Synthesis of nornicotine, nicotine and other functionalised derivatives using solid-supported reagents and scavengers

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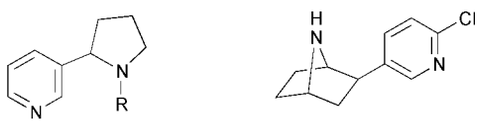
The sequential use of solid-supported reagents and scavengers has led to an efficient synthesis of the natural products nornicotine **1**, nicotine **2** and further fuctionalised derivatives. Also reported is a diastereoselective route to both enantiomers of nicotine **2**.

Introduction

The natural products nornicotine **1**, nicotine **2** and epibatidine **3** are all species which have attracted considerable interest from medicinal chemists owing to their potent biological activity as ligands at the nicotinic acetylcholine receptors (nAChR)[1] (Fig. 1). The pharmacological effects of these compounds on



1; R = H
2; R = CH_3

3

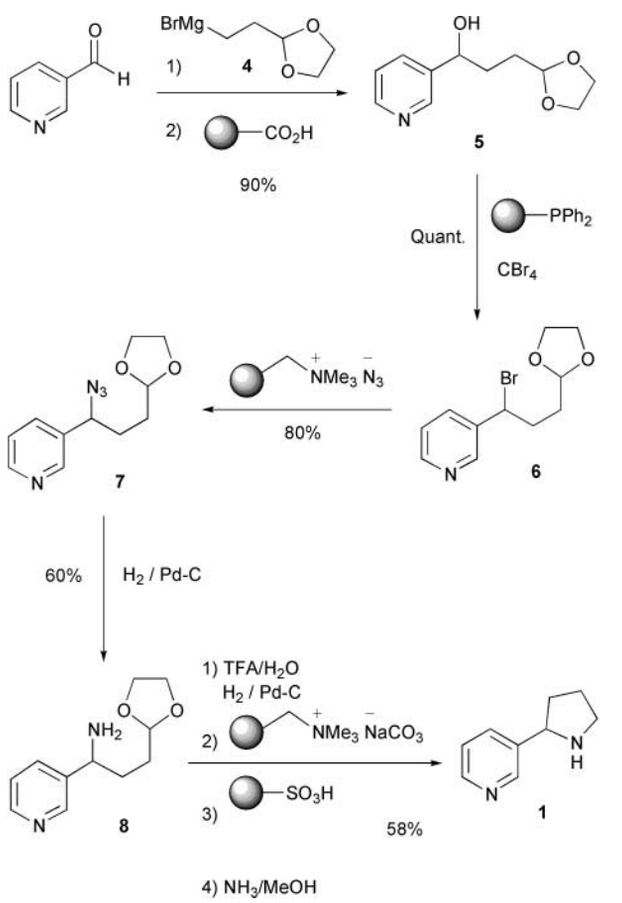
Fig. 1 Nornicotine **1**, nicotine **2** and epibatidine **3**.

cognitive function and neuroprotection are particularly well documented.[2] They have shown substantial therapeutic benefits in the specific treatment of Tourette's syndrome, Alzheimer's and Parkinson's disease[3] and in a more general application as anxiolytic, antidepressive and schizopherenic corrective agents.[4]

Likewise epibatidine **3** has also shown extraordinary analgesic activity which has led to the demand for other structural analogues of these materials.[5] We have previously reported on the use of a sequential multi-step synthesis for the preparation of epibatidine **3** using solid-supported reagents and scavengers[6] to effect all the individual steps.[7] As a consequence only filtration and solvent removal were required to afford pure products and hence the route avoided conventional work-up procedures such as chromatography, crystallisation or distillation. We now report a similar strategy for the preparation of **1** and **2** since this process can be adapted for multi-parallel synthesis of related structural arrays or alternatively the product can be derivatised further for extended biological evaluation. This concept is exemplified by the synthesis of a small collection of nicotine analogues as described below.

Results and discussion

The route began by reaction of the Grignard reagent **4** with pyridine-3-carbaldehyde in THF at −78 °C. After warming to room temperature the reaction was quenched by the addition of Amberlite IRC-50 carboxylic acid functionalised resin[8] to give the addition product **5** in 85% yield. LC-MS indicated this material to be approximately 95% pure after only filtration and evaporation of the solvent (Scheme 1).



Scheme 1 Preparation of nornicotine **1**.

Conversion of the alcohol **5** to the corresponding bromide **6** was achieved in dichloromethane using carbon tetrabromide and polymer-supported triphenylphosphine in essentially quantitative yield.[9] The bromide was subsequently transformed to the azide **7** using an azide ion exchange resin[10] and then reduced to the primary amine **8** *via* hydrogenation with palladium on carbon. The polymer-supported azide reagent used

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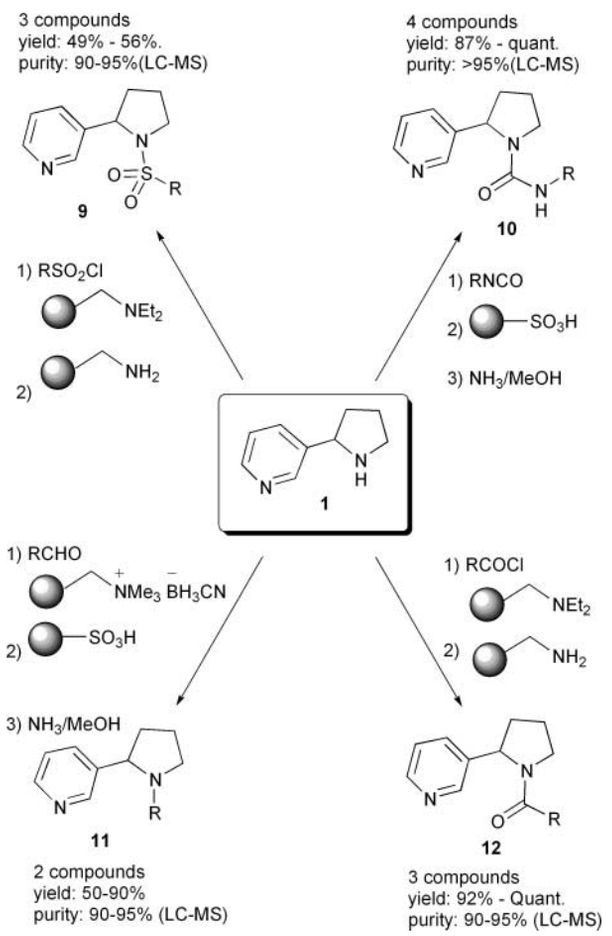
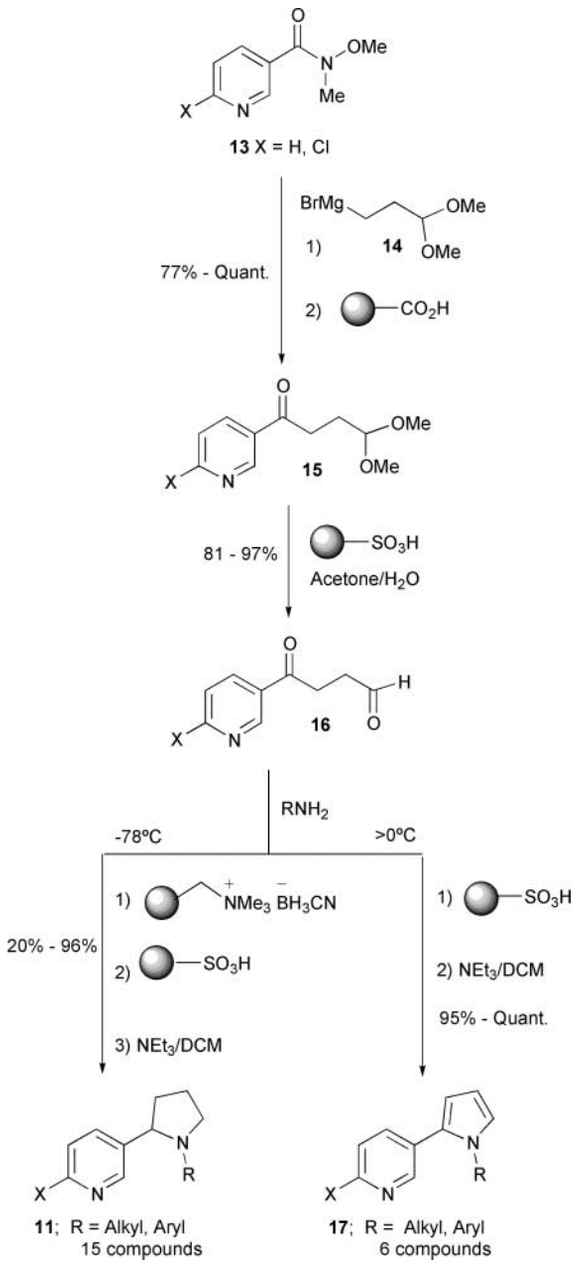
in the reaction of **6** to **7** was readily prepared by an ion exchange reaction of a commercially available Amberlyst resin, functionalised as the quaternary ammonium chloride, with an aqueous solution of sodium azide. Treatment of amine **8** with an aqueous solution of trifluoroacetic acid (TFA) and a further portion of palladium on carbon under a reducing atmosphere of hydrogen furnished nornicotine **1** as the TFA salt. Evaporation of the solution followed by dissolving the residue in ethyl acetate and addition of a polymer-supported carbonate base[11] liberated the free amine which in turn was captured on an Amberlyst 15 resin. This allowed for the facile purification of the bound material by simple elution of the resin with dichloromethane resulting in removal of contaminants such as ethylene diol a by-product of the previous conversion. Release of the nornicotine **1** from the resin was achieved by suspending the polymer in a 2 M solution of ammonia in methanol, filtration and concentration of the filtrate under reduced pressure yielded the adduct **1**. The material obtained from this reaction sequence was determined to be of >90% purity as determined by LC-MS analysis.

Starting from nornicotine **1**, obtained as described above, we were able to demonstrate the rapid construction of a small collection of nicotine derivatives using a range of readily available monomers (Scheme 2).



Scheme 2 Preparation of nicotine derivatives.

During the course of these investigations we also embarked on a second synthetic approach to the preparation of the nicotine structural motif. Starting from a commercially available acid or acid chloride we prepared the corresponding Weinreb amides **13** in high yields using standard literature procedures (Scheme 3).[12] The reaction of the Weinreb **13** with the Grignard reagent **14** followed by the standard work up with Amberlite IRC-50 furnished the carbonyl compound **15** in excellent yield. Deprotection of the aldehyde by Amberlyst 15



Scheme 3 Preparation of pyrrolidine and pyrrole systems.

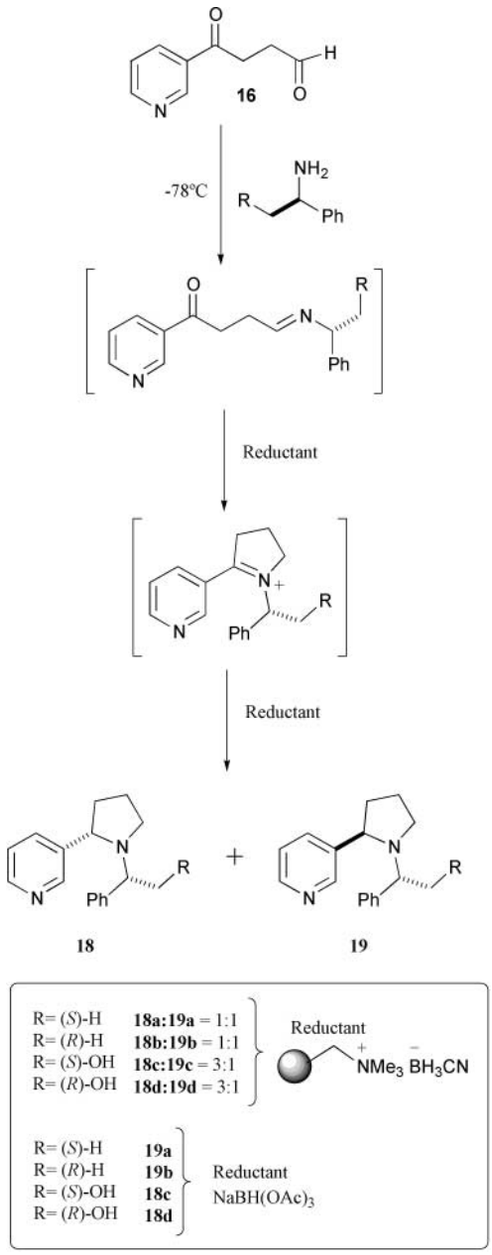
catalysed hydrolysis also proceeded smoothly to yield the 1,4-dicarbonyl system **16**, again in excellent yield. Unfortunately, this material was found to have only a limited stability and was advanced to the next product as soon as prepared. The next step allowed access not only to substituted nicotine derivatives **11** but also the fully aromatic pyrrole substituted compounds **17**. This selectivity was achieved by using only a slight modification of the reaction conditions. It was discovered that conducting the reactions at −78 °C in the presence of either sodium triacetoxyborohydride or polymer-supported cyanoborohydride generated only the pyrrolidine system **11**. Whereas at elevated temperatures (>0 °C) spontaneous formation of the pyrrole **17** was observed even in the presence of the reducing agents.

