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Synthesis of Bridgehead-Substituted Azabicyclo[2.2.1]heptane and -[3.3.1]nonane Derivatives for the Elaboration of α7 Nicotinic Ligands

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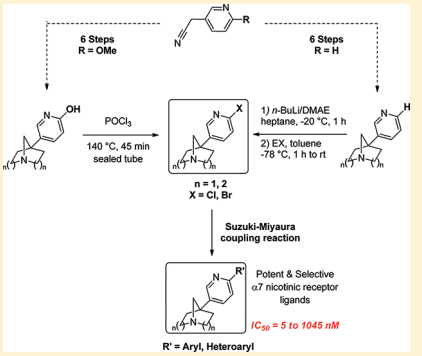
Supporting Information

ABSTRACT: Azabicyclo[2.2.1]heptane and -[3.3.1]nonane scaffolds (X = Cl, Br) containing a pyridinyl substituent at the bridgehead position were prepared via two complementary chemical pathways, either by the transformation of a methoxy group into a synthetically valuable chlorine atom at the C-6 position of the pyridine moiety or by means of a regioselective C-6 deprotonation/halogenation process of the pyridine moiety exemplified by chlorination or bromination. These newly generated scaffolds were then engaged in Suzuki−Miyaura coupling reactions to provide α7 nicotinic ligands. Both chemical series were evaluated in vitro for their affinity at α7 nicotinic receptors, revealing nanomolar potency with significant selectivity over the α4β2 nicotinic subtype. These approaches offer a general access to these α7 nicotinic scaffolds and ligands.



INTRODUCTION

For over 10 years, the identification of new potent and selective α7 nicotinic ligands has attracted both pharmaceutical companies and academic groups.[1−6] These molecules open the opportunity of new promising treatments for cognitive dysfunction related pathologies (e.g., schizophrenia, Alzheimer's disease).[7−10] Among the wide panel of chemical series developed for this purpose, some of them carry an azabicyclic moiety where the nitrogen atom is positioned at the bridgehead.[1−3] In most cases, aromatic or heteroaromatic functional groups are carried by the carbon atoms located on the bridges but not on the opposing bridgehead position of the azabicyclic moiety (Figure 1).

We have envisaged the synthesis of nitrogen bridgehead azabicyclic molecules carrying a functional group (a substituted pyridinyl) on the other bridgehead. Starting from the structure of epibatidine (**A**),[11] a natural substance described as a nonselective nicotinic receptor ligand,[12] we imagined displacing virtually (a) the nitrogen atom onto the first bridgehead position and (b) the chloropyridinyl group onto the second bridgehead. This generates the new original and achiral azabicyclo[2.2.1]heptane structure **1** (Figure 2). This latter species and its superior homologue **2** were our targeted scaffolds.

Azabicyclo[2.2.1]heptanes and -[3.3.1]nonanes derivatives possessing an aromatic or heteroaromatic group at the bridgehead position have been rarely described in the literature.[13−16] [2.2.1] analogues are mostly derived from the transformation of the ester group of the common intermediate **B** (except for **G**). Only one example of an azabicyclo[3.3.1]nonane substituted

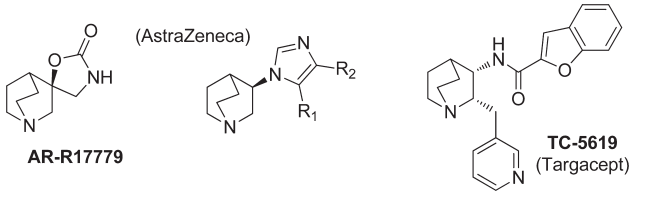


Figure 1. Examples of nitrogen bridgehead azabicyclic α7 nicotinic ligands.

with a phenyl group at the bridgehead position (**J**) has been reported with moderate yield (Figure 3).

In a previous publication,[17] scaffolds **1** and **2** were prepared via a nine-step chemical synthetic pathway, starting from the commercially available 6-methoxynicotinic acid methyl ester **3** (Figure 4). The chlorine atom on the 6-position of the pyridinyl moiety was then used to incorporate aromatic or heteroaromatic groups by means of Suzuki−Miyaura coupling reactions in order to generate a library of α7 nicotinic ligands.

Our objective was to extend the access of such final compounds but also to reduce the number of synthetic steps. A shorter complementary synthesis of these scaffolds was then conducted in which the chlorine atom and also a bromine atom were introduced at the 6-position of the pyridinyl moiety in the late stages of the synthetic pathway. This has been carried out by

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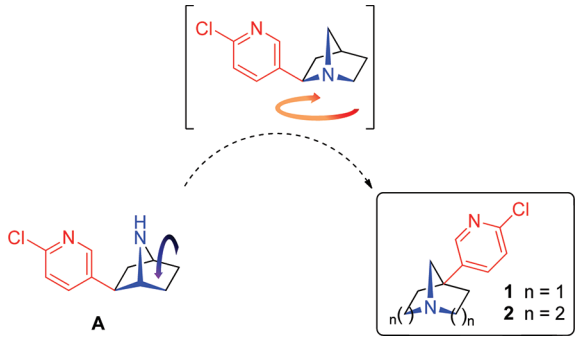

Figure 2. From epibatidine (**A**) to targeted scaffolds **1** and **2**.

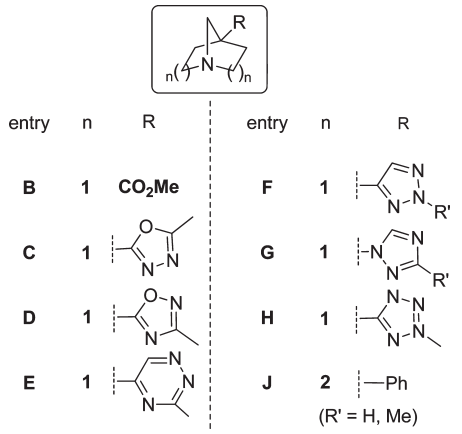

Figure 3. Known bridgehead (hetero)aromatic-substituted [2.2.1] and [3.3.1] azabicyclic derivatives.

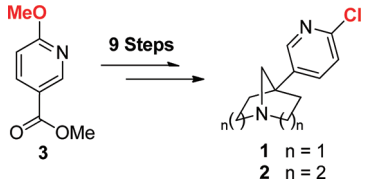

Figure 4. Previous synthetic approach of the targeted scaffolds **1** and **2**.[17]

means of a regioselective deprotonation−halogenation sequence of the pyridine. We have also examined the reaction conditions of the deprotonation−halogenation process. Moreover, the presence of a bromine atom in place of the chlorine allows us to increase the yields of the final coupling reaction. We report these two complementary synthetic accesses, the optimization study of the regioselective halogenation process, the access of the final $\alpha 7$ nicotinic ligands, and their in vitro biological activity as $\alpha 7$ nicotinic ligands.

RESULTS AND DISCUSSION

Although synthon **6** is commercially available, we have synthesized it for multigram accessibility and cost reasons. Reduction of the ester group of compound **3** using diisobutylaluminium hydride (DIBAl-H) furnished the corresponding alcohol **4** in 95% yield. The resulting alcohol function was converted into a chlorine atom quantitatively using thionyl chloride in toluene, providing compound **5**. Substitution of the chlorine atom by potassium cyanide led to the desired starting synthon **6** with 72% yield (Scheme 1).

The two complementary syntheses of the scaffolds for both chemical series were then conducted following the same five-step chemical pathway, one starting from the aforementioned compound **6** and the other from commercially gram-scale available pyridin-3-ylacetonitrile **17** (Scheme 2).

The synthesis of the azabicyclo[2.2.1]heptane chemical series began with a double alkylation of the starting synthon **6** or **17** with ethyl bromoacetate, providing **7** and **18** in 79 and 84% yields, respectively. These latter species were then subjected to hydrogenation in the presence of Raney nickel as a catalyst. During this step, the reduction of the cyano group was followed by an intramolecular cyclization of the newly generated terminal amine on one of the ester functions, providing the corresponding lactams **8** and **19** in 92 and 65% yield. Lithium aluminum hydride reduction of both the remaining ester group and the carbonyl function of the lactam led to the desired pyrrolidines **9** and **20** in good yields. Preparation of compounds **18**−**20** was previously reported, following closely related procedures.[18] The exchange of the terminal alcohol of these latter to bromide (compounds **10** and **21**) was performed quantitatively in concentrated hydrobromic acid. A concomitant hydrolysis of the methoxy group on the pyridine moiety of **9** occurred during this transformation, leading to a hydroxy group. Finally, the azabicyclo[2.2.1]heptane core was constructed by treatment with potassium carbonate, furnishing **11** and **22** in 74 and 66% yields, respectively. The synthesis of the azabicyclo[3.3.1]nonane chemical series differs only in the nature of the reagent used for the elaboration of the three-carbon side chains. In the first step, a double 1,4-addition of **6** or **17** on ethyl acrylate following reported procedures,[19,20] led to the superior homologues **12** and **23** in excellent yields. The subsequent four steps were then the same as described above for the synthesis of the azabicyclo[2.2.1]heptane chemical series.

In the first approach, the desired targeted scaffolds **1** and **2** were obtained by the action of $POCl_3$ in a sealed tube on compounds **11** and **16** with 90 and 91% yields, respectively (Scheme 3).

