An Expeditious Library Synthesis of *N*-Monoalkylated Aminopiperidines and -pyrrolidines

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N-Monosubstituted aminopiperidines and -pyrrolidines are important building blocks for the synthesis of small-molecule compound libraries. We have developed a practical solid-phase route to *N*-monosubstituted aminopiperidines and -pyrrolidines utilizing a selective reductive alkylation of primary or secondary amines attached to a Merrifield or Wang resin. Purification is achieved by simple filtration after each reaction step. The synthetic route developed can be readily applied to an extensive pool of commercially available aromatic and aliphatic aldehydes for conversion into the corresponding *N*-monoalkylated diamino templates. Solid-phase NMR spectroscopy was used to monitor the reactions. The new pulse sequences described in this report have further extended the usefulness of this nondestructive analytical methodology.

Introduction

Designer building blocks are key elements for the synthesis of structure-activity relationship (SAR) directed combinatorial libraries. In recent years this development has been manifested in numerous reports describing developments in solid-phase synthesis[1,2] and combinatorial chemistry adapted to polymeric supports.[3−5] These technologies are now widely applied in the preparation of drug-like libraries in high-throughput screening (HTS) against a multitude of drug targets. However, there are still several challenges that need to be addressed in the design and execution of compound libraries. One such important consideration is the choice of linker, which has to be stable under the reaction conditions employed and has to be selectively cleaved under mild conditions after the synthesis sequence is completed to yield pure product.

A major general drawback of solid-supported reactions has been the difficulty experienced in analyzing the reaction products on the solid phase. To circumvent this problem analytical control is frequently carried out in solution after cleavage from the polymer, which is time-consuming and results in loss of material. Consequently, recent developments have focused on techniques for nondestructive on-bead analysis adapted to solid-phase chemistry[6] utilizing both single-bead FT-IR and high-resolution magic-angle spinning (HRMAS) NMR spectroscopy.[7−9] An issue encountered with 1D and 2D homo- and heteronuclear HRMAS NMR experiments is the multitude of non-relevant signals arising from the resin, residual solvents and from organics encapsulated in the beads, making the interpretation of the spectra nontrivial. In this report we have included the use of 1D techniques[10−14] to remove unwanted signals and we also report on an extension of these techniques for 2D gHSQC spectra.

We also report a useful extension to the synthesis of *N*-monosubstituted aminopiperidine and -pyrrolidine compound libraries through a reductive alkylation of commercially available aromatic and aliphatic aldehydes. The methodology described provides ready access to diverse sets of *N*-monoalkylated aminopiperidine and -pyrrolidine compound libraries. This procedure nicely complements methodologies of amide reductions[15] and of reversed reductive aminoalkylations.[16,17]

Results

The synthesis of *N*-monoalkylated piperidine and pyrrolidine compound libraries are depicted in Schemes 1 and 2, respectively, with *p*-nitrophenyl carbonate Merrifield (0.8 mmol/g loading) and Wang (1 mmol/g loading) resins as polymeric supports. Attachment of the starting amines to the resins (step *a*) was performed at 20 °C in DMF for 24 h and the products were analyzed by single-bead FT-IR, ninhydrin[18−19] test and HRMAS NMR spectroscopy.

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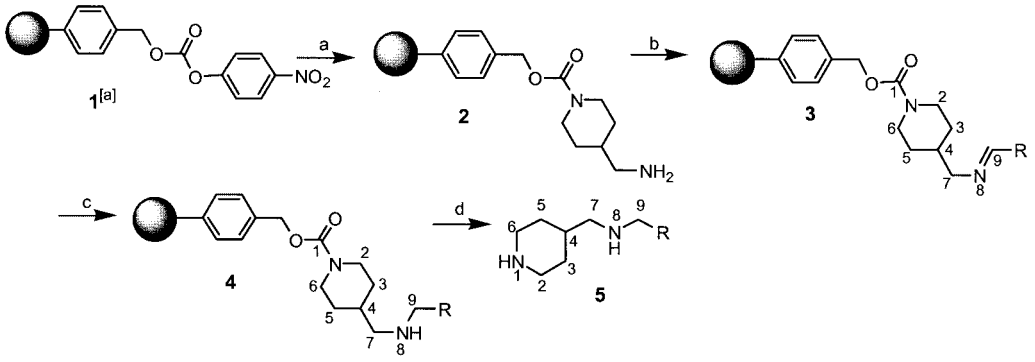
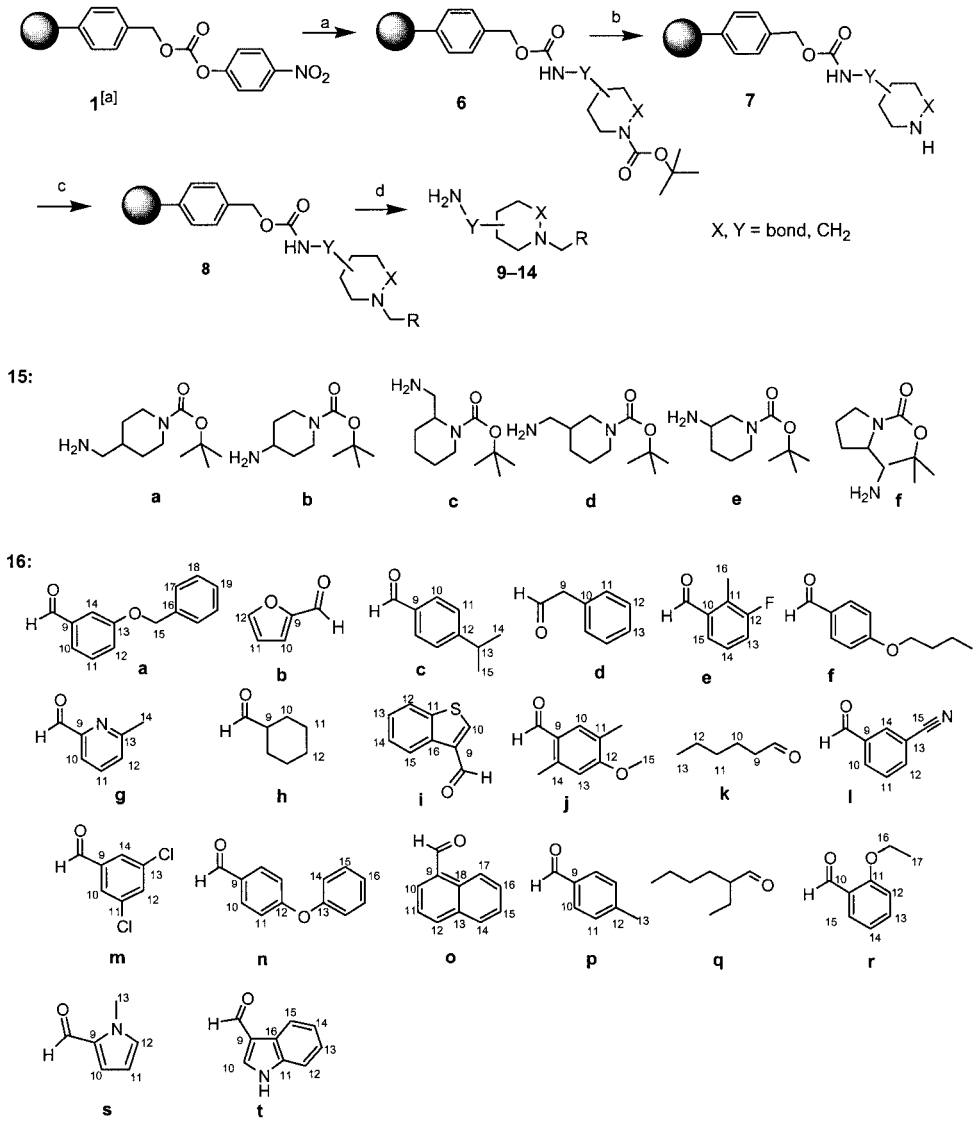
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1. Reagents and conditions: (a) 4-(aminomethyl)piperidine (5 equiv. in anh. DMF), room temp., overnight; (b) RCHO (**16**) (5 equiv. in TMOF) see Scheme 2, room temp., overnight; (c) BH_3·py complex (BAP) (4 equiv.), DCM/MeOH/AcOH (2:2:1), room temp., overnight; (d) 75% TFA in DCM, room temp., 1 h; [a] Merrifield or Wang resin



Scheme 2. Reagents and conditions: (a) Boc-protected amines **15** (5 equiv. in anhydrous DMF), room temp., overnight; (b) selective Boc deprotection with 10% TFA in DCM, room temp., 2 h; (c) RCHO **16** (10 equiv. in TMOF/(DMF/EtOH, 3:1) (1:1), BH_3·py complex (BAP) (10 equiv.), room temp., 4 d; (d) 75% TFA in DCM, room temp., 4 h; [a] Merrifield resin gave better yields than Wang resin, see text and Table 6

Typically, during *step a*, the absorption bands at 1760 and 1350 cm^{-1} of the FT-IR spectra, corresponding to the carbonate group and the nitro group, respectively, were transformed into a new absorption band at 1720 cm^{-1}, corresponding to the carbonyl group of the carbamate function. For *N*-monoalkylated (aminomethyl)piperidines with structure **5** (Scheme 1), it was not possible to determine from the FT-IR data whether the attachment to the resin was through the secondary or primary amino group.

While conventional HRMAS NMR[10−14] spectroscopy was used for the characterization of compounds **6** (Scheme 2), having a BOC-protected secondary amino group, the additional CPMG T_2/diffusion filter gHSQC HRMAS NMR experiment was implemented (vide infra) to allow the determination of the attachment of the amino group to the polymer. This additional experiment is exemplified for compounds **3** and **4** (Scheme 1).

Reductive Alkylation of the Primary Amines and Use of FT-IR and HRMAS NMR Spectroscopy to Monitor the Reactions

Alkylation of the primary amine **2** on solid phase (Scheme 1) with aldehydes **16** in solution was performed in a two-step procedure to minimize dialkylations.[20−21] The imine-forming step proceeds readily with the amine on the solid phase and the aldehyde in solution.[22] $(MeO)_3CH$ (TMOF) was employed as both solvent and dehydrating agent.[23−24] Reduction of the imine to the corresponding amine was achieved by reaction with borane−pyridine complex[25] (BH_3·Py, BAP) at room temperature overnight. This reaction was also monitored by FT-IR spectroscopy, exhibiting the characteristic N=C absorption band at 1645 cm^{-1}.

