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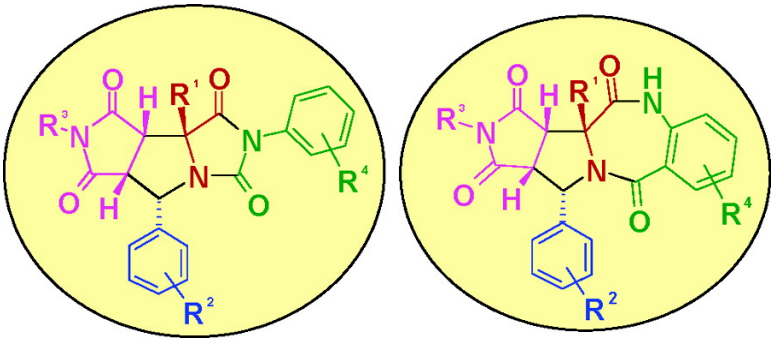

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Fluorous Mixture Synthesis of Two Libraries with Hydantoin-, and Benzodiazepinedione-Fused Heterocyclic Scaffolds

Wei Zhang,*,† Yimin Lu,† Christine Hiu-Tung Chen,† Lu Zeng,‡ and Daniel B. Kassel‡

Fluorous Technologies, Inc., University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, Pennsylvania 15238, Takeda San Diego, Analytical and Discovery Technologies, 10410 Science Center Drive, San Diego, California 92121

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Diversity-oriented synthesis (DOS) and fluorous mixture synthesis (FMS) are two aspects of combinatorial chemistry. DOS generates library scaffolds with skeletal, substitution, and stereochemistry variations, whereas FMS is a highly efficient tool for library production. The combination of these two aspects in solution-phase synthesis of two novel heterocyclic compound libraries is presented in this paper. Mixtures of different fluorous amino acids undergo [3 + 2] cycloadditions followed by postcondensation reactions. The mixtures are then demixed by fluorous HPLC. Fluorous tags are removed by cyclization to afford hydantoin- and benzodiazepinedione-fused heterocyclic compounds as individual, pure, and structurally defined molecules. The application of MS-directed HPLC purification and parallel four-channel LC/MS analysis further increases the efficiency of FMS.

Introduction

Fluorous synthesis is a highly efficient solution-phase synthetic technology.[1] It employs perfluoroalkyl (Rf) groups as "phase tags" to facilitate reaction mixture separations.[2,3] This "beadless" combinatorial technology has been applied to parallel and mixture synthesis of small molecules,[1c−d] peptides,[4] oligosaccharides,[5] and other biomolecules.[6] In fluorous mixture synthesis (FMS),[7] a mixture of substrates paired with distinct homologous fluorous tags is taken through a sequence of reactions to produce mixtures of tagged products (Scheme 1). The mixtures are then demixed by tag-controlled fluorous HPLC,[3] followed by tag cleavage to give a collection of individual, pure, and structurally defined products. The efficiency of FMS has been demonstrated in the synthesis of enantiomers, diastereomers, and analogues of natural products.[8]

Diversity-oriented synthesis (DOS) is an important aspect of combinatorial chemistry.[9] Multicomponent reactions and cycloaddition reactions are commonly used in DOS to construct complex library scaffolds with skeletal, substitution, and stereochemistry variations. We report here a new approach that combines DOS and FMS technologies in the synthesis of novel heterocyclic compound libraries.[10] The reaction sequence involves the formation of pyrrolidine (proline) ring **1** by 1,3-dipolar cycloaddition[11,12] of azomethine ylides, followed by postcondensation reactions to form tri- and tetracyclic compounds **2** and **3** (Scheme 2). These two heterocyclic skeletons have up to four points of substitution diversity, and each has four stereocenters around the central proline ring. Scaffold **2** is structurally related to tricyclic thrombin inhibitors,[13] whereas scaffold **3** contains a privileged benzodiazepine moiety that has a wide range of pharmaceutical utilities.[14]

Results and Discussion

At the method development stage, a three-component reaction involving a fluorous amino acid,[15] a benzaldehyde, and a maleimide was conducted under standard solution-phase conditions using Et_3N as a base and DMF as a solvent.[16] The proline derivative **1** was found to be a single diastereomer;[12c,17] two ring-fused hydrogen atoms are cis to the R^1 and trans to the PhR^2. The stereochemistry was confirmed by X-ray analysis of compound **1a** (R^1 = Me, R^2 = *p*-MeO, R^3 = Et) (Figure 1).

Synthesis of Hydantoin-Fused Tricyclic Compound Library 2{*R*^{1},*R*^{2},*R*^{3},*R*^{4}}. A hydantoin-fused tricyclic compound library containing 420 analogues was synthesized by a five-component FMS (Scheme 3). Five α-amino acids bearing different R^1 groups were paired with five perfluoroalkyl alcohols in such: C_2F_5/*i*-Bu, C_4F_9/Bn, C_6F_{13}/*p*-ClBn, C_8F_{17}/Me, and C_9F_{19}/Et. An equal molar mixture of five fluorous amino acids M-**4**{*1*−*5*} was split to seven portions for 1,3-dipolar cycloaddition reactions with one of the seven benzaldehydes **5**{*1*−*7*} and one of the four maleimides **6**{*1*−*4*}. A slight excess amount of aldehyde (1.2 equiv) and maleimide (1.5 equiv) were used to consume the fluorous amino acids. The resulting seven mixtures of M-**7** were each split to 12 portions and reacted with one of the 12 phenylisocyanates **8**{*1*−*12*} to form 84 mixtures of M-**9**. The efficiency of FMS was demonstrated in two steps of mixture synthesis (M-**4** → M-**7** → M-**9**). Four hundred twenty ureas M-**9** (84 × 5) were prepared by 91 reactions (7 cycloaddition + 84 isocyanate reactions). Conducting

* To whom correspondence should be addressed. E-mail: w.zhang@fluorous.com.
† Fluorous Technologies, Inc.
‡ Takeda San Diego.