As depicted in Figure 4 and in Schemes 2 and 3, the methoxy group at the C-6 position of the pyridine of compound **3** was used to generate a synthetic valuable chlorine in the late stages of the synthesis. This approach allowed the generation of both scaffolds **1** and **2**, exhibiting a chlorine atom exclusively at the C-6 position. Direct functionalization of a pyridine ring still remains a synthetic challenge due to the π-deficient character of this heterocycle. Previously reported direct functionalization of pyridines often requires excess of the pyridine reagent[21−24] or the use of pyridine *N*-oxide[25−28] or pyridinium salt derivatives.[29,30] Moreover, recent methodologies have been developed to introduce aromatic substituents directly at the C-2 or C-6 positions of a pyridine.[31,32] On our substrates, attempts to introduce directly a phenyl group at the C-6 position of compounds **22** and **27** using Baran's protocol[31] failed. Only starting material was recovered. Directed ortho metalation[33−37] is so far the only efficient method for the direct introduction on a pyridine of a synthetic valuable group, such as an halogen or a tributylstannyl group. Thus, we envisaged introducing directly the chlorine atom (or a bromine) at the C-6 position of the pyridine without using a prefunctionalization group such as the aforementioned methoxy. This was carried out by following the procedure described by Fort with Comins' modifications.[33−36] Compounds **22** and **27** were regioselectively deprotonated at the C-6 position of the

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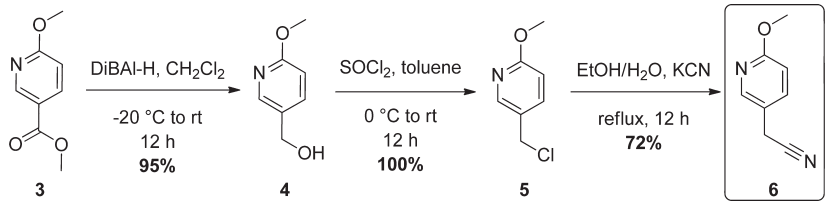
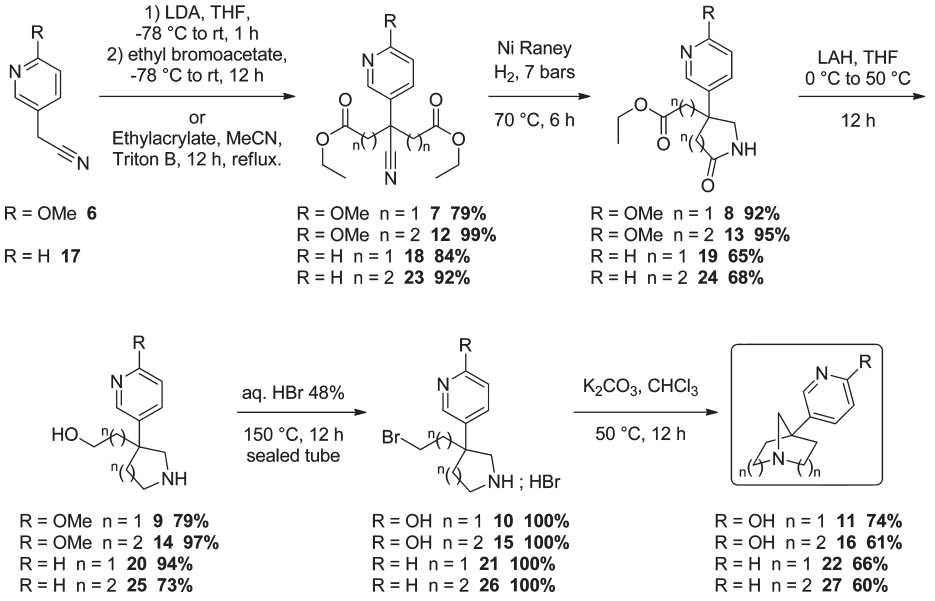
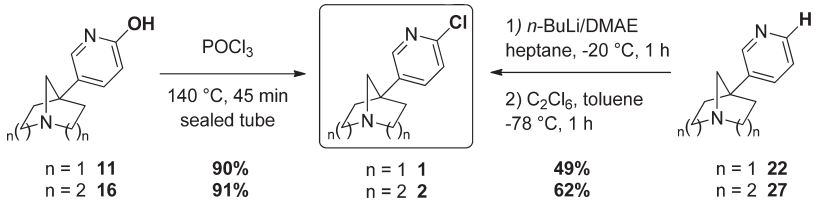
Scheme 1. Synthesis of Starting Synthon 6



Scheme 2. Common Synthetic Pathway of the Two Complementary Syntheses and for Both Chemical Series (n = 1, 2)



Scheme 3. Generation of Scaffolds 1 and 2



pyridine using the n-BuLi−LiDMAE (LiDMAE = Me_2N-$(CH_2)_2OLi$) superbase and quenched with C_2Cl_6 as electrophile. No C-2 chlorinated regioisomers were detected. The desired key chlorinated scaffolds **1** and **2** were thus obtained in 49 and 62% yields, respectively (Scheme 3). NMR (^1H and ^{13}C) and melting point data are identical with those obtained in our previous work.[17] Using this strategy, we save three steps in the global synthesis of both scaffolds starting with the same gram-scale affordable commercial reagent, pyridin-3-ylacetonitrile (**17**), while we had to synthesize **3** in the first synthesis. As for compounds **22** and **27**, no acidic proton was available at the bridgehead position. This excludes the mechanism of lithium migration previously described by Fort for the selective lithiation−functionalization of 3-picoline[33,35] and 3,5-lutidine.[34] Only direct abstraction of the hydrogen atoms at the C-2 and C-6 positions of the pyridine could be envisioned. As observed, no lithiation−functionalization occurred at the C-2 position of compounds **22** and **27**, which is probably due to steric hindrance between the azabicyclic moiety and the base aggregate (n-BuLi−LiDMAE),providing exclusively the desired targeted scaffolds **1** and **2** (Figure 5).

Reaction conditions of the C-6 lithiation−chlorination process are givenable 1.

Starting from the optimized protocol described by Comins[36] (entries 1 and 3), using 3 equiv of DMAE and 5.4 equiv of n-butyllithium at −20 °C to generate the pyridine anion, followed by the addition of C_2Cl_6 at −78 °C and hydrolysis at this temperature after 1 h, we were able to isolate **1** or **2** in moderate yields. Under the same conditions except that the mixture was warmed to room temperature after 1 h at −78 °C in the second step (entries 2 and 5), compounds **1** and **2** were isolated with good yields of 62 and 83%, respectively. The use of a supplemental amount of the

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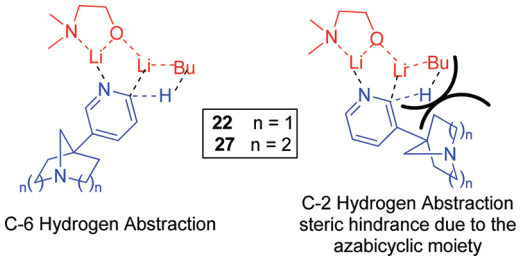
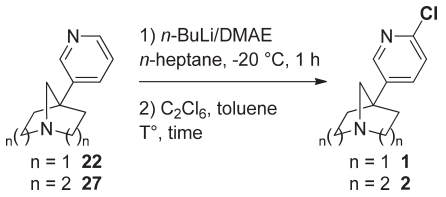


Figure 5. Regioselectivity of the lithiation process.

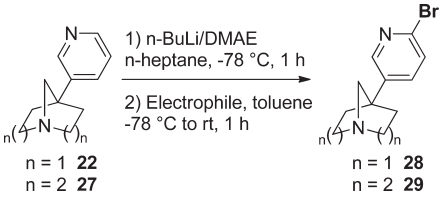
Table 1. Reaction Conditions for the C-6 Regioselective Lithiation−Chlorination of the Pyridine Moiety of 22 and 27



entry	n	amt of n-BuLi (equiv)	amt of DMAE (equiv)	amt of C_2Cl_6 (equiv)	step 2 (T (°C), time (h))	yield (%)[a]
1[b]	1	5.4	3	4	−78, 1	43−49
2	1	5.4	3	4	−78 to room temp, 1	62
3	2	5.4	3	4	−78 to room temp, 1	48−62
4	2	8	4	5	−78, 1	73
5	2	5.4	3	4	−78 to room temp, 1	83
6	2	8	4	5	−78 to room temp, 1	74

[a] Isolated yields. [b] Inverse addition: base aggregate *n*-BuLi−LiDMAE in cyclohexane was added at −20 °C to a suspension of **22** in *n*-heptane.

Table 2. C-6 Regioselective Bromination of the Pyridine Moiety of Scaffolds 22 and 27

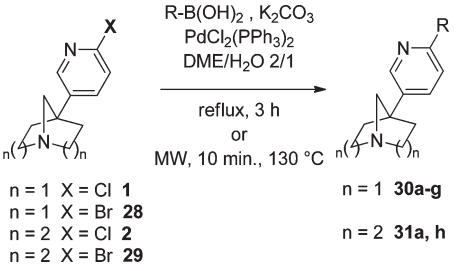


entry	n	compd	electrophile	yield (%)[a]
1	1	**28**	CBr_4	39
2	1	**28**	$C_2Br_2Cl_4$	69[b]
3	2	**29**	CBr_4	35
4	2	**29**	$C_2Br_2Cl_4$	81[c]

[a] Isolated yields. [b] **28** was isolated as a mixture with chloro compound **1** in a 97/3 ratio. [c] **29** was isolated as a mixture with chloro compound **2** in a 93/7 ratio.

base/electrophile system (entries 4 and 6) did not increase the yields significantly. This could be also related to solubility issues we have encountered with compound **27** in apolar solvents. C-6 regioselective bromination was also explored on scaffolds **22** and **27** (Table 2).

Table 3. Suzuki−Miyaura Coupling Reactions on 1, 2, 28, and 29



starting compound	final compound	R	yield (%)
1	**30a**		**54**[d] / **42**[e]
1	**30b**[a,c]		**61**[d] / **62**[e]
1	**30c**		**68**[d]
1	**30d**		**79**[d]
1	**30e**[b]		**55**[d]
28	**30e**[b]		**92**[e]
1	**30f**		**72**[d]
1	**30g**[a]		**42**[d]
28	**30g**[a]		**61**[e]
2	**31a**		**37**[d] / **41**[e]
29	**31a**		**79**[e]
2	**31h**		**46**[d]

[a] Boronic acid pinacol ester was used instead of boronic acid. [b] Subsequent salification was performed, providing **30e** as its hydrobromide salt. [c] Subsequent salification was performed, providing **30b** as its hydrochloride salt. [d] Yields obtained under thermal conditions. [e] Yields obtained with microwave assistance.

