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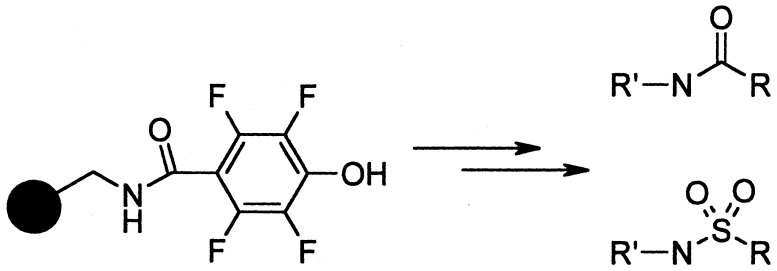

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Polymer-Supported Tetrafluorophenol: A New Activated Resin for Chemical Library Synthesis

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A new tetrafluorophenol activated resin that facilitates the use of ^{19}F NMR to quantitate loading is presented. This new resin provides a useful tool for acylation, and a novel activated polymeric sulfonate ester to generate sulfonamides. This activated resin reacts with a wide scope of N-nucleophiles including primary and secondary amines, and anilines. This new activated resin methodology provides a powerful tool for pure single-compound library synthesis.

A variety of polymeric activated resins have been reported in the literature.[1−5] Major shortcomings for the production of pure compound libraries using previous activated resin strategies[1−5] have included: (1) the limited scope of reactivity of N-nucleophiles toward the polymeric reagents, and (2) measuring the absolute loading of the activated resin so that a limiting amount of N-nucleophile may be used.

A new polymeric 4-hydroxy-2,3,5,6-tetrafluorobenzamido (TFP) resin (**1**) is described. The TFP resin is prepared by amide bond formation between commercially available 4-hydroxy-2,3,5,6-tetrafluorobenzoic acid and amino-methyl polystyrene. During this coupling procedure, a small percentage of ester is formed by reaction of the unprotected phenol oxygen with the activated carboxyl moiety. This is evident by the ester carbonyl stretch at 1765 cm^{-1} in the IR spectra of the resin and by the two extra F signals in the ^{19}F NMR spectra. The phenol is easily unmasked by incubating the resin with a slight excess of piperidine. Acidification and excess solvent washes provide the desired TFP resin.

Carboxyl (**2**) and sulfonyl (**3**) activated esters are prepared from the resin (Scheme 1). The quality of the base resin (**1**) and the resulting polymeric activated resins (**2** and **3**) may be quantitatively determined in a nondestructive analysis by ^{19}F NMR spectroscopy.[6] We empirically found that loading diverse acids to generate polymeric activated resins requires optimization of the loading conditions for each class of acid to load. For example, acids containing a basic amine, or phenylacetic acids, are difficult to load to form the activated resin. This is possibly due to the stability of the resulting activated resin. However, it is critical to be able to quantify the resin loading of the activated resin before use in production to ensure synthesis of a pure single-compound library.

This is the first activated resin to take advantage of this simple, quantitative technique to measure the loading of the activated resin. This approach takes advantage of the high sensitivity, natural abundance (100%), and large chemical shift dispersion (∼200 ppm) of the ^{19}F nucleus. The ^{19}F NMR spectrum of TFP resin (**1**) shows two resonances at −148 and −165 ppm, each resonance corresponding to 2 equiv fluorine nuclei. It is simple to quantify the loading from the integration values corresponding to the signals resulting from the free and activated forms of polymeric TFP. The gel-phase ^{19}F NMR spectra are simple to interpret unlike gel-phase ^{1}H NMR spectra. ^{19}F NMR spectroscopy is a sensitive and simple means to monitor both the loading to the resin and its subsequent release from the resin by a N-nucleophile. The ability to quantify the loading of the TFP esters by ^{19}F NMR constitutes a major advantage over other activated resin methodologies with respect to synthesis of pure single-compound libraries.

Polymeric activated TFP sulfonate esters (**3**) have also been examined in detail. These novel polymeric TFP sulfonate esters (**3**) react smoothly with N-nucleophiles to yield sulfonamides. No aromatic substitution was observed in these reactions. These reagents, in general, are more stable and less reactive than the corresponding activated ester (**2**). Both **2** and **3** are stable when dry at room temperature for extended periods of time, with a shelf life of several years. This is a convenient method of storing custom carboxylic and sulfonic acids in an activated form ready for use. In contrast, solutions of acid chlorides and sulfonyl chlorides need to be stored under an inert atmosphere and refrigeration, and they tend to decompose after several months.