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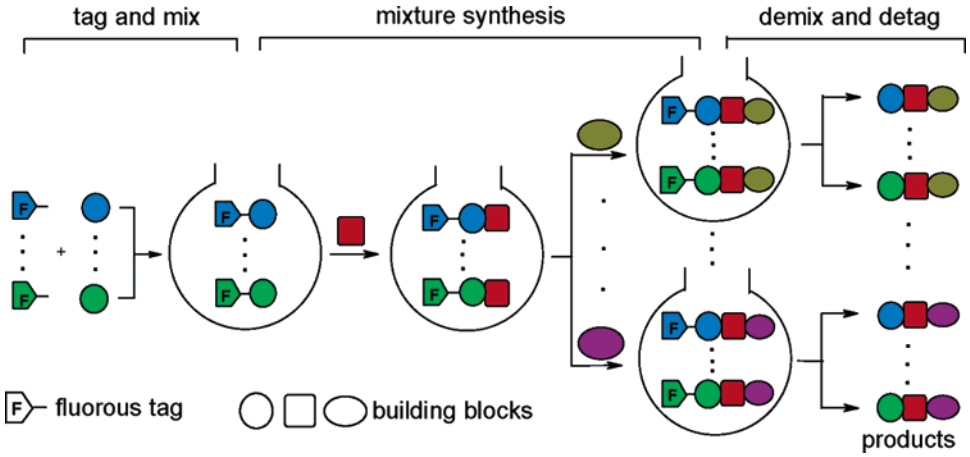
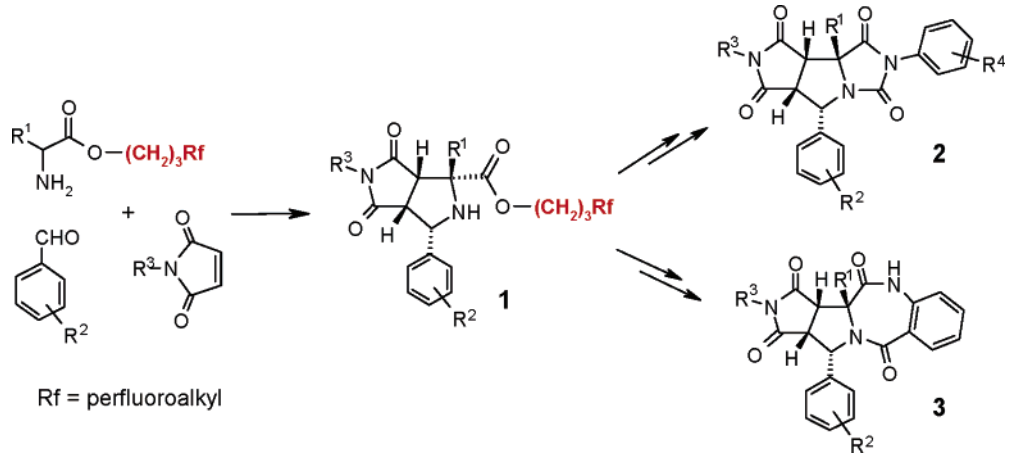
Scheme 1. Schematic Overview of FMS



Scheme 2. DOS of Hydantoin- and Benzodiazepine-Fused Heterocyclic Scaffolds **2** and **3**



similar transformations by individual parallel synthesis would require 455 reactions (35 cycloadditions + 420 isocyanate reactions).

Conventional analytical methods, such as TLC, LC/MS, NMR, and purification methods such as chromatography and crystallization, can be applied to FMS. These tasks are difficult to accomplish in solid-phase synthesis with immobilized resin supports. In the synthesis of M-**7**, the excess amounts of aldehyde, maleimide, and other byproducts were removed by flash column chromatography with normal silica gel. Five components in the M-**7** mixture have homologous Rf tags, but they share the same parent molecule and, thus, possess similar polarities. The M-**7** mixture was collected as a single fraction without demixing the five components.[18] Mixtures of reaction intermediates M-**7** and M-**9** were analyzed by HPLC with a Fluoro*Flash* column.[19] Partition of fluorous molecules between a perfluoroctyl stationary phase ($-Si(Me)_2CH_2CH_2C_8F_{17}$) and a gradient MeOH$-H_2O$ mobile phase separated the mixture in an order of increasing fluorine content of the Rf group (Figure 2). The fluorous analytical method was readily scaled up for semipreparative and even preparative HPLC demixing of M-**9** samples. In