The low yield of bromination with CBr_4 was assumed to result from decomposition of the starting material (Table 3, entries 1 and 3). The use of $C_2Br_2Cl_4$ afforded the corresponding 6-bromopyridinyl azabicyclic compounds **28** and **29** in good yields but in the presence of a small amount of the corresponding chlorinated derivatives **1** and **2** in 97/3 and 93/7 ratios, respectively (entries 2 and 4). In addition with the previously described chlorinated scaffolds **1** and **2**, we now have a wider panel of halogenated scaffolds which opens the access to a larger range of final compounds. A library of final compounds was then generated using scaffolds **1** and **2** (Table 3).

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Table 4. In Vitro Evaluation of 30a−g and 31a,h as $\alpha7$ Nicotinic Receptor Ligands and Selectivity over the $\alpha4\beta2$ Subtype[a]

compd	$\alpha7$ receptor IC_{50} (nM) ±SD	$\alpha4\beta2$ receptor IC_{50} (nM)
SSR180711	30 ± 5	>10 000
30a	23	nd
30b	37	4150
30c	14	>10 000
30d	9	>10 000
30e	596 ± 19	>10 000
30f	1045 ± 146	nd
30g	5 ± 0.3	1960
31a	260	nd
31h	21	nd

[a] SD = standard deviation. The results with no SD were only performed once but with the **SSR180711** as the internal reference drug compound exhibiting reproducible values. nd = : not determined. For $\alpha7$ ligands, in vitro evaluation was performed on OFA male rat brain tissues in the presence of [^{3}H]-α-bungarotoxine at 1 nM concn, and for $\alpha4\beta2$ ligands, in vitro evaluation was performed on Sprague Dawley rat brain tissues in the presence of [^{3}H]-cytisine at 1 nM concn.

Representative examples **30a−g** and **31a,h** were synthesized via classical Suzuki−Miyaura coupling reactions in moderate to good yields. Coupling reactions were performed either under classical thermal conditions or with microwave assistance (130 °C, 10 min, very high absorption mode) with comparable yields. Compounds **30b,e** were subsequently salified to their hydrochloride and hydrobromide salts, respectively, in order to obtain satisfactory purity. Then, Suzuzi−Miyaura coupling reactions using the more reactive scaffolds **28** and **29** allowed an improvement in yields for some products obtained from **1** and **2** for some examples (**30e,g**, **31a**).

These final compounds were then evaluated in vitro for their affinity toward the $\alpha7$ nicotinic receptor. This was carried out on rat brain tissues by the reported protocol (Table 4).[38,39]

All compounds exhibited potent $\alpha7$ nicotinic receptor affinities with IC_{50} values from 5 nM (**30g**) to 1045 nM (**30f**). Six examples (**30a−d,g**, **31h**) exhibited activity with IC_{50} below 50 nM, comparable to or more potent than **SSR180711**[40,41] ($\alpha7$ nicotinic receptor partial agonist reference). In terms of structure−activity relationships, the influence of the size of the azabicyclic moiety has been observed by comparing the IC_{50} value of **30a** with that of its superior homologue **31a**. This latter compound appeared to be 10-fold less potent but still had affinity in the 100 nmol range. Moreover, five compounds were evaluated in vitro for their affinity toward the $\alpha4\beta2$ nicotinic receptor,[42,43] the other major nicotinic receptor subtype present in the brain. Three compounds (**30c−e**) were inactive (IC_{50} > 10 000 nM), whereas compounds **30b,g** exhibited $\alpha4\beta2$ nicotinic receptor affinity with IC_{50} values of 4150 and 1960 nM, respectively. In these cases, $\alpha7$ selectivity versus the $\alpha4\beta2$ subtype is more than 100-fold.

CONCLUSION

In conclusion, we have developed a general route to pyridinyl bridgehead substituted azabicyclo[2.2.1]heptane and -[3.3.1]-nonane scaffolds **1**, **2**, **28**, and **29**, with a nitrogen atom at the opposing bridgehead position. These were prepared via two complementary chemical pathways (six steps) either by the transformation of a methoxy group into a chlorine atom at the C-6 position of the pyridine moiety or by means of an optimized regioselective C-6 deprotonation−halogenation process on compounds **22** and **27**, in the last step. By means of Suzuki−Miyaura coupling reactions, a library of $\alpha7$ nicotinic ligands was generated. These ligands revealed nanomolar potency in vitro for $\alpha7$ nicotinic receptors with significant selectivity over the $\alpha4\beta2$ nicotinic subtype. These approaches open new and efficient access to a wider range of $\alpha7$ nicotinic scaffolds and ligands, increasing the possibilities of introducing substituents at the C-6 position of the pyridine moiety.

EXPERIMENTAL SECTION

General Methods. Unless otherwise indicated, all starting materials, reagents, and catalysts were obtained from commercial suppliers and used without further purification. Anhydrous tetrahydrofuran (THF), toluene, dimethoxyethane (DME), methanol (MeOH), ethanol (EtOH), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$),and ethyl acetate (AcOEt) were purchased with quality standards for analysis. Acetonitrile (MeCN) was purchased with quality standards for HPLC. Prior to use, THF, toluene, and DME were subsequently dried over activated molecular sieves (4 Å). Reactions involving air- or moisture-sensitive reagents or intermediates were carried out under an inert atmosphere of nitrogen or argon in glassware that had been oven-dried followed by a nitrogen purge. Reaction temperatures are reported as the temperature of the bath surrounding the vessel, unless otherwise indicated. Flash chromatography was conducted according to the established Still protocol[44] on an automated flash chromatography apparatus with the appropriate size disposable columns of normal phase silica with the indicated solvents. ^{1}H and ^{13}C (or J-MOD) NMR spectra were respectively collected at 400.13 MHz for proton and at 100.63 MHz for carbon. All NMR spectra were taken in deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) unless otherwise noted. Chemical shifts (δ) are expressed as ppm referenced to the residual solvent (i.e., for chloroform ^{1}H δ 7.24 ppm and ^{13}C δ 77.1 ppm and for dimethyl sulfoxide ^{1}H δ 2.50 ppm and ^{13}C δ 39.5 ppm). Splitting patterns are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent. IR spectra are reported in cm^{-1} and were recorded as films or in solution with the indicated solvent. Reactions with microwave assistance were performed using a Biotage Initiator 2.0 apparatus in a Biotage 10−20 mL microwave vial, at 130 °C (detected by IR sensor), on very high absorption mode, in 10 min.

General Procedure A: Double Alkylation with Ethyl Bromoacetate. In a 1 L three-necked flask equipped with an addition funnel, a thermometer, and an argon entry at −78 °C, to 400 mL of anhydrous THF was added 202.5 mL of a 2 M solution of LDA (405 mmol,) in THF, followed by a solution of (pyridin-3-yl)acetonitrile derivative (135 mmol) in THF (50 mL) dropwise. The resulting mixture was warmed to 0 °C and then stirred fo r1 h at 0 °C. After 1 h, the mixture was cooled to −78 °C and pure bromoethyl acetate (45 mL, 67.63 g, 405 mmol) was added dropwise. The whole mixture was slowly warmed to room temperature and stirred overnight. After one night, the mixture was slowly hydrolyzed with 250 mL of a saturated aqueous solution of ammonium chloride and transferred in a separating funnel, diluted with 800 mL of diethyl ether. The aqueous phase was basified with solid Na_2CO_3 and washed with diethyl ether (2 × 300 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography with AcOEt/cyclohexane (5−20%) as eluent, providing the desired compound.

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General Procedure B: Double 1,4-Addition on Ethyl Acrylate. To a solution of (pyridin-3-yl)acetonitrile derivatives (49.78 mmol) in acetonitrile (200 mL) was added Triton B (40% w/w in methanol, 2.3 mL, 4.98 mmol). The mixture was refluxed, and a solution of ethyl acrylate (27.28 mL, 25.04 g, 248.9 mmol) in acetonitrile (65 mL) was added dropwise. When the addition was complete, the resulting mixture was stirred under reflux overnight. After one night, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with chloroform (250 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was washed with chloroform (2 × 200 mL), and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography with CH_2Cl_2/[CH_2Cl_2/MeOH/NH_4OH 80/20/2] (in a 100/0 to 90/10 ratio) as eluent, furnishing the desired compound.

General Procedure C: Hydrogenation using Raney Nickel. A solution of 3-cyano-3-(pyridin-3-yl) acid diethyl ester derivative (37.77 mmol) and Raney nickel (slurry in water, 3 spatulas) in ethanol (300 mL) was submitted to hydrogenation in a Parr apparatus at 70 °C, under 7 bar of hydrogen, for 6 h. After 6 h, the catalyst was removed by filtration on Celite, and the resulting mixture was concentrated under reduced pressure, yielding the corresponding lactam.

General Procedure D: Reduction of the Lactam with $LiAlH_4$. In a 1 L three-necked flask equipped with a reflux condenser, a thermometer, and an argon entry, at 0 °C, to a solution of the corresponding lactam (32.77 mmol) in anhydrous THF (540 mL) was added portionwise lithium aluminum hydride (12.44 g, 327.7 mmol). When the addition was complete, the mixture was stirred overnight at 50 °C. After one night, the mixture was cooled to 0 °C, slowly hydrolyzed with a saturated aqueous solution of Na_2SO_4 until white flakes appeared, and then filtered on Celite. The Celite cake was washed with dichloromethane (3 × 200 mL), and the combined filtrates were concentrated under reduced pressure. The residue was purified via flash chromatography with CH_2Cl_2/MeOH/NH_4OH (in a 90/10/1 to 80/20/2 ratio) as eluent, providing the corresponding desired compound.

General Procedure E: Bromination with Concentrated HBr. A solution of the starting alcohol (25.9 mmol) in hydrobromic acid (130 mL, 48 wt % in water) was distributed in four sealed tubes (pressure vessels, 4 × 50 mL). The contents of the tubes were then stirred at 150 °C overnight. After one night, the tubes were cooled to room temperature and opened, and the combined reaction mixtures were concentrated under reduced pressure. The residue was diluted with 150 mL of toluene and concentrated under reduced pressure (this operation was repeated twice) to furnish the desired brominated compound, which was engaged in the next step without purification.

