

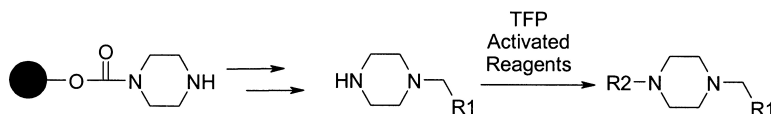
Article

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The Solid-Phase Synthesis and Use of N-Monosubstituted Piperazines in Chemical Library Synthesis

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An efficient solid-phase synthesis of mono-N-substituted piperazines is presented. The key transformation involves a selective borane amide bond reduction in the presence of a carbamate resin linkage. This synthetic route takes advantage of the large diverse pool of commercially available carboxylic acids, acid chlorides, and sulfonyl chlorides. The solid-phase approach facilitates parallel processing by eliminating the need for column chromatography after each synthetic step. The N-monosubstituted piperazines were shown to react with polymeric activated tetrafluorophenol (TFP) reagents to generate arrays of amides and sulfonamides in good purity for biological testing.

Introduction

The piperazine moiety is a common pharmacophore found in many compounds of biological interest.¹ For example, a piperazine core is found in indinavir, a potent HIV protease inhibitor that has been approved for use in man;^{1a} clozapine, an antipsychotic agent that blocks dopamine and 5HT_{2A} receptors;^{1b} quipazine, a 5HT₃ antagonist^{1c}; and GR89696, a potent selective κ -opioid receptor agonist.^{1d} These are only a few of the many examples in which the piperazine core has been used as a scaffold to generate biologically active molecules. Thus, it appears that the piperazine core acts as a privileged motif,² because derivatives lead to biologically active compounds against enzyme and receptor targets. For this reason, we chose to develop a robust, parallel synthetic route to piperazine derivatives to add to our general screening collection.

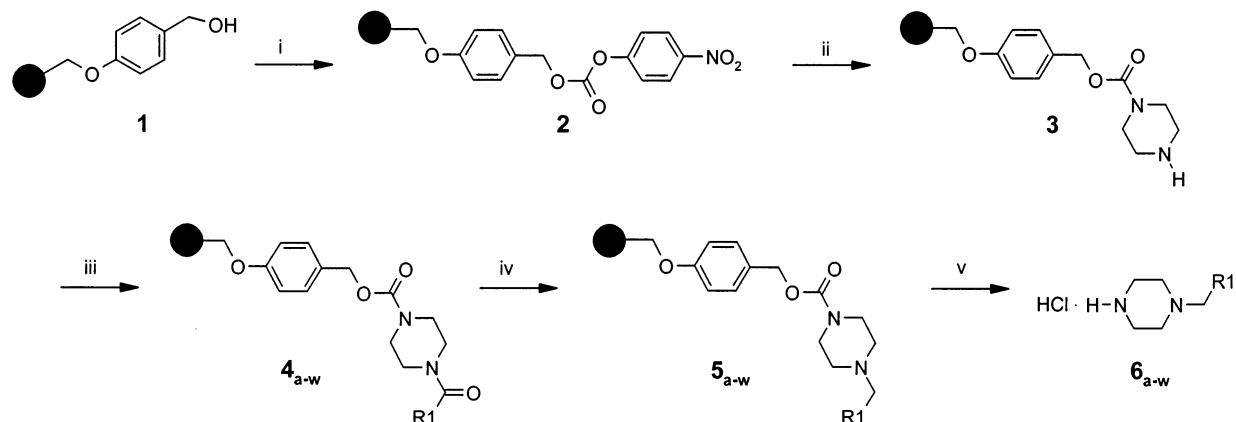
In general, solid-phase syntheses of piperazine derivatives have been accomplished using multistep approaches by attaching the piperazine core to Wang resin via a carbamate linkage,³ by derivatization followed by alkylation and Hoffman elimination using a REM resin linker,⁴ and by using resin-bound piperazine as a component in Mannich and Petassis boro-Mannich reactions.⁵ This paper describes a convenient, highly convergent approach to N-monosubstituted piperazines using a selective borane-mediated amide bond reduction in the presence of a carbamate linkage⁶ to generate diversity using commercially available carboxylic acids and acid chlorides as starting materials. These custom piperazines were then further reacted with polymeric activated TFP resins⁷ to yield arrays of amide and sulfonamide derivatives. The advantage of this production approach is that the custom piperazines can be fully characterized and evaluated separately for biological activity. The TFP reagents are stable activated forms of the reagent that are fully characterized and, in addition, may be stored for later use, unlike acid chlorides or sulfonyl chlorides, which tend to

decompose over time. Highly pure single compounds are generated by arraying a limiting amount of amine with an excess of the TFP reagent, followed by filtration. This method also eliminates the need to develop a scavenger strategy or the concern with TFA cleavage at the end of the library production.

