Synthesis of 3-Substituted Pyrrolidines via Palladium-Catalysed Hydroarylation

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Metal-catalysed reactions have revolutionised 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 the first palladium-catalysed alkene hydroarylation to give 3-aryl pyrrolidines, a class of small molecule with potency in a diverse range of biological scenarios. The process has broad substrate scope and can be used to directly deliver drug-like molecules in a single step from readily available precursors.

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

Joseph B. Sweeney, †,* Julien Doulcet, ‡ and Bimod Thapa‡

Summary. Metal-catalysed reactions have revolutionised 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 the first palladium-catalysed alkene hydroarylation to give 3-aryl pyrrolidines, a class of small molecule 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.

Keywords. Catalytic; hydroarylation; pyrrolidine; leishmaniasis; dopaminergic; serotonergic; HDAC inhibitors.

Introduction. Small molecules with saturated and unsaturated heterocyclic cores are ubiquitous in biochemistry, and there has been intense attention 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 currently FDA-approved small molecule drugs contain such a motif.¹ 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).

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Methods to deliver functionalised 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 favourably to ring modification than others: thus, whilst there have been elegant efforts for both non-catalytic and catalytic conversion of unsubstituted pyrrolidines to 2-substituted derivatives, there are few methods which efficiently deliver 3-substituted pyrrolidines, a structural class with diverse biological activity. For the latter compounds, there is usually a requirement for a directing group 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 was the first reported method to execute direct, substoichiometric catalytic modification of simple alkenes; for cycloalkenes, the MH reaction proceeds by overall functionalization of an sp³– rather than an sp²–CH bond, due to the stereoelectronic control for β-hydride elimination in the key palladium(II) intermediates (Figure 1).
In addition to the parent cycloalkene systems, the reaction can be applied to 2,3-
dihydropyrans\(^2\)\(^{21, 22}\) (2, \(X=\text{O}\)) and the analogous N-acyl pyrrolines\(^3\)\(^{23, 24, 25, 26, 27, 28}\) (2, \(X=\text{N}–\text{C}[\text{O}]\text{R}\)) (Figure 2), but the reactions can be unpredictable (cf. Figure 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; since many biologically active piperidines and pyrrolidines have this substitution pattern, this is a drastic limitation to the method. In addition, higher N-alkyl analogues (which can possess enhanced activity,\(^3\)\(^9\) Figure 1b) are difficult to access directly using existing MH methodology, often requiring deacylation-alkylation strategies. We recently reported\(^10\) conditions to effect 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.

**Figure 2.** Mizoroki-Heck arylation of unsaturated heterocycles proceed by overall \(sp^3\)-functionalization. a. Carba- and heterocycloalkene MH arylation favours allylic functionalisation, controlled by stereoelectronics; 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.

\[
\text{Pd(dba)}_2 \ 2.5 \text{ mol\%} \\
(R)-\text{Xyl-SDP(O)} \ 3.0 \text{ mol\%} \\
\text{iPrNEt} \ 300 \text{ mol}\% \\
4-\text{NO}_2\text{C}_6\text{H}_4\text{CO}_2\text{H} \ 100 \text{ mol}\% \\
\text{ethylene glycol} \ 80 ^\circ\text{C}
\]

\[
\begin{align*}
\text{Ar–Hal} & \xrightarrow{\text{\text{Pd\(\text{db}_{2}\), Ar–Hal}}\ \text{Pd}^0} \text{Ar} \\
\text{Ar–N}_2\text{BF}_4 & \xrightarrow{\text{Pd}^0} \text{Ar} \\
n & = 2
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{Pr} \xrightarrow{1. \text{PdCl}_2, 1 \text{ mol}\%} \text{P(o-Tol)}_3, 1.5 \text{ mol}\%} \\
\text{I} & \xrightarrow{2. \text{H}_2, \text{Pd(C)}} \text{OH}
\end{align*}
\]

\[
\text{H}_2 \text{Pd(C)}
\]
In theory, interception of 1 and 5 by a hydride source could lead to saturated products, rather than alkenes; in practice, such hydroarylation reactions\textsuperscript{31, 32} are narrowly confined to conjugate-like additions (Figure 3a),\textsuperscript{33} constrained alkenes,\textsuperscript{34, 35} and intramolecular processes (Figure 3b).\textsuperscript{36, 37, 38, 39} Though a rhodium-catalysed process has been reported (Figure 3c),\textsuperscript{40} to date, only one intermolecular palladium-catalysed hydroarylation reaction to give pyrrolidines has been described (Figure 3d);\textsuperscript{41} we report here the first broad-scope palladium-catalysed hydroarylation of pyrrolines (Figure 3e), directly furnishing 3-substituted pyrrolidines efficiently.
Results and discussion.