This technology facilitates the synthesis of arrays of pure single-compound libraries by providing a very reactive acylating and sulfonylating reagent, with the absolute loading known. Thus for a typical library synthesis, a set of carboxylic acids or sulfonic acids are loaded to the TFP resin. The loading of each resin is then determined using the ^{19}F NMR technique. Usually, several of the acids do not load well and must either be re-submitted to the loading conditions

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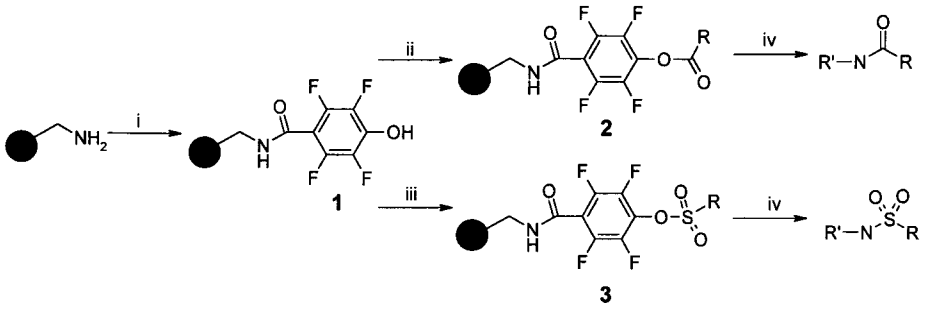
Scheme 1[a]



[a] Key: (i) 2,3,5,6,-tetrafluoro-4-hydroxybenzoic acid (1.7 equiv), DIC (1.5 equiv), DMF, HOBt (1.5 equiv), 25 °C, 16 h; (ii) acid (2 equiv), DIC (2 equiv), DMAP (0.2 equiv), DMF, 25 °C, 3−22 h; (iii) sulfonyl chloride (2.0 equiv), DIEA (3.0 equiv), DMF, 25 °C, 2 h; (iv) amine (0.8 equiv), DMF, 25 °C, 1−12 h.

or discarded from this particular library production. Next, the dry activated resins are distributed to 96-deep-well plates, one TFP activated resin per plate. Next, a limiting amount of an N-nucleophile, either a primary or secondary amine, or an aniline, diluted to a known molar solution in a solvent such as DMF, is added to the TFP activated resin and incubated for a period of time. Typical reactions are completed in about 3 h. Reactions are sometimes allowed to proceed overnight to facilitate the process. Workup of the library simply requires filtration of the excess TFP activated resin from the product that is in solution. HPLC-MS analysis of either a subset of the library or every member confirms the identity and purity of the library samples. This simple, well-defined process cleanly isolates and enables quality control (QC) at each step in the synthetic process. In contrast, solution phase library generation of amides or sulfonamides is more difficult to QC at each step. For example, solutions of either acid chlorides or sulfonyl chlorides tend to decompose over short periods of time, thus it is more difficult to maintain a standard stock solution. In addition, the production process is more complicated for a solution synthesis. For example, a base may be needed in a solution synthesis and possibly excess reagents that must be removed by some method. In general the TFP methodology offers a convenient, simple method to array amides and sulfonamides, which compliments other library production processes.