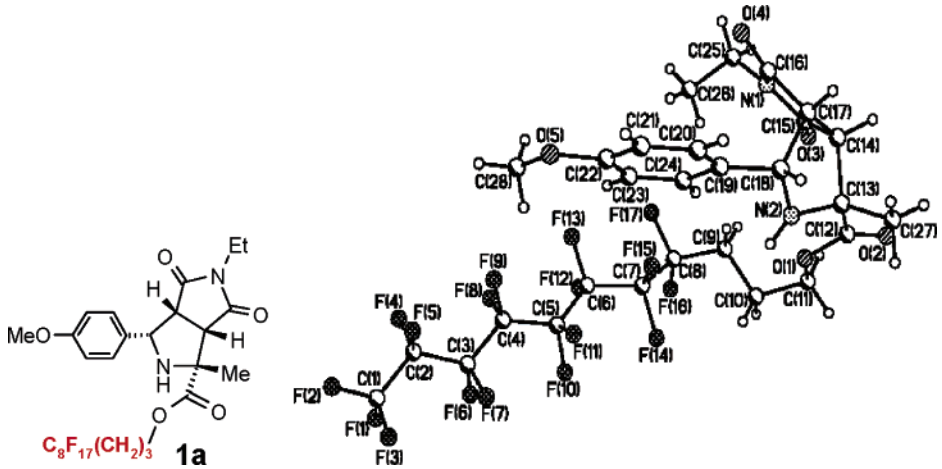
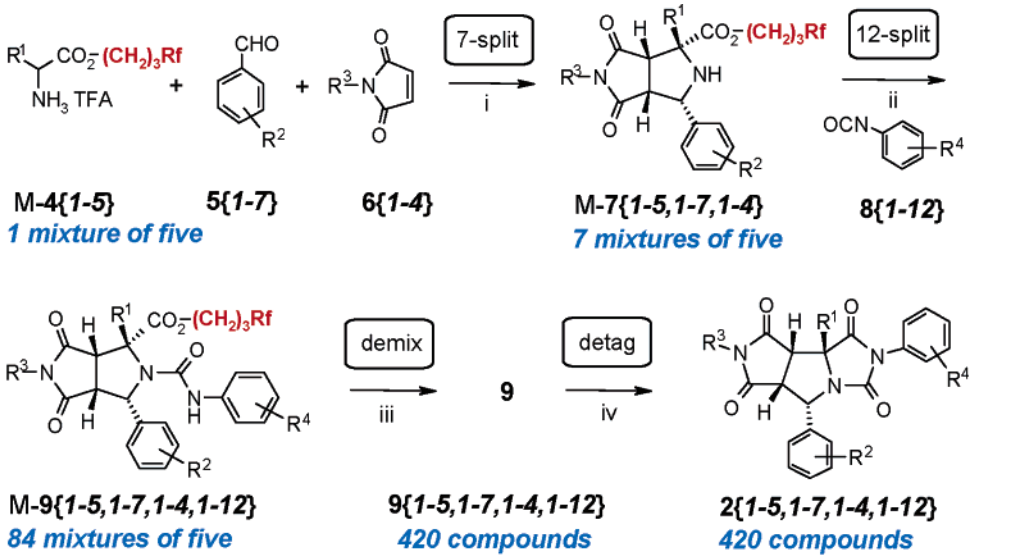


Figure 1. X-ray structure of proline derivative **1a**.

Scheme 3. FMS of a 420-Member Hydantoin-Fused Tricyclic Compound Library **2**



Rf/R¹{1-5}	R²{1-7}	R³ {1-4}	R⁴ {1-12}
{1} C_2F_5/*i*-Bu	{1} H	{1} Et	{1} H
{2} C_4F_9/Bn	{2} *p*-Me	{2} *t*-Bu	{2} *p*-Me
{3} C_6F_{13}/*p*-ClBn	{3} *p*-Br	{3} *c*-C_6H_{11}	{3} *p*-Br
{4} C_8F_{17}/ Me	{4} *p*-OMe	{4} Bn	{4} *p*-OMe
{5} C_9F_{19}/Et	{5} *p*-F		{5} *p*-F
	{6} *p*-Cl		{6} *p*-Cl
	{7} *m*-Me		{7} *p*-CF3
			{8} 3,4-diCl
			{9} *m*-Me
			{10} *m*-Br
			{11} *m*-F
			{12} *m*-Cl

i) M-**4** (1 equiv), **5** (1.2 equiv), **6** (1.5 equiv), Et_3N (3 equiv), DMF, 130 °C, 2 h, flash chromatography, 70-85%. ii) **8** (5.0 equiv), DMAP (0.5 equiv), toluene, 130 °C, 2 h. iii) Fluoro*Flash* semipreparative (20 x 250 mm, 5 μm) or preparative (50 x 300 mm, 10 μm) HPLC demixing, 45-60%. iv) K_2CO_3, DMF, 100 °C, 5 min; C_{18} HPLC.

the preparative HPLC demixing, up to 1 g of a crude sample was loaded onto a 50 × 300-mm Fluoro*Flash* column. Each mixture was separated to five pure compounds in less than 30 min (Figure 3). Only 84 HPLC separations were performed to demix and, at the same time, to purify 420 ureas **9**. The purification efficiency of FMS is obvious.

The formation of the hydantoin ring and removal of the fluorous tag was accomplished by a single-step cyclative cleavage reaction[14] promoted by K_2CO_3 at 110 °C in DMF. The final products were purified by C_{18} reversed-phase HPLC. A total of 380 out of 420 final products were obtained in >90% purities. The amounts of the final products were in the range of 5−30 mg.

MS-Directed HPLC Purification and Parallel Four-Channel LC/MS Analysis. Analysis with a 4.6 × 50 mm column and separation with a semipreparative 2.0 × 30-mm column at higher flow rate have been developed for high-speed HPLC.[20] MS-triggered HPLC makes the purification process more efficient.[21] The incorporation of multiple column HPLC coupled with multiple channel UV or MS interface (MUX) further increases the speed 4−8 times faster.[22] All of these techniques can be applied to fluorous HPLC for sample analysis and demixing of fluorous components in FMS. We developed a 5-min analysis method for M-**9** samples; five components in the mixture were separated with baseline resolutions. This method has been successfully extended to four-channel LC/MS/MUX for parallel analysis (Figure 4). We also explored high-speed and mass-triggered HPLC for demixing of M-**9** samples. The run time was only 8 min, much faster than the 30-min run time shown in Figure 3. A representative chromatogram for the separation of M-**9**{*1−5,4,2,12*} is shown in Figure 5. The purities of each component after demixing are >95% (Figure 6). It clearly demonstrates that four mixture samples of M-**9** could be separated in parallel to give 20 demixed products, which dramatically improves the efficiency of FMS.

