In summary, we have described a broad-scope palladium-catalyzed pyrroline hydroarylation to prepare pyrrolidines: the method is operationally simple and delivers potent bioactive small molecules in short

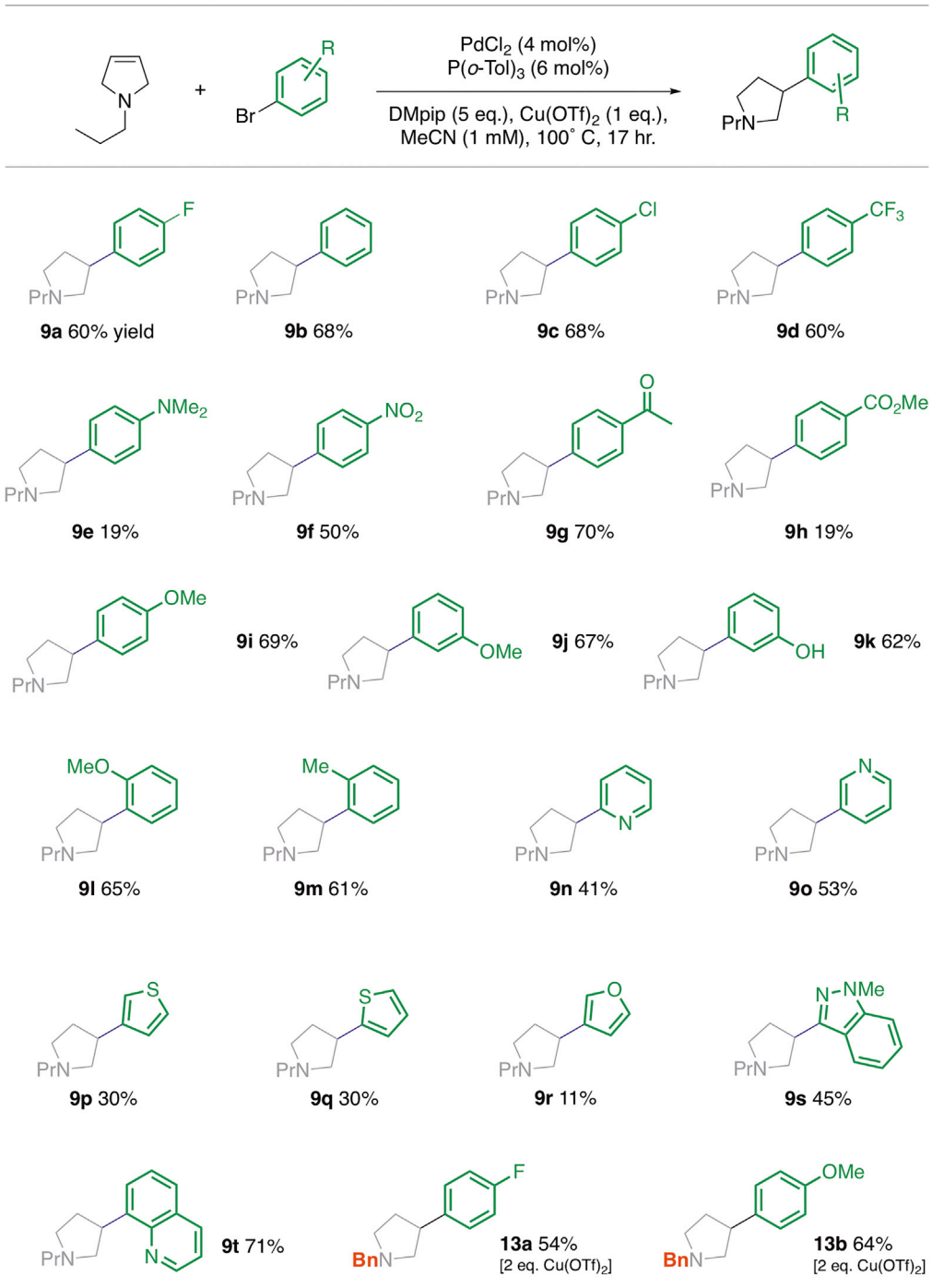


Figure 6. Scope of Pyrroline Reductive Mizoroki-Heck Arylation

order, and in good yields. The precise mechanistic features of these reactions are a focus of our research at present, and these data will be disclosed elsewhere, in due course.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

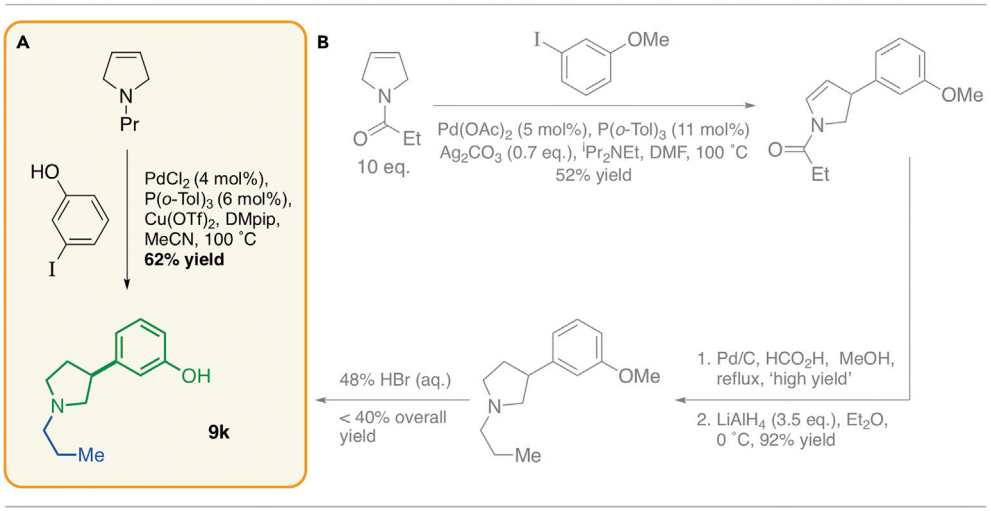


Figure 7. Palladium-Catalyzed Hydroarylation of Pyrrolines: an Improved Entry To Dopamine Receptor Antagonists

(A) This work: one-step synthesis of nanomolar compound **9k**.

(B) Reported synthesis of **9k** (Sonesson et al., 1997).

SUPPLEMENTAL INFORMATION

Supplemental Information includes Transparent Methods and 22 figures and can be found with this article online at https://doi.org/10.1016/j.isci.2018.10.025.

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AUTHOR CONTRIBUTIONS

J.D. and B.T. carried out all the experiments, under the supervision of J.B.S. The ideas were conceived by J.B.S. Reactions were conceived and designed by J.B.S. The manuscript was written by J.B.S.

DECLARATION OF INTERESTS

The authors declare no competing interests.

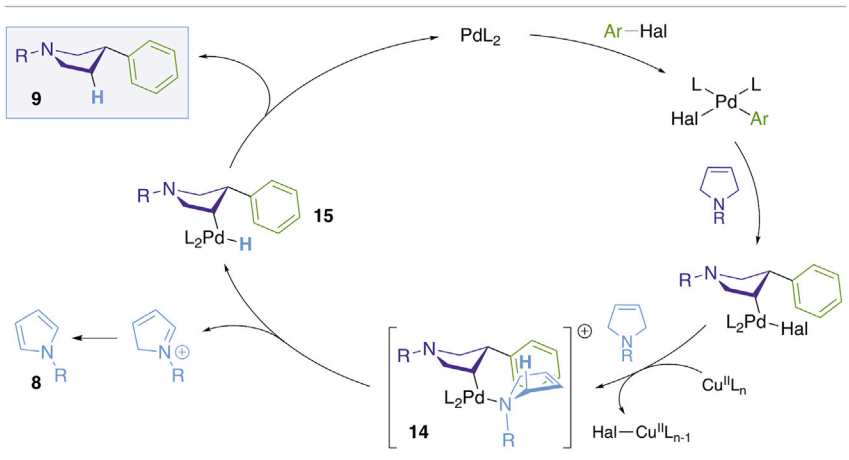

Figure 8. Plausible Mechanism for Palladium-Catalyzed Pyrroline Hydroarylation

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Supplemental Information

Synthesis of 3-Substituted Pyrrolidines via Palladium-Catalyzed Hydroarylation

Joseph B. Sweeney, Julien Doulcet, and Bimod Thapa

Synthesis of 3-substituted pyrrolidines via palladium-catalysed hydroarylation.

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Supplemental information

Transparent methods

General methods

Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific and were not purified unless otherwise stated. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation using potassium permanganate solution, phosphomolybdic acid and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (40-63 microns) supplied by Sigma-Aldrich unless otherwise stated.

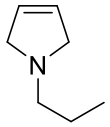
Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, ^{19}F at 376 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from tetramethylsilane, in ^{13}C NMR spectra are relative to the respective residual NMR solvent, in ^{19}F NMR spectra are relative to internal standard hexafluorobenzene (–161.68 ppm) and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.1 Hz. Mass spectrometry was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm^{-1}.

General procedure for hydroarylation of *N*-propyl-3-pyrroline

In a 20-mL microwave vial was added, $PdCl_2$ (21 mg, 0.12 mmol, 0.04 eq), P(*o*-Tol)$_3$ (54 mg, 0.18 mmol, 0.06 eq), *N*,*N*-dimethylpiperazine (2.1 mL, 15 mmol, 5 eq), arylbromide (3 mmol, 1 eq), $Cu(OTf)_2$ (1.08 g, 3 mmol, 1 eq), *N*-propyl-3-pyrroline (1.17 mL, 9 mmol, 3 eq) and acetonitrile (3 mL). The vial was closed and then heated at 100 °C for 17 h. The reaction mixture was then allowed to cool down to r.t. and was then diluted with DCM (10 mL). Then, Et_2O (100 mL) was added and the mixture was washed with NH_4OH_{aq} (28%, 100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by column chromatography (70 g silica, gradient DCM : NH_3 (7 N in MeOH), 100:0 to 97:3 v/v) affording the pure title compound. (If necessary a second column chromatography step was performed using the same conditions).

Experimental procedures and NMR spectra

1-Propyl-2,5-dihydro-1H-pyrrole **10**



Chemical Formula: $C_7H_{13}N$
Molecular Weight: 111.19

In a dry 2-L round-bottomed flask flushed with nitrogen, *cis* 1,4-dichlorobut-2-ene (100 g, 0.8 mol, 1 eq) was added to DCM (1.2 L). The reaction mixture was cooled to 0 °C and propylamine (330 mL, 4.0 mol, 5 eq) was added dropwise. The reaction was then left to warm up to RT and was stirred for 18 h. The reaction mixture was washed with $NaOH_{aq.}$ (1M, 1.2 L), the organic layer was separated, and the aqueous layer was extracted with DCM (2 × 1 L). The combined organic layers were dried over $MgSO_4$, filtered and concentrated carefully under reduced pressure (500 mbar 40 °C) yielding the crude product containing traces of DCM. This crude mixture was then purified by Kugelrohr distillation (25 mbar, 90 °C) to yield the desired product (42.1 g, 47 %).

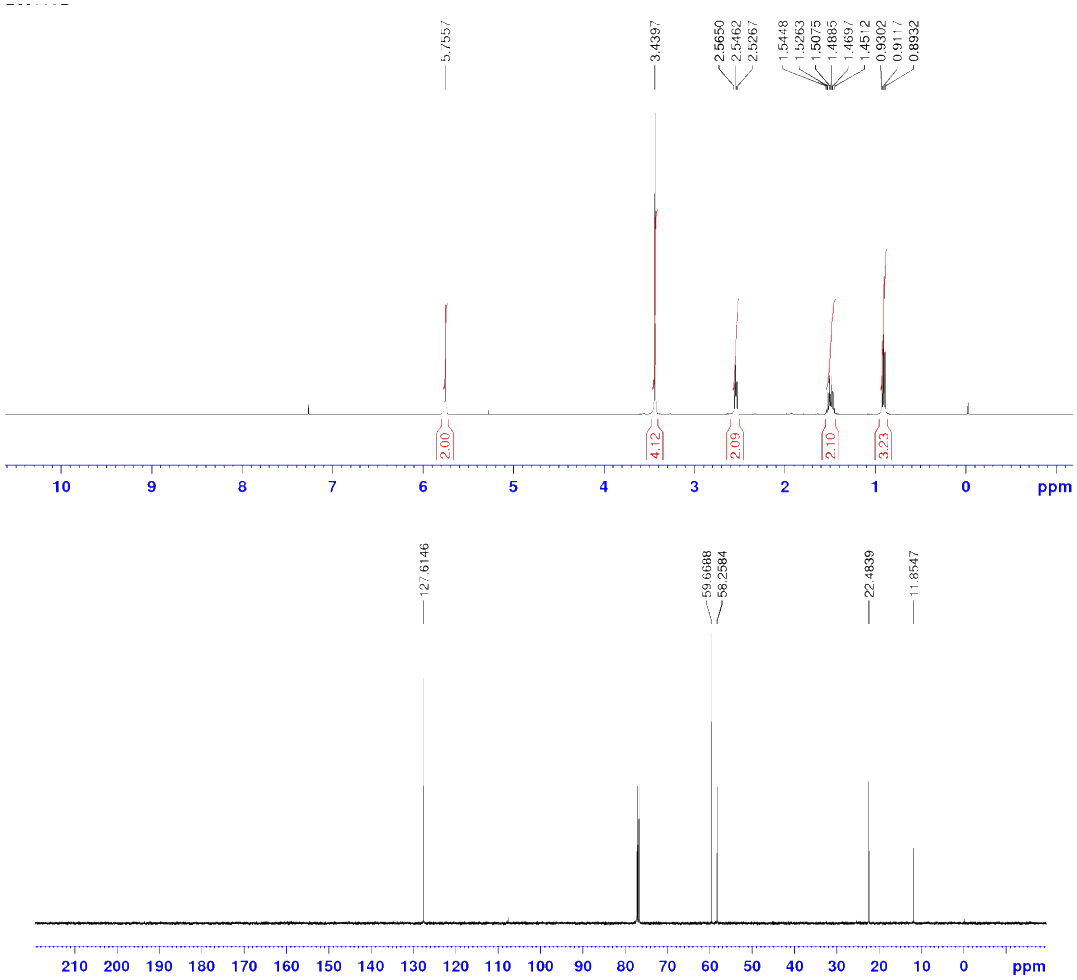
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.76 (s, 2H), 3.44 (s, 1H), 2.53-2.57 (m, 2H), 1.50 (app sext, *J* 7.5 Hz, 2H) 0.91 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 127.6 (2CH), 59.7 ($2CH_2$), 58.3 ($1CH_2$), 22.5 ($1CH_2$), 11.9 ($1CH_3$).

IR ν_{max} (thin film, cm^{-1}): 3074 (CH), 2957 (CH), 2931 (CH), 2872 (CH), 2784 (CH), 2755 (CH).

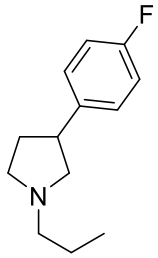
HRMS *m/z* (ESI^+) calculated for $C_7H_{13}N$ $(M+H)^+$ expected 112.1121, found 112.1121.

Figure S1. NMR spectra for compound 10, related to Figure 6.



3-(4-Fluorophenyl)-1-propylpyrrolidine **9a**

3-(4-fluorophenyl)-1-propylpyrrolidine **9a**



Chemical Formula: $C_{13}H_{18}FN$
Molecular Weight: 207.29

9a was isolated from 4-bromofluorobenzene as a brown oil (375 mg, 60%) and from 4-iodofluorobenzene as a brown oil (365 mg, 59%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.20-7.24 (m, 2H), 6.94-6.99 (m, 2H), 3.32-3.41 (m, 1H), 3.09 (dd, *J* 8.1 Hz, 9.1 Hz, 1H), 2.86-2.92 (m, 1H), 2.67-2.73 (m, 1H), 2.42-2.58 (m, 3H), 2.28-2.37 (m, 1H), 1.81-1.90 (m, 1H), 1.57 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

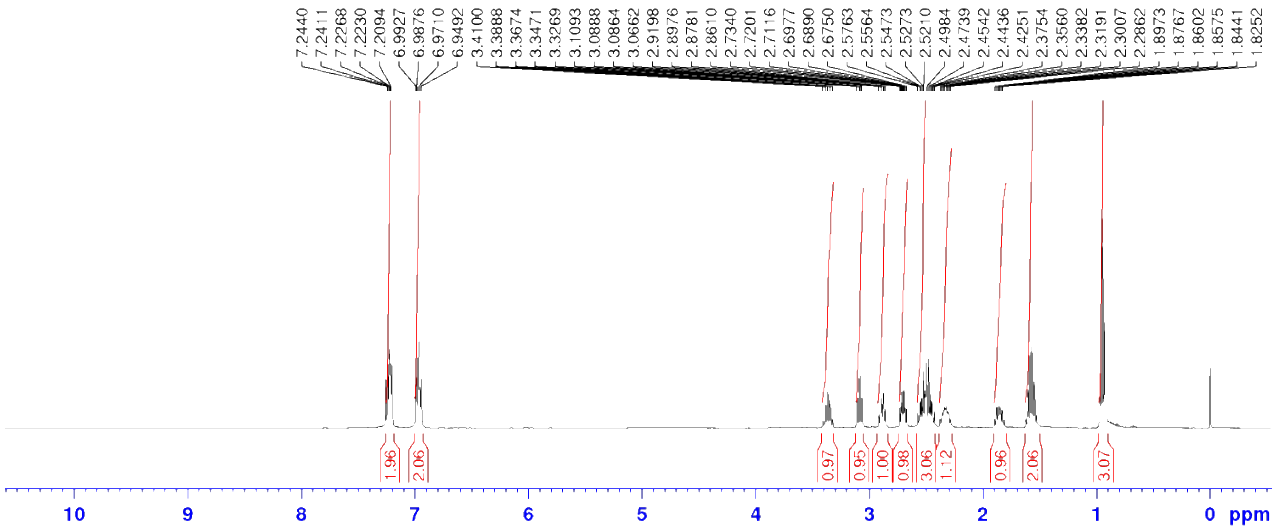
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 161.3 (d, *J* 242.4 Hz, 1C), 140.6 (1C), 128.6 (d, *J* 7.8 Hz, 2CH), 115.1 (d, *J* 20.9 Hz, 2CH), 62.2 ($1CH_2$), 58.5 ($1CH_2$), 54.6 ($1CH_2$), 42.6 (1CH), 33.2 ($1CH_2$), 21.9 ($1CH_2$), 12.0 ($1CH_3$).