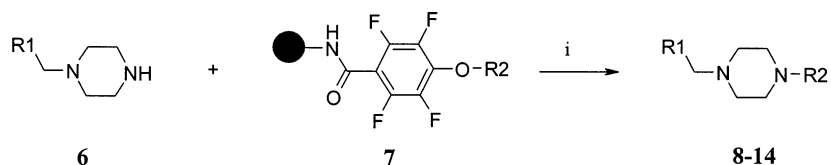
Results and Discussion

Mono-N-substituted piperazines were efficiently synthesized using the approach outlined in Scheme 1. Wang resin **1** was treated with *p*-nitrophenyl chloroformate in the presence of base to afford the nitrophenol carbonate resin **2**. This reaction was easily monitored by single-bead IR to confirm the presence of a carbonate carbonyl near 1765 cm⁻¹. The loading of the resin was determined by N elemental analysis. Nitrophenol carbonate resin **2** was then acylated by reaction with piperazine at room temperature in DMF to form the piperazine carbamate resin **3**. A significant advantage of this approach was the exclusive formation of monocarbamate-protected piperazine⁸ from the symmetric diamine. In addition, treatment of the nitrophenyl carbonate resin **2** with multiple aliquots of piperazine ensures complete reaction.

Acylation of piperazine carbamate resin **3** with acid chlorides or carboxylic acids produced the corresponding amide resin **4**.^{3a,b} The amide bond was then selectively reduced over the carbamate linkage by the action of BH₃–THF complex to yield the tertiary amine **5**.^{6,9} This approach was preferred over reductive amination because it afforded products of higher purity. In addition, this approach takes advantage of the wide availability of carboxylic acids as inputs to the synthesis. The piperazine coupling and BH₃–THF reductions were typically carried out on a 4-g resin scale to ensure synthesis of enough material (0.75–1.0 g) for the final TFP derivatization step. Cleavage of **5** from the solid support using a 50% TFA/DCM gave the target

Scheme 1^a

^a Key: i. 4-Nitrophenyl chloroformate, NMM, THF, 0 → 25 °C, 1 h. ii. Piperazine, DMF, 25 °C, 12 h. iii. Acid chloride, NMM, DMF, 25 °C, 4 h or carboxylic acid, DIC, HOBT, DMF, 3.5 h, 25 °C. iv. BH₃-THF, THF, 0 → 25 °C, 24 h. v. 50% TFA in DCM, 0 → 25 °C, 45 min, then 20% 6 N HCl in MeOH, 25 °C, 1 h.

Scheme 2^a

^a Key: i. Incubate amine with MP-carbonate resin (Argonaut Technologies, 3.0 mmol/g) 3–5 equiv relative to substrate, 2 h, 25 °C, then incubate with TFP resin reagent (0.8 equiv relative to TFP reagent), DMF, 25 °C, 12 h. Filter, and evaporate the solvent (see Table 2 for purities).

Table 1. N-Monosubstituted Piperazines

compd	R1 ^a	purity ^b %	yield %	compd	R1 ^a	purity %	yield %
6a	A	96	80	6m	M	<i>c</i>	54
6b	B	88	58	6n	N	<i>c</i>	50
6c	C	85	56	6o	O	<i>c</i>	47
6d	D	98	55	6p	P	<i>c</i>	59
6e	E	85	60	6q	Q	<i>c</i>	47
6f	F	84	72	6r	R	<i>c</i>	56
6g	G	89	70	6s	S	90	94
6h	H	92	64	6t	T	84	52
6i	I	80	66	6u	U	99	76
6j	J	95	82	6v	V	83	62
6k	K	90	72	6w	W	98	64
6l	L	98	56				

^a See Table 3 for R1 group structures. ^b Purity was measured by UV₍₂₂₀₎ detection without correction for extinction coefficient or slight variance in concentration. ^c Product confirmed by MS; however, UV₍₂₂₀₎ purity not measurable as a result of lack of a chromophore.

mono-N-substituted piperazine, **6**, as the TFA salt. To prevent possible trifluoroacylation, the HCl salt of **6** was formed by treatment with a methanolic HCl solution followed by concentration. This process was well-suited for use in a Quest 205 parallel synthesizer.¹⁰ This simple process was efficient and produced the 23 custom monosubstituted piperazines listed in Table 1 in good overall yield and purity. In general, the purity of the monosubstituted piperazines ranged from 80 to 99% by HPLC using UV 220 detection, and the isolated yields were 47–94%. Increasing the amount of resin used for the synthesis of the custom piperazines for those examples

with modest yields gave the required ~1.0 g amount of material.

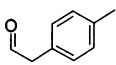
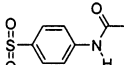

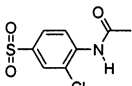

The custom piperazines were then reacted with polymeric activated TFP reagents⁷(Scheme 2). The purities of the products listed in Table 2 are based on UV without correction for differences in extinction coefficients for various chromophores or slight differences in concentrations. The average purity of the set listed in Table 2 is 77%, including the four samples that were produced in <50% purity. This range of purity is sufficient for most in vitro assays to rank-order compounds for potency.¹¹ In general, a resynthesis of a small number of compounds from the library is conducted to confirm structure activity relationships and potency of individual compounds.

