Gram-Scale Synthesis of *N*-Aryl- and *N*-Aryl-*N′*-methylpiperazines on a Novel, Water-Swellable, Oxethane-Linked Poly(ethylene glycol) High-Loading Resin

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This article is dedicated to Prof. Steven Ley on the occasion of his 60th birthday.

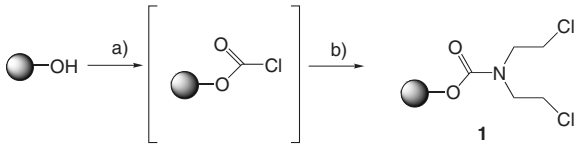
Abstract: A new methodology for the synthesis of *N*-arylpiperazines was developed using a poly(ethylene glycol)-derived solid support. The reactions proceeded in up to 60% overall yield over four steps. The scope and limitations of the method are discussed, as well as the utility of ^{13}C gel-phase NMR spectroscopy for reaction monitoring.

Key words: *N*-arylpiperazines, solid-phase synthesis, heterocycles, cleavage, ^{13}C gel-phase NMR spectroscopy

The synthesis of organic molecules on solid phase holds several advantages compared to traditional solution-phase chemistry. Due to the high cost of commercially available solid-phase supports, only a few examples of larger-scale solid-phase syntheses of small molecules exist in the literature.[1] We report herein a high-yielding solid-phase synthesis employing a comparatively inexpensive oxethane-linked poly(ethylene glycol)-derived resin.[2,3] The main advantage of such poly(ethylene glycol)-derived resins over the cheaper polystyrene-based resins is their much-improved swelling properties in water, allowing reaction on the support in aqueous media.

N-arylpiperazines represent a common structural motif in many compounds of pharmaceutical interest.[4] They are commonly synthesized from bis(chloroethyl)amine and derivatives via ring closure under weakly basic conditions.[5] However, this method suffers from the drawback that the toxic bis(chloroethyl)amine must be used under forcing conditions. A solid-phase approach where the bis(chloroethyl)amine is first immobilized on resin under mild, aqueous, and therefore safer, conditions is desirable.

Bis(chloroethyl)amine was immobilized by means of a chloroformate handle, generated from the reaction of Versabeads™ VO400 with a commercially available 20% w/w solution of phosgene in toluene, a method originally developed by Hauske and Dorff.[6] Upon addition of bis(chloroethyl)amine as the hydrochloride salt in aqueous solution, complete conversion into resin **1** was achieved in a total reaction time of eight hours (final loading: 1.48 mmol·g^{-1}, confirmed by chloride analysis) (Scheme 1).



Scheme 1 *Reagents and conditions*: (a) $COCl_2$ in toluene (20% w/w, 2 equiv), THF, r.t., 2 h; (b) bis(chloroethyl)amine hydrochloride (3.5 equiv), K_2CO_3 (6 equiv), H_2O, r.t., 6 h.

This reaction was conveniently monitored by ^{13}C gel-phase NMR spectroscopy.[7] In particular, the ^{13}C NMR spectroscopic shifts of the two backbone carbons closest to the terminal hydroxy group were diagnostic of the immobilization of the bis(chloroethyl)amine. The carbons derived from the remainder of the synthesized molecule could also be observed easily. Usually, 1024 scans were sufficient to produce a rough picture of the extent of reaction, and a longer acquisition period (13312 scans) produced a fairly clear picture of the resin-bound product (Figure 1).

A number of syntheses were then performed where anilines with various substituents were added to the resin on a 10-g scale (ca. 15 mmol of resin **1**) in isobutyl methyl ketone (MIBK) at 100 °C (Scheme 2).[5c,8] These reactions were again monitored conveniently through the use of ^{13}C gel-phase NMR spectroscopy (e.g., Figure 2). As expected, the electron-rich 4-methoxyaniline reacted relatively fast with resin **1** to give the resin-bound *N*-arylpiperazine **2a** in 28 hours, while the reaction between resin **1** and the other, less-nucleophilic anilines required at least two days of reaction time (Table 1). Reaction between the sterically hindered 2,6-dimethylaniline and resin **1** only reached 25% conversion after six days, judged by ^{13}C gel-phase NMR spectroscopy. A similar lack of reactivity was observed for 2,6-dimethoxyaniline, which implies that steric hindrance is the dominating factor in this instance.