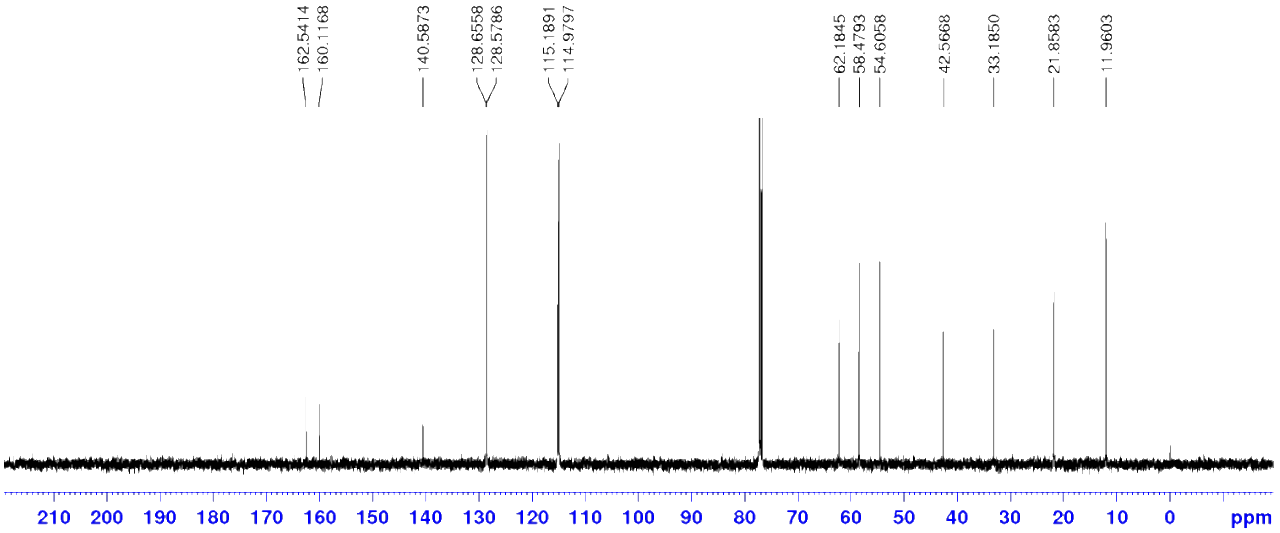
^{19}F {^{1}H} NMR ($CDCl_3$, 376 MHz) δ_F –117.5.

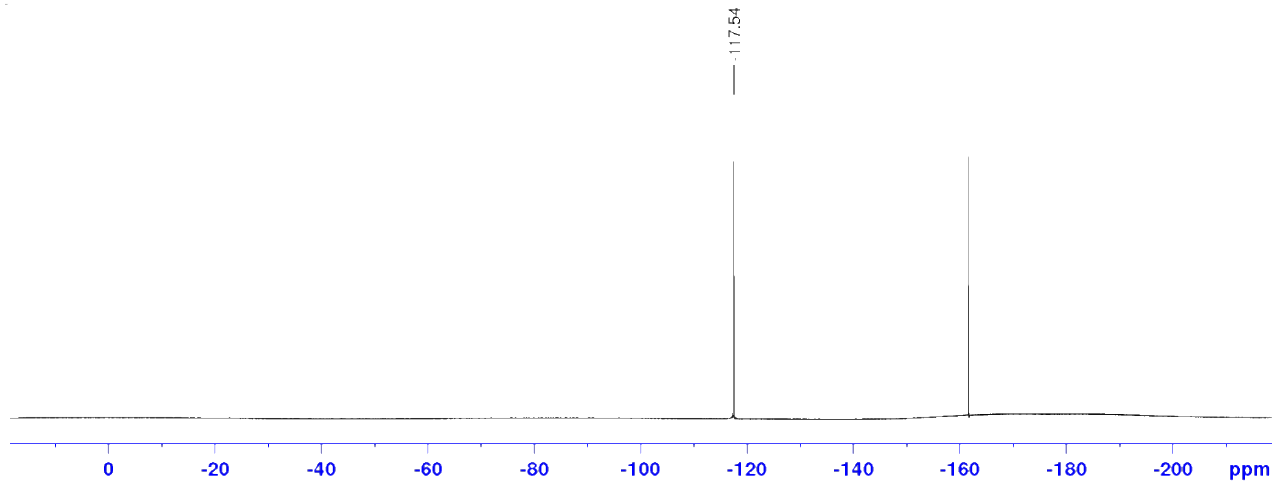
IR ν_{max} (thin film, cm^{-1}): 2958 (C-H), 2931 (C-H), 2874 (C-H), 2790 (C-H), 1509 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{13}H_{18}FN$ $[M+H]^+$: 208.1496, found 208.1496.

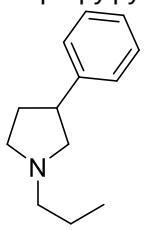
Figure S2. NMR spectra for compound 9a, related to Figure 6.







3-Phenyl-1-propylpyrrolidine **9b**



Chemical Formula: $C_{13}H_{19}N$
Molecular Weight: 189.30

9b was isolated as a brown oil (385 mg, 68%).

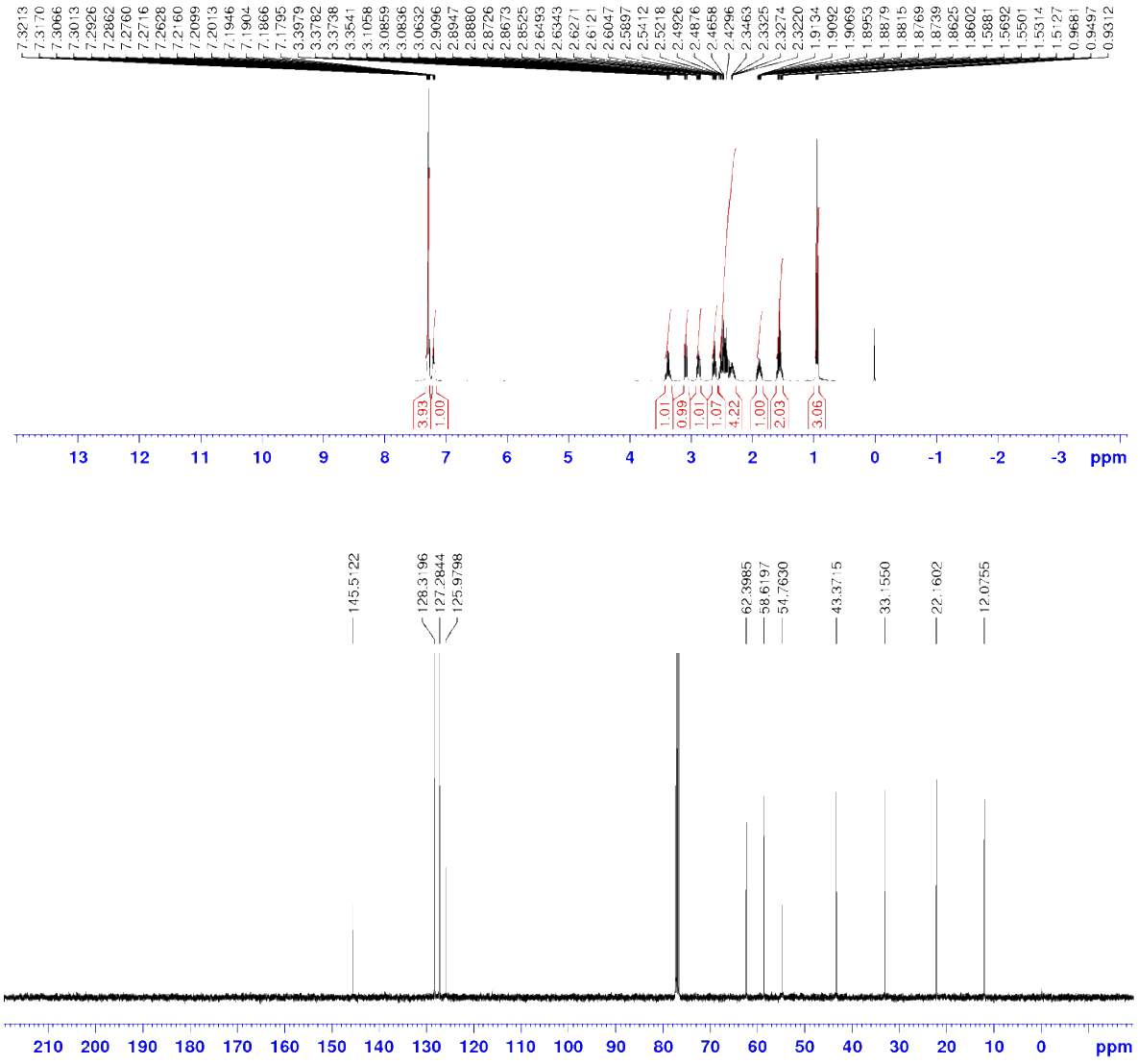
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.27-7.32 (m, 4H), 7.17-7.22 (m, 1H), 3.34-3.42 (m, 1H), 3.08 (dd, *J* 8.1 Hz, 8.8 Hz, 1H), 2.87-2.92 (m, 1H), 2.61-2.67 (m, 1H), 2.29-2.55 (m, 4H), 1.85-1.94 (m, 1H), 1.57 (sext, *J* 7.5 Hz, 2H), 0.95 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 145.5 (1C), 128.3 (2CH), 127.3 (2CH), 126.0 (1CH), 62.4 ($1CH_2$), 58.6 ($1CH_2$), 54.8 ($1CH_2$), 43.4 (1CH), 33.2 ($1CH_2$), 22.2 ($1CH_2$), 12.1 ($1CH_3$).

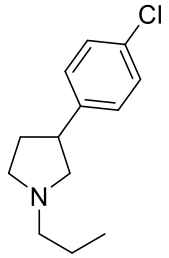
IR ν_{max} (thin film, cm^{-1}): 3027 (C-H, Ar), 2957 (C-H), 2929 (C-H), 2876 (C-H), 2787 (C-H), 1479 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{13}H_{19}N$ $[M+H]^+$: 190.1590, found 190.1591.

Figure S3. NMR spectra for compound 9b, related to Figure 6.



3-(4-Chlorophenyl)-1-propylpyrrolidine **9c**



Chemical Formula: $C_{13}H_{18}ClN$
Molecular Weight: 223.74

9c was isolated as a brown oil (455 mg, 68%).

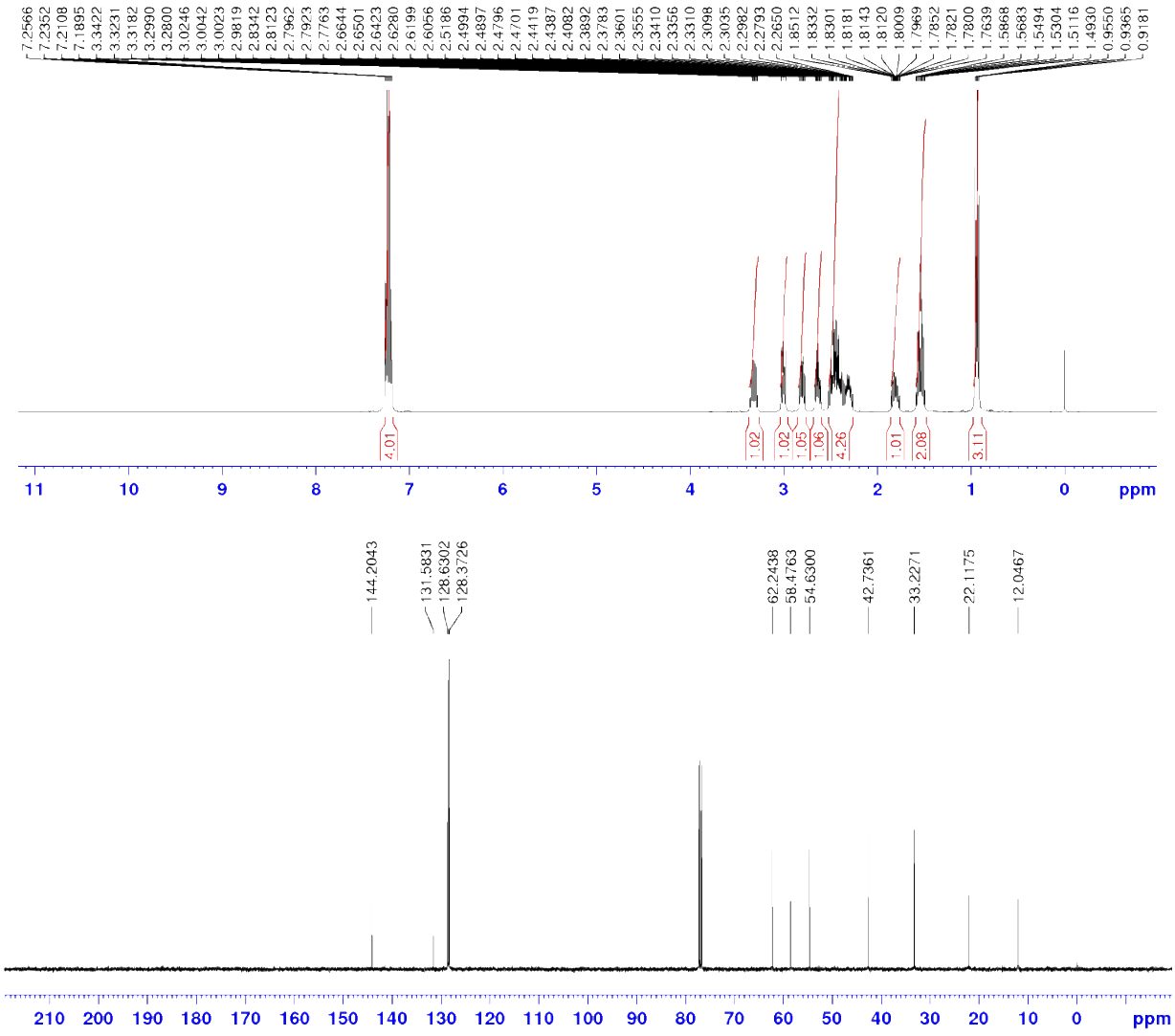
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.24 (d, *J* 8.6 Hz, 2H), 7.20 (d, *J* 8.6 Hz, 2H), 3.28-3.36 (m, 1H), 3.00 (dd, *J* 8.2 Hz, 8.5 Hz, 1H), 2.77-2.83 (m, 1H), 2.60-2.66 (m, 1H), 2.26-2.52 (m, 4H), 1.76-1.85 (m, 1H), 1.54 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 144.2 (1C), 131.6 (1C), 128.6 (2CH), 128.4 (2CH), 62.2 ($1CH_2$), 58.5 ($1CH_2$), 54.6 ($1CH_2$), 42.7 (1CH), 33.2 ($1CH_2$), 22.1 ($1CH_2$), 12.0 ($1CH_3$).

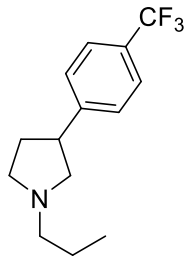
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2930 (C-H), 2874 (C-H), 2784 (C-H), 1491 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{13}H_{18}ClN$ $[M+H]^+$: 224.1201, found 224.1202.

Figure S4. NMR spectra for compound 9c, related to Figure 6.



1-Propyl-3-(4-(trifluoromethyl)phenyl)pyrrolidine **9d**



Chemical Formula: $C_{14}H_{18}F_3N$
Molecular Weight: 257.30

9d was isolated as a brown oil (460 mg, 60%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.54 (d, *J* 8.1 Hz, 2H), 7.44 (d, *J* 8.1 Hz, 2H), 3.36-3.44 (m, 1H), 3.01 (dd, *J* 8.2 Hz, 8.9 Hz, 1H), 2.76-2.83 (m, 1H), 2.69 (m, 1H), 2.30-2.54 (m, 4H), 1.81-1.90 (m, 1H), 1.55 (sext, *J* 7.5 Hz, 2H), 0.95 (t, *J* 7.4 Hz, 3H).