In conclusion, a practical solid-phase synthesis of N-monosubstituted piperazines is presented. The synthetic route is robust and easily amenable to parallel synthesis on a milligram-to-gram scale. These custom piperazines were then further processed by reaction with polymeric activated TFP reagents to form libraries of piperazine amides and sulfonamides of high purity for biological testing.

Experimental Section

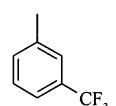

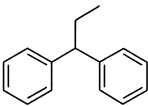
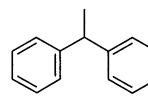
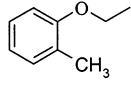
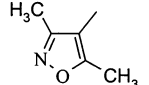

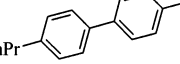
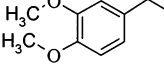
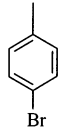

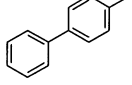





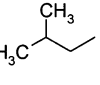

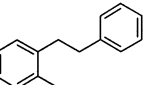
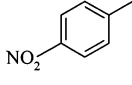
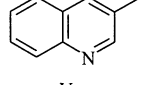
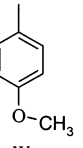
General Procedures. ¹H NMR spectra were recorded in 5-mm tubes on a 300 MHz spectrometer in CDCl₃ unless otherwise stated. FT-IR were recorded at 4 cm⁻¹ resolution on a spectrometer interfaced to an InspectIR attenuated total reflectance microscope with Si sampling optics. Solvents used were EM Science of OmniSolv distilled grade unless specified otherwise. The following abbreviations are used: DCM = dichloromethane, DMF = dimethylformamide, THF = tetrahydrofuran.

Table 2. UV Purities of a Representative Sampling of Acylated and Sulfonylated Piperazines

compd	R1 ^a	R2=				
						
8a–e	A	80	79	78	70	43
9a–e	B	84	92	87	89	89
10a–e	C	77	87	49	76	85
11a–e	D	78	82	80	69	62
12a–e	E	86	88	86	85	88
13a–e	F	75	85	71	83	87
14a–e	G	80	74	81	75	91

^a See Table 3 for structures of R1 side chains.

Table 3. Structures R1 Side Chains in Tables 1 and 2

				
A	B	C	D	E
				
F	G	H	I	J
				
K	L	M	N	O
				
P	Q	R	S	T
				
U	V	W		

4-Nitrophenol-carbonate Resin (2). Wang resin (100 g; 170 mmol) was swelled in anhydrous THF (1500 mL) for 15 min at room temperature. The resin was cooled in an ice bath, and *N*-methyl morpholine (120 mL, 1090 mmol) and 4-nitrophenyl chloroformate (110 g, 545 mmol) were added. The reaction mixture was allowed to warm to room temperature and was agitated on an orbital shaker overnight. The solvent was removed by vacuum filtration, and the resin was washed with THF (5 × 200 mL), 20% H₂O in DMF (5 × 200 mL), DMF (5 × 200 mL), THF (5 × 200 mL), and Et₂O (5 × 200 mL). The resin was dried in vacuo at 25 °C overnight. IR analysis showed two sharp peaks at 1525 and 1350 cm⁻¹ for the nitro group and a sharp peak at 1765 cm⁻¹ for the carbonate carbonyl group.

ν_{CO} (cm⁻¹) = 1765, ν_{NO_2} (cm⁻¹) = 1525, 1350. Loading: 1.56 mmol/g by N microanalysis. Analysis found: N, 2.18.

Piperazine Carbamate Resin (3). In a 2-L round-bottomed flask, the nitrocarbonate resin (2) (100 g, ~156

mmol) was swelled in anhydrous DMF (1000 mL) for 15 min. Piperazine (65 g, 750 mmol) was added to the mixture at room temperature. The mixture was then stirred overnight at room temperature on an orbital shaker. The solvent was removed by vacuum filtration, and the resin was washed with 30% H₂O in DMF (5 × 200 mL) and DMF (5 × 200 mL). Then the resin was subjected to a second reaction cycle with piperazine (65 g, 750 mmol). The solvent was removed by vacuum filtration, and resin **3** was washed with 30% H₂O in DMF (10 × 200 mL), DMF (10 × 200 mL), THF (10 × 200 mL), Et₂O (10 × 100 mL), and MeOH (2 × 100 mL). Resin **3** was then dried in vacuo at ambient temperature overnight. IR analysis showed the loss of the two sharp peaks at 1525 and 1350 cm⁻¹ corresponding to the nitro group in the starting material and the shift of the carbonyl signal to 1700 cm⁻¹.

General Coupling Procedure Method A. The piperazine carbamate resin (**3**) (4 g, ~4.88 mmol) was added to a 100

mL polypropylene *Quest* reaction vessel. The resin was swelled in DMF (25 mL) and *N*-methyl morpholine (54 mL, 48.8 mmol) for 10 min at room temperature. The acyl chloride (24.4 mmol) was added, and then the reaction mixture was gently agitated for 4 h at room temperature. The resin was drained off and washed successively with DMF (5 × 25 mL), THF (5 × 25 mL), DCM (5 × 25 mL), and MeOH (5 × 25 mL) and dried in vacuo. IR analysis showed the formation of two new signals at 1640 and 1660 cm⁻¹. The resin was then reduced and cleaved using the general procedure below.