Both these reactions lead directly to the ring substituted derivatives without the need for further elaboration, thus providing a simplified approach to these structures. Additionally these products could be purified in an analogous way to that used for nornicotine **1** using a "capture and release" protocol with Amberlyst 15.[13]

As an extension of the previous work we were interested in the possibility of obtaining enantiomerically pure nicotine

derivatives. It is known from the extensive medicinal literature that both enantiomeric forms of nicotine **2** show interesting biological activity and that this trend also repeated in the analogous compounds.[14]

We were attracted by the simplicity of modifying our previous preparative route to include a chiral amine auxiliary to control the reduction step (Scheme 4). This is a process that has

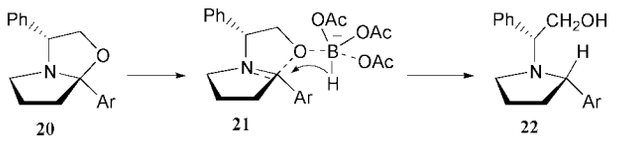


Scheme 4 Diastereoselective preparation of nicotine derivatives.

been utilised in similar systems by Polniaszek[15] among others for the reduction of substituted tetrahydroisoquinolines and by Meyers[16] and Periasamy[17] for 2-substituted pyrrolidinones. This strategy proved to be particularly useful when the correct reducing agent was determined. The initial investigation using a polymer-supported cyanoborohydride reagent gave a mixture of diastereoisomers, interestingly, the system with the pendant hydroxy group gave a better ratio than the simple methylbenzylamine. It was also noted that changing the configuration of the auxiliary had the effect of reversing the diastereoisomer formed, hence a degree of "chirality transfer" was observed. However, using sodium triacetoxyborohydride for the reduction drastically altered the diastereoselectivity, giving essentially a single isomer of each compound. The stereoselectivites of the reductions were determined by obtaining the crystal structures of compounds **18c** and **18d**, proving the enantiomeric relationship. Subsequently, the configuration of the centers in the simplified systems **19a** and **19b** were confirmed by conversion of the known hydroxy functionalised compounds **18c** and **18d** to the matching reduced forms **18a** and **18b**. This was achieved *via* the preparation of the tosylate followed by reaction with lithium aluminium hydride. Compounds **18a** and **18b** both show an enantiomeric relationship to **19b** and **19a** respectively. This enabled a cross reference to be made between the two series and consequently the determination of the absolute stereochemistry of each compound.

Stereochemical control

At the low temperatures employed the reaction mechanism will probably involve the initial intramolecular trapping of the intermediate iminium ion by the pendant hydroxy of the chiral auxiliary to give **20** (Scheme 5). This would be consistent with



Scheme 5 Proposed mechanism for hydroxy substituted derivatives.

the work of Meyers[17] and Periasamy[16] in their work on the pyrrolidinone systems.

Assisted cleavage of the C–O bond through coordination of the Lewis acidic triacetoxyborohydride promoting formation of the iminium ion **21** followed by directed delivery of the hydride to the same face would give products consistent with the observed stereochemistry **22** (*cf.* acetal cleavage[18]).

The origin of the stereoselectivity in the simple methyl benzyl substituted system must otherwise originate from a conformational preference in the transition state structures. There are two possible reactive conformations **23** and **24** (Fig. 2) that lead

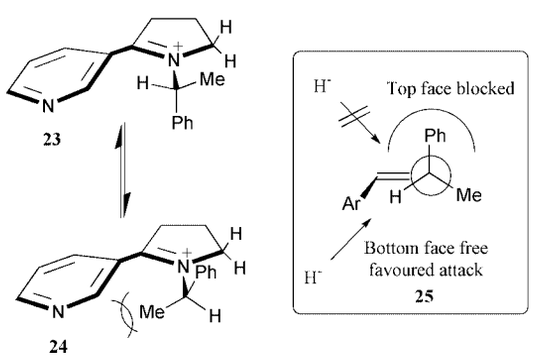


Fig. 2 Possible reactive conformations

to the possible diastereomers if one assumes that the phenyl group acts as a diastereofacial block **25**.

In the two possible conformations there is a potential steric interaction; in **23** with the methyl and the geminal protons and in **24** between the methyl and the pyridine moiety. Molecular modeling studies[19] predict that conformer **23** is a calculated 2 kcal mol^{-1} more stable than **24** indicating the steric interaction of the methyl and aryl unit is the major contributing factor to the conformational preference. This would dictate that the reaction with (*R*)-methylbenzylamine would proceed by attack on **23** to yield **19**, which is observed experimentally.

Summary

In summary, the work reported above illustrates further the power of using immobilised reagent and scavenger systems in a multi-step fashion to produce organic products without the need for conventional work-up methods.

Experimental

Unless otherwise specified, all reactions involving polymers were carried out on a laboratory shaker IKA 125 at 250 rpm. All moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Amberlyst resins were of technical grade and washed with methanol and dichloromethane before use and dried in vacuum at 60 °C. Diethyl ether and tetrahydrofuran were distilled over sodium benzophenone and dichloromethane over calcium hydride. All other solvents and reagents were used as supplied unless otherwise specified. Analytical TLC was performed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualized by ultra-violet radiation, acidic ammonium molybdate(IV) or potassium permanganate. Infra-red spectra were obtained on Perkin–Elmer Spectrum One FT-IR spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker Advance DPX-400 spectrometer at 400 MHz with residual chloroform as the internal reference (δ_H = 7.26 ppm). ^{13}C-NMR spectra were recorded in $CDCl_3$ on the same spectrometer at 100 MHz with the central peak of chloroform as the internal reference (δ_C = 77.0 ppm). DEPT 135 and two-dimensional (COSY, HMQC and HMBC) NMR spectroscopy were used, where appropriate, to aid in the assignment of signal in the ^{1}H-NMR and ^{13}C-NMR spectra. Mass spectra and accurate mass data were obtained on Hewlett Packard LC/MSD, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometers at the Department of Chemistry, University of Cambridge. LC-MS analysis was performed on a Hewlett-Packard HPLC 1050 chromatograph (Supelcosil ABZ + PLUS; 3 μ, 33 mm × 4.6 mm) attached to a Micromass Platform LC Electrospray Mass Spectrometer. Elution was carried out using the gradient given in Table 1.

Table 1 Elution gradient

Time/min	A %[a]	B %[b]	Flow rate/ml min^{-1}
0.00	100	0	1
0.70	100	0	1
4.20	0	100	1
7.70	0	100	1
8.00	100	0	1

[a] 10 mmol solution of ammonium acetate in water with 0.1% formic acid. [b] 95% acetonitrile + 5% water + 0.05% formic acid.

Preparation of polymer-supported azide

Amberlyst 26 (10 g) was washed thoroughly with methanol (until the odour of amines was no longer detectable) and dried in vacuum. The resin was shaken for 1 h in a solution of sodium azide (9.5 g) in water (60 ml). The resin was filtered off and re-suspended in a new solution of sodium azide (9.5 g) in water (60 ml), and shaken for a further 1 h. The resin was then filtered and washed with water until the addition of an aqueous solution of silver nitrate to the washings showed no precipitate. The polymer reagent was finally washed with methanol and dried under reduced pressure.

Preparation of 3-[3-(1,3-dioxolan-2-yl)-1-hydroxypropyl]-pyridine 5

A solution of 2-(2-bromoethyl)-1,3-dioxolane (2.48 ml, 21.2 mmol) in tetrahydrofuran (22 ml) was added dropwise to magnesium turnings (515 mg, 21.2 mmol). The mixture was stirred at ambient temperature for 1 h. A solution of pyridine-3-carbaldehyde (1 ml, 10.6 mmol) in 5 ml of tetrahydrofuran was cooled to −78 °C and the preformed Grignard reagent was added dropwise. The mixture was stirred at −78 °C for 10 min and warmed to ambient temperature for 2 h. Polymer supported carboxylic acid (Amberlite IRC-50) was added and the mixture stirred for 1 h before being filtered through Celite and washed thoroughly with ethyl acetate. The solvent was concentrated under reduced pressure. The residue was re-dissolved in diethyl ether and filtered through a pad of silica, washing with diethyl ether and afterwards with ethyl acetate. The solution was concentrated under reduced pressure to yield the title compound (2.0 g, 90%) as a pale yellow oil; δ_H (400 MHz; $CDCl_3$) 8.55 (s, 1H), 8.47 (1H, d, *J* 4.0), 7.70 (1H, d, *J* 7.8), 7.25 (2H, m), 4.91 (1H, t, *J* 4.3), 4.78 (1H, t, *J* 6.3), 3.99–3.96 (2H, m), 3.88–3.84 (2H, m), 3.35 (br s, 1H), 1.92–1.78 (2H, m), 1.84–1.78 (2H, m); δ_C (100 MHz; $CDCl_3$) 148.49, 147.69, 140.15, 133.59, 123.40, 104.04, 71.49, 64.96, 64.91, 33.03, 29.80; LC-MS: 2.96 min (210.20, $[M + H]^+$).

Preparation of 3-[1-bromo-3-(1,3-dioxolan-2-yl)propyl]pyridine 6

Polymer supported triphenylphosphine (9.5 g, 3 mmol g^{-1}) and carbon tetrabromide (3.48 g, 10.5 mmol) were suspended in dichloromethane (80 mL) and shaken for 1 h then cooled at 0 °C. 3-[3-(1,3-Dioxolan-2-yl)-1-hydroxypropyl]pyridine (2 g, 9.56 mmol) was added and the mixture shaken overnight. The resin was then filtered off and washed with dichloromethane. After evaporation of the solvent under reduced pressure, the title compound was obtained (2.6 g, quant.) as a brown oil; δ_H (400 MHz; $CDCl_3$) 8.60 (d, 1H, *J* 1.7), 8.51 (dd, 1H, *J* 4.6, 1.0), 7.75 (dt, 1H, *J* 6.2, 1.7), 7.28 (dd, 1H, *J* 6.2, 4.6), 5.01 (dd, 1H, *J* 8.4, 6.7), 4.89 (t, 1H, *J* 4.3), 3.92–3.81 (m, 4H), 2.44–1.66 (m, 4H); δ_C (100 MHz; $CDCl_3$) 149.51, 148.55, 137.77, 134.90, 123.63, 103.38, 64.97, 51.27, 33.86, 32.05; LC-MS: 4.24 min (272 [*M*], 274 $[M + 2H]^+$).

Preparation of 3-[1-azido-3-(1,3-dioxolan-2-yl)propyl]pyridine 7

Polymer supported sodium azide (8 g) was added to a solution of 3-[1-bromo-3-(1,3-dioxolan-2-yl)propyl]pyridine (2.6 g, 9.56 mmol) in dichloromethane (30 ml) and the mixture was shaken overnight. The reaction mixture was filtered through a pad of silica and washed thoroughly with diethyl ether. After evaporation of the solvent under reduced pressure, the title compound was obtained (1.78 g, 80%) as a yellow oil; δ_H (400 MHz; $CDCl_3$) 8.5 (br s, 2H), 7.58 (dd, 1H, *J* 7.9, 1.5), 7.26–7.22 (m, 1H), 4.82–4.79 (m, 1H), 4.51–4.48 (t, 1H, *J* 7), 3.85–3.76 (m, 4H), 1.82–1.66 (m, 4H); δ_C (100 MHz; $CDCl_3$) 149.70, 148.60, 135.27, 134.22, 123.70, 103.61, 64.96, 63.50, 30.24, 30.01; LC-MS: 4.00 min (235.27 [M + H]+).

Preparation of 3-[1-amino-3-(1,3-dioxolan-2-yl)propyl]pyridine 8

3-[1-Azido-3-(1,3-dioxolan-2-yl)propyl]pyridine (1.78 g, 7.6 mmol) was dissolved in dichloromethane (80 ml) and Pd–C (10%, 500 mg) was added. The mixture was stirred overnight under a H_2 balloon then filtered through Celite and washed with ethyl acetate. The residue was re-dissolved in ethyl acetate and filtered through a pad of silica washing with ethyl acetate and afterwards with dichloromethane–methanol (10 : 1). The reaction was concentrated under reduced pressure to yield amine (940 mg, 60%) as a yellow oil; δ_H (400 MHz; $CDCl_3$) 8.54 (s, 1H), 8.47 (dd, 1H, *J* 4.7, 1.8), 7.67 (dt, 1H, *J* 7.9, 1.7), 7.24 (dd, 1H, *J* 7.9, 4.7), 4.84 (t, 1H, *J* 4.5), 3.96 (t, 1H, *J* 6.6), 3.94–3.79 (m, 4H), 1.8–1.61 (m, 4H); δ_C (100 MHz; $CDCl_3$) 148.59, 148.55, 141.16, 133.86, 123.50, 104.11, 64.90, 64.87, 53.66, 33.42, 30.53.

Preparation of 3-(pyrrolidin-2-yl)pyridine (nornicotine) 1

3-[1-Amino-3-(1,3-dioxolan-2-yl)propyl]pyridine (252 mg, 1.21 mmol) was dissolved in dichloromethane (12 ml) and Pd–C (10%, 68.5 mg) was added. The mixture was stirred under H_2 balloon and trifluoroacetic acid (235 μl, 3.04 mmol) and water (200 μl, 7.26 mmol) were added. After 24 h further trifluoroacetic acid (40 μl, 0.51 mmol) was added, and the mixture

vigorously stirred for 12 h. After addition of water (150 µl, 5.44 mmol) and vigorous stirring for a further 8 h, the mixture was concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate and polymer supported carbonate was added. After 1 h the resin was filtered off and washed thoroughly with ethyl acetate. The combined filtrates were concentrated under reduced pressure and the residue was re-dissolved in dichloromethane. Amberlyst 15 was added to the solution and the mixture was shaken for 1 h. After filtration, the resin was suspended in 2 M solution of ammonia in methanol (10 ml) and shaken for 2 h. The resin was filtered off and washed thoroughly with a 2 M solution of ammonia in methanol. Evaporation of the solvent under reduced pressure and subsequent drying of the residue under high vacuum yielded the title compound (104 mg, 58%) as a yellow oil; δ_H (400 MHz; $CDCl_3$) 8.55 (s, 1H), 8.44 (d, 1H, *J* 4.9), 7.71–7.68 (m, 1H), 7.22 (dd, 1H, *J* 7.9, 4.8), 4.15 (t, 1H, *J* 7.8), 3.17–3.04 (m, 2H), 2.06 (br s, 1H), 1.95–1.66 (m, 4H); δ_C (100 MHz; $CDCl_3$) 147.61, 147.51, 135.22, 123.81, 60.05, 46.04, 33.03, 24.80.