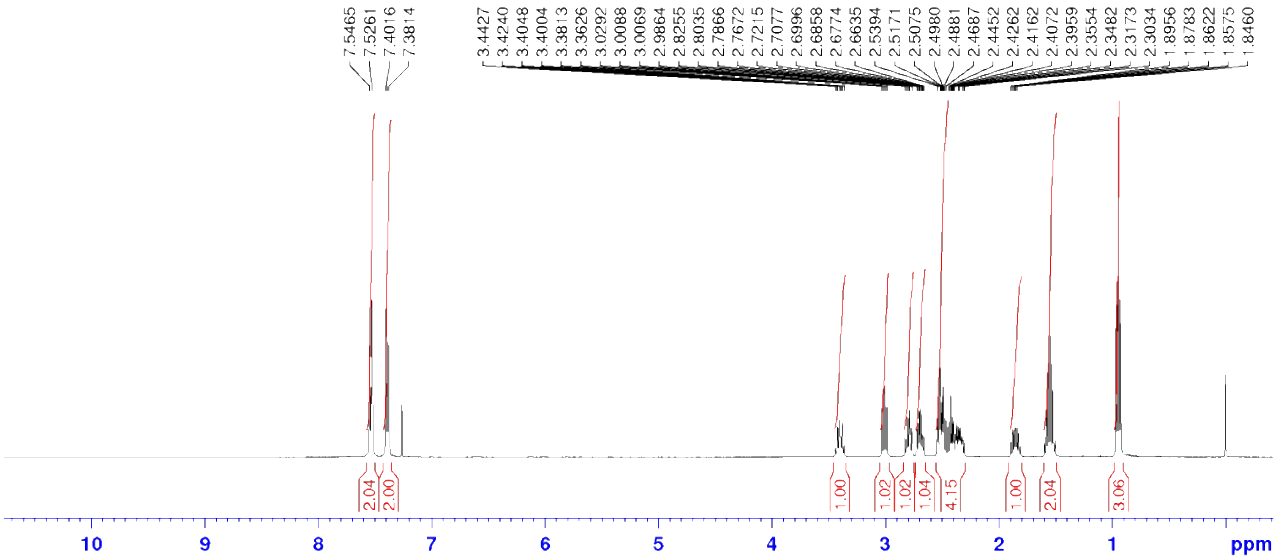
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 150.0 (1C), 128.3 (q, *J* 32.0 Hz, 1C), 127.6 (2CH), 125.3 (q, *J* 3.8 Hz, 2CH), 124.3 (q, *J* 270.2 Hz, 1C), 62.1 ($1CH_2$), 58.4 ($1CH_2$), 54.7 ($1CH_2$), 43.2 (1CH), 32.2 ($1CH_2$), 22.1 ($1CH_2$), 12.1 ($1CH_3$).

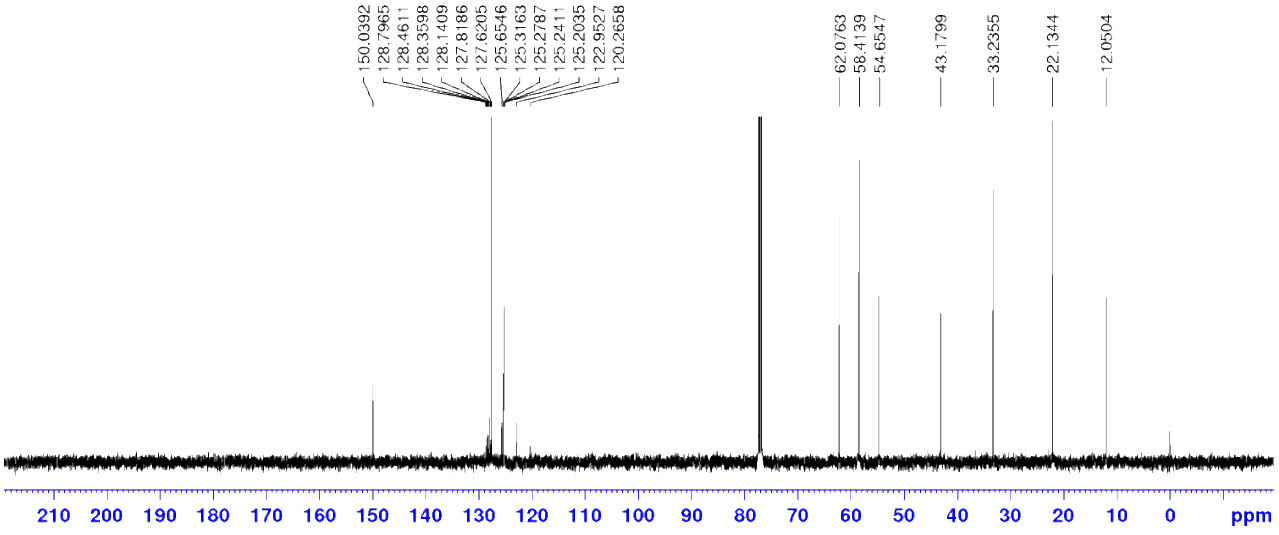
^{19}F {^{1}H} NMR ($CDCl_3$, 376 MHz) δ_F –62.3.

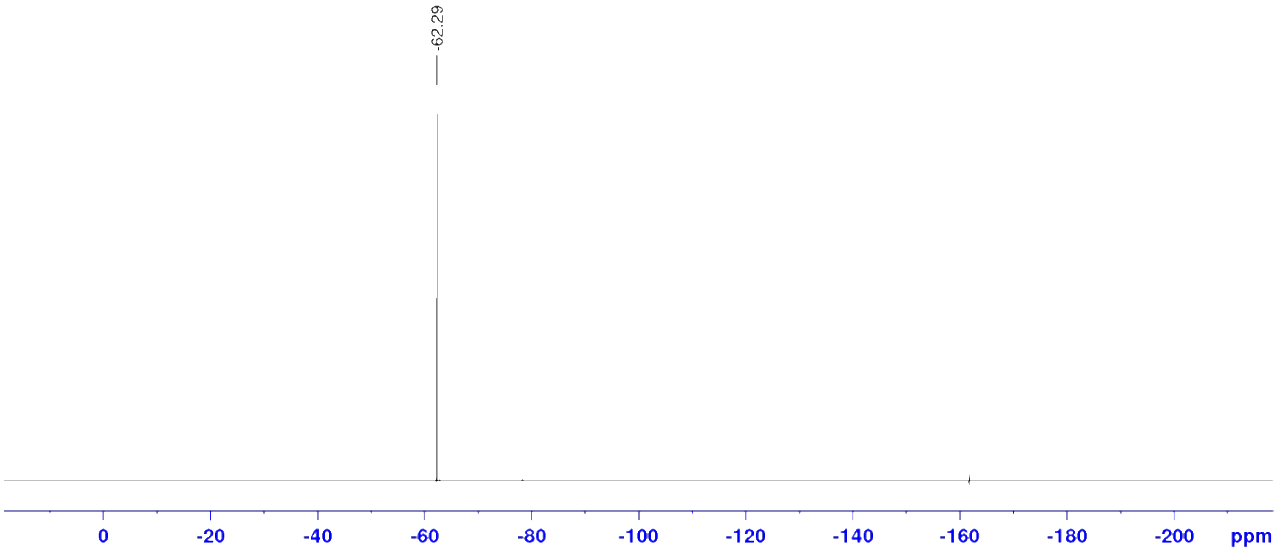
IR ν_{max} (thin film, cm^{-1}): 2960 (C-H), 2933 (C-H), 2876 (C-H), 2792 (C-H).

HRMS *m/z* (ESI^+) calculated for $C_{14}H_{18}F_3N$ $[M+H]^+$: 258.1464, found 258.1465.

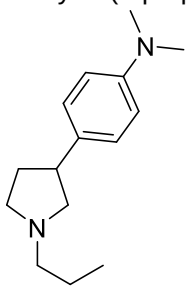
Figure S5. NMR spectra for compound 9d, related to Figure 6.







N,*N*-Dimethyl-4-(1-propylpyrrolidin-3-yl)aniline **9e**



Chemical Formula: $C_{15}H_{24}N_2$
Molecular Weight: 232.37

9e was isolated as a brown oil (135 mg, 19%).

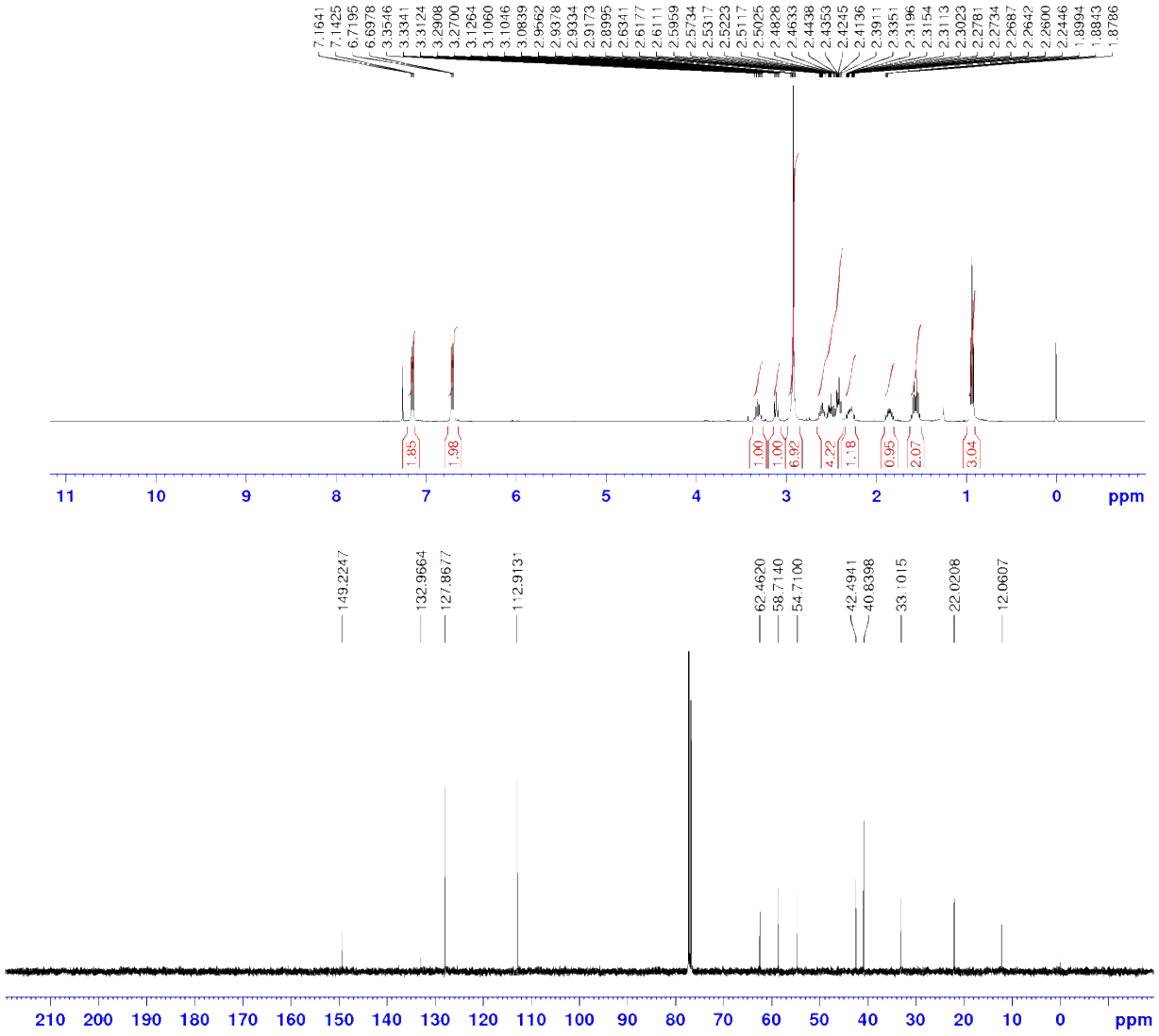
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.15 (d, *J* 8.6 Hz, 2H), 6.71 (d, *J* 8.6 Hz, 2H), 3.27-3.35 (m, 1H), 3.11 (dd, *J* 8.2 Hz, 8.7 Hz, 1H), 2.89-2.95 (m, 1H), 2.92 (s, 6H), 2.39-2.63 (m, 4H), 2.24-2.31 (m, 1H), 1.81-1.90 (m, 1H), 1.56 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 149.2 (1C), 133.0 (1C), 127.9 (2CH), 112.9 (2CH), 62.5 ($1CH_2$), 58.7 ($1CH_2$), 54.7 ($1CH_2$), 42.5 (1CH), 40.8 ($2CH_3$), 33.1 ($1CH_2$), 22.0 ($1CH_2$), 12.1 ($1CH_3$).

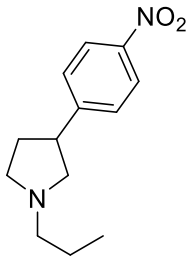
IR ν_{max} (thin film, cm^{-1}): 2956 (C-H), 2929 (C-H), 2873 (C-H), 2788 (C-H), 1614 (Ar), 1514 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{15}H_{24}N_2$ $[M+H]^+$: 233.2012, found 233.2012.

Figure S6. NMR spectra for compound 9e, related to Figure 6.



3-(4-Nitrophenyl)-1-propylpyrrolidine **9f**



Chemical Formula: $C_{13}H_{18}N_2O_2$
Molecular Weight: 234.30

9f was isolated as a brown oil (350 mg, 50%).

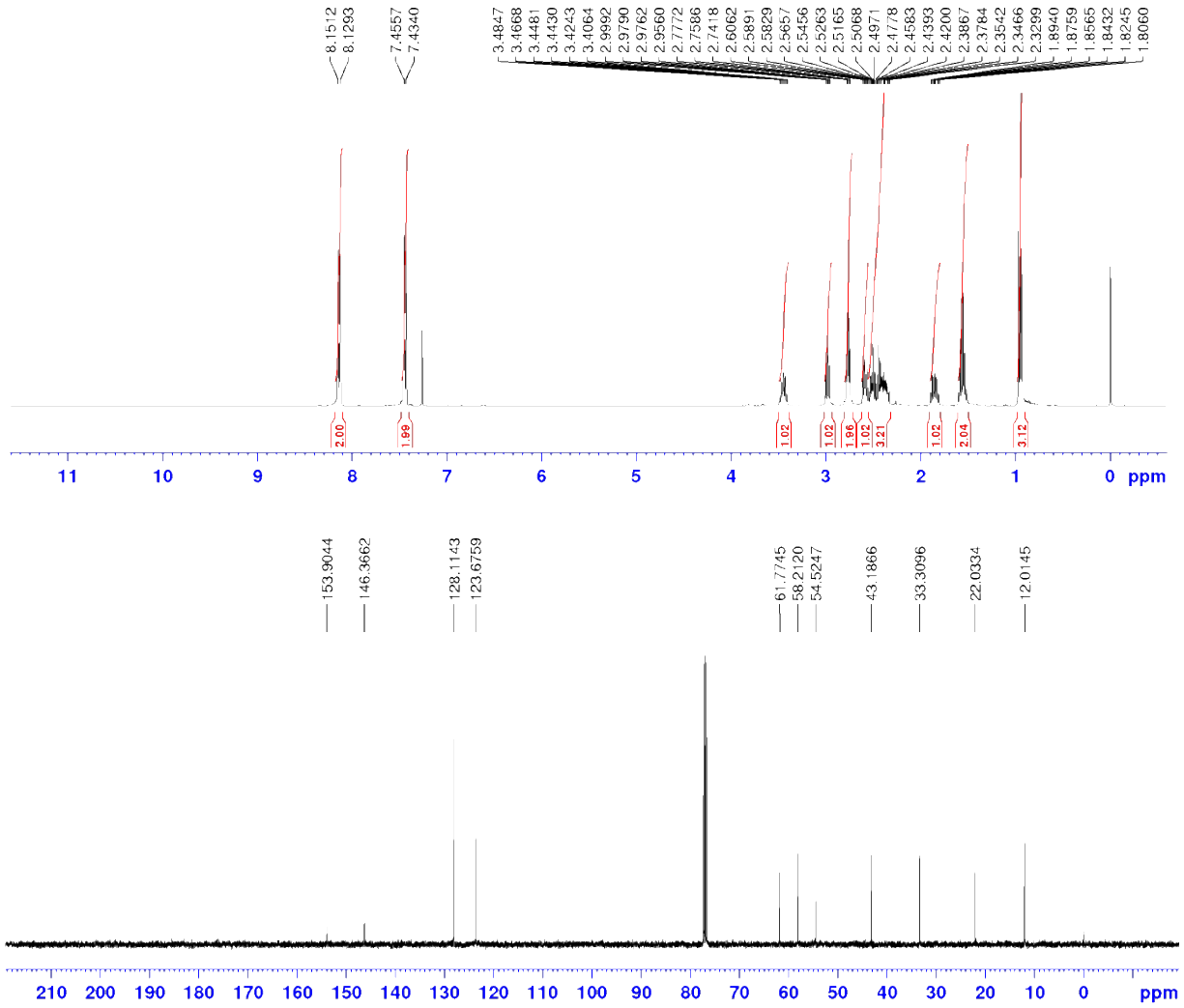
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.14 (d, *J* 8.8 Hz, 2H), 7.44 (d, *J* 8.8 Hz, 2H), 3.40-3.48 (m, 1H), 2.98 (dd, *J* 8.1 Hz, 9.2 Hz, 1H), 2.74-2.78 (m, 2H), 2.59 (dd, *J* 6.9 Hz, 9.3 Hz, 1H), 2.33-2.55 (m, 3H), 1.81-1.89 (m, 1H), 1.55 (sext, *J* 7.5 Hz, 2H), 0.95 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 153.9 (1C), 146.4 (1C), 128.1 (2CH), 123.7 (2CH), 61.8 ($1CH_2$), 58.2 ($1CH_2$), 54.5 ($1CH_2$), 43.2 (1CH), 33.3 ($1CH_2$), 22.0 ($1CH_2$), 12.0 ($1CH_3$).