General Coupling Procedure Method B. Diisopropylcarbodiimide (3.8 mL, 24.4 mmol), carboxylic acid (24.4 mmol), and HOBt (0.33 g; 2.44 mmol) were added to a 100-mL polypropylene *Quest* reaction vessel containing DMF (25 mL). The mixture was stirred at room temperature for 1.5 h, and then the piperazine carbamate resin (**3**) (4 g, ~4.88 mmol) was added. The reaction mixture was stirred for an additional 2 h at room temperature, and the solvent was drained off. The resin was washed successively with DMF (5 × 25 mL), THF (5 × 25 mL), DCM (5 × 25 mL), and MeOH (2 × 20 mL) and dried in vacuo. IR analysis showed the formation of two new signals near 1640 and 1660 cm⁻¹. The resin was then reduced and cleaved using the general procedure below.

General Amide Bond Reduction and Cleavage Procedure. The amide resin contained in the 100-mL polypropylene *Quest* reaction vessel was swelled in anhydrous THF (50 mL) for 15 min. The resin was cooled to 0 °C, and BH₃-THF complex (42.5 mL, 42.5 mmol, 1.0 M solution in THF) was added slowly over a 15-min period at 0 °C. The resulting suspension was agitated for 24 h at room temperature. The reaction mixture was then quenched by the slow addition of 10% H₂O in THF (30 mL). After draining away the solvent, the resin was washed with THF (10 × 30 mL), DCM (5 × 30 mL), and MeOH (5 × 30 mL) and dried overnight under vacuum to give ~4 g of resin. IR analysis showed the disappearance of the amide carbonyl signal near 1640 cm⁻¹.

The resulting resin was placed in a 100-mL polypropylene reaction vessel, and a solution of 50% TFA in DCM (20 mL) was added to the reaction mixture slowly at room temperature. The mixture was stirred on an orbital shaker for 45 min at room temperature. The resin was filtered and washed with 20 mL of DCM. The filtrate was concentrated to yield the corresponding piperazine trifluoroacetate salt. The piperazine trifluoroacetate salt was added to a solution of 20% 6 M HCl in methanol (50 mL) at room temperature. The resulting suspension was stirred for 60 min at room temperature, then concentrated.

3-Trifluoromethyl-benzyl-piperazine Hydrochloride (6a). Prepared according to method A. 1.10 g; 80% yield; ¹H NMR (DMSO) δ 9.20 (2H, s), 7.90 (1H, s), 7.85 (2H, m), 7.65 (1H, m), 4.15 (2H, s), 3.30 (4H, t), 3.30 (4H, t). EI-MS *m/z* 245 [M + H]⁺. LC_(UV220) = 96%.

1-Furanyl-2-yl-methyl-piperazine Hydrochloride (6b). Prepared according to method A. 0.572 g; 58% yield; ¹H NMR (DMSO) δ 9.85 (2H, s), 7.80 (1H, dd), 6.70 (1H, dd), 6.55 (1H, dd), 4.50 (2H, s), 3.40 (8H, m). EI-MS *m/z* 167 [M + H]⁺; A% LC_(UV220) = 88%.

3,3-Diphenyl-propyl-piperazine Hydrochloride (6c). Prepared according to method A. 1.00 g; 56% yield; ¹H NMR (CD₃OD) δ 7.3 (10H, m), 4.15 (1H, t), 3.85 (4H, m), 3.65 (4H, m), 3.25 (2H, t), 2.60 (2H, t). ESI-MS *m/z* 281 [M + H]⁺; A% LC_(UV220) = 85%.

2,2-Diphenylethyl-piperazine Hydrochloride (6d). Prepared according to method A. 0.811 g; 55% yield; ¹H NMR (CD₃OD) δ 7.55 (4H, t), 7.40 (4H, t), 7.30 (2H, dd), 4.85 (1H, t), 4.15 (2H, d), 3.65 (8H, m). ESI-MS *m/z* 267 [M + H]⁺; A% LC_(UV220) = 98%.

1-(2-*o*-Tolyloxy-ethyl)-piperazine Hydrochloride (6e). Prepared according to method A. 0.750 g; 60% yield; ¹H NMR (CD₃OD) δ 7.15 (1H, d), 6.90 (1H, d), 6.85 (2H, t), 4.45 (2H, t), 3.95 (2H, t), 3.80 (4H, m), 3.75 (2H, m), 3.70 (4H, m), 2.30 (3H, s). EI-MS *m/z* 221 [M + H]⁺; A% LC_(UV220) = 85%.

1-(3,5-Dimethyl-isoxazol-4-ylmethyl)-piperazine Hydrochloride (6f). Prepared according to method A. 0.812 g; 72% yield; ¹H NMR (CD₃OD) δ 4.40 (2H, s), 3.70 (8H, m), 2.6 (3H, s), 2.3 (3H, s). EI-MS *m/z* 196 [M + H]⁺; A% LC_(UV220) = 84%.