Preparation of 3-[1-(4-fluorophenylsulfonyl)pyrrolidin-2-yl]-pyridine 9a; general procedure for 3-(1-arylsulfonylpyrrolidin-2-yl)pyridine

Diethylaminomethyl-polystyrene (122 mg, 0.389 mmol, 3.2 mmol g^{-1}) was suspended in dichloromethane (1 ml) and stirred for 10 min. A solution of 4-fluorobenzenesulfonyl chloride (25 mg, 0.129 mmol) in dichloromethane (0.4 ml) was added and the mixture was stirred at ambient temperature for 5 min. A solution of 3-(pyrrolidin-2-yl)pyridine (19.2 mg, 0.129 mmol) in dichloromethane (1 ml) was added dropwise and the mixture was stirred until disappearance of the starting material was observed by TLC (1–2 h). Aminomethyl resin (92 mg, 0.258 mmol, 2.8 mmol g^{-1}) was added and the mixture was stirred for a further 1 h. The mixture was filtered through a small pad of silica washing thoroughly with diethyl ether. Evaporation of the solvent under reduced pressure yielded the title compounds (19.4 mg, 49%); ν_{max}/cm^{-1} 2955, 2922, 1692, 1590, 1334, 1160, 1090, 1001, 840, 712 and 673; δ_H (400 MHz; $CDCl_3$) 1.70–1.95 (3H, m, C(3)-Ha, C(4)-H_2), 2.05–2.15 (1H, m, C(3)-Hb), 3.42–3.50 (1H, m, C(5)-Ha), 3.58–3.66 (1H, m, C(5)-Hb), 4.78 (1H, dd, *J* 8.0, 4.0, C(2)-H), 7.16 (2H, dd, *J* 8.8, 8.4, C(3″)-H and C(5″)-H), 7.23 (1H, dd, *J* 7.9, 4.8, C(5′)-H), 7.63 (1H, d, *J* 7.9, C(4′)-H), 7.77 (2H, dd, *J* 8.8, 5.1, C(2″)-H and C(6″)-H), 8.49 (1H, d, *J* 4.8, C(6′)-H), 8.50 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 24.07 (C(4)H_2), 35.75 (C(3)H_2), 49.42 (C(5)H_2), 61.22 (C(2)H), 116.30 (d, *J* 22.3, C(3″)H and C(5″)H), 123.28 (C(5′)H), 130.04 (d, *J* 9.3, C(2″)H and C(6″)H), 133.90 (C(4′)H), 134.08 (d, *J* 3.3, C(1″)), 138.13 (C(3′)), 147.95 (C(6′)H), 148.66 (C(2′)H), 165.16 (d, *J* 253.6, C(4″)); MS (EI) *m*/*z* 306.08 (M^+).

Preparation of 3-[1-(3-trifluoromethylphenylsulfonyl)pyrrolidin-2-yl]pyridine 9b

Following the general procedure described above, diethylaminomethyl-polystyrene (120 mg, 0.384 mmol, 3.2 mmol g^{-1}), 3-(trifluoromethyl)benzenesulfonyl chloride (31 mg, 0.128 mmol), 3-(pyrrolidin-2-yl)pyridine (18.9 mg, 0.128 mmol) and aminomethyl resin (91 mg, 0.256 mmol, 2.8 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (23.8 mg, 52%); ν_{max}/cm^{-1} 2929, 2876, 1429, 1325, 1170, 1105, 715 and 697; δ_H (400 MHz; $CDCl_3$) 1.75–2.00 (3H, m, C(3)-Ha, C(4)-H_2), 2.10–2.25 (1H, m, C(3)-Hb), 3.50–3.58 (1H, m, C(5)-Ha), 3.60–3.68 (1H, m, C(5)-Hb), 4.83 (1H, dd, *J* 7.8, 4.2, C(2)-H), 7.20 (1H, dd, *J* 7.9, 4.8, C(5′)-H), 7.58 (1H, d, *J* 7.9, C(4′)-H), 7.62 (1H, dd, *J* 8.0, 7.8, C(5″)-H), 7.81 (1H, d, *J* 7.8, C(4″)-H), 7.91 (1H, d, *J* 8.0, C(6″)-H), 7.94 (1H, s, C(2″)-H), 8.47 (1H, s, C(2′)-H), 8.48 (1H, d, *J* 4.8, C(6′)-H); δ_C (100 MHz; $CDCl_3$) 24.56 (C(4)H_2), 36.22 (C(3)H_2), 49.85 (C(5)H_2), 61.82 (C(2)H), 123.68 (C(5′)H), 124.67 (q, *J* 3.8, C(2″)H), 129.75 (q, *J* 3.4, C(4″)H), 130.28 (C(5″)H), 130.83 (C(6″)H), 132.15 (q, *J* 33.3, C(3″)), 134.36 (C(4′)H), 138.08 (C(3′)), 140.01 (C(1″)), 148.38 (C(6′)H), 149.21 (C(2′)H); MS(EI) *m*/*z* 356.08 (M^+).

Preparation of 3-{1-[5-(isoxazol-3-yl)-2-thienylsulfonyl]-pyrrolidin-2-yl}pyridine 9c

Following the general procedure described above, diethylaminomethyl-polystyrene (108 mg, 0.388 mmol, 3.2 mmol g^{-1}), 5-(isoxazol-3-yl)-2-thiophenesulfonyl chloride (29 mg, 0.116 mmol), 3-(pyrrolidin-2-yl)pyridine (17.2 mg, 0.116 mmol) and aminomethyl resin (83 mg, 0.232 mmol, 2.8 mmol g−1) in dichloromethane (4 mL) gave the title compound (23.5 mg, 56%); ν_{max}/cm^{-1} 2951, 2876, 1689, 1595, 1417, 1351, 1150, 1011, 806, 713 and 677; δ_H (400 MHz; $CDCl_3$) 1.75–1.85 (1H, m, C(4)-Ha), 1.85–2.00 (1H, m, C(3)-Ha and C(4)-Hb), 2.05–2.20 (1H, m, C(3)-Hb), 3.45–3.55 (1H, m, C(5)-Ha), 3.78–3.88 (1H, m, C(5)-Hb), 4.82 (1H, dd, *J* 8.3, 4.1, C(2)-H), 6.53 (1H, d, *J* 1.7, C(4‴)-H), 7.27 (1H, dd, *J* 7.9, 4.6, C(5′)-H), 7.48 (1H, d, *J* 3.9, C(4″)-H), 7.53 (1H, d, *J* 3.9, C(3″)-H), 7.72 (1H, d, *J* 7.9, C(4′)-H), 8.32 (1H, d, *J* 1.7, C(5‴)-H), 8.51 (1H, dd, *J* 4.6, 1.5, C(6′)-H), 8.32 (1H, d, *J* 1.5, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 24.04 (C(4)H_2), 35.64 (C(3)H_2), 49.78 (C(5)H_2), 61.72 (C(2)H), 100.55 (C(4‴)H), 123.37 (C(5′)H), 126.57 (C(4″)H), 132.69 (C(3″)H), 133.90 (C(4′)H), 134.72 (C(2″)), 137.89 (C(3′)), 139.47 (C(5″)), 147.88 (C(6′)H), 148.76 (C(2′)H), 150.90 (C(5‴)H), 162.38 (C(3‴)); MS(EI) *m*/*z* 361.06 (M^+).

Preparation of *N*-(4-bromophenyl)-2-(3-pyridyl)pyrrolidine-1-carboxamide 10a; general procedure for *N*-aryl-2-(3-pyridyl)-pyrrolidine-1-carboxamides

4-Bromophenyl isocyanate (26 mg, 0.132 mmol) was added to a solution of 3-(pyrrolidin-2-yl)pyridine (17 mg, 0.11 mmol) in dichloromethane (1.6 ml) and the mixture was stirred for 1 h. Amberlyst 15 was added to the solution and the mixture was shaken for 1 h. After filtration, the resin was suspended in 2 M solution of ammonia in methanol (5 ml) and shaken for 2 h. The resin was filtered off and washed thoroughly with a 2 M solution of ammonia in methanol. Evaporation of the solvent under reduced pressure and subsequent drying of the residue under high vacuum yielded the title compounds (42 mg, quant.); ν_{max}/cm^{-1} 3294, 2975, 1644, 1520, 1489, 1400, 1355, 1238, 819, 727 and 713; δ_H (400 MHz; $CDCl_3$) 1.85–1.94 (1H, m, C(3)-Ha), 1.95–2.04 (2H, m, C(4)-H_2), 2.35–2.46 (1H, m, C(3)-Hb), 3.62–3.74 (2H, m, C(5)-H_2), 5.05 (1H, br d, *J* 4.5, C(2)-H), 6.37 (1H, br s, N*H*Ph), 7.17 (2H, d, *J* 8.7, C(3″)-H and C(5″)-H), 7.24–7.31 (1H, m, C(5′)-H), 7.30 (2H, d, *J* 8.7, C(2″)-H and C(6″)-H), 7.55 (1H, d, *J* 7.4, C(4′)-H), 8.45–8.60 (2H, m, C(2′)-H and C(6′)-H); δ_C (100 MHz; $CDCl_3$) 23.54 (C(4)H_2), 35.40 (C(3)H_2), 47.23 (C(5)H_2), 59.04 (C(2)H), 115.45 (C(4″)), 121.19 (C(2″)H and C(6″)H), 123.64 (C(5′)H), 131.66 (C(3″)H and C(5″)H), 131.64 (C(1″)), 133.42 (C(4′)H), 137.94 (C(3′)), 147.50 (C(6′)H), 148.76 (C(2′)H), 153.70 (C=O); MS(EI) *m*/*z* 345.05 (M^+).

Preparation of *N*-(4-iodophenyl)-2-(3-pyridyl)pyrrolidine-1-carboxamide 10b

Following the general procedure described above, 4-iodophenyl isocyanate (28 mg, 0.113 mmol), 3-(pyrrolidin-2-yl)pyridine (14 mg, 0.094 mmol) and Amberlyst **15** in dichloromethane gave the title compound (32.6 mg, 88%); ν_{max}/cm^{-1} 3329, 2959, 1645, 1585, 1516, 1390, 1370, 1240, 812 and 709; δ_H (400 MHz; $CDCl_3$) 1.88–1.98 (1H, m, C(3)-Ha), 1.98–2.10 (2H, m, C(4)-H_2), 2.40–2.50 (1H, m, C(3)-Hb), 3.65–3.78 (2H, m, C(5)-H_2), 5.07 (1H, br s, C(2)-H), 6.19 (1H, br s, N*H*Ph), 7.07 (2H, d, *J* 8.4, C(3″)-H and C(5″)-H), 7.25–7.35 (1H, m, C(5′)-H), 7.51 (2H, d, *J* 8.4, C(2″)-H and C(6″)-H), 7.59 (1H, d, *J* 8.4, C(4′)-H), 8.40–8.70 (2H, m, C(2′)-H and C(6′)-H); δ_C (100 MHz;

$CDCl_3$) 23.54 (C(4)H_2), 38.96 (C(3)H_2), 47.25 (C(5)H_2), 57.33 (C(2)H), 85.78 (C(4″)), 121.37 (C(2″)H and C(6′)H), 125.30 (C(5′)H), 136.15 (C(4′)H), 137.65 (C(3″)H and C(5″)H), 138.60 (C(3′)), 143.50 (C(1″)), 147.46 (C(6′)H), 149.27 (C(2′)H), 153.54 (C=O); MS(EI) *m*/*z* 393.03 (M^+).

Preparation of *N*-(4-trifluoromethylphenyl)-2-(3-pyridyl)pyrrolidine-1-carboxamide 10c

Following the general procedure described above, 4-(trifluoromethyl)phenyl isocyanate (22 mg, 0.12 mmol), 3-(pyrrolidin-2-yl)pyridine (15 mg, 0.10 mmol) and Amberlyst 15 in dichloromethane gave the title compound (29 mg, 87%); ν_{max}/cm^{-1} 3305, 2976, 1711, 1652, 1528, 1412, 1320, 1112, 1064, 731 and 715; δ_H (400 MHz; $CDCl_3$) 1.86–1.95 (1H, m, C(3)-Ha), 1.95–2.15 (2H, m, C(4)-H_2), 2.35–2.48 (1H, m, C(3)-Hb), 3.65–3.78 (2H, m, C(5)-H_2), 5.08 (1H, br s, C(2)-H), 6.63 (1H, br s, N*H*Ph), 7.23–7.33 (1H, m, C(5′)-H), 7.39 (2H, d, *J* 8.6, C(3″)-H and C(5″)-H), 7.44 (2H, d, *J* 8.6, C(2″)-H and C(6″)-H), 7.57 (1H, d, *J* 6.9, C(4′)-H), 8.40–8.70 (2H, m, C(2′)-H and C(6′)-H); δ_C (100 MHz; $CDCl_3$) 23.96 (C(4)H_2), 35.77 (C(3)H_2), 47.71 (C(5)H_2), 59.56 (C(2)H), 119.29 (C(2″)H and C(6″)H), 123.28 (C(4′)H), 125.07 (q, *J* 32.4, C(4″)), 126.42 (q, *J* 3.8, C(3″)H and C(5″)H), 133.86 (C(4′)H), 138.26 (C(3′)), 142.44 (C(1″)), 147.73 (C(6′)H), 149.14 (C(2′)H), 153.92 (C=O); MS(EI) *m*/*z* 335.12 (M^+).

Preparation of *N*-[3-(methylthio)phenyl]-2-(3-pyridyl)-pyrrolidine-1-carboxamide 10d

Following the general procedure described above, 3-(methylthio)phenyl isocyanate (20 mg, 0.12 mmol), 3-(pyrrolidin-2-yl)pyridine (15 mg, 0.10 mmol) and Amberlyst 15 in dichloromethane gave the title compound (30 mg, 96%); ν_{max}/cm^{-1} 3281, 2977, 2871, 1661, 1593, 1532, 1480, 1346, 780, 714 and 687; δ_H (400 MHz; $CDCl_3$) 1.90–1.98 (1H, m, C(3)-Ha), 1.98–2.10 (2H, m, C(4)-H_2), 2.38–2.48 (1H, m, C(3)-Hb), 2.43 (3H, s, SCH_3), 3.66–3.78 (2H, m, C(5)-H_2), 5.07 (1H, dd, *J* 4.6, 3.0, C(2)-H), 6.17 (1H, br s, N*H*Ph), 6.88 (1H, d, *J* 7.5, C(4″)-H), 6.97 (1H, d, *J* 7.8, C(6″)-H), 7.12 (1H, dd, *J* 7.8, 7.5, C(5″)-H), 7.28 (1H, dd, *J* 7.2, 4.9, C(5′)-H), 7.32 (1H, s, C(2″)H), 7.58 (1H, d, *J* 7.2, C(4′)-H), 8.53 (1H, d, *J* 4.9, C(6′)-H), 8.57 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 15.72 (s, S*C*H_3), 23.51 (C(4)H_2), 35.53 (C(3)H_2), 47.24 (C(5)H_2), 59.00 (C(2)H), 116.12 (C(6″)H), 117.37 (C(2″)H), 121.20 (C(4″)H), 123.65 (C(5′)H), 129.03 (C(5″)H), 133.37 (C(4′)H), 134.61 (C(3″)), 138.47 (C(3′)), 139.37 (C(1″)), 147.60 (C(6′)H), 148.88 (C(2′)H), 153.74 (C=O); MS(EI) *m*/*z* 313.12 (M^+).