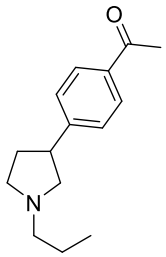
IR ν_{max} (thin film, cm^{-1}): 2960 (C-H), 2932 (C-H), 2874 (C-H), 2792 (C-H), 1597 (Ar), 1514 (N-O), 1341 (N-O).

HRMS *m/z* (ESI^+) calculated for $C_{13}H_{18}N_2O_2$ $[M+H]^+$: 235.1441, found 235.1440.

Figure S7. NMR spectra for compound 9f, related to Figure 6.



1-(4-(1-Propylpyrrolidin-3-yl)phenyl)ethan-1-one **9g**



Chemical Formula: $C_{15}H_{21}NO$
Molecular Weight: 231.34

9g was isolated as a brown oil (485 mg, 70%).

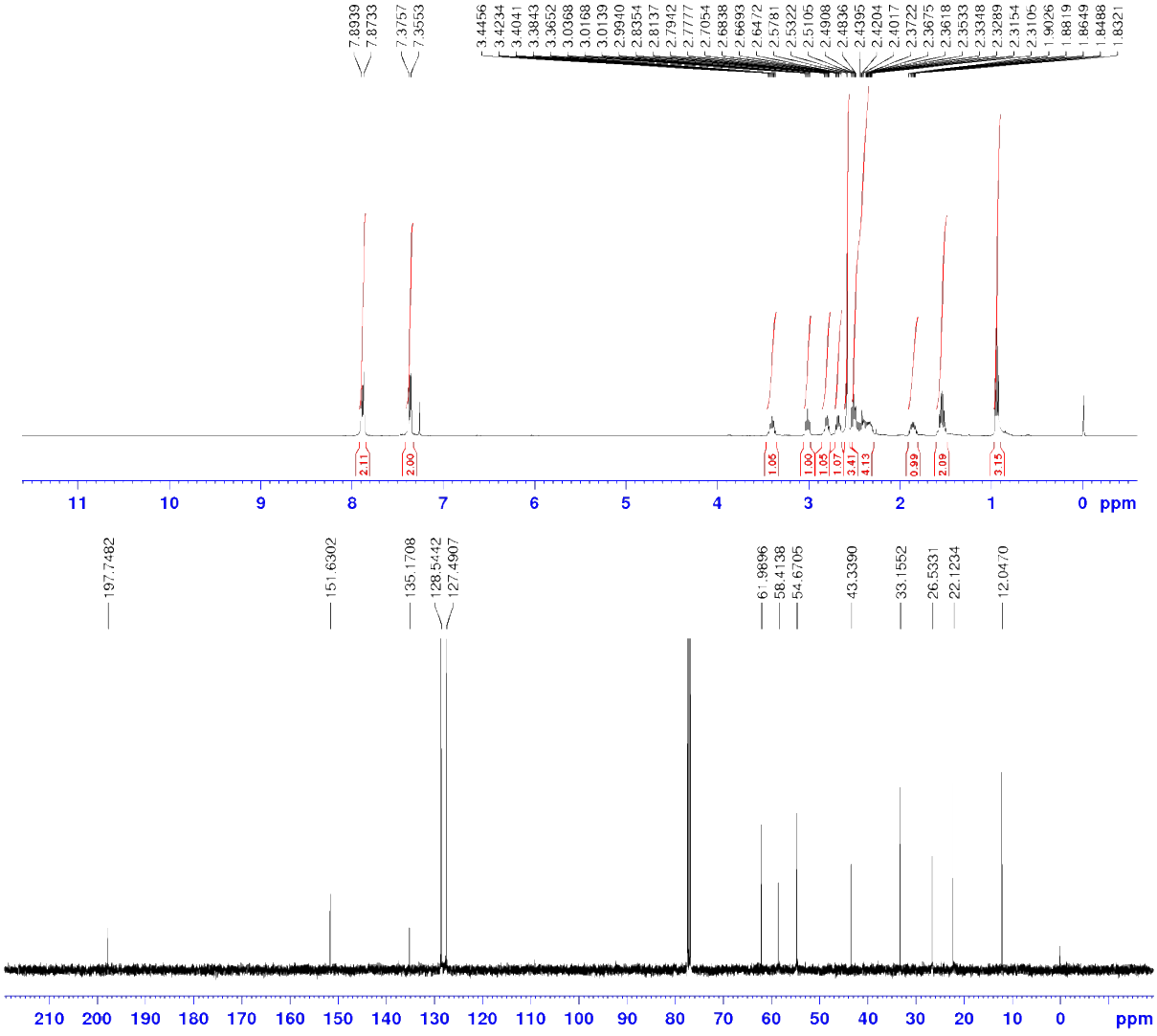
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.88 (d, *J* 8.2 Hz, 1H), 7.36 (d, *J* 8.2 Hz, 1H), 3.37-3.45 (m, 1H), 3.02 (dd, *J* 8.0 Hz, 8.8 Hz, 1H), 2.77-2.83 (m, 1H), 2.64-2.70 (m, 1H), 2.58 (s, 3H), 2.31-2.53 (m, 4H), 1.82-1.90 (m, 1H), 1.54 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 197.7 (1C), 151.6 (1C), 135.2 (1C), 128.5 (2CH), 127.5 (2CH), 62.0 ($1CH_2$), 58.4 ($1CH_2$), 54.7 ($1CH_2$), 43.3 (1CH), 33.2 ($1CH_2$), 26.5 ($1CH_3$), 22.1 ($1CH_2$), 12.0 ($1CH_3$).

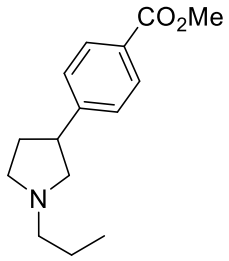
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2931 (C-H), 2874 (C-H), 2790 (C-H), 1688 (C=O), 1605 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{15}H_{21}NO$ $[M+H]^+$: 232.1696, found 232.1695.

Figure S8. NMR spectra for compound 9g, related to Figure 6.



Methyl 4-(1-propylpyrrolidin-3-yl)benzoate **9h**



Chemical Formula: $C_{15}H_{21}NO_2$
Molecular Weight: 247.34

9h was isolated as a brown oil (425 mg, 57%).

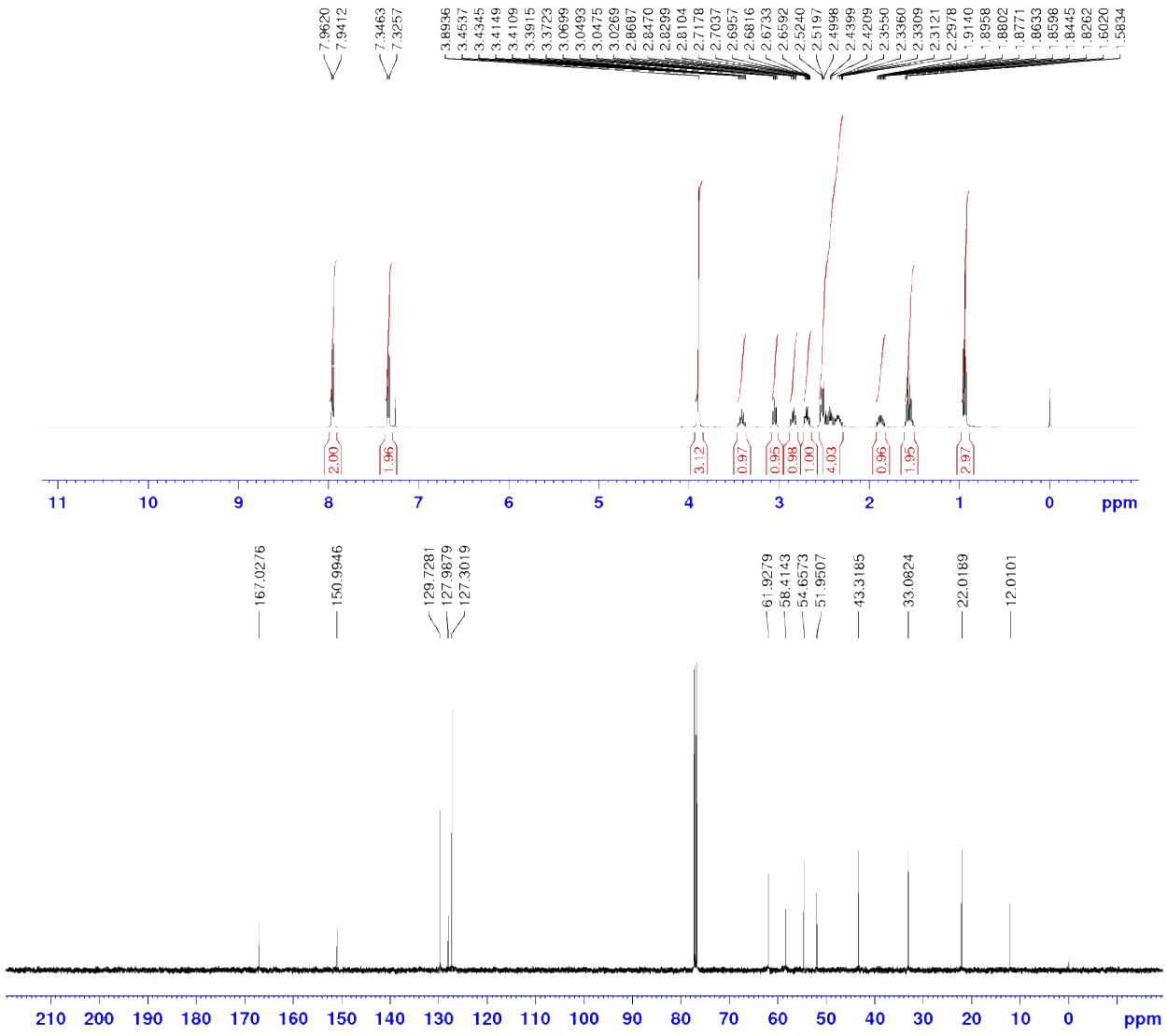
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.95 (d, *J* 8.3 Hz, 2H), 7.33 (d, *J* 8.3 Hz, 2H), 3.93 (s, 3H), 3.37-3.45 (m, 1H), 3.05 (dd, *J* 8.2 Hz, 9.0 Hz, 1H), 2.81-2.86 (m, 1H), 2.65-2.71 (m, 1H), 2.29-2.52 (m, 4H), 1.82-1.91 (m, 1H), 1.55 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 167.0 (1C), 151.0 (1C), 129.7 (2CH), 128.0 (1C), 127.3 (2CH), 61.9 ($1CH_2$), 58.4 ($1CH_2$), 54.7 ($1CH_2$), 52.0 ($1CH_3$), 43.3 (1CH), 33.1 ($1CH_2$), 22.0 ($1CH_2$), 12.0 ($1CH_3$).

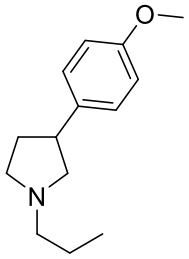
IR ν_{max} (thin film, cm^{-1}): 2956 (C-H), 2874 (C-H), 2790 (C-H), 1718 (C=O), 1609 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{15}H_{21}NO_2$ $[M+H]^+$: 248.1645, found 248.1645.

Figure S9. NMR spectra for compound 9h, related to Figure 6.



3-(4-Methoxyphenyl)-1-propylpyrrolidine **9i**



Chemical Formula: $C_{14}H_{21}NO$
Molecular Weight: 219.33

9i was isolated as a brown oil (455 mg, 69%).

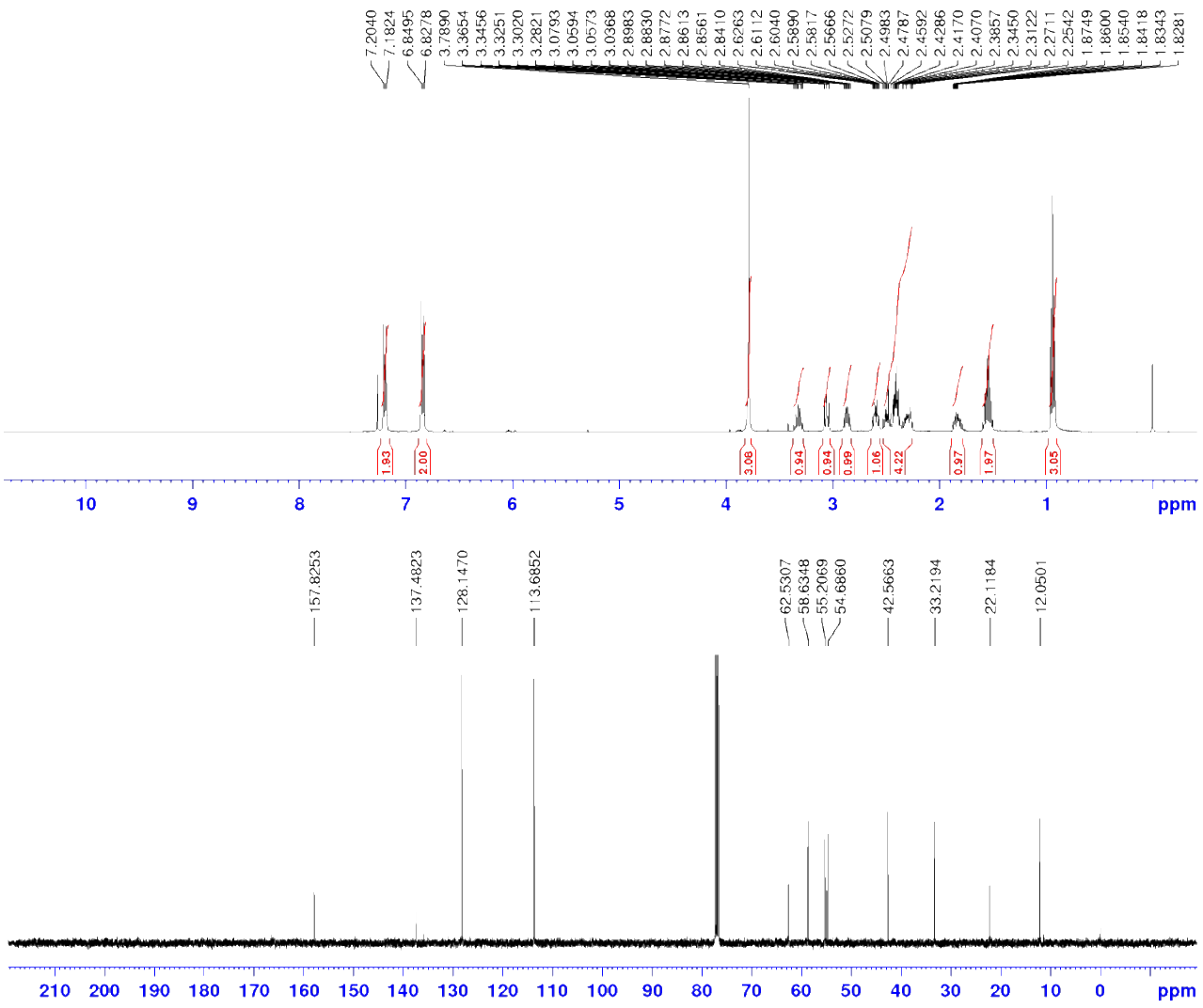
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.19 (d, *J* 8.6 Hz, 2H), 6.84 (d, *J* 8.6 Hz, 2H), 3.79 (s, 3H), 3.28-3.36 (m, 1H), 3.06 (dd, *J* 8.1 Hz, 8.8 Hz, 1H), 2.84-2.90 (m, 1H), 2.56-2.62 (m, 1H), 2.25-2.53 (m, 4H), 1.78-1.87 (m, 1H), 1.55 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 157.8 (1C), 137.5 (1C), 128.1 (2CH), 113.7 (2CH), 62.5 ($1CH_2$), 58.6 ($1CH_2$), 55.2 ($1CH_3$), 54.7 ($1CH_2$), 42.6 (1CH), 33.2 ($1CH_2$), 22.1 ($1CH_2$), 12.1 ($1CH_3$).

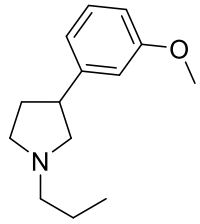
IR ν_{max} (thin film, cm^{-1}): 2956 (C-H), 2931 (C-H), 2873 (C-H), 2783 (C-H), 1511 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{14}H_{21}NO$ $[M+H]^+$: 220.1696, found 220.1694.

Figure S10. NMR spectra for compound 9i, related to Figure 6.



3-(3-Methoxyphenyl)-1-propylpyrrolidine **9j**



Chemical Formula: $C_{14}H_{21}NO$
Molecular Weight: 219.33

9j was isolated as a brown oil (440 mg, 67%).