We purposely sought an activated resin that would react with a wide scope of N-nucleophiles, particularly anilines. Polymeric TFP activated carboxylate esters would be expected to show a similar or increased reactivity toward N-nucleophiles as compared to the well-known reactivity of pentafluorophenol carboxylate esters[7] commonly used for solution amide coupling. This is due to the additional electron withdrawal by the carbonyl in the 4 position of the aromatic ring. Amides and sulfonamides produced using this technique are typically very pure. The amine is used as the limiting reagent and is usually completely consumed after a 1−12 h incubation period, depending on the nucleophilicity of the amine. The activated resins and compounds listed in Table 1 are fully characterized (see Experimental Section). It is interesting to note that all four of the activated carboxylic acid esters loaded only to about 80% completion. We find this to be typical, and it may have to do with the stability/reactivity of the activated ester. In contrast, the sulfonate esters tend to load to 100%. These reagents are also more stable and require a stronger nucleophile for reaction. Compound **4** is cleanly generated by reaction of a limiting amount of the corresponding aniline nucleophile. Compound **5** is cleanly generated by reaction of the corresponding secondary amine with the sterically hindered ortho-substituted benzoic acid activated ester. Compounds **8**, **9**, and **10** are cleanly produced by reaction of the corresponding secondary amine on the respective activated sulfonate ester. Tables 2 and 3 show analytical data for 33 samples generated from a typical library produced in our laboratory. This library was generated from a set of custom 5-alkyl-1*H*-pyrazole-3-carboxylates and 3-amido-4-substituted benzoic acids.[8] These data demonstrate the wide scope of N-nucleophiles that react with the TFP activated esters. Note that a number of different anilines work well to produce pure samples, for example compounds **11b, 11g, 11i,** and **12a**. However, 5-aminoisoquinoline and 1-aminonaphthalene are examples of weak nucleophiles that do not work well in this system, for example, **11j** and **13b**. This methodology is well-suited for lead optimization as well as large library synthesis. An example from our laboratory of using the TFP sulfonate ester technology to optimize factor Xa inhibitors has been recently disclosed.[9]

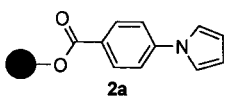
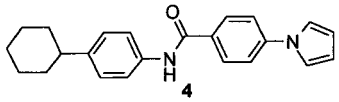
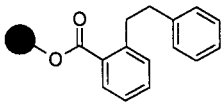
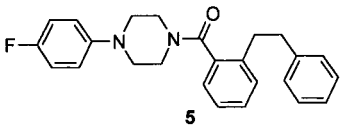
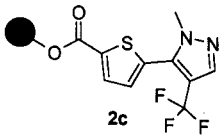
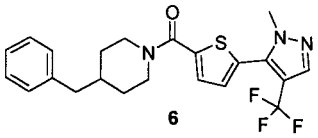
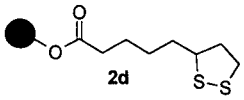
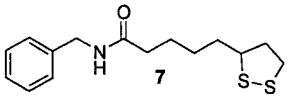
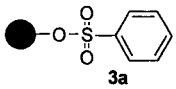
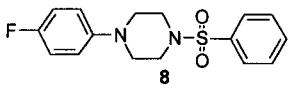
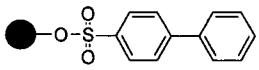
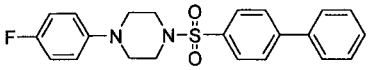
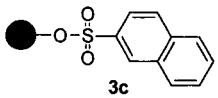
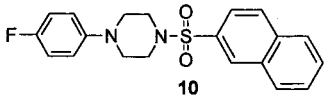
We routinely use this technology to produce single-compound libraries on a 10 K-member scale as part of a lead discovery effort.

In summary, a new polymer-bound tetrafluorophenol resin (**1**) has been synthesized. This is the first example of the use of ^{19}F NMR to quantitate the loading of activated resins. Polymeric TFP sulfonate esters provide a new tool for the clean synthesis of sulfonamides. Polymeric TFP activated esters (**2**) and sulfonate esters (**3**) react with a diverse set of N-nucleophiles to generate arrays of amides and sulfonamides which are useful for lead discovery as well as lead optimization single-compound libraries.

Experimental Section

General Procedures. ^{19}F NMR spectra were obtained on a NMR spectrometer operating at a ^{19}F frequency of 470.2 MHz. The ^{1}H Nanoprobe was tuned to ^{19}F frequency. Typical spectral width was 100 000 Hz, and the chemical shifts were referenced relative to $CFCl_3$ using the transmitter frequency. The spectra were acquired using a Nanoprobe in which the sample was oriented at the magic angle (54.7°) and was spun at a rate of 1000−1500 Hz. The samples were prepared by swelling 1−2 mg of resin with about 40 μL of deuterated

Table 1. Structures of TFP Activated Resins, Products, and Purity Data

TFP Activated Resin	Product	Purity % ELS	Purity % UV 220
 **2a**	 **4**	100	99
 **2b**	 **5**	100	100
 **2c**	 **6**	95	91
 **2d**	 **7**	100	88
 **3a**	 **8**	100	97
 **3b**	 **9**	100	100
 **3c**	 **10**	100	100

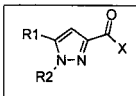
dimethylformamide (DMF). ^{1}H NMR spectra were recorded in 5 mm tubes on a 300 MHz spectrometer in $CDCl_3$ unless otherwise stated. FT-IR were recorded at 4 cm^{-1} resolution on a spectrometer interfaced to an InspectIR attenuated total reflectance microscope with Si sampling optics. Solvents used were EM Science of OmniSolv distilled grade unless specified otherwise. The following abbreviations were used: DCM = dichloromethane, DMF = dimethylformamide, THF = tetrahydrofuran.