During the course of the optimisation 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 mono-arylated product, hydroarylated product 6 was also obtained (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\textsuperscript{42}), and we deduced that this would explain the relatively low yields of MH products compared with carbo cycloalkenes. Based on this analysis, we proposed that reaction of the lower homologue, pyrroline, should proceed more efficiently, since the analogous oxidised 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.

Figure 4. Hijacking redox side-reactions to deliver an efficient alkene hydroarylation reaction.

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); N-propyl pyrrole 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.

Table 1. Optimisation of reaction conditions

| Entry | x/eq. | y/mol% | z/mol% | Hal  | Additive  | Base       | t/hr | Yield/%  |
|-------|-------|--------|--------|------|-----------|------------|------|----------|
| 1     | 4     | 5      | 5      | I    | AgNO₃     | DABCO      | 17   | 20       |
| 2     | 4     | 5      | 7.5    | I    | Cu(OTf)₂  | DMpip      | 17   | 78       |
| 3     | 4     | 5      | 7.5    | I    | Zn(OTf)₂  | DMpip      | 17   | 47       |
| 4     | 4     | 5      | 7.5    | Br   | Cu(OTf)₂  | DMpip      | 17   | 77       |
| 5     | 4     | 5      | 7.5    | Br   | Zn(OTf)₂  | DMpip      | 17   | 32       |
| 6     | 3     | 1      | 1.5    | Br   | Cu(OTf)₂  | DMpip      | 17   | 62 (83)  |
| 7     | 3     | 5      | 7.5    | Br   | none      | DMpip      | 20   | 0        |
| 8     | 3     | 1      | 1.5    | Br   | Cu(OTf)₂  | DMpip      | 90   | 71 (83)  |
| 9     | 3     | 2      | 3      | Br   | Cu(OTf)₂  | DMpip      | 26   | 71       |
| 10    | 3     | 3      | 4.5    | Br   | Cu(OTf)₂  | DMpip      | 26   | 78       |
| 11    | 3     | 4      | 6      | Br   | Cu(OTf)₂  | DMpip      | 17   | 77       |
| 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       |

a 1 equivalent; b 5 equivalents; c Calculated from ¹H NMR; d N,N-dimethylpiperazine; e fluorobenzene obtained in 26% yield; f fluorobenzene obtained in 61% yield; g yield based on remaining starting material; h fluorobenzene obtained in 97% 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) whilst 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 pyrrolines 9a-9t generally in good yields (Figure 6). The process was also applicable to N-benzylpyrroline, giving the synthetically tractable pyrrolidines 13a and 13b.

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 to the multi-step process which is the only previously described synthetic strategy to obtain 9k (Figure 7).

**Figure 7.** Palladium-catalysed 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.$^{13}$

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: 14 (formed by ligand exchange of halide for pyrroline, promoted by Cu(OTf)$_2$)$^{13,44}$ can rapidly be converted to palladium hydride 15.
Figure 6. Scope of pyrroline reductive Mizoroki-Heck arylation

Conditions: Aryl bromide, N-propyl-3-pyrroline (3 eq.), PdCl₂ (4 mol%), P(o-Tol)₃ (6 mol%), N,N-dimethylpiperazine (5 eq), Cu(OTf)₂ (1 eq), MeCN (1 mM), sealed vial, 100 °C, 17 h; b isolated yield
(generating pyrrole 8 as by-product), which reductively eliminates the hydroarylated product and returns the catalyst to the cycle.

**Figure 8.** Plausible mechanism for palladium-catalysed pyrroline hydroarylation

![Mechanism Diagram](image)

In summary, we have described the first broad-scope palladium-catalysed hydroarylation to prepare pyrrolidines: the method is operationally simple and delivers potent bioactive small molecules in short order, and in good yields. The precise mechanistic features of these reactions are a focus of our research at this time and these data will be disclosed elsewhere, in due course.

**Experimental procedures.** General procedure for hydroarylation. To a 20 mL microwave vial was added PdCl₂ (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), aryl bromide (3 mmol), Cu(OTf)₂ (1.08 g, 3 mmol), N-propyl-3-pyrroline (1.17 mL, 9 mmol) 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 to room temperature and was then diluted with CH₂Cl₂ (10 mL). Then Et₂O (100 mL) was added and the mixture was washed with NH₄OH (aq., 28%, 100 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 x 100 mL). The combined organic layers were dried (MgSO₄)
and evaporated under reduced pressure. The crude product was purified by column chromatography, affording the pure product. Full experimental procedures and spectral data are contained in the Supplemental Information.