HRMAS NMR spectroscopy was used to monitor the reductive alkylation steps and cleavage from the resin (Scheme 1) and is exemplified by the two aldehydes **16e** and **16r** in Figure 1 (a−e), with the numbering of carbon atoms in the **16e** and **16r** groups as shown in Scheme 2. In the gHMBC spectrum of compound **3** (corresponding to **16e** on Wang resin; Figure 2 a), a cross peak is clearly observed between the protons of the methylene group 7-H_2 and the carbon atom C-9, further supporting the formation of the primary amine **2** in Scheme 1. The full assignment of compound **3** (with **16e**) was achieved using gHMBC, gHSQC and COSY experiments (Figure 2, a−c). Similar results were obtained for compound **3** containing the

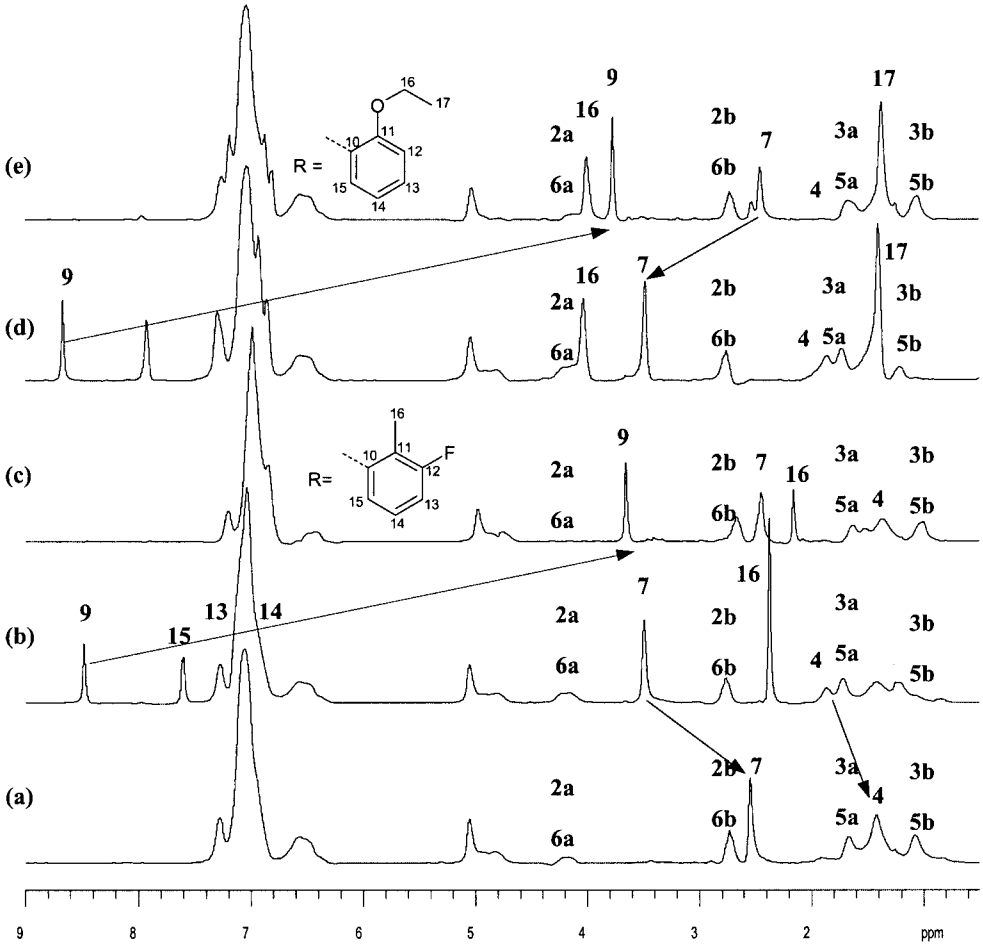


Figure 1. ^1H NMR spectra with T_2 and diffusion filters of the products of the reaction presented in Scheme 1: (a) **2**; (b) **3** (with R **16e**, see Scheme 2); (c) **4** (with R **16e**, see Scheme 2) corresponding to compound **5d** (see Table 1) once cleaved from the solid support; (d) **3** and (e) **4** (with R **16f**, see Scheme 2) corresponding to compound **5j** (see Table 1) once cleaved from the solid support

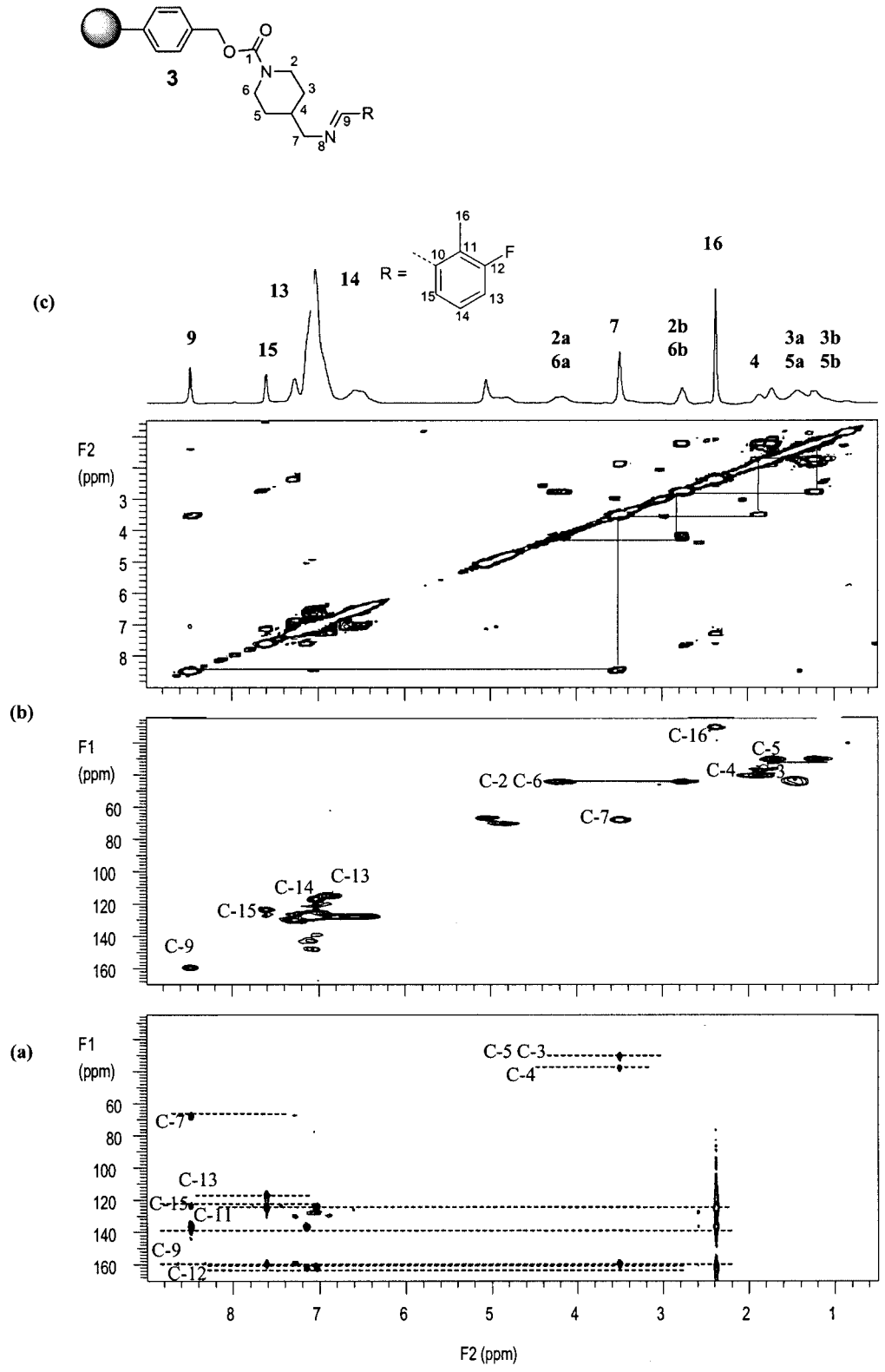


Figure 2. (a) gHMBC, (b) gHSQC and (c) COSY experiments of the imine product **3** (with R **16e**, see Scheme 2)

aldehyde **16r** (Figure 1, d); assignments of the proton and carbon resonances from COSY, gHSQC and gHMBC spectra are presented in Figure S1 (Supporting Information; see also the footnote on the first page of this article). It is noteworthy that the proton signals of the piperidine fragment of compounds **3** are much broader than for the imine fragment, similar to amines **2** (Figure 1, a, b, d).

This set of experiments clearly shows that the attachment of the unprotected 4-(aminomethyl)piperidine to the *p*-nitrophenyl carbonate resin occurs exclusively through the secondary cyclic amino group.

Use of CPMG-T_2/Diffusion Filtered Ghsqc Experiments to Monitor the Amine Reduction Steps

To remove the residual resin signals from the high-resolution NMR spectra, CPMG-T_2 type filters $(\text{delay}-180°-\text{delay})_n$ were used (Figure 3.). The basis of this method is the discrepancy in the mobility of the resin part of the molecule and the resin-bound moieties. The first, being mainly in the solid phase, has very low mobility compared with the resin-bound moieties, which still retain reasonably free rotational diffusion[13]. Therefore, it is expected that a nucleus belonging to the resin part would have a considerably shorter T_2 relaxation time than the nuclei belonging to the resin-bound moieties. Filtering times of 20−80 ms are usually employed. A few reports[10−14] on the use of such filters have appeared, but mainly dealing with 1D techniques. The T_2 filter parameters have to be carefully selected since the signals of interest are attenuated to a lesser degree. Indeed, in the gHMBC spectrum (Figure 2, a) of compound **3**, the protons belonging to the piperidine and resin fragments already do not show any cross peaks with carbon atoms two or three bonds away due to short T_2 relaxation. However, in the HSQC experiments the transfer times are very short (usually not more than 10−15 ms), which is not long enough for the resin signals to die out (example Figure 2, b). Additionally, the method usually used to separate out the signals from the unbound molecules in the sample is to use a diffusion filter.[13,23] The species bound to the resin are restricted in their movement, while the small molecules diffuse much faster.

Figure 4 shows two HSQC spectra of compounds **4** (Scheme 1), a conventional gHSQC experiment (Figure 4, a) and a modified CPMG-T_2/diffusion-filtered gHSQC experiment (Figure 4, b). With careful selection of the T_2-filter parameters and diffusional parameters (see Exp. Sect.), most of the polymer signals, as well as those belonging to the methylene fragments 2-H_2, 3-H_2, 5-H_2 and 6-H_2 of piperidine, are removed and give rise to the signals of interest, those of the R group. The monitoring of the imine reduction was possible by the detection of new carbon and proton signals of the $-N^8H-C^9H_2$ fragment of compounds **4** (Figure 4, b) and the disappearance of the $-N^8=C^9H$ fragment of compounds **3** (Figure 2, b). The proton chemical shift of the methylene group, 7-H_2, in compounds **4** [with both **16e** and **16r** (Figure S1)] has moved upfield compared to the corresponding signal in compounds **3** from $\delta = 3.5$ to 2.3 ppm. This is due to the reduction of the imine moiety. Full data with proton and carbon assignments of compound **4** (with both **16e** and **16r**), based on the gCOSY, gHMBC, gHSQC and modified gHSQC spectra are presented in the Supporting Information (Figures S2 and S3, respectively).

Synthesis of Compounds 5

These compounds were obtained as bis(trifluoroacetate) salts in good yields and purities after trifluoroacetic acid (TFA) treatment of resins **4** (see Table 1 and Exp. Sect. for MS data and NMR characterization).

Synthesis of Compounds 6

The primary amines on solid support were prepared from the corresponding Boc-protected secondary amines.

Analysis of Compounds 6 (Scheme 2) by HRMAS NMR Spectroscopy

Conventional 2D ^{1}H COSY, ^{1}H, ^{13}C-HMBC and gHSQC experiments (data not shown) were employed. In Figure 5 (a) the ^{1}H NMR spectrum of compound **6** with CPMG-T_2 and diffusion filters[11] is shown corresponding to amine **15e**. The intense signal of a proton at $\delta = 1.44$ ppm is as-

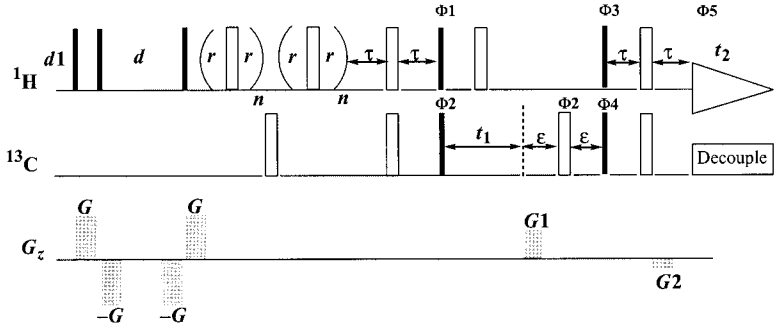


Figure 3. Pulse sequence for the CPMG-T_2 filtered HSQC experiment; narrow and open bar symbols represent 90° and 180° pulses, respectively; the pulse-field-gradient pulses are indicated by filled bar symbols; gradient pulses *G*, *G*1, *G*2 and delays *r* and τ are as described in the text; all pulses are applied along the *x* axis unless otherwise indicated; phase cycling: Φ_1 90,90,270,270, Φ_2 0,180, Φ_3 (0)*4 (180)*4, Φ_4 (0)*8 (180)*8, Φ_5 0,180,180,0,180,0,0,180,180,0,0,180,0,180,180,0; broadband GARP-1 ^{13}C decoupling was applied during acquisition