Synthesis of Benzodiazepine-Fused Tetracyclic Compound Library 3{*R*¹,*R*²,*R*³}. The synthesis of benzodiazepine-fused tricyclic prolines **3** was also accomplished by FMS. At the stage of method development, we found that N-acylation of M-**10** mixtures with 2-nitrobenzoyl chloride was sensitive to the R^1 substitution; only small R^1 groups (H and Me) gave clean acylation products. Thus, a mixture of two fluorous amino acids (R^1 = H and Me) attached to C_6F_{13} and C_8F_{17} was reacted with 10 aldehydes and three maleimides to give 30 mixtures of M-**10** (Scheme 4). The crude products were purified by fluorous solid-phase extraction (F-SPE) over Fluoro*Flash* cartridges.[19] The N-acylation followed by nitro group reduction with zinc dust in acetic acid under sonication gave 30 mixtures of M-**12**. The preparative HPLC demixing of M-**12** gave 60 individual compounds. These compounds then underwent cyclative tag cleavage with 1,8-diazabicyclo[4.3.0]non-5-ene (DBU) to

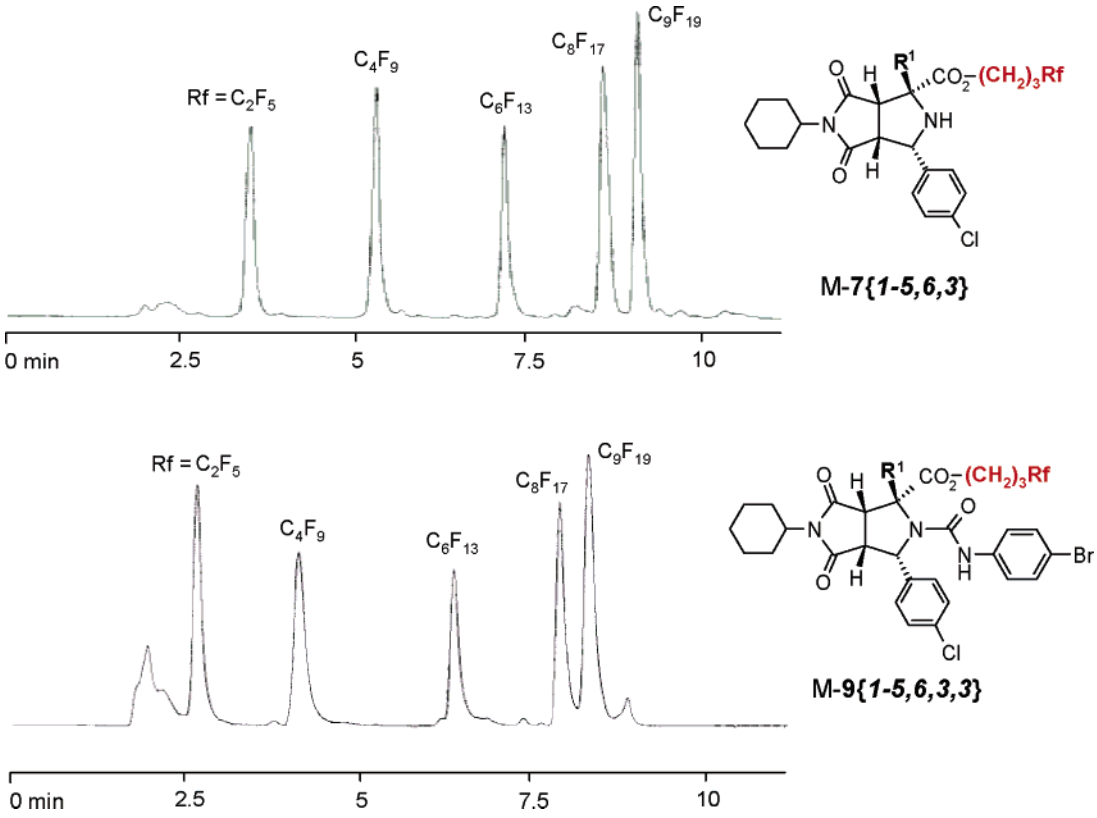


Figure 2. HPLC analysis of representative reaction mixtures M-**7**{*1*−*5,6,3*} and M-**9**{*1*−*5,6,3,3*}. Fluoro*Flash* column (4.6 × 150 mm, 5 μm), gradient 80:20 MeOH−H_2O to 100% MeOH in 5 min, then 100% MeOH for 5 min; flow rate 1 mL/min.

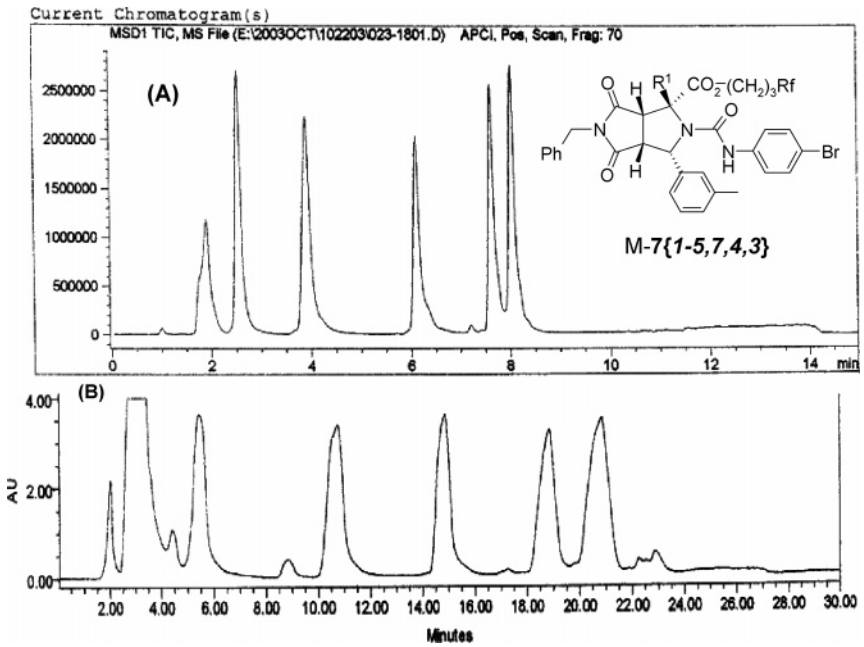


Figure 3. HPLC analysis (top) and demixing (bottom) of M-**7**{*1*−*5,7,4,3*}. (A) Fluoro*Flash* column (4.6 × 150 mm, 5 μm), gradient 80:20 MeOH−H_2O to 100% MeOH in 5 min, then 100% MeOH for 5 min; flow rate 1 mL/min; (B) Fluoro*Flash* column (20 × 250 mm, 5 μm), gradient 80:20 MeOH−H_2O to 100% MeOH in 23 min, then THF for 4 min; flow rate 20 mL/min.