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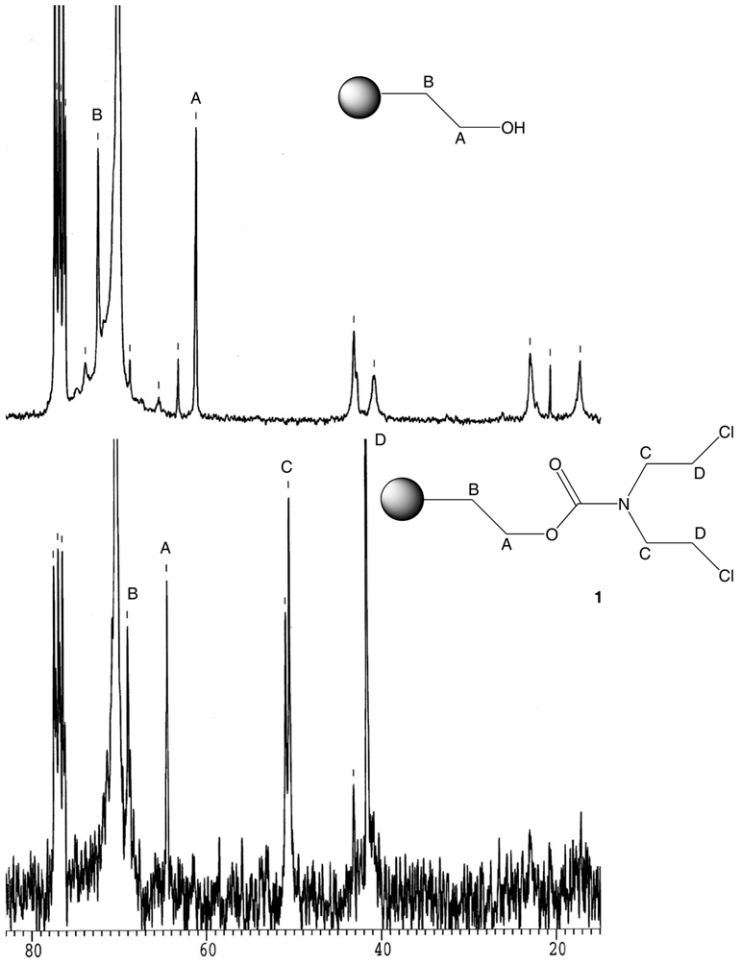
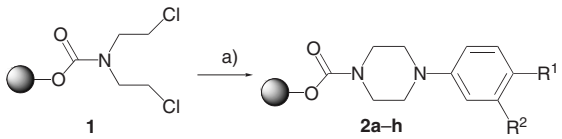


Figure 1 The monitoring of the on-resin immobilization of bis(chloroethyl)amine. Note the change in the position of the carbon peaks from the carbons α (A) and β (B) to the binding site (from 61.2 to 64.5 ppm and from 72.4 to 69.0 ppm, respectively). The two carbon atoms (C) are nonequivalent due to hindered rotation. The upper spectrum was acquired using 13312 scans, and the lower was acquired using 1024 scans.



2a,**2e**: $R^1 = OCH_3$ $R^2 = H$
2b,**2f**: $R^1 = H$ $R^2 = H$
2c,**2g**: $R^1 = F$ $R^2 = H$
2d,**2h**: $R^1 = Cl$ $R^2 = Cl$

Scheme 2 *Reagents and conditions*: (a) aniline derivative (5 equiv), py (10 equiv), KI (0.2 equiv), MIBK, 100 °C.

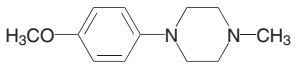
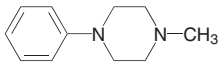
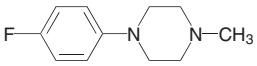
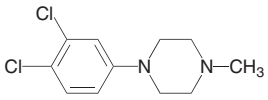
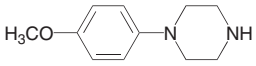
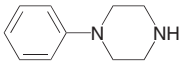
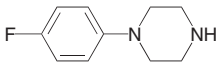
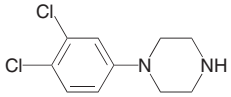
The final products were cleaved from the resin under either reductive or basic conditions (Scheme 3). Reductive cleavage with lithium aluminum hydride, following a procedure developed by Ho and Kukla,[9] yielded *N*′-aryl-*N*-methylpiperazines **3a**–**d** in crude overall yields (for four steps) ranging from 22–60% (based on the initial hydroxyl loading on the Versabeads™ VO400) with excellent to moderate purities upon aqueous workup (Table 1, entries 1–4).