Benzylpiperazine Hydrochloride (6g). Prepared according to method A. 0.724 g; 70% yield; ¹H NMR (CD₃OD) δ 7.65 (2H, m), 7.50 (3H, m), 4.50 (2H, s), 3.65 (8H, m). EI-MS *m/z* 177 [M + H]⁺; A% LC_(UV220) = 89%.

4-(4'-Propylphenyl)benzyl-piperazine Hydrochloride (6h). Prepared according to method A. 1.031 g; 64% yield; ¹H NMR (DMSO) δ 9.70 (2H, s), 7.75 (2H, d), 7.70 (2H, d), 7.60 (2H, d), 7.30 (2H, d), 4.40 (2H, s), 3.50 (8H, m), 2.65 (2H, t), 1.60 (2H, m), 0.9 (3H, t). EI-MS *m/z* 295 [M + H]⁺; A% LC_(UV220) = 92%.

2-(3', 4'-Dimethoxy)phenyl-ethyl-piperazine Hydrochloride (6i). Prepared according to method A. 0.921 g; 66% yield; ¹H NMR (CD₃OD) δ 6.90 (3H, m), 3.85 (3H, s), 3.80 (3H, s), 3.70 (2H, t), 3.60 (8H, m), 3.10 (2H, t). EI-MS *m/z* 251 [M + H]⁺; A% LC_(UV220) = 80%.

4-Bromobenzyl-piperazine Hydrochloride (6j). Prepared according to method B. 1.156 g; 82% yield; ¹H NMR (CD₃OD) δ 7.90 (1H, d), 7.60 (2H, m), 7.40 (1H, t), 4.50 (2H, s), 3.65 (8H, m). EI-MS *m/z* 254 [M + H]⁺; A% LC_(UV220) = 95%.

1-Pyridin-3-ylmethyl-piperazine Hydrochloride (6k). Prepared according to method B. 0.748 g; 72% yield; ¹H NMR (CD₃OD) δ 7.45 (1H, dd), 7.30 (1H, s), 7.20 (1H, d), 7.05 (1H, d), 4.50 (2H, s), 3.65 (8H, m). EI-MS *m/z* 178 [M + H]⁺; A% LC_(UV220) = 90%.

4-Phenyl-benzyl-piperazine Hydrochloride (6l). Prepared according to method B. 0.787 g; 56% yield; ¹H NMR (CD₃OD) δ 7.80 (1H, d), 7.65 (5H, m), 7.50 (2H, m), 7.40 (1H, d), 4.50 (2H, s), 3.65 (8H, m). EI-MS *m/z* 253 [M + H]⁺; A% LC_(UV220) = 98%.

Cyclopropyl-methyl-piperazine Hydrochloride (6m). Prepared according to method B. 0.464 g; 54% yield; ¹H NMR (DMSO) δ 9.60 (2H, s), 3.70 (4H, m), 3.50 (4H, m), 3.05 (2H, d), 1.05 (1H, q), 0.60 (2H, d), 0.40 (2H, d); EI-MS *m/z* 141 [M + H]⁺;

Cyclobutyl-methyl-piperazine Hydrochloride (6n). Prepared according to method B. 0.464 g; 50% yield; ¹H NMR

(DMSO) δ 9.60 (2H, s), 3.70 (8H, m), 3.25 (2H, m), 2.85 (1H, m), 2.15 (2H, m), 1.85 (4H, m). EI-MS m/z 155 [M + H]⁺

Cyclohexyl-methyl-piperazine Hydrochloride (6o). Prepared according to method B. 0.500 g; 47% yield; ¹H NMR (DMSO) δ 6.95 (2H, s), 3.65 (8H, m), 3.20 (2H, t), 1.90 (1H, m), 1.75 (4H, m), 1.25 (4H, m), 0.95 (2H, m). EI-MS m/z 155 [M + H]⁺

Isobutyl-piperazine Hydrochloride (6p). Prepared according to method B. 0.510 g; 59% yield; ¹H NMR (DMSO) δ 9.6 (2H, s), 3.69 (8H, m), 2.95 (2H, d), 2.05 (1H, m), 1.05 (6H, d). EI-MS m/z 143 [M + H]⁺

Tetrahydrofuran-2-yl-methyl-piperazine Hydrochloride (6q). Prepared according to method A. 0.472 g; 47% yield; ¹H NMR (DMSO) δ 9.6 (2H, s), 4.25 (1H, m), 3.85 (1H, m), 3.75 (1H, m), 3.55 (8H, m), 3.15 (2H, m), 2.10 (1H, m), 1.85 (2H, m), 1.55 (1H, m). EI-MS m/z 171 [M + H]⁺.

Isopentylpiperazine Hydrochloride (6r). Prepared according to method B. 0.525 g; 56% yield; ¹H NMR (DMSO) δ 9.5 (2H, s), 3.55 (8H, m), 3.10 (2H, m), 1.60 (2H, m), 0.95 (6H, d). EI-MS m/z 157 [M + H]⁺ EI-MS m/z 171 [M + H]⁺.