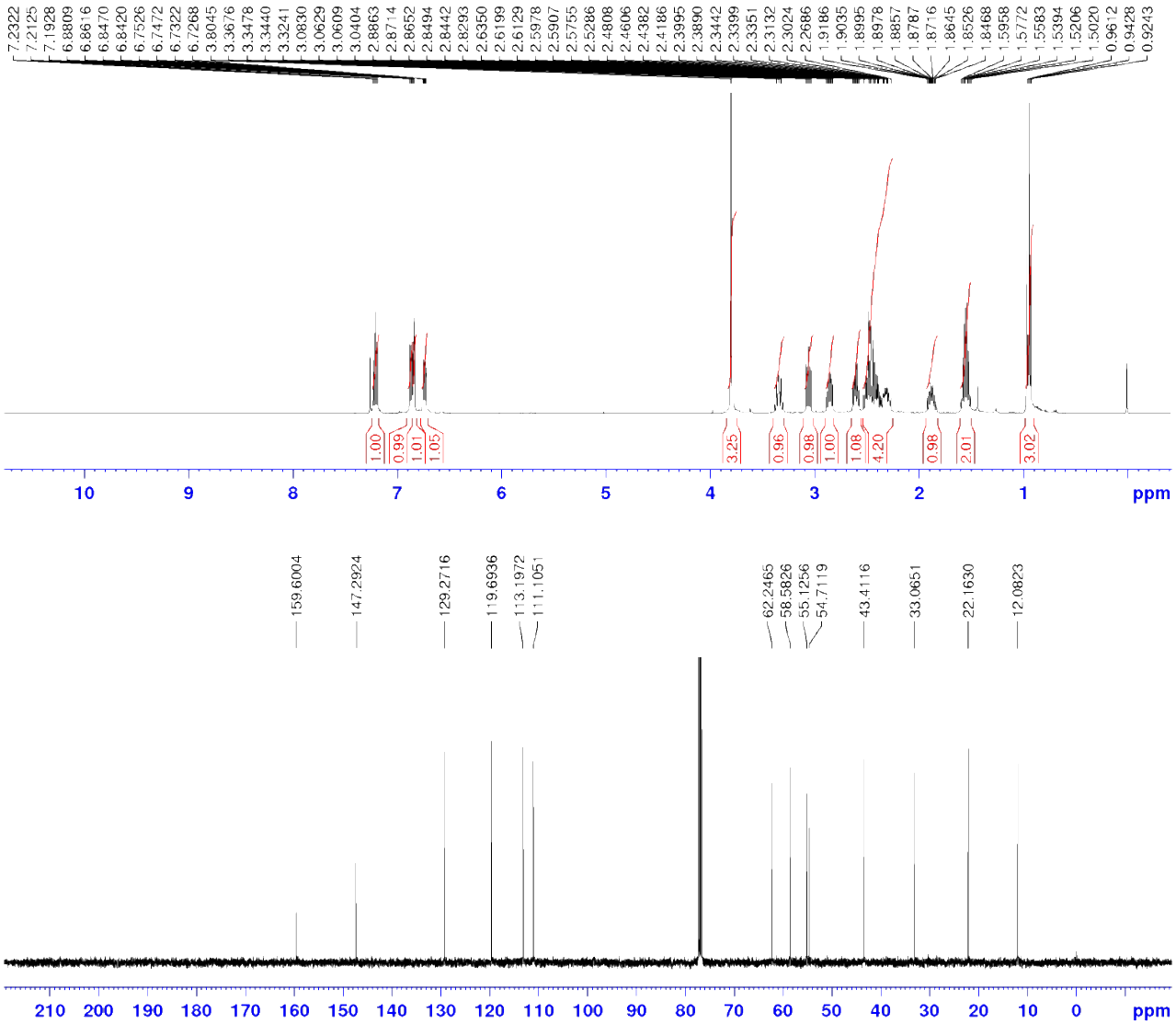
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.21 (dd, *J* 7.9 Hz, 7.9 Hz, 1H), 6.87 (d, *J* 7.7 Hz, 1H), 6.84-6.86 (m, 1H), 6.74 (dd, *J* 2.2 Hz, 8.2 Hz, 1H), 3.80 (s, 3H), 3.30-3.38 (m, 1H), 3.06 (dd, *J* 8.1 Hz, 8.8 Hz, 1H), 2.82-2.88 (m, 1H), 2.57-2.63 (m, 1H), 2.26-2.53 (m, 4H), 1.83-1.92 (m, 1H), 1.55 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 159.6 (1C), 147.3 (1C), 129.3 (1CH), 119.7 (1CH), 113.2 (1CH), 111.1 (1CH), 62.2 ($1CH_2$), 58.6 ($1CH_2$), 55.1 ($1CH_3$), 54.7 ($1CH_2$), 43.4 (1CH), 33.1 ($1CH_2$), 22.2 ($1CH_2$), 12.1 ($1CH_3$).

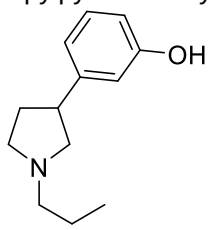
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2930 (C-H), 2873 (C-H), 2786 (C-H), 1608 (Ar), 1582 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{14}H_{21}NO$ $[M+H]^+$: 220.1696, found 220.1696.

Figure S11. NMR spectra for compound 9j, related to Figure 6.



3-(1-Propylpyrrolidin-3-yl)phenol **9k**



Chemical Formula: $C_{13}H_{19}NO$
Molecular Weight: 205.30

9k was isolated as a brown oil (380 mg, 62%).

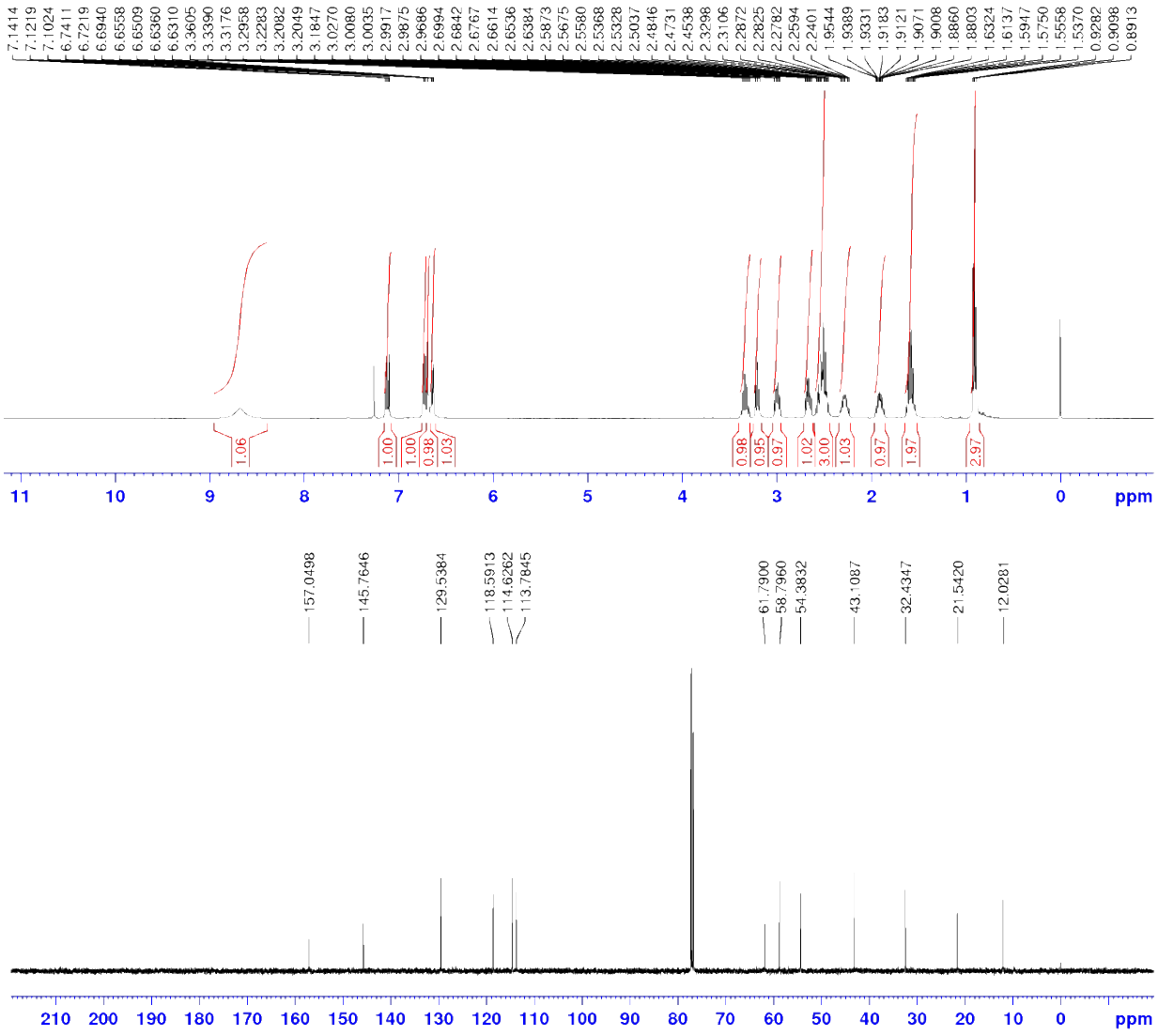
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.68 (s, 1H), 7.12 (dd, *J* 7.8 Hz, 7.8 Hz, 1H), 6.73 (d, *J* 7.7 Hz, 1H), 6.69 (m, 1H), 6.64 (dd, *J* 2.0 Hz, 7.9 Hz, 1H), 3.29-3.38 (m, 1H), 3.21 (dd, *J* 8.1Hz, 9.4 Hz, 1H), 2.96-3.02 (m, 1H), 2.63-2.70 (m, 1H), 2.45-2.58 (m, 3H), 2.24-2.33 (m, 1H), 1.86-1.95 (m, 1H), 1.58 (sext, *J* 7.6 Hz, 2H), 0.91 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 157.0 (1C), 145.8 (1C), 129.5 (1CH), 118.6 (1CH), 114.6 (1CH), 113.8 (1CH), 61.8 ($1CH_2$), 58.8 ($1CH_2$), 54.4 ($1CH_2$), 43.1 (1CH), 32.4 ($1CH_2$), 21.5 ($1CH_2$), 12.0 ($1CH_3$).

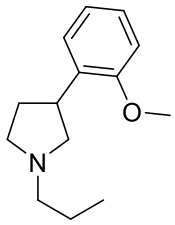
IR ν_{max} (thin film, cm^{-1}): 3500-2500 (C-H, Ar), 2958 (C-H), 2932 (C-H), 2874 (C-H), 2804 (C-H), 1585 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{13}H_{19}NO$ $[M+H]^+$: 206.1539, found 206.1540.

Figure S12. NMR spectra for compound 9k, related to Figure 6.



3-(2-Methoxyphenyl)-1-propylpyrrolidine **9l**



Chemical Formula: $C_{14}H_{21}NO$
Molecular Weight: 219.33

9l was isolated as a brown oil (430 mg, 65%).

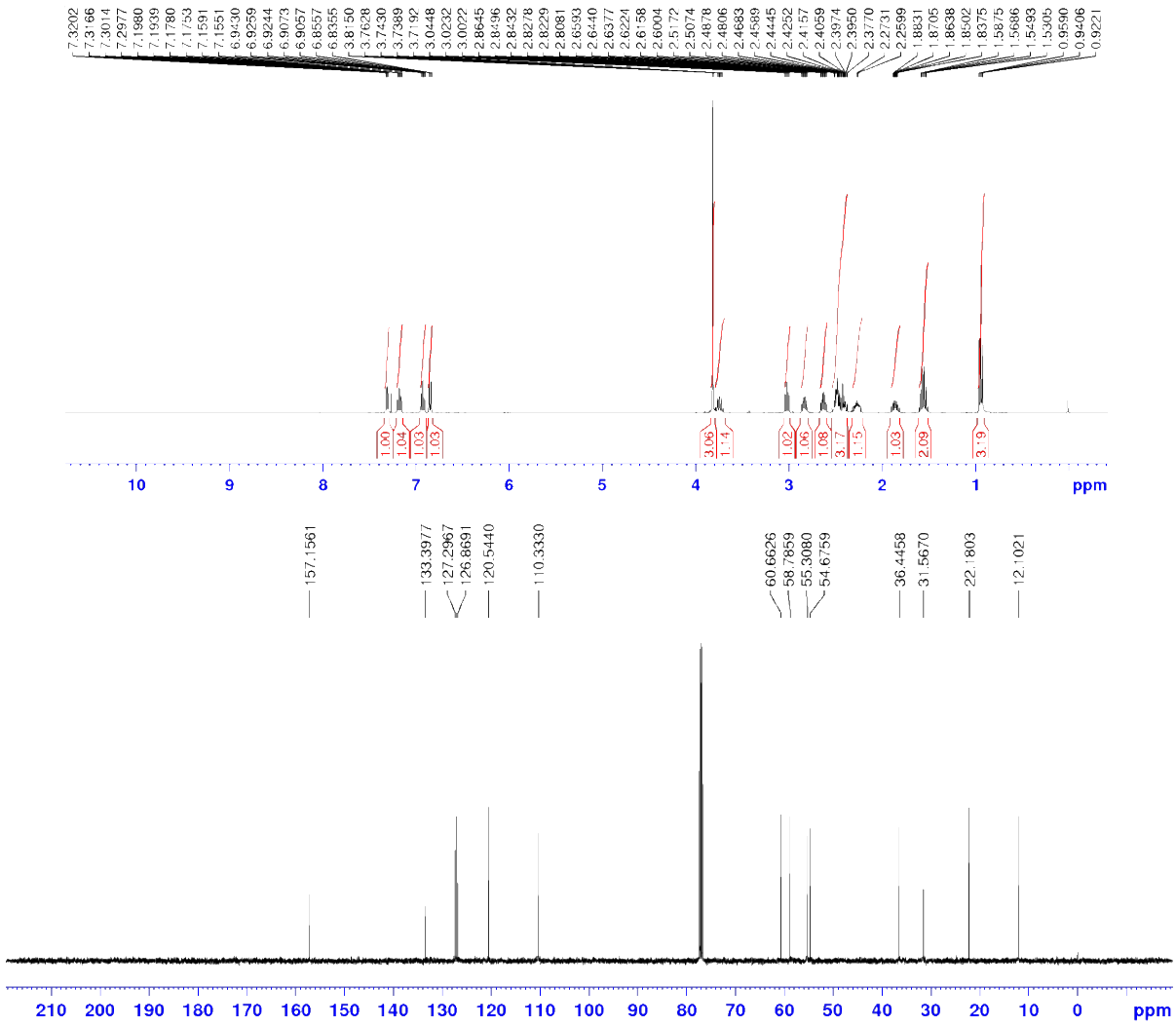
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.31 (dd, *J* 1.4 Hz, 7.5 Hz, 1H), 7.15-7.20 (m, 1H), 6.90-6.94 (m, 1H), 6.85 (d, *J* 8.1 Hz, 1H), 3.82 (s, 3H), 3.69-3.79 (m, 1H), 3.02 (dd, *J* 8.5 Hz, 8.5 Hz, 1H), 2.80-2.86 (m, 1H), 2.60-2.66 (m, 1H), 2.37-2.53 (m, 3H), 2.22-2.32 (m, 1H), 1.81-1.90 (m, 1H), 1.56 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 157.2 (1C), 133.4 (1C), 127.3 (1CH), 126.9 (1CH), 120.5 (1CH), 110.3 (1CH), 60.7 ($1CH_2$), 58.8 ($1CH_2$), 55.3 ($1CH_3$), 54.7 ($1CH_2$), 36.4 (1CH), 31.6 ($1CH_2$), 22.2 ($1CH_2$), 12.1 ($1CH_3$).

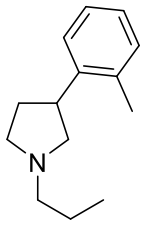
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2931 (C-H), 2873 (C-H), 2787 (C-H), 1492 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{14}H_{21}NO$ $[M+H]^+$: 220.1696, found 220.1696.

Figure S12. NMR spectra for compound 9l, related to Figure 6.



1-Propyl-3-(o-tolyl)pyrrolidine **9m**



Chemical Formula: $C_{14}H_{21}N$
Molecular Weight: 203.33

9m was isolated as a brown oil (375 mg, 61%).