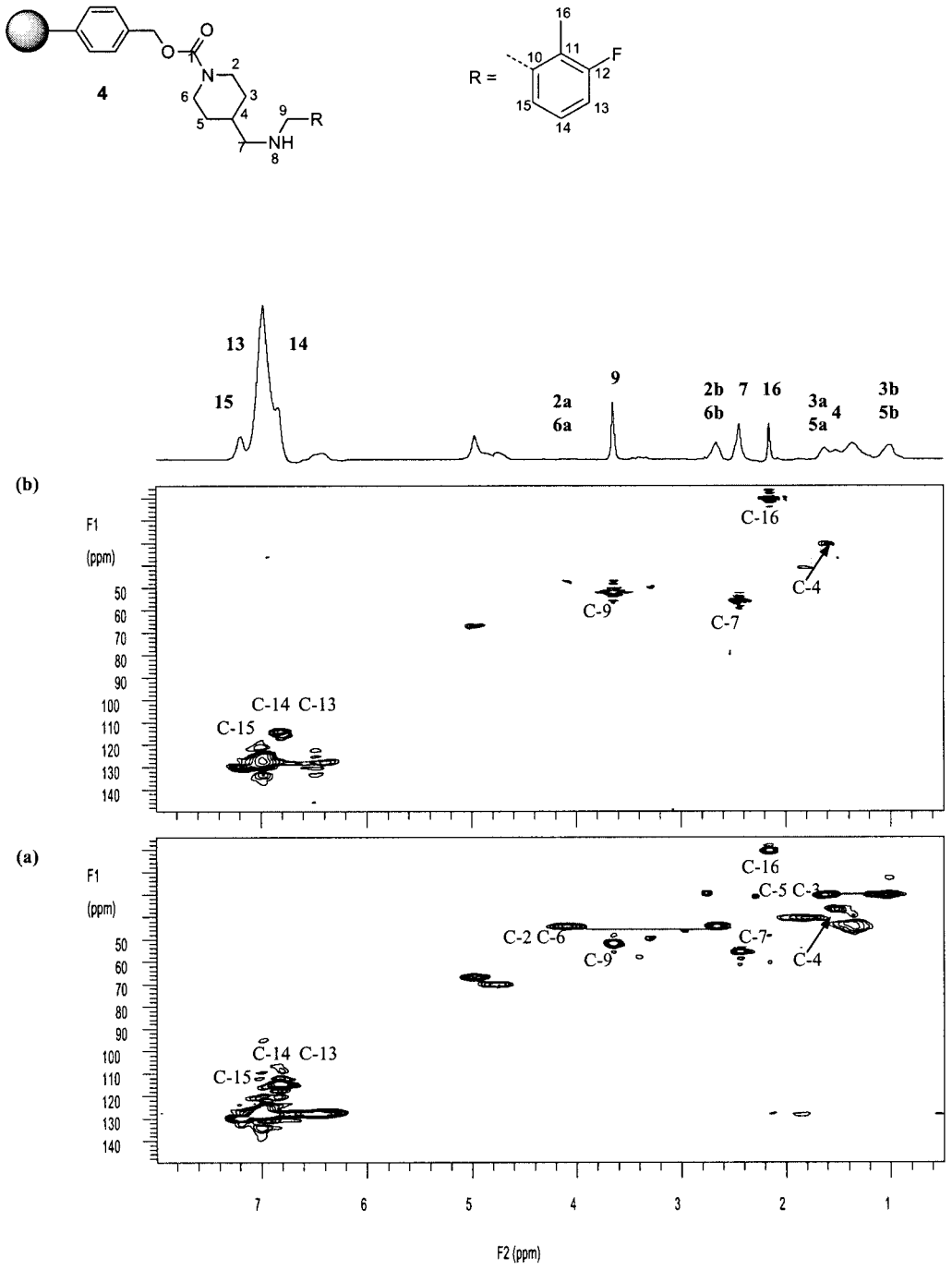


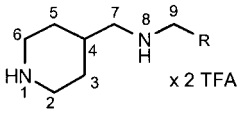
Figure 4. 2D ^{1}H-^{13}C correlation experiments of compound **4** (with R **16e**, see Scheme 2) performed by: (a) conventional gHSQC, and (b) modified CPMG-T_2 diffusion-filtered gHSQC experiments

signed to the methyl group of the BOC fragment and is clearly observed.

Synthesis of Compounds 8 by Reductive Alkylation of the Secondary Amine Moiety of Compounds 7

Selective BOC group deprotection of compounds **6** was initially examined employing various acidic conditions (Figure 5, a). The best results were obtained using 10% TFA in dichloromethane (DCM).[25] Essentially quantitative yields of compounds **7** (Figure 5, b) were obtained, as estimated from the 1D-^{1}H (Figure 5) NMR spectrum with a CPMG-T_2/diffusion filter. After the deprotection step, the resulting secondary amines were subjected to reductive alkylation with aldehydes **16** (Scheme 2). This was achieved in situ using BAP,[26] resulting in clean reactions and high yields of products. Other reducing reagents examined, including $NaBH_3CN$, $NaBH(OAc)_3$, and $Ti(OiPr)_4$, were found to be less effective.[27–29] As an illustration, alkylation products **8** (Scheme 2), corresponding to the cleaved products **13d** and **13o** (Table 6), were analyzed by HRMAS NMR spec-

Table 1. Purity and MS characterization of **5**



Product[a]	RCHO (**16**)[b]	*m/z* [M + H$^+$]	LCMS purity[c] (%)	^{1}H NMR purity (%)
5a	**a**	310.9	85	N.A.[d]
5b	**b**	194.9	82	N.A.
5c	**c**	247.0	93	N.A.
5d[e]	**e**	236.9	97	> 95
5e	**f**	277.0	94	N.A.
5f	**g**	219.9	86	N.A.
5g	**h**	211.0	94	N.A.
5h	**i**	260.9	94	N.A.
5i	**q**	227.0	82	N.A.
5j[e]	**r**	248.0	92	93

[a] The yields obtained were > 90% in all the cases with respect to the initial loading of the resin (0.8 mequiv./g). [b] See precursor aldehyde in Scheme 2.[c] The crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 2−40−90% acetonitrile in water (0.1% HCOOH) at 214 nm for 6 min. [d] Not analyzed (N.A.). [e] See NMR spectroscopic data in the Exp. Sect.

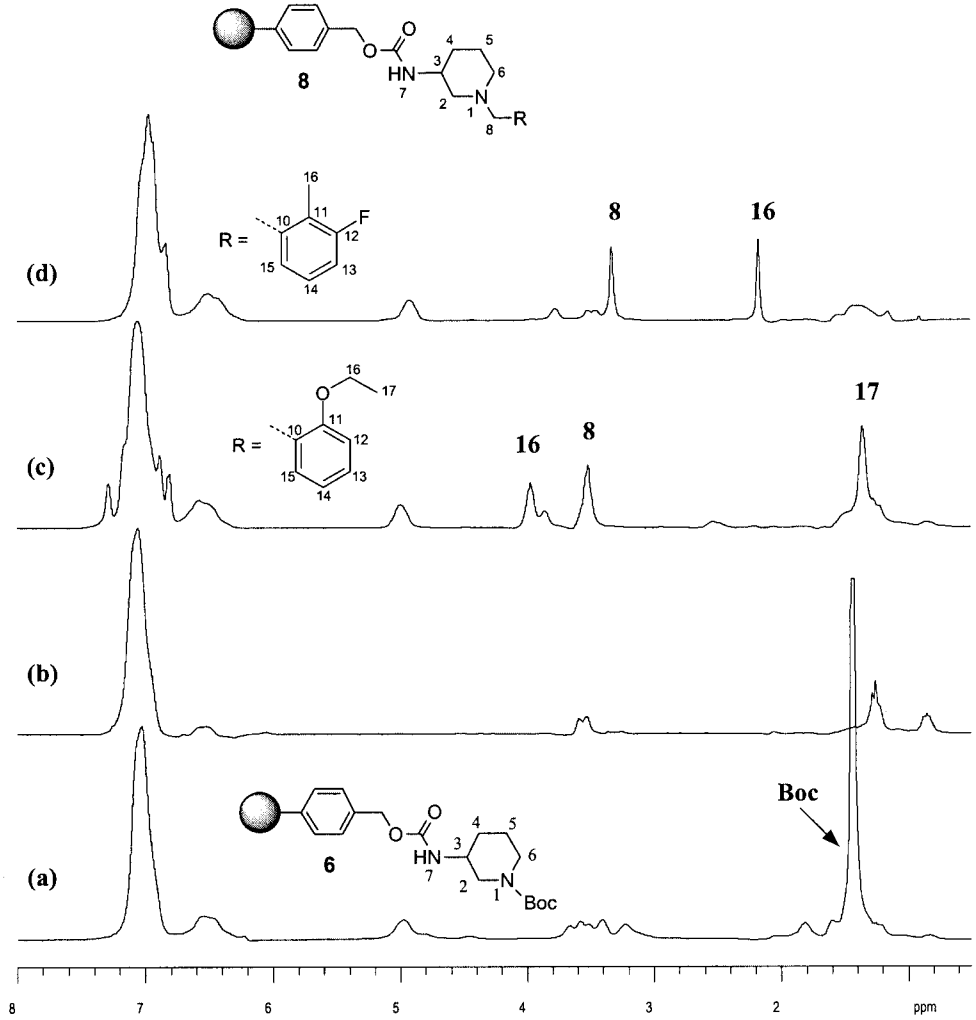


Figure 5. ^{1}H NMRspectra with T_2 and diffusion filters of the products of the reaction presented in Scheme 2: (a) **6**, (b) **7**, (c) **8** (with R **16r** and amine **15e**, Scheme 2); (d) **8** (with R **16e** and amine **15e**, Scheme 2)

troscopy (Figure 5, c, d). The assignment of resonances 8 and 16 (compound **8** with R **16e**) and resonances 8, 16, 17 (compound **8** with R **16r**) is based on CPMG-T_2/diffusion-filtered gHSQC experiments (Figure S4).

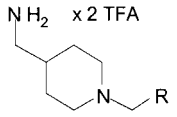
Synthesis of Final Products 9−14

Compounds **9**−**14** were obtained as bis(trifluoroacetate) salts in good overall yields and with high LCMS purities after cleavage from the solid support with TFA (75% in DCM; Tables 2−7). From the library, 36% of the products were characterized by NMR spectroscopy (see Exp. Sect.).

Conclusion

A practical solid-phase synthesis of *N*-monosubstituted aminopiperidines and -pyrrolidines has been developed. Selective alkylation of the primary or secondary amine moiety was accomplished by use of the two synthetic routes

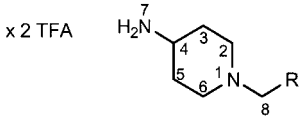
Table 2. Yields, purity and MS characterization for compounds **9**



Product	RCHO (**16**)[a]	*m*/*z* [M + H$^+$]	Yields[b] (%)	LCMS purity[c] (%)	^{1}H NMR purity (%)
9a	**a**	310.9	93	90	N.A.[d]
9b	**b**	194.9	90	85	N.A.
9c	**c**	247.0	93	91	N.A.
9d	**d**	219.0	90	85	N.A.
9e	**e**	236.9	93	93	N.A.
9f	**f**	277.0	95	98	N.A.
9g	**g**	220.0	90	89	N.A.
9h	**h**	211.0	94	96	N.A.
9i	**i**	260.9	89	85	N.A.
9j	**q**	227.0	96	93	N.A.

[a] See precursor aldehyde in Scheme 2. [b] Yields obtained with respect to the initial loading of the resin (0.8 mequiv./g for Merrifield resin). [c] The crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 2−40−90% acetonitrile in water (0.1% HCOOH) at 214 nm for 6 min. [d] Not Analyzed (N.A.).