In the case of the 1-(3,4-dichlorophenyl)-4-methylpiperazine **3d**, a significant amount (10–15%) of the corresponding 1-(4-chlorophenyl)-4-methylpiperazine was observed in the crude product. The dechlorination of arenes under reductive conditions is a well-known phenomenon.[10] Preliminary results suggest that this byproduct can be avoided through the use of in situ generated zinc borohydride as reducing agent.[11,12]

Basic cleavage of the resin-bound piperazine was achieved using potassium *tert*-butoxide in refluxing 1,2-dimethoxyethane. The free amines were isolated in 34–46% crude overall yield (Table 1, entries 5–8) and were purified by means of precipitation as the corresponding oxalates.

In one instance, potassium hydroxide in refluxing methanol was used to cleave the *N*-arylpiperazine from the resin. Here, the methyl carbamate **4** was formed as the sole product in reasonable yield and excellent purity (32% overall yield, pure by C,H,N analysis) (Scheme 4). It is known that other nucleophiles can be used in similar

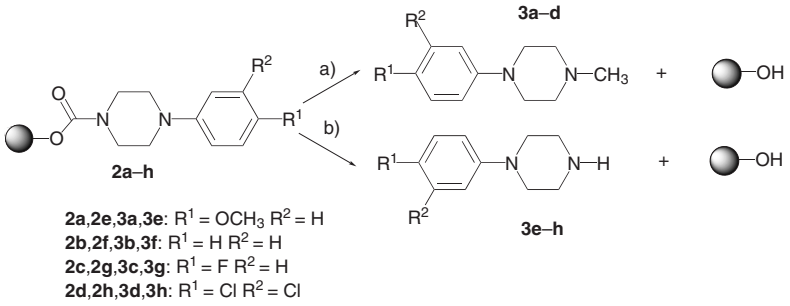
Table 1 Reaction Times and Crude Yields from the Addition of Various Anilines to Resin **1**

Entry	Compound	Number	Reaction time (h)	Crude isolated yield[a] (%)	Purity of the crude product[b] (%)	Purified yield (%)
1		3a	28	60[c]	100	60
2		3b	86	50	75–80[d]	37
3		3c	49	41	99	21
4		3d	112	22	ca. 60[d,e]	4
5		3e	32	46	55[f]	20[g]
6		3f	60	40	ca. 70[d,f]	17[g]
7		3g	66	39	77	23[g]
8		3h	111	34	85	6[g]

[a] Overall yield based on 1.97 mmol·g^{-1} loading of Versabeads™.
[b] Purity obtained from HPLC.
[c] Pure by C,H,N analysis.
[d] Due to problems from overlapping peaks on the HPLC, the purity of the crude product is estimated from ^{1}H NMR spectroscopy.
[e] 10–15% of 1-(4-chlorophenyl)-4-methylpiperazine was also present.
[f] Due to contamination of DME with MeOH, a significant amount of the corresponding methyl carbamate was formed during cleavage (entry 5: 35%, entry 6: 5–10%).
[g] Isolated as the oxalate.

cleavage reactions,[13] which broadens the scope of this linking approach.

The cost of the resin itself is an important factor in the synthesis of small molecules on a larger scale, i.e. 0.1 mol or greater. In such cases, the solid support itself must be reusable, otherwise its cost would outweigh the practical advantages. To this end, we have examined briefly the possibility of reusing the resin. Following the reductive cleavage of **3c** from the resin, the resin was washed with 4 M hydrogen chloride and water to remove residual aluminum salts, and then examined by ^{13}C gel-phase NMR spectroscopy for traces of noncleaved material. No peaks other than those originating from the polymer backbone were observed. The resin was then converted into resin **1** using identical conditions to those used previously. Chloride analysis and ^{13}C gel-phase NMR spectroscopy of this resin showed essentially identical loading compared to similar analyses from the first use of the resin (Cl analysis: 1.68 mmol·g^{-1}, identical to resin **1**). These results indicate that the resin is capable of being reused a number of times



Scheme 3 *Reagents and conditions*: (a) $LiAlH_4$ (10 equiv), THF, reflux, 19 h; (b) *t*-BuOK (2.2 equiv), DME, reflux, 3 h.