2, 3-Difluorobenzyl-piperazine Hydrochloride (6s). Prepared according to method B. 1.138 g; 94% yield; ¹H NMR (DMSO) δ 9.2 (2H, s), 7.45 (1H, m), 7.35 (1H, m), 7.25 (1H, m), 4.10 (2H, s), 3.30 (4H, t), 3.05 (4H, t). EI-MS m/z 213 [M + H]⁺; A% LC_(UV220) = 90%.

2-(2'-Phenylethyl)-benzyl-piperazine Hydrochloride (6t). Prepared according to method A. 0.804 g; 52% yield; ¹H NMR(DMSO) δ 9.70 (2H, s), 7.40 (9H, m), 4.10 (2H, s), 3.50 (8H, m), 3.05 (2H, t), 2.85 (2H, t). ESI-MS m/z = 281 [M + H]⁺; A% LC_(UV220) = 84%.

4-Nitrobenzyl-piperazine Hydrochloride (6u). Prepared according to method B. 0.949 g; 76% yield; ¹H NMR (DMSO) δ 9.60 (2H, s), 8.35 (2H, d), 7.85 (2H, d), 4.45 (2H, s), 3.45 (4H, t), 3.25 (4H, t). EI-MS m/z 221 [M + H]⁺; A% LC_(UV220) = 99%.

3-Piperazin-1-ylmethyl-quinoline Hydrochloride (6v). Prepared according to method A. 0.796 g; 62% yield; ¹H NMR (DMSO) δ 9.80 (2H, s), 9.45 (1H, s), 9.05 (1H, s), 8.40 (1H, d), 8.20 (1H, d), 8.00 (1H, t), 7.80 (1H, t), 4.70 (2H, s), 3.55 (8H, m). EI-MS m/z 228 [M + H]⁺; A% LC_(UV220) = 83%.

4-Methoxybenzylpiperazine Hydrochloride (6w). Prepared according to method A. 0.756 g; 64% yield; ¹H NMR (CD₃OD) δ 8.90 (2H, d), 8.2 (2H, d), 4.25 (2H, s), 3.45 (4H, t), 3.35 (3H, s), 3.10 (4H, t). EI-MS m/z 207 [M + H]⁺; A% LC_(UV220) = 98%.

General Procedure for Synthesis of Tetrafluorophenol (TFP)-Activated Reagents. Procedure A. TFP-Activated Carboxylic Acid Esters. TFP resin (2 g, 1.9 mmol, 0.95 mmol/g) was added to a 100-mL polypropylene reaction vessel. The resin was swelled in DCM (30 mL) for 15 min at room temperature, then carboxylic acid (3.8 mmol), DIC (0.595 mL, 3.8 mmol), HOBT (51.34 mg, 0.38 mmol), and DCM (20 mL) were added to the reaction vessel. The reaction mixture was gently agitated at room temperature

for 2 h, then washed with DMF (3 × 30 mL) and DCM (3 × 30 mL) and dried under vacuum at ambient temperature overnight.

Procedure B. TFP-Activated Sulfonate Esters. TFP resin (2 g, 1.9 mmol, 0.95 mmol/g) was added to a 100-mL polypropylene reaction vessel. The resin was swelled in DMF (20 mL) for 15 min at room temperature, then DIEA (0.98 mL, 2.85 mmol) followed by a solution of sulfonyl chloride (2.85 mmol) dissolved in 10 mL of DMF was added to the reaction mixture. The reaction mixture was gently agitated at room temperature for 3 h, then washed with DMF (3 × 30 mL) and DCM (3 × 30 mL) and dried under vacuum at ambient temperature overnight.

Loading Determination. TFP-activated ester or sulfonate ester (50 mg, ~0.05 mmol, ~0.95 mmol/g) was treated with a DMF (2.5 mL) solution of 2-methylbenzylamine (5.74 mg; 0.05 mmol). The reaction mixture was agitated at room temperature for 3 h. The reaction mixture was then filtered, and the filtrate was concentrated. The resulting residue was evaluated by ¹H NMR and LC/MS. Loading was determined by integration and comparison of the aromatic methyl protons and the α -methylene protons of product amide relative to the starting amine.

Polymeric TFP-*p*-Tolyl Acetate Ester (7a). Prepared according to procedure A. Loading by ¹H NMR, >95% by formation of *N*-(2-methyl-benzyl)-2-*p*-tolyl acetamide; ¹H NMR (CDCl₃) δ 7.12 (8H, m), 5.50 (1H, bs), 4.40 (2H, d), 5.99 (2H, s), 2.31 (3H, s), 2.22 (3H, s). ESI(+)-MS m/z 254 [M + H]⁺; A% LC_(UV220) = 96%.

Polymeric TFP-4-Acetylamino-benzenesulfonic Acid Ester (7b). Prepared according to procedure B. Loading by ¹H NMR, 56%¹² by formation of *N*-[4-(2-methyl-benzylsulfamoyl)-phenyl]-acetamide; ¹H NMR (CDCl₃) δ 7.81 (2H, d), 7.65 (2H, d), 7.15 (4H, m), 4.10 (2H, s), 2.26 (3H, s), 2.22 (3H, s). ESI(-)-MS m/z 317 [M-H]⁻; A% LC_(UV220) = 95%.