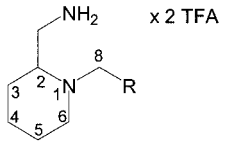
Table 3. Yields, purity and MS characterization for compounds **10**



Product	RCHO (**16**)[a]	*m*/*z* [M + H$^+$]	Yields[b] (%)	LCMS purity[c] (%)	^{1}H NMR purity (%)
10a	**a**	297.0	93	89	N.A[d]
10b	**b**	181.9	88	85	N.A.
10c	**c**	233.0	95	96	N.A.
10d	**d**	205.0	80	75	N.A.
10e	**e**	223.0	96	90	N.A.
10f	**f**	263.0	97	98	N.A.
10g	**g**	206.0	97	98	N.A.
10h	**h**	197.1	92	90	N.A.
10i[e]	**i**	246.9	95	90	> 95
10j[e]	**j**	249.0	89	93	90
10k	**k**	185.1	86	80	N.A.
10l[e]	l	216.0	96	95	90
10m[e]	**m**	260.9	90	93	95
10n	**n**	283.0	98	99	N.A.
10o	**o**	241.0	95	97	N.A.
10p	r	235.0	92	86	N.A.
10q[e]	**t**	230.1	88	87	88

[a] See precursor aldehyde in Scheme 2. [b] Yields obtained with respect to the initial loading of the resin (0.8 mequiv./g for Merrifield resin). [c] The crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 2−40−90% acetonitrile in water (0.1% HCOOH) at 214 nm for 6 min. [d] Not analyzed (N.A.). [e] See NMR spectroscopic data in the Exp. Sect.

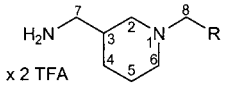
Table 4. Yields, purity and MS characterization for compounds **11**



Product	RCHO (**16**)[a]	*m/z* [M + H$^+$]	Yields[b] (%)	LCMS purity[c] (%)	^{1}H NMR purity (%)
11a	**a**	311.0	95	96	N.A[d]
11b	**b**	195.0	86	82	N.A.
11c[e]	**c**	247.0	93	94	95
11d	**d**	219.0	89	90	N.A.
11e[e]	**e**	237.0	92	91	95
11f	**f**	277.0	94	95	N.A.
11g	**g**	220.0	94	97	N.A.
11h[e]	**h**	211.1	89	98	95
11i	**i**	260.9	88	86	N.A.
11j	**j**	263.0	92	93	N.A.
11k	**k**	199.1	93	94	N.A.
11l	**l**	230.0	92	90	N.A.
11m	**m**	274.9	90	88	N.A.
11n	**n**	297.0	98	99	N.A.
11o[e]	**o**	255.0	93	92	92
11p[e]	**r**	249.0	90	92	>95

[a] See precursor aldehyde in Scheme 2. [b] Yields obtained with respect to the initial loading of the resin (0.8 mequiv./g for Merrifield resin). [c] The crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 2−40−90% acetonitrile in water (0.1% HCOOH) at 214 nm for 6 min. [d] Not analyzed (N.A.).[e] See NMR spectroscopic data in the Exp. Sect.

Table 5. Yields, purity and MS characterization for compounds **12**



Product	RCHO (**16**)[a]	*m/z* [M + H$^+$]	Yields[b] (%)	LCMS purity[c] (%)	^{1}H NMR purity (%)
12a[d]	**a**	311.0	97	95	92
12b[d]	**b**	195.0	80	82	85
12c	**c**	247.0	94	96	N.A[e]
12d	**d**	219.0	80	81	N.A
12e	**e**	237.0	92	90	N.A
12f	**f**	277.0	95	98	N.A
12g	**g**	220.0	89	88	N.A
12h[d]	**h**	211.1	94	92	90
12i[d]	**i**	260.9	91	93	90
12j	**j**	263.0	90	88	N.A
12k	**k**	199.1	88	85	N.A
12l	**l**	230.0	94	97	N.A
12m[d]	**m**	274.9	90	89	82
12n[d]	**n**	297.0	97	93	90
12o[d]	**o**	255.0	95	92	95
12p	**r**	249.0	92	93	N.A
12q[d]	**s**	208.0	90	90	90

[a] See precursor aldehyde in Scheme 2. [b] Yields obtained with respect to the initial loading of the resin (0.8 mequiv./g for Merrifield resin). [c] The crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 2−40−90% acetonitrile in water (0.1% HCOOH) at 214 nm for 6 min. [d] See NMR spectroscopic data in the Exp. Sect. [e] Not analyzed (N.A.).

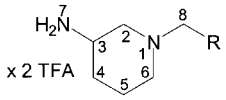
outlined in this study. The products were isolated in good yields and purities after simple filtration steps, which enable easy parallel processing.

The 2D NMR CPMG-T_2 filter gHSQC experiment together with the present solid-phase methodology aimed at novel diamine building blocks will further broaden the scope of solid-phase methodologies and assist in the preparation of novel drug-like compounds.

Experimental Section

General Methods: Commercially available chemicals were used as purchased. BOC-protected amines were purchased from Asta Tech

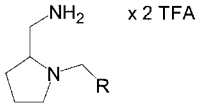
Table 6. Yields, purity and MS characterization for compounds **13**



Product	RCHO (**16**)[a]	*m/z* [M + H$^+$]	Yields[b] (%)	LCMS purity[c] (%)	^{1}H NMR purity (%)
13a	**a**	297.0	(8)	94	N.A[d]
13b	**b**	181.0	(7)	88	N.A
13c[e]	**d**	205.0	81 (7)	91 (85)	(80)
13d[e]	**e**	223.2	90 (7)	93	95
13e	**f**	263.0	(9)	95	N.A
13f[e]	**g**	206.0	100 (9)	98 (80)	(80)
13g[e]	**h**	197.0	82	97	> 95
13h[e]	**i**	246.9	80 (8)	95 (75)	> 95
13i[e]	**k**	185.1	86 (6)	95	90
13j[e]	**l**	216.0	100	98	> 95
13k[e]	**m**	260.0	83	95	> 95
13l[e]	**n**	283.0	68 (6)	96	92
13m[e]	**o**	241.0	78 (6)	96	92
13n[e]	**p**	205.0	92	98	> 95
13o[e]	**r**	235.3	82	98	> 95

[a] See precursor aldehyde in Scheme 2. [b] The yields obtained with respect to the initial loading of the resin [0.8 mequiv./g for Merrifield or 1.0 mequiv./g for Wang resin (data shown in brackets)]. [c] The crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 2−40−90% acetonitrile in water (0.1% HCOOH) at 214 nm for 6 min. Results for reactions with Wang resins are shown in brackets. [d] Not analyzed (N.A.). [e] See NMR spectroscopic data in the Exp. Sect.

Table 7. Yields, purity and MS characterization for compounds **14**



Product	RCHO (**16**)[a]	*m/z* [M + H$^+$]	Yields[b] (%)	LCMS purity[c] (%)	^{1}H NMR purity (%)
14a	**a**	297.0	75	95	N.A[d]
14b	**b**	181.0	70	70	N.A
14c	**c**	233.1	75	85	N.A
14d	**e**	223.0	80	90	N.A
14e	**f**	263.0	95	98	N.A
14f	**j**	249.0	84	92	N.A
14g	**r**	235.0	87	94	N.A

[a] See precursor aldehyde in Scheme 2; performing the reaction with aldehydes **16d**, **16g**−**l**, **16k**−**m** on Wang resin resulted in poor yields (4−5%). [b] Yields obtained with respect to the initial loading of the resin (0.8 mequiv./g for Merrifield resin). [c] The crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 2−40−90% acetonitrile in water (0.1% HCOOH) at 214 nm for 6 min. [d] Not analyzed (N.A.).

Inc., and unprotected amines and 4-methylmorpholine (NMM) from Lancaster. Aldehydes were purchased from Lancaster or Aldrich. Borane−pyridine complex (BH_3·py, BAP) was purchased from Aldrich. *p*-Nitrophenyl carbonate Merrifield resin (0.8 mmol/g) was purchased from Novabiochem and *p*-nitrophenyl carbonate Wang resin SS (1% DVB, 100−200 mesh, 1 mmol/g) from Advanced ChemTech. Aminomethylated polystyrene resin (100−200 mesh, 1.13 mmol/g) was purchased from Novabiochem. For reactions, 4- and 8-mL Wheaton vials with screw caps were used. Racks 12 × 8 from Chiron Technologies (SKJL9650-02, SKJL9650-01, SKJL9651-01, SKJL9651-02) were used for shaking with an IKA KS 260 basic shaker. A Multi-Wash Head System from Chiron Technologies was used for washing and rinsing of the resins. A Manual Cleavage Station from Chiron, as well as a VacMaster from IST, were used for cleavage reactions. A vial-adapted Vaporator Station from Chiron was used for evaporations, and a vacuum centrifuge HT-4 from Genevac Technologies was used for concentration and lyophilization of the library samples. A Perkin−Elmer FT-IR spectrophotometer was used for recording IR spectra on solid support. A Water-Micromass instrument, using Waters 2790 Alliance, Waters 996 photodiode array detector and Micromass ZMD (API ES pos. and neg.) mass detector were used for recording LCMS. Synergi MAX-RP 50 × 4.6 mm 80A, 4u from Phenomex was used as reverse-phase column for the LCMS analysis, and acetonitrile/water/0.1% HCOOH was used as the mobile phase. The ninhydrin test was performed according to the procedure described by Kaiser[18,19] with aminomethylated polystyrene resin as positive control.

NMR Methods: NMR spectra were acquired using a Varian Unity Inova spectrometer at a magnetic field strength of 11.7 T operating at 499.84 MHz for ^{1}H, and 125.67 MHz for ^{13}C. The spectrometer was equipped with a 5-mm indirect detection probe, with a deuterium lock coil and a pulsed-field-gradient coil along the *z* axis and an inverse detection HRMAS probe with a one-axis pulsed-field-gradient coil. The gradient coil was parallel to the sample, at 54.7° angle relative to the magnetic field. Hard ^{1}H pulses were applied with a 28.6 kHz field strength. ^{13}C hard pulses were applied with a 20.8 kHz field strength. ^{13}C decoupling was performed using GARP with a 4.2 kHz field strength. Spectra were recorded with the HRMAS probe by spinning the samples at rates of 2500 Hz with 40 μL of 1−2 mg swollen resin in $CDCl_3$ (99.8%). Chemical shifts for ^{1}H NMR spectra are reported in ppm with TMS as internal reference. Chemical shifts for ^{13}C NMR spectra are reported in ppm relative to the chemical shifts of TMS. The temperature in all experiments was set to 25 °C. Gradient-enhanced CPMG-T_2 and diffusion-filtered HSQC pulse sequences are shown in Figure 3. The total T_2 filtering time was set at 20 ms, and the refocusing delay, *r*, in the filter was set at 2.5 ms. The diffusion delay, *d*, was set at 30 ms. The selection gradients were synchronized to the spinning speed of the sample. The diffusion selection gradients, *G*, had a strength of 10 G·cm^{-1} for 2 ms, which means that the sample performs five rotations during these pulses. The coherence pathway selection was effected with the gradient pulses *G*1 and *G*2, with strengths of 3 and −0.75 G·cm^{-1}, respectively, with gradient duration 1.2 ms corresponding to three sample rotations during the pulses. All the gradient pulses are rectangular pulses. The relaxation delay *d*1 was set to 1.0 s. The transfer delay, τ (τ = 1/4$J_{C,H}$), was set to 1.78 ms, corresponding to a ^{1}H-^{13}C coupling constant of 140 Hz. The delay ε was set to 3.6 ms. 2048 × 64 point matrixes with 64 (or 128) scans per increment were acquired with total acquisition times of 3 (or 6) h, respectively. In *F*1, linear prediction to 512 points was performed followed by zero filling to 1 K points. A squared cosine window function was applied in both dimensions. Standard COSY-type experiments were recorded as 1 K × 128 real matrix with 4 scans per increment and a spectral width of 10 ppm. In all cases the recycle delay used was 1.0 s. The total acquisition times were 10 min. In *F*1, linear prediction to the 256 points was performed followed by zero filling to 1024 points. A sine bell window function was applied in both dimensions. 2D-HMBC experiments were performed using gradient coherence selection, a relaxation delay of 1.0 s. The evolution delay for long-range $J_{C,H}$ coupling constants was 125 ms. 2048 × 256 point matrixes with 128 scans per increment were acquired. The total acquisition time was 6 h. A squared cosine window function was applied in both dimensions.