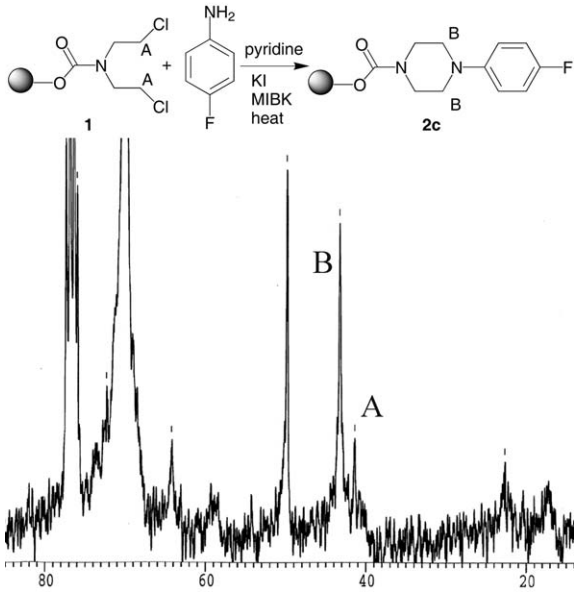


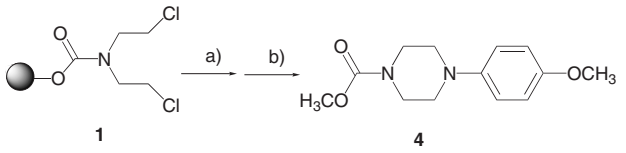
Figure 2 A section of the ^{13}C gel-phase NMR spectrum of the resin after a 42-h reaction with 4-fluoroaniline. Note how peak A at 41.2 ppm (–CH_2Cl) is gradually replaced by peak B at 43.2 ppm (piperazine).

without loss of utility, thereby lowering the effective per-synthesis resin cost. Work in this area is continuing.

To further demonstrate an application of the method, resin **1** (7.5 mmol) was reacted with 2-benzylaniline to yield 3% of the experimental antidepressant Sifaprazine (**5**)[14] upon reductive cleavage (Scheme 5). Here, an excess of potassium iodide was employed in the piperazine-forming step as this was shown to accelerate the reaction.

In summary, we have developed a safe, versatile method for the synthesis of arylpiperazines. We have demonstrated that this linker system can be multidirectional, with production of *N*-arylpiperazines plus their *N*′-methyl and methyl carbamate derivatives from a single resin-bound intermediate. We have shown that the reactions can be conveniently monitored by ^{13}C gel-phase NMR spectroscopy, and have demonstrated the scope of poly(ethylene glycol)-based resins in gram-scale reactions.

All solvents and chemicals were used as received except for Versabeads™ VO400, which were washed with THF and MeOH (10 mL·g^{-1}) and dried before use, and aniline, 2,6-dimethylaniline, and 4-fluoroaniline, which were purified by precipitation with dry HCl



Scheme 4 *Reagents and conditions*: (a) 4-methoxyaniline (5 equiv), py (5 equiv), KI (0.2 equiv), MIBK, 100 °C, 15 h; (b) KOH (10 equiv), MeOH, reflux, 3.5 h.

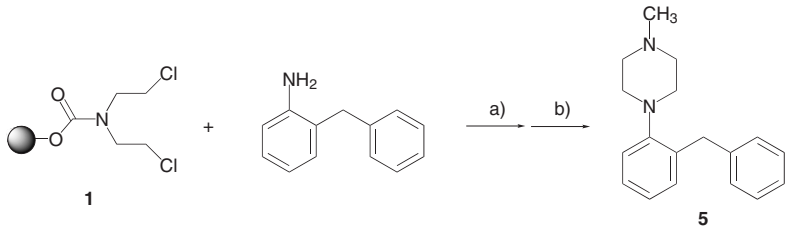
in Et_2O prior to reaction. All reactions were run under N_2. All final compounds gave satisfactory NMR spectroscopic and, for solid compounds, C,H,N analysis data.