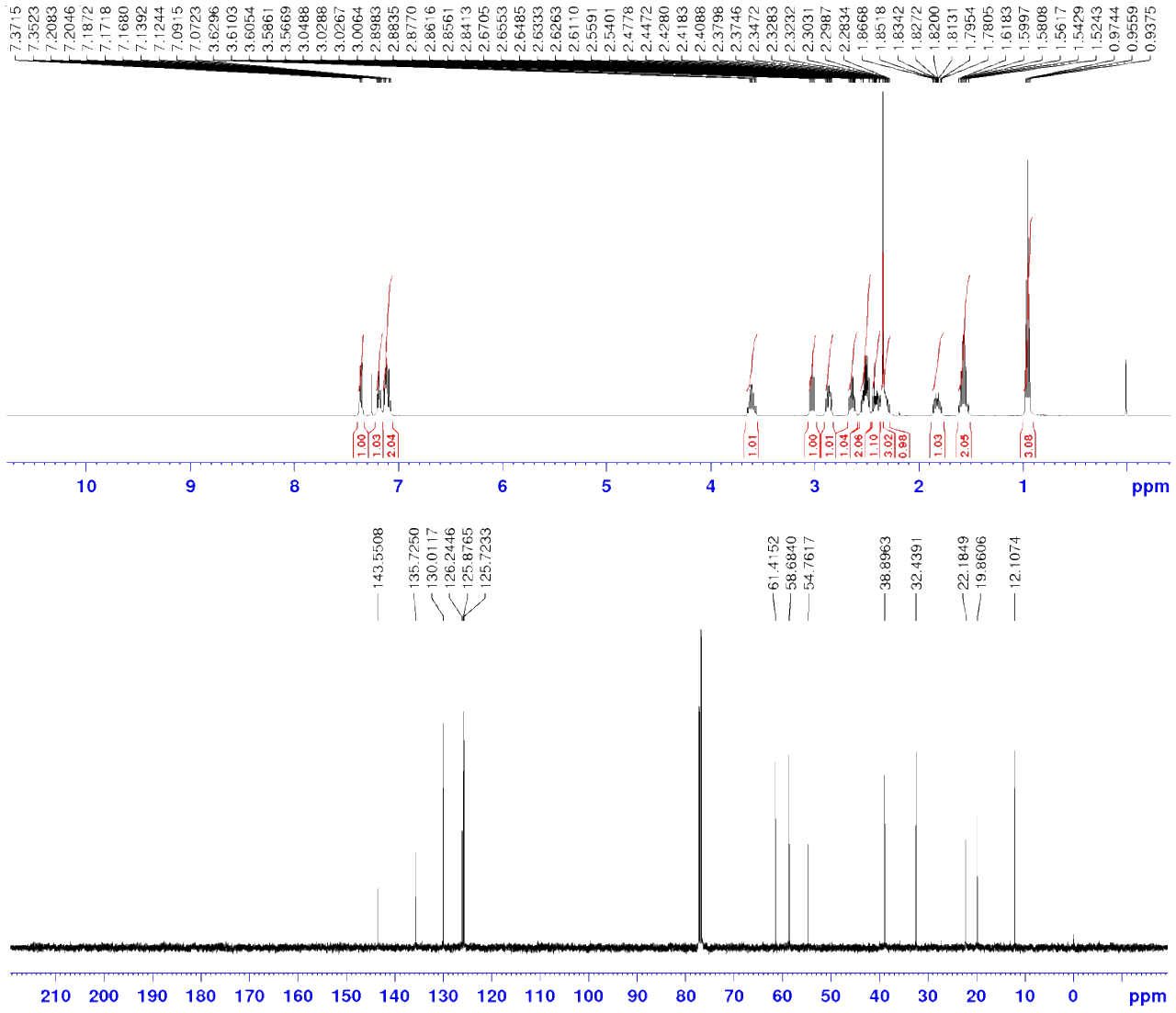
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.36 (d, *J* 7.7 Hz, 1H), 7.16-7.20 (m, 1H), 7.07-7.14 (m, 2H), 3.56-3.65 (m, 1H), 3.03 (dd, *J* 8.1 Hz, 8.8 Hz, 1H), 2.84-2.90 (m, 1H), 2.61-2.67 (m, 1H), 2.48-2.56 (m, 2H), 2.37-2.44 (m, 1H), 2.35 (s, 3H), 2.28-2.33 (m, 1H), 1.78-1.87 (m, 1H), 1.54 (sext, *J* 7.5 Hz, 2H), 0.96 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 143.6 (1C), 135.7 (1C), 130.0 (1CH), 126.2 (1CH), 125.9 (1CH), 125.7 (1CH), 61.4 ($1CH_2$), 58.7 ($1CH_2$), 54.8 ($1CH_2$), 38.9 (1CH), 32.4 ($1CH_2$), 22.2 ($1CH_2$), 19.9 ($1CH_3$), 12.1 ($1CH_3$).

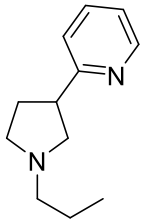
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2930 (C-H), 2873 (C-H), 2788 (C-H), 1683 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{14}H_{21}N$ $[M+H]^+$: 204.1747, found 204.1746.

Figure S13. NMR spectra for compound 9m, related to Figure 6.



2-(1-Propylpyrrolidin-3-yl)pyridine **9n**



Chemical Formula: $C_{12}H_{18}N_2$
Molecular Weight: 190.29

9n was isolated as a brown oil (235 mg, 41%).

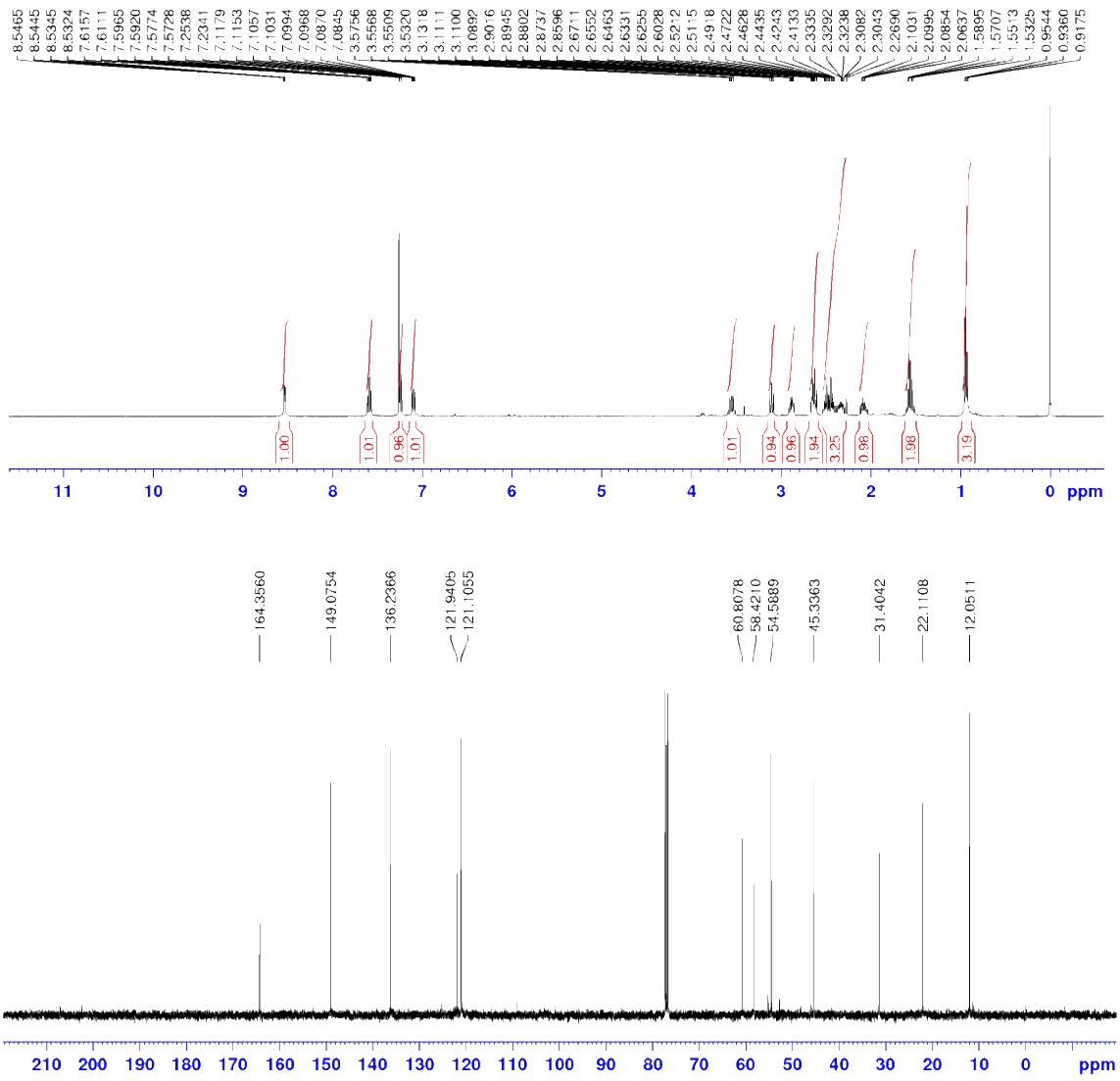
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.54 (dd, *J* 0.8 Hz, 4.8 Hz, 1H), 7.59 (ddd, *J* 1.8 Hz, 7.7 Hz, 7.7 Hz, 1H), 7.24 (br. d, *J* 7.9 Hz, 1H), 7.10 (ddd, *J* 1.0 Hz, 5.9 Hz, 7.4 Hz, 1H), 3.51-3.59 (m, 1H), 3.03 (dd, *J* 8.3 Hz, 8.7 Hz, 1H), 2.85-2.92 (m, 1H), 2.60-2.67 (m, 2H), 2.26-2.54 (m, 3H), 2.03-2.12 (m, 1H), 1.54 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 164.4 (1C), 149.1 (1CH), 136.2 (1CH), 121.9 (1CH), 121.1 (1CH), 60.8 ($1CH_2$), 58.4 ($1CH_2$), 54.6 ($1CH_2$), 45.3 (1CH), 31.4 ($1CH_2$), 22.1 ($1CH_2$), 12.1 ($1CH_3$).

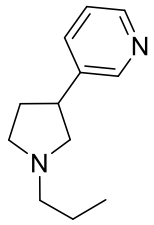
IR ν_{max} (thin film, cm^{-1}): 2959 (C-H), 2932 (C-H), 2874 (C-H), 2794 (C-H), 1590 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{12}H_{18}N_2$ $[M+H]^+$: 191.1543, found 191.1543.

Figure S14. NMR spectra for compound 9n, related to Figure 6.



3-(1-Propylpyrrolidin-3-yl)pyridine **9o**



Chemical Formula: $C_{12}H_{18}N_2$
Molecular Weight: 190.29

9o was obtained as a brown oil (200 mg, 53%, 2 mmol scale reaction).

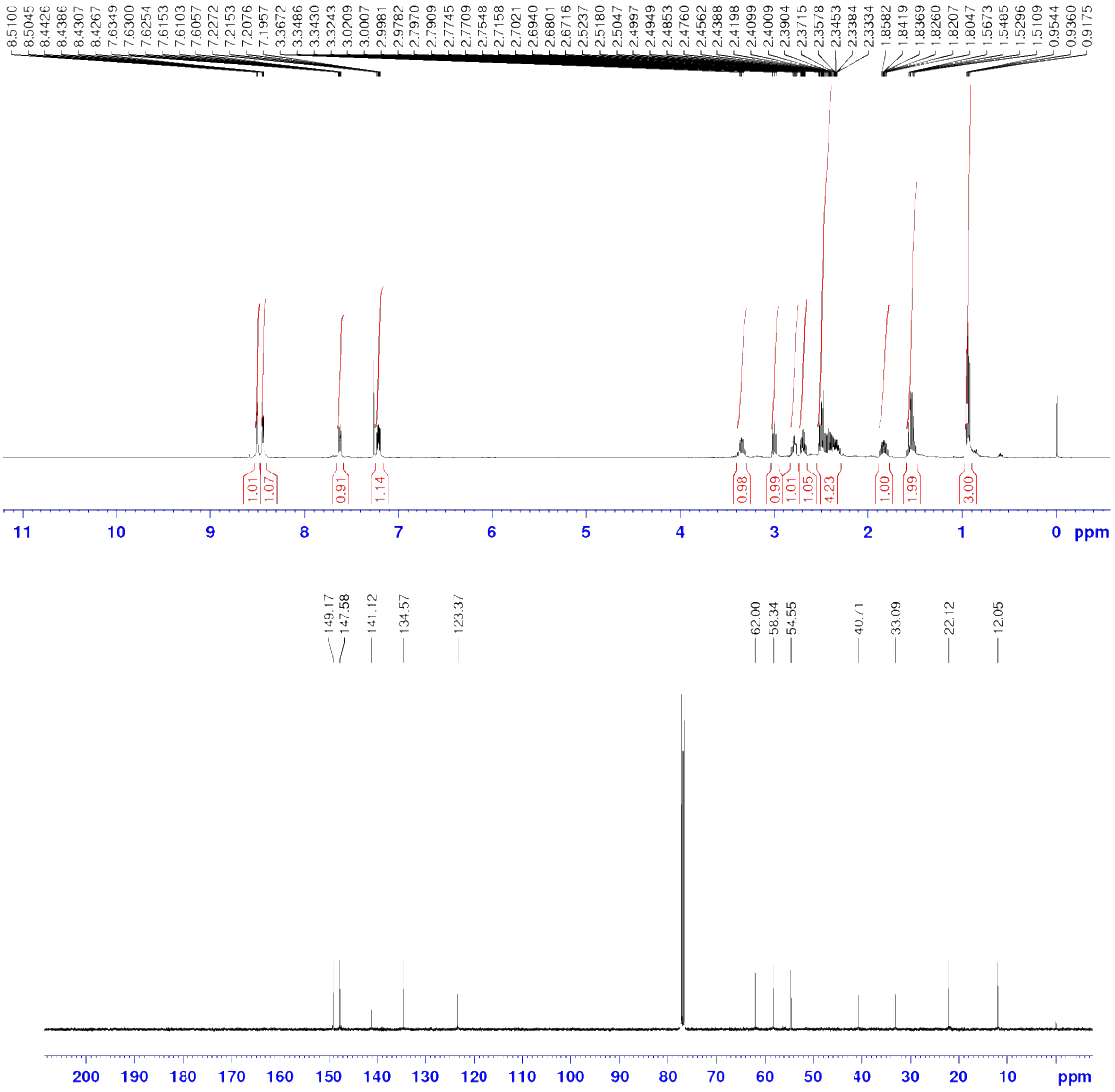
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.51 (d, *J* 2.2 Hz, 1H), 8.43 (dd, *J* 1.6 Hz, 4.8 Hz, 1H), 7.62 (ddd, *J* 2.0 Hz, 2.2 Hz, 7.9 Hz, 1H), 7.10 (dd, *J* 4.8 Hz, 7.9 Hz, 1H), 3.31-3.39 (m, 1H), 3.00 (dd, *J* 8.0 Hz, 9.0 Hz, 1H), 2.75-2.81 (m, 1H), 2.69 (td, *J* 5.4 Hz, 8.8 Hz, 1H), 2.30-2.52 (m, 4H), 1.78-1.87 (m, 1H), 1.54 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 149.2 (1CH), 147.6 (1CH), 141.1 (1C), 134.6 (1CH), 123.4 (1CH), 62.0 ($1CH_2$), 58.3 ($1CH_2$), 54.6 ($1CH_2$), 40.7 (1CH), 33.1 ($1CH_2$), 22.1 ($1CH_2$), 12.0 ($1CH_3$).

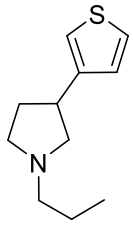
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2930 (C-H), 2873 (C-H), 2788 (C-H), 1573 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{12}H_{18}N_2$ $[M+H]^+$: 191.1543, found 191.1542.

Figure S15. NMR spectra for compound 9o, related to Figure 6.



1-Propyl-3-(thiophen-3-yl)pyrrolidine **9p**



Chemical Formula: $C_{11}H_{17}NS$
Molecular Weight: 195.32

9p was isolated as a brown oil (175 mg, 30%).

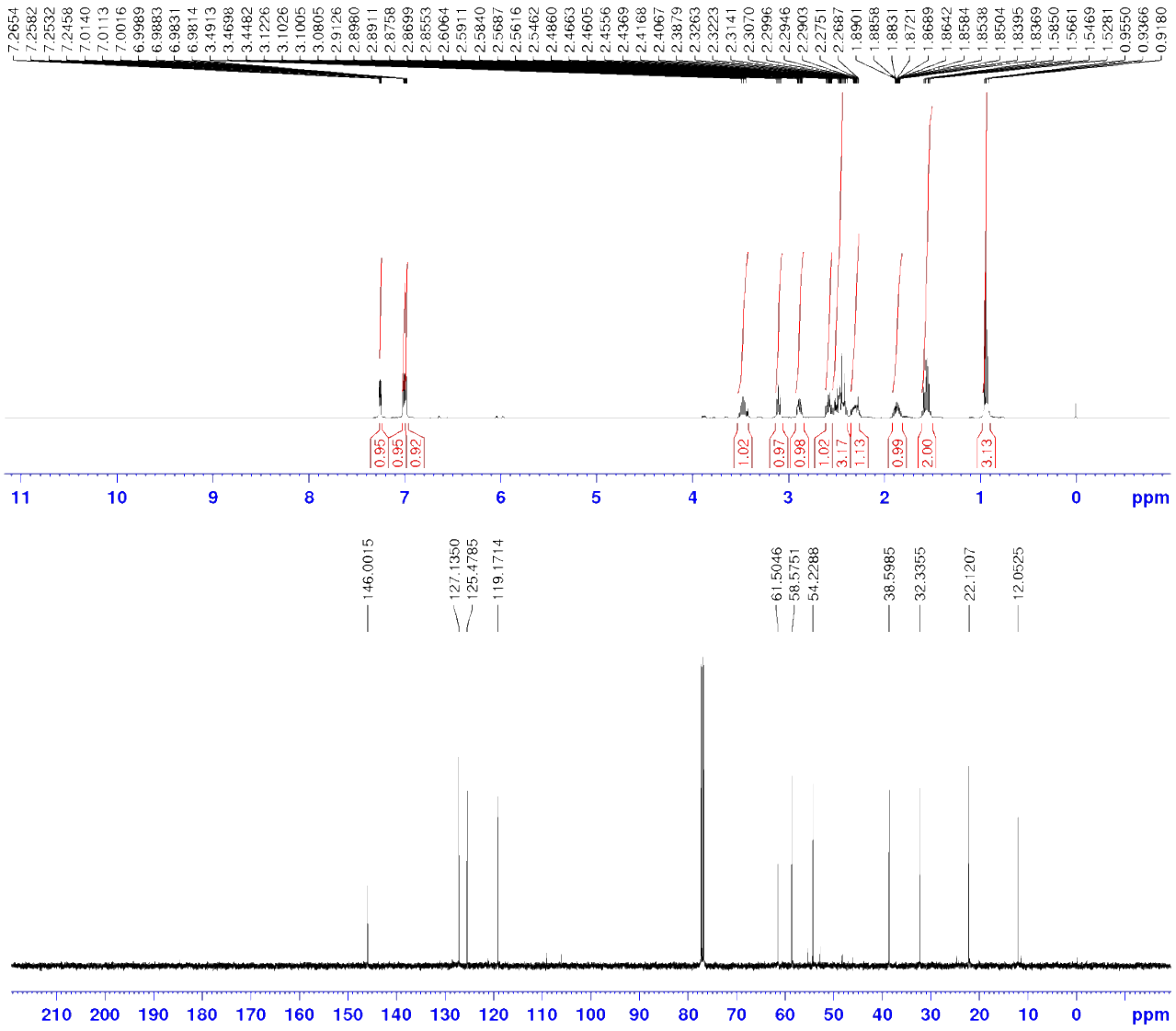
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.26 (dd, *J* 2.9 Hz, 4.9 Hz, 1H), 7.01 (dd, *J* 1.1 Hz, 4.9 Hz, 1H), 6.99 (m, 1H), 3.42-3.51 (m, 1H), 3.10 (dd, *J* 8.0 Hz, 8.8 Hz, 1H), 2.85-2.91 (m, 1H), 2.54-2.60 (m, 1H), 2.38-2.48 (m, 3H), 2.25-2.32 (m, 1H), 1.81-1.90 (m, 1H), 1.56 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 146.0 (1C), 127.1 (1CH), 125.5 (1CH), 119.2 (1CH), 61.5 ($1CH_2$), 58.6 ($1CH_2$), 54.2 ($1CH_2$), 38.6 (1CH), 33.3 ($1CH_2$), 22.1 ($1CH_2$), 12.1 ($1CH_3$).