Preparation of 4-Hydroxy-2,3,5,6-tetrafluorobenzamidomethyl-copoly(styrene-1%-divinylbenzene)-resin (1). Into a 12 L round-bottom three-necked flask provided with a thermometer and overhead stirrer was placed DMF (6.0 L) and amino-methyl polystyrene resin (600 g, 1.6 mmol/g loading; Polymer Labs). The mixture was gently stirred. Into a 4 L Erlenmeyer flask provided with a magnetic stirrer was placed DMF (1.43 L) and 2,3,5,6,-tetrafluoro-4-hydroxybenzoic acid hydrate (342 g, 1.63 mol). An exotherm was observed to 27 °C. Into a 1 L Erlenmeyer flask provided with a magnetic stirrer was placed DMF (364 mL) and 1-hydroxybenzotriazole hydrate (194 g, 1.44 mol). An endotherm was observed to 15 °C. To the resin slurry was added the acid solution, followed by the 1-hydroxybenzotriazole hydrate solution, followed by 1,3-diisopropylcarbodiimide (225 mL, 1.44 mol). The reaction mixture was allowed to stir at room temperature for 16 h. A small sample of the resin is removed, filtered, and washed well with DMF, THF, and DCM. FT-IR 1765, 1656 cm^{-1}. The reaction mixture was filtered on a 24 cm Buchner funnel and washed with DMF (12 L). [The 1765 cm^{-1} infrared absorption reveals that some TFP-tetrafluorobenzoic acid ester is formed in the reaction. This undesired esterification can also be observed by ^{19}F NMR.]

Removal of TFP-Tetrafluorobenzoic Acid Ester. Into a 12 L round-bottom three-necked flask provided with a thermometer and overhead stirrer was placed DMF (6.0 L) and piperidine (104 mL, 1.05 mol). Into the flask was placed the resin. The mixture is stirred for 1.5 h. A small sample of the resin is removed, filtered, and washed well with DMF. FT-IR 1656 cm^{-1}. The reaction mixture was filtered on a 24 cm Buchner funnel and washed with DMF (6 L). [The above process leads to the formation of the piperidine salt of the tetrafluorohydroxybenzoic amino-methyl resin.]

Removal of the Piperidine Salt. Into a 12 L round-bottom flask provided with an overhead stirrer was placed DMF (8.0 L). Into the flask was placed, slowly, in portions HCl (2 M, 900 mL). A temperature increase occurs. The mixture was allowed to cool to room temperature. Into the flask was placed the resin, and the mixture stirred for 1.5 h. The reaction mixture was filtered on two 24 cm Buchner funnels and washed with DMF (4.0 L), THF (6.0 L), and DCM (4.0 L). The resin was dried in vacuo at 45 °C to give an off-

Table 2. 5-Alkyl-1*H*-pyrazole-3-carboxamides Products[a]

	R1	R2	X	Purity % ELS
11a	$CH_2CH(CH_3)_2$	2, 4-difluorophenyl	A1	100
11b	$CH_2CH(CH_3)_2$	2, 4-difluorophenyl	A2	100
11c	$CH_2CH(CH_3)_2$	2, 4-difluorophenyl	A3	99
11d	$CH_2CH(CH_3)_2$	4-methoxyphenyl	A4	100
11e	$CH_2CH(CH_3)_2$	4-methoxyphenyl	A5	99
11f	$CH_2CH(CH_3)_2$	3-nitrophenyl	A6	100
11g	$CH_2CH(CH_3)_2$	3, 4-dimethylphenyl	A7	100
11h	$CH_2CH(CH_3)_2$	4-bromophenyl	A8	99
11i	$CH_2CH(CH_3)_2$	4-nitrophenyl	A9	83
11j	$CH_2CH(CH_3)_2$	4-(tert-butyl)phenyl	A10	15
12a	CH_3	2-chlorophenyl	A11	99
12b	CH_3	phenyl	A12	99
12c	CH_3	2-chlorophenyl	A13	99
12d	CH_3	4-(tert-butyl)phenyl	A14	99

[a] For X, see Table 4.

white solid (855 g). FT-IR 1650 cm^{-1}. ^{19}F NMR (500 MHz, DMF) δ −148 and −165 ppm. Loading of resin was determined by elemental analysis by F ion selective chromatography. Found: %F = 8.87 corresponding to 1.17 mmol/g.