Preparation of (±)-nicotine 2

Formaldehyde (1 ml, 37% solution in water) was added into a suspension of polymer-supported cyanoborohydride (180 mg, 0.86 mmol, 4.62 mmol g^{-1}) and 3-(pyrrolidin-2-yl)pyridine (14.5 mg, 0.097 mmol). The mixture was stirred for 4 h. The resin was filtered off and washed thoroughly with methanol, the solvent was concentrated under reduced pressure and the residue re-dissolved in dichloromethane. Amberlyst 15 was added to the solution and the mixture was shaken for 1 h. After filtration, the resin was suspended in 5 ml of 2 M solution of ammonia in methanol and shaken for 2 h. The resin was filtered off and washed thoroughly with 2 M solution of ammonia in methanol. Evaporation of the solvent under reduced pressure and subsequent drying of the residue under high vacuum afforded the title compound (13.9 mmol, 88%) as a colourless oil. The structure of this product was confirmed by comparison with an authentic sample.

Preparation of 3-[1-(4-nitrobenzyl)pyrrolidin-2-yl]pyridine 11a

To a solution of 3-(pyrrolidin-2-yl)pyridine (16 mg, 0.11 mmol) in dichloromethane (1.5 ml) was added 4-nitrobenzaldehyde (100 mg, 0.66 mmol) and a spatula tip of magnesium sulfate. The mixture was stirred for 5 min, then polymer-supported cyanoborohydride (70 mg, 0.33 mmol, 4.6 mmol g^{-1}) was added and the mixture stirred for a further 2 h. The solution was filtered through a pad of silica and washed thoroughly with dichloromethane. The solvent was concentrated under reduced pressure and the residue re-dissolved in dichloromethane. Amberlyst 15 was added to the solution and the mixture was shaken for 1 h. After filtration, the resin was suspended in a 2 M solution of ammonia in methanol (5 ml) and shaken for 2 h. The resin was filtered off and washed thoroughly with 2 M solution of ammonia in methanol (20 ml). Evaporation of the solvent under reduced pressure and subsequent drying of the residue under high vacuum afforded the title compound (25 mg, 80%) as an orange oil; LC-MS: 3.36 min (284.35 $[M + H]^+$), ν_{max}/cm^{-1} 2965, 2807, 1599, 1516, 1350, 1109, 855, 807 and 716; δ_H (400 MHz; $CDCl_3$) 1.70–2.00 (3H, m, C(3)-Ha and C(4)-H_2), 2.20–2.32 (2H, m, C(3)-Hb and C(5)-Ha), 3.10 (1H, td, *J* 8.6, 2.5, C(5)-Hb), 3.26 (1H, d, *J* 14.0, NC*Ha*Ph), 3.48 (1H, dd, *J* 8.3, 8.0, C(2)-H), 3.86 (1H, d, *J* 14.0, NC*Hb*Ph), 7.28 (1H, dd, *J* 7.8, 4.8, C(5′)-H), 7.43 (2H, d, *J* 8.5, C(2″)-H and C(6″)-H), 7.78 (1H, d, *J* 7.8, C(4′)-H), 8.13 (2H, d, *J* 8.5, C(3″)-H and C(5″)-H), 8.50 (1H, dd, *J* 4.8, 1.3, C(6′)-H), 8.64 (1H, d, *J* 1.3, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.68 (C(4)H_2), 35.14 (C(3)H_2), 53.70 (C(5)H_2), 57.61, (N*C*H_2Ph), 67.23 (C(2)H), 123.46 (C(3″)H and C(5″)H), 123.68 (C(5′)H), 128.97 (C(2″)H and C(6″)H), 134.98 (C(4′)H), 138.91 (C(3′)), 147.02 (C(1″)), 147.27 (C(4″)), 148.78 (C(6′)H), 149.43 (C(2′)H); MS(EI) *m*/*z* 283.13 (M^+).

Preparation of 1-(6-chloronicotinyl)-2-(3-pyridyl)pyrrolidine 12a; general procedure for 1-acyl-2-(3-pyridyl)pyrrolidine

Diethylaminomethyl-polystyrene (128 mg, 0.385 mmol, 3.0 mmol g^{-1}) was suspended in dichloromethane (1 ml) and stirred for 10 min. A solution of 6-chloronicotinoyl chloride (22.5 mg, 0.128 mmol) in dichloromethane (0.4 mL) was added and the mixture was stirred at ambient temperature for 5 min. A solution of 3-(pyrrolidin-2-yl)pyridine (19 mg, 0.128 mmol) in dichloromethane (1 ml) was added dropwise and the mixture stirred until disappearance of the starting material was observed by TLC (1–2 h). Aminomethyl resin (92 mg, 0.258 mmol, 2.8 mmol g^{-1}) was added and the mixture was stirred for a further 1 h. The mixture was filtered through a small pad of silica washing thoroughly with dichloromethane. Evaporation of the solvent under reduced pressure yielded the title compound (34 mg, 92%); ν_{max}/cm^{-1} 2973, 1630, 1584, 1413, 1103 and 715; δ_H (400 MHz; $CDCl_3$) 1.90–2.20 (3H, m, C(3)-Ha and C(4)-H_2), 2.35–2.55 (1H, m, C(3)-Hb), 3.60–3.90 (2H, m, C(5)-H_2), 5.28 (1H, br s, C(2)-H), 7.26 (1H, br s, C(5′)-H), 7.39 (1H, d, *J* 7.5, C(5″)-H), 7.61 (1H, d, *J* 6.6, C(4′)-H), 7.87 (1H, d, *J* 7.5, C(4″)-H), 8.20–8.30 (1H, m, C(6′)-H), 8.50 (1H, s, C(2′)-H), 8.62 (1H, s, C(2″)-H); δ_C (100 MHz; $CDCl_3$) 25.41 (C(4)H_2), 34.41 (C(3)H_2), 51.01 (C(5)H_2), 59.64 (C(2)H), 123.51 (C(5′)H), 124.20 (C(5″)H), 130.98 (C(1″)), 133.65 (C(4′)H), 137.11 (C(3′)), 138.10 (C(4″)), 147.64 (C(6′)H), 148.52 (C(2′)H), 149.07 (C(2″)H), 153.21 (C(4″)H), 166.45 (C=O); MS(EI) *m*/*z* 287.08 (M^+).

Preparation of 1-(4-nitrobenzoyl)-2-(3-pyridyl)pyrrolidine 12b

Following the general procedure described above, diethylaminomethyl-polystyrene (47 mg, 0.15 mmol, 3.2 mmol g^{-1}), 4-nitrobenzoyl chloride (9.3 mg, 0.05 mmol), 3-(pyrrolidin-2-yl)pyridine (7.4 mg, 0.05 mmol) and aminomethyl resin (36 mg, 0.10 mmol, 2.8 mmol g^{-1}) in dichloromethane gave the title compound (15 mg, quant.); ν_{max}/cm^{-1} 2980, 1632, 1520, 1419, 1349, 1045, 1020, 855, 749 and 710; δ_H (400 MHz; $CDCl_3$) 1.90–2.15 (3H, m, C(3)-Ha and C(4)-H_2), 2.40–2.55 (1H, m, C(3)-Hb), 3.55–3.65 (1H, m, C(5)-Ha), 3.70–3.80 (1H, m,

C(5)-Ha), 5.32 (1H, t, *J* 6.5, C(2)-H), 7.25–7.35 (1H, m, C(5′)-H), 7.66 (1H, d, *J* 7.5, C(4′)-H), 7.74 (2H, d, *J* 8.3, C(2″)-H and C(6″)-H), 8.29 (2H, d, *J* 8.3, C(3″)-H and C(5″)-H), 8.53 (1H, d, *J* 3.8, C(6′)-H), 8.64 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 25.25 (C(4)H_2), 34.38 (C(3)H_2), 50.85 (C(5)H_2), 59.44 (C(2)H), 123.56 (C(3″)H and C(5″)H), 123.73 (C(5′)H), 128.38 (C(2″)H and C(6″)H), 133.94 (C(4′)H), 138.10 (C(3′)), 147.30 (C(6′)H), 148.27 (C(2′)H), 168.80 (C=O); MS(EI) *m*/*z* 297.11 (M^+).

Preparation of 1-(2-naphthoyl)-2-(3-pyridyl)pyrrolidine 12c

Following the general procedure described above, diethylaminomethyl-polystyrene (74 mg, 0.237 mmol, 3.2 mmol g^{-1}), 2-naphthoyl chloride (15 mg, 0.078 mmol), 3-(pyrrolidin-2-yl)pyridine (11.7 mg, 0078 mmol) and aminomethyl resin (55 mg, 0.156 mmol, 2.8 mmol g^{-1}) in dichloromethane gave the title compound (22.5 mg, 95%); ν_{max}/cm^{-1} 2973, 2872, 1620, 1471, 1403, 755 and 715; δ_H (400 MHz; $CDCl_3$) 1.85–2.25 (3H, m, C(3)-Ha and C(4)-H_2), 2.45–2.55 (1H, m, C(3)-Hb), 3.71 (1H, br s, C(5)-Ha), 3.85 (1H, br s, C(5)-Hb), 5.38 (1H, br s, C(2)-H), 7.20–8.10 (9H, m, C(4′)-H, C(5′)-H and NC(O)C10*H7*), 8.47 (1H, br s, C(6′)-H), 8.68 (1H, br s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 25.38 (C(4)H_2), 34.58 (C(3)H_2), 51.18 (C(5)H_2), 59.23 (C(2)H), 123.61 (C(5′)H), 124.42 (C(9″)H), 126.68, 127.05, 127.29 and 127.76 (C(2″)H, C(3″)H, C(7″)H and C(8″)H), 128.56 (C(6″)H), 133.78 (C(4′)H), 139.79 (C(3′)), 147.33 (C(6′)H), 148.19 (C(2′)H), 170.19 (C=O); MS(EI) *m*/*z* 302.14 (M^+).

Preparation of *N*-methoxy-*N*-methylnicotinamide 13a

To a cooled (0 °C) stirred solution of nicotinic acid (26.5 g, 215 mmol), *N,O*-dimethylhydroxylamine hydrochloride (23.1 g, 237 mmol) and triethylamine (24.0 g, 237 mmol) in dichloromethane (200 mL) was added 1,3-dichlorocyclohexylcarbodiimide (48.9 g, 237 mmol) and stirred at ambient temperature overnight. To the reaction mixture was added *n*-hexane (400 mL) and the insoluble matter was filtered off and washed with *n*-hexane. The combined filtrates were concentrated under reduced pressure and the residue was re-dissolved in *n*-hexane (200 mL). The insoluble matter was filtered off and washed with *n*-hexane. The combined filtrates were concentrated under reduced pressure to yield the title compound (30.6 g, 85%) as a colorless oil; ν_{max}/cm^{-1} 2928, 2853, 2110, 1646, 1449, 1025, 890 and 725; δ_H (400 MHz; $CDCl_3$) 3.32 (3H, s, NCH_3), 3.49 (3H, s, OCH_3), 7.28 (1H, dd, *J* 7.8, 4.8, C(5)-H), 7.95 (1H, dd, *J* 7.8, 1.5, C(4)-H), 8.61 (1H, d, *J* 4.8, C(6)-H), 8.88 (1H, s, C(2)-H); δ_C (100 MHz; $CDCl_3$) 33.50 (N*C*H_3), 61.61 (O*C*H_3), 123.31 (C(5)H), 130.26 (C(3)), 136.42 (C(4)H), 149.69 (C(2)H), 151.75 (C(6)H), 167.81 (C=O); MS(EI) *m*/*z* 166.07 (M^+).

Preparation of *N*-methoxy-*N*-methyl-6-chloronicotinamide 13b

To a cooled (0 °C) stirred solution of 6-chloronicotinoyl chloride (1.76 g, 10 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.07 g, 11 mmol) in chloroform (25 mL) was added dropwise pyridine (1.74 g, 22 mmol) and the mixture was stirred for 1 h at ambient temperature. The reaction mixture was concentrated under reduced pressure and the residue was suspended in ethyl acetate (25 mL). The insoluble matter was filtered off and washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure to yield the title compound (2.00 g, quant.) as a pale yellow oil; ν_{max}/cm^{-1} 2937, 1639, 1584, 1105, 976 and 753; δ_H (400 MHz; $CDCl_3$) 3.32 (3H, s, NCH_3), 3.50 (3H, s, OCH_3), 7.32 (1H, d, *J* 8.3, C(5)-H), 7.95 (1H, dd, *J* 8.3, 2.2, C(4)-H), 8.70 (1H, d, *J* 2.2, C(2)-H); δ_C (100 MHz; $CDCl_3$) 33.50 (N*C*H_3), 61.76 (O*C*H_3), 124.16 (C(5)H), 128.96 (C(3)), 139.46 (C(4)H), 150.12 (C(2)H), 153.76 (C(6)), 166.59 (C=O); MS(EI) *m*/*z* 200.04 (M^+) and 202.03 ($[M + 2]^+$).