General Procedure F: Cyclization Leading to the Azabicyclic Core. To a suspension of the bromide obtained above (25.9 mmol) in chloroform (530 mL) was added portionwise potassium carbonate (25.83 g, 186.9 mmol) and 20 mL of water. The resulting mixture was stirred at 50 °C overnight. After one night, the layers were separated and the aqueous layer was washed with chloroform (3 × 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was then triturated in diethyl ether and filtered to yield the corresponding azabicyclic compound.

General Procedure G: Generation of Chlorinated Scaffolds by Action of $POCl_3$. A solution of azabicyclopyridin-2-ol derivative (11.77 mmol) in $POCl_3$ (32.9 mL, 54.16 g, 353.2 mmol) was equally distributed in two sealed tubes. The contents of the tubes were then stirred at 140 °C for 45 min. After 45 min, the tubes were cooled to room temperature and the combined reaction mixtures were slowly poured into crushed ice. The whole mixture was carefully basified to pH 10 with a saturated aqueous solution of Na_2CO_3 and then stirred an additional 1 h. After 1 h, this aqueous layer was washed with dichloromethane (4 × 150 mL) and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was diluted once with 200 mL of EtOH, concentrated under reduced pressure, and then diluted with 200 mL of toluene and concentrated under reduced pressure to dryness to yield the corresponding chlorinated scaffold.

General Procedure H: Regioselective Deprotonation−Halogenation of the Pyridine Moiety. Under an argon atmosphere, at 0 °C, to 0.17 mL of 2-dimethylaminoethanol (1.72 mmol) in solution in *n*-heptane (1.5 mL) was added 1.94 mL of a 1.6 M solution of *n*-butyllithium (3.1 mmol) in hexane. The resulting mixture was stirred for 30 min at 0 °C, and then at −20 °C pure nonhalogenated scaffold (0.57 mmol) was added. The resulting medium was stirred for 1 h at −20 °C and then cooled to −78 °C and the electrophile (2.3 mmol) in solution in toluene (1.5 mL) was added. The whole mixture was stirred an additional 1 h at −78 °C and then warmed to room temperature and stirred for 1 h. After 1 h, the whole mixture was hydrolyzed with an aqueous saturated solution of $NaHCO_3$, transferred to a separating funnel, and extracted twice with chloroform (2 × 150 mL). The combined organic layers were dried on sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel) with $CHCl_3$/MeOH/NH_4OH (90/10/1) as eluent to furnish the desired halogenated scaffold.

General Procedure I: Suzuki−Miyaura Coupling Reaction. To a solution of the chlorinated azabicyclic scaffold (0.24 mmol) in a 2/1 mixture of DME and water (8 and 4 mL) was added the corresponding boronic acid (0.6 mmol) and potassium carbonate (83 mg, 0.6 mmol). The resulting mixture was bubbled for 30 min while being stirred with an argon flush. After 30 min, $PdCl_2(PPh_3)_2$ (45 mg, 0.07 mmol) was added and the resulting mixture was bubbled for an additional 30 min while being stirred with an argon flush. After 30 min, the resulting mixture was stirred under reflux for 3 h. After 3 h, 30 mL of a saturated aqueous solution of Na_2CO_3 was added, and the whole mixture was washed with chloroform (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography with $CHCl_3$/MeOH/NH_4OH (in a 95/5/0.5 ratio) as eluent, providing the desired final compound.

General Procedure J: Suzuki−Miyaura Coupling Reaction Followed by Salification (HCl). To a solution of the chlorinated azabicyclic scaffold (0.26 mmol) in a 2/1 mixture of DME and water (7 and 3 mL) was added the corresponding boronic acid pinacol ester (0.66 mmol) and potassium carbonate (91 mg, 0.66 mmol). The resulting mixture was bubbled for 30 min while being stirred with an argon flush. After 30 min, $PdCl_2(PPh_3)_2$ (56 mg, 0.08 mmol) was added and the resulting mixture was bubbled for an additional 30 min while being stirred with an argon flush. After 30 min, the resulting mixture was stirred under reflux for 3 h. After 3 h, 30 mL of a saturated aqueous solution of Na_2CO_3 was added, and the whole mixture was washed with chloroform (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography with $CHCl_3$/MeOH/NH_4OH (in a 85/15/1.5 ratio) as eluent. The purified fraction was concentrated under reduced pressure, and the resulting residue was diluted with 3.5 mL of a 5−6 N solution of HCl in i-PrOH. The mixture was stirred at room temperature for 3 h. After 3 h, a precipitate was formed, which was collected by filtration, washed with diethyl ether, and dried under vacuum at 90 °C for one night to yield the corresponding hydrochloride salt of the final compound.

General Procedure K: Suzuki−Miyaura Coupling Reaction Followed by Salification (HBr). To a solution of chlorinated azabicyclic scaffold (0.24 mmol) in a 2/1 DME/water mixture (8 and 4 mL) was added the corresponding boronic acid (0.6 mmol) and potassium carbonate (83 mg, 0.6 mmol). The resulting mixture was bubbled for 30 min while being stirred with an argon flush. After 30 min,

$PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) was added and the resulting mixture was bubbled for an additional 30 min while being with an argon flush. After 30 min, the resulting mixture was stirred under reflux for 3 h. After 3 h, 30 mL of a saturated aqueous solution of Na_2CO_3 was added, and the whole mixture was washed with chloroform (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography with $CHCl_3$/MeOH/NH_4OH (in a 90/10/1 ratio) as eluent. The purified fraction was concentrated under reduced pressure, and the resulting residue was diluted with 3 mL of isopropyl alcohol and 0.15 mL of a 5.7 M solution of hydrobromic acid in acetic acid was added. The mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was diluted with methanol and concentrated under reduced pressure. This operation was repeated three times. The resulting residue was then triturated in diethyl ether and the precipitate formed was collected by filtration, washed with diethyl ether, and dried under vacuum at 60 °C for one night to furnish the corresponding hydrobromide salt of the final compound.

General Procedure L: Suzuki−Miyaura Coupling Reactions with Microwave Assistance. In a 20 mL microwave vial were placed 100 mg of the corresponding halogenated azabicyclic scaffold, potassium carbonate (2.5 equiv), the corresponding boronic acid or boronic acid pinacol ester (2.5 equiv), and $PdCl_2(PPh_3)_2$ (0.3 equiv). Then, a 2/1 mixture of DME and water (8 and 4 mL) was added and the microwave vial was sealed. The resulting mixture was then submitted to microwave irradiation and stirred for 10 min at 110 °C using a Biotage Initiator 2.0 apparatus (on very high absorption mode). After 10 min, the whole mixture was cooled to room temperature, the microwave vial was opened, and the reaction mixture was poured into a separating funnel containing 50 mL of a saturated aqueous solution of Na_2CO_3. The whole mixture was washed with chloroform (3 × 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel) with $CHCl_3$/MeOH/NH_4OH (90/10/1) as eluent to yield the corresponding final compound.

(6-Methoxypyridin-3-yl)methanol (4). In a 2 L three-necked flask equipped with an addition funnel, a thermometer, and an argon entry, at −20 °C, to a solution of 6-methoxynicotinic acid methyl ester (**3**; 45.29 g, 270.7 mmol) in dichloromethane (900 mL) was added dropwise a 1.19 M solution of diisobutylaluminium hydride in toluene (499 mL, 596 mmol) over a 3 h period. The mixture was stirred an additional 2 h at −20 °C, and then, at 0 °C, 150 mL of methanol was added dropwise followed by 300 mL of water. The resulting mixture was stirred overnight at room temperature. The layers were then separated, and the aqueous layer was washed with dichloromethane (3 × 200 mL). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate, and concentrated under reduced pressure. A 35.88 g (95% yield) amount of desired compound **4** was thus isolated as a pale yellow oil and was engaged in the following step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 2.4 Hz, 1 H), 7.58 (dd, J = 8.5, 2.4 Hz, 1 H), 6.71 (d, J = 8.5 Hz, 1 H), 4.59 (s, 2 H), 3.90 (s, 3 H), 1.92 (br s, 1 H); J-MOD ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 145.7, 138.4, 129.0, 110.9, 62.5, 53.5; IR (film, cm^{-1}) 3346, 1611, 1574, 1496, 1393, 1291, 1026, 831; mass spectrum EI+ m/z 139.0628 [$C_7H_9NO_2$ (M^+) requires 139.0633].

5-Chloromethyl-2-methoxypyridine (5). At 0 °C, to a solution of (6-methoxy-pyridin-3-yl)methanol (**4**; 58 g, 416.8 mmol) in toluene (480 mL) was added 39.5 mL (64.46 g, 541.8 mmol) of thionyl chloride dropwise, the temperature being maintained around 0 °C. The resulting mixture was then stirred at room temperature overnight. After one night, the mixture was concentrated under reduced pressure and the resulting residue was diluted with 400 mL of dichloromethane and washed carefully with a saturated aqueous solution of potassium carbonate. The aqueous layer was then washed with dichloromethane (3 × 150 mL) and the combined organic layers were dried on sodium sulfate and concentrated under reduced pressure, providing 65.7 g (quantitative yield) of the desired product **5** as a pale yellow oil, which was engaged in the next step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 2.4 Hz, 1 H), 7.59 (dd, J = 8.5, 2.4 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 1 H), 4.52 (s, 2 H), 3.92 (s, 3 H); J-MOD ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 146.7, 139.2, 126.1, 111.2, 53.6, 43.3; IR (film, cm^{-1}) 3015, 2983, 2947, 2900, 1613, 1573, 1495, 1391, 1311, 1293, 1258, 1025, 832, 757, 685; mass spectrum EI+ m/z 157.0302 [C_7H_8ClNO (M^+) requires 157.0294].