form the corresponding benzodiazepine-fused tetracyclic compounds **3**. Fifty-two out of 60 final products were obtained after C_{18} reversed-phase HPLC purification with >90% purities.

Conclusions

We have developed a fluorous protocol for synthesis of two discovery libraries with novel heterocyclic scaffolds. Amino acids attached to different fluorous tags are used as starting materials for FMS. The stereochemistry of the proline derivatives is accomplished by [3 + 2] cycloadditions. Two sets of postcondensation reactions lead to formation of hydantoin-fused tricyclic and benzodiazepine-fused tetracyclic ring systems. The scaffold *diversity* and *complexity* generated from DOS are integrated with the reaction and separation *efficiency* resulted from FMS. The application of

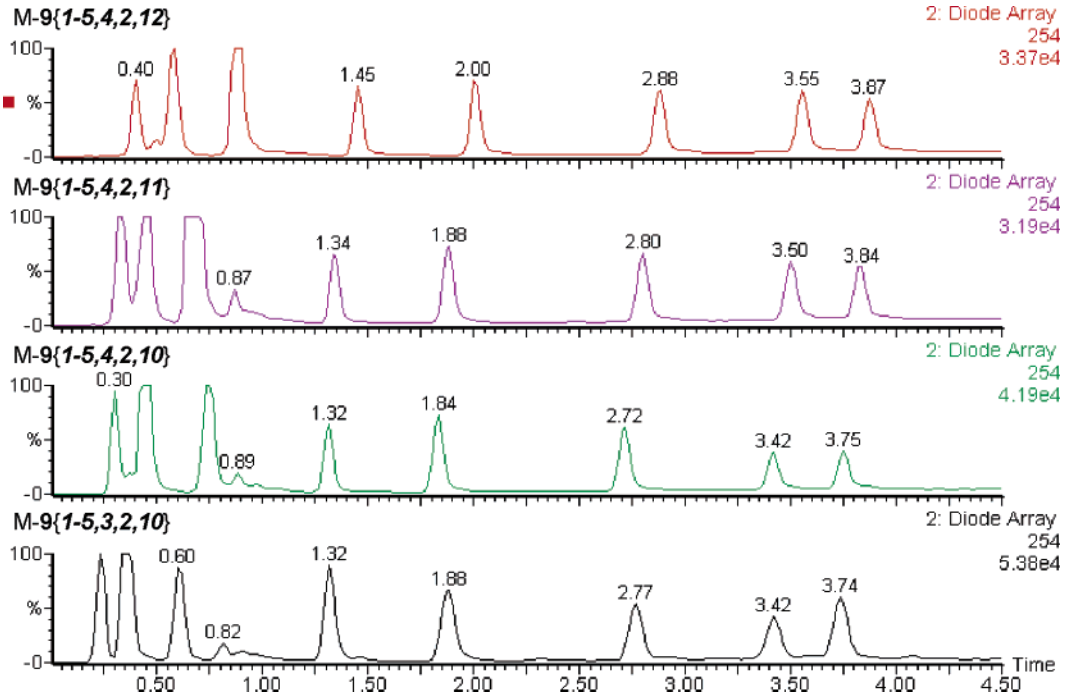


Figure 4. Analysis of four M-**9** mixtures by four-channel LC/MS with four Fluoro*Flash* columns (4.6 × 50 mm, 5 μm), gradient 70:30 MeCN−H_2O−TFA to 5:95 in 3 min, then 95% MeCN−TFA for 1 min; total flow rate 12 mL/min, 3 mL/min per channel.