Polymeric TFP 4-(1*H*-pyrrol-1-yl)benzoate Ester (2a). Polymeric tetrafluorophenol esters (**2**) were prepared by adding TFP resin (200 mg, 0.202 mmol, 1.01 mmol/g) to a 25 mL polypropylene reaction vessel at room temperature. The resin was swelled with DMF (4 mL) for 10 min with mild agitation. 4-(1*H*-Pyrrol-1-yl) benzoic acid (76 mg, 0.404 mmol) was added to the resin mixture and agitated gently until all of the acid dissolved. DMAP (5 mg, 0.0404 mmol) was added to the reaction. The reaction was agitated for 5 min, then DIC (63 μL, 0.404 mmol) was added to the mixture. The polypropylene reaction vessel was capped and agitated for 16 h. The resin was washed with DMF (3 × 12 mL), THF (3 × 12 mL), and DCM (3 × 12 mL) and dried in vacuo. FT-IR 1758 cm^{-1}. ^{19}F NMR (500 MHz, DMF) δ −144, −155. Percent loading 84%.

Polymeric TFP 2-Bibenzylcarboxylate Ester (2b). Prepared according to the procedure to prepare **2a**. FT-IR 1761 cm^{-1}. ^{19}F NMR (500 MHz, DMF) δ −143, −154. Percent loading 73%.

Polymeric TFP 2-[1-Methyl-3-(trifluoromethyl) pyrazol-5-yl]thiophene-5-carboxylate Ester (2c). Prepared according to the procedure to prepare **2a**. FT-IR 1750 cm^{-1}. ^{19}F NMR (500 MHz, DMF) δ −144, −154. Percent loading 70%.

Polymeric TFP 5-[1,2]Dithiolan-3-yl-pentanoic Ester (2d). Prepared according to the procedure to prepare **2a**. FT-IR 1789 cm^{-1}. ^{19}F NMR (500 MHz, DMF) δ −144, −154. Percent loading 78%.

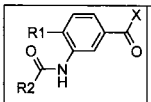
Polymeric TFP Benzenesulfonate Ester (3a). TFP resin (2.0 g, 2.2 mmol, 1.1 mmol/g) was added to a 100 mL polypropylene reaction vessel. The resin was swelled with DCM (20 mL) for 10 min with mild agitation. DIEA (1.15 mL, 6.6 mmol) was added to the reaction. Benzenesulfonyl chloride (0.832 mL, 6.6 mmol) was added to the resin mixture and agitated vigorously until all of the sulfonyl chloride dissolved. The polypropylene reaction vessel was capped and gently agitated for 16 h at room temperature. The resin was washed with DMF (3 × 30 mL), THF (3 × 30 mL), and DCM (3 × 30 mL) and dried in vacuo. ^{19}F NMR (500 MHz, DMF) δ −144, −154. Percent loading 100%.

Polymeric TFP 4-Biphenylsulfonate Ester (3b). Prepared according to the procedure for **3a**. ^{19}F NMR (500 MHz, DMF) δ −144, −154. Percent loading 100%.

Polymeric TFP 2-Naphthalenesulfonate Ester (3c). Prepared according to the procedure for **3a**. ^{19}F NMR (500 MHz, DMF) δ −144, −154. Percent loading 100%.

***N*-(4-Cyclohexylphenyl)-4-pyrrol-1-yl-benzamide (4).** The amide was prepared by adding TFP 4-(1*H*-pyyrol-1-yl) benzoate ester (100 mg, 0.0808 mmol) (**2a**) to a 3 mL polypropylene reaction vessel. The resin was swelled with DMF (1 mL) for 10 min with gentle agitation. 4-Cyclohexylaniline (11.3 mg, 0.0646 mmol) was added, and the mixture

Table 3. 3-Amido-4-substituted Benzoic Carboxamide Products[a]