Preparation of 3-(4,4-dimethoxy-1-oxobutyl)pyridine 15a

To a stirred suspension of magnesium turnings (2.43 g, 100 mmol) in anhydrous THF (25 mL) was added dropwise a solution of 3-bromopropionaldehyde dimethyl acetal (20.4 g, 100 mmol) in anhydrous THF (100 mL) at ambient temperature. The suspension was stirred for 1 h to give Grignard reagent. A solution of *N*-methoxy-*N*-methylnicotinamide (8.31 g, 50 mmol) in anhydrous THF (40 mL) was cooled to −78 °C and preformed Grignard reagent was slowly added. The reaction mixture was stirred for 1 h, warmed to ambient temperature in 30 min and stirred overnight. To the resulting solution was added polymer supported carboxylic acid (Amberlite IRC-50, ~10 g) and shaken at ambient temperature for 2 h. The resin was filtered off through Celite and washed thoroughly with dichloromethane. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in dichloromethane and filtered through a small pad of silica gel. The combined filtrates were concentrated under reduced pressure to yield the title compound (8.0 g, 77%) as a pale yellow oil; ν_{max}/cm^{-1} 3325, 2927, 2850, 1690, 1624, 1585, 1571, 1125, 1050 and 704; δ_H (400 MHz; $CDCl_3$) 2.04 (2H, td, *J* 7.2, 5.4, CH_2CH(OMe)$_2$), 3.03 (2H, t, *J* 7.2, PyC(=O)CH_2), 3.30 (6H, s, CH_3 × 2), 4.43 (1H, t, *J* 5.4, C*H*(OMe)$_2$), 7.38 (1H, dd, *J* 7.9, 4.8, C(5)-H), 8.19 (1H, dt, *J* 7.9, 1.7, C(4)-H), 8.73 (1H, dd, *J* 4.8, 1.7, C(6)-H), 9.14 (1H, d, *J* 1.7, C(2)-H); δ_C (100 MHz; $CDCl_3$) 27.13 (*C*H_2CH(OMe)$_2$), 33.83 (PyC(=O)*C*H_2), 53.73 (O*C*H_3 × 2), 104.11 (*C*H(OMe)$_2$), 123.91 (C(5)H), 132.49 (C(3)), 135.62 (C(4)H), 149.94 (C(2)H), 153.74 (C(6)H), 198.75 (C=O); MS(ESI) *m*/*z* 210.10 ($[M + 1]^+$).

Preparation of 6-chloro-3-(4,4-dimethoxy-1-oxobutyl)pyridine 15b

To a stirred suspension of magnesium turnings (0.24 g, 10 mmol) in anhydrous THF (3 mL) was added dropwise a solution of 3-bromopropionaldehyde dimethyl acetal (1.83 g, 10 mmol) in anhydrous THF (10 mL) at ambient temperature. The suspension was stirred for 1 h to give Grignard reagent. A solution of *N*-methoxy-*N*-methyl-6-chloronicotinamide (1.0 g, 5 mmol) in anhydrous THF (5 mL) was cooled to −78 °C and preformed Grignard reagent was slowly added. The reaction mixture was stirred for 1 h, warmed to ambient temperature over 30 min and then stirred overnight. To the resulting solution was added polymer-supported carboxylic acid (Amberlite IRC-50, ~1 g) and shaken at ambient temperature for 2 h. The resin was filtered off through Celite and washed thoroughly with dichloromethane. The combined filtrates were concentrated under reduced pressure. The residue was dissolved in dichloromethane and filtered through a small pad of silica gel. The combined filtrates were concentrated under reduced pressure to yield the title compound (1.21 g, quant.) as a pale yellow oil; ν_{max}/cm^{-1} 2939, 2832, 1692, 1580, 1362, 1125, 1105, 1055, 989 and 837; δ_H (400 MHz; $CDCl_3$) 2.01 (2H, dt, *J* 7.2, 5.3, CH_2CH(OMe)$_2$), 2.97 (2H, t, *J* 7.2, PyC(=O)CH_2), 3.28 (6H, s, OCH_3 × 2), 4.39 (1H, t, *J* 5.3, C*H*(OMe)$_2$), 7.67 (1H, d, *J* 8.3, C(5)-H), 8.13 (1H, dd, *J* 8.3, 2.4, C(4)-H), 8.88 (1H, d, *J* 2.4, C(2)-H); δ_C (100 MHz; $CDCl_3$) 26.78 (*C*H_2CH(OMe)$_2$), 33.47 (PyC(=O)*C*H_2), 53.49 (O*C*H_3 × 2), 103.69 (*C*H(OMe)$_2$), 124.46 (C(5)H), 131.06 (C(3)), 137.98 (C(4)H), 149.86 (C(2)H), 155.54 (C(6)), 197.21 (C=O); MS(ESI) *m*/*z* 244.1 ($[M + 1]^+$) and 246.0 ($[M + 3]^+$).

Preparation of 4-(3-pyridyl)-4-oxobutyraldehyde 16a

A mixture of 3-(4,4-dimethoxy-1-oxobutyl)pyridine (1.05 g, 5 mmol), Amberlyst 15 (~1.0 g), and water (1 ml) in acetone (10 mL) was shaken at ambient temperature for 4 h. The resin was filtered and washed with acetone. A suspension of washed resin and triethylamine (0.5 g) in dichloromethane (10 mL) was shaken at ambient temperature for 2 h. The resin was filtered

off through a small pad of silica gel and washed with dichloromethane. The combined filtrates were concentrated under reduced pressure to yield the title compound 4-(3-pyridyl)-4-oxobutyraldehyde (0.66 g, 81%) as a pale yellow oil; ν_{max}/cm^{-1} 3259, 2975, 2936, 2738, 2675, 2490, 1687, 1586, 1475, 1397, 1170, 1035, 804 and 704; δ_H (400 MHz; $CDCl_3$) 2.85–2.95 (2H, m, CH_2C(=O)H), 3.26 (2H, t, *J* 6.5, PyC(=O)CH_2), 7.38 (1H, dd, *J* 7.7, 4.9, C(5)-H), 8.15–8.25 (1H, m, C(4)-H), 8.72 (1H, dd, *J* 4.7, 1.4, C(6)-H), 9.14 (1H, s, C(2)-H), 9.84 (1H, s, C(=O)*H*); δ_C (100 MHz; $CDCl_3$) 31.18 (PyC(=O)*C*H$_2$), 37.30 (*C*H$_2$C(=O)H), 123.65 (C(5)H), 131.71 (C(3)), 135.35 (C(4)H), 149.51 (C(2)H), 153.63 (C(6)H), 196.72 (Py*C*=O), 200.06 (*C*(=O)H); MS(EI) *m*/*z* 163.06 (M$^+$).

Preparation of 4-(6-chloropyridin-3-yl)-4-oxobutyraldehyde 16b

A mixture of 6-chloro-3-(4,4-dimethoxy-1-oxobutyl)pyridine (121 mg, 0.5 mmol), Amberlyst 15 (120 mg), and water (0.018 g) in acetone (2 mL) was shaken at ambient temperature for 4 h. The resin was filtered off and washed with acetone. The combined filtrates were concentrated under reduced pressure to yield the title compound 4-(3-pyridyl)-4-oxobutyraldehyde (96 mg, 97%) as a pale yellow oil; ν_{max}/cm^{-1} 2913, 2830, 2728, 1717, 1689, 1579, 1368, 1105, 981, 836 and 739; δ_H (400 MHz; $CDCl_3$) 2.89 (2H, t, *J* 6.1, CH_2C(=O)H), 3.21 (2H, t, *J* 6.1, PyC(=O)CH_2), 7.38 (1H, d, *J* 8.3, C(5)-H), 8.13 (1H, dd, *J* 8.3, 2.3, C(4)-H), 8.89 (1H, d, *J* 2.3, C(2)-H), 9.80 (1H, s, C(=O)*H*); δ_C (100 MHz; $CDCl_3$) 35.58 (PyC(=O)*C*H$_2$), 37.65 (*C*H$_2$C(=O)H), 124.94 (C(5)H), 131.06 (C(3)), 138.41 (C(4)H), 150.18 (C(2)H), 156.10 (C(6)), 195.97 (Py*C*=O), 200.31 (*C*(=O)H); MS(EI) *m*/*z* 197.02 (M$^+$).

Preparation of 3-(1-methylpyrrolidin-2-yl)pyridine 2; general procedure for 3-(1-substitutedpyrrolidin-2-yl)pyridine

To a cooled (−78 °C), stirred suspension of 4-(3-pyridyl)-4-oxobutyraldehyde (0.22 g, 1.35 mmol), acetic acid (0.2 mL) and sodium triacetoxyborohydride (0.573 g, 2.70 mmol) in dichloromethane (4 mL) was added a solution of methylamine (1.35 mL, 2.7 mmol of 2.0 M solution in THF). The reaction mixture was stirred at −78 °C for 1 h, warmed to ambient temperature in 30 min and stirred overnight. The reaction mixture was filtered through a small pad of silica gel and washed with dichloromethane. To the combined filtrates were added Amberlyst 15 (~1.0 g) and shaken at ambient temperature for 1 h. The resin was filtered and washed with dichloromethane. A suspension of washed resin and triethylamine (0.50 g) in dichloromethane (10 mL) was shaken at ambient temperature for 1 h. The resin was filtered off and washed with dichloromethane. The combined filtrates were concentrated under reduced pressure to yield the title compound (100 mg, 46%) as a pale yellow oil; ν_{max}/cm^{-1} 2928, 2853, 2110, 1646, 1449, 1025, 890 and 725; δ_H (400 MHz; $CDCl_3$) 1.65–1.75 (1H, m, C(3)-Ha), 1.75–1.85 (1H, m, C(4)-Ha), 1.90–2.00 (1H, m, C(4)-Hb), 2.15–2.25 (1H, m, C(3)-Hb), 2.16 (3H, s, NCH_3), 2.30 (1H, q, *J* 8.9, C(5)-Ha), 3.07 (1H, t, *J* 8.3, C(2)-H), 3.23 (1H, t, *J* 8.9, C(5)-Hb), 7.24 (1H, dd, *J* 7.9, 4.9, C(5′)-H), 7.69 (1H, d, *J* 7.9, C(4′)-H), 8.48 (1H, d, *J* 4.9, C(6′)-H), 8.52 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 23.02 (C(4)H$_2$), 35.61 (C(3)H$_2$), 40.77 (N*C*H$_3$), 57.41 (C(5)H$_2$), 69.28 (C(2)), 123.97 (C(5′)H), 135.24 (C(4′)H), 139.17 (C(3′)), 149.01 (C(6′)H), 149.96 (C(2′)H); MS(EI) *m*/*z* 162.12 (M$^+$).

Preparation of 3-(1-ethylpyrrolidin-2-yl)pyridine 11b

Following the general procedure described above, ethylamine (68 mg, 1.5 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (163 mg, 1.0 mmol), acetic acid (0.2 mL) and sodium triacetoxyborohydride (0.424 g, 2.0 mmol) in dichloromethane (4 mL) gave the title compound (145 mg, 84%); ν_{max}/cm^{-1} 2969, 2937, 1712, 1578, 1427, 1366, 1261, 1025, 808 and 720; δ_H (400 MHz; $CDCl_3$) 1.11 (3H, t, *J* 7.4, NCH$_2$CH_3), 1.88–2.00 (2H, m, C(3)-Ha and C(4)-Ha), 2.05–2.15 (1H, m, C(4)-Hb), 2.22–2.35 (2H, m, C(3)-Hb and NC*Ha*CH$_3$), 2.47 (1H, dd, *J* 17.8, 8.7, C(5)-Ha), 2.71 (1H, dt, *J* 19.5, 7.4, NC*Hb*CH$_3$), 3.45–3.60 (2H, m, C(2)-H and C(5)-Hb), 7.37 (1H, dd, *J* 7.7, 4.9, C(5′)-H), 7.98 (1H, d, *J* 7.7, C(4′)-H), 8.56 (1H, d, *J* 4.9, C(6′)-H), 8.59 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 13.11 (NCH$_2$*C*H$_3$), 22.53 (C(4)H$_2$), 34.45 (C(3)H$_2$), 48.33 (N*C*H$_2$CH$_3$), 53.16 (C(5)H$_2$), 68.07 (C(2)), 124.46 (C(5′)H), 136.54 (C(4′)H), 148.67 (C(6′)H), 149.26 (C(2′)H); MS(EI) *m*/*z* 176.13 (M$^+$).

Preparation of 3-[1-(2-fluoroethyl)pyrrolidin-2-yl]pyridine 11c

Following the general procedure described above, 2-fluoroethylamine hydrochloride (149 mg, 1.5 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (163 mg, 1.0 mmol), acetic acid (0.2 mL) and sodium triacetoxyborohydride (0.424 g, 2.0 mmol) in dichloromethane (4 mL) gave the title compound (90 mg, 46%); ν_{max}/cm^{-1} 2973, 2940, 2676, 1712, 1428, 1364, 1263, 1026, 806 and 720; δ_H (400 MHz; $CDCl_3$) 1.60–1.70 (1H, m, C(3)-Ha), 1.80–1.90 (1H, m, C(4)-Ha), 1.90–2.00 (1H, m, C(4)-Hb), 2.10–2.22 (1H, m, C(3)-Hb), 2.39 (1H, q, *J* 8.9, C(5)-Ha), 2.40–2.55 (1H, m, NC*Ha*CH$_2$F), 2.76 (1H, ddt, *J* 29.5, 13.9, 5.1, NC*Hb*CH$_2$F), 3.35–3.45 (2H, m, C(2)-H and C(5)-Hb), 4.40 (2H, dt, *J* 47.5, 5.1, NCHCH_2F), 7.27 (1H, dd, *J* 8.0, 3.8, C(5′)-H), 7.78 (1H, d, *J* 8.0, C(4′)-H), 8.45 (1H, br s, C(6′)-H), 8.51 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 23.22 (C(4)H$_2$), 35.13 (C(3)H$_2$), 54.01 (d, *J* 20.1, N*C*H$_2$CH$_2$F), 54.63 (C(5)H$_2$), 67.76 (C(2)H), 83.06 (d, *J* 166.9, NCH$_2$*C*H$_2$F), 124.37 (C(5′)H), 136.24 (C(4′)H), 139.63 (C(3′)), 148.09 (C(6′)H), 148.83 (C(2′)H); MS(EI) *m*/*z* 194.12 (M$^+$).