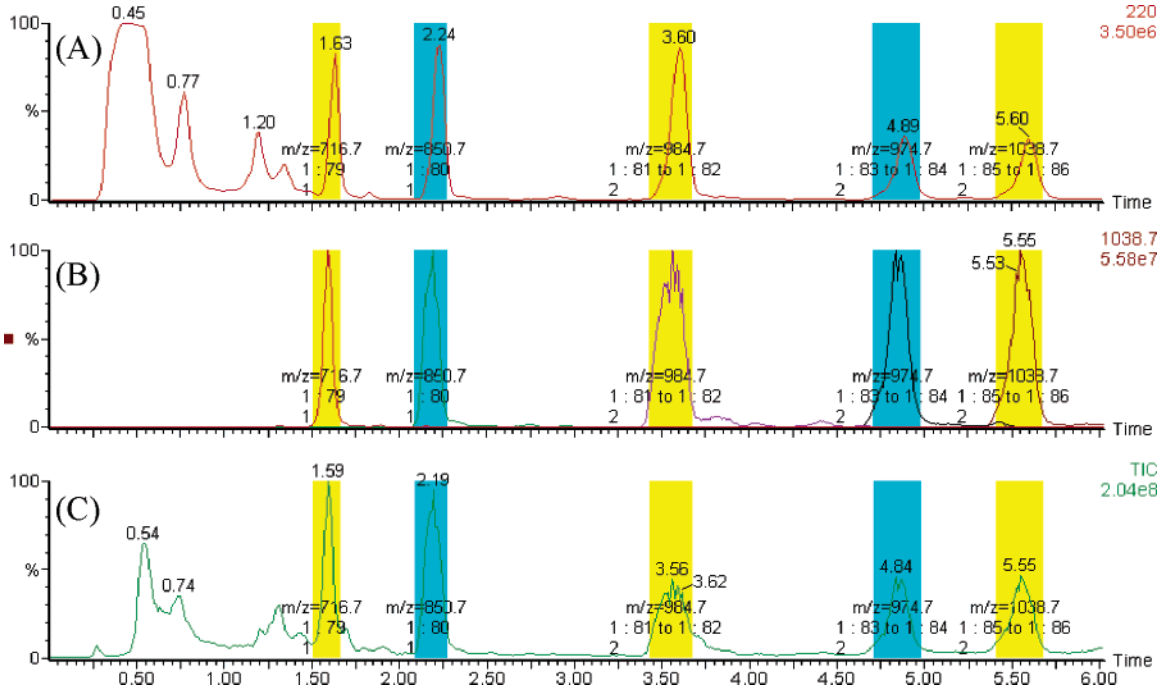


Figure 5. Chromatograms of the mass-triggered purification of M-**9**{*1*−*5,4,2,12*}. Fluoro*Flash* column (20 × 50 mm, 5 μm), gradient 70:30 MeCN−H_2O−TFA to 5:95 in 5.5 min, then 95% MeCN−TFA for 1 min; flow rate 60 mL/min. (A) UV 220-nm chromatograms; (B) extracted ion chromatograms with each targeted mass labeled on each peak; (C) total ion current chromatogram (TIC).

MS-directed HPLC techniques to demixing the reaction mixtures and using parallel four-channel LC/MS for analysis dramatically increase the efficiency of FMS. Results shown in this paper demonstrate that FMS as a new high-throughput synthetic technology has great potential in solution-phase library synthesis.

Experimental Section

Materials and Methods. All starting materials, solvents, and reagents were commercially available and used without further purification. Fluoro*Flash* SPE cartridges were obtained from Fluorous Technologies, Inc. SPE purification was conducted in parallel on a 2 × 12 SPE manifold available from Supelco and Fisher. Microwave reactions were conducted sequentially on a CEM Explorer single-mode microwave reactor with 10-mL cap-sealed tubes. NMR spectra were obtained on a Bruker AC-270 spectrometer (270 MHz). $CDCl_3$ was used as the solvent unless otherwise specified. ^1H and ^{13}C NMR spectra were recorded at 270 and 67.5 MHz, respectively. Chemical shifts are in parts-per-million

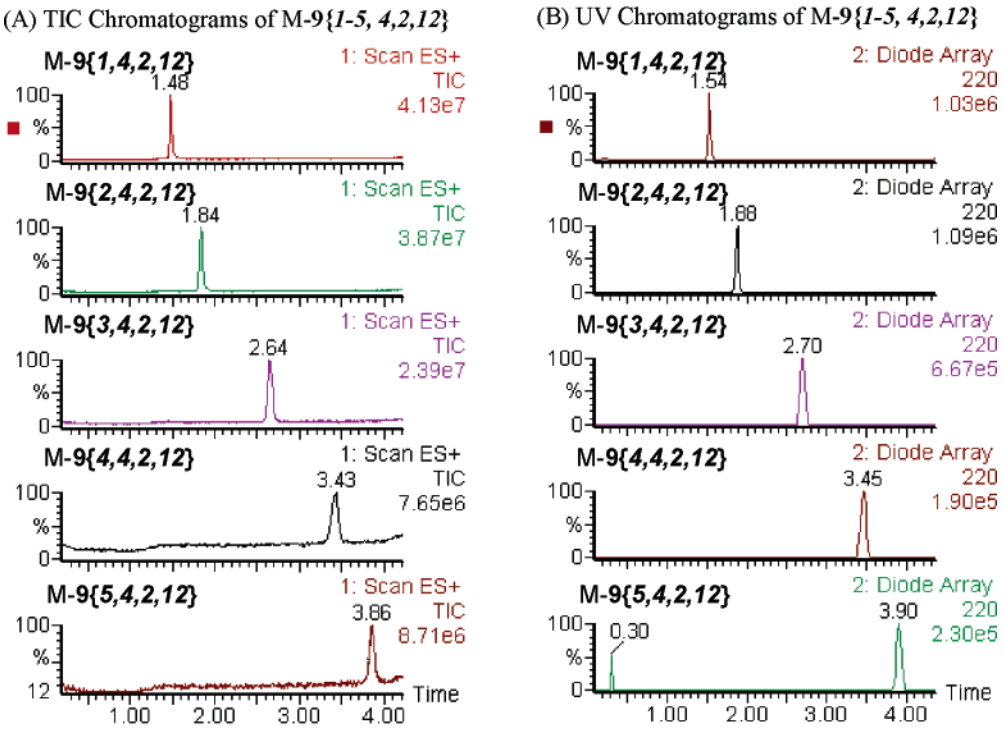
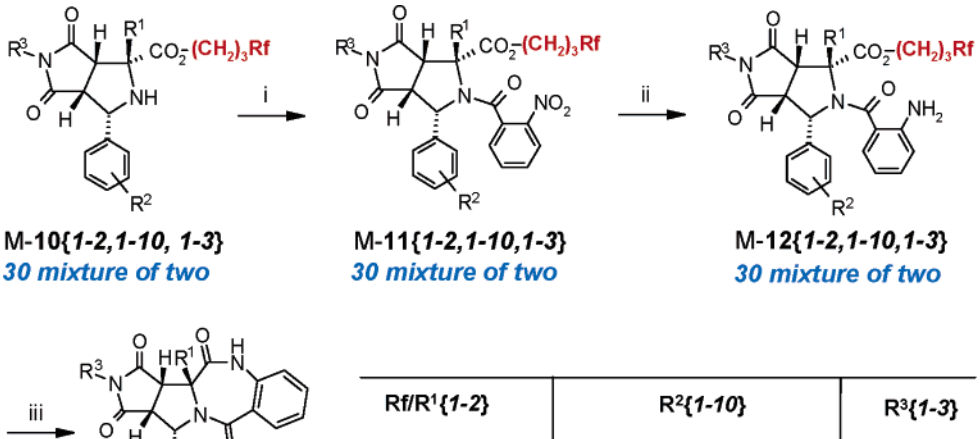