Solution-phase NMR spectra were recorded on a Bruker 500 MHz spectrometer. The ^{13}C gel-phase NMR spectra were recorded at 62.5 MHz on a Bruker 250 MHz spectrometer. Automated flash chromatography was performed on an Argonaut Flash Master II using Isolute Flash Si II prepacked columns. LC/MS, UV and ELSD was run in an integrated system on a Waters Symmetry C18 column (4.6 × 30 mm, particle diameter 0.035 mm), using a H_2O/MeCN gradient at pH 6. Mass spectra were acquired using an Applied Biosystems API300 triple quadrupole mass spectrometer with Atmospheric Pressure Photoionization (APPI) ion source. The UV spectra were recorded with a Shimadzu SPD10A UV detector at 254 nm and Evaporative Light Scattering Detection (ELSD) data were recorded with a Polymer Laboratories PL-ELS 2100 ELS-detector. The HPLC of crude products was taken on a Varian Star HPLC using a LiChrosobe RP-8 column (4 × 250 mm, particle diameter 0.005 mm). The eluent used was MeCN–H_2O (50:50) buffered to pH 3 with a Et_3N–phosphate buffer. GC/MS were performed on a Varian 2000 mass spectrometer connected to a Varian 3400 GC, equipped with a Phenomex column (15 m, 0.25 mm internal diameter) and EI at 70 eV; He was used as the carrier gas. Melting points were recorded on a Büchi B-540 melting point apparatus and appear uncorrected.

Resin-Bound Bis(chloroethyl)amine 1

Versabeads™ VO400 (90.0 g, 177 mmol) were suspended in THF (900 mL). A solution of $COCl_2$ in toluene (20% w/w, 190 mL, 355 mmol, 2.0 equiv) was slowly added and the suspension was stirred mechanically at r.t. for 2 h. The liquid was removed and the resin was washed successively with THF (750 mL), MeOH (2 × 500 mL), and THF (900 mL).

Bis(chloroethyl)amine hydrochloride (110 g, 0.61 mol, 3.5 equiv) was dissolved in H_2O (450 mL) and was added to the resin. The suspension was cooled on an ice–water bath and K_2CO_3 (147 g, 1.06 mol, 6.0 equiv) was added portionwise with mechanical stirring. The ice–water bath was removed and the suspension was stirred for 6 h at r.t. The resin was recovered by filtration and washed successively with H_2O (3 × 500 mL), THF (3 × 500 mL), MeOH (3 × 500



Scheme 5 Formation of Sifaprazine on resin. *Reagents and conditions*: (a) 2-benzylaniline (5 equiv), py (9.5 equiv), KI (3 equiv), MIBK, 100 °C, 67 h; (b) $LiAlH_4$ (10 equiv), THF, reflux, 19 h.

mL), H_2O (2 × 500 mL), THF (1 × 750 mL), and MeOH (2 × 500 mL) before drying in vacuo.

End weight: 123.1 g (103% of theoretical weight gain).

Cl analysis: 11.9% Cl [1.68 mmol bis(chloroethyl)amine·g^{-1} resin, 113% of theoretical maximum loading].

^{13}C NMR ($CDCl_3$): δ = 155.4, 73.8, 70.2, 69.0, 66.7, 64.5, 63.2, 50.9, 50.5, 43.1, 42.3, 23.0, 20.6, 17.2, 7.5.

Resin-Bound *N*-Arylpiperazines 2a–h; General Procedure

Resin **1** (10.0 g, 14.8 mmol) was suspended in MIBK (75 mL) in the presence of the aniline (74 mmol, 5 equiv) and KI (0.5 g, 3 mmol, 0.2 equiv). Then, py (12.0 mL, 0.15 mol, 10 equiv) was added and the suspension was heated to 100 °C with mechanical stirring. After the reaction time stated in Table 1, the solvent was removed and the resin was washed successively with THF (3 × 100 mL), MeOH (3 × 100 mL), H_2O (3 × 100 mL), and THF (3 × 100 mL), and dried in vacuo to give the immobilized piperazines **2a–h**. The completion of the reactions were confirmed through ^{13}C gel-phase NMR spectroscopy.