Preparation of 3-[1-(2-methoxyethyl)pyrrolidin-2-yl]pyridine 11d

Following the general procedure described above, 2-methoxyethylamine (113 mg, 1.5 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (163 mg, 1.0 mmol), acetic acid (0.2 mL) and sodium triacetoxyborohydride (0.424 g, 2.0 mmol) in dichloromethane (4 mL) gave the title compound (90 mg, 44%); ν_{max}/cm^{-1} 2932, 2874, 2809, 1577, 1426, 1130, 1025, 808 and 717; δ_H (400 MHz; $CDCl_3$) 1.56–16.7 (1H, m, C(3)-Ha), 1.72–1.82 (1H, m, C(4)-Ha), 1.84–1.96 (1H, m, C(4)-Hb), 2.05–2.16 (1H, m, C(3)-Hb), 2.23–2.32 (2H, m, C(5)-Ha and NC*Ha*CH$_2$OCH$_3$), 2.66 (1H, dt, *J* 12.8, 6.2, C(5)-Hb), 3.18 (3H, s, OCH_3), 3.25–3.38 (4H, m, C(2)-H and NC*Hb*CH$_2$OCH$_3$), 7.20 (1H, dd, *J* 7.8 and 4.8, C(5′)-H), 7.69 (1H, d, *J* 7.8, C(4′)-H), 8.42 (1H, d, *J* 4.8, C(6′)-H), 8.49 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.76 (C(4)H$_2$), 34.92 (C(3)H$_2$), 53.59 (C(5)H$_2$), 54.39 (O*C*H$_3$), 58.62 (N*C*H$_2$CH$_2$OCH$_3$), 67.67 (C(2)H), 71.42 (NCH$_2$*C*H$_2$OCH$_3$), 123.66 (C(5′)H), 135.24 (C(4′)H), 139.50 (C(3′)), 148.09 (C(6′)H), 149.08 (C(2′)H); MS(EI) *m*/*z* 206.14 (M+).

Preparation of 3-[1-(2-methylpropyl)pyrrolidin-2-yl]pyridine 11e

Following the general procedure described above, isobutylamine (110 mg, 1.5 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (163 mg, 1.0 mmol), acetic acid (0.2 mL) and sodium triacetoxyborohydride (0.424 g, 2.0 mmol) in dichloromethane (4 mL) gave the title compound (90 mg, 44%); ν_{max}/cm^{-1} 2953, 2926, 2870, 1727, 1577, 1466, 1426, 1081, 805 and 720; δ_H (400 MHz; $CDCl_3$) 0.76 and 0.85 (3H × 2, d × 2, *J* 6.5, CH(CH_3)$_2$), 1.55–1.75 (3H, m, C(3)-Ha, C(4)-Ha and C*H*(CH$_3$)$_2$), 1.75–1.85 (1H, m, C(4)-Hb), 1.85–2.20 (4H, m, C(3)-Hb, C(5)-Ha and NCH_2C*H*(CH$_3$)$_2$), 3.25 (1H, t, *J* 8.1, C(2)-H), 3.31 (1H, br t, *J* 7.9, C(5)-Hb), 7.23 (1H, dd, *J* 7.4, 4.9, C(5′)-H), 7.71 (1H, d, *J* 7.4, C(4′)-H), 8.47 (1H, br s, C(6′)-H), 8.54 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 20.28 and 21.18 (NCH$_2$CH(*C*H$_3$)$_2$), 22.86 (C(4)H$_2$), 27.37 (NCH$_2$*C*H(CH$_3$)$_2$), 35.37 (C(3)H$_2$), 53.56 (C(5)H$_2$), 62.88 (N*C*H$_2$CH(CH$_3$)$_2$), 67.78

(C(2)H), 123.42 (C(5′)H), 135.02 (C(4′)H), 140.12 (C(3′)), 148.26 (C(6′)H), 149.53 (C(2′)H); MS(EI) *m*/*z* 204.16 (M^+).

Preparation of 3-(1-benzylpyrrolidin-2-yl)pyridine (11f)

Following the general procedure described above, benzylamine (150 mg, 1.23 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (100 mg, 0.61 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.37 g, 1.23 mmol, 3.0 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (80 mg, 55%); ν_{max}/cm^{-1} 2923, 1656, 1454, 1426, 1026 and 715; δ_H (400 MHz; $CDCl_3$) 1.65–1.95 (3H, m, C(3)-Ha and C(4)-H_2), 2.10–2.30 (2H, m, C(3)-Hb and C(5)-Ha), 3.05–3.15 (2H, m, C(5)-Hb and NC*Ha*Ph), 3.35–3.45 (1H, m, C(2)-H), 3.74 (1H, d, *J* 13.1, NC*Hb*Ph), 7.10–7.25 (6H, m, C(5′)-H and NCH_2C6H5), 7.81 (1H, br s, C(4′)-H), 8.43 (1H, d, *J* 3.8, C(6′)-H), 8.56 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.45 (C(4)H_2), 32.91 (C(3)H_2), 53.41 (C(5)H_2), 65.81 (N*C*H_2Ph), 66.94 (C(2)H), 123.61 (s, C(5′)H), 128.12, 128.58 and 128.99 (C(2″)H, C(3″)H, C(4″)H, C(5″)H and C(2″)H), 135.01 (C(4′)H), 148.57 (C(6′)H), 149.60 (C(2′)H); MS(EI) *m*/*z* 283.15 (M^+).

Preparation of 3-[1-(4-methoxybenzyl)pyrrolidin-2-yl]pyridine 11g

Following the general procedure described above, 4-methoxybenzylamine (0.169 g, 1.23 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (100 mg, 0.61 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.37 g, 1.23 mmol, 3.0 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (70 mg, 43%); ν_{max}/cm^{-1} 2932, 1611, 1511, 1250, 1174, 1030, 810 and 716; δ_H (400 MHz; $CDCl_3$) 1.65–2.15 (3H, m, C(3)-Ha and C(4)-H_2), 2.15–2.35 (2H, m, C(3)-Hb and C(5)-Ha), 3.05–3.20 (1H, m, C(5)-Hb), 3.43 (1H, d, *J* 12.9, NC*Ha*Ph), 3.51 (1H, br s, C(2)-H), 3.74 (1H, d, *J* 12.9, NC*Hb*Ph), 3.80 (3H, s, C_6H_5–O*C*H_3), 6.84 (2H, d, *J* 8.3, C(3″)-H and C(5″)-H), 7.18 (2H, d, *J* 8.3, C(2″)-H and C(6″)-H), 7.24–7.34 (1H, m, C(5′)-H), 7.83 (1H, d, *J* 6.3, C(4′)-H), 8.52 (1H, d, *J* 3.4, C(6′)-H), 8.65 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.88 (C(4)H_2), 35.67 (C(3)H_2), 53.76 (C(5)H_2), 55.65 (PhO*C*H_3), 57.35 (N*C*H_2Ph), 67.18 (C(2)H), 113.96 (C(3″)H and C(5″)H), 123.99 (s, C(5′)H), 130.15 (C(2″)H and C(6″)H), 135.38 (C(4′)H), 148.94 (C(6′)H), 150.02 (C(2′)H), 159.00 (C(4″)); MS(EI) *m*/*z* 268.16 (M+).

Preparation of 3-[1-(4-chlorobenzyl)pyrrolidin-2-yl]pyridine 11h

Following the general procedure described above, 4-chlorobenzylamine (280 mg, 2.0 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (160 mg, 1.0 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.67 g, 2.0 mmol, 3.0 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (55 mg, 20%); ν_{max}/cm^{-1} 2933, 1688, 1656, 1490, 1100, 1016, 807 and 716; δ_H (400 MHz; $CDCl_3$) 1.65–1.95 (3H, m, C(3)-Ha and C(4)-H_2), 2.15–2.30 (2H, m, C(3)-Hb and C(5)-Ha), 3.05–3.15 (1H, m, C(5)-Hb), 3.40–3.55 (2H, m, C(2)-H and NC*Ha*Ph), 3.71 (1H, d, *J* 13.2, NC*Hb*Ph), 7.17 (2H, d, *J* 8.4, C(2″)-H and C(6″)-H), 7.22 (2H, d, *J* 8.3, C(3″)-H and C(5″)-H), 7.28 (1H, dd, *J* 7.7, 4.9, C(5′)-H), 7.82 (1H, d, *J* 7.7, C(4′)-H), 8.49 (1H, d, *J* 4.9, C(6′)-H), 8.61 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 25.29 (C(4)H_2), 35.05 (C(3)H_2), 53.83 (C(5)H_2), 57.77 (PhO*C*H_3), 67.34 (C(2)H), 124.20 (s, C(5′)H), 128.71 (C-(3″)H and C(5″)H), 129.30 (s, C(3′)), 130.30 (C(2″)H and C(6″)H), 133.00 (C(1″)), 135.72 (C(4″)), 135.78 (C(4′)H), 148.61 (C(6′)H), 149.47 (C(2′)H); MS(EI) *m*/*z* 272.11 (M+).

Preparation of 3-[1-(4-fluorobenzyl)pyrrolidin-2-yl]pyridine 11i

Following the general procedure described above, 4-fluorobenzylamine (125 mg, 1.0 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (80 mg, 0.5 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.33 g, 1.0 mmol, 3.0 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (120 mg, 94%); ν_{max}/cm^{-1} 2967, 2803, 1602, 1520, 1427, 1219, 1153, 824 and 715; δ_H (400 MHz; $CDCl_3$) 1.70–2.00 (3H, m, C(3)-Ha and C(4)-H_2), 2.15–2.30 (1H, m, C(3)-Hb), 2.25 (1H, dd, *J* 17.5, 8.7, C(5)-Ha), 3.05–3.15 (1H, m, C(5)-Hb), 3.11 (1H, d, *J* 13.1, NC*Ha*Ph), 3.43 (1H, t, *J* 8.1, C(2)-H), 3.74 (1H, d, *J* 13.1, NC*Hb*Ph), 6.96 (2H, dd, *J* 8.6 and 8.5, C(3″)-H and C(5″)-H), 7.22 (2H, dd, *J* 8.5, 5.7, C(2″)-H and C(6″)-H), 7.28 (1H, dd, *J* 7.7, 5.5, C(5′)-H), 7.80 (1H, d, *J* 7.7, C(4′)-H), 8.51 (1H, d, *J* 5.5, C(6′)-H), 8.61 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.94 (C(4)H_2), 35.65 (C(3)H_2), 53.86 (C(5)H_2), 57.79 (N*C*H_2Ph), 67.36 (C(2)H), 115.31 (d, *J* 21.1, C(3″)H and C(5″)H), 123.98 (C(5′)H), 130.39 (d, *J* 7.9, C(2″)H and C(6″)H), 135.32 (C(4′)H), 135.40 (C(1″)), 139.71 (C(3′)), 149.04 (C(6′)H), 150.00 (C(2′)H), 162.23 (d, *J* 43.1, C(4″)); MS(EI) *m*/*z* 256.14 (M^+).

Preparation of 3-[1-(3,4-methylenedioxobenzyl)pyrrolidin-2-yl]pyridine 11j

Following the general procedure described above, piperonylamine (151 mg, 1.0 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (80 mg, 0.5 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.33 g, 1.0 mmol, 3.0 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (120 mg, 85%); ν_{max}/cm^{-1} 2877, 2794, 1501, 1488, 1441, 1243, 1050, 926, 808 and 716; δ_H (400 MHz; $CDCl_3$) 1.65–2.00 (3H, m, C(3)-Ha and C(4)-H_2), 2.15–2.30 (2H, m, C(3)-Hb and C(5)-Ha), 3.05 (1H, d, *J* 13.0, NC*Ha*Ph), 3.13 (1H, td, *J* 8.5, 2.3, C(5)-Hb), 3.41 (1H, t, *J* 8.5, C(2)-H), 3.69 (1H, d, *J* 13.1, NC*Hb*Ph), 5.93 (2H, d, *J* 1.6, O*C*H_2O), 6.70 and 6.72 (1H × 2, d, *J* 7.8, C(5″)-H and C(6″)-H), 6.79 (1H, s, C(2″)-H), 7.29 (1H, dd, *J* 7.8, 5.0, C(5′)-H), 7.81 (1H, d, *J* 7.8, C(4′)-H), 8.51 (1H, dd, *J* 5.0, 1.3, C(6′)-H), 8.63 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.93 (C(4)H_2), 35.66 (C(3)H_2), 53.80 (C(5)H_2), 58.23 (N*C*H_2Ph), 67.19 (C(2)H), 101.20 (O*C*H_2O), 108.20 (C(5″)H), 109.42 (C(2″)H), 121.90 (C(6″)H), 124.00 (C(5′)H), 133.62 (C(1″)), 135.34 (C(4′)H), 139.82 (C(3′)), 146.80 and 147.93 (C(3″) and C(4″)), 148.96 (C(6′)H), 149.98 (C(2′)H); MS(EI) *m*/*z* 282.14 (M+).