(6-Methoxypyridin-3-yl)acetonitrile (6). At room temperature, to a solution of 5-chloromethyl-2-methoxypyridine (**5**; 33 g, 209.4 mmol) in ethanol (280 mL) was added dropwise a solution of potassium cyanide (19.1 g; 293.3 mmol) in water (140 mL). The resulting mixture was then stirred under reflux overnight (oil bath temperature 100 °C). After one night, the mixture was concentrated under reduced pressure and the resulting residue was diluted with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was washed with dichloromethane (3 × 300 mL) and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography, with $CHCl_3$/MeOH/NH_4OH (in a 99/1/0.1 ratio) as eluent to yield 22.4 g (72%) of **6** as a colorless oil, which was triturated in cyclohexane to give a white powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (dd, J = 2.5, 0.6 Hz, 1 H), 7.69 (dd, J = 8.5, 2.5 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H), 3.97 (s, 2 H), 3.84 (s, 3 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 146.1, 139.1, 120.3, 119.0, 110.8, 53.2, 19.0; IR (CH_2Cl_2, cm^{-1}) 3055, 3015, 2943, 2845, 2255, 1612, 1575, 1493, 1394, 1291; mp 60−61 °C; mass spectrum CI+ m/z 149.0709 [$C_8H_9N_2O$ (M + 1) requires 149.0715].

3-Cyano-3-(6-methoxypyridin-3-yl)pentanedioic Acid Diethyl Ester (7). The title compound was obtained in 79% yield (34 g) as a brown oil from **6** according to general procedure A: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (dd, J = 2.8, 0.7 Hz, 1 H), 7.85 (dd, J = 8.8, 2.8 Hz, 1 H), 6.85 (dd, J = 8.8, 0.7 Hz, 1 H), 3.97 (qd, J = 7.1, 1.8 Hz, 4 H), 3.85 (s, 3 H), 3.34 (d, J = 16.6 Hz, 2 H), 3.21 (d, J = 16.6 Hz, 2 H), 1.05 (t, J = 7.1 Hz, 6 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3 (2 C), 163.0, 144.7, 137.0, 126.2, 120.3, 110.1, 60.4 (2 C), 53.3, 42.5 (2 C), 38.7, 13.8 (2 C); IR (film, cm^{-1}) 2981, 2942, 2899, 2844, 2241, 1733, 1604, 1565, 1491, 1377, 1291, 1189, 1017, 837; mass spectrum CI + m/z 321.1437 [$C_{16}H_{21}N_2O_5$ (M + 1) requires 321.1450].

[3-(6-Methoxypyridin-3-yl)-5-oxo-pyrrolidin-3-yl]acetic Acid Ethyl Ester (8). The title compound was obtained in 92% yield (9.6 g) as an orange oil from **7** according to general procedure C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (dd, J = 2.6, 0.5 Hz, 1 H), 7.71 (br s, 1 H), 7.63 (dd, J = 8.7, 2.6 Hz, 1 H), 6.77 (dd, J = 8.7, 0.6 Hz, 1 H), 3.87 (q, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 3.64 (dd, J = 9.8, 0.6 Hz, 1 H), 3.48 (d, J = 9.8 Hz, 1 H), 2.82 (d, J = 14.8 Hz, 1 H), 2.77 (d, J = 14.8 Hz, 1 H), 2.65 (d, J = 16.2 Hz, 1 H), 2.55 (d, J = 16.2 Hz, 1 H), 0.98 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.9, 170.2, 162.2, 144.4, 137.5, 132.7, 109.9, 59.7, 53.0, 51.6, 44.1, 43.4, 42.2, 13.8; IR (film, cm^{-1}) 3371, 3245, 3114, 2980, 2941, 2905, 1723, 1696, 1605, 1569, 1490, 1463, 1443, 1380, 1332, 1289, 1261, 1198, 1178, 1020, 830; mass spectrum CI+ m/z 279.1350 [$C_{14}H_{19}N_2O_4$ (M + 1) requires 279.1345].

2-[3-(6-Methoxypyridin-3-yl)pyrrolidin-3-yl]ethanol (9). The title compound was obtained in 79% yield (7.3 g) as a colorless oil from **8** according to general procedure D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 2.4 Hz, 1 H), 7.43 (dd, J = 8.6, 2.6 Hz, 1 H), 6.69 (d, J = 8.6 Hz, 1 H), 3.89 (s, 3 H), 3.59 (m, 1 H), 3.51 (m, 1 H), 3.38 (d, J = 9.9 Hz, 1 H), 3.24 (m, 1 H), 3.07 (m, 2 H), 2.97 (br s, 2 H), 2.15 (m, 2 H), 1.84 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 144.6, 138.0, 133.9, 109.8, 57.9, 56.6, 52.9, 47.1, 44.3, 42.2, 36.7; IR (CH_2Cl_2; cm^{-1}) 3352, 3048, 2946, 2920, 2882, 2847, 1602, 1567, 1496, 1373, 1288, 1136, 1069, 1023, 828; mass spectrum CI+ m/z 223.1445 [$C_{12}H_{19}N_2O_2$ (M + 1) requires 223.1446].

5-[3-(2-Bromoethyl)pyrrolidin-3-yl]pyridin-2-ol Hydrobromide (10). The title compound was obtained in quantitative yield (9.12 g) as a brown powder from **9** according to general procedure E: ^{1}H NMR (400 MHz, D_2O) δ 7.92 (d, J = 8.9 Hz, 1 H), 7.69 (s, 1 H), 6.86 (d, J = 9.0 Hz, 1 H), 3.75 (d, J = 11.8 Hz, 1 H), 3.57 (m, 2 H), 3.43 (m, 1 H), 3.33 (m, 1 H), 3.22 (m, 1 H), 2.56 (m, 1 H), 2.40 (m, 3 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 141.1, 133.3, 119.5, 119.1, 52.8, 48.0, 43.2, 40.7, 33.7, 29.1; mass spectrum (free base) ESI+ m/z 271.0437 [$C_{11}H_{16}BrN_2O$ (M + 1) requires 271.0441]; mp 218−220 °C.

5-(1-Azabicyclo[2.2.1]hept-4-yl)pyridin-2-ol (11). The title compound was obtained in 74% yield (3.63 g) as a brown powder from **10** according to general procedure F: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (br s, 1 H), 7.49 (dd, J = 9.4, 2.7 Hz, 1 H), 7.12 (d, J = 2.5 Hz, 1 H), 6.30 (d, J = 9.4 Hz, 1 H), 2.86 (m, 2 H), 2.55 (m, 2 H), 2.43 (s, 2 H) 1.64 (m, 2 H), 1.44 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 141.0, 131.3, 119.7, 119.0, 63.2, 55.0 (2 C), 49.8, 36.6 (2 C); IR (CH_2Cl_2, cm^{-1}) 3386, 3037; 2957, 2930, 1679, 1662, 1624, 1545, 1469, 1313, 1237, 1002, 961; mp 170−172 °C; mass spectrum ESI+ m/z 191.1174 [$C_{11}H_{15}N_2O$ (M + 1) requires 191.1184].

4-Cyano-4-(6-methoxypyridin-3-yl)heptanedioic Acid Diethyl Ester (12). The title compound was obtained in 99% yield (17.22 g) as a yellow oil from **6** according to general procedure B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 2.6 Hz, 1 H), 7.52 (dd, J = 8.7, 2.6 Hz, 1 H), 6.75 (d, J = 8.7 Hz, 1 H), 4.05 (m, 4 H), 3.92 (s, 3 H), 2.47 (m, 2 H), 2.33 (m, 2 H), 2.18 (m, 4 H), 1.19 (t, J = 7.2 Hz, 6 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2 (2 C), 163.4, 144.7, 136.9, 125.2, 120.7, 111.0, 60.1 (2 C), 53.3, 44.3, 34.2 (2 C), 30.0 (2 C), 13.9 (2 C); IR (film, cm^{-1}) 2978, 2937, 2902, 2837, 2239, 1733, 1602, 1568, 1495, 1460, 1380, 1291, 1260, 1190, 1023, 832; mass spectrum EI+ m/z 348.1683 [$C_{18}H_{24}N_2O_5$ (M^+) requires 348.1685].

3-(6′-Methoxy-6-oxo-1,4,5,6-tetrahydro-2*H*-[3,3′]bipyridinyl-3-yl)propionic Acid Ethyl Ester (13). The title compound was obtained in 95% yield (10.7 g) as a colorless oil from **12** according to general procedure C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 2.5 Hz, 1 H), 7.72 (dd, J = 8.7, 2.5 Hz, 1 H), 7.49 (d, J = 2.2 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 1 H), 3.92 (d, J = 7.1 Hz, 2 H), 3.84 (s, 3 H), 3.55 (d, J = 12.4 Hz, 1 H), 3.24 (d, J = 12.4 Hz, 1 H), 2.15 (m, 2 H), 1.90 (m, 6 H), 1.10 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 169.5, 162.2, 145.4, 137.8, 129.9, 110.2, 59.8, 54.9, 53.0, 37.6, 34.6, 30.6, 28.6, 28.1, 13.9; IR (CH_2Cl_2; cm^{-1}) 3396, 3044, 2979, 2946, 2870, 1727, 1665, 1603, 1491, 1375, 1295, 1219, 1186, 1023, 830; mass spectrum EI+ m/z 306.1583 [$C_{16}H_{22}N_2O_4$ (M^+) requires 306.1579].

3-(6′-Methoxy-1,4,5,6-tetrahydro-2*H*-[3,3′]bipyridinyl-3-yl)propan-1-ol (14). The title compound was obtained in 97% yield (8.5 g) as a pale yellow oil from **13** according to general procedure D. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, J = 2.5 Hz, 1 H), 7.50 (dd, J = 8.7, 2.6 Hz, 1 H), 6.70 (d, J = 8.7 Hz, 1 H), 3.89 (s, 3 H), 3.45 (t, J = 6.5 Hz, 2 H), 3.43 (s, 1 H), 3.19 (d, J = 12.8 Hz, 1 H), 2.83 (d, J = 12.8 Hz, 1 H), 2.76 (m, 2 H), 2.05 (m, 1 H), 1.65 (m, 5 H + H_2O), 1.45 (m, 1 H), 1.19 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 145.3, 137.9, 134.3, 109.6, 61.3, 55.1, 52.8, 46.5, 38.3, 35.9, 34.6, 26.7, 22.4; IR (film; cm^{-1}) 3281, 2935, 2852, 2816, 2729, 1601, 1569, 1498, 1454, 1378, 1280, 1256, 1168, 1129, 1057, 1022, 894, 823; mass spectrum CI+ m/z 251.1756 [$C_{14}H_{23}N_2O_2$ (M + 1) requires 251.1759].