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**Author contributions.** J.D. and B.T. carried out all 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.

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Catalytic synthesis of 3-substituted pyrrolidines ms.pdf (573.27 KiB)
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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 (1H NMR at 400 MHz, 13C NMR at 100 MHz, 19F at 376 MHz) with the appropriate deuterated solvent. Chemical shifts in 1H NMR spectra are expressed as ppm downfield from tetramethylsilane, in 13C NMR spectra are relative to the respective residual NMR solvent, in 19F 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, PdCl₂ (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, Et₂O (100 mL) was added and the mixture was washed with NH₄OHaq (28%, 100 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 x 100 mL). The combined organic layers were dried over MgSO₄ and evaporated under reduced pressure. The crude was purified by column chromatography (70 g silica, gradient DCM : NH₃ (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$_7$H$_{13}$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) $\delta$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) $\delta$C: 127.6 (2CH), 59.7 (2CH$_2$), 58.3 (1CH$_2$), 22.5 (1CH$_2$), 11.9 (1CH$_3$).

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

HRMS m/z (ESI$^+$) calculated for C$_7$H$_{13}$N (M+H)$^+$ expected 112.1121, found 112.1121.
3-(4-Fluorophenyl)-1-propylpyrrolidine 9a

![Chemical structure of 9a](image)

Chemical Formula: C₁₃H₁₈FN  
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%).

**¹H NMR** (CDCl₃, 400 MHz) δH 7.20-7.24 (m, 2H), 6.94-6.99 (m, 2H), 3.32-3.41 (m, 1H), 3.09 (dd, 1H, ³J = 9.1 Hz, ²J = 8.1 Hz), 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, 2H, ³J = 7.5 Hz), 0.94 (t, 3H, ³J = 7.4 Hz).

**¹³C NMR** (CDCl₃, 100 MHz) δC 161.3 (d, 1C, ¹J = 242.4 Hz), 140.6 (1C, C), 128.6 (d, 2C, CH, ³J = 7.8 Hz), 115.1 (d, 2C, CH, ³J = 20.9 Hz), 62.2 (1C, CH₂), 58.5 (1C, CH₂), 54.6 (1C, CH₂), 42.6 (1C, CH), 33.2 (1C, CH₂), 21.9 (1C, CH₂), 12.0 (1C, CH₃).

**¹⁹F {¹H} NMR** (CDCl₃, 376 MHz) δF −117.5.

**IR** νmax (thin film, cm⁻¹): 2958 (C-H), 2931 (C-H), 2874 (C-H), 2790 (C-H), 1509 (Ar).

**HRMS** m/z (ESI⁺) calculated for C₁₃H₁₈FN [M+H]^+: 208.1496, found 208.1496.
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) $\delta$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) $\delta$C 145.5 (1C), 128.3 (2CH), 127.3 (2CH), 126.0 (1CH), 62.4 (1CH$_2$), 58.6 (1CH$_3$), 54.8 (1CH$_2$), 43.4 (1CH), 33.2 (1CH$_2$), 22.2 (1CH$_2$), 12.1 (1CH$_3$).

IR $\nu_{max}$ (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.

[Chemical structures and spectra images]
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) $\delta$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) $\delta$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 $\nu_{\text{max}}$ (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.
1-Propyl-3-(4-(trifluoromethyl)phenyl)pyrrolidine 9d

Chemical Formula: C$_{14}$H$_{18}$F$_3$N
Molecular Weight: 257.30

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

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$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) $\delta$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) $\delta$F $-62.3$.

IR $\nu_{\text{max}}$ (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$_3$N [M+H]$^+$: 258.1464, found 258.1465.
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) \(\delta\) 7.15 (d, \(J = 8.6\) Hz, 2H), 6.71 (d, \(J = 8.7\) Hz, 1H), 2.89-2.95 (m, 1H), 2.92 (s, 6H), 2.97-3.23 (m, 4H), 2.42-2.52 (m, 1H), 1.62 (sext, \(J = 7.5\) Hz, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H).

\(^1^3\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 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 \(\nu_{\text{max}}\) (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.
3-(4-Nitrophenyl)-1-propylpyrrolidine 9f

Chemical Formula: C_{13}H_{18}N_{2}O_{2}

Molecular Weight: 234.30

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

\(^1H\) NMR (CDCl\(_3, 400\) MHz) \(\delta_H\) 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).