Preparation of 3-[1-(2-naphthylmethyl)pyrrolidin-2-yl]pyridine 11k

Following the general procedure described above, 1-(aminomethyl)naphthalene (157 mg, 1.0 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (80 mg, 0.5 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.33 g, 1.0 mmol, 3.0 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (110 mg, 76%); ν_{max}/cm^{-1} 2952, 2800, 1688, 1595, 1577, 1510, 1427, 1105, 1025, 753 and 715; δ_H (400 MHz; $CDCl_3$) 1.73–1.97 (3H, m, C(3)-Ha and C(4)-H_2), 2.20–2.40 (2H, m, C(3)-Hb and C(5)-Ha), 3.07 (1H, br t, *J* 7.6, C(5)-Hb), 3.50 (1H, t, *J* 7.9, C(2)-H), 3.61 (1H, d, *J* 13.1, NC*Ha*$C_{10}H_7$), 4.18 (1H, d, *J* 13.1, NC*Hb*$C_{10}H_7$), 7.24 (1H, dd, *J* 7.7, 4.8, C(5′)-H), 7.30–7.50 (4H, m, C(2″)-H, C(3″)-H, C(7″)-H and C(8″)-H), 7.72 (1H, d, *J* 8.1, C(4″)-H), 7.75–7.85 (1H, m, C(6″)-H), 7.82 (1H, d, *J* 7.7, C(4′)-H), 7.90–7.96 (1H, m, C(9″)-H), 8.49 (1H, d, *J* 4.8, C(6′)–H), 8.67 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 23.19 (C(4)H_2), 35.65 (C(3)H_2), 54.67 (C(5)H_2), 57.03 (N*C*$H_2C_{10}H_7$), 68.25 (C(2)H), 123.83 (C(5′)H), 124.64 (C(9″)H), 125.58, 125.89, 125.99 and 127.61 (C(2″)H, C(3″)H, C(7″)H and C(8″)H), 128.13 (C(4″)H), 128.78 (C(6″)H), 132.49 (C(10″)), 134.08 (C(5″)), 135.44 (C(1″)), 135.66 (C(4′)H), 139.85 (C(3′)), 149.02 (C(6′)H), 150.07 (C(2′)H); MS(EI) *m*/*z* 288.16 (M^+).

Preparation of 3-[1-(4-pyridyl)pyrrolidin-2-yl]pyridine 11l

Following the general procedure described above, 4-(aminomethyl)pyridine (108 mg, 1.0 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (80 mg, 0.5 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.33 g, 1.0 mmol, 3.0

mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (50 mg, 42%); ν_{max}/cm^{-1} 2925, 1692, 1602, 1420, 1116, 808 and 716; δ_H (400 MHz; $CDCl_3$) 1.70–2.10 (3H, m, C(3)-Ha and C(4)-H_2), 2.15–2.30 (2H, m, C(3)-Hb and C(5)-Ha), 3.18 (1H, d, *J* 14.1, NC*Ha*-4-Py), 3.40–3.55 (2H, m, C(2)-H and C(5)-Hb), 3.77 (1H, d, *J* 14.1, NC*Hb*-4-Py), 7.23 (2H, d, *J* 5.2, C(2″)-H and C(6″)-H), 7.27 (1H, br d, *J* 7.9, C(5′)-H), 7.80 (1H, d, *J* 7.9, C(4′)-H), 8.45–8.55 (1H, m, C(6′)-H), 8.50 (2H, d, *J* 5.2, C(3″)-H and C(5″)-H), 8.63 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.65 (C(4)H_2), 35.08 (C(3)H_2), 53.66 (C(5)H_2), 57.08 (N*C*H_2-4-Py), 67.20 (C(2)H), 123.52 (C(2″)H and C(6″)H), 123.73 (C(5′)H), 135.09 (C(4′)H), 138.77 (C(3′)), 146.82 (C(1″)), 148.71 (C(6′)H), 149.36 (C(2′)H), 150.08 (C(3″)H and C(5″)H); MS(EI) *m*/*z* 239.14 (M+).

Preparation of 3-(1-furfurylpyrrolidin-2-yl)pyridine 11m

Following the general procedure described above, furfurylamine (97 mg, 1.0 mmol), 4-(3-pyridyl)-4-oxobutyraldehyde (80 mg, 0.5 mmol), acetic acid (0.2 mL) and polymer-supported cyanoborohydride (0.30 g, 1.0 mmol, 3.0 mmol g^{-1}) in dichloromethane (4 mL) gave the title compound (60 mg, 53%); ν_{max}/cm^{-1} 2966, 2806, 1675, 1577, 1426, 1148, 1013, 806, 733 and 720; δ_H (400 MHz; $CDCl_3$) 1.55–1.65 (1H, m, C(3)-Ha), 1.65–1.75 (1H, m, C(4)-Ha), 1.75–1.92 (1H, m, C(4)-Hb), 2.05–2.15 (1H, m, C(3)-Hb), 2.37 (1H, dd, *J* 17.7, 8.9, C(5)-Ha), 3.12 (1H, td, *J* 17.7, 2.3, C(5)-Hb), 3.24 (1H, d, *J* 14.3, NC*Ha*-2-Furan), 3.32 (1H, t, *J* 8.1, C(2)-H), 3.60 (1H, d, *J* 14.3, NC*Hb*-2-Furan), 5.98 (1H, d, *J* 3.0, C(3″)-H), 6.16 (1H, dd, *J* 3.0, 1.9, C(4″)-H), 7.16 (1H, dd, *J* 7.9, 4.6, C(5′)-H), 7.22 (1H, d, *J* 1.9, C(5″)-H), 7.67 (1H, br d, *J* 7.9, C(4′)-H), 8.39 (1H, br d, *J* 4.6, C(6′)-H), 8.48 (1H, br s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.87 (C(4)H_2), 35.60 (C(3)H_2), 49.58 (N*C*H_2-2-Furan), 53.87 (C(5)H_2), 66.18 (C(2)H), 108.47 (C(3″)H), 110.39 (C(4″)H), 123.98 (C(5′)H), 135.26 (C(4′)H), 139.29 (C(3′)), 142.21 (C(5″)H), 148.97 (C(6′)H), 150.00 (C(2′)H), 152.87 (C(2″)); MS(EI) *m*/*z* 228.13 (M+).

Preparation of 3-(1-methylpyrrolidin-2-yl)-6-chloropyridine 11n

Following the general procedure described above, methylamine (0.195 mL, 0.39 mmol of 2.0 M solution in THF), 4-(6-chloropyridin-3-yl)-4-oxobutyraldehyde (70 mg, 0.35 mmol), acetic acid (0.1 mL) and sodium triacetoxyborohydride (112 mg, 0.53 mmol) in dichloromethane (2 mL) gave the title compound (46 mg, 49%); ν_{max}/cm^{-1} 2916, 1709, 1563, 1395, 1256, 1106, 1012, 836 and 750; δ_H (400 MHz; $CDCl_3$) 1.80–2.20 (4H, m, C(3)-H_2 and C(4)-H_2), 2.40 (1H, q, *J* 9.1, C(5)-Ha), 2.53 (3H, s, N*C*H_3), 3.20–3.30 (1H, m, C(2)-H), 3.35–3.45 (1H, m, C(5)-Hb), 7.27 (1H, d, *J* 8.3, C(5′)-H), 7.74 (1H, dd, *J* 8.3, 2.4, C(4′)-H), 8.26 (1H, d, *J* 2.4, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.11 (C(4)H_2), 33.95 (C(3)H_2), 39.57 (N*C*H_3), 56.30 (C(5)H_2), 68.31 (C(2)H), 124.56 (C(5′)H), 135.12 (C(3′)), 138.31 (C(4′)H), 149.46 (C(2′)H), 150.86 (C(6′)H); MS(EI) *m*/*z* 196.08 (M^+).

Preparation of 3-(1-benzylpyrrolidin-2-yl)-6-chloropyridine 11o

Following the general procedure described above, benzylamine (22 mg, 0.2 mmol), 4-(6-chloropyridin-3-yl)-4-oxobutyraldehyde (40 mg, 0.2 mmol), acetic acid (0.1 mL) and polymer-supported cyanoborohydride (0.13 g, 0.4 mmol, 3.0 mmol g^{-1}) in dichloromethane (2 mL) gave the title compound (25 mg, 46%); ν_{max}/cm^{-1} 2924, 1727, 1586, 1454, 1131 and 1120; δ_H (400 MHz; $CDCl_3$) 1.60–1.75 (1H, m, C(3)-Ha), 1.75–1.95 (2H, m, C(4)-H_2), 2.15–2.33 (2H, m, C(3)-Hb and C(5)-Ha), 3.05–3.15 (1H, m, C(5)-Hb), 3.14 (1H, d, *J* 13.1, NC*Ha*Ph), 3.43 (1H, dd, *J* 8.2, 8.1, C(2)-H), 3.75 (1H, d, *J* 13.1, NC*Hb*Ph), 7.20–7.32 (6H, m, C(5′)-H and N$CH_2C_6H_5$), 7.78 (1H, dd, *J* 8.1, 2.0, C(4′)-H), 8.40 (1H, d, *J* 2.0, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 22.57 (C(4)H_2), 35.30 (C(3)H_2), 53.38 (C(5)H_2), 58.11 (N*C*H_2Ph), 66.08 (C(2)H), 124.23 (C(5′)H), 126.91 (C(4″)H), 128.18 (C(3″)H and C(5″)H), 128.54 (C(2″)H and C(6″)H), 137.88 and 138.98 (C(3′) and C(1″)), 139.63 (C(4′)H), 149.24 (C(2′)H), 151.27 (C(6′)); MS(EI) *m*/*z* 272.11 (M^+).

Preparation of 3-(1-methylpyrrol-2-yl)pyridine 17a; general procedure for 3-(1-substituted pyrrol-2-yl)pyridine

To a stirred solution of 4-(3-pyridyl)-4-oxobutyraldehyde (0.10 g, 0.61 mmol) in dichloromethane (2 mL) was added methylamine (0.61 mL, 1.2 mmol of 2.0 M solution in methanol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 1 h and concentrated under reduced pressure to yield the title compound (95 mg, 98%) as a pale yellow oil; ν_{max}/cm^{-1} 2933, 1649, 1450, 1121, 1023 and 710; δ_H (400 MHz; $CDCl_3$) 3.60 (3H, s, NCH_3), 6.15 (1H, dd, *J* 3.5, 3.0, C(4)-H), 6.22 (1H, dd, *J* 3.5, 1.7, C(3)-H), 6.70 (1H, br s, C(5)-H), 7.25 (1H, dd, *J* 7.9, 4.9, C(5′)-H), 7.63 (1H, br d, *J* 7.9, C(4′)-H), 8.44 (1H, dd, *J* 4.9, 1.7, C(6′)-H), 8.60 (1H, d, *J* 1.7, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 35.47 (NCH_3), 108.64 (C(4)H), 110.21 (C(3)H), 123.63 (C(5′)H), 125.16 (C(5)H), 129.73 (C(2)), 131.20 (C(3′)), 135.90 (C(4′)H), 148.06 (C(6′)H), 149.62 (C(2′)H); MS(EI) *m*/*z* 158.08 (M^+).

Preparation of 3-(1-ethylpyrrol-2-yl)pyridine 17b

By the general procedure described above, ethylamine (55 mg, 1.23 mmol) and 4-(3-pyridyl)-4-oxobutyraldehyde (100 mg, 0.613 mmol) in dichloromethane (2 mL) gave the title compound (100 mg, 95%); ν_{max}/cm^{-1} 2974, 2932, 2677, 1652, 1585, 1473, 1397, 1025, 800 and 715; δ_H (400 MHz; $CDCl_3$) 1.26 (3H, t, *J* 7.3, NCH_2CH_3), 3.90 (2H, q, *J* 7.3, NCH_2CH_3), 6.17 (2H, br s, C(3)-H and C(4)-H), 6.77 (1H, t, *J* 2.1, C(5)-H), 7.25 (1H, dd, *J* 7.8, 4.9, C(5′)-H), 7.61 (1H, dt, *J* 7.8, 1.8, C(4′)-H), 8.47 (1H, dd, *J* 4.9, 1.8, C(6′)-H), 8.58 (1H, d, *J* 1.8, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 17.10 (NCH_2CH_3), 42.33 (NCH_2CH_3), 108.81 (C(4)H), 110.25 (C(3)H), 122.74 (C(5)H), 123.64 (C(5′)H), 129.98 (C(2)), 130.57 (C(3′)), 136.16 (C(4′)H), 148.17 (C(6′)H), 149.77 (C(2′)H); MS(EI) *m*/*z* 173.10 (M^+).

Preparation of 3-(1-benzylpyrrol-2-yl)pyridine 17c

Following the general procedure described above, benzylamine (54 mg, 0.5 mmol) and 4-(3-pyridyl)-4-oxobutyraldehyde (80 mg, 0.50 mmol) in dichloromethane (2 mL) gave the title compound (117 mg, quantitative); ν_{max}/cm^{-1} 2929, 1689, 1656, 1453, 1312, 1024 and 715; δ_H (400 MHz; $CDCl_3$) 5.05 (2H, s, NCH_2Ph), 6.23 (1H, dd, *J* 6.0, 3.2, C(3)-H), 6.25 (1H, br s, C(4)-H), 6.74 (1H, br s, C(5)-H), 6.89 (2H, d, *J* 7.1, C(2″)-H and C(6″)-H), 7.10–7.23 (4H, m, C(5′)-H, C(3″)-H, C(4″)-H and C(5″)-H), 7.48 (1H, d, *J* 7.8, C(4′)-H), 8.40 (1H, d, *J* 4.4, C(6′)-H), 8.52 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 51.28 (N*C*H_2Ph), 109.29 (C(4)H), 110.63 (C(3)H), 123.54 (C(5′)H), 124.55 (C(5)H), 126.67 (C(2″)H and C(6″)H), 127.94 (C(4″)H), 129.19 (C(3″)H and C(5″)H), 129.66 (C(2)), 131.47 (C(3′)), 136.10 (C(4′)H), 138.67 (C(1″)), 148.40 (C(6′)H), 149.95 (C(2′)H); MS(EI) *m*/*z* 235.12 (M^+).