Preparation of Resin 2: Scheme 1. *p*-Nitrophenyl carbonate Merrifield resin (0.8 mmol/g, 4 mmol, 5 g) was placed in a 100-mL round-bottomed flask and pre-swollen in anhydrous DMF (25 mL). 4-(Aminomethyl)piperidine (2.3 g, 20 mmol) in DMF (5 mL) was added to the resin and the suspension was stirred at room temperature overnight. The resin was filtered and washed with DMF (100 mL), DCM (2 × 100 mL), MeOH (2 × 100 mL) and DCM (2 × 100 mL). After drying in vacuo, 4.18 g of resin **2** was obtained. Solid support FT-IR: Carbamide band at 1700 cm^{-1}. Positive ninhydrin test. See MAS NMR spectroscopic data in Figure 1 (a).

Preparation of Resins 3. General Procedure for the Reductive Alkylation of Resin-Bound Primary Amine: Scheme 1. Dry resin-bound amine **2** (1.3 g, 0.24 mmol) was dispensed into 10 screw-cap vials (8 mL) and then suspended in trimethyl orthoformate (TMOF) (2 mL). Aldehyde **16** (see Table 1) (1.2 mmol), dissolved in TMOF (2−3 mL), was added. The vials were closed and placed in a rack, which was shaken overnight. The resins were then filtered, washed (3 × DCM) and dried. An FT-IR spectrum was recorded for all the resins (imine absorption band at 1645 cm^{-1}). See also MAS NMR spectroscopic data in the results section, Figure 2, corresponding to resins **3** (with R **16e**), and Figure S1 corresponding to resins **3** (with R **16r**), which correspond to cleaved compounds **5d** and **5j**, respectively, in Table 1.

Preparation of Resins 4. Imine Reduction: Scheme 1. Resin **3** (0.24 mmol) was suspended in DCM/MeOH/AcOH (2:2:1) and borane−pyridine complex (BH_3·py, BAP) (0.96 mmol, 100 μL) was added. The vials were shaken overnight. The resin was filtered and then washed with DMF (2 × 10 mL), water (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL), DCM (2 × 10 mL) and then dried. See MAS NMR data in Figures S2 and S3 corresponding to resins **4** (with R **16e**) and **4** (with R **16r**), respectively, which correspond to cleaved compounds **5d** and **5j**, respectively, in Table 1.

General Procedure for the TFA Cleavage of Resins 4: Scheme 1. Cleavage from the resin was performed by acidic treatment with 75% TFA/DCM (2−3 mL). The cleavage solution was added to the vials containing resin **4** (0.24 mmol). The vials were closed and shaken for 1 h. The resin was then filtered and the solution kept in 8-mL vials together with the DCM washes (2 × 2 mL). The vials were then placed under vacuum for concentration of the TFA solution. The residues were redissolved in acetonitrile/water, placed in preweighed 4-mL vials, and lyophilized. Yields were > 90% in all cases, with high purity, as determined by LCMS. The compounds were obtained as TFA salts. The structure of the final compounds **5** was confirmed by LCMS (positive ES) (see Table 1), and by NMR spectroscopy (**5d** and **5j**, see below).

***N*-(3-Fluoro-2-methylbenzyl)-*N*-(piperidin-4-ylmethyl)amine Bis(trifluoroacetate) Salt (5d):** For atom numbering see Table 1. ^{1}H NMR ([D$_6$]DMSO): δ = 9.07 (s, 2 H, 8$^+$-H$_2$), 7.97 (s, 2 H, 1$^+$-H$_2$), 7.33−7.26 (m, 2 H, 13-H, 15-H), 7.22−7.18 (m, 1 H, 14-H), 4.20 (s, 2 H, 9-H′, 9-H′′), 3.28 (m, 2 H, 2-H′, 6-H′), 2.97 (s, 2 H, 7-H′, 7-H′′), 2.85 (m, 2 H, 2-H′′, 6-H′′), 2.25 (s, 3 H, 11-CH$_3$), 2.04 (m, 1 H, 4-H), 1.92−1.78 (m, 2 H, 3-H′, 5-H′), 1.41−1.27 (m, 2 H, 3-H′′, 5-H′′) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 159.26, 162.80 (C-12), 133.71 (C-10), 127.95 (C-15), 126.91 (C-13), 125.01 (C-11), 116.36 (C-14), 52.18 (C-7), 48.10 (C-9), 43.72 (C-2), (C-6), 32.30 (C-4), 26.79 (C-3), (C-5), 11.05 (C-16) ppm. MS (ESI): *m*/*z* = 236.9 [M + H]$^+$.

***N*-(2-Ethoxybenzyl)-*N*-(piperidin-4-ylmethyl)amine Bis(trifluoroacetate) Salt (5j):** For atom numbering see Table 1. ^{1}H NMR ([D$_6$]DMSO): δ = 8.82 (s, 2 H, 8$^+$-H$_2$), 7.95 (s, 2 H, 1$^+$-H$_2$), 7.39 (d, *J* = 7.8 Hz, 1 H, 15-H), 7.38 (t, *J* = 7.2 Hz, 1 H, 13-H), 7.06 (d, *J* = 8.3 Hz, 1 H, 12-H), 6.97 (t, *J* = 8.3 Hz, 1 H, 14-H), 4.09 (m, 4 H, 9-H′, 9-H′′, 16-H′, 16-H′′), 3.29 (m, 2 H, 2-H′, 6-H′), 2.88−2.83 (m, 4 H, 7-H′, 7-H′′, 2-H′′, 6-H′′), 2.04 (m, 1 H, 4-H), 1.92−1.83 (m, 2 H, 3-H′, 5-H′), 1.39−1.29 (m, 2 H, 3-H′′, 5-H′′), 1.53 (t, *J* = 7.6 Hz, 3 H, 17-H$_3$) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 157.57 (C-11), 132.04 (C-15), 131.57 (C-13), 121.77 (C-14), 120.35 (C-10), 112.68 (C-12), 64.33 (C-16), 51.98 (C-7), 46.15 (C-9), 43.10 (C-2), (C-6), 31.25 (C-4), 26.88 (C-3), (C-5), 15.25 (C-17) ppm. MS (ESI): *m*/*z* = 248.0 [M + H]$^+$.

Preparation of Resins 6. Attachment of BOC-Amines to the Solid Support: Scheme 2. The procedure for a typical experiment is as follows. *p*-Nitrophenyl carbonate Merrifield resin (0.8 mmol/g, 4 mmol, 5 g) was pre-swollen in anhydrous DMF (25 mL). 3-Amino-1-BOC-piperidine (**15e**) (3.9 g, 18 mmol) was dissolved in DMF (5 mL) and added to the resin. The suspension was stirred

at 20 °C for 20 h. The resin was filtered and washed with DMF (100 mL), DCM (2 × 100 mL), MeOH (2 × 100 mL) and DCM (2 × 100 mL). After drying in vacuo, 4.94 g of resin **6** (corresponding to **15e**) was obtained. Solid support FT-IR: Broad band with two peaks at 1728, 1684 cm^{-1}. Negative ninhydrin test. See HRMAS NMR spectroscopic data in Figure 5, a.

Preparation of Resins 7. Removal of the BOC Group: Scheme 2. The procedure for a typical experiment is as follows. Resin **6** (corresponding to **15e**; 4.94 g, 4 mmol assumed) was treated with 10%TFA/DCM solution for 2 h. The resin was then filtered and washed with DCM (2 × 40 mL), 10% NMM/DCM (1 × 40 mL), DCM (2 × 40 mL), MeOH (2 × 40 mL) and DCM (2 × 40 mL). After drying in a vacuum oven, 4 g of resin was obtained. FT-IR spectroscopy showed a weak absorption band corresponding to the remaining carbamate band. Positive ninhydrin test. See HRMAS NMR spectroscopic data in Figure 5, b.

Preparation of Resins 8. Reductive Alkylation of Resin-Bound Secondary Amine: Scheme 2. The procedure for a typical experiment is as follows. Resin **7** (corresponding to amine **15e**, 275 mg, 0.22 mmol) was suspended in TMOF (2 mL) in a screw-cap vial (8 mL). Aldehyde **16e** (304 mg, 2.2 mmol) was dissolved in DMF/EtOH (3:1) (2 mL) and added to the resin, followed by the addition of BAP (2.2 mmol, 280 μL). The closed vial was placed in a rack and shaken for 4−5 d. The resin was filtered and washed once with DMF/EtOH (3:1), twice with DCM and finally with MeOH. See HRMAS NMR spectroscopic data in Figure 5, c and d corresponding to resins **8** with cleavage products **13o** and **13d**, respectively, in Table 6.

General Procedure for the TFA Cleavage from Resins 8: Scheme 2. Cleavage from the resin was obtained by acidic treatment with 75% TFA/DCM (2−3 mL). The cleavage solution was added to the vials containing the solid-supported amine derivatives **8** (0.2 mmol for Wang resin derivatives and 0.18 mmol for Merrifield resin derivatives). The closed vials were shaken for 1 h. The resins were filtered and the solutions were placed into 8-mL vials together with the DCM washes (2 × 2 mL). The TFA solutions were then concentrated under vacuum. The residues were redissolved in acetonitrile/water, placed in pre-weighed 4-mL vials, and lyophilized. The final compounds **9**−**14** were obtained as TFA salts. Yields were > 90% in most cases, with high purity, as determined by LCMS and ^1H NMR spectroscopy. The structure of the final compounds **9**−**14** was confirmed by API mass spectrometry (positive ES); see Tables 2−7 for purities and yields.

1-(1-Benzothien-3-ylmethyl)piperidin-4-amine Bis(trifluoroacetate) Salt (10i): For atom numbering see Table 3. ^1H NMR ([D_6]DMSO): δ = 8.23 (s, 3 H, N^+H_3), 8.09−8.05 (m, 2 H, 15-H, 12-H), 8.07 (s, 1 H, 10-H), 7.49−7.41 (m, 2 H, 14-H, 13-H), 4.54 (s, 2 H, 8-H′, 8-H′′), 3.49 (m, 2 H, 2-H′, 6-H′), 3.25 (m, 1 H, 4-H), 3.10 (m, 2 H, 2-H′′, 6-H′′), 2.07 (m, 2 H, 3-H′, 5-H′), 1.74 (m, 2 H, 3-H′′, 5-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 140.21 (C-11), 139.07 (C-16), 132.78 (C-10), 125.53 (C-13), 125.30 (C-14), 123.77 (C-12), 122.93 (C-15), 125.26 (C-9), 51.86 (C-8), 50.49 (C-2, C-6), 45.82 (C-4), 27.89 (C-3, C-5) ppm. MS (ESI): *m*/*z* = 246.9 [M + H]$^+$.

1-(4-Methoxy-2,5-dimethylbenzyl)piperidin-4-amine Bis(trifluoroacetate) Salt (10j): For atom numbering see Table 3. ^1H NMR ([D_6]DMSO): δ = 8.23 (s, 3 H, N^+H_3), 7.18 (s, 1 H, 10-H), 6.83 (s, 1 H, 13-H), 4.15 (s, 2 H, 8-H′, 8-H′′), 3.77 (s, 3 H, 15-H_3), 3.41 (m, 2 H, 2-H′, 6-H′), 3.25 (m, 1 H, 4-H), 3.08 (m, 2 H, 2-H′′, 6-H′′), 2.32 (s, 3 H, 14-CH_3), 2.08 (s, 3 H, 11-CH_3), 2.05 (m, 2 H, 3-H′, 5-H′), 1.75 (m, 2 H, 3-H′′, 5-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 158.63 (C-12), 138.37 (C-14), 134.77 (C-10), 123.93 (C-11), 120.03 (C-9), 113.08 (C-13), 56.90 (C-8), 56.01 (C-15), 50.25 (C-2, C-6), 45.90 (C-4), 27.77 (C-3, C-5), 19.99 (14-CH_3), 16.18 (11-CH_3) ppm. MS (ESI): *m*/*z* = 249.0 [M + H]$^+$.