3′-(3-Bromopropyl)-1′,2′,3′,4′,5′,6′-hexahydro[3,3′]bipyridinyl-6-ol Hydrobromide (15). The title compound was obtained in quantitative yield (12.9 g) as a brown powder from **14** according to general procedure E: ^{1}H NMR (400 MHz, D_2O) δ 7.93 (d, J = 9.3 Hz, 1 H), 7.66 (s, 1 H), 6.85 (d, J = 9.5 Hz, 1 H), 3.68 (d, J = 13.2 Hz, 1 H), 3.44 (s, 2 H), 3.33 (d, J = 13.9 Hz, 1 H), 3.23 (m, 2 H), 2.35 (m, 1 H), 1.88 (m, 6 H), 1.54 (m, 1 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 141.6, 134.2, 121.0, 118.7, 49.7, 43.4, 37.5, 37.3, 34.9, 29.6, 26.4, 18.4; mass spectrum (free base) ESI+ m/z 299.0755 [$C_{13}H_{19}BrN_2O$ (M + 1) requires 299.0753]; mp 236−238 °C.

5-(1-Azabicyclo[3.3.1]non-5-yl)pyridin-2-ol (16). The title compound was obtained in 61% yield (4.5 g) as an orange powder from **15** according to general procedure F: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (br s, 1 H), 7.54 (dd, J = 9.6, 2.6 Hz, 1 H), 6.98 (d, J = 2.3 Hz, 1 H), 6.29 (d, J = 9.6 Hz, 1 H), 2.91 (m, 4 H), 2.86 (s, 2 H), 2.02 (m, 4 H), 1.64 (m, 2 H), 1.43 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 139.4, 129.7, 126.9, 119.8, 57.8, 51.2 (2 C), 35.4 (2 C), 29.6, 23.2 (2 C); IR ($CHCl_3$; cm^{-1}) 3387 (weak), 2993, 2932, 2853, 1662, 1619, 1547, 1464, 1085, 881, 838; mass spectrum CI+ m/z 219.1498 [$C_{13}H_{19}N_2O$ (M + 1) requires 219.1497]; mp 191−192 °C.

3-Cyano-3-pyridin-3-ylpentanedioic Acid Diethyl Ester (18). The title compound was obtained in 84% yield (17 g) as a brown oil from **17** according to general procedure A: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (dd, J = 2.5, 0.6 Hz, 1 H), 8.52 (dd, J = 4.7, 1.5 Hz, 1 H), 7.95 (ddd, J = 8.1, 2.5, 1.5 Hz, 1 H), 7.43 (ddd, J = 8.1, 4.8, 0.7 Hz, 1 H), 3.95 (qd, J = 7.1, 2.2 Hz, 4 H), 3.39 (d, J = 16.7 Hz, 2 H), 3.29 (d, J = 16.7 Hz, 2 H), 1.03 (t, J = 7.1 Hz, 6 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.2 (2 C), 148.9, 147.4, 133.8, 133.2, 123.3, 120.0, 60.4 (2 C), 42.5 (2 C), 39.4, 13.8 (2 C); mass spectrum CI+ m/z 291.1335 [$C_{15}H_{19}N_2O_4$ (M + 1) requires 291.1344].

(5-Oxo-3-pyridin-3-ylpyrrolidin-3-yl)acetic Acid Ethyl Ester (19). The title compound was obtained in 65% yield (9.5 g) as an orange oil from **18** according to general procedure C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (dd, J = 2.4, 0.5 Hz, 1 H), 8.44 (dd, J = 4.7, 1.5 Hz, 1 H), 7.75 (br s, 1 H), 7.70 (ddd, J = 8.0, 2.4, 1.6 Hz, 1 H), 7.35 (ddd, J = 8.0, 4.7, 0.7 Hz, 1 H), 3.85 (q, J = 7.1 Hz, 2 H), 3.68 (d, J = 10.1, 0.7 Hz, 1 H), 3.54 (d, J = 10.1 Hz, 1 H), 2.88 (d, J = 14.9 Hz, 1 H), 2.83 (d, J = 14.9 Hz, 1 H), 2.69 (d, J = 16.2 Hz, 1 H), 2.60 (d, J = 16.2 Hz, 1 H), 0.96 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.8, 170.2, 147.7, 147.6, 139.7, 134.0, 123.2, 59.7, 51.4, 44.1, 44.0, 42.0, 13.8; mass spectrum CI+ m/z 249.1239 [$C_{13}H_{17}N_2O_3$ (M + 1) requires 249.1239].

2-(3-Pyridin-3-yl-pyrrolidin-3-yl)ethanol (20). The title compound was obtained in 94% yield (4.414 g) as a colorless oil from **19** according to general procedure D: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 2.1 Hz, 1 H), 8.44 (dd, J = 4.7, 1.4 Hz, 1 H), 8.31 (s, 1 H), 7.72 (dt, J = 8.2, 2.0 Hz, 1 H), 7.35 (dd, J = 7.9, 4.7 Hz, 1 H), 3.28 (d, J = 11.2, 1 H), 3.19 (d, J = 10.8 Hz, 1 H), 3.13 (m, 3 H), 2.94 (m, 1 H), 2.14 (m, 2 H), 1.87 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.1, 147.4, 140.1, 134.4, 123.2, 57.6, 55.3, 47.7, 43.9, 41.8, 36.9; mass spectrum CI+ m/z 193.1343 [$C_{11}H_{17}N_2O$ (M + 1) requires 193.1340].

3-[3-(2-Bromoethyl)pyrrolidin-3-yl]pyridine Hydrobromide (21). The title compound was obtained in quantitative yield (0.437 g) as a brown powder from **20** according to general procedure E: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (br s, 2 H), 8.97 (d, J = 2.6 Hz, 1 H), 8.88 (d, J = 6.4 Hz, 1 H), 8.58 (d, J = 11.2 Hz, 1 H), 8.03 (dd, J = 10.9, 7.4 Hz, 1 H), 3.68 (m, 1 H), 3.58 (m, 1 H), 3.41 (m, 1 H), 3.25 (m, 3 H), 2.41 (m, 4 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) spectrum was not exploitable due to degradation of the compound in DMSO during the J-MOD experiment; mass spectrum (free base) ESI+ m/z 255.0488 [$C_{11}H_{16}BrN_2$ (M + H) requires 255.0491]; mp 169−171 °C.

4-Pyridin-3-yl-1-azabicyclo[2.2.1]heptane (22). The title compound was obtained in 66% yield (0.96 g) as a yellow oil from **21** according to general procedure F: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (dd, J = 2.4, 0.8 Hz, 1 H), 8.42 (dd, J = 4.8, 1.6 Hz, 1 H), 7.74 (ddd, J = 7.8, 2.3, 1.6 Hz, 1 H), 7.33 (ddd, J = 7.8, 4.7, 0.8 Hz, 1 H), 2.93 (m, 2 H), 2.62 (m, 4 H), 1.76 (m, 2 H), 1.64 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.1, 147.3, 138.4, 134.6, 123.3, 63.2 (2 C), 55.0 (2 C), 51.2, 37.3 (2 C); mass spectrum EI+ m/z 174.1155 [$C_{11}H_{14}N_2$ (M^+) requires 174.1157].

4-Cyano-4-pyridin-3-ylheptanedioic Acid Diethyl Ester (23). The title compound was obtained in 92% yield (24.797 g) as a orange oil from **17** according to general procedure B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.3 Hz, 1 H), 8.60 (dd, J = 4.7, 1.4 Hz, 1 H),

7.72 (ddd, J = 8.1, 2.3, 1.6 Hz, 1 H), 7.34 (dd, J = 8.0, 4.7 Hz, 1 H), 8.69 (d, J = 2.3 Hz, 1 H), 4.03 (m, 4 H), 2.39 (m, 6 H), 2.12 (m, 2 H), 1.19 (t, J = 7.1 Hz, 6 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2 (2 C), 149.5, 147.3, 134.1, 132.3, 123.9, 120.4, 60.1 (2 C), 45.1, 34.1 (2 C), 30.0 (2 C), 13.9 (2 C); IR (film, cm^{-1}) 3607, 3441, 3033, 2982, 2931, 2865, 2864, 2235, 1729, 1567, 1480, 1456, 1413, 1370, 1290, 1192, 1089, 1030, 860, 812, 709; mass spectrum CI+ m/z 319.1649 [$C_{17}H_{23}N_2O_4$ (M + 1) requires 319.1657].

3-(6-Oxo-1,4,5,6-tetrahydro-2*H*-[3,3′]bipyridinyl-3-yl)-propionic Acid Ethyl Ester (24). The title compound was obtained in 68% yield (9.416 g) as a yellow oil from **23** according to general procedure C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 2.1 Hz, 1 H), 8.51 (d, J = 4.6 Hz, 1 H), 7.61 (d, J = 8.1 Hz, 1 H), 7.29 (dd, J = 8.0, 4.8 Hz, 1 H), 6.45 (br s, 1 H), 4.00 (q, J = 7.1 Hz, 2 H), 3.72 (d, J = 12.5 Hz, 1 H), 3.40 (d, J = 12.4 Hz, 1 H), 2.12 (m, 8 H), 1.16 (t, J = 7.1 Hz, 3 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 169.4, 148.4, 147.6, 137.3, 134.6, 123.4, 59.8, 48.1, 38.2, 34.6, 30.5, 28.6, 28.1, 13.9; IR (film; cm^{-1}) 3386, 3234, 3036, 2983, 2930, 2873, 1722, 1646, 1498, 1471, 1418, 1372, 1350, 1300, 1228, 1187, 1087, 1023, 715; mass spectrum CI+ m/z 277.1551 [$C_{15}H_{21}N_2O_3$ (M + 1) requires 277.1552].