Preparation of 3-[1-(4-methoxybenzyl)pyrrol-2-yl]pyridine 17d

Following the general procedure described above, 4-methoxybenzylamine (42 mg, 0.31 mmol) and 4-(3-pyridyl)-4-oxobutyraldehyde (50 mg, 0.31 mmol) in dichloromethane (2 mL) gave the title compound (82 mg, quantitative); ν_{max}/cm^{-1} 2931, 2835, 1638, 1611, 1513, 1250, 1176, 1033, 815 and 716; δ_H (400 MHz; $CDCl_3$) 3.56 (3H, s, $C_6H_4OCH_3$), 4.86 (2H, s, NCH_2Ph), 6.08 (1H, dd, *J* 3.5, 2.9, C(4)-H), 6.11 (1H, dd, *J* 3.5, 1.8, C(3)-H), 6.60 (1H, d, *J* 2.9, C(5)-H), 6.60 (2H, d, *J* 8.7, C(3″)-H and C(5″)-H), 6.70 (2H, d, *J* 8.7, C(2″)-H and C(6″)-H), 7.03 (1H, dd, *J* 7.9, 4.8, C(5′)-H), 7.37 (1H, br d, *J* 7.9, C(4′)-H), 8.28 (1H, dd, *J* 4.8, 1.2, C(6′)-H), 8.39 (1H, d, *J* 1.2, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 50.82 (NCH_2Ph), 55.66 ($C_6H_4OCH_3$), 109.14 (C(4)H), 110.60 (C(3)H), 114.58 (C(3″)H

and C(5″)H), 123.55 (C(5′)H), 124.38 (C(5)H), 128.07 (C(2″)H and C(6″)H), 129.76, 130.58 and 131.32 (C(2), C(3′) and C(1″)), 136.14 (C(4′)H), 148.31 (C(6′)H), 149.92 (C(2′)H), 159.42 (C(4″)H); MS(EI) *m/z* 264.13 (M^+).

Preparation of 3-[1-(4-chlorobenzyl)pyrrol-2-yl]pyridine 17e

Following the general procedure described above, 4-chlorobenzylamine (44 mg, 0.31 mmol) and 4-(3-pyridyl)-4-oxobutyraldehyde (50 mg, 0.31 mmol) in dichloromethane (2 mL) gave the title compound (80 mg, 96%); ν_{max}/cm^{-1} 2926, 1722, 1491, 1311, 1091, 1015, 806 and 720; δ_H (400 MHz; $CDCl_3$) 5.11 (2H, s, NCH_2Ph), 6.30–6.35 (2H, m, C(3)-H and C(4)-H), 6.81 (1H, br s, C(5)-H), 6.89 (2H, d, *J* 8.1, C(3″)-H and C(5″)-H), 7.20–7.30 (3H, m, C(5′)-H, C(2″)-H and C(6″)-H), 7.55 (1H, br d, *J* 6.1, C(4′)-H), 8.51 (1H, br s, C(6′)-H), 8.59 (1H, s, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 50.70 (NCH_2Ph), 109.56 (C(4)H), 110.91 (C(3)H), 123.61 (C(5)H), 124.42 (C(5′)H), 128.01 (C(3″)H and C(5″)H), 129.37 (C(2″)H and C(6″)H), 129.51, 131.44 and 133.82 (C(2), C(3′) and C(4″)), 136.11 (C(4′)H), 137.16 (C(1″)), 148.56 (C(6′)H), 149.90 (C(2′)H); MS(EI) *m/z* 268.08 (M^+).

Preparation of 3-(1-benzylpyrrol-2-yl)-6-chloropyridine 17f

Following the general procedure described above, benzylamine (49 mg, 0.40 mmol) and 4-(6-chloropyridin-3-yl)-4-oxobutyraldehyde (40 mg, 0.20 mmol) in dichloromethane (2 mL) gave the title compound (50 mg, quantitative); ν_{max}/cm^{-1} 3298, 1699, 1557, 1170 and 693; δ_H (400 MHz; $CDCl_3$) 5.12 (2H, s, NCH_2Ph), 6.31 (1H, dd, *J* 3.5, 2.9, C(4)-H), 6.34 (1H, dd, *J* 3.5, 1.7, C(3)-H), 6.85 (1H, br s, C(5)-H), 6.96 (2H, d, *J* 7.1, C(2″)-H and C(6″)-H), 7.23–7.40 (4H, m, C(5′)-H, C(3″)-H, C(4″)-H and C(5″)), 7.51 (1H, dd, *J* 8.3, 2.5, C(4′)-H), 8.33 (1H, d, *J* 2.5, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 51.34 (NCH_2Ph), 109.44 (C(4)H), 111.09 (C(3)H), 124.23 (C(5′)H), 125.09 (C(5)H), 128.07 and 129.29 (C(2) and C(3′)), 128.38 (C(3″)H and C(5″)H), 128.76 (C(4″)H), 129.47 (C(2″)H and C(6″)H), 136.22 (C(4′)H), 138.77 (C(1″)), 149.40 (C(2′)H), 150.13 (C(6′)); MS(EI) *m/z* 268.08 (M^+).

Preparation of (3*S*)-3-[1-(1*S*)-(1-phenylethyl)pyrrolidin-2-yl]-pyridine 19a

Following the general procedure described above, (*S*)-(+)-2-methylbenzylamine (242 mg, 1.05 mmol), 4-(pyridin-3-yl)-4-oxobutyraldehyde (115 mg, 0.70 mmol), acetic acid (0.1 mL) and sodium triacetoxyborohydride (297 mg, 1.4 mmol) in dichloromethane (2 mL) gave the title compound (100 mg, 57%); ν_{max}/cm^{-1} 3027, 2968, 2873, 1576, 1451, 1426, 1025, 716 and 700; δ_H (400 MHz; $CDCl_3$) 1.35 (3H, d, *J* 6.7, NCH(Ph)C*H3*), 1.62–1.72 (1H, m, C(3)-Ha), 1.75–1.85 (1H, m, C(4)-Ha), 1.85–1.97 (1H, m, C(4)-Hb), 2.15–2.27 (1H, m, C(3)-Hb), 2.63 (1H, dd, *J* 16.6, 8.9, C(5)-Ha), 3.05 (1H, td, *J* 8.9, 2.6, C(5)-Hb), 3.65–3.80 (2H, m, C(2)-H and NC*H*(Me)Ph), 7.10–7.25 (6H, m, C(5′)-H and NCH(Me)C_6H_5), 7.62 (1H, br d, *J* 7.8, C(4′)-H), 8.40 (1H, dd, *J* 4.7, 1.7, C(6′)-H), 8.47 (1H, d, *J* 1.7, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 15.45 (NCH(Ph)*C*H_3), 23.75 (C(4)H_2), 36.04 (C(3)H_2), 49.05 (C(5)H_2), 59.26 (N*C*H-(CH_3)Ph), 63.89 (C(2)H), 123.54 (C(5′)H), 126.98 (C(4″)H), 128.01 (C(3″)H and C(5″)H), 128.24 (C(2″)H and C(6″)H), 135.14 (C(4′)H), 141.72 and 144.47 (C(3′) and C(1″)), 148.23 (C(6′)H), 149.72 (C(2′)H); MS(EI) *m/z* 252.16 (M+). $[a]^{25}$ = +48 (*c* = 0.5, $CHCl_3$).

Preparation of (3*R*)-3-[1-(1*R*)-(1-phenylethyl)pyrrolidin-2-yl]-pyridine 19b

Following the general procedure described above, (*R*)-(+)-α-methylbenzylamine (182 mg, 1.5 mmol), 4-(pyridin-3-yl)-4-oxobutyraldehyde (163 mg, 1.0 mmol), acetic acid (0.2 mL) and sodium triacetoxyborohydride (424 mg, 2 mmol) in dichloromethane (4 mL) gave the title compound (110 mg, 44%); ν_{max}/cm^{-1} 3027, 2968, 2873, 1576, 1451, 1426, 1025, 716 and 700; δ_H (400 MHz; $CDCl_3$) 1.35 (3H, d, *J* 6.7, NCH(Ph)C*H*$_3$), 1.62–1.72 (1H, m, C(3)-Ha), 1.75–1.85 (1H, m, C(4)-Ha), 1.85–1.97 (1H, m, C(4)-Hb), 2.15–2.27 (1H, m, C(3)-Hb), 2.63 (1H, dd, *J* 16.6, 8.9, C(5)-Ha), 3.05 (1H, td, *J* 8.9, 2.6, C(5)-Hb), 3.65–3.80 (2H, m, C(2)-H and NC*H*(Me)Ph), 7.10–7.25 (6H, m, C(5′)-H and NCH(Me)C_6H_5), 7.62 (1H, br d, *J* 7.8, C(4′)-H), 8.40 (1H, dd, *J* 4.7 and 1.7, C(6′)-H), 8.47 (1H, d, *J* 1.7, C(2′)-H); δ_C (100 MHz; $CDCl_3$) 15.45 (NCH(Ph)*C*H_3), 23.75 (C(4)H_2), 36.04 (C(3)H_2), 49.05 (C(5)H_2), 59.26 (N*C*H-(CH_3)Ph), 63.89 (C(2)H), 123.54 (C(5′)H), 126.98 (C(4″)H), 128.01 (C(3″)H and C(5″)H), 128.24 (C(2″)H and C(6″)H), 135.14 (C(4′)H), 141.72 and 144.47 (C(3′) and C(1″)), 148.23 (C(6′)H), 149.72 (C(2′)H); MS(EI) *m/z* 252.16 (M+). $[a]^{25}$ = −50 (*c* = 3.0, $CHCl_3$).

Preparation of (3*S*)-3-[1-(1*S*)-(2-hydroxy-1-phenylethyl)pyrrolidin-2-yl]pyridine 18c

Following the general procedure described above (*S*)-(+)-2-phenylglycinol (309 mg, 2.25 mmol), 4-(pyridin-3-yl)-4-oxobutyraldehyde (245 mg, 1.5 mmol), acetic acid (0.25 mL) and sodium triacetoxyborohydride (945 mg, 4.5 mmol) in dichloromethane (5 mL) gave the title compound (325 mg, 81%); $[a]^{25}$ = −89 (*c* = 2.0, $CHCl_3$), mp 88–89 °C; ν_{max}/cm^{-1} 2934, 2872, 1690, 1584, 1063, 1026 and 710; δ_H (400 MHz; $CDCl_3$) 1.50–1.60 (1H, m, C(3)-Ha), 1.70–1.80 (1H, m, C(4)-Ha), 1.84–1.97 (1H, m, C(4)-Hb), 1.98–2.12 (1H, m, C(3)-Hb), 2.79 (1H, dd, *J* 16.3, 9.1, C(5)-Ha), 3.27 (1H, br d, *J* 9.1, C(5)-Hb), 3.62–3.75 (4H, m, C(2)-H and NC*H*(Ph)CH_2OH), 7.00–7.15 (6H, m, C(5′)-H and NCH(CH_2OH)C_6H_5), 7.45 (1H, d, *J* 7.9, C(4′)-H), 8.24 (1H, s, C(2′)-H), 8.29 (1H, d, *J* 4.1, C(6′)-H); δ_C (100 MHz; $CDCl_3$) 24.13 (C(4)H_2), 36.15 (C(3)H_2), 53.70 (C(5)H_2), 62.71 (N*C*H(Ph)CH_2OH), 63.75 (NCH(Ph)*C*H_2OH), 68.83 (C(2)H), 123.65 (C(5′)H), 128.14 (C(4″)H), 128.56 (C(3″)H and C(5″)H), 129.40 (C(2″)H and C(6″)H), 134.95 (C(4′)H), 138.42 (C(3′)), 142.37 (C(1″)), 148.06 (C(6′)H), 148.97 (C(2′)H); MS(EI) *m/z* 268.16 (M^+).

CCDC reference number(s) 174514. See http://www.rsc.org/suppdata/p1/b1/b109482n/ for crystallographic files in .cif or other electronic format. Crystal structure determination of compound **18c**. Crystals of **18c** were obtained by recrystallisation from ethyl acetate.

Crystal data: $C_{17}H_{20}N_2O$, *M* = 286.35, monoclinic, *a* = 8.9473(8), *b* = 6.0399(3), *c* = 13.4384(10), β = 91.719(3)°, *U* = 725.89(9)A^3, *T* = 180(2) K, space group $P2_1$, *Z* = 2, μ = 0.077 mm^{-1}, 5004 reflections collected, 2945 independent reflections (R_{int} = 0.0391). The final $wR(F^2)$ was 0.0501.

Preparation of (3*R*)-3-[1-(1*R*)-(2-hydroxy-1-phenylethyl)-pyrrolidin-2-yl]pyridine 18d

Following the general procedure described above, (*R*)-(−)-2-phenylglycinol (236 mg, 1.72 mmol), 4-(pyridin-3-yl)-4-oxobutyraldehyde (140 mg, 0.86 mmol), acetic acid (0.1 mL) and sodium triacetoxyborohydride (365 mg, 1.72 mmol) in dichloromethane (2 mL) gave the title compound (190 mg, 82%); $[a]^{25}$ = +92 (*c* = 2.0, $CHCl_3$), mp 89–90 °C, ν_{max}/cm^{-1} 2939, 1709, 1578, 1397, 1261, 1029, 751 and 710; δ_H (400 MHz; $CDCl_3$) 1.30–1.40 (1H, m, C(3)-Ha), 1.55–1.65 (1H, m, C(4)-Ha), 1.65–1.80 (1H, m, C(4)-Hb), 1.80–1.95 (1H, m, C(3)-Hb), 2.61 (1H, dd, *J* 16.0, 9.2, C(5)-Ha), 3.08 (1H, ddd, *J* 16.0, 9.2, 2.6, C(5)-Hb), 3.50–3.58 (4H, m, C(2)-H and NC*H*(Ph)CH_2OH), 6.83–6.95 (3H, m, C(2″)-H, C(4″)-H and C(6″)-H), 6.95–7.20 (3H, m, C(5′)-H, C(3″)-H and C(5″)-H), 7.30 (1H, dd, *J* 7.9, 1.6, C(4′)-H), 7.80–8.00 (1H, br s, CH_2OH), 8.00–8.10 (2H, m, C(2′)-H and C(6′)-H); δ_C (100 MHz; $CDCl_3$) 24.09 (C(4)H_2), 35.96 (C(3)H_2), 53.09 (C(5)H_2), 63.15 (N*C*H(Ph)CH_2OH), 63.67 (NCH(Ph)*C*H_2OH), 68.65 (C(2)H), 123.53 (C(5′)H), 127.89 (C(4″)H), 128.41 (C(3″)H and C(5″)H), 129.26 (C(2″)H and

C(6″)H), 135.47 (C(4′)H), 138.98 (C(3′)), 142.59 (C(1″)), 147.87 (C(6′)H), 148.47 (C(2′)H); MS(EI) *m/z* 268.16 (M+). Crystals of **18d** were obtained by recrystallisation from ethyl acetate. The cell dimensions were analysed and compared to the crystal structure of **18c**.

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