3-[(4-Aminopiperidin-1-yl)methyl]benzonitrile Bis(trifluoroacetate) Salt (10l): For atom numbering see Table 3. ^1H NMR ([D_6]DMSO): δ = 8.25 (s, 3 H, N^+H_3), 7.93 (s, 1 H, 14-H), 7.91 (d, *J* = 7.8 Hz, 1 H, 12-H), 7.79 (d, *J* = 7.8 Hz, 1 H, 10-H), 7.65 (t, *J* = 7.8 Hz, 1 H, 11-H), 4.29 (s, 2 H, 8-H′, 8-H′′), 3.37 (m, 2 H, 2-H′, 6-H′), 3.26 (m, 1 H, 4-H), 2.99 (m, 2 H, 2-H′′, 6-H′′), 2.06 (m, 2 H, 3-H′, 5-H′), 1.76 (m, 2 H, 3-H′′, 5-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 136.84 (C-10), 135.58 (C-14), 133.81 (C-12), 132.08 (C-9), 130.69 (C-11), 118.99 (C-15), 112.40 (C-13), 58.64 (C-8), 50.44 (C-2, C-6), 45.77 (C-4), 27.82 (C-3, C-5) ppm. MS (ESI): *m*/*z* = 216.0 [M + H]$^+$.

1-(3,5-Dichlorobenzyl)piperidin-4-amine Bis(trifluoroacetate) Salt (10m): For atom numbering see Table 3. ^1H NMR ([D_6]DMSO): δ = 8.21 (s, 3 H, N^+H_3), 7.71 (s, 1 H, 12-H), 7.56 (s, 2 H, 14-H, 10-H), 4.21 (s, 2 H, 8-H′, 8-H′′), 3.37 (m, 2 H, 2-H′, 6-H′), 3.25 (m, 1 H, 4-H), 2.95 (m, 2 H, 2-H′′, 6-H′′), 2.06 (m, 2 H, 3-H′, 5-H′), 1.74 (m, 2 H, 3-H′′, 5-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 134.94 (C-13), (C-11), 130.57 (C-14, C-10), 129.74 (C-12), 119.18 (C-9), 58.34 (C-8), 50.61 (C-2, C-6), 45.87 (C-4), 27.96 (C-3, C-5) ppm. MS (ESI): *m*/*z* = 260.9 [M + H]$^+$.

1-(1*H*-Indol-3-ylmethyl)piperidin-4-amine Bis(trifluoroacetate) Salt (10q): For atom numbering see Table 3. ^1H NMR ([D_6]DMSO): δ = 8.30 (s, 3 H, N^+H_3), 7.86 (d, 1 H, 15-H), 7.67 (s, 1 H, 10-H), 7.57 (d, 1 H, 12-H), 7.28 (t, 1 H, 13-H), 7.22 (t, *J* = 7.3 Hz, 1 H, 14-H), 4.56 (s, 2 H, 8-H′, 8-H′′), 3.62 (m, 2 H, 2-H′, 6-H′), 3.37 (m, 1 H, 4-H), 3.14 (m, 2 H, 2-H′′, 6-H′′), 2.20 (m, 2 H, 3-H′, 5-H′), 1.87 (m, 2 H, 3-H′′, 5-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 136.70 (C-11), 129.64 (C-10), 128.17 (C-16), 122.43 (C-13), 120.37 (C-14), 119.18 (C-12), 112.63 (C-15), 102.84 (C-9), 51.17 (C-8), 49.66 (C-2, C-6), 45.78 (C-4), 27.85 (C-3, C-5) ppm. MS (ESI): *m*/*z* = 230.1 [M + H]$^+$.

[1-(4-Isopropylbenzyl)piperidin-2-yl]methylamine Bis(trifluoroacetate) Salt (11c): For atom numbering see Table 4. ^1H NMR ($CDCl_3$): δ = 7.29 (d, 2 H, 10-H), 7.23 (d, 2 H, 11-H), 4.65 (m, 1 H, 8-H′), 4.11 (m, 1 H, 8-H′′), 3.81−3.66 (m, 3 H, 7-H′, 2-H′, 7-H′′), 3.17 (s, 1 H, 6-H′), 2.87 (m, *J* = 6.6 Hz, 1 H, 13-H), 2.74 (m, 1 H, 6-H′′), 2.16 (d, *J* = 13 Hz, 1 H, 3-H′), 1.94 (m, 1 H, 3-H′′), 1.83 (s, 1 H, 4-H′), 1.76 (m, 2 H, 5-H′, 5-H′′), 1.55 (s, 1 H, 4-H′′), 1.22 (d, *J* = 6.6 Hz, 6 H, 14-H_3, 15-H_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 151.38 (C-12), 131.12 (C-10), 127.75 (C-11), 125.49 (C-9), 61.50 (C-2), 55.82 (C-8), 51.03 (C-6), 40.22 (C-7), 34.09 (C-13), 27.27 (C-3), 23.91 (C-14, C-15), 21.09 (C-5, C-4) ppm. MS (ESI): *m*/*z* = 247.0 [M + H]$^+$.

[1-(3-Fluoro-2-methylbenzyl)piperidin-2-yl]methanamine Bis(trifluoroacetate) Salt (11e): For atom numbering see Table 4. ^1H NMR ($CDCl_3$): δ = 7.26−7.15 (m, 2 H, 15-H, 13-H), 7.06 (t, 1 H, 14-H), 4.65 (d, *J* = 11.3 Hz, 1 H, 8-H′), 4.20 (d, *J* = 13.2 Hz, 1 H, 8-H′′), 3.84 (d, *J* = 13.0 Hz, 1 H, 7-H′), 3.77 (s, 1 H, 2-H′), 3.64 (d, *J* = 13.2 Hz, 1 H, 7-H′′), 3.13 (m, 1 H, 6-H′), 2.74 (m, 1 H, 6-H′′), 2.26 (s, 3 H, 16-H_3), 2.17 (d, *J* = 16 Hz, 1 H, 3-H′), 1.92 (d, *J* = 10.7 Hz, 1 H, 3-H′′), 1.85 (d, *J* = 14.5 Hz, 1 H, 4-H′), 1.76 (m, 2 H, 5-H′, 5-H′′), 1.59 (s, 1 H, 4-H′′) ppm. ^{13}C NMR ($CDCl_3$): δ = 162.93, 160.49 (C-12), 130.23 (C-10), 128.04 (C-15), 127.17 (C-13), 126.08 (C-11), 116.97 (C-14), 63.00 (C-2), 53.01 (C-8), 50.50 (C-6), 39.56 (C-7), 26.00 (C-3), 21.24 (C-5), (C-4), 11.00 (C-16) ppm. MS (ESI): *m*/*z* = 237.0 [M + H]$^+$.

[1-(Cyclohexylmethyl)piperidin-2-yl]methanamine Bis(trifluoroacetate) Salt (11h): For atom numbering see Table 4. ^{1}H NMR ($CDCl_3$): δ = 3.70 (m, 1 H, 2-H), 3.60−3.55 (m, 1 H, 7-H′), 3.48−3.38 (m, 2 H, 6-H′, 7-H′′), 3.25−3.05 (m, 1 H, 8-H′), 3.05−3.00 (m, 1 H, 6-H′′), 2.70−2.60 (q, *J* = 6.4, *J* = 13.3 Hz, 1 H, 8-H′′), 2.12 (d, *J* = 12.3 Hz, 1 H, 3-H′), 1.85−1.27 (m, 9 H, 3-H′′, 4-H′, 4-H′′, 5-H′, 5-H′′, 10-H′, 11-H′, 9-H, 12-H′), 1.30−1.13 (m, 2 H, 11-H′′, 12-H′′), 1.10−0.99 (q, 1 H, 10-H′′) ppm. ^{13}C NMR ($CDCl_3$): δ = 61.68 (C-2), 58.14 (C-8), 51.95 (C-6), 39.32 (C-7), 33.82 (C-9), 30.93 (C-10), 25.77 (C-11), 25.51 (C-12), 24.95 (C-3), 21.32 (C-5, C-4) ppm. MS (ESI): *m*/*z* = 211.1 [M + H]$^+$.

[1-(1-Naphthylmethyl)piperidin-2-yl]methanamine Bis(trifluoroacetate) Salt (11o): For atom numbering see Table 4. ^{1}H NMR ($CDCl_3$): δ = 8.05 (d, 1 H, 17-H), 7.85 (t, 2 H, 12-H, 14-H), 7.63 (d, 1 H, 10-H), 7.54 (t, 1 H, 16-H), 7.48 (t, 1 H, 15-H), 7.42 (t, 1 H, 11-H), 5.06 (d, *J* = 11.2 Hz, 1 H, 8-H′), 4.70 (d, *J* = 13.4 Hz, 1 H, 8-H′′), 3.98−3.95 (m, 3 H, 7-H′, 2-H′), 3.75 (d, *J* = 11.8 Hz, 1 H, 7-H′′), 2.95 (d, *J* = 12.4 Hz, 1 H, 6-H′), 2.75 (m, 1 H, 6-H′′), 2.20 (d, *J* = 14.7 Hz, 1 H, 3-H′), 1.96 (q, 1 H, 3-H′′), 1.80 (d, *J* = 13.3 Hz, 1 H, 4-H′), 1.64 (m, 2 H, 5-H′, 5-H′′), 1.55 (m, 1 H, 4-H′′) ppm. ^{13}C NMR ($CDCl_3$): δ = 134.02 (C-13), 132.45 (C-18), 131.10 (C-12), (C-10), 129.34 (C-14), 127.72 (C-16), 126.64 (C-15), 125.68 (C-11), 125.34 (C-9), 122.92 (C-17), 63.00 (C-2), 52.96 (C-8), 51.03 (C-6), 40.00 (C-7), 27.27 (C-3), 21.32 (C-5, C-4) ppm. MS (ESI): *m*/*z* = 255.0 [M + H]$^+$.

[1-(2-Ethoxybenzyl)piperidin-2-yl]methanamine Bis(trifluoroacetate) Salt (11p): For atom numbering see Table 4. ^{1}H NMR ($CDCl_3$): δ = 7.39 (t, *J* = 7.8 Hz, 1 H, 13-H), 7.39 (d, *J* = 7.4 Hz, 1 H, 15-H), 6.96 (t, *J* = 7.8 Hz, 1 H, 14-H), 6.92 (d, *J* = 8.3 Hz, 1 H, 12-H), 4.42−4.25 (m, 2 H, 8-H′, 8-H′′), 4.08 (m, 2 H, 16-H′, 16-H′′), 3.74 (m, 2 H, 7-H′, 2-H′), 3.48 (m, 1 H, 7-H′′), 3.29 (s, 1 H, 6-H′), 2.90 (m, 1 H, 6-H′′), 2.21 (m, 1 H, 3-H′), 1.87−1.81 (m, 4 H, 3-H′′, 4-H′, 5-H′, 5-H′′), 1.58 (s, 1 H, 4-H′′), 1.41 (t, *J* = 7.3 Hz, 3 H, 17-H_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 157.75 (C-11), 132.39 (C-15, C-13), 121.27 (C-14), 116.69 (C-10), 112.07 (C-12), 64.28 (C-16), 61.32 (C-2), 51.02 (C-8), 50.50 (C-6), 39.84 (C-7), 26.00 (C-3), 21.19 (C-5, C-4), 14.57 (C-17) ppm. MS (ESI): *m*/*z* = 249.0 [M + H]$^+$.