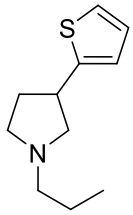
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2930 (C-H), 2873 (C-H), 2789 (C-H), 1456 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{11}H_{17}NS$ $[M+H]^+$: 196.1154, found 196.1157.

Figure S16. NMR spectra for compound 9p, related to Figure 6.



1-Propyl-3-(thiophen-2-yl)pyrrolidine **9q**



Chemical Formula: $C_{11}H_{17}NS$
Molecular Weight: 195.32

9q was isolated as a brown oil (175 mg, 30%).

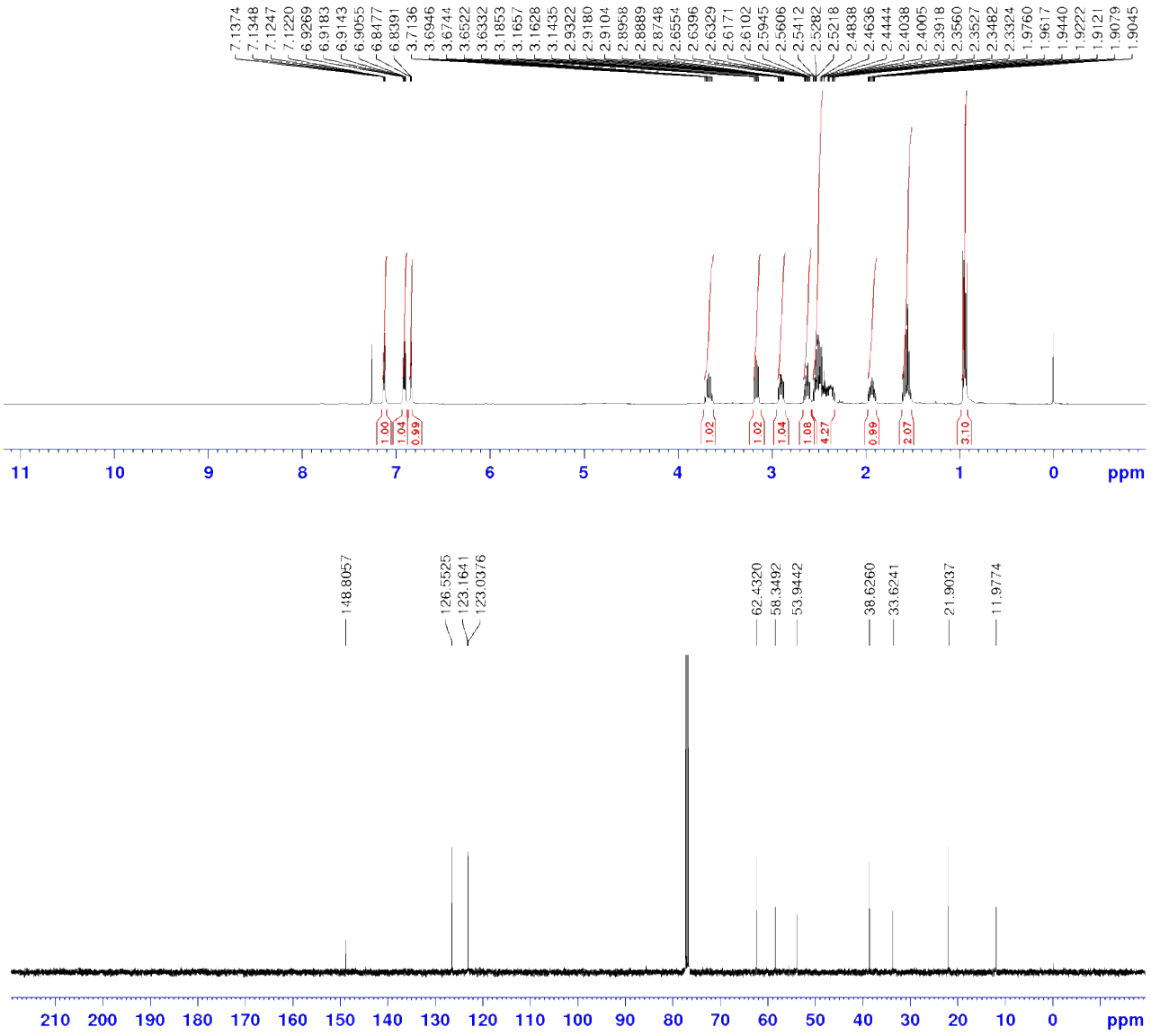
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.13 (dd, *J* 1.1 Hz, 5.1 Hz, 1H), 6.92 (dd, *J* 3.5 Hz, 5.1 Hz, 1H), 6.84 (br d, *J* 3.5 Hz, 1H), 3.63-3.71 (m, 1H), 3.16 (dd, *J* 7.8 Hz, *J* 9.0 Hz, 1H), 2.87-2.93 (m, 1H), 2.59-2.66 (m, 1H), 2.33-2.56 (m, 4H), 1.89-1.98 (m, 1H), 1.56 (sext, *J* 7.5 Hz, 2H), 0.94 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 148.8 (1C), 126.6 (1CH), 123.2 (1CH), 123.0 (1CH), 62.4 ($1CH_2$), 58.3 ($1CH_2$), 53.9 ($1CH_2$), 38.6 (1CH), 33.6 ($1CH_2$), 21.9 ($1CH_2$), 12.0 ($1CH_3$).

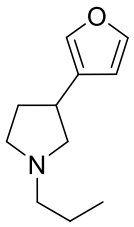
IR ν_{max} (thin film, cm^{-1}): 2957 (C-H), 2930 (C-H), 2873 (C-H), 2789 (C-H).

HRMS *m/z* (ESI^+) calculated for $C_{11}H_{17}NS$ $[M+H]^+$: 196.1154, found 196.1156.

Figure S17. NMR spectra for compound 9q, related to Figure 6.



3-(Furan-3-yl)-1-propylpyrrolidine **9r**



Chemical Formula: $C_{11}H_{17}NO$
Molecular Weight: 179.26

9r was isolated as a brown oil (60 mg, 11%).

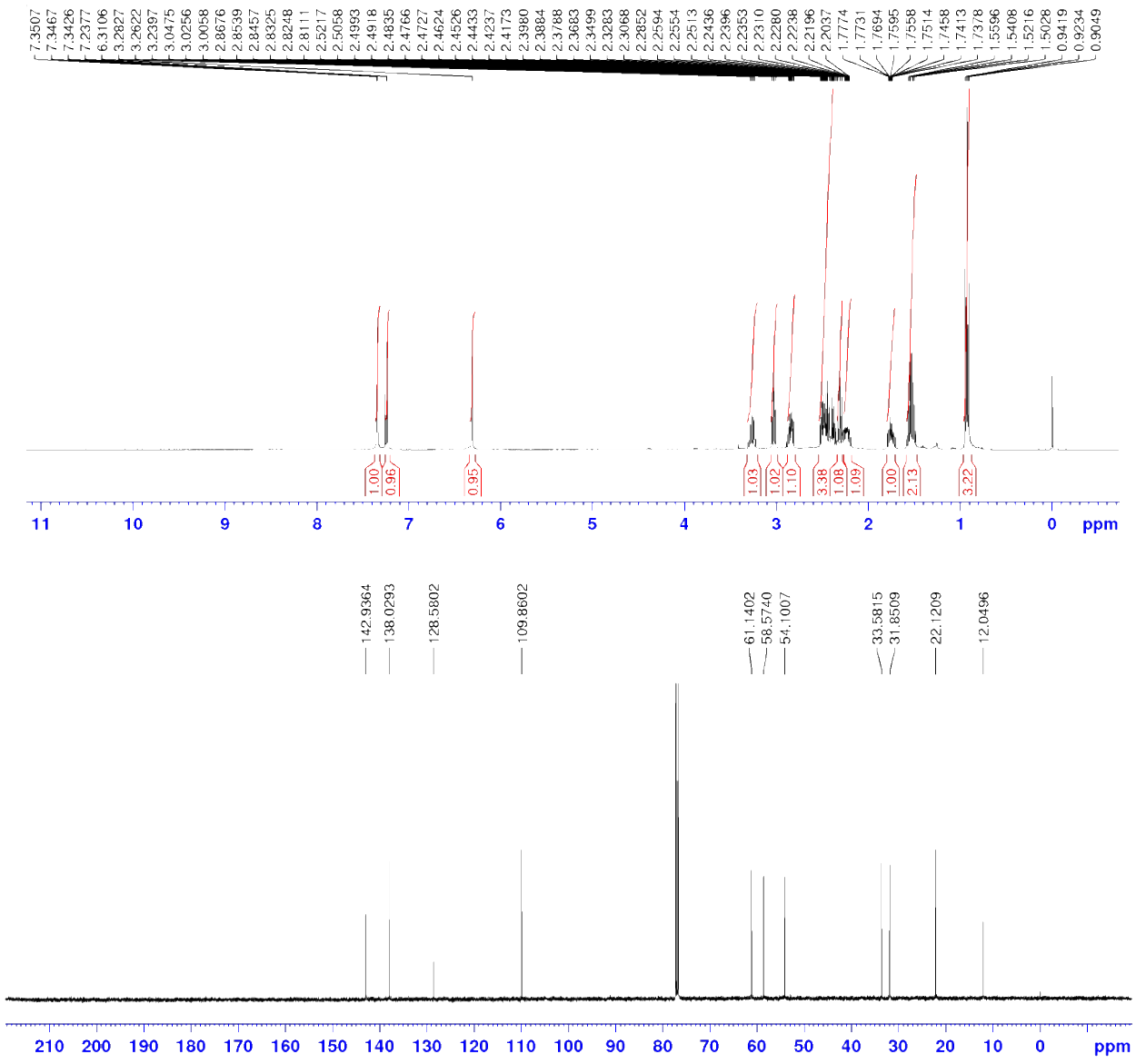
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.35 (app t, *J* 1.6 Hz, 1H), 7.24 (br. s, 1H), 6.31 (br s, 1H), 3.22-3.30 (m, 1H), 3.04 (app t, *J* 8.3 Hz, 1H), 2.81-2.87 (m, 1H), 2.35-2.52 (m, 3H), 2.31 (app t, *J* 8.6 Hz, 1H), 2.18-2.26 (m, 1H), 1.71-1.79 (m, 1H), 1.53 (sext, *J* 7.5 Hz, 2H), 0.92 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 142.9 (1C, CH), 138.0 (1C, CH), 128.6 (1C, C), 109.9 (1C, CH), 61.1 (1C, CH_2), 58.6 (1C, CH_2), 54.1 (1C, CH_2), 33.6 (1C, CH), 31.9 (1C, CH_2), 22.1 (1C, CH_2), 12.0 (1C, CH_3).

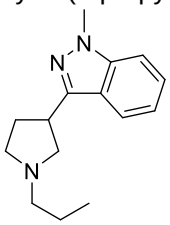
IR ν_{max} (thin film, cm^{-1}): 2959 (C-H), 2932 (C-H), 2874 (C-H), 2795 (C-H), 1667 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{11}H_{17}NO$ $[M+H]^+$: 180.1383, found 180.1382.

Figure S18. NMR spectra for compound 9r, related to Figure 6.



1-Methyl-3-(1-propylpyrrolidin-3-yl)-1H-indazole **9s**



Chemical Formula: $C_{15}H_{21}N_3$
Molecular Weight: 243.35

9s was isolated as a brown oil (220 mg, 45%, 94% BRSM, 2 mmol scale reaction).

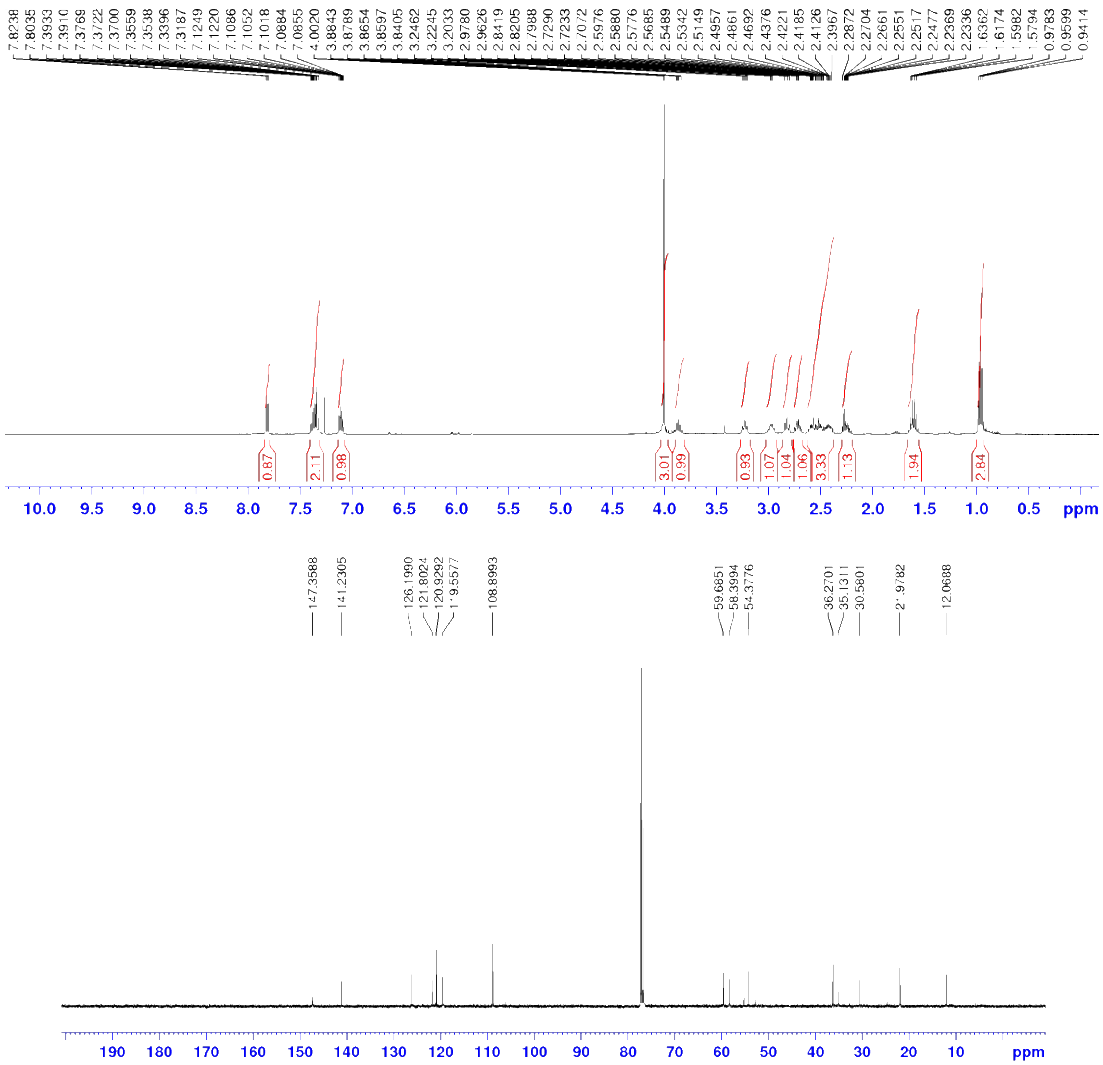
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.81 (d, *J* 8.1 Hz, 1H), 7.31-7.39 (m, 2H), 7.10 (ddd, *J* 1.2 Hz, 6.5 Hz, 6.5 Hz, 1H), 4.00 (s, 3H), 3.82-3.90 (m, 1H), 3.22 (dd, *J* 8.6 Hz, 8.6 Hz, 1H), 2.94-3.00 (m, 1H), 2.82 (dd, *J* 8.6 Hz, 8.6 Hz, 1H), 2.68-2.74 (m, 1H), 2.38-2.62 (m, 3H), 2.20-2.28 (m, 1H), 1.61 (sext, *J* 7.5 Hz, 2H), 0.96 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 147.4 (1C), 141.2 (1C), 126.2 (1CH), 121.8 (1C), 120.9 (1CH), 119.6 (1CH), 108.9 (1CH), 59.7 ($1CH_2$), 58.4 ($1CH_2$), 54.4 ($1CH_2$), 36.3 (1CH), 35.1 ($1CH_3$), 30.6 ($1CH_2$), 22.0 ($1CH_2$), 12.1 ($1CH_3$).