	R1	R2	X	Purity % ELS
13a	O-C_6H_4-C_6H_5	4-nitrophenyl	A15	98
13b	O-C_6H_4-C_6H_5	4-nitrophenyl	A16	9
13c	O-C_6H_4-C_6H_5	4-CF_3-phenyl	A17	98
13d	O-C_6H_4-C_6H_5	CH_2OPh	A18	100
13e	O-C_6H_4-C_6H_5	3, 4-dichlorophenyl	A19	99
13f	O-C_6H_4-C_6H_5	3, 4-dichlorophenyl	A20	97
14a	O-C_6H_5	4-nitrophenyl	A21	96
14b	O-C_6H_5	CH_2OPh	A22	91
14c	O-C_6H_5	3, 4-dichlorophenyl	A6	97
14d	O-C_6H_5	2-thienyl	A23	99
14e	O-C_6H_5	4-CF_3-phenyl	A24	98
14f	O-C_6H_5	4-CF_3-phenyl	A25	97
15a	S-cyclohexyl	4-CF_3-phenyl	A26	98
15b	S-cyclohexyl	4-CF_3-phenyl	A27	94
16a	S-$CH_2CH_2CH_2CH_3$	4-CF_3-phenyl	A28	98
16b	S-$CH_2CH_2CH_2CH_3$	4-CF_3-phenyl	A29	98
16c	S-$CH_2CH_2CH_2CH_3$	biphenyl	A30	97
16d	S-$CH_2CH_2CH_2CH_3$	biphenyl	A3	93
16e	S-$CH_2CH_2CH_2CH_3$	CH_2OPh	A2	93

[a] For X, see Table 4.

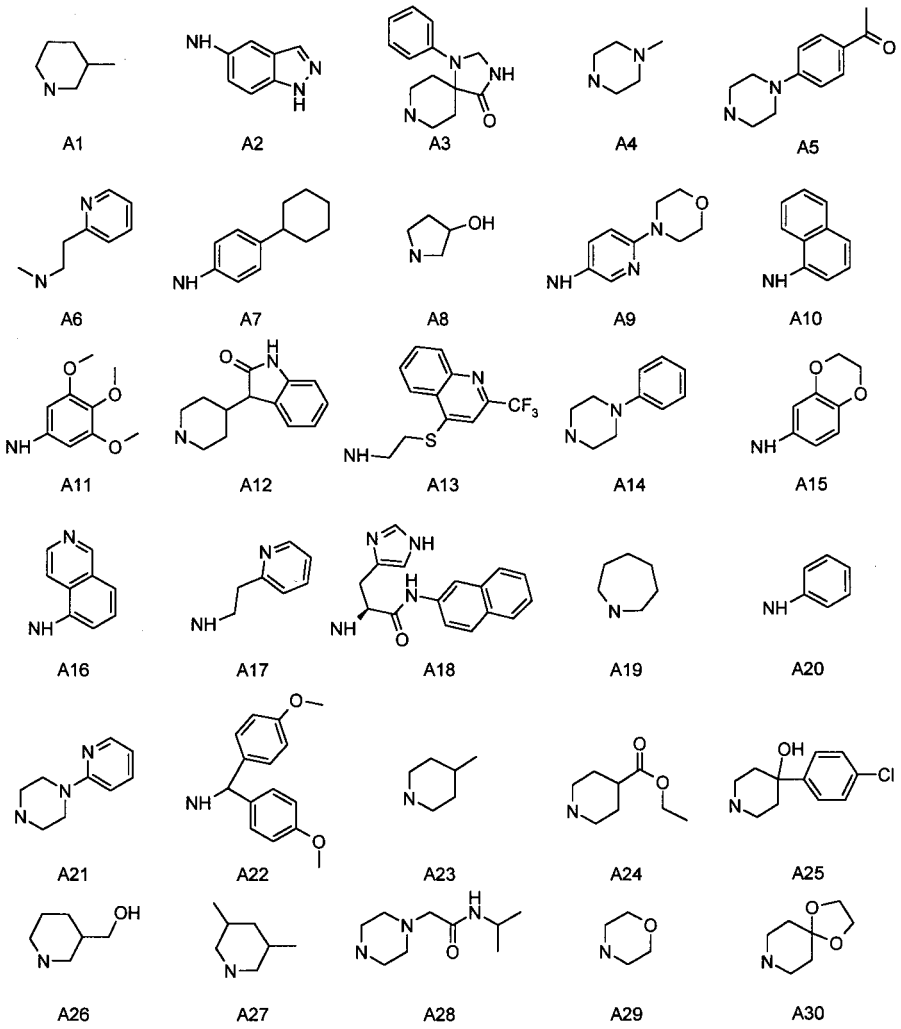
was capped. The reaction was agitated for 16 h. The mixture was filtered and washed with DCM (2 mL × 3). The washes were collected and evaporated in vacuo. The product **5** was obtained as a solid (18.6 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, 2H), 7.55 (d, 2H), 7.50 (d, 2H), 7.23 (d, 2H), 7.16 (t, 2H), 6.40 (t, 2H), 2.51−2.50 (m, 1H), 1.89−1.83 (m, 4H), 1.28−1.24 (m, 2H). EI-MS *m*/*z* 345 $[M + H]^+$. LC_{area} (UV_{220}) = 99%. Anal. calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 79.78; H, 7.16; N, 8.03.