{1-[3-(Benzyloxy)benzyl]piperidin-3-yl}methanamine Bis(trifluoroacetate) Salt (12a): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 7.95 (s, 3 H, N^+H_3), 7.45−7.31 (m, 6 H, 17-H, 18-H, 19-H, 11-H), 7.16 (s, 1 H, 14-H), 7.10 (d, 1 H, 10-H), 7.04 (d, 1 H, 12-H), 5.10 (s, 2 H, 15-H′, 15-H′′), 4.24 (q, 2 H, 8-H′, 8-H′′), 3.39 (m, 2 H, 2-H′, 6-H′), 2.74 (m, 2 H, 7-H′, 7-H′′), 2.65 (m, 2 H, 2-H′′, 6-H′′), 2.05 (m, 1 H, 3-H′), 1.84 (m, 2 H, 4-H′, 5-H′), 1.63 (q, 1 H, 5-H′′), 1.07 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 159.13 (C-16), (C-9), 137.42 (C-3), 130.67 (C-11), 129.16 (C-17), 128.65 (C-19), 128.40 (C-18), 124.43 (C-12), 118.48 (C-14), 116.47 (C-10), 69.97 (C-15), 60.37 (C-8), 53.90 (C-2), 52.36 (C-6), 41.87 (C-7), 33.07 (C-3), 26.01 (C-4), 22.31 (C-5) ppm. MS (ESI): *m*/*z* = 311.0 [M + H]$^+$.

[1-(2-Furylmethyl)piperidin-3-yl]methanamine Bis(trifluoroacetate) Salt (12b): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 7.96 (s, 3 H, N^+H_3), 7.80 (d, *J* = 2 Hz, 1 H, 12-H), 7.67 (d, *J* = 3 Hz, 1 H, 10-H), 6.55 (q, 1 H, 11-H), 4.34 (q, 2 H, 8-H′, 8-H′′), 3.36 (m, 2 H, 2-H′, 6-H′), 2.78 (m, 2 H, 7-H′, 7-H′′), 2.73−2.61 (m, 2 H, 2-H′′, 6-H′′), 2.06 (m, 1 H, 3-H′), 1.88−1.79 (m, 2 H, 4-H′, 5-H′), 1.63 (q, 1 H, 5-H′′), 1.03 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 145.82 (C-12), 145.50 (C-9), 115.07 (C-10), 111.93 (C-11), 53.77 (C-2), 52.09 (C-8), (C-6), 41.81 (C-7), 33.16 (C-3), 25.83 (C-4), 22.33 (C-5) ppm. MS (ESI): *m*/*z* = 195.0 [M + H]$^+$.

[1-(Cyclohexylmethyl)piperidin-3-yl]methanamine Bis(trifluoroacetate) Salt (12h): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 8.51 (s, 3 H, N^+H_3), 3.96 (d, 1 H, 2-H′), 3.85 (d, 1 H, 6-H′), 3.30−3.15 (m, 5 H, 7-H′, 7-H′′, 8-H′, 8-H′′, 6-H′′), 3.01 (q, 1 H, 2-H′′), 2.54 (m, 1 H, 3-H′), 2.26−2.01 (m, 10 H, 4-H′, 4-H′′, 5-H′, 5-H′′, 11-H′, 9-H, 10-H′, 12-H′), 1.65 (m, 2 H, 11-H′′), 1.53 (m, 1 H, 12-H′′), 1.36 (m, 2 H, 10-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 63.32 (C-8), 54.23 (C-2), 53.56 (C-6), 41.89 (C-7), 32.90 (C-3), 32.56 (C-9), 31.08 (C-10), 26.09 (C-12), 25.71 (C-11), 25.54 (C-4), 22.22 (C-5) ppm. MS (ESI): *m*/*z* = 211.1 [M + H]$^+$.

[1-(1-Benzothien-3-ylmethyl)piperidin-3-yl]methanamine Bis(trifluoroacetate) Salt (12i): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 8.10−8.03 (m, 3 H, 15-H, 12-H, 10-H), 8.02 (s, 3 H, N^+H_3), 7.49−7.41 (m, 2 H, 14-H, 13-H), 4.57 (q, 2 H, 8-H′, 8-H′′), 3.49 (m, 2 H, 2-H′, 6-H′), 2.89 (m, 1 H, 6-H′′), 2.76−2.68 (m, 3 H, 7-H′, 7-H′′, 2-H′′), 2.08 (m, 1 H, 3-H′), 1.85 (m, 2 H, 4-H′, 5-H′), 1.66 (m, 1 H, 5-H′′), 1.09 (m, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 140.17 (C-11), 139.05 (C-16), 132.90 (C-10), 126.02 (C-9), 125.31 (C-14), 125.31 (C-14), 123.75 (C-12), 122.95 (C-15), 54.05 (C-2), 52.54 (C-8), 52.47 (C-6), 41.85 (C-7), 33.15 (C-3), 25.93 (C-4), 22.41 (C-5) ppm. MS (ESI): *m*/*z* = 260.9 [M + H]$^+$.

[1-(3,5-Dichlorobenzyl)piperidin-3-yl]methanamine Bis(trifluoroacetate) Salt (12m): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 8.00 (s, 3 H, N^+H_3), 7.71 (s, 1 H, 12-H), 7.56 (s, 2 H, 14-H, 10-H), 4.29 (m, 2 H, 8-H′, 8-H′′), 3.42 (m, 2 H, 2-H′, 6-H′), 2.77−2.69 (m, 4 H, 7-H′, 7-H′′, 2-H′′, 6-H′′), 2.06 (m, 1 H, 3-H′), 1.83 (m, 2 H, 4-H′, 5-H′), 1.64 (m, 1 H, 5-H′′), 1.11 (m, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 134.96 (C-13), (C-11), 130.71 (C-14), (C-10), 129.80 (C-12), 119.23 (C-9), 58.98 (C-8), 54.07 (C-2), 52.74 (C-6), 41.84 (C-7), 33.16 (C-3), 26.03 (C-4), 22.41 (C-5) ppm. MS (ESI): *m*/*z* = 274.9 [M + H]$^+$.

[1-(4-Phenoxybenzyl)piperidin-3-yl]methanamine Bis(trifluoroacetate) Salt (12n): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 7.83 (s, 3 H, N^+H_3), 7.27 (d, 2 H, 10-H), 7.21 (t, 2 H, 15-H), 6.98 (t, 1 H, 16-H), 6.85−6.82 (m, 4 H, 14-H, 11-H), 4.03 (m, 2 H, 8-H′, 8-H′′), 3.19−3.16 (m, 2 H, 2-H′, 6-H′), 2.57−2.44 (m, 4 H, 7-H′, 7-H′′, 2-H′′, 6-H′′), 1.88 (m, 1 H, 3-H′), 1.68−1.64 (m, 2 H, 4-H′, 5-H′), 1.49 (m, 1 H, 5-H′′), 0.90 (m, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 159.28 (C-9), 158.63 (C-12), 156.51 (C-13), 134.07 (C-10), 130.88 (C-15), 124.80 (C-16), 119.94 (C-14), 118.86 (C-11), 59.71 (C-8), 53.65 (C-2), 52.13 (C-6), 41.84 (C-7), 33.09 (C-3), 26.99 (C-4), 22.41 (C-5) ppm. MS (ESI): *m*/*z* = 297.0 [M + H]$^+$.

[1-(1-Naphthylmethyl)piperidin-3-yl]methanamine Bis(trifluoroacetate) Salt (12o): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 8.33 (d, *J* = 8.3 Hz, 1 H, 17-H), 8.11−8.01 (m, 5 H, N^+H_3, 12-H, 14-H), 7.78 (d, *J* = 6.8 Hz, 1 H, 10-H), 7.70−7.61 (3 t, 3 H, 16-H, 15-H, 11-H), 4.80 (q, 2 H, 8-H′, 8-H′′), 3.50 (m, 2 H, 2-H′, 6-H′), 3.04 (m, 1 H, 6-H′′), 2.90 (m, 1 H, 2-H′′), 2.79 (m, 1 H, 7-H′), 2.70 (m, 1 H, 7-H′′), 2.10 (m, 1 H, 3-H′), 1.87 (m, 2 H, 4-H′, 5-H′), 1.68 (q, 1 H, 5-H′′), 1.15 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 134.16 (C-13), 132.74 (C-18), 132.15 (C-10), 131.18 (C-12), 129.47 (C-14), 127.70 (C-16), 127.01 (C-15), 126.32 (C-9), 126.05 (C-11), 124.63 (C-17), 57.08 (C-8), 54.48 (C-2), 52.90 (C-6), 41.88 (C-7), 33.04 (C-3), 26.07 (C-4), 22.32 (C-5) ppm. MS (ESI): *m*/*z* = 255.0 [M + H]$^+$.

{1-[1-(1*H*-Pyrrol-2-yl)methyl]piperidin-3-yl}methanamine Bis(trifluoroacetate) Salt (12q): For atom numbering see Table 5. ^{1}H NMR ([D_6]DMSO): δ = 7.98 (s, 3 H, N^+H_3), 6.85 (t, *J* = 2.2 Hz,

1 H, 12-H), 6.27 (d, J = 3 Hz, 1 H, 10-H), 6.04 (t, J = 3 Hz, 1 H, 11-H), 4.25 (q, 2 H, 8-H′, 8-H′′, 3.63 (s, 3 H, 13-H_3), 3.39 (m, 1 H, 2-H′), 3.21 (m, 1 H, 6-H′), 2.86−2.59 (m, 4 H, 7-H′, 7-H′′, 2-H′′, 6-H′′), 1.99 (m, 1 H, 3-H′), 1.85−1.81 (m, 2 H, 4-H′, 5-H′), 1.57 (m, 1 H, 5-H′′), 1.05 (m, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO): δ = 125.77 (C-12), 120.83 (C-9), 114.28 (C-10), 108.05 (C-11), 51.74 (C-8), 45.99 (C-2), 43.84 (C-6), 41.85 (C-7), 33.10 (C-3), 32.37 (C-13), 26.11 (C-4), 21.72 (C-5) ppm. MS (ESI): m/z = 208.0 $[M + H]^+$.

1-(2-Phenylethyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13c): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.45 (s, 3 H, N^+H_3), 7.41−7.28 (m, 5 H, 11-H, 12-H, 13-H), 3.71 (m, 1 H, 2-H′), 3.67 (m, 2 H, 3-H, 6-H′), 3.41 (q, 2 H, 8-H′, 8-H′′), 3.00 (q, 2 H, 9-H′, 9-H′′), 2.94 (m, 2 H, 6-H′′, 2-H′′), 2.07 (m, 1 H, 4-H′), 2.00 (m, 1 H, 5-H′), 1.76 (q, 1 H, 5-H′′), 1.52 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 129.49−127.79 (C-13, C-12, C-11), 58.31 (C-8), 53.67 (C-2), 52.69 (C-6), 45.33 (C-3), 30.86 (C-9), 27.29 (C-4), 20.86 (C-5) ppm. MS (ESI): m/z = 205.0 $[M + H]^+$.

1-(3-Fluoro-2-methylbenzyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13d): For atom numbering see Table 6. ^{1}H NMR ($CDCl_3$): δ = 7.13 (m, 1 H, 13-H), 7.07 (d, J = 7.6 Hz, 1 H, 15-H), 6.98 (t, J = 8.6 Hz, 1 H, 14-H), 3.76 (m, 2 H, 8-H′, 8-H′′), 3.56 (m, 1 H, 3-H), 2.83 (m, 1 H, 2-H′′), 2.61 (m, 1 H, 6-H′′), 2.23 (s, 3 H, 16-H_3), 1.94 (m, 1 H, 4-H′), 1.82 (m, 1 H, 5-H′), 1.71 (m, 2 H, 5-H′′, 4-H′′) ppm. ^{13}C NMR ($CDCl_3$, gHSQC): δ = 162.71 (C-11), 160.76 (C-12), 133.71 (C-10), 127.11 (C-13), 126.43 (C-15), 115.54 (C-14), 59.45 (C-8), 55.06 (C-2), 52.49 (C-6), 46.82 (C-3), 27.16 (C-4), 21.31 (C-5), 10.81 (C-16) ppm. MS (ESI): m/z = 222.3 $[M + H]^+$.