Polymeric TFP-*o*-Tolyl Acetate Ester (7c). Prepared according to procedure A. Loading by ¹H NMR, >95% by formation of *N*-(2-methyl-benzyl)-2-*o*-tolyl-acetamide; ¹H NMR (CDCl₃) δ 7.15 (8H, m), 5.43 (1H, bs), 4.40 (2H, d), 3.61 (2H,s), 2.28 (3H, s), 2.20 (3H, s). ESI(+)-MS m/z 254 [M + H]⁺; A% LC_(UV220) = 96%.

Polymeric TFP-4-acetylamino-3-chloro-benzenesulfonic Acid Ester (7d). Prepared according to procedure B. Loading by ¹H NMR, 84% by formation of *N*-[2-chloro-4-(2-methyl-benzylsulfamoyl)-phenyl]-acetamide; ¹H NMR (CDCl₃) δ 7.15 (8H, m), 5.43 (1H, bs), 4.40 (2H, d), 3.61 (2H,s), 2.28 (3H, s), 2.20 (3H, s). ESI(+)-MS m/z 353 [M + H]⁺; A% LC_(UV220) = 97%.

Polymeric TFP-4-fluoro-benzenesulfonic Acid Ester (7e). Prepared according to procedure B. Loading by ¹H NMR, 79% by formation of 4-fluoro-*N*-(2-methyl-benzyl)-benzenesulfonamide; ¹H NMR (CDCl₃) δ 7.89 (1H, m), 7.18 (8H, m), 4.12 (2H, s), 2.21 (3H, s). ESI(-)-MS m/z 278 [M - H]⁻; A% LC_(UV220) = 88%.

2-*p*-Tolyl-1-[4-(3-trifluoromethyl-benzyl)-piperazin-1-yl]-ethanone (8a). Polymeric TFP-*p*-tolyl-acetate ester (7a) (14 mg; 0.0126 mmol, ~0.90 mmol/g based on 95% loading from NMR experiment), dispensed into a well of a 96-deep-

well polypropylene plate, was treated with 1-(3-trifluoromethyl-benzyl)-piperazine (2.44 mg, 0.010 mmol) dissolved in DMF (1 mL). The resulting mixture was allowed to stand at room temperature overnight. The reaction mixture was filtered and then concentrated to yield 2-*p*-tolyl-1-[4-(3-trifluoromethyl-benzyl)-piperazin-1-yl]-ethanone (**8a**). ESI(+)-MS m/z 377 [M + H]⁺; A% LC_(UV220) = 80%.

Compounds **8b–e**, **9a–e**, **10a–e**, **11a–e**, **12a–e**, **13a–e**, and **14a–e** were prepared according to the above procedure in a parallel array.

N-{4-[4-(3-Trifluoromethyl-benzyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**8b**). ESI(+)-MS m/z 442 [M + H]⁺; A% LC_(UV220) = 79%.

2-*o*-Tolyl-1-[4-(3-trifluoromethyl-benzyl)-piperazin-1-yl]-ethanone (8c). ESI(+)-MS m/z 377 [M + H]⁺; A% LC_(UV220) = 78%.

N-{2-Chloro-4-[4-(3-trifluoromethyl-benzyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**8d**). ESI(+)-MS m/z 476 [M + H]⁺; A% LC_(UV220) = 70%.

1-(4-Fluoro-benzenesulfonyl)-4-(3-trifluoromethyl-benzyl)-piperazine (8e). ESI(+)-MS m/z 403 [M + H]⁺; A% LC_(UV220) = 43%.

1-(4-Furan-2-ylmethyl-piperazin-1-yl)-2-*p*-tolyl-ethanone (9a). ESI(+)-MS m/z 299 [M + H]⁺; A% LC_(UV220) = 84%.

N-[4-(4-Furan-2-ylmethyl-piperazine-1-sulfonyl)-phenyl]-acetamide (**9b**). ESI(+)-MS m/z 364 [M + H]⁺; A% LC_(UV220) = 92%.

1-(4-Furan-2-ylmethyl-piperazin-1-yl)-2-*o*-tolyl-ethanone (9c). ESI(+)-MS m/z 299 [M + H]⁺; A% LC_(UV220) = 87%.

N-[2-Chloro-4-(4-furan-2-ylmethyl-piperazine-1-sulfonyl)-phenyl]-acetamide (**9d**). ESI(+)-MS m/z 398 [M + H]⁺; A% LC_(UV220) = 89%.

1-(4-Fluoro-benzenesulfonyl)-4-furan-2-ylmethyl-piperazine (9e). ESI(+)-MS m/z 325 [M + H]⁺; A% LC_(UV220) = 89%.

1-[4-(3,3-Diphenyl-propyl)-piperazin-1-yl]-2-*p*-tolyl-ethanone (10a). ESI(+)-MS m/z 413 [M + H]⁺; A% LC_(UV220) = 77%.

N-{4-[4-(3,3-Diphenyl-propyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**10b**). ESI(+)-MS m/z 478 [M + H]⁺; A% LC_(UV220) = 87%.