[4-(4-Fluorophenyl)piperazin-1-yl]-(2-phenethylphenyl-)methanone (5). This material was prepared from TFP 2-bibenzylcarboxylate ester (**2b**) using a procedure similar to that for compound **4**. The product **5** was obtained as a solid (20.1 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.17 (m, 9H), 6.99−6.95 (m, 2H), 6.87−6.85 (m, 2H), 4.04 (m, 1H), 3.90 (m, 1H), 3.38 (m, 1H), 3.30 (m, 1H), 3.16 (m, 2H), 3.0−2.9 (m, 6H). ^{19}F NMR (500 MHz, $CDCl_3$) δ −125.49 (m, 1F). EI-MS *m*/*z* 389 $[M + H]^+$. LC_{area} (UV_{220}) = 100%. Anal. calcd for $C_{25}H_{25}FN_2O$: C, 77.29; H, 6.49; N, 7.21. Found: C, 76.27; H, 6.62; N, 6.97.

(4-Benzylpiperidin-1-yl)-[5-(2-methyl-5-trifluoromethyl-2*H*-pyrazol-3-yl)thiophen-2-yl]methanone (6). This material was prepared from TFP 2-[1-methyl-3-(trifluoromethyl) pyrazol-5-yl]thiophene-5-carboxylate ester (**2c**) using a procedure similar to that for compound **4**. The product **6** was obtained as a solid (26.4 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2H), 7.22 (dd, 2H), 7.20 (m, 1H), 7.15 (d, 2H), 6.81 (s, 1H), 4.45 (m, 2H), 4.00 (s, 3H), 2.90 (m, 2H), 2.58 (d, 2H), 1.83 (m, 1H), 1.74 (d, 2H), 1.29 (dq, 2H). ^{19}F NMR (500 MHz, $CDCl_3$) δ −63.06 (s, 3F). EI-MS *m*/*z* 434 $[M + H]^+$. LC_{area} (UV_{220}) = 91%. Anal. calcd for $C_{22}H_{22}F_3N_3OS$: C, 60.96; H, 5.12; N, 9.69. Found: C, 60.91; H, 5.27; N, 9.36.

5-[1,2]Dithiolan-3-yl-pentanoic Acid Benzylamide (7). This material was prepared from TFP 5-[1,2]dithiolan-3-yl-pentanoate ester (**2d**) using a procedure similar to that for compound **4**. The compound **7** was obtained as a yellow solid (19.1 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.28 (m, 2H), 5.67 (br, 1H), 4.45 (d, 2H), 3.57 (m, 1H), 3.15 (m, 2H), 2.45 (m, 1H), 2.23 (t, 2H), 1.90 (m, 1H),

Table 4. Amines (X) Used in Tables 2 and 3



1.70 (m, 4H), 1.50 (m, 2H). EI-MS *m/z* 296 $[M + H]^+$. LC_{area} (UV_{220}) = 88%. Anal. calcd for $C_{15}H_{21}F_3NOS_2$: C, 60.98; H, 7.16; N, 4.74. Found: C, 60.86; H, 7.28; N, 4.45.