3-(1,4,5,6-Tetrahydro-2*H*-[3,3′]bipyridinyl-3-yl)propan-1-ol (25). The title compound was obtained in 73% yield (5.411 g) as a pale yellow oil from **24** according to general procedure D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, J = 1.9 Hz, 1 H), 8.36 (dd, J = 4.7, 1.6 Hz, 1 H), 7.73 (ddd, J = 8.0, 2.4, 1.7 Hz, 1 H), 7.31 (ddd, J = 8.0, 4.6, 0.6 Hz, 1 H), 4.21 (br s, 1 H), 3.21 (t, J = 6.7 Hz, 1 H), 3.17 (s, 1 H), 3.14 (d, J = 12.3 Hz, 1 H), 2.74 (d, J = 12.4 Hz, 1 H), 2.65 (m, 2 H), 2.00 (m, 1 H), 1.67 (m, 2 H), 1.49 (m, 2 H), 1.27 (m, 1 H), 1.00 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.7, 146.3, 141.5, 134.6, 123.0, 61.2, 54.8, 46.5, 39.1, 36.1, 34.5, 26.7, 22.4; mass spectrum CI+ m/z 221.1661 [$C_{13}H_{21}N_2O$ (M + 1) requires 221.1653].

3-(3-Bromopropyl)-1,2,3,4,5,6-hexahydro[3,3′]bipyridinyl Hydrobromide (26). The title compound was obtained in quantitative yield (5.454 g) as a orange powder from **25** according to general procedure E: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J = 1.5 Hz, 1 H), 8.95 (br s, 1 H), 8.88 (d, J = 5.3 Hz, 1 H), 8.66 (d, J = 8.3 Hz, 1 H), 8.47 (br s, 1 H), 8.08 (dd, J = 8.2, 5.6 Hz, 1 H), 3.86 (d, J = 13.2 Hz, 1 H), 3.37 (m, 2 H), 3.01 (br s, 2 H), 2.40 (d, J = 14.4 Hz, 1 H), 1.83 (m, 4 H), 1.56 (m, 2 H), 1.33 (m, 1 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.0, 141.7, 141.2, 140.4, 127.1, 60.4, 49.5, 43.2, 38.3, 34.6, 29.3, 26.1, 18.3; mass spectrum (free base) ESI+ m/z 283.0808 [$C_{13}H_{20}BrN_2$ (MH$^+$) requires 283.0804]; mp 230−232 °C.

5-Pyridin-3-yl-1-azabicyclo[3.3.1]nonane (27). The title compound was obtained in 60% yield (1.821 g) as a pale yellow solid from **26** according to general procedure F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1 H), 8.40 (d, J = 4.6 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.19 (dd, J = 7.9, 4.8 Hz, 1 H), 3.16 (s, 2 H), 3.07 (m, 4 H), 2.20 (m, 4 H), 1.81 (m, 2 H), 1.55 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.8, 146.6, 145.8, 132.4, 123.2, 58.0, 51.3 (2 C), 36.2 (2 C), 30.9, 23.4 (2 C); EI+ m/z 202.1464 [$C_{13}H_{18}N_2$ (M$^+$) requires 202.1470]; mp 84−86 °C.

4-(6-Chloropyridin-3-yl)-1-azabicyclo[2.2.1]heptane (1). The title compound was obtained as a brown gum either according to general procedure G in 91% yield (2.23 g) from **11** or according to general procedure H using C_2Cl_6 as electrophile in 62% yield (74 mg) from **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 2.4 Hz, 1 H), 7.58 (dd, J = 8.2, 2.5 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 1 H), 3.29 (td, J = 10.7, 5.0 Hz, 2 H), 2.93 (s, 2 H), 2.89 (m, 2 H), 1.95 (td, J = 10.6, 4.7 Hz, 2 H), 1.80 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.3, 148.2, 138.4, 137.2, 123.8, 62.6, 54.5 (2 C), 50.3, 36.4 (2 C); mp 70−72 °C; mass spectrum CI+ m/z 209.0850 [$C_{11}H_{14}ClN_2$ (M + 1) requires 209.0845].

5-(6-Chloropyridin-3-yl)-1-azabicyclo[3.3.1]nonane (2). The title compound was obtained as a brown powder either according to general procedure G in 90% yield (0.68 g) from **16** or according to general procedure H using C_2Cl_6 as electrophile in 83% yield (97 mg) from **27**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 2.4 Hz, 1 H), 7.54 (dd, J = 8.4, 2.6 Hz, 1 H), 7.26 (d, J = 8.6 Hz, 1 H), 3.21 (s, 2 H), 3.19 (m, 4 H), 2.23 (m, 4 H), 1.82 (m, 2 H), 1.68 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.6, 147.0, 145.4, 136.6, 123.7, 57.8, 51.2 (2 C), 36.0 (2 C), 30.8, 23.3 (2 C); IR ($CHCl_3$; cm^{-1}) 2985, 2934, 2880, 2852, 1577, 1566, 1480, 1459, 1365, 1111, 1079, 1028, 874; mass spectrum EI+ m/z 236.1106 [$C_{13}H_{17}ClN_2$ (M$^+$) requires 236.1080]; mp 103−104 °C.

4-(6-Bromopyridin-3-yl)-1-azabicyclo[2.2.1]heptane (28). The title compound was obtained as a pale yellow solid according to general procedure H using CBr_4 or $C_2Br_2Cl_4$ as electrophile in 39% (56 mg) and 69% yield (99 mg) respectively, from **22**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (dd, J = 2.5, 0.3 Hz, 1 H), 7.72 (dd, J = 8.2, 2.6 Hz, 1 H), 7.58 (dd, J = 8.3, 0.4 Hz, 1 H), 2.93 (td, J = 10.5, 5.0 Hz, 2 H), 2.65 (s, 2 H), 2.63 (m, 2 H), 1.75 (m, 2 H), 1.64 (m, 2 H); J-MOD ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.9, 138.9, 138.3, 138.2, 127.5, 63.1, 54.9 (2 C), 50.7, 37.1 (2 C); mass spectrum CI+ m/z 253.0351 [$C_{11}H_{14}BrN_2$ (M + 1) requires 253.0340]; mp 92−93 °C.

5-(6-Bromopyridin-3-yl)-1-azabicyclo[3.3.1]nonane (29). The title compound was obtained as a pale yellow solid according to general procedure H using CBr_4 or $C_2Br_2Cl_4$ as electrophile in 35% (49 mg) and 81% yields, (112 mg), respectively, from **27**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 2.4 Hz, 1 H), 7.71 (dd, J = 8.4, 2.7 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 3.04 (s, 2 H), 2.95 (m, 4 H), 2.10 (m, 4 H), 1.73 (m, 2 H), 1.48 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.6, 145.6, 138.6, 136.5, 127.5, 57.6, 51.1 (2 C), 35.8 (2 C), 31.0, 23.1 (2 C); mass spectrum EI+ m/z 280.0569 [$C_{13}H_{17}BrN_2$ (M$^+$) requires 280.0575]; mp 110−112 °C.

5-(1-Azabicyclo[2.2.1]hept-4-yl)-6′-fluoro[2,3′]bipyridinyl (30a). The title compound was obtained as a white powder either according to general procedure I using 2-fluoro-5-pyridylboronic acid in 54% yield (35 mg) from **1** or according to general procedure L using 2-fluoro-5-pyridylboronic acid in 42% yield (106 mg) from **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (d, J = 2.0 Hz, 1 H), 8.68 (d, J = 1.8 Hz, 1 H), 8.61 (td, J = 8.2, 2.4 Hz, 1 H), 7.98 (d, J = 8.2 Hz, 1 H), 7.87 (dd, J = 8.2, 2.3 Hz, 1 H), 7.29 (dd, J = 8.6, 2.8 Hz, 1 H), 2.94 (td, J = 10.4, 4.9 Hz, 2 H), 2.65 (s, 2 H), 2.62 (m, 2 H), 1.80 (m, 2 H), 1.66 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2 (d, J = 235.7 Hz, 1 C), 150.6, 148.3, 145.6 (d, J = 15.5 Hz, 1 C), 139.9 (d, J = 8.2 Hz, 1 C), 138.1, 135.9, 132.8 (d, J = 4.4 Hz, 1 C), 120.0, 109.6 (d, J = 37.6 Hz, 1 C), 63.3, 55.1 (2 C), 51.2, 37.4 (2 C); ^{19}F NMR (188 MHz, DMSO-d_6) δ −69.5; mass spectrum CI+ m/z 270.1399 [$C_{16}H_{17}FN_3$ (M + 1) requires 270.1406]; mp 108−109 °C.

6-[5-(1-Azabicyclo[2.2.1]hept-4-yl)pyridin-2-yl]quinoline Hydrochloride 1/3 (30b). The title compound was obtained as a white powder either according to general procedure J using 6-quinolineboronic acid pinacol ester in 61% yield (165 mg) from **1** or according to general procedure L using 6-quinolineboronic acid pinacol ester followed by salification (as described in general procedure J), providing **30b** as its hydrochloride salt in 62% yield (188 mg) from **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (br s, 1 H), 9.30 (dd, J = 5.0, 1.4 Hz, 1 H), 9.23 (d, J = 8.6 Hz, 1 H), 8.90 (d, J = 1.8 Hz, 1 H), 8.52 (d, J = 8.5 Hz, 1 H), 8.20 (dd, J = 8.5, 7.4 Hz, 1 H), 8.16 (dd, J = 8.2, 2.4 Hz, 1 H), 8.09 (dd, J = 7.2, 0.8 Hz, 1 H), 8.01 (dd, J = 8.7, 5.0 Hz, 1 H), 7.93 (d, J = 8.2 Hz, 1 H), 3.67 (s, 2 H), 3.57 (m, 2 H), 3.49 (m, 2 H), 2.26 (m, 4 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.3, 147.3, 146.2, 142.6, 140.3, 137.7, 136.7, 134.3, 132.9, 130.1, 126.2, 125.2, 123.3, 122.4, 60.0, 52.4 (2 C), 49.1, 33.6 (2 C); mass spectrum (free base) CI+ m/z 302.1644 [$C_{20}H_{20}N_3$ (M + 1) requires 302.1657]; mp 327−328 °C.