Figure 6. Purity analysis of five components of M-**9**{*1*−*5,4,2,12*} after demixing. Fluoro*Flash* columns (4.6 × 50 mm, 5 μm), gradient 70:30 MeCN−H_2O−TFA to 5:95 in 3 min, then 95% MeCN−TFA for 1 min; flow rate 3 mL/min. (A) TIC chromatograms; (B) UV 220 chromatograms.

Scheme 4. FMS of a 60-Member Benzodiazepine-Fused Tetracyclic Compound Library **3**



Rf/R¹{1-2}	R²{1-10}		R³{1-3}
{1} C_6F_{13}/Me	{1} H	{6} *p*-Br	{1} Me
{2} C_8F_{17}/H	{2} *p*-Me	{7} *m*-Br	{2} Et
	{3} *m*-Me	{8} *p*-Cl	{3} Bn
	{4} *p*-OMe	{9} *m*-Cl	
	{5} *m*-OMe	{10}*p*-F	

i) 2-nitrobenzoylchloride (3 equiv), Et_3N (1 equiv), DMF, 80 °C, 2 h, F-SPE, 50-65%. ii) Zn dust (10 equiv), AcOH, sonication, 2 h, F-HPLC demixing, 55-70%. iii) DBU (2 equiv), dioxane, μw (150 w, 130 °C, 5 min); C_{18} HPLC.

relative to TMS (0 ppm). LC/MS spectra were obtained on an Agilent 1100 system. Purities were calculated on the basis of UV254 absorption. APCI was used as the ion source for all MS. Analytical HPLCs were performed under the following conditions. Method 1: Column, XTerra MS C18 3.5 μm 4.6 × 100 mm. Eluent A, water; B, MeOH. Flow rate, 1 mL/min. Detection, UV (254 nm). 65−100% B in A over 5 min, 100% B for 5 min. Method 2: Column, XTerra MS C18 3.5 μm 4.6 × 100 mm. Eluent A, water; B, MeOH. Flow rate, 1 mL/min. Detection, UV (254 nm). 50−100% B in A over 7 min, 100% B for 5 min. Method 3: Column, Fluoro*Flash* 5 μm 4.6 × 150 mm. Flow rate, 1 mL/min. Eluent A, water; B, MeOH. Detection, UV (254 nm). 80−100% B in A over 5 min, 100% B for 5 min. Semipreparative and preparative liquid chromatographies were performed on a Waters PrepLC2100 system. Method 4: Column, Fluo-

ro*Flash* 5 μm 20 × 250 mm. Flow rate, 20 mL/min. Eluent A, wate; B, MeOH; C, THF. Detection, UV (254 nm). 80−100% B in A over 23 min, 100% C for 4 min. Method 5: Column, Fluoro*Flash* 10 μm 50 × 300 mm. Flow rate, 100 mL/min. Eluent A, water; B, MeOH; C, THF. Detection, UV (254 nm). 80−100% B in A over 23 min, 100% C for 7 min. Method 6: Column, Luna C18 5 μm 21.2 × 250 mm. Eluent A, water; D, acetonitrile. Flow rate, 20 mL/min. Detection, UV (254 nm). 40−100% D in A over 10 min, 100% D for 5 min.

General Procedure for Mixture Synthesis of M-7 by [3 + 2] Cycloadditions. A mixture of five amino esters (M-**4**; 26.3 mmol), an aldehyde (31.5 mmol), a maleimide (39.4 mmol), and Et_3N (78.8 mmol) in DMF (75 mL) was heated at 130 °C for 2 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (500 mL). The solution was washed with brine (2 × 400 mL), and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography (1000 g silica gel) and eluted with EtOAc−hexane (20:80 to 50:50) to afford M-**7** in 70−85% yields.

General Procedure for M-9 and HPLC Demixing. A mixture of M-**7** (1.3 mmol), an isocyanate (6.5 mmol), and DMAP (0.65 mmol) in toluene was heated at 130 °C for 2 h. The concentrated crude product was injected to a preparative Fluoro*Flash* HPLC column (method 4 or 5) to afford 420 demixed ureas **9** in 45−60% yields.

Representative NMR of 9{*4,2,1,10*}. ^{1}H 0.87 (t, J = 7.1 Hz, 3H), 1.91 (s, 3H), 1.97−2.33 (m, 4H), 2.38 (s, 3H), 3.08−3.42 (m, 3H), 4.00 (dd, J = 10.7, 9.2 Hz, 1 H), 4.24−4.52 (m, 2H), 5.27 (d, J = 10.7 Hz, 1H), 6.12 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.10−7.33 (m, 3H), 7.34−7.60 (m, 2H); ^{13}C 12.4, 19.8, 21.2, 24.1, 27.8 (t, J = 89 Hz), 34.0, 49.5, 54.3, 62.7, 64.4, 69.0, 117.7, 105−130 (m), 122.1, 122.4, 126.3, 129.9, 130.4, 132.9, 139.2, 140.2, 152.6, 170.1, 172.9, 173.6.

General Procedure for Cyclization Reactions of 9. Urea **9** (0.05−0.1 mmol) and K_2CO_3 (10−20 mg) in DMF (0.25 mL) was heated at 100 °C for 5 min in an open vial. The crude product was purified by a C_{18} HPLC (method 6) to afford **2**.