***N*-Aryl-*N*′-methylpiperazines 3a–d; General Procedure**

Resin **2a–d** (14.8 mmol) was suspended in THF (100 mL). Then, $LiAlH_4$ (5.7 g, 0.15 mol, 10 equiv) was added as pellets and the suspension was refluxed for 19 h with mechanical stirring. The reaction was cooled on an ice–water bath, quenched by the sequential addition of H_2O (6 mL), NaOH soln (13% w/v, 6 mL), and H_2O (17 mL). The suspension was filtered and the resin was washed successively with THF (3 × 100 mL), HCl (3 × 100 mL, 1 M), THF (1 × 60 mL), and 1 M HCl (2 × 100 mL).

The THF was removed from the filtrate under reduced pressure. The residual filtrate was washed with EtOAc (2 × 50 mL) and made basic with aq NH_3 (25% w/v, 100 mL). The resulting suspension was shaken with toluene (100 mL) and filtered. The solid was washed with toluene (2 × 100 mL). The filtrate was separated and the aqueous phase was washed with toluene (3 × 100 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (40 mL), sat. aq NaCl (40 mL), and H_2O (2 × 40 mL), dried (anhyd Na_2SO_4), and evaporated.

1-(4-methoxyphenyl)-4-methylpiperazine (3a)[15]

Red solid. Yield: 1.85 g (60%). Mp 63–65 °C (Lit.[15a] 62–64 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.57 (t, *J* = 4,7 Hz, 4 H), 3.10 (t, *J* = 5.2 Hz, 4 H), 3.76 (s, 3 H) 6.83 (ddd, J^1 = 10.4 Hz, J^2 = 9.0 Hz, J^3 = 2.8 Hz, 2 H), 6.90 (ddd, J^1 = 10.4 Hz, J^2 = 9.0 Hz, J^3 = 2.3 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 154.2, 146.1, 118.5, 114.8, 55.9, 55.7, 51.0, 46.5.

Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.86; H, 8.80; N, 13.58. Found: C, 69.70; H, 8.88; N, 13.43.

1-Methyl-4-phenylpiperazine (3b)[15]

Purified by flash chromatography (EtOAc–heptane–Et_3N). Yellow oil; yield: 0.96 g (37%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.53 (t, *J* = 4.7 Hz, 4 H), 3.18 (t, *J* = 4.7 Hz, 4 H), 6.81–6.85 (m, 1 H), 6.88–6.92 (m, 2 H), 7.21–7.26 (m, 2 H).

^{13}C NMR (250 MHz, $CDCl_3$): δ = 151.7, 129.5, 120.1, 116.5, 55.6, 49.5, 46.6.

1-(4-Fluorophenyl)-4-methylpiperazine (3c)

Purified by flash chromatography (EtOAc–heptane–Et_3N). Yellow solid; yield: 0.6 g (21%); mp 42–44 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.56 (t, *J* = 5.2 Hz, 4 H), 3.12 (t, *J* = 5.2 Hz, 4 H), 6.84–6.88 (m, 2 H), 6.92–6.98 (m, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 158.5, 156.6, 148.3, 118.2, 118.1, 115.9, 115.8, 55.5, 50.5, 46.5.

Anal. Calcd for $C_{11}H_{15}N_2F$: C, 68.01; H, 7.78; N, 14.42. Found: C, 67.89; H, 7.89; N, 14.38.

1-(3,4-Dichlorophenyl)-4-methylpiperazine (3d)

Byproduct 1-(4-chlorophenyl)-4-methylpiperazine was removed by Kugelrohr distillation at 160–165 °C (1 mbar), and the residue was purified by flash chromatography (EtOAc–heptane–Et_3N).

Brown oil, which solidified upon standing; yield: 0.13 g (4%); mp 52–53 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.55 (t, *J* = 5.2 Hz, 4 H), 3.18 (t, *J* = 4.7 Hz, 4 H), 6.74 (dd, J^1 = 9.0 Hz, J^2 = 2.8 Hz, 1 H), 6.95 (d, *J* = 2.8 Hz, 1 H), 7.26 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 151.1, 133.1, 130.8, 122.4, 117.5, 115.6, 55.2, 49.0, 46.5.

Anal. Calcd for $C_{11}H_{14}N_2Cl_2$: C, 53.89; H, 5.76; N, 11.43. Found: C, 54.12; H, 5.97; N, 11.38.