4-[6-(3-Fluorophenyl)pyridin-3-yl]-1-azabicyclo[2.2.1]heptane (30c). The title compound was obtained as a white powder according to general procedure I using 3-fluorophenylboronic acid in 68% yield (48 mg) from **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 1.8 Hz,

1 H), 7.88 (m, 4 H), 7.52 (dd, J = 14.2, 8.0 Hz, 1 H), 7.25 (td, J = 8.6, 2.1 Hz, 1 H), 2.95 (td, J = 10.4, 4.8 Hz, 2 H), 2.66 (s, 2 H), 2.63 (m, 2 H), 1.81 (td, J = 10.2, 4.5 Hz, 2 H), 1.67 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7 (d, J = 241.2 Hz, 1 C), 152.4, 148.1, 141.2 (d, J = 7.7 Hz, 1 C), 138.0, 135.8, 130.7 (d, J = 8.3 Hz, 1 C), 122.2 (d, J = 2.4 Hz, 1 C), 120.0, 115.5 (d, J = 21.1 Hz, 1 C), 112.8 (d, J = 22.6 Hz, 1 C), 63.3, 55.1 (2 C), 51.1, 37.3 (2 C); ^{19}F NMR (188 MHz, DMSO-d_6) δ −112.9; mass spectrum CI+ m/z 269.1449 [$C_{17}H_{18}FN_2$ (M + 1) requires 269.1454]; mp 88−90 °C.

4-(6-Benzo[1,3]dioxol-5-ylpyridin-3-yl)-1-azabicyclo[2.2.1]heptane (30d) . The title compound was obtained as a white powder according to general procedure I using 3,4-(methylenedioxy)phenylboronic acid in 79% yield (61 mg) from **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 1.7 Hz, 1 H), 7.88 (d, J = 8.3 Hz, 1 H), 7.83 (dd, J = 8.3, 2.2 Hz, 1 H), 7.63 (m, 2 H), 7.01 (d, J = 8.7 Hz, 1 H), 6.08 (s, 2 H), 3.33 (m, 2 H), 3.28 (s, 2 H), 3.17 (m, 2 H), 2.03 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.2, 148.1, 147.9, 147.6, 135.5, 133.7, 132.8, 120.5, 119.3, 108.4, 106.5, 101.3, 61.1, 53.3 (2 C), 49.6, 34.7 (2 C); mass spectrum EI+ m/z 294.1370 [$C_{18}H_{18}N_2O_2$ (M^+) requires 294.1368]; mp 256−258 °C.

4-[6-(2-Methoxyphenyl)pyridin-3-yl]-1-azabicyclo[2.2.1]-heptane Hydrobromide 1/2 (30e). The title compound was obtained as a brown powder either according to general procedure K using 2-methoxyphenylboronic acid in 55% yield (58 mg) from **1** or according to general procedure L using 2-methoxyphenylboronic acid in 92% yield (161 mg) from **28**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (br s, 1 H), 8.87 (d, J = 1.9 Hz, 1 H), 8.44 (d, J = 8.1 Hz, 1 H), 8.14 (d, J = 8.4 Hz, 1 H), 7.68 (dd, J = 7.6, 1.7 Hz, 1 H), 7.59 (td, J = 7.9, 1.7 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 3.86 (s, 3 H), 3.71 (s, 2 H), 3.54 (m, 4 H), 2.27 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.7, 150.5, 142.6, 141.2, 135.3, 132.5, 131.6, 126.8, 122.3, 121.0, 112.2, 60.1, 55.9, 52.7 (2 C), 48.9, 33.2 (2 C); mass spectrum (free base) EI+ m/z 280.1580 [$C_{18}H_{20}N_2O$ (M^+) requires 280.1575]; mp 114−116 °C.

5-[5-(1-Azabicyclo[2.2.1]hept-4-yl)pyridin-2-yl]quinoline (30f). The title compound was obtained as a white powder according to general procedure I using 5-quinolineboronic acid in 72% yield (72 mg) from **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (dd, J = 4.1, 1.6 Hz, 1 H), 8.78 (d, J = 2.1 Hz, 1 H), 8.60 (d, J = 8.5 Hz, 1 H), 8.10 (d, J = 8.5 Hz, 1 H), 7.95 (dd, J = 8.1, 2.3 Hz, 1 H), 7.85 (t, J = 7.3 Hz, 1 H), 7.75 (d, J = 7.1 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.53 (dd, J = 8.6, 4.1 Hz, 1 H), 2.99 (td, J = 10.5, 4.8 Hz, 2 H), 2.72 (s, 2 H), 2.67 (m, 2 H), 1.87 (td, J = 10.0, 4.3 Hz, 2 H), 1.72 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 150.4, 148.1, 147.8, 138.2, 137.3, 135.8, 134.1, 129.6, 128.9, 127.6, 125.7, 124.3, 121.6, 63.4, 55.0 (2 C), 51.1, 37.4 (2 C); mass spectrum EI+ m/z 301.1571 [$C_{20}H_{19}N_3$ (M^+) requires 301.1579]; mp 129−131 °C.

4-[6-(3-Pyrazol-1-ylphenyl)pyridin-3-yl]-1-azabicyclo-[2.2.1]heptane (30g). The title compound was obtained as a white powder either according to general procedure I using 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-pyrazole in 42% yield (64 mg) from **1** or according to general procedure L using 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-pyrazole in 61% yield (76 mg) from **28**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (dd, J = 2.3, 0.6 Hz, 1 H), 8.60 (d, J = 2.3 Hz, 1 H), 8.52 (t, J = 1.8 Hz, 1 H), 8.00 (m, 2 H), 7.88 (m, 2 H), 7.78 (d, J = 1.6 Hz, 1 H), 7.60 (t, J = 7.9 Hz, 1 H), 6.57 (td, J = 1.8, 0.6 Hz, 1 H), 2.95 (m, 2 H), 2.67 (s, 2 H), 2.64 (m, 2 H), 1.82 (m, 2 H), 1.68 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.1, 148.1, 141.0, 140.2, 140.0, 137.7, 135.8, 129.9, 127.9, 124.0, 120.0, 118.7, 116.2, 107.9, 63.3, 55.0 (2 C), 51.1, 37.3 (2 C); IR (CH_2Cl_2, cm^{-1}) 3041, 2957, 2884, 1610, 1593, 1555, 1516, 1478, 1397, 1334, 1194, 1044, 967, 946, 841, 817; mass spectrum EI+ m/z 316.1679 [$C_{20}H_{20}N_4$ (M^+) requires 316.1688]; mp 114−116 °C.

5-(1-Azabicyclo[3.3.1]non-5-yl)-6′-fluoro[2,3′]bipyridinyl (31a). The title compound was obtained as a white powder according to general procedure I using 2-fluoro-5-pyridylboronic acid in 37% yield (23 mg) from **2**, according to general procedure L using 2-fluoro-5-pyridylboronic acid in 41% yield (104 mg) from **2**, or according to general procedure L using 2-fluoro-5-pyridylboronic acid in 79% yield (68 mg) from **29**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (br s, 1 H), 8.65 (br s, 1 H), 8.40 (t, J = 7.5 Hz, 1 H), 7.64 (m, 2 H), 7.00 (d, J = 6.7 Hz, 1 H), 3.21 (s, 2 H), 3.12 (m, 4 H), 2.22 (m, 4 H), 1.88 (m, 2 H), 1.59 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2 (d, J = 235.6 Hz, 1 C), 150.0, 146.8, 145.6 (d, J = 15.5 Hz, 1 C), 145.3, 139.9 (d, J = 8.2 Hz, 1 C), 133.9, 132.7 (d, J = 4.0 Hz, 1 C), 119.9, 109.5 (d, J = 37.6 Hz, 1 C), 58.0, 51.2 (2 C), 36.0 (2 C), 31.0, 23.4 (2 C); ^{19}F NMR (188 MHz, DMSO-d_6) δ −69.5; IR ($CHCl_3$; cm^{-1}) 2985, 2932, 2896, 2850, 1590, 1473, 1392, 1082, 824; mass spectrum CI+ m/z 298.1728 [$C_{18}H_{21}FN_3$ (M + 1) requires 298.1719]; mp 121−122 °C.

5-(6-Naphthalen-2-ylpyridin-3-yl)-1-azabicyclo[3.3.1]nonane (31h). The title compound was obtained as a white powder according to general procedure I using 2-naphthylboronic acid in 46% yield (32 mg) from **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 2.1 Hz, 1 H), 8.45 (s, 1 H), 8.11 (d, J = 8.6 Hz, 1 H), 7.92 (m, 2 H), 7.84 (m, 1 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.67 (dd, J = 8.4, 2.3 Hz, 1 H), 7.47 (m, 2 H), 3.24 (s, 2 H), 3.14 (m, 4 H), 2.23 (m, 4 H), 1.91 (m, 2 H), 1.60 (m, 2 H); J-MOD ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.2, 146.6, 144.5, 135.9, 133.7, 133.1, 133.0, 128.5, 128.2, 127.5, 126.5, 126.4, 125.4, 124.2, 119.9, 57.9, 51.2 (2 C), 36.0 (2 C), 31.0, 23.3 (2 C); IR ($CHCl_3$; cm^{-1}) 3057, 3042, 2931, 2878, 2849, 1589, 1553, 1482, 1460, 1449, 1443, 1346, 1081, 1024, 821; mass spectrum EI+ m/z 328.1953 [$C_{23}H_{24}N_2$ (M^+) requires 328.1940]; mp 163−165 °C.

■ ASSOCIATED CONTENT

Supporting Information. Figures giving ^{1}H, ^{13}C NMR, or J-MOD ^{13}C NMR and ^{19}F spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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