1-[(6-Methylpyridin-2-yl)methyl]piperidin-3-amine Bis(trifluoroacetate) (13f): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.33 (s, 3 H, N^+H_3), 7.88 (t, J = 7.8 Hz, 1 H, 11-H), 7.41 (d, J = 7.6 Hz, 2 H, 10-H, 12-H), 4.45 (q, 2 H, 8-H′, 8-H′′), 3.49 (m, 2 H, 2-H′, 3-H), 3.35 (q, 1 H, 6-H′), 2.95 (m, 2 H, 6-H′′, 2-H′′), 2.56 (s, 3 H, 14-H_3), 2.01 (m, 1 H, 4-H′), 1.95 (m, 1 H, 5-H′), 1.91 (q, 1 H, 5-H′′), 1.51 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 158.77 (C-13), 150.42 (C-9), 139.31 (C-11), 124.64 (C-12), 123.11 (C-10), 60.30 (C-8), 53.13 (C-2), 52.55 (C-6), 45.33 (C-3), 26.88 (C-4), 24.11 (C-14), 20.86 (C-5) ppm. MS (ESI): m/z = 206.0 $[M + H]^+$.

1-(Cyclohexylmethyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13g): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.41 (s, 3 H, N^+H_3), 3.64 (d, J = 10 Hz, 1 H, 2-H′), 3.50 (m, 2 H, 6-H′, 3-H′), 3.01 (d, J = 5.9 Hz, 2 H, 8-H′, 8-H′′), 2.85 (m, 2 H, 6-H′′, 2-H′′), 2.05 (m, 1 H), 1.94 (m, 1 H, 5-H′), 1.74−1.62 (m, 7 H, 5-H′′, 11-H′, 9-H, 10-H′, 12-H′), 1.49 (q, 1 H, 4-H′′), 1.26 (m, 2 H, 10-H′′), 1.18 (m, 1 H, 12-H′′), 0.97 (m, 2 H, 11-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 63.12 (C-8), 53.52 (C-2), 52.53 (C-6), 45.14 (C-3), 33.07 (C-9), 30.85 (C-11), 27.16 (C-4), 25.68 (C-12), 25.58 (C-10), 21.20 (C-5) ppm. MS (ESI): m/z = 197.0 $[M + H]^+$.

1-(1-Benzothien-3-ylmethyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13h): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.28 (s, 3 H, N^+H_3), 8.14−8.12 (2 d, J = 7.8 Hz, 2 H, 15-H, 12-H), 8.06 (s, 1 H, 10-H), 7.52−7.45 (2 t, J = 7.9 Hz, 2 H, 14-H, 13-H), 4.69 (q, 2 H, 8-H′, 8-H′′), 3.50 (m, 1 H, 2-H′), 3.40 (m, 2 H, 6-H′, 3-H), 2.97 (m, 2 H, 2-H′′, 6-H′′), 2.03 (m, 1 H, 4-H′), 1.96 (m, 1 H, 5-H′), 1.74 (q, 1 H, 5-H′′), 1.47 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 140.21 (C-16), 139.07 (C-11), 132.78 (C-10), 125.53 (C-14), 125.30 (C-13), 123.77 (C-15), 122.93 (C-12), 53.00 (C-8), 52.00 (C-2, C-6), 45.82 (C-3), 27.89 (C-2, C-5) ppm. MS (ESI): m/z = 246.9 $[M + H]^+$.

1-Hexylpiperidin-3-amine Bis(trifluoroacetate) Salt (13i): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.41 (s, 3 H, N^+H_3), 3.61 (m, 1 H, 2-H′), 3.49 (m, 1 H, 6-H′), 3.43 (m, 1 H, 3-H), 3.13 (q, 2 H, 8-H′, 8-H′′), 2.85 (m, 2 H, 2-H′′, 6-H′′), 2.03 (m, 1 H, 4-H′), 1.94 (m, 1 H, 5-H′), 1.72 (m, 1 H, 5-H′′), 1.63 (m, 2 H, 9-H′, 9-H′′), 1.47 (m, 1 H, 4-H′′), 1.29 (m, 6 H, 10-H′, 10-H′′, 11-H′, 11-H′′, 12-H′, 12-H′′), 0.89 (t, J = 6.7 Hz, 3 H, 13-H_3) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 56.94 (C-8), 53.21 (C-2), 52.23 (C-6), 45.85 (C-3), 27.37 (C-4), 26.36 (C-10, C-11, C-12), 24.01 (C-9), 21.66 (C-5), 14.60 (C-13) ppm. MS (ESI): m/z = 185.1 $[M + H]^+$.

3-[(3-Aminopiperidin-1-ylmethyl)]benzonitrile Bis(trifluoroacetate) Salt (13j): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.31 (s, 3 H, N^+H_3), 7.98 (s, 1 H, 14-H), 7.94 (d, J = 7.8 Hz, 1 H, 12-H), 7.83 (d, J = 7.8 Hz, 1 H, 10-H), 7.69 (t, J = 7.8 Hz, 1 H, 11-H), 4.43 (q, 2 H, 8-H′, 8-H′′), 3.41 (m, 3 H, 2-H′, 3-H, 6-H′), 2.88 (m, 2 H, 6-H′′, 2-H′′), 2.03 (m, 1 H, 4-H′), 1.94 (m, 1 H, 5-H′), 1.72 (q, 1 H, 5-H′′), 1.52 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 136.49 (C-10), 135.23 (C-14), 133.70 (C-12), 130.76 (C-11), 59.29 (C-8), 52.60 (C-2), (C-6), 45.97 (C-3), 27.12 (C-4), 21.88 (C-3, C-5) ppm. MS (ESI): m/z = 216.0 $[M + H]^+$.

1-(3,5-Dichlorobenzyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13k): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.26 (s, 3 H, N^+H_3), 7.71 (s, 1 H, 12-H), 7.59 (s, 2 H, 14-H, 10-H), 4.25 (m, 2 H, 8-H′, 8-H′′), 3.42 (m, 1 H, 3-H), 3.29 (m, 2 H, 2-H′, 6-H′), 2.78 (m, 2 H, 2-H′′, 6-H′′), 1.99 (m, 1 H, 4-H′), 1.93 (m, 1 H, 5-H′), 1.71 (q, 1 H, 5-H′′), 1.49 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 134.00 (C-13, C-11), 130.13 (C-14, C-10), 129.20 (C-12), 59.20 (C-8), 52.77 (C-2, C-6), 46.33 (C-3), 27.40 (C-4, C-5) ppm. MS (ESI): m/z = 260.0 $[M + H]^+$.

1-(4-Phenoxybenzyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13l): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.37 (s, 3 H, N^+H_3), 7.51 (d, J = 8.3 Hz, 2 H, 10-H), 7.44 (t, J = 8.3, J = 7.3 Hz, 2 H, 15-H), 7.22 (t, J = 7.3 Hz, 1 H, 16-H), 7.08−7.06 (m, 4 H, 14-H, 11-H), 4.42 (m, 2 H, 8-H′, 8-H′′), 3.45 (m, 3 H, 2-H′, 6-H′, 3-H), 3.45 (m, 2 H, 2-H′′, 6-H′′), 2.06 (m, 1 H, 4-H′), 2.04 (m, 1 H, 5-H′), 1.73 (q, 1 H, 5-H′′), 1.49 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 159.28 (C-9), 158.63 (C-12), 156.51 (C-13), 133.79 (C-10), 130.75 (C-15), 124.55 (C-16), 119.32 (C-14), 118.77 (C-11), 59.94 (C-8), 51.92 (C-2, C-6), 45.93 (C-3), 26.15 (C-4), 21.36 (C-5) ppm. MS (ESI): m/z = 283.0 $[M + H]^+$.

1-(1-Naphthylmethyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13m): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.36 (d, J = 8.3 Hz, 1 H, 17-H), 8.25 (s, 3 H, N^+H_3), 8.08−8.04 (2d, J = 8.6 Hz, 2 H, 12-H, 14-H), 7.77 (d, J = 6.8 Hz, 1 H, 10-H), 7.68−7.60 (3t, J = 6.7 Hz, 3 H, 16-H, 15-H, 11-H), 4.85 (q, 2 H, 8-H′, 8-H′′), 3.97 (m, 1 H, 2-H′), 3.44 (m, 2 H, 6-H′, 3-H), 3.08 (m, 2 H, 2-H′′, 6-H′′), 2.03 (m, 1 H, 4-H′), 1.96 (m, 1 H, 5-H′), 1.74 (q, 1 H, 5-H′′), 1.49 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 134.16 (C-13), 132.74 (C-18), 131.60 (C-10), 131.37 (C-12), 129.32 (C-14), 127.95 (C-16), 127.27 (C-15), 126.13 (C-11), 124.53 (C-17), 53.00 (C-8), 52.76 (C-2, C-6), 45.82 (C-3), 27.92 (C-4, C-5) ppm. MS (ESI): m/z = 241.0 $[M + H]^+$.

1-(4-Methylbenzyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13n): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.30 (s, 3 H, N^+H_3), 7.38 (d, J = 8.0 Hz, 2 H, 10-H), 7.28 (d,

J = 8.0 Hz, 2 H, 11-H), 4.41 (q, 2 H, 8-H′, 8-H′′), 3.41 (m, 3 H, 2-H′, 6-H′, 3-H), 2.86 (m, 2 H, 2-H′′, 6-H′′), 2.34 (s, 3 H, 13-H_3), 2.02 (m, 1 H, 4-H′), 1.97 (m, 1 H, 5-H′), 1.72 (q, 1 H, 5-H′′), 1.46 (q, 1 H, 4-H′′) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 132.31 (C-10), 130.19 (C-11), 60.14 (C-8), 52.18 (C-2, C-6), 45.28 (C-3), 27.24 (C-4), 21.93 (C-13, C-5) ppm. MS (ESI): *m/z* = 205.0 [M + H]$^+$.

1-(2-Ethoxybenzyl)piperidin-3-amine Bis(trifluoroacetate) Salt (13o): For atom numbering see Table 6. ^{1}H NMR ([D_6]DMSO): δ = 8.36 (s, 3 H, N^+H_3), 7.44 (d, J = 8.0 Hz, 1 H, 15-H), 7.43 (t, J = 7.0 Hz, 1 H, 13-H), 7.10 (d, J = 8.3 Hz, 1 H, 12-H), 6.99 (t, J = 8.3 Hz, 1 H, 14-H), 4.31 (q, 2 H, 8-H′, 8-H′′), 4.08 (q, 2 H, 16-H′, 16-H′′), 3.47−3.38 (m, 3 H, 3-H, 2-H′, 6-H′), 2.90−2.84 (m, 2 H, 2-H′′, 6-H′′), 2.00−1.97 (m, 1 H, 4-H), 1.94−1.91 (m, 1 H, 5-H′), 1.71 (q, 1 H, 5-H′′), 1.45 (q, 1 H, 4-H′′), 1.36 (t, J = 7.6 Hz, 3 H, 17-H_3) ppm. ^{13}C NMR ([D_6]DMSO, gHSQC): δ = 133.83 (C-13), 132.25 (C-15), 121.70 (C-14), 113.25 (C-12), 64.72 (C-16), 55.22 (C-8), 52.59 (C-2, C-6), 45.73 (C-3), 26.74 (C-4), 21.46 (C-5), 15.13 (C-17) ppm. MS (ESI): *m/z* = 235.3 [M + H]$^+$.

Supporting Information Available: Figures mentioned in text but not shown are available as Supporting Information, see also the footnote on the first page of this article.

Glossary of Acronyms: BAP = Borane−pyridine complex; BOC = *tert*-butoxycarbonyl; CPMG = Carr−Purcell−Meiboom−Gill T_2-dependent spin-echo sequence; COSY = Correlation spectroscopy; DCM = Dichloromethane; DMF = Dimethylformamide; GARP = Globally optimized, alternating-phase, rectangular pulses (for broad-band decoupling); FT-IR = Fourier transformation infrared spectroscopy; HMBC = Heteronuclear multiple bond correlation; HRMAS = High-resolution magic-angle spinning; HSQC = Heteronuclear single-quantum correlation; HTS = High-throughput screening; HPLC = High-pressure liquid chromatography; LCMS = Liquid chromatography mass spectrometry; MeOH = Methanol; NMM = 4-Methylmorpholine; SAR = Structure-activity relationship; TMOF = Trimethyl orthoformate; TFA = Trifluoroacetic acid.

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