***N*-Arylpiperazines 3e–h; General Procedure**

Resin **2e–h** (14.8 mmol) was suspended in DME (100 mL). Then, *t*-BuOK (3.7 g, 33 mmol, 2.2 equiv) was added and the suspension was refluxed for 3 h. The suspension was filtered and washed successively with DME (3 × 100 mL), 1 M HCl (3 × 100 mL), DME (1 × 50 mL), 1 M aq HCl (3 × 100 mL), and DME (2 × 50 mL). The DME was removed from the filtrate under reduced pressure, and the residual filtrate was washed with EtOAc (2 × 50 mL) and made basic with aq NH_3 (25% w/v, 100 mL). The aqueous phase was extracted with toluene (6 × 100 mL). The combined organic phases were filtered to remove impurities, washed with sat. aq $NaHCO_3$ (50 mL), sat. aq NaCl (50 mL), and H_2O (2 × 50 mL), dried (anhyd Na_2SO_4), and evaporated.

The crude products were dissolved in abs EtOH (10 mL) and a solution of oxalic acid dihydrate (1.1 equiv) in abs EtOH (9 mL) was added with stirring. The oxalate formed was allowed to precipitate in the fridge overnight. In the case of **3e**, the equivalents of acid were calculated based on the HPLC purity, otherwise they were calculated on the total weight of the crude product.

1-(4-Methoxyphenyl)piperazine Oxalate (3e)

Light-brown crystals; yield: 0.85 g (20%); mp 199–200 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.30–3.40 (m, 8 H), 3.76 (s, 3 H), 6.97 (ddd, J^1 = 10.8 Hz, J^2 = 3.8 Hz, J^3 = 2.4 Hz, 2 H), 7.08 (ddd, J^1 = 10.4 Hz, J^2 = 3.8 Hz, J^3 = 2.4 Hz, 2 H).

^{13}C NMR (62.5 MHz, D_2O): δ = 166.4, 155.2, 143.8, 120.3, 115.3, 56.1, 48.5, 43.5.

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.20; H, 6.49; N, 9.91. Found: C, 55.22; H, 6.48; N, 9.80.

1-Phenylpiperazine Oxalate (3f)

Light-brown crystals; yield: 0.64 g (17%); mp 167–169 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.35–3.43 (m, 8 H), 7.03–7.07 (m, 1 H), 7.08–7.12 (m, 2 H), 7.34–7.39 (m, 2 H).

^{13}C NMR (62.5 MHz, D_2O): δ = 166.5, 149.9, 130.1, 123.0, 118.2, 47.3, 43.5.

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 56.90; H, 6.77; N, 11.06. Found: C, 56.65; H, 6.49; N, 11.10.

1-(4-Fluorophenyl)piperazine Oxalate (3g)
Light-brown crystals; yield: 0.93 g (23%); mp 172–173 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.32–3.40 (m, 8 H), 7.07–7.12 (m, 4 H).

^{13}C NMR (62.5 MHz, D_2O): δ = 166.3, 157.8, 146.3, 120.2, 120.2, 116.4, 116.2, 48.1, 43.5.

Anal. Calcd for $C_{12}H_{15}N_2O_4F$: C, 53.33; H, 5.59; N, 10.37. Found: C, 53.35; H, 5.68; N, 10.37.

1-(3,4-Dichlorophenyl)piperazine Oxalate (3h)
Recrystallized (*i*-PrOH). Light-brown crystals; yield: 0.27 g (6%); mp 230–232 °C.

^{1}H NMR (500 MHz, D_2O): δ = 3.22–3.32 (m, 8 H), 6.86 (dd, J^1 = 8.9 Hz, J^2 = 2.8 Hz, 1 H), 7.11 (d, J = 2.8 Hz, 1 H), 7.32 (d, J = 9.0 Hz, 1 H).

^{13}C NMR (62.5 MHz, D_2O): δ = 149.7, 131.2, 119.1, 117.6, 46.7, 43.3.[16]

Anal. Calcd for $C_{12}H_{14}N_2O_4Cl_2$: C, 44.81; H, 4.39; N, 8.71. Found: C, 45.21; H, 4.61; N, 8.58.