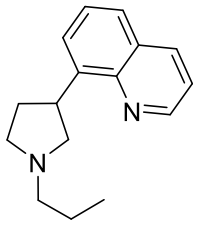
IR ν_{max} (thin film, cm^{-1}): 2958 (C-H), 2930 (C-H), 2873 (C-H), 2790 (C-H), 1614 (Ar), 1504 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{15}H_{21}N_3$ $[M+H]^+$: 244.1808, found 244.1814.

Figure S19. NMR spectra for compound 9s, related to Figure 6.



8-(1-Propylpyrrolidin-3-yl)quinoline **9t**



Chemical Formula: $C_{16}H_{20}N_2$
Molecular Weight: 240.35

9t was isolated as a brown oil (510 mg, 71%).

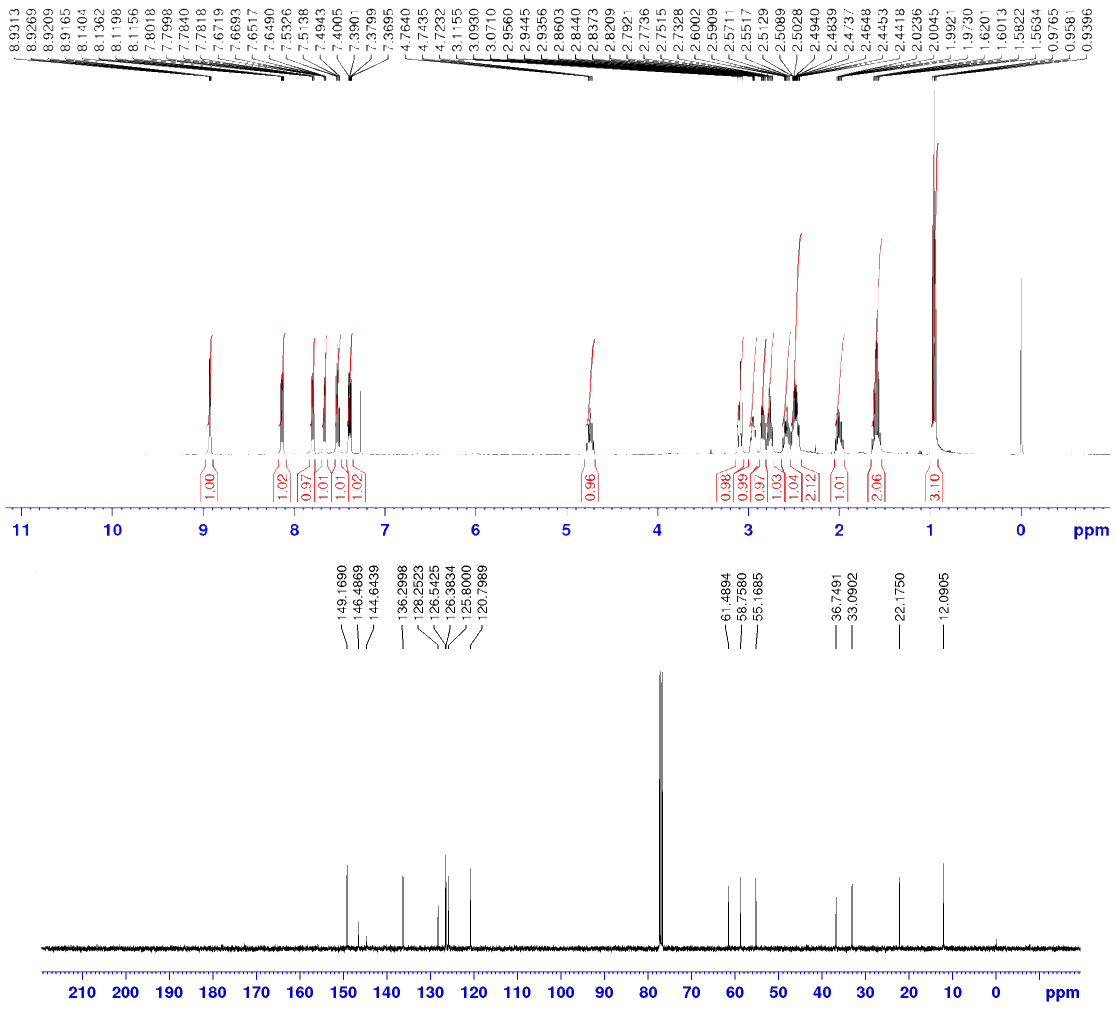
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.92 (dd, *J* 1.8 Hz, 4.2 Hz, 1H), 8.13 (dd, *J* 1.7 Hz, 8.2 Hz, 1H), 7.79 (dd, *J* 7.1 Hz, 0.8 Hz, 1H), 7.66 (dd, *J* 1.1 Hz, 8.1 Hz, 1H), 7.51 (dd, *J* 7.7 Hz, 7.7 Hz, 1H), 7.38 (dd, *J* 4.2 Hz, 8.2 Hz, 1H), 4.70-4.78 (m, 1H), 3.09 (dd, *J* 8.9 Hz, 8.9 Hz, 1H), 2.92-2.97 (m, 1H), 2.84 (dd, *J* 6.5 Hz, 9.2 Hz, 1H), 2.73-2.79 (m, 1H), 2.55-2.62 (m, 1H), 2.44-2.51 (m, 2H), 1.95-2.04 (m, 1H), 1.59 (sext, *J* 7.5 Hz, 2H), 0.96 (t, *J* 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 149.2 (1CH), 146.5 (1C), 144.6 (1C), 136.3 (1CH), 128.3 (1C), 126.5 (1CH), 126.4 (1CH), 125.8 (1CH), 120.8 (1CH), 61.5 ($1CH_2$), 58.8 ($1CH_2$), 55.2 ($1CH_2$), 36.7 (1CH), 33.1 ($1CH_2$), 22.2 ($1CH_2$), 12.1 ($1CH_3$).

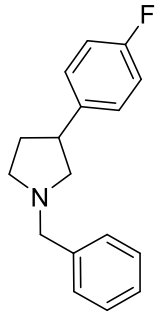
IR ν_{max} (thin film, cm^{-1}): 297 (C-H), 2930 (C-H), 2873 (C-H), 2787 (C-H), 1497 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{16}H_{20}N_2$ $[M+H]^+$: 241.1699, found 241.1699.

Figure S20. NMR spectra for compound 9t, related to Figure 6.



1-Benzyl-3-(4-fluorophenyl)pyrrolidine **13a**



Chemical Formula: $C_{17}H_{18}FN$
Molecular Weight: 255.34

13a was isolated as a brown oil (137 mg, 54%, 1 mmol scale reaction, 2 equivalents of $Cu(OTf)_2$ used).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.31-7.38 (m, 4H), 7.21-7.28 (m, 3H), 6.94-6.99 (m, 2H), 3.68 (s, 2H), 3.31-3.39 (m, 1H), 3.00 (dd, *J* 8.2 Hz, 8.7 Hz, 1H), 2.78-2.84 (m, 1H), 2.69-2.75 (m, 1H), 2.47-2.51 (m, 1H), 2.29-2.40 (m, 1H), 1.80-1.89 (m, 1H).

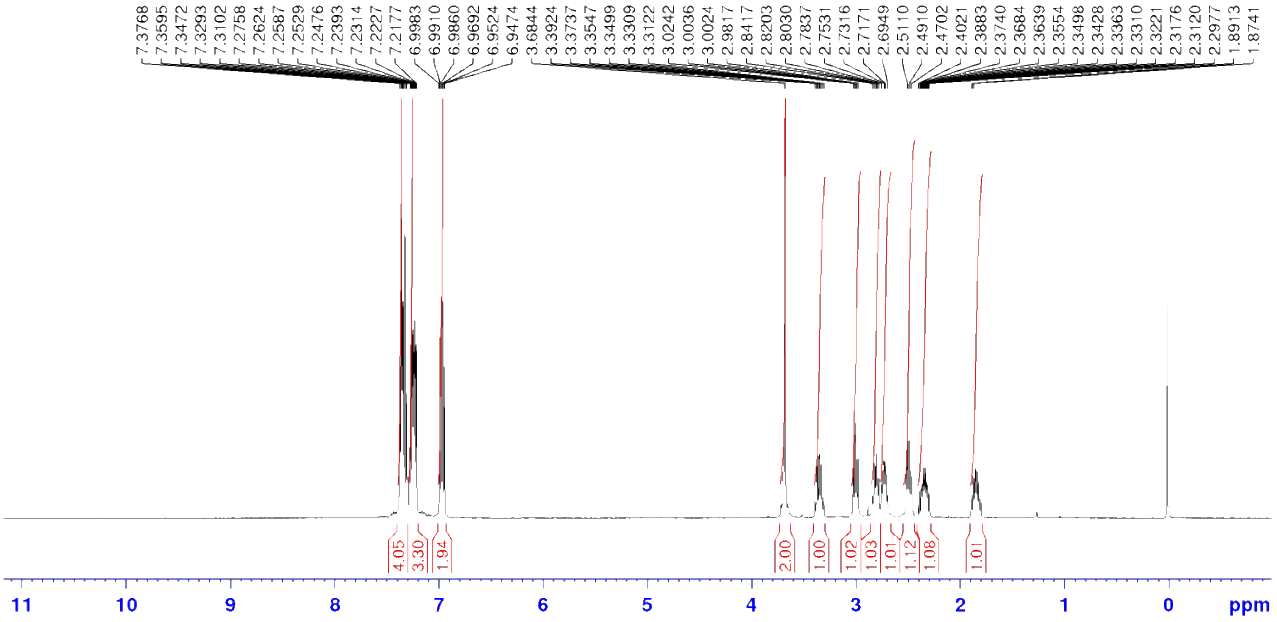
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 161.3 (d, *J* 242.2 Hz, 1C), 141.4 (1C), 139.1 (1C), 128.8 (2CH), 128.6 (d, *J* 7.7 Hz, 2CH), 128.2 (2CH), 126.9 (1CH), 115.0 (d, *J* 20.9 Hz, 2CH), 62.3 ($1CH_2$), 60.5 ($1CH_2$), 54.5 ($1CH_2$), 42.6 (1CH), 33.4 ($1CH_2$).

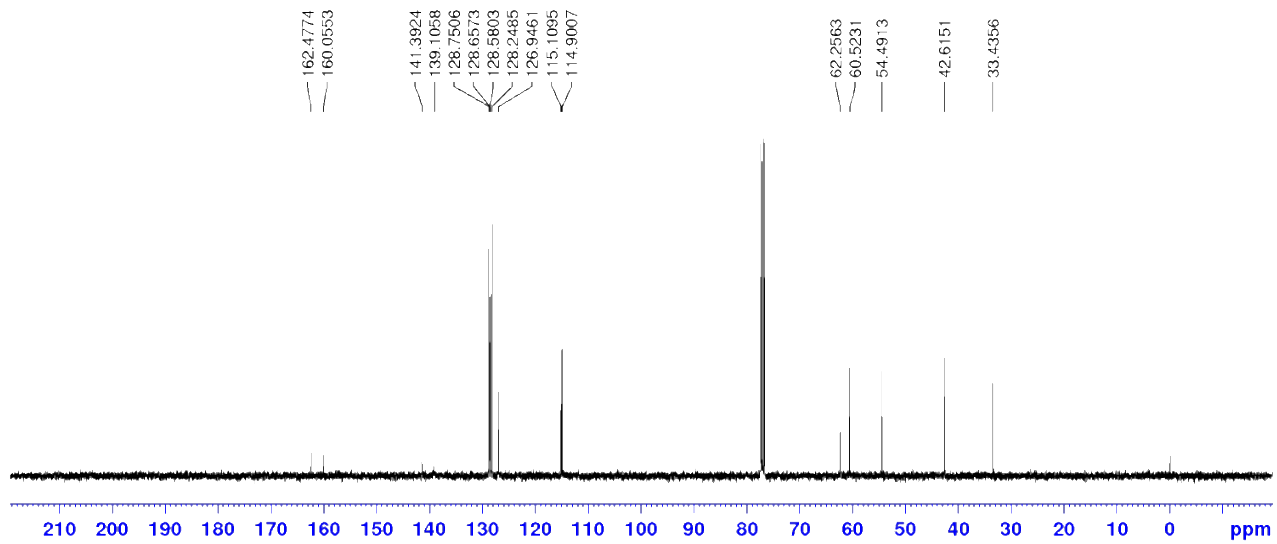
^{19}F {^{1}H} NMR ($CDCl_3$, 376 MHz) δ_F -117.5.

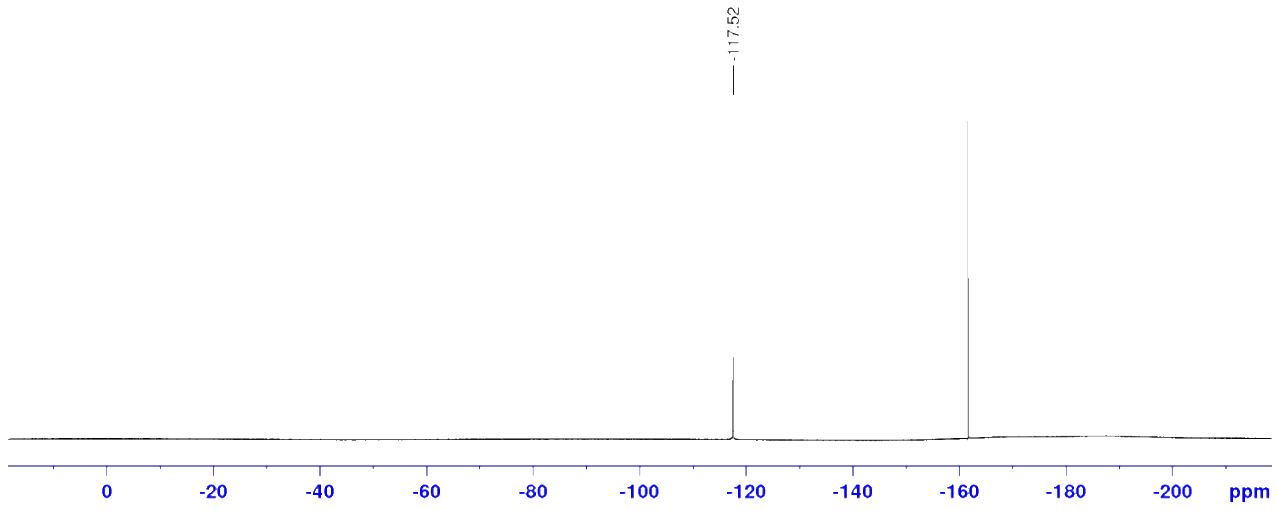
IR ν_{max} (thin film, cm^{-1}): 3062 (C-H, Ar), 3029 (C-H, Ar), 2955 (C-H), 2913 (C-H), 2790 (C-H), 1678 (Ar), 1509 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{17}H_{18}FN$ $[M+H]^+$: 256.1496, found 256.1498.

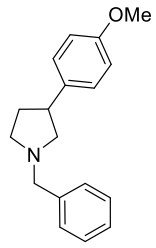
Figure S21. NMR spectra for compound 13a, related to Figure 6.







1-Benzyl-3-(4-methoxyphenyl)pyrrolidine **13b**



Chemical Formula: $C_{18}H_{21}NO$
Molecular Weight: 267.37

13b was isolated as a brown oil (510 mg, 64%, 3 mmol scale reaction, 2 equivalents of $Cu(OTf)_2$ used).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.30-7.38 (m, 4H), 7.23-7.27 (m, 1H), 7.20 (d, *J* 8.6 Hz, 2H), 6.84 (d, *J* 8.6 Hz, 2H), 3.79 (s, 3H), 3.69 (s, 2H), 3.29-3.38 (m, 1H), 3.04 (dd, *J* 8.2 Hz, 8.7 Hz, 1H), 2.82-2.88 (m, 1H), 2.66-2.72 (m, 1H), 2.47 (dd, *J* 8.6 Hz, 8.6 Hz, 1H), 2.28-2.37 (m, 1H), 1.82-1.91 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 157.9 (1C), 139.1 (1C), 137.6 (1C), 128.8 (2CH), 128.21 (2CH), 128.17 (2CH), 126.9 (1CH), 113.7 (2CH), 62.4 ($1CH_2$), 60.6 ($1CH_2$), 55.2 ($1CH_3$), 54.5 ($1CH_2$), 42.6 (1CH), 33.3 ($1CH_2$).

IR ν_{max} (thin film, cm^{-1}): 3028 (C-H, Ar), 2953 (C-H), 2908 (C-H), 2832 (C-H), 2785 (C-H), 1610 (Ar), 1511 (Ar).

HRMS *m/z* (ESI^+) calculated for $C_{18}H_{21}NO$ $[M+H]^+$: 268.1696, found 268.1700.

Figure S22. NMR spectra for compound 13b, related to Figure 6.