Representative NMR of 2{*1,3,2,12*}. ^{1}H 0.95 (d, J = 6.5 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H), 1.49 (s, 9H), 1.65−1.90 (m, 2H), 2.24 (dd, J = 13.6, 5.3 Hz, 1H), 3.39 (d, J = 8.0 Hz, 1H), 3.77 (dd, J = 9.5, 8.0 Hz, 1 H), 5.01 (d, J = 9.5 Hz, 1H), 7.04 (d, J = 6.8 Hz, 2H), 7.30−7.44 (m, 4H), 7.47 (d, J = 6.8 Hz, 2H); ^{13}C 23.7, 24.5, 28.1, 29.8, 43.7, 53.5, 53.8, 59.8, 62.8, 72.1, 123.8, 124.2, 126.2, 128.5, 130.1, 131.1, 131.3, 132.6, 134.7, 151.6, 169.3, 173.2, 174.6.

General Procedure for Parallel LC/MS Analysis. The parallel four-channel LC/MS analyses were conducted on a Waters ZQ 2000 single quadruple mass spectrometer equipped with a four-way multiple index ESI source (MUX) and a Waters 2525 binary gradient pump, a Waters 2488 dual wavelength four-channel UV detector (220 and 254 nm), and a four-channel CTC autosampler. MassLynx 4.0 was used for data acquisition. The chromatographic separations were carried on Fluorous Technologies Inc. Fluoro*Flash* HPLC analytical columns (4.6 × 50 mm, 5 μm). The flow rate was set at 12 mL/min through a four-way manifold to split the flow to four individual columns and then to a four-channel UV detector. Following the initial hold at 70% buffer B (B, MeCN with 0.035% TFA; A, water with 0.05% TFA) for 0.5 min, the separations were performed by using a gradient of 70−95% buffer B in 3 min with a hold at 95% buffer B for 1 min. The equilibration time between the analyses was 1 min. A flow splitter was situated at the outlet of each column, and a small portion of effluent (∼100 μL) was diverted to each inlet of a four-way MUX interface for mass spectrometric analysis.

General Procedure for Separations of Fluorous Mixtures by Mass-Directed HPLC. The mass-directed purifications were conducted on a Waters ZQ 2000 single quadruple mass spectrometer equipped with an electrospray ion (ESI) source and a Waters 2767 sample manager for autosampling and fraction collection, a Waters 2487 dual wavelength UV detector (220 and 254 nm), a Waters 2525 binary gradient pump for the separation, and a Waters 515 pump as the makeup flow for mass triggered fractionation. MassLynx 4.0 was used for data acquisition. The HPLC separations were carried on a Fluoro*Flash* semipreparative column (20 × 50 mm, 5 μm). The flow rate was set at 60 mL/min for the 2525 pump. Following the initial hold at 70% buffer B (B, MeCN with 0.035% TFA; A, water with 0.05% TFA) for 0.5 min, the separations were conducted with a gradient of 70−95% buffer B for 5.5 min with a hold at 95% buffer B for 1 min. The equilibration time between the analyses was 1 min. A flow splitter was situated at the outlet of the column, and a small portion of effluent (about 100 μL) was mixed with makeup flow (515 pump) at 1.0 mL/min of MeOH and water (80/20) with 0.1% formic acid, which was further split by a tee to diverted ∼100 μL to the ESI interface for mass spectrometric triggered fractionation.

General Procedure for N-Acylation of M-10. A mixture of M-**10** (2.4 mmol), 2-nitrobenzoyl chloride (7.3 mmol), and Et_3N (2.4 mmol) in DMF (1 mL) was stirred at 80 °C for 2 h. Upon reaction completion, the crude mixture was loaded directly onto a 5 g Fluoro*Flash* cartridge. The cartridge was eluted with 80:20 MeOH−H_2O (2 × 8 mL) and acetone (2 × 8 mL). The acetone fractions were collected and concentrated to give the N-acylated product M-**11** in 50−65% yields.

General Procedure for Preparation of M-12 and HPLC Demixing. A mixture of M-**11** (0.64 mmol) and zinc dust (6.4 mmol) in acetic acid (3 mL) was sonicated for 2 h. The crude mixture was filtered through a plug of Celite, and the solid was washed with EtOAc (2 mL). The filtrate was washed with aq $NaHCO_3$ (2 × 2 mL) and concentrated. The residue was demixed by preparative fluorous HPLC (method 5) to give demixed ureas **12** in 55−70% yields.

General Procedure for Cyclization Reactions of 12. A mixture of **12** (0.1 mmol) and DBU (0.2 mmol) in dioxane (0.5 mL) was irradiated in a microwave reactor (150 w, 130 °C, 5 min). The reaction mixture was loaded onto a 2-g Fluoro*Flash* cartridge and eluted with MeOH−H_2O (2 × 8 mL). The concentrated MeOH−H_2O fraction was further purified by C_{18} HPLC (method 6) to afford **3**.

Representative NMR of 3{*1,4,2*}. ^{1}H 1.14 (t, J = 7.2 Hz, 3H), 1.65 (s, 3H), 3.52 (q, J = 7.2 Hz, 2H), 3.60 (d, J = 10.2 Hz, 1H), 3.72 (s, 3H), 3.86 (t, J = 10.5 Hz, 1H), 5.88 (d, J = 11.1 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.48 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.95 (dd, J = 7.8, 1.1 Hz, 1H), 8.26 (s, 1H); ^{13}C 12.4, 25.7, 34.2, 46.1, 55.1, 56.7, 66.0, 67.9, 113.9, 120.0, 125.3, 128.5, 129.1, 131.5, 133.6, 135.7, 159.1, 164.3, 170.5, 173.2, 173.9.

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Supporting Information Available. Spectra of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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