Methyl 4-(4-methoxyphenyl)piperazine-1-carboxylate (4)
Resin **1** (10.0 g, 14.8 mmol) was suspended in MIBK (100 mL). 4-Methoxyaniline (8.9 g, 75 mmol, 5 equiv) and KI (0.48 g, 3 mmol, 0.2 equiv) were added, followed by py (6 mL, 75 mmol, 5 equiv). The mixture was heated to 100 °C for 15 h. The resin was washed successively with THF (2 × 100 mL), MeOH (2 × 100 mL), H_2O (2 × 100 mL), THF (2 × 100 mL), and MeOH (2 × 100 mL), and then was suspended in MeOH (100 mL). Then, KOH (8.2 g, 140 mmol, 10 equiv) was added and the suspension was refluxed for 3.5 h. The suspension was filtered and the resin was washed successively with THF (2 × 100 mL), 1 M HCl (2 × 100 mL), THF (1 × 100 mL), 1 M HCl (2 × 100 mL), and THF (1 × 100 mL). The THF was removed by evaporation in vacuo and the remaining solution was washed with EtOAc (2 × 50 mL). The aqueous phase was made basic with aq NH_3 (25 w/v, 25 mL) and extracted with Et_2O (5 × 100 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (50 mL), sat. aq NaCl (50 mL), and H_2O (2 × 50 mL), dried (anhyd Na_2SO_4), and evaporated to give compound **4** as an oil that solidified upon standing.

Yield: 1.15 g (32%); mp 94–97 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00–3.04 (m, 4 H), 3.59–3.65 (m, 4 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 6.84 (ddd, J^1 = 9.4 Hz, J^2 = 3.3 Hz, J^3 = 2.8 Hz, 2 H), 6.90 (ddd, J^1 = 9.4 Hz, J^2 = 3.3 Hz, J^3 = 2.8 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 156.3, 154.7, 146.0, 119.3, 114.9, 55.9, 53.0, 51.3, 44.3.

Anal Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.06; H, 7.30; N, 11.06.

Sifaprazine (5)
Resin **1** (5.1 g, 7.5 mmol) was suspended in MIBK (40 mL) with 2-benzylaniline (6.87 g, 37 mmol, 5 equiv) and KI (3.74 g, 22.5 mmol, 3 equiv). Then, py (6 mL, 5.6 g, 71 mmol, 9.5 equiv) was added and the suspension was heated to 100 °C for 67 h with magnetic stirring. The resin was washed successively with NMP (3 × 50 mL), THF (3 × 50 mL), MeOH (3 × 50 mL), H_2O (3 × 50 mL), NMP (3 × 50 mL), THF (3 × 50 mL), MeOH (3 × 50 mL), and THF (3 × 50 mL), and then dried. The resin was suspended in THF (50 mL). Pellets of $LiAlH_4$ (2.8 g, 75 mmol, 10 equiv) were added and the suspension was refluxed for 19 h with magnetic stirring.[17] The suspension was cooled on ice and quenched by the sequential addition of H_2O (3 mL), aq NaOH (13% w/v, 3 mL), and H_2O (10 mL). The suspension was filtered and the resin washed successively with THF (3 × 50 mL), 1 M aq HCl (3 × 50 mL), THF (1 × 50 mL), 1 M aq HCl (3 × 50 mL), and THF (3 × 50 mL). The filtrate was filtered through Celite and the THF was removed under reduced pressure. The aqueous phase was made strongly acidic with concd aq HCl and was washed with EtOAc (2 × 25 mL). The aqueous phase was then made basic with aq NH_3 (25% w/v, 50 mL). The resulting suspension of salts was shaken with toluene (50 mL) and filtered. The solid was washed with toluene (2 × 50 mL). The filtrate was separated and the aqueous phase was washed with toluene (3 × 50 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (25 mL), sat. aq NaCl (25 mL), and H_2O (2 × 40 mL), dried (Na_2SO_4), and evaporated to give a brown oil (134 mg). Purification through automated flash chromatography yielded **5** as a slightly yellow oil that solidified upon standing.

Yield: 53 mg (2.7%); mp 77–79 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.39–2.74 (m, 4 H), 2.89 (t, J = 4.8 Hz, 4 H), 4.07 (s, 2 H), 7.08–7.28 (m, 9 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 152.0, 142.2, 137.0, 131.3, 129.4, 128.7, 127.5, 126.1, 124.4, 121.0, 56.1, 53.0, 46.6, 37.0.

Anal Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.33; N, 10.20. Found: C, 80.72; H, 8.37; N, 10.46.

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