1-[4-(3,3-Diphenyl-propyl)-piperazin-1-yl]-2-*o*-tolyl-ethanone (10c). ESI(+)-MS m/z 413 [M + H]⁺; A% LC_(UV220) = 49%.

N-{2-Chloro-4-[4-(3,3-diphenyl-propyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**10d**). ESI(+)-MS m/z 512 [M + H]⁺; A% LC_(UV220) = 76%.

1-(3,3-Diphenyl-propyl)-4-(4-fluoro-benzenesulfonyl)-piperazine (10e). ESI(+)-MS m/z 439 [M + H]⁺; A% LC_(UV220) = 85%.

1-(4-Benzhydryl-piperazin-1-yl)-2-*p*-tolyl-ethanone (11a). ESI(+)-MS m/z 385 [M + H]⁺; A% LC_(UV220) = 78%.

N-[4-(4-Benzhydryl-piperazine-1-sulfonyl)-phenyl]-acetamide (**11b**). ESI(+)-MS m/z 450 [M + H]⁺; A% LC_(UV220) = 82%.

1-(4-Benzhydryl-piperazin-1-yl)-2-*o*-tolyl-ethanone (11c). ESI(+)-MS m/z 385 [M + H]⁺; A% LC_(UV220) = 80%.

N-[4-(4-Benzhydryl-piperazine-1-sulfonyl)-2-chloro-phenyl]-acetamide (**11d**). ESI(+)-MS m/z 484 [M + H]⁺; A% LC_(UV220) = 69%.

1-Benzhydryl-4-(4-fluoro-benzenesulfonyl)-piperazine (11e). ESI(+)-MS m/z 411 [M + H]⁺; A% LC_(UV220) = 62%.

2-*p*-Tolyl-1-[4-(2-*o*-tolylloxy-ethyl)-piperazin-1-yl]-ethanone (12a). ESI(+)-MS m/z 353 [M + H]⁺; A% LC_(UV220) = 86%.

N-{4-[4-(2-*o*-Tolylloxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**12b**). ESI(+)-MS m/z 418 [M + H]⁺; A% LC_(UV220) = 88%.

2-*o*-Tolyl-1-[4-(2-*o*-tolylloxy-ethyl)-piperazin-1-yl]-ethanone (12c). ESI(+)-MS m/z 353 [M + H]⁺; A% LC_(UV220) = 86%.

N-{2-Chloro-4-[4-(2-*o*-tolylloxy-ethyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**12d**). ESI(+)-MS m/z 452 [M + H]⁺; A% LC_(UV220) = 85%.

1-(4-Fluoro-benzenesulfonyl)-4-(2-*o*-tolylloxy-ethyl)-piperazine (12e). ESI(+)-MS m/z 379 [M + H]⁺; A% LC_(UV220) = 88%.

1-[4-(3,5-Dimethyl-isoxazol-4-yl-methyl)-piperazin-1-yl]-2-*p*-tolyl-ethanone (13a). ESI(+)-MS m/z 328 [M + H]⁺; A% LC_(UV220) = 75%.

N-{4-[4-(3,5-Dimethyl-isoxazol-4-yl-methyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**13b**). ESI(+)-MS m/z 393 [M + H]⁺; A% LC_(UV220) = 85%.

1-[4-(3,5-Dimethyl-isoxazol-4-yl-methyl)-piperazin-1-yl]-2-*o*-tolyl-ethanone (13c). ESI(+)-MS m/z 328 [M + H]⁺; A% LC_(UV220) = 71%.

N-{2-Chloro-4-[4-(3,5-dimethyl-isoxazol-4-yl-methyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**13d**). ESI(+)-MS m/z 427 [M + H]⁺; A% LC_(UV220) = 83%.

1-(3,5-Dimethyl-isoxazol-4-yl-methyl)-4-(4-fluoro-benzenesulfonyl)-piperazine (13e). ESI(+)-MS m/z 354 [M + H]⁺; A% LC_(UV220) = 87%.

1-(4-Benzyl-piperazin-1-yl)-2-*p*-tolyl-ethanone (14a). ESI(+)-MS m/z 309 [M + H]⁺; A% LC_(UV220) = 80%.

N-[4-(4-Benzyl-piperazine-1-sulfonyl)-phenyl]-acetamide (**14b**). ESI(+)-MS m/z 374 [M + H]⁺; A% LC_(UV220) = 74%.

1-(4-Benzyl-piperazin-1-yl)-2-*o*-tolyl-ethanone (14c). ESI(+)-MS m/z 309 [M + H]⁺; A% LC_(UV220) = 81%.

N-[4-(4-Benzyl-piperazine-1-sulfonyl)-2-chloro-phenyl]-acetamide (**14d**). ESI(+)-MS m/z 408 [M + H]⁺; A% LC_(UV220) = 75%.

1-Benzyl-4-(4-fluoro-benzenesulfonyl)-piperazine (14e). ESI(+)-MS m/z 335 [M + H]⁺; A% LC_(UV220) = 91%.

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- (12) Reaction of polymeric TFP–4-acetylamino-benzenesulfonic acid ester (**7b**) with 2-methylbenzylamine overnight gave equivalent loading results compared to reaction after 3 h.

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