1-Benzenesulfonyl-4-(4-fluorophenyl)-piperazine (8). TFP benzenesulfonate ester (500 mg, 0.55 mmol) (**3a**) was added to a 10 mL polypropylene reaction vessel. The resin was swelled in DMF (5 mL) for 10 min. 1-(4-Fluorophenyl)-piperazine (79 mg, 0.44 mmol) was added and the mixture capped. The reaction was agitated for 16 h. The mixture was filtered then washed with DCM (×3), and the filtrates were combined and evaporated. The product **8** was obtained as a solid (135 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.60 (m, 3H), 6.95 (m, 2H), 6.81 (m, 2H), 3.16 (m, 8H). EI-MS *m/z* 320 $[M + H]^+$. LC_{area} (UV_{220}) = 97%. Anal. calcd for $C_{16}H_{17}F\ N_2O_2S$: C, 59.98; H, 5.35; N, 8.74. Found: C, 59.04; H, 5.35; N, 8.39.

1-(Biphenyl-4-sulfonyl)-4-(4-fluoro-phenyl)piperazine (9). This material was prepared from TFP 1-biphenyl-4-sulfonate ester (**3b**) using a procedure similar to that for compound **8**. The product **9** was obtained as a solid (168 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, 2H), 7.75 (dd, 2H), 7.60 (d, 2H), 7.49 (m, 2H), 7.42 (m, 1H), 6.94 (m, 2H), 6.83 (m, 2H), 3.20 (m, 8H); EI-MS *m/z* 396 $[M + H]^+$. LC_{area} (UV_{220}) = 100%. Anal. calcd for $C_{22}H_{21}FN_2O_2S$: C, 66.65; H, 5.34; N, 7.07. Found: C, 66.29; H, 5.51; N, 6.88.

1-(4-Fluorophenyl)-4-(naphthalene-2-sulfonyl)-piperazine (10). This material was prepared from polymeric TFP naphthalene-2-sulfonate ester (**3c**) using a procedure similar to that for compound **8**. The product **10** was obtained as a solid (158 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.99 (d, 2H), 7.93 (d, 1H), 7,78 (dd, 1H), 7.65 (m, 2H), 6.92 (m, 2H), 6.80 (m, 2H), 3.24 (m, 4H), 3.15 (m, 4H). EI-MS *m/z* 370 $[M + H]^+$. LC_{area} (UV_{220}) = 100%. Anal. calcd for $C_{20}H_{19}FN_2O_2S$: C, 64.85; H, 5.17; N, 7.56. Found: C, 64.76; H, 5.15; N, 7.31.

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Supporting Information Available. HPLC traces of crude samples and ^{1}H, ^{19}F NMR, and FT-IR spectra are available for compounds **1**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem Soc*. **1977**, *99*, 4165.

(2) Cohen, B. J.; Karoly-Hafeli, H.; Patchornik, A. *J. Org Chem*. **1984**, *49*, 922.
(3) Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, *35*, 867.
(4) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc*. **1994**, *116*, 11171.
(5) Pop, I. E.; Deprez, B. P.; Tartar, A. L. *J. Org. Chem*. **1997**, *62*, 2594.
(6) (a) Drew, M.; Orton, E.; Krolikowski, P.; Salvino, J. M.; Kumar, N. V. *J. Comb. Chem.* **2000**, *2*, 8. (b) Shapiro, M. J.; Kumaravel, G.; Petter, R. C.; Beveridge, R. *Tetrahedron Lett.* **1996**, *37*, 4671. (c) Svensson, A.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1996**, *37*, 7649. (d) Svensson, A.; Bergquist, K.-E.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1998**, *39*, 7193.
(7) KisFaludy, L.; Schon, I.; Nyeki, O.; Low, M. *Tetrahedron Lett.* **1974**, *39*, 1785.
(8) Alkyl-1*H*-pyrazole-3-carboxylates were synthesized using a route described in the following: Ashton, W. T.; Doss, G. A. J. *Heterocycl. Chem.* **1993**, *30*, 307 and Seiki, K.; Isegawa, J.; Fukuda, M.; Ohki, M. *Chem. Pharm. Bull.* **1984**, *32* (4), 1568. 3-Amido-4-substituted benzoic acids were synthesized using modified procedures based on the route reported in Lee, J.; Murray, V.; Rivero, R. *J. Org. Chem.* **1997**, *62*, 3874 and Yan, B.; Kumaravel, G.; Anjara, H.; Wu, A.; Petter, R. C.; Jewell, C. F.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736.
(9) Gong, Y.; Becker, M.; Choi-Sledeski, Y. M.; Davis, R. S.; Salvino, J. M.; Chu, V.; Brown, K. D.; Pauls, H. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1033.

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