\(^13C\) NMR (CDCl\(_3, 100\) MHz) \(\delta_C\) 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 \(\nu_{\text{max}}\) (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\(_2\)O\(_2\) [M+H\(^+\)]: 235.1441, found 235.1440.
1-(4-(1-Propylpyrrolidin-3-yl)phenyl)ethan-1-one 9g

Chemical Formula: C₁₉H₂₁NO
Molecular Weight: 231.34

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

$^1$H NMR (CDCl₃, 400 MHz) δₜ 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 (CDCl₃, 100 MHz) δC 197.7 (1C), 151.6 (1C), 135.2 (1C), 128.5 (2CH), 127.5 (2CH), 62.0 (1CH₂), 58.4 (1CH₂), 54.7 (1CH₂), 43.3 (1CH), 33.2 (1CH₂), 26.5 (1CH₃), 22.1 (1CH₂), 12.0 (1CH₃).

IR νmax (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 C₁₉H₂₁NO [M+H]⁺: 232.1696, found 232.1695.
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) \(\delta_H\) 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) \(\delta_C\) 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\(_3\)), 33.1 (1CH\(_2\)), 22.0 (1CH\(_2\)), 12.0 (1CH\(_3\)).

IR \(\nu_{\text{max}}\) (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.
3-(4-Methoxyphenyl)-1-propylpyrrolidine 9i

Chemical Formula: C₁₄H₂₁NO
Molecular Weight: 219.33

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

¹H NMR (CDCl₃, 400 MHz) δH 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).

¹³C NMR (CDCl₃, 100 MHz) δC 157.8 (1C), 137.5 (1C), 128.1 (2CH), 113.7 (2CH), 62.5 (1CH₂), 58.6 (1CH₂), 55.2 (1CH₃), 54.7 (1CH₂), 42.6 (1CH), 33.2 (1CH₂), 22.1 (1CH₂), 12.1 (1CH₃).

IR νmax (thin film, cm⁻¹): 2956 (C-H), 2931 (C-H), 2873 (C-H), 2783 (C-H), 1511 (Ar).

HRMS m/z (ESI⁺) calculated for C₁₄H₂₁NO [M+H⁺]: 220.1696, found 220.1694.
3-(3-Methoxyphenyl)-1-propylpyrrolidine 9j

![Chemical structure](image)

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) $\delta$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) $\delta$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 $\nu_{\text{max}}$ (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.
3-(1-Propylpyrrolidin-3-yl)phenol 9k

Chemical Formula: C\textsubscript{13}H\textsubscript{19}NO  
Molecular Weight: 205.30

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

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \)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 8.1 Hz, 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).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \)C 157.0 (1C), 145.8 (1C), 129.5 (1CH), 118.6 (1CH), 114.6 (1CH), 113.8 (1CH), 61.8 (1CH\textsubscript{2}), 58.8 (1CH\textsubscript{2}), 54.4 (1CH\textsubscript{2}), 43.1 (1CH), 32.4 (1CH\textsubscript{2}), 21.5 (1CH\textsubscript{2}), 12.0 (1CH\textsubscript{3}).

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

HRMS \( m/z \) (ESI\textsuperscript{+}) calculated for C\textsubscript{13}H\textsubscript{19}NO [M+H]\textsuperscript{+}: 206.1539, found 206.1540.
3-(2-Methoxyphenyl)-1-propylpyrrolidine 9I

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

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

\(^1\text{H NMR}\) (CDCl\(_3\), 400 MHz) \(\delta\) 7.31 (dd, \(J\) 1.4 Hz, 7.5 Hz, 1H), 7.15-7.20 (m, 1H), 7.00-6.94 (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 (s, \(J\) 7.5 Hz, 2H), 0.94 (t, \(J\) 7.4 Hz, 3H).

\(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz) \(\delta\) 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 \(\nu_{\text{max}}\) (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.
1-Propyl-3-(α-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) $\delta_H$ 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) $\delta_C$ 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 $\nu_{\text{max}}$ (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.
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) $\delta$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) $\delta$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 $\nu_{\text{max}}$ (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.
3-(1-Propylpyrroloidin-3-yl)pyridine 9o

![Chemical Structure](Image)

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) $\delta$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) $\delta$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 $\nu_{\text{max}}$ (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.
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\text{H NMR} \text{ (CDCl}_3, \text{ 400 MHz)} \delta\text{H} 7.26 \text{ (dd, J 2.9 Hz, 4.9 Hz, 1H), 7.01 \text{ (dd, J 1.1 Hz, 4.9 Hz, 1H), 6.99 \text{ (m, 1H),}}
3.42-3.51 \text{ (m, 1H), 3.10 \text{ (dd, J 8.0 Hz, 8.8 Hz, 1H), 2.85-2.91 \text{ (m, 1H), 2.54-2.60 \text{ (m, 1H), 2.38-2.48 \text{ (m, 3H),}}}
2.25-2.32 \text{ (m, 1H), 1.81-1.90 \text{ (m, 1H), 1.56 \text{ (sext, J 7.5 Hz, 2H), 0.94 \text{ (t, J 7.4 Hz, 3H).}}}

\(^{13}\text{C NMR} \text{ (CDCl}_3, \text{ 100 MHz)} \delta\text{C} 146.0 \text{ (1C), 127.1 \text{ (1CH), 125.5 \text{ (1CH), 119.2 \text{ (1CH), 61.5 \text{ (1CH}_2), 58.6 \text{ (1CH}_2), 54.2 \text{ (1CH}_2), 38.6 \text{ (1CH), 33.3 \text{ (1CH}_2), 22.1 \text{ (1CH}_2), 12.1 \text{ (1CH}_3).}}

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

\text{HRMS } m/z \text{ (ESI\(^{+}\)) calculated for C}_{11}\text{H}_{17}\text{NS [M+H]}^{+}: 196.1154, \text{ found 196.1157.}
1-Propyl-3-(thiophen-2-yl)pyrrolidine 9q

Chemical Formula: C\textsubscript{11}H\textsubscript{17}NS
Molecular Weight: 195.32

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

\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 400 MHz) \(\delta\)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).

\textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 100 MHz) \(\delta\)C 148.8 (1C), 126.6 (1CH), 123.2 (1CH), 123.0 (1CH), 62.4 (1CH\textsubscript{2}), 58.3 (1CH\textsubscript{2}), 53.9 (1CH\textsubscript{2}), 38.6 (1CH), 33.6 (1CH\textsubscript{2}), 21.9 (1CH\textsubscript{2}), 12.0 (1CH\textsubscript{3}).

\textbf{IR} \(\nu\textsubscript{max}\) (thin film, cm\textsuperscript{-1}): 2957 (C-H), 2930 (C-H), 2873 (C-H), 2789 (C-H).

\textbf{HRMS} \textit{m/z} (ESI\textsuperscript{+}) calculated for C\textsubscript{11}H\textsubscript{17}NS [M+H]\textsuperscript{+}: 196.1154, found 196.1156.
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) $\delta$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) $\delta$C 142.9 (1C, CH), 138.0 (1C, CH), 128.6 (1C, C), 109.9 (1C, CH), 61.1 (1C, CH$_3$), 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 $\nu_{\text{max}}$ (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.
1-Methyl-3-(1-propylpyrrolidin-3-yl)-1H-indazole 9s

![Chemical Structure](image)

**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) $\delta_H$ 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) $\delta_C$ 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** $\nu_{max}$ (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.
8-(1-Propylpyrrolidin-3-yl)quinoline 9t

Chemical Formula: C₁₆H₂₀N₂
Molecular Weight: 240.35

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

$^1$H NMR (CDCl₃, 400 MHz) $\delta$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 (CDCl₃, 100 MHz) $\delta$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 (1CH₂), 58.8 (1CH₂), 55.2 (1CH₂), 36.7 (1CH), 33.1 (1CH₂), 22.2 (1CH₂), 12.1 (1CH₃).

IR $\nu$$_{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 C₁₆H₂₀N₂ [M+H]⁺: 241.1699, found 241.1699.
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)\textsubscript{2} used).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta H\) 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).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta C\) 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\textsubscript{2}), 60.5 (1CH\textsubscript{2}), 54.5 (1CH\textsubscript{2}), 42.6 (1CH), 33.4 (1CH\textsubscript{2}).

\textsuperscript{19}F {\textsuperscript{1}H} NMR (CDCl\textsubscript{3}, 376 MHz) \(\delta F\) -117.5.

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

HRMS \textit{m/z} (ESI\textsuperscript{+}) calculated for C_{17}H_{18}FN [M+H]\textsuperscript{+}: 256.1496, found 256.1498.
1-Benzyl-3-(4-methoxyphenyl)pyrrolidine 13b

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) $\delta$ 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) $\delta$ 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 $\nu_{\text{max